Development and Application of Asymmetric C-N Bond Formation

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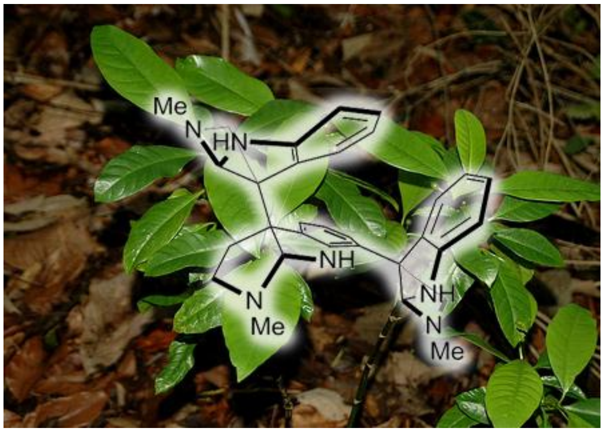
Abstract

A synthetic investigation on the chemistry of cyclotryptamine derived natural products, with a particular focus on the synthesis of the trimeric-alkaloid, hodgkinsine (see below). Methodology has been developed to tackle this complex natural product which utilises a desymmetrization approach; this strategy hinges on the development and applications of asymmetric C-N bond forming reactions.



Chapter one examines elements of symmetry in natural products, looking in particular at the synthesis of compounds which contain cyclotryptamine functionality.

Chapter two contains a brief review of enantioselective desymmetrization paying attention, if possible, on its application in the synthesis of natural products.

In the remaining chapters we discuss our own progress and results in our pursuit of an efficient enantioselective total synthesis of hodgkinsine.

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Acknowledgements

Firstly I would like to thank Dr. Michael Willis for giving me the opportunity to take on this project and for his untiring support and enthusiasm throughout my time in the group. I am also extremely grateful for the help and support of the Willis Group both past and present. I would greatly like to thank my predecessor Dr. Matthew Durbin who got the ball rolling for the total synthesis, as well as Dr. Robert Woodward for his help during my time at AstraZeneca. I would also like to thank the EPSRC and AstraZeneca for funding my research, without their support this project would not have been possible.

Additionally I would like to thank the following for their help and advice along the way: Rod, Doug, Mary, Luke, Tadd, Santi, Paul and Phil. For taking on a massive amount of proof reading I would particularly like to thank Radleigh Foster, Cat and Fiona.

Thanks also goes to all the CRL support staff especially Tim Claridge and Barbara Odell for help with NMR and to Amber Thompson and Paul Ylioja for X-ray crystallography.

Finally I would like to thank my family for their support and encouragement; I would also like to dedicate this work to my grandparents both of whom sadly passed away during my time in Oxford.

Abbreviations

General

Abbreviation	**Term**
δ	chemical shift
app	Apparent
aq	Aqueous
b	broad (spectral)
cm^{-1}	wavenumber(s)
conc	Concentrated
COSY	correlation spectroscopy
d	doublet (spectral)
DEPT	distortionless enhancement by polarization transfer
DMG	directing metalation group
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
eq	equivalent(s)
ESI	electrospray ionization
Fig.	Figure
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IR	Infrared
J	coupling constant
LCMS	liquid chromatography mass spectrometry
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet (spectral)

m/z	mass-to-charge ratio
M^+	parent molecular ion
max	Maximum
MHz	Megahertz
min	minute(s); minimum
mol	mole(s)
mp	melting point
MS	mass spectrometry; molecular sieves
μW	microwave (in schemes)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	Nucleophile
o	Overlapping
ppm	part(s) per million
q	quartet (spectral)
Quant	Quantitative
quin	quintet (spectral)
rt	room temperature
s	singlet (spectral); second(s); selectivity factor
sept	septet (spectral)
sext	sextet (spectral)
t	triplet (spectral)
t	Time
T	temperature (in tables)
TLC	thin-layer chromatography
TOF	time-of-flight
$t_\mathbf{R}$	retention time (chromatography)
UV	Ultraviolet
vis	Visible

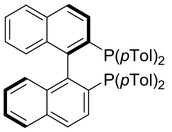
Reagents, Solvents, Substituents and Protecting Groups

Abbreviation	**Compound Name**
Ac	Acetyl
AIBN	2,2'-azobis(isobutyronitrile)
Ar	Aryl
BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Bz	Benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	Benzyloxycarbonyl
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethlamine
DIPT	diisopropyl tartrate
DMA	*N,N*-dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone / *N,N*'-dimethylpropylene urea
DMSO	dimethyl sulfoxide
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
Fmoc	9-fluorenylmethoxycarbonyl
Fod	1,1,1,2,2,3,3-hepta-fluoro-7,7,dimethyl-4,6-octanedionato
HBTU	*N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide

MOM	methoxymethyl
Ms	mesyl / methanesulfonyl
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NDMBA	1,3-dimethylbarbituric acid
NIS	*N*-iodosuccinimide
NMDA	*N*-methyl D-aspartate
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
N-PSP	*N*-phenylselenophthalimide
PEPPSI	[1,3-*bis*(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Phth	phthaloyl
PIFA	[*bis*(trifluoroacetoxy)iodo]benzene
i-Pr	isopropyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PMPi	(1,2,2,6,6-pentamethylpiperidene)
PPTS	pyridinium *p*-toluenesulfonate
PS	Proton sponge
Pv	pivaloyl
py	2-pyridyl
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
T3P	propylphosphonic anhydride
TASF	*tris*(dimethylamino)sulfonium difluorotrimethylsilicate
TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflyl / trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	Tetramethylsilane / trimethylsilyl

TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	4-methylphenyl
Tr	trityl / triphenylmethyl
Troc	2,2,2-trichloroethoxycarbonyl
Trs	(2,3,4-triisopropylbenzenesulfonyl)
Ts	tosyl / *p*-toluenesulfonyl

Ligands



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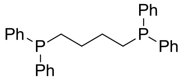
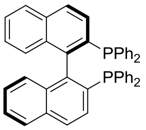


dppb

L2



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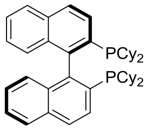

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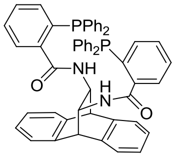
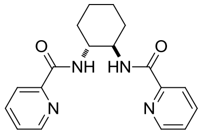


(*R*,*R*)-ANDEN-Phenyl Trost Ligand

L5



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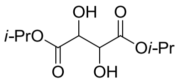

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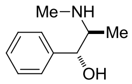

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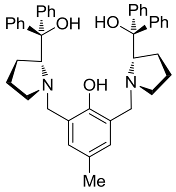

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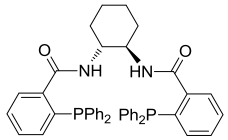

(*R*,*R*)-DACT-Ph-Trost Ligand

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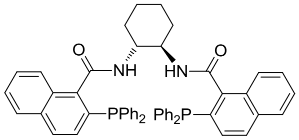

(*R*,*R*)-DACT-Naphthyl-Trost Ligand

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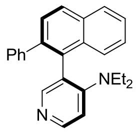

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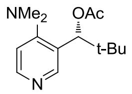

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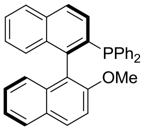

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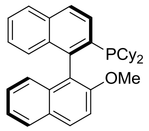

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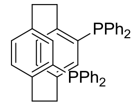
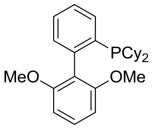


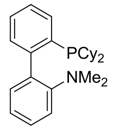
Phanephos

L16



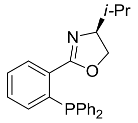
S-Phos

L17



Dave-Phos

L18



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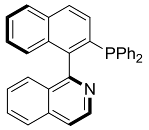
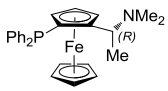


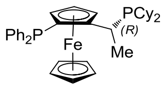
(*R*)-QUINAP

L20



(*R*,*S*) PPFA

L21



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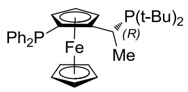

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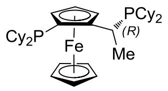

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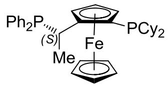

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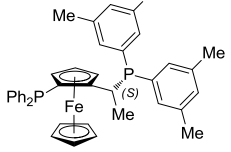

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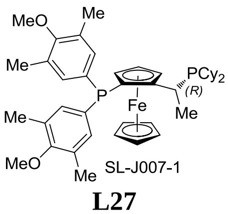

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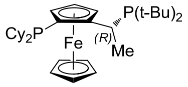

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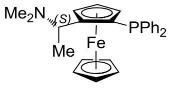
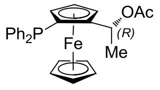


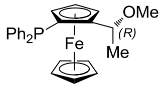
(*S*,*S*) PPFA

L29



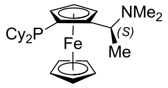
(*R*,*S*) PPFOAc

L30



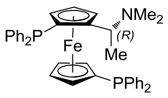
(*R*,*S*) PPFOMe

L31



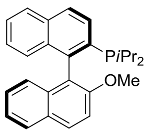
(*S*,*R*) CyPFA

L32



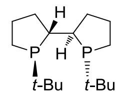
(*R*,*S*) BPPFA

L33



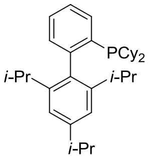
(*R*)-*i*Pr-MOP

L34



(*S*,*S*,*R*,*R*)-Tangphos

L35



X-Phos

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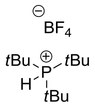
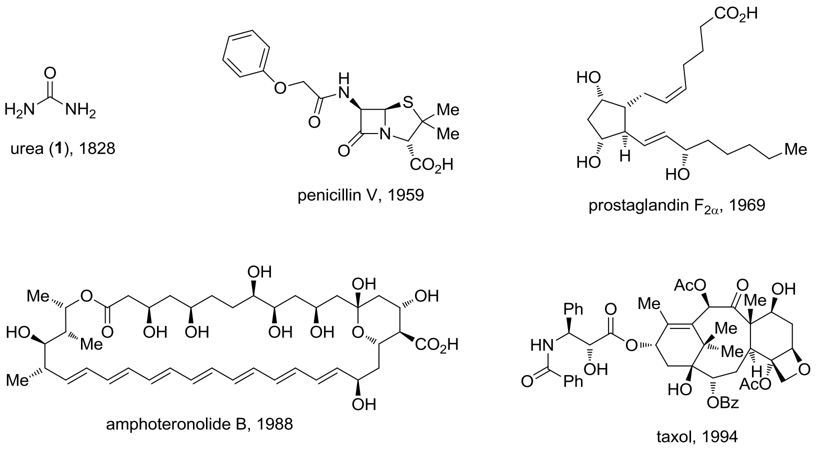


Fu's Salt

L37

1.0 Symmetry in Natural Products

The synthesis of natural products is now accepted as a vital area in synthetic organic chemistry. Total synthesis drives forward the development and application of new methodology as well as pushing the boundaries of existing techniques. In historical terms natural product synthesis is a fairly new discipline, with origins in the 19th century and the synthesis of urea **1** by Wöhler in 1828. Since this landmark discovery, the breadth of the field has grown astronomically, as has the complexity of the targets.[1-3] Advances in synthetic organic chemistry have gone hand in hand with total synthesis, and the advent of asymmetric synthesis and catalysis has made the synthesis of previously unimaginable compounds a reality (Fig. 1).[1,4-8]


urea (**1**), 1828

penicillin V, 1959

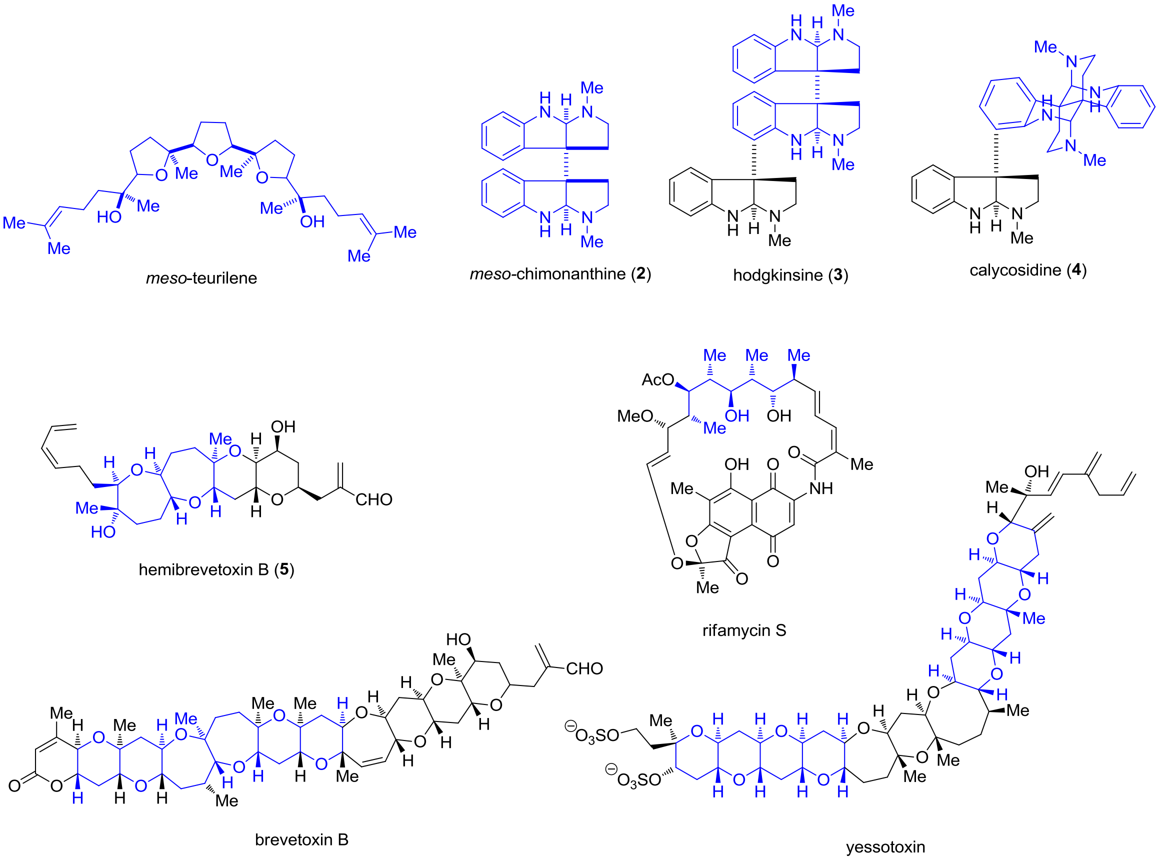
prostaglandin $F_{2\alpha}$, 1969

amphoteronolide B, 1988

taxol, 1994

Fig. 1: Selected examples of landmark total syntheses

Amongst the countless natural products identified to date, many contain a discrete or sometimes obvious element of symmetry (Fig. 2). This esoteric fragment of natural products chemistry opens new windows into the beauty and elegance of the subject.[9-13]


meso-teurilene

meso-chimonanthine (**2**)

hodgkinsine (**3**)

calycosidine (**4**)

hemibrevetoxin B (**5**)

rifamycin S

brevetoxin B

yessotoxin

Fig. 2: Examples of natural products containing elements of *meso* or centro-symmetry

With respect to synthetic strategy, the element of symmetry can be a benefit or a curse, causing the existing challenge of stereo and regioselectivity to take on a whole new dimension of intricacy. Many synthetic approaches utilise the target molecules' symmetry in their approach, for example, the elegant synthesis of hemibrevetoxin B **5** by Nelson.[14] Meanwhile others, such as Overman's synthesis of the polypyrrolidinoindoline alkaloid hodgkinsine **3**, cleverly circumvent the issue by using a resolution tactic.[15,16]

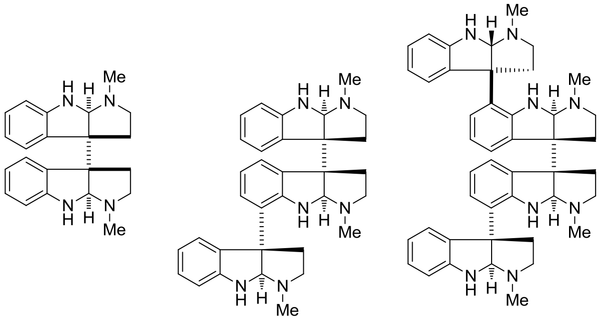
1.1 Synthesis of Polypyrrolidinoindoline Alkaloids

1.1.1 Synthesis of Chimonanthine

The *meso* and C_2 symmetric forms of chimonanthine **2** belong to a complex family of cyclotryptamine based natural products.[17] These have been isolated from a variety of flora,[10,18-20] and, in the case of (+)-chimonanthine **13**, fauna in the form of the Colombian poison dart frog *Phyllobates terribilis* (Fig. 3).[21] Chimonanthine also forms the base for many of the higher order cyclotryptamine alkaloids including hodgkinsine **3** and quadrigemine C **6** (Fig. 4).[11,22]

Fig. 3: Phyllobates terribilis

Chimonanthine **2** has generally been observed in the *Calycanthus*, *Chimonanthus*, *Palicourea*, and *Psychotria* genera of plants and was first isolated in 1961 from the leaves of *Chimonanthus fragrans*.[10] However, it was not until 1965 that the precise structure of chimonanthine was confirmed by X-ray crystallographic analysis of the dihydrobromide salt.[23] For an extensive review on the identification and characterisation of chimonanthine **2** and related polypyrrolidinoindoline alkaloids see Saxton.[24]



meso-chimonanthine (**2**) hodgkinsine (**3**) quadrigemine C (**6**)

Fig. 4: Examples of cyclotryptamine alkaloids

Studies into the pharmacological activity of chimonanthine **2** have shown it to produce a dose-dependent, naloxone reversible, analgesic effect in thermal models of nociception[i] and in capsaicin-induced pain.[25,26]

Chimonanthine **2** poses a serious synthetic challenge. It possesses four contiguous stereogenic centres, two of which are quaternary; the synthesis of such stereocentres is notoriously difficult.[27] As a result, chimonanthine **2** has been the subject of many synthetic investigations.[17,25,28-40] Early reports of synthetic methods for chimonanthine **2** were racemic syntheses and generally resulted in a statistical mixture of *meso* and racemic C_2 isomers, usually in modest to low yields. Such early routes often took the form of a bio-mimetic strategy based around an oxidative dimerization of two tryptamine-derived units (Scheme 1).[32,39,41,42]

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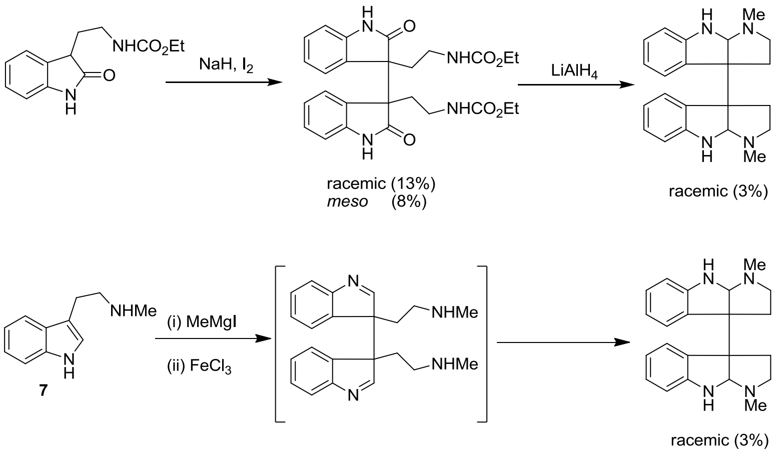
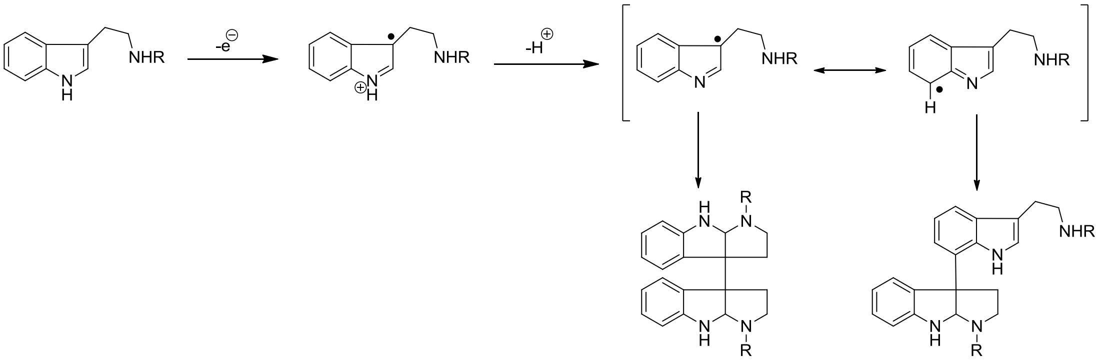
[i] Nociception is the physiological sense for perception of physical pain.



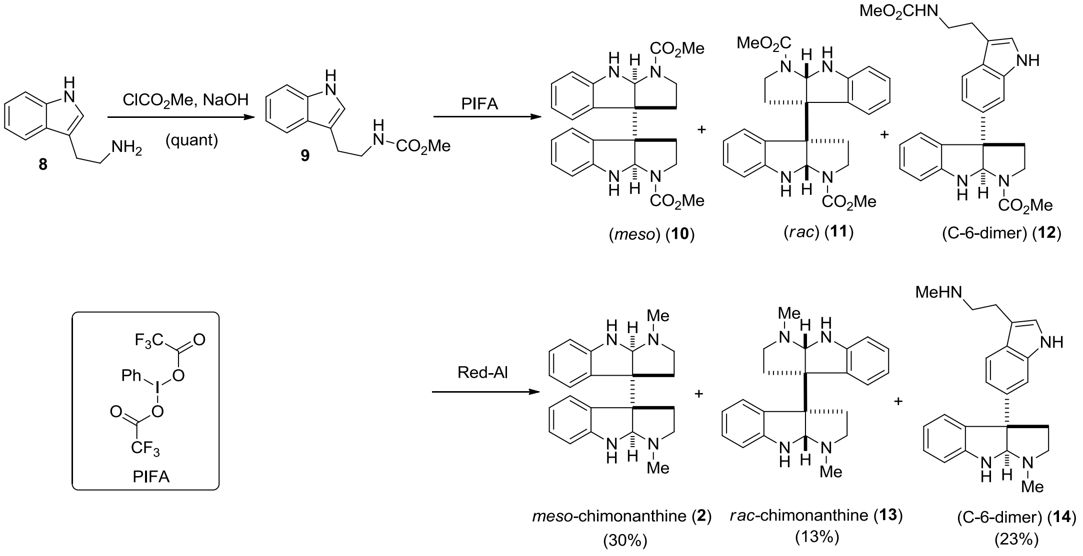
Scheme 1: Oxidative dimerizations of tryptamine derivatives

Although the precise mechanism of the biosynthesis is unknown, it has long been thought to involve a single electron oxidation of a tryptamine derivative, generating a radical which could facilitate the dimerization to yield linked cyclotryptamine units (Scheme 2).[17,32,35,39] Weight was added to this proposal by a series of isotopic labelling experiments where the leaf bearing shoots of *Chimonanthus fragrans* were fed with [β-^{14}C,2-^{3}H]-tryptamine. It was observed that there was significant incorporation of the labels into the chimonanthine **2** subsequently isolated from the plant.[35]



Scheme 2: Proposed biosynthetic route

Recently, despite the development of several enantioselective routes to chimonanthine **2**, a new oxidative dimerization procedure has been reported, which represents the most feasible procedure for the large scale synthesis of *meso*-chimonanthine **2**. The Takayama group were able to synthesise *meso*-chimonanthine in a 30% yield in just three steps from commercial starting materials.[43] The route utilizes hypervalent iodine[44,45] to effect the dimerization of methyl carbamate protected tryptamine **9** to give a separable mixture of stereo- and regioisomers (**10-12**).[46] The carbamate protecting groups were then readily reduced to the corresponding *N*-methyl groups using Red-Al. This facile route represents a significant improvement over earlier methods and makes synthesis of the higher cyclotryptamine alkaloids a far less challenging endeavour (Scheme 3).[43]



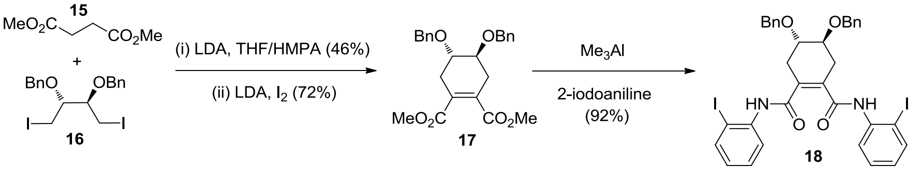
Scheme 3: Practical three-step route to chimonanthine

1.1.2 Overman's Synthesis of Chimonanthine

In recent years, the field of cyclotryptamine chemistry has been dominated by the Overman group at the University of California, Irvine.[17] His seminal work on the synthesis of (-)- and *meso*-chimonanthine **2** beautifully created all of the molecule's stereocentres and utilised his group's cascade Heck methodology to complete the synthesis in seventeen high yielding linear steps. An overall yield of 6% of *meso*-

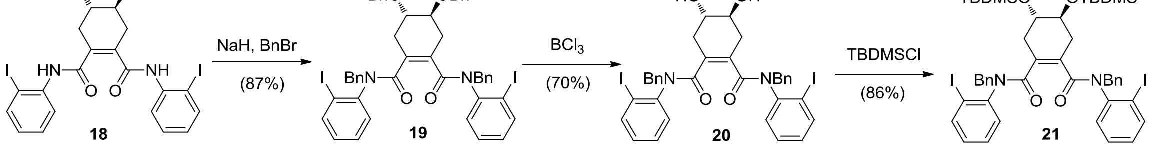
chimonanthine **2** was reported.[29,33,34] This route built upon Overman's first stereocontrolled path to *meso*-chimonanthine **2**[17] and the methodology employed also facilitated the stereoselective synthesis of (+) calycanthine **27**.

The synthesis commences from the C$_2$-symmetric diiodide **16**, prepared from the corresponding tartrate,[47] *via* a double alkylation under basic conditions with dimethyl succinate **15**. Subsequent oxidation (LDA and iodine) gave **17** in a 33% yield over two steps. Aminolysis of **17** with the dimethylaluminium amide of 2-iodoaniline gave diamide **18** in 92% yield (Scheme 4).



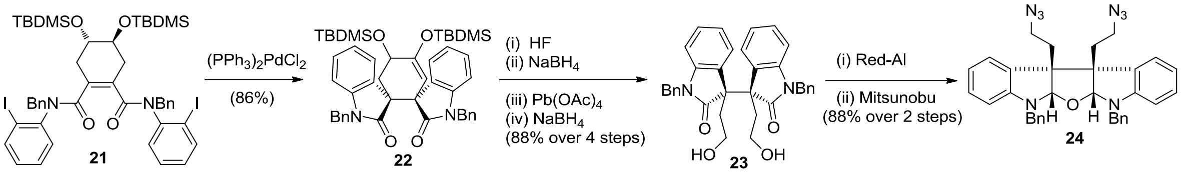
Scheme 4: Synthesis of diamide **18**

The Heck precursor **21** was synthesised from diamide **18** by a series of functional group manipulations. Firstly the free amide groups were protected by a conventional *N*-benzylation, and subsequently the benzyl ethers were cleaved using borontrichloride. The resultant free alcohols were then protected using TBDMSCl to give the Heck precursor **21** in a 52% yield (over three steps) (Scheme 5).



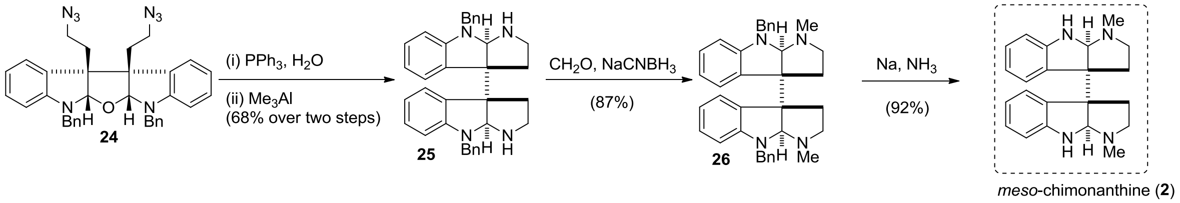
Scheme 5: Protecting group manipulations to give Heck precursor **21**

The key cascade Heck cyclisation proceeded smoothly at 100 °C to give *spiro*-amide **22** in an 86% yield as a single diastereoisomer. With the Heck product in hand, the silyl protecting groups were removed and the resultant *alpha*-hyroxy ketone reduced with sodium borohydride. The ensuing cleavage of the diol with lead tetra-acetate furnished a dialdehyde which was immediately reduced with sodium borohydride to give *meso*-diol **23** in an 88% yield (over four steps). Reduction of diol **23** followed by swift conversion to the *meso*-diazide **24** (a key intermediate in Overman's first synthesis of *meso*-chimonanthine)[33] was accomplished in an 88% yield over two steps (Scheme 6).



Scheme 6: Synthesis of *meso* precursor **24**

Reduction of diazide **24** to the corresponding diamine followed by exposure to trimethyl aluminium gave the desired bis(pyrroloindoline) **25** in a 68% yield (over two steps). Reductive methylation of the free secondary amines, and finally cleavage of the two benzyl groups with sodium in ammonia gave *meso*-chimonanthine in 80% yield, over two steps (Scheme 7).



Scheme 7: Conversion of **24** to *meso*-chimonanthine **2**

Despite the success of this route, which represents a significant achievement, the Overman group went on to further develop this synthetic pathway with another route published in 2000.[29]

1.1.3 Calycanthine and Its Relation to Chimonanthine

Long before the isolation and full characterisation of chimonanthine, the isolation of (+)-calycanthine **27** in 1888 from *Calycanthus glaucus* sparked a wealth of chemical research into the calycanthus alkaloids.[48] Between 1888 and 1960 there were several formulaic and structural revisions but it was not until Woodward *et al.* resumed work in this area that a universally agreed structure was assigned.[49] This structure was later unequivocally confirmed by X-ray crystallographic data.[50-52] Calycanthine **27** (Fig. 5) itself has long been recognized as a central convulsant and has recently been shown to inhibit the potassium-stimulated release of [^{3}H]GABA from slices of rat hippocampus.[53]

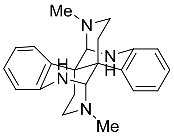
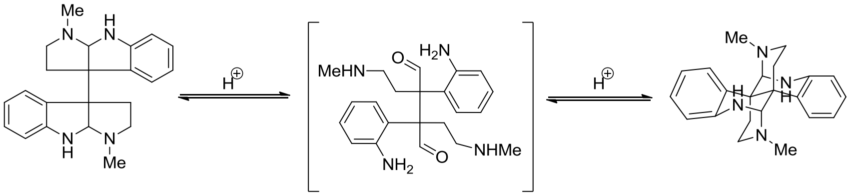


Fig. 5: Calycanthine **27**

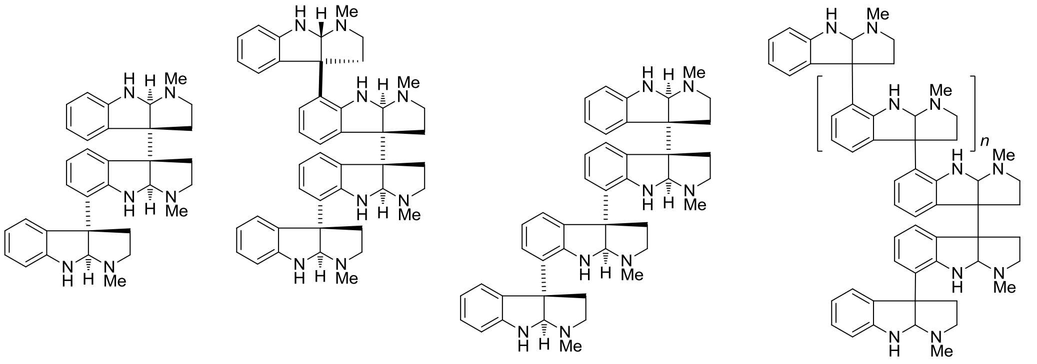
Early research on the calycanthus alkaloids identified that under acidic conditions chimonanthine can be converted to calycanthine in appreciable yields of *ca.* 25% (Scheme 8).[19,42] This rearrangement begs the question as to whether calycanthine is a genuine natural product or just a relic of isolation.[17] Nevertheless, Overman utilised this rearrangement in his synthesis of calycanthine to great effect.[29,33,34]



Scheme 8: Acid mediated rearrangement of chimonanthine

1.1.4 Hodgkinsine and the High-Order Cyclotryptamine Alkaloids

Hodgkinsine **3** (Fig. 6) was first isolated in 1961 from the leaves of *Hodgkinsonia frutescens* (Fig. 7) in tropical Queensland.[11] This complex natural product comprises three linked cyclotryptamine units and belongs to the calycanthus family of alkaloids.



hodgkinsine (**3**) quadrigemine C (**6**) quadrigemine H (**28**)

n = 1 psychotridine
n = 2 vatine
n = 3 vatamine
n = 4 vatamidine

Fig. 6: Hodgkinsine **3** and some of the other high-order polypyrrolidinoindoline alkaloids

Hodgkinsine **3** is based around a *meso*-symmetric core with a third cyclotryptamine unit bound to the C-7 position. Since its first isolation, hodgkinsine **3** has been identified in a variety of vegetation including *Psychotria oleoides,*[54-56] *Psychotria colorata,*[20,57] *Psychotria lyciiflora*[55] and *Calycondendron milnei*.[56] It is currently proposed that hodgkinsine **3** is formed *via* a similar biosynthetic pathway to that of chimonanthine **2** involving the oxidative oligomerisation of tryptamine derivatives (Scheme 2).[17]

A survey amongst native tribes in Amazonian Brazil highlighted *Psychotria colorata* as a source of pharmaceutical interest. It had long been used as a traditional remedy for ear ache and abdominal pain.[25,58] More recently, hodgkinsine **3**, one of the principal alkaloid components, has been shown to exhibit a dose dependent naloxone reversible analgesic effect in thermal models of nociception. Hodgkinsine **3** also acts as a potent analgesic in capsaicin-induced pain models, behaving like the NMDA[i] antagonist dizolcipine (MK801).[25,57] Hodgkinsine **3** and several of the other higher-order cyclotryptamine alkaloids also exhibit potent cytotoxic and anti-tumour activity against rat hepatoma and human leukaemia cell lines. These polypyrrolidinoindoline alkaloids are also effective anti-viral, anti-bacterial and anti-fungal agents.[59]

Fig. 7: Hodgkinsonia frutescens

The synthesis of hodgkinsine **3** and related compounds poses a far greater synthetic challenge than that of chimonanthine **2**. This is by no means limited to the trimeric nature of the compound but also the fact that, despite possessing a *meso*-symmetric core, the molecule is chiral. Consequently, to date, there are only two reported syntheses of hodgkinsine, of which both originate from the Overman group.[15,16] However, many groups have undertaken research into methodology for the formation of cyclotryptamines, generally with a view towards the synthesis of some of the higher-order calycanthus alkaloids.[38,60,61] The first reported total synthesis of a higher-order member of this family was that of quadrigemine C **6** by Overman in 2002.[62] The key to this, and Overman's later

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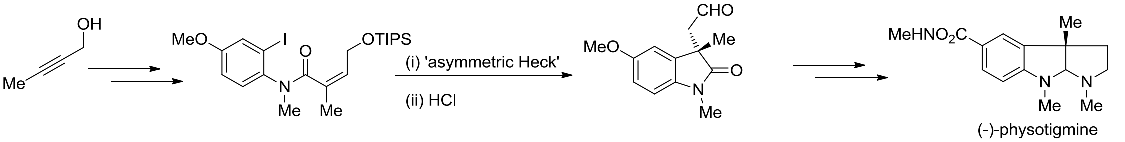
[i] NMDA (*N*-methyl *D*-aspartate)

synthesis of other polypyrrolidinoindoline alkaloids, was the development and elegant application of an asymmetric Heck reaction.[15,16,62,63] The Overman group first pioneered use of this reaction in 1993 with the synthesis of (-)-physostigmine **32**, a naturally occurring alkaloid found in the seeds of African Calabar beans.[63] The route used the asymmetric Heck reaction to establish the alkaloid's quaternary chiral centre, and thus set up the molecule for a diastereoselective reductive amination to yield the target compound (Scheme 9).

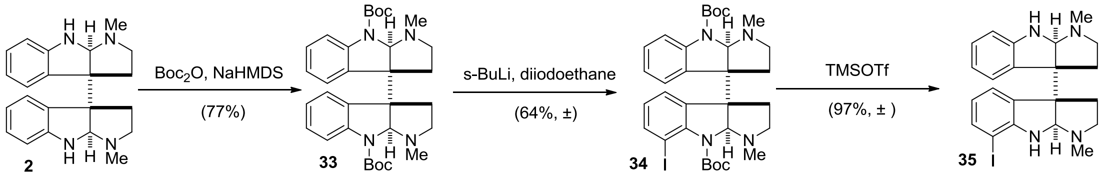


Scheme 9: Synthesis of (-)-physotigmine **32** employing an asymmetric Heck coupling

1.1.5 Overman's Synthesis of Hodgkinsine

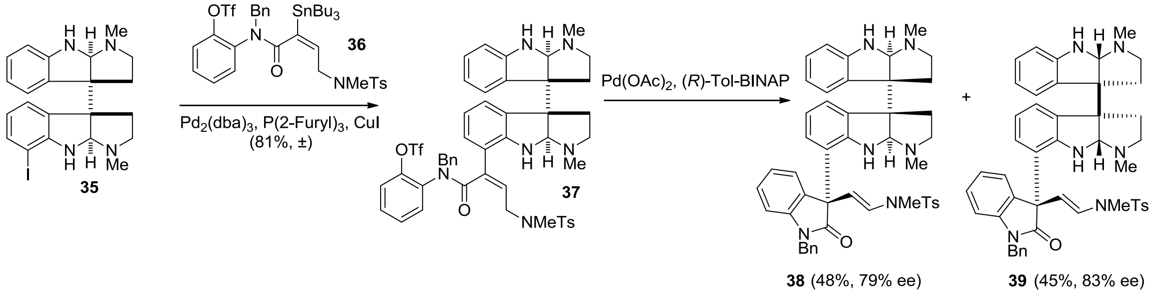
With the route to *meso*-chimonanthine **2** firmly established[33,34] and a stereoselective means of forming cyclotryptamines identified, utilising the asymmetric Heck reaction,[62,63] the way was paved for the total synthesis of hodgkinsine **3**. The strategy adopted by the Overman group was based around a diastereomeric resolution which resulted from the deployment of an asymmetric Heck reaction on a racemic mono-halogenated chimonanthine derivative **35**. The route facilitated the synthesis in seven linear steps from *meso*-chimonanthine **2** with a yield of 5%, equating to ~0.003% from commercially available starting materials.[15,16]

The pathway commenced with installation of directing metalation groups (DMG),[64] Boc, on both the free secondary amines of *meso*-chimonanthine **2**. Directed *ortho*-lithiation with *s*-BuLi and TMEDA followed by quenching with diiodoethane, gave the racemic mono-iodide derivative **34** in a 49% yield (over two steps) which was deprotected in a nearly quantitative yield to give 7-iodo-chimonanthine **35** (Scheme 10).

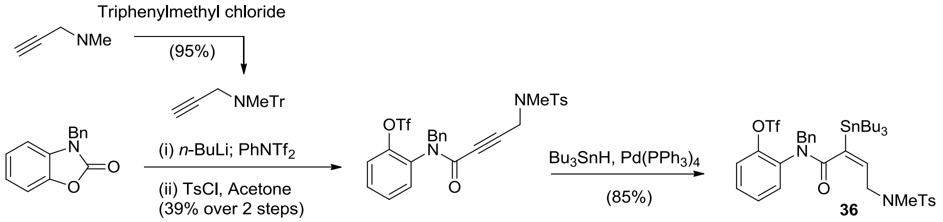


Scheme 10: Synthesis of racemic mono iodide **35**

The mono-iodide **35** was now perfectly set up for a Stille coupling which proceeded in an efficient 81% yield, to give the Heck precursor **37** (Scheme 11). The vinyl stannane **36** necessary for the Stille coupling was prepared *via* a multi-step procedure from commercially available *3H*-benzooxazol-2-one (Scheme 12).[62]



Scheme 11: Diastereomeric resolution using an asymmetric Heck reaction



Scheme 12: Synthesis of Stille precursor **36**

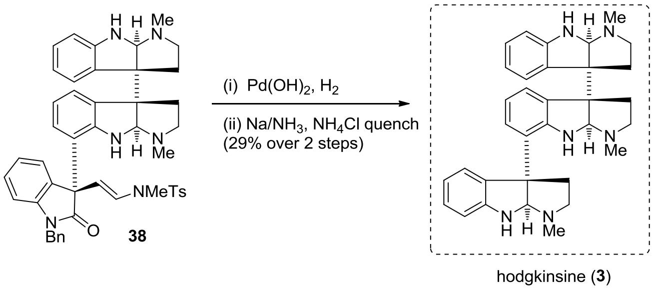
The key step of this reaction was probed in detail; a ligand screen highlighted (*R*)-Tol-BINAP as giving the highest stereoselectivity, which was further enhanced in polar solvents such as acetonitrile. Replacement of 'proton sponge' with PMPi also resulted in an enhancement, with respect to yield, while temperature variation within the range of 65-80 °C bore little effect (Table 1).

Table 1: Optimization of *intra*-molecular Heck reaction

Ligand	Solvent	Base	Yield of **38** [%] (% ee)	Yield of **39** [%] (% ee)
dppb	MeCN	PS[a]	50 (-)	24 (-)
(*R*)-BINAP	MeCN	PS	40 (68)	38 (69)
(*R*)-Tol-BINAP	MeCN	PS	37 (78)	37 (82)
(*S*)-Cy-BINAP	MeCN	PS	7 (11)	6 (6)
(*R*)-Tol-BINAP	DMA	PS	31 (71)	28 (82)
(*R*)-Tol-BINAP	PhMe	PS	24 (55)	24 (48)
(*R*)-Tol-BINAP	MeCN	PMPi[b]	48 (79)	45 (83)

Conditions: $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), base (4.0 eq), [0.05 M], 12 h. [a]Proton Sponge (1,8-*bis*(dimethylamino)naphthalene), [b]PMPi (1,2,2,6,6-pentamethylpiperidene)

After optimization, the asymmetric Heck reaction proceeded in acceptable yields and a high enantiomeric excess, 48% and 79% respectively, for the desired diastereoisomer **38** (Table 1). The Heck product **38** was then hydrogenated to reduce the double bond. Finally, reductive deprotection with sodium and ammonia at -78 °C simultaneously cleaved both the *N*-benzyl and tosyl protecting groups as well as facilitating a reductive amination to give the natural product, hodgkinsine **3**, in a 29% yield over two steps (Scheme 13).[15]



Scheme 13: Final hydrogenation and reductive de-protection

1.1.6 Synthesis of Monomeric Pyrrolidinoindoline Alkaloids

Polymeric cyclotryptamine alkaloids are by no means the only natural products that possess the characteristic fused pyrrolidinoindoline ring system; there are in fact a multitude of secondary metabolites based around this skeleton (Fig. 8).[63,65-71]

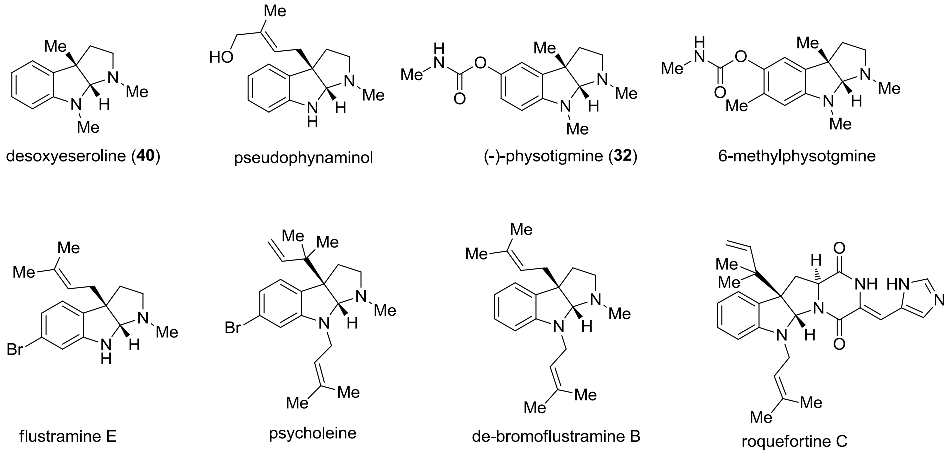
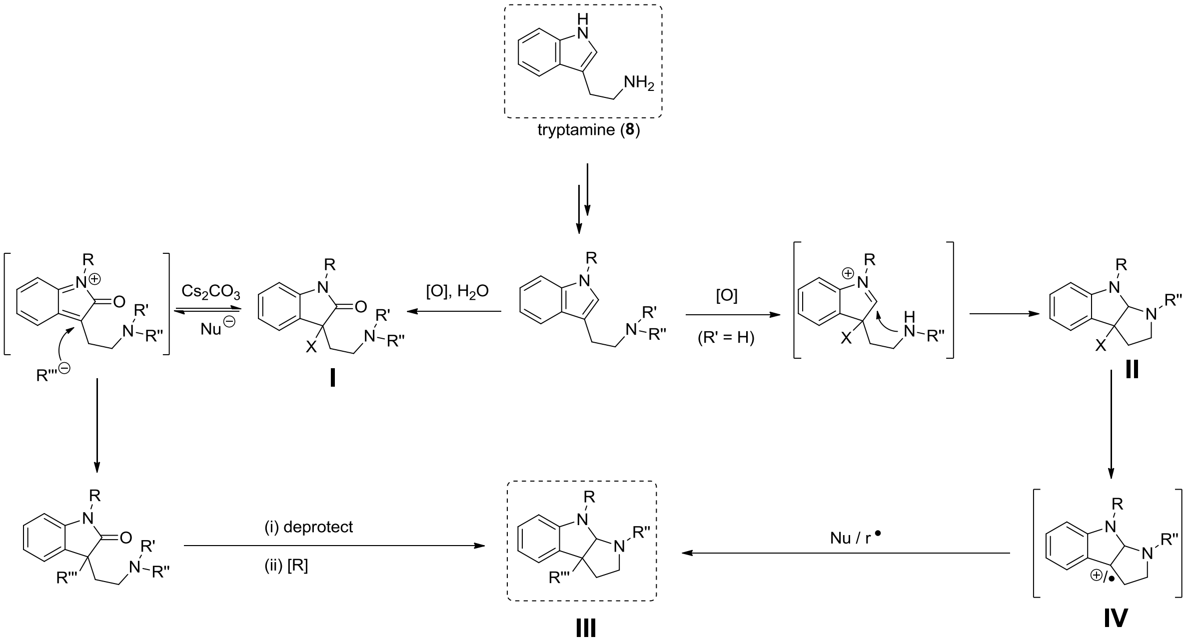

desoxyeseroline (**40**) pseudophynaminol (-)-physotigmine (**32**) 6-methylphysotgmine
flustramine E psycholeine de-bromoflustramine B roquefortine C

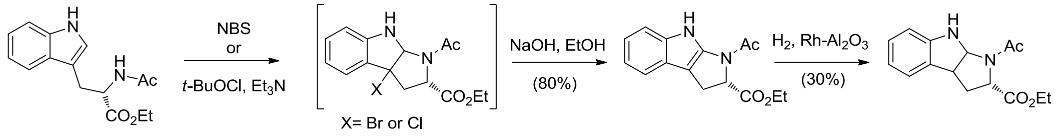
Fig. 8: Examples of natural products containing a single cyclotryptamine unit

Many of these natural products exhibit potent biological activity, for example, physostigmine **32** (Fig. 8) is used to treat myasthenia gravis, glaucoma and Alzheimer's disease.[63,67] Such pharmacological significance coupled with their challenging structures has resulted in this series of natural products being the subject of continued investigation by many research groups over a period spanning several decades.[72-74] Although numerous strategies for the synthesis of the cyclotryptamine core have been developed,[61,70] some of the most successful ones involve the reaction of a tryptamine or tryptophan derivative under oxidative conditions (similar to those used earlier in the dimerization of tryptamine carbamates, Scheme 1 and Scheme 3). Such a procedure generates a reactive intermediate which, depending on its substitution, can react with a nucleophile, such as water, to form an oxindole (Scheme 14, **I**) or close to form the core directly[75] (Scheme 14, **II**). Generally both methods use a halogenating agent such as NBS to effect the oxidation.[73,76] When considering the oxindole variant it should be noted that two equivalents of NBS are required to form bromo-oxindole **I**, subsequently an additional reduction step is also required for the final ring-closure to generate **III**.[76] The direct approach is far more redox-economic,[77] and once compound **II** is formed it can, depending on the oxidant, eliminate 'X' to form a cationic compound (or probably a radical with respect to dimerization) which should react quickly with a nucleophile such as an amine.[73] Although there are examples of isolating compound **II** (when 'X' is chlorine), such species were observed to be highly unstable and readily decomposed.[72] Conversely bromo-oxindoles (**I**) were often stable crystalline solids that could be handled in air making them an attractive means of synthesising the cyclotryptamine core in spite of the less efficient approach.[76,78]



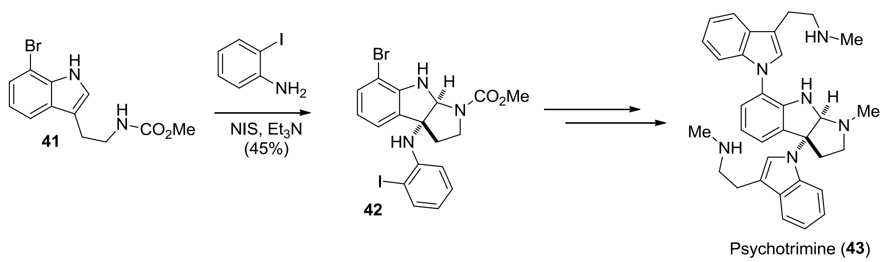
Scheme 14: Generalized routes to cyclotryptamine units

Representative examples of synthetic strategies to monomeric pyrrolidinoindoline alkaloids are illustrated herein; these are by no means comprehensive. The first example of an oxidative cyclisation being used to form a pyrrolidinoindoline ring system was reported in 1968 by Witkop and co-workers. The group were able to cyclise a variety of tryptophan and tryptamine derivatives in good yields; however, they only managed to install a halide or acetate group in the C-3 position. The halo-pyrrolidinoindoline products were generally treated with base to give the corresponding pyrrolidinoindole presumably *via* an E1 mechanism (Scheme 15).[72]



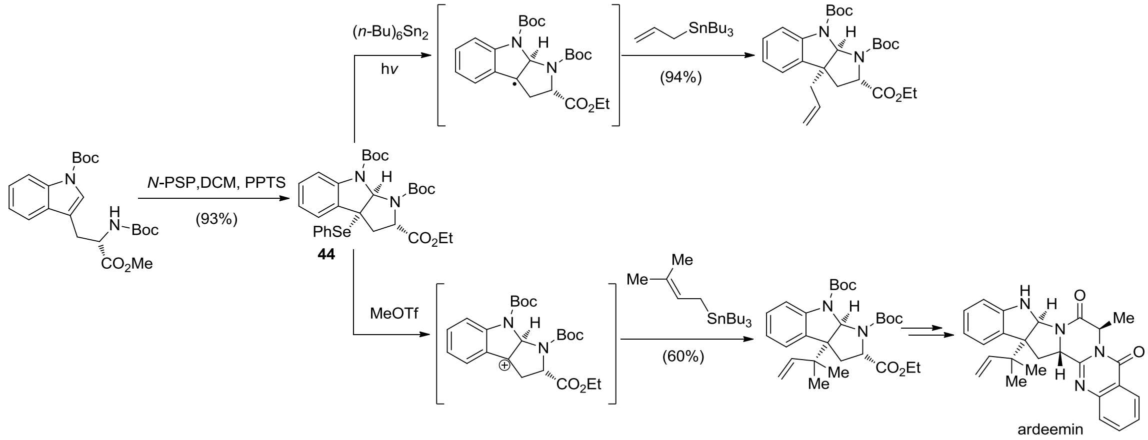
Scheme 15: Early oxidative cyclisation

Since the work of Witkop, numerous other groups have used halogenating agents to generate the cyclotryptamine framework; Scheme 16 shows a recent example from Baran *et al.*[73] Treatment of tryptamine derivative **41** with NIS in the presence of an aniline resulted in the formation of *N*-subsituted pyrrolidinoindoline **42**, a key intermediate in their concise synthesis of racemic psychotrimine **43**.[73] This presumably occurs *via* nucleophilic attack on a cationic intermediate (Scheme 14, **IV**).[79]



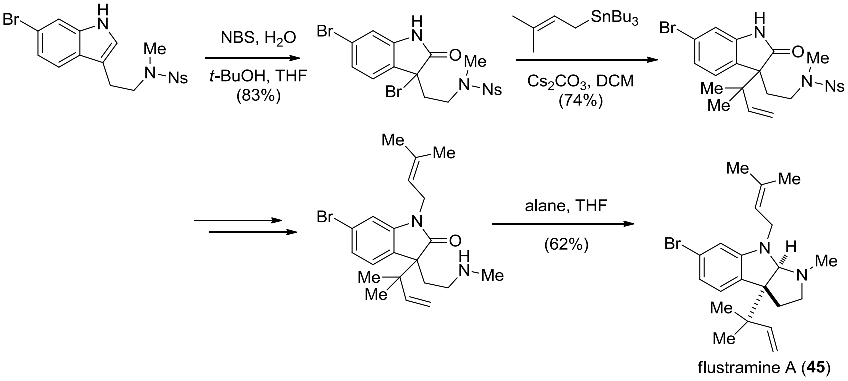
Scheme 16: Modern application of an oxidative cyclisation

Danishefsky and co-workers have published several papers regarding the use of *N*-phenylseleno phthalimide (*N*-PSP) to generate selenides of cyclotryptophan derivatives in excellent yields and high diastereoselectivity (9:1). Selenide **44** undergoes homolysis in the presence of a free radical source; the resultant species can react in high yields with an appropriate coupling partner such as an allyl stannane. Additionally, the group showed that treatment of selenide **44** with methyl triflate would generate the corresponding carbocation which would react with a suitable nucleophile (Scheme 17).[80,81] Subsequently the Ley research group in Cambridge used this methodology to great effect in their synthesis of okaramine C.[82]



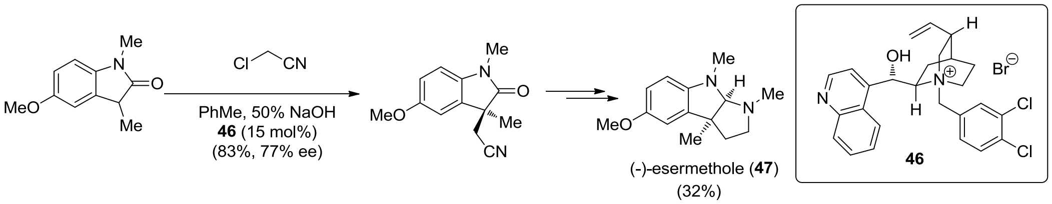
Scheme 17: Danishefsky's total synthesis of ardeemin

As outlined previously (Scheme 14), almost identical reaction conditions can be utilised to generate 3-bromo-oxindoles from their corresponding indoles in a single high yielding step. These compounds have shown high levels of reactivity with soft nucleophiles such as alcohols, amines, stannanes and even electron rich-aromatic groups (*N*,*N*-dimethylanaline). Funk *et al.* have used this methodology in the total synthesis of several natural products including flustramines A **45** and C as well as the alkaloid perophoramidine (Scheme 18).[76,78] It is proposed that the halide eliminates to generate a highly electrophilic planar indol-2-one intermediate which is particularly susceptible to attack at the C-3 position (exemplified in Scheme 14).[76,78]



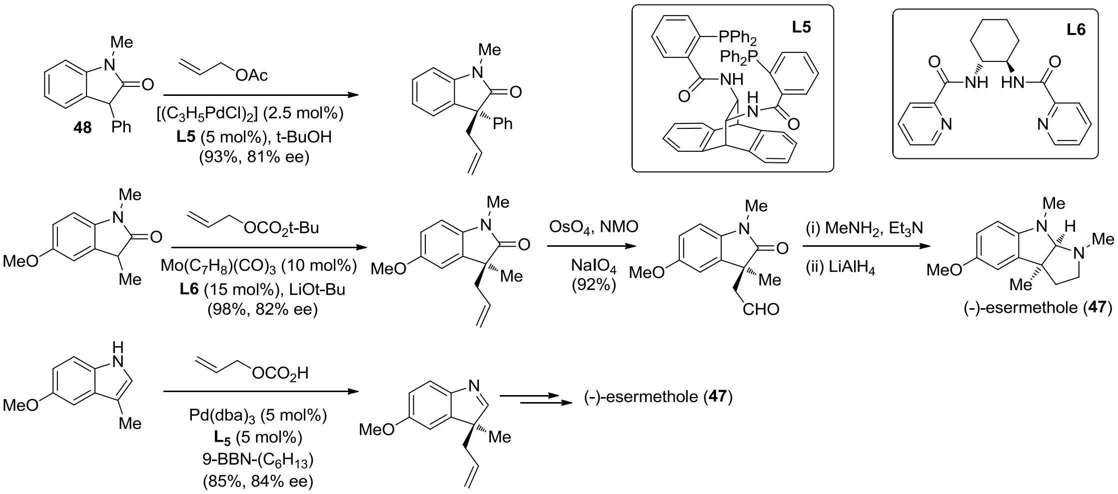
Scheme 18: Racemic synthesis of flustramine A **45**

The synthetic strategies covered so far have, at best, been diastereoselective and as a result have generated the target molecule, albeit elegantly, as the racemate. The main issue with an enantioselective synthesis of the cyclotryptamine alkaloids is the installation of a quaternary chiral centre. Several different methodologies have been reported generally utilising a pro-chiral indole or oxindole; a notable exception being the asymmetric Heck coupling employed by Overman *et al.* (Scheme 9). Some of the first successful work in this area was published by Wong and co-workers, based on the pioneering work into asymmetric phase transfer catalysis at Merck by Dolling and Grabowski.[83,84] They were able to synthesise (-)-esermethole **47** on a multi-gram scale with enantiomeric excesses to the order of 77% (Scheme 19).[85]



Scheme 19: Synthesis of (-)-esermethole **47** *via* phase transfer catalysis

Trost *et al.* were another group which exploited the C-3 nucleophilicity of indoles and oxindoles in their synthesis of (-)-esermethole **47**. Their first publication in this area utilised a palladium catalysed allylation, already pioneered within the group,[86] to form the desired quaternary chiral centre on aryl oxindole **48**. Regrettably application of this methodology proved far less successful on alkyl oxindoles.[87] Following their failure to apply a palladium-catalysed allylation to alkyl oxindoles, Trost and co-workers developed a complementary protocol, employing a molybdenum catalyst. This procedure matched the inspiring results that were obtained before with the aryl oxindole substrates. It was this protocol that they used in their primary synthesis of (-)-esermethole **47**.[88] Within a month, the group disclosed a third publication, this time performing the now familiar C-3 allylation on an indole substrate, using a palladium catalysed system. The results were, as before, impressive and the group were able to perform a series of simple functional group manipulations to give them the natural product (-)-esermethole **47** (Scheme 20).[89]



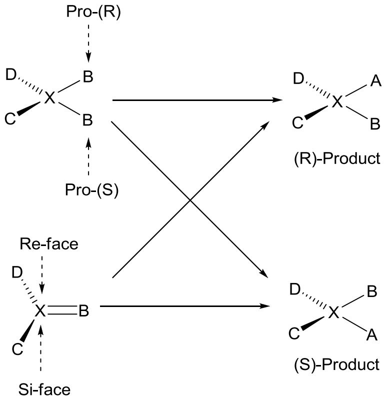
Scheme 20: Asymmetric allylation of oxindoles and indoles

For an in-depth review of the structure, bioactivity and synthesis of natural products containing this cyclotryptamine functionality see Álvarez *et al.*[90]

2.0 Enantioselective Desymmetrization

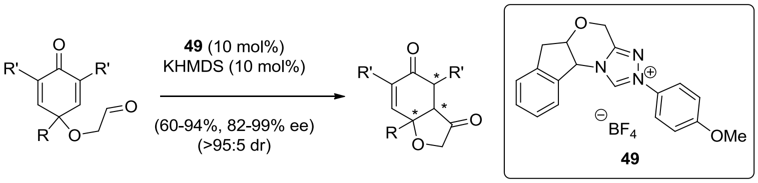
2.1 Desymmetrization: The Theory

Enantioselective desymmetrization is a process where a *meso* or pro-chiral starting material is stereoselectively functionalised by treatment with a stoichiometric or catalytic amount of chiral material. The effectiveness of such a reaction depends on the ability of the chiral reagent to distinguish between the different enantiotopic groups of the symmetric starting material (Scheme 21).[91,92]



Scheme 21: Desymmetrization of generic *meso* and pro-chiral starting materials[i]

The beauty and power of desymmetrization lies in its capacity to establish numerous stereocentres simultaneously, in addition to the capability of generating quaternary chiral centres, a notoriously challenging undertaking (Scheme 22).[17,28,93]



Scheme 22: Formation of three contiguous stereocentres *via* a desymmetrizing Stetter reaction

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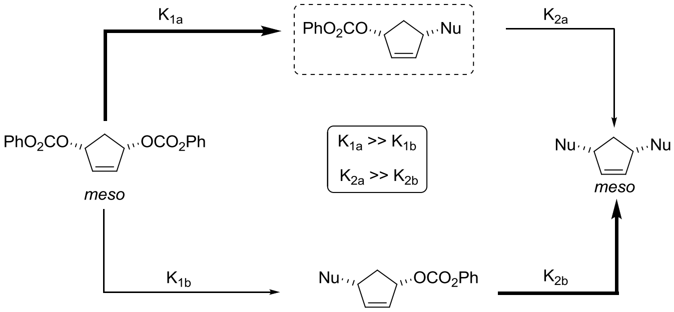
[i] *X is a C atom or a heteroatom and A, B, C, and D are substituents with decreasing CIP priority*

Another advantage of certain desymmetrization approaches is the potential for the enantiomeric excess of a reaction with poor selectivity to be enhanced by forcing it past ‘completion’. By subjecting enantio-enriched product to a subsequent kinetic resolution step one can potentially increase optical purity of the target compound to an acceptable level (Scheme 23).[86,94]



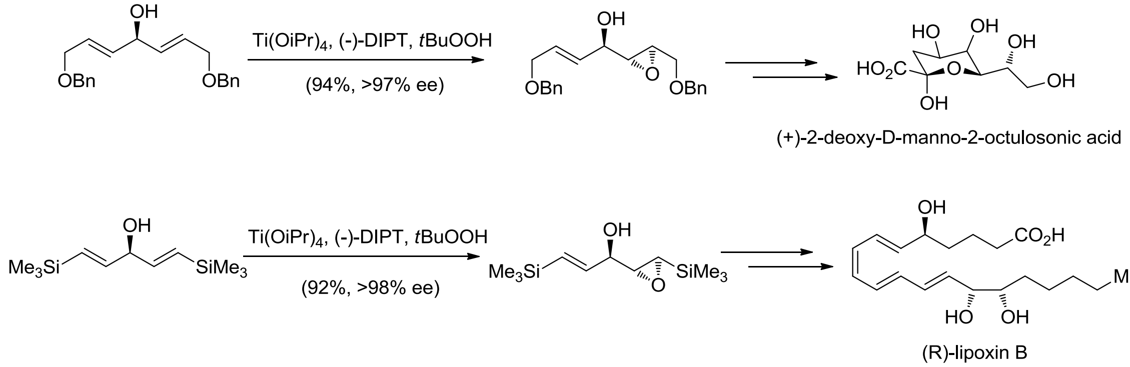
Scheme 23: Kinetic resolution

This review principally focuses on transition metal-catalysed enantioselective desymmetrization, with a particular emphasis on its synthetic utility. The topic of desymmetrization has been extensively reviewed in the literature and therefore only selective examples are shown.[12,91,92,95,96]

2.2 Desymmetrization: A Brief Review

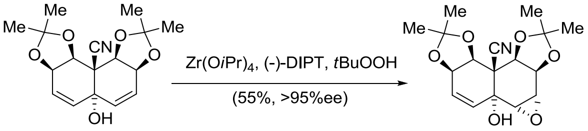
2.2.1 Desymmetrization of Dienes

One of the earliest non-enzymatic procedures for the desymmetrization of dienes utilises the Sharpless asymmetric epoxidation reaction.[97] Total syntheses by Schreiber[98] and Sato[99] exemplify the power of this transformation (Scheme 24). To date this procedure is one of the most effective asymmetric transformations, regularly giving quantitative yields in excellent enantiomeric excesses.[95,100]



Scheme 24: Selected examples of asymmetric epoxidations

Spivey *et al.* used the ability to establish multiple stereocentres in a single step to great effect in their synthesis of the core fragment from hypoglaunine B, where eight contiguous stereocentres were defined in their key step (Scheme 25).[101]



Scheme 25: Intermediate for the synthesis of hypoglaunine B

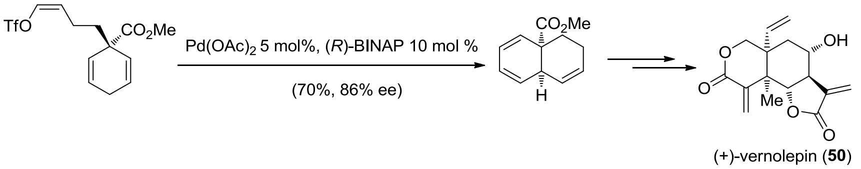
The desymmetrization of dienes is by no means limited to epoxidations. Shibasaki *et al.* were able to form quaternary chiral centres in high yields and modest enantiomeric excesses by means of the first asymmetric Heck coupling in 1989 (Table 2).[102]

Table 2: Intramolecular asymmetric Heck reaction

Entry	R	T [°C]	*t* [h]	Yield [%] (%ee)
1	CO_2Me	60	37.5	74 (46)
2	$CH_2OTBDMS$	40	44	70 (44)
3	CH_2OAc	40	88	66 (36)

Conditions: Diene (1.0 eq), $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP (5 mol%), Ag_2CO_3 (2.0 eq), NMP

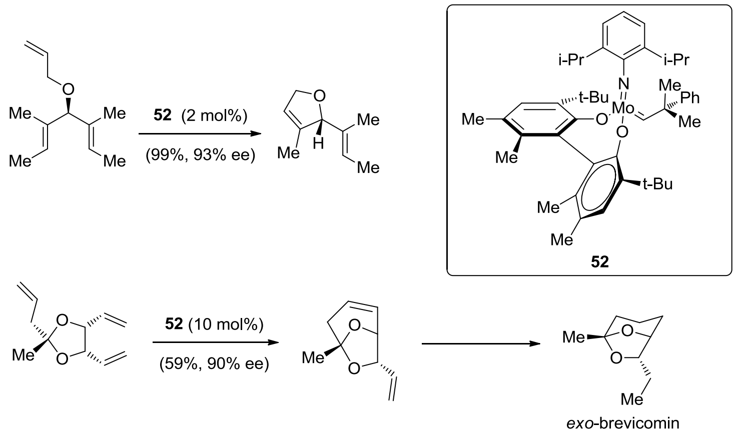
Since its unassuming beginnings, the asymmetric Heck coupling has been developed into a very versatile reaction, largely thanks to the pioneering work by the Shibasaki[103] and Overman[104] research groups. Scheme 26 illustrates how an asymmetric Heck coupling was used in Shibasaki's synthesis of (+)-vernolepin **50**; here the key step was a desymmetrization of a pro-chiral diene.[105]



Scheme 26: Use of asymmetric Heck coupling in the total synthesis of (+)-vernolepin **50**

The power of the asymmetric Heck coupling is further illustrated in sections 1.2.2, 1.2.4 and 1.2.5 by Overman's syntheses of polypyrrolidinoindoline alkaloids, however these examples did not utilise an asymmetric desymmetrization step.

Since the versatility of olefin metathesis was first realised, the field of ring-closing and cross-metathesis has been dominated by the work of Grubbs and Schrock.[106-108] Thanks largely to their endeavours, olefin metathesis is now one of the most commonly used transition metal-catalysed processes.[109,110] Although the importance of this methodology cannot be overstated, comparatively few examples have been reported where the reaction was used in an asymmetric fashion.[111] Early examples in particular only focussed on kinetic resolution and were often plagued with low enantiomeric purity.[111-113] More recently, however, many reports of the asymmetric desymmetrization of dienes have been published, a multitude of which show extremely high yields and enantiomeric excesses (Scheme 27).[111,114,115] For a recent review of asymmetric olefin metathesis in natural product synthesis, see Hoveyda.[116]



Scheme 27: Selected examples of asymmetric olefin metathesis

2.2.2 Enantioselective Opening of Epoxides

The stereoselective formation of epoxides, generally from a range of readily available dienes, now allows researchers to gain access to a myriad of compounds which has in turn lead to epoxides becoming a popular substrate for enantioselective desymmetrization.[92,117-121] For an extensive review of desymmetrization by the enantioselective opening of epoxides see Hodgson *et al.*[122] and Paterson *et al.*[123]

The vast majority of desymmetrizing epoxide openings depend on the presence of a Lewis acid where the chirality may be imparted from a ligand such as (-)-ephedrine (Fig. 9).

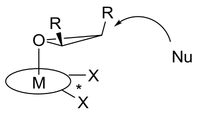
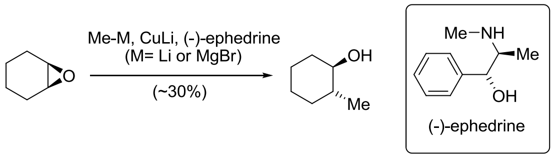


Fig. 9: Lewis acid activation of a *meso* epoxide

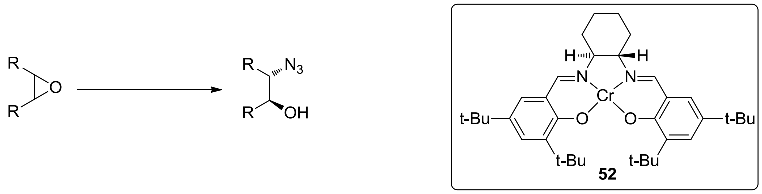
The first reported reaction of this type was by Davies and Wollowitz in 1980, where they were able to add an alkyl lithium, or Grignard reagent, to an epoxide. This was, however, with an extremely low optical purity to the order of 3% (Scheme 28).[124] Although modest this result has paved the way for the highly efficient reactions that followed.



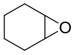
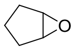
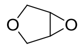
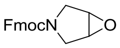
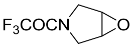
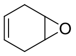
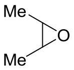
Scheme 28: Davies' asymmetric opening of *meso*-epoxides

To date probably the most efficient system for enantioselective desymmetrization *via* epoxide opening is based around work by Jacobson.[125] Here epoxides are very efficiently opened using a variety of nucleophiles catalysed by (salen)Cr(III) complexes **52** (Table 3).[117]

Table 3: Jacobson's desymmetrization of *meso* epoxides

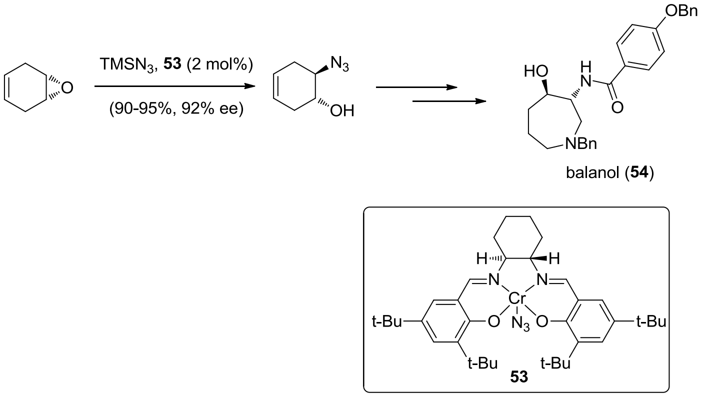


52

Entry	Epoxide	*t* [h]	Yield [%] (% ee)
1		18	80 (88)
2		28	80 (94)
3		18	80 (98)
4	 FmocN	36	80 (95)
5	 F3COCN	16	90 (95)
6		46	72 (81)
7		30	65 (82)

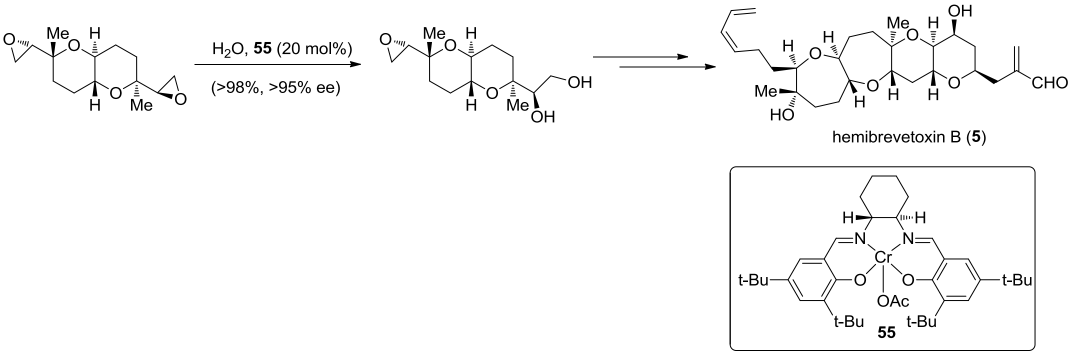
Conditions: Epoxide (1.0 eq), Me_3SiN_3 (1.05 eq), **52** (2 mol%), Et_2O, rt

After these initial results Jacobson and co-workers were able to optimise the reaction's efficiency on more challenging substrates to the order of 90% yield with an enantiomeric excess of 92%, culminating in the total synthesis of balanol (**54**) in 1997 (Scheme 29, see Table 3, Entry 6).[126]



Scheme 29: Jacobson's total synthesis of balanol (**54**)

Jacobson's inspiring work on epoxide chemistry has spawned many impressive applications of this methodology. Of particular note is the synthesis of a late stage intermediate of hemibrevetoxin B **5** by Nelson *et al.* Nelson's synthesis represents the first desymmetrization of a centro, rather than *meso*-symmetric, compound in a total synthesis (Scheme 30).[14,127-129]

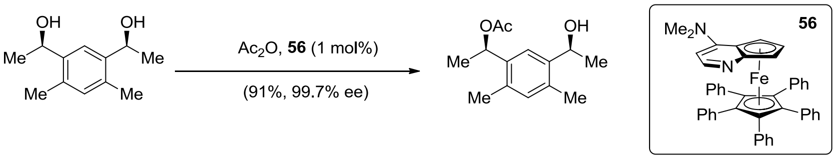


Scheme 30: Synthesis of key fragment of hemibrevetoxin B **5**

2.2.3 Diols

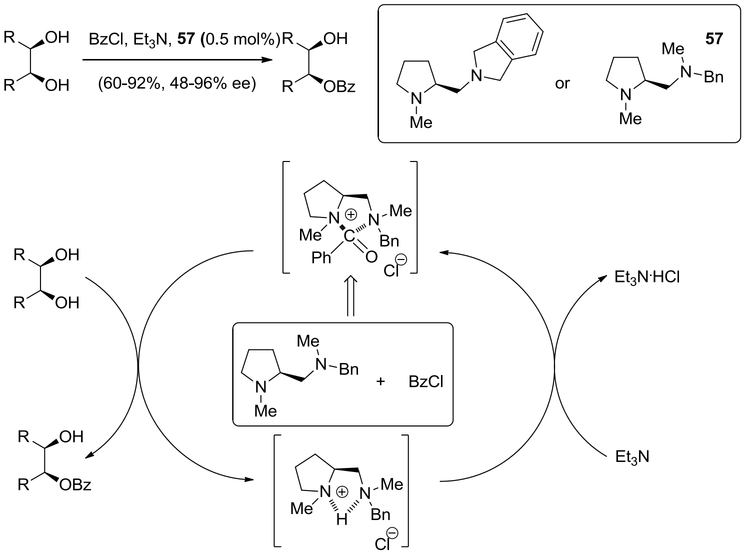
Like epoxides, diols have established themselves as a favourable substrate for desymmetrization, again due to their ease of preparation and predictable reactivity.[92] Diols have a comparatively long history with respect to desymmetrization, nevertheless much of the work focuses on enzymatic procedures and is outside the scope of this report. For an excellent review of enzymatic desymmetrization see Gotor.[91]

The vast majority of desymmetrization reactions associated with diols are acylations using a stoichiometric chiral acetylating agent and an enzyme e.g. pig pancreatic lipase[130] or more recently, a catalytic chiral acetylating agent. The field of catalytic asymmetric acylation has been spearheaded by the work of Fu *et al.* who have managed to design a version of DMAP that exhibits planar chirality. This has been used to great effect in a variety of asymmetric transformations (Scheme 31).[131-136]



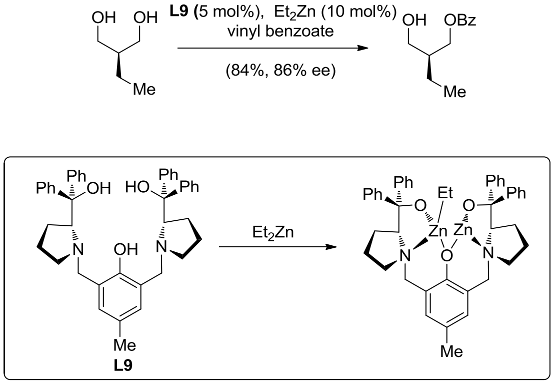
Scheme 31: Selected example of desymmetrization *via* catalytic actylation

Oriyama and co-workers have disclosed several examples of asymmetric benzoylation where they were able to use an organocatalyst, typically in low loading, to desymmetrize several *meso* diols. Although in many cases high enantiomeric excesses were reported, the scope of the reaction was limited to just 1,2-diols. The authors proposed that enantio-discrimination depended on the ability of their chiral diamine to coordinate to benzoylchloride (Scheme 32).[137,138]



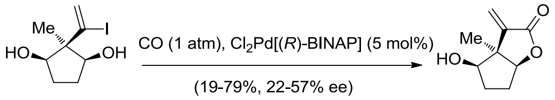
Scheme 32: Proposed mechanism for asymmetric benzoylation of *meso*-diols

Trost and co-workers have reported another interesting mono-benzoylation, this time using an amphoteric chiral dinuclear zinc catalyst. They were able to desymmetrize a variety of acyclic 2-substituted-1,3-propanediols in good yields and impressive enantiomeric excesses. The results are particularly striking when considering there is no need for a cyclic 'rigid' *meso* starting diol and the hydroxyl groups are situated remotely; *beta* to the pro-chiral centre (Scheme 33).[139]



Scheme 33: Asymmetric benzoylation, *in-situ* catalyst generation

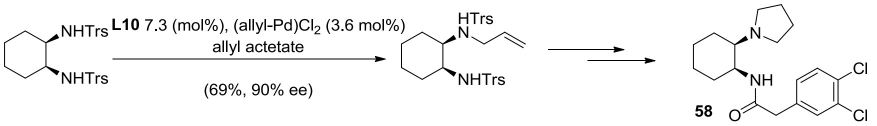
An interesting, if a little esoteric, example of diol desymmetrization was published by Shibasaki in 1991, and is of particular interest as it is one of few examples where alcohols are used as substrates in palladium catalysis.[140-142] Shibasaki and co-workers were able to form five-membered lactones in modest to good yields and low to acceptable enantioselectivities *via* an asymmetric carbonylation reaction. However, when they applied their methodology to six membered rings, they were plagued by racemisation and low yields, their optimal result being just 41% yield and 39% enantiomeric excess (Scheme 34).[143]



Scheme 34: Asymmetric carbonylation of *meso*-diols

2.2.4 Diamines

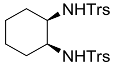
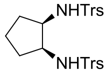
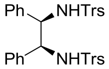
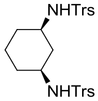
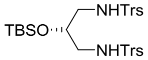
Unlike diols there are comparatively few examples where diamines have been used as a substrate for asymmetric desymmetrization. The first desymmetrization of a *meso*-diamine was reported relatively recently by Taguchi *et al.* in 2004.[144] Taguchi and co-workers proposed that enantiocontrol with diamine substrates may be difficult because of the high nucleophilic reactivity of the amino group and its strong ability to chelate with transition metals. This chelation may result in dissociation of the chiral ligand from the catalyst. It is worthwhile to note that in their primary publication in this area, extensive screening was undertaken to find a suitable bulky electron-withdrawing group to sufficiently deactivate the diamine. Eventually a 2,4,6-triisopropylbenzenesulfonyl (Trs) group was selected. The group used the popular asymmetric allylation chemistry developed by Trost and co-workers[86,145,146] to effect their desymmetrization, with modest to excellent results. With a reliable route in hand, they employed their methodology in the synthesis of a σ-receptor agonist **58** (Scheme 35).[144]



Scheme 35: Synthesis of σ-receptor agonist **58**

Over several publications, Taguchi and co-workers investigated the scope of this seminal reaction. It appeared that as well as the dependence on the Trs group, substrates were limited to cyclic compounds where the amine groups were positioned *alpha* to each other (Table 4).[144,147]

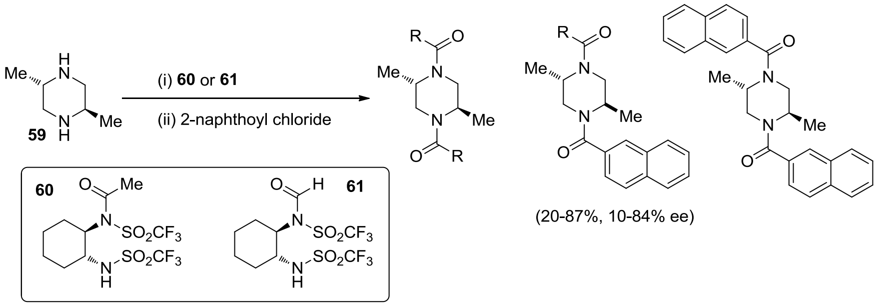
Table 4: Substrate scope

Entry	Diamine	T [°C]	Yield [%] (% ee)
1		-15 to -10	85 (93)
2		-15 to -10	84 (85)
3		-15 to 4	65 (96)
4		-15 to -10	61 (57)
5		-15 to -10	78 (18)

Conditions: Amine (1.0 eq), KO*t*Bu (1.0 eq), (allyl-Pd-Cl)$_2$ (3.6 mol%, Pd), (*R,R*)-DACT napthyl Trost Ligand (7.3 mol%), allyl acetate (1.0 eq), PhMe : dioxane (1 : 1). Trs =(2,4,6-triisopropylbenzenesulfony)

During the course of this report, Hou and co-workers have published work on the kinetic resolution on indolines using an almost identical Trost allylation approach. They too reported excellent results, resolving 10 indolines with yields of up to 50% and enantiomeric excesses in the range of 36-97%.[148]

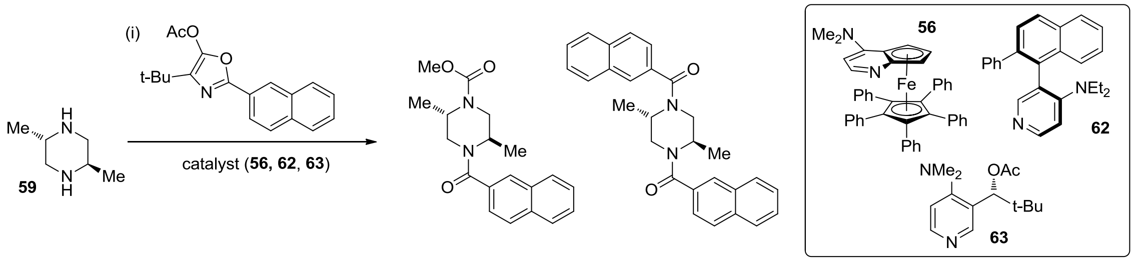
In 2003 Nelson *et al.* published a review on desymmetrizing centrosymmetric molecules, where they proposed that piperazines could be desymmetrized using a chiral acylating agent in much the same way as diols (see section 2.2.3).[12] This idea was realised in 2006 when they were able to desymmetrize *trans*-dimethylpiperazine **59** using both catalytic and stoichiometric acylating agents (Scheme 36, Table 5).



Scheme 36: Stoichiometric acylation

The reaction developed with stoichiometric acylating agents managed to give the group some excellent results with yields up to 87% and enantiomeric excesses as high as 84% (Scheme 36).

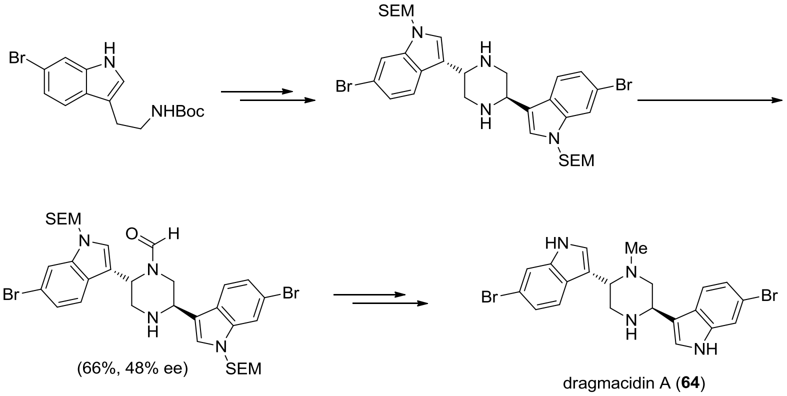
Table 5: Desymmetrization of *trans*-dimethyl piperazine



Entry	Catalyst	ROAc [eq]	T [°C]	*t* [h]	Yield *mono* [%] (% ee)	Yield *bis* [%]
1	DMAP	1	-42	2	25 (±)	40
2	(*R*)-**56**	1	-18	164	25 (44)	39
3	(*R*)-**56**	1	0	16	23 (33)	37
4	(*S*)-**62**[a]	1	-42	7	20 (-70)	43
5	(*S*)-**62**[a]	10	-42	4	43 (-26)	-
6	(*R*)-**63**	1	-42	14	22 (64)	34
7	(*R*)-**63**	10	-42	7	49 (23)	-

Conditions: (i) **59** (1.0 eq), 2-naphthoyl chloride (1.05 eq), cat (20 mol%), $CHCl_3$. (ii) Et_3N (3.2 eq), 2-napthoylchloride (2.3 eq), 0 °C ; [a]cat (5 mol%)

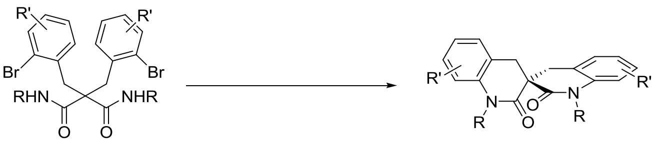
Regrettably, the group found that using a variety of catalysts, including those developed by Fu and co-workers (see section 2.2.3),[149-151] they were unable to match the results achieved by their stoichiometric system (Table 5).[152] Having settled upon using a stoichiometric acylating agent Nelson and co-workers showed the scope of this methodology with the total synthesis of dragamacidin A **64**. Unfortunately changing the methyl substituents on the piperazine for indole units gave a marked drop in enantio-discrimination, with enantiomeric excesses only to the order of 48% (Scheme 37).[152]

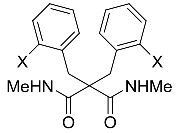
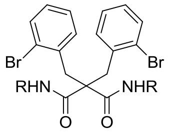
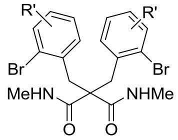
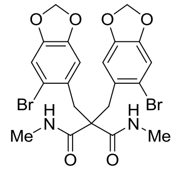
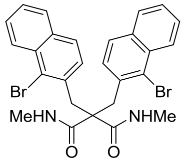


Scheme 37: Total synthesis of dragmacidin A **64**

Very recently Sasai *et al.* reported that *spiro*-bilactams could be synthesised by desymmetrization of the corresponding diamide *via* an asymmetric Buchwald-Hartwig cross coupling. This is one of few examples where the Buchwald-Hartwig cross coupling has been carried out enantioselectively (also see section 2.2.7). All other existing examples are kinetic resolutions, or are used in the formation of axially chiral compounds, generally with varying degrees of sucess.[153-157] Nevertheless Sasai and co-workers were able to obtain yields and enantiomeric excesses up to 99% and 70% respectively; however their results were highly dependent on their substrate (Table 6).[158]

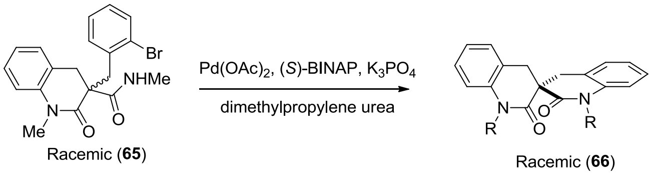
Table 6: Substrate scope



Entry	Core	Substituent	Yield [%] (% ee)
1		X = Br	99 (70)
2		X= Cl	8 (6)
3		X = I	94 (38)
4		R = Et	99 (52)
5		R = Bn	99 (49)
6[a]		R′ = 5-Cl	85 (48)
7[a]		R′ = 5-MeO	90 (6)
8		R′ = 3-NO_2	42 (5)
9			99 (57)
10[a]			95 (±)

Conditions: $Pd(OAc)_2$ (0.066 mol%), (*S*)-BINAP (0.13 mol%), K_3PO_4 (2.8 eq), dimethylpropylene urea (DMPU) (2.5 eq), NMP, 100 °C, [a]Cs_2CO_3, PhMe

Table 6 illustrates some interesting observations, such as the consequence of the substitution pattern and halogen source. Aside from the well precedented effect on yield,[159] enantiomeric purity also varied dramatically (Table 6, Entries 1-3). A possible explanation is that during the enantiodiscriminating step the halide is still bound to the catalyst, and is therefore involved in defining the configuration of the complex. Simply changing the *N*-substituent from a methyl group to an ethyl group gave an 18% drop in enantiomeric excess (Table 6, Entries 1, 4). Alteration of the aryl group was tolerated even less; changing from a benzyl to a naphthyl group destroyed all enantiodiscrimination (Table 6, Entries 1, 10). These results suggest that the system is very finely balanced and that significant optimization would be required for even minor substrate alteration. Whilst investigating the possibility that a kinetic resolution was occurring in the reaction, it was observed that subjecting racemic mono-coupled product to the reaction conditions only yielded racemic products. This again shows how substrate dependent the catalytic conditions are (Scheme 38).



Scheme 38: Attempted kinetic resolution

Shortly after the publication by Sasai *et al.*, Viirre and co-workers disclosed very similar observations; again desymmetrizing malonamides *via* an enantioselective intramolecular Buchwald-Hartwig cross coupling reaction. The group formed lactams in excellent yields with modest to good enantioselectivity. As previously demonstrated by Sasai *et al.* the reaction was highly substrate dependant (Table 7). However, unlike the previous publication Viirre and co-workers noted that chiral mono-phosphine ligands were most suited to the reaction, eventually selecting MOP as their ligand of choice.[160]

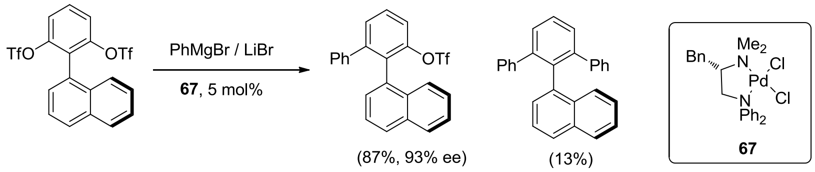
Table 7: Substrate scope

Entry	R	Base	Yield [%] (% ee)
1	Me	K_3PO_4	99 (38)
2	*n*-Bu	Cs_2CO_3	99 (50)
3	*i*-Pr	K_3PO_4	90 (70)
4	Bn	K_3PO_4	99 (58)
5	4-methoxybenzyl	Cs_2CO_3	99 (76)
6	Ph	Cs_2CO_3	99 (58)
7	2,6-dimethylphenyl	Cs_2CO_3	54 (34)
8	1-napthyl	K_3PO_4	79 (±)

Conditions: $Pd(OAc)_2$ (3.3 mol%), (*R*)-MOP (6.6 mol%), Base (1.4 eq), THF, 65 °C

2.2.5 Halides and Pseudo-Halides

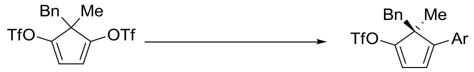
Unlike many of the previous examples, halides and pseudo-halides pose a very different practical challenge with respect to asymmetric catalysis. Numerous transition metal catalysed processes involve oxidative addition into a carbon-halogen bond as the first step in the mechanism. Therefore for these examples, enantiodiscrimination relies upon the catalyst species oxidatively adding to the correct enantiotopic position. In 1995, Hayashi and co-workers published work that showed axially chiral ditriflates could be desymmetrized *via* palladium-catalysed addition of Grignard reagents. They observed good yields and enantiomeric excesses which could be enhanced by kinetic resolution (Scheme 39).[161] Subsequently the group published a second paper where alkynyl Grignards were utilised with similar degrees of success.[162] In both publications it was noted that the addition of lithium bromide was essential for the high enantioselectivity and for high catalytic activity; other metal salts were far less effective.



Scheme 39: Palladium-catalysed ‘enantioposition-selective’ cross-coupling

In 2000 Cammidge and co-workers reported the first asymmetric Suzuki coupling, successfully generating axially chiral biaryls with enantiomeric excesses up to 85%.[163] Within the Willis research group it has been demonstrated that ditriflates containing a pro-chiral quaternary centre can be efficiently desymmetrized in good enantiomeric excesses utilizing a Suzuki coupling. This report represents the first example of a Suzuki coupling being used to produce compounds containing stereo defined sp^3 carbon centres (Table 8).[28]

Table 8: Desymmetrization *via* asymmetric Suzuki coupling

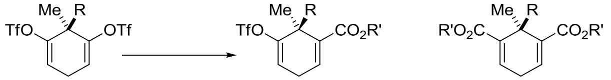


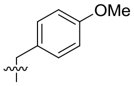
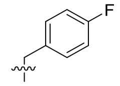
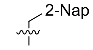
Entry	Ar-$B(OH)_2$	Yield [%] (% ee)
1	4-$C_6H_5C(O)Me$	46 (77)
2	3-$C_6H_5C(O)Me$	51 (86)
3	4-C_6H_5CHO	47 (73)
4	3-C_6H_5CHO	57 (80)
5	2-C_6H_5CHO	41 (82)
6	4-C_6H_5OH	43 (74)
7	3-furyl	53 (72)
8	3-*N*-Bs-indolyl	66 (85)

Conditions: $Pd(OAc)_2$ (10 mol%), (*R*)-MOP (11 mol%), CsF (2.0 eq), Ar-$B(OH)_2$ (2.0 eq), dioxane, rt

Following the success of asymmetric Suzuki coupling protocol, the group used a similar *meso*-di-triflate starting material in an asymmetric palladium catalysed carbonylation reaction. They were able to desymmetrize a variety of substrates in moderate yields (*ca.* 40%) with modest to good enantiomeric purity (61 – 95% ee). Some of the results are summarised in Table 9.[164]

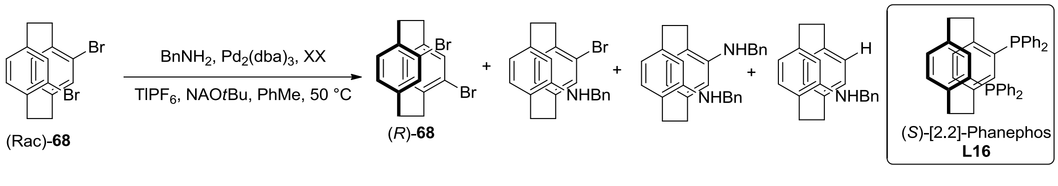
Table 9: Desymmetrization *via* asymmetric carbonylation



Entry	R	R'	Yield [%] (% ee)
1	Bn	Me	27 (96)
2	Bn	Et	34 (94)
3	Bn	*i*Pr	48 (90)
4		Me	34 (94)
5		Me	35 (95)
6		Me	44 (93)
7	Et	Me	31 (61)
8	Pr	Me	32 (87)

Conditions: $Pd(OAc)_2$ (10 mol%), (*S*)-CyMOP (10 mol%), CO (balloon), $MeOH/Et_3N$ (2 : 1) [0.1 M], 45 °C.

In 1997 Rossen and Pye *et al.* disclosed the first asymmetric example of a Buchwald-Hartwig cross coupling reaction. They reported that exposure of racemic paracyclophane **68** to benzylamine in the presence of a palladium source and a chiral ligand yielded an enantioenriched mixture of products. It was discovered that optimal conditions for the kinetic resolution of **68** involved the ligand Phanephos **L16** in the presence of the halide scavenger thallium hexafluorophosphate. These optimised conditions gave enantiomeric excesses to the order of 93% and 99.9%, at 79% and 90% conversion respectively (Scheme 40).[165,166]



Scheme 40: Kinetic resolution *via* first asymmetric Buchwald-Hartwig cross coupling

2.3 Summary

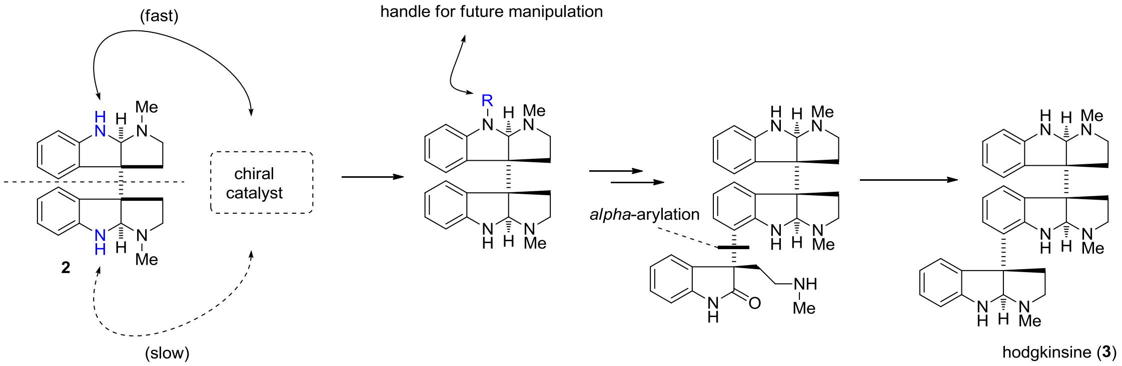
Desymmetrization remains a fertile area of research with a plethora of synthetic applications. One of the main advantages of desymmetrization as a strategy is the potential for rapidly establishing a great deal of stereochemical complexity in a single step. However, care must be taken when devising a strategy to ensure that desymmetrization is indeed the most efficient route to a target molecule.

Although far from comprehensive, this review covers some of the main transformations used to date. Other functionality favoured for desymmetrization not covered in this review include: aldehydes,[167,168] esters[169,170] and anhydrides[171,172] in addition to numerous redox strategies.[173-175]

3.0 Research Proposal: An Enantioselective Total Synthesis of Hodgkinsine

Highlighted works in section 2 show the power of a desymmetrization strategy in synthesis; we hoped to add to the existing wealth of knowledge by the development of an asymmetric C-N bond forming reaction. As mentioned previously there are few such desymmetrization reactions in the literature and of these, many employ simple or contrived substrates (Section 2.2.4). We selected the cyclotryptamine alkaloid, *meso*-chimonanthine **2** as a suitably complex target. Its four contiguous stereocentres and distant pro-chiral amines represent a considerably more challenging desymmetrization-substrate than those reported in the literature. If successful we planned to use our desymmetrization of *meso*-chimonanthine **2** in an enantioselective total synthesis of hodgkinsine **3**.

As well as the increased efficiency of a desymmetrization approach (*vs* the diastereomeric resolution used in previous syntheses[176]) our aim was also to eliminate the need for extensive flash chromatography or prep-HPLC. Scheme 41 shows our synthetic strategy, highlights of which include the use of a palladium-catalysed *alpha*-arylation protocol developed within the group to install the third cyclotryptamine fragment,[177] in addition to our proposed desymmetrization.

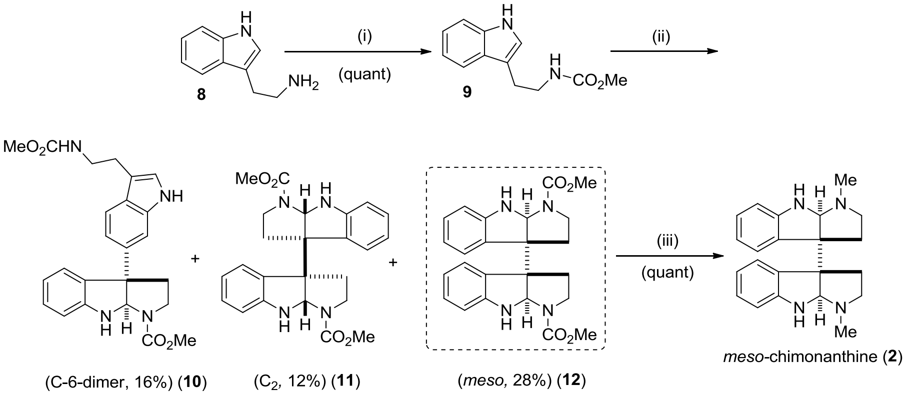


Scheme 41: Proposed desymmetrization of *meso*-chimonanthine and subsequent synthesis of hodgkinsine

4.0 Synthesis of meso-Chimonanthine

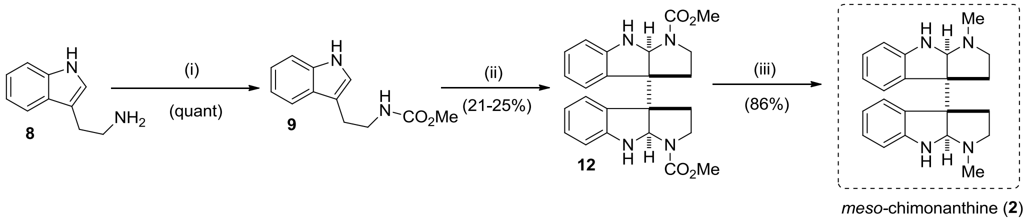
4.1 Large Scale Synthesis without Chromatographic Purification

The synthesis of *meso*-chimonanthine methyl carbamate from the corresponding tryptamine derivative can be achieved *via* a variety of methods, as discussed previously,[25,43] but by far the most efficient was reported by Takayama and co-workers using PIFA in trifluoroethanol.[43] The group were able to synthesise *meso*-chimonanthine from tryptamine in just three steps in a 30% yield, however, the group (and subsequent citing papers) failed to report any experimental details or allude to the mechanism of the reaction. Within the Willis group we observed, using Takayama's conditions, that the desired *meso*-carbamate derivative could be isolated from the mixture of C_2 and C-6 isomeric products in *ca.* 30% yield. This material could be subsequently reduced quantitatively to *meso*-chimonanthine **2** by treatment with Red-Al, thereby replicating Takayama's result (Scheme 42).



Scheme 42: Conditions: (i) Tryptamine (1.0 eq), $ClCO_2Me$ (2.0 eq), NaOH (3.0 eq), DCM/H_2O (1:1) [0.45 M], 0 °C – rt , 2 h; (ii) Indole (1.0 eq), PIFA (0.65 eq), CF_3CH_2OH [0.38 M], -30 °C, 22 h; (iii) *meso*-dimer (1.0 eq), Red-Al (10.0 eq), PhMe [0.03 M], reflux, 16 h.

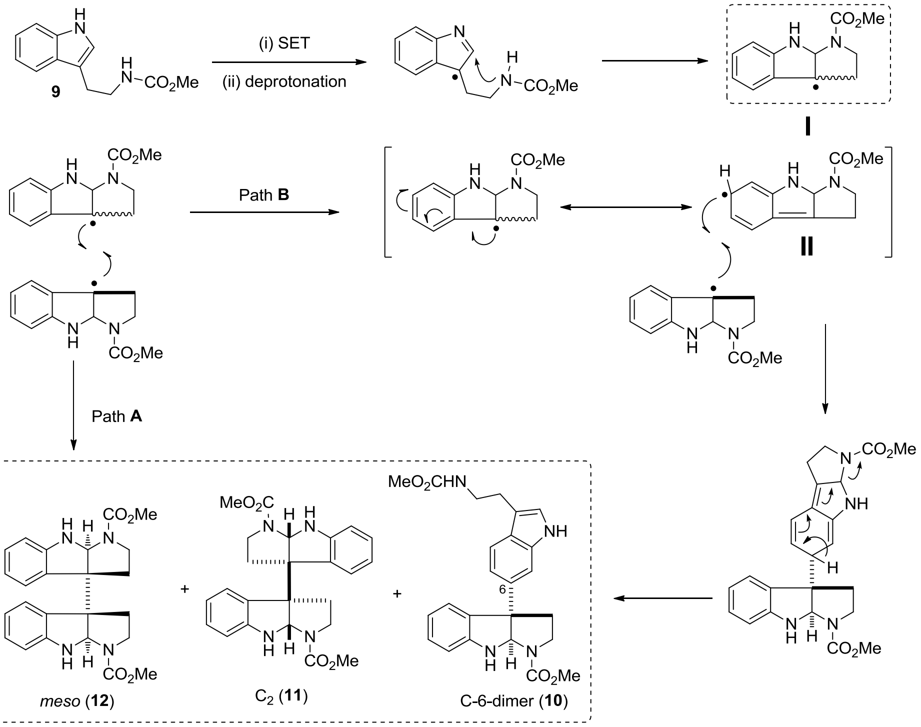
The isolation of the desired *meso* isomer **12** from the mixture of diastereo and regio-isomers required extensive flash chromatography to give an enriched mixture of *meso* **12** and C_2 isomers **11**. A further step involving recrystallisation from a mixture of DCM and hexane afforded the desired *meso*-isomer **12**. Unfortunately, scaling the reaction above ~5 g gave severely diminished yields. We decided to address some of the reactions shortfalls, namely the dependence on chromatography and poor scalability. By observing the consumption of starting tryptamine-carbamate **9** *via* LCMS, we were able to ascertain that dimerization is far quicker than we originally postulated,[178] with the reaction reaching completion in just over 3 h (*vs.* 22 h). Based on this result, we postulated that a slower addition of PIFA may be beneficial to the reaction (especially on a larger scale). Unfortunately, addition of the hypervalent iodine reagent as a solution in trifluoroethanol over 3 h *via* syringe pump had a detrimental effect leaving large amounts of un-reacted starting material. Presumably, the oxidant is not completely stable as a solute in trifluoroethanol at room temperature. Addition of the oxidant in smaller portions (as a solid) appeared to have no significant effect on the reaction. With this in mind, the scale-up issue was approached from another angle; observing the reaction mixture at low temperature revealed large quantities of an un-dissolved material. Assuming the precipitate was in fact the oxidant, a mass transfer issue could explain why large scale reactions were proving problematic. Gratifyingly, performing the reaction with highly efficient overhead stirring in a jacketed vessel not only gave a homogenous mixture but also allowed the transformation to be easily carried out on a >40 g scale. Performing the reaction on so much material brings the second issue to light; flash chromatography on such a scale is not only challenging but prohibitively expensive. Previous attempts to develop a crystallisation protocol on a 5 g scale proved unsuccessful, generally yielding amorphous gums. However, on this larger scale, the *meso* isomer **12** could be selectively crystallised in a >20% yield (as a >10:1 mixture of *meso* **12**: C-6 isomers **10**). This was achieved by seeding a saturated solution of the crude products (in 10% EtOAc and DCM) with pure crystals of the desired *meso*-isomer **12**. Although the isolated yield for the crystallisation procedure is appreciably lower than that obtained *via* flash chromatography, it is a far more economically and practically favourable procedure. The reduction of the carbamate groups to generate *meso*-chimonanthine **2** proceeded cleanly allowing pure product to be isolated by a trivial recrystallisation from a mixture of DCM and *i*-hexane. These simple modifications to the literature procedure allow *meso*-chimonanthine **2** to be prepared in >18% overall yield from tryptamine **8** with no chromatographic steps (Scheme 43).



Scheme 43: Conditions: (i) Tryptamine (1.0 eq), $ClCO_2Me$ (2.0 eq), NaOH (3.0 eq), DCM/H_2O (1:1) [0.45 M], 0 °C – rt , 2 h; (ii) Indole (1.0 eq), PIFA (0.65 eq), CF_3CH_2OH [0.38 M], -30 °C, 5.5 h; (ii) *meso*-Dimer (1.0 eq), Red-Al (10.0 eq), PhMe [0.03 M], reflux, 16 h.

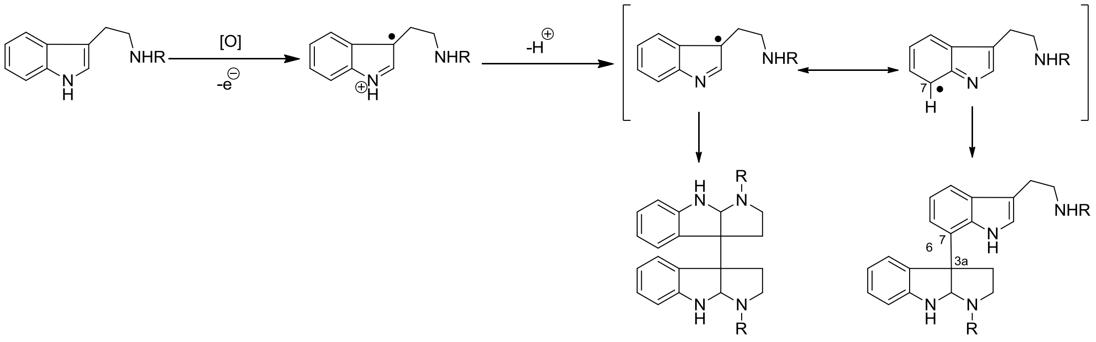
4.2 Mechanism for the Formation of meso-Chimonanthine

Several plausible mechanisms have been drawn to explain the PIFA mediated dimerization,[46,179] however, to the best of our knowledge, there have been no investigations carried out to ascertain the precise reaction pathway. Scheme 44 shows the most likely reaction mechanism; tryptamine carbamate undergoes a single electron transfer (SET) followed by deprotonation[180] and consequent ring closure to generate cyclotryptamine radical **I**. This radical can proceed *via* 'path A' quenching with its symmetrical coupling partner to yield the *meso* **12** and C_2 symmetric **11** products. The C-6 dimer **10** may result from the quenching of radical **I** by resonance form **II** (illustrated by 'path B') re-aromatization yields the regio-isomeric product **10** (Scheme 44).[46]



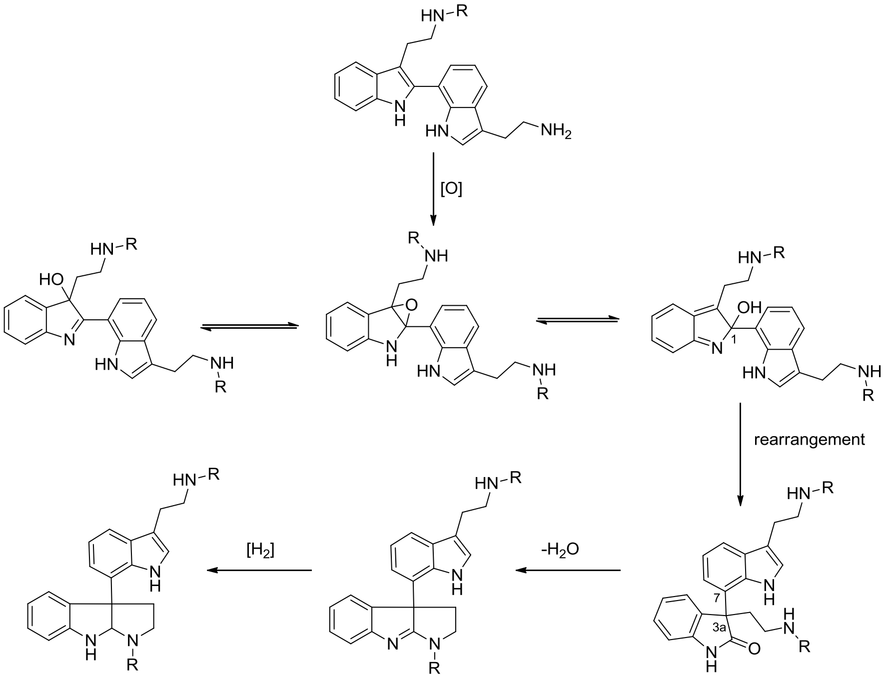
Scheme 44: Proposed mechanism for oxidative dimerization

Assuming the above mechanism is correct, attention should be drawn to the postulated biosynthetic route to the high-order cyclotryptamine alkaloids (Scheme 45).[17]



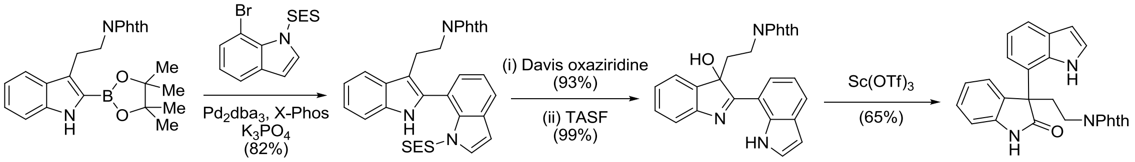
Scheme 45: Proposed biosynthetic route

Here it is proposed that a stable radical forms at the C-7 position, resulting in the high-order oligomers. Yet no C-7 products have been observed during any oxidative dimerizations of tryptamine derivatives (with the exception of those involving directing groups[181]).[25,73,182] This suggests that in nature the C-7 position of a tryptamine unit is held in close proximity to a C-3a radical or that an alternative mechanism is in effect. Recently Movassaghi *et al.* disclosed an alternative proposal for the biosynthetic pathway of the polypyrrolidinoindoline alkaloids involving an oxidative rearrangement (Scheme 46).[38]



Scheme 46: Recent biosynthetic proposal for C-3a – C-7 linkage

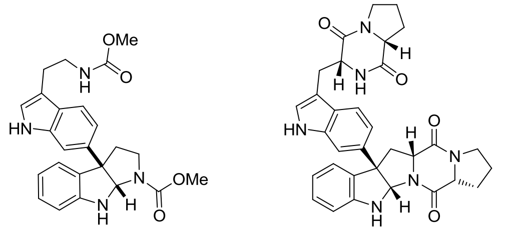
This theory evolved from extensive rearrangement studies available in the literature, generally involving the migration of alkyl, allyl and occasionally aryl groups.[61,183-185] However, in order for this to be a successful synthetic strategy, an efficient procedure for forming C-2 – C-7 bonds would be required; potentially a more challenging undertaking than a direct C-3a – C-7 coupling. Movassaghi and co-workers were able to rearrange model polypyrrolidinoindoline systems in good yields; however, their methodology still required a DMG for the initial functionalisation at the C-7 position (Scheme 47).[61]



Scheme 47: Scandium triflate mediated rearrangement

4.3 Nasesazine B

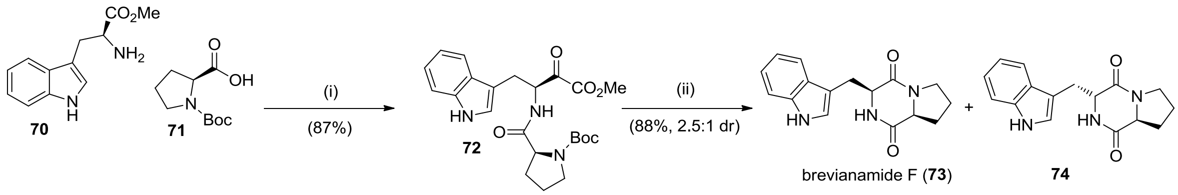
A recent report by Capon and co-workers disclosed the structure of several new dimeric natural products based around a diketopiperazine framework. These were isolated from a marine-derived actinomycete, *Streptomyces* sp. (CMB-MQ030).[186]



C-6 dimer (**10**) nasesazine B (**69**)

Fig. 10: C-3a – C-6 linked compounds

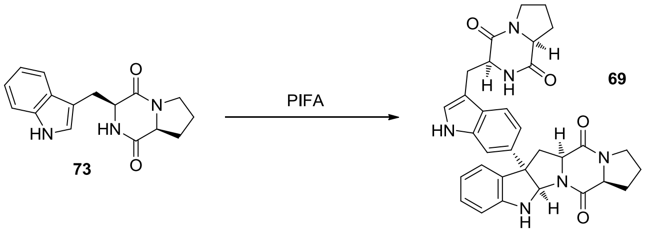
Interestingly, these natural products all possess the same C-3a – C-6 linkage as the C-6-dimeric product **10** isolated during the synthesis of *meso*-chimonanthine **2**. One such natural product is nasesazine B **69** (Fig. 10). It was hoped that we could use the same chemistry used in Takayama's synthesis of *meso*-chimonanthine to quickly synthesise this complex natural product. Nasesazine B is constructed from four amino acid units all possessing D configuration, however, due to the prohibitive cost of the un-natural D-isomers, we proposed to synthesise the opposite enantiomer of the product. Synthesis of the cyclo(Trp-Pro) monomer unit (a natural product in its own right, brevianamide F **73**) was carried out in accordance with the literature procedure, giving the product in two steps from readily available commercial starting materials (Scheme 48).[187]



Scheme 48: Conditions: (i) L-Tryptophan methyl ester **70** (1.0 eq), L-*N*-Boc proline **71** (1.0 eq), EDC (1.0 eq), DCM [0.18 M], rt, 24 h. (ii) *N*-Boc-Pro-Trp-OMe **72**, neat, 200 °C, 4 h.

With the monomer unit in-hand attempts were made to effect the dimerization. Surprisingly, exposure of brevianamide F **73** to the reaction conditions repeatedly resulted in the recovery of un-reacted starting materials, even at elevated temperatures. Increasing the reaction concentration *ca.* six fold (Table 10, Entry 4) did appear to result in trace amounts of a dimeric product. Seemingly, very high concentrations are required to maximise the probability for the short lived racial species to dimerise. Even when the reaction was performed at very high concentrations *ca.* 2 M (at which point solubility became problematic, especially at cryogenic temperatures), we were still unable to isolate any product. In all cases, the only identifiable component in the reactions was recovered brevianamide F **73** (Table 10).

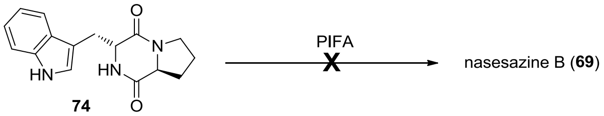
Table 10: Oxidative dimerizations of brevianamide F **69**



Entry	Solvent (concentration, M)	T [°C]	Yield [%]
1	CF_3CH_2OH (0.12)	-30	0
2	CF_3CH_2OH (0.12)	0 – rt	0
3	CF_3CH_2OH (0.12)	40	0
4	CF_3CH_2OH (0.71)	0 – rt	Trace by MS
5	CF_3CH_2OH (2.0)	-30 – rt	Trace by MS
6	DCM (0.1)	0 – rt	0
7	DCM (0.1)	40	0

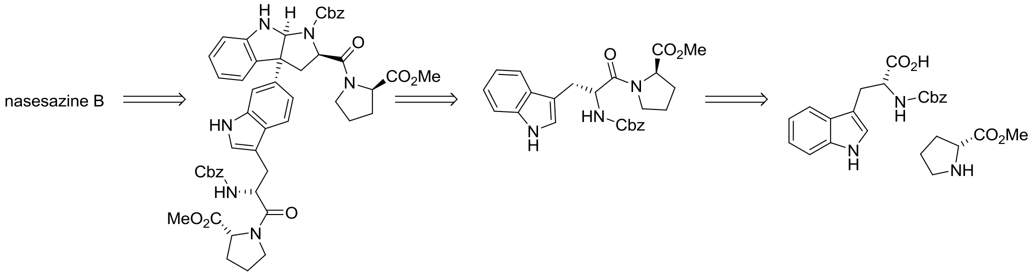
Conditions: Cyclo(Trp-Pro) **73** (1.0 eq), PIFA (0.65 eq), 16 h.

To eliminate the chance that there was a misassignment during the determination of the relative configuration of the natural product, we also investigated the dimerization of the other diastereomer. Assuming this was the case the other diastereomer may be more sterically predisposed to the formation of the complex pyrrolidinoindoline core. Using identical conditions to Table 10, Entry 4, trace quantities of what appeared to be dimeric product were detected (Scheme 49).



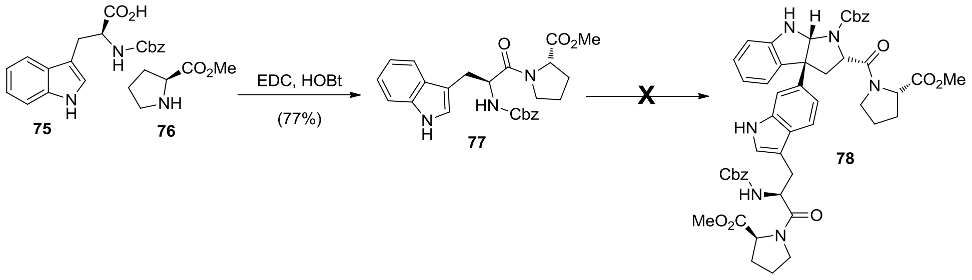
Scheme 49: Conditions: Cyclo(Trp-Pro)**74** (1.0 eq), PIFA (0.65 eq), CF_3CH_2OH [0.71 M], 16 h, rt.

Presumably brevianamide F is too deactivated to dimerise in an analogous fashion to tryptamine methyl carbamate (under our reaction conditions). Danishefsky *et al.* reported similar problems in their synthesis of 5-*N*-acetylardeemin and amauromine. They observed that tryptophan derivatives bearing a lactam moiety failed to close to the desired pyrrolidinoindoline framework. The group overcame this problem by forming the lactam at a later stage in the synthesis.[80] Scheme 50 shows a revised route where the tryptophan nitrogen is furnished with a carbamate group to facilitate dimerization. Cleavage of similar Cbz groups and subsequent ring lactamisation under hydrogenation conditions is well precedented.[188]



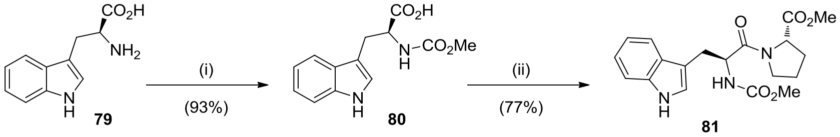
Scheme 50: Revised strategy

The amide **77** was prepared from commercially available *N*-Cbz-L-tryptophan and L-proline methyl ester *via* the procedure reported by Evano and co-workers.[188] Unfortunately, all attempts to dimerise this compound using varying amounts of PIFA in trifluoroethanol at a range of temperatures all yielded recovered starting material or a complex mixture of products, none of which appeared to be the desired dimer (Scheme 51).



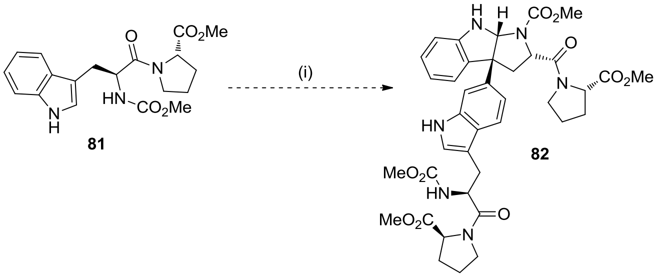
Scheme 51: Unsuccessful dimerization of *N*-Cbz-tryptophan derivative

The failure of this compound to react was attributed in part to the steric bulk of the Cbz group and as a result we attempted to dimerise a simpler methyl carbamate analogue. The methyl carbamate was installed in a 93% yield using methyl chloroformate in a mixture of aqueous sodium hydroxide and tetrahydrofuran. The product readily crystallised from a mixture of DCM and petrol. The carbamate was then subjected to coupling conditions utilising EDC and HOBt and the resultant amide was obtained in good yields, again without the need for chromatography (Scheme 52).



Scheme 52: Conditions: (i) Tryptophan **79** (1.0 eq), methylchloroformate (1.1 eq), NaOH (1.1 eq), THF/H_2O (1:1) [0.5 M], rt, 16 h. (ii) Carbamate **80** (1.0 eq), proline methyl ester **76** (1.0 eq), Et_3N (2.0 eq), EDC (1.3 eq), HOBt (0.46 eq), DCM [0.04 M], rt, 16 h.

With the amide **81** in hand, we exposed it to our hypervalent iodine dimerization conditions, pleasingly, this analogue quickly reacted to generate what appeared by mass-spectrometry to be dimeric products. The identity of these products has yet to be confirmed by ^{1}H NMR spectroscopy or by X-ray crystallography.



Scheme 53: Conditions: Amide **81** (1.0 eq), PIFA (1.0 eq), CF_3CH_2OH [0.17 M], -30 °C – rt , 16 h.

Assuming the products are a mixture of C-3a and C-7 dimers, it should be possible to selectively cleave the methyl carbamate groups in the presence of the amide linkages to generate the desired product. Work is still on-going in this area.

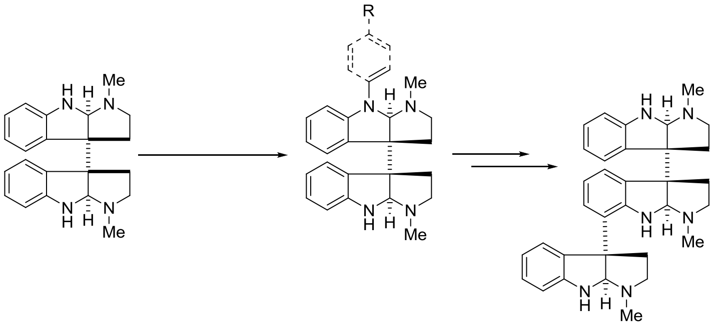
4.4 Summary

We have enhanced the dimerization method of Takayama *et al.* to be applicable on a >40 g scale, synthesising *meso*-chimonanthine **2** without chromatography. We have also proposed a strategy for the synthesis of nasesazine B **69** based on this methodology.

5.0 Desymmetrization of meso-Chimonanthine

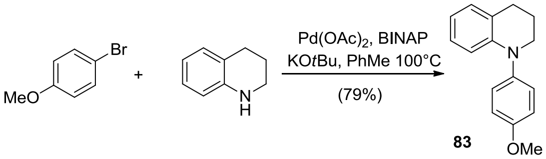
5.1 Asymmetric Buchwald-Hartwig Cross Coupling

Our preliminary strategy for the desymmetrization of *meso*-chimonanthine utilised the under-exploited asymmetric Buchwald-Hartwig cross coupling (Scheme 54).



