Rhodium-Catalysed Hydroacylation Reactions in the Synthesis of Heterocycles

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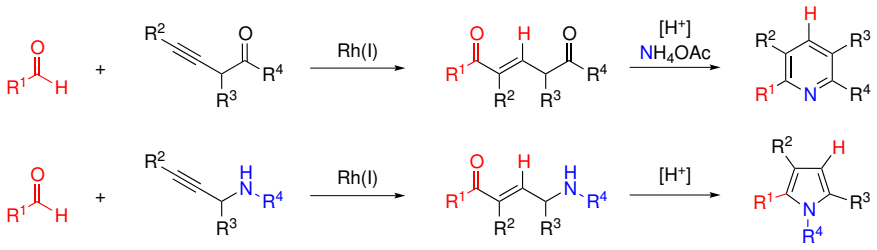
Abstract

Rhodium-catalysed hydroacylation provides a highly atom economic synthesis of ketone products from the combination of aldehydes and multiple bond systems by C-H bond activation. This work evaluates the combination of intermolecular hydroacylation for the synthesis of classical heterocycle precursors and their dehydrative cyclisation to give rise to a range of substituted heterocyclic compounds (Scheme 1).



Scheme 1: A hydroacylation approach for the synthesis of heterocycles.

Chapter 1 outlines recent developments in the chemistry of hydroacylation. Particular attention is paid to the various chelation strategies employed in intermolecular hydroacylation. Chapter 2 discusses some relevant and recent developments in the field of pyridine and pyrrole synthesis.

Having established that β-sulphur chelation controlled hydroacylation can be used to synthesise pyridines in Chapter 3; attention was turned to hydroacylation of propargyl amines in Chapter 4. The methodology was expanded to provide a synthesis of γ-amino enones. The hydroacylation reaction and cyclisation is combined in a procedure that utilises thermal Boc-deprotection and cyclisation to give a range of highly-substituted pyrroles.

The regioselectivity of the hydroacylation of propargyl amines is investigated in Chapter 5 by application of statistical Design of Experiments methodology. Optimised conditions were identified with minor improvements in the selectivity of the reaction.

Acknowledgements

I would like to thank Dr. Michael Willis for the opportunity to carry out this research and for help and guidance throughout my three years and seven months in CRL, F2. I would also like to thank my industrial supervisor, Dr. Catherine Howsham, for her insight and for the signing of endless risk assessments. I hope the thioether chemistry hasn't made a lasting impression on the labs at Novartis.

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Finally, I thank my beautiful wife Kate for her patience, support and acting as a complete life-support system, providing an endless supply of cakes while I've been writing. Without her, this would have been an unbearable ordeal.

Contents

List of Abbreviations

2D	2-dimensional
Å	Ångstrom
μW	microwave
acac	acetylacetonate
Ar	aryl
$[BAr_4^F]^-$	$[B(3,5\text{-}CF_{32}C_6H_3)_4]^-$
BINAP	2,2-bis(diphenylphosphanyl)-1,1-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc-ON	2-(Boc-oxyimino)-2-phenylacetonitrile
Bra	branched
Bu	butyl
cat	catalytic
CBz	benzyloxycarbonyl
CI	chemical ionization
cod	cyclooctadiene
coe	cyclooctene
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl

Davephos	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dcpm	dicyclohexylphosphinomethane
DEPT	Distortionless Enhancement by Polarization Transfer
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DPEphos	bis(2-diphenylphosphine)-phenyl ether
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppf	diphenylphosphinoferrocene
dppm	diphenylphosphinomethane
dppp	diphenylphosphinopropane
E	entgegen
ee	enantiomeric excess
equiv.	equivalents
e.r.	enantiomeric ratio
ESI	electrospary ionization
Et	ethyl
FI	field ionization
Fmoc	9-fluorenylmethoxycarbonyl
FT	fourier transform
GC	gas chromatography

HA	hydroacylation
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	high performance liquid chromatography
hr	hour(s)
HRMS	high resolution mass spectrometry
Hydrog.	hydrogenation
ID	inner diameter
i-Pr	*iso*-propyl
IR	infra-red
isol.	isolated
J	coupling constant J in Hz
LC	liquid chromatography
Lin	linear
Me	methyl
min	minute(s)
M	molar, moles per litre
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
MS	molecular sieves
MTM	methylthiomethyl
MW	molecular weight
m/z	mass to charge ratio
nbd	norbornadiene
n-Bu	*normal*-butyl
nd	none detected

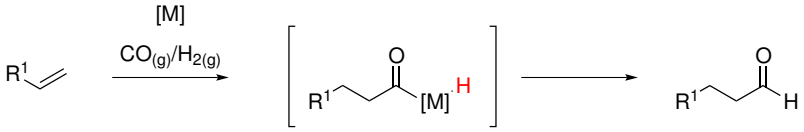
n-Hex	*normal*-hexyl
n-Pr	*normal*-propyl
NMR	nuclear magnetic resonance
PC	propylene carbonate
PCP	1,1-bis(diphenylphosphino)pentane
Ph	phenyl
ppm	parts per million
psi	pounds per square inch
p-TSA	*para*-toluene sulfonic acid
quant.	quantitative
rt	room temperature
s	selectivity factor for kinetic resolutions, s = k_f/k_s
SM	starting material
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TCE	trichloroethane
Tf	trifluoromethanesulfonic
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet
W	watt(s)
X	generic halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	zusammen

Chapter 1

Rhodium-Catalysed Hydroacylation

1.1 Introduction

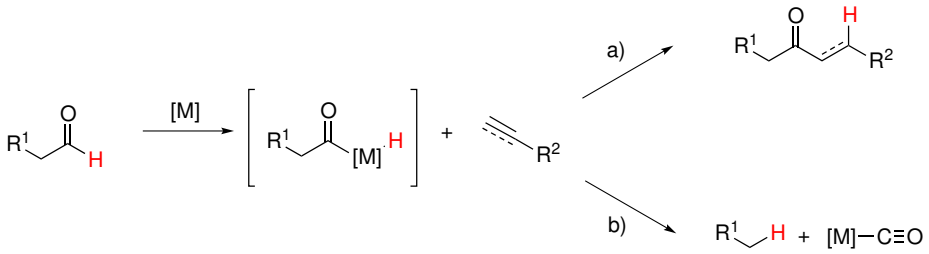
Hydroformylation is an important homogenenous transition metal-catalysed process for the manufacture of aldehydes from alkenes, carbon monoxide and hydrogen (Scheme 1.1).[1–3] This process is the principle use of rhodium in chemical synthesis.[1]



Scheme 1.1: Synthesis of aldehydes by hydroformylation

A process related to hydroformylation is hydroacylation, where aldehydes are converted to ketones *via* highly atom economic[4] C-H activation. C-H activation reactions are of increasing importance in organic synthesis.[5] Hydroacylation is the addition of an acyl unit and a hydrogen atom across an unsaturated bond and is an attractive example of C-H activation as it makes use of umpolung reactivity,

allowing unconventional retrosynthetic disconnections. Both intramolecular[6,7] and intermolecular examples of hydroacylation have been reported using a variety of catalytic species, most commonly rhodium but also ruthenium[8–12] and cobalt.[13–17] Hydroacylation reactions are complicated by decarbonylation of the aldehyde substrate resulting in formation of a stable rhodium-carbonyl complex; this deactivates the catalyst and reduces the starting material (Scheme 1.2).[18] The area of hydroacylation has been subject to a recent review by Willis.[19]

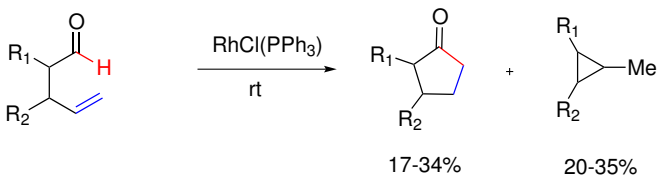


Scheme 1.2: a) hydroacylation; b) decarbonylation

1.2 Intramolecular Hydroacylation

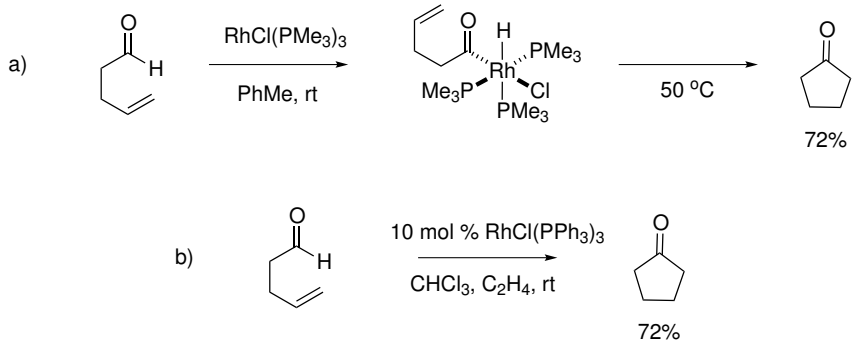
1.2.1 Synthesis of Cyclopentanones

The early examples of rhodium-catalysed hydroacylation were cyclopentanone syntheses. The first example reported by Sakai in 1972 used stoichiometric rhodium (Scheme 1.3).[20] The cyclopentanones were isolated as a mixture with cyclopropanes resulting from decarbonylation of the starting material. This side reaction is a known catalytic reaction facilitated by rhodium[10,18,21,22] and iridium.[23,24]



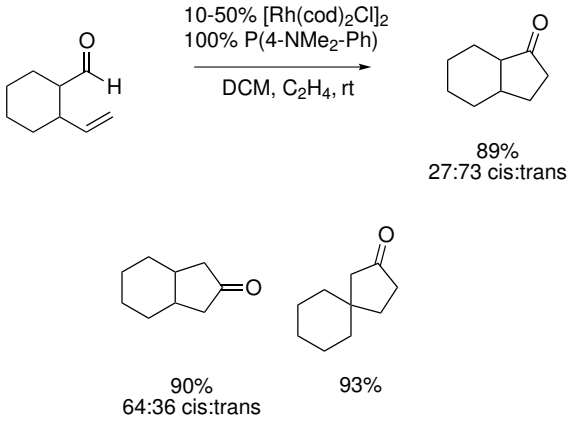
Scheme 1.3: First example of hydroacylation by Sakai.

The intramolecular hydroacylation of 4-pentenals was developed further by Milstein. Using stoichiometric $Rh(PMe_3)_3Cl$, he isolated a rhodium acyl species that gave the cyclopentanone when heated in toluene.[25] Miller found that Wilkinson's catalyst could be used in sub-stoichiometric amounts provided that ethene saturated solvent was used to suppress the decarbonylation pathway (Scheme 1.4).[26–28]



Scheme 1.4: a) Milstein; b) Miller

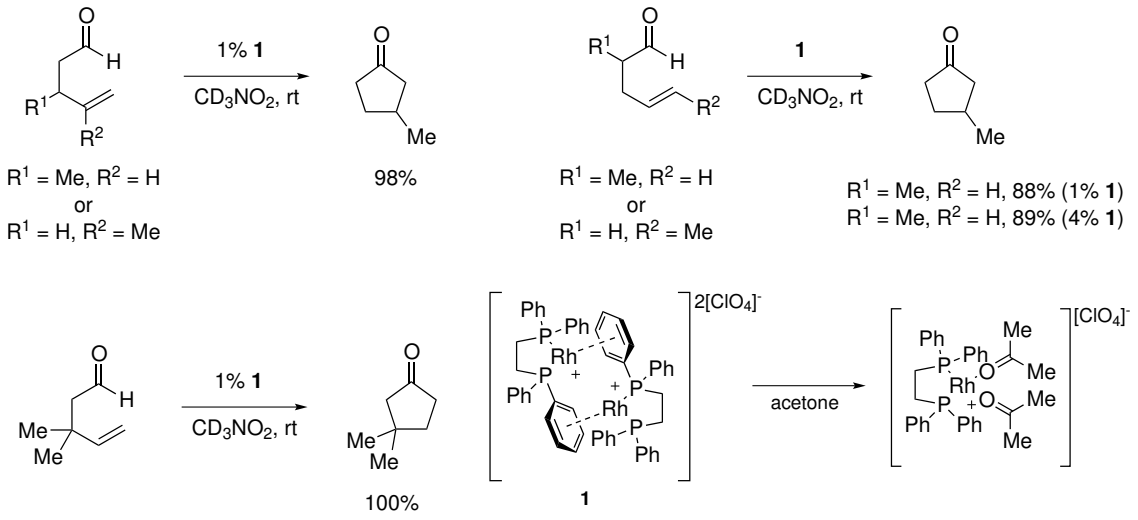
Extensive catalyst optimisation of rhodium chloride tertiary phosphine complexes by Larock allowed a wider scope of cyclopentanones to be synthesised. Again, the authors carried out the reaction in ethene saturated solvent and employed high loadings of catalyst and ligand (Scheme 1.5).[29]



Scheme 1.5: Fused and spirocyclic cyclopentanones by Larock.

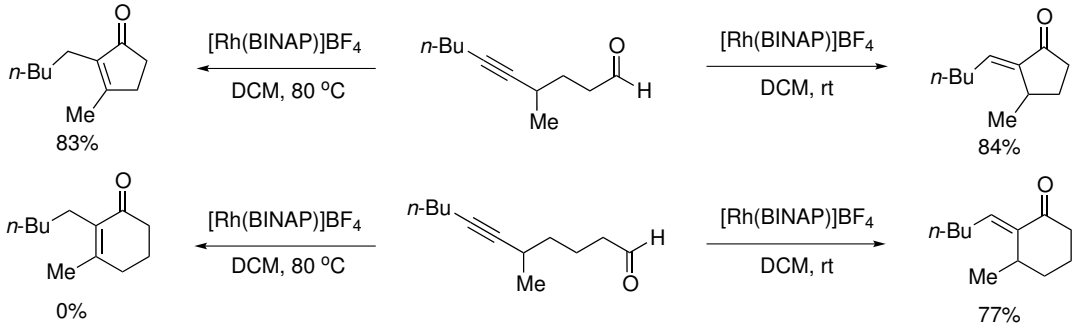
The work by Miller and Larock led to considerable development by Bosnich in the cyclisation of a large variety of 4-pentenals. Bosnich and Fairlie pioneered the use of

cationic $[Rh(dppe)]ClO_4$ catalysts formed *in situ* from $[Rh(dppe)]_2(ClO_4)_2$ **1** which allowed low catalyst loadings to be used for the synthesis of a range of cyclopentanones (Scheme 1.6).[6] Phenyl terminated alkenes could also be synthesised in 70% yield at a 65 °C employing 10 mol % of the same catalyst. Fu and Tanaka used 4-alkynals with these cationic catalysts for the synthesis of cyclopentenones.[30–32]



Scheme 1.6: Synthesis of cyclopentanones using cationic $[Rh(dppe)_2]_2ClO_4$.

The Tanaka group found that intramolecular hydroacylation of 4- and 5-alkynals at room temperature lead to the exo-methylene products. At a higher reaction temperature, the authors noted that the double bond is in some cases isomerised by a rhodium catalysed process i to give the cyclopentenone or cyclohexenone products.[33]

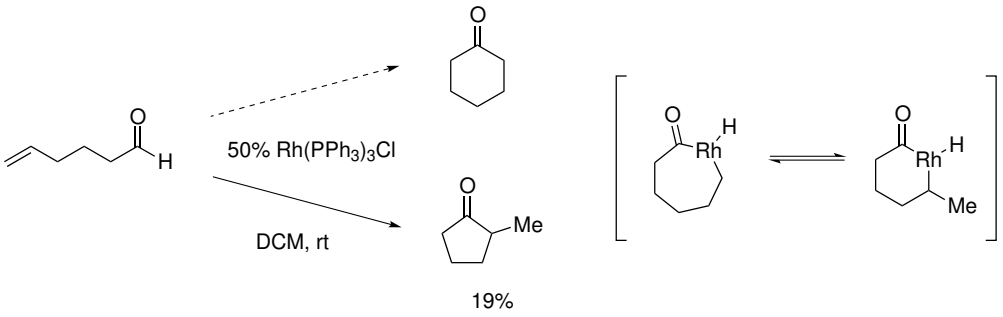


Scheme 1.7: Hydroacylation of 4- and 5-alkynals and isomerisation.

The area of cyclopentanone and cyclopentenone synthesis is the most investigated area of hydroacylation, which has been recently reviewed and discussed in detail.[19]

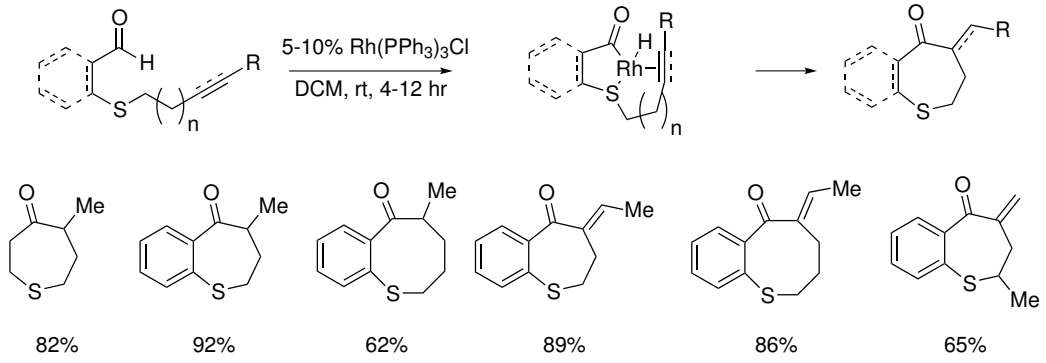
1.2.2 Synthesis of Medium-Rings

The synthesis of rings larger than 5-membered cycles by intramolecular hydroacylation poses a number of problems. If the intermediate rhodium acyl species is able to isomerise to a 6-membered rhodium acyl, the resulting 5-membered product is preferentially formed (Scheme 1.8).[27] The synthesis of 3- and 4-membered rings would involve the formation of 4- and 5-membered rhodacycles. Presumably, the reductive decarbonylation pathway is favourable as it would result in the release of ring-strain, while the reductive elimination to form the hydroacylation product would result in increased strain.

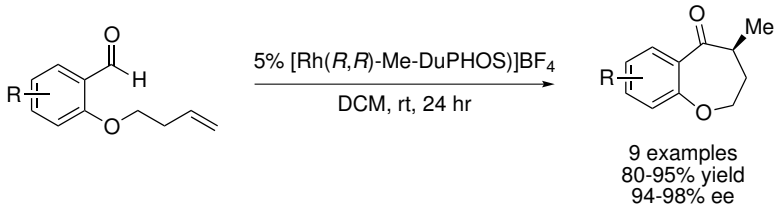


Scheme 1.8: Preferential formation of 5-membered cycles.

Various strategies have been employed to enable the synthesis of larger ring systems. The Bendorf group reported the intramolecular hydroacylation of thio-ether bearing alkenes and alkynes. The authors proposed that the β-sulphur forms a stabilised intermediate rhodium acyl species that allows a range of medium-rings to form (Scheme 1.9).[7] Utilising Wilkinson's catalyst, both alkenes and alkynes gave excellent yields. The more reactive alkyne substrates tolerated an α-methyl substituent on the sulphur or on the alkyne. While Bendorf was unable to cyclise ether-linked alkenes, Dong recently reported their enantioselective cyclisation using [Rh((*R*,*R*)-Me-DuPHOS)]BF_4 as catalyst (Scheme 1.10).[34] Dong has also reported interesting examples of the hydroacylation of ketones, a topic that has been subject to fewer studies.[35–38]

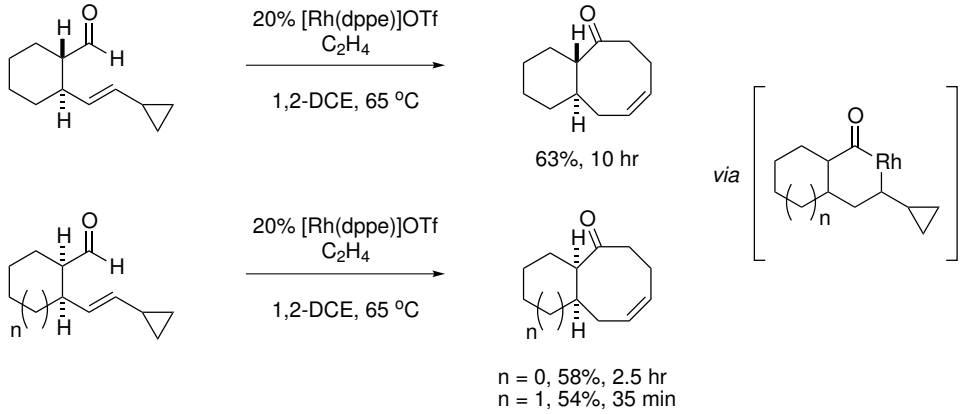


Scheme 1.9: Use of sulphur-chelation for the synthesis of medium-rings by Bendorf.



Scheme 1.10: Synthesis of medium-ring ethers by Dong.

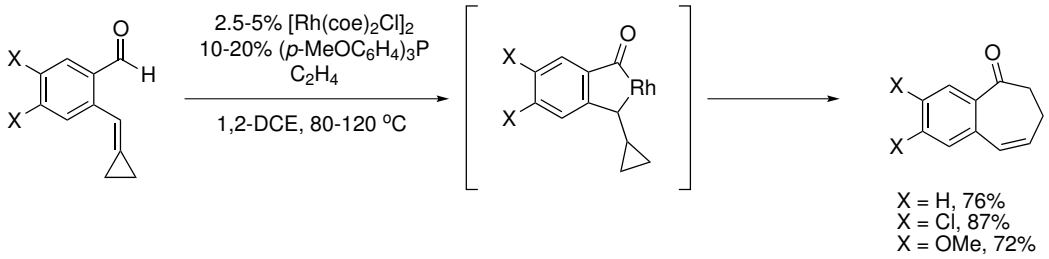
Another approach for the synthesis of medium-rings employs the reactivity of strained cyclopropane rings. Shair and co-workers developed a synthesis of cyclooctenones from the intramolecular hydroacylation of vinyl cyclopropanes (Scheme 1.11).[39] The authors noted that the cationic rhodium $[Rh(dppe)]^+$ species gave superior reactivity to neutral Wilkinson's catalyst. Both ClO_4^- and TfO^- counterions were evaluated with the latter achieving better yields for bicyclic substrates.



Scheme 1.11: Intramolecular hydroacylation of allyl cyclopropanes

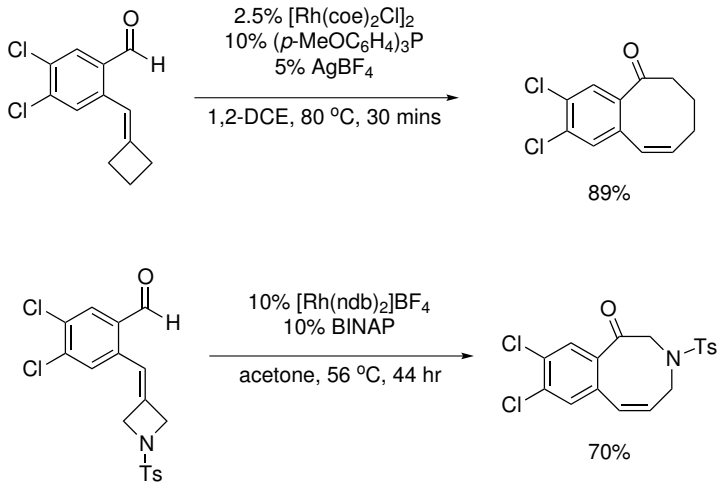
More recently, Fürstner and Aïssa reported a tandem rhodium-catalysed C-H acti-

vation/cycloisomerisation process for the synthesis of cycloheptenes and heptanones. The authors proposed a similar rhodium acyl intermediate for their process. Like Shair's work, ethene was used to suppress decarbonylative processes; in these examples, neutral rhodium species were used successfully to obtain the 7-membered rings (Scheme 1.12).[40]



Scheme 1.12: Intramolecular hydroacylation of vinyl cyclopropanes.

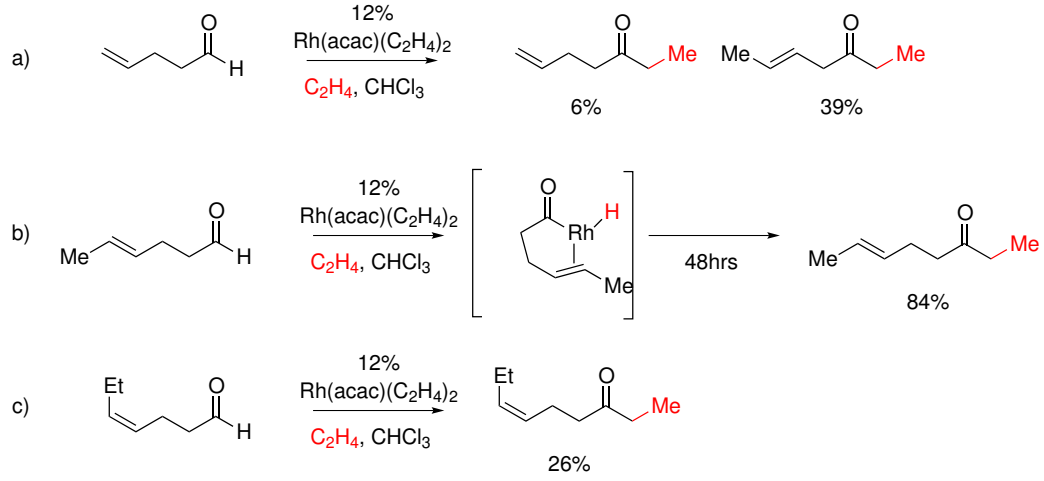
In a recent report, Aïssa demonstrated the hydroacylation of cyclobutanes and azetidines using cationic rhodium-catalysts to give rise to 8-membered rings without the need for ethene saturated solvents (Scheme 1.13).[41]



Scheme 1.13: Intramolecular hydroacylation of vinyl cyclobutanes.

1.3 Intermolecular Hydroacylation

The use of saturated solutions of ethene also led to the first examples of intermolecular hydroacylation. Miller found that $Rh(acac)(C_2H_4)_2$ catalysed the intermolecular hydroacylation of 4-pentenal with ethene to obtain a mixture 6-hepten-3-one and *E*-5-hepten-3-one with trace amounts of the intramolecular hydroacylation product (Scheme 1.14).[28] Miller later found that 4-hexenal underwent the same transformation but gave predominantly the *E*-6-octen-3-one in good yield.[42] Vora found that *Z*-4-heptenal and ethene would react using the same conditions to give *Z*-6-nonen-3-one without isomerization of the double bond.[43] This work by Miller includes a mechanistic study of the reaction and proposes the idea of chelation to enable intermolecular hydroacylation.

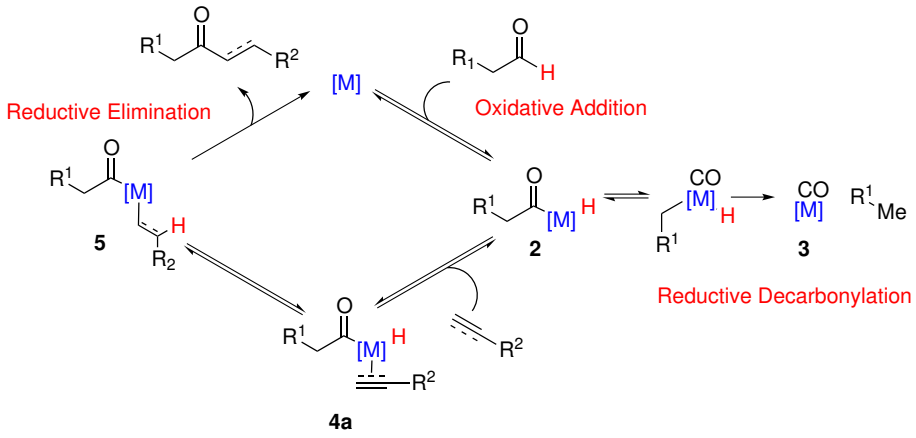


Scheme 1.14: a) and b) Miller; c) Vora

1.3.1 Mechanism of Rhodium-catalysed Hydroacylation

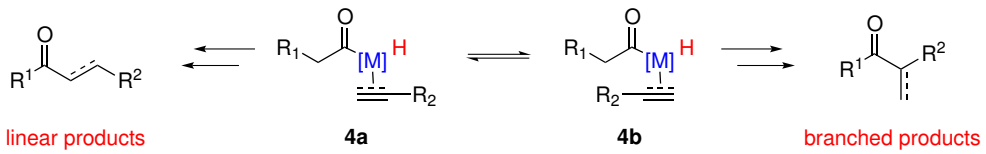
A number of mechanistic studies have been carried out for transition metal-catalysed alkene hydroacylation. Deuterium-labelling experiments by Miller[26,27] and extensive NMR spectroscopic experiments by Bosnich[6,44] established a widely accepted cat-

alytic cycle (Scheme 1.15). Oxidative addition of the metal species into the aldehyde C-H bond results in a rhodium acyl species **2**. Carbonyl deinsertion followed by reductive decarbonylation at this stage results in a stable rhodium carbonyl complex **3**. This pathway is responsible for catalyst inactivation and limits the catalyst turnover for hydroacylation. The use of ethene to suppress the decarbonylation process feasibly acts by forcing the equilibrium toward **4a** and therefore reducing the amount of rhodium acyl **2** that is available for the decarbonylation pathway. Coordination of multiple bond system to the rhodium acyl species is followed by insertion to form intermediate **5**. This then undergoes irreversible reductive elimination, which was proposed by Bosnich and co-workers to be the rate-determining step.



Scheme 1.15: A generally accepted mechanism for hydroacylation.

The rhodium acyl intermediate **4a** is also able to undergo isomerisation; subsequent insertion by the metal and reductive elimination gives rise to either linear or branched products (Scheme 1.16).



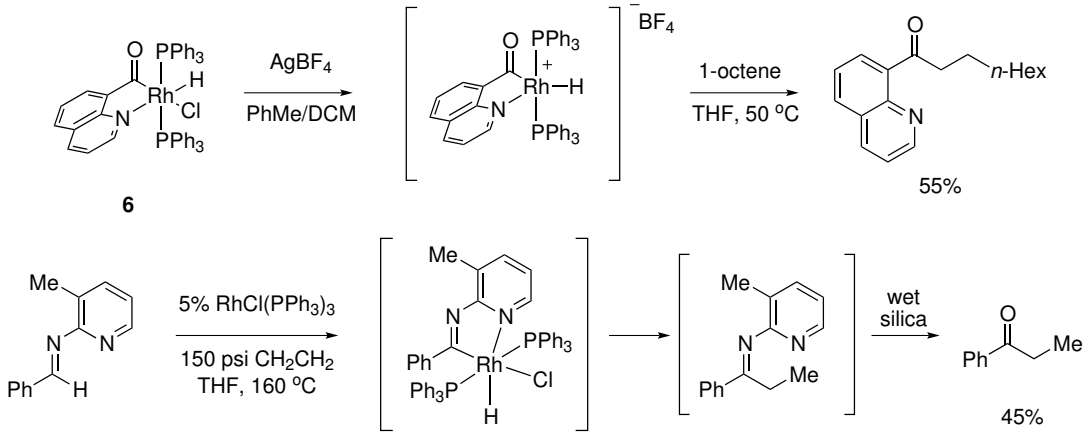
Scheme 1.16: Regioselectivity in hydroacylation.

Minor alterations to the mechanism of intermolecular hydroacylation have been suggested by Morehead and Sargent following their computational study [45] and Brookhart

et al while investigating the hydroacylation of vinyl silanes.[46] Brookhart confimed the suggestion by Bosnich that the reductive elimination step is rate limiting. They also proposed that all steps of the cycle are reversible, except for the final reductive elimination leading to the ketone products and the reductive decarbonylation pathway.

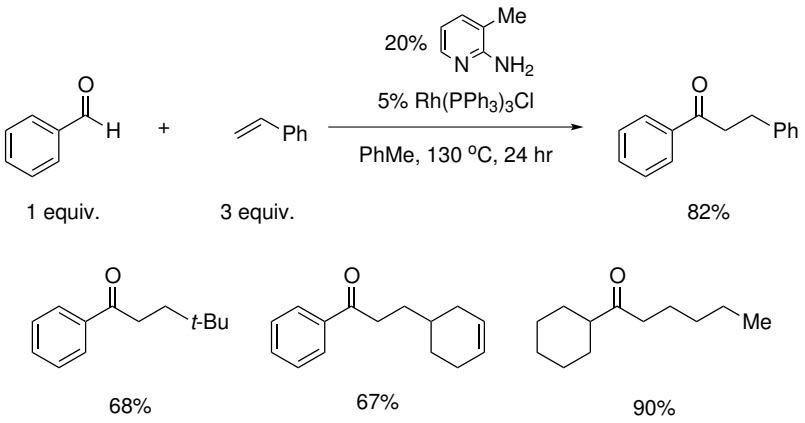
1.3.2 Intermolecular Chelation-Controlled Hydroacylation

The use of high pressures of ethene gas to enable hydroacylation reactions significantly limits the synthetic practicality of the reaction. A number of other chelation strategies have been developed to overcome the propensity of aldehydes to undergo decarbonylation. In the pioneering work by Suggs,[47,48] he isolated a stable rhodium acyl species **6** by treatment of 8-quinolinecarboxaldehyde with Wilkinson's catalyst.[49] He then investigated a related (2-aminopicolinyl)imine as a removable chelating group and was then able to demonstrate its ability to participate in a hydroacylation reaction with 1-octene. His attempts to perform catalytic hydroacylation of (2-aminopicolinyl)imines required high pressures of ethene and high reaction temperatures using 5 mol % of Wilkinson's catalyst and achieved a 45% yield after hydrolysis of the imine on wet silica (Scheme 1.17).[50]



Scheme 1.17: Use of *N*-chelating intermediates in hydroacylation of alkenes.

The Jun group amassed a formidable body of work utilising imines in hydroacylation. Jun initially worked on the hydroacylation of acyl ferrocenes using the imines developed by Suggs.[51–53] This methodology was then used in the hydroacylation of benzaldehydes (Scheme 1.18).[54] In the same year the Jun group published a similar approach for the hydroacylation of heteroaromatic aldehydes in good yields, employing titanium or zirconium additives.[55]

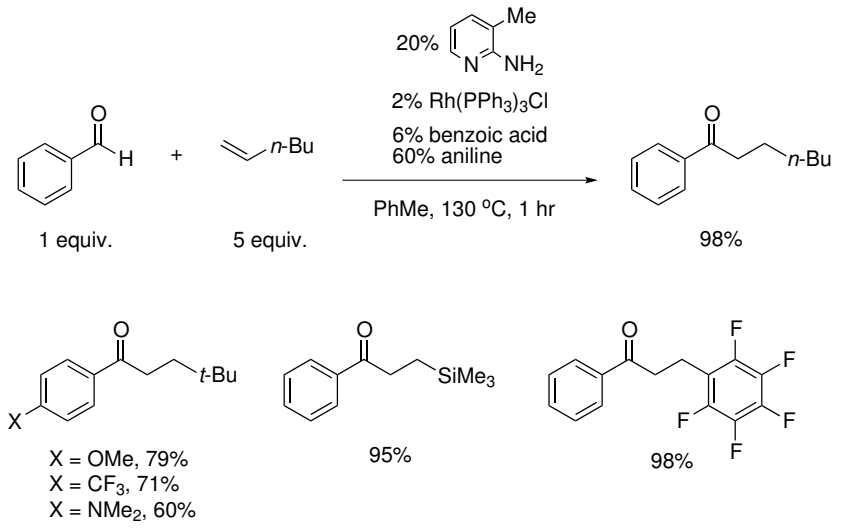


Scheme 1.18: 2-aminopicolinyl)imine intermediates in the hydroacylation of alkenes.

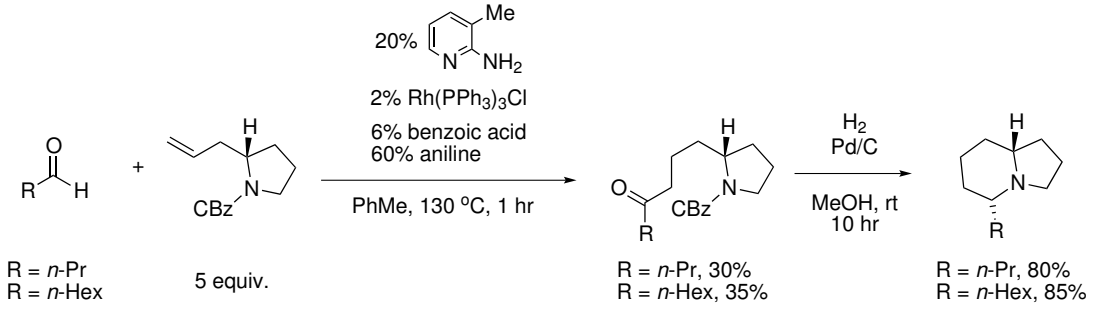
Further development of the methodology lead to the addition of benzoic acid and aniline. The authors proposed that benzoic acid catalysed the formation of the imine intermediate, while aniline catalysed the hydrolysis of the imine formed after hydroacylation. Thus a combination of these two additives allowed a more general reaction and lower catalyst loadings than previously. Although a large excess of alkene and relatively high reaction temperatures were required, the reaction was complete in 1 hour (Scheme 1.19).[56]

The conditions developed by the Jun group were then used by the Kim group in the synthesis of indolizidine alkaloids with retention of chirality of the pyrrolidine, but only in moderate yield (Scheme 1.20).[57] Further development of the methodology by Jun has been covered in detail in the recent review by Willis.[19]

For the Jun chemistry, Wilkinson's catalyst is used for the hydroacylation over the



Scheme 1.19: Jun's improved 2-aminopicolinyl)imine hydroacylation conditions.

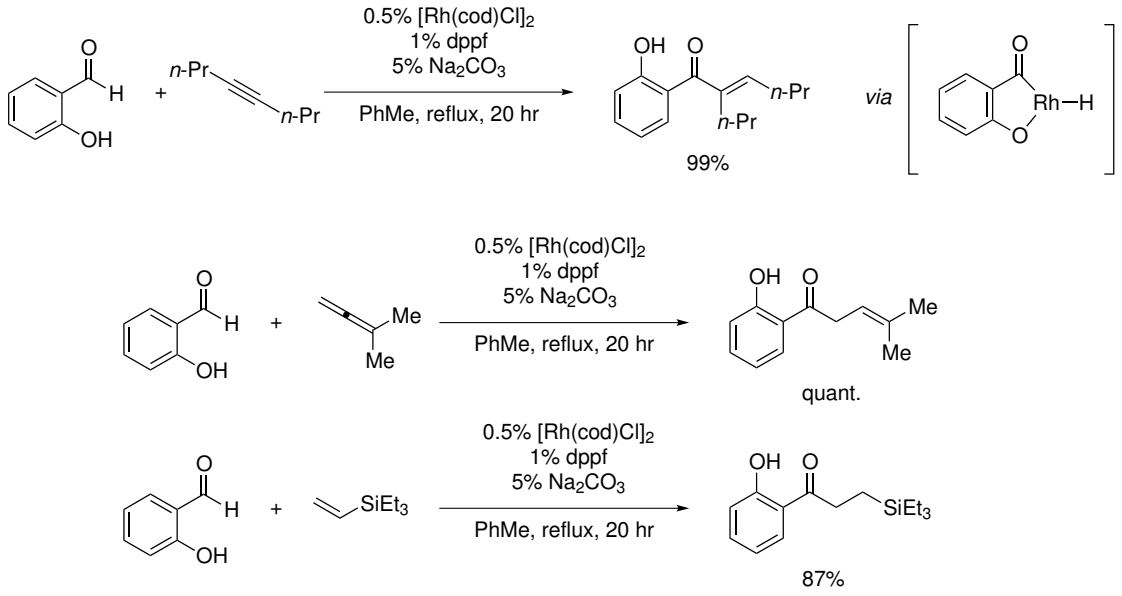


Scheme 1.20: A hydroacylation approach for the synthesis of indolizidine alkaloids.

more generally reactive $[Rh(diphosphine)]^+$ catalysts. A recent computational and NMR spectroscopic study by Bo and Castillón indicates that neutral rhodium chloride catalysts undergo the oxidative addition into the imine C-H bond to form a relatively stable rhodium acyl species, while the low thermodynamic stability of the cationic C-H inserted complexes prevents high conversions using cationic catalysts.[58]

2-Salicylaldehydes have been employed in hydroacylation by several groups. The Miura group demonstrated the hydroacylation of alkenes, allenes and alkynes using a low loading of catalyst in presence of a sub-stoichiometric amount of base (Scheme 1.21).[59,60]

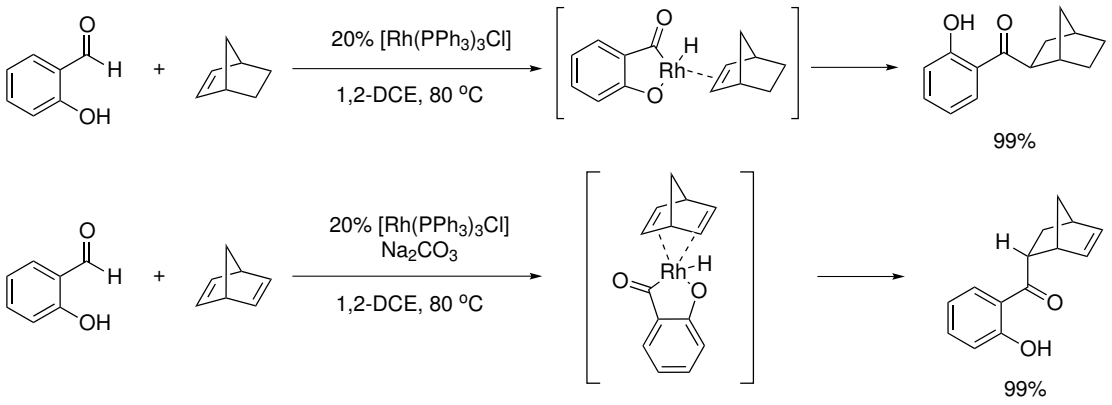
While Miura achieved only a 6% yield while attempting to hydroacylate norbornene



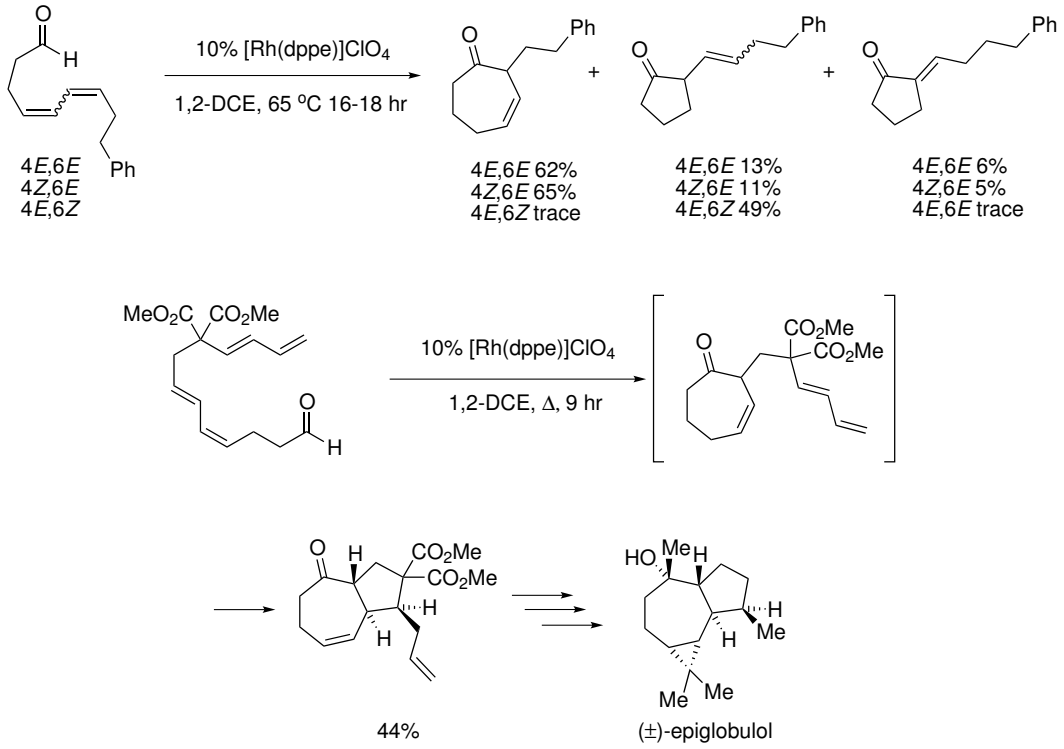
Scheme 1.21: The use of 2-salicylaldehydes in hydroacylation by the Miura Group.

using the conditions described above, Tanaka and Suemune developed a method to form *endo*-coupled products using Wilkinson's catalyst (Scheme 1.22).[61] Using norbornadienes, the *exo*-product was formed. The authors had previously investigated the intermolecular hydroacylation of dienes and proposed a double chelated rhodium acyl intermediate.[62,63] Again, the authors invoked this intermediate to explain the substrate selectivity switch. An enantioselective variant of this reaction was developed by the Bolm group which allowed catalyst control of regioselectivity using norbornadiene as the alkene component of the reaction.[64] Ferrocenyl phosphine or phophoramidite ligands could be used to access either the *exo*- or *endo*-products, respectively.

Dienes have also been used in intramolecular hydroacylation by the Mori group to obtain β-γ-cycloheptenones *via* a proposed π-allyl rhodium species.[65,66] The same group then used this in the synthesis by a hydroacylation/cycloisomerisation cascade reaction in the synthesis of epiglobulol (Scheme 1.23).[67]

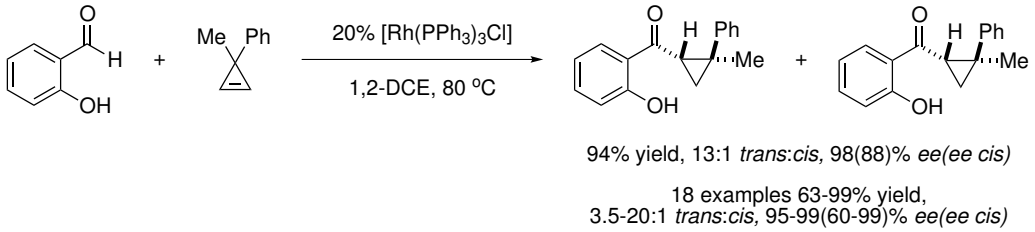


Scheme 1.22: Control of regioselectivity by "double chelation" of alkenes.



