Total Synthesis of (–)-Nakadomarin A and an Approach to the Diazatricyclic Core of the Madangamines



A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (D.Phil.)

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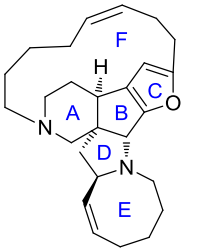
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Abstract

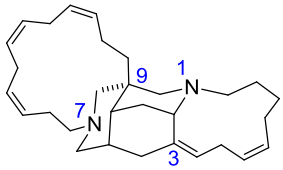
Total Synthesis of (–)-Nakadomarin A and an Approach to the Diazatricyclic Core of the Madangamines

Andrew Kyle Wadham College D. Phil. Trinity Term 2012

This dissertation describes work towards two marine alkaloid natural products of the manzamine family. The total synthesis of (–)-nakadomarin A, *via* two conceptually different strategies is described along with the development of a novel nitro-Mannich-Mannich cascade reaction, which has been applied in a synthesis of the diazatricyclic core of the madangamines.



(–)-Nakadomarin A



Madangamine A

A short and highly stereoselective synthesis of (–)-nakadomarin A has been developed. A sequential alkyne ring-closing metathesis/*syn* selective reduction strategy enabled the stereoselective construction of the *Z*-configured alkene in the fifteen-membered macrocycle of the molecule. 'Matched' catalyst and substrate control facilitated a highly diastereoselective nitro olefin Michael addition to fix two of the four stereocentres in one key step. Furthermore, a nitro-Mannich/lactamization cascade, furan *N*-acyl iminium ion cyclisation and alkene ring-closing metathesis enabled the total synthesis of the natural product in 19 steps.

In collaboration with Prof. Amir Hoveyda and Prof. Richard Schrock, an alternative approach to a highly *Z*-selective macrocyclic ring closure in the synthesis of (–)-nakadomarin A has been developed. Three diene substrates were prepared and the *Z*-selectivity of alkene ring-closing metathesis investigated using a range of molybdenum MAP (monoaryloxide pyrrolide) catalysts. Initial studies using these catalysts produced promising results (*Z*:*E* = ~1.2:1), relative to commercially available ruthenium metathesis catalysts (*Z*:*E* = 2:3). Using a recently developed chiral tungsten MAP complex, alkene ring-closing metathesis was found to proceed in excellent yield (90%) with exceptional *Z:E*-selectivity (*Z*:*E* ~1.2:1) and requiring only low catalyst loadings (5 mol%).

A novel nitro-Mannich-Mannich cyclisation cascade has been developed allowing access to highly functionalized piperidines. Application of this unprecedented mode of reactivity using a substrate derived from a Michael-addition of methylcyanoacetate to a functionalized cyclic nitro olefin allowed the preparation of a *cis*-fused 6,6'-bicycle in excellent yield. Further elaboration of this 6,6'-bicycle enabled the synthesis of the diazatricyclic core of the madangamine alkaloids to be achieved.

Declarations and Copyright

I declare that thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Any work done in collaboration with a research colleague or undergraduate student has been fully acknowledged and referenced within the text.

I was admitted as a probationary research student in October 2008 and as a candidate for the degree of Doctor of Philosophy in January 2010; the higher study for which this is a record was carried out in the University of Oxford between 2008 and 2012.

Andrew F. Kyle

Date Signature of candidate

I hereby certify that the candidate has fulfilled the conditions of the Regulations appropriate for the degree of Doctor of Philosophy in the University of Oxford and that the candidate is qualified to submit this dissertation in application for that degree.

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I would like to thank: Ben Brash, Matt M, Ben Darses, Isabelle, Lei-Shi, Swarup, Chris Kourra, Angel, Andrej, Lucia, Linus, Felix, Jonás, Raquel, Bea, Tetsuhiro, Leonardo, Maria and Matt Rattley who have all contributed in their own unique way to my time in the group. I would like to thank my part II student Rob for his hard work to achieve some great results in the nitro-Mannich-Mannich project.

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I would like give a special thanks to my third favourite Slovak and good friend/colleague Pavol Jakubec. Pavol is the finest chemist I have ever met and it has been an honour to have worked with him on the (−)-nakadomarin A project. I will forever be indebted to him for the help he has given me over the past four years and for the many enjoyable evenings of triple whiskies/‘Birds’ that we have shared.

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Abbreviations

°C	degrees Celsius
9-AECN	9-amino(9-deoxy) *epi*-cinchonine
Å	ångström
Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aromatic group, not phenyl
Atm.	standard atmosphere
Bn	benzyl
Boc	Di-*tert*-butyl dicarbonate
br	broad
Bu	butyl
c	concentration
cf.	confer
CI	chemical ionisation
cm	centimetre
COSY	correlation spectroscopy
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dd	doublet of doublets
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DFT	density functional theory

DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
E^+	electrophile
ED	effective dose
ee	enantiomeric excess
EI	electron impact
eq.	equivalents
ES	electrospray
Et	ethyl
EWG	electron withdrawing group
g	gram
h	hour(s)
HBMC	heteronuclear multiple-bond correlation experiment
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single-quantum coherence experiment
HOBt	Hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry

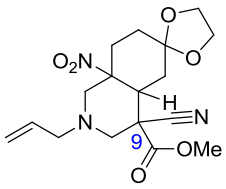
HWE	Horner-Wadsworth-Emmons reaction
Hz	hertz
IC_{50}	half maximal inibitory concentration
IPA	isopropylalcohol
IR	infrared
LDA	lithium diisopropylamide
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
m	*meta*
m	multiplet
max	maximum
m/z	mass-to-charge ratio
MAP	monoaryloxide-pyrrolide
Me	methyl
mg	milligram
MHz	megahertz
Min	minute
mL	millilitre
µl	microlitre
MM	molecular modeling
mmol	millimole
MO	molecular orbital
Mol	mole
mp	melting point

MS	molecular sieves / mass spectrometry
Ms	mesylate
N	normal
n	straight chain
nm	nanometre
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nosyl
Nuc	nucleophile
o	*ortho*
p	*para*
Ph	phenyl
Pr	propyl
ppm	parts per million
q	quartet
quat.	quaternary
R	alkyl group
rac	racemic
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerisation
RT	room temperature
s	singlet
t	retention time (HPLC) / triplet (NMR)
t/*tert*	tertiary
TBAF	tetra-*n*-butylammonium fluoride

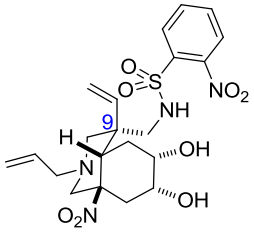
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TCDI	1,1’-thiocarbonyldiimidazole
Temp.	temperature
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TS	transition state
TSA	toluene sulfonic acid
WSC.HCl	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride

Stereochemistry and Numbering

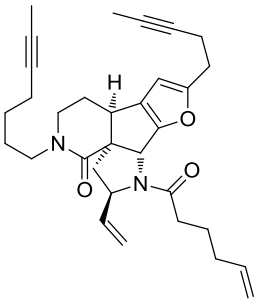
Stereochemistry is drawn in accord with the conventions proposed by Maehr.[‡] Normal bond thickness is used for racemic compounds or enantioenriched compounds where stereochemistry is unknown. Solid and broken wedges are used to indicate absolute configuration when known (or inferred from other results) in enantioenriched or enantiopure compounds. Solid and broken lines are used to indicate the relative stereochemistry (when known) of diastereopure or diastereoenriched, racemic compounds.



racemic or enantioenriched compound with unknown stereochemistry

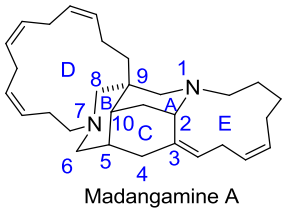


racemic diastereopure or diastereoenriched compound with known relative stereochemistry

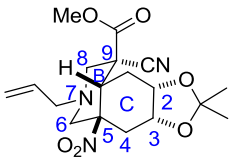


enantiopure or enantioenriched compound where stereochemistry is known (or assumed)

For the madangamine alkaloids the following numbering and labelling scheme is used. All fragments and intermediates in the text are numbered according to the carbon, proton, or ring that they will become in the final madangamine molecule.



Madangamine A



[‡] Maehr, H. *J. Chem. Educ*. **1985**, *62*, 114–120.

1. Total Synthesis of (–)-Nakadomarin A

1.1. (–)-Nakadomarin A – Isolation, Structure and Biological Activity

(–)-Nakadomarin A (**1**) is a marine alkaloid of the manzamine family. It was first isolated by Kobayashi and co-workers in 1997 from the *Haplosclerida* sponge *Amphimedon sp.*, which was collected off the coast of the Kerama Islands, Okinawa (Figure 1.1).[1,2] The intricate structure of this alkaloid was determined through exhaustive NMR studies and found to possess a hexacyclic 8/5/5/5/15/6 ring system incorporating four stereogenic centres, with one quaternary carbon and a *Z*-configured alkene in the macrocyclic F-ring.

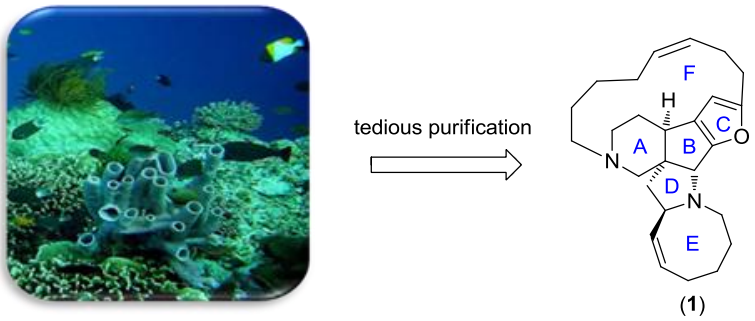


Figure 1.1. (–)-nakadomarin A (**1**)

The manzamine alkaloids are a naturally occurring family of β-carboline containing alkaloids. Despite its lack of β-carboline functionality, (–)-nakadomarin A (**1**) is considered to be a member of the family and was proposed by Kobayashi to arise through a biosynthetic pathway from ircinal A (**4**). Ircinal A (**4**) is in turn derived from a tetracyclic biogenic precursor **3**, of manzamine A (**2**) as proposed by Baldwin and Whitehead in their seminal report (Figure 1.2).[1,3] A more detailed analysis of the biosynthesis of the manzamine alkaloids is covered in Chapter 5.

Manzamine A (**2**), the prototype of the family, was first isolated in 1986 by Higa and co-workers as the hydrochloride salt from the sponge genus *Haliclona.*[4] It was subsequently isolated from genus *Pellina* by Nakamura.[5] The high *in vitro* activity displayed by manzamine A (**2**) against P388 mouse leukaemia cells (IC_{50} 0.07 μg/mL) along with potent antibacterial, antimalarial, insecticidal, anti-inflammatory and anti-HIV activity have made it, and its related compounds highly desirable synthetic targets.[5-12]

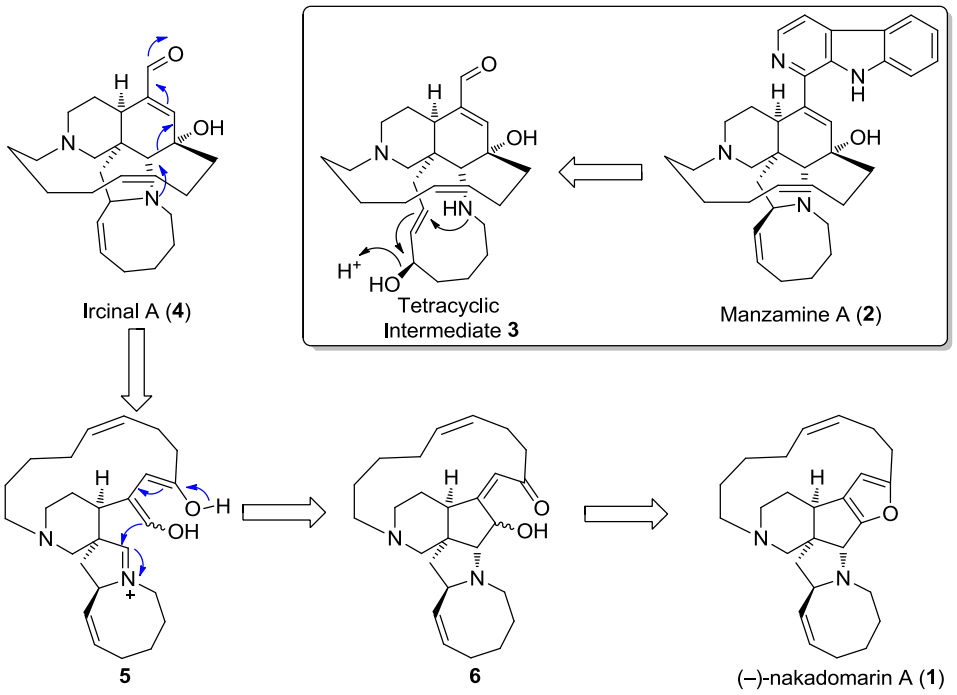


Figure 1.2. Biosynthesis of (–)-nakadomarin A (**1**)

While manzamine A (**2**) is readily isolated by extraction from its marine sponge source (100 mg can be obtained from 735 g of the wet sponge), only minute quantities of nakadomarin A can be isolated by similar means (6 mg from 1 kg of wet sponge). Its limited availability from its natural source and promising biological activity have made (–)-nakadomarin A (**1**) a popular target within the synthetic community. Initial biological studies by Kobayashi showed that (–)-nakadomarin A (**1**) displayed cytotoxic activity against

murine lymphoma L1210 cells (IC_{50} = 1.3 μg/mL), inhibition of cyclin dependent kinase 4 (IC_{50} = 9.9 μg/mL) and antimicrobial activity against the fungus *Trichophyton mentagrophytes* (MIC = 23 μg/mL) and the gram-positive bacterium *Corynebacterium xerosis* (MIC = 11 μg/mL).[1]

1.2. Previous Synthetic Strategies

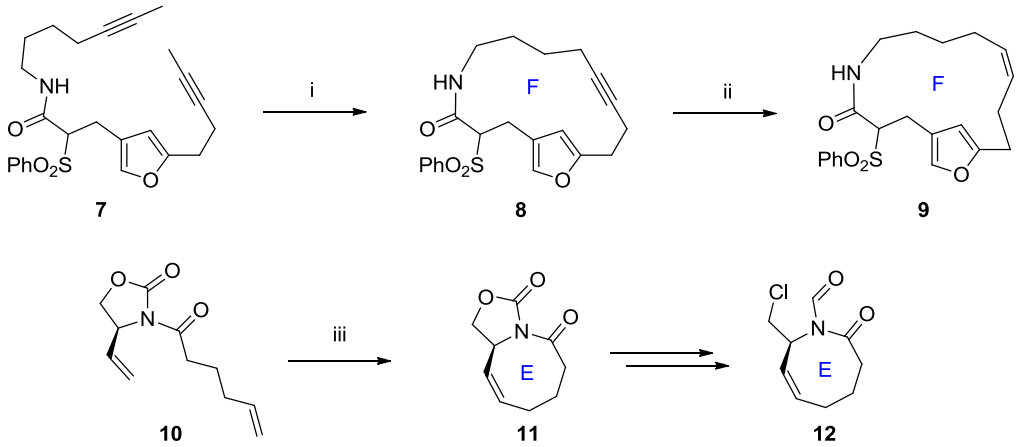
At the commencement of this research, three total syntheses of nakadomarin A had been reported, one of the natural enantiomer (–)-nakadomarin A (**1**) and two of its antipode (+)-nakadomarin A.[13-15] In addition, several reports detailing strategies towards the ABCD tetracyclic core and other ring fragments had been published.[16-24] Considerable synthetic effort towards (–)-nakadomarin A (**1**) had already been carried out in the Dixon research group which formed the basis of the work described in chapters 2 and 3 of this dissertation.

Summarised below is a brief overview of selected synthetic strategies towards (–)-nakadomarin A (**1**) which were reported prior to the commencement of this research. Although not exhaustive this section highlights the reports which were influential on the work described in this dissertation.

1.3. Fürstner – Alkyne Ring-Closing Metathesis Studies

Fürstner synthesized the macrocyclic F-ring of nakadomarin A using an alkyne ring-closing metathesis (RCM)/*syn* selective reduction strategy on a model substrate **7** (Scheme 1.1).[16] At the time of its publication, this example represented the most elaborate application of an alkyne ring-closing

metathesis strategy. However, the model substrate **7** used contained limited functionality that would be expected to be present in a late stage synthetic intermediate, although the potentially labile furan was present. A Grubbs alkene RCM approach in the synthesis of the hexahydroazocine E-ring fragment **12** was also reported.

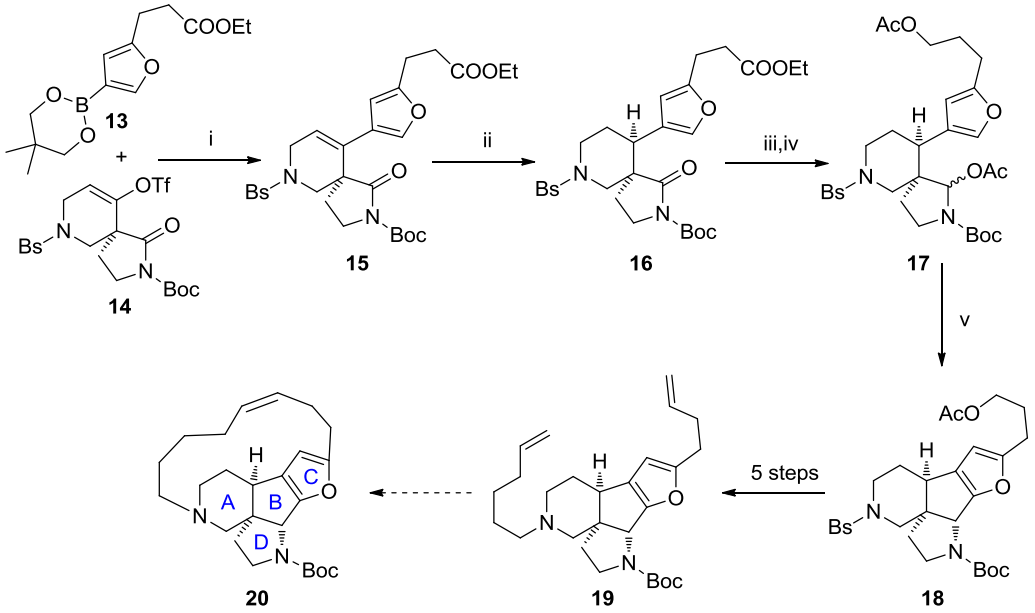


Scheme 1.1. Fürstner: Synthesis of macrocyclic rings.[16] Reagents and conditions: i) $(^tBuO)_3W{\equiv}CCMe_3$ (10 mol%), PhCl, 80 °C, 2 h, 90%; ii) H_2, Lindlar catalyst, quinoline, hexane, RT, 2 h, 92%; iii) Grubbs 1st generation catalyst, 76%.

1.4. Nishida – Racemic Synthesis of the Tetracyclic Core

In 2001 Nishida, who would later achieve the first total synthesis of both antipodes of nakadomarin A, reported a strategy to the racemic ABCD tetracyclic core (Scheme 1.2).[19] Suzuki-Miyaura coupling of enol triflate **14** with boronic ester **13** introduced the furan moiety. The key steps that introduced the required relative stereochemistry of three stereogenic centres, included a selective hydrogenation from the least hindered face of tetrahydropyridine **15**, followed by an intramolecular furan cyclisation to the *N*-acyliminium ion generated from **17** under acidic conditions after selective reduction and activation of spiro-γ-lactam **16**. Using a model system, Nishida noted that the hydrogenation step had to be carried out prior to cyclisation to

avoid concurrent hydrogenation of the strained furan ring. Although appropriate functionality was introduced, the results of attempted RCM experiments to complete the macrocyclic F-ring **20** were not reported.



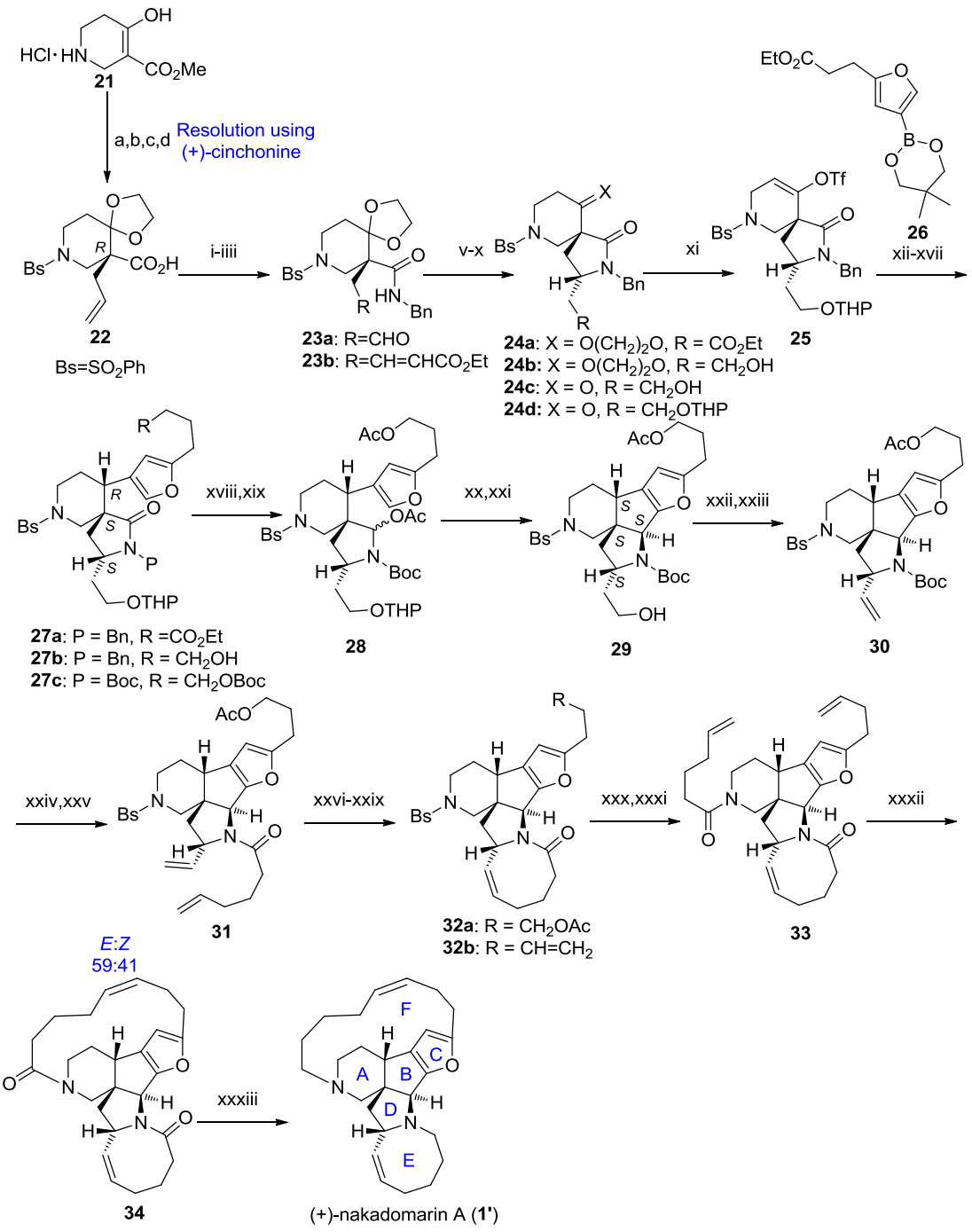
Scheme 1.2. Nishida: Racemic synthesis of the tetracyclic core of nakadomarin A.[19] Reagents and conditions: (i) $Pd(PPh_3)_4$, LiCl, DME, aq. Na_2CO_3, 7 h, 80 °C (68% over 2 steps from ketone form of **14**); ii) H_2, 10% Pd/C, 87%; iii) DIBAL-H, toluene, −65 °C to RT; (iv) Ac_2O, pyridine; (v) *p*-TsOH, CH_2Cl_2 (49% over 3 steps).

1.5. Nishida – Total Synthesis of (+)-Nakadomarin A (2003)

The first synthesis of nakadomarin A was reported by Nishida in 2003 and was of the unnatural enantiomer (Scheme 1.3).[13] The synthesis built upon Nishida's previously reported strategy to the tetracyclic core (*vide supra*, Chapter 1.4). Acid **22** was prepared in its racemic form in a similar fashion to the previous report, however a resolution with (+)-cinchonine gave the (*R*)-isomer in enantiopure form as its cinchonium salt.

A modified oxidative cleavage/Wittig olefination/intramolecular Michael addition sequence utilizing the allyl group of **22** provided a functional handle with which to construct the 8-membered E-ring after formation of spiro-γ-

lactam **24**, which was absent in the original study. A Suzuki-Miyaura coupling of enol triflate **25** with functionalized furan **26** again, after some functional group manipulations, set up an intramolecular furan cyclisation to the *N*-acyliminium ion generated from **28**, to complete the tetracyclic core **29**. The key to Nishida's strategy was the introduction of diene functionality for the sequential closure of the E- and F-rings by alkene ring-closing metathesis. The E-ring closure to give **32** was unproblematic; however closure of the 15-membered F-ring produced a separable mixture of geometrical isomers 3:2 in favour of the undesired *E*-alkene, yielding only 26% of the required *Z*-isomer. Nonetheless, 16 mg of the unnatural enantiomer were synthesized after a double amide reduction with Red-Al completed the synthesis in 37 steps.



Scheme 1.3. Nishida: First total synthesis of (+)-nakadomarin A (2003).[13] Reagents and conditions: (a) $PhSO_2Cl$, $NaHCO_3$, EtOAc:H_2O (2:1), RT, 2 h, 98%; (b) allyl bromide, NaH, DMF, RT, 12 h, 85%; (c) ethylene glycol, *p*-TsOH, benzene, 48 h, reflux, 94%; (d) NaOH, DMSO, 2 h, 130 °C, 95%; i) $BnNH_2$, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC·HCl), HOBt, DMF, 91%; ii) OsO_4 (cat.), NMO, aq. THF, RT; iii) $NaIO_4$, CH_2Cl_2:H_2O (2:1), RT; iv) $PH_3P{=}CHCO_2Et$, CH_2Cl_2, reflux; v) DBU, EtOH; vi) 2N NaOH, MeOH; vii) AcCl, EtOH, 54% (over 8 steps); viii) $LiBH_4$, MeOH, THF 99%; ix) 70% $HClO_4$, CH_2Cl_2, RT, 91%; x) DHP, CSA (cat.), 91%; xi) (a) $LiN(TMS)_2$, THF, -78 °C, (b) $PhNTf_2$, 87%; xii) **25**, $PdCl_2$(dppf), K_3PO_4, 80 °C, 3 h, 95%; xiii) (a) H_2, 10% Pd/C, MeOH, RT, 1.5 h, 71%, (b) PPTS, EtOH, (c) separation of diastereomers, (d) DHP, CSA (cat.), 69%; xiv) $LiBH_4$, MeOH, THF, 99%; xv) Li, liq. NH_3; xvi) $PhSO_2Cl$, aq. $NaHCO_3$, 80% (over 2 steps); xvii) $(Boc)_2O$, Et_3N, DMAP (cat.), 98%; xviii) DIBAL-H, CH_2Cl_2, toluene; xix) Ac_2O, pyridine, 80% (over 2 steps); xx) *p*TsOH, CH_2Cl_2; xxi) 1N HCl, THF, 87% (over 2 steps); xxii) 2-nitrophenylselenocyanate, *n*-Bu_3P; xxiii) *m*CPBA, aq. K_2HPO_4; xxiv) TFA, CH_2Cl_2; xxv) 5-hexenoic acid, (WSC)·HCl, HOBt, 73% (over 4 steps); xxvi) Grubbs 2nd generation catalyst (20 mol%), CH_2Cl_2, 50 °C, 1.5 h; xxvii) 2N NaOH, MeOH, RT, 1.5 h, 64% (over 2 steps); xxviii)

Dess-Martin periodinane, 80%; xxix) $Ph_3P{=}CH_2$, 72%; xxx) Na, naphthalene; xxxi) 5-hexenoic acid, WSC·HCl, HOBt, 77% (over 2 steps); xxxii) Grubbs 1st generation catalyst (15 mol%), CH_2Cl_2, 0.5 mM, 50 °C, 24 h, 26% (*Z*), 44% (*E*); xxxiii) Red-Al, toluene, reflux, 86%.

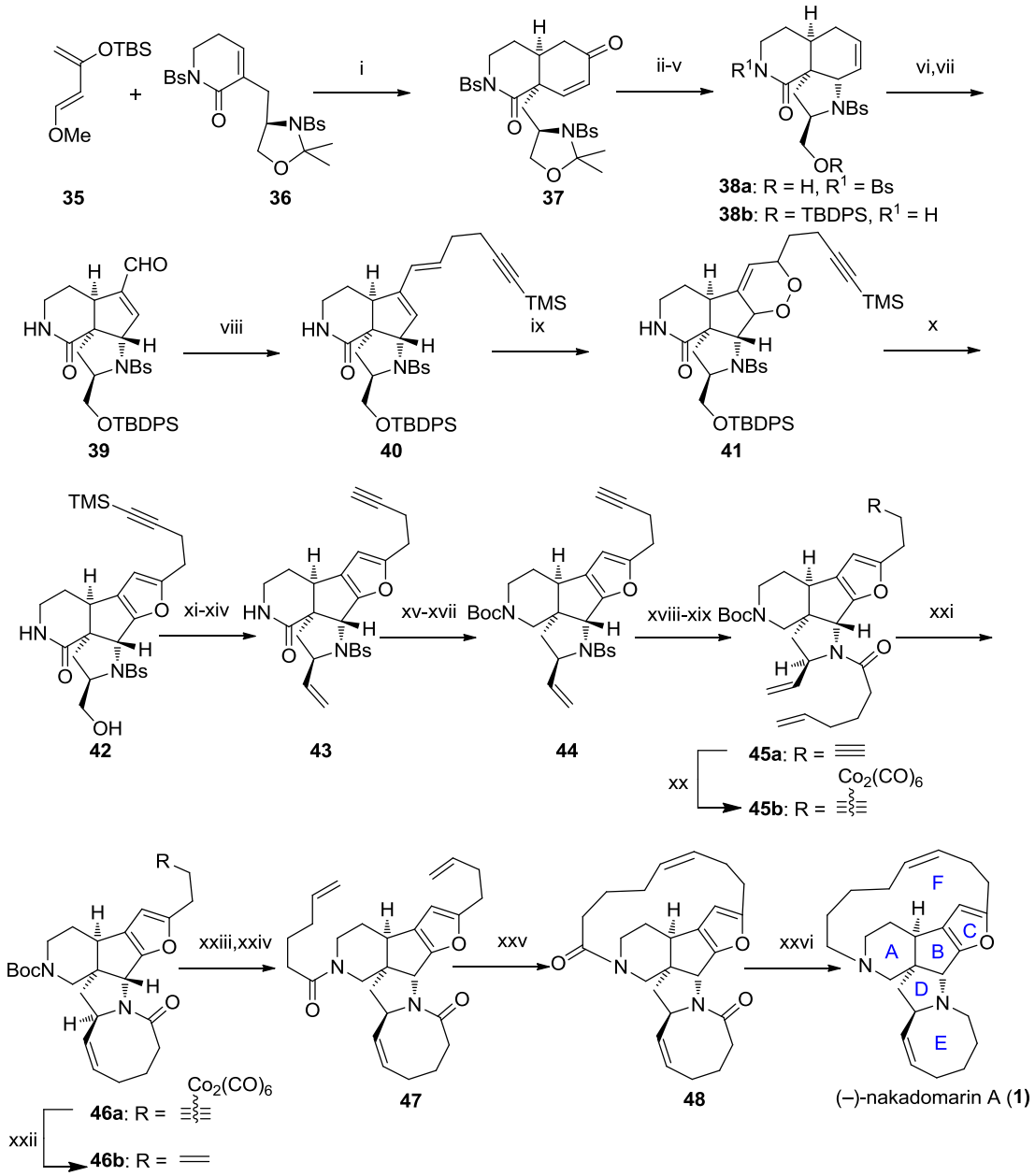
1.6. Nishida – Total Synthesis of (–)-Nakadomarin A (1) (2004)

One year after his initial synthesis, Nishida published a conceptually different route this time to the natural enantiomer, (–)-nakadomarin A (**1**) (Scheme 1.4).[14] The necessity for a new approach arose due to the inability to resolve the required *S*-enantiomer from the racemic form of acid **22**.

The required stereochemistry was obtained using L-serine, from which chiral dienophile **36** was prepared in 10 steps. A Diels-Alder cycloaddition between **36** and diene **35** yielded the highly functionalized hydroisoquinoline **37**, which Nishida had originally intended to use as a building block for the synthesis of ircinal A (**4**). A Luche reduction of enone **37**, followed by acetonide deprotection and a chemoselective and moderately stereoselective S_N2' cyclisation introduced the D-ring. Double bond cleavage by ozonolysis and recyclisation of the formed unstable bis-aldehyde gave access to the required 5-membered B-ring **39**. Exposure of diene **40** to singlet oxygen formed an endoperoxide **41** as a mixture of diastereomers, which both converged to the required furan **42** after treatment with KO^{t}Bu, followed by acid promoted dehydration.

With the stereoselective construction of the tetracyclic core achieved, Nishida again opted for an alkene RCM strategy to close the macrocyclic rings. E-ring closure proceeded smoothly in the presence of a terminal alkyne protected as a dicobalt hexacarbonyl complex **45b**. Nishida installed the alkyne (originally TMS protected) to circumvent problems with terminal to internal

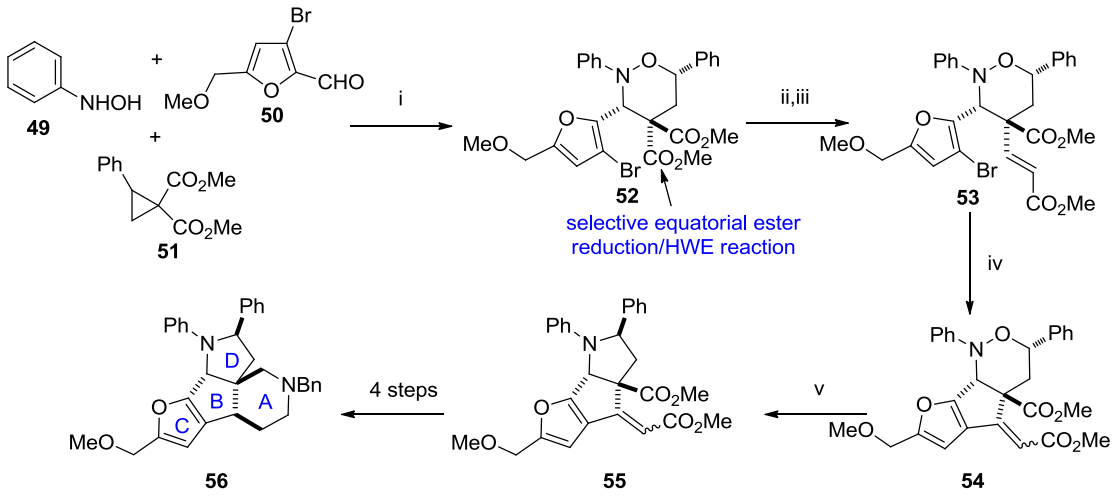
alkene isomerisation in the furan forming step. Interestingly no attempts of an alkyne RCM approach to construct the F-ring were reported and instead the dicobalt complex was converted into an alkene by reductive decomplexation with *n*Bu_3SnH. The subsequent alkene RCM again gave an unfavourable mixture of geometrical isomers, however, with the *Z*-isomer isolated in only 26% yield. Nishida's second route to nakadomarin A (**1**) incorporated some very elegant chemistry, and more importantly accessed the natural enantiomer for the first time. However, in terms of step count (36 steps) and overall yield (only 2.5 mg of (–)-nakadomarin A (**1**) was isolated) this route offered little improvement over his original synthesis.



Scheme 1.4. Nishida: Total synthesis of (–)-nakadomarin A (**1**) (2004).[14] Reagents and conditions: i) neat, 180 °C, 1 h; then TFA, CH_2Cl_2, RT, 52% (diastereomer 35%); ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2:MeOH, −78 °C, 98% (2:1 dr); iii) HCl (6N), benzene, reflux, 1 h, 70%; iv) TBDPSCl, imidazole; v) Na/anthracene, DME, −65 °C, 74% (over 2 steps); vi) O_3, CH_2Cl_2, −78 °C; then SMe_2, RT; vii) *N*-methylanilinium trifluoroacetate, THF, reflux, 75% (over 2 steps); viii) $IPh_3PCH_2CH_2CH_2CCTMS$, NaH, THF, −78 °C to RT, 76%; ix) O_2, halogen lamp, Rose Bengal, CH_2Cl_2:MeOH, 0 °C, quant.; x) ^{t}BuOK, THF, −78 °C; then HCl (6N), RT, 88%, ^{t}BuOK, THF, −30 °C, then HCl (6N), RT, 69%; xi) Dess-Martin periodinane, 90%; xii) $TMSCH_2MgCl$, Et_2O, RT, 83% (2:1 dr); xiii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT; xiv) K_2CO_3, MeOH, 81% (over 2 steps); xv) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 93%; xvi) DIBAL-H, toluene, −78 °C; xvii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C, 84% (over 2 steps); xviii) Na/Naphthalene, DME, −65 °C; xix) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92% (over 2 steps); xx) $Co_2(CO)_8$, CH_2Cl_2, 91%; xxi) Grubbs 2nd generation catalyst (25 mol%), CH_2Cl_2 (0.1 mM), reflux, 1.5 h, 83%; xxii) *n*-Bu_3SnH, benzene, 65 °C, 75%; xxiii) TFA, CH_2Cl_2; xxiv) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92% (over two steps); xxv) Grubbs 1st generation catalyst (20 mol%), CH_2Cl_2 (0.5 mM), reflux, 24 h, *Z*-isomer 26%, *E*-isomer 46%; xxvi) Red-Al, toluene, reflux, 92%.

1.7. Kerr – Total Synthesis of (+)-Nakadomarin A (1) (2007)

In 2005 Kerr reported a synthesis of the ABCD tetracyclic core of nakadomarin A. A diastereoselective Lewis acid catalyzed [3+2] dipolar cycloaddition of a nitrone, prepared *in situ* from substituted furan aldehyde **50** and hydroxylamine **49**, with cyclopropane **51** generated tetrahydrooxazine **52** (>5.7:1 dr). N-O bond cleavage of this key intermediate followed by alcohol activation and ring closure, provided the 2,5-*trans*-substituted pyrrolidine D ring. A Heck reaction completed the B ring while double amine displacement of a bis-mesylate generated from **55** yielded the piperidine A ring of **56** (Scheme 1.5).[22]



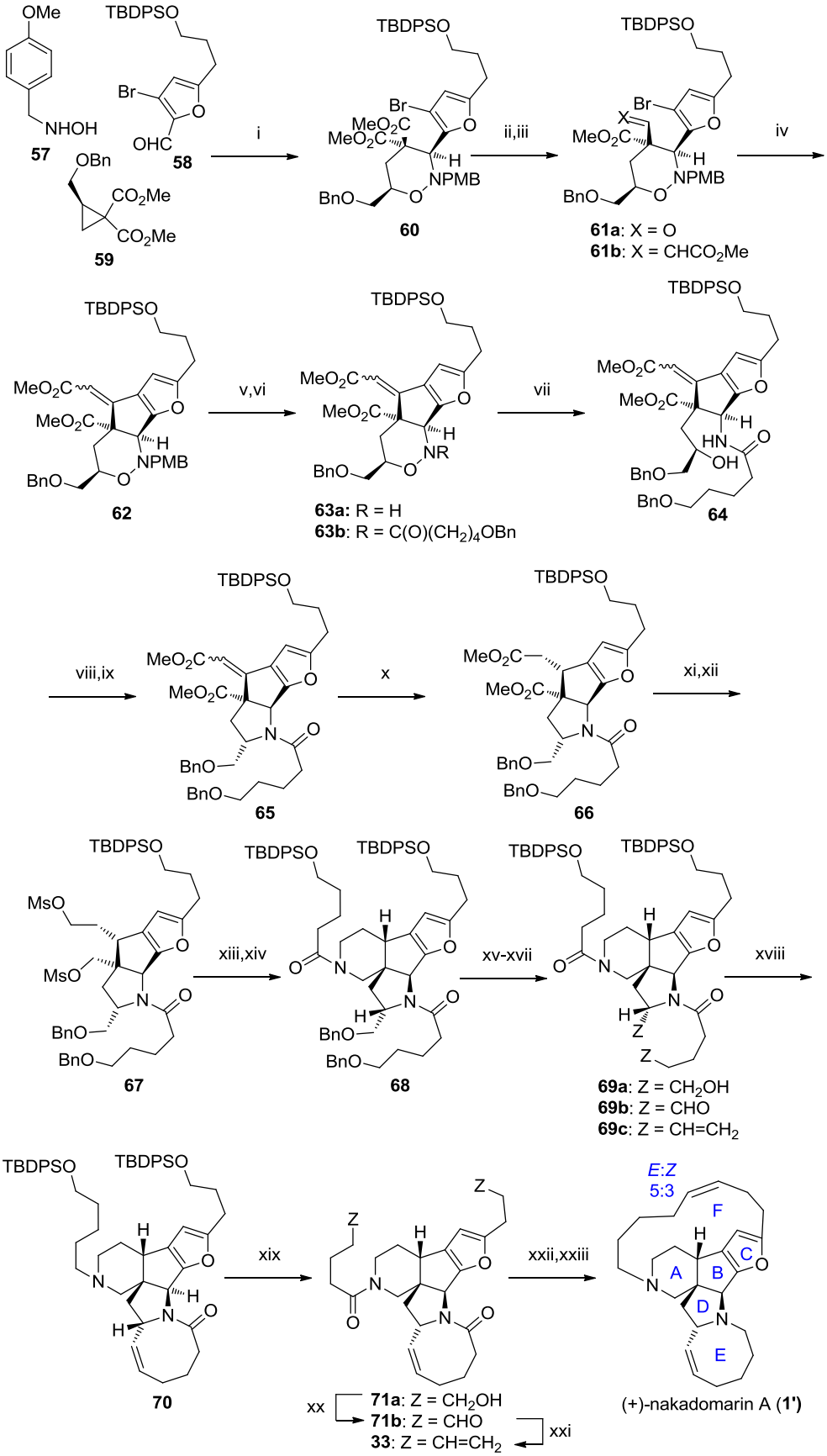
Scheme 1.5. Kerr: Synthesis of ABCD tetracyclic core **56**.[22] Reagents and conditions: i) $Yb(OTf)_3$ 10 mol%), MS 4 Å, toluene, 18 h, RT, 68%; ii) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 95%; iii) $(MeO)_2P(O)CH_2CO_2Me$, ^tBuOK, THF, RT, 2 h, 73 %; iv) $Pd(PPh_3)_4$, Ag_2SO_4, NEt_3, DMF, reflux, 4.5 h, 64%; v) H_2, Pd/C, MeOH, RT, 2 h then MsCl, NEt_3, CH_2Cl_2, RT, 66% (over 2 steps).

Building on this strategy, Kerr subsequently reported the total synthesis of (+)-nakadomarin A using a highly diastereoselective Lewis acid catalyzed [3+2] dipolar nitrone/cyclopropane cycloaddition in 2007 (Scheme 1.6).[15]

A chiral pool approach, utilizing the natural stereochemistry of D-mannitol, yielded malonyl cyclopropane **59** in six steps in enantiopure form. The key

cycloaddition step proceeded as expected and gave tetrahydrooxazine **60** in 87% yield, with high enantiomeric purity. SmI_2 promoted N-O bond scission, alcohol activation and S_N2 cyclisation converted the tetrahydrooxazine into the 5-membered D-ring, after an intramolecular Heck cyclisation had installed the B-ring. Formation of the piperidine A-ring initially by ester reduction and mesylate activation of **66** followed by double displacement with an aliphatic amine, prevented the separation of *E*/*Z* geometrical isomers later in the synthesis. A modification involving displacement with ammonia followed by amine acylation gave bis-amide **68**. Kerr adopted Nishida's double alkene RCM approach to introduce the macrocyclic rings and as a consequence suffered from the same issues regarding *E*/*Z* selectivity (5:3 in favour of the *E*-isomer). The desired *Z*- isomer was isolated in 20% over the final three steps, due to difficulties encountered isolating pure samples of **71b** and **33**.

As a result of his efficient synthesis of the tetacyclic core, Kerr's route required only 29 linear steps, representing a significant reduction on Nishida's step count. Despite this, the overall yield of Nishida's route compared favourably to Kerr's, who isolated only 2.1 mg of pure (+)-nakadomarin A.



Scheme 1.6 Kerr: Total synthesis of (+)-nakadomarin A (2007).[15] Reagents and conditions: i) 15% $Yb(OTf)_3$, 4 Å MS, 100 °C, 87%; ii) DIBAL-H, CH_2Cl_2, −78 °C, 87%; iii) $(MeO)_2P(O)CH_2CO_2Me$, ^tBuOK, THF, RT, 93%; iv) $Pd(PPh_3)_4$, Ag_2SO_4, NEt_3, DMF, reflux, 82%; v) DDQ, CH_2Cl_2:H_2O (9:1), 56% after 1

recycle; vi) $ClC(O)(CH_2)_4OBn$, NEt_3, CH_2Cl_2, 0 °C to RT, 89%; vii) 0.1 M SmI_2, THF, 0 °C (5:1 ratio of double bond isomers); viii) MsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C; ix) ^tBuOK, THF, −25 °C, 65% combined yield (three steps); x) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, Na_2CO_3, MeOH/THF (10:1), −40 °C, 67% (14:1 dr); xi) $LiAlH_4$, THF, 0 °C; xii) MsCl, NEt_3, DMAP, CH_2Cl_2, −78 °C to RT, 79% (over 2 steps) (14:1 dr); xiii) NH_3, EtOH:THF (10:1), reflux; xiv) $TBDPSO(CH_2)_4(O)CCl$, NEt_3, CH_2Cl_2, 0 °C to RT, 77% (over 2 steps); xv) BCl_3, CH_2Cl_2, −78 °C (71%); xvi) IBX, DMSO, RT; xvii) ^tBuOK, $MePPh_3Br$, THF:toluene (1:1), RT, 30-45% (over two steps); xviii) Grubbs 2nd generation catalyst (20 mol%), CH_2Cl_2 (0.7 mM), reflux, 84%; xix) MeOH, AcCl, RT; xx) Dess-Martin periodinane, CH_2Cl_2, 0 °C to RT, 70% (over 2 steps); xxi) ^tBuOK, $MePPh_3I$, THF:toluene, RT; xxii) Grubbs 1st generation catalyst (30 mol%), CH_2Cl_2 (0.2 mM), reflux, 28% (*E*-isomer); xxiii) Red-Al, toluene, reflux, 20% (over 3 steps).

1.8. Dixon – Previous Studies on (–)-Nakadomarin A (1)

Considerable development towards a synthesis of (–)-nakadomarin A (**1**) had been carried out in the Dixon research group prior to the commencement of this dissertation work. Two distinct but conceptually similar strategies had been developed in tandem by Dr P. Jakubec and a Dr D. Cockfield.

Jakubec completed the first generation Dixon synthesis of (–)-nakadomarin A (**1**) in 2009 (Scheme 1.7).[25] This 12 step (longest linear sequence) represented a significant improvement on the previous syntheses in terms of step count (previous average 34 steps) and the amount of the natural product obtained (101 mg vs 8.5 mg previously from extraction and synthesis).

Crucial to the synthesis was a key C-C bond forming diastereoselective nitro olefin Michael addition to form the tertiary and quaternary stereocentres in a single step. This reaction, catalyzed by cinchonine derived bifunctional organocatalyst **88**, was a development of previous studies in the Dixon group on the use of bifunctional organocatalysis in the enantioselective organocatalytic Michael addition of malonate esters to nitro olefins.[26]

In addition to malonate addition to nitro alkenes,[26-29] asymmetric bifunctional organic catalysts, possessing a combination of suitably separated Brønsted base and Brønsted acid functionalities attached to a rigid chiral scaffold have been used for a variety of transformations including asymmetric Michael

additions of arylthiols to α,β-unsaturated carbonyl compounds,[30] asymmetric organocatalytic Henry reactions,[31] and nitromethane addition to chalcones.[32]

Based on the cinchona alkaloid structural backbone, catalysts of type **72-75** (Figure 1.3), introduced by Dixon,[26] Hiemstra,[31] Deng,[27] Takemoto,[29] Connon,[28] Soós,[32] Chen,[30] and others,[33] operate by a dual mechanism. Pro-nucleophile activation by the bridgehead nitrogen is coupled with electrophile activation, through a hydrogen bond interaction with a readily tunable (by introduction of suitable electron withdrawing groups) (thio)urea donor group. The need for both the tertiary amine and the thiourea moieties to be present for efficient and selective catalysis to take place, was illustrated in seminal work by Takemoto.[29]

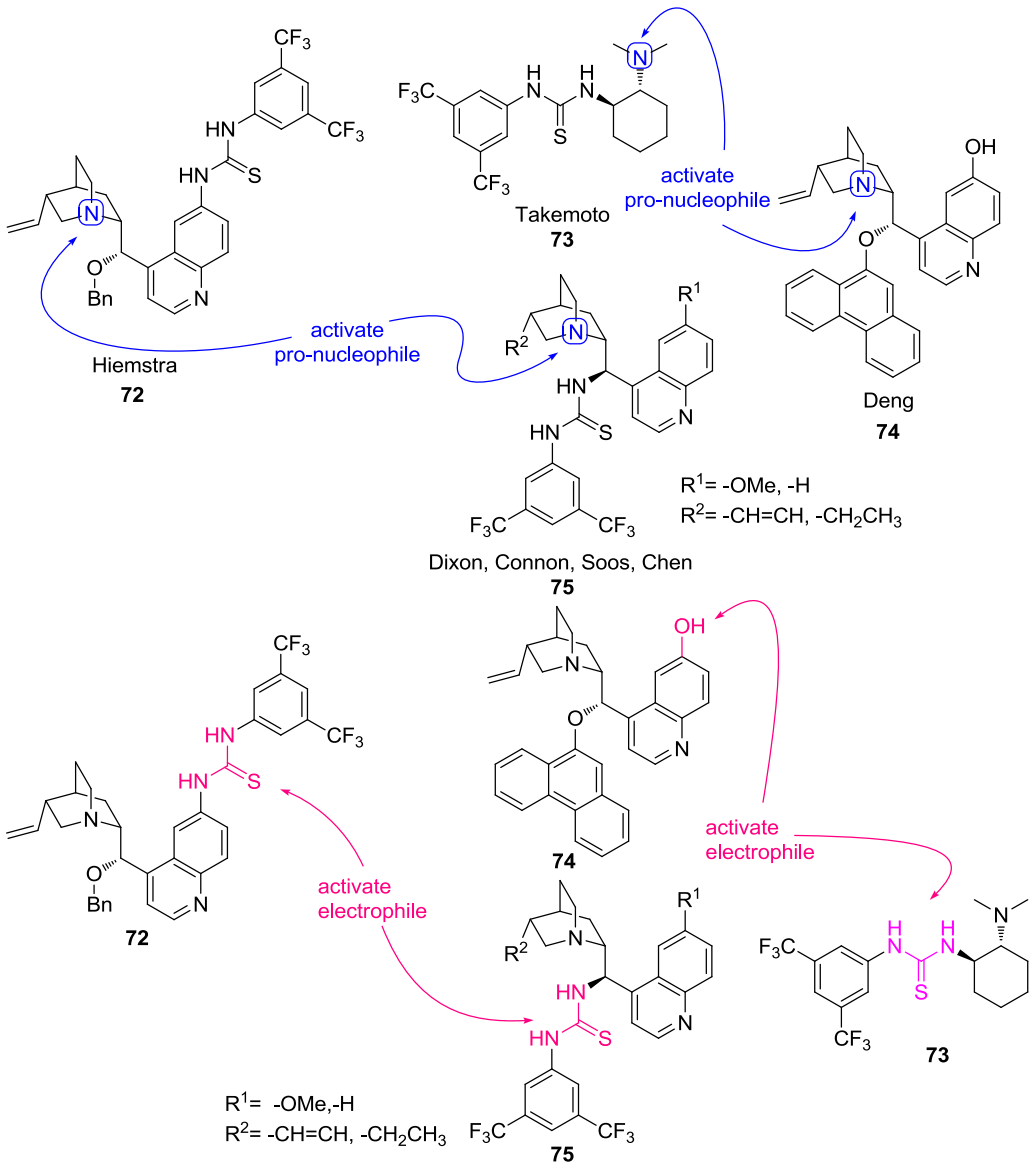
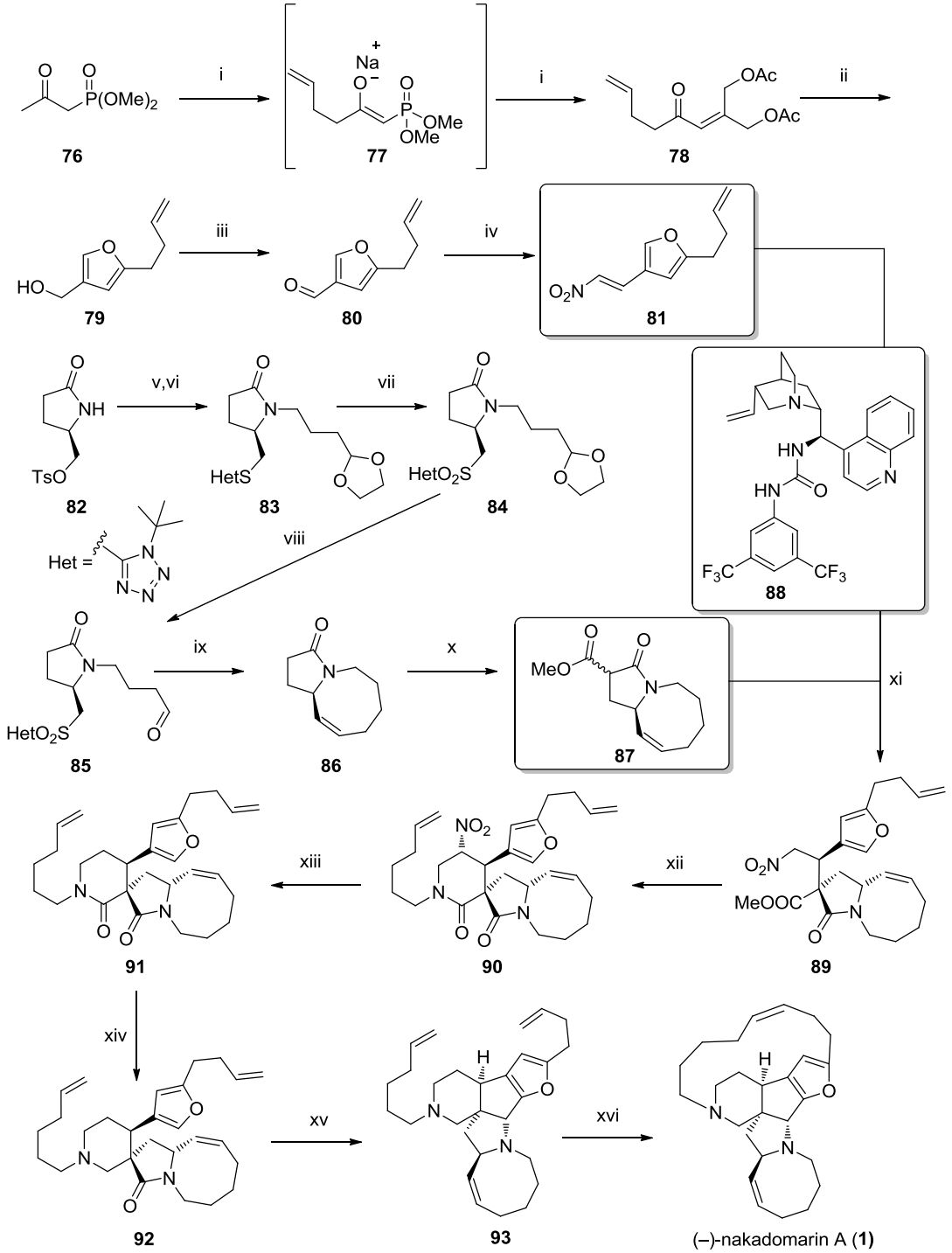


Figure 1.3. Dual activation by cinchona alkaloid derived organocatalysts.

While Jakubec's synthesis offered considerable improvement over the previous routes with respect to step count, several key steps offered room for improvement. The long reaction time (8 days) of the key Michael addition step needed to be addressed along with the poor yielding intramolecular furan/iminium ion cyclisation (**92**→**93**). While a novel, elegant intramolecular Julia-Kocienski olefination was employed to close the E-ring, an alkene RCM approach was again used in the F-ring synthesis, and as in previous

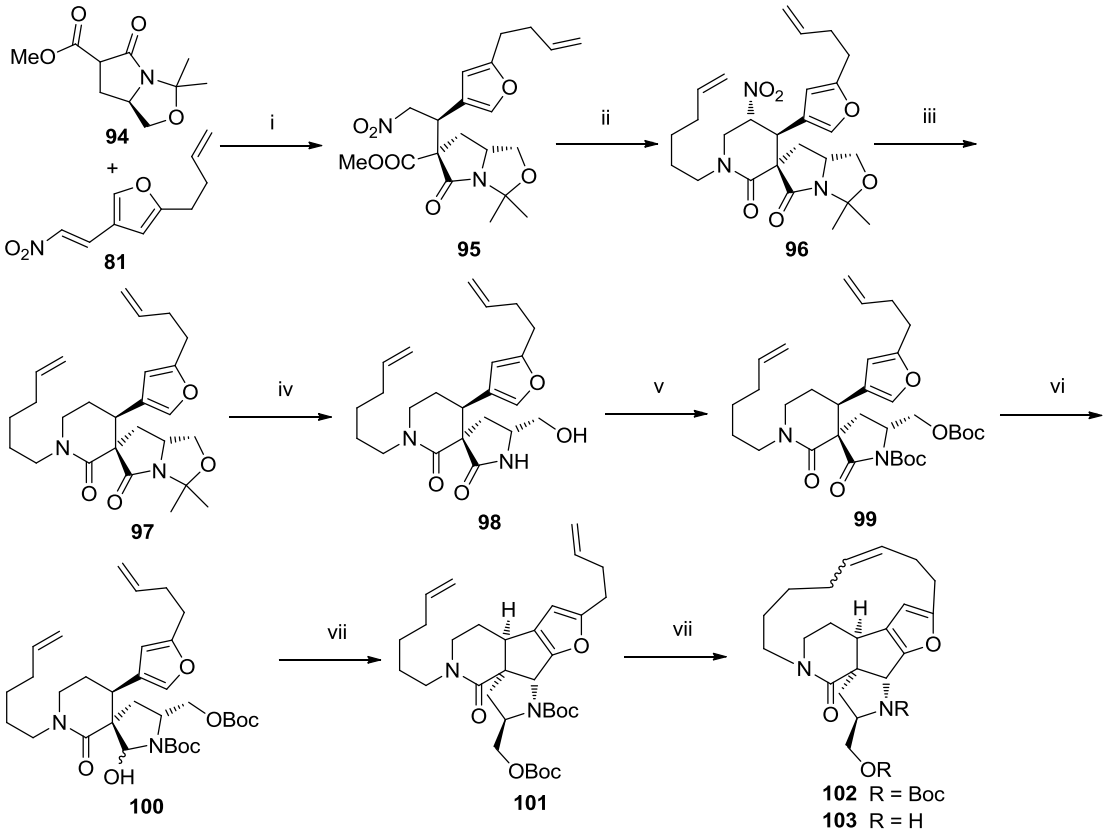
syntheses, *E*/*Z* mixtures were obtained. While this selectivity was biased in favour of the required *Z*-isomer (63:37 *Z*:*E*) by protonation of the free amines of **93** prior to metathesis, a non-trivial separation of the isomers by HPLC was required to isolate pure (–)-nakadomarin A (**1**).



Scheme 1.7. Dixon/Jakubec: Total synthesis of (–)-nakadomarin A (**1**) (2009).[25] Reagents and conditions: i) NaH, *n*-BuLi, THF, 0 °C, 1 h, then allylbromide, 10 min, then 2-oxopropane-1,3-diyl diacetate, THF, RT, 2 h, 42%; ii) HCl, EtOH, 65 °C, 24 h, 69%; iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78

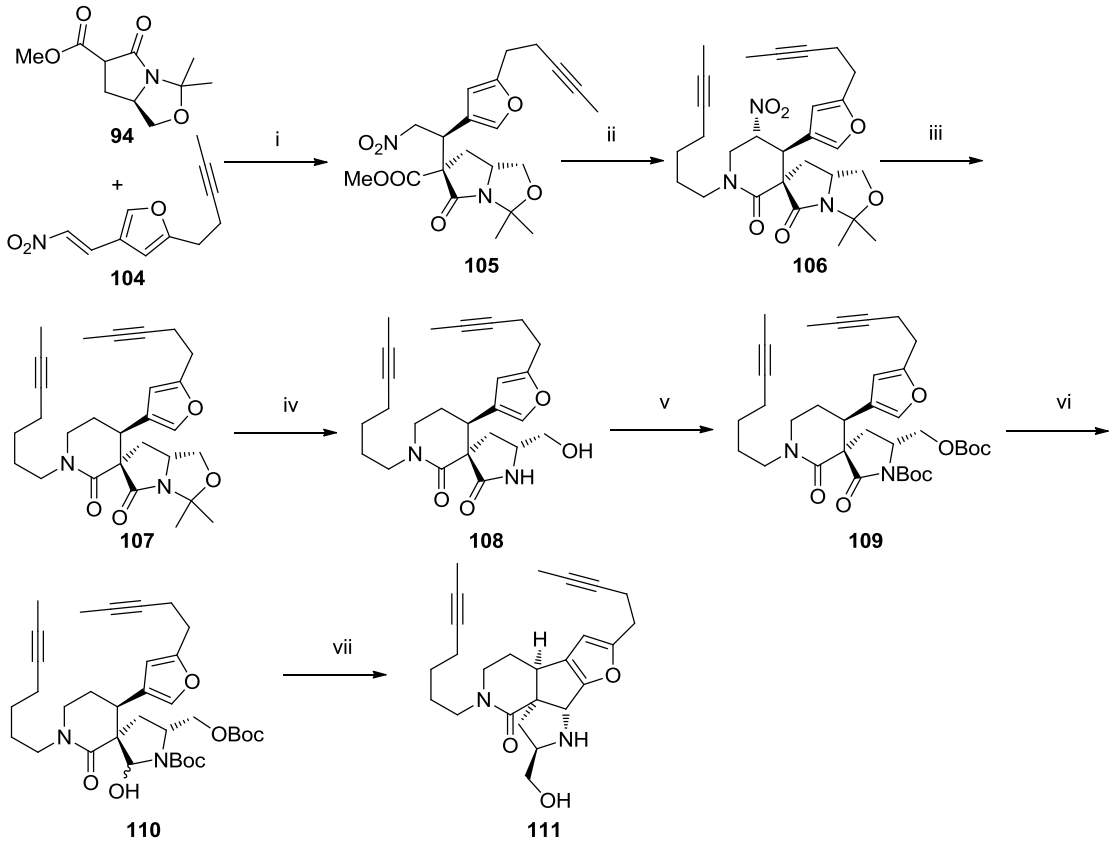
°C to RT, 0.5 h, 86%; iv) $MeNO_2$, KOH, EtOH, 0 °C, 2 h, then MsCl, Et_3N, −15 °C, 15 min, 88%; v) NaH, 1-*tert*butyl-1H-tetrazole-5-thiol, THF, reflux, 12 h, 96%; vi) 2-(4-bromobutyl)-1,3-dioxolane, NaH, Bu_4NI (cat), DMSO, 12 h, RT, 71%; vii) *m*CPBA, CH_2Cl_2, 14 h, RT, 78%; viii) HCl, THF, 2 h, RT, 98%; ix) Cs_2CO_3, DMF, THF, H_2O, 70 °C, 10 h, 56%; x) LHMDS, dimethylcarbonate, THF, −78 °C to 0 °C, 2.5 h, 82%, ~55:45 dr; xi) organocatalyst **88** (15 mol%), toluene, 30 °C, 8 days, 57%, 91:9 dr; xii) hept-5-en-1-amine, H_2C=O, MeOH, reflux, 3 h, 68%; xiii) AIBN, Bu_3SnH, toluene, reflux, 4 h, 70%; xiv) $LiAlH_4$, toluene, −20 °C, 1 h, then HCOOH, RT, 14 h, 86%; xv) DIBAL-H, toluene, −20 °C, 1 h, then HCl, 90 °C, 24 h, 41% (yield of **93**); xvi) Grubbs 1st generation catalyst, (+)-CSA, CH_2Cl_2, reflux, 3.5 h, 62%, *E*:*Z* 37:63, then HPLC separation.

To address the problems of the long reaction times required for the key Michael addition step, Cockfield introduced 5,5'-bicyclic pro-nucleophile **94** (Scheme 1.8).[34] This system offered considerable improvement in terms of diastereoselectivity, reaction time and overall yield in the Michael addition with nitro olefin **81**. The use of a furan *N*-acyliminium ion cyclisation reaction to complete the tetracyclic core (**100**→**101**) also offered an improvement relative to the equivalent transformation in Jakubec's route. However, a late stage alkene RCM approach was again adopted and the ring closed product was isolated as a mixture of inseparable diastereomers **103** (*Z*:*E* = 2:3) after removal of the Boc protecting groups. Although further structural advancements towards (–)-nakadomarin A (**1**) were described, only limited characterisation data was reported.



Scheme 1.8. Dixon/Cockfield: Alkene Route to Pentacycle **103**.[25] Reagents and conditions: i) organocatalyst **88** (10 mol%), toluene, 30 °C, 5 days 85% (single diastereoisomer); ii) hex-5-en-1-amine, CH_2=O, MeOH, reflux, 18 h, 71%; iii) AIBN, Bu_3SnH, mesitylene, reflux, 4 h, 71%; iv) *p*TsOH, MeOH, reflux, 2 h, 83%; v) Boc_2O, DMAP, Et_3N, CH_2Cl_2, RT, 15 h, 93%; vi) lithium triethylborohydride, THF, −78 °C, 2 h, 87%; vii) Ac_2O, DMAP, CH_2Cl_2, then (+)-CSA, CH_2Cl_2, 93% (over 2 steps); viii) Grubbs 1st generation catalyst (20 mol%), CH_2Cl_2, reflux, 2 h then TFA, neat, $NaHCO_3$, 56% (over 2 steps) (*Z*:*E* 2:3).

Cockfield initiated a modified route to (–)-nakadomarin A (**1**), adopting an alkyne ring-closing metathesis/*syn* selective reduction strategy in order to gain exclusive access to the *Z*-alkene in the F-ring (Scheme 1.9).[34] Building on the work developed in his original alkene route, Cockfield was able to access tetracycle **111**. However, limitations of the route, particularly the poor yielding synthesis of nitro olefin **104** provided insufficient material for further development of the synthesis. Consequently, no significant attempts to achieve the key alkyne ring-closing metathesis step were made.



Scheme 1.9. Dixon/Cockfield: Alkyne route to tetracyclic core **111**.[34] Reagents and conditions: i) organocatalyst **88** (10 mol%), CH_2Cl_2, 30 °C, 5 days 72% (single diastereoisomer); ii) hept-5-yn-1-amine, CH_2=O, MeOH, reflux, 9 h, 55%; iii) AIBN, Bu_3SnH, mesitylene, reflux, 4 h, 60%; iv) *p*TsOH, MeOH, reflux, 3 h, 84%; v) Boc_2O, DMAP, Et_3N, CH_2Cl_2, RT, 14 h, 86%; vi) lithium triethylborohydride, THF, −78 °C, 2 h, 86%; vii) HCOOH, RT, 15 h, then LiOH, MeOH, 50 °C, 3 h, 86%.

1.9. Summary

The previous synthetic work highlighted several key points for consideration in the completion of the synthesis of (–)-nakadomarin A (**1**) by the development of an alkyne ring-closing metathesis route. Kerr, Nishida and Dixon (Jakubec and Cockfield) had all highlighted the challenges of separating mixtures of *E*/*Z* isomers of late stage synthetic intermediates, which were obtained using an alkene RCM approach. The resulting tedious purifications and low isolated yields of the desired *Z*-isomer, illustrated the need for an improved strategy. Cockfield's route to the ABCD tetracyclic core bearing suitable alkyne handles **111**, presented a potentially useful substrate

from which to probe the potential for an alkyne RCM approach to (–)-nakadomarin A (**1**). Improvement and scale up of this route would initially be required to allow access to sufficient quantities of this intermediate, for detailed investigation of this transformation to be conducted. Cockfield had not been able to achieve any success in this transformation previously, although only one attempt had been made. Fürstner's report of a successful alkyne RCM strategy on a model (–)-nakadomarin A (**1**) system, containing the labile furan moiety, provided some positive evidence that such a strategy would be possible.

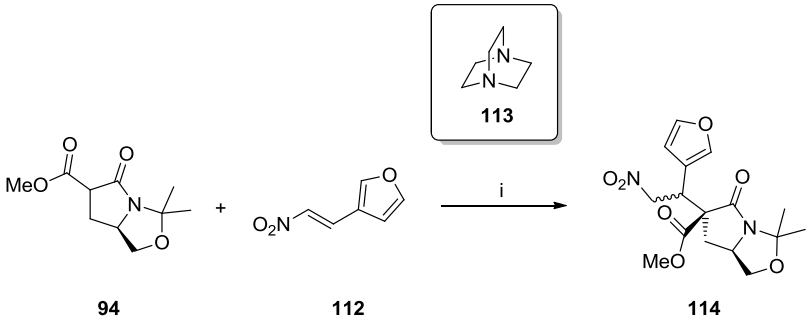
2. Synthesis of Tetracyclic Core of (–)-Nakadomarin A

2.1. Overview of Chapter Objectives

With a route to the tetracyclic core **111** of (–)-nakadomarin A (**1**) established in the work of Cockfield,[34] the initial aim of this chapter was focussed on the synthesis of sufficient quantities of this material to allow successful completion of the synthesis of (–)-nakadomarin A (**1**) to be achieved. The limited quantities of this key intermediate accessed by Cockfield prevented any investigation of strategies to complete the remaining rings. Optimization of poor yielding steps in the synthesis of the tetracyclic core was therefore a key consideration. With gram quantities of this intermediate in hand, subsequent work would focus on the development of an alkyne metathesis/*syn*-selective hydrogenation sequence allowing exclusive access to the desired *Z*-isomer in the macrocyclic F ring.

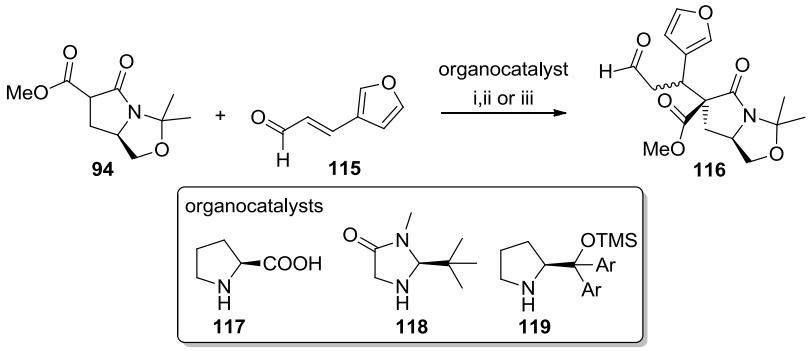
2.2. Diastereoselective Nitro Olefin Michael Addition – Seminal Work

Pivotal to the success of our synthesis was the stereoselective construction of the C-C bond linking the quaternary stereocentre to the tertiary stereocentre bearing the functionalized furan heterocycle. Seminal work by Cockfield in earlier generation routes to (–)-nakadomarin A (**1**) had shown that this key conjugate addition of pro-nucleophile **94** to simple unfunctionalized nitro olefin **112** could be achieved using achiral base 1,4-diazabicyclo[2.2.2]octane (DABCO) **113** (Scheme 2.1).



Scheme 2.1. Conjugate addition to nitro olefin **112** catalyzed by DABCO **113**. Reagents and conditions: i) DABCO **113** (10 mol%), CH_2Cl_2, RT, 14 days, 60% conv., 1:1.1 dr.

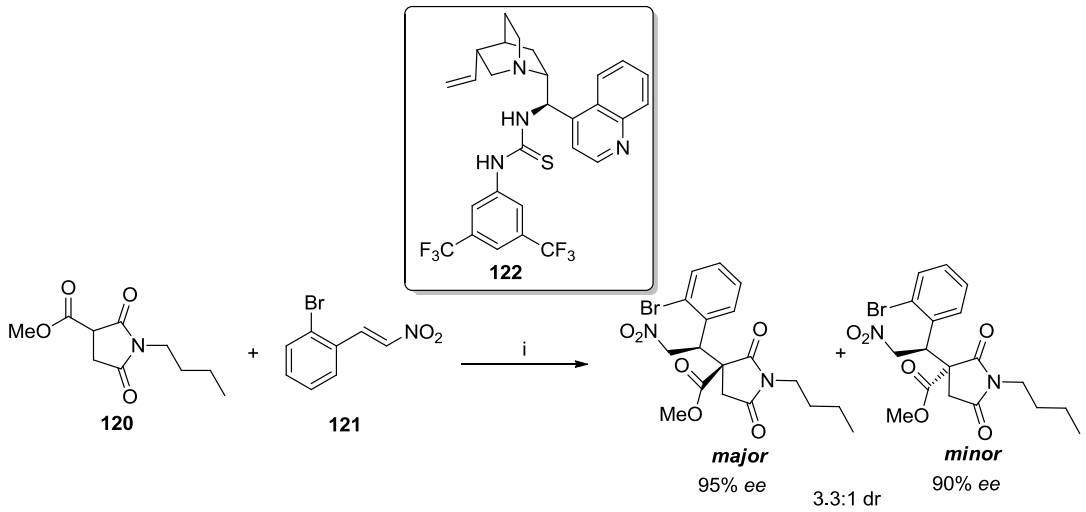
This result, in particular the formation of only two of four possible diastereomers, mirrored that of earlier studies in the conjugate addition of 5,5'-bicycle **94** to α,β-unsaturated aldehyde **115** catalyzed by pyrrolidine and imidazolidinone derived organocatalysts **117**-**119** (Scheme 2.2).[34]



Scheme 2.2. Conjugate addition to α,β-unsaturated aldehydes. Reagents and conditions: i) Catalyst **117** (10 mol%), benzoic acid (10 mol%), EtOH, RT, 48 h, 40%, 1:1.1 dr; ii) Catalyst **118** (10 mol%), benzoic acid (10 mol%), EtOH, RT, 48 h, <10%, 1:1.1 dr; iii) Catalyst **119** (10 mol%), benzoic acid (10 mol%), EtOH, RT, 48 h, 86%, 3:1 dr.

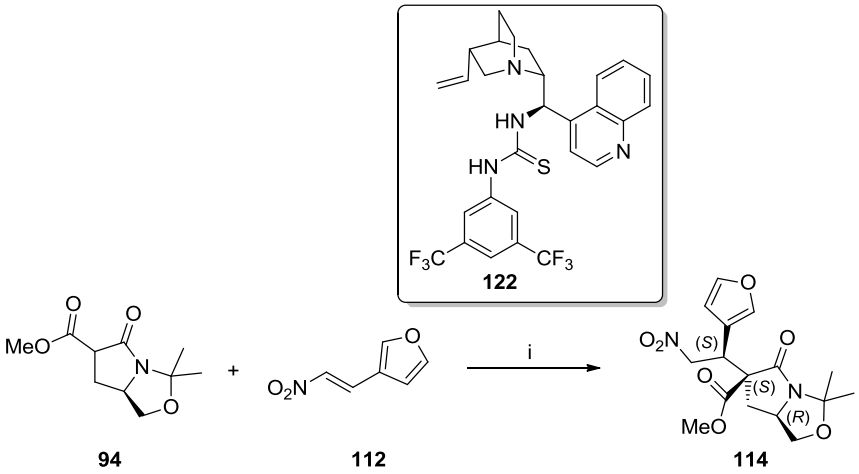
These conjugate addition reactions, forming contiguous quaternary and tertiary stereocentres give rise to four possible stereoisomers. The observed formation of two of these four possible stereoisomers, presumed to be epimeric at the tertiary centre, with both achiral and chiral organocatalysts was assigned to an inherent substrate bias originating from a selective approach of the electrophile to the nucleophile controlled by the substrate stereocentre. Seminal work by Cockfield showed that the conjugate addition

of achiral *C*-acyl succinimide pro-nucleophile **120** to nitro olefin **121** catalyzed by bifunctional organocatalyst **122** also resulted in the formation of two of four possible diastereomers. The absolute stereochemistry of both the major and minor diastereomer was confirmed by single crystal X-ray analysis showing them to be epimeric at the quaternary centre, thus denoting excellent catalyst facial control at the tertiary centre (Scheme 2.3).



Scheme 2.3. Conjugate addition of *C*-acyl succinimide pro-nucleophile **120** to nitro olefin **121**. Reagents and conditions: i) Catalyst **122** (10 mol%), CH_2Cl_2, RT, 48 h, 84%, 3.3:1 dr.

In the case of the conjugate addition of pro-nucleophile **94** to α,β-unsaturated aldehyde **115** (Scheme 2.2) the diastereomers proved to be chromatographically inseperable; consequently, their absolute stereochemistry was not confirmed. In the case of the conjugate addition of pro-nucleophile **94** to furanyl nitro olefin **112**, subsequent work by Cockfield showed that this could be catalyzed using thiourea catalyst **122** with superior diastereoselectivity relative to the DABCO **113** reaction (1:1.1 dr **113** vs. >10:1 dr catalyst **122**) (Scheme 2.4) c.f.(Scheme 2.1).



Scheme 2.4. Conjugate addition to nitro olefin **112** with catalyst **122**. Reagents and conditions: i) Catalyst **122** (10 mol%), CH_2Cl_2, RT, 14 days, 67%, >10:1 dr.

A single crystal X-ray structure of the major diastereomer was obtained and the absolute stereochemistry assigned as (*R*), (*S*), (*S*), the required stereochemistry for the synthesis of (–)-nakadomarin A (**1**). Isolation of the minor isomer was not achieved and therefore the minor isomer was only assumed to be epimeric at the tertiary stereocentre, with complete substrate control at the quaternary centre.

Development of these initial findings by Cockfield was required to prove that the minor isomer formed in the conjugate addition of pro-nucleophile **94** to furan nitro olefin **112** was epimeric at the tertiary centre.

2.3. Catalyst Control Studies

Additional work by Cockfield in his 2nd generation route to (−)-nakadomarin A (**1**) had shown that catalyst **88**, the urea analogue of thiourea catalyst **122** resulted in more than a doubling of reaction rate in the conjugate addition (5 days vs. 14 days).[34]

This rate increase had previously been observed by Hynes in kinetic studies,[35] and is in contrast to the intuitive result that the more acid thiourea moiety, resulting from the greater inherent ability of sulfur than oxygen to stabilise a negative charge, should be a better H-bond donor and therefore increase the reaction rate.[36] The increased reactivity with urea catalyst **88** was attributed to its increased H-bond acceptor ability, facilitating an increased intramolecular hydrogen bonding interaction between the urea oxygen atom and a polarised *o*-aryl proton in the phenyl ring.[37] The resulting increased planarity according to Hynes, results in increased conjugation with the aryl appendage, rendering the N-Hs more acidic (Figure 2.1).[35]

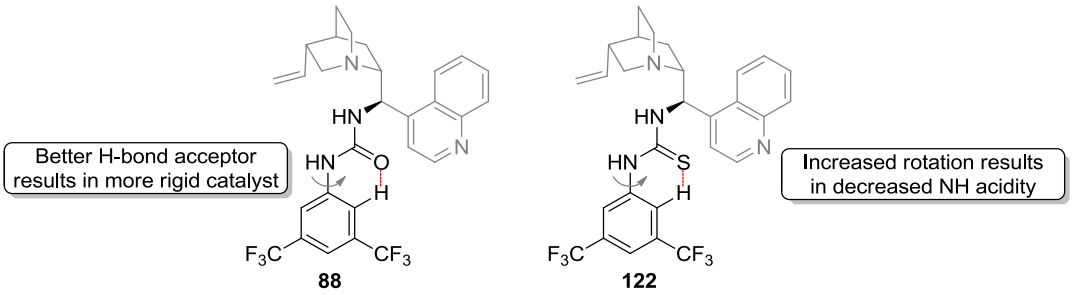


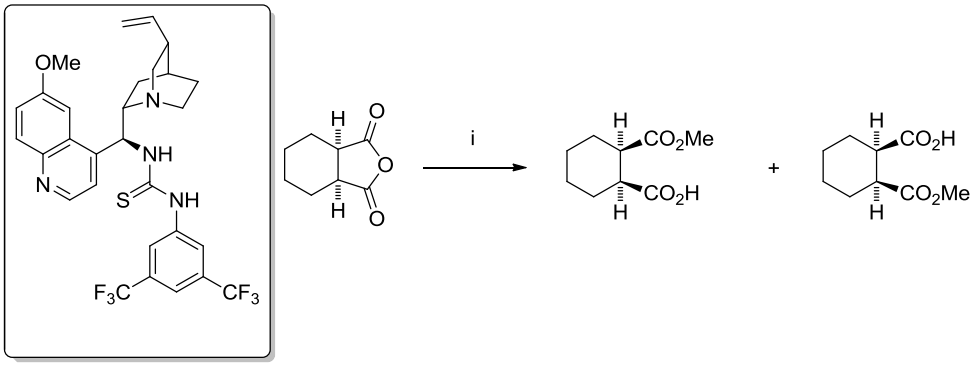
Figure 2.1. Effect of catalyst rigidity on reactivity

Consideration must be given however to the fact that catalyst **88** and **122** cannot be regarded as conformationally rigid molecules in solution. Density functional theory studies of cinchona derived bifunctional catalysts by Hiemstra[38] and of the related Takemoto thiourea catalyst **73** (Figure 1.3) by Pápai and Soós,[39] have shown that other low-lying conformers of these catalysts are easily accessible.

In addition, self association of the catalysts to form dimeric or higher order assemblies, through intermolecular H-bonding and CH/π interactions as proposed independently by Soós and Song could result in differential reactivity between catalysts **88** and **122** under different reaction

conditions.[40,41] In the quinine derived bifunctional organocatalyst, catalyzed methanolytic desymmetrization of a cyclic anhydride (Scheme 2.5), Song reported unusual concentration, temperature and solvent effects on enantioselectivity. This was attributed to a monomer−dimer equilibration of the catalytic species. H-bond accepting solvents such as THF, low catalyst concentration and increased reaction temperature all favoured the existence of the catalyst in its monomeric form and as a result gave increased enantioselectivities.

Despite the potential for subtle variations in reaction conditions affecting catalyst reactivity, based on Cockfield's observations urea catalyst **88** was selected for the catalyst control studies.

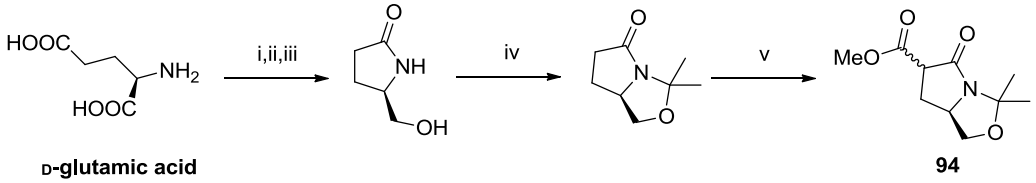


Entry	Solvent	Temperature	Time (h)	Yield (%)	*ee* (%)
1	Dioxane (40 mL)	RT	10	85	97
2	THF (40 mL)	RT	10	84	95
3	Toluene (40 mL)	RT	10	75	74
4	THF (2.5 mL)	RT	0.6	82	82
5	THF (2.5 mL)	0 °C	5.5	81	81
6	THF (2.5 mL)	−20 °C	11	80	77

Scheme 2.5. Song reaction condition effects on catalyst self association.[41] Reagents and conditions**:** i) Reaction conditions from table.

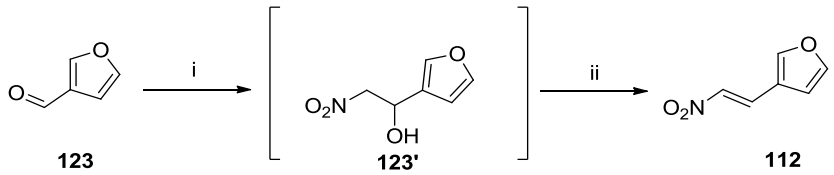
2.4. Synthesis of Starting Materials

Pro-nucleophile **94** was constructed on multigram scale in five steps from D-glutamic acid using the protocol of Davies and co-workers (Scheme 2.6).[42,43]



Scheme 2.6. Synthesis of pro-nucleophile **94**. Reagents and conditions: i) $SOCl_2$ (2.3 eq.), EtOH, 0 °C to RT, 1.5 h then reflux, 0.5 h; ii) vacuum (7.5 torr), 140 °C, 36 h; iii) $NaBH_4$ (1.2 eq.), EtOH, 0 °C to RT, 1.3 h, 61% (over 3 steps); iv) 2,2-dimethoxypropane (2.5 eq.), *p*TsOH (0.02 eq.), toluene, reflux, 4 h, 75%; v) Dimethyl carbonate (1.2 eq.), LHMDS (2.0 eq.), AcOH (5.0 eq.), THF, −78°C to 0 °C, 74%.

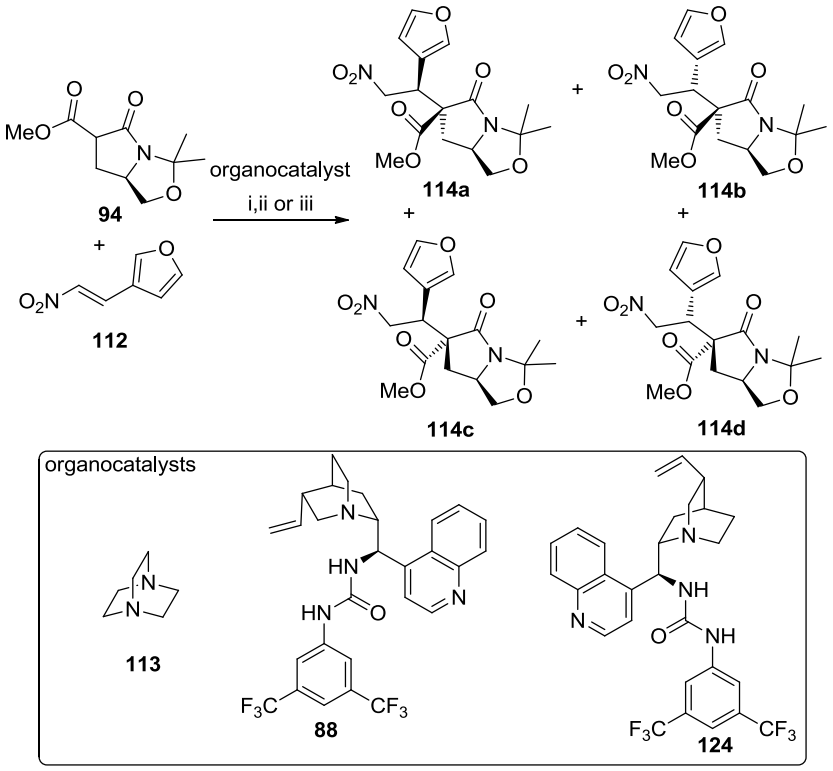
Unsubstituted nitro olefin **112** was synthesized using the procedure of Fujii.[44] The crystalline nitro olefin was isolated by filtration in 61% yield directly from the Henry reaction (reaction i). Subsequent activation and elimination of the isolated nitro aldol intermediate **123'** gave additional nitro olefin **112**, resulting in a 79% overall yield from aldehyde **123** (reaction ii) (Scheme 2.7).



Scheme 2.7. Synthesis of nitro olefin **112**. Reagents and conditions: i) KOH (1.1 eq.), $MeNO_2$ (1.1 eq.), 0 °C, 3 h, **112** = 61%; ii) MsCl (1.0 eq.), Et_3N (2.0 eq.), CH_2Cl_2, −15 °C to RT, 30 min, 79% overall yield of **112** from **123**.

2.5. Model System – 'Matched' and 'Mismatched' Catalyst and Substrate Control Studies

Preliminary investigations into the levels of diastereocontrol that could be achieved in the Michael addition were carried out using pro-nucleophile **94** and model nitro olefin **112** (Scheme 2.8).



Scheme 2.8. Preliminary nitro olefin Michael addition studies. i) **113** (10 mol%), toluene, 30 °C, 7 days, 5:1:0:0 crude dr, 38%, mixture of diastereomers (4.3:1:0:0 dr); ii) Catalyst **88** (10 mol%), toluene, 30 °C, 48 h, 15:1:0:0 crude dr, 80% (single diastereoisomer **114a**); iii) Catalyst **124** (10 mol%), toluene, 30 °C, 5 days, 4:12:1:1 crude dr, 61%, mixture of diastereoisomers (6:19:1:1 dr).

Treatment of **94** and **112** with achiral DABCO **113** in toluene led to the formation of two of the possible four diastereoisomers, in a 5:1 ratio respectively with the major diastereomer matching that identified as **114a** by Cockfield. This result indicated slightly higher levels of control at the tertiary stereocentre than had been observed previously. Pleasingly using cinchonine derived urea **88** as catalyst at 10 mol% a significantly improved diastereoselectivity was observed; after 48 hours the diastereomers were formed in a ratio of 15:1 and the isolated yield of pure **114a** after flash column chromatography *and* a recrystallisation was 80% (Figure 2.2). The relative stereochemistry of the major diastereoisomer **114a** was unambiguously determined by single crystal X-ray analysis for complete confidence in assignment (Figure 2.3). The switch in solvent from

dichloromethane, in Cockfield's work, to toluene resulted in a significant improvement in the reaction rate (5 days vs 2 days).[34]

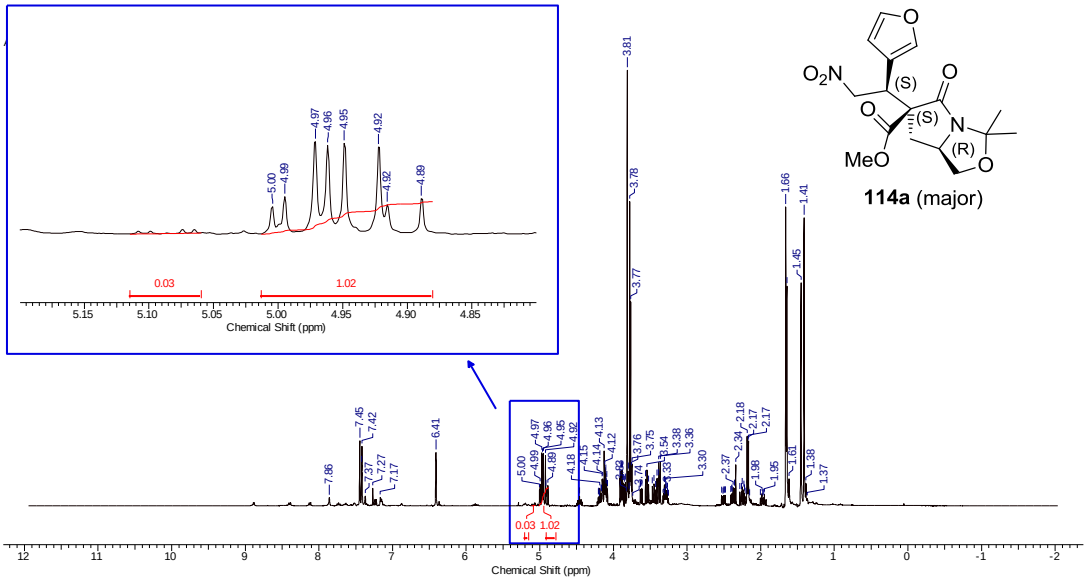


Figure 2.2. Crude ^{1}H NMR of Michael addition reaction using catalyst **88**.

Interestingly, use of pseudoenantiomeric cinchonidine derived urea **124** resulted in a reduced reaction rate (5 days), as well as a poor and reversed diastereoselection with all four diastereoisomers being observed (4:12:1:1 dr). The major diastereomer was enriched by chromatographic purification (6:19:1:1 dr). Further purification by repeated recrystallization from diethyl ether cooled to −20 °C, gave a mixture of **114a** and the other major diastereomer (1:4 dr). Attempts to separate these diastereomers completely by recrystallization were unsuccessful. Recrystallization from a diethyl ether:methanol:petroleum ether solvent system however gave large block crystals. The diastereomeric ratio of the combined crystals remained unchanged (1:4 dr), however a large single crystal from this mixture was removed and the structure confirmed as **114b**, epimeric with respect to **114a** at the tertiary centre, by single crystal X-ray analysis (Figure 2.3). ^{1}H-NMR

analysis of this single crystal confirmed that a single diastereoisomer **114b** was present (Figure 2.4).

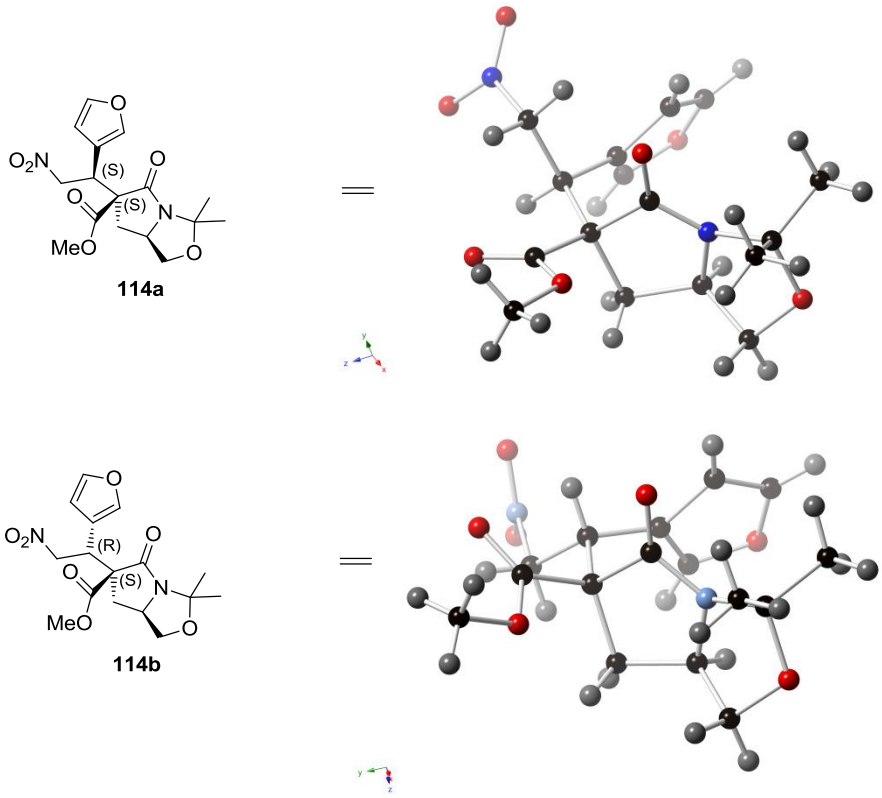


Figure 2.3. Stick and ball representation of the X-ray crystal structures of **114a** and **114b**

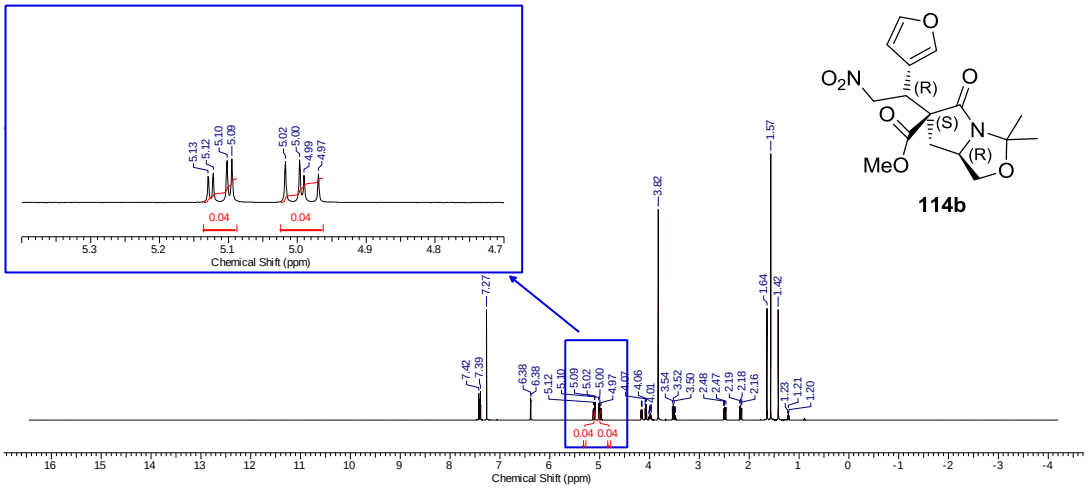


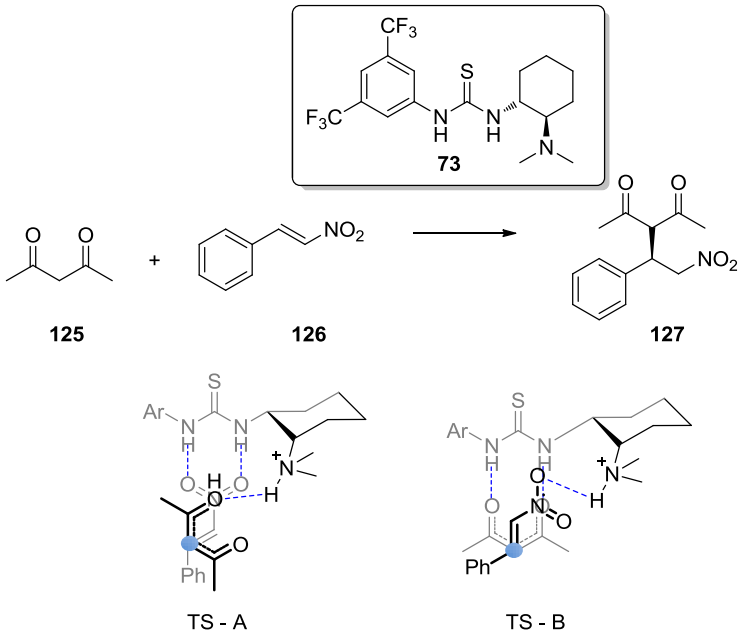
Figure 2.4. ^{1}H NMR of single crystal of diastereoisomer **114b** obtained using catalyst **124** and used for X-ray analysis.

These data confirmed that substrate control was responsible for the selectivity observed at the quaternary centre while bifunctional organocatalyst stereocontrol dominates the inherent substrate stereocontrol

at the tertiary stereocentre. They also confirmed that 5,5'-bicyclic pro-nucleophile **94** and cinchonine derived organocatalyst **88** are matched for the production of the desired diastereoisomer **114a**, whereas cinchonidine derived organocatalyst **124** and **94** are mismatched.

2.6. Catalyst Mode of Action

Potential rationalisation of the matched effect observed in the Michael addition of pro-nucleophile **94** to nitro olefin **112**, catalyzed by cinchonine derived organocatalyst **88** can be made by considering the ternary complex formed. The catalytic mode of action of has been investigated for analogous systems by Pápai and Soós, who studied the mechanism of the addition of acetylacetone **125** to nitrostyrene **126** using Takemoto's thiourea bifunctional organocatalyst **73** (Scheme 2.9).[39,40]



Scheme 2.9. Pápai and Soós catalyst mode of action studies.[39,40]

Based on DFT calculations, Pápai and Soós, predicted that more than one mode of activation of the two reacting partners in the ternary complex was

possible. In addition to Takemoto's proposed mechanism involving electrophile activation through substrate binding to the thiourea moiety (TS-A), an alternative reaction pathway in which the nitro olefin is activated by the quinuclidine tertiary amino group was also proposed and in fact found to be marginally energetically favoured (TS-B) (Scheme 2.9).[39]

Similar observations were made by Hiemstra and co-workers using DFT calculations to calculate possible reaction pathways in a cinchonidine thiourea catalyzed Henry reaction.[38] Two energetically similar reaction pathways were proposed with the nitro group activated either exclusively by the thiourea moiety of catalyst **130** (TS-B) or through dual activation by both the quinuclidine amine and thiourea moiety (TS-A) (Figure 2.5).

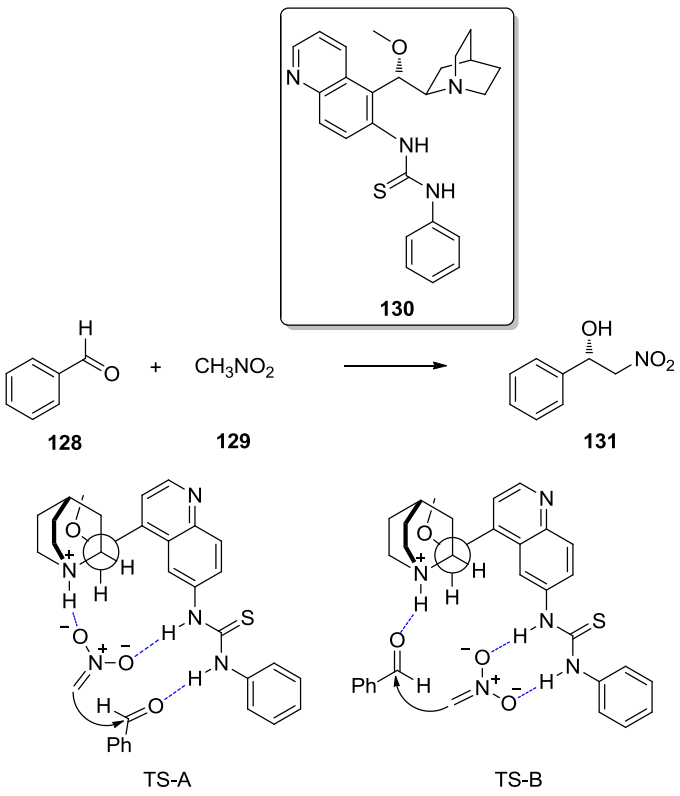


Figure 2.5. Hiemstra Catalyst Mode of Action Studies.[38]

Using the reaction pathway through thiourea activation of nitro olefin **112** as a working model (Figure 2.6), formation of the desired Michael adduct **114a**

can be rationalised by addition of pro-nucleophile **94** to the *Re* face of nitro olefin **112**. This would likely arise through an energetically favoured staggered arrangement of bonds around the newly forming C-C bond. Assuming the conformation of the ternary complex is not altered, a flip in facial approach of nitro olefin **112** (*Si* face approach), whilst maintaining a staggered arrangement of bonds could potential disrupt the hydrogen bonding network between the nitro olefin/thiourea moieties. Alternatively a conformational change of the ternary complex to maintain the H-bonding network between the nitro olefin/thiourea moieties may result in a higher energy eclipsed arrangement of the substituents around the new C-C bond. Both situations would represent a mismatched case and would account for the limited formation of adduct **114b** observed when cinchonine derived organocatalyst **88** is used.

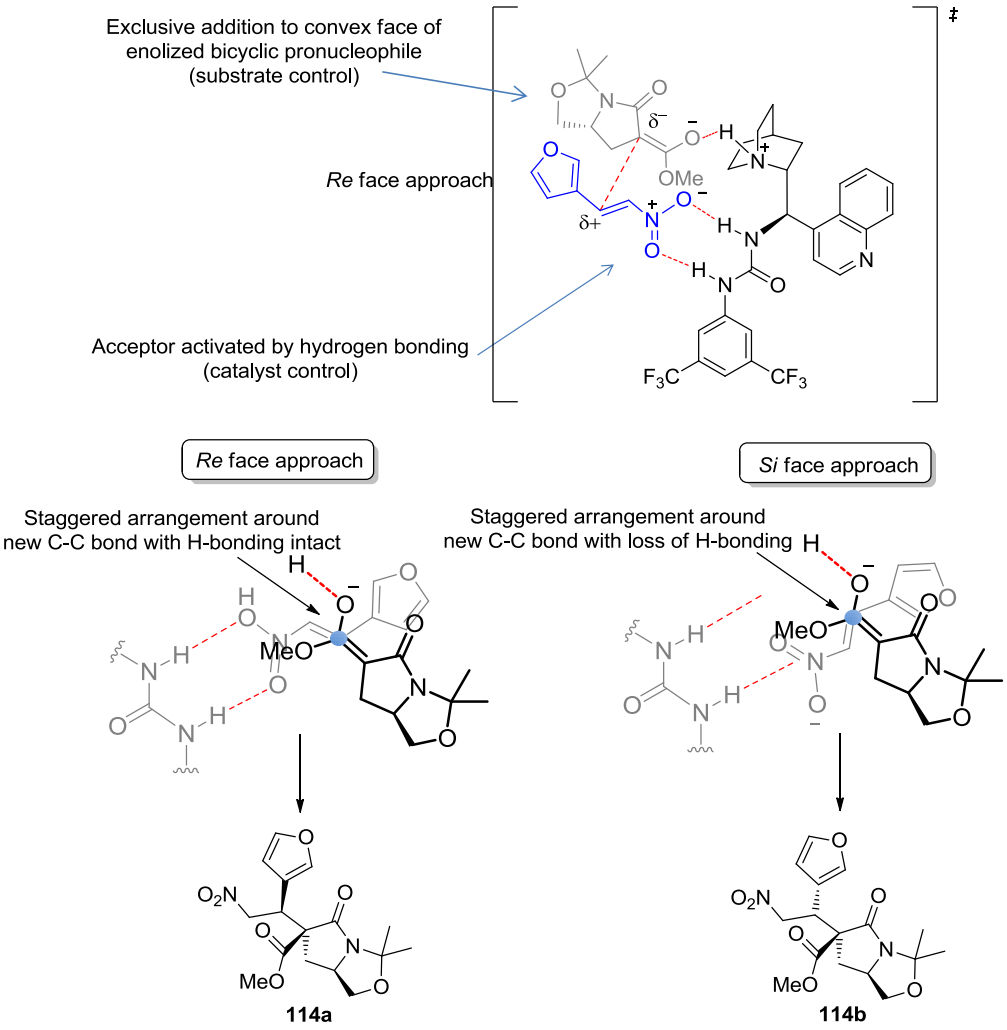


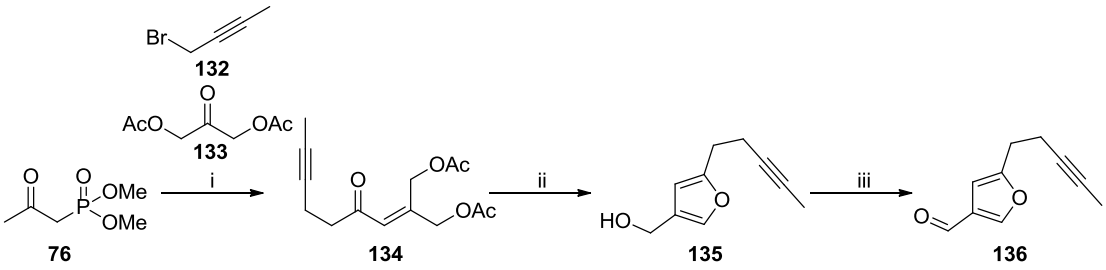
Figure 2.6. Representation of 'matched' and 'mismatched' transition states.

2.7. Application to Alkyne Nitro Olefin Conjugate Addition

With studies into the 'matched' and 'mismatched' effects arising from the replacement of a cinchonine derived bifunctional organocatalyst **88** with a pseudoenantiomeric cinchonidine derived catalyst **124** complete, attention was turned to the synthesis of the tetracyclic core of (–)-nakadomarin A (**1**), where catalyst **88** would be used along with 5,5'-bicyclic pro-nucleophile **94**. With the synthesis of both achievable on multi-gram scale, the synthesis of alkyne substituted nitro olefin **104** in significant quantities was the next challenge, as it had proven to be the limiting reagent in previous attempts to synthesize large quantities of tetracycle **111** (Scheme 1.9).

2.8. Synthesis of Alkyne Nitro Olefin

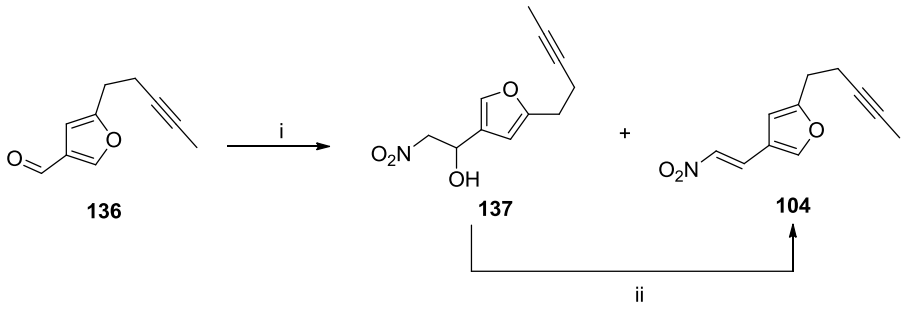
Following the same procedures adopted by Jakubec and Cockfield, aldehyde **137** was obtained in three steps from ketophosphonate **76**. A one-pot sequential alkylation[45,46]/HWE reaction procedure[47] using 1-bromobut-2-yne **132** and 2-oxopropane-1,3-diyl diacetate **133** afforded enone **134**. Cyclisation under acidic conditions gave furanol **135** in good yield.[47] Oxidation using the Swern protocol then afforded furan aldehyde **136** (Scheme 2.10).[48]



Scheme 2.10. Synthesis of aldehyde **136**. Reagents and conditions: i) NaH (1.8 eq.), BuLi (1.3 eq.), THF, 0 °C, 1 h, then 1-bromobut-2-yne **132** (1.0 eq.), 10 min then 2-oxopropane-1,3-diyl diacetate **133** (1.5 eq.), THF, RT, 2 h, 38%; ii) HCl (1.0 eq.), EtOH, 65 °C, 15 h, 71%; iii) $(COCl)_2$ (1.0 eq.), DMSO (2.1 eq.), Et_3N (5.0 eq.), CH_2Cl_2, −78 °C to RT, 0.5 h, 90%.

Cockfield reported an instability of nitro olefin **104** to Henry condensation reaction conditions, particularly on addition of water during work-up, which resulted in apparent hydration of the olefin back to the β-hydroxy nitro intermediate.[34] This instability led to inconsistent yields in range of 30-60%. Attempts to follow Cockfield's procedure, which eliminated the β-hydroxy group of adduct **137** upon treatment of the crude reaction mixture from the Henry reaction (approx. 2:1 mixture of nitro olefin **104**:Henry adduct intermediate **137**) with methylsulfonyl chloride and triethylamine, was found to result in considerable decomposition of the nitro olefin already present in the starting material. A modification of the original procedure, whereby nitro olefin **104** was first separated from Henry intermediate **137** after step (i) gave

vastly improved and consistent yields. Elimination of the β-hydroxy group of isolated intermediate **137** with acetic anhydride in pyridine yielded the desired nitro olefin in 82% overall yield (Scheme 2.11).