Scheme 54: Proposed asymmetric Buchwald-Hartwig cross coupling reaction

In order for the reaction to be used in a successful synthesis, the desymmetrizing moiety must be easily cleaved or transformed into a group present in the target molecule. The aryl halide selected for primary screenings was 4-bromoanisole as it is well precedented that such *para*-methoxyphenyl (PMP) groups can be easily cleaved from amines under oxidative conditions such as aqueous ceric ammonium nitrate (CAN).[189,190] The drawback with this choice of aryl halide arises from its electron-rich nature which slows oxidative addition.[191-193] The starting point for our investigation was based on the arylation shown in Scheme 55. Typically, even with simple amines low yields are generally associated with electron rich aryl halides.[193]



83

Scheme 55: Arylation of secondary amines

5.1.1 Ligand Screening

Originally the exact conditions for the coupling shown in Scheme 55 were utilised in our reaction; however, the elevated temperature (100 °C) only resulted in the formation of racemic product in the presence of a wide variety of ligands. Consequently, further screening was carried out at a significantly reduced temperature (50 °C). This appeared to give an immediate enhancement with respect to enantiomeric purity (Table 11, Entry 3). In excess of thirty chiral phosphine ligands were tested for activity in our reaction and the results from this screening are summarised in Table 11. This extensive study highlighted several interesting results. From the BINAP family of ligands MOP was most effective (Table 11, Entry 4), yet the highest levels of yield and enantiomeric excess were obtained in the presence of chiral ferrocene ligands (Table 11, Entries 7, 11 & 16). The ligand screen highlighted the Josiphos ligands, in addition to (*R*,*S*)-PPFA. as being particularly effective. The activity of these ligands could be increased by forming a pre-complex with palladium dichloride (Entries 8, 12 & 16).[194] It is worth noting that when the reaction using (*R*,*S*)-PPFA was repeated with an extended reaction time (65 h), the results obtained were identical to those of the pre-complex (Entry 8). A possible explanation for the increased reactivity of the pre-complexes is that it is easier to generate the active Pd(0) species from the complex. For many of the reactions, appreciable quantities of the *bis*-arylated product were also isolated from the reaction mixture, along with recovered starting material, for instance in the case of [(*R*,*S*)-SL-J009-1]$PdCl_2$ there was a 24% yield of the *bis*-arylated product (Entry 12). Based on the success of (*R*,*S*)-PPFA, we synthesised several analogues of this ligand (Entries 18-21) including (*S*,*S*)-PPFA where the relative stereochemistry of the planar portion of the ligand is inverted (Fig. 11).

Regrettably none of these analogues offered any improvement on their commercial counterparts.

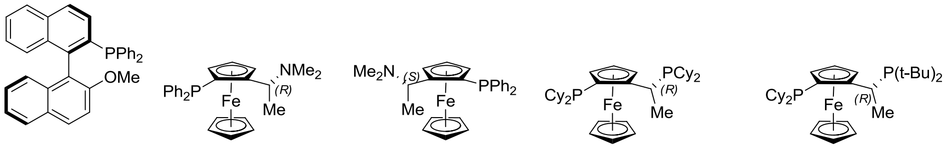
Table 11: Selected examples of screened ligands

2 → **84**

Entry	Ligand	Yield [%]^{a} (%ee)
1	S-Phos	34 (±)
2	Dave Phos	21 (±)
3	(*R*)-BINAP	9 (25)
4	**(*R*)-MOP**	**38 (26)**
5	(*S*)-PHOX	Trace (-)
6	(*R*)-Quinap	Trace (55)
7	**(*R,S*)-PPFA**	**31 (40)**
8	**[(*R,S*)-PPFA]PdCl$_2$^{b}**	**44 (42)**
9	(*R,S*)-SL-J001-1	15 (40)
10	(*R,S*)-SL-J002-1	Trace (36)
11	**(*R,S*)-SL-J003-1**	**48 (47)**
12	**[(*R,S*)-SL-J003-1]PdCl$_2$^{b}**	**45 (55)^{c}**
13	(*S,R*)-SL-J004-2	Trace (-)
14	(*R,S*)-SL-J005-1	13 (27)
15	(*R,S*)-SL-J007-1	Trace
16	(*R,S*)-SL-J009-1	0 (-)
17	**[(*R,S*)-SL-J009-1]PdCl$_2$^{b}**	**57 (53)**
18	(*S,S*)-PPFA^{b}	0 (-)
19	(*R,S*)-PPFOAc^{b}	0 (-)
20	(*R,S*)-PPFOMe^{b}	31 (28)
21	(*S,R*)-CyPPFA^{b}	21 (37)
22	(*R,S*)-BPPFA	7 (22)
23	(*R*)-Phanephos	20 (±)

Conditions: *meso*-Chimonanthine (1.0 eq), 4-bromoanisole (1.3 eq), KO*t*Bu (1.5 eq), Pd(OAc)$_2$, Ligand (6 mol%), PhMe [0.3 M], 50 °C, 16 h. ^{a}Isolated yield, ^{b}Non commercially available ligand, Ligands were synthesised in accordance with the following literature procedures: [(*R,S*)-SL-J009-1]PdCl$_2$,[194] (*S,S*)-PPFA, (*R,S*)-PPFOAc, (*R,S*)-PPFOMe, (*S,R*)-CyPPFA.[195] ^{c}in addition to 24% *bis*-product.

We noted that the racemic products from this reaction were fairly crystalline and this allowed us to trivially increase the enantiomeric excess of the product to >99%. Starting with an enantioenriched product we selectively formed racemic crystals (from a mixture of IPA and hexane), which left us with product of high enantiomeric purity.



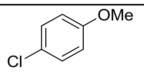
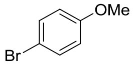
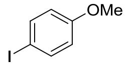
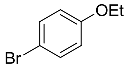
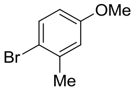
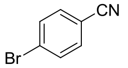
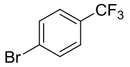
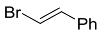
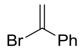
(*R*)-MOP (*R*,*S*) PPFA (*S*,*S*) PPFA SL-J003-1 SL-J009-1

Fig. 11: Structures of selected Ligands

5.1.2 Variation of Aryl-Halide Coupling Partner

It has been shown in the literature that one of the greatest factors involved in obtaining a high enantiomeric excess for an asymmetric Buchwald-Hartwig cross coupling is substrate choice.[158,160] After an extensive ligand screen failed to yield acceptable levels of enantiomeric purity (Table 11), we chose to vary our aryl-halide coupling partner. Table 12 shows a screen of nine aryl-halides utilising our two most effective ligands.

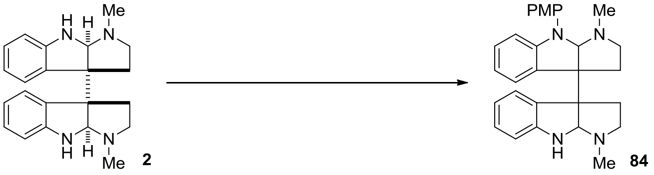
Table 12: Aryl halide screening

Entry	Ar-X	Yield [%] (%ee) (*R*)-MOP	Yield [%] (%ee) (*R,S*)-PPFA
1		0 (0)	-
2		**38 (26)**	**31 (40)**
3		**9 (±)**	**49 (41)**
4		26 (7)	11 (40)
5		Trace (0)	-
6		7 (±)	Trace (-)
7		35 (10)	18 (13)
8		-	34 (8)
9		-	0

Conditions: *meso*-Chimonanthine (1.0 eq), Ar-X (1.3 eq), KO*t*Bu (1.5 eq), Pd(OAc)$_2$ (5 mol%), Ligand (6 mol%), PhMe [0.3 M], 50 °C, 16 h. [a]*meso*-chimonanthine (1.0 eq), vinyl halide (1.2 eq), KO*t*Bu (3.0 eq), Pd(OAc)$_2$, (5 mol%), ligand (6 mol%), PhMe [0.3 M], 65 °C, 16 h. Absolute configuration of product was not determined.

Our substrate screen uncovered several unexpected results: the electron-rich aryl halides 4-iodo and 4-bromoanisole (Table 12, Entries 2 & 3) both seemed to outperform theoretically more activated coupling partners (Table 12, Entries 6 & 7). This result was attributed to the idea that the system is highly sensitive to change and that although PPFA has proved a good ligand for coupling 4-bromoanisole, it may not be the optimal choice for more electron-poor coupling partners. Another interesting observation was that when using MOP as a ligand, shifting from a bromo- to an iodo- group resulted in a marked decrease in yield and optical purity (Table 12, Entries 2 & 3). Again, this was attributed to the susceptibility of the reaction to change. Nevertheless Table 12, Entry 3 suggested that 4-iodoanisole may be a superior coupling partner; this prompted an additional ligand screen, using the ligands highlighted in Table 11. Although 4-iodoanisole often outperformed the bromo- analogue (Table 13), results obtained using 4-bromoanisole were comparable and appeared far more consistent. As a result, we chose to continue optimisation using 4-bromoanisole as the coupling partner.

Table 13: Ligand screen for 4-iodoanisole



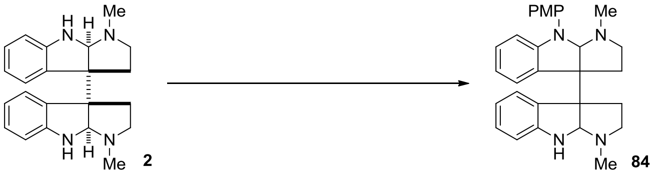
Entry	Ligand	Base	Yield [%][a] (%ee)
1	(*R*)-MOP	KO*t*Bu	9 (±)
2	**(*R,S*)-PPFA**	**KO*t*Bu**	**49 (41)**
3	(*R,S*)-PPFA	NaO*t*Bu	24 (36)
4	[(*R,S*)-PPFA]$PdCl_2$[b]	KO*t*Bu	10 (34)
5	**[(*R,S*)-SL-J003-1]$PdCl_2$[b]**	**KO*t*Bu**	**52 (46)**
6	[(*R,S*)-SL-J009-1]$PdCl_2$[b]	KO*t*Bu	Trace (41)

Conditions: *meso*-Chimonanthine (1.0 eq), 4-iodoanisole (1.3 eq), base (1.5 eq), $Pd(OAc)_2$ (5 mol%), Ligand (6 mol%), PhMe [0.3 M], 50 °C, 16 h. [a]HPLC Yield, calibrated by ^1H NMR spectroscopy, see appendix. [b]Non commercially available ligand. Absolute configuration of product was not determined.

5.1.3 Solvent Screening

When screening solvents for the reaction, we based our choices on a principal component analysis (PCA).[196] With a PCA, solvents with similar properties are assigned a proximal position in chemical space (See Appendix). In the literature there are several 'solvent maps' available and these can be loosely divided into quadrants.[196] A chemically compatible solvent was selected from each of the quadrants along with one from the centre. Subsequently, additional solvents were screened which were in close proximity to 'hits'; the results from these screens are summarised in Table 14.

Table 14: PCA based solvent screen



Entry	Ligand	Solvent	Yield^{a} [%] (%ee)
1	**(*R,S*)-PPFA**	**PhMe**	**31 (40)**
2	(*R,S*)-PPFA	Dioxane	15 (45)
3	(*R,S*)-PPFA	DMF	Trace (0)
4	(*R,S*)-PPFA	DME	Trace (40)
5	(*R,S*)-PPFA	THF	Trace (0)
6	(*R,S*)-PPFA	MeCN	0
7	(*R,S*)-PPFA	*t*BuOH	Trace (0)
8	(*R,S*)-PPFA	Et_3N^{b}	26 (55)
9	(*R,S*)-PPFA	Cyclohexane	Trace (0)
10	(*R,S*)-PPFA	CCl_4	Trace (0)
11	(*R,S*)-PPFA	di-*n*Bu ether	Trace (0)
12	**(*R,S*)-PPFA**	**PhH**^{c}	**47 (41)**
13	(*S,R*)-PPFA	DMSO	Trace (0)

Conditions: *meso*-Chimonanthine (1.0 eq), 4-bromoanisole (1.3 eq), KO*t*Bu (1.5 eq), $Pd(OAc)_2$ (5 mol%), Ligand (6 mol%), Solvent [0.3 M], 50 °C, 16 h. [a]Isolated Yield [b]Capricious yields and ees, [c]Reaction performed in a sealed tube.

The solvent screen highlighted benzene (Table 14, Entry 12) as being a potential alternative for toluene in the reaction. However, benzene is considerably more harmful and does not offer a significant improvement over toluene. Another noteworthy observation was that, despite being somewhat capricious, triethylamine gave the highest enantiomeric excess of the solvents tested in the screen. However, all the optimization to date appears to show that, at least with respect to enantiomeric excess, the main factors remain the choice of ligand and coupling partner.

5.1.4 Additional Screening

Aside from the conditions described previously, we undertook extensive screens in an attempt to further optimise the reaction, including but not limited to: temperature, concentration, reagent loading and the effect of additives. Regrettably, none of these gave any significant improvements. Despite substantial precedent for sodium *tert*-butoxide being the optimal base for Buchwald-Hartwig cross coupling reactions,[197,198] we observed no change in either yield or enantiomeric excess, when using the MOP ligand, and a sharp decrease in yield when using PPFA as the ligand. Trials with an additional six bases all resulted in significant retardation in the reactions' performance; consequently, potassium *tert*-butoxide remained the base of choice. As mentioned previously elevated temperatures appeared to decrease the enantiomeric purity of the reaction. It was also observed that heating the reaction *via* microwave irradiation hampered the enantioselectivity of the reaction, often yielding only racemic product. The limited literature precedent regarding enantioselective Buchwald-Hartwig reactions suggests that additives may have potential for improving yields and enantiodiscrimination.[199,200] Regrettably, in our hands such additives only appeared to have a detrimental effect, perhaps with the exception of 18-crown-6 and (*R*)-BINAP (Table 15, Entry 2). BINAP had previously failed to give significant amounts of product, yet in the presence of sodium *tert*-butoxide and a suitable additive yields were dramatically increased, albeit at the cost of enantiodiscrimination (Table 15).

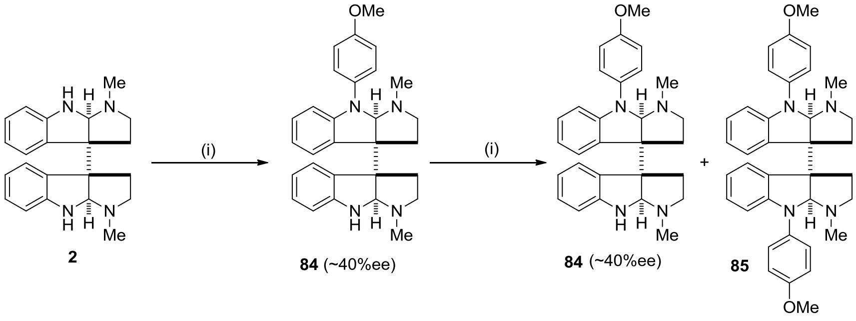
Table 15: Additive screening

Entry	Additive (eq)	Ligand (mol %)	Yield [%] (% ee)
1	18-crown-6 (8.4)	[(*R,S*)-SL-J003-1]$PdCl_2$ (7.5)	14 (±)
2	**18-crown-6 (2.0)**	**(*R*)-BINAP (6.0)[a]**	**41 (±)**
3	Ag_2O (2.0)	[(*R,S*)-SL-J003-1]$PdCl_2$ (5.0)	0
4	Ag_2CO_3 (2.0)	[(*R,S*)-SL-J003-1]$PdCl_2$ (5.0)	0
5	LiCl (2.0)	[(*R,S*)-SL-J003-1]$PdCl_2$ (5.0)	Trace (0)
6	AgOTf (1.0)	(*R,S*)-PPFA (5.0)	Trace (19)
7	Mg(OTf) (1.0)	(*R,S*)-PPFA (5.0)	Trace (28)
8	LiCl (1.0)	(*R,S*)-PPFA (5.0)	Trace (8)
9	Bu_4NBr (1.0)	(*R,S*)-PPFA (5.0)	Trace (±)

Conditions: *meso*-chimonanthine **2** (1.0 eq), 4-bromo-anisole (1.2 eq), KO*t*Bu (3.0 eq), PhMe [0.3 M], 75 °C; [a] $Pd(OAc)_2$ (5 mol%), NaO*t*Bu (2.0 eq).

5.1.5 Kinetic Resolution

In order to ascertain whether a kinetic resolution was in effect,[94] we re-subjected enantioenriched product to the reaction conditions. Surprisingly it was observed that no kinetic resolution was occurring in our desymmetrization of *meso*-chimonanthine *via* an asymmetric Buchwald-Hartwig cross coupling reaction with PPFA (Scheme 56).



Scheme 56: Conditions: *meso*-chimonanthine **2** (1.0 eq), 4-bromoanisole (1.3 eq), KO*t*Bu (1.5 eq), $Pd(OAc)_2$ (5 mol%), (*R,S*)-PPFA (6 mol%), PhMe [0.3 M], 50 °C, 16 h.

The absence of a kinetic resolution was attributed to the low selectivity of the reaction and its sensitivity to subtle stereo-electronic changes. Fig. 12 shows an overlay of the X-ray structures of meso-chimonanthine and the product from the asymmetric Buchwald-Hartwig coupling. The diagram shows that, in the solid state, the cyclotryptamine ring systems sit in very different configurations. Also, worthy of note is the fact that the puckering of the un-substituted cyclotryptamine unit is not identical to that of *meso*-chimonanthine. These observations may go some way towards explaining why there is no enantioselectivity associated with the second substitution.

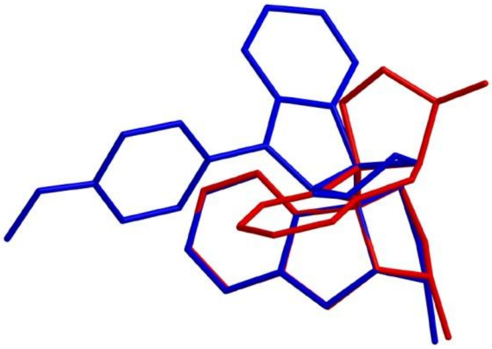


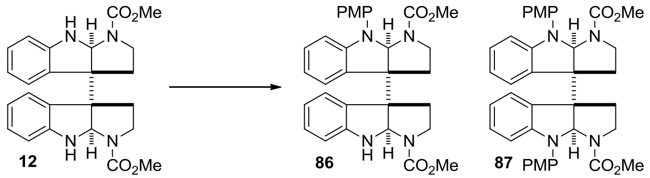
Fig. 12: X-ray superposition, *meso*-chimonanthine **2** (red), *N*-PMP-chimonanthine **84** (blue)

5.1.6 Variation of the meso-Symmetric Core

A recent report by Sasai and co-workers used an asymmetric Buchwald-Hartwig coupling in the synthesis of C_2-symmetric *spiro*-bilactams and they were able to obtain their desired lactam in up to quantitative yields with enantiomeric excesses ≤70%. These impressive results arose more from careful choice of substrate than the reaction conditions themselves.[201] With this in mind we looked at varying our *meso*-symmetric starting material. The most obvious source of variation is the methyl carbamate groups left over from the initial oxidative dimerization reaction. Attempts to directly desymmetrize *meso*-chimonanthine-methylcarbamate **12** only resulted in trace quantities of the mono-substituted product. Surprisingly when S-Phos was used as a ligand the *bis*-substituted compound was the only product to be isolated in appreciable yields (Table 16).

Why the doubly substituted product is favoured is unclear, but with all the ligands screened, the reaction failed to come close to the reactivity exhibited by *meso*-chimonanthine.

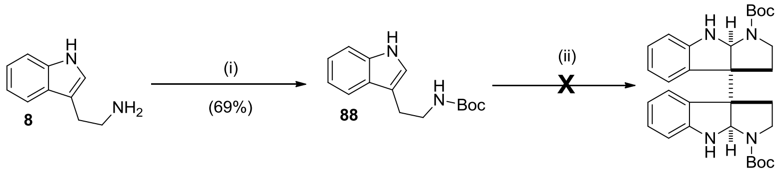
Table 16: Attempted Desymmetrization of *meso*-chimonanthine-methylcarbamat**e**



Entry	Ligand	Yield, *mono* **86** [%] (% ee)	Yield, *bis* **87** [%]	Recovered **12** [%]
1	S-Phos	Trace (±)	18	60
2	(*S*)-BINAP	Trace (0)	Trace	60
3	(*R,S*)-PPFA	0	0	quant

Conditions: *meso*-Chimonanthine-carbamate **12** (1.0 eq), 4-bromoanisole (1.3 eq), KO*t*Bu (1.5 eq), $Pd(OAc)_2$ (5 mol %), Ligand (6 mol%), PhMe [0.2 M], 50 °C, 16 h.

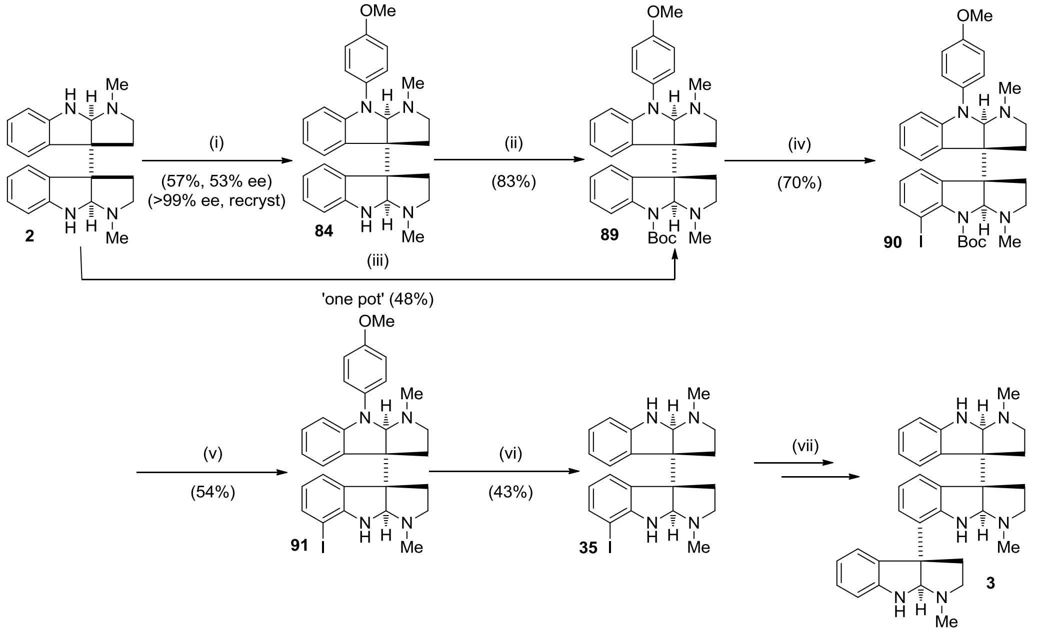
It was proposed that changing from a methylcarbamate group to a Boc group could potentially increase the selectivity of the hypervalent iodine dimerization step, but could also facilitate desymmetrization at the carbamate stage. Disappointingly the use of a Boc group failed to yield any of the desired product under our hypervalent iodine dimerization conditions, presumably due to instability of the Boc group to acid (Scheme 57). Although the modification of *meso*-chimonanthine-methylcarbamate **12** is possible, such functional group interconversions would be very step intensive and therefore not desirable for the synthesis, as a result no further investigation was carried out in this area.



Scheme 57: Conditions: (i) Tryptamine **8** (1.0 eq), Boc_2O (1.5 eq), $NaHCO_3$ (2.2 eq), THF [0.3 M], rt, 2 h. (ii) *N*-Boc-tryptamine **87** (1.0 eq), PIFA (0.65 eq), CF_3CH_2OH [0.2 M], -30 °C, 24 h.

5.1.7 Formal Synthesis of Hodgkinsine: The Synthesis of Enantioenriched 7-Iodo-Chimonanthine

Although we were not able to achieve the levels of selectivity that we desired for our asymmetric Buchwald-Hartwig cross coupling reaction, we were able to highlight its possible synthetic utility with a formal synthesis of hodgkinsine **3**. Scheme 58 shows the synthetic pathway used to generate enantioenriched 7-iodo-chimonanthine **35**; this intermediate (in its racemic form) was used by the Overman research group in both of their syntheses of hodgkinsine **3**.[15] Our methodology (assuming crystallisation to >99% ee) should facilitate the synthesis of hodgkinsine **3** or hodgkinsine B **146** without the requirement of the formation of the undesired diastereomer.



Scheme 58: Conditions (i) *meso*-chimonanthine **2** (1.0 eq), 4-bromoanisole (1.3 eq), $Pd(OAc)_2$ (5 mol%), [(*R,S*)-SL-J009-1]$PdCl_2$ (6 mol%), KO*t*Bu (1.5 eq), PhMe [0.3 M], 50 °C, 16 h. Absolute configuration not determined. (ii) *N*-PMP-chimonanthine **84** (1.0 eq), NaHMDS (2.2 eq), Boc_2O (1.3 eq), THF [0.1 M], rt, 16 h (iii) *meso*-chimonanthine **2** (1.0 eq), 4-bromoanisole (1.2 eq), $Pd(OAc)_2$ (5 mol%), (*R,S*)-PPFA (6 mol%), KO*t*Bu (1.5 eq), PhMe [0.2 M], 65 °C, 16 h; Boc_2O (1.5 eq), NaHMDS (2.2 eq), rt, 6 h. (iv) *N*-PMP-*N′*-Boc-chimonanthine **89** (1.0 eq), s-BuLi (2.0 eq), TMEDA (3.0 eq), I_2 (2.0 eq), Et_2O [0.07 M], -78 °C, 30 min, 0 °C, 1 h. (v) *N*-PMP-*N′*-Boc-iodochimonanthine **90** (1.0 eq), TMSOTf (2.2 eq), DCM [0.03 M], rt, 3 h. (vi) *N*-PMP-iodochimonanthine **91** (1.0 eq), MeCN [0.06 M], CAN (3.0 eq), H_2O [0.2 M], 0 °C, 30 min. (vii) see Overman[15]

The desymmetrized material had an *ortho*-directing group (Boc) installed on the exposed amine group in 83% yield. Gratifyingly we were able to prepare the same *N*-PMP-*N'*-Boc-chimonanthine **89** in a 'one pot' procedure from *meso*-chimonanthine **2**. This was carried out on a gram scale to give the product in a synthetically useful 48% yield (over two steps). Pleasingly we obtained X-ray structures of both (±)-*N*-PMP-chimonanthine **84** and (±)-*N*-PMP-*N*'-Boc-chimonanthine **89** (crystallised from a mixture of isopropanol and hexane, Fig. 13). Lithiation with *s*-BuLi and subsequent halogenation with di-iodoethane occurred in a modest 47% yield, which is somewhat lower than reported by Overman *et al.* for similar transformations (*ca.* 60%).[176] Pleasingly, switching the electrophile from di-iodoethane to molecular iodine afforded the desired aryl-halide **90** in a 70% yield. Two deprotection steps gave us C-7-iodo-chimonanthine **35**; the yields for both these steps were somewhat disappointing, they are however entirely un-optimised. We noted that the reaction mixture was fairly acidic during the final cleavage of the *para*-methoxyphenyl group using CAN, and there is the possibility that this step could have been used to globally cleave both the *para*-methoxyphenyl and Boc groups simultaneously.[202] Fortunately this acidity was not sufficient to effect the rearrangement to iodo-calycanthine.[29] As a result of the poor enantioselectivity of the initial desymmetrization step, no further work was carried out on increasing the efficiency of this formal synthesis.

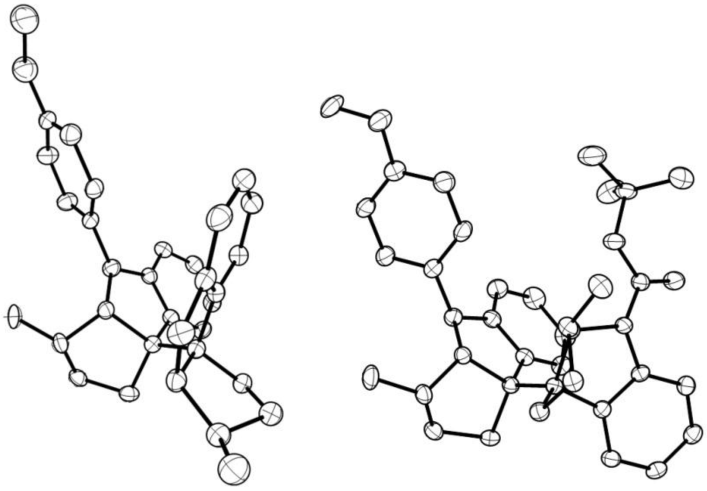
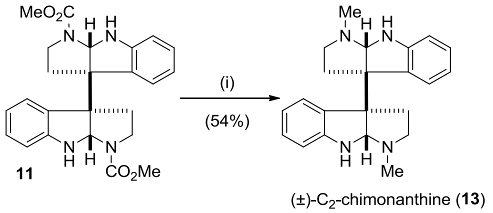


Fig. 13: X-ray structures of compounds **84** & **89**, protons omitted for clarity

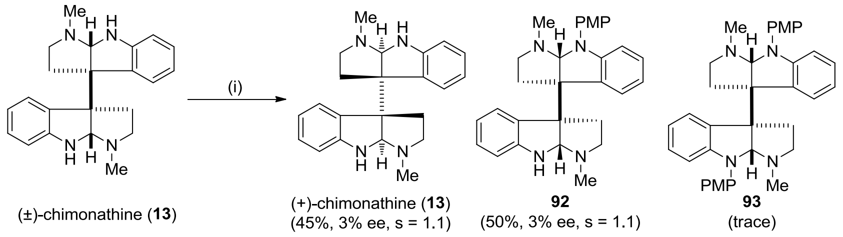
5.1.8 Kinetic Resolution of (±)-C$_2$-Chimonanthine

Following our partial success with the desymmetrization of *meso*-chimonanthine **2**, we investigated the application of the methodology on the kinetic resolution of racemic C$_2$-symmetric chimonanthine **13**. The racemic carbamate derivative **11**, isolated (by flash chromatography) in *ca.* 12% yield as a bi-product from our existing synthesis of *meso*-chimonanthine **2** (Scheme 42), was reduced to (±)-C$_2$-chimonanthine **13** using Red-Al.[30,43]



Scheme 59: Conditions: (i) (±)-C$_2$-Chimonanthine-carbamate **11** (1.0 eq), Red-Al (10.0 eq), PhMe [0.06 M], reflux 16 h.

We subjected (±)-C$_2$-chimonanthine **13** to our optimal Buchwald-Hartwig coupling conditions (Scheme 60).



(±)-chimonathine (**13**)

(+)-chimonathine (**13**) (45%, 3% ee, s = 1.1)

92 (50%, 3% ee, s = 1.1)

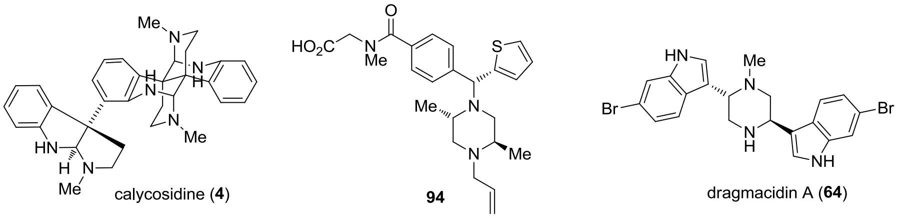
93 (trace)

Scheme 60: (i) Conditons: (±)-C_2-Chimonanthine **13** (1.0 eq), 4-bromoanisole (0.55 eq), [(*R,S*)-J009-1]PdCl_2 (6 mol%), KO*t*Bu (1.5 eq), PhMe [0.3 M], 50 °C, 16 h.

Regrettably, the selectivity of our Buchwald-Hartwig conditions was dramatically lower than that observed for our desymmetrization (s = 1.1).[i] As a result of this almost complete absence of selectivity, no further work was carried out in this area.

5.1.9 Desymmetrization of trans-Dimethylpiperiazine

The scope of our asymmetric Buchwald coupling was explored further, looking this time at centrosymmetric molecules. A host of natural products and drug molecules contain a centrosymmetric core[12,203-205] including the δ-opioid receptor agonist **94**[206] as well as calycosidine **4**, a natural product related to hodgkinsine **3** (Fig. 14).[17,25] Currently molecules such as **94** are synthesised using a kinetic resolution strategy. However, as discussed in (section 2.2.4), Nelson and co-workers were able to utilise the desymmetrization of a centrosymmetric piperazine core in their synthesis of dragmacidin A **64** (Fig. 14).[12,152]



calycosidine (**4**)

94

dragmacidin A (**64**)

Fig. 14: Compounds possessing a centrosymmetric core

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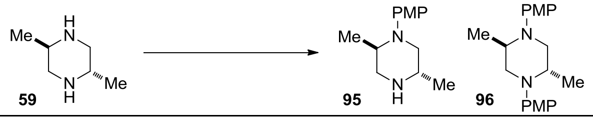
[i] Selectivity factors (s) calculated using s = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)] & s'= ln[1-C(1+ee')]/ln[1-C(1-ee')] in accordance with *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 3974 & *Adv. Synth. Catal.*, **2001**, *343*, 5.

We applied our asymmetric Buchwald-Hartwig conditions to the desymmetrization of *trans*-dimethylpiperazine **59** (Table 17). Like the desymmetrization of *meso*-chimonanthine **2**, the results were fairly poor; our optimal result being 72% yield and 15% enantiomeric excess (Table 17, Entry 5). These levels of enantioselectivity, although sufficient for a proof of concept, need significant enhancement for this is to be considered a viable protocol.

Table 17: Desymmetrization of trans-dimethylpiperazine



Entry	Ligand	T [°C]	Yield[a], *mono* [%] (% ee)	Yield[a], *bis* [%]
1	S-Phos[b]	50	25 (±)	24
2	(*R*)-BINAP	50	15 (12)	0
3	(*R*)-MOP	50	7 (15)	0
4	(*R*)-MOP	20	0	0
5	**(*R*)-*i*PrMOP**	**50**	**72 (15)**	**23**
6	(*R*)-*i*PrMOP	20	40 (13)	4
7	**(*R*)-CyMOP**	**50**	**50 (14)**	**36**
8	(*S*)-QUINAP	50	0	0
9	(*S,S,R,R*)-Tangphos	50	0	0
10	(*R*)-PHOX	50	0	0
11	(*R,S*)-PPFA	50	12 (4)	0
12	(*R,S*)-SL-J004-1	50	0	0
13	(*R,S*)-SL-J007-1	50	19 (±)	0
14	[(*R,S*)-SL-J001-1]$PdCl_2$	50	19 (5)	0

Conditions: *trans*-Dimethylpiperazine **59** (1.0 eq), 4-bromoanisole (1.3eq), KO*t*Bu (1.5eq), $Pd(OAc)_2$ (5 mol%), Ligand (6 mol%), PhMe [0.3 M], 50 °C, 16 h; [a]Isolated Yield; [b]Reaction performed at 100 °C for 3 h.

5.1.10 Summary

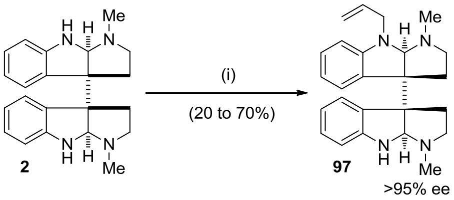
We have demonstrated that the Buchwald-Hartwig cross coupling reaction can be used asymmetrically to desymmetrize *meso*-chimonanthine **2** in yields and enantiomeric excesses both to the order of 50%. In addition we have shown that the enantioenriched product can easily be isolated as a single enantiomer by crystallisation and can be utilised in further synthetic transformations, exemplified by a formal synthesis of hodgkinsine **3**.

5.2 Desymmetrization via Trost Allylation

Recently Taguchi *et al.* showed that *meso*-symmetric diamines could be desymmetrized by means of an asymmetric Trost allylation. Yields were generally good, but the enantiomeric excess was very substrate dependant. It was also noted that the electronics of the amines needed to be precisely tuned to facilitate the reaction (Section 2.2.4, Table 4).[144,147] We were intrigued by this chemistry as such a result could potentially be applied to the desymmetrization of *meso*-chimonanthine **2**.

5.2.1 Preliminary Investigation

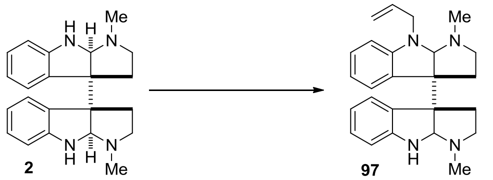
Preliminary trials of the allylation proved very successful, using the literature conditions and either the phenyl or the napthyl Trost Ligands we recorded consistently high results for enantiopurity. However, the yield for the reaction was somewhat capricious, ranging from 20 to 70%, occasionally only unreacted starting material was recovered (Scheme 61).



Scheme 61: Conditions: (i) *meso*-Chimonanthine **2** (1.0 eq), allyl acetate (1.1 eq), KO*t*Bu (2.0 eq), (*R,R*)-DACT-Ph-Trost Ligand (7.3 mol%), (allyl-Pd-Cl)$_2$ (3.6 mol%), PhMe /dioxane (1:1) [0.07 M], -15 –0 °C, 16 h.

The initial lead for the allylation utilised potassium *tert*-butoxide as a base in a 1:1 mixture of toluene and dioxane. One possible explanation for the poor reproducibility was the low solubility of the base in the reaction media. It has been observed that amines themselves are in fact effective bases for such allylation reactions.[148,207] Following this precedent, triethylamine was selected as an alternative base. Pleasingly, the amine base not only improved the robustness of the reaction, but when neat toluene was used as the solvent it resulted in an increased yield (Table 18, Entry 3); the enantiodiscrimination of the reaction was also improved. To our surprise, we noticed that the reactions' selectivity was maintained at elevated temperatures, *ca.* 50 °C (Table 18).

Table 18: Base & Solvent Screen

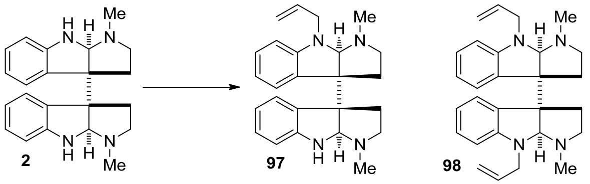


Entry	Solvent	Base	Yield [%] (% ee)
1	PhMe / Dioxane (1:1)	KO*t*Bu	6–75(>99)
2	PhMe / Dioxane (1:1)	Et_3N	55 (>99)
3	PhMe	Et_3N	83 (>99)[a]

Conditions: *meso*-Chimonathine **2** (1.0 eq), allyl acetate (1.2 eq), base (2.0 eq), (allyl-Pd-Cl)$_2$ (2.5 mol%, Pd), (*R,R*)-DACT-phenyl Trost Ligand (3.8 mol%), [0.144 M], 50 °C, 16 h. [a]1 h

It was observed that the allylation, although highly selective, still gave detectable amounts of *bis*-allylated product **98** suggesting that, in part, the high enantiomeric purity may be a result of a kinetic resolution. In an effort to improve the specificity of the reaction we repeated our screening, with the optimised solvent and base. It was observed that changing to the more bulky napthyl derived Trost ligand resulted in a higher selectivity at the cost of decreased rate of reaction. This catalyst system failed to give complete conversion after 16 h with large quantities of unreacted *meso*-chimonanthine **2** recovered. A brief investigation into other ligands failed to identify a candidate that could outperform the initial selection of phenyl Trost Ligand. We also re-evaluated the temperature dependence of the reaction, this time on a multi gram scale. At elevated temperatures selectivity was marginally impaired; characterised by increased levels of *bis*-allylated material **98**. Pleasingly enantiopurity of the product **97** remained unaffected, presumably the result of a 'proof reading' kinetic resolution step (Table 19).

Table 19: Conditions screen

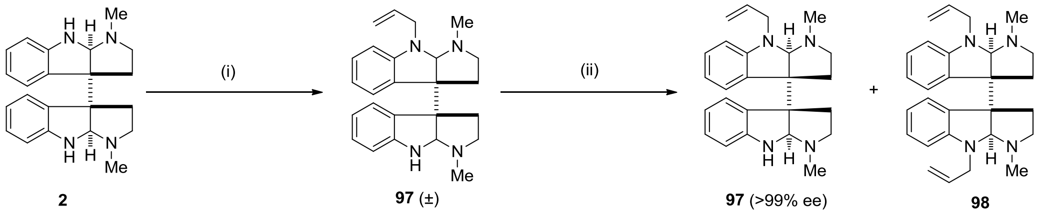


Entry	Ligand	T [°C]	*t* [h]	Yield **97** [%] (% ee)	Yield **98** [%]
1	(*R,R*)-DACT-Ph-Trost Ligand	0	1.5	76 (>99)[a]	24
2	(*R,R*)-DACT-Napthyl-Trost Ligand	0	16	56 (>99)	9
3	(*R,R*)-DACT-Ph-Trost Ligand	50	2	62 (>99)	37

Conditions: *meso*-Chimonanthine 2 (1.0 eq), allyl acetate (1.2 eq), Et_3N (2.0 eq), $(allyl\text{-}Pd\text{-}Cl)_2$ (2.5 mol%, Pd), ligand (3.8 mol%), PhMe [0.144 M]. [a]3 g scale.

5.2.2 Kinetic-Resolution of N-allyl-Chimonanthine

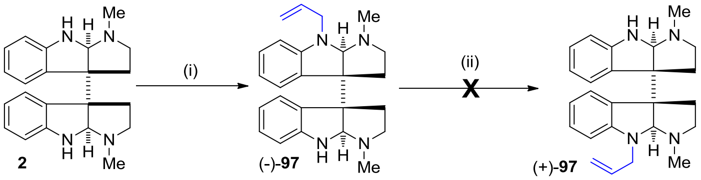
During the course of this report, Hou and co-workers disclosed that racemic indolines could be resolved using almost identical conditions to those identified by us.[148] Following this and our observation that *bis*-allylated product **98** was recovered from our desymmetrization (presumably from a kinetic resolution), a racemic sample of the mono-allylated product **97** was prepared, by desymmetrizing *meso*-chimonanthine **2** using (±)-DACT-phenyl Trost Ligand. Re-exposure of the racemic product to the reaction conditions, this time using the (*R*,*R*)-ligand, yielded product with an enantiomeric excess >99% (Scheme 62).



Scheme 62: Conditions: (i) *meso*-Chimonathine **2** (1.0 eq), allyl acetate (1.2 eq), Et_3N (3.0 eq), $(allyl\text{-}Pd\text{-}Cl)_2$ (5.0 mol%, Pd), (±)-DACT-phenyl Trost Ligand (6.0 mol%), [0.144 M], 50 °C, 45min (ii) (±)-*N*-Allyl-chimonanthine **97** (1.0 eq), allyl acetate (1.2 eq), Et_3N (3.0 eq), $(allyl\text{-}Pd\text{-}Cl)_2$ (5.0 mol%, Pd), (*R,R*)-DACT-phenyl Trost Ligand (6.0 mol%), [0.144 M], 50 °C, 1 h.

These results suggest that a kinetic resolution is indeed in effect during the reaction, and that the allylation protocol is far less sensitive to changes in the substrate than our

Buchwald-Hartwig strategy (Scheme 56). We postulated that a dynamic kinetic resolution could also be in effect. It is well precedented that under palladium catalysis in the presence of a proton source (e.g. barbituric acid), *N*-allyl groups can be cleaved.[208] This gave rise to the idea that the allyl group could migrate, resulting in a dynamic process. Although the migration cannot be completely discounted, the initial dynamic kinetic resolution theory was disproved by exposing product formed using (*R*,*R*) Trost ligand to catalytic conditions employing (*S*,*S*) Trost Ligand. The product from this reaction was identical by chiral HPLC to the starting material, showing no dynamic process was occurring (Scheme 63).

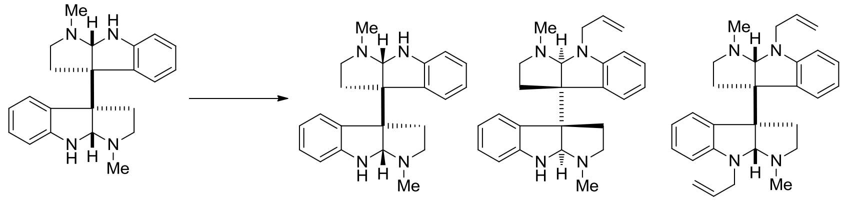


Scheme 63: Conditions: (i) *meso*-Chimonanthine **2** (1.0 eq), allyl acetate (4.0 eq), Pd(OAc)$_2$ (5 mol%), (*R,R*)-DACT-phenyl Trost ligand (6 mol%), KO*t*Bu (2.0 eq), PhMe/Dioxane (1:1), 20–70 °C. (ii) (-)-*N*-Allyl-chimonantine **97** (1.0 eq), Pd(OAc)$_2$ (5 mol%), (*S,S*)-DACT-phenyl Trost Ligand (6 mol%), KO*t*Bu (2.0 eq), PhMe/Dioxane (1:1), 20–70 °C.

5.2.3 Kinetic Resolution of (±)-C2-Chimonanthine

With (±)-C$_2$-chimonanthine **13** still in hand, from our previous attempts at a kinetic resolution using our Buchwald-Hartwig strategy (see Section 5.1.8), we subjected it to our Trost allylation conditions. The reaction was carried out using both the phenyl and naphthyl derived Trost ligands; the results of this screen are summarised in Table 20.

Table 20: Kinetic resolution of (±)-C_2-chimonanthine



(±)-chimonathine (**13**) (-)-chimonathine (**13**) **99** **100**

Entry	T [°C]	Ligand	Yield **13** [%] (% ee)	Yield **99** [%] (% ee')	Yield **100** [%]
1	**0**	**(*R,R*)-DACT-Ph-Trost Ligand**	**57 (44) s = 5.8**[i]	**40 (60) s'= 6.2**	**3**
2	-10[a]	(*S,S*)-DACT-Ph-Trost Ligand[b]	55 (46) s = 5.3	45 (46) s' = 3.8	trace
3	-10[a]	(*R,R*)-DACT-Ph-Trost Ligand[b]	46 (59) s = 5.3	45 (43) s' = 4.0	9
4	50	(*S,S*)-DACT-Ph-Trost Ligand[b]	44 (55) s = 4.2	50 (32) s' = 2.8	6
5	**0**	**(*R,R*)-DACT-Naphthyl-Trost Ligand**	**63 (36) s = 5.9**	**28 (69) s' = 8.1**	**9**
6[c]	rt	(*R,R*)-DACT-Naphthyl-Trost Ligand	48 (51) s = 4.5	45 (43) s' = 3.9	7

Conditions: (±)-C_2-Chimonanthine **13** (1.0 eq), allyl acetate (0.55 eq), Et_3N (3.0 eq), $(allyl\text{-}Pd\text{-}Cl)_2$ (2.5 mol%, Pd), Ligand (3.8 mol%), PhMe [0.144 M], 2 h. [a]t = 4 h. [b]gave opposite enantiomer. [c](±)-C_2-chimonanthine **13** (1.0 eq), allyl acetate (0.55 eq), NaOAc (1.0 eq), $(allyl\text{-}Pd\text{-}Cl)_2$ (2.5 mol%, Pd), ligand (3.8 mol%), PhMe [0.2 M], 2 h. s = Selectivity factor.

At 0 °C (for the first allylation step), the selectivity factors for both ligands are comparable (Table 20, Entries 1, 5), however, the naphthyl ligand appears far more selective for the second allylation step (Table 20, Entry 5). The increased selectivity factor for allylation of the *mono*-allylated product **99** is presumably a result of a secondary kinetic resolution step.[94] Predictably, increasing the temperature to 50 °C resulted in a slight drop in the selectivity of the reaction, with the second allylation step seeming to be particularly affected by the elevated temperature. Surprisingly, decreasing the temperature to -10 °C offered no increase in selectivity (Table 20, Entries 2, 3); this observation was also noted by Hou *et al.*[148] As mentioned previously, during the course of our investigations a paper was released by Hou and co-workers which described the

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[i] Selectivity factors (s) calculated using s = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)] & s'= ln[1-C(1+ee')]/ln[1-C(1-ee')] in accordance with *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 3974 & *Adv. Synth. Catal.*, **2001**, *343*, 5.

kinetic resolution of 2-substituted-indolines. The group reported that using sodium acetate (or in fact no base at all) gave the highest levels of selectivity in their system.[148] With this in mind we applied their conditions to our kinetic resolution, unfortunately these failed to show any noticeable improvement relative to our triethylamine system (Table 20, Entry 6). Overall the selectivity of the kinetic resolution is far lower than would be predicted from our work on the desymmetrization of *meso*-chimonanthine **2**; this could be the result of the change in environment for the secondary amines in the *meso* verses C_2 substrates. To test this, a slight variant in substrate (±)-C_2-chimonanthine-carbmate **11**, was subjected to the reaction conditions, and unfortunately at 0 °C this only yielded recovered starting material. Another plausible explanation is that the chiral palladium complex associates with a chimonanthine **2** molecule prior to reacting. For (±)-C_2-chimonanthine **13** this association could be with either stereo isomer, conceivably with some degree of enantiodiscrimination. Association of the undesired isomer could potentially overcome the higher energy barrier linked to its reaction. However with *meso*-chimonanthine **2**, both enantiotopic N-H groups are present in each molecule, therefore this initial association should not influence the enantioselectivity of the process.

It was observed that, when using (*R*,*R*)- Trost ligands, allylation occurred on the (+)-(*R*)-enantiomer of C_2-chimonanthine leaving enantioenriched (-)-C_2-chimonanthine **13**. Based on this result we predicted that for our desymmetrization the allylation would occur in an analogous fashion on the (*R*,*R*) fragment, meaning that we would require the (*S*,*S*)-ligand in our synthesis.

5.2.4 Prediction of Absolute Configuration

Several papers have been published regarding the prediction of the stereochemical outcome of Trost allylations, however, to the best of our knowledge none deal with pro-chiral nucleophiles or substrates as complex as *meso*-chimonanthine **2**.[209]

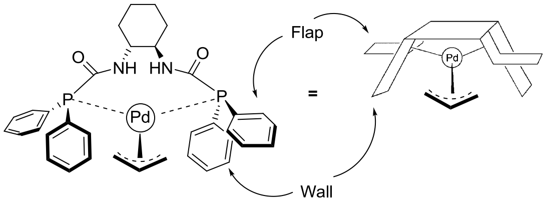


Fig. 15: Trost's 'cartoon' model for (*R,R*)-DACT-phenyl-Trost ligand

Although only a loose approximation, the model developed by Trost *et al.* has been used to accurately predict the outcome of various allylations, including several desymmetrizations, albeit utilizing a pro-chiral allyl unit.[210]

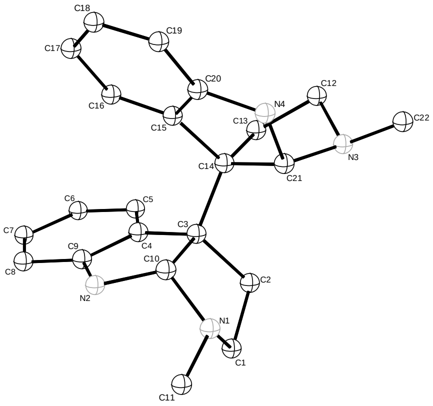


Fig. 16: Crystal structure of *meso*-chimonanthine[23]

It is possible to envisage at least two low energy configurations for the interaction of *meso*-chimonanthine **2** and the Trost ligand, illustrated in Fig. 17 and Fig. 18. In the preliminary model we assume that the second ring (which can undergo free rotation, observed by ^{1}H NMR spectroscopy) prevents attack from the bottom face of the molecule. The "open book"-like ring structure of *meso*-chimonanthine **2**, clearly visible in Fig. 16, presumably orientates with the ‘flap’ on the ligand to minimise steric interaction (Fig. 17, **I**). Attack by the other enantiotopic amine should result in a steric clash with the ‘wall’ on the ligand, thereby disfavouring attack by this group. However, this more hindered configuration may have some degree of π interaction which, if strong enough, could dominate (Fig. 17, **II**).

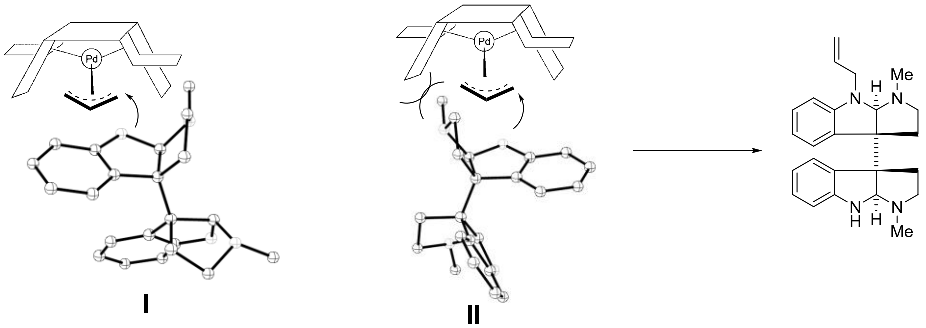


Fig. 17: Application of cartoon to predict stereochemical outcome

Although in the solid state (Fig. 16), the two halves of meso-chimonanthine are almost completely eclipsed, there is free rotation about the C-3a axis so attack from the bottom face cannot be entirely ruled out. Fig. 18 shows the application of Trost and co-workers ‘cartoon’ model to predict the outcome of attack from the bottom face. Fig. 18 (**I**) shows the theoretically most favourable configuration; here the “open book” section of the molecule is bent away from the ‘wall’ and there is also potential for some favourable π-stacking.

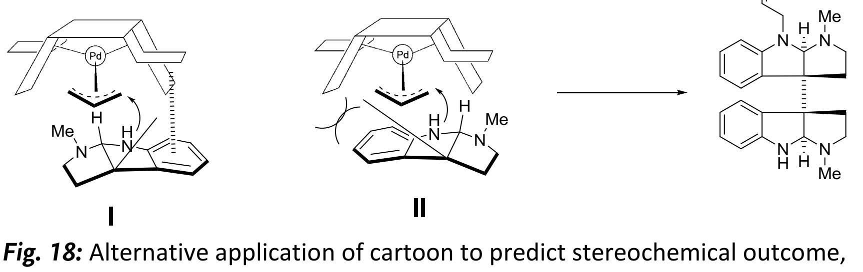


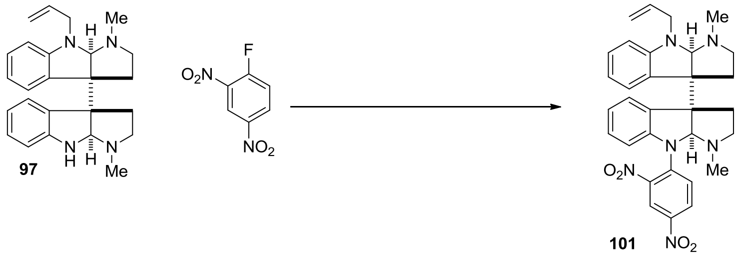
Fig. 18: Alternative application of cartoon to predict stereochemical outcome, second half of molecule omitted for clarity

It is interesting to note that the stereochemistry of the product predicted by each of the two models is identical thereby increasing the degree of confidence given by this prediction. This ‘wall and flap’ model for predicting stereochemistry is highly limited and does not take into account many important factors such as hydrogen bonding. Although more sophisticated models for predicting the outcome of asymmetric allylation reactions exist, these are largely outside the scope of this investigation.[207]

5.2.5 Determination of Absolute Configuration

Although the application of Trost’s model to predict the outcome of our desymmetrization gave some encouraging results, a more reliable method for the determination of absolute configuration was required. *N*-Allyl-chimonanthine **97** failed to crystallise from a variety of solvents, and simple derivatization with tartric acid, iodomethane, HBr and Resolve-Al (Yb[fod]$_3$) also failed to generate a crystalline product. This led us to synthesise several more complex derivatives which would hopefully exhibit an increased crystallinity. The 2,4-dinitrophenyl (2,4-DNP) derivative **101** was easily prepared in a modest 37% yield *via* nucleophilic aromatic substitution (Table 21). Surprisingly this product only yielded a glass during all attempts at crystallisation.

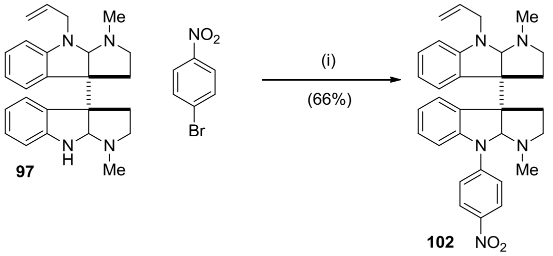
Table 21: S_NAr of desymmetrized *meso*-chimonanthine



Entry	Ar-F [eq]	Solvent	T [°C]	Base (eq)	*t* [h]	Yield [%]
1	1	DMA	100 µw	K_2CO_3 (1)	0.25	0
2	1	DMA	200 µw	K_2CO_3 (1)	0.25	Trace
3	3	DMA	200 µw	K_2CO_3 (3)	1	Trace
4	1.01	Acetone:H_2O^a	20	$NaHCO_3$ (3)	1	Trace
5	1.01	Acetone:H_2O^a	20	$NaHCO_3$ (3)	62	37

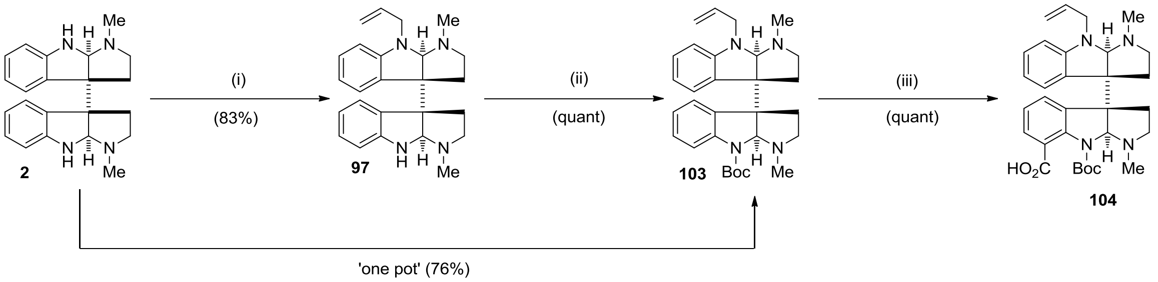
Conditions: [0.19 M, relative to **97**], ^{a} (1:1) [0.07 M, relative to **97**].

Following the somewhat time consuming nucleophilic aromatic substitution reaction used to prepare the 2,4-DNP derivative **101** (*ca.* 60 h), we opted to synthesise the *para*-nitro phenyl derivative **102** using a Buchwald-Hartwig cross coupling. The product was obtained in a 66% yield after just four hours (Scheme 64); unfortunately this product also failed to crystallise.



Scheme 64: Conditions: (i) *N*-Allyl-chimonanthine **97**(1.0 eq), 1-bromo-4-nitrobenzene (1.2 eq), KO*t*Bu (2.0 eq), $Pd(OAc)_2$ (5 mol%), S-Phos (6 mol%), PhMe [0.13 M], 100 °C, 4 h.

Following the failure of the crystallisation of the nitrophenyl derivatives **10** and **102**, we postulated that the presence of an acidic group combined with the molecules inherent basicity should yield a crystalline product. Installation of a DMG (Boc) on the free amine of *N*-allyl-chimonanthine **97** allowed us to selectively lithiate at the C-7 position. This aryl-lithium species was quenched in a quantitative yield with carbon dioxide to afford the desired *N*-allyl-*N*'-Boc-chimonanthine-7'-carboxylate **104**. We observed that although the product of our Trost allylation was not crystalline, it was of sufficient purity to allow a 'one pot' protocol for the desymmetrization of *meso*-chimonanthine **2** and subsequent installation of a Boc group. This 'one pot' protocol gave **103** in a 76% yield over two steps (Scheme 65). Attempts to use carbon dioxide itself as the DMG for this transformation proved unsuccessful, with only un-reacted starting material recovered from the reaction mixture.[211]



Scheme 65: Conditions: (i) *meso*-Chimonanthine **2** (1.0 eq), allyl acetate (1.2 eq), Et_3N (3.0 eq), (allyl-Pd-Cl)$_2$ (5.0 mol%, Pd), (*R,R*)-DACT-Ph Trost ligand (6.0 mol%), PhMe [0.14 M], 50 °C, 45 min. (ii) Allyl-chimonanthine **97** (1.0 eq), Boc_2O (1.3 eq), NaHMDS (2.2 eq), THF [0.02 M], rt, 30 min. (iii) Boc-allyl-chimonanthine **103** (1.0 eq), *s*-BuLi (2.0 eq), TMEDA (3.0 eq), CO_2 (excess), Et_2O [0.02 M], -78 – 0 °C, 1 h. Product was crystallised from wet MeOH.
'one pot' procedure: *meso*-Chimonanthine **2** (1.0 eq), allyl acetate (1.2 eq), Et_3N (3.0 eq), (allyl-Pd-Cl)$_2$ (5.0 mol%, Pd), (*R,R*)-DACT-Ph Trost ligand (6.0 mol%), PhMe [0.14 M], 50 °C, 45 min, then Boc_2O (1.1 eq), rt, 16 h.

It was observed that *N*-allyl-*N*'-Boc-chimonanthine-7'-carboxylate **104** readily crystallised from wet methanol giving crystals of X-ray quality. In the absence of heavy atoms it is difficult to say with certainty that our assignment possesses the correct absolute configuration (Flack parameter, X = 0.3). However, the data available strongly supports the configuration shown in Fig. 19.[i] The observed configuration matches that predicted by the Trost 'cartoon' model, yet contradicts that suggested by our kinetic resolution studies. Regrettably we cannot say with an absolute certainty which enantiomer of product we obtain, however, for further investigation we chose to rely on our crystallographic studies.

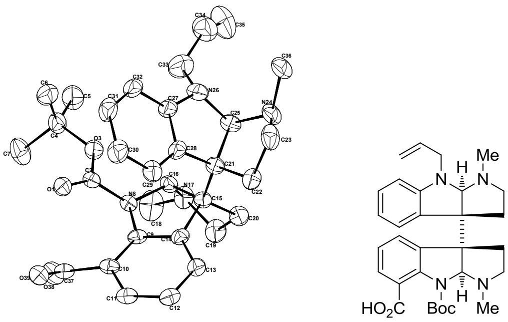


Fig. 19: X-ray structure of *N*-allyl-*N*'-Boc-chimonanthine-7'-carboxylate **104**

5.2.6 Summary

We have developed a highly efficient method for the desymmetrization of *meso*-chimonanthine **2**, obtaining the product **97** essentially as a single enantiomer on a multi gram scale in yields to the order of 80%. In addition to this we have had some success on the development of a kinetic resolution of C_2-chimonanthine **13**. Finally, we have gained some insight on the stereochemical preferences of the reaction and, by means of Trost and co-workers' model, predicted the stereochemistry of our desymmetrized product.

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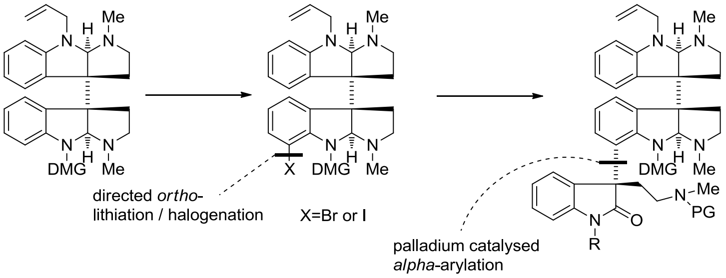
[i] Analysis of the Bijvoet differences using CRYSTALS gave the Hooft Y parameter as 0.24(33), and the probability the configuration is correct assuming the material is enantiopure was determined to be 91.5%. (See appendix)

6.0 C-7 Functionalisation

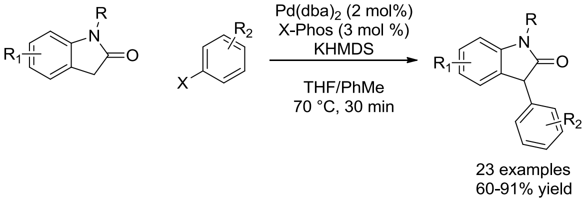
Functionalisation at the C-7 position of indoles is well precedented; we selected the directed *ortho* lithiation strategy of Snieckus *et al*. as the most robust.[64,212] This, as mentioned previously, was used to great effect by Overman and co-workers in their synthesis of cyclotryptamine alkaloids.[213] The viability of this protocol was demonstrated by us previously with the synthesis of *N*-allyl-*N*'-Boc-chimonanthine-7-carboxylate **104** (Scheme 65). In a directly analogous fashion to Overman *et al.* we planned to install a halogen at C-7 and use this in subsequent transformations. Our investigations focused on the development of a palladium-catalysed reaction capable of establishing the C-7 – C-3a linkage present in the natural product, in a more environmentally benign and atom economic manner than the Stille coupling used in previous syntheses (Scheme 11, Scheme 66).



Scheme 66: *alpha*-Arylation strategy

6.1 Palladium Catalysed alpha-Arylation

Previously within the group it has been demonstrated that aryl-halides could be coupled to *N*-substituted oxindoles at the C-3 position in good to excellent yields on a variety of substrates (Scheme 67).[177]

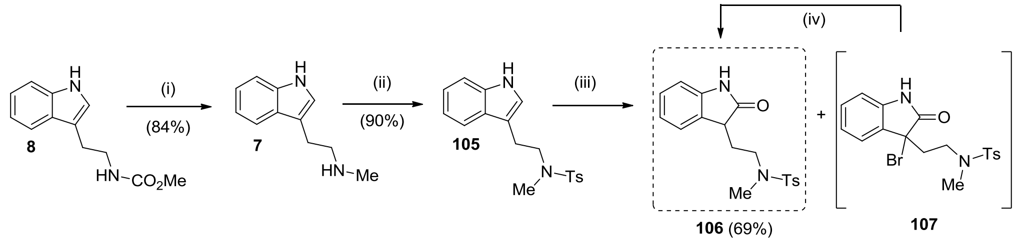


Scheme 67: Willis' palladium catalysed *alpha*-arylation

Subsequently Buchwald *et al.* published a complementary paper where aryl-halides could be coupled to un-substituted oxindoles at either the C-3 or *N*- position by employment of either a palladium or copper catalyst, respectively. The group showed that their protocol was tolerant to a free oxindole NH.[214] We hoped to use this *alpha*-arylation methodology to install an oxindole at the C-7 position of *meso*-chimonanthine.

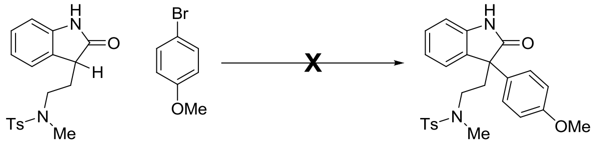
6.1.1 Tertairy Oxindoles

We synthesised a suitable oxindole fragment from tryptamine methyl carbamate **9**; the same starting material used in our synthesis of *meso*-chimonanthine **2**. The carbamate moiety was reduced to a methyl group with Red-Al and the resultant free amine protected as the tosylate. Oxidation of indoles to oxindoles is generally accomplished by the use of a mixture of *conc*. HCl and DMSO, however, in our hands this failed to give the desired oxindole **106**.[215,216] Instead we found that a combination of NBS and water could mildly effect the desired oxidation, yielding a mixture of the oxindole **106** and bromo-oxindole **107**.[217] Pleasingly, addition of sodium borohydride to the crude reaction mixture cleanly converted the bromo-oxindole **107** to the desired oxindole **106** (Scheme 68).



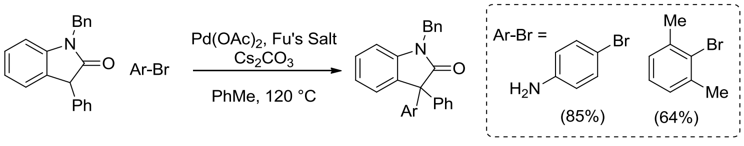
Scheme 68: Conditions: (i) Tryptamine methyl carbamate **9** (1.0 eq), Red-Al (5.0 eq), PhMe [0.05 M], 120 °C, 3 h. (ii) *N*-Methyl-tryptamine **7** (1.0 eq), tosylchloride (1.1 eq), Et_3N (1.4 eq), DMAP (9 mol%), DCM [0.2 M], 0 °C – rt, 6 h. (iii) *N*-Methyl-*N*-tosyl-tryptamine **105** (1.0 eq), NBS (2.4 eq), H_2O (4.0 eq), *t*BuOH : THF [1:1, 0.1 M], rt, 30 min. (iv) $NaBH_4$ (6.0 eq).

The palladium-catalysed coupling was modelled using 4-bromo anisole as a simplified aryl halide. Unfortunately, attempts to couple our cyclotryptamine precursor **106** directly to 4-bromoanisole using the conditions of Buchwald *et al.* only resulted in the recovery of starting materials (Scheme 69).



Scheme 69: Conditions: Oxindole (1.0 eq), 4-bromoanisole (1.2 eq), $Pd_2(dba)_3$ (5 mol%, Pd), X-Phos (5 mol%), K_2CO_3 (2.0 eq), PhMe [0.3 M], 100 °C, 48 h.

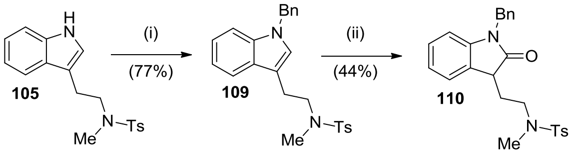
A follow up paper published by Sammakia *et al.* disclosed that they were able to react substituted oxindoles with aryl halides in good yields (Scheme 70).[218]



Scheme 70: Selected arylations from Sammakia and co-workers

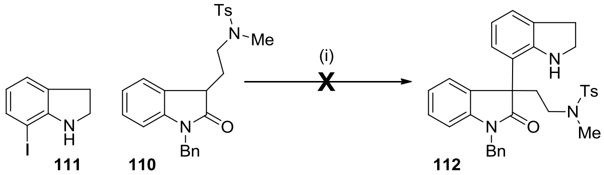
The reactions described in this paper were tolerant to *ortho*-substitution, unprotected aniline functionality, and allowed the formation of a quaternary centre. The authors noted that a protecting group on the oxindole nitrogen was essential for reactivity, an observation in keeping with the original Willis *alpha*-arylation paper.[177]

To model these conditions, we selected a Bn / tosyl protecting group strategy, in line with the functionality used in the Overman group's synthesis of hodgkinsine **3**.[176] The oxindole was prepared in an analogous fashion to before (Scheme 68), using sodium hydride and benzyl bromide to install the second protecting group. The absence of the 'borohydride recovery step' resulted in diminished yields of 44% (Scheme 71).



Scheme 71: Conditions: (i) *N*-Methyl-*N*-tosyl-tryptamine **105** (1.0 eq), NaH (1.4 eq), BnBr (1.1 eq), DMF [0.5 M], rt, 3 h. (ii) *N*'-Bn-*N*-methyl-*N*-tosyl-tryptamine **109** (1.0 eq), NBS (2.4 eq), H_2O (4.0 eq), *t*BuOH : THF [1 : 1, 0.1 M], rt, 30 min.

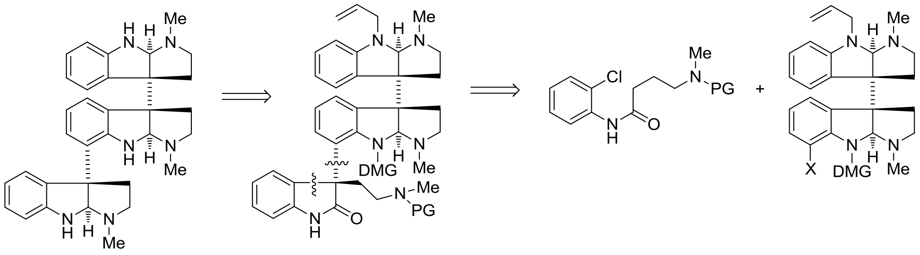
Application of the Sammakia conditions to our model system, this time utilising 7-iodo-indoline,[219] failed to yield the desired linkage. We attributed this poor reactivity to steric crowding around the C-3 position (Scheme 72).



Scheme 72: Conditions: (i) Oxindole **110** (1.0 eq), 7-iodoindoline **111** (1.1 eq), $Pd(OAc)_2$ (5 mol%, Pd), Fu's Salt (10 mol%), Cs_2CO_3 (3.0 eq), PhMe [0.04 M], 100 °C, 16 h.

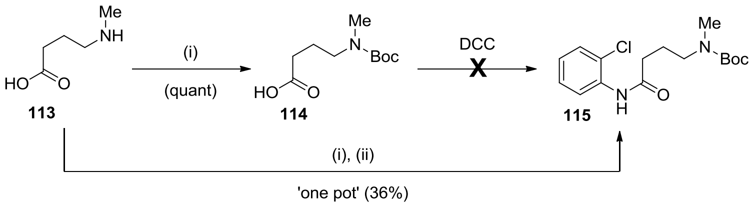
6.1.2 Tandem inter-/intra Molecular Coupling

Scheme 73 shows an alternative strategy, this time performing the intermolecular step prior to the formation of the desired quaternary centre by means of a tandem palladium-catalysed *inter- / intra*-molecular C-C bond forming protocol.



Scheme 73: Retrosynthetic Strategy

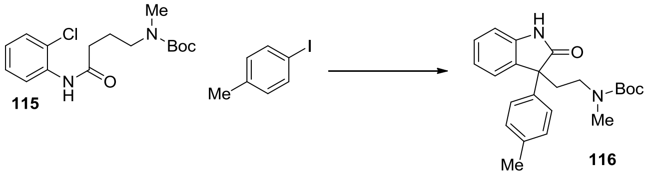
The enolate precursor could be easily synthesised by a trivial two step, 'one pot' reaction, albeit in a modest 36% yield (over two steps). Initial attempts to form the amide linkage with DCC resulted in cleavage of the Boc group, however, the use of EDC in the presence of HOBt allowed the desired product to be synthesised in useful quantities, *ca.* 1 g (Scheme 74).



Scheme 74: Conditions: (i) 4-(Methylamino)butanoic acid **113** (1.0 eq), Et_3N (3.2 eq), Boc_2O (1.1 eq), DCM [0.65 M], rt, 1 h; (ii) EDC (1.1 eq), HOBt (0.46 eq), 2-chloroaniline (1.1 eq), rt, 16 h.

Using the conditions developed by Buchwald and co-workers, in their reactions of un-protected oxindoles,[214] we obtained only recovered enolate precursor **115**. Screening a variety of bases again resulted in the recovery of our starting amide **115** (Table 22, entries 1-5). We trialled several ligands using sodium *tert*-butoxide as a base, this again yielded un-reacted starting material **115** (Table 22, Entries 6-9).

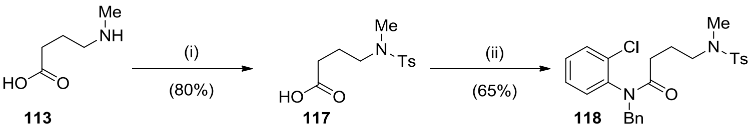
Table 22: Enolate coupling reactions



Entry	Ligand	Base	Yield [%]
1	X-Phos	KOtBu	0
2	X-Phos	NaOtBu	0
3	X-Phos	KHMDS	0
4	X-Phos	NaOMe	0
5	X-Phos	NaH	0
6	S-Phos	NaOtBu	0
7	Dave-Phos	NaOtBu	0
8	Fu's Salt	NaOtBu	0
9	PEPPSI	NaOtBu	0

Conditions: 4-Iodotoluene (1.0 eq), **115** (1.1 eq), base (2.0 eq), $Pd_2(dba)_3$ (5 mol%, Pd), ligand (5 mol %), PhMe, 100 °C, 24 h.

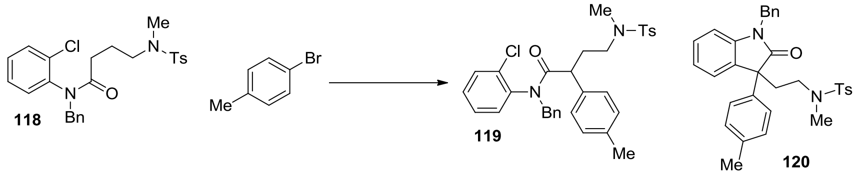
We concluded that an additional substituent is required at the *N*-position, such as benzyl, for the reaction to proceed. Due to the propensity for Boc cleavage, we returned to our Bn / tosyl system. A tosyl group was installed on 4-(methylamino)butanoic acid **113** using tosyl chloride and triethylamine; the acid **117** was then coupled with *N*-benzyl-2-chloroaniline[220] *via* the acid chloride to give the desired amide **118** in a 52% yield over two steps (Scheme 75).



Scheme 75: Conditions: (i) 4-(Methylamino)butanoic acid **113** (1.0 eq), Ts-Cl (1.2 eq), Et_3N (3.0 eq), DCM [0.13 M], rt, 1 h. (ii) **117**(1.2 eq), $(COCl)_2$ (2.0 eq), DMF (5 mol%), *N*-benzyl-2-bromoaniline (1.0 eq), DCM [0.08 M], rt, 2 h.

We trialled a variety of coupling conditions but none managed to yield any more than a trace of product (observed by LRMS), with generally only unreacted amide being isolated (Table 23).

Table 23: Enolate coupling reactions

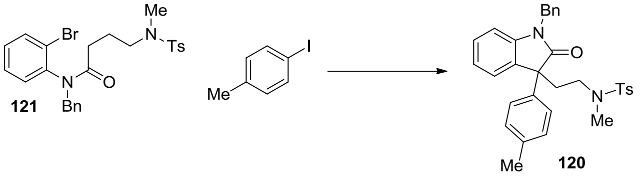


Entry	Base	Ligand	T [°C]	**119** [%]	**120** [%]
1	Cs_2CO_3	Fu's Salt	80	0	0
2	Cs_2CO_3	(*R*)-MOP	80	0	0
3	K_2CO_3	PEPPSI	100	0	0
4	NaOtBu	PEPPSI	100	0	0
5	**KHMDS**	**PEPPSI**	**100**	**~30**	**0**
6	KHMDS	PEPPSI	100^a	Trace	0
7	KHMDS	Fu's Salt	100	0	0
8	KHMDS	X-Phos	100	Trace	0

Conditions: 4-Bromotoluene (1.0 eq), **118** (1.1 eq), base (2.0 eq), $Pd_2(dba)_3$ (5 mol%, Pd), ligand (5 mol%), PhMe [0.05 M], 100 °C, 24 h. ^{a}Dioxane

When KHMDS was used as a base were able to isolate what appeared to be the un-cyclised product **119** along with a complex mixture of compounds (Table 23, Entry 5). We decided to increase the reactivity of the system by switching from a bromo / chloro substitution pattern to an iodo / bromo system. This should increase the favourability of the final *intra*-molecular cyclisation step occurring. The 'bromo-amide' **121** was synthesised in an analogous fashion to the 'chloro' system **118** (Scheme 75) in a 73% yield. This amide was then exposed to a variety of cyclisation conditions, the results of which are summarised in Table 24.

Table 24: Enolate coupling reactions

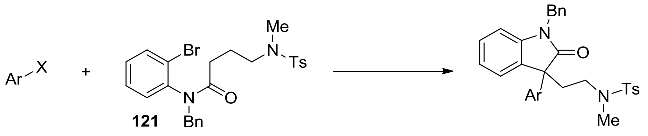


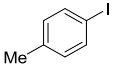
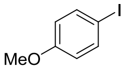
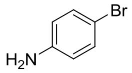
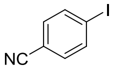
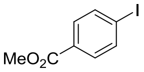
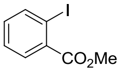
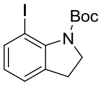
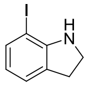
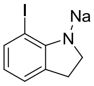
Entry	Catalyst	Yield [%]
1	PEPPSI	Trace
2	**$([tBu_3P]PdBr)_2$**	**70**
3	$([tBu_3P]PdBr)_2^a$	0
4	[(*R*,*S*)-SL-J009-1]$PdCl_2$	0
5	[(±)-BINAP]$PdCl_2$	0

Conditions: 4-Iodotoluene (1.0 eq), **121** (1.1 eq), KHMDS (3.0 eq), ligand complex (5 mol%), PhMe [0.05 M], 100 °C, 24 h. ^{a}Dioxane

Our screening highlighted a pre-complex of palladium(I) bromide and tri-*tert*-butylphosphine as being particularly active for our desired transformation. The majority of reactions only yielded un-reacted starting amide **121**; however, our most successful conditions afforded our desired oxindole **120** in a 70% yield. Following this success, the functional group compatibility of the reaction was investigated (Table 25).

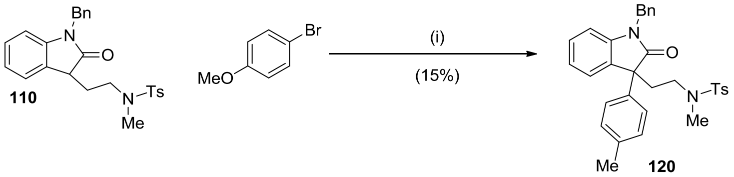
Table 25: Substrate scope



Entry	Ar-X	Yield [%]
1		**70**
2		43
3		0
4		0
5		0
6		0
7		0
8		0
9	 [a]	0

Conditions: **121** (1.1 eq), Ar-X (1.0 eq), NaHMDS (3.0 eq), ([*t*Bu$_3$P]PdBr)$_2$ (5 mol%), PhMe [0.22 M], 100 °C, 2 h. [a]Prepared using 7-iodoindoline and NaH in THF at reflux.

Unfortunately, free NH groups, bulky substituents and all indoline based coupling partners only yielded recovered amide. Surprisingly, electron-poor aryl halides gave only recovered starting material (Table 25, Entries 4-6). In most of the successful reactions we observed some levels of ring closure to the secondary oxindole **110** prior to addition of the second aryl unit. The formation of this secondary oxindole could be minimised by the addition of the amine to a mixture of the other reagents (as opposed to adding the iodo-toluene last). However, in a control experiment it was observed that using these reaction conditions, the secondary oxindole product **110** could be coupled directly with 4-iodotoluene in a modest 15% yield (Scheme 76). This suggests that the reaction proceeds through a mixed pathway involving both *inter* and *intra*-molecular couplings as the first step.

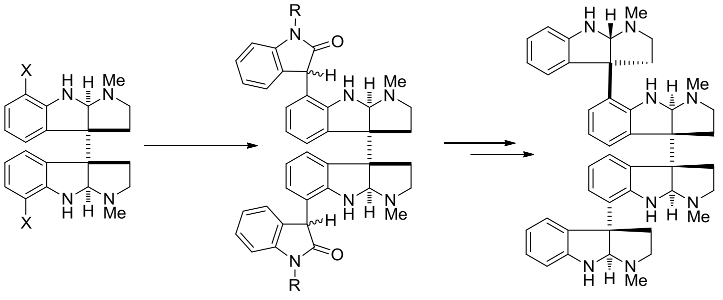


Scheme 76: Conditions: **110** (1.1 eq), 4-iodotoluene (1.0 eq), NaHMDS (3.0 eq), ([tBu$_3$P]PdBr)$_2$ (5 mol%), PhMe [0.22 M], 100 °C, 2 h.

Subsequent to our investigations in this area, Zhang and co-workers published a paper utilising similar methodology in a synthesis of esermethole and its analogues.[221]

6.1.3 Secondary Oxindoles

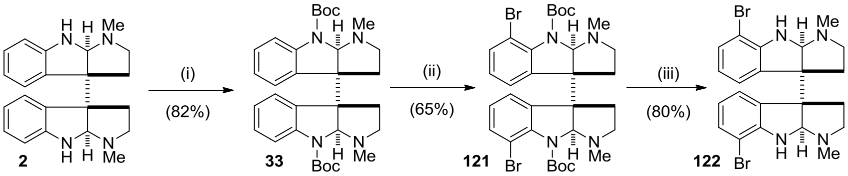
Following our limited success with the coupling of substituted oxindoles and substituted oxindole precursors directly, we returned to our original *alpha*-arylation of un-substituted oxindoles (Scheme 67).[177] We envisaged that such a reaction would be less effected by the inherent bulk of our chimonanthine derived system. With an oxindole moiety in place, subsequent reactions with electrophiles could facilitate the formation of the final cyclotryptamine segment. As noted previously there are numerous procedures reported in the literature for the asymmetric installation of a side-chain to 3-subsituted oxindoles (see section 1.2.6). To model this reaction we decided to use a symmetric system for ease of characterisation and its almost identical reactivity to our desymmetrized product. It is worth noting that the symmetric product could potentially be utilised in a synthesis of quadrigemine C **6** (Scheme 77).



quadrigemine C (**6**)

Scheme 77: Proposed synthesis of quadrigemine C **6**

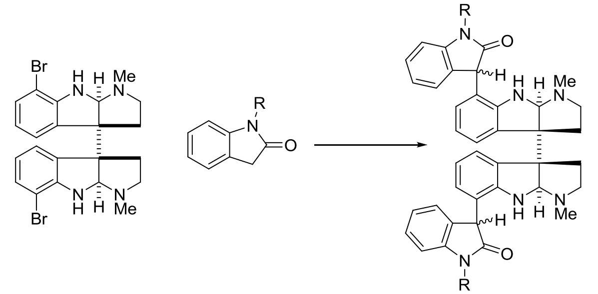
The *meso*-dibromide **122** core was synthesised in three high yielding steps from *meso*-chimonanthine **2** *via* the well precedented *ortho*-lithiation protocol shown in Scheme 78.



Scheme 78: Conditions: (i) *meso*-Chimonanthine **2** (1.0 eq), Boc_2O (2.5 eq), NaHMDS (4.5 eq), THF [0.32 M], rt, 2 h. (ii) *meso-bis*-Boc-chimonanthine **33** (1.0 eq), s-BuLi (4.0 eq), TMEDA (6.0 eq), dibromoethane (10.0 eq), Et_2O [0.39 M], -78 – 0 °C, 2 h. (iii) *meso*-Dibromo-*bis*-Boc-chimonanthine **121** (1.0 eq), TMSOTf (6.0 eq), DCM [0.30 M], rt, 16 h.

With the *meso*-dibromide **122** in hand we subjected it to our *alpha*-arylation conditions; initially we used un-protected oxindole as the coupling partner, regrettably this failed to yield any of the desired product. However, when *N*-protected systems were utilised, the reaction proceeded in high yields, to the order of 70–90% (Table 26). These products were isolated as an inseparable mixture of diastereoisomers; presumably the newly formed stereocentres can be readily racemised under fairly mild conditions.

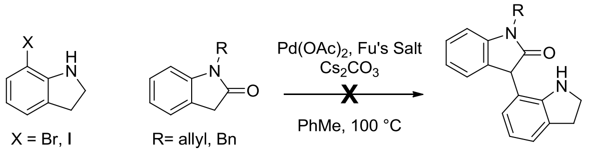
Table 26: *alpha*-arylation



Entry	R	Yield [%][a]
1	H	0
2	Bn	73
3	**Allyl**	**92**

Conditions: *meso*-Dibromo-chimonanthine **122** (1.0 eq), Pd(OAc)$_2$ (5 mol%), Fu's Salt (10 mol%), oxindole (2.2 eq), Cs$_2$CO$_3$ (6.0 eq), PhMe [0.05 M], 100 °C, 3 h. [a]Isolated as a mixture of diastereoisomers.

For the sake of streamlining future experimentation, we attempted to generate a simpler model by carrying out the same *alpha*-arylation using a 7-halo-indoline system. To our surprise using identical conditions to those outlined in Table 26 we were unable to obtain any product using 7-bromo or 7-iodoindoline with either *N*-allyl or *N*-benzyloxindole (Scheme 79).

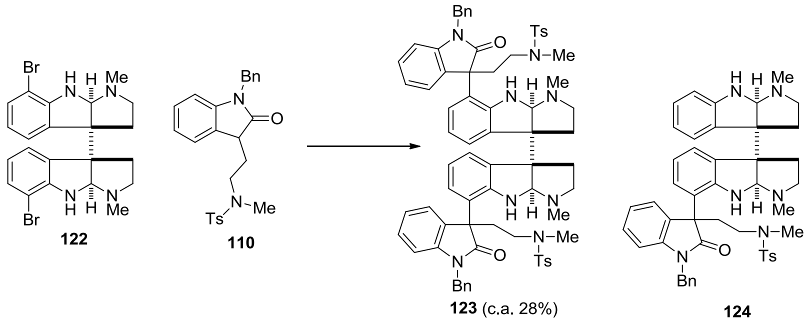


Scheme 79: Failed *alpha*-arylation of indolines

6.1.4 Tertiary Oxindoles Revisited

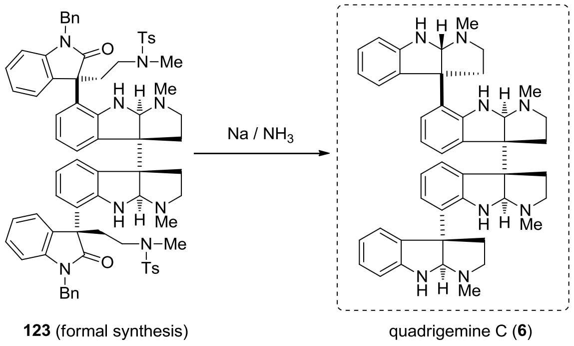
From this unforeseen result (Scheme 79) we drew the conclusion that very subtle steric and electronic factors were at play during the coupling reaction, perhaps involving co-ordination of the catalyst to the amine functionality of *meso*-chimonanthine. We were forced to re-evaluate our previous conclusions that forming the final quaternary centre in a single step could not be achieved *via* this chemistry (Table 25). The *meso*-dibromide

122 was re-subjected to our *alpha*-arylation conditions, this time using a tryptamine derived oxindole coupling partner. When oxindoles bearing no substitution on the oxindole nitrogen were used, again we only recovered starting materials, a result in keeping with our previous observations (Table 26). To our delight, when we utilised benzyl protected oxindole **110** we managed to isolate appreciable quantities of the *mono*- and *bis*-arylated products **123** and **124** (Scheme 80). Unfortunately, due to the presence of a complex mixture of diastereoisomers, as well as difficulty separating the *mono*- and *bis*-products, we were unable to precisely confirm either the structure or yield of the products from this reaction.



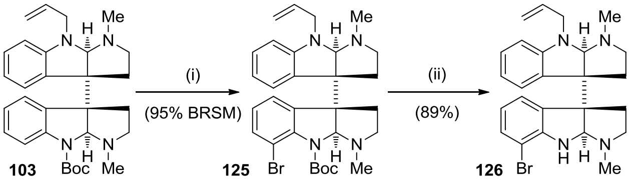
Scheme 80: Conditions: *meso*-Dibromo-chimonanthine **122** (1.0 eq), Pd(OAc)$_2$ (5 mol%), Fu's Salt (10 mol%), oxindole (2.5 eq), Cs$_2$CO$_3$ (6.0 eq), PhMe [0.05 M], 100 °C, 20 h. *Mono*-product appeared to have de-brominated.

It is worth noting that, assuming the transformation can be achieved in an enantioselective fashion, the product from this reaction would constitute a formal synthesis of quadrigemine C **6**(Scheme 81).[222]



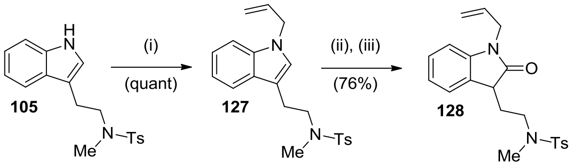
Scheme 81: Final step in Overman *et al'*s total synthesis of quadrigemine C **6**

These promising results prompted further investigation, this time on our desymmetrized material. Bromine was installed at the C-7 position of *N'*-Boc-*N*-allyl-chimonanthine **103** *via* a directed *ortho*-lithiation reaction; this proceeded in a 53% yield on ~1.5 g scale (75% based on recovered starting material). Recovered **103** was re-subjected to the reaction conditions yielding a second batch of **125** in a 61% yield (95%, BRSM). The Boc directing group was removed quantitatively using TMS-triflate (gram scale).[15] The crude product from this cleavage was sufficiently pure to be used in subsequent reactions without chromatography (Scheme 82).



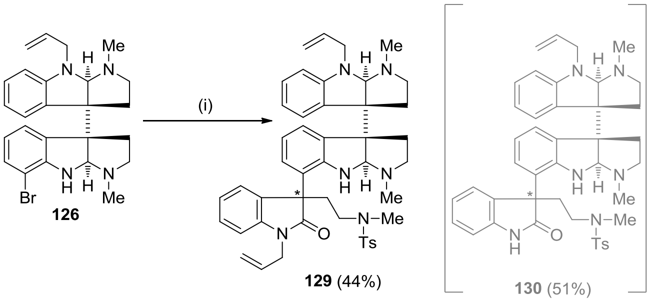
Scheme 82: Conditions: (i) *N'*-Boc-*N*-allyl-chimonanthine **103** (1.0 eq), TMEDA (3.0 eq), s-BuLi (2.5 eq), dibromoethane (4.0 eq), Et_2O [0.04 M], -78 – 0 °C, 1.5 h. (ii) 7'-Bromo-*N'*-Boc-*N*-allyl-chimonanthine **125** (1.0 eq), TMSOTf (2.5 eq), DCM [0.06 M], rt, 3 h.

To facilitate an efficient global de-protection strategy we opted to use an *N*-allyl group on our oxindole unit; it is also worth noting that in our model reactions *N*-allyl protection gave a *ca.* 20% increase in yield relative to *N*-benzyl (Table 26). We synthesised the desired oxindole **128** in good yields *via* our NBS / water / $NaBH_4$ oxidation protocol (Scheme 83).



Scheme 83: Conditions: (i) *N*-Methyl-*N*-tosyl-tryptamine **105** (1.0 eq), KO*t*Bu (1.2 eq), allylbromide (1.5 eq), THF [0.06 M], rt, 16 h. (ii) *N*'-Allyl-*N*-methyl-*N*-tosyl-tryptamine **127** (1.0 eq), NBS (2.4 eq), H_2O (4.0 eq), *t*BuOH : THF [1:1, 0.1 M], rt, 30 min. (iii) $NaBH_4$ (6.0 eq).

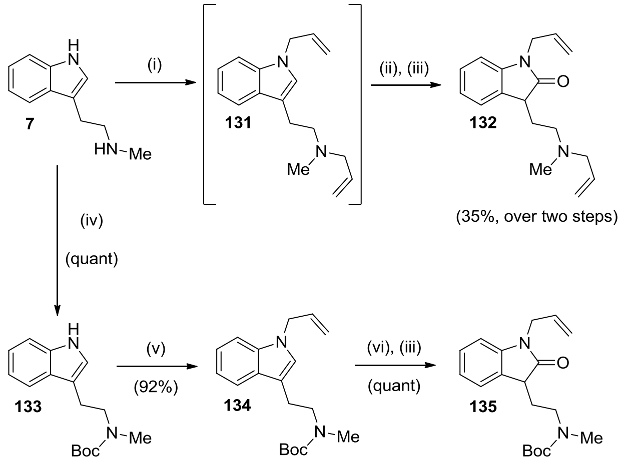
Subjecting the desymmetrized aryl halide **126** to our reaction conditions generated the desired C-7–C-3a linkage in a modest 44% yield. An additional compound was isolated which appeared to correspond to *mono*-de-allyllated product **130** (based on fragmentation in LRMS), presumably as a result of palladium catalysed deprotection with the excess oxindole although the identity of this product could not be confirmed (Scheme 84).



Scheme 84: Conditions: (i) 7'Br-*N*-allyl-chimonanthine **126** (1.0 eq), oxindole **128** (2.0 eq), Cs_2CO_3 (6.0 eq), $Pd(OAc)_2$ (5 mol%), Fu's Salt (10 mol%), PhMe [0.05 M], 100 °C, 16 h.

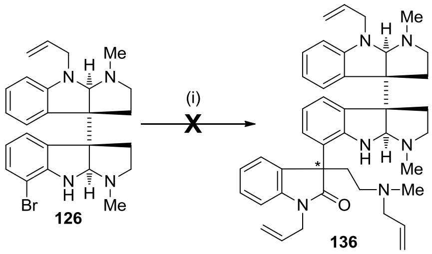
Pleasingly the product from this reaction appeared to be a single diastereoisomer (^{1}H NMR). Although the relative configuration of this final quaternary chiral centre remains unknown, we hoped that the configuration adopted in the natural product would be thermodynamically more favourable. Once de-allylated this compound should be readily transformed into hodgkinsine **3** *via* the reductive protocol described by Overman *et al.*[176] Overman and co-workers reported a relatively poor yield for the final steps in their synthesis *ca.* 29% (Scheme 13); admittedly, these involved numerous transformations which in part must account for this low yield. Their final cascade sequence consisted of a benzyl and tosyl cleavage followed by a reductive amination; all facilitated by Na / NH_3.[176] We predicted that their low yield may have arisen from the necessity to cleave the tosyl group prior to reductive amination. To circumvent this issue we devised complimentary strategies that would allow us to cleave the amine protecting group prior to reductive amination. The choice of amine protecting group was vital; we selected Boc, as we knew the molecule was tolerant to its cleavage with TMSOTf, and allyl, as this could be used in a global deprotection strategy.

The oxindoles were prepared in an analogous manner to our benzyl / tosyl system; it is worth noting that the Boc example **135** was prepared from commercial starting materials in a near quantitative yield without chromatography (Scheme 85).



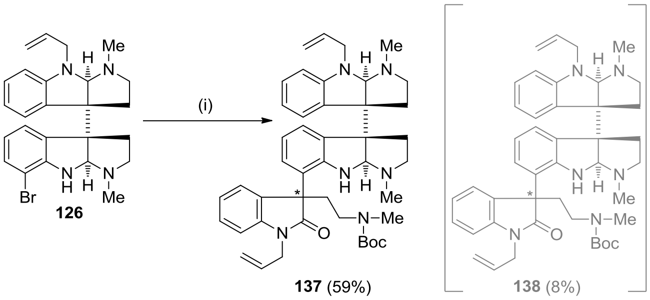
Scheme 85: Conditions: (i) *N*-Methyl-tryptamine **7** (1.0 eq), KO*t*Bu (2.4 eq), allylbromide (3.0 eq), THF [0.1 M], rt, 16 h. (ii) *N*,*N'*-Allyl-*N*-methyl-tryptamine **131** (1.0 eq), NBS (2.4 eq), H_2O (4.0 eq), *t*BuOH : THF [1 : 1, 0.1 M], rt, 30 min. (iii) $NaBH_4$ (6.0 eq). (iv) *N*-methyl-tryptamine **7** (1.0 eq), Boc_2O (1.2 eq), Et_3N (3.0 eq), THF [0.2 M], rt, 1.5 h. (v) *N*-Boc-*N*-methyl-tryptamine **133** (1.0 eq), KO*t*Bu (1.2 eq), allylbromide (1.5 eq), THF [0.1 M], rt, 2 h. (vi) *N'*-Allyl-*N*-Boc-*N*-methyl-tryptamine **134** (1.0 eq), NBS (2.4 eq), H_2O (4.0 eq), *t*BuOH : THF [1 : 1, 0.1 M], rt, 30 min.

We exposed the *bis*-allyl-oxindole **132** to our *alpha*-arylation conditions, after 2 h all the aryl halide **126** appeared to have been consumed; however, there was also no evidence of product formation (Scheme 86).



Scheme 86: Conditions: 7’Br-*N*-allyl-chimonanthine **126** (1.0 eq), oxindole **132** (1.7 eq), Cs_2CO_3 (6.0 eq), $Pd(OAc)_2$ (5 mol%), Fu’s Salt (10 mol%), PhMe [0.05 M], 100 °C, 2 h

Pleasingly, the allyl / Boc-oxindole **135** proved a good coupling partner, giving the *alpha*-arylated product **137** in yields to the order of 60%. In addition we isolated small amounts of what appeared to be the other diastereoisomer **8**, although we were unable to confirm its precise identity (Scheme 87).

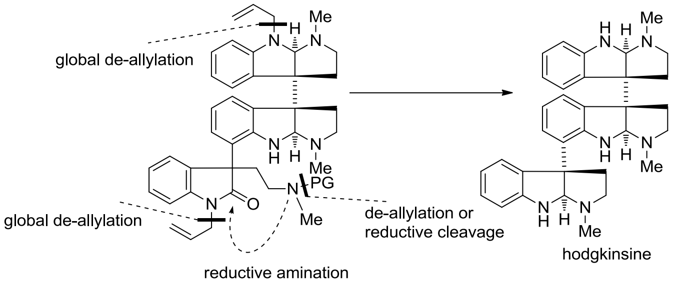


Scheme 87: Conditions: (i) 7’Br-*N*-allyl-chimonanthine **126** (1.0 eq), oxindole **135** (2.0 eq), Cs_2CO_3 (6.0 eq), $Pd(OAc)_2$ (5 mol%), Fu’s Salt (10 mol%), PhMe [0.05 M], 100 °C, 2 h.

Unfortunately for all examples we remained unable to determine the relative stereochemistry of the newly formed quaternary centre. Although we hoped that the intrinsic chirality of the molecule would impart the correct stereochemical-information on this newly formed stereocentre. Options remained open for switching it’s configuration by the use of chiral ligands in the *alpha*-arylation reaction. We are currently attempting to identify the major bi-products from these reactions; hopefully the added insight will allow us to avoid their formation and increase the overall yield.

7.0 End Game

With the final tryptamine unit in place, theoretically only three major steps were necessary in order to complete the total synthesis. Namely: global deprotection of the indoline / oxindole protecting groups, (cleavage of the tosyl or Boc group) and a reductive aminiation to generate the third cyclotryptamine unit.



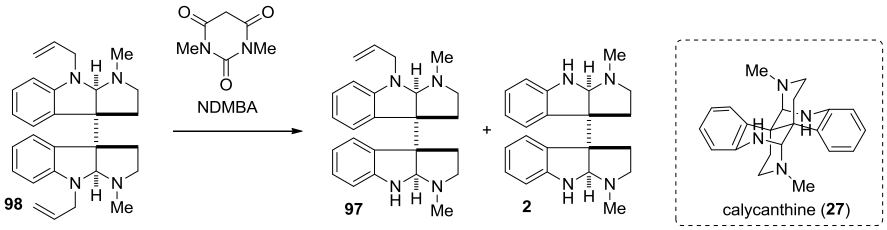
Scheme 88: End game strategy

7.1 Global Deprotection / Reductive Amination

7.1.1 Allyl Cleavage

A plethora of de-allylation protocols exist in the literature; these generally involve a double bond isomerisation and subsequent hydrolysis, radical reactions or procedures where the amine acts as a leaving group in organometallic and polar processes.[208,223,224] To model these deprotection reactions we chose *meso-N,N*'-diallyl-chimonanthine **98** (a bi-product of our previous desymmetrization); this substrate should quickly reveal if the conditions will affect our targets acid sensitive core. Exposure to acid is known to give rise to the thermodynamically favoured rearrangement product calycanthine **27**.[19] One of the most attractive strategies was a tandem *alpha*-arylation / deprotection procedure possibly utilising palladium catalysis. Here, a palladium π-allyl intermediate is attacked by a suitable carbon nucleophile (e.g. 1,3-dimethylbarbituric acid, NDMBA) in an irreversible fashion to expose the free amine Table 27.[208]

Table 27: Model global deprotection

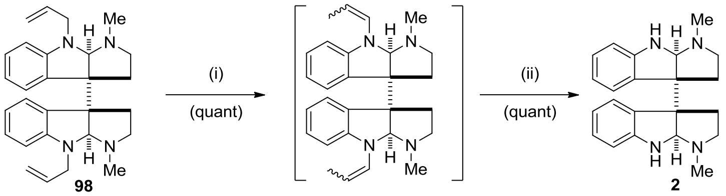


Entry	NDMBA [eq]	T [h]	Yield **97** [%]	Yield **2** [%]
1	4[a]	24	23	10
2	4	24	42	Trace
3	10	24	Complex mixture	Complex mixture

Conditions: *meso-N,N′*-diallyl-chimonanthine **98** (1.0 eq), NDMBA, $Pd(OAc)_2$ (5 mol%), Fu's Salt (10 mol%), PhMe [0.06 M], 100 °C. [a]Cs_2CO_3 (6.0 eq).

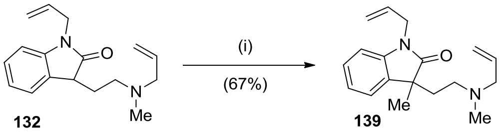
Pleasingly the conditions did indeed appear to cleave the allyl protecting groups; the products were generally isolated as a mixture of *mono* **97** and *bis* de-allylated material **2**, with the residual mass being made up of un-reacted starting material **98**. Unfortunately none of the conditions gave complete conversion, our best result utilised 4 eq of NDMBA to give *N*-allyl-chimonanthine **97** in a modest 42% yield. The products of this deprotection were also accompanied by a complex mixture of bi-products. Generally the rearrangement of chimonanthine **2** to calycanthine **27** is facilitated by acetic acid whose pKa is comparable to that of NDMBA (4.76 *vs* 4.70, H_2O). It was encouraging to observe that, by ^{1}H NMR spectrometry, there was no evidence that any of the components of the reaction underwent re-arrangement to the *centro*-symmetric calycanthine **27** form.

Numerous other conditions could be compatible with our *alpha*-arylation step. We investigated the practicality of isomerisation of the allyl group into a vinyl group and subsequent hydrolysis. Addition of the strong base, potassium *tert*-butoxide failed to yield any product (in toluene), however, when DMSO was used as the solvent the compound appeared to quantitatively isomerise. Disappointingly, hydrolysis *via* aqueous work-up or exposure to SiO_2 failed to yield any *meso*-chimonanthine **2** (the vinyl groups remained intact). Treatment with ammonium chloride solution also failed to perform the desired hydrolysis. Finally, brief exposure of the enamine to 1 M HCl solution resulted in complete cleavage of the protecting groups and no evidence of rearrangement (Scheme 89).



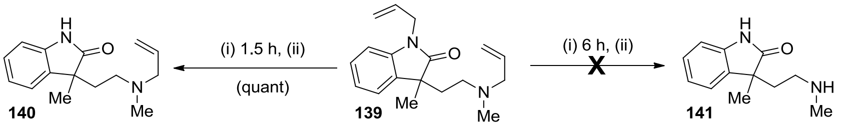
Scheme 89: Conditions: (i) *meso-N,N'*-Diallyl-chimonanthine **98** (1.0 eq), KO*t*Bu (6.0 eq), DMSO [0.23 M], 100 °C, 16 h. (ii) $HCl_{(aq)}$ (1 M), rt, 20 min then $NaHCO_{3(aq)}$.

To ascertain the robustness of this deprotection strategy, we synthesised a model of the final oxindole unit. This was made by exposing the *bis*-allyl-oxindole **132** synthesised previously (Scheme 85) to iodomethane under basic conditions (Scheme 90).



Scheme 90: *bis*-Allyloxindole **132** (1.0 eq), *n*-BuLi (2.2 eq), TMEDA (3.3 eq), MeI (1.5 eq), THF [0.07 M], -78 – 0 °C, 2 h.

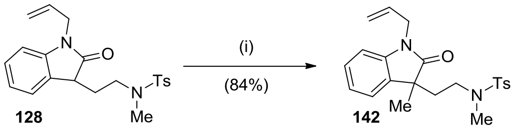
With the model system **139** in hand we subjected it to our de-allylation conditions; we observed that after 1.5 h there was a quantitative chemoselective cleavage of the oxindole allyl group. In an effort to achieve the desired global deprotection, the reaction time was increased to 6 h; regrettably this only resulted in a complex mixture of products. Unfortunately, although the chimonanthine core appeared stable to extended reaction times *ca.* 16 h (Scheme 89), the oxindole unit was not (Scheme 91).



Scheme 91: *bis*-Allyl-3-methyl-oxindole **139** (1.0 eq), KO*t*Bu (6.0 eq), DMSO [0.23 M], 100 °C. (ii) $HCl_{(aq)}$ (1 M), DCM, rt, 20 min then $NaHCO_{3(aq)}$.

7.1.2 Reductive Cyclisation and the Formal Synthesis of Desoxyeseroline

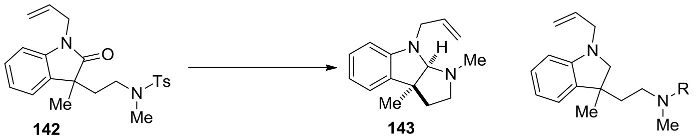
We returned to the original allyl / tosyl protecting group strategy, a similar 3-methyl substituted oxindole compound **142** was selected to model the reductive tosyl cleavage / amination. This was prepared in an analogous fashion to the *bis*-allyl version (Scheme 92).



Scheme 92: Tosyl-allyloxindole **128** (1.0 eq), *n*-BuLi (2.2 eq), TMEDA (3.3 eq), MeI (1.5 eq), THF [0.07 M], -78–0 °C, 2 h.

The model system was subjected to a variety of reductive conditions; hydride sources such as $LiAlH_4$ and Red-Al cleanly reduced the lactam to the indoline prior to tosyl cleavage (Red-Al), thus preventing formation of our desired cyclotryptamine **143**; when using $LiAlH_4$ the tosyl group remained intact (Table 28). The *alpha*-arylated natural product precursor was subjected to the same Red-Al conditions; again we observed carbonyl reduction and no indication of tosyl cleavage.

Table 28: Model reductive cyclisation

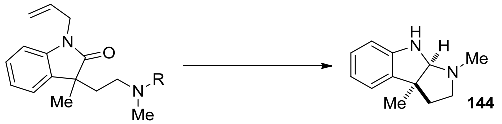


Entry	Reducing Agent	Yield **143** [%]	Yield [%] (R)
1	$LiAlH_4$	0	83 (Ts)
2	Red-Al	0	90 (H)

Conditions: **142** (1.0 eq), reducing agent (6.0 eq), PhMe [0.06 M], 100 °C, 16 h.

A reductive amination strategy for the synthesis of cyclotryptamine natural products is common in the literature. From early work on the synthesis of physostigmine **32** and related alkaloids[65] to the recent synthesis of hodgkinsine **3** by the Overman group,[176] dissolving metal reductions have proved effective. Such reactions are not only capable of performing the desired reductive amination,[222] but can also cleave *N*-tosyl and *N*-allyl groups.[225] This should enable a global deprotection and cyclisation in a single operation from either our tosyl or allyl systems (Table 29).

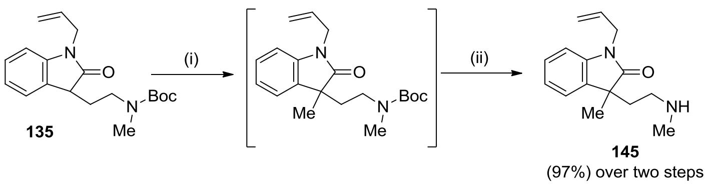
Table 29: Model reductive cyclisation



Entry	R	Metal	Radical Carrier	Yield [%]
1	Allyl	Na	$C_{10}H_8$	0
2	Tosyl	Na	$C_{10}H_8$	0
3[a]	Tosyl	Na	NH_3	0
4	Tosyl	Li	$C_{10}H_8$	0

Conditions: Oxindole (1.0 eq), metal (30.0 eq), radical Carrier (15.0 eq), THF [0.01 M], 0 °C, 30 min, NH_4Cl quench. [a]Oxindole (1.0 eq), metal (30.0 eq), THF [0.01 M] & $NH_{3(l)}$ [~0.003 M], -78 °C, 15 min, NH_4Cl quench.

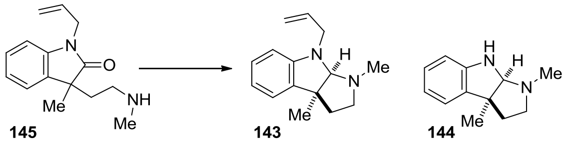
Unfortunately despite indication of allyl and tosyl cleavage occurring in these reactions (^{1}H NMR spectrometry), there was no evidence that we formed any of the desired cyclotryptamine **144**. As mentioned previously, in Overman's syntheses of cyclotryptamine alkaloids, yields for the final global deprotection / reductive amination were low. As our attempts to achieve a global de-allylation prior to cyclisation, in order to facilitate a more facile reductive amination, were unsuccessful (Scheme 91). We hoped that a more labile protecting group would be tolerated which would replace the problematic second allyl unit. A model was synthesised from allyl / Boc oxindole **135** (Scheme 85) which was readily methylated at the 3-position under basic conditions; the crude product was treated with TMSOTf , cleanly cleaving the Boc group (Scheme 93).



Scheme 93: Conditions: **135** (1.0 eq), *n*-BuLi (2.2 eq), TMEDA (3.3 eq), MeI (1.5 eq), THF [0.07 M], -78–0 °C, 2 h. (ii) TMSOTf (2.2 eq), DCM [0.07 M], rt, 1 h.

With the free amine oxindole **145** in hand, we subjected it to an assortment of reductive conditions (Table 30). The reductive amination proceeded smoothly with hydride sources, albeit in modest yield, to generate the desired cyclotryptamine ring system **143**. Attempts to effect a tandem process utilising sodium metal proved unsuccessful, with no evidence of the product being observed by ^{1}H NMR spectrometry (Table 30, Entry 3).

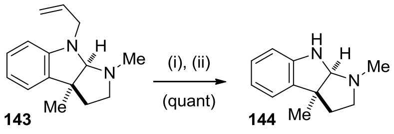
Table 30: Model reductive cyclisation



Entry	Reductant	T [°C]	Yield **143** [%]	Yield **144** [%]
1	$LiAlH_4$ / THF	reflux	32	0
2	**Red-Al / PhMe**	**reflux**	**62**	**0**
3	Na / $C_{10}H_8$ / THF	0	0	0

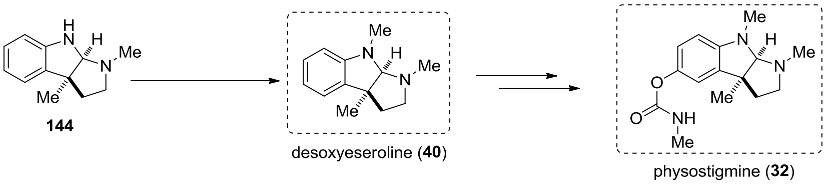
Conditions: (Entries 1 & 2) **145** (1 eq), [R] (4 eq), solvent [0.1 M], 1.5 h. (Entry 3) **145** (1.0 eq), Na (20 eq), $C_{10}H_8$ (1.0 eq), THF [0.1 M], 2 h.

The cyclotryptamine product was subjected to our de-allylation conditions (KO*t*Bu, DMSO) which cleanly cleaved the *N*-allyl group in a quantitative yield without the need for chromatography (Scheme 94).



Scheme 94: Conditions: (i) *N*-Allyl-desoxyeseroline **143** (1.0 eq), KO*t*Bu (6.0 eq), DMSO [0.23 M], 100 °C, 16 h. (ii) $HCl_{(aq)}$ (1 M), DCM, rt, 20 min then $NaHCO_{3(aq)}$.

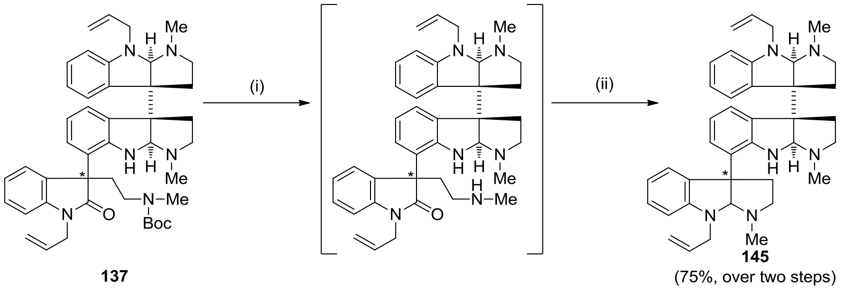
The synthesis of cyclotryptamine **144** constitutes a formal synthesis of desoxyeseroline **40**,[226] and therefore a formal synthesis of physostigmine **32**[227] (Scheme 95).



Scheme 95: Formal synthesis of desoxyeseroline **40** and physostigmine **32**

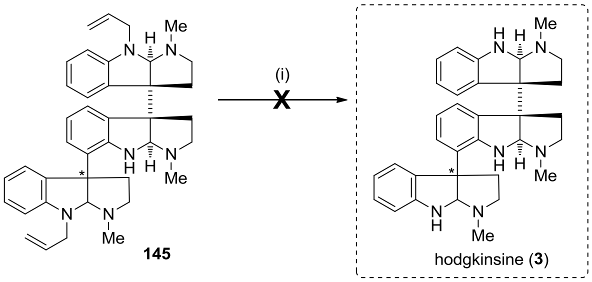
7.1.3 The Enatioselective Total Synthesis of Hodgkinsine B

The success of this strategy led us to pursue it as a possible means of completing the total synthesis. Exposure of the *alpha*-arylated product **137** synthesised previously to TMSOTf appeared to smoothly generate the free amine. However, isolation of this free amine proved problematic. Fortunately we found that the crude amine could readily close to form the desired cyclotryptamine **145** in an excellent yield in the presence of $LiAlH_4$; surprisingly the use of Red-Al gave no product (Scheme 96).



Scheme 96: Conditions: (i) *N*-Boc-amine **137** (1.0 eq), TMSOTf (2.2 eq), DCM [0.03 M], 16 h. (ii) Oxindole (1.0 eq), $LiAlH_4$ (3.7 eq), THF [0.02 M], reflux 1.5 h.

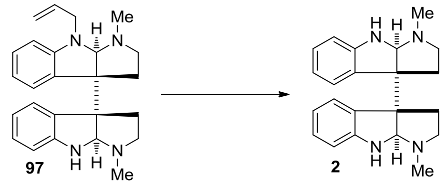
This ring-closure completes the tri-cyclotryptamine skeleton of hodgkinsine; unfortunately, at this stage the relative stereochemistry of the final cyclotryptamine unit remained unknown. Now only the seemingly trivial de-allylation remained in the synthetic sequence. To our immense disappointment, when we exposed *N,N''-bis*-allyl-hodgkinsine **145** to our de-allylation conditions, we only recovered a complex mixture of products.



Scheme 97: Conditions: (i) *N,N''-bis*-Allyl-hodgkinsine **145** (1.0 eq), KO*t*Bu (6.0 eq), DMSO [0.23 M], 100 °C, 16 h. (ii) $HCl_{(aq)}$ (1 M), DCM, rt, 20 min then $NaHCO_{3(aq)}$.

The complete absence of any evidence of product (^{1}H NMR spectroscopy comparison to literature spectra) caused us to re-investigate the plethora of de-allylation protocols described in the literature.[223] We theorised that the free secondary amine could be in part to blame for the observed reactivity, and as a result we selected *N*-allyl-chimonanthine **97** as a model substrate (Table 31).

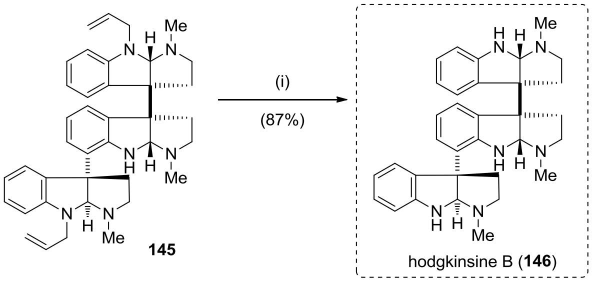
Table 31: Model De-allylation screen



Entry	Conditions	Yield [%][a]
1	**KO*t*Bu, DMSO, 100 °C, 3 h, HCl quench**	**80**
2	NaOH, DMSO, 100 °C, 4 h, HCl quench	Trace
3	$RhCl(PPh_3)_3$, DABCO, EtOH/H_2O, 100 °C ,2 h	Trace
4	$RhCl(PPh_3)_3$, DABCO, EtOH/H_2O, 100 °C ,6 h	Trace
5	$RhCl(PPh_3)_3$, MeCN/H_2O, 100 °C ,5 h	Trace
6	$RhCl_3{\cdot}3H_2O$, EtOH/H_2O, 100 °C ,4 h	Trace
7	$HRh(CO)(PPh_3)_3$, THF, reflux, 6 h	0
8	Grubbs I, PhMe, reflux, 6 h	Trace
9	Grubbs II, DCM, rt, 20 h, HCl quench	Trace
10	Pd/C, Ethanolamine, EtOH, 16 h, HCl quench	Trace
11	**Na / NH_3, THF, -78 °C, 1 h, NH_4Cl quench**	**70**

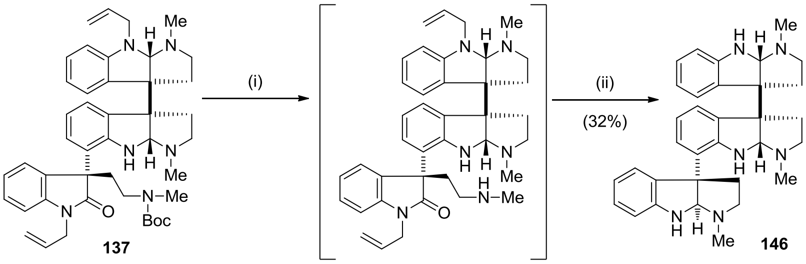
[a] Measured by ^1H NMR

The majority of transition metal-catalysed conditions only yielded un-reacted *N*-allyl-chimonanthine **97**; we postulated that for these processes the free amine could coordinate to the catalyst rendering it inactive (Table 31, Entries 2-10). Surprisingly our original conditions (KO*t*Bu, DMSO) yielded clean product **2**, with the free amine seemingly having no effect (Table 31, Entry 1). Why we only recovered a complex mixture of products when trying to de-allylate *N,N''-bis*-allyl-hodgkinsine **145** remains a mystery. However, sodium metal in condensed ammonia cleanly cleaved the allyl groups to regenerate *meso*-chimonanthine **2** (Table 31, Entry 11). Encouraged by this result we subjected *N,N''-bis*-allyl-hodgkinsine **145** to the same reductive conditions, and de-allylation proceeded smoothly and the natural product was isolated in an 87% yield. Regrettably, analysis of the product by ^1H NMR spectroscopy identified it as hodgkinsine-B **146**, showing that our *alpha*-arylation yielded the undesired diastereoisomer. The optical rotation for our synthetic (-)-hodgkinsine B **146** matched the literature data ($[\alpha]_D^{25.0}$ -55.6, lit $[\alpha]_D^{27.0}$ -55.0). This indicates that the absolute stereochemistry assigned by X-ray crystallography was erroneous and that our stereochemical assignment established *via* the kinetic resolution of (±)-C_2-chimonanthine **13** was correct (Scheme 98). We therefore require (*S*,*S*)-DACT-phenyl-Trost ligand to synthesise the correct enantiomer of hodgkinsine **3**. These results show that, in our hands, application of the 'cartoon' model of Trost and co-workers was inadequate for use in such a complex system. We hoped that the more sophisticated hydrogen bonding model of Llyod-Jones *et al.* may be more applicable to our system.[228]



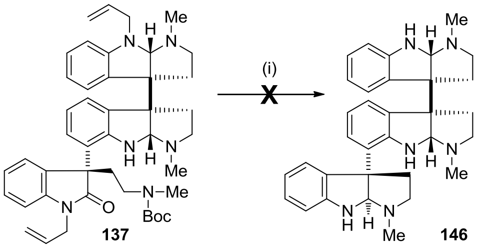
Scheme 98: Conditions: (i) *N,N''-bis*-Allyl-hodgkinsine **145** (1 eq) in THF [0.014 M], added to Na (60 eq), $NH_{3(l)}$ [0.004 M, relative to *N,N''-bis*-Allyl-hodgkinsine], -78 °C, 2 h, $NH_4Cl_{(s)}$ quench.

Before tackling the issue of diastereoselectivity, we attempted to improve the efficiency of our final synthetic sequence. Efforts focused on using a sodium metal reduction to effect the reductive amination as well as the global de-allylation. Pleasingly subjecting the crude product from our Boc cleavage to the reductive conditions afforded hodgkinsine-B **146** in a modest 32% yield (Scheme 99). It is worth noting that the same transformation utilising $LiAlH_4$ then Na/NH_3 generated the product in a 65% yield.



Scheme 99: Conditions: (i) *N*-Boc-amine **137** (1.0 eq), TMSOTf (2.2 eq), DCM [0.03 M], 16 h. (ii) Oxindole (1.0 eq) in THF [0.014 M], added to Na (100 eq), $NH_{3(l)}$ [0.004 M, relative to the oxindole], -78 °C, 1 h, $NH_4Cl_{(s)}$ quench.

Attention is drawn to a review article by Overman *et al.* where it was claimed that yields for similar Bouveault-Blanc reductions were doubled by the addition of *t*-BuOH (29% *vs* 53%). This increase this was not substantiated by published experimental evidence.[213] In an effort to shorten our synthesis further, we subjected our *alpha*-arylation product directly to the dissolving metal conditions. It was hoped this would cleave the Boc group, effect the reductive amination and remove the allyl groups in a single operation, unfortunately, this reaction only yielded a complex mixture of products (Scheme 100).

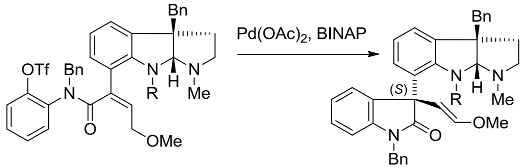


Scheme 100: (i) **137** (1.0 eq) in THF [0.014 M], added to Na (100 eq), $NH_{3(l)}$ [0.004 M, relative to the oxindole], -78 °C, 2 h, $NH_4Cl_{(s)}$ quench.

7.1.4 Diastereoselectivity Switch

Obtaining the undesired isomer, although disappointing was not entirely unexpected. Model reactions carried out by Overman *et al.* showed that in their asymmetric Heck couplings, there was a high degree of substrate control, favouring the un-desired isomer. However, the use of (*S*)-BINAP in their least sterically-encumbered system allowed them to obtain a 3:1 dr favouring the desired (*R*)-isomer (Table 32).

Table 32: Overman and co-workers asymmetric Heck model

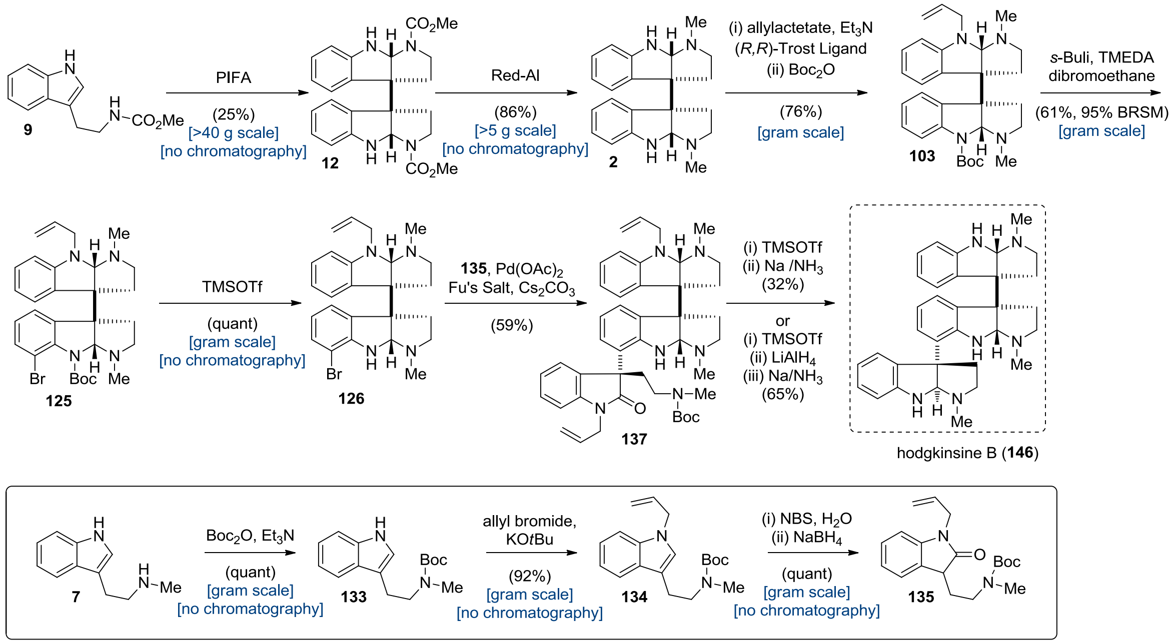


Entry	R	Ligand	*S:R*
1	Bn	(*R*)-BINAP	20:1
2	Bn	(*S*)-BINAP	6:1
3	H	(*R*)-BINAP	3:1
4	H	(*S*)-BINAP	1:3

We hoped that the use of a chiral ligand in our *alpha*-arylation would switch the diastereoselectivity of the reaction. Initial investigations using the BINAP derived ligand, MOP, provided promising results. By ^{1}H NMR spectrometry a new compound was identified with a molecular weight corresponding to the *alpha*-arylated product. However the alternative catalyst system appeared to favour de-halogenation of the product and we were only able to isolate trace amounts of *alpha*-arylated product by prep-TLC. Work in this area is on going.