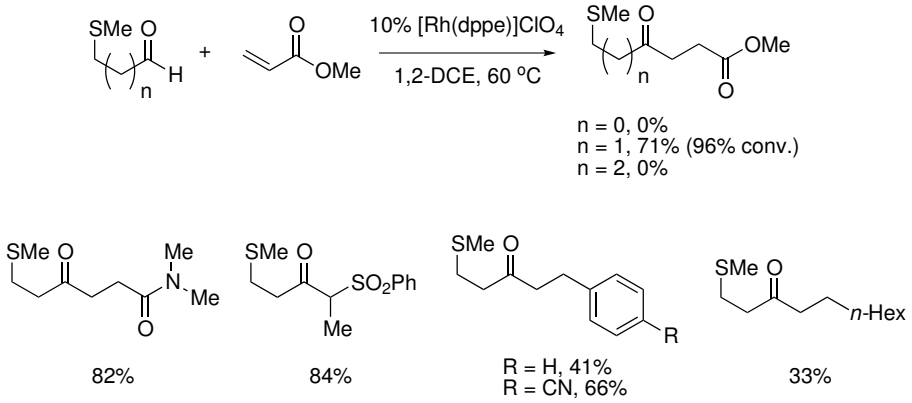
Scheme 1.23: Intramolecular hydroacylation of dienes by Mori and Sato.

A recent communication by the Dong group employed 2-salicylaldehyde chelation in the enantioselective hydroacylation of cyclopropenes.[68] Again, a neutral rhodium comple was used along with ferrocenyl ligands to effect excellent enantiomeric excess, yield and selectivity of a variety of substituted α-cyclopropane aldehydes (Scheme 1.24).

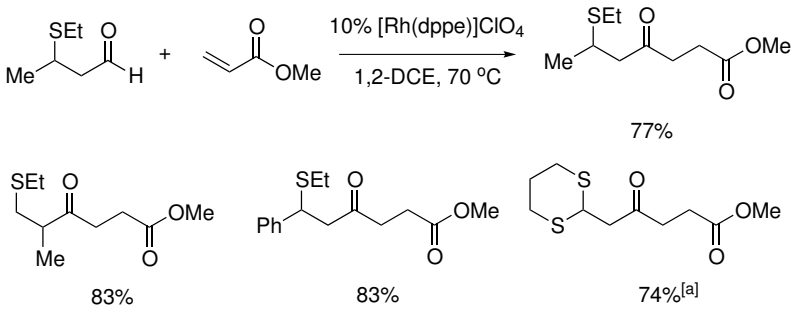


Scheme 1.24: Hydroacylation of cyclopropenes by the Dong group.

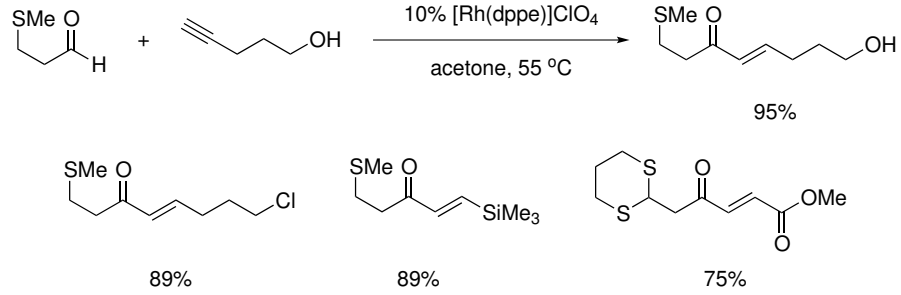
Willis initially utilised Sugg's (2-aminopicolyl)imine methodolody for the synthesis of 1,4-dicarbonyls[69] before investigating sulphur-rhodium acyl chelation, as proposed by Bendorf (page 5), to enable the intermolecular hydroacylation of electron-poor alkenes. Willis employed $[Rh(dppe)]ClO_4$ as the catalyst and found that the position of the sulphur was critical in the success of the reaction. Provided that a β-sulphur aldehyde was used, a range of functionalised alkenes could be employed in the reaction (Scheme 1.25).[70] Using the same conditions, this methodology was then shown to be effective for a wide range of substrates; α- and β-branched aldehydes could be employed (Scheme 1.26)[71] as well as terminal alkynes bearing alcohols, chloride and silyl groups (Scheme 1.27).[72]



Scheme 1.25: The use of β-sulphur chelation in hydroacylation of activated alkenes.

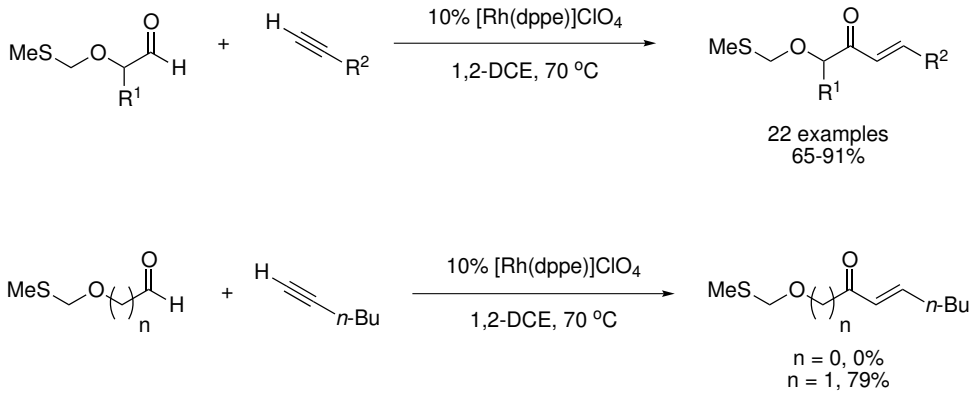


Scheme 1.26: β-sulphur aldehyde scope in hydroacylation. [a] acetone, 50 °C.

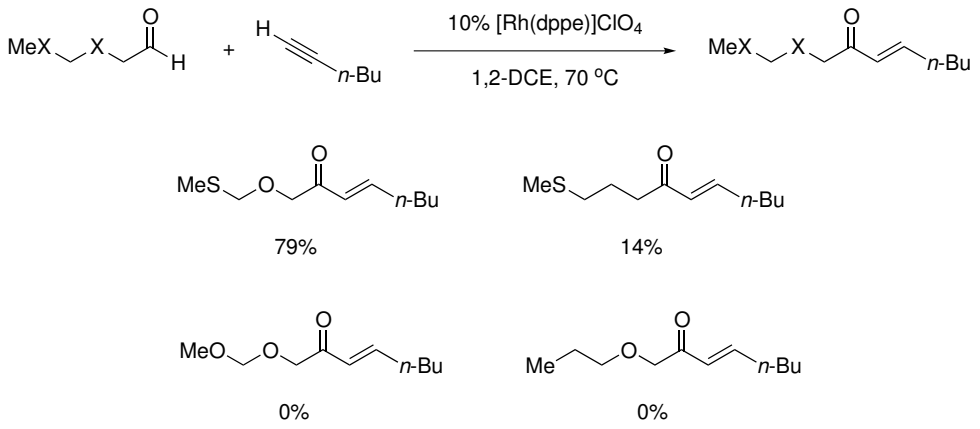


Scheme 1.27: Functional group tolerance in hydroacylation reactions.

A recent report by Willis and co-workers utilised MTM ethers as an alternative chelating moiety.[73] These were highly capable substrates in the hydroacylation of terminal alkynes (Scheme 1.28). Like the β-sulphur chelating aldehydes exploited by the group previously, the position of the oxygen and sulphur were critical in the reaction (Scheme 1.29). Omission of the oxygen resulted in a greatly reduced yield. If the sulphur was replaced by another oxygen atom or omitted, the reaction failed completely.

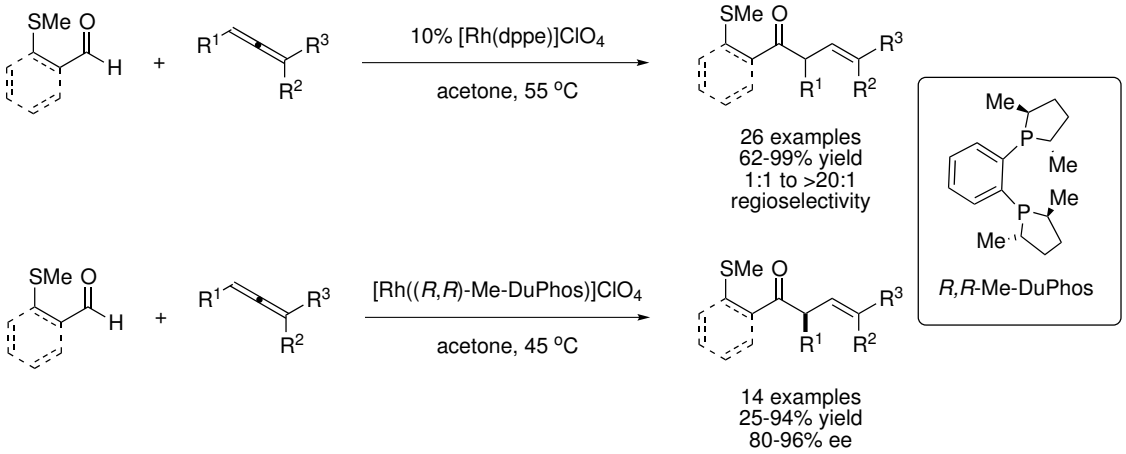


Scheme 1.28: Methylthiomethyl ether chelation controlled hydroacylation.



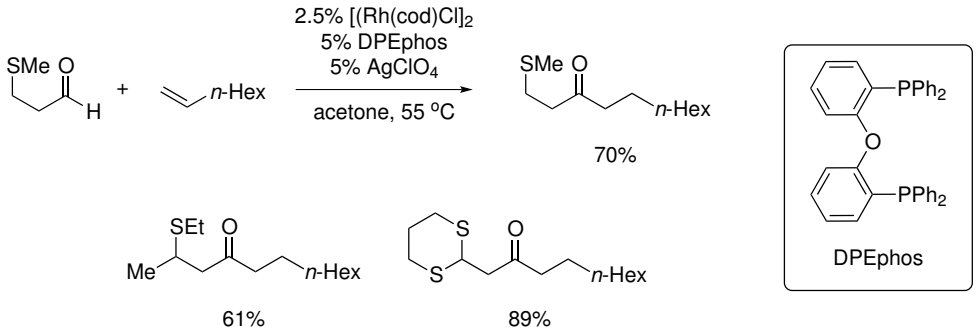
Scheme 1.29: Methylthiomethyl ether chelation controlled hydroacylation.

The Willis methodology was also effective for the hydroacylation of allenes boasting good regioselectivities. The group also proposed a dynamic kinetic resolution of allenes using Me-DuPhos as ligand. Again, excellent yields and enantioselectivities were achieved using an aromatic β-sulphur aldehyde (Scheme 1.30).[74,75]



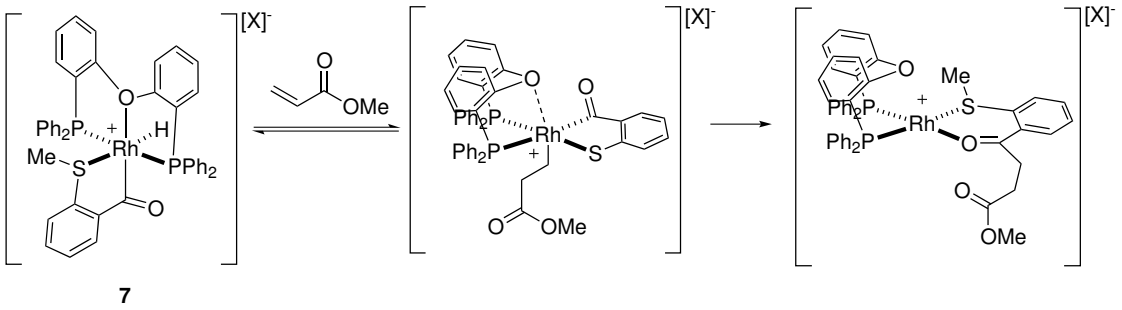
Scheme 1.30: The hydroacylation of allenes.

After further development of β-sulphur chelation-controlled hydroacylation by Weller and Willis, the use of [Rh(DPEphos)]ClO_4 enabled the hydroacylation of electron-neutral alkenes, in good yields.[76] The catalyst could be used effectively in acetone or 1,2-DCE solvent systems and could also be prepared *in situ*, simplifying the methodology experimentally (Scheme 1.31).



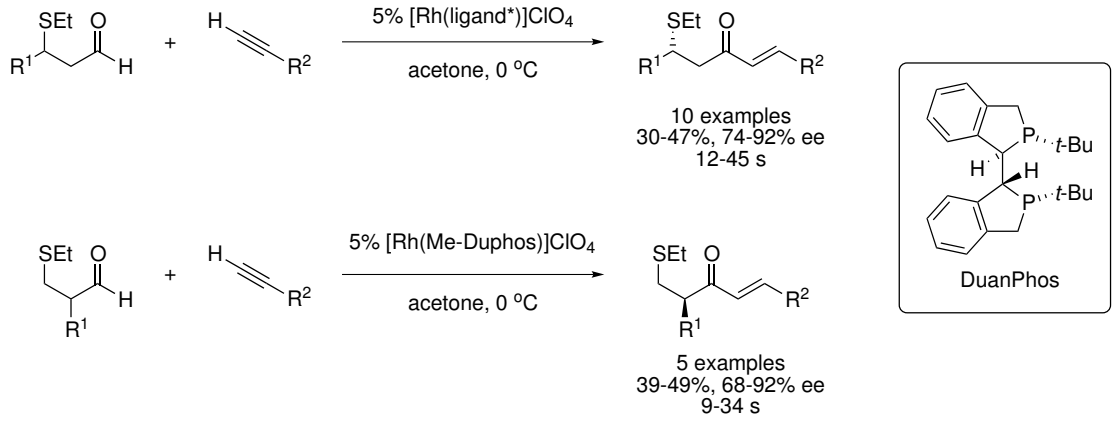
Scheme 1.31: A second generation catalyst system for hydroacylation of alkenes.

Weller and Willis proposed that the ether linkage on the DPEphos ligand participates in hemilabile coordination to the rhodium centre, providing an additional stabilising effect on the intermediate rhodium acyl species (Scheme 1.32). These catalytically active species were confirmed by NMR spectroscopy, mass spectrometry and, for the oxygen chelate rhodium acyl species **7**, by X-ray crystallography.[77]



Scheme 1.32: Hemilabile chelation of DPEphos to rhodium.

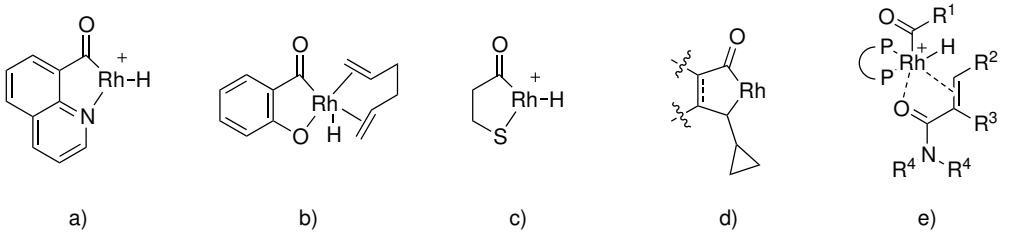
Very recently, the Willis group have reported enantioselective syntheses of α- and β-substituted ketones by kinetic resolutions of racemic aldehydes.[78,79] A range of chiral aldehydes gave excellent yields and enantiomeric ratios. The best selectivites for α-substitited aldehydes and β-aryl aldehydes were obtained with Me-DuPhos as ligand. For β-alkyl aldehydes Duanphos was used, again, to good effect (Scheme 1.33).



Scheme 1.33: Kinetic resolution of aldehydes by hydroacylation of alkynes.

1.3.3 Expanding Chelation-Controlled Hydroacylation

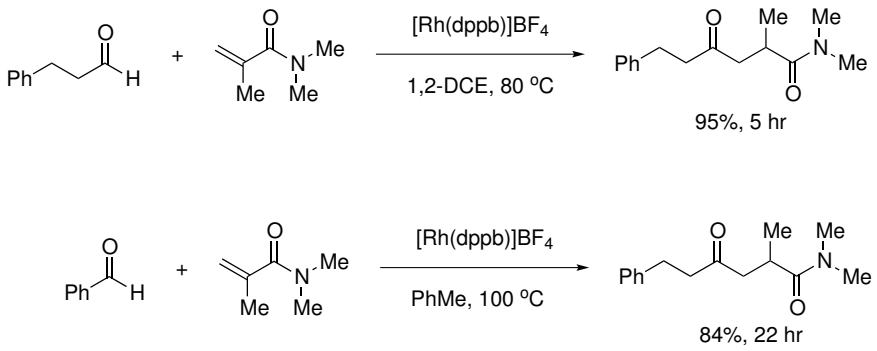
As described in the preceeding sections, various strategies have been employed to overcome the problem of decarbonylation in hydroacylation reactions (Scheme 1.34).



Scheme 1.34: a) Suggs and Jun; b) Miura, Suemune and Tanaka; c) Bendorf and Willis; d) Shair and Fürstner; e) Tanaka

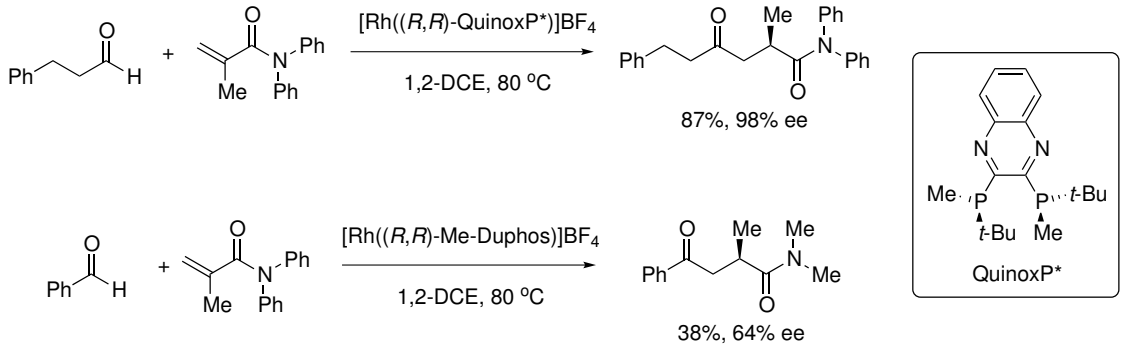
Recently, Tanaka developed a method for the direct hydroacylation of *N*,*N*-dialkylacrylamides using either aliphatic or aromatic aldehydes using his proposed intermediate shown in Scheme 1.34. A good range of alkyl and aryl aldehydes achieved excellent yields with a range of acrylamides (Scheme 1.35).[80] In general, reactions with aryl aldehydes required extended reaction times and elevated temperatures but gave good yields nonetheless.

Tanaka also demonstrated an enantioselective variant of the same reaction.[81] After



Scheme 1.35: Direct hydroacylation of *N*,*N*-dialkylacrylamides.

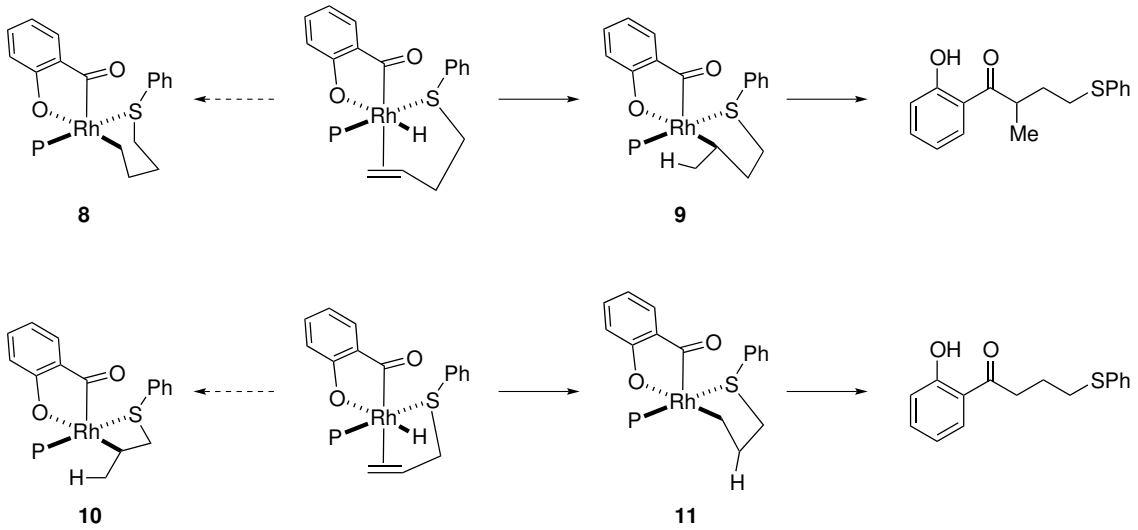
a brief screen of ligands, Quinox and Duphos type ligands were identified to be suitable for the hydroacylation of alkyl aldehydes. They reported a small number of examples which gave excellent yields and enantiomeric excesses (Scheme 1.36). The enantioselective hydroacylation employing an aryl aldehyde was restricted to a single example using benzaldehyde and achieved only a moderate yield and selectivity in the asymmetric variant.



Scheme 1.36: Enantioselective hydroacylation of *N*,*N*-dialkylacrylamides.

The Dong group proposed another double chelation strategy combining, 2-salicylaldehyde chelation and homoallylic sulfides.[82] Dong noted that the position of the sulphur-chelating group had a pronounced effect on the regioselectivity of the reaction. Homoallyl sulfides gave almost exclusively the branched isomer, while allyl sulfides gave the linear product, regardless of either alkene geometry or ligand identity. The proposed rationale stated that the 5-membered rhodacycles **9** and **11** are preferred over the 6- or 4-membered rhodacycles **8** and **10** that would give the linear

and branched products respectively (Scheme 1.37).



Scheme 1.37: Regioselectivity in hydroacylation of allyl and homoallyl sulfides.

1.4 Summary

Much of the research into the hydroacylation reaction has been directed at controlling the, generally unwanted, decarbonylation pathway. For the synthesis of 5-membered rings the methodology is relatively mature but for the synthesis of larger ring systems and for intermolecular reactions significant limitations still exist.

The principle approach to allow intermolecular hydroacylation has been through various chelation strategies, either employing chelation of the aldehyde component, alkene component or a combination of both. Recently the area has seen significant development and a considerable range of substrates can be combined by hydroacylation. Utilising the ability of other reaction components to coordinate to the rhodium acyl species provides an excellent way to increase the reaction scope of intermolecular hydroacylation. If a larger variety of suitable hemilabile substrates can be identified, then this approach may enable intermolecular hydroacylation to become a more general method. Although the methodology of hydroacylation is becoming more established, its use in more targeted synthesis remains limited.

Chapter 2

Synthesis of Heterocycles

2.1 Introduction

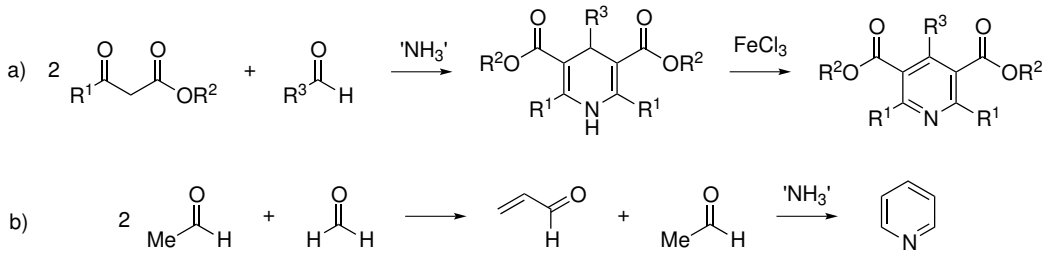
The synthesis of heterocycles has been one of the main occupations of synthetic chemists throughout the history of chemistry. The scope of this thesis cannot hope to describe the entire area of the synthesis of heterocycles. The two main classes of heterocycles that are of concern for the scope of this study are pyrroles and pyridines. Recent and relevant methods for their synthesis are outlined briefly below.

2.2 Synthesis of Pyridines

The synthesis of pyridines, despite being the target of some of the oldest examples of organic synthesis, is still a very active area of research.

2.2.1 Early Syntheses of Pyridines

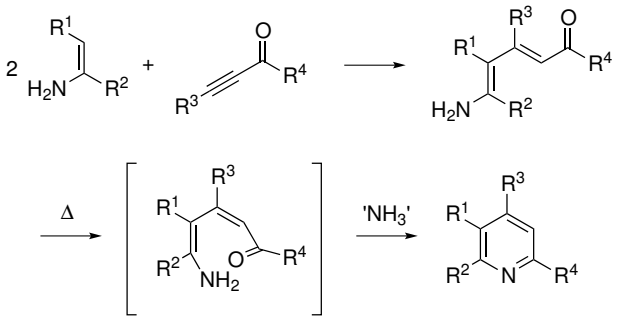
The first synthesis of pyridine was by Hantzsch in 1881.[83] In 1898, Knoevenagel used the method by Hantzsch to produce unsymmetrical substituted pyridines.[84] The Chichibabin synthesis was developed in 1924 to provide the first industrially relevant synthesis of pyridine (Scheme 2.1).[85] Modifications of this synthesis are still used industrially.[86,87]



Scheme 2.1: a) Hantzsch; b) Chichibabin

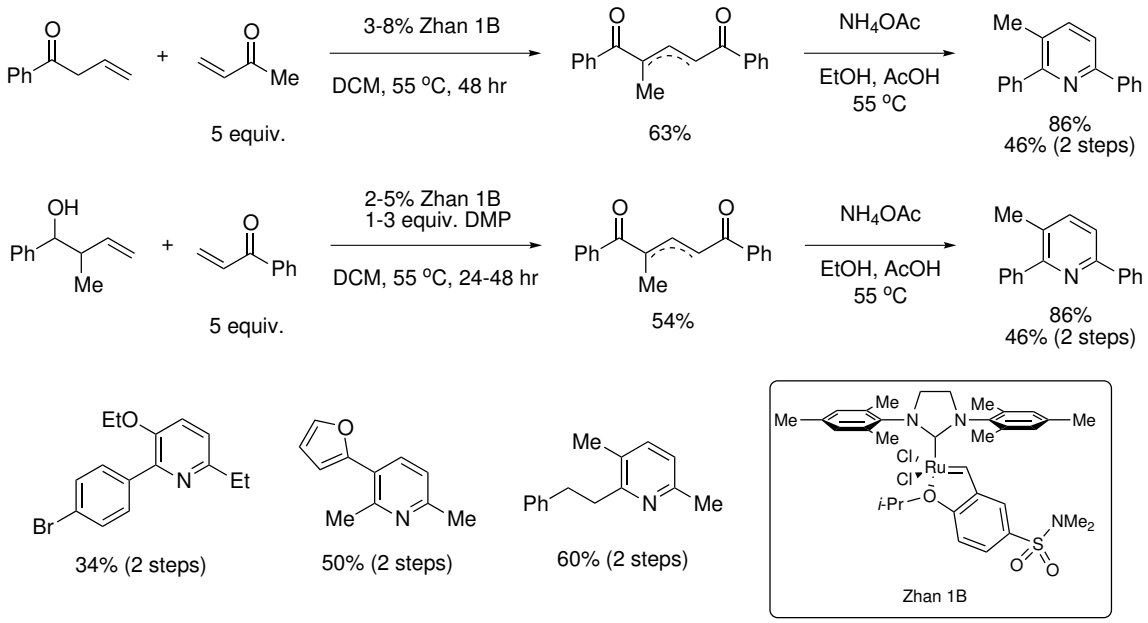
2.2.2 Bohlmann-Rahtz Pyridine Synthesis

Bohlmann and Rahtz reported a synthesis of tri-substituted pyridines from enamines and ethynyl aldehydes or ketones in 1957.[88] The method has since been enhanced and provides a versatile method for the synthesis of tetra-substituted pyridines, as documented by Bagley (Scheme 2.2).[89] The original syntheses required high temperatures for the dehydrative cyclisation step. Modern methods utilise a range of Brønsted or Lewis acids and careful choice of solvent to facilitate the isomerisation of the intemediate dienone.[89–91]



Scheme 2.2: Bohlmann-Rahtz synthesis of tetra-substituted pyridines.

Numerous reports for the cyclisation of 1,5-dicarbonyls and their derivatives in the presence of sources of ammonia to afford pyridines exist and it is now regarded as a well known classical method.[92,93] Very recently, a synthesis of pyridines has been reported by the Donohoe group *via* a cross-metathesis reaction and a subsequent dehydrative cyclisation.[94] This approach provides a range of tri-substituted pyridines by enone-enone or homoallyl alcohol-enone cross-metathesis followed by oxidation and cyclisation. The cross-metathesis step required 5–10 equivalents of the enone component and prolonged reaction times in a sealed tube to achieve good yields (Scheme 2.3). In the same report the Donohoe group utilitised a Heck arylation[95,96] to decorate the intermediate enone and ultimately provide tetra-substituted pyridines.



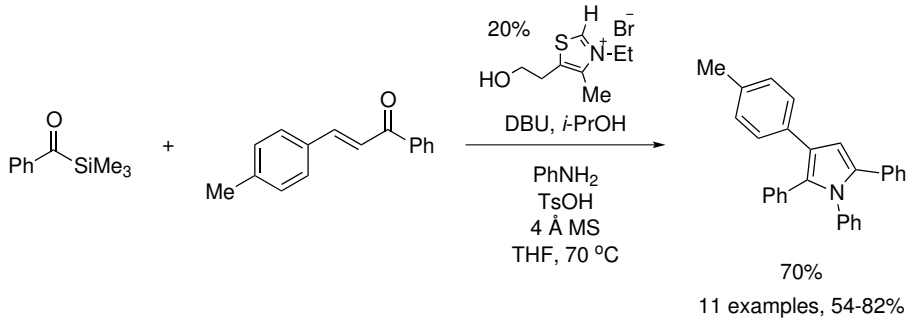
Scheme 2.3: Synthesis of pyridines by a cross-metathesis approach.

2.3 Synthesis of Pyrroles

The synthesis of heterocycles from 1,4-dicarbonyl compounds was independently reported by Paal and Knorr in 1884.[97,98] This has since become a popular method for the synthesis of pyrroles. Approaches for the synthesis of pyrroles are the subject of considerable efforts within industrial and academic environments.[99–101]

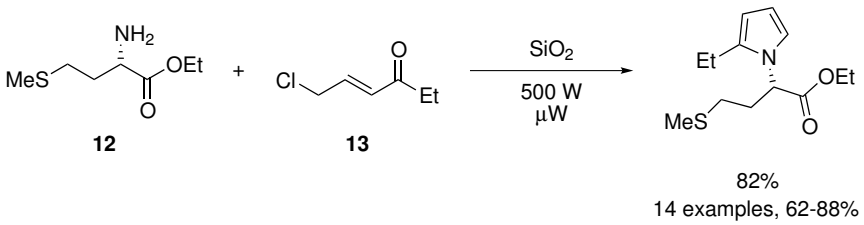
The Scheidt group reported a tandem sila-Stetter/Paal-Knorr procedure for the synthesis of tetra-substituted pyrroles from acyl silanes, enones and primary amines.[102] A thiazolium catalyst, base and *iso*-propanol was used to promote the sila-Stetter reaction in THF,[103] then addition of a primary amine, toluenesulfonic acid and 4 Å molecular sieves converted the intermediate 1,4-dicarbonyl into a range of pyrroles. Good yields of aryl substituted pyrroles were isolated but no alkyl examples were reported, except as the *N*-substituent (Scheme 2.4). The authors were also able to use microwave heating at 160 °C to reduce the reaction times to 15 minutes per step,

rather than the 8 hours usually required at 70 °C, albeit in a slightly reduced yield of 55%.



Scheme 2.4: Tandem sila-Stetter/Paal-Knorr synthesis of pyrroles.

Amino-enones were also employed for the synthesis of *N*-amino acid derivative substituted pyrroles by Demir. Again, microwaves were used to heat a mixture of amino acid derivatives, such as **12** and chloro-enones **13** to give rise to a range of pyrroles in excellent yields (Scheme 2.5)[104]

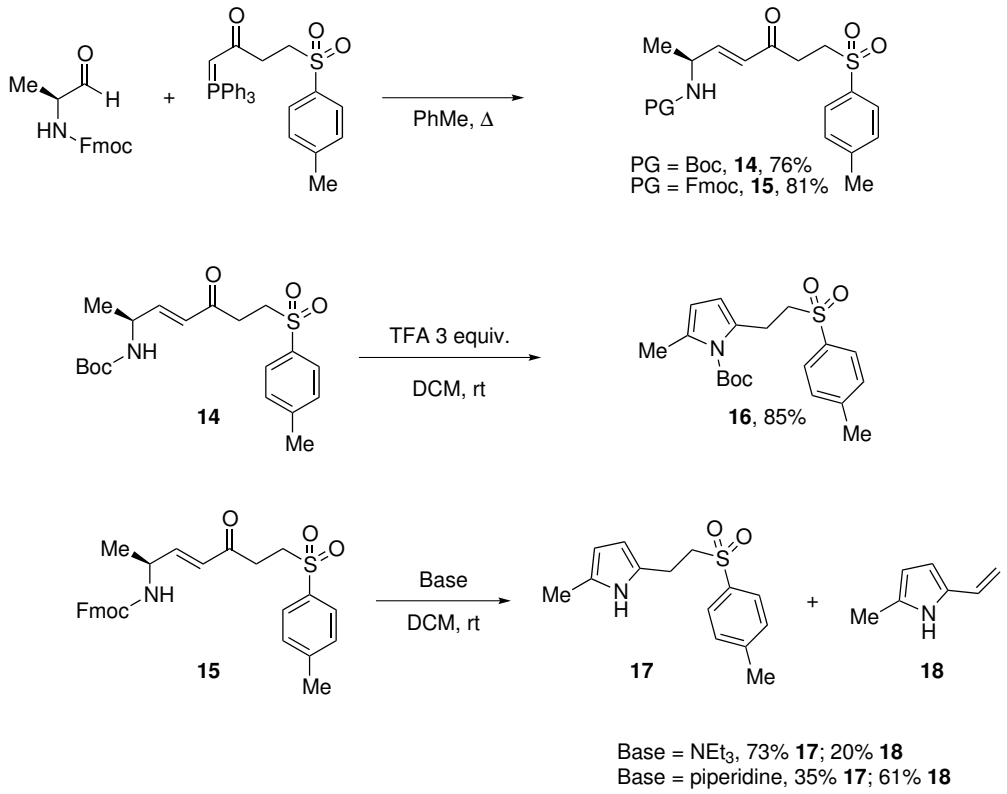


12 **13**

Scheme 2.5: Synthesis of *N*-amino acid derivative substituted pyrroles.

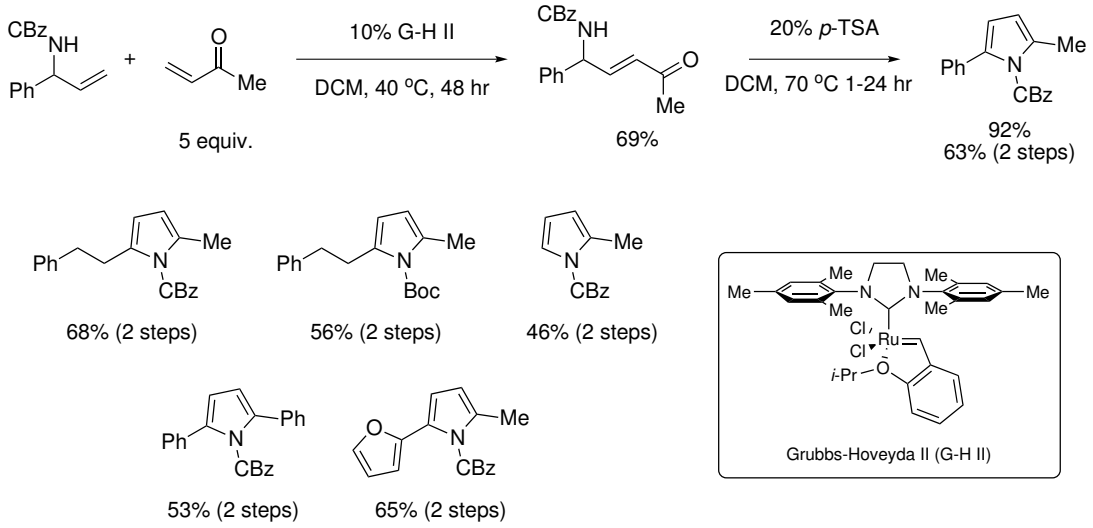
The Pollini group used Wittig chemistry to synthesise protected γ-amino enones bearing a sulphone, which were then converted to the pyrroles (Scheme 2.6).[105] Boc-protected γ-amino enone **14** was then formed into to the corresponding pyrrole **16** by trifluoroacetic acid. Interestingly, the protecting group was retained in the final product. The authors found that treatment of the Fmoc protected analogue **15** with base resulted in a mixture of pyrroles **17** and **18**, resulting from elimination of the sulfone.

Prior to his work with pyridines, Donohoe published the synthesis of mono- or di-substituted pyrroles (Scheme 2.7).[106] The cross-metathesis was carried out using 10 mol % of Grubbs-Hoveyda II (G-H II) catalyst[107] in DCM with 5 equivalents of the

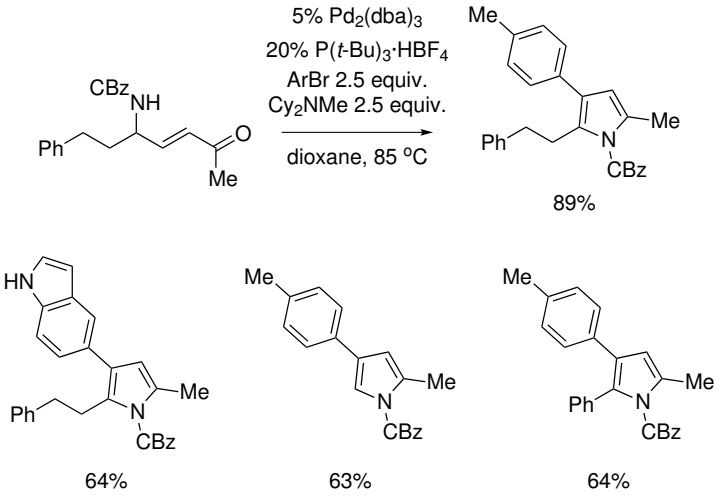


Scheme 2.6: Acid and base promoted cyclisation of γ-amino enones.

enone component. The use of a large excess of enone limits this chemistry to the use of readily available enone components. The subsequent cyclisation was carried out using catalytic *p*-TSA · H_2O in the same solvent at 70 °C in a sealed tube. Like the work on pyridines (page 25) and furans,[108,109] Heck reactions could be used in tandem with cross-metathesis to furnish di- and tri-substituted pyrroles (Scheme 2.8). In this case, cyclisation occurred during the Heck coupling. The authors proposed that the intermediate carbopalladated species facilitates the isomerisation to the *cis*-γ-amino enone which is required for the dehydrative cyclisation. In the same publication, the group demonstrated the use of this methodology with the synthesis of the pyrrole core of Atorvastatin.[110]



Scheme 2.7: A cross-metathesis approach for the synthesis of pyrroles.



Scheme 2.8: Elaboration γ-amino enones by Heck chemistry and *in situ* cyclisation.

2.4 Summary

The synthesis of heterocyclic compounds continues to drive organic chemistry. Increasingly, multi-component and transition metal catalysed reactions[111–116] are being employed for their synthesis. γ-Amino enones have been synthesised by a diverse range of methods and often microwave heating of γ-amino enones is used to isomerise and cyclise these compounds to highly-substituted pyrrole products.

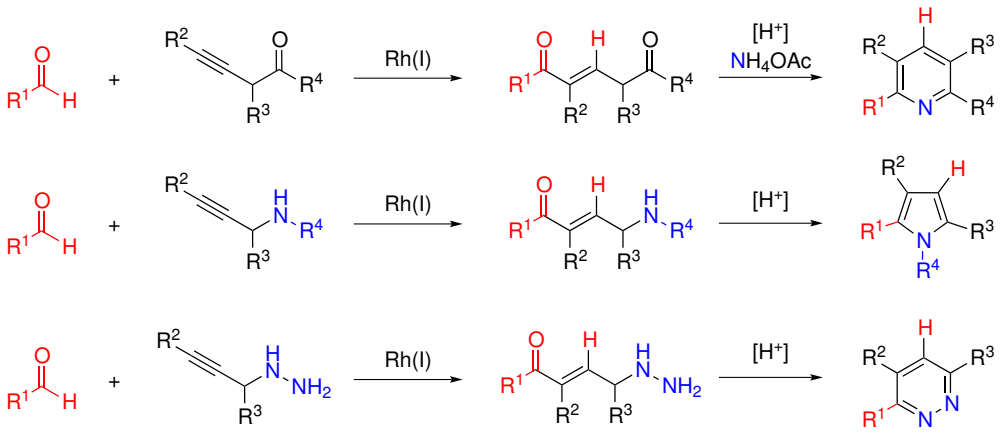
Chapter 3

A Hydroacylation Approach to Pyridines

3.1 Introduction

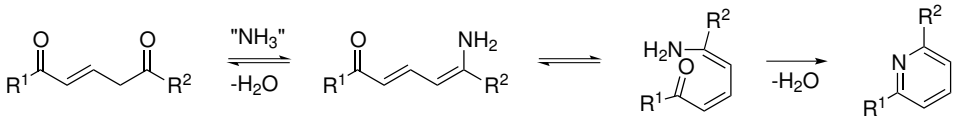
As described previously in chapter 2, the synthesis of heterocycles continues to drive research in synthetic chemistry. Considering the potential scope and high atom-efficiency of the hydroacylation reactions developed by Dong, Tanaka, Willis and others, the synthesis of various cyclisation precursors by an unusual retrosynthetic disconnection could be envisaged . This project aims to make use of this approach to evaluate the combination of the hydroacylation reaction and classical dehydrative cyclisations in the synthesis of a number of heterocyclic systems (Scheme 3.1).

The chemistry is based on combining aldehydes and a range of functionalised alkynes using hydroacylation to effect the umpolung connection. The use of homopropargyl ketones, propargyl amines or propargyl hydrazines would give pyridines, pyrroles or



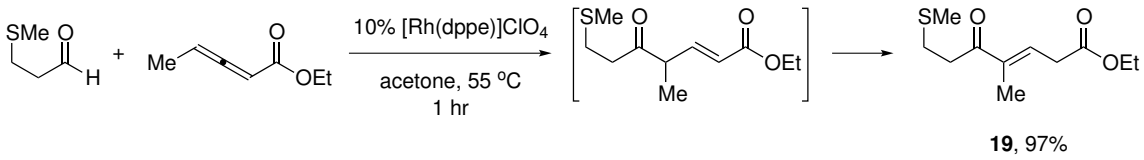
Scheme 3.1: A hydroacylation approach for the synthesis of heterocycles.

pyridazines, respectively. We proposed that the intermediate enones would undergo an isomerisation followed by a dehydrative cyclisation to form the final heterocycle (Scheme 3.2). Potentially, the use of the less reactive alkene hydroacylation substrates[19,28,71] would provide substrates for the synthesis of dihydropyridines and pyrrolines while avoiding the need for the isomerisation of the double bond.



Scheme 3.2: Cyclisation of 1,5-ketoenones in presence of ammonia.

The cyclisation of 1,5-dicarbonyls in the presence of ammonium acetate to afford pyridines is a well known method.[92,93] However, the synthesis of these 1,5-dicarbonyl derivatives is not always trivial. Hydroacylation of an allene or a homopropargylic ketone would provide an elegant entry into these compounds, allowing variation on all but the 4-position of the final pyridine. Previous work in the Willis laboratory has shown allenes and allenic esters to be excellent substrates for the hydroacylation reaction in terms of selectivity and yield (Scheme 3.3).[74,75] Following this promising result it was decided that allenic ketones would provide a good starting point for the investigation of a hydroacylation approach towards the synthesis of pyridines.

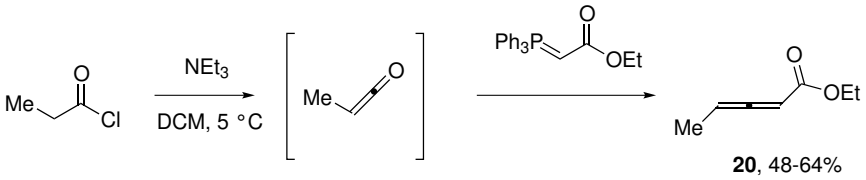


Scheme 3.3: Hydroacylation of an allenic ester.[74]

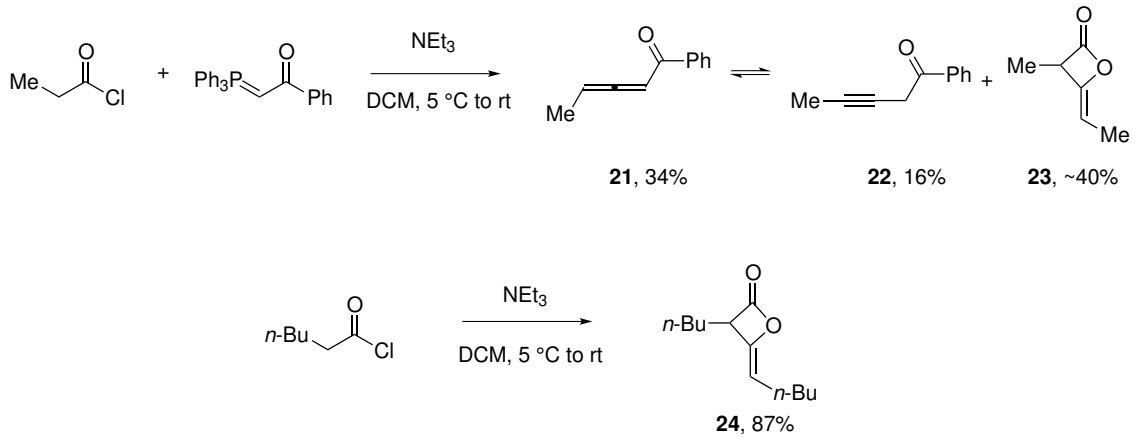
3.2 Synthesis of Substrates

3.2.1 Synthesis of Allenic Ketones

While the synthesis of the allenic ester **20** *via* a Wittig reaction between a ketene and phosphorane was successful (Scheme 3.4),[113,117–119] this approach was more problematic for the synthesis of allenic ketones (Scheme 3.5). A considerable amount of the ketene dimer **23** was formed during the reaction.