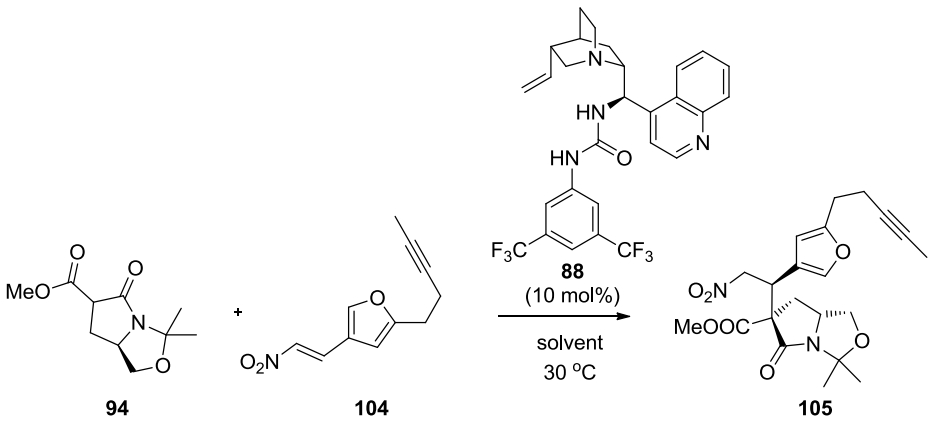


Scheme 2.11. Synthesis of nitro olefin **104**. Reagents and conditions: i) $MeNO_2$ (1.1 eq.), KOH (1.1 eq.), EtOH, 0 °C, 1.5 h, 49% (**104**), 41% (**137**); ii) Ac_2O (1.5 eq.), DMAP (0.2 eq.), pyridine, 0 °C, 0.5 h, 82% (overall yield of **104**).

In total more than 10 g of nitro olefin **104** were synthesized using this route.

2.9. Diastereoselective Nitro Olefin Michael Addition: Alkyne System

As a result of the observed increase in reaction rate and diastereoselectivity resulting from a solvent switch from dichloromethane[34] to toluene in the conjugate addition of pro-nucleophile **94** to unsubstituted nitro olefin **112**, a solvent screen in the conjugate addition to alkyne nitro olefin **104** was undertaken (Scheme 2.12).



Scheme 2.12. Solvent screen in nitro olefin Michael addition

All reactions were carried out with nitro olefin **104** (1 eq.), nucleophile **94** (2 eq.), a catalyst loading of 10 mol% and 0.03 M catalyst concentration. The reactions were followed by TLC analysis to monitor consumption of the nitro olefin and the dr established from crude ^{1}H NMR analysis. The results are summarised in Table 2.1.

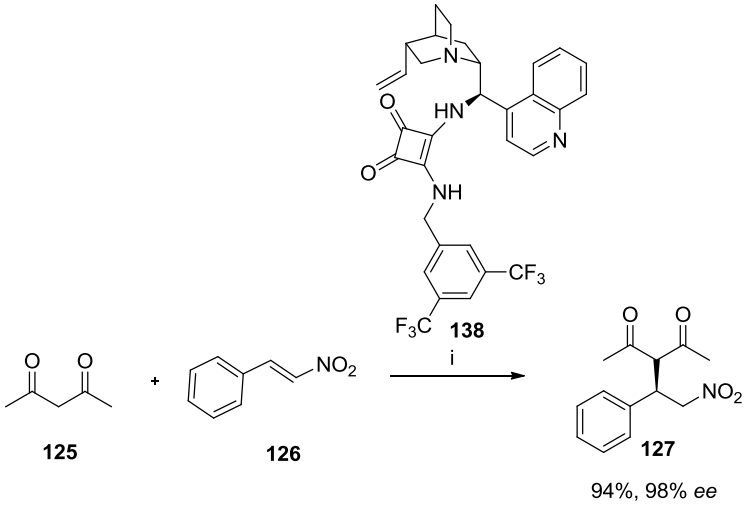
Table 2.1. Diastereoselectivity and reaction rate in Michael addition solvent screen

	Toluene	Mesitylene	Chlorobenzene	CH_2Cl_2
dr	18:1	16:1	18:1	12:1
Reaction time	42-52 h	28-42 h	>4 days	>4 days

Based on these findings, toluene was selected as the solvent of choice for the conjugate addition using alkyne nitro olefin **104**.

2.10. Squaramide Catalyst in Michael Addition

At the time these model conjugate addition studies were being conducted, Rawal and co-workers reported the use of cinchonine-derived squaramide catalyst **138** as an effective bifunctional organocatalyst for the conjugate addition of 2,4-pentanedione **125** to *β*-nitrostyrene **126** (Scheme 2.13).[49]

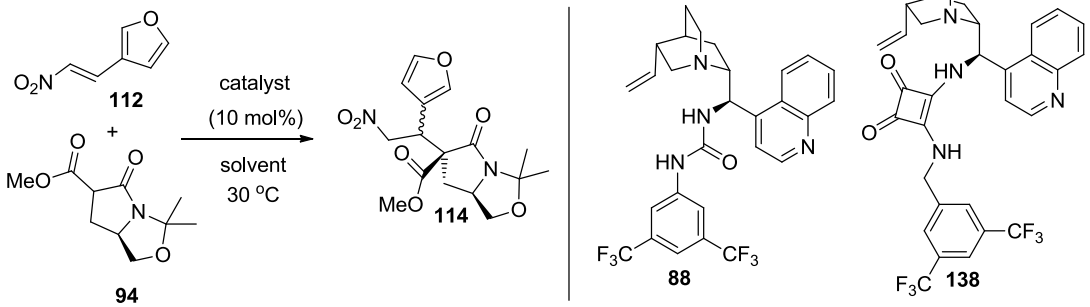


Scheme 2.13. Squaramide catalyzed conjugate addition of 2,4-pentanedione **125** to *β*-nitrostyrene **126**. Reagents and conditions: i) Catalyst **138** (0.5 mol%), CH_2Cl_2, RT, 8 h.

These results compared favourably with results obtained by Dixon for the conjugate addition of dimethyl malonate to *β*-nitrostyrene catalyzed by thiourea catalyst **122**.[26] The increased acidity of **125** and its existence mainly as its enol tautomer, limits the direct comparisons that can be made between the two transformations. Nonetheless, based on the potential for improvement in the conjugate addition of nucleophile **94** to furan nitro olefin **104** that these findings presented, squaramide catalyst **138** was synthesized using the procedures described by Rawal.[49]

Although dichloromethane was shown by Rawal to be the optimal solvent for this transformation, equally impressive results were reported when toluene was employed. Model nitro olefin **112** was employed for these studies and a comparison of the performance of urea catalyst **88** and squaramide catalyst **138** conducted (Table 2.2). Pro-nucleophile **94** (2 eq.), nitro olefin **112** (1 eq.) and catalyst (10 mol%) were dissolved in toluene and 60 µl aliquots were removed at the reported time intervals. The aliquots were concentrated and filtered through a pipette silica column to remove the catalyst before being analysed by ^{1}H NMR.

Table 2.2. Conjugate addition catalyst rate studies.



Entry	Reaction Time (h)	Catalyst **88** % conversion[a]	Catalyst **138** % conversion[a]
1	1	14%	-[b]
2	3	34%	-[b]
3	5	56%	-[b]

4	20	95%	~2%
5	48	>99%	5%

[a] NMR conversion calculated by integration of the (H-4) furan signal of nitro olefin **112** and adduct **114**.

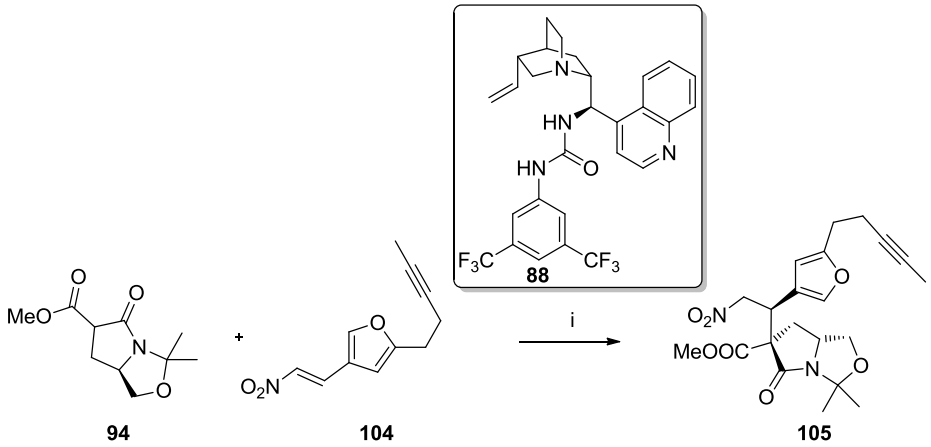
[b] NMR conversion too low to be accurately measured.

Almost no reactivity was observed in the conjugate addition with squaramide catalyst **138**. A solvent switch to dichloromethane resulted in a modest improvement in reactivity although this was still minimal in comparison to the reactivity observed with urea catalyst **88**. Attenuated Brønsted basicity of the quinuclidine amine in squaramide catalyst **138** is a possible reason for the almost complete lack of reactivity observed with pro-nucleophile **94**. Rawal's initial report did not include any examples of conjugate additions involving malonate type pro-nucleophiles.[49]

With **88** maintaining its status as the champion catalyst for this transformation, the preparation of the tetracyclic intermediate of (–)-nakadomarin A (**1**) on multigram scale commenced.

2.11. Synthesis of the Tetracycle Core of (–)-Nakadomarin A (1)

Using the optimised conditions, Michael adduct **105** was synthesized on up to 27 mmol (nitro olefin **104**) scale. The reaction was complete within 52 hours, and pleasingly the high diastereoselectivity observed in the small scale catalyst studies (dr ~18:1:0:0) was maintained. Michael adduct **105** was isolated as a single diastereomer in 81% yield after purification of the crude product by column chromatography and a recrystallization from diethyl ether cooled to −20 °C (Scheme 2.14). A largest single batch of 6.1 g was prepared using this method and in total more than 16 g of **105** were prepared.



Scheme 2.14. Conjugate addition. Reagents and conditions: i) catalyst **88** (10 mol%), toluene, 30 °C, 52 h, ~18:1:0:0 crude dr, 81% (single diastereoisomer).

The good reactivity and high selectivity achieved in this key C-C bond forming transformation using the optimised conditions and 5,5'-bicyclic pro-nucleophile **94** represented a significant improvement in reactivity, diastereoselectivity and isolated yield when compared with the similar transformation reported by Jakubec using 8,5-bicyclic pro-nucleophile **87** (Scheme 1.7) (Table 2.3).[25]

Table 2.3. Comparison of Michael addition with that of Jakubec using 8,5-pro-nucleophile.

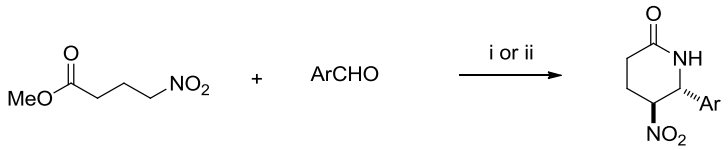
	This transformation (5,5'-pro-nucleophile) **94**	Jakubec Route (8,5-pro-nucleophile) **87**
Reaction time	52 h	8 days
Diastereoselectivity	18:1	10:1
Yield	81% (single diastereomer)	57% (91:9 dr)

The route to tetracycle **111** from Michael adduct **105** had been optimised extensively by Jakubec and Cockfield during the course of earlier generation routes to (–)-nakadomarin A (**1**). It was anticipated that little further optimization would be required and accordingly our attention was focussed

on the rapid synthesis of **111** in sufficient quantity to allow further development of the route at the front line.

2.12. Nitro-Mannich/Lactamization Cascade

With Michael adduct **105** in hand, the next key step was a nitro-Mannich/lactamization cascade, which would result in a one carbon homologation and cyclisation to form the A-ring of (–)-nakadomarin A (**1**). An example of a simple nitro-Mannich/lactamization cascade reaction was first reported in the mid-1970's independently by Mühlstädt and soon after by Jain.[50,51] Both authors reported that the condensation of methyl 4-nitrobutanoate **139** with aromatic aldehydes **140** and ammonium acetate provided access to simple 6-aryl-substituted 5-nitropiperidin-2-ones **141** (Scheme 2.15).

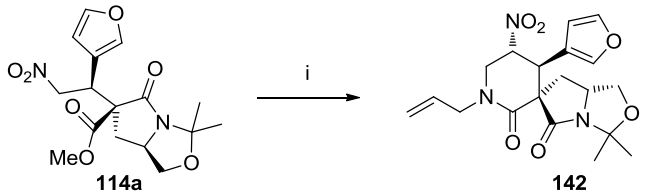


139 **140** **141**

Scheme 2.15. Mühlstädt and Jain: nitro-Mannich/lactamization cascade.[50,51] Reagents and conditions: [50] i) NH_4OAc, AcOH, reflux, 15-58%; [51] ii) NH_4OAc, EtOH, reflux, 12 h, up to 95%.

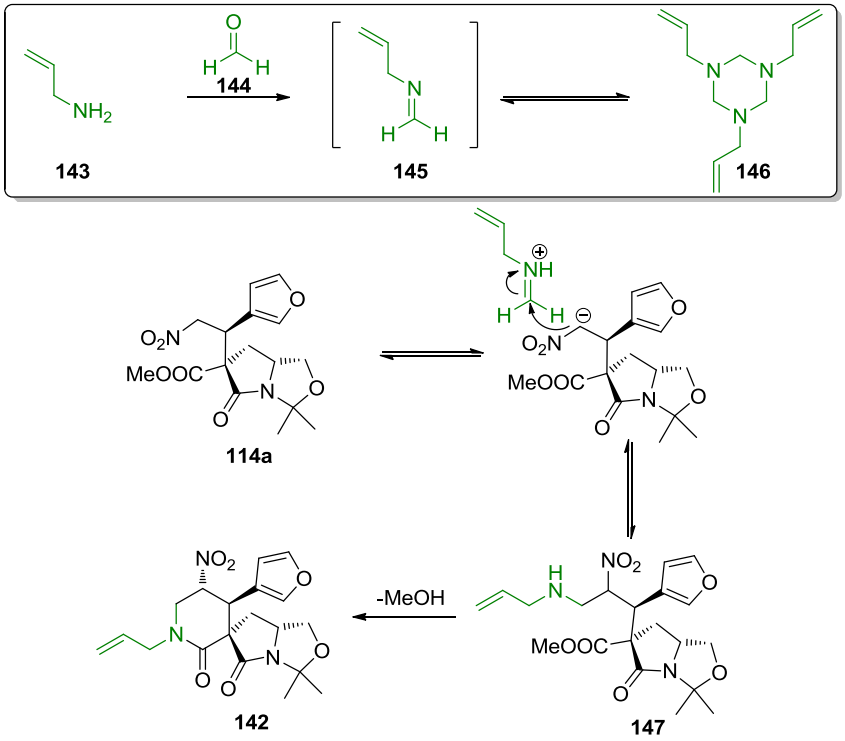
Mühlstädt did not make any comment on the stereochemical outcome of the products obtained from this reaction, however Jain highlighted the *trans* relationship observed between the nitro and aryl substituent. The synthetic potential of this transformation was not immediately recognised and it is only in the past two decades that it has been further developed and applied in the synthesis of biologically active molecules and small molecule precursors.[25,52-56] Further discussion on the development of nitro-Mannich lactamization cascade reactions and related transformations can be found in Chapter 5.7.

In earlier generation routes towards (–)-nakadomarin A (**1**), Cockfield and Jakubec identified that polar protic solvents and elevated temperatures were required to obtain the desired cyclised product **142** from Michael adducts of type **114** in acceptable yields. Both also reported that the desired piperidinone was isolated as a single isomer with the NO_2 substituent *trans* to the furan ring, in an equatorial position around the newly formed piperidine ring (Scheme 2.16).



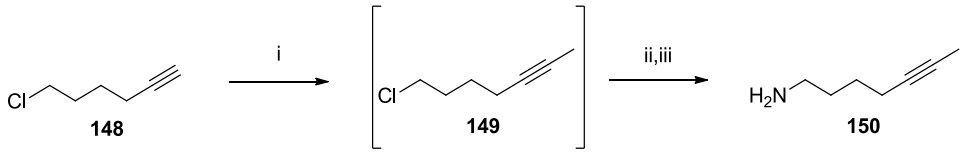
Scheme 2.16. Cockfield 1st generation nitro-Mannich/lactamization cascade. Reagents and conditions: i) Allylamine (1.5 eq.), CH_2O (1.5 eq.), MeOH, reflux, 3 d, 75%.

Mechanistically, it has been proposed that the *in situ* generated imine **145** exists in the solution, in equilibrium with its corresponding amine trimer **146**.[57-59] The basic imine can reversibly deprotonate one of the acidic methylene protons α- to the nitro group. Combination of the mutually reactive ion pair thus formed, followed by irreversible lactamization with the loss of methanol gives the desired piperidinone product **142**. The formation of only one diastereomer in this reaction was initially attributed to post lactamization epimerization of the nitro group. Recent results from our research group however, suggest that an alternative pathway involving a reversible nitro-Mannich reaction, in which only one of the diastereomeric products can undergo cyclisation *via* an irreversible lactamization step giving the most thermodynamically stable product, may be responsible for the complete stereocontrol observed (Scheme 2.17).[34,53]



Scheme 2.17. Proposed mechanism of nitro-Mannich/lactamization cascade.

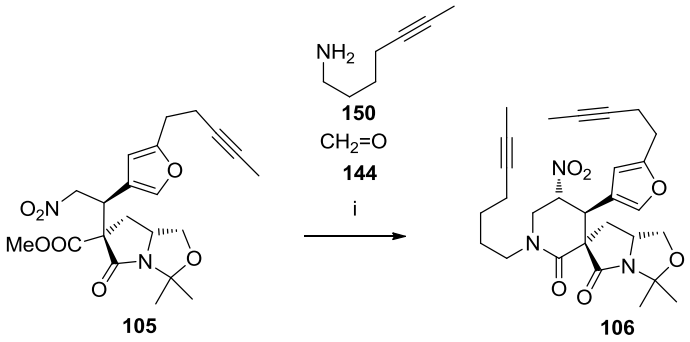
For the synthesis of (–)-nakadomarin A (**1**) using an alkyne ring-closing metathesis approach, an imine bearing suitable alkyne functionality was required. To achieve this, hept-5-yn-1-amine **150** was synthesized in three steps from 6-chlorohex-1-yne **148**. Methylation of **148** was followed by azide displacement of the chloride in intermediate **149** and a one-pot Staudinger/hydrolysis reaction sequence were used to obtain the desired amine **150** (Scheme 2.18).



Scheme 2.18. Synthesis of hept-5-yne amine **150**. Reagents and conditions: i) *n*-BuLi (1.5 eq.), MeI (1.6 eq.), THF, 0 °C, 1.5 h; ii) NaN_3 (3.0 eq.), DMSO, 50 °C, 6 h; iii) PPh_3 (1.6 eq.), H_2O, RT, 14 h, 51% (over 3 steps).

Using the optimised conditions of Cockfield,[34] alkyne Michael adduct **105** was treated with hept-5-yn-1-amine **150** and aqueous formaldehyde **144**

solution in refluxing methanol (Scheme 2.19). The nitro-Mannich lactamization cascade was carried out multiple times and the yield of nitro piperidinone **106** was in the range 48-52% when the reaction was carried on less than 1 g scale, which was consistent with the observation of Cockfield (Scheme 2.19). On larger scale (5-6 g) a higher mass return was obtained (66-74%), however part of this increase in apparent yield can be attributed to difficulties separating the product from amine trimer derived impurities (~10% impurity). Removal of this impurity was facile in the subsequent nitro removal step and it was therefore carried through with the nitro-Mannich lactamization product on large scale.

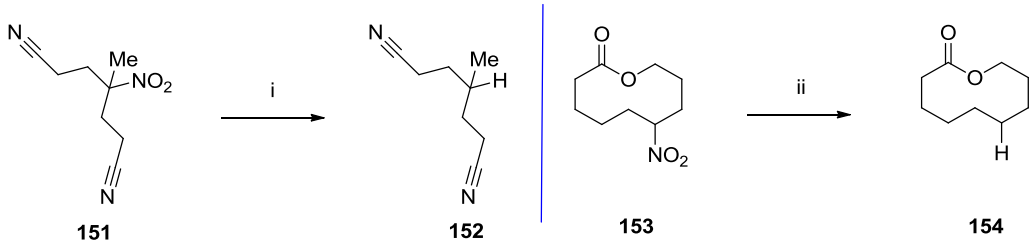


Scheme 2.19. Nitro-Mannich lactamization cascade. Reagents and conditions: i) Hept-5-yn-1-amine **150** (1.5 eq.), CH_2=O **144** (1.5 eq.), MeOH, reflux, 8 h, 52%.

2.13. Nitro Group Removal

Having served its purpose in the synthesis, efficient removal of the nitro group was required. This was achieved using radical conditions, first described by Ono and co-workers.[60,61] Ono initially reported the reductive removal of tertiary (eg **151**) and benzylic nitro groups using Bu_3SnH (1.2 eq.) and azobisisobutyronitrile (AIBN) (0.2 eq.) in refluxing benzene. This methodology was further extended to include the denitration of secondary nitro group containing lactones (eg **153**), by increasing the amount of

Bu_3SnH (5 eq.) and azobisisobutyronitrile (AIBN) (0.8 eq) used and the reaction temperature (refluxing toluene), however only poor yields (26%) were obtained (Scheme 2.20).



Scheme 2.20. Ono: Removal of tertiary and secondary nitro groups.[60,61] Reagents and conditions: i) Bu_3SnH (1.2 eq.), AIBN (0.2 eq.), benzene, reflux, 1.5 h, 92%; ii) Bu_3SnH (5 eq.), AIBN (0.8 eq.), toluene, reflux, 0.5 h, 26%.

Ono proposed that the high selectivity observed in the reaction (selective hydrogenation is observed in the presence of keto, ester, cyano, chloro and organic sulfur groups among others) could be attributed to a one electron transfer mechanism. Transfer of an electron from tin radical **155a** to the nitro group of **155b** would form an intermediate nitro radical **155c**. This species would collapse giving an alkyl radical **155f** which could then abstract a hydrogen from Bu_3SnH **155g** thus continuing the chain (Figure 2.7).

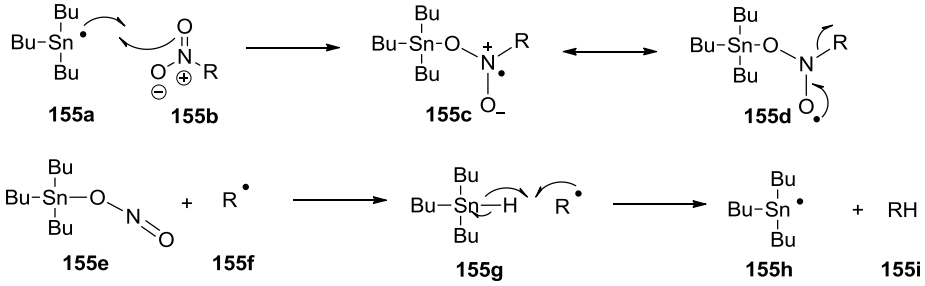
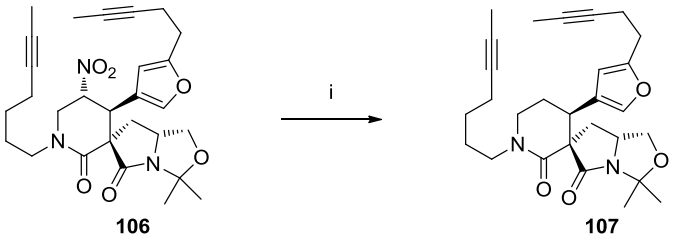


Figure 2.7. Mechanism of reductive nitro removal proposed by Ono.

Cockfield established that by increasing the temperature of the reaction further using refluxing mesitylene as reaction solvent, improved yields of the desired denitrated product could be obtained.[34] Using Cockfield's modified conditions more than 6 g of piperidinone **107** was synthesized with yields

ranging from 50-61% and a largest single batch of 2.57 g (58% yield) (Scheme 2.21). These yields were similar to the levels obtained by Cockfield (55%) although it was found that shorter reaction times were required than those previously reported (2.5 h vs. 9 h).



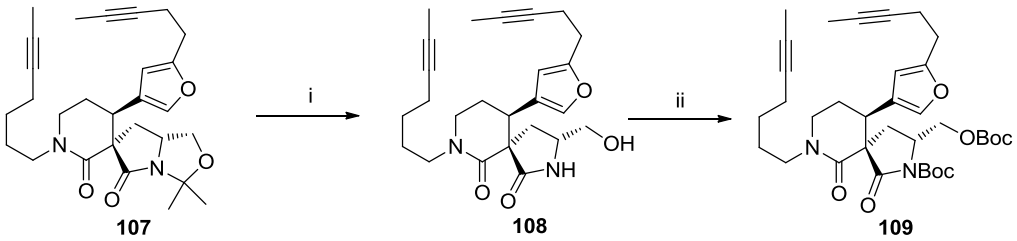
Scheme 2.21. Removal of nitro group. Reagents and conditions: i) Bu_3SnH (5.0 eq.), AIBN (0.2 eq.), mesitylene, reflux, 2.5 h, 58%.

2.14. Synthesis of Tetracyclic Intermediate 111

With multi-gram quantities of piperidinone **107** in hand only three further steps were required to access the key tetracyclic intermediate **111** following the synthetic procedures developed by Cockfield. Construction of the tetracyclic core would be achieved *via* an intramolecular cyclisation of the furan moiety to an *N*-acyliminium ion, in a similar manner to the work of Nishida who pioneered this approach for the construction of the B ring of nakadomarin A (**1**) (see chapters 1.4 and 1.5).[13,19]

To achieve the desired transformation selective delivery of one hydride to the carbonyl of the 5-membered lactam of **109** was needed. A change in protecting groups was required to render the carbonyl group of the 5-membered lactam more reactive than its 6-membered lactam counterpart.

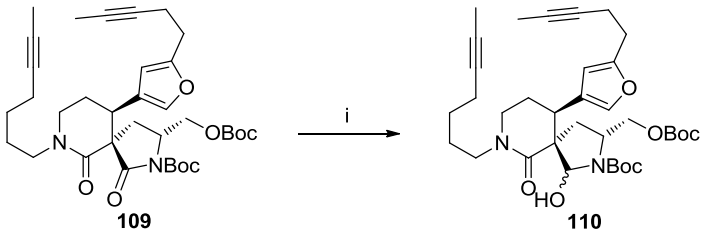
Using Cockfield's optimised procedures, this protecting group switch was readily achieved. Acid catalyzed methanolysis of the isopropylidene protecting group of **107** was followed by exhaustive Boc protection of the −NH and −OH functionality to yield di-Boc substrate **109** (Scheme 2.22).



Scheme 2.22. Synthesis of **109**. Reagents and conditions: i) *p*-TsOH (0.05 eq.), MeOH, reflux, 5 h, 87%; ii) di-*tert*-butyl dicarbonate (5.0 eq.), DMAP (1.0 eq.), Et_3N (5.0 eq.), CH_2Cl_2, RT, 15 h, 88%.

Both transformations proceeded in good yields which, were in excellent agreement with those reported by Cockfield. Over 4 g of aminol **108** was prepared with yields ranging from 77-87% and a largest single batch of 1.77 g. The Boc protected aminol **109** was prepared with yields ranging from 86-88% and a largest single batch of 2.3 g. Approximately 5.5 g of this compound was prepared.

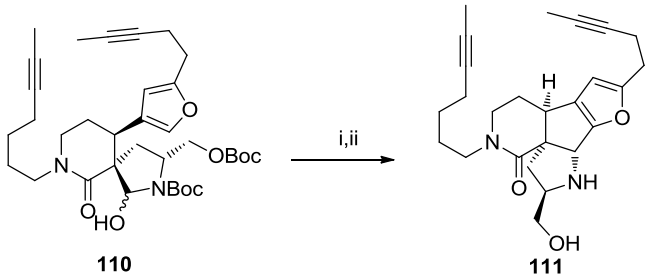
The chemoselective reduction of this pyrrolidinone carbonyl was readily achieved by treatment with lithium triethylborohydride (Superhydride®) at low temperature, affording substrate **110**, which was observed by ^1H NMR as a mixture of rotamers at 298 K (Scheme 2.23).



Scheme 2.23. Synthesis of **110**. Reagents and conditions: i) Lithium triethylborohydride (Superhydride®) (2.3 eq.), THF, −78 °C, 2 h, 79%.

Cockfield used modified conditions to those of Nishida to invoke the furan *N*-acyliminium ion cyclisation. These were based on work by Tanis and co-workers who had shown that tethered furan compounds would react rapidly with *N*-acylaminols in the presence of formic acid.[62] Subjecting substrate **110** to neat formic acid for 15 hours followed by an alkaline hydrolytic work-up

afforded the aminol tetracyclic core **111** of (–)-nakadomarin A (**1**) as a single diastereoisomer (Scheme 2.24). Dissolution in formic acid facilitated the desired *N*-acyliminium ion formation/cyclisation and to a large extent the double Boc deprotection. However it also afforded hydrolysable formic acid derived side products which were successfully converted to aminol **111** with methanolic lithium hydroxide solution.



Scheme 2.24. *N*-acyliminium cyclisation to access tetracyclic core. Reagents and conditions: i) HCOOH, RT, 15 h; ii) LiOH (20 eq.), MeOH, 50 °C, 5 h, 86%.

The selective formation of only one diastereomer in this transformation is in agreement with the observation of both Nishida and Cockfield, who both postulate that the spirocyclic quaternary centre constrains the reacting furan to one face (*Si* face) of the formed iminium ion making *trans* cyclisation impossible.[19,34] The yields of tetracyclic aminol **111** obtained from this reaction after column chromatography (68-86%) were almost identical to those reported by Cockfield, who used the crude aminol after aqueous work-up in subsequent attempted transformations.

2.15. Summary

In total over 2 g of the tetracyclic aminol core **111** of (–)-nakadomarin A (**1**) was synthesized by optimising the procedures developed by Cockfield. Improvement of the capricious Henry reaction allowed nitro olefin **104** to be synthesized on greater than 10 g scale, which, coupled with optimisation of

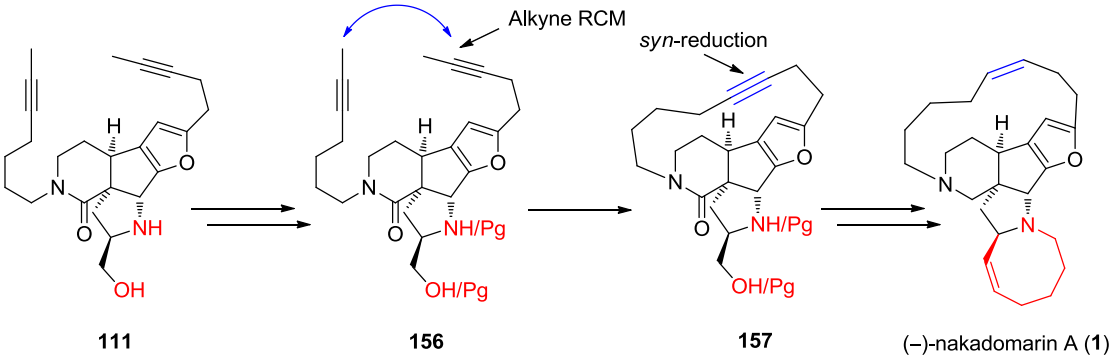
the key nitro olefin Michael addition step, allowed access to larger quantities of **111** than had previously been synthesized.

With the tetracyclic core in hand, strategies for the completion of the synthesis of (–)-nakadomarin A (**1**) by closure of the remaining E- and F-rings rings could be investigated. With abundant evidence of the successful closure of the 8-membered E ring of (–)-nakadomarin (**1**) and the identical 8-membered E-ring of manzamine A (**2**) using alkene ring-closing metathesis strategies[13-15,17,63-68] and others methods,[25,67,69] attention first focussed on the closure of the 15-membered F-ring by alkyne ring-closing metathesis, for which there was no good literature precedent beyond Fürstner's relatively simple model system (Chapter 1.3).[16]

3. Completion of Synthesis of (–)-Nakadomarin A (1)

3.1. F-Ring Closure by Alkyne RCM Approach

With multigram quantities of tetracycle **111** in hand, work described in this chapter was focussed on the identification, guided by the seminal literature, of a suitable substrate **156** that would undergo alkyne ring closing metathesis to form the F-ring of (–)-nakadomarin A (**1**) (Scheme 3.1). Further work would focus on the selective *syn* reduction of the formed C≡C bond and closure of the remaining E-ring of (–)-nakadomarin A (**1**) to complete the synthesis.



Scheme 3.1. Alkyne RCM/*syn* reduction strategy.

3.2. Introduction to Alkyne Ring-Closing Metathesis

Despite their almost simultaneous discovery, alkyne metathesis has not been as widely used in the synthetic chemistry as alkene metathesis has.[70] The apparent reason behind this is that while alkene metathesis catalysts such as Grubbs commercially available, bench stable and highly active ruthenium complexes are available,[71-73] alkyne metathesis has been impeded by a lack of available catalysts and performance issues with regarding ease of handling, substrate scope and temperature required for catalytic activity.

The earliest account of the disproportionation of alkynes was in 1968 by Banks, Bailey and Pennella of the Phillips Petroleum Company.[74] In this report the authors showed that heterogeneous silica supported tungsten oxides catalyzed the disproportionation of pent-2-yne to but-2-yne and hex-3-yne at atmospheric pressure in a continuous flow system. The high temperature required for this transformation (200 to 450 °C) rendered it impractical for preparative purposes and for more complex substrates.

3.3. Mechanism of Alkyne Metathesis

The mechanism of alkyne metathesis, first proposed by Katz in 1975, is a metal carbyne promoted sequence of formal [2+2] cycloaddition and cycloreversion steps. (Figure 3.1).[75]

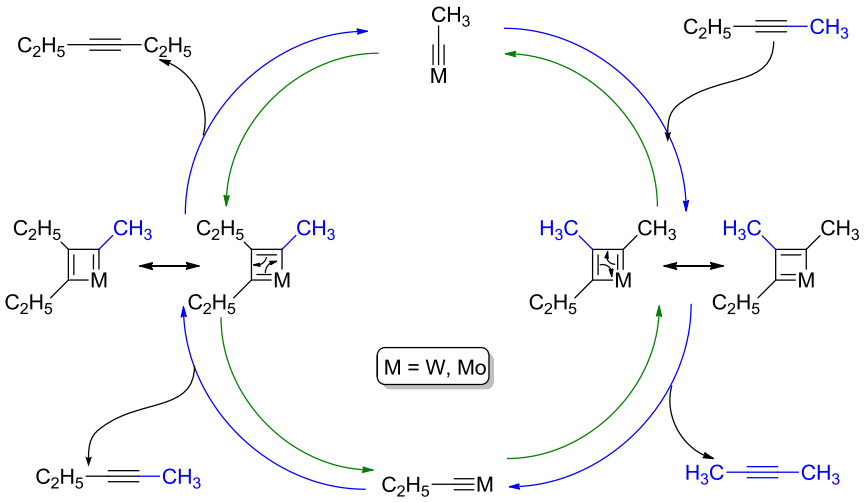
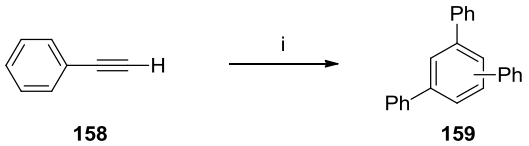


Figure 3.1. Mechanism of alkyne metathesis proposed by Katz.[75]

Alkyne metathesis is amenable only to non-terminal alkynes. Subjecting a terminal alkyne to metathesis conditions has been shown to yield trisubstituted benzenes by cyclotrimerisation (Scheme 3.2).[76]

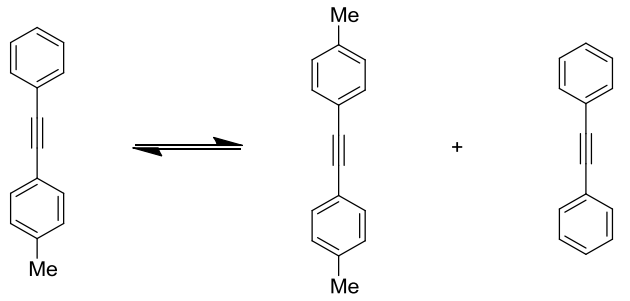


158 159

Scheme 3.2. Example of alkyne metathesis with terminal alkyne to give 1,2,4- or 1,3,5-trisubstituted benzene. Reagents and conditions: i) $Mo(CO)_6$ (5 mol%), 2-fluorophenol (1 eq.), PhCl, reflux, 6 h, 43%.

3.4. Development of Alkyne Metathesis Catalysts

Mortreux and co-workers showed that a structurally undefined homogenous catalytic system formed *in situ* from $Mo(CO)_6$/resorcinol could promote the cross metathesis of simple substituted alkynes at a much lower temperature (160 ºC) than the original conditions of Pennella (Scheme 3.3).[77-79].



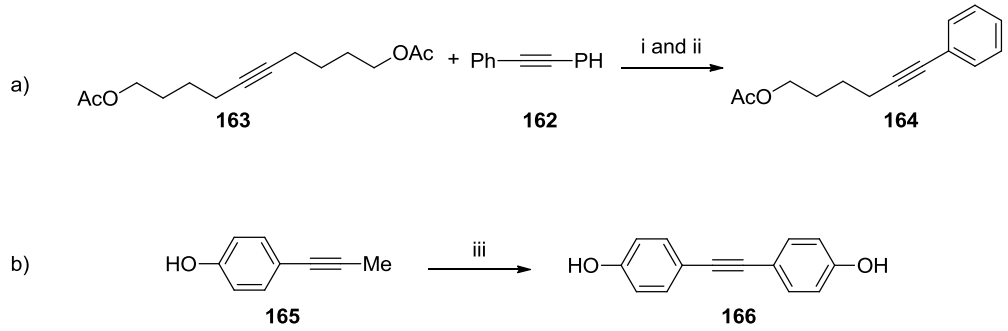
	160	**161**	**162**
Product distribution	55%	21.5%	23.5%

Scheme 3.3. Mortreux alkyne metathesis.[77] Reagents and conditions: i) $Mo(CO)_6$, resorcinol, decaline, 160 °C, 3 h.

The “Mortreux system” attracted considerable attention due to its simplicity. Cheap, commercially available reagents could be used and the active catalytic species could be handled without the need for inert atmosphere reaction conditions and rigorous drying of solvent. Although the exact structure of the active catalysts species is not known it has been proposed by Bunz and Schrock that it is most likely a molybdenum(VI) alkylidyne, Schrock type carbyne, with a structural formula $(ArO)_3Mo{\equiv}C\text{-}R$. This species would be

accessed *via in situ* phenol induced decarbonylation and oxidation of $Mo(CO)_6$.[80,81]

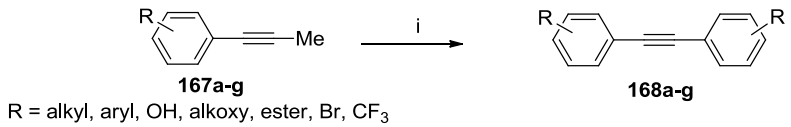
Mori subsequently showed that unsymmetrically substituted alkynes could be generated by cross metathesis using Mortreux's 'instant' catalyst system ($Mo(CO)_6$/*p*-ClC_6H_4OH) in the presence of an excess of one alkyne (Scheme 3.4, reaction a).[82] Mori also showed that cross metathesis of *p*-hydroxyphenylpropyne **165** could be achieved with $Mo(CO)_6$ in the absence of any additional phenol additive (Scheme 3.4, reaction b).[83]



Scheme 3.4. Mori: Metathesis conditions.[82,83] Conditions and reagents: i) $Mo(CO)_6$ (0.008 eq.), *p*-ClC_6H_4OH (0.16 eq.), toluene, 110 °C, 5 h, 19%; ii) $Mo(CO)_6$ (0.05 eq.), *p*-ClC_6H_4OH (1 eq.), toluene, 110 °C, 5 h, 74%; iii) $Mo(CO)_6$ (0.05 eq.), toluene, 110 °C, 78%.

Subsequent modification and improvement of the Mortreux system has also been carried out by:

1. Bunz, who reported that an increase in reaction temperature (140 °C) and removal of 2-butyne by introducing a stream of pure N_2 into the reaction vessel enhanced the efficiency of the dimerization of a range of propynylated arenes **167a-g** (Scheme 3.5).[84]

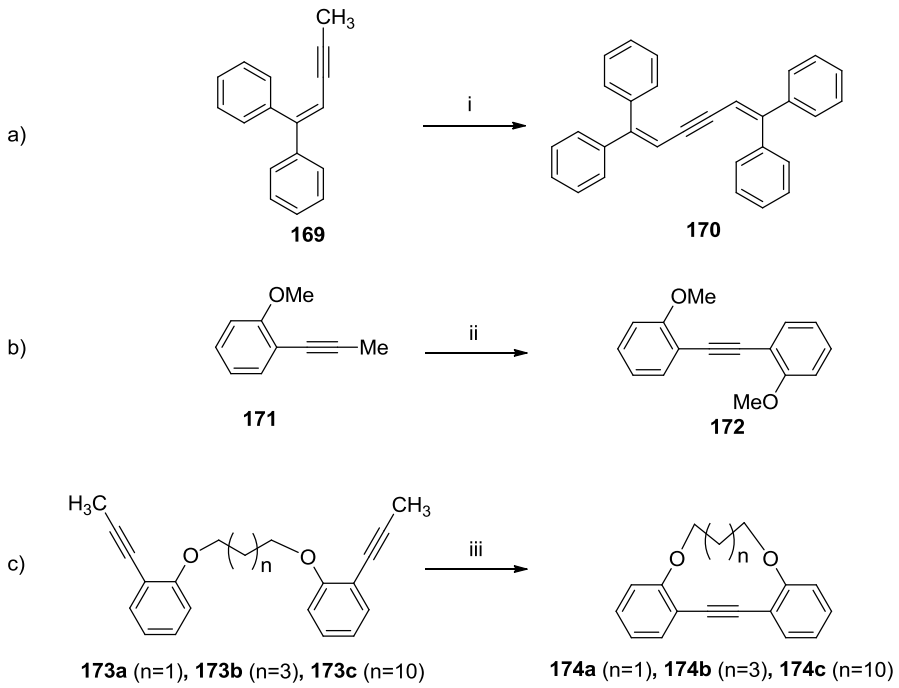


R = alkyl, aryl, OH, alkoxy, ester, Br, CF_3

Scheme 3.5. Bunz: Modification of Mortreux system.[84] Reagents and conditions: i) $Mo(CO)_6$ (0.05 eq.), *p*-ClC_6H_4OH or *p*-trifluoromethylphenol (0.3 eq.), 1,2-dichloroethane, 140 °C, 12-16 h, 10-96%.

The presence of propynylated arenes bearing an electron withdrawing *p*-nitro substituent, electron accepting *o*-,*m*- or *p*-CF_3 substituent, *o*-alkoxy or *o*-ester groups, which potentially have the ability to coordinate to the active Mo-containing species during the reaction, resulted in either diminished yields or a complete lack of reactivity. Heterocyclic and aldehyde containing substrates were also unreactive.

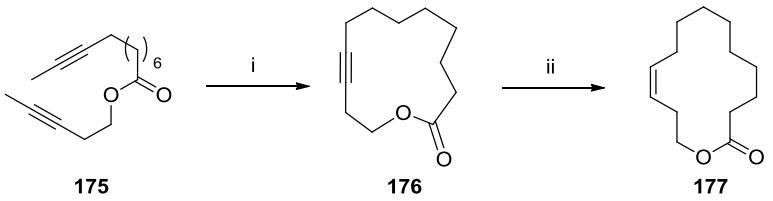
Subsequently Bunz reported an observed increase in catalytic activity in the cross metathesis of 1,1-diphenylsubstituted enyne **169** resulting from a pre-activation protocol with 3-hexyne, to form an active catalyst species, (Scheme 3.6, reaction a).[85] An excess of 3-hexyne was added to a solution of catalytic $Mo(CO)_6$ and 4-chlorophenol in 1,2-dichlorbenzene sealed in a high pressure tube which was heated to 130 °C for 1 h. The pressure was released and excess hexyne removed by purging with nitrogen at 130 °C before addition of the substrate. This pre-activation enabled the cross metathesis of previously problematic *o*-methoxy propynylated arene **171** in near quantitative yield (Scheme 3.6, reaction b) as well some examples of simple ring-closing metathesis reactions of dipropynylarenes **173a**, **173b** and **173c**, albeit generally in very low yields (reaction c).



Scheme 3.6. Bunz: Pre-activated catalyst system.[85] Reagents and conditions: i) $Mo(CO)_6$ (0.1 eq.), 4-ClC_6H_4OH (3 eq.), 3-hexyne (1.06 eq.), 1,2-dichloroethane, 130 °C, 24 h, 80%; ii) $Mo(CO)_6$ (0.1 eq.), 4-ClC_6H_4OH (3 eq.), 3-hexyne (1.06 eq.), 1,2-dichloroethane, 130 °C, 1 h, 98%; iii) $Mo(CO)_6$ (0.1 eq.), 4-ClC_6H_4OH (3 eq.), 3-hexyne (1.06 eq.), 1,2-dichloroethane, 130 °C, 15 h, 5% **173a**, 79% **173b**, 8% **173c**.

Bunz also reported that the use of the more acidic 4-trifluoromethylphenol as an additive in place of 4-chlorophenol improved the reaction protocol in the synthesis of poly(*p*-phenyleneethynylene)s.[80]

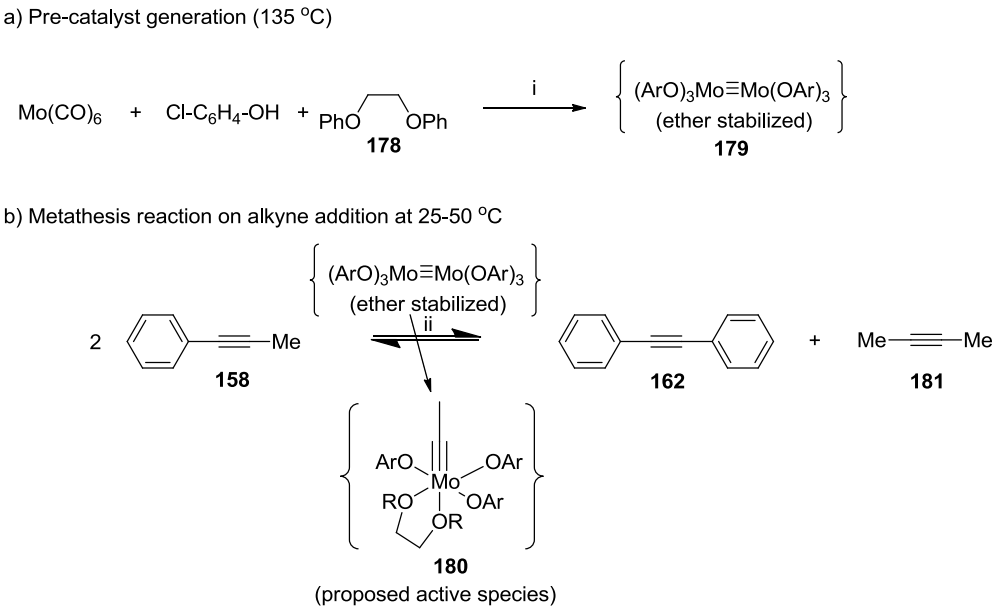
2. Grela, who developed an 'instant' catalyst system using 2-fluorophenol as the phenolic addictive, which was capable of performing alkyne ring-closing metathesis on relatively simple diyne substrates, such as Yuzu lactone precursor **175**, more efficiently than when 4-chlorophenol was employed as the additive (Scheme 3.7).[86]



Scheme 3.7. Grela: 'Instant' catalyst system using 2-fluorophenol.[86] Reagents and conditions: i) $Mo(CO)_6$ (0.05 eq.), 2-FC_6H_4OH (1 eq.), chlorobenzene, reflux, 2 h, 79%; or $Mo(CO)_6$ (0.05 eq.), 4-ClC_6H_4OH (1 eq.), chlorobenzene, reflux , overnight, 62%;[16] ii) Lindlar catalyst, quinoline, H_2, (1 atm), hexanes, 98%.

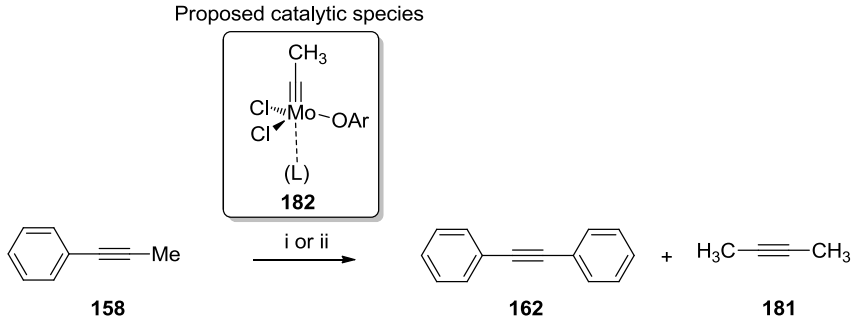
Grela proposed that phenol acidity was key to the catalytic activity observed in the Mortreux or 'instant' catalytic system, with phenols having pK_a values in the range 8-9 proving to be the best activators.[76]

3. Chauvin, who proposed that a rate enhancement of Mo-catalyzed alkyne metathesis could be achieved by addition of a stoichiometric amount of a bidentate ether ligand such as diphenoxyethane **178**. However, only the simple example of the homocoupling of phenylacetylene **158** was described (Scheme 3.8).[87] Chauvin explained that the effect of the ether was to reduce decarbonylation time of $Mo(CO)_6$ and proposed that this oxidative decarbonylation may generate a transient dimolybdenum hexaaryloxide species, possibly stabilised by the ether at high temperature, which is subsequently split to provide the catalytically active mononuclear alkylidyne species **180** on addition of an alkyne at lower temperatures.



Scheme 3.8. Chauvin: Ether-induced rate enhancement.[87] Reagents and conditions: i) N_2 stream, C_6H_5Cl, MS 4 Å, reflux, 3 h; ii) 50 °C, 72 h, 95 %.

Chauvin subsequently introduced a simplified and efficient system containing no additional additives but using 1,2-dichloroethane as solvent. The simple model system phenylacetylene **158** underwent homodimerisation in the presence of a 3:1 mixture of $Mo(CO)_6$ and 4-chlorophenol in 1,2-dichloroethane at 85 °C, with an impressive rate enhancement compared to the same reaction using chlorobenzene as solvent (Scheme 3.9).[88]



Scheme 3.9. Chauvin: Dichloroethane induced rate enhancement:[88] Reagents and conditions: i) $Mo(CO)_6$ (0.01 eq.), 4-ClC_6H_4OH (0.32 eq.), 1,2-dichloroethane, 85 °C, 9 h, 96%; ii) $Mo(CO)_6$ (0.01 eq.), 4-ClC_6H_4OH (0.32 eq.), chlorobenzene, 85 °C, 9 h, 5% conversion.

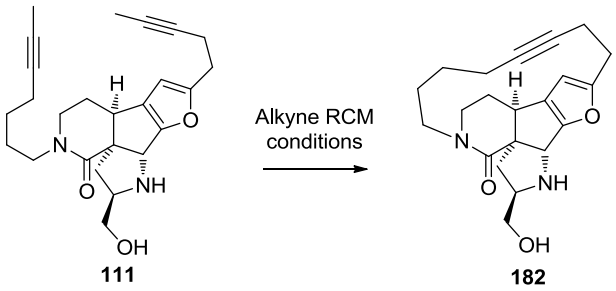
This rate enhancement was attributed to a specific 'chlorine effect', with the solvent generating an active 4-coordinate/two-chloride containing Mo(VI)-

carbyne complex **182**, although no conclusive evidence was given in the manuscript to prove this.[88]

Despite the obvious benefits, namely its user friendly nature, the Mortreux 'instant' catalytic system and its subsequent modifications by Mori, Bunz Grela and Chauvin still suffers from poor reactivity and poor tolerance of functional groups of complex substrates beyond the standard alkyne metathesis 'model' systems. Subsequent development has therefore been focussed in the area of structurally well-defined high valent tungsten and molybdenum precatalysts.

3.5. Structurally Well-Defined catalysts and their Role in Alkyne Ring-Closing Metathesis Reactions

With its limited functional group tolerance, the use of the Mortreux catalytic system to achieve closure of the 15-membered F-ring macrocycle of (–)-nakadomarin A (**1**) using tetracycle **111** was ambitious due to the amide, free amine/alcohol and furan moieties present (Scheme 3.10).



111 **182**

Scheme 3.10. Alkyne RCM of tetracycle **111**

Alternative catalysts with enhanced substrate tolerance and reactivity were therefore sought (Figure 3.2). Tungsten alkylidyne **183** introduced by Schrock[89,90] and trisamidomolybdenum complex **184** introduced by Fürstner[91] were the most prevalent catalysts in the literature when this work on (–)-

nakadomarin A (**1**) commenced. Fürstner's stabilised molybdenum nitride catalyst **185** was subsequently introduced.[92] The commercial availability of these catalysts, all of which require anhydrous glove box conditions for their preparation, made them attractive options.

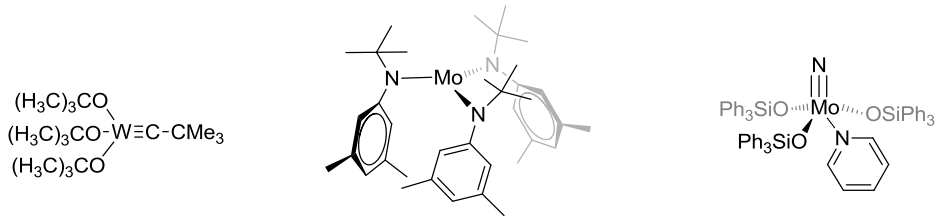
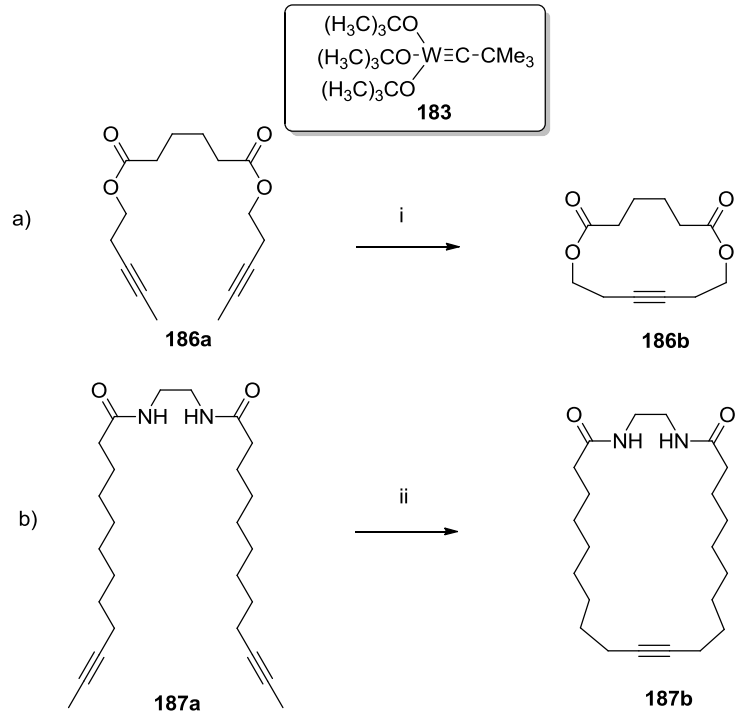


Figure 3.2. Commercially available alkyne metathesis precatalysts

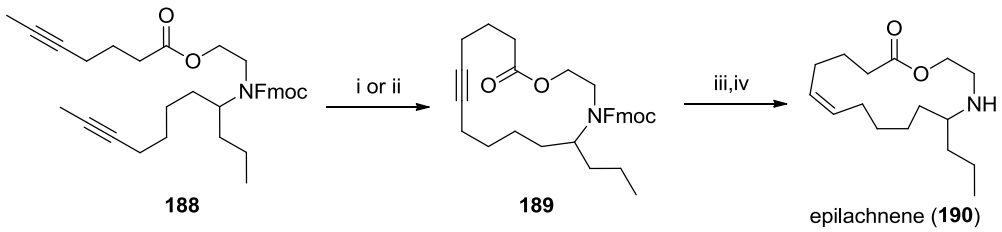
Schrock prepared a range of well-defined tungsten alkylidyne complexes, although **184,** accessed *via* metathesis of $(t\text{BuO})_3\text{W}{\equiv}\text{W}(O t\text{Bu}_3)_3$ with neoheptyne, remains the most widely used and is the only tungsten based catalyst in common usage in alkyne ring-closing metathesis reactions.[16,89]

It was Fürstner who really championed the use of catalyst **183** in the macrocyclic ring closure of simple functionalized alkynes by RCM. Fürstner found this catalyst to possess excellent reactivity although some functional group incompatibility, such as basic nitrogen atoms, thioethers and polyether chains was observed (Scheme 3.11).[91,93]



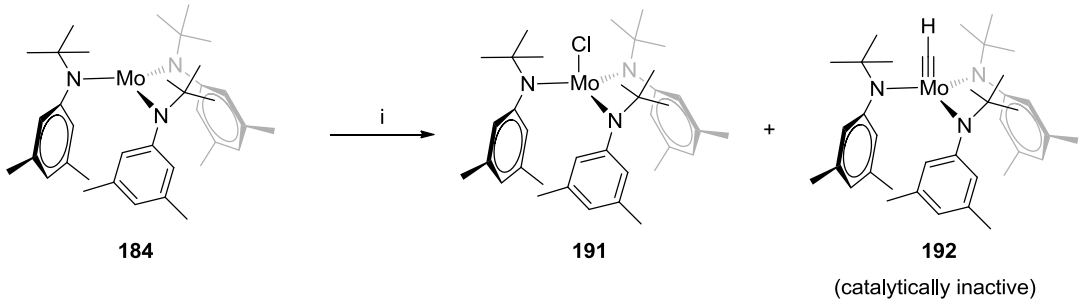
Scheme 3.11. Macrocyclic alkyne RCM catalyzed by **183**. Reagents and conditions**:** i) **183** (6 mol%), PhCl, 80 °C, 2 h, 73%; ii) **183** (6 mol%), PhCl, 80 °C, 2 h, 90%.

These results were nicely exemplified in an alkyne RCM/*syn* selective reduction approach to the 15-membered macrocycle of the insect repellent epilachnene (**190**) (Scheme 3.12). This transformation was also achieved in similar yield using the Mortreux system, although a longer reaction time was required. Another example is described in the previously mentioned model studies in the alkyne RCM approach to the F-ring **8** of (–)-nakadomarin A (**1**) (Chapter 1.3).[16]



Scheme 3.12. Synthesis of epilachnene.[16] Reagents and conditions: i) **183** (5 mol%), PhCl, 80 °C, 1 h, 71%; ii) $Mo(CO)_6$ (5 mol%), 4-ClC_6H_4OH (1 eq.), PhCl, reflux, 26 h, 67%; iii) H_2, Lindlar catalyst, quinoline (0.007 eq.), MeOH, RT, 1 h, 94%; iv) TBAF·$3H_2O$, THF:H_2O, RT, 1 h, 62%.

Fürstner subsequently introduced trisamidomolybdenum precatalyst **184**, based on the seminal work of Cummins on the activation of the triple bond of molecular nitrogen by complexes of type Mo[N(*t*Bu)(Ar)]$_3$.[94-98] Pre-catalyst **184** itself is not an active metathesis catalyst, however activation of **184** with dichloromethane (~25 eq./per mol of **184**) generates the four-coordinate chloro complex **191**, which is the active precatalyst, and catalytically inactive methylidyne complex **192** (Scheme 3.13).[91]

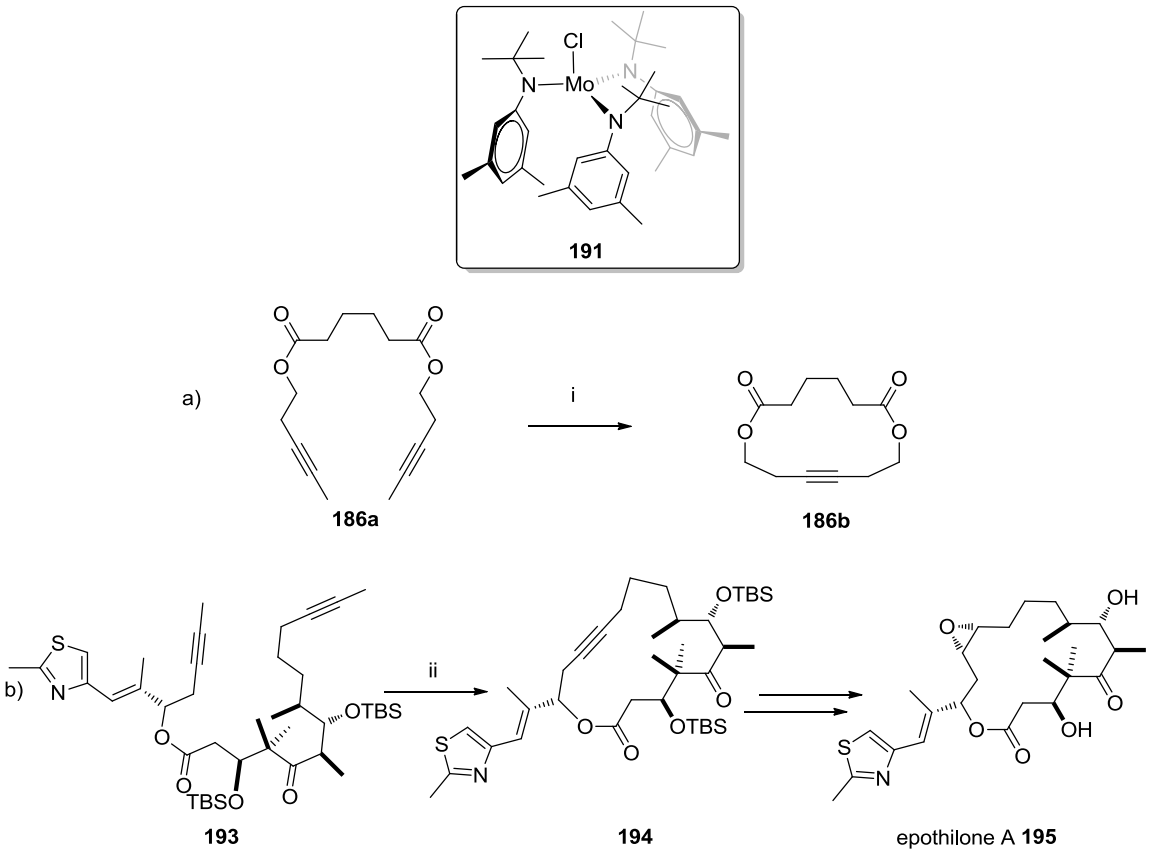


Scheme 3.13. *In situ* activation of **184** with CH_2Cl_2. Reagents and conditions: CH_2Cl_2, toluene, 80 °C.

Catalyst **191** complimented catalyst **183** in terms of functional group tolerance. Catalyst **191** had been shown to tolerate nitro containing compounds and basic nitrogen atoms, which would potentially be present in (–)-nakadomarin A (**1**) metathesis substrates, while catalyst **183** was known to be unreactive towards such substrates. Attenuated Lewis acidity of the Mo centre due to steric crowding in **191** was proposed for this reactivity change. As a result of this **191** was selected as a potential catalyst candidate, despite its reported intolerance towards amide groups, which were know to be unproblematic for catalyst **183**.[91,99]

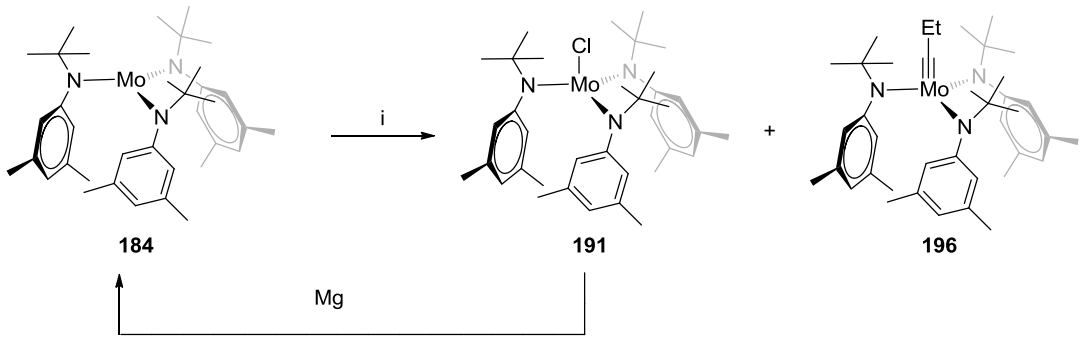
Complex **191** suffers from reduced reactivity compared to **183** (cf. Scheme 3.14, reaction (a) with Scheme 3.11 reaction (a)), [91,100] however some nice examples of macrocycle alkyne RCM reactions of complex substrates were

disclosed by Fürstner such as substrate **193**, a precursor to the microtubule function inhibitor epothilone A (**195**) (Scheme 3.14).[101]



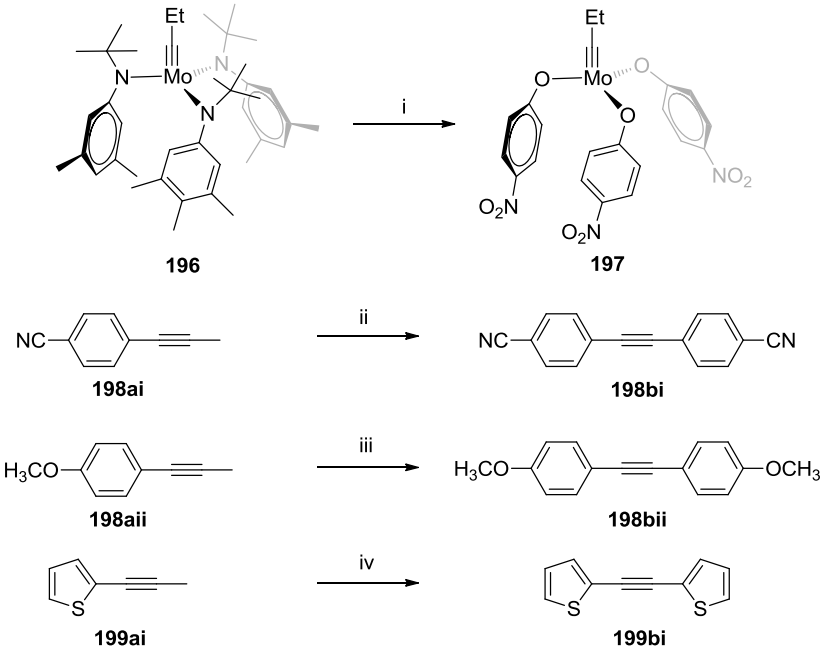
Scheme 3.14. Macrocyclic alkyne RCM with catalyst **191**.[101] Reagents and conditions: i) **191** (10 mol%), toluene, 80 °C, 48 h, 81%; ii) **191** (10 mol%), toluene, 80 °C, 8 h, 80%.

Moore reported an improvement of the catalytic behaviour of this system using a 'reductive recycle' strategy by addition of a *gem*-dihalide such as 1,1-dichloropropane and magnesium which selectively reduced the chloro complex **191** giving high conversion to the active alkylidyne species **196**.[102]



Scheme 3.15. Moore: 'Reductive recycle' strategy.[102] Reagents and conditions: i) $EtCHCl_2$ (2 eq.), Mg (12.5 eq.), THF, RT, 1.5 h, 89% **196**.

Moore subsequently showed that alcoholysis of molybdenum(VI) propylidyne **196** could be achieved with various phenols/alcohols to produce active trisalkoxy alkyne metathesis catalysts which functioned at ambient temperatures.[103] Electronic effects of the ligands were found to be important for metathesis activity, as previously shown by Schrock.[104] Increasing activity was observed with increasing electron withdrawing character of the ligands, making the molybdenum metal centre more electron deficient. *p*-Nitrophenol Mo(VI) **197** catalyst showed the highest catalytic activity.

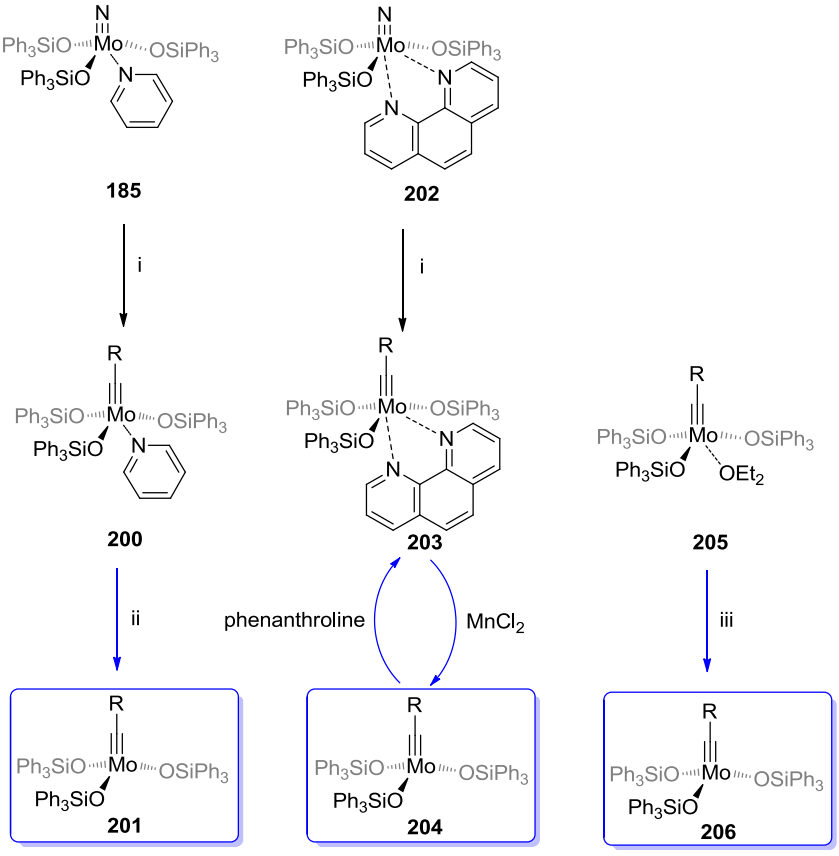


Scheme 3.16. Moore: Trialkoxy molybdenum (VI) catalyst.[103] Reagents and conditions: i) *p*-nitrophenol (3 eq.), THF, 5 min then vacuum (0.09 torr), 60 °C, 15 h; ii) **197** (10 mol%), 1,2,4-trichlorobenzene,

1 torr, 30 °C, 22 h, 93%; iii) **197** (10 mol%), 1,2,4-trichlorobenzene, 1 torr, 30 °C, 22 h, 97%; iv) **197** (10 mol%), 1,2,4-trichlorobenzene, 1 torr, 30 °C, 22 h, 91%;

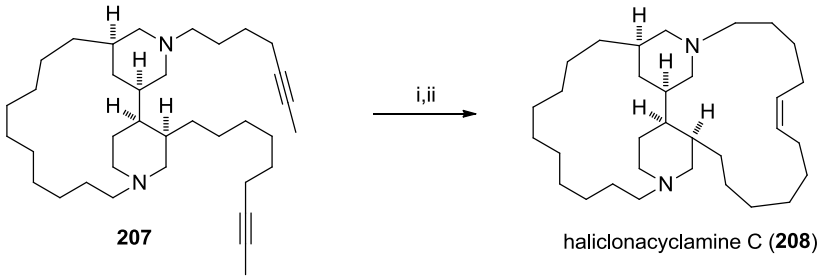
Despite the impressive activity observed, especially considering the use of ambient temperature for the reaction, Moore's system was only tested on relatively simple cross-metathesis reaction with limited substrate scope. The requirement of additional manipulation of highly air sensitive complex **196** also created further practical complications.

Most recently Fürstner developed molybdenum nitride derived silyloxy-based catalyst of type **185** (Scheme 3.17).[92,105] This discovery was inspired by the earlier work of Johnston who showed that certain molybdenum nitride complexes upon treatment with sacrificial alkynes, equilibrated with the corresponding metal alkylidynes.[106,107]



Scheme 3.17. Fürstner: Silyloxy based molydbenum catalysts.[92,105] Reagents and conditions: i) Alkyne, toluene, 80 °C; ii) Toluene, 80 °C; iii) Toluene, ambient temperature.

Pyridine **185** and phenanthroline **202** complexes exhibit remarkable stability and both can be handled without the need for inert conditions. It is believed that these nitride complexes act as a reservoir, slowly releasing small amounts of active alkylidynes **201** and **204.** Phenanthroline complex **202** has been shown to be stable for several weeks under aerobic conditions, however alkylidyne **203** is catalytically inactive and must first be treated with $MnCl_2$ to generate the active catalytic species *in situ*. Etherate complex **205** displayed excellent reactivity with the active catalytic species forming even at ambient temperature. Pyridine complex **185** formed the active catalytic species under standard reaction conditions (toluene, 80 °C) and was particularly attractive due to its commercial availability.[108] The substrate scope of these catalysts is impressive: ester, ketone, amide, carbamate, sulfonate, nitro, ether, thioether, silylether, alkene, acetal, glycoside, thiazole, pyridine and thiophene moieties have been shown to be tolerated. Perhaps the most impressive example of this tolerance and potentially the most relevant to the synthesis of (–)-nakadomarin A (**1**) was shown by Sulikowski and co-workers in their synthesis of haliclonacyclamine C (**208**).[109] Catalyst **201** (generated *in situ* from addition of Ph_3SiOH to $[(Me_3SiO)_2\{(Me_3Si)_2N\}MoN]$)[92] was shown to be catalytically active despite the presence of a challenging unprotected tertiary amine containing substrate (Scheme 3.18).



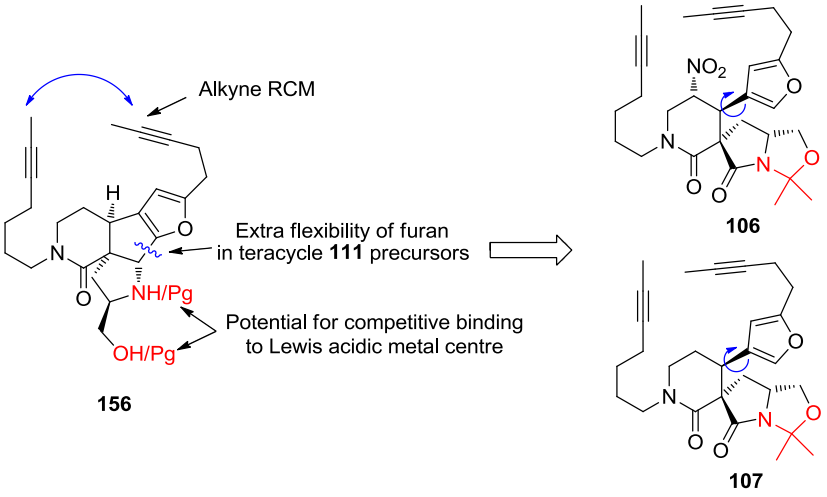
Scheme 3.18. Synthesis of haliclonacyclamine *via* alkyne RCM.[109] Reagents and conditions: i) Ph_3SiOH (3 eq.), $[(Me_3SiO)_2\{(Me_3Si)_2N\}MoN]$, toluene, 130 °C, 2 h, 63%; ii) H_2, Lindlar catalyst, quinoline (16 eq.), EtOAc, 23 °C, 2.5 h, 88%.

3.6. Initial Substrate Screen for Alkyne RCM

Tetacyclic aminol **111** represented an attractive intermediate from which to probe the potential feasibility of an alkyne RCM/*syn* reductive strategy to (–)-nakadomarin A (**1**). Based on evidence drawn from the seminal literature it was anticipated that the free amine and alcohol moieties of **111** would show high affinity for the Lewis acidic metal centre, suppressing reactivity by preventing alkyne coordination.[16,91] Suitable protection of these functional groups would therefore be a key consideration.

Despite tetracycle **111** representing the most structurally advanced intermediate, it was decided to first investigate the alkyne RCM of precursors such as nitro piperidinone **106** and piperidinone **107** (Scheme 3.19). The reason for this was two-fold. Firstly, these intermediates contained protected forms of the amine and alcohol and had been synthesized on multi-gram scale, therefore significant amounts of material would be available for optimisation studies. In addition, it was thought that the extra flexibility of the furan moiety in these substrates, relative to the furan moiety of tetracycle **111**, may be beneficial in lowering the energy barrier for the formation of the ring-closed product. This extra flexibility could limit the strain energy of the

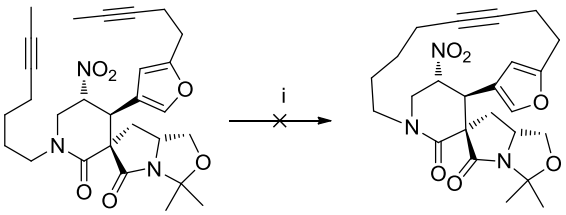
15-membered macrocycle containing the alkyne bond, although would undoubtedly come at an entropic cost.



Scheme 3.19. Strategy for alkyne RCM

Alkyne RCM trials were carried out on small scale (<50 mg) and the reactions monitored by mass spectrometry (MS) and thin-layer chromatography (TLC) to assess potential reactivity.

The initial attempt at alkyne RCM was conducted with nitro piperidinone **106** using the Mortreux catalytic system, with 4-chlorophenol as the phenolic additive. Despite its known lack of functional group tolerance, the simplicity of the Mortreux system made it an obvious starting point. No conversion of piperidinone **106** was observed even after prolonged reaction times (24 h). Pleasingly, despite this lack of catalytic activity, limited degradation of nitro piperidinone **106** was observed, suggesting some stability of the substrate towards the harsh reaction conditions.

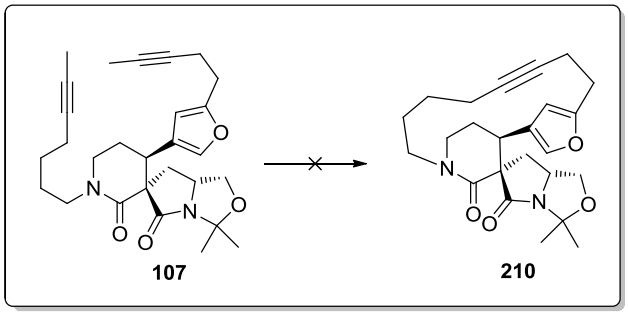


106 209

Scheme 3.20. Failed alkyne RCM of **106**. Reagents and conditions: i) 4-chlorophenol (1 eq.), $Mo(CO)_6$ (10 mol%), PhCl [5.3×10^{-4} mol dm^{-3}] w.r.t. substrate, reflux, 24 h.

Due to the potential incompatibility of the nitro group of **106** towards the active catalyst species[110] and the necessity to subsequently remove it, it was decided to instead focus attention on piperidinone **107** (Table 3.1).

Table 3.1. Catalyst and condition screen for alkyne RCM of **107**



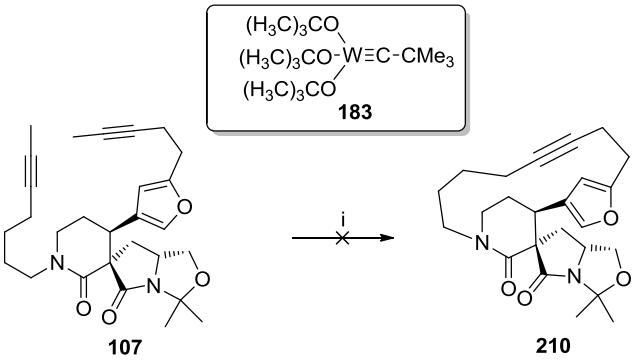
107 210

Entry	$Mo(CO)_6$ Loading	Phenol additive	Solvent [substrate] (mol dm^{-3})	Reaction Conditions	Result
1	50 mol%	4-ClC_6H_4OH	PhCl [5.4×10^{-4}]	reflux, 24 h, N_2	**107** 40% recovered yield
2	20 mol% (sublimed)	4-ClC_6H_4OH (recrystallized)	PhCl (distilled) [4.7×10^{-3}]	reflux, 15 h, N_2	**107** and decomp.
3	10 mol%	4-ClC_6H_4OH	PhCl [6.8×10^{-3}]	reflux, 24 h, N_2, DME, MS 4 Å	**107** and decomp.
4	10 mol%	4-$CF_3C_6H_4OH$	PhCl [4.0×10^{-3}]	reflux, 24 h, N_2	MS evidence of **210**
5	30 mol%	4-$CF_3C_6H_4OH$	PhCl [5.4×10^{-4}]	reflux, 24 h, N_2	**107** and decomp.

6	15 mol%	2-FC_6H_4OH	PhCl [1.0×10^{-2}]	reflux, 24 h, N_2	**107** and decomp.

Using the Mortreux catalytic system with 4-chlorophenol as additive (entry 1) no reactivity was observed and 40% of starting material was recovered, suggesting that the substrate was not as stable to the reaction conditions as initially thought. Rigorous purification of all reagents (entry 2) offered no improvement. Attempted ether stabilization of the pre-catalyst following the modification of Chauvin[87] (entry 3) again resulted in only returned starting material and decomposition (indicated by baseline TLC spot). The use of 4-trifluoromethylphenol introduced by Bunz gave some promise (entry 4).[80] Mass spectrometry showed only the product **210** mass ion (70%, relative intensity), and starting piperidinone **107** mass ion (100%, relative intensity) after 12 h reaction time. However no traces of product were isolated and TLC analysis showed a complex mixture of products. Repeating this result at higher dilution (entry 5) to reduce the probability of dimer/polymer formation gave no indication of product formation. Using Grela's modified conditions (entry 6), no conversion of the starting piperidinone was observed.[86]

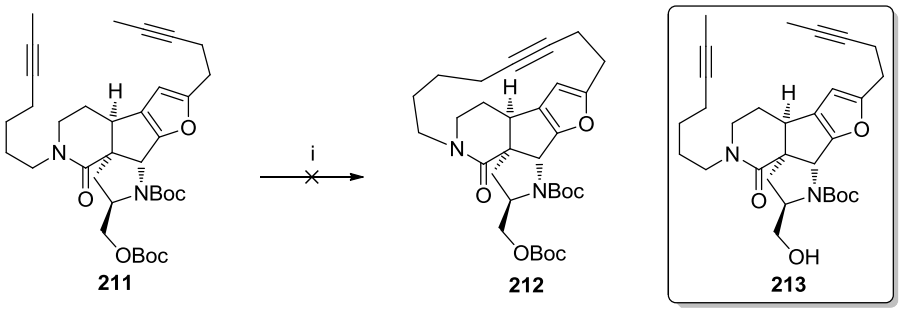
A similar lack of reactivity was observed using Schrock's tungsten alkylidyne catalyst **183** in this transformation (Scheme 3.21).



Scheme 3.21. Alkyne metathesis of **107** using Schrock catalyst **183**. Reagents and conditions: i) Catalyst **183** (10 mol%), PhCl, 80 °C, 15 h, 73% (recovered **107**).

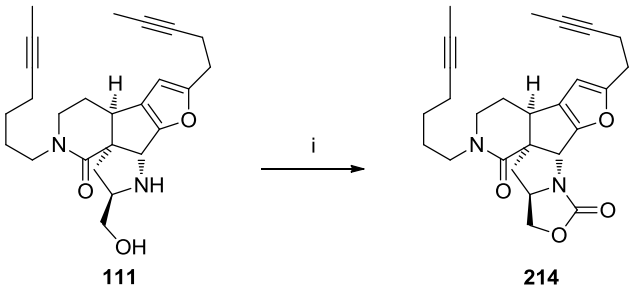
3.7. Alternative Substrate for Alkyne RCM

With no success achieved in the alkyne RCM of substrates **106** and **107** attention returned to the tetracyclic aminol core **111**. Cockfield had previously shown in his single attempt at alkyne RCM that di-Boc protected aminol **211** suffered only loss of one of the Boc protecting groups when subjected to Mortreux reaction conditions.



Scheme 3.22. Cockfield: Failed alkyne RCM. Mono-deprotection of **211**. Reagents and conditions: i) $Mo(CO)_6$ (10 mol%), 4-chlorophenol (1 eq.), PhCl, reflux, 2 h.

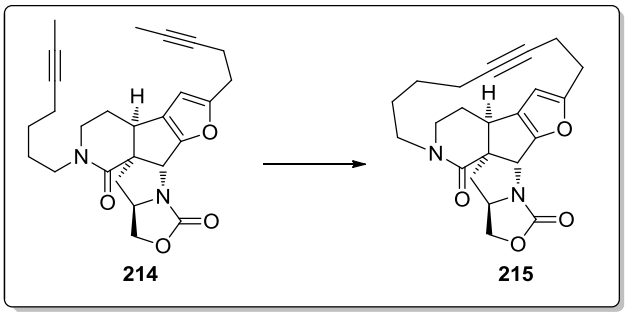
With this in mind, a more robust protecting group was sought. Oxazolidinone **214** was an attractive option and could be synthesized easily in near quantitative yield (Scheme 3.23).



Scheme 3.23. Synthesis of oxazolidinone **214**. Reagents and conditions: i) 1,1'-carbonyldiimidazole (1.1 eq.), CH_2Cl_2, RT, 20 h, 92%.

Oxazolidinone **214** was subjected to a range of catalysts and reaction conditions to assess any potential reactivity (Table 3.2).

Table 3.2. Catalyst and condition screen for alkyne RCM of **214**



Entry	$Mo(CO)_6$ Loading/ catalyst	Phenol additive	Solvent [substrate] (mol dm^{-3})	Reaction Conditions	Result (Isolated yield)
1	10 mol%	4-ClC_6H_4OH	PhCl [5.8×10^{-4}]	reflux, 18 h, N_2	**214** and decomp.
2	20 mol%	2-FC_6H_4OH	PhCl [3.6×10^{-3}]	reflux, 50 min, N_2	**215** (36%)
3	20 mol%	4-$CF_3C_6H_4OH$	PhCl [1.3×10^{-3}]	reflux, 48 h, N_2	MS/TLC evidence of **215**
4	10 mol% **183**	–	PhCl [3.5×10^{-3}]	80 °C, 6 h, Ar	**214** only
5	20 mol% **184**	–	PhCl [4.4×10^{-3}]	80 °C, 20 h, Ar	**214** only
6	20 mol%	2-FC_6H_4OH	$ClCH_2CH_2Cl$ [1.3×10^{-3}]	reflux, 20 h, N_2	**214** only
7	20 mol%	2-FC_6H_4OH	PhCl [3.4×10^{-3}]	reflux, 3-hexyne 20 h, N_2	**214** only

As with substrates **106** and **107**, the Mortreux catalytic system with 4-chlorophenol as additive (entry 1) showed no evidence of successful reactivity. More promising results were obtained with 4-trifluoromethylphenol, however incomplete conversion of starting material **214** was observed. Pleasingly however when 2-fluorophenol was employed, complete consumption of the starting oxazolidinone **214** was observed after only 50 minutes (entry 2). These reaction conditions were repeated multiple times with rapid consumption (<1 h) of the starting material by MS and TLC analysis being observed in most cases. Despite this, the isolated yield of the cyclised product **215** was found to be irreproducible. The highest yield obtained using these conditions was 36% (47 mg scale), however, yields below 20% were common and occasionally no reactivity was observed. Attempts to improve the reactivity by increasing reaction temperature and utilizing Chauvin's 'chlorine effect' with 1,2-dichloroethane (entry 6) and by using Bunz's catalyst pre-activation method with 3-hexyne[85] (entry 7) resulted in a complete loss of reactivity. Both Schrock catalyst **183** (entry 4), and Fürstner catalyst **184** (entry 5), handled under an argon atmosphere to avoid catalyst activation of N_2, showed no evidence of successful metathesis. The lack of reactivity of **184** was expected given its reported incompatibility to amides.[91]

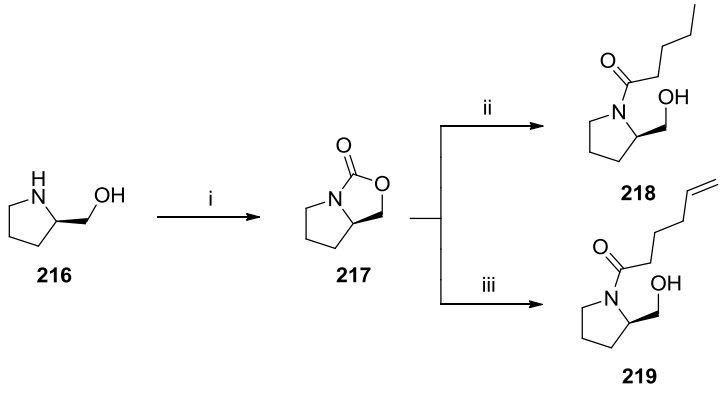
3.8. Summary of Initial Substrate Screening

Positive evidence for the potential of an alkyne ring-closing metathesis strategy in the synthesis of (–)-nakadomarin A (**1**) had been obtained with the successful synthesis of ring-closed substrate **215** using the Mortreux catalytic

system. Despite this, the low yields and lack of reproducibility of this transformation made it unlikely to yield the amounts of material required for completion of the synthesis.

In addition, the removal of the oxazolidinone protecting group in high yield did not appear to be trivial. Attempts to hydrolyse **215** to reveal the free aminol with KOH/MeOH on small scale showed some promise by MS analysis however no free aminol product was ever isolated. Based on work by Aoyagi, a more desirable transformation was the productive nucleophilic ring opening of **215** with an organometallic species,[111] which would remove the protecting group while also providing a handle from which to begin construction of the E-ring.

Using the simple model oxazolidinone **217**, *n*-BuLi provided some promising results with the ring opened product **218** being isolated in 66% yield. Opening of the oxazolidinone with pent-4-enyllithium, an ideal *N*-substituent from which to construct the E ring by alkene RCM, repeatedly gave yields which were considerably poorer. (Scheme 3.24).



Scheme 3.24. Model system oxazolidinone opening. Reagents and conditions: i) $(C_2H_5O)_2CO$ (1.2 eq.), K_2CO_3 (0.07 eq.), 130 °C, 15 h, 60%; ii) *n*-BuLi (2.0 eq.), Et_2O, −78 °C, 2 h, 66%; iii) Pent-4-enyllithium (2.0 eq.), Et_2O, −78 °C, 2.5 h, 16%.

3.9. Alkyne RCM on a Late Stage Intermediate

Reassessment of the initial results obtained in the substrate and catalyst screen and the seminal literature produced some key considerations for the direction of future studies:

- Despite its operational simplicity and initial positive results, the Mortreux reaction conditions appeared to be too harsh to produce reproducible results with sensitive late stage intermediates. Further studies would focus initially on the use of Schrock tungsten alkylidyne **183**.
- Oxazolidinone **214** offered some promising results but further manipulation was required to convert it into a substrate amenable to completion of the synthesis. Further studies would therefore focus on substrates which could easily be manipulated to complete the remaining 8-membered ring.
- The orthogonality of alkyne RCM with alkene functionality, documented in the literature,[110,112] offered potential in the synthesis.

Based on these findings, the most attractive alkyne RCM precursor was diene **220** (Figure 3.3). This substrate offered the advantage of the free amine and alcohol of tetracycle **111** being protected (amine as amide) or removed (alcohol as methylene). Despite this, substrate **220** would not require any additional protection/deprotection sequences, the five-membered lactam amide could potentially be reduced concomitantly with the six-membered lactam amide, meaning **220** could potentially be easily converted to (–)-nakadomarin A (**1**).

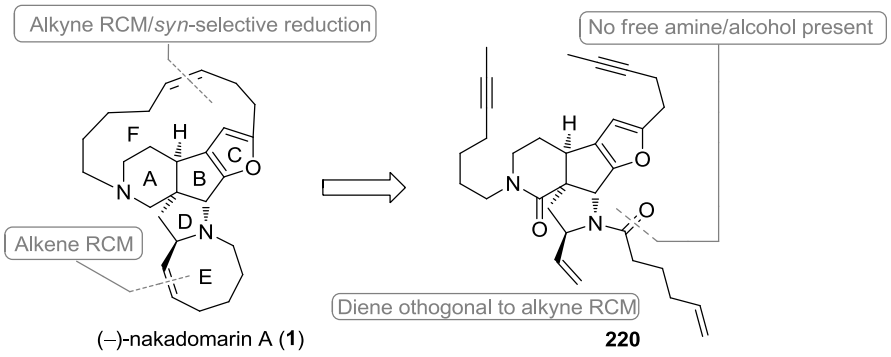
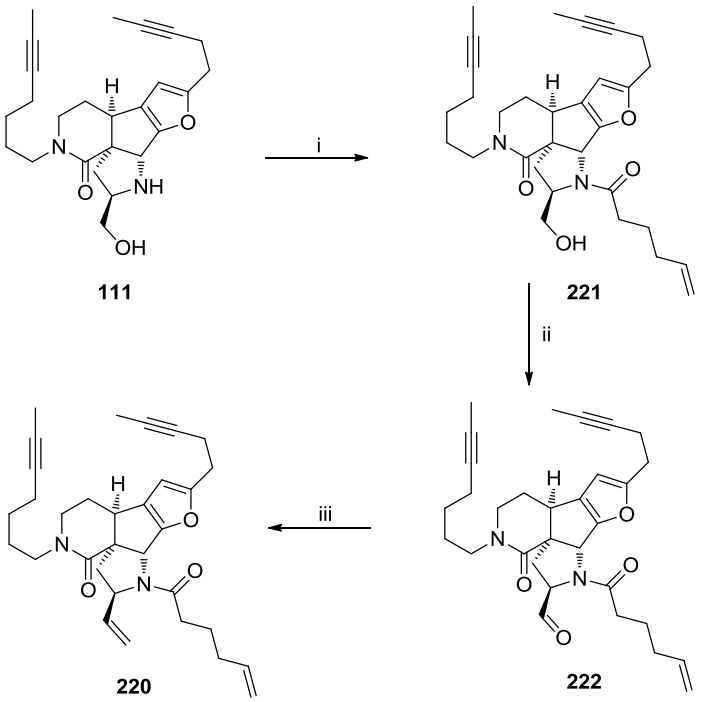


Figure 3.3. Proposed substrate for alkyne RCM.

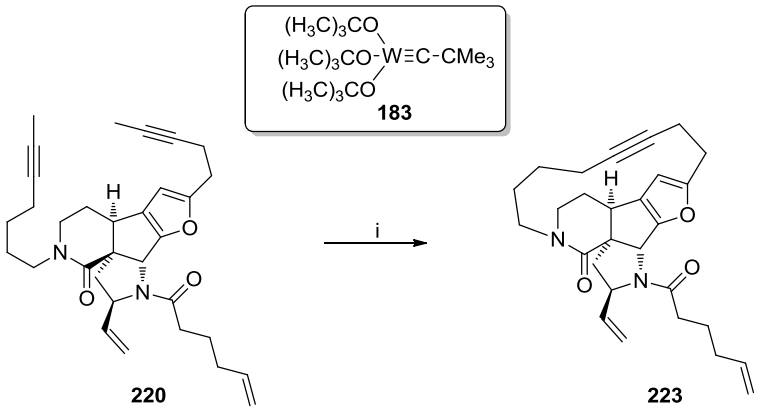
Diene **220** was prepared in three steps using modifications of Kerr's procedures (Scheme 3.25).[15] Amide coupling to form **221** was achieved consistently in excellent yield (85-90%) on up to 700 mg scale using hex-5-enoyl chloride. Addition of DMAP to the reaction was not required and resulted in the formation of considerable amounts (up to 30%) of the undesired *O*-acylated product. Coupling could also be achieved with hex-5-enoic acid and standard peptide coupling reagents (HOBt/WSC·HCl) although yields were lower (53%). Treatment of alcohol **221** with IBX resulted in the formation of aldehyde **222** which only required an aqueous work-up before undergoing Wittig olefination with a pre-formed ylide, generated from methyltriphenylphosphonium bromide in the presence of KO^{t}Bu, to give diene **220**. Both of these reactions proceeded cleanly by TLC analysis although some variation in yield was observed (60-88%). No evidence of deformylation was observed in the Wittig olefination of aldehyde **222**, which proceeded rapidly. The ^{1}H and ^{13}C NMR spectra of diene **220** appeared to indicate the presence of more than one compound, however when these were collected at elevated temperature (373 K) the signals coalesced to a single compound, confirming the presence of amide rotamers rather than any undesired epimerization at the adjacent stereocentre.



Scheme 3.25. Synthesis of diene **220**. Reagents and conditions: i) Hex-5-enoyl chloride (1.05 eq.), Et_3N (5.0 eq.), CH_2Cl_2, −20 °C to RT, 3 h, 89%; ii) IBX (4.5 eq.), DMSO, RT, 24 h; iii) $MePPh_3Br$ (6.0 eq.), KO^tBu (4.7 eq.), THF/Toluene, RT, 15 min, 74% (over 2 steps).

3.10. Alkyne RCM of a Late Stage Diene

Initial metathesis trials on diene **220** were carried out using Schrock's tungsten alkylidyne **183**. Pleasingly on the first attempt, with an excess of alkylidyne **183** present, complete conversion of diene **220** was observed after 2 hours and metathesis product **223** was isolated in 54% yield (Scheme 3.26).



Scheme 3.26. Alkyne metathesis of diene **220**. Reagents and conditions: i) Catalyst **183** (106 mol%), PhCl, 80 °C, 2 h, 54%.

The reaction set-up was rigorously controlled to ensure that anaerobic and anhydrous conditions were attained. The reaction solvent (PhCl) was distilled three times over P_2O_5 under an argon atmosphere prior to use. Diene **220** was dissolved in the anhydrous solvent and the solution concentrated under an argon stream prior to addition to the catalyst. Tungsten catalyst **183** was weighed in an argon filled glove box, however it was then removed and the reaction run in a standard fumehood under an argon atmosphere.

Lowering the loading of catalyst **183** to acceptable levels was found to be possible without excessive loss of reactivity (Table 3.3).

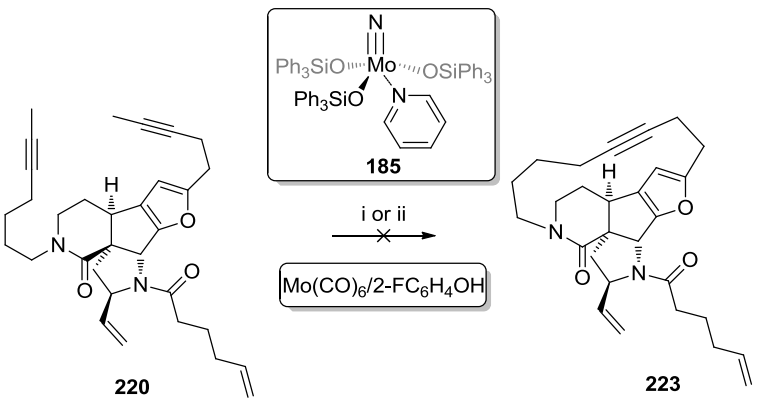
Table 3.3. Reduction in catalyst loading in alkyne metathesis of **220**.

Entry	Catalyst Loading	[substrate] (mol dm^{-3})	Reaction Time	Yield **223**
1	106 mol%	2×10^{-3}	2 h	54%
2	50 mol%	2×10^{-3}	80 min	47%
3	30 mol%	2×10^{-3}	2.5 h	69%
4	20 mol%	2×10^{-3}	8 h	49% 33% (**220**)
5	20 mol%	2.5×10^{-3}	20 h	52% 25% (**220**)

When the catalyst loading was dropped to 50 mol% (entry 2) complete conversion of diene **220** was observed after 80 min and the cyclised product **223** was isolated in 47% yield. The apparent increase in reaction rate relative to the higher catalyst loading (entry 1) can be attributed to closer monitoring of the reaction rather than any catalyst concentration effects. Lowering the catalyst loading to 20 mol% (entry 4) still resulted in good yield of **223** however incomplete conversion of **220** was achieved despite extended reaction time. A repeat reaction at 20 mol% catalyst loading (entry 5) also failed to progress to completion, with similar yields of **220** and **223** being obtained as before. A catalyst loading of 30 mol% (entry 3) was found to be sufficient to give complete conversion of diene **220** within 2.5 h in multiple repeat reactions and cyclised product **223** was isolated in up to 69% yield. At the substrate concentration used (2×10^{-3} mol dm^{-3}), the reaction proceeded cleanly by TLC analysis. No evidence of homodimerisation of **220** was obtained and the lost yield in the reaction could only be attributed to a baseline spot (on TLC plate) even at high polarity, possibly resulting from substrate degradation or oligomerisation. Evidence for degradation/polymerisation was obtained in one reaction where the reaction solution containing cyclised product **223** was concentrated on a rotary evaporator (40 °C bath temperature) with minimal prior air contact. Complete degradation of **223** to a baseline TLC spot was observed, presumably due to the presence of active catalyst at much higher substrate concentrations causing ring-opening/polymerisation to occur. As a result of this observation, reaction mixtures were left open to the air for 0.5 h prior to being concentrated at ambient temperature, to ensure catalyst deactivation and to

minimise any undesired polymerisation. The ring-closed product **223** exhibited amide rotamers in a similar fashion to metathesis precursor **220**. ^{1}H and ^{13}C NMR spectra collected at elevated temperature again confirmed the presence of a single compound.

Further attempts to improve the alkyne RCM of diyne **220** were carried out using the best Mortreux catalytic system conditions previously found with oxazolidinone **214** and Fürstner's air stable, pyridine stabilised molybdenum nitride catalyst **185** which had recently become commercially available. Previous attempts to synthesize this catalyst following literature procedures had given inconclusive and unreliable results.[105] Despite the considerable stability of **185** in solid form, its synthetic precursors and **185** in solution phase were found to be extremely sensitive to atmospheric conditions. These catalysts would have offered the advantage of avoiding the requirement of glove-box conditions for handling the catalyst; however the Mortreux system resulted only in decomposition of diene **220**, while catalyst **185** returned only unreacted starting material (Scheme 3.27).



Scheme 3.27. Failed alkyne RCM reactions on substrate **220**. Reagents and conditions: i) $Mo(CO)_6$ (0.2 eq.), 2-fluorophenol (1.0 eq.), PhCl, reflux, 5 h; ii) Catalyst **185** (20 mol%), toluene, 80 °C, 24 h.

3.11. Summary of Alkyne Metathesis

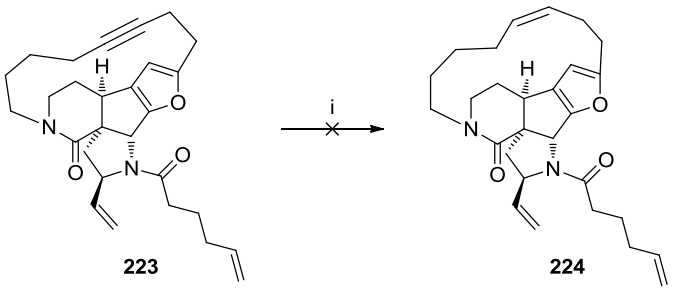
Diene **220** was found to be an ideal precursor for alkyne RCM. Treatment of this substrate with Schrock's tungsten alkylidyne catalyst **183** allowed the synthesis of ring-closed substrate **223** on sufficient scale (>200 mg) to allow for further advancement of the synthetic route to (–)-nakadomarin A (**1**). Three challenges remained in the synthesis:

1. *Syn*-selective reduction of the alkyne bond to give exclusively the required *Z*-alkene.
2. Completion of the 8-membered E-ring by alkene ring-closing metathesis.
3. Reduction of both the 5- and 6-membered lactams to give the required tertiary amines.

3.12. *Syn*-Selective Alkyne Reduction

Several recent examples exist of an alkyne RCM/*syn*-selective reduction strategy being adopted to circumvent issues of poor *E*/*Z* selectivity in macrocyclic ring-closures by alkene RCM.[113-116] In most cases reduction using Lindlar catalyst gave access to the *syn*-reduced product in excellent yield.[117]

Attempted reduction of alkyne **223** using Lindlar reduction conditions resulted in no apparent reactivity by TLC analysis (Scheme 3.28).



Scheme 3.28. Lindlar Reduction of **223**. Reagents and conditions: i) Lindlar catalyst ($Pd/CaCO_3/Pb(OAc)_2$) (2 eq. wt./wt.), quinoline (1.6 eq.), H_2 (1 atm.), EtOH, 0.5 h.

MS analysis however indicated the presence of a major mass ion (M_r = 452), which was attributed to over reduction of the terminal alkene bonds of **223**, despite the short reaction time (Figure 3.4). Subsequent modification of the reaction procedure including increasing the amount of quinoline added, altering the reaction solvent and reducing the reaction time, did not produce any significant improvement.

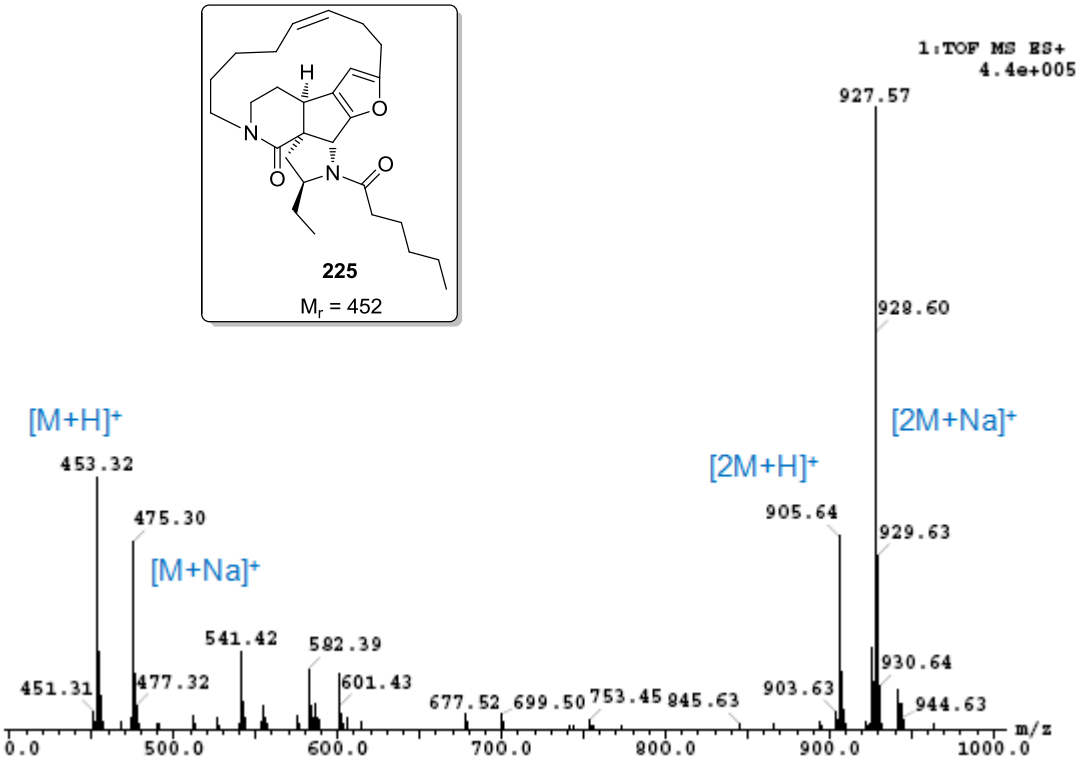
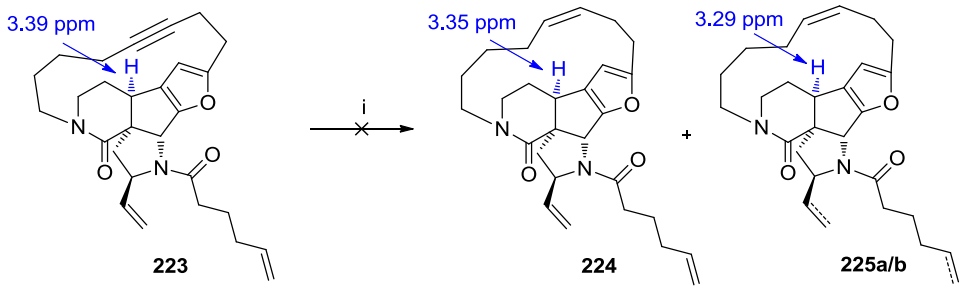


Figure 3.4. MS analysis of Lindlar reduction of alkyne **225**.

Brown's P-2 nickel boride (Ni_2B) catalyst provided a potential alternative method of *syn*-reduction.[118,119] This heterogeneous catalyst, prepared by

treating a vigorously stirred ethanolic solution of nickel acetate tetrahydrate with sodium borohydride in a hydrogen atmosphere, was shown by Brown to give excellent selectivity in the *cis*-reduction of intenal alkynes. *Z*:*E* selectivities of up to 30:1 were achieved in the reduction of hex-3-yne although this could be increased to up to 200:1 by addition of ethylenediamine (3.2 eq. relative to catalyst).



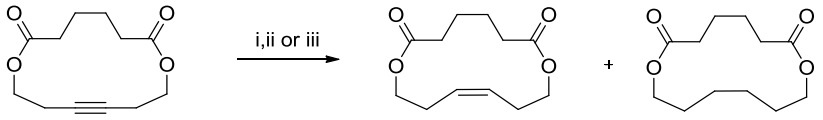
223 **224** **225a/b**

Scheme 3.29. Ni_2B reduction of **223**. Reagents and conditions: i) $Ni(OAc)_2{\cdot}4H_2O$ (1 eq.), $NaBH_4$ (2 eq.), H_2 (1 atm.), EtOH, RT, 1 h; ii) $Ni(OAc)_2{\cdot}4H_2O$ (1 eq.), $NaBH_4$ (2 eq.), ethylene diamine (4 eq.), H_2 (1 atm.), EtOH, RT, 40 min, **224**:**225a/b** 75:25. Chemical shifts for furan-C*H* proton obtained in $CDCl_3$ at 273 K.

Initial attempts using Brown's P-2 Ni_2B catalyst in the absence of ethylene diamine resulted in rapid reduction of the terminal alkenes of **223**, and **224** was not observed. Introducing ethylene diamine (4 eq.) to the reaction inhibited this over reduction however up to 25% of side products containing partially or fully reduced alkenes, **225a** or **225b** were observed (Scheme 3.29). MS provided a convenient and reliable method of analysing the composition of the reaction mixture and was the preferred method of analysis. ^{1}H NMR spectroscopy was used to corroborate the MS data although the ^{1}H NMR spectra obtained were complicated by the presence of amide rotamers. Distinction between alkyne **223**, desired product **224** and over reduced products **225a** and **225b** was possible by ^{1}H NMR analysis however due to small changes in chemical shift of the furan-C*H* proton for each compound. This proton signal was reasonably isolated from the other

signals in the ^{1}H NMR spectrum and therefore problems due to overlapping signals were avoided.

Model alkyne system **226** was used to gain a better understanding of the relationship between the amount of ethylene diamine in the reaction and the amount of over reduced side products obtained (Scheme 3.30).

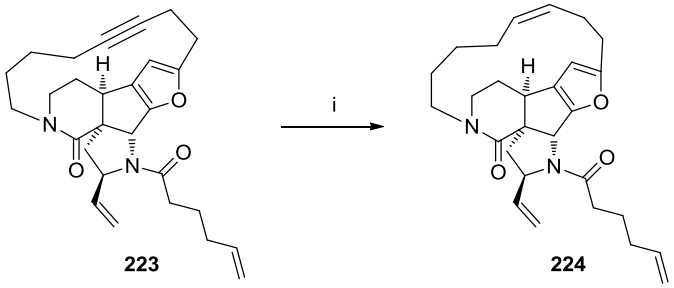


226 **227** **228**

Scheme 3.30. Ni_2B reduction of **226**. Reagents and conditions: $Ni(OAc)_2 \cdot 4H_2O$ (1 eq.), $NaBH_4$ (2 eq.), ethylene diamine (i,ii or iii)*, H_2 (~1 atm.), EtOH, RT, 2.5 h.* i) Ethylene diamine (0 eq.), ii) ethylene diamine (4 eq.), iii) ethylene diamine (20 eq.).

All reactions were carried out simultaneously and were identical except for the amount of ethylene diamine added to each. Mass spectrometry analysis after 2.5 h indicated that alkyne **226** had been consumed in all cases. Reaction (i) containing no ethylene diamine contained only the mass ion corresponding to over reduced compound **228**. Reaction (ii) with 4 equivalents of ethylene diamine showed the mass ion of the desired product **227** (80% relative intensity) and **228** (10 % relative intensity), while reaction (iii) (20 equivalents of ethylenediamine) contained only the mass ion for **227**, with no evidence of over reduction. While these results could not be considered quantitative, they provided useful information for reduction on the real system **223**, in particular showing that the reduction could be achieved with short reaction times even with a large excess of ethylene diamine present.