7.2 Summary

Although we have yet to achieve our goal of a total synthesis of hodgkinsine **3**, we have developed a highly effective synthesis of hodgkinsine B **146**. Our route involves just six isolated intermediates and only four chromatographic operations; the overall yield for our longest linear sequence is 4%. Comparing our synthesis to that of Overman *et al.* our yield from *meso*-chimonanthine **2** is 18% (28% BRSM) *vs* 5% representing a ~4 fold increase in yield (Scheme 101).

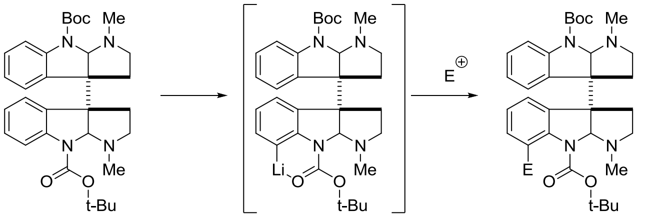


Scheme 101: Our enantioselective total synthesis of hodgkinsine B

Despite the dramatic increase in overall yield, our synthesis has several areas of inefficiency which we hoped to address, of these, including the comparatively low yield of our *alpha* arylation and the step intensive means utilised to install the halogen used in this reaction.

8.0 Optimisation: C-7 Functionalisation

To date probably the most widely used method for the installation of groups at the C-7 position relies on directed *ortho*-metallation.[64]

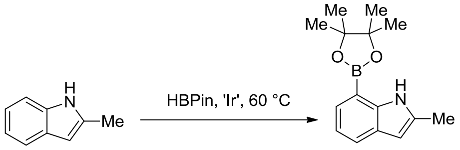


Scheme 102: *ortho*-Lithiation

As discussed previously, Overman and co-workers were able to use a Boc group to install an iodine atom at the C-7 position of *meso*-chimonanthine (Scheme 102). The generation of an aryl halide opens up the possibility of numerous transition metal catalysed C-C bond forming reactions; the Overman research group chose to use a Stille coupling in their synthesis of high order cyclotryptamine alkaloids. We have demonstrated the utility of our methodology for the *alpha*-arylation of oxindoles[177] with a synthesis of hodgkinsine-B. However, the initial installation of functionality at C-7 still relies on the directed *ortho*-lithiation protocol used by Overman *et al.* This is rather a lengthy process for a simple switch of a proton for a bromine atom and requires in essence four steps: installation of DMG, lithiation, bromination and removal of the DMG. A simple way to improve the step count of our synthesis would be eliminate some of these stages.

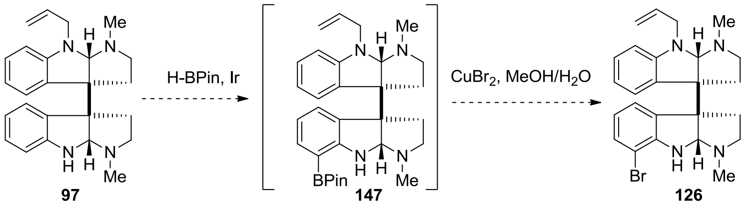
8.1 Direct C-H Functionalisation

Recently Smith and co-workers disclosed that they were able to directly borylate indoles at the C-7 position in the presence of an iridium catalyst. The group used the reaction to great effect on a variety of indole substrates (Scheme 103).[229]



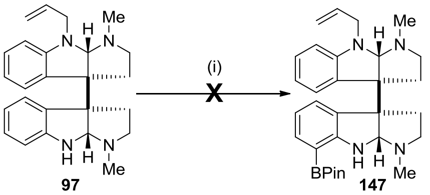
Scheme 103: Iridium catalysed functionalisation of 2-substituted indoles

Although no mention regarding the reactivity of indolines was made by the authors, we hypothesised that such a reaction could be used to directly borylate our desymmetrized material. Subsequently, Hartwig and co-workers reported that such boronic esters (synthesised using similar Ir catalysis) could be efficiently converted to halides using stoichiometric copper(II) halides.[230] Combined, these methodologies should allow direct halogenation at the C-7 position of our desymmetrized chimonanthine without the use of directing groups (Scheme 104).



Scheme 104: Proposed *ortho*-halogenation

A single experiment was carried out where we subjected *N*-allyl chimonanthine to the borylation conditions; regrettably after 20 h there was no evidence of any product (Scheme 105). Although this result does not altogether rule out this strategy, no further reactions were carried out in this area.



Scheme 105: Conditions: *N*-Allyl-chimonanthine **97** (1.0 eq), HBPin (1.8 eq), [Ir(OMe)(COD)]$_2$ (3 mol%, Ir), d*t*bpy (3 mol%), *n*-hexane [0.2 M], 60 °C, 20 h.

9.0 Bio-Mimetic Strategies

In nature, activating groups such as aryl halides or DMG's are not required for the installation of functionality at the C-7 position of tryptamine or indoline derived compounds. We hoped that by analysis of current biosynthetic hypotheses we could devise a more efficient synthetic strategy.

9.1 C-7 bond Formation via Tethered Cyclotryptamine Unit

Previously we discussed a widely accepted biosynthetic pathway for the production of polypyrrolidinoindoline alkaloids; this involved the formation of a radical at the C-3a position and subsequent dimerization to generate the chimonanthine core.[17] We also noted that the C-7 position is one of the least stable sites for a radical to form (Section 4.2). Based on this observation, we postulated that in nature the C-7 position is held in close proximity to additional cyclotryptamine units in such a way that the observed C-7 – C-3a linkage becomes the most favourable outcome (Fig. 20).

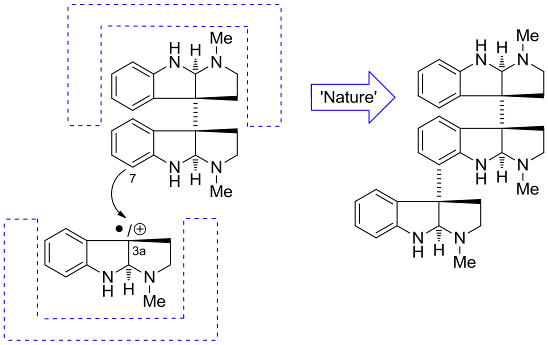
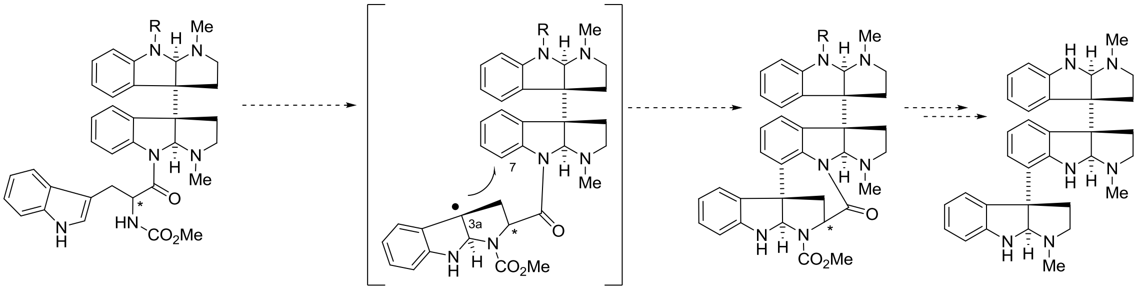


Fig. 20: Our proposed biosynthetic pathway for C-7 bond formation

In order to mimic this restricted configuration we proposed that a cyclotryptamine unit could be covalently tethered to a *meso*-chimonanthine core allowing us to form the desired C-C bond.

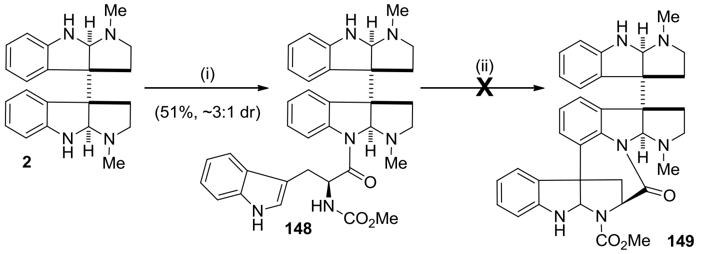
9.1.1 Tryptophan Linkage

Our initial strategy was to use the acid side chain from tryptophan to form an amide bond with the chimonanthine core; exposure of the resultant compound to our hypervalent iodine oxidative dimerization conditions should form the desired C-7 – C-3a bond (Scheme 106).



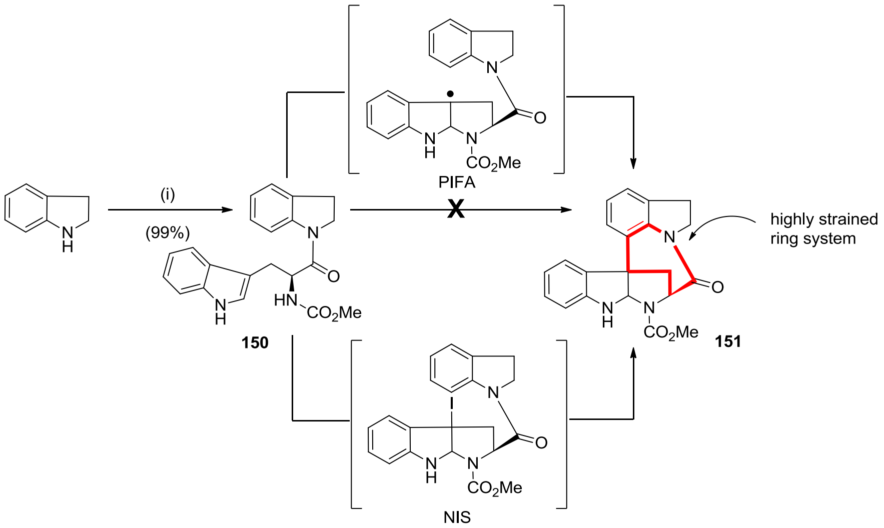
Scheme 106: Proposed biomimetic strategy involving a tethered tryptophan unit

Pleasingly reacting *meso*-chimonanthine **2** with L-tryptophan methyl carbamate gave the desired amide **148** as a separable 3:1 mixture of diastereomers in a 51% yield (along with recovered starting material). However, exposure of the product to PIFA had no effect.



Scheme 107: Conditions: (i) *meso*-Chimonanthine **2** (1.0 eq), tryptophan methyl carbamate (1.0 eq), EDC (1.3 eq), HOBt (0.46 eq), DCM [0.03 M], 22 °C, 16 h. (ii) **148** (1.0 eq), PIFA (0.65 eq), CF_3CH_2OH [0.23 M], -30 °C, 16 h (absolute configurations not determined).

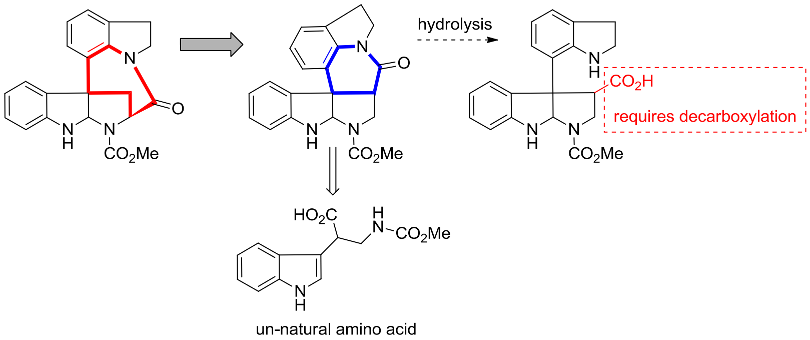
Additional screening was carried out using a model indoline system **150**. This not only simplified spectroscopic analysis but also minimised the possibility of forming diastereomers. The model system again failed to give the desired product upon treatment with PIFA. It was hoped that treatment with *N*-iodosuccinimide would install an iodine atom at the C-3a position[72] which, either *via* a radical or a cationic intermediate, would react at the C-7 position of the indoline unit. The failure of both of these strategies led us to conclude that the bridged 7-membered ring system **151** is too highly strained to be readily formed (Scheme 108).



Scheme 108: Conditions: (i) Tryptophan methyl carbamate (1.0 eq), indoline (1.2 eq), EDC (1.3 eq), HOBt (0.46 eq), DCM [0.05 M], 22 °C, 16 h.

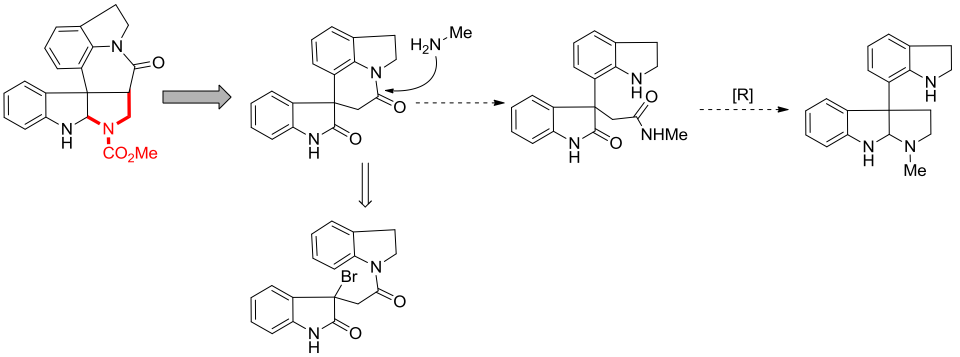
9.1.2 Lewis Acid Mediated Ring Closure

Scheme 109 shows conceptually how we arrived at our next area of investigation. Contraction from a 7- to a 6-membered ring system should dramatically reduce the associated ring strain. This idea has two main drawbacks, firstly an un-natural amino acid would be required and secondly the compound would require a potentially tricky decarboxylation in order to form the desired natural product.[30]



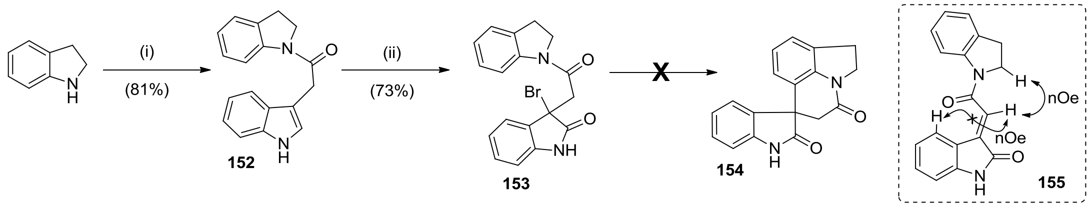
Scheme 109: Alternative 6-membered ring strategy

We realised that the linkage itself could be used to form the final cyclotryptamine unit by the opening of the newly formed 6-membered ring with methylamine and subsequent reductive amination. This is far more atom economic than our initial strategy (as the tether now would be incorporated into the final product) and the ring system generated should have only minimal strain associated with it (Scheme 110).



Scheme 110: Proposed formation of cyclotryptamine unit from 2-carbon tether

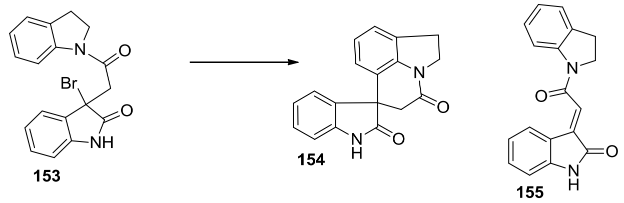
Although formation of the desired bromo-oxindole **153** proceeded smoothly, chromatographic purification frequently resulted in poor isolated yields (*ca.* 15 – 65%). Additionally it was observed that over time an undesired E1 or E2 elimination was occurring to give the highly conjugated acrylamide **155** shown in Scheme 111.[76] In our previous experience with bromo-oxindoles we had never observed any of this type of elimination (Scheme 68). We attributed its prevalence to existence of the amide group which allows the formation of a stable conjugated system. Isolation of these bromo-oxindoles appeared to be the bottleneck for this section of the synthesis, however, we observed that at a precise concentration (0.1 M) the desired bromo-oxindole **153** precipitated from the reaction mixture and could be isolated cleanly in a 73% yield without chromatography (Scheme 111).



Scheme 111: Conditions: (i) 3-Indoleacetic acid (1.1 eq), indoline (1.0 eq), EDC (1.3 eq), HOBt (0.46 eq), DCM [0.1 M], 0 °C – rt, 16 h. (ii) **152** (1.0 eq), NBS (2.3 eq), H_2O (2.0 eq), tBuOH / THF (1:1) [0.1 M], rt, 2.5 h. (Most probably double bond geometry illustrated above)

Table 33 illustrates the effect of solvent and additive choice on our proposed cyclisation reaction. Despite screening a variety of conditions for the ring closure, all attempts resulted in recovery of starting material **153**, conjugated bi-product **155** or decomposition of our bromo-oxindole. Based on recent work from Movassaghi and co-workers we attempted to generate a radical to effect the ring closure;[30,231] to our chagrin this was also un-effective (Table 33, Entries 9 & 10).

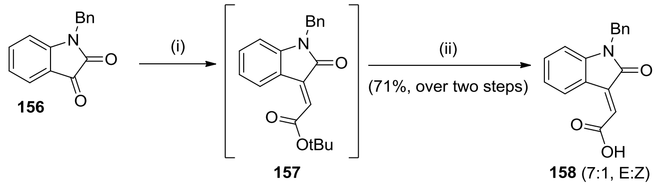
Table 33: Attempted intramolecular cyclisation



Entry	Additive	Solvent	Product (% yield)
1	**Cs_2CO_3**	**DCM**	**155 (46)**
2	**Cs_2CO_3**	**DCM[a]**	**155 (quant)**
3	AgOTf	DCM	**155** (36)
4	AgOTf	MeCN	0
5	$AlCl_3$	DCM	SM
6	$AlCl_3$	PhCl	**155** (trace)
7	BF_3·(OEt_2)	DCM	SM
8	ScOTf	DCM	SM
9	$CoCl(PPh_3)_2$[b]	Acetone	0
10	Bu_3SnH/AIBN[c]	PhH	0

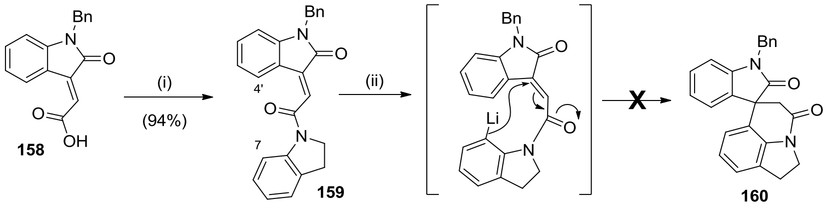
Conditions: (i) Bromo-oxindole (1.0 eq), Additive (2.0 eq), DCM [0.01 M], rt, 16 h. [a]100 °C µw, 1.25 h. [b](1.2 eq). [c] Bu_3SnH (1.0 eq), AIBN (1.0 eq), reflux, 2 h.

Owing to the favourability of the formation of the acrylamide **155**, we hoped that this sort of functionality could be used to form our desired *spiro*-lactam **154**. We anticipated that the amide carbonyl would be able to direct an *ortho*-lithiation at the C-7-position; the lithiated ring system could then attack the acrylamide **155** in a conjugate addition. To test this, we synthesised the unsaturated acid fragment *via* a Wittig coupling of *N*-benzyl isatin **156**. Subsequent deprotection gave the desired oxindole **158** in a 71% yield over two steps.[232] The acidic nature of the product allowed us to remove excess *N*-benzyl isatin **156** and the triphenylphospine oxide bi-product by means of a simple aqueous workup (Scheme 112).



Scheme 112: Conditions: (i) *N*-Benzyl-isatin **156** (1.05 eq), phosphorane (1.0 eq), PhMe [0.16 M], reflux, 1 h – 20 °C, 16 h. (ii) TFA (20.0 eq), 50 °C, 2 h.

With the acid portion in hand we formed the desired acrylamide **159** in an essentially quantitative yield *via* the acid chloride (Scheme 113).



Scheme 113: Conditions: (i) **158** (1.1 eq), $(COCl)_2$ (2.0 eq), DMF (1 mol%), indoline (1.0 eq), DCM [0.08 M], rt, 2 h. (ii) **159** (1.0 eq), TMEDA (3.0 eq), *s*-BuLi (2.0 eq), Et_2O [0.03 M], -78 – 0 °C, 1 h.

Regrettably our attempts at lithiation only resulted in a complex mixture of products. This may due to a propensity for the molecule to deprotonate first at the C-4' position. This undesired species may then dimerise or decompose. Circumstantial evidence for this was provided by ^{1}H NMR spectrometry, which showed that the C-4' proton is significantly more de-shielded than its C-7 counterpart.

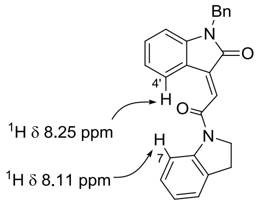
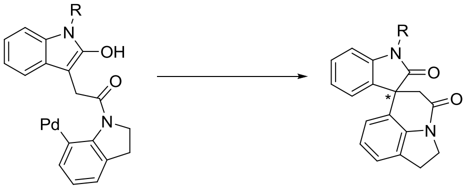


Fig. 21: ^{1}H NMR signals for C-4' and C-7 protons

To test our hypothesis we subjected the amide to our lithiation conditions and quenched directly with excess methanol-d_4. This resulted in a complex mixture of products and no evidence for deuterium incorporation at either the C-4' or C-7 position. As a result we suspended further investigation in this area.

9.1.3 Intramolecular-Palladium Catalysed Ring Closure

As mentioned previously we have shown that oxindoles can be effectively coupled to aryl halides under palladium catalysis.[177,178] Within the group we noted that the reaction was highly sensitive to steric factors, and that the formation of a quaternary centre from a C-3 substituted oxindole was not trivial.[178] To overcome this problem we devised a second enolate coupling strategy, this time an intramolecular approach loosely based around our *intra*-molecular Friedel-Crafts reaction (Scheme 114).



Scheme 114: Palladium catalysed *intra*-molecular ring closure

With such a stratagem there is the risk of forming an undesired five-membered cyclisation product resulting from attack by the amide enolate. Basic MM2 energy minimisation calculations showed that the energy associated with the desired *spiro*-lactam was an order of magnitude lower than that of the 5-membered product (Fig. 22). However, it is worth noting that in spite of the higher strain associated with the 5-membered product, it should be formed *via* a more energetically favourable 6-membered transition state.

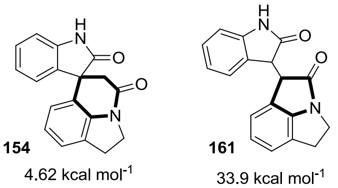
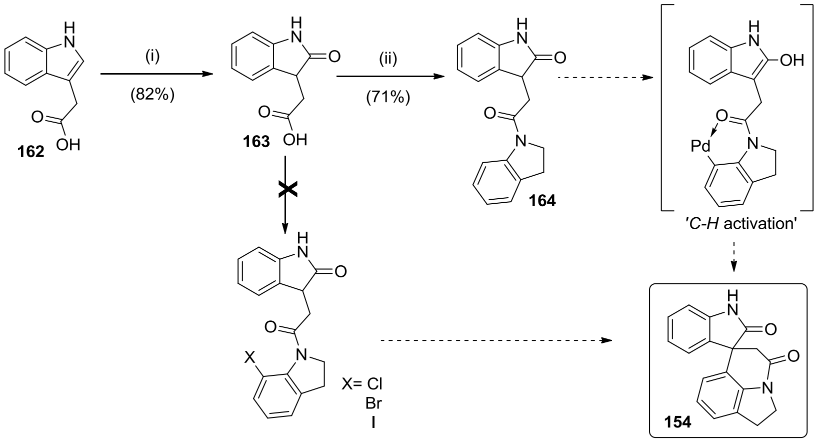


Fig. 22: MM2 energy minimisation calculations[i]

The required oxindole was formed in good yields by exposure of the corresponding indole to a 2:1 mixture of *conc.* hydrochloric acid and DMSO followed by crystallisation of the product.[215,216] The condensation reaction with indoline took place rapidly in the presence of EDC and HOBt. Eventually we hoped to use the amide carbonyl generated in this step to effect an *ortho*-palladation to give rise to our desired *spiro*-lactam. To model this cyclisation we opted to use a 7-halo-indoline unit. Regrettably, we were unable to couple the corresponding 7-halo-indolines under analogous reaction conditions (Scheme 115). In a control experiment we found that in the absence of indoline, the acid rapidly formed oligomers under our amide coupling conditions.



Scheme 115: Conditions: (i) 3-Indoleacetic acid (1.0 eq), DMSO (1.0 eq), conc. HCl (2.0 eq), rt, 4 h. (ii) Indoline (1.0 eq), Acid (1.1 eq), EDC (1.3 eq), HOBt (0.46 eq), DCM [0.08 M], rt, 16 h.

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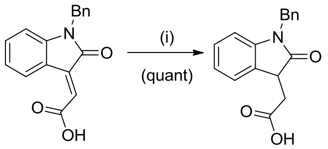
[i] ChemBio3D Ultra v 11.0.1

To prevent oligermerisation of the starting acid we synthesised an *N*-benzyl protected version of our oxindole-acid. Treatment of the unprotected oxindole-acid **163** with two equivalents of *n*-BuLi followed by addition of benzyl bromide failed to generate the desired product. Fortunately, a hydrogenation of unsaturated acid **158** used previously gave the reduced product **165** in a quantitative yield (Scheme 116).[233]

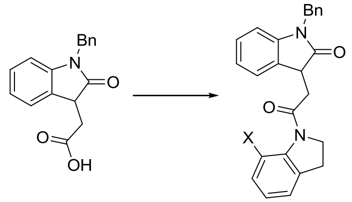


158 (7:1, E:Z) **165**

Scheme 116: Conditions: (i) **158** (1.0 eq), Pd/C (5 mol%, Pd), H_2 (balloon), MeOH [0.05 M], rt, 16 **h.**

With the *N*-benzyl protected oxindole-acid **165** in hand we screened amide coupling conditions; pleasingly the protected oxindole **165** showed no signs of oligomerisation in control experiments. The primary coupling partner, 7-iodo-indoline **111**, gave no product **166** under our standard amide coupling conditions. This result was attributed to the bulk of the iodo group and as a result, subsequent reactions utilised the less sterically encumbered 7-chloro-indoline. The acid chloride proved the optimal means of activation giving the product in up to 60% yield. Switching to the bromide gave a sharp decrease in yield; this again was attributed to its size (Table 34).

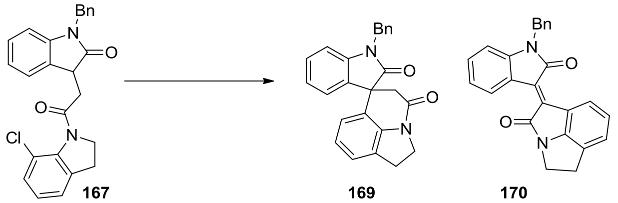
Table 34: Amide coupling screen



Entry	X	Coupling agent	Yield [%]	Compound
1	I	EDC / HOBt	0	**166**
2	Cl	EDC / HOBt	12	**167**
3	**Cl**	**$(COCl)_2$ / DMF**	**60**	**167**
4	Br	$(COCl)_2$ / DMF	21	**168**

With the amide **167** in hand we trialled a range of coupling conditions, which are summarised in Table 35. The system gave the desired *spiro*-lactam **169** in modest to acceptable yields. The optimal conditions were caesium carbonate as the base and MOP as the ligand in toluene, which gave the desired product in a 61% yield (Table 35, Entry 11).

Table 35: Conditions screen



Entry	Ligand	Base	Solvent	**169** [%]	**170** [%]
1^{ab}	X-Phos	KHMDS	THF/PhMe	11	Trace
2^{a}	X-Phos	KHMDS	THF/PhMe	0	0
3^{a}	X-Phos	K_2CO_3	THF/PhMe	0	0
4^{a}	PEPPSI	K_2CO_3	THF/PhMe	0	0
5	PEPPSI	K_2CO_3	PhMe	20	24
6	PEPPSI	NaOtBu	PhMe	24	11
7	**PEPPSI**	$\mathbf{Cs_2CO_3}$	**PhMe**	**48**	**33**
8	S-Phos	Cs_2CO_3	PhMe	28	37
9	X-Phos	Cs_2CO_3	PhMe	41	33
10	Fu's salt	Cs_2CO_3	PhMe	33	28
11	**(*R*)-MOP**	$\mathbf{Cs_2CO_3}$	**PhMe**	**61**	**26**
12^{c}	(*R*)-MOP	Cs_2CO_3	PhMe	42	13
13	(*R,S*)-PPFA	Cs_2CO_3	PhMe	24	20
14	(*R*)-MOP	Cs_2CO_3	Dioxane	15	39
15	S-Phos precomplex	Cs_2CO_3	PhMe	26	33

Conditions: Amide (1.0 eq), Base (1.1 eq), $Pd(OAc)_2$ (5 mol%), Ligand (6 mol%), PhMe [0.12 M], 100 °C, 16–24 h. ^{a} 70 °C, ^{b} KHMDS (2.0 eq), ^{c} 7-bromo-indoline used.

All the successful reactions gave an appreciable quantity of bi-product, this was identified as the 5-membered ring system in its unsaturated form **170**. The bi-product itself was a highly crystalline ruby red solid, the structure of which we were able to confirm by X-Ray crystallography (Fig. 23). The precise mechanism of the oxidation of the bi-product is unclear, however, we postulated it may arise from attack by a Pd(II) species on one of the enolates. To minimise oxidation we used strictly anaerobic conditions, surprisingly this appeared to have no effect on the level of bi-product obtained.

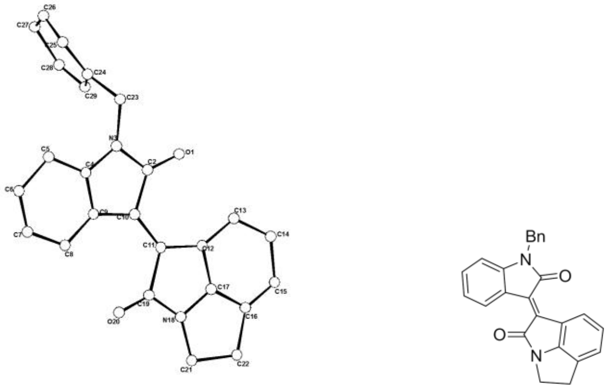


Fig. 23: X-Ray structure of tricyclic bi-product **170**

The formation of the bi-product is almost certainly triggered by attack of the amide enol in preference to the oxindole enol. We hoped that switching from a benzyl protecting group to an electron withdrawing group (e.g. carbamate) would favour enolisation of the oxindole, which should give rise to solely our desired *spiro*-lactam product (Fig. 24).

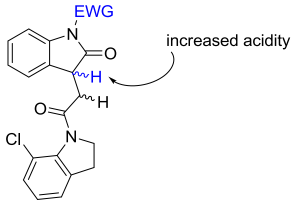
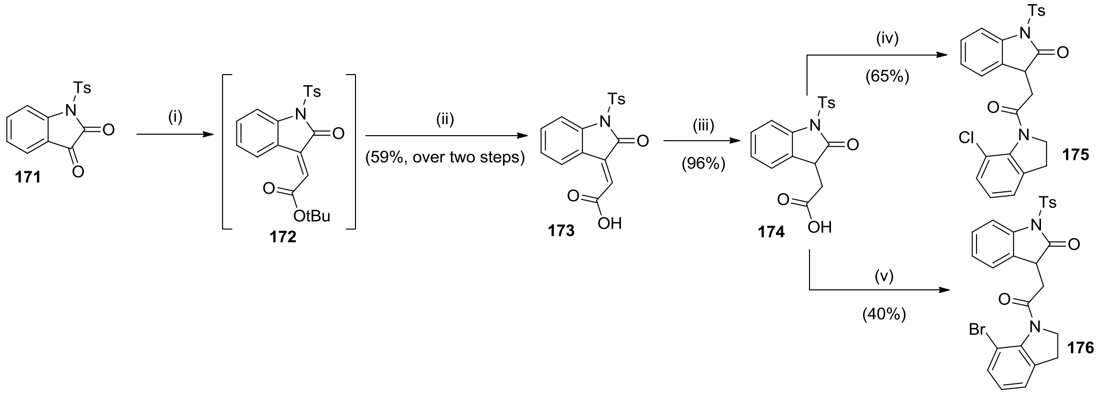


Fig. 24: Installation of electron withdrawing group to favour enolisation of the oxindole

Our electron withdrawing group of choice was a tosyl group (it was found carbamates such as *N*-Boc were cleaved during our ester hydrolysis); the resultant amides could be prepared in an identical fashion to the *N*-benzyl analogues. As was observed previously (Table 34) more sterically encumbered coupling partners (Br *vs.* Cl) gave a marked decrease in efficiency. Nevertheless the desired amides were formed in synthetically useful yields (Scheme 117).



Scheme 117: Conditions: (i) *N*-Tosyl-isatin **171** (1.05 eq), phosphorane (1.0 eq), PhMe [0.16 M], reflux, 1 h. (ii) TFA (20.0 eq), 50 °C, 2 h. (iii) **173** (1.0 eq), Pd/C (8 mol%, Pd), H_2 (balloon), MeOH [0.05 M], rt, 16 h. (iv) **174** (1.2 eq), $(COCl)_2$ (2.0 eq), DMF (1 drop), 7-chloro-indoline (1.0 eq), DCM [0.1 M], rt, 16 h. (v) **174** (1.2 eq), $(COCl)_2$ (2.0 eq), DMF (1 drop), 7-bromo-indoline (1.0 eq), DCM [0.1 M], rt, 16 h.

The tosyl group appeared to have the desired electron withdrawing effect. The chemical shift of the H-3 proton in the ^{1}H NMR spectrum showed it had shifted downfield by *ca.* 0.2 ppm.

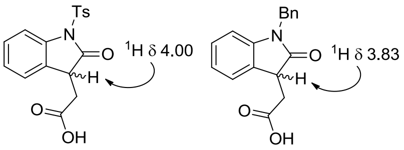
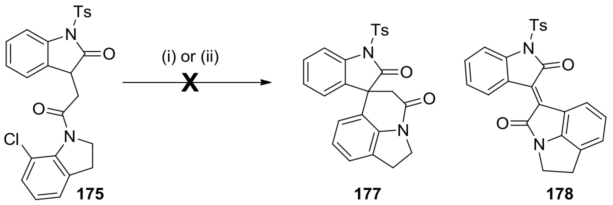


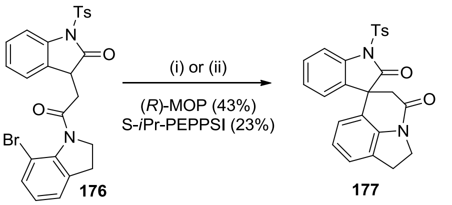
Fig. 25: Chemical shifts of H-3 protons

Surprisingly, exposing the chloro-tosyl-amide **175** to our reaction conditions only yielded a complex mixture of products (Scheme 118).



Scheme 118: Conditions: (i) **175** (1.0 eq), $Pd(OAc)_2$ (5 mol%), (*R*)-MOP (6 mol%), Cs_2CO_3 (1.1 eq), PhMe [0.1 M], 100 °C, 16 h. (ii) Amide (1.0 eq), S*i*-Pr PEPPSI (5 mol%), Cs_2CO_3 (1.1 eq), PhMe [0.1 M], 100 °C, 16 h.

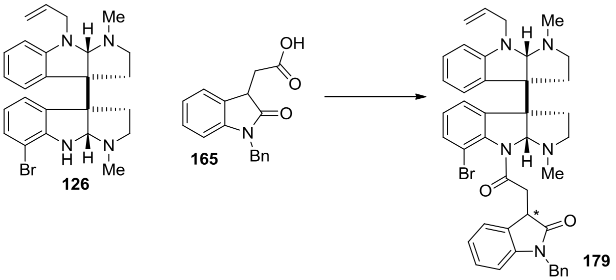
However, when using the bromo-tosyl-amide **176** the desired *spiro*-lactam **177** could be isolated in a 43% yield (Scheme 119). An additional product was observed but its precise structure was not established. It should be noted that there was no evidence of the product resulting from the reaction of the amide enolate. The yield, although modest, was directly comparable to those achieved using the benzyl protected system (Table 35).



Scheme 119: Conditions: (i) **176** (1.0 eq), $Pd(OAc)_2$ (5 mol%), (*R*)-MOP (6 mol%), Cs_2CO_3 (1.1 eq), PhMe [0.1 M], 100 °C, 3 h. (ii) **176** (1.0 eq), S-*i*Pr-PEPPSI (5 mol%), Cs_2CO_3 (1.1 eq), PhMe [0.1 M], 100 °C, 3 h.

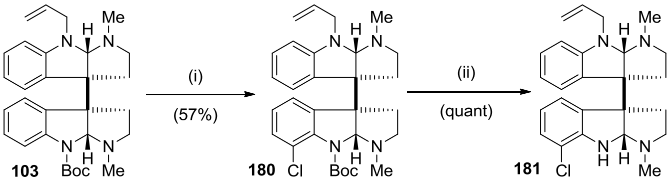
The success of our model reactions led us to attempt the ring closure on our desymmetrized material. We screened conditions for the installation of the amide linker, however, the increased bulk of the substituted cyclotryptamine unit and the presence of the bromine group appeared to greatly inhibit the coupling reaction and we were unable to isolate appreciable quantities of the coupling product **179** (Table 36).

Table 36: Amide Coupling



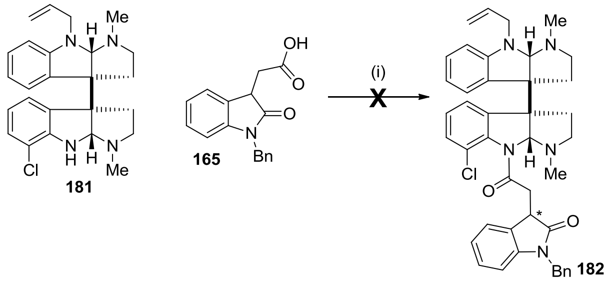
Entry	Coupling Conditions	Solvent	Yield [%]
1	$(COCl)_2$, DMF	DCM	Trace + SM
2	$(COCl)_2$, DMF, DMAP	DCM	SM
3	HBTU, DIPEA	DCM	Trace
4	HBTU, DIPEA	DMF	Trace
5	EDC, HOBt	DMF	Trace
6	T3P, Et_3N	EtOAc	0

Our failure to produce acceptable levels of the amide resulted in the preparation of the less hindered chloro-analogue. This was generated in an analogous fashion to our bromo-system (Scheme 82), using carbon tetrachloride[234] as the halogen source (Scheme 120).



Scheme 120: Conditions: (i) *N'*-Boc-*N*-allyl-chimonanthine **103** (1.0 eq), TMEDA (3.0 eq), s-BuLi (2.5 eq), carbon tetrachloride (10.0 eq), Et_2O [0.04 M], -78 – 0 °C, 1.5 h. (ii) 7'-Chloro-*N'*-Boc-*N*-allyl-chimonanthine **180** (1.0 eq), TMSOTf (2.5 eq), DCM [0.06 M], rt, 16 h.

7-Chloro-*N*-allyl-chimonanrthine was exposed to our amide coupling conditions, unfortunately, the reduced reactivity was mirrored in this system with only recovred starting material isolated from the reaction.



Scheme 121: **165** (2.0 eq), $(COCl)_2$ (3.0 eq), DMF (1 drop), 7'-Chloro-*N*-allyl-chimonanthine **181** (1.0 eq), DCM [0.1 M], rt, 16 h.

Although we were unsuccessful in applying our tethered arylation methodology to the synthesis of polypyrrolidinoindoline alkaloids, its utility is still under investigation.

9.1.4 Ring Opening Reactions

It was hoped that the *spiro*-lactam **169** synthesised in section 9.1.3 would adopt a 'twisted amide' configuration, where the carbonyl and the amine behave almost independently of each other (as the nitrogen lone pair is unable to donate into the carbonyl).[235,236] If this were the case, spectroscopically the carbonyl should appear as a 'ketone'. This would increase the propensity for methyl amine to react at the desired carbonyl in the ring opening reaction. Unfortunately, infrared and ^{13}C NMR spectrometry suggested that this was not the case (Fig. 26). Although these observations do not entirely rule out the ring opening reaction, they are not encouraging.

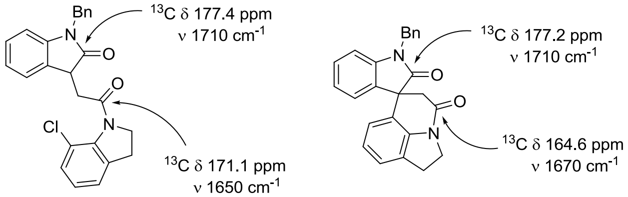
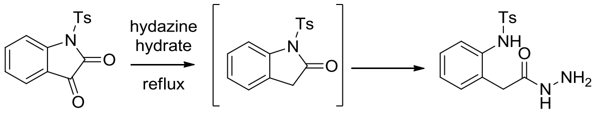


Fig. 26: IR frequencies & ^{13}C NMR shifts for carbonyls

Circumstantial evidence suggested that the tosyl *spiro*-lactam **177** was not suitable for such ring opening reactions, was provided by the observation that similar oxindoles could be opened by a nucleophile such as hydrazine. Presumably the highly electron withdrawing nature of the tosyl group favours the formation of a nitrogen anion (Scheme 122).

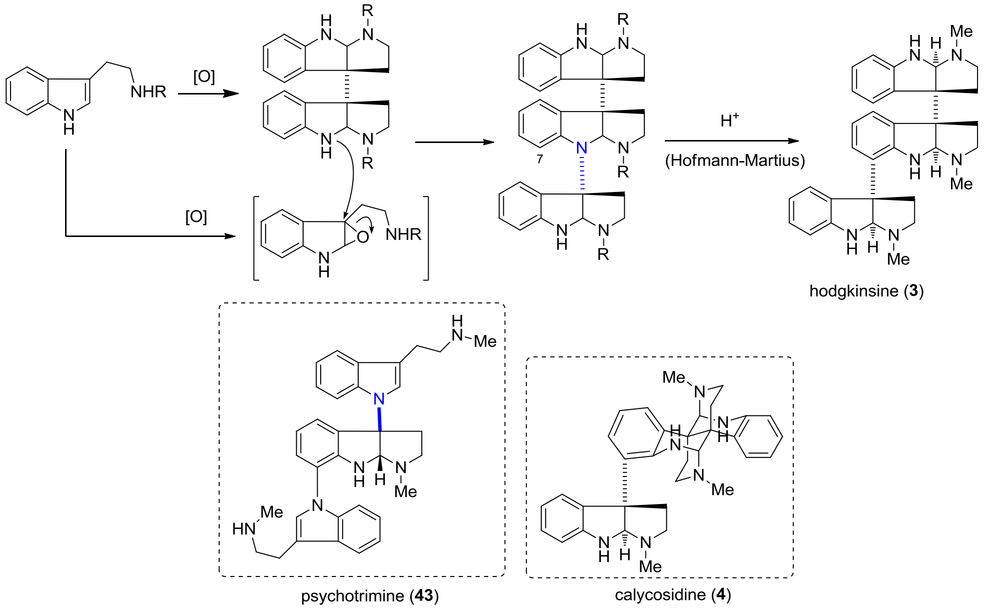


Scheme 122: Ring opening of oxindoles

Work is currently on-going to establish a method for the selective ring opening of the 6-membered fragment on the *spiro*-lactam product.

9.2 Hofmann Martius Rearrangement

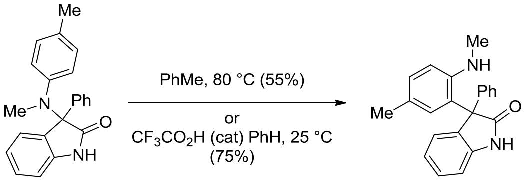
It has been noted on numerous occasions, both in our hands and the literature,[76] that bromo-oxindoles are highly susceptible to attack by soft nucleophiles including alcohols and amines. Assuming that these bromo-oxindoles can be considered analogous in reactivity to the 'oxidised' intermediates involved in cyclotryptamine bio-synthesis, one could easily envisage the free amines of *meso*-chimonanthine attacking such an 'oxidised' intermediate. We propose that this is as probable as the formation of a radical at the C-7 position, hypothesised in previous biosynthetic pathways. The resultant C-N linked product (in a ring open, or ring closed form) could conceivably undergo an acid catalysed Hofmann-Martius type rearrangement to form the observed C-3a – C-7 linkage (Scheme 123).[237,238]



Scheme 123: Our alternative bio-synthetic pathway

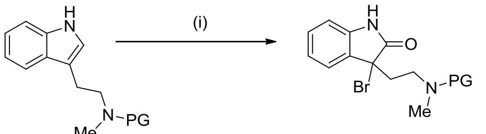
Such an acid catalysed rearrangement may also explain the existence of calycosidine, the natural product generated when hodgkinsine is treated with acid. Our proposed C-N linked intermediate is not entirely unprecedented in nature, as several natural products including psychotrimine and psychopentamine contain just such functionality (highlighted in blue in Scheme 123).[239]

Recently Magnus *et al.* showed that *N*-aniline substituted oxindoles could rearrange thermally or under acid catalysis to the corresponding C-C linked product (Scheme 124).[237] We postulated that similar chemistry could be used to in a 'bio-mimetic' synthesis of hodgkinsine.



Scheme 124: Hofmann-Martius rearrangement

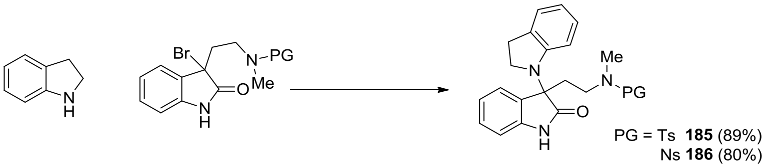
In our oxidations of tryptamine derivatives we utilised bromo-oxindoles (Scheme 68), which have been shown by Funk and co-workers to be highly susceptible to attack by suitable nucleophiles (e.g. amines).[217,240] This made them the ideal building blocks for our re-arrangement precursors. Methyl tryptamine was protected as the nosylate in an analogous fashion to our previous tosylation (Scheme 68) (86% yield). We synthesised both the tosyl- and nosyl-bromo-oxindoles in comparable yields *ca*. 70% using NBS and water.



PG = Ts **183** (76%)
Ns **184** (70%)

Scheme 125: Conditions: *N*-Methyl-*N*-PG-tryptamine (1.0 eq), NBS (2.5 eq), H_2O (4.0 eq), *t*BuOH : THF [1:1, 0.1 M], rt, 2 h.

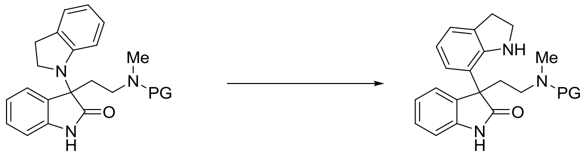
Pleasingly, the reaction of indoline with *N*-protected bromo-oxindoles proceeded without difficulty. The products from these reactions were easily purified by crystallisation from DCM and *iso*-hexane (Scheme 126).

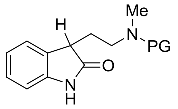


Scheme 126: Conditions: Indoline (1.0 eq), bromo-oxindole (1.1 eq), Cs_2CO_3 (1.2 eq), DCM [0.04 M], rt, 2 h.

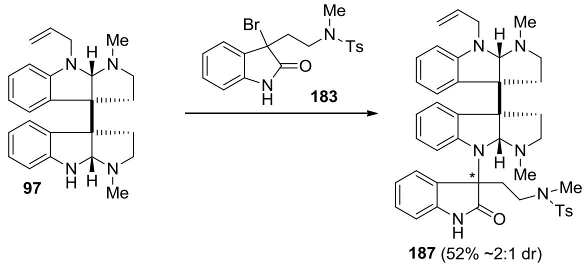
With indoline substituted oxindoles in-hand we attempted to effect a rearrangement both thermally and with Brønsted and Lewis acids. Initial results were inconclusive with reactions yielding either recovered starting materials or a complex mixture of products. An interesting result was observed when the oxindole was heated at 150 °C *via* microwave irradiation (Table 37, Entry 5), as it cleaved the indoline unit. This result could be evidence that the rearrangement is possible, or could just have arisen from homolysis caused by the extreme conditions (Table 37).[237]

Table 37: Attempted model Hofmann-Martius rearrangement



Entry	PG	Additive	T [°C]	Solvent	Product
1	Ns	-	Reflux	d_6-benzene	SM
2	Ns	TFA (1.0 eq)	22	d_6-benzene	SM
3	Ns	$ZnCl_2$ (1.0 eq)	22	PhMe	Complex mixture
4	Ts	$Sc(OTf)_3$ (1.0 eq)	120	PhMe	Complex mixture
5	Ts	-	150 (μw)	PhMe	

Our previous experience with cyclotryptamine alkaloids prompted us to disregard the results of the model system. We chose to attempt the re-arrangement using desymmetrized chimonanthine. The synthesis of the *N*-linked substrate did not occur as smoothly for the chimonanthine derived compound, the additional bulk appeared to have a detrimental effect. Excess bromo-oxindole and long reaction times were necessary for the reaction to go to completion (Scheme 127).

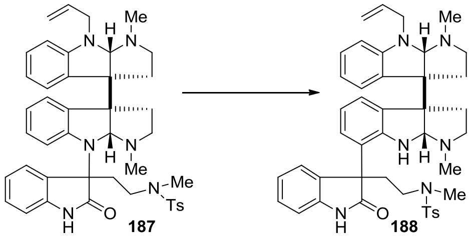


Scheme 127: Conditions: *N*-Allyl-chimonanthine **97** (1.0 eq), bromo-oxindole **183** (2.0 eq), Cs_2CO_3 (3.0 eq), DCM [0.06 M], 0 °C – rt, 24 h, (52%, ~2:1 dr, by HPLC, ~6:1 dr by recovery).

Unlike the indoline model, for this system, there were many bi-products; presumably these arose from decomposition of the bromo-oxindole or from protonation and subsequent re-arrangement of the chimonanthine core. Previously we observed a rapid acceleration of the reaction in the presence of AgOTf; it was hoped that a faster reaction would prevent the decomposition of the bromo-oxindole giving a better yield. In addition to this, triethylamine was investigated as a replacement base due its high solubility relative to caesium carbonate. Regrettably, both these modifications resulted in increased levels of decomposition product in addition to large quantities of un-reacted starting amine.

We subjected the *N*-linked compound **187** to re-arrangement conditions (Table 38), heat and mild acid had no effect, yielding only un-reacted starting material. When TFA was added (using DMSO as a solvent) a new product was observed by ^{1}H NMR spectroscopy, however, no peaks corresponding to H-8a or H-8a’ could be detected indicating the chimonanthine core was no longer intact. The results do not rule out our proposed biosynthetic pathway, but our failure to effect any migration in any of our systems caused us to suspend further research in this area.

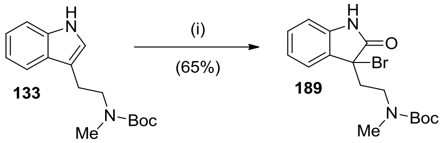
Table 38: Attempted Hofmann-Martius rearrangement



Entry	T [h]	T [°C]	Additive	Solvent	Product
1	48	80	-	DMSO	SM
2	16	50	Amberlyst-16	DMSO	SM
3	48	Rt	TFA	DMSO	0
4	24	80	-	PhH	SM
5	24	Rt	TFA	PhH	SM

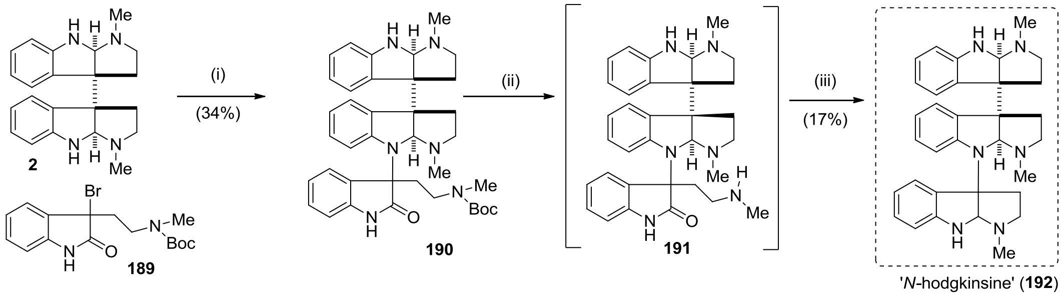
Reactions were carried out on *ca.* 5 mg scale in an NMR tube.

Undiscouraged by our unsuccessful migration chemistry we decided to synthesise polypyrrolidinoindoline alkaloid analogue '*N*-hodgkinsine' **192** employing the same bromo-oxindole coupling strategy. These natural product analogues contain the cyclotryptamine functionality of hodgkinsine **3** but with the characteristic C-3a – *N*-linkage of psychotrimine **43**. To streamline the synthesis we opted to generate racemic product, eliminating the allyl cleavage steps. The required bromo-oxindole coupling partner **189** was synthesised using our NBS / water oxidation system (Scheme 128). The Boc protected version was selected so the synthesis would be directly comparable to our synthesis of hodgkinsine-B **3**. We noted that this product **189** was somewhat less stable than the other analogues with a propensity for Boc cleavage; presumably decomposition generates HBr which facilitates the deprotection.



Scheme 128: Conditions: *N*-Methyl-*N*-Boc-tryptamine **133** (1.0 eq), NBS (2.5 eq), H_2O (4.0 eq), *t*BuOH : THF [1:1, 0.1 M], rt, 2 h.

Despite the instability of the bromo-oxindole, we were able to combine it directly with *meso*-chimonanthine in the presence of base to form the desired C-3a – *N* linkage. We isolated the *mono*-product in a modest 34% yield, the mass balance being made by recovered *meso*-chimonanthine. The instability of the bromo-oxindole prevented us from forcing the reaction to completion by addition of more substrate. Finally, telescoping the Boc cleavage and reductive amination steps afforded (±)-*N*-hodgkinsine in a modest 17% yield, over two steps (Scheme 129).



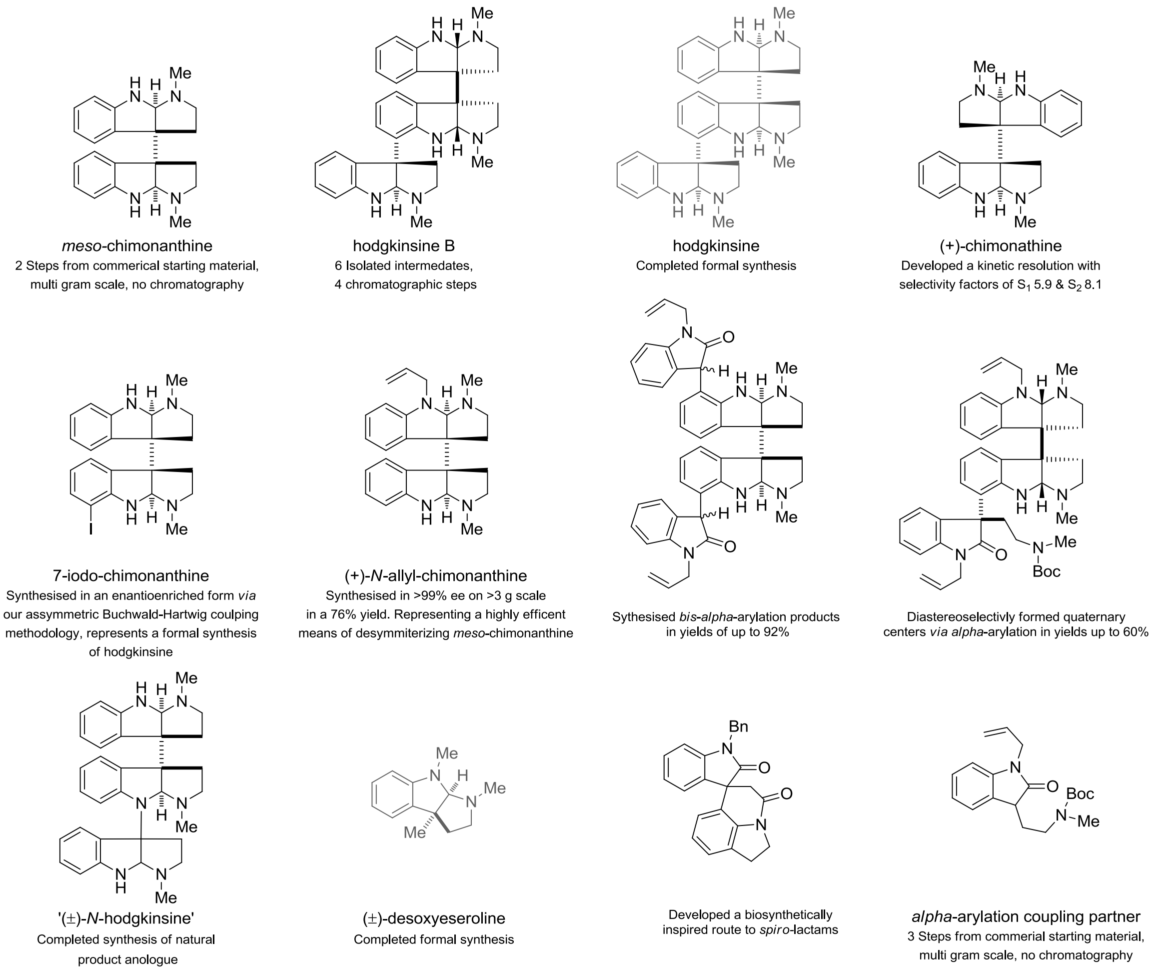
Scheme 129: Conditions: (i) *meso*-chimonanthine **2** (1.0 eq), bromo-oxindole **189** (1.5 eq), Cs_2CO_3 (3.0 eq), DCM [0.01 M], rt, 16 h. (ii) **190** (1.0 eq), TMSOTf (2.2 eq), DCM [0.04 M], rt, 16 h. (iii) **192** (1.0 eq), $LiAlH_4$ (3.7 eq), THF [0.02 M], reflux, 1.5 h.

9.3 Summary

We have developed a tethered biosynthetically inspired method for the formation of C-3 – C-7 linkages utilising palladium enolate chemistry. Additionally we devised an alternative biosynthetic proposal for the synthesis of polypyrrolidinoindoline alkaloids and completed the synthesis of a novel natural product analogue, '(±)-*N*-hodgkinsine' **192**.

10.0 Conclusions and Future Investigations

Our research has led to numerous synthetic innovations and enhancements which we have showcased with an enantioselective total synthesis hodgkinsine B. Fig. 27 shows selected highlights from our investigations including the novel application of two asymmetric C-N bond forming protocols in the synthesis of complex natural products.



meso-chimonanthine
2 Steps from commerical starting material, multi gram scale, no chromatography

hodgkinsine B
6 Isolated intermediates, 4 chromatographic steps

hodgkinsine
Completed formal synthesis

(+)-chimonathine
Developed a kinetic resolution with selectivity factors of S$_1$ 5.9 & S$_2$ 8.1

7-iodo-chimonanthine
Synthesised in an enantioenriched form *via* our assymmetric Buchwald-Hartwig coulping methodology, represents a formal synthesis of hodgkinsine

(+)-*N*-allyl-chimonanthine
Synthesised in >99% ee on >3 g scale in a 76% yield. Representing a highly efficent means of desymmiterizing *meso*-chimonanthine

Sythesised *bis-alpha*-arylation products in yields of up to 92%

Diastereoselectivly formed quaternary centers *via alpha*-arylation in yields up to 60%

'(±)-*N*-hodgkinsine'
Completed synthesis of natural product anologue

(±)-desoxyeseroline
Completed formal synthesis

Developed a biosynthetically inspired route to *spiro*-lactams

alpha-arylation coupling partner
3 Steps from commerial starting material, multi gram scale, no chromatography

Fig. 27: Selected highlights

In the immediate future, we hope to continue our investigations into cyclotryptamine alkaloids and attempt to apply our desymmetrization and *alpha*-arylation methodologies to the synthesis of other members of this interesting family of natural products.

11.0 Experimental

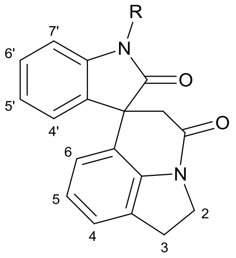
Reactions were conducted with continuous magnetic stirring under an inert nitrogen or argon atmosphere with HPLC grade solvents unless otherwise stated. Nitrogen and argon were passed through a Drierite filled drying tube before use. Glassware was allowed to dry in air. Anhydrous reactions were carried out using dry solvents in glassware which was oven-dried at >200 °C, and allowed to cool to room temperature under a positive nitrogen pressure or vacuum. Cooling of reaction vessels to 0 °C was achieved by an ice-water slush bath, cooling to -30 °C was achieved using a Neslab Cryotrol CB-80 cryostat or by using a jacketed vessel equipped with a Huber Julabo FT902 cryostat, cooling to -78 °C was achieved by a dry ice-acetone bath.

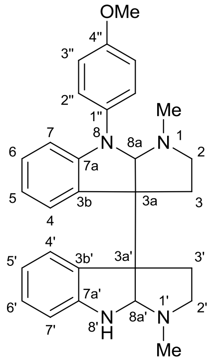
Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd, Avocado, Fluorochem or Lancaster Synthesis Ltd. and used as supplied. Anhydrous diethyl ether, dichloromethane, tetrahydrofuran and toluene were collected fresh from an in-house solvent purification system, Innovative Technology Inc. PS-400-7, having been passed through anhydrous alumina columns.

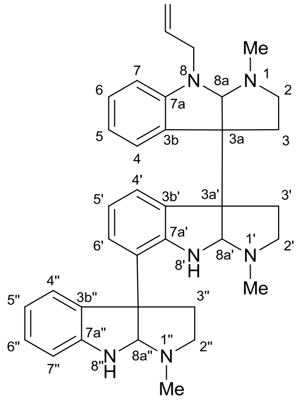
Reactions were monitored by TLC until deemed complete using aluminium backed silica plates (Merck Kieselgel 60 F254) or (Alugram Sil G/UV$_{254}$). Plates were visualised under ultraviolet light (254 nm) and/or by staining with potassium permanganate, vanillin or ceric ammonium molybdate (CAM). LCMS was carried out using an Agilent 1100 series LCMS equipped with symmetry C-18 and X-bridge C-18 reverse phase columns. Flash column chromatography was carried out using Zeochem ZEOprep hyd. 40-63 micron silica with pre-absorption of the crude product onto silica. Pressure was applied at the column head *via* house nitrogen line. Alternatively, Flash column chromatography was carried out using a Jones Chromatography Flash Master Personal pump in conjunction with Biotage KP-Sil 10, 50, 100 or 340 g silica columns.

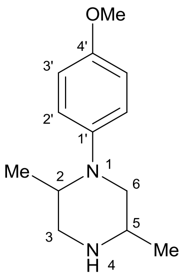
^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DPX-200, DPX-250, DQX-400, DRX-500, AVC-500 and Varian 300, 400 or 500 MHz spectrometers at room temperature unless otherwise stated. Chemical shifts are reported in parts per million from the residual solvent peak. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), septet (sep), multiplet (m), broad (b), apparent (app), overlapping (o) and aryl (Ar). Where required, proton assignment was achieved using 2D NMR spectroscopy techniques, predominantly COSY and HMQC spectroscopy. Chiral HPLC analysis was carried out using a Dionex HPLC system utilising Daicel chiral columns; HPLC grade solvents were purchased from Rathburn and Fisher chemical companies and were used as supplied. Specific optical rotations were measured on Perkin-Elmer 241 polarimeter at 589 nm and are reported in °cm^{2}g^{-1}. Melting points were determined using a Leica Galen III hot-stage microscope. Infrared measurements were carried out neat on a Perkin Elmer spectrum one FT-IR spectrometer with internal calibration in the range 4000-600 cm^{-1} or on a Bruker Tensor 27 FT-IR spectrometer retrofitted with a diamond attenuated total reflectance (ATR) module, alternatively samples were prepared as a KBr Disc or a thin film on a NaCl plate for use on the unmodified spectrometer. Accurate mass measurements were carried out on a Bruker MicroTOF mass spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford.

Compounds are characterised in a uniform manner herein. Numbers, according to the following nomenclature, are utilised to assign the structural core of indoles, pyrrolidinoindolines and piperazines where possible/required, with the aid of 2D NMR spectroscopy techniques.



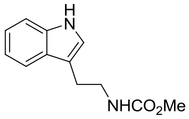






11.1 Synthesis of meso-chimonanthine

Methyl 2-(1H-indol-3-yl)ethylcarbamate[i] 9



Tryptamine (**8**) (50 g, 75 mmol) was suspended in a vigorously stirred 1 : 1 v/v mixture of aqueous sodium hydroxide solution (2 M, 470 mL, 940 mmol) and dichloromethane (470 mL). After cooling to 0 °C, methyl chloroformate (48 mL, 625 mmol) was added drop-wise. Once the addition was complete, the mixture was allowed to warm to room temperature. After 2 h, the phases were separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by crystallisation from a mixture of *iso*-propanol and hexane to give the carbamate **9** as a pale beige powder. Further recrystallisation of the filtrate from a mixture of *iso*-propanol and hexane gave a second batch of the carbamate **9** (total yield 64 g, 94%). mp 79-81 °C (lit. 79 °C); ν_{max} (KBr disk)/cm^{-1} 3400, 3280 (NH), 3070 (CH), 2960, 2940, 2890, 2850 (CH), 1690 (C=O), 1550 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.23 (1H, bs, N*H*), 7.62 (1H, d, *J* 7.8, H-4), 7.37 (1H, d, *J* 8.0, H-7), 7.22 (1H, dd, *J* 7.8, 7.0, H-6), 7.14 (1H, dd, *J* 8.0, 7.0, H-5), 7.00 (1H, s, H-2), 4.82 (1H, bs, N*H*), 3.68 (3H, s, O*Me*), 3.52 (2H, m, NCH_2CH_2), 2.98 (2H, t, *J* 6.8, NCH_2CH_2); ^{13}C (100 MHz, $CDCl_3$, 25 °C) δ 157.6, 136.9, 127.7, 122.9, 122.5, 119.9, 119.1, 113.2, 111.7, 52.5, 41.7, 26.2; *m/z* (ESI +) 219 (*MH*$^+$, 100%); (Found C, 65.8; H, 6.35; N, 12.8%; $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.84%).

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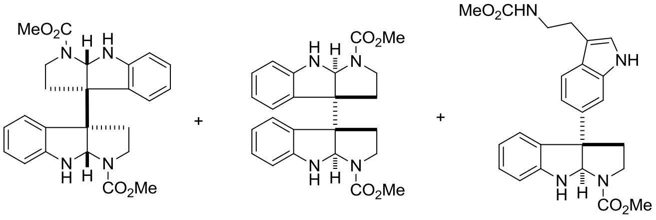
[i] *Tetrahedron Lett.*, **2002**, *43*, 5637

Dimethyl 3,3a,3',3'a,8,8a,8',8'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indole-1,1'(2H,2'H)-dicarboxylate, 11

(3a*S*,3'a*R*,8aS,8'a*R*)-Dimethyl 3,3a,3',3'a,8,8a,8',8'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indole-1,1'(2H,2'H)-dicarboxylate, 12

Methyl 3a-(3-(2-(methoxycarbonylamino)ethyl)-1H-indol-6-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate,[i,ii] 10



rac-C_2 *meso* C-6-dimer

Methyl 2-(1H-indol-3-yl)ethylcarbamate **9** (41.0 g, 188 mmol) was dissolved in trifluoroethanol (80 mL) and cooled to -30 °C in a jacketed vessel equipped with an efficient overhead stirrer. Phenyliodide bis(triflouroacetate) (52.5 g, 122 mmol) was added in six equal portions 30 min apart, and after the last addition the reaction was stirred for a further 2 h before being warmed to 0 °C. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution before being diluted with dichloromethane. The phases were isolated and the aqueous phase extracted thoroughly with further dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in the minimum volume of a 9:1 mixture of dichloromethane : ethyl acetate. This was seeded with crystals of *meso*-chimonanthine-methyl carbamate **12** (obtained by flash chromatography and

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[i] *Tetrahedron Lett.*, **2002**, *43*, 5637
[ii] *Bioorg. Med. Chem. Lett.*, **2002**, *10*, 2133

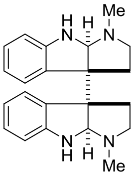
subsequent crystallisation) then left to stand for 16 h at rt. The resultant mixture was filtered and the filter cake washed with a 1:1 mixture of dichloromethane : ether to give the *meso*-carbamate **12** as a colourless needles (10.3 g, 25%, >10:1 *meso* **12** : C-6 **10**, by ^{1}H NMR spectroscopy). The liquors from the crystallisation were concentrated and purified by flash chromatography, eluting with 1 : 19 – 30 : 70 (ethyl acetate : dichloromethane), giving (in order of elution) the *rac*-C_2 **11** and *meso*-carbomethoxychimonanthines **12** and the C-6-dimer **10** as a beige foam. The C_2 enriched mixture of diastereomers recovered from the column could be further purified by recrystallisation from a mixture of chloroform and hexane to give an additional batch of *meso*-carbomethoxychimonanthine (2.5 g, 6%).

***rac*-dimer 11**: mp 187-188 °C (lit. 191 °C); ν_{max} (KBr disk)/cm^{-1} 3360 (NH), 3040, 2950, 2880 (CH), 1700 (C=O), 1450 (C=C); ^{1}H (400 MHz, $(CD_3)_2SO$, 120 °C) δ 7.24 (2H, d, *J* 7.5, H-4, 4’), 7.03 (2H, ddd, *J* 7.6, 7.5, 1.0, H-6, 6’), 6.65 (2H, app td), *J* 7.5, 1.0, H-5, 5’), 6.60 (2H, d, *J* 7.6, H-7, 7’), 6.04 (2H, bs, N*H*), 4.96 (2H, s, H-8a, 8a’), 3.61-3.54 (8H, m, H-2, 2’[incl. 3.57, 6H, s, O*Me*]), 2.81-2.74 (2H, m, H-2, 2’), 2.58-2.50 (2H, m, H-3, 3’), 2.16-2.09 (2H, dd, *J* 12.6, 5.9, H-3, 3’); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 154.5, 151.4, 129.1, 129.0, 124.9, 118.0, 109.2, 78.5, 60.0, 52.2, 45.2, 32.9; *m/z* (ESI +) 435 (MH^+, 30%).

***meso*-dimer 12**: mp 279-280 °C ($CHCl_3$/hexane) (lit. 276 °C); ν_{max} (KBr disk)/cm^{-1} 3360 (NH), 3060, 3000, 2960, 2890 (CH), 1690 (C=O), 1450, 1390, 1320, 1280, 1200, 1070, 890, 770, 750; ^{1}H (400 MHz, $(CD_3)_2SO$, 120 °C) δ 6.99 (2H, dd, *J* 7.6, 7.5, H-6, 6’), 6.63 (2H, d, *J* 7.3, H-4, 4’), 6.53-6.46 (4H, m, H-7, 7’, 5, 5’), 5.91 (2H, bs, H-8, 8’), 5.35 (2H, d, *J* 1.2, H-8a, 8a’), 3.68-3.62 (8H, m, H-2, 2’[incl. 3.66, 6H, s, O*Me*]), 2.89-2.81 (2H, m, H-2, 2’), 2.34-2.18 (4H, m, H-3, 3’); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 154.6, 151.3, 129.5, 128.9, 124.2, 117.8, 108.8, 77.6, 62.5, 52.3, 45.3, 34.3; *m/z* (ESI +) 435 (*MH*$^+$, 100%), 457, 869, 891; ; *m/z* (ESI +) 435 (*MH*$^+$, 30%) ; (Found C, 66.0; H, 5.97; N, 12.7%; $C_{24}H_{26}N_4O_4$ requires C, 66.34; H, 6.03; N, 12.89%).

C-6-dimer 10: mp 131-133 °C; ν_{max} (KBr disk)/cm^{-1} 3400, 3340 (NH), 3050, 2954 (CH), 1700 (C=O), 1520, 1460, 1390, 1250, 1200, 1050, 780, 750; ^{1}H (400 MHz, $(CD_3)_2SO$, 120 °C) δ 10.39 (1H, bs, H-1″), 7.46 (1H, d, *J* 8.3, H-4′), 7.30 (1H, s, H-7`), 7.09-6.98 (4H, m, H-4, 6, 2’, 5’), 6.69-6.54 (3H, m, H-5, 7, 1′), 6.11 (1H, bs, H-8), 5.49 (1H, s, H-8a), 3.84-3.77 (1H, m, H-2), 3.68 (3H, s, O*Me*), 3.56 (3H, s, O*Me*), 3.33-3.26 (2H, m, NC*H*$_2$CH$_2$), 3.09-3.01 (2H, m, H-2), 2.87-2.81 (2H, m, NCH$_2$C*H*$_2$), 2.72-2.57 (2H, m, H-3); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 156.1, 153.8, 149.0, 136.9, 136.0, 132.6, 127.3, 125.6, 123.2, 122.3, 117.7, 117.5, 116.0, 111.3, 108.7, 107.9, 82.5, 59.0, 51.3, 50.4, 45.3, 40.9, 36.3, 25.0; ; *m/z* (ESI +) 435 (*MH*$^+$, 15%) .

(3a*S*,3'a*R*,8a*S*,8'a*R*)-1,1'-Dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *meso*-chimonanthine,[i] **2**



Red-Al (65% [~3.5 M] in toluene, 55 mL, 193 mmol) was added drop-wise to a suspension of *meso*-dimer **12** (8.4 g, 19.3 mmol) in toluene (700 mL) at room temperature. The reaction was heated at reflux for 16 h, and was allowed to cool to room temperature before being quenched with 5% aqueous sodium hydroxide (200 mL). The crude mixture

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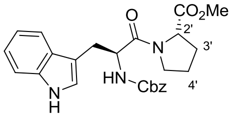
[i] *J. Am. Chem. Soc.*, **1996**, *118*, 8166

was filtered through celite and the phases separated. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from a mixture of dichloromethane and *iso*-hexane to give *meso*-chimonanthine **2** as a white crystalline solid (5.4 g, 81%), concentration of the liquors and subsequent recrystallization yielded an additional batch of product (~5%). [If required, the product can be purified by flash chromatography, eluting with 9 : 1 : 0.15 ($CHCl_3$: MeOH : NH_3), ≥95% when purified by chromatography alone, on *ca* 5 g scale]. mp 197-198 °C ($CHCl_3$/hexane) (lit. 196-197 °C); ν_{max} (KBr disk)/cm^{-1} 3400 (NH), 3050, 2960, 2950, 2860, 2820 (CH), 1600, 1490, 1470, 1350, 1320, 1250, 1160, 1120, 990, 910, 750; ^1H (400 MHz, $(CD_3)_2SO$, 120 °C) δ 6.87 (2H, odd, *J* 7.6, 7.5, H-6, 6’), 6.55 (2H, bs, H-4, 4’), 6.40-6.34 (4H, m, H-5, 5’, 7, 7’), 5.49 (2H, s, N*H*), 4.58 (2H, s, H-8a, 8a’), 2.70 (2H, m, H-2, 2’), 2.52-2.43 (2H, m, H-2, 2’), 2.37-2.29 (8H, m, H-3, 3’[incl. 2.28, 6H, s, N*Me*]), 1.92-1.86 (2H, m, H-3, 3’); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 153.1, 133.5, 127.8, 124.3, 116.7, 107.8, 83.6, 63.7, 52.2, 35.9, 22.6; *m/z* (ESI +) 347 (MH^+, 100%), 693; (Found C, 75.9; H, 7.55; N, 16.1%. $C_{22}H_{26}N_4$ requires C, 76.27; H, 7.56; N, 16.17%).

11.2 Towards the Total Synthesis of Nasesazine B

(*S*)-Methyl 1-((*S*)-2-(benzyloxycarbonylamino)-3-(1H-indol-3-yl)propanoyl)pyrrolidine-2-carboxylate, 77



Triethylamine (5.56 mL, 40.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.96 g, 26.0 mmol), hydroxybenzotriazole (1.24 g, 9.20 mmol) and proline methyl ester hydrochloride **76** (3.00 g, 18.2 mmol) were added sequentially to a stirred solution of (*S*)-2-(benzyloxycarbonylamino)-3-(1H-indol-3-yl)propanoic acid **75** (6.76 g, 20.0 mmol) in dichloromethane (250 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for a further 5 h, before being partitioned between saturated aqueous sodium bicarbonate and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with dichloromethane, the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 3 : 17 (petrol : ethyl acetate) to give the *amide* **77** as a white solid (6.28 g, 77%). ν_{max} (neat)/cm^{-1} 3420 (NH), 3000, 2950 (CH), 1710 (C=O), 1680, 1510 (C=C); ^{1}H (300 MHz, $(CD_3)_2SO$, 82 °C) δ 10.64 (1H, s, N*H*), 7.57 (1H, d, *J* 7.7, Ar*H*), 7.39-7.24 (7H, m, Ar*H*), 7.19 (1H, s, H-2), 7.09 (1H, td, *J* 7.9, 1.2, Ar*H*), 7.00 (1H, td, *J* 7.4, 0.9, Ar*H*), 5.00 (2H, s), 4.59 (1H, app q, *J* 7.7), 4.40-4.37 (1H, m), 3.64 (3H, s, O*Me*), 3.65-3.55 (1H, br m), 3.47-3.36 (1H, br m), 3.13 (1H, dd, *J* 14.9, 5.6, CH_2CHN), 2.99 (1H, dd, *J* 14.9, 7.9, CH_2CHN), 2.21-2.07 (1H, br m), 1.93-1.77 (3H, br m); ^{13}C (75 MHz, $(CD_3)_2SO$, 82 °C) δ 171.7, 169.9, 155.7, 136.6, 135.8, 127.8, 127.2, 127.0, 123.6, 120.4, 118.0, 117.5, 111.0, 109.3, 65.1, 58.3, 53.0, 51.1, 46.0, 28.0, 26.8, 24.1; *m/z* (ESI +) 472 ($M+Na^+$, 100%); $[\alpha]_D^{20.0}$ -25 (c = 1.1, $CHCl_3$).

(*S*)-3-(1H-Indol-3-yl)-2-(methoxycarbonylamino)propanoic acid,[i] 80

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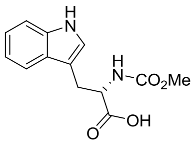
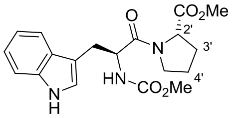
[i] *Chem. Pharm. Bull.*, **1984**, *32*, 2126



Methyl chloroformate (4.2 mL, 54.0 mmol) was added drop-wise t0 a stirred solution of tryptophan **79** (10.0 g, 49.0 mmol) and sodium hydroxide (2.2 g, 54.0 mmol) in a 1 : 1 mixture of tetrahydrofuran and water (100 mL). The reaction was stirred overnight at room temperature before being concentrated *in vacuo*; the residue was dissolved in dichloromethane and acidified to pH 4 with aqueous hydrochloric acid (1 M). The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from a mixture of dichloromethane and *iso*-hexane to give the carbamate **80** as a colourless solid (11.9 g, 93%). mp 145-146 °C (DCM/petrol); ν_{max} (neat)/cm^{-1} 3380 (OH), 3340 (NH), 2920, 2850 (CH), 1730, 1670 (C=O), 1620, 1550, 1510 (C=C); ^{1}H (400 MHz, $(CD_3)_2SO$) δ 12.66 (1H, s, O*H*), 10.84 (1H, s, H-1), 7.53 (1H, d, *J* 7.9, H-4), 7.43 (1H, d, *J* 8.1, N*H*), 7.34 (1H, d, *J* 7.9, H-7), 7.15 (1H, s, H-2), 7.07 (1H, app t, *J* 7.9, H-6), 6.99 (1H, app t, *J* 7.9, H-5), 4.20 (1H, ddd, *J* 9.7, 8.1, 4.3, CH_2C*H*N), 3.48 (3H, s, O*Me*), 3.17 (1H, dd, *J* 14.5, 4.3, CH_2CHN), 2.97 (1H, dd, *J* 14.5, 9.7, CH_2CHN); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 174.6, 157.4, 137.0, 127.9, 124.6, 121.8, 119.2, 118.9, 112.3, 110.9, 55.7, 52.2, 27.7; *m/z* (ESI +) 261 (*M-H*$^-$, 100%).

(*S*)-Methyl 1-((*S*)-3-(1H-indol-3-yl)-2-(methoxycarbonylamino)propanoyl)pyrrolidine-2-carboxylate, 81

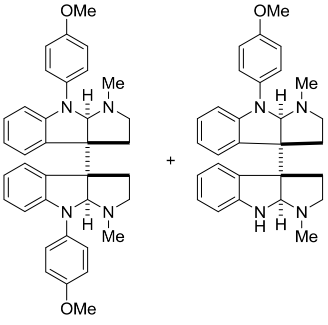


Triethylamine (3.18 mL, 22.9 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.84 g, 14.9 mmol), hydroxybenzotriazole (0.71 g, 5.3 mmol) and L-proline methyl ester hydrochloride **76** (1.89 g, 11.4 mmol) were added sequentially to a stirred solution of (*S*)-3-(1H-indol-3-yl)-2-(methoxycarbonylamino)propanoic acid **80** (3.00 g, 11.4 mmol) in dichloromethane (300 mL). The reaction was stirred overnight at room temperature before being partitioned between aqueous hydrochloric acid (1 M) and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from a mixture of *iso*-propanol, dichloromethane and *iso*-hexane to give the *amide* **81** as a colourless solid (3.92 g, 77%). mp 164-165 °C (DCM/petrol); ν_{max} (neat)/cm^{-1} 3320 (NH), 3060, 2950, 2880 (CH), 1740, 1710 (C=O), 1640, 1530, 1450 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.26 (1H, s, N*H*), 7.71 (1H, d, *J* 7.7, H-4), 7.36 (1H, d, *J* 7.6, H-7), 7.23-7.07 (3H, m, Ar*H*), 5.54 (1H, d, *J* 8.3, N*H*), 4.82 (1H, m, CH_2C*H*N), 4.51 (1H, dd, *J* 8.3, 4.4, H-2’), 3.73 (3H, s, O*Me*), 3.64 (3H, s, O*Me*), 3.59-3.48 (1H, m, H-5’), 3.27 (1H, dd, *J* 14.4, 5.4, CH_2CHN), 3.18 (1H, dd, *J* 14.4, 5.6, CH_2CHN), 3.12-3.03 (1H, m, H-5’), 2.20-2.09 (3H, m, H-3’), 1.95-1.79 (1H, m, H-3’, H-4’); ^{13}C (100 MHz, $CDCl_3$) δ 172.5, 171.0, 156.6, 136.0, 127.7, 123.9, 121.9, 119.6, 118.5, 111.2, 109.8, 58.9, 58.7, 52.8, 52.2, 46.9, 29.0, 28.6, 24.9; *m/z* (ESI +) 396 ($M+Na^+$, 100%); (ESI, HRMS) Found 396.1535 ($M+Na^+$), $C_{19}H_{23}N_3O_5$ Na requires 396.1530. $[\alpha]_D^{25}$ -36 (c = 1.1, $CHCl_3$).

11.3 Asymmetric Buchwald-Hartwig Cross Coupling

(3a*S*,3'a*R*,8a*R*,8'a*S*)-8,8'-*bis*(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *bis-Product,* 85

8-(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *mono-Product,* 84



bis -product *mono*-product

General Procedure for the screening of aryl halide, base, ligand, palladium source and solvent: *meso*-Chimonanthine **2** (100 mg, 0.29 mmol), palladium source (5 mol%, Pd), ligand (6 mol%) and base (0.49 mmol) were combined in a dry flask and purged with argon before being dissolved in dry degassed toluene (1 mL). The reaction was stirred at 50 °C for ~2 min before the aryl halide (0.38 mmol) was added drop-wise *via* syringe over ~1 min. The reaction was stirred at 50 °C for 16 h, before being allowed to cool to room temperature. The reaction was diluted with dichloromethane (5 mL) and loaded directly onto a silica column. The crude mixture was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give, in order of elution; the *bis-product* **85**, the *mono-product* **84** and recovered *meso*-chimonanthine **2**.

Optimised Procedure: *meso*-Chimonanthine **2** (100 mg, 0.289 mmol), (*R,S*)-[(CyPF-*t*Bu)PdCl$_2$] (10 mg, 5 mol%)[i] and potassium *tert*-butoxide (50 mg, 0.446 mmol) were combined in a dry flask, before being dissolved in dry degassed toluene (1 mL) and warmed to 50 °C for 5 min. 4-Bromoanisole (0.047 mL, 0.376 mmol) was added dropwise *via* syringe over ~1 min. The reaction was stirred at 50 °C for 16 h before being allowed to cool to room temperature. The reaction was diluted with dichloromethane (5 mL) and loaded onto silica. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 (CHCl$_3$: MeOH : NH$_3$) to give, in order of elution, the *bis-product* **85** (22 mg, 13%), the *mono-product* **84** (74 mg, 57%) and recovered *meso*-chimonanthine **2** (20 mg, 20%) as colourless foams.

bis **product 85:** mp 188-189 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3040, 2930, 2850, 2790, 2670 (C-H), 1650, 1600, 1510, 1480, 1460 (C=C); ^{1}H (250 MHz, (CD$_3$)$_2$SO, 120 °C) δ 6.97 (2H, app t, *J* 7.9, Ar*H*), 6.88-6.63 (10H, m, Ar*H*), 6.54 (2H, app t, *J* 6.9, Ar*H*), 6.35 (2H, app d, *J* 7.9, H-7, 7’), 4.94 (2H, s, H-8a, 8a’), 3.71 (6H, s, 2 × O*Me*), 2.87-2.78 (2H, m, H-2, 2’), 2.63-2.45 (4H, m, H-2, 2’, 3, 3’), 2.27 (6H, s, N*Me*), 2.16-2.05 (2H, m, H-3, 3’); ^{13}C (63 MHz, (CD$_3$)$_2$SO, 90 °C) δ 157.2, 139.3, 134.0, 128.7, 125.2, 118.9, 115.5, 108.5, 91.1, 80.0, 70.8, 63.5, 56.2, 53.0, 37.8, 36.8; *m/z* (ESI +) 559 (*MH*$^+$, 100%), 560; (ESI, HRMS) Found 559.3068 (*MH*$^+$), $C_{36}H_{39}N_4O_2$ requires 559.3068.

mono **product 84:** mp: 89-90 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3380 (br, NH), 3040, 2960, 2860, 2780 (CH), 1602, 1510, 1480, 1460 (C=C); ^{1}H (250 MHz, (CD$_3$)$_2$SO, 120 °C) δ 6.97-6.86 (3H, m, Ar*H*), 6.80-6.67 (2H, m, Ar*H*), 6.69-6.66 (2H, m, Ar*H*), 6.59 (1H, t, *J* 7.3, Ar*H*), 6.44 (1H, d, *J* 7.8, Ar*H*), 6.31-6.24 (3H, m, Ar*H*), 5.69 (1H, bs, N*H*), 4.82 (1H,

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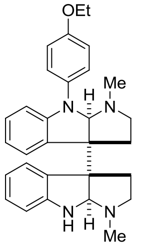
[i] (*R,S*)-[(CyPF-*t*Bu)PdCl$_2$] prepared in accordance with *Org. Lett.*, **2008**, *10*, 4109

bs, H-8a), 4.68 (1H, bs, H-8a’), 3.73 (3H, s, O*Me*), 2.81-2.72 (2H, m), 2.58-2.43 (3H, m), 2.40-2.29 (4H, m, [incl. 2.33, 3H, s, N*Me*]), 2.23 (3H, s, N*Me*), 2.07-2.01 (1H, m, H-3), 1.93 (1H, ddd, *J* 11.3, 5.1, 1.6, H-3’); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 157.2, 153.4, 139.4, 134.2, 133.2, 128.6, 128.4, 127.9, 127.8, 125.0, 124.9, 118.6, 117.1, 115.3, 108.3, 108.0, 91.1, 83.7, 64.1, 63.4, 56.2, 52.9, 52.6, 37.82, 37.80, 36.5, 36.2; *m/z* (ESI +) 454 (MH^+, 100%), 905; (ESI, HRMS) Found 453.2643 (MH^+), $C_{29}H_{33}N_4O_1$ requires 453.2649. Enantiomers of the *title compound* were separated by HPLC using Chiracel AD-H column; [91.9 : 0.1] : 8 ([hexane : diethylamine] : *iso*-propanol); 0.5 mL / min; t_r= 9.61 min and t_r= 10.31 min; 53% ee.

General Procedure 01 exemplified by the synthesis of: 8-(4-ethoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 4

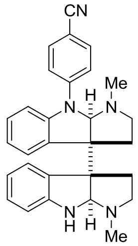


meso-Chimonanthine **2** (100 mg, 0.29 mmol), palladium acetate (3 mg, 5 mol%), potassium *tert*-butoxide (48 mg, 0.49 mmol), (*R*,*S*)-PPFA (8 mg, 6 mol%) were combined in a dry flask and purged with argon. Anhydrous, degassed toluene (1 mL) was added and the reaction mixture stirred for 5 min at room temperature. 4-Bromophenetole (0.054 mL, 0.38 mmol) was added drop-wise *via* syringe before the reaction was warmed to 50 °C and stirred for 16 h. The reaction was allowed to cool to room temperature before being absorbed onto silica, the crude product was purified by flash chromatography eluting with

21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *title compound* as a pale beige foam (15 mg, 11%). mp 120-123 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3380 (br, NH), 3940, 2960, 2930, 2860, 2790 (CH), 1600, 1510, 1483 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 6.99-6.91 (3H, m, Ar*H*), 6.80-6.76 (2H, m, Ar*H*), 6.70-6.67 (2H, m, Ar*H*), 6.61 (1H, t, *J* 7.3, Ar*H*), 6.46 (1H, d, *J* 7.8, Ar*H*), 6.33-2.26 (3H, m, Ar*H*), 5.71 (1H, bs, N*H*), 4.84 (1H, bs, H-8a), 4.70 (1H, bs, H-8a'), 4.02 (2H, q, *J* 6.9, OCH_2CH_3), 2.83-2.74 (2H, m, H-2, 2'), 2.60-2.44 (3H, m), 2.42-2.32 (4H, m, [incl. 2.35, 3H, s, N*Me*]), 2.26 (3H, s, N*Me*), 2.09-2.03 (1H, m, H-3), 1.95 (1H, ddd, *J* 11.6, 5.3, 1.8, H-3'), 1.32 (3H, t, *J* 6.9, OCH_2CH_3) ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 156.4, 153.4, 139.4, 134.3, 133.3, 128.6, 128.4, 127.8, 127.7, 125.0, 124.9, 118.6, 117.1, 116.0, 108.3, 108.1, 91.1, 83.8, 64.2, 64.1, 63.4, 52.9, 52.6, 37.9, 37.8, 36.5, 36.2, 15.5; *m/z* (ESI +) 468 (*MH*$^+$, 100%), 489, 933; (ESI, HRMS) Found 467.2805 (*MH*$^+$), $C_{30}H_{35}N_4O$ requires 467.2805.

Enantiomers of the title compound were separated by HPLC using Chiracel AD-H column; [91.9 : 0.1] : 8 ([hexane : diethylamine] : *iso*propanol); 0.5 mL / min; t_r= 8.493 min and t_r= 9.247 min; 40% ee.

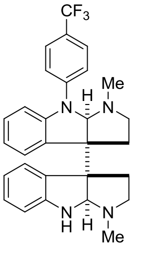
4-(1,1'-Dimethyl-1,1',2,2',3,3a,3',3'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH,8'aH)-yl)benzonitrile, Table 12, Entry 6



Synthesised using general procedure **01** using: *meso*-chimonanthine **2** (100 mg, 0.29 mmol), palladium acetate (3 mg, 5 mol%), potassium *tert*-butoxide (48 mg, 0.49 mmol), (*R*)-MOP (8 mg, 6 mol%), bromobenzonitrile (68 mg, 0.38 mmol). The general procedure afforded the title compound as a pale beige foam (9 mg, 7%). mp 91-92 °C (Et_2O); ν_{max} (film)/cm^{-1} 3380 (br, NH), 2930, 2790 (CH), 2220 (CN), 1590, 1509, 1480 (C=C); ^1H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.55 (2H, app d, *J* 8.1, H-3''), 7.21-7.12 (4H, m, Ar*H*), 7.02 (2H, app d, *J* 7.9, Ar*H*), 6.87 (1H, app t, *J* 7.2, Ar*H*), 6.75-6.68 (1H, m, Ar*H*), 6.26 (2H, app d, *J* 8.1, H-2''), 5.76 (1H, bs, N*H*), 4.92 (1H, bs, H-8a), 4.41 (1H, bs, H-8a'), 2.83-2.74 (1H, m), 2.71-2.65 (1H, m), 2.56-2.29 (7H, m, [incl. 2.40, 3H, s, N*Me*]), 2.26-2.10 (4H, m, [incl. 2.21, 3H, s, N*Me*]), 1.93-1.86 (1H, m, H-3'); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 152.8, 149.4, 147.2, 137.1, 133.8, 132.4, 128.5, 128.4, 125.7, 124.4, 122.2, 120.1, 119.0, 117.3, 113.0, 108.5, 103.3, 90.9, 84.4, 65.6, 63.6, 63.1, 53.8, 52.7, 38.6, 37.5, 36.4; *m/z* (ESI +) 448 (MH^+, 100%), 895; (ESI, HRMS) Found 448.2499 (MH^+), $C_{29}H_{30}N_5$ Requires 448.2496.

Enantiomers of the title compound were separated by HPLC using Chiracel AD-H column; [96.9 : 0.1] : 3 ([hexane : diethylamine] : *iso*propanol); 0.5 mL / min; t_r= 29.86 min and t_r= 31.67 min; 4% ee.

1,1'-Dimethyl-8-(4-(trifluoromethyl)phenyl)-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 7

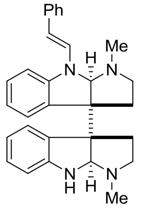


Synthesised using general procedure **01** using: *meso*-Chimonanthine **2** (100 mg, 0.29 mmol), palladium acetate (3 mg, 5 mol%), potassium *tert*-butoxide (48 mg, 0.49 mmol),

(R)-MOP (8 mg, 6 mol%), 1-bromo-4-(trifluoromethyl) benzene (0.051 mL, 0.38 mmol). The general procedure afforded the title compound as a pale beige foam (50 mg, 35%). mp 60-62 °C (as foam from Et_2O); ν_{max} (film)/cm^{-1} 3050, 2960, 2930, 2860, 2790 (CH), 1650, 1600, 1320 (C=C); ^1H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.47 (2H, d, *J* 8.5, H-3''), 7.14-7.07 (3H, m, Ar*H*), 6.97 (1H, br d, *J* 7.1, Ar*H*), 6.88-6.70 (3H, m, Ar*H*), 6.31-6.24 (3H, m, [incl. 6.30, 2H, d, *J* 8.5, H-2'']), 5.63 (1H, bs, N*H*), 4.94 (1H, s, H-8a), 4.46 (1H, bs, H-8a'), 2.82-2.65 (2H, m, H-2, 2'), 2.57-2.29 (7H, m, [incl. 2.36, 3H, s, N*Me*]), 2.21 (3H, s, N*Me*), 2.17-2.07 (1H, m, H-3), 1.94-1.87 (1H, m, H-3'); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 152.9, 149.2, 148.5, 136.4, 132.6, 128.5, 128.3, 126.8 (q, *J* 3.8), 125.6, 124.5, 123.1, 121.3, 120.5 (2 × C), 117.3, 111.6, 108.4, 90.9, 84.2, 63.6, 63.3, 53.6, 52.6, 38.4, 37.6, 36.3, 35.3; *m/z* (ESI +) 491 (MH^+, 100%); (ESI, HRMS) Found 491.2417 (MH^+), $C_{29}H_{30}F_3N_4$ requires 491.2417.

Enantiomers of the title compound were separated by HPLC using Chiracel AD-H column; [91.9 : 0.1] : 8 ([hexane : diethylamine] : *iso*-propanol); 0.5 mL / min; t_r= 8.311 min and t_r= 8.688 min; 10% ee.

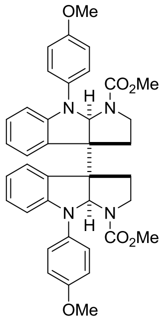
1,1'-Dimethyl-8-(1-phenylvinyl)-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 8



Anhydrous toluene (1.45 mL) was added with stirring to a dry flask containing *meso*-chimonanthine **2** (100 mg, 0.289 mmol), palladium acetate (3 mg, 5 mol%), potassium *tert*-butoxide (97 mg, 0.867 mmol) and (*R*,*S*)-PPFA (8 mg, 6 mol%) before the mixture was warmed to 65 °C. *Trans*-(2-bromovinyl)benzene (0.044 mL, 0.347 mmol) was added drop-wise *via* syringe and the reaction stirred for 16 h at 65 °C. The reaction was allowed to cool to room temperature before being absorbed onto silica, and the crude product was purified by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *title compound* as a pale beige foam (44 mg, 34%). mp 75-77 °C (as foam from Et_2O); ν_{max} (film)/cm^{-1} 3390 (NH), 3050, 2960, 2940, 2860, 2790 (CH), 1640, 1590, 1570, 1480, 1460 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.24-7.11 (5H, m, Ar*H*), 7.08-6.92 (3H, m, Ar*H*, H-1’’), 6.86-6.64 (3H, m, Ar*H*), 6.42-6.29 (3H, m, Ar*H*), 5.83 (1H, d, *J* 14.3, H-2’’), 5.59 (1H, s, N*H*), 4.89 (1H, s, H-8a’), 4.42 (1H, s, H-8a), 2.82-2.62 (2H, m, H-2, 2’), 2.55-2.20 (10H, m, [incl. 2.30, 3H, s, N*Me*]), 2.16-2.00 (1H, m, H-3), 1.99-1.84 (1H, m, H-3’); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 153.1, 149.0, 139.5, 135,1, 132.7, 131.4, 129.1, 129.0, 128.4, 125.3, 125.2, 125.0, 124.4, 120.9, 117.1, 109.4, 108.6, 104.7, 87.7, 84.3, 63.9, 63.5, 54.0, 52.8, 38.6, 37.4, 36.5, 35.4 ; *m/z* (ESI -) 447 (M-H^+,100%); (ESI, HRMS) Found 447.2554 (M-H^+) $C_{30}H_{31}N_4$ Requires 447.2554.

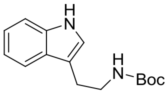
Enantiomers of the *title compound* were separated by HPLC using Chiracel OD-H column; [97.6 : 0.4] : 2 ([hexane : diethylamine] : *iso*-propanol); 1 mL / min; t_r= 10.71 min and t_r= 23.30 min; 8% ee.

(3a*S*,3'a*R*,8a*S*,8'a*R*)-Dimethyl 8,8'-*bis*(4-methoxyphenyl)-3,3a,3',3'a,8,8a,8',8'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indole-1,1'(2H,2'H)-dicarboxylate, 87



meso-Carbamate **12** (127 mg, 0.29 mmol), palladium acetate (3 mg, 5 mol%), S-Phos (7 mg, 6 mol%) and caesium carbonate (141 mg, 0.49 mmol) were combined in a dry flask. Anhydrous, degassed toluene (1 mL) was added and the reaction mixture stirred for 5 min at 65 °C. 4-Bromoanisole (0.047 mL, 0.39 mmol) was added drop-wise *via* syringe, and the reaction was stirred for 64 h. The reaction was allowed to cool to room temperature before being diluted with dichloromethane (5 mL) and loaded onto silica, the crude product was purified by flash chromatography eluting with 4 : 21 (ethyl acetate : chloroform), giving in order of elution; *bis-product* **87** (33 mg, 18%) and recovered starting material as colourless foams. mp 152-153 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3010, 2950, 2840 (CH), 1700 (C=O), 1600 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.35 (2H, d, *J* 7.3, H-4, 4’), 7.13 (4H, d, *J* 8.9, H-3’’), 7.03 (2H, app t, *J* 7.3, H-6, 6’), 6.92 (4H, d, *J* 8.9, H-2’’), 6.68 (2H, app t, *J* 7.3, H-5, 5’), 6.41 (2H, d, *J* 7.3, H-7, 7’), 5.60 (2H, s, H-8a, 8a’), 3.91 (2H, app dd, *J* 11.3, 7.6, H-2, 2’), 3.79 (6H, s, O*Me*), 3.24 (6H, s, CO_2*Me*), 2.90 (2H, app td, *J* 11.3, 5.6, H-2, 2’), 2.57 (2H, ddd, *J* 12.3, 11.4, 7.6, H-3, 3’), 2.26 (2H, app dd, *J* 12.3, 5.4, H-3, 3’); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 157.8, 154.8, 150.5, 135.4, 130.8, 129.5, 127.1, 125.1, 119.1, 115.4, 108.5, 80.0, 62.8, 56.3, 52.6, 45.5, 35.7; *m/z* (ESI +) 647 (*MH*$^+$, 100%), 669; (ESI, HRMS) Found 669.2676 (*M*+*Na*$^+$), $C_{38}H_{38}N_4O_6Na$ requires 669.2684.

tert-Butyl 2-(1H-indol-3-yl)ethylcarbamate,[i,ii] 88



Saturated aqueous sodium bicarbonate solution (55 mL), and di-*tert*-butyl dicarbonate (10.2 g, 47.0 mmol) were added sequentially to a stirred solution of tryptamine **8** (5.0 g, 31.2 mmol) in tetrahydrofuran (110 mL) at room temperature. The resultant suspension was stirred for 2 h before being partitioned between water and ethyl acetate. The organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation from a mixture of *iso*-propanol and hexane to give the *tert*-butyl carbamate **88** as a colourless crystalline solid (5.6 g, 69%). mp 95-97 °C (IPA/hexane) (lit. 94-95 °C); ν_{max} (KBr disk)/cm^{-1} 3410, 3320 (NH), 3060, 3000, 2980, 2930 (CH), 1690, 1620 (C=O), 1510, 1460 (C=C); ^{1}H (400 MHz, $CDCl_3$, 25 °C) δ 8.20 (1H, bs, N*H*), 7.62 (1H, d, *J* 7.8, H-4), 7.38 (1H, d, *J* 7.8, H-7), 7.22 (1H, app td, *J* 7.8, 1, H-6), 7.14 (1H, app td, *J* 7.8, 1, H-5), 7.03 (1H, bs, H-2), 4.65 (1H, bs, N*H*), 3.48 (2H, m, CH_2CH_2NH), 2.97 (2H, t, *J* 6.7, CH_2CH_2NH), 1.46 (9H, s, *t-Bu*); ^{13}C (100 MHz, $CDCl_3$, 25 °C) δ 153.3, 136.6, 127.6, 122.4, 122.3, 119.6, 119.1, 113.3, 111.5, 79.4, 41.1, 28.7, 26.0.

tert-Butyl 8'-(4-methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate, 89

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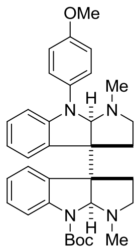
[i] *J. Am. Chem. Soc.*, **2004**, *126*, 12888
[ii] *Synthesis,* **2006**, *23*, 3948

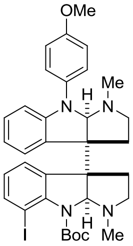


Method A**:** Potassium *bis*(trimethylsilyl)amide (0.5 M in THF, 3.87 mL, 1.93 mmol) was added drop-wise *via* syringe pump over 30 min to a stirred solution of (±)-*desymmetrized product* **84** (398 mg, 0.88 mmol) and di-*tert*-butyl dicarbonate (294 mg, 1.14 mmol) in tetrahydrofuran (15 mL) at room temperature. The reaction was stirred for a further 2 h before being diluted with dichloromethane and loaded onto silica. The crude product was purified by flash chromatography, eluting with 4 : 1 (ethyl acetate : hexane) to give the *title compound* **89** as a colourless foam (403 mg, 83%).

Method B**:** Potassium *tert*-butoxide (480 mg, 4.30 mmol), *meso*-chimonanthine **2** (1.00g, 2.89 mmol) and 4-bromo-anisole (0.43 mL, 3.47 mmol) were added sequentially to a stirred solution of palladium acetate (32 mg, 5 mol%), and (*R,S*)-PPFA (76 mg, 6 mol%) in toluene (20 mL). The reaction was warmed to 65 °C and stirred for 16 h. The reaction was allowed to cool to room temperature before being treated sequentially with di-*tert*-butyl dicarbonate (819 mg, 3.75 mmol) and sodium *bis*(trimethylsilyl)amide (1.5 M in THF, 4.24 mL, 6.36 mmol). The reaction was stirred at room temperature for an additional 6 h before being partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was isolated and the aqueous layer extracted with additional ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give *title compound* **89** as a colourless foam

(771 mg, 48%). mp 171-173 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3040, 2960, 2920, 2850 (CH), 1700 (CO), 1600, 1510, 1480 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.52 (1H, d, *J* 8.0, H-7'), 7.19 (1H, app t, *J* 7.5, H-6'), 7.96-6.81 (6H, m, Ar*H*), 6.76 (1H, bs, Ar*H*), 6.50 (2H, bs, Ar*H*), 6.34 (1H, d, *J* 8.0, H-7), 5.20 (1H, bs, H-8a'), 4.72 (1H, bs, H-8a), 3.77 (3H, s, O*Me*), 2.79 (2H, m, H-2, 2'), 2.65-2.38 (7H, m, [incl. 2.45, 3H, s, N*Me*]), 2.28 (3H, s, N*Me*), 2.13-2.03 (2H, m, H-3, 3'), 1.37 (9H, s, *t-Bu*); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 157.2, 153.0, 152.0, 138.7, 136.2, 132.8, 128.8, 128.6, 126.9, 125.0, 124.6, 123.3, 118.6, 116.3, 115.5, 108.0, 91.3, 85.4, 84.4, 81.1, 62.9, 62.2, 56.2, 53.6, 53.2, 38.4, 37.1, 36.5, 35.5, 28.7; *m/z* (ESI +) 553 (*MH*$^+$, 100%); (ESI, HRMS) Found 553.3160 (*MH*$^+$), $C_{34}H_{41}N_4O_3$ Requires 553.3173.

tert-Butyl 7-iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate, 90

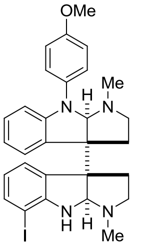


Method A**:** *sec*-Butyl lithium (1.05 mL, 1.37 mmol) was added drop-wise *via* syringe, to a stirred solution of *tert*-butyl 8'-(4-methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate **89** (378 mg, 0.68 mmol) and tetramethylethylenediamine (0.31 mL, 1.37 mmol) in ether (10 mL) at -78 °C. The reaction was stirred for 30 min before di-iodoethane (394 mg, 1.37 mmol) was added portionwise over 15 min. The reaction was warmed to 0 °C and stirred for a further 1 h. The reaction was partitioned between saturated aqueous ammonium chloride solution and dichloromethane, the organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *carbamate* **90** as a light purple foam (217 mg, 47%).

Method B**:** *sec*-Butyl lithium (0.15 mL, 0.20 mmol) was added drop-wise *via* syringe, to a stirred solution of *tert*-Butyl 8'-(4-methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate **89** (54 mg, 0.098 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.05 mL, 0.29 mmol) in ether (2 mL) at -78 °C. The reaction was stirred for 30 min before iodine (50 mg, 0.20 mmol) was added in a single portion. The reaction was stirred at -78 °C for 5 min before being warmed to 0 °C and stirred for an additonal 1 h. The reaction was partitioned between aqueous sodium hydroxide solution (1 M) and dichloromethane, the organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 4 : 1 (EtOAc : petrol) to give the *carbamate* **90** as a pale amber foam (46 mg, 70%). mp 85-87 °C (foam, DCM); ν_{max} (film)/cm^{-1} 2970, 2940, 2870, 2850, 2800 (CH), 1710 (C=O), 1650, 1640, 1600, 1590, 1570, 1550, 1500 (C=C); ^1H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.62 (1H, d, *J* 7.9, H-6'), 7.13 (1H, bs, Ar*H*), 7.07-6.85 (4H, m, Ar*H*), 6.81 (1H, bs, Ar*H*), 6.74-6.55 (2H, m, Ar*H*), 6.42 (1H, bs, Ar*H*), 6.34 (1H, d, *J* 7.9, H-7), 5.25 & 5.22 (1H, 2 × s, H-8a'), 4.66 & 4.60 (1H, 2 × bs, H-8a), 3.80 & 3.74 (3H, 2 × s, O*Me*), 2.92-2.72 (2H, m, H-2, 2'), 2.67-2.34 (6H, m, [incl. 2.50, 3H, s, N*Me*]), 2.32-2.10 (5H, m, [incl. 2.29, 3H, s, N*Me*]), 1.96-1.86

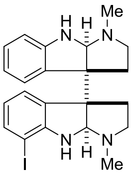
(1H, m, H-3); *Major Rotamer* ^{13}C (125 MHz, $(CD_3)_2SO$, 90 °C) δ 156.5, 152.9, 147.4, 128.9, 139.4, 136.4, 129.4, 127.8, 127.4, 126.4, 125.1, 125.0, 119.7, 115.7, 113.0, 108.9, 91.4, 88.1, 87.1, 85.7, 82.1, 63.6, 62.7, 57.7, 53.1, 52.8, 38.2, 36.7, 36.5, 28.9; *m/z* (ESI +) 679 (*MH*$^+$, 100%); (ESI, HRMS) Found 679.2138 (*MH*$^+$), $C_{34}H_{40}N_4O_3{}^{127}I$ Requires 679.2140.

7-Iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 91



Trimethylsilyl trifluoromethanesulfonate (0.055 mL, 0.30 mmol) was added drop-wise to a stirred solution of *tert*-butyl 7-iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate **90** (94 mg, 0.138 mmol) in dichloromethane (4 mL). The reaction was stirred at room temperature for 3 h, left open to air. The reaction was partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane, the organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *amine* **91** as a colourless foam (43 mg, 54%). mp 181-182 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 3280 (NH), 3040, 2960, 2930, 2860, 2790, 2660 (CH), 1680, 1600, 1510 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.30 (1H, d, *J* 7.4, H-6’), 7.09-6.87 (4H, m, Ar*H*), 6.82 (1H, d, *J* 8.6, Ar*H*), 6.77-6.58 (2H, m, Ar*H*), 6.33 (1H, app t, *J* 8.3, Ar*H*), 6.18-6.06 (2H, m, Ar*H*), 5.53 (1H, bs, N*H*), 4.83 (1H, bs, H-8a), 4.76 (1H, bs, H-8a'), 3.83 & 3.76 (3H, 2 × s, O*Me*), 2.87-2.76 (2H, m, H-2, 2'), 2.63-2.22 (10H, m, [incl. 2.40 & 2.38, 3H, 2 × s, N*Me*, 2.27 & 2.26, 3H, 2 × s, N*Me*]), 2.13-2.03 (1H, m, H-3), 1.99-1.87 (1H, m, H-3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) Appeared to exist as a complex mixture of rotary isomers, see appendix for spectra. *m/z* (ESI +) 579 (*MH*$^+$, 100%); (ESI, HRMS) Found 579.1606 (*MH*$^+$), $C_{29}H_{32}N_4O^{127}I$ Requires 579.1615.

7-Iodo-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 35

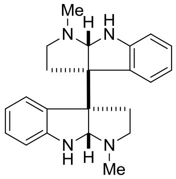


A solution of ceric ammonium nitrate (99 mg, 0.18 mmol) in water (1 mL) was added drop-wise to a stirred solution of 7-iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole **91** (35 mg, 0.06 mmol) in acetonitrile (1 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min before being partitioned between water and ethyl acetate, the organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *amine* **35** as a colourless foam (12 mg, 43%). mp 91-94 °C (DCM) (lit. 92-95 °C); ν_{max} (film)/cm^{-1} 3370 (NH), 2930 (CH), 1640, 1450 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$, 100 °C) δ 7.26 (1H, d, *J* 7.9, H-6'), 6.90 (1H, app t, *J* 8.5, Ar*H*), 6.69-6.39 (4H, m, Ar*H*), 6.20 (1H, bs, Ar*H*), 5.44

(1H, bs, N*H*), 5.12 (1H, bs, N*H*), 4.62 (1H, bs, H-8a), 4.50 (1H, bs, H-8a'), 2.73-2.67 (2H, m), 2.45-2.38 (2H, m, H-2, 2'), 2.31-2.27 (8H, m, [incl. 2.31, 3H, s, N*Me*, 2.27 & 3H, s, N*Me*]), 1.89-1.87 (2H, m, H-3, 3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 154.1, 153.0, 136.6, 134.2, 130.0, 128.4, 124.5, 124.4, 119.5, 117.1, 108.3, 83.6, 82.5, 73.7, 65.5, 63.9, 52.4, 52.4, 37.3, 37.0, 36.1, 36.0; *m/z* (ESI +) 473 (MH^+, 100%); (ESI, HRMS) Found 473.1195 (MH^+), $C_{22}H_{26}N_4{}^{127}I$ Requires 473.1197.

Data in accordance with literature[i]

1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, (±)-C_2-chimonanthine, 13[ii]



Red-Al (65% [~3.5 M] in toluene, 17 mL, 55.2 mmol) was added drop-wise to a suspension of C_2-dimer **11** (2.42 g, 5.5 mmol) in toluene (250 mL) at room temperature. The reaction was heated at reflux for 16 h, and was allowed to cool to room temperature before being quenched with 5% aqueous sodium hydroxide (100 mL). The crude mixture was filtered through celite and the phases separated. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 9 : 1 : 0.15 ($CHCl_3$: MeOH : NH_3) to give C_2-chimonantine **13** as a white crystalline solid (1.03 g, 54%). mp 175-176 °C (PhH) (lit.

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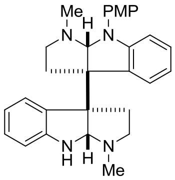
[i] *Angew. Chem. Int. Ed. Engl.*, **2003**, *42*, 2528

[ii] *Angew. Chem. Int. Ed. Engl.*, **2007**, *46*, 3725

176-178 °C); ν_{max} (neat)/cm^{-1} 3300 (NH), 3080, 3050, 3030, 3000, 2960, 2930, 2860, 2800 (CH), 1600, 1480 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.02 (2H, d, *J* 7.4, H-4, 4'), 6.77 (2H, app t, *J* 7.6, H-6, 6'), 6.41-6.33 (4H, m, H-5, 5', 7, 7'), 5.77, (2H, bs, N*H*), 4.53 (2H, bs, H-8a, 8a'), 2.55-2.22 (12H, m, [incl. 2.26, 6H, s, N*Me*]), 1.82-1.75 (2H, m, H-3, 3'); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 152.5, 134.1, 127.6, 124.2, 116.9, 108.1, 84.9, 63.4, 52.1, 36.8, 36.4; *m/z* (ESI +) 347 (*MH*$^{+}$, 100%).

Data in accordance with the literature.[i]

8-(4-Methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, *N-PMP-C$_2$-chimonanathine*, 92



Toluene (0.5 mL) and 4-bromo-anisole (0.01 mL, 0.08 mmol) were added sequentially to a flask containing (±)-C_2-chimonanthine **13** (50 mg, 0.14 mmol), [(*R*,*S*)-J009-1]$PdCl_2$ (6.1 mg, 6 mol%) and potassium *tert*-butoxide (23 mg, 0.21 mmol) under an inert atmosphere. The reaction was heated at 50 °C for 16 h before being allowed to cool to room temperature. The crude mixture was loaded directly onto a silica column and purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give in order of elution *bis-N-PMP-C$_2$-chimonanathine* (trace), *N-PMP-C$_2$-chimonanathine* **92** (22 mg, 50%) and *C$_2$-chimonanathine* **13** (32 mg, 45%) as a colourless foams.

N-PMP-C$_2$-chimonanathine **92:** mp 75-76 °C (foam, DCM); ν_{max} (film)/cm^{-1} 3390 (NH), 3040, 2930, 2840, 2790 (CH), 1600, 1510 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.33

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[i] *Angew. Chem. Int. Ed. Engl.*, **2007**, *46*, 3725

(2H, d, *J* 8.0, H-3''), 7.25 (1H, d, *J* 7.4, Ar*H*), 7.09 (1H, d, *J* 7.2, Ar*H*), 6.99 (2H, d, *J* 8.0 H-2''), 6.96-6.84 (2H, m, Ar*H*), 6.62 (1H, app t *J* 7.4, Ar*H*), 6.57-6.42 (3H, m, Ar*H*), 5.97 (1H, bs, N*H*), 4.78 (1H, bs, H-8a), 4.36 (1H, bs, H-8a'), 3.81 (3H, s, O*Me*), 2.63-2.34 (6H, m), 2.25 (3H, s, N*Me*), 2.16 (3H, s, N*Me*), 2.07-1.94 (2H, m, H-3, 3'); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 156.6, 152.7, 150.1, 138.1, 134.6, 133.7, 128.4, 128.3, 125.4, 125.1, 124.9, 118.6, 117.4, 115.7, 108.6, 107.9, 92.1, 85.7, 63.4, 63.3, 56.3, 53.4, 52.9, 39.9, 37.5, 36.4, 35.6; *m/z* (ESI +) 453 (MH^+, 100%); (ESI, HRMS) Found 453.2637 (MH^+), $C_{29}H_{33}N_4O$ Requires 453.2649.

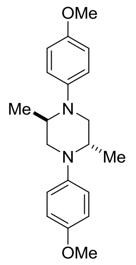
Enantiomers of *N-PMP-*C_2*-chimonanathine* **92** and C_2*-chimonanathine* **13** were separated by HPLC using Chiracel OD-H column; [97.6 : 0.4] : 2 ([hexane : diethylamine] : *iso*-propanol); 1 mL / min:

N-PMP-C_2*-chimonanathine* **92**: t_r= 14.4 min and t_r= 17.2 min; 3% ee.

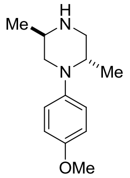
C_2*-chimonanathine* **13**: t_r= 20.14 min and t_r= 21.92 min; 3% ee.

(2*S*,5*R*)-1,4-*bis*(4-Methoxyphenyl)-2,5-dimethylpiperazine, *bis-Product,* 96

1-(4-Methoxyphenyl)-2,5-dimethylpiperazine, *mono*-Product, 95



Bis-product



Mono-product

trans-2,5-Dimethylpiperazine **59** (50 mg, 0.44 mmol), palladium acetate (5 mg, 5 mol%), (*R*)-*i*-Pr-MOP (10 mg, 6 mol%) and potassium *tert*-butoxide (74 mg, 0.66 mmol) were combined in a dry flask and purged with argon before being dissolved in toluene (1.5 mL) and warmed to 50 °C. The reaction was stirred at 50 °C for ~5 min before 4-bromoanisole (0.06 mL, 0.48 mmol) was added drop-wise; and the reaction stirred for a further 16 h. The reaction was allowed to cool to room temperature before being diluted with dichloromethane (5 mL) and loaded directly onto a silica column. The crude mixture was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give, in order of elution; the *bis-product* **96** and the *mono*-product **95** as a pale yellow crystalline solid and a pale yellow oil respectively.

***bis*-Product 96:** (29 mg, 23%); mp 92-93 °C; ν_{max} (film)/cm^{-1} 2930, 2830 (CH), 1580, 1510 (C=C); ^1H (500 MHz, $CDCl_3$) δ 7.06 (4H, d, *J* 9.0, H-3'), 6.87 (4H, d, *J* 9.0, H-2'), 3.79 (6H, s, O*Me*), 3.46 (2H, ddq, *J* 7.4, 3.2, 6.2, H-3, H-6), 3.21 (2H, dd, *J* 11.5, 3.2, H-2, 5), 2.86 (2H, dd, *J* 11.5, 7.4, H-2, 5), 0.94 (6H, d, *J* 6.2, 2 × *Me*); ^{13}C (63 MHz, $CDCl_3$) δ 155.8, 145.2, 123.6, 114.7, 59.2, 55.9, 54.6, 16.0; *m/z* (ESI +) 327 (MH^+, 100%)

***mono*-Product 95:** (70 mg, 72%); ν_{max} (film)/cm^{-1} 3280 (NH), 2960 (CH), 1610, 1580 (C=O); ^1H (500 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* 8.9, H-3'), 6.83 (2H, d, *J* 8.9, H-2'), 3.76 (3H, s, O*Me*), 3.05-2.95 (3H, m), 2.86-2.79 (1H, m, H-5), 2.67 (1H, dd, *J* 12.0, 10.0, H-3), 2.40 (1H, dd, *J* 11.2, 9.9, H-6), 1.90 (1H, bs, N*H*), 1.03 (3H, d, *J* 6.3, C-2 *Me*), 0.82 (3H, d, *J* 6.0, C-5 *Me*); ^{13}C (126 MHz, $CDCl_3$) δ 157.0, 145.5, 126.5, 114.5, 64.8, 55.8, 55.4, 54.4, 51.8, 20.1, 18.2; *m/z* (ESI +) 221 (MH^+, 100%).

Data in accordance with literature[i]

Enantiomers of the *mono* product were separated by HPLC using Chiracel AD-H column; [94.9 : 0.1] : 5 ([hexane : diethylamine] : *iso*-propanol); 0.3 mL / min; t_r= 24.168 min and t_r= 25.172 min; 15% ee.

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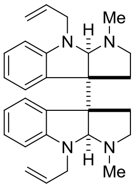
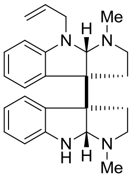
[i] *Tetrahedron Lett.*, **1997**, *37*, 4463

11.4 Desymmetrization via Trost Allylation

(3a*S*,3'a*R*,8a*R*,8'a*S*)-8,8'-Diallyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *bis-product*, 98

(-)-(3a*R*,3'a*S*,8a*S*,8'a*S*)-8-Allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *mono-product*, 97





Allyl palladium chloride dimer (40 mg, 2.5 mol%, Pd) and (*R*,*R*)-DACT-Phenyl Trost Ligand (224 mg, 3.7 mol%) were combined in degassed toluene (90 mL) and stirred at 0 °C for 5 min. Triethylamine (3.75 mL, 26.0 mmol), *meso*-chimonanthine **2** (3.00 g, 8.67 mmol) and allyl acetate (1.03 mL, 9.54 mmol) were added sequentially at 30 sec intervals. The mixture was stirred at 0 °C for an additional 1.5 h before being concentrated *in vacuo*. The crude product was loaded onto a silica column and was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) which gave, in order of elution, *bis-allyl-chimonanthine* **98** (287 mg, 4%) and the (-)-*N-allyl-chimonanthine* **97** (2.54 g, 76%) as colourless foams.[i]

***Bis*-Product 98:** mp 65 °C (DCM); ν_{max} (film)/cm^{-1} 3070, 3050, 3000, 2960, 2930, 2850, 2790 (CH), 1640, 1600, 1490 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.13-6.94 (4H, m, Ar*H*), 6.53-6.35 (4H, m, Ar*H*), 5.61-5.36 (2H, m, $CH_2CH{=}CH_2$), 5.12 (2H, d, *J* 16.8, $CH_2CH{=}CH_2$), 5.01 (2H, d, *J* 10.1, $CH_2CH{=}CH_2$), 4.40 (2H, bs, H-8a, 8a’), 3.71 (2H, dd, *J* 15.8, 4.8, $CH_2CH{=}CH_2$), 3.55 (2H, dd, *J* 15.8, 5.4, $CH_2CH{=}CH_2$), 2.81-2.64 (2H, m, H-

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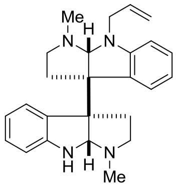
[i] Method adapted from *Org. Lett.*, **2004**, 6, 3605; *J. Org. Chem.*, **2006**, 71, 2524

2, 2'), 2.49-2.27 (10H, m, [incl. 2.41, 3H, s, N*Me*]), 1.98-1.86 (2H, m, H-3, 3'); ^{13}C (100 MHz, $(CD_3)_2SO$, 90 °C) δ 153.1, 134.6, 133.2, 127.7, 123.8, 116.9, 116.6, 107.2, 88.4, 62.7, 51.8, 51.6, 36.4, 36.1; *m/z* (ESI +) 427 (*MH*$^+$, 100%); (ESI, HRMS) Found 427.2844 (*MH*$^+$), $C_{28}H_{35}N_4$ requires 427.2856.

(-)-*mono-P*roduct 97: mp 77-78 °C (DCM); ν_{max} (film)/cm^{-1} 3380 (NH), 3074, 3050, 3030, 3000, 2960, 2930, 2860, 2800 (CH), 1640, 1600, 1490 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.00 (1H, app t, *J* 7.6, H-6), 6.87 (1H, app t, *J* 7.6, H-6'), 6.78 (1H, bs, H-4'), 6.53 (1H, app t, *J* 7.6, ,H-5), 6.45-6.14 (4H, m, Ar*H*), 5.62 (1H, bs, N*H*), 5.46-5.23 (1H, m, $CH_2CH{=}CH_2$), 5.06 (1H, d, *J* 17.2, $CH_2CH{=}CH_2$), 4.95 (1H, d, *J* 10.1, $CH_2CH{=}CH_2$), 4.60 (1H, bs, H-8a'), 4.39 (1H, bs, H-8a), 3.63 (1H, dd, *J* 16.2, 5.2, $CH_2CH{=}CH_2$), 3.47 (1H, dd, *J* 16.2, 5.2, $CH_2CH{=}CH_2$), 2.73 (2H, app t, *J* 6.7), 2.48-2.25 (10H, m, [incl. 2.38, 3H, s, N*Me* & 2.33, 3H, s, N*Me*]), 2.01-1.82 (2H, m, H-3, 3'); ^{13}C (63 MHz, $(CD_3)_2SO$, 120 °C) δ 154.1, 153.4, 135.8, 134.5, 133.5, 128.6, 128.3, 124.8, 124.5, 117.8, 117.3, 117.0, 108.2, 108.1, 89.8, 83.9, 64.1, 63.6, 52.8, 52.63, 52.57, 37.7, 37.5, 36.8, 36.2; *m/z* (ESI +) 387 (*MH*$^+$, 100%); (ESI, HRMS) Found 387.2542 (*MH*$^+$), $C_{25}H_{31}N_4$ requires 387.2543.