Scheme 3.4: Synthesis of allenic esters by Wittig chemistry

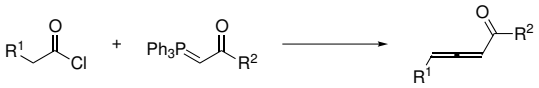


Scheme 3.5: Synthesis of allenic ketones using Wittig chemistry.

The [2+2] dimerisation of ketenes is a well known process[120] and for the reaction to provide a useful yield of allenic ketone, the rate of Wittig coupling must be substan-

tially faster than the dimerisation process. The reaction is further complicated by isomerisation of the allenic ketone to the homopropargyl ketone during the coupling, although this would be a suitable substrate for the hydroacylation in itself.

Despite the inefficient nature of this Wittig chemistry approach for the synthesis of allenic ketones, it was utilised to provide a small range of substrates for the purpose of evaluation in the hydroacylation reaction (Table 3.1).

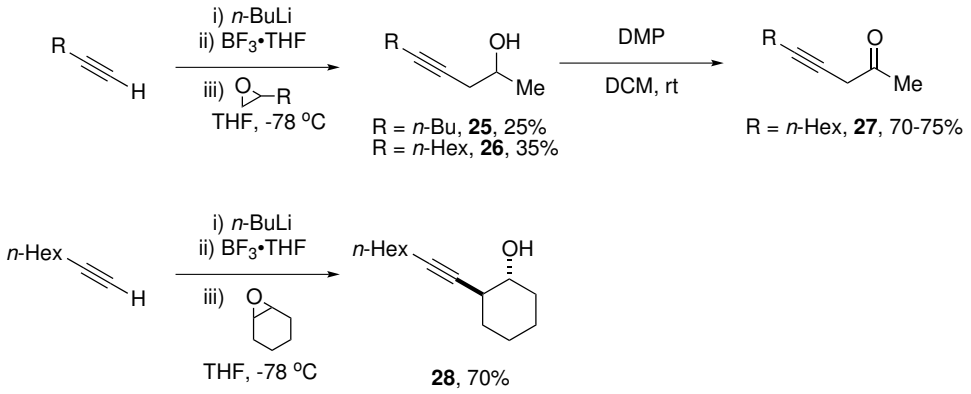


Entry	R^1	R^2	Yield,%
1	Me	OEt	48
2	Me	Ph	34
3	*n*-Bu	Ph	6
4	*n*-Bu	Me	trace
5	Me	Me	complex mix

Table 3.1: Conditions: triethylamine (2–4 mmol, 1 equiv.), acid chloride (2–4 mmol, 1 equiv.), phosphorane (2–4 mmol, 1 equiv.), DCM, 0–5 °C, 10 min then allowed to warm to room temperature over 40 min.

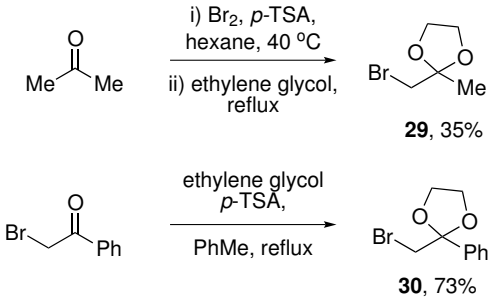
3.2.2 Synthesis of Homopropargylic Substrates

Homopropargyl compounds benefit from a wider range of syntheses than allenic compounds. Opening of epoxides by lithium acetylides in the presence of boron trifluoride gave the desired alcohols reliably but in poor yields (Scheme 3.6).[121–124] Using $BF_3 \cdot THF$ in place of $BF_3 \cdot OEt_2$ gave a minor improvement in yield.[125] Cyclohexene epoxide was opened by the lithium acetylide in good yield to give the cyclohexanol substrate **28**. Homopropargyl alcohol **26** was then oxidised to the homopropargyl ketone **27** using Dess-Martin periodinane in good yield.



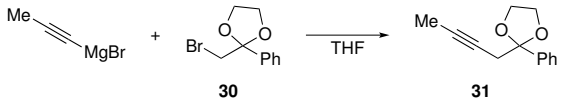
Scheme 3.6: Synthesis of homopropargylic alcohols and ketones

The synthesis of protected homopropargylic substrates was also investigated. α-Bromination of ketones followed by protection of the carbonyl using ethylene glycol gave α-bromo ketals (Scheme 3.7),[126,127] which could furnish the desired homopropargyl ketals.



Scheme 3.7: Synthesis of α-bromo-ketals.

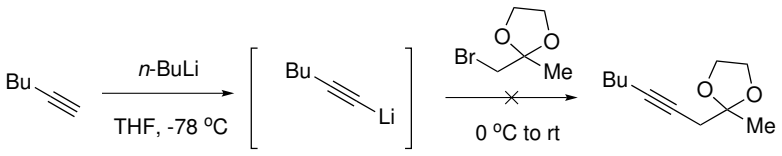
Unfortunately the direct alkylation of **30** using acetylenic Grignard reagents was unsuccessful, resulting in only the recovery of the bromo-ketal starting material. The use of either copper or cobalt additives[128] gave the same result (Table 3.2). An attempt to convert the bromo-ketal **30** to the iodo-ketal by a Finkelstein reaction was also unsuccessful.



Entry	Additive	Temp, °C	Result
1	—	0	SM
2	—	20	SM
3	—	66	SM
4	20 mol % CuI	0	SM
4	20 mol % Li_2CuCl_4	0	SM
5	40 mol % $Co(acac)_3$, TMEDA[128]	20	SM

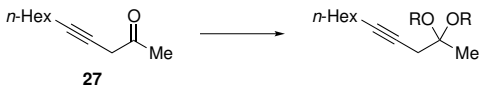
Table 3.2: Attempted alkylation of α-bromo-ketal **xxx**.

Alkylation of the methyl substituted α-bromo ketal was also attempted using *n*-butyl lithium acetylide but, again, no desired product being obtained (Scheme 3.8). With hindsight, this substrate is a poor choice of electrophile because of the hindered neopentyl-type leaving group. Although accounts of the use of **29** and **30** as an electrophile exist, they commonly employ nitrogen nucleophiles.[129] Their most common use is as lithium[130] or magnesium[131,132] nucleophiles.



Scheme 3.8: Attempted alkylation of α-bromo ketal using lithium acetylide.

As this did not result in any useful products, ketal protection of homopropargyl ketones was attempted using a variety of methods.[112,133] The synthesis of ketal-protected homopropargylic ketones again proved to be troublesome, resulting in the isomerisation of the homopropargylic ketone to the allene or isolation of starting material (Table 3.3).



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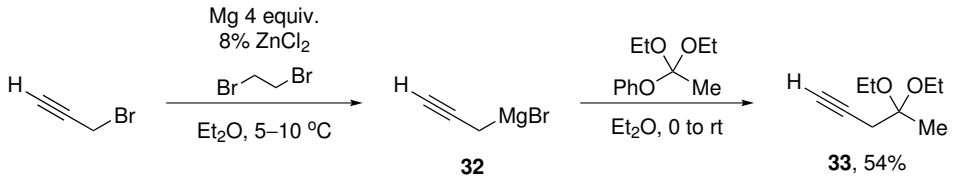
Entry	R	Conditions	Solvent	Temp, °C	Result
1	Me	$C(OMe)_3$, *p*-TSA[112]	MeOH	65	SM consumed
2	-CH_2CH_2-	*p*-TSA, 4 Å MS	DCM	rt	trace
3	-CH_2CH_2-	*p*-TSA, 4 Å MS	DCM	40	trace
4	-CH_2CH_2-	*p*-TSA, 4 Å MS	PhMe	115	allene
5	-CH_2CH_2-	*p*-TSA, 4 Å MS	DCM	20	SM
6	Me	TMSOTf, MeOTMS[133]	DCM	-78	SM
7	-CH_2CH_2-	TMSOTf, glycolTMS[133]	DCM	-78	SM

Table 3.3: Attempted protection of homopropargyl ketones.

The substitution reaction between an orthoester and propargylic Grignard reagents to give the corresponding homopropargylic ketals is known in the literature.[134–136] However, the synthesis of the propargylic Grignard **32** required the use of mercury(II) chloride, which we were keen to avoid. Yuichi Kobayashi reported a high yield mercury-free preparation of propargylic Grignard reagents using catalytic zinc halides in place of mercury.[137] With this in mind, numerous attempts were made to form the Grignard reagent **32** using various methods of activation.[138] Typically, yields of 30–59% (titrated against methyl orange) of the Grignard reagent were achieved (Scheme 3.9). The difficulty with the reaction seemed to be matching the control of reaction temperature and addition rate of propargyl bromide solution. Initially, magnesium, zinc chloride, dibromoethane and 4–8 mol % of the propargyl bromide solution in Et_2O were heated to 30 °C to initiate the formation of the Grignard reagent. The reaction then needed to be cooled to between 5–10 °C. Addition of the propargyl bromide solution is then carried out by syringe pump over 1–3 hours. If the reaction cools below 5 °C the reaction stopped; if it is allowed to rise further,

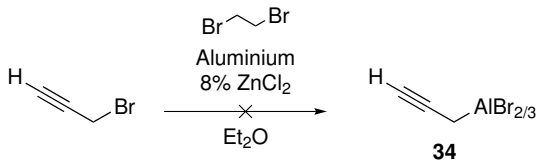
precipitates form and no Grignard reagent is detected after the reaction, probably due to dimerisation.[139] The temperature control may improve with an increase in scale as this reaction has been described in a patent on a one mole scale.[140]



Scheme 3.9: Improved homopropargylic ketal synthesis

The subsequent reaction of the Grignard reagent **32** with the orthoester required the phenyl diethyl orthoester[141] rather than the more common triethyl orthoester. Practical yields are only achieved with the mixed orthoester, which was consistent with the literature.[136] The synthesis of the diethyl orthoester is facile and involves distilling the product from a mixture of phenol and excess triethylorthoacetate. The substitution reaction gave an acceptable 54% (32% overall) yield after aqueous work-up and distillation of the homopropargylic ketal, demonstrating an improvement on the multi-step route used for the cyclic ketals.

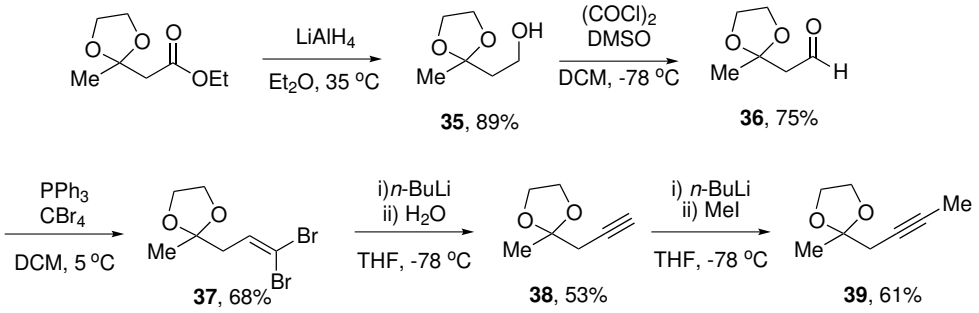
The analogous propargyl aluminium reagent **34** has been shown to react with triethylorthoacetate.[136] Again, the synthesis of the reagent uses mercury. Our attempts to form the aluminum reagent using premilling or zinc chloride were unsuccessful (Scheme 3.10). This would be an attractive alternative to the Grignard reagent, if activation could be achieved without the use of mercury, as it enables the use of readily available orthoesters.



Scheme 3.10: Unsuccessful aluminium reagent synthesis

Finally ketals **38** and **39** were obtained by a multi-step route utilising a Corey-Fuchs

elimination to yield the terminal or internal alkynes (Scheme 3.11).[142]

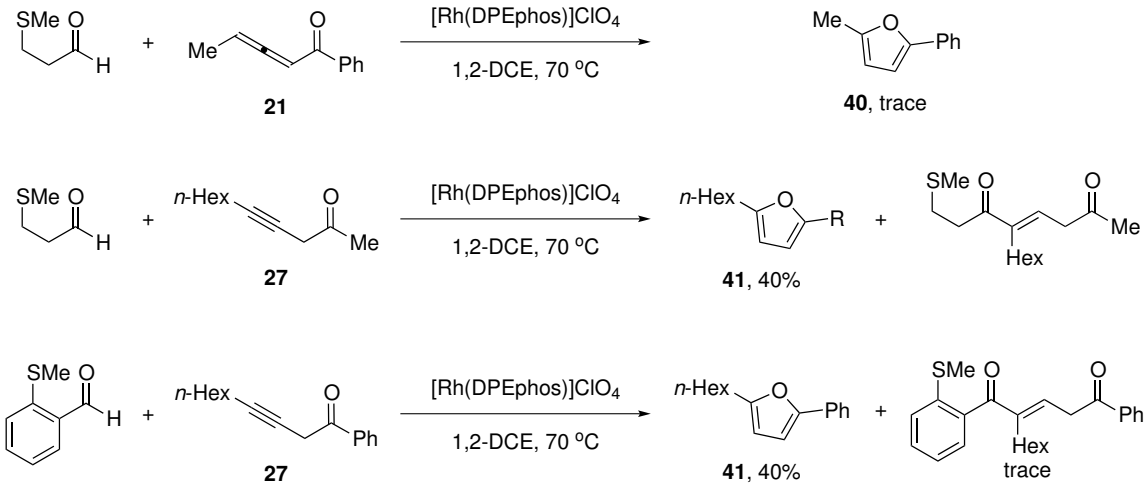


Scheme 3.11: Synthesis of protected homopropargylic alcohols

3.3 Hydroacylation of homopropargyl ketones and allenic ketones

3.3.1 Hydroacylation of Allenic Ketones and Homopropargyl Ketones

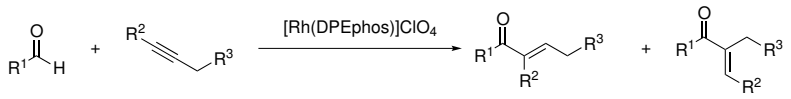
Previous work within the group has established an α-allenic ester to be an excellent hydroacylation substrate (Scheme 3.3).[119] However, it was found that the allenic ketone **21** undergoes intramolecular cyclisation to form the furan product **40** in preference to the hydroacylation product (Scheme 3.12). The furan formation is catalysed by a variety of transition metals and is highly favourable,[113,143–145] and therefore it is unlikely that we would be able to identify a suitable hydroacylation catalyst that does not form the furan. Homopropargylic ketone **27** was also found to form furan **41**[143,146] along with traces of the desired 1,5-dicarbonyl compound when subjected to hydroacylation conditions. The need to avoid the formation of the furan lead us to investigate alcohol and ketal substrates.



Scheme 3.12: Attempted hydroacylation of allenic and homopropargyl ketones.

3.3.2 Hydroacylation of Other Homopropargyl systems

With the substrates in hand, the scope of the reaction was investigated (Table 3.4). In general, high yields were only achieved using terminal alkynes as substrates (entries 1, 5 and 12). Pleasingly, the reaction was able to tolerate a 1 mol % catalyst loading while retaining an excellent yield (entry 1). While internal alkynes bearing a free alcohol gave poor conversions (entries 2-4), a good yield was achieved with the methyl ether **48** (entry 8). The TBS-protected substrate **50** gave only a moderate isolated yield (entry 9). The aromatic aldehyde was able to reach a reasonable yield but with a poorer selectivity for the linear isomer (entries 11 and 12).[147] Usually, the reaction proceeds cleanly with only minor impurities in addition to recovered starting material and desired products. Some dimerisation of terminal alkynes was observed by mass spectrometry and ^{1}H NMR spectroscopy after prolonged reaction times.[148]



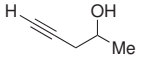
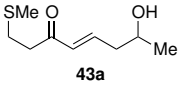
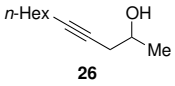
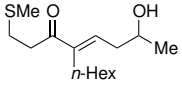
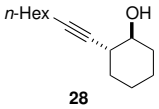
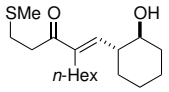
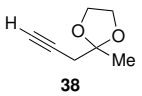
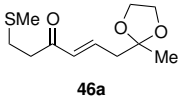
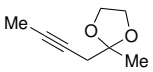
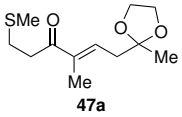
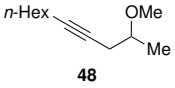
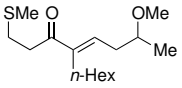
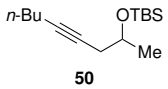
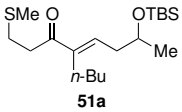
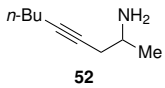
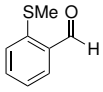
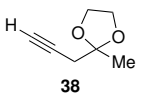
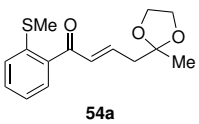
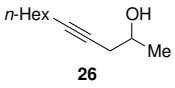
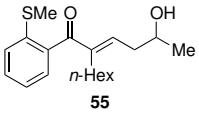
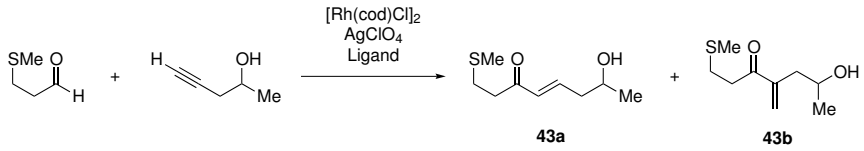
Entry	Aldehyde	Alkyne	Solvent	Product	**a**:**b**	Yield, %
1	 **42**		1,2-DCE	 **43a**	5:1	84[a]
2		 **26**	1,2-DCE	 **44**	>10:1	13
3			acetone		>10:1	12
4		 **28**	1,2-DCE	 **45**	>10:1	11
5		 **38**	1,2-DCE	 **46a**	3:1	>90
6			acetone		10:1	56[b]
7		 **39**	1,2-DCE	 **47a**	∼1:1	27
8		 **48**	1,2-DCE	 **49a**	∼1:1	80
9		 **50**	1,2-DCE	 **51a**	3:1	37[b]
10		 **52**	1,2-DCE	complex mix.		
11	 **53**	 **38**	1,2-DCE	 **54a**	3:2	86
12		 **26**	1,2-DCE	 **55**	3:1	62[b]

Table 3.4: Homopropargylic alkynes: aldehyde (0.15 mmol), alkyne (0.30 mmol), 5 mol % catalyst, 70 °C in 1,2-DCE, 50 °C for acetone, 16 hours. Ratio of isomers determined by ^{1}H NMR spectroscopy. [a]aldehyde (1 mmol), alkyne (2 mmol), 1 mol % catalyst, 20 hours. [b]Using *in situ* generated catalyst.

The DPEphos ligand has been shown to give excellent reactivities in hydroacylation reactions, even with relatively unreactive alkenyl substrates.[76] A thorough optimisation screen of catalyst systems had not previously been carried out on alkynyl substrates. A brief ligand screen using a catalyst formed *in situ* from $[Rh(cod)Cl]_2$, $AgClO_4$ and ligand failed to identify an alternative to DPEphos, which could produce any of the desired product with internal alkynes in 3.5 hours (Table 3.5).



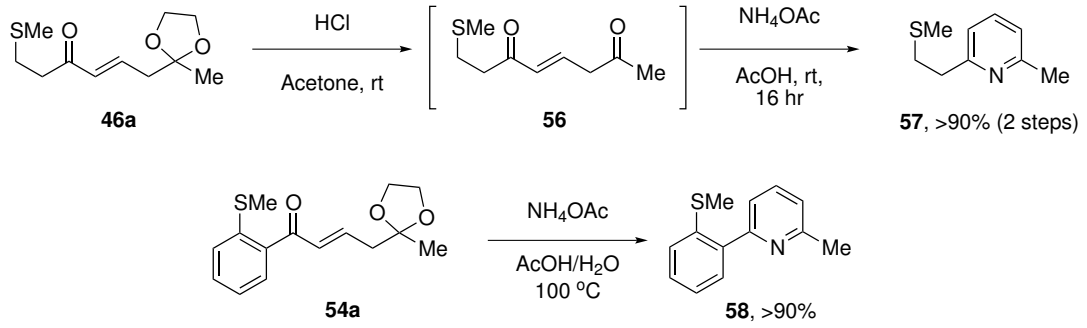
Entry	Ligand	Result
1	dppm	SM
2	dppe	SM
3	dppp	SM
4	dppb	SM
5	dppf	SM
6	Xantphos	SM
7	**DPEphos**	**56%**
8	BINAP	SM

Table 3.5: Ligand optimisation: aldehyde (0.15 mmol, 0.25 M), alkyne (0.3 mmol), 2.5 mol % $[Rh(cod)Cl]_2$, 5 mol % $AgClO_4$ with hydrogen activation, 5 mol % ligand, DCE (1.5 mL), 50 °C. Reaction stopped after 3.5 hours.

3.4 Synthesis of Pyridines

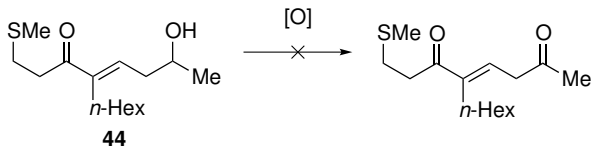
The ketal protected 1,5-dicarbonyls **46a** and **54a** were cyclised into pyridines **57** and **58** in the presence of ammonium acetate and acetic acid under classical conditions[93,149] in excellent yields. The deprotected dicarbonyl **56** quickly degraded after work-up. Fortunately, the crude mixture was converted completely to the pyridine

57 when treated with ammonium acetate (Scheme 3.13). It was found that the deprotection step could also be telescoped and the pyridine **58** obtained directly from the ketal. This method was also used by the Donohoe group in the recent publication described on page 25. This result represents a proof of principle for a hydroacylation approach for the synthesis of pyridines. A facile synthesis of a larger range of homopropargyl substrates and further optimisation of their hydroacylation would be required before this approach becomes synthetically useful. In particular, the synthesis of highly substituted pyridines would need to be demonstrated.



Scheme 3.13: Synthesis of substituted pyridines

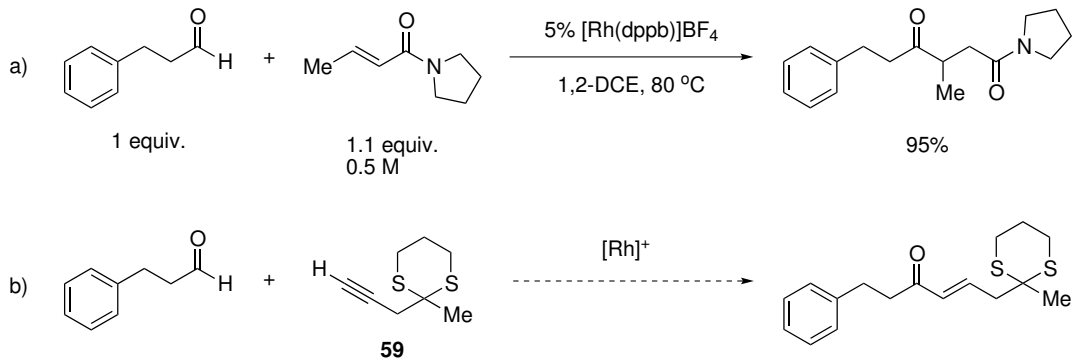
Access to pyridines from the keto-alcohol would have been preferable to the ketal as their synthesis requires fewer steps. Attempts to oxidise keto alcohol **44** by Swern oxidation[150] to obtain the dicarbonyl were unsuccessful (Scheme 3.14). The Donohoe group were able to carry out very similar oxidations using 1–3 equivalents of Dess-Martin periodinane.[94] In our hands, this only resulted in a complex mixture of products. In order for the synthesis of pyridines by this hydroacylation approach to be synthetically useful, the starting materials for hydroacylation need to be readily available and a facile oxidation[151–156] of the alcohol to yield the cyclisation precursor would be required.



Scheme 3.14: Attempted oxidation of 1,5-enone alcohol

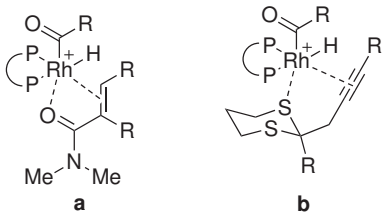
3.5 Hydroacylation of Homopropargyl Dithianes

The concept of double chelation was used by the Tanaka group to facilitate hydroacylation of *N*,*N*-dialkylacrylamides (see page 19).[80] Due to the challenging Grignard reagent preparation and Tanaka's interesting work, it was decided to investigate homopropargylic dithianes as an alternative protecting group to the cyclic or acyclic ketals (Scheme 3.15).



Scheme 3.15: a) Tanaka's direct hydroacylation; b) Proposed dithiane hydroacylation

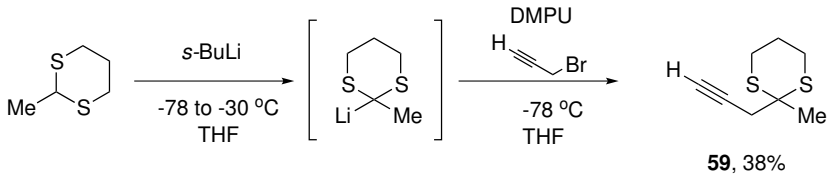
The rhodium chelate formed by the amide group was proposed as the key intermediate by Tanaka.[80] In an analogous fashion we hoped to use the potential chelation of the dithiane to stabilise the rhodium-acyl species to prevent the decarbonylation reaction (Scheme 3.16). Dithiane **59** could conceivably form a bidentate chelate through a sulphur atom of the dithiane and the alkyne. A similar chelate was recently proposed by the Dong group in the hydroacylation of allyl- and homoallyl sulfides (page 20).[82]



Scheme 3.16: Proposed chelated intermediates: a) Tanaka; b) dithiane chelation

3.5.1 Synthesis of Homopropargyl Dithianes and Oxathiolanes

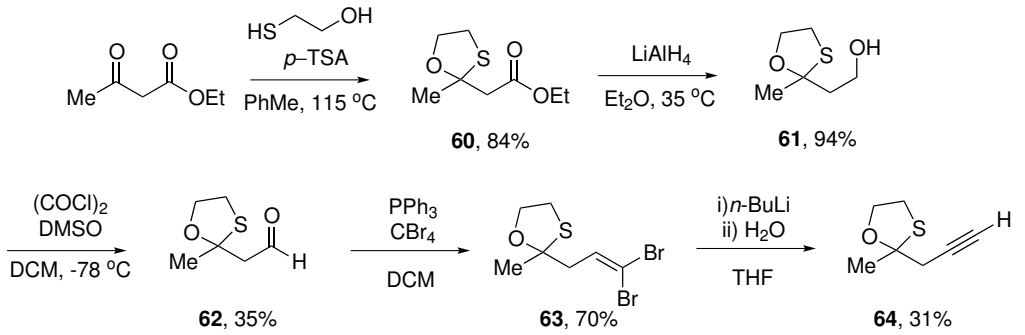
Synthesis of the dithiane **59** from 2-lithium-2-methyl-1,3-dithane and propargyl bromide was relatively simple. However, it was only achieved in an unoptimised 38% yield (Scheme 3.17). Deprotonation of the acidic alkynyl proton of the product by the dithiane possibly limits the yield of this reaction to 50%. This could potentially be overcome by use of a silyl-protected alkyne but this reaction gave a sufficient quantity of the desired substrate to begin investigations. Initially terminal substrates were investigated due to their higher reactivity in hydroacylation reactions but this method should be applicable to synthesis of internal alkyne substrates without the complication of the acidic proton. Use of a mesylate leaving group instead of bromine was unsuccessful resulting in decomposition of the mesylate and recovery of the dithiane.



Scheme 3.17: Lithiation and alkylation of dithianes.

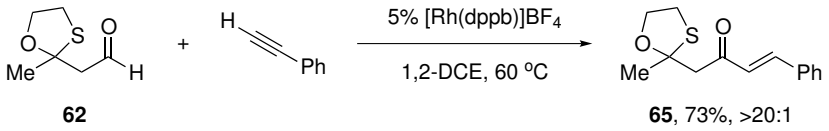
In an analogous fashion to the synthesis of the ketals (Scheme 3.11), the oxothiolanes were synthesised using the same linear sequence (Scheme 3.18).

The intermediate aldehyde **62** was tested in a standard hydroacylation reaction with phenyl acetylene and was found to be a suitable chelating substrate with excellent selectivity for the linear product (Scheme 3.19). The catalyst was prepared as described by Tanaka; *in situ* formation of the catalyst from $[Rh(cod)_2]BF_4$ and the ligand in DCM. After hydrogenation, the solvent was removed under reduced pressure and the reagents added as a solution.[80] This enables high concentrations of



Scheme 3.18: Synthesis of protected homopropargylic alcohols

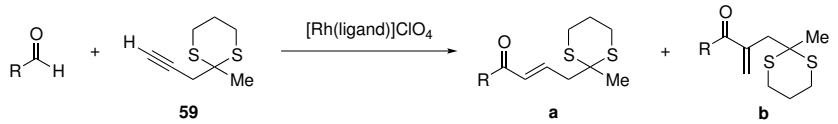
substrate to be added and the catalyst to be prepared in a different solvent to that used in the reaction.



Scheme 3.19: Oxothiolane chelation-assisted hydroacylation.

3.5.2 Hydroacylation of Homopropargyl Dithianes

The standard chelating aldehydes were tested to confirm if the dithiane inhibits the reaction (Table 3.6). Only modest conversions were achieved and, unfortunately, no desired product was isolated. Previous work within the group has used an excess alkyne in order to push the reaction to completion.[76,77,119] In our case, we were keen to avoid possible issues with inhibition from excess coordination of the substrates to the rhodium. Given that no product was isolated, it is clear that these substrates had a detrimental effect on the hydroacylation reaction.



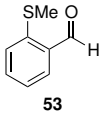
Entry	Aldehyde	Ligand	Solvent	Temp, °C	Conversion, % (a:b)[a]
1	 42	DPEphos	1,2-DCE	60	27 (1:1)
2		dppb	1,2-DCE	60	12 (∼1:1)
3		dppe	PhCl	120	trace
4	 53	DPEphos	1,2-DCE	60	28 (1:0.8)

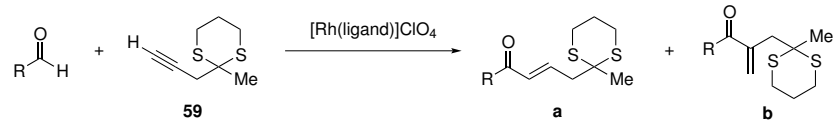
Table 3.6: Conditions: aldehyde (0.15 mmol), alkyne (0.15 mmol), 10 mol % catalyst. [a] Products and ratio of isomers determined by ^{1}H NMR spectroscopy, not isolated. [b]Using *in situ* generated catalyst from $[Rh(nbd)_2]ClO_4$ and ligand.

3.5.3 Alkyne Chelation Assisted Hydroacylation

Although the β-sulphur aldehydes show minimal reactivity in the hydroacylation of dithianes, hydroacylation of non-chelating aldehydes was attempted (Table 3.7). The aldehydes used by Tanaka were used to investigate this reaction. This screen failed to identify suitable conditions to allow hydroacylation of non-chelating aldehydes to occur. Only starting materials were observed by NMR spectroscopy, TLC and in some cases GC/MS. The use of chlorobenzene as a solvent was attempted to allow higher temperatures to be reached with better catalyst solubility than toluene (entry 4). For Tanaka's system, a concentration of 0.5 M of the aldehyde was required for the reaction to be effective.[80] At these concentrations in toluene, the $[Rh(dppb)]BF_4$ catalyst used by Tanaka is mostly insoluble at room temperature.

Only DPEphos, dppe, dppb and 1,1-bis(diphenylphosphine)pentane (PCP) ligands

have been screened. All of the screening was carried out using isolated catalyst (except entry 7) with a high catalyst loading. Further ligand screening will have to be carried out to establish if this system will work in hydroacylations. The presence of two potentially coordinating sulphur atoms could cause additional complications and the chelation of our dithiane to the catalyst has not been proven. Until a lead is identified, it is difficult to evaluate what may be causing the inactivity.



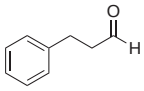
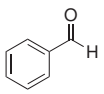
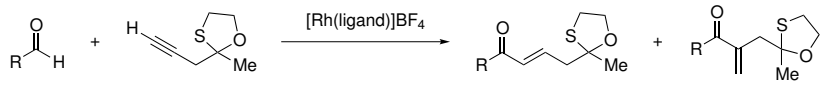
Entry	Aldehyde	Ligand	Solvent	Temp, °C	Yield[a], %	Conds.
1		DPEphos	1,2-DCE	60	0	–
2		DPEphos		60	0	0.4 M
3		DPEphos	PhMe	100	0	–
4		DPEphos	PhCl	120	0	*in situ cat*[b]
5		dppe	1,2-DCE	60	0	–
6		dppe		60	0	0.5 M
7		dppe		60	0	aldehyde (2 equiv.)
8		dppe		60	0	alkyne (3 equiv.)
9		dppe	Acetone	60	0	–
10		dppb		60	0	$[Rh(dppb)]BF_4$
11		PCP[c]		60	0	$[Rh(PCP)]B(ArF_5)_4$
12		DPEphos	1,2-DCE	60	0	–
13		dppe	1,2-DCE	60	0	aldehyde (2 equiv.)

Table 3.7: Homopropargylic dithiane: aldehyde (0.15 mmol, 015 M), alkyne (0.15 mmol), 10 mol % catalyst. [a] Products and ratio of isomers determined by ^{1}H NMR spectroscopy, not isolated. [b]Using *in situ* generated catalyst from $[Rh(nbd)_2]ClO_4$ and ligand. [c]PCP = 1,1-bis(diphenylphosphino)pentane.

The catalyst preparation method developed by Tanaka proved very user friendly and was subsequently used to investigate the hydroacylation of the oxathiolane substrates using hydrocinnamaldehyde and benzaldehyde. Disappointingly, only starting materials were recovered. In most cases, at least some enyne formation was observed by mass spectrometry and ^{1}H NMR spectroscopy. The oxathiolane was shown to react with the standard sulphur-chelating aldehyde in appreciable conversion, although poor isolated yield after chromatography (Table 3.8).



64 a b

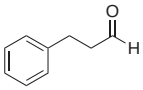
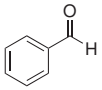
Entry	Aldehyde	Ligand	Solvent	Temp, °C	Conversion, % (a:b)[a]
1	 42	dppb	1,2-DCE	60	70 (31 isol. **66a**)
2		DPEphos	1,2-DCE	60	SM
3		dppb		60	SM
4		DPEphos	PhCl	120	SM
5		dppe		120	SM

Table 3.8: Homopropargylic oxathiolane: Aldehyde (0.15 mmol, 0.25 M), alkyne (0.30 mmol), 10 mol % catalyst. [a]Products and ratio of isomers determined by ^{1}H NMR spectroscopy.

3.6 Summary

This chapter provides a proof of concept for the synthesis of pyridines in high overall yield by the combination of β-sulphur chelation-controlled hydroacylation of homopropargyl ketals and classical heterocyclic synthesis, employing an *in situ* ketal-deprotection. The synthesis of starting materials was an obstacle to efficient in-

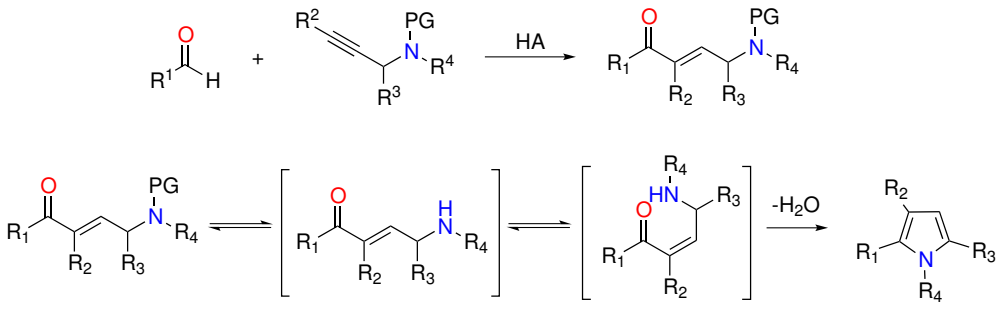
vestigation of this area. As such, the identification of more efficient syntheses for homopropagyl ketals would allow the scope of this reaction to be expanded to include a wider range of pyridines and, in particular, highly substituted pyridines.

Chapter 4

A Hydroacylation Approach to Pyrroles

4.1 Introduction

Hydroacylation of propargylic amine derivatives should provide a route into γ-amino enones. Our proposal was that these would be ideal substrates for the synthesis of highly substituted pyrroles in a "one-pot" deprotection, isomerisation, cyclisation sequence if a suitably labile protecting group is used (Scheme 4.1).



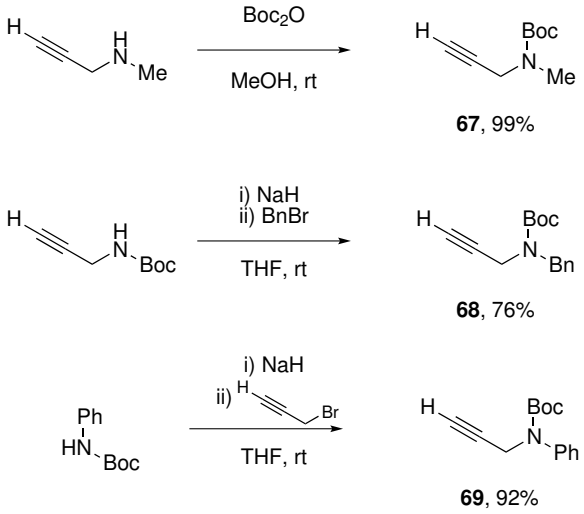
Scheme 4.1: Hydroacylation approach to pyrroles

4.2 Synthesis of Propargylamines

There are numerous methods to synthesise the propargyl amine substrates. When compared to the synthesis of homopropargyl substrates described previously (Section 3.2), this is a significant advantage as it would allow a wide range of substrates to be investigated with relative ease.

4.2.1 Terminal propargyl amines by *N*-Alkylation

N-Methyl propargyl amine was Boc-protected in quantitative yield using a literature procedure.[157] *N*-Phenyl and -benzyl substrates were prepared by the alkylation of *N*-Boc-aniline and *N*-Boc-propargylamine respectively (Scheme 4.2).[158]

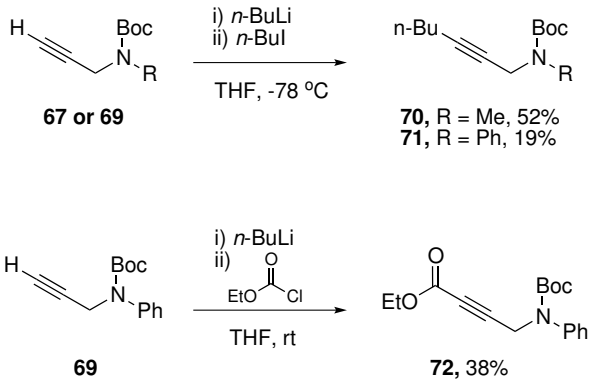


Scheme 4.2: Synthesis of terminal *N*-propargyl amines

4.2.2 Alkylation of terminal acetylenes

The propargyl amines **67** and **69** were treated with *n*-butyl lithium, followed by *n*-butyl iodide to obtain the respective internal alkynes **70** and **71**. The interesting alkyne formate **72** substrate was made by treatment of the lithium acetylide with

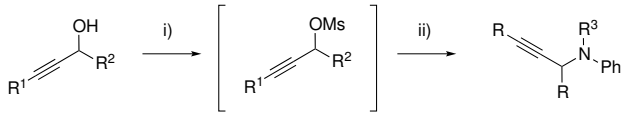
ethyl chloroformate (Scheme 4.3). Only moderate yields were achieved with these substrates, presumably due to incomplete lithiation of the acetylene.



Scheme 4.3: Synthesis of internal alkynes

4.2.3 Synthesis of internal alkynes by substitution of a mesylate

Alkylation of *N*-Boc-aniline or *N*-Boc-benzylamine using secondary mesylates was used to obtain α-alkyl propargyl amines (Table 4.1). This approach worked acceptably well in the case of the internal alkynes (entries 1–4), improving on the previous synthesis of **71** (Scheme 4.3). The reaction failed to yield any of the terminal alkyne **76** (entry 5) and gave only small amounts of the desired product with terminal alkynes (entries 6 and 7). This is presumably due to the harsh reaction conditions which may cause decomposition of the mesylate to allene-type products. Attempts to form **76** by protection of **77** using Boc_2O or Boc-ON also failed.



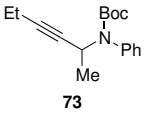
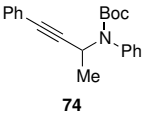
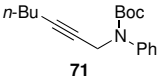
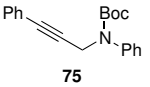
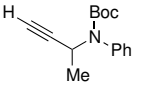
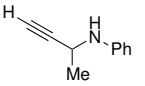
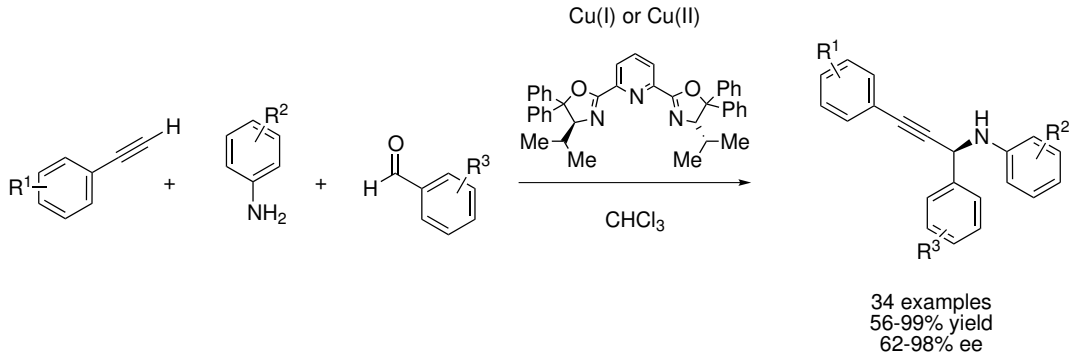
Entry	R^1	R^2	R^3	Yield, %	Product
1	Et	Me	Boc	61	 **73**
2	Ph	Me	Boc	45	 **74**
3	Bu	H	Boc	57	 **71**
4	Ph	H	Boc	60	 **75**
5	H	Me	Boc	0	 **76**
6	H	Me	H	19	 **77**

Table 4.1: Conditions: i) mesyl chloride (1 equiv.), triethylamine (1 equiv.), DCM, 0 °C; ii) sodium Boc-aniline (1–1.2 equiv.), DMF, 0–130 °C, 3–20 hours.

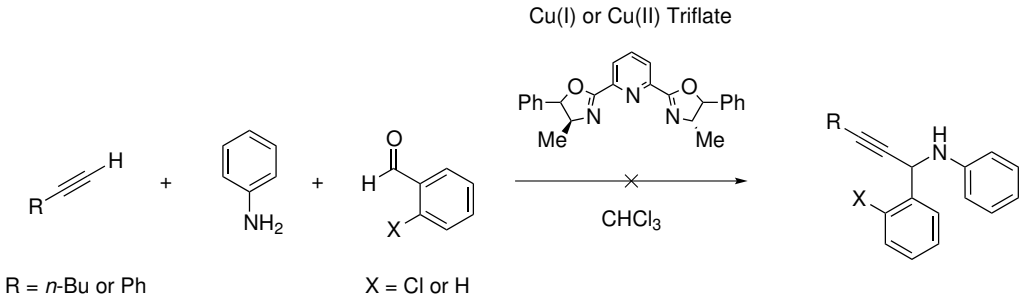
4.2.4 A Three-Component Synthesis of Propargyl Amines

The synthesis of the propargylamine substrates could be improved by the use of a multi-component reaction between an amine, an aldehyde, an alkyne and an appropriate catalyst (Scheme 4.4). There is good precedent for the reaction using secondary amines and some precedent by Singh using primary amines and a bis(oxazolinyl)pyridine ligand.[159] Most of the examples bear aryl substituents on the alkyne component and achieve excellent yields and enantioselectities.[160]



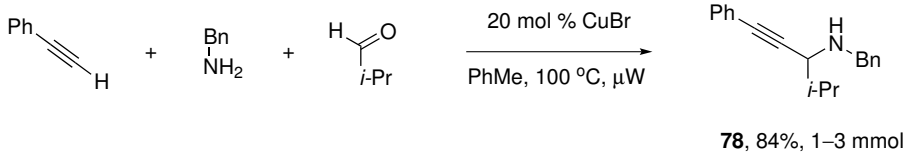
Scheme 4.4: Multi-component synthesis of propargylic amines

In our hands, using the closely related commercially available ligand, no reactivity was observed with a number of substrates that were used in the literature (Scheme 4.5). Only the imines were obtained after the reaction.