Applying these optimised conditions to **223** resulted in the formation of the desired product **224** in excellent yield, without any significant over reduction being observed (Scheme 3.31).



Scheme 3.31. Successful Ni_2B reduction of **223**. Reagents and conditions: i) $Ni(OAc)_2{\cdot}4H_2O$ (1 eq.), $NaBH_4$ (2 eq.), ethylene diamine (25 eq.), H_2 (~1 atm.), EtOH, RT, 1 h, 87%.

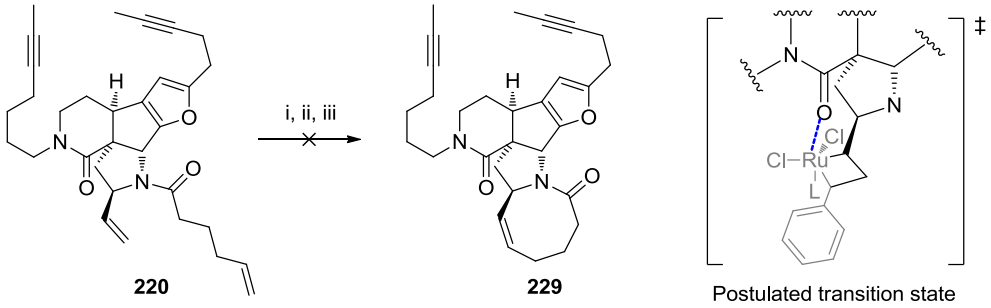
Reactions were monitored by mass spectrometry and stopped when the mass ion of alkyne **223** was no longer observed (45 min – 1.5 h). ^{1}H NMR analysis at elevated temperature (363 K) confirmed the presence of a single compound, with amide rotamers again being observed at ambient temperature. The coupling pattern of the protons of the newly formed alkene were complicated by coupling with nearby protons, however the largest coupling observed (J = 8.5 Hz), indicated that a *Z*-alkene had been formed.

3.13. Synthesis of E-ring and Completion of Synthesis

With the *Z*-alkene of the 15-membered macrocycle of (–)-nakadomarin A (**1**) in place, only an alkene RCM reaction to close the E-ring and a double amide reduction were required to complete the synthesis.

Initial attempts to carry out the alkene RCM on diene **220** with both amides still in place, prior to alkyne RCM, had met with no success and starting

material was recovered as the major reaction component after prolonged reaction times using Grubbs 1st and 2nd generation catalysts. The reaction with Grubbs-Hoveyda 2nd generation catalyst at high loading did show consumption of starting material, although ^{1}H NMR analysis indicated a complex mixture of products in this case. This was perhaps unsurprising giving the additional possibility of undesired ring-closing-ene-yne and cross-ene-yne metathesis with this substrate.

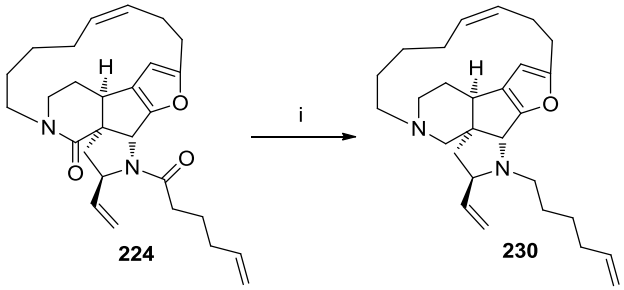


Scheme 3.32. Unsuccessful alkene RCM on diene **220**. Reagents and conditions: i) Grubbs 1st generation catalyst (20 mol%), CH_2Cl_2, reflux, 20 h; ii) Grubbs 2nd generation catalyst (20 mol%), CH_2Cl_2, reflux, 20 h; iii) Grubbs-Hoveyda 2nd generation catalyst (80 mol%), CH_2Cl_2, reflux, 35 h.

This lack of reactivity may have resulted from attenuated activity of the catalyst due to coordination of the Lewis basic oxygen of the 6-membered lactam with the ruthenium centre, although a successful example of alkene RCM to form the 8-membered ring of manzamine A (**2**) on a similar diamide substrate had been described previously by Martin, using a Schrock Mo(VI) alkylidene catalyst.[120] In general however, similar transformations in previous (–)-nakadomarin A (**1**) syntheses had been performed without this amide bond in place.[13-15]

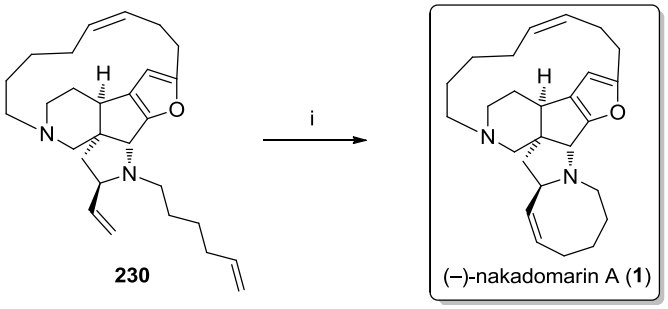
With this in mind it was decided to first reduce **224** to diamine **230**. This transformation was successfully achieved using DIBAL-H, which was found to give more satisfactory results than $LiAlH_4$ or Red-Al®. Critical to achieving a good yield in this reaction was the use of a non-aqueous work-up

procedure ($NaSO_4 \cdot 10H_2O$) and purification of diamine **230** using neutral alumina (Scheme 3.33).



Scheme 3.33. Reduction of diamide **224**. Reagents and conditions: DIBAL-H (10 eq.), toluene, 0 °C to RT, 6 h, 59%.

With diamine **230** in hand the stage was set for a final alkene RCM to complete the synthesis of (–)-nakadomarin A (**1**). Based on the work of Jakubec, it was known that prior protonation of amines with camphorsulfonic acid did not adversely affect subsequent metathesis reactions using Grubbs 1st generation catalyst.[25] These conditions were therefore adopted in order to eliminate any potential for an unsuccessful reaction resulting from deactivation of the ruthenium catalyst by the free amines. Using these conditions, metathesis of diamine **230** was found to proceed cleanly, giving (–)-nakadomarin A (**1**) in excellent yield (Scheme 3.34).



Scheme 3.34. Final alkene RCM in the synthesis of (–)-nakadomarin A (**1**). Reagents and conditions: Grubbs 1st generation catalyst (30 mol%), (+)-CSA (3 eq.), CH_2Cl_2, reflux, 8 h, 70%.

^{1}H and ^{13}C spectra (Figure 3.6, Figure 3.9) and specific rotation values of the synthetic sample of (–)-nakadomarin A (**1**) were in good agreement with the

data previously reported for the *Z*-isomer of (–)-nakadomarin A (**1**).[13-15,25] Non-stereoselective reduction of the alkyne present in **223** and ring opening/isomerisation of the F-ring alkene in the final alkene RCM step were potential sources of 'leakage' to the *E*-isomer. Despite this, no evidence of the presence of any of the *E*-isomer was detected.

3.14. Comparison with Nishida and Dixon ^{1}H NMR Spectra

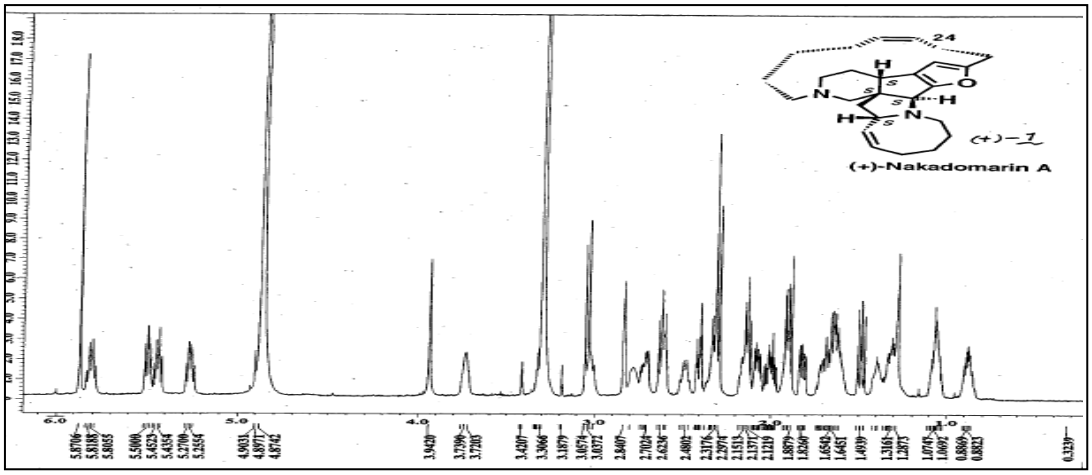


Figure 3.5. Nishida 1H NMR (600 MHz, CD_3OD) spectrum of (+)-nakadomarin A **1** (2003).

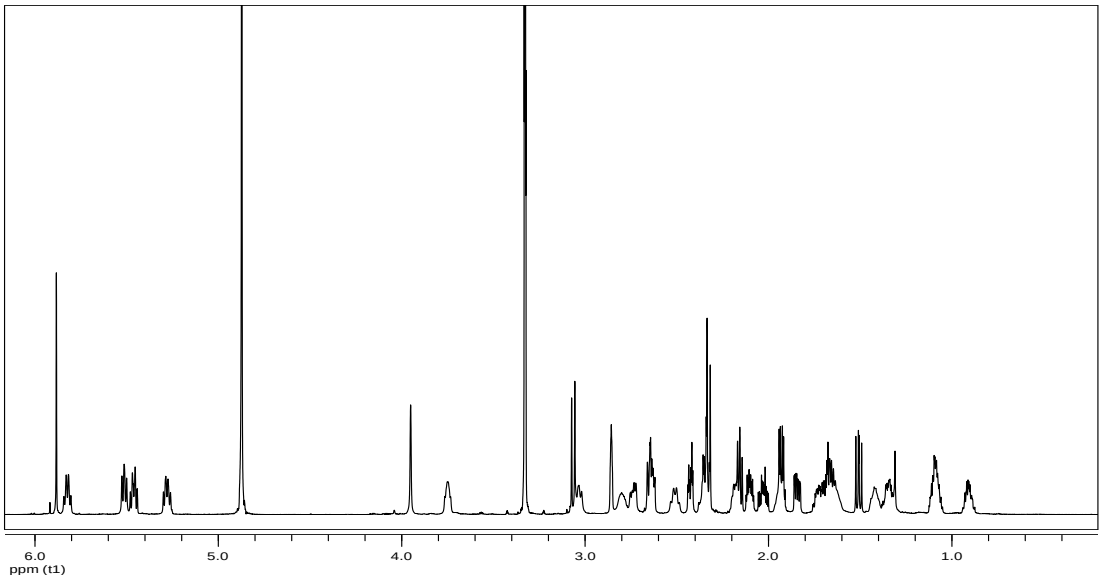


Figure 3.6. ^{1}H-NMR (700 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1**. (Present work).

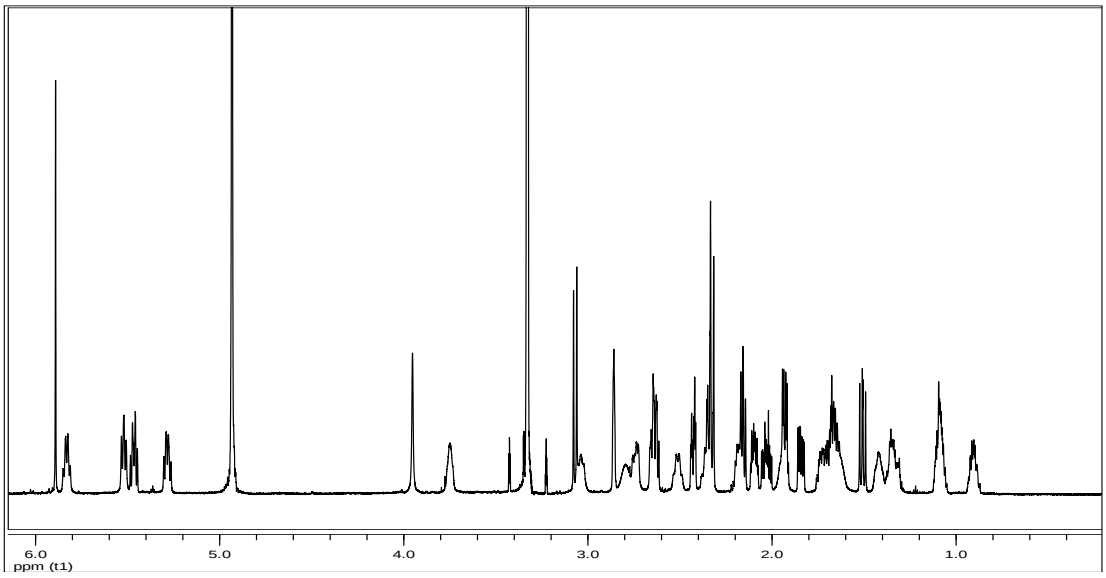


Figure 3.7. Dixon ^{1}H-NMR (700 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1**. (2009).

3.15. Comparison with Nishida and Dixon ^{13}C NMR Spectra

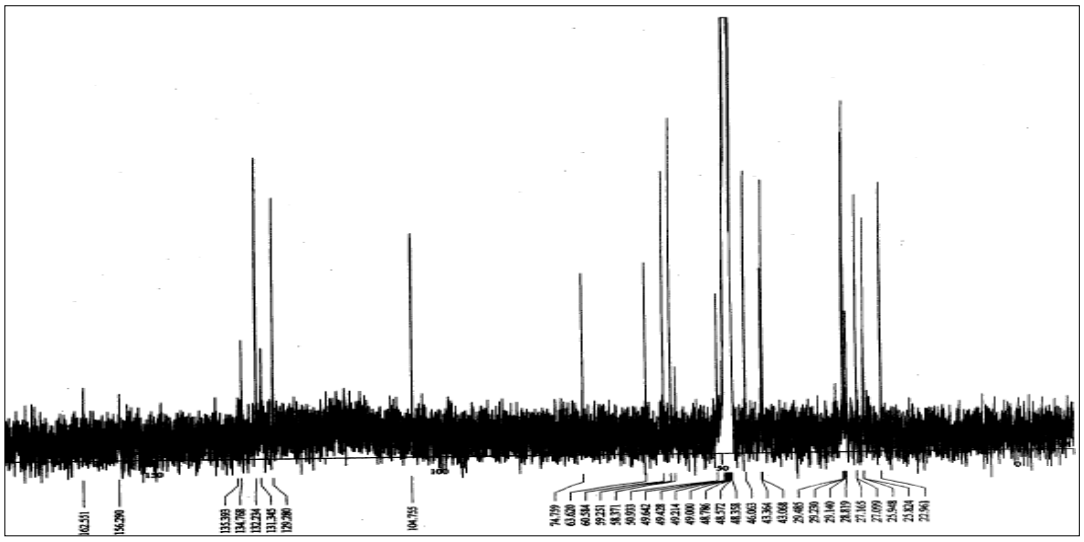


Figure 3.8. Nishida ^{13}C NMR (100 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1** (2004).

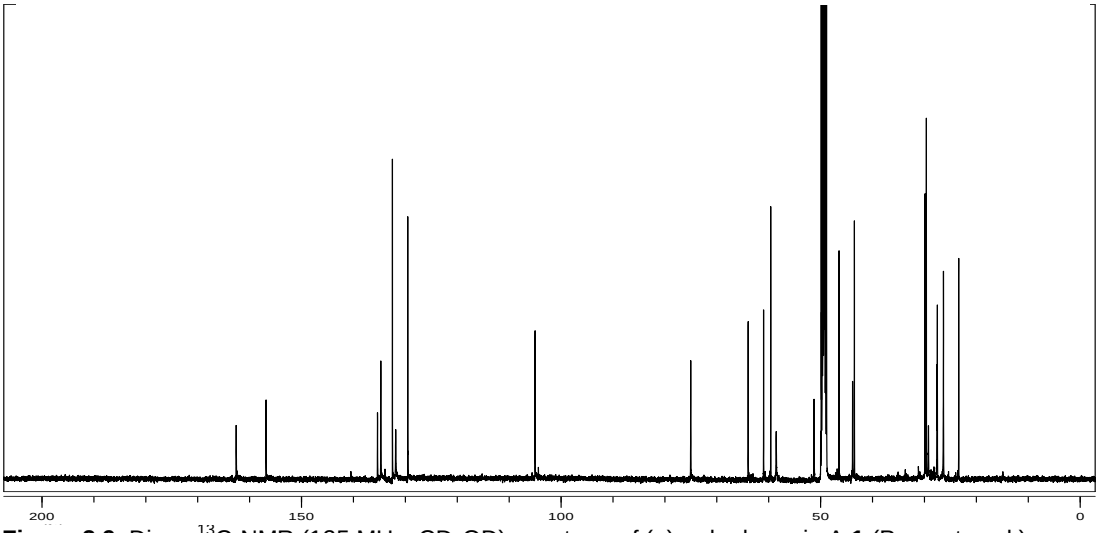


Figure 3.9. Dixon ^{13}C-NMR (125 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1** (Present work).

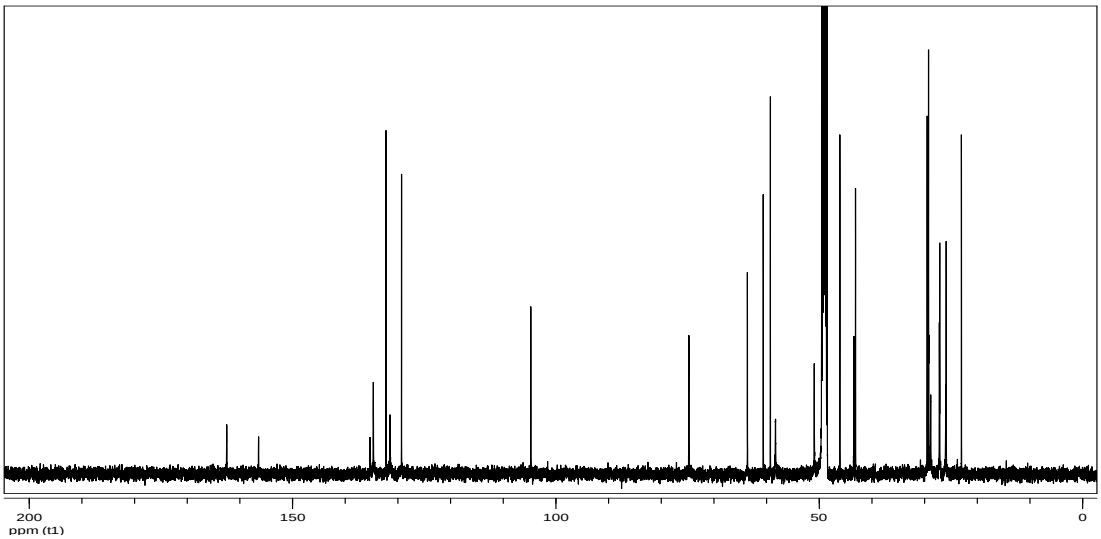


Figure 3.10. Dixon ^{13}C-NMR (125 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1** (2009).

3.16. Summary of (–)-Nakadomarin A (1) Synthesis and Future Work

A short and highly stereoselective synthesis of (–)-nakadomarin A (**1**) has been developed. 'Matched' catalyst and substrate control facilitated a highly diastereoselective nitro olefin Michael addition to create two of the four stereocentres in one key step. Further key steps including a nitro-Mannich/lactamization cascade and furan *N*-acyl iminium cyclisation allowed access to the tetracyclic core **111** of (–)-nakadomarin A (**1**) in multi-gram scale. Sequential alkyne ring-closing metathesis/*syn* reduction using Schrock tungsten alkylidyne catalyst **183** and Brown's P-2 Ni_2B enabled the stereoselective construction of the *Z*-alkene in the fifteen-membered macrocycle, before an alkene ring-closing metathesis, completed the total synthesis of the natural product in 19 steps. In total ~9 mg of pure (–)-nakadomarin A (**1**) were isolated and this route represented the shortest reported *Z*-selective route to (–)-nakadomarin A (**1**) at the time of its completion.

Since the completion of this total synthesis of (–)-nakadomarin A (**1**), three additional syntheses by other research groups have achieved. In 2010 Mukai reported a formal synthesis of (+)-nakadomarin A in 26 steps, using a Pauson-Khand strategy as a key step.[121]

While the work described in chapters 2 and 3 of this thesis was being prepared for publication, Funk and co-workers reported a synthesis of (–)-nakadomarin A using a similar alkyne RCM/*syn* selective reduction strategy. Overall, 21 steps were required to access (–)-nakadomarin A, making this route longer than the alkyne RCM route reported in this thesis.[122]

In 2011 Zhai and co-workers used a Pt(II)-promoted cascade cyclisation as a key step to achieve the synthesis of (–)-nakadomarin A in 21 steps from commercially available starting materials.[123]

Despite its advantage of yielding only a single isomer, an alkyne RCM/*syn* reduction approach has a major disadvantage of requiring one additional step compared to an alkene RCM approach. The ideal solution to address the problem of poor *E*/*Z*-selectivity in macrocyclic ring closures would instead be a *Z*-selective alkene RCM approach. Pioneering work by Prof. Richard Schrock and Prof. Amir Hoveyda in this field was the inspiration for further work in this thesis.

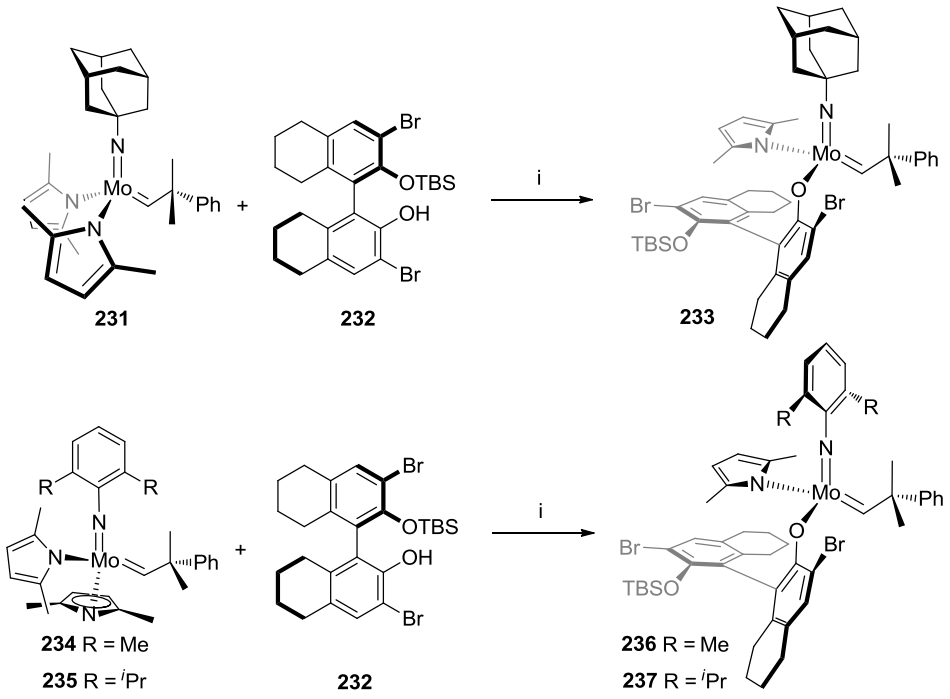
4. *Z*-Selective Alkene RCM Route to (–)-Nakadomarin A

4.1. Preface

This chapter details work which was carried out in collaboration with Prof. Amir Hoveyda and his research group at Boston College, into the use of *Z*-selective alkene metathesis catalysts to promote a stereoselective macrocyclic ring closure in the synthesis of (–)-nakadomarin A (**1**). Full acknowledgement of work carried out by Miao Yu a PhD student in Prof. Hoveyda's group who was involved in the collaboration, is present in the text. Substrate synthesis was carried out at the University of Oxford while initial metathesis studies were carried out during a two week placement in Prof. Hoveyda's laboratory at Boston College.

4.2. Background to *Z*-selective Alkene Metathesis Catalysts

The synthesis of highly reactive molybdenum monoaryloxide–pyrrolide (MAP) olefin metathesis catalyst developed by Schrock, is achieved by addition of a binaphthol-derived alcohol **232** to a bispyrrolide precursor **231, 234** and **235** (Scheme 4.1) .[124]

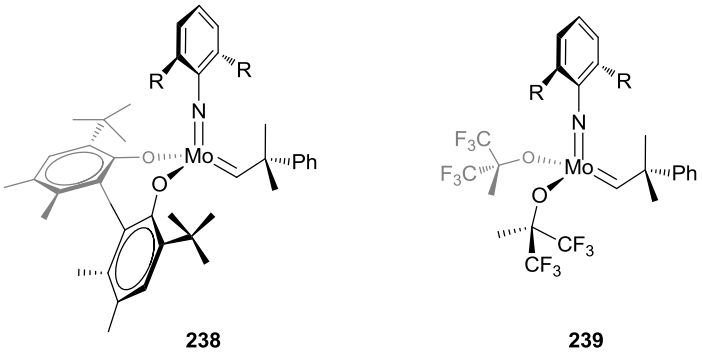


Scheme 4.1. Preparation of MAP olefin metathesis catalysts **233**, **236** and **237**. Reagents and conditions: i) Benzene, 22 °C, 1 h.

Bispyrrolyl complexes (eg **231**) exist as an unsymmetrical dimer in which an η^5–pyrrolyl bound to one Mo centre acts as an η^1-donor to another. It is believed that the dimer breaks up into monomers in which facile conversion between η^5– and η^1-binding modes is possible.[125] Preparation of the MAP catalysts can be carried out *in situ* and stored as a stock solution in benzene, at −20 °C, under inert conditions. Catalysts prepared using this method are known to maintain good activity for prolonged periods (several months). The released pyrrole molecules have been shown to have no adverse effect on catalyst actvity,[126] while the adventitious formation of relatively inactive bisaryloxides marginally reduce the amount of active catalyst to below the molar amounts of bispyrrolide and alcohol used.[127]

These chiral stereogenic-at-Mo complexes **233**/**236**/**237**, containing a sterically demanding but freely rotating aryloxide ligand, have been shown through a combination of steric and stereoelectronic effects to be more

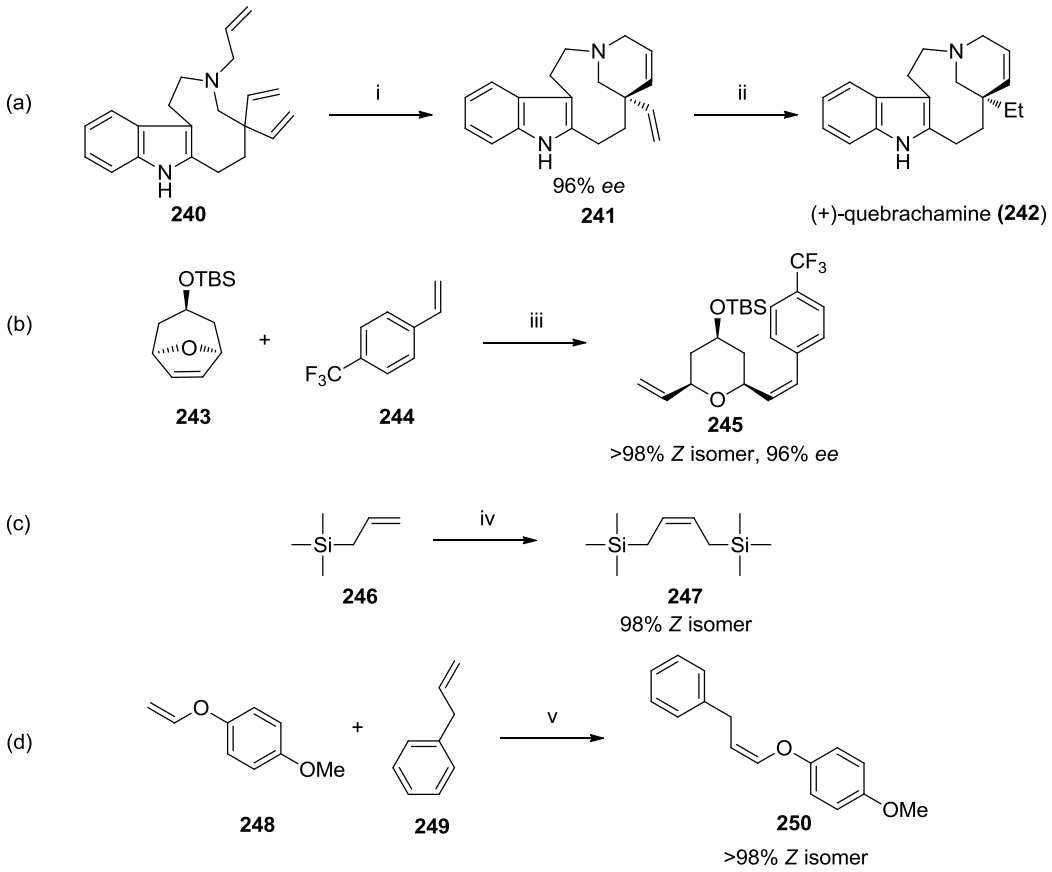
effective olefin metathesis catalysts than earlier generation rigidly held bidentate ligands of Mo diolates **238** [128] and achiral Mo complex of type **239** (Scheme 4.2).[129,130]



Scheme 4.2. Structure of less reactive Mo diolate catalyst **238** and achiral catalyst **239.**

The Schrock and Hoveyda groups had previously shown catalysts such as **233**, **236**, and **237** (Scheme 4.3) to be highly effective for:

1. Enantioselective alkene RCM, which was illustrated nicely in the total synthesis of the alkaloid (+)-quebrachamine (**242**) (reaction a).[130]
2. Highly *Z*-selective and enantioselective ring-opening/cross-metathesis reactions (reaction b).[127]
3. Highly *Z*-selective homocoupling of terminal alkenes (reaction c).[131]
4. Highly *Z*-selective cross metathesis of enol ethers or allylic amides (reaction d).[132]



Scheme 4.3. i) MAP catalyst (1.0 mol%), C_6H_6, 22 °C, 1 h, 84%, 96% ee; ii) Pt_2O (5 mol%), H_2 (1 atm.), EtOH, 22 °C, 1 h, 97%; iii) MAP catalyst (1.0 mol%), C_6H_6, 22 °C, 1 h, 67%, 96% *ee,* >98% *Z* isomer. iv) MAP catalyst (4 mol%), C_6D_6, 22 °C, 3 h, 33% conv., 98% *Z* isomer; v) MAP catalyst (1.2 mol%), C_6H_6, 22 °C, 2 h, 57%, >98% *Z* isomer.

The examples of highly *Z*-selective cross metathesis (reactions b-d) were potentially very relevant to the synthesis of (–)-nakadomarin A (**1**), if they could be extended to macrocyclic alkene RCM.

The high *Z*-selectivity attained in these reactions is a direct result of steric effects, however stereoelectronic effects of the donor (pyrrolide) ligand and acceptor (aryloxide) ligand play a critical role in the reaction mechanism as described by theoretical studies from Eisenstein and co-workers (Figure 4.1).[133,134]

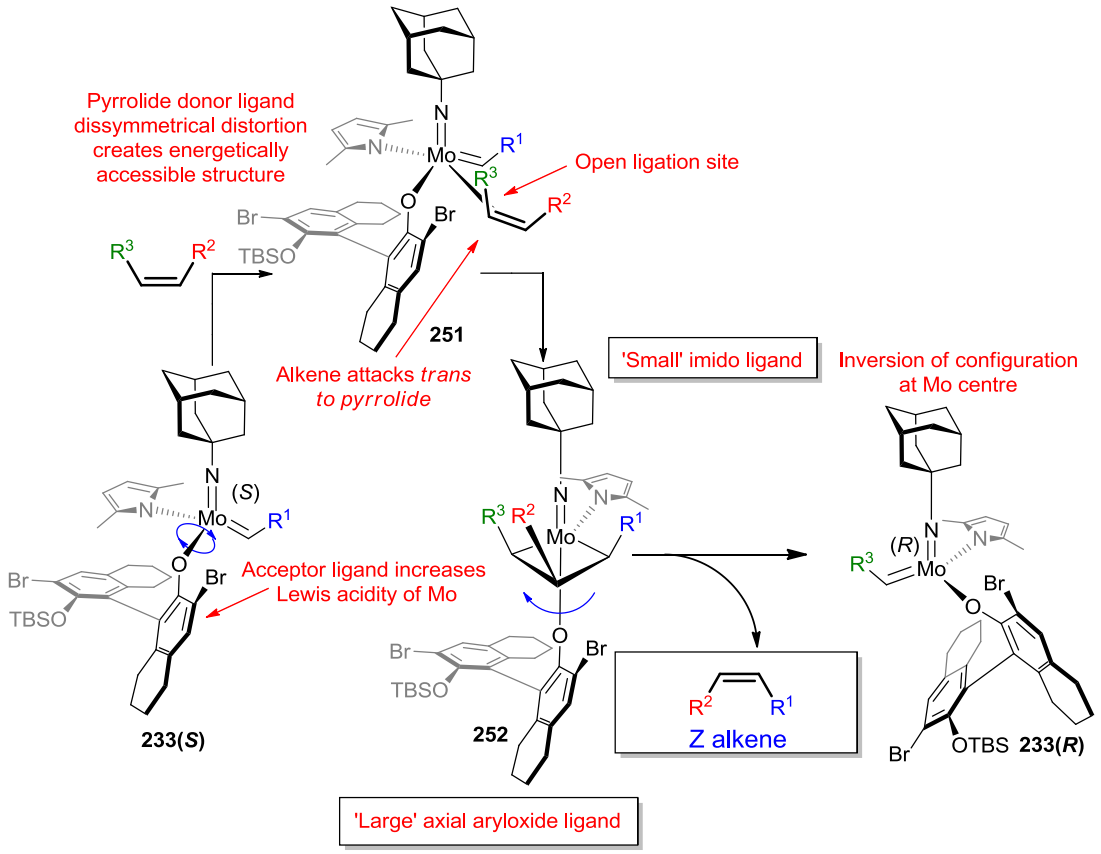


Figure 4.1. MAP olefin metathesis reaction pathway illustrating critical role of donor/acceptor ligands and size differential effects on Z-selectivity.

The combination of a good σ-acceptor ligand (aryloxide) and good donor ligand (pyyrolide) helps to decrease the energy barrier of olefin coordination/decoordination preventing the reaction stalling at a stable metallacyclobutane intermediate. Hoveyda has reported, based on Eisenstein's findings, that dissymmetrical distortion of complex **233** is required for alkene coordination to occur.[130,135] The alkene approaches *trans* to the donor (pyrrolide) ligand which associates with the energetically most favourable metal orbital, placing it in an axial site, minimising electronic repulsion (*trans* effect). The carbon of the released olefin is also situated *trans* to the pyrrolide, therefore the *trans* effect can also account for the facile degradation of metallacyclobutane intermediate **252**. These subtle stereoelectronic effects are proposed as the reason that MAP catalysts

perform more effectively than bisalkoxide catalysts **238** and **239,** which bear two electronically identical acceptor ligands.

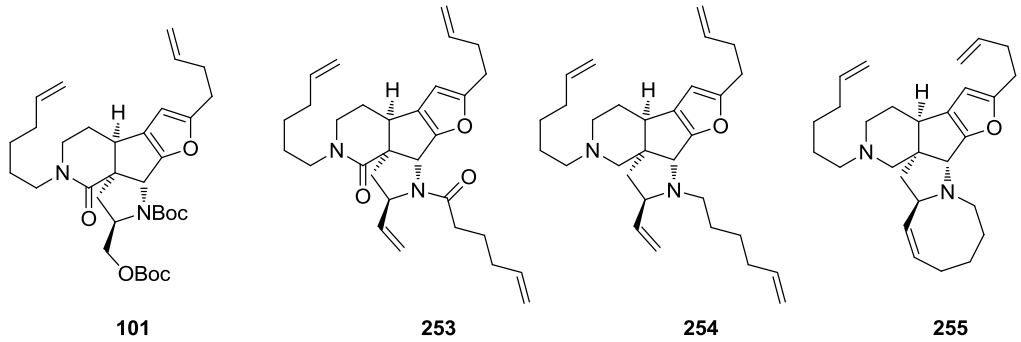
The reason for the high Z-selectivity obtained is a result of catalyst induced kinetic control dominating the inherent substrate induced thermodynamic control. The alkene approaches the coordination sphere *trans* to the pyrrolidide generating all *cis* metallocyclobutane **252** in which the R substituents are directed in a *syn* fashion away from the sterically demanding and freely rotating aryloxide ligand and towards the imido substituent which is suffciently smaller. It should be noted that the Mo centre undergoes inversion of stereochemistry with each metathesis event. In the case of ring-closing metathesis two independent metathesis events are involved and therefore the original stereochemistry of the Mo centre is retained after each catalytic cycle.

4.3. Application to the Synthesis of (–)-Nakadomarin A (1)

With impressive results having been achieved already in *Z*-selective alkene cross metathesis and homodimerisation it was decided to prepare a range of (–)-nakadomarin A (**1**) precursors which could be used to probe the catalyst efficiency in *Z*-selective macrocyclic alkene ring-closing metathesis. No examples of a single step highly *Z*-selective approach had been previously reported with the state of the art for such a transformation being an alkyne RCM/*syn* reduction approach (see chapter 3) or a recent approach by Young and co-workers involving a reaction between an internal vinylsilane and a terminal alkene followed by protodesilylation.[136] The problem associated with

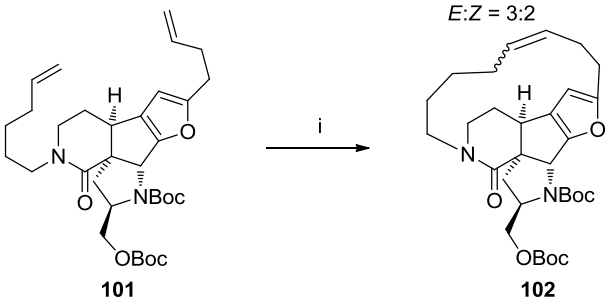
both of these approaches is the requirement of additional manipulations required to access the required substrates. Grubbs subsequently reported the use of highly *Z*-selective C-H activated chelated ruthenium catalysts. While these catalysts have been shown to be effective for cross metathesis or homodimersiation[137-139] and ROMP,[140] no examples of *Z*-selective macrocyclic ring closure have been described.

Substrates **101**,**253**-**255** were selected as potential substrates with which to test and challenge the effectiveness of Schrock/Hoveyda MAP catalysts (Scheme 4.4).



Scheme 4.4. Potential substrates for *Z*-selective alkene RCM.

Di-Boc substrate **101** had previously been synthesized by Cockfield in his second generation route to (–)-nakadomarin A (**1**).[34] Cockfield had shown that **101** underwent RCM with Grubbs 1st generation catalyst to give an unfavourable mixture of chromatographically inseperable geometrical isomers (*E*:*Z* = 3:2) (Scheme 4.5).

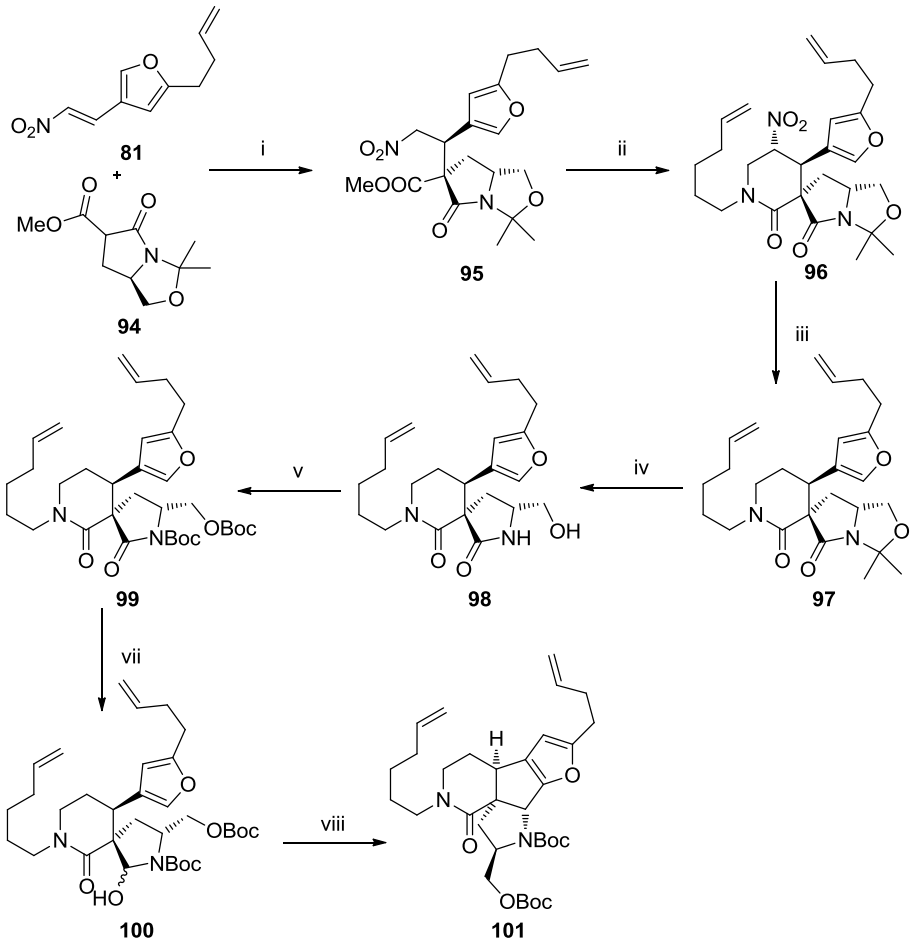


Scheme 4.5. Cockfield RCM of **101**. Reagents and conditions: i) Grubbs 1st generation catalyst (20 mol%), CH_2Cl_2, reflux, 24 h, 67%, *E*:*Z* 3:2

Tetraene substrates **253** and **254** had not been synthesized previously and offered the potential for a challenging but highly impressive double alkene RCM step to complete the synthesis of both the E- and F-rings of (–)-nakadomarin A (**1**) simultaneously. Substrate **254** provided the added challenge of containing free amines which are known to be problematic substrates for alkyne RCM catalysts. Substrate **255** was prepared by Dr Pavol Jakubec using reported procedures and its synthesis will therefore not be discussed further. This substrate had also been shown to undergo RCM with Grubbs 1st generation catalyst (*E*:*Z* = 3:2), with *Z*-selectivity being enhanced by protonation of the amines with (+)-CSA (*E*:*Z* = 37:63).[25]

4.4. Synthesis of Substrates for RCM Studies.

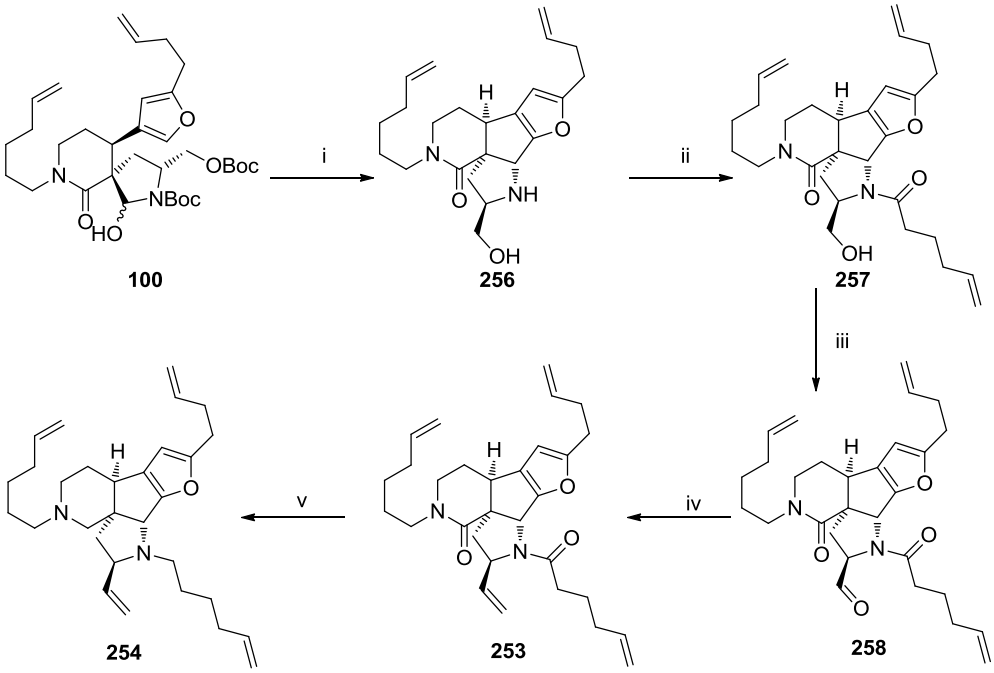
Synthesis of substrates **101**, **253** and **254** was achieved using the procedures of Cockfield and Jakubec.[25,34] Many of the steps involved in this synthesis are analogous to those reported in the alkyne RCM approach to (–)-nakadomarin A (**1**) (chapters 2 and 3) with methylated alkynes being replaced with terminal alkenes (Scheme 4.6). As a result only brief mention will be given to the synthetic procedures involved.



Scheme 4.6. Synthetic route to alkene RCM precursor **101**. Reagents and conditions: i) **94** (1 eq.), **81** (1.5 eq.), catalyst **88** (30 mol%), toluene, 30 °C, 3 days, 72% (single diastereomer); ii) hex-5-en-1-amine (1.5 eq.), formaldehyde (37% aq.) (1.5 eq.), MeOH, reflux, 5 h, 65%; iii) Bu_3SnH (5 eq.), AIBN (0.2 eq.), mesitylene, 165 °C, 2.5 h, 58%; iv) *p*-TsOH (0.05 eq.), MeOH, reflux, 5 h, 80%; v) Boc_2O (5 eq.), Et_3N (5 eq.), DMAP (0.1 eq.), CH_2Cl_2 , RT, 15 h, 97%; vi) Superhydride® (2.7 eq.), THF, -78 °C, 3 h, 81%; vii) Ac_2O (5.6 eq), Et_3N (5.6 eq.), DMAP (cat.), RT, 21 h; viii) (+)-CSA (0.018 eq.), CH_2Cl_2, RT, 2 h, 92%.

Nitro olefin Michael addition of pro-nucleophile **94** to nitro olefin **81** catalyzed by cinchonine derived bifunctional organocatalyst **88** proceeded with similar levels of diastereoselectivity as in the alkyne route to give 13 g of enantiopure Michael adduct **95** (7.5 g largest single batch). The nitro-Mannich/lactamization cascade and nitro removal steps proceeded with similar yields as obtained in the alkyne route to give 5 g of piperidinone **97**. Protecting group switch by acid catalyzed methanolysis of the isopropylidene protecting group of **97** was followed by Boc protection of the free amine and alcohol in near quantitative yield. Chemoselective reduction of **99** with

superhydride® gave almost 4 g of cyclisation precursor **100**, at which point the routes to **101** and **253/254** diverged. Acetylation of **100** with acetic anhydride followed by treatment with catalytic (+)-CSA induced a furan − *N*-acyliminium ion cyclisation, with the milder reaction conditions leaving both Boc protecting groups in place. Using this method over a gram of **101** was prepared for metathesis studies. *N*-acyliminium ion cyclisation using the same formic acid/LiOH hydrolysis conditions used in the alkyne route yielded tetracyclic aminol **256** (Scheme 4.7).



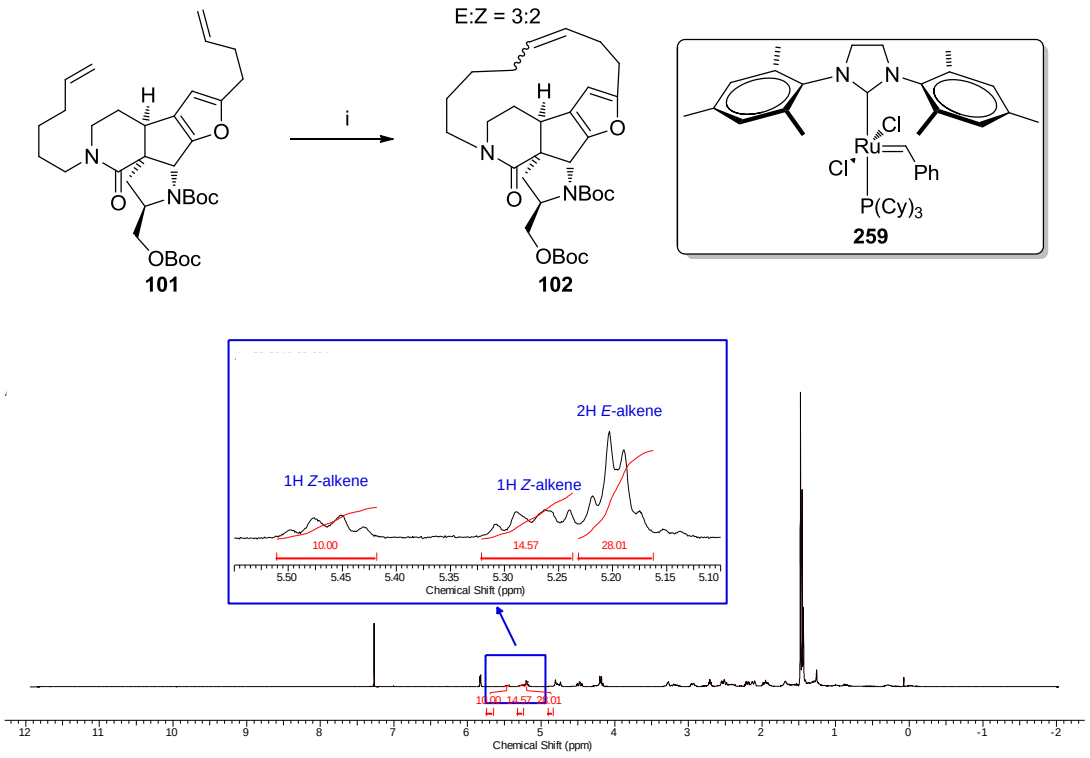
Scheme 4.7. Synthetic route to alkene RCM precursors **253** and **254**. Reagents and conditions: i) HCOOH, RT, 15 h, then $LiOH{\cdot}H_2O$ (20 eq.), MeOH, 50 °C, 5 h, 95%; ii) hex-5-enoyl chloride (1.05 eq.), Et_3N (5 eq.), CH_2Cl_2, RT, 2 h, 89%; iii) IBX (4.5 eq.), DMSO, RT, 24 h; iv) $MePPh_3Br$ (6 eq.), KO^tBu (4.77 eq.), THF/toluene, RT, 15 min, 94% (2 steps); v) DIBAL-H (6.75 eq.), toluene, 0 °C to RT, 57%.

Amide formation, IBX oxidation and Wittig olefination all proceeded in excellent yield using the previously described alkyne route conditions to give over 600 mg of tetraene substrate **253** for metathesis studies. Double amide reduction of **253** to give diamine **254** was achieved using the same reaction and work-up conditions adopted in the alkyne route to (–)-nakadomarin A (**1**). Attempts to improve the efficiency of this double reduction *via* a catalytic

hydrosilylation/reduction sequence using rhodium complex ($RhH(CO)(PPh_3)_3$) failed to yield any of the desired diamine.[141]

4.5. Grubbs Metathesis Studies

Metathesis studies were first carried out on substrates **101**, **253** and **254** using conventional ruthenium alkene metathesis catalysts to establish reactivity and natural *E*/*Z* selectivity bias of the substrates, prior to conducting *Z*-selectivity studies with MAP catalysts. Using Grubbs 2nd generation catalyst **259** the ring closed product **102** was isolated in 60% yield with a similar level of *E*:*Z* selectivity as observed by Cockfield using Grubbs 1st generation catalyst (Scheme 4.8).

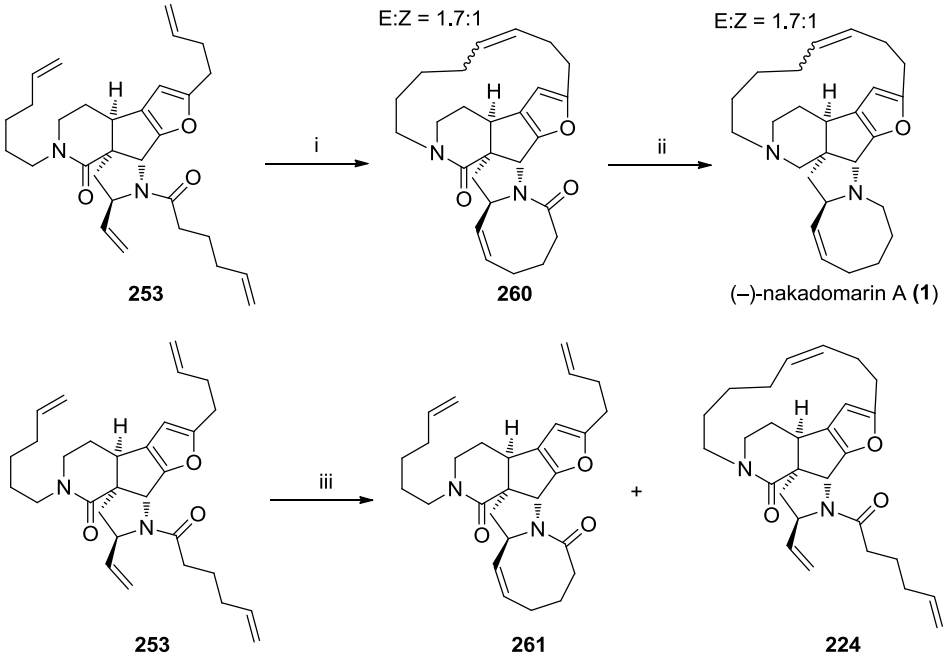


Scheme 4.8. Alkene RCM of **101** using Grubbs 2nd generation catalyst **259**. Reagents and conditions: Grubbs 2nd generation catalyst (30 mol%), CH_2Cl_2, reflux, 5 h, 60%.

The variation in ^{1}H NMR chemical shift of the alkene signals of the *E*- (2H at 5.23-5.16 ppm) and *Z*- (1H each at 5.51-5.42 ppm and 5.32-5.23 ppm) isomers, allowed easy determination of the selectivity (Scheme 4.8).

Studies on the alkene RCM of tetraene **253** were also conducted (Scheme 4.9). When the metathesis was carried out at high dilution with Grubbs 1st and 2nd generation catalysts and Hoveyda-Grubbs 2nd generation catalyst, complete conversion of the tetraene **253** was observed after 5 h. With Grubbs 2nd generation, three new products were initially observed by TLC analysis (R_f = 0.48, 0.31 and 0.14 (Et_2O)). As the reaction progressed, the two less polar products were consumed and a single product, **260** was isolated in 23% yield as a mixture of isomers (1.7:1). DIBAL-H promoted double amide reduction confirmed that these were geometrical isomers of **260** and (–)-nakadomarin A (**1**) was obtained (*E*:*Z* = 1.7:1) by ^{1}H NMR analysis of the crude reaction mixture. A similar reaction profile was observed with Hoveyda-Grubbs 2nd generation catalyst with **260** being isolated in 23% yield on small scale (10 mg), with similar levels of stereocontrol. However, when Grubbs 1st generation catalyst was used only the two less polar products were observed. Based on mass spectrometry evidence and the transient presence of these products when Grubbs 2nd generation catalyst was used, they were assigned as **261** and **224**, resulting from a single ring closure. The product at R_f = 0.31 was confirmed as **224**, by comparison with the ^{1}H NMR of the *Z*-isomer of **224** obtained from the alkyne route. The structure of **261** was not determined unambiguously and a product arising from a single ring closure between any two or the four alkene units present is

also possible. Nonetheless, both products were isolated in only trace amounts and no evidence of **260** was observed with this catalyst. A feature of all of these metathesis reactions was the formation of significant quantities of insoluble material suggesting that polymerisation of the tetraene was the dominant reaction pathway. (–)-Nakadomarin A (**1**) was not isolated when metathesis of diamine **254** was attempted with Grubbs 2nd generation catalyst, with polymerisation again appearing to be a problem even at high dilution.



Scheme 4.9. Alkene RCM studies on tetraene **253**. Reagents and conditions: Metathesis reactions [substrate] = 8.16 x 10^{-4} M i) Grubbs 2nd generation catalyst (30 mol%), CH_2Cl_2, reflux, 5 h, 23% or Hoveyda-Grubbs 2nd generation catalyst (20 mol%), CH_2Cl_2, reflux, 6 h, 28% ii) DIBAL-H (15 eq.), toluene, 0 °C to RT, 9 h; iii) Grubbs 1st generation catalyst (30 mol%), CH_2Cl_2, reflux, 5 h, 32%.

4.6. *Z*-selective Alkene RCM Studies

With the reactivity and limitations of the alkene RCM of substrates **101**, **253** and **254** with Grubbs ruthenium catalysts investigated, attention turned to metathesis studies with MAP catalysts (Table 4.1). All reactions were carried out under an argon atmosphere in a glove box. Catalysts **233**, **236** and **237** (Figure 4.2) were used in the studies and prepared as discussed previously

(Scheme 4.1) as a stock solution in benzene using alcohol **232** and bispyrrolides **231**, **234** and **235** respectively, which were synthesized by the Hoveyda group.

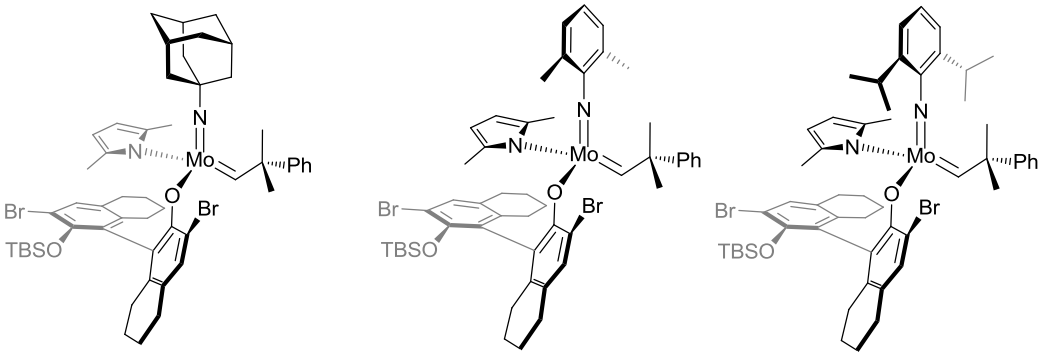
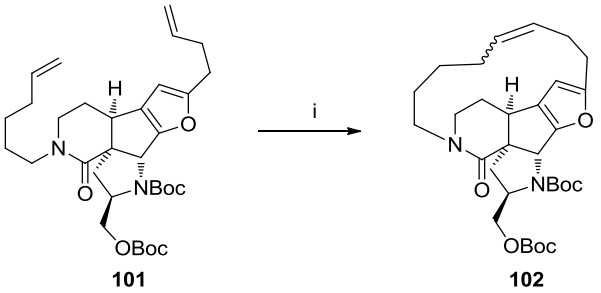


Figure 4.2. MAP catalysts used in metathesis studies

Table 4.1. Alkene metathesis studies on substrate **101** using MAP catalysts



Entry	Catalyst (loading)	Solvent (additive)	Reaction time	(Conversion)[a] Yield	*E*/*Z* ratio[b]	[substrate] [mol dm^{-3}] (pressure)
1	**236** (5 mol%)	C_6H_6	1 h	(~30%) –	48:52	8.6×10^{-4} (atm.)
2	**236** (5 mol%)	C_6H_6	1 h	– 67%	47:53	5.0×10^{-3} (atm.)
3	**236** (5 mol%)	C_6H_6	2 h	– 66%	46:54	5.0×10^{-3} (atm.)
4	**236** (5 mol%)	C_6H_6	1 h	(~60%) –	55:45	10×10^{-3} (atm.)
5	**236** (5 mol%)	C_6H_6	1 h	– polymerisation	–	10×10^{-2} (atm.)
6	**236** (5 mol%)	PhMe	1 h	(<2%) –	–	5.0×10^{-3} (7 torr)
7	**236** (10 mol%)	PhMe	1 h	– 68%	52:48	5.0×10^{-3} (7 torr)
8	**236** (5 mol%)	PhMe (allyl ether)	1 h	(<5%) –	–	5.0×10^{-3} (7 torr)

9	**236** (5 mol%)	C_6H_6 (60 °C)	1 h	− 84%	57:43	5.0×10^{-3} (atm.)
10	**237** (5 mol%)	C_6H_6	1 h	(<2%) −	−	8.6×10^{-4} (atm.)
11	**237** (5 mol%)	C_6H_6	1 h	No conversion	−	5.0×10^{-3} (atm.)
12	**237** (5 mol%)	PhMe	1 h	No conversion −	−	5.0×10^{-3} (7 torr)
13	**233** (5 mol%)	C_6H_6	1 h	(~15%) −	49:51	8.6×10^{-4} (atm.)
14	**233** (5 mol%)	C_6H_6	1 h	− 65%	45:55	5.0×10^{-3} (atm.)
15	**233** (5 mol%)	C_6H_6	2 h	− 63%	46:54	5.0×10^{-3} (atm.)
16	**233** (5 mol%)	C_6H_6	1 h	(~49%) −	48:52	10×10^{-3} (atm.)
17	**233** (5 mol%)	PhMe	1 h	No conversion −	−	5.0×10^{-3} (7 torr)
18	**233** (10 mol%)	PhMe	1 h	(<2%) −	−	5.0×10^{-3} (7 torr)
19	**233** (5 mol%)	PhMe (allyl ether)	1 h	No conversion −	−	5.0×10^{-3} (7 torr)
20	**233** (5 mol%)	C_6H_6 (60 °C)	2 h	− 84%	42:58	5.0×10^{-3} (atm.)

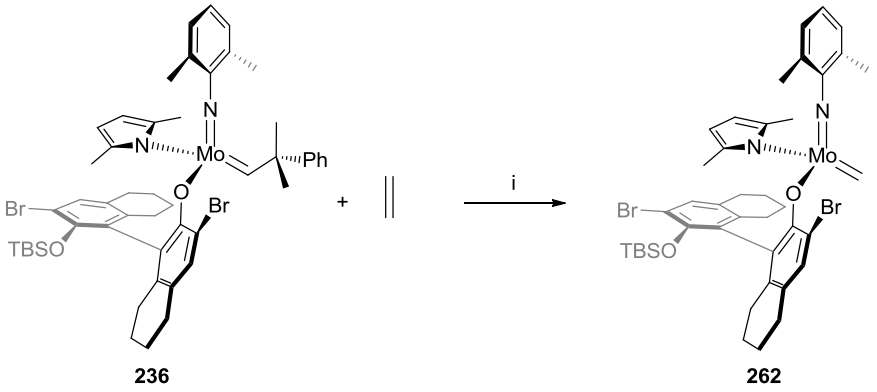
[a] Conversion measured using CH_3 signal of TBS group of catalyst at a chemical shift of −0.36 ppm.

[b] *E*/*Z* content of cyclised products analysed by ^{1}H NMR of the crude reaction mixture.

Initial metathesis attempts using catalyst **236** at high dilution (entry 1) gave only ~30% conversion, however an improved *Z*/*E* selectivity over Grubbs metathesis catalysts was observed. Increasing the substrate concentration (entry 2) allowed cyclised product **102** to be isolated in 67% yield, requiring only 5 mol% catalyst loading and 1 h reaction time at ambient temperature. This represents a remarkable improvement in reactivity relative to Grubbs catalysts although no improvement in *Z*/*E* was observed at this higher conversion. Using the same conditions but with a longer reaction time (entry 3) did not result in any improvements in yield or selectivity. Increasing the substrate/catalyst concentration further (entry 4) had a detrimental effect on

selectivity with the *E*-isomer again becoming the major isomer present. Increasing the substrate concentration to 0.1 M resulted in considerable amounts of decomposition being observed by TLC and ^{1}H NMR analysis, presumably due to dimerisation/oligomerisation/polymerisation of **101** (entry 5).

In an attempt to remove the ethylene formed, the metathesis reactions were run under reduced pressure (7.0 torr). Ethylene present in the reaction mixture can undergo metathesis with a catalytic species forming the highly reactive Mo-methylidene species **262** (Scheme 4.10).



236 **262**

Scheme 4.10. Generation of highly reactive species **262**

It has been proposed by Hoveyda that high *Z*-isomer content in the reaction mixture is initially achieved. Highly reactive species **262** however is thought to be capable of ring-opening the cyclised product **102** and equilibrating the isomeric mixture thus diminishing *Z*:*E* selectivity. No evidence has been provided to unequivocally prove this theory however, and the reason for subsequent ring closing events not attaining the same high levels of *Z*-selectivity as initially achieved are not entirely clear. It is feasible however that even a tiny fraction of leakage of stereochemical integrity in the metathesis would be magnified significantly if multiple ring-opening/closing

events were to occur. Nonetheless, limited reactivity was observed when the reaction was run at reduced pressure and 5 mol% catalyst loading (entry 6). Increasing the catalyst loading (entry 7) restored reactivity although the expected improvement in *E*:*Z* selectivity was not achieved. Addition of allyl ether to the reaction, an alternative strategy to remove Mo-methylidene species **262**, by converting it into a more stable alkoxy-substituted alkylidene, also resulted in a loss of reactivity when run under reduced pressure (entry 8). Running the reaction at increased temperature gave an improvement in isolated yield at the expense of diminished *E*:*Z* selectivity compared to the same reaction conditions at ambient temperature (cf. entries 9 & 2). Isopropyl catalyst **237** gave no evidence of reactivity in initial trials (entries 10-12) and was therefore not pursued further. Adamantyl substituted imido catalyst **233** showed a similar reactivity profile to the methyl catalyst **236**. The highest level of *Z*-selectivity (*E*:*Z* = 42:58) was obtained using this catalyst at 5 mol% loading, in benzene at 60 °C and a reaction time of 2 h (entry 20). Most reaction conditions which displayed good reactivity imparted similar levels of stereocontrol.

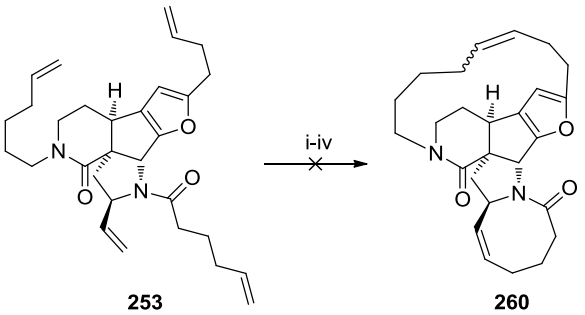
Despite a reversal of the *E*:*Z* selectivity relative to those achieved with Grubbs ruthenium metathesis catalysts, the expected high levels of stereocontrol were not attained. It was considered that the use of enantiopure ligand **232** may have created a ‘mismatched’ catalyst/substrate situation. Racemic alkoxy ligand was therefore used in the preparation of adamantyl *rac*-**233** and methyl *rac*-**236** catalysts. Similar levels of stereocontrol were obtained with the catalysts containing the racemic ligand, confirming that a

'mismatched' situation was not responsible for the poor *Z*:*E* selectivity obtained (Table 4.2).

Table 4.2. Alkene metathesis studies on substrate **101** using MAP catalyst prepared with racemic **232**

Entry	Catalyst (loading)	Solvent/ (additives)	Reaction time	(Conversion)[a] Yield	*E*/*Z* ratio[b]	[substrate] [mol dm^{-3}] (pressure)
1	*rac*-**236** (10 mol%)	C_6H_6	2 h	(~80%) –	49:51	8.6×10^{-4} (atm.)
2	*rac*-**233** (10 mol%)	C_6H_6	2 h	(~80%) –	44:56	5.0×10^{-3} (atm.)

Despite the disappointing *Z*/*E* selectivity afforded, Di-Boc substrate **101** gave the best reactivity of the substrates selected for metathesis studies. Tetraene **253** displayed no appreciable reactivity towards metathesis, and starting material was the major component of all reactions by ^{1}H NMR analysis along with small amounts of multiple unidentified side products (Scheme 4.11).

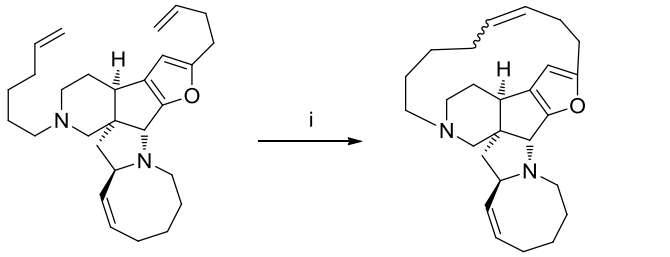


253 **260**

Scheme 4.11. Metathesis of tetraene **252** with MAP catalysts. Reagents and conditions: All reactions [substrate] = 5×10^{-3} mol dm^{-3} i) catalyst **233** (10 mol%), C_6H_6, RT, 1 h; ii) catalyst **236** (10 mol%), C_6H_6, RT, 1 h; iii) catalyst **233** (10 mol%), C_6H_6, 60 °C, 1 h; iv) catalyst **236** (10 mol%), C_6H_6, 60 °C, 1 h.

Based on these results attention was focussed on (–)-nakadomarin A precursor **255** rather than the diamine tetraene **254**. **255** was found to exhibit some reactivity towards metathesis with MAP catalysts, although the small amounts of material available limited the studies which were carried out. Applying the optimal conditions identified from studies on di-Boc substrate **101** to **255** on small scale (2 mg), trace amounts of (–)-nakadomarin A (**1**)

were isolated. ^{1}H NMR analysis of this sample indicated that an *Z*:*E* ratio of approximately 1:1 had been obtained (Scheme 4.12).



255 (–)-nakadomarin (**1**) and *E*-(**1**)

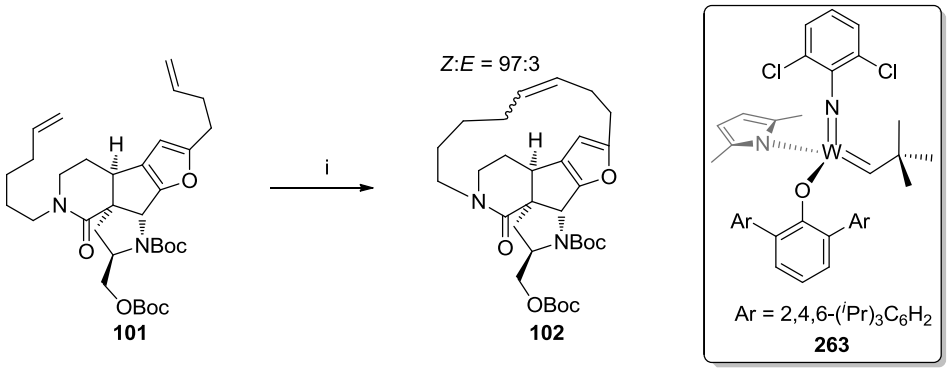
Scheme 4.12. Metathesis of (–)-nakadomarin A precursor **255**. Reagents and conditions: i) catalyst **233** (20 mol%), C_6H_6, 60 °C, 2 h, *E*:*Z* = ~1:1.

This result again indicated that while improvement of *Z*-selectivity relative to that obtained with Grubbs ruthenium catalysts could be achieved, the increase in selectivity was modest compared to the results expected based on previous *Z*-selective cross-metathesis and homodimerisation studies carried out by Hoveyda and Schrock.

4.7. Summary and Further Work

Use of molybdenum monoaryloxide–pyrrolide (MAP) olefin metathesis enabled the ring closing metathesis of substrate **101** to be achieved in excellent yield and modest *Z*-selectivity, using low catalyst loading and short reaction times at ambient temperatures. This transformation in itself represents a significant improvement when compared to similar transformations in previous syntheses of (–)-nakadomarin A (**1**) using an alkene RCM approach,[13-15,25] which required higher catalyst loadings, elevated temperatures, longer reaction times and delivered the ring closed product in lower yield and generally poorer *Z*:*E* selectivity.

Miao Yu of Prof. Hoveyda's research group continued research on the MAP promoted *Z*-selective alkene RCM of substrate **101**, using newly developed tungsten catalysts. Yu found that the ring-closed product **102** could be obtained in excellent yield with exceptional *Z*-selectivity under optimised conditions using low loadings of tungsten catalyst **263** (Scheme 4.13).[142]



Scheme 4.13. Highly Z-selective alkene RCM promoted by catalyst **263**. Reagents and conditions: catalyst **263** (5 mol%), 7.0 torr, [5×10^{-3} mol dm^{-3}], toluene, RT, 2 h, 90%, *Z*:*E* = 97:3.

Using the procedures developed in the alkyne route (chapter 3), Yu was able to complete the synthesis of (–)-nakadomarin A (**1**) with high *Z*-selectivity (91% Z isomer). Partial isomerisation of the *Z*-alkene during the alkene RCM step to close the 8-membered E-ring, using catalyst **263**, was reported to be responsible for the slight erosion of stereochemical purity.[142]

Similar levels of selectivity were also obtained in the transformation of diamine **255** to (–)-nakadomarin A (**1**) using this catalyst. It is proposed that the attenuated activity of tungsten catalysts such as **263** relative to molybdenum catalysts such as **233** and **236** is responsible for this dramatic increase in selectivity for the *Z*-isomer. It is believed that the tungsten alkylidene promotes efficient RCM, without possessing the activity to engage

in detrimental ring-opening/isomerisation events in the way that the molybdenum catalysts can.

5. Approach to the Diazatricyclic Core of the Madangamines

5.1. Preface to Chapter

With two distinct, successful approaches to a *Z*-selective synthesis of (–)-nakadomarin A (**1**) developed, a new synthetic challenge was sought. The madangamine alkaloids were selected due to their structural relationship, through a biomimetic pathway, with the manzamine alkaloids, their potent anticancer activity and their challenging structures. It was anticipated that some of the key steps used in the synthesis of (–)-nakadomarin A (**1**) could be developed and employed in the synthesis of the madangamines.

5.2. Introduction to the Madangamine alkaloids

Madangamine A (**264**) was the first member of a novel family of pentacyclic marine alkaloid to be isolated by Andersen and co-workers in 1994. Madangamine A was obtained from a marine sponge, *Xestospongia ingens*, of the order *Haplosclerida*, which was collected off the coast of Madang Province, Papua New Guinea.[143]

Andersen isolated 50 mg of madangamine A from 200 g of dry sponge, which allowed some biological activity to be evaluated.[143] Madangamine A showed significant *in vitro* cytotoxicity against murine leukaemia P388 (ED_{50} 0.93 μg/mL), human lung A549 (ED_{50} 0.93 μg/mL), brain U373 (ED_{50} 0.93 μg/mL) and breast MCF-7 (ED_{50} 5.7 μg/mL) cancer cell lines.

In 1998 Andersen identified four new members of the madangamine family (madangamines B-E **265**-**268**) from the same marine sponge source (Figure 5.1).[144]

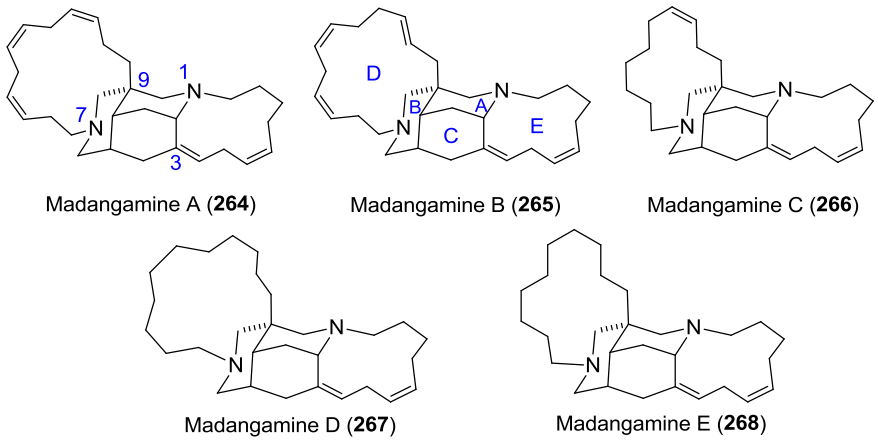


Figure 5.1. Structure of madangamines A-E

Structural variation within these members of the madangamine family occurs only in the bridging connection from N-7 to C-9, which varies in both chain length and degree of unsaturation. A key structural feature for consideration in any attempted synthesis of the madangamines, is the *cis*-fused ring system between rings B and C. The tricyclic core of the madangamines possesses a diamond-lattice structure in which all three of the six-membered rings are in a chair conformation.[144]

The isolation of alkaloids containing the pentacyclic structural motif of the madangamines was not unexpected. In 1992 Baldwin and Whitehead proposed an elegant biosynthesis of the manzamines through a biosynthetic equivalent of an intramolecular [4+2] cycloaddition of a bis-3-alkyldihydropyridine macrocycle **272**.[3] This macrocycle is the tautomeric form of the symmetrical species **273**, which it was proposed could be easily reached by the reductive coupling of two C_3 aldehyde units **274**, two C_{10}

dialdehyde units **275** and two molecules of NH_3. The most striking outcome of this proposal was the anticipated occurrence of two new classes of alkaloids corresponding to the proposed pentacyclic **270** and tetracyclic **3** intermediates (Figure 5.2).

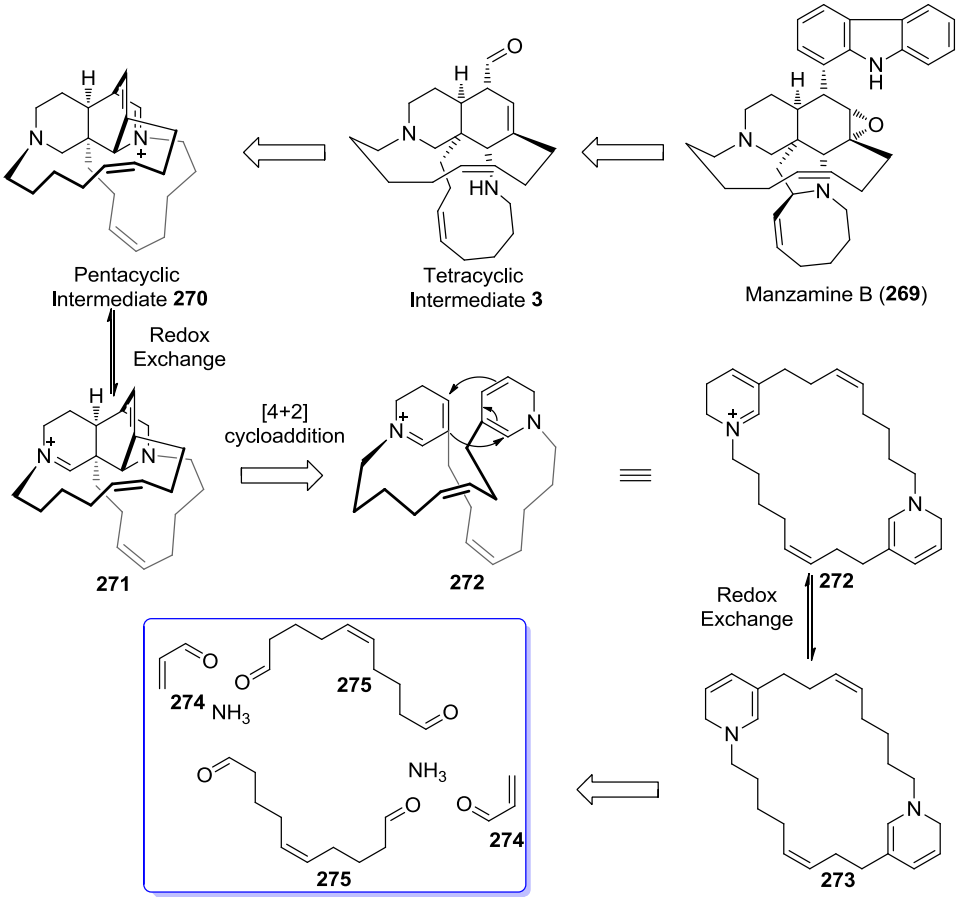


Figure 5.2. Baldwin and Whitehead proposed synthesis of the manzamine alkaloids.

Isolation of ircinal B (**276**), to which (–)-nakadomarin A (**1**) is closely related, by Kobayashi provided the first example of the Baldwin and Whitehead tetracyclic intermediate (Figure 5.3).[145]

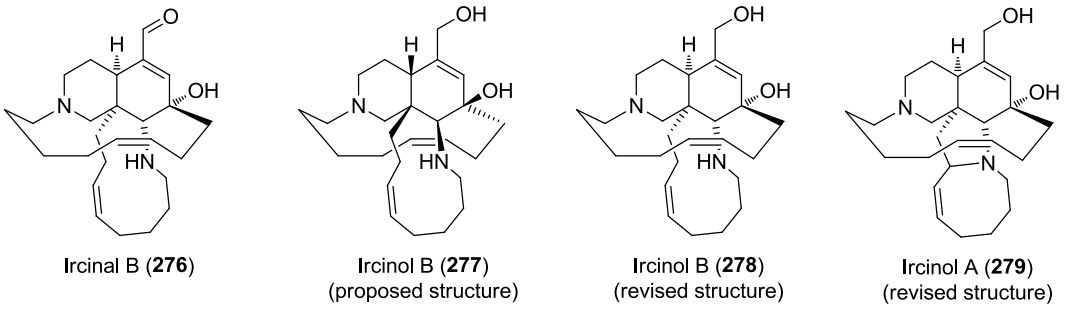


Figure 5.3. Baldwin and Whitehead's tetracyclic intermediate Ircinal B (**276**) and related ircinol B (**278**) and ircinol A (**279**).

Isolation of keramaphidin B (**280**), by Kobayashi from the Okinawan marine sponge *Amphimedon sp.*[146] and subsequently by Andersen from *Xestospongia ingens*,[147] along with xestocyclamine A, isolated by Crews[148,149] and ingenamines A-F[147,150] and ingamines A/B[151] isolated by Andersen from *Xestospongia ingens sp.,* provided skeletons identical to that of the pentacyclic intermediate in Baldwin and Whitehead's proposal (Figure 5.4).

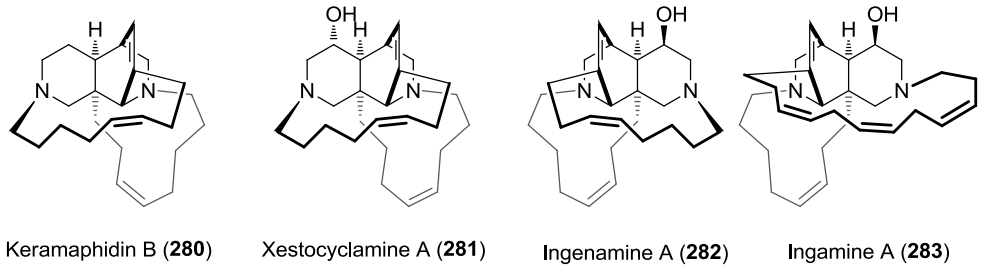


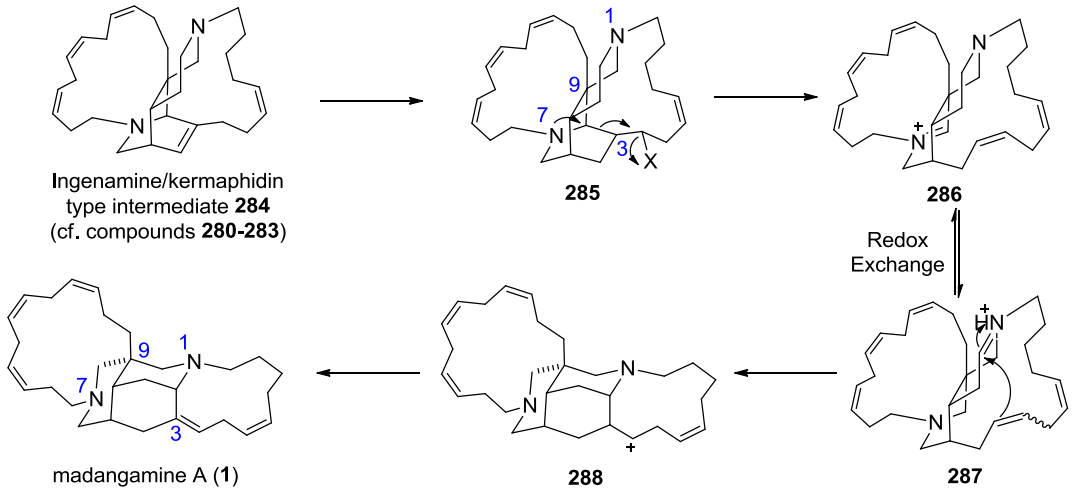
Figure 5.4. Alkaloids corresponding to Baldwin and Whitehead's pentacyclic intermediate

It is interesting to note that two antipodal series of the manzamine alkaloids are formed *via* the [4+2] cycloaddition pathway of achiral macrocycle **273**, suggesting catalysis of this intermolecular condensation by stereoselective enzymes. Keramaphidin B (**280**) isolated by Kobayashi was reported as a naturally occurring racemate, while keramaphidin B (**280**) isolated from *Xestospongia ingens sp.,* was found to be optically active. Erroneous reporting of the antipodal nature of ircinols A (**279**) and B (**278**) relative to the

corresponding ircinals and manzamines by Kobayashi, confused matters somewhat in this area (Figure 5.3).[66,145] On the total synthesis of Ircinol A (**279**) by Martin corrected this original structural mis-assignment. [66]

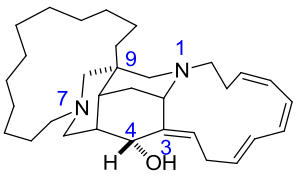
The ingamines and ingenamines are reported to be found in the opposite configurational series compared to the xestocyclamines, ircinals, ircinols and manzamines.[152] The absolute configuration of the madangamines (**264**-**268**) however is unknown and to date no total syntheses have been realised.

Andersen has proposed that the madangamine skeleton arises from the rearrangement of an ingenamine-type intermediate (Scheme 5.1).[143]



Scheme 5.1. Biosynthetic origin of the madangamines proposed by Andersen

In 2007 Berlinck indentified a new member of the madangamine family from the Brazilian marine sponge *Pachychalina alcaloidifera*. Madangamine F (**289**) differs from all other members of the madangamine family in that it's structure contains a C-4 hydroxyl group, possibly a result of enzyme promoted hydrolysis of the C3-4 alkene in **284**, and also possesses a longer carbon chain in the E-ring (Figure 5.5).[153]



madangamine F (**289**)

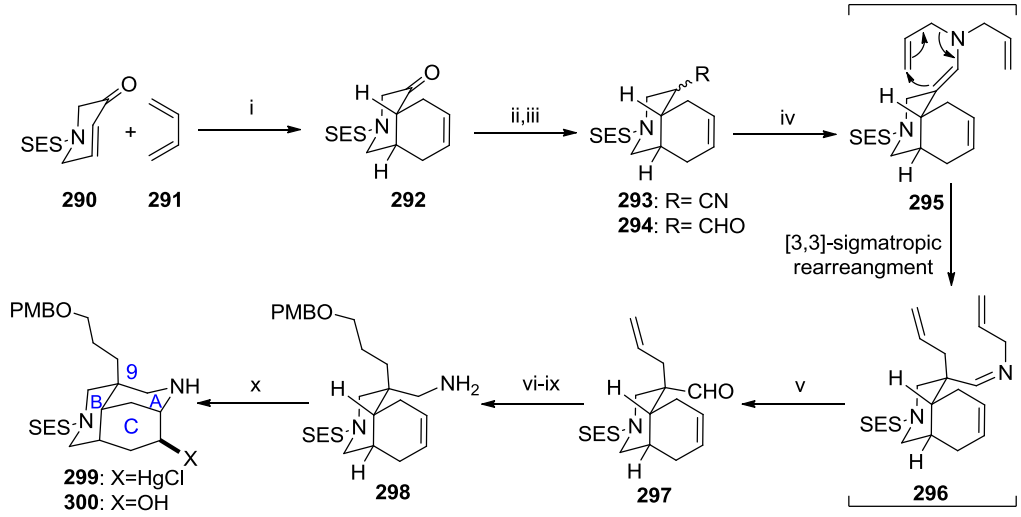
Figure 5.5. Unusual structure of madangamine F

5.3. Previous Synthetic Efforts Towards the Madangamines

Despite their interesting structures and the potent cytotoxicity against a number of cancer cell lines exhibited by madangamine A, no synthesis of any of the madangamines has been reported. Only five reports of the synthesis of the ABC diazatricyclic core have been published,[154-158] the most recent of which, in 2010, was the first enantioselective route.[158] One additional publication has documented a synthesis of a tricycle (ACE) containing the macrocyclic E ring.[159] A brief summary documenting the synthetic strategies used to date follows below:

1. Weinreb synthesized the *cis*-fused hydroisoquinoline (BC rings) by a [4+2] Diels–Alder cycloaddition of enone **290** with butadiene **291** under high pressure (Scheme 5.2). Conversion of ketone **292** to nitrile **293**, followed by reduction resulted in an overall one carbon homologation. To attain the correct stereochemistry at C-9, aldehyde **294** was treated with diallylamine and $Pd(OCOCF_3)_2/PPh_3$. The initially generated enamine **295** underwent a stereospecific [3+3]-sigamatropic rearrangement from the less congested convex face to give imine **296**. After further manipulation including an extension of the C-9 chain to install some useful functionality with which to potentially complete the F-ring, the ABC core was completed by an

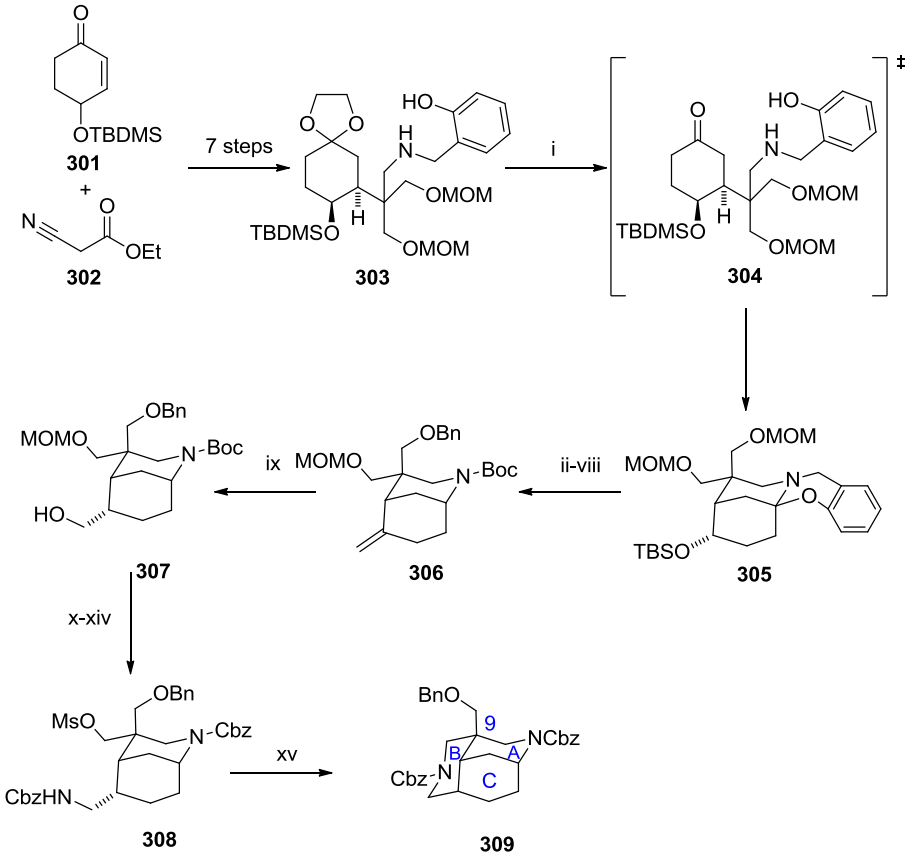
aminomercuration reaction. Treatment of amine **298** with mercuric trifluoroacetate followed by exposure to oxygen and $NaBH_4$ yielded alcohol **300** which was suitably poised for construction of the E-macrocyclic ring, although no further advances were reported.



Scheme 5.2. Weinreb: Synthesis of ABC core.[154] Selected reagents and conditions: i) CH_2Cl_2, 12 kbar, RT, 75%; ii) TosMIC, KO^{t}Bu, MeOH, DMF, 68%; iii) DIBAL-H, PhMe, −78 to 0 °C, 90%; iv) Diallylamine, PPh_3, $Pd(OCOCF_3)_2$, C_6H_6, reflux; v) 5% HCl, 68% (two steps); vi) $NH_2OCH_2Ph{\cdot}HCl$, 0 °C to RT, 97%; vii) disiamylborane, THF, 0 °C then H_2O_2, NaOH, 84%; viii) NaH, TBAI, THF, *p*-$OMeC_6H_4CH_2Cl$, reflux, 73%; ix) $LiAlH_4$, THF, −78 °C to RT, 74%; x) $Hg(OCOCF_3)_2$, THF, 0 °C then $NaCl/O_2$, $(CF_3)_2CHOH$, $NaBH_4$, RT, 39%.

2. Kibayashi first prepared the 2-azabicyclo[3.3.1]nonane ring system, bearing the required quaternary carbon at the C-4 position by *N*,*O*-acetalization of keto-aminophenol intermediate **304**. The protected form of **304** was prepared in 7 steps, starting with the Michael addition of cyclohexenone **301** to ethylcyanoacetate **302**. Treatment of **305** with AlH_3 resulted in reductive C-O bond cleavage of the *N*,*O*-acetal and chelation controlled selective deprotection of one of the MOM groups. Removal of the 2-hydroxyphenyl)methyl protecting group by hydrogenation followed by some functional group manipulations, allowed the required stereochemistry for the *cis*-fused ring junction to be achieved by hydroboration from the less congested convex face of **306**. After further manipulations, a base promoted

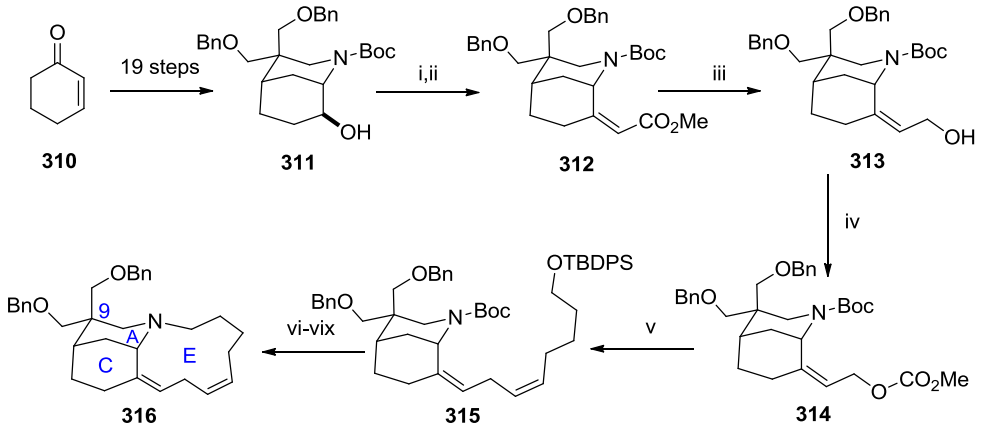
S_N2 mesylate displacement completed the ABC core **309** in 20 steps. The absence of any functional handles for facile synthesis of the E ring is a limitation of this route however. (Scheme 5.3).



Scheme 5.3. Kibayashi: Synthesis of ABC core.[155] Selected reagents and conditions: i) PPTS, acetone/H_2O, reflux, 48 h, 75%; ii) AlH_3, Et_2O, RT, 10 h, 84%; iii) H_2, Pd/C, MeOH, 86%; iv) Boc_2O, NaH, dioxane, 0 °C; v) BnBr, NaH, DMF, 0 °C; vi) TBAF, THF, 0 °C to RT, 85% (over 3 steps); vii) PCC, CH_2Cl_2, RT, 99%; viii) Tebbe Reagent, THF, RT, 8 h, 73%; ix) 9-BBN, THF, RT then NaOH, H_2O_2, RT, 91% (two steps); x) PhthNH, DEAD, Ph_3P, THF, RT, 72%; xi) HCl, MeOH, 60 °C; xii) $H_2NNH_2 \cdot xH_2O$, EtOH, reflux, 72% (over two steps); xiii) CbzCl, Na_2CO_3, dioxane/H_2O, RT, 71%; xiv) MsCl, Et_3N, CH_2Cl_2, 0 °C; xv) KO^{t}Bu, THF, RT, 76% (two steps).

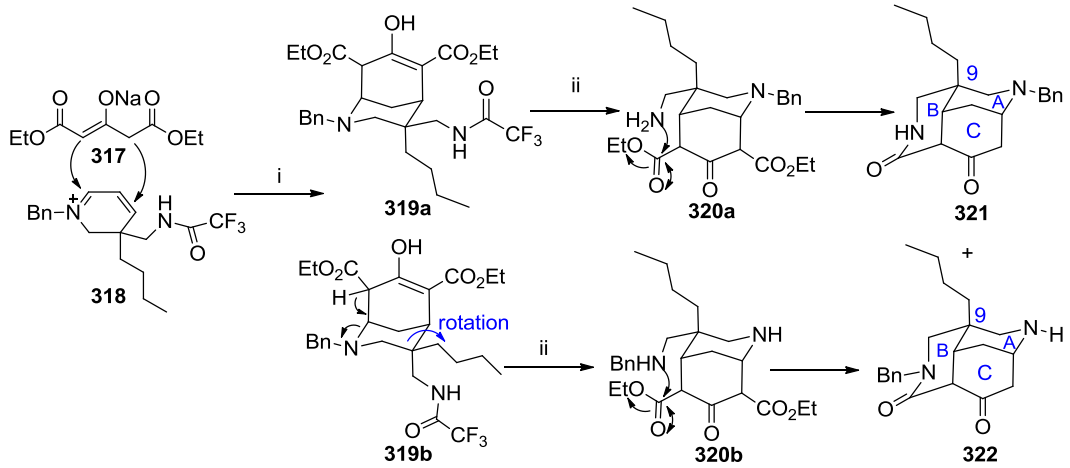
The same group used a similar strategy in an approach to the 'Eastern fragment' (ACE rings) of madangamines A-E (Scheme 5.4). From alcohol **311**, oxidation followed by a *Z*-selective olefination using the Still modification of the Horner-Wadsworth-Emmons reaction,[160] gave **312**, which was reduced to *Z*-allylic alcohol **313** with DIBAL-H. Skipped diene **315** was isolated as a single diastereomer by palladium-catalyzed coupling of carbonate **314** with an appropriately substituted *Z*-vinyl stannane, with selectivity retained *via* an

^{3}η-allylpalladium intermediate.[161] A deprotection, oxidation and reductive amination sequence completed the ACE rings. It is not clear why the authors chose to use unfunctionalized cyclohexenone **310** rather than cyclohexenone **301** as the starting material, as in their first route, which would have allowed the synthesis of the ABCE core to potentially be achieved.



Scheme 5.4. Kibayashi: Synthesis of ACE core.[159] Selected reagents and conditions: i) Dess-Martin periodinane, CH_2Cl_2, RT, 99%; ii) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, RT, 83%, *Z*/*E* = 11:1; iii) DIBAL-H, CH_2Cl_2, −78 °C, 85%; iv) $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C, 88%; v) (*Z*)-$Bu_3SnCH{=}CH(CH_2)_4OTBDPS$, $Pd(dba)_2$, LiCl, DMF, RT, 92%; vi) TBAF, THF, RT, 97%; vii) Dess-Martin periodinane, CH_2Cl_2, RT; viii) TFA, CH_2Cl_2, RT; vix) $NaBH(OAc)_3$, MeOH:THF, RT, 35% (over 3 steps).

3. Marazano and co-workers used an interesting biomimetic approach to the diazatricyclic core based on their modified proposal linking madangamine to ircinal derivatives rather than ingenamine derivatives, as proposed by Andersen. The key step in this route was a novel '3+3' nucleophilic addition of an acetone dicarboxylate ester **317** to a dihydropyridinium salt **318** (Scheme 5.5).

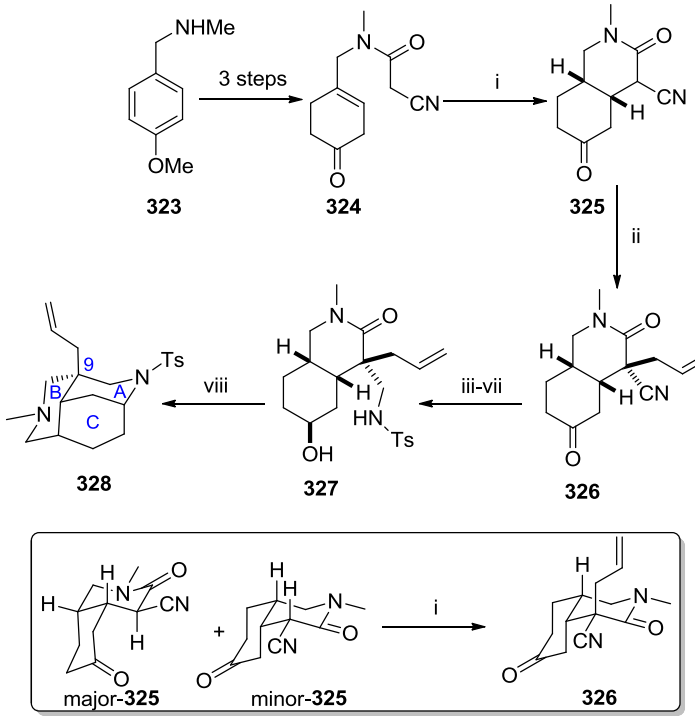


Scheme 5.5. Marazano: Biomimetic approach to ABC core.[156] Selected reagents and conditions: i) THF, RT, 16 h; ii) K_2CO_3, EtOH:H_2O (5:2), reflux, 50% (3 steps), **321**:**322** = 65:35.

Diastereomer **319a**, the desired diastereomer from the '3+3' nucleophilic addition reaction gave diastereomer **321** after a base promoted cyclisation. The unexpected formation of diastereomer **322** from the 'wrong' diastereomer **319b** arose due to a proposed retro-Michael addition of the benzylic amino group/C-C rotation/Michael addition of primary amine/amide formation sequence, followed by decarboxylation. In total, 12 steps were required to access the diazatricyclic core, although limited functional group handles were available for completion of the remaining rings.

4. Bonjoch utilized a base induced double bond isomerization/intramolecular Michael addition of intermediate **324**, synthesized in 3 steps from *N*-methyl-4-methoxybenzylamine **323**, to obtain the required *cis*-fused B-C ring junction. Sterically controlled kinetic allylation from the top face of **325** introduced the required stereochemistry at the quaternary centre. Functional group manipulations were followed by an L-Selectride reduction of the ketone at the C-2 position of **326** to achieve the required alcohol stereochemistry allowing a Mitsunobu transformation to complete the diazatricyclic core in 11 linear

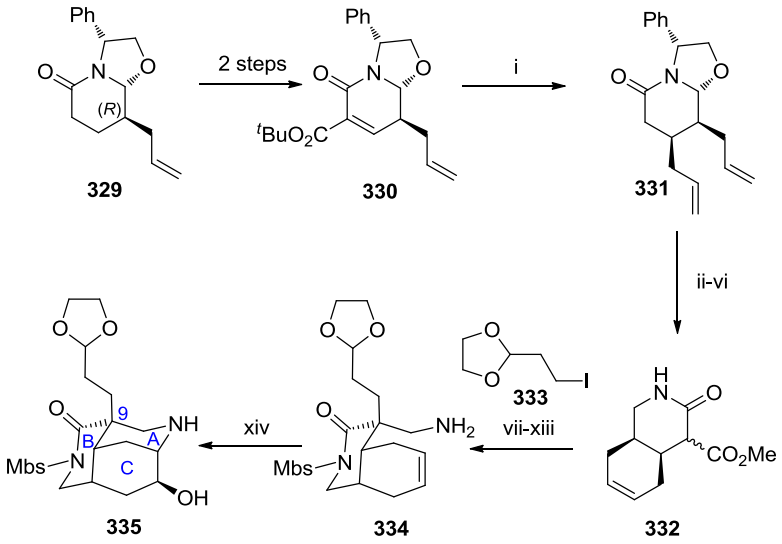
steps. Again no obvious functionality was present to allow the synthesis of the E ring to be achieved (Scheme 5.6).



Scheme 5.6. Bonjoch: Synthesis of ABC core.[157] Selected reagents and conditions: i) NaOEt, EtOH, RT, 1h, 77%; ii) allyl bromide, LDA, −78 °C, 3 h then RT, 15 h, 76%; iii) $HOCH_2CH_2OH$, *p*TsOH, benzene, reflux, 3 h, 75%; iv) AlH_3, THF, RT, 5 h, 68%; v) NsCl, Et_3N, CH_2Cl_2, RT, 2 h, 64%; vi) 2 N HCl, MeOH, RT, 15 h, 94%; vii) L-selectride, THF, −78 °C, 2 h, 89%; viii) DEAD, PPh_3, Et_3N, C_6H_6, RT, 20 h, 68%.

5. In 2010 Amat and Bosch published the only enantioselective synthesis of the ABC madangamine core (Scheme 5.7). Dynamic kinetic resolution was used to obtain the key enantiopure substrate **329**. Stereoselective conjugate addition of an allyl group to activated unsaturated lactam **330**, under stereoelectronic control, followed by an alkene RCM provided the required *cis*-B/C ring junction. This also provided an alkene handle with which to complete the tricyclic core later in the synthesis using the aminomercuration method developed by Weinreb.[154] The required stereochemistry at the quaternary centre was introduced by a stereoselective alkylation, controlled

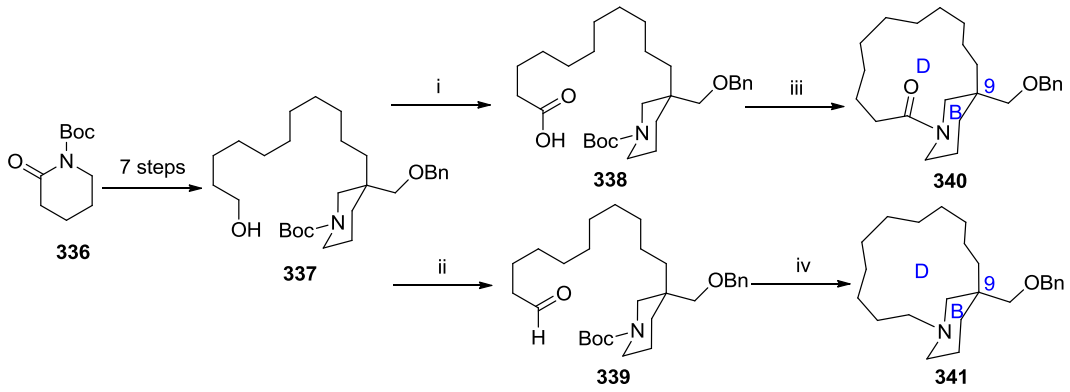
by the methyl ester of **332** which directed the alkyl chain to the most accessible face.



Scheme 5.7. Amat and Bosch: Synthesis of ABC core.[158] Selected Reagents and conditions: i) Allylmagnesium bromide, CuI, LiCl, TMSCl then TFA, toluene, reflux, 77%; ii) Grubbs 2nd generation (10 mol%), CH_2Cl_2, RT, 4 h, 93%; iii) Et_3SiH, $TiCl_4$, CH_2Cl_2, reflux, 24 h, 92%; iv) Na, liq. NH_3, THF, −33 °C, 1 min, 93%; v) *n*BuLi, Boc_2O, THF, −78 °C, 40 min, 90%; vi) $(TMS)_2NLi$, $ClCO_2Me$, THF, −78 °C, 2 h, 97%; vii) NaH, **333**, DMF, 60 °C, 16 h, 50%; viii) TFA, CH_2Cl_2, RT, 40 min, 84%; ix) $LiAlH_4$, THF, reflux, 3 h, 74%; x) $ClSO_2C_6H_4$-*p*-OMe, Et_3N, CH_2Cl_2, 0 °C, 3 h, 75%; xi) MsCl, Et_3N, CH_2Cl_2, RT, 2 h, 80%; xii) NaN_3, DMF, 90 °C, 62 h, 84%; xiii) $LiAlH_4$, THF, reflux, 3 h, 76%; xiv) $Hg(OCOCF_3)_2$, THF, RT, 3 h, then sat. aq. NaCl, CH_2Cl_2, 1 h, then O_2, $NaBH_4$, $(CF_3)_2CHOH$, 10 °C, 4h, 43%.

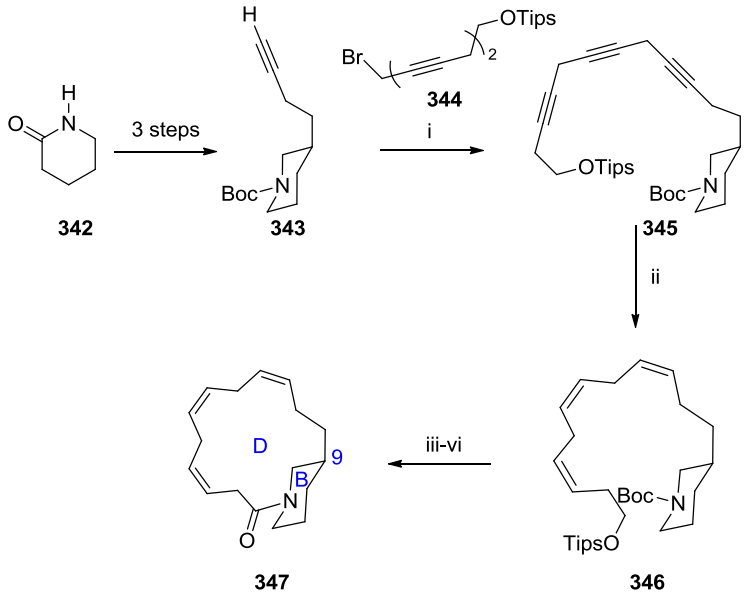
6. Very recently, during the writing of this dissertation, Amat and Bosch, reported the assembly of the macrocyclic D-ring of madangamines A and D, on a piperidine model system, as well as assembly of the 11-membered E-ring using an improved strategy compared to the work of Kibayashi.[159,162]

Preparation of the D-ring of madangamine D was achieved using an lactamization strategy with acid **338** to access **340**, as well as by a reductive amination approach using aldehyde **339** to access **341** (Scheme 5.8).



Scheme 5.8. Amat and Bosch model assembly of the macrocyclic D-ring of madangamine D.[162] Selected Reagents and conditions: i) PDC, DMF, RT, 72 h, 65%; ii) $NaHCO_3$, Dess-Martin periodinane, RT, 1 h, 90% iii) TFA, CH_2Cl_2, RT, 0.5 h, then HOBt, EDCI, CH_2Cl_2:DMF (9:1), RT, 15 h, 32%; iv) TFA, CH_2Cl_2, RT, 0.5 h, then Na_2CO_3, MeOH:CH_2Cl_2 (6:1), RT, 15 h, then $NaBH_3CN$, AcOH, RT, 5 h, 40%.

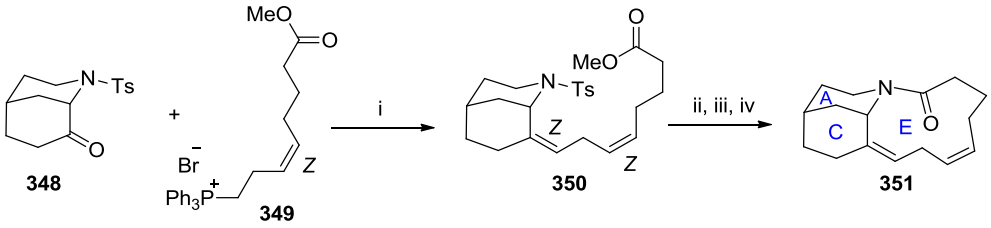
Construction of the unconjugated triene of the D-ring of madangamine A was elegantly achieved by selective reduction of the triyne chain of **345** which was installed by a cuprous iodide catalyzed coupling of the terminal alkyne of **343** with diyne **344**. Using *in situ* generated dicyclohexylborane, the apparently unstable all *cis*-triene was accessed in good yield. The final annulation step was again performed by macrolactamization using standard coupling reagents (Scheme 5.9).