Enantiomers of the *mono-product* were separated by HPLC using Chiracel OD-H column [97.6 : 0.4] : 2 ([hexane : diethylamine] : *iso*-propanol); 1 mL / min; t_r= 5.13 min and t_r= 10.65 min; 99% ee, (racemic material prepared using [dppf]$PdCl_2$); t_1 $[\alpha]_D^{25.0}$ -16 (c = 0.4, $CHCl_3$) [(*R,R*)-DACT-phenyl-Trost ligand], t_2 $[\alpha]_D^{25.0}$ + 13 (c = 1, $CHCl_3$) [(*S,S*)-DACT-phenyl-Trost ligand].

8-Allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, *N-allyl-C$_2$-chimonanthine*, 99



Degassed toluene (4.5 mL) was added to a flask containing allyl palladium chloride dimer (2 mg, 2.5 mol%, Pd) and (*R,R*)-DACT-phenyl Trost ligand (11 mg, 3.7 mol%), the mixture was stirred at 0 °C under an inert atmosphere for 5 min. Triethylamine (0.19 mL, 1.29 mmol), C_2-chimonanthine **13** (150 mg, 0.43 mmol) and allyl acetate (0.025 mL, 0.24 mmol) were added sequentially at 30 sec intervals. The reaction was stirred at 0 °C for an additional 2 h before being loaded directly onto a silica column and being purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 ($CHCl_3$: MeOH : NH_3) to give, in order of elution, *bis-N-allyl-*C_2*-chimonathine* **100** (trace), *N-allyl-*C_2*-chimonathine* **99** (67 mg, 40%) and (-)-C_2-chimonathine **13** (86 mg, 57%).

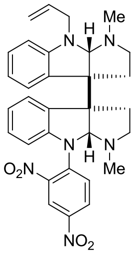
***N-Allyl-*C_2*-chimonanthine* 99:** mp 124-125 °C (IPA/petrol); ν_{max} (film)/cm^{-1} 3250 (NH), 3000, 2960, 2940, 2860, 2810, 2790 (CH), 1600, 1540 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.07 (1H, d, *J* 7.5, H-4’), 6.98 (1H, d, *J* 7.3, H-4), 6.86 (1H, app t, *J* 7.7, H-6), 6.80 (1H, app t, *J* 7.5, H-6’), 6.48-6.34 (3H, m, H-5, 5’, 7’), 6.28 (1H, d *J* 7.7, H-7), 5.96 (1H, app ddt, *J* 17.2, 10.2, 5.2, $NCH_2CH{=}CH_2$), 5.80 (1H, bs, N*H*), 5.28 (1H, dd, *J* 17.2, 1.6, $NCH_2CH{=}CH_2$), 5.17 (1H, dd, *J* 10.2, 1.6, $NCH_2CH{=}CH_2$), 4.49 (1H, bs, H-8a’), 4.42 (1H, bs, H-8a), 3.96 (1H, dd, *J* 16.4, 5.2, $NCH_2CH{=}CH_2$), 3.79 (1H, dd, *J* 16.4, 5.2, $NCH_2CH{=}CH_2$), 2.62-2.23 (12H, m, [incl. 2.31, 3H, s, N*Me*, 2.25, 3H, s, N*Me*]), 1.89-1.79 (2H, m, H-3, 3’); ^{13}C (63 MHz, $(CD_3)_2SO$, 100 °C) δ 153.0, 152.8, 136.6, 134.1, 134.0, 128.2, 128.1, 124.8, 124.3, 117.4, 117.2, 116.8, 108.5, 107.0, 91.9, 85.4, 63.6, 63.4, 52.7, 52.6, 52.1, 38.8, 37.3, 36.4, 36.3; *m/z* (ESI +) 387 (*MH*$^+$, 100%); (ESI, HRMS) Found 387.2528 (*MH*$^+$), $C_{25}H_{31}N_4$ requires 387.2543.

Enantiomers of the title compound were separated by HPLC using Chiracel OD-H column; [97.6 : 0.4] : 2 ([hexane : diethylamine] : *iso*-propanol); 1 mL / min; t_r= 7.81 min and t_r= 8.84 min; 60% ee

(-)C$_2$-chimonanathine 13: Enantiomers of the title compound were separated by HPLC using Chiracel OD-H column; [97.6 : 0.4] : 2 ([hexane : diethylamine] : *iso*-propanol); 1 mL / min;t_r= 20.14 min and t_r= 21.92 min; 44% ee.

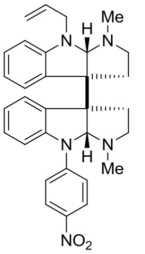
$[\alpha]_D^{25.0}$ -99 (c = 1, $CHCl_3$) [(*R*,*R*)-DACT-napthyl-Trost ligand], note 36% ee.

(3a*R*,3'a*S*,8a*S*,8'a*R*)-8-Allyl-8'-(2,4-dinitrophenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 101



(-)-*Desymmetrized product* **97** (54 mg, 0.14 mmol), 2,4,dinitro-1-flourobenzene (26 mg, 0.14 mmol) and sodium bicarbonate (5 mg, 0.42 mmol) were combined in a mixture of acetone and water (1:1, 2 mL). The reaction was stirred at room temperature for 64 h. The reaction was diluted with dichloromethane and passed through a phase separation column before being purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 ($CHCl_3$: MeOH : NH_3) to give the *title compound* **101** as a bright yellow gum (29 mg, 37%). ν_{max} (film)/cm^{-1} 3080, 3011, 2970, 2940, 2870, 2800 (CH), 1600, 1590 (C=C), 1530, 1340 (N=O); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 8.79 (1H, d, *J* 2.7, H-3''), 8.36 (1H, dd, *J* 9.0, 2.7, H-5’’), 7.23-7.00 (3H, m, [incl. 7.05, 1H, app q, *J* 7.2, Ar*H*]), 6.77-6.39 (5H, m, Ar*H* [incl. 6.50, 1H, d, *J* 7.8, Ar*H*]), 6.23 (1H, d, *J* 8.0, H-7’’), 5.75-5.28 (2H, m, $NCH_2CH=CH_2$, [incl. 5.34, 1H, s, H-8a’]), 5.13 (1H, d, *J* 16.8, $NCH_2CH=CH_2$), 4.99 (1H, d, *J* 9.8, $NCH_2CH=CH_2$), 4.54 (1H, s, H-8a), 3.77 (1H, dd, *J* 16.8, 5.7, $NCH_2CH=CH_2$), 3.58 (1H, dd, *J* 16.8, 4.8, $NCH_2CH=CH_2$), 2.97-2.64 (2H, m, H-2, 2’), 2.60-2.32 (7H, m), 2.25 (3H, s, N*Me*), 2.15-1.97 (2H, m, H-3, 3’); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 153.6, 144.4, 143.7, 143.4, 135.0, 134.7, 133.3, 129.3, 129.1, 128.6, 128.4, 125.8, 124.7, 123.1, 121.3, 118.2 (2×C), 117.9, 108.5, 107.9, 91.4, 89.6, 80.0, 64.2, 63.5, 52.8, 52.5, 52.2, 37.3, 37.0, 36.8; *m/z* (ESI +) 553 (*MH*$^+$, 100%); (ESI, HRMS) Found 553.2551 (*MH*$^+$), $C_{31}H_{33}N_6O_4$ Requires 553.2558.

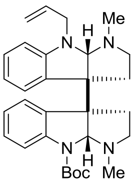
(3a*R*,3'a*S*,8a*S*,8'a*R*)-8-Allyl-1,1'-dimethyl-8'-(4-nitrophenyl)-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 102



(-)-*Desymmetrized product* **97** (100 mg, 0.26 mmol), 1-bromo-4-nitrobenzene (63 mg, 0.31 mmol), palladium acetate (3 mg, 5 mol%), S-Phos (6 mg, 6 mol%) and potassium *tert*-butoxide (58 mg, 0.52 mmol) were combined in toluene (2 mL) and heated at 100 °C for 4 h. The reaction was diluted with dichloromethane and loaded onto silica. The crude product was purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 ($CHCl_3$: MeOH : NH_3) to give the *title compound* **102** as a bright yellow foam (86 mg, 66%). mp 95-97 °C (IPA/hexane); ν_{max} (film)/cm^{-1} 3020, 2940, 2870, 2800 (CH), 1600, 1580, 1500

(C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 8.07 (1H, d, *J* 9.2, H-3’’), 7.32-7.17 (4H, m [incl. 7.27, 2H, d, *J* 9.2, H-2’’]), 6.91-6.74 (3H, m, Ar*H*), 6.56-6.39 (2H, m, Ar*H* [incl. 6.42, 1H, app t, *J* 7.4]), 6.25 (1H, d, *J* 7.9, H-7’), 5.54-5.35 (1H, m, $NCH_2CH{=}CH_2$), 5.09 (1H, d, *J* 16.2, $NCH_2CH{=}CH_2$), 5.00 (2H, app d, *J* 15.1, $NCH_2CH{=}CH_2$ [incl. 4.96, 1H, s, H-8a’]), 4.23 (1H, s, H-8a), 3.73 (1H, dd, *J* 16.0, 5.0, $NCH_2CH{=}CH_2$), 3.48 (1H, dd, *J* 16.0, 5.8, $NCH_2CH{=}CH_2$), 2.88-2.77 (1H, m, H-2’), 2.77-2.66 (1H, m, H-2), 2.59-2.31 (7H, m), 2.31-2.10 (4H, m, H-3’ [incl. 2.25, 3H, s, N*Me*]), 2.03-1.88 (1H, m, H-3); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 153.1, 151.1, 146.4, 141.2, 137.4, 135.4, 128.8, 128.7, 126.0, 125.8, 124.3, 122.9, 117.9, 117.6, 117.4 (2×C), 114.2, 107.9, 91.3, 89.9, 63.8, 62.7, 54.0, 52.9, 51.7, 38.6, 37.8, 37.1, 35.0; *m/z* (ESI +) 508 (MH^+, 100%); (ESI, HRMS) Found 508.2706, $C_{31}H_{34}N_5O_2$ Requires 508.2707.

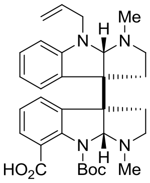
(+)- (3a*S*,3'a*R*,*R8*'a*S*)-*tert*-Butyl 8'-allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate, 103



***Method A*:** Sodium bis(trimethylsilyl)amide (2.0 M in THF, 3.1 mL, 6.27 mmol) was added drop-wise *via* syringe pump over 30 min to a stirred solution of (-)-*desymmetrized product* **97** (1.10 g, 2.85 mmol) and di-*tert*-butyl-dicarbonate (0.81 g, 3.70 mmol) in tetrahydrofuran (110 mL) at room temperature. The reaction was stirred for a further 30 min before being partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane, the organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* **103** as a colourless foam (1.38 g, quant).

Method B**:** Allyl palladium chloride dimer (1.3 mg, 2.5 mol%, Pd) and (*R,R*)-DACT-Phenyl Trost Ligand (7.5 mg, 3.7 mol%) were combined in degassed toluene (2 mL) and stirred at room temerpature for 5 min. Triethylamine (0.13 mL, 0.89 mmol), *meso*-chimonanthine **2** (100 mg, 0.29 mmol) and allyl acetate (0.04 mL, 0.35 mmol) were added sequentially at 30 sec intervals. The mixture was stirred at room temperature 1h then warmed at 50 °C for an additional 30 min before being allowed to cool to room temperature. Di-*tert*-butyl-dicarbonate (82 mg, 0.38 mmol) was added and the reaction stirred at room temperature for an addional 16 h. The crude product was loaded directly onto a silica column and purified by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) which gave, in order of elution, the *bis-ally-chimonanthine* **98** (19 mg, 15%) and the *title compound* **103** (122 mg, 76%) as colourless foams. mp 66-68 °C (as foam from Et_2O); ν_{max} (film)/cm^{-1} 3050, 2970, 2940, 2870, 2800 (CH), 1730, 1660, 1600 (C=C); ^1H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.53 (1H, d, *J* 8.1, H-7’), 7.17 (1H, app td, *J* 8.3, 1.2, H-6’), 6.96 (1H, app td, *J* 7.9, 1.3, H-6), 6.86 (1H, app t, *J* 7.4, H-5’), 6.78-6.67 (1H, m, H-4’), 6.47-6.28 (3H, m, Ar*H*), 6.61-5.42 (1H, m, $NCH_2CH{=}CH_2$), 5.20-4.98 (3H, m, [incl. 5.04, 1H, s, H-8a’], $NCH_2CH{=}CH_2$), 4.29 (1H, s, H-8a), 3.73 (1H, dd, *J* 15.9, 4.8, $NCH_2CH{=}CH_2$), 3.58 (1H, dd, *J* 15.9, 6.0, $NCH_2CH{=}CH_2$), 2.80-2.66 (2H, m, H-2, 2’), 2.55-2.29 (10H, m, [incl. 2.44, 3H, s, N*Me*, 2.42, 3H, s, N*Me*]), 2.08-1.90 (2H, m, H-3, 3’), 1.44 (9H, s, *t-Bu*); ^{13}C (125 MHz, $(CD_3)_2SO$, 120 °C) δ 153.4, 152.9, 144.8, 136.4, 135.5, 132.7, 128.9, 128.5, 124.9, 124.2, 123.1, 117.8, 117.5, 116.2, 107.9, 89.6, 85.5, 81.0, 63.0, 62.2, 53.6, 52.9, 52.1, 37.9, 37.2, 37.0, 35.3, 28.8; *m/z* (ESI +) 487 (*MH*$^+$, 100%); (ESI, HRMS) Found 487.3066 (*MH*$^+$), $C_{30}H_{39}N_4O_2$ requires 487.3068; $[\alpha]_D^{25.0}$ +45 (c = 0.36, $CHCl_3$) [(*R*,*R*)-DACT-phenyl-Trost ligand], $[\alpha]_D^{25.0}$ -40 (c = 0.35, $CHCl_3$) [(*S*,*S*)-DACT-phenyl-Trost ligand].

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-8'-Allyl-8-(*tert*-butoxycarbonyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-7-carboxylic acid, 104

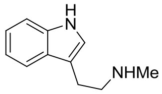


sec-Butyl lithium (~1.4 M in hexane, 0.83 mL, 1.15 mmol) was added drop-wise *via* syringe to a stirred solution of (+)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-tert-butyl 8'-allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate **103** (280 mg, 0.58 mmol) and tetramethylethylenediamine (0.26 mL, 1.73 mmol) in ether (25 mL) at -78 °C. The reaction was stirred for 45 min before carbon dioxide was bubbled through the reaction mixture for 5 min. The reaction was warmed to 0 °C whilst carbon dioxide was bubbled through for an additional 30 min. The reaction was partitioned between water and dichloromethane, the biphasic mixture was acidified to pH 5 and the organic layer isolated. The aqueous layer was extracted with further dichloromethane and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 15 : 85 (methanol : chloroform) to give the (-)-*acid* **104** as an amber solid (304 mg, quant). X-Ray quality crystals of the product could be formed from wet methanol, see appendix. mp 202-204 °C (MeOH); ν_{max} (film)/cm^{-1} 2970, 2930, 2870, 2850, 2780 (CH), 1700 (C=O), 1600, 1490 (C=C); ^{1}H (500

MHz, $(CD_3)_2SO$, 100 °C) δ 11.78 (1H, bs, CO_2*H*), 7.48 (1H, d, *J* 7.6, H-6’), 7.00 (1H, app t, *J* 7.8, H-6), 6.88 (1H, app t, *J* 7.6, H-5’), 6.76-6.56 (2H, m, H-4, 4’), 6.52 (1H, app t, *J* 7.8, H-5), 6.39 (1H, d, *J* 7.8, H-7), 5.49-5.37 (1H, m, $NCH_2CH=CH_2$), 5.16 (1H, bs, H-8a’), 5.08 (1H, d, *J* 17.4, $NCH_2CH=CH_2$), 4.98 (1H, d, *J* 10.1, $NCH_2CH=CH_2$), 4.19 (1H, bs, H-8a), 3.69 (1H, dd, *J* 16.0, 3.5, $NCH_2CH=CH_2$), 3.51 (1H, dd, *J* 16.0, 4.6, $NCH_2CH=CH_2$), 2.80-2.71 (2H, m, H-2, 2’), 2.55-2.35 (8H, m), 2.29-2.22 (2H, m, H-3, 3’), 2.05-1.99 (1H, m, H-3’), 1.93 (1H, ddd, *J* 11.8, 5.1, 2.1, H-3), 1.40 (9H, s, *t-Bu*); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 168.5, 153.4, 143.2, 138.9, 135.3, 133.0, 129.2, 129.1, 127.6, 124.3, 123.5, 118.1, 117.3, 108.2, 104.0, 90.1, 87.5, 81.5, 79.9, 62.8, 62.3, 53.0, 52.9, 52.1, 37.9, 37.0, 36.5, 36.1, 28.8; *m/z* (ESI +) 531 (*MH*$^+$, 100%); (ESI, HRMS) Found 531.2976 (*MH*$^+$), $C_{31}H_{39}N_4O_4$ Requires 531.2966; $[\alpha]_D^{25.0}$ -123 (c = 0.31, $CHCl_3$)

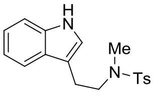
11.5 C-7 Functionalisation

N-Methyl-typtamine, 7



Red-Al (65% [~3.5 M] in toluene, 21 mL, 68.8 mmol) was added drop-wise to a stirred solution of methyl 2-(1H-indol-3-yl)ethylcarbamate **9** (3.0 g, 13.8 mmol), in toluene (300 mL) at room temperature. The reaction was heated at reflux for 3 h, and was allowed to cool to room temperature before being quenched with 5% aqueous sodium hydroxide. The aqueous phase was extracted with chloroform and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation from a mixture of *iso*-hexane and dichloromethane to give *N*-methyl-tryptamine **7** as an off white solid (2.0 g, 84%). ν_{max} (film)/cm^{-1} 3300 (NH), 3060, 2970 (CH), 1620, 1500 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.14 (1H, bs, H-1), 7.64 (1H, d, *J* 7.9, H-4), 7.36 (1H, d, *J* 8.1, H-7), 7.19 (1H, ddd, *J* 8.1, 7.1, 1.1, H-6), 7.12 (1H, ddd, *J* 7.9, 7.1, 1.0, H-5), 7.03 (1H, s, H-2), 3.00-2.96 (2H, m, CH_2CH_2NMe), 2.93-2.89 (2H, m, CH_2CH_2NMe), 2.44 (3H, s, N*Me*), 1.49 (1H, bs, N*H*Me); ^{13}C (100 MHz, $CDCl_3$) δ 136.5, 127.4, 122.0, 121.9, 119.1, 118.8, 113.6, 111.2, 51.9, 36.2, 25.5; *m/z* (ESI +) 175 (*MH*$^+$, 100%). Data in accordance with the literature[i]

_N_-(2-(1H-Indol-3-yl)ethyl)-_N_,4-dimethylbenzenesulfonamide, 105



Tosyl chloride (600 mg, 3.16 mmol), was added to a stirred solution of *N*-methyl-tryptamine **7** (500 mg, 2.97 mmol), triethylamine (0.6 mL, 4.3 mmol) and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in dichloromethane (15 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 6 h before being partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation from a mixture of *iso*-hexane and dichloromethane to give the tosyl-protected methyl tryptamine **105** as an off white solid (845 mg, 90%). mp 104-105 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 3380 (NH), 3050, 2910 (CH), 1640, 1620, 1600 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.23 (1H, bs, N*H*), 7.65 (2H, d, *J* 8.2, H-2’), 7.56 (1H, d, *J* 7.8, H-4), 7.34 (1H, d, *J* 8.1, H-7), 7.26 (2H, d, *J* 8.2, H-3’), 7.17 (1H, dd, *J* 8.1, 8.0 H-6), 7.09 (1H, dd, *J* 8.0, 7.8, H-5), 7.04 (1H, bs, H-2), 3.32 (2H,

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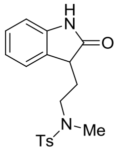
[i] *Tetrahedron*, **2000**, *56*, 1165

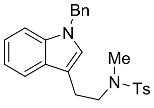
t, *J* 7.4, CH_2CH_2N), 3.01 (2H, t, *J* 7.4, CH_2CH_2N), 2.78 (3H, s, N*Me*), 2.39 (3H, s, *Me*); ^{13}C (100 MHz, $CDCl_3$) δ 143.2, 136.2, 134.7, 129.6, 127.3, 127.2, 122.2, 122.0, 119.3, 118.4, 112.2, 111.3, 50.7, 35.0, 24.3, 21.4; *m/z* (ESI +) 329 (MH^+, 100%); Compound is commercially available.

_N_,4-Dimethyl-_N_-(2-(2-oxoindolin-3-yl)ethyl)benzenesulfonamide, 106



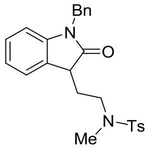
N-Bromosuccinimide (185 mg, 1.56 mmol) was added portionwise over 30 min to a stirred solution of *N*-(2-(1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **105** (214 mg, 0.65 mmol) and water (0.05 mL, 2.6 mmol) in a 1:1 mixture of *tert*-butanol and tetrahydrofuran (6 mL) at room temperature. The reaction was stirred at room temperature in the absence of light for a further 30 min. Sodium borohydride (148 mg, 3.9 mmol) was added portion wise over 5 min before the mixture was diluted with methanol (1 mL). The reaction was stirred for 30 min before being cautiously quenched, sequentially with water and 1 M aqueous hydrochloric acid. The reaction mixture was partitioned by the addition of dichloromethane, the organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 4 : 1 (hexane : ethyl acetate) to give the *oxindole* **106** as a colourless foam (154 mg, 69%). mp 119-120 °C (DCM); ν_{max} (neat)/cm^{-1} 3260 (NH), 3060, 2920 (CH), 1710 (C=O), 1620, 1600 (C=C); ^1H (400 MHz, $CDCl_3$) δ 8.37 (1H, s, N*H*), 7.65 (2H, d, *J* 8.3, Ts), 7.38 (1H, d, *J* 7.3, H-4), 7.31 (2H, d, *J* 8.3, Ts), 7.24 (1H, dd, *J* 7.7, 7.6, H-6), 7.07 (1H, dd, *J* 7.6, 7.3, H-5), 6.90 (1H, d, *J* 7.7, H-7), 3.57 (1H, t, *J* 6.6, H-3), 3.33 (1H, app dt, *J* 13.7, 7.3, MeNC*H*$_2$CH$_2$), 3.11 (1H, ddd, 13.7, 7.3, 6.4, MeNC*H*$_2$CH$_2$), 2.76 (3H, s, N*Me*), 2.43 (3H, s, Ar*Me*), 2.27-2.09 (2H, m, MeNCH$_2$C*H*$_2$); ^{13}C (100 MHz, CDCl$_3$) δ 179.7, 143.4, 141.4, 123.1, 129.7, 128.9, 128.1, 127.5, 124.4, 122.6, 109.8, 47.2, 43.1, 35.0, 28.8, 21.5; *m/z* (ESI +) 367 (*M*+*Na*, 50%); (ESI, HRMS) Found 367.1086 (*M*+*Na*$^+$), $C_{18}H_{20}N_2O_3NaS$ Requires 367.1087.

N-(2-(1-Benzyl-1H-indol-3-yl)ethyl)-N,4-dimethylbenzenesulfonamide, 109



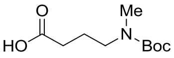
Sodium hydride (60% dispersion in mineral oil, 300 mg, ~7.0 mmol), was added to a solution of *N*-(2-(1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **105** (1.69 g, 5.15 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature and the reaction stirred for 20 min before benzyl bromide (0.67 mL, 5.66 mmol) was added *via* syringe. The reaction was stirred at room temperature for 3 h before being partitioned between water and ethyl acetate. The organic layer was isolated and the aqueous layer extracted with further ethyl acetate, the combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was recrystallised from a mixture of dichloromethane and *iso*-hexane to give the *indole* **109** as a pale yellow solid (1.65 g, 77%). mp 102-103 °C (DCM/*iso*-hexane); ν_{max} (neat)/cm^{-1} 3060, 3030, 2920, 2860 (CH), 1600, 1550, 1500 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 7.66 (2H, d, *J* 6.7, Ar*H*), 7.57 (1H, d, *J* 7.8, H-4), 7.38-7.22 (6H, m, Ar*H*), 7.21-7.07 (4H, m, Ar*H*), 6.97 (1H, s, H-2), 5.26 (2H, s, C*H*$_2$Ph), 3.32 (2H, t, *J* 7.2, CH$_2$C*H*$_2$N), 3.02 (2H, t, *J* 7.2, C*H*$_2$CH$_2$N), 2.78 (3H, s, N*Me*), 2.40 (3H, s, Ar*Me*); ^{13}C (75 MHz, CDCl$_3$) δ 143.1, 137.5, 136.6, 134.9, 129.6, 128.7, 128.4, 127.9, 127.4, 126.8, 126.3, 121.8, 119.2, 118.8, 111.6, 109.8, 50.9, 50.0, 35.1, 24.4, 21.5; *m/z* (ESI +) 419 (*MH*$^+$, 100%); (ESI, HRMS) Found 441.1608 (*M+Na*$^+$), $C_{25}H_{26}N_2O_2NaS$ Requires 441.1607.

N-(2-(1-Benzyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 110



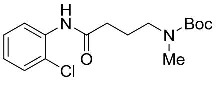
N-Bromosuccinimide (0.92 g, 7.8 mmol) was added portion-wise over 1.5 h to a stirred solution of *N*-(2-(1-benzyl-1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **109** (1.42 g, 3.4 mmol) and water (0.25 mL, 13.6 mmol) in a 1:1 mixture of *tert*-butanol and tetrahydrofuran (38 mL) at room temperature. The reaction was stirred for an additional 1 h before being concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 1 : 3 (*iso*-hexane : ethyl acetate) to give the *oxindole* **110** as a colourless foam (0.65 g, 44%). mp 82-85 °C (DCM); ν_{max} (neat)/cm^{-1} 3020, 2930, 2870, 2820 (CH), 1710 (C=O), 1610, 1520, 1480 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.69-7.62 (2H, m, Ts), 7.41 (1H, dd, *J* 7.4, 1.7, H-4), 7.34-7.22 (7H, m, Ts, Bn), 7.20 (1H, app td, *J* 7.7, 1.8, H-6), 7.07 (1H, app td, *J* 7.4, 2.7, H-5), 6.75 (1H, dd, *J* 7.4, 2.7, H-7), 4.97 (1H, app dd, *J* 15.7, 3.0, NCH_2Ph), 4.86 (1H, app dd, *J* 15.7, 3.0, NCH_2Ph), 3.69-3.62 (1H, m, H-3), 3.35 (1H, app quin. d, *J* 7.0, 3.0, CH_2CH_2NMe), 3.14 (1H, app quin. d, *J* 7.0, 3.0, CH_2CH_2NMe), 2.77 (3H, d, *J* 3.0, N*Me*), 2.43 (3H, d, *J* 3.0, Ar*Me*), 2.29-2.11 (2H, m, CH_2CH_2NMe); ^{13}C (100 MHz, $CDCl_3$) δ 177.5, 143.42, 143.38, 135.9, 134.1, 129.7, 128.8, 128.3, 128.1, 127.6, 127.5, 127.3, 124.2, 122.7, 109.2, 47.2, 43.8, 42.6, 35.0, 29.1, 21.5; *m/z* (ESI +) 435 (*MH*$^+$, 100%); (ESI, HRMS) Found 457.1556 (*M+Na*$^+$), $C_{25}H_{26}N_2O_3Na S$ Requires 457.1556.

4-((*tert*-Butoxycarbonyl)amino)butanoic acid, 114[i]



Triethylamine (7.26 mL, 52.1 mmol) and di-*tert*-butyl dicarbonate (9.91 g, 17.9 mmol) were added sequentially to a stirred solution of 4-(methylamino)butric acid hydrochloride **113** (2.50 g, 16.3 mmol) in dichloromethane (50 mL) at room temperature. The reaction was stirred for 16 h before being quenched with saturated aqueous ammonium chloride solution; the mixture was acidified with aqueous hydrochloric acid (1 M) to the order of pH 4. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the acid **114** as a slow crystallising low melting colourless solid (3.50 g, quant). ν_{max} (neat)/cm^{-1} 2980, 2930 (CH), 1810 (C=O), 1740, 1700 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.69 (1H, bs, CO_2H), 3.28 (2H, t, *J* 6.8, $NCH_2CH_2CH_2$), 2.84 (3H, s, N*Me*), 2.35 (2H, t, *J* 7.2, $NCH_2CH_2CH_2$), 1.85 (2H, tt, *J* 7.2, 6.8, $NCH_2CH_2CH_2$), 1.45 (9H, s, *t-Bu*); ^{13}C (125 MHz, $CDCl_3$) Several rotary isomers present see appendix; *m/z* (ESI -) 216 (*M-H*$^-$, 100%).

tert-Butyl 4-(2-chlorophenylamino)-4-oxobutyl(methyl)carbamate, 115



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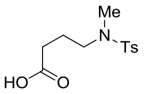
[i] *J. Org. Chem.*, **1985**, *50*, 1302; *Bioorg. Med. Chem.*, **2008**, *16*, 1376

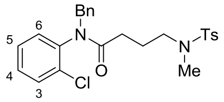
Triethylamine (2.9 mL, 20.9 mmol) and di-*tert*-butyl dicarbonate (1.56 g, 7.18 mmol) were added sequentially to a stirred solution of 4-(methylamino)butric acid hydrochloride **113** (1.0 g, 6.53 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred for 1 h before 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.37 g, 7.18 mmol), hydroxybenzotriazole (970 mg, 7.18 mmol) and 2-chloroanaline (0.75 mL, 7.18 mmol) were added sequentially. The reaction was stirred at room temperature for 16 h before being partitioned between saturated aqueous sodium bicarbonate solution and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 1 : 4 (ethyl acetate : petrol) to afford the *amide* **115** as a colourless oil (773 mg, 36%). ν_{max} (neat)/cm^{-1} 3320 (NH), 3090, 3060, 3030, 2980, 2920, 2970 (CH), 1730 (C=O), 1600, 1520, 1500 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.34 (1H, bs, H-3), 7.37 (1H, d, *J* 7.8, H-6), 2.27 (1H, app t, *J* 7.8, H-4), 7.04 (1H, app t, *J* 7.8, H-5), 3.42-3.27 (2H, m, $CH_2CH_2CH_2N$), 2.88 (3H, s, N*Me*), 2.43 (2H, t, *J* 7.1, $CH_2CH_2CH_2N$), 1.97 (2H, tt, *J* 7.8, 7.1, $CH_2CH_2CH_2N$), 1.45 (9H, s, *t-Bu*); ^{13}C (125 MHz, $CDCl_3$) δ 171.1, 156.4, 134.8, 129.0, 127.5, 124.6, 123.3, 122.3, 79.5, 53.4, 47.4, 34.1, 28.4, 23.7; *m/z* (ESI +) 327 (*MH*$^+$, 100%); (ESI, HRMS) Found 349.1281 (*M+Na*$^+$), $C_{16}H_{23}ClN_2O_3Na$ Requires 349.1289.

4-(*N*,4-Dimethylphenylsulfonamido)butanoic acid, 117



Triethylamine (2.8 mL, 19.5 mmol) and tosyl chloride (1.48 g, 7.8 mmol) were added sequentially (with a 5 min interval) to a stirred solution of 4-(methylamino)butanoic acid **113** (1.00 g, 6.5 mmol) in dichloromethane (50 mL). The reaction was stirred at room temperature for 1 h before being quenched with saturated aqueous sodium bicarbonate solution. The aqueous layer was isolated and the organic layer extracted with additional sodium bicarbonate solution. The combined aqueous extracts were acidified to pH 4 with aqueous hydrochloric acid (1 M). The acidified mixture was extracted thoroughly with ethyl acetate, the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the acid **117** as slowly crystallizing low melting colourless plates (1.4 g, 80%). ν_{max} (neat)/cm^{-1} 3540 (CO_2H), 3030, 2930, 2880 (CH), 1710 (C=O), 1600, 1500 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* 8.1, Ts), 7.32 (2H, d, *J* 8.1, Ts), 3.05 (2H, t, *J* 6.6, $NCH_2CH_2CH_2$), 2.72 (3H, s, N*Me*); 2.48 (2H, t, *J* 7.1, $NCH_2CH_2CH_2$), 2.43 (3H, s, Ar*Me*), 1.92-1.82 (2H, m, $NCH_2CH_2CH_2$); ^{13}C (125 MHz, $CDCl_3$) δ 178.2, 143.4, 134.3, 129.7, 127.4, 49.2, 34.8, 30.6, 22.5, 21.5; *m/z* (ESI +) 294 (*M+Na*$^+$, 100%). Data in accordance with literature.[i]

General Procedure 02 exemplified by the synthesis of: *N*-Benzyl-*N*-(2-chlorophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide, 118



Oxalyl chloride (0.32 mL, 3.69 mmol) and a drop of dimethyl formamide were added sequentially to a stirred solution of 4-(*N*,4-dimethylphenylsulfonamido)butanoic acid **117**

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[i] *Chemische Berichte*., **1962**, *95*, 2424; *Journal of Applied Biochem*., **1980**, 2, 495

(500 mg, 1.84 mmol) in dichloromethane (20 mL). The reaction was stirred at room temperature for 15 min before being concentrated *in vacuo*, to remove any excess oxalyl chloride. The residue was re-dissolved in dichloromethane (5 mL) before being treated with a solution of *N*-benzyl-2-chloroaniline[i] (333 mg, 1.53 mmol) in dichloromethane (15 mL). The reaction was stirred for an additional 2 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with dichloromethane, the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 1 : 4 (ethyl acetate : petrol) to afford the *amide* **118** as a colourless crystalline solid (465 mg, 65%). mp 85-86 °C (DCM); ν_{max} (neat)/cm^{-1} 3060, 3030, 2930, 2870 (CH), 1660 (C=O), 1600, 1590, 1490 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* 8.0, Ts), 7.50 (1H, d, *J* 7.9, H-3), 7.34-7.15 (9H, m, Ts, Bn, H-4, 5), 7.93 (1H, d, *J* 7.8, H-6), 5.56 (1H, d, *J* 14.4, CH_2Ph), 4.12 (1H, d, *J* 14.4, CH_2Ph), 3.03 (1H, app dt, *J* 13.3, 7.0, $NCH_2CH_2CH_2$), 2.90 (1H, app dt, *J* 13.3, 6.7, $NCH_2CH_2CH_2$), 2.66 (3H, s, N*Me*), 2.42 (3H, s, Ph*Me*), 2.19-1.96 (2H, m, $NCH_2CH_2CH_2$), 1.92 (1H, app td, *J* 13.7, 6.9, $NCH_2CH_2CH_2$), 1.79 (1H, app td, *J* 13.7, 6.9, $NCH_2CH_2CH_2$); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 143.2, 139.0, 136.9, 134.3, 133.1, 131.5, 129.7, 129.6, 129.1, 128.3, 127.9, 127.43, 127.39 (2×C), 51.5, 49.5, 34.6, 30.6, 22.7, 21.5; *m/z* (ESI +) 471(*MH*$^+$, 100%); (ESI, HRMS) Found 493.1321 (*M+Na*$^+$), $C_{25}H_{27}{}^{35}ClN_2O_3SNa$ Requires 493.1323.

N-Benzyl-*N*-(2-bromophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide, 121

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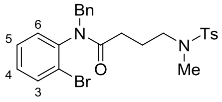
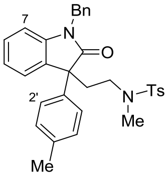
[i] *J. Am. Chem. Soc.*, **2009**, *131*, 8344



Synthesised using general procedure **02** using: Oxalyl chloride (0.5 mL, 5.67 mmol), 4-(*N*,4-dimethylphenylsulfonamido)butanoic acid **117** (1.0 g, 2.84 mmol) and *N*-benzyl-2-bromoaniline[i] (570 mg, 2.18 mmol). The general procedure afforded the *title compound* **121** as a colourless crystalline solid (812 mg, 73%). mp 105-106 °C (DCM); ν_{max} (neat)/cm^{-1} 3060, 3030, 2920, 2870 (CH), 1660 (C=O), 1570, 1580 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 7.68 (1H, app t, *J* 5.0, H-3), 7.62 (2H, d, *J* 7.8, Ts), 7.32-7.18 (9H, m, Ar*H*), 6.90 (1H, app t, *J* 3.9, H-6), 5.63 (1H, d, *J* 14.4, C*H*$_2$Ph), 4.04 (1H, d, *J* 14.4, C*H*$_2$Ph), 3.03 (1H, app dt, *J* 13.3, 7.0, NC*H*$_2$CH$_2$CH$_2$), 2.90 (1H, app dt, *J* 13.3, 6.6, NC*H*$_2$CH$_2$CH$_2$), 2.66 (3H, s, N*Me*), 2.43 (3H, s, Ar*Me*), 2.18-1.96 (2H, m, NCH$_2$CH$_2$C*H*$_2$), 1.93 (1H, app td, *J* 13.7, 7.5, NCH$_2$C*H*$_2$CH$_2$), 1.80 (1H, app td, *J* 13.7, 6.9, NCH$_2$C*H*$_2$CH$_2$); ^{13}C (100 MHz, CDCl$_3$) δ 171.8, 143.2, 140.5, 136.9, 134.4, 133.8, 131.7, 129.8, 129.6, 129.2, 128.5, 128.3, 127.44, 127.40, 123.7, 51.5, 49.5, 34.6, 30.8, 22.7, 21.5; *m/z* (ESI +) 517 (*MH*(^{81}Br)$^+$, 90%), 515 (*MH*(^{79}Br)$^+$, 90%); (ESI, HRMS) Found 515.0996 (*MH*$^+$), C$_{25}$H$_{28}$^{79}BrN$_2$O$_3$S Requires 515.0999.

N-(2-(1-Benzyl-2-oxo-3-p-tolylindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 120



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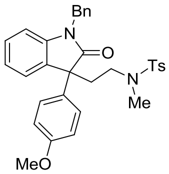
[i] *J. Am. Chem. Soc.,* **2009**, *131*, 8344

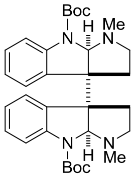
4-Iodotoluene (19 mg, 0.088 mmol) in toluene (1 mL) was added to a dry flask containing a stirred solution of *N*-benzyl-*N*-(2-bromophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide **121** (50 mg, 0.097 mmol), potassium bis(trimethylsilyl)amide (52 mg, 0.26 mmol) and ([*t*Bu$_3$P]PdBr)$_2$ (3 mg, 5 mol%) in dry toluene (1 mL). The reaction was warmed to 100 °C and stirred for 16 h. The reaction was allowed to cool to room temperature before being absorbed onto silica, the crude product was purified by flash chromatography eluting with 4 : 1 (petrol : ethyl acetate) to give the *oxindole* **120** as a pale yellow foam (32 mg, 70%). mp 58-60 °C (foam, Et$_2$O); ν_{max} (neat)/cm^{-1} 3060, 3030, 2920, 2870 (CH), 1710 (C=O), 1650, 1610 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 7.51 (2H, d, *J* 8.1, H-2'), 7.28-7.20 (11H, m, Ar*H*), 7.15-7.09 (3H, m, Ar*H* [incl. 1.73, 2H, d, *J* 6.8, Ts]), 6.82 (1H, d, *J* 8.0, H-7), 5.03 (1H, d, *J* 15.7, NC*H*$_2$Ph), 4.84 (1H, d, *J* 15.7, NC*H*$_2$Ph), 2.94-2.61 (6H, m, NC*H*$_2$CH$_2$, NCH$_2$C*H*$_2$, [incl. 2.68, 3H, s, N*Me*]), 2.50-2.39 (4H, m, NCH$_2$C*H*$_2$, [incl. 2.41, 3H, s, Ar*Me*]), 2.32 (3H, s, Ar*Me*); ^{13}C (100 MHz, CDCl$_3$) δ 178.0, 143.2, 143.0, 137.2, 136.7, 136.0, 134.5, 131.4, 129.6, 129.4, 128.7, 128.4, 127.5, 127.4, 127.3, 126.5, 124.6, 122.9, 109.7, 54.5, 46.5, 44.0, 35.1, 35.0, 21.5, 21.0; *m/z* (ESI +) 547 (*MH*$^+$, 100%); (ESI, HRMS) Found 547.2025 (*M*+*Na*$^+$), C$_{32}$H$_{32}$N$_2$O$_3$SNa Requires 547.2026.

N-(2-(1-Benzyl-3-(4-methoxyphenyl)-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, Table 25, Entry 2



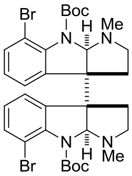
4-Iodoanisole (21 mg, 0.088 mmol) and *N*-benzyl-*N*-(2-bromophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide **121** (50 mg, 0.097 mmol) were added sequentially to a stirred suspension of potassium *bis*(trimethylsilyl)amide (48 mg, 0.26 mmol) and ([*t*Bu$_3$P]PdBr)$_2$ (2 mg, 5 mol%) in dry toluene (2 mL). The reaction was warmed to 100 °C and stirred for 3 h. The reaction was allowed to cool to room temperature before being absorbed onto silica, the crude product was purified by flash chromatography eluting with 4 : 1 (petrol : ethyl acetate) to give the *oxindole* as a pale yellow foam / gum (20 mg, 43%). ν_{max} (neat)/cm^{-1} 3060, 3030, 2930 (CH), 1710, 1650, 1600 (C=C); ^{1}H (250 MHz, CDCl$_3$) δ 7.57 (2H, d, *J* 8.1, Ar*H*), 7.46-7.15 (12 H, m, Ar*H*), 6.98-6.86 (3H, m, Ar*H*), 5.11 (1H, d, *J* 15.7, NC*H*$_2$Ph), 4.90 (1H, d, *J* 15.7, NC*H*$_2$Ph), 3.84 (3H, s, O*Me*), 3.89-3.70 (6H, m, NC*H*$_2$C*H*$_2$, [incl. 2.74, 3H, s, N*Me*]), 2.60-2.40 (4H, m, NCH$_2$C*H*$_2$, [incl. 2.47, 3H, s, Ar*Me*]); ^{13}C (63 MHz, CDCl$_3$) δ 178.6, 159.3, 143.7, 143.4, 136.5, 134.8, 132.1, 131.7, 130.1, 129.2, 128.9, 128.3, 128.0, 127.8, 127.7, 125.1, 123.4, 114.5, 110.2, 55.7, 54.6, 47.0, 44.4, 35.7, 35.5, 22.0; *m/z* (ESI +) 541 (*MH*$^+$, 100%); (ESI, HRMS) Found 563.1978 (*M*+*Na*$^+$), C$_{32}$H$_{32}$N$_2$O$_4$SNa Requires 563.1975.

meso-Di-*tert*-butyl 1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′abipyrrolo[2,3-b]indole-8,8′(8aH,8a′H)-dicarboxylate, 33



Sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.5 mL, 6.50 mmol) was added drop-wise *via* syringe pump over 30 min to a stirred solution of *meso*-chimonanthine **2** (500 mg, 1.45 mmol) and di-*tert*-butyl dicarbonate (787 mg, 3.61 mmol) in tetrahydrofuran (20 mL). After 2 h the solution was partitioned between saturated aqueous ammonium chloride and dichloromethane and the phases separated. The aqueous phase was extracted with dichloromethane and the combined organic phases dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography eluting with 4 : 1 (ethyl acetate : petrol) gave the biscarbamate **33** as a white foam (645 mg, 82%). ν_{max} (KBr disc)/cm^{-1} 3040, 2980, 2940, 1710 (C=O); ^1H (400 MHz, $(CD_3)_2SO$, 120 °C) δ (2H, d, *J* 8.0, 2 × H-7), 7.14 (2H, dd, *J* 8.0 and 7.5, 2 × H-6), 6.82 (2H, dd, *J* 7.5 and 7.2, 2 × H-5), 6.55 (2H, bs, 2 × H-4), 4.92 (2H, s, 2 × H-8a), 2.76-2.70 (2H, m, 2 × H-2), 2.47-2.36 (10H, m, 2 × *Me*, 2 × H-2 and 2 × H-3), 2.07-2.00 (2H, m, 2 × H-3), 1.44 (18H, s, 2 × *t-Bu*); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 152.2, 143.9, 134.9, 128.3, 124.1, 122.7, 115.7, 85.4, 80.8, 61.3, 53.3, 37.4, 34.9, 28.4; *m/z* (ESI +) 547 (*MH^+*, 100%); Anal. calc. for $C_{32}H_{42}N_4O_4$, requires C: 70.3%, H: 7.74%, N: 10.25%, found C, 70.2%, H, 7.75%, N: 10.2%. Data in accordance with the literature.[i]

meso-Di-_tert_-butyl-7,7′-dibromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a-octahydro-3a,3′a-bipyrrolo[2,3-b]indole-8,8′(8aH,8′aH)-dicarboxylate, 121



sec-Butyllithium (1.4 M in cyclohexane, 7 mL, 9.80 mmol) was added drop-wise to a stirred solution of biscarbamate **33** (1.34 g, 2.45 mmol) and *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (2.2 mL, 14.70 mmol) in diethyl ether (25 mL) at -78 °C. After 1 h, dibromoethane (2.12 mL, 24.50 mmol) was added drop-wise. After 10 min at -

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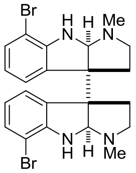
[i] *J. Am. Chem. Soc.*, **2002**, *124*, 9008

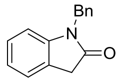
78 °C, the reaction was warmed to 0 °C and stirred for 2 h then quenched with water and saturated aqueous sodium hydrogen carbonate. The phases were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography eluting with 1 : 1 (ethyl acetate : petrol) and subsequent recrystallisation of the solid from hot toluene gave the *bis-bromide* **121** (1.12 g, 65%) as colourless plates. mp 203-205 °C (toluene); ν_{max} (KBr disc)/cm^{-1} 3040, 2980, 2950, 2800, 1720 (C=O), 1570 (C=C); ^{1}H (400 MHz, $(CD_3)_2SO$, 120 °C) δ 7.40 (2H, d, *J* 7.7, H-6), 6.92 (2H, dd, *J* 7.7, 7.7, H-5), 6.82 (2H, bs, H-4), 4.96 (2H, s, H-8a), 2.76-2.70 (2H, m, H-2), 2.45 (6H, s, N*Me*), 2.44-2.37 (2H, m, H-2), 2.28-2.20 (2H, m, H-3), 1.97 (2H, ddd, *J* 12.0, 5.4, 2.9, H-3), 1.43 (18H, s, *t-Bu*); ^{13}C (100 MHz, $(CD_3)_2SO$, 120 °C) δ 152.7, 143.7, 140.0, 133.4, 126.6, 124.1, 112.5, 88.5, 81.9, 62.5, 52.6, 36.7, 36.5, 28.4; *m/z* (CI +) 705 (*MH*(^{81}Br)$^+$,75%); (ESI, HRMS) found 703.1487 (*MH*)$^+$, $C_{32}H_{41}{}^{79}Br_2N_4O_4$ requires 703.1489.

***meso*-7,7′-Dibromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-b]indole, 122**



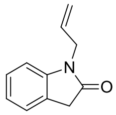
Trimethylsilyl trifluoromethanesulfonate (2.07 mL, 12.0 mmol) was added in three equal portions at 1 h intervals to a stirred solution of *meso-bis*-Boc-dibromo-chimonanthine **121** (1.4 g, 2.0 mmol) in dichloromethane (40 mL) at room temperature. The septum was removed to allow the formation of small quantities of triflic acid. After 16 h the reaction was quenched with saturated aqueous sodium hydrogen carbonate, the phases separated and the aqueous phase extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and reduced *in vacuo*. The *bis-amine* **122** was precipitated from a mixture of dichloromethane and petrol as colourless needles (799 mg, 80%). mp 207-209 °C (dec); ν_{max} (neat)/cm^{-1} 3410 (NH), 3060, 2930, 2860 (CH), 1600, 1480 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.14 (2H, d, *J* 8.5, H-6), 6.50 (2H, bs, H-4), 6.39 (2H, dd, *J* 8.5, 7.8, H-5), 5.80 (2H, bs, N*H*), 4.69 (2H, bs, H-8a), 3.01-2.91 (2H, m, H-2), 2.88-2.80 (2H, m, H-2), 2.45-2.32 (8H, m, *Me*, H-3), 2.02-1.94 (2H, m, H-3); ^{13}C (63 MHz, $(CD_3)_2SO$, 100 °C) δ 150.9, 134.7, 131.4, 123.8, 119.1, 101.7, 83.5, 65.0, 52.6, 37.1, 36.2; *m/z* (ESI +) 505 (*M*(^{79}Br, ^{81}Br)+*H*$^+$, 100%); *m/z* HRMS (ESI+, $[M + H]^+$) found 503.0440, $C_{22}H_{24}{}^{79}Br_2N_4$ requires 503.0450.

1-Benzylindolin-2-one



A suspension of *N*-benzyl-isatin (1.10 g, 4.60 mmol) in hydrazine hydrate (5 mL) was heated at reflux for 1.5 h. The reaction was allowed to cool to room temperature before being quenched with water. The crude product was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 2 : 1 (petrol : ether) to give the oxindole as slow crystallising colourless needles (0.90 g, 88%). ν_{max} (neat)/cm^{-1} 1710 (C=O); ^{1}H (400 MHz, $CDCl_3$) δ 7.35-7.24 (6H, m, H-4, Ar*H*), 7.18 (1H, dd, *J* 7.8, 7.7, H-6), 7.02 (1H, dd, *J* 7.7, 7.4, H-5), 6.74 (1H, d, *J* 7.8, H-7), 4.94 (2H, s, C*H*$_2$Ph), 3.64 (2H, s, H-3); ^{13}C (100 MHz, $CDCl_3$) δ 175.1, 144.2, 135.8, 128.7, 127.8, 127.6, 127.3, 124.4, 124.3, 122.3, 109.0, 43.7, 35.7; *m/z* (ESI +) 246 (*M+Na*$^+$, 45%). Data consistent with the literature.[i]

1-Allylindolin-2-one



To a solution of isatin (2.00 g, 13.6 mmol) in dimethylformamide (24 mL) at 0 °C was added sodium hydride (0.57 g, ~14.3 mmol, 60% in mineral oil). The reaction was stirred for 20 min before allylbromide (1.4 mL, 16 mmol) was added drop-wise *via* syringe. The reaction was stirred for 16 h before being partitioned between water and ethyl acetate. The organic layer was isolated and the aqueous layer extracted thoroughly with ethyl acetate, the combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The pale yellow residue was triturated with a mixture of ether and petrol, was dried under reduced pressure before being heated at reflux for 2 h in hydrazine hydrate (7 mL). The crude mixture was partitioned between water and ethyl acetate, the organic layer was isolated and the aqueous layer extracted thoroughly with further ethyl acetate, the combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 2 : 1 (petrol : ether) to give the oxindole as slow crystallising colourless needles. (467 mg, 20%, over two steps). mp 44-45 °C; ν_{max} (neat)/cm^{-1} 3060, 3010, 2920 (CH), 1700 (C=O), 1640, 1610 1490 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.19-7.15 (2H, m, Ar*H*), 6.96 (1H, t, *J* 7.3, Ar*H*), 6.75 (1H, d, *J* 7.8, Ar*H*), 5.82-5.73 (1H, m, C*H*=CH$_2$), 5.19-5.14 (2H, m, CH=C*H*$_2$), 4.29-4.27 (2H, m, C*H*$_2$N), 3.50 (2H, s, H-3); ^{13}C (100 MHz, $CDCl_3$) δ 174.8, 144.4, 131.4, 127.8, 124.45,

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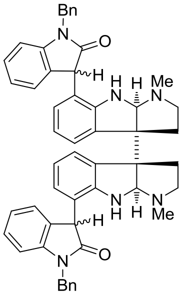
[i] *J. Am. Chem. Soc.*, **2005**, *127*, 11505

124.37, 122.3, 117.5, 108.9, 42.3, 35.7; *m/z* (ESI +) 196 (*M+Na*$^+$, 50%). Data in accordance with the literature.[i]

3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-benzylindolin-2-one), Table 26, Entry 2



A solution of *meso*-chimonanthine-dibromide **122** (50 mg, 0.10 mmol) in degased toluene (2 mL) was added to a mixture of palladium acetate (1.1 mg, 5 mol%), Fu's salt (3 mg, 6 mol%), caesium carbonate (195 mg, 0.60 mmol) and *N*-benzyl-oxindole (49 mg, 0.22 mmol) under an atmosphere of nitrogen. The mixture was evacuated under vacuum and charged with nitrogen three times before being warmed at 100 °C for 2 h. The crude reaction mixture was allowed to cool to room temperature before being loaded directly onto a silica column. The crude product was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give the *bis-oxindole* as a colourless foam (57 mg, 73%). mp 126-127 °C (EtOAc); ν_{max} (neat)/cm^{-1} 3030, 2970, 2930, 2860, 2190 (CH), 1710 (C=O), 1610, 1500 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$, 95 °C) showed mixture of diastereoisomers, see appendix for spectra; ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) showed

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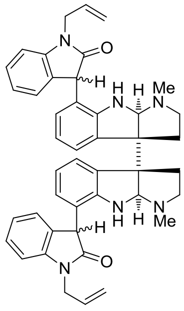
[i] *J. Org. Chem.*, **2006**, *71*, 6497

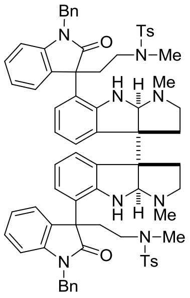
mixture of diastereoisomers, see appendix for spectra; *m/z* (ESI +) 789 (*MH*$^+$, 50%); (ESI, HRMS) Found 789.3923 (*MH*$^+$), $C_{52}H_{49}N_6O_2$ Requires 789.3912.

3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-allylindolin-2-one), Table 26, Entry 92



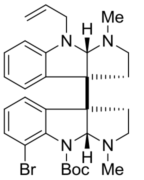
A solution of *meso*-chimonanthine-dibromide **122** (100 mg, 0.20 mmol) in degassed toluene (4 mL) was added to a mixture of palladium acetate (2 mg, 5 mol%), Fu's salt (6 mg, 6 mol%), caesium carbonate (389 mg, 1.19 mmol) and *N*-allyl-oxindole (86 mg, 0.50 mmol) under an atmosphere of nitrogen. The mixture was evacuated under vacuum and charged with nitrogen three times before being warmed at 100 °C for 2 h. The crude reaction mixture was allowed to cool to room temperature before being loaded directly onto a silica column. Purification by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) gave the *bis-oxindole* as a colourless foam (126 mg, 92%). mp 122-123 °C (DCM); ν_{max} (neat)/cm^{-1} 3350 (NH), 3050, 2960, 2930, 2860, 2790 (CH), 1700 (C=O), 1640, 1610 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) showed mixture of diastereoisomers, see appendix for spectra; ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) showed mixture of diastereoisomers, see appendix for spectra; *m/z* (ESI +) 689 (*MH*$^+$, 100%); (ESI, HRMS) Found 689.3604 (*MH*$^+$), $C_{44}H_{45}N_6O_2$ Requires 689.3599.

N,*N*'-((3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-benzyl-2-oxoindoline-3,3-diyl))bis(ethane-2,1-diyl))bis(*N*,4-dimethylbenzenesulfonamide), 123



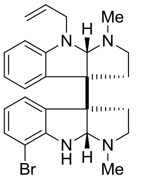
Toluene (2 mL) was added to a mixture of *meso*-chimonanthine-dibromide **122** (50 mg, 0.10 mmol), *N*-(2-(1-benzyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (106 mg, 0.24 mmol), palladium acetate (1 mg, 5 mol%), Fu’s salt (3 mg, 6 mol%) and caesium carbonate (194 mg, 0.59 mmol). The reaction was heated at 100 °C 24 h before being allowed to cool to room temperature. The crude mixture was loaded directly onto a silica column and was purified by flash chromatography, eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) gave the *bis-oxindole* **123** as a pale beige foam (34 mg, 28%). ^1H (250 MHz, $(CD_3)_2SO$, 120 °C) showed mixture of diastereoisomers, see appendix for spectra. *m/z* (ESI +) 1211 (*MH*$^+$, 100%); (ESI, HRMS) Found 1211.5245 (*MH*$^+$), $C_{72}H_{75}N_8O_6S_2$ Requires 1211.5245.

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-Butyl 8'-allyl-7-bromo-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate, 125



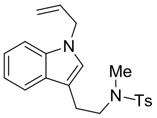
sec-Butyl lithium (1.2 M in hexanes, 5.9 mL, 7.10 mmol) was added drop-wise *via* syringe over 10 min to a stirred solution of (3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-Butyl 8'-allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate **103** (1.38 g, 2.84 mmol) and *N,N,N',N'*-tetramethylethylenediamine (1.41 mL, 8.52 mmol) in ether (86 mL) at -78 °C. The reaction was stirred for 23 min before dibromoethane (0.98 mL, 11.36 mmol) was added drop-wise *via* syringe over 1 min. The reaction was stirred at -78 °C for 5 min before being warmed to 0 °C and stirred for an additional 1 h. The reaction was partitioned between saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was isolated, the aqueous layer extracted with further ethyl acetate and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give in order of elution (-)-*7'-bromo-N'-Boc-N-allyl-chimonanthine* **125** (841 mg, 53%) and recovered (+)-*N'-Boc-N-allyl-chimonanthine* **103** (310 mg, 22%) as colourless foams. The recovered stating material was resubjected to the reaction conditions. To give **125** (61%) and recovered starting material **103** (34%). mp 193-194 °C (DCM/petrol); ν_{max} (neat)/cm^{-1} 2970, 2940, 2870, 2790 (CH), 1700 (C=O), 1600, 1490 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.36 (1H, d, *J* 8.0, H-6'), 7.02 (1H, app t, *J* 7.5, H-6), 6.88-6.73 (2H, m, H-4', 5'), 6.56 (1H, app t, *J* 7.7, H-5), 6.48-6.36 (2H, m, H-4, 7), 5.51-5.27 (1H, m, $NCH_2CH{=}CH_2$), 5.13 (1H, s, H-8a'), 5.07 (1H, d, *J* 17.8, $NCH_2CH{=}CH_2$), 4.95 (1H, d, *J* 10.0, $NCH_2CH{=}CH_2$), 4.20 (1H, s, H-8a), 3.74 (1H, dd, *J* 16.3, 4.8, $NCH_2CH{=}CH_2$), 3.49 (1H, dd, *J* 16.3, 4.9, $NCH_2CH{=}CH_2$), 2.81-2.68 (2H, m, H-2, 2'), 2.55-2.27 (9H, m, H-2, 2', 3', [incl. 2.47, 3H, s, N*Me*, 2.36, 3H, s, N*Me*]), 2.22-2.10 (1H, m, H-3), 2.07-1.96 (1H, m, H-3'), 1.89 (1H, ddd, *J* 11.8, 5.1, 2.2, H-3), 1.45 (9H, s, *t-Bu*); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 168.1, 153.5, 153.1, 143.8, 141.2, 135.1, 132.9, 129.2, 126.2, 124.4, 118.3, 117.5, 112.2, 108.4, 89.9, 88.7, 81.8, 80.0, 63.7, 62.6, 52.8 (2×C), 52.2, 37.7, 37.1, 36.6 (2×C), 28.8; *m/z* (ESI +) 567 (*MH*(^{81}Br)$^+$, 90%), 565 (*MH*(^{79}Br)$^+$, 90%); (ESI, HRMS) Found 565.2174 (MH^+), $C_{30}H_{38}N_4O_2$(^{79}Br) Requires 565.2173. $[\alpha]_D^{25.0}$ -56.2 (c = 0.6, $CHCl_3$) [(*R*,*R*)-DACT-phenyl-Trost ligand], $[\alpha]_D^{25.0}$ +51.1 (c = 0.61, $CHCl_3$) [(*S*,*S*)-DACT-phenyl-Trost ligand].

(-)-(3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-Allyl-7-bromo-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 126



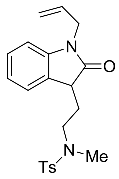
To a stirred solution of (3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-Butyl 8'-allyl-7-bromo-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate **125** (1.10 g, 1.95 mmol) in dichloromethane (40 mL) was added trimethylsilyl trifluoromethanesulfonate (0.8 mL 4.29 mmol) drop-wise *via* syringe. The reaction was stirred open to the air for 16 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer was extracted with further dichloromethane, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the (-)-*7'-bromo-N-allyl-chimonathine* **126** as a pale amber foam (904 mg, quant). mp 126-127 °C (DCM); ν_{max} (neat)/cm^{-1} 3420 (NH), 3000, 2960, 2930, 2860, 2790 (CH), 1640, 1600, 1570 (C=C); ^1H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.08 (1H, d, *J* 8.0, H-6'), 7.03 (1H, app t, *J* 7.2, H-6), 6.91-6.72 (1H, m, H-4'), 6.56 (1H, app t, *J* 7.2, H-5), 6.40 (1H, d, *J* 7.2, H-7), 6.24 (1H, app t, *J* 8.0, H-5'), 6.17-6.95 (1H, m, H-4), 5.74 (1H, bs, N*H*), 5.37-5.09 (1H, m, $NCH_2CH{=}CH_2$), 5.06 (1H, d, *J* 16.2, $NCH_2CH{=}CH_2$), 4.95 (1H, d, *J* 9.8, $NCH_2CH{=}CH_2$), 4.71 (1H, bs, H-8a'), 4.36 (1H, bs, H-8a), 3.67 (1H, dd, *J* 15.2, 3.2, $NCH_2CH{=}CH_2$), 3.46 (1H, dd, *J* 15.2, 3.2, $NCH_2CH{=}CH_2$), 2.82-2.69 (2H, m, H-2, 2'), 2.57-2.25 (10H, m, H-2, 2', 3, 3' [incl. 2.38, 3H, s, N*Me*, 2.36, 3H, s, N*Me*]), 2.00-1.84 (2H, m, H-3, 3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 154.1, 151.3, 135.4, 133.9, 130.9, 128.8, 124.5, 124.1, 118.5, 118.0, 117.3, 108.2, 101.4, 89.0, 83.2, 65.3, 63.6, 60.5, 52.7, 52.6, 52.4, 37.8, 37.3, 36.6, 36.2; *m/z* (ESI +) 467 ($MH(^{81}Br)^+$, 90%), 465 ($MH(^{79}Br)^+$, 90%); (ESI, HRMS) Found 465.1646 ($M{+}Na^+$), $C_{25}H_{30}N_4(^{79}Br)Na$ Requires 465.1648; $[\alpha]_D^{25.0}$ -47.5 (c = 0.2, $CHCl_3$) [(*R*,*R*)-DACT-Phenyl Trost Ligand], $[\alpha]_D^{25.0}$ +43.7 (c = 0.6, $CHCl_3$) [(*S*,*S*)-DACT-Phenyl Trost Ligand].

_N_-(2-(1-Allyl-1H-indol-3-yl)ethyl)-_N_,4-dimethylbenzenesulfonamide, 127



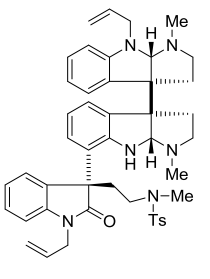
Potassium *tert*-butoxide (83 mg, 0.73 mmol) and allyl bromide (0.08 mL, 0.92 mmol) were added sequentially to a stirred solution of *N*-(2-(1H-Indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **105** (200 mg, 0.61 mmol) in tetrahydrofuran (10 mL). The reaction was stirred at room temperature for 16 h before being partitioned between water and dichloromethane. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 4 : 1 (petrol : ethyl acetate) to give the *N-allyl indole* **127** as a colourless oil (216 mg, 96%). ν_{max} (neat)/cm^{-1} 3050, 2920, 2860 (CH), 1640, 1610, 1600, 1550 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 7.67 (2H, d, *J* 8.2, Ts), 7.56 (1H, d, *J* 7.9, H-4), 7.32-7.26 (3H, m, Ts, H-7), 7.21 (1H, app t, *J* 7.8, H-6), 7.11 (1H, app t, *J* 7.8, H-5), 6.97 (1H, s, H-2), 5.98 (1H, ddt, *J* 17.0, 10.2, 5.5, NCH$_2$C*H*=CH$_2$), 5.20 (1H, app dq, *J* 10.2, 1.4, NCH$_2$CH=C*H*$_2$), 5.10 (1H, app dq, *J* 17.0, 1.4, NCH$_2$CH=C*H*$_2$), 4.69 (2H, app dt, *J* 5.5, 1.4, NC*H*$_2$CH=CH$_2$), 3.33 (2H, t, *J* 7.5, NC*H*$_2$CH$_2$), 3.03 (2H, t, *J* 7.5, NCH$_2$C*H*$_2$), 2.81 (3H, s, N*Me*), 2.42 (3H, s, Ar*Me*); ^{13}C (100 MHz, CDCl$_3$) δ 143.2, 136.4, 134.8, 133.5, 129.6, 127.8, 127.4, 125.9, 121.7, 119.1, 118.7, 117.3, 111.3, 109.7, 50.9, 48.7, 35.1, 24.4, 21.5; *m/z* (ESI +) 391 (*M+Na*$^+$, 100%); (ESI, HRMS) Found 391.1447 (*M+Na*$^+$), C$_{21}$H$_{24}$N$_2$O$_2$NaS Requires 391.1451.

N-(2-(1-Allyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 128



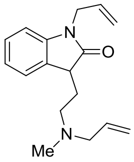
N-Bromosuccinimide (331 mg, 2.80 mmol) was added portionwise over 30 min to a stirred solution of *N*-(2-(1-Allyl-1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **127** (430 mg, 1.17 mmol) and water (0.08 mL, 4.68 mmol) in a 1:1 mixture of *tert*-butanol and tetrahydrofuran (12 mL) at room temperature. The reaction was stirred at room temperature in the absence of light for a further 30 min. Sodium borohydride (228 mg, 7.0 mmol) was added portion wise over 5 min before the mixture was diluted with methanol (1 mL). The reaction was stirred for 30 min before being cautiously quenched, sequentially with water and 1 M aqueous hydrochloric acid. The reaction mixture was partitioned by the addition of dichloromethane, the organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 4 : 1 (hexane : ethyl acetate) to give the *oxindole* **128** as a colourless oil (343 mg, 76%). ν_{max} (neat)/cm^{-1} 3080, 3060, 2960, 2920, 2870, 2820 (CH), 1710 (C=O), 1640, 1610, 1600 (C=C); ^{1}H (500 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* 8.2, Ts), 7.40 (1H, d, *J* 7.6, H-4), 7.33-7.25 (3H, m, Ts, H-6), 7.09 (1H, app t, *J* 7.6, H-5), 6.85 (1H, d, *J* 7.8, H-7), 5.88-5.79 (1H, m, NCH$_2$C*H*CH$_2$), 5.25-5.16 (2H, m, NCH$_2$CHC*H*$_2$), 4.41-4.28 (2H, m, NC*H*$_2$CHCH$_2$), 3.58 (1H, t, *J* 6.4, H-3), 3.31 (1H, app dt, *J* 13.7, 7.3, MeNC*H*$_2$CH$_2$), 3.12 (1H, app dt, *J* 13.7, 6.6, MeNC*H*$_2$CH$_2$), 2.75 (3H, s, N*Me*), 2.43 (3H, s, Ar*Me*), 2.21-2.10 (2H, m, MeNCH$_2$C*H*$_2$); ^{13}C (125 MHz, $CDCl_3$) δ 177.1, 143.4, 134.1, 131.5, 130.8, 129.8, 129.7, 128.0, 127.5, 124.1, 122.5, 117.4, 109.0, 47.2, 42.6, 42.3, 35.0, 29.0, 21.5; *m/z* (ESI +) 407 (*M+Na*, 60%); (ESI, HRMS) Found 407.1395 (*M+Na*$^{+}$), $C_{21}H_{24}N_2O_3NaS$ Requires 407.1400.

(-)-*N*-(2-((*S*)-1-Allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 129



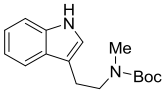
A solution of *N*-(2-(1-allyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **128** (76 mg, 0.20 mmol) in dry degassed toluene (2 mL) was added to a dry flask containing (-)-7'bromo-*N*-allyl-chimonanthine **126** (46 mg, 0.10 mmol), palladium acetate (5 mol%), Fu's salt (10 mol%) and caesium carbonate (215 mg, 0.59 mmol) under an inert atmosphere. The reaction was heated to 100 °C and stirred for 2 h before being allowed to cool to room temperature. The crude reaction mixture was loaded directly onto a silica column and was purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give the (-)-*alpha*-arylated product **129** as a pale amber glass (34 mg, 44%). mp 99-101 °C (DCM); ν_{max} (neat)/cm^{-1} 3340 (NH), 3060, 2930, 2870, 2790 (CH), 1700 (C=O), 1640, 1610, 1600 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.51 (2H, d, *J* 7.6, Ts), 7.43-7.27 (3H, m, Ar*H*, [incl. 7.37, 2H, d, *J* 8.1]), 7.22-6.95 (5 H, m, Ar*H*), 6.90-6.70 (2H, m, Ar*H*, [incl. 1H, d, *J* 7.6, H-7'']), 6.54 (1H, app t, *J* 7.0, H-5), 6.45-6.31 (2H, m, Ar*H*, [incl. 6.37, 1H, d, *J* 7.56, H-7]), 6.12 (1H, bs, N*H*), 5.85 (1H, app ddt, *J* 16.3, 9.9, 5.8, N''$CH_2CH{=}CH_2$), 5.42-4.88 (6H, m), 4.55 (1H, s, H-8a), 4.42-4.21 (2H, m, N''$CH_2CH{=}CH_2$), 3.59 (1H, dd, *J* 16.5, 5.6, N$CH_2CH{=}CH_2$), 3.40 (1H, dd, *J* 16.5, 5.7, N$CH_2CH{=}CH_2$), 3.1-1.8 (24H, m, [incl. 2.62, 3H, s, N*Me* & 2.40, 3H, s, N*Me* & 2.39 3H, s, N*Me* & 2.14 3H, s, Ar*Me*]);^{13}C (125 MHz, $(CD_3)_2SO$, 90 °C) δ 177.9, 144.0, 143.2, 135.7, 135.6, 132.7, 131.3, 130.5, 129.3, 128.8, 127.8, 127.1, 125.4, 124.42, 124.37, 123.5, 118.3, 118.2, 117.3, 110.3, 108.3, 90.1, 84.0, 63.5, 63.1, 54.6, 52.9, 52.8, 52.4, 46.6, 42.8, 41.5, 41.3, 41.1, 41.0, 40.8, 37.5, 36.3, 36.0, 35.8, 35.4, 32.8, 29.6, 21.7; *m/z* (ESI +) 769 (*MH*$^{+}$, 100%); (ESI, HRMS) Found 769.3894 (*MH*$^{+}$), $C_{46}H_{53}N_6O_3S$ Requires 769.3894. $[\alpha]_D^{25.0}$ -113.8 (c = 0.58, $CHCl_3$)

1-Allyl-3-(2-(allyl(methyl)amino)ethyl)indolin-2-one, 132



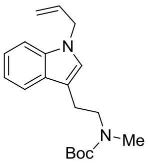
Potassium *tert*-butoxide (927 mg, 8.3 mmol) and allylbromide (0.89 mL, 10.4 mmol) were added sequentially to a stirred solution of *N*-methyl-tryptamine **7** (600 mg, 3.4 mmol) in tetrahydrofuran (30 mL). The reaction was stirred at room temperature for 4 h before being filtered through a plug of celite. The crude mixture was reduced in volume to c.a. 18 mL *in vacuo.* To this mixture *tert*-butanol (18 mL), water (0.25 mL, 13.8 mmol) and *N*-bromosuccinimide (977 mg, 8.3 mmol) were added sequentially and the reaction stirred for 30 min. Sodium borohydride (786 mg, 20.7 mmol) was added portion wise over 5 min before the mixture was diluted with methanol (2 mL). The reaction was stirred for 30 min before being cautiously quenched, sequentially with water and 1 M aqueous hydrochloric acid. The reaction mixture was partitioned by the addition of dichloromethane, the organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 4 : 1 (hexane : ethyl acetate) to give the *oxindole* **132** as an amber oil (331 mg, 35%). ν_{max} (neat)/cm^{-1} 3080, 2930, 2850, 2790 (CH), 1710 (C=O), 1640, 1610 (C=C); ^{1}H (500 MHz, $CDCl_3$) δ 7.28-7.21 (2H, m, H-4, 6), 7.04 (1H, app t, *J* 8.0, H-5), 6.82 (1H, d, *J* 7.6, H-7), 5.87-5.79 (1H, m, $NCH_2CH{=}CH_2$), 5.74-5.65 (1H, m, $MeNCH_2CH{=}CH_2$), 5.25-5.18 (2H, m, $NCH_2CH{=}CH_2$), 5.13-5.05 (2H, m, $MeNCH_2CH{=}CH_2$), 4.37 (1H, app ddt, *J* 16.3, 3.5, 1.6, $NCH_2CH{=}CH_2$), 4.30 (1H app ddt, *J* 16.3, 5.3, 1.5, $NCH_2CH{=}CH_2$), 3.56 (1H, t, *J* 6.05, H-3), 3.00-2.89 (2H, m, $MeNCH_2CH{=}CH_2$), 2.53-2.39 (2H, m, $MeNCH_2CH_2$), 2.21-2.12 (5H, m MeNCH$_2$C*H*$_2$ [incl. 2.18, 3H, s, N*Me*]); ^{13}C (125 MHz, CDCl$_3$) δ 177.6, 143.6, 135.5, 131.6, 128.8, 127.6, 123.9, 122.1, 117.4, 117.3, 108.7, 60.8, 53.2, 43.5, 42.2, 41.8, 28.0; *m/z* (ESI +) 271 (*MH*$^+$, 60%); (ESI, HRMS) Found 271.1804 (*MH*$^+$), $C_{17}H_{23}N_2O$ Requires 271.1805.

tert-Butyl 2-(1H-indol-3-yl)ethyl(methyl)carbamate, 133



Di-*tert*-butyl dicarbonate (3.91 g, 17.9 mmol) was added to a solution of *N*-methyl-tryptamine **7** (2.6 g, 14.9 mmol) and triethylamine (6.2 mL, 44.7 mmol) in tetrahydrofuran (78 mL). The reaction was stirred at room temperature for 1.5 h before being partitioned between water and ethyl acetate, the organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-Boc-*N*-methyl tryptamine **133** as a slow crystallising solid (4.07 g, quant). mp 57-58 °C (DCM); ν_{max} (neat)/cm^{-1} 3310 (NH), 3050, 2980, 2930, 2870 (CH), 1670 (C=O), 1620, 1480, (C=C); ^{1}H (300 MHz, CDCl$_3$) δ 8.03 (1H, bs, H-1), 7.63 (1H, d, *J* 7.6, H-4), 7.36 (1H, d, *J* 7.9, H-7), 7.19 (1H, app t, *J* 7.6, H-5), 7.12 (1H, app t, *J* 7.9, H-6), 6.99 (1H, bs, H-2), 3.51 (2H, app t, *J* 6.8, CH$_2$C*H*$_2$NMe), 2.97 (2H, app t, *J* 6.8, C*H*$_2$CH$_2$NMe), 2.86 (3H, bs, N*Me*), 1.35 (9H, bs, *t-Bu*); ^{13}C (100 MHz, (CD$_3$)$_2$SO, 90 °C) δ 154.8, 136.5, 127.4, 122.7, 122.6, 120.8, 118.1, 111.7, 111.3, 78.2, 49.2, 33.9, 28.1, 23.4; *m/z* (CI -) 274 (M^-), 175 (*M-Boc*$^-$). Data in accordance with the literature[i]

tert-Butyl (2-(1-allyl-1H-indol-3-yl)ethyl)(methyl)carbamate, 134



Potassium *tert*-butoxide (1.46 g, 13.1 mmol) and allylbromide (1.41 mL, 16.4 mmol) were added sequentially to a stirred solution of *N*-Boc-*N*-methyl-tryptamine **133** (2.99 g, 10.9 mmol) in tetrahydrofuran (150 mL). The reaction was stirred at room temperature for 2 h before being partitioned between water and ethyl acetate, the organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and filtered through a plug of silica before being *in vacuo* to yield the *indole* **134** as an amber oil (3.15 g, 92%). ν_{max} (neat)/cm^{-1} 3060, 3000, 2980, 2930, 2860 (CH), 1690, 1610, 1560 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.59 (1H, d, *J* 8.0, H-4), 7.39 (1H, d, *J* 8.0, H-7), 7.19-7.02 (2H, m, [incl.7.12, 1H, s, H-2]), 7.04 (1H, app t, *J* 8.04, H-5), 6.02 (1H, ddt, *J* 18.4, 10.9, 5.4, $NCH_2CH{=}CH_2$), 5.17 (1H, od, *J* 10.9, $NCH_2CH{=}CH_2$), 5.11 (1H, od, *J* 16.4, $NCH_2CH{=}CH_2$), 4.76 (1H, d, *J* 5.4, $NCH_2CH{=}CH_2$), 3.48 (1H, t, *J* 7.2, NCH_2CH_2), 2.92 (1H, t, *J* 7.2, NCH_2CH_2), 2.82 (3H, s, N*Me*), 1.38 (9H, s, *t-Bu*); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 155.7, 137.3, 135.2, 128.9, 126.9, 122.0, 119.4, 119.3, 117.4, 112.6, 110.6, 79.1, 50.1, 48.8, 34.8, 29.0, 24.2; *m/z*

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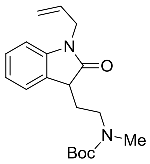
[i] *Tetrahedron*, **2000**, *56*, 1165

(ESI +) 315 (MH^+, 40%); (ESI, HRMS) Found 315.2063 (MH^+), $C_{19}H_{27}N_2O_2$ Requires 315.2067.

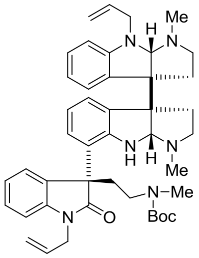
tert-Butyl (2-(1-allyl-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 135



N-Bromosuccinimide (1.51 g, 12.8 mmol) was added portionwise over 30 min to a stirred solution of *tert*-Butyl (2-(1-allyl-1H-indol-3-yl)ethyl)(methyl)carbamate **134** (1.68 g, 5.3 mmol) and water (0.38 mL, 21.2 mmol) in a 1:1 mixture of *tert*-butanol and tetrahydrofuran (68 mL) at room temperature. The reaction was stirred at room temperature in the absence of light for a further 30 min. Sodium borohydride (1.15 g, 31.8 mmol) was added portion wise over 5 min before the mixture was diluted with methanol (2 mL). The reaction was stirred for 30 min before being cautiously quenched, sequentially with water and saturated aqueous ammonium chloride solution. The reaction mixture was partitioned by the addition of dichloromethane, the organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the *oxindole* **135** as a pale yellow oil (1.75 g). If required product can be purified by flash chromatography, eluting with 4 : 1 (hexane : ethyl acetate) (83%). ν_{max} (neat)/cm^{-1} 3080, 3060, 2980, 2930 (CH), 1690 (C=O), 1610 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.36 (1H, d, *J* 7.5, H-4), 7.26 (1H, app t, *J* 7.5, H-6), 7.05 (1H, app t, *J* 7.5, H-5), 6.93 (1H, d, *J* 7.5, H-7), 5.87 (1H, app ddt, *J* 17.0, 10.1, 5.0, $NCH_2CH{=}CH_2$), 5.19 (1H, o app d, *J* 17.0,

$NCH_2CH=CH_2$), 5.18 (1H, o app d, *J* 10.1, $NCH_2CH=CH_2$), 4.31 (2H, d, *J* 5.0, $NCH_2CH=CH_2$), 3.53 (1H, t, *J* 6.3, H-3), 3.39-3.17 (2H, m, NCH_2CH_2), 2.77 (3H, s, N*Me*), 2.19-1.96 (2H, m, NCH_2CH_2), 1.39 (9H, s, *t-Bu*); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 177.1, 155.7, 144.1, 133.1, 129.4, 128.5, 124.6, 122.7, 117.7, 109.6, 79.4, 46.4, 43.5, 42.4, 34.7, 29.2, 29.0; *m/z* (ESI +) 331 (MH^+, 100%); (ESI, HRMS) Found 353.1840 ($M+Na^+$), $C_{19}H_{26}N_2O_3Na$ Requires 353.1836.

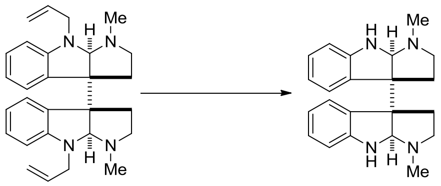
(-)-*tert*-Butyl (2-((*S*)-1-allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 137



A solution of *tert*-butyl (2-(1-allyl-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **135** (284 mg, 0.86 mmol) in dry degassed toluene (8 mL) was added to a dry flask containing (-)-7’bromo-*N*-allyl-chimonanthine **126** (200 mg, 0.43 mmol), palladium acetate (5 mol%), Fu’s salt (10 mol%) and caesium carbonate (934 mg, 2.58 mmol) under an inert atmosphere. The reaction was heated to 100 °C and stirred for 2 h before being allowed to cool to room temperature. The crude reaction mixture was loaded directly onto a silica column and was purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give the (-)-*alpha*-arylated product **137** as a pale amber glass (183 mg, 59%). ν_{max} (neat)/cm^{-1}3340 (NH), 2970, 2930, 2870, 2790 (CH), 1700 (C=O), 1610 C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.35 (1H, app t, *J* 8.1, Ar*H*), 7.24 (1H, d, *J* 6.8, Ar*H*), 7.15 (1H, d, *J* 7.2, Ar*H*), 7.12-6.95 (2H, m, Ar*H*), 6.87-6.71 (2H, m, [incl. 6.83, 1H, d, *J* 7.6, Ar*H*]), 6.55 (1H, app t, *J* 7.2, Ar*H*), 6.41-6.28 (2H, m, [incl. 6.36, 1H, d, *J* 7.6, Ar*H*]), 6.23-6.02 (1H, m, Ar*H*), 5.86 (1H, app ddt, *J* 17.2, 10.8, 5.6, N''$CH_2CH=CH_2$), 5.45-4.92 (6H, m, $NCH_2CH=CH_2$, N''$CH_2CH=CH_2$, H-8a'), 4.52-4.25 (3H, m, N''$CH_2CH=CH_2$, [incl. 4.46, 1H, s, H-8a]), 3.61 (1H, dd, *J* 16.7, 4.2, $NCH_2CH=CH_2$), 3.42 (1H, dd, *J* 16.7, 5.2, $NCH_2CH=CH_2$), 3.14-2.89 (2H, m, CH_2CH_2NMe), 2.86-2.05 (16H, m, [incl. 2.65, 3H, s, N*Me* & 2.37, 3H, s, N*Me* & 2.14, 3H, s, N*Me*]), 2.01-1.79 (3H, m), 1.37 (9H, s, *t*Bu); ^{13}C (125 MHz, $(CD_3)_2SO$, 90 °C) δ 178.2, 155.5, 143.3, 135.8, 132.7, 131.5, 129.1, 128.7, 126.8, 125.5, 124.4, 124.3, 123.4, 119.6, 118.3, 118.0, 117.1, 110.3, 108.1, 90.0, 84.0, 80.0, 79.4, 63.7, 63.1, 54.8, 52.9, 52.8, 52.5, 45.4, 42.7, 41.3, 41.1, 41.0, 37.6, 37.3, 36.6, 36.0, 34.7, 32.4, 29.6, 29.0; *m/z* (ESI +) 715 (*MH*$^+$, 100%); (ESI, HRMS) Found 715.4333 (*MH*$^+$), $C_{44}H_{55}N_6O_3$ Requires 715.4330. $[\alpha]_D^{25.0}$ -110.0 (c = 0.55, $CHCl_3$).

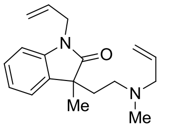
11.6 End Game

Model de-allylation



Potassium *tert*-butoxide (78 mg, 0.70 mmol) was added to a stirred solution of *bis*-allyl-chimonanthine **98** (50 mg, 0.12 mmol) in dimethylsulfoxide (0.5 mL). The mixture was heated at 100 °C for 16 h before being allowed to cool to room temperature. The crude reaction was diluted with dichloromethane (20 mL) before being treated with aqueous hydrochloric acid (1M, 50 mL). The mixture was stirred vigorously for 30 min before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give *meso*-chimonanthine **2** as colourless foam (40 mg, quant).

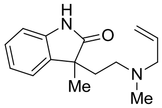
General Procedure 03 exemplified by the synthesis of: 1-Allyl-3-(2-(allyl(methyl)amino)ethyl)-3-methylindolin-2-one, 139



n-Butyl lithium (0.49 mL, 1.22 mmol) was added drop-wise to a stirred solution of 1-allyl-3-(2-(allyl(methyl)amino)ethyl)indolin-2-one **132** (150 mg, 0.55 mmol) and *N,N,N',N'*-tetramethylethyldiamine (0.30 mL, 1.83 mmol) in tetrahydrofuran (7.5 mL) at -78 °C. The reaction was stirred for 30 min before iodomethane (0.05 mL, 0.83 mmol) was added *via* syringe. The reaction was allowed to slowly warm to room temperature before being loaded directly onto a silica column and being purified by flash chromatography eluting with ethyl acetate to give the *oxindole* **139** as an amber oil (105 mg, 67%). ν_{max} (neat)/cm^{-1} 2920, 2850, 2790 (CH), 1710 (C=O), 1640, 1610 (C=C); ^{1}H (500 MHz, $CDCl_3$) δ 7.23 (1H, app td, *J* 7.6, 1.0, H-6), 7.18 (1H, dd, *J* 7.6, 1.0, H-4), 7.05 (1H, app td, *J* 7.6, 1.0, H-5), 6.83 (1H, d, *J* 7.6, H-7), 5.83 (1H, app ddt, *J* 15.6, 10.4, 5.3, $NCH_2CH{=}CH_2$), 5.59 (1H, app ddt, *J* 17.2, 10.0, 6.6, $MeNCH_2CH{=}CH_2$), 5.25-5.17 (2H, m, $NCH_2CH{=}CH_2$), 5.02 (1H, dd, *J* 17.2, 1.5, $MeNCH_2CH{=}CH_2$), 5.00 (1H, d, *J* 10.0, Me

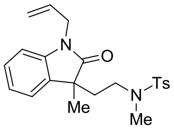
$NCH_2CH=CH_2$), 4.38 (1H, app ddt, *J* 16.3, 5.3, 1.6, $NCH_2CH=CH_2$), 4.28 (1H, app ddt, *J* 16.3, 5.3, 1.6, $NCH_2CH=CH_2$), 2.85 (1H, dd, *J* 13.4, 6.6, $MeNCH_2CH=CH_2$), 2.77 (1H, dd, *J* 13.4, 6.6, $MeNCH_2CH=CH_2$), 2.28-2.20 (1H, m, NCH_2CH_2), 2.14-2.02 (4H, m, [incl. 2.06, 3H, s, N*Me*]), 1.99-1.88 (2H, m, NCH_2CH_2), 1.38 (3H, s, C-3*Me*); ^{13}C (125 MHz, $CDCl_3$) δ 180.1, 142.6, 135.2, 133.5, 131.7, 127.5, 122.6, 122.3, 117.4, 117.3, 108.8, 60.6, 52.4, 47.0, 42.2, 41.7, 35.2, 24.8; *m/z* (ESI +) 285 (MH^+, 60%); (ESI, HRMS) Found 285.1960 (MH^+), $C_{18}H_{25}N_2O$ Requires 285.1960.

3-(2-(Allyl(methyl)amino)ethyl)-3-methylindolin-2-one, 140



Potassium *tert*-butoxide (118mg, 1.08 mmol), was added to a stirred solution of 1-allyl-3-(2-(allyl(methyl)amino)ethyl)-3-methylindolin-2-one **139** (50 mg, 0.176 mmol) in dimethylsulfoxide (0.5 mL). The mixture was stirred at 100 °C for 1.5 h before being allowed to cool to room temperature; aqueous hydrochloric acid (3 mL, 1 M) and dichloromethane (3 mL) were added and the mixture stirred vigorously for 20 min. The reaction was quenched with saturated aqueous sodium bicarbonate solution and diluted with additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give the *oxindole* **140** as a pale amber oil (43 mg, quant). ν_{max} (neat)/cm^{-1} 3210 (NH), 2960, 2930, 2800 (CH), 1710 (C=O), 1620 (C=C); ^1H (400 MHz, $CDCl_3$) δ 8.48 (1H, bs, N*H*), 7.20 (1H, app t, *J* 7.4, H-6), 7.16 (1H, d, *J* 7.4, H-4), 7.04 (1H, app t, *J* 7.4, H-5), 6.91 (1H, d, *J* 7.4, H-7), 5.63 (1H, app ddt, *J* 16.1, 10.3, 6.6, $NCH_2CH{=}CH_2$), 5.03 (1H, d, *J* 16.1, $NCH_2CH{=}CH_2$), 5.00 (1H, d, *J* 10.3, $NCH_2CH{=}CH_2$), 2.86 (1H, dd, *J* 13.5, 6.6, $NCH_2CH{=}CH_2$), 2.79 (1H, dd, *J* 13.5, 6.6, $NCH_2CH{=}CH_2$), 2.28-2.11 (2H, m, NCH_2CH_2), 2.08 (3H, s, N*Me*), 2.05-1.88 (2H, m, NCH_2CH_2), 1.40 (3H, s, C-3*Me*); ^{13}C (100 MHz, $CDCl_3$) δ 182.9, 140.6, 135.3, 134.0, 127.7, 122.9, 122.3, 117.4, 109.6, 60.7, 52.5, 47.5, 41.7, 35.2, 24.6; *m/z* (ESI +) 245 (MH^+, 80%); (ESI, HRMS) Found 245.1648 (MH^+), $C_{15}H_{21}N_2O$ Requires 245.1648.

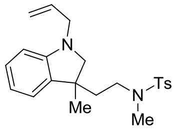
N-(2-(1-Allyl-3-methyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 142



Synthesised using general procedure **03** using: *N*-(2-(1-Allyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **128** (300 mg, 0.78 mmol), *n*-butyl lithium (0.7 mL, 1.72 mmol), *N,N,N',N'*-tretramethylethyldiamine (0.43 mL, 2.57 mmol) and iodomethane (0.07 mL, 1.17 mmol). The general procedure afforded the *title compound* **142** as a pale beige solid (260 mg, 84%). mp 140-150 °C ($CHCl_3$ / Petrol); ν_{max} (neat)/cm^{-1} 3020, 2970, 2930, 2870 (CH), 1710 (C=O), 1650, 1610, 1490 (C=C); ^1H (500 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* 8.2, *Ts*), 7.30-7.20 (4H, m, Ar*H*), 7.11 (1H, app t, *J* 7.5, H-5), 6.87 (1H, d, *J* 7.7, H-7), 5.83 (1H, app ddt *J* 18.4, 13.3, 5.2, $NCH_2CH{=}CH_2$), 5.21-5.14 (2H, m, $NCH_2CH{=}CH_2$), 4.38 (1H, app ddt, *J* 16.4, 5.2, 1.7, $NCH_2CH{=}CH_2$), 4.31 (1H, app ddt, *J*

16.4, 5.2, 1.7, NC*H*$_2$CH=CH$_2$), 4.75-4.65 (2H, m, NC*H*$_2$CH$_2$), 2.60 (3H, s, N*Me*), 2.40 (3H, s, Ar*Me*), 2.23 (1H, ddd, *J* 16.2, 13.6, 4.6, NCH$_2$C*H*$_2$), 1.98 (1H, ddd, *J* 13.9, 9.0, 5.1, NCH$_2$C*H*$_2$), 1.39 (3H, s, C-3*Me*); ^{13}C (125 MHz, CDCl$_3$) δ 179.5, 143.2, 142.5, 134.2, 132.6, 131.6, 129.5, 128.0, 127.4, 122.7, 122.6, 117.2, 109.3, 46.6, 46.3, 42.3, 35.2, 34.7, 24.5, 21.4; *m/z* (ESI +) 421 (*M*+*Na*$^+$, 100%); (ESI, HRMS) Found 421.1540 (*M*+*Na*$^+$), $C_{22}H_{26}N_2O_3SNa$ Requires 421.1556.

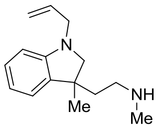
N-(2-(1-Allyl-3-methylindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, Table 28, Entry 1



Lithium aluminium hydride (11 mg, 0.30 mmol) was added to a stirred solution of *N*-(2-(1-allyl-3-methyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **142** (20 mg, 0.05 mmol) in toluene (1 mL). The mixture was heated at 100 °C for 30 min then allowed to stand at room temperature for 16 h. The reaction was quenched cautiously with water then extracted with dichloromethane. The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* before being purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH$_3$) to give the *indoline* as a pale amber oil (16 mg, 83%). ν_{max} (neat)/cm^{-1} 2960, 2930, 2870 (CH), 1640, 1600 (C=C); ^{1}H (500 MHz, CDCl$_3$) δ 7.61 (2H, d, *J* 8.2, *Ts*), 7.28 (2H, d, *J* 8.2, *Ts*), 7.07 (1H, app td, *J* 7.7, 1.3, H-6), 6.96 (1H, dd, *J* 7.7, 1.3, H-4), 6.68 (1H, app td, *J* 7.7, 0.9, H-5), 6.48 (1H, dd, *J* 7.7, 0.9, H-7), 5.87 (1H, dddd, *J* 17.1, 10.2, 6.0, 5.6, NCH$_2$C*H*=CH$_2$), 5.25 (1H, dq, *J* 17.1, 1.5,

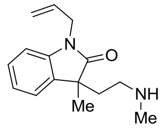
$NCH_2CH=CH_2$), 5.19 (1H, dq, *J* 10.2, 1.5, $NCH_2CH=CH_2$), 3.75 (1H, app ddt, *J* 15.4, 5.6, 1.4, $NCH_2CH=CH_2$), 3.64 (1H, app ddt, *J* 15.4, 6.0, 1.5, $NCH_2CH=CH_2$), 3.26 (1H, d, *J* 9.0, H-2), 3.15 (1H, ddd, *J* 16.2, 10.4, 5.8, NCH_2CH_2), 3.06 (1H, d, *J* 9.0, H-2), 2.87 (1H, ddd, *J* 16.2, 10.4, 5.8, NCH_2CH_2), 2.67 (3H, s, N*Me*), 2.42 (3H, s, Ar*Me*), 1.91-1.81 (2H, m, NCH_2CH_2), 1.32 (3H, s, C-3*Me*); ^{13}C (125 MHz, $CDCl_3$) δ 151.0, 143.1, 136.5, 134.7, 133.9, 129.6, 127.8, 127.3, 122.2, 117.7, 117.2, 107.3, 65.0, 51.4, 46.8, 42.3, 38.3, 34.8, 25.8, 21.5; *m/z* (ESI +) 385 (*MH*$^+$, 80%); (ESI, HRMS) Found 385.1914 (*MH*$^+$), $C_{22}H_{29}N_2O_2S$ Requires 385.1944.

2-(1-Allyl-3-methylindolin-3-yl)-N-methylethanamine, Table 28, Entry 2



Red-Al (0.12 mL, 0.39 mmol) was added to a stirred solution of *N*-(2-(1-allyl-3-methyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **142** (26 mg, 0.06 mmol) in toluene (1 mL) and the mixture was heated at reflux for 16 h. The reaction was quenched cautiously with water then extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before filtering through a plug of silica, washing with 9 : 1 : 0.15 (DCM : MeOH : NH_3) to give the *indoline* as a pale amber oil (14 mg, 90%). ν_{max} (neat)/cm^{-1} 3300 (NH), 3050, 3020, 2960, 2930, 2860, 2810 (CH), 1644, 1610, 1520 (C=C); ^{1}H (400 MHz, $CDCl_3$) see appendix; ^{13}C (125 MHz, $CDCl_3$) see appendix; *m/z* (ESI +) 231 (*MH*$^+$, 80%); (ESI, HRMS) Found 231.1846 (*MH*$^+$), $C_{15}H_{23}N_2$ Requires 231.1856.

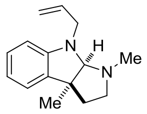
1-Allyl-3-methyl-3-(2-(methylamino)ethyl)indolin-2-one, 145



n-Butyl lithium (1.33 mL, 3.33 mmol) was added drop-wise to a stirred solution of *tert*-butyl (2-(1-allyl-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **135** (500 mg, 1.52 mmol) and *N,N,N',N'*-tetramethylethyldiamine (0.83 mL, 5.00 mmol) in tetrahydrofuran (25 mL) at -78 °C. The reaction was stirred for 30 min before iodomethane (0.14 mL, 2.27 mmol) was added *via* syringe. The reaction was allowed to warm slowly to room temperature with stirring over 30 min. The reaction was partitioned between saturated aqueous ammonium chloride solution and dichloromethane. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane, the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to *ca.* (25 mL). Trimethylsilyl trifluoromethanesulfonate (0.60 mL, 3.30 mmol) was added *via* syringe and the reaction stirred open to the air for 2 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane, dried ($MgSO_4$) and concentrated *in vacuo* to yield the *free amine* **145** as amber oil (387 mg, 97%). ν_{max} (neat)/cm^{-1} 3050, 2960, 2930, 2850, 2800 (CH), 1700 (C=O), 1640, 1610 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.25-7.17 (2H, m, H-6, 4), 7.05 (1H, app t, *J* 9.3, H-5), 6.82 (1H, d, *J* 9.8, H-7), 5.83 (1H, app ddt, *J* 17.4, 10.3, 5.2, $NCH_2CH{=}CH_2$), 5.23-5.16 (2H, m $NCH_2CH{=}CH_2$), 4.40 (1H, ddt, *J* 16.4, 5.2, 1.7, $NCH_2CH{=}CH_2$), 4.27 (1H, ddt, *J* 16.4, 5.2, 1.7, $NCH_2CH{=}CH_2$), 2.32-2.08 (6H, m, [incl. 2.25, 3H, s, N*Me*]), 2.03-1.95 (1H, m, NCH_2CH_2), 1.38 (3H, s, C-3*Me*); ^{13}C (100 MHz,

$CDCl_3$) δ 180.2, 142.3, 133.6, 131.5, 127.6, 122.6, 122.5, 117.3, 108.9, 47.6, 47.1, 42.2, 38.0, 36.2, 24.6; *m/z* (ESI +) 245 (*MH^+*, 100%); (ESI, HRMS) Found 245.1648 (*MH^+*), $C_{15}H_{21}N_2O$ Requires 245.1648.

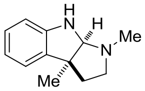
8-Allyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole, *N*-allyl-desoxyeseroline, 143



Red-Al (0.5 mL, 1.64 mmol) was added to a stirred solution of 1-allyl-3-methyl-3-(2-(methylamino)ethyl)indolin-2-one **145** (100 mg, 0.41 mmol) in toluene (4 mL) at room temperature. The mixture was heated at reflux for 1.5 h before being allowed to cool to room temperature. The reaction was quenched with 5% aqueous sodium hydroxide solution and diluted with dichloromethane. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash chromatography eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give *N-allyl-desoxyeseroline* **143** as a colourless amorphous solid (57 mg, 62%). ν_{max} (neat)/cm^{-1} 3050, 3020, 2960, 2930, 2860, 2790 (CH), 1600, 1490 (C=C); ^{1}H (500 MHz, $CDCl_3$) δ 7.06 (1H app td, *J* 7.5, 1.0, H-6), 7.02 (1H, dd, *J* 7.5, 1.0, H-4), 6.70 (1H, app td, *J* 7.5, 1.0, H-5), 6.47 (1H, dd, *J* 7.5, 1.0, H-7), 5.85 (1H, dddd, *J* 17.3, 10.3, 6.2, 4.6, $NCH_2CH{=}CH_2$), 5.25 (1H, app dq, *J* 17.3, 1.7, $NCH_2CH{=}CH_2$), 5.19 (1H, app dq, *J* 10.3, 1.7, $NCH_2CH{=}CH_2$), 4.32 (1H, s, H-8a), 3.99 (1H, app ddt, *J* 16.5, 4.6, 1.7, $NCH_2CH{=}CH_2$), 3.80 (1H, app ddt, *J* 16.5, 6.2, 1.7, $NCH_2CH{=}CH_2$), 2.80-2.74 (1H, m, H-2), 2.70-2.63 (1H, m, H-2), 2.54

(3H, s, N*Me*), 2.06-1.96 (2H, m, H-3), 1.45 (3H, s, C3a*Me*); ^{13}C (125 MHz, $CDCl_3$) δ 150.9, 136.8, 134.2, 127.6, 122.3, 117.9, 116.8, 107.5, 95.2, 53.0, 52.8, 52.1, 40.7, 37.9, 27.3; *m/z* (ESI +) 229 (MH^+, 100%); (ESI, HRMS) Found 229.1702 (MH^+), $C_{15}H_{21}N_2$ Requires 229.1699.

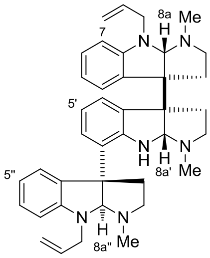
1,3a-Dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole, 144



Potassium *tert*-butoxide (44 mg, 0.39 mmol) was added to a stirred solution of *N*-allyl-desoxyeseroline **143** (30 mg, 0.13 mmol) in dimethylsulfoxide (0.5 mL). The mixture was heated at reflux for 16 h before being allowed to cool to room temperature. The reaction was treated with 1 M aqueous hydrochloric acid (1 mL) and dichloromethane (1 mL) and stirred vigorously for 20 min before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the amine **143** as a colourless crystalline solid (24 mg, quant). mp 109-111 °C (DCM), Lit (110-112 °C, hexane); ν_{max} (neat)/cm^{-1} 2960, 2930, 2860, 2790 (CH), 1610 (C=C); ^{1}H (500 MHz, $CDCl_3$) δ 7.06 (1H, d, *J* 7.6, H-4), 7.03 (1H, app t, *J* 7.6, H-6), 6.74 (1H, app t, *J* 7.6, H-5), 6.60 (1H, d, *J* 7.6, H-7), 4.43 (1H, s, H-8a), 4.26 (1H, bs, N*H*), 2.77-2.72 (1H, m, H-2), 2.67-2.60 (1H, m, H-2), 2.48 (3H, s, N*Me*), 2.06-2.00 (2H, m, H-3), 1.46 (3H, s, C-3a*Me*); ^{13}C (125 MHz, $CDCl_3$) δ 149.4, 136.8, 127.5, 122.8, 118.9, 109.1, 89.6, 53.5, 52.5, 40.8, 36.8, 26.9; *m/z* (ESI +) 189 (MH^+, 100%); (ESI, HRMS) Found 189.1385 (MH^+), $C_{12}H_{17}N_2$ Requires 189.1386.

Data in accordance with the literature.[i]

(-)-(3a*R*,3'a*S*,3''a*S*,8a*S*,8'a*S*,8''a*S*)-8,8''-diallyl-1,1',1''-trimethyl-2,2',2'',3,3',3'',8,8a,8',8'a,8'',8''a-dodecahydro-1H,1'H,1''H-3a,3'a:7',3''a-terpyrrolo[2,3-b]indole, (-)-*bis*-allyl-hodgkinsine B, 145



Trimethylsilyl trifluoromethanesulfonate (0.08 mL, 0.43 mmol) was added drop-wise *via* syringe to a stirred solution of *tert*-Butyl (2-((*S*)-1-allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **137** (140 mg, 0.20 mmol) in dichloromethane (6 mL). The reaction was stirred at room temperature for 16 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (10 mL) and treated with lithium aluminum hydride (28 mg, 0.73 mmol) before being heated at reflux for 1.5 h. The mixture was allowed to cool to room temperature and was cautiously quenched with 5% aqueous sodium hydroxide solution. The organic layer was isolated and the aqueous layer extracted with dichloromethane.

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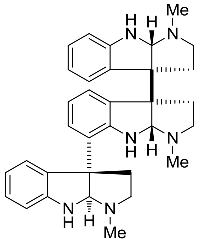
[i] *Tetrahedron*, **2005**, *61*, 9147

The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give (-)-*N,N''-bis*-allyl-*hodgkinsine* **145** as an off white foam (88 mg, 75%). ν_{max} (neat)/cm^{-1} 3270 (NH), 2960, 2930, 2850, 2790 (CH), 1600, 1490 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) δ 7.10-6.89 (5H, m, Ar*H*), 6.67 (1H, app t, *J* 7.3, H-5''), 6.57-6.47 (2H, m, [incl. 6.53 1H, d, *J* 7.8] Ar*H*), 4.42-6.21 (3H, m, [incl. 6.37, 1H, d, *J* 7.8, H-7, 6.27, 1H, app t, *J* 6.3, H-5']), 5.75 (1H, app ddt, *J* 18.0, 10.5, 5.3, N''$CH_2CH{=}CH_2$), 5.52 (1H, bs, N*H*), 5.36-4.89 (5H, m, $NCH_2CH{=}CH_2$, N''$CH_2CH{=}CH_2$), 4.69 (1H, s, H-8a'), 4.53 (1H, bs, H-8a''), 4.38 (1H, bs, H-8a), 3.99 (1H, dd, *J* 16.6, 5.0, N''$CH_2CH{=}CH_2$), 3.84-3.62 (2H, m, $NCH_2CH{=}CH_2$,[incl. 3.77, 1H, dd, *J* 16.6, 5.9, N''$CH_2CH{=}CH_2$]), 3.49 (1H, dd, *J* 15.5, 5.3, $NCH_2CH{=}CH_2$), 2.91 (1H, app t, *J* 6.5), 2.82-2.59 (3H, m), 2.58-2.23 (9H, m, [incl. 2.46, 3H, s, N*Me* & 2.39 3H, s, N*Me*]), 2.21-2.04 (4H, m, [incl. 2.08, 3H, s, N*Me*]), 1.98-1.81 (4H, m); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 153.8, 152.3, 150.6, 135.6, 135.2, 132.2, 133.6, 133.5, 128.6, 125.7, 125.3, 124.5, 124.0, 123.1, 118.4, 117.7, 117.4, 117.0, 116.6, 107.9, 93.1, 89.5, 83.3, 80.0, 63.7, 63.3, 60.3, 53.2, 52.9, 52.7, 52.3, 51.5, 38.6, 38.5, 37.7, 37.3, 36.6, 35.5; *m/z* (ESI +) 599 (MH^+, 100%); (ESI, HRMS) Found 599.3843 (MH^+), $C_{39}H_{47}N_6$ Requires 599.3857. $[\alpha]_D^{25.0}$ -80.8 (c = 0.6, $CHCl_3$).

(-)-(3a*R*,3'aS,3''a*R*,8a*R*,8'aS,8''a*R*)-1,1',1''-trimethyl-2,2',2'',3,3',3'',8,8a,8',8'a,8'',8''a-dodecahydro-1H,1'H,1''H-3a,3'a:7',3''a-terpyrrolo[2,3-b]indole, (-)-hodgkinsine B, 146



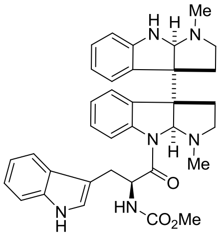
Method A**:** A solution of (-)-*bis*-allyl-hodgkinsine B, **145** (25 mg, 0.04 mmol) in tetrahydrofuran (4 mL) was added dropwise *via* syringe to a stirred solution of sodium metal (100 mg, 4.30 mmol) in condensed ammonia (~15 mL) at -78 °C. The reaction was stirred for 2 h before being quenched with ammonium chloride and allowed to warm to room temperature. The resultant slurry was partitioned between water and dichloromethane. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give (-)-hodgkinsine-B, **146** as a colourless foam (19 mg, 87%).

Method B**:** Trimethylsilyl trifluoromethanesulfonate (0.04 mL, 0.22 mmol) was added drop-wise *via* syringe to a stirred solution of (-)-*tert*-butyl (2-((*S*)-1-allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **137** (70 mg, 0.10 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 16 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (4 mL) and added to a stirred solution of sodium metal (220 mg, 9.57 mmol) in condensed ammonia (~15 mL) at -78 °C. The reaction was stirred for 2.5 h before being quenched with ammonium chloride and allowed to warm to room temperature. The resultant slurry was partitioned between water and dichloromethane. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before being purified by flash chromatography eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give (-)-hodgkinsine-B **146** as a colourless foam (16 mg, 32%). ν_{max} (neat)/cm^{-1} 3380, 3250 (NH), 3050, 2960, 2930, 2860, 2790 (CH), 1600 C=C; NMR run at -30 °C, at this temperature, (-)-hodgkinsine B exists as two conformers (3:2 ratio); ^{1}H (500 MHz, $CDCl_3$, -30 °C) δ 7.37(3H, d, *J* 7.8), 7.23-7.16 (8H, m), 7.13-7.06 (10 H, m), 6.99-6.95 (6H, m), 6.83-6.78 (8H, m), 6.64-6.55 (9H, m), 6.48 (3H, d, *J* 7.8), 6.39 (2H, t, *J* 7.4), 6.13 (3H, t, *J* 7.6), 5.84 (3H, d, *J* 7.4), 5.63 (3H, d, *J* 7.5), 5.06-5.02 (8H, m), 4.91 (2H, bs), 4.40 (3H, d, *J* 3.5), 4.28 (2H, s), 4.17-4.09 (7H, m), 3.83 (3H, s), 2.96 (3H, t, *J* 7.9), 2.87-2.70 (14H, m), 2.58-2.32 (64H, m), 2.15-2.04 (22H, m), 1.96-1.93 (3H, m), 1.84 (2H, bs), 1.25-1.23 (3H, m); ^{13}C (125 MHz, $CDCl_3$, -30 °C) δ 152.3, 151.4, 151.2, 150.7, 149.9, 137.8, 133.5, 132.6, 132.5, 132.2, 132.1, 131.9, 130.2, 128.5, 128.3, 128.3, 128.0, 127.0, 125.6, 125.3, 125.1, 124.6, 122.9, 122.4, 118.9, 118.6, 118.3, 115.8, 115.2, 109.5, 109.3, 108.1, 86.2, 85.8, 83.6, 83.1, 82.2, 63.7, 63.6, 63.3, 63.0, 60.8, 60.7, 58.9, 52.9, 52.7, 52.6, 52.4, 52.1, 40.0, 39.2, 38.2, 38.0, 36.6, 36.1, 35.8, 35.7, 35.6, 21.6, 18.9; *m/z* (ESI +) 519 (MH^+, 100%); (ESI, HRMS) Found 519.3215 (MH^+), $C_{33}H_{39}N_6$ Requires 519.3231; $[\alpha]_D^{25.0}$ -55.6 (c = 0.8, $CDCl_3$), lit $[\alpha]_D^{27.0}$ -55.0 (c = 0.8, $CHCl_3$) [Desymmetrized using (*R*,*R*)-DACT-Phenyl- Trost Ligand].

Data in accordance with the literature.[i]

11.7 Biomimetic Strategies

Methyl (2*S*)-1-(1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH)-yl)-3-(1H-indol-3-yl)-1-oxopropan-2-ylcarbamate, 148



1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (357 mg, 1.87 mmol), hydroxybenzotriazole (89 mg, 0.66 mmol) and *meso*-chimonanthine **2** (500 mg, 1.44 mmol) were added sequentially to a stirred solution of (*S*)-3-(1H-indol-3-yl)-2-(methoxycarbonylamino)propanoic acid (378 mg, 1.44 mmol) in dichloromethane (300 mL). The reaction was stirred for 16 h at room temperature before being partitioned between saturated aqueous sodium bicarbonate solution and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) which gave in order of elution minor diastereomer **148** (113 mg, 13%), major diastereomer **148** (322 mg, 38%) and *meso*-chimonanthine **2** (226 mg, 45%).

Minor Diastereomer (absolute configuration not established):

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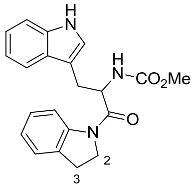
[i] *Angew. Chem. Int. Ed.* **2003**, *42*, 2528

mp 159-160 °C ($CDCl_3$); ν_{max} (neat)/cm^{-1} 3290 (NH), 3060, 3010, 2950, 2920, 2850 (CH), 1770, 1710 (C=O), 1640, 1550 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$) δ See appendix; *m/z* (ESI +) 591 (*MH*$^+$, 100%); (ESI, HRMS) Found 591.3075 (*MH*$^+$), $C_{35}H_{39}N_6O_3$ Requires 591.3078.

Major Diastereomer (absolute configuration not established):

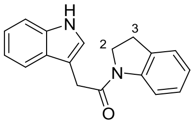
mp 190-200 °C ($CDCl_3$); ν_{max} (neat)/cm^{-1} 3380 (NH), 2950, 2830 (CH), 1700 (C=O), 1640, 1560 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$) δ See appendix; *m/z* (ESI +) 591 (*MH*$^+$, 100%); (ESI, HRMS) Found 591.3075 (*MH*$^+$), $C_{35}H_{39}N_6O_3$ Requires 591.3078.

Methyl 3-(1H-indol-3-yl)-1-(indolin-1-yl)-1-oxopropan-2-ylcarbamate, 150



1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (1.89 g, 9.92 mmol), hydroxybenzotriazole (474 mg, 3.51 mmol) and indoline (1.03 mL, 9.16 mmol) were added sequentially to a stirred solution of 3-(1H-indol-3-yl)-2-(methoxycarbonylamino)propanoic acid (2.00 g, 7.63 mmol) in dichloromethane (150 mL). The reaction was stirred overnight at room temperature before being partitioned between aqueous hydrochloric acid (1 M) and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was crystallised from a mixture of dichloromethane and *iso*-hexane to give the *amide* **150** as a colourless solid (2.76 g, 99%). mp 128-130 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 3310 (NH), 3120, 3060, 3010, 2970, 2920, 2860 (CH), 1700 (C=O), 1600, 1520 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.43 (1H, s, N*H*), 8.25 (1H, d, *J* 8.1, H-4), 7.67 (1H, d, *J* 7.8, Ar*H*), 7.31 (1H, d, *J* 8.0, Ar*H*), 7.21-7.11 (2H, m, Ar*H*), 7.11-7.05 (2H, m, Ar*H*), 7.04-6.98 (1H, m, Ar*H*), 6.96 (1H, s, H-2), 5.90 (1H, d, *J* 8.5, N*H*CO_2Me), 4.98-4.88 (1H, m, CH_2C*H*N), 4.08-3.98 (1H, m, H-2'), 3.67 (3H, s, O*Me*), 3.41-3.31 (1H, m, H-2'), 3.31-3.21 (2H, m, C*H_2*CHN), 2.90 (1H, ddd, *J* 16.2, 10.2, 6.3, H-3'), 2.64 (1H, ddd, *J* 16.2, 10.1, 6.8, H-3'); ^{13}C (100 MHz, $CDCl_3$) δ 170.6, 156.7, 142.3, 136.1, 131.9, 127.4, 124.7, 124.5, 124.3, 123.2, 122.1, 119.6, 118.5, 117.5, 111.3, 109.9, 53.8, 52.3, 47.9, 29.4, 27.8; *m/z* (ESI +) 364 (*MH^+*, 100%); (ESI, HRMS) Found 386.1472 (*$M+Na^+$*), $C_{21}H_{21}N_3O_3Na$ Requires 386.1475.

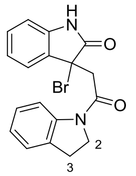
2-(1H-indol-3-yl)-1-(indolin-1-yl)ethanone, 152



1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (6.45 g, 33.7 mmol), hydroxybenzotriazole (1.61 g, 11.9 mmol) and indoline (2.9 mL, 26.0 mmol) were added sequentially to a stirred solution of 2-(1H-indol-3-yl)acetic acid (5.00 g, 28.6 mmol) in dichloromethane (250 mL). The reaction was stirred for 24 h at room temperature before being partitioned between saturated aqueous sodium bicarbonate solution and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from a mixture of ethyl acetate and diethyl ether to give the *amide* **152** as a colourless solid (5.81 g, 81%). mp 190 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 2850, 2720 (CH), 1600, 1460 C=C); ^{1}H (400 MHz,

$(CD_3)_2SO$) δ 11.0 (1H, bs, N*H*), 8.10 (1H, d, *J* 8.0, H-4'), 7.62 (1H, d, *J* 7.8, H-7'), 7.38 (1H, d, *J* 8.1, H-4), 7.29 (1H, s, H-2'), 7.20 (1H, d, *J* 7.2, H-7), 7.13 (1H, app t, *J* 8.1, H-5), 7.09 (1H, app t, *J* 8.0, H-5'), 7.02-6.93 (2H, m, H-6, 6'), 4.18 (2H, t, *J* 8.5, H-2), 3.89 (2H, s, CH_2C(O)N), 3.10 (2H, t, *J* 8.5, H-3); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 170.3, 144.1, 137.1, 132.5, 128.3, 127.8, 125.6, 124.9, 124.0, 121.9, 119.7, 119.3, 116.8, 112.2, 108.2, 48.5, 34.1, 28.3; *m/z* (ESI +) 277 (*MH*$^+$, 100%); (ESI, HRMS) Found 299.1152 (*M*+*Na*$^+$), $C_{18}H_{16}N_2ONa$ Requires 299.1155.

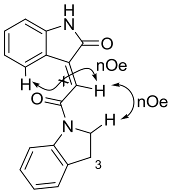
3-Bromo-3-(2-(indolin-1-yl)-2-oxoethyl)indolin-2-one, 153



N-Bromosuccinimide (673 mg, 3.8 mmol) was added portion wise over 1 h to a stirred suspension of 2-(1H-indol-3-yl)-1-(indolin-1-yl)ethanone **152** (456 mg, 1.65 mmol) and water (0.059 mL, 3.3 mmol) in a 1 : 1 mixture of tetrahydrofuran and *tert*-butanol (16 mL). The reaction was allowed to stand at room temperature for a further 1 h before the product was isolated by filtration. Washing with tetrahydrofuran (0.5 mL) afforded the *bromo-oxindole* **153** as an off white solid (445 mg, 73%). mp 60-120 °C (dec). (DCM/hexane); ν_{max} (neat)/cm^{-1} 3160 (NH), 2920, 2730, 2670 (CH), 1730 (C=O), 1650, 1610, 1600 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$, 82 °C) δ 7.73 (1H, d, *J* 7.0, Ar*H*), 7.49 (1H, d, *J* 7.4, Ar*H*), 7.25-7.18 (2H, m, Ar*H*), 7.08-7.01 (1H, m, Ar*H*), 6.99-6.92 (2H, m, Ar*H*), 6.88 (1H, d, *J* 7.6, Ar*H*), 4.27-4.11 (2H, m, H-2), 4.03 (1H, d, *J* 17.6, CH_2C(O)N), 3.66 (1H, d, *J* 17.6, CH_2C(O)N), 3.15 (2H, app t, *J* 8.1, H-3); ^{13}C (100 MHz, $(CD_3)_2SO$) δ

176.1, 167.1, 143.0, 142.5, 132.6, 131.8, 130.6, 127.7, 125.7, 124.6, 124.4, 122.6, 116.6, 110.9, 55.6, 48.0, 44.5, 28.2; *m/z* (ESI +) 395 (*M*+*Na*($_{81}$Br)$^+$, 100%), 393 (*M*+*Na*($_{79}$Br)$^+$, 100%); (ESI, HRMS) Found 393.0204 (*M*+*Na*$^+$), $C_{18}H_{15}(^{79}Br)N_2O_2Na$ Requires 393.0209.

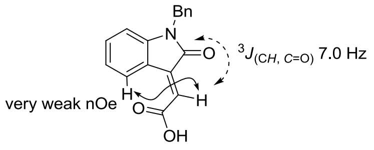
(*E*)-3-(2-(Indolin-1-yl)-2-oxoethylidene)indolin-2-one, 155



Method A**:** To a stirred suspension of (*E*)-2-(2-oxoindolin-3-ylidene)acetic acid (200 mg, 1.06 mmol) in dichloromethane (30 mL) was added oxalyl chloride (0.10 mL, 1.16 mmol) and a drop of *N*,*N*-dimethylformamide. The mixture was stirred for 3 min before indoline (0.16 mL, 1.38 mmol) was added and the reaction stirred at room temperature for 16 h before being partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 1 : 1 (ethyl acetate : petrol) to give *the amide* **155** as a bright orange solid (120 mg, 39%).

Method B**:** 3-Bromo-3-(2-(indolin-1-yl)-2-oxoethyl)indolin-2-one **153** (50 mg, 0.135 mmol) and caesium carbonate (96 mg, 0.30 mmol) were combined in dichloromethane (2 mL) and were heated at 100 °C *via* microwave irradiation for 1.25 h. The mixture was allowed to cool to room temperature before being filtered through a pad of celite and concentrated *in vacuo* to give *the amide* **155** as a bright orange solid (39 mg, quant.). mp 190 °C ($CDCl_3$); ν_{max} (neat)/cm^{-1} 3260 (NH), 2960, 2920, 2850 (CH), 1710 (C=O), 1650, 1620, 1600, 1530 (C=C); ^{1}H (500 MHz, $(CD_3)_2SO$) δ 10.73 (1H, s, N*H*), 8.26 (1H, d, *J* 8.0, H-4'), 8.10 (1H, d, *J* 7.7, H-7), 7.33-7.26 (2H, m, H-5, 7'), 7.24 (1H, app t, *J* 8.0, H-5'), 7.15 (1H, s, C*H*C(O)N), 7.09 (1H, app t, *J* 8.0, H-6'), 6.97 (1H, app t, *J* 7.7, H-6), 6.88 (1H, d, *J* 7.8, H-4), 4.23 (2H, t, *J* 8.4, H-2), 3.18 (2H, t, *J* 8.4, H-3); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 169.1, 163.8, 145.0, 143.2, 135.3, 133.4, 132.8, 128.0, 127.6, 125.9, 125.6, 125.2, 122.5, 120.9, 117.4, 111.0, 48.9, 28.4; *m/z* (ESI +) 313 (*M+Na*$^+$, 100%); (ESI, HRMS) Found 313.0948 (*M+Na*$^+$), $C_{18}H_{14}N_2O_2Na$ Requires 313.0947.

(*E*)-2-(1-Benzyl-2-oxoindolin-3-ylidene)acetic acid, 158



(*tert*-Butoxycarbonylmethylene)triphenylphosphorane[i] (4.9 g, 13.2 mmol) was added to a stirred suspension of *N*-benzylisatin **156**[ii] (3.29 g, 13.9 mmol) in toluene (80 mL). The mixture was heated to reflux and stirred for 1.5 h before being allowed to cool to ~50 °C. Trifluoroacetic acid (20 mL) was added and the reaction stirred for an additional 2 h. The reaction was basified by the cautious addition of saturated aqueous sodium bicarbonate solution; the organic layer was isolated and discarded. The aqueous layer was acidified with aqueous hydrochloric acid (1 M) and extracted thoroughly with ethyl acetate, the combined organic extracts were concentrated *in vacuo*, and petrol was added to

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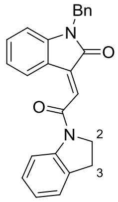
[i] *Chem. Ber.*, **1986**, *119*, 1196
[ii] *J. Am. Chem. Soc.*, **2005**, *127*, 11505

precipitate the acid **158** as bright orange needles (2.60 g, 71%). mp 155-156 °C (EtOAc/petrol) (lit. 160-163 °C); ^{1}H (400 MHz, $(CD_3)_2SO$) δ 13.45 (1H, bs, O*H*), 8.36 (1H, d, *J* 7.6, H-4), 7.39-7.30 (5H, m, Ar*H*), 7.30-7.23 (1H, m, Ar*H*), 7.06 (1H, app t, *J* 7.6, H-5), 6.98 (1H, d, *J* 7.8, H-4'), 6.77 (1H, s, C=C*H*), 4.95 (2H, s, NC*H*$_2$); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 167.7, 167.3, 145.5, 136.9, 136.6, 133.3, 129.6, 128.5, 128.3, 128.1, 124.5, 123.4, 120.1, 110.5, 43.7; *m/z* (ESI -) 278 (*M-H*$^-$, 100%).

Data in accordance with the literature.[i]

(*E*)-1-Benzyl-3-(2-(indolin-1-yl)-2-oxoethylidene)indolin-2-one, 159



Synthesised using general procedure **02** using: Oxalyl chloride (0.11 mL, 1.3 mmol), (*E*)-2-(1-Benzyl-2-oxoindolin-3-ylidene)acetic acid **158** (200 mg, 0.72 mmol) and indoline (0.07 mL, 0.65 mmol). The general procedure afforded the *title compound* **159** as a bright orange solid (234 mg, 94%). mp 150-151 °C ($CHCl_3$); ν_{max} (neat)/cm^{-1} 3060, 3030, 2920, 2860 (CH), 1790, 1710 (C=O), 1650, 1600 (C=O); ^{1}H (400 MHz, $(CD_3)_2SO$) δ 8.25 (1H, d, *J* 8.0, H-4'), 8.11 (1H, d, *J* 7.6, H-7), 7.38-7.21 (9H, m), 7.10 (1H, app t, *J* 7.4, H-6'), 7.02 (1H, app t, *J* 7.6, H-6), 6.98 (1H, d, *J* 7.9, H-4), 4.98 (2H, s, C*H*$_2$Ph), 4.26 (2H, t, *J* 8.4, H-2), 3.19 (2H, t, *J* 8.4, H-3); ^{13}C (125 MHz, $(CD_3)_2SO$) δ 167.0, 162.8, 144.1, 142.3, 136.2, 133.0, 132.7, 131.8, 128.7, 127.5, 127.3, 127.2, 126.4, 126.1, 125.1, 124.4, 122.4,

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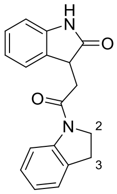
[i] *Tetrahedron*, **1967**, *23*, 901

119.4, 116.6, 109.6, 48.0, 42.8, 27.6; *m/z* (ESI +) 403 ($M+Na^+$, 100%); (ESI, HRMS) Found 403.1409 ($M+Na^+$), $C_{25}H_{20}N_2O_2Na$ Requires 403.1417.

3-(2-(Indolin-1-yl)-2-oxoethyl)indolin-2-one, 164



1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (470 mg, 2.46 mmol), hydroxybenzotriazole (117 mg, 0.87 mmol) and indoline (0.28 mL, 1.89 mmol) were added sequentially to a stirred solution of 2-(2-oxoindolin-3-yl)acetic acid **163**[i] (397 mg, 2.08 mmol) in dichloromethane (25 mL). The reaction was stirred for 24 h at room temperature before being partitioned between saturated aqueous sodium bicarbonate solution and additional dichloromethane. The organic layer was isolated and the aqueous layer extracted with further dichloromethane, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from a mixture of ethyl acetate and petrol to give the *amide* **164** as a colourless solid (395 mg, 71%). mp 115 °C (DCM/hexane); ν_{max} (nujol)/cm^{-1} 2920, 2730 (CH), 1700, 1670 (C=O), 1610, (C=C); ^1H (400 MHz, $(CD_3)_2SO$) δ 10.39 (1H, s, N*H*), 8.00 (1H, d, *J* 8.0, H-7), 7.25 (1H, d, *J* 7.4, H-4'), 7.21 (1H, d, 7.4, H-4), 7.18-7.07 (2H, m, H-6, 6'), 6.97 (1H, app t, *J* 7.4, H-5), 6.88 (1H, app t, *J* 7.4, H-5'), 6.83 (1H, d, *J* 7.7, H-7'), 4.11 (2H, app q, *J* 8.5, H-2), 3.76 (1H, dd, *J* 7.7, 3.4, H-3'), 3.22 (1H, dd, *J* 17.3, 3.4, C*H*$_2$C(O)), 3.12 (2H, app t, *J* 8.5,

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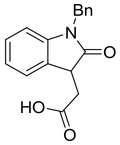
[i] *Synthesis*, **1979**, 276

H-3), 2.95 (1H, dd, *J* 17.3, 7.7, C*H*$_2$C(O)). ^{13}C (100 MHz, CDCl$_3$) δ 179.7, 168.0, 142.8, 141.3, 131.0, 129.7, 128.1, 127.6, 125.0, 124.6, 123.9, 122.5, 117.1, 109.6, 48.0, 42.2, 37.1, 28.0; *m/z* (ESI -) 291 (*M-H*$^-$, 100%); (ESI, HRMS) Found 315.1098 (*M+Na*$^+$), $C_{18}H_{16}N_2O_2Na$ Requires 315.1104.