Scheme 4.5: Attempted multi-component synthesis

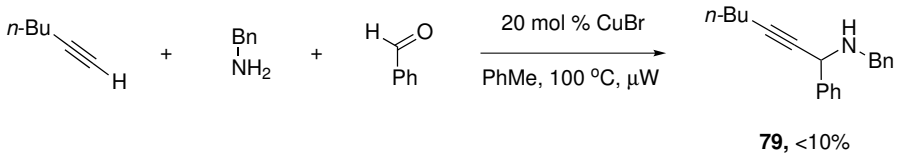
However, a related three-component reaction developed by Van der Eycken was then used to obtain **78** in good yield using copper bromide as a catalyst (Scheme 4.6).[161]



Scheme 4.6: Copper bromide-catalysed three component coupling

Although these reactions give excellent yields in the literature, they are highly substrate specific. Using this methodology, it was hoped that aryl aldehydes could be

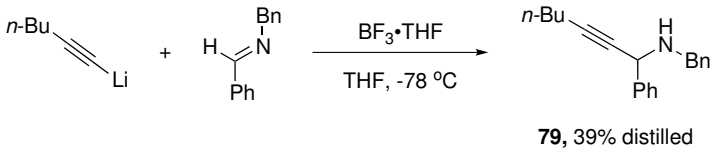
utilised to obtain α-aryl propargylic amines. Unfortunately, alkyl alkynes were found to react slowly with aryl imines under the same conditions resulting in only poor conversion to the product (Scheme 4.7). A gold-catalysed approach was also attempted but to no avail.[162]



Scheme 4.7: Synthesis of α-aryl propargyl amines

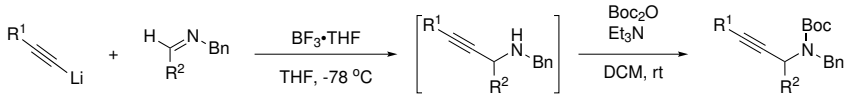
4.2.5 Synthesis of Propargyl Amines By Addition of Acetylides to Imines

The failure of a three-component approach for the synthesis of propargyl amines prompted the attempt to utilise preformed imines. The propargyl amine **79** was obtained in reasonable yield if the preformed imine was treated with the lithium acetylide in presence of boron trifluoride (Scheme 4.8).[163]



Scheme 4.8: Synthesis of α-aryl propargyl amines

This method was then used provide a range of *N*-benzyl substituted substrates (Table 4.2) which were converted into the respective Boc-protected compounds. Surprisingly, the use of Grignard reagents did not result in addition to imine, which could be recovered even after 16 hours.



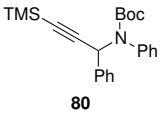
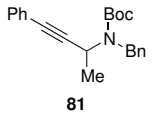
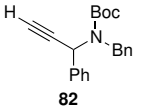
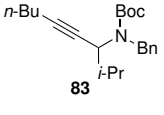
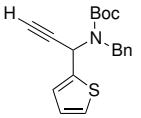
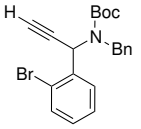
Entry	R^1	R^2	Yield (intermediate), %	Product
1	TMS	Ph	18(61)	 **80**
2	Ph	Me	14(23)	 **81**
3	H	Ph	30(32)	 **82**
4	Bu	*i*-Pr	29(31)	 **83**
5	H	2-thiophene	28(32)	 **84**
6	H	2-bromobenzene	23(60)	 **85**

Table 4.2: Conditions: aldehyde (9 mmol, 1 equiv.), benzylamine (9 mmol, 1 equiv.) in Et_2O, 5 °C, 3–16 hours. Then dried ($MgSO_4$) and added to acetylide (13.5 mmol, 1.5 equiv) and $BF_3 \cdot THF$ (2 equiv.), THF, allowed to warm from -78 °C to room temperature, 3 hours.

4.3 Hydroacylation of Propargyl Amines

4.3.1 *N*-Boc Propargyl Amines in Chelation Assisted Hydroacylation

As mentioned in Section 3.5, Tanaka successfully used *N*-*N*-dialkylacrylamides to stabilise the rhodium-acyl intermediate. We hoped that *N*-Boc propargyl amines

could also behave in this manner to enable sulphur-free hydroacylation of propargyl amines. (Figure 4.1).

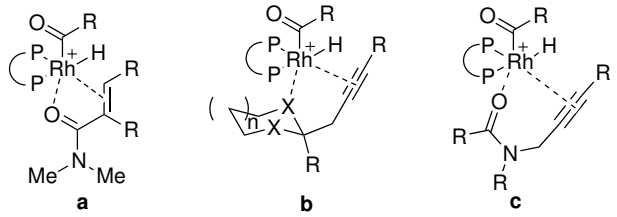
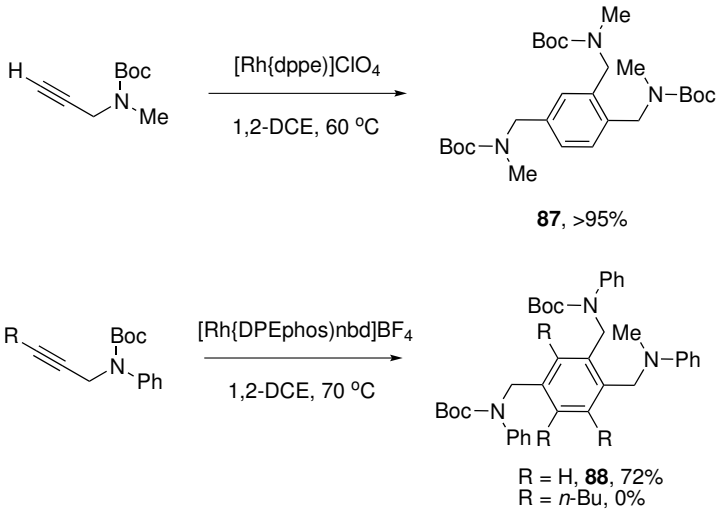
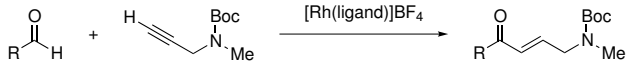


Figure 4.1: Proposed chelated intermediates: a) Tanaka; b) dithiane chelation (Section 3.5); c) Boc-propargyl amine chelation

The aldehydes used by Tanaka were tested against these propargyl amine substrates (Table 4.3). Even at 120 °C in chlorobenzene starting materials were recovered and none of the expected products were isolated, nor observed by mass spectrometry. The isolated [Rh(dppe)]ClO_4 catalyst resulted in the consumption of the alkyne in under 30 minutes (entry 4). This was verified in a separate control experiment without the aldehyde resulting in cyclotrimerisation of the alkyne to form benzene **87**. Using DPEphos as ligand also resulted in cyclotrimerisation, but required longer reaction times (16 hours). The cyclotrimerization could be avoided by utilising internal alkynes (Scheme 4.9).



Scheme 4.9: Cyclotrimerisation of alkynes.



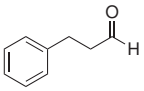
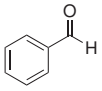
Entry	Aldehyde	Ligand	Solvent	Temp, °C	Products, %[a]
1		dppb	1,2-DCE	60	100 (52 isol. **86a**)
2		DPEphos	1,2-DCE	60	SM
3		dppb		60	SM
4		dppe[b]		60	SM & **87**
5		dppp		60	SM
6		Davephos		60	SM
7		dppp	PhCl	120	SM
8		Davephos		120	SM
9		dppb		120	SM
10		Davephos		120	SM

Table 4.3: Propargylic amine: Aldehyde (0.15 mmol, 0.25 M), alkyne (0.30 mmol), 10 mol % catalyst, 16 hours. [a] Products and ratio of isomers determined by ^{1}H NMR spectroscopy. [b]Isolated catalyst, [Rh(dppe)(nbd)]ClO_4 used to prepare catalyst *in situ* by hydrogenation.

4.3.2 Optimisation of catalyst

Hydroacylation without the need for hydrogen activation of the catalyst would be a significant improvement in the safety and accessibility of the reaction as most industrial pharmaceutical laboratories struggle to use hydrogen outside of specialist laboratories. Using the simple substrate **67**, a number of ligands were investigated in the hydroacylation reaction without the use of hydrogen activation (Table 4.4). A number of useful ligands in addition to the usual dppe and DPEphos were identified; dppm, dppp and dppb. In these cases however, dppm gave the cleanest reactions.

The screen was repeated using the highly substituted substrate **73**. Encouragingly, dppm and DPEphos were, again, identified as the favoured catalysts, giving the product γ-amino enone **89a** (Figure 4.2) in excellent conversions. The *in situ* catalyst can be prepared from either $[Rh(cod)_2]BF_4$ or from $[Rh(nbd)_2]BF_4$ with the latter being preferable due to its less hygroscopic nature. $[Rh(cod)_2]BF_4$ quickly forms hydrates which were found to be very poorly soluble in organic solvents.

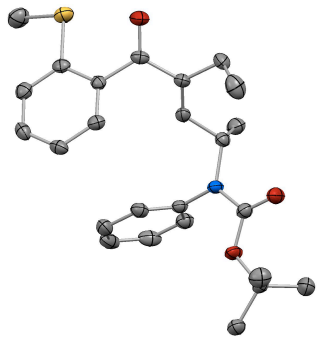
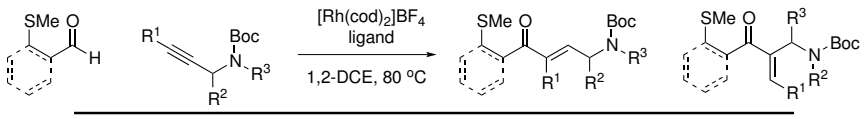


Figure 4.2: X-ray crystal structure of γ-amino enone **89a**

The comparison of *in situ* formed $[Rh(cod)dppb]BF_4$ and isolated catalyst shows a marked improvement (entries 4 and 5). In our hands, attempts to isolate the active dppm catalyst species were unsuccessful. However, the Weller group kindly provided some closely related, dppm and dcpm rhodium complexes for evaluation in this reaction (Figure 4.3). These species were then compared to the $[Rh(nbd)_2]BF_4$ *in situ* catalyst system (Table 4.5). Again the labile fluorobenzene is displaced, presumably by the reaction solvent, without the need for hydrogen activation of the catalyst. After 4 hours, the isolated dcpm species had reached completion and the reactions were stopped for comparison. Both dcpm based catalyst systems behaved extremely well giving excellent conversions (entries 1 and 2). Surprisingly, the *in situ* dppm catalyst outperformed the isolated species (entries 3 and 4), indicating that the catalyst species is probably not the expected rhodium bis-phosphine complex and the true loading in this *in situ* system could be far below 10% of the active catalyst if only a small component of the mixture is active.



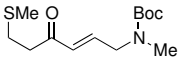
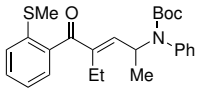
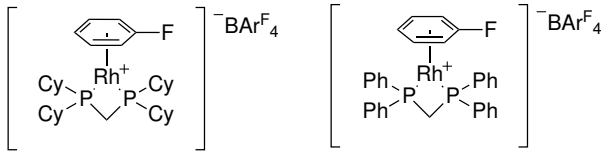
Entry	Ligand	Conversion, %  **86**	 **89a**
1	dppm	100 (8.6:1)	100
2	dppe	68 (6.0:1)	66
3	dppp	60 (19.6:1)	18
4	dppb	63	47
5	dppb[a]	–	81
6	Xantphos	trace	0
7	DPEphos	100 (2.5:1)	100
8	Davephos	trace	–
9	BINAP	–	100
10	–	trace	–

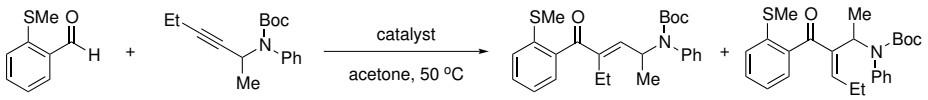
Table 4.4: Ligand optimisation: Aldehyde (0.15 mmol, 0.25 M), alkyne (0.3 mmol), 10 mol % $[Rh(cod)_2]BF_4$ and 10 mol % ligand. 5 hours. Products conversion determined by ^1H NMR spectroscopy and LC/MS spectrometry. [a] Using commercially available $[Rh(cod)dppb]BF_4$.



90 **91**

Figure 4.3

Although these are very competent catalysts for the present study, it was more practical to employ the the readily available $[Rh(nbd)_2]BF_4$ and ligand to prepare the catalyst *in situ* than to use the more exotic isolated species **90** and **91**.



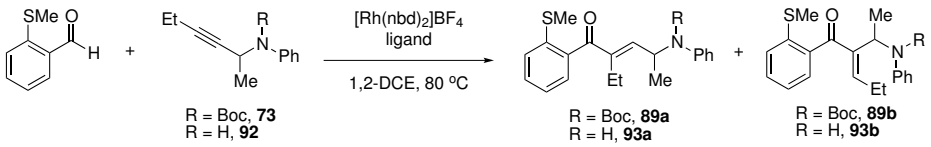
73 89a 89b

Entry	Catalyst	Conv., %
1	$[Rh(C_6H_5F)dcpm]BAr^F{}_4$	100
2	$[Rh(nbd)_2]BF_4$, dcpm	75
3	$[Rh(C_6H_5F)dppm]BAr^F{}_4$	17
4	$[Rh(nbd)_2]BF_4$, dppm	54

Table 4.5: Comparison of rhodium species: Aldehyde (0.08 mmol, 0.15 M), alkyne (0.12 mmol), 10 mol % rhodium species and 10 mol % ligand, acetone, 50 °C, 4 hours.

4.3.3 The Effect of Hydrogen Activation of Catalyst

A comparison of hydrogenated and unhydrogenated *in situ* and isolated catalyst was also carried out in the hydroacylation of protected and unprotected substrates **73** and **92** (Table 4.6). There was a generally a small increase in yield when the catalyst was hydrogenated. DPEphos was generally the optimal ligand for this reaction.



R = Boc, **73**
R = H, **92**

R = Boc, **89a**
R = H, **93a**

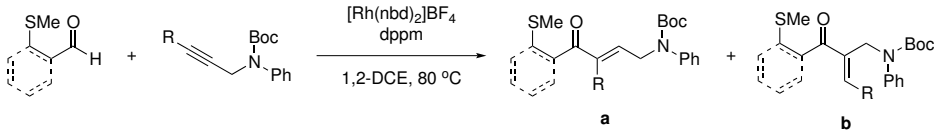
R = Boc, **89b**
R = H, **93b**

			Conversion, %	
Entry	Ligand	R	Hydrog.	No hydrog.
1	dppm	Boc	95	95
2	dppm	H	∼50	∼40
3	DPEphos	H	36(95)	(95)
4	dppe isol.	H	60	69
5	DPEphos isol.	Boc	80	35 (44)

Table 4.6: Aldehyde (0.23 mmol, 0.15 M), alkyne (0.45 mmol), 10 mol % $[Rh(cod)_2]BF_4$ and 10 mol % ligand, 1–3hrs. (conversion).

4.3.4 Effect of Substitution on the Hydroacylation Reaction

The effect of the alkyne substituent on the propargylic amine systems was investigated. A comparison of a terminal alkyne and alkyl and aryl substituents was carried out in parallel. It was found that in this system, the usually excellent, terminal alkyne substrates achieved only 30% yield while the more substituted groups achieved higher yields (Table 4.7). As our intention was to access highly substituted pyrroles after the hydroacylation reaction, it is no great loss that less substituted alkynes perform unfavourably.



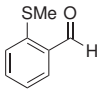
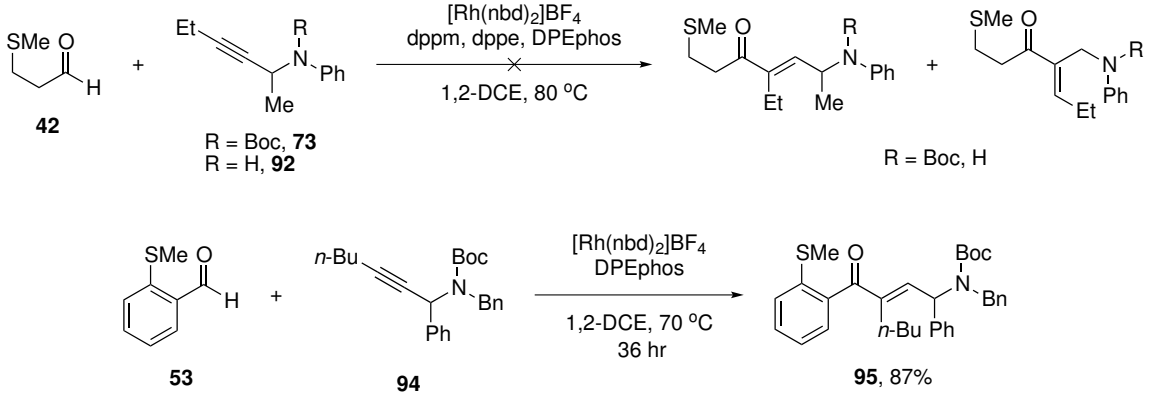
		Yield, %		
Aldehyde	R =	H	Bu	Ph
		30 (∼1:11:1)	64 (∼1:1)	85 (∼1:11:1)
		30	19 (1:1.2)	54 (2:1)

Table 4.7: Effect of alkyne substitution: Aldehyde (0.23 mmol, 0.15 M), alkyne (0.25 mmol), 10 mol % $[Rh(nbd)_2]BF_4$ and 10 mol % dppm, 5 hours. Isolated yield (linear + branched). Linear:branched ratio determined by ^1H NMR.

In these cases, the aliphatic aldehyde gave generally lower yields of the hydroacylation products than the aromatic aldehyde. The reaction failed using alkyl aldehyde **42** under the usually efficient conditions. The dppm and dppe ligands also failed to react when using the aromatic aldehyde on the very demanding α-aryl substituted substrate **94** (Scheme 4.10). Pleasingly, when carried out using DPEphos, this reaction did give an excellent yield after 36 hours. Although dppm is able to reach excellent yields, it appears that the lifetime of the active catalyst is quite short. Substrates requiring longer reaction times benefit from the longer lived but less reactive DPEphos ligand.

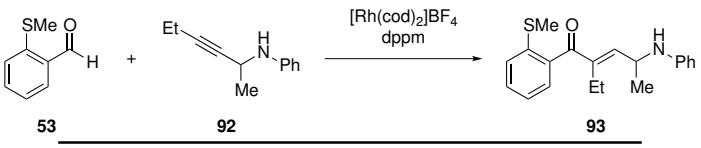


Scheme 4.10: Unsuccessful substrates with the aliphatic aldehyde

4.3.5 Development of an Alternative Solvent System

The use of 1,2-dichloroethane as a solvent generally prevents the usability of the hydroacylation reaction on process scale due to its toxicity and cost of disposal. A screen of a variety of solvents was carried out to determine their suitability for the reaction (Table 4.8).

We also investigated propylene carbonate (PC) as a non-toxic and biodegradable[164] alternative that also benefits from efficient synthesis leading to its current evaluation as a sustainable solvent. It was found to perform very favourably in the reaction (Table 4.9, entry 1). A range of usual hydroacylation substrates were tested using propylene carbonate as the solvent and were found to achieve excellent yields. The concentration of the reation was increased from 0.15 M to 0.30 M to facilitate the removal of propylene carbonate from the product by chromatography. The increase in concentration was found not to affect the regioselectivity, as a reaction carried out at 0.15 M concentration gave an identical ratio (entry 5).



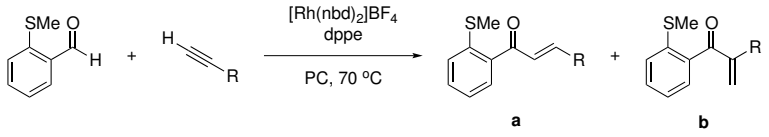
53 92 93

Entry	Solvent	Conversion, %	**a**:**b**
1	1,2-DCE	51	5:1
2	acetone	53	6:1
3	PhMe	4	–
4	PhCl	11	3:1
5	THF	10	4:1
6	water	59	2:1
7	MeCN	43	5:1
8	PC	87	4.7:1

Table 4.8: Aldehyde (0.15 mmol, 0.17 M, 1 equiv.), alkyne (0.30 mmol, 2 equiv.), 10 mol % $[Rh(cod)_2]BF_4$ and 10 mol % dppm, 55 °C, 2.5 hours. Conversion by ^{1}H NMR spectroscopy. Linear:branched ratio determined by ^{1}H NMR and LC/MS.

4.3.6 Scope of Propargyl Amines in Hydroacylation

With the catalyst and reaction conditions optimised, the full reactivity scope was investigated (Table 4.10). The aromatic aldehyde was chosen due to its high reactivity in our systems (as discussed in Section 4.3.4). The reaction showed tolerance for variation of the *N*-substituent, achieving excellent yields with alkyl, aryl and benzyl substituents (entries 1–3). Alkyl- and aryl-substituted internal alkynes gave excellent yields using DPEphos as ligand but gave a poor regioselectivity (entries 4 and 5). Again, alkyl and aryl groups were tolerated with α-methyl substituted propargyl amines (entries 6 and 7), with a slight loss in yield while employing dppm as a ligand with the more challenging aryl substituent (entry 7). α-Aryl substituents also achieved excellent yields and regioselectivities (entries 8–10) and aryl-bromides,



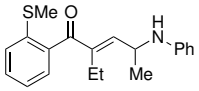
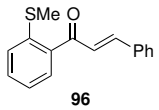
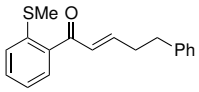
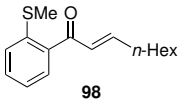
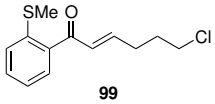
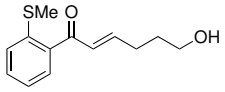
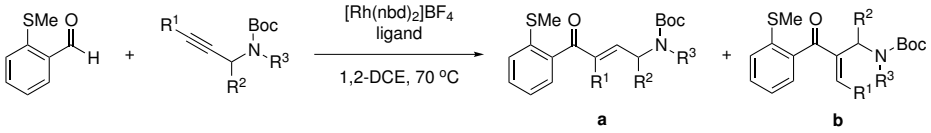
Entry	Product	Yield, %	**a**:**b**
1	 **93**	87 conv.[a]	4.7:1
2	 **96**	84	>12:1
3	 **97**	94	2.9:1
4	 **98**	>95	4.8:1
5	 **99**	99	2:1(2:1)[b]
6		0	

Table 4.9: Hydroacylation in propylene carbonate: aldehyde (0.75 mmol, 0.3 M), alkyne (0.83 mmol), 5 mol % $[Rh(nbd)_2]BF_4$ and 5 mol % dppe, 1 hour. Isolated yield. Linear:branched ratio determined by ^{1}H NMR spectroscopy. [a] 16 hours. [b] 0.15M.

that are relatively unstable to transition metals, were tolerated (entry 9). A longer reaction time was required for α-aryl internal alkynes (entry 10). The use of silyl protected propargyl amines resulted in a complex mixture. α-*iso*-Propyl substitutents prevented the reaction from occurring (entry 12) with only a trace obtained with the alkyl substituted substrate (entry 13). The use of a thiophene substituted propargyl amine **84** resulted in a complex mixture, with considerable amounts of hydroacylation product by ^{1}H NMR spectroscopy and mass spectrometry. This was unfortunate as this entry would lead to linked heterocyclic pyrroles after cyclisation.



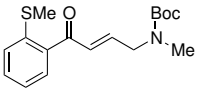
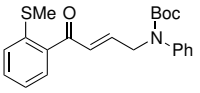
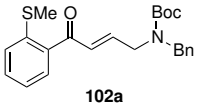
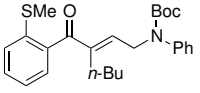
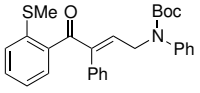
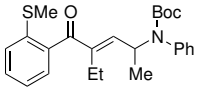
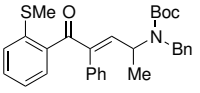
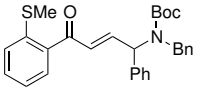
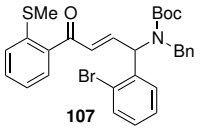
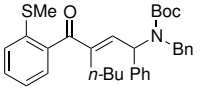
Entry	Product	DPEphos Yield, %	DPEphos **a**:**b**	dppm Yield, %	dppm **a**:**b**
1	 **100a**	80	1.8:1	78	5:1
2	 **101a**	86	1.1:1	95	3:1
3	 **102a**	94	1.7:1	–	–
4	 **103a**	84	∼1:1	55	3:1
5	 **104a**	80	1:1	–	–
6	 **89a**	82	∼5:1	80	>20:1
7	 **105**	54	3.2:1	35	1:1
8	 **106a**	88	∼5:1	–	–
9	 **107**	74	>20:1	–	–
10	 **95**	87[a]	>20:1	0	—

Table continued on next page.

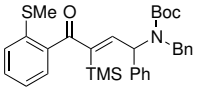
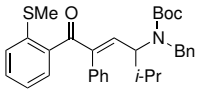
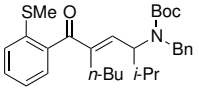
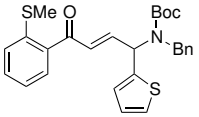
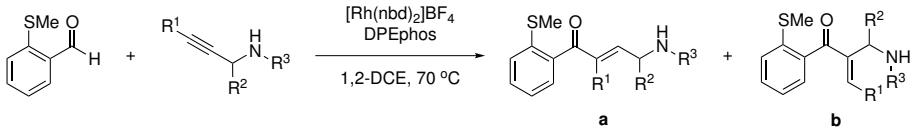
		DPEphos		dppm	
Entry	Product	Yield, %	**a**:**b**	Yield, %	**a**:**b**
11		complex mix.		–	–
12		0 [a]	—	–	–
13		trace[a]	–	–	–
14		complex mix.		0	—

Table 4.10: Scope of Alkyne: aldehyde (0.45 mmol, 0.15M), Alkyne (0.68 mmol, 1.5 equiv.), 10 mol % $[Rh(nbd)_2]BF_4$, 10 mol % ligand, DCE, 70 °C, 16 hours. *a* 36 hours.

4.3.7 Hydroacylation of Unprotected Propargyl Amines

Unprotected substrates can sometimes be used to obtain good yields of hydroacylation product (Table 4.11, entry 2 and 3). In all the successful cases, small amounts of the corresponding pyrroles were also obtained during the reaction.



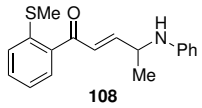
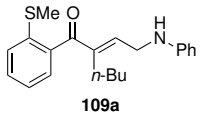
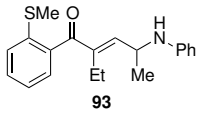
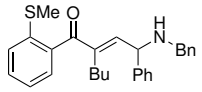
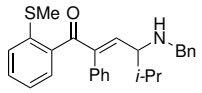
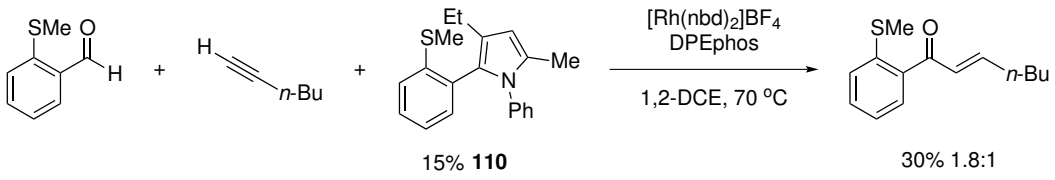
Entry	Linear product	Yield, %	**a**:**b**
1	 **108**	29	2:1[a]
2	 **109a**	68	3:1[a]
3	 **93**	68	5:1[a]
4		0	—
5		trace	—

Table 4.11: Aldehyde (0.45 mmol, 0.15M), Alkyne (0.90 mmol, 1.5 equiv.), 10 mol % $[Rh(nbd)_2]BF_4$, 10 mol % DPEphos, DCE, 70 °C, 16 hours. [a] ∼10% pyrrole isolated.

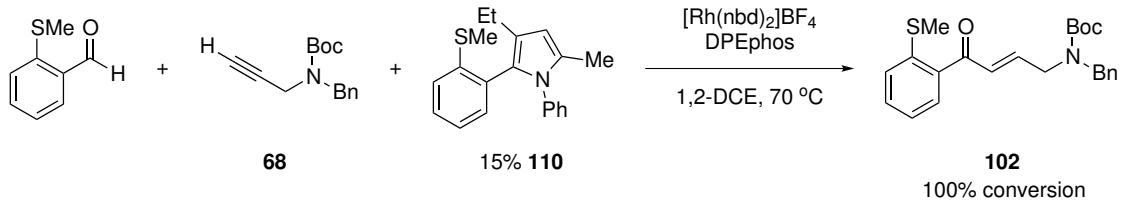
4.3.8 Inhibition of Catalyst by Pyrroles

Given the discrepancy in the reactivity of protected and unprotected substrates, it was suspected that the pyrrole formed during the reaction may be inhibiting the reaction by co-ordination to the catalyst. The yield of a generally facile reaction was significantly decreased when carried out in presence pyrrole **110** (Scheme 4.11).



Scheme 4.11: Inhibition of hydroacylation by a pyrrole.

The reaction was then repeated but using the *N*-benzyl substrate **68**. This reaction proceeded to completion in presence of the pyrrole (Scheme 4.12). Although this is inconclusive, the apparent inhibition could be caused not by the pyrrole but one of the cyclisation intermediates.

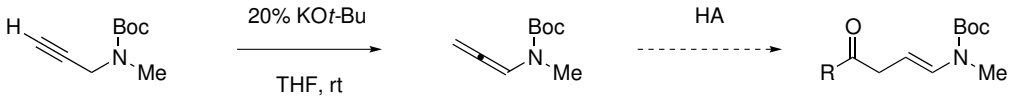


68 15% **110** **102** 100% conversion

Scheme 4.12

4.3.9 Hydroacylation of Allenamides

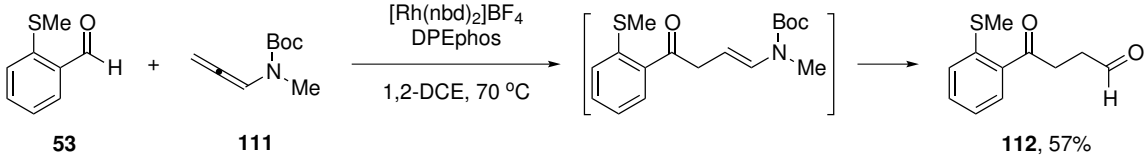
An alternative class of substrates that would lead to suitable cyclisation precursors are allenamides. The isomerisation of propargyl amines to allenamides was used to obtain **111**.[165] This would allow the synthesis of 1,4-ketoenamides by hydroacylation (Scheme 4.13). Treatment of propargyl amine **67** with catalytic potassium *tert*-butoxide gave the allenamide **111** in good yield.



67 **111**, 76%

Scheme 4.13

Using the conditions identified previously, some hydroacylation of the allenamide was observed. However, the isolated product was aldehyde **112**, formed by hydrolysis of the hydroacylation adduct (Scheme 4.14). This is a potentially useful reaction as the resulting aldehydes could be converted into a number of products such as pyrroles by addition of a primary amine.



Scheme 4.14

4.4 Aldehyde Scope in Hydroacylation of Propargyl Amines

Up to this point, the hydroacylation of proparylic amine derivatives has been mostly restricted to 2-(methylthio)benzaldehyde and a few examples using its alkyl analogue. A range of β-thio chelating aldehydes have been shown to be tolerated by the hydroacylation reaction. The ability to use a range of functionalised aldehydes could lead to very interesting pyrrole products that allow further functionalisation, such as those shown in Figure 4.4.

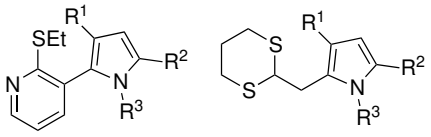
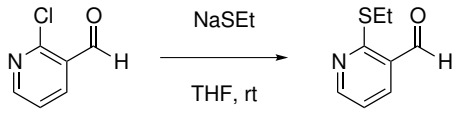


Figure 4.4: Functionalised pyrroles.

4.4.1 Synthesis of Aldehydes

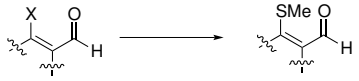
We wished to increase the range of β-sulphur aldehydes that have been shown to participate in the hydroacylation reaction. In addition to the aldehydes that had already been investigated in this study and previously by the group, we also hoped to include a heterocyclic aldehyde. A thioether-bearing nicotinaldehyde **113** was identified as a likely substrate. We proposed that the electron withdrawing thiomethyl group would deactivate the pyridine toward coordination with the rhodium catalyst and prevent interference in the hydroacylation reaction. Aldehyde **113** was readily

available from 2-chloronicotinaldehyde in good yield after chromatography and distillation (Scheme 4.15). This method was then used to synthesise a number of other aldehydes in good yields (Table 4.12).



113, 9.13 g, 77%

Scheme 4.15: Synthesis of 2-(ethylthio)nicotinaldehyde



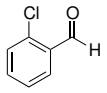
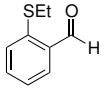
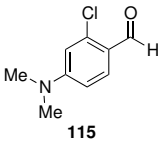
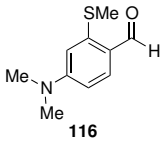
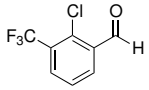
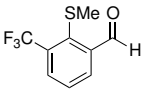
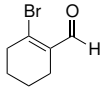
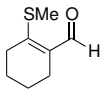
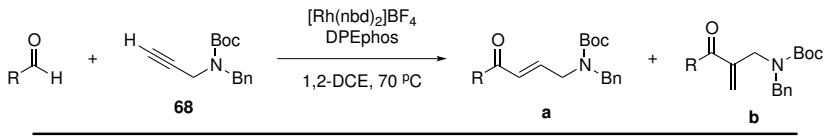
	Halide	Yield, %	Product
1		81	 **114**
2	 **115**	76	 **116**
3		36	 **117**
4	 **118**	75	 **119**

Table 4.12: Conditions: NaSEt or NaSMe, DMF, 0–45 °C, 1–16 hours.

4.4.2 Scope of Aldehydes in Hydroacylation of Propargyl Amines

This range of chelating aldehydes reacted well under the usual DPEphos conditions to provide the desired hydroacylation products in high yields (Table 4.13). Surprisingly 3-methylthiopropionaldehyde **42** resulted in a relatively poor isolated yield

(entry 1). This low yield is probably due to isolation of the product, as all of the aldehyde was consumed and no ketone hydroacylation type products were observed during the reaction. The α-methyl aldehyde **121**, used previously by the group in kinetic resolution experiments,[79] gave an excellent yield and acceptable regioselectivity (entry 2) whilst its phenyl analogue **123** gave a complex mixture of products that did contain hydroacylation products by mass spectrometry and ^{1}H NMR spectroscopy (entry 3). The aromatic aldehyde **53** gave an excellent yield (entry 4). Its electron-poor **117** and electron-rich **116** analogues both gave reductions in yield but improved regioselectivity (entries 5 and 6). Pleasingly, the functionalised aldehydes **126**, **113** and **119** all gave excellent yields (entries 7–9). Unfortunately the recently published MTM-protected substrate **130**[73] gave a poor yield but only the linear product was observed (entry 10).



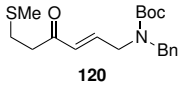
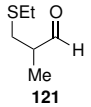
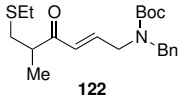
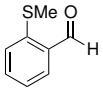
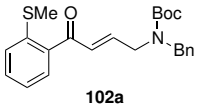
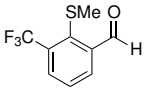
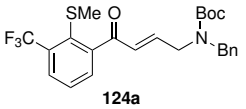
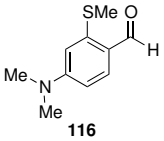
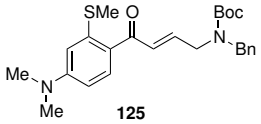
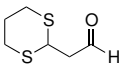
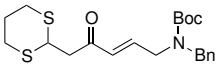
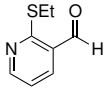
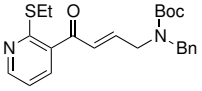
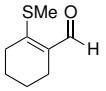
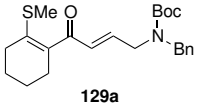
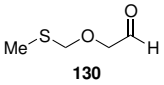
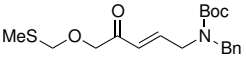
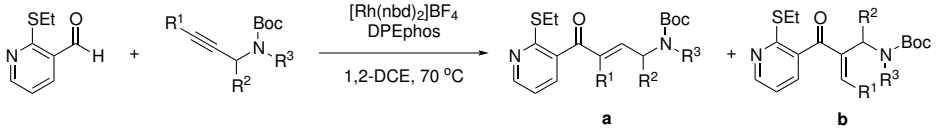
	Aldehyde	Yield	**a**:**b**	Product
1	 **42**	55%	>20:1	 **120**
2	 **121**	93%	3.5:1	 **122**
3	 **123**	complex mix.		
4	 **53**	94%	1.7:1	 **102a**
5	 **117**	41%	2.4:1	 **124a**
6	 **116**	65%	4.3:1	 **125**
7	 **126**	89%	4:1	 **127**
8	 **113**	87%	1.7:1	 **128a**
9	 **119**	99%	1.7:1	 **129a**
10	 **130**	trace	—	

Table 4.13: Scope of Aldehydes: aldehyde (0.45 mmol, 0.15 M), alkyne (0.90 mmol, 2 equiv.), 10 mol % $[Rh(nbd)_2]BF_4$, 10 mol % DPEphos, DCE, 70 °C, 16 hours

4.4.3 Pyridine Aldehyde Scope

Given that nicontinaldehyde **113** gave an excellent yield with alkyne **68**, we hoped to use it to produce a range of γ-amino enones that would allow further functionalisation of the hydroacylation product or the subsequent pyrroles. Frustratingly, the nicotinaldehyde was found to react poorly under identical reaction conditions. Only the most reactive systems gave trace amounts of product under the usual hydroacylation conditions (Table 4.14). Most substrates furnished no reaction, or a complex mixtures of products with a substantial proportion of starting materials being recovered.



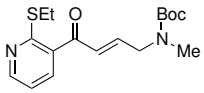
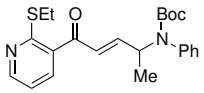
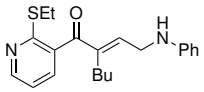
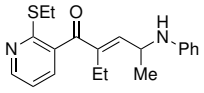
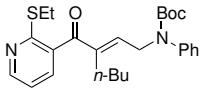
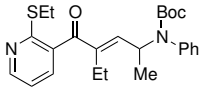
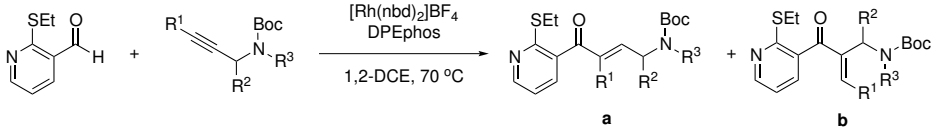
	Product	Yield	**a**:**b**
1		trace	3:1
2		complex mix.[a]	
3		trace	—
4		0	—
5		trace	—
6		trace	—

table continued on the next page.



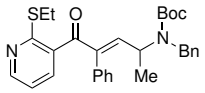
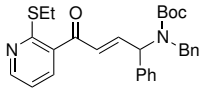
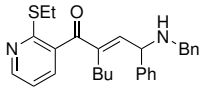
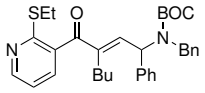
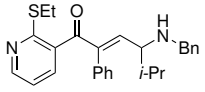
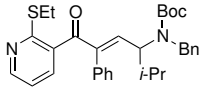
	Product	Yield	**a**:**b**
7		trace	—
8		trace	>1:1
9		0	
10		0	*b*
11		0	
12		0	

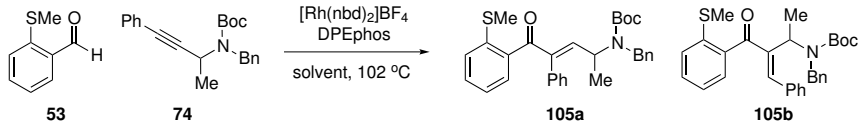
Table 4.14: Conditions: aldehyde (0.45 mmol, 0.15M), alkyne (0.90 mmol, 1.5 equiv.), 10 mol % $[Rh(nbd)_2]BF_4$, 10 mol % DPEphos, DCE, 70 °C, 16 hours. *a* ∼15% pyrrole isolated.[*b*] 64 hours.

4.4.4 Effect of Increased Reaction Temperatures

The disappointing results with nicontinaldehyde **113** lead to the investigation of more forcing reaction conditions. Propargyl amine **74** was chosen as a suitable substrate due to its ready availability and good but incomplete reactivity with aldehyde **53** (Table 4.10, entry 7).

The reaction was carried out at 102 °C, compared to the usual 70 °C, and in a wider range of solvents (Table 4.15). Compared to the previous yield of 54%, these experiments showed only a marginal improvement, with 3-pentanone, propylene carbonate and DCE in a sealed tube giving the best results. The nicotinaldehyde **113** was then

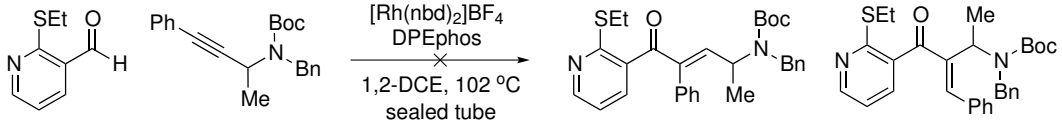
tested under these conditions, but unfortunately without success (Scheme 4.16).



53 74 105a 105b

Entry	Solvent	Yield, %	**a**:**b**
1	3-pentanone	54	3:1
2	PC	58	4:1
3	$PhCF_3$	46	2.9:1
4	1,1,2-TCE	48	2.6:1
5	DCE (sealed)	60	3.2:1

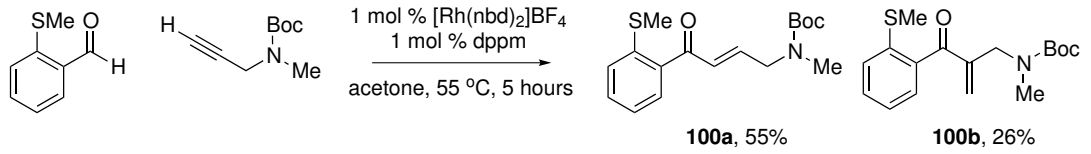
Table 4.15: Conditions: aldehyde (0.23 mmol, 0.15 M), alkyne (0.35 mmol), 10 mol % $[Rh(nbd)_2]BF_4$ and 10 mol % DPEphos, 16 hours. Isolated yield. Linear:branched ratio determined by ^1H NMR spectroscopy.



Scheme 4.16: Attempted hydroacylation in a sealed tube.

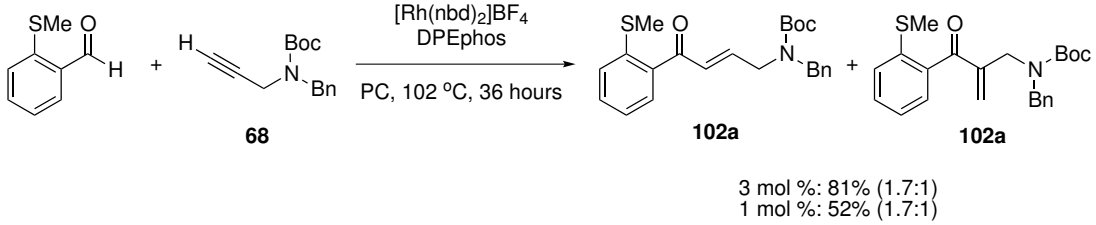
4.4.5 Effect of Catalyst Loading

The hydroacylation reaction has been demonstrated using 1 mol % of catalyst during hydroacylation of homopropagyl substrates in Chapter 3, Section 3.3.2. The early optimisation using dppm as a ligand was carried out with a catalyst loading of 5 mol % and in one example the reaction was demonstrated on a 1 mol % loading and using only a slight excess of the alkyne on a synthetically useful 2 g scale (Scheme 4.17). The reaction reached an 81% yield in just 5 hours, demonstrating the high activity of the dppm catalyst system, which unfortunately is short lived. Longer reaction times did not result in increased yields.



Scheme 4.17: Low catalyst loading dppm: aldehyde (5.9 mmol, 1 equiv.), alkyne (7.1 mmol, 1.2 equiv.)

A more general reactivity was achieved with 10 mol % of DPEphos or dppm derived catalysts. Attempts to reduce the catalyst loading further using a higher reaction temperature, propylene carbonate as solvent and an alkyne loading of 1.1 equivalents, showed that loadings of 3 mol % can be used with a small reduction of yield. Lowering the loading further to 1 mol % results in a loss of yield to 52%.

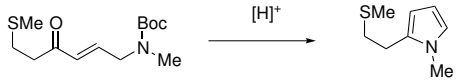


Scheme 4.18: Low catalyst loading DPEphos: aldehyde (1 mmol, 1 equiv.), alkyne (1.1 mmol, 1.1 equiv).

4.5 Cyclisation of γ-amino enones

4.5.1 Acidic promoted cyclisation

With a general method for the synthesis of γ-amino enones in hand, the attention of the project was turned toward their conversion to a range of pyrroles. As discussed in chapter 2, section 2.3, various reports of acid-promoted cyclisation of amino enones exist. Initially, we attempted this using the Boc-protected γ-amino enone **86a** which was converted into the 1,2-substituted pyrrole, albeit in a poor yield (Table 4.16).

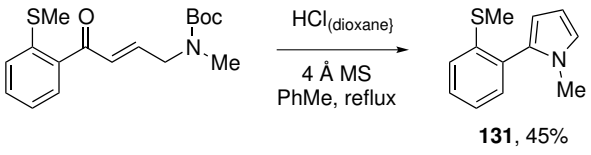


Entry	Acid	Solvent	Yield, %
1	20% TFA (28 equiv.)	DCM	complex mix
2	TFA (2equiv.)	DCM	SM
3	50% AcOH	water	26
4	HCl	THF	complex mix + SM

Table 4.16: Initial pyrrole synthesis attempts

Using typical trifluoroacetic acid Boc-deprotection conditions,[166] a number of highly coloured, polar and unstable side products formed during the reaction, resulting in a poor reaction mass balance (entry 1). Lowering the amount of TFA did not cleave the Boc-group (entry 2). Use of acetic acid gave no reaction at room temperature, even after 2 days. However, after 1 hour at 100 °C, a 26% yield of the desired product was obtained (entry 3). Hydrochloric acid in THF resulted in rapid decomposition of the starting material (entry 4).

Switching to the aryl analogue **131** gave a modest yield using hydrogen chloride in toluene (Scheme 4.19). A slightly lower yield of 36% was achieved using *p*-TSA as the acid catalyst.



Scheme 4.19: Synthesis of 1-methyl-2-aryl-pyrrole

Greater success was enjoyed with the synthesis of the more substituted 1,2,3,5-substituted pyrroles, presumably due to the increased stability of more highly-substituted

pyrroles. The Boc-protected γ-amino enone **89a** was subjected to a range of conditions (Table 4.17).

89a **110**

Entry	Acid	Solvent	Temp, °C	Yield, %
1	TFA	THF	20	SM
2	TFA	THF	66	SM
3	HCl	THF	rt	35

Table 4.17: Synthesis of 1,2,3,5-substituted pyrrole.