Scheme 5.9. Amat and Bosch model assembly of the macrocyclic D-ring of madangamine A.[162] Selected Reagents and conditions: i) **344**, CuI, NaI, K_2CO_3, RT, 15 h, 86%; ii) $(CH_3)_2S{\cdot}BH_3$ cyclohexene, THF, 0 °C to RT, 4 h, 84%; iii) 2 N aq. HCl, MeOH, 0.5 h, 85%; iv) $NaHCO_3$, Dess-Martin

periodinane, CH_2Cl_2, RT, 18 h, 60%; v) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, RT, 1.5 h; vi) TFA, CH_2Cl_2, RT, 0.5 h, then HOBt, EDCI, CH_2Cl_2:DMF (9:1); RT, 15 h, 35%.

A Wittig reaction using non-stabilised phosphonium salt **349** was used to install the required *Z*-configured alkene adjacent to the 6-membered C-ring with similar levels of selectivity to those achieved by Kibayashi (*Z*:*E* = 10:1). Tosyl group deprotection and alkaline hydrolysis of the methyl ester of **350** was followed by macrolactamization of the resulting crude amino acid yielding **351** as a single diastereomer (Scheme 5.10).

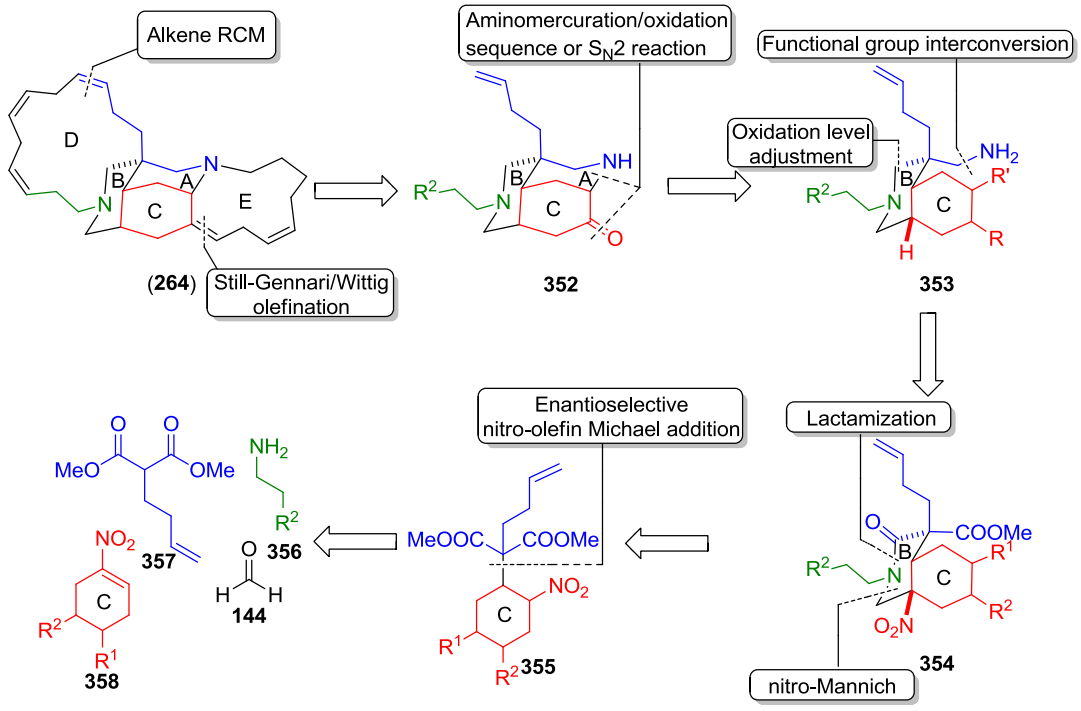


Scheme 5.10. Amat and Bosch model assembly of the macrocyclic E-ring of madangamines A-E.[162] Selected Reagents and conditions: i) KHMDS (0.5 M in toluene), **349**, THF, RT, 3 h, THF, RT, 1.5 h, 45% (*Z*,*Z*:*Z*,*E* 10:1); ii) Na, napthalene, THF, −78 °C, 10 min; iii) LiOH, THF, RT, 3.5 h; iv) HOBt, EDCI, CH_2Cl_2:DMF (9:1), RT, 15 h, 13%.

5.4. Retrosynthetic Plan for the Madangamine Alkaloids

The initial retrosynthetic plan devised for the synthesis of the ABC diazatricyclic core of the madangamine alkaloids was based on the key steps used in the synthesis of (–)-nakadomarin A (**1**) (Scheme 5.11). The formation of the macrocyclic D ring of madangamine A (**1**) would be achieved *via* a *Z*-selective alkene RCM strategy utilizing the functional handles introduced with building blocks **356** and **357**. Variation in these functional handles and oxidation state manipulations would be required to access other members of the family, madangamines **B**-**E** (**265**-**268**). Synthesis of the E ring would be achieved using the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction or a *Z*-selective Wittig olefination using a non-stabilised

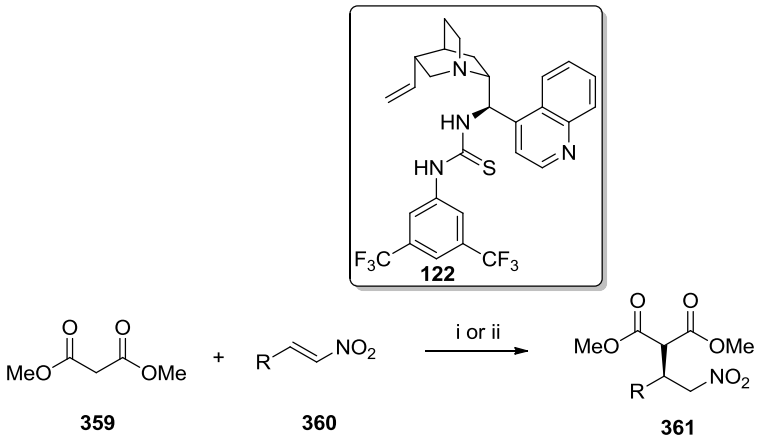
ylide, based on precedent from the work of Kibayashi and Bosch.[159,162] An aminomercuration reaction/oxidation sequence following the example of Weinreb, would form the diazatricyclic core bearing the required ketone functional handle.[154] An S_N2 cyclisation approach as adopted by Bonjoch, would present an alternative method of achieving this transformation.[157] A nitro-Mannich/lactamization sequence using Michael adduct **355** and an imine derived from amine **356** would be used to form the B ring of the madangamines. Michael adduct **355** would in turn be synthesized *via* an enantioselective nitro-olefin Michael addition, using suitably functionalized pro-nucleophile **357** and nitro olefin **358**, catalyzed by a bifunctional organocatalyst (e.g. **88**).



Scheme 5.11. Retrosynthetic plan for the synthesis of the ABC diazatricyclic core of the madangamines.

The enantioselective Michael addition of malonate esters to nitro olefins catalyzed by bifunctional thiourea organocatalysts (e.g. **122**) had previously been described by Hynes and Ye in the Dixon research group and others.[26-

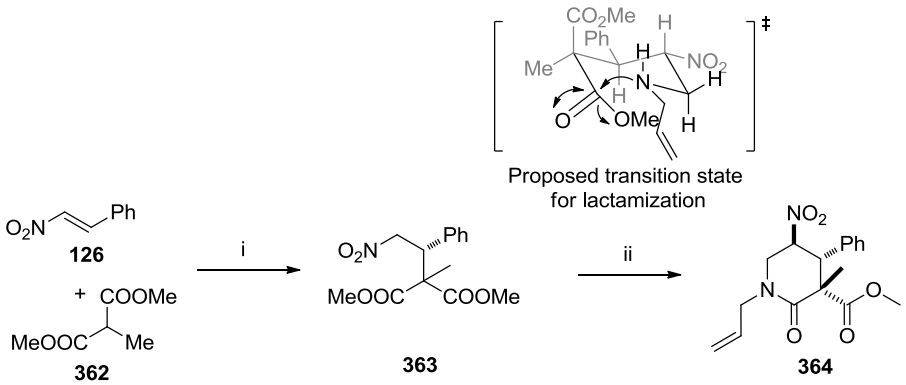
[28,157,163] In our report the resulting Michael adducts were isolated in high yield with high *ee* (Scheme 5.12). Aromatic nitro olefins were generally employed however, and in the few examples of aliphatic nitro olefins presented, yields and ee's were generally lower and reaction times longer. In addition to this, no examples of conjugate additions of substituted malonates were reported.



Scheme 5.12. Michael addition of dimethyl malonate to nitro olefins. Selected reagents and conditions: catalyst **122** (10 mol%), i) CH_2Cl_2, −20 °C; ii) neat, RT. Selected examples: R = Ph, conditions (i), yield = 95%, ee = 94%, reaction time = 30 h; R = 2-Cl phenyl, conditions (i), 99%, 94% ee, 30 h; R = 4-OMe phenyl, conditions (i), 96%, 92% ee, 30 h; R = *n*-pentyl, conditions (ii), 81%, 87% ee, 72 h (ii); R = cyclohexyl, 82%, 82% ee, 31 h.

More recently Jakubec reported a DABCO promoted Michael addition of methyl substituted dimethyl malonate **362** to nitrostyrene **126**, followed by a nitro Mannich/lactamization cascade to access 5-nitropiperidin-2-one **364** as a single diastereomer (Scheme 5.13).[53] The high diastereocontrol, which was also observed in the nitro-Mannich/lactamization step in the synthesis of (–)-nakadomarin A (**1**) (chapter 2), was postulated as being a consequence of either: i) A fast and reversible (possibly non stereoselective) nitro-Mannich reaction, in which only one of the diastereomeric nitro-Mannich products cyclised *via* an irreversible lactamization step to give the most thermodynamically stable product or ii) A post-cyclisation epimerization at the

carbon bearing the nitro group allowing equilibration to the thermodynamic product, barring any crystallization induced selectivity effects.



Scheme 5.13. Jakubec conjugate addition/nitro-Mannich/lactamization cascade. Reagents and conditions: i) DABCO (30 mol%), THF, RT, 6 days ,70%; ii) allylamine (2 eq.), formaldehyde (2 eq.), MeOH, reflux, 4 h, 67%.

Based on these studies, the isolated diastereomer possessed the required stereochemistry for the synthesis of the madangamine core (Figure 5.6). The axial methyl ester and equatorial methyl substituent of **364** matched the required stereochemistry for the alkyl substituent and amine handle at C-9 of the madangamines. Moreover a *cis* relationship between the H atom and nitro group at the B/C ring junction was predicted, therefore reductive denitration from the same face as the nitro group would install the required geometry.

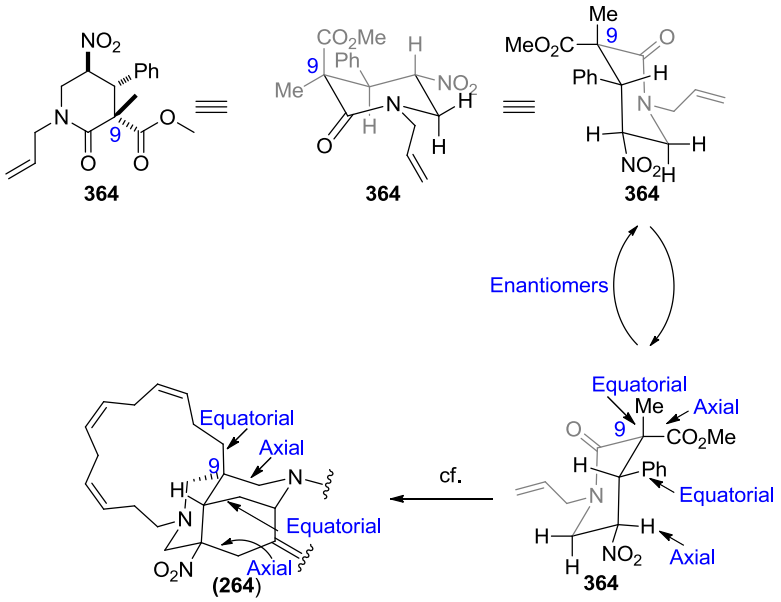


Figure 5.6. Comparison of relative stereochemistry of nitropiperidinone **364** with madangamine A (**264**)

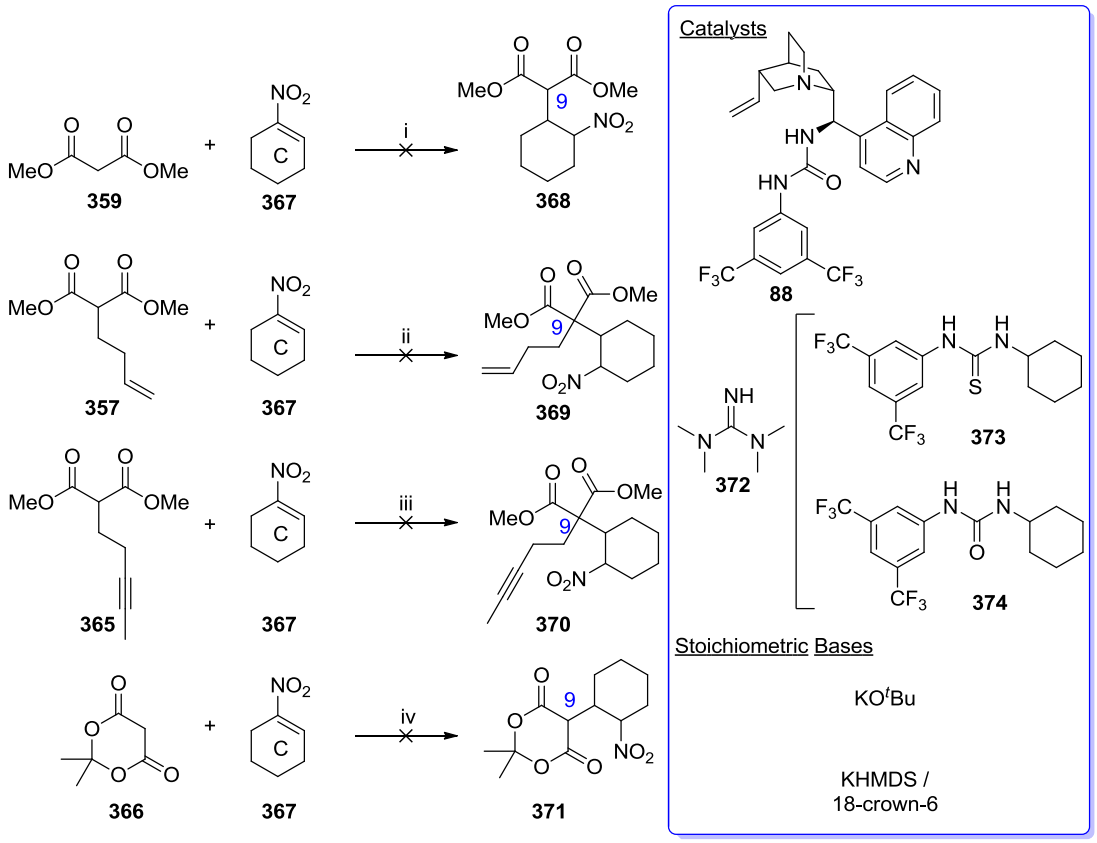
While these studies by Jakubec, Hynes and Ye provided a solid basis with which to plan a synthesis of the diazatricyclic core of the madangamines, several key problems would have to be addressed:

- Conjugate additions to non aromatic nitro olefins were known to be sluggish. A conjugate addition to a cyclic nitro olefin had not been achieved previously.
- Only one example of a conjugate addition of a substituted malonate (methyl) had been described. The introduction of an alkyl chain, suitable for further functionalisation into the macrocyclic D-ring of the madangamines, coupled with the cyclic nitro olefin substrate, presented significant challenges in this transformation.
- Changes in the observed diastereoselectivity as a consequence of the introduction of a cyclic nitro olefin were possible.
- Even if the required stereochemistry was achieved, the reductive denitration step presented the potential for the *trans* ring junction

product to form. Being a radical process (see chapter 2.13), sterics were likely to play a key role in the outcome of this transformation.

5.5. Model Studies – Conjugate Addition

Initial efforts towards the required conjugate addition were attempted using a range of nucleophiles **357**,**359**,**365** and **366** and commercially available model nitro olefin **367**. The lack of reactivity that was encountered in these initial trials highlighted the challenge of this transformation (Scheme 5.14).

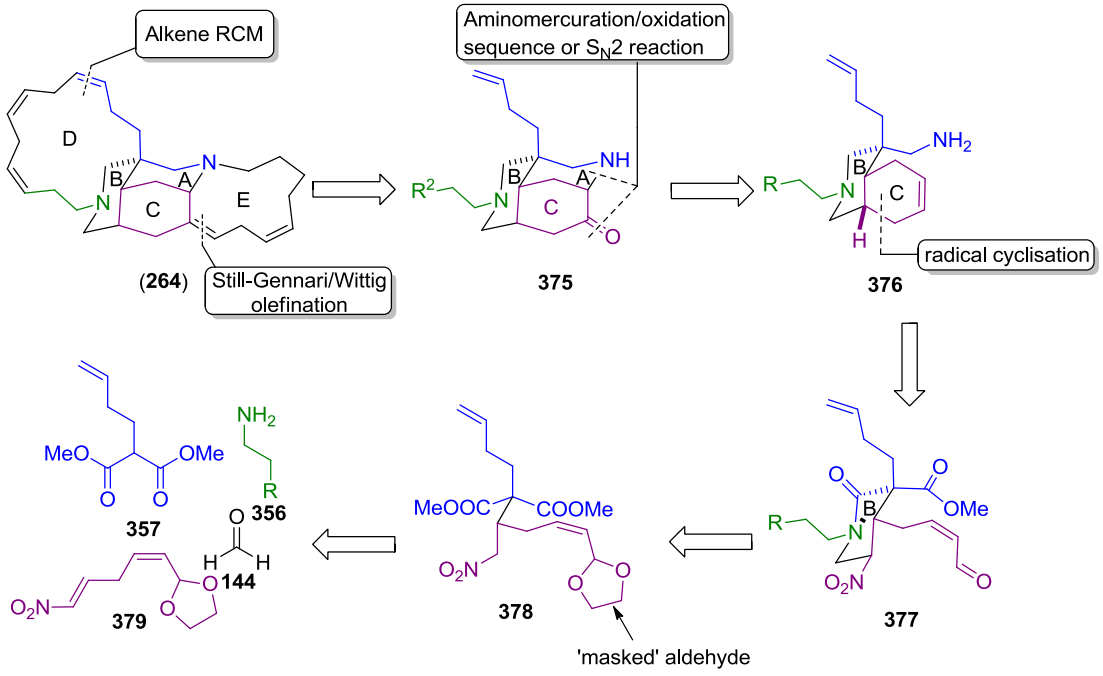


Scheme 5.14. Failed conjugate additions to 1-nitro-1-cyclohexene. Reagents and conditions: i) catalyst **88** (15 mol%), **359** (3.0 eq.), **367** (1.0 eq.), THF, RT, 24 h or KHMDS (1.05 eq.), 18-crown-6 (1.05 eq.), **359** (1.0 eq.), **367** (1.4 eq.), THF, -78 °C, 5 h or KO^{t}Bu (1.05 eq.), **359** (1.0 eq.), **367** (1.3 eq.), THF/^{t}BuOH, 0 °C-RT, 15 h; ii) catalyst **88** (20 mol%), **357** (1.1 eq.), **367** (1.0 eq.), THF, RT, 24 h or catalyst **372**/**373** (20 mol%), **357** (3.0 eq.), **367** (1.0 eq.), THF, RT, 2.5 days or catalyst **372**/**374** (20 mol%), **357** (3.0 eq.), **367** (1.0 eq.), THF, RT, 2.5 days or **372** (20 mol%), **357** (3.0 eq.), **367** (1.0 eq.), THF, RT, 2.5 days; iii) KO^{t}Bu (1.2 eq.), **365** (1.3 eq.), **367** (1.0 eq.), THF/^{t}BuOH, 0 °C to RT, 15 h or KHMDS (1.05 eq.), 18-crown-6 (1.05 eq.), **365** (1.0 eq.), **367** (1.4 eq.), THF, −78 °C, 2 h; iv) catalyst **88** (15 mol%), **366** (3.0 eq.), **367** (1.0 eq.), THF, RT, 20 h.

Catalytic bifunctional organocatalyst **88**, a catalytic system using separate base (1,1,3,3-tetramethylguanidine **372**) and thiourea/urea **373**/**374** components as well as complete deprotonation of the nucleophile using stoichiometric KO^{t}Bu or KHMDS all failed to yield any of the desired adducts **368**-**371** with decomposition of nitro olefin **367** occurring in many cases. Even when highly acidic Meldrum's acid (pKa (H_2O) = 4.97) **366** was employed as the nucleophile, no reaction was observed.

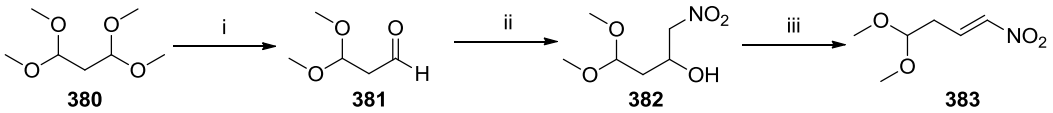
5.6. Alternative Retrosynthetic Plan

As a result of the seemingly insurmountable challenges posed by addition to a cyclic nitro olefin, a new retrosynthetic plan was devised incorporating acyclic nitro olefin **379**. Subsequent acetal deprotection to reveal an aldehyde would provide a functional handle to complete the C-ring potentially *via* a radical cyclisation.



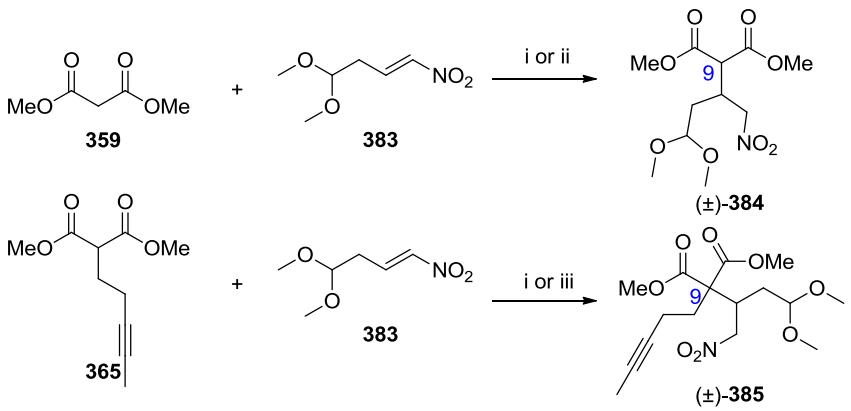
Scheme 5.15. Alternative retrosynthetic plan avoiding a cyclic nitro olefin

A truncated nitro olefin **383** was prepared to establish the feasibility of this strategy. Nitro olefin **383** was prepared in 3 steps from tetramethoxypropane **380** (Scheme 5.16). Phosphoric acid promoted mono-deprotection gave aldehyde **381** in low yield; however the cheap commercially available reagents used allowed this reaction to be carried out on scale. A Henry reaction gave nitro alcohol **382** in respectable yield. Unlike the synthesis of nitro olefin **104** in the nakadomarin A project (Chapter 2.8), no evidence of elimination to the nitro olefin directly was observed in this step. Instead, mesylate activation of the alcohol followed by base promoted elimination furnished nitro olefin **383** in good yield.



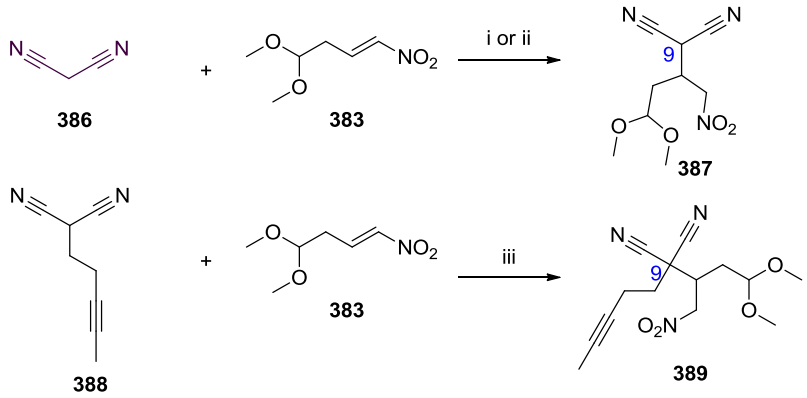
Scheme 5.16. Synthesis of nitro olefin **383**. Reagents and conditions: i) 6% aq. H_3PO_4, RT, 5 days, 28%; ii) $MeNO_2$ (1.1 eq.), KOH (1.1 eq.), EtOH, 0 °C, 1 h, 43%; iii) MsCl (1.0 eq.), Et_3N (2.0 eq.), CH_2Cl_2, −15 °C to RT, 15 min, 70%.

Conjugate addition of unsubstituted **359** and alkyne substituted **365** dimethyl malonate nucleophiles to acyclic nitro olefin **383** still displayed no reactivity when bifunctional catalyst **88** was employed. Stoichiometric deprotonation of the pro-nucleophile with either KHMDS or KO^{t}Bu prior to addition of the nitro olefin was found to be successful however, and Michael adducts **384** and **385** were both accessed in average to good yields.



Scheme 5.17. Synthesis of (±)-**384** and (±)-**385**. Reagents and conditions: i) catalyst **88** (20 mol%), **359** or **365** (2.0 eq.), **383** (1.0 eq.), toluene, 72 h, no reaction; ii) KO^{t}Bu (1.0 eq.), **359** (1.2 eq.), **383** (1.0 eq.), THF/^{t}BuOH, 0 °C to RT, 20 h, 74%; iii) KHMDS (1.05 eq.), 18-crown-6 (1.05 eq.), **365** (1.0 eq.), **383** (1.4 eq.), THF, −78 °C, 2 h, 39%.

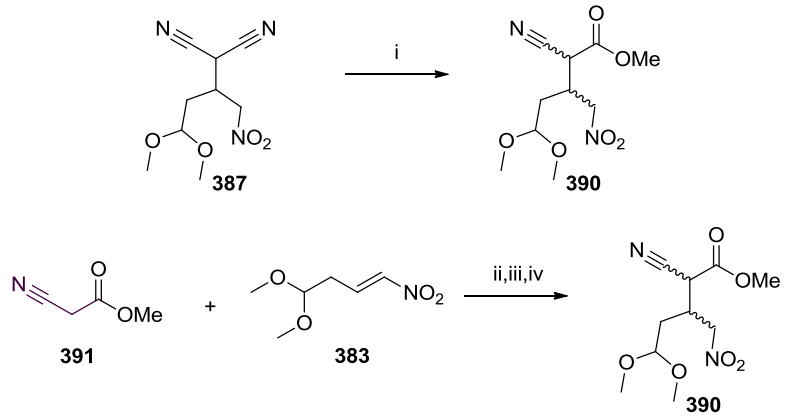
A change in pro-nucleophile to malononitrile **386** allowed the successful synthesis of adduct **387** in 40% yield, using catalytic DABCO. More significantly, this transformation could be achieved using bifunctional organocatalyst **88**, with adduct **387** being isolated in 75% after 48 h reaction time. Alkylated Michael adduct **389** could also be formed from pro-nucleophile **388** using catalyst **88** with only slightly diminished yield.



Scheme 5.18. Synthesis of **387** and **389**. Reagents and conditions: i) DABCO (20 mol%), **386** (1.0 eq.), **383** (1.2 eq.), toluene, RT, 48 h, 40%; ii) catalyst **88** (10 mol%), **386** (1.0 eq.), **383** (1.2 eq.), toluene, RT, 48 h, 75%; iii) catalyst **88** (20 mol%), **388** (1.0 eq.), **383** (1.2 eq.), toluene, RT, 48 h, 62%.

While this result was pleasing from a reactivity perspective, the presence of two identical nitrile substituents posed a potential problem for selective manipulation at a later stage. Lewis acid promoted methanolysis of one nitrile

group of Michael adduct **387** allowed adduct **390** to be accessed as an inseparable mixture of diastereomers **390**a:**390**b = ~1:1 in 12% yield (Scheme 5.19). A more practical solution was a Michael addition using commercially available methyl cyanoacetate **391** as the nucleophile. Pleasingly this change of nucleophile did not diminish reactivity and Michael adduct **390** was accessed using catalyst **88** (**390**a:**390**b) = 51:49 dr), DABCO **390a**:**390b** = 51:49 dr) and KHMDS (**390a**:**390b** = 49:51 dr).

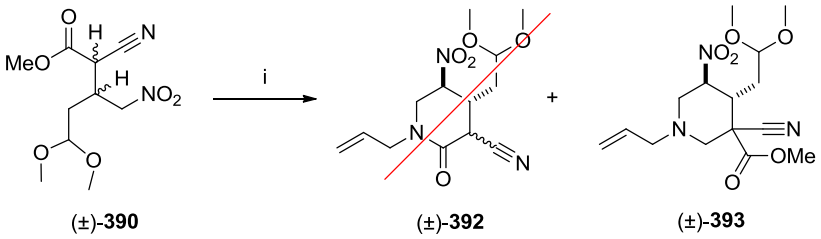


Scheme 5.19. Synthesis of Michael adduct **390**. Reagents and conditions: i) $FeCl_3$, MeOH, reflux, 2 h, 12%; ii) DABCO (20 mol%), **391** (1.0 eq.), **383** (1.3 eq.), toluene, RT, 48 h, 8% iii) catalyst **88** (10 mol%), **391** (1.0 eq.), **383** (1.3 eq.), toluene, RT, 48 h, 58%; iv) KHMDS (1.05 eq.), 18-crown-6 (1.05 eq.), **391** (1.0 eq.), **383** (1.4 eq.), THF, −78 °C, 1.5 h, 41%.

Considerable decomposition was observed in the reaction with DABCO, which could account for the poor yield obtained. This was presumably due to nitro olefin degradation, as unreacted nucleophile **391** was present in the reaction mixture. DABCO was therefore eliminated from any further studies. Despite determined efforts using a selection of chiral columns, Michael adducts **387**, **389** and **390** were not observed by HPLC under any wavelength, and no meaningful HPLC data was collected. It was decided that establishing a proof of reactivity to ascertain whether a route to the madangamines would be feasible was an immediate priority. HPLC studies to establish the enantioselectivity, if any, achieved in the Michael addition would

subsequently be carried out. Racemic Michael adduct **390** was used in further studies.

Michael adduct **390** (~1:1 dr) was subjected to the standard nitro-Mannich/lactamization conditions developed in the nakadomarin A project on small scale (15 mg) (Scheme 5.20). Under these conditions, none of the desired piperidinone product **392** was observed, however closer inspection of the reaction mixture led to the isolation of piperidine **393** in low yield, but as a single diastereomer.



(±)-**390** (±)-**392** (±)-**393**

Scheme 5.20. Unexpected formation of piperidine (±)-**393**. Reagents and conditions: i) allylamine (1.5 eq.), formaldehyde (1.5 eq.), MeOH, 3 h, 26%.

It was proposed that the formation of piperidinone **393** arose due to the amine of nitro-Mannich adduct **394**, reacting with a second molecule of formaldehyde (pathway B), rather than undergoing lactamization (pathway A), followed by a subsequent intramolecular Mannich type trapping of the generated iminium ion resulting from deprotonation of the acidic H bearing C-9 centre (Figure 5.7).

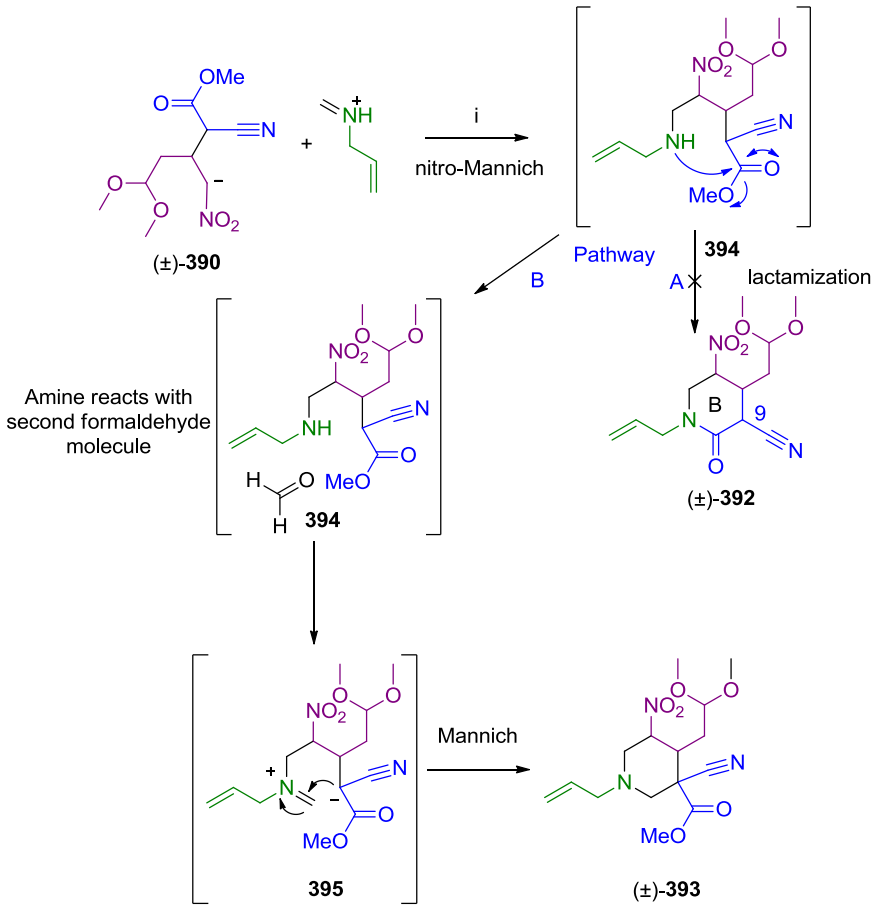
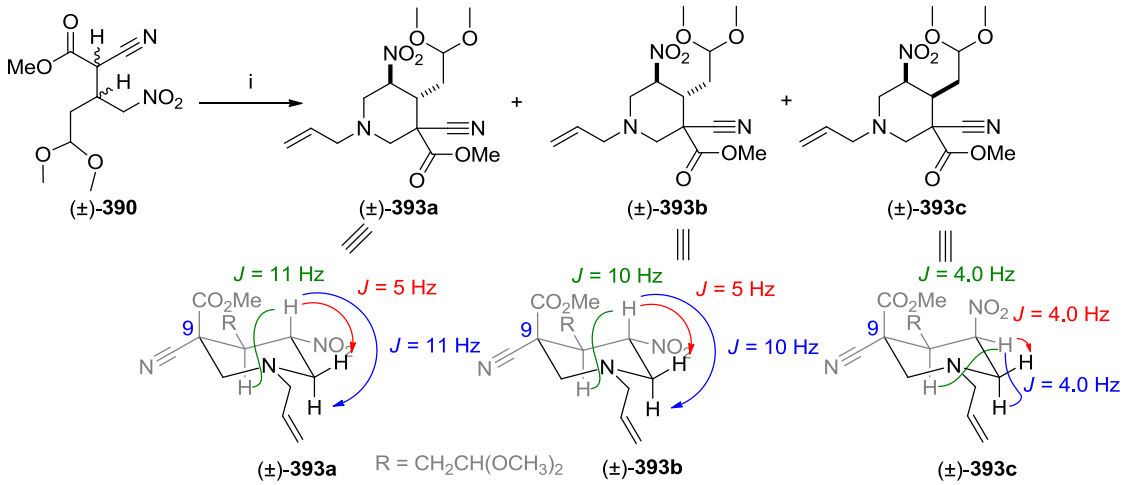


Figure 5.7. Proposed mechanism for the formation of (±)-**393**. Reagents and condition: i) MeOH, reflux.

It was proposed that unintentional overcharging of the system with formaldehyde had occurred, as a result of the small scale of the reaction. To test this hypothesis, a repeat reaction was conducted using an excess of formaldehyde. (Scheme 5.21).

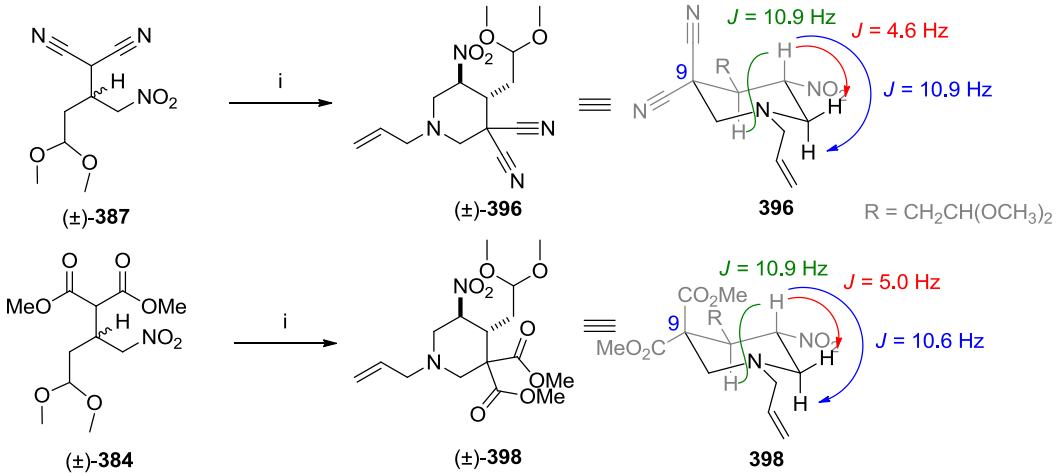


Scheme 5.21. Nitro-Mannich/Mannich sequence. Reagents and conditions: i) Allylamine (1.2 eq.), formaldehyde (8.6 eq., added rapidly in one portion), MeOH, reflux. 7 h, 87% overall yield (±)-**393a**: 62%, (±)-**393b**: 6%, (±)-**393c**: 19%.

Again no evidence of piperidinone **392** was observed, however three diastereomeric products **393a**, **393b** and **393c** were isolated from the reaction mixture. The major diastereomer **393a** was assigned as having a *trans* relationship between the nitro and acetal substituents with both occupying an equatorial position in the major conformer based on the coupling constants observed for the α-nitro proton. Diastereomer **393b** was only isolated in small amounts and was not observed in all reactions. It is assumed to be epimeric relative to **393a** at the C-9 position based on the observed coupling constants. Based on the three small coupling constants observed, diastereomer **393c** was assigned as having a *cis* relationship between the nitro and acetal substituents, assuming that the major conformer of the piperidine ring is as drawn, with the acetal group occupying an equatorial position. Diastereomer **393a** was found to display excellent stability and was recovered unchanged after heating overnight in refluxing methanol containing silica (100 mg silica/7 mg **393a**). Diastereomer **393c** however was found to partially epimerize to **393a** on silica, making the

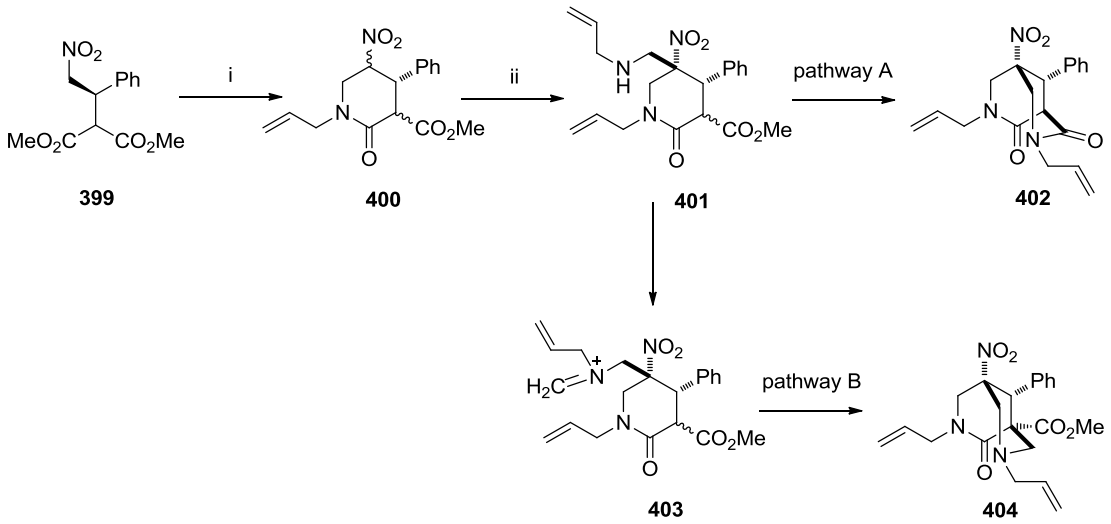
isolation of pure **393c** challenging and suggesting that the nitro-Mannich step was reversible. 8.6 eq. of formaldehyde was arbitrarily chosen and found to give good results, in practice however a large excess of formaldehyde (6-20 equivalents) was found to give similar results.

When Michael adducts **387** and **384** were treated with an excess of formaldehyde, similar results were observed, however only a single diastereomer was isolated in each case. Based on the coupling constants of the α-nitro proton these were assigned as *trans* diastereomers **396** and **398**.



Scheme 5.22. Nitro-Mannich/Mannich sequence in the synthesis of **396** and **398**. Reagents and conditions: i) Allylamine (1.2 eq.), formaldehyde (8.6 eq.), MeOH, reflux. 3 h, **396**: 55%, **398**: 24%.

No reports have previously documented a nitro-Mannich/Mannich cyclisation cascade to access piperidines. Xu and co-workers have reported a similar transformation however to form bispidine derivatives **402** and **404** (Scheme 5.23).[57] Addition of either a strong or weak acid to the reaction mixture was used to control the major reaction pathway by attenuation of the nucleophilicity of the amine of intermediate **401**.



Scheme 5.23 Xu: Bispidine synthesis.[57] Reagents and conditions: i) Allylamine (1.3 eq.), formaldehyde (1.05 eq.), ^{i}PrOH:H_2O (5:1), 50 °C, 10 h; **ii**) Allylamine (2.5 eq.), formaldehyde (3.2-6 eq. added dropwise over 1.5-3 h), ^{i}PrOH/H_2O (5:1), 50-60 °C, acid additive (0.5 eq.) Pathway A: ^{t}BuCO$_2$H: **402**:**404** = 16:1 86%; Pathway B $MeSO_3H$: **402**:**404** = 1:14, 80%.

The reaction solvent, increase in ratio of amine:formaldehyde, rate of formaldehyde addition and acid additive presumably may all play a role in this alternative pathway. No evidence of lactamization or bispidine formation was observed in the current work.

5.7. Development of Nitro-Mannich/Mannich Cascade

Working under my supervision, Robert Powell, an undergraduate Part II research student, developed the nitro-Mannich/Mannich reaction cascade and showed it to be general for a range of malononitrile and dimethyl malonate derived Michael adducts, with aliphatic, cyclic and aromatic substituents and a range of amines (Figure 5.8).[164] A single *trans* diastereomer (±)-**405a-j** was isolated in most cases. Importantly, Powell showed that the enantiopurity of the starting Michael adduct was maintained in the nitro-Mannich/Mannich cascade.

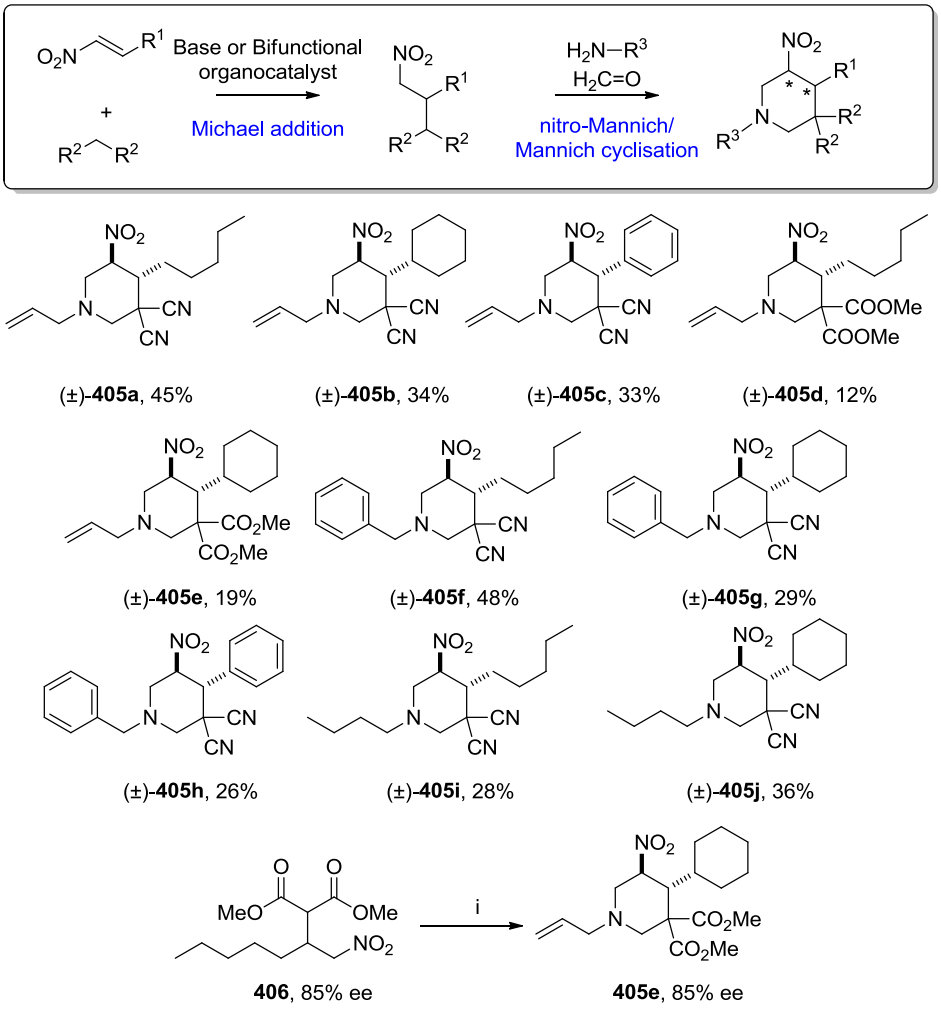


Figure 5.8. Powell reaction scope studies.[164] Reagents and conditions: i) Allylamine (1.2 eq.), formaldehyde (8.6 eq.), MeOH, reflux. 3 h.

5.8. Application to Synthesis of the Madangamine Alkaloids

While some attempts were made to functionalize nitro-Mannich/Mannich adduct **393**, limited success was achieved. A reassessment of the original retrosynthetic plan was carried out as a result of the unexpected nitro-Mannich/Mannich reactivity observed in the cyclisation step and the increased reactivity observed in the Michael addition step when more acidic pro-nucleophiles were used (Figure 5.9).

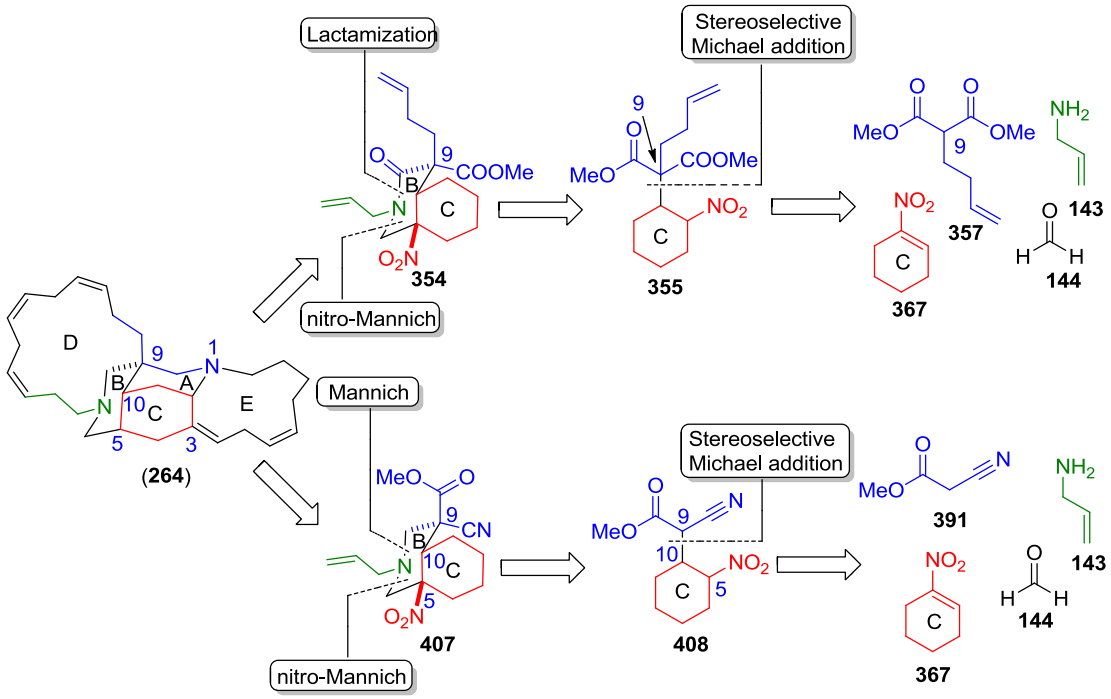
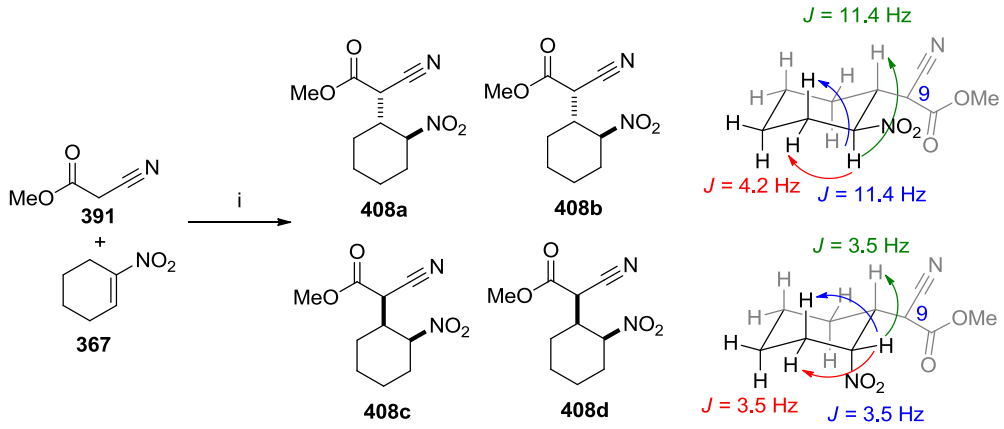


Figure 5.9. Modified retrosynthetic plan using nitro-Mannich/Mannich cascade.

Highly functionalized piperidine **407**, bearing two functional handles, a nitrile and methyl ester, at C-9 had the potential to be used to construct the A and D rings of the madangamines, without the need for an alkyl substituent on the pro-nucleophile **391**. This simplification, combined with the increased reactivity observed with more acidic nitrile containing nucleophiles, offered the potential for reactivity using cyclic nitro olefin **367** and a bifunctional organocatalyst (e.g. **88**) in the key Michael addition step.

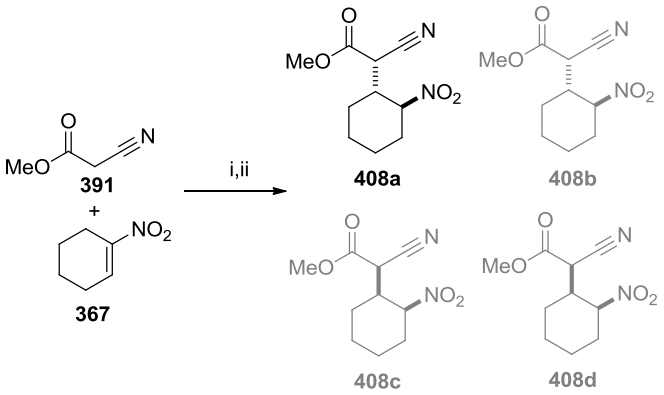
Pleasingly, initial attempts at the conjugate addition of methyl cyanoacetate **391** to 1-nitro-1-cyclohexene **367** using catalyst **88**, were successful and Michael adducts **408a-d** were formed rapidly (25 h), as a mixture of four diastereomers (**408a**:**408b**:**408c**:**408d** 1.3:0.5:1.1:1.0 crude dr) (Scheme 5.24). Diastereomers **408a** and **408b** were assigned as having a *trans* relationship between the nitro and C-9 bearing substituent based on coupling

constants for the α-nitro proton (J = 2 × 11.4, 4.2 Hz) and **408c** and **408d** were assigned as having a *cis* relationship (J = 3 × 3.5 Hz). The two sets of two diastereomers (*cis* and *trans*) were partially separable and enriched diastereomeric ratios of each were obtained (**408a**:**408b**:**408c**:**408d** 10:3.7:1.2:1.1 dr) and (**408a**:**408b**:**408c**:**408d** 2.3:5.6:10:8.9 dr).



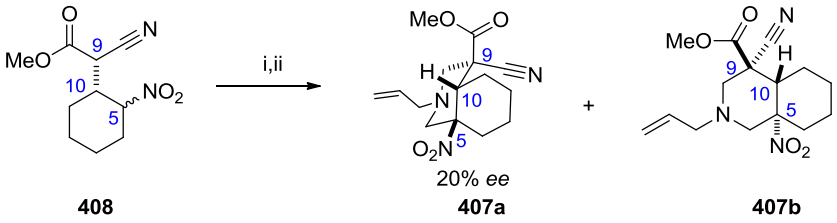
Scheme 5.24. Michael addition of **391** to cyclic nitro olefin **367**. Reagents and conditions: i) Catalyst **88** (10 mol%), **391** (1.2 eq.), **367** (1 eq.), toluene, RT, 25 h, 76% combined yield.

In a subsequent repeat reaction using catalyst **88**, the crude reaction mixture was stored at 20 °C for one week prior to analysis, during which time crystallization was observed. The ^{1}H NMR of this sample indicated the presence of only the *trans* diastereomers (**408a**:**408b**:**408c**:**408d** 2.7:1.0:0:0 dr). Purification by column chromatography and a recrystallization from diethyl ether/petrol gave a single diastereomer as a colourless solid. Similarly when KO^{t}Bu was used as base, 5 g of a single diastereomer **408a** was isolated in 71% yield (Scheme 5.25). The variable diastereoselectivity obtained in this reaction suggest that under certain conditions, a dynamic crystallization-driven process allows the *cis* isomer in the crude reaction mixture to equilibrate to the favoured *trans* isomer, which gradually crystallizes from the reaction solution.



Scheme 5.25. Formation of a single diastereomer. Reagents and conditions: i) Catalyst **88** (10 mol%), **391** (1.2 eq.), **367** (1 eq.), toluene, RT, 25 h, 86% single diastereomer; ii) KO^{t}Bu (1.0 eq.), **391** (1.2 eq.), **367** (1.0 eq.), THF/^{t}BuOH, 0 °C to RT, 20 h, 71% single diastereomer.

Irrespective of whether a single diastereomer or a mixture of all four diastereomers of **408** was used in the subsequent nitro-Mannich/Mannich cascade, two new products **407a** and **407b** were obtained, which were assigned as being *cis* and *trans* isomers at the 6,6-bicyclic ring junction (Scheme 5.26).



Scheme 5.26. Nitro-Mannich/Mannich Cascade using **408**. Reagents and conditions: i) (**408a**:**408b**:**408c**:**408d** 34:12:29:25 dr) allylamine (1.2 eq.), formaldehyde (8.6 eq.), MeOH, reflux, 20 h, **407a**: 24%, **407b**: 15%; ii) (**408a**:**408b**:**408c**:**408d** 1.0:0:0:0 dr) (single diastereomer), allylamine (2.4 eq.), formaldehyde (26 eq.), MeOH, reflux, 20 h, **407a**: 25%, 20% *ee*, **407b**: 14%.

When only 8.6 eq. of formaldehyde was used, inconsistent results were obtained and a number of additional minor products were generally observed. Increasing the equivalents of formaldehyde used (>20 eq.), with either 1.2 or 2.4 equivalents of allylamine was found to give reproducible results; although only 35-43% combined yield of the *cis* and *trans* diastereomers was obtained. Diastereomer **407a** was found to be stable on storage at −20 °C for several months, while diastereomer **407b** was found to

decompose to a complex mixture of products, although epimerization to **407a** was not observed. No other products were identified from the reaction. Only a complex mixture of baseline products and impurities derived from amine trimer **146** (Chapter 2.12) were obtained.

The structure of diastereomer **407b** was confirmed as having a *trans* relationship across the 6,6-bicycle ring junction by single crystal X-ray analysis (Figure 5.10).

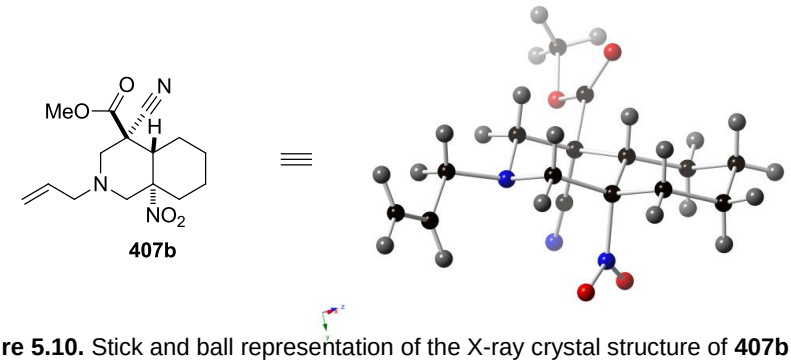
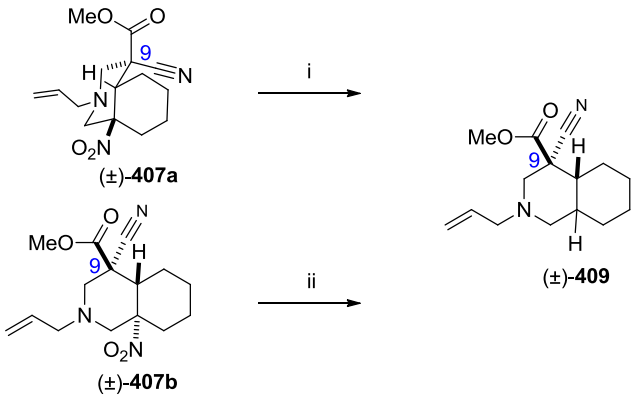


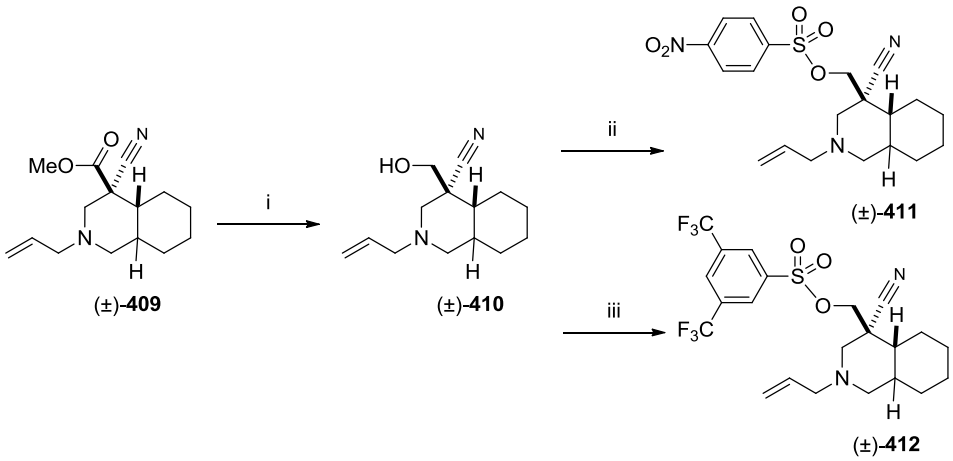
Figure 5.10. Stick and ball representation of the X-ray crystal structure of **407b**

The modified conditions of Ono's radical denitration procedure, developed in the synthesis of (–)-nakadomarin A (**1**), were employed to remove the nitro group from **407a** and **407b**. Pleasingly both reactions proceeded cleanly giving a single product, with identical spectroscopic data, in each case (Scheme 5.27).



Scheme 5.27. Nitro removal. Reagents and conditions: i) Bu_3SnH (5 eq.), AIBN (0.2 eq.), toluene, reflux, 2.5 h, 77%; ii) Bu_3SnH (5 eq.), AIBN (0.2 eq.), toluene, reflux, 2.5 h, 52%.

The implication of these findings was that **407a** and **407b** were epimeric at the nitro carbon only, with the relative configuration at the quaternary (C-9) centre fixed. The nitrile substituent occupying an axial position *trans* to the adjacent ring junction H atom, as present in the chair conformer shown in the single crystal X-ray structure of **407b** (Figure 5.10), presented an ideal situation whereby this would become the amine handle with which to construct the A ring, while the equatorial ester substituent would become the alkyl chain of the macrocyclic D ring. Both a *cis* and *trans* 6,6-bicyclic product were possible from this reaction, depending on the facial selectivity of the incoming H radical, with a *cis* geometry required for the synthesis of the madangamine core. The formation of a single diastereomer showed that facial selectivity was high. Overlap of the ring junction H's with several H's of the cyclohexane ring of **409**, prevented any meaningful NOE data from being collected and despite determined efforts no crystalline derivatives could be prepared for single crystal X-ray analysis (Scheme 5.28). The relative stereochemistry at the B/C ring junctions was therefore not determined for substrate **409**.



Scheme 5.28. Attempts to prepare a crystalline derivative. Reagents and conditions: i) $NaBH_4$ (10 eq.), THF/H_2O (9:1), 50 °C, 3 h, 77%; ii) 4-nitrobenzenesulfonyl chloride (4 eq.), Et_3N (5 eq.), DMAP (2 eq.), CH_2Cl_2, RT, 17 h, 67%; iii) 3,5-bistrifluoromethylbenzenesulfonyl chloride (4 eq.), Et_3N (5 eq.), DMAP (2 eq.), CH_2Cl_2, RT, 20 h, 77%.

5.9. Diastereoselectivity/Enantioselectivity and Mechanistic Analysis

No accurate enantioselectivity values were obtained for Michael adduct **408a** derived as a single diastereomer from the conjugate addition of **391** to nitro olefin **367** catalyzed by bifunctional catalyst **88**. This was a result of irreproducible HPLC traces, possibly resulting from the lability of adduct **408a** to epimerization. From the best HPLC traces obtained an approximate *ee* = 20-25% was achieved. The *ee* of 6,6'-bicycle **407a** derived from a (**408a**:**408b**:**408c**:**408d** 34:12:29:25 dr) diastereomeric mixture of Michael adduct **408** prepared using catalyst **88** was accurately measured and found to be 20% (Scheme 5.26). This result supports the findings of Powell[164] that the stereochemical integrity of Michael adduct **408** is maintained in the nitro-Mannich/Mannich cyclisation step. Based on the proposed mechanism (Figure 5.7) deprotonation of both the labile C-9 and nitro bearing C-5 stereocentres (Scheme 5.26) occurs during the nitro-Mannich/Mannich cyclisation cascade. Only the C-10 stereocentre, controlled by the facial selectivity of addition of methyl cyanoacetate **391** to 1-nitro-1-cyclohexene **367** is retained and is responsible for the observed enantioselectivity in **407a**. No data on the absolute stereochemistry of adducts **408a-d** was obtained.

The observed diastereoselectivity, modestly favouring *cis* diastereomer **407a**, which would intuitively be considered thermodynamically less stable than *trans* diastereomer **407b** can be explained by more than one possible reaction pathway (Figure 5.11). Consideration must be given to the fact that assuming both 6-membered rings exist as a chair-chair system, *cis* decahydroisoquinoline **407a**, can exist as two conformers of unequal energy,

in an analogous fashion to *cis* decalin, while *trans* decahydroisoquinoline **407b** is conformationally locked. Basic molecular mechanics calculations (MM2) suggest that in their lowest energy conformation the 6,6'-ring system of each diastereomer is puckered and may not exist as a chair-chair conformation.

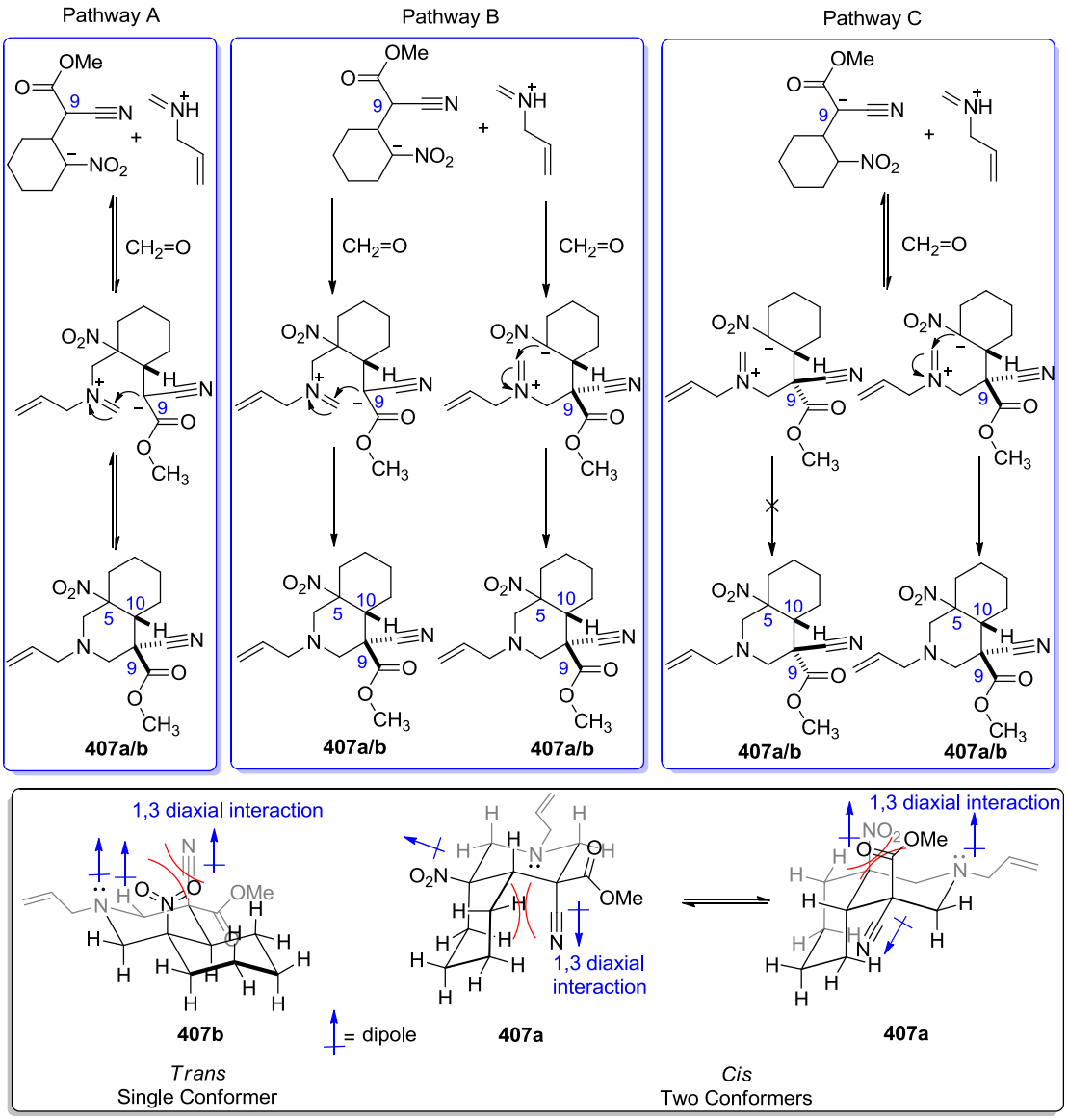


Figure 5.11. Possible reaction pathways.

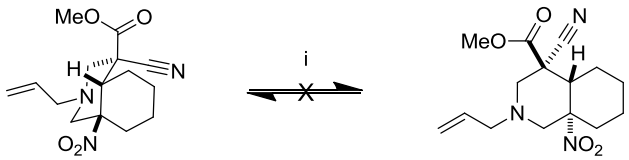
Pathway A

In this potential pathway both the nitro-Mannich and Mannich steps are reversible and the product distribution is under thermodynamic control.

This would suggest that *cis* diastereomer **407a** can adopt a lower energy conformation than *trans* diastereomer **407b**. This lower energy conformation could potentially arise through minimisation of 1,3-diaxial interactions. The lower A-value (derived from energy measurements of a monosubstituted cyclohexane ring)[165-167] of the nitrile (A-value = 0.2) and nitro (A-value = 1.1) substituents relative to the methyl ester (A-value = 1.3) and alky substituents (A-value = ~1.7) which would be responsible for the unfavourable 1,3-diaxial interaction in the conformations drawn (Figure 5.11), suggest that this is unlikely. Another possibility is that unfavourable alignment of dipoles arising from the C-NO_2 and C-C≡N bonds along with nitrogen lone pair in the *trans* diastereomer, may result in it being of higher energy than the lowest energy conformation of *cis* diastereomer **407a**.

However, this pathway is not supported by the fact that the product distribution does not significantly change with prolonged reaction times and when pure **407a** and **407b** are re-submitted to the reaction conditions interconversion between the diastereomers is not observed (Scheme 5.29). This result is in contrast to that of the earlier acyclic system **393** (Scheme 5.21) in which *cis* diastereomer **393c** was found to epimerize to *trans* diastereomers **393a** and **393b**. This result suggests that the 6,6'-bicyclic system attenuates the reactivity of the lone pair of electrons of the amine

present in **407a** and **407b**, thus preventing retro nitro-Mannich/Mannich reactions from occurring.



(±)-**407a** (±)-**407b**

Scheme 5.29. Supporting evidence of irreversibility of nitro-Mannich/Mannich cyclisation. Reagents and conditions: i) Allylamine (1.2 eq.), formaldehyde (20.0 eq.), MeOH, reflux. 24 h.

Pathway B

Another reaction pathway could arise from both of the reaction steps being irreversible with the Mannich highly diastereoselective and nitro-Mannich step less so. This would account for the excellent stereocontrol observed at the C-9 stereocentre.

Pathway C

An additional pathway could arise from the Mannich reaction occurring first and being both fast and reversible (but not necessarily diastereoselective). The high stereocontrol at the C-9 stereocentre could be accounted for if only one of the diastereomeric Mannich products undergoes cyclisation in an irreversible nitro-Mannich step. The distribution of *cis*/*trans* products at the B/C ring junction would be under kinetic control. The combined inductive electron withdrawing effect of the nitrile and nitro substituents may attenuate any further reactivity of the amine lone pair of electrons after the nitro-Mannich step. This pathway could also explain why no evidence of lactamization by the free amine is observed.

As a result of the lack of reversibility observed in the nitro-Mannich/Mannich cyclisation reaction, pathways B and C are considered to be the most plausible explanations for the reactivity observed.

5.10. Summary

Initial studies on the conjugate addition of methyl cyanoacetate **391** to cyclic nitro olefin **367** proved to be highly successful. Good reactivity was achieved with bifunctional organocatalyst **88**, yielding Michael adduct **408** with modest but potentially optimizable enantioselectivity. The nitro-Mannich/Mannich cascade observed previously was also found to be amenable to this system, yielding only two diastereomers albeit in poor yields.

Several challenges still had to be addressed namely:

1. Confirmation of the *cis*/*trans* nature of the B/C ring junction upon denitration and strategies to address the problem if the *trans* isomer was formed.
2. Improvement of enantioselectivity and cyclisation reaction yield.
3. Synthesis of a suitably functionalized nitro olefin which would allow the synthesis of the A-ring.

5.11. Synthesis Development – Nitro Olefin Synthesis

While 1-nitro-1-cyclohexene **367** had been useful for model studies, the lack of a suitable functional handle limited its potential in the synthesis of the madangamines. Nitro olefins **413-415** were selected as potential synthetically useful building blocks (Scheme 5.12).

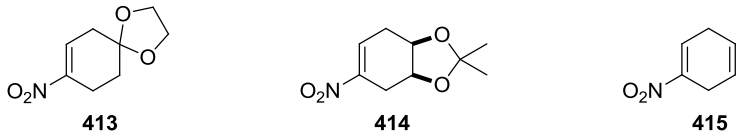
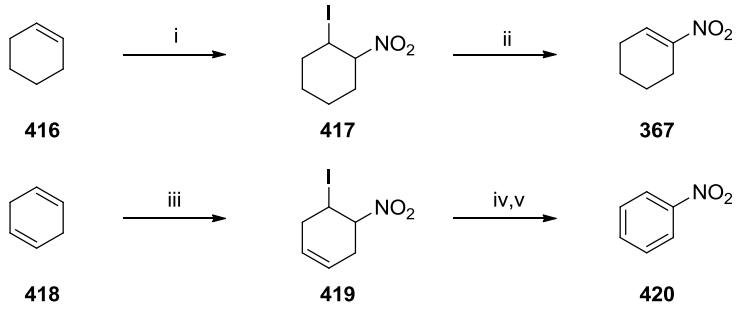


Figure 5.12. Synthetically useful nitro olefins

Despite the wealth of methods developed for the nitration of aromatic, acyclic and simple cyclic systems,[168] no examples of 6-membered nitro olefins of type **413**-**415**, bearing functionality meta-/para- to the nitro group, other than simple alkyl substituents, have been reported.

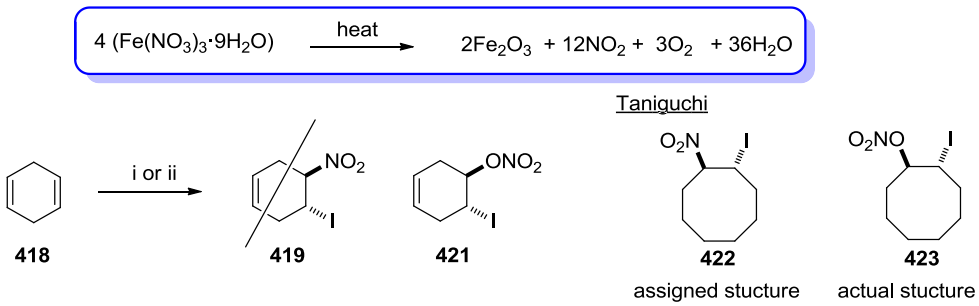
Following the procedures of Jew and Efremova,[169,170] nitryl iodide (NO_2I)[171] addition across the double bond of cyclohexene, yielded 1-nitro-1-cyclohexene **367** *via* the intermediate iodide **417**. Attempts to access **415** by this route were unsuccessful with only traces of aromatic residues found to be present in the crude reaction mixture (Scheme 5.30).



Scheme 5.30. Nitryl iodide addition across alkene. Reagents and conditions: i) I_2 (1.5 eq.), $NaNO_2$ (4 eq.), $HOCH_2CH_2OH$ (3 eq.), EtOAc:H_2O (7.5:1), RT, 4 days, 21%; ii) Et_3N (1.1 eq.), CH_2Cl_2, RT, 3h, 79%; iii) I_2 (1.5 eq.), $NaNO_2$ (4 eq.), $HOCH_2CH_2OH$ (3 eq.), EtOAc:H_2O (7.5:1), RT, 4 days, 13%; iv) Et_3N (1.1 eq.), CH_2Cl_2, RT, 2 h; v) NaHMDS, (1 eq.), THF, −78 °C, 1 h.

Following the procedures of Taniguchi, iron mediated radical halo-nitration of 1,4-cyclohexadiene **418** was attempted (Scheme 5.31).[172,173] Thermal decomposition of iron(III) nitrate nonahydrate is known to generate NO_2.[174] Taniguchi proposed that radical NO_2 addition to an alkene is followed by a halide radical trapping sequence to yield the desired iodo-nitro compounds.

While this procedure initially appeared promising, with a single product isolated in good yield, closer inspection revealed that iodo-nitrate **421** had been formed. This compound is easily distinguishable from **419** by their characteristic IR bands (ONO_2: 1629 cm^{-1} vs. NO_2: 1554 cm^{-1}). Attempts to avoid nitrate formation by prolonged thermal decomposition of $Fe(NO_3)_3 \cdot 9H_2O$ prior to 1,4-cyclohexadiene addition offered no improvements and the same reaction product was observed. Inspection of the reports by Taniguchi and comparison with literature data showed that some nitrate compounds (e.g **423**) had erroneously been reported as nitro compounds (e.g **422**).[172,173,175]



Scheme 5.31. Attempted iron mediated halo-nitration. Reagents and conditions: i) LiI (1.2 eq.), $Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.), MeCN, reflux, 2 h, 70% (**421**); ii) LiI (1.2 eq.), $Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.), MeCN, reflux, 2 h then **418** (1 eq.), reflux, 2 h.

Inspired by the work of Ono,[176,177] a Diels-Alder approach using electron deficient β-sulfinylnitroethylene **424** and 1,3-butadiene **291** followed by thermal elimination of sulfenic acid from intermediate **425** to access nitro olefin **415** was also attempted.

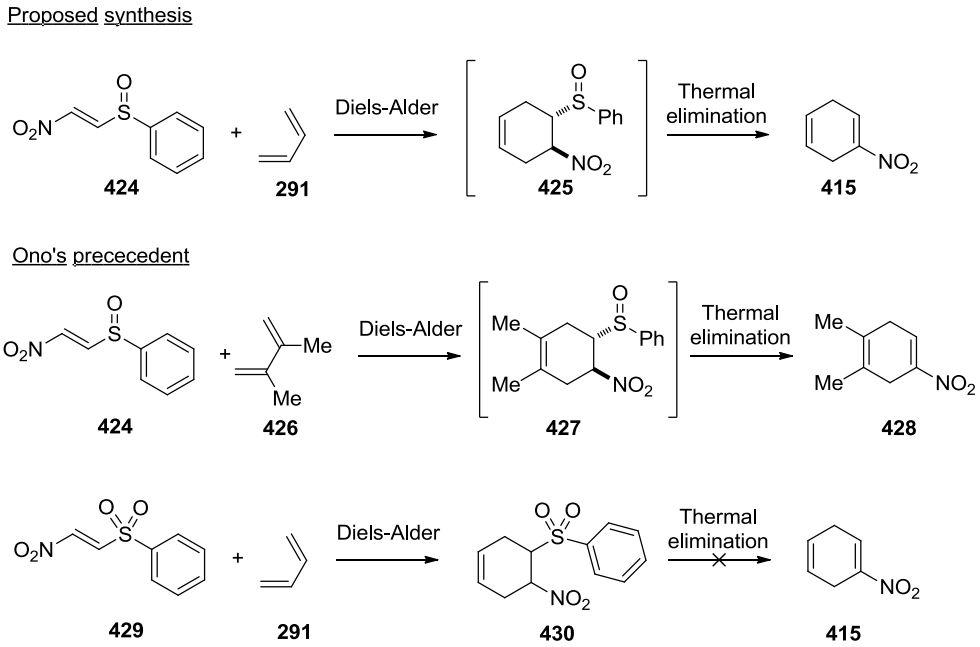
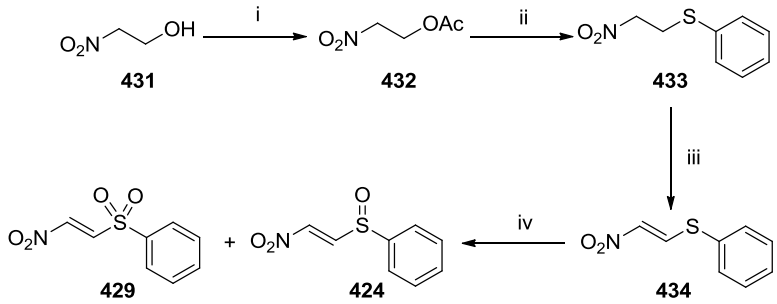


Figure 5.13 Diels Alder/elimination approach to **415.**

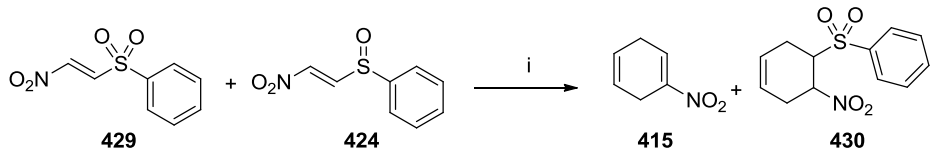
β-sulfinylnitroethylene **424** was accessed in four steps from 2-nitroethanol **431** (Scheme 5.32).[176,177] Alcohol activation (i), thiophenol displacement (ii) and chlorination/elimination (iii) to give sulfide **434**, all proceeded in excellent yields following Ono's procedures. Oxidation of **434,** contrary to Ono's report, was found to be problematic.



Scheme 5.32. Synthesis of **424**. Reagents and conditions: i) Ac_2O (1 eq.), pyridine (1 eq.), CH_2Cl_2, RT, 16 h, 93%; ii) Thiophenol (1 eq.), Et_3N (1.1 eq.), MeCN, 0 °C, 1.5 h, 87%; iii) Sulfuryl chloride (1.06 eq.), Et_3N (1.6 eq.), CH_2Cl_2, 0 °C, 0.5 h, 88%; iv) *m*CPBA (1 eq.), CH_2Cl_2, 0 °C , 5 h, ~45-50% (**424**:**429** 83:17)

Treatment of **419** with 1 equivalent of *m*CPBA at 0 °C, gave an inseparable mixture of **424**:**429** (83:17) after recrystallization from hot ethanol. Heating

this mixture with 1,3-butadiene **291** in a sealed tube gave nitro olefin **415** and cyclic sulfone **430** in 34% and 95% yield respectively (Scheme 5.33).

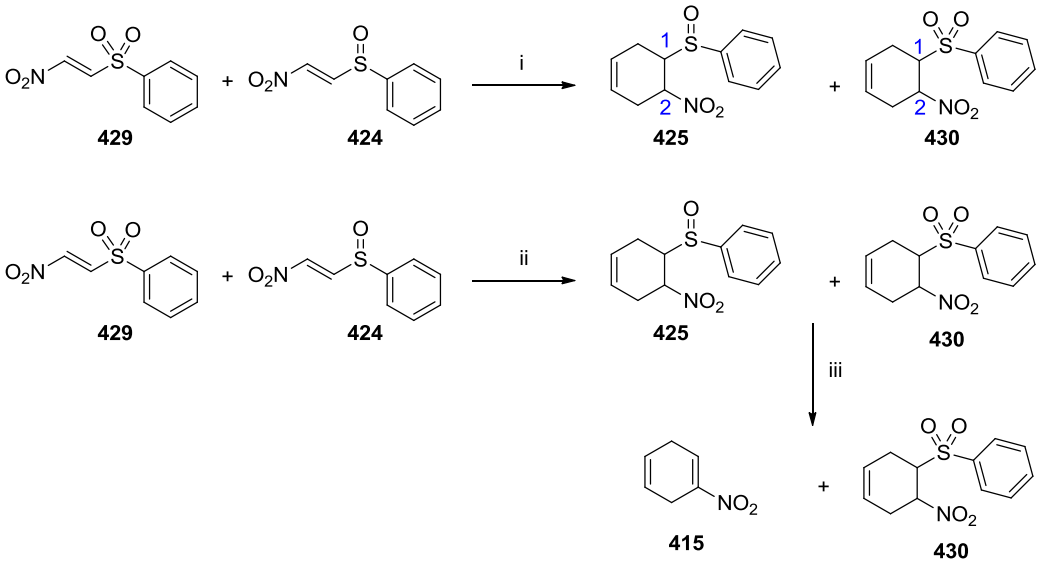


Scheme 5.33. Diels-Alder cycloaddition. Reagents and conditions: i) 83:17 mixture of **424**:**429** (1 eq.), 1,3-butadiene **291** (6 eq.), toluene, 110 °C, sealed tube, 1.75 h, **415** = 34%, **430** = 95%.

The structures of sulfones **429** and **430** were confirmed by comparison with literature.[176,178] When 1 equivalent of *m*CPBA was used, an ~80:20 **424**:**429** ratio was regularly achieved. Enrichment of **424** (95:5 **424**:**429**) was achieved by running the reaction with <1 equivalent of *m*CPBA and stopping the reaction at low conversion. The ratio of **424**:**429** was found to decrease when the solid sample was recrystallized from hot ethanol or heated in toluene in the absence of 1,3-butadiene. In addition a volatile yellow oil was observed when sulfoxide **424** in ethanol, was concentrated on a rotary evaporator at 40 °C under reduced pressure. These observations suggest that sulfoxide **424** suffers from thermal instability and elimination of sulfenic acid from **424** prior to undergoing cycloaddition may account for the low yield of nitro olefin **415** obtained.

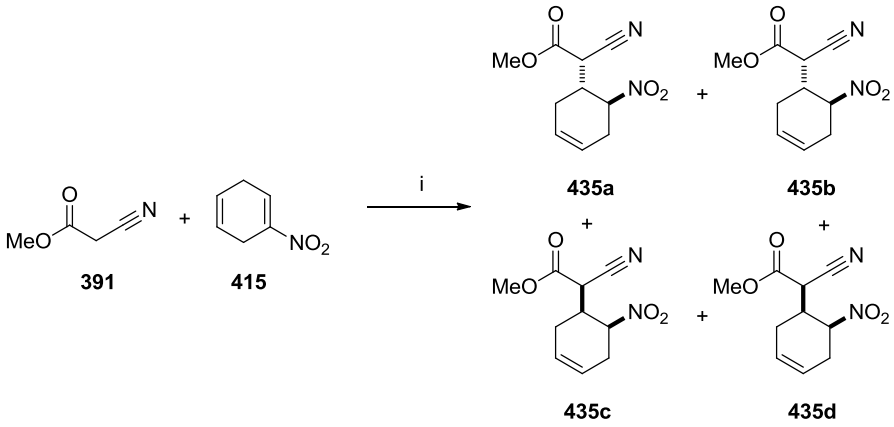
Attempts to improve the yield of nitro olefin **415** by carrying out the Diels-Alder cycloaddition at lower temperature followed by sulfenic acid elimination from the presumably more stable cyclic adduct **425** at elevated temperature showed some promise. At ambient temperature the more electron deficient sulfone dienophile **429** underwent the cycloaddition with modest conversion. Cyclic sulfoxide **425** was not formed. **425** and **430** were easily identified from their H-1 and H-2 chemical shifts (4.11 and 5.05 ppm respectively for **430**)

and (3.35 and 4.98 ppm respectively for **425**) (Scheme 5.34). At 60 °C partial conversion of sulfoxide **424** was observed and a mixture of **424**:**425**:**430** was obtained after column chromatography. Heating this complex mixture at 110 °C for 2 h resulted in complete conversion of **425** with the ratio of nitro olefin **415** to cyclic sulfone **430** only slightly diminished from the ratio of **425** to **430** initially present.



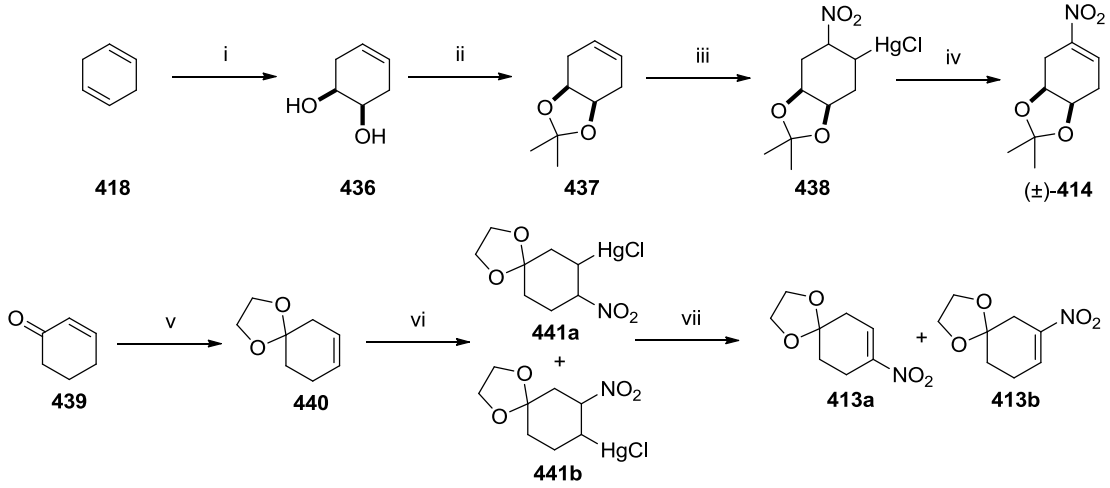
Scheme 5.34. Diels Alder cycloaddition at reduced temperature. Reagents and conditions: i) **429**:**424** 13:87 (1 eq.), 1,3-butadiene **291** (3 eq.), toluene, RT, 3 h, quant., **429**:**424**:**425**:**430** 4:90:0:6); ii) **429**:**430** 13:87 (1 eq.),1,3-butadiene **291** (5 eq.), toluene, 60 °C, 2 h, 52% mass return, (**429**:**424**:**425**:**430** 0:52:19:29); iii) toluene, 110 °C, 2 h, (**424**:**425**:**430**:**415** 49:0:36:15) crude dr.

Despite these initial positive findings, no further development of the synthesis of nitro olefin **415** was attempted. The conjugate addition of pro-nucleophile **391** to **415,** pleasingly, was found to be possible, with Michael adduct **435** isolated as a complex mixture of diastereomers (**a**-**d**), without migration of the nitro olefin alkene (Scheme 5.35), however as a result of the poor yield of this transformation and the problematic synthesis of nitro olefin **415** alternative strategies were explored.



Scheme 5.35. Michael addition of **391** to nitro olefin **415**. Reagents and conditions: i) Catalyst **88** (20 mol%), toluene, RT, 48 h, 29%, (**435a**:**435b**: **435c**:**435d** 1.0:0.44:0.09:0.09 dr).

Nitro olefins **413** and **414** were synthesized in 2 and 4 steps respectively from commercially available starting materials (Scheme 5.36). Dihydroxylation of 1,4-cyclohexadiene **418** followed by acetonide protection gave **437**. Ketal protection of 2-cyclohexenone **439** accompanied by isomerisation of the double bond afforded key intermediate **440**.[179] Initial efforts to convert **437** and **440** to the desired nitro olefins using several documented procedures,[168] were unsuccessful and starting material was recovered in all cases. Only when Corey's nitro-mercuration/de-mercuration strategy was used were both nitro olefins isolated.[180,181]



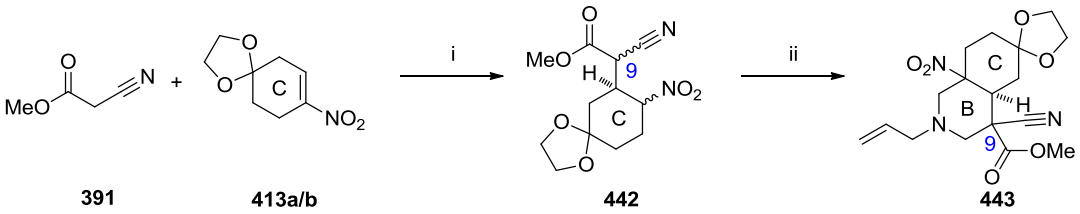
Scheme 5.36. Synthesis of nitro olefins **413** and **414**. Reagents and conditions: i) $K_2OsO_4.2H_2O$ (0.15 mol%), NMO (1 eq.), acetone:H_2O (4:1), RT, 24 h, 82%; ii) 2,2-dimethoxypropane (1.3 eq.), *p*TsOH

(0.02 eq), toluene, reflux, 7.5 h, 89%; iii) $HgCl_2$ (1 eq.), $NaNO_2$ (2 eq.), H_2O, RT, 24 h, 64%; iv) NaOH (1 eq.), CH_2Cl_2:H_2O (4:1), RT, 20 min, 70%; v) $HO(CH_2)_2OH$ (3.7 eq.), *p*TsOH (0.1 eq.), toluene, reflux, 24 h, 61%; vi) $HgCl_2$ (1 eq.), $NaNO_2$ (2 eq.), H_2O, RT, 15 h, 71%; NaOH (1 eq.), CH_2Cl_2:H_2O (4:1), RT, 20 min, 60% (**413a**:**413b** 77:23).

While this nitro-mercuration procedure was highly undesirable due to the high toxicity of the reagents used and nitromercurial intermediates formed, it allowed further reactivity studies to be conducted. Nitromercurial intermediates **438** and **441a/b** precipitated from the aqueous reaction medium and were easily removed by filtration, thus limiting risks. For safety reasons, no analytical data was collected for these compounds which were used directly in the de-mercuration step. A thick silvery/grey mercury precipitate was observed almost immediately on addition of NaOH, which was easily removed by filtration on celite, prior to safe disposal.

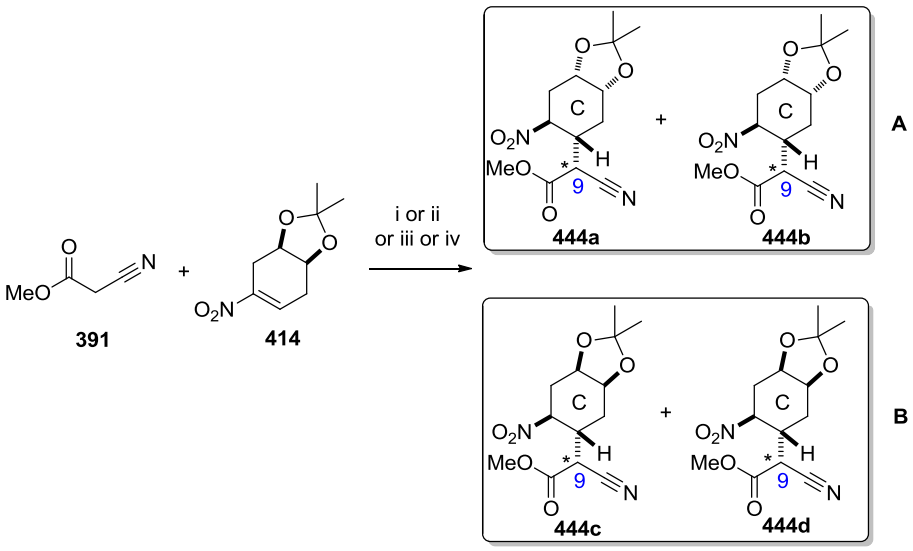
5.12. Michael Addition with Functionalized Nitro Olefins

Nitro olefin **413a/b**, isolated as an inseparable 77:23 mixture of regioisomers, was quickly eliminated as a useful madangamine building block. Despite the conjugate addition using catalyst **88** proceeding in excellent overall yield, with impressive reactivity at low catalyst loading (4 mol%), giving a complex mixture of diastereomers (**442a**:**442b**:**442c**:**442d** 1.0:0.7:0.5:0.4 arising from nitro olefin **413a** + minor impurities presumed to be diastereomers arising from nitro olefin **413b**), the nitro-Mannich/Mannich cascade performed poorly (Scheme 5.37). Only a single compound **443** isolated in 21% yield (~85-90% purity) could be identified as the desired cyclisation product. The other isolated fractions consisted of complex mixtures of compounds. The relative stereochemistry of **443** was not unambiguously determined.



Scheme 5.37. Trial studies using nitro olefin **413a**:**413b** (77:23). Reagents and conditions: i) Catalyst **88** (4 mol%), toluene, RT, 48 h, 98% (1.0:0.7:0.5:0.4 dr of major regioisomer diastereomers); ii) Allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, RT, 20 h, 21%.

Nitro olefin **414** by contrast was found to be an excellent building block with which to construct the madangamine ABC tricyclic core. The conjugate addition of methyl cyanoacetate **391** to nitro olefin **414** using KO^{t}Bu as base proceeded in good yield giving only four, of eight possible diastereomers (two sets of separable diastereomers (**A**/**B**), each containing two inseparable diastereomers) (Scheme 5.38).



Scheme 5.38. Michael addition of **391** to **414**. Reagents and conditions: i) **391** (1.2 eq.), **414** (1 eq.), KO^{t}Bu (1 eq.), THF:^{t}BuOH (30:1), RT, 15 h, (**A:B** 1:3.8 crude dr), **A** = 14%, **B** = 67%; ii) catalyst **88** (10 mol%), toluene, RT, 15 h, (**A:B** 1:1.3 crude dr), **A** = 32%, **B** = 40%; iii) catalyst **122** (10 mol%), toluene, RT, 24 h, (**A:B** 1:1.9 crude dr), **A** = 16%, **B** = 28%; iv) catalyst **124** (10 mol%), toluene, RT, 24 h, (**A:B** 1:1.4 crude dr), **1** = 31%, **2** = 43%.

These diastereomer sets resulted from addition of pro-nucleophile **391** to the same (**A**) or opposite (**B**) face of the nitro olefin as the acetonide protected diol. The ratio of diastereomer using KO^{t}Bu was found to be 1:3.8 in favour of (**B**), resulting from addition of the nucleophile to the least sterically hindered

face of nitro olefin **414** (Figure 5.1). The isolated mass of diastereomers **A**:**B** was consistently in the range 1:(3.8-4.6). Interestingly the use bifunctional urea catalyst **88**, thiourea catalyst **122** and pseudo-enantiomer urea catalyst **124** all resulted in diminished selectivity for diastereomer set (**B**).

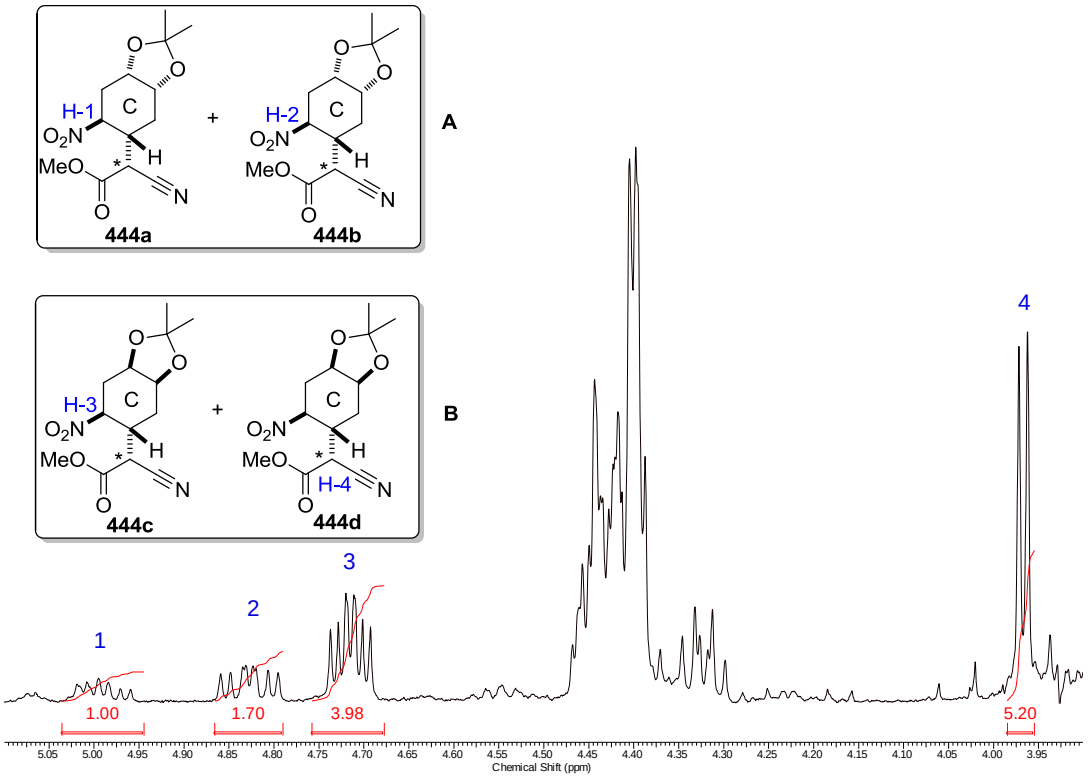
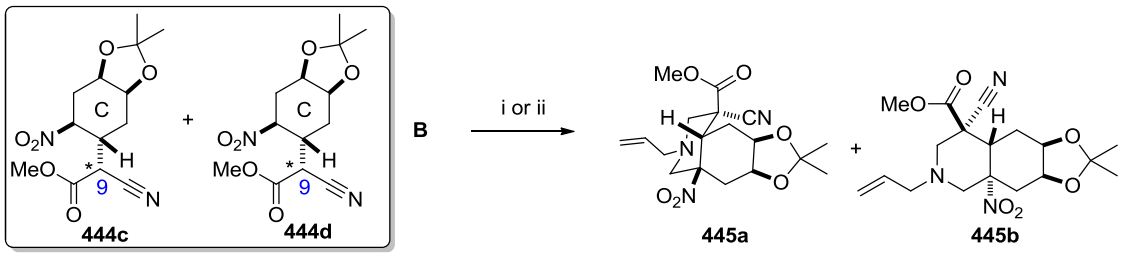


Figure 5.14. Crude diastereomeric ratio of Michael addition using KO^{t}Bu

The diastereomers within (**A**) and (**B**) were again proposed to be epimeric at the C-9 position. The relative stereochemistry at this position was not determined and **444a/b** and **444c/d** are arbitrary assignments. Epimerization between these diastereomers was possible in $CDCl_3$, illustrated by the fact that an enriched sample of diastereomer **444d**, obtained by trituration of (**B**) with methanol, epimerized from a (**444c**:**444d** 1:20) mixture to a (**444c**:**444d** 3:5) mixture when kept in solution overnight in $CDCl_3$.

The relative stereochemistry of diastereomer sets (**A**) and (**B**) was only conclusively established from the products obtained in the subsequent nitro-Mannich/Mannich cyclisation reactions.

When diastereomers (**B**) were subjected to our developed nitro-Mannich/Mannich reaction conditions using 20 equivalents of formaldehyde, two new products **445a** and **445b** were isolated in 71% combined yield (645 mg scale) after 6.5 h reaction time. Pleasingly on larger scale [1g of (**B**)] these yields were essentially maintained (62% combined yield). Yields and ratios of **445a**:**445b** were generally consistent between reactions for this transformation with the desired *cis* diastereomer **445a** again being the major product isolated. Complete selectivity was again achieved at the C-9 quaternary stereocentre.



Scheme 5.39. Nitro-Mannich/Mannich cyclisation. Reagents and conditions: i) **B** (**444c**:**444d** 1.0:1.4), allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, reflux, 6 h, **445a**: 43%, **445b**: 28%; ii) **B** (**444c**:**444d** 1.3:1.0), allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, reflux, 6 h, **445a**: 41%, **445b**: 21%.

The structures of **445a** and **445b** were both confirmed by single crystal X-ray analysis (Figure 5.15).

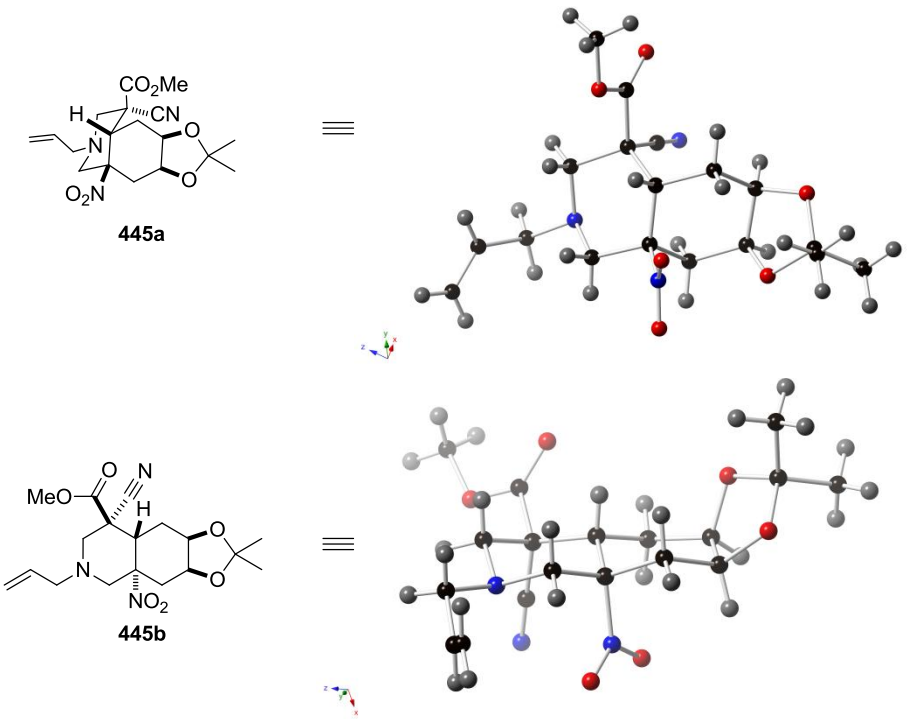
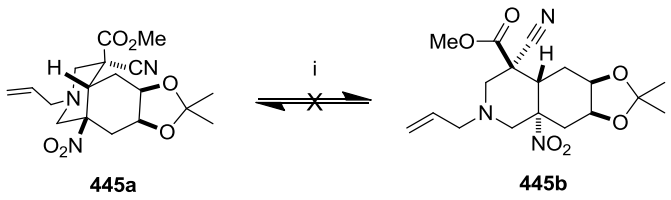


Figure 5.15. Stick and ball representation of the X-ray crystal structure of **445a** and **445b**

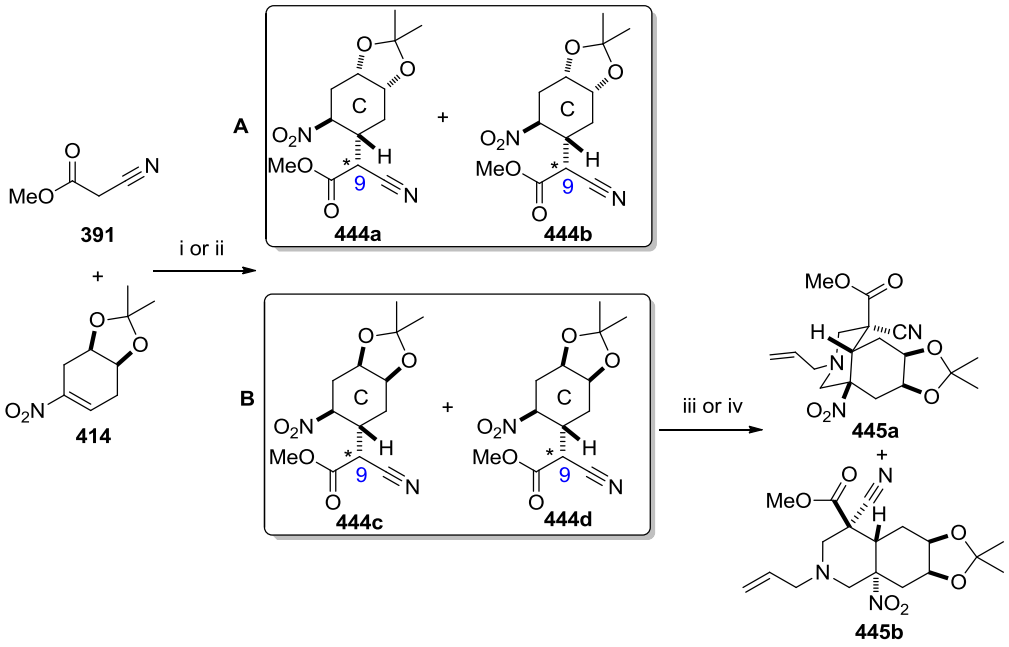
Re-subjecting isolated diastereomers **445a** and **445b** independently, to the nitro-Mannich/Mannich cyclisation conditions did not yield any traces of the other diastereomer by ^{1}H NMR analysis (Scheme 5.40). This provided supporting evidence for the proposed irreversibility of the cyclisation mechanism based on similar results observed with *cis* and *trans* diastereomers **407a** and **407b** (Scheme 5.29).



Scheme 5.40. Irreversibility of nitro-Mannich Mannich cyclisation. Reagents and conditions: i) Allylamine (1.2 eq.), formaldehyde (20.0 eq.), MeOH, reflux. 24 h.

5.13. Enantioselective Michael Addition Studies

Enantioselectivity studies in the Michael addition/cyclisation sequence were carried out using catalyst **122** and catalyst **124**, with two equivalents of nitro olefin **414** (Scheme 5.41).

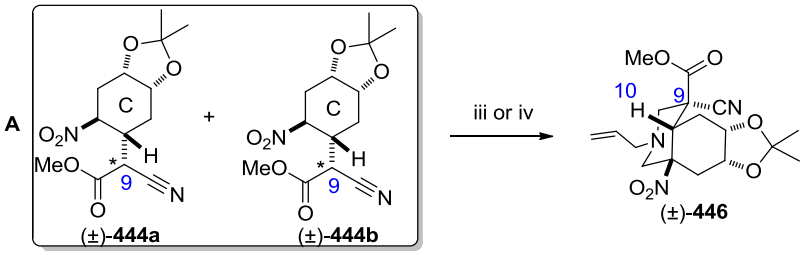


Scheme 5.41. Enantioselectivity studies. Reagents and conditions: i) Catalyst **122** (10 mol%), toluene, RT, 48 h, (**A:B** 1:2.2 crude dr), **A**: 17%, **B**: 37%, recovered **414**: 40%, 16% ee; ii) Catalyst **124** (10 mol%), toluene, RT, 48 h, (**A:B** 1:1.6 crude dr), **A**: 27%, **B**: 44%, recovered **414**: 37%, 14% ee; iii) **B** (from i), allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, reflux, 6 h, **445a**: 19%, 27% ee, **445b**: 15%, 33% ee; iv) **B** (from ii), allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, reflux, 6 h, **445a**: 28%, 29% ee, **445b** = 19%, 31% ee.

Pleasingly enantioenriched **445a** could be accessed (27% ee, catalyst **122** and 29% ee, catalyst **124**), with opposite enantiomers favoured by the pseudo-enantiomeric catalysts. Despite only moderate enantioselectivity being achieved this result nicely exemplified the possibility of accessing both enantiomers of the madangamines by a simple catalyst switch which was of particular significance given that the absolute stereochemistry of the madangamines is unknown. In these enantioselectivity studies, the yields of the cyclisation reactions were reduced as a consequence of the reactions being carried out on small scale (20-30 mg). All subsequent synthesis development was carried out using racemic material due to the higher yields of diastereomer set (**B**) obtained using KO^{t}Bu.

5.14. Cyclisation of Diastereomer set (A)

Interestingly when diastereomers (**A**) were subjected to our developed nitro-Mannich/Mannich reaction conditions, only a single diastereomer **446** was isolated in good yields (55%-67%) (Scheme 5.42). This was assigned as having a *cis* relationship at the B/C-ring junction by its characteristic chemical shift values for H-10. The chemical shifts for this proton in **446** and **445a**, are 3.47 ppm and 3.40 ppm respectively. In *trans* diastereomer **445b**, this proton, now diaxial to the nitro group, is found at a considerably higher field (2.62 ppm).



Scheme 5.42. Nitro-Mannich/Mannich cyclisation. Reagents and conditions: i) **1** (**444a**:**444b** 1.0:1.8), allylamine (1.2 eq.), formaldehyde (20 eq.), MeOH, reflux, 6 h, 67% (**446**).

No evidence of the *trans* diastereomer was observed in this cyclisation reaction in this series.

5.15. Studies Towards the Diazatricyclic Core of the Madangamines

Diastereomer **445a** (Scheme 5.39) was isolated as the major product from these reactions, in good yield considering the complexity introduced to the system in just two transformations. This was particularly pleasing as **445a** had the required relative stereochemistry already in place to allow the A-ring closure to be achieved *via* an S_N2 process (Figure 5.16). *Trans* diastereomer **445b** was potentially useful if denitration under reductive radical conditions gave the *cis* product. Diastereomer **446** would require inversion of the

hydroxy group at C-2 before any cyclisation would occur, but was still potentially useful.