2-(1-Benzyl-2-oxoindolin-3-yl)acetic acid,[i] 165



Palladium on carbon (5% Pd, 100 mg, 0.05 mmol) was added to a stirred solution of 2-(1-benzyl-2-oxoindolin-3-ylidene)acetic acid **158** (2.19 g, 7.85 mmol) in methanol (150 mL). The mixture was purged with nitrogen before being charged with a balloon of hydrogen. The bright orange mixture was stirred at room temperature for 16 h by which time it had completely decolourised. The hydrogen source was removed and the vessel purged with nitrogen before being filtered through a pad of celite. The mixture was concentrated *in vacuo* and the residue precipitated from a mixture of ethyl acetate and petrol to afford the *acid* **165** as a white solid (2.20 g, quant.). mp 133-135 °C (EtOAc/petrol) (lit. 126-127 °C); ^{1}H (400 MHz, (CD$_3$)$_2$SO) δ 12.42 (1H, bs, O*H*), 7.40-7.21 (6H, m, Ar*H*), 7.15 (1H, app t, *J* 7.6, H-6), 6.97 (1H, app t, *J* 7.6, H-5), 6.78 (1H, d, *J* 7.6, H-7), 4.96 (1H, d, *J* 15.9, NC*H*$_2$), 4.83 (1H, d, *J* 15.9, NC*H*$_2$), 3.83 (1H, bs, H-3), 3.03 (1H, dd, *J* 16.8, 3.8, C*H*$_2$CO$_2$H), 2.87 (1H, dd, *J* 16.8, 5.9, C*H*$_2$CO$_2$H); ^{13}C (100 MHz, (CD$_3$)$_2$SO) δ 177.3,

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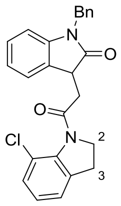
[i] *Tetrahedron*, **1967**, *23*, 901

176.5, 143.3, 136.4, 128.53, 128.47, 127.6, 127.2, 127.1, 123.4, 121.9, 108.8, 42.6, 41.3, 33.8; *m/z* (ESI +) 304 ($M+Na^+$, 100%).

Data in accordance with the literature.[i]

1-Benzyl-3-(2-(7-chloroindolin-1-yl)-2-oxoethyl)indolin-2-one, 167



Synthesised using general procedure **02** using: Oxalyl chloride (0.18 mL, 2.0 mmol), 2-(1-benzyl-2-oxoindolin-3-yl)acetic acid **165** (309 mg, 1.1 mmol) and 7-chloroindoline (153 mg, 1.0 mmol). colourless foam (251 mg, 60%). mp 74-74 °C (EtOAc/petrol); ν_{max} (neat)/cm^{-1} 3090, 3060, 3030, 2920 (CH), 1710, 1650 (C=O), 1600, 1490 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* 7.1, H-6), 7.33-7.21 (6H, m, Ar*H*), 7.19-7.13 (2H, m, H-4, 6’), 7.05 (1H, app t, *J* 7.6, H-3’), 7.00 (1H, app t, *J* 7.1, H-5), 6.72 (1H, d, *J* 7.76, H-7’), 4.94 (2H, s, NCH_2), 4.23-4.09 (3H, m, H-2, 3’), 3.38 (1H, dd, *J* 15.9, 4.2, CH_2C(O)), 3.05 (2H, app q, *J* 7.3, H-3), 2.95 (1H, dd, *J* 15.9, 8.9, CH_2C(O)); ^{13}C (125 MHz, $CDCl_3$) δ 177.4, 171.1, 143.3, 140.2, 137.7, 135.8, 129.1, 128.7 (2×C), 128.0, 127.5, 127.2, 126.2, 124.5, 124.3, 123.1, 122.6, 109.0, 51.4, 43.8, 42.7, 37.0, 30.3; *m/z* (ESI +) 239 ($M+Na^+$, 100%); (ESI, HRMS) Found 439.1183 ($M+Na^+$), $C_{25}H_{21}(^{35}Cl)N_2O_2Na$ Requires 439.1184.

1-Benzyl-3-(2-(7-bromoindolin-1-yl)-2-oxoethyl)indolin-2-one, 168

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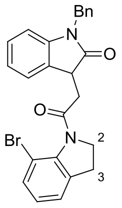
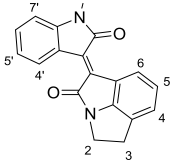
[i] *Tetrahedron: Asymmetry,* **2009**, *20*, 2374



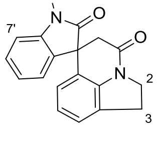
Synthesised using general procedure **02** using: Oxalyl chloride (0.15 mL, 1.70 mmol), 2-(1-benzyl-2-oxoindolin-3-yl)acetic acid **165** (270 mg, 0.96 mmol) and 7-bromoindoline (170 mg, 0.86 mmol). The general procedure afforded the *title compound* **168** as a colourless foam (85 mg, 21%). mp 100-102 °C (EtOAc/petrol); ν_{max} (neat)/cm^{-1} 3060, 3030, 2960, 2910, 2850 (CH), 1710 (C=O), 1680, 1600 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 7.49-7.30 (2H, m, Ar*H*), 7.37-7.22 (7H, m, Ar*H*), 7.21-7.13 (2H, m, Ar*H*), 6.72 (1H, d, *J* 7.8, H-7'), 4.94 (2H, s, NC*H*$_2$Ph), 4.22-4.08 (3H, m, H-2, 3'), 3.38 (1H, dd, *J* 16.0, 4.4, C*H*$_2$C(O)), 3.12-2.94 (3H, m, H-3, C*H*$_2$C(O)); ^{13}C (125 MHz, CDCl$_3$) δ 177.4, 171.1, 143.3, 142.1, 137.8, 135.8, 132.1, 128.7, 128.6, 128.1, 127.5, 127.2, 124.6, 123.6, 122.5, 117.1, 113.0, 109.0, 51.3, 43.9, 42.6, 37.1, 30.5; *m/z* (ESI +) 485 (*M*(^{81}Br)+*Na*$^{+}$, 45%), 483 (*M*(^{79}Br)+*Na*$^{+}$, 45%); (ESI, HRMS) Found 483.0680 (*M*+*Na*$^{+}$), $C_{25}H_{21}(^{79}Br)N_2O_2Na$ Requires 483.0679.

General procedure 04 exemplified by the synthesis of: (*E*)-1-(1-Benzyl-2-oxoindolin-3-ylidene)-4,5-dihydropyrrolo[3,2,1-hi]indol-2(1H)-one, Tri-cyclic product, 170

1-Benzyl-1',2'-dihydrospiro[indoline-3,6'-pyrrolo[3,2,1-ij]quinoline]-2,4'(5'H)-dione, s*piro*-lactam, 169



tri-cyclic product



spiro-lactam

1-Benzyl-3-(2-(7-chloroindolin-1-yl)-2-oxoethyl)indolin-2-one **167** (50 mg, 0.12 mmol), palladium acetate (1.3 mg, 5 mol%), (*R*)-MOP (3.3 mg, 6 mol%) and caesium carbonate (43 mg, 0.13 mmol) were combined in a dry flask and purged with nitrogen. Dry degassed toluene (1 mL) was added *via* syringe before the reaction was heated to 100 °C and stirred for 16 h. The reaction was allowed to cool to room temperature before being directly loaded onto a silica column and purified by flash chromatography, eluting with 1 : 1 (ethyl acetate : petrol) to afford, in order of elution, the *tri-cyclic product* **170** (13 mg, 26%) and the *spiro-lacatam* **169** (28 mg, 61%).

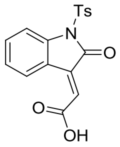
Tri-cyclic product 170:

mp 208-209 °C (EtOAc/DCM); ν_{max} (neat)/cm^{-1} 3060, 3060, 3010, 2960, 2930, 2850 (CH), 1700 (C=O), 1610, 1580 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 9.30 (1H, d, *J* 7.9, H-4'), 8.65 (1H, d, *J* 7.8, H-6), 7.37-7.23 (6H, m, Ar*H*), 7.16 (1H, d, *J* 7.3, H-4), 7.05 (1H, app t, *J* 7.9, H-5'), 6.94 (1H, app t, *J* 7.8, H-5), 6.71 (1H, d, *J* 7.8, H-7'), 5.02 (2H, s, NCH_2Ph), 4.14 (2H, t, *J* 7.8, H-2), 3.54 (2H, t, *J* 7.8, H-3); ^{13}C (125 MHz, $CDCl_3$) δ 168.3, 165.9, 153.8, 144.5, 139.3, 135.8, 132.4, 132.0, 130.2, 129.1, 128.8, 127.9, 127.6, 127.2, 123.7, 122.5, 121.6, 121.3, 116.6, 108.5, 44.9, 43.6, 32.9; *m/z* (ESI +) 379 (MH^+, 50%); (ESI, HRMS) Found 379.1441 (MH^+), $C_{25}H_{19}N_2O_2$ Requires 379.1441.

Spiro-lactam 169:

mp 95-96 °C (Et_2O); ν_{max} (neat)/cm^{-1} 3060, 3030, 2960, 2930, 2860 (CH), 1710, 1670 (C=O), 1610, 1600 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.37-7.26 (5H, m, Ar*H*), 7.23 (1H, app t, *J* 7.8, Ar*H*), 7.16 (2H, app t, *J* 7.6, Ar*H*), 7.03 (1H, app t, *J* 7.8, Ar*H*), 6.86 (1H, app t, *J* 7.6, Ar*H*), 6.81 (1H, d, *J* 7.8, Ar*H*), 6.51 (1H, d, *J* 7.6, Ar*H*), 4.99 (1H, d, *J* 15.6, NCH_2Ph), 4.90 (1H, d, *J* 15.6, NCH_2Ph), 4.29-4.18 (2H, m, H-2), 3.31 (2H, app t, *J* 8.7, H-3), 3.07 (1H, d, *J* 16.6, CH_2C(O)), 2.95 (1H, d, *J* 16.6, CH_2C(O)); ^{13}C (125 MHz, $CDCl_3$) δ 117.2, 164.6, 142.2, 141.9, 135.5, 131.6, 130.1, 129.0, 128.9, 127.8, 127.2, 125.1, 124.0, 123.61, 123.59, 123.4, 120.3, 109.6, 51.3, 45.3, 43.9, 40.6, 28.0; *m/z* (ESI +) 403 ($M+Na^+$, 100%); (ESI, HRMS) Found 403.1418 ($M+Na^+$), $C_{25}H_{20}N_2O_2Na$ Requires 403.1417.

(*E*)-2-(2-Oxo-1-tosylindolin-3-ylidene)acetic acid, 173



(*tert*-Butoxycarbonylmethylene)triphenylphosphorane[i] (1.19 g, 3.16 mmol) was added to a stirred suspension of *N*-tosylisatin **171** (1.00 g, 3.32 mmol) in toluene (40 mL). The mixture was heated to reflux and stirred for 30 min before being allowed to cool to ~50 °C. Trifluoroacetic acid (5 mL) was added and the reaction stirred for an additional 2 h at 50 °C. The reaction was allowed to cool to room temperature and was stirred for 16 h. The reaction was basified by the cautious addition of saturated aqueous sodium bicarbonate solution; the organic layer was isolated and discarded. The aqueous layer was acidified with aqueous hydrochloric acid (10 M) and extracted thoroughly with ethyl acetate, the combined organic extracts were concentrated *in vacuo*, and petrol was added to precipitate the *acid* **173** as bright yellow needles (636 mg, 59%). mp 205-206 °C (EtOAc/petrol); ν_{max} (nujol)/cm^{-1} 2850, 2720, 2670 (CH), 1750, 1690 (C=O), 1640, 1600 (C=C); ^{1}H (400 MHz, $(CD_3)_2SO$) δ 13.6 (1H, bs, CO_2H), 8.42 (1H, d, *J* 7.8, H-4), 7.94 (2H, d, *J* 8.2, Ts), 7.89 (1H, d, *J* 8.2, H-7), 7.57 (1H, dd, *J* 8.2, 7.6, H-6), 7.47 (2H, d, *J*

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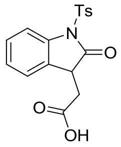
[i] *Chem. Ber.*, **1986**, *119*, 1196

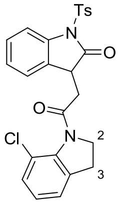
8.2, Ts), 7.29 (1H, dd, *J* 7.8, 7.6, H-5), 6.72 (1H, s, C*H*), 2.38 (3H, s, *Me*); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 166.7, 166.1, 147.1, 140.8, 135.2, 133.8, 133.7, 131.1, 128.5, 128.3, 126.5, 126.0, 120.7, 114.1, 22.0; *m/z* (ESI -) 342 (*M-H*$^-$, 100%), (ESI, HRMS) Found 366.0407 (*M+Na*$^+$), $C_{17}H_{13}NNaO_5S$ Requires 366.0407.

2-(2-Oxo-1-tosylindolin-3-yl)acetic acid, 174



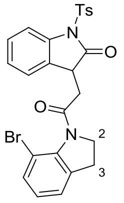
Palladium on carbon (5% Pd, 100 mg, 0.05 mmol) was added to a stirred solution of (*E*)-2-(2-oxo-1-tosylindolin-3-ylidene)acetic acid **173** (1.89 g, 5.51 mmol) in methanol (100 mL). The mixture was purged with nitrogen before being charged with a balloon of hydrogen. The bright orange mixture was stirred at room temperature for 16 h by which time it had completely decolourised. The hydrogen source was removed and the vessel purged with nitrogen before being filtered through a pad of celite. The mixture was concentrated *in vacuo* and the residue precipitated from a mixture of ethyl acetate and petrol to afford the *oxindole* **174** as a white solid (1.93 g, 96%). mp 171-172 °C (EtOAc/petrol); ν_{max} (neat)/cm^{-1} 3070, 3050, 3030, 2960, 2920 (CH), 1750, 1750 (C=O), 1610, 1600 (C=C); ^{1}H (400 MHz, $(CD_3)_2SO$) δ 12.3 (1H, bs, CO_2*H*), 7.90 (2H, d, *J* 8.1, Ts), 7.72 (1H, d, *J* 8.1, H-7), 7.43 (2H, d, *J* 8.1, Ts), 7.36 (1H, d, *J* 7.7, H-4), 7.33 (1H, dd, *J* 8.1, 7.4, H-6), 7.16 (1H, dd, *J* 7.7, 7.4, H-5), 4.04-3.97 (1H, m, H-3), 3.05 (1H, dd, *J* 17.7, 4.3, C*H*$_2$CO$_2$H), 2.93 (1H, dd, *J* 17.7, 4.3, C*H*$_2$CO$_2$H), 2.38 (3H, s, *Me*); ^{13}C (100 MHz, $(CD_3)_2SO$) δ 175.9, 172.2, 146.2, 144.0, 135.6, 130.7, 129.0, 128.8, 128.2, 125.3, 124.6, 113.4, 42.6, 34.4, 22.0; *m/z* (ESI -) 344 (*M-H*$^-$, 100%), (ESI, HRMS) Found 368.0560 (*M+Na*$^+$), $C_{17}H_{15}NNaO_5S$ Requires 368.0563.

3-(2-(7-Chloroindolin-1-yl)-2-oxoethyl)-1-tosylindolin-2-one, 175



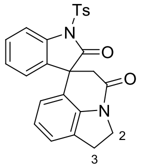
Synthesised using general procedure **02** using: Oxalyl chloride (0.08 mL, 0.96 mmol), 2-(2-oxo-1-tosylindolin-3-yl)acetic acid **174** (200 mg, 0.58 mmol) and 7-chloroindoline (74 mg, 0.48 mmol). The general procedure afforded the *title compound* **175** as a colourless foam (150 mg, 65%). mp 97-98 °C ($CDCl_3$); ν_{max} (neat)/cm^{-1} 3070, 3050, 3030, 2960, 2920, 2850 (CH), 1760 (C=O), 1670, 1600 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.98 (2H, d, *J* 8.3, Ts), 7.91 (1H, d, *J* 8.3, Ar*H*), 7.35-7.25 (4H, m, [incl. 7.28, 2H, d, 8.3 Ts]), 7.19-7.10 (3H, m, Ar*H*), 7.03 (1H, app t, *J* 7.6, Ar*H*), 4.10-3.92 (3H, m, H-2, 3’), 3.23 (1H, dd, *J* 16.1, 4.3, CH_2C(O)), 3.06-2.89 (3H, m, [incl. 2.97, 1H, dd, *J* 16.1, 7.7, CH_2C(O)]), 2.40 (3H, s, *Me*); ^{13}C (125 MHz, $CDCl_3$) δ 175.5, 175.4, 145.5, 139.9, 139.6, 137.7, 135.1, 129.7, 129.0, 128.7, 128.0, 127.4, 126.3, 124.7, 124.3, 124.1, 123.1, 113.5, 51.3, 43.0, 36.8, 30.2, 21.7; *m/z* (ESI +) 503 (*M+Na*$^+$, 100%); (ESI, HRMS) Found 503.0803 (*M+Na*$^+$), $C_{25}H_{21}(^{35}Cl)N_2O_4SNa$ Requires 503.0803.

3-(2-(7-Bromoindolin-1-yl)-2-oxoethyl)-1-tosylindolin-2-one, 176



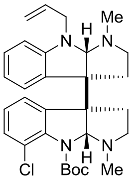
Synthesised using general procedure **02** using: Oxalyl chloride (0.18 mL, 2.03 mmol), 2-(2-oxo-1-tosylindolin-3-yl)acetic acid **173** (418 mg, 1.21 mmol) and 7-bromoindoline (200 mg, 1.01 mmol). The general procedure afforded the *title compound* **176** as a colourless foam (210 mg, 40%). mp 96-97 °C (DCM); ν_{max} (neat)/cm^{-1} 3070, 3050, 3020, 2960, 2920 (CH), 1760 (C=O), 1670, 1600 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* 8.0, Ts), 7.92 (1H, d, *J* 8.2 Ar*H*), 7.38-7.25 (4H, m, [incl. 7.28, 2H, d, *J* 8.0, Ts]), 7.18-7.09 (3H, m, Ar*H*), 6.95 (1H, app t, *J* 7.6, Ar*H*), 4.10-3.91 (3H, m, H-2, 3'), 3.24 (1H, dd, *J* 16.0, 4.3, CH_2C(O)), 3.04-2.90 (3H, m, H-3, CH_2C(O)), 2.39 (3H, s, *Me*); ^{13}C (125 MHz, $CDCl_3$) δ 175.5, 175.4, 145.5, 141.9, 139.7, 135.1, 132.0, 129.65, 129.58, 128.7, 128.2, 128.0, 127.3, 126.6, 124.7, 124.4, 123.6, 113.5, 51.2, 43.0, 37.0. 30.4, 21.7; *m/z* (ESI +) 549 (*MNa*($_{81}$Br)$^+$, 100%), 547 (*MNa*($_{79}$Br)$^+$, 95%); (ESI, HRMS) Found 547.0303 (*M*+*Na*$^+$), $C_{25}H_{21}(^{79}Br)N_2O_4NaS$ Requires 547.0298.

1-Tosyl-1',2'-dihydrospiro[indoline-3,6'-pyrrolo[3,2,1-ij]quinoline]-2,4'(5'H)-dione, spiro-lactam, 177



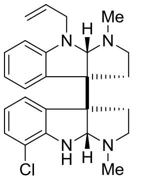
Prepared using general method **04** using: 3-(2-(7-bromoindolin-1-yl)-2-oxoethyl)-1-tosylindolin-2-one **176** (54 mg, 0.10 mmol), palladium acetate (1 mg, 5 mol%), (*R*)-MOP (3 mg, 6 mol%) and caesium carbonate (37 mg, 0.11 mmol). The general procedure afforded the *title compound* **177** as an off white foam (20 mg, 43%). mp 173-174 °C (IPA/petrol); ν_{max} (neat)/cm^{-1} 3120, 3070, 3050, 2960, 2920, 2860 (CH), 1750 (C=O), 1670, 1600 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* 8.2, H-7'), 7.95 (2H, d, *J* 8.2, Ts), 7.42 (1H, app t, *J* 8.2, H-6'), 7.33 (2H, d, *J* 8.2, Ts), 7.20 (1H, app t, *J* 8.2, H-5'), 7.14 (1H, d, *J* 8.2, H-4'), 7.11 (1H, d, *J* 8.2, H-4), 6.76 (1H, dd, *J* 8.2, 7.7, H-5), 6.23 (1H, d, *J* 7.7, H-6), 4.16 (2H, t, *J* 8.4, H-2), 3.25 (2H, t, *J* 8.4, H-3), 2.84 (1H, d, *J* 16.7, C*H*$_2$C(O)), 2.78 (1H, d, *J* 16.7, C*H*$_2$C(O)), 2.44 (3H, s, Ar*Me*); ^{13}C (125 MHz, CDCl$_3$) δ 175.3, 163.5, 146.0, 141.5, 138.6, 134.8, 130.3, 130.2, 129.9, 129.8, 127.8, 125.7, 125.5, 124.0, 123.9, 123.7, 119.2, 114.1, 51.6, 45.2, 40.4, 27.9, 21.7; *m/z* (ESI +) 467 (*M*+*Na*$^+$, 100%); (ESI, HRMS) Found 467.1036 (*M*+*Na*$^+$), $C_{25}H_{20}N_2O_4NaS$ Requires 467.1036.

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-butyl 8'-allyl-7-chloro-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-8(8aH)-carboxylate, 180



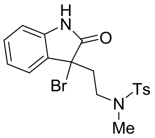
sec-Butyl lithium (1.3 mL, 1.54 mmol) was added drop-wise *via* syringe over 10 min to a stirred solution of (3a*S*,3'a*R*,8a*R*,*8*'a*S*)-*tert*-Butyl 8'-allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate **103** (300 mg, 0.62 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.3 mL, 1.86 mmol) in ether (20 mL) at -78 °C. The reaction was stirred for 17 min before carbontetrachloride (0.6 mL, 6.2 mmol) was added drop-wise *via* syringe over 1 min. The reaction was stirred at -78 °C for 5 min before being warmed to 0 °C and stirred for an additional 1 h. The reaction was partitioned between saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was isolated, the aqueous layer extracted with further ethyl acetate and the combined organic extracts dried (MgSO$_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH$_3$) to give (-)-*7'-chloro-N'-Boc-N-allyl-chimonanthine* **180** as a pale yellow foam (185 mg, 57%). ν_{max} (neat)/cm^{-1} 2970, 2940, 2870, 2800 (CH), 1850 (C=O), 1710, 1600 (C=C); ^{1}H (250 MHz, (CD$_3$)$_2$SO, 90 °C) δ 7.20, (1H, d, *J* 8.0, H-6'), 7.02 (1H, app t, *J* 7.8, *J* 7.8, H-6), 6.94-6.70 (2H, m, H-4’, [incl. 6.88, 1H, app t, *J* 8.0, H-5’]), 6.56 (1H, app t, *J* 7.8, H-5), 6.49-6.36 (2H, m, H-4, [incl. 6.41 1H, d, *J* 7.8, H-7]), 5.49-5.26 (1H, m, $NCH_2CH{=}CH_2$), 5.20-4.90 (3H, m, [incl. 5.11, 1H, s, H-8a’ & 5.09, 1H, od, *J* 17.6, $NCH_2CH{=}CH_2$ & 4.96, 1H, d, *J* 10.1, $NCH_2CH{=}CH_2$]), 4.22 (1H, s, H-8a), 3.76 (1H, dd, *J* 18.8, 4.8, $NCH_2CH{=}CH_2$), 5.50 (1H, dd, *J* 18.8, 4.8, $NCH_2CH{=}CH_2$), 2.83-2.67 (2H, m, H-2, 2’), 2.55-2.26 (9H, m, [incl. 2.47, 3H, s, N*Me* & 2.37, 3H, s, N*Me*]), 2.27-2.12 (1H, m, H-3), 2.10-2.00 (1H, m, H-3’), 1.96-1.83 (1H, m, H-3), 1.43 (9H, s, *tBu*); ^{13}C (63 MHz, $(CD_3)_2SO$, 90 °C) δ 153.2, 142.1, 141.1, 135.0, 132.8, 129.8, 129.2, 125.9, 124.5, 123.8, 123.3, 118.2, 117.6, 108.4, 89.7, 88.8, 81.6 (2×C), 63.5, 62.5, 52.8, 52.7, 52.1, 37.5, 37.1, 36.5, 36.4, 28.6; *m/z* (ESI +) 521 (MH^+, 100%); (ESI, HRMS) Found 521.2665 (MH^+), $C_{30}H_{38}N_4O_2(^{35}Cl)$ Requires 521.2678. $[\alpha]_D^{25.0}$ -47.7 (c = 0.6, $CHCl_3$) [(*R*,*R*)-DACT-phenyl-Trost ligand]

(-)-(3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-7-chloro-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 181



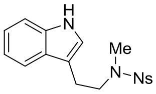
To a stirred solution of (3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-Butyl 8'-allyl-7-chloro-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate **180** (159 mg, 0.31 mmol) in dichloromethane (11 mL) was added trimethylsilyl trifluoromethanesulfonate (0.12 mL, 0.67 mmol) drop-wise *via* syringe. The reaction was stirred open to the air for 16 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer was extracted with further dichloromethane, the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the *7'-chloro-N-allyl-chimonathine* **181** as a pale amber foam (127 mg, quant). ν_{max} (neat)/cm^{-1} 3420 (NH), 2960, 2930, 2860, 2790 (CH), 1600 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 100 °C) δ 7.02 (1H, app t, *J* 7.3, H-6), 6.94 (1H, d, *J* 7.8, H-6'), 6.90-6.68 (1H, m, H-4'), 6.56 (1H, app t, *J* 7.3, H-5), 6.40 (1H, d, *J* 7.3, H-7), 6.30 (1H, app t, *J* 7.8, H-5'), 6.21-5.97 (1H, m, H-4), 5.86 (1H, s, N*H*), 5.39-5.10 (1H, m, NCH_2CH=CH_2), 5.05 (1H, od, *J* 16.8, NCH_2CH=CH_2), 4.95 (1H, d, *J* 10.0, NCH_2CH=CH_2), 4.71 (1H, s, H-8a'), 4.37 (1H, s, H-8a), 3.68 (1H, d, *J* 16.0, NCH_2CH=CH_2), 3.47 (1H, d, *J* 16.0, NCH_2CH=CH_2), 2.83-2.67 (2H, m, H-2, 2'), 2.57-2.19 (10H, m, [incl. 2.38, 3H, s, N*Me* & 2.36, 3H, s, N*Me*]), 1.99-1.84 (2H, m, H-3, 3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 154.0, 149.9, 135.5, 135.3, 133.9, 128.8, 128.1, 124.4, 123.5, 118.1, 118.0, 117.3, 112.8, 108.2, 89.1, 83.6, 65.0, 63.5, 52.7, 52.6, 52.4, 37.7, 37.3, 36.6, 36.1; *m/z* (ESI +) 421 (MH^+, 100%); (ESI, HRMS) Found 421.2147 (MH^+), $C_{25}H_{30}N_4(^{35}Cl)$ Requires 421.2154; $[\alpha]_D^{25.0}$ -27.3 (c = 0.6, $CHCl_3$) [(*R*,*R*)-DACT-Phenyl Trost Ligand].

General procedure 05 exemplified by the synthesis of: *N*-(2-(3-Bromo-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 183



N-Bromosuccinimide (321 mg, 2.72 mmol) was added portion-wise over 1.5 h to a stirred solution of *N*-(2-(1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **105** (358 mg, 1.09 mmol) and water (0.58 mL, 3.27 mmol) in a 1:1 mixture of *tert*-butanol and tetrahydrofuran (10 mL) at room temperature. The reaction was stirred at room temperature in the absence of light for a further 2 h. The reaction mixture was concentrated *in vacuo* before being purified by flash chromatography, eluting with 1 : 3 (*iso*-hexane : ethyl acetate) to give the *bromo-oxindole* **183** as a colourless foam (352 mg, 76%). mp 60-70 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 3280 (NH), 3060, 3030, 2920, 2880, 2820 (CH), 1720 (C=O), 1620, 1600, 1470 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 7.94 (1H, bs, N*H*), 7.54 (2H, d, *J* 8.3, H-2'), 7.39 (1H, d, *J* 7.2, H-7), 7.31 (1H, dd, *J* 7.7, 7.2, H-6), 7.26 (2H, d, *J* 8.3, H-3'), 7.13 (1H, dd, *J* 7.8, 7.7, H-5), 6.91 (1H, d, *J* 7.8, H-4), 3.12 (1H, ddd, *J* 13.4, 8.0, 7.5, CH_2CH_2N), 2.19 (1H, ddd, *J* 13.4, 8.3, 4.6, CH_2CH_2N), 2.75 (1H, ddd, *J* 14.5, 8.0, 7.5, CH_2CH_2N), 2.64 (3H, s, N*Me*), 2.57 (1H, ddd, *J* 14.5, 8.3, 4.6, CH_2CH_2N), 2.40 (3H, s, *Me*); ^{13}C (100 MHz, $CDCl_3$) δ 175.1, 143.4, 139.7, 133.9, 130.5, 129.6, 129.3, 127.4, 124.7, 123.5, 110.8, 54.4, 46.9, 36.6, 34.9, 21.4; *m/z* (ESI +) 425 (*MH*(^{81}Br)$^+$, 100%), 423 (*MH*(^{79}Br)$^+$, 95%); (ESI, HRMS) Found 445.0199 (*M*+*Na*$^+$), $C_{18}H_{19}(^{79}Br)N_2O_3NaS$ Requires 445.0192.

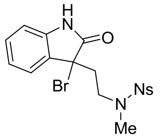
N-(2-(1H-Indol-3-yl)ethyl)-N-methyl-4-nitrobenzenesulfonamide



Nosyl chloride (698 mg, 3.16 mmol), was added to a stirred solution of *N*-methyl-tryptamine (500 mg, 2.97 mmol), triethylamine (0.6 mL, 4.30 mmol) and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in dichloromethane (15 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 6 h before being partitioned between saturated aqueous sodium bicarbonate and dichloromethane, the organic layer was isolated and the aqueous layer extracted with further dichloromethane.

The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation from a mixture of *iso*-hexane and dichloromethane to give the *nosyl-protected methyl tryptamine* as an off white solid (885 mg, 86%). mp 133-134 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 3390 (NH), 3100, 3060, 2920 (CH), 1620, 1600 (C=C), 1530, 1350 (NO_2); ^{1}H (400 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* 8.7, H-3'), 8.04 (1H, bs, N*H*), 7.83 (2H, d, *J* 8.7, H-2'), 7.51 (1H, d, *J* 7.8, H-4), 7.33 (1H, d, *J* 8.12, H-7), 7.18 (1H, dd, *J* 8.1, 7.1, H-6), 7.10 (1H, dd, *J* 7.8, 7.1, H-5), 7.02 (1H, app d, *J* 2.3, H-2), 3.44 (2H, t, *J* 7.1, CH_2CH_2N), 3.04 (2H, t, *J* 7.1, CH_2CH_2N), 2.89 (3H, s, N*Me*); ^{13}C (100 MHz, $CDCl_3$) δ 149.6, 144.0, 136.1, 128.1, 126.9, 124.0, 122.2, 122.1, 119.6, 118.3, 111.9, 111.2, 50.6, 34.6, 24.2; *m/z* (ESI +) 360 (*MH*$^+$, 100%); (ESI, HRMS) Found 382.0829 (*M+Na*$^+$), $C_{17}H_{17}N_3O_4NaS$ Requires 382.0832.

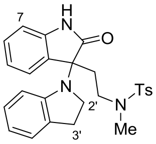
N-(2-(3-Bromo-2-oxoindolin-3-yl)ethyl)-*N*-methyl-4-nitrobenzenesulfonamide, 184



Synthesised using general procedure **05** using: *N*-bromosuccinimide (476 mg, 4.04 mmol), *N*-(2-(1H-indol-3-yl)ethyl)-*N*-methyl-4-nitrobenzenesulfonamide (630 mg, 1.75 mmol) and water (0.063 mL, 3.5 mmol). The general procedure afforded the *title compound* **184** as a white foam (561 mg, 70%). mp 149-150 °C (DCM/hexane); ν_{max} (neat)/cm^{-1} 3400 (NH), 3100, 3060, 3030, 2930, 2870 (CH), 1730 (S=O), 1620 (C=C), 1530 (C=O), 1480 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.33 (2H, d, *J* 8.9, H-3'), 7.94 (1H, s, N*H*), 7.86 (2H, d, *J* 8.9, H-2'), 7.40 (1H, d, *J* 7.7, H-7), 7.33 (1H, app td, *J* 7.7, 1.1, H-5), 7.16 (1H, app td, *J* 7.7, 0.9, H-6), 6.93 (1H, d, *J* 7.7, H-4), 3.20 (1H, ddd, *J* 13.5, 8.4, 7.1, NCH_2CH_2), 3.06

(1H, ddd, *J* 13.5, 8.6, 4.7, NC*H*$_2$CH$_2$), 2.80-2.72 (4H, m, [inc. 2.74, 3H, s, N*Me*]), 2.58 (1H, ddd, *J* 13.6, 8.4, 4.7, NCH$_2$C*H*$_2$); ^{13}C (100 MHz, CDCl$_3$) δ 174.8, 150.1, 143.0, 139.5, 130.6, 129.2, 128.4, 124.6, 124.4, 123.6, 110.8, 53.8, 46.9, 36.6, 34.9; *m/z* (ESI +) 456 (*MH*($_{81}$Br)$^+$, 100%), 454 (*MH*(^{79}Br)$^+$, 100%); (ESI, HRMS) Found 475.9886 (*M*+*Na*$^+$), $C_{17}H_{16}(_{79}Br)N_3O_5NaS$ Requires 475.9886.

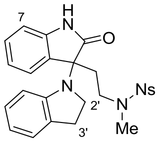
General procedure 06 exemplified by the synthesis of *N*,4-Dimethyl-*N*-(2-(2'-oxo-1,3'-biindolin-3'-yl)ethyl)benzenesulfonamide, 185



Indoline (93 mg, 0.78 mmol), *N*-(2-(3-bromo-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **183** (300 mg, 0.71 mmol) and caesium carbonate (300 mg, 0.92 mmol) were combined in dichloromethane (15 mL) and stirred at room temperature for 2 h. The reaction mixture was diluted with further dichloromethane before being filtered through a pad of celite and being concentrated *in vacuo*. The crude product was purified by crystallisation from a mixture of dichloromethane and *iso*-hexane, to yield the *oxindole* **185** as a pale beige solid (219 mg, 89%). mp 86-87 °C (CDCl$_3$); ν_{max} (neat)/cm^{-1} 3180 (NH), 3060, 3020, 2960, 2930, 2870 (CH), 1720 (C=O), 1620, 1470 (C=C); ^{1}H (400 MHz, CDCl$_3$) δ 8.71 (1H, s, N*H*), 7.55 (2H, s, *J* 8.0, 2’’), 7.34-7.24 (5H, m, H-7, 4, 3’’, 5’), 7.08-7.02 (1H, app t, *J* 7.2, H-6), 7.92 (1H, d, *J* 7.9, H-4’), 6.71 (1H, app t, *J* 7.9, H-6’), 6.63 (1H, app t, *J* 7.2, H-5), 5.77 (1H, d, *J* 7.9, H-7’), 4.11-4.01 (1H, m, H-2’), 3.89-3.80 (1H, m, H-2’), 3.16-3.04 (2H, m, CH$_2$C*H*$_2$NMe), 3.02-2.95 (2H, m, H-3’), 2.68 (3H, s, N*Me*), 2.52-2.36 (5H, m, C*H*$_2$CH$_2$NMe [incl. 2.41, 3H, s, Ar*Me*]); ^{13}C (125 MHz,

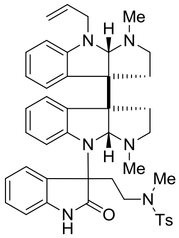
$CDCl_3$) δ See appendix; *m/z* (ESI +) 462 (*MH*$^+$, 100%); (ESI, HRMS) Found 484.1655 (*M+Na*$^+$), $C_{26}H_{27}N_3O_3NaS$ Requires 484.1655.

N-Methyl-4-nitro-N-(2-(2'-oxo-1,3'-biindolin-3'-yl)ethyl)benzenesulfonamide, 186



Synthesised using general procedure **06** using: Indoline (24 mg, 0.20 mmol), *N*-(2-(3-bromo-2-oxoindolin-3-yl)ethyl)-*N*-methyl-4-nitrobenzenesulfonamide (100 mg, 0.22 mmol) and caesium carbonate (78 mg, 0.24 mmol). The general procedure afforded the *title compound* **186** as a pale beige solid (78 mg, 80%). mp 95-96 °C (DCM/*iso*-hexane); ν_{max} (neat)/cm^{-1} 3250 (NH), 3100, 3060, 2960, 2870 (CH), 1720 (C=O), 1620, 1600 (C=C), 1530 (N=O), 1470 (C=C); ^{1}H (400 MHz, $CDCl_3$) δ 8.31 (2H, d, *J* 8.8, H-3’’), 8.08 (1H, bs, N*H*), 7.84 (2H, d, *J* 8.8, H-2’’), 7.34-7.28 (2H, m, H-5, 7), 7.09-7.03 (2H, m, H-6, 4’), 6.93 (1H, d, *J* 7.7, H-4), 6.72 (1H, app t, *J* 7.5, H-6’), 6.62 (1H, app t, *J* 7.5, H-5’), 5.80 (1H, d, *J* 7.5, H-7’), 3.98 (1H, app q, *J* 9.0, CH_2CH_2N), 3.81 (1H, app q, *J* 9.0, CH_2CH_2N), 3.20-3.14 (2H, m, H-2’), 3.00-2.94 (2H, m, CH_2CH_2N), 2.77 (3H, s, N*Me*), 2.51-2.42 (2H, m, H-3’); ^{13}C (100 MHz, $CDCl_3$) δ 178.4, 150.0, 149.3, 143.4, 139.8, 131.1, 129.5, 128.43, 128.39, 127.1, 124.6, 124.5, 124.3, 123.4, 119.3, 110.5, 109.0, 65.2, 50.2, 45.4, 35.9, 35.3, 28.0; *m/z* (ESI +) 493 (*MH*$^+$, 100%); (ESI, HRMS) Found 515.1353 (*M+Na*$^+$), $C_{25}H_{24}N_4O_5NaS$ Requires 515.1360.

***N*-(2-(3-((3a*S*,3'a*R*,8a*R*,8'a*S*)-8'-Allyl-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH)-yl)-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 187**



Synthesised using general procedure **06** using: *N*-allyl-chimonanthine (498 mg, 1.29 mmol), *N*-(2-(3-bromo-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **183** (600 mg, 1.42 mmol) and caesium carbonate (504 mg, 1.55 mmol). The crude product was purified by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give, in order of elution; the *minor diastereomer* (66 mg, 7%) and the *major diastereomer* (422 mg, 45%) as pale beige foams.

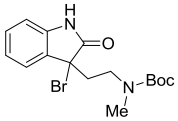
Minor Diastereomer (relative configuration not established):

mp 109-110 °C (DCM); ν_{max} (neat)/cm^{-1} 3190 (NH), 3060, 3030, 2960, 2870, 2800 (CH), 1720, 1640, 1620, 1600, 1550 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 10.27 (1H, bs, N*H*), 7.53 (2H, d, *J* 7.8, Ts), 7.39 (2H, d, *J* 7.8, Ts), 7.30-7.18 (3H, m, Ar*H*), 7.07-6.88 (4H, m, Ar*H*), 6.75 (1H, app t, *J* 7.8, Ar*H*), 6.64-6.52 (1H, m, Ar*H*), 6.38 (1H, d, *J* 6.9, Ar*H*), 6.24 (1H, app t, *J* 6.8, Ar*H*), 5.10-5.98 (1H, m, Ar*H*), 5.33-5.15 (1H, m, $CH_2CH{=}CH_2$), 5.03 (1H, d, *J* 16.4, $CH_2CH{=}CH_2$), 4.89 (1H, d, *J* 9.9, $CH_2CH{=}CH_2$), 4.72 (1H, s, H-8a'), 4.49 (1H, s, H-8a), 3.50 (1H, d, *J* 12.4, $CH_2CH{=}CH_2$),), 3.31 (1H, d, *J* 12.4, $CH_2CH{=}CH_2$), 3.17-2.03 (22H, m, [incl. 2.67, 3H, s, N*Me* & 2.41, 3H, s, N*Me*]), 1.96-1.86 (2H, m, H-3, 3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 178.6, 149.6, 144.0, 142.6, 136.1, 135.8, 130.5, 129.7, 128.8, 128.3, 127.7, 125.8, 124.7, 124.5, 122.6, 117.4, 110.8, 90.6, 65.8, 64.2, 62.5, 64.0, 52.9, 52.6, 46.0, 41.8, 41.5, 41.3, 41.2, 41.0, 40.8, 35.9, 35.2, 21.7; *m/z* (ESI +) 729 (*MH*$^+$, 100%); (ESI, HRMS) Found 729.3577 (*M+Na*$^+$), $C_{43}H_{49}N_6O_3S$ Requires 729.3581.

Major Diastereomer (relative configuration not established):

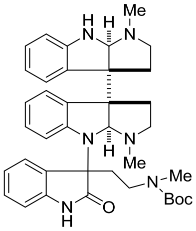
mp 112-115 °C (DCM); ν_{max} (neat)/cm^{-1} 3190 (NH), 3060, 3030, 2960, 2870, 2800 (CH), 1720, 1640, 1620, 1600, 1550 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) δ 7.59-7.47 (1H, m, Ar*H*), 7.44-7.30 (2H, m, Ar*H*), 7.25-7.12 (1H, m, Ar*H*), 7.09-6.93 (2H, m, Ar*H*, [incl. 7.00, 1H, app t, *J* 7.3, Ar*H*]), 6.94-6.71 (3H, m, Ar*H*, [incl. 6.88, 1H, app t, *J* 7.5, Ar*H*]), 6.59-6.48 (2H, m, Ar*H*), 6.47-6.25 (4H, m, Ar*H*, [incl. 6.43, 1H, d, *J* 7.9, Ar*H* & 6.37, 1H, d, *J* 7.8, Ar*H*]), 6.25-6.14 (1H, m, Ar*H*), 5.66 (1H, s, N*H*), 5.44-5.26 (1H, m, $CH_2CH{=}CH_2$), 5.06 (1H, d, *J* 17.0, $CH_2CH{=}CH_2$), 4.96 (1H, d, *J* 10.2, $CH_2CH{=}CH_2$), 4.63 (1H, s, H-8a'), 4.39 (1H, s, H-8a), 3.62 (1H, dd, *J* 16.4, 5.3, $CH_2CH{=}CH_2$), 3.48 (1H, dd, *J* 16.4, 5.6, $CH_2CH{=}CH_2$), 2.90-2.28 (22H, m, [incl. 2.39, 3H, s, N*Me* & 2.35, 3H, s, N*Me*]), 2.00-1.85 (2H, m, H-3, 3'); ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ 175.8, 154.0, 153.2, 135.7, 134.3, 133.2, 130.5, 128.6, 128.4, 127.7, 124.8, 124.5, 122.4, 117.9, 117.1, 110.6, 108.3, 108.2, 89.7, 83.9, 64.1, 63.5, 52.8, 52.6, 52.5, 41.5, 41.3, 41.2, 41.0, 40.8, 37.5, 37.4, 36.2, 21.7; *m/z* (ESI +) 729 (*MH*$^+$, 100%); (ESI, HRMS) Found 729.3577 (*M+Na*$^+$), $C_{43}H_{49}N_6O_3S$ Requires 729.3581.

***tert*-butyl (2-(3-bromo-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 189**



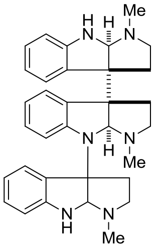
Synthesised using general procedure **05** using: *N*-bromosuccinimide (1.61 g, 13.7 mmol), *N*-Boc-*N*-methyl-tryptamine **133** (1.5 g, 5.5 mmol) and water (0.39 mL, 21.9 mmol). The general procedure afforded the *title compound* **189** as an unstable amber gum (1.3 g, 65%).

***tert*-Butyl (2-(3-(-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-8(8aH)-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 190**



To a stired solution of *meso*-chimonanthine **2** (200 mg, 0.58 mmol) and caesium carbonate (630 mg, 1.74 mmol) in dichloromethane (50 mL) was added *tert*-butyl (2-(3-bromo-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **189** (319 mg, 0.87 mmol). The reaction was stirred at room temperature for 16 h. (Note. due decomposition of of the bromo oxindole, reaction wasn't driven to completion) The reaction was quenched with water and the organic layer isolated, the aqueous layer was extracted with additional dichloromethane. The comebined organic extracts were drid (MgSO4) and concentrated *in vacuo*, the crude product was puridies by flash chromatography eluting with 21 : 2 : 1 ($CHCl_3$: MeOH : NH_3) to give, in order of elution; the *N-linked product* **190** (126 mg, 34%) and recovered *meso*-chimonantine **2** (130 mg, 65%). mp 135-140 °C (glass, DCM); ν_{max} (neat)/cm^{-1} 3250 (NH), 3060, 2970, 2930, 2870, 2800 (CH), 1716, 1690 (C=O), 1620, 1600, 1560 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 120 °C) see appendix; ^{13}C (125 MHz, $(CD_3)_2SO$, 100 °C) δ see appendix; *m/z* (ESI +) 635 (*MH*$^+$, 100%); (ESI, HRMS) Found 635.3713 (*MH*$^+$), $C_{38}H_{47}N_6O_3$ Requires 635.3704.

1,1',1''-Trimethyl-1',2,2',2'',3,3',3'',8,8a,8'a,8'',8''a-dodecahydro-1H,1''H-3a,3'a:8',3''a-terpyrrolo[2,3-b]indole, *N*-hodgkinsine, 192



Trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.33 mmol) was added drop-wise *via* syringe to a stirred solution of *tert*-butyl (2-(3-(-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-8(8aH)-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate **190** (94 mg, 0..15 mmol) in dichloromethane (4 mL). The reaction was stirred at room temperature for 16 h before being quenched with saturated aqueous sodium bicarbonate solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (10 mL) and treated with lithium aluminum hydride (21 mg, 0.55 mmol) before being heated at reflux for 1.5 h. The mixture was allowed to cool to room temperature and was cautiously quenched with 5% aqueous sodium hydroxide solution. The organic layer was isolated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 98.8 : 0.98 : 0.22 (DCM : MeOH : NH_3) to give '*N-hodgkinsine*' **192** as a colourless foam (13 mg, 17%). ν_{max} (neat)/cm^{-1} 3290 (NH), 2960, 2860, 2790 (CH), 1600 (C=C); ^{1}H (250 MHz, $(CD_3)_2SO$, 90 °C) see appendix; ^{13}C

(63 MHz, $(CD_3)_2SO$, 90 °C) see appendix; *m/z* (ESI +) 519 (*MH*$^+$, 100%); (ESI, HRMS) Found 519.3216 (*MH*$^+$), $C_{33}H_{39}N_6$ Requires 519.3231.

12.0 References

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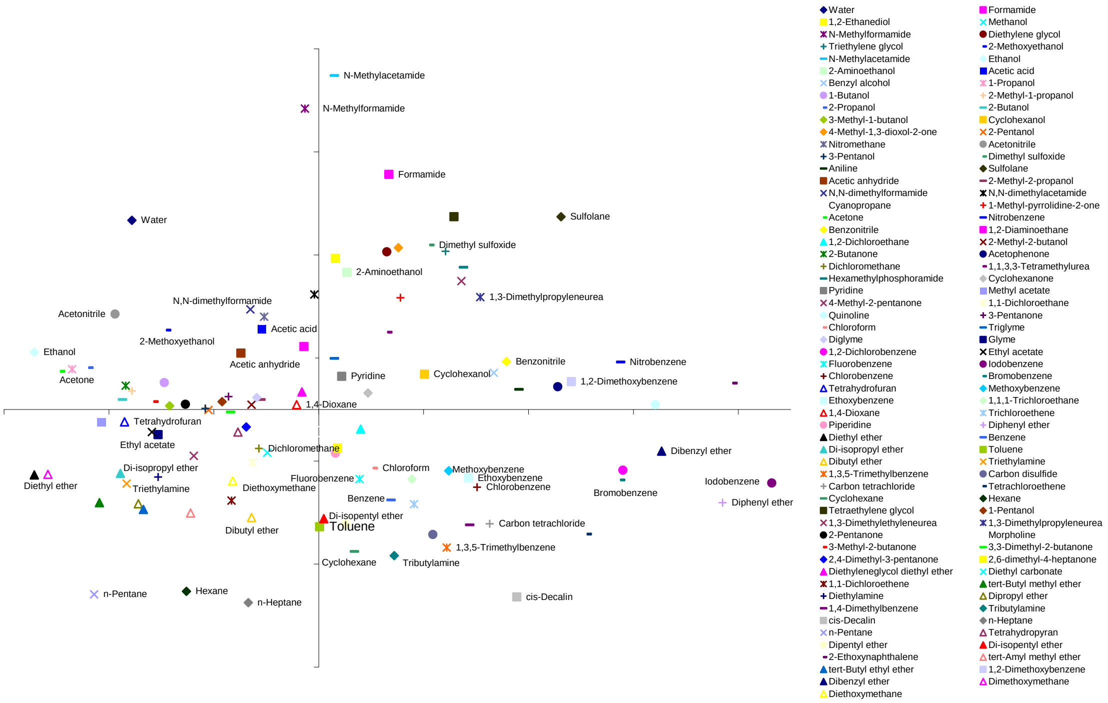
13.0 Appendix

13.1 Principle Component Analysis of Solvents



Principle component analysis (PCA) of a variety of solvents[i]

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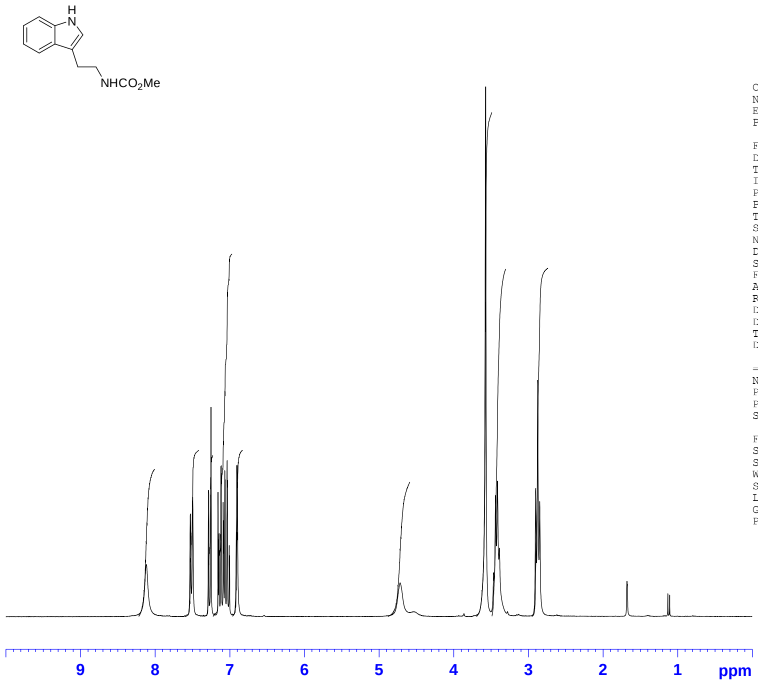
[i] *ARKIOVOC*, **2002**, *xi*, 54

13.2 NMR Spectra of Key Compounds

Methyl 2-(1H-indol-3-yl)ethylcarbamate, 9



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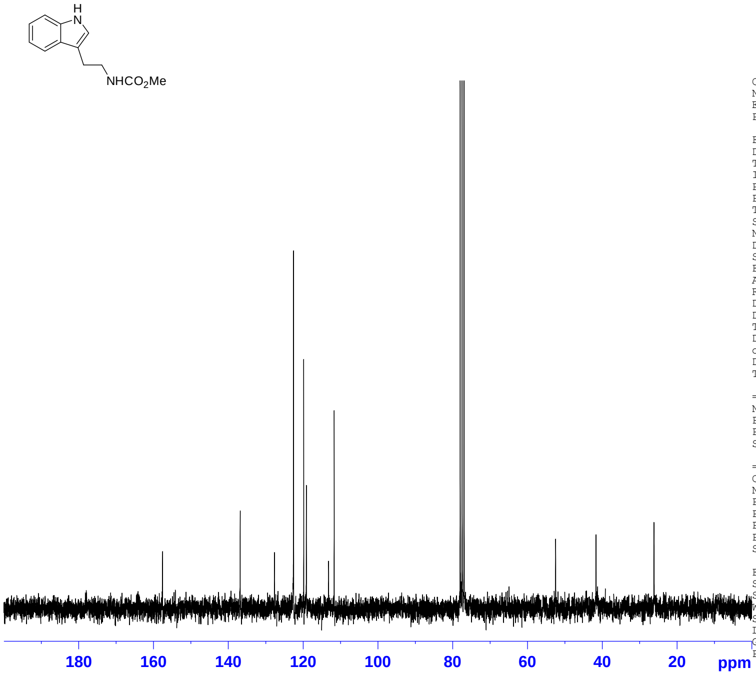
NAME          RS-01-006
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20071011
Time              14.40
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT           CDCl3
NS                   18
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                203.2
DW              100.200 usec
DE                 6.00 usec
TE                296.7 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz

F2 - Processing parameters
SI                16384
SF          250.1300341 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME          RS-01-006
EXPNO                 2
PROCNO                1

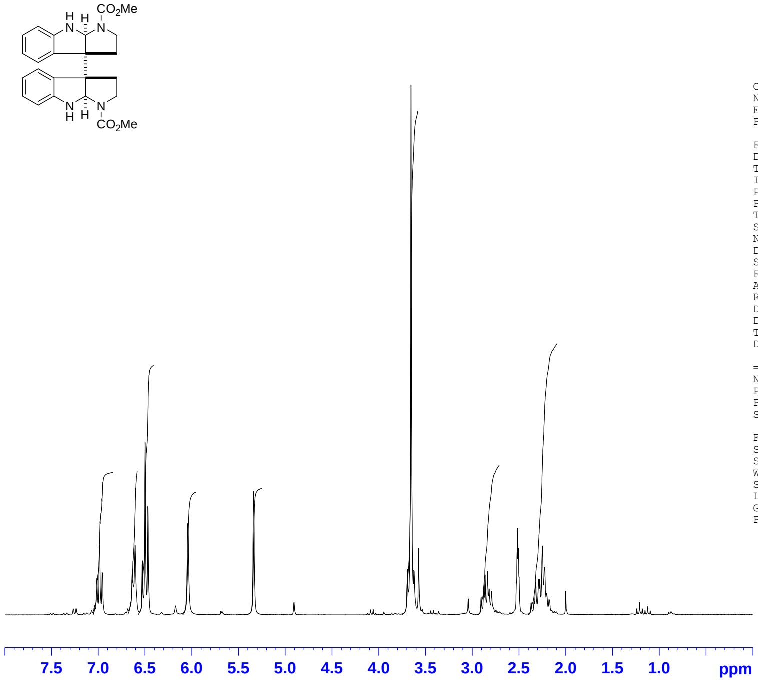
F2 - Acquisition Parameters
Date_          20071011
Time              14.49
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  276
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG                16384
DW               31.800 usec
DE                30.00 usec
TE                296.7 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

(3a*R*,3'a*S*,8a*R*,8'a*S*)-Dimethyl 2,2',3,3',8,8a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-1,1'(8'H,8'aH)-dicarboxylate, 10



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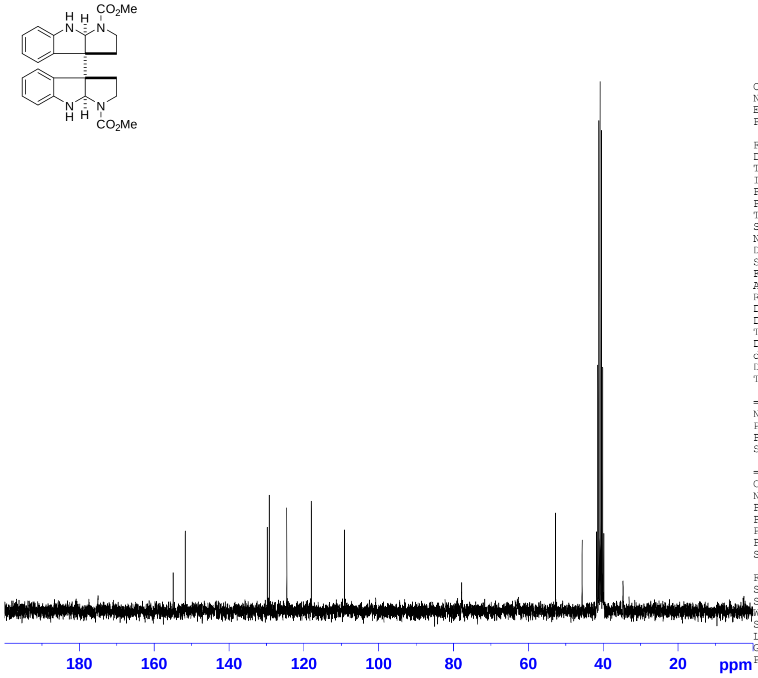
Current Data Parameters
NAME           RS-01-066
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080325
Time               16.12
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    18
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   181
DW               100.200 usec
DE                  6.00 usec
TE                 363.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



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Current Data Parameters
NAME     RS-01-066 carbon
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
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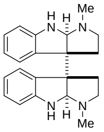
Time               16.15
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   311
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG               10321.3
DW                31.800 usec
DE                 30.00 usec
TE                 363.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

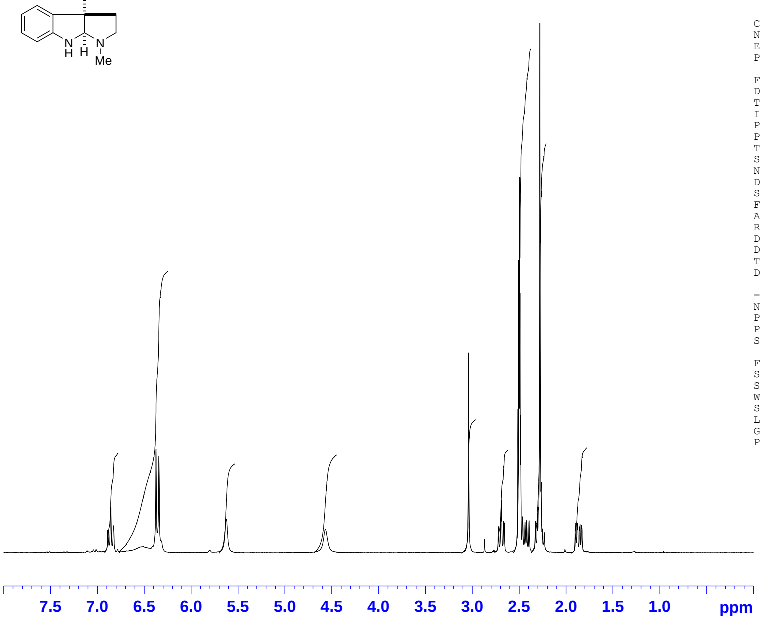
======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(3a*S*,3'a*R*,8a*S*,8'a*R*)-1,1'-Dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *meso*-chimonanthine, 2



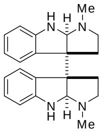


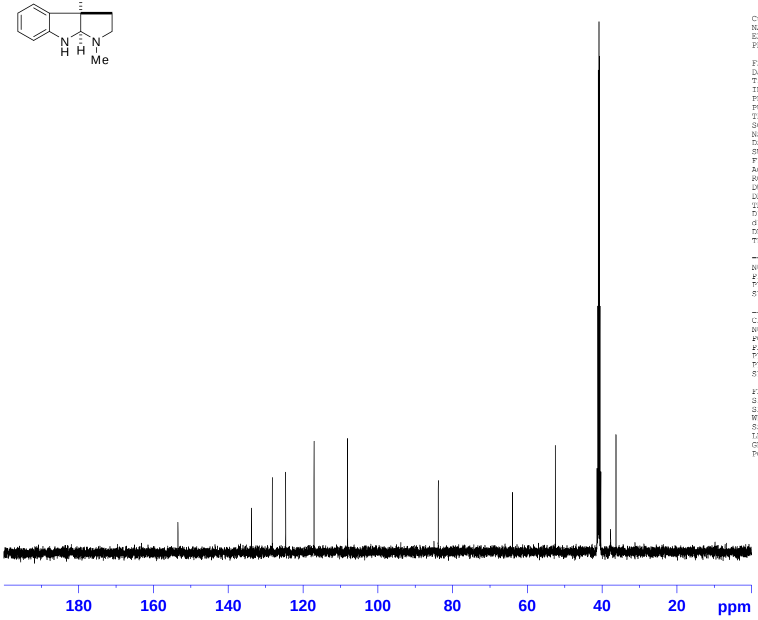
```
Current Data Parameters
NAME      RS-01-meso di methyl
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20071102
Time                 17.14
INSTRUM             dpx250
PROBHD   5 mm Multinucl
PULPROG               zg60
TD                   32768
SOLVENT               DMSO
NS                      53
DS                       2
SWH               4990.020 Hz
FIDRES            0.152283 Hz
AQ               3.2834036 sec
RG                     362
DW                 100.200 usec
DE                    6.00 usec
TE                   363.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.00 usec
PL1                   0.00 dB
SFO1           250.1312507 MHz

F2 - Processing parameters
SI                   16384
SF             250.1299972 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





```
Current Data Parameters
NAME     RS-meso chimonanthine carbon
EXPNO                    2
PROCNO                   1

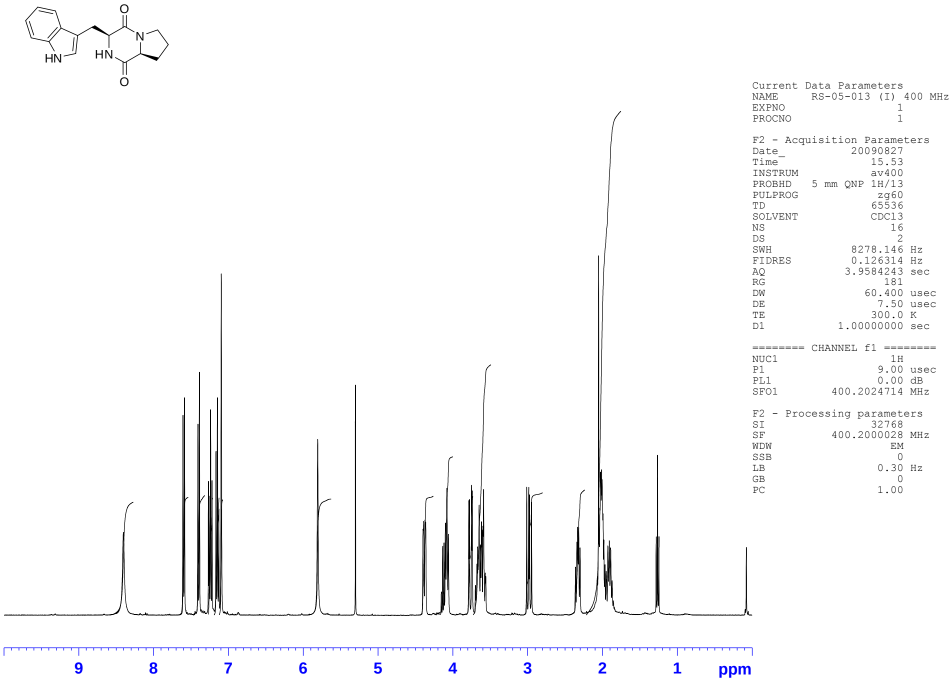
F2 - Acquisition Parameters
Date_             20100611
Time                 16.16
INSTRUM             drx500
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     140
DS                       4
SWH              27777.777 Hz
FIDRES            0.423855 Hz
AQ               1.1797160 sec
RG                 11585.2
DW                  18.000 usec
DE                   11.00 usec
TE                   363.5 K
D1              1.00000000 sec
d11             0.03000000 sec
DELTA           0.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.70 usec
PL1                   6.00 dB
SFO1           125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   0.00 dB
PL12                 19.50 dB
PL13                 22.50 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                   32768
SF             125.7577390 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

(3*S*,8a*S*)-3-((1H-Indol-3-yl)methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione, brevianamide F, 73

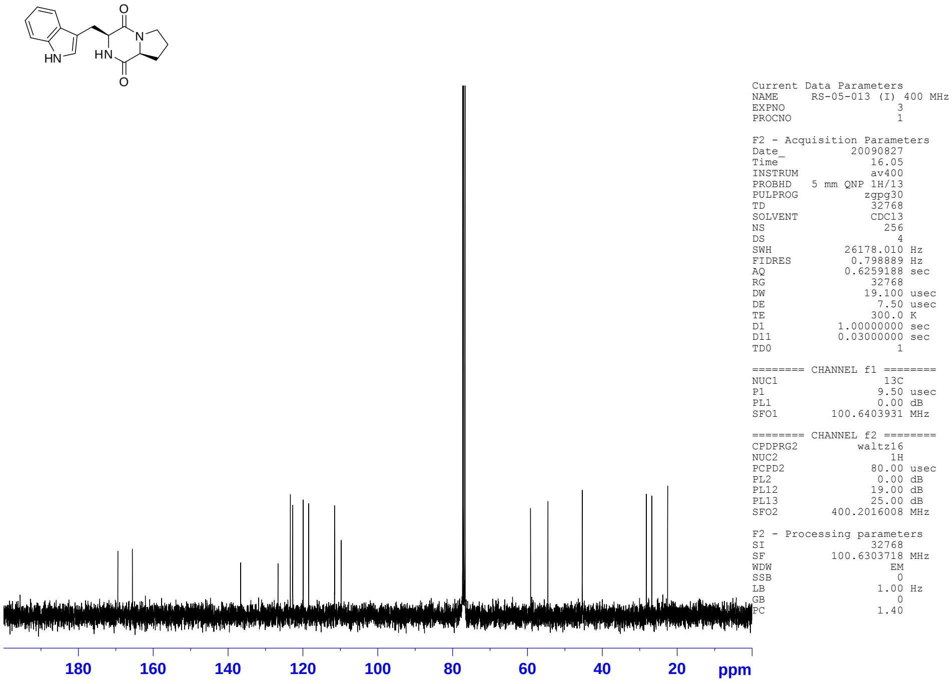


```
Current Data Parameters
NAME      RS-05-013 (I) 400 MHz
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090827
Time                  15.53
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                      181
DW                60.400 usec
DE                  7.50 usec
TE                  300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1        400.2024714 MHz

F2 - Processing parameters
SI                    32768
SF          400.2000028 MHz
WDW                      EM
SSB                       0
LB                  0.30 Hz
GB                        0
PC                     1.00
```



```
Current Data Parameters
NAME      RS-05-013 (I) 400 MHz
EXPNO                     3
PROCNO                    1

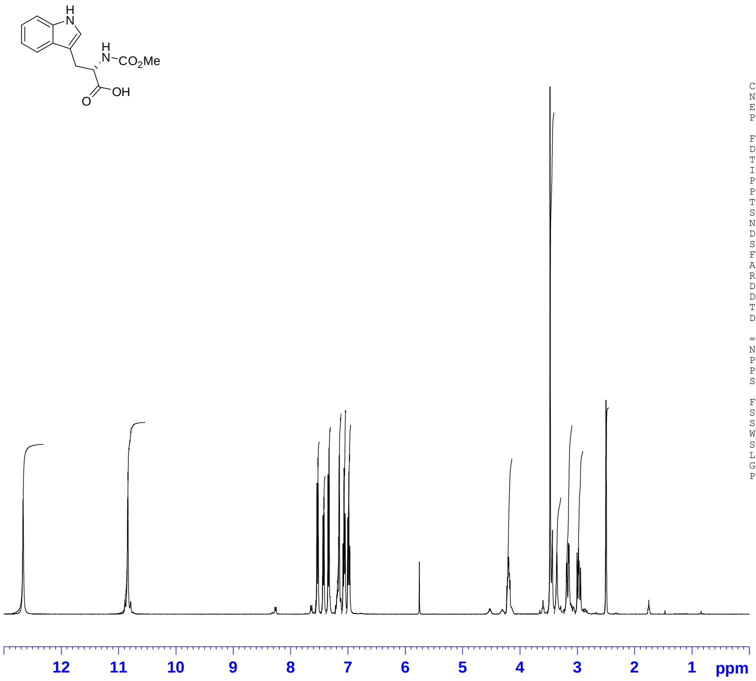
F2 - Acquisition Parameters
Date_              20090827
Time                  16.05
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG             zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      256
DS                        4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                    32768
DW                19.100 usec
DE                  7.50 usec
TE                  300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2        400.2016008 MHz

F2 - Processing parameters
SI                    32768
SF          100.6303718 MHz
WDW                      EM
SSB                       0
LB                  1.00 Hz
GB                        0
PC                     1.40
```

(*S*)-3-(1H-Indol-3-yl)-2-(methoxycarbonylamino)propanoic acid, 70



```
Current Data Parameters
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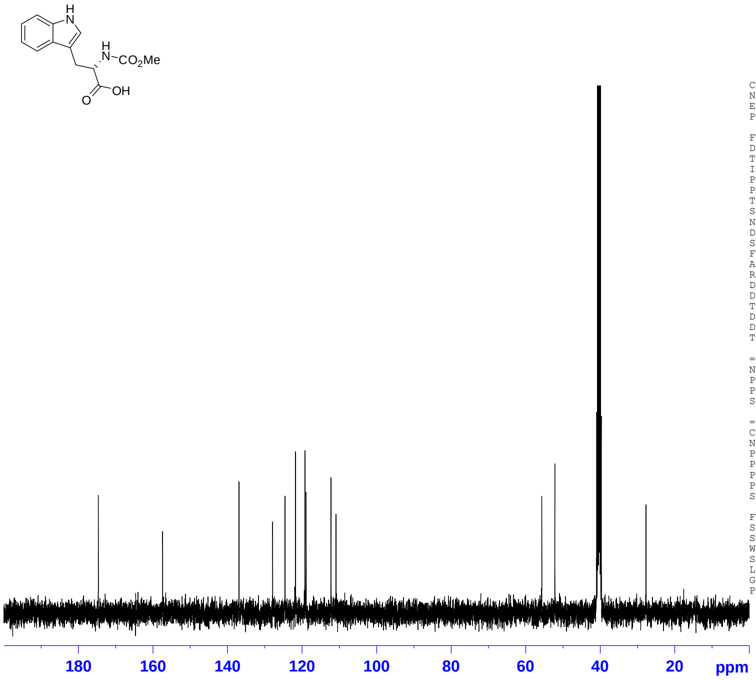
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091114
Time                1.07
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                 161.3
DW                60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz

F2 - Processing parameters
SI                 32768
SF           400.2000000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME      RS-05-067 DMSO 400 MHz
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
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Time                1.18
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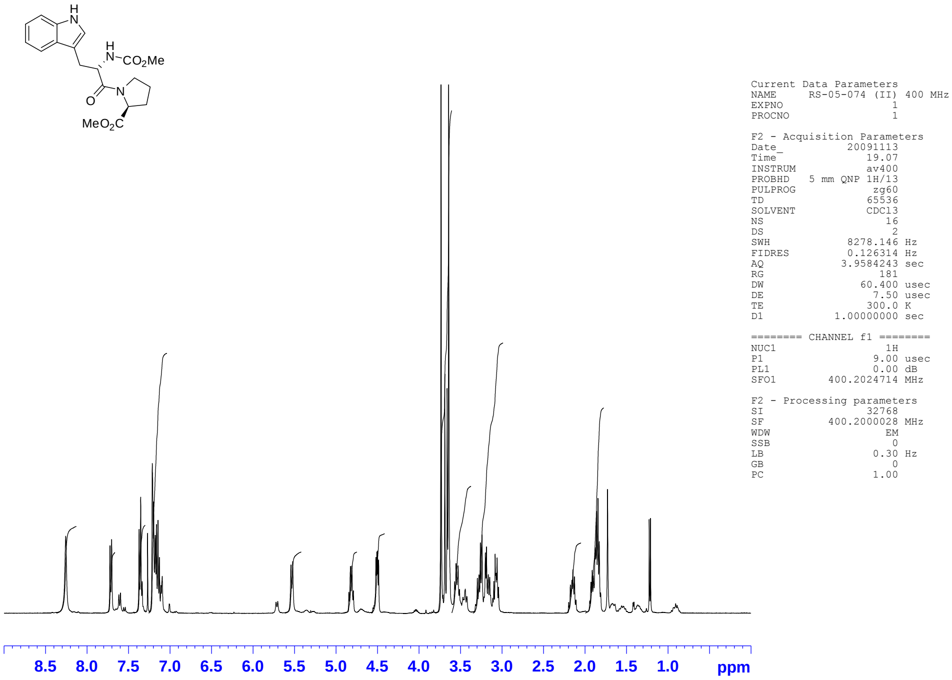
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 32768
SOLVENT             DMSO
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                 32768
DW                19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz

F2 - Processing parameters
SI                 32768
SF           100.6303300 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(*S*)-Methyl 1-((*S*)-3-(1H-indol-3-yl)-2-(methoxycarbonylamino)propanoyl)pyrrolidine-2-carboxylate, 81



```
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PROCNO                   1

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Time                 19.07
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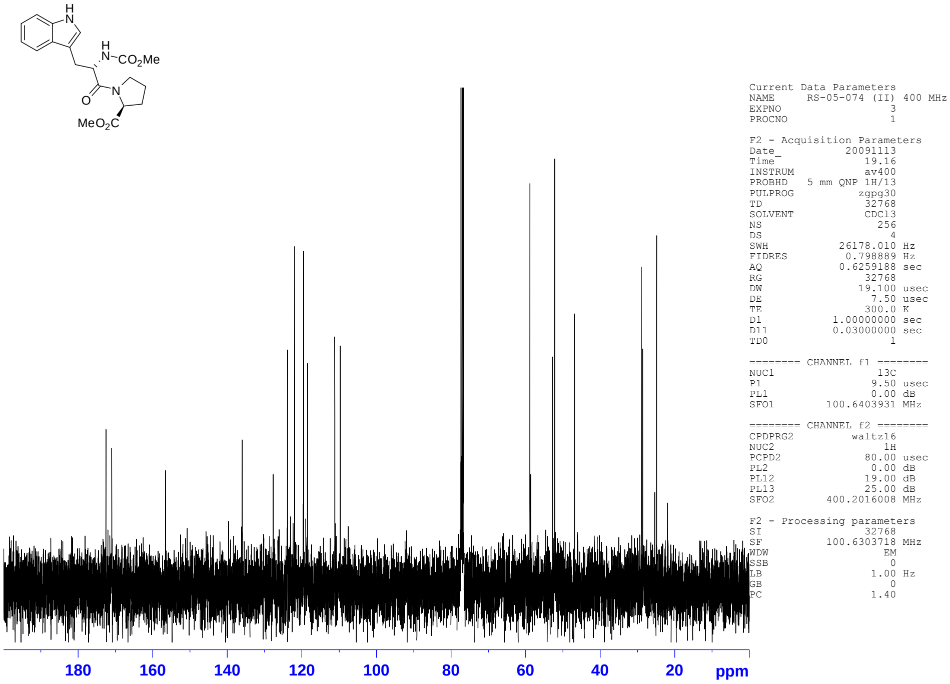
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     181
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-05-074 (II) 400 MHz
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PROCNO                   1

F2 - Acquisition Parameters
Date_             20091113
Time                 19.16
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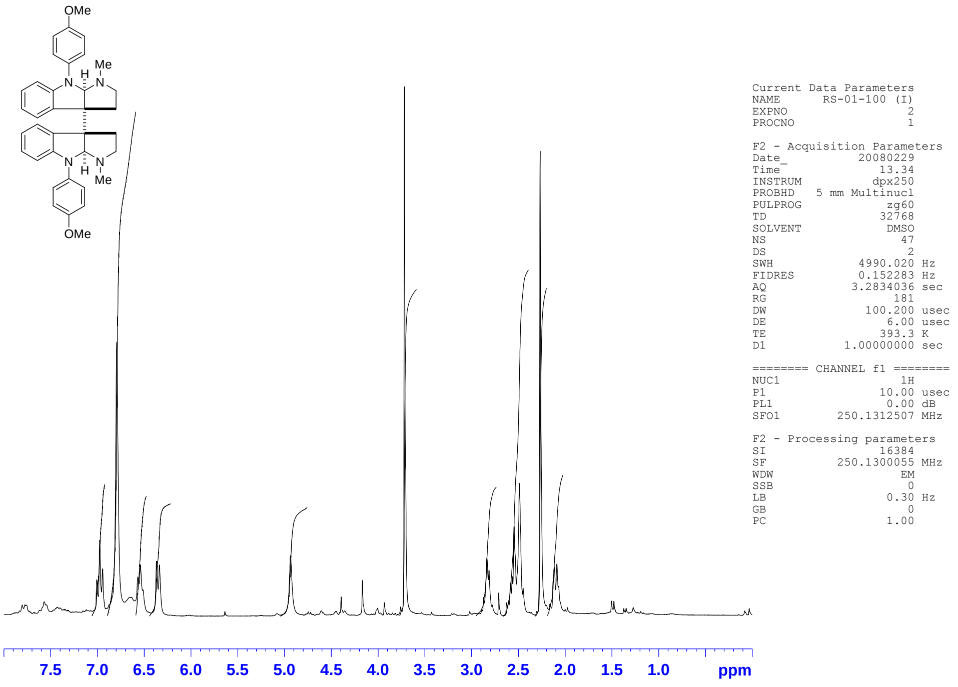
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz

F2 - Processing parameters
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

(3a*S*,3'a*R*,8a*R*,8'a*S*)-8,8'-*bis*(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *bis-product*, 85

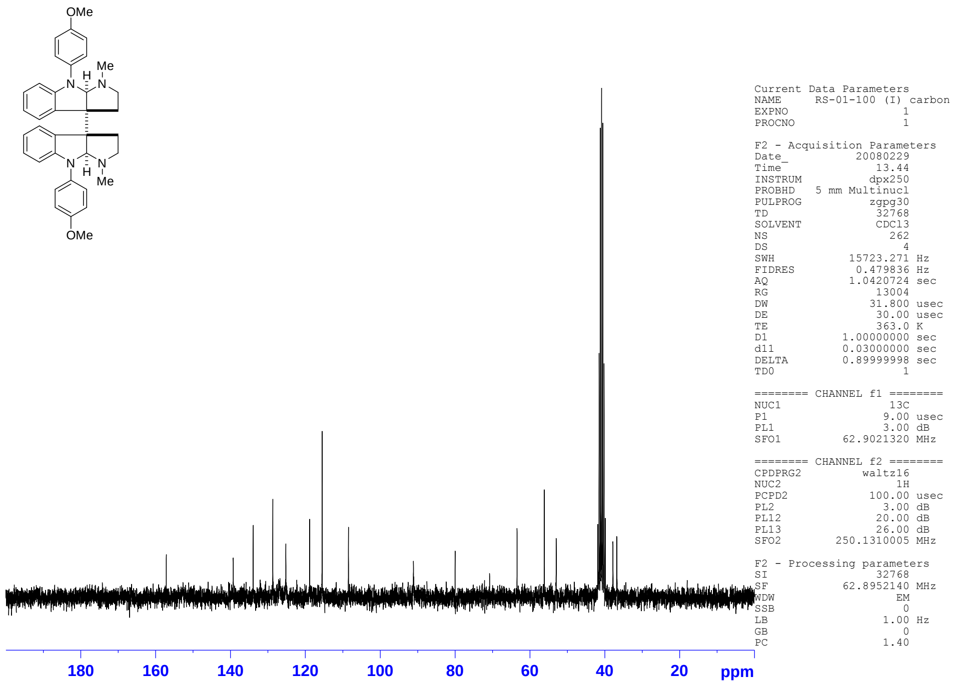


```
Current Data Parameters
NAME      RS-01-100 (I)
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20080229
Time              13.34
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   47
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  181
DW              100.200 usec
DE                 6.00 usec
TE                393.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                0.00 dB
SFO1        250.1312507 MHz

F2 - Processing parameters
SI                16384
SF          250.1300055 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME     RS-01-100 (I) carbon
EXPNO                 1
PROCNO                1

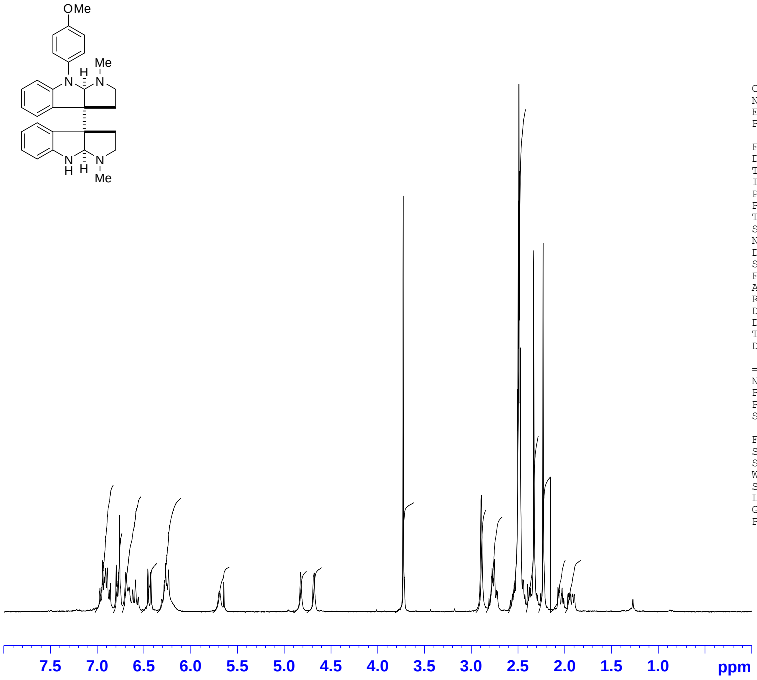
F2 - Acquisition Parameters
Date_          20080229
Time              13.44
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDC13
NS                  262
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG                13004
DW               31.800 usec
DE                30.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

8-(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *mono-product*, 84

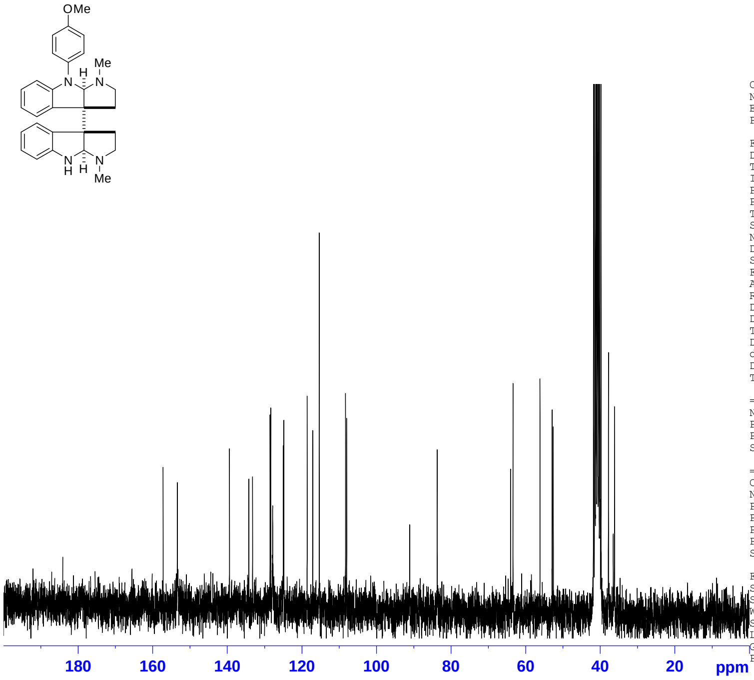


```
Current Data Parameters
NAME          RS-01-056
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20071213
Time              15.47
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   37
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                456.1
DW              100.200 usec
DE                 6.00 usec
TE                393.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                0.00 dB
SFO1        250.1312507 MHz

F2 - Processing parameters
SI                16384
SF          250.1299987 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME          RS-01-056
EXPNO                 7
PROCNO                1

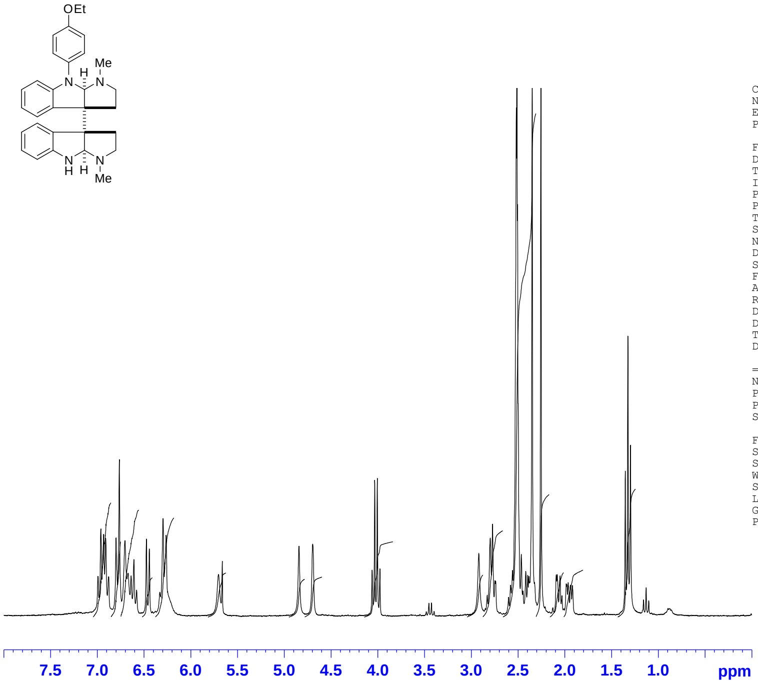
F2 - Acquisition Parameters
Date_          20071217
Time              11.47
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                 5251
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG              10321.3
DW               31.800 usec
DE                30.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

8-(4-Ethoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 4

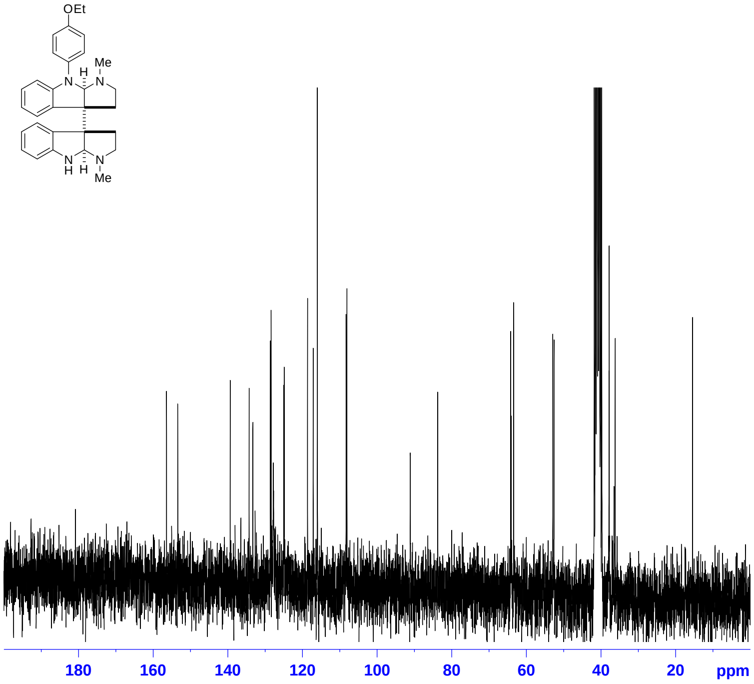


```
Current Data Parameters
NAME             RS-01-102
EXPNO                    3
PROCNO                   1

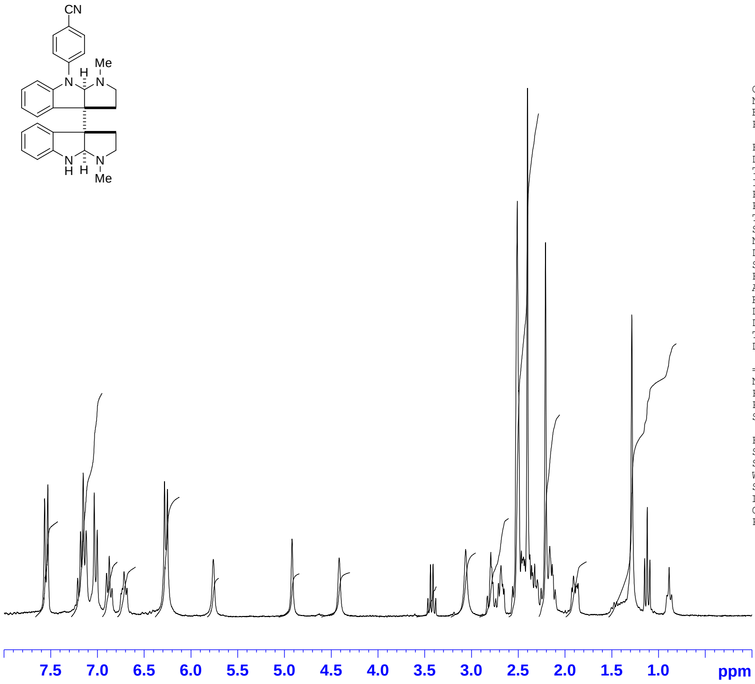
F2 - Acquisition Parameters
Date_             20080317
Time                 12.38
INSTRUM             dpx250
PROBHD   5 mm Multinucl
PULPROG               zg60
TD                   32768
SOLVENT               DMSO
NS                      28
DS                       2
SWH               4990.020 Hz
FIDRES            0.152283 Hz
AQ               3.2834036 sec
RG                     362
DW                 100.200 usec
DE                    6.00 usec
TE                   393.3 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.00 usec
PL1                   0.00 dB
SFO1           250.1312507 MHz

F2 - Processing parameters
SI                   16384
SF             250.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



4-(1,1'-Dimethyl-1,1',2,2',3,3a,3',3'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH,8'aH)-yl)benzonitrile, Table 12, Entry 6

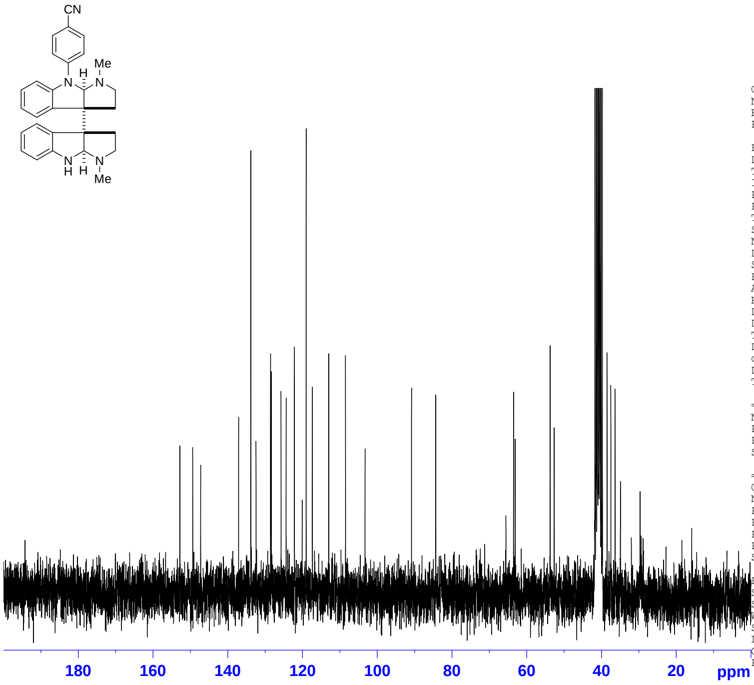


```
Current Data Parameters
NAME            RS-01-082
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20080207
Time                14.25
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG              zg60
TD                  32768
SOLVENT             CDCl3
NS                     60
DS                      2
SWH              4990.020 Hz
FIDRES           0.152283 Hz
AQ              3.2834036 sec
RG                  456.1
DW                100.200 usec
DE                   6.00 usec
TE                  363.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                  3.00 dB
SFO1          250.1312507 MHz

F2 - Processing parameters
SI                  16384
SF            250.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-01-082 carbon
EXPNO                   1
PROCNO                  1

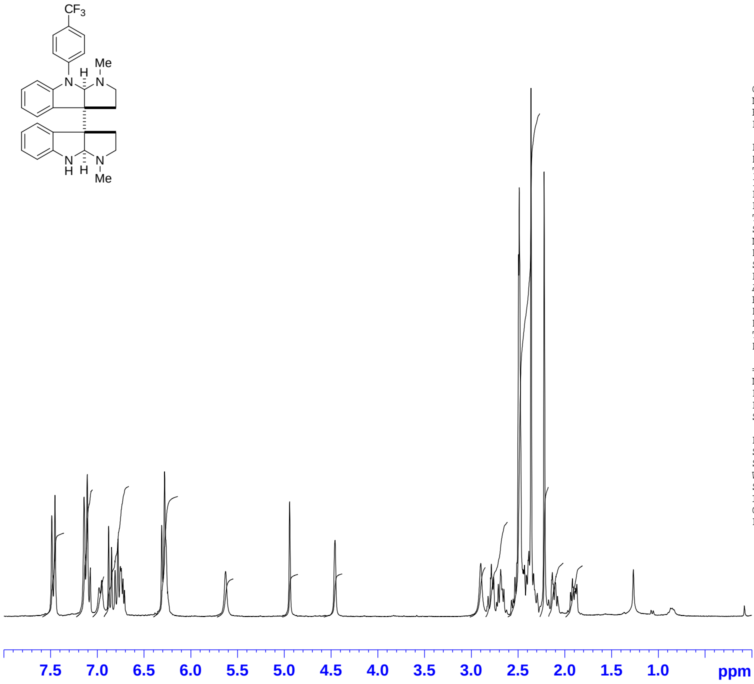
F2 - Acquisition Parameters
Date_            20080206
Time                17.00
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG            zgpg30
TD                  32768
SOLVENT              DMSO
NS                   1839
DS                      4
SWH             15723.271 Hz
FIDRES           0.479836 Hz
AQ              1.0420724 sec
RG                  13004
DW                 31.800 usec
DE                  30.00 usec
TE                  363.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.00 usec
PL1                  3.00 dB
SFO1           62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  3.00 dB
PL12                20.00 dB
PL13                26.00 dB
SFO2          250.1310005 MHz

F2 - Processing parameters
SI                  32768
SF             62.8952140 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

1,1'-Dimethyl-8-(4-(trifluoromethyl)phenyl)-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 7

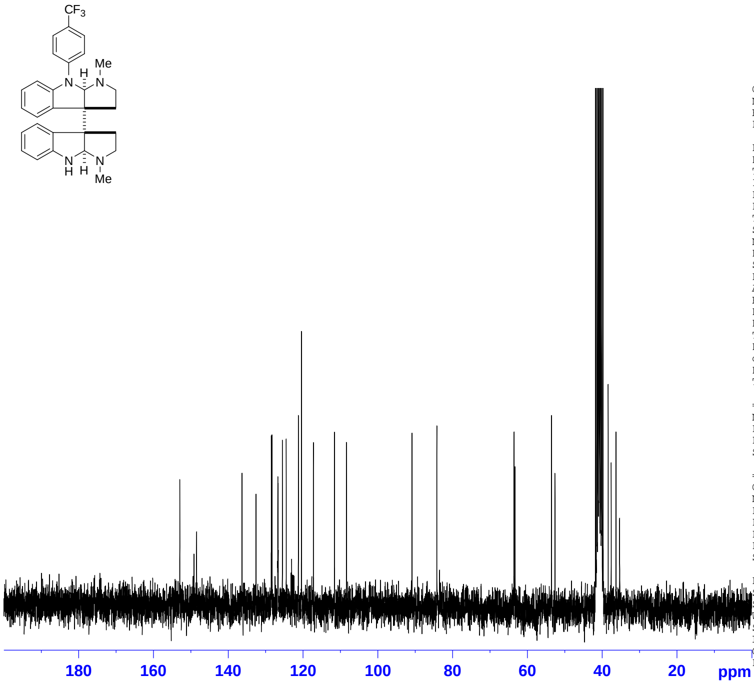


```
Current Data Parameters
NAME          RS-01-102B
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080805
Time               13.34
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    35
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 322.5
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME          RS-01-102B
EXPNO                  4
PROCNO                 1

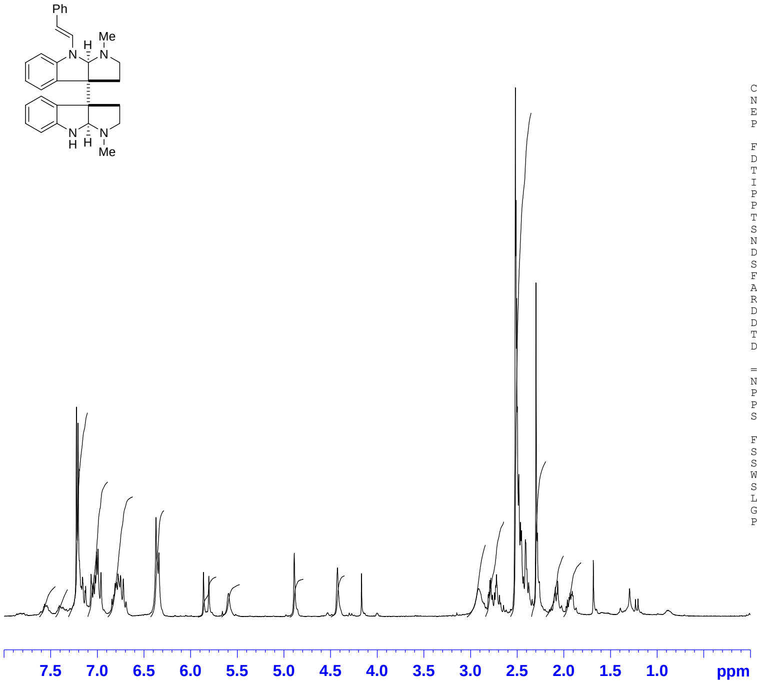
F2 - Acquisition Parameters
Date_           20080806
Time               11.24
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                 32768
SOLVENT             DMSO
NS                  3356
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG               14596.5
DW                31.800 usec
DE                 30.00 usec
TE                 363.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1,1'-Dimethyl-8-(1-phenylvinyl)-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, Table 12, Entry 8

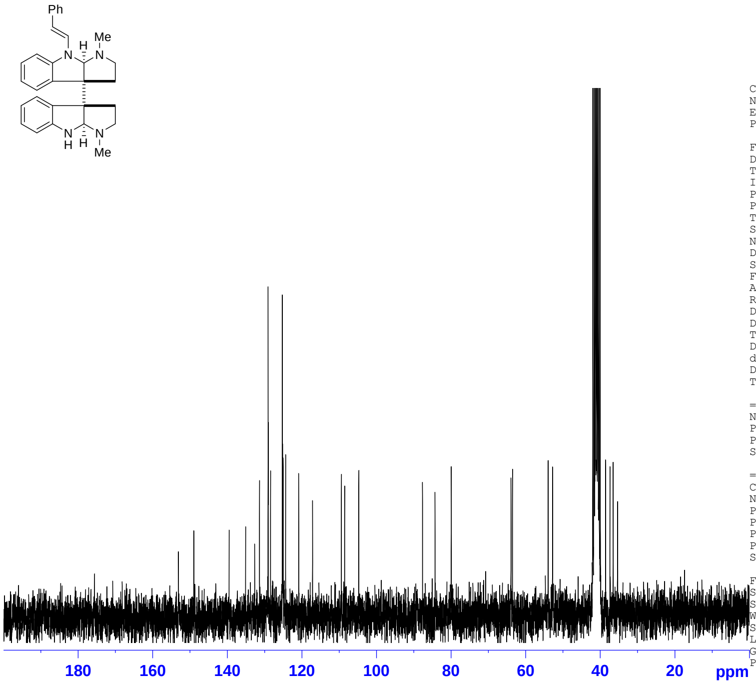


```
Current Data Parameters
NAME     RS-03-050 B (II)
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20090212
Time               13.36
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    26
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   362
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME     RS-03-050 B (II)
EXPNO                   4
PROCNO                  1

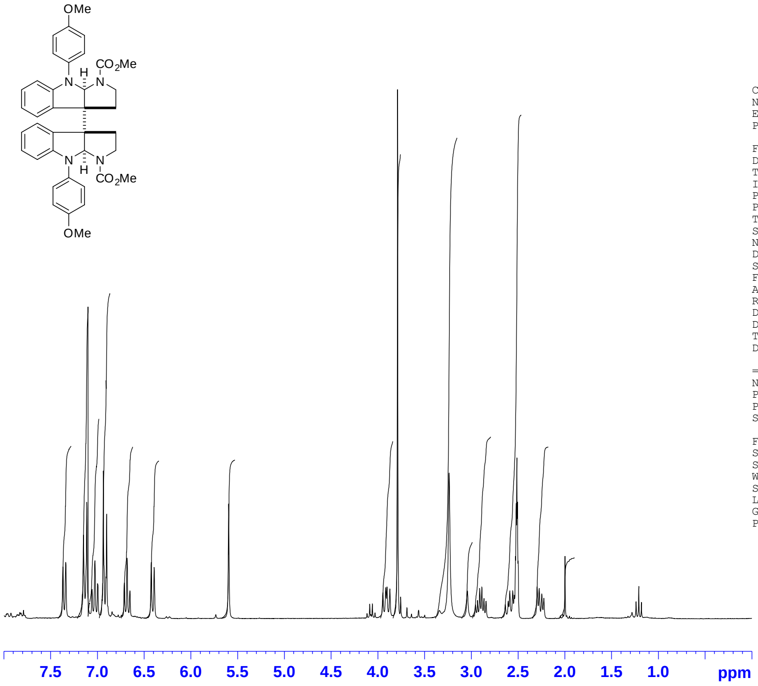
F2 - Acquisition Parameters
Date_           20090224
Time               10.34
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG           zgpg30
TD                 32768
SOLVENT             DMSO
NS                  2470
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG               10321.3
DW                31.800 usec
DE                 30.00 usec
TE                 392.1 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(3a*S*,3'a*R*,8a*S*,8'a*R*)-Dimethyl 8,8'-bis(4-methoxyphenyl)-3,3a,3',3'a,8,8a,8',8'a-octahydro-3a,3'a-bipyrrolo[2,3-b]indole-1,1'(2H,2'H)-dicarboxylate, 87

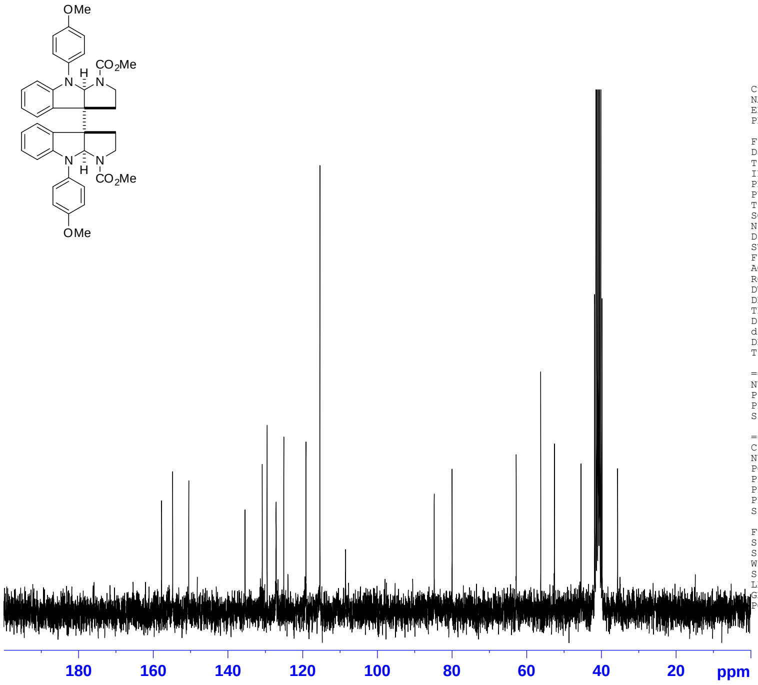


```
Current Data Parameters
NAME      RS-01-121 (iib)
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20080414
Time                10.49
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG              zg60
TD                  32768
SOLVENT              DMSO
NS                     47
DS                      2
SWH              4990.020 Hz
FIDRES           0.152283 Hz
AQ              3.2834036 sec
RG                  228.1
DW                100.200 usec
DE                   6.00 usec
TE                  363.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                  0.00 dB
SFO1          250.1312507 MHz

F2 - Processing parameters
SI                  16384
SF            250.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME      RS-01-121 (iib) carbon
EXPNO                   1
PROCNO                  1

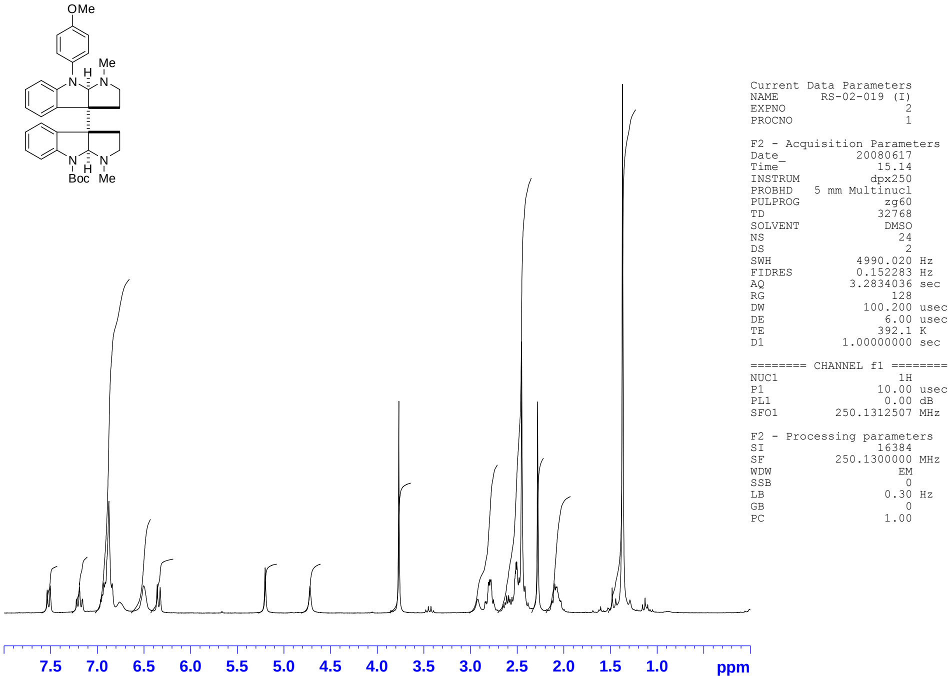
F2 - Acquisition Parameters
Date_            20080414
Time                10.55
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG           zgpg30
TD                 32768
SOLVENT            CDC13
NS                  1033
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG               14596.5
DW                31.800 usec
DE                 30.00 usec
TE                 363.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

tert-Butyl 8'-(4-methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate, 89

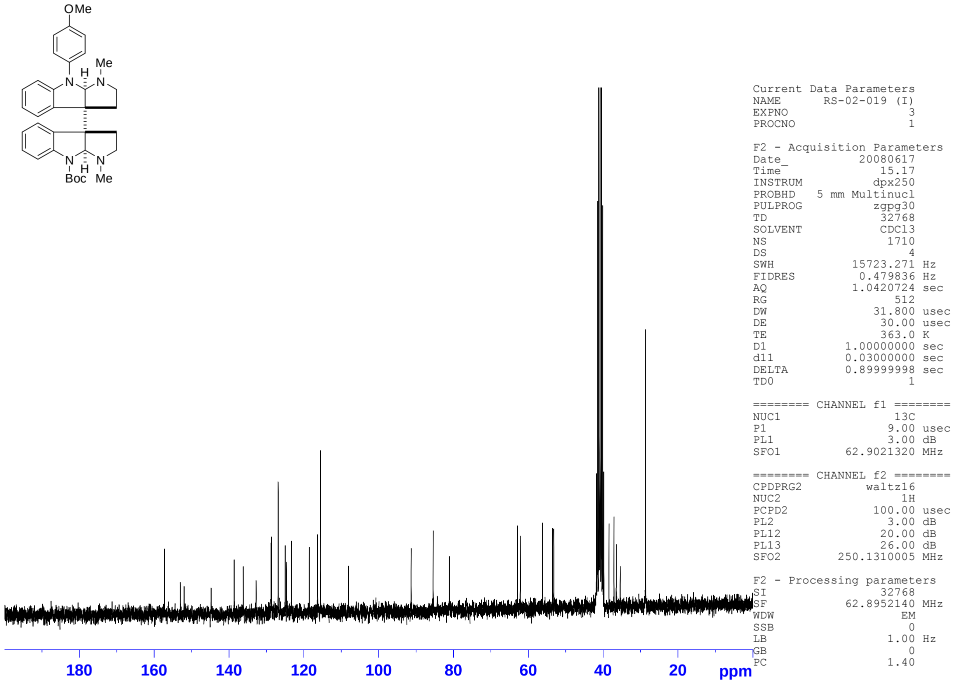


```
Current Data Parameters
NAME       RS-02-019 (I)
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080617
Time               15.14
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    24
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   128
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME       RS-02-019 (I)
EXPNO                  3
PROCNO                 1

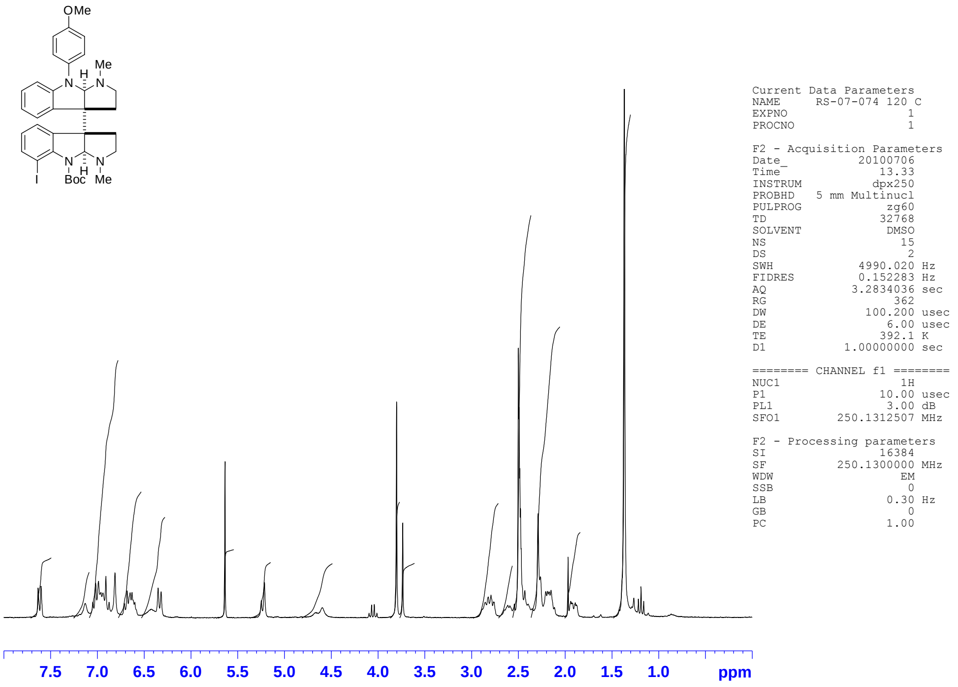
F2 - Acquisition Parameters
Date_           20080617
Time               15.17
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                  1710
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG                   512
DW                31.800 usec
DE                 30.00 usec
TE                 363.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

***tert*-Butyl 7-iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate, 90**

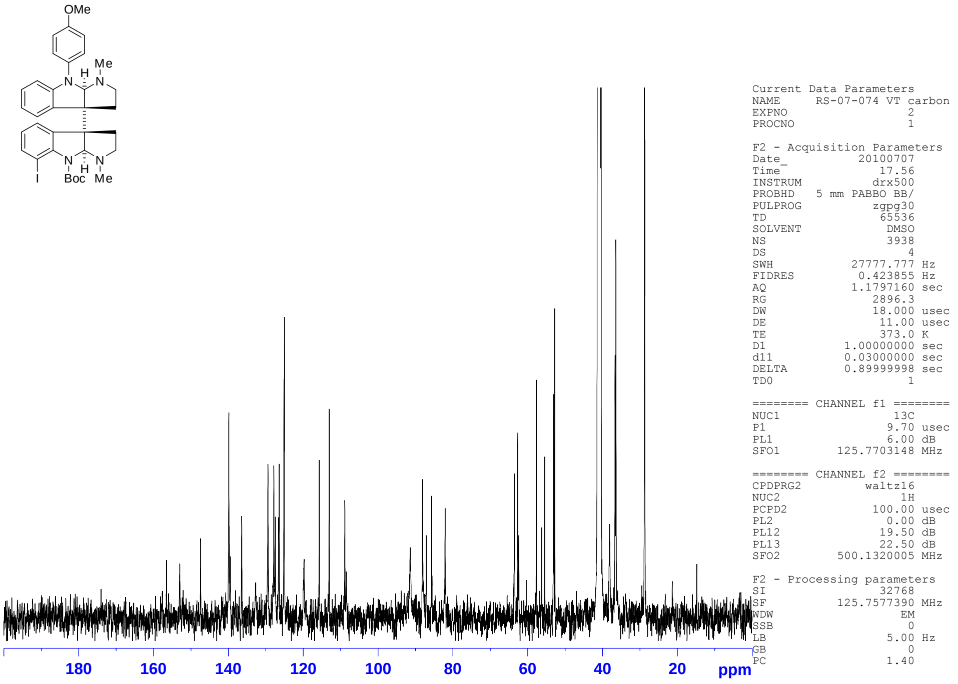


```
Current Data Parameters
NAME     RS-07-074 120 C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100706
Time               13.33
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    15
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   362
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME     RS-07-074 VT carbon
EXPNO                  2
PROCNO                 1

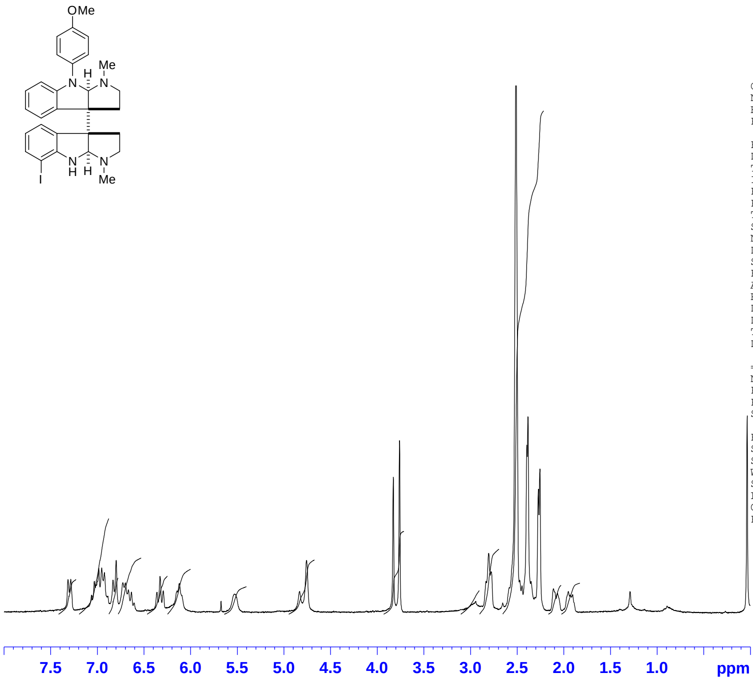
F2 - Acquisition Parameters
Date_           20100707
Time               17.56
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  3938
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG                2896.3
DW                18.000 usec
DE                 11.00 usec
TE                 373.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.70 usec
PL1                 6.00 dB
SFO1         125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  5.00 Hz
GB                     0
PC                  1.40
```

7-Iodo-8'-(4-methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 91

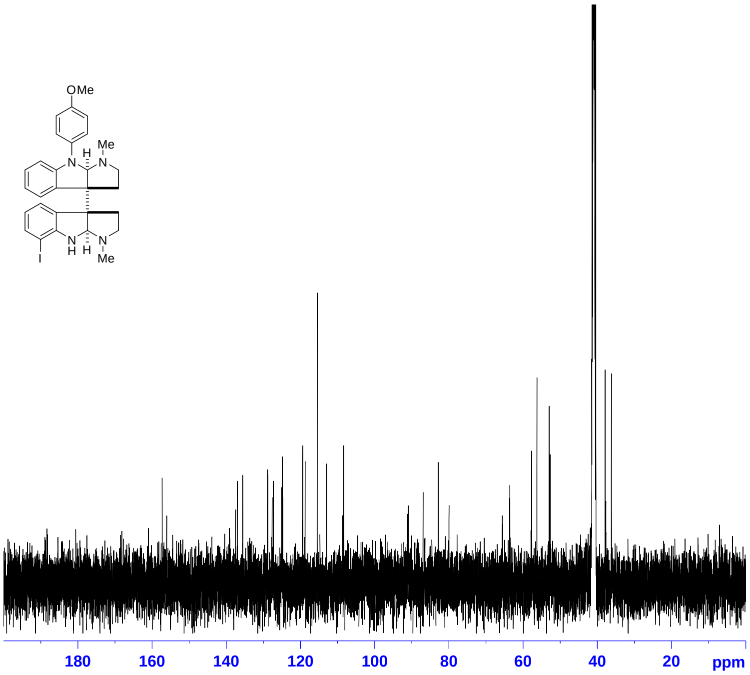


```
Current Data Parameters
NAME       RS-05-056 (I)
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091102
Time               15.50
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    58
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 812.7
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME      RS-05-056  carbon
EXPNO                  2
PROCNO                 1

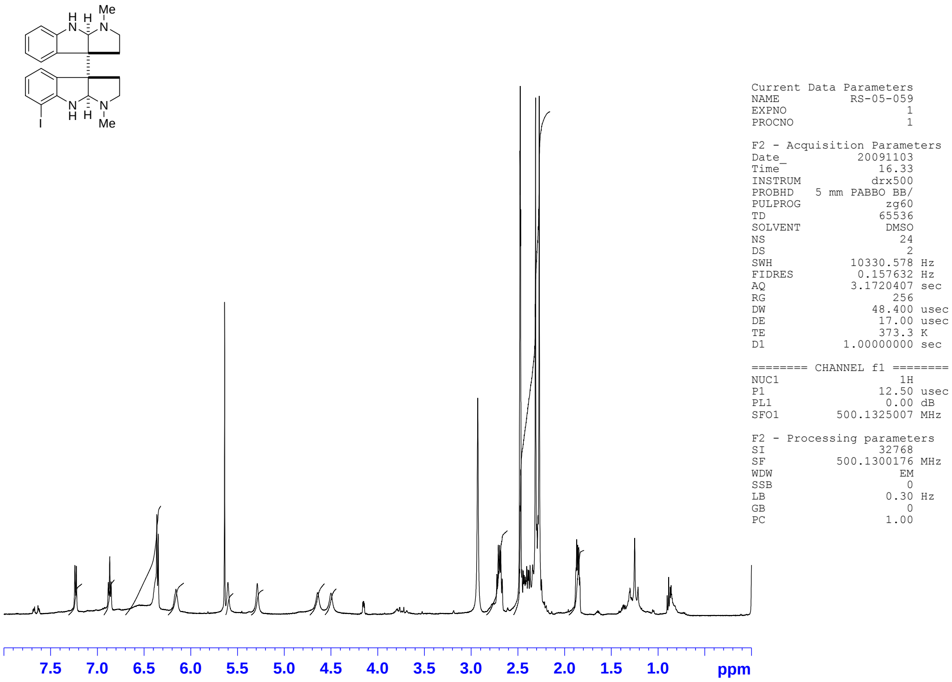
F2 - Acquisition Parameters
Date_           20091126
Time               16.20
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                  3702
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG               11585.2
DW                18.000 usec
DE                 11.00 usec
TE                 373.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.70 usec
PL1                 6.00 dB
SFO1         125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.00
```

7-Iodo-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 35[i]

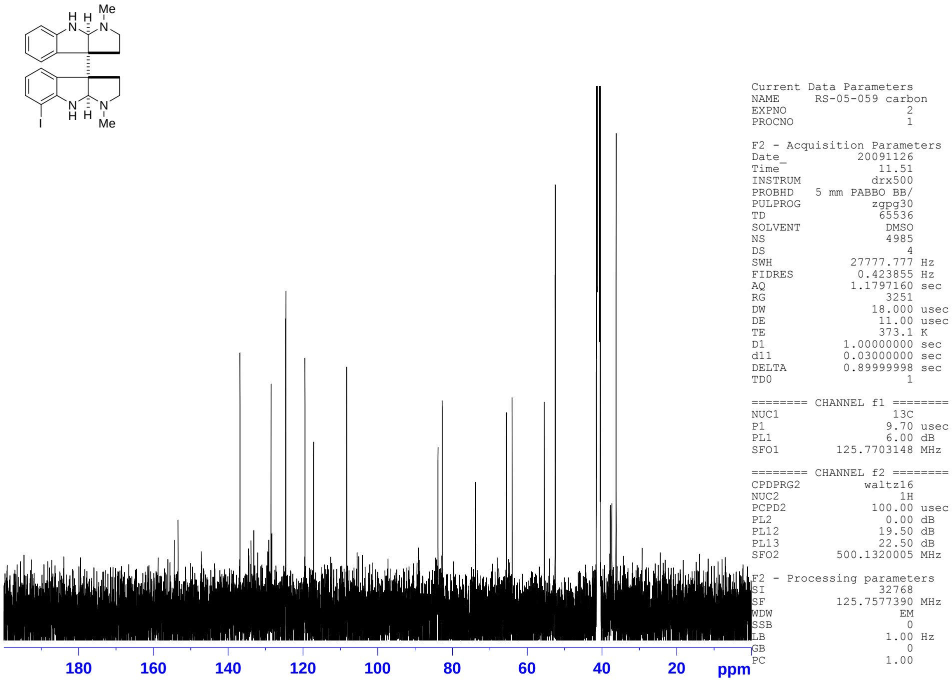


```
Current Data Parameters
NAME              RS-05-059
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20091103
Time                  16.33
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       24
DS                        2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                3.1720407 sec
RG                      256
DW                   48.400 usec
DE                    17.00 usec
TE                    373.3 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    12.50 usec
PL1                    0.00 dB
SFO1            500.1325007 MHz

F2 - Processing parameters
SI                    32768
SF              500.1300176 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



```
Current Data Parameters
NAME      RS-05-059 carbon
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20091126
Time                  11.51
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     4985
DS                        4
SWH               27777.777 Hz
FIDRES             0.423855 Hz
AQ                1.1797160 sec
RG                     3251
DW                   18.000 usec
DE                    11.00 usec
TE                    373.1 K
D1               1.00000000 sec
d11              0.03000000 sec
DELTA            0.89999998 sec
TD0                       1

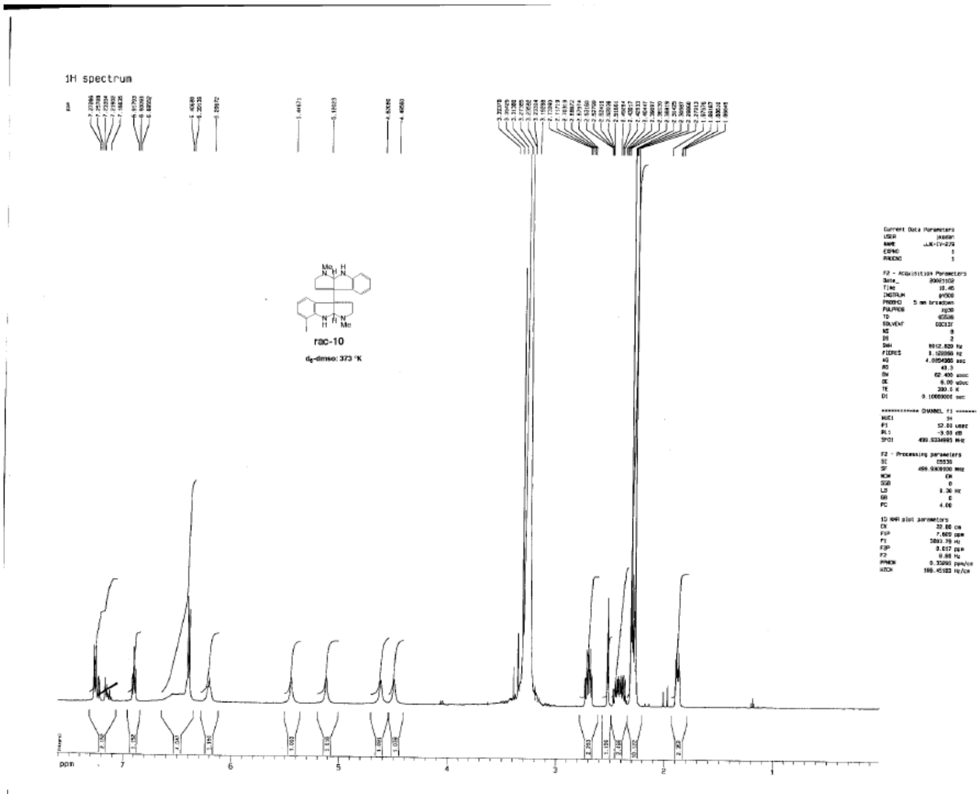
======== CHANNEL f1 ========
NUC1                    13C
P1                     9.70 usec
PL1                    6.00 dB
SFO1            125.7703148 MHz