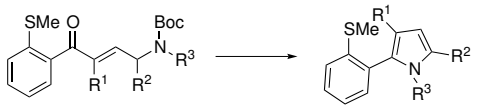
A higher yield was achieved using the unprotected γ-amino enone **93** (Table 4.18). In this case the harsh conditions required to remove the protecting group were avoided, and the reaction needed only to isomerise the double bond and cyclise to give the desired compound. TFA and hydrogen chloride, both aqueous and anhydrous in toluene, gave no reaction after several hours at room temperature (entries 1-3). If tetrahydrofuran was used as solvent the reaction resulted in a complex mixture of products (entry 4). Treatement with acidic Amberlyst-15 resin in propylene carbonate at 100 °C resulted in a moderate yield of the desired pyrrole (entry 5). Finally, it was found that triflic acid in toluene could be used to obtain the desired compound in a clean reaction (entry 7).

93 **110**

Entry	Acid	Solvent	Temp, °C	Yield, %
1	TFA	DCM	20	SM
2	1 M $HCl_{(aq)}$	PhMe	20	SM
3	2.8 M HCl	PhMe	20	trace
4	2.8 M HCl	THF	20	complex mix
5	Amberlyst-15	propylene carbonate	100	32
6	TfOH	DCM	20	complex mix
7	TfOH	PhMe	20	77

Table 4.18: Synthesis of 1,2,3,5-substituted pyrrole from unprotected γ-amino enones.

The triflic acid conditions were also found to successfully cyclise a range of Boc-protected substrates (Table 4.19). Although an extremely powerful acid, it is immiscible in toluene which may temper its reactivity and enable it to be used to produce the relatively unstable pyrroles **132** and **133** (entries 1 and 2). The use of these conditions on the more acid sensitive substrates such as the *N*-benzyl substituted γ-amino enone **102a** resulted in the formation of the same 1,4-dicarbonyl compounds **112** isolated in Scheme 4.14 (entry 4). The use of TMSOTf to deprotect the Boc-group[167] resulted in the cyclised product (entries 4 and 5). This method failed when subjected to the bromide-bearing γ-amino enone **132** (entry 6) and resulted only in the deprotection of the substrate.



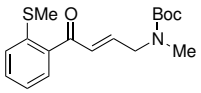
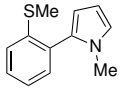
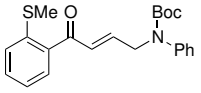
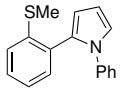
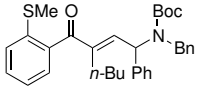
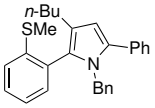
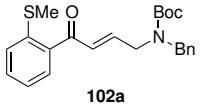
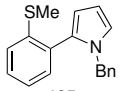
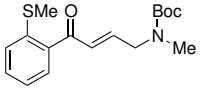
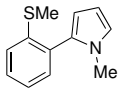
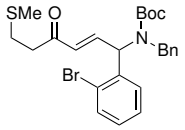
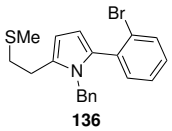
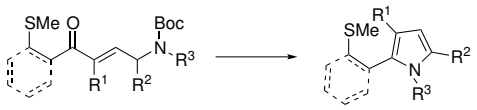
Entry	γ-aminoenone	Conditions	Yield, %	Pyrrole
1	 **100a**	[a]	92	 **131**
2	 **101a**	[a]	75	 **133**
3	 **95**	[a]	74	 **134**
4	 **102a**	[a]	0, **112**	 **135**
5		[b]	72	
6	 **100a**	[b]	67	 **131**
7	 **132**	[b]	0	 **136**
8		[c]	0	

Table 4.19: Conditions: [a] γ-aminoenone (0.1–0.4 mmol), TfOH (2 equiv.), PhMe (0.07–0.15 M), room temperature, 10 minutes then $K_2CO_{3\,(s)}$ added; [b] γ-aminoenone (0.1–0.4 mmol), TMSOTf (1 equiv.), THF (0.07–0.15 M), 0 °C, 1 hour. [c] as for [b] except 70 °C.

4.5.2 Thermal cyclisation of γ-amino enones

Given the of degree sensitivity of the pyrroles and cyclisation intermediates, it was decided to attempt a cyclisation under neutral conditions. Thermal cleavage of Boc-groups is known to occur at temperatures above 150 °C[168,169] and some Paal-

Knorr pyrrole syntheses in water have been reported[170] often using microwave heating.[99,103,104] Initially the deprotection of **100a** was attempted in propylene carbonate under strong microwave heating achieving a yield of 12% of the pyrrole; no deprotected product was detected (Table 4.20). Alcoholic solvents are frequently used for cyclisations of 1,4- and 1,5-dicarbonyl or amino enone cyclisations.[89,92–94] A difficult substrate to cyclise using TMSOTf was γ-amino enone **132**. Initially heating this in methanol gave no reaction. The maximum operating pressure of the microwave was reached at 128 °C without deprotection of the Boc-group. The higher boiling *i*-butanol also did not reach the desired temperature even when heated at 300 watts. Ethanol has a higher dielectric constant, allowing it to absorb microwaves more strongly. It reached just below the temperature required for the thermal deprotection. However, the addtion of water (∼1:1) to the solvent allowed the temperature to reach 170 °C, which resulted in an excellent yield of the desired product **136**.



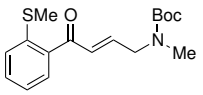
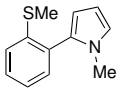
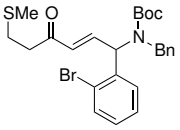
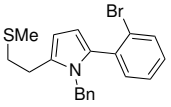
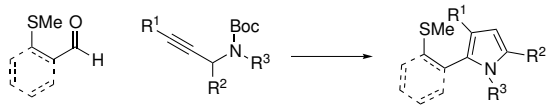
Entry	γ-aminoenone	Solvent	Temp., °C	Yield, %	Pyrrole
1	 **100a**	PC	250	12	 **131**
2	 **132**	MeOH	128	0	 **136**
3		*i*-BuOH	139	0	
4		EtOH	145	0	
5		EtOH/water	170	79	

Table 4.20: Conditions: γ-aminoenone (0.1–0.4 mmol), solvent (2.5 mL) dynamic μW heating (up to 300 W), maximum pressure 250 psi, 1 hour.

4.6 Telescoped Hydroacylation-Cyclisations

If the hydroacylation and subsequent deprotection, isomerisation and cyclisation could be carried out in "one-pot" without purification of intermediates then it would provide an experimentally facile manner to access pyrroles. The discovery of the thermal cyclisation conditions provides an excellent step toward achieving this goal. The first attempts at this consisted of carrying out the hydroacylation as normal then, after completion of the reaction, adding in a relevant acid catalyst. These attempts, before the thermal cyclisation was discovered, resulted in complex mixtures from which only a small (∼10%) quantity of desired pyrrole could usually be isolated. The stability of the final pyrroles in chlorinated solvents is usually poor, as shown in Scheme 4.18. However, using the thermal conditions for the cyclisation after the hydroacylation step gave an excellent range of pyrroles in good yields, considering the inherent selectivity of the hydroacylation (Table 4.21). High tolerance was observed for the *N*-substituent, with all three examples achieving uniform yields (entries 1–3). Tetra-substituted pyrroles **134** and **110** (entries 4 and 5) also gave good yields with the latter requiring a an extended reaction time. Poorer yields were obtained with substrates that are less competent in the hydroacylation reaction. For example entry 7, which proceeds in only a 29% yield and 3:1 linear to branched selectivity in the hydroacylation step, gave 21% of the pyrrole. A lower was observed with entry 8, despite a good hydroacylation yield. A strong odour of methanethiol was observed after this reaction, potentially indicating that the pyridine may have decomposed as a result of high reaction temperatures. This was also noted for the thioenol-substituted pyrrole **142**.



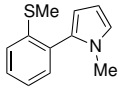
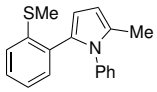
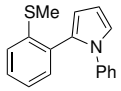
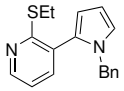
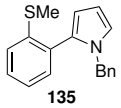
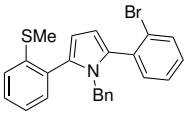
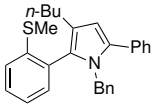
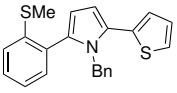
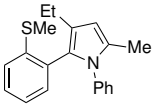
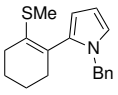
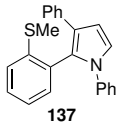
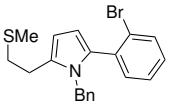
Entry	Pyrrole	Yield, %	Entry	Pyrrole	Yield, %
1	 **131**	50	7	 **138**	21
2	 **133**	48	8	 **139**	29
3	 **135**	48	9	 **140**	44
4	 **134**	44	10	 **141**	8
5	 **110**	46[a]	11	 **142**	36
6	 **137**	24	12	 **136**	41

Table 4.21: Conditions: aldehyde (0.45 mmol, 1 equiv.), alkyne (0.50 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol %), DPEphos (10 mol %), 1,2-DCE, 70 °C, 16 hours. Et_2O added, filtered and concentrated. 50% $EtOH_{(aq)}$ (2.5 mL) dynamic μW heating (up to 300 W), maximum pressure 250 psi, 1 hour. [a] 7 hours.

4.7 Summary

This chapter demonstrates the effectiveness of a large range of propargyl amines in the hydroacylation reaction using an *in situ* prepared DPEphos derived catalyst system that avoids the need for activation of the catalyst by hydrogenation. Good and excellent yields are achieved with terminal, internal and α-substituted

propargylamines and a range of β-sulphur aldehydes. With these examples a poorer regioselectivity is observed than is typical for most hydroacylation reactions in the literature. A wide range of solvents can be used for the reaction and reasonably low catalyst loadings of 3 mol % can be used in some cases.

The hydroacylation reaction can be combined with a classical dehydrative cyclisation to form a range of di-, tri- and tetra-substituted pyrroles in good yields. The hydroacylation conditions employ only 1.1 equivalents of the alkyne component relative to the aldehyde, allowing substrates that are not readily available to be used. The optimised deprotection and cyclisation is carried out under neutral conditions to affect the cyclisation in reliably high yield.

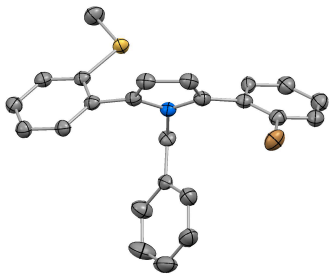


Figure 4.5: X-ray crystal structure of pyrrole **140**

Chapter 5

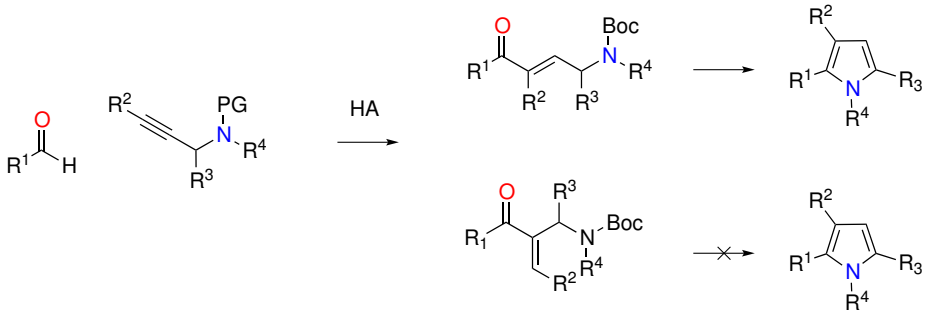
Investigation of Regioselectivity

5.1 Introduction

Work prior to this thesis in the Willis group has not encountered a significant problem with the regioselectivity of the β-sulphur chelating aldehydes. In most cases, the linear product was formed in large excess of the branched isomer. As shown in chapters 3 and 4, when using the more complex homopropargyl and propargyl substrates, considerable amounts of the branched isomers are formed. As the synthesis of pyridines and pyrroles used in this work relies on use of the linear product only (Scheme 5.1), it was pertinent to investigate the source of the selectivity in more detail.

5.2 Design of Experiments investigation

Traditional experimental design investigates the effect of one experimental variable (e.g. temperature) at a time. In a complex system such as a chemical reaction in-



Scheme 5.1

volving a catalyst and several components, investigating the effects of the various factors with traditional methods would take numerous experiments. Furthermore, it would not be possible to quantify the influence of each variable over others. Statistical design of experiments can be used to investigate the combined affects of factors (independent variables). Variation of more than one experimental variable in each experiment complicates the analysis of the experimental data and statistical software packages are used to design the experiments and analyse the results. Stat-Ease Design Expert 7 (DX7)© software was used in order to gain a more in-depth understanding of the hydroacylation of propargyl amines.

Design of experiments is routinely used to optimise industrial processes however it has, so far, only seen limited application in the academic environment. Notable academic studies have been carried out by Aggarval in the optimisation of a Heck reaction, resulting in an increase of yield from 56% to 89% while reducing the loading of palladium from 3% to 0.5%.[171]

5.2.1 Statistical Concepts

A full factorial design includes all the possible combinations of the investigated variables, which would be a considerable undertaking even if each variable was investigated only at two levels (high and low). A reaction involving just two variables

at two levels requires four experimental runs for a full factorial experiment. With four variables (e.g. temperature, time, stoichiometry, catalyst loading) the number increases to 16. This rapidly increases with the number of variables (n) according to 2^n.[172]

A fractional factorial design can be used to reduce the number of experiments required to analyse a reaction by eliminating interactions that are least likely to have a substantial effect. If we assume that the main factors (e.g. temperature, A; time, B; catalyst loading, C) and their two-way combinations (e.g. temperature-time, AB etc.) are the most influential then we can eliminate the three-way combinations of factors (temperature-time-catalyst loading, ABC) as they have only a smaller effect on the reaction. The loss in experimental resolution means that the apparent effect of each main factor is in-fact a sum of the effect of the main factor and its three-way combination ($[A] = A + ABC$). If there are a larger number of factors, even higher level interactions are possible and even less likely to have a significant effect on the overall reaction. This means that fractional factorial design can be used more effectively for larger numbers of factors.

In DoE, there are established standards of fractional factorial designs that are used to describe the "resolution" of identifiable factor combinations:

Resolution III

Main effects are confounded with 2 factor interactions

$[A] = A + AB$

Resolution IV

Main effects are confounded with 3 factor interactions, 2 factor interactions are confounded with other two factor interactions

$[A] = A + ABC$ and $[AB] = AB + CD$

Resolution V

Main effects and 2 factor interactions are unconfounded. 3 factors interactions may be confounded by 2 factor interactions.

$[A] = A$, $[AB] = AB$ and $[ABC] = ABC + DE$

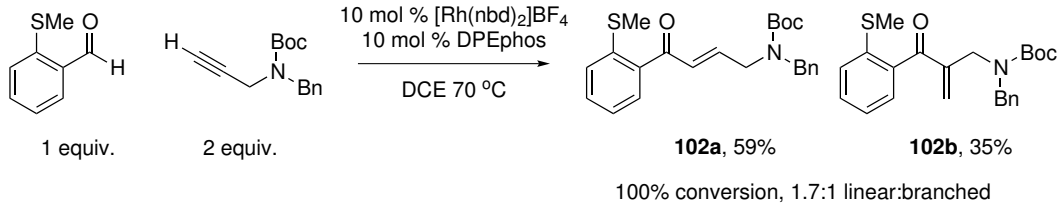
In practice resolution III experiments are best avoided as there is a large chance that 2 factor interactions affect the reaction. Resolution IV requires some care as it is likely that some significant effects may be confounded with others, but this type of screen can be used to identify which factors are most significant, so that some may be eliminated in a subsequent resolution V screen. Resolutions beyond V are generally not worth investigating as higher order interactions are unlikely to have an experimentally significant effect in the reaction.

After the experimental results are gathered, they are analysed and the results plotted as 3-dimensional contour plots describing the interaction of 2 factors against measured responses (e.g. conversion, selectivity).

5.2.2 Design of Initial Screen

An initial screen was used to identify which variables provide the main effects in the reaction. A 2-level reduced factorial design was chosen (resolution IV) with a view to carry out a further resolution V screen.

The reaction chosen for investigation was the hydroacylation of *N*-benzyl propargyl amine using 2-methylthiobenzaldehyde (Scheme 5.2). Although both the linear **102a** and branched **102b** products are rotameric, the characteristic enone protons of both the linear and branched isomer are easily distinguished by ^{1}H NMR spectroscopy and their ratio easily calculated from the integrals of the peaks.



Scheme 5.2: The DoE test reaction

The numeric factors chosen to be investigated were:

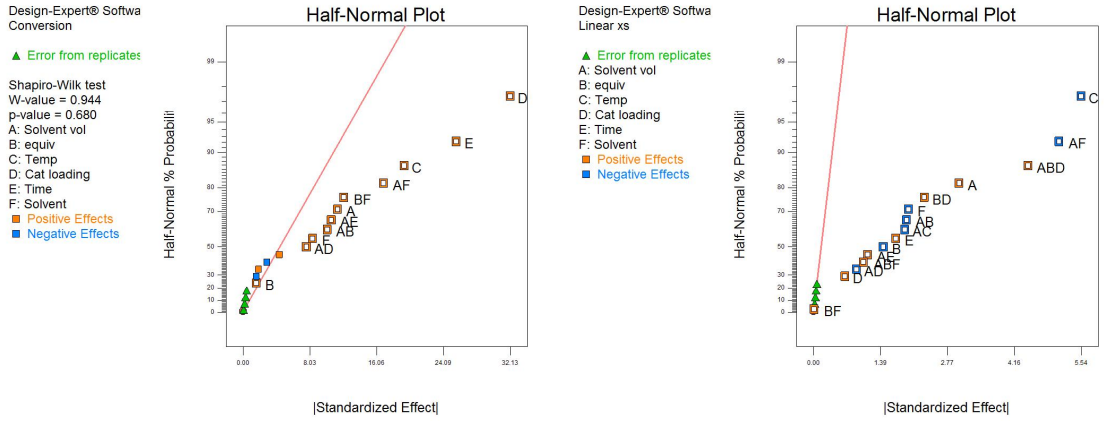
- stoichiometry of alkyne relative to the aldehyde (0.5–2.0 equiv.)
- catalyst loading (2–20 mol %)
- concentration (0.07 M–0.50 M relative to aldehyde)
- temperature (20–50 °C)
- reaction time (1–16 hours)

These were then carried out in both acetone and 1,2-DCE as solvents (a categoric factor). A full factorial design in this case would require 64 (2^6) experimental runs, however the use of a 2-level factorial reduced design reduces this to 16 reactions (full experimental details and results are given in Appendix 8.2, Table 8.1). To estimate experimental error and to look for any curvature in the relationships between the factors, 6 mid-point reactions, where all the factors are at a level between the levels of "high" and "low", are carried out.

5.2.3 Results of Initial Resolution IV Screen

Analysis of the results using Stat-Ease DX7 produced plots of effect against probability of that effect being relevant to the results (Figure 5.1). Factors that diverge from a linear relationship have a significant effect on the model. In terms of conversion (5.1a), catalyst loading, time and temperature were identified as the as the main

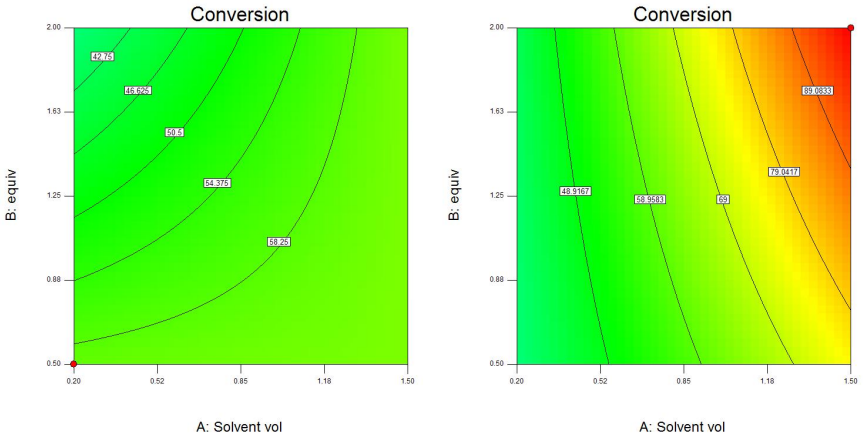
factors affecting the conversion. The combined effect of concentration-solvent was also as statistically relevant as the main factors. Concentration and solvent also had a relevant influence on the conversion. Numerous combinations gave significant but minor effects. The selectivity of the reaction was, again, governed by a large number of statistically relevant factors (5.1b). The most influential was the temperature and the combination of concentration-solvent and concentration-stoichiometry-catalyst loading. Concentration also had a significant effect but a third of that of temperature.



(a) Conversion **(b)** Selectivity

Figure 5.1: Effects of factors.

The model predicted that, at 55 °C, acetone gave best conversions in dilute conditions employing an excess of aldehyde, while 1,2-DCE achieved best results employing an excess of alkyne in dilute conditions (Figure 5.2). The effect of reaction stoichiometry on conversion diminishes in acetone as the solvent volume increases (5.2a). In 1,2-DCE, the effect of stoichiometry is minimal throughout, but its effect increases with an increase in solvent volume (5.2b).



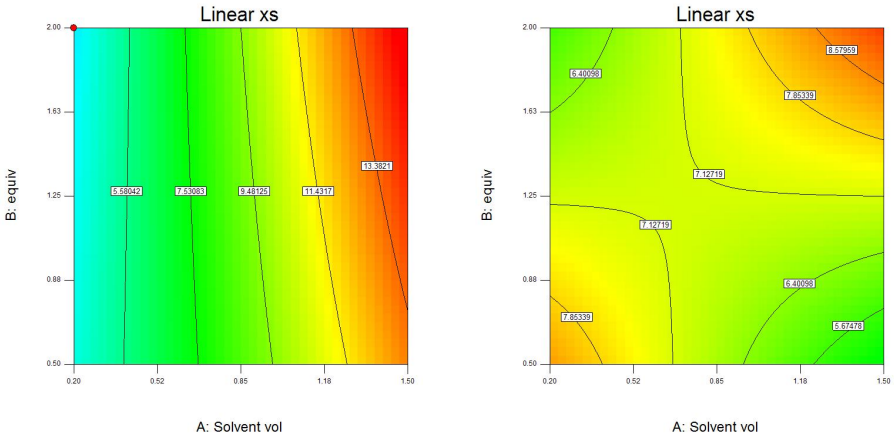
(a) acetone, 55 °C **(b)** 1,2-DCE, 55 °C

Figure 5.2: Comparison of conversion in solvents.

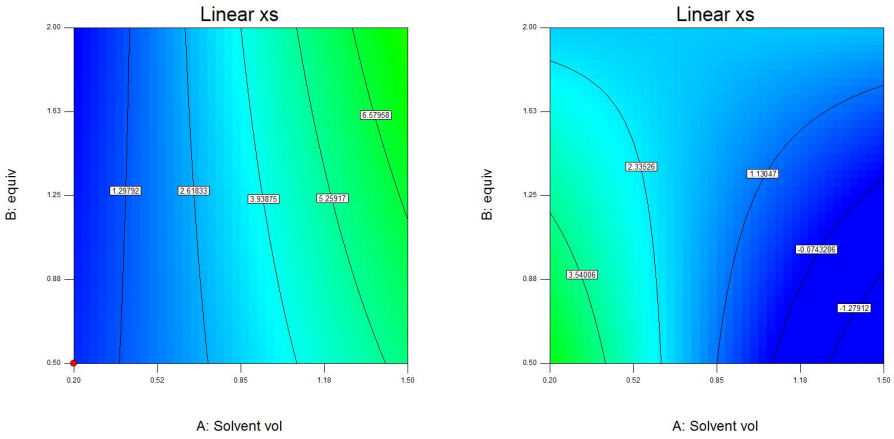
The selectivity of the reaction was markedly improved (>12:1) at colder temperatures (Figure 5.3). However, at the poor conversions obtained at 20 °C, the amount of the minor branched isomer is near or at the limit of detection by ^{1}H NMR spectroscopy, which would artifically inflate the selectivity to the high figures. Nevertheless, the effect is significant, but the magnitude is likely to have a large error.

Selectivity of reactions carried out in acetone was largely independent of reaction stoichiometry (5.3a and 5.3c). In 1,2-DCE, however, the reaction showed considerable curvature. Good selectivities were predicted in either dilute conditions employing an excess of alkyne or in concentrated conditions, employing an excess of aldehyde. However, as these results were obtained with low conversions (Appendix 8.1), they are of less practical value than the reactions carried out at higher temperatures but poorer selectivity.

Catalyst loading and time did not have a major effect on the linear branched selective when compared to the effect of concentration (Figure 5.4).

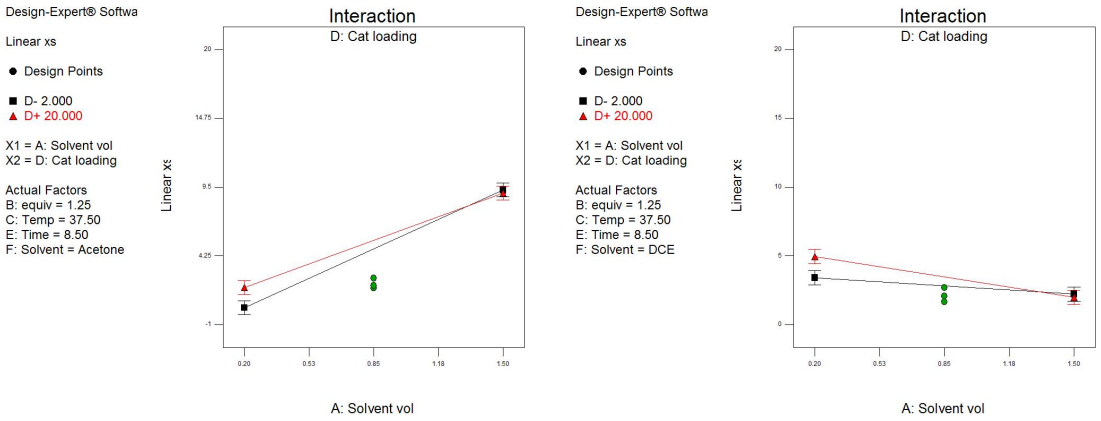


(a) acetone, 20 °C **(b)** 1,2-DCE, 20 °C



(c) acetone, 55 °C **(d)** 1,2-DCE, 55 °C

Figure 5.3: Comparison of selectivity in solvents and temperatures.



(a) acetone **(b)** 1,2-DCE

Figure 5.4: Effect of catalyst loading on selectivity.

5.2.4 Further Investigations of Conditions

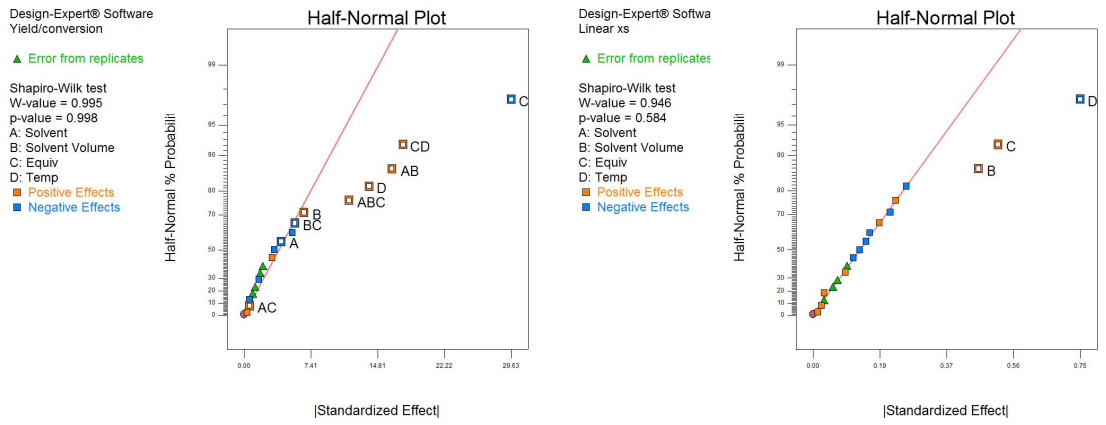
The initial evaluation identified a need for higher temperatures to reach complete conversions to products and that dilute conditions may be amenable to better selectivites. A second screen was designed with a view to explore these conditions. As the initial model includes a large number of terms that may be confounded with others, giving an apparently high level of complexity to the reaction, a second resolution V screen was designed.

It was clear that a 16 hour reaction time was required to reach synthetically useful conversions, so this factor could be eliminated from the second screen. The relatively low boiling point of acetone limited the maximum temperature of the previous screen. The closest analogous solvent to acetone with a higher boiling point was identified as 3-pentanone (bpt 101 °C). As the reaction did not reach completion until the 55 °C, this was chosen as the lower limit with the upper limit as 80 °C, close to the boiling point of DCE (bpt 84 °C). As shown in Figure 5.4, the catalyst loading did not appear to have an effect on the selectivity, so this was fixed at 10 mol %. The remaining factors were then included in the design:

- stoichiometry of alkyne relative to the aldehyde (0.5–2.0 equiv.)
- concentration (0.04M–0.50 M relative to aldehyde)
- temperature (55–80 °C)
- 3-pentanone and 1,2-DCE

5.2.5 Results of Resolution V Screen

A 2-level reduced factorial analysis was carried out against the reaction conversion and selectivity. In the previous screen reaction stoichiometry was only identified as a minor effect. In this design, the reaction stoichiometry was identified as the greatest contributing factor to the reaction conversion. Temperature, solvent-concentration and stoichiometry-temperature were approximately equal contributors and a minor influence was observed from solvent-concentration-stoichiometry. In terms of selectivity, concentration and stoichiometry were approximately equal contributors while temperature was most significant. (Figure 5.5). Significant curvature was observed for both the conversion and the selectivity of the reaction.

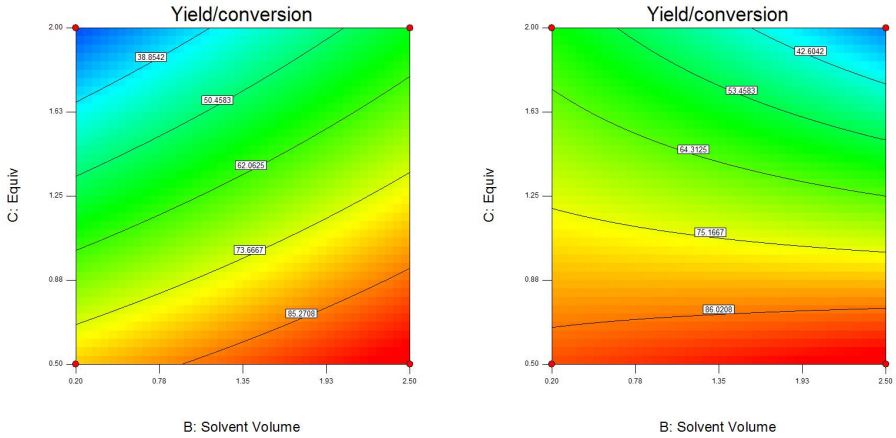


(a) Conversion **(b)** Selectivity

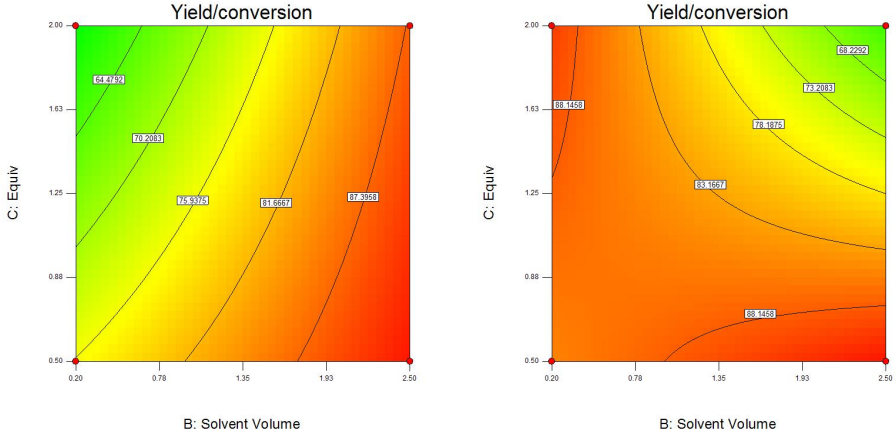
Figure 5.5: Effects of factors.

Reactions carried out in 3-pentanone showed higher conversions in dilute conditions employing an excess of aldehyde, analogous to the results obtained with acetone (Figure 5.2a). At higher temperatures good conversions could be achieved regardless of stoichiometry (Figure 5.6). In 1,2-DCE, at the lower temperature, surprisingly, concentration of the reaction does not have a major affect on the conversion, however stoichiometry does. Once again 1,2-DCE shows considerable curvature with a broad

saddle point of high conversion (Figure 5.6d). Best conversions could be achieved using either concentrated conditions and an excess of alkyne or dilute conditions with an excess of aldehyde.



(a) 3-pentanone, 55 °C **(b)** DCE, 55 °C

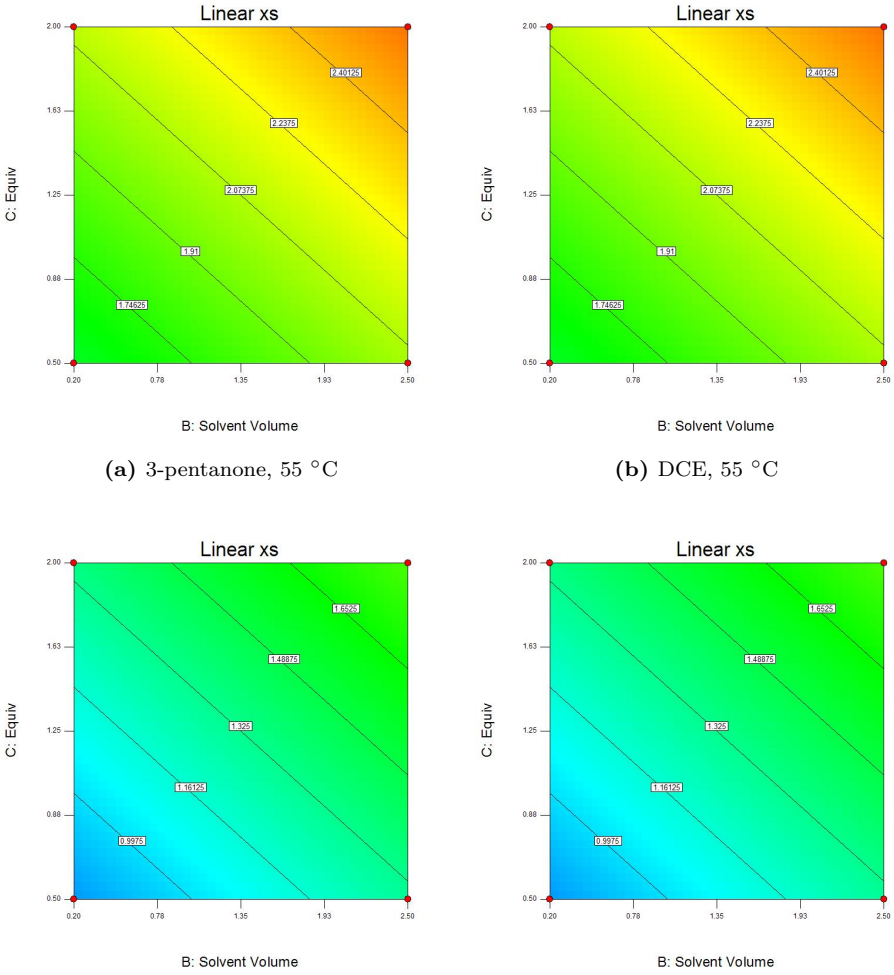


(c) 3-pentanone, 80 °C **(d)** DCE, 80 °C

Figure 5.6: Comparison of conversion in solvents and temperatures.

The main factor affecting the selectivity of the reaction was temperature. A clear improvement could be seen for reactions carried out at the lower temperature of 55 °C compared to 80 °C (Figure 5.7). The identity of the solvent did not have a statistically significant effect on the selectivity, and as such it was excluded from the model. Best selectivities were predicted in dilute conditions employing an excess of alkene. It is worth noting that small quantities of hydrolysis product **112** (See section 4.3.9) was observed in the hotter reactions conditions. This hydrolysis will have a

negative effect on the observed selectivity. Presumably, the branched isomer may also undergo hydrolysis in a similar fashion, but this has not been experimentally observed.



(a) 3-pentanone, 55 °C **(b)** DCE, 55 °C

(c) 3-pentanone, 80 °C **(d)** DCE, 80 °C

Figure 5.7: Comparison of selectivity in solvents and temperatures.

5.2.6 Verification of Findings

A number of points were repeated to further compare the findings of the model with experimental results (Table 5.1). The model gave a very good correlation of the predicted and actual results (entries 1-4 and 6). Entry 5 gave a selectivity in excess of the prediction.

				Predicted		Experimental	
Entry	Solvent	Conc, M	Equiv.	Conv., %	Linear xs	Conv., %	Linear xs
1	3-pentanone	0.50	0.50	78	1.6	68	1.5
2	1,2-DCE			95	1.6	100	1.5
3	3-pentanone	0.04	2.00	60	2.3	65	2.3
4	1,2-DCE			35	1.88	54	2.2
5	3-pentanone	0.04	0.50	95	1.9	100 (78)	2.6 (2.0)[a]
6	1,2-DCE			95	1.9	100	1.6

Table 5.1: Conditions: Limiting reagent (0.1 mmol), $[Rh(nbd)_2]BF_4$ (10 mol %), DPEphos (10 mol %), 55 °C, 16 hours. Conversion determined by ^{1}H NMR spectroscopy. [a] alkyne (0.25 mmol), (isolated yield).

The model indicates better selectivity using an excess of alkyne therefore it would be useful to investigate if a significant increase in selectivity can be achieved using a larger excess of alkyne or if the selectivity can be diminished or reversed using a large excess of aldehyde. Although using a large excess of either starting material is not synthetically useful in most cases, this was tested experimentally (Table 5.2).

Entry	Aldehyde	Alkyne	Conv., %	Linear xs
1	0.1 mmol	0.5 mmol	nd	–
2	0.5 mmol	0.1 mmol	>95	2.8

Table 5.2: Conditions: $[Rh(nbd)_2]BF_4$ (10 mol %), DPEphos (10 mol %), 3-pentanone (2.5 mL), 55 °C, 16 hours. Conversion determined by ^{1}H NMR spectroscopy.

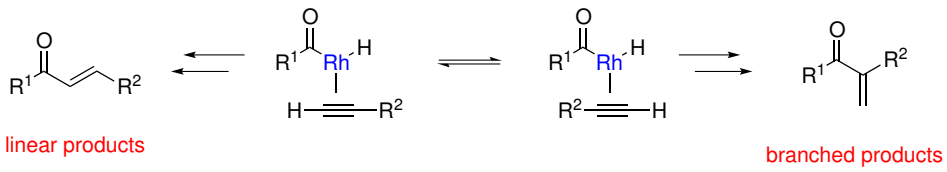
It was found that 5 equivalents of alkyne did not result in formation of the desired product, presumably due to over coordination to the catalyst (entry 1). Using a large

excess of aldehyde resulted in a relatively good selectivity and complete conversion (entry 2).

The conditions identified by the model do give a moderate increase of selectivity and the trends appear to correlate with further experimental findings. Unfortunately, the magnitude of the effects on regioselectivity are minor, with a maximum selectivity of 2.6:1 being achieved from the original 1.7:1 linear to branched ratio.

5.3 Electronics of Aldehyde

In section 4.4.2 a range of aldehydes were tested in the hydroacylation reaction. It was hypothesised that the electronics of the aldehyde could play a part in the rate of hydroacylation of the intermediate rhodium-acyl/alkyne complex (see section 1.3.1) which would in turn affect the regioselectivity of the reaction (Scheme 5.3).



Scheme 5.3: Isomerisation of the rhodium-intermediate.

5.3.1 Hydroacylation

To probe the effect of the aldehyde electronics, the ^{13}C and ^{1}H NMR shifts of the aldehyde carbon and hydrogen were correlated with the linear:branched selectivity obtained with each of the aldehydes (Table 5.3 and Figure 5.8) .

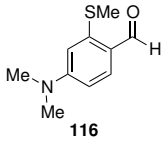
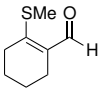
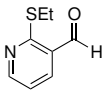
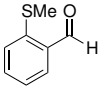
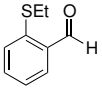
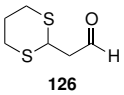
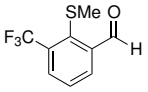
	Aldehyde	^{1}H, ppm	^{13}C, ppm	Yield	Linear:branched
1	 **116**	9.95	189.0	65%	4.3:1
2	 **119**	10.21	189.5	99%	1.7:1
3	 **113**	10.19	190.0	87%	1.7:1
4	 **53**	10.28	191.4	94%	1.7:1
5	 **114**	10.30	191.4	90%	1.6:1
6	 **126**	9.72	199.0	89%	4.0:1
7	 **117**	10.82	192.4	41%	2.4:1
8	 **42**	9.77	200.6	55%	>20:1
9	 **121**	9.69	203.4	93%	3.5:1

Table 5.3: Scope of Aldehydes: aldehyde (0.45 mmol, 0.15M), Alkyne (0.90 mmol, 2 equiv.), 10 mol % $[Rh(nbd)_2]BF_4$, 10 mol % DPEphos, DCE, 70 °C, 16 hours

Clearly, the aldehyde has a significant effect on the selectivity of the reaction. The best selectivity for arylaldehydes was achieved with the electron-rich *p*-dimethylamino-

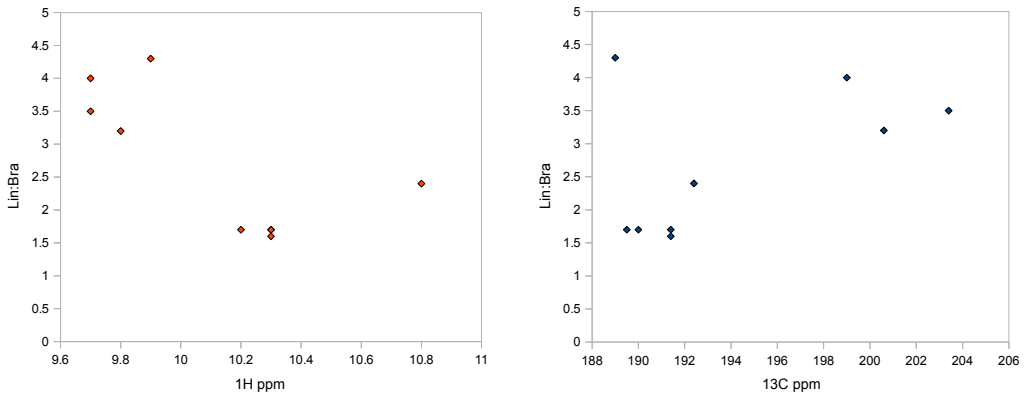
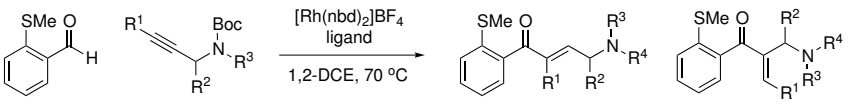


Figure 5.8: ^{1}H and ^{13}C NMR shift of aldehydes against hydroacylation regioselectivity

benzaldehyde **116**. However, this result is clearly outside the norm and more in-line with the alkyl aldehydes investigated. No clear trend is observed within either the aromatic or the alkyl aldehydes. Unfortunately an aldehyde with a ^{13}C NMR shift of around 196 ppm was not synthesised, which would fill the significant gap between the aryl and alkyl aldehydes. Without this data point it is difficult to ascertain if there a relationship exists between the NMR spectroscopic shift and the selectivity of the reaction.

A potentially significant effect that was not investigated at length was the effect of the *N*-substituent on the selectivity. In comparison of selectivity between unprotected and Boc-protected substrates, the selectivities varied (Table 5.4). While comparison of the unprotected **109a** with its analogue **103a**, the protected amine gave a worse selectivity toward the linear product. Conversely, the α-methyl substituted **89a** and **93** gave the opposite relationship.

Reaction with *N*-methyl and *N*-dimethyl propargylamine failed with both of the usual aldehydes, **42** and **53** (Scheme 5.4). A systematic study on the effects of other *N*-substituents would be likely to yield useful results regarding both the selectivity and reactivity.



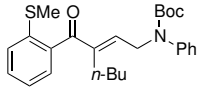
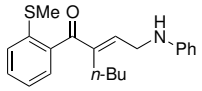
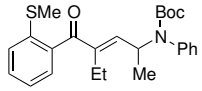
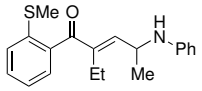
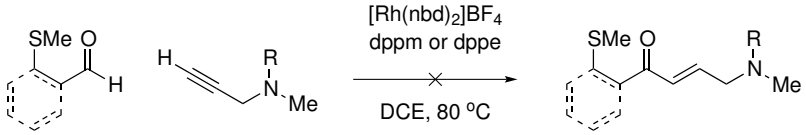
Entry	Product	Yield	Lin:bra
1	 **103a**	84	1:1
2	 **109a**	68	3:1
3	 **89a**	82	>10:1
4	 **93**	68	5:1

Table 5.4: Effect of Boc-group on selectivity.



Scheme 5.4: Failed hydroacylation of simple propargyl amines.

5.4 Summary

The DoE investigation indicated that the principle factors affecting the selectivity of the reaction are temperature, stoichiometry and concentration. The identity of the solvent has an important effect on the conversion of the reaction, but does not have a significant effect on the selectivity of the reaction. The reaction stoichiometry has a very significant effect on the conversion. The reaction reaches higher conversion when the aldehyde is employed in excess and the use of a large excess of alkyne can result in failure of the reaction. However, although these are statistically important factors, only minor improvements in the selectivity could be achieved in practice. The

highest selectivity predicted by the model was probably outside of the investigated area as the highest selectivities and conversions were at the limits of the investigated factors. Given that the model shows significant curvature and that a peak of maximum selectivity was not observed, a further study could be used to try to identify the optimum conditions for selectivity. A response surface study (RSM), where the factors are varied non-linearly, could be used to further optimise the reaction conditions. The model did not investigate the effect of different ligands and a design of experiments screen of categoric factors is considerable challange. The Willis group has recently shown that the ligand used can be used to control the regioselectivity of the reaction.[173] To perform a DoE study on the effect of the ligand, a principle component analysis[174] of usual rhodium ligands would be required in order to carry out a DoE study. Unfortunately to our knowledge this is not publicly available in the literature.