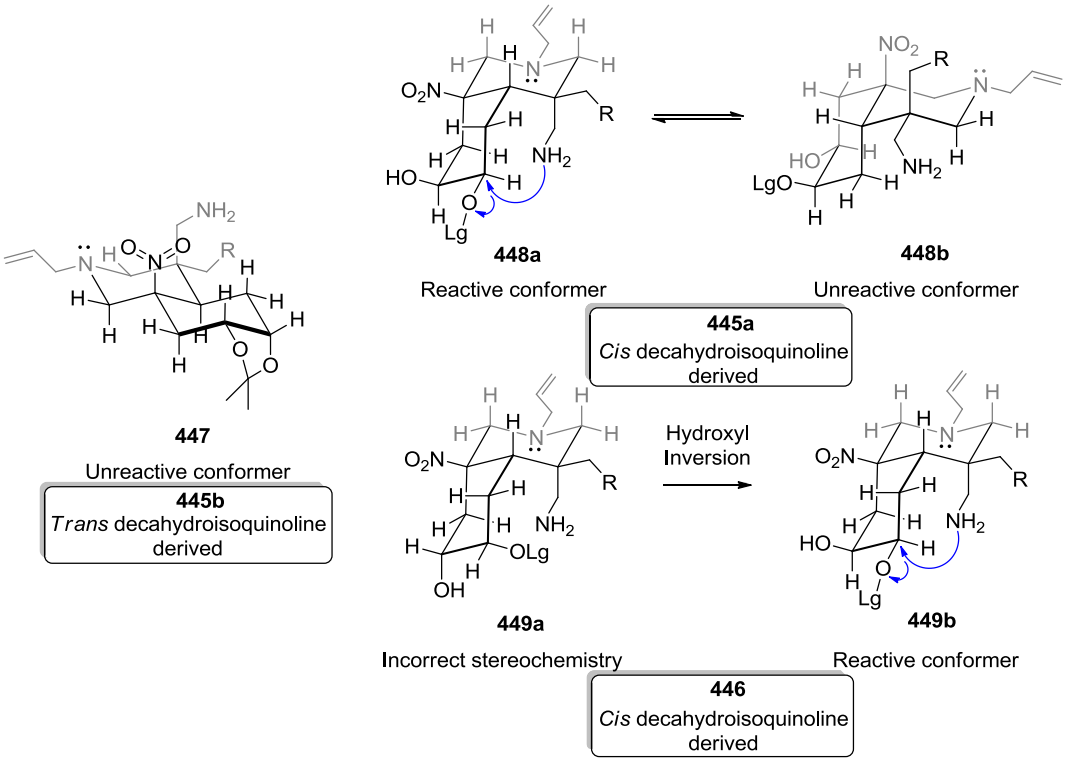
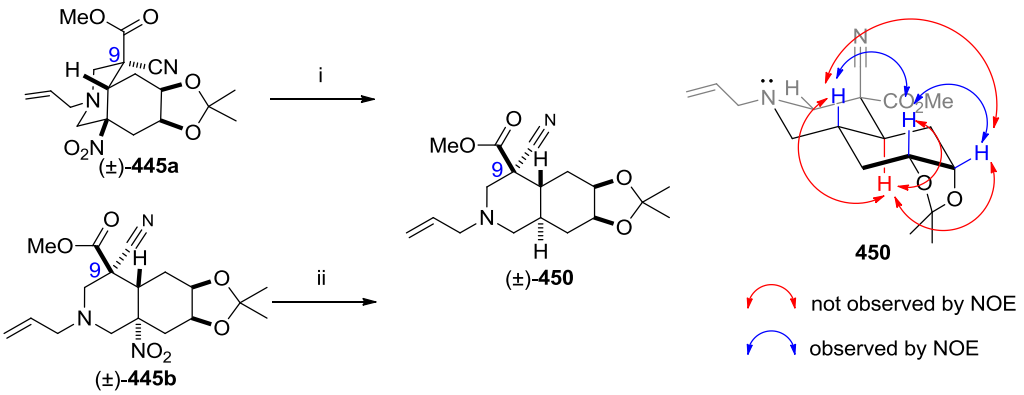


Figure 5.16. Potential synthesis of A-ring of the madangamine alkaloids

Reductive denitration of **445a** and **445b** proceeded cleanly giving the same single diastereomer **450** in a similar fashion to the reductive denitration of **407a** and **407b**. Good separation of the ^{1}H signals of **450** allowed NOE data to be collected, however this data indicated that exclusive formation of the undesired *trans* isomer had occurred (Scheme 5.43).



Scheme 5.43. Denitration of **445a** and **445b**. Reagents and conditions: i) Bu_3SnH (5 eq.), AIBN (0.2 eq.), toluene, reflux, 2.5 h, 77%; ii) Bu_3SnH (5 eq.), AIBN (0.2 eq.), toluene, reflux, 2.5 h, 83%.

Undeterred by this result, it was decided that a late stage nitro removal with the ABC diazatricyclic core of the madangamines in place, would promote formation of the required *cis* ring junction due to steric effects and high strain energy of the tricyclic *trans* ring junction substrate **453** (Figure 5.17).

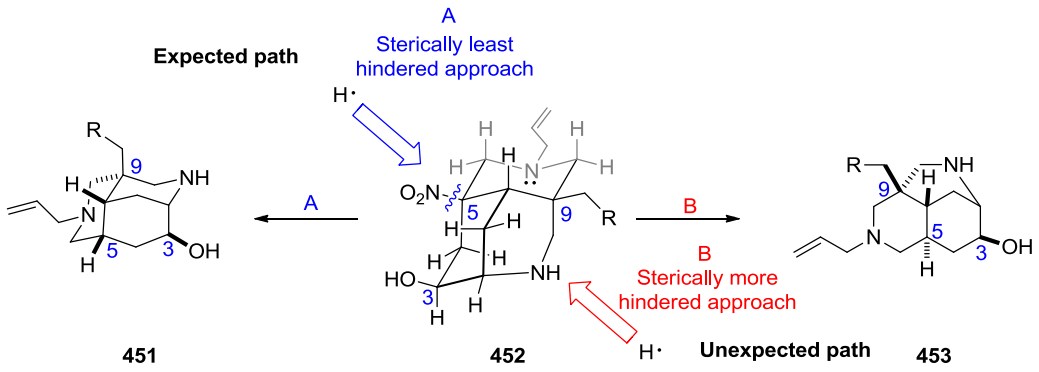


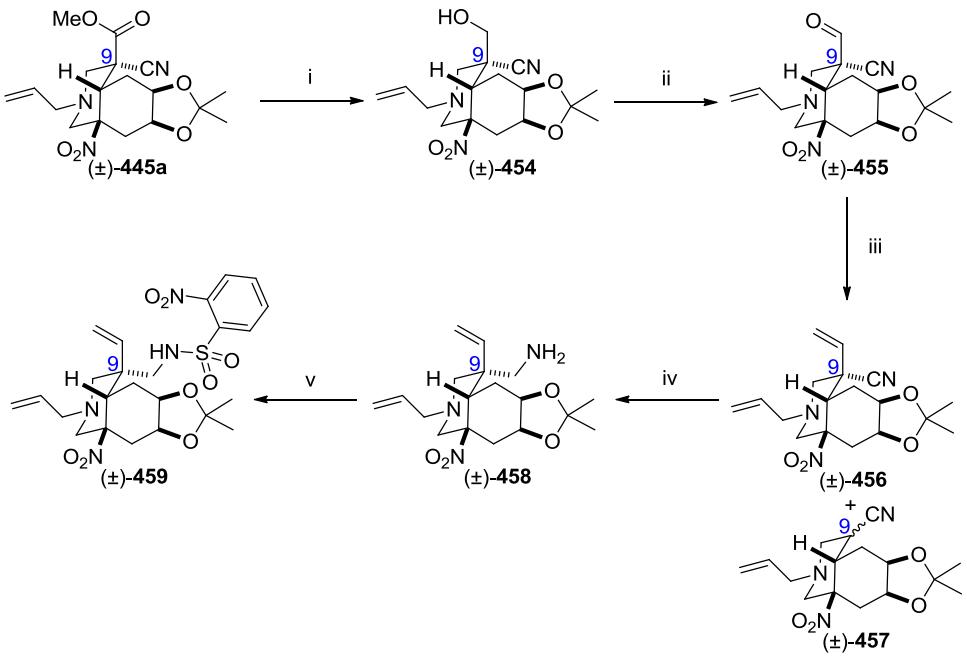
Figure 5.17. Possible pathways in denitration of diazatricyclic core **452**

A direct consequence of this proposal was that the minor *trans* adduct **445b** would be rendered synthetically useless, unless epimerization to **445a** was possible. It had already been established that re-subjecting **445b** to the nitro-Mannich/Mannich cyclisation conditions did not result in epimerization to **445a** (Scheme 5.40). No reactions conditions were subsequently found which could promote this transformation.

In order to establish if the desired *cis* B/C ring junction could be attained using this strategy, synthesis of the diazatricyclic core of the madangamines had to first be achieved using diastereomer **445a**.

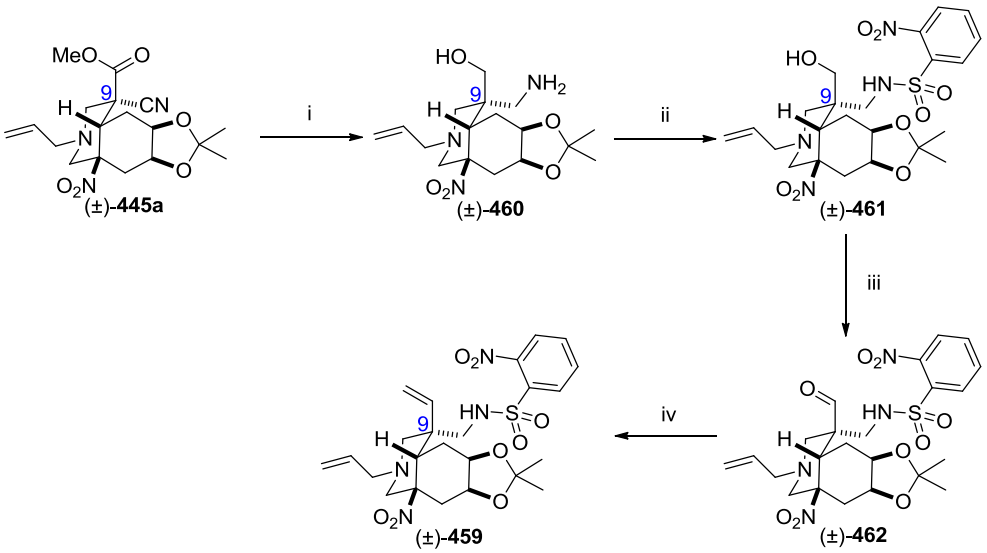
5.16. Synthesis of Diazatricyclic Core

Cis adduct **445a** was initially converted into cyclisation precursor **459** in 5 steps (Scheme 5.44). Chemoselective reduction of the ester in **445a** with $NaBH_4$ proceeded in good yield. This was followed by an IBX oxidation/Wittig olefination sequence to install a simple alkene model functional handle. The overall yield for this transformation was poor, with alcohol **454** returned in 10% yield due to incomplete oxidation, and more significantly deformylation resulting in the formation of **457** as a mixture of diastereomers, with diene **456** isolated in only 22% yield over the two steps. Despite this low yield, protected amine **459** could be isolated by an alane reduction/nosylation sequence, inspired by the work of Bonjoch,[157] which left the nitro group untouched.



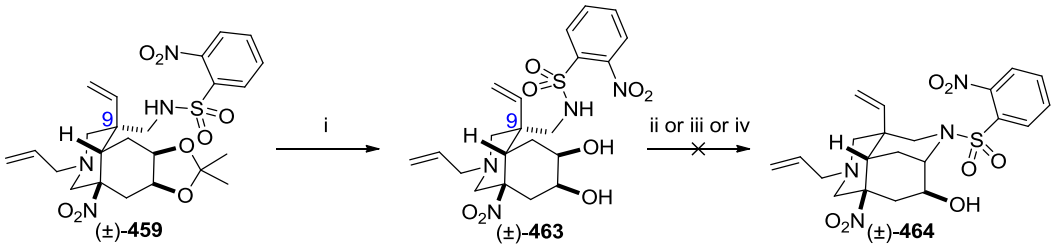
Scheme 5.44. Synthesis of cyclisation precursor **459**. Reagents and conditions: i) $NaBH_4$ (10 eq.), THF:H_2O (17:1), 50 ^{o}C, 3 h, 71%; ii) IBX (3 eq.), DMSO, RT, 20 h; iii) KO^{t}Bu (4.8 eq.), $MePPh_3Br$ (6 eq.), toluene:THF (1:1), RT, 0.5 h, **456** = 22% (over 2 steps), **457** = 39% (1:0.44 dr), **454** = 10% (recovered yield); iv) $AlCl_3$ (1 eq.), $LiAlH_4$ (3 eq.), THF, RT, 5 h; v) 2-Nitrobenzenesulfonyl chloride (1.1 eq.), Et_3N (1 eq.), CH_2Cl_2, RT, 6 h, 85% (over 2 steps).

A 13% overall yield for the transformation of **445a** to **459**, was insufficient to allow any significant studies on the cyclisation of **459** to be undertaken. Simple adjustment of the order of reactions allowed an improved 4 step route to be developed, yielding **459** in 67% overall yield from **445a** (Scheme 5.45). A double ester/nitrile reduction with alane, followed by selective nosylation of the primary amine gave **461**. An improved oxidation procedure using Dess-Martin periodinane, gave aldehyde **462** in 92% isolated yield. When Dess-Martin periodinane was used as oxidant, purification of the aldehyde, to remove all acidic residues was essential to achieving reactivity in the subsequent Wittig olefination, which proceeded in excellent yield, with no evidence of deformylation.



Scheme 5.45. Modified synthesis of cyclisation precursor **459**. Reagents and conditions: i) $AlCl_3$ (2 eq.), $LiAlH_4$ (6 eq.), THF, RT, 5 h; ii) 2-Nitrobenzenesulfonyl chloride (1 eq.), Et_3N (1 eq.), CH_2Cl_2, RT, 4 h, 78% (over 2 steps); iii) Dess-Martin periodinane (1.05 eq.), CH_2Cl_2, 0 °C, 3.5 h, 92%; iv) KO^tBu (4.8 eq.), $MePPh_3Br$ (6 eq.), toluene:THF (1:1), RT, 0.5 h, 94%.

Initial cyclisation attempts using a Mitsunobu procedure on diol **463**, accessed by removal of the acetonide protecting group under acidic conditions, were unsuccessful with starting material recovered in all cases (Scheme 5.46).

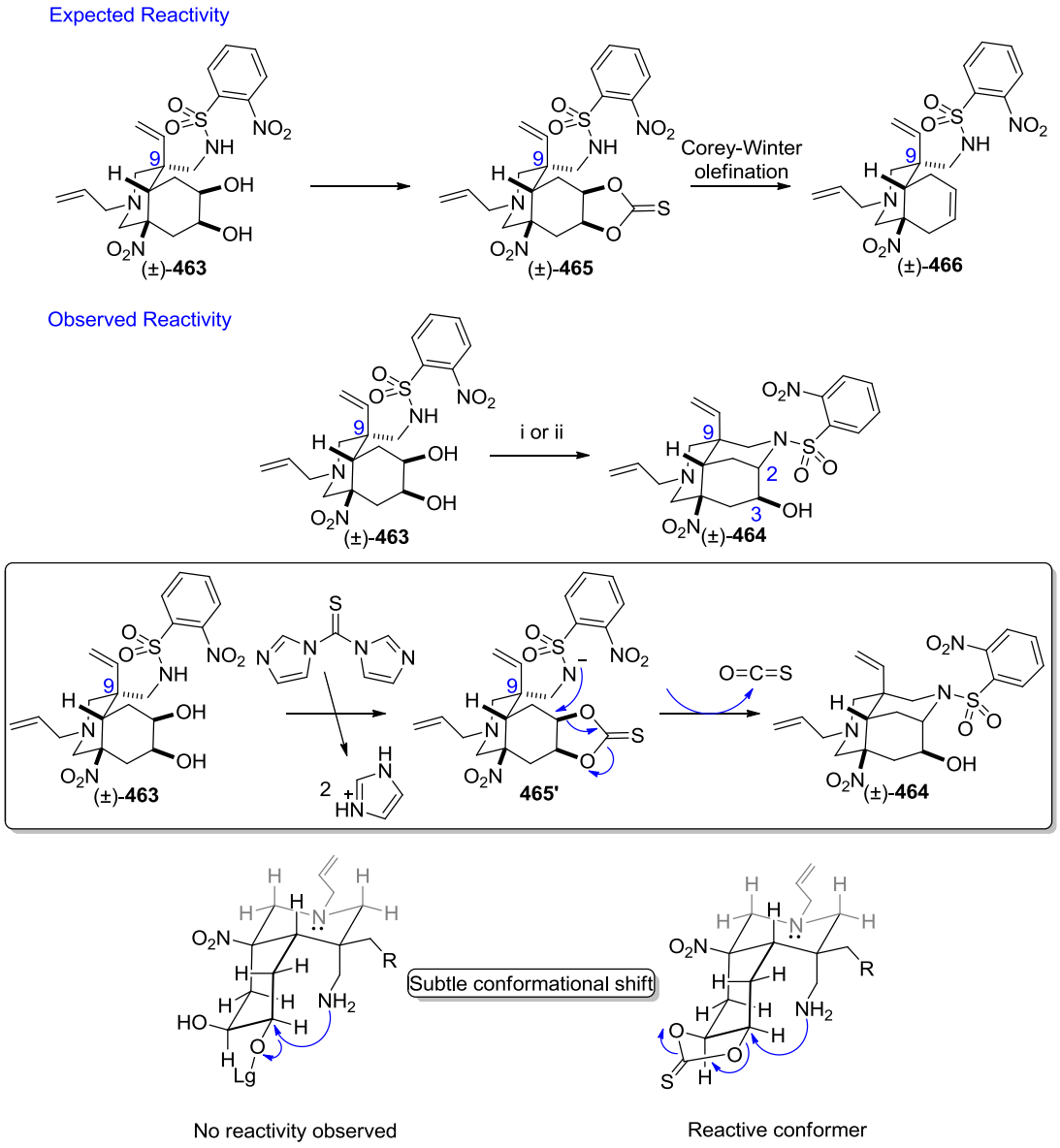


Scheme 5.46. Mitsunobu cyclisation. Reagents and conditions: i) *p*TsOH (1.05 eq), MeOH, reflux, 7.5 h, 90%; ii) Diisopropyl azodicarboxylate (1.05 eq.), PPh_3 (1.05 eq.), benzene, RT, 20 h; iii) Diethyl azodicarboxylate (1.3 eq.), PPh_3 (1.3 eq.), THF, RT, 20 h; iv) Diisopropyl azodicarboxylate (2.0 eq.), PPh_3 (2.0 eq.), THF, RT, 20 h.

Attempts to activate the hydroxyl groups of **463** by bis-mesylation or tosylation, with concomitant cyclisation under basic reaction conditions resulted in complex mixtures of products, with no evidence of cyclisation. This apparent, and completely unexpected, lack of reactivity of diol **463** prompted a new cyclisation strategy. It was anticipated that formation of

dioxolanethione intermediate **465** followed by a Corey-Winter olefination[182] would yield alkene **466**, which would be primed to undergo cyclisation by the aminomercuration approach adopted by Weinreb (Scheme 5.47).[154] Dioxolanethione **465** was not isolated from the reaction mixture; however cyclised product **464** was unexpectedly isolated in 20% yield (Scheme 5.47). A salient feature of the ^{13}C NMR spectrum of **464** was an upfield shift of C-2 (51.1 ppm) relative to C-3 (67.3 ppm). A possible mechanism for this transformation is proposed, with the generated imidazolide acting as a base to promote the cyclisation reaction with subsequent loss of carbonyl sulfide gas. Introduction of additional base (Et_3N) to the reaction resulted in improved isolated yield of **464**, however only limited optimisation of this reaction was carried out.

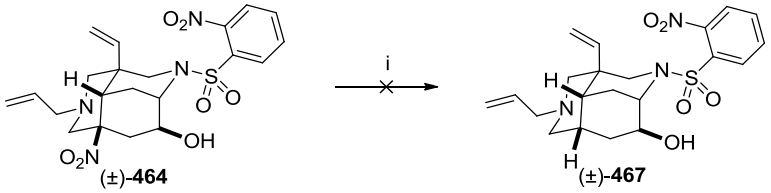
It is possible that this unexpected cyclisation arises due to subtle changes in conformation between substrates **465** and **463** (Scheme 5.47). The 6,6',5-ring system in **465**, may ease the approach of the nosyl protected amine to the C−O anti-bonding orbital, relative to the 6,6'-ring system with activated hydroxyl substituents, obtained from **463** *via* a Mitsunobu reaction.



Scheme 5.47. Modified cyclisation approach. Reagents and conditions: i) 1,1'-Thiocarbonyldiimidazole (2 eq.), toluene, reflux, 6 h, 20%; ii) 1,1-Thiocarbonyldiimidazole (1.05 eq.), Et_3N (2 eq.), toluene, reflux, 6 h, 35%.

The formation of tricycle **464** was pleasing; however the low yield of this late stage intermediate provided limited material with which to carry out studies into the key denitration step. Initial trials met with unsuccessful results. When **464** was subjected to the standard reductive radical conditions, several products were observed by TLC analysis (Scheme 5.48). The ^{1}H NMR spectra of all isolated fractions were complex, containing multiple products none of which were successfully identified. It is possible that the nitro group

present in the nosyl protecting group of **464** may have an adverse effect on the denitration reaction, making it unsuitable as a substrate with which to trial this reaction.

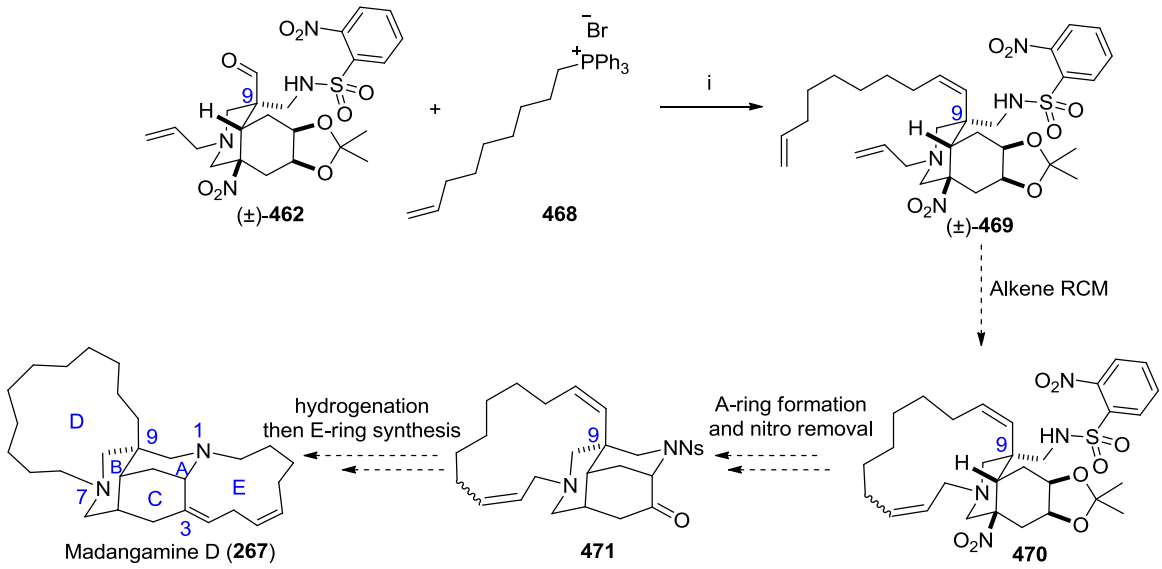


Scheme 5.48. Attempted denitration. Reagents and conditions: i) Bu_3SnH (5.0 eq.), AIBN (0.2 eq.), toluene, reflux, 2.5 h.

5.17. Additional Synthesis Studies

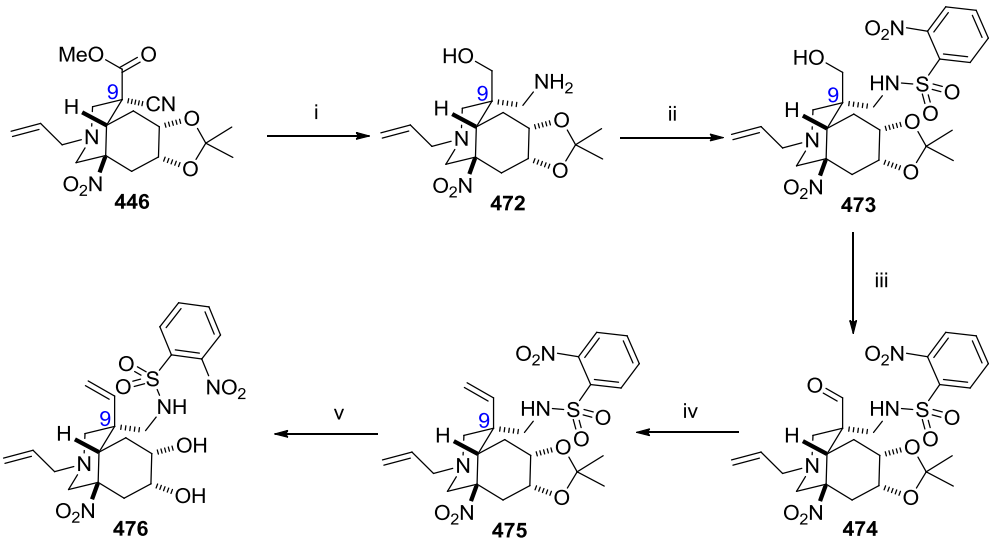
Tricycle **464** represents the most advanced intermediate prepared in the synthetic efforts towards the madangamine alkaloids. Several other studies have been carried out to probe potentially useful reactivity.

Using Wittig salt **468**, prepared in 3 steps from commercially available starting material following literature procedures, triene **469** containing an extended alkyl chain could be synthesized (Scheme 5.49).[183,184] A subsequent alkene RCM and alkene hydrogenation could provide a route with which to construct the Western macrocycle of madangamine D, although poor yields in the unoptimised Wittig olefination limited any additional progress.



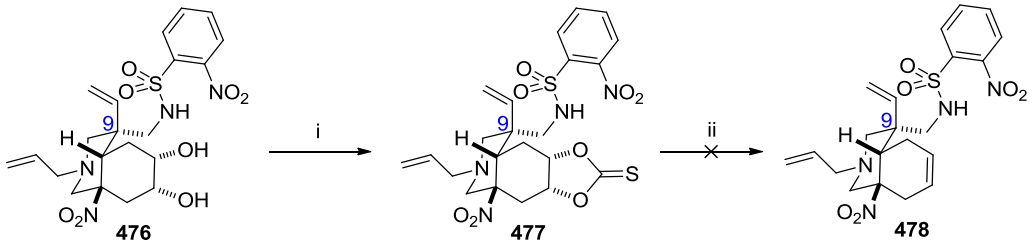
Scheme 5.49. Extended alkyl chain Wittig olefination. Reagents and conditions: i) **468** (6 eq.), KO^{t}Bu (4.77 eq.), toluene:THF (1:1), RT, 1.5 h, 25%.

While synthetic studies focused on the use of diastereomer **445a**, which contained the correct diol stereochemistry for subsequent S_N2 cyclisation to close the A ring, diastereomer **446** could equally be used by inversion of the diol stereochemistry or removal of the diol completely. The latter approach was trialled, with the planned introduction of an alkene moiety *via* a Corey-Winter olefination, in a similar fashion as had been previously attempted with cyclisation precursor **463**. Using the previously developed conditions diol **476** was accessed in 5 steps in 42% overall yield (Scheme 5.50).



Scheme 5.50. Synthesis of diol **476**. Reagents and conditions: i) $AlCl_3$ (2 eq.), $LiAlH_4$ (6 eq.), THF, RT, 5 h; v) 2-Nitrobenzenesulfonyl chloride (1 eq.), Et_3N (1 eq.), CH_2Cl_2, RT, 3 h, 65% (over 2 steps); iii) Dess-Martin periodinane (1.05 eq.) CH_2Cl_2, 0 °C, 3 h, 82%; iv) KO^{t}Bu (4.8 eq.), $MePPh_3Br$ (6 eq.), toluene:THF (1:1), RT, 0.5 h, 89%; v) *p*TsOH (1.05 eq), MeOH, reflux, 5 h, 88%.

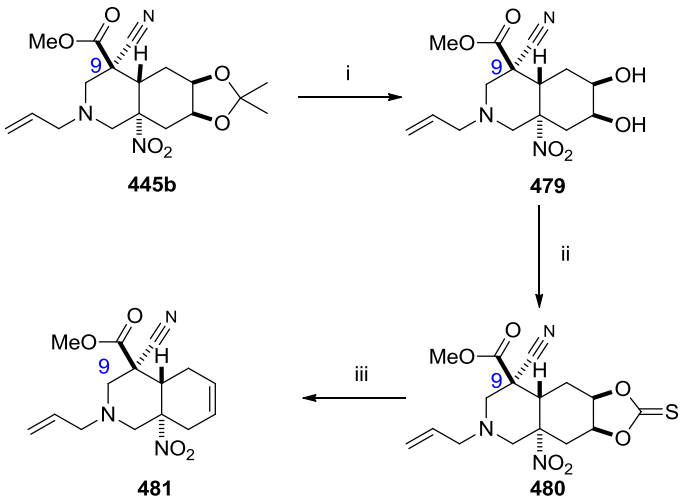
With subsequent cyclisation not possible, dioxolanethione **477** was prepared in good yield from diol **476**. Initial attempts to carry out the Corey-Winter olefination were unsuccessful however, with only decomposition of the starting material observed (Scheme 5.51).



Scheme 5.51. Attempted Corey-Winter olefination. Reagents and conditions: i) 1,1'-Thiocarbonyldiimidazole (3.7 eq.), Et_3N (2 eq.), toluene, reflux, 7 h, 92%; ii) $P(OMe)_3$, reflux, 5 h.

Using a less advanced substrate, *trans* diastereomer **445b**, evidence for the Corey-Winter olefination strategy being successful was achieved (Scheme 5.52). Acetonide deprotection proceeded cleanly and crude diol **479** was treated with 1,1'-thiocarbonyldiimidazole, to give dioxolanethione **480** in acceptable yield. Subsequent treatment with trimethylphosphite at reflux gave bicyclic alkene **481** in good yield. These anomalous results using

substrates **477** and **480** suggest that the nosyl protecting group may again have been responsible for the lack of reactivity observed.



Scheme 5.52. Corey-Winter olefination in *trans* series. Regents and conditions: i) *p*TsOH (1.05 eq.), MeOH, reflux, 6 h, 88% ii) 1,1'-Thiocarbonyldiimidazole (2 eq.), toluene, reflux, 5 h, 45%; iii) $P(OMe)_3$, reflux, 8 h, 79%.

5.18. Summary and Further Work

The key synthetic steps developed in the synthesis of (–)-nakadomarin A (**1**) were applied in an approach to the madangamine alkaloids. Unexpected reactivity, particularly of acidic nitrile containing Michael adducts in the presence of a large excess of formaldehyde resulted in the formation of highly functionalized piperidines through an unprecedented multi-component nitro-Mannich/Mannich cascade pathway. This cyclisation reaction was found to be highly diastereoselctive with excellent stereocontrol at the newly formed quaternary centre.

When cyclic nitro olefins were employed in the Michael addition step, a mixture of *cis*- and *trans*-ring junction bicyclic systems were obtained after cyclisation, with the *cis* diastereomer being the major product. This novel mode of reactivity provided useful synthetic intermediates, which were subsequently transformed into a substrate containing the ABC tricyclic core of the madangamine alkaloids and suitable functionality with which to complete the remaining D and E macrocyclic rings.

Good proof of principle was achieved in the enantioselective nitro olefin Michael addition using bifunctional organocatalysts (27-29% *ee*), with both enantiomers of the madangamines potentially accessible by a simple catalyst switch. 12 linear steps were required to access the most advanced intermediate which compares favourably with the only previous enantioselective route reported (15 linear steps to functionalized tricyclic core).

The preliminary results obtained in this project, enabled a successful application for future funding through a Marie Curie Postdoctoral Fellowship. Several key issues need to be addressed in the future work which will be carried out in this project:

1. Successful denitration must be achieved to yield the required *cis* ring junction at the B/C rings of the madangamines. It is anticipated that removal of the sensitive nosyl protecting group of tricycle **464** will allow this to be achieved using the reported denitration conditions.
2. Improved enantioselectivity of the key nitro olefin Michael addition step is required, either through development of better catalysts or the synthesis of an enantiopure nitro olefin.
3. A strategic plan for the completion of the D and E macrocyclic rings is required. Based on previous reports, the functional handles present in tricycle **464** should be amenable to the synthesis of these remaining rings.

6. Experimental Section

6.1. General Experimental

6.1.1. General Techniques

For reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C for at least 2 h prior to use. Glassware was cooled to ambient temperature under vacuum and a nitrogen or argon atmosphere introduced using a Schlenk manifold. All manipulations involving molybdenum or tungsten complexes were carried out in a glovebox under an argon atmosphere with oxygen levels of <10 ppm.

6.1.2. Solvents and Reagents

The evaporation of bulk solvents ‘under reduced pressure' refers to the use of a Büchi rotary evaporator. THF, Et_2O, CH_2Cl_2, MeCN and toluene were purified by passing through an alumina column (Grubbs still).[185,186] Chlorobenzene was distilled from P_2O_5 under an atmosphere of argon. Et_3N and pyridine were distilled from CaH_2 and stored over KOH. All work-up solvents and commercial reagents were used as supplied without further purification unless otherwise stated. Petroleum ether (PE) refers to the fractions boiling in the range 30-40 °C.

6.1.3. Chromatography

Flash column chromatography was performed on VWR Kieselgel 60 (40-63 μm) silica or Fluka neutral aluminium oxide (alumina) (0.05-0.15 mm) in the isocratic or gradient solvent system stated. All reactions were followed by thin-layer chromatography (TLC) where practical, using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica plates which were visualised

under UV light (250 nm) or by staining with aqueous basic potassium permanganate solutions as appropriate. Enantiomeric excesses (*ee*) were determined using high performance liquid chromatography (HPLC) performed on an agilent 1200 series HPLC system using the conditions specified.

6.1.4. Compound Analysis

Infrared spectroscopy was recorded on a Bruker Tensor 27 FT-IR spectrometer deposited as a thin film, with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). Only diagnostic absorbances are reported.

^{1}H and ^{13}C-NMR spectroscopy was recorded on either a Bruker DPX-300 (300 MHz ^{1}H, 75 MHz ^{13}C), Bruker DPX-400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AV400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AVII 500 (500 MHz ^{1}H, 125 MHz ^{13}C) or Bruker AVIII 700 (700MHz ^{1}H) in the deuterated solvent stated. Chemical shift values (δ) are given in parts per million (ppm) reported relative to the residual protiosolvent peak, downfield from tetramethylsilane. The multiplicity of each signal is designated using the following abbreviations; s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet. DEPT and two-dimensional (COSY, HSQC, HMBC and NOE) NMR techniques were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C-NMR spectra. Coupling patterns and *J* values for ^{1}H NMR are reported as they were observed using the stated spectrometers at the given frequency and not as deemed correct by coupling environment.

Low resolution mass spectrometry was recorded on a Waters LCT premier XE mass spectrometer.

High resolution mass spectrometry was recorded on a Bruker Microtof (ES) mass spectrometer.

Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter; specific rotations ($[\alpha]_D$) are reported in 10^{-1}deg.cm^{-2}.g^{-1}; concentrations (*c*) are quoted in g/100 mL of solution; *D* refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C).

Melting points were obtained using a Leica-Galen III apparatus and remain uncorrected.

Compound naming was carried out in accordance with IUPAC nomenclature using ACD 12 I-Lab service.

X-ray Crystallographic Data was collected on a Nonius Kappa CCD diffractometer and structure refinement and analysis carried out using CRYSTALS software package.

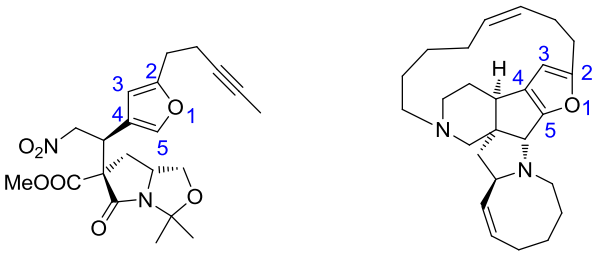
6.1.5. Starting Materials

The following synthetic intermediates are commercially available: furan-3-carbaldehyde **123**, (5*R*)-5(hydroxymethyl)pyrrolidin-2-one, 1-bromobut-2-yne **132**, dimethyl (2-oxopropyl)phosphonate **76**, 2-oxopropane-1,3-diyl diacetate **133**, dimethylsquarate **S4**, 1-[3,5-bis(trifluoromethyl) phenyl]methanamine **S3**, 6-chlorohex-1-yne **148**, formaldehyde (37% solution in water) **144**, prolinol **216**, hex-5-enoyl chloride **S8**, hex-5-en-1-amine **S9**, 1,1,3,3-tetramethoxypropane **380**, methyl cyanoacetate **391**, 1-nitrocyclohexene **367**, dimethyl malonate **359**, malononitrile **386**, cyclohexa-1,4-diene **418**,

butadiene **291**, cyclohex-2-en-1-one **439**, 2-nitroethanol **431**. 9-(deoxy)-epi-amino-cinchonine **S1** was readily synthesized from (+)-cinchonine according to literature procedures.[32,187] Catalyst **124** was prepared by Angel Fuentes.[188] Pro-nucleophiles **365** and **388** were prepared by Filippo Sladojevich

6.1.6. Furan Compound Numbering

NMR data (–)-nakadomarin A and related compounds, the furan moiety has been numbered according to the following system.

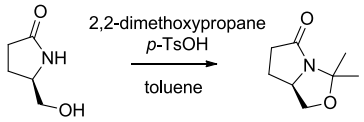


Representative examples of furan numbering

Practical Experimental

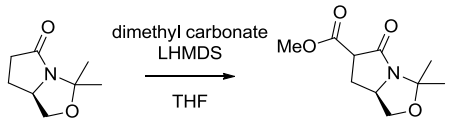
6.2. Chapter 2: Experimental

6.2.1. Synthesis of (7a*R*)-3,3-dimethyltetrahydro-5*H*-pyrrolo[1,2-*c*][1,3]oxazol-5-one



To a stirred suspension of (5*R*)-5-(hydroxymethyl)pyrrolidin-2-one (20.7 g, 0.178 mol) in toluene (200 mL) was added *p*-TsOH (0.600 g, 3.15 mmol) and 2,2-dimethoxypropane (28 mL, 0.23 mol). The reaction was heated at reflux with the azeotropic removal of methanol for 2 h after which a second portion of 2,2-dimethoxypropane (28 mL, 0.23 mol) was added and the reaction continued at reflux with the azeotropic removal of methanol for 2 h. The reaction mixture was then cooled to RT and concentrated *in vacuo* before being purified by flash column chromatography (PE:Et_2O 1:1→Et_2O) to afford the title compound as a crystalline colourless solid (20.8 g, 75%) which gave data in agreement with literature: mp 36-37 °C, lit.[42] 38 °C; $[\alpha]_D^{20}$ = +108.1 (*c* 1.0, $CHCl_3$); lit.[42] $[\alpha]_D^{20}$ = +114.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 4.26 (tt, *J* = 9.1, 6.0 Hz, 1H, C*H*N), 4.08 (dd, *J* = 8.3, 5.7 Hz, 1H, C*H*H'O), 3.45 (dd, *J* = 9.1, 8.5 Hz, 1H, CH*H*'O), 2.80 (ddd, *J* = 16.6, 12.2, 8.5 Hz, 1H, C*H*H'C=O), 2.53 (ddd, *J* = 16.6, 9.2, 1.2 Hz, 1H, CH*H*'C=O), 2.17 (dddd, *J* = 12.5, 8.5, 6.4, 1.2 Hz, 1H, C*H*H'CHN), 1.81 - 1.71 (m, 1H, CH*H*'CHN), 1.67 (s, 3H, CH_3), 1.46 (s, 3H, CH_3).

6.2.2. Synthesis of methyl (7a*R*)-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate 94

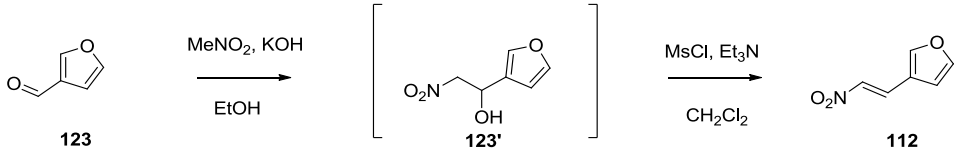


94

A solution of (7a*R*)-3,3-dimethyltetrahydro-5*H*-pyrrolo[1,2-*c*]oxazol-5-one (9.20 g, 59.3 mmol) and dimethyl carbonate (6.40 g, 71.0 mmol) in THF (214 mL) was added dropwise over 50 min to LHMDS (1 M solution in THF) (119 mL, 119 mmol) cooled to -78 °C. The mixture was stirred at -78 °C for 0.5 h before being slowly warmed to 0 °C over 3 h. Glacial acetic acid (17.0 mL, 296 mmol) was added dropwise at 0 °C, followed by addition of Et_2O (225 mL). The resulting mixture was stirred at RT for 10 min before being concentrated *in vacuo* to give an off white paste. Purification by flash column chromatography (PE:Et_2O 1:1→Et_2O) gave the title compound **94** as a colourless oil (2.3:1 mixture of diastereoisomers), which epimerized upon crystallization with complete conversion to a single diastereoisomer as a colourless solid (9.3 g, 74%): mp 73-74 °C lit.[34] mp 85-87 °C; $[\alpha]_D^{24} = -55.9$ (*c* 0.5, $CHCl_3$); lit.[34] $[\alpha]_D^{20} = -157.3$ (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2986 (C-H), 2953 (C-H), 1741 (C=O), 1699 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 4.22 - 4.13 (m, 1H, C*H*N), 4.10 (dd, *J* = 8.1, 5.8 Hz, 1H, C*H*H'O), 3.83 (dd, *J* = 11.9, 8.1 Hz, 1H, C*H*C=O), 3.77 (s, 3H, OCH_3), 3.58 - 3.50 (m, 1H, CH*H*'O), 2.41 - 2.32 (m, 1H, C*H*H'CHN), 2.29 - 2.18 (m, 1H, CH*H*'CHN), 1.64 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.7 (*C*=O), 166.1 (*C*=O), 91.7 (N*C*$(CH_3)_2$O), 69.7 (*C*H_2O), 59.0 (*C*HN), 53.9 (*C*HC=O), 52.6 (O*C*H_3), 28.0 (*C*H_2CHN), 26.6 (*C*H_3), 23.7 (*C*H_3); *m/z* (ESI$^+$) 449 (95%, $[2M+Na]^+$),

236 (100%, $[M+Na]^+$), 214 (23, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 236.0893, $C_{10}H_{15}NNaO_4$ requires 236.0893.

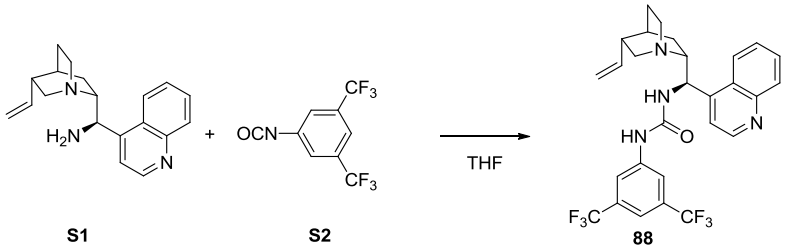
6.2.3. Synthesis of 3-[(*E*)-2-nitrovinyl]furan 124



KOH (28.62 mL of 2 M solution in absolute EtOH, 57.23 mmol) was added dropwise to a solution of furan-3-carbaldehyde **123** (5.00 g, 52.03 mmol) and nitromethane (3.49 g, 3.24 mL, 57.23 mmol) in EtOH (absolute, 73 mL) at 0 °C. The resulting solution was vigorously stirred at 0 °C. After 3 h the resulting suspension was poured portionwise onto a mixture of aqueous HCl (1 M, 132 mL) and ice (66 g) with vigorous stirring. The insoluble solid was filtered off, washed (water, 2 × 30 mL) and dried (Na_2SO_4) to yield nitro olefin **112** (4.44 g, 61%) as a yellow solid. The filtrate was extracted (Et_2O, 3 × 70 mL) and the organic phase washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue containing Henry adduct 1-(3-furyl)-2-nitroethanol **123'** (2.41 g, 15.34 mmol) was dissolved in CH_2Cl_2 (64 mL) and the solution was cooled to −15 °C. MsCl (1.76 g, 1.19 mL, 15.34 mmol) was added followed by dropwise addition of Et_3N (3.11 g, 4.28 mL, 30.68 mmol). The mixture was warmed to RT over 0.5 h and water (40 mL) was added. The separated water phase was further extracted (CH_2Cl_2, 2 × 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:Et_2O 90:10→65:35) yielding **112** (1.30 g, 61% for transformation **123'** → **112**) as a yellow solid. The overall isolated amount of **112** was 3.72 g, which represents 79% overall yield from aldehyde **123** to the title compound **112**: mp 100-102 °C, lit.[189] mp 101-103 °C, lit.[44] mp 68-70 °C; ν_{max}(film)/cm^{-1} 1640 (C=C), 1492, 1360 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.94 (dd, *J* = 13.5, 2.8 Hz,

1H, $NO_2CH=CH$), 7.84 (broad s, 1H, C*H*(2-furan)), 7.52 (br. s, 1H, C*H*(5-furan)), 7.40 (dd, *J* = 13.5, 3.0 Hz, 1H, $NO_2CH=CH$), 6.58 (br. s, 1H, C*H*(4-furan)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 147.3 (*C*H(furan)), 145.3 (*C*H(furan)), 136.6 ($CH=CHNO_2$), 129.6 ($CH=CHNO_2$), 118.1 (*C*(furan)), 107.2 (*C*H(furan)); HRMS m/z (FI^+) found $[M]^+$ 139.0271, $C_6H_5NO_3$ requires 139.0269.

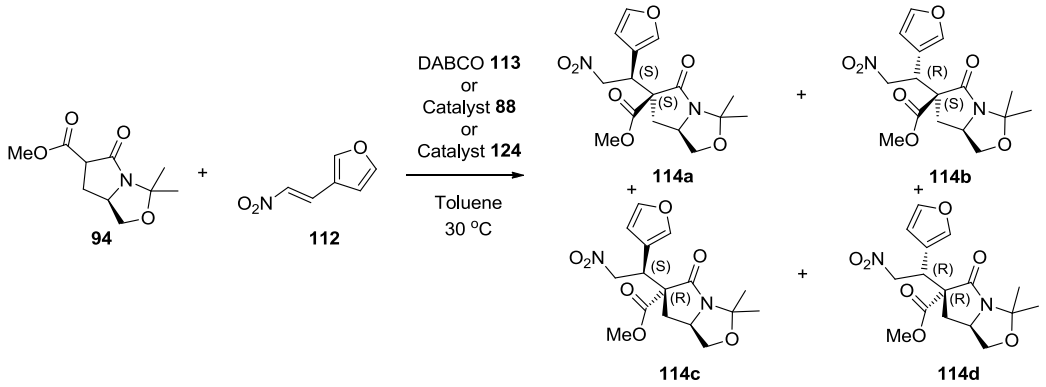
6.2.4. Synthesis of 1-[3,5-bis(trifluoromethyl)phenyl]-3-[(9*R*)-cinchonan-9-yl]urea 88



S1 **S2** **88**

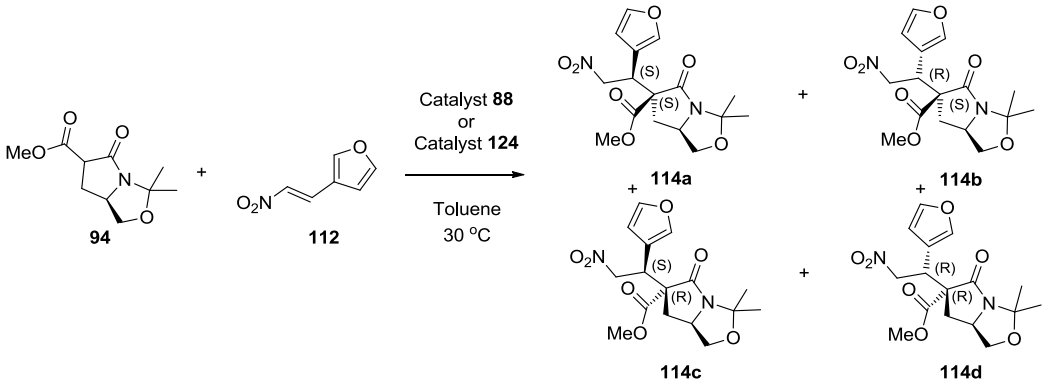
Following a modified procedure of Ye *et al.*,[26] 9-(deoxy)-epi-amino-cinchonine **S1** (2.50 g, 8.52 mmol) in THF (12 mL) was added slowly to bis(trifluoromethyl)phenyl isocyanate **S2** (2.37 g, 9.29 mmol) in THF (5 mL) at 0 °C. The reaction mixture was warmed slowly to RT and stirred for 8 h before being concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2:MeOH:Et_3N 10:1:1) to give **88** as an off-colourless solid (4.02 g, 86%): mp 197-199 °C (MeOH); lit.[34] 200-202 °C; lit.[190] 200-204 °C; $[\alpha]_D^{24}$ = +129.3. (*c* 0.67, $CHCl_3$); lit.[34] $[\alpha]_D^{24}$ = +125.5. (*c* 1.2, $CHCl_3$); lit.[190] $[\alpha]_D^{20}$ = +134.0. (*c* 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3082 (=C-H), 2941 (C-H), 1704 (C=O); ^{1}H NMR (400 MHz ,MeOD) δ_H 8.86 (d, *J* = 4.6 Hz, 1H, Ar*H*), 8.53 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.09 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.92 (s, 2H, Ar*H*), 7.81 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.72 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.65 (d, *J* = 4.6 Hz, 1H, Ar*H*), 7.45 (s, 1H, Ar*H*), 5.94 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H, CH_2=C*H*), 5.62 (br. s., 1H, NHC*H*), 5.23 - 5.11 (m, 2H, CH_2=CH), 3.31 - 3.20 (m, 1H, C*H*N), 3.21 - 3.11 (m, 1H, C*H*N), 3.09 - 2.95 (m, 3H, C*H*N), 2.35 (q, *J* = 8.0 Hz, 1H, quinuclidine-*H*), 1.66 - 1.55 (m, 3H, quinuclidine-*H*), 1.26 - 1.16 (m, 1H, quinuclidine-*H*), 1.04-0.88 (m, 1H, quinuclidine-*H*); *m/z* (ESI^-) 547 (100%, $[M-H]^+$).

6.2.5. Comparison of ‘matched’ and ‘mismatched’ substrate and catalyst control



Entry	Catalyst	Reaction Conditions	Yield	dr **114 a**:**b**:**c**:**d**
1	**113**	Toluene, 30 °C, 7 days	38% 4.3:1:0:0 dr	Crude 5:1:0:0 After purification 4.3:1:0:0
2	**88**	Toluene, 30 °C, 2 days	80% single diastereomer	Crude 15:1:0:0 After purification 1:0:0:0
3	**124**	Toluene, 30 °C, 5 days	61% 6:19:1:1 dr	Crude 4:12:1:1 After purification 6:19:1:1

6.2.6. 'Matched' and 'mismatched' substrate and catalyst control studies



To a solution of furan **112** (65 mg, 0.47 mmol) and pro-nucleophile **94** (200 mg, 0.94 mmol) in toluene (1.6 mL) was added catalyst **88** or catalyst **124** (26 mg, 0.047 mmol). The reaction was stirred at 30 °C until complete by TLC analysis (catalyst **88**, 2 days; catalyst **124**, 5 days) before being concentrated and the diastereomeric ratio established from the crude ^{1}H-NMR spectrum (catalyst **88**, 15:1:0:0 dr; catalyst **124**, 4:12:1:1 dr).

For the 'matched' case with catalyst **88**, the reaction mixture was purified by column chromatography (PE:EtOAc:CH_2Cl_2 5.5:4.5:0.8) to obtain the title compound as an off-colourless solid which was further purified by recrystallization from diethyl ether cooled to −20 °C to give **114a** as a colourless crystalline solid (131 mg, 80%): mp 157 °C; $[\alpha]_D^{26}$ = +2.1 (*c* 0.75, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2988 (C-H), 1721 (C=O), 1688 (C=O), 1547 (NO_2), 1381 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.45 (s, 1H, C*H*(2-furan)), 7.44 - 7.41 (m, 1H C*H*(5-furan)), 6.42 (s, 1H, C*H*(4-furan)), 5.03 - 4.88 (m, 2H, NO_2CH_2), 4.14 (dd, *J* = 10.6, 3.8 Hz, 1H, C*H*CH_2NO_2), 3.90 (dd, *J* = 7.8, 5.3 Hz, 1H, C*H*H'O), 3.82 (s, 3H, CH_3O), 3.40 (dd, *J* = 9.6, 7.8 Hz, 1H, CH*H*'O), 3.35 - 3.26 (m, 1H, C*H*N), 2.21 - 2.15 (m, 2H, CH_2CHN), 1.67 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 171.6 (*C*=O), 167.2

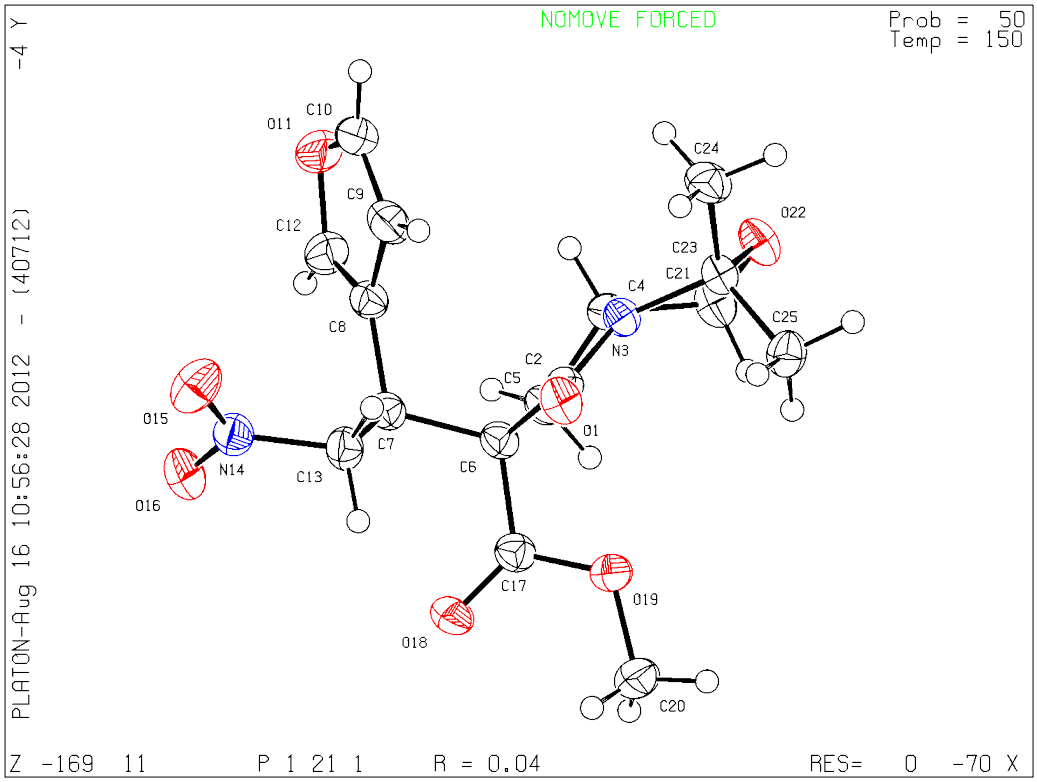
(*C*=O), 144.0 (*C*(5-furan)), 142.0 (*C*(2-furan)), 119.2 (*C*(3-furan)), 109.4 (*C*(4-furan), 91.9 (N*C*$(CH_3)_2$O), 76.8 (NO_2CH_2), 69.9 (CH_2O), 63.5 (C_{quat}), 58.6 (CH_2CHN), 53.4 (OCH_3), 38.6 (*C*H-furan), 33.3 (CH_2CHN), 26.2 (CCH_3), 23.3 (CCH_3); *m/z* (ESI^+) 375 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 375.1163, $C_{16}H_{20}N_2NaO_7$ requires 375.1163.

For the 'mismatched' case with catalyst **124**, the reaction mixture was purified by column chromatography (PE:EtOAc:CH_2Cl_2 5.5:4.5:0.8) to give **114a**:**114b**:**114c**:**114d** as a 6:19:1:1 mixture of diastereoisomers as a colourless solid (100 mg, 61%). Further purification by repeated recrystallization from diethyl ether cooled to −20 °C, gave a mixture of **114a** and **114b** (1:4 dr). Attempts to separate **114a** and **114b** completely by recrystallization were unsuccessful. Recrystallization from (Et_2O:MeOH:PE 10.0:0.2:1.0) gave large block crystals (the diastereomeric ratio of the combined crystals remained **114a**:**114b**, 1:4 dr). A large single crystal from this mixture was removed and the structure confirmed as **114b** by single crystal X-ray analysis. ^{1}H-NMR analysis of this single crystal confirmed that a single diastereoisomer **114b** was present: ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.43 (s, 1H, C*H*(2-furan)), 7.39 (t, *J* = 1.5 Hz, 1H, C*H*(5-furan)), 6.38 (dd, *J* = 1.7, 0.9 Hz, 1H, C*H*(4-furan)), 5.11 (dd, *J* = 13.6, 3.7 Hz, 1H, NO_2CHH'), 5.00 (dd, *J* = 13.5, 10.4 Hz, 1H, NO_2CHH'), 4.15 (dd, *J* = 10.3, 3.7 Hz, 1H, C*H*CH_2NO_2), 4.07 (dd, *J* = 8.0, 5.5 Hz, 1H, C*H*H'O), 4.03-3.94 (m, 1H, C*H*N), 3.81 (s, 3H, CH_3O), 3.52 (dd, *J* = 9.2, 8.0 Hz, 1H, CH*H*'O), 2.49 (dd, *J* = 13.7, 7.9 Hz, 1H, C*H*H'CHN), 2.17 (dd, *J* = 13.6, 6.9 Hz, 1H, CH*H*'CHN), 1.63 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 169.9 (*C*=O), 167.1 (*C*=O), 143.8 (*C*(5-furan)), 141.5 (*C*(2-furan)), 120.0 (*C*(3-furan)),

110.1 (*C*(4-furan), 92.1 (N*C*(CH_3)$_2$O), 76.6 (NO_2*C*H_2), 69.7 (*C*H_2O), 65.2 (*C*$_{quat}$), 58.0 (CH_2*C*HN), 53.3 (O*C*H_3), 37.8 (*C*H-furan), 30.5 (*C*H_2CHN), 26.5 (C*C*H_3), 23.4 (C*C*H_3); *m/z* (ESI$^+$) 375 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 375.1162, $C_{16}H_{20}N_2NaO_7$ requires 375.1163.

6.2.7. Single crystal X-ray analysis of diastereomer 114a

Thermal ellipsoid Plot drawn at 50% probability



Crystal data **114a**

$C_{16}H_{20}N_2O_7$	$F(000)$ = 372
M_r = 352.34	D_x = 1.384 Mg m^{-3}
Monoclinic, $P2_1$	Melting point: 157 °C
Hall symbol: P 2yb	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 9.5453 (3) Å	Cell parameters from 1788 reflections
b = 6.9928 (2) Å	θ = 5–27°
c = 13.4491 (4) Å	μ = 0.11 mm^{-1}
β = 109.6310 (13)°	T = 150 K
V = 845.53 (4) Å^3	Plate, Colourless
Z = 2	0.34 × 0.08 × 0.06 mm

Data collection

Area diffractometer	1676 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.027$
ω scans	$\theta_{max} = 27.1°$, $\theta_{min} = 5.2°$
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -12 \rightarrow 12$
$T_{min} = 0.92$, $T_{max} = 0.99$	$k = -8 \rightarrow 7$
5923 measured reflections	$l = -17 \rightarrow 17$
1988 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Inferred from neighbouring sites
Least-squares matrix: Full	No H atoms present
$R[F^2 > 2\sigma(F^2)] = 0.039$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed belo*w* and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 10.5 14.7 6.96 1.84
$wR(F^2) = 0.093$	$(\Delta/\sigma)_{max} = 0.0001134$
$S = 0.94$	$\Delta\rho_{max} = 0.29$ e Å^{-3}
1988 reflections	$\Delta\rho_{min} = -0.29$ e Å^{-3}
227 parameters	Extinction correction: Larson (1970), Equation 22
1 restraint	Extinction coefficient: 180 (20)

Primary atom site location:

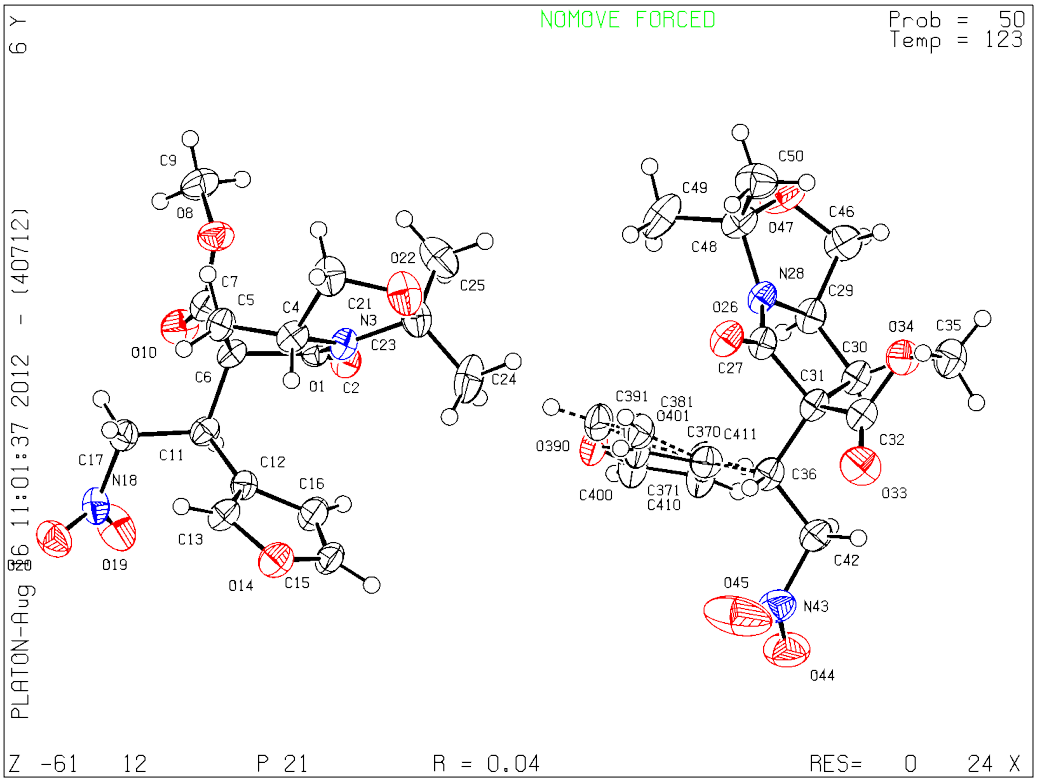
Structure-invariant direct methods

Special details

Refinement. The ADP of O(11) is enlarged due to a small amount of residual disorder, estimated at approximately 5%.

6.2.8. Single crystal X-ray analysis of diastereomer 114b

Thermal ellipsoid Plot drawn at 50% probability



Crystal data **114b**

$C_{16}H_{20}N_2O_7$	$F(000)$ = 744
M_r = 352.34	D_x = 1.367 Mg m^{-3}
Monoclinic, $P2_1$	Melting point: not measured K
Hall symbol: P 2yb	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 9.0669 (2) Å	Cell parameters from 3777 reflections
b = 15.7455 (4) Å	θ = 5–27°
c = 12.0613 (3) Å	μ = 0.11 mm^{-1}
β = 96.0302 (13)°	T = 123 K
V = 1712.38 (7) Å^3	Block, Colourless
Z = 4	0.34 × 0.16 × 0.06 mm

Data collection

Nonius KappaCCD diffractometer	2716 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.044$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.1°$
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -11 \rightarrow 11$
$T_{min} = 0.87$, $T_{max} = 0.99$	$k = -20 \rightarrow 19$
15585 measured reflections	$l = -15 \rightarrow 15$
4032 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Inferred from neighbouring sites
Least-squares matrix: Full	No H atoms present
$R[F^2 > 2\sigma(F^2)] = 0.044$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.19P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2) = 0.098$	$(\Delta/\sigma)_{max} = 0.023$
$S = 0.96$	$\Delta\rho_{max} = 0.46$ e Å^{-3}
4032 reflections	$\Delta\rho_{min} = -0.44$ e Å^{-3}
489 parameters	Extinction correction: Larson (1970), Equation 22

91 restraints Extinction coefficient: 770 (60)

Primary atom site location:

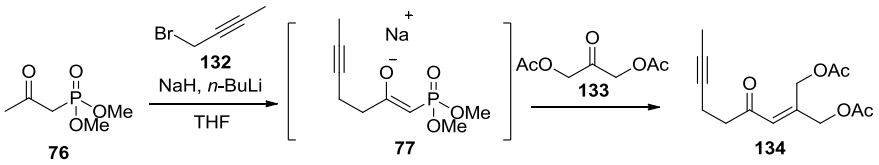
Structure-invariant direct methods

Special details

Refinement. The unit cell contains two independent molecules (Z'=2) related by a pseudo 2-fold axis. The molecular geometries are very similar except for the orientation of one of furan residues.

In one of the molecules, the furan residue is disordered by rotation about the C36—C37x bond.

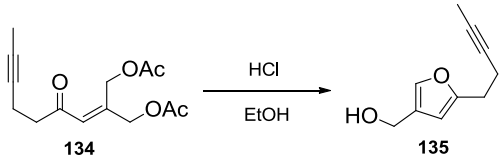
6.2.9. Synthesis of 2-(acetoxymethyl)-4-oxonon-2-en-7-yn-1-yl acetate 134



To a suspension of NaH (60 % dispersion in mineral oil) (13.9 g, 347 mmol) in THF (640 mL) was added dimethyl (2-oxopropyl)phosphonate **76** (32.0 g, 193 mmol) dropwise at 0 °C. A white suspension was formed upon complete addition. The suspension was stirred for 0.5 h before *n*-BuLi (2.5 M in hexanes) (104 mL, 260 mmol) was added dropwise over 5 min and the resultant orange solution stirred for 20 min at 0 °C. 1-Bromobut-2-yne **132** (25.6 g, 193 mmol) was added dropwise, forming a white suspension, and the reaction mixture stirred for a further 10 min. 2-Oxopropane-1,3-diyl diacetate **133** (50.3 g, 289 mmol) was added in one portion at 0 °C and the reaction was allowed to warm to RT and stirred at RT for 2 h before being quenched with sat. aq. NH_4Cl solution (500 mL). After extraction with CH_2Cl_2 (2 x 500 mL) and drying ($MgSO_4$) the title compound **134** was obtained by column chromatography (PE:Et_2O 1:3→1:5) as a pale yellow oil (19.5 g, 38%): ν_{max}(film)/cm^{-1} 2923 (C-H), 2860 (C-H), 1745 (C=O), 1697 (C=O), 1630 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.33 (br. s, 1H, C(O)C*H*=C), 5.20 (s, 2H, CH_2OAc), 4.73 (s, 2H, CH_2OAc), 2.72 (t, *J* = 7.2 Hz, 2H, CH_2CO), 2.44-2.38 (m, 2H, C≡CCH_2), 2.13 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 1.75 (t, *J* = 2.5 Hz, 3H, C≡CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 198.5 (*C*=O), 170.5 (*C*=O), 170.2 (*C*=O), 147.6 (C=*C*), 124.2 (*C*=C), 77.5 (*C*≡C), 76.2 (C≡*C*), 63.6 (*C*H_2O), 62.1 (*C*H_2O), 43.3 (*C*H_2CO), 20.8 (C(O)*C*H_3), 20.7 (C(O)*C*H_3), 13.3 (C≡C*C*H_2), 3.5 (*C*H_3); *m/z* (ESI$^+$) 571 (52%, [2M+K]$^+$), 555 (89,

$[2M+Na]^+$), 305 (33, $[M+K]^+$), 289 (100, $[M+Na]^+$), 267 (28, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 289.1042, $C_{14}H_{18}NaO_5$ requires 289.1046.

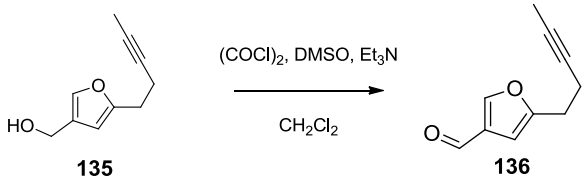
6.2.10. Synthesis of 5-(pent-3-yn-1-yl)-3-furyl]methanol 135



134 135

To a solution of **134** (18.0 g, 67.6 mmol) in ethanol (1650 mL) at RT was added 1 M aq. HCl (67.6 mL, 67.6 mmol). The resulting pale yellow solution was heated to 65 °C for 15 h before being cooled to RT. The reaction was concentrated to ~800 mL and poured into water (600 mL) and neutralised with solid K_2CO_3. The solution was extracted with CH_2Cl_2 (3 x 500 mL), dried (Na_2SO_4) and concentrated to give a crude oil which was purified by column chromatography (PE:Et_2O 3:1) to give furanol **135** as an orange oil (7.8 g, 71%): ν_{max}(film)/cm^{-1} 3421 (O-H), 2920 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 (s, 1H, C*H*(5-furan)), 6.10 (s, 1H, C*H*(3-furan)), 4.45 (s, 2H, CH_2OH), 2.76 (t, *J* = 7.6 Hz, 2H, furan-CH_2), 2.46-2.39 (m, 2H, C≡CCH_2), 2.17 (s, 1H, O*H*), 1.75 (t, *J* = 2.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.6 (*C*(2-furan)), 138.3 (*C*(5-furan)), 125.8 (*C*(4-furan)), 105.7 (*C*(3-furan)), 78.0 (*C*≡C), 76.3 (C≡*C*), 56.7 (*C*H_2OH), 28.0 (furan-*C*H_2), 17.8 (C≡C*C*H_2), 3.5 (*C*H_3); *m/z* (ESI$^+$) 165 (3%, $[M+H]^+$); HRMS *m/z* (TOF FI$^+$) found $[M]^+$ 164.0840, $C_{10}H_{12}O_2$ requires 164.0837.

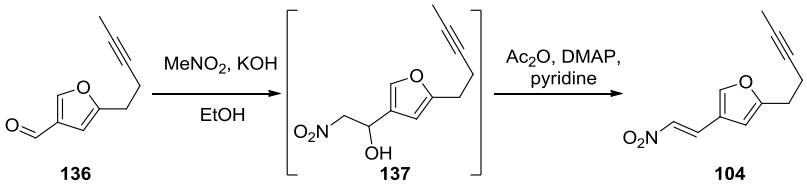
6.2.11. 5-(Pent-3-yn-1-yl)-3-furaldehyde 136



135 136

DMSO (8.29 g, 7.53 mL, 106.1 mmol) was added dropwise over 5 min to a solution of oxalyl chloride (6.85 g, 4.63 mL, 54.0 mmol) in CH_2Cl_2 (116 mL) cooled to −78 °C and the resulting solution stirred for 10 min at this temperature. A solution of furanol **135** (8.30 g, 50.5 mmol) in CH_2Cl_2 (84 mL) was added dropwise and the solution stirred for a further 15 min at −78 °C before Et_3N (25.55 g, 35.20 mL, 252.5 mmol) was added and the solution warmed to RT over 0.5 h. The reaction mixture was partitioned with water (90 mL) and the aqueous phase was back extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the crude aldehyde which was purified by column chromatography (PE:Et_2O 5:1→2:1), yielding aldehyde **136** as a yellow oil (7.36 g, 90%): ν_{max}(film)/cm^{-1} 3124 (C-H), 2920 (C-H), 1686 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.85 (s, 1H, C(O)*H*), 7.94 (s, 1H, C*H*(5-furan)), 6.46 (s, 1H, C*H*(3-furan)), 2.81 (t, *J* = 7.3 Hz, 2H, furan-CH_2), 2.48-2.42 (m, 2H, C≡CCH_2), 1.75 (t, *J* = 2.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 184.6 (C=O), 157.7 (*C*(2-furan)), 150.6 (*C*(5-furan)), 129.5 (*C*(4-furan)), 102.7 (*C*(3-furan)), 77.2 (*C*≡C), 76.8 (C≡*C*), 27.7 (furan-*C*H_2), 17.5 (C≡C*C*H_2), 3.4 (*C*H_3); *m/z* (ESI$^+$) 185 (37%, $[M+Na]^+$); HRMS *m/z* (TOF FI$^+$) found $[M]^+$ 162.0685, $C_{10}H_{10}O_2$ requires 162.0681.

6.2.12. Synthesis of 4-[(*E*)-2-nitrovinyl]-2-(pent-3-yn-1-yl)furan 104

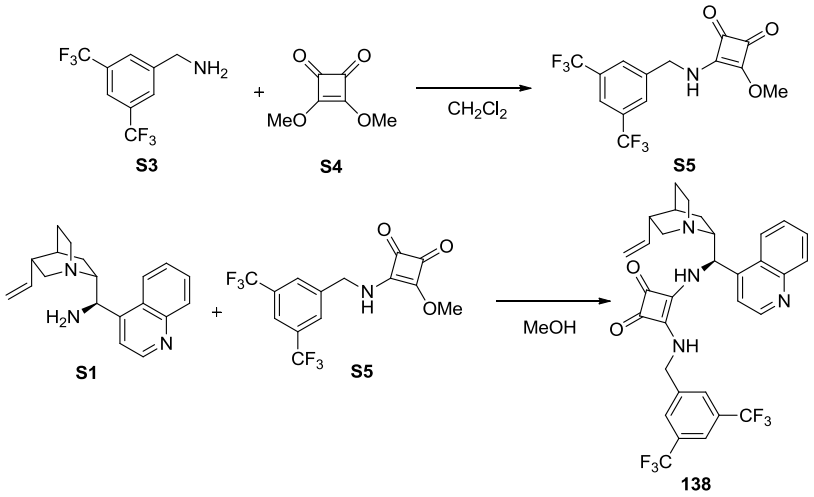


To a solution of aldehyde 1**36** (0.92 g, 5.67 mmol) and nitromethane (0.34 mL, 6.24 mmol) in EtOH (11 mL) cooled to 0 °C was added dropwise KOH (2 M solution in ethanol) (3.12 mL, 6.24 mmol). After 1 h the reaction mixture (yellow suspension) was poured into a vigorously stirred mixture of ice (10 g) and 2 M aq. HCl (5 mL). The resulting slurry was stirred for 10 min before being extracted with diethyl ether (3 x 30 mL), dried (Na_2SO_4) and concentrated to give a yellow solid containing a mixture of **137** and **104**. The crude material was purified by column chromatography (PE:Et_2O 8:1→1:1) to give nitro olefin **104** (0.58 g, 49%) as a fluffy yellow solid (R_f 0.65 PE:Et_2O 3:1) and 2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethanol **137** (0.52 g, 41%) as an orange oil (R_f 0.22 3:1 PE:Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 (s, 1H, *CH*(5-furan)), 6.10 (s, 1H, *CH*(3-furan)), 5.41-5.35 (m, 1H, C*H*OH), 4.63 (dd, *J* = 13.4, 9.1 Hz, 1H, C*H*'HNO_2), 4.53 (dd, *J* = 13.4, 3.2 Hz, 1H, CH'*H*NO_2), 2.78 (t, *J* = 7.9 Hz, 2H, furan-CH_2), 2.48-2.41 (m, 2H, C≡CCH_2), 1.77 (t, *J* = 2.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5 (*C*(2-furan)), 138.4 (*C*(5-furan)), 123.9 (*C*(4-furan)), 103.8 (*C*(3-furan)), 80.2 (*C*NO_2), 77.7 (*C*≡C), 76.6 (C≡*C*), 64.4 (H*C*OH), 27.9 (furan-*C*H_2), 17.7 (C≡C*C*H_2), 3.5 (*C*H_3).

Nitro alcohol **137** (0.52 g, 2.23 mmol) was dissolved in pyridine (20 mL) and the solution cooled to 0 °C. Acetic anhydride (0.33 mL, 3.49 mmol) and DMAP (0.05 g, 0.47 mmol) in pyridine (8 mL) were added and the resulting solution stirred for 30 min before being quenched with sat. aq. $NaHCO_3$

(50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 40 mL) and the organic extracts washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated until 10 mL of pyridine remained. Attempts to concentrate the crude product fully lead to rapid decomposition. The crude product/pyridine mixture was purified by column chromatography (PE:Et_2O 8:1→1:1) to give nitro olefin **104** (0.37 g, 82% overall yield from **136**) as a fluffy yellow solid: mp 91-93 °C; ν_{max}(film)/cm^{-1} 3106, 2923 (C-H), 1640 (C=C), 1490 (NO_2), 1355 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.88 (d, *J* = 13.4 Hz, 1H, NO_2C*H*), 7.72 (s, 1H, *CH*(5-furan)), 7.36 (d, *J* = 13.4 Hz, 1H, NO_2CH=C*H*), 6.26 (s, 1H, *CH*(3-furan)), 2.83 (t, *J* = 7.3 Hz, 2H, furan-CH_2), 2.52-2.45 (m, 2H, C≡CCH_2), 1.77 (t, *J* = 2.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.0 (*C*(2-furan)), 146.5 (*C*(5-furan)), 136.3 (NO_2CH=*C*H), 130.0 (NO_2*C*H=CH), 119.0 (*C*(4-furan)), 103.0 (*C*(3-furan)), 77.2 (*C*≡C), 76.9 (C≡*C*), 27.8 (furan-*C*H_2), 17.5 (C≡C*C*H_2), 3.5 (*C*H_3); *m/z* (ESI$^+$) 228 (100%, $[M+Na]^+$); HRMS *m/z* (TOF FI$^+$) found $[M]^+$ 205.0744, $C_{11}H_{11}NO_3$ requires 205.0739.

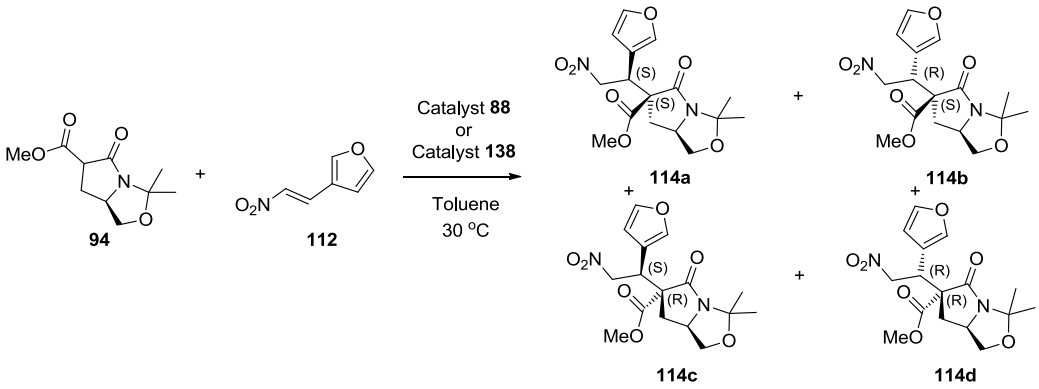
6.2.13. Synthesis of 3-{[3,5-bis(trifluoromethyl)benzyl]amino}-4-[(9*R*)-cinchonan-9-ylamino]cyclobut-3-ene-1,2-dione 138



Following the procedures of Rawal and co-workers.[49] To a solution of dimethylsquarate **S4** (0.150 g, 1.06 mmol) in CH_2Cl_2 (4.2 mL) was added a solution of 1-[3,5-bis(trifluoromethyl)phenyl]methanamine **S3** (0.270 g, 1.11 mmol) in CH_2Cl_2 (1.2 mL) and the reaction mixture left to stir for 24 h. After this time a second portion of amine **S3** (0.013 g, 0.053 mmol), after stirring for a further 15 h the reaction mixture was filtered and the filtrate was washed with 1 M aq. HCl (10 mL) before being concentrated under reduced pressure to yield **S5** as a colourless solid (0.29 g, 78%). To a solution of **S5** (0.255 g, 0.72 mmol) in MeOH (8 mL), was added a solution of amine **S1** (0.176 g, 0.62 mmol) in MeOH (2 mL). After 24 h the reaction mixture was filtered and washed with cold MeOH (2 x 1 mL) to yield the title compound **138** as an off-white solid (0.280 g, 65%): mp 305-306 °C (MeOH) decomp.; ^{1}H NMR (400MHz, DMSO-d_6) δ_H 8.94 (d, *J* = 4.5 Hz, 1H, Ar*H*), 8.42 (d, *J* = 8.1 Hz, 1H, Ar*H*), 8.16 - 7.91 (m, 5H, Ar*H*), 7.78 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.73 - 7.58 (m, 3H, Ar*H,* 2 x N*H*), 6.08 (br. s., 1H, NHC*H*), 5.82 (ddd, *J* = 17.2, 10.5, 6.4 Hz, 1H, C*H*=CH_2), 5.21 - 4.98 (m, 2H, CH=CH_2), 4.86 (d, *J* = 6.1

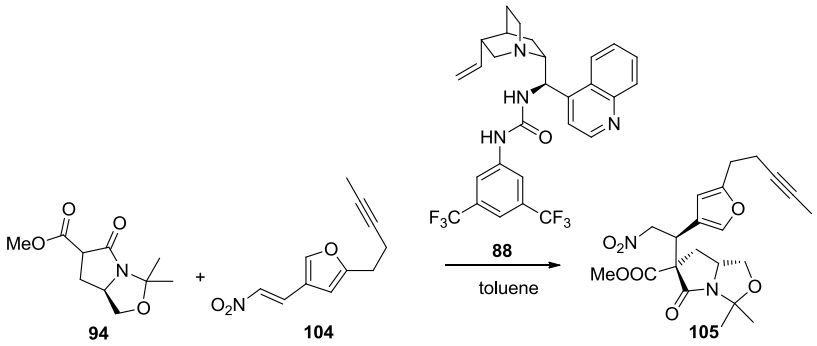
Hz, 2H, NHCH_2), 3.33 - 3.24 (m, 1H, NC*H*), 3.10 (dd, *J* = 13.6, 7.1 Hz, 1H, NC*H*H'CH), 2.96 - 2.68 (m, 3H, NCH*H*'CH, NCH_2CH_2), 2.19 (d, *J* = 7.3 Hz, 1H, C*H*CH=CH_2), 1.59 - 1.40 (m, 3H, NCH$_2$CH_2, C*H*CHCH=CH_2), 1.05 - 0.83 (m, 2H, NCHCH_2); *m/z* (ESI$^+$) 614 (52 %, [M+H]$^+$). Data are in good agreement with that previously reported.[49]

Catalyst Reactivity Studies



To a solution of furan **112** (50 mg, 0.36 mmol) and pro-nucleophile **94** (150 mg, 0.70 mmol) in toluene (1.8 mL) was added catalyst **88** or catalyst **138** (10 mol%). The reaction was stirred at 30 °C and aliquots (60 µl) removed from the reaction at 1,3,5,20 and 48 h. The aliquots were filtered rapidly through a silica pipette column (Et_2O) to remove the catalyst and the conversion established from the crude ^{1}H-NMR spectrum.

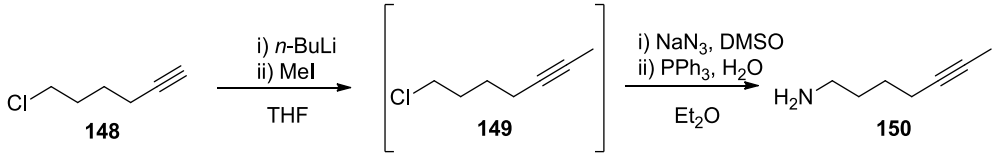
6.2.14. Synthesis of methyl (6*S*,7a*R*)-3,3-dimethyl-6-{(1*S*)-2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethyl}-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate 105



To a solution of nitro olefin **104** (1.20 g, 5.85 mmol) and pro-nucleophile **94** (2.49 g, 11.70 mmol) in toluene (19.5 mL) was added catalyst **88** (0.32 g, 0.58 mmol). The reaction was stirred at 30 °C for 52 h before being concentrated and purified by column chromatography (PE:Et_2O 9:1→3:7). The title compound was obtained as a yellow crystalline solid (dr = 18:1) which was further purified by recrystallization from diethyl ether cooled to -30 °C. Further purification of the mother liquors were also required in a similar manner to give the title compound **105** as a colourless crystalline solid (1.99 g, 81%, single diastereoisomer): mp 90-92 °C; $[\alpha]_D^{26}$ = +10.8 (*c* 0.25, $CHCl_3$); ν_{max}(film)/cm^{-1} 2985 (C-H), 2921 (C-H), 1738 (C=O), 1696 (C=O), 1555 (NO_2), 1380 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 (s, 1H, C*H*(5-furan)), 6.09 (s, 1H, C*H*(3-furan)), 4.96 (dd, *J* = 13.3, 3.8 Hz, 1H, NO_2C*H*'H), 4.89 (dd, *J* = 13.3, 10.7 Hz, 1H, NO_2CH'*H*), 4.07 (dd, *J* = 10.7, 3.8 Hz, 1H, C*H*-furan), 3.91 - 3.88 (m, 1H, CHC*H*H'O), 3.82 (s, 3H, CH_3O), 3.44 - 3.37 (m, 2H, C*H*N, CHCH*H*'O), 2.74 (t, *J* = 7.2 Hz, 2H, furan-CH_2), 2.52 - 2.35 (m, 2H, C≡CCH_2), 2.22 - 2.15 (m, 2H, CH_2CHN), 1.74 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.68 (s, 3H, CCH_3), 1.45 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.7 (*C*=O), 167.2 (*C*=O), 156.2 (*C*(2-furan)), 140.6 (*C*(5-furan)), 119.6 (*C*(4-

furan)), 105.4 (*C*(3-furan)), 91.9 (N*C*(CH_3)$_2$O), 77.5 (*C*≡C), 76.8 (C≡*C*), 76.6 (NO_2CH_2), 70.0 (*C*H_2O), 63.5 (C_{quat}), 58.7 (CH_2*C*HN), 53.4 (O*C*H_3), 38.8 (*C*H-furan), 33.4 (*C*H_2CHN), 27.9 (furan-*C*H_2), 26.2 (C*C*H_3), 23.3 (C*C*H_3), 17.6 (C≡C*C*H_2), 3.3 (alkyne-*C*H_3); *m/z* (ESI$^+$) 859 (100%, $[2M+Na]^+$), 441 (34, $[M+Na]^+$), 419 (91, $[M+H]^+$]; HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 441.1638, $C_{21}H_{26}N_2NaO_7$ requires 441.1632.

6.2.15. Synthesis of hept-5-yne amine 5

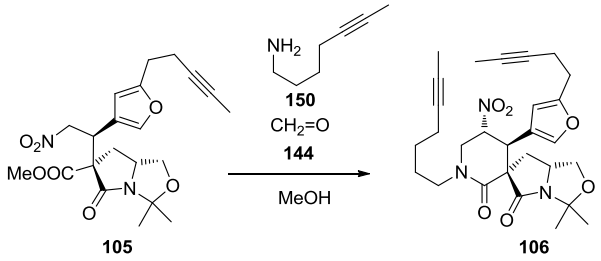


6-Chlorohex-1-yne **148** (7.04 g, 7.28 mL, 60.38 mmol) was dissolved in THF (90 mL) and cooled to 0 °C. *n*-BuLi (56.3 mL, 90 mmol, 1.6 M in hexanes) was added dropwise, and the solution stirred at 0 °C for 1 h before methyl iodide (13.63 g, 5.98 mL, 96.03 mmol) was added slowly and the solution warmed to RT over 0.5 h. The reaction was quenched with sat. aq. $NHCl_4$, (100 mL) extracted with diethyl ether (2 x 150 mL) and the organic phase dried (Na_2SO_4) and concentrated to give crude 7-chlorohept-2-yne **149**, which was used without further purification.

7-Chlorohept-2-yne **149** (7.00 g, 53.59 mmol) was dissolved in DMSO (50 mL) at ambient temperature. To this solution was added sodium azide (10.45 g, 160.74 mmol) portionwise and the reaction heated to 50 °C for 6 h after which it was cooled to ambient temperature and water (100 mL) and diethyl ether (50 mL) added. The organic phase was separated and the DMSO-water phase extracted further with diethyl ether (3 x 50 mL). The combined organics were then washed with water (40 mL) and brine (40 mL) before being dried ($MgSO_4$). The azide/ether solution was used without concentration or further purification. To this solution was added triphenylphosphine (22.60 g, 86.16 mmol) in small portions over 0.5 h. Water (3.87 mL, 214.82 mmol) was added and the reaction mixture was stirred at RT for 14 h. 1 M aq. HCl (70 mL) was added and the aqueous phase and the organic phase separated. The aqueous was washed with diethyl ether (2 x 50 mL) before being basified by the addition of 1 M aq. NaOH until pH 14

was reached. The aqueous phase was extracted with diethyl ether (3 x 60 mL) and the organic extracts dried (Na_2SO_4) and fractionally distilled to afford hept-5-yn-1-amine **150** as a colourless liquid (3.40 g, 51%) with data in good agreement with literature[16,191]: bp 90-92 °C/30 mbar; lit[191]. bp 95-98 ºC/25 Torr); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.76 - 2.63 (m, 2H, C*H*$_2$NH$_2$), 2.21 - 2.07 (m, 2H, alkyne-C*H*$_2$), 1.83 - 1.73 (m, 3H, alkyne-C*H*$_3$), 1.60 - 1.45 (m, 4H, 2 x C*H*$_2$), 1.26 - 1.15 (m, 2H, N*H*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 79.5 (*C*≡C), 76.1 (C≡*C*), 42.3 (NH$_2$*C*H$_2$), 33.5 (*C*H$_2$), 26.8 (*C*H$_2$), 19.1 (*C*H$_2$), 3.9 (*C*H$_3$).

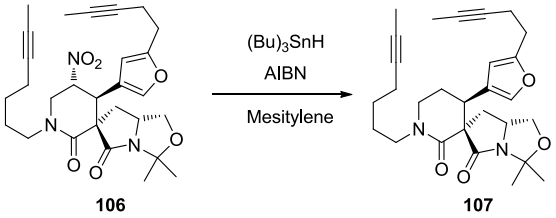
6.2.16. Synthesis of (3*R*,4*S*,5*R*,7a'*R*)-1-(hept-5-yn-1-yl)-3',3'-dimethyl-5-nitro-4-[5-(pent-3-yn-1-yl)-3-furyl]dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione 106



A solution of Michael adduct **105** (0.60 g, 1.43 mmol), hept-5-yn-1-amine **150** (0.24 g, 2.15 mmol) and formaldehyde **144** (37% solution in water) (0.16 mL, 2.15 mmol) in MeOH (30 mL) was refluxed for 8 h (a deep purple solution was formed after 5-10 min before slowly forming a dark brown solution). The solution was cooled to RT and concentrated before being purified by column chromatography (PE:Et_2O 9:1→Et_2O) to afford the title compound **106** as a brown oil (0.38 g, 52%): $[\alpha]_D^{26}$ = +91.8 (*c* 0.34, $CHCl_3$); ν_{max}(film)/cm^{-1} 2920 (C-H), 1690 (C=O), 1650 (C=O), 1556 (NO_2), 1349 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.30 (d, *J* = 0.6 Hz, 1H, C*H*(5-furan)), 6.14 (d, *J* = 0.6 Hz, 1H, C*H*(3-furan)), 5.90 (ddd, *J* = 12.0, 9.4, 6.4 Hz, 1H, NO_2C*H*), 4.02 (dd, *J* = 12.0, 6.4 Hz, 1H, NC*H*H'), 3.90 (dd, *J* = 7.8, 5.2 Hz, 1H, CHC*H*H'O), 3.86 - 3.78 (m, 1H, NCH*H*'), 3.62 - 3.48 (m, 3H, NC*H*H', C*H*-furan, CHCH*H*'O), 3.47 - 3.35 (m, 2H, C*H*N, NCH*H*'), 3.02 (dd, *J* = 13.1, 7.2 Hz, 1H, C*H*H'CHN), 2.78 - 2.71 (m, 2H, furan-CH_2), 2.48 - 2.38 (m, 2H, C≡CCH_2), 2.23 - 2.12 (m, 2H, C≡CCH_2), 1.92 (dd, *J* = 13.2, 7.3 Hz, 1H, CH*H*'CHN), 1.78 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.76 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.74 - 1.65 (m, 2H, $NCH_2CH_2CH_2$), 1.59 (s, 3H, CCH_3), 1.55 - 1.45 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.36 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2 (*C*=O), 167.2 (*C*=O), 156.2 (*C*(2-furan)), 140.1 (*C*(5-furan)), 118.7, (*C*(4-furan)), 105.3 (*C*(3-furan)),

91.5 (N*C*(CH_3)$_2$O), 81.3 (NO_2*C*H) 78.5 (*C*≡C), 77.4 (C≡*C*), 76.7 (*C*≡C), 76.1 (C≡*C*), 69.7 (*C*H_2O), 62.9 (C_{quat}), 58.7 (CH_2*C*HN), 49.3 (*C*H_2N), 47.9 (*C*H_2N), 42.9 (*C*H-furan), 31.6 (*C*H_2CHN), 27.9 (furan-*C*H_2), 26.1 (C*C*H_3), 25.9 (NCH_2*C*H_2CH_2), 25.8 (NCH_2CH_2*C*H_2), 23.3 (C*C*H_3), 18.4 (C≡C*C*H_2), 17.6 (C≡C*C*H_2), 3.5 (alkyne-CH_3), 3.3 (alkyne-*C*H_3); *m/z* (ESI$^+$) 532 (100 %, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 532.2415, $C_{28}H_{35}N_3NaO_6$ requires 532.2418.

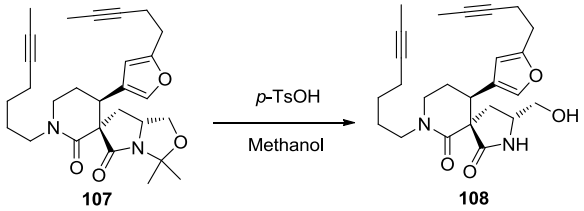
6.2.17. Synthesis of (3*R*,4*S*,7a'*R*)-1-(hept-5-yn-1-yl)-3',3'-dimethyl-4-[5-(pent-3-yn-1-yl)-3-furyl]dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione 107



Nitro substrate **106** (4.84 g, 9.50 mmol) was dissolved in freshly distilled mesitylene (215 mL). To this was added AIBN (0.31 g, 1.90 mmol) and tributyltin hydride (12.77 mL, 47.48 mmol) and the mixture degassed by repeated cycles of vacuum/argon purge. The reaction was then heated rapidly to reflux in a pre-heated oil bath for 2.5 h before being cooled to RT. The reaction mixture was loaded directly onto silica and the mesitylene and excess tin compounds eluted with petroleum ether before ramping the solvent system (PE:Et_2O 2:1→Et_2O), to obtain the title compound **107** as a pale yellow oil (2.87 g, 58%): $[\alpha]_D^{24}$ = +117.0 (*c* 1.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2982 (C-H), 2936 (C-H), 1692 (C=O), 1634 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23 (s, 1H, C*H*(5-furan)), 6.09 (s, 1H, C*H*(3-furan)), 3.85 (dd, *J* = 7.3, 5.1 Hz, 1H, C*H*H'O), 3.57 - 3.27 (m, 6H, 2 x CH_2N, CH_2C*H*N, CH*H*'O), 2.97 (dd, *J* = 12.8, 7.2 Hz, 1H, C*H*H'CHN), 2.94 - 2.85 (m, 2H, C*H*-furan, furan-CHC*H*H'), 2.76 - 2.70 (m, 2H, furan-CH_2), 2.45 - 2.36 (m, 2H, C≡CCH_2), 2.18 - 2.09 (m, 2H, C≡CCH_2), 1.83 (dd, *J* = 12.8, 6.9 Hz, 1H, CH*H*'CHN), 1.76 – 1.71 (m, 7H, 2 x alkyne-CH_3, furan-CHCH*H*'), 1.71 - 1.61 (m, 2H, $NCH_2CH_2CH_2$), 1.58 (s, 3H, CCH_3), 1.53 - 1.41 (m, 2H, $NCH_2CH_2CH_2$), 1.27 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.4 (*C*=O), 168.6 (*C*=O), 155.2 (*C*(2-furan)), 138.0 (*C*(5-furan)), 124.7, (*C*(4-furan)), 105.9 (*C*(3-furan)), 91.1 (N*C*$(CH_3)_2$O), 78.8 (*C*≡C), 77.7 (C≡*C*), 76.4

(*C*≡C), 75.7 (C≡*C*), 69.9 (*C*H_2O), 63.3 (C_{quat}), 58.5 (CH_2*C*HN), 47.9 (*C*H_2N), 47.3 (*C*H_2N), 40.0 (*C*H-furan), 33.0 (*C*H_2CHN), 27.9 (furan-*C*H_2), 26.2 (C*C*H_3), 2 x 26.1 (NCH_2*C*$H_2$$CH_2$, N$CH_2$$CH_2$*C*$H_2$), 25.2 (furan-CH*C*$H_2$), 23.3 (C*C*$H_3$), 18.4 (C≡C*C*$H_2$), 17.7 (C≡C*C*$H_2$), 3.5 (alkyne-$CH_3$), 3.4 (alkyne-*C*$H_3$); *m/z* (ESI$^+$) 951 (100 %, [2M+Na]$^+$), 487 (99, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 487.2565, $C_{28}H_{36}N_2NaO_4$ requires 487.2567.

6.2.18. Synthesis of (3*R*,5*S*,10*S*)-7-(hept-5-yn-1-yl)-3-(hydroxymethyl)-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5] decane-1,6-dione 108

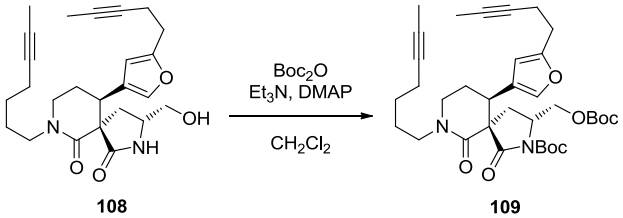


107 108

p-TsOH (0.038 g, 0.22 mmol) was added to a solution of **107** (2.03 g, 4.37 mmol) in methanol (235 mL) and the solution heated at reflux for 4 h. A further addition of *p*-TsOH (0.050 g, 0.29 mmol) was required after this time. After heating at reflux for a further 1 h, the solution was cooled to RT, concentrated and purified by column chromatography (Et_2O→ Et_2O:MeOH 9:1) to yield the title compound **108** as a colourless oil (1.61 g, 87%): $[\alpha]_D^{26}$ = +112.2 (*c* 0.18, $CHCl_3$); ν_{max}(film)/cm^{-1} 3271 (O-H), 2919 (C-H), 2862 (C-H), 1692 (C=O), 1619 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.21 (s, 1H, C*H*(5-furan)), 6.71 (br. s., 1H, N*H*), 6.10 (s, 1H, C*H*(3-furan)), 4.52 (t, *J* = 5.4 Hz, 1H, O*H*), 3.56 - 3.51 (m, 2H, CH_2O), 3.51 - 3.35 (m, 3H, NCH_2, NC*H*H'), 3.32 - 3.18 (m, 2H, CH_2C*H*NH, NCH*H*'), 3.10 - 2.96 (m, 1H, furan-CHC*H*H'), 2.84 (dd, *J* = 13.3, 2.4 Hz, 1H, furan-C*H*), 2.73 (t, *J* = 7.5 Hz, 2H, furan-CH_2), 2.62 (dd, *J* = 13.5, 5.7 Hz, 1H, C*H*H'CHNH), 2.40 (td, *J* = 7.5, 2.5 Hz, 2H, C≡CCH_2), 2.18 - 2.10 (m, 2H, C≡CCH_2), 2.05 (dd, *J* = 13.5, 9.0 Hz, 1H, CH*H*'CHNH), 1.77 – 1.73 (m, 7H, alkyne-CH_3, furan-CHCH*H*'), 1.69 - 1.57 (m, 2H, NCH_2CH_2CH_2), 1.53 - 1.37 (m, 2H, NCH_2CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.8 (*C*=O), 170.6 (*C*=O), 155.3 (*C*(2-furan)), 138.3 (*C*(5-furan)), 124.3, (*C*(4-furan)), 106.1 (*C*(3-furan)), 78.7 (*C*≡C), 77.9 (C≡*C*), 76.2 (*C*≡C), 75.9 (C≡*C*), 65.7 (*C*H_2O), 55.9 (C_{quat}), 53.2 (CH_2*C*HN), 48.1 (*C*H_2N), 47.6 (CH_2N), 40.5 (*C*H-furan), 34.0 (*C*H_2CHN), 28.0 (furan-*C*H_2),

26.1 ($NCH_2\mathit{C}H_2CH_2$), 26.0 ($NCH_2CH_2\mathit{C}H_2$), 25.3 (furan-$CH\mathit{C}H_2$) 18.5 ($C{\equiv}C\mathit{C}H_2$), 17.9 ($C{\equiv}C\mathit{C}H_2$), 3.5 (alkyne-CH_3), 3.4 (alkyne-$\mathit{C}H_3$); *m/z* (ESI^+) 871 (100%, $[2M+Na]^+$), 447 (78, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 447.2256, $C_{25}H_{32}N_2NaO_4$ requires 447.2254.

6.2.19. Synthesis of *tert*-butyl (3*R*,5*R*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy] methyl}-7-(hept-5-yn-1-yl)-1,6-dioxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate 109

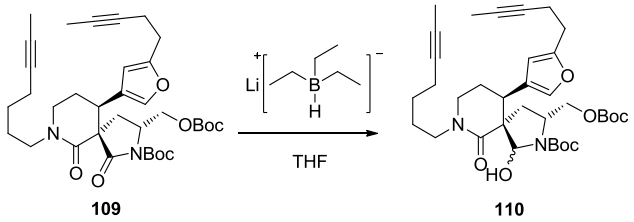


108 109

To a solution of aminol **108** (1.77 g, 4.17 mmol) in CH_2Cl_2 (85 mL) was added DMAP (0.050 g, 4.17 mmol) and Et_3N (2.90 mL, 20.87 mmol) before the portionwise addition of di-*tert*-butyl dicarbonate (4.54 g, 20.80 mmol). The solution was stirred for 15 h at RT. The dark yellow solution formed was concentrated and purified by column chromatography (PE:Et_2O 9:1→1:4), to give the title compound **109** as a colourless oil (2.29 g, 88%): $[\alpha]_D^{26}$ = +88.3 (*c* 0.41, $CHCl_3$); ν_{max}(film)/cm^{-1} 2973 (C-H), 2935 (C-H), 1778 (C=O), 1743 (C=O), 1639 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (s, 1H, C*H*(5-furan)), 5.97 (s, 1H, C*H*(3-furan)), 4.42 (dd, *J* = 9.9, 4.3 Hz, 1H, C*H*H'O), 4.16 (dd, *J* = 9.8, 8.6 Hz, 1H, CH*H*'O), 3.82 (tt, *J* = 8.9, 4.6 Hz, 1H, CH_2C*H*N), 3.50 - 3.40 (m, 3H, NCH_2, NC*H*H'), 3.32 – 3.28 (m, 1H, NCH*H*'), 3.07 - 2.92 (m, 1H, furan-CHC*H*H'), 2.92 - 2.82 (m, 1H, furan-C*H*), 2.75 - 2.67 (m, 3H, C*H*H'CHN, furan-CH_2), 2.46 - 2.33 (m, 2H, C≡CCH_2), 2.17 - 2.13 (m, 2H, C≡CCH_2), 2.08 (dd, *J* = 13.6, 9.3 Hz, 1H, CH*H*'CHN), 1.78 - 1.74 (m, 7H, 2 x alkyne-CH_3, furan-CHCH*H*'), 1.69 - 1.65 (m, 2H, $NCH_2CH_2CH_2$), 1.51 - 1.44 (m, 20H, 2 x (C(CH_3)$_3$, $NCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.8 (*C*=O), 167.7 (*C*=O), 155.7 (*C*(2-furan)), 153.0 (C=O), 149.3 (C=O), 138.5 (*C*(5-furan)), 123.9 (*C*(4-furan)), 105.5 (*C*(3-furan)), 83.3 (*C*(CH_3)$_3$), 82.1 (*C*(CH_3)$_3$) 78.8 (*C*≡C), 77.7 (C≡*C*), 76.3 (*C*≡C), 75.8 (C≡*C*), 68.1 (*C*H_2O), 57.0 (C_{quat}), 53.4 (CH_2*C*HN), 47.9 (*C*H_2N), 47.3 (*C*H_2N), 41.6 (*C*H-furan),

31.3 (*C*H_2CHN), 28.1 (furan-*C*H_2), 27.9 (3 x C*C*H_3), 27.7 (3 x C*C*H_3), 26.1 (NCH_2*C*H_2CH_2), 26.1 (NCH_2CH_2*C*H_2), 25.1 (furan-CH*C*H_2) 18.5 (C≡C*C*H_2), 17.9 (C≡C*C*H_2), 3.5 (alkyne-CH_3), 3.4 (alkyne-*C*H_3); *m/z* (ESI$^+$) 647 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 647.3305, $C_{35}H_{48}N_2NaO_8$ requires 647.3303.

6.2.20. Synthesis of *tert*-Butyl (3*R*,5*S*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy]methyl}-7-(hept-5-yn-1-yl)-1-hydroxy-6-oxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate 110

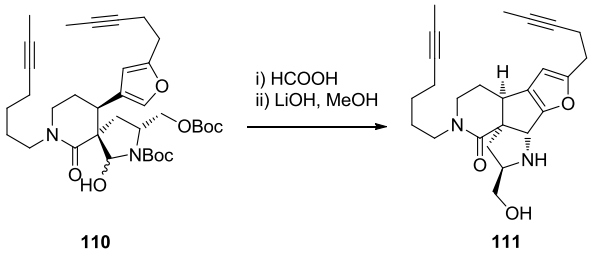


109 110

To a solution of **109** (0.34 g, 0.54 mmol) in THF (14 mL) was added dropwise lithium triethylborohydride (1.25 mL, 1.25 mmol, 1 M solution in THF) at −78 °C and the solution stirred at this temperature for 2 h before being quenched with sat. aq. NH_4Cl solution (15 mL). The reaction was allowed to warm to RT over 1 h and then diluted with diethyl ether (15 mL). The aqueous layer was extracted and the organics dried (Na_2SO_4) and concentrated. The crude oil was purified by column chromatography (PE:Et_2O 95:5→1:1.5) to yield the title compound **110** as a colourless oil (0.27 g, 79%). The ^{1}H NMR spectrum of the title compound suffers from considerable broadening due to rotamers when run in $CDCl_3$ at 298 K. NMR data were collected in toluene-d_8 at 363 K: ν_{max}(film)/cm^{-1} 2932 (C-H), 1776 (C=O), 1743 (C=O), 1698 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) (rotameric) δ_H 7.11 (br. s, 1H), 5.92 - 5.85 (m, 1H), 5.35 (br. s, 1H), 4.46 (br. s, 1H), 4.09 - 3.97 (m, 2H), 3.53 - 3.32 (m, 4H), 2.75 (t, *J* = 7.3 Hz, 3H), 2.42 (td, *J* = 2.6, 7.4 Hz, 3H), 2.23 - 2.12 (m, 3H), 1.82 - 1.75 (m, 6H), 1.75 - 1.61 (m, 3H), 1.48 (s, 13H), 1.44 - 1.32 (m, 8H); ^{1}H NMR (500 MHz, 363 K, toluene-d_8) δ_H 6.95 (br. s., 1H, C*H*(5-furan)), 5.85 (br. s., 1H, C*H*(3-furan)), 5.58 - 5.51 (m, 1H, C*H*OH), 4.54 (dd, *J*= 10.1, 4.1 Hz, 1H, C*H*H'O), 4.41 - 4.32 (m, 1H, CH*H*'O), 3.94 ('br. s.', 1H, CH_2C*H*N), 3.30 - 3.22 (m, 1H, NC*H*H'$(CH_2)_3$), 3.22

- 3.11 (m, 1H, NCH*H*'$(CH_2)_3$), 3.05 - 2.94 (m, 1H, NC*H*H'CH_2CH), 2.82 - 2.74 (m, 2H, NCH*H*'(CH_2)CH, C*H*H'CHN), 2.72 - 2.64 (m, 2H, furan-CH_2), 2.50 - 2.42 (m, 1H, furan-C*H*), 2.42 - 2.34 (m, 2H, furan- CH_2CH_2), 2.17 - 2.05 (m, 3H, C≡CC$H_2(CH_2)_3$, -O*H*), 2.05 - 1.97 (m, 1H, CH*H*'CHN), 1.76 - 1.33 (m, 30H, furan-CHCH_2, 2 x (C(C$H_3)_3$, 2 x alkyne-CH_3, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) δ_C 171.8 (*C*=O), 155.4 (*C*(2-furan)), 153.4 (*C*=O), 152.9 (*C*=O), 138.2 (*C*(5-furan)), 124.4 (*C*(4-furan)), 106.1 (*C*(3-furan)), 85.1(*C*HOH), 80.6 (*C*$(CH_3)_3$), 79.2 (*C*$(CH_3)_3$), 78.5 (*C*≡C), 77.6 (*C*≡C), 76.1 (*C*≡C), 75.5 (*C*≡C), 68.5 (*C*H_2O), 54.6 (CH_2*C*HN), 54.2 (C_{quat}), 47.2 (*C*H_2N), 45.0 (C*H*$_2$N), 37.5 (*C*H_2CHN), 37.1 (*C*H-furan), 28.1 furan-*C*H_2), 27.9 (3 x C*C*H_3), 27.4 (3 x C*C*H_3), 26.4 (NCH_2*C*H_2CH_2), 26.0 (NCH_2CH_2*C*H_2), 25.8 (furan-CH*C*H_2), 18.3 (C≡C*C*H_2), 17.8 (C≡C*C*H_2), 2.6 (alkyne-CH_3), 2.6 (alkyne-CH_3); *m/z* (ESI^+) 649 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 649.3454, $C_{35}H_{50}N_2NaO_8$ requires 649.3459.

6.2.21. (2*R*,3a*S*,7a*S*,10b*R*)-5-(Hept-5-yn-1-yl)-2-(hydroxymethyl)-9-(pent-3-yn-1-yl)-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one 111



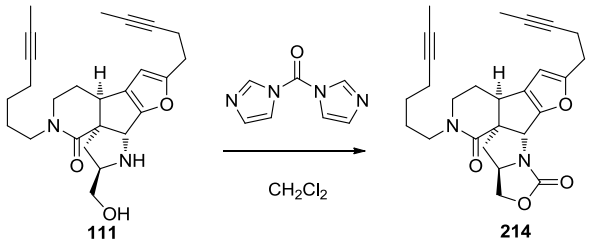
110 111

Substrate **110** (1.00 g, 1.60 mmol) was dissolved in formic acid (15.80 mL) and the solution stirred at RT for 15 h before being concentrated to a crude oil. The crude oil was dissolved in methanol (37 mL) and $LiOH{\cdot}H_2O$ (1.30 g, 31.91 mmol) added. The reaction was heated to 50 °C for 5 h before being concentrated to approximately 20% of the original volume. Water (30 mL) was added and the product extracted with 4:1 $CHCl_3$:IPA (5 x 55 mL). The organics were dried (Na_2SO_4) and concentrated to give a brown oil, which was purified by column chromatography (EtOAc→EtOAc:MeOH 9:1) to give the tetracyclic product **111** as a pale yellow oil (0.56 g, 86%): $[\alpha]_D^{26} = -78.1$ (*c* 0.32, $CHCl_3$); ν_{max}(film)/cm^{-1} 3301 (O-H), 2920 (C-H), 2860 (C-H), 1615 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.90 (s, 1H, C*H*(3-furan)), 4.72 (s, 1H, furan-C*H*NH), 3.84 (dd, *J* = 11.3, 3.6 Hz, 1H, C*H*H'O), 3.74 (dd, *J* = 11.3, 3.9 Hz, 1H, CH*H*'O), 3.42 (td, *J* = 7.3, 1.5 Hz, 2H, CH_2N), 3.36 - 3.26 (m, 2H, CH_2N), 3.26 - 3.19 (m, 1H, CH_2C*H*NH), 3.14 - 3.05 (m, 1H, furan-C*H*), 2.80 (t, *J* = 7.6 Hz, 2H, furan-CH_2), 2.51 - 2.41 (m, 2H, C≡CCH_2), 2.36 (dd, *J* = 12.8, 8.7 Hz, 1H, C*H*H'CHNH), 2.22 - 2.09 (m, 3H, C≡CCH_2, furan-CHC*H*H'), 1.91 (dd, *J* = 12.8, 7.4 Hz, 1H, CH*H*'CHNH), 1.83-1.76 (m, 6H, alkyne-CH_3), 1.70 - 1.57 (m, 3H, $NCH_2CH_2CH_2$, furan-CHCH*H*'), 1.52 - 1.39 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5 (*C*=O), 160.7 (*C*(5-

furan)), 154.6 (*C*(2-furan)), 128.9, (*C*(4-furan)), 102.5 (*C*(3-furan)), 78.7 (*C*≡C), 78.0 (C≡*C*), 76.2 (*C*≡C), 75.8 (C≡*C*), 69.0 (furan-*CH*NH), 65.8 (C_{quat}), 62.6 (CH_2O), 61.3 (CH_2CHN), 47.5 (CH_2N), 47.3 (CH_2N), 43.7 (*C*H-furan), 43.1 (CH_2CHN), 29.6 (furan-$CHCH_2$), 28.8 (furan-CH_2), 26.5 ($NCH_2CH_2CH_2$), 26.1 ($NCH_2CH_2CH_2$) 18.4 ($C{\equiv}CCH_2$), 17.8 ($C{\equiv}CCH_2$), 3.5 (alkyne-CH_3), 3.4 (alkyne-CH_3); *m/z* (ESI^+) 839 (95%, $[2M+Na]^+$), 817 (100, $[2M+H]^+$), 409 (96, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 431.2306, $C_{25}H_{32}N_2NaO_3$ requires 431.2305.