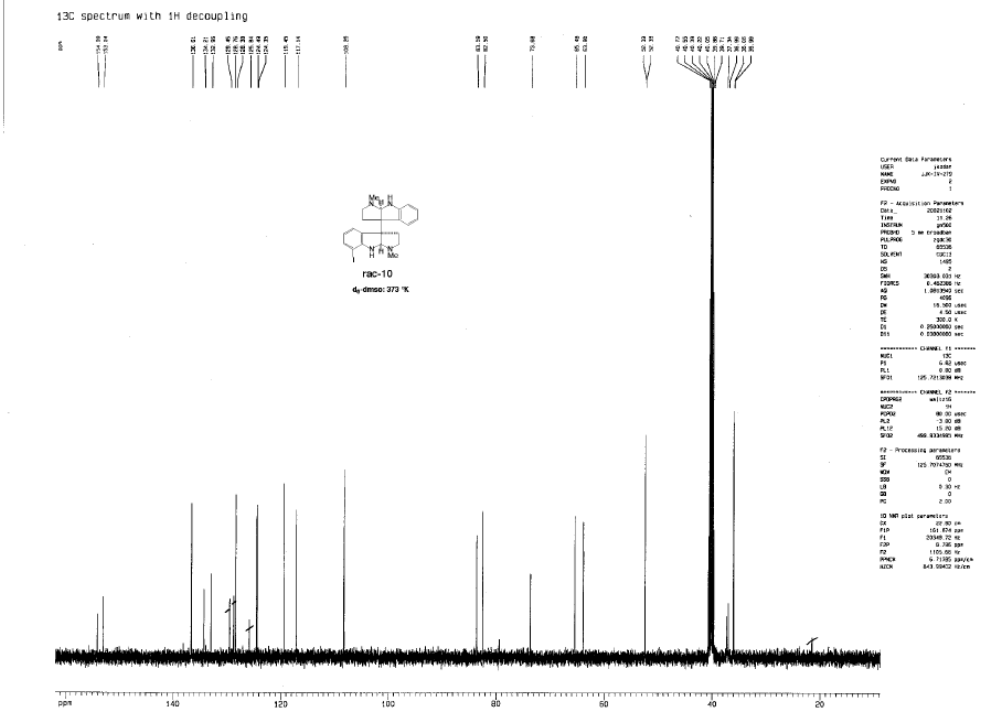
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                    0.00 dB
PL12                  19.50 dB
PL13                  22.50 dB
SFO2            500.1320005 MHz

F2 - Processing parameters
SI                    32768
SF              125.7577390 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.00
```

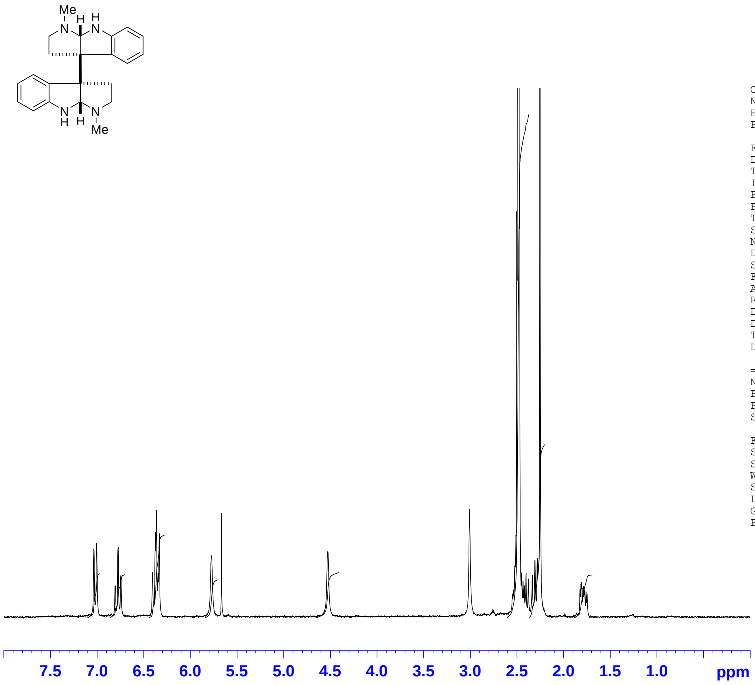
---

[i] *Angew. Chem. Int. Ed.*, **2003**, *42*, 2528


1H spectrum
rac-10
d6-dmso: 373 °K
ppm
7
6
5
4
3
2
1


13C spectrum with 1H decoupling
rac-10
d6-dmso: 373 °K
ppm
140
120
100
80
60
40
20

(±)-(3a*S*,3'a*S*,8a*S*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 13

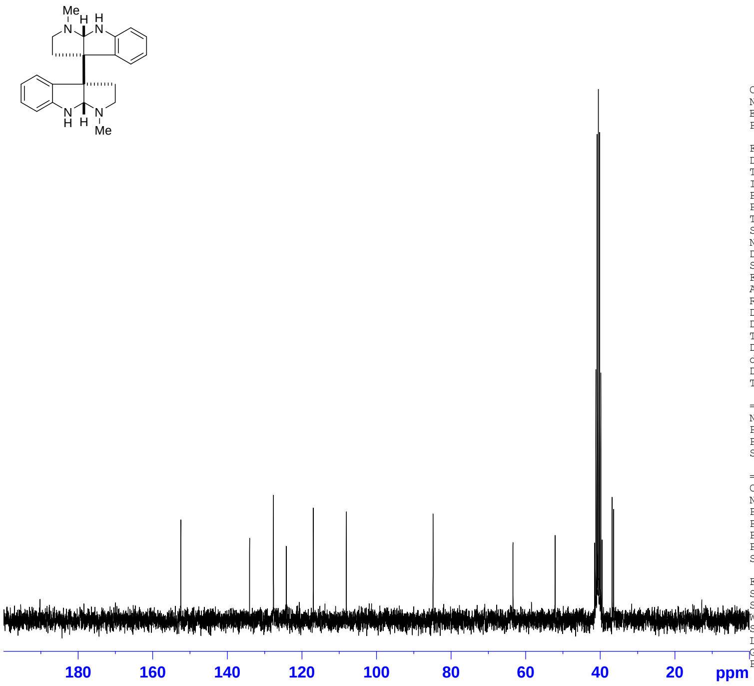


```
Current Data Parameters
NAME        RS-08-035 II
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100825
Time               15.37
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    25
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 724.1
DW               100.200 usec
DE                  6.00 usec
TE                 363.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME         RS-08-035 I
EXPNO                  2
PROCNO                 1

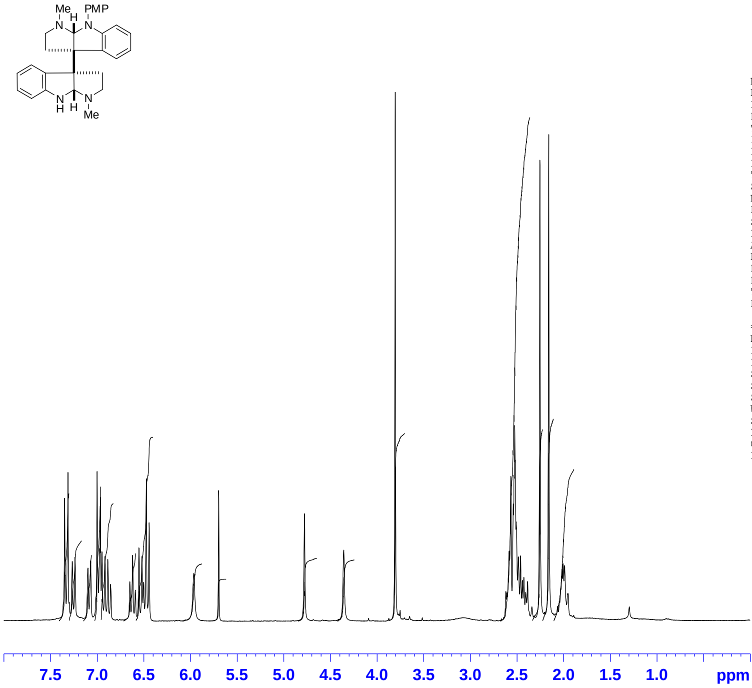
F2 - Acquisition Parameters
Date_           20100825
Time               15.47
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   185
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG               14596.5
DW                31.800 usec
DE                 30.00 usec
TE                 363.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz

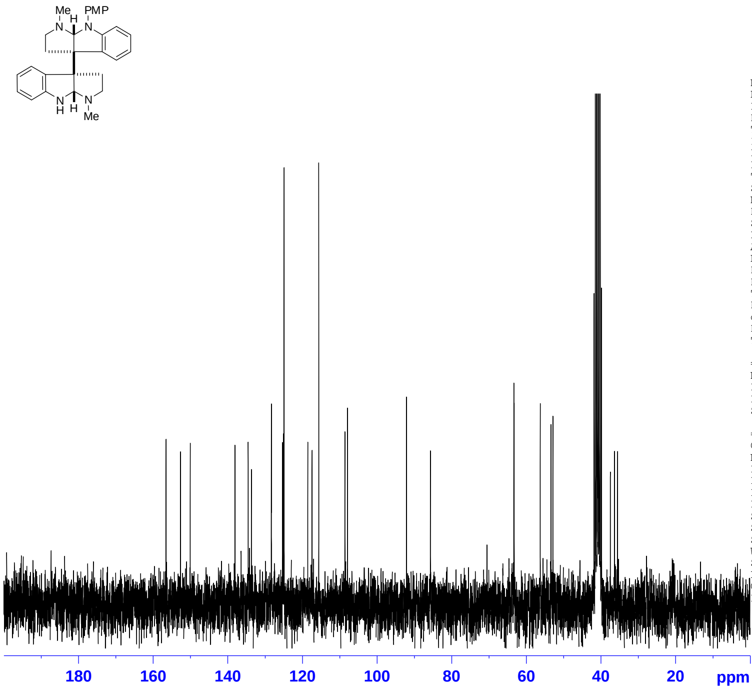
F2 - Processing parameters
SI                 32768
SF            62.8952319 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

8-(4-Methoxyphenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, *N-PMP-C₂-chimonanathine*, 92



```
NAME            RS-10-030
EXPNO                   1
PROCNO                  1
Date_            20110326
Time                15.26
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG              zg60
TD                  32768
SOLVENT              DMSO
NS                     16
DS                      2
SWH              4990.020 Hz
FIDRES           0.152283 Hz
AQ              3.2834036 sec
RG                  322.5
DW                100.200 usec
DE                   6.00 usec
TE                  363.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                  0.00 dB
SFO1          250.1312507 MHz
SI                  16384
SF            250.1299972 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

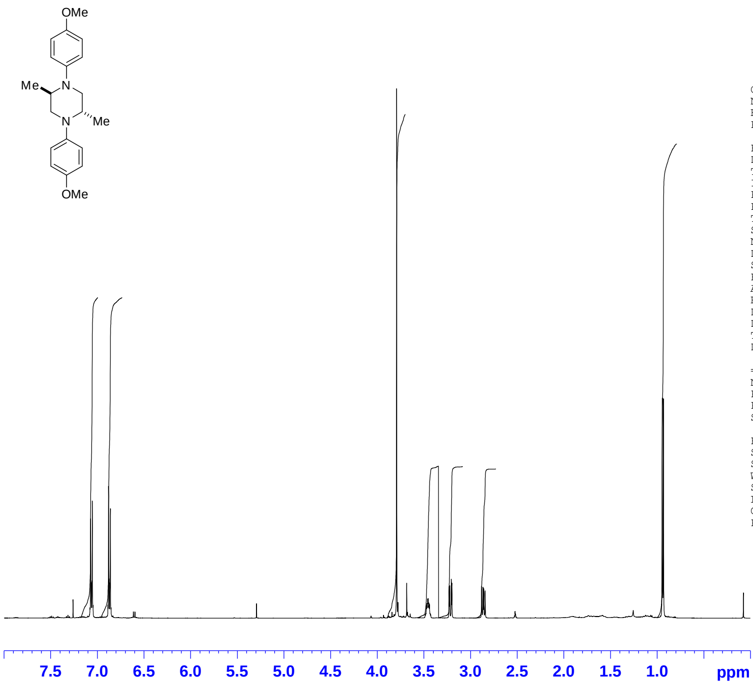


```
NAME            RS-10-030
EXPNO                   2
PROCNO                  1
Date_            20110326
Time                15.29
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    378
DS                      4
SWH             15723.271 Hz
FIDRES           0.479836 Hz
AQ              1.0420724 sec
RG                  13004
DW                 31.800 usec
DE                  30.00 usec
TE                  363.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.00 usec
PL1                  3.00 dB
SFO1           62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  3.00 dB
PL12                20.00 dB
PL13                26.00 dB
SFO2          250.1310005 MHz
SI                  32768
SF             62.8952140 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

(2*S*,5*R*)-1,4-*bis*(4-Methoxyphenyl)-2,5-dimethylpiperazine, 96

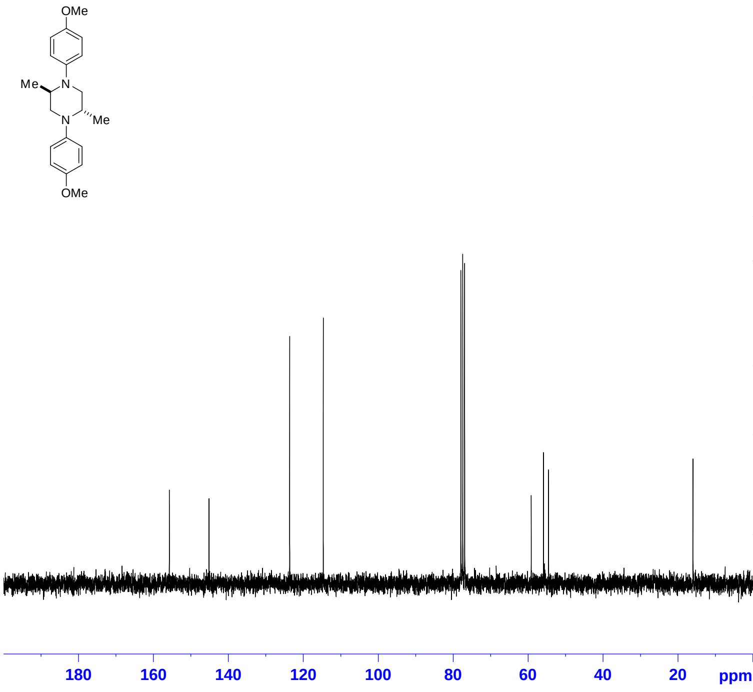


```
Current Data Parameters
NAME     RS-02-034 (A) (I)
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20080722
Time                 12.52
INSTRUM             drx500
PROBHD   5 mm PABBO BB/
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      13
DS                       2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1720407 sec
RG                    35.9
DW                  48.400 usec
DE                   17.00 usec
TE                   291.5 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   12.50 usec
PL1                   0.00 dB
SFO1           500.1325007 MHz

F2 - Processing parameters
SI                   32768
SF             500.1300294 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-02-034 (A) (I) 250MHz
EXPNO                    2
PROCNO                   1

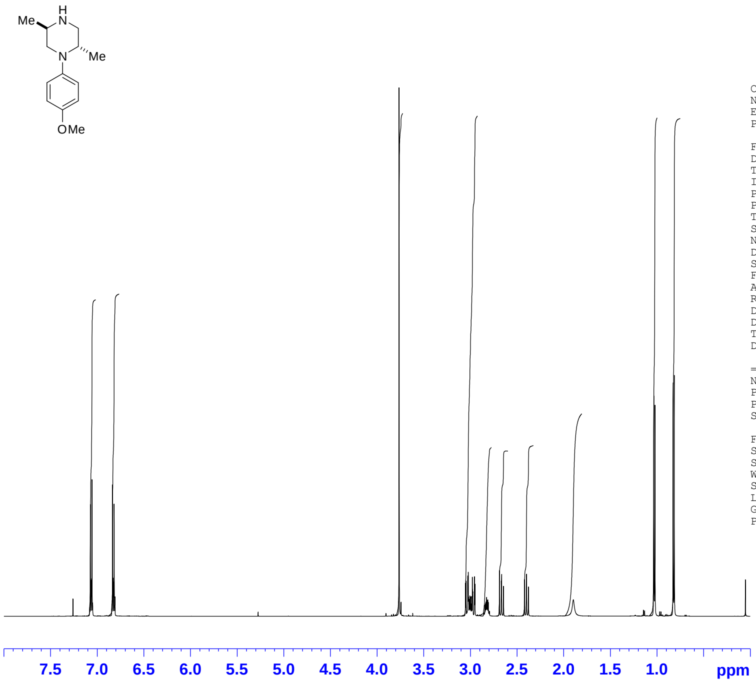
F2 - Acquisition Parameters
Date_             20080721
Time                 18.02
INSTRUM             dpx250
PROBHD   5 mm Multinucl
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     100
DS                       4
SWH              15723.271 Hz
FIDRES            0.479836 Hz
AQ               1.0420724 sec
RG                 14596.5
DW                  31.800 usec
DE                   30.00 usec
TE                   297.9 K
D1              1.00000000 sec
d11             0.03000000 sec
DELTA           0.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.00 usec
PL1                   3.00 dB
SFO1            62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   3.00 dB
PL12                 20.00 dB
PL13                 26.00 dB
SFO2           250.1310005 MHz

F2 - Processing parameters
SI                   32768
SF              62.8952140 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1-(4-Methoxyphenyl)-2,5-dimethylpiperazine, *mono*-product, 95

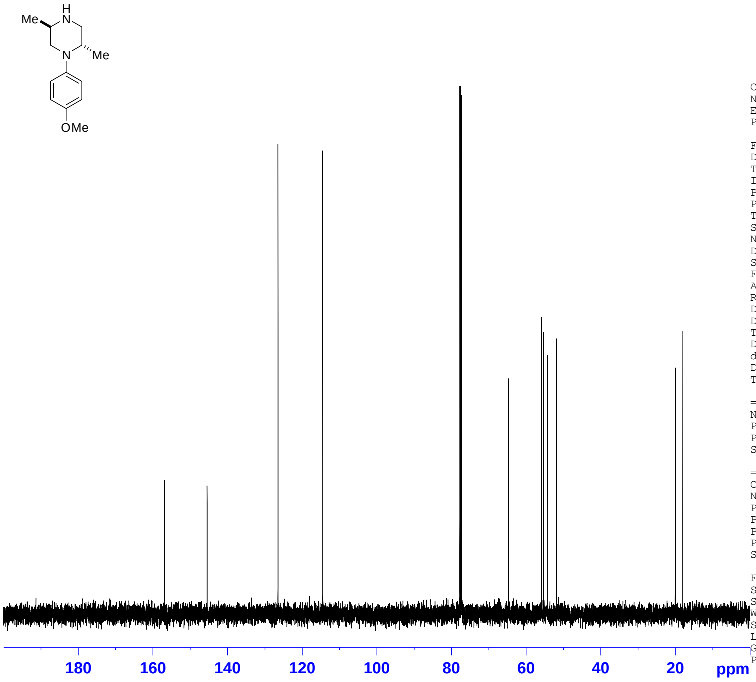


```
Current Data Parameters
NAME     RS-02-034 (A) (II)
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20080722
Time                12.58
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     34
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                   35.9
DW                 48.400 usec
DE                  17.00 usec
TE                  291.5 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  12.50 usec
PL1                  0.00 dB
SFO1          500.1325007 MHz

F2 - Processing parameters
SI                  32768
SF            500.1300293 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-02-034 (A) (II)
EXPNO                   3
PROCNO                  1

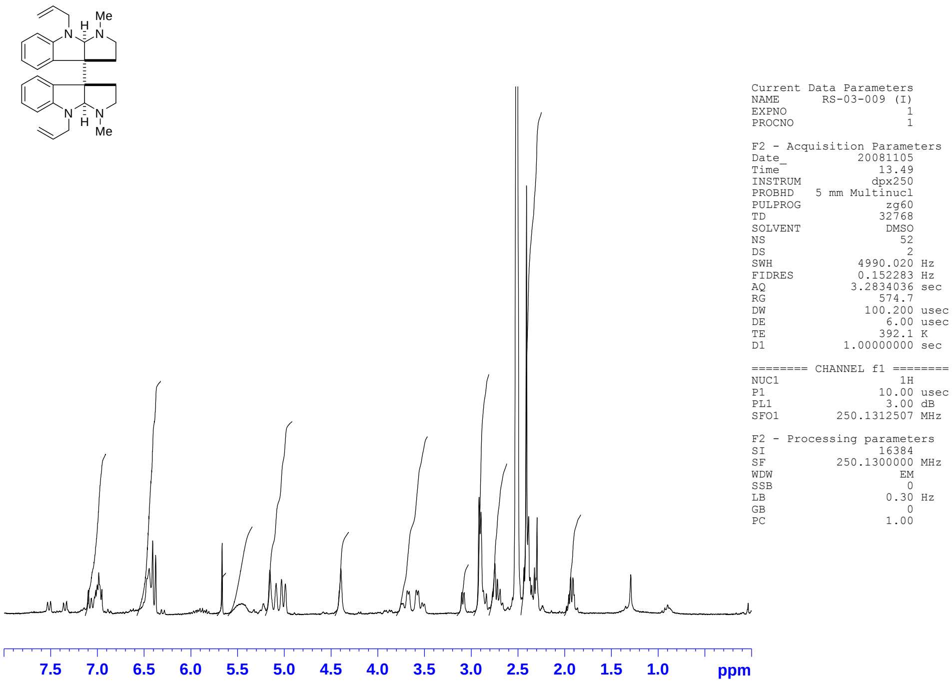
F2 - Acquisition Parameters
Date_            20080722
Time                13.20
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                     38
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                 3649.1
DW                 18.000 usec
DE                  11.00 usec
TE                  292.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   6.80 usec
PL1                  3.00 dB
SFO1          125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

(3a*R*,3'a*S*,8a*S*,8'a*R*)-8,8'-Diallyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, *bis-product*, 98

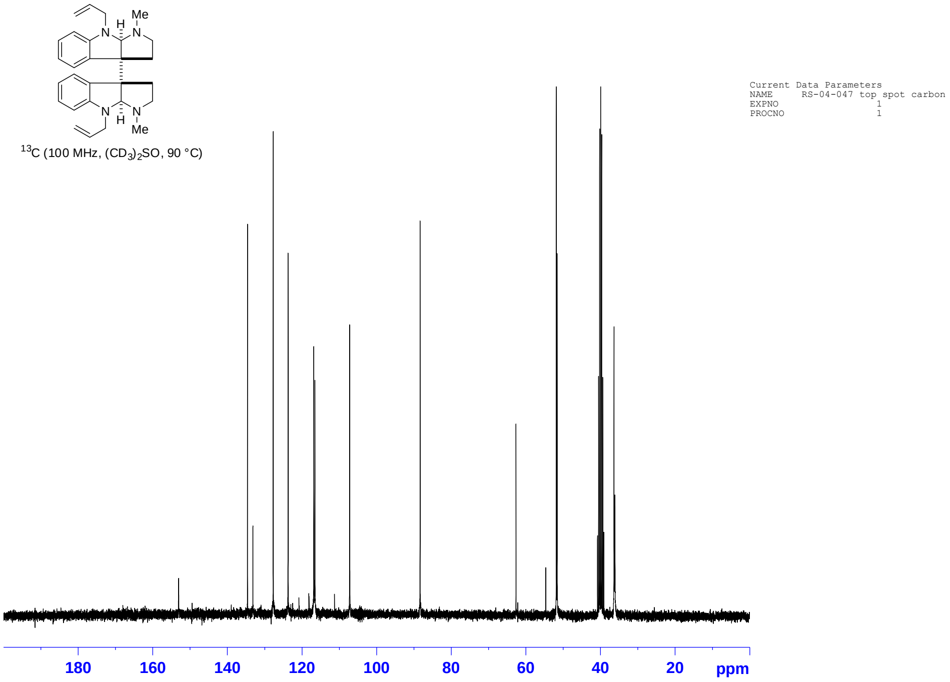


```
Current Data Parameters
NAME       RS-03-009 (I)
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081105
Time               13.49
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    52
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 574.7
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

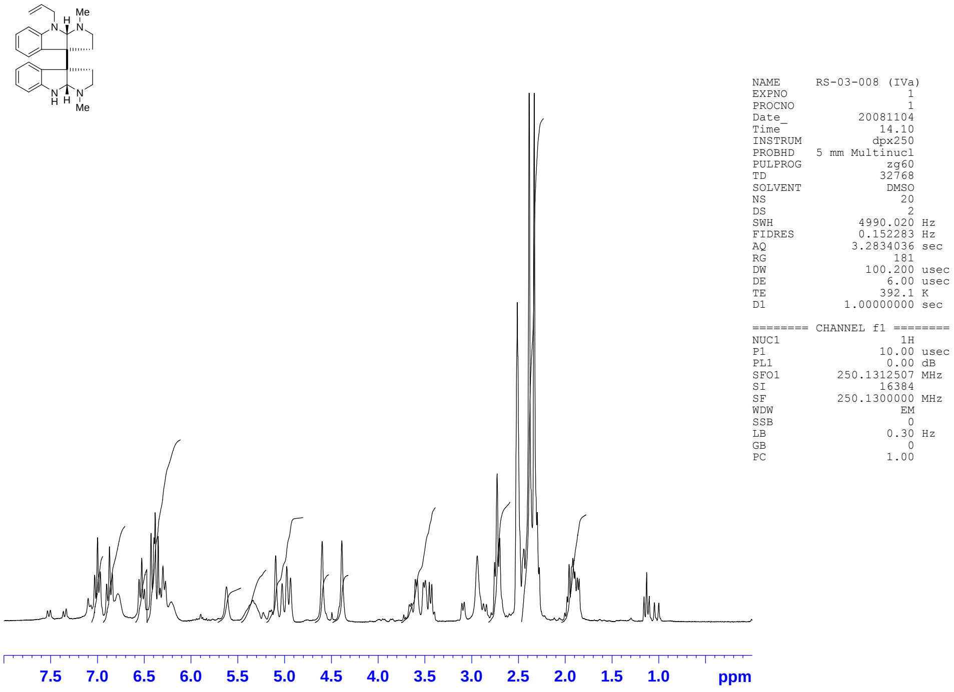
F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



^{13}C (100 MHz, $(CD_3)_2SO$, 90 °C)

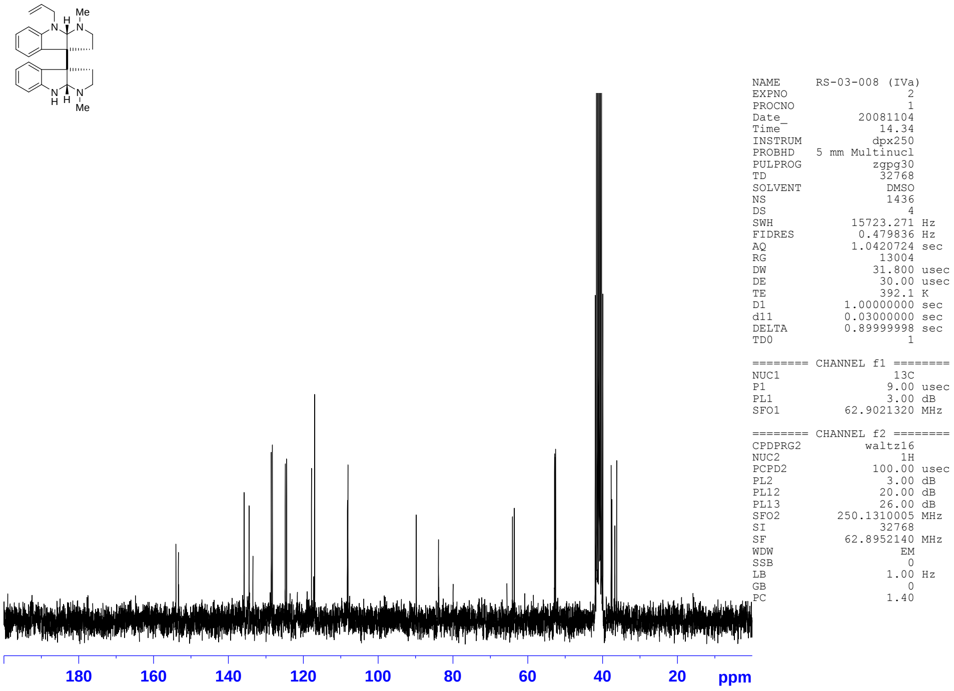
```
Current Data Parameters
NAME     RS-04-047 top spot carbon
EXPNO                  1
PROCNO                 1
```

(-)-(3a*R*,3'a*S*,8a*S*,8'a*S*)-8-Allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, (-)-*mono*-product, 97



```
NAME     RS-03-008 (IVa)
EXPNO                  1
PROCNO                 1
Date_           20081104
Time               14.10
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    20
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   181
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

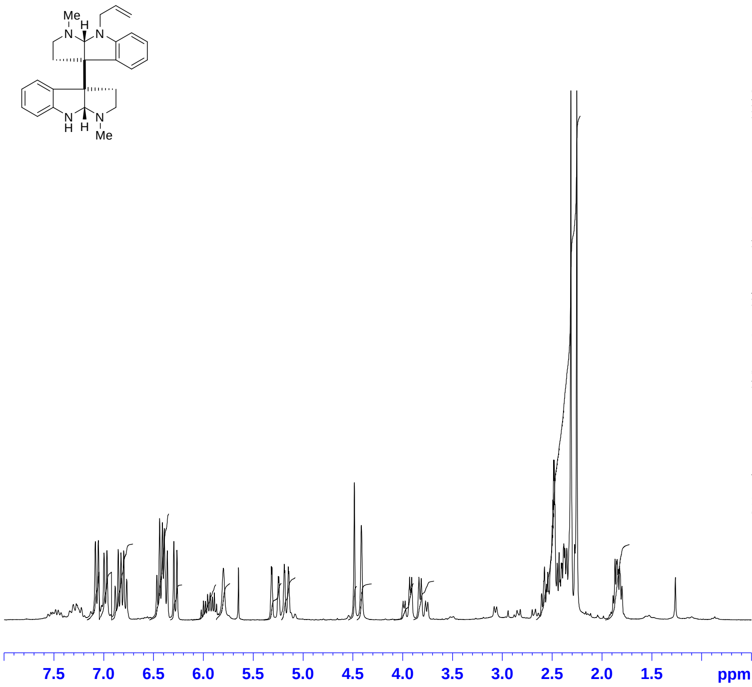


```
NAME     RS-03-008 (IVa)
EXPNO                  2
PROCNO                 1
Date_           20081104
Time               14.34
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                 32768
SOLVENT             DMSO
NS                  1436
DS                     4
SWH            15723.271 Hz
FIDRES          0.479836 Hz
AQ             1.0420724 sec
RG                 13004
DW                31.800 usec
DE                 30.00 usec
TE                 392.1 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
PL1                 3.00 dB
SFO1          62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 3.00 dB
PL12               20.00 dB
PL13               26.00 dB
SFO2         250.1310005 MHz
SI                 32768
SF            62.8952140 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(3a*S*,3'a*S*,8a*R*,8'a*S*)-8-Allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 99

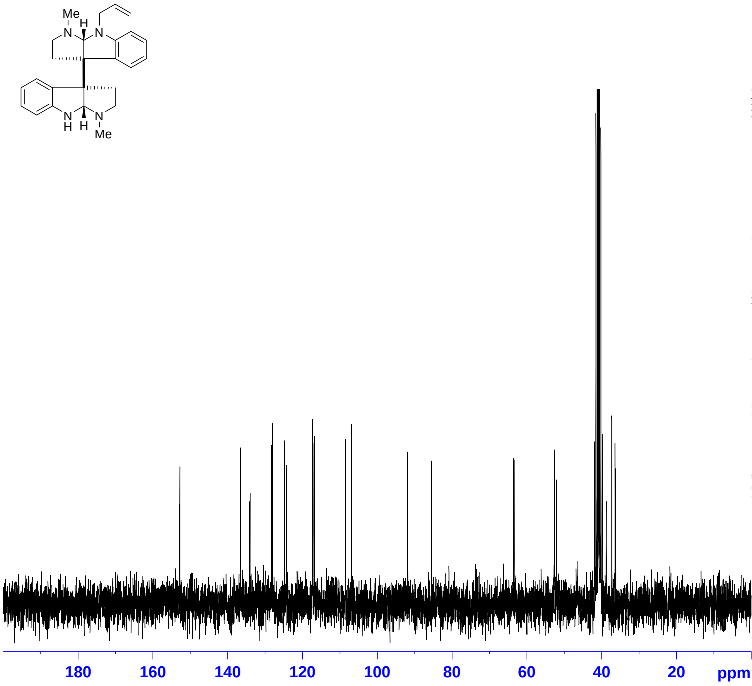


```
Current Data Parameters
NAME      RS-08-037 A Y
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20100831
Time              14.03
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   15
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                143.7
DW              100.200 usec
DE                 6.00 usec
TE                372.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz

F2 - Processing parameters
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME      RS-08-037 A Y
EXPNO                 2
PROCNO                1

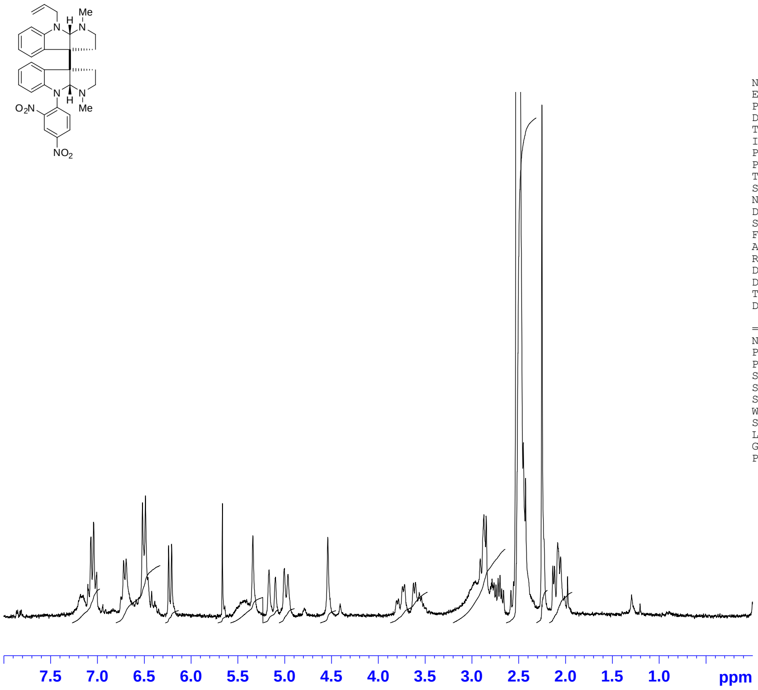
F2 - Acquisition Parameters
Date_          20100831
Time              14.06
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  136
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG              10321.3
DW               31.800 usec
DE                30.00 usec
TE                372.3 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz

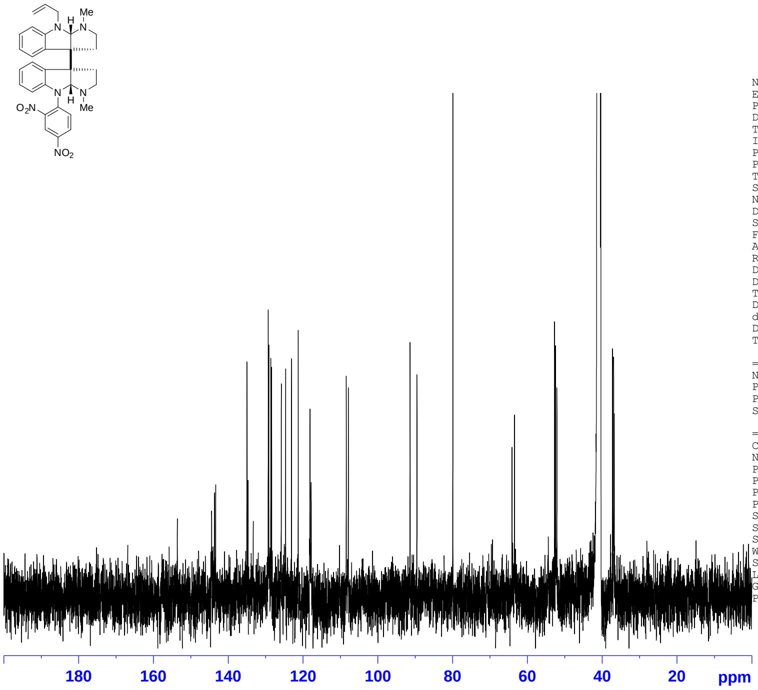
F2 - Processing parameters
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

(3a*R*,3'a*S*,8a*S*,8'a*R*)-8-Allyl-8'-(2,4-dinitrophenyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 101



```
NAME       RS-03-070 (I)
EXPNO                  1
PROCNO                 1
Date_           20090309
Time               14.17
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                   102
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 812.7
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

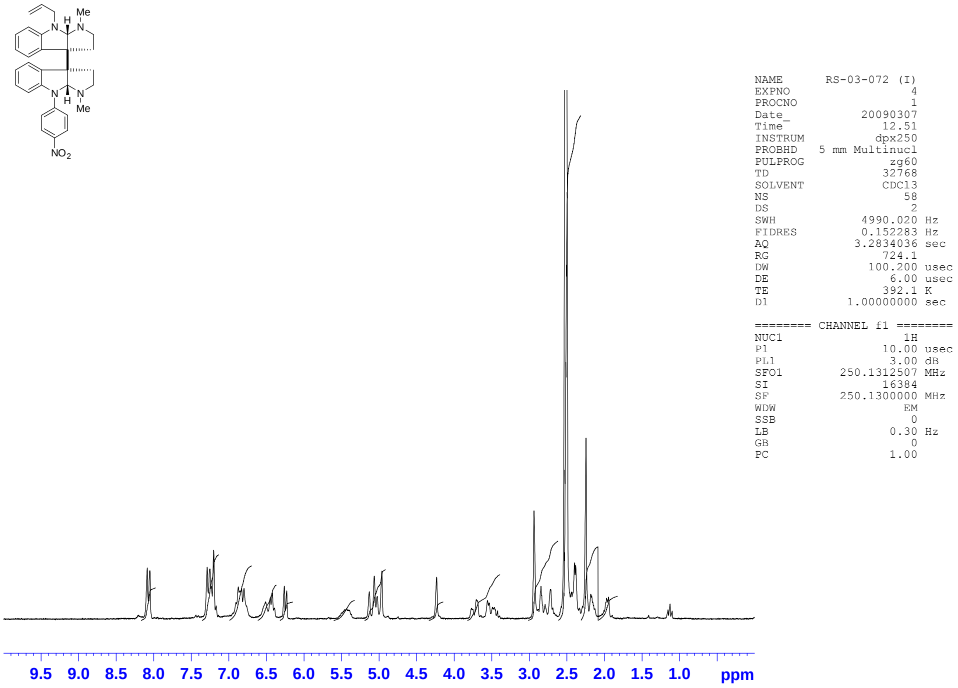


```
NAME     RS-03-070 DRX 500
EXPNO                  2
PROCNO                 1
Date_           20090909
Time               12.52
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                  7119
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG                5160.6
DW                18.000 usec
DE                 11.00 usec
TE                 373.3 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 14.00 usec
PL1                 0.00 dB
SFO1         125.7703148 MHz

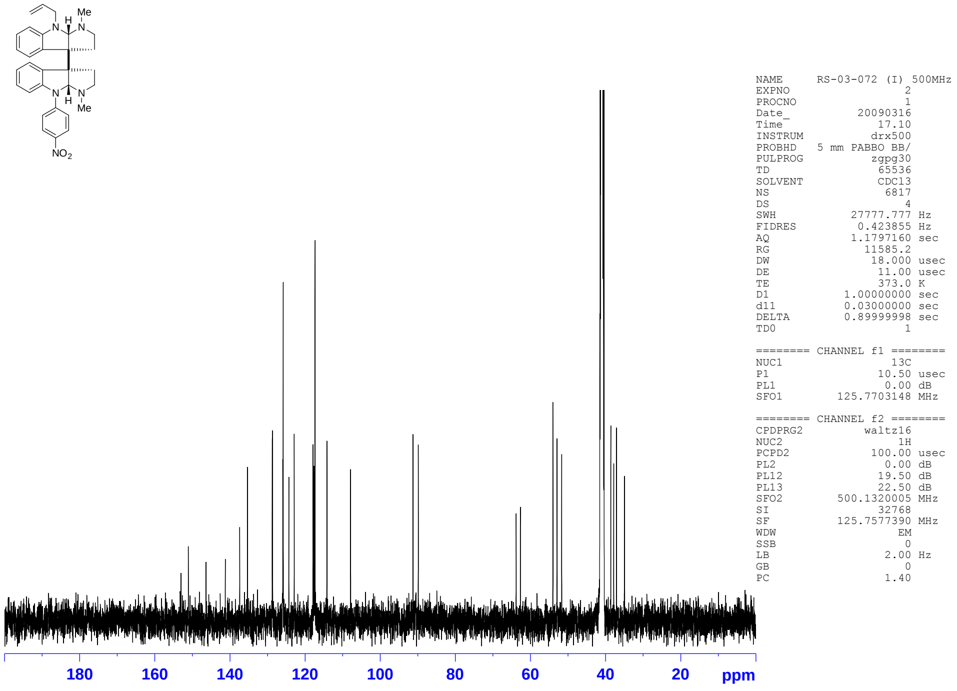
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
```

(3a*R*,3'a*S*,8a*S*,8'a*R*)-8-Allyl-1,1'-dimethyl-8'-(4-nitrophenyl)-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 102



```
NAME       RS-03-072 (I)
EXPNO                  4
PROCNO                 1
Date_           20090307
Time               12.51
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT            CDCl3
NS                    58
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 724.1
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

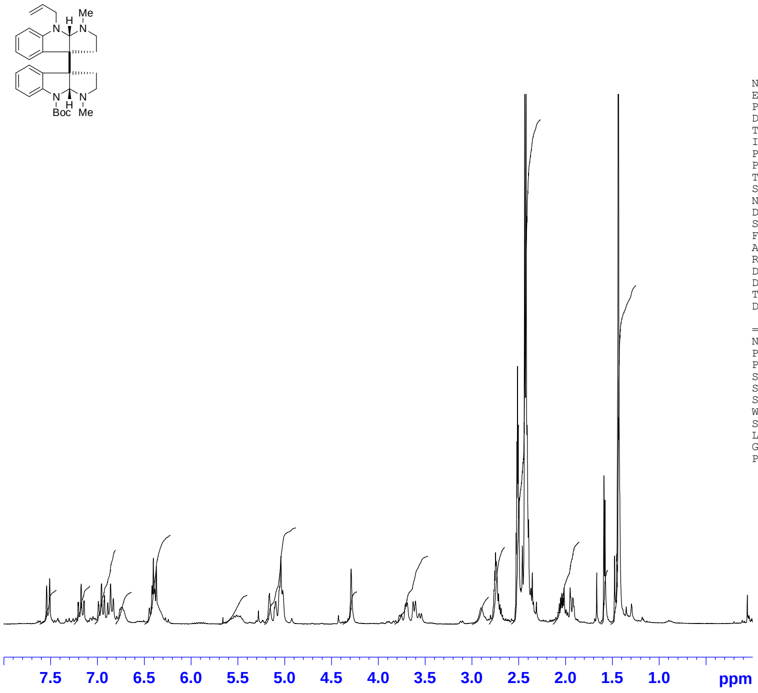


```
NAME      RS-03-072 (I) 500MHz
EXPNO                  2
PROCNO                 1
Date_           20090316
Time               17.10
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  6817
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG               11585.2
DW                18.000 usec
DE                 11.00 usec
TE                 373.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.50 usec
PL1                 0.00 dB
SFO1         125.7703148 MHz

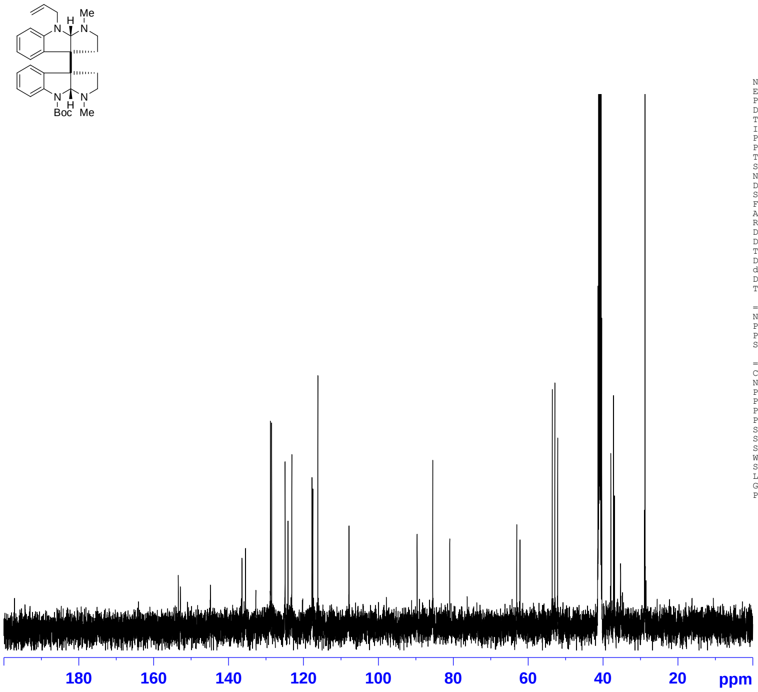
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
```

(+)- (3a*S*,3'a*R*,*R8*'a*S*)-*tert*-Butyl 8'-allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate, 103



```
NAME       RS-03-015 (II) DMSO
EXPNO                   1
PROCNO                  1
Date_            20081117
Time                17.09
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG              zg60
TD                  32768
SOLVENT              DMSO
NS                     29
DS                      2
SWH              4990.020 Hz
FIDRES           0.152283 Hz
AQ              3.2834036 sec
RG                    256
DW                100.200 usec
DE                   6.00 usec
TE                  392.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                  0.00 dB
SFO1          250.1312507 MHz
SI                  16384
SF            250.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

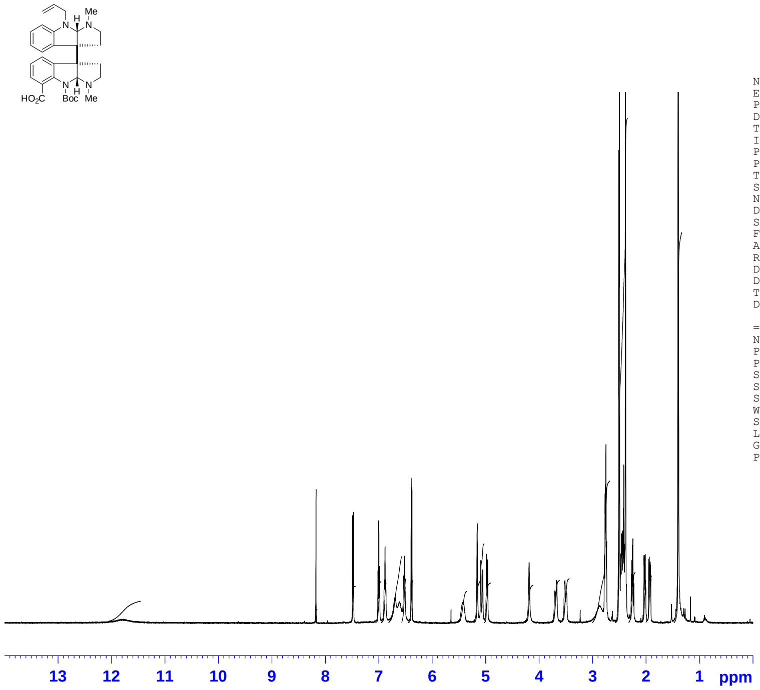


```
NAME     RS-03-015 (II) DMSO 500MHz
EXPNO                  4
PROCNO                 1
Date_           20081117
Time               17.45
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   691
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG                3649.1
DW                18.000 usec
DE                 11.00 usec
TE                 358.5 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.50 usec
PL1                 0.00 dB
SFO1         125.7703148 MHz

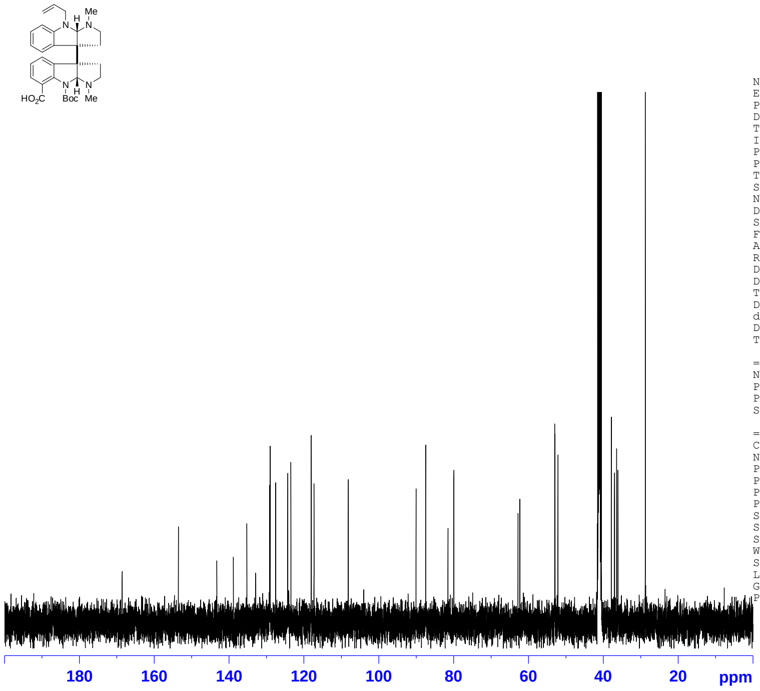
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-8'-Allyl-8-(*tert*-butoxycarbonyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-7-carboxylic acid, 104



```
NAME     RS-03-090 500MHz
EXPNO                   1
PROCNO                  1
Date_            20090423
Time                10.45
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG              zg60
TD                  65536
SOLVENT              DMSO
NS                     33
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                    181
DW                 48.400 usec
DE                  17.00 usec
TE                  393.6 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  12.50 usec
PL1                  0.00 dB
SFO1          500.1325007 MHz
SI                  32768
SF            500.1300000 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
```

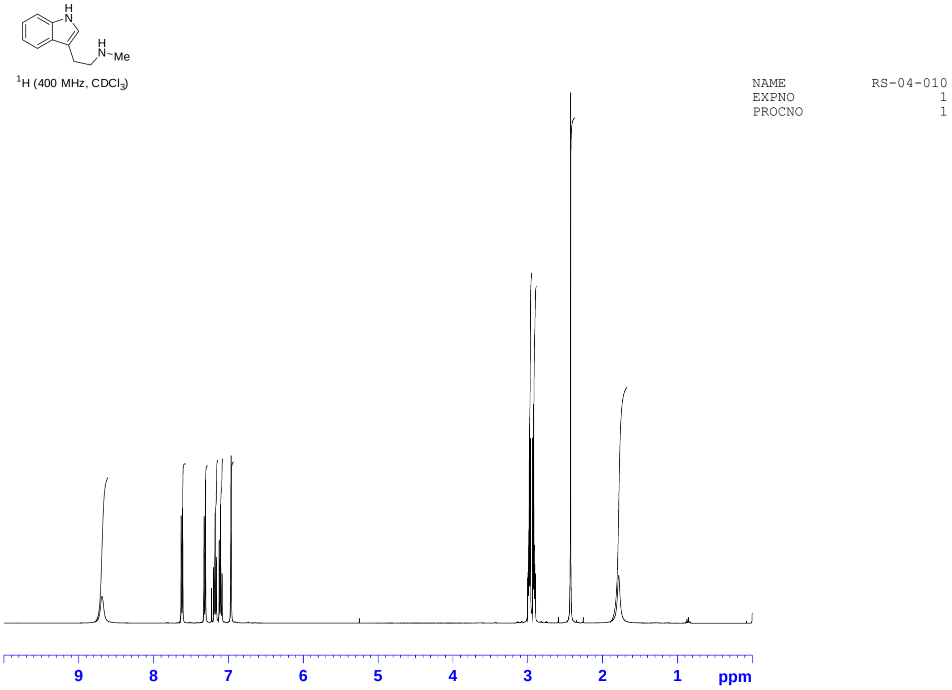


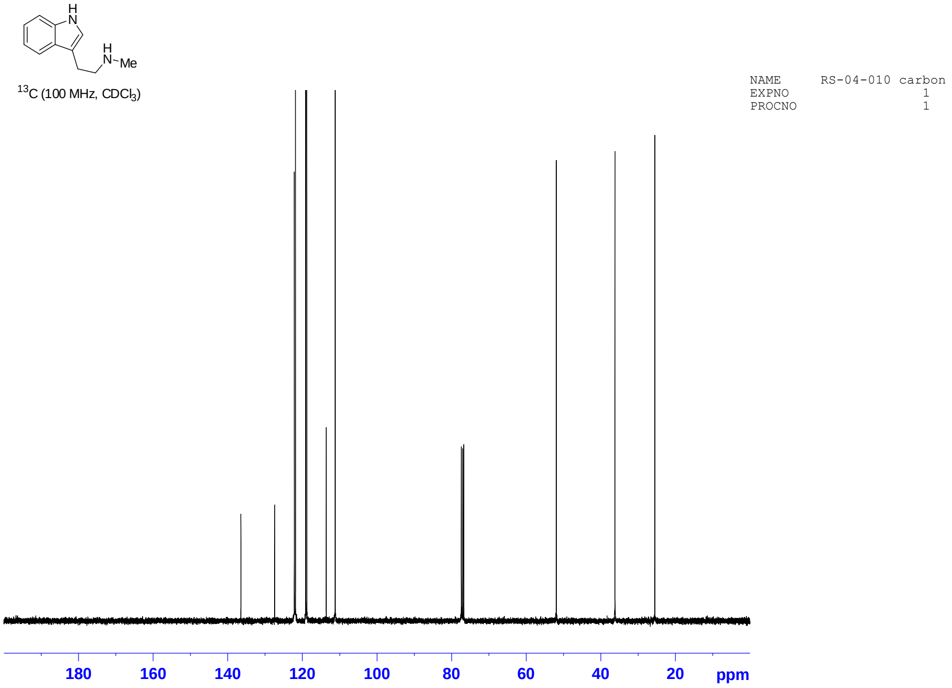
```
NAME     RS-03-090 500MHz
EXPNO                   2
PROCNO                  1
Date_            20090423
Time                10.51
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                  65536
SOLVENT              DMSO
NS                   1306
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                 4597.6
DW                 18.000 usec
DE                  11.00 usec
TE                  393.3 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  14.00 usec
PL1                  0.00 dB
SFO1          125.7703148 MHz

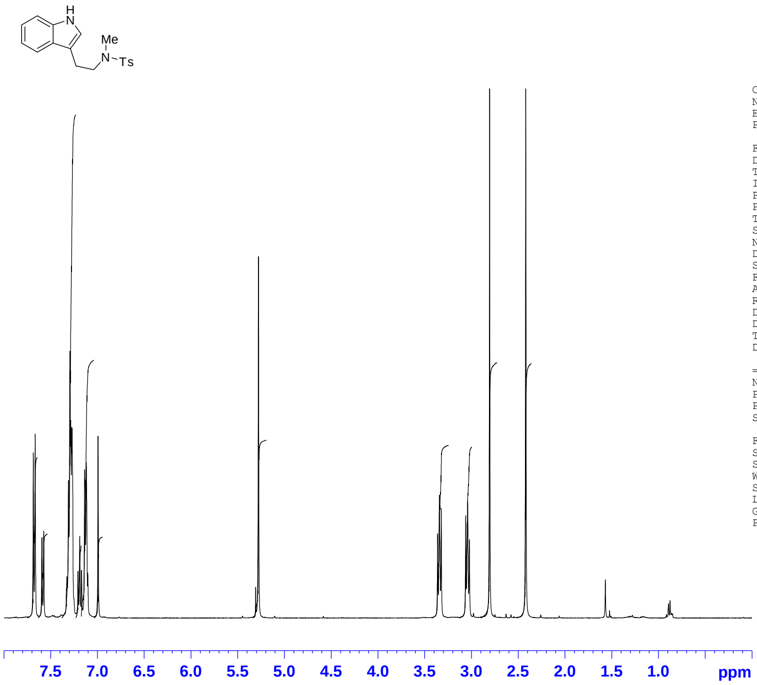
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

N-Methyl tryptamine, 9





N-(2-(1-Benzyl-1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 105

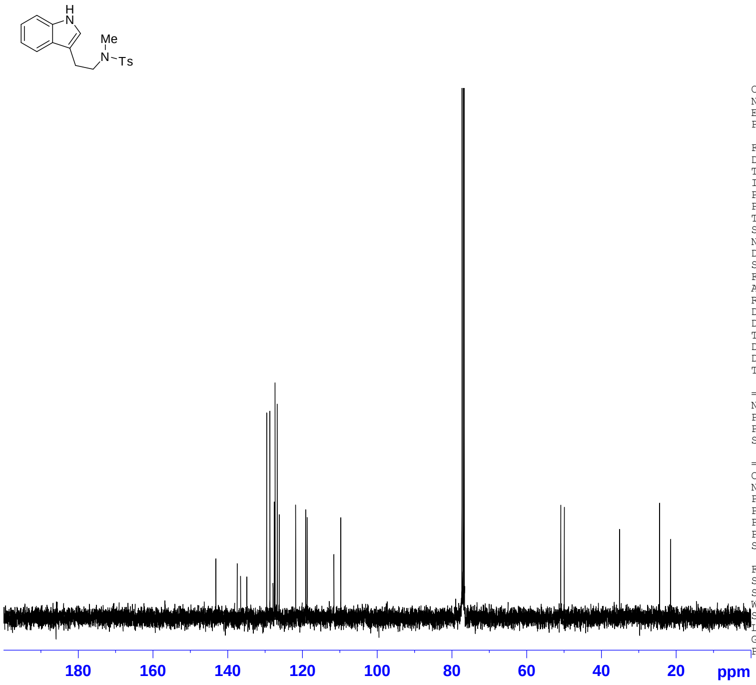


```
Current Data Parameters
NAME     RS-04-064 400 MHz
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20100712
Time                16.12
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                    181
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-04-064 400 MHz
EXPNO                   2
PROCNO                  1

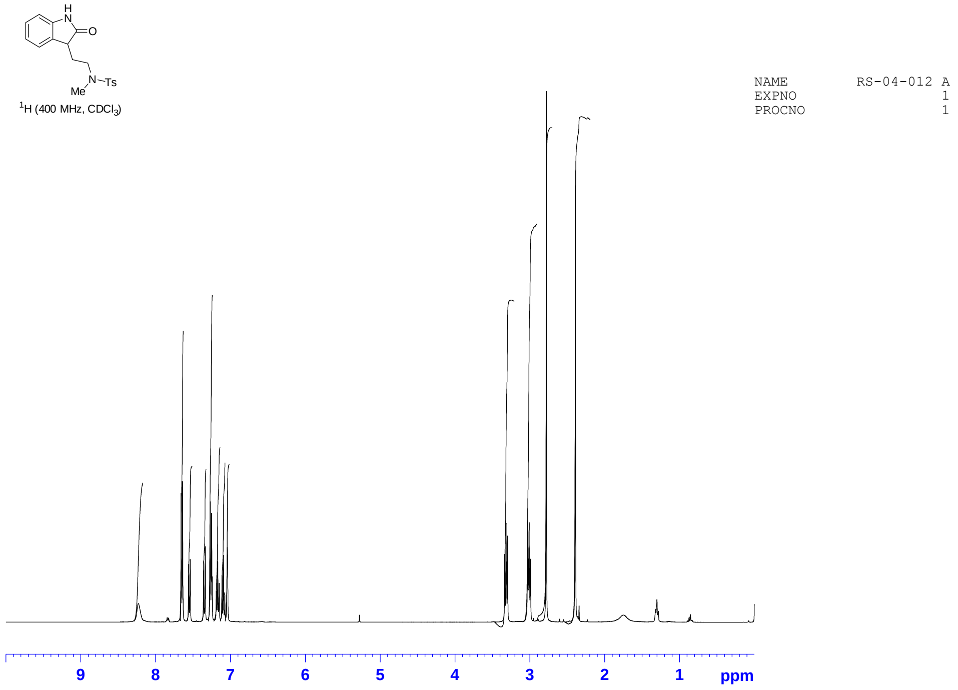
F2 - Acquisition Parameters
Date_            20100712
Time                16.19
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

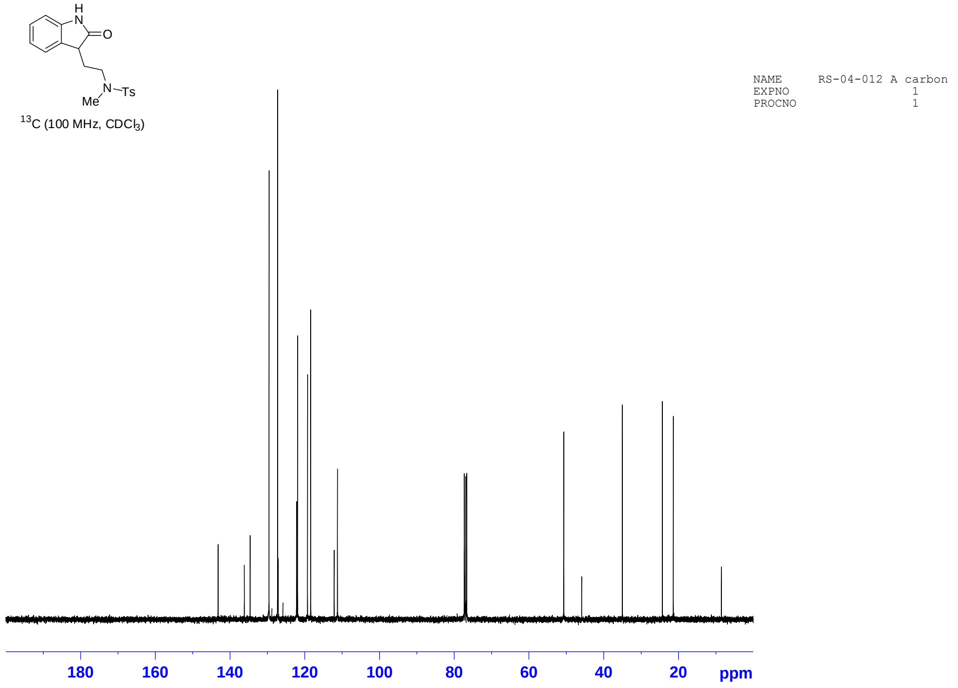
======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

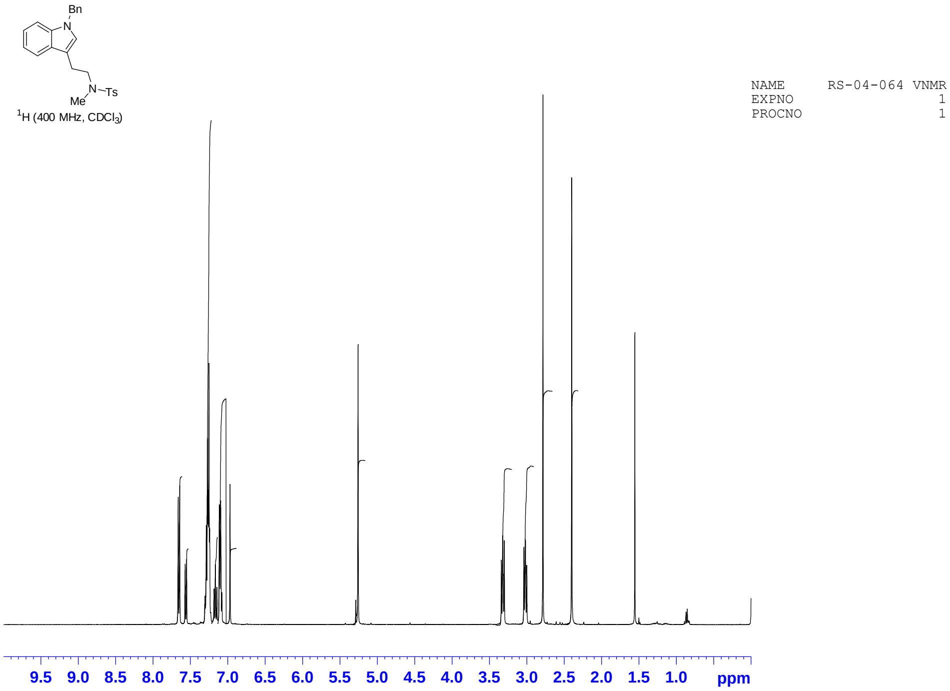
F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

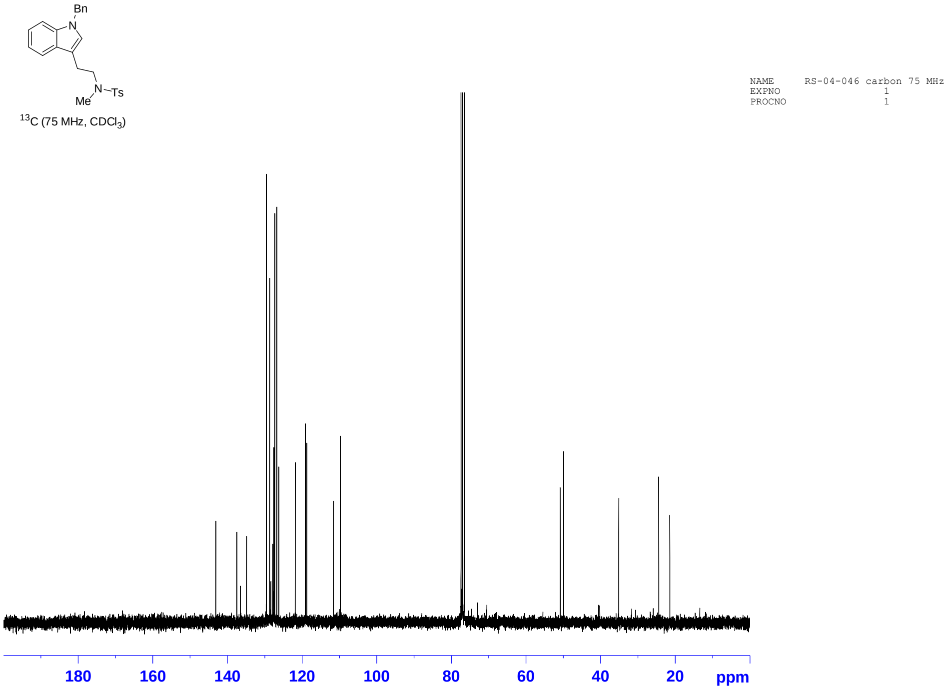
N,4-Dimethyl-*N*-(2-(2-oxoindolin-3-yl)ethyl)benzenesulfonamide, 106



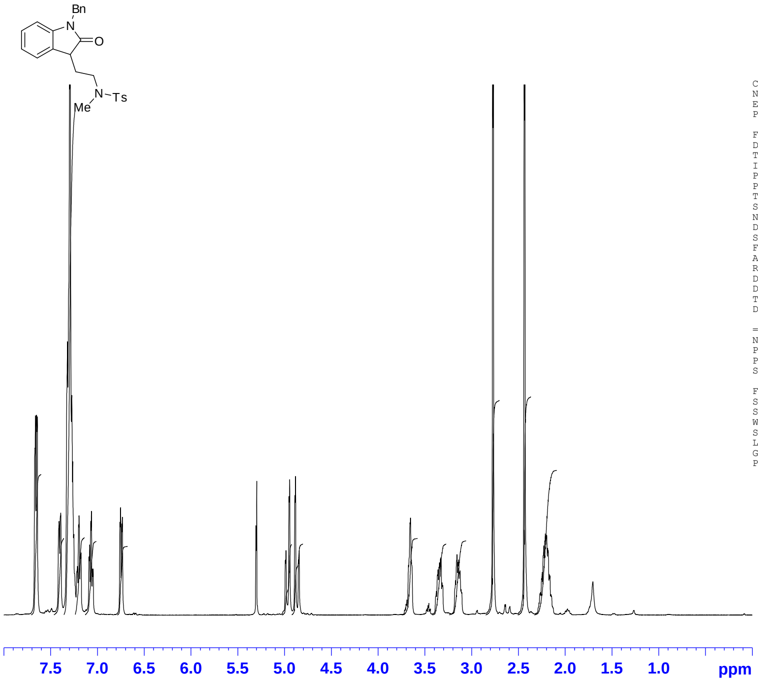


N-(2-(1-Benzyl-1H-indol-3-yl)-*N*,4-dimethylbenzenesulfonamide, 109





N-(2-(1-Benzyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 110

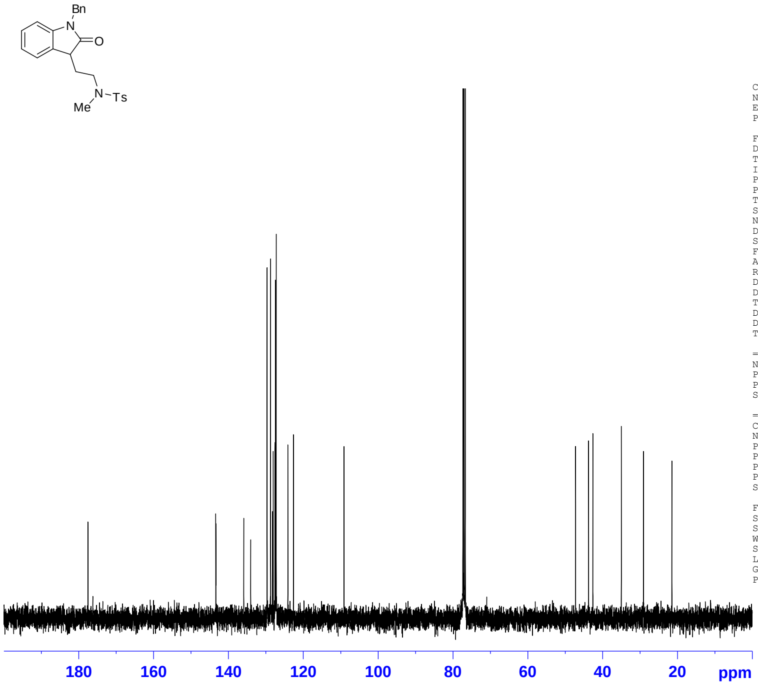


```
Current Data Parameters
NAME     RS-04-072 (III) 400 MHz
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_          20090722
Time              19.18
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz

F2 - Processing parameters
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME     RS-04-072 (III) 400 MHz
EXPNO                     3
PROCNO                    1

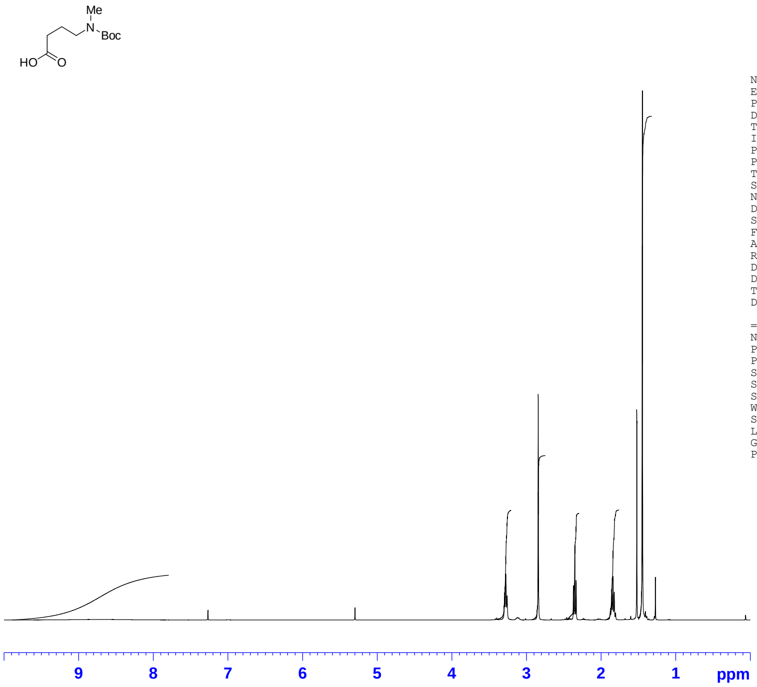
F2 - Acquisition Parameters
Date_          20090722
Time              19.29
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz

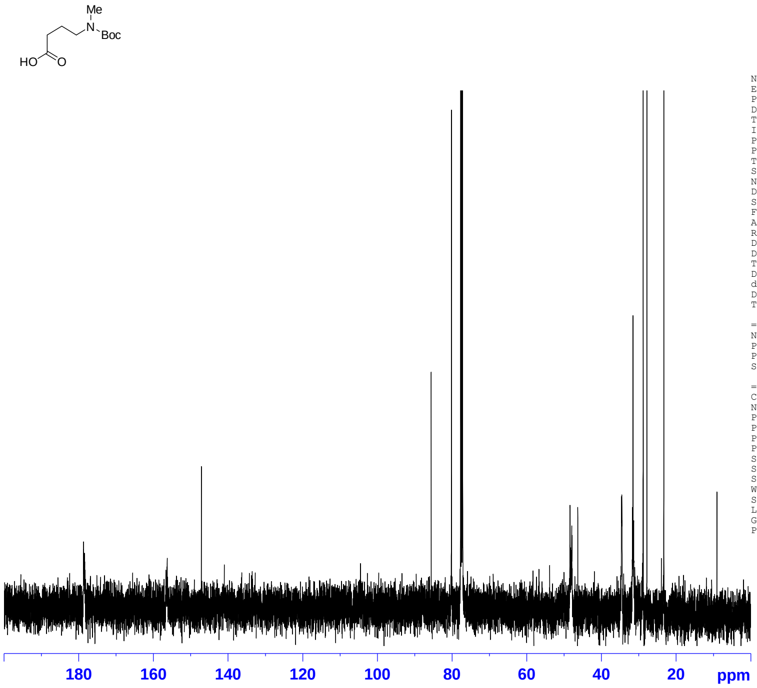
F2 - Processing parameters
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

4-((*tert*-Butoxycarbonyl)(methyl)amino)butanoic acid, 114



```
NAME      RS-05-037 400 MHz
EXPNO                     1
PROCNO                    1
Date_              20090929
Time                  12.43
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                3.9584243 sec
RG                     90.5
DW                   60.400 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1            400.2024714 MHz
SI                    32768
SF              400.2000028 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

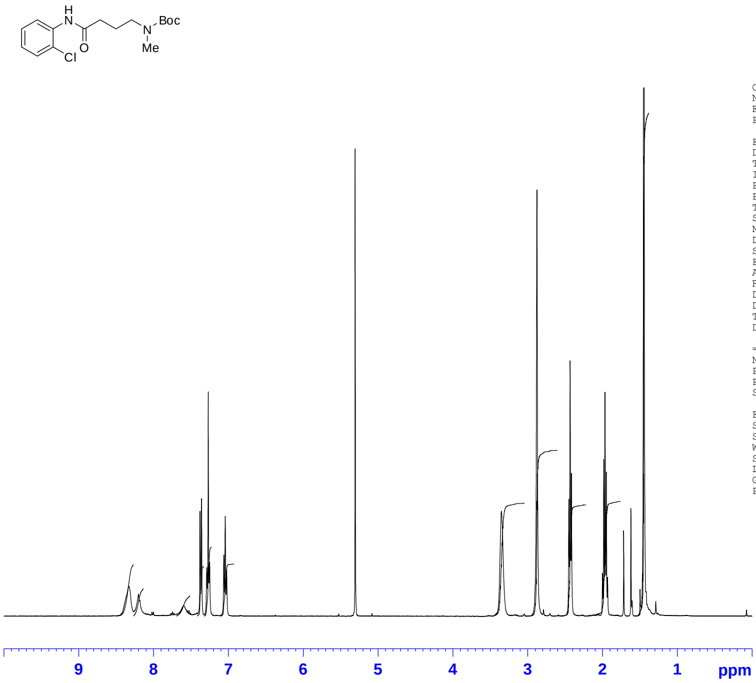


```
NAME     RS-05-037 crude 500 MHz
EXPNO                    1
PROCNO                   1
Date_             20091005
Time                 10.13
INSTRUM             drx500
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     712
DS                       4
SWH              27777.777 Hz
FIDRES            0.423855 Hz
AQ               1.1797160 sec
RG                  5792.6
DW                  18.000 usec
DE                   11.00 usec
TE                   298.1 K
D1              1.00000000 sec
d11             0.03000000 sec
DELTA           0.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   14.00 usec
PL1                   0.00 dB
SFO1           125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   0.00 dB
PL12                 19.50 dB
PL13                 22.50 dB
SFO2           500.1320005 MHz
SI                   32768
SF             125.7577390 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

tert-Butyl 4-(2-chlorophenylamino)-4-oxobutyl(methyl)carbamate, 115

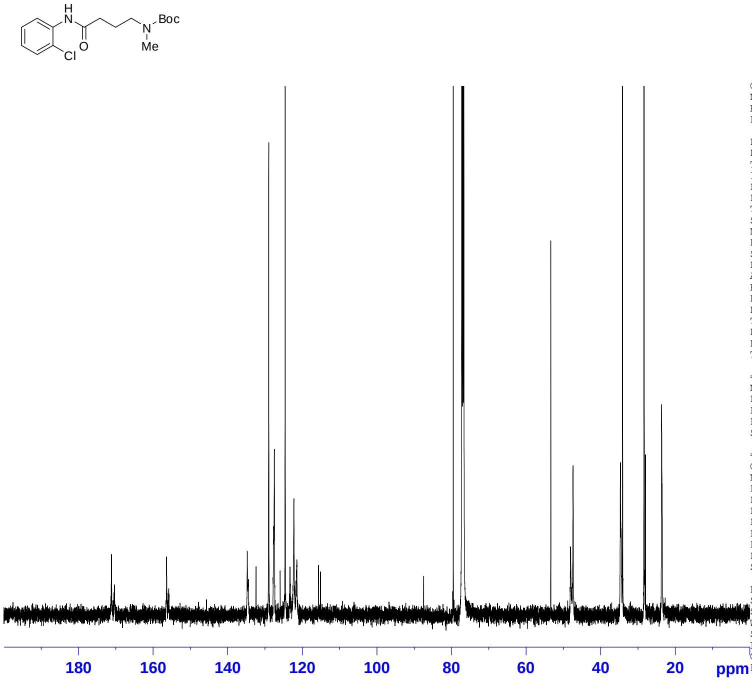


```
Current Data Parameters
NAME      RS-05-045 (P) 400 MHz
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20091014
Time              15.00
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                  256
DW               60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz

F2 - Processing parameters
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME      RS-05-045 carbon
EXPNO                 1
PROCNO                1

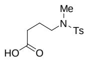
F2 - Acquisition Parameters
Date_          20091020
Time               6.11
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                 1820
DW               16.000 usec
DE                20.00 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

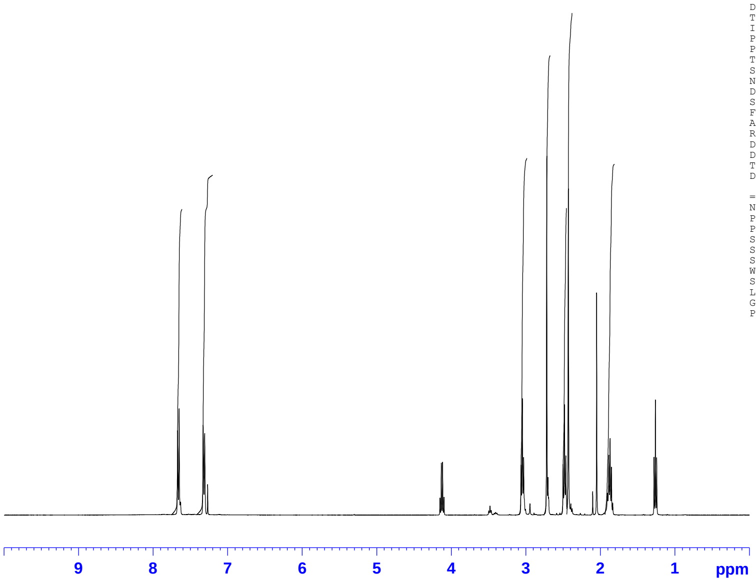
======== CHANNEL f1 ========
NUC1                13C
P1                 8.00 usec
PL1               -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               -6.00 dB
PL12              12.40 dB
PL13              17.00 dB
PL2W        15.19999981 W
PL12W        0.21970686 W
PL13W        0.07618046 W
SFO2        500.3020012 MHz

F2 - Processing parameters
SI                32768
SF          125.8005438 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

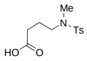
4-(*N*,4-Dimethylphenylsulfonamido)butanoic acid, 117

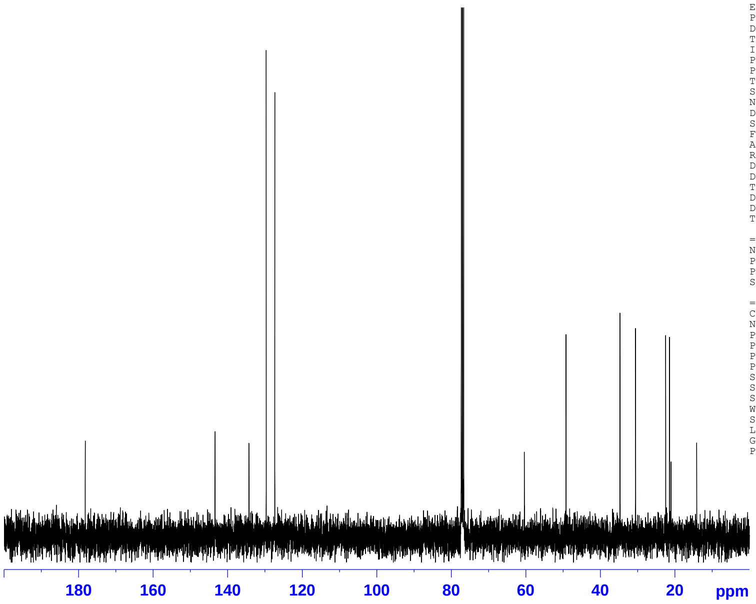




```
NAME     RS-07-008 acid 400 MHz
EXPNO                    1
PROCNO                   1
Date_             20100506
Time                 23.03
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     181
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



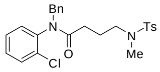


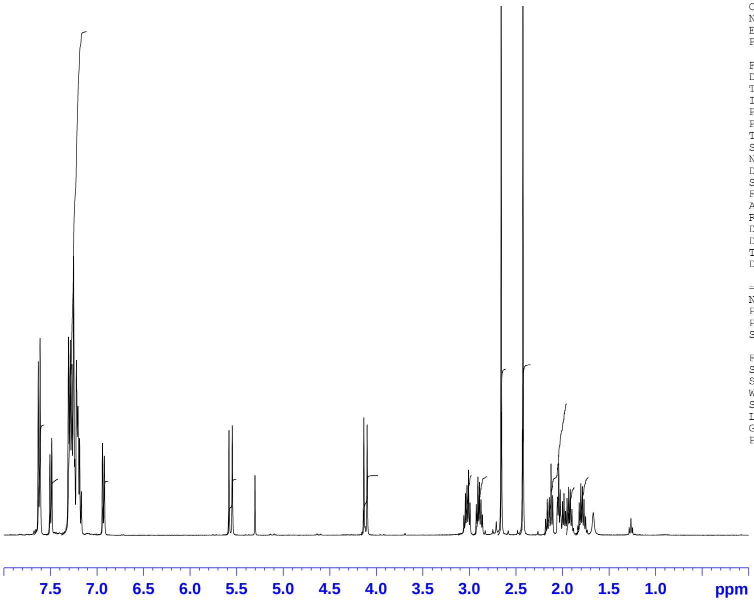
```
NAME     RS-07-008 acid 400 MHz
EXPNO                    3
PROCNO                   1
Date_             20100506
Time                 23.14
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG             zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

N-Benzyl-*N*-(2-chlorophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide, 118



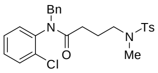


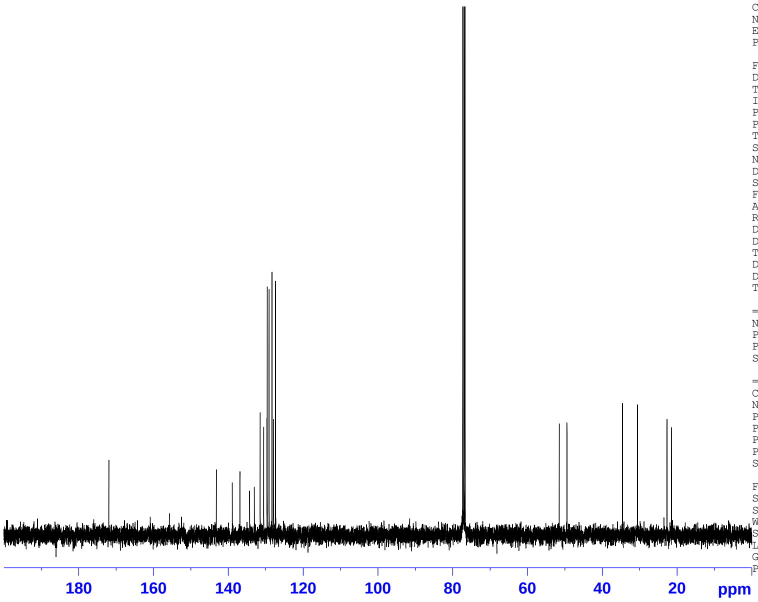
```
Current Data Parameters
NAME     RS-07-009 400 MHz
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20100510
Time                13.19
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                    128
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```





```
Current Data Parameters
NAME     RS-07-009 400 MHz
EXPNO                   3
PROCNO                  1

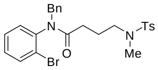
F2 - Acquisition Parameters
Date_            20100510
Time                13.30
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

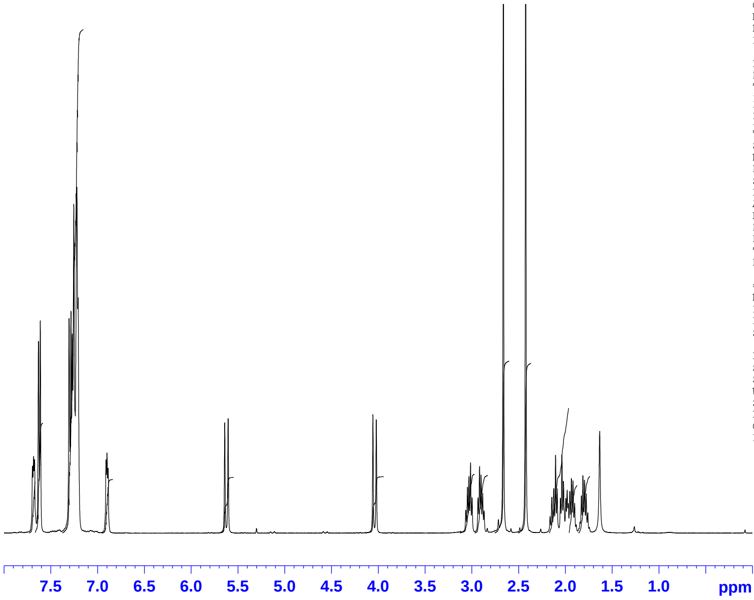
======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

N-Benzyl-N-(2-bromophenyl)-4-(*N*,4-dimethylphenylsulfonamido)butanamide, 121



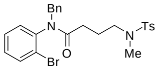


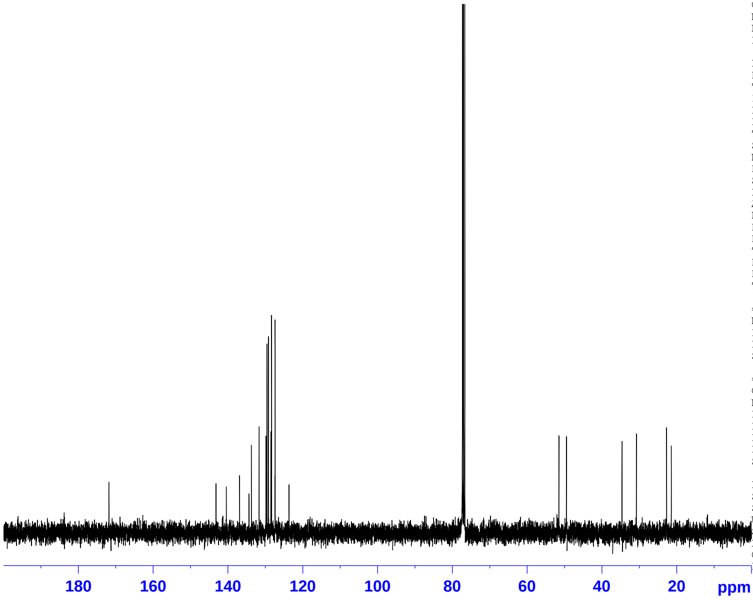
```
Current Data Parameters
NAME     RS-07-025 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100524
Time                 18.19
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     181
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





```
Current Data Parameters
NAME     RS-07-025 400 MHz
EXPNO                    3
PROCNO                   1

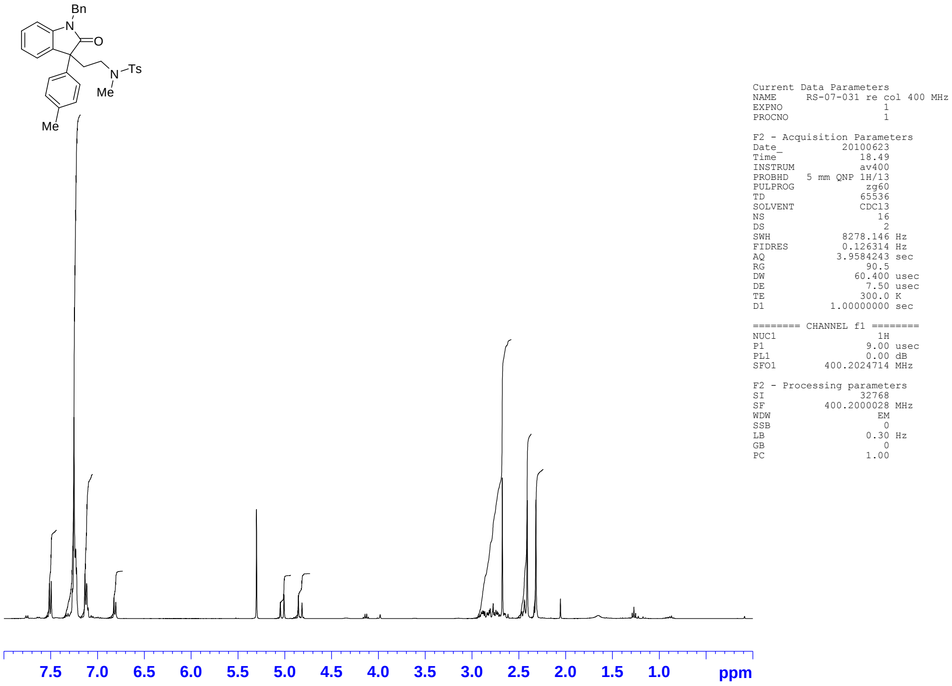
F2 - Acquisition Parameters
Date_             20100524
Time                 18.30
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz

F2 - Processing parameters
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

N-(2-(1-Benzyl-2-oxo-3-p-tolylindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 120

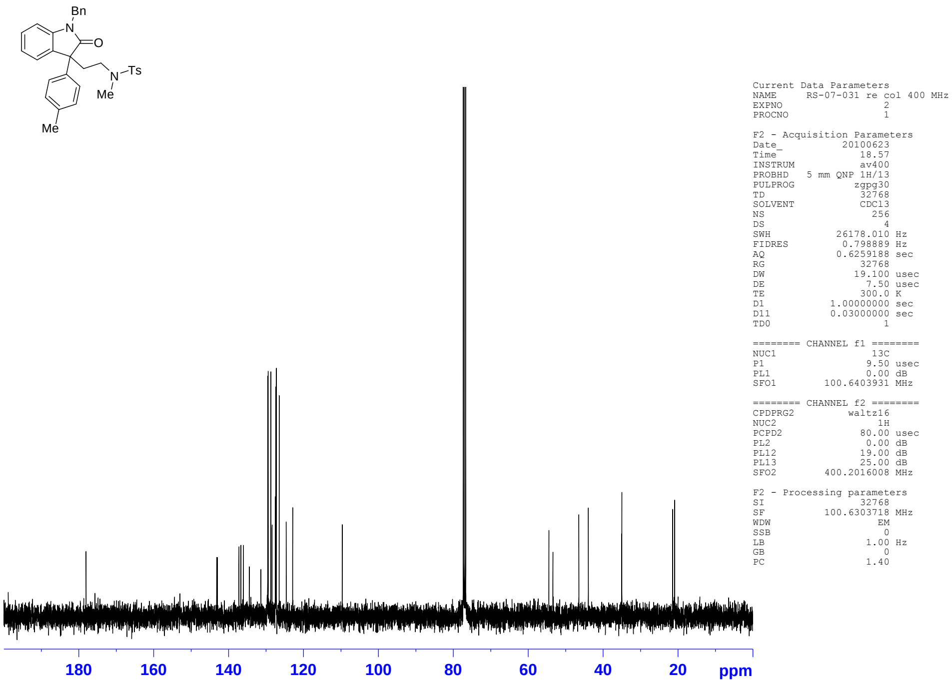


```
Current Data Parameters
NAME     RS-07-031 re col 400 MHz
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20100623
Time                18.49
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                   90.5
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-07-031 re col 400 MHz
EXPNO                   2
PROCNO                  1

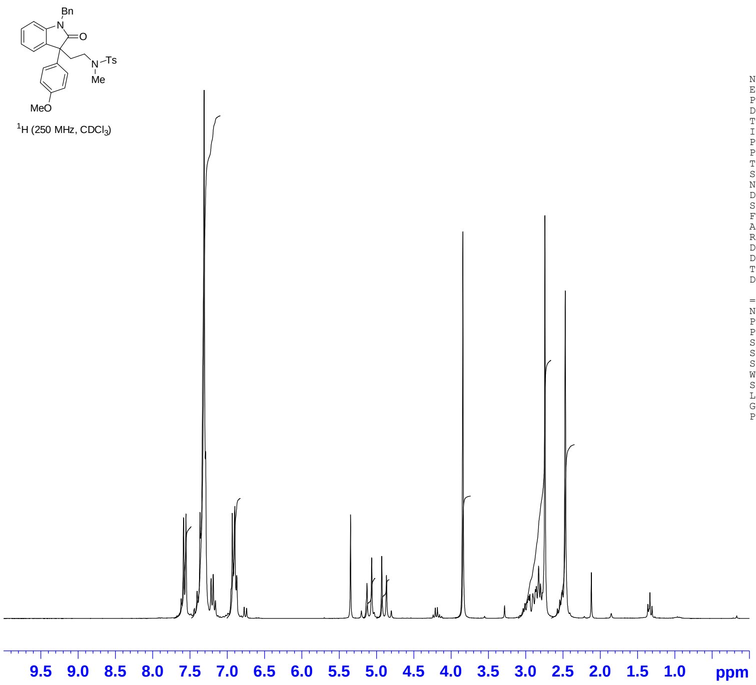
F2 - Acquisition Parameters
Date_            20100623
Time                18.57
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

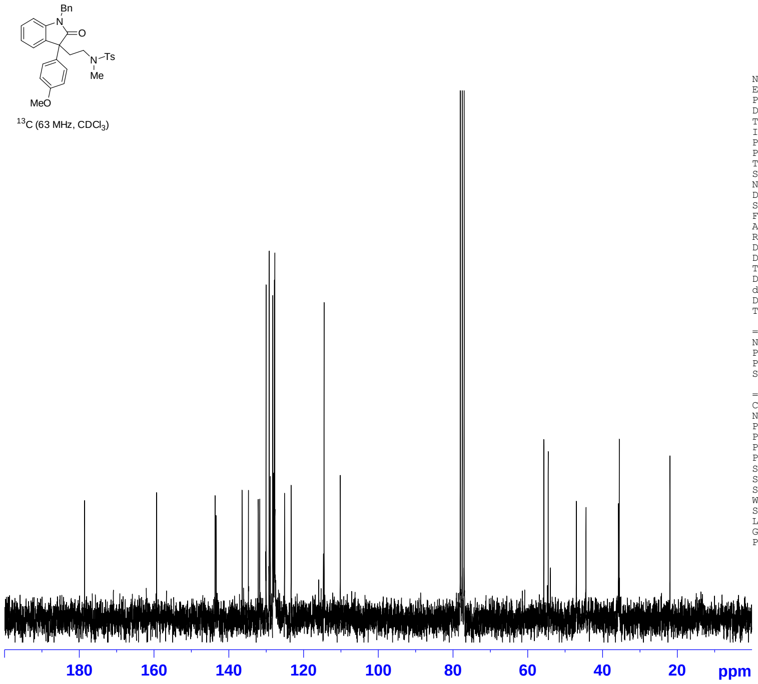
N-(2-(Benzyl-3-(40methoxyphenyl)-2-oxoindoline-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, Table 25, Entry 2



^{1}H (250 MHz, CDCl$_3$)

```
NAME      RS-10-017 pure 250 MHz
EXPNO                        1
PROCNO                       1
Date_                 20110319
Time                     19.00
INSTRUM                 dpx250
PROBHD    5 mm Multinucl
PULPROG                   zg60
TD                       32768
SOLVENT                  CDCl3
NS                          13
DS                           2
SWH                   4990.020 Hz
FIDRES                0.152283 Hz
AQ                   3.2834036 sec
RG                        45.3
DW                     100.200 usec
DE                        6.00 usec
TE                       294.0 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                       10.00 usec
PL1                       0.00 dB
SFO1               250.1312507 MHz
SI                       16384
SF                 250.1299972 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
```



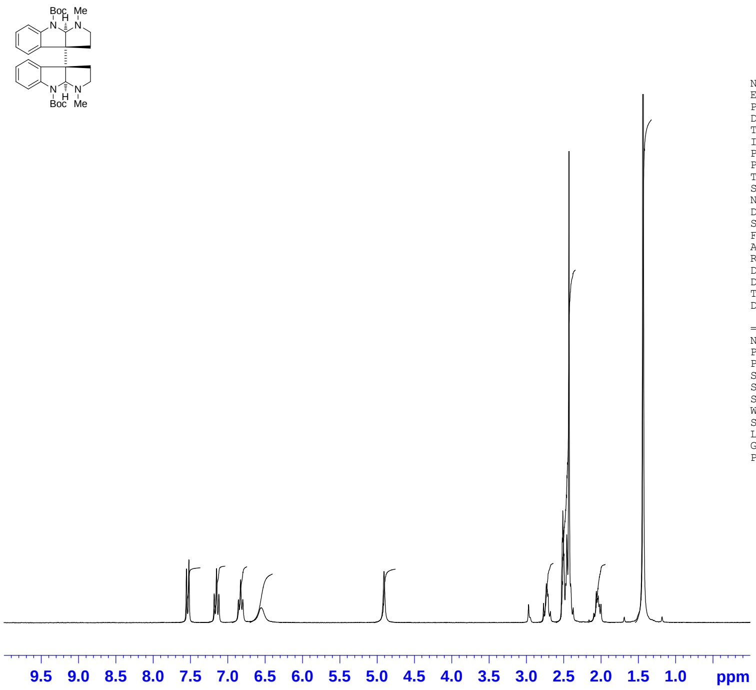
^{13}C (63 MHz, CDCl$_3$)

```
NAME      RS-10-017 pure 250 MHz
EXPNO                        2
PROCNO                       1
Date_                 20110319
Time                     19.03
INSTRUM                 dpx250
PROBHD    5 mm Multinucl
PULPROG                 zgpg30
TD                       32768
SOLVENT                  CDCl3
NS                          96
DS                           4
SWH                  15723.271 Hz
FIDRES                0.479836 Hz
AQ                   1.0420724 sec
RG                     14596.5
DW                      31.800 usec
DE                       30.00 usec
TE                       294.0 K
D1                  1.00000000 sec
d11                 0.03000000 sec
DELTA               0.89999998 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       13C
P1                        9.00 usec
PL1                       3.00 dB
SFO1                62.9021320 MHz

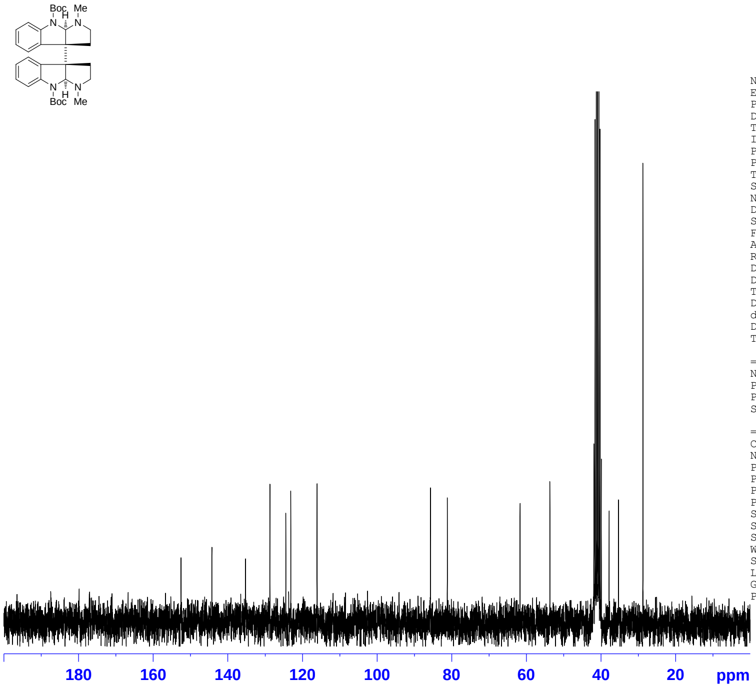
======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   100.00 usec
PL2                       3.00 dB
PL12                     20.00 dB
PL13                     26.00 dB
SFO2               250.1310005 MHz
SI                       32768
SF                  62.8952140 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

meso-Di-tert-butyl 1,1'-dimethyl-2,2',3,3'-tetrahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-8,8'(8aH,8'aH)-dicarboxylate, 33



```
NAME     RS-10-meso bis boc
EXPNO                     1
PROCNO                    1
Date_              20110318
Time                  15.45
INSTRUM              dpx250
PROBHD   5 mm Multinucl
PULPROG                zg60
TD                    32768
SOLVENT                DMSO
NS                       13
DS                        2
SWH                4990.020 Hz
FIDRES             0.152283 Hz
AQ                3.2834036 sec
RG                      181
DW                  100.200 usec
DE                     6.00 usec
TE                    373.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.00 usec
PL1                    3.00 dB
SFO1            250.1312507 MHz
SI                    16384
SF              250.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

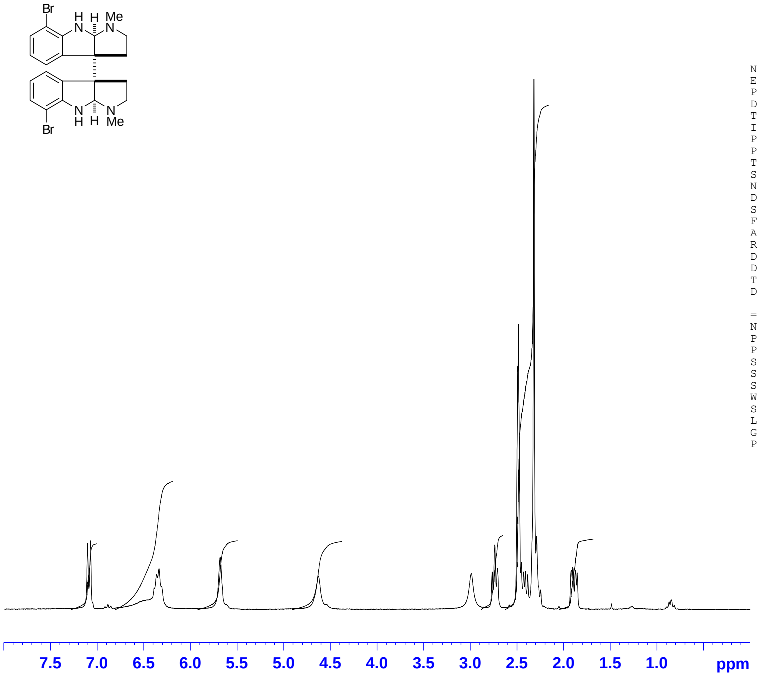


```
NAME     RS-10-meso bis boc
EXPNO                     2
PROCNO                    1
Date_              20110318
Time                  15.47
INSTRUM              dpx250
PROBHD   5 mm Multinucl
PULPROG             zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      230
DS                        4
SWH               15723.271 Hz
FIDRES             0.479836 Hz
AQ                1.0420724 sec
RG                    16384
DW                   31.800 usec
DE                    30.00 usec
TE                    373.0 K
D1               1.00000000 sec
d11              0.03000000 sec
DELTA            0.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.00 usec
PL1                    3.00 dB
SFO1             62.9021320 MHz

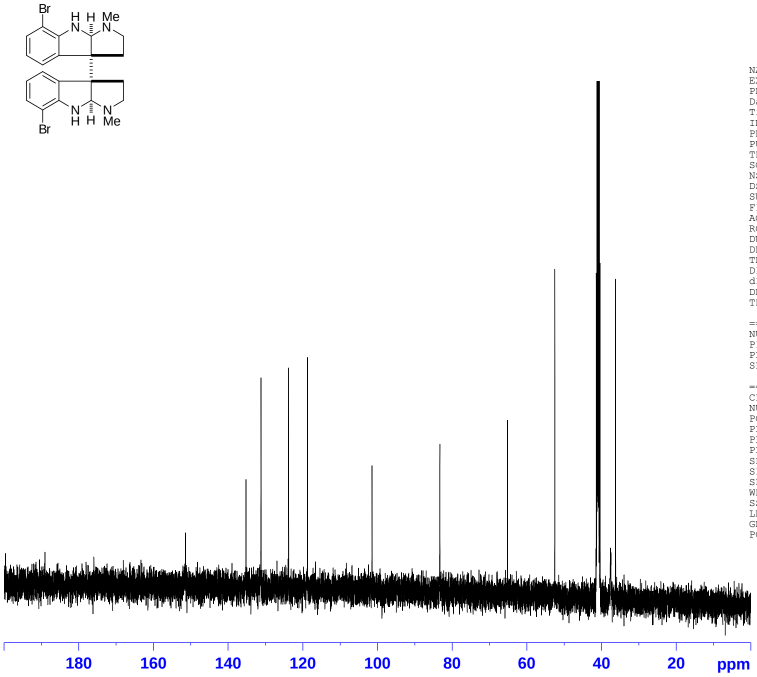
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                    3.00 dB
PL12                  20.00 dB
PL13                  26.00 dB
SFO2            250.1310005 MHz
SI                    32768
SF               62.8952140 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

meso-7,7′-Dibromo-1,1′-dimethyl-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-3a,3′a-bipyrrolo[2,3-b]indole, 122



```
NAME          RS-08-044
EXPNO                 1
PROCNO                1
Date_          20100909
Time               9.41
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   14
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                456.1
DW              100.200 usec
DE                 6.00 usec
TE                372.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

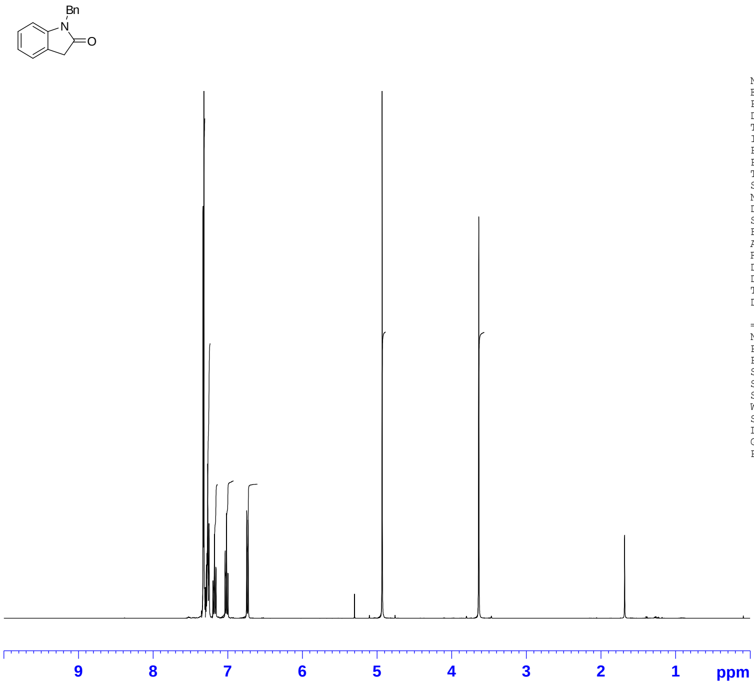


```
NAME     RS-08-044 dmso 500 mhz
EXPNO                 2
PROCNO                1
Date_          20100907
Time              11.47
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  367
DS                    4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG                 3251
DW               18.000 usec
DE                11.00 usec
TE                363.1 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                5.00 dB
SFO1        125.7703148 MHz

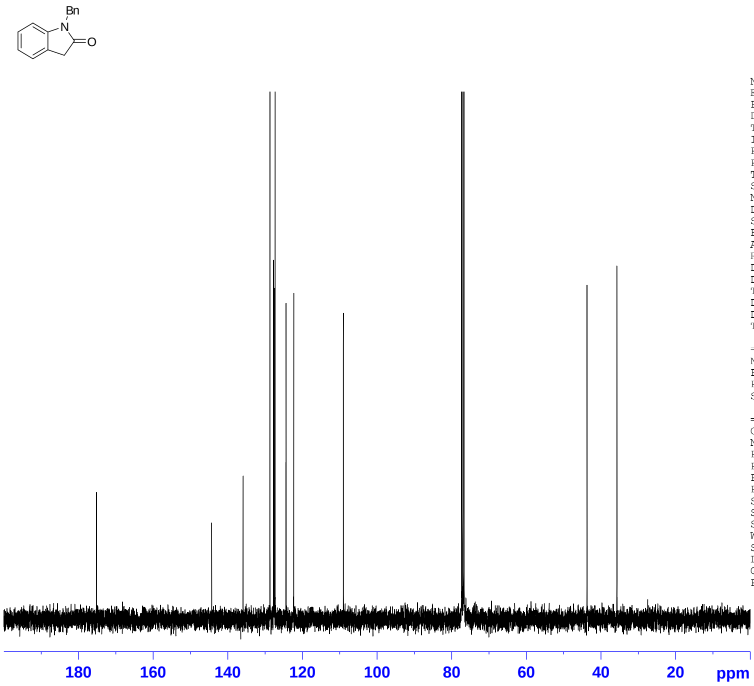
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz
SI                32768
SF          125.7577390 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

1-Benzylindolin-2-one



```
NAME     RS-08-043 400 MHz
EXPNO                    1
PROCNO                   1
Date_             20100907
Time                 23.17
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     128
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

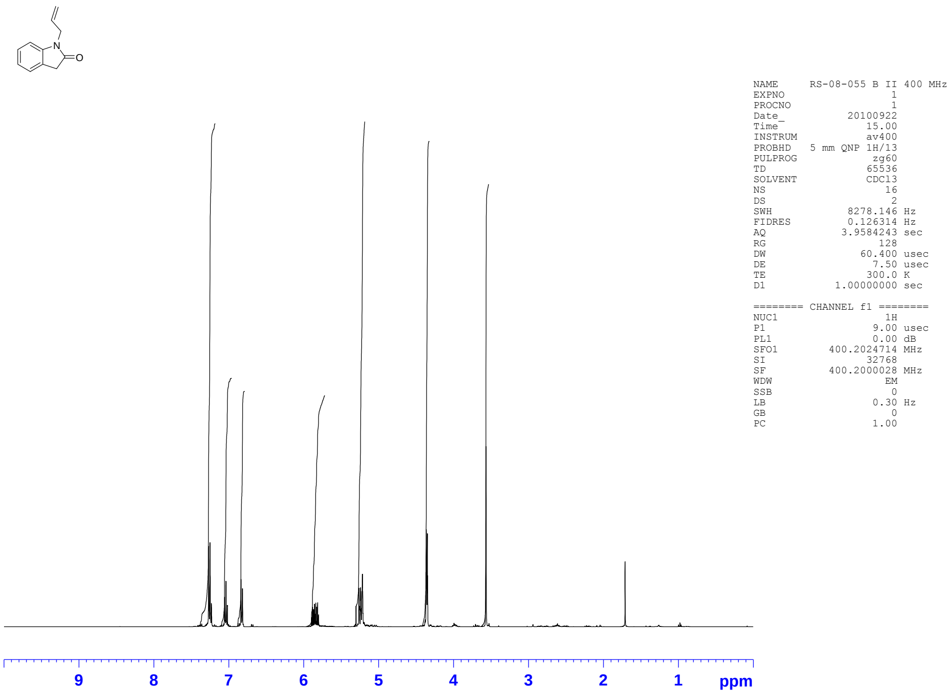


```
NAME     RS-08-043 400 MHz
EXPNO                    3
PROCNO                   1
Date_             20100907
Time                 23.25
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG             zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

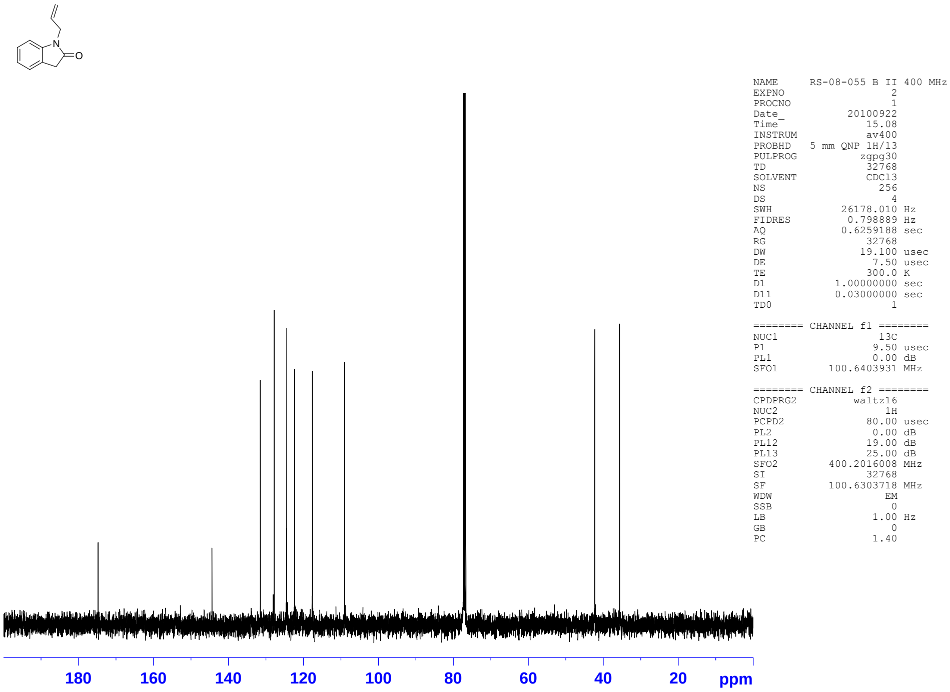
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1-Allylindolin-2-one



```
NAME     RS-08-055 B II 400 MHz
EXPNO                  1
PROCNO                 1
Date_           20100922
Time               15.00
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                   128
DW                60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz
SI                 32768
SF           400.2000028 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

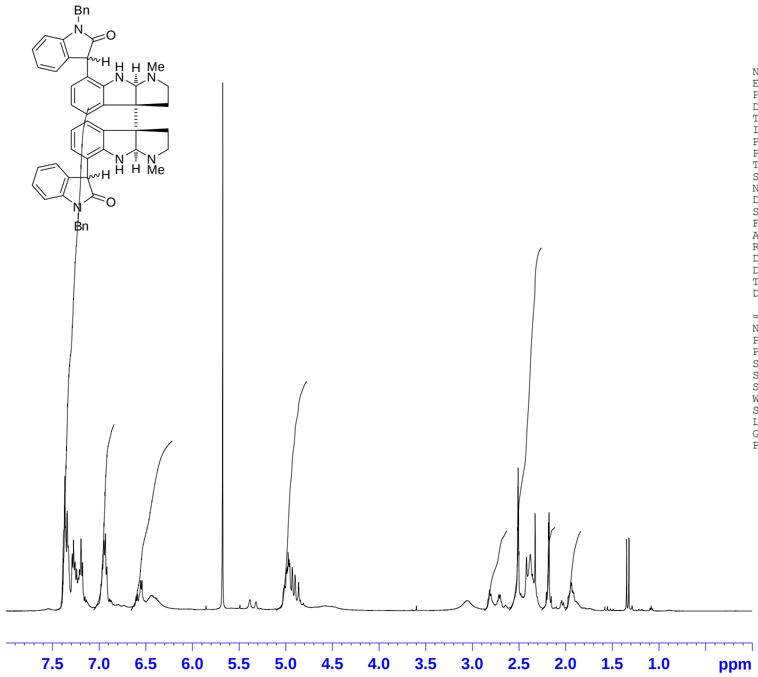


```
NAME     RS-08-055 B II 400 MHz
EXPNO                  2
PROCNO                 1
Date_           20100922
Time               15.08
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                 32768
DW                19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

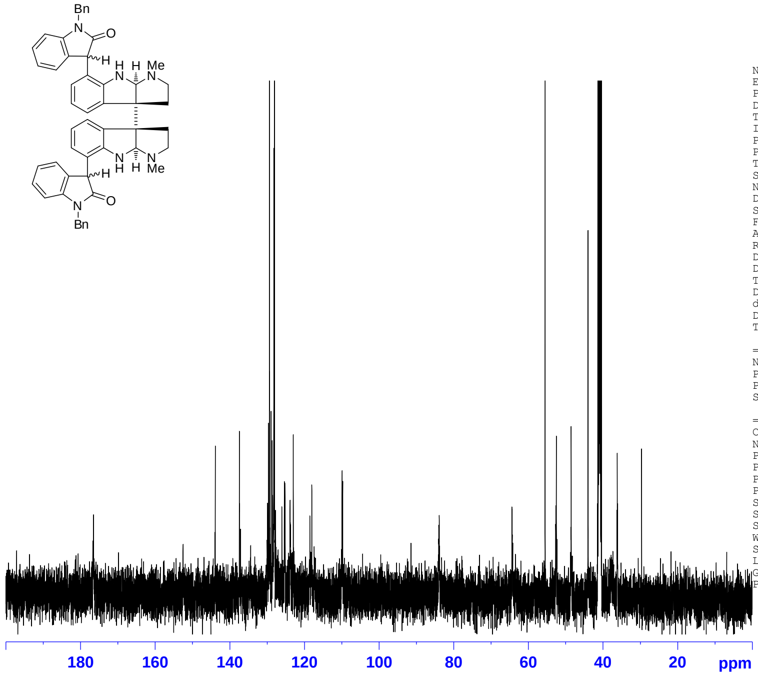
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-benzylindolin-2-one), Table 26, Entry 2



```
NAME      RS-08-051 500 MHz
EXPNO                     1
PROCNO                    1
Date_              20100917
Time                   9.42
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       42
DS                        2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1720407 sec
RG                     71.8
DW                   48.400 usec
DE                    17.00 usec
TE                    368.3 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    12.50 usec
PL1                    0.00 dB
SFO1           500.1325007 MHz
SI                    32768
SF             500.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

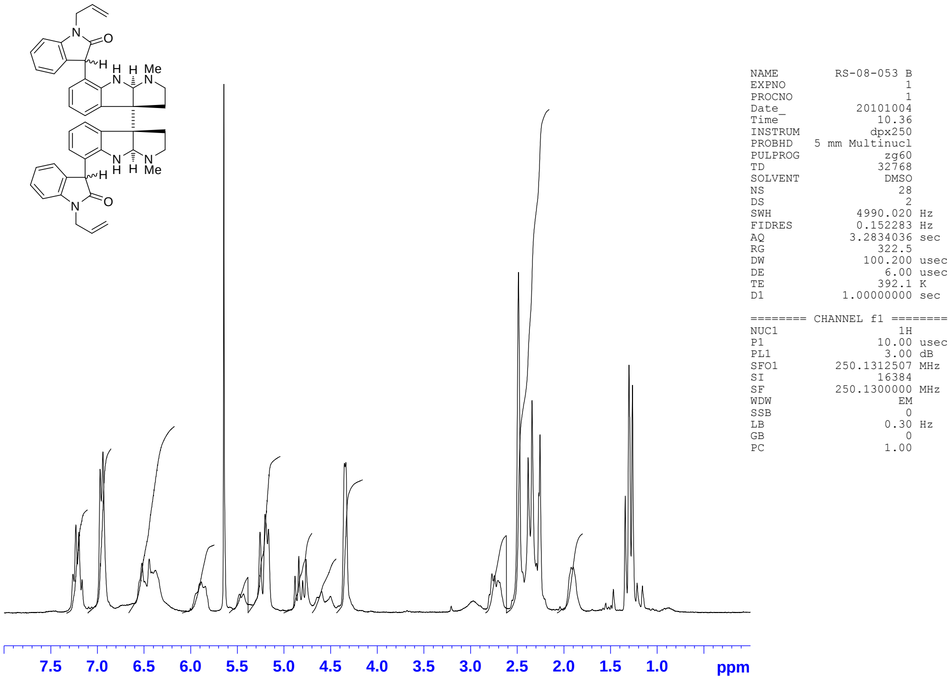


```
NAME      RS-08-051 500 MHz
EXPNO                     2
PROCNO                    1
Date_              20100917
Time                   9.43
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      470
DS                        4
SWH              27777.777 Hz
FIDRES            0.423855 Hz
AQ               1.1797160 sec
RG                   2896.3
DW                   18.000 usec
DE                    11.00 usec
TE                    368.3 K
D1               1.00000000 sec
d11              0.03000000 sec
DELTA            0.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                    5.00 dB
SFO1           125.7703148 MHz

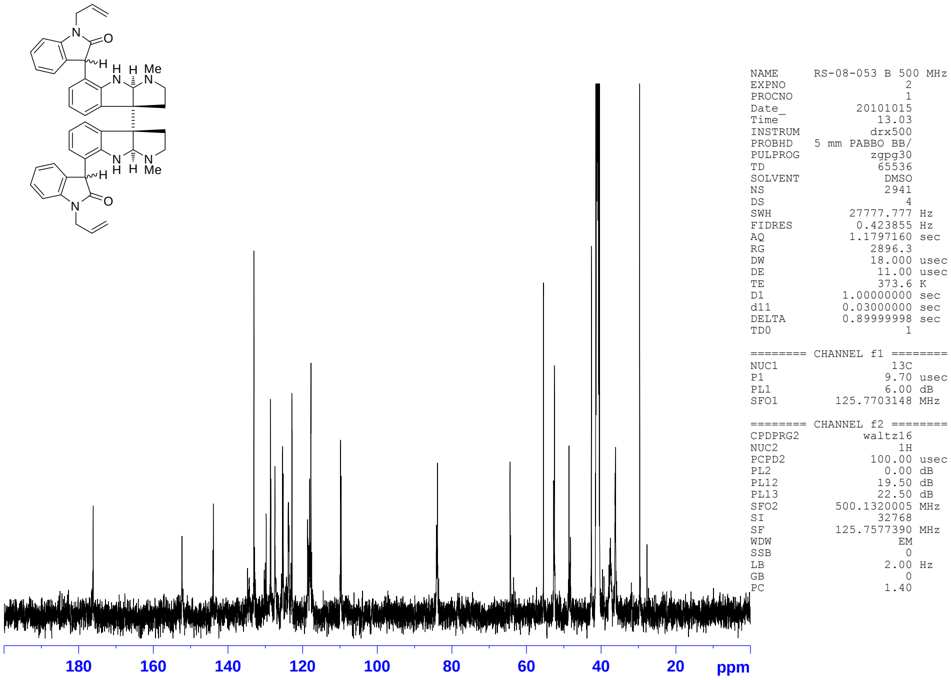
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                    0.00 dB
PL12                  19.50 dB
PL13                  22.50 dB
SFO2           500.1320005 MHz
SI                    32768
SF             125.7577390 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-allylindolin-2-one), Table 26, Entry 3



```
NAME        RS-08-053 B
EXPNO                 1
PROCNO                1
Date_          20101004
Time              10.36
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   28
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                322.5
DW              100.200 usec
DE                 6.00 usec
TE                392.1 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

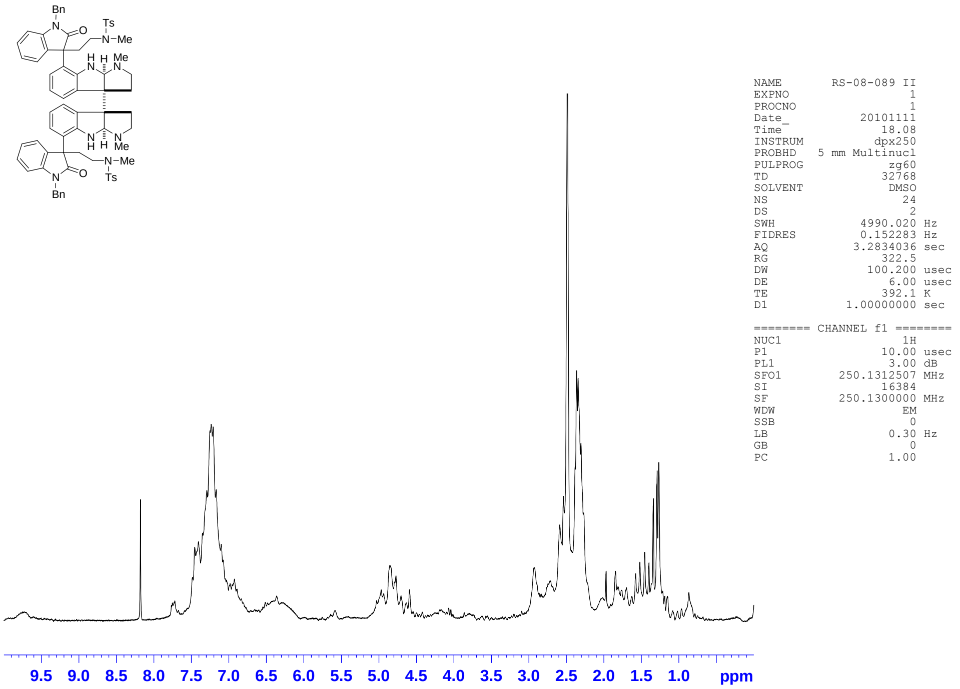


```
NAME     RS-08-053 B 500 MHz
EXPNO                 2
PROCNO                1
Date_          20101015
Time              13.03
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 2941
DS                    4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG               2896.3
DW               18.000 usec
DE                11.00 usec
TE                373.6 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.70 usec
PL1                6.00 dB
SFO1        125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz
SI                32768
SF          125.7577390 MHz
WDW                  EM
SSB                   0
LB                 2.00 Hz
GB                    0
PC                 1.40
```

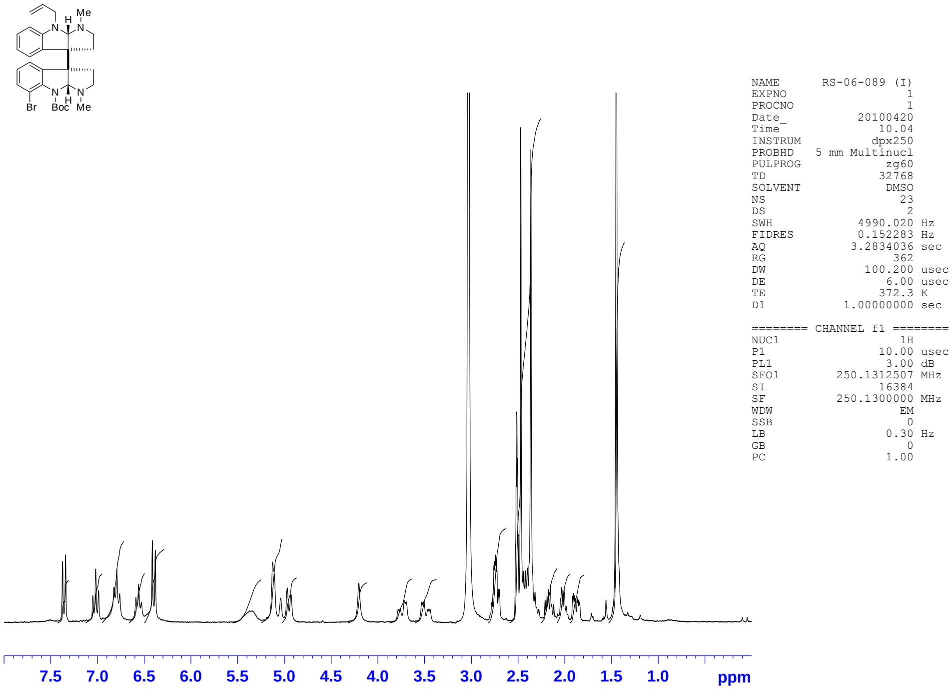
N,*N*'-((3,3'-((3a*R*,3'a*S*,8a*R*,8'a*S*)-1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-7,7'-diyl)bis(1-benzyl-2-oxoindoline-3,3-diyl))bis(ethane-2,1-diyl))bis(N,4-dimethylbenzenesulfonamide), 123