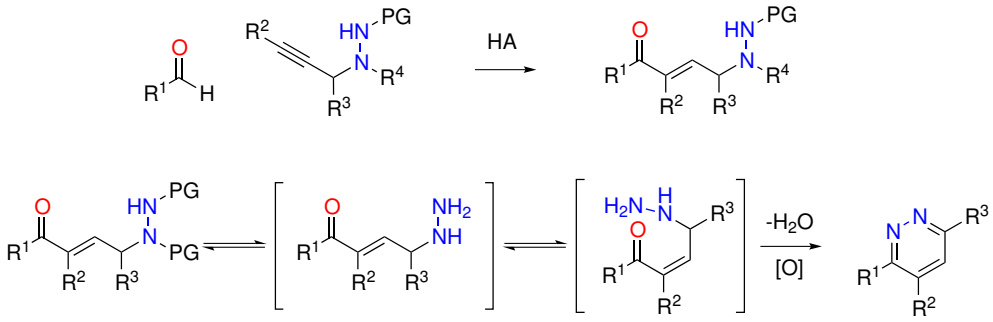
The effect of the identity of the aldehyde and alkyne require more investigation. The electronics of the aldehyde did not show a clear effect on the selectivity of the reaction but further experiments are required to show if this is the case. The effect of the *N*-substituent of the propargylamine also requires further investigation in order to gain a fuller understanding of the control of regioselectivity in intermolecular rhodium-catalysed hydroacylation of propargyl amines.

Chapter 6

Future Work

6.1 Introduction

Having demonstrated that a hydroacylation approach to pyridines and pyrroles is viable in Chapters 3 and 4, respectively, our attention was turned toward the synthesis of pyridazines (Scheme 6.1). We envisaged that we could modify the methodology used for the synthesis of pyrroles by introducing a propargyl hydrazine moiety and use this to synthesis γ-hydrazino enones that could then be converted to heterocycles.

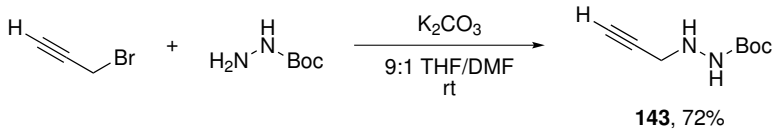


Scheme 6.1: Synthesis of Pyridazines.

6.2 A Hydroacylation Approach to Pyridazines

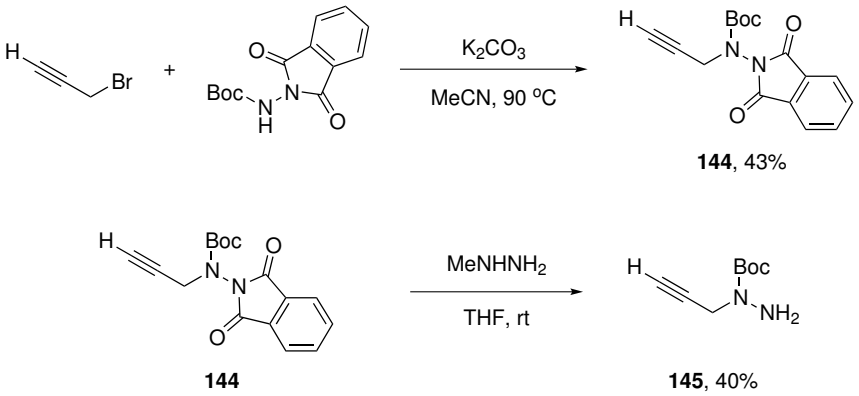
6.2.1 Synthesis of Propargyl Hydrazines

The simplest mono-Boc-protected propargyl hydrazine **143** was readily available in good yield using a literature method (Scheme 6.2).[175]

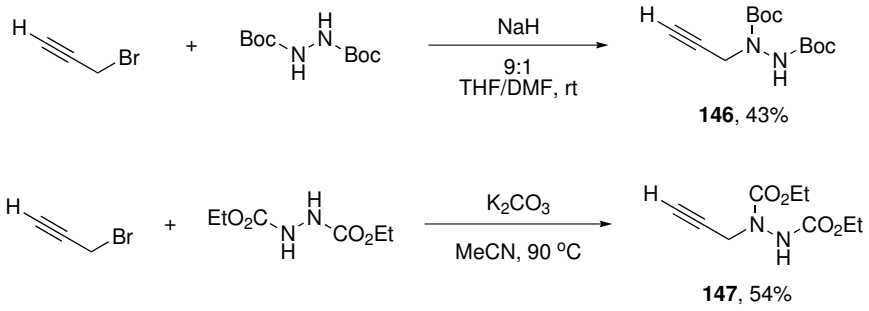


Scheme 6.2: Synthesis of propargyl hydrazine.

Alkylation of phthalimide-protected hydrazine was attempted in order to access a propargyl hydrazine bearing a free primary amine. The alkylation failed in toluene but by switching the solvent to acetonitrile, the reaction gave excellent yields (Scheme 6.3). This was then deprotected using methylhydrazine to obtain the primary hydrazine **145**.[176] The bis-Boc-protected and bis-ethylcarbamate hydrazines **146** and **147** were prepared in a similar fashion (Scheme 6.4).



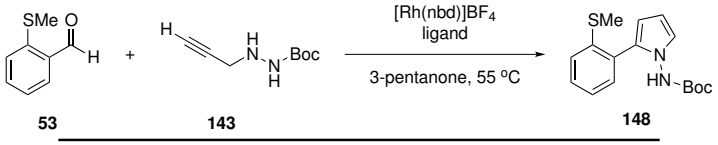
Scheme 6.3: Synthesis of primary propargyl hydrazine.



Scheme 6.4: Synthesis of bis-Boc-propargyl hydrazine.

6.2.2 Hydroacylation of Propargyl Hydrazines

The hydroacylation of mono-Boc-protected propargylamine **143**, under the conditions employed for pyrroles, gave a single product, consistent with a dehydrative cyclisation product, by mass spectrometry in 14% yield (Table 6.1, entry 1). Unfortunately, it was clear that the product was in-fact the amino-pyrrole by NMR spectroscopy. A comparison of the three most active hydroacylation ligands was carried out using hydrogen activation of the catalyst. All three ligands completely consumed the alkyne to give the amino-pyrrole **148** with dcpm giving the cleanest reaction. Signals consistent with traces of the branched hydroacylation product were observed by ^{1}H NMR spectroscopy using dppe and DPEphos as ligands.



53 **143** **148**

Entry	Ligand	Conversion (yield), %
1	DPEphos	(14)[a]
2	dcpm	>95 (90)
3	dppe	>95
4	DPEphos	>95

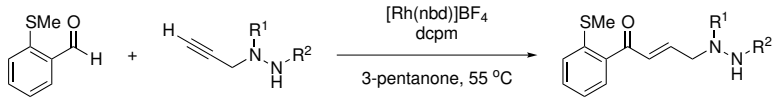
Table 6.1: Alkyne (0.1 mmol, 1 equiv.), aldehyde (0.15 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol %), ligand (10 mol %), 3-pentanone, 55 °C. Catalyst activated by hydrogen prior to reaction. [a] Without hydrogen activation of the catalyst.

Dcpm was shown to be a very effective ligand whilst being evaluated against dppm and DPEphos on the propargyl substrates in Chapter 4. The hydroacylation of **143** proved successful using these catalysts but required activation by hydrogenation, while propargyl amines did not.

6.2.3 Protecting group positions

The protection strategy was investigated in order to determine if the formation of the amino-pyrrole could be avoided. Using the conditions identified above, various combinations of protecting groups were investigated (Table 6.2). The unprotected primary amine, predictably, gave the hydrazone **152**. If primary hydrazine **145** is stirred in 3-pentanone for 16 hours, the hydrazone **149** can be obtained. Unfortunately, this too resulted in incomplete reaction to give a complex mixture of products (Scheme 6.5). Although phthalimide-protected propargyl hydrazine **144** would be a viable hydroacylation substrate, the usual deprotection conditions would in all

likelihood be incompatible with the hydroacylation product. Addition of hydrazine would form the pyrazoline with the enone functionality. Reductive methods would also destroy the enone functionality.



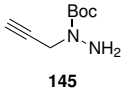
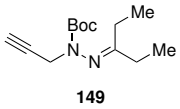
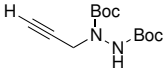
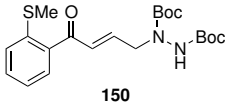
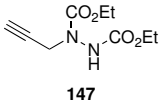
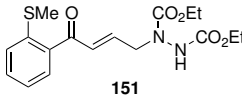
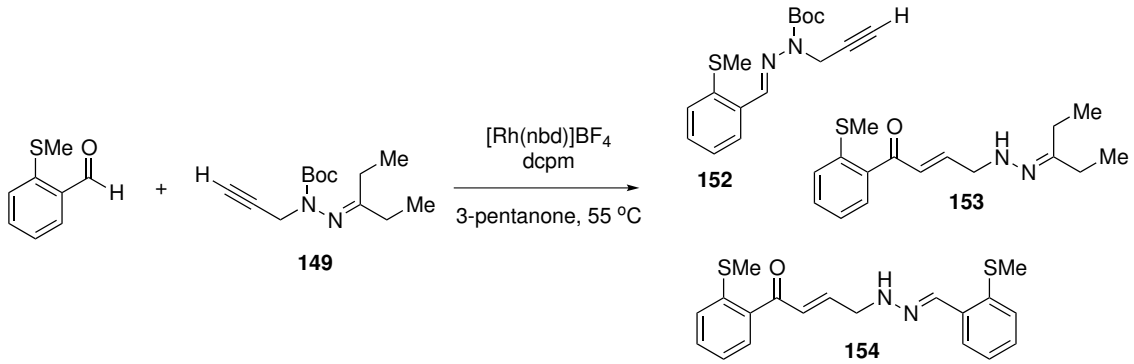
Entry	Alkyne	Product	Yield, %s	**a**:**b**
1	 **145**	imine	–	–
2	 **149**	HA, imine	–	–
2	 **146**	 **150**	40%	6.5:1
3	 **147**	 **151**	65%	2:1

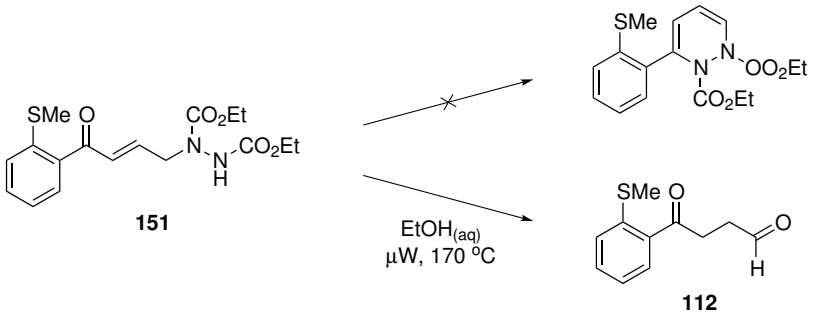
Table 6.2: Alkyne (0.1 mmol, 1 equiv.), aldehyde (0.15 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol %), ligand (10 mol %), 3-pentanone, 55 °C, hydrogen activation.



Scheme 6.5: Complex mixture of products

The hydroacylation product **151** was subjected to microwave heating at 170 °C. After 1 hour, no reaction had occurred. After 3 hours, traces of the hydrolysis product **112** was observed by ^{1} H NMR spectroscopy along with the starting material (Scheme

6.6).



Scheme 6.6: Failed cyclisation of γ-hydrazino enone **151**

6.3 Conclusions and Future Work

This work presented a new rhodium-catalysed synthesis of protected 1,5-ketoenones and γ-aminoenones that were then converted to a variety of pyridines and pyrroles under classical dehydrative cyclisation conditions. The hydroacylation of β-sulphur aldehydes and homopropargyl ketals could be used to synthesise protected 1,5-ketoenones that were then converted to both alkyl- and aryl-substituted pyridines. The synthesis of the requisite homopropargyl ketals proved troublesome and an alternative method must be found before the scope of the reaction can be expanded further.

The synthesis of pyrroles entailed a novel combination of thermal *N*-Boc deprotection, isomerisation and cyclisation that provided a general method for the synthesis of poly-substitituted pyrroles in a good yields. The hydroacylation of propargylamines gave mixtures of regioisomers, although this does not inhibit the the synthesis of pyrroles, it provides a challenge that requires further investigation to increase the efficiency of the reaction.

The work presented in this thesis has been limited to the use of β-sulphur chelation in

hydroacylation. Attempts to find a mode of coordination that facilitates the hydroacylation reaction through the use of potentially chelating homopropargyl dithianes were unsuccessful. However, many potential avenues of investigation exist that could provide another robust chelation strategy to limit the decarbonylation pathway.

The control of regioselectivity and various chelation strategies are subjects of continuing investigation in the Willis group. Provided that these two challenges can be overcome, hydroacylation could provide a general method for the synthesis of highly functionalised precursors for the synthesis of heterocycles.

Chapter 7

Experimental

7.1 General Considerations

Reactions were conducted with continuous magnetic stirring under an inert nitrogen atmosphere with dry solvents unless otherwise stated. Nitrogen and argon were passed through a Drierite® filled drying tube before use. Glassware was oven-dried (>200 °C), assembled and then allowed to cool to room temperature under a positive pressure of inert gas pressure or vacuum.

Cooling of reactions was carried out using low temperature baths: -10–5 °C was achieved by an ice-brine slush bath, -15 °C using acetone/ice slush, cooling to -30 °C was achieved using a Neslab Cryotrol CB-80 cryostat, cooling to -78 °C was achieved by a dry ice-acetone bath. Quoted temperatures are internal reaction temperatures to the nearest 5 °C. Distillation vapour temperatures were measured using a type K thermocouple. Microwave heated reactions were carried out in a CEM Discover® microwave.

Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd, Avocado, Fluorochem or Lancaster Synthesis Ltd. and used as supplied. The following chemicals were distilled prior to use: pyridine (dist. KOH), triethylamine (dist. over KOH and stored over CaH_2), dimethyl sulfoxide (dist. CaH_2) or purchased from Sigma-Aldrich Co. Ltd. 1,2-Dichloroethane, purchased from Rathburn (HPLC grade), was distilled from CaH_2. Acetone, purchased from Fischer (HPLC grade), was distilled from Drierite® and stored as received over 4 Å molecular sieves. Diethyl ether, THF, dichloromethane and toluene were collected fresh from an in-house solvent purification system having been passed through anhydrous alumina columns.

Reactions were monitored by TLC until deemed complete using aluminium backed silica plates (Merck Kieselgel 60 F254). Plates were visualised under ultraviolet light (254 nm) followed by staining with vanillin or $KMnO_4$. Flash column chromatography was carried out using Zeochem ZEOprep hyd. 40-63 micron silica, the compound to be purified either applied as an oil or pre-absorbed onto silica. Pressure was applied at the column head by hand bellows or using ∼1 bar of nitrogen pressure.

^{1}H and ^{13}C nuclear magnetic resonance spectroscopy experiments were carried out using Bruker DPX-200, DPX-250, DPX-400, DQX-400 or AVC-500 MHz NMR spectrometers. Acquisitions were carried out at room temperature unless otherwise stated. Chemical shifts are reported in parts per million from the residual solvent peak. Chemical shifts (δ) are given in parts per million, ppm) and coupling constants (J) in Hertz (Hz). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), septet (sep), multiplet (m), broad (br), apparent (app), overlapping (o) and aryl (Ar). Where required, proton assignment was achieved using 2D NMR spectroscopy techniques, predominantly COSY

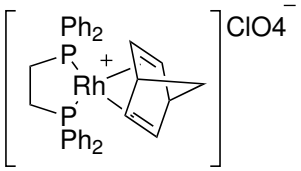
and HMQC spectroscopy. ^{1}H NMR spectroscopic determinations of the ratio of linear and branched hydroacylation products were calibrated for compounds **102a** and **102b** but not for other hydroacylation products.[177] All samples were dried with high vacuum to remove traces of solvents and water present before weighing to give the reported yields. Minor impurities (such as silicone grease) may be present in some compound spectra. Many propargyl amines and hydroacylation products furnished with *N*-Boc groups existed as rotamers.

Melting points were determined using a Leica Galen III hot-stage microscope. Infrared measurements were carried out as a thin film on a KBr disc, as a solution in $CDCl_3$ or neat using a attenuated total reflectance module on a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}. Electrospray accurate mass measurements were carried out on a Bruker MicroTOF mass spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Gas chromatography was performed using an Agilent 6890 series GC system with a ZB-5, 15 m, 0.25 μm ID column and a Micromass GCT TOF mass spectrometer was used to provide chemical ionisation accurate mass measurements.

Aldehydes **121** and **123** were kindly provided by Dr. Carlos González-Rodríguez,[78,79,173] aldehyde **130** was made by Dr. Joel Hooper[73] and aldehyde **126** by Philip Lenden.[76,77]

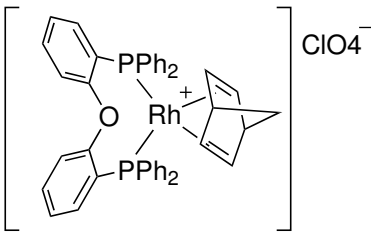
7.2 Experimental Procedures

(Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino) ethane)rhodium (I) perchlorate, [Rh(dppe)nbd]ClO_4



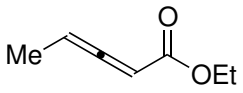
Prepared according to a literature method.[72] $[Rh(nbd)Cl]_2$ (115 mg, 0.25 mmol, 1.1 equiv.) was dissolved in DCM (8 mL) under argon at room temperature. 2,5-norbornadiene (70 μL, 0.65 mmol, 1.5 equiv.) and $AgClO_4$ (135 mg, 0.65 mmol, 1.5 equiv.) were added. After 30 minutes, dppe (175 mg, 0.44 mmol, 1 equiv.) was added. After a further 3 hours, the mixture was filtered under argon and concentrated under reduced pressure to ~2 mL. The product was crystallised by layering with ethanol (10 mL) followed by cooling to -20 °C for 16 hours. The red crystals were filtered,washed with ethanol (10 mL), and dried under vacuum to obtain red crystals of [Rh(dppe)nbd]ClO_4 (130 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.50 (20H, m, Ar*H*), 5.36 (4H, br s, C*H*=C*H*) 4.27 (2H, br s, C*H*), 2.40 (4H, d, *J* 20, PCH_2), 1.82 (2H, br s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 131.8, 129.8, 55.9, 12.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 57.4 (d, *J* 157). Data consistent with literature.[72]

(Bicyclo[2.2.1]hepta-2,5-diene)(2-[2-(diphenylphosphino) phenoxy]phenyl(diphenyl)phosphine)rhodium (I) perchlorate, [Rh(DPEphos)ndb]ClO_4



Prepared as for [Rh(dppe)nbd]ClO_4 using DPEphos (236 mg, 0.44 mmol, 1 equiv.) in place of dppe to obtain Rh(DPEphos)nbd]ClO_4 as orange crystals (157 mg, 43%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52-6.95 (28H, m, Ar*H*), 4.30 (4H, s, C*H*=C*H*), 3.87, (2H, s, C*H*), 1.53 (2H, s, CH_2); ^{31}P NMR (162 MHz, CD_2Cl_2) δ 17.2 (d, *J* 159). Data consistent with literature.[77]

Di-*tert*-butyl 1-(prop-2-yn-1-yl)hydrazine-1,2-dicarboxylate

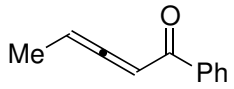


20

(Carbethoxymethylene)triphenylphophorane (5.00 g, 14.5 mmol, 1 equiv.) was dissolved in DCM (40 mL) and stirred at 0 °C. Triethylamine (2.00 mL, 14.5 mmol, 1 equiv.) in DCM (2 mL) was added dropwise over 10 minutes. After a further 10 minutes, propionyl chloride (1.25 mL, 14.5 mmol, 1 equiv.) was added dropwise over 10 minutes. After 15 minutes, the reaction was allowed to warm to room temperature and stirred for 2 hours. Hexane (25 mL) was added and the reaction stirred for a further hour. The reaction was then filtered through a pad of silica (petrol) and the solvent removed under vacuum. The products were then isolated by chromatography

on silica (DCM) to give the allene **20** (0.87 g, 48%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.56-5.46 (2H, m,C*H*=C=C*H*), 4.12 (2H, q, *J* 7.1, OCH_2CH$_3$), 1.71 (3H, dd, *J* 7.1 and 3.6, CH_3CH=C=CH), 1.21 (3H, t, *J* 7.1, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 165.8, 89.9, 87.4, 60.5, 14.0, 12.5; ν_{max} (neat) /cm^{-1} 2972, 1955, 1713, 1143. Data consistent with literature.[178] Appendix page 268.

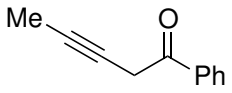
1-Phenylpenta-2,3-dien-1-one



21

1-Phenyl-2-(triphenylphosphoranylidene)ethanoate (1.00 g, 2.63 mmol, 1 equiv.) was dissolved in DCM (8 mL) and stirred at 0 °C. Triethylamine (367 μL, 2.63 mmol, 1 equiv.) in DCM (2 mL) was added dropwise over 10 minutes. After a further 10 minutes, propionyl chloride (173 μL, 2.63 mmol, 1 equiv.) was added dropwise over 10 minutes. After 15 minutes, the reaction was allowed to warm to room temperature and stirred for 2 hours. Hexane (25 mL) was added and the reaction stirred for a further hour. The reaction was then filtered through a pad of silica (petrol) and the solvent removed under vacuum. The products were then isolated by chromatography on silica (DCM) to give the *allene* **21** (127 mg, 31%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (2H, m, Ar*H*), 7.58-7.53 (1H, m, Ar*H*), 7.47-7.43 (2H, m, Ar*H*), 6.33 (1H, dd, *J* 6.2 and 3.2,CH_3CH=C=C*H*), 5.60 (1H, dq, *J* 6.2 and 7.4, CH_3C*H*=C=CH), 1.82 (3H, dd, *J* 7.4 and 3.3, CH_3CH=C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 192.2, 137.7, 132.6, 128.6, 128.3, 93.5, 89.9, 12.9; ν_{max} (film) /cm^{-1} 3061, 3028, 2974, 2929, 2878, 1946, 1727, 1675, 1597, 1578, 1448, 1277, 1215, 1071, 1023, 1002, 754, 735; *m*/*z* (ESI) found 181.0625 (M+Na), $C_{11}H_{10}NaO$ requires 181.0624. Appendix page 269.

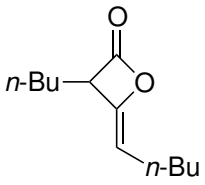
1-Phenylpent-3-yn-1-one



22

Isolated from the synthesis of 1-phenylpenta-2,3-dien-1-one as a colourless oil **22** (64 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.98 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.50-7.46 (2H, m, ArH), 3.83 (2H, q, J 2.6, $CH_3C{\equiv}CH_2C(O)Ph$), 1.85 (3H, t, J 2.6, $CH_3C{\equiv}CCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 135.6, 133.5, 128.6, 128.6, 81.2, 71.3, 30.80, 3.75; Data consistent with literature.[179] Appendix page 270.

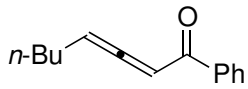
(*Z*)-3-Butyl-4-pentylideneoxetan-2-one



24

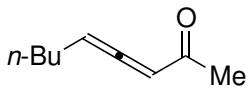
Triethylamine (0.49 mL, 3.5 mmol, 1 equiv.) was stirred in DCM (8 mL) at 5 °C. Caproyl chloride (0.48 mL, 3.5 mmol, 1 equiv.) was added dropwise. After 5 minutes the reaction was concentrated under reduced pressure and the residue purified by chromatography on silica (DCM) to obtain the pure product **24** as a colourless oil (0.61 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, td, J 7.6 and 1.3, C=CHCH$_2$), 3.93 (1H, td, J 7.2 and 1.0, CH2$_2$CHC=CH), 2.15-2.10 (2H, m, C=CHCH_2), 1.81-1.75 (2H, m, CH_2CHC=CH), 1.47-1.30 (8H, m, alkyl), 0.93-0.88 (6H, m, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 145.6, 101.7, 53.7, 31.5, 28.5, 27.2, 24.3, 22.3, 22.1, 13.83, 13.78; ν_{max} (neat) /cm^{-1} 2959, 2933, 2861, 1864, 1725. Data consistent with literature.[180] Appendix page 271.

1-Phenylocta-2,3-dien-1-one



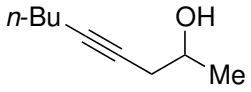
Prepared as for 1-phenylpenta-2,3-dien-1-one **21** using 1-phenyl-2-(triphenylphosphoranylidene)ethanoate (1.04 g, 2.70 mmol, 1equiv.), triethylamine (380 μL, 2.70 mmol, 1 equiv.) and caproyl chloride (380 μL, 2.70 mmol, 1 equiv.) in DCM (8 mL) at 5 °C. Caproyl chloride (0.48 mL, 3.5 mmol, 1 equiv.) was added dropwise. After 5 minutes the reaction was concentrated under reduced pressure and the residue purified by chromatography on silica (DCM) to obtain the *allene* product as a yellow oil (163 mg, 30% yield, containing approximately 30% by ^{1}H NMR spectroscopy of an impurity analogous to 1-phenylpent-3-yn-1-one) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.86 (1H, m, Ar*H*), 7.59-7.40 (4H, m, Ar*H*), 6.35 (1H, dt, *J* 6.1 and 3.0, $CH_2CH{=}C{=}CH$), 5.61 (1H, td, *J* 7.2 and 6.1, $CH_2CH{=}C{=}CH$), 2.24-2.12 (2H, m, $CH_2CH{=}C{=}CH$), 1.52-1.26 (4H, m, alkyl), 0.88 (3H, t, *J* 7.1, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 192.1, 133.4, 132.5, 128.7, 128.2, 95.0, 94.0, 30.9, 27.4, 22.1, 13.8. Appendix page 272.

Nona-3,4-dien-2-one



Prepared as for 1-phenylpenta-2,3-dien-1-one **21** using 1-(triphenylphosphoranylidene)propan-2-one (2.00 g, 6.30 mmol, 1 equiv.), Triethylamine (880 μL, 6.30 mmol, 1 equiv.) and caproyl chloride (870 μL, 6.30 mmol, 1 equiv). Purified by chromatography on silica (8% EtOAc/petrol) to obtain the *allene* product as a yellow oil (35 mg, 4% yield) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (1H, dt, J 6.1 and 3.1, $CH_2CH{=}C{=}CH$), 5.63 (1H, q, J 6.6, $CH_2CH{=}C{=}CH$), 2.23 (3H, s, $C(O)CH_3$), 2.21-2.15 (2H, m, $CH_2CH{=}C{=}CH$), 1.49-1.33 (4H, m, alkyl), 0.92 (3H, t, J 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 199.4, 98.0, 95.3, 31.0, 27.4, 26.4, 22.2, 13.8. Appendix page 273.

7.2.1 General Procedure A for the preparation of homopropargylic alcohols by nucleophilic attack on epoxides, exemplified by 4-nonyn-2-ol

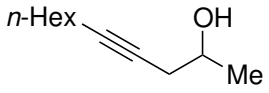


25

According to a literature procedure.[122,125] 1-Hexyne (3.5 mL, 30 mmol, 1 equiv.) was stirred in THF (100 mL) at -78 °C. *n*-Butyl lithium (1.6 M in hexanes, 25.0 mL, 39 mmol, 1.3 equiv.) was added slowly, keeping the temperature below -65 °C. After stirring for 30 minutes, $BF_3 \cdot THF$ (4.3 mL, 39 mmol, 1.3 equiv.) was added dropwise. After a further 20 minutes, propylene oxide (2.5 mL, 36 mmol, 1.2 equiv.) was dissolved in THF (5 mL) and added dropwise to the reaction. The reaction

was stirred for 2 hours and then quenched with saturated $NH_4Cl_{(aq)}$ (200 mL). The organic layer was separated and the aqueous was extracted with Et_2O (3 × 50 mL). The combined organics were washed with brine (2 × 50 mL) and then dried using $MgSO_4$. The solvent was removed under reduced pressure and the crude oil passed through a short pad of silica (15% Et_2O/Petrol) before being purified by distillation (46-47 °C, 0.8 mbar) to obtain the pure product **25**(1.1 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92-3.84 (1H, m, CH(OH)CH_3), 2.39-2.32 (1H, m, C≡C$H_A H_B$CH(OH)), 2.32-2.28 (1H, m, C≡CH_AH$_B$CH(OH)), 2.18-2.14 (3H, m, CH_2CH_2C≡C and OH), 1.50-1.34 (4H, m, $CH_3CH_2CH_2CH_2$), 1.22 (3H, d, J 6.2, CH(OH)CH_3), 0.89 (3H, t, J 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2, 76.0, 66.5, 31.0, 29.4, 22.1, 21.9, 18.4, 13.6; ν_{max} (neat) /cm^{-1} 3356, 2960, 2932, 2873, 1642, 1458, 1433, 1377, 1327, 1115, 1085, 940, 831; m/z (CI) 141.1 [M+H]$^+$; HRMS (CI) found 141.1283 [M+H]$^+$, $C_9H_{17}O$ requires 141.1279. Data consistent with literature.[181] Appendix page 301.

4-Undecyn-2-ol

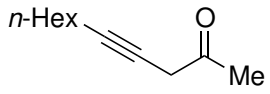


26

Prepared according to general method **A** using 1-octyne (4.4 mL, 30 mmol, 1 equiv.), *n*-butyl lithium (1.5 M in hexanes, 22.0 mL, 33 mmol, 1.1 equiv.), $BF_3 \cdot THF$ (4.3 mL, 39 mmol, 1.3 equiv.) and propylene oxide (2.5 mL, 36 mmol, 1.2 equiv.) to obtain the product **26** as a clear oil (1.41 g, 35%) after distillation (104-108 °C, 12 mbar). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94-3.87 (1H, m, CH(OH)CH_3), 2.42-2.35 (1H, m, C≡C$H_A H_B$CH(OH)), 2.31-2.24 (1H, m, C≡CH_AH$_B$CH(OH)), 2.20-2.15 (2H, m, CH_2CH_2C≡C), 1.98 (1H, br s, OH), 1.53-1.46 (2H, m, CH_2CH_2C≡C), 1.42-1.28

(6H, m, $CH_3CH_2CH_2CH_2$), 1.24 (3H, d, J 6.2, $CH(OH)CH_3$), 0.89 (3H, t, J 7.1, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.4, 76.0, 66.5, 31.3, 29.4, 29.0, 28.6, 22.6, 22.2, 18.7, 14.1; ν_{max} (neat) /cm^{-1} 3357 (O-H), 2959, 2930, 2858, 1459, 1115, 1085, 940; m/z (CI) 169.2 $[M+H]^+$, 186.2 $[M+NH_4]^+$; HRMS (CI) found 186.1860 $[M+NH_4]^+$, $C_{11}H_{24}NO$ requires 186.1858. Data consistent with literature.[146] Appendix page 274.

4-Undecyn-2-one

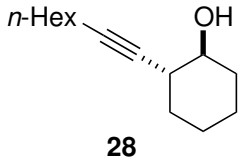


27

Prepared according to a modified literature method:[121,143] 4-undecyn-2-ol **26** (1.00 g, 6 mmol, 1 equiv.) was stirred in DCM (20 mL) at room temperature. Dess-Martin periodane (5.05 g, 12 mmol, 2 equiv.) was added in one portion. After 16 hours, saturated $Na_2S_2O_{3\,(aq)}$ (20 mL) and saturated $NaHCO_{3\,(aq)}$ (20 mL) was added. The reaction was filtered through Celite® then the layers separated. The aqueous was extracted with DCM (20 mL). The combined organic layers were then washed with further saturated $NaHCO_{3\,(aq)}$ (2 × 20 mL), brine (20 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure to obtain the crude product as a yellow oil was purified by filtration through a silica pad (20% Et_2O/ petrol) to yield homopropargylic alcohol **27** as a yellow oil (0.72 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (2H, t, J 2.5, $CH_2C{\equiv}CH_2C(O)$), 2.31 (3H, s, $C(O)CH_3$), 2.13 (2H, tt, J 2.5 and 7.1), 1.50-1.43 (2H, m, $CH_2CH_2C{\equiv}C$), 1.38-1.19 (6H, m, alkyl), 0.85 (3H, t, J 7.1, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 85.0, 72.2, 35.0, 31.3, 28.6, 28.5, 28.4, 22.5, 18.7, 14.0; m/z (CI) 167.1 $[M+H]^+$, HRMS (CI) found 167.1434 $[M+H]^+$, $C_{11}H_{19}O$ requires 167.1436. Data consistent with literature.[146]

Appendix page 275.

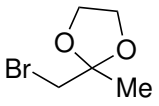
trans-2-(1-Octynyl)cyclohexanol



28

Prepared according to general method **A** using 1-octyne (4.4 mL, 30 mmol, 1 equiv.), *n*-butyl lithium (1.48 M in hexanes, 26.4 mL, 39 mmol, 1.3 equiv.), $BF_3 \cdot THF$ (4.3 mL, 39 mmol, 1.3 equiv.) and cyclohexene oxide (2.5 mL, 36 mmol, 1.2 equiv.) to give the product **28** as a clear oil (4.36 g, 70%) after chromatography (25% EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (1H, td, J 9.8 and 4.2, CHC*H*(OH)CH), 2.38 (1H, br s, O*H*), 2.17 (2H, td, J 6.9 and 1.7, $CH_2CH_2C{\equiv}CCH$), 2.05-1.09 (17H, m), 0.88 (3H, t, J 7.1, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 82.8, 74.7, 73.9, 45.1, 39.1, 32.9, 31.3, 29.0, 28.5, 25.0, 24.3, 22.5, 18.7, 14.1; ν_{max} (film) $/cm^{-1}$ 3357 (O-H), 2959, 2930, 2858, 1459, 1115, 1085, 940; m/z (CI) 209.2 $[M+H]^+$, 226.2 $[M+NH_4]^+$; HRMS (CI) found 209.1901, $C_{14}H_{25}O$ requires 209.1905. Data consistent with literature.[182] Appendix page 289.

2-Methyl-2-bromomethyl-1,3-dioxolane

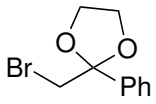


29

Prepared according to a modified literature method.[183] Acetone (11.6 mL, 0.2 mol, 1 equiv.), *p*-TSA $\cdot H_2O$ (0.1 g, 0.5 mmol, 2.5×10^{-4} mol %) were heated in hexanes

(200 mL) to 35 °C in a flask fitted with a $NaOH_{(aq)}$ gas scrubber and a Dean-Stark condenser. Bromine (10.1 mL, 0.2 mol, 1 equiv) was added dropwise, allowing the colour to disappear after each drop and maintaining the temperature at 35-40 °C. After the addition, the reaction was stirred for a further 30 minutes. Ethylene glycol (16.8 mL, 0.30 mol, 1.5 equiv.) was added and the reaction heated to reflux. After 5 hours the reaction was cooled and solid Na_2CO_3 added until neutralised. The mixture was then diluted with further hexanes (200 mL) and washed with water (3 × 100 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude oil distilled to obtain the unstable product **29** as a colourless oil (12.7 g, 35%). Bpt 39–42 °, 15 mbar; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07-3.99 (4H, m, OCH_2CH_2O), 3.40 (2H, br s, BrCH_2), 1.52 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.5, 65.5 (2C), 33.7, 22.9; ν_{max} (neat) /cm^{-1} 2960, 2870. Data consistent with literature.[127] Appendix page 276.

2-Phenyl-2-bromomethyl-1,3-dioxolane

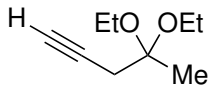


30

2-Bromoacetophenone (5.97 g, 30 mmol, 1 equiv.), *p*-TSA · H_2O (285 mg, 1.5 mmol, 5 mol %) and ethylene glycol (1.70 ml, 45 mmol, 1.5 equiv.) were stirred in PhMe (75 mL) at reflux in a flask fitted with a Dean-Stark condenser for 8 hours. The reaction was then cooled to room temperature and saturated $Na_2CO_{3\,(aq)}$ (5 mL) was added. The mixture was then washed with water (3 × 20 mL), brine (15 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product **30** was recrystallised (Et_2O) to obtain the product as white crystals (5.32 g, 73%). Mpt 57-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (2H, m, ArH), 7.40-7.36 (2H,

m, ArH), 7.20-7.17 (1H, m, ArH), 4.24-4.16 (2H, m, OCH_2CH$_2$O), 3.95-3.87 (2H, m, OCH$_2$CH_2O), 3.68 (2H, s, BrCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 128.8, 128.3, 126.0, 107.2, 65.8, 38.3; ν_{max} (neat) /cm^{-1} 3361, 2960, 2888. Data consistent with literature.[127] Appendix page 277.

4,4-Diethoxy-pent-1-yne



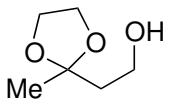
33

1,2-Dibromoethane (approx. 50 μL) was added to magnesium (1.90 g, 78 mmol, 4 equiv.) in Et_2O (5 mL).The reaction was heated briefly to 30 °C then cooled to 5 °C and zinc chloride (1 M in Et_2O, 1.6 mL, 1.6 mmol, 8 mol %) was added. Propargyl bromide (1.5 mL, 20 mmol, 1 equiv.) in Et_2O (15 mL) was added by a syringe pump over 3 hours whilst a temperature of 5-10 °C was maintained. Consumption of magnesium was observed, as was the formation of a fine dark grey precipitate. Toward the end of the addition, the reaction was pale green with an off-white precipitate. After the addition was complete, the reaction was stirred for a further 60 minutes. An aliquot (1.0 mL) of the supernatant was injected into water (20 mL) and the concentration of Grignard determined to be 0.5 M (11 mmol, 59% yield) by titration against methyl orange.

Phenyl diethyl orthoacetate (2.12 g, 10.1 mmol, 1 equiv.) in Et_2O (10 mL) was added dropwise to the Grignard solution ($\sim$11 mmol, $\sim$1.1 equiv.). After the addition, the reaction was allowed to warm to room temperature over one hour and stirred for a further hour. A saturated solution of $NH_4Cl_{(aq)}$ (10 mL) was added and the reaction stirred for a further 2 hours. Further Et_2O (10 mL) was added and the layers separated. The ethereal layer was washed with 10% $NaOH_{(aq)}$ (3 $\times$ 20 mL), brine

(20 mL) and then dried (Na_2SO_4). The solvent was removed under vacuum to obtain the crude product as a brown oil which was purified by distillation under reduced pressure to obtain the product **33** as a clear oil (385 mg, 24%) bpt: 33-35 °C, 9 mbar; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (4H, m, OCH_2CH$_3$), 2.49 (2H, m, HC≡CCH_2C), 1.98 (1H, m, HC≡CCH$_2$), 1.41 (3H, s, CCH_3), 1.13 (6H, m, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.1, 80.0, 70.2, 56.0 (2C), 28.2, 22.5, 15.2 (2C); m/z (CI) 157.1 $[M+H]^+$. Data consistent with literature.[134,135] Appendix page 284.

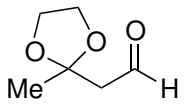
2-(2-Methyl-1,3-dioxalan-2-yl)ethanol



35

Prepared according to a literature method.[184] $LiAlH_4$ (1.63 g, 43 mmol, 3 hydride equiv.) was suspended in Et_2O (100 mL). A solution of ethyl 2-methyldioxolan-2-yl acetate (10.00 g, 57 mmol, 1 equiv.) in Et_2O (40 mL) was added dropwise over 15 minutes. The reaction was then heated to 35 °C to maintain reflux for 90 minutes. The reaction was then cooled to 0 °C and water (3.5 mL) was added dropwise. Once foaming had stopped, Na_2SO_4 (approx. 4 g) was added and the reaction stirred for 20 minutes. The reaction was then filtered through a pad of Celite® and washed through with further Et_2O (2 × 40 mL). The solvent was removed under reduced pressure to yield the title compound **35** as a colourless oil (6.76 g, 89%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (4H, m, C(OCH_2CH_2O)), 3.74 (2H, t, J 5.2, CH_2CH$_2$OH), 2.89 (1H, br s, OH), 1.93 (2H, t, J 5.2, CH$_2$CH_2OH), 1.31 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 64.5 (2C), 58.9, 40.2, 23.8; m/z (CI) 133.1 $[M+H]^+$; HRMS (CI) found 133.0864 $[M+H]^+$, $C_6H_{13}O_3$ requires 133.0865. Data consistent with literature.[184] Appendix page 278.

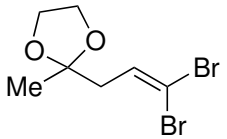
2-(2-Methyl-1,3-dioxalan-2-yl)acetaldehyde



36

Prepared according to a literature method.[184] Oxalyl chloride (2.8 mL, 33 mmol, 1.3 equiv.) was dissolved in DCM (110 mL) at -78 °C. DMSO (2.3 mL, 33 mmol, 1.3 equiv.) was added dropwise, maintaining the temperature below -65 °C. The reaction was stirred for 10 minutes and alcohol **35** (3.30 g, 25 mmol, 1 equiv.) was added dropwise as a solution in DCM (10 mL). After a further 30 minutes, triethylamine (13.8 mL, 100 mmol, 4 equiv.) was added dropwise, the reaction stirred for 5 minutes and then allowed to warm to room temperature. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the layers separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (3 × 50 mL) and then dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by filtration through a silica pad (50% EtOAc/cyclohexane) to give the aldehyde **36** (2.43 g, 75%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (1H, t, J 2.9, CH(O)), 3.92-3.88 (4H, m, C(OCH_2CH_2O), 2.60 (2H, d, J 2.9, CH_2CH(O)), 1.32 (3H, s, CH_3C(OCH$_2$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 107.5, 64.7 (2C), 52.0, 24.8; Data consistent with literature.[184] Appendix page 279.

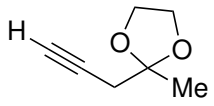
2-(3,3-Dibromoallyl)-2-methyl-1,3-dioxalane



37

Triphenylphosphine (4.65 g, 17.7 mmol, 3.3 equiv.) was stirred in DCM (40 mL) at 5 °C. On addition of carbon tetrabromide (2.51 g, 8.1 mmol, 1.5 equiv.) portionwise, the reaction turned orange. After 1 hour, aldehyde **36** (0.70 g, 5.4 mmol, 1 equiv.) was added. After a further 2 hours, petroleum ether (200 mL) was added and the reaction stirred for a further 10 minutes. The precipitate was filtered out, the cake washed with further petrol (20 mL) and the solvent removed under reduced pressure to obtain the *dibromide* **37** as an oil (1.04 g, 68%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (1H, t, J 7.2, $CH_2CH{=}CBr_2$), 3.99-3.95 (4H, m, $C(OCH_2CH_2O)$), 2.46 (2H, d, J 7.2, $CCH_2CH{=}CBr_2$), 1.38 (3H, s, CH_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 108.6, 90.9, 64.9 (2C), 42.6, 21.16; ν_{max} (neat) $/cm^{-1}$ 2985, 2883, 2360, 1621, 1476, 1445, 1378, 1245, 1230, 1142, 1108, 1054, 949, 846; m/z (CI) 286.9 $[M+H]^+$; HRMS (CI) found 286.9123 $[M+H]^+$, $C_7H_{10}{}^{79}Br^{81}BrO_2$ requires 286.9027. Appendix page 281.

2-Methyl-2-(2-propynyl)-1,3-dioxolane

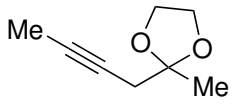


38

Prepared according to a modified literature procedure.[142] Dibromide **37** (3.43 g, 12 mmol, 1 equiv.) was dissolved in THF (40 mL) and cooled to -78 °C. *n*-Butyl lithium (1.5 M in hexanes, 16.8 mL, 25 mmol, 2.1 equiv.) was added dropwise over 10 minutes. A saturated solution of $NH_4Cl_{(aq)}$ (20 mL) was added and the reaction allowed to warm to room temperature. The reaction was extracted with Et_2O (3 × 20 mL) and washed with water (10 mL) then brine (10 mL). The organic layers were dried using Na_2SO_4. The solvent removed under reduced pressure and the residue purified by chromatography on silica (5-20% Et_2O/petrol) to obtain the terminal

alkyne **38** (0.80 g, 53%) as a thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.93 (4H, m, C(OCH_2CH_2O)), 2.49 (2H, d, J 2.7, HC≡CH_2), 2.02 (1H, t, J 2.7, HC≡CH_2), 1.42 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.4, 80.0, 70.1, 65.1 (2C), 29.8, 23.7; ν_{max} (film) /cm^{-1} 2958, 2934, 2876, 1666.8, 1630, 1551, 1449, 1210, 1147, 1099, 1049, 950, 803; m/z (CI) 127.1 $[M+H]^+$; HRMS (CI) found 127.0690 $[M+H]^+$, $C_7H_{11}O_2$ requires 127.0759. Appendix page 282.

2-(2-Butynyl)-2-methyl-1,3-dioxolane



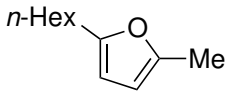
39

Terminal alkyne **38** (200 mg, 1.6 mmol, 1 equiv.) was dissolved in THF (10 mL) and cooled to -78 °C. *n*-Butyl lithium (1.5 M in hexanes, 1.6 mL, 2.4 mmol, 1.5 equiv.) was added dropwise. After 20 minutes of stirring, methyl iodide (0.5 mL, 8 mmol, 5 equiv.) was added. After 40 minutes saturated $NH_4Cl_{(aq)}$ (5 mL) was added. Reaction allowed to warm to room temperature then extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and then dried with Na_2SO_4 and the solvent removed under reduced pressure. The crude product was then purified by chromatography on silica (20% Et_2O/petrol) to obtain the internal *alkyne* **39** (126 mg, 56%) as a thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02-3.94 (4H, m, C(OCH_2CH_2O)), 2.47 (2H, q, J 2.6, CH_3C≡CH_2), 1.80 (3H, t, J 2.6, CH_3C≡C), 1.44 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.8, 77.4, 74.6, 65.0 (2C), 30.1, 23.6, 3.6; ν_{max} ($CDCl_3$) /cm^{-1} 2958, 2877, 1602, 1451, 1430; m/z (CI) 141.1 $[M+H]^+$; HRMS (CI) found 141.0920 $[M+H]^+$, $C_8H_{13}O_2$ requires 141.0916. Appendix page 283.