6.3. Chapter 3: Experimental

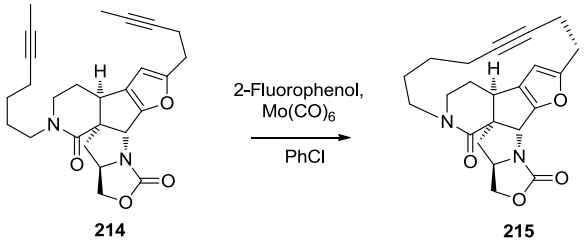
6.3.1. Synthesis of (3a*R*,4a*S*,8a*S*,11b*R*)-6-(hept-5-yn-1-yl)-10-(pent-3-yn-1-yl)-3a,4,7,8,8a,11b-hexahydro-3*H*-furo[3',2':3,4][1,3]oxazolo [3'',4'':1',5']pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridine-1,5(6*H*)-dione 214



Aminol **111** (0.100 g, 0.245 mmol) was dissolved in CH_2Cl_2 (15 mL) and 1,1'carbonyldiimidazole (0.044 g, 0.27 mmol) added. The reaction mixture was stirred for 15 h at RT before being concentrated and purified directly by column chromatography (EtOAc) to yield the title compound **214** as a light brown oil (0.098 g, 92%): $[\alpha]_D^{26}$ = −26.2 (*c* 0.21, $CHCl_3$); ν_{max}(film)/cm^{-1} 2920 (C-H), 2859 (C-H), 1756 (C=O$_{oxazolidinone}$), 1633 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.91 (s, 1H, C*H*(3-furan)), 5.30 (s, 1H, furan-C*H*NH), 4.49 (dd, *J* = 8.7, 7.7 Hz, 1H, C*H*H'O), 4.27 (dd, *J* = 8.7, 2.6 Hz, 1H, CH*H*'O), 4.09 - 3.98 (m, 1H, CH_2C*H*NH), 3.51 - 3.41 (m, 1H, C*H*H'N), 3.40 - 3.31 (m, 1H, CH*H*'N), 3.27 - 3.21 (m, 2H, CH_2N), 3.21 - 3.16 (m, 1H, furan-C*H*), 2.80 (t, *J* = 7.5 Hz, 2H, furan-CH_2), 2.55 (dd, *J* = 12.6, 9.4 Hz, 1H, C*H*H'CHNH), 2.51 - 2.40 (m, 2H, C≡CCH_2), 2.22 - 2.06 (m, 4H, CH*H*'CHNH, C≡CCH_2, C*H*H'), 1.81 - 1.73 (m, 7H, 2 x alkyne-CH_3, CH*H*'), 1.69 - 1.55 (m, 2H, CH_2), 1.50 - 1.37 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.4 (*C*=O), 161.9 (*C*=O), 160.2 (*C*(5-furan)), 152.3 (*C*(2-furan)), 130.0, (*C*(4-furan)), 102.6 (*C*(3-furan)), 78.7 (*C*≡C), 77.8 (C≡*C*), 76.4 (*C*≡C), 75.9 (C≡*C*), 67.7 (CH_2O), 67.2 (furan-*C*HNH), 66.4 (C_{quat}), 58.8 (CH_2*C*HN), 47.8 (CH_2N), 44.6 (CH_2N), 43.9 (CH_2CHN), 42.3 (*C*H-furan), 28.8 (CH_2), 28.7 (CH_2), 26.4 (CH_2), 26.2 (CH_2)

18.4 (C≡C*C*H_2), 17.8 (C≡C*C*H_2), 3.5 (2 x alkyne-CH_3); *m/z* (ESI^+) 891 (75%, $[2M+Na]^+$), 536 (100, $[M+Et_3N]^+$), 457 (97, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 457.2101, $C_{26}H_{30}N_2NaO_4$ requires 457.2098.

6.3.2. Synthesis of (3a*R*,4a*S*,8a*S*,11b*R*)-3a,4,7,8,8a,11b-Hexahydro-3*H*-10,6oct[3]ynofuro[3',2':3,4][1,3]oxazolo[3'',4'':1',5']pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridine-1,5-dione 215

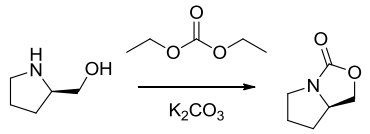


214 215

Oxazolidinone **214** (0.047 g, 0.108 mmol) was dissolved in chlorobenzene (30 mL) which had been thoroughly degassed and re-filled with argon. To this was added 2-fluorophenol (10 µl, 0.012 g, 0.108 mmol) and the pale yellow solution heated to 165 °C (oil bath temperature). As soon as this temperature had been attained, $Mo(CO)_6$ (0.0057 g, 0.021 mmol) was added and the reaction heated under reflux. A dark brown solution was observed 2-5 min after $Mo(CO)_6$ is added. After 50 min mass spec analysis showed complete consumption of the starting material and alumina (40 mg) was added to the hot reaction mixture, which was then cooled to RT. The reaction mixture was filtered through a small celite® plug to give a pale yellow solution which was concentrated and purified by column chromatography (EtOAc→EtOAc:MeOH 9:1) to give the title cyclised product **215** as an off-colourless solid (0.015 g, 36%): mp 132 °C (EtOAc); $[\alpha]_D^{26}$ = +7.1 (*c* 0.07, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928 (C-H), 1749 (C=O$_{oxazolidinone}$), 1629 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.98 (s, 1H, C*H*(3-furan)), 4.99 (s, 1H, furan-C*H*NH), 4.52 (dd, *J* = 8.8, 7.6 Hz, 1H, C*H*H'O), 4.47- 4.39 (m, 1H, $(CH_2)_3$C*H*H'N), 4.30 (dd, *J* = 8.8, 2.5 Hz, 1H, CH*H*'O), 4.27 - 4.19 (m, 1H, CH_2C*H*NH), 3.36 (br. s., 1H, furan-C*H*$(CH_2)_2$N), 3.30 (dt, *J* = 12.3, 3.3 Hz, 1H, NC*H*H'CH_2CH), 2.99 (dt, *J* = 12.3, 2.2 Hz, 1H, NCH*H*'CH_2CH), 2.86 - 2.74 (m, 2H, furan-CH_2), 2.67 - 2.60 (m, 1H,

C≡CC*H*H'CH_2-furan), 2.60 - 2.55 (m, 1H, $(CH_2)_3$CH*H*'N), 2.46 (t, *J* = 11.7 Hz, 1H, C*H*H'CHNH), 2.36 - 2.27 (m, 1H, C≡CCH*H*'CH_2-furan), 2.27 - 2.13 (m, 2H, C≡CC*H*H'$(CH_2)_3$, NCH_2C*H*H'CH), 2.08 - 1.96 (m, 2H, CH*H'*CHN, NCH_2CH*H*'CH), 1.80 - 1.67 (m, 1H, C≡CCH*H*'$(CH_2)_3$), 1.52 - 1.33 (m, 3H, C≡C$(CH_2)_2$C*H*$_2$, C≡CCH_2C*H*H'), 0.79 - 0.68 (m, 1H, C≡CCH_2CH*H*'); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.2 (*C*=O), 162.0 (*C*=O), 160.3 (*C*(5-furan)), 154.0 (*C*(2-furan)), 129.8, (*C*(4-furan)), 103.0 (*C*(3-furan)), 82.5 (*C*≡C), 78.0 (C≡*C*), 71.2 (C_{quat}), 68.1 (furan-*C*HNH), 66.7 (*C*H_2O), 60.5 (CH_2*C*HN), 46.7 ($(CH_2)_3$*C*H_2N), 43.8 (CHCH_2*C*H_2N), 39.8 (CH_2*C*H-furan), 39.2 (*C*H_2CHN), 27.7 (furan-*C*H_2), 26.8 (C≡C$(CH_2)_2$*C*H_2), 26.3 (C≡CCH_2*C*H_2), 23.6 (NCH_2*C*H_2CH) 19.6 (C≡C*C*H_2CH_2-furan), 18.3 (C≡C*C*$H_2(CH_2)_3$); *m/z* (ESI$^+$) 783 (98%, $[2M+Na]^+$), 482 (58, $[M+Et_3N]^+$), 403 (100, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 403.1630, $C_{22}H_{24}N_2NaO_4$ requires 403.1628.

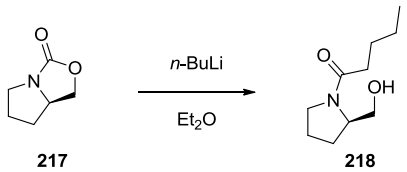
6.3.3. Synthesis of (7a*R*)-Tetrahydro-*1H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one 217



216 **217**

Prolinol **216** (1.67 g, 16.5 mmol), diethyl carbonate (2.80 g, 19.7 mmol) and potassium carbonate (0.160 g, 1.16 mmol) were heated neat at 130 °C for 15 h. The reaction mixture was cooled, poured into $CHCl_3$ and washed with sat. NaCl (aq) solution (2 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude oxazolidinone **217**, which was purified by column chromatography (EtOAc:PE 1:1) to give the title compound **217** as a colourless oil (1.25 g, 60%): $[\alpha]_D^{24}$ = +36.2 (*c* 1.0, $CHCl_3$); lit.[111] $[\alpha]_D^{24}$ = + 37.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.47 (dd, *J* = 8.8, 8.3 Hz, 1H, C*H*H'O), 4.13 (dd, *J* = 8.8, 3.5 Hz, 1H, CH*H'*O), 3.94 - 3.81 (m, 1H, NC*H*), 3.60 (dt, J = 11.3, 7.6 Hz, 1H, C*H*H'N), 3.14 (ddd, *J* = 11.4, 9.2, 4.2 Hz, 1H, CH*H*'N), 2.10 - 1.97 (m, 2H, CH_2), 1.97 - 1.81 (m, 1H, CH_2), 1.44 (dq, J = 12.5, 9.5 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.7 (*C*=O), 67.8 (*C*H_2O), 59.4 (*C*HN), 45.8 (*C*H_2N), 30.7 (*C*H_2CHN), 25.7 (*C*H_2CH_2N). Data are in agreement with that previously reported.[111]

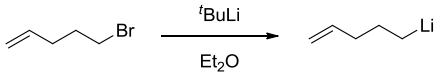
6.3.4. Synthesis of 1-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]pentan-1-one 218



217 218

n-BuLi (1.6 M in hexanes, 197 µL, 0.315 mmol) was added dropwise to a solution of oxazolidinone **217** (0.020 g, 0.157 mmol) in diethyl ether (2 mL) cooled to −78 °C. The solution was stirred at −78 °C for 2 h before being quenched with acetic acid (100 µL). The reaction mixture was warmed to RT and then concentrated *in vacuo* before being purified by column chromatography (EtOAc:PE 1:1→4:1) to give the title compound **218** as a colourless oil (19.3 mg, 66%): $[\alpha]_D^{24}$ = −30.9 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3395 (C-H), 2958 (C-H), 1620 (C=O), 1445 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.30 (br. s, 1H, -O*H*), 4.28 - 4.19 (m, 1H, NC*H*), 3.74 - 3.63 (m, 1H, C*H*H'OH), 3.63 - 3.40 (m, 3H, CH*H*'OH, NCH_2), 2.31 (t, *J* = 7.7 Hz, 2H, C=OCH_2), 2.13 – 1.99 (m, 1H, C*H*H'), 1.99 - 1.81 (m, 2H, CH_2), 1.69 - 1.53 (m, 3H, CH*H*', CH_2), 1.38 (dq, *J* = 15.0, 7.4 Hz, 2H, C$H_2$$CH_3$), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.8 (C=O), 67.6 (*C*H_2OH), 61.1 (N*C*H), 48.1 (N*C*H_2), 34.8 (C=O*C*H_2), 28.3 (*C*H_2), 26.9 (*C*H_2), 24.4 (*C*H_2), 22.5 (*C*H_2), 13.9 (*C*H_3); *m/z* (ESI$^+$) 393 (100%, $[2M+Na]^+$), 377 (36, $[2M+Li]^+$), 208 (48, $[M+Na]^+$), 186 (33, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 208.1306, $C_{10}H_{19}NNaO_2$ requires 208.1308.

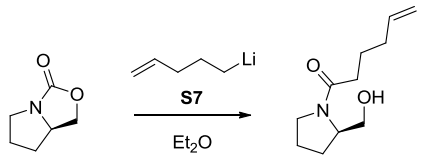
6.3.5. Synthesis of pent-4-enyllithium S7



S6 **S7**

5-Bromo-1-pentene **S6** (0.10 g, 0.67 mmol) was dissolved in diethyl ether (3 mL) and the solution cooled to −78 °C. *tert*-Butyllithium (1.7 M in pentane, 0.87 mL, 1.48 mmol) was added dropwise and the reaction mixture stirred at −78 °C for 1.25 h followed by 1 h at 0 °C. The solution was used directly without further analysis, assuming quantitative conversion to pent-4-enyllithium **S7**.

6.3.6. Synthesis of 1-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]hex-5-en-1-one 219

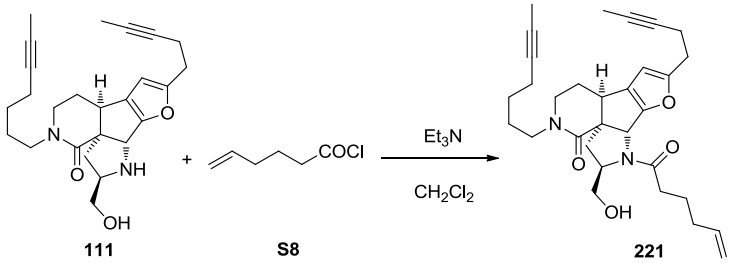


217 **219**

Pent-4-enyllithium **S7** (0.22 M in diethyl ether, 2.85 mL, 0.63 mmol) was added dropwise to a solution of oxazolidinone **217** (0.040 g, 0.315 mmol) in diethyl ether (1 mL) cooled to −78 °C. The solution was stirred at −78 °C for 2 h before being quenched with acetic acid (200 µl). The reaction mixture was warmed to RT and then concentrated before being purified by column chromatography (EtOAc:PE 1:1→4:1) to give the title compound **219** as a colourless oil (0.010 g, 16%): $[\alpha]_D^{24}$ = −31.3 (*c* 0.54, $CHCl_3$); ν_{max}(film)/cm^{-1} 3391 [41], 2929 (C-H), 1618 (C=O), 1440 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.86 - 5.75 (m, 1H, C*H*=CH_2), 5.19 (br. s, 1H, O*H*) 5.07 - 4.97 (m, 2H, CH=CH_2), 4.27 - 4.20 (m, 1H, NC*H*), 3.67 (dd, *J* = 11.2, 2.7 Hz, 1 H, C*H*H'OH), 3.43 - 3.60 (m, 3H, CH*H*'OH, CH_2N), 2.28 - 2.35 (m, 2H, CH_2),

2.16 - 2.09 (m, 2H, C*H*$_2$), 2.09 - 2.00 (m, 1H, C*H*H'), 1.94 (td, *J* = 13.0, 6.5 Hz, 1H, CH*H*'), 1.90 - 1.83 (m, 1H, C*H*H'), 1.73 - 1.83 (m, 2H, C*H*$_2$), 1.58 (app. dq, *J* = 12.8, 6.6 Hz, 1H, CH*H*'); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.4 (C=O), 138.0 (*C*H=CH$_2$), 115.2 (CH=*C*H$_2$), 67.7 (*C*H$_2$OH), 61.2 (N*C*H), 48.1 (N*C*H$_2$), 34.2 (*C*H$_2$), 33.2 (*C*H$_2$), 28.3 (*C*H$_2$), 24.4 (*C*H$_2$), 23.8 (*C*H$_2$); *m/z* (ESI$^+$) 417 (100%, [2M+Na]$^+$), 401 (77, [2M+Li]$^+$), 220 (54, [M+Na]$^+$), 198 (38, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 220.1307, $C_{11}H_{19}NNaO_2$ requires 220.1308.

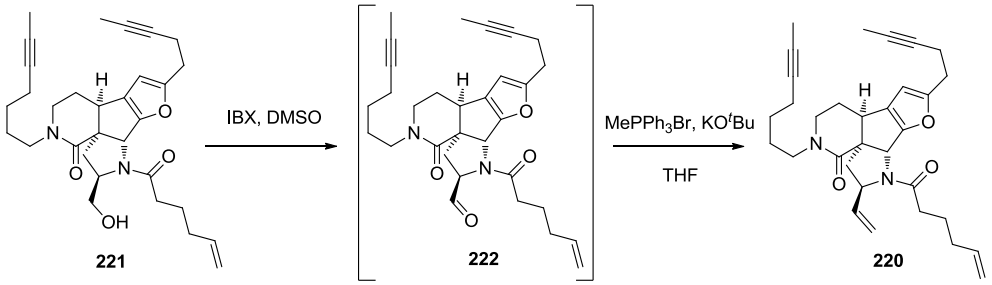
6.3.7. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-5-(hept-5-yn-1-yl)-1-(hex-5-enoyl)-2-(hydroxymethyl)-9-(pent-3-yn-1-yl)-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo [3',2':1,5]cyclopenta[1,2-*c*] pyridin-4-one 221



Tetracycle **111** (0.475 g, 1.16 mmol) and Et_3N (810 µl, 5.81 mmol) were dissolved in CH_2Cl_2 (24 mL) and the resulting solution was cooled to −20 °C. A solution of hex-5-enoyl chloride **S8** (159 µl, 1.22 mmol) in CH_2Cl_2 (9 mL) pre-cooled to −20 °C was added and the reaction mixture warmed to RT over 0.5 h. After stirring at RT for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to give amide **221** as a colourless oil (0.520 g, 89%): $[\alpha]_D^{25}$ = −0.82 (*c* 0.51, $CHCl_3$); ν_{max}(film)/cm^{-1} 3340 (O-H), 2920 (C-H), 2859 (C-H), 1634 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.92 (s, 1H, C*H*(3-furan)), 5.90 - 5.75 (m, 1H, C*H*=CH_2), 5.26 (s, 1H, furan-C*H*N), 5.10 – 4.95 (m, 2H, CH=C*H*$_2$), 4.01 – 3.91 (m, 1H, CH_2C*H*N), 3.81 (dd, *J* = 12.5, 6.9 Hz, 1H, C*H*H'OH), 3.71-3.63 (m, 1H, CH*H*'OH), 3.43 (ddd, *J* = 13.7, 7.3, 7.0 Hz, 1H, C*H*H'N), 3.36 - 3.26 (m, 1H, CH*H*'N), 3.26 - 3.10 (m, 3H, furan-C*H*, C*H*$_2$N), 2.76 (t, *J* = 7.6 Hz, 2H, furan-C*H*$_2$), 2.72 - 2.64 (m, 1H, NC(O)C*H*H'), 2.60 - 2.50 (m, 1H, NC(O)CH*H*'), 2.45 - 2.37 (m, 2H, C≡CC*H*$_2$), 2.29 (dd, *J* = 12.9, 9.9 Hz, 1H, C*H*H'CHN), 2.18 - 2.08 (m, 5H, C≡CC*H*$_2$, H_2C=CHC*H*$_2$, furan-CHC*H*H'), 2.04 (dd, *J* = 12.9, 6.8 Hz, 1H, CH*H*'CHN), 1.85 - 1.77 (m, 3H, H_2C=CHCH_2C*H*$_2$, furan-CHCH*H*'), 1.77 - 1.72 (m, 6H, 2 x alkyne-C*H*$_3$), 1.59 (qd, *J* = 7.5, 7.3 Hz, 2H, NCH_2C*H*$_2$CH_2), 1.46 - 1.36 (m, 2H, NCH_2C*H*$_2$C*H*$_2$); ^{13}C NMR (100

MHz, $CDCl_3$) δ_C 174.0 (*C*=O), 171.5 (*C*=O), 161.1 (*C*(5-furan)), 153.2 (*C*(2-furan)), 138.1 (*C*H=CH_2), 129.8 (*C*(4-furan)), 115.1 (CH=*C*H_2), 102.7 (*C*(3-furan)), 78.5 (*C*≡C), 77.5 (C≡*C*), 76.5 (*C*≡C), 75.9 (C≡*C*), 66.6 (furan-*C*HN), 65.3 (C_{quat}), 64.1 (*C*H_2O), 63.6 (CH_2*C*HN), 47.8 (*C*H_2N), 44.6 (*C*H_2N), 42.4 (*C*H-furan), 40.4 (*C*H_2CHN), 34.2 (NC(O)*C*H_2), 33.2 (H_2C=CH*C*H_2), 28.7 (furan-*C*H_2), 27.8 (furan-CH*C*H_2), 26.3 (NCH_2*C*H_2CH_2), 26.1 (NCH_2CH_2*C*H_2), 24.1 (H_2C=CHCH_2*C*H_2), 18.4 (C≡C*C*H_2), 17.7 (C≡C*C*H_2), 3.4 (2 x alkyne-*C*H_3); *m/z* (ESI^+) 527 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 527.2876, $C_{31}H_{40}N_2NaO_4$ requires 527.2880.

6.3.8. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-5-(hept-5-yn-1-yl)-1-(hex-5-enoyl)-9-(pent-3-yn-1-yl)-2-vinyl-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*] pyridin-4-one 220



2-Iodoxybenzoic acid (IBX) (0.512 g, 1.83 mmol) was added to a solution of **221** (0.205 g, 0.41 mmol) in DMSO (20 mL) and the resulting solution stirred at RT for 24 h. The solution was poured into sat. aq. $NaHCO_3$ solution (60 mL) and extracted with diethyl ether (4 x 60 mL). The combined organic extracts were washed with water (30 mL), dried (Na_2SO_4) and concentrated to give aldehyde **222** as a yellow oil (0.200 g), which was used directly without further purification.

[Preparation of ylide solution: KO^{t}Bu (0.217 g, 1.93 mmol) was added to $MePPh_3Br$ (0.870 g, 2.44 mmol) in toluene (13.5 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT].

The crude aldehyde **222** was dissolved in THF (13.5 mL) and the solution added rapidly to the above freshly prepared ylide solution, at RT. After 15 min TLC analysis indicated complete consumption of starting material. Water (12 mL) was added and THF/toluene were removed under reduced pressure. Water (30 mL) and ethyl acetate (35 mL) were added to the residue. The layers were separated and the aqueous layer was further extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4) and concentrated. The crude

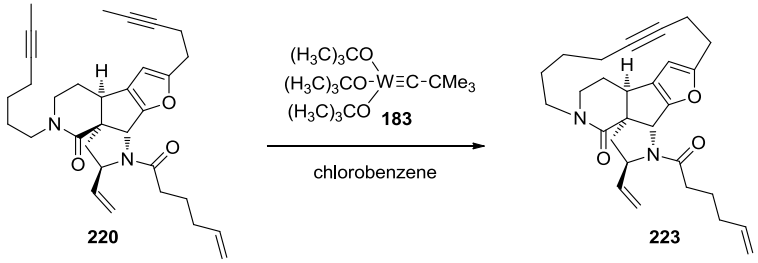
residue was purified by column chromatography (EtOAc:PE 2:3→3:2) to yield the title compound **220** as a yellow oil (0.150 g, 74% over 2 steps). The compound was rotameric resulting in complex ^{1}H and ^{13}C NMR spectra at 298 K. Data was collected at 373 K. At this temperature ^{1}H NMR and ^{13}C signals coalesced: $[\alpha]_D^{25}$ = −0.56 (*c* 0.65, $CHCl_3$); ν_{max}(film)/cm^{-1} 2920 (C-H), 2859 (C-H), 1640 (C=O); ^{1}H NMR (500 MHz, 373 K, toluene-d_8) δ_H 6.48 (ddd, *J* = 17.0, 9.0, 8.7 Hz, 1H, CHC*H*=CH_2), 5.89 - 5.78 (m, 2H, C*H*(3-furan), CH_2C*H*=CH_2), 5.59 (br. s., 1H, furan-C*H*N), 5.10 - 4.93 (m, 4H, CHCH=CH_2, CH_2CH=CH_2), 4.32 (br. s., 1H, C*H*CH=CH_2), 3.31 (ddd, *J* = 13.5, 7.1, 6.9 Hz, 1H, C*H*H'N), 3.23 (ddd, *J* = 13.5, 7.1, 6.9 Hz, 1H, C*H*H'N), 2.91 - 2.80 (m, 2H, CH_2N), 2.79 - 2.75 (m, 1H, furan-C*H*), 2.71 (t, *J* = 7.3 Hz, 2H, furan-CH_2), 2.60-2.49 (m, 2H, NC(O)C*H*H', C*H*H'CHN), 2.43 - 2.30 (m, 3H, NC(O)CH*H*', furan-CH_2CH_2), 2.19 - 2.12 (m, 2H, CH_2CH=CH_2), 2.12 - 2.06 (m, 2H, $(CH_2)_3$CH_2C≡C), 2.06 – 1.98 (m, 1H, CH*H*'CHN), 1.97 - 1.84 (m, 2H, NC(O)CH_2CH_2), 1.77 - 1.70 (m, 1H, furan-CHC*H*H'), 1.64 (t, *J* = 2.5 Hz, 3H, C≡CCH_3), 1.61 (t, *J* = 2.5 Hz, 3H, C≡CCH_3), 1.55-1.48 (m, 2H, C$H_2$$(CH_2)_2$C≡C), 1.43 - 1.34 (m, 3H, C$H_2$$CH_2$C≡C, furan-CHCH*H*'); ^{13}C NMR (125 MHz, 373 K, toluene-d_8) δ_C 172.0 (*C*=O), 171.6 (*C*=O), 161.3 (*C*(5-furan)), 155.6[a] (*C*(2-furan)), 139.2 (CH*C*H=CH_2), 137.9 (CH_2*C*H=CH_2), 128.4 (*C*(4-furan)), 114.8 (CH=*C*H_2), 113.8 (CH=*C*H_2), 102.8 (*C*(3-furan)), 79.2 (*C*≡C), 78.4 (C≡*C*), 76.6 (*C*≡C), 76.0 (C≡*C*), 66.6 (furan-*C*HN), 66.4[b] (C_{quat}), 62.5 (*C*HCH=CH_2), 47.9 (N$CH_2$$(CH_2)_3$), 2 x 45.3 (*C*$H_2$N), (*C*$H_2$CHN), 44.2 (*C*H-furan), 34.9 (NC(O)*C*H_2), 33.8 (*C*H_2CH=CH_2), 29.9 (furan-CH*C*H_2), 29.5 (furan-*C*H_2), 27.2 (NCH_2*C*$H_2$$CH_2$), 27.0 (N$CH_2$$CH_2$*C*$H_2$), 25.1 ($H_2$C=CHC$H_2$*C*$H_2$), 18.9 (C≡C*C*$H_2$), 18.5 (C≡C*C*$H_2$), 2 x 3.2 (2 x C≡C*C*$H_3$);

^{13}C NMR (rotameric) (125 MHz, 298 K, $CDCl_3$) δ_C 172.9, 172.8, 172.1, 171.6, 161.0, 160.8, 155.6, 154.0, 141.3, 139.7, 138.4, 129.2, 127.7, 114.9, 114.9, 114.8, 113.7, 102.7, 102.4, 78.7, 78.6, 78.0, 77.6, 76.5, 76.2, 75.9, 66.4, 65.4, 65.1, 62.3, 62.1, 61.7, 47.8, 47.7, 44.9, 44.8, 44.7, 43.9, 43.4, 42.7, 34.1, 34.1, 33.3, 33.2, 30.0, 29.7, 28.8, 28.8, 28.1, 26.6, 26.4, 26.2, 26.2, 24.2, 24.1, 18.5, 18.5, 17.9, 17.9, 3.5; *m/z* (ESI$^+$) 523 (100%, $[M+Na]^+$), 501 (15, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 523.2928, $C_{32}H_{40}N_2NaO_3$ requires 523.2931.

[a] Quaternary *C*(furan) signal not observed in ^{13}C NMR spectrum , however it is observed in the rotameric ^{13}C NMR spectrum (298 K, $CDCl_3$) at 155.6 and 154.0 ppm (2 rotamers).

[b] Quaternary *C*(quat) signal not observed in ^{13}C NMR spectrum , however it is observed in the rotameric ^{13}C NMR spectrum (298 K, $CDCl_3$) 66.4 ppm.

6.3.9. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-1-(hex-5-enoyl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]ynofuro[3',2':3,4]pyrrolo [3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one 223



Tris(*t*-butoxy)(2,2-dimethylpropylidyne)tungsten(VI) **183** (0.010 g, 0.022 mmol) was weighed into a Schlenk tube in a glovebox under an argon atmosphere. The flask was removed from the glovebox and maintained under argon. A solution of diyne **220** (0.036 g, 0.072 mmol) in chlorobenzene (40 mL) was added to the catalyst and the reaction mixture heated to 80 ^{o}C under argon for 2 h. The reaction mixture was cooled to RT and opened to air. After stirring the reaction mixture for 0.5 h, the reaction mixture was concentrated under reduced pressure. (The rotary evaporator water bath was kept at RT when concentrating the reaction mixture. Decomposition of the product presumably by polymerisation occurred when the reaction mixture was concentrated using a warm (40 ^{o}C) water bath and without first exposing the reaction mixture to air). The crude residue was purified by column chromatography (Et_2O:PE 7:3→Et_2O:EtOAc 1:1) to yield the title compound **223** as a colourless oil (0.022 g, 69%). The compound was rotameric resulting in complex ^{1}H and ^{13}C NMR spectra at 298 K. Data was collected at 363 K: $[\alpha]_D^{25} = -48.1$ (*c* 0.50, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928 (C-H), 1632 (C=O); ^{1}H NMR (500 MHz, 363 K, toluene-d_8) δ_H 5.93 (br. s., 1H, CHC*H*=CH_2), 5.78 - 5.66 (m, 1H, CH_2C*H*=CH_2), 5.65 (s, 1H, C*H*(3-furan)), 5.19 (br. s, 1H, furan-C*H*N), 5.14 - 5.00 (m, 1H, CHCH=C*H*H'), 5.00 - 4.83 (m, 3H, CH_2CH=CH_2,

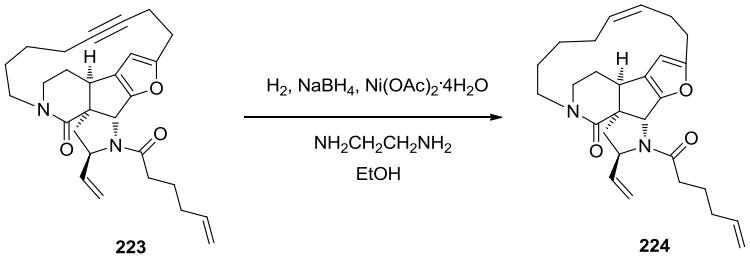
CHCH=CH*H*'), 4.55 (br. s., 1H, C*H*CH=CH_2), 4.46 (ddd, *J* = 13.6, 10.6, 3.0 Hz, 1H, C*H*H'N), 3.09 (td, *J* = 12.1, 3.5 Hz, 1H, C*H*H'N), 3.02 (br. s., 1H, furan-C*H*), 2.61 - 2.50 (m, 2H, furan-C*H*H', C*H*H'CHN), 2.50 – 2.45 (m, 1H, CH*H*'N), 2.44 - 2.30 (m, 3H, NC(O)C*H*H', furan-CH_2C*H*H', furan-CH*H*'), 2.29 - 2.14 (m, 1H, NC(O)CH*H*'), 2.07 - 1.97 (m, 4H, C*H*$_2$CH=CH_2, furan-CH_2CH*H*', CH*H*'N), 1.97 – 1.89 (m, 1H, $(CH_2)_3$C*H*H'C≡C), 1.82 (dd, *J* = 12.8, 6.8 Hz, 1H, CH*H*'CHN), 1.78 - 1.62 (m, 3H, C*H*$_2$$CH_2$CH=$CH_2$, furan-CHC*H*H'), 1.62 - 1.49 (m, 2H, furan-CHCH*H*', $(CH_2)_3$CH*H*'C≡C), 1.31 - 1.11 (m, 2H, C*H*H'CH_2C≡C, C*H*H'$(CH_2)_2$C≡C), 1.09 - 0.99 (m, 1H, CH*H*'$(CH_2)_2$C≡C), 0.90 - 0.79 (m, 1H, CH*H*'CH_2C≡C); ^{13}C NMR (125 MHz, 373 K, toluene-d_8) δ_C 170.9 (C=O), 170.4 (C=O), 159.5 (*C*(5-furan)), 156.6[a] (*C*(2-furan)), 140.3 (CH*C*H=CH_2), 137.0 (CH_2*C*H=CH_2), 128.6 (*C*(4-furan)), 114.0 (CH=*C*H_2), 113.2 (CH=*C*H_2), 102.5 (*C*(3-furan)), 82.1 (*C*≡C), 78.1 (*C*≡C), 70.4[b] (C_{quat}), 67.5[c] (furan-*C*HN), 62.7 (*C*HCH=CH_2), 46.8 (NC$H_2$$(CH_2)_3$), 44.1 (*C*$H_2$N), 39.7 (*C*H-furan), 38.7[c] (*C*H_2CHN), 34.3 (NC(O)*C*H_2), 33.1 (*C*H_2CH=CH_2), 27.7 (furan-*C*H_2), 27.4 (NCH_2CH_2*C*H_2), 27.3 (NCH_2*C*H_2CH_2), 24.4 (H_2C=CHCH_2*C*H_2), 22.3 (furan-CH*C*H_2), 19.0 (C≡C*C*H_2), 18.2 (C≡C*C*H_2); ^{13}C NMR (rotameric) (125 MHz, 298 K, toluene-d_8) δ_H 171.9, 171.5, 171.2, 171.0, 160.5, 158.5, 157.0, 141.8, 141.0, 139.4, 130.8, 115.1, 114.9, 113.8, 103.7, 102.6, 83.0, 82.8, 79.0, 78.7, 70.8, 69.3, 67.6, 63.7, 63.6, 47.5, 47.4, 44.5, 41.0, 40.4, 39.8, 38.9, 35.1, 34.1, 28.5, 28.1, 28.0, 27.9, 25.3, 24.9, 23.4, 22.8, 19.1; *m/z* (ESI$^+$) 915 (97%, $[2M+Na]^+$), 469 (100, $[M+Na]^+$), 447 (38, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 469.2463, $C_{28}H_{34}N_2NaO_3$ requires 469.2462.

[a] Quaternary *C*(furan) signal not observed in ^{13}C NMR spectrum , however it is observed in the rotameric ^{13}C NMR spectrum (298 K, toluene-d_8) at 158.5 and 157.0 ppm.

[b] Quaternary C_{quat} signal not observed in ^{13}C NMR spectrum , however it is observed in the rotameric ^{13}C NMR spectrum (298 K, toluene-d_8) at 69.3 ppm.

[c] These signals are not observed in ^{13}C NMR spectrum , however they are observed in the 2D HSQC NMR spectrum (363 K, toluene-d_8).

6.3.10. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*,13*Z*)-1-(hex-5-enoyl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]enofuro[3',2':3,4]pyrrolo [3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one 224



Under an atmosphere of H_2 (~1 atm.), sodium borohydride (3 mg, 0.09 mmol, 0.7 mL of a stock solution in ethanol (0.024 g in 5 mL of ethanol)) was added to a suspension of $Ni(OAc)_2{\cdot}4H_2O$ (11 mg, 0.045 mmol) in ethanol (1.2 mL) at RT. Ethylene diamine (67 mg, 0.075 mL, 1.1 mmol) was added immediately in one portion to the black suspension which was then stirred for 0.5 h. Pentacycle **223** (20 mg, 0.045 mmol) in ethanol (1.2 mL) was added to the black suspension. The desired product **224** and starting material **223** co-elute by TLC analysis therefore the reaction was closely monitored by mass spectrometry until all starting material had been consumed (typically 0.75 h – 1.25 h). The reaction mixture was filtered through a celite plug washing with ethyl acetate. The solvent was removed under reduced pressure and the crude residue was re-dissolved in ethyl acetate and passed through a second celite plug to remove any remaining inorganic salts. The solvent was removed under reduced pressure and the crude residue purified by column chromatography ($Et_2O \rightarrow EtOAc$) to give the title compound **224** as a colourless oil (18 mg, 87%). The compound was rotameric resulting in complex ^1H and ^{13}C NMR spectra at 298 K. Data was collected at 373 K: $[\alpha]_D^{25} = -93.3$ (*c* 0.43, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931 (C-H), 2862 (C-H), 1633 (C=O); ^1H NMR (500 MHz, 373 K, toluene-d_8) δ_H 6.07 - 5.84 (m, 1H,

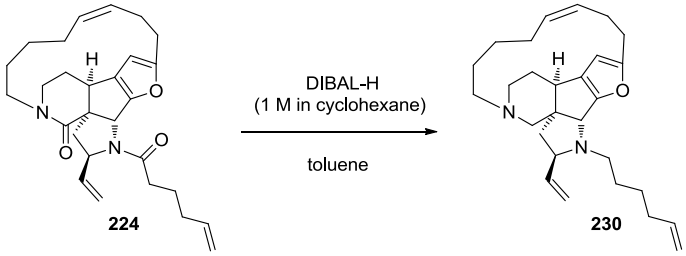
CHC*H*=CH_2), 5.80 - 5.67 (m, 1H, CH_2C*H*=CH_2), 5.55 (s, 1H, C*H*(3-furan)), 5.45 - 5.34 (m, 1H, $(CH_2)_4$C*H*=CH), 5.23 - 5.15 (m, 1H, CH=C*H*$(CH_2)_2$), 5.15 - 5.04 (m, 2H, furan-C*H*N, CHCH=C*H*H'), 5.01 - 4.87 (m, 3H, CH_2CH=C*H*$_2$, CHCH=CH*H*'), 4.63 - 4.50 (m, 2H, C*H*CH=CH_2, C*H*H'N), 3.00 (br. s, 1H, furan-C*H*), 2.91 (td, *J* = 12.3, 3.8 Hz, 1H, C*H*H'N), 2.69 - 2.61 (m, 1H, furan-C*H*H'), 2.53 (dd, *J* = 12.9, 9.8 Hz, 1H, C*H*H'CHN), 2.47 - 2.42 (m, 1H, CH*H*'N), 2.38 - 2.18 (m, 4H, NC(O)C*H*$_2$, furan-CH*H*', furan-CH_2C*H*H'), 2.18 - 2.14 (m, 1H, CH*H*'N), 2.07 – 2.01 (q, *J* = 6.7 Hz, 2H, C*H*$_2$CH=CH_2), 2.01 - 1.90 (m, 1H, furan-CH_2CH*H*'), 1.87 - 1.73 (m, 4H, C*H*$_2$$CH_2$CH=$CH_2$, $(CH_2)_3$C*H*H'CH=CH, CH*H*'CHN), 1.71 – 1.63 (m, 1H, furan-CHC*H*H'), 1.57 - 1.44 (m, 2H, furan-CHCH*H*', $(CH_2)_3$CH*H*'CH=CH), 1.32 - 1.18 (m, 1H, C*H*H'$(CH_2)_2$CH=CH), 1.10 - 1.00 (m, 1H, CH*H*'$(CH_2)_2$CH=CH), 0.98 - 0.85 (m, 1H, C*H*H'CH_2CH=CH), 0.19 - 0.06 (m, 1H, CH*H*'CH_2CH=CH); ^{13}C NMR (125 MHz, 373 K, toluene-d_8) δ_C 171.1 (C=O), 170.9[a] (C=O), 160.4 (*C*(5-furan)), 157.6[a] (*C*(2-furan)), 141.0[b] (CH*C*H=CH_2), 139.2 (CH_2*C*H=CH_2), 131.0 ($(CH_2)_4$*C*H=CH), 128.6 (CH=*C*H$(CH_2)_2$), 128.4 (*C*(4-furan)), 114.7 (CH=*C*H_2), 113.9 (CH=*C*H_2), 103.4[b] (*C*(3-furan)), 69.3[a] (C_{quat}), 68.1[b] (furan-*C*HN), 63.4 (*C*HCH=CH_2), 47.2 (N*C*$H_2$$(CH_2)_3$), 43.9 (*C* H_2N), 40.2 (*C*H-furan), 40.0[b] (*C*H_2CHN), 35.0 (NC(O)*C*H_2), 33.8 (*C*H_2CH=CH_2), 29.1 (furan-*C*H_2), 28.1 (furan-CH_2*C*H_2), 27.3 (N$CH_2$$CH_2$*C*$H_2$), 27.2 ($(CH_2)_3$*C*$H_2$CH=CH), 26.4 (N$CH_2$*C*$H_2$$CH_2$), 25.1 ($H_2$C=CHC$H_2$*C*$H_2$), 22.6 (furan-CH*C*$H_2$); ^{13}C NMR (rotameric) (125 MHz, toluene-d_8) δ_C 171.8, 171.4, 171.3, 170.9, 160.5, 160.1, 159.2, 157.5, 141.8, 140.9, 139.4, 131.2, 130.8, 130.4, 128.6, 115.1, 114.9, 113.9, 104.0, 103.2, 71.4, 69.3, 68.1, 67.6, 63.7, 63.6, 47.1, 46.9, 43.5, 40.6, 40.1, 39.6, 38.5, 35.1, 34.1, 29.3, 29.2, 27.2, 26.3, 25.3, 24.9,

22.9, 22.3; *m/z* (ESI^+) 919 (100%, $[2M+Na]^+$), 471 (97, $[M+Na]^+$), 449 (27, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 471.2615, $C_{28}H_{36}N_2NaO_3$ requires 471.2618.

[a] Signal not observed in ^{13}C NMR spectrum , however it is observed in the rotameric ^{13}C NMR spectrum (298 K, toluene-d_8).

[b] These signals are not observed in ^{13}C NMR spectrum , however they are observed in the 2D HSQC NMR spectrum (373 K, toluene-d_8).

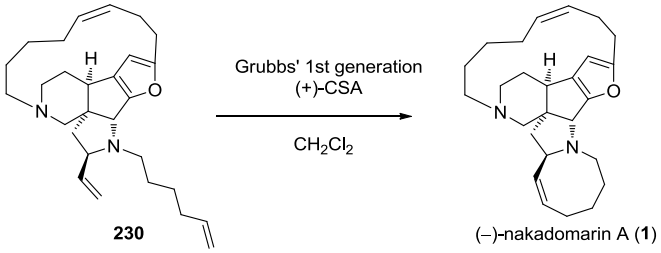
6.3.11. Synthesis of (2*R*,3a*R*,7a*R*,10b*R*,13*Z*)-1-(hex-5-en-1-yl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]enofuro[3',2':3,4]pyrrolo [3',2':1,5]cyclopenta[1,2-*c*]pyridine 230



DIBAL-H (0.19 mL, 0.19 mmol, 1 M solution in cyclohexane) was added to a solution of triene **224** (17 mg, 0.038 mmol) in toluene (1.8 mL) at 0 ^{o}C. The reaction mixture was stirred for 4 h at 0 ^{o}C followed by addition of a second portion of DIBAL-H (0.19 mL, 0.19 mmol, 1 M solution in cyclohexane). The reaction mixture was warmed to RT and stirred for a further 2 h followed by addition of methanol (0.3 mL). After a further 0.5 h, $Na_2SO_4{\cdot}10H_2O$ (50 mg) and diethyl ether (3.5 mL) were added and the reaction mixture stirred for 5 h before being filtered through celite, washing with diethyl ether, and concentrated under reduced pressure. The crude residue was purified by column chromatography using neutral alumina (Et_2O:PE 3:7→1:1) to give diamine **230** as a colourless oil (9.4 mg, 59%): $[\alpha]_D^{25} = -17.1$ (*c* 0.37, $CHCl_3$); ν_{max}(film)/cm^{-1} 2924 (C-H), 2854 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.94 - 5.84 (m, 1H, CH_2CH=CH_2), 5.78 (s, 1H, C*H*(3-furan)), 5.70 - 5.60 (m, 1H, CHC*H*=CH_2), 5.53 - 5.45 (m, 1H, $(CH_2)_4$C*H*=CH), 5.32 - 5.22 (m, 1H, CH=C*H*$(CH_2)_2$), 5.16 – 4.93 (m, 4H, CH_2CH=C*H*$_2$, CHCH=C*H*$_2$), 4.16 (s, 1H, furan-C*H*N), 3.16 - 3.08 (m, 1H, C*H*CH=CH_2), 3.01 (d, *J* = 12.0 Hz, 1H, NC*H*H'C_{quat}), 2.78 (br. s., 1H, furan-C*H*), 2.76 - 2.70 (m, 1H, furan-C*H*H'), 2.65 - 2.54 (m, 3H, , furan-CH*H*', NC*H*H'CH_2CH, NC*H*H'$(CH_2)_3$CH=CH_2), 2.54 - 2.46 (m, 1H, furan-CH_2C*H*H'), 2.41 (dt, *J* = 12.0, 3.3 Hz, 1H,

NC*H*H'(CH_2)$_3$CH=CH), 2.34 - 2.22 (m, 3H, NCH*H*'(CH_2)$_3$CH=CH, NCH*H*'CH_2CH, NCH*H*'C_{quat}), 2.21 – 2.13 (m, 1H, furan-CHCH*H*'), 2.15 - 2.08 (m, 3H, N(CH_2)$_3$C*H*$_2$CH=CH_2, NCH*H*'(CH_2)$_3$CH=CH_2), 2.01 – 1.86 (m, 3H, (CH_2)$_3$C*H*H'CH=CH, furan-CHC*H*H', C*H*H'(CH_2)$_2$CH=CH_2), 1.78 (ddd, *J* = 14.0, 7.0, 2.7 Hz, 1H, furan-CHCH*H*'), 1.69 (dd, *J* = 12.0, 4.4 Hz, 1H, C*H*H'CHN), 1.66 - 1.61 (m, 1H, (CH_2)$_3$CH*H*'CH=CH), 1.59 - 1.54 (m, 1H, CH*H*'(CH_2)$_2$CH=CH_2), 1.48 - 1.39 (m, 3H, CH*H*'CHN, C*H*$_2$CH$_2$CH=CH_2), 1.33 - 1.28 (m, 1H, C*H*H'(CH_2)$_2$CH=CH), 1.09 - 0.97 (m, 2H, C*H*H'(CH_2)$_2$CH=CH, C*H*H'CH_2CH=CH), 0.86 - 0.76 (m, 1H, C*H*H'CH_2CH=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.5 (*C*(2-furan)), 156.1 (*C*(5-furan)), 140.7 (CH*C*H=CH_2), 139.3 (CH_2*C*H=CH_2), 133.5 (*C*(4-furan)), 131.6 ((CH_2)$_4$*C*H=CH), 127.9 (CH=*C*H(CH_2)$_2$), 116.6 (CH=*C*H$_2$), 114.1 (CH=*C*H$_2$), 103.2 (*C*(3-furan)), 70.9 (furan-*C*HN), 66.6 (*C*HCH=CH_2), 62.4 (C_{quat}), 59.5 (NCH$_2$$C_{quat}$), 58.2 (N*C*H$_2$($CH_2$)$_3$CH=CH) , 49.7 (N($CH_2$)$_2$*C*H), 45.0 (N*C*H$_2$($CH_2$)$_3$CH=$CH_2$), 42.5 (*C*H$_2$CHN), 41.3 (*C*H-furan), 33.7 (*C*H$_2$CH=CH_2), 29.7, 28.7 (furan-*C*H$_2$), 28.1 (N(CH_2)$_2$*C*H$_2$CH$_2$CH=CH), 27.7 (furan-CH$_2$*C*H$_2$), 27.5 (NCH$_2$*C*H$_2$(CH_2)$_2$CH=CH_2), 27.1 (*C*H$_2$CH$_2$CH=CH_2), 26.3 ((CH_2)$_3$*C*H$_2$CH=CH), 26.2 (NCH$_2$*C*H$_2$(CH_2)$_2$CH=CH), 22.1 (furan-CH*C*H$_2$); *m/z* (ESI$^+$) 421 (100%, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+H]^+$ 421.3212, $C_{28}H_{41}N_2O$ requires 421.3213.

6.3.12. Synthesis of (–)-nakadomarin A 1

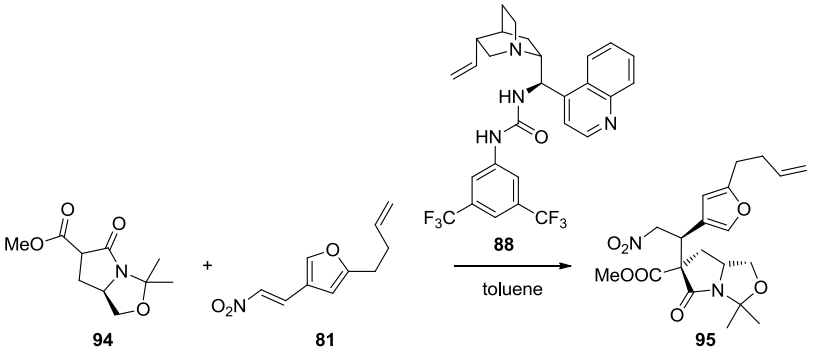


Diamine **230** (10.0 mg, 0.024 mmol) and (+)-CSA (16.6 mg, 0.072 mmol) were dissolved in CH_2Cl_2 (4 mL) and stirred for 10 min at RT. The reaction mixture was diluted with CH_2Cl_2 (83 mL) and a solution of Grubbs 1st generation catalyst (5.9 mg, 0.007 mmol) in CH_2Cl_2 (1 mL) added. The solution was heated at reflux for 5 h before addition of a further portion of Grubbs 1st generation catalyst (2.0 mg, 0.002 mmol) in CH_2Cl_2 (0.5 mL). After a further 3 h the reaction mixture was concentrated to ~10 mL and extracted with 1 M aq. HCl (4 x 10 mL). The aqueous extracts were combined, cooled to 0 °C and the pH adjusted to 14 by addition of sat. aq. NaOH solution. The product was extracted with diethyl ether (2 x 10 mL) and CH_2Cl_2 (3 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography using neutral alumina (Et_2O:PE 3:7→1:1) to give (–)-nakadomarin A (**1**) as a colourless oil (6.5 mg, 70%): $[\alpha]_D^{25}$ = −67.0 (*c* 0.50, MeOH), lit.[25] $[\alpha]_D^{25}$ −65.6 (*c* 0.66, MeOH), lit.[14] $[\alpha]_D^{23}$ −73.0 (*c* 0.08, MeOH), lit.[13] (ent)-(+)-nakadomarin A $[\alpha]_D^{25}$ +70.4 (*c* 0.94, MeOH), lit.[13] (ent)-(+)-nakadomarin A, $[\alpha]_D^{25}$ +79.2 (*c* 0.12, MeOH), lit.[15] (ent)-(+)-nakadomarin A $[\alpha]_D^{25}$ +60.7 (*c* 0.27, MeOH); ^{1}H NMR (700 MHz, CD_3OD) δ_H 5.88 (s, 1H), 5.82 (dd, *J* = 9.5, 8.5 Hz, 1 H), 5.51 (dd, *J* = 9.5, 8.5 Hz, 1H), 5.49 - 5.43 (m, 1H), 5.31 - 5.24 (m, 1H), 3.95 (s, 1H), 3.78 - 3.72 (m, 1H), 3.06 (d, *J* = 11.9 Hz, 1H), 3.10 - 3.01 (m, 1H), 2.87 - 2.84 (m, 1H), 2.84 - 2.76 (m, 1H), 2.76 - 2.70 (m, 1H), 2.67 - 2.60 (m, 2H), 2.54 - 2.47 (m, 1H),

2.42 (dt, *J* = 11.8, 3.6 Hz, 1H), 2.32 (d, *J* = 11.9 Hz, 1H), 2.37 - 2.30 (m, 2H), 2.21 - 2.13 (m, 2H), 2.12 - 2.07 (m, 1H), 2.05-1.99 (m, 1H), 1.97 - 1.88 (m, 1H), 1.92 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.84 (ddd, *J* = 14.0, 7.1, 2.7 Hz, 1H), 1.75 - 1.59 (m, 4H), 1.50 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.44 - 1.38 (m, 1H), 1.38 - 1.31 (m, 1H), 1.12 - 1.03 (m, 2H), 0.94 - 0.85 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ_C 162.5, 156.7, 135.3, 134.6, 132.4, 131.8, 129.4, 104.9, 74.8, 63.8, 60.8, 59.4, 58.3, 51.1, 46.2, 43.6, 43.3, 29.6, 2 x 29.4, 29.0, 27.3, 27.3, 2 x 26.1, 23.1; *m/z* (ESI^+) 393 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 393.2901, $C_{26}H_{37}N_2O$ requires 393.2900.

6.4. Chapter 4: Experimental

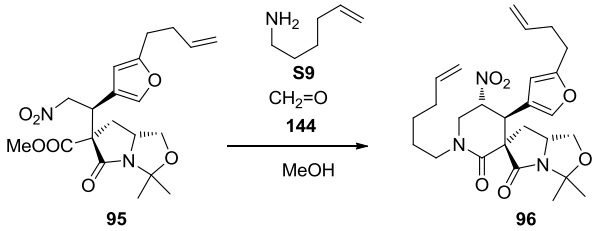
6.4.1. Synthesis of methyl (6*S*,7a*R*)-6-{(1*S*)-1-[5-(but-3-en-1-yl)-3-furyl]-2-nitroethyl}-3,3-dimethyl-5-oxotetrahydro-1H-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate 95



To a solution of 5,5-bicyclic pro-nucleophile **94** (8.28 g, 38.83 mmol) and nitro olefin **81** (4.95 g, 25.62 mmol) in toluene (82 mL) was added catalyst **88** (4.26 g, 7.77 mmol) in one portion. The reaction was stirred for 3 days at 30 °C before being concentrated *in vacuo* and purified by column chromatography (Et_2O:PE 3:7→7:3). The title compound **95** was obtained as a yellow crystalline solid which was further purified by recrystallization from Et_2O cooled to −20 °C. Further purification of the mother liquors were also required in a similar manner to give Michael adduct **95** as a colourless crystalline solid (7.50 g, 72%, single diastereomer): mp 94-95 °C; lit.[34] mp 90-92 °C); $[\alpha]_D^{24}$ = +14.5 (*c* 1.01, $CHCl_3$); lit.[34] $[\alpha]_D^{21}$ = +0.9 (*c* 0.67, $CHCl_3$); ν_{max}(film)/cm^{-1} 2986 (C-H), 2935 (C-H), 1725 (C=O), 1687 (C=O), 1552 (NO_2), 1380 (NO_2), 1277 (m), 1223 (m) 1037 (w), 919 (w), 819 (w); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.30 (d, *J* = 0.8 Hz, 1H, C*H*(5-furan)), 6.03 (d, *J* = 0.8 Hz, 1H, C*H*(3-furan)), 5.78 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H, C*H*=CH_2), 5.06 - 4.86 (m, 4H, C*H*$_2$$NO_2$,CH=C*H*$_2$), 4.07 (dd, *J* = 10.6, 3.8 Hz, 1H, C*H*-furan), 3.94 - 3.88 (m, 1H, C*H*H'O), 3.82 (s, 3H, OC*H*$_3$), 3.43 - 3.30 (m, 2H, CH*H*'O, C*H*N), 2.67 (t, *J* = 7.5 Hz, 2H, furan-C*H*$_2$), 2.40 - 2.31 (m, 2H, CH_2=CHC*H*$_2$),

2.21 - 2.17 (m, 2H, C*H*$_2$CHN), 1.68 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 171.7 (*C*=O), 167.3 (*C*=O), 157.1 (*C*(2-furan)), 140.3 (*C*(5-furan)), 137.0 (*C*H=CH$_2$), 119.6 (*C*(4-furan)), 115.6 (CH=*C*H$_2$), 105.0 (*C*(3-furan)), 91.9 (*C*(CH$_3$)$_2$), 76.8 (NO_2*C*H$_2$), 69.9 (*C*H$_2$O), 63.5 (C_{quat}), 58.7 (*C*HN), 53.3 (O*C*H$_3$), 38.8 (*C*H-furan), 33.4 (*C*H$_2$CHN), 31.8 (CH$_2$=CH*C*H$_2$), 27.5 (furan-*C*H$_2$), 26.3 (*C*H$_3$), 23.3 (*C*H$_3$); *m/z* (ES$^+$) 429 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 429.1625, $C_{20}H_{26}N_2NaO_7$ requires 429.1632.

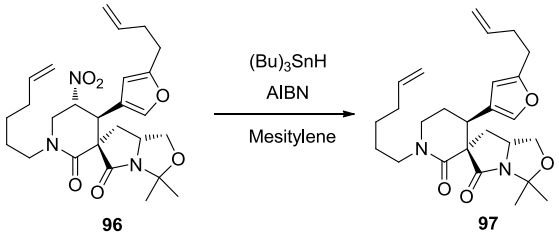
6.4.2. Synthesis of (3*R*,4*S*,5*R*,7a'*R*)-4-[5-(but-3-en-1-yl)-3-furyl]-1-(hex-5-en-1-yl)-3',3'-dimethyl-5-nitrodihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione 96



A solution of Michael adduct **95** (7.50 g, 18.32 mmol), hex-5-en-1-amine **S9** (2.73 g, 27.48 mmol) and formaldehyde **144** (37% solution in water) (2.23 g, 2.04 mL, 27.52 mmol) in MeOH (140 mL) was refluxed for 5 h. The solution was cooled to RT and concentrated *in vacuo* before being purified by column chromatography (PE:Et_2O 1:1→2:8) to afford the title compound **96** as a brown oil (5.80 g, 65%): $[\alpha]_D^{24}$ = +73.8 (*c* 0.53, $CHCl_3$); lit.[34] $[\alpha]_D^{21}$ = +97.3 (*c* 0.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 2982 (C-H), 2933 (C-H), 1689 (C=O), 1648 (C=O), 1555 (NO_2), 1349 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.28 (d, *J* = 1.0 Hz, 1H, C*H*(5-furan)), 6.06 (d, *J* = 1.0 Hz, 1H, C*H*(3-furan)), 5.89 (ddd, *J* = 12.0, 9.5, 6.5 Hz, 1H NO_2C*H*), 5.84 - 5.72 (m, 2H, 2 x C*H*=CH_2), 5.06 - 4.93 (m, 4H, 2 x CH=CH_2), 4.01 (dd, *J* = 12.0, 6.4 Hz, 1H, NC*H*H'CNO_2), 3.90 (dd, *J* = 8.0, 5.4 Hz, 1H, C*H*H'O), 3.79 (dd, *J* = 12.0, 9.1 Hz, 1H, CH*H*'CNO_2), 3.57 - 3.47 (m, 3H, CH*H*'O, C*H*-furan, NC*H*H'$(CH_2)_3$), 3.46 - 3.34 (m, 2H, NCH*H*'$(CH_2)_3$, C*H*N), 3.01 (dd, *J* = 13.2, 7.2 Hz, 1H, C*H*H'CHN), 2.66 (t, *J* = 7.5 Hz, 2H, furan-CH_2), 2.38 - 2.30 (m, 2H, furan-CH_2CH_2), 2.13 - 2.05 (m, 2H, CH_2=CHC$H_2(CH_2)_3$), 1.90 (dd, *J* = 13.2, 7.3 Hz, 1H, CH*H*'CHN), 1.70 - 1.56 (m, 2H, NCH_2CH_2), 1.58 (s, 3H, CH_3), 1.47 - 1.37 (m, 2H, NCH_2CH_2CH_2), 1.35 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 168.3 (*C*=O), 167.1 (*C*=O), 157.2 (*C*(2-furan)), 139.9 (*C*(5-furan)), 138.3 (*C*H=CH_2),

136.9 (*C*H=CH_2), 118.7 (*C*(4-furan)), 115.6 (CH=*C*H_2), 114.9 (CH=*C*H_2), 104.9 (*C*(3-furan)), 91.5 (*C*$(CH_3)_2$), 81.4 (NO_2*C*H), 69.7 (*C*H_2O), 62.8 (C_{quat}), 58.7 (*C*HN), 49.4 (N*C*H_2CNO_2), 48.2 (N*C*$H_2(CH_2)_3$), 42.9 (*C*H-furan), 33.2 (CH_2=CH*C*$H_2(CH_2)_3$), 31.8 (furan-CH_2*C*H_2), 31.6 (*C*H_2CHN), 27.5 (furan-*C*H_2), 26.2 (*C*H_3), 26.1 (NCH_2*C*H_2), 25.8 (NCH_2CH_2*C*H_2), 23.3 (*C*H_3); *m/z* (ES^+) 508 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 508.2421, $C_{26}H_{35}N_3NaO_6$ requires 508.2418.

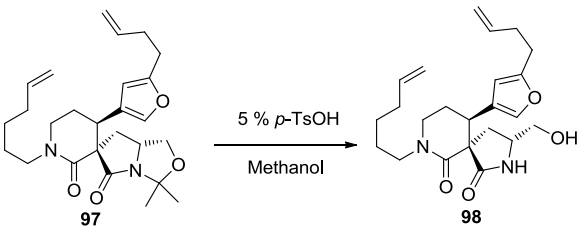
6.4.3. Synthesis of (3*R*,4*S*,7a'*R*)-4-[5-(but-3-en-1-yl)-3-furyl]-1-(hex-5-en-1-yl)-3',3'-dimethyldihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione 97



Nitro substrate **96** (5.60 g, 11.53 mmol) was dissolved in mesitylene (160 mL). To this was added AIBN (0.38 g, 2.31 mmol) and tributyltin hydride (16.78 g, 15.28 mL, 57.65 mmol) and the mixture was degassed by repeated cycles of vacuum/nitrogen purge. The reaction was then heated rapidly to reflux in a pre-heated oil bath for 2.5 h before being cooled to RT. The reaction mixture was loaded directly onto silica and the mesitylene and excess tin compounds eluted with petroleum ether before ramping the solvent system (PE:Et_2O 9:1→1:8), to obtain the title compound **97** as a pale yellow oil (2.95 g, 58%): $[\alpha]_D^{24}$ = +76.7 (*c* 1.3, $CHCl_3$); lit.[34] $[\alpha]_D^{21}$ = +94.1 (*c* 2.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 2980 (C-H), 2932 (C-H), 1688 (C=O), 1634 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.24 (br. s, 1H, C*H*(5-furan)), 6.05 (br. s, 1H, C*H*(3-furan)), 5.87 - 5.74 (m, 2H, 2 x C*H*=CH_2), 5.08 - 4.91 (m, 4H, 2 x CH=CH_2), 3.88 (dd, *J* = 7.7, 5.2 Hz, 1H, C*H*H'O), 3.54 - 3.31 (m, 6H, CH*H*'O, C*H*N, NCH_2, NCH_2), 2.99 (dd, *J* = 12.7, 7.5 Hz, 1H, C*H*H'CHN), 2.95 - 2.87 (m, 2H, C*H*-furan, C*H*H'CH-furan), 2.70 - 2.63 (m, 2H, furan-CH_2), 2.40 - 2.32 (m, 2H, furan-CH_2CH_2), 2.14 - 2.03 (m, 2H, CH_2=CHCH_2(CH_2)$_3$), 1.84 (dd, *J* = 12.7, 7.1 Hz, 1H, CH*H*'CHN), 1.78 - 1.71 (m, 1H, CH*H*'CH-furan), 1.67 - 1.53 (m, 5H, NCH_2CH_2, CH_3), 1.48 - 1.36 (m, 2H, NCH_2CH_2CH_2), 1.29 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 169.5 (*C*=O), 168.6 (*C*=O), 156.2 (*C*(2-

furan)), 138.6 (*C*H=CH_2), 137.8 (*C*(5-furan)), 137.2 (*C*H=CH_2), 124.7 (*C*(4-furan)), 115.4 (CH=*C*H_2), 114.6 (CH=*C*H_2), 105.5 (*C*(3-furan)), 91.2 (*C*$(CH_3)_2$), 69.9 (*C*H_2O), 63.3 (C_{quat}), 58.5 (*C*HN), 48.2 (N*C*H_2) 47.3 (N*C*H_2) 40.0 (*C*H-furan), 33.4 (CH_2=CH*C*$H_2(CH_2)_3$), 33.0 (*C*H_2CHN), 31.9 (furan-CH_2*C*H_2), 27.6 (furan-*C*H_2), 26.3 (*C*H_3), 26.0 (NCH_2*C*H_2), 26.0 (NCH_2CH_2*C*H_2), 25.2 (C*H*$_2$CH-furan), 23.3 (*C*H_3); *m/z* (ES^+) 463 (80%, $[M+Na]^+$), 441 (100, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 463.2567, $C_{26}H_{36}N_2NaO_4$ requires 463.2567.

6.4.4. Synthesis of (3*R*,5*S*,10*S*)-10-[5-(but-3-en-1-yl)-3-furyl]-7-(hex-5-en-1-yl)-3-(hydroxymethyl)-2,7-diazaspiro[4.5]decane-1,6-dione 98

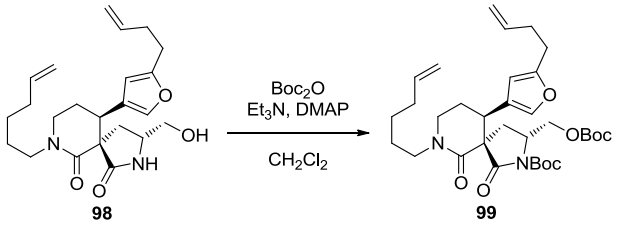


97 98

p-TsOH (0.063 g, 0.33 mmol) was added to a solution of **97** (2.91 g, 6.61 mmol) in methanol (150 mL) and the solution heated at reflux for 4 h. A further addition of *p*-TsOH (0.010 g, 0.05 mmol) was required after this time. After heating at reflux for a further 1 h, the solution was cooled to RT, concentrated and purified by column chromatography (EtOAc → EtOAc:MeOH 98:2) to yield the title compound **98** as a colourless oil (2.11 g, 80%): $[\alpha]_D^{24}$ = +100.3 (*c* 1.25, $CHCl_3$); lit.[34] $[\alpha]_D^{21}$ = +112.0 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3406 (N-H), 3273 (O-H), 2931 (C-H), 1691 (C=O), 1618 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.26 - 7.18 (m, 1H, C*H*(5-furan)), 6.33 (s, 1H, N*H*), 6.06 (s, 1H, C*H*(3-furan)), 5.86 – 5.74 (m, 2H, 2 x C*H*=CH_2), 5.08 - 4.91 (m, 4H, 2 x CH=CH_2), 3.60 (d, *J* = 4.1 Hz, 2H, CH_2O), 3.51 - 3.37 (m, 3H, NC$H_2(CH_2)_3$, NC*H*H'CH_2CH-furan), 3.37 - 3.25 (m, 2H, NCH*H*'CH_2CH-furan), 3.15 - 3.00 (m, 1H, C*H*H'CH-furan), 2.84 (dd, *J* = 13.4, 2.7 Hz, 1H, C*H*-furan), 2.72 - 2.59 (m, 3H, C*H*H'CHN, furan-CH_2), 2.42 - 2.30 (m, 2H, furan-CH_2CH_2), 2.18 - 2.03 (m, 3H, CH*H*'CHN, CH_2=CHC$H_2(CH_2)_3$), 1.79 – 1.73 (m, 1H, CH*H*'CH-furan), 1.67 - 1.50 (m, 2H, NCH_2CH_2), 1.46 - 1.33 (m, 2H, NCH_2CH_2CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 175.6 (*C*=O), 170.5 (*C*=O), 156.3 (*C*(2-furan)), 138.5 (*C*H=CH_2), 138.1 (*C*(5-furan)), 137.4 (*C*H=CH_2), 124.3 (*C*(4-furan)), 115.3 (CH=*C*H_2), 114.7 (CH=*C*H_2), 105.7 (*C*(3-furan)), 65.6 (*C*H_2O), 55.5 (C_{quat}), 52.8 (*C*HN), 48.5 (N*C*H_2), 47.6

(N*C*H_2), 40.4 (*C*H-furan), 34.0 (*C*H_2CHN), 33.4 (CH_2=CH*C*H_2(CH_2)$_3$), 32.0 (furan-CH_2*C*H_2), 27.5 (furan-*C*H_2), 26.3 (NCH_2*C*H_2), 26.0 (N$CH_2$$CH_2$*C*$H_2$), 25.3 (C*H*$_2$CH-furan); *m/z* (ES$^+$) 423 (90%, [M+Na]$^+$), (100, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 423.2241, $C_{23}H_{32}N_2NaO_4$ requires 423.2254.

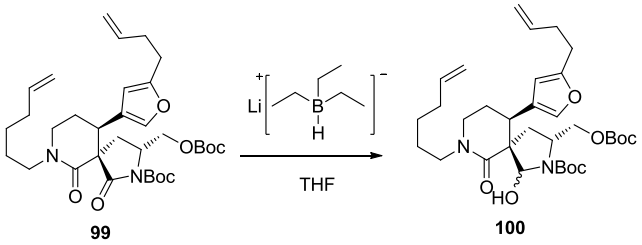
6.4.5. Synthesis of *tert*-butyl(3*R*,5*R*,10*S*)-10-[5-(but-3-en-1-yl)-3-furyl]-3-{[(*tert*-butoxycarbonyl) oxy] methyl}-7-(hex-5-en-1-yl)-1,6-dioxo-2,7-diazaspiro[4.5]decane-2-carboxylate 99



To a solution of aminol **98** (1.75 g, 4.37 mmol) in CH_2Cl_2 (75 mL) was added DMAP (0.053 g, 0.43 mmol) and triethylamine (2.21 g, 3.04 mL, 21.86 mmol) before the portionwise addition of di-*tert*-butyl dicarbonate (4.77 g, 21.86 mmol). The solution was stirred for 15 h at RT. The dark yellow solution formed was concentrated and purified by column chromatography (PE:EtOAc 4:1→3:7), to give the title compound **99** as a colourless oil (2.55 g, 97%): $[\alpha]_D^{24}$ = +89.9 (*c* 1.13, $CHCl_3$); lit.[34] $[\alpha]_D^{21}$ = +120.0 (*c* 1.10, $CHCl_3$); ν_{max}(film)/cm^{-1} 2979 (C-H), 2934 (C-H), 1779 (C=O), 1741 (C=O), 1637 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.17 (br. s, 1H, C*H*(5-furan)), 5.93 (br. s, 1H, C*H*(3-furan)), 5.85 - 5.73 (m, 2H, 2 x C*H*=CH_2), 5.06 - 4.92 (m, 4H, 2 x CH=CH_2), 4.44 (dd, *J* = 10.0, 4.4 Hz, 1H, C*H*H'O), 4.19 (dd, *J* = 10.0, 8.6 Hz, 1H, CH*H*'O), 3.82 (tt, *J* = 8.9, 4.5 Hz, 1H, C*H*N), 3.52 - 3.40 (m, 3H, NC$H_2$$CH_2$CH-furan, NC*H*H'$(CH_2)_3$), 3.29 (ddd, *J* = 13.1, 8.7, 6.4 Hz, 1H, NCH*H*'$(CH_2)_3$), 3.06 - 2.92 (m, 1H, C*H*H'CH-furan), 2.84 (dd, *J* = 13.4, 2.8 Hz, 1H, C*H*-furan), 2.73 (dd, *J* = 13.8, 4.7 Hz, 1H, C*H*H'CHN), 2.65 - 2.58 (m, 2H, furan-CH_2), 2.37 - 2.29 (m, 2H, furan-CH_2CH_2), 2.13 - 2.03 (m, 3H, CH*H*'CHN, CH_2=CHC$H_2$$(CH_2)_3$), 1.79 - 1.71 (m, 1H, CH*H*'CH-furan), 1.66 - 1.52 (m, 2H, NCH_2CH_2), 1.48 (s, 9H, C(CH_3)$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 1.45 - 1.36 (m, 2H NCH_2CH_2CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 172.8 (*C*=O),

167.7 (*C*=O), 156.6 (*C*(2-furan)), 153.0 (*C*=O (Boc)), 149.4 (*C*=O (Boc)), 138.5 (*C*H=CH_2), 138.2 (*C*(5-furan)), 137.1 (*C*H=CH_2), 123.9 (*C*(4-furan)), 115.3 (CH=*C*H_2), 114.7 (CH=*C*H_2), 105.0 (*C*(3-furan)), 83.3 (*C*$(CH_3)_3$), 82.1 (*C*$(CH_3)_3$), 68.1 (*C*H_2O), 57.0 (C_{quat}), 53.4 (*C*HN), 48.2 (N*C*$H_2(CH_2)_3$), 47.3 (N*C*H_2CH_2CH-furan), 41.6 (*C*H-furan), 33.4 (CH_2=CH*C*$H_2(CH_2)_3$), 32.0 (furan-CH_2*C*H_2), 31.3 (*C*H_2CHN), 27.9 (C(*C*$H_3)_3$), 27.7 (C(*C*$H_3)_3$), 27.6 (furan-*C*H_2), 26.3 (NCH_2*C*H_2), 26.0 (NCH_2CH_2*C*H_2), 25.1 (C*H*$_2$CH-furan); *m/z* (ES^+) 623 (60%, $[M+Na]^+$), 601 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 623.3297, $C_{33}H_{48}N_2NaO_8$ requires 623.3303.

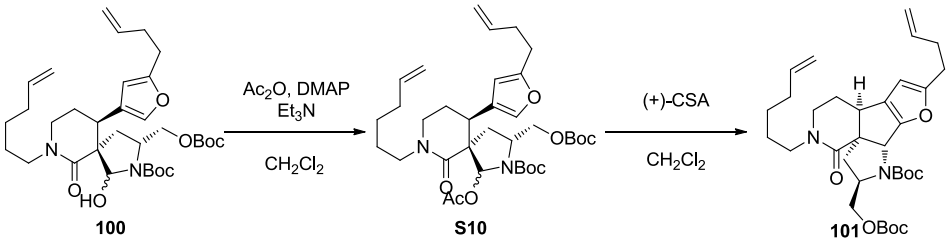
6.4.6. Synthesis of *tert*-butyl(1*R*,*S*,3*R*,5*S*,10*S*)-10-[5-(but-3-en-1-yl)-3-furyl]-3-{[(*tert*-butoxycarbonyl)oxy] methyl}-7-(hex-5-en-1-yl)-1-hydroxy-6-oxo-2,7-diazaspiro[4.5]decane-2-carboxylate 100



99 100

To a solution of **99** (2.50 g, 4.16 mmol) in THF (105 mL) was added dropwise lithium triethylborohydride (11.20 mL, 11.20 mmol, 1 M solution in THF) at −78 °C and the solution stirred at this temperature for 3 h before being quenched with sat. aq. NH_4Cl solution (100 mL). The reaction was allowed to warm to RT over 1 h and then diluted with Et_2O (150 mL). The aqueous layer was extracted and the organics dried (Na_2SO_4) and concentrated. The crude oil was purified by column chromatography (PE:EtOAc 4:1→7:3) to yield the title compound **100** as a colourless oil (2.04 g, 81%): The ^{1}H- NMR spectrum of the title compound suffers from considerable broadening due to rotamers when run in $CDCl_3$ at 298 K. Attempts to improve this spectrum by collecting the data in toluene-d_8 at 363 K resulted in decomposition of the compound. The compound was therefore used in the next step without full characterisation: *m/z* (ES^+) 1228 (48%, $[2M+Na]^+$), 625 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 625.3460, $C_{33}H_{50}N_2NaO_8$ requires 625.3459.

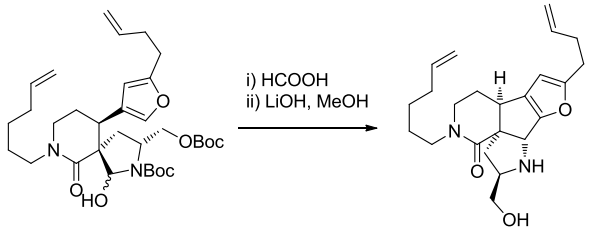
6.4.7. Synthesis of *tert*-butyl (2*R*,3a*S*,7a*S*,10b*R*)-9-(but-3-en-1-yl)-2-{[(*tert*-butoxycarbonyl) oxy]methyl}-5-(hex-5-en-1-yl)-4-oxo-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo [3',2':1,5]cyclopenta[1,2-*c*]pyridine-1-carboxylate 101



To a solution of **100** (300 mg, 0.498 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.28 g, 0.39 mL, 2.79 mmol), acetic anhydride (0.29 g, 0.26 mL, 2.79 mmol) and DMAP (3 mg). The reaction was stirred at RT for 6 h followed by the addition of a second portion of DMAP (20 mg). The reaction was stirred for 15 h, before being filtered through a silica pad, which was washed with diethyl ether. The filtrate was concentrated and the crude residue was dissolved in CH_2Cl_2 (10 mL), (+)-camphorsulfonic acid (21 mg, 0.09 mmol) was added and the reaction stirred at RT for 2 h. The mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (PE:EtOAc 9:1→6:4), to give the title compound **101** as a colourless solid (268 mg, 92%). The ^{1}H- NMR spectrum of the title compound suffers from broadening due to rotamers when run in $CDCl_3$ at 298 K. The major rotamer has been assigned: mp 72-75 °C; $[\alpha]_D^{24}$ = +34.4 (*c* 3.40, $CHCl_3$); lit.[34] $[\alpha]_D^{23}$ = +28.9 (*c* 3.40, $CHCl_3$); ν_{max}(film)/cm^{-1} 2978 (C-H), 2931 (C-H), 1743 (C=O), 1699 (C=O), 1640 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.91 - 5.68 (m, 3H, C*H*(3-furan), 2 x C*H*=CH_2), 5.11 – 5.05 (m, 1H, furan-C*H*NBoc), 5.05 - 4.90 (m, 4H, 2 x CH=CH_2), 4.72 (dd, *J* = 9.6, 3.5 Hz, 1H, C*H*H'O), 4.35 (dd, *J* = 9.5, 9.5 Hz, 1H, CH*H*'O), 4.13 - 4.04 (m, 1H,

$OCH_2CHNBoc$), 3.37 (t, *J* = 7.3 Hz, 2H, $NCH_2(CH_2)_3$), 3.27 - 3.12 (m, 2H, NCH_2CH_2CH-furan), 3.02 (t, *J* = 6.1 Hz, 1H, NCH_2CH_2CH-furan), 2.69 (t, *J* = 7.6 Hz, 2H, furan-CH_2), 2.59 (dd, *J* = 13.4, 4.5 Hz, 1H, CHH'CHNBoc), 2.38 (q, *J* = 7.1 Hz, 2H, furan-CH_2CH_2), 2.16 - 1.99 (m, 4H, CHH'CHNBoc, CH_2=$CHCH_2(CH_2)_3$, $NCH_2CHH'CH$-furan), 1.71 - 1.60 (m, 1H, $NCH_2CHH'CH$-furan), 1.56 - 1.43 (m, 20H, 2 x $C(CH_3)_3$, NCH_2CH_2), 1.40 - 1.30 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 172.2 (*C*=O), 161.1 (*C*(5-furan)), 154.9, 153.9, 153.1 (*C*(2-furan), *C*=O (Boc), *C*=O (Boc)), 138.4 ($CH=CH_2$), 137.3 ($CH=CH_2$), 128.1 (*C*(4-furan)), 115.4 ($CH=CH_2$), 114.7 ($CH=CH_2$), 102.1 (*C*(3-furan)), 81.7 ($C(CH_3)_3$), 80.0 ($C(CH_3)_3$), 66.9 (CH_2O), 65.9 (furan-CHNBoc), 63.8 (C_{quat}), 56.8 (OCHNBoc), 47.9 ($NCH_2(CH_2)_3$), 45.1 (NCH_2CH_2CH-furan), 43.4 (NCH_2CH_2CH-furan), 40.4 ($CH_2CHNBoc$), 33.3 ($CH_2=CHCH_2(CH_2)_3$), 32.0 (furan-CH_2CH_2), 29.1 (furan-CH_2), 28.5 (NCH_2CH_2CH-furan), 28.3 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$), 26.7 (NCH_2CH_2), 26.0 0 ($NCH_2CH_2CH_2$); *m/z* (ES^+) 607 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 607.3349, $C_{33}H_{48}N_2NaO_7$ requires 607.3354.

6.4.8. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-9-(but-3-en-1-yl)-5-(hex-5-en-1-yl)-2-(hydroxymethyl)-1,2,3,5,6, 7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta [1,2-*c*]pyridin-4-one 256

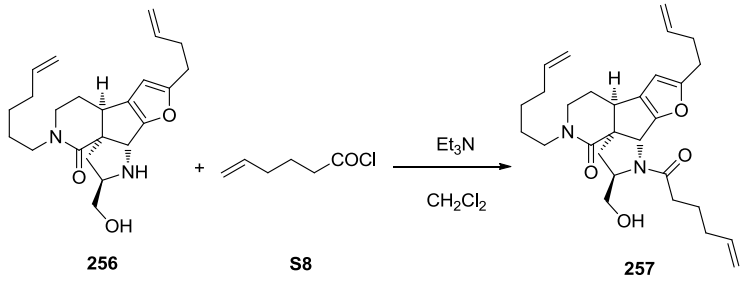


100 256

Compound **100** (1.37 g, 2.27 mmol) was dissolved in formic acid (22 mL) and the solution stirred at RT for 15 h before being concentrated to a crude oil. The crude oil was dissolved in methanol (50 mL) and $LiOH.H_2O$ (1.90 g, 45.28 mmol) added. The reaction was heated at 50 ºC for 5 h before being concentrated to approximately 20% of the original volume. Water (40 mL) was added and the product extracted with 4:1 chloroform:IPA (6 x 50 mL). The organics were dried (Na_2SO_4) and concentrated to give a brown oil, which was purified by column chromatography (Et_2O:MeOH 9:1) to give the tetracyclic product **256** as a pale yellow oil (0.83 g, 95%): $[\alpha]_D^{26}$ = −72.8 (*c* 0.97, $CHCl_3$); ν_{max}(film)/cm^{-1} 3299 (O-H, N-H), 2927 (C-H), 2859 (C-H), 1625 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.91 - 5.68 (m, 3H, C*H*(3-furan), 2 x C*H*=CH_2), 5.11 - 4.90 (m, 4H, 2 x CH=CH_2), 4.84 (s, 1H, furan-C*H*NH), 4.10 (br. s., 2H, N*H*, O*H*), 3.92 (dd, *J* = 11.8, 3.3 Hz, 1H, C*H*H'OH), 3.79 (dd, *J* = 11.8, 4.4 Hz, 1H, CH*H*'OH), 3.49 – 3.42 (m, 1H, NC*H*H'$(CH_2)_3$), 3.41 - 3.35 (m, 2H, OCH_2C*H*N, NCH*H*'$(CH_2)_3$), 3.31 - 3.23 (m, 1H, NC*H*H'CH_2CH-furan), 3.22 - 3.16 (m, 1H, NCH*H*'CH_2CH-furan), 3.14 (ddd, *J* = 7.3, 5.7, 1.3 Hz, 1H, NCH_2CH_2C*H*-furan), 2.73 - 2.66 (m, 2H, furan-CH_2), 2.44 (dd, *J* = 12.9, 9.8 Hz, 1H, C*H*H'CHNH), 2.41 - 2.33 (m, 2H, furan-CH_2CH_2), 2.21 - 2.10 (m, 1H, NCH_2C*H*H'CH-furan), 2.06 (q, *J* = 7.0 Hz, 2H, CH_2=CHC$H_2(CH_2)_3$), 1.96 (dd,

J = 12.9, 6.6 Hz, 1H, CH*H*'CHNH), 1.67 (dtd, *J* = 13.5, 7.8, 3.3 Hz, 1H, NCH_2CH*H*'CH-furan), 1.58 - 1.46 (m, 2H, NCH_2C*H_2*), 1.41 - 1.25 (m, 2H, NCH_2CH_2C*H_2*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 173.4 (*C*=O), 162.5 (*C*(5-furan)), 152.4 (*C*(2-furan), 138.4 (*C*H=CH_2), 137.4 (*C*H=CH_2), 130.2 (*C*(4-furan)), 115.3 (CH=*C*H_2), 114.8 (CH=*C*H_2), 102.2 (*C*(3-furan)), 68.0 (furan-C*H*NH), 65.6 (*C_{quat}*), 62.2 (*C*H_2O), 61.4 (OCH_2*C*HN), 48.0 ($NCH_2(CH_2)_3$), 45.2 (NCH_2CH_2CH-furan), 43.2 (NCH_2CH_2C*H*-furan), 42.4 (*C*H_2CHNH), 33.3 (CH_2=CH*C*$H_2(CH_2)_3$), 31.8 (furan-CH_2*C*H_2), 29.3 (NCH_2*C*H_2CH-furan), 28.4 (furan-*C*H_2), 26.7 (NCH_2*C*H_2), 26.0 (NCH_2CH_2*C*H_2); *m/z* (ESI^+) 791 (95%, $[2M+Na]^+$), 769 (96, $[2M+H]^+$), 407 (68, $[M+Na]^+$), 385 (69, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 385.2486, $C_{23}H_{33}N_2O_3$ requires 385.2486.

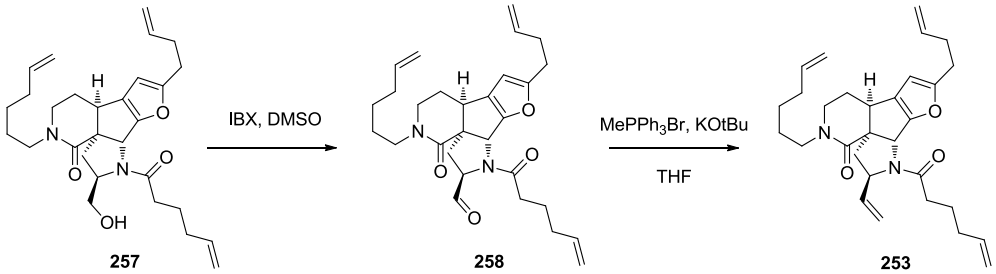
6.4.9. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-9-(but-3-en-1-yl)-1-(hex-5-enoyl)-5-(hex-5-en-1-yl)-2-(hydroxymethyl)-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo [3',2':1,5] cyclopenta[1,2-*c*]pyridin-4-one 257



Tetracycle **256** (0.700 g, 1.82 mmol) and Et_3N (0.920 g, 1.27 mL, 9.10 mmol) were dissolved in CH_2Cl_2 (39 mL) and the resulting solution was cooled to −20 °C. A solution of hex-5-enoyl chloride **S8** (0.253 g, 250 µl, 1.91 mmol) in CH_2Cl_2 (14 mL) pre-cooled to -20 °C was added and the reaction mixture warmed to RT over 0.5 h. After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (Et_2O) to give amide **257** as a colourless oil (0.780 g, 89%): $[\alpha]_D^{25} = -15.0$ (*c* 3.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 3346 (O-H), 2931 (C-H), 2859 (C-H), 1636 (C=O), 1427 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.91 - 5.67 (m, 4H, C*H*(3-furan), 3 x C*H*=CH_2), 5.25 (s, 1H, furan-C*H*N), 5.11 - 4.87 (m, 6H, 3 x CH=CH_2), 4.03 - 3.91 (m, 1H, OCH_2CHN), 3.81 (dd, *J* = 12.4, 6.8 Hz, 1H, C*H*H'OH), 3.68 (d, *J* = 12.4 Hz, 1H, CH*H*'OH), 3.47 – 3.28 (m, 2H, NC$H_2(CH_2)_3$), 3.27 - 3.10 (m, 3H, NCH_2CH_2CH-furan, NCH_2CH_2C*H*-furan), 2.77 - 2.63 (m, 3H, furan-CH_2, NC=OC*H*H') 2.63 - 2.48 (m, 1H, NC=OCH*H*'), 2.41 - 2.24 (m, 3H, furan-CH_2CH_2, C*H*H'CHNH), 2.20 - 2.11 (m, 2H, NC=O$(CH_2)_2$CH_2), 2.12 - 2.07 (m, 1H, NCH_2C*H*H'CH-furan), 2.08 - 1.99 (m, 3H, CH*H*'CHNH, CH_2=CHC$H_2(CH_2)_3$), 1.86 - 1.74 (m, 3H, NCH_2CH*H*'CH-furan, NC=OCH_2CH_2), 1.51 (quin., *J* = 7.5 Hz, 2H, NCH_2CH_2), 1.38 – 1.27 (m, 2H, NCH_2CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.0 (*C*=O), 171.5

(*C*=O), 162.1 (*C*(5-furan)), 153.0 (*C*(2-furan), 138.2 (*C*H=CH_2), 138.1 (*C*H=CH_2), 136.9 (*C*H=CH_2), 129.7 (*C*(4-furan)), 115.5 (CH=*C*H_2), 115.0 (CH=*C*H_2), 114.7 (CH=*C*H_2), 102.3 (*C*(3-furan)), 66.7 (furan-C*H*N), 65.3 (*C*H_2O), 64.1 (OCH_2*C*HN), 63.6 (C_{quat}), 48.1 (N*C*H_2(CH_2)$_3$), 44.6 (N*C*$H_2$$CH_2$CH-furan), 42.3 (N$CH_2$$CH_2$C*H*-furan), 40.3 (*C*$H_2$CHNH), 34.2 (NC=O*C*$H_2$), 33.2 ($CH_2$=CH*C*$H_2$), 33.2 ($CH_2$=CH*C*$H_2$), 31.8 (furan-$CH_2$*C*$H_2$), 28.3 (furan-*C*$H_2$), 27.7 3 (N$CH_2$*C*$H_2$CH-furan), 26.5 (N$CH_2$*C*$H_2$), 25.8 (N$CH_2$$CH_2$*C*$H_2$), 24.1 (NC=O$CH_2$*C*$H_2$); *m/z* ($ESI^+$) 983 (99%, $[2M+Na]^+$), 503 (100, $[M+Na]^+$), 481 (10, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 503.2879, $C_{29}H_{40}N_2NaO_4$ requires 503.2880.

6.4.10. Synthesis of (2*R*,3a*S*,7a*S*,10b*R*)-9-(but-3-en-1-yl)-1-(hex-5-enoyl)-5-(hex-5-en-1-yl)-2-vinyl-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5] cyclopenta[1,2-*c*]pyridin-4-one 253



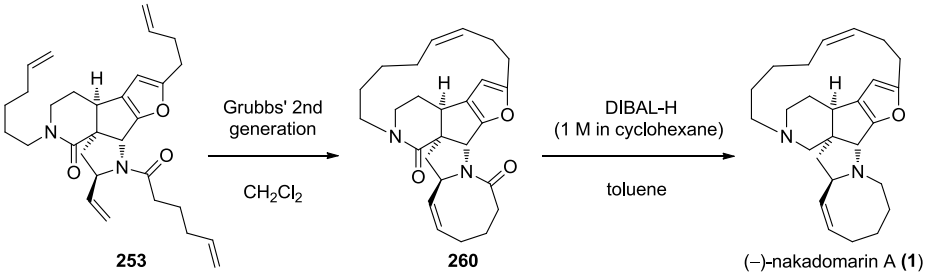
IBX (0.524 g, 1.87 mmol) was added to a solution of **257** (0.200 g, 0.42 mmol) in DMSO (20 mL) and the resulting solution stirred at RT for 24 h. The solution was poured into sat. aq. $NaHCO_3$ solution (45 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with water (30 mL), dried (Na_2SO_4) and concentrated to give aldehyde **258** as a yellow oil (0.219 g), which was used directly without further purification.

[Preparation of ylide solution: KO^{t}Bu (0.223 g, 1.99 mmol) was added to $MePPh_3Br$ (0.891 g, 2.49 mmol) in toluene (14 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT].

The crude aldehyde **258** was dissolved in THF (14 mL) and the solution added rapidly to the above freshly prepared ylide solution, at RT. After 15 min TLC analysis indicated complete consumption of starting material. Water (12 mL) was added and THF/toluene were removed under reduced pressure. Water (30 mL) and ethyl acetate (35 mL) were added to the residue. The layers were separated and the aqueous layer was further extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by

column chromatography (EtOAc:PE 2:3→1:1) to yield the title compound **253** as a yellow oil (0.186 g, 94% over 2 steps). The compound was rotameric resulting in complex ^{1}H and ^{13}C NMR spectra at 298 K as had been observed in the alkyne series: $[\alpha]_D^{25}$ = −2.60 (*c* 3.48, $CHCl_3$); ν_{max}(film)/cm^{-1} 3076 (=C-H), 2930 (C-H), 2859 (C-H), 1641 (C=O), 1406 (C=C); ^{1}H NMR (400 MHz, 298 K, $CDCl_3$) δ_H 6.41 - 6.22 (m, 1H), 6.14 - 5.97 (m, 1.35H), 5.90 - 5.68 (m, 8.85H), 5.44 (s, 1H), 5.28 (s, 1.35H), 5.15 - 4.86 (m, 18.75H), 4.42 (q, *J* = 7.8 Hz, 1.35H), 4.35 (td, *J* = 8.9, 2.9 Hz, 1H), 3.38 (qdt, *J* = 14.1, 7.1, 6.8 Hz, 4.88H), 3.29 - 3.08 (m, 6.37H), 3.03 (t, *J* = 4.9 Hz, 1H), 2.75 - 2.59 (m, 7.14H), 2.57 - 2.46 (m, 1.43H), 2.29 - 2.43 (m, 8.08H), 2.29 - 2.18 (m, 1.48H), 2.18 - 2.09 (m, 4.80H), 2.09 - 1.98 (m, 8.65H), 1.84 - 1.65 (m, 7.17H), 1.58 – 1.45 (m, 4.83H), 1.40 - 1.29 (m, 4.82H); ^{13}C NMR (rotameric) (125 MHz, 298 K, $CDCl_3$) δ_C 172.8, 172.8, 172.0, 171.6, 161.9, 161.7, 155.4, 153.8, 141.3, 139.7, 138.4, 138.4, 138.3, 137.4, 137.1, 129.1, 127.6, 125.5, 115.5, 115.2, 114.8, 114.7, 113.6, 102.3, 101.9, 66.4, 65.5, 65.1, 62.3, 62.1, 61.7, 48.0, 48.0, 44.9, 44.8, 44.6, 43.8, 43.3, 42.6, 34.2, 34.1, 34.1, 33.3, 33.3, 33.2, 33.2, 31.9, 31.8, 30.3, 29.9, 29.6, 28.3, 28.3, 28.0, 26.8, 26.6, 26.0, 25.9, 24.2, 24.1; *m/z* (ESI^+) 975 (100%, $[2M+Na]^+$), 953 (22, $[2M+H]^+$), 499 (76, $[M+Na]^+$), 477 (29, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 499.2930, $C_{30}H_{40}N_2NaO_3$ requires 499.2931.

6.4.11. Synthesis of (–)-nakadomarin A (1)



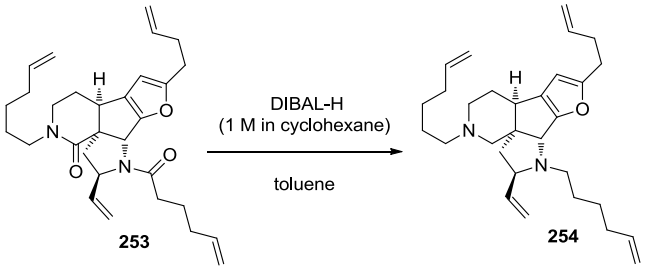
Tetraene **253** (0.050 g, 0.105 mmol) was dissolved in CH_2Cl_2 (100 mL) and a solution of Grubbs 2nd generation catalyst (0.013 mg, 0.015 mmol) in CH_2Cl_2 (1 mL) was added. The solution was heated at reflux for 4 h before addition of a further portion of Grubbs 1st generation catalyst (0.005 g, 0.006 mmol) in CH_2Cl_2 (0.5 mL). After a further 12 h the reaction mixture was concentrated and the crude residue was purified by column chromatography (Et_2O→EtOAc) to give bis-lactam **260** (0.010 g, 23%) as a colourless oil as an inseperable mixture of *E:Z* isomers (*E:Z* = 1.73:1)[1]; *m/z* (ESI$^+$) 863 (85%, $[2M+Na]^+$), 443 (100, $[M+Na]^+$), 421 (20, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 443.2305, $C_{26}H_{32}N_2NaO_3$ requires 443.2305.

DIBAL-H (60 µL, 0.060 mmol, 1 M solution in cyclohexane) was added to a solution of bis-lactam **260** (5.0 mg, 0.012 mmol) in toluene (0.8 mL) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C followed by addition of a second portion of DIBAL-H (120 µL, 0.120 mmol, 1 M solution in cyclohexane). The reaction mixture was warmed to RT and stirred for a further 4 h followed by addition of methanol (0.15 mL). After a further 0.5 h, $Na_2SO_4 \cdot 10H_2O$ (30 mg) and diethyl ether (2.0 mL) were added and the reaction mixture stirred for 15 h before being filtered through celite, washing with diethyl ether, and concentrated under reduced pressure. The crude

[1] *E*:*Z* isomer ratio calculated from both furanC*H*N and CH_2C*H*N signals in ^{1}H NMR.

residue contained two inseperable major products by ^{1}H NMR with chemical shifts matching those reported for the *E*:*Z* isomers of (−)-nakadomarin A (*E:Z* = 1.74:1).[25] The crude residue was purified by column chromatography using neutral alumina (Et_2O:PE 3:7→1:1) to give (–)-nakadomarin A **1** as a colourless oil as a mixture of *E:Z* isomers (*E:Z* = 1.73:1) (1.5 mg, 32%).

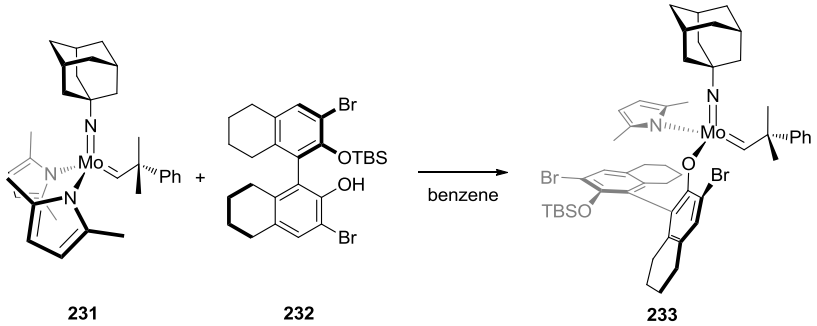
6.4.12. Synthesis of (2*R*,3a*R*,7a*R*,10b*R*)-9-(but-3-en-1-yl)-1,5-di(hex-5-en-1-yl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta [1,2-*c*]pyridine 254



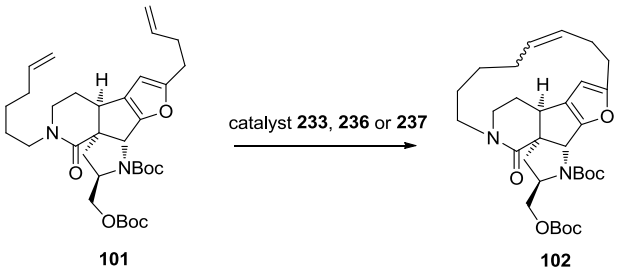
DIBAL-H (315 µl, 0.315 mmol, 1 M solution in cyclohexane) was added to a solution of tetraene **253** (0.030 g, 0.063 mmol) in toluene (3 mL) at 0 °C. The reaction mixture was stirred for 4 h at 0 °C before being warmed to RT and left to stir for 15 h. The reaction mixture was cooled to 0 °C and a second portion of DIBAL-H (110 µl, 0.110 mmol, 1 M solution in cyclohexane) was added. The reaction mixture was stirred for 0.5 h at 0 °C and then warmed to RT and stirred for a further 0.5 h. Methanol (0.6 mL) was added and stirring continued for 0.5 h before the addition of $Na_2SO_4{\cdot}10H_2O$ (70 mg) and diethyl ether (5 mL) and further stirring for 2 h. The reaction mixture was filtered through celite, washing with diethyl ether, and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc→Et_2O:MeOH 9:1) using neutral alumina to give diamine **254** as a colourless oil (0.016 g, 57%): $[\alpha]_D^{25}$ = −17.1 (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.95 - 5.75 (m, 4H, C*H*(3-furan), 3 x C*H*=CH_2), 5.62 (ddd, *J* = 17.3, 9.1, 8.8 Hz, 1H, CHC*H*=CH_2), 5.09 - 4.90 (m, 8H, 4 x CH=CH_2), 4.37 (s, 1H, furan-C*H*N), 2.97 (d, *J* = 11.7 Hz, 1H, NC*H*H'C_{quat}), 2.78 - 2.62 (m, 5H, furan-CH_2, H_2C*H*N, NC*H*H'CH_2CH-furan, $N_{5\text{-ring}}$C*H*H'$(CH_2)_3$), 2.61 - 2.54 (m, 1H, $N_{5\text{-ring}}$CH*H*'$(CH_2)_3$), 2.50 (dd, *J* = 9.5, 6.9 Hz, 1H, CH_2C*H*-furan), 2.42 - 2.27 (m, 4H, $N_{6\text{-ring}}$C$H_2(CH_2)_3$, furan-CH_2CH_2),

2.15 - 2.04 (m, 4H, 2 x C*H*$_2$CH=CH$_2$), 2.04 - 1.95 (m, 2H, NCH*H*'CH$_2$CH-furan, NCH$_2$C*H*H'CH-furan), 1.95 – 1.88 (m, 2H, C*H*H'CHN, NCH*H*'C$_{quat}$), 1.84 - 1.72 (m, 1H, N$_{5\text{-ring}}$ CH$_2$C*H*H'), 1.71 - 1.59 (m, 1H, N$_{5\text{-ring}}$ CH$_2$CH*H*'), 1.57 - 1.35 (m, 7H, CH*H*'CHN, 2 x NCH$_2$CH$_2$C*H*$_2$, NCH$_2$C*H*$_2$), 1.35 - 1.21 (m, 1H, NCH$_2$CH*H*'CH-furan); ^{13}C NMR (125 MHz, CDCl$_3$) δ_C 160.1 (*C*(5-furan)), 154.7 (*C*(2-furan), 141.4 9 (*C*H=CH$_2$), 139.2 9 (*C*H=CH$_2$), 138.9 9 (*C*H=CH$_2$), 137.6 9 (*C*H=CH$_2$), 133.2 (*C*(4-furan)), 116.3 (CH=*C*H$_2$), 115.1 (CH=*C*H$_2$), 114.3 (CH=*C*H$_2$), 114.2 (CH=*C*H$_2$), 102.3 (*C*(3-furan)), 66.3 (CH$_2$*C*HN), 66.1 (furan-C*H*N), 62.6 (N*C*H$_2$C$_{quat}$), 58.6 (N$_{6\text{-ring}}$*C*H$_2$(CH$_2$)$_3$), 56.2 (*C*$_{quat}$), 52.1 (N*C*H$_2$CH$_2$CH-furan), 49.6 (N$_{5\text{-ring}}$*C*H$_2$(CH$_2$)$_3$), 47.3 (*C*H$_2$CHNH), 40.8 (CH$_2$C*H*-furan), 33.6 (2 x CH$_2$=CH*C*H$_2$), 32.7 (NCH$_2$*C*H$_2$CH-furan), 32.2 (furan-CH$_2$*C*H$_2$), 28.5 (furan-*C*H$_2$), 27.9 N$_{5\text{-ring}}$*C*H$_2$CH$_2$)$_3$, 27.1, 26.9, 26.4 (NCH$_2$*C*H$_2$), (2 x NCH$_2$CH$_2$*C*H$_2$); *m/z* (ESI$^+$) 449 (100%, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+H]$^+$ 449.3525, $C_{30}H_{45}N_2O$ requires 449.3526.

6.4.13. Representative procedures for MAP catalyst studies



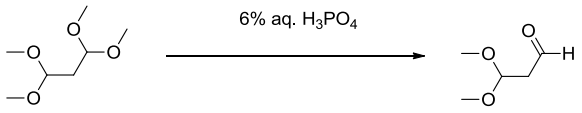
In an argon filled glovebox, benzene (1.0 mL) was added to Mo bispyrrolide **231** (0.012 g, 0.021 mmol) and alcohol **232** (0.012 g, 0.021 mmol). The solution was stirred for 15 h at RT and then stored as a stock solution at −20 °C under an argon atmosphere.



In an argon filled glovebox, diene **101** (0.010 g, 0.017 mmol) was dissolved in benzene (3.4 mL) and a stock solution of catalyst **233** in benzene (0.043 mL, 0.00086 mmol) added. The solution was stirred for 1 h at RT before being removed from the glovebox, concentrated under reduced pressure and purified by column chromatography (hexane:Et_2O 1:1→3:7) to give the title compound **102** as a colourless oil (6.2 mg, 65%, *E*:*Z* = 45:55), with data in good agreement with that previously reported.[34]

6.5. Chapter 5: Experimental

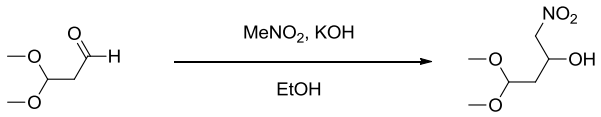
6.5.1. Synthesis of 3,3-dimethoxypropanal 381



380 381

6% aq. H_3PO_4 (3 mL) was added to 1,1,3,3-tetramethoxypropane **380** (10 g, 60.90 mmol) and the resulting solution was stirred at room temperature for 5 days. The reaction was diluted with Et_2O (150 mL) and K_2CO_3 (6 g) was added. The reaction was stirred for 5 min before being filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (Et_2O:PE 1:2) to give the title compound **381** (2 g, 28%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (t, *J* = 2.3 Hz, 1H, *H*C=O), 4.83 (t, *J* = 5.5 Hz, 1H, C*H*CH_2), 3.36 (s, 6H, 2 x OC*H*$_3$), 2.71 (dd, *J* = 5.5, 2.3 Hz, 2H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 199.4 (*C*=O), 100.3 (*C*HCH_2), 53.6 (O*C*H$_3$), 47.0 (CH*C*H$_2$). Data are in good agreement with that previously reported.[192]

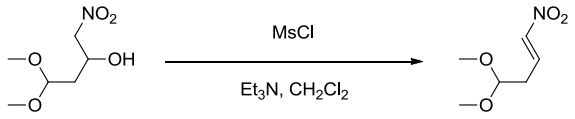
6.5.2. Synthesis of 4,4-dimethoxy-1-nitrobutan-2-ol 382



381 **382**

2 M aq. KOH solution (9.31 mL, 18.62 mmol) was added dropwise to a solution of $MeNO_2$ (1.13 g, 1.00 mL, 18.62 mmol) and 3,3-dimethoxypropanal **381** (2.00 g, 16.93 mmol) in EtOH (30 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h before being neutralised by the dropwise addition of acetic acid (1.12 g, 1.07 mL, 18.62 mmol). Water (50 mL) was added and the product extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound **382** (1.3 g, 43%) as a yellow oil, which was used without further purification: ν_{max}(film)/cm^{-1} 3418 (C-H), 2939 (C-H), 1550 (NO_2), 1378 (NO_2), 1126 (C-O), 1044 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.61 (t, *J* = 5.2 Hz, 1H, C*H*CH_2), 4.59 - 4.50 (m, 1H, C*H*OH), 4.47 - 4.42 (m, 2H, C*H*$_2NO_2$), 3.40 (s, 3H, OC*H*$_3$), 3.39 (s, 3H, OC*H*$_3$), 1.89 - 1.83 (m, 2H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 103.0 (*C*HCH_2), 80.3 (*C*H_2NO_2), 65.6 (*C*HOH), 54.2 (O*C*H_3), 53.8 (O*C*H_3), 36.2 (CH*C*H_2); *m/z* (ESI$^+$) 202 (30%, $[M+Na]^+$). ESI and TOF ionisation methods did not provide any useful HRMS data for nitro alcohol **382**.

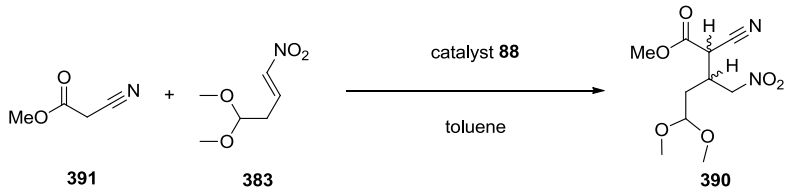
6.5.3. Synthesis of (1*E*)-4,4-dimethoxy-1-nitrobut-1-ene 383



382 **383**

Methanesulfonyl chloride (0.83 g, 0.56 mL, 7.25 mmol) was added to a solution of 4,4-dimethoxy-1-nitrobutan-2-ol **382** (1.30 g, 7.25 mmol) in CH_2Cl_2 (35 mL) cooled to −15 °C. Et_3N (1.47 g, 2.00 mL, 14.53 mmol) was added dropwise and the resulting solution was warmed to RT over 15 min. Water (50 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 65 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc:PE 3:7) to give the title compound **383** (0.82 g, 70%) as a pale yellow oil: ν_{max}(film)/cm^{-1} 2940 (C-H), 1523 (NO_2), 1350 (NO_2), 1121 (C-O), 1062 (C-O), 948 (C=C-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.22 (dt, *J* = 13.6, 7.4 Hz, 1H, C*H*=CHNO_2), 7.05 (dd, *J* = 13.6, 1.4 Hz, 1H, CH=C*H*NO_2), 4.51 (t, *J* = 5.4 Hz, 1H, C*H*CH_2), 3.36 (s, 6H, 2 x OC*H*$_3$), 2.57 (ddd, *J* = 7.4, 5.4, 1.4 Hz, 2H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 141.1 (CH=*C*HNO_2), 136.9 (*C*H=CHNO_2), 102.2 (*C*HCH_2), 53.5 (O*C*H$_3$), 32.1 (CH*C*H$_2$); *m/z* (ESI$^-$) 160 (100%, [M-H]$^-$); ESI and TOF ionisation methods did not provide any useful HRMS data for nitro olefin **383**.

6.5.4. Synthesis of methyl 2-cyano-5,5-dimethoxy-3-(nitromethyl)pentanoate 390

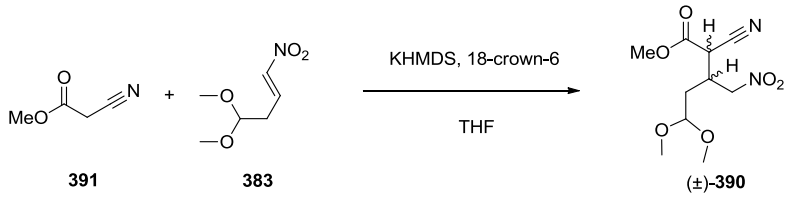


Methyl cyanoacetate **391** (0.300 g, 265 µl, 3.02 mmol), nitro olefin **383** (0.650 g, 4.03 mmol) and catalyst **88** (0.165 g, 0.30 mmol) were dissolved in toluene (16 mL) and the reaction mixture was stirred for 48 h at RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (Et_2O:PE 2:3) to give the title compound **390** (0.454 g, 58%) as a colourless oil as an inseparable mixture of diastereomers (**390a**:**390b** :51:49 dr).