```
NAME       RS-08-089 II
EXPNO                 1
PROCNO                1
Date_          20101111
Time              18.08
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   24
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                322.5
DW              100.200 usec
DE                 6.00 usec
TE                392.1 K
D1           1.00000000 sec

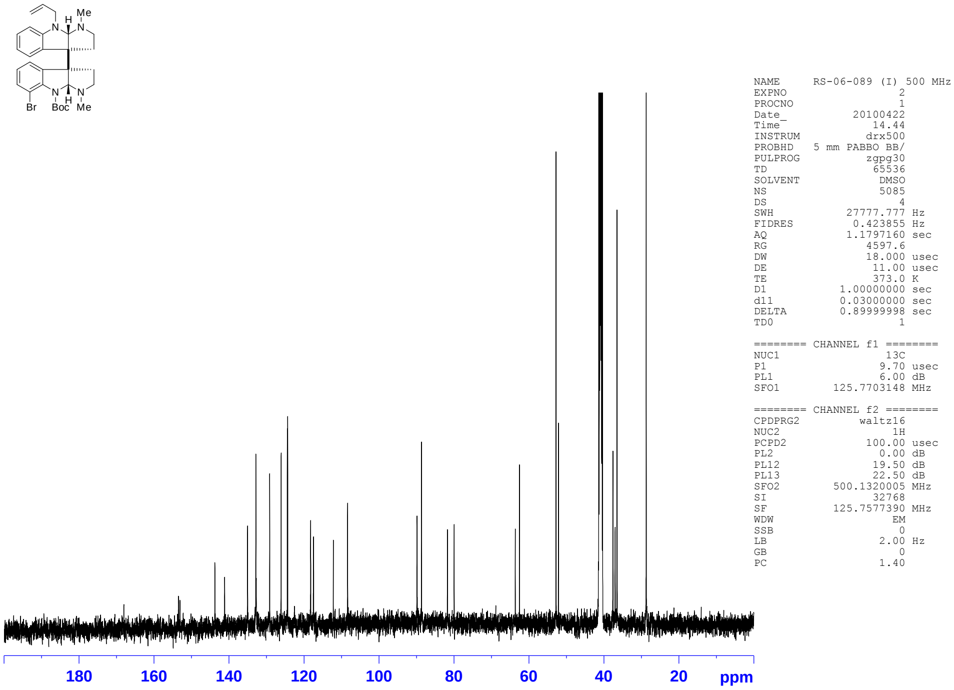
======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-Butyl 8'-allyl-7-bromo-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-8(8aH)-carboxylate, 125



```
NAME       RS-06-089 (I)
EXPNO                  1
PROCNO                 1
Date_           20100420
Time               10.04
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    23
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   362
DW               100.200 usec
DE                  6.00 usec
TE                 372.3 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

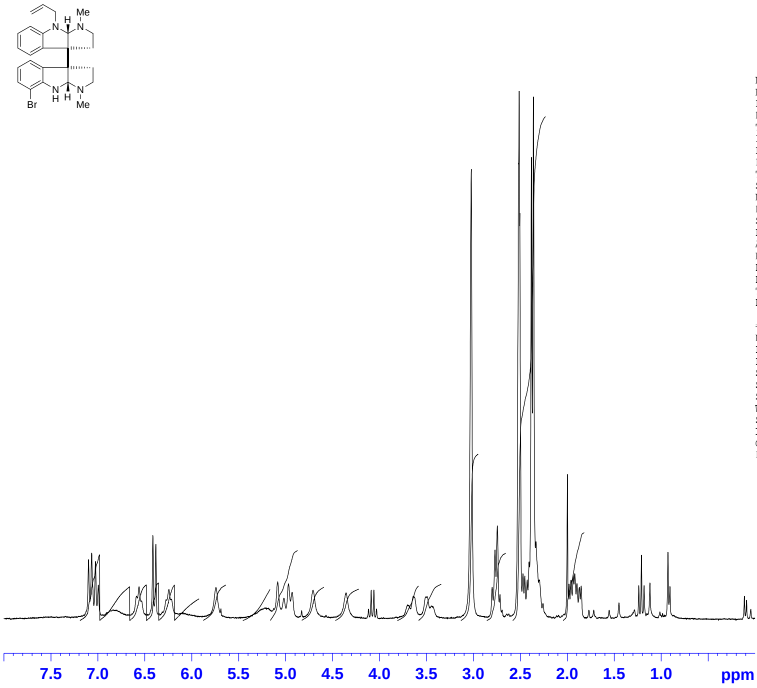


```
NAME     RS-06-089 (I) 500 MHz
EXPNO                 2
PROCNO                1
Date_          20100422
Time              14.44
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD                65536
SOLVENT            DMSO
NS                 5085
DS                    4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG               4597.6
DW               18.000 usec
DE                11.00 usec
TE                373.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.70 usec
PL1                6.00 dB
SFO1        125.7703148 MHz

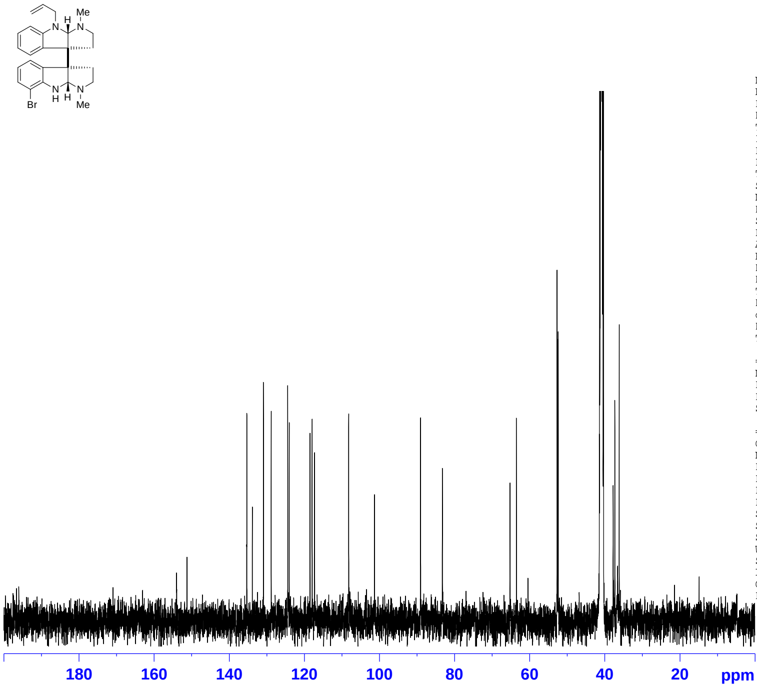
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz
SI                32768
SF          125.7577390 MHz
WDW                  EM
SSB                   0
LB                 2.00 Hz
GB                    0
PC                 1.40
```

(-)-(3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-Allyl-7-bromo-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 126



```
NAME          RS-07-002
EXPNO                 1
PROCNO                1
Date_          20100427
Time              10.07
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   19
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                406.4
DW              100.200 usec
DE                 6.00 usec
TE                372.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                0.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

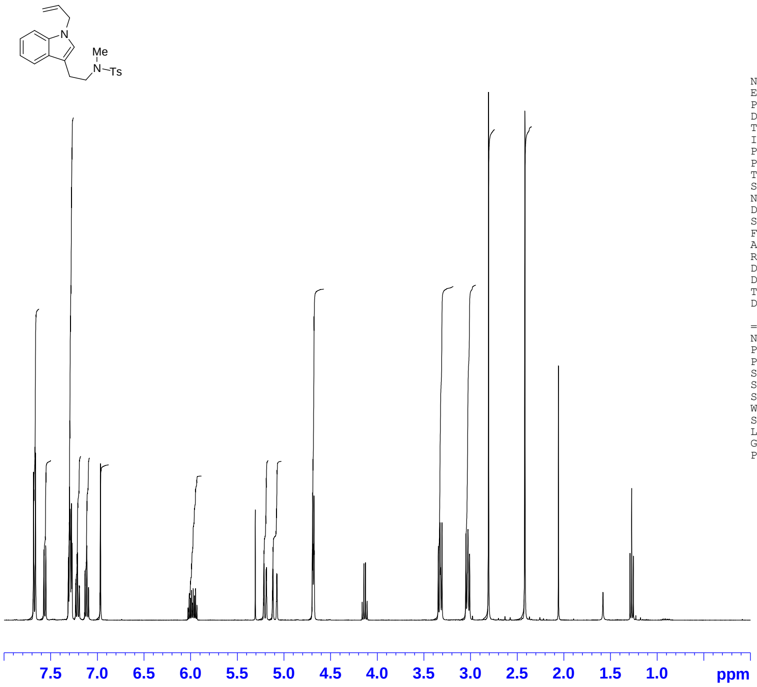


```
NAME     RS-07-002 500 MHz
EXPNO                 2
PROCNO                1
Date_          20100507
Time              13.03
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 4989
DS                    4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG               2896.3
DW               18.000 usec
DE                11.00 usec
TE                373.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.70 usec
PL1                6.00 dB
SFO1        125.7703148 MHz

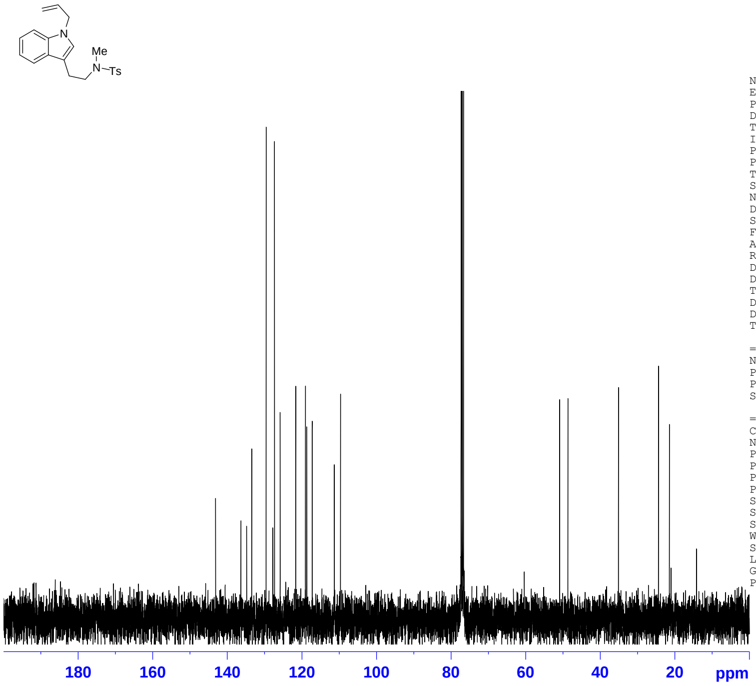
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz
SI                32768
SF          125.7577390 MHz
WDW                  EM
SSB                   0
LB                 2.00 Hz
GB                    0
PC                 1.40
```

N-(2-(1-Allyl-1H-indol-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 127



```
NAME     RS-08-093 400 MHz
EXPNO                    1
PROCNO                   1
Date_             20101110
Time                  0.38
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     181
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

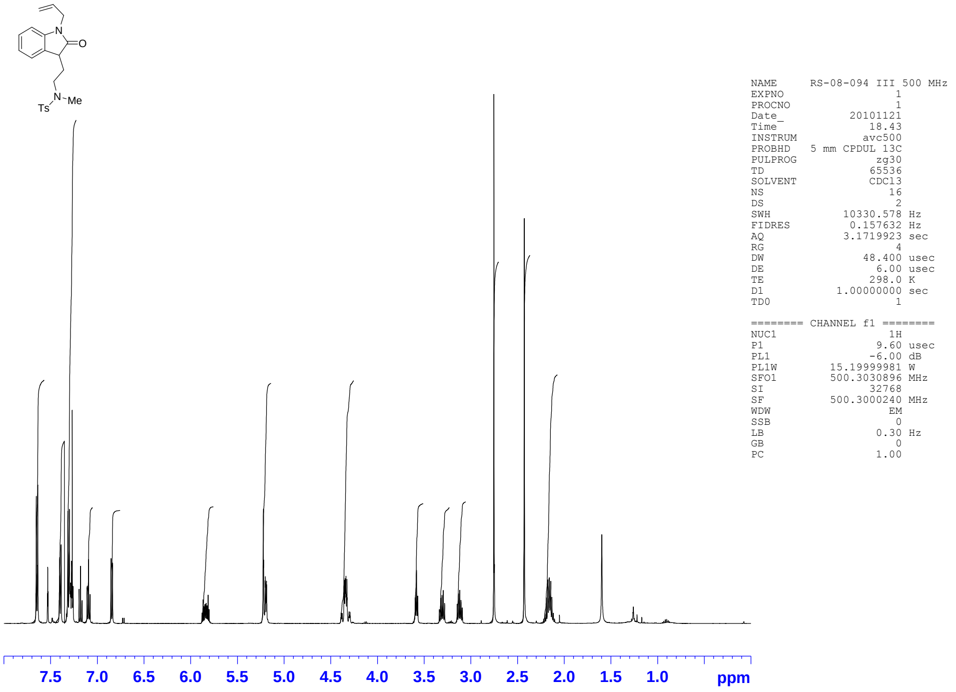


```
NAME     RS-08-093 400 MHz
EXPNO                    3
PROCNO                   1
Date_             20101110
Time                  0.50
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

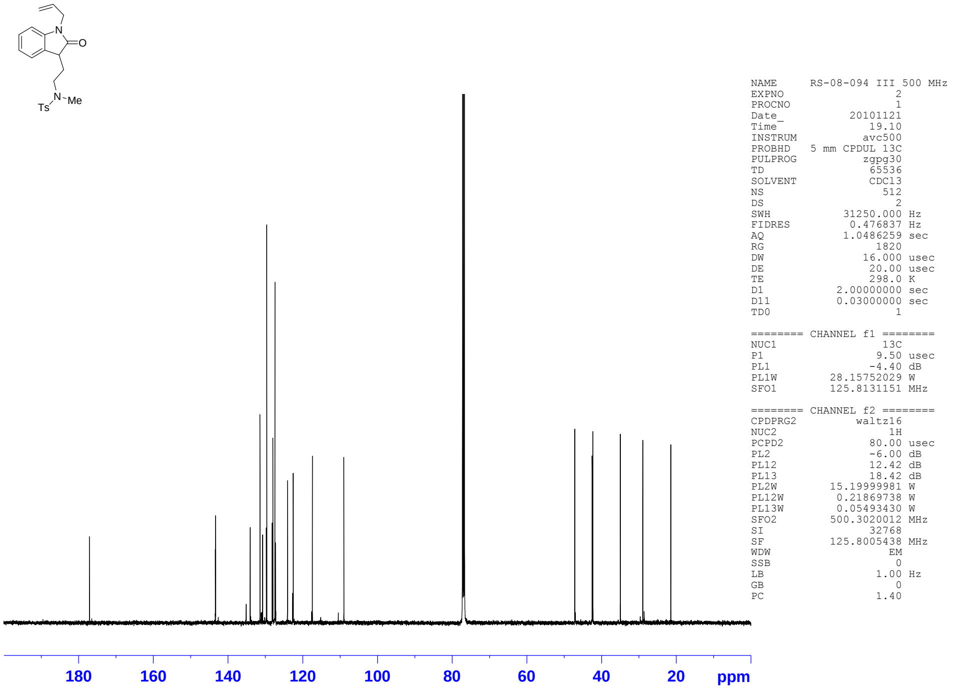
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

N-(2-(1-Allyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 128



```
NAME     RS-08-094 III 500 MHz
EXPNO                    1
PROCNO                   1
Date_             20101121
Time                 18.43
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1719923 sec
RG                       4
DW                  48.400 usec
DE                    6.00 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.60 usec
PL1                  -6.00 dB
PL1W           15.19999981 W
SFO1           500.3030896 MHz
SI                   32768
SF             500.3000240 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

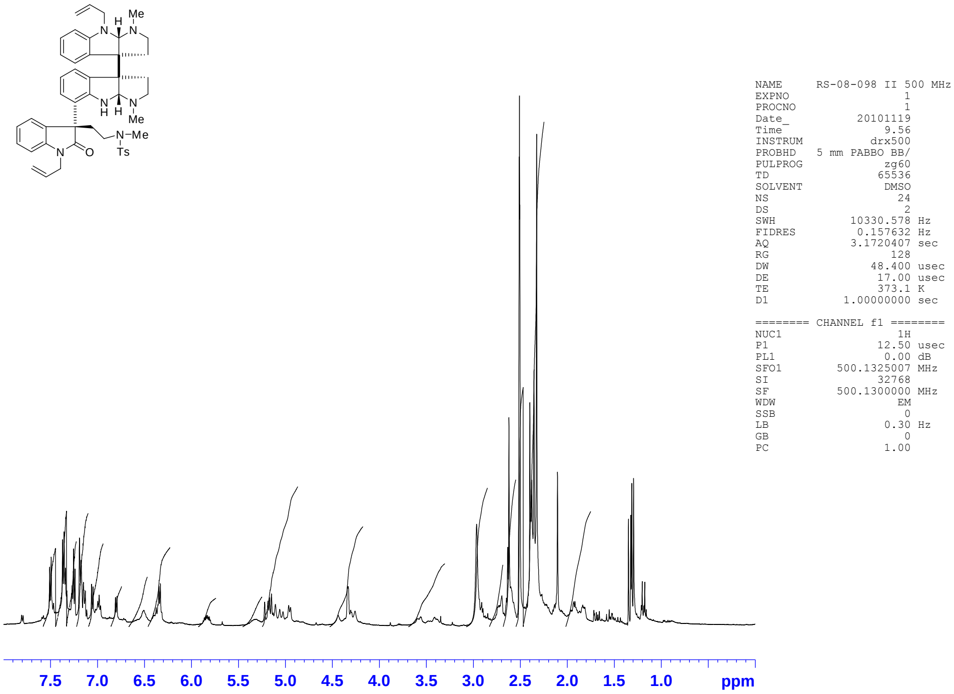


```
NAME     RS-08-094 III 500 MHz
EXPNO                    2
PROCNO                   1
Date_             20101121
Time                 19.10
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

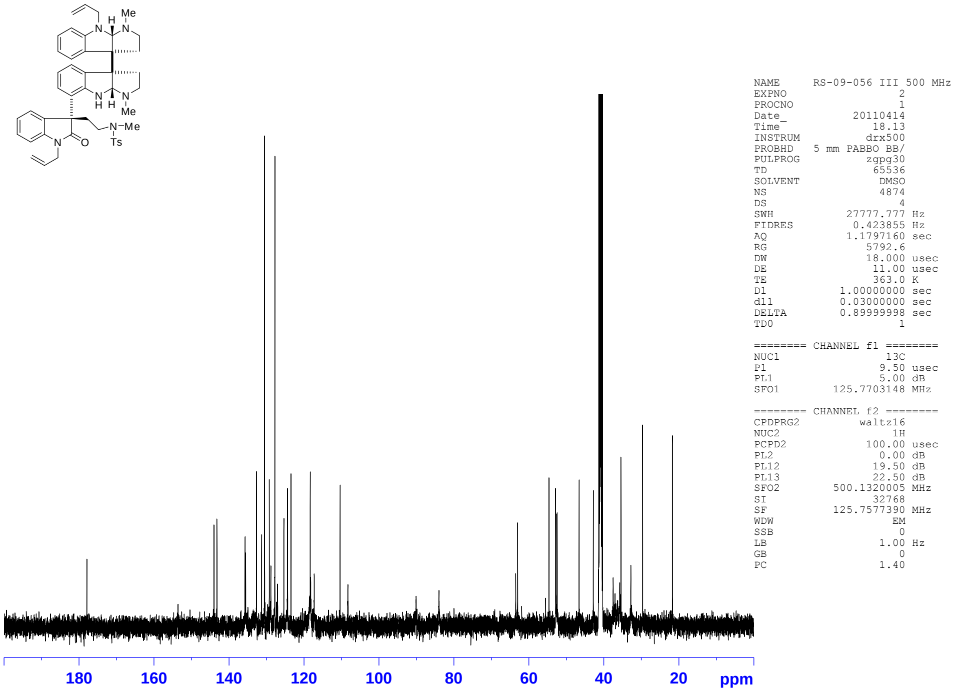
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                 18.42 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.05493430 W
SFO2           500.3020012 MHz
SI                   32768
SF             125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

N-(2-(1-Allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S* *N*-(2-(1-allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 129



```
NAME     RS-08-098 II 500 MHz
EXPNO                   1
PROCNO                  1
Date_            20101119
Time                 9.56
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG              zg60
TD                  65536
SOLVENT              DMSO
NS                     24
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                    128
DW                 48.400 usec
DE                  17.00 usec
TE                  373.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  12.50 usec
PL1                  0.00 dB
SFO1          500.1325007 MHz
SI                  32768
SF            500.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

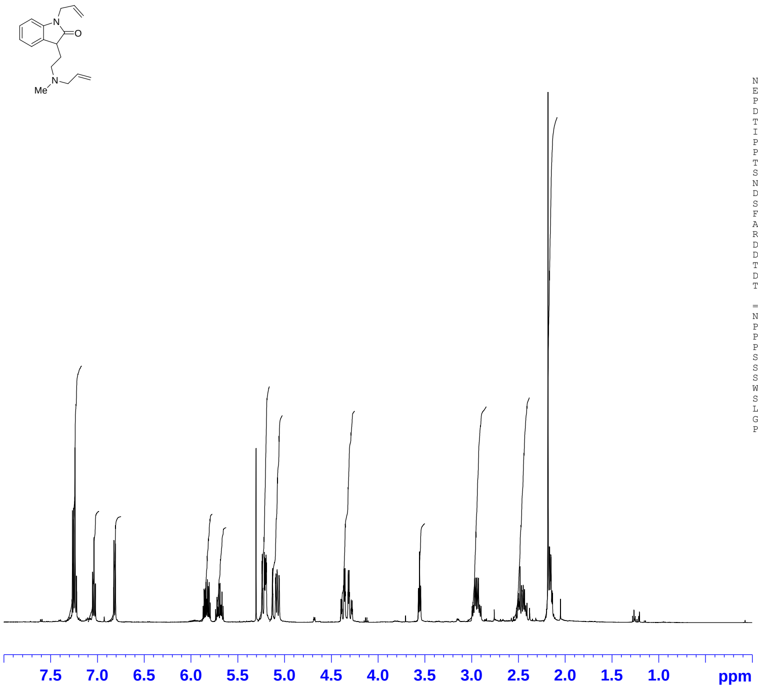


```
NAME     RS-09-056 III 500 MHz
EXPNO                   2
PROCNO                  1
Date_            20110414
Time                18.13
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                  65536
SOLVENT              DMSO
NS                   4874
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                 5792.6
DW                 18.000 usec
DE                  11.00 usec
TE                  363.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  5.00 dB
SFO1          125.7703148 MHz

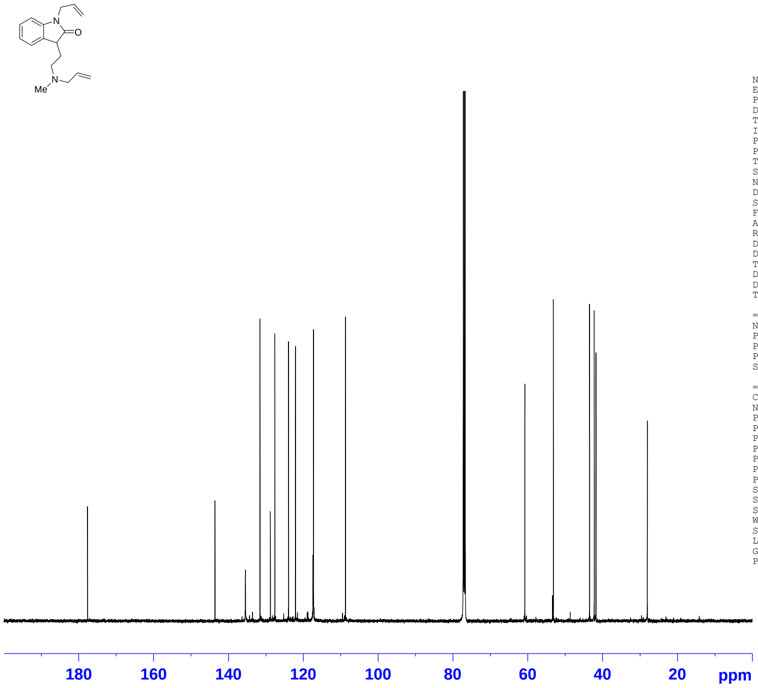
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

1-Allyl-3-(2-(allyl(methyl)amino)ethyl)indolin-2-one, 132



```
NAME     RS-09-012 (IVa) 500 MHz
EXPNO                  1
PROCNO                 1
Date_           20101210
Time                6.43
INSTRUM           avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10330.578 Hz
FIDRES          0.157632 Hz
AQ             3.1719923 sec
RG                     4
DW                48.400 usec
DE                  6.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W         15.19999981 W
SFO1         500.3030896 MHz
SI                 32768
SF           500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

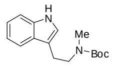


```
NAME     RS-09-012 (IVa) 500 MHz
EXPNO                  2
PROCNO                 1
Date_           20101210
Time                7.37
INSTRUM           avc500
PROBHD   5 mm CPDUL 13C
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     2
SWH            31250.000 Hz
FIDRES          0.476837 Hz
AQ             1.0486259 sec
RG                  1820
DW                16.000 usec
DE                 20.00 usec
TE                 298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

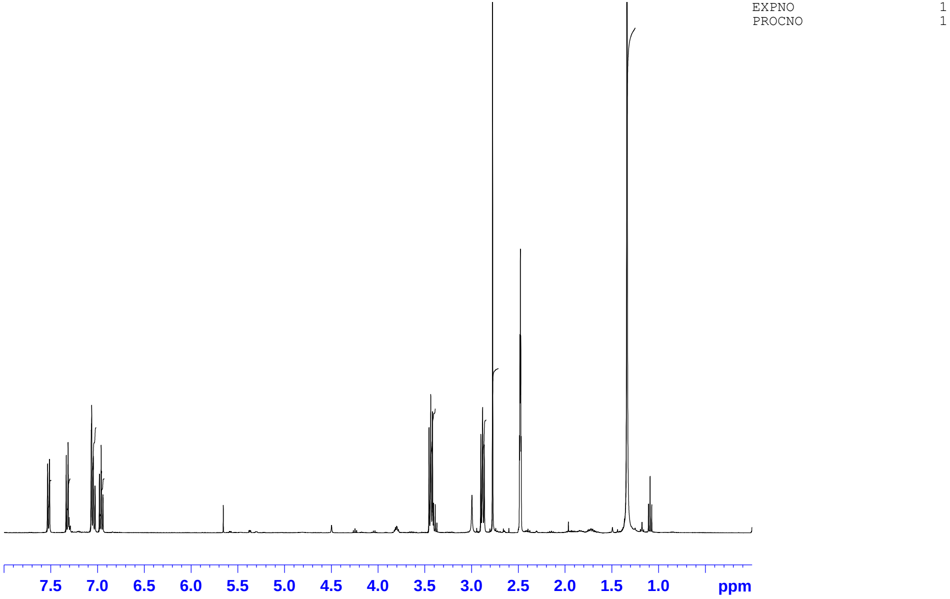
======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                -4.40 dB
PL1W         28.15752029 W
SFO1         125.8131151 MHz

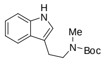
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W         15.19999981 W
PL12W         0.21869738 W
PL13W         0.05493430 W
SFO2         500.3020012 MHz
SI                 32768
SF           125.8005438 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

tert-Butyl 2-(1H-indol-3-yl)ethyl(methyl)carbamate, 133

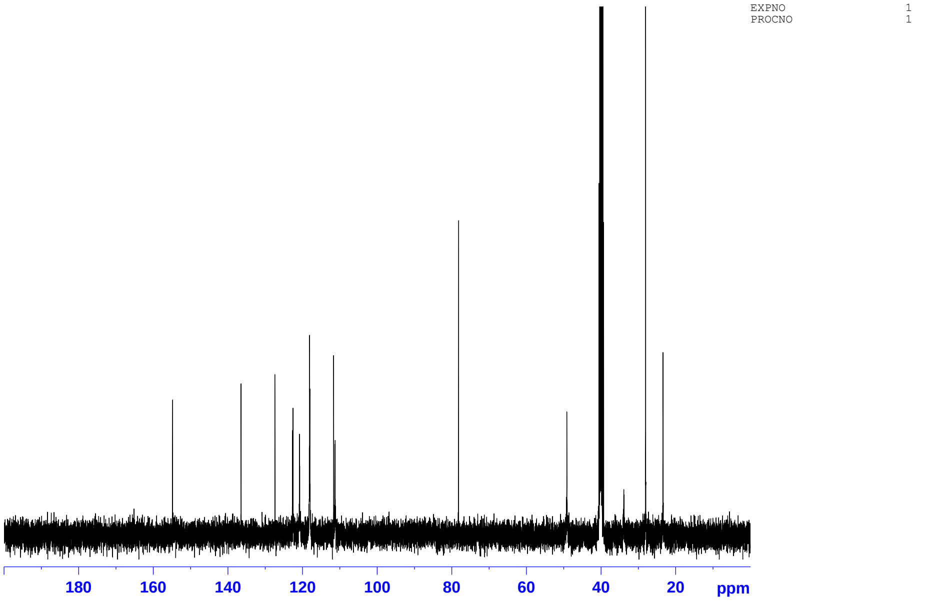


^{1}H (400 MHz, DMSO, 90 °C)

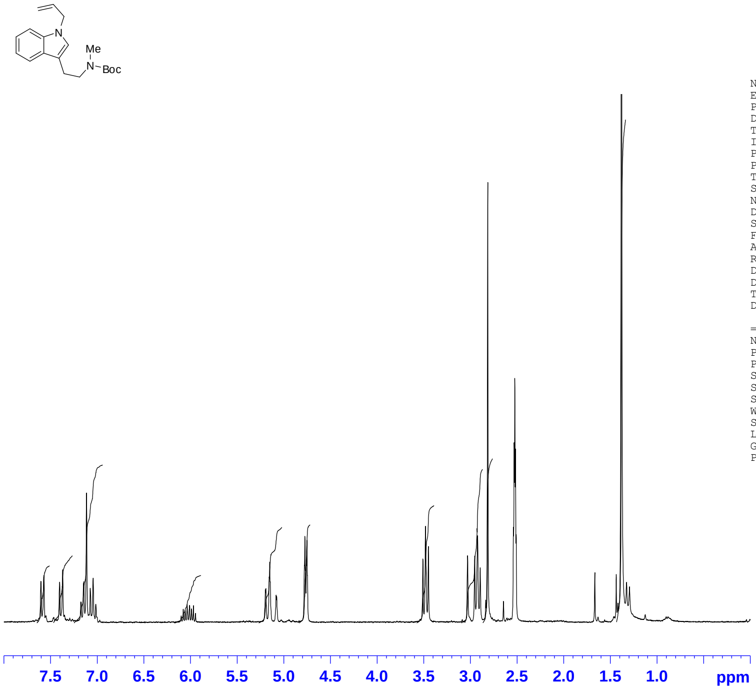




^{13}C (100 MHz, DMSO, 90 °C)

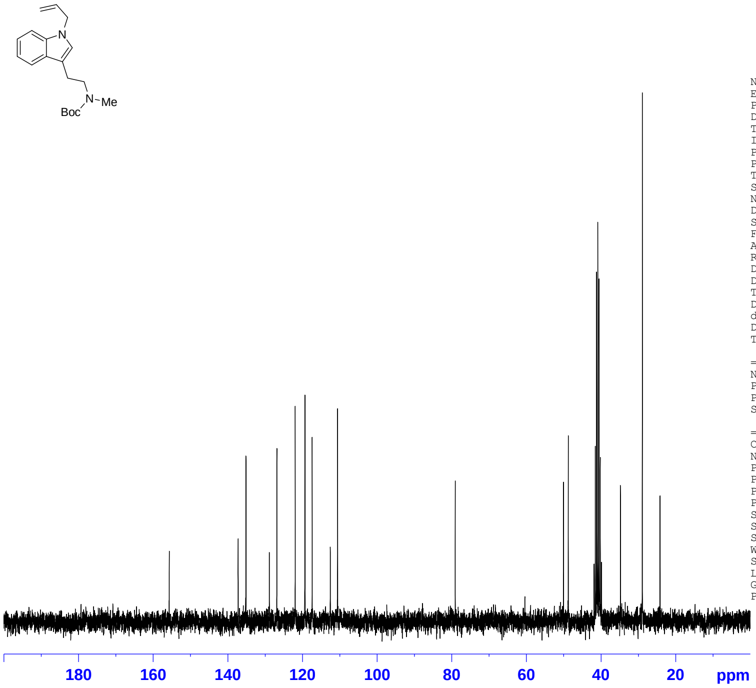


tert-Butyl (2-(1-allyl-1H-indol-3-yl)ethyl)(methyl)carbamate, 134



```
NAME          RS-09-082
EXPNO                 1
PROCNO                1
Date_          20110328
Time              10.07
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   12
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  512
DW              100.200 usec
DE                 6.00 usec
TE                363.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                0.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1299972 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

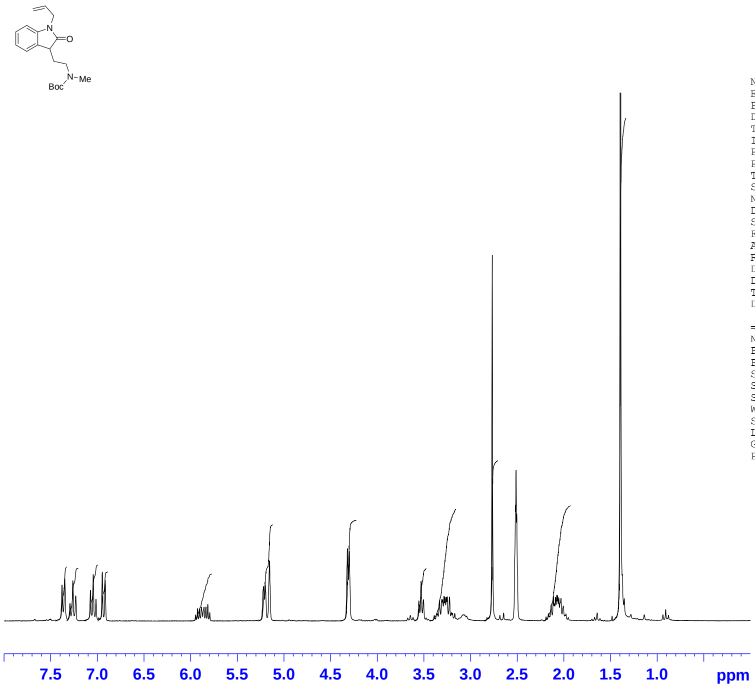


```
NAME          RS-10-048
EXPNO                 2
PROCNO                1
Date_          20110407
Time              15.36
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  103
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG                13004
DW               31.800 usec
DE                30.00 usec
TE                373.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

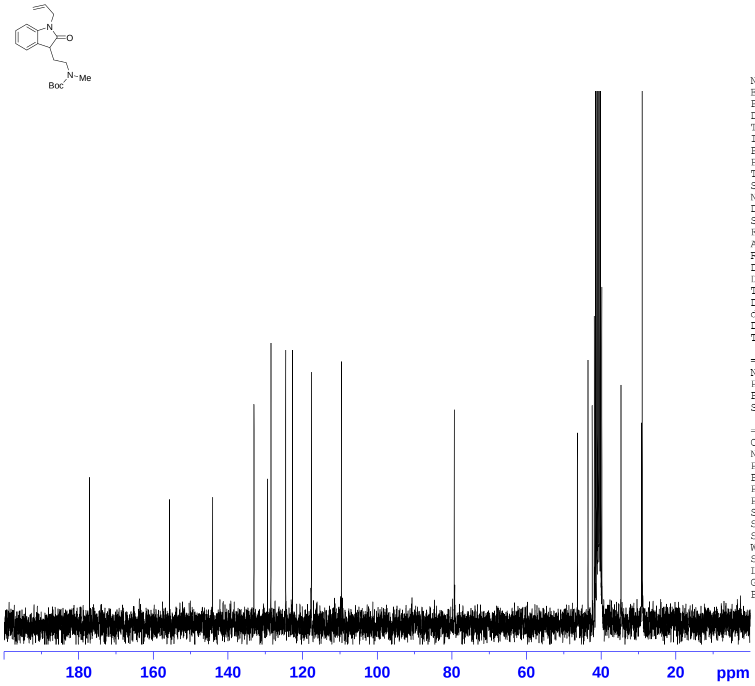
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

tert-Butyl (2-(1-allyl-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 135



```
NAME       RS-09-083 VT
EXPNO                 1
PROCNO                1
Date_          20110311
Time              14.10
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   19
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  362
DW              100.200 usec
DE                 6.00 usec
TE                363.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

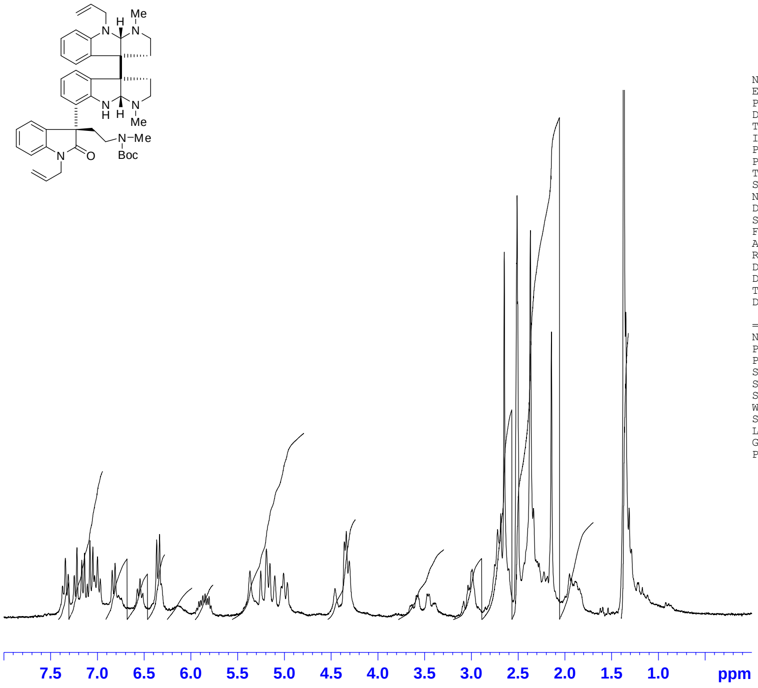


```
NAME       RS-09-083 VT
EXPNO                 2
PROCNO                1
Date_          20110311
Time              14.12
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                 1238
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG                16384
DW               31.800 usec
DE                30.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

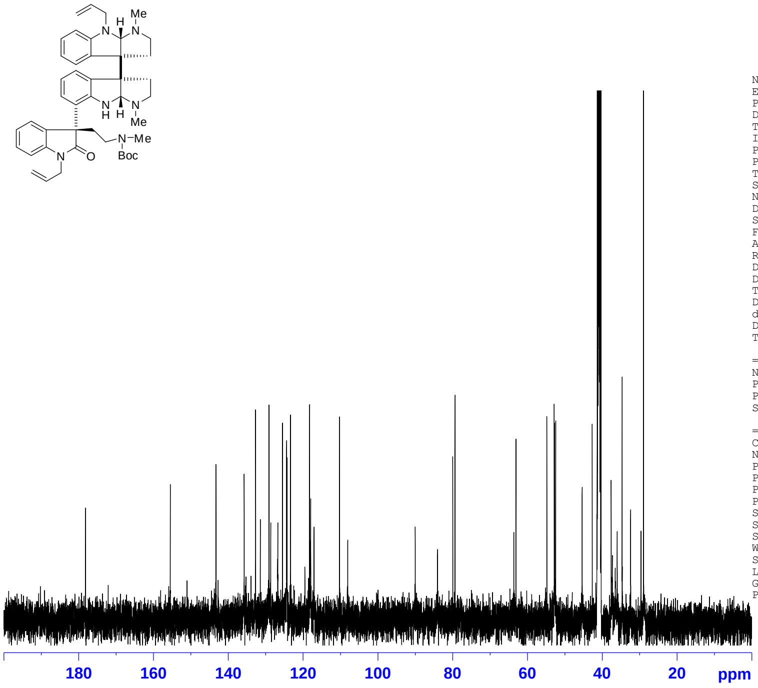
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

tert-Butyl (2-(1-allyl-3-((3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-allyl-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-7-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 137



```
NAME        RS-10-034 I
EXPNO                 1
PROCNO                1
Date_          20110330
Time              18.42
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   23
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  362
DW              100.200 usec
DE                 6.00 usec
TE                373.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

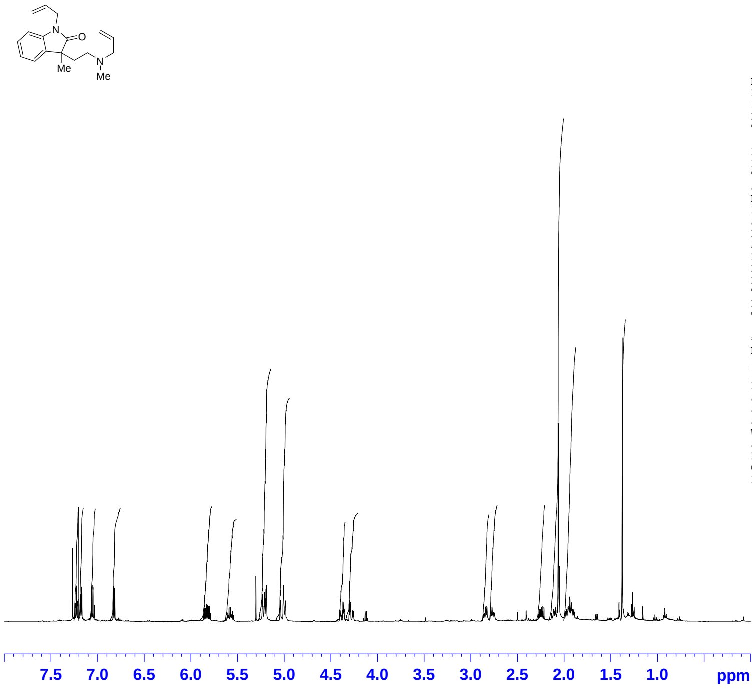


```
NAME     RS-10-034 I 500 MHz
EXPNO                 2
PROCNO                1
Date_          20110414
Time              14.45
INSTRUM          drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 5380
DS                    4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG               5792.6
DW               18.000 usec
DE                11.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                5.00 dB
SFO1        125.7703148 MHz

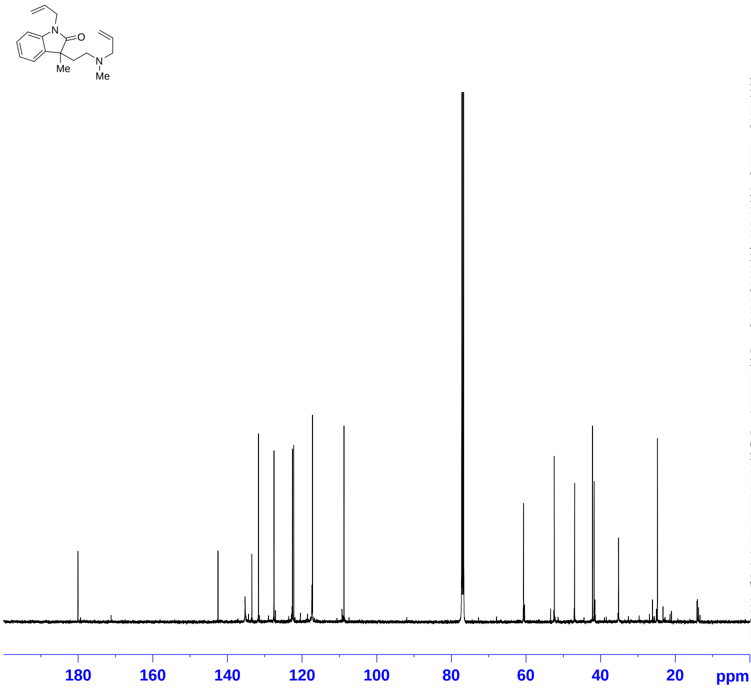
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                0.00 dB
PL12              19.50 dB
PL13              22.50 dB
SFO2        500.1320005 MHz
SI                32768
SF          125.7577390 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

1-Allyl-3-(2-(allyl(methyl)amino)ethyl)-3-methylindolin-2-one, 139



```
NAME     RS-09-068 I 500 MHz
EXPNO                     1
PROCNO                    1
Date_              20110221
Time                  17.08
INSTRUM              avc500
PROBHD   5 mm CPDUL 13C
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                3.1719923 sec
RG                        4
DW                   48.400 usec
DE                     6.00 usec
TE                    298.0 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.60 usec
PL1                   -6.00 dB
PL1W            15.19999981 W
SFO1            500.3030896 MHz
SI                    32768
SF              500.3000240 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

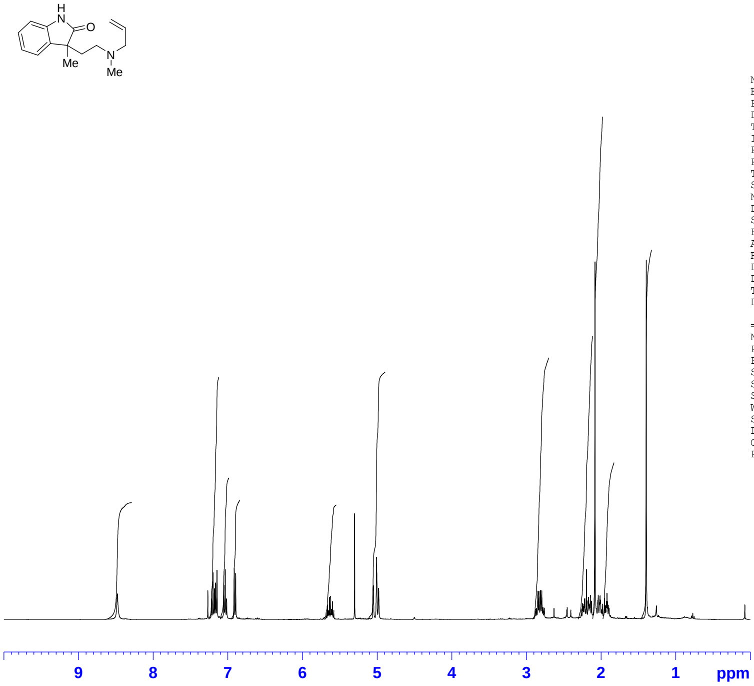


```
NAME     RS-09-068 I 500 MHz
EXPNO                     2
PROCNO                    1
Date_              20110221
Time                  18.02
INSTRUM              avc500
PROBHD   5 mm CPDUL 13C
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        2
SWH               31250.000 Hz
FIDRES             0.476837 Hz
AQ                1.0486259 sec
RG                     1820
DW                   16.000 usec
DE                    20.00 usec
TE                    298.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                   -4.40 dB
PL1W            28.15752029 W
SFO1            125.8131151 MHz

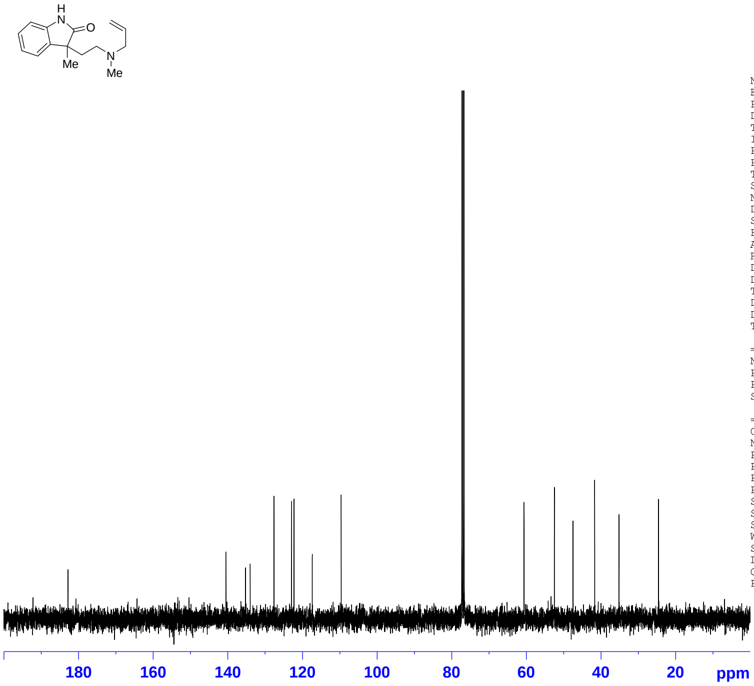
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -6.00 dB
PL12                  12.42 dB
PL13                  18.42 dB
PL2W            15.19999981 W
PL12W            0.21869738 W
PL13W            0.05493430 W
SFO2            500.3020012 MHz
SI                    32768
SF              125.8005438 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

3-(2-(Allyl(methyl)amino)ethyl)-3-methylindolin-2-one, 140



```
NAME       RS-09-070 400 MHz
EXPNO                     1
PROCNO                    1
Date_              20110218
Time                  14.17
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                      128
DW                   60.400 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1            400.2024714 MHz
SI                    32768
SF              400.2000028 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



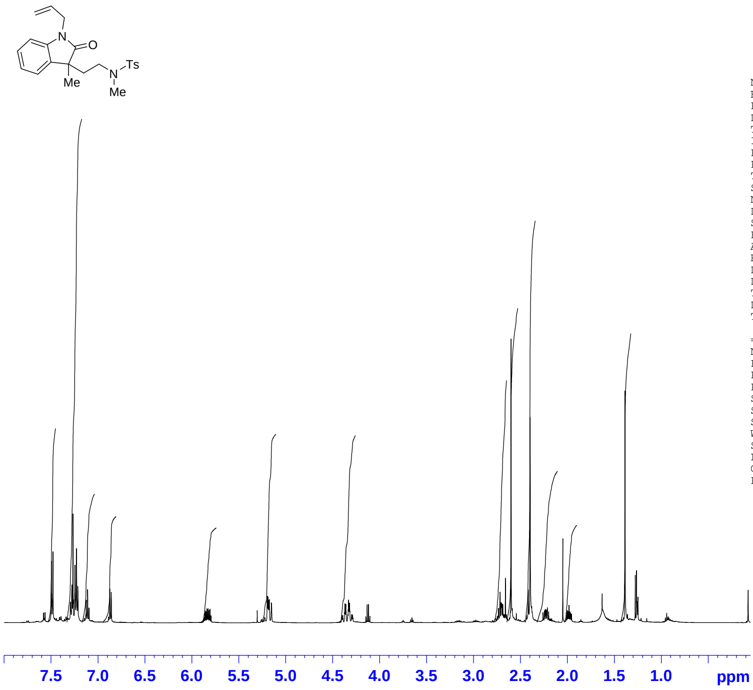
```
NAME       RS-09-070 400 MHz
EXPNO                     3
PROCNO                    1
Date_              20110218
Time                  14.28
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      256
DS                        4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                    32768
DW                   19.100 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                    0.00 dB
SFO1            100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  19.00 dB
PL13                  25.00 dB
SFO2            400.2016008 MHz
SI                    32768
SF              100.6303718 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

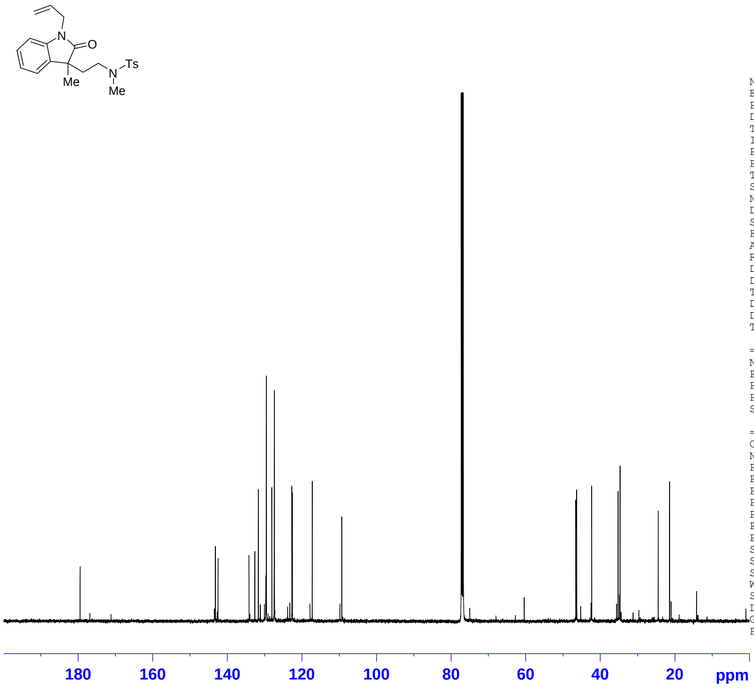
N-(2-(1-Allyl-3-methyl-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide,

142



```
NAME      RS-09-069 500 MHz
EXPNO                     1
PROCNO                    1
Date_              20110221
Time                  18.08
INSTRUM              avc500
PROBHD    5 mm CPDUL 13C
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                3.1719923 sec
RG                        4
DW                   48.400 usec
DE                     6.00 usec
TE                    298.0 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.60 usec
PL1                   -6.00 dB
PL1W            15.19999981 W
SFO1            500.3030896 MHz
SI                    32768
SF              500.3000240 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

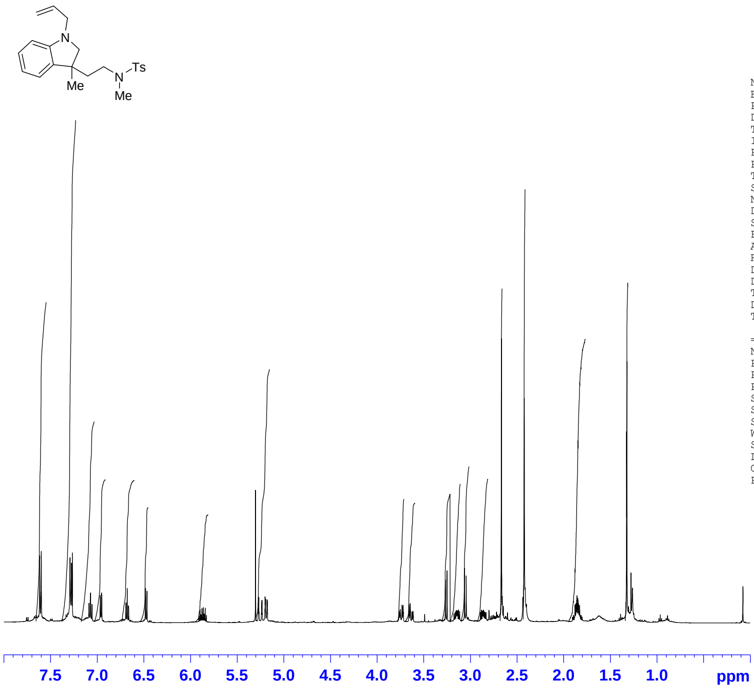


```
NAME      RS-09-069 500 MHz
EXPNO                     2
PROCNO                    1
Date_              20110221
Time                  19.02
INSTRUM              avc500
PROBHD    5 mm CPDUL 13C
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        2
SWH               31250.000 Hz
FIDRES             0.476837 Hz
AQ                1.0486259 sec
RG                      812
DW                   16.000 usec
DE                    20.00 usec
TE                    298.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                   -4.40 dB
PL1W            28.15752029 W
SFO1            125.8131151 MHz

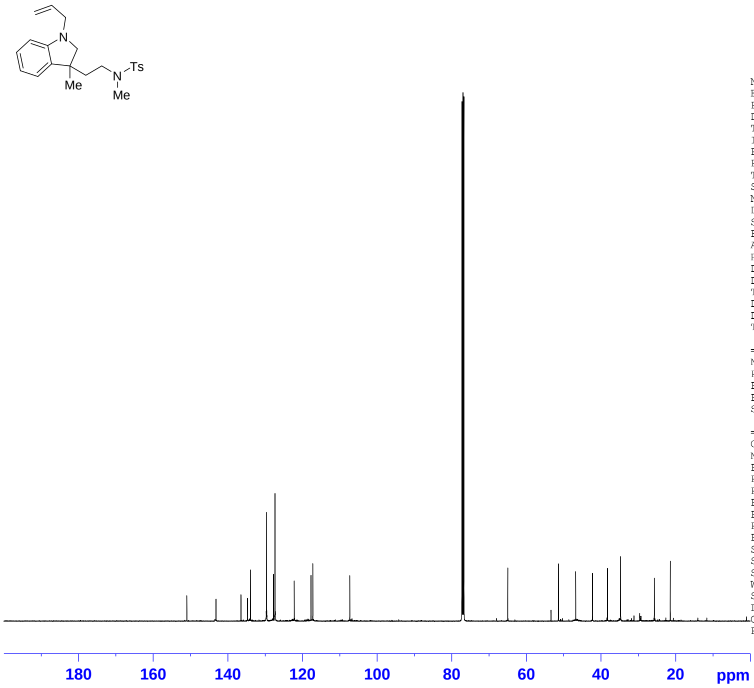
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -6.00 dB
PL12                  12.42 dB
PL13                  18.42 dB
PL2W            15.19999981 W
PL12W            0.21869738 W
PL13W            0.05493430 W
SFO2            500.3020012 MHz
SI                    32768
SF              125.8005438 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

N-(2-(1-Allyl-3-methylindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, Table 28, Entry 1



```
NAME     RS-09-072 500 MHz
EXPNO                    1
PROCNO                   1
Date_             20110222
Time                  8.22
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1719923 sec
RG                       4
DW                  48.400 usec
DE                    6.00 usec
TE                   298.0 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.60 usec
PL1                  -6.00 dB
PL1W           15.19999981 W
SFO1           500.3030896 MHz
SI                   32768
SF             500.3000240 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

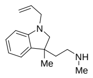


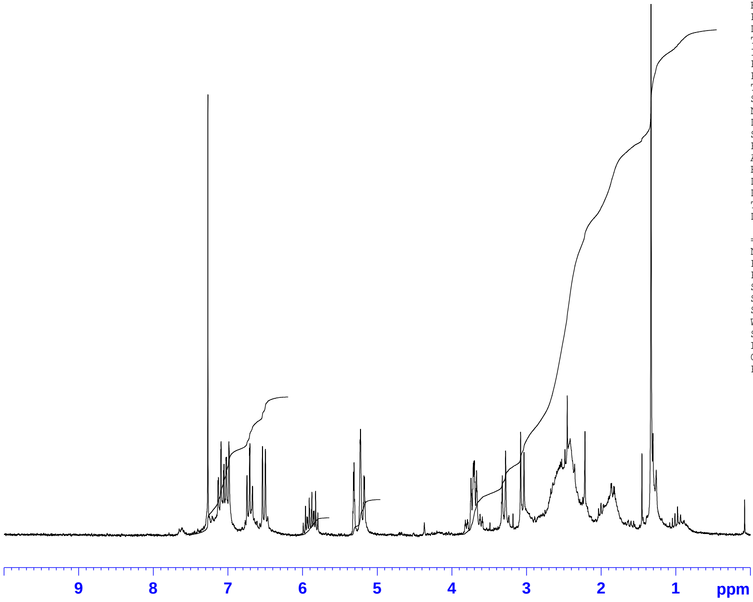
```
NAME     RS-09-072 500 MHz
EXPNO                    2
PROCNO                   1
Date_             20110222
Time                  9.15
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       2
SWH             31250.000 Hz
FIDRES           0.476837 Hz
AQ              1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                 18.42 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.05493430 W
SFO2           500.3020012 MHz
SI                   32768
SF             125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

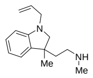
2-(1-Allyl-3-methylindolin-3-yl)-*N*-methylethanamine, Table 28, Entry 2

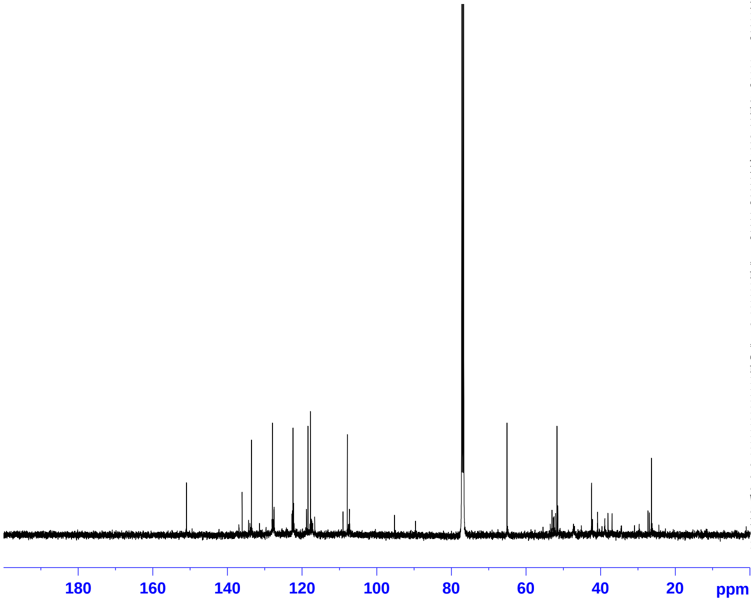




```
NAME     RS-10-029 200 MHz
EXPNO                    1
PROCNO                   1
Date_             20110331
Time                 16.01
INSTRUM             dpx200
PROBHD   5 mm Dual 13C/
PULPROG               zg60
TD                   16384
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               2796.421 Hz
FIDRES            0.170680 Hz
AQ               2.9295092 sec
RG                   912.3
DW                 178.800 usec
DE                    6.00 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    7.80 usec
PL1                  -3.00 dB
SFO1           200.1310007 MHz
SI                   32768
SF             200.1300125 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



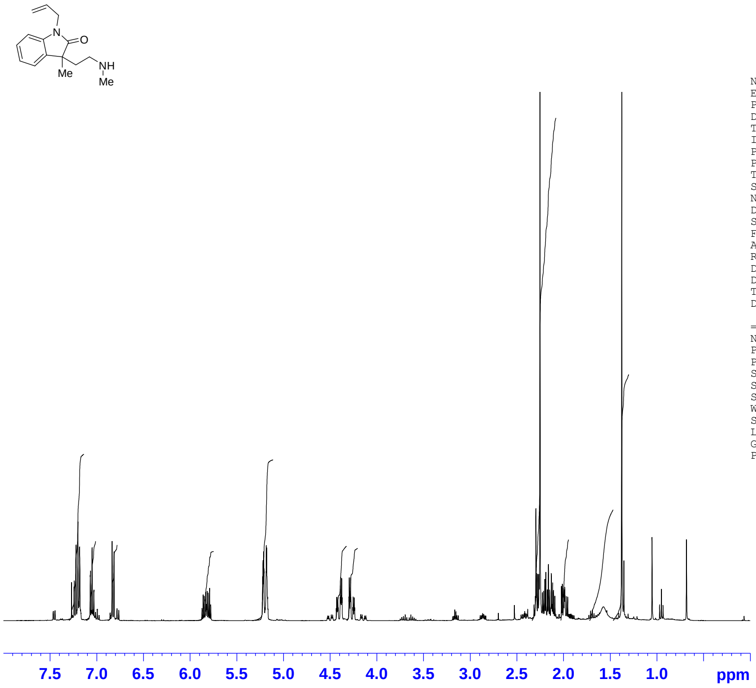


```
NAME     RS-10-029 500 MHz 1
EXPNO                    2
PROCNO                   1
Date_             20110408
Time                 13.29
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.10 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

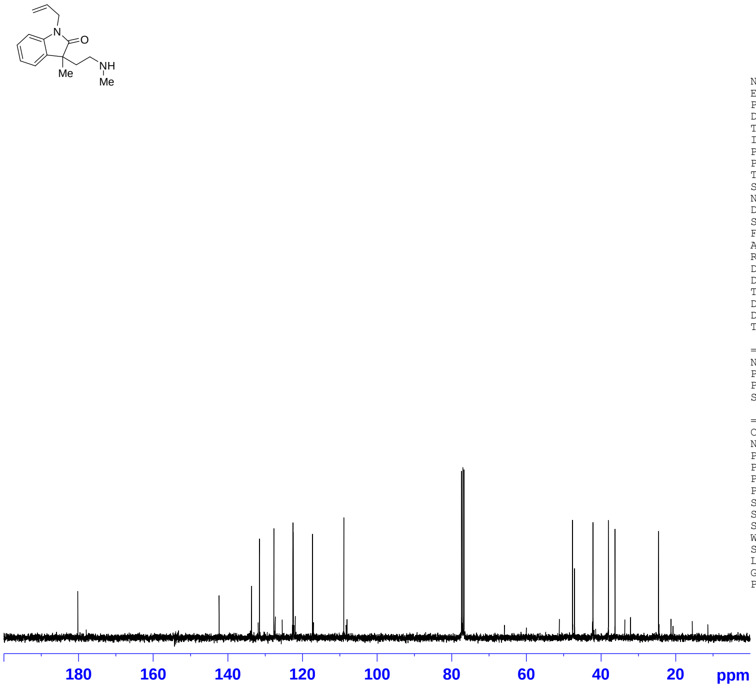
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                 18.42 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.05493430 W
SFO2           500.3020012 MHz
SI                   32768
SF             125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1-Allyl-3-methyl-3-(2-(methylamino)ethyl)indolin-2-one,



```
NAME     RS-09-086 B 400 MHz
EXPNO                    1
PROCNO                   1
Date_             20110227
Time                 20.16
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                    40.3
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

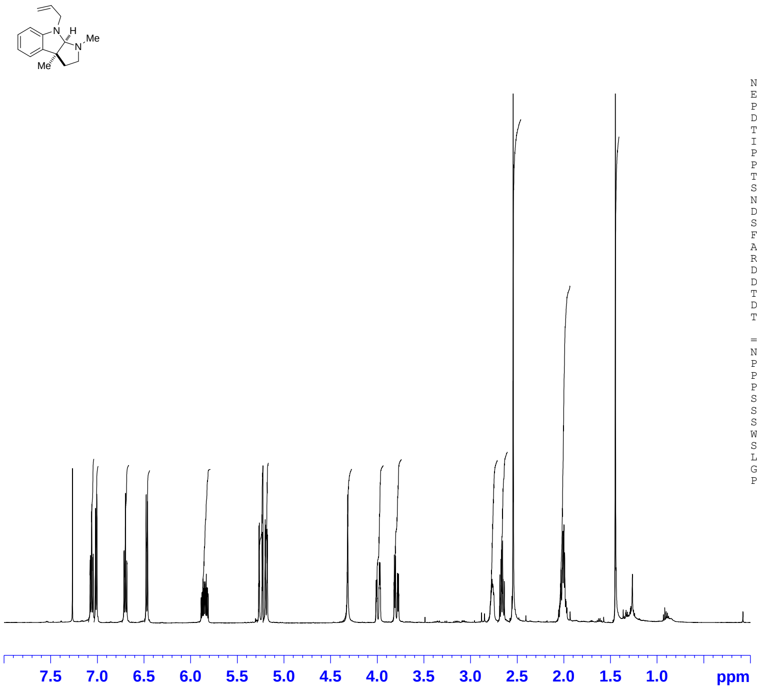


```
NAME     RS-09-086 B 400 MHz
EXPNO                    3
PROCNO                   1
Date_             20110227
Time                 20.28
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

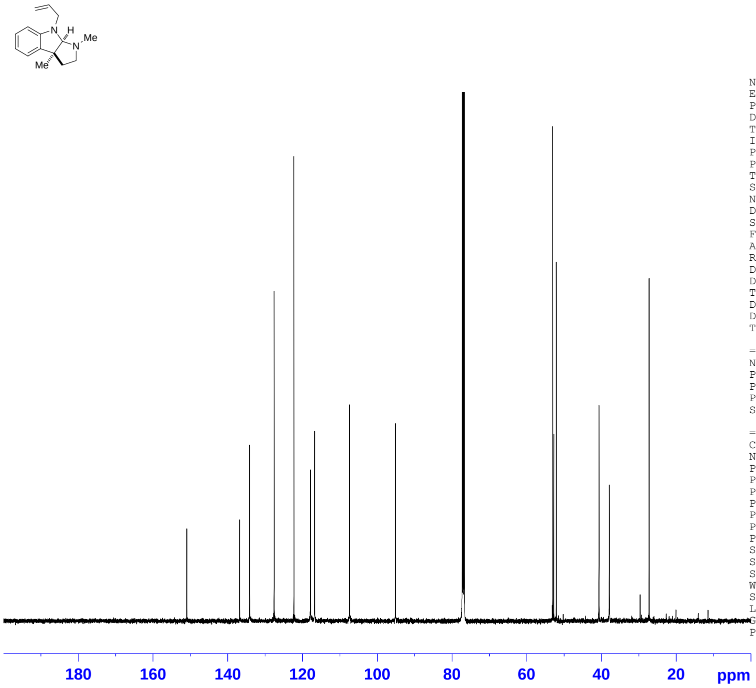
======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

8-Allyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole, *N*-allyl-desoxyeseroline, 143



```
NAME      RS-09-091 500 MHz
EXPNO                     1
PROCNO                    1
Date_              20110303
Time                   7.09
INSTRUM              avc500
PROBHD    5 mm CPDUL 13C
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1719923 sec
RG                        4
DW                   48.400 usec
DE                     6.00 usec
TE                    298.0 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.60 usec
PL1                   -6.00 dB
PL1W            15.19999981 W
SFO1            500.3030896 MHz
SI                    32768
SF              500.3000240 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

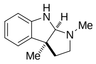


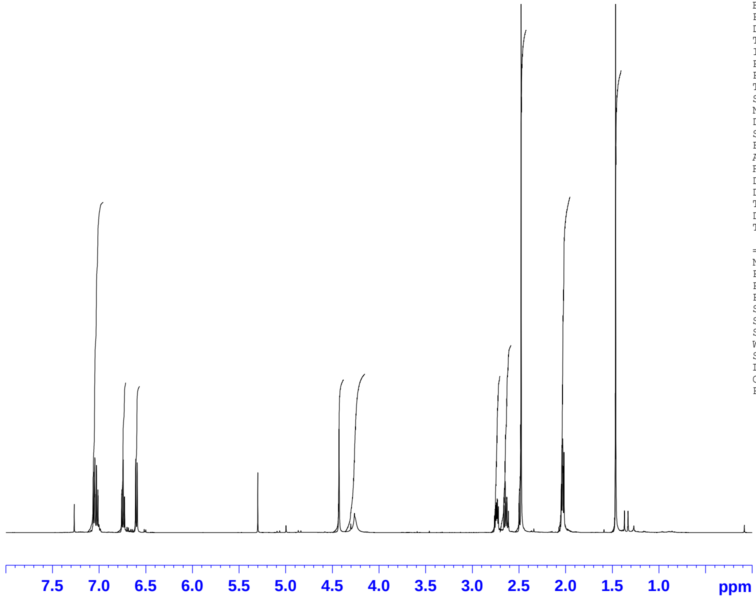
```
NAME      RS-09-091 500 MHz
EXPNO                     2
PROCNO                    1
Date_              20110303
Time                   7.36
INSTRUM              avc500
PROBHD    5 mm CPDUL 13C
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      512
DS                        2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                     1820
DW                   16.000 usec
DE                    20.00 usec
TE                    298.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                   -4.40 dB
PL1W            28.15752029 W
SFO1            125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -6.00 dB
PL12                  12.42 dB
PL13                  18.42 dB
PL2W            15.19999981 W
PL12W            0.21869738 W
PL13W            0.05493430 W
SFO2            500.3020012 MHz
SI                    32768
SF              125.8005438 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

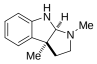
1,3a-Dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole, 144

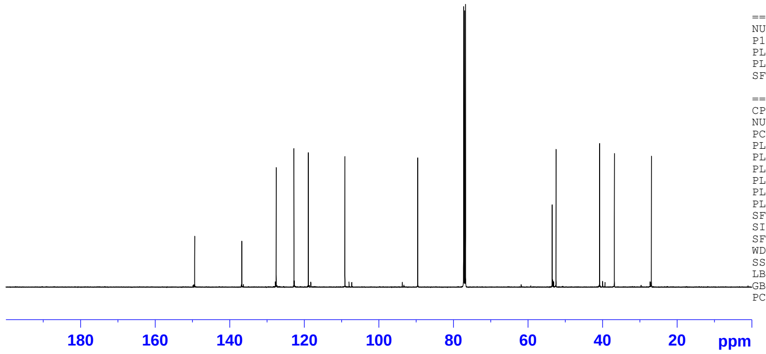




```
NAME     RS-10-001 500 MHz
EXPNO                  1
PROCNO                 1
Date_           20110307
Time               22.20
INSTRUM           avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                     4
DW               48.400 usec
DE                 6.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.60 usec
PL1                -6.00 dB
PL1W         15.19999981 W
SFO1         500.3030896 MHz
SI                 32768
SF           500.3000240 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



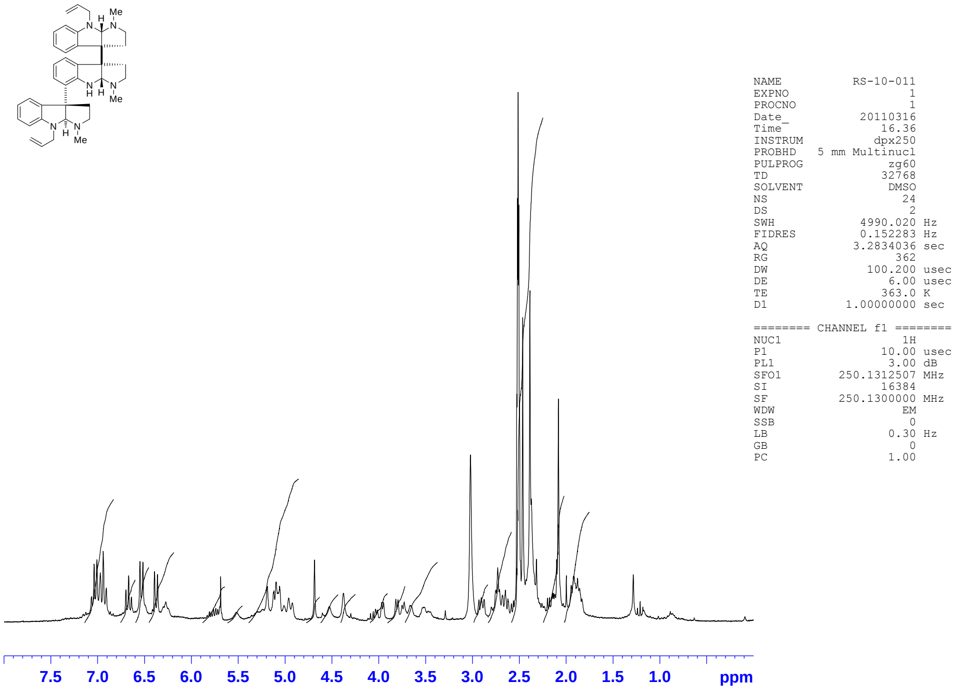


```
NAME     RS-10-001 500 MHz
EXPNO                  2
PROCNO                 1
Date_           20110307
Time               22.35
INSTRUM           avc500
PROBHD   5 mm CPDUL 13C
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                  1440
DW               16.000 usec
DE                20.00 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                -4.40 dB
PL1W         28.15752029 W
SFO1         125.8131151 MHz

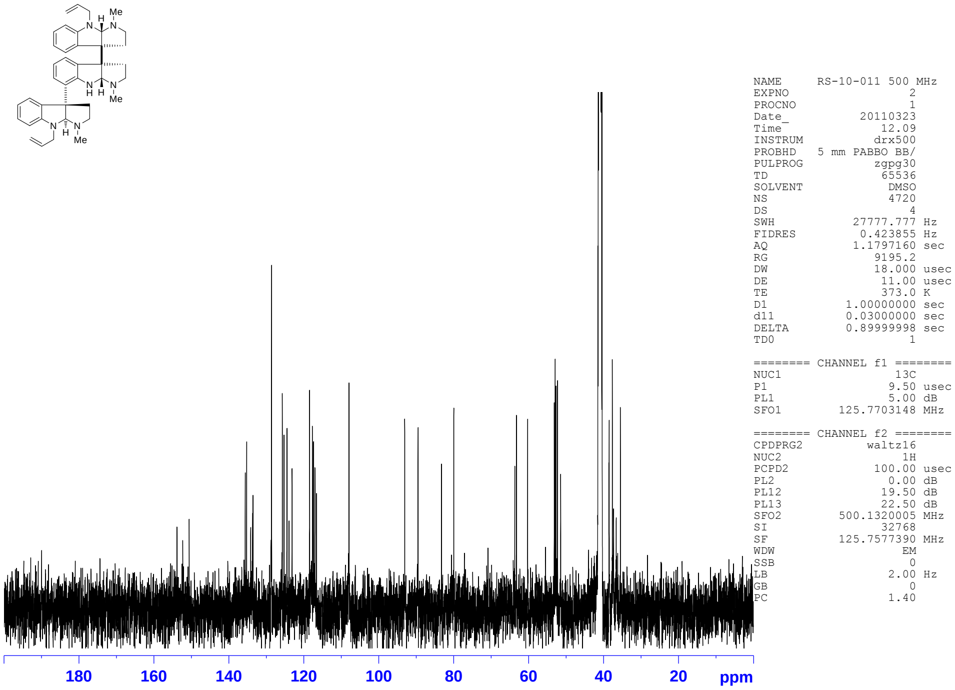
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -6.00 dB
PL12               12.42 dB
PL13               18.42 dB
PL2W         15.19999981 W
PL12W         0.21869738 W
PL13W         0.05493430 W
SFO2         500.3020012 MHz
SI                 32768
SF           125.8005438 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

(-)-(3a*R*,3'a*S*,3''a*S*,8a*S*,8'a*S*,8''a*S*)-8,8''-Diallyl-1,1',1''-trimethyl-2,2',2'',3,3',3'',8,8a,8',8'a,8'',8''a-dodecahydro-1H,1'H,1''H-3a,3'a:7',3''a-terpyrrolo[2,3-b]indole, (-)-*bis*-allyl-hodgkinsine B, 145



```
NAME           RS-10-011
EXPNO                  1
PROCNO                 1
Date_           20110316
Time               16.36
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    24
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                   362
DW               100.200 usec
DE                  6.00 usec
TE                 363.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

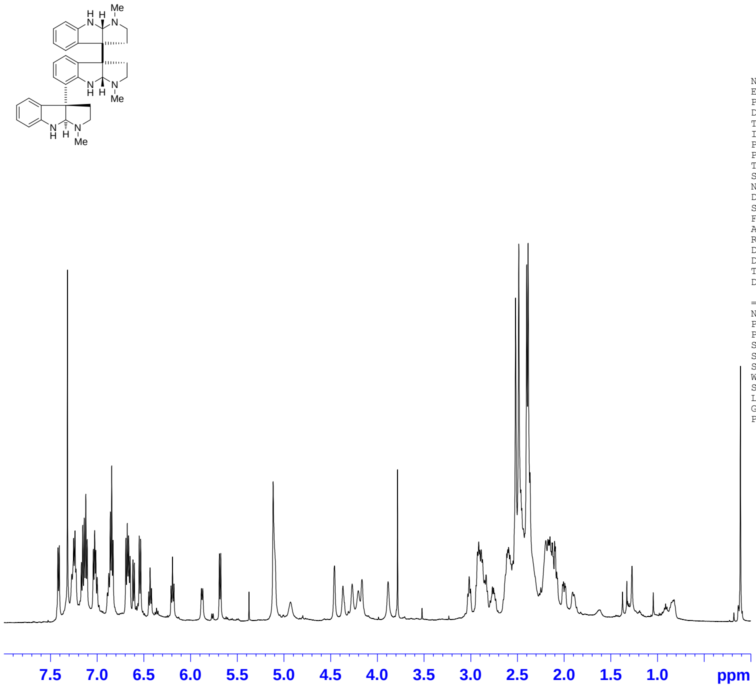


```
NAME     RS-10-011 500 MHz
EXPNO                  2
PROCNO                 1
Date_           20110323
Time               12.09
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  4720
DS                     4
SWH            27777.777 Hz
FIDRES          0.423855 Hz
AQ             1.1797160 sec
RG                9195.2
DW                18.000 usec
DE                 11.00 usec
TE                 373.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                 5.00 dB
SFO1         125.7703148 MHz

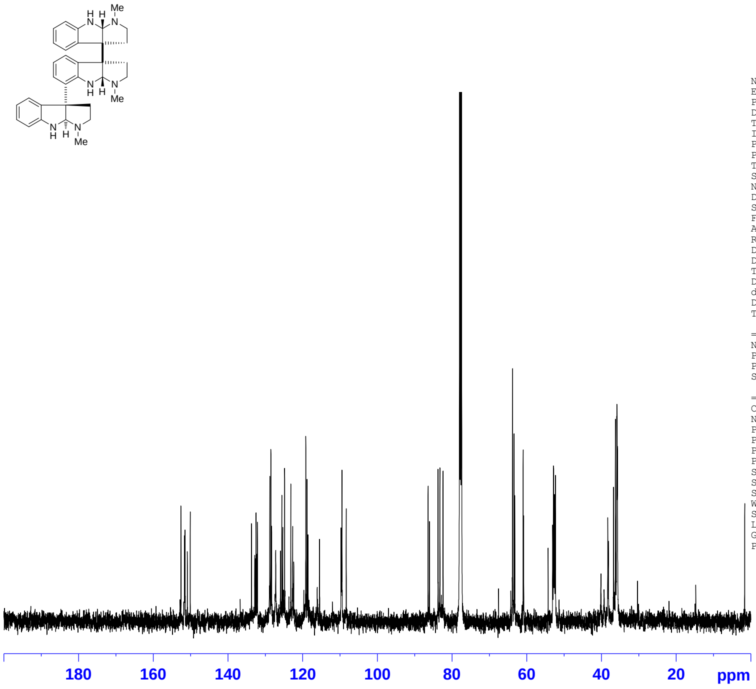
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
```

(-)-(3a*R*,3'aS,3''a*R*,8a*R*,8'aS,8''a*R*)-1,1',1''-trimethyl-2,2',2'',3,3',3'',8,8a,8',8'a,8'',8''a-dodecahydro-1H,1'H,1''H-3a,3'a:7',3''a-terpyrrolo[2,3-b]indole, (-)-hodgkinsine B, 146[i]



```
NAME     RS-10-hodgkinsine B II
EXPNO                   1
PROCNO                  1
Date_            20110419
Time                16.20
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     36
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                  101.6
DW                 48.400 usec
DE                  17.00 usec
TE                  242.9 K
D1             1.00000000 sec

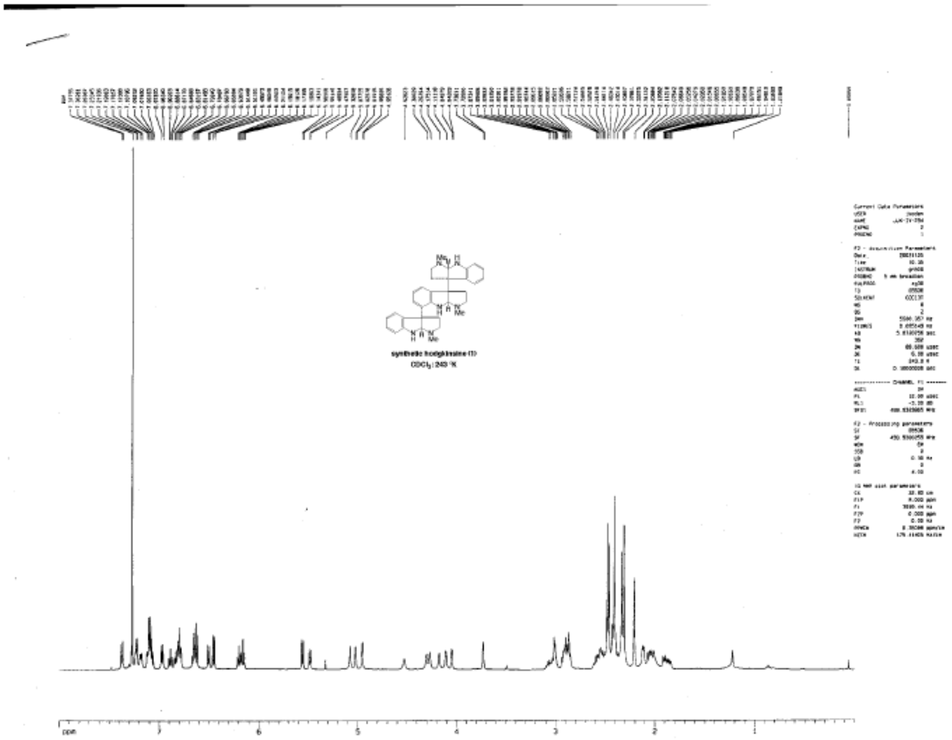
======== CHANNEL f1 ========
NUC1                   1H
P1                  12.50 usec
PL1                  0.00 dB
SFO1          500.1325007 MHz
SI                  32768
SF            500.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

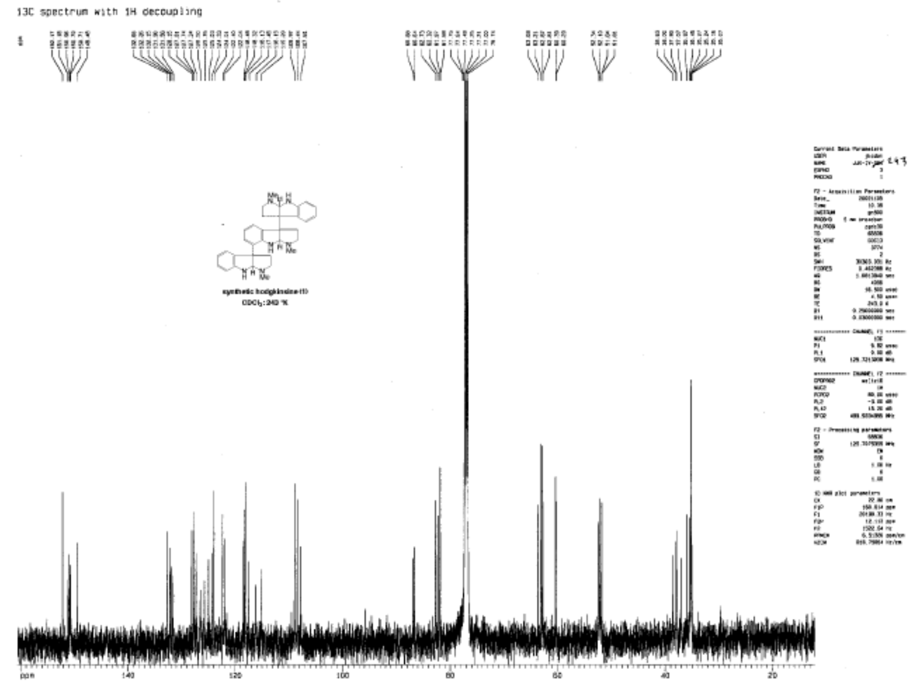


```
NAME     RS-10-hodgkinsine B II
EXPNO                   2
PROCNO                  1
Date_            20110419
Time                16.51
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1614
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                 3649.1
DW                 18.000 usec
DE                  11.00 usec
TE                  242.3 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  5.00 dB
SFO1          125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   2.00 Hz
GB                      0
PC                   1.40
```





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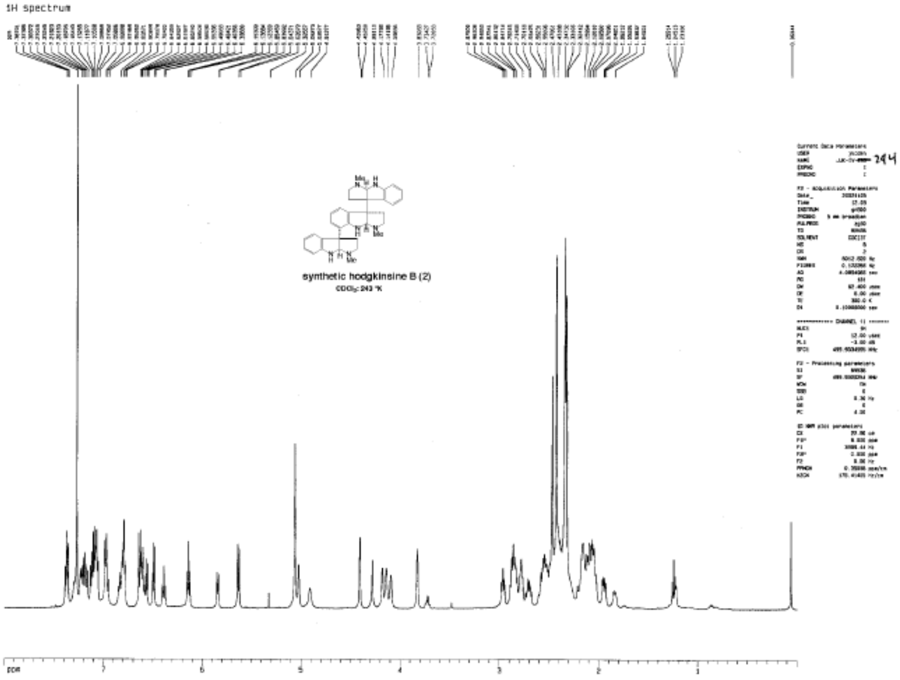
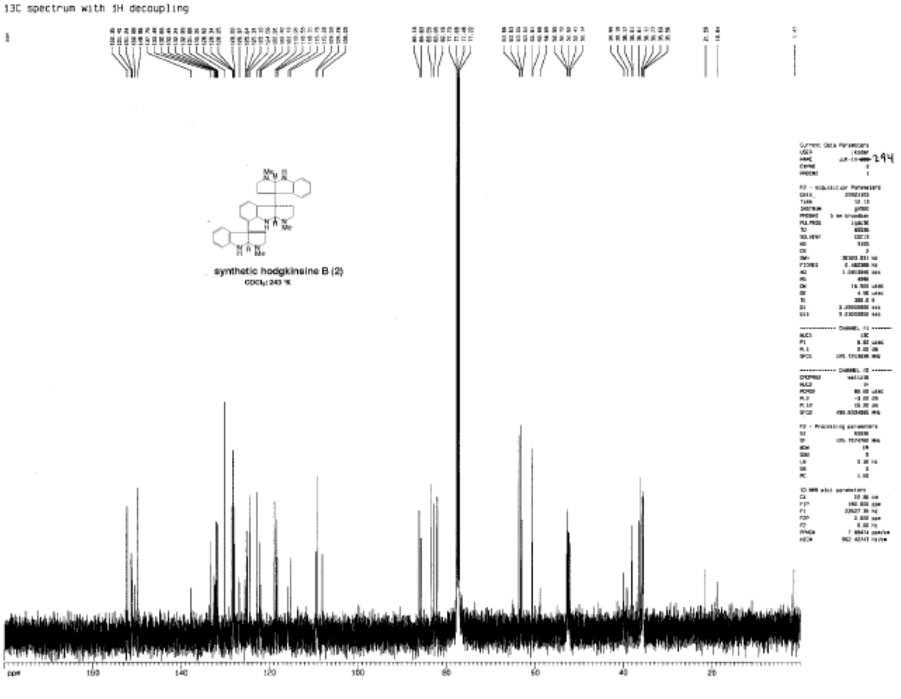
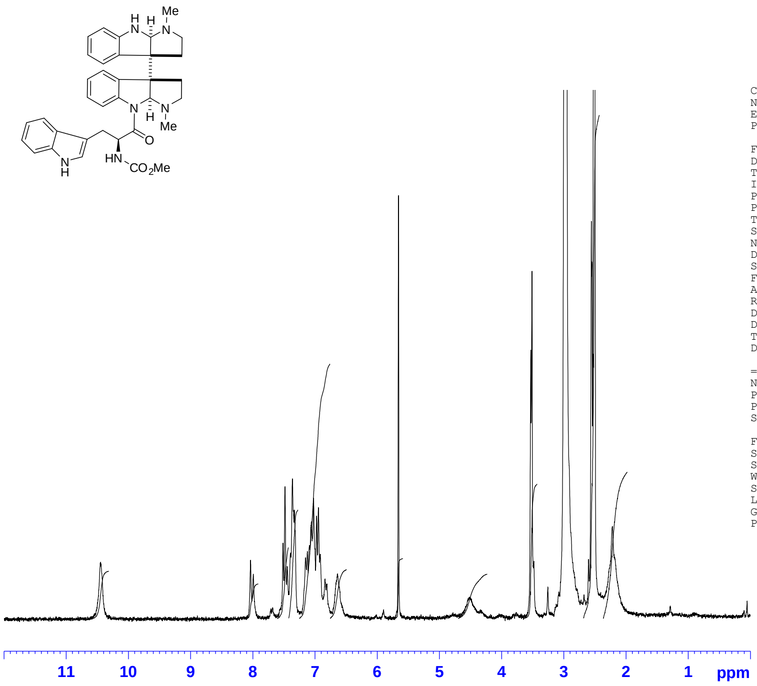
[i] *Angew. Chem. Int. Ed.*, **2003**, *42*, 2528


1H spectrum
synthetic hodgkinsine B (2)
CDCl3; 243 °K
294
ppm
7
6
5
4
3
2
1


13C spectrum with 1H decoupling
synthetic hodgkinsine B (2)
CDCl3; 243 °K
294
ppm
160
140
120
100
80
60
40
20

Methyl (2*S*)-1-(1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH)-yl)-3-(1H-indol-3-yl)-1-oxopropan-2-ylcarbamate, 148 *major isomer*



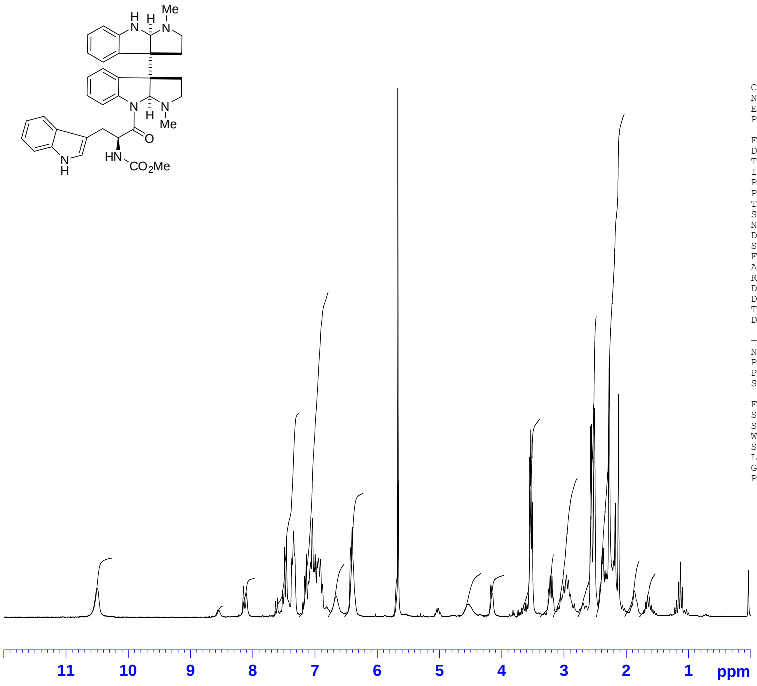
```
Current Data Parameters
NAME       RS-05-071 (I)
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091111
Time               13.49
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    26
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 322.5
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

Minor isomer



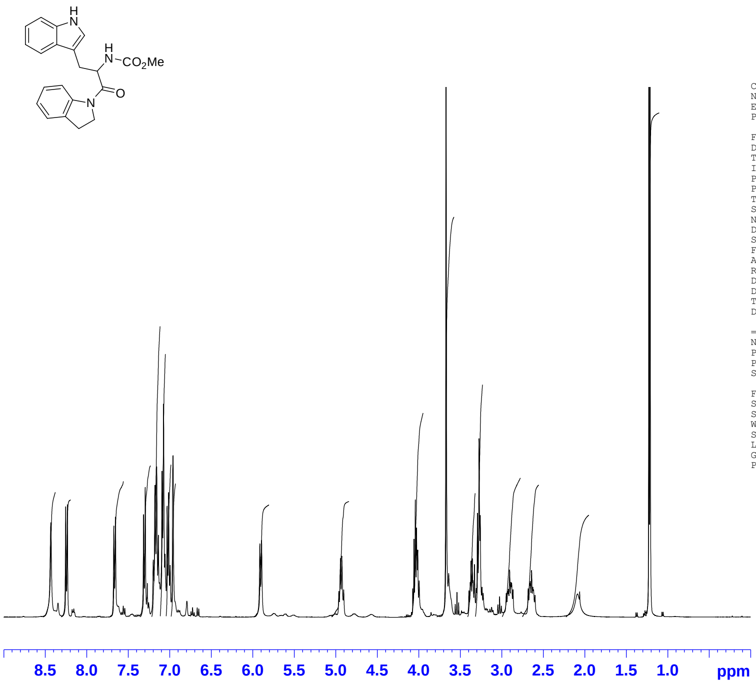
```
Current Data Parameters
NAME     RS-05-071 (II) 250 MHZ
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091111
Time               13.06
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    19
DS                     2
SWH             4990.020 Hz
FIDRES          0.152283 Hz
AQ             3.2834036 sec
RG                 287.4
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz

F2 - Processing parameters
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

Methyl 3-(1H-indol-3-yl)-1-(indolin-1-yl)-1-oxopropan-2-ylcarbamate, 150

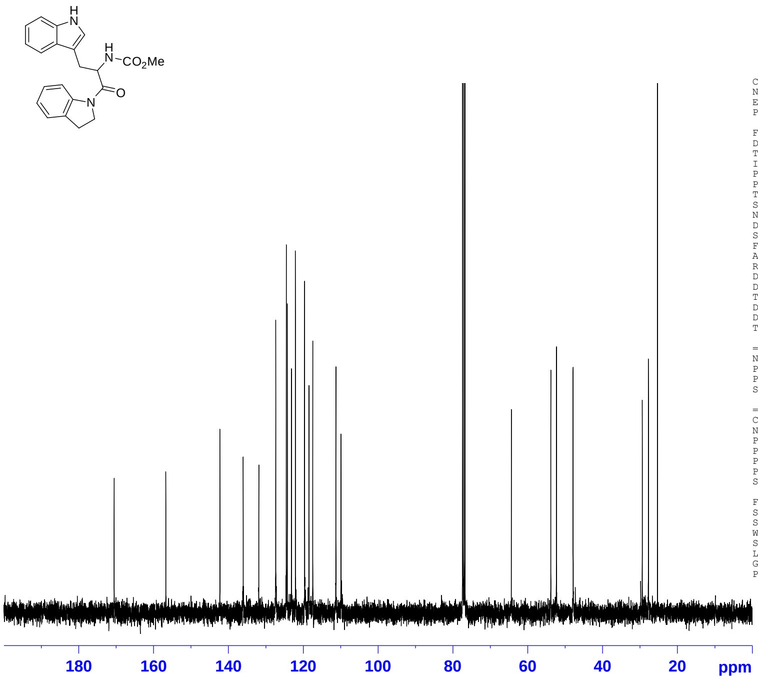


```
Current Data Parameters
NAME     RS-05-075 crude 400 MHz
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20091114
Time               0.04
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                 35.9
DW               60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz

F2 - Processing parameters
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME     RS-05-075 crude 400 MHz
EXPNO                  3
PROCNO                 1

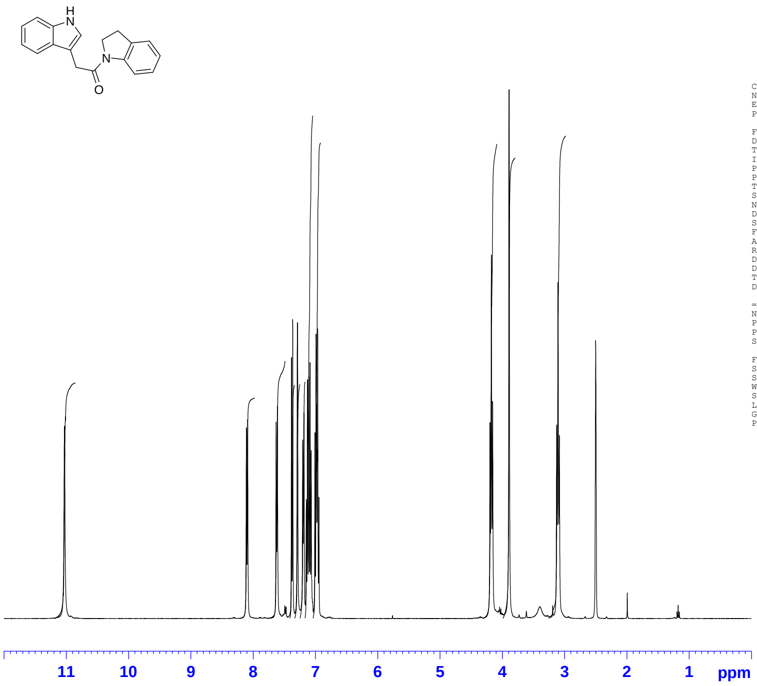
F2 - Acquisition Parameters
Date_          20091114
Time               0.15
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG         zgpg30
TD                32768
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                32768
DW               19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz

F2 - Processing parameters
SI                32768
SF          100.6303718 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

2-(1H-Indol-3-yl)-1-(indolin-1-yl)ethanone, 152

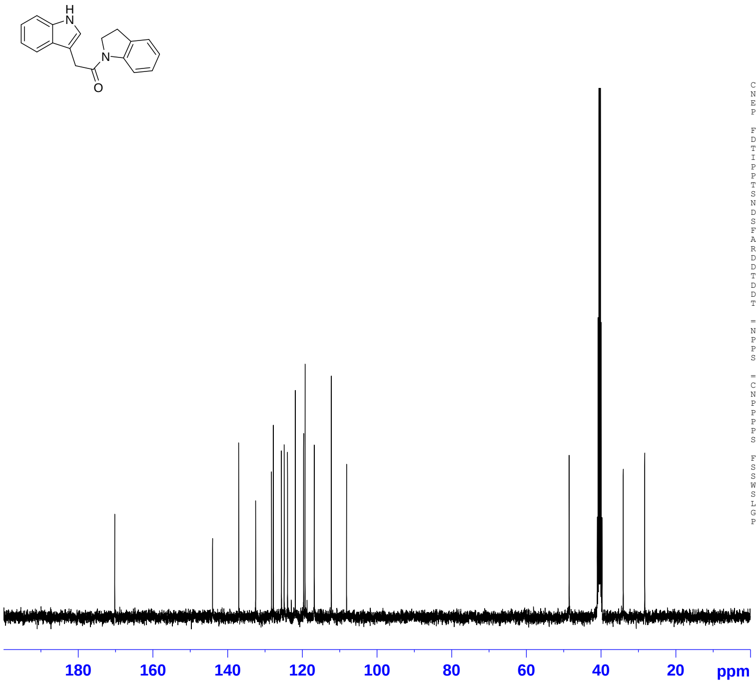


```
Current Data Parameters
NAME     RS-05-087 (II) DMSO 400 MHz
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_            20091130
Time                12.14
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                   90.5
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-05-087 (II) DMSO 400 MHz
EXPNO                       3
PROCNO                      1

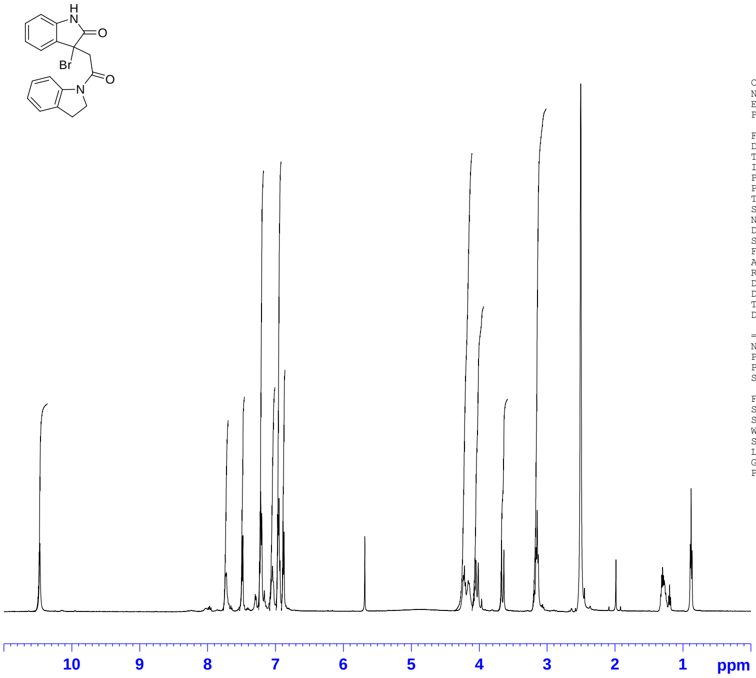
F2 - Acquisition Parameters
Date_            20091130
Time                12.25
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT              DMSO
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303300 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

3-Bromo-3-(2-(indolin-1-yl)-2-oxoethyl)indolin-2-one, 153

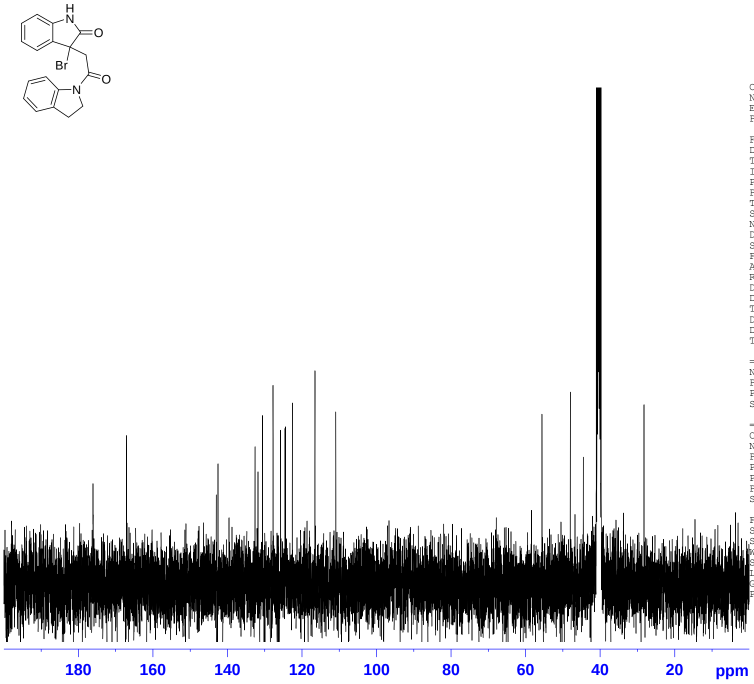


```
Current Data Parameters
NAME     RS-05-088 top spot ppt
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20091201
Time                  13.42
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       11
DS                        2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1720407 sec
RG                    161.3
DW               48.400 usec
DE                17.00 usec
TE                355.3 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                12.50 usec
PL1                0.00 dB
SFO1        500.1325007 MHz

F2 - Processing parameters
SI                    32768
SF          500.1300000 MHz
WDW                      EM
SSB                       0
LB                 0.30 Hz
GB                        0
PC                     1.00
```



```
Current Data Parameters
NAME     RS-06-017 DMSO 400 MHz
EXPNO                     2
PROCNO                    1

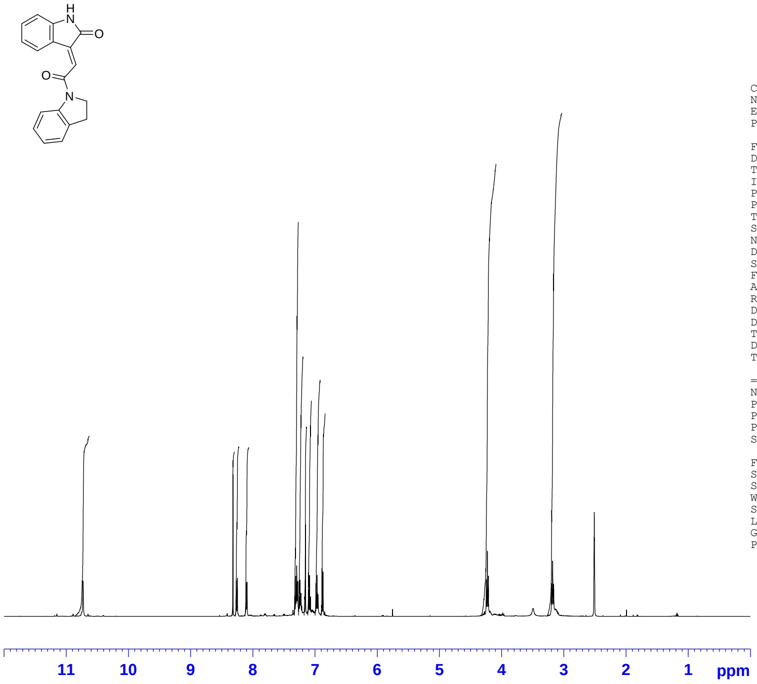
F2 - Acquisition Parameters
Date_              20100118
Time                  18.38
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG              zgpg30
TD                    32768
SOLVENT                DMSO
NS                      256
DS                        4
SWH           26178.010 Hz
FIDRES         0.798889 Hz
AQ            0.6259188 sec
RG                    32768
DW               19.100 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                 9.50 usec
PL1                0.00 dB
SFO1        100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2        400.2016008 MHz

F2 - Processing parameters
SI                    32768
SF          100.6303300 MHz
WDW                      EM
SSB                       0
LB                 1.00 Hz
GB                        0
PC                     1.40
```

(*E*)-3-(2-(Indolin-1-yl)-2-oxoethylidene)indolin-2-one, 155

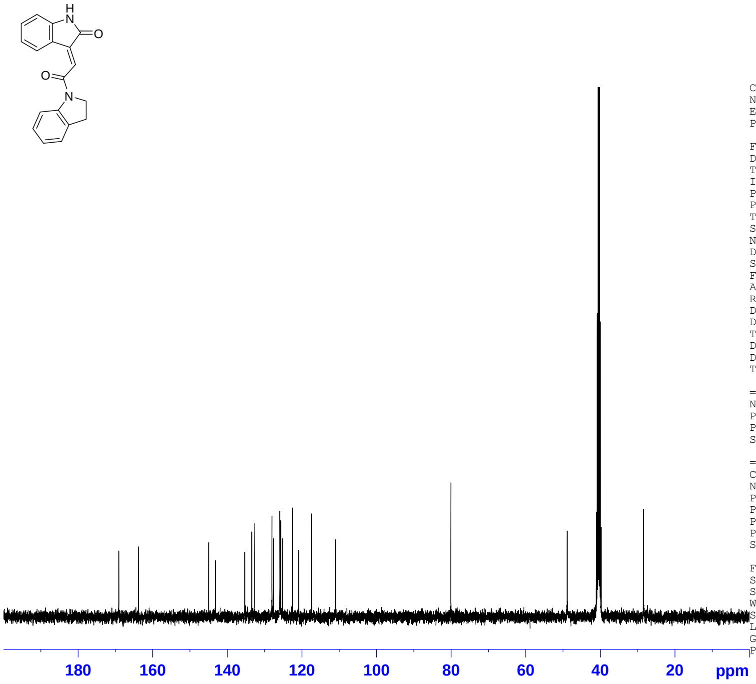


```
Current Data Parameters
NAME     RS-05-091 500 MHz
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parameters
Date_            20091207
Time                 9.30
INSTRUM            avc500
PROBHD   5 mm CPDUL 13C
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1719923 sec
RG                      4
DW                 48.400 usec
DE                   6.00 usec
TE                  298.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.60 usec
PL1                 -6.00 dB
PL1W          15.19999981 W
SFO1          500.3030896 MHz

F2 - Processing parameters
SI                  32768
SF            500.3000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-05-091 400 MHz
EXPNO                   2
PROCNO                  1

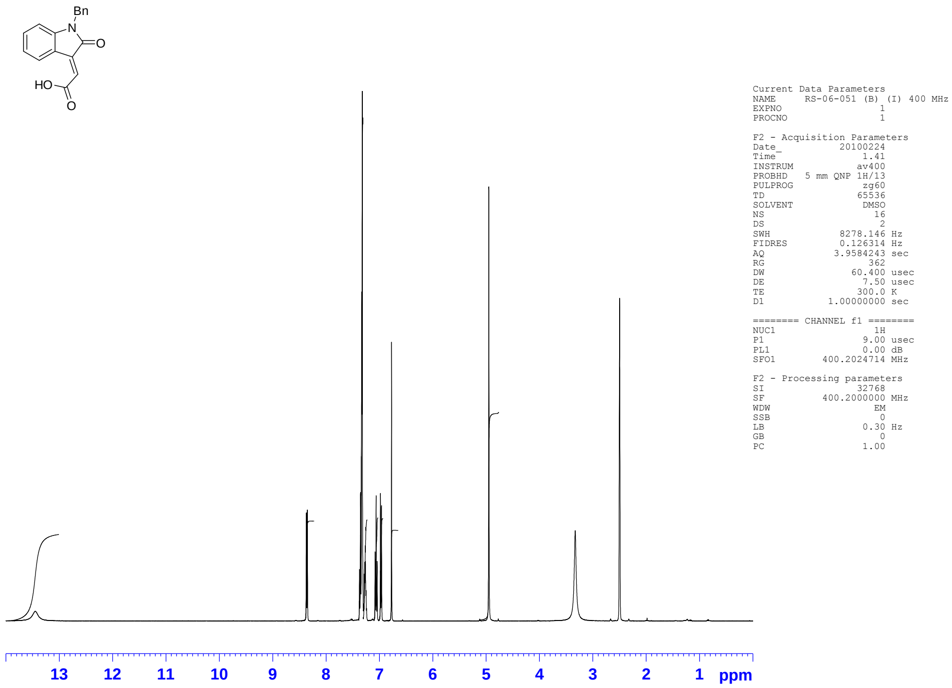
F2 - Acquisition Parameters
Date_            20091208
Time                20.26
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT              DMSO
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303300 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

(*E*)-2-(1-Benzyl-2-oxoindolin-3-ylidene)acetic acid, 158

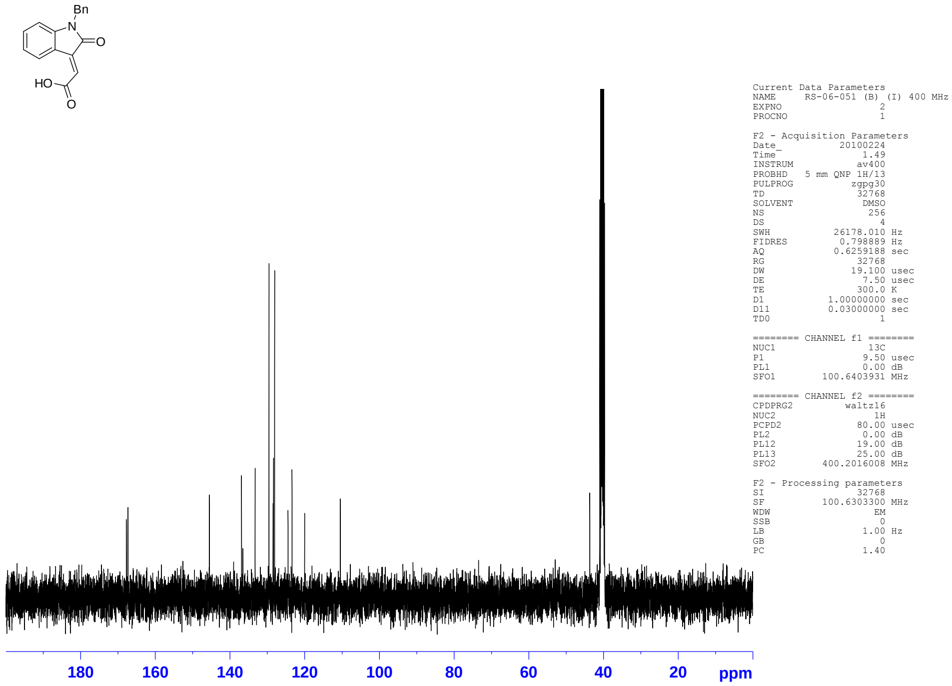


```
Current Data Parameters
NAME     RS-06-051 (B) (I) 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100224
Time                  1.41
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     362
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-06-051 (B) (I) 400 MHz
EXPNO                    2
PROCNO                   1

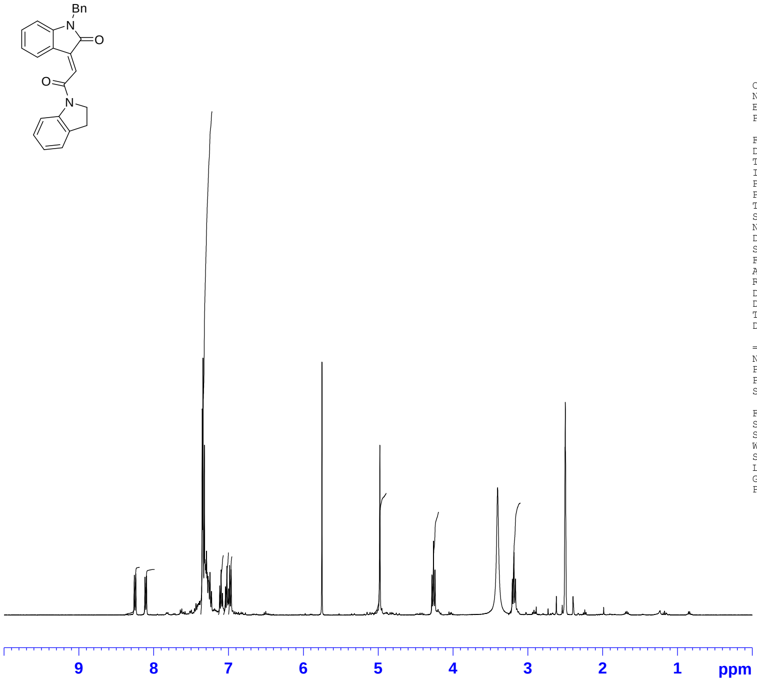
F2 - Acquisition Parameters
Date_             20100224
Time                  1.49
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG             zgpg30
TD                   32768
SOLVENT               DMSO
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz

F2 - Processing parameters
SI                   32768
SF             100.6303300 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

(*E*)-1-Benzyl-3-(2-(indolin-1-yl)-2-oxoethylidene)indolin-2-one, 159

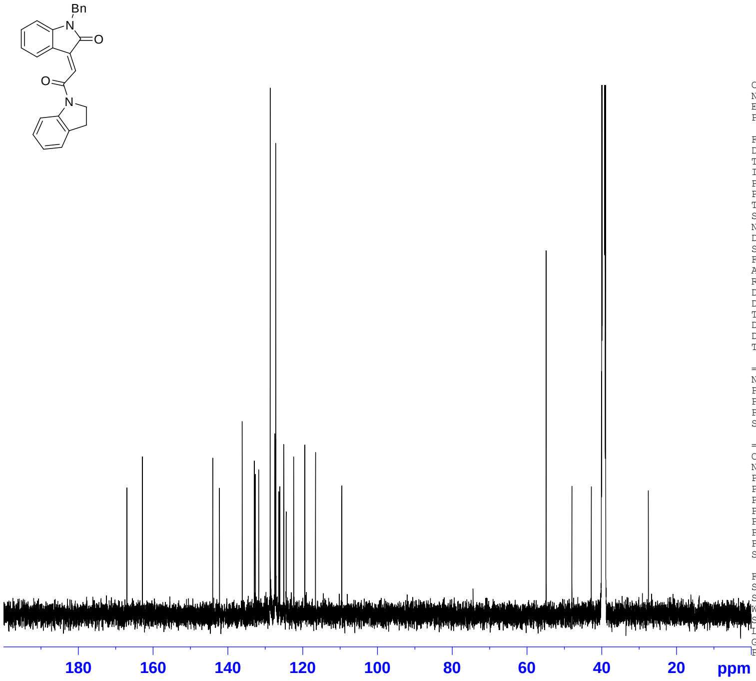


```
Current Data Parameters
NAME     RS-07-017 (S) 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100524
Time                 21.06
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                   322.5
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-07-017 (S) 500 MHz
EXPNO                    2
PROCNO                   1

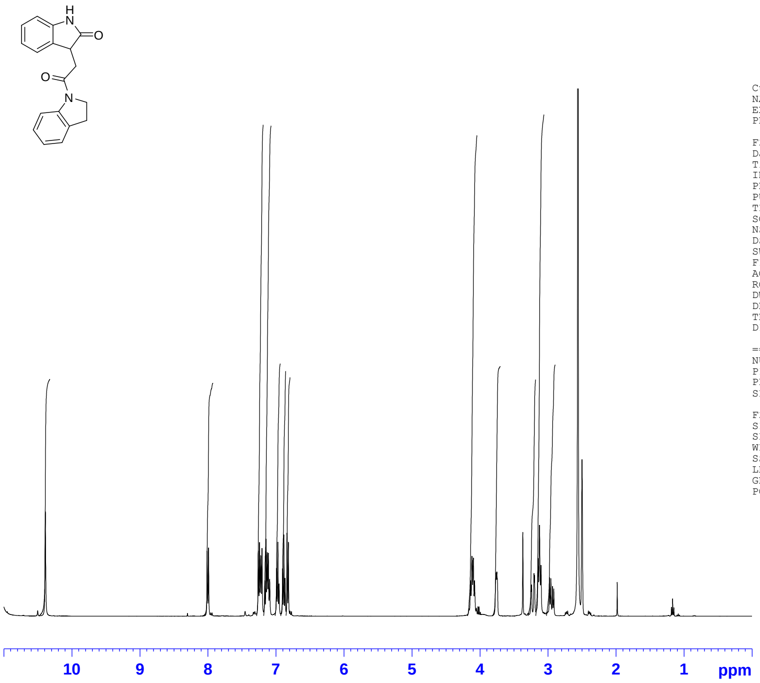
F2 - Acquisition Parameters
Date_             20100520
Time                 15.00
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG            zgpg30
TD                   65536
SOLVENT               DMSO
NS                     294
DS                       2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                     912
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                120.00 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.00000000 W
SFO2           500.3020012 MHz

F2 - Processing parameters
SI                   32768
SF             125.8005954 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

3-(2-(Indolin-1-yl)-2-oxoethyl)indolin-2-one, 164

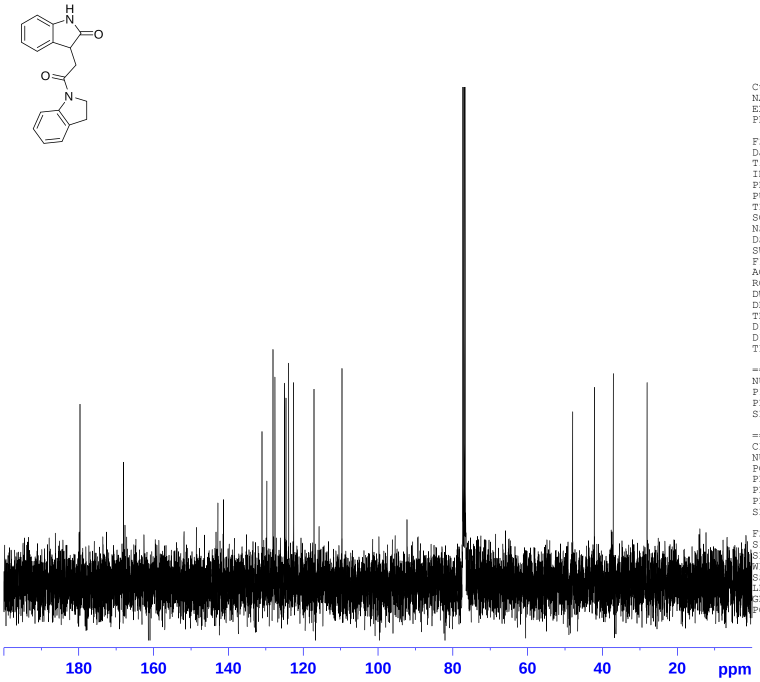


```
Current Data Parameters
NAME     RS-05-088 bottom spot
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20091205
Time                15.34
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                   45.3
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-06-024 (I) 400 MHz
EXPNO                   2
PROCNO                  1

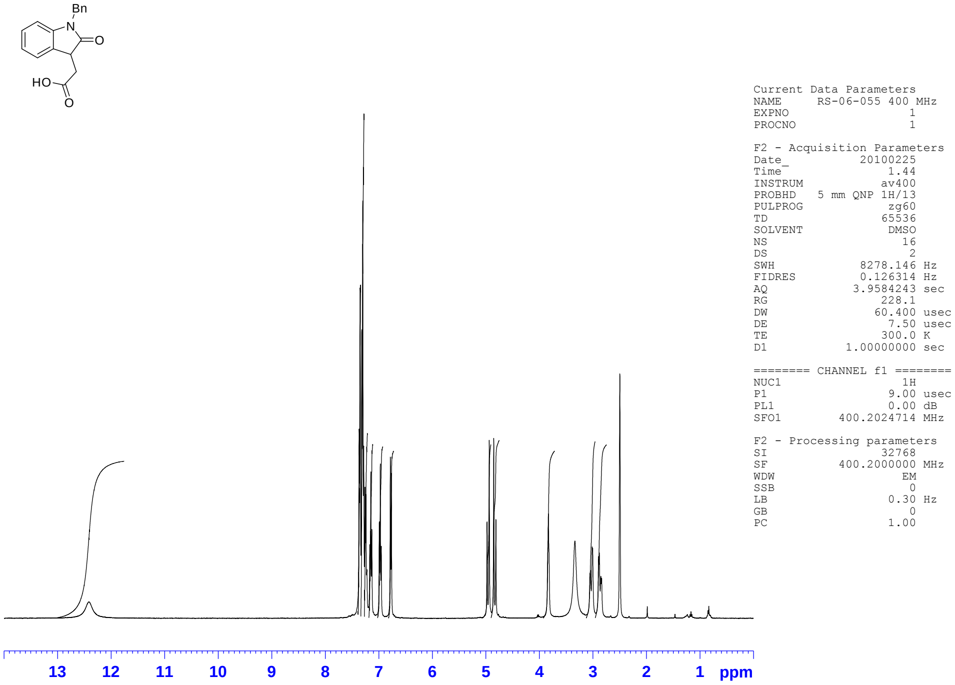
F2 - Acquisition Parameters
Date_            20100125
Time                13.39
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