7.2.2 General Procedure B for Hydroacylation Reactions Using Isolated Precatalyst

Precatalyst [Rh(ligand)nbd]X^- (1-10 mol %) in a Schlenck tube was dissolved in 1,2-DCE or acetone (0.1 M relative to aldehyde). Hydrogen was bubbled through the solution at room temperature for 3-4 minutes to generate the active catalyst species. The hydrogen gas was purged using argon for 3 minutes then the appropriate aldehyde (1 equiv.) was added immediately followed by the substrate alkyne (2 equiv.). The reaction was then immersed into an oil bath at 70 °C and the reaction monitored by TLC until complete. Upon completion the reaction was cooled to room temperature and Et_2O (5 mL) was added to precipitate the catalyst. The reaction was then filtered through a pad of silica (Et_2O) and the solvent removed under vacuum to obtain the crude product. The crude product was analysed with ^1H NMR spectroscopy to measure the approximate ratio of linear to branched products. The crude was then purified by chromatography on silica (typically eluted with 5–25% Et_2O/petrol).

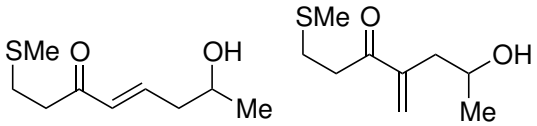
2-Hexyl-5-methylfuran



41

Isolated from an attempted hydroacylation reaction using general method **B**. 3-Methylthiopropionaldehyde (15 μL, 0.15 mmol, 1 equiv.), 4-undecyn-2-one (50 mg, 0.30 mmol, 2 equiv.) and [Rh(DPEphos)(nbd)]ClO_4 (8 mg, 0.01 mmol, 6 mol %) in 1,2 DCE (1.5 mL), 70 °C, 24 hours. Purified by chromatography on silica (10-20% Et_2O/petrol) to obtain the furan **41** (27 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (2H, s, ArH), 2.56 (2H, t, J 7.6, CH_2CH_2), 2.25 (3H, s, CH_3), 1.65-1.58 (2H, m, CH_2CH_2Ar), 1.39-1.22 (6H, m, alkyl), 0.89 (3H, t, J 7.0, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 150.0, 105.7, 105.0, 31.6, 28.9, 28.15, 28.09, 22.6, 14.1, 13.5; ν_{max} (neat) /cm^{-1} 1562, 1440, 1220; m/z (CI) 166.1 [M+H]$^+$. Data consistent with literature.[146] Appendix page 285.

(E)-7-Hydroxy-1-(methylthio)4-octen-3-one, a and 6-hydroxy-4-methylene-1-(methylthio)heptan-3-one, b



43a **43b**

Prepared according to general method **B** using 3-(methylthio)propionaldehyde (100 μL, 1.00 mmol, 1 equiv.), 4-pentyn-2-ol (188 μL, 2 mmol, 2 equiv.) with [Rh(DPE-phos)(nbd)]ClO_4 (8 mg, 0.01 mmol, 1 mol %) to obtain the title compounds after chromatography (20-80% Et_2O/petrol). **43a** (136 mg, 72%), **43b** (22 mg, 12%). **43a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, dt, J 15.9 and 7.3, HC=CHCH_2), 6.20

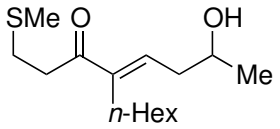
(1H, dt, J 15.9 and 1.5, HC=CHCH$_2$), 4.03-3.98 (1H, m, CH$_2$CH(OH)CH$_3$), 2.91-2.86 2H, m, H$_3$CSCH$_2$CH_2C(O)), 2.81-2.79 (2H, m, H$_3$CSCH_2CH$_2$C(O)), 2.44-2.34 (2H, m, C=CHCH_2CH(OH)), 2.14 (3H, s, H_3CS), 1.26 (3H, d, J 6.2, CH(OH)CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 144.3, 132.0, 65.7, 42.0, 39.7, 28.2, 23.2, 15.8; ν_{max} (neat) /cm^{-1} 3424, 2969, 2918, 1668, 1628, 1427, 1410, 1356, 1176, 1121, 1026, 941; m/z (CI) 189.1 [M+H]$^+$; HRMS (CI) found 189.0957 [M+H]$^+$, C$_9$H$_{17}$O$_2$S requires 189.0949. Appendix page 286. **43b** ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.13 (1H, s, H_ACH$_B$), 5.91 (1H, s, H$_A$CH_B), 3.88 (1H, m, CH(OMe)CH$_3$), 3.10-2.97 (2H, m, CH$_3$SCH$_2$CH_2C(O)), 2.78 (2H, app t, J 7.4, CH$_3$SCH_2CH$_2$), 2.56-2.52 (1H, m, C=CCHH)CH(OH)), 2.35-2.30 (1H, m, C=CHHCH(OH)), 2.25 (1H, br s, OH), 2.12 (3H, s, CH_3S), 1.18 (3H, d, J 6.2, CH(OH)CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.2, 145.6, 127.5, 66.9, 41.1, 37.6, 28.7, 23.3, 15.8; ν_{max} (neat) /cm^{-1} 3417, 2968, 2919, 1673, 1626, 1427, 1370, 1120, 1089, 1011, 935, 841; m/z (CI) 189.1 [M+H]$^+$; HRMS (CI) found 189.0957 [M+H]$^+$, C$_9$H$_{17}$O$_2$S requires 189.0949. Appendix page 287.

7.2.3 General Procedure C for hydroacylation reactions with *in situ* generated catalyst from [Rh(cod)Cl]$_2$

Chloro(1,5-cyclooctadiene)rhodium(I) dimer (3.7 mg, 0.0075 mmol, 5 mol %) in Schlenck tube at room temperature was dissolved in acetone or 1,2-DCE (1.5 mL). Silver perchlorate (3.1 mg, 0.015 mmol, 10 mol %) was added. The reaction turned hazy yellow on stirring for 10 minutes after which time the ligand (0.015 mmol, 10 mol %) was added and the reaction stirred for a further 15 minutes while the reaction turned orange. The appropriate aldehyde (0.15 mmol, 1 equiv.) was added immediately followed by the substrate alkyne (0.30 mmol, 2 equiv.). The reaction was

then immersed into an oil bath at 70 °C and the reaction monitored by TLC until complete. Upon completion the reaction was cooled to room temperature and Et_2O (3 mL) was added to precipitate the catalyst. The reaction was then filtered through a pad of silica (Et_2O) and the solvent removed under vacuum to obtain the crude product. The crude product was analysed with ^1H NMR spectroscopy to measure the approximate ratio of linear to branched products. The crude was then purified by chromatography on silica (typically eluted with 5–25% Et_2O/Petrol).

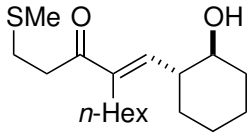
(*E*)-4-(3-Hydroxybutylidene)-1-(methylthio)decan-3-one



44

Prepared according to general method **C** using 3-methylthiopropionaldehyde (150 μL, 1.5 mmol, 1 equiv.), alkyne **7** (500 mg, 3.0 mmol, 2 equiv.), $[Rh(cod)Cl]_2$ (18.5 mg, 0.038 mmol, 2.5 mol %), $AgClO_4$ (16 mg, 0.075 mmol, 5 mol %) and DPEphos (40 mg, 0.075 mmol, 5 mol %) to give *product* **44** (49 mg, 12%) after purification by chromatography (5-50% Et_2O/petrol). ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, J 7.2, C=CHCH$_2$CH(OH)CH$_3$), 4.02-3.98 (1H, m, CH$_2$CH(OH)CH$_3$), 3.00-2.96 (2H, m, SCH$_2$CH_2C(O)), 2.80-2.76 (2H, m, SCH_2CH$_2$C(O)), 2.44 (2H, t, J 7.0, C=CHCH_2CH(OH)), 2.31-2.28 (2H, m , CH$_2$CH_2C=CH), 2.13 (3H, s, H_3CS), 1.34-1.21 (8H, m, alkyl), 1.28 (3H, d, J 6.2, CH(OH)CH_3), 0.88 (3H, t, J 6.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 143.8, 138.3, 67.3, 38.3, 37.4, 31.6, 29.5, 29.2, 29.1, 26.0, 23.6, 22.6, 15.9, 14.1; ν_{max} (neat) /cm^{-1} 3425, 2958, 2926, 2858, 1666, 1458, 1377, 1115, 892; m/z (ESI−) 271.2 [M-H]$^-$; HRMS (ESI) found 295.1697 [M+Na]$^+$, $C_{15}H_{28}NaO_2S$ requires 295.1702. Appendix page 288.

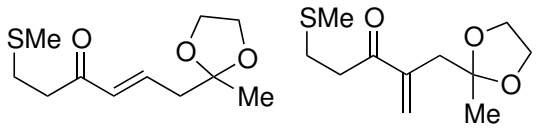
(*E*)-4-((2-Hydroxycyclohexyl)methylene)-1-(methylthio)-decan-3-one



45

Prepared according to general method **B** using 3-methylthiopropionaldehyde (65 μL, 0.75 mmol, 1 equiv.), alkyne **28** (313 mg, 1.5 mmol, 2 equiv.), [Rh(DPEphos)-(nbd)]ClO_4 (13 mg, 0.016 mmol, 2 mol %) to give *product* **45** (26 mg, 11%) after purification by chromatography (5-50% Et_2O/petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (1H, d, J 9.9, C=C*H*CH), 3.43-3.37 (1H, m, C=CHC*H*(OH)CH_AH_B), 3.04-2.90 (2H, m, SCH_2CH_2C(O), 2.80-2.73 (2H, m, SCH_2CH_2C(O)), 2.42-2.36 (1H, m, C=CHC*H*CH(OH), 2.34-2.30 (2H, m, CH_2C=CH), 2.13 (3H, s, H_3CS), 2.07-2.03 (1H, m, CH(OH)CH_AH_B), 1.84-1.81 (1H, m, CH(OH)CH_AH_B), 1.73-1.63 (4H, m, alkyl), 1.39-1.18 (10H, m, alkyl), 0.87 (3H, t, J 6.9, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 144.4, 143.5, 73.9, 46.5, 37.6, 34.3, 31.6, 31.0, 29.8, 29.5, 29.1, 26.2, 24.8, 24.7, 22.6, 16.0, 14.1; ν_{max} (neat) /cm^{-1} 3454, 2928, 2856, 1666, 1449, 1338, 1110, 1057, 952, 880; m/z (ESI) 335.2 $[M+Na]^+$; HRMS (ESI) found 335.2009 $[M+Na]^+$, $C_{18}H_{32}NaO_2S$ requires 335.2015. Appendix page 290.

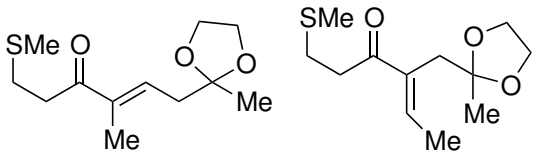
(*E*)-6-(2-Methyl-1,3-dioxolan-2-yl)-1-(methylthio)hex-4-en-3-one, a and 2-((2-methyl-1,3-dioxolan-2-yl)methyl)-5-(methylthio)pent-1-en-3-one, b



46a **46b**

Prepared according to general method **B** using 3-methylthiopropionaldehyde (15 μL, 0.15 mmol, 1 equiv.), alkyne **38** (38 mg, 0.30 mmol, 2 equiv.), and [Rh(DPEphos)-(nbd)]ClO_4 (8 mg, 0.01 mmol, 7 mol %) to give the title *compounds* as a partially separable mixture of isomers (32 mg, 93%, ~3:1 **a**:**b**). **46a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, dt, J 16.0 and 7.4, CH=CHCH_2), 6.16 (1H, app d, J 16.0, CH=CHCH_2), 4.00-3.92 (4H, m, C(OCH_2CH_2O)), 2.89-2.85 (2H, m, SCH_2CH_2C(O)), 2.80-2.75 (2H, m, SCH_2CH_2C(O)), 2.57 (2H, d, J 7.4, C=CHCH_2), 2.12 (3H, s, H_3CS), 1.34 (3H, s, C(OCH_2CH_2O)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.1, 133.0, 108.9, 64.9 (2C), 42.5, 39.7, 28.3, 24.3, 15.8; ν_{max} (neat) /cm^{-1} 2982, 2962, 2918, 2887, 1695, 1671, 1631, 1427, 1377, 1353, 1260, 1213, 1042; m/z (ESI) 231.1 $[M+H]^+$, 253.1 $[M+Na]^+$; HRMS (ESI) found 253.0867 $[M+Na]^+$, $C_{11}H_{18}NaO_3S$ requires 253.0869. Appendix page 291. **46b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (1H, app s, H_A), 5.84 (1H, app br s, H_B), 3.92-3.89 (4H, m, C(OCH_2CH_2O)), 3.00 (2H, t, J 7.7, SCH_2CH_2C(O)), 2.79 (2H, t, J 7.7, SCH_2CH_2C(O)), 2.72 (2H, s, C=CCH_2C((OCH_2CH_2O)), 2.14 (3H, s, H_3CS), 1.31 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 144.6, 126.5, 109.2, 64.7 (2C), 39.0, 38.0, 28.6, 24.0, 15.9; ν_{max} (neat) /cm^{-1} 2960, 2921, 1712, 1680, 1626, 1430, 1377, 1135, 1099, 1045; m/z (ESI) 231.1 $[M+H]^+$, 253.1 $[M+Na]^+$; HRMS (ESI) found 253.0867 $[M+Na]^+$, $C_{11}H_{18}NaO_3S$ requires 253.0869. Appendix page 292.

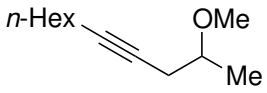
(*E*)-4-Methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-(methylthio)-hex-4-en-3-one, a and (*E*)-4-((2-methyl-1,3-dioxolan-2-yl)-methyl)-1-(methylthio)-4-hexen-3-one, b



47a **47b**

Prepared according to general method **B** using 3-methylpropionaldehyde (15 μL, 0.15 mmol, 1 equiv.), alkyne **39** (39 mg, 0.3 mmol, 2 equiv.) and [Rh(DPEphos)(nbd)]ClO_4 (8 mg, 0.01 mmol, 7 mol %), purified by chromatography (5–30% Et_2O/petrol) to give inseparable mixture of isomers (10 mg, 27%, ≈1:1 **a**:**b**). ^{1}H NMR (400 MHz, $CDCl_3$) **a**: δ 6.70 (1H, app dt, J 7.2 and 0.8, $CH_3C{=}CHCH_2$), 4.03-3.95 (4H, m, $C(OCH_2CH_2O)$), 3.01-2.95 (2H, m, $SCH_2CH_2C(O)$), 2.80-2.76 (2H, m, $SCH_2CH_2C(O)$), 2.62 (3H, d, J 7.2, $C{=}CHCH_2$), 2.13 (3H, o s, H_3CS), 1.81 (3H, s, $CH_3C{=}CH$), 1.29 (3H, s, CH_3); **b** δ 6.79 (1H, q, J 7.0, $CH_3CH{=}C$), 3.88 (4H, br s, $C(OCH_2CH_2O)$), 3.01-2.95 (2H, m, $SCH_2CH_2C(O)$), 2.80-2.76 (2H, m, $SCH_2CH_2C(O)$), 2.13 (3H, o s, H_3CS), 1.92 (3H, d, J 7.0, $CH_3CH{=}C$), 1.36 (3H, s, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) **a** and **b**: δ200.1, 199.9, 139.2, 137.2, 110.4, 109.4, 64.9 (2C), 64.7 (2C), 39.0, 27.9, 37.2, 34.0, 29.04, 28.98, 24.6, 24.3, 15.91, 15.89, 15.4, 11.7; ν_{max} (neat) /cm^{-1} 2983, 2959, 2918, 2884, 1711, 1667, 1428, 1377, 1211, 1135, 1101, 1089, 1045, 855; m/z (CI) 245.1 $[M+H]^+$; HRMS (CI) found 245.1208 $[M+H]^+$, $C_{12}H_{21}O_3S$ requires 245.1211. Appendix page 293.

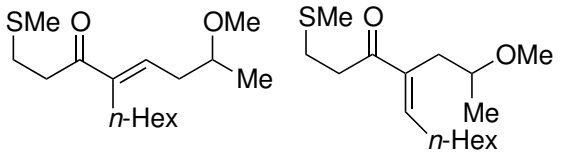
2-Methoxyundec-4-yne



48

4-Undecyn-2-ol **26** (168 mg, 1.0 mmol, 1 equiv.) was stirred in THF (5 mL) at room temperature. Sodium hydride (40 mg, 60% in mineral oil, 1.0 mmol, 1 equiv.) was added in one portion to the solution and the reaction stirred for 10 minutes before iodomethane (0.20 mL, 3.2 mmol, 3.2 equiv.) was added. After 1 hour a saturated solution of $NH_4Cl_{(aq)}$ (5 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organics washed with brine (10 mL), dried with $MgSO_4$ and the solvent removed under vacuum to yield the title *compound* **48** as a yellow oil (130 mg, 71%) and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45-3.37 (1H, m, $CH_2CH(OCH_3)CH_3$), 3.34 (3H, s, OCH_3), 2.45-2.39 (1H, m, J 16.4 and 2.4, $CH_2C{\equiv}CCH_AH_BCH(OCH_3)CH_3$), 2.24 (1H, app ddt , J 16.4, 7.2 and 2.4, $CH_2C{\equiv}CCH_AH_BCH(OCH_3)$), 2.13 (2H, app tt, J 7.1 and 2.4, $CH_2CH_2C{\equiv}C$), 1.50-1.43 (2H, m, alkyl), 1.39-1.22 (6H, m, alkyl), 1.23-1.22 (3H, d, J 6.1, $CH(OC_3)CH_3$), 0.87 (3H, t, J 6.8, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 82.0, 76.4, 75.9, 56.3, 31.9, 29.0, 28.5, 25.8, 22.6, 19.0, 18.8, 14.0; ν_{max} (neat) $/cm^{-1}$ 2928, 2858, 1461, 1377, 1107; m/z (CI) 200.2 $[M+NH_4]^+$; HRMS (CI) found 183.1752 $[M+H]^+$, $C_{12}H_{23}O$ requires 183.1749. Appendix page 280.

(*E*)-4-(3-Methoxybutylidene)-1-(methylthio)decan-3-one, a and (*E*)-4-(2-methoxypropyl)-1-(methylthio)undec-4-en-3-one, b

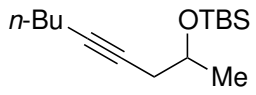


49a **49b**

Prepared according to general method **B** using 3-methylthiopropionaldehyde (30 μL, 0.30 mmol, 1 equiv.), alkyne **48** (130 mg, 0.71 mmol, 2.4 equiv.) with [Rh(DPEphos)-(nbd)]ClO_4 catalyst (15 mg, 0.018 mmol, 6 mol %) to give a mixture of isomers (69 mg, 80%, approx. 1:1 **a**:**b**). Chromatography (5-30% Et_2O/petrol) gave partial separation of isomers. **49a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (1H, t, J 6.1, C=CHCH_2), 3.50-3.45 (1H, m, CH_2CH(OCH_3)CH_3), 3.36 (3H, s, OCH_3), 2.97 (2H, t, J 7.1, H_3CSCH_2CH_2C(O)), 2.77 (2H, t, J 7.1, H_3CSCH_2CH_2C(O)), 2.51-2.38 (2H, m, C=CHCH_2CH(OCH_3)), 2.32-2.36 (2H, m, CH_2), 2.13 (3H, s, H_3CS), 1.33-1.22 (8H, m, alkyl), 1.18 (3H, d, J 6.2, CH(OCH_3)CH_3), 0.87 (3H, t, J 6.7, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 143.3, 138.7, 75.8, 56.3, 37.4, 35.5, 31.7, 29.5, 29.1, 26.0, 22.6, 19.3, 15.9, 14.1; ν_{max} (neat) /cm^{-1} 2957, 2926, 2857, 1668, 1638, 1461, 1378, 1348, 1177, 1133, 1092, 906; m/z (ESI) 287.2 $[M+H]^+$, 309.2 $[M+Na]^+$; HRMS (ESI) found 287.2039 $[M+H]^+$, $C_{16}H_{31}O_2S$ requires 287.2039. Appendix page 295. **49b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, t, J 7.3, CH_2CH=C), 3.38-3.32 (1H, m, CH(OCH_3)CH_3), 3.29 (3H, s, OCH_3), 3.03-2.90 (2H, m, SCH_2CH_2(O)), 2.81-2.72 (2H, m, SCH_2CH_2C(O)), 2.58 (1H, app dd, J 13.2 and 6.7, C=CCH_AH$_B$CH(OCH_3)), 2.37 (1H, app dd, J 13.2 and 6.4), 2.33-2.26 (2H, m, CH_2CH_2CH=C), 2.13 (3H, s, H_3CS), 1.49-1.42 (2H, m, alkyl), 1.37-1.25 (6H, m, alkyl), 1.07 (3H, d, J 6.2, CH(OCH_3)CH_3), 0.89 (3H, t, J 7.0, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 145.4, 138.5, 76.3, 56.4, 37.3, 32.7, 31.7, 29.4, 29.15, 29.1, 28.8, 22.6, 19.3,

15.9, 14.1; ν_{max} (neat) /cm^{-1} 2959, 2923, 2857, 2821, 1667, 1637, 1460, 1377, 1345, 1268, 1177, 1133, 1090; m/z (ESI) 287.2 $[M+H]^+$. Appendix page 296.

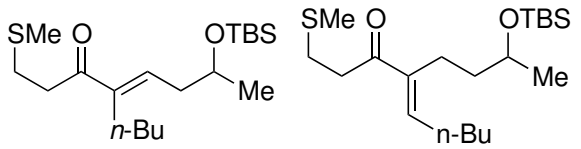
tert-Butyldimethylsilyloxy(4-nonyl-2-ol)



50

4-Nonyn-2-ol **25** (284 mg, 2.0 mmol, 1 equiv.) was stirred in pyridine (20 mL) at room temperature. *tert*-Butyldimethylsilyl chloride (332 mg, 2.2 mmol, 1.1 equiv.) was added and the reaction stirred for 16 hours. A saturated solution of $NH_4Cl_{(aq)}$ (10 mL) was added followed by extraction with DCM (3 × 15 mL). The combined organics were washed with a saturated solution of $CuSO_{4\,(aq)}$ (10 mL), then with brine (15 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was purified by chromatography (0-50% Et_2O/petrol) to give the *title compound* **50** as a clear oil (183 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94-3.86 (1H, m, $CH_2CH(OTBS)CH_3$), 2.34-2.29 (1H, m, $C{\equiv}CH_AH_BCH(OTBS)$), 2.02 (1H, app dt, J 7.3 and 2.4, $C{\equiv}CH_AH_BCH(OTBS)$), 2.17-2.12 (2H, m, $CH_2C{\equiv}CH_AH_B$), 1.50-1.35 (4H, m, alkyl), 1.21 (3H, d, J 6.0, $CH(OTBS)CH_3$), 0.90 (3H, o t, J 7.2, $CH_3CH_2CH_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, app d, J 2.3, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6, 77.4, 68.1, 31.1, 29.7, 25.8 (3C), 23.3, 21.9, 18.4, 18.1, 13.6, -4.7 (2C) ; ν_{max} ($CDCl_3$) /cm^{-1} 2958, 2930, 2858, 1463, 1376, 1361, 1255, 1127, 1098, 1002, 862, 775; m/z (CI) 255.2 $[M+H]^+$; HRMS (CI) found 255.2146 $[M+H]^+$, $C_{15}H_{31}OSi$ requires 255.2144. Appendix page 297.

(*E*)-4-Butyl-7-(tert-butyldimethylsilyloxy)-1-(methylthio)oct-4-en-3-one, a and (*E*)-4-(2-(tert-butyldimethylsilyloxy)propyl)-1-(methylthio)-non-4-en-3-one, b

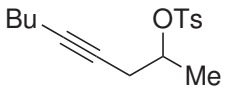


51a **51b**

Prepared according to general method **B** using 3-methylthipropionaldehyde (15 μL, 0.15 mmol, 1 equiv.), **50** (75 mg, 0.30 mmol, 2 equiv.), [Rh(DPEphos)(nbd)]ClO_4 (6 mg, 0.0075 mmol, 5 mol %) to obtain the *product* yellow oil containing an inseparable mixture of isomers (20 mg, 37%, approx. 3:1 **a**:**b** by ^{1} NMR spectroscopy). ^{1}H NMR (400 MHz, $CDCl_3$) δ **51b**: 6.71 (1H, t, J 7.2, BuCH=C), 3.90 (1H, m, $CH_2CHC(OTBS)CH_3$), 2.99-2.94 (2H, m, SCH_2CH_2)C(O)), 2.79-2.75 (2H, m, $SCH_2CH_2C(O)$), 2.44-2.26 (4H, m, CH_2CH=CCH_2CH(OTBS)), 2.133 (3H, s, H_3CS), 1.47-1.23 (4H, alkyl), 1.10 (3H, d, J 6.1, CH(OTBS)CH_3), 0.95-0.88 (3H, o t, CH(OTBS)CH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 0.01 (3H, s, SiCH_3CH_3), 0.03 (3H, s, $SiCH_3CH_3$). **51a**: 6.68 (1H,o t, J 7.2, CH_2C=CHCH_2), 3.96 (1H, m, CH_2CH(OTBS)CH_3), 2.99-2.94 (2H, m, SCH_2CH_2)C=O), 2.79-2.75 (2H, m, SCH_2CH_2C=O), 2.44-2.26 (4H, m, CH_2C=CHCH_2CH(OTBS)), 2.13 (3H, s, H_3CS), 1.47-1.23 (4H, m, alkyl), 1.19 (3H, d, J 6.1, CH(OTBS)CH_3), 0.95-0.88 (3H, o t, CH_3CH_2), 0.90 (9H, s, SiC(CH_3)$_3$), 0.07 (6H, app d, J 4.3, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ **51a** and **51b**: 199.8 (b), 199.7 (a), 145.8 (a), 143.1 (b), 139.7 (a), 139.0 (b), 68.0 (b), 67.95 (a), 39.1, 37.48, 37.45, 36.1, 31.6, 31.2, 31.0, 29.7, 29.3, 29.20, 29.15, 26.0 (3C), 25.95 (3C), 25.8, 24.2, 23.1, 22.7, 18.2, 16.0, 15.9, 14.1 (2C), -4.3, -4.4, -4.6; ν_{max} ($CDCl_3$) /cm^{-1} 3024, 3014, 2959, 2931, 2898, 2859, 1665, 1472, 1378, 1256, 1130, 1083, 997, 837; m/z (ESI) 359.9 [M+H]$^+$, 381.2 [M+Na]$^+$; HRMS (ESI) found

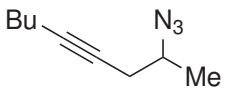
359.2436 $[M+H]^+$, $C_{19}H_{39}O_2SSi$ requires 359.2435. Appendix page 298.

4-Nonyn-2-yl 4-methylbenzenesulphonate



Prepared according to a literature method from 4-nonyn-2-ol:[185,186] Using alcohol **25** (561 mg, 4.0 mmol, 1 equiv.), pyridine (0.97 mL, 12.0 mmol, 3 equiv.) and *p*-toluenesulphonyl chloride (1.53 g, 8.0 mmol, 2 equiv.) in DCM (5 mL) to obtain the *title compound* (794 mg, 67%) as a clear oil after chromatography (5-35% Et_2O/petrol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (2H, m, ArH), 7.35-7.33 (2H, m, ArH), 4.67-4.59 (1H, m, C≡CH_ACH_BCH(OTs)CH_3), 2.53-2.43 (1H, o m, C≡CH_ACH_B), 2.43 (3H, o s, ArCH_3), 2.43-2.36 (1H, m, C≡CH_ACH_B), 2.08 (2H, tt, J 7.0 and 2.4), 1.46-1.31 (4H, m, alkyl) 1.36 (3H, d, J 6.3, CH(OTs)CH_3), 0.89 (3H, t, J 7.1, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 134.2, 129.7 (2C), 127.7 (2C), 83.4, 77.9, 74.0, 30.8, 26.8, 21.9, 21.6, 20.0, 18.3, 13.6; ν_{max} ($CDCl_3$) /cm^{-1} 3030, 3018, 3014, 2933, 2867, 1672, 1504, 1437, 1409, 1387, 1093, 928, 909; m/z (CI) 312.2 $[M+NH_4]^+$; HRMS (CI) found 312.1615 $[M+NH_4]^+$, $C_{16}H_{26}NO_3S$ requires 312.1633. Appendix page 294.

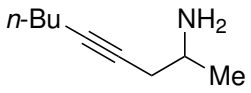
4-Azidonon-4-yne



Prepared according to a literature method[185] using 4-nonyn-2-yl 4-methylbenzenesulphonate (758 mg, 2.6 mmol, 1 equiv.) and sodium azide (418 mg, 6.4 mmol, 2.5 equiv.) in DMF (10 mL) to obtain the *title compound* (425 mg, 99%) as a clear oil

which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63-3.55 (1H, m, $CH_2CH(N_3)$), 2.44-2.30 (2H, m, $C{\equiv}CCH_2CH(N_3)$), 2.19-2.15 (2H, m, $CH_2CH_2C{\equiv}CH_2$), 1.52-1.36 (4H, m, alkyl), 1.32 (3H, d, J 6.5, $CH_3CH(N_3)CH_2$), 0.91 (3H, t, J 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2, 75.4, 56.6, 30.9, 26.6, 21.9, 18.8, 18.4, 13.6; ν_{max} ($CDCl_3$) 2961, 2934, 2874, 2112,1259; m/z (FI) 165.1$[M]^+$; HRMS (FI) found 165.1265 $[M]^+$, $C_9H_{15}N_3$ requires 165.1266. Appendix page 302.

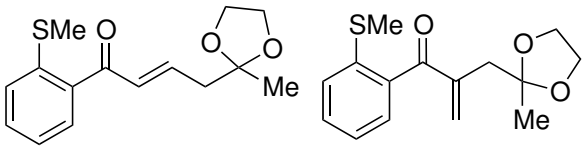
4-Nonyn-2-amine



52

Prepared according to a litererature method[185] using 4-azidonon-4-yne (425 mg, 2.6 mmol, 1 equiv.) in Et_2O (3 mL) and $LiAlH_4$ (99 mg, 2.6 mmol, 4 hydride equiv.) in Et_2O (10 mL) to yield the product amine **52** (220 mg, 61%) as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08-3.00 (1H, m, $C{\equiv}CCH_AH_BCH(NH_2)CH_3$), 2.29-2.22 (1H, m, CH_AH_B), 2.20-2.08 (3H, m, $C{\equiv}CCH_AH_BCH(NH_2)$ and $CH_2CH_2C{\equiv}C$), 1.51-1.36 (6H, m, alkyl), 1.12 (3H, d, J 6.3, $CH_3CH(NH_2)$), 0.91 (3H, t, J 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.4, 77.3, 46.5, 31.2, 30.1, 23.0, 21.9, 18.4, 13.6; ν_{max} ($CDCl_3$ solution) 3372, 2962, 2932, 2874, 2499, 1581, 1457, 1380, 1085, 908, 869; m/z (ESI) 140.1 $[M+H]^+$. Data consistent with literature.[185] Appendix page 303.

(*E*)-4-(2-Methyl-1,3-dioxolan-2-yl)-1-(2-(methylthio)phenyl)2-buten-1-one, a and 2-((2-methyl-1,3-dioxolan-2-yl)methyl)-1-(2-(methylthio)phenyl)-2-propen-1-one, b

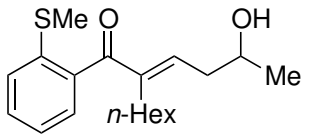


54a **54b**

Prepared according to general method **B** using 2-methythiobenzaldehyde (60 μL, 0.45 mmol, 1 equiv.), alkyne **12** (114 mg, 0.9 mmol, 2 equiv.) and [Rh(DPEphos)(nbd)]ClO_4 (24 mg, 0.03 mmol, 3 mol %) gave the products **54a** (65 mg, 52%) and **54b** (43 mg, 34%) after chromatography (0–40% Et_2O). **54a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.59 (1H, m, Ar*H*), 7.46-7.41 (1H, m, Ar*H*), 7.36-7.33 (1H, m, Ar*H*), 7.21-7.17 (1H, m, Ar*H*), 6.85 (1H, dt, *J* 15.6 and 7.3, C(O)CH=C*H*CH_2), 6.73 (1H, dt, *J* 15.6 and 1.1, C(O)C*H*=CHCH_2), 3.99-3.91 (4H, m, C(OCH_2CH_2O), 2.63 (2H, dd, *J* 7.3 and 0.7, CHC=CHCH_2C), 2.44 (3H, s, SCH_3), 1.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 144.6, 140.6, 136.6, 131.4, 129.5, 126.1, 123.8, 109.0, 64.9 (2C), 42.7, 24.6, 16.4; ν_{max} (film) /cm^{-1} 3058, 2983, 2958, 2922, 2886, 1715, 1660, 1617, 1585, 1558, 1462, 1433, 1378, 1339, 1282, 1252, 1211, 1141, 1114, 1045, 759; *m*/*z* (ESI) 279.1 $[M+H]^+$, 301.1 $[M+Na]^+$; HRMS (ESI) found 301.0867 $[M+Na]^+$, $C_{15}H_{18}NaO_3S$ requires 301.0869. **54b** Yellow crystals (Et_2O) Mpt 80–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (2H, m, Ar*H*), 7.34-7.32 (1H, m, Ar*H*), 7.17-7.13 (1H, m, Ar*H*), 5.96 (1H, d, *J* 1.0, H_AC*H*$_B$), 5.64 (1H, d, *J* 1.0, *H*$_A$CH_B), 3.97-3.89 (4H, m, C(OCH_2CH_2O), 2.87 (2H, s, CH_2C), 2.43 (3H, s, SCH_3), 1.41 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 144.8, 139.6, 137.0, 130.9, 130.3, 130.1, 126.4, 123.8, 109.4, 64.6 (2C), 39.3, 24.0, 16.5; ν_{max} (film) /cm^{-1} 2958, 2922, 2852, 1765, 1650; *m*/*z* (ESI) 279.1 $[M+H]^+$, 301.1 $[M+Na]^+$; HRMS (ESI) found

279.1050 $[M+H]^+$ $C_{15}H_{19}O_3S$, requires 279.1049. Appendix page 304

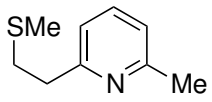
(*E*)-2-(3-Hydroxybutylidene)-1-(2-(methylthio)phenyl)octan-1-one



55

Prepared according to general method **B** using 2-methylthiobenzaldehyde (133 μL, 1.0 mmol, 1 equiv.), alkyne **26** (336mg, 2.0 mmol, 2 equiv.) $[Rh(DPEphos)(nbd)]ClO_4$ (21 mg, 0.025 mmol, 2.5 mol %) in 1,2-DCE (2 mL), to give a mixture of isomers (199 mg, 62%, approx 3:1 **a**:**b**) partially separated by chromatography (5-60% Et_2O/petrol). **55** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (1H, m, Ar*H*), 7.32-7.29 (1H, m, Ar*H*), 7.27-7.16 (2H, m, Ar*H*), 6.20 (1H, t, *J* 7.5, C=C*H*CH_2), 3.94-3.86 (1H, m, CH(OH)CH_3), 2.49-2.36 (4H, m, CH_2C=CHCH_2), 2.42 (3H, s, H_3CS), 1.51-1.23 (8H, m, alkyl), 1.21 (3H, d, *J* 6.2, CH(OH)CH_3), 0.89 (3H, t, *J* 7.0, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 144.3, 144.2, 139.6, 137.0, 130.2, 128.5, 126.9, 124.8, 67.3, 38.8, 31.7, 29.6, 29.0, 26.0, 23.2, 22.6, 16.8, 14.1; ν_{max} (film) /cm^{-1} 2957, 2924, 2853, 1760; m/z (ESI) 321.2 $[M+H]^+$; HRMS (ESI) found 343.1696 $[M+Na]^+$, $C_{19}H_{28}NaO_2S$ requires 343.1702. Appendix page 305.

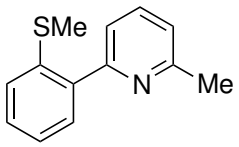
2-Methyl-6-(2-(methylthio)ethyl)pyridine



57

Prepared according to a modified literature method.[93] The acetal **46a** (82mg, 0.35 mmol) was stirred in acetone (3 mL) at room temperature. A few crystals of *p*-TSA $\cdot$ H_2O were added. After 1 hour the reaction was heated to 40 °C. After 2 hours the reaction was cooled to room temperature and concentrated $HCl_{(aq)}$ (4 drops) was added. After 1 hour reaction was complete. K_2CO_3 (0.5 g) was added followed by DCM (20 mL) and water (3 mL). After separation the aqueous was extracted once more with DCM (15 mL) and the combined organic layers washed with brine (15 mL), dried ($Na_2SO_{4\,(aq)}$) then solvent removed under reduced pressure to yield the crude diketone (68 mg, 0.35 mmol). The diketone (68 mg, 0.35 mmol, 1 equiv.) was added to a solution of NH_4OAc (162 mg, 2.1 mmol, 6 equiv.) in acetic acid (2 mL). The reaction was stirred at room temperature for 16 hours after which the reaction was complete. Water (20 mL) was added to the reaction and then 25% $NH_4OH_{(aq)}$ was added until pH 9 was achieved. The product was extracted using EtOAc (3 $\times$ 20 mL) and the organic layer then washed with brine (20 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield pyridine **57** (70 mg, quant) as thick brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, app. t, J 7.6, ArH), 7.00-6.98 (2H, m, ArH), 3.03 (2H, t, J 7.1, $SCH_2CH_2C(O)$), 2.89 (2H, t, J 7.0, SCH_2CH_2), 2.53 (3H, s, pyCH_3), 2.11 (3H, s, CH_3S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 158.0, 136.6, 121.0, 120.0, 38.2, 34.1, 24.5, 15.7; ν_{max} (film) /cm^{-1} 3060, 2925, 2858, 1728, 1658, 1592, 1578, 1455; m/z (ESI) 168.1 $[M+H]^+$; HRMS (CI) found 168.0842 $[M+H]^+$, $C_9H_{14}NS$ requires 168.0847. Appendix page 299.

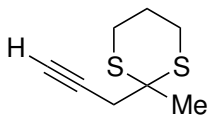
2-Methyl-6-(2-(methylthio)phenyl)pyridine



58

Acetal **54a** (63 mg, 0.27 mmol, 1 equiv.) and NH_4OAc (0.50 g, 6.49 mmol, 24 equiv.) were stirred in a solution of acetic acid (5 mL) and water (5 mL). The reaction was heated to 100 °C for 8 hours, after which the reaction was complete. A solution of ammonium hydroxide ($\sim$ 25% in water) was added until pH 9 was achieved. The product was then extracted using EtOAc (3 $\times$ 20 mL) and the organic layer washed with brine (20 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the product *pyridine* **58** (65 mg, quant) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, app. t, J 7.7, ArH), 7.44-7.41 (1H, m, pyH), 7.39-7.32 (3H, m, ArH), 7.25-7.21 (1H, m, ArH), 7.14 (1H, d, J 7.7, ArH), 2.64 (3H, s, CH_3S), 2.40 (3H, s, pyCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.8, 139.9, 137.4, 136.4, 129.8, 128.7, 125.9, 124.9, 121.7, 121.1, 24.6, 16.5; ν_{max} (film) /cm^{-1} 3058, 2920, 2852, 2360, 2342, 1670, 1584, 1573, 1446, 1053, 801, 755; m/z (CI) 216.1 [M+H]; HRMS (CI) found 216.0853 $[M+H]^+$, $C_{13}H_{14}NS$ requires 216.0847. Appendix page 300.

2-Methyl-2-propyn-2-yl-1,3-dithiane

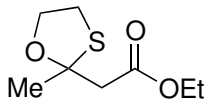


59

Prepared according to a modified literature method.[187] 2-Methyl-1,3-dithiane (0.6 mL, 5 mmol, 1 equiv.) was dissolved in THF (15 mL) and cooled to -78 °C. *sec*-

Butyl lithium (1.4 M in cyclohexane, 4.0 mL, 5.5 mmol, 1.1 equiv.) was added dropwise. The reaction was allowed to warm to -30 °C. After 1.5 hours, the reaction was cooled to -78 °C. A solution of propargyl bromide (0.5 ml, 6.5 mmol, 1.3 equiv.) and DMPU (2.4 mL, 20 mmol, 4 equiv.) in THF (2 mL) was added dropwise. The reaction was stirred for 2 hours and then quenched with water (10 mL). After warming to room temperature, Et_2O (20 ml) was added. The layers were separated and the organic phase washed with 10% $NaOH_{(aq)}$ solution (2 × 20 mL), water (2 × 20 mL), brine (20 mL) then dried (Na_2SO_4). The solvent was then removed under vacuum to obtain the crude product as a yellow oil which was then purified by chromatography on silica (5-30% Et_2O/Petrol) to obtain the pure *product* **59** as a yellow oil (325 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91-2.84 (2H, m), 2.86 (2H, d, J 2.9, HC≡CCH_2), 2.76-2.70 (2H, m), 2.11 (1H, td, J 2.7 and 0.6, HC≡CCH_2), 2.02-1.94 (1H, m), 1.88-1.78 (1H, m), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.7, 71.7 (2C), 47.2, 32.3, 27.8, 26.8, 24.8; ν_{max} (film) /cm^{-1} 3287, 2905, 2827, 2359, 2341, 1488, 1371, 1276, 1071; m/z (CI) 173.0 $[M+H]^+$; HRMS (CI) found 173.0464 $[M+H]^+$, $C_8H_{13}S_2$ requires 173.0459. Appendix page 306.

Ethyl 2-(2-methyl-1,3-oxathiolan-2-yl)acetate

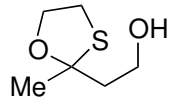


60

Ethyl acetoacetate (10.0 g, 77.0 mmol, 1 equiv.), mercaptoethanol (5.4 mL, 77 mmol, 1 equiv.) and p-TSA · H_2O (a few crystals) were stirred in toluene (35 mL) with Dean-Stark distillation. After 4 hours, the reaction was cooled and K_2CO_3 (approx 5 g) was added. The reaction was diluted with EtOAc (100 mL) and washed with water (3 × 50 mL), brine (20 mL) then dried ($MgSO_4$) and the solved was removed

under reduced pressure to obtain the crude product **60** as a colourless oil (12.3 g, 84%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.10 (2H, m, OCH_2CH$_2$S), 4.16 (2H, o q, J 7.2, CH_2CH$_3$), 3.11 (2H, m, OCH$_2$CH_2S), 2.90-2.88 (2H, m, CCH_2C(O)), 2.17 (3H, s, CH_3C), 1.27 (3H, t, J 7.2, CH$_2$CH_3); ν_{max} (film) /cm^{-1} 2978, 2938, 2872, 1740. Data inconsistent with literature.[188] Appendix page 307.

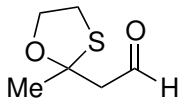
2-(2-Methyl-1,3-oxathionan-2-yl)ethanol



61

The ester **60** (12.0 g, 63.0 mmol, 1 equiv.) in Et_2O (40 mL) was added slowly to a suspension of $LiAlH_4$ (1.8 g, 48.0 mmol, 3 hydride equiv.) in Et_2O (100 mL) at room temperature (water bath). After the addition, the reaction was heated to reflux (35 °C) for 90 minutes. The reaction was then cooled to 0 °C and water (6 mL) was added dropwise. After stirring for 15 minutes, Na_2SO_4 (10 g) was added and the reaction mixture filtered through a pad of celite (Et_2O) before the solvent was removed under reduced pressure to yield the crude *product* **61** as a pale yellow oil (8.5 g, 91%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-4.18 (1H, m, OH_AH$_B$CH$_2$S), 4.04-3.98 (1H, m, OH$_A$$H_BCH_2$S), 3.74 (2H, td, J 5.8 and 1.9, CH$_2$CH_2OH), 3.05-3.02 (2H, m, OCH$_A$H$_B$CH_2S), 2.90 (1H, br s, OH), 2.05 (2H, t, J 5.8, CH_2CH$_2$OH), 1.55 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.5, 70.2, 59.7, 44.1, 33.8, 29.8. Appendix page 308.

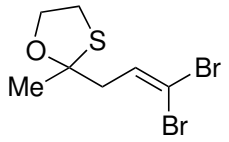
2-(2-Methyl-1,3-oxathiolan-2-yl)acetaldehyde



62

The alcohol **61** (2.21 g, 14.9 mmol, 1 equiv.) was stirred in DCM (20 mL) at 0 °C. Dess-Martin Periodinane (6.97 g, 16.4 mmol, 1.1 equiv.) was added portionwise. After the addition the reaction was stirred for 45 minutes then a 1:1 mixture of 10% $Na_2S_2O_{3\,(aq)}$ and saturated $NaHCO_3$ (50 mL) was added. The reaction was stirred until a clear biphasic solution was obtained and the layers separated. The aqueous layer was extracted with DCM (3 × 30 mL) and then washed with 10% $NaHCO_{3\,(aq)}$ (50 mL), water (3 × 50 mL) and brine (30 mL) then dried ($MgSO_4$). The solvent was removed under reduced pressure to obtain the crude product which was purified by chromatography on silica (5-20% Et_2O/Petrol) to give the *compound* **62** as a yellow oil (0.70 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76-9.75 (1H, m, C*H*O), 4.31-4.27 (1H, m, OH_AH$_B$CH$_2$S), 3.15-4.10 (1H, m, OH$_A$*H*$_B$CH$_2$S), 3.20-3.09 (2H, m, OH$_A$H$_B$C*H*$_2$S), 2.90 (2H, d, *J* 2.5, C*H*$_2$CHO), 1.68 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 90.8, 70.4, 54.9, 34.5, 30.2; ν_{max} (film) /cm^{-1} 1737; m/z (CI) 147.0 [M+H]$^+$; HRMS (CI) found 147.0486 [M+H]$^+$, $C_6H_{11}O_2S$ requires 147.0480. Appendix page 309.