The assignments **390a** and **390b** are arbitrary, no information on the relative stereochemistry of each diastereomer was obtained: ν_{max}(film)/cm^{-1} 2958 (C-H), 1749 (C=O), 1557 (NO_2), 1382 (NO_2), 1127 (C-O), 1068 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.81 (dd, *J* = 14.4, 4.8 Hz, 1H, C*H*H'NO_2), 4.60 (dd, *J* = 11.6, 6.6 Hz, 2H, CH_2NO_2), 4.52 (dd, *J* = 14.4, 8.3 Hz, 1H, CH*H*'NO_2), 4.45 (dd, *J* = 9.2, 4.3 Hz, 2H, 2 x C*H*(OCH_3)$_2$), 4.19 (d, *J* = 4.3 Hz, 1H, C*H*C≡N), 3.99 (d, *J* = 4.3 Hz, 1H, C*H*C≡N), 3.86 (s, 3H, COOCH_3), 3.84 (s, 3H, COOCH_3), 3.36 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3) 3.35 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.26 - 3.15 (m, 2H, 2 x C*H*CHC≡N), 1.96 - 1.76 (m, 4H, 2 x CH_2CH(OCH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.0 (*C*=O), 164.8 (*C*=O), 114.5 (*C*≡N), 114.2 (*C*≡N), 103.0 (*C*H(OCH_3)$_2$), 102.8 (*C*H(OCH_3)$_2$), 75.9 (CH_2NO_2), 75.8 (CH_2NO_2), 54.5 (CHO*C*H_3), 54.4 (CHO*C*H_3), 54.3 (CHO*C*H_3), 53.8 (COO*C*H_3), 53.8 (COO*C*H_3), 53.7 (COO*C*H_3), 39.8 (*C*HC≡N), 39.5 (*C*HC≡N), 33.6 (*C*HCHC≡N), 33.4 (*C*HCHC≡N), 32.6 (*C*H_2CH(OCH_3)$_2$), 31.9

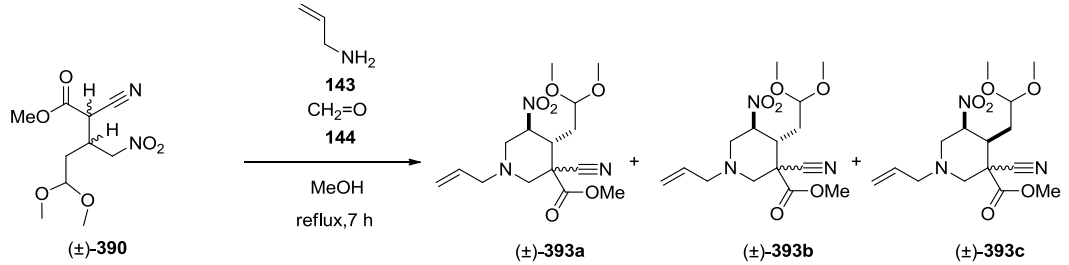
($CH_2CH(OCH_3)_2$); *m/z* (ESI$^-$) 259 (100%, $[M-H]^-$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 283.0905, $C_{10}H_{16}N_2NaO_6$ requires 283.0901.

6.5.5. Synthesis of methyl 2-cyano-5,5-dimethoxy-3-(nitromethyl)pentanoate (±)-390



To a solution of methyl cyanoacetate **391** (0.132 g, 118 µl, 1.33 mmol) in THF (8.5 mL) was added dropwise KHMDS (0.5 M in toluene) (2.80 mL, 1.40 mmol) at −78 °C and the solution was stirred at this temperature for 15 min. To the reaction mixture was added a solution of nitro olefin **383** (0.300 g, 1.86 mmol) and 18-crown-6 (0.370 g, 1.40 mmol) in THF (5 mL) at −78 °C and the resulting solution was stirred for 1 h. The reaction mixture was warmed to RT over 15 min before acetic acid (glacial) (0.080 g, 76 µl, 1.33 mmol) was added dropwise and the reaction mixture stirred for a further 10 min. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (EtOAc:PE 1:4) to give the title compound (±)-**390** (0.142 g, 41%) as a colourless oil as an inseparable mixture of diastereomers (**390a**:**390b** 49:51 dr). With data in good agreement with that previously reported (*vide supra*).

6.5.6. Synthesis of 393a, 393b and 393c



To a solution of Michael adduct (±)-**390** (0.165 g, 0.635 mmol, (**390a**:**390b** ~1:1 dr) in MeOH (9 mL) was added allylamine **143** (0.043 g, 57 µl, 0.753 mmol); a dark yellow solution was immediately observed; followed by formaldehyde **144** (37% solution in water) (0.444 g, 0.407 mL, 5.47 mmol) and the resulting colourless solution was refluxed for 7 h. The solution was cooled to RT and concentrated before being purified by column chromatography (EtOAc:PE 1:4) to give the title compounds as separable diastereomers (±)-**393a** (0.133 g, 62%), (±)-**393b** (0.014 g, 6%) and (±)-**393c** (0.040 g, 19%) as colourless oils.

Data for diastereomer (±)-**393a**

R_f = 0.65 (EtOAc:PE 3:7); ν_{max}(film)/cm^{-1} 2958 (C-H), 1746 (C=O), 1553 (NO_2), 1371 (NO_2), 1253 (C-O), 1070 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.80 (ddt, *J* = 17.0, 10.4, 6.3 Hz, 1H, CH_2=C*H*), 5.31 - 5.20 (m, 2H, C*H*$_2$=CH), 4.70 (ddd, *J* = 11.1, 11.0, 4.4 Hz, 1H, C*H*NO_2), 4.26 (dd, *J* = 6.7, 4.4 Hz, 1H, C*H*$(OCH_3)_2$), 3.87 (s, 3H, COOC*H*$_3$), 3.43 (ddd, *J* = 10.8, 4.5, 1.7 Hz, 1H, NC*H*H'CHNO_2), 3.29 - 3.25 (m, 4H, CHOC*H*$_3$, NC*H*H'CC≡N), 3.24 (s, 3H, CHOC*H*$_3$), 3.21 - 3.09 (m, 2H, CH_2=CHC*H*$_2$), 2.85 (ddd, *J* = 11.1, 6.2, 5.0 Hz, 1H, NO_2CHC*H*), 2.58 - 2.50 (m, 2H, NCH*H*'CHNO_2, NCH*H*'CC≡N), 1.96 (dt, *J* = 15.1, 6.7, 6.2 Hz, 1H, C*H*H'CH$(OCH_3)_2$), 1.80 (ddd, *J* = 15.1, 5.0, 4.4 Hz,

1H, CH*H*'CH(OCH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 166.3 (*C*=O), 132.9 (CH_2=*C*H), 119.7 (*C*H_2=CH), 116.4 (*C*≡N), 102.1 (*C*H(OCH_3)$_2$), 85.7 (*C*NO_2), 59.8 (CH_2=CH*C*H_2), 58.4 (N*C*H_2CC≡N), 56.1 (N*C*H_2CNO_2), 54.0 (COO*C*H_3), 53.7 (CHO*C*H_3), 52.9 (CHO*C*H_3), 50.9 (*C*C≡N), 39.7 (NO_2CHC*H*), 34.2 (*C*H_2CH(OCH_3)$_2$); *m/z* (ESI$^+$) 705 (100%, [2M+Na]$^+$), 364 (78, [M+Na]$^+$), 342 (45, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 364.1477, $C_{15}H_{23}N_3NaO_6$ requires 364.1479.

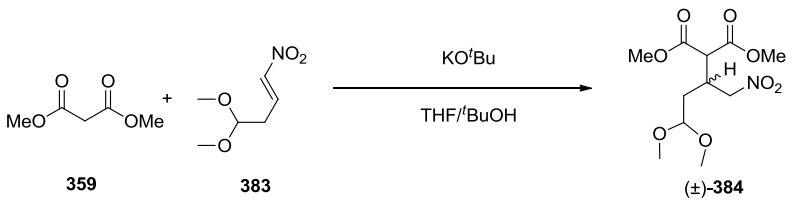
Data for diastereomer (±)-**393b**

R_f = 0.75 (EtOAc:PE 3:7); ν_{max}(film)/cm^{-1} 2918 (C-H), 1751 (C=O), 1544 (NO_2), 1373 (NO_2), 1229 (C-O), 1071 (C-O); ^{1}H NMR (500 MHz, CD_3OD) δ_H 5.75 (ddt, *J* = 16.9, 10.5, 6.3 Hz, 1H, CH_2=C*H*), 5.28 - 5.16 (m, 2H, C*H*$_2$=CH), 5.09 (ddd, *J* = 9.8, 9.8, 4.7 Hz, 1H, C*H*NO_2), 4.37 (t, *J* = 5.5 Hz, 1H, C*H*(OCH_3)$_2$), 3.84 (s, 3H, COOC*H*$_3$), 3.46 - 3.36 (m, 1H, NC*H*H'CC≡N), 3.33 - 3.29 (m, 4H, CHOC*H*$_3$, NC*H*H'CHNO_2), 3.29 - 3.28 (m, 3H, CHOC*H*$_3$), 3.17 - 3.04 (m, 2H, CH_2=CHC*H*$_2$), 2.79 - 2.68 (m, 3H, NCH*H*'CHNO_2, NCH*H*'CC≡N, NO_2CHC*H*), 1.96 (dd, *J* = 5.8, 5.5 Hz, 2H, C*H*$_2$CH(OCH_3)$_2$); ^{13}C NMR (125 MHz, CD_3OD) δ_C 167.5 (*C*=O), 135.0 (CH_2=*C*H), 119.6 (*C*H_2=CH), 118.6 (*C*≡N), 104.3 (*C*H(OCH_3)$_2$), 85.5 (*C*NO_2), 60.8 (CH_2=CH*C*H_2), 59.8 (N*C*H_2CC≡N), 56.5 (N*C*H_2CNO_2), 54.4 (CHO*C*H_3), 54.3 (COO*C*H_3), 54.2 (CHO*C*H_3), 49.8 (*C*C≡N), 41.2 (NO_2CHC*H*), 35.2 (*C*H_2CH(OCH_3)$_2$); *m/z* (ESI$^+$) 705 (100%, [2M+Na]$^+$), 364 (58, [M+Na]$^+$), 342 (45, [M+H]$^+$). HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 364.1475, $C_{15}H_{23}N_3NaO_6$ requires 364.1479.

Data for diastereomer (±)-**393c**

R_f = 0.30 (EtOAc:PE 3:7); ν_{max}(film)/cm^{-1} 2957 (C-H), 1744 (C=O), 1555 (NO_2), 1372 (NO_2), 1249 (C-O), 1070 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.76 (ddt, *J* = 16.8, 10.5, 6.3 Hz, 1H, CH_2=C*H*), 5.33 - 5.13 (m, 2H, CH_2=CH), 4.90 (ddd, *J* = 4.0, 4.0, 4.0 Hz, 1H, C*H*NO_2), 4.42 (t, *J* = 4.7 Hz, 1H, C*H*$(OCH_3)_2$), 3.88 (s, 3H, COOCH_3), 3.55 - 3.37 (m, 1H, NC*H*H'CHNO_2), 3.34 (s, 3H, CHOCH_3), 3.29 (s, 3H, CHOCH_3), 3.25 (d, *J* = 8.5 Hz, 1H, NC*H*H'CC≡N), 3.13 - 3.03 (m, 2H, CH_2=CHCH_2), 2.89 - 2.75 (m, 1H, NO_2CHC*H*), 2.73 – 2.59 (m, 2H, NCH*H*'CHNO_2, NCH*H*'CC≡N), 2.38 - 2.22 (m, 1H, C*H*H'C$H(OCH_3)_2$), 1.79 (ddd, *J* = 14.6, 4.8, 4.7 Hz, 1H, CH*H*'C$H(OCH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.6 (*C*=O), 133.0 (CH_2=*C*H), 119.4 (*C*H_2=CH), 117.0 (*C*≡N), 102.9 (*C*$H(OCH_3)_2$), 80.3 (*C*NO_2), 59.9 (CH_2=CH*C*H_2), 58.4 (N*C*H_2CC≡N), 56.1 (N*C*H_2CNO_2), 54.7 (CHO*C*H_3), 54.2 (COO*C*H_3), 53.5 (CHO*C*H_3), 48.3 (*C*C≡N), 36.5 (NO_2CHC*H*), 30.9 (*C*H_2C$H(OCH_3)_2$); *m/z* (ESI^+) 705 (100%, $[2M+Na]^+$), 364 (33, $[M+Na]^+$), 342 (48, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 364.1479, $C_{15}H_{23}N_3NaO_6$ requires 364.1479.

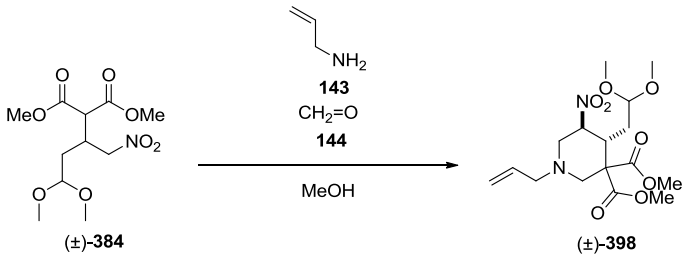
6.5.7. Synthesis of *rac*-dimethyl (4,4-dimethoxy-1-nitrobutan-2-yl)malonate (±)-384



359 383 (±)-384

KO^{t}Bu (0.070 g, 0.624 mmol) was added to a solution of dimethyl malonate **359** (0.098 g, 0.085 mL, 0.742 mmol) in THF/^{t}BuOH (2.6 mL:66 µl) cooled to 0 °C and the reaction mixture was stirred for 2 h at this temperature. Nitro olefin **383** (0.100 g, 0.621 mmol) in THF (0.7 mL) was added and the resulting yellow solution was warmed to RT and stirred at this temperature for 24 h. After cooling the solution to 0 °C, acetic acid (0.112 g, 106 µl, 1.87 mmol) was added carefully and the reaction mixture was stirred for 0.5 h before being concentrated under reduced pressure and purified by column chromatography (Et_2O:PE 1:1) to give the title compound (±)-**384** (0.135 g, 74%) as a colourless oil: ν_{max}(film)/cm^{-1} 2957 (C-H), 1733 (C=O), 1553 (NO_2), 1383 (NO_2), 1126 (C-O), 1068 (C-O), 1050 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.68 (dd, *J* = 6.1, 1.8 Hz, 2H, C*H*$_2$NO$_2$), 4.44 (t, *J* = 5.2 Hz, 1H, C*H*(OCH$_3$)$_2$), 3.78 (d, *J* = 5.3 Hz, 1H, C*H*(COOCH$_3$)$_2$), 3.77 (s, 3H, COOC*H*$_3$), 3.76 (s, 3H, COOC*H*$_3$), 3.32 (s, 3H, OC*H*$_3$), 3.32 (s, 3H, OC*H*$_3$), 3.17 - 3.02 (m, 1H, C*H*CH(COOCH$_3$)$_2$), 1.84 – 1.78 (m, 2H, C*H*$_2$CH(OCH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.3 (*C*=O), 168.2 (*C*=O), 103.1 (*C*H(OCH$_3$)$_2$), 76.4 (*C*H$_2$NO$_2$), 53.8 (CHO*C*H$_3$), 53.3 (CHO*C*H$_3$), 52.8 (*C*H(COOCH$_3$)$_2$), 52.7 (COO*C*H$_3$), 52.5 (COO*C*H$_3$), 33.1 (*C*HCH(COOCH$_3$)$_2$), 32.7 (*C*H$_2$CH(OCH$_3$)$_2$); *m/z* (ESI$^+$) 609 (90%, [2M+Na]$^+$), 316 (100, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 316.0997, $C_{11}H_{19}NNaO_8$ requires 316.1003.

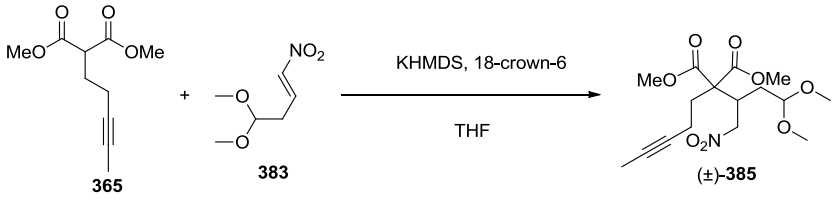
6.5.8. Synthesis of dimethyl *rac*-(4*R*,5*S*)-1-allyl-4-(2,2-dimethoxyethyl)-5-nitropiperidine-3,3-dicarboxylate (±)-398



To a solution of Michael adduct (±)-**384** (0.050 g, 0.170 mmol) in MeOH (2.5 mL) was added allylamine **143** (0.012 g, 16 µl, 0.205 mmol); a dark yellow solution was immediately observed; followed by formaldehyde **144** (37% solution in water) (0.119 g, 0.110 mL, 1.47 mmol) and the resulting colourless solution was refluxed for 5 h. The solution was cooled to RT and concentrated before being purified by column chromatography (Et_2O:PE 3:7) to give the title compound (±)-**398** (0.015 g, 24%) as a colourless oil: ν_{max}(film)/cm^{-1} 2955 (C-H), 1734 (C=O), 1551 (NO_2), 1370 (NO_2), 1257 (C-O), 1071 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.75 - 5.61 (m, 1H, CH_2=C*H*CH_2), 5.23 - 5.11 (m, 2H, C*H*$_2$=CHCH_2), 5.06 (ddd, *J* = 10.9, 10.6, 5.0 Hz, 1H, C*H*NO_2), 4.03 (dd, *J* = 8.0, 3.7 Hz, 1H, C*H*$(OCH_3)_2$), 3.75 (s, 3H, COOC*H*$_3$), 3.74 (s, 3H, COOC*H*$_3$), 3.41 (dd, *J* = 11.7, 1.9 Hz, 1H, NC*H*H'C$(COOCH_3)_2$), 3.30 (s, 3H, OC*H*$_3$), 3.30 – 3.25 (m, 1H, NC*H*H'CNO_2), 3.24 (s, 3H, OC*H*$_3$), 3.06 (ddt, *J* = 13.6, 6.0, 1.3 Hz, 1H, CH_2=CHC*H*H'), 2.99 (ddt, *J* = 13.6, 6.9, 1.1 Hz, 1H, CH_2=CHCH*H*'), 2.62 (d, *J* = 11.7 Hz, 1H, NCH*H*'C$(COOCH_3)_2$), 2.56 (dd, *J* = 10.6, 10.6 Hz, 1H, NCH*H*'CNO_2), 2.41 (ddd, *J* = 10.9, 5.0, 3.5 Hz, 1H, NO_2CHC*H*), 2.21 (ddd, *J* = 15.8, 8.0, 3.5 Hz, 1H, C*H*H'CH$(OCH_3)_2$), 1.90 (ddd, *J* = 15.8, 5.0, 3.7 Hz, 1H, CH*H*'CH$(OCH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.5 (*C*=O), 169.0 (*C*=O), 133.6 (CH_2=*C*H), 118.8 (*C*H_2=CH), 104.6 (*C*H$(OCH_3)_2$), 86.0 (*C*NO_2), 60.4 (CH_2=CH*C*H_2), 59.5 (*C*$(COOCH_3)_2$),

58.4 ($NCH_2C(COOCH_3)_2$), 56.8 (NCH_2CNO_2), 55.4 (OCH_3), 53.0 (OCH_3), 52.7 ($COOCH_3$), 52.4 ($COOCH_3$), 40.4 NO_2CHCH), 33.4 ($CH_2CH(OCH_3)_2$); *m/z* (ESI^+) 397 (100%, $[M+Na]^+$), 375 (88, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 397.1573, $C_{16}H_{26}N_2NaO_8$ requires 397.1581.

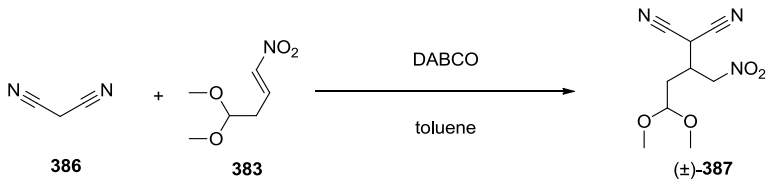
6.5.9. Synthesis of dimethyl (4,4-dimethoxy-1-nitrobutan-2-yl)(pent-3-yn-1-yl)malonate (±)-385



To a solution of pro-nucleophile **365** (0.070 g, 0.35 mmol) in THF (2.5 mL) was added dropwise KHMDS (0.5 M in toluene) (0.74 mL, 0.37 mmol) at −78 °C and the solution was stirred at this temperature for 15 min. To this solution was added dropwise a solution of nitro olefin **383** (0.080 g, 0.50 mmol) and 18-crown-6 (0.098 g, 0.37 mmol) in THF (1.3 mL) at −78 °C over 1 h. The reaction mixture was warmed to RT over 20 min before acetic acid (glacial) (0.063 g, 61 µl, 1.05 mmol) was added dropwise and the reaction mixture stirred for a further 10 min. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (Et_2O:PE 1:1) to give the title compound (±)-**385** (0.050 g, 39%) as a colourless oil: ν_{max}(film)/cm^{-1} 2958 (C-H), 1734 (C=O), 1554 (NO_2), 1380 (NO_2), 1127 (C-O), 1068 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.63 (dd, *J* = 15.1, 3.3 Hz, 1H, C*H*H'NO_2), 4.52 (dd, *J* = 15.1, 6.2 Hz, 1H, CH*H*'NO_2), 4.36 (dd, *J* = 6.3, 4.5 Hz, 1H, C*H*$(OCH_3)_2$), 3.74 (s, 3H, COOC*H*$_3$), 3.73 (s, 3H, COOC*H*$_3$), 3.30 (s, 3H, OC*H*$_3$), 3.25 (s, 3H, OC*H*$_3$), 3.22 - 3.14 (m, 1H, C*H*CH_2NO_2), 2.26 - 2.05 (m, 4H, C*H*$_2$C≡CCH_3, C*H*$_2$$CH_2$C≡C$CH_3$), 1.80 (ddd, *J* = 14.3, 4.5, 2.4 Hz, 1H, C*H*H'$CH(OCH_3)_2$), 1.75 (t, *J* = 2.1 Hz, 3H, C≡CC*H*$_3$), 1.55 (ddd, *J* = 14.3, 10.5, 6.3 Hz, 1H, CH*H*'$CH(OCH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.2 (*C*=O), 169.9 (*C*=O), 103.7 (*C*$H(OCH_3)_2$), 77.9 (*C*H_2NO_2), 76.7 (*C*≡C), 76.5 (C≡*C*), 60.2 (*C*$(COOCH_3)_2$), 54.2 ($CHOCH_3$), 53.0 ($CHOCH_3$), 52.7 ($COOCH_3$), 52.7 ($COOCH_3$), 36.9 (*C*$HC(COOCH_3)_2$),

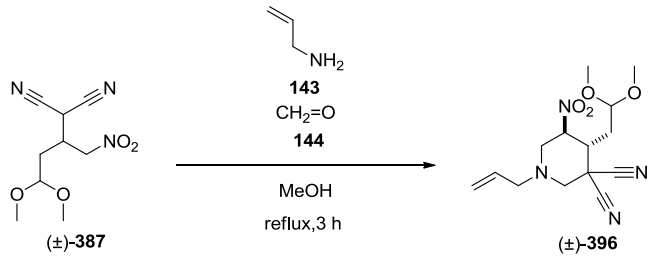
33.7 ($CH_2CH(OCH_3)_2$), 33.2 ($CH_2CH_2C{\equiv}C$), 14.6 ($CH_2C{\equiv}C$), 3.4 ($C{\equiv}CCH_3$); *m/z* (ESI^+) 741 (100%, $[2M+Na]^+$), 398 (28, $[M+K]^+$), 382 (75, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 382.1467, $C_{16}H_{25}NNaO_8$ requires 382.1472.

6.5.10. Synthesis of (4,4-dimethoxy-1-nitrobutan-2-yl)malononitrile (±)-387



Malononitrile **386** (0.102 g, 1.54 mmol), nitro olefin **383** (0.300 g, 1.86 mmol) and DABCO (0.035 g, 0.31 mmol) were dissolved in toluene (8 mL) and the reaction mixture was stirred for 48 h at RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (Et_2O:PE 1:1) to give the title compound (±)-**387** (0.141 g, 40%) as an orange oil: ν_{max}(film)/cm^{-1} 2930 (C-H), 1556 (NO_2), 1382 (NO_2), 1125 (C-O), 1065 (C-O), 1049 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.75 (dd, *J* = 14.4, 6.6 Hz, 1H, C*H*H'NO_2), 4.65 (dd, *J* = 14.4, 6.4 Hz, 1H, CH*H*'NO_2), 4.57 (d, *J* = 5.3 Hz, 1H, C*H*(C≡N)$_2$), 4.48 (t, *J* = 3.9 Hz, 1H, C*H*(OCH_3)$_2$), 3.41 (s, 3H, OC*H*$_3$), 3.40 (s, 3H, OC*H*$_3$), 3.27 - 3.11 (m, 1H, C*H*CH_2NO_2), 2.04 (ddd, *J* = 14.8, 6.7, 3.9 Hz, 1H, C*H*H'CH(OCH_3)$_2$), 1.94 (ddd, *J* = 14.8, 6.8, 3.9 Hz, 1H, CH*H*'CH(OCH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 111.0 (*C*≡N), 110.9 (*C*≡N), 103.0 (*C*H(OCH_3)$_2$), 74.9 (*C*H_2NO_2), 55.4 (O*C*H_3), 55.1 (O*C*H_3), 34.4 (*C*HC(C≡N)$_2$), 31.8 (*C*H_2CH(OCH_3)$_2$), 25.7 (*C*(C≡N)$_2$); *m/z* (ESI$^+$) 250 (100%, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 250.0800, $C_9H_{13}N_3NaO_4$ requires 250.0798.

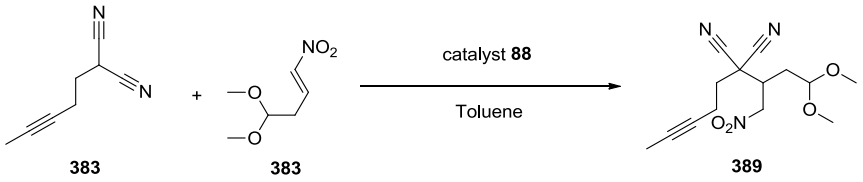
6.5.11. Synthesis of *rac*-(4*R*,5*S*)-1-allyl-4-(2,2-dimethoxyethyl)-5-nitropiperidine-3,3-dicarbonitrile (±)-396



To a solution of Michael adduct (±)-**387** (0.087 g, 0.384 mmol) in MeOH (6 mL) was added allylamine **143** (0.026 g, 34 µl, 0.461 mmol); a dark yellow solution was immediately observed; followed by formaldehyde **144** (37% solution in water) (0.269 g, 0.246 mL, 3.31 mmol) and the resulting colourless solution was refluxed for 3 h. The solution was cooled to RT and concentrated before being purified by column chromatography (EtOAc:PE 1:4) to give the title compound (±)-**396** (0.065 g, 55%) as colourless oil: ν_{max}(film)/cm^{-1} 2937 (C-H), 1556 (NO_2), 1372 (NO_2), 1123 (C-O), 1053 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.79 (ddt, *J* = 16.8, 10.6, 6.5 Hz, 1H, CH_2=C*H*CH_2), 5.35 - 5.25 (m, 2H, C*H*$_2$=CHCH_2), 4.65 (ddd, *J* = 10.9, 10.9, 4.6 Hz, 1H, C*H*NO_2), 4.51 (t, *J* = 5.5 Hz, 1H, C*H*$(OCH_3)_2$), 3.52 (dd, *J* = 11.9, 1.7 Hz, 1H, NC*H*H'$C(CN)_2$), 3.45 (ddd, *J* = 11.1, 4.6, 1.9 Hz, 1H, NC*H*H'CNO_2), 3.36 (s, 3H, OC*H*$_3$), 3.32 (s, 3H, OC*H*$_3$), 3.27 - 3.16 (m, 2H, CH_2=CHC*H*$_2$), 2.77 (dt, *J* = 10.9, 6.0 Hz, 1H, NO_2CHC*H*), 2.68 (d, *J* = 11.9 Hz, 1H, NCH*H*'$C(CN)_2$), 2.62 (dd, *J* = 10.9, 10.9 Hz, 1H, NCH*H*'$CHNO_2$), 2.18 - 2.10 (ddd, *J* = 14.9, 6.0, 5.5 Hz, 1H, C*H*H'$CH(OCH_3)_2$), 2.02 (ddd, *J* = 14.9, 6.0, 5.5 Hz, 1H, CH*H*'$CH(OCH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 132.1 (CH_2=*C*H), 120.5 (*C*H_2=CH), 113.3 (*C*≡N), 112.6 (*C*≡N), 101.0 (*C*$H(OCH_3)_2$), 84.0 (*C*NO_2), 59.5 (CH_2=CH*C*H_2), 58.3 (N*C*$H_2C(C{\equiv}N)_2$), 55.5 (N*C*H_2CNO_2), 53.7 (O*C*H_3), 53.5 (O*C*H_3), 41.1 (NO_2CHC*H*), 38.1 (*C*$(C{\equiv}N)_2$),

34.7 ($CH_2CH(OCH_3)_2$); *m/z* (ESI^+) 331 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 331.1365, $C_{14}H_{20}N_4NaO_4$ requires 331.1377.

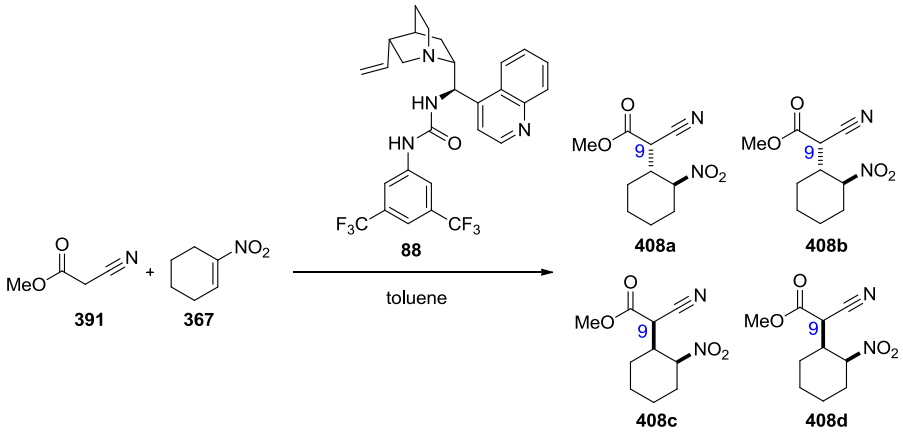
6.5.12. Synthesis of (4,4-dimethoxy-1-nitrobutan-2-yl)(pent-3-yn-1-yl)malononitrile 389



383 383 389

Pro-nucleophile **388** (0.102 g, 0.772 mmol), nitro olefin **383** (0.149 g, 0.925 mmol) and catalyst **88** (0.085 g, 0.155 mmol) were dissolved in toluene (4 mL) and the reaction mixture was stirred for 48 h at RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (EtOAc:PE 1:4) to give the title compound **389** (0.140 g, 62%) as a colourless oil: ν_{max}(film)/cm^{-1} 2923 (C-H), 1559 (NO_2), 1382 (NO_2), 1122 (C-O), 1065 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.82 (dd, *J* = 14.8, 5.3 Hz, 1H, C*H*H'NO_2), 4.62 (dd, *J* = 14.8, 4.9 Hz, 1H, CH*H*'NO_2), 4.48 (t, *J* = 4.8 Hz, 1H, C*H*$(OCH_3)_2$), 3.36 (s, 3H, OC*H*$_3$), 3.36 (s, 3H, OC*H*$_3$), 3.27 - 3.16 (m, 1H, C*H*CH_2NO_2), 2.56 (tq, *J* = 7.6, 2.5 Hz, 2H, C*H*$_2$C≡CCH_3), 2.23 - 2.04 (m, 3H, C*H*$_2$$CH_2$C≡C$CH_3$, C*H*H'$CH(OCH_3)_2$), 1.96 (ddd, = 14.7, 9.9, 5.1 Hz, 1H, CH*H*'$CH(OCH_3)_2$), 1.78 (t, *J* = 2.5 Hz, 3H, CH_2C≡CC*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 113.4 (*C*≡N), 113.3 (*C*≡N), 102.6 (*C*H$(OCH_3)_2$), 79.3 (*C*≡C), 75.3 (*C*H_2NO_2), 74.3 (*C*≡C), 54.9 (CHO*C*H_3), 54.0 (CHO*C*H_3), 40.8 (*C*$(C≡N)_2$), 39.1 (*C*HC$(C≡N)_2$), 34.3 (*C*$H_2$$CH_2$C≡C), 33.1 (*C*$H_2CH(OCH_3)_2$), 15.9 (*C*$H_2$C≡C), 3.3 (C≡C*C*$H_3$); *m/z* (ESI$^+$) 316 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 316.1259, $C_{14}H_{19}N_3NaO_4$ requires 316.1268.

6.5.13. Synthesis of diastereomers of methyl cyano(2-nitrocyclohexyl)acetate 408



To a solution of methyl cyanoacetate **391** (0.080 g, 0.071 mL, 0.807 mmol) and 1-nitrocyclohexene **367** (0.086 g, 0.076 mL, 0.676 mmol) in toluene (4 mL) was added catalyst **88** (0.036 g, 0.066 mmol). The resulting solution was stirred for 15 h at RT. ^{1}H NMR analysis indicated consumption of 1-nitrocyclohexene **367** and the formation of four new products (**408**a:**408**b:**408**c:**408**d 1.3:0.5:1.1:1.0 dr). The reaction mixture was concentrated and purified immediately by column chromatography (EtOAc:PE 1:4), to give two diastereomeric mixtures (I and II) as colourless oils. (I) (0.070 g, **408a**:**408b**:**408c**:**408d** 10:3.7:1.2:1.1 dr) and (II) (0.047 g, **408a**:**408b**:**408c**:**408d** 2.3:5.6:10:8.9 dr). Overall yield of **408** (0.117 g, 76%). **408a/b** and **408c/d** are arbitrary assignments representing *trans* and *cis* diastereomers respectively, which are epimeric at the C-9 position. No evidence supporting the relative stereochemistry at this position was obtained.

Preparation of single diastereomer **408a**

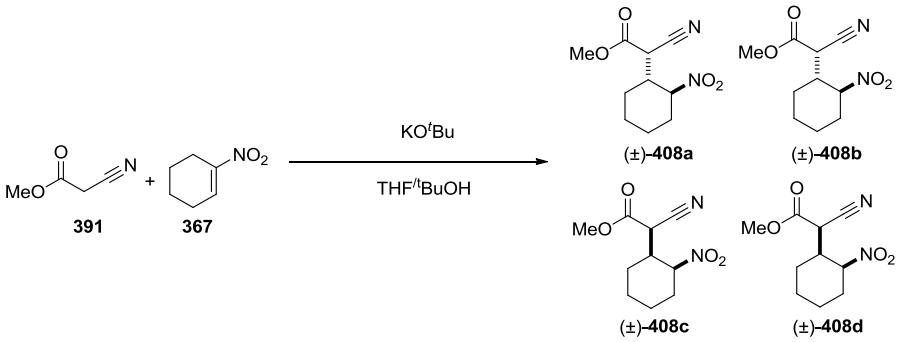
To a solution of methyl cyanoacetate **391** (0.30 g, 0.27 mL, 3.03 mmol) and 1-nitrocyclohexene **367** (0.32 g, 0.28 mL, 2.52 mmol) in toluene (15 mL) was added catalyst **88** (0.069 g, 0.13 mmol). The resulting solution was stirred for 15 h at RT before being concentrated and stored at 20 °C under an N_2 atmosphere for 1 week. ^{1}H NMR analysis indicated a diastereomeric ratio (**408a**:**408b**:**408c**:**408d** 2.7:1:0:0 dr). The reaction mixture was concentrated and purified by column chromatography (EtOAc:PE 1:9), to give a single diastereomeric mixture (0.489 g, 86% **408a**:**408b**:**408c**:**408d** 1.0:0.13:0:0 dr) a colourless solid. Recrystallization of this diastereomeric mixture (Et_2O:PE) yielded a sample **408a** as a single diastereomer, which was used in selected further studies:

Data for diastereomer **408a**

mp 90-94 °C (Et_2O); ν_{max}(film)/cm^{-1} 2946 (C-H), 2867 (C-H), 2252 (C≡N), 1747 (C=O), 1546 (NO_2), 1336 (NO_2), 1259 (C-O), 1208 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.51 (ddd, *J* = 11.4, 11.4, 4.2 Hz, 1H, C*H*NO_2), 3.84 (s, 3H, OC*H*$_3$), 3.67 (d, *J* = 3.3 Hz, 1H, C*H*C≡N), 2.76 (dddd, *J* = 2 x 11.6, 2 x 3.4 Hz, 1H, C*H*CHC≡N), 2.47 - 2.36 (m, 1H, C*H*H'CHNO_2), 2.00 – 1.75 (m, 4H, CH*H*'CHNO_2, C*H*H'CHCHC≡N, C*H*H'CH_2CHCHC≡N, C*H*H'CH_2CHNO_2), 1.57 - 1.31 (m, 3H, CH*H*'CHCHC≡N, CH*H*'CH_2CHCHC≡N, CH*H*'CH_2CHNO_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.8 (*C*=O), 113.8 (*C*≡N), 86.9 (*C*NO_2), 53.9 (O*C*H_3), 40.5 (*C*HNO_2), 40.2 (*C*HC≡N), 31.8 (*C*H_2CHNO_2), 26.6 (*C*H_2CHCHC≡N), 24.0 (*C*H_2CH_2CHNO_2), 23.8 (*C*H_2CH_2CHCHC≡N); *m/z* (ESI$^+$) 265 (88%, $[M+K]^+$), 249 (100, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found

$[M+Na]^+$ 249.0846, $C_{10}H_{14}N_2NaO_4$ requires 249.0845; 25% *ee* (Chiralcel AD, 98:2 hexane:isopropanol, 1.0 mL/min, 220 nm, major t_R = 42.8 min, minor t_R = 27.5 min).

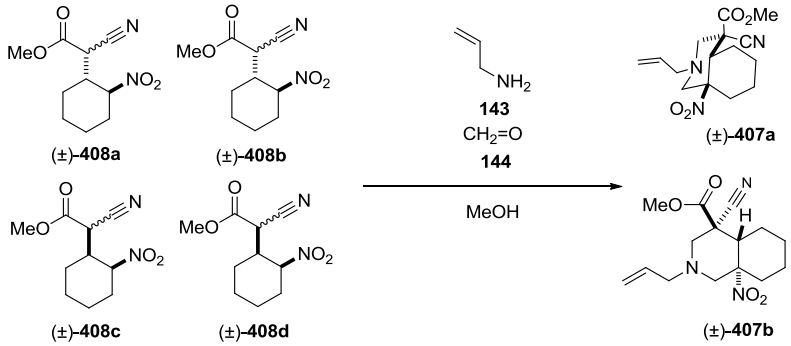
6.5.14. Synthesis of methyl cyano(2-nitrocyclohexyl)acetate (±)-408



KO^{t}Bu (3.78 g, 33.68 mmol) was added to a solution of methyl cyanoacetate **391** (4.00 g, 3.56 mL, 40.37 mmol) in THF/^{t}BuOH (141 mL:4.60 mL) cooled to 0 °C and the reaction mixture stirred for 2 h at 0 °C. 1-nitrocyclohexene **367** (4.28 g, 3.79 mL, 33.66 mmol) in THF (10 mL) was added and the resulting yellow solution was warmed to RT and stirred at this temperature for 15 h. ^{1}H NMR analysis indicated a diastereomeric ratio ((±)-**408a**:(±)-**408b**:(±)-**408c**:(±)-**408d** 1.0:0.35:0.01:0.01 dr). After cooling the solution to 0 °C, acetic acid (6.06 g, 5.80 mL, 100.92 mmol) was added carefully and the reaction mixture was stirred for 0.5 h before being concentrated under reduced pressure and purified by column chromatography (EtOAc:PE 1:4), to give a single diastereomer (5.41 g, 71%, (±)-**408a**:(±)-**408b**:(±)-**408c**:(±)-**408d** 1.0:0.0:0.0:0.0 dr) as a colourless solid with data in good agreement with that reported previously: mp 79-84 °C (Et_2O); Racemic sample (Chiralcel AD, 98:2 hexane:isopropanol, 1.0 mL/min, 220 nm, t_R = 26.3 min, t_R = 40.2 min).

6.5.15. Analysis of nitro-Mannich-Mannich products using starting materials of varying composition

Using (±)-**408a-d** as a mixture of diastereomers (34:12:29:25 dr)



To a solution of methyl cyano(2-nitrocyclohexyl)acetate ((±)-**408 a**:**b**:**c**:**d** 34:12:29:25 dr). (50 mg, 0.22 mmol) in MeOH (3.1 mL) was added allylamine **143** (15 mg, 20 µl, 0.27 mmol), followed by formaldehyde **144** (37% solution in water) (57 mg, 142 µl, 1.91 mmol) and the resulting colourless solution was refluxed for 15 h. The solution was cooled to RT and concentrated before being purified by column chromatography (PE:Et_2O 7:3) to give separable diastereomers (±)-**407a** (16 mg, 24%) and (±)-**407b** (10 mg, 15%) as colourless oils.

Using starting material **408a** (single diastereomer)

To a solution of **408a** (500 mg, 2.21 mmol) in MeOH (30 mL) was added allylamine **143** (303 mg, 397 µl, 5.30 mmol); followed by formaldehyde **144** (37% solution in water) (4.66 g, 4.27 mL, 57.46 mmol) and the resulting colourless solution was refluxed for 20 h. The solution was cooled to RT and concentrated before being purified by column chromatography (PE:Et_2O 4:1→1:1) to give separable diastereomers **407a** (173 mg, 25%) and **407b** (97 mg, 14%) as colourless oils.

Data for diastereomer **407a**

v_{max}(film)/cm^{-1} 2953 (C-H), 2870 (C-H), 2361 (C≡N), 1744 (C=O), 1547 (NO_2), 1341 (NO_2), 1253 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.82 (dddd, *J* = 17.0, 10.4, 6.3, 6.3 Hz, 1H, C*H*=CH_2), 5.30 - 5.18 (m, 2H, CH=CH_2), 3.90 (s, 3H, OCH_3), 3.27 (dd, *J* = 5.2, 2.5 Hz, 1H, C*H*CNO_2), 3.21 - 3.04 (m, 4H, NC*H*H'CNO_2, C*H*H'CC≡N, CH=CH_2CH_2), 2.67 - 2.55 (m, 2H, CH*H*'CC≡N, CNO_2C*H*H'), 2.51 (d, *J* = 11.3 Hz, 1H, NCH*H*'CNO_2), 2.36 (ddd, *J* = 15.2, 3.9, 3.9 Hz, 1H, CNO_2CH*H*'), 2.14 (app. dddd, *J* = 17.7, 13.2, 8.6, 4.4 Hz, 1H, $CHCH_2$C*H*H'), 1.94 - 1.83 (dddd, *J* = 14.8, 13.2, 5.7, 5.4 Hz, 1H, CHC*H*H'), 1.75 (dddd, *J* = 14.0, 4.1, 4.0, 4.0 Hz, 1H, NO_2CCH_2C*H*H'), 1.69 - 1.60 (dddd, *J* = 15.2, 3.4, 3.4, 3.4 Hz, 1H, CHCH*H*'), 1.51 - 1.41 (m, 1H, $CHCH_2$CH*H*'), 1.37 - 1.23 (m, 1H, NO_2CCH_2CH*H*'); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.3 (*C*=O), 133.2 (CH_2=*C*H), 119.5 (*C*≡N), 119.4 (*C*H_2=CH), 90.3 (*C*NO_2), 61.6 (N*C*H_2CNO_2), 60.0 (CH_2=CH*C*H_2), 59.1 (C*C*H_2N), 54.1 (O*C*H_3), 49.1 (*C*C≡N), 38.9 (NO_2C*C*H), 30.4 (NO_2C*C*H_2), 24.4 (CCH*C*H_2), 21.1 (NO_2CCH_2*C*H_2), 18.8 ($CHCH_2$*C*H_2); *m/z* (ESI^+) 330 (100%, $[M+Na]^+$), 308 (95, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 330.1422, $C_{15}H_{21}N_3NaO_4$ requires 330.1424.

Using Michael adduct **408a** obtained using catalyst **88**, **407a** was isolated: 20% *ee* (Chiralcel OD, 85:15 hexane:isopropanol, 0.5 mL/min, 220 nm, major t_R = 12.2 min, minor t_R = 13.3 min).

An analytical crystalline sample of diastereomer **407b** was obtained by crystallization from (EtOAc/PE) and the structure confirmed by single crystal

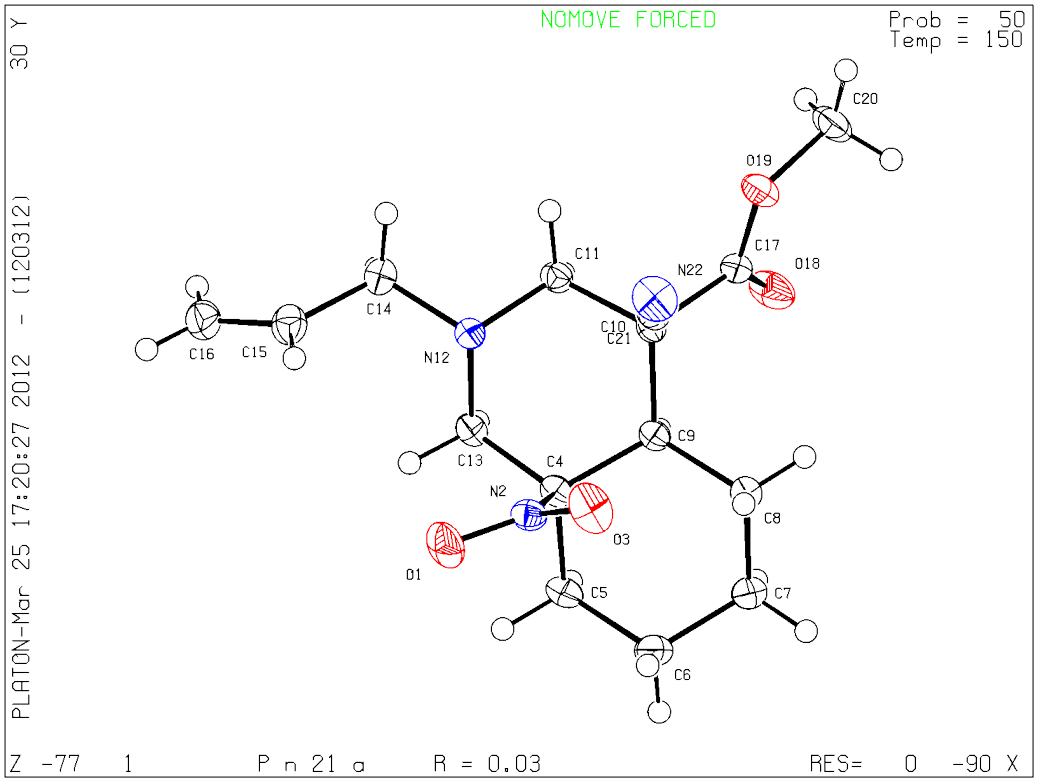
X-ray analysis. The melting point was collected using this sample however all other data were collected from the bulk material.

Data for diastereomer **407b**

mp 156-164 °C (EtOAc/PE); ν_{max}(film)/cm^{-1} 2940 (C-H), 2361 (C≡N), 1745 (C=O), 1548 (NO_2), 1349 (NO_2), 1251 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.81 - 5.71 (m, 1H, CH_2=C*H*), 5.25 - 5.18 (m, 2H, C*H*$_2$=CH), 3.87 (s, 3H, OC*H*$_3$), 3.70 (dd, *J* = 12.6, 2.2 Hz, 1H, NC*H*H'CNO_2), 3.41 (dd, *J* = 11.5, 2.0 Hz, 1H, C*H*H'CC≡N), 3.13 - 3.03 (m, 2H, CH_2=CHC*H*$_2$), 2.52 (d, *J* = 11.5 Hz, 1H, CH*H*'CC≡N), 2.45 (dddd, *J* = 12.8, 12.8, 12.8, 4.4 Hz, 1H, CHC*H*H'), 2.31 - 2.23 (m, 2H, C*H*CNO_2, NO_2CC*H*H'CH_2), 2.18 (d, *J* = 12.6 Hz, 1H, NCH*H*'CNO_2), 1.96 - 1.88 (m, 1H, $CHCH_2$C*H*H'), 1.73 - 1.65 (m, 1H, NO_2CCH_2C*H*H'), 1.57 - 1.50 (m, 2H, CHCH*H*', NO_2CCH*H*'CH_2), 1.48 - 1.38 (m, 1H, $CHCH_2$CH*H*'), 1.38-1.28 (ddddd, *J* = 13.5, 13.5, 13.5, 3.3, 3.2, 1H, NO_2CCH_2CH*H*'); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2 (*C*=O), 133.2 (CH_2=*C*H), 119.2 (*C*H_2=CH), 117.4 (*C*≡N), 88.3 (*C*NO_2), 62.1 (N*C*H_2CNO_2), 60.8 (C*C*H_2N), 59.9 (CH_2=CH*C*H_2), 54.1 (O*C*H_3), 48.5 (*C*C≡N), 46.2 (NO_2C*C*H), 35.8 (NO_2C*C*H_2), 25.2 ($CHCH_2$*C*H_2), 23.9 (CH*C*H_2), 20.7 (NO_2CCH_2*C*H_2); *m/z* (ESI$^+$) 637 (100%, [2M+Na]$^+$), 330 (24, [M+Na]$^+$), 308 (96, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 330.1432, $C_{15}H_{21}N_3NaO_4$ requires 330.1424.

6.5.16. Single crystal X-ray analysis of diastereomer 407b

Thermal ellipsoid Plot drawn at 50% probability



Crystal data **407b**

$C_{15}H_{21}N_3O_4$	D_x = 1.326 Mg m^{-3}
M_r = 307.35	Melting point: 156-164 °C
Orthorhombic, *Pn*2$_1$*a*	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: P -2ac -2n	Cell parameters from 2004 reflections
a = 9.1977 (1) Å	θ = 5–27°
b = 11.2057 (2) Å	μ = 0.10 mm^{-1}
c = 14.9391 (2) Å	*T* = 150 K
V = 1539.72 (4) Å^3	Block, Colourless

Z = 4	0.42 × 0.22 × 0.18 mm
F(000) = 656	

Data collection

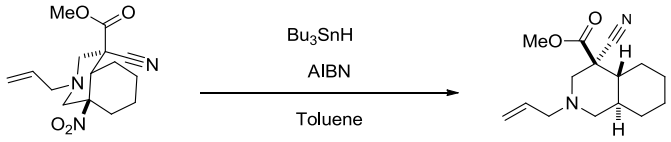
Nonius KappaCCD diffractometer	1627 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.021
ω scans	θ_{max} = 27.5°, θ_{min} = 5.2°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	h = −11→11
T_{min} = 0.84, T_{max} = 0.98	k = −14→14
14524 measured reflections	l = −19→19
1833 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.031	No H atoms present
$wR(F^2)$ = 0.072	Method = Modified Sheldrick w = $1/[\sigma^2(F^2) + (0.04P)^2 + 0.29P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
S = 0.96	$(\Delta/\sigma)_{max}$ = 0.0003

1833 reflections	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
199 parameters	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
1 restraint	

6.5.17. Synthesis of methyl *rac*-(4*R*,4a*S*,8a*S*)-2-allyl-4-cyanodecahydroisoquinoline-4-carboxylate (±)-409

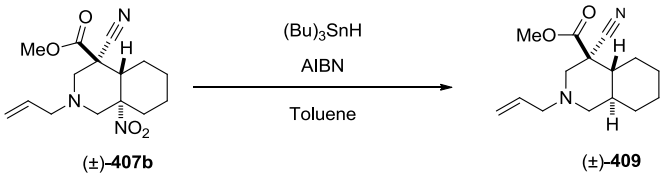


(±)-**407a** (±)-**409**

Tributyltin hydride (0.606 g, 0.552 mL, 2.08 mmol) and AIBN (0.014 mg, 0.085 mmol) were added to a solution of nitro substrate (±)-**407a** (0.128 g, 0.416 mmol) in toluene (10 mL). The reaction mixture was degassed by ten cycles of vacuum/N_2 purge. The resulting solution was heated rapidly to reflux and stirred at this temperature for 2.5 h before being cooled to RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (PE→PE:Et_2O 4:1) to give the title compound (±)-**409** as a colourless oil (0.084 g, 77%). ^{1}H NMR analysis of the crude and purified reaction residues confirmed that only a single diastereomer was present: ν_{max}(film)/cm^{-1} 2927 (C-H), 1741 (C=O), 1448 (C-H), 1254 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.85 (dddd, *J* = 17.0, 10.3, 6.8, 5.8 Hz, 1H, CH_2=C*H*), 5.22 (dddd, *J* = 17.0, 1.6, 1.6, 1.5 Hz, 1H, C*H*H'=CH), 5.17 (dddd, *J* = 10.3, 1.5, 1.4 1.1 Hz, 1H, NCH*H*'=CH), 3.82 (s, 3H, OCH_3), 3.26 (dd, *J* = 11.1, 1.7 Hz, 1H, C*H*H'CC≡N), 3.14 (ddt, *J* = 13.8, 5.8, 1.4 Hz, 1H, CH_2=CHC*H*H'), 2.97 (ddt, *J* = 13.8, 6.8, 1.2 Hz, 1H, CH_2=CHCH*H*'), 2.87 - 2.79 (m, 1H, NC*H*H'CH), 2.34 (d, *J* = 11.1 Hz, 1H, CH*H*'CC≡N), 1.83 - 1.77 (m, 2H, NCH*H*'CH, N≡CCCHCH_2C*H*H'), 1.77 - 1.63 (m, 3H, NCH_2C*H,* NCH_2CHC*H*H', NCH_2CHCH_2C*H*H'), 1.61 - 1.52 (m, 2H, N≡CCC*H*, N≡CCCHC*H*H'), 1.42 - 1.22 (m, 3H, N≡CCCHCH_2CH*H'*, N≡CCCHCH*H'*, NCH_2CHCH_2CH*H'*), 1.08 - 0.94 (m, 1H, NCH_2CHCH*H'*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.4 (*C*=O), 134.5 (CH_2=*C*H), 118.1 (*C*H_2=CH), 117.8 (*C*≡N),

60.6 (CH_2=CH*C*H_2), 59.4 (N*C*H_2CH), 59.0 (N*C*H_2CC≡N), 53.3 (O*C*H_3), 51.8 (*C*C≡N), 46.5 (N≡CC*C*H), 37.6 (NCH_2*C*H), 30.2 (NCH_2CH*C*H_2), 28.1 (N≡CCCH*C*H_2), 25.7 (N≡CCCHCH_2*C*H_2), 25.2 (NCH_2CHCH_2*C*H_2); *m/z* (ESI^+) 547 (100%, $[2M+Na]^+$), 285 (51, $[M+Na]^+$), 263 (78, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 263.1745, $C_{15}H_{23}N_2O_2$ requires 263.1754.

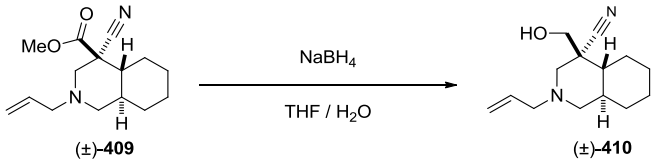
6.5.18. Synthesis of methyl *rac*-(4*R*,4a*S*,8a*S*)-2-allyl-4-cyanodecahydroisoquinoline-4-carboxylate (±)-409



(±)-**407b** (±)-**409**

Tributyltin hydride (0.308 g, 0.281 mL, 1.06 mmol) and AIBN (0.007 mg, 0.043 mmol) were added to a solution of nitro compound (±)-**407b** (0.065 g, 0.211 mmol) in toluene (5 mL). The reaction mixture was degassed by ten cycles of vacuum/N_2 purge. The resulting solution was heated rapidly to reflux and stirred at this temperature for 2.5 h before being cooled to RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (PE→PE:Et_2O 4:1) to give the title compound (±)-**409** (0.029 g, 52%) as a colourless oil. Full characterisation data were collected for diastereomer (±)-**409** synthesized via this route and were found to match the data collected for diastereomer (±)-**409** derived from (±)-**407a**.

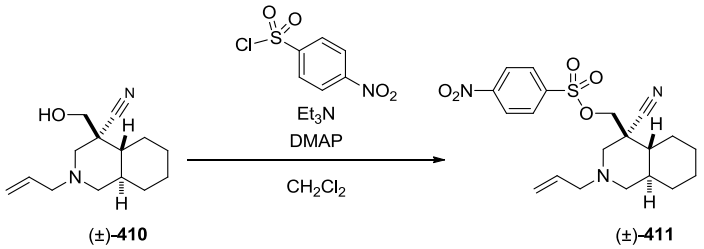
6.5.19. Synthesis of *rac*-(4*R*,4a*S*,8a*S*)-2-allyl-4-(hydroxymethyl)decahydroisoquinoline-4-carbonitrile (±)-410



To a solution of sodium borohydride (0.144 g, 3.81 mmol) in THF:H_2O (9 mL:1 mL) was added a solution of ester (±)-**409** (combined products) (0.100 g, 0.38 mmol) in THF (2 mL) and the resulting solution stirred at 50 °C for 3 h. The reaction mixture was cooled to RT, water (20 mL) was added and the excess borohydride destroyed by dropwise addition of 10% aq. HCl solution until pH = 7 was reached. THF was removed under reduced pressure and the aqueous phase extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE:Et_2O 1:1) to give the title compound (±)-**410** (0.069 g, 77%) as a colourless oil: ν_{max}(film)/cm^{-1} 3451 (O-H), 2927 (C-H), 2237 (C≡N), 1448 (C-H), 1070 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.80 (ddd, *J* = 16.9, 10.4, 6.4 Hz, 1H, CH_2=C*H*), 5.25 – 4.98 (m, 2H, C*H*$_2$=CH), 3.88 (d, *J* = 11.2 Hz, 1H, C*H*H'OH), 3.46 (d, *J* = 11.2 Hz, 1H, CH*H*'OH), 3.27 (dd, *J* = 11.6, 1.8 Hz, 1H, C*H*H'CC≡N), 3.03 (dddd, *J* = 13.7, 6.0 , 1.3, 1.3 Hz, 1H, CH_2=CHC*H*H'), 2.91 (dd, *J* = 13.7, 6.7 Hz, 1H, CH_2=CHCH*H*'), 2.75 (dd, *J* = 7.3, 1.6 Hz, 1H, NC*H*H'CH), 2.21 (br. s, 1H, O*H*), 1.89 (d, *J* = 11.6 Hz, 1H, CH*H*'CC≡N), 1.84 - 1.70 (m, 2H, N≡CCCHC*H*H', N≡CCCHCH_2C*H*H'), 1.70 - 1.49 (m, 4H, NCH*H*'CH, NCH_2C*H*, NCH_2CHC*H*H', NCH_2CHCH_2C*H*H'), 1.34 - 1.08 (m, 3H, N≡CCCHCH_2CH*H'*, N≡CCCHCH*H'*, NCH_2CHCH_2CH*H'*), 1.05 - 0.77 (m, 2H, N≡CCC*H*, NCH_2CHCH*H'*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.8

(CH_2=*C*H), 121.5 (*C*≡N), 117.9 (*C*H_2=CH), 64.7 (*C*H_2OH), 61.1 (CH_2=CH*C*H_2), 60.0 (N*C*H_2CH), 58.9 (N*C*H_2CC≡N), 46.1 (*C*C≡N), 44.5 (N≡CC*C*H), 38.4 (NCH_2*C*H), 30.4 (NCH_2CH*C*H_2), 26.9 (N≡CCCH*C*H_2), 25.9 (N≡CCCHCH_2*C*H_2), 25.2 (NCH_2CHCH_2*C*H_2); *m/z* (ESI^+) 491 (100%, $[2M+Na]^+$), 257 (65, $[M+Na]^+$), 235 (58, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 257.1628, $C_{14}H_{22}N_2NaO$ requires 257.1624.

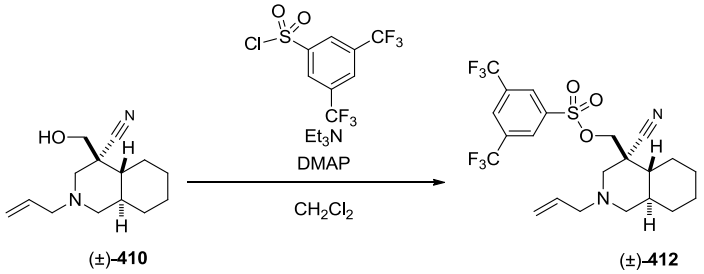
6.5.20. Synthesis of *rac*-[(4*R*,4a*S*,8a*S*)-2-allyl-4-cyano-decahydroisoquinolin-4-yl]methyl4-nitrobenzene sulfonate (±)-411



To a solution alcohol (±)-**410** (0.025 g, 0.107 mmol) in CH_2Cl_2 (5.5 mL) was added 4-nitrobenzenesulfonyl chloride (0.095 mg, 0.428 mmol), Et_3N (0.054 mg, 0.074 mL, 0.533 mmol) and DMAP (0.026 g, 0.213 mmol) and the resulting solution stirred at RT for 17 h. Sat. aq. $NaHCO_3$ solution (20 mL) was added and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (PE:Et_2O 3:2) to give the title compound (±)-**411** (0.030 g, 67%) as a colourless oil: ν_{max}(film)/cm^{-1} 2929 (C-H), 1534 (NO_2), 1351 (NO_2), 1189 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.51 - 8.33 (d, *J* = 8.8 Hz, 2H, Ar*H*), 8.22 - 8.04 (m, *J* = 8.8 Hz, 2H, Ar*H*), 5.81 (dddd, *J* = 17.0, 10.4, 6.3, 6.3 Hz, 1H, CH_2=C*H*), 5.28 - 5.06 (m, 2H, C*H*$_2$=CH), 4.25 (d, *J* = 10.0 Hz, 1H, C*H*H'OSO_2), 4.09 (d, *J* = 10.0 Hz, 1H, CH*H'*OSO_2), 3.26 - 3.15 (dd, *J* = 11.5, 1.1 Hz, 1H, C*H*H'CC≡N), 3.08 (dd, *J* = 13.7, 6.0 Hz, 1H, CH_2=CHC*H*H'), 2.97 (dd, *J* = 13.7, 6.5 Hz, 1H, CH_2=CHCH*H*'), 2.90 - 2.73 (m, 1H, NC*H*H'CH), 1.97 (d, *J* = 11.5 Hz, 1H, CH*H*'CC≡N), 1.85 - 1.54 (m, 6H, NCH*H*'CH, NCH_2C*H*, N≡CCCHC*H*H', N≡CCCHCH_2C*H*H', NCH_2CHC*H*H', NCH_2CHCH_2C*H*H'), 1.38 - 1.13 (m, 3H, N≡CCCHCH*H'*, N≡CCCHCH_2CH*H'*, NCH_2CHCH_2CH*H'*), 1.12 - 0.85 (m, 2H, N≡CCC*H*, NCH_2CHCH*H'*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.1 (Ar*C*-NO_2), 140.8 (Ar*C*SO_3), 134.4 (CH_2=*C*H), 129.4 (2 x Ar*C*CSO_3), 124.7 (2 x

Ar*C*CNO$_2$), 118.9 (*C*≡N), 118.1 (*C*H$_2$=CH), 70.6 (*C*H$_2$OSO$_2$), 60.7 (CH$_2$=CH*C*H$_2$), 59.4 (N*C*H$_2$CH), 58.3 (N*C*H$_2$CC≡N), 44.6 (N≡CC*C*H), 43.8 (*C*C≡N), 38.1 (NCH$_2$*C*H), 30.1 (NCH$_2$CH*C*H$_2$), 26.8 (N≡CCCH*C*H$_2$), 25.6 (N≡CCCHCH$_2$*C*H$_2$), 24.9 (NCH$_2$CHCH$_2$*C*H$_2$); *m/z* (ESI$^+$) 861 (100%, [2M+Na]$^+$), 442 (82, [M+Na]$^+$), 420 (73, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 442.1399, $C_{20}H_{25}N_3NaO_5S$ requires 442.1407.

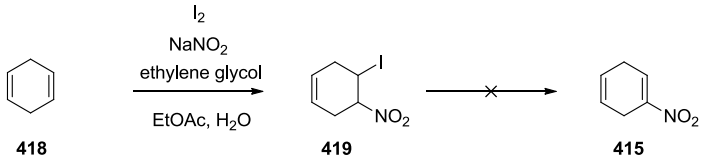
6.5.21. Synthesis of *rac*-[(4*R*,4a*S*,8a*S*)-2-allyl-4-cyanodecahydroisoquinolin-4-yl]methyl-3,5-bis(trifluoromethyl) benzenesulfonate (±)-412



To a solution alcohol (±)-**410** (0.022 g, 0.094 mmol) in CH_2Cl_2 (4.8 mL) was added 3,5-bistrifluoromethylbenzenesulfonyl chloride (0.117 mg, 0.374 mmol), Et_3N (0.048 mg, 0.066 mL, 0.474 mmol) and DMAP (0.023 g, 0.188 mmol) and the resulting solution stirred at RT for 20 h. Sat. aq. $NaHCO_3$ solution (20 mL) was added and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (PE:Et_2O 7:3) to give the title compound (±)-**412** (0.037 g, 77%) as a colourless oil: ν_{max}(film)/cm^{-1} 2930 (C-H), 1361 (SO_2), 1280 (C-O), 1181, 1142 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.38 (s, 2H, 2 x *H*CCSO_2), 8.20 (s, 1H, *H*CCCF_3), 5.81 (dddd, *J* = 17.0, 10.5, 6.2, 6.2 Hz, 1H, CH_2=C*H*), 5.25 - 5.10 (m, 2H, CH_2=CH), 4.31 (d, *J* = 10.1 Hz, 1H, C*H*H'OSO_2), 4.14 (d, *J* = 10.1 Hz, 1H, CH*H'*OSO_2), 3.21 (dd, *J* = 11.4, 1.3 Hz, 1H, C*H*H'CC≡N), 3.09 (dd, *J* = 13.7, 5.9 Hz, 1H, CH_2=CHC*H*H'), 2.97 (dd, *J* = 13.7, 6.6 Hz, 1H, CH_2=CHCH*H*'), 2.88 - 2.76 (m, 1H, NC*H*H'CH), 1.97 (d, *J* = 11.4 Hz, 1H, CH*H*'CC≡N), 1.82 (d, *J* = 11.6 Hz, 1H, N≡CCCHCH_2C*H*H'), 1.77 - 1.59 (m, 5H, NCH*H*'CH, NCH_2C*H*, N≡CCCHC*H*H', NCH_2CHC*H*H', NCH_2CHCH_2C*H*H'), 1.38 - 1.13 (m, 3H, N≡CCCHCH*H'*, N≡CCCHCH_2CH*H'*, NCH_2CHCH_2CH*H'*), 1.12 - 1.02 (m, 1H, N≡CCC*H*), 1.02 - 0.86 (m, 1H,

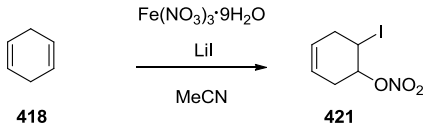
$NCH_2CHCH\mathit{H}'$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.1 (Ar*C*SO_3), 134.4 (CH_2=*C*H), 133.7 (Ar*C*CF_3), 133.4 (Ar*C*CF_3), 128.2 (Ar*C*CSO_3), 127.9 (Ar*C*CCF_3), 123.5 (*C*F_3), 120.8 (*C*F_3), 118.8 (*C*≡N), 118.2 (*C*H_2=CH), 70.9 (*C*H_2OSO_2), 60.8 (CH_2=CH*C*H_2), 59.5 (N*C*H_2CH), 58.3 (N*C*H_2C*C*≡N), 44.5 (N≡C*C*C*H*), 43.8 (*C*C≡N), 38.1 (NCH_2*C*H), 30.1 (NCH_2C*H*CH_2), 26.8 (N≡CC*C*HCH_2), 25.6 (N≡CCCH*C*H_2), 24.9 (NCH_2CHCH_2*C*H_2); *m/z* (ESI^+) 533 (100%, $[M+Na]^+$), 511 (45, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 533.1307, $C_{22}H_{24}F_6N_2NaO_3S$ requires 533.1304.

6.5.22. Synthesis of 4-Iodo-5-nitrocyclohexene 419



To a solution of $NaNO_2$ (2.76 g, 40.00 mmol) and ethylene glycol (1.86 g, 1.67 mL, 29.97 mmol) in H_2O (3.5 mL) was added a solution of cyclohexa-1,4-diene **418** (0.80 g, 0.94 mL, 9.98 mmol) in EtOAc (30 mL). The solution was cooled to 0 °C before iodine (2.53 g, 9.98 mmol) was added and the reaction mixture was stirred at RT for 5 days. The reaction mixture was poured into H_2O (50 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the organic extracts were washed with 10% aq. sodium thiosulfate solution (20 mL) and brine (20 mL) before being dried (Na_2SO_4). The crude residue was purified by column chromatography (PE:Et_2O 95:5) to give the title compound **419** (330 mg, 13%) as a pale yellow solid: ν_{max}(film)/cm^{-1} 1554 (NO_2), 1369 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 - 5.71 (m, 1H, C*H*=CH), 5.60 - 5.48 (m, 1H, CH=C*H*), 4.88 (dt, *J* = 9.8, 7.0 Hz, 1H, C*H*NO_2), 4.71 - 4.58 (m, 1H, C*H*I), 3.06 - 2.94 (m, 1H, C*H*H'), 2.90 - 2.75 (m, 3H, CH*H*', CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 125.5 (*C*H=CH), 122.3 (CH=*C*H), 88.0 (*C*HNO_2), 36.4 (*C*H_2CHI), 30.1 (*C*H_2CHNO_2), 18.9 (*C*HI); HRMS m/z (TOF, FI^+) found $[M]^+$ 252.9603, $C_6H_8INO_2$ requires 252.9600.

6.5.23. Synthesis of 6-iodocyclohex-3-en-1-yl nitrate 421



418 421

Method 1

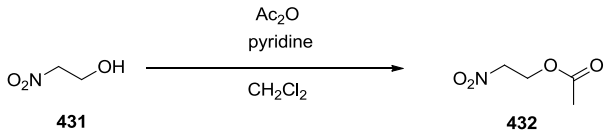
To a solution of cyclohexa-1,4-diene **418** (0.50 g, 0.60 mL, 6.24 mmol) and LiI (1.00 g, 7.49 mmol) in MeCN (30 mL) was added $Fe(NO_3)_3 \cdot 9H_2O$ (2.52 g, 6.24 mmol) and the reaction mixture was heated at reflux for 2 h. The solution was cooled to RT, diluted with *t*BME (10 mL) before being filtered to remove solid residues. The filtrate was concentrated under reduced pressure and purified by column chromatography (heptane:EtOAc 9:1) to give the title compound **421** (1.17 g, 70%) as a pale yellow oil: ν_{max}(film)/cm^{-1} 1629 (ONO_2), 1273 (ONO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.80 - 5.64 (m, 1H, C*H*=CH), 5.64 - 5.50 (m, 1H, CH=C*H*), 5.44 - 5.26 (m, 1H, C*H*ONO_2), 4.46 - 4.32 (m, 1H, C*H*I), 3.12 – 2.68 (m, 3H, C*H*H', CH_2), 2.48 - 2.33 (m, 1H, CH*H*'); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 124.5 (*C*H=CH), 122.4 (CH=*C*H), 88.6 (*C*HONO_2), 34.4 (*C*H_2CHI), 28.1 (*C*H_2CHONO_2), 19.6 (*C*HI). Data are in agreement with those previously reported.[193]

Method 2

To a solution of LiI (1.00 g, 7.49 mmol) in MeCN (30 mL) was added $Fe(NO_3)_3 \cdot 9H_2O$ (2.52 g, 6.24 mmol) and the reaction mixture heated at reflux for 0.5 h. The solution was transferred by cannula to a solution of cyclohexa-1,4-diene **418** (0.50 g, 0.60 mL, 6.24 mmol) in MeCN (5 mL) and the reaction heated at reflux for a further 2 h before being cooled to RT. The reaction mixture was diluted with *t*BME (10 mL) and filtered to remove solid residues.

The filtrate was concentrated under reduced pressure and ^{1}H NMR analysis of the crude reaction mixture indicated that clean conversion to undesired nitrate **421** had again occurred.

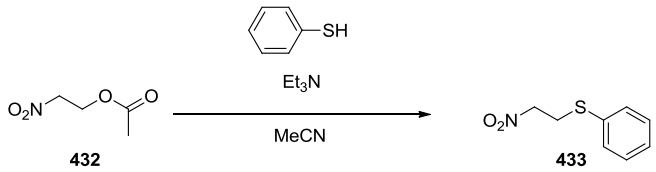
6.5.24. Synthesis of 2-nitroethyl acetate 432



431 **432**

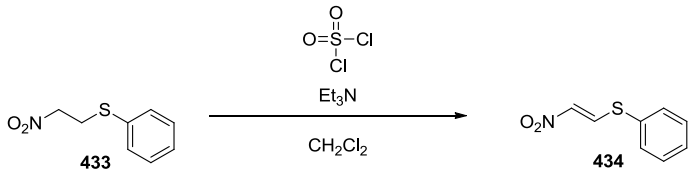
2-Nitroethanol **431** (5.00 g, 54.90 mmol), pyridine (4.34 g, 4.42 mL, 54.90 mmol) and acetic anhydride (5.60 g, 5.18 mL, 54.90 mmol) were dissolved in CH_2Cl_2 (88 mL) and the resulting solution stirred at RT for 16 h. The reaction mixture was poured into 1 N aq. HCl (80 mL) and CH_2Cl_2 was removed under reduced pressure. The aqueous phase was extracted with Et_2O (3 x 80 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound **432** (6.80 g, 93%) as a yellow oil which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.61 (s, 4H, NO_2CH_2, $NO_2CH_2CH_2$), 2.09 (s, 3H, O=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.3 (*C*=O), 73.6 (NO_2CH_2), 59.4 ($NO_2CH_2CH_2$), 20.55 (O=C*C*H$_3$). Data are in agreement with those previously reported.[194,195]

6.5.25. Synthesis of 2-Nitroethyl phenyl sulfide 433



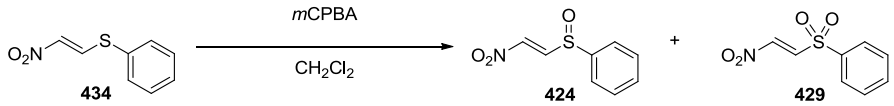
To a solution of 2-nitroethyl acetate **432** (2.70 g, 20.28 mmol) and thiophenol (2.24 g, 2.08 mL, 20.28 mmol) in MeCN (54 mL) cooled to 0 ^{o}C, was added a solution of Et_3N (2.26 g, 3.11 mL, 22.33 mmol) in MeCN (14 mL) over 0.5 h. The resulting reaction mixture was stirred at 0 ^{o}C for 1 h before being poured into 1 N HCl (20 mL). MeCN was removed under reduced pressure and product extracted from the aqueous phase with hexane (3 x 40 mL). The combined organics were washed with water (60 mL), dried (Na_2SO_4) and concentrated to yield the title compound **433** as a light yellow oil (3.25 g, 87%) which was used without further purification: ν_{max}(film)/cm^{-1} 3059 (C-H(Ar)), 2919 (C-H), 1551 (NO_2), 1375 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 - 7.41 (m, 2H, Ar*H*), 7.39 - 7.28 (m, 3H, Ar*H*), 4.51 (t, *J* = 7.2 Hz, 2H, $NO_2CH_2CH_2S$), 3.44 (t, *J* = 7.2 Hz, 2H, $NO_2CH_2CH_2S$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 132.9 (*C*SCH_2), 131.6 (2 x SC*C*H), 129.5 (2 x SCCH*C*H), 127.9 (SCCHCH*C*H), 73.9 ($NO_2CH_2CH_2S$), 31.1 ($NO_2CH_2CH_2S$). Data are in good agreement with that previously reported.[176]

6.5.26. Synthesis of (*E*)-2-nitrovinyl phenyl sulfide 434



To a solution of **433** (3.20 g, 17.46 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added sulfuryl chloride (2.42 g, 1.45 mL, 17.93 mmol) and the resulting solution stirred at 0 ^oC for 5 minutes. The volatiles were evaporated from the reaction mixture under reduced pressure and the resulting residue dissolved in CH_2Cl_2 (25 mL). Et_3N (1.81 g, 2.50 mL, 17.93 mmol) was added dropwise at 0 °C and the resulting solution stirred at this temperature for 0.5 h before being poured into water (90 mL). The organic layer was washed with 0.5 M aq. HCl solution (80 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE:Et_2O 9:1) to give the title compound **434** (2.70 g, 88%) as a yellow oil: ν_{max}(film)/cm^{-1} 3104 (=C-H), 1576 (NO_2), 1320 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.27 (d, *J* = 12.9 Hz, 1H, NO_2CH=C*H*S), 7.61 - 7.36 (m, 5H, Ar*H*), 6.71 (d, *J* = 12.9 Hz, 1H, NO_2C*H*=CHS); *m/z* (ESI$^+$) 204 (100%, $[M+Na]^+$). Data are in agreement with that previously reported.[176]

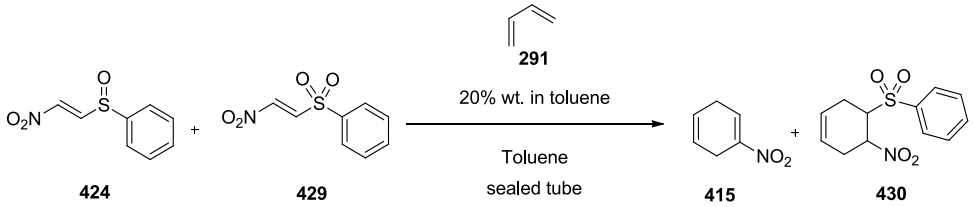
6.5.27. Synthesis of (*E*)-2-nitrovinyl phenyl sulfoxide 424



*m*CPBA (75% wet with H_2O) (1.90 g, 8.28 mmol) was added to a solution of **434** (1.50 g, 8.28 mmol) in CH_2Cl_2 (80 mL) cooled to 0 °C and the resulting yellow solution was stirred at this temperature for 5 h. The reaction mixture was washed sequentially with water (80 mL), 1 M aq. NaOAc solution (60 mL) and brine (60 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a fluffy yellow solid which was purified by recrystallization (EtOH, 60 °C) to yield an 83:17 (**424**:**429**) mixture of the compounds (900 mg) as a fluffy pale yellow solid.

Under these reaction conditions the undesired sulfone **429** was observed in varying quantities. A sufficiently pure sample of sulfone **429** could not be isolated from this product mixture to allow full characterisation. The structural assignment of **429** is based on the identity of characterised compounds isolated in the subsequent Diels Alder reaction. An analytical sample of sulfoxide **424** was prepared by stopping the reaction at low conversion of **434**: ν_{max}(film)/cm^{-1} 3029 (=C-H), 1520 (NO_2), 1367 (NO_2) 1054 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (d, *J* = 12.8 Hz, 1H, NO_2C*H*=CHS), 7.75 - 7.66 (m, 2H, Ar*H*), 7.66 - 7.60 (m, 3H, Ar*H*), 7.57 (d, *J* = 12.8 Hz, 1H, NO_2CH=C*H*S); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.1 (NO_2*C*H=CHS), 141.4 (NO_2CH=*C*HS), 139.9 (*C*S=O), 132.7 (SCCHCH*C*H), 130.2 (2 x SCCH*C*H), 124.9 (2 x SC*C*H). Data are in good agreement with that previously reported.[176]

6.5.28. Synthesis of 1-nitrocyclohexa-1,4-diene 415



To a solution of a mixture containing sulfoxide **424** and sulfone **429** (145 mg, **424**:**429** = ~ 80:20) in toluene (2 mL) in a microwave vial, was added butadiene **291** (20 wt% solution in toluene) (1.19 g, 1.48 mL, 4.41 mmol). The vial was sealed and the reaction mixture heated rapidly to 110 °C and maintained at this temperature for 1.75 h. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography (PE:Et_2O 95:5) to give nitro olefin **415** (24 mg, ~30%) as a yellow oil and cyclic sulfone **430** (40 mg) as a colourless oil.

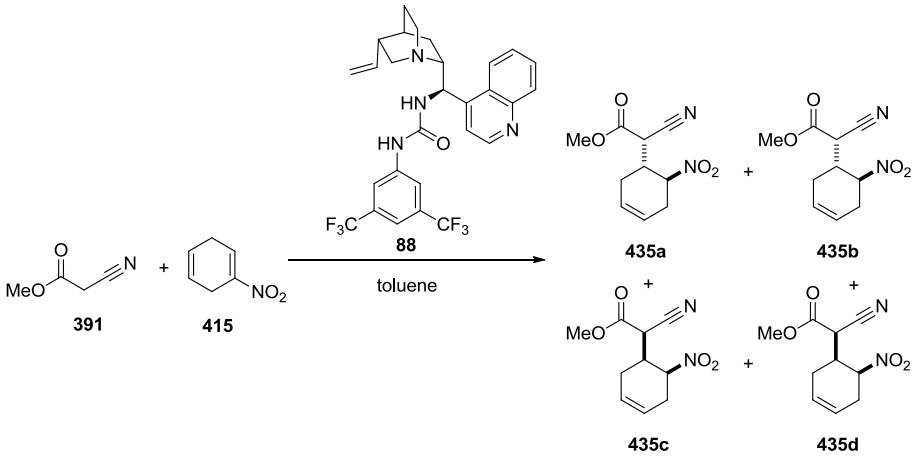
Data for 1-nitrocyclohexa-1,4-diene **415**

v_{max}(film)/cm^{-1} 1514 (NO_2), 1336 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 - 7.28 (m, 1H, NO_2C=C*H*), 5.86 - 5.76 (m, 1H, NO_2CCH_2C*H*), 5.73 - 5.66 (m, 1H, NO_2C=CHCH_2C*H*), 3.29 - 3.15 (m, 2H, NO_2CC*H*H'CH, NO_2C=CHC*H*H'CH), 3.15 - 2.98 (m, 2H, NO_2CCH*H*'CH, NO_2C=CHCH*H*'CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 147.3 (*C*NO_2), 131.1 (NO_2C=*C*H), 123.1 (NO_2C=CHCH_2*C*H), 121.8 (NO_2CCH_2*C*H), 27.1 (NO_2C=CH*C*H_2), 25.1 (NO_2CCH_2); HRMS m/z (TOF, FI^+) found $[M]^+$ 125.0477, $C_6H_7NO_2$ requires 125.0477.

Data for 2-nitrocyclohex-1-en-1-yl phenyl sulfone **430**

ν_{max}(film)/cm^{-1} 1558 (NO_2), 1369 (NO_2), 1310 (SO_2), 1148 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97 - 7.90 (m, 2H, 2 x SCC*H*), 7.76 - 7.69 (m, 1H, SCCHCHC*H*), 7.66 - 7.58 (m, 2H, 2 x SCCHC*H*), 5.76 - 5.64 (m, 2H, C*H*=C*H*), 5.10 - 5.00 (m, 1H, C*H*NO_2), 4.12 (dd, *J* = 7.3, 7.3 Hz, 1H, C*H*SO_2), 2.97 - 2.76 (m, 2H, NO_2CHCH_2), 2.62 - 2.47 (m, 2H, SO_2CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 137.1 (S*C*), 134.5 (SCCHCH*C*H), 129.5 (2 x SCCH*C*H), 128.8 (2 x SC*C*H), 123.2 (*C*H=CH), 122.3 (CH=*C*H), 79.1 (*C*HNO_2), 59.8 (*C*HSO_2Ph), 29.1 (NO_2CH*C*H_2), 23.0 (SO_2CH*C*H_2); *m/z* (ESI$^+$) 557 (95%, [2M+Na]$^+$), 290 (100, [M+Na]). Data are in good agreement with that previously reported.[177]

6.5.29. Synthesis of diastereomers of methyl cyano(6-nitrocyclohex-3-en-1-yl)acetate 435a/b/c/d



To a solution of methyl cyanoacetate **391** (0.017 g, 0.015 mL, 0.172 mmol) and 1-nitrocyclohexa-1,4-diene **415** (0.018 g, 0.144 mmol) in toluene (2 mL) was added catalyst **88** (0.016 g, 0.029 mmol). The resulting solution was stirred for 48 h at RT. ^{1}H NMR analysis indicated consumption of nitro olefin **415**. The diastereomer ratio of the new products formed could not be accurately determined from the crude ^{1}H NMR spectrum. The reaction mixture was concentrated and purified immediately by column chromatography (PE:EtOAc 5:1) to give the title compounds **435a-d** (0.09 g, 28%) as a colourless oil, as an complex inseparable mixture of diastereomers (**435a**:**435b**:**435c**:**435d** = 1.00:0.44:0.09:0.09 dr). **435a/b** and **435c/d** are arbitrary assignments representing *trans* and *cis* diastereomers respectively, which are believed to be epimeric at the C-9 position. No evidence supporting the relative stereochemistry at this position was obtained. IR and mass spectrometry data for this mixture are reported along with complete NMR shifts for the major **435a** and minor **435b** *trans* diastereomers. Complete assignment of NMR shifts for the *cis* diastereomers **435c** and **435d** was not possible from this mixture therefore only the

characteristic C*H*NO_2 shift is reported for each: ν_{max}(film)/cm^{-1} 2958 (C-H), 2361 (C≡N), 1749 (C=O), 1551 (NO_2), 1374 (NO_2), 1265 (C-O); *m/z* (ESI^+) 449 (75%, $[2M+H]^+$), 247 (82, $[M+Na]^+$), 225 (9, $[M+H]^+$).

Data for major *trans* diastereomer **435a**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.77 - 5.66 (m, 2H, C*H*=C*H*), 4.80 (ddd, *J* = 11.3, 10.1, 6.0 Hz, 1H, C*H*NO_2), 3.87 (s, 3H, OCH_3), 3.74 (d, *J* = 3.8 Hz, 1H, C*H*C≡N), 3.10 - 2.99 (m, 1H, C*H*CHC≡N), 2.87 - 2.72 (m, 2H, CH_2CHNO_2), 2.38 - 2.31 (m, 2H, CH_2CHCHC≡N); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.6 (*C*=O), 124.5 (*C*H=CH), 122.5 (CH=*C*H), 113.6 (*C*≡N), 83.7 (*C*NO_2), 54.0 (O*C*H_3) 39.6 (*C*HC≡N), 37.1 (*C*HCHC≡N), 30.6 (*C*H_2CHNO_2), 26.5 (*C*H_2CHCHC≡N).

Data for minor *trans* diastereomer **435b**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.77 - 5.66 (m, 2H, C*H*=C*H*), 4.93 (ddd, *J* = 10.3, 9.1, 6.1 Hz, 1H, C*H*NO_2), 3.88 - 3.83 (s, 3H, OCH_3), 3.79 (d, *J* = 4.4 Hz, 1H, C*H*C≡N), 3.11 - 2.98 (m, 1H, C*H*CHC≡N), 2.88 - 2.71 (m, 2H, CH_2CHNO_2), 2.65 - 2.54 (m, 1H, C*H*H'CHCHC≡N), 2.29 - 2.19 (m, 1H, CH*H*'CHCHC≡N); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.5 (*C*=O), 124.6 (*C*H=CH), 122.9 (CH=*C*H), 114.5, (*C*≡N), 82.7 (*C*NO_2), 53.8 (O*C*H_3), 38.9 (*C*HC≡N), 37.4 (*C*HCHC≡N), 30.6 (*C*H_2CHNO_2), 27.2 (*C*H_2CHCHC≡N).

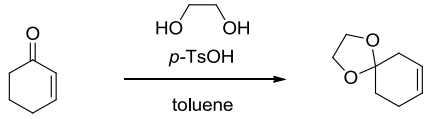
Selected data for *cis* diastereomer **435c**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.77 - 5.66 (m, 2H, C*H*=C*H*), 5.07 (ddd, *J* = 4.9, 2.4, 2.2 Hz, 1H, C*H*NO_2).

Selected data for *cis* diastereomer **435d**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.77 - 5.66 (m, 2H, C*H*=C*H*), 4.97 – 4.93 (m, 1H, C*H*NO_2).

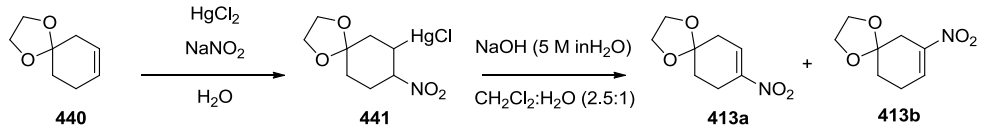
6.5.30. Synthesis of 1,4-dioxaspiro[4.5]dec-7-ene 440



439 440

A solution of cyclohex-2-en-1-one **439** (1.0 g, 1.0 mL, 10.4 mmol), ethylene glycol (2.4 g, 2.2 mL, 38.5 mmol) and *p*-TsOH (0.2 g, 1.0 mmol) in toluene (100 mL) was heated at reflux for 24 h using Dean-Stark apparatus. After cooling to RT the reaction mixture was washed with brine (50 mL) and the aqueous layer extracted with CH_2Cl_2 (2 x 35 mL). The organic extracts were dried (Na_2SO_4), concentrated and the crude residue was purified by column chromatography (PE:Et_2O 18:7) to give the title compound **440** (910 mg, 61%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.76 - 5.67 (m, 1H, C*H*=CH), 5.67 - 5.58 (m, 1H, CH=C*H*), 3.99 (s, 4H, OCH_2CH_2O), 2.33 - 2.22 (m, 4H, CH_2CH=CHCH_2), 1.83 - 1.72 (m, 2H, CH_2CH_2CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 126.5 (*C*H=CH), 124.3 (CH=*C*H), 107.9 (C_{quat}), 64.4 (O*C*H_2*C*H_2O), 35.7 (C_{quat}*C*H_2CH=CH), 30.9 (C_{quat}*C*H_2CH_2), 24.5 (C_{quat}CH_2*C*H_2). Data are in good agreement with those previously reported.[179]

6.5.31. Synthesis of 8-nitro-1,4-dioxaspiro[4.5]dec-7-ene 413a and 7-nitro-1,4-dioxaspiro[4.5]dec-7-ene 413b

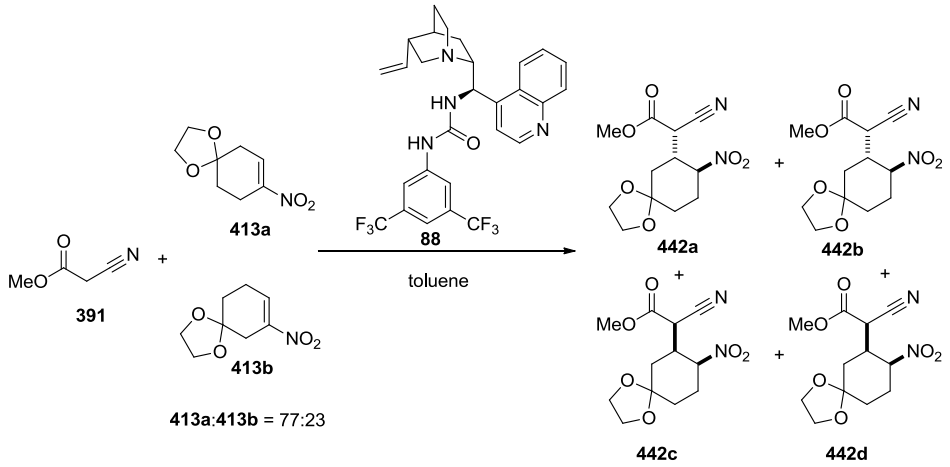


Based on the procedure of Bitha.[181] Sodium nitrite (1.97 g, 28.55 mmol) was dissolved in water (20 mL) and to this solution was added mercury(II) chloride (3.87 g, 14.25 mmol) producing a bright yellow solution. 1,4-dioxaspiro[4.5]dec-7-ene **440** (2.00 g, 14.27 mmol) was added and the reaction mixture stirred vigorously at RT for 24 h to ensure complete reaction. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extracts were washed once with water (30 mL) before being concentrated under an N_2 stream to give crude nitromercurial **441** (4.3 g) as a mixture of regioisomers, as a thick colourless oil which was used without further purification.

Crude nitromercurial compound **441** (4.3 g) was slurried in CH_2Cl_2:H_2O (200 mL:80 mL) at RT and 5 M aq. NaOH solution (3.31 mL, 16.57 mmol) was added. A thick dark grey metallic suspension was observed almost immediately after addition of NaOH. The reaction mixture was stirred for 0.5 h and then conc. aq. HCl added until pH = 3 was reached. The mercury precipitate was removed by filtration through a pad of celite and the organic layer separated from the aqueous, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE:Et_2O 3:1) to give the title compound **413** (1.07 g, 40% over 2 steps) as a yellow oil in an 77:23 (**413a**:**413b**) mixture of inseparable regioisomers: R_f = 0.55 (1:1, PE:Et_2O); ν_{max}(film)/cm^{-1} 2889 (C-H), 1513

(NO_2), 1338 (NO_2), 1122 (C-O), 1059 (C-O), 1037 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.37 - 7.31 (m, 1H, C=C*H*$_{(b)}$), 7.18 (t, *J* = 4.2 Hz, 1H, C=C*H*$_{(a)}$), 4.06 - 3.94 (m, 8H OC*H*$_2$C*H*$_2$O$_{(a+b)}$), 2.87 - 2.74 (m, 4H, C*H*$_2$CNO$_{2(a+b)}$), 2.59 - 2.47 (m, 4H, C*H*$_2$CH=CNO$_{2(a+b)}$), 1.89 (t, *J* = 6.7 Hz, 2H, C*H*$_2$C$_{quat(a)}$), 1.82 - 1.72 (m, 2H, C*H*$_2$C$_{quat(b)}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.8 (*C*NO$_{2(a)}$), 147.1(*C*NO$_{2(b)}$), 133.4 (*C*H=CNO$_{2(b)}$), 131.4 (*C*H=CNO$_{2(a)}$), 107.0 (*C*$_{quat(b)}$), 106.3 (*C*$_{quat(a)}$), 64.7 (O*C*H$_2$*C*H$_2$O$_{(a)+(b)}$), 35.0 (*C*H$_2$CH$_{(a)}$), 34.9 (*C*H$_2$CNO$_{2(b)}$), 30.4 (*C*H$_2$C$_{quat(a)}$), 29.9 (*C*H$_2$C$_{quat(b)}$), 23.0 (*C*H$_2$CNO$_{2(a)}$), 22.9 (*C*H$_2$CH$_{(b)}$); *m/z* (ESI$^+$) 208 (24%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 208.0585, $C_8H_{11}NNaO_4$ requires 208.0580.

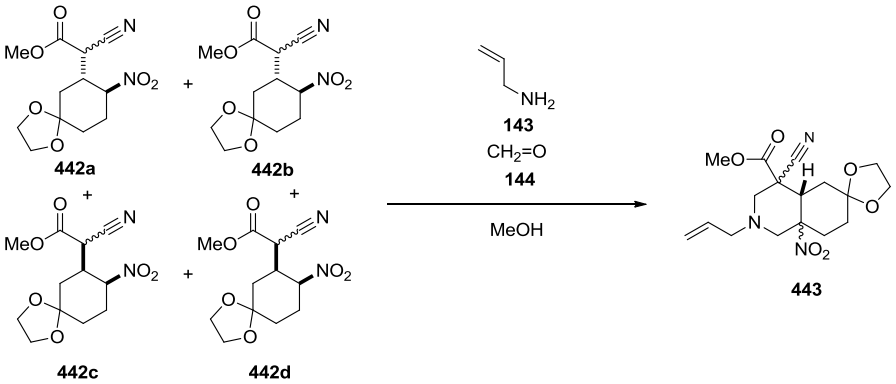
6.5.32. Synthesis of diastereomers of methyl cyano(8-nitro-1,4-dioxaspiro[4.5]dec-7-yl)acetate 442a/b/c/d



To a solution of methyl cyanoacetate **391** (0.642 g, 0.571 mL, 6.48 mmol) and nitro olefin **413** (1.000 g, 5.40 mmol, **a**:**b** = 77:23) in toluene (30 mL) was added catalyst **88** (4 mol%) (0.120 g, 0.22 mmol). The resulting solution was stirred for 48 h at RT, before being concentrated and purified by column chromatography (PE:Et_2O 3:2→1:1) to give the title compounds **442a-d** (1.50 g, 98%), as an inseparable mixture of diastereomers (**a**:**b**:**c**:**d** = 1.0:0.7:0.5:0.04 dr + minor impurities presumed to be diastereomers arising from nitro olefin **413b**) as a colourless wet solid. NMR data for the mixture of diastereomers derived from nitro olefin **413a** only is reported: R_f = 0.28 (1:1, PE:Et_2O); ν_{max}(film)/cm^{-1} 2960 (C-H), 2252 (C≡N), 1747 (C=O), 1549 (NO_2), 1437 (CH_2), 1337 (NO_2), 1227 (C-O), 1146 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.94 (ddd, *J* = 3.3 Hz, 1H, C*H*$NO_{2(d)}$), 4.81 (ddd, *J* = 3.5 Hz, 1H, C*H*$NO_{2(c)}$), 4.77 - 4.67 (m, 1H, C*H*$NO_{2(b)}$), 4.53 (ddd, *J* = 11.4, 4.5 Hz, 1H, C*H*$NO_{2(a)}$), 4.04 - 3.69 (m, 32H, OC*H*$_2$C*H*$_2$O$_{(a-d)}$, OC*H*$_{3(a-d)}$, C*H*C≡N$_{(a-d)}$), 3.18 - 3.02 (m, 2H, C*H*CH$NO_{2(a+b)}$), 2.86 - 2.67 (m, 1H, C*H*CH$NO_{2(c+d)}$), 2.68 - 1.63 (m, 24H, C*H*$_2$CHCH$NO_{2(a-d)}$, C*H*$_2$CH$NO_{2(a-d)}$, C*H*$_2$C$_{quat.\ (a-d)}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.1, 165.0, 164.7, 164.4 (*C*=O$_{(a-d)}$), 114.6, 114.4, 114.2,

113.6 (*C*≡N$_{(a-d)}$), 106.7, 106.7, 106.2, 106.0 (*C*$_{quat.(a-d)}$), 85.2 (*C*HNO$_{2(a)}$), 84.3 (*C*HNO$_{2(b)}$), 81.0 (*C*HNO$_{2(d)}$), 80.5 (*C*HNO$_{2(c)}$), 64.8, 64.8, 64.7, 64.7 64.6, 64.6, 64.5, 64.4 (O*C*H$_2$*C*H$_2$O$_{(a-d)}$), 53.9, 53.8, 53.7, 53.6 (O*C*H$_{3(a-d)}$) 39.8, 39.7, 39.6, 39.5, 39.5, 39.3, 39.1, 38.9, 38.3, 38.0, 37.6, 35.6, 34.7, 34.2, 34.1, 33.2, 32.6, 32.3, 29.7, 29.4, 28.9, 28.4, 27.3, 27.2, 23.2 (*C*HC≡N$_{(a-d)}$, *C*HCHC≡N$_{(a-d)}$, *C*H$_2$C$_{quat.(a-d)}$, *C*H$_2$CHNO$_{2(a-d)}$, *C*H$_2$CHCHNO$_{2(a-d)}$); *m/z* (ESI$^+$) 591 (32%, [2M+Na]$^+$), 323 (100, [M+K]$^+$), 307 (92, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 307.0893, $C_{12}H_{16}N_2NaO_6$ requires 307.0901.

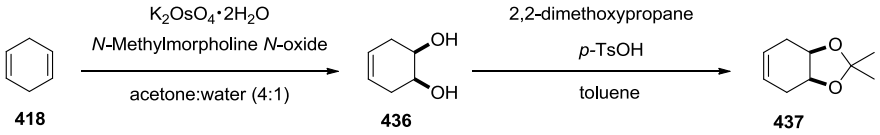
6.5.33. Synthesis of methyl 2'-allyl-4'-cyano-8a'-nitrooctahydro-2'*H*-spiro[1,3-dioxolane-2,6'-isoquinoline]-4'-carboxylate 443



To a solution of Michael adduct **442a-d** (0.200 g, 0.704 mmol, **a**:**b**:**c**:**d** = 1.0:0.7:0.5:0.04 dr) in MeOH (10 mL) was added allylamine **143** (0.048 g, 0.063 mL, 0.844 mmol); followed by formaldehyde **144** (37% solution in water) (1.14 g, 1.04 mL, 14.05 mmol) and the resulting colourless solution was refluxed for 6.5 h. The solution was cooled to RT and concentrated before being purified by column chromatography (PE:Et_2O 1:1→Et_2O) to give the title compound **443** (0.055 g, 21%) as a colourless oil, along with several additional impure, unidentified minor by-products: ν_{max}(film)/cm^{-1} 2959 (C-H), 1744 (C=O), 1549 (NO_2), 1379 (NO_2), 1252 (C-O), 1100 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 - 5.66 (m, 1H, CH_2=C*H*), 5.26 - 5.15 (m, 2H, C*H*$_2$=CH), 4.03 - 3.90 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.87 (s, 3H, OC*H*$_3$), 3.78 - 3.72 (m, 1H, NC*H*H'), 3.45 - 3.36 (m, 1H, NC*H*H'), 3.09 (d, *J* = 6.3 Hz, 2H, CH_2=CHC*H*$_2$), 2.73 - 2.55 (m, 2H, NO_2CC*H*, NO_2CCHC*H*H'), 2.49 (d, *J* = 11.6 Hz, 1H, NCH*H*'), 2.29 - 2.14 (m, 2H, NO_2CCH_2C*H*H', NCH*H*'), 1.88 (ddd, *J* = 14.3, 14.3, 4.0 Hz, 1H, NO_2CCH_2CH*H*'), 1.80 - 1.67 (m, 1H, NO_2CC*H*H'), 1.67 - 1.53 (m, 2H, NO_2CCH*H*', NO_2CCHCH*H*'); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.5 (*C*=O), 133.1 (CH_2=*C*H), 119.2 (*C*H_2=CH), 117.0 (*C*≡N), 107.2 (*C*O(CH_2)$_2$O), 87.3 (*C*NO_2), 64.7 (O*C*H_2CH_2O), 64.2 (OCH_2*C*H_2O), 61.3

(N*C*H_2), 60.2 (N*C*H_2), 59.8 (CH_2=CH*C*H_2), 54.2 (O*C*H_3), 47.9 (*C*C≡N), 43.1 (*C*HCC≡N), 33.4 (*C*H_2CHCC≡N), 32.8 ($NO_2CCH_2CH_2$), 30.4 (NO_2CCH_2); *m/z* (ESI^+) 753 (100%, $[2M+Na]^+$), 388 (80, $[M+Na]^+$), 366 (41, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 388.1484, $C_{17}H_{23}N_3NaO_6$ requires 388.1479.

6.5.34. Synthesis of *rac*-(3a*R*,7a*S*)-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole 437

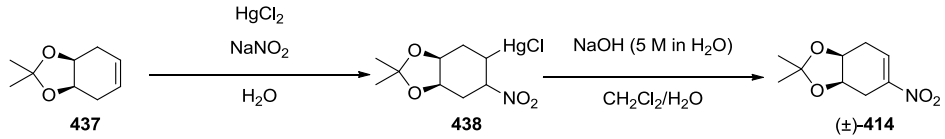


To a solution of cyclohexa-1,4-diene **418** (2.40 g, 2.83 mL, 29.9 mmol) and *N*-methylmorpholine *N*-oxide (3.51 g, 29.9 mmol) in acetone:water (60 mL:15 mL) was added $K_2OsO_4 \cdot 2H_2O$ (0.015 g, 0.041 mmol) and the resulting colourless solution was stirred for 24 h. The reaction mixture turned black during this time. Sodium sulfite (1.5 g) dissolved in water (1.50 mL) was added to the reaction mixture and stirring continued for a further 0.5 h. The reaction mixture was poured into brine (100 mL) and extracted with ethyl acetate (4 x 80 mL). The organic extracts were dried (Na_2SO_4) and concentrated to yield diol **436** as a colourless solid (2.80 g, 82%) which was used without further purification: mp 77-79 °C (EtOAc); lit.[196] mp 79-80 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.55 (s, 2H, C*H*=C*H*), 3.91 (t, *J* = 5.1 Hz, 2H, 2 x C*H*OH), 3.32 (br. s, 2H, 2 x CHO*H*), 2.40 - 2.11 (m, 4H, 2 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 123.7 (*C*H=*C*H), 68.9 (H*C*OH), 31.0 (CH_2). Data are in good agreement with those previously reported.[197]

To a stirred suspension of diol **436** (3.63 g, 31.80 mmol) in toluene (90 mL) was added 2,2-dimethoxypropane (4.25 g, 5.00 mL, 40.7 mmol) and *p*-TsOH (0.11 g, 0.58 mmol). The resulting solution was heated at reflux with the azeotropic removal of methanol for 7.5 h. The reaction mixture was then concentrated and purified by column chromatography (9:1 PE:Et_2O) to give the title compound **437** (4.36 g, 89%) as colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.79 (t, *J* = 2.6 Hz, 2H, C*H*=C*H*), 4.39 - 4.33 (m, 2H, 2 x

*H*COC(CH_3)$_2$), 2.31 - 2.22 (m, 4H, 2 x C*H*$_2$), 1.44 (s, 3H, *C*H_3), 1.34 (s, 3H, *C*H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 125.5 (*C*H=*C*H), 107.4 (*C*(CH_3)$_2$), 73.0 (2 x H*C*OC(CH_3)$_2$), 28.2 (2 x *C*H_2), 27.0 (*C*H_3), 24.8 (*C*H_3). Data are in good agreement with that previously reported.[198,199]

6.5.35. Synthesis of *rac*-(3a*R*,7a*S*)-2,2-dimethyl-5-nitro-3a,4,7,7a-tetrahydro-1,3-benzodioxole (±)-414



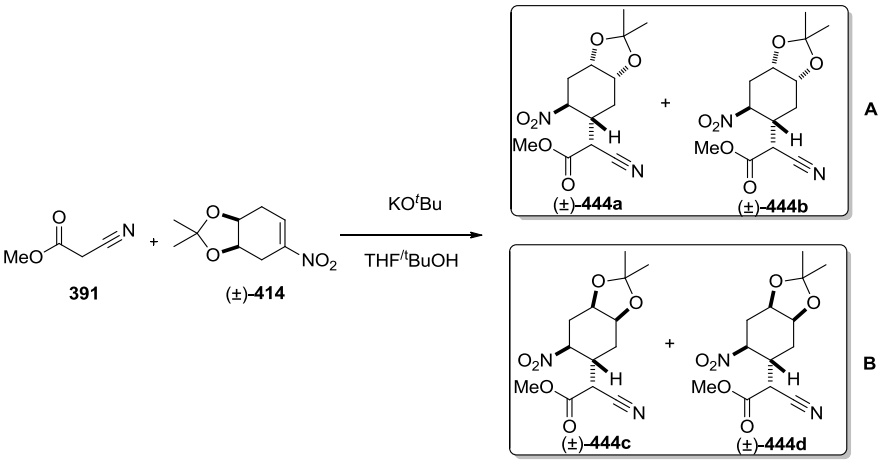
437 438 (±)-414

Sodium nitrite (3.58 g, 51.88 mmol) was dissolved in water (35 mL) and to this solution was added mercury(II) chloride (7.04 g, 25.94 mmol) producing a bright yellow solution. Protected diol **437** (4.00 g, 25.94 mmol) was added and the reaction mixture stirred vigorously at RT. After 3-5 h a colourless suspension was observed, however the reaction was stirred for 24 h to ensure complete reaction. For safety reasons no monitoring of the reaction mixture by TLC analysis was carried out. After 24 h the thick colourless suspension was filtered and the solid washed once with ice-cold water (10 mL). The colourless solid was dried for 1 h under suction filtration yielding crude nitromercurial **438** (7.23 g, 64%), which was transferred directly into a new reaction flask without any attempts to purify or analyse the crude product.

Crude nitromercurial compound **438** (7.23 g, 16.57 mmol) was slurried in CH_2Cl_2:H_2O (275 mL:112 mL) at RT and 5 M aq. NaOH solution (3.31 mL, 16.57 mmol) was added. A thick dark grey metallic suspension was observed almost immediately after addition of NaOH. The reaction mixture was stirred for 0.5 h and then conc. aq. HCl added until pH = 3 was reached. The mercury precipitate was removed by filtration through a pad of celite and the organic layer separated from the aqueous, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE:Et_2O 17:8) to give the title compound (±)-**414** (2.30 g,

70%) as a yellow oil: ν_{max}(film)/cm^{-1} 2988 (C-H), 1514 (NO_2), 1340 (NO_2), 1051 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 - 7.28 (m, 1H, NO_2C=C*H*), 4.61 (ddd, *J* = 6.4, 5.4, 2.9 Hz, 1H, NO_2CCH_2CH), 4.49 (ddd, *J* = 6.0, 2.9, 2.6 Hz, 1H, =$CHCH_2CH$), 3.19 - 3.10 (m, 1H, NO_2CCHH'), 2.77 - 2.67 (m, 1H, =CHCH*H*'), 2.63 (ddd, *J* = 17.4, 5.1, 2.4 Hz, 1H, NO_2CCH*H*') 2.47 - 2.37 (m, 1 H, =CHCH*H*'), 1.38 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 147.7 (HC=CNO_2), 131.3 (HC=CNO_2), 108.6 ($C(CH_3)_2$), 72.9 (NO_2CCH_2CH), 71.6 (=$CHCH_2CH$), 28.6 (=$CHCH_2$), 27.2 (NO_2CCH_2), 26.8 (CH_3), 24.6 (CH_3); *m/z* (ESI$^+$) 222 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 222.0742, $C_9H_{13}NNaO_4$ requires 222.0737. Racemic separated (Chiralcel OC, 98:2 hexane:isopropanol, 0.8 mL/min, 220 nm, t_{Ri} = 26.3 min, t_{Rii} = 27.7 min.

6.5.36. Synthesis of racemic Michael adducts (±)-444a-d



KO^{t}Bu (1.30 g, 11.55 mmol) was added to a solution of methyl cyanoacetate **391** (1.37 g, 1.22 mL, 13.83 mmol) in THF/^{t}BuOH (50 mL:1.65 mL) cooled to 0 °C and the reaction mixture stirred for 2 h at this temperature. Nitro olefin (±)-**414** (2.30 g, 11.55 mmol) in THF (3 mL) was added and the resulting yellow solution was warmed to RT and stirred at this temperature for 15 h. After cooling the solution to 0 °C, acetic acid (2.08 g, 1.98 mL, 34.64 mmol) was added carefully and the reaction was stirred for 0.5 h before being concentrated under reduced pressure (**A**:**B** 1:3.8 crude dr). Purification by column chromatography (PE:Et_2O 6:5→2:3) gave two separable sets of diastereomers (**A** and **B**) each containing two inseparable diastereomers (±)-**444a**/**b** (0.50 g, 14%, **a**:**b** = 1.82:1.00 dr) as a colourless foam and (±)-**444c**/**d** (2.31 g, 67%, **c**:**d** 1.59:1.00 dr) as a beige solid.

This reaction was repeated four times on scales of 100 mg – 1.30 g of nitro olefin (±)-**414**. The combined yield of (**A** and **B**) was in the range 79-82%, and the isolated mass of inseparable diastereomers **A**:**B** was in the range 1:(3.8-4.7).