2-(1-Benzyl-2-oxoindolin-3-yl)acetic acid, 165

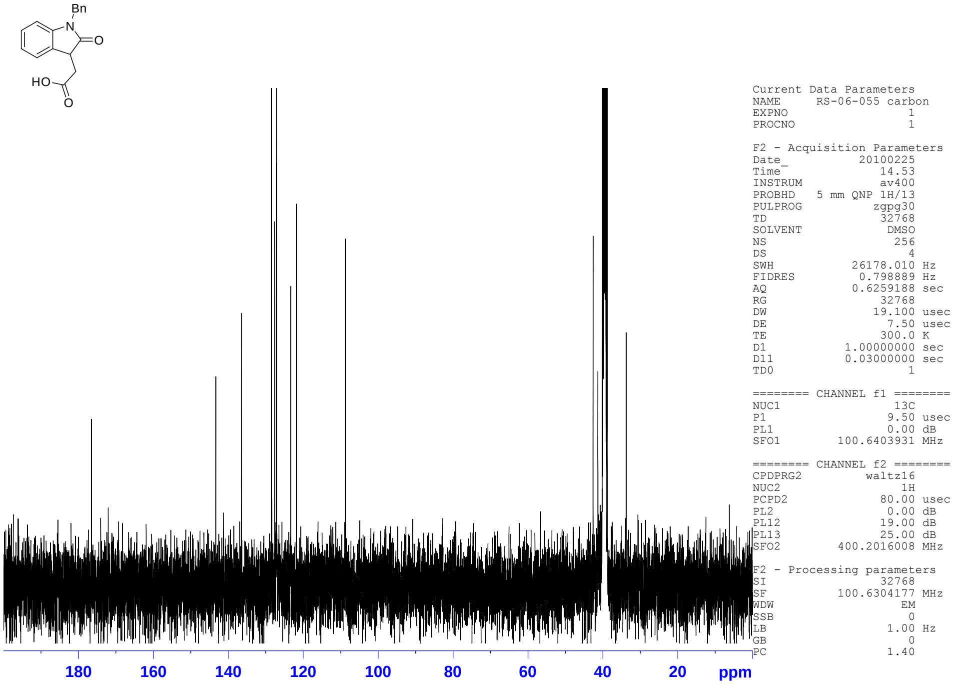


```
Current Data Parameters
NAME     RS-06-055 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100225
Time                  1.44
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                   228.1
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-06-055 carbon
EXPNO                    1
PROCNO                   1

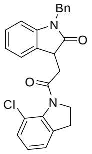
F2 - Acquisition Parameters
Date_             20100225
Time                 14.53
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG             zgpg30
TD                   32768
SOLVENT               DMSO
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

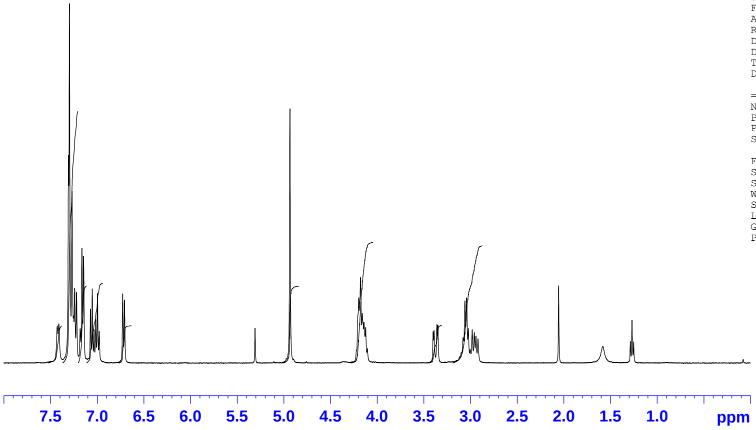
======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz

F2 - Processing parameters
SI                   32768
SF             100.6304177 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1-Benzyl-3-(2-(7-chloroindolin-1-yl)-2-oxoethyl)indolin-2-one, 167



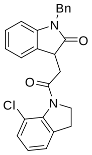


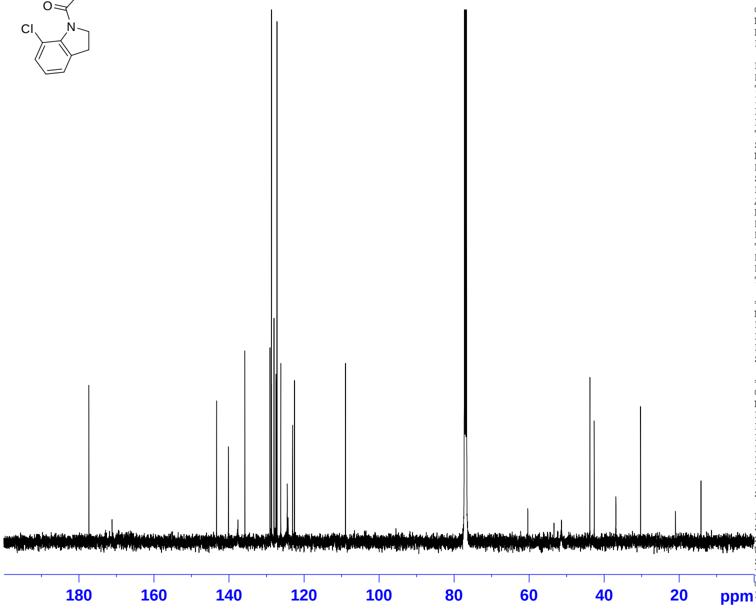
```
Current Data Parameters
NAME     RS-06-059 (I) 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100301
Time                 23.51
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     512
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





```
Current Data Parameters
NAME     RS-06-059 (I) carbon
EXPNO                    1
PROCNO                   1

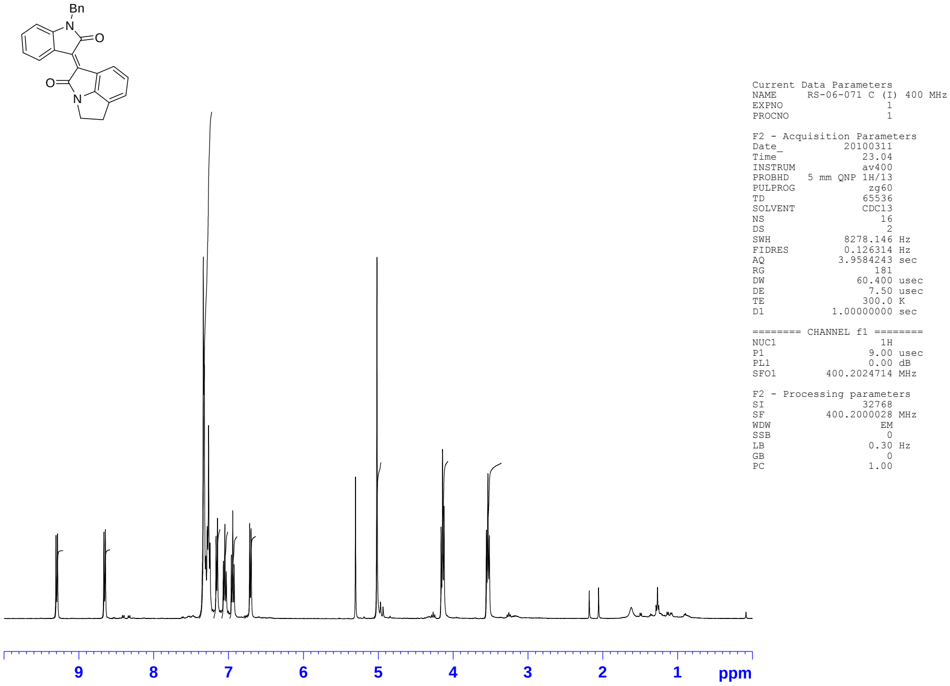
F2 - Acquisition Parameters
Date_             20100302
Time                 13.37
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                    1820
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                120.00 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.00000000 W
SFO2           500.3020012 MHz

F2 - Processing parameters
SI                   32768
SF             125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

(*E*)-1-(1-Benzyl-2-oxoindolin-3-ylidene)-4,5-dihydropyrrolo[3,2,1-hi]indol-2(1H)-one

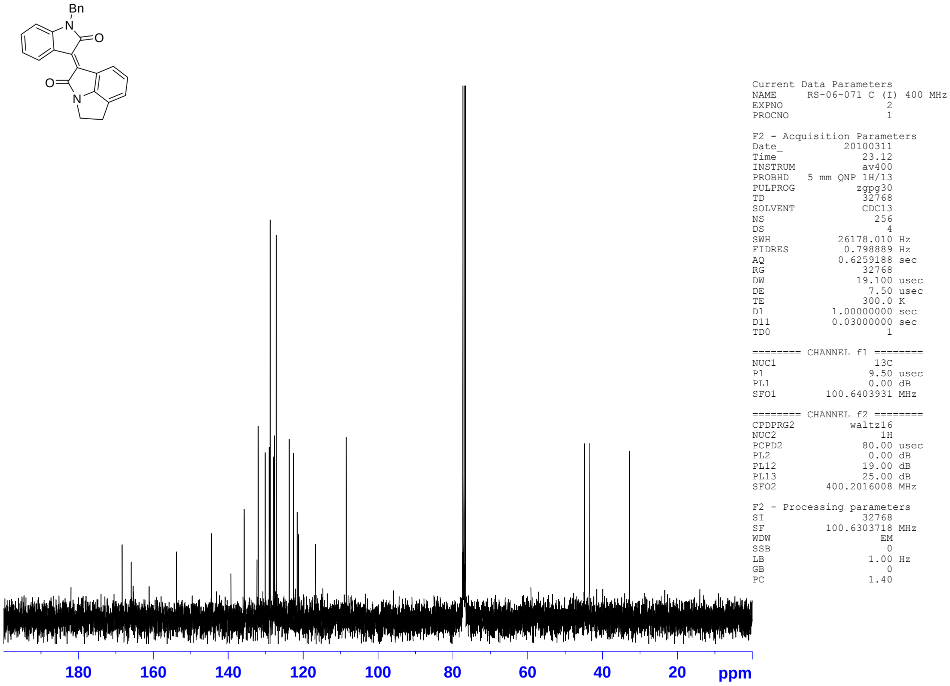


```
Current Data Parameters
NAME     RS-06-071 C (I) 400 MHz
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20100311
Time                   23.04
INSTRUM                av400
PROBHD   5 mm QNP 1H/13
PULPROG                 zg60
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                 3.9584243 sec
RG                       181
DW                    60.400 usec
DE                      7.50 usec
TE                     300.0 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                      9.00 usec
PL1                     0.00 dB
SFO1             400.2024714 MHz

F2 - Processing parameters
SI                     32768
SF               400.2000028 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



```
Current Data Parameters
NAME     RS-06-071 C (I) 400 MHz
EXPNO                      2
PROCNO                     1

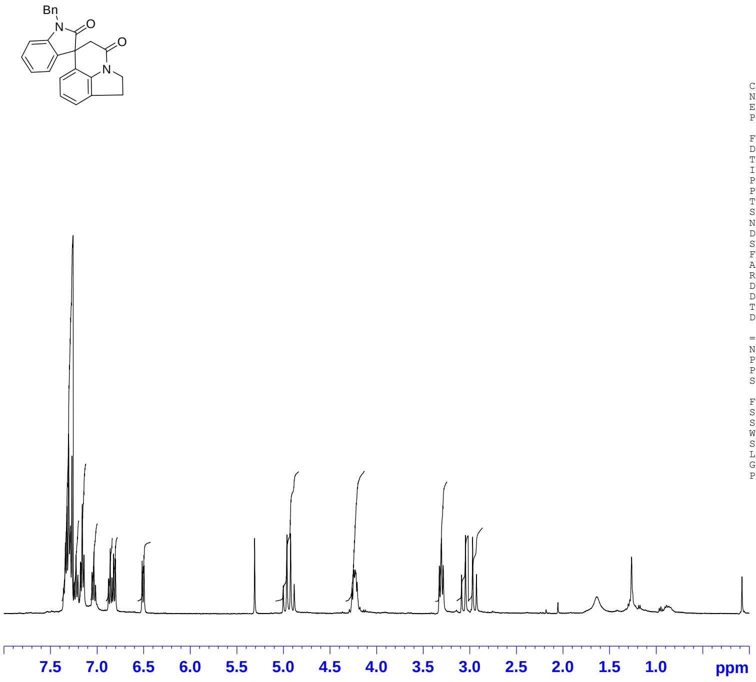
F2 - Acquisition Parameters
Date_               20100311
Time                   23.12
INSTRUM                av400
PROBHD   5 mm QNP 1H/13
PULPROG               zgpg30
TD                     32768
SOLVENT                CDCl3
NS                       256
DS                         4
SWH                26178.010 Hz
FIDRES              0.798889 Hz
AQ                 0.6259188 sec
RG                     32768
DW                    19.100 usec
DE                      7.50 usec
TE                     300.0 K
D1                1.00000000 sec
D11               0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                      9.50 usec
PL1                     0.00 dB
SFO1             100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                     0.00 dB
PL12                   19.00 dB
PL13                   25.00 dB
SFO2             400.2016008 MHz

F2 - Processing parameters
SI                     32768
SF               100.6303718 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

1-Benzyl-1',2'-dihydrospiro[indoline-3,6'-pyrrolo[3,2,1-ij]quinoline]-2,4'(5'H)-dione, 169

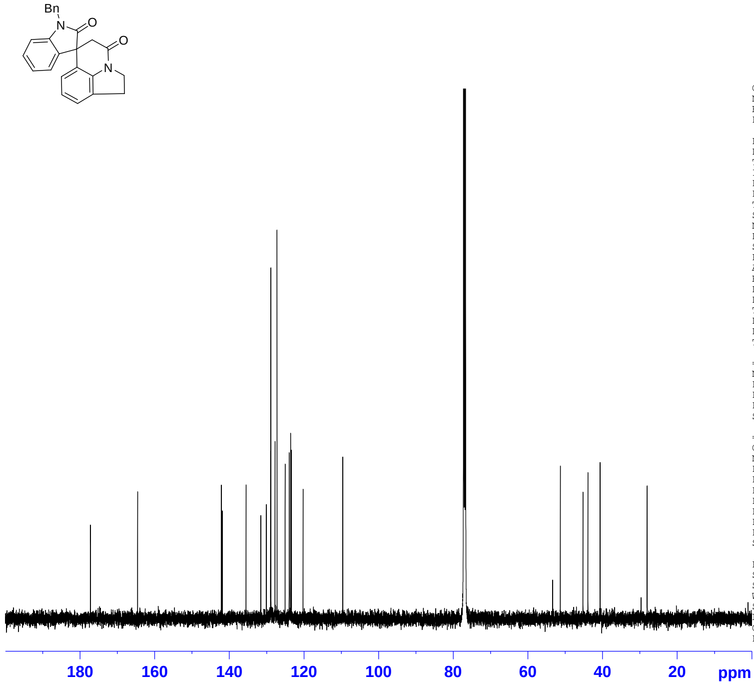


```
Current Data Parameters
NAME     RS-06-062 (II) 400 MHz
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100304
Time                 22.17
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                     512
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



```
Current Data Parameters
NAME     RS-06-062 (II) 500 MHz
EXPNO                    1
PROCNO                   1

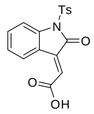
F2 - Acquisition Parameters
Date_             20100306
Time                  3.03
INSTRUM             avc500
PROBHD   5 mm CPDUL 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       2
SWH              31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0486259 sec
RG                     812
DW                  16.000 usec
DE                   20.00 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

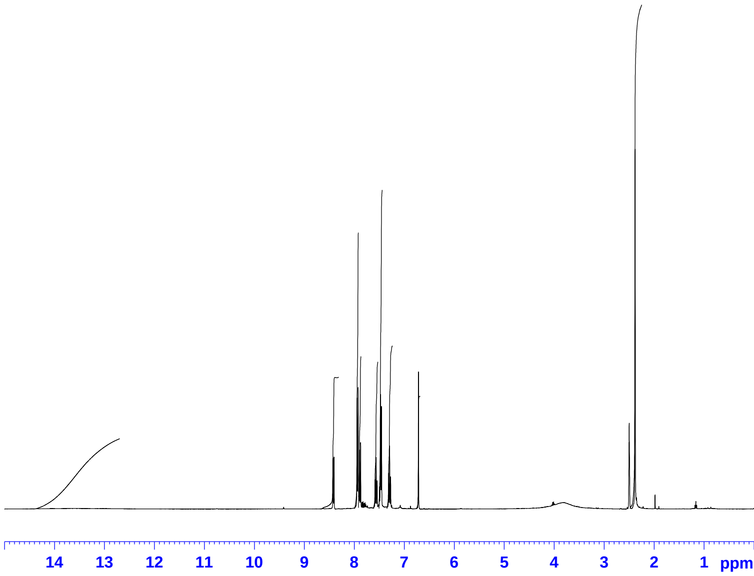
======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                  -4.40 dB
PL1W           28.15752029 W
SFO1           125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 12.42 dB
PL13                120.00 dB
PL2W           15.19999981 W
PL12W           0.21869738 W
PL13W           0.00000000 W
SFO2           500.3020012 MHz

F2 - Processing parameters
SI                   32768
SF             125.8005438 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

(*E*)-2-(2-Oxo-1-tosylindolin-3-ylidene)acetic acid, 173



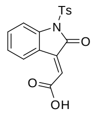


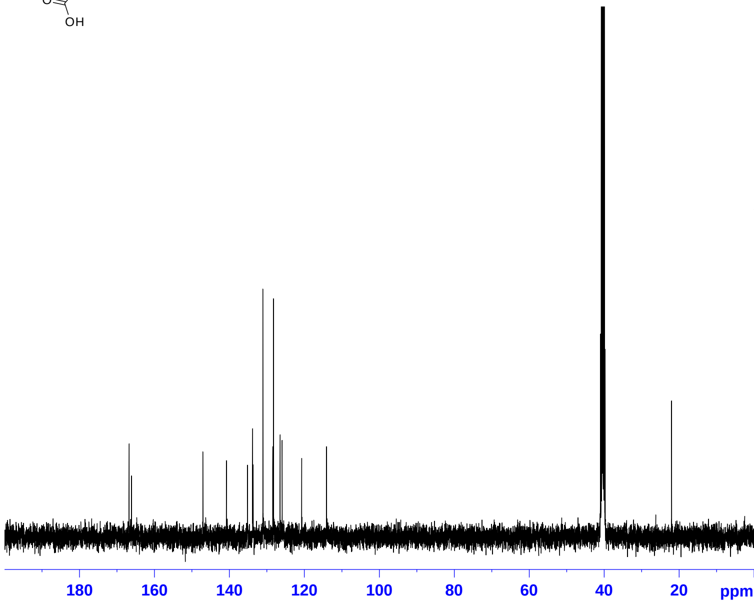
```
Current Data Parameters
NAME      RS-08-016 400 MHz
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20100804
Time                  14.41
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                3.9584243 sec
RG                      181
DW                   60.400 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1            400.2024714 MHz

F2 - Processing parameters
SI                    32768
SF              400.2000000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```





```
Current Data Parameters
NAME      RS-08-016 400 MHz
EXPNO                     3
PROCNO                    1

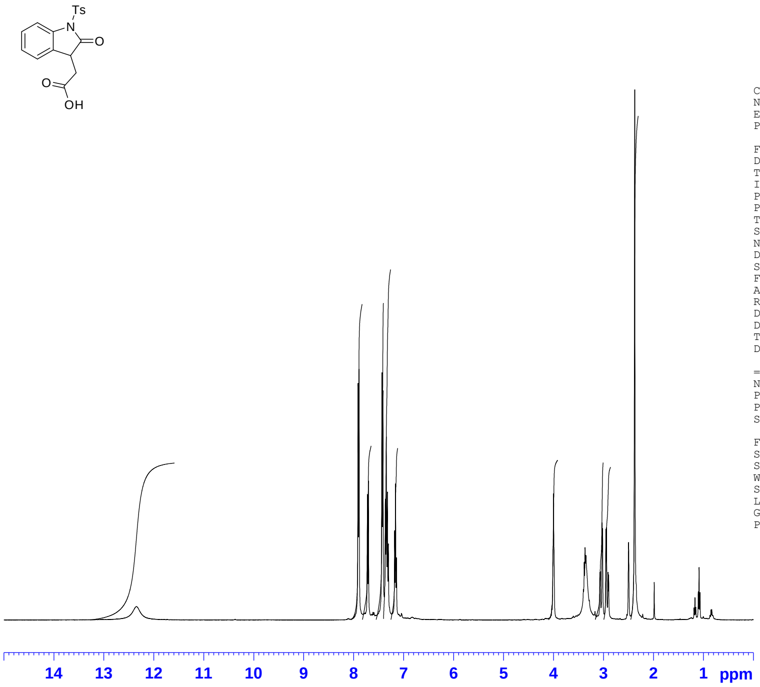
F2 - Acquisition Parameters
Date_              20100804
Time                  14.52
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG              zgpg30
TD                    32768
SOLVENT                DMSO
NS                      256
DS                        4
SWH               26178.010 Hz
FIDRES             0.798889 Hz
AQ                0.6259188 sec
RG                    32768
DW                   19.100 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                    0.00 dB
SFO1            100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  19.00 dB
PL13                  25.00 dB
SFO2            400.2016008 MHz

F2 - Processing parameters
SI                    32768
SF              100.6303300 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

2-(2-Oxo-1-tosylindolin-3-yl)acetic acid, 174

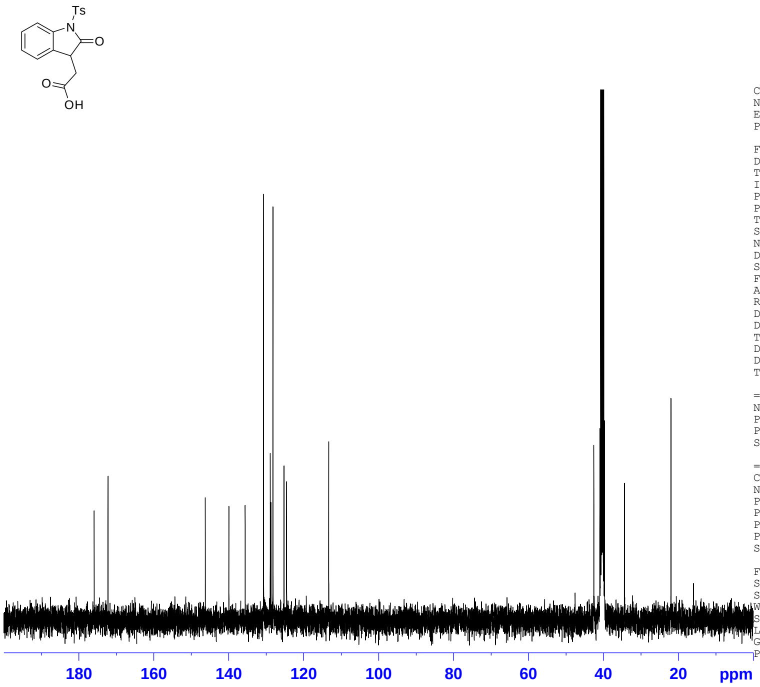


```
Current Data Parameters
NAME     RS-08-18 I 400 MHz
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20100805
Time                  20.14
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                3.9584243 sec
RG                      128
DW                   60.400 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                     9.00 usec
PL1                    0.00 dB
SFO1            400.2024714 MHz

F2 - Processing parameters
SI                    32768
SF              400.2000000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



```
Current Data Parameters
NAME     RS-08-18 I 400 MHz
EXPNO                     3
PROCNO                    1

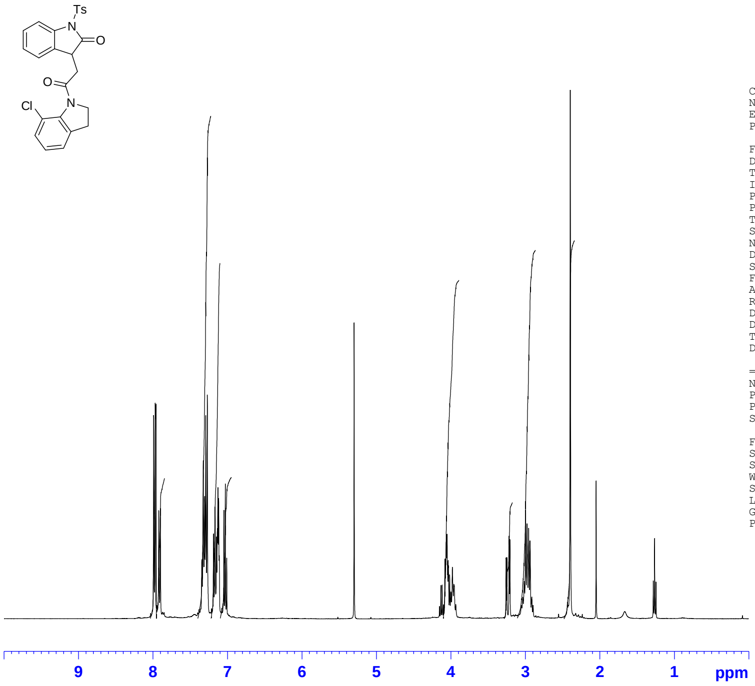
F2 - Acquisition Parameters
Date_              20100805
Time                  20.25
INSTRUM               av400
PROBHD   5 mm QNP 1H/13
PULPROG              zgpg30
TD                    32768
SOLVENT                DMSO
NS                      256
DS                        4
SWH               26178.010 Hz
FIDRES             0.798889 Hz
AQ                0.6259188 sec
RG                    32768
DW                   19.100 usec
DE                     7.50 usec
TE                    300.0 K
D1               1.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                    0.00 dB
SFO1            100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  19.00 dB
PL13                  25.00 dB
SFO2            400.2016008 MHz

F2 - Processing parameters
SI                    32768
SF              100.6303300 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

3-(2-(7-Chloroindolin-1-yl)-2-oxoethyl)-1-tosylindolin-2-one, 175

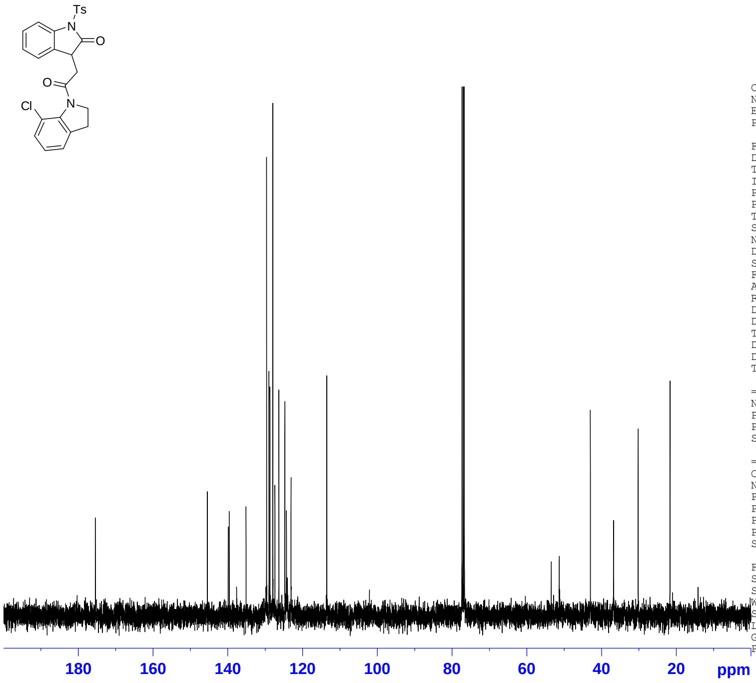


```
Current Data Parameters
NAME      RS-08-020 400 MHz
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20100806
Time                  21.48
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG                zg60
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                     90.5
DW               60.400 usec
DE                 7.50 usec
TE                  300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                 9.00 usec
PL1                0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                    32768
SF            400.2000028 MHz
WDW                      EM
SSB                       0
LB                 0.30 Hz
GB                        0
PC                     1.00
```



```
Current Data Parameters
NAME      RS-08-020 400 MHz
EXPNO                     2
PROCNO                    1

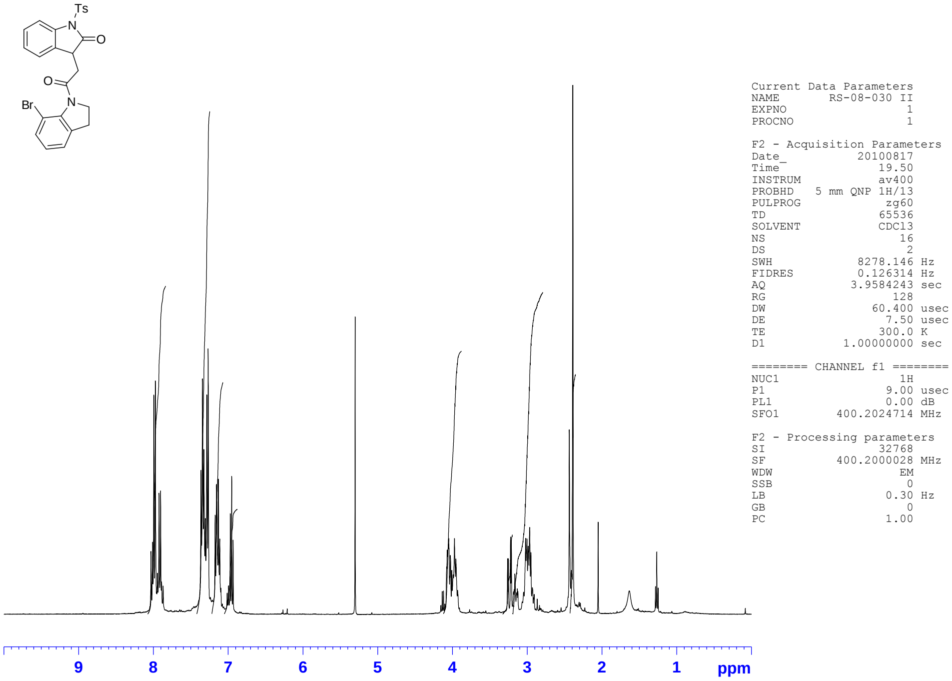
F2 - Acquisition Parameters
Date_              20100806
Time                  21.56
INSTRUM               av400
PROBHD    5 mm QNP 1H/13
PULPROG             zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      256
DS                        4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                    32768
DW               19.100 usec
DE                 7.50 usec
TE                  300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                 9.50 usec
PL1                0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              19.00 dB
PL13              25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                    32768
SF            100.6303718 MHz
WDW                      EM
SSB                       0
LB                 1.00 Hz
GB                        0
PC                     1.40
```

3-(2-(7-Bromoindolin-1-yl)-2-oxoethyl)-1-tosylindolin-2-one, 176

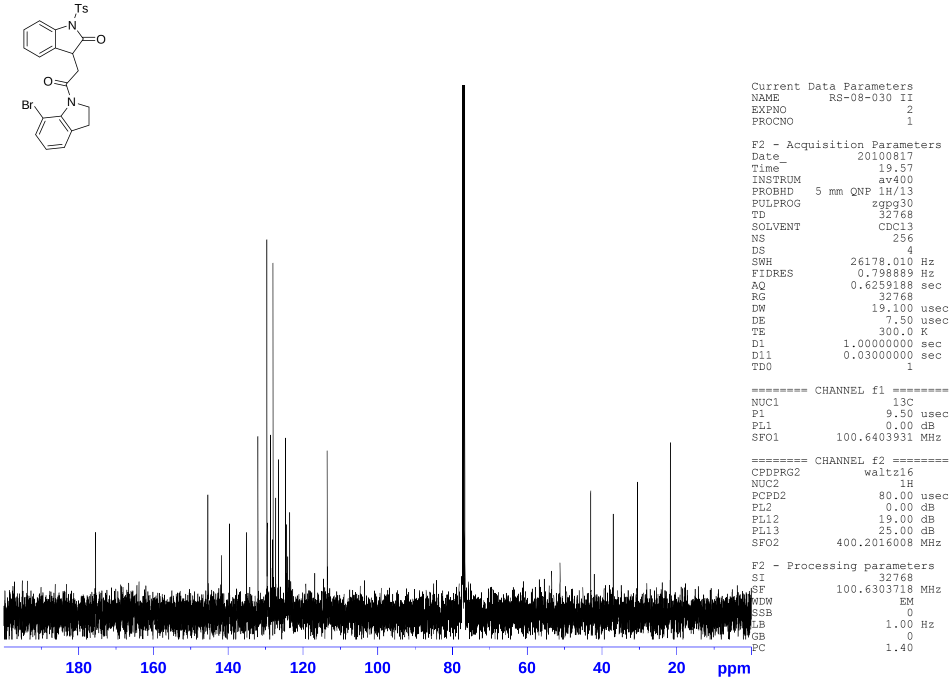


```
Current Data Parameters
NAME         RS-08-030 II
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20100817
Time                19.50
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                    128
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME         RS-08-030 II
EXPNO                   2
PROCNO                  1

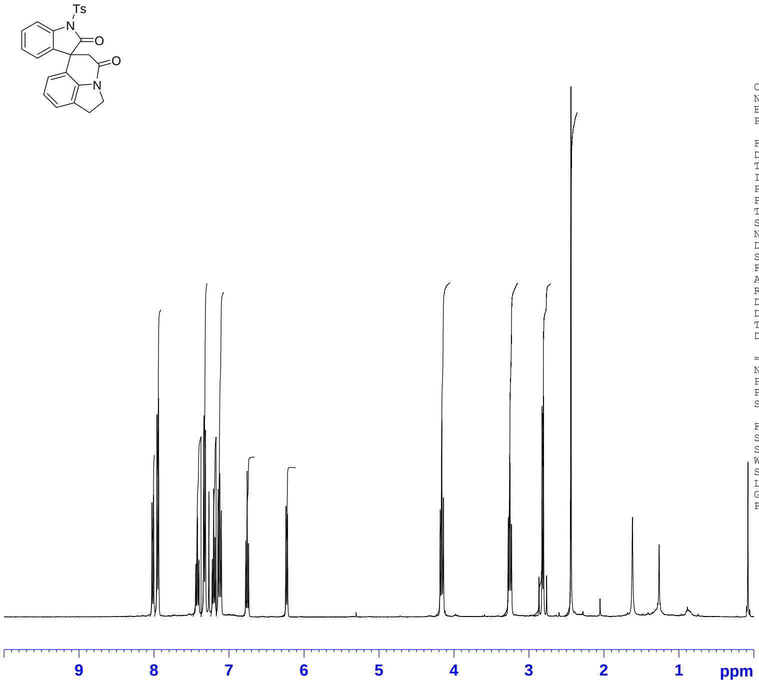
F2 - Acquisition Parameters
Date_            20100817
Time                19.57
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

1-Tosyl-1',2'-dihydrospiro[indoline-3,6'-pyrrolo[3,2,1-ij]quinoline]-2,4'(5'H)-dione, *spiro*-lactam, 177

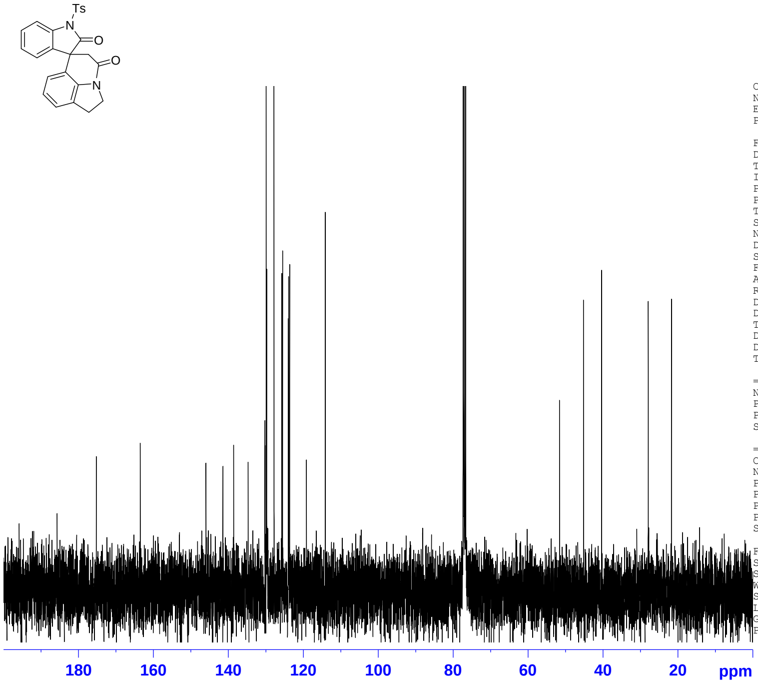


```
Current Data Parameters
NAME     RS-08-032 II 400 MHz
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20100820
Time                 0.19
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG              zg60
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ              3.9584243 sec
RG                  228.1
DW                 60.400 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.00 usec
PL1                  0.00 dB
SFO1          400.2024714 MHz

F2 - Processing parameters
SI                  32768
SF            400.2000028 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



```
Current Data Parameters
NAME     RS-08-032 II 400 MHz
EXPNO                   2
PROCNO                  1

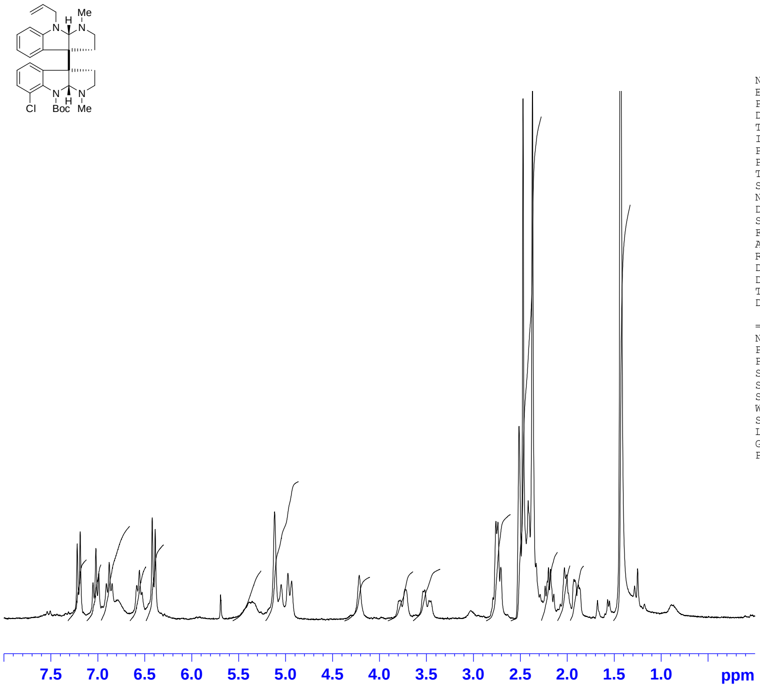
F2 - Acquisition Parameters
Date_            20100820
Time                 0.26
INSTRUM             av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                  32768
SOLVENT             CDCl3
NS                    256
DS                      4
SWH             26178.010 Hz
FIDRES           0.798889 Hz
AQ              0.6259188 sec
RG                  32768
DW                 19.100 usec
DE                   7.50 usec
TE                  300.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  0.00 dB
SFO1          100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                19.00 dB
PL13                25.00 dB
SFO2          400.2016008 MHz

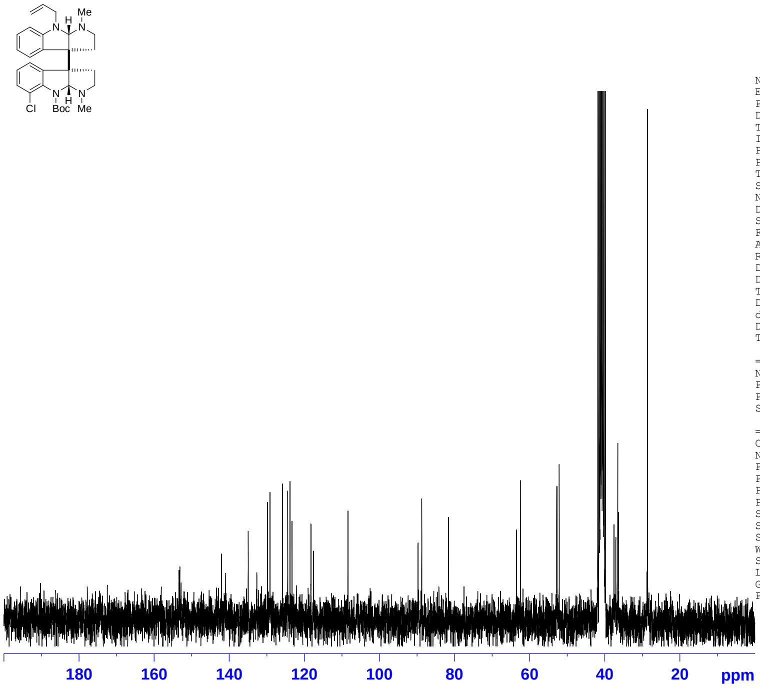
F2 - Processing parameters
SI                  32768
SF            100.6303718 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

(-)-(3a*S*,3'a*R*,8a*R*,8'a*S*)-*tert*-butyl 8'-allyl-7-chloro-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indole]-8(8aH)-carboxylate, 180



```
NAME          RS-10-056
EXPNO                 1
PROCNO                1
Date_          20110413
Time              16.36
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   12
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  362
DW              100.200 usec
DE                 6.00 usec
TE                363.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

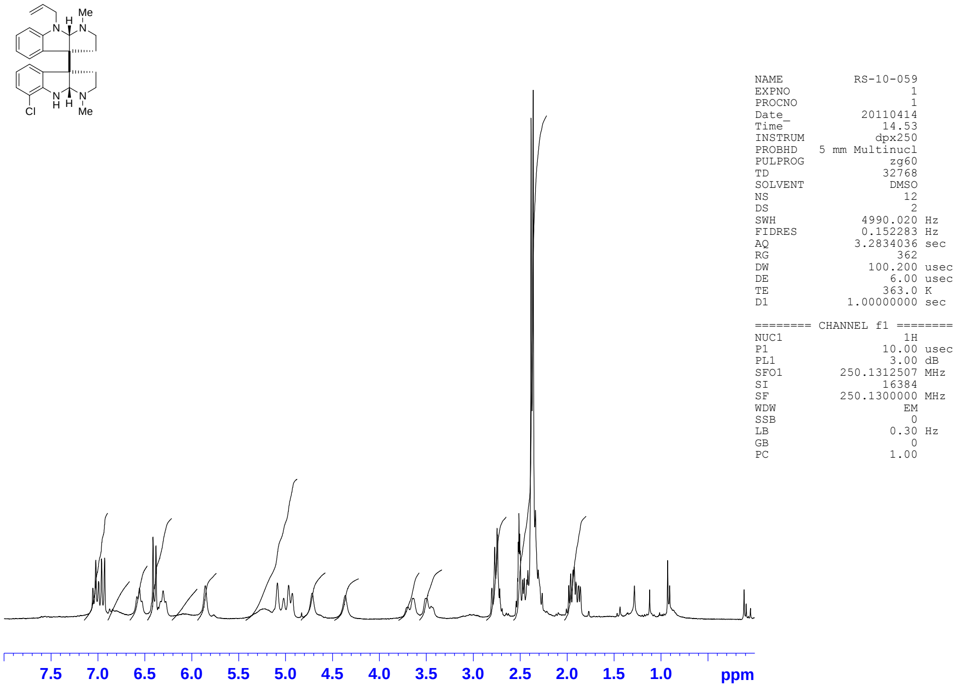


```
NAME          RS-10-056
EXPNO                 2
PROCNO                1
Date_          20110413
Time              16.41
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                 2448
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG              14596.5
DW               31.800 usec
DE                30.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

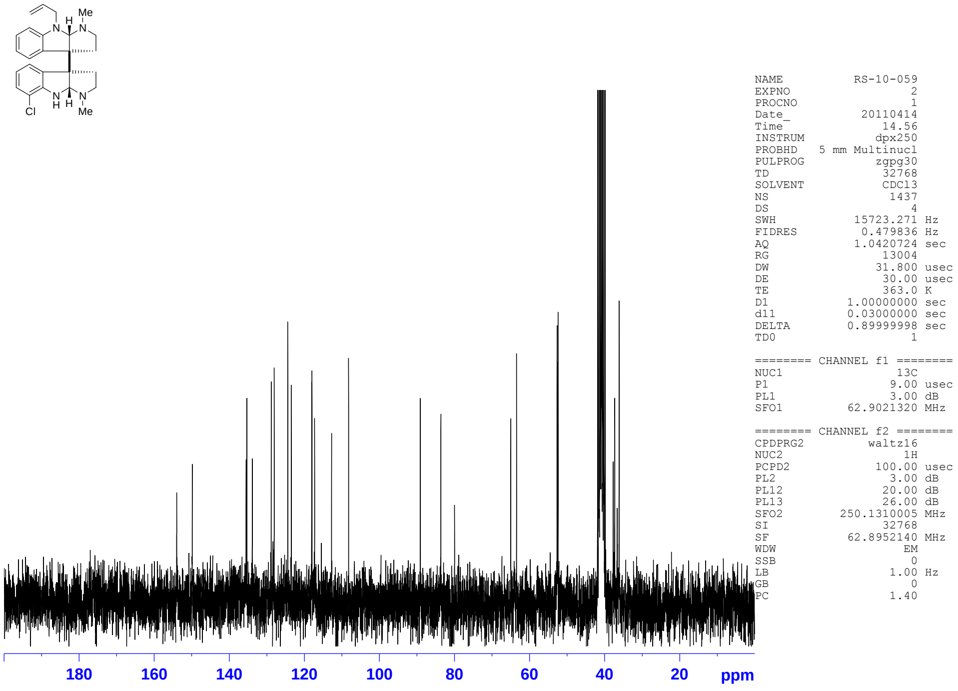
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

(-)-(3a*S*,3'a*R*,8a*S*,8'a*S*)-8'-Allyl-7-chloro-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, 182



```
NAME          RS-10-059
EXPNO                 1
PROCNO                1
Date_          20110414
Time              14.53
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG            zg60
TD                32768
SOLVENT            DMSO
NS                   12
DS                    2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                  362
DW              100.200 usec
DE                 6.00 usec
TE                363.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                3.00 dB
SFO1        250.1312507 MHz
SI                16384
SF          250.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

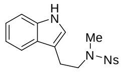


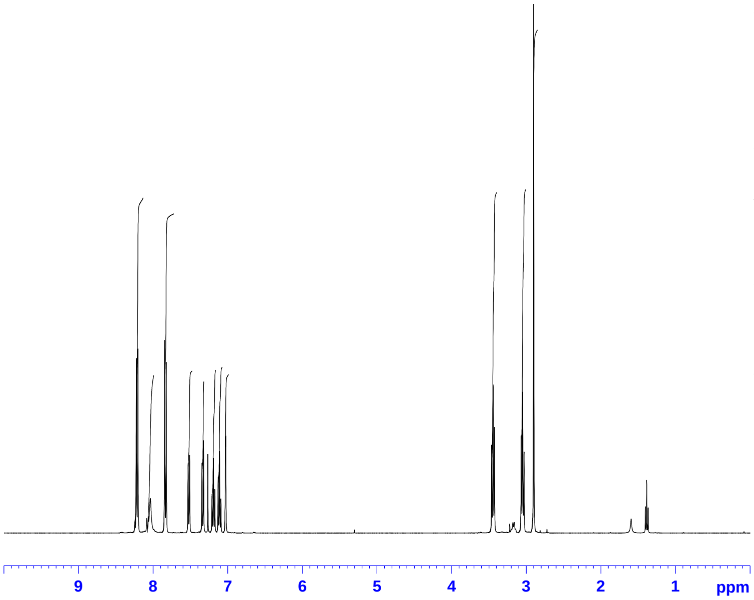
```
NAME          RS-10-059
EXPNO                 2
PROCNO                1
Date_          20110414
Time              14.56
INSTRUM          dpx250
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                 1437
DS                    4
SWH           15723.271 Hz
FIDRES         0.479836 Hz
AQ            1.0420724 sec
RG                13004
DW               31.800 usec
DE                30.00 usec
TE                363.0 K
D1           1.00000000 sec
d11          0.03000000 sec
DELTA        0.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 9.00 usec
PL1                3.00 dB
SFO1         62.9021320 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                3.00 dB
PL12              20.00 dB
PL13              26.00 dB
SFO2        250.1310005 MHz
SI                32768
SF           62.8952140 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

N-(2-(1H-Indol-3-yl)ethyl)-*N*-methyl-4-nitrobenzenesulfonamide



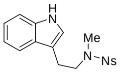


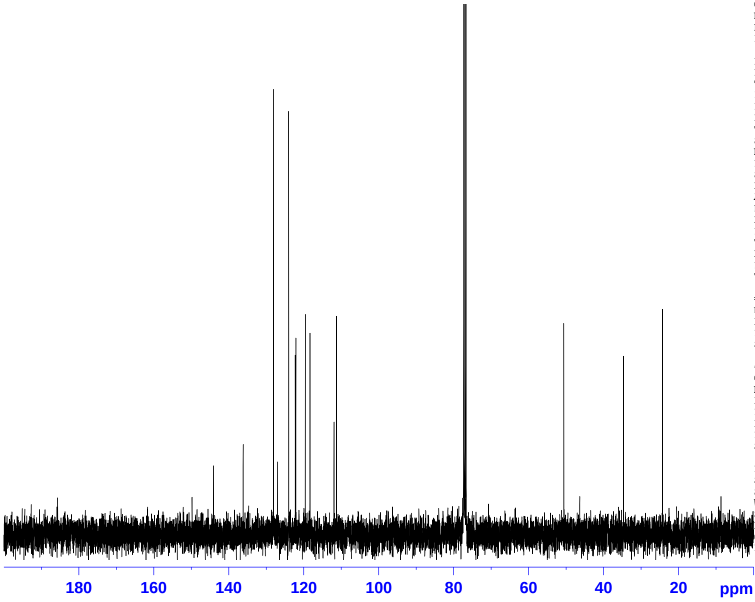
```
Current Data Parameters
NAME      RS-05-064 400 MHz NS
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20100712
Time                 18.50
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG               zg60
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ               3.9584243 sec
RG                   228.1
DW                  60.400 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.00 usec
PL1                   0.00 dB
SFO1           400.2024714 MHz

F2 - Processing parameters
SI                   32768
SF             400.2000028 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```





```
Current Data Parameters
NAME      RS-05-064 400 MHz NS
EXPNO                    2
PROCNO                   1

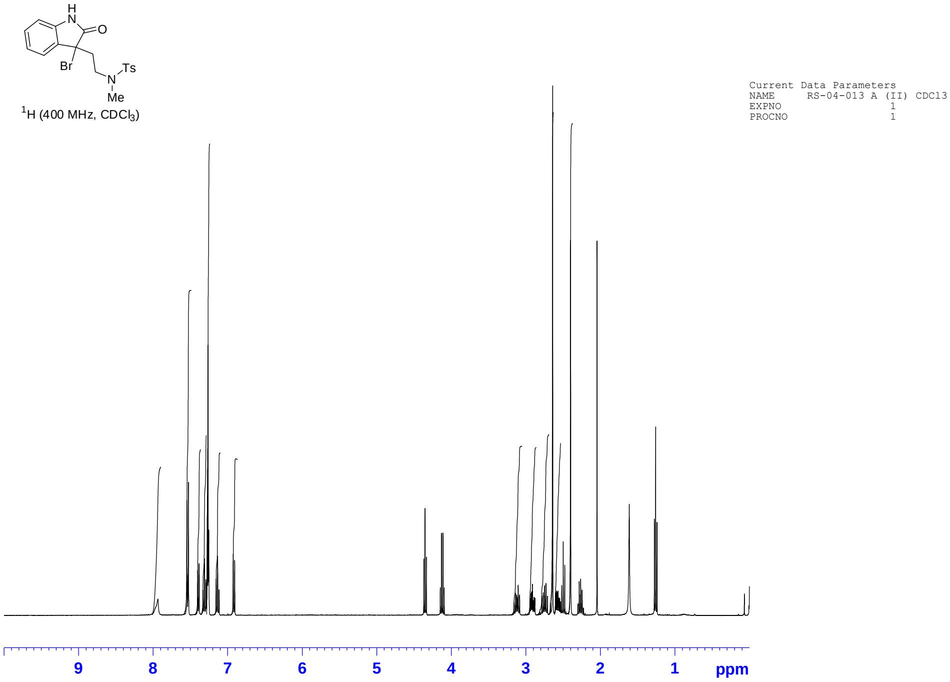
F2 - Acquisition Parameters
Date_             20100712
Time                 18.58
INSTRUM              av400
PROBHD   5 mm QNP 1H/13
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              26178.010 Hz
FIDRES            0.798889 Hz
AQ               0.6259188 sec
RG                   32768
DW                  19.100 usec
DE                    7.50 usec
TE                   300.0 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

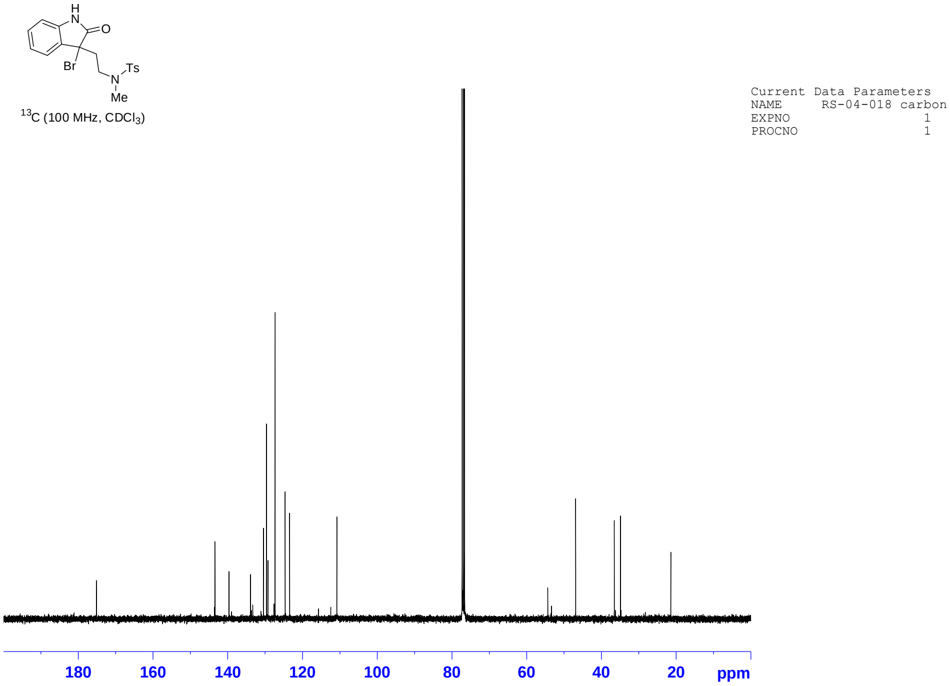
======== CHANNEL f1 ========
NUC1                   13C
P1                    9.50 usec
PL1                   0.00 dB
SFO1           100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 19.00 dB
PL13                 25.00 dB
SFO2           400.2016008 MHz

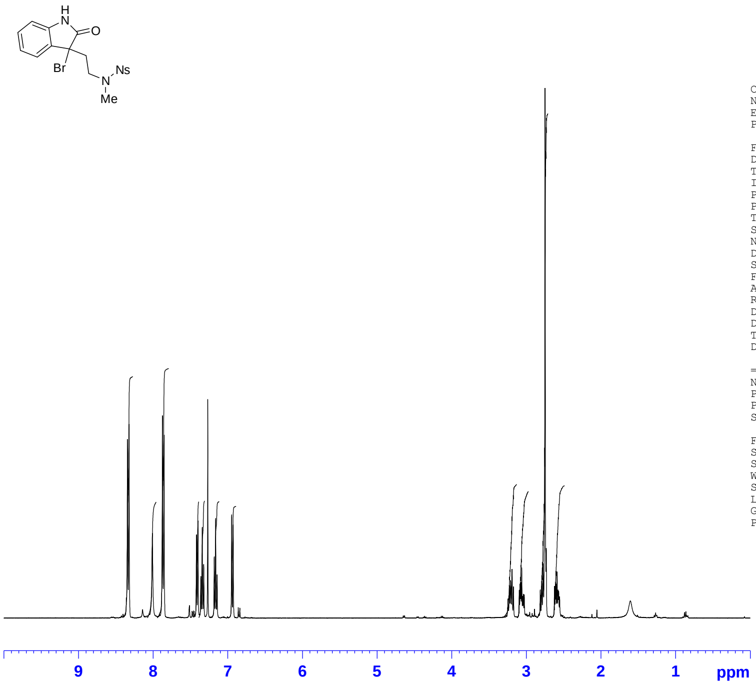
F2 - Processing parameters
SI                   32768
SF             100.6303718 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

N-(2-(3-Bromo-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, 183





N-(2-(3-Bromo-2-oxoindolin-3-yl)ethyl)-*N*-methyl-4-nitrobenzenesulfonamide, 184

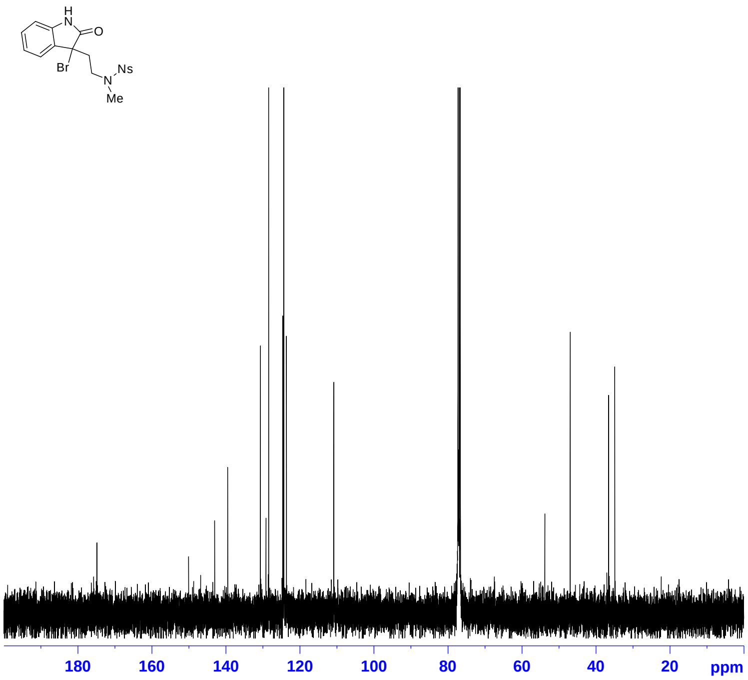


```
Current Data Parameters
NAME     RS-04-020 400 MHz
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20100712
Time               15.58
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG             zg60
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                   512
DW                60.400 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.00 usec
PL1                 0.00 dB
SFO1         400.2024714 MHz

F2 - Processing parameters
SI                 32768
SF           400.2000028 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



```
Current Data Parameters
NAME     RS-04-020 400 MHz
EXPNO                  2
PROCNO                 1

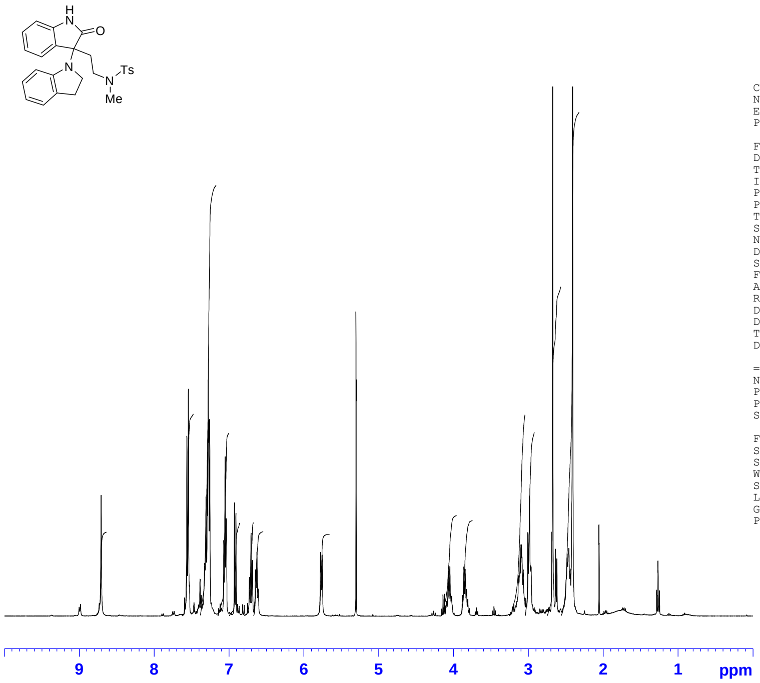
F2 - Acquisition Parameters
Date_           20100712
Time               16.06
INSTRUM            av400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            26178.010 Hz
FIDRES          0.798889 Hz
AQ             0.6259188 sec
RG                 32768
DW                19.100 usec
DE                  7.50 usec
TE                 300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.50 usec
PL1                 0.00 dB
SFO1         100.6403931 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               19.00 dB
PL13               25.00 dB
SFO2         400.2016008 MHz

F2 - Processing parameters
SI                 32768
SF           100.6303718 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

N,4-Dimethyl-*N*-(2-(2'-oxo-1,3'-biindolin-3'-yl)ethyl)benzenesulfonamide, 185

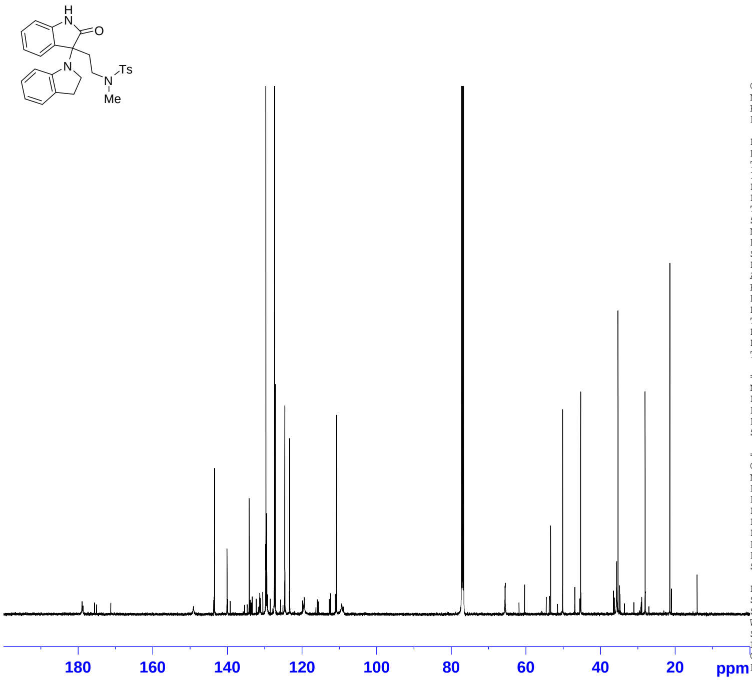


```
Current Data Parameters
NAME     RS-05-025 (II)
EXPNO              1
PROCNO             1

F2 - Acquisition Parameters
Date_          20090908
Time               9.37
INSTRUM           av400
PROBHD   5 mm QNP 1H/13
PULPROG            zg60
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ            3.9584243 sec
RG                 90.5
DW               60.400 usec
DE                 7.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.00 usec
PL1                0.00 dB
SFO1        400.2024714 MHz

F2 - Processing parameters
SI                32768
SF          400.2000028 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



```
Current Data Parameters
NAME         rs58340809
EXPNO                 1
PROCNO                1

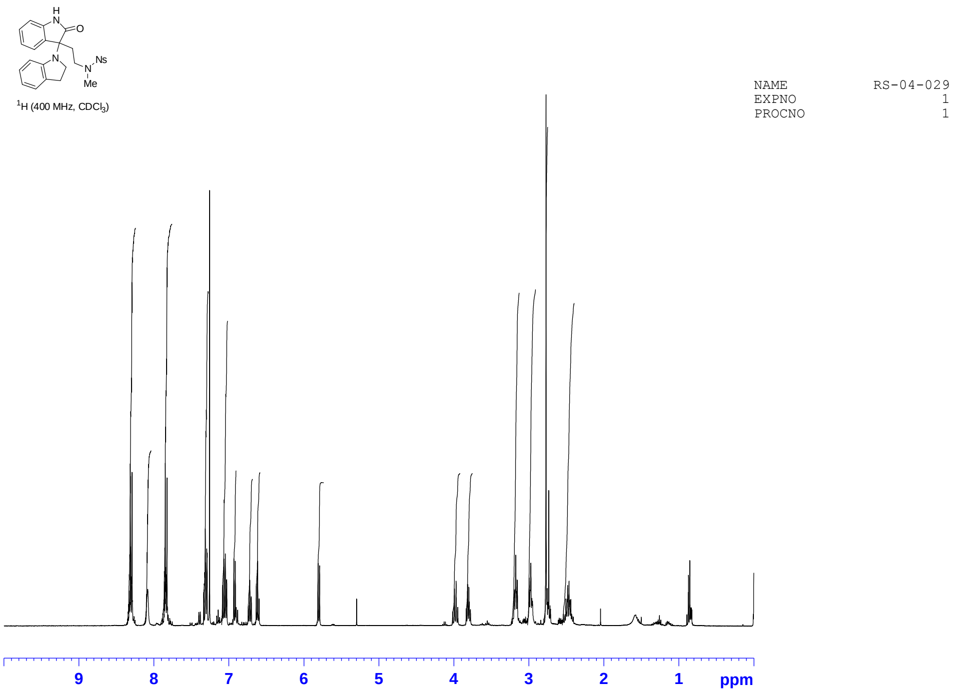
F2 - Acquisition Parameters
Date_          20090909
Time               3.09
INSTRUM          avc500
PROBHD   5 mm CPDUL 13C
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ            1.0486259 sec
RG                  645
DW               16.000 usec
DE                20.00 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

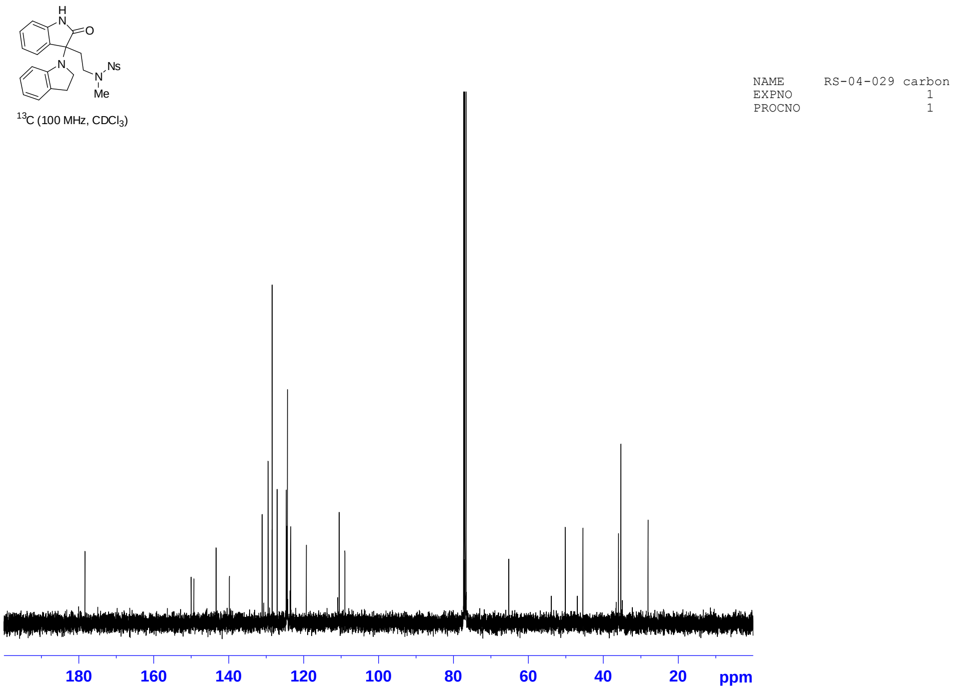
======== CHANNEL f1 ========
NUC1                13C
P1                 8.00 usec
PL1               -4.40 dB
PL1W        28.15752029 W
SFO1        125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               -6.00 dB
PL12              12.40 dB
PL13              17.00 dB
PL2W        15.19999981 W
PL12W        0.21970686 W
PL13W        0.07618046 W
SFO2        500.3020012 MHz

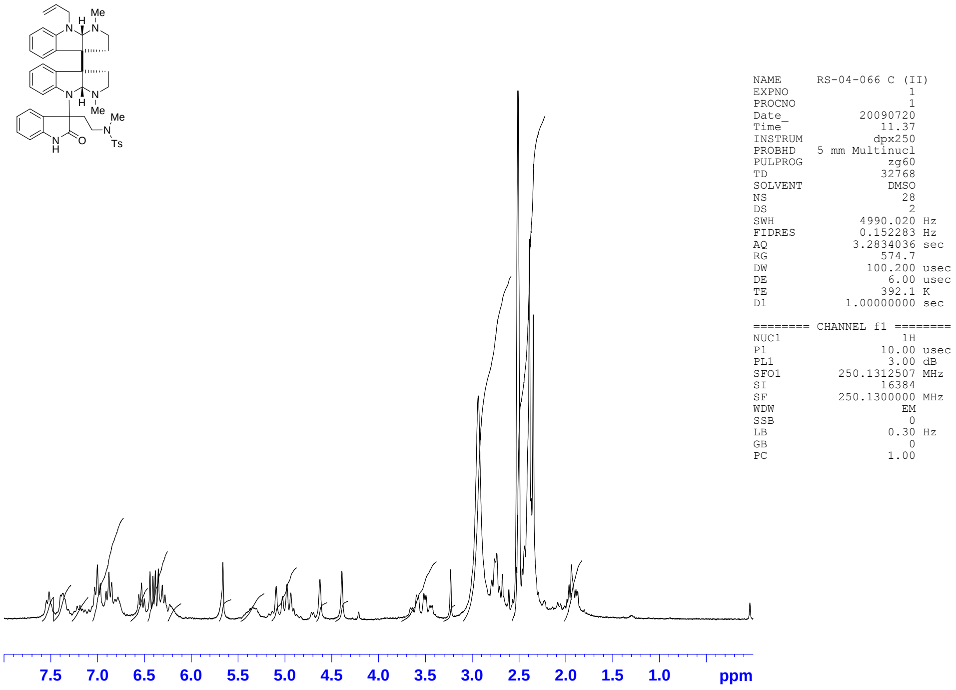
F2 - Processing parameters
SI                32768
SF          125.8005438 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

N-Methyl-4-nitro-*N*-(2-(2'-oxo-1,3'-biindolin-3'-yl)ethyl)benzenesulfonamide, 186



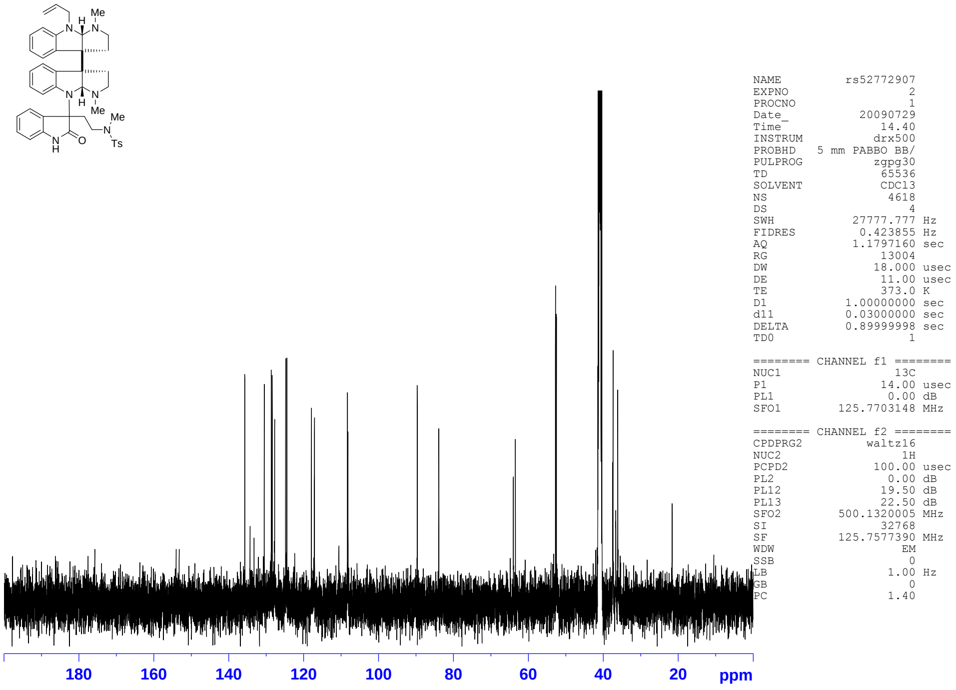


N-(2-(3-((3a*S*,3'a*R*,8a*R*,8'a*S*)-8'-Allyl-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indol-8(8aH)-yl)-2-oxoindolin-3-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide, *major diastereoisomer*, 187



```
NAME     RS-04-066 C (II)
EXPNO                   1
PROCNO                  1
Date_            20090720
Time                11.37
INSTRUM            dpx250
PROBHD   5 mm Multinucl
PULPROG              zg60
TD                  32768
SOLVENT              DMSO
NS                     28
DS                      2
SWH              4990.020 Hz
FIDRES           0.152283 Hz
AQ              3.2834036 sec
RG                  574.7
DW                100.200 usec
DE                   6.00 usec
TE                  392.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.00 usec
PL1                  3.00 dB
SFO1          250.1312507 MHz
SI                  16384
SF            250.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

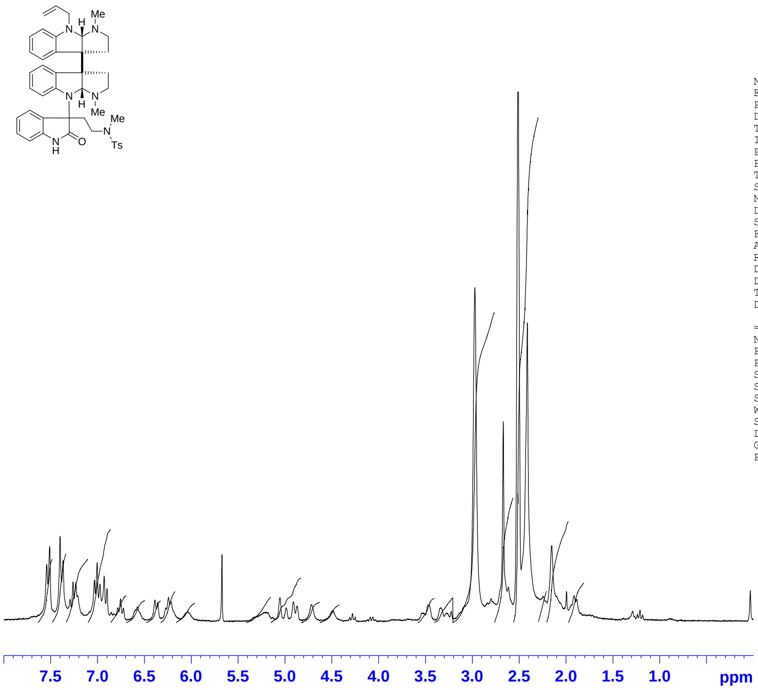


```
NAME           rs52772907
EXPNO                   2
PROCNO                  1
Date_            20090729
Time                14.40
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   4618
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                  13004
DW                 18.000 usec
DE                  11.00 usec
TE                  373.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  14.00 usec
PL1                  0.00 dB
SFO1          125.7703148 MHz

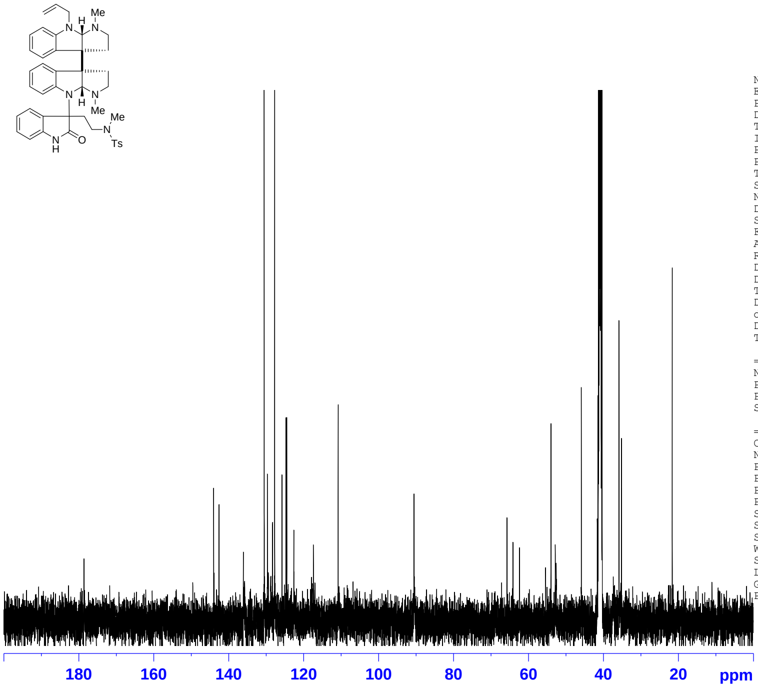
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

Minor diastereoisomer, 187



```
NAME         RS-04-066 B
EXPNO                  1
PROCNO                 1
Date_           20090720
Time               11.23
INSTRUM           dpx250
PROBHD   5 mm Multinucl
PULPROG             zg60
TD                 32768
SOLVENT             DMSO
NS                    21
DS                     2
SWH            4990.020 Hz
FIDRES         0.152283 Hz
AQ            3.2834036 sec
RG                 574.7
DW               100.200 usec
DE                  6.00 usec
TE                 392.1 K
D1            1.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 3.00 dB
SFO1         250.1312507 MHz
SI                 16384
SF           250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

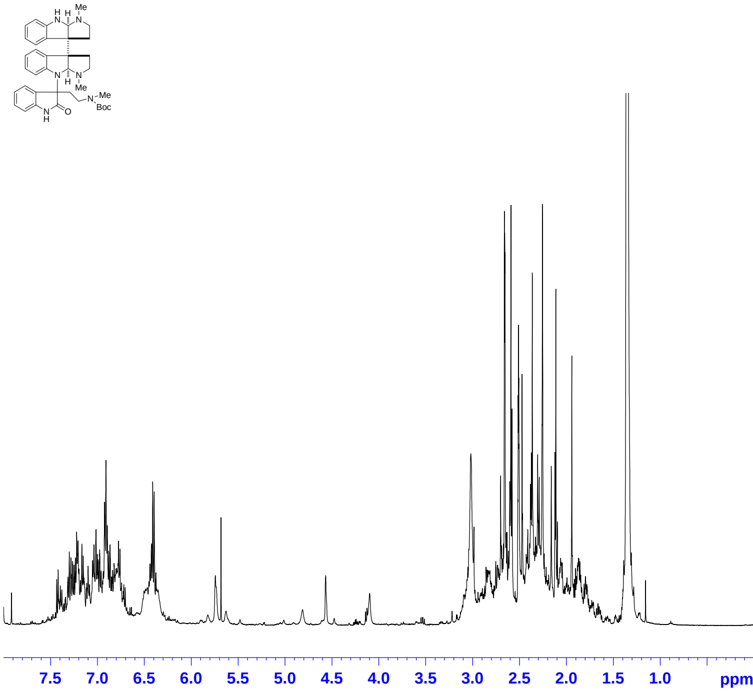


```
NAME          rs52782907
EXPNO                  2
PROCNO                 1
Date_           20090729
Time               18.05
INSTRUM           drx500
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2098
DS                     4
SWH           27777.777 Hz
FIDRES         0.423855 Hz
AQ            1.1797160 sec
RG                  6502
DW                18.000 usec
DE                 11.00 usec
TE                 373.0 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 14.00 usec
PL1                 0.00 dB
SFO1         125.7703148 MHz

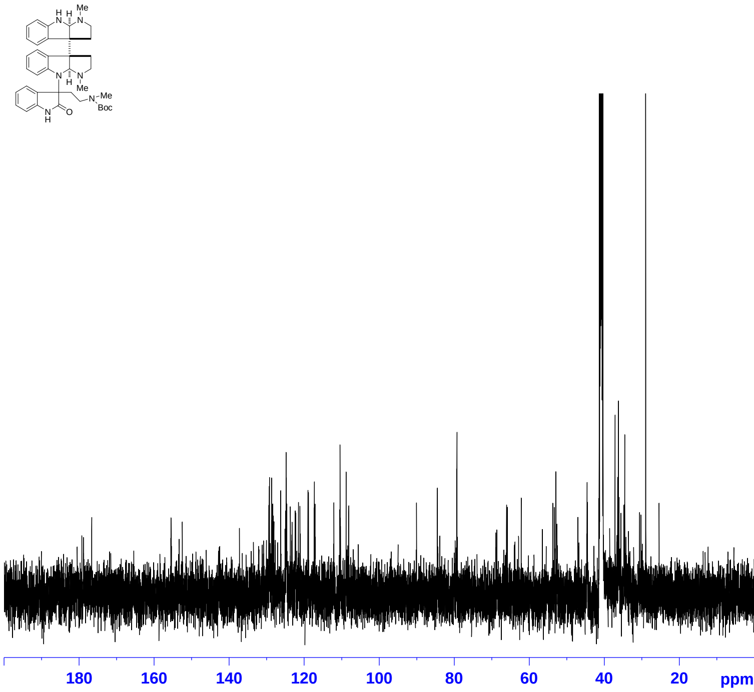
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 0.00 dB
PL12               19.50 dB
PL13               22.50 dB
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577390 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

tert-butyl (2-(3-(-1,1'-dimethyl-2,2',3,3',8',8'a-hexahydro-1H,1'H-[3a,3'a-bipyrrolo[2,3-b]indol]-8(8aH)-yl)-2-oxoindolin-3-yl)ethyl)(methyl)carbamate, 190



```
NAME     RS-10-044 II 500 MHz
EXPNO                   1
PROCNO                  1
Date_            20110411
Time                15.39
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG              zg60
TD                  65536
SOLVENT              DMSO
NS                     64
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                  161.3
DW                 48.400 usec
DE                  17.00 usec
TE                  363.1 K
D1             1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  12.50 usec
PL1                  0.00 dB
SFO1          500.1325007 MHz
SI                  32768
SF            500.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

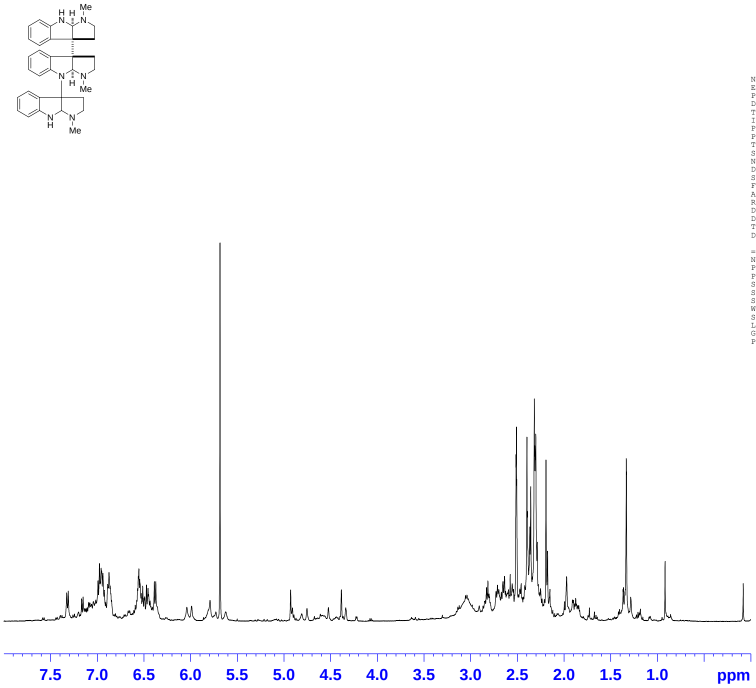


```
NAME     RS-10-044 II 500 MHz
EXPNO                   2
PROCNO                  1
Date_            20110411
Time                16.56
INSTRUM            drx500
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   3472
DS                      4
SWH             27777.777 Hz
FIDRES           0.423855 Hz
AQ              1.1797160 sec
RG                 5792.6
DW                 18.000 usec
DE                  11.00 usec
TE                  363.0 K
D1             1.00000000 sec
d11            0.03000000 sec
DELTA          0.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  5.00 dB
SFO1          125.7703148 MHz

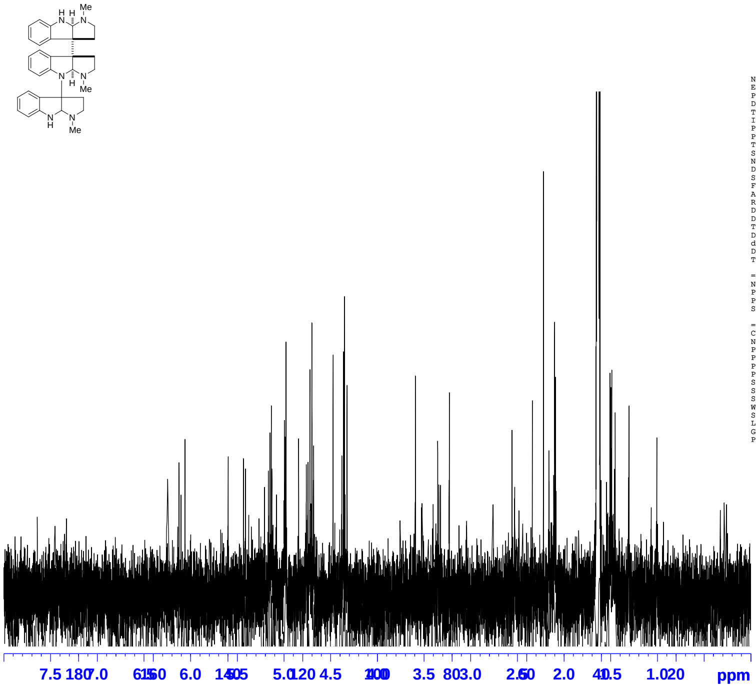
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                19.50 dB
PL13                22.50 dB
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577390 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

1,1',1''-Trimethyl-1',2,2',2'',3,3',3'',8,8a,8'a,8'',8''a-dodecahydro-1H,1''H-3a,3'a:8',3''a-terpyrrolo[2,3-b]indole, *N*-hodgkinsine, 192



```
NAME     RS-10-046 N Hodgkinsine 500 MHz
EXPNO                     1
PROCNO                    1
Date_              20110415
Time                  16.45
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       36
DS                        2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                3.1720407 sec
RG                    287.4
DW                   48.400 usec
DE                    17.00 usec
TE                    363.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    12.50 usec
PL1                    0.00 dB
SFO1            500.1325007 MHz
SI                    32768
SF              500.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



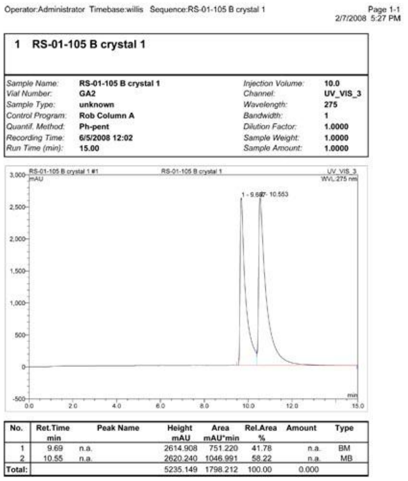
```
NAME     RS-10-046 N Hodgkinsine 500 MHz
EXPNO                     2
PROCNO                    1
Date_              20110415
Time                  15.04
INSTRUM              drx500
PROBHD   5 mm PABBO BB/
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     5501
DS                        4
SWH               27777.777 Hz
FIDRES             0.423855 Hz
AQ                1.1797160 sec
RG                   5792.6
DW                   18.000 usec
DE                    11.00 usec
TE                    363.0 K
D1               1.00000000 sec
d11              0.03000000 sec
DELTA            0.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.50 usec
PL1                    5.00 dB
SFO1            125.7703148 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                    0.00 dB
PL12                  19.50 dB
PL13                  22.50 dB
SFO2            500.1320005 MHz
SI                    32768
SF              125.7577390 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

13.3 Chiral HPLC Traces of Key Compounds

8-(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, 84



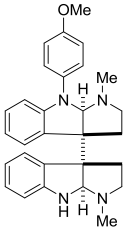
Operator:Administrator Timebase:willis Sequence:RS-01-105 B crystal 1

Page 1-1
2/7/2008 5:27 PM

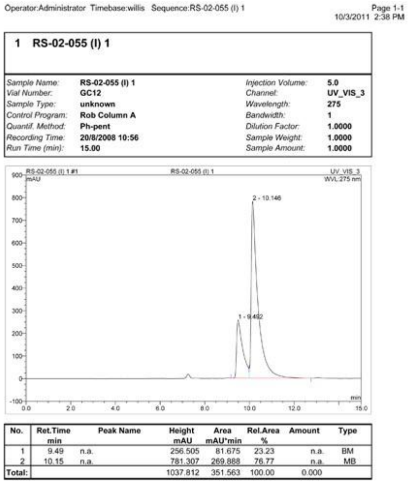
1 RS-01-105 B crystal 1

Sample Name:	**RS-01-105 B crystal 1**	*Injection Volume:*	**10.0**
Vial Number:	**GA2**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**275**
Control Program:	**Rob Column A**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**6/5/2008 12:02**	*Sample Weight:*	**1.0000**
Run Time (min):	**15.00**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.69	n.a.	2614.908	751.220	41.78	n.a.	BM
2	10.55	n.a.	2620.240	1046.991	58.22	n.a.	MB
Total:			5235.149	1798.212	100.00	0.000	



(±)
S-Phos



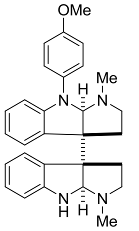
Operator:Administrator Timebase:willis Sequence:RS-02-055 (I) 1

Page 1-1
10/3/2011 2:38 PM

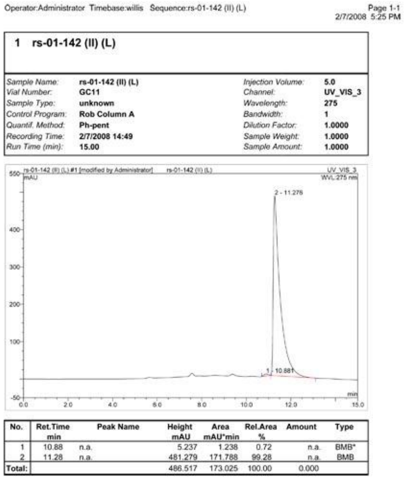
1 RS-02-055 (I) 1

Sample Name:	**RS-02-055 (I) 1**	*Injection Volume:*	**5.0**
Vial Number:	**GC12**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**275**
Control Program:	**Rob Column A**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**20/8/2008 10:56**	*Sample Weight:*	**1.0000**
Run Time (min):	**15.00**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.49	n.a.	256.505	81.675	23.23	n.a.	BM
2	10.15	n.a.	781.307	269.888	76.77	n.a.	MB
Total:			1037.812	351.563	100.00	0.000	



53 % ee
(*R*,*S*)-[(CyPF-*t*Bu)PdCl$_2$]



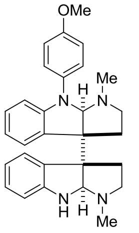
Operator:Administrator Timebase:willis Sequence:rs-01-142 (II) (L)

Page 1-1
2/7/2008 5:25 PM

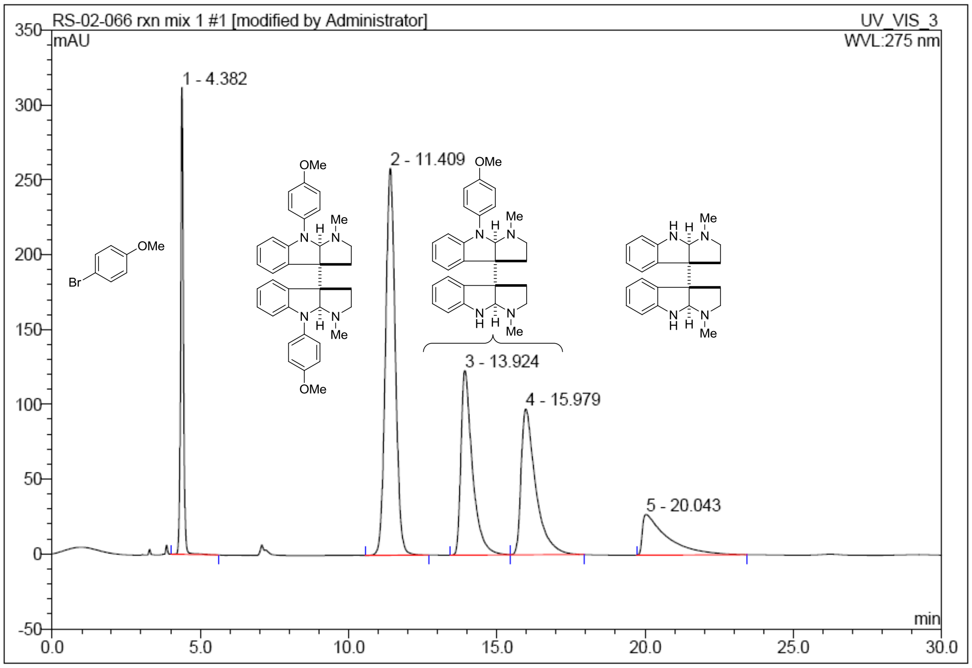
1 rs-01-142 (II) (L)

Sample Name:	**rs-01-142 (II) (L)**	*Injection Volume:*	**5.0**
Vial Number:	**GC11**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**275**
Control Program:	**Rob Column A**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**2/7/2008 14:49**	*Sample Weight:*	**1.0000**
Run Time (min):	**15.00**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.88	n.a.	5.237	1.238	0.72	n.a.	BMB*
2	11.28	n.a.	481.279	171.788	99.28	n.a.	BMB
Total:			486.517	173.025	100.00	0.000	

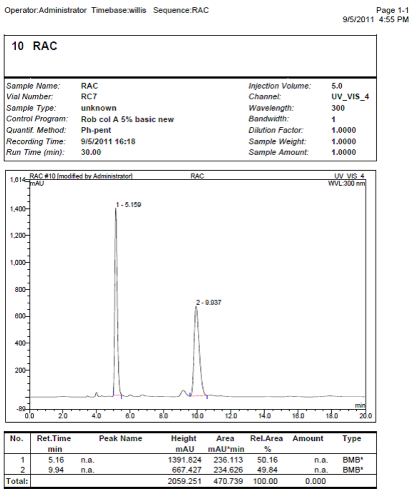


99% ee
Crystallisation from IPA/Hexane



Example spectra from HPLC assay

(3a*S*,3'a*R*,8a*R*,8'a*R*)-8-Allyl-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, 97

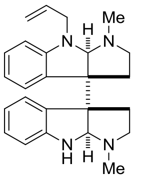

Operator:Administrator Timebase:willis Sequence:RAC

Page 1-1
9/5/2011 4:55 PM

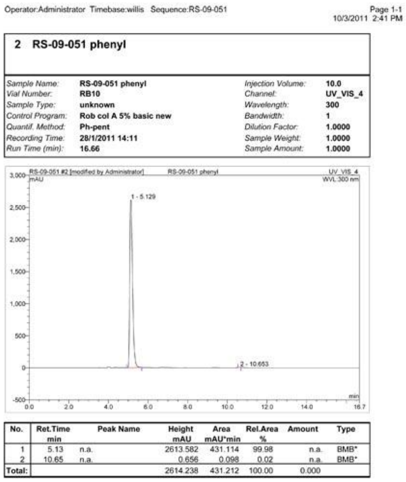
10 RAC

Sample Name:	RAC	*Injection Volume:*	5.0
Vial Number:	RC7	*Channel:*	UV_VIS_4
Sample Type:	unknown	*Wavelength:*	300
Control Program:	Rob col A 5% basic new	*Bandwidth:*	1
Quantif. Method:	Ph-pent	*Dilution Factor:*	1.0000
Recording Time:	9/5/2011 16:18	*Sample Weight:*	1.0000
Run Time (min):	30.00	*Sample Amount:*	1.0000

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.16	n.a.	1391.824	236.113	50.16	n.a.	BMB*
2	9.94	n.a.	667.427	234.626	49.84	n.a.	BMB*
Total:			2059.251	470.739	100.00	0.000	



(±)
dppf



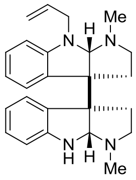
Operator:Administrator Timebase:willis Sequence:RS-09-051

Page 1-1
10/3/2011 2:41 PM

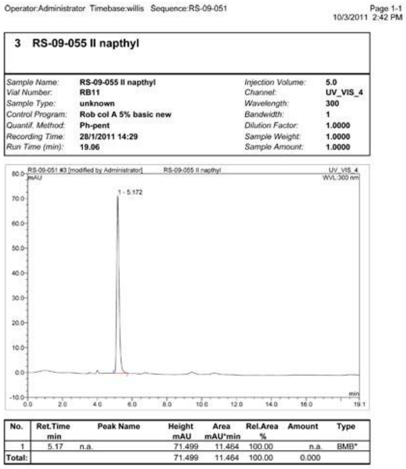
2 RS-09-051 phenyl

Sample Name:	**RS-09-051 phenyl**	*Injection Volume:*	**10.0**
Vial Number:	**RB10**	*Channel:*	**UV_VIS_4**
Sample Type:	**unknown**	*Wavelength:*	**300**
Control Program:	**Rob col A 5% basic new**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**28/1/2011 14:11**	*Sample Weight:*	**1.0000**
Run Time (min):	**16.66**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.13	n.a.	2613.582	431.114	99.98	n.a.	BMB*
2	10.65	n.a.	0.656	0.098	0.02	n.a.	BMB*
Total:			2614.238	431.212	100.00	0.000	



(-)-99% ee
[*R*,*R*]-DACT-Phenyl-Trost Ligand



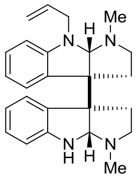
Operator:Administrator Timebase:willis Sequence:RS-09-051

Page 1-1
10/3/2011 2:42 PM

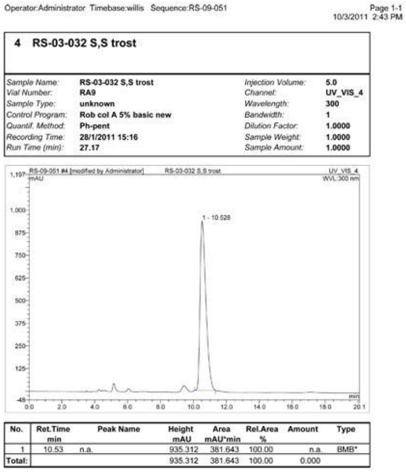
3 RS-09-055 II napthyl

Sample Name:	**RS-09-055 II napthyl**	*Injection Volume:*	**5.0**
Vial Number:	**RB11**	*Channel:*	**UV_VIS_4**
Sample Type:	**unknown**	*Wavelength:*	**300**
Control Program:	**Rob col A 5% basic new**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**28/1/2011 14:29**	*Sample Weight:*	**1.0000**
Run Time (min):	**19.06**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.17	n.a.	71.499	11.464	100.00	n.a.	BMB*
Total:			71.499	11.464	100.00	0.000	



(-)-99%ee
[*R*,*R*]-DACT-Napthyl-Trost Ligand



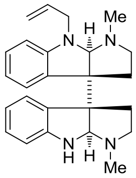
Operator:Administrator Timebase:willis Sequence:RS-09-051

Page 1-1
10/3/2011 2:43 PM

4 RS-03-032 S,S trost

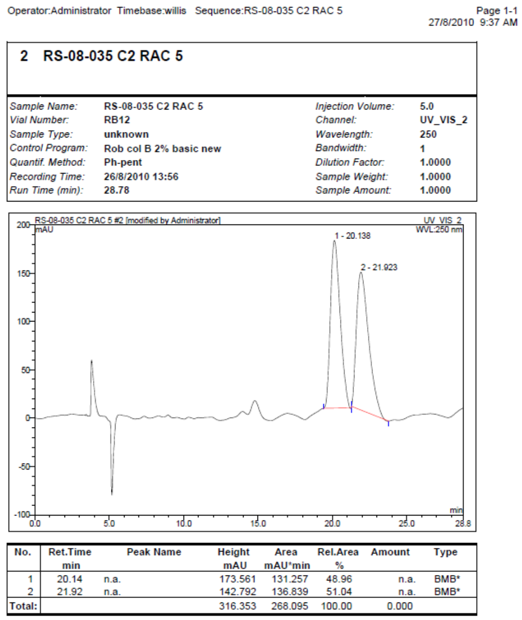
Sample Name:	**RS-03-032 S,S trost**	*Injection Volume:*	**5.0**
Vial Number:	**RA9**	*Channel:*	**UV_VIS_4**
Sample Type:	**unknown**	*Wavelength:*	**300**
Control Program:	**Rob col A 5% basic new**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**28/1/2011 15:16**	*Sample Weight:*	**1.0000**
Run Time (min):	**27.17**	*Sample Amount:*	**1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.53	n.a.	935.312	381.643	100.00	n.a.	BMB*
Total:			935.312	381.643	100.00	0.000	



(+)-99% ee
[*S*,*S*]-DACT-Phenyl-Trost Ligand

1,1'-Dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole, C_2-chimonanthine, 13

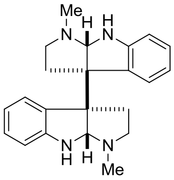


Operator:Administrator Timebase:willis Sequence:RS-08-035 C2 RAC 5
Page 1-1
27/8/2010 9:37 AM

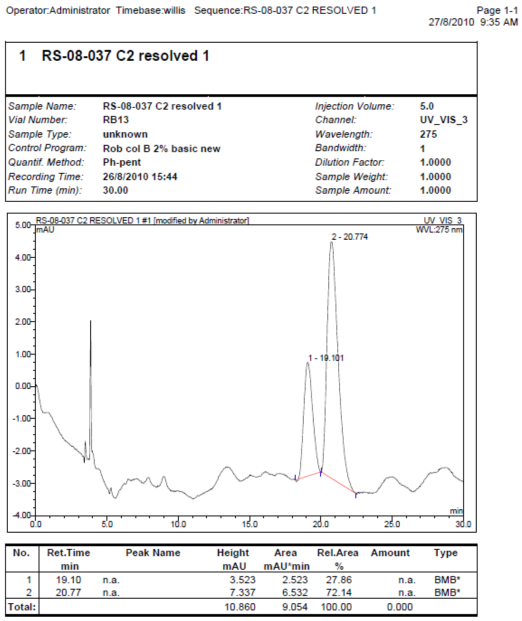
2 RS-08-035 C2 RAC 5

Sample Name: **RS-08-035 C2 RAC 5**
Vial Number: **RB12**
Sample Type: **unknown**
Control Program: **Rob col B 2% basic new**
Quantif. Method: **Ph-pent**
Recording Time: **26/8/2010 13:56**
Run Time (min): **28.78**
Injection Volume: **5.0**
Channel: **UV_VIS_2**
Wavelength: **250**
Bandwidth: **1**
Dilution Factor: **1.0000**
Sample Weight: **1.0000**
Sample Amount: **1.0000**

No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.14	n.a.	173.561	131.257	48.96	n.a.	BMB*
2	21.92	n.a.	142.792	136.839	51.04	n.a.	BMB*
Total:			316.353	268.095	100.00	0.000	



(±)

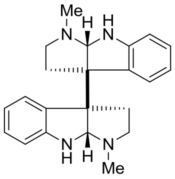


Operator:Administrator Timebase:willis Sequence:RS-08-037 C2 RESOLVED 1
Page 1-1
27/8/2010 9:35 AM

1 RS-08-037 C2 resolved 1

Sample Name: **RS-08-037 C2 resolved 1**
Vial Number: **RB13**
Sample Type: **unknown**
Control Program: **Rob col B 2% basic new**
Quantif. Method: **Ph-pent**
Recording Time: **26/8/2010 15:44**
Run Time (min): **30.00**
Injection Volume: **5.0**
Channel: **UV_VIS_3**
Wavelength: **275**
Bandwidth: **1**
Dilution Factor: **1.0000**
Sample Weight: **1.0000**
Sample Amount: **1.0000**

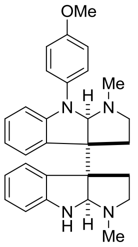
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.10	n.a.	3.523	2.523	27.86	n.a.	BMB*
2	20.77	n.a.	7.337	6.532	72.14	n.a.	BMB*
Total:			10.860	9.054	100.00	0.000	

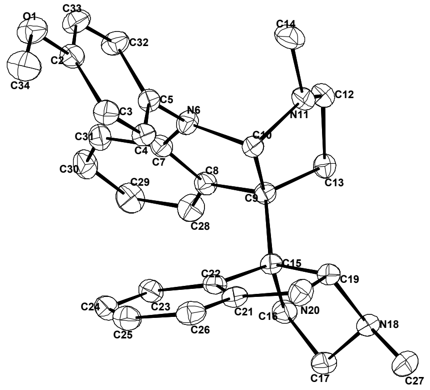


(-)-44% ee
[*R*,*R*]-DACT-Phenyl-Trost Ligand

13.4 Crystallography Data

8-(4-Methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole, *Mono-Product*, 84





Chemical formula (sum): C32 N4 O2
Chemical formula (moiety): C32 N4 O2
Chemical formula weight: 472.38

Crystal Structure Data

Spacegroup Symbol:	P -1
Origin Offset:	(none)
Lattice Type:	P

General Equivalent Positions		
+x +y +z	-x -y -z	

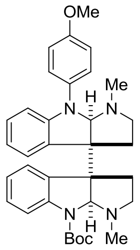
Unit Cell Parameters

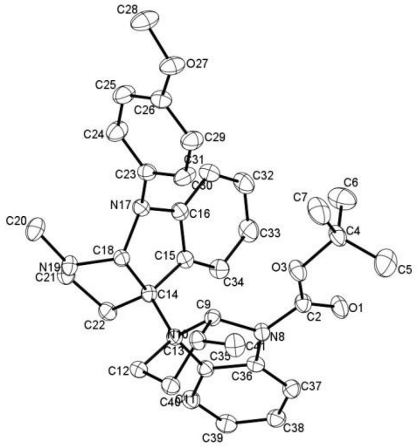
a [Å]	b [Å]	c [Å]	alpha [°]	beta [°]	gamma [°]
9.2243	9.4367	17.1962	98.465	91.603	111.338

Fractional Coordinates of Atoms in the Asymmetric Unit

Site Label	Element	x	y	z
C2	C	0.0058	0.1301	0.3819
C3	C	0.0379	0.2494	0.3386
C4	C	0.1869	0.3131	0.3134
C5	C	0.3016	0.2559	0.3287
C7	C	0.5847	0.4080	0.3550
C8	C	0.7045	0.4973	0.3149
C9	C	0.6469	0.4846	0.2297
C10	C	0.4812	0.3531	0.2224
C12	C	0.6566	0.2442	0.1680
C13	C	0.7407	0.4178	0.1724
C14	C	0.3842	0.0737	0.1708
C15	C	0.6366	0.6388	0.2132
C16	C	0.7972	0.7716	0.2183
C17	C	0.7711	0.8661	0.1593
C19	C	0.5621	0.6255	0.1276
C21	C	0.3963	0.6813	0.2173
C22	C	0.5244	0.6855	0.2644
C23	C	0.5332	0.7274	0.3458
C24	C	0.4098	0.7590	0.3797
C25	C	0.2815	0.7496	0.3324
C26	C	0.2727	0.7117	0.2507
C27	C	0.6175	0.8065	0.0318
C28	C	0.8492	0.5857	0.3546
C29	C	0.8713	0.5918	0.4358
C30	C	0.7484	0.5104	0.4757
C31	C	0.6035	0.4160	0.4364
C32	C	0.2662	0.1340	0.3711
C33	C	0.1204	0.0729	0.3984
C34	C	0.7481	0.1224	0.3996
C36	C	0.0342	0.3429	0.0347
C37	C	0.0609	0.2652	0.1011
C38	C	0.9215	0.2328	0.9684
N6	N	0.4539	0.3200	0.3031
N11	N	0.4931	0.2275	0.1654
N18	N	0.6808	0.7466	0.0926
N20	N	0.4160	0.6492	0.1375
O1	O	0.8653	0.0618	0.4117
O35	O	0.1804	0.4285	0.0065

tert-Butyl 8'-(4-methoxyphenyl)-1,1'-dimethyl-1,1',2,2',3,3a,3',3'a,8,8a,8',8'a-dodecahydro-3a,3'a-bipyrrolo[2,3-b]indole-8-carboxylate, 89





Chemical formula (sum): C34 H40 N4 O3
Chemical formula (moiety): C34 H40 N4 O3
Chemical compound source: .
Chemical formula weight: 552.72

Crystal Structure Data

Spacegroup Symbol:	P 21 21 21
Origin Offset:	(none)
Lattice Type:	P

General Equivalent Positions

+x +y +z	-x 1/2+y 1/2-z	1/2+x 1/2-y -z
1/2-x -y 1/2+z		

Unit Cell Parameters

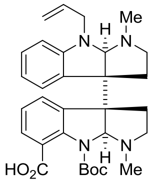
a [Å]	b [Å]	c [Å]	alpha [°]	beta [°]	gamma [°]
11.0989	14.4711	18.3551	90.000	90.000	90.000

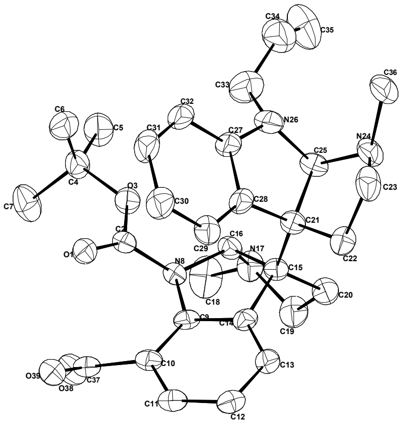
Fractional Coordinates of Atoms in the Asymmetric Unit

Site Label	Element	x	y	z
C2	C	0.7179	0.3206	0.7908
C4	C	0.9135	0.2449	0.7774
C5	C	0.9005	0.1898	0.8474
C6	C	0.8828	0.1894	0.7102
C7	C	0.0390	0.2852	0.7716
C9	C	0.7201	0.4891	0.7556
C11	C	0.6901	0.6237	0.8256
C12	C	0.6237	0.6418	0.7549
C13	C	0.6118	0.5438	0.7221
C14	C	0.6148	0.5412	0.6371
C15	C	0.6150	0.4435	0.6063
C16	C	0.7172	0.4300	0.5638
C18	C	0.7354	0.5832	0.6067
C20	C	0.7838	0.7111	0.5220
C21	C	0.5791	0.6508	0.5399
C22	C	0.5153	0.6022	0.6023
C23	C	0.9157	0.4989	0.5519
C24	C	0.9745	0.5220	0.4888
C25	C	0.0976	0.5057	0.4799
C26	C	0.1620	0.4661	0.5355
C28	C	0.3432	0.4603	0.4652
C29	C	0.1048	0.4422	0.6001
C30	C	0.9820	0.4583	0.6078
C31	C	0.7402	0.3455	0.5301
C32	C	0.6567	0.2752	0.5383
C33	C	0.5523	0.2886	0.5791
C34	C	0.5311	0.3731	0.6131
C35	C	0.5032	0.4947	0.7533
C36	C	0.5366	0.4150	0.7909
C37	C	0.4520	0.3578	0.8231
C38	C	0.3310	0.3808	0.8157
C39	C	0.2959	0.4606	0.7791
C40	C	0.3822	0.5188	0.7486
C41	C	0.8529	0.5178	0.8626
H51	H	0.8187	0.1625	0.8482
H52	H	0.9130	0.2341	0.8877
H53	H	0.9628	0.1414	0.8487
H61	H	0.9390	0.1365	0.7085
H62	H	0.8938	0.2281	0.6676
H63	H	0.8002	0.1664	0.7138
H71	H	0.0456	0.3232	0.7266

H72	H	0.0560	0.3235	0.8154
H73	H	0.0965	0.2346	0.7672
H91	H	0.7779	0.4659	0.7180
H111	H	0.7280	0.6795	0.8441
H112	H	0.6352	0.5989	0.8633
H121	H	0.6710	0.6807	0.7216
H122	H	0.5433	0.6685	0.7617
H181	H	0.7964	0.5978	0.6441
H201	H	0.7928	0.6750	0.4768
H202	H	0.8633	0.7153	0.5465
H203	H	0.7556	0.7736	0.5099
H211	H	0.5414	0.7102	0.5254
H212	H	0.5850	0.6095	0.4968
H221	H	0.4849	0.6495	0.6374
H222	H	0.4466	0.5638	0.5855
H241	H	0.9297	0.5501	0.4510
H251	H	0.1377	0.5212	0.4341
H281	H	0.4266	0.4377	0.4723
H282	H	0.3426	0.5268	0.4519
H283	H	0.3029	0.4237	0.4270
H291	H	0.1492	0.4146	0.6386
H301	H	0.9414	0.4409	0.6511
H311	H	0.8120	0.3376	0.5025
H321	H	0.6703	0.2159	0.5160
H331	H	0.4947	0.2407	0.5829
H341	H	0.4594	0.3820	0.6417
H371	H	0.4743	0.3024	0.8506
H381	H	0.2723	0.3428	0.8385
H391	H	0.2109	0.4752	0.7759
H401	H	0.3591	0.5743	0.7253
H411	H	0.9151	0.4785	0.8405
H412	H	0.8035	0.4811	0.8966
H413	H	0.8902	0.5714	0.8881
N8	N	0.6640	0.4061	0.7906
N10	N	0.7792	0.5547	0.8037
N17	N	0.7871	0.5108	0.5581
N19	N	0.6982	0.6682	0.5712
O1	O	0.6646	0.2487	0.8015
O3	O	0.8370	0.3283	0.7790
O27	O	0.2826	0.4452	0.5328

(3a*R*,3'a*S*,8a*S*,8'a*R*)-8'-Allyl-8-(*tert*-butoxycarbonyl)-1,1'-dimethyl-2,2',3,3',8,8a,8',8'a-octahydro-1H,1'H-3a,3'a-bipyrrolo[2,3-b]indole-7-carboxylic acid, 104





Chemical formula (sum): C31.735 H42.738 N4 O5.634
Chemical formula (moiety): C31 H38 N4 O4, 0.735(C H4 O), 0.899(H2 O)
Chemical formula weight: 570.40

Crystal Structure Data

Spacegroup Symbol:	P 1 21 1
Origin Offset:	(none)
Lattice Type:	P

General Equivalent Positions		
+x +y +z	-x 1/2+y -z	

Unit Cell Parameters					
a [Å]	**b [Å]**	**c [Å]**	**alpha [°]**	**beta [°]**	**gamma [°]**
9.5559	16.9796	9.8875	90.000	108.409	90.000

Fractional Coordinates of Atoms in the Asymmetric Unit				
Site Label	**Element**	**x**	**y**	**z**

C2	C	0.1997	0.3331	0.5650
C4	C	0.4018	0.3951	0.7544
C5	C	0.3077	0.4404	0.8254
C6	C	0.5349	0.3586	0.8643
C7	C	0.4509	0.4443	0.6488
C9	C	0.0319	0.2457	0.3888
C10	C	0.9717	0.2923	0.2688
C11	C	0.0378	0.3671	0.2339
C14	C	0.8427	0.2642	0.1660
C15	C	0.7815	0.1925	0.1809
C16	C	0.8460	0.1460	0.3013
C17	C	0.9699	0.1733	0.4061
C18	C	0.0520	0.1365	0.5485
C19	C	0.1941	0.1878	0.5984
C21	C	0.2443	0.0726	0.4854
C22	C	0.1090	0.0534	0.5289
C23	C	0.4354	0.1776	0.5535
C24	C	0.9605	0.1410	0.6523
C25	C	0.9149	0.2253	0.6717
C26	C	0.8200	0.2748	0.5760
C27	C	0.8019	0.3521	0.6171
C28	C	0.8778	0.3774	0.7521
C29	C	0.9709	0.3276	0.8520
C30	C	0.9885	0.2507	0.8102
C32	C	0.0540	0.1189	0.8114
C34	C	0.8047	0.0714	0.7579
C35	C	0.8287	0.0843	0.6150
C36	C	0.9706	0.0578	0.0066
C37	C	0.2367	0.2134	0.9874
C38	C	0.2786	0.1780	0.1296
C39	C	0.3928	0.1302	0.1731
C42	C	0.5295	0.3599	0.2541
H51	H	0.3582	0.4871	0.8690
H52	H	0.2156	0.4550	0.7552
H53	H	0.2855	0.4082	0.8959
H61	H	0.5021	0.3255	0.9285
H62	H	0.5960	0.3998	0.9195
H63	H	0.5916	0.3279	0.8199
H71	H	0.4884	0.4092	0.5914
H72	H	0.3677	0.4734	0.5897
H73	H	0.5266	0.4805	0.6971
H141	H	0.7989	0.2946	0.0850
H151	H	0.6974	0.1749	0.1132
H161	H	0.8028	0.0981	0.3101

H191	H	0.2187	0.2021	0.6995
H211	H	0.3126	0.0276	0.5032
H212	H	0.2149	0.0889	0.3821
H221	H	0.0383	0.0249	0.4523
H222	H	0.1327	0.0225	0.6140
H231	H	0.3990	0.2037	0.4620
H232	H	0.4788	0.2163	0.6277
H233	H	0.5092	0.1381	0.5497
H261	H	0.7694	0.2585	0.4830
H271	H	0.7392	0.3859	0.5546
H281	H	0.8667	0.4295	0.7767
H291	H	0.0187	0.3445	0.9460
H321	H	0.1488	0.0948	0.8156
H332	H	0.9854	0.0109	0.8326
H341	H	0.7471	0.0243	0.7580
H342	H	0.7609	0.1171	0.7880
H351	H	0.8539	0.0348	0.5839
H352	H	0.7434	0.1065	0.5472
H361	H	0.9222	0.1045	0.0264
H362	H	0.9195	0.0118	0.0258
H363	H	0.0745	0.0574	0.0639
H371	H	0.3070	0.1946	0.9437
H372	H	0.2446	0.2704	0.9993
H381	H	0.2215	0.1900	0.1903
H391	H	0.4385	0.1133	0.1048
H392	H	0.4269	0.1131	0.2732
H401	H	0.4326	0.0883	0.7812
H402	H	0.4907	0.0277	0.8230
H411	H	0.3438	0.4102	0.2146
H421	H	0.5278	0.3365	0.3411
H422	H	0.5007	0.3211	0.1812
H423	H	0.6245	0.3812	0.2608
N8	N	0.1590	0.2593	0.5083
N20	N	0.3121	0.1377	0.5824
N31	N	0.0760	0.1911	0.8939
N33	N	0.9583	0.0591	0.8543
O1	O	0.1383	0.3938	0.5174
O3	O	0.3209	0.3254	0.6812
O12	O	0.1692	0.3669	0.2384
O13	O	0.9475	0.4243	0.1933
O40	O	0.4702	0.0676	0.8610
O41	O	0.4303	0.4206	0.2228

Initial refinement of the Flack x parameter gave a value of 0.30(119), suggesting that the absolute configuration could not be determined (Flack, 1983; Flack & Bernardinelli, 2000). Analysis of the Bijvoet differences using CRYSTALS gave the Hooft y parameter as 0.24(33), and the probability the configuration is correct assuming the material is enantiopure was determioned to be 91.5% (Hooft et al., 2008; Thompson et al. 2008; Thompson & Watkin 2009). In the absence of significant anomalous scattering (FRIEDIF = 5.75; Flack and Shmueli, 2007), Friedel pairs were merged for the final refinement. R. W. W. Hooft, L. H. Straver and A. L. Spek, J. Appl. Cryst. (2008), 41, 96-103.

A. L. Thompson, D. J. Watkin, Z. A. Gal, L. Jones, J. Hollinshead, S. F. Jenkinson, G. W. J. Fleet and R. J. Nash, Acta Cryst. (2008), C64, o649-o652 A. L. Thompson & D. J. Watkin, Tetrahedron: Asymmetry (2009), 20, 712-717.

Flack, H. D.; Shmueli, U. Acta Crystallogr., Sect. A 2007, 63, 257-265.

H. D. Flack, Acta Cryst. (1983). A39, 876-881; H. D. Flack and G. Bernardinelli, J. Appl. Cryst. (2000), 33, 1143-1148.

Full Crystals Listing below.

ALT, 28/08/09.

CRYSTALS Listing:

```
#TON CRITER= 999999.
         Notification of SPECIAL conditions
 Initialising Special positions
 Floating origin in  y direction
              molecular weight,  calculated density, absorption coefficient
                                  (gm/cm**3)           (cm-1)
  From LIST    5       572.123           1.248            0.862
  From LIST   29       530.667           1.158            0.773
  Friedif =     5.8   Estimated Friedel difference =     0.5029
  f computed from scattering factors, including f-prime

 Plotting (Fo+ - Fo-) vs (Fc+ - Fc-)
 Gradient for zero intercept =             -3.727
 Slope, intercept and Cc (R) of Fo/Fc  Plot = -3.722      0.19  -0.13290

 Computing normal probability plot for         2132 reflections.
 Gradient for zero intercept =              0.889
 Slope, intercept and Cc (R) of  NPP   Plot =  0.889      0.02   0.99892

 The slope shoud be unity and the intercept zero

 No of Reflections processed =   4454
 No of Friedel Pairs found =     2132 No of Friedel Pairs used  =     2132
 No of Unpaired Reflections  =    190
 Flack parameter obtained from original refinement
 Hooft parameter obtained with Flack x set to zero
 Reflections only used if /Fo+ - Fo-/ < 999999.00 * /Fc+ - Fc-/
 Friedif =       5.75 Acta A63, (2007), 257-265
 Flack & Bernardinelli (2008) recommend a value >200
 for general structures and >80 for enantiopure crystals

 Flack Parameter & su    0.2957    1.1883
```

```
 Hooft Parameter & su    0.2409    0.3303
          Ton G & su    0.5181    0.6607

 The absolute configuration has not been reliably determined
^^WI SAFESET [ _MT_REF_NREF TEXT   4454. ]
deltaF = F^2(+) - F^2(-)
          Number +ve   mean(deltaF)   rms(deltaF)   Number -ve   mean(deltaF)   rms(deltaF)
For Fo
            1071         4.4539         7.4866         1061        -4.1088        6.2133
For Fc
            1105         0.1312         0.2211         1027        -0.1448        0.2696

No of reflections for which delta(Fo) has same sign as delta(Fc)
Same sign   Opposite sign
    1019          1113

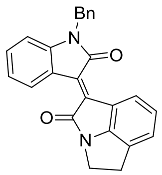
 Distribution of Delta(F^2)/<F^2>
Delta Fo^2     0     0     0     1     6    88   494   981   463    87    12     0     0     0     0
Delta Fc^2     0     0     0     0     0     0     0  2132     0     0     0     0     0     0     0
    n         -7    -6    -5    -4    -3    -2    -1     0     1     2     3     4     5     6     7

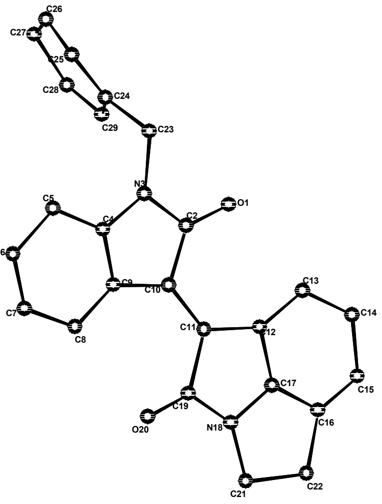
 For an enantiopure material, there are 2 choices, P2
P2(correct)     0.9146   (0.914606E+00)

 If 50:50 twinning is possible, there are 3 choices, P3
P3(correct)     0.4868   (0.486771E+00)
P3(rac-twin)    0.4678   (0.467780E+00)
P3(inverse)     0.0454   (0.454484E-01)
G              0.5181
G S.U.          0.6607
FLEQ            0.2409
FLEQ S.U.       0.3303   (0.330332E+00)
```

(*E*)-1-(1-Benzyl-2-oxoindolin-3-ylidene)-4,5-dihydropyrrolo[3,2,1-hi]indol-2(1H)-one,

Tri-cyclic product, 170





Chemical formula (moiety): C25 H18 N2 O2
Chemical formula (sum): C25 H18 N2 O2
Chemical formula weight: 378.41

Crystal Structure Data

Spacegroup Symbol:	(not used)
Origin Offset:	(none)
Lattice Type:	P

General Equivalent Positions		
+x +y +z	-x -y -z	

Unit Cell Parameters					
a [Å]	**b [Å]**	**c [Å]**	**alpha [°]**	**beta [°]**	**gamma [°]**
6.6223	8.5296	17.7914	95.795	97.985	110.487

Fractional Coordinates of Atoms in the Asymmetric Unit

Site Label	Element	x	y	z
C1	C	0.7601	0.5397	0.3439
C2	C	0.6087	0.3498	0.3254
C3	C	0.7428	0.2582	0.3609
C4	C	0.7365	0.0962	0.3718
C5	C	0.9255	0.0792	0.4096
C6	C	0.1243	0.2157	0.4379
C7	C	0.1344	0.3778	0.4287
C8	C	0.3024	0.5590	0.4468
C9	C	0.1744	0.6708	0.4164
C10	C	0.9446	0.3850	0.3914
C11	C	0.2571	0.1053	0.2676
C12	C	0.4004	0.2918	0.2836
C13	C	0.2624	0.3766	0.2469
C14	C	0.2893	0.5420	0.2380
C15	C	0.1158	0.5764	0.2004
C16	C	0.9135	0.4488	0.1713
C17	C	0.8814	0.2813	0.1781
C18	C	0.0555	0.2487	0.2157
C19	C	0.8672	0.9322	0.2079
C20	C	0.8053	0.8633	0.1222
C21	C	0.9575	0.8465	0.0787
C22	C	0.8895	0.7754	0.0013
C23	C	0.6692	0.7213	0.9675
C24	C	0.5170	0.7381	0.0110
C25	C	0.5850	0.8091	0.0883
C120	C	0.8171	0.8577	0.1250
C121	C	0.9946	0.8769	0.0884
C122	C	0.9599	0.8043	0.0119
C123	C	0.7477	0.7124	0.9720
C124	C	0.5702	0.6932	0.0087
C125	C	0.6049	0.7658	0.0851
H4	H	0.6058	0.9994	0.3539
H5	H	0.9191	0.9686	0.4164
H6	H	0.2489	0.1977	0.4629
H8A	H	0.4275	0.5698	0.4203
H8B	H	0.3586	0.5931	0.5029
H9A	H	0.1667	0.7514	0.4590
H9B	H	0.2445	0.7350	0.3776
H11A	H	0.7375	0.9528	0.2214
H11B	H	0.8931	0.8488	0.2390
H14	H	0.4264	0.6315	0.2577

H15	H	0.1358	0.6900	0.1945
H16	H	0.7963	0.4759	0.1464
H17	H	0.7444	0.1924	0.1577
H19A	H	0.7402	0.9505	0.2252
H19B	H	0.8980	0.8460	0.2358
H21	H	0.1081	0.8835	0.1018
H22	H	0.9936	0.7639	0.9716
H23	H	0.6227	0.6727	0.9146
H24	H	0.3664	0.7011	0.9879
H25	H	0.4809	0.8206	0.1181
H121	H	0.1396	0.9397	0.1157
H122	H	0.0812	0.8174	0.9869
H123	H	0.7240	0.6628	0.9198
H124	H	0.4252	0.6304	0.9814
H125	H	0.4836	0.7526	0.1102
N1	N	0.9548	0.5451	0.3818
N2	N	0.0570	0.0904	0.2287
O1	O	0.7187	0.6638	0.3298
O2	O	0.3040	0.9855	0.2848

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