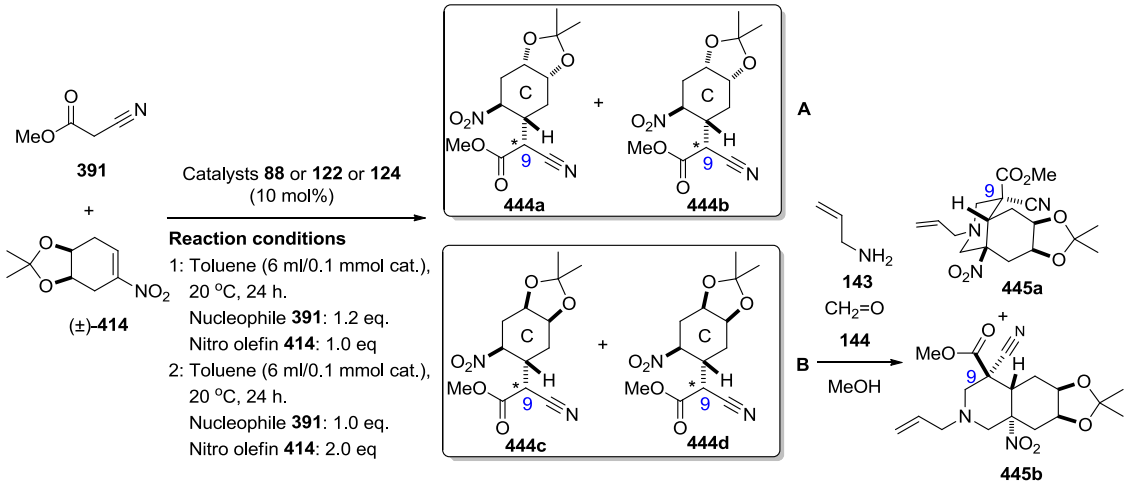
Data for minor diastereomers (**A**)

R_f = 0.20 (PE:Et_2O 1:1); ν_{max}(film)/cm^{-1} 2989 (C-H), 2361 (C≡N), 1748 (C=O), 1553 (NO_2), 1377 (NO_2), 1220 (C-O); Diastereomer (±)-**444a** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.82 (ddd, *J* = 11.1, 9.9, 4.5 Hz, 1H, C*H*NO_2), 4.47 - 4.37 (m, 1H, OC*H*CH_2CHNO_2), 4.32 (ddd, *J* = 7.8, 5.6, 5.6 Hz, 1H, OC*H*CH_2CHCHC≡N), 3.86 - 3.80 (m, 4H, OCH_3, C*H*C≡N), 2.97 - 2.86 (m, 1H, C*H*CHC≡N), 2.65 (ddd, *J* = 14.4, 4.3, 3.0 Hz, 1H, C*H*H'$CHNO_2$), 2.31 - 2.21 (m, 1H, CH*H*'$CHNO_2$), 2.05 - 1.96 (m, 1H, C*H*H'CHCHC≡N), 1.96 - 1.89 (m, 1H, CH*H*'CHCHC≡N), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.6 (*C*=O), 113.8 (*C*≡N), 109.3 (*C*$(CH_3)_2$), 82.0 (*C*NO_2), 71.7 (O*C*HCH$_2$CHCHC≡N), 71.6 (O*C*HCH_2CHNO_2), 54.0 (O*C*H_3), 40.7 (*C*HC≡N), 36.8 (*C*HCHC≡N), 31.8 (*C*H_2CHNO_2), 28.4 (*C*H_2CHCHC≡N), 27.7 (*C*H_3), 25.2 (*C*H_3); Diastereomer (±)-**444b** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.98 (ddd, *J* = 9.7, 9.7, 4.5 Hz, 1H, C*H*NO_2), 4.47 - 4.37 (m, 1H, OC*H*CH_2CHNO_2), 4.32 (ddd, *J* = 7.8, 5.6, 5.6 Hz, 1H, OC*H*CH_2CHCHC≡N), 3.86 - 3.80 (m, 4H, OCH_3, C*H*C≡N), 2.97 - 2.86 (m, 1H, C*H*CHC≡N), 2.54 (ddd, *J* = 14.7, 4.2, 4.2 Hz, 1H, C*H*H'$CHNO_2$), 2.31 - 2.21 (m, 1H, CH*H*'$CHNO_2$), 2.16 (ddd, *J* = 14.3, 5.4, 5.3 Hz, 1H, C*H*H'CHCHC≡N), 1.89 - 1.79 (m, 1H, CH*H*'CHCHC≡N), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.4 (*C*=O), 114.4 (*C*≡N), 109.2 (*C*$(CH_3)_2$), 81.3 (*C*NO_2), 71.8 (O*C*HCH$_2$CHCHC≡N), 71.5 (O*C*HCH_2CHNO_2), 53.8 (O*C*H_3), 40.2 (*C*HC≡N), 36.8 (*C*HCHC≡N), 32.0 (*C*H_2CHNO_2), 28.9 (*C*H_2CHCHC≡N), 27.6 (*C*H_3), 25.1 (*C*H_3); *m/z* (ESI$^+$) 619 (100%, $[2M+Na]^+$), 321 (72, $[M+Na]^+$), 299 (17, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 321.1067, $C_{13}H_{18}N_2NaO_6$ requires 321.1057.

Data for major diastereomers (**B**)

R_f = 0.28 (PE:Et_2O 1:1); mp 100-103 °C (Et_2O); ν_{max}(film)/cm^{-1} 2989 (C-H), 1747 (C=O), 1553 (NO_2), 1374 (NO_2), 1211 (C-O), 1038 (C-O); Diastereomer (±)-**444c** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.47 – 4.39 (m, 1H, C*H*NO_2), 4.40 - 4.35 (m, 2H, OC*H*CH_2CHNO_2, OC*H*CH_2CHCHC≡N), 3.96 (d, *J* = 3.8 Hz, 1H, C*H*C≡N), 3.86 (s, 3H, OCH_3), 3.43 (ddd, *J* = 13.0, 9.1, 3.8 Hz, 1H, C*H*CHC≡N), 2.82 (ddd, *J* = 15.4, 4.9, 4.9 Hz, 1H, C*H*H'CHNO_2), 2.27 - 2.14 (m, 1H, CH*H*'CHNO_2), 2.00 - 1.91 (m, 1H, C*H*H'CHCHC≡N), 1.71 - 1.59 (m, 1H, CH*H*'CHCHC≡N), 1.45 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 164.6 (*C*=O), 114.3 (*C*≡N), 108.8 (*C*$(CH_3)_2$), 81.2 (*C*NO_2), 71.3 (O*C*HCH_2CHCHC≡N), 70.6 (O*C*HCH_2CHNO_2), 53.9 (O*C*H_3), 41.2 (*C*HC≡N), 32.6 (*C*HCHC≡N), 29.9 (*C*H_2CHNO_2), 27.6 (*C*H_2CHCHC≡N), 26.3 (*C*H_3), 24.4 (*C*H_3); Diastereomer (±)-**444d** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.70 (ddd, *J* = 7.1, 7.1, 3.4 Hz, 1H, C*H*NO_2), 4.40 - 4.35 (m, 2H, OC*H*CH_2CHNO_2, OC*H*CH_2CHCHC≡N), 3.79 (s, 3H, OCH_3), 3.77 (d, *J* = 3.5 Hz, 1H, C*H*C≡N), 3.53 (ddd, *J* = 13.4, 7.5, 3.5 Hz, 1H, C*H*CHC≡N), 2.94 (ddd, *J* = 15.9, 3.8, 3.8 Hz, 1H, C*H*H'CHNO_2), 2.11 (ddd, *J* = 13.4, 7.5, 3.7 Hz, 1H, CH*H*'CHNO_2), 2.06 (ddd, *J* = 18.4, 3.7, 2.3 Hz, 1H, C*H*H'CHCHC≡N), 1.71 - 1.59 (m, 1H, CH*H*'CHCHC≡N), 1.39 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.1 (*C*=O), 114.8 (*C*≡N), 108.4 (*C*$(CH_3)_2$), 79.8 (*CH*NO_2), 71.2 (O*C*HCH_2CHCHC≡N), 70.2 (O*C*HCH_2CHNO_2), 53.9 (O*C*H_3), 41.2 (*C*HC≡N), 32.0 (*C*HCHC≡N), 29.5 (*C*H_2CHNO_2), 29.0 (*C*H_2CHCHC≡N), 25.5 (*C*H_3), 23.8 (*C*H_3); *m/z* (ESI$^+$) 619 (100%, $[2M+Na]^+$), 321 (93, $[M+Na]^+$), 299 (27, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 321.1060, $C_{13}H_{18}N_2NaO_6$ requires 321.1057.

6.5.37. Investigation of organocatalyst control in nitro olefin Michael addition



To a solution of methyl cyanoacetate **391** and nitro olefin (±)-**414** in toluene, in the quantities stated (entries 1-5) was added either catalyst **88**, **122** or **124** (10 mol%) and the resulting yellow solution stirred at RT for 15-48 h. The reaction mixtures were concentrated under reduced pressure and the diastereomeric ratio established from the crude ^{1}H NMR spectrum. The crude products were purified by column chromatography (PE:Et_2O 3:2) to give two separable sets of diastereomers (**A** and **B**) each containing two inseparable diastereomers (**444a/b** and **444c/d** respectively) with data in good agreement with those reported previously. The *ee* of recovered nitro olefin **414** was determined by chiral HPLC. Diastereomers **444c/d** were subjected to the standard reported cyclisation conditions (*vide infra*) and the *ee* of adducts **445a** and **445b** was determined by chiral HPLC.

6.5.38. Analysis of bifunctional organocatalyst control studies

Entry	Catalyst (reaction)	Yield	dr (crude) (**A:B**)	*ee* recovered **414** (yield)	*ee* isolated **445a**[a] (yield)	*ee* isolated **445b**[a] (yield)
1	**88** (1)	72% overall 32% (**A**) 40% (**B**)	1:1.34	–	–	
2	**122** (1)	44% overall 16% (**A**) 28% (**B**)	1:1.91	–	–	
3	**124** (1)	74% overall 31% (**A**) 43% (**B**)	1:1.40	–	–	
4	**122** (2)	54% overall 17% (**A**) 37% (**B**)	1:2.17	16%[b] (40%)	27%[c] (19%)	33%[d] (15%)
5	**124** (2)	71% overall 27% (**A**) 44% (**B**)	1:1.55	14%[e] (37%)	29%[f] (28%)	31%[g] (19%)

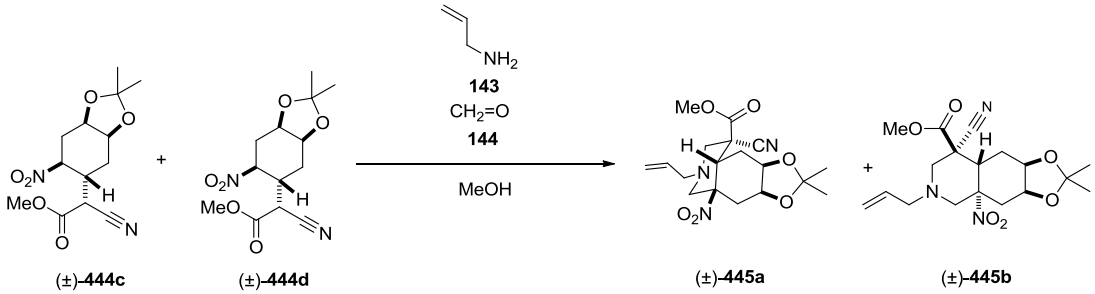
[a] No accurate *ee* data could be established using Michael adducts **444a-d** therefore the *ee* of the cyclised products **405a/b** is reported. [b] 16% (Chiralcel OC, 98:2 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 25.7 min, minor t_R = 27.1 min.) [c] 27% (Chiralcel OD, 95:5 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 16.4 min, minor t_R = 19.3 min.) [d] 33% (Chiralcel OD-H, 95:5 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 31.9 min, minor t_R = 29.8 min). [e] 14% (Chiralcel OC, 98:2 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 29.2 min, minor t_R = 27.7 min). [f] 29% (Chiralcel OD, 95:5 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 19.7 min,

minor t_R = 16.9 min.). [g] 31% (Chiralcel OD-H, 95:5 hexane:isopropanol, 0.8 mL/min, 220 nm, major t_R = 29.6 min, minor t_R = 32.0 min).

6.5.39. Optical rotation values

Entry	Catalyst Used	Substrate	Optical Rotation
1	**122**	**444c/d** (**B**)	$[\alpha]_D^{24}$ = +14.46 (*c* 0.50, $CHCl_3$)
2	**122**	**414**	$[\alpha]_D^{24}$ = +13.70 (*c* 0.65, $CHCl_3$)
3	**122**	**445a**	$[\alpha]_D^{24}$ = +4.74 (*c* 0.19, $CHCl_3$)
4	**122**	**445b**	$[\alpha]_D^{24}$ = −2.11 (*c* 0.19, $CHCl_3$)
5	**124**	**444c/d** (**B**)	$[\alpha]_D^{24}$ = −6.02 (*c* 0.49, $CHCl_3$)
6	**124**	**414**	$[\alpha]_D^{24}$ = −9.15 (*c* 0.82, $CHCl_3$)
7	**124**	**445a**	$[\alpha]_D^{24}$ = −3.49 (*c* 0.86, $CHCl_3$)
8	**124**	**445b**	$[\alpha]_D^{24}$ = +2.17 (*c* 0.6, $CHCl_3$)

6.5.40. Synthesis of *rac* -methyl (3a*R*,4a*S*,8*R*,8a*R*,9a*S*)-6-allyl-8-cyano-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-445a and *rac*-methyl (3a*R*,4a*R*,8*R*,8a*R*,9a*S*)-6-allyl-8-cyano-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-445b



To a solution of Michael adducts (**B**) (±)-**444c**/**d** (1.00 g, 3.35 mmol, **c**:**d** = 1.3:1.0) in MeOH (47 mL) was added allylamine **143** (0.23 g, 0.30 mL, 4.03 mmol) followed by formaldehyde (37% solution in water) **144** (5.44 g, 5.00 mL, 67.03 mmol) and the resulting colourless solution was refluxed for 6.5 h. The solution was cooled to RT and concentrated before being purified by column chromatography (PE:Et_2O 1:1) to give the title compounds as separable diastereomers (±)-**445a** (0.525 g, 41%) and (±)-**445b** (270 mg, 21%) as colourless solids. Both diastereomers were recrystallized (EtOH) and their structures were confirmed by single crystal X-ray analysis.

Data for diastereomer (±)-**445a**

R_f = 0.83 (Et_2O:PE 7:4); mp 96-97 °C (EtOH); ν_{max}(film)/cm^{-1} 2986 (C-H), 1746 (C=O), 1551 (NO_2), 1373 (NO_2), 1251 (C-O), 1040 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.88 - 5.71 (m, 1H, CH_2=C*H*), 5.30 - 5.21 (m, 2H, C*H*$_2$=CH), 4.76 - 4.65 (m, 1H, CHCH_2C*H*O), 4.37 (ddd, *J* = 5.1, 3.3, 2.4 Hz, 1H, NO_2CCH_2C*H*O), 3.91 (s, 3H, OCH_3), 3.43 - 3.37 (m, 1H, NO_2CC*H*), 3.20 (d, *J* = 12.0 Hz, 2H, NC*H*H', NC*H*H'), 3.18 - 3.07 (m, 3H, CH_2=CHCH_2,

NO_2CCHH'), 2.98 (dd, *J* = 16.7, 3.5 Hz, 1H, NO_2CCHH'), 2.55 (d, *J* = 12.0 Hz, 1H, NCH*H*'), 2.45 (d, *J* = 11.6 Hz, 1H, NCH*H*'), 2.13 (ddd, *J* = 15.5, 9.1, 6.3 Hz , 1H, $NO_2CCHCHH$'), 1.86 (ddd, *J* = 15.5, 7.0, 3.0 Hz, 1H, $NO_2CCHCHH$'), 1.37 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.8 (*C*=O), 132.8 (CH_2=*C*H), 119.7 (*C*H_2=CH), 119.4 (*C*≡N), 108.7 (*C*$(CH_3)_2$), 84.8 (*C*NO_2), 71.7 (O*C*HCH_2CNO_2), 69.2 (O*C*HCH_2CHC≡N), 61.2 (N*C*H_2), 59.8 (CH_2=CH*C*H_2), 58.3 (N*C*H_2), 54.3 (O*C*H_3), 49.0 (*C*C≡N), 39.7 (*C*HC≡N), 31.1 (NO_2CCH_2), 28.1 (NO_2CHCH_2), 27.6 (*C*H_3), 26.0 (*C*H_3); *m/z* (ESI$^+$) 781 (100%, $[2M+Na]^+$), 402 (92, $[M+Na]^+$), 380 (30, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 402.1639, $C_{18}H_{25}N_3NaO_6$ requires 402.1636.

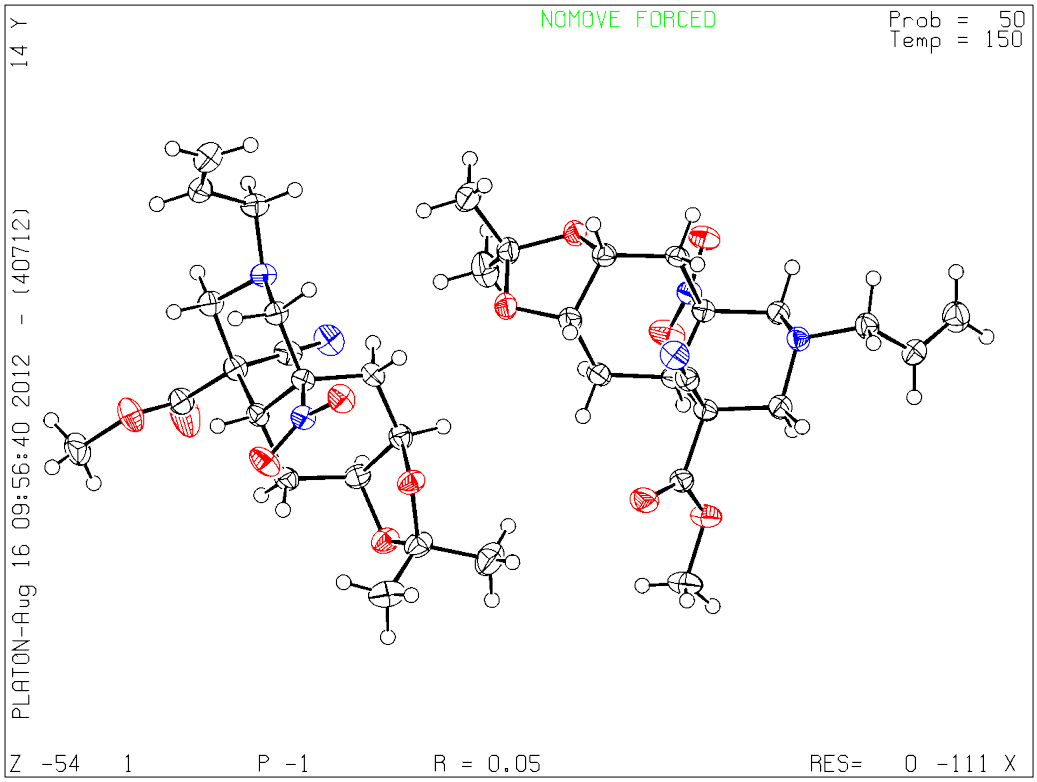
Data for diastereomer (±)-**445b**

R_f = 0.59 (Et_2O:PE 7:4); mp 157-159 °C (EtOH); ν_{max}(film)/cm^{-1} 2985 (C-H), 1744 (C=O), 1548 (NO_2), 1370 (NO_2), 1249 (C-O), 1059 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.89 - 5.68 (m, 1H, CH_2=C*H*), 5.27 – 5.20 (m, 2H, C*H*$_2$=CH), 4.40 (t, *J* = 4.3 Hz, 1H, $CHCH_2CHO$), 4.06 (ddd, *J* = 10.1, 6.0, 4.8 Hz, 1H, NO_2CCH_2CHO), 3.89 (s, 3H, OC*H*$_3$), 3.71 (dd, *J* = 12.9, 1.8 Hz, 1H, NC*H*H'), 3.42 (dd, *J* = 11.6, 1.8 Hz, 1H, NC*H*H'), 3.13 (dd, *J* = 6.4, 1.1 Hz, 2H, CH_2=CHC*H*$_2$), 2.88 (ddd, *J* = 14.5, 13.0, 4.5 Hz, 1H, $NO_2CCHCHH$'), 2.62 (dd, *J* = 13.0, 4.4 Hz, 1H, NO_2CCH), 2.58 (d, *J* = 11.6 Hz, 1H, NCH*H*'), 2.35 (dd, *J* = 14.0, 6.4 Hz, 1H, NO_2CCHH'CHO), 2.21 (d, *J* = 12.9 Hz, 1H, NCH*H*'), 2.10 (dd, *J* = 14.5, 4.4 Hz, 1H, $NO_2CCHCHH$'), 1.65 (dd, *J* = 14.0, 10.1 Hz, 1H, NO_2CCHH'CHO), 1.48 (s, 3H, C*H*$_3$), 1.34 (s, 3H, C*H*$_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.3 (*C*=O), 133.1 (CH_2=*C*H), 119.4 (*C*H_2=CH), 116.5

(*C*≡N), 108.6 (*C*(CH_3)$_2$), 86.4 (*C*NO_2), 72.2 (O*C*HCH_2CHC≡N), 70.6 (O*C*HCH_2CNO_2), 60.9 (N*C*H_2), 60.0 (CH_2=CH*C*H_2), 59.8 (N*C*H_2), 54.2 (O*C*H_3), 48.1 (*C*C≡N), 40.2 (*C*HCC≡N) , 37.7 (NO_2C*C*H_2), 28.5 (*C*H_3), 26.2 (NO_2CCH*C*H_2), 26.1 (*C*H_3); *m/z* (ESI$^+$) 781 (100%, [2M+Na]$^+$), 759 (48, [2M+H]$^+$), 402 (29, [M+Na]$^+$), 380 (88, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 402.1634, $C_{18}H_{25}N_3NaO_6$ requires 402.1636.

6.5.41. Single crystal X-ray analysis of diastereomer 445a

Thermal ellipsoid Plot drawn at 50% probability



Crystal data **445a**

$C_{18}H_{25}N_3O_6$	Z = 4
M_r = 379.41	F(000) = 808
Triclinic, P1	D_x = 1.302 Mg m^{-3}
Hall symbol: -P 1	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 10.8083 (1) Å	Cell parameters from 8163 reflections
b = 12.1525 (2) Å	θ = 5–27°
c = 16.5883 (3) Å	μ = 0.10 mm^{-1}
α = 69.2776 (6)°	T = 150 K

β = 77.9109 (6)°	Lath, Colourless
γ = 73.0406 (7)°	0.50 × 0.25 × 0.10 mm
V = 1935.47 (5) Å^3	

Data collection

Nonius KappaCCD diffractometer	5727 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.033
ω scans	θ_{max} = 27.5°, θ_{min} = 5.2°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	h = −14→14
T_{min} = 0.98, T_{max} = 0.99	k = −15→15
15223 measured reflections	l = −20→21
8783 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.050	No H atoms present
$wR(F^2)$ = 0.163	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) +

$A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed below and x = *F*/*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 18.3 27.6 13.4 3.49

S = 0.97

$(\Delta/\sigma)_{max}$ = 0.0004

8783 reflections

$\Delta\rho_{max}$ = 0.51 e Å^{-3}

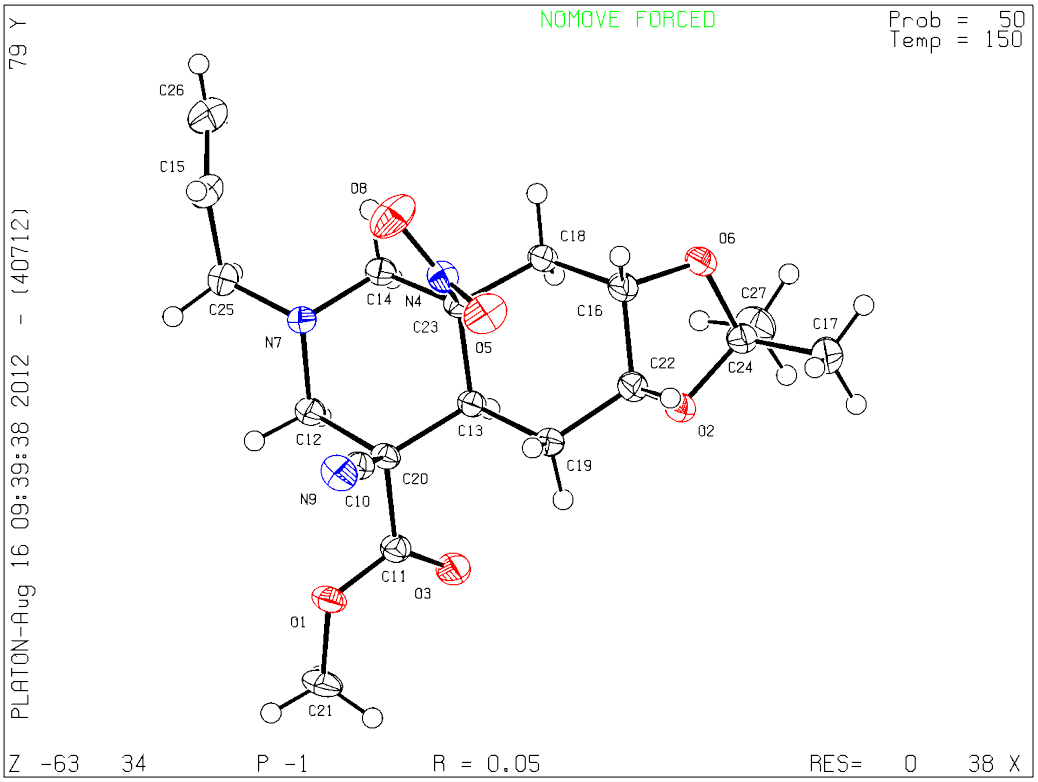
487 parameters

$\Delta\rho_{min}$ = −0.50 e Å^{-3}

0 restraints

6.5.42. Single crystal X-ray analysis of diastereomer 445b

Thermal ellipsoid Plot drawn at 50% probability



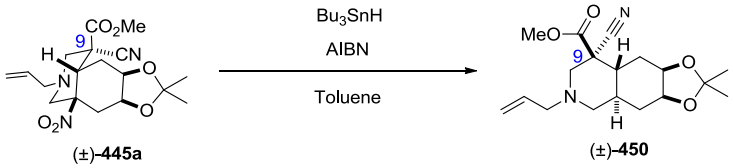
Crystal data **445b**

$C_{18}H_{25}N_3O_6$	Z = 2
M_r = 379.41	F(000) = 404
Triclinic, P1	D_x = 1.334 Mg m^{-3}
Hall symbol: -P 1	Melting point: 157-159 °C
a = 6.2039 (1) Å	Mo $K\alpha$ radiation, λ = 0.71073 Å
b = 10.0048 (2) Å	Cell parameters from 3979 reflections
c = 16.2519 (3) Å	θ = 5–27°
α = 104.5905 (8)°	μ = 0.10 mm^{-1}

β = 97.7564 (8)°	*T* = 150 K
γ = 99.9695 (9)°	Block, Colourless
V = 944.44 (3) Å^3	0.68 × 0.30 × 0.20 mm
Data collection	
Nonius KappaCCD diffractometer	3324 reflections with *I* > 2.0σ(*I*)
Graphite monochromator	R_{int} = 0.021
ω scans	θ_{max} = 27.5°, θ_{min} = 5.1°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	*h* = −7→8
T_{min} = 0.81, T_{max} = 0.98	*k* = −12→12
15106 measured reflections	*l* = −21→21
4268 independent reflections	
Refinement	
Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.046	No H atoms present
$wR(F^2)$ = 0.155	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) +

	$A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 37.7 58.3 28.9 7.48
S = 0.91	$(\Delta/\sigma)_{max}$ = 0.0004
4268 reflections	$\Delta\rho_{max}$ = 0.33 e Å^{-3}
244 parameters	$\Delta\rho_{min}$ = −0.36 e Å^{-3}
0 restraints	

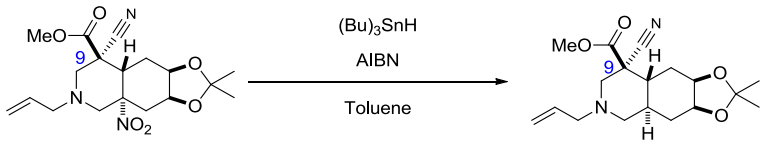
6.5.43. Synthesis of *rac*-methyl (3a*R*,4a*S*,8*R*,8a*S*,9a*S*)-6-allyl-8-cyano-2,2-dimethyldecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-450



Tributyltin hydride (0.096 g, 0.087 mL, 0.330 mmol) and AIBN (0.002 g, 0.013 mmol) were added to a solution of (±)-**445a** (0.025 g, 0.066 mmol) in toluene (1.5 mL). The reaction mixture was degassed by ten cycles of vacuum/N_2 purge. The resulting solution was heated rapidly to reflux and stirred at this temperature for 2.5 h before being cooled to RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (PE→PE:Et_2O 2:3) to give the title compound (±)-**450** as a colourless oil (0.017 g, 77%). ^{1}H NMR analysis of the crude and purified reaction residues confirmed that only a single diastereomer was present: ν_{max}(film)/cm^{-1} 2937 (C-H), 1742 (C=O), 1254 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.83 (dddd, *J* = 16.9, 10.4, 6.2, 6.2 Hz, 1H, CH_2=C*H*), 5.29 - 5.12 (m, 2H, C*H*$_2$=CH), 4.34 - 4.24 (m, 1H, N≡CCCHCH_2C*H*O), 4.15 - 4.02 (m, 1H, CHCH_2C*H*O), 3.83 (s, 3H, OC*H*$_3$), 3.28 (dd, *J* = 11.3, 1.4 Hz, 1H, NC*H*H'CC≡N), 3.14 (dd, *J* = 13.7, 5.8 Hz, 1H, CH_2=CHC*H*H'), 3.00 (dd, *J* = 13.7, 6.8 Hz, 1H, CH_2=CHCH*H*'), 2.88 - 2.81 (m, 1H, NC*H*H'CH), 2.38 (d, *J* = 11.3 Hz, 1H, NCH*H*'CC≡N), 2.12 (ddd, *J* = 14.1, 2.8, 2.6 Hz, 1H, N≡CCCHC*H*H'), 1.95 - 1.87 (m, 1H, N≡CCC*H*), 1.86 - 1.77 (m, 3H, NCH*H*'CH, N≡CCCHCH*H*', N≡CCCHCHC*H*H'), 1.70 - 1.58 (m, 1H, N≡CCCHC*H*), 1.49 (s, 3H, C*H*$_3$), 1.35 (s, 3H, C*H*$_3$), 1.24 (ddd, *J* = 12.8, 12.8 10.4 Hz, 1H, N≡CCCHCHCH*H*'); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.7

(*C*=O), 134.2 (CH_2=*C*H), 118.4 (*C*H_2=CH), 117.4 (*C*≡N), 108.4 (*C*$(CH_3)_2$), 73.1 (N≡CCCHCHCH_2*C*HO), 72.8 (N≡CCCHCH_2*C*HO), 60.4 (CH_2=C*H*CH_2), 58.7 (N*C*H_2CH), 58.5 (N*C*H_2CC≡N), 53.6 (O*C*H_3) 51.3 (*C*C≡N), 40.2 (*C*HCC≡N), 33.8 (*C*HCHCC≡N), 33.7 (*C*H_2CHCHCC≡N), 29.1 (*C*H_2CHCC≡N), 28.7 (*C*H_3), 26.4 (*C*H_3); *m/z* (ESI^+) 691 (100%, $[2M+Na]^+$), 357 (57, $[M+Na]^+$), 335 (98, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 357.1786, $C_{18}H_{26}N_2NaO_4$ requires 357.1785.

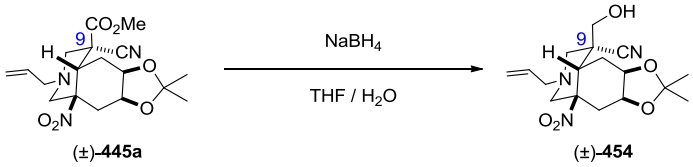
6.5.44. Synthesis of *rac*-methyl (3a*R*,4a*S*,8*R*,8a*S*,9a*S*)-6-allyl-8-cyano-2,2-dimethyldecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-450



(±)-**445b** (±)-**450**

Tributyltin hydride (0.073 g, 0.066 mL, 0.250 mmol) and AIBN (0.002 g, 0.013 mmol) were added to a solution of (±)-**445b** (0.019 g, 0.050 mmol) in toluene (1.0 mL). The reaction mixture was degassed by ten cycles of vacuum/N_2 purge. The resulting solution was heated rapidly to reflux and stirred at this temperature for 2.5 h before being cooled to RT. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (PE→PE:Et_2O 1:1) to give the title compound (±)-**450** as a colourless oil (0.014 g, 83%). ^{1}H NMR analysis of the crude and purified reaction residues confirmed that only a single diastereomer was present. All spectroscopic data accurately matched that previously reported for (±)-**450** derived from compound (±)-**445a**.

6.5.45. Synthesis of *rac*-(3a*R*,4a*S*,8*R*,8a*R*,9a*S*)-6-allyl-8-(hydroxymethyl)-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carbonitrile (±)-454

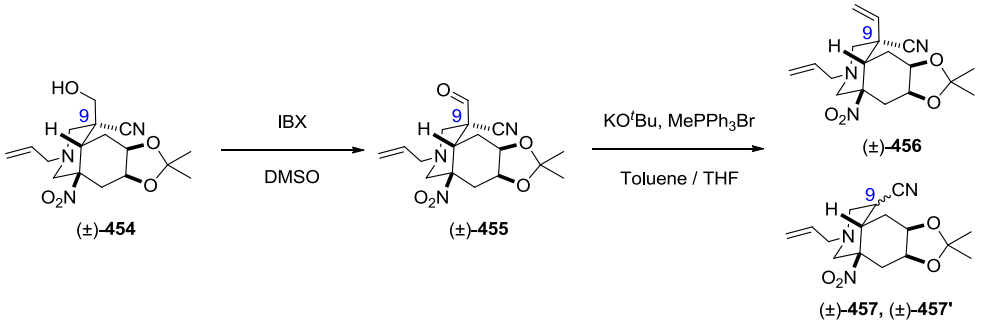


(±)-**445a** (±)-**454**

To a solution of sodium borohydride (0.469 g, 12.40 mmol) in THF:H_2O (21 mL:2.4 mL) was added a solution of (±)-**445a** (0.470 g, 1.24 mmol) in THF (10 mL) and the resulting solution stirred at 50 °C for 3 h. The reaction mixture was cooled to 0 °C and sat. aq. NH_4Cl solution (40 mL) was added. The product was extracted with EtOAc (5 x 30 mL) and the combined organic extracts were washed sequentially with sat. aq. NH_4Cl solution (15 mL), water (15mL) and brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE:Et_2O 2:3) to give the title compound (±)-**454** (0.307 g, 71%) as a colourless solid: mp 140-141 °C (Et_2O); ν_{max}(film)/cm^{-1} 3459 (O-H), 2986 (C-H), 1547 (NO_2), 1340 (NO_2), 1240 (C-O), 1049 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.86 - 5.70 (m, 1H, CH_2=C*H*), 5.28 - 5.16 (m, 2H, C*H*$_2$=CH), 4.69 - 4.57 (m, 1H, N≡CCCHCH_2C*H*O), 4.36 (ddd, *J* = 5.9, 3.8, 3.1 Hz, 1H, NO_2CH_2C*H*O), 3.96 (d, *J* = 11.0 Hz, 1H, C*H*H'OH), 3.74 (d, *J* = 11.0 Hz, 1H, CH*H*'OH), 3.11 - 3.05 (m, 3H, CH_2=CHC*H*$_2$, N≡CCC*H*), 3.00 (dd, *J* = 12.0, 0.6 Hz, 1H, NC*H*H'CC≡N), 3.00 - 2.95 (m, 1H, NO_2CC*H*H'), 2.93 (d, *J* = 12.0 Hz, 1H, NC*H*H'CNO_2), 2.75 (d, *J* = 12.0 Hz, 1H, NCH*H*'CNO_2), 2.66 (dd, *J* = 16.7, 3.8 Hz, 1H, NO_2CCH*H*'), 2.56 (br. s, 1H, O*H*), 2.48 (d, *J* = 12.0 Hz, 1H, NCH*H*'CC≡N), 2.14 (ddd, *J* = 15.3, 7.3, 5.2 Hz, 1H, N≡CCCHC*H*H'), 1.97 (ddd, *J* = 15.3, 6.1, 6.0 Hz, 1H, N≡CCCHCH*H*'), 1.41 (s, 3H, C*H*$_3$), 1.29 (s,

3H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 133.2 (CH_2=*C*H), 122.1 (*C*≡N), 119.3 (*C*H_2=CH), 108.7 (*C*$(CH_3)_2$), 86.6 (*C*NO_2), 71.4 (NO_2CCH_2*C*HO), 70.2 (N≡CCCHCH_2*C*HO), 65.3 (*C*H_2OH), 60.9 (N*C*H_2CNO_2), 60.1 (CH_2=CH*C*H_2), 56.9 (N*C*H_2CC≡N), 43.6 (*C*C≡N), 35.2 (*C*HCNO_2), 32.6 (NO_2C*C*H_2), 27.4 (NO_2CCH*C*H_2), 27.2 (*C*H_3), 25.4 (*C*H_3); *m/z* (ESI$^+$) 725 (100%, $[2M+Na]^+$), 390 (27, $[M+K]^+$), 374 (46, $[M+Na]^+$), 352 (51, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 374.1685, $C_{17}H_{25}N_3NaO_5$ requires 374.1686.

6.5.46. Synthesis of *rac*-(3a*R*,4a*S*,8*S*,8a*R*,9a*S*)-6-allyl-2,2-dimethyl-4a-nitro-8-vinyldecahydro[1,3]dioxolo [4,5-*g*]isoquinoline-8-carbonitrile (±)-456



To a solution of (±)-**454** (0.280 g, 0.797 mmol) in DMSO (30 mL) was added IBX (0.670 g, 2.39 mmol) in one portion and the resulting solution stirred at RT for 24 h. The solution was poured into sat. aq. $NaHCO_3$ solution (30 mL) and extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed once with water (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give crude aldehyde (±)-**455** as a yellow oil which was used immediately in the next reaction without further purification.

[Preparation of ylide solution: KO^{t}Bu (0.426 g, 3.80 mmol) was added to $MePPh_3Br$ (1.71 g, 4.79 mmol) in toluene (26 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT].

Crude aldehyde (±)-**455** was dissolved in THF (26 mL) and the solution added rapidly to the freshly prepared ylide solution, at RT. After 0.5 h TLC analysis indicated the complete consumption of starting material and the presence of three products. Water (50 mL) was added and THF/toluene were removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by

column chromatography (PE:Et_2O 3:2→2:3) to yield the title compound (±)-**456** as a colourless solid (0.061 g, 22% over 2 steps), side-product (±)-**457** as a mixture of inseparable diastereomers (0.107 g, 39%, (±)-**457**:(±)-**457'** 1:0.44 dr) and recovered alcohol (±)-**454** (0.049 g, 10%).

Data for compound (±)-**456**

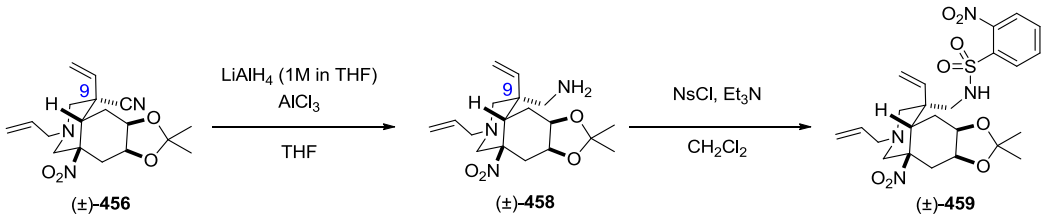
R_f = 0.88 (PE:EtOAc 3:2); ν_{max}(film)/cm^{-1} 2986 (C-H), 1548 (NO_2), 1373 (NO_2), 1239 (C-O), 1059 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.89 - 5.72 (m, 2H, CH_2=C*H*CH_2, C*H*H'=CHCC≡N), 5.61 - 5.49 (m, 2H, CH*H*'=CHCC≡N, CHH'=C*H*CC≡N), 5.29 - 5.19 (m, 2H, CH_2=CHCH_2), 4.64 (ddd, *J* = 9.4, 7.3, 5.2 Hz, 1H, N≡CCCHCH_2C*H*O), 4.37 (ddd, *J* = 5.2, 3.3, 2.4 Hz, 1H, NO_2CCH_2C*H*O), 3.27 (dd, *J* = 11.3, 1.9 Hz, 1H, NC*H*H'CC≡N), 3.20 - 3.07 (m, 4H, CH_2=CHCH_2, NO_2CCH_2CHO), 3.02 (dd, *J* = 12.0, 1.9 Hz, 1H, NC*H*H'CNO_2), 2.73 (ddd, *J* = 6.2, 2.4, 2.2 Hz, 1H, N≡CCC*H*), 2.35 (d, *J* = 11.3 Hz, 1H, NCH*H*'CC≡N), 2.19 (d, *J* = 12.0 Hz, 1H, NCH*H*'CNO_2), 2.09 (ddd, *J* = 15.3, 7.3, 2.4 Hz, 1H, N≡CCCHC*H*H'), 1.95 (ddd, *J* = 15.3, 9.5, 6.2 Hz, 1H, N≡CCCHCH*H*'), 1.36 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 134.0 (CH_2=*C*HCC≡N), 133.1 (CH_2=*C*HCH_2), 121.6 (*C*≡N), 120.5 (*C*H_2=CHCC≡N), 119.4 (*C*H_2=CHCH_2), 108.5 (*C*(CH_3)$_2$), 85.2 (*C*NO_2), 71.9 (NO_2CCH_2*C*HO), 69.2 (N≡CCCHCH_2*C*HO), 61.7 (N*C*H_2CC≡N), 61.0 (N*C*H_2CNO_2), 59.9 (CH_2=CH*C*H_2), 45.7 (*C*C≡N), 42.1 (*C*HCNO_2), 31.0 (NO_2C*C*H_2), 27.7 (*C*H_3), 26.1 ((NO_2CCH*C*H_2), 26.0 (*C*H_3); *m/z* (ESI$^+$) 717 (100%, $[2M+Na]^+$), 386 (44, $[M+K]^+$), 370 (67, $[M+Na]^+$), 348 (48, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 370.1731, $C_{18}H_{25}N_3NaO_4$ requires 370.1737.

Data for compound (±)-**457** (**457**:**457'** 1:0.44 dr)

R_f = 0.45 (PE:EtOAc 3:2); ν_{max}(film)/cm^{-1} 2986 (C-H), 1545 (NO_2), 1382 (NO_2), 1211 (C-O), 1048 (C-O); Diastereomer (±)-**457** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.79 - 5.61 (m, 1H, CH_2=C*H*CH_2), 5.26 - 5.12 (m, 2H, C*H*$_2$=CHCH_2), 4.41 (ddd, *J* = 5.7, 3.2, 3.0 Hz, 1H, N≡CCHCHCH_2C*H*O), 4.32 - 4.25 (m, 1H, NO_2CCH_2C*H*O), 3.49 (ddd, *J* = 11.4, 5.4, 5.2 Hz, 1H, N≡CC*H*), 3.42 (d, *J* = 13.1 Hz, 1H, NC*H*H'CNO_2), 3.32 (ddd, *J* = 13.2, 4.5, 4.5 Hz, 1H, N≡CCHC*H*), 3.16 - 2.86 (m, 3H, NC*H*H'CHC≡N, CH_2=CHC*H*$_2$), 2.50 (dd, *J* = 15.6, 5.6 Hz, 1H, NO_2CC*H*HCHO), 2.36 - 2.27 (m, 3H, NCH*H*'CNO_2, NCH*H*'CHC≡N, N≡CCHCHC*H*H'), 1.97 (dd, *J* = 15.6, 4.2 Hz, 1H, NO_2CCH*H*CHO), 1.66 (ddd, *J* = 14.8, 13.2, 3.7 Hz, 1H, N≡CCHCHCH*H*'), 1.47 (s, 3H, C*H*$_3$), 1.30 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 133.1 (CH_2=*C*H), 119.2 (*C*H_2=CH), 118.6 (*C*≡N), 108.8 (*C*$(CH_3)_2$), 87.8 (*C*NO_2), 71.6 (N≡CCHCHCH_2*C*HO), 71.2 (NO_2CCH_2*C*HO), 60.1 (CH_2=CH*C*H_2), 57.0 (N*C*H_2CNO_2), 50.5 (N*C*H_2CHC≡N), 35.3 (NO_2C*C*H_2), 29.2 (*C*HCHC≡N), 29.0 (CH*C*HC≡N), 26.9 (NO_2CCH*C*H_2) 26.8 (*C*H_3) 24.7 (*C*H_3); Diastereomer (±)-**457'** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.79 - 5.61 (m, 1H, CH_2=C*H*CH_2), 5.26 - 5.12 (m, 2H, C*H*$_2$=CHCH_2), 4.25 - 4.20 (m, 1H, NO_2CCH_2C*H*O), 4.19 - 4.12 (m, 1H, N≡CCHCHCH_2C*H*O), 3.13 (dd, *J* = 11.6, 3.3 Hz, 1H, NC*H*H'CHC≡N), 3.11 - 2.86 (m, 5H, NC*H*H'CNO_2, N≡CCHC*H*, CH_2=CHC*H*$_2$, NO_2CC*H*HCHO), 2.68 (ddd, *J* = 10.9, 10.9, 4.0 Hz, 1H, N≡CC*H*), 2.57 (dd, *J* = 16.9, 4.0 Hz, 1H, NO_2CCH*H*CHO), 2.41 (d, *J* = 11.4 Hz, 1H, NCH*H*'CNO_2), 2.38 - 2.27 (m, 1H, NCH*H*'CHC≡N), 2.15 (ddd, *J* = 15.0, 6.3, 4.0 Hz, 1H, N≡CCHCHC*H*H'), 2.05 – 1.97 (m, 1H, N≡CCHCHCH*H*') 1.40 (s, 3H, C*H*$_3$), 1.29 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 132.8 (CH_2=*C*H), 119.7 (*C*H_2=CH), 118.2

(*C*≡N), 108.7 (*C*(CH_3)$_2$), 84.9 (*C*NO_2), 71.4 (NO_2CCH_2*C*HO), 69.8 (N≡CCHCHCH_2*C*HO), 60.8 (N*C*H_2CNO_2), 60.0 (CH_2=CH*C*H_2), 54.1 (N*C*H_2CHC≡N), 37.2 (*C*HCHC≡N), 30.4 (CH*C*HC≡N), 29.9 (NO_2CCH_2), 27.9 (*C*H_3), 27.8 (NO_2CCH*C*H_2) 25.9 (*C*H_3); *m/z* (ESI$^+$) 665 (100%, [2M+Na]$^+$), 643 (36, [2M+H]$^+$), 344 (100, [M+Na]$^+$), 322 (37, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 344.1576, $C_{16}H_{23}N_3NaO_4$ requires 344.1581.

6.5.47. Synthesis of *rac*-(*N*-{[(3a*S*,4a*R*,8*R*,9a*R*)-6-allyl-2,2-dimethyl-4a-nitro-8-vinyldecahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-459

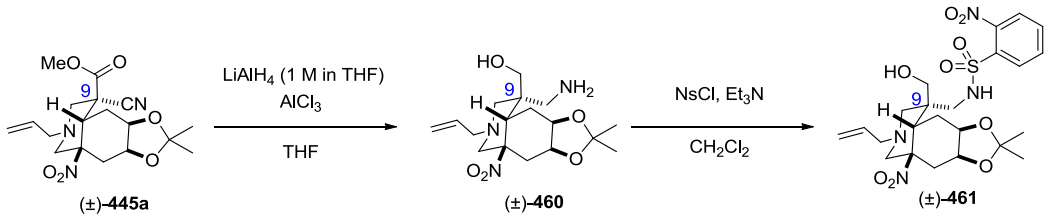


To a suspension of $AlCl_3$ (0.023 g, 0.170 mmol) in THF (0.8 mL) was added $LiAlH_4$ (1 M solution in THF) (0.510 mL, 0.510 mmol) and the resulting solution stirred at RT for 15 min. A solution of (±)-**456** (0.059 g, 0.170 mmol) in THF (0.8 mL) was added and the reaction mixture was stirred for 5 h. The reaction mixture was then cooled to 0 °C and carefully quenched with 30% aq. KOH solution (5 mL) until effervescence ceased. Water (5 mL) was added and the product was extracted from the aqueous phase sequentially with CH_2Cl_2 (2 x 5 mL), $CHCl_3$ (2 x 5 mL) and $CHCl_3$:IPA (4:1) (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude amine (±)-**458** (0.060 g) as a colourless oil which was used in the next step without further purification.

To a solution of crude amine (±)-**458** (60 mg) in CH_2Cl_2 (2 mL) cooled to 0 °C was added 2-nitrobenzenesulfonyl chloride (0.042 g, 0.190 mmol) and Et_3N (0.017 g, 0.024 mL, 0.170 mmol). The reaction mixture was warmed to RT and stirred for 6 h, before being concentrated and purified by column chromatography (PE:EtOAc 1:1) to give the title compound (±)-**459** [0.078 g, 86% (over two steps)] as a colourless oil: ν_{max}(film)/cm^{-1} 2985 (C-H), 1543 (NO_2), 1348 (NO_2), 1347 (SO_2), 1168 (N-S), 1055 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.13 - 8.03 (m, 1H, C*H*CSO_2), 7.92 - 7.83 (m, 1H, C*H*CNO_2CSO_2), 7.80 – 7.73 (m, 2H, 2 x Ar*H*), 5.88 - 5.73 (m, 1H, CH_2=C*H*CH_2), 5.62 - 5.41

(m, 2H, CH_2=C*H*C,N*H*SO_2), 5.30 - 5.10 (m, 4H, C*H*$_2$=CHCH_2, C*H*$_2$=CHC), 4.34 - 4.28 (m, 1H, NO_2CCHCH_2C*H*O), 4.21 – 4.13 (m, 1H, NO_2CCH_2C*H*O), 3.33 (d, *J* = 12.9 Hz, 1H, NC*H*H'CNO_2), 3.22 - 3.16 (m, 1H, C*H*H'NHSO_2), 3.13 (dd, *J* = 12.0, 4.7 Hz, 1H, C*H*CNO_2), 3.02 (d, *J* = 6.3 Hz, 2H, CH_2=CHC*H*$_2$), 2.86 (d, *J* = 12.4 Hz, 1H, NC*H*H'CCH=CH_2), 2.75 (d, *J* = 10.6 Hz, 1H, CH*H*'NHSO_2), 2.43 - 2.32 (m, 2H, NCH*H*'CNO_2, NO_2CC*H*H'CHO), 2.28 (d, *J* = 12.4 Hz, 1H, NCH*H*'CCH=CH_2), 2.09 - 1.95 (m, 2H, NO_2CCH*H*'CHO, NO_2CCHC*H*H'), 1.70 (ddd, *J* = 15.1, 12.0, 3.9 Hz, 1H, NO_2CCHCH*H*'), 1.46 (s, 3H, C*H*$_3$), 1.29 (s, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 148.1 (Ar*C*NO_2), 140.4 (CH_2=*C*HC), 133.9 (CH_2=*C*HCH_2), 133.8 (Ar*C*H), 133.0 (*C*SO_2NH) 132.8 (Ar*C*H), 131.0 (*C*HCSO_2NH), 125.5 (*C*HCNO_2), 118.9 (*C*H_2=CH), 117.9 (*C*H_2=CH), 108.7 (*C*(CH_3)$_2$), 88.3 (*C*NO_2), 71.6 (NO_2CCHCH_2*C*HO), 70.8 (NO_2CCH_2*C*HO), 60.7 (CH_2=CH*C*H_2), 55.9 (N*C*H_2CNO_2), 53.4 (N*C*H_2CCH=CH_2), 48.5 (*C*H_2NHSO_2), 42.9 (*C*CH=CH_2), 37.2 (NO_2C*C*H_2) 35.5 (NO_2C*C*H), 27.1 (*C*H_3), 25.3 (NO_2CCH*C*H_2), 25.3 (*C*H_3); *m/z* (ESI$^+$) 559 (77%, [M+Na]$^+$), 537 (27, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+H]$^+$ 537.2020, $C_{24}H_{33}N_4O_8S$ requires 537.2014.

6.5.48. Synthesis of *rac*-*N*-{[(3a*S*,4a*R*,8*S*,8a*S*,9a*R*)-6-allyl-8-(hydroxymethyl)-2,2-dimethyl-4a-nitro decahydro[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-461

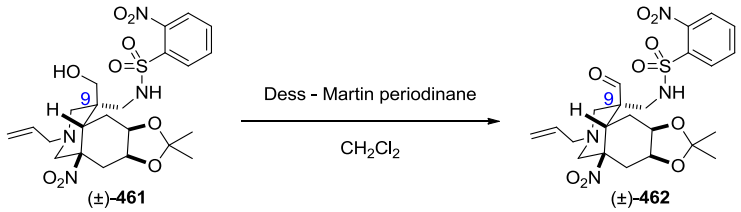


To a suspension of $AlCl_3$ (0.28 g, 2.10 mmol) in THF (5.5 mL) was added $LiAlH_4$ (1 M solution in THF) (6.33 mL, 6.33 mmol) and the resulting solution stirred at RT for 15 min. A solution of (±)-**445a** (0.40 g, 1.05 mmol) in THF (5.5 mL) was added and the reaction mixture was stirred for 5 h. The reaction mixture was then cooled to 0 °C and carefully quenched with 30% aq. KOH solution (10 mL) until effervescence ceased. Water (10 mL) was added and the product was extracted from the aqueous phase sequentially with CH_2Cl_2 (2 x 15 mL), $CHCl_3$ (2 x 15 mL) and $CHCl_3$:IPA (4:1) (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude aminol (±)-**460** (0.45 g) as a colourless oil which was used in the next step without further purification.

To a solution of the crude aminol (±)-**460** in CH_2Cl_2 (13 mL) cooled to 0 °C was added 2-nitrobenzenesulfonyl chloride (0.23 g, 1.05 mmol) and Et_3N (0.11 g, 0.15 mL, 1.05 mmol). The reaction mixture was warmed to RT and stirred for 4 h, before being concentrated and purified by column chromatography (Et_2O) to give the title compound (±)-**461** (0.44 g, 78% over two steps) as a colourless foam: ν_{max}(film)/cm^{-1} 2986 (C-H), 1540 (NO_2), 1347 (SO_2), 1345 (NO_2), 1166 (SO_2), 1052 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.13 - 8.02 (m, 1H, C*H*CSO_2), 7.92 - 7.82 (m, 1H, C*H*CNO_2CSO_2), 7.78 - 7.66 (m, 2H, 2 x Ar*H*), 6.81 (dd, *J* = 8.0, 2.9 Hz, 1H, N*H*SO_2), 5.68 (ddt, *J* =

17.9, 9.5, 6.4 Hz, 1H, CH_2=C*H*CH_2), 5.21 - 5.07 (m, 2H, C*H*$_2$=CHCH_2), 4.34 (ddd, *J* = 5.9, 2.8, 2.6 Hz, 1H, NO_2CCHCH_2CHO), 4.28 - 4.18 (m, 1H, NO_2CCH_2CHO), 3.71 (d, *J* = 12.5 Hz, 1H, C*H*H'OH), 3.64 (d, *J* = 13.1 Hz, 1H, NC*H*H'CNO_2), 3.51 (dd, *J* = 12.6, 2.6 Hz, 1H, C*H*CNO_2), 3.34 (dd, *J* = 12.5, 7.9 Hz, 1H, CH*H*'OH), 3.24 - 3.14 (m, 1H, C*H*H'$NHSO_2$), 2.92 (d, *J* = 6.4 Hz, 2H, CH_2=CHC*H*$_2$), 2.76 (dd, *J* = 11.9, 3.2 Hz, 1H, CH*H*'$NHSO_2$), 2.63 (br. s., 1H, CH_2OH), 2.37 (dd, *J* = 15.4, 5.4 Hz, 1H, NO_2CCHH'CHO), 2.31 - 2.16 (m, 3H, NCH*H*'CNO_2, NC*H*H'CCH_2OH, NO_2CCHCHH') 1.97 (d, *J* = 11.9 Hz, 1H, NCH*H*'CCH_2OH), 1.83 (dd, *J* = 15.4, 3.9 Hz, 1H, NO_2CCH*H*'CHO), 1.55 - 1.44 (m, 4H, C*H*$_3$, NO_2CCHCH*H*'), 1.28 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.2 (Ar*C*NO_2), 133.9 (CH_2=*C*HCH_2), 133.5 (Ar*C*H), 133.4 (*C*SO_2NH), 132.6 (Ar*C*H), 130.8 (*C*HSO_2NH), 125.4 (*C*HNO_2CSO_2), 118.5 (*C*H_2=CHCH_2), 108.7 (*C*$(CH_3)_2$), 90.0 (*C*NO_2), 72.2 (NO_2CCHCH_2*C*HO), 70.6 (NO_2CCH_2*C*HO), 68.7 (*C*H_2OH), 60.5 (CH_2=CH*C*H_2), 58.1 (N*C*H_2CNO_2), 54.8 (N*C*H_2CCH_2OH), 50.0 (*C*H_2NHSO_2), 40.3 (*C*CH_2OH), 37.1 (NO_2CCH_2CHO), 28.2 (NO_2CCH), 26.6 (*C*H_3), 25.6 (NO_2CCHCH_2), 24.7 (*C*H_3); *m/z* (ESI$^+$) 563 (100%, $[M+Na]^+$), 541 (99, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+H]^+$ 541.1948, $C_{23}H_{33}N_4O_9S$ requires 541.1963.

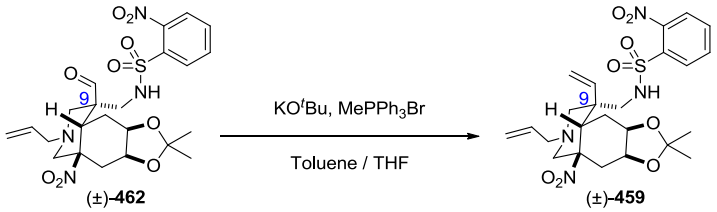
6.5.49. *Synthesis of rac-N-*{[(3a*S*,4a*R*,8*S*,8a*S*,9a*R*)-6-allyl-8-formyl-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo [4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzene sulfonamide (±)-462



To a solution of alcohol (±)-**461** (0.218 g, 0.403 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added Dess-Martin periodinane (0.180 g, 0.424 mmol). The resulting solution was stirred at 0 °C for 3.5 h before being concentrated under reduced pressure and purified by column chromatography (Et_2O) to give the title compound (±)-**462** (0.200 g, 92%) as a colourless oil: ν_{max}(film)/cm^{-1} 2987 (C-H), 1715 (C=O), 1542 (NO_2), 1349 (NO_2), 1168 (N-S), 1050 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.62 (s, 1H, *H*C=O), 8.12 - 8.02 (m, 1H, C*H*CSO_2), 7.91 - 7.83 (m, 1H, C*H*CNO_2CSO_2), 7.80 - 7.72 (m, 2H, 2 x Ar*H*), 5.84 (t, *J* = 5.8 Hz, 1H, N*H*SO_2), 5.79 - 5.65 (m, 1H, CH_2=C*H*CH_2), 5.25 - 5.12 (m, 2H, C*H*$_2$=CHCH_2), 4.42 - 4.37 (m, 1H, NO_2CCHCH_2C*H*O), 4.35 - 4.25 (m, 1H, NO_2CCH_2C*H*O), 3.58 (d, *J* = 12.7 Hz, 1H, NC*H*H'CNO_2), 3.40 (d, *J* = 12.6 Hz, 1H, C*H*CNO_2), 3.26 (dd, *J* = 11.8, 5.8 Hz, 1H, C*H*H'NHSO_2), 3.13 (d, *J* = 12.8 Hz, 1H, NC*H*H'CCHO), 3.10 - 2.96 (m, 3H, CH*H*'NHSO_2,CH_2=CHC*H*$_2$), 2.71 (dd, *J* = 15.5, 3.3 Hz, 1H, NO_2CC*H*H'CHO), 2.36 (d, *J* = 12.7 Hz, 1H, NCH*H*'CNO_2), 2.26 (d, *J* = 12.8 Hz, 1H, NCH*H*'CCHO), 1.94 (d, *J* = 14.2 Hz, 1H, NO_2CCHC*H*H'), 1.80 (d, *J* = 15.5 Hz, 1H, NO_2CCH*H*'CHO), 1.48 - 1.36 (m, 4H, C*H*$_3$, NO_2CCHCH*H*'), 1.26 (s, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 205.0 (H*C*=O), 148.2 (Ar*C*NO_2), 133.9 (Ar*C*H), 133.4 (CH_2=*C*HCH_2), 133.1 (*C*SO_2NH), 132.8 (Ar*C*H), 130.7 (*C*HCSO_2NH), 125.5 (*C*HCNO_2CSO_2), 119.2 (*C*H_2=CHCH_2), 108.9 (*C*$(CH_3)_2$),

88.7 (*C*NO_2), 72.2 (NO_2CCHCH_2CHO), 70.4 (NO_2CCH_2CHO), 60.5 (CH_2=$CHCH_2$), 59.3 (NCH_2CNO_2), 53.3 (NCH_2CCHO), 49.2 (*C*CHO), 46.3 (CH_2NHSO_2), 35.1 (NO_2CCH_2), 31.6 (NO_2CCH), 26.0 (CH_3), 25.5 (NO_2CCHCH_2), 24.3 (CH_3); *m/z* (ESI^-) 537 (100%, $[M-H]^-$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 561.1606, $C_{23}H_{30}N_4NaO_9S$ requires 561.1626.

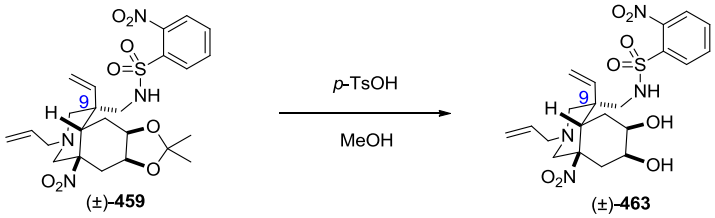
6.5.50. Synthesis *of rac*-(*N*-{[(3a*S*,4a*R*,8*R*,8a*S*,9a*R*)-6-allyl-2,2-dimethyl-4a-nitro-8-vinyldecahydro [1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-459



[Preparation of Ylide solution: KO^{t}Bu (0.180 g, 1.61 mmol) was added to MePPh$_3$Br (0.728 g, 2.04 mmol) in toluene (13 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT].

Aldehyde (±)-**462** (0.183 g, 0.34 mmol) was dissolved in THF (13 mL) and the solution was added rapidly to the freshly prepared ylide solution at RT. After stirring the reaction mixture for 0.5 h at RT, water (35 mL) was added and THF/toluene were removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (Et_2O) to yield the title compound (±)-**459** (0.171 g, 94%) as a colourless solid with data in excellent agreement with that previous reported for compound (±)-**459** when it was accessed from compound (±)-**458.**

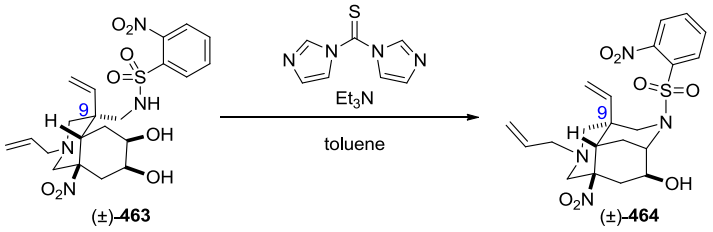
6.5.51. Synthesis of *rac*-*N*-{[(4*R*,4a*S*,6*R*,7*S*,8a*R*)-2-allyl-6,7-dihydroxy-8a-nitro-4-vinyldecahydro-isoquinolin-4-yl]methyl}-2-nitrobenzenesulfonamide (±)-463



To a solution of (±)-**459** (0.162 g, 0.302 mmol) in MeOH (10 mL) was added *p*-TsOH (0.017 g, 0.089 mmol) and the resulting solution was refluxed for 5 h. After this time a second portion of *p*-TsOH (0.043 g, 0.226 mmol) was added and the solution was heated at reflux for a further 2.5 h. The reaction mixture was concentrated under reduced pressure and water (15 mL) was added to the crude residue. The resulting aqueous suspension was basified (solid K_2CO_3) and the product was extracted with CH_2Cl_2 (5 x 20 mL). The combined organics were dried ($MgSO_4$) before being concentrated under reduced pressure and purified by column chromatography (EtOAc) to give the title compound (±)-**463** (0.135 g, 90%) as a colourless solid: R_f = 0.38 (EtOAc); mp 208-211 °C (EtOAc); ν_{max}(film)/cm^{-1} 3348 (O-H), 2926 (C-H), 1541 (NO_2), 1355 (NO_2), 1167 (SO_2), 1052 (C-O); ^{1}H NMR (500MHz, DMSO-d_6) δ_H 8.03 - 7.98 (m, 1H, C*H*CSO$_2$), 7.98 - 7.93 (m, 1H, C*H*CNO$_2$CSO$_2$), 7.89 - 7.83 (m, 2H, 2 x Ar*H*), 7.60 (br. s., 1H, N*H*SO$_2$), 5.81 (ddt, *J* = 17.0, 10.4, 6.3 Hz, 1H, CH$_2$=C*H*CH$_2$), 5.46 (dd, *J* = 17.4, 11.0 Hz, 1H, CH$_2$=C*H*C), 5.25 - 5.13 (m, 2H, C*H*$_2$=CHCH$_2$), 5.03 (dd, *J* = 17.4, 1.2 Hz, 1H, CH$_{cis}$*H*$_{trans}$=CHC), 4.85 (dd, *J* = 11.0, 1.2 Hz, 1H, C*H*$_{cis}$H$_{trans}$=CHC), 4.70 (d, *J* = 6.3 Hz, 1H, NO$_2$CCH$_2$CHO*H*), 4.67 (d, *J* = 2.5 Hz, 1H, NO$_2$CCHCH$_2$CHO*H*), 3.78 ('br. s.', 1H, NO$_2$CCHCH$_2$C*H*OH), 3.51 - 3.41 (m, 1H, NO$_2$CCH$_2$C*H*OH), 3.30 (d, *J* = 13.1 Hz, 1H, NC*H*H'CNO$_2$), 3.07 - 2.91

(m, 3H, C*H*CNO_2, CH_2=CHC*H*$_2$), 2.80 (d, *J* = 12.5, 2.4 Hz, 1H, C*H*H'$NHSO_2$), 2.76 - 2.63 (m, 2H, CH*H*'$NHSO_2$, NC*H*H'CCH=CH_2), 2.47 (d, *J* = 13.1 Hz, 1H, NCH*H*'CNO_2), 2.12 (dd, *J* = 12.3, 12.3 Hz, 1H, NO_2CC*H*H'CHOH), 1.98 (d, *J* = 12.0 Hz, 1H, NCH*H*'CCH=CH_2), 1.83 (ddd, *J* = 13.9, 4.4, 4.4 Hz, 1H, NO_2CCHC*H*H'), 1.62 - 1.50 (m, 2H, NO_2CCH*H*'CHOH, NO_2CCHCH*H*'); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 147.8 (Ar*C*NO_2), 140.8 (CH_2=*C*HC), 134.9 (CH_2=*C*HCH_2), 134.0 (Ar*C*H), 132.6 (Ar*C*H), 132.4 (*C*SO_2NH), 129.6 (*C*HCSO_2NH), 124.2 (*C*HCNO_2CSO_2), 117.9 (*C*H_2=CHCH_2), 115.8 (*C*H_2=CHC), 90.3 (*C*NO_2), 67.0 (NO_2CCHCH_2*C*HOH), 66.9 (NO_2CCH_2*C*HOH), 60.3 (CH_2=CH*C*H_2) 52.3 (N*C*H_2CNO_2), 51.6 (N*C*H_2CCH=CH_2), 49.1 (*C*H_2NHSO_2), 42.3 (*C*CH=CH_2), 39.6 (NO_2C*C*H_2), 34.5 (NO_2C*C*H), 28.0 (NO_2CCH*C*H_2); *m/z* (ESI$^+$) 519 (100%, [M+Na]$^+$), 497 (72, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 519.1512, $C_{21}H_{28}N_4NaO_8S$ requires 519.1520.

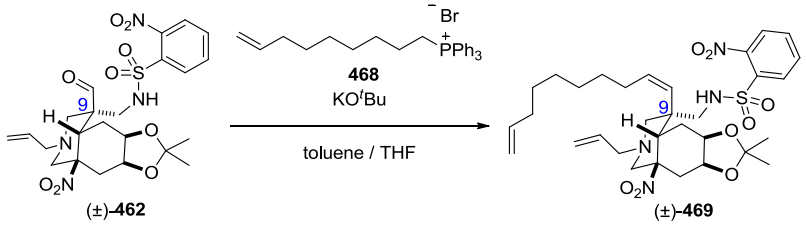
6.5.52. Synthesis of *rac*-(4*R*,4a*S*,7*S*,8a*R*)-2-allyl-8a-nitro-9-[(2-nitrophenyl)sulfonyl]-4-vinyldecahydro-6,4-(epiminomethano)isoquinolin-7-ol (±)-464



To a suspension of diol (±)-**463** (0.033 g, 0.066 mmol) in toluene (1.8 mL) was added 1,1′-thiocarbonyldiimidazole (0.012 mg, 0.070 mmol) and Et_3N (0.013 mg, 18 µl, 0.133 mmol) and the reaction mixture was stirred at reflux, at which temperature diol (±)-**463** became soluble in toluene. TLC analysis was used to follow the reaction until complete consumption of diol (±)-**463** (R_f = 0.38 (EtOAc) and the disappearance of a transient intermediate (R_f = 0.52 (Et_2O) was observed (9 h). The reaction mixture was concentrated before being purified by column chromatography (Et_2O:PE 9:1→Et_2O) to give the title compound (±)-**464** (0.011 g, 35%) as colourless solid: R_f = 0.81 (Et_2O); mp 165-167 °C (Et_2O); ν_{max}(film)/cm^{-1} 3535 (O-H), 2919 (C-H), 1540 (NO_2), 1338 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.11 (dd, *J* = 7.4, 1.4 Hz, 1H, C*H*CSO_2), 7.85 - 7.63 (m, 3H, 3 x Ar*H*), 5.84 - 5.70 (m, 1H, CH_2=C*H*CH_2), 5.58 (dd, *J* = 17.7, 11.0 Hz, 1H, CH_2=C*H*C), 5.26 - 5.13 (m, 2H, C*H*$_2$=CHCH_2), 5.09 (d, *J* = 11.0 Hz, 1H, C*H*$_{cis}$H$_{trans}$=CHC), 4.95 (d, *J* = 17.7 Hz, 1H, CH$_{cis}$*H*$_{trans}$=CHC), 4.02 - 3.97 (m, 1H, C*H*NSO_2), 3.95 - 3.90 (m, 1H, C*H*OH), 3.82 (d, *J* = 13.6 Hz, 1H, C*H*H'NSO_2), 3.60 (d, *J* = 13.6 Hz, 1H, CH*H*'NSO_2), 3.10 - 2.94 (m, 3H, CH_2=CHC*H*$_2$, NC*H*H'CNO_2), 2.93 - 2.81 (m, 2H, C*H*$_2$COH), 2.55 - 2.41 (m, 2H, C*H*CNO_2, NC*H*H'CCH=CH_2), 2.32 (d, *J* = 10.7 Hz, 1H, NCH*H*'CNO_2), 2.21 - 2.07 (m, 2H, C*H*H'CHNSO_2, CHO*H*), 2.04

(d, *J* = 12.0 Hz, 1H, NCH*H*'CCH=CH_2), 1.89 (ddd, *J* = 14.2, 3.0, 3.0 Hz, 1H, CH*H*'CHNSO_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 147.8 (Ar*C*NO_2), 141.4 (CH_2=*C*HC), 133.8 (Ar*C*H), 133.7 (CH_2=*C*HCH_2), 132.9 (*C*SO_2N), 131.8 (Ar*C*H), 131.3 (*C*HCSO_2N), 124.5 (*C*HCNO_2CSO_2), 119.1 (*C*H_2=$CHCH_2$), 116.1 (*C*H_2=CHC), 88.2 (*C*NO_2), 67.3 (*C*HOH), 62.3 (N*C*$H_2C$$NO_2$), 61.2 (N*C*$H_2$CCH=$CH_2$), 60.3 ($CH_2$=CH*C*$H_2$), 51.1 (C*H*$NSO_2$), 45.9 (*C*$H_2$$NSO_2$), 39.2 (*C*CH=$CH_2$), 37.6 ($NO_2$C*C*H), 35.2 ($NO_2$C*C*$H_2$), 18.9 ($NO_2$CCH*C*$H_2$); *m/z* (ESI$^+$) 501 (100%, $[M+Na]^+$), 479 (80, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 501.1423, $C_{21}H_{26}N_4NaO_7S$ requires 501.1414.

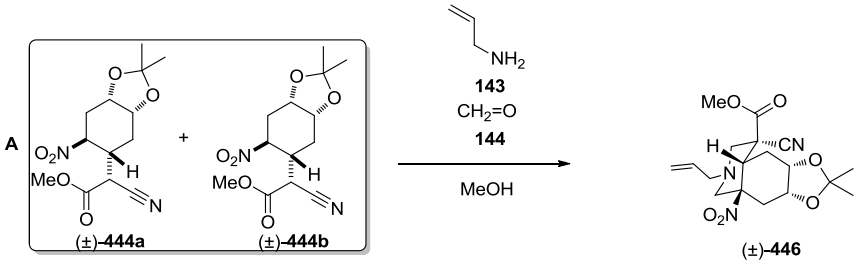
6.5.53. Synthesis of *rac*-*N*-({(3a*S*,4a*R*,8*R*,8a*S*,9a*R*)-6-allyl-8-[(1*Z*)-deca-1,9-dien-1-yl]-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl}methyl)-2-nitrobenzenesulfonamide (±)-469



KO^{t}Bu (0.060 g, 0.535 mmol) was added to Wittig salt **468** (0.312 g, 0.667 mmol) in toluene (3.5 mL) and the resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT. A solution of aldehyde (±)-**462** (0.060 g, 0.111 mmol) in THF (3.5 mL) was added rapidly to the prepared ylide solution at RT. After 2.5 h water (20 mL) was added and THF/toluene were removed under reduced pressure. The aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (Et_2O:PE 4:1) to yield the title compound (±)-**469** as a colourless oil (0.018 g, 25%): R_f = 0.72 (Et_2O); ν_{max}(film)/cm^{-1} 2928 (C-H), 1542 (NO_2), 1348 (SO_2), 1346 (NO_2), 1169 (SO_2), 1054 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.11 - 8.06 (m, 1H, C*H*CSO_2), 7.88 - 7.83 (m, 1H, C*H*CNO_2CSO_2), 7.80 - 7.74 (m, 2H, 2 x Ar*H*), 5.89 - 5.73 (m, 2H, CH_2=C*H*CH_2, CH_2=C*H*(CH_2)$_6$), 5.51 (d, *J* = 9.1 Hz, 1H, N*H*SO_2), 5.47 - 5.39 (m, 1H, CC*H*=CH), 5.27 - 5.15 (m, 3H, C*H*$_2$=CHCH_2, C*H*=CHC), 5.05 - 4.89 (m, 2H, C*H*$_2$=CH(CH_2)$_6$), 4.40 - 4.31 (m, 1H, CHCH_2C*H*O), 4.19 (ddd, *J* = 5.8, 5.6, 5.6 Hz, 1H, NO_2CCH_2C*H*O), 3.53 (d, *J* = 12.9 Hz, 1H, NC*H*H'CNO_2), 3.43 (dd, *J* = 12.6, 3.8 Hz, 1H, C*H*CNO_2), 3.21 - 3.12 (m, 1H,

C*H*H'$NHSO_2$), 3.12 - 3.04 (m, 2H, CH*H*'$NHSO_2$, CH_2=CHC*H*H'), 3.04 - 2.96 (m, 1H, CH_2=CHCH*H*'), 2.84 (d, *J* = 12.0 Hz, 1H, NC*H*H'CCH=CH), 2.31 (dd, *J* = 15.3, 5.8 Hz, 1H, NO_2CC*H*H'CHO), 2.22 (d, *J* = 12.9 Hz, 1H, NCH*H*'CNO_2), 2.16 (d, *J* = 12.0 Hz, 1H, NCH*H*'CCH=CH), 2.08 (td, *J* = 15.1, 7.3 Hz, 1H, C*H*H'CH=CHC), 2.04 - 1.93 (m, 3H, CH_2=CHC*H*$_2$(CH_2)$_5$, CHC*H*H'CHO), 1.89 - 1.75 (m, 2H, CH*H*'CH=CHC, NO_2CCH*H*'CHO), 1.69 - 1.55 (m, 1H, CHCH*H*'CHO), 1.53 - 1.45 (m, 3H, C*H*$_3$), 1.40 - 1.28 (m, 6H, C*H*$_3$, CH_2=CHCH$_2$C*H*$_2$, CCH=CHCH$_2$C*H*H'),1.23 - 1.06 (m, 5H, CCH=CHCH$_2$CH*H*', 2 x C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 148.1 (Ar*C*NO_2), 139.0 (CH_2=*C*H(CH_2)$_6$), 135.4 (C*C*H=CH), 134.1 (CH_2=*C*HCH$_2$N), 133.6 (Ar*C*H), 133.1 (*C*SO_2NH), 132.8 (Ar*C*H), 130.9 (*C*HCSO_2NH), 130.5 (CCH=*C*H), 125.3 (*C*HCNO_2CSO_2), 118.6 (*C*H_2=CHCH$_2$N), 114.2 (*C*H_2=CH(CH_2)$_6$), 108.5 (*C*(CH_3)$_2$), 88.1 (*C*NO_2), 71.7 (CHCH$_2$*C*HO), 70.7 (NO_2CCH$_2$*C*HO), 60.7 (CH_2=CH*C*H$_2$N), 57.3 (N*C*H$_2$CCH=CH), 55.7 (N*C*H$_2$CNO_2), 48.5 (*C*H$_2$NHSO_2), 41.9 (*C*CH=CH), 37.2 (NO_2C*C*H$_2$), 34.4 (NO_2C*C*H), 33.7 (CH_2=CH*C*H$_2$(CH_2)$_5$), 29.2, 29.1, 28.9, 28.9, 28.8, (5 x *C*H_2 (CH_2=CHCH$_2$(*C*H_2)$_5$)), 26.9 (*C*H_3), 25.0 (NO_2CCH*C*H$_2$) , 24.9 (*C*H_3); *m/z* (ESI$^+$) 647 (100%, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 669.2920, $C_{32}H_{46}N_4NaO_8S$ requires 669.2929.

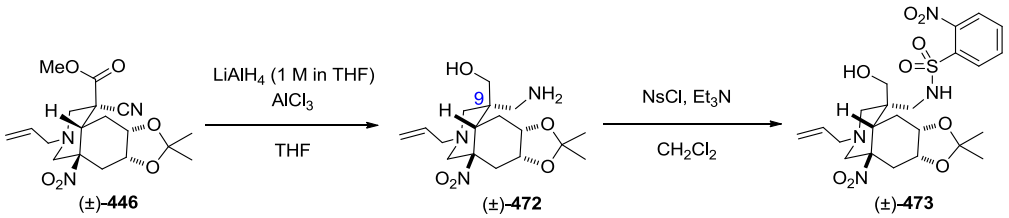
6.5.54. Synthesis of *rac*-Methyl (3a*R*,4a*R*,8*S*, 8a*S*,9a*S*)-6-allyl-8-cyano-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-446



To a solution of Michael adducts (**A**) (±)-**444a/b** (0.450 g, 1.51 mmol, **a**:**b** = 1.0:1.8) in MeOH (21 mL) was added allylamine **143** (0.100 g, 0.135 mL, 1.81 mmol); followed by formaldehyde **144** (37% solution in water) (2.45 g, 2.25 mL, 30.17 mmol) and the resulting colourless solution was refluxed for 6.5 h. The solution was cooled to RT and concentrated before being purified by column chromatography (Et_2O:PE 2:3) to give the title compound (±)-**446** (0.382 g, 67%) as a colourless oil: ν_{max}(film)/cm^{-1} 2985 (C-H), 1750 (C=O), 1548 (NO_2), 1382 (NO_2), 1251 (C-O), 1217 (C-O), 1059 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.78 (ddt, *J* =17.7, 9.8, 6.4 Hz, 1H, CH_2=C*H*), 5.30 - 5.19 (m, 2H, C*H*$_2$=CH), 4.27 (ddd, *J* = 7.6, 6.2, 6.0 Hz, 1H, $CHCH_2CHO$), 4.20 (ddd, *J* = 8.6, 6.0, 5.9 Hz, 1H, NO_2CCH_2CHO), 3.87 (s, 3H, OCH_3), 3.47 (dd, *J* = 9.6, 6.1 Hz, 1H, NO_2CCH), 3.17 - 3.11 (m, 2H, CH_2=CHC*H*$_2$), 3.09 (d, *J* = 12.6 Hz, 1H, NC*H*H'CNO_2), 3.00 (d, *J* = 12.6 Hz, 1H, NCH*H*'CNO_2), 2.98 (s, 2H, NC*H*$_2$CC≡N) 2.52 - 2.39 (m, 2H, NO_2CCHH', NO_2CCHCHH'), 2.30 (dd, *J* = 14.9, 8.6 Hz, 1H, NO_2CCHH'), 1.82 (ddd, *J* = 14.5, 9.6, 7.6 Hz, 1H, $NO_2CCHCHH$'), 1.53 (s, 3H, C*H*$_3$), 1.32 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.7 (*C*=O), 133.1 (CH_2=*C*H), 119.4 (*C*H_2=CH), 117.6 (*C*≡N), 109.2 (*C*$(CH_3)_2$), 89.2 (*C*NO_2), 71.5 (O*C*HCH_2CHCC≡N), 71.1 (O*C*HCH_2CNO_2), 59.8 (CH_2=CH*C*H_2), 58.3 (N*C*H_2CNO_2), 56.2 (N*C*H_2CC≡N),

54.2 (O*C*H_3), 48.9 (*C*C≡N), 36.6 (*C*HCC≡N), 35.3 (NO_2C*C*H_2), 28.2 (NO_2CCH*C*H_2), 27.7 (*C*H_3), 25.3 (*C*H_3); *m/z* (ESI$^+$) 781 (100%, $[2M+Na]^+$), 402 (98, $[M+Na]^+$), 380 (66, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 402.1636, $C_{18}H_{25}N_3NaO_6$ requires 402.1636.

6.5.55. Synthesis of *rac*-*N*-{[(3a*R*,4a*R*,8*S*,8a*S*,9a*S*)-6-allyl-8-(hydroxymethyl)-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-473

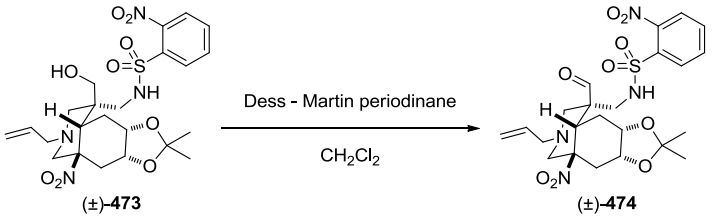


To a suspension of $AlCl_3$ (0.079 g, 0.60 mmol) in THF (1.6 mL) was added $LiAlH_4$ (1 M solution in THF) (1.79 mL, 1.79 mmol) and the resulting solution stirred at RT for 15 min. To this solution was added a solution of ester (±)-**446** (0.113 g, 0.298 mmol) in THF (1.6 mL) and the reaction mixture was stirred at RT for 5 h. The reaction mixture was then cooled to 0 °C and carefully quenched with 30% aq. KOH solution (10 mL) until effervescence ceased. Water (4 mL) was added and the product was extracted from the aqueous phase sequentially with CH_2Cl_2 (2 x 15 mL), $CHCl_3$ (2 x 15 mL) and $CHCl_3$:IPA (4:1) (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude aminol (±)-**472** (0.100 g) as a colourless oil which was used in the next step without further purification.

To a solution crude aminol (±)-**472** in CH_2Cl_2 (4 mL) cooled to 0 °C was added 2-nitrobenzenesulfonyl chloride (0.062 g, 0.28 mmol) and Et_3N (0.028 g, 0.039 mL, 0.28 mmol). The reaction mixture was warmed to RT and stirred for 3 h, before being concentrated and purified by column chromatography (Et_2O:PE 3:1→4:1) to give the title compound (±)-**473** (0.105 g, 65% over two steps) as a colourless oil: ν_{max}(film)/cm^{-1} 3295 (O-H), 2984 (C-H), 1538 (NO_2), 1347 (SO_2), 1345 (NO_2), 1166 (SO_2), 1057 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (dd, *J* = 5.8, 3.3 Hz, 1H, C*H*CSO_2), 7.97 - 7.78 (m, 1H, Ar*H*), 7.78 - 7.67 (m, 2H, 2 x Ar*H*), 6.83 (dd, *J* = 7.8, 1.8 Hz, 1H,

N*H*SO_2), 5.71 (ddt, *J* = 16.8, 10.5, 6.3 Hz, 1H, CH_2=C*H*CH_2), 5.23 - 5.06 (m, 2H, C*H*$_2$=$CHCH_2$), 4.47 (ddd, *J* = 8.5, 6.9, 6.8 Hz, 1H, $CHCH_2$C*H*O), 4.28 (ddd, *J* = 9.1, 5.6, 5.4 Hz, 1H, NO_2CCH_2C*H*O), 3.73 (d, *J* = 13.4 Hz, 1H, NC*H*H'CNO_2), 3.63 (d, *J* = 12.4 Hz, 1H, C*H*H'OH), 3.35 - 3.16 (m, 2H, CH*H*'OH, C*H*H'$NHSO_2$), 3.07 (d, *J* = 13.4 Hz, 1H, C*H*CNO_2), 3.02 - 2.87 (m, 2H, CH_2=CHC*H*$_2$), 2.68 (dd, *J* = 11.9, 1.8 Hz, 1H, CH*H*'$NHSO_2$), 2.51 (br. s., 1H, CH_2O*H*), 2.47 - 2.36 (m, 2H, NCH*H*'CNO_2, NO_2CCHC*H*H'), 2.26 (d, *J* = 11.8 Hz, 1H, NC*H*H'CCH_2OH), 2.08 (dd, *J* = 15.2, 4.8 Hz, 1H, NO_2CC*H*H'), 1.96 (d, *J* = 11.8 Hz, 1H, NCH*H*'CCH_2OH), 1.83 (dd, *J* = 15.2, 9.1 Hz, 1H, NO_2CCH*H*'), 1.51 - 1.37 (m, 4H, C*H*$_3$, NO_2CCHCH*H*'), 1.31 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.2 (Ar*C*NO_2), 133.9 (CH_2=*C*HCH_2), 133.7 (Ar*C*H), 132.8 (*C*SO_2NH), 132.7 (Ar*C*H), 131.0 (*C*HCSO_2NH), 125.4 (*C*$HCNO_2CSO_2$), 118.5 (*C*H_2=$CHCH_2$), 109.2 (*C*$(CH_3)_2$), 89.7 (*C*NO_2), 73.9 ($CHCH_2$*C*HO), 71.0 (NO_2CCH_2*C*HO), 68.7 (*C*H_2OH), 60.5 (CH_2=CH*C*H_2), 56.9 (N*C*H_2CNO_2), 54.4 (N*C*H_2CCH_2OH), 50.2 (*C*H_2NHSO_2), 40.2 (*C*CH_2OH), 38.4 (NO_2C*C*H_2), 32.3 (NO_2C*C*H), 27.8 (*C*H_3), 25.3 (NO_2CCHCH_2), 25.3 (*C*H_3); *m/z* (ESI$^+$) 563 (48%, $[M+Na]^+$), 541 (100, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+H]^+$ 541.1956, $C_{23}H_{33}N_4O_9S$ requires 541.1963.

6.5.56. Synthesis of *rac*-*N*-{[(3a*R*,4a*R*,8*S*,8a*S*,9a*S*)-6-allyl-8-formyl-2,2-dimethyl-4a-nitrodecahydro[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-474

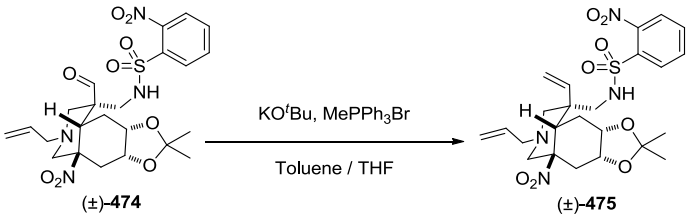


(±)-**473** (±)-**474**

To a solution of alcohol (±)-**473** (0.110 g, 0.203 mmol) in CH_2Cl_2 (8 mL) cooled to 0 °C was added Dess-Martin periodinane (0.091 g, 0.215 mmol). The resulting solution was stirred at 0 °C for 3 h before being concentrated under reduced pressure and purified by column chromatography (Et_2O:PE 9:2→9:1) to give the title compound (±)-**474** (0.090 g, 82%) as a colourless solid: R_f = 0.31 (Et_2O); mp 174-178 °C (CH_2Cl_2); ν_{max}(film)/cm^{-1} 2987 (C-H), 1716 (C=O), 1539 (NO_2), 1353 (NO_2), 1168 (SO_2), 1057 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.50 (s, 1H, *H*C=O), 8.11 - 8.01 (m, 1H, C*H*CSO_2), 7.93 - 7.82 (m, 1H, C*H*CNO_2CSO_2), 7.82 - 7.71 (m, 2H, 2 x Ar*H*), 6.15 (dd, *J* = 7.1, 4.5 Hz, 1H, N*H*SO_2), 5.87 - 5.61 (m, 1H, CH_2=C*H*CH_2), 5.29 - 5.12 (m, 2H, C*H*$_2$=CHCH_2), 4.37 (ddd, *J* = 8.2, 6.8, 6.7 Hz, 1H, NO_2CCHCH_2C*H*O), 4.30 - 4.14 (m, 1H, NO_2CCH_2C*H*O), 3.65 (d, *J* = 13.4 Hz, 1H, NC*H*H'CNO_2), 3.20 (dd, *J* = 12.3, 8.7 Hz, 1H, C*H*H'$NHSO_2$), 3.14 - 2.97 (m, 3H, C*H*CNO_2, CH_2=CHC*H*$_2$), 2.90 – 2.80 (m, 2H, CH*H*'$NHSO_2$, NC*H*H'CCHO), 2.70 (d, *J* = 13.4 Hz, 1H, NCH*H*'CNO_2), 2.38 - 2.22 (m, 2H, NCH*H*'CCHO, NO_2CCHC*H*H'), 2.17 (dd, *J* = 15.2, 4.8 Hz, 1H, NO_2CC*H*H'), 2.02 (dd, *J* = 15.2, 7.3 Hz, 1H, NO_2CCH*H*'), 1.56 - 1.40 (m, 4H, C*H*$_3$, NO_2CCHCH*H*'), 1.31 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 205.2 (H*C*=O), 148.1 (Ar*C*NO_2), 134.0 (Ar*C*H), 133.4 (CH_2=*C*HCH_2), 132.8 (Ar*C*H), 132.5 (*C*SO_2NH), 130.9 (*C*HCSO_2NH), 125.6 (*C*HNO_2CSO_2), 119.2 (*C*H_2=CHCH_2), 109.2 (*C*$(CH_3)_2$),

89.3 (*C*NO_2), 73.1 (NO_2CCHCH_2*C*HO), 71.1 (NO_2CCH_2*C*HO), 60.4 (CH_2=CH*C*H_2), 56.3 (N*C*H_2CNO_2), 52.2 (N*C*H_2CCHO), 49.7 (*C*CHO), 45.3 (*C*H_2NHSO_2), 37.3 (NO_2C*C*H_2), 35.2 (NO_2C*C*H), 28.0 (*C*H_3), 25.4 (*C*H_3), 24.8 (NO_2CCHCH_2); *m/z* (ESI^-) 537 (100%, $[M-H]^-$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 561.1624, $C_{23}H_{30}N_4NaO_9S$ requires 561.1626.

6.5.57. Synthesis of *rac*-*N*-{[(3a*R*,4a*R*,8*R*,9a*S*)-6-allyl-2,2-dimethyl-4a-nitro-8-vinyldecahydro [1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-475



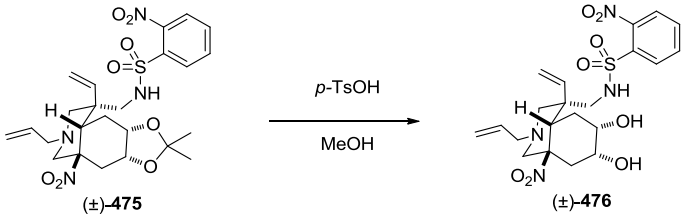
(±)-**474** (±)-**475**

[Preparation of Ylide solution: KO^{t}Bu (0.089 g, 0.79 mmol) was added to MePPh$_3$Br (0.385 g, 1.08 mmol) in toluene (6 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at RT].

Aldehyde (±)-**474** (0.090 g, 0.167 mmol) was dissolved in THF (6 mL) and the solution added rapidly to the freshly prepared ylide solution at RT. After stirring the reaction mixture at this temperature for 0.5 h, water (35 mL) was added and THF/toluene were removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (Et_2O:PE 9:2→Et_2O) to yield the title compound (±)-**475** (0.080 g, 89%) as a colourless oil: R_f = 0.56 (Et_2O:PE 9:2); ν_{max}(film)/cm^{-1} 2985 (C-H), 1538 (NO_2), 1416 (SO_2), 1354 (NO_2), 1166 (SO_2), 1057 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.10 (dd, *J* = 5.4, 3.4 Hz, 1H, C*H*CSO_2), 7.93 - 7.82 (m, 1H, C*H*CNO_2CSO_2), 7.80 – 7.73 (m, 2H, 2 x Ar*H*), 5.91 – 5.76 (m, 1H, CH_2=C*H*CH_2), 5.51 (dd, *J* = 17.3, 11.2 Hz, 1H, CH_2=C*H*C), 5.38 (br. s., 1H, N*H*SO_2), 5.31 - 5.10 (m, 4H, C*H*$_2$=CHCH_2, C*H*$_2$=CHC), 4.38 - 4.16 (m, 2H, 2 x CH_2C*H*O), 3.47 (d, *J* = 13.4 Hz, 1H, NC*H*H'CNO_2), 3.14 - 2.94 (m, 3H, C*H*H'NHSO_2,CH_2=CHC*H*$_2$), 2.89 (dd, *J* = 11.1, 3.0 Hz, 1H, CH*H*'NHSO_2), 2.83 – 2.69 (m, 2H, C*H*CNO_2,

NC*H*H'CCH=CH_2), 2.57 (d, *J* = 13.4 Hz, 1H, NCH*H*'CNO_2), 2.23 - 2.04 (m, 3H, NCH*H*'CCH=CH_2, NO_2CC*H*H', NO_2CCHC*H*H'), 1.93 (dd, *J* = 15.3, 7.2 Hz, 1H, NO_2CCH*H*'), 1.55 (ddd, *J* = 13.3, 13.2, 8.8 Hz, 1H, NO_2CCHCH*H*'), 1.46 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.1 (Ar*C*NO_2), 139.6 (CH_2=*C*HC), 133.9 (CH_2=*C*HCH_2), 133.8 (Ar*C*H), 133.0 (Ar*C*H), 132.8 (*C*SO_2NH), 131.1 (*C*HCSO_2NH), 125.4 (Ar*C*HCNO_2), 118.7 (*C*H_2=CH), 118.4 (*C*H_2=CH), 109.1 (*C*$(CH_3)_2$), 88.5 (*C*NO_2), 73.3 (CH_2*C*HO), 71.2 (CH_2*C*HO), 60.8 (CH_2=CH*C*H_2), 56.1 (N*C*H_2CNO_2), 54.1 (N*C*H_2CCH=CH_2), 48.5 (*C*H_2NHSO_2), 42.8 (*C*CH=CH_2), 38.7 (NO_2C*C*H), 37.9 (NO_2C*C*H_2), 28.0 (*C*H_3), 25.5 (NO_2CCHC*H*$_2$), 25.3 (*C*H_3); *m/z* (ESI$^-$) 535 (100%, $[M-H]^-$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 559.1829, $C_{24}H_{32}N_4NaO_8S$ requires 559.1833.

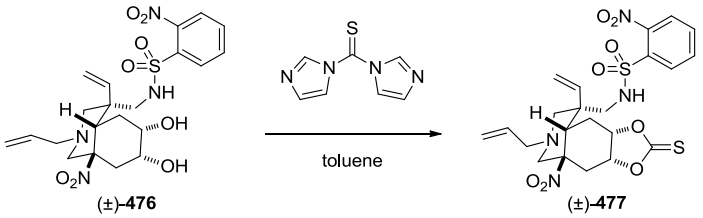
6.5.58. Synthesis of *rac*-*N*-{[(4*R*,4a*S*,6*S*,7*R*,8a*R*)-2-allyl-6,7-dihydroxy-8a-nitro-4-vinyldecahydroisoquinolin-4-yl]methyl}-2-nitrobenzenesulfonamide (±)-476



To a solution of sulfonamide (±)-**475** (0.080 g, 0.149 mmol) in MeOH (5 mL) was added *p*-TsOH (0.030 g, 0.157 mmol) and the resulting solution was refluxed for 5 h. After this time the reaction mixture was concentrated under reduced pressure and water (10 mL) was added to the crude residue. The resulting aqueous suspension was basified (solid K_2CO_3) and the product was extracted with CH_2Cl_2 (5 x 15 mL). The combined organics were dried ($MgSO_4$) before being concentrated under reduced pressure to give the title compound (±)-**476** (0.065 g, 88%) as a colourless solid which was sufficiently pure to be used without further purification: R_f = 0.38 (EtOAc); mp 109-111 °C (CH_2Cl_2); ν_{max}(film)/cm^{-1} 3496, 3402, 3320 (O-H), 2922 (C-H), 1550 (NO_2), 1537 (NO_2) 1368 (NO_2), 1333 (SO_2), 1171 (SO_2), 1060 (C-O); ^{1}H NMR (400MHz, CD_3CN) δ_H 8.10 - 7.96 (m, 1H, C*H*CSO_2), 7.76 - 7.91 (m, 3H, 3 x Ar*H*), 5.89 - 5.73 (m, 1H, CH_2=C*H*CH_2), 5.54 - 5.32 (m, 2H, CH_2=C*H*C, N*H*SO_2), 5.22 - 5.05 (m, 3H, C*H*$_2$=CHCH_2, C*H*H=CHC), 5.04 – 4.97 (m, 1H, CH*H*=CHC), 3.82 (d, *J* = 2.4 Hz, 1H, NO_2CCH_2C*H*OH), 3.72 - 3.61 (m, 1H, $CHCH_2$C*H*OH), 3.29 (d, *J* = 13.7 Hz, 1H, NC*H*H'CNO_2), 3.12 (br. s., 1H, NO_2CCH_2CHO*H*), 3.05 (d, *J* = 5.5 Hz, 1H, $CHCH_2CHO$*H*), 3.02 - 2.82 (m, 6H, CH_2=CHC*H*$_2$, C*H*$_2$NHSO_2, NCH*H*'CNO_2, C*H*CNO_2), 2.75 (d, *J* = 11.9 Hz, 1H, NC*H*H'CCH=CH_2), 2.05 - 1.88 (m, 3H, NO_2CC*H*$_2$CHOH, NCH*H*'CCH=CH_2), 1.71 - 1.59 (m, 2H, NO_2CCHC*H*$_2$); ^{13}C NMR (125 MHz,

CD_3CN) δ_C 148.0 (Ar*C*NO_2), 140.7 (CH_2=*C*HC), 135.1 (CH_2=*C*HCH_2), 134.3 (Ar*C*H), 133.0 (Ar*C*H), 132.2 (*C*SO_2NH), 130.8 (*C*HCSO_2NH), 125.1 (*C*HCNO_2CSO_2), 117.3 (*C*H_2=$CHCH_2$), 116.8 (*C*H_2=CHC), 90.0 (*C*NO_2), 69.4 ($CHCH_2$*C*HOH), 67.6 (NO_2CCH_2*C*HOH), 60.6 (CH_2=CH*C*H_2), 54.1 (N*C*H_2CNO_2), 52.4 (N*C*H_2CCH=CH_2), 48.8 (*C*H_2NHSO_2), 43.2 (*C*CH=CH_2), 42.3 (NO_2*C*CH_2), 40.8 (NO_2*C*CH), 25.4 (NO_2CCH*C*H_2); *m/z* (ESI^+) 519 (55%, $[M+Na]^+$), 497 (100, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 519.1524, $C_{21}H_{28}N_4NaO_8S$ requires 519.1520.

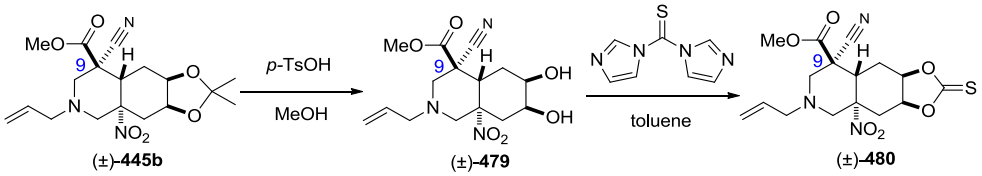
6.5.59. Synthesis of *rac*-*N*-{[(3a*R*,4a*R*,8*R*,8a*S*,9a*S*)-6-allyl-4a-nitro-2-thioxo-8-vinyldecahydro[1,3]dioxolo[4,5-*g*]isoquinolin-8-yl]methyl}-2-nitrobenzenesulfonamide (±)-477



To a solution of diol (±)-**476** (0.020 g, 0.040 mmol) in toluene (1 mL) was added 1,1'-thiocarbonyldiimidazole (0.014 g, 0.079 mmol) and the reaction mixture was stirred at reflux for 5 h. A second portion of 1,1'-thiocarbonyldiimidazole (0.012 g, 0.067 mmol) was added and heating continued for 2 h. The reaction mixture was concentrated before being purified by column chromatography (EtOAc:PE 7:3) to give the title compound (±)-**477** (0.020 g, 92%) as a colourless solid: mp 188-193 °C (EtOAc); ν_{max}(film)/cm^{-1} 2961 (C-H), 1542 (NO_2), 1344 (NO_2), 1278 (C=S), 1169 (SO_2); ^{1}H NMR (500 MHz, CD_3CN) δ_H 8.12 - 7.99 (m, 1H, C*H*CSO_2), 7.91 - 7.75 (m, 3H, 3 x Ar*H*), 5.82 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H, CH_2=C*H*CH_2), 5.56 - 5.46 (m, 2H, CH_2=C*H*C, N*H*SO_2), 5.28 - 5.07 (m, 6H, C*H*$_2$=CHCH_2, C*H*$_2$=CHC, CHCH_2C*H*O, NO_2CCH_2C*H*O), 3.53 (d, *J* = 13.6 Hz, 1H, NC*H*H'CNO_2), 3.06 - 2.92 (m, 4H, CH_2=CHC*H*$_2$, C*H*$_2$NHSO_2), 2.79 – 2.72 (m, 2H, C*H*CNO_2, NC*H*H'CCH=CH_2), 2.43 - 2.35 (m, 2H, NO_2CCHC*H*H', NCH*H*'CNO_2), 2.31 (dd, *J* = 15.4, 5.4 Hz, 1H, NO_2CC*H*H'), 2.17 - 2.03 (m, 2H, NCH*H*'CCH=CH_2, NO_2CCH*H*'), 1.68 (td, *J* = 13.6, 9.6 Hz, 1H, NO_2CCHCH*H*'); ^{13}C NMR (125 MHz, CD_3CN) δ_C 192.5 (*C*=S), 149.1 (Ar*C*NO_2), 141.3 (CH_2=*C*HC), 135.6 (CH_2=*C*HCH_2), 135.4 (Ar*C*H), 134.1 (Ar*C*H), 133.1 (*C*SO_2NH), 131.9 (*C*HCSO_2NH), 126.2 (*C*HCNO_2CSO_2), 118.9 (*C*H_2=CH), 118.7 (*C*H_2=CH), 88.0 (*C*NO_2), 81.1 (CHCH_2*C*HO), 78.8

(NO_2CCH_2CHO), 61.2 ($CH_2=CHCH_2$), 56.3 (NCH_2CNO_2), 54.7 ($NCH_2CCH=CH_2$), 49.8 (CH_2NHSO_2), 43.5 ($CCH=CH_2$), 38.8 (NO_2CCH), 36.4 (NO_2CCH_2), 24.2 (NO_2CCHCH_2); *m/z* (ESI^+) 561 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 561.1090, $C_{22}H_{26}N_4NaO_8S_2$ requires 561.1084.

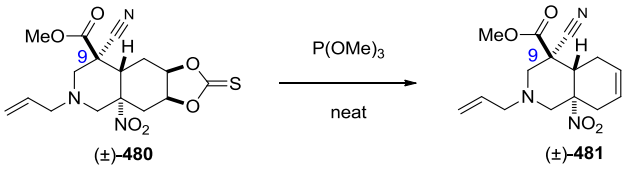
6.5.60. Synthesis of methyl *rac*-(3a*S*,4a*S*,8*S*,8a*S*,9a*R*)-6-allyl-8-cyano-4a-nitro-2-thioxodecahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (±)-480



To a solution of protected diol (±)-**445b** (0.255 g, 0.672 mmol) in methanol (23 mL) was added p-TsOH (0.134 g, 0.706 mmol) and the reaction mixture was stirred at reflux for 6 h. The reaction mixture was concentrated under reduced pressure and water (20 mL) was added to the crude residue. The resulting aqueous suspension was basified (solid K_2CO_3) and the product was extracted with CH_2Cl_2 (5 x 20 mL). The combined organics were dried ($MgSO_4$) before being concentrated under reduced pressure to give the crude diol (±)-**479** (0.240 g) as a colourless oil. To a solution of diol (±)-**479** (0.110 g, 0.324 mmol) in toluene (5 mL) was added 1,1'-thiocarbonyldiimidazole (0.116 g, 0.651 mmol) and the reaction mixture was stirred at reflux for 5 h. The reaction mixture was cooled to RT and diluted with EtOAc (30 mL). The solution was washed with water (20 mL) and brine (20 mL) and the organics dried ($MgSO_4$) and concentrated before being purified by column chromatography (Et_2O:PE 1:1→3:2) to give the title compound (±)-**480** (0.063 g, 51%) as a colourless foam: R_f = 0.39 (Et_2O:PE 3:2); ν_{max}(film)/cm^{-1} 2958 (C-H), 1734 (C=O), 1547 (NO_2), 1359 (NO_2), 1280 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.88 - 5.74 (m, 1H, CH_2=C*H*CH_2), 5.30 – 5.23 (m, 2H, C*H*$_2$=CHCH_2), 5.19 (dd, *J* = 5.3, 5.3 Hz, 1H, $CHCH_2$C*H*O), 4.99 (ddd, *J* = 9.9, 6.6, 6.6 Hz, 1H, NO_2CCH_2C*H*O), 3.90 (s, 3H, OC*H*$_3$), 3.75 (dd, *J* = 12.9, 1.4 Hz, 1H, NC*H*H'CNO_2), 3.44 (dd, *J* = 11.6, 1.5 Hz, 1H,

NC*H*H'CC≡N), 3.19 (d, *J* = 6.5 Hz, 2H, CH_2=CHC*H*$_2$), 2.92 (ddd, *J* = 15.5, 13.0, 4.9 Hz, 1H, CHC*H*H'CHO), 2.72 - 2.56 (m, 3H, NO_2CC*H*H', NCH*H*'CC≡N, NO_2CC*H*), 2.41 (dd, *J* = 15.5, 4.9 Hz, 1H, CHCH*H*'CHO), 2.28 (d, *J* = 12.9 Hz, 1H, NCH*H*'CNO_2), 1.79 (dd, *J* = 14.7, 9.9 Hz, 1H, NO_2CCH*H*'); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 190.4 (*C*=S), 166.3 (*C*=O), 132.7 (CH_2=*C*HCH_2), 119.7 (*C*H_2=CHCH_2), 115.3 (*C*≡N), 84.5 (*C*NO_2), 79.5 (CHCH_2*C*HO), 76.0 (CCH_2*C*HO), 59.7 (N*C*H_2CNO_2), 59.5 (CH_2=CH*C*H_2), 59.5 (N*C*H_2CC≡N), 54.5 (O*C*H_3), 48.1 (*C*C≡N), 39.6 (NO_2CC*H*), 35.3 (NO_2C*C*H_2), 25.2 (NO_2CCH*C*H_2); *m/z* (ESI$^+$) 404 (100%, $[M+Na]^+$), 382 (8, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 404.0872, $C_{16}H_{19}N_3NaO_6S$ requires 404.0887.

6.5.61. Synthesis of methyl *rac*-(4*S*,4a*S*,8a*S*)-2-allyl-4-cyano-8a-nitro-1,2,3,4,4a,5,8,8a-octahydroisoquinoline-4-carboxylate (±)-481



(±)-**480** (±)-**481**

Compound (±)-**480** (0.060 g, 0.157 mmol) was dissolved in $P(OMe)_3$ (3 mL) and the solution was heated at 110 °C for 8 h before being concentrated and purified by column chromatography (Et_2O:PE 1:1) to give the title compounds (±)-**481** (0.038 g, 79%) as a colourless oil: R_f = 0.52 (Et_2O:PE 3:2); ν_{max}(film)/cm^{-1} 3010 (=C-H), 2920 (C-H), 1740 (C=O), 1547 (NO_2), 1344 (NO_2), 1250 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) 5.84 – 5.69 (m, 2H, CH_2=C*H*CH_2, $CHCH_2$C*H*=CH), 5.54 (ddd, *J* = 10.1, 5.4, 2.0 Hz, 1H, $CHCH_2$CH=C*H*), 5.28 - 5.16 (m, 2H, C*H*$_2$=$CHCH_2$), 3.88 (s, 3H, OC*H*$_3$), 3.79 (dd, *J* = 12.9, 1.8 Hz, 1H, NC*H*H'CNO_2), 3.46 (dd, *J* = 11.6, 2.0 Hz, 1H, NC*H*H'C≡N), 3.10 (dd, *J* = 6.3, 0.8 Hz, 2H, CH_2=CHC*H*$_2$), 2.97 – 2.85 (m, 1H, NO_2CCHC*H*H'), 2.76 (dd, *J* = 18.2, 5.4 Hz, 1H, NO_2CC*H*H'), 2.59 (dd, *J* = 11.4, 6.6 Hz, 1H, NO_2CC*H*), 2.54 (d, *J* = 11.6 Hz, 1H, NCH*H*'CC≡N), 2.36 (d, *J* = 18.2 Hz, 1H, NO_2CCH*H*'), 2.24 (d, *J* = 12.9 Hz, 1H, NCH*H*'CNO_2), 2.24 - 2.13 (m, 1H, NO_2CCHCH*H*'); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.8 (*C*=O), 133.1 (CH_2=*C*HCH_2), 126.5 ($CHCH_2$*C*H=CH), 120.6 ($CHCH_2CH$=*C*H), 119.3 (*C*H_2=$CHCH_2$), 117.2 (*C*≡N), 85.0 (*C*NO_2), 61.6 (N*C*H_2CNO_2), 60.4 (N*C*H_2CC≡N), 59.8 (CH_2=CH*C*H_2), 54.2 (OC*H*$_3$), 48.3 (*C*C≡N), 41.4 (NO_2C*C*H), 35.4 (NO_2C*C*H_2), 25.9 (NO_2CCHC*H*$_2$); *m/z* (ESI$^+$) 328 (100%, $[M+Na]^+$), 306 (70, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 328.1258, $C_{15}H_{19}N_3NaO_4$ requires 328.1268.

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