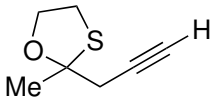
2-(3,3-Dibromoallyl)-2-methyl-1,3-oxathiolane



63

Triphenylphosphine (5.79 g, 22.1 mmol, 2.5 equiv.) was stirred in DCM (40 mL) at 0 °C. Carbon tetrabromide (3.51 g, 10.6 mmol, 1.2 equiv.) in DCM (5 mL) was added dropwise. After 45 minutes of stirring, aldehyde **62** (1.29 g, 8.8 mmol, 1 equiv.) in DCM (5 mL) was added dropwise over 5 minutes. After 1 hour, petrol (200 mL) was added and the reaction stirred for a further 10 minutes. The precipitate was removed by filtration through celite. Then solvent is removed under reduced pressure and the crude adsorbed onto silica before being purified by filtration through a silica pad (10% Et_2O/Petrol) to give the *product* **63** as a colourless oil (1.85 g, 70%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, t, J 7.1, $CH_2CHC{=}CBr_2$), 4.24-4.11 (2H, m, OCH_2CH_2S), 3.14-3.08 (2H, m, OCH_2CH_2S), 2.70-2.59 (2H, m, $CCH_2CH{=}C$), 1.61 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 93.2, 90.9, 70.6, 46.3, 34.3, 29.1. Appendix page 311.

2-Methyl-2-(prop-2-ynyl)-1,3-oxathiolane



64

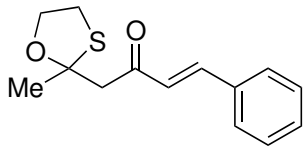
Prepared according to a modified literature method.[142] Dibromide **63** (1.85 g, 6.1 mmol, 1 equiv.) was stirred in THF (30 mL) at -78 °C. *n*-Butyl lithium (2.5 M in hexane, 6.1 mL, 15.3 mmol, 2.5 equiv.) was added dropwise. After stirring for 30 minutes, a saturated solution of NH_4Cl(aq) (20 mL) was added and the reaction

allowed to warm to room temperature. The reaction was extracted with Et_2O (3 × 30 mL) and washed with water (3 × 30 mL), then brine (10 mL) before being dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude purified by chromatography on silica (5-10% Et_2O/Petrol) to obtain the pure *product* **64** as a pale yellow oil (271 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (2H, t, J 5.8, OCH_2CH$_2$S), 3.07 (2H, t, J 5.8, OCH$_2$CH_2S), 2.74-2.63 (2H, m, CH$_2$C≡CH), 2.05 (1H, t, J 2.6, C≡CH), 1.68 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.0, 80.5, 71.1, 70.4, 34.2, 34.1, 28.4; ν_{max} (film) /cm^{-1} 1996, 1728, 1711, 1586; m/z (CI) 143.1 [M+H]$^+$; HRMS (CI) found 143.0530 [M+H]$^+$, $C_7H_{11}OS$ requires 143.0531. Appendix page 312.

7.2.4 General Procedure D for hydroacylation reactions with *in situ* generated catalyst from $[Rh(cod)_2]BF_4$ or $[Rh(nbd_2)]BF_4$

$[Rh(cod)_2]BF_4$ or $[Rh(nbd_2)]BF_4$ (1–10 mol %) and ligand (1–10 mol %) in a microwave tube were dissolved in solvent at room temperature and stirred for 5 minutes. Hydrogen gas was bubbled through the mixture for 5 minutes after which the solution was purged with nitrogen for 1–2 minutes. The aldehyde (1 equiv., 0.15 M) followed by alkyne (1.5–2 equiv.) were added and the mixture immersed in an oil bath or heating block at the appropriate temperature. After the reaction was determined to be complete by TLC, the reaction was cooled to room temperature and Et_2O (3–4 solvent volumes) was added. The mixture was filtered and concentrated under reduced pressure. The crude product was analysed with ^{1}H NMR spectroscopy to measure the approximate ratio of linear to branched products. The crude was then purified by chromatography on silica (typically eluted with 5–25% Et_2O/Petrol).

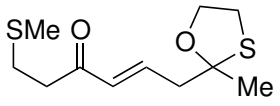
(*E*)-1-(2-Methyl-1,3-oxathiolan-2-yl)-4-phenylbut-3-en-2-one



65

Prepared according to general method **C** using aldehyde **62** (37 mg, 0.25 mmol, 1 equiv), phenyl acetylene (82 mg, 0.75 mmol, 3 equiv.), $[Rh(cod)_2]BF_4$ (5.1 mg, 5 mol %), dppb (5.4 mg, 5 mol %) in 1,2-DCE (1 mL) to give the title *compound* **65** as a brown oil (47 mg, 73%) after chromatography on silica (5-15% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, J 16.1, C(O)CH=C*H*Ph), 7.57-7.54 (2H, m, Ar*H*), 7.41-7.39 (3H, m, Ar*H*), 6.82 (1H, d, J 16.1, C(O)C*H*=CHPh), 4.24-4.14 (2H, m, OCH_2CH_2S), 3.33-3.21 (2H, m, CH_2C(O)), 3.11-3.03 (2H, m, OCH_2CH_2S), 1.74 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 142.9, 134.4, 130.6, 129.0, 298.4, 126.4, 91.8, 70.0, 54.1, 33.8, 29.6; ν_{max} (film) /cm^{-1} 2971, 2924, 2869, 1692, 1658, 1610; m/z (ESI) 271.1 $[M+Na]^+$; HRMS (ESI) found 271.0763 $[M+Na]^+$, $C_{14}H_{16}NaO_2S$ requires 271.0763. Appendix page 310.

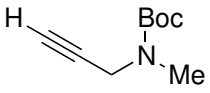
(*E*)-6-(2-Methyl-1,3-oxathiolan-2-yl)-1-(methylthio)hex-4-en-3-one



66

Prepared according to general method **D** using methylthiopropionaldehyde (15 μL, 0.15 mmol, 1 equiv), alkyne **64** (42 mg, 0.3 mmol, 2 equiv.), $[Rh(COD)_2]BF_4$ (6.2 mg, 10 mol %) and dppb (6.4 mg, 10 mol %) in 1,2-DCE (0.6 mL). After 16 hours the reaction gave the title *compound* **66** as a yellow oil (11 mg, 31%) after chromatography on silica (5-25% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, dt, J 16.0 and 7.3, C(O)CH=C*H*CH_2), 6.18 (1H, dt, J 16.0 and 1.4, C(O)C*H*=CHC*H*$_2$), 4.24-4.11 (2H, m, OC*H*$_2$CH$_2$S), 3.16-3.04 (2H, m, OCH$_2$C*H*$_2$S), 2.91-2.87 (2H, m, SCH$_2$C*H*$_2$C(O)), 2.80-2.74 (4H, m, SC*H*$_2$CH$_2$C and CH=CHC*H*$_2$), 2.13 (3H, s, SC*H*$_3$), 1.61 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.6, 132.9, 93.5, 70.7, 46.1, 39.8, 34.3, 29.5, 28.3, 15.9; ν_{max} (film) /cm^{-1} 2968, 2916, 2873, 2358, 2343, 1667, 1672; m/z HRMS (FI) found 246.0752 $[M]^+$, $C_{11}H_{18}O_2S_2$ requires 246.0748. Appendix page 313.

tert-Butyl methyl(prop-2-ynyl)carbamate

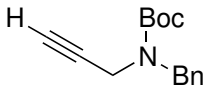


67

Prepared according to a literature method.[157]. *N*-Methyl propargylamine (1.00 g, 14.5 mmol, 1 equiv.) in methanol (10 mL) was stirred at room temperature. Di-*tert*-butyl dicarbonate (3.16 g, 14.5 mmol, 1 equiv.) was added portionwise. After the

addition the reaction was stirred for 1 hour. The solvent was removed under reduced pressure to obtain the crude product **67** which was purified by chromatography on silica (5-10% Et_2O/Petrol) to obtain a pale yellow oil of (2.45 g, quant.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (2H, br s, C≡CCH_2), 2.90 (3H, s, NCH_3), 2.20 (1H, t, J 2.5, HC≡CCH_2), 1.45 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 79.7, 78.9, 71.6, 37.7 (rotamer) 33.1, 28.1; ν_{max} (film) /cm^{-1} 3298, 3254, 2976, 2932, 1734, 1690, 1390; m/z (ESI) 192.1 [M+Na]$^+$. Data consistent with literature.[157] Appendix page 314.

tert-Butyl benzyl(prop-2-yn-1-yl)carbamate

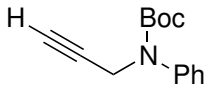


68

Sodium hydride (0.72 g, 60% in mineral oil, 18.0 mmol, 1.2 equiv.) in THF (35 mL) was stirred at room temperature. A solution of *N*-Boc-propargylamine (2.33 g, 15.0 mmol, 1 equiv.) in THF (5 mL) was added dropwise over 10 minutes and allowed to stir for 1 hour. Benzyl bromide (2.7 mL, 22.5 mmol, 1.5 equiv.) was added dropwise. After 3 hours the reaction was cooled to 0 °C and the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL). The reaction mixture was extracted with Et_2O (3 × 20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica (0-15% EtOAc/petrol) to obtain the product **68** as a colourless oil (2.80 g, 76%) ^{1}H NMR (250 MHz, DMSO−d_6, 90 °C) δ 7.39-7.27 (5H, m, ArH), 4.48 (2H, s, NCH_2Ph), 4.00 (2H, d, J 2.4, HC≡CCH_2), 3.00 (1H, t, J 2.4, HC≡CCH_2), 1.44 (9H, s, C(CH_3)$_2$); ^{13}C NMR (63 MHz, DMSO−d_6) 90 °C) δ 155.3, 138.7, 129.2, 128.2, 127.9, 80.6 (2C), 74.7, 50.4, 36.8, 28.9; ν_{max} (neat) /cm^{-1} 3294, 2977, 2931, 1693, 1242, 1160; m/z (ESI)

268.2 [M+Na]$^+$. Data consistent with literature.[189] Appendix page 329.

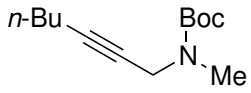
tert-Butyl phenyl(prop-2-yn-1-yl)carbamate



69

Sodium hydride (0.46 g, 60% in mineral oil , 11.4 mmol, 1.1 equiv.) in DMF (20 mL) was stirred at 0 °C. A solution of N-Boc-aniline (2.00 g, 10.3 mmol, 1 equiv.) in DMF (10 mL) was added dropwise over 10 minutes and allowed to stir for 1 hour. Propargyl bromide (80% in PhMe, 1.23 mL, 11.4 mmol, 1.1 equiv.) was added dropwise. After 30 minutes the reaction was allowed to warm to room temperature for 1 hour. The reaction was cooled to 0 °C and water (10 mL) was added dropwise. The reaction mixture was extracted with Et_2O (3 × 20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica (0-20% EtOAc/petrol) to obtain the product **69** as a slightly yellow oil (2.18 g, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (4H, m, ArH), 7.26-7.22 (1H, m, ArH), 4.39 (2H, d, J 2.4, HC≡CCH_2), 2.27 (1H, t, J 2.4, HC≡CCH$_2$), 1.48 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 142.2, 128.7, 126.3 (2C), 81.1, 80.0, 71.7, 39.8, 28.3; ν_{max} (neat) /cm^{-1} 3294, 2972, 2932, 1699,1378,1367; m/z (ESI) 254.1 [M+Na]$^+$. Data consistent with literature.[158] Appendix page 328.

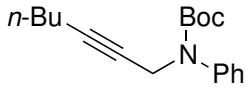
tert-Butyl hept-2-yn-1-yl(methyl)carbamate



70

tert-Butyl methyl(prop-2-ynyl)carbamate **67** (1.00 g, 5.9 mmol, 1 equiv.) in THF (20 mL) was cooled to -78 °C. *N*-Butyl lithium (3.5 mL, 1.6 M in hexanes, 6.5 mmol, 1.1 equiv.) was added dropwise and the reaction stirred for 45 minutes. 1-Iodobutane (0.74 mL, 6.5 mmol, 1.1 equiv.) was added dropwise and the reaction allowed to stir for a further 1 hour before warming to room temperature over 16 hours. The reaction was quenched with a saturated solution of $NH_4Cl_{(aq)}$ (10 mL). The layers were separated and the organic washed with a saturated solution of $NaHCO_{3\,(aq)}$ (20 mL), water (3 × 20 mL) and brine (20 mL) then dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by chromatography on silica (0-10% EtOac/petrol) to obtain the title compound **70** (691 mg, 52%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (2H, br s, C≡CCH_2), 2.91 (3H, s, NCH_3), 2.22-2.18 (2H, m, $CH_2CH_2C{\equiv}C$), 1.54-1.39 (4H, m, $CH_3CH_2CH_2CH_2C{\equiv}C$), 1.40 (9H, s, C(C$H_3$)$_3$), 0.93 (3H, t, *J* 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 84.0, 79.8, 75.2, 33.3, 30.8, 28.4 (2C), 21.9, 18.4, 13.6; ν_{max} (neat) /cm^{-1} 2960, 2933, 2873, 1734, 1694, 1143; m/z (ESI) 248.2 $[M+H]^+$. Previously reported in literature.[190] Appendix page 346.

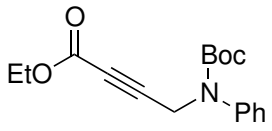
(*E*)-*tert*-Butyl hept-2-yn-1-yl(phenyl)carbamate



71

Prepared as for *tert*-butyl hept-2-yn-1-yl(methyl)carbamate, **70** using *tert*-butyl phenyl(prop-2-yn-1-yl)carbamate (1.00 g, 4.3 mmol, 1 equiv.), *n*-butyl lithium (1.90 mL, 2.5 M in hexane, 4.7 mmol, 1.1 equiv.) and 1-iodobutane (0.53 mL, 4.7 mmol, 1 equiv.) in THF (20 mL) to obtain the *title compound* **71** (225 mg, 19%) after chromatography on silica (0-10% EtOAc/petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (4H, m, Ar*H*), 7.24-7.21 (1H, m, Ar*H*), 4.36 (2H, t, *J* 2.1, $CH_2C{\equiv}CH_2N$), 2.19-2.16 (2H, m, $CH_2CH_2C{\equiv}CCH_2$), 1.48 (9H, s, $C(CH_3)_3$), 1.48-1.35 (4H, m, $CH_3CH_2CH_2CH_2$), 0.90 (3H, t, *J* 7.2, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 142.4, 128.5, 126.3, 126.0, 84.1, 80.7, 76.1, 40.1, 30.7, 28.3, 21.8, 18.4, 13.6; ν_{max} (neat) /cm^{-1} 2959, 2931, 2873, 1699, 1378, 1367, 1150; *m*/*z* (ESI) 310.2 $[M+Na]^+$; HRMS (ESI) found 310.1773 $[M+Na]^+$, $C_{18}H_{25}NNaO_2$ requires 310.1778. Appendix page 347.

Ethyl 4-((*tert*-butoxycarbonyl)(phenyl)amino)but-2-ynoate

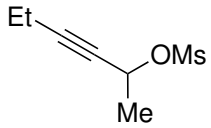


72

tert-Butyl phenyl(prop-2-yn-1-yl)carbamate **69** (1.00 g, 4.3 mmol, 1 equiv.) in THF (20 mL) was cooled to -78 °C. *n*-Butyl lithium (2 M in hexane, 2.35 mL, 4.7 mmol, 1.1 equiv.) was added dropwise and the reaction allowed to warm briefly to -10 °C. The reaction was cooled to -78 °C and ethyl chloroformate (0.45 mL, 4.7 mmol,

1.1 equiv.) added dropwise. The reaction was then stirred for 20 minutes before allowing to warm to room temperature over 2 hours. The reaction was quenched with saturated $NH_4Cl_{(Aq)}$ (3 mL). Water (20 mL) was added and the mixture extracted with DCM (2 × 20 mL). The organic extracts were then washed with water (3 × 20 mL), brine (20 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to a dark brown oil. The product was purified by chromatography on silica (0-30% EtOAc/hexane) to obtain the *product* **72** as a yellow oil (0.54 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (5H, m, ArH), 5.52 (2H, s, C≡CCH_2N), 4.24 (2H, q, J 7.1, CH_3CH_2O), 1.48 (9H, br. s, C(CH_3)$_3$), 1.32 (3H, t, J 7.1, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 153.3, 141.8, 128.9, 126.6, 83.7, 81.5, 77.0, 75.6, 62.1, 39.9, 28.2, 14.0; ν_{max} (neat) /cm^{-1} 2979, 2933, 2236, 1699, 1366, 1242, 1145; m/z (ESI) 326.2 [M+Na]$^+$; HRMS (ESI) found 326.1362 [M+Na]$^+$, $C_{17}H_{21}NNaO_4$ requires 326.1363. Appendix page 348.

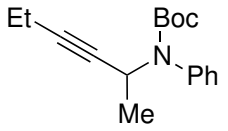
Hex-3-yn-2-yl methanesulfonate



3-Hexyne-2-ol (1.10 ml, 10.2 mmol, 1 equiv.) and triethylamine (1.40 ml, 10.2 mmol, 1 equiv.) were stirred in DCM (10 mL) at 0 °C. Mesyl chloride (0.80 mL, 30.0 mmol, 1 equiv.) was added dropwise. After 30 minutes the reaction was washed with water (20 mL), followed by HCl(aq) (0.5M, 10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil which was used without further purification (1.80 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.28 (1H, m, C≡CCHCH$_3$), 3.13 (3H, s, SO_2CH_3), 2.28 (2H, qd, J 7.5 and J 2.0, CH_3CH_2C≡CCH_2), 1.64 (3H, d, J 6.6, CCHCH_3), 1.18 (3H, t, J 7.5,

$CH_3CH_2C{\equiv}C$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 90.6, 69.0, 39.1, 23.0, 13.4, 12.3; m/z (ESI) 216.1 $[M+Na]^+$. Appendix page 351.

(*E*)-*tert*-Butyl hex-3-yn-2-yl(phenyl)carbamate

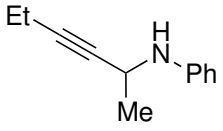


73

Sodium hydride (60% in mineral oil, 0.41 g, 10.2 mmol, 1 equiv.) was stirred in DMF (20 mL) at 0 °C. *N*-Boc-aniline (1.97 g, 10.2 mmol, 1 equiv.) in DMF (10 mL) was added dropwise to the slurry of sodium hydride. After stirring for 30 minutes, a solution of hex-3-yn-2-yl methanesulfonate (1.80 g, 10.2 mmol, 1 equiv) in DMF (5 mL) was added dropwise and the reaction was allowed to warm to room temperature overnight. The reaction was then heated to 80 °C for 30 minutes then cooled to 15 °C (water bath). Saturated NH_4Cl(aq) (20 mL) was added followed by water (20 mL). The mixture was then extracted using Et_2O (3 × 20 mL). The organic layer was washed with water (2 × 20 mL), brine (10 mL) then dried ($MgSO_4$) and concentrated under reduce pressure to yield the crude product as an orange oil (2.65 g). The crude product was purified by chromatography on silica (12% EtOAc/hexane) to obtain a mixture of desired product and *N*-Boc-aniline. Trituration (hexane) and concentration under reduced pressure gave the desired *product* **73** as a colourless oil (1.70 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m, Ar*H*), 7.22-7.16 (3H, m, Ar*H*), 5.18-5.16 (1H, br. m, $C{\equiv}CC\mathit{H}CH_3$), 2.06 (2H, qd, *J* 7.5 and 2.2, $CH_3C\mathit{H}_2C{\equiv}C$), 1.32 (9H, br. s, $C(C\mathit{H}_3)_3$), 1.20 (3H, d, *J* 7.0, $CCHC\mathit{H}_3$), 1.00 (3H, t, *J* 7.5, $C\mathit{H}_3CH_2C{\equiv}C$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.2, 129.7, 128.2, 127.0, 85.5, 80.2, 79.6, 44.8, 28.3, 21.3, 13.8, 12.4; ν_{max} (neat) $/cm^{-1}$ 2976, 2935, 1694, 1379, 1366, 1317, 1163; m/z (ESI) 274.2 $[M+H]^+$; HRMS (ESI) found 296.1619

$[M+Na]^+$, $C_{17}H_{23}NNaO_2$ requires 296.1621. Appendix page 352.

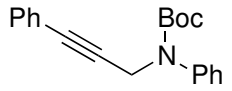
N-(Hex-3-yn-2-yl)aniline



92

Propargyl amine **73** (1.00 g, 3.7 mmol, 1 equiv.) was stirred in DCM (10 mL) at room temperature. Trifluoroacetic acid (1.40 mL, 18.5 mmol, 5 equiv.) was added and the reaction stirred for 1 hour. $NaHCO_3$ (approx. 3 g) and water (20 mL) was added and the layers separated. The organic layer was washed with brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then purified by chromatography on silica (0–20% EtOAc/hexane) to yield the pure *product* **92** as a pale yellow oil (0.36 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (2H, m, Ar*H*), 6.80-6.72 (3H, m, Ar*H*), 4.25-4.20 (1H, m, C≡CC*H*CH_3), 3.74 (1H, br s, N*H*), 2.19 (2H, qd, *J* 7.5 and 2.0, CH_3CH_2C≡CCH), 1.52 (3H, d, *J* 6.7, CHCH_3), 1.12 (3H, t, *J* 7.5, CH_3CH_2C≡C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 129.1, 118.1, 114.0, 83.8, 81.0, 41.1, 22.9, 14.0, 12.4; ν_{max} (neat) /cm^{-1} 3396, 3051, 3020, 2974, 2933, 2876, 1601, 1501; m/z (ESI) 174.1 $[M+H]^+$; HRMS (ESI) found 174.1294 $[M+Na]^+$, $C_{12}H_{16}N$ requires 174.1283. Appendix page 353.

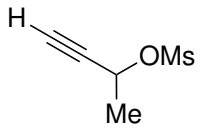
tert-Butyl phenyl(4-phenylbut-3-yn-2-yl)carbamate



75

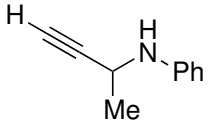
3-Phenyl-2-propyn-1-ol (1.9 mL, 15.0 mmol, 1 equiv.) and triethylamine (2.1 mL, 15.0 mmol, 1 equiv.) was stirred in DCM (20 mL) at 0 °C. Mesyl chloride (1.2 mL, 15.0 mmol, 1 equiv.) was added dropwise and the reaction stirred for 10 minutes. The reaction was then washed with water (20 mL), followed by $HCl_{(aq)}$ (0.5M, 10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to yield the mesylate as a yellow oil. The mesylate was then added dropwise to a solution of *N*-Boc-aniline sodium salt (0.77 M in DMF, 19.5 mL, 15.0 mmol, 1 equiv.) at 0 °C. The reaction was allowed to warm to room temperature over 16 hours. Saturated $NH_4Cl_{(aq)}$ (20 mL) was added followed by water (20 mL). The mixture was then extracted using Et_2O (3 × 20 mL). The organic layer was washed with water (2 × 20 mL), brine (10 mL) then dried ($MgSO_4$) and concentrated under reduce pressure to yield the crude product as an orange oil (2.65 g). The crude product was purified by chromatography on silica (12% EtOAc/hexane) to obtain a mixture of desired product and *N*-Boc-aniline. Trituration (hexane) and concentration under reduced pressure gave the desired *product* **75** as an colourless oil (2.76 g, 60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.27 (10H, m, Ar*H*), 4.60 (2H, s, C≡CCH_2), 1.49 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 142.3, 131.7, 128.8, 128.3, 126.5, 126.3, 123.0, 85.7, 83.8, 80.9, 40.6, 28.4; ν_{max} (neat) $/cm^{-1}$ 2977, 2928, 1699; m/z (ESI) [2M+Na]$^+$; HRMS (ESI) found 330.1454 [M+Na]$^+$, $C_{20}H_{21}NNaO_2$ requires 330.1465. Appendix page 367

But-3-yn-2-yl methanesulfonate



3-Butyn-2-ol (2.4 ml, 30.0 mmol, 1 equiv.) and triethylamine (4.2 ml, 30.0 mmol, 1 equiv.) were stirred in DCM (20 mL) at 0 °C. Mesyl chloride (2.3 mL, 30 mmol, 1 equiv.) was added dropwise. After 30 minutes the reaction was washed with water (40 mL), followed by $HCl_{(aq)}$ (0.5M, 20 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, acetone−d_6) δ 5.21 (1H, qd, J 6.7 and J 2.2, C≡CCHCH$_3$), 3.23 (1H, d, J 2.2, HC≡CCH) 3.05 (3H, s, OS(O)$_2$CHH_3), 1.48 (3H, d, J 6.7, CHCH_3). Appendix page 361.

N-(But-3-yn-2-yl)aniline

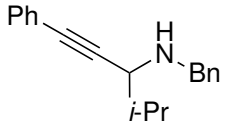


77

Prepared according to a modified literature procedure.[191] But-3-yn-2-yl methanesulfonate (2.43 g, 15.0 mmol, 1 equiv.) and triethylamine (3.10 mL, 22.5 mmol, 1.5 equiv.) and aniline (1.40 mL, 15.0 mmol, 1 equiv.) were stirred in DMF (20 mL) and heated to 130 °C for 20 hours. The reaction was then cooled to 5 °C and water added dropwise. The mixture was the extracted with Et_2O (3 × 20 mL). The organic extracts were then washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica (0–10% EtOAc/hexane) to obtain yellow crystals of the desired product which were

further purified by trituration (hexane) to obtain the *product* **77** as white crystals (410 mg, 19%). Mpt. 70-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (2H, m, Ar*H*), 6.84-6.81 (1H, m, Ar*H*), 6.77-6.75 (2H, m, Ar*H*), 4.24 (1H, qd, *J* 6.8 and *J* 2.1, C≡CC*H*CH_3), 2.24 (1H, d, *J* 2.11, *H*C≡CCH), 1.57 (3H, d, *J* 6.8, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 129.2, 118.9, 114.3, 85.3, 70.2, 41.0, 22.2; ν_{max} (neat) /cm^{-1} 3393, 3283, 3053, 2979, 1602, 1504, 1314, 1252, 1155, 751; *m*/*z* (ESI) 146.3 $[M+H]^+$; *m*/*z* HRMS (ESI) found 146.0969 $[M+H]^+$, $C_{10}H_{12}N$ requires 146.0964. Appendix page 362.

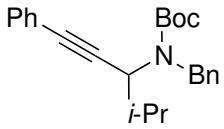
N-Benzyl-4-methyl-1-phenylpent-1-yn-3-amine



78

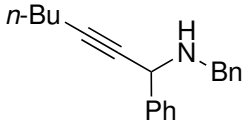
Prepared according to a literature method.[161] *iso*-Butyraldehyde (0.27 mmol, 3 mmol, 1 equiv), benzylamine (0.50 mL, 4.5 mmol, 1.5 mmol), phenylacetylene (0.99 mL, 9 mmol, 3 equiv.) and CuBr (87 mg, 20 mol %) in toluene (1.5 mL) were heated in a microwave at 100 °C for 1 hour. The reaction was purified by chromatography on silica (5–25% EtOAc/petrol) to obtain the product **78** as a colourless oil (0.69 g, 87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48 (2H, dd, *J* 6.4 and 2.8, Ar*H*), 7.43 (2H, d, *J* 7.4, Ar*H*), 7.38-7.32 (5H, m, Ar*H*), 7.29 (1H, d, *J* 7.2, Ar*H*), 4.13 (1H, d, *J* 13.0, NHCH_AH$_B$Ph), 3.92 (1H, d, *J* 13.0, NHCH$_A$$H_B$Ph), 3.43 (1H, d, *J* 5.4, C≡CC*H*CH), 2.02-1.94 (1H, m, CHC*H*$(CH_3)_2$), 1.55 (1H, br s, N*H*), 1.10 (6H, dd, *J* 6.7 and 2.1, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 131.7, 128.42, 128.37, 128.26, 127.9, 127.0, 123.6, 89.7, 84.7, 56.2, 51.8, 33.0, 19.8, 18.1; *m*/*z* (ESI) 286.2 $[M+Na]^+$. Data consistent with literature.[161] Appendix page 349.

tert-Butyl benzyl(4-methyl-1-phenylpent-1-yn-3-yl)carbamate



N-Benzyl-4-methyl-1-phenylpent-1-yn-3-amine **78** (400 mg, 1.5 mmol, 1 equiv.) and triethylamine (0.32 mL, 2.3 mmol, 1.5 equiv) were stirred in DCM (5 mL). Boc_2O (0.33 g, 1.5 mmol, 1 equiv) was added as a solution in DCM (5 mL). After 4 hours, a further Boc_2O (0.11 g, 0.5 mmol, 0.5 equiv) was added and the reaction stirred for 2 days. The mixture was then concentrated under reduced pressure and the residue purified by chromatography silica (0–5% EtOAc/petrol) to obtain the *product* as a colourless oil (0.23 g, 41%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.21 (10H, m, Ar*H*), 5.04 (1H, br s, C≡CC*H*CH), 4.55 (2H, br s, NCH_2Ph), 2.11-1.93 (1H, m, CHC*H*$(CH_3)_2$), 1.47-1.27 (9H, br m, C(CH_3)$_3$), 1.12 (3H, d, J 6.6, CH(CH_3)$_2$), 0.97-0.94 (3H, m, CH(CH_3)$_2$); ^{13}C NMR (125Hz MHz, $CDCl_3$) δ 155.6, 140.2, 131.5, 128.1, 128.0, 128.0, 127.0, 126.5, 122.9, 87.3, 85.5, 80.1, 55.4, 48.3, 33.2, 28.2, 19.5, 19.2; ν_{max} (neat) /cm^{-1} 2968, 2929, 2873, 1693; m/z (ESI) 364.2 $[M+H]^+$; HRMS (ESI) found 386.2079 $[M+Na]^+$, $C_{24}H_{29}NNaO_2$ requires 386.2091. Appendix page 363.

7.2.5 General Procedure E for the synthesis of propargyl amine substrates as exemplified by *N*-benzyl-1-phenyl-hept-2-yn-1-amine

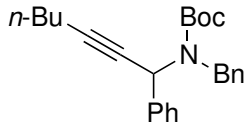


79

Prepared accoding to a method described by Hayes.[192] Benzylamine (1.1 mL, 10.0 mmol, 1 equiv.) and benzaldehyde (1.0 mL, 10.0 mmol, 1 equiv.) was stirred in Et_2O (10 mL) for 4 hours. The solution was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to obtain the imine which was used without further purification. 1-Hexyne (3.5 mL, 30.0 mmol, 3 equiv.) was stirred in THF (10 mL) at -78 °C and *n*-butyl lithium (12 mL, 2.5M in hexanes, 30.0 mmol, 3 equiv.) was added dropwise. The reaction was allowed to stir for 30 minutes before addition of $BF_3 \cdot THF$ (4.1 mL, 39.0 mmol, 3.9 equiv.) in THF (5 mL) to the solution of lithium acetylide. The reaction was allowed to stir for a further 20 minutes before addition of the imine in THF (5 mL). The reaction turned pink on addition of the imine. The reaction was allowed to warm to room temperature over 3 hours, whereupon it turned yellow. The reaction was quenched using pH 7.2 aqueous potassium phosphate buffer solution (20 mL). The organic layer was separated and the aqueous extracted with Et_2O (3 × 20 mL). The combined organic extracts were then washed with water (2 × 20 mL) and brine (20 mL) and then dried using $MgSO_4$. The solvent was removed under reduced pressure to obtain an orange gel. The title compound **79** was obtained as a yellow oil (1.09 g, 39%) after Kügeröhl distillation (190–220 °C, 1 mbar). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, m, Ar*H*), 7.44-7.27 (8H, m, Ar*H*), 4.61 (1H, t, *J* 1.9, C≡CC*H*), 3.95 (2H, app. dd, *J* 17.0 and 13.0, NCH_2Ph), 2.35 (2H, td, *J* 7.0 and 2.1, $CH_2CH_2C{\equiv}CCH$), 1.73 (1H, br s, N*H*), 1.49-1.63 (4H, m, alkyl), 0.99

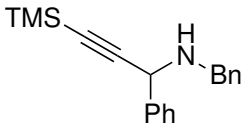
(3H, t, J 7.3, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.1, 128.5, 128.5, 127.7 (2C), 127.6, 127.1, 86.1, 79.9, 53.4, 51.2, 31.1, 22.1, 18.7, 13.8; ν_{max} (neat) /cm^{-1} 3317, 3085, 3062, 3028, 2957, 2931, 2872, 2235, 1603, 1494, 1453, 1028, 740, 698; m/z (ESI) 278.2 $[M+H]^+$; HRMS (ESI) found 278.1896 $[M+H]^+$, $C_{20}H_{24}N$ requires 278.1903. Previously reported.[193] Appendix page 357

tert-Butyl benzyl(1-phenylhept-2-yn-1-yl)carbamate



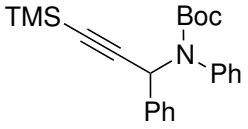
N-Benzyl-1-phenylhept-2-yn-1-amine **79** (305 mg, 1.1 mmol, 1 equiv.) was stirred in DCM (5 mL) with Boc_2O (264 mg, 1.2 mmol, 1.09 equiv.) and triethylamine (0.17 mL, 1.2 mmol, 1.09 equiv.) and a crystal of 4-dimethylaminopyridine. After 16 hours the, solvent was removed and the residue purified by chromtatography on silica (0–10% EtOAc/petrol) to obtain the title *compound* as a colourless oil (269 mg, 65%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.49 (2H, m, ArH), 7.36-7.26 (3H, m, ArH), 7.22-7.14 (5H, m, ArH), 6.47 (1H, br s, C≡CCH), 4.32-4.18 (2H, m, NCH_2Ph), 2.22-2.14 (2H, m, CH_2C≡C), 1.43-1.32 (13H, m, alkyl and C(CH_3)$_3$), 0.92-0.84 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (rotameric), 139.8 (rotameric), 138.9, 128.4, 127.8, 127.1, 127.6 (rotameric), 127.0 (rotameric), 126.3, 87.6, 80.4, 76.6, 51.5 (rotameric), 47.9, 30.6, 28.3, 22.0, 18.4, 13.6; ν_{max} (neat) /cm^{-1} 2960, 2932, 2873, 1688; m/z (ESI) 777.4 $[2M+Na]^+$; HRMS (ESI) found 400.2246 $[M+Na]^+$, $C_{25}H_{31}NNaO_2$ requires 400.2247. Appendix page 358.

N-Benzyl-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-amine



Prepared according to general procedure **E** using benzylamine (1.0 mL, 9.0 mmol, 1 equiv.), benzaldehyde (0.92 mL, 9.0 mmol, 1 equiv.), (trimethylsilyl)acetylene (1.91 mL, 13.5 mmol, 1.5 equiv.), *n*-butyl lithium (5.4 mL, 2.5 M in hexanes, 15.0 mmol, 1.5 equiv.) and $BF_3 \cdot THF$ (2.0 mL, 18.0 mmol, 2 equiv.). The *title compound* was obtained as a yellow oil (1.24 g, 47%) after Kügeröhl distillation (250 °C, 1 mbar) and used immediately in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (3zH, m, Ar*H*), 7.44-7.26 (18H, m, Ar*H*), 4.61 (1H, s, C≡CC*H*Ph), 3.97-3.90 (2H, m, NCH_2Ph), 2.27 (1H, br s, N*H*), 0.24 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 128.56, 128.45, 128.42, 127.9, 127.69, 127.66, 127.1, 105.5, 90.3, 53.7, 51.0, 0.1; ν_{max} (neat) /cm^{-1}3062, 3029, 2958, 2164; m/z (ESI) 294.2 [M+H]$^+$; HRMS (ESI) found 294.1671 [M+H]$^+$, $C_{19}H_{24}NSi$ requires 294.1673. Appendix 359.

tert-Butyl phenyl(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)-carbamate

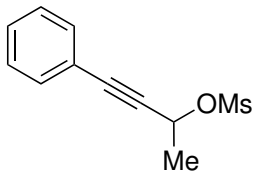


80

N-Benzyl-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-amine (0.60 g, 2.0 mmol, 1 equiv.) was stirred in DCM (5 mL) with Boc_2O (0.49 g, 2.2 mmol, 1.1 equiv.) and triethylamine (0.31 mL, 2.2 mmol, 1.1 equiv.) and a crystal of 4-dimethylaminopyridine. After 16 hours the solvent was removed and the residue purified by chromtatography

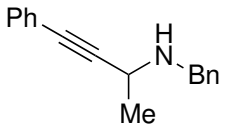
on silica (0–20% EtOAc/petrol) to obtain the title *compound* **80** as a colourless oil containing ∼25% Boc_2O (239 mg, ∼30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.36 (2H, m, Ar*H*), 7.23-7.02 (8H, m, Ar*H*), 6.48-6.25 (1H, m, C≡CC*H*Ph), 4.12-4.07 (2H, m, NCH_2Ph), 1.22 (9H, s, C(CH_3)$_3$), -0.00 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.0, 138.3, 128.7, 128.1, 128.0, 127.8, 127.5, 126.6, 102.5, 92.1, 80.8, 52.4, 48.4, 28.5, 0.0; ν_{max} (neat) /cm^{-1} 3064, 3052, 2976, 2177, 1691; m/z (ESI) 809.5 [2M+Na]$^+$; HRMS (ESI) found 416.2010 [M+Na]$^+$, $C_{24}H_{31}NNaO_2Si$ requires 416.2016. Appendix 360

4-Phenylbuty-3-yn-2-yl methanesulfonate



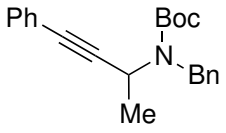
4-Phenyl-3-butyn-2-ol (1.48 ml, 10.2 mmol, 1 equiv.) and triethylamine (1.40 ml, 10.2 mmol, 1 equiv.) were stirred in DCM (10 mL) at 0 °C. Mesyl chloride (0.80 mL, 30 mmol, 1 equiv.) was added dropwise. After 30 minutes the reaction was washed with water (20 mL), followed by $HCl_{(aq)}$ (0.5M, 10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (2H, m, Ar*H*), 7.31-7.25 (3H, m, Ar*H*), 5.46 (1H, q, *J* 6.7, C≡CC*H*CH_3), 3.09 (3H, s, OS(O)$_2$CH_3), 1.68 (3H, d, *J* 6.7, CHCH_3). Appendix page 356.

N-Benzyl-4-phenylbut-3-yn-2-amine



Prepared according to general procedure **E** using benzylamine (1.1 mL, 10.0 mmol, 1 equiv.), acetaldehyde (0.56 mL, 10.0 mmol, 1 equiv.), Phenyl acetylene (1.65 mL, 15 mmol, 1.5 equiv.), *n*-butyl lithium (6.4 mL, 2.5 M in hexanes, 16.0 mmol, 1.6 equiv.) and $BF_3 \cdot THF$ (2.2 mL, 20.0 mmol, 2 equiv.). The crude product was purified by chromatography on silica (0–40% EtOAc/petrol) to obtain the title *compound* as a yellow oil (533 mg, 23%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.34 (2H, m, Ar*H*), 7.27 (2H, d, *J* 7.3, Ar*H*), 7.18-7.23 (5H, m, Ar*H*), 7.14 (1H, t, *J* 7.1, Ar*H*), 3.96 (1H, d, *J* 12.8, NHCH_AH$_B$Ph), 3.78 (1H, d, *J* 12.8, NHCH$_A$$H_B$Ph), 3.61 (1H, q, *J* 6.8, C*H*CH$_3$), 1.35 (3H, d, *J* 6.8, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 131.7, 128.4 (2C), 128.3, 128.0, 127.1, 123.3, 91.6, 83.2, 51.6, 45.1, 22.4; ν_{max} (neat) /cm^{-1} 3312, 3061, 3029, 2971, 2929; m/z (ESI) 236.1 $[M+H]^+$; HRMS (ESI) found 263.1435 $[M+H]^+$, $C_{17}H_{18}N$ requires 236.1434. Appendix page 364.

tert-Butyl benzyl(4-phenylbut-3-yn-2-yl)carbamate

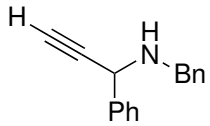


81

N-Benzyl-4-phenylbut-3-yn-2-amine (0.52 g, 2.2 mmol, 1 equiv.) was stirred in DCM (5 mL) with Boc_2O (0.53 g, 2.4 mmol, 1.1 equiv.) and triethylamine (0.33 mL, 2.4 mmol, 1.1 equiv.) and a crystal of 4-dimethylaminopyridine. After 6 hours the solvent was removed and the residue purified by chromatography on silica (0–20%

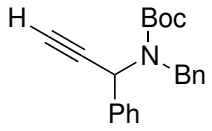
EtOAc/petrol) to obtain the title *compound* **81** as a yellow oil (460 mg, 62%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.28 (10H, m, ArH), 5.48 (1H, br s, $CHCH_3$), 4.67-4.50 (2H, m, NCH_2Ph), 1.51-1.30 (9H, br s, C(CH_3)$_3$), 1.40 (3H, o d, J 6.9, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 131.5, 130.0, 129.9, 128.2, 128.1, 127.0, 126.6, 122.8, 88.8, 84.0, 80.3, 47.4, 28.3, 27.4, 21.4; ν_{max} (neat) /cm^{-1} 2977, 1688, 1161; m/z (ESI) 693.4 [2M+Na]$^+$; HRMS (ESI) found 358.1765 [M+Na]$^+$, $C_{22}H_{25}NNaO_2$ requires 358.1778. Appendix page 366

N-benzyl-1-phenylprop-2-yn-1-amine



Prepared according to general procedure **E** using benzylamine (1.1 mL, 10.0 mmol, 1 equiv.), acetaldehyde (0.56 mL, 10.0 mmol, 1 equiv.), sodium acetylide (17.2 mL, 18% in xylenes and mineral oil, 20.0 mmol, 2 equiv.), $BF_3 \cdot THF$ (2.1 mL, 20.0 mmol, 2 equiv.). The crude product was purified by chromatography on silica (0-25% EtOAc/petrol) to obtain the title compound as a yellow oil (0.71 g) containing ~25% benzaldehyde and was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66-7.52 (3H, m, ArH), 7.45-7.27 (7H, m, ArH), 4.60 (1H, d, J 2.3, HC≡CCH), 4.02-3.88 (2H, m, NCH_2Ph), 2.56 (1H, d, J 2.3, HC≡CCH), 1.85 (1H, s, NH); m/z (ESI) 236.1 [M+H]$^+$. Data consistent with literature.[194] Appendix page 365.

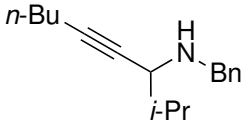
tert-Butyl benzyl(1-phenylprop-2-yn-1-yl)carbamate



82

Crude *N*-benzyl-1-phenylprop-2-yn-1-amine (0.73 g, ∼3.3 mmol, 1 equiv.) was stirred in DCM (5 mL) with Boc_2O (0.79 g, 3.6 mmol, ∼1.1 equiv.) and triethylamine (0.50 mL, 3.6 mmol, ∼1.1 equiv.) and a crystal of 4-dimethylaminopyridine. After 16 hours the solvent was removed and the residue purified by chromatography on silica (0–20% EtOAc/petrol) to obtain the title *compound* **82** as a yellow oil (1.00 g, ∼94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.41 (2H, m, Ar*H*), 7.27-7.18 (3H, m, Ar*H*), 7.15-7.03 (4H, m, Ar*H*), 6.36 (1H, br s, HC≡CC*H*), 4.24 (2H, br s, NCH_2Ph), 2.42 (1H, d, *J* 2.5, *H*C≡CCH), 1.28 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 139.1, 137.5, 128.4, 128.0, 127.8, 127.5, 127.2, 126.4, 80.8, 80.5, 74.9, 51.5, 48.2, 28.2; ν_{max} (neat) /cm^{-1}3296, 3064, 3032, 2977, 2930, 1695; m/z (ESI) 665.3 [2M+Na]$^+$; HRMS (ESI) found 344.1621 $C_{21}H_{23}NNaO_2$ requires 344.1621. Appendix page 368.

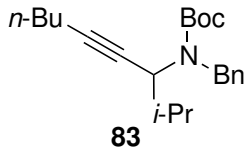
N-Benzyl-2-methylnon-4-yn-3-amine



Prepared according to general procedure **E** using benzylamine (1.1 mL, 10.0 mmol, 1 equiv.), *iso*-butyraldehyde (0.91 mL, 10.0 mmol, 1 equiv.), 1-hexyne (2.9 mL, 25.0 mmol, 2.5 equiv.), *n*-butyl lithium (10 mL, 2.5 M in hexanes, 25 mmol, 2.5 equiv.) and $BF_3 \cdot THF$ (3.1 mL, 30.0 mmol, 3 equiv.). The crude product was

purified by chromatography on silica (0–25% EtOAc/petrol) to obtain the title *compound* as a yellow oil (0.75 g, 31%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (2H, d, J 7.3, ArH), 7.34-7.31 (2H, m, ArH), 7.24 (1H, d, J 7.2, ArH), 4.03 (1H, d, J 13.0, NCH_AH$_B$Ph), 3.81 (1H, d, J 13.0, NCH$_A$$H_B$Ph), 3.17 (1H, dt, J 5.2 and 2.1, CH_2C≡CCHCH), 2.25 (2H, td, J 6.9 and 2.1, $CH_2C$$H_2$C≡CCH), 1.84 (1H, dq, J 12.5 and 6.4, CHCHC$(CH_3)_2$), 1.55-1.41 (4H, m, alkyl), 0.99 (3H, d, J 6.7, CH(CH_3)$_2$), 0.98 (3H, d, J 6.7, CH(CH_3)$_2$), 0.93 (3H, t, J 7.3, CH_3CH$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 128.4, 128.3, 126.9, 84.9, 79.4, 55.8, 51.6, 32.7, 31.2, 21.9, 19.8, 18.4z, 17.8, 13.6; ν_{max} (neat) /cm^{-1} 2958, 2931, 2872; m/z (ESI) 236.1 [M+H]$^+$. Data consistent with literature.[195] Appendix page 369.

tert-Butyl benzyl(2-methylnon-4-yn-3-yl)carbamate

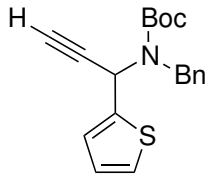


83

N-Benzyl-2-methylnon-4-yn-3-amine (0.75 g, 3.1 mmol, 1 equiv.)) was stirred in DCM (5 mL) with Boc_2O (0.74 g, 3.4 mmol, 1.1 equiv.) and triethylamine (0.47 mL, 3.4 mmol, 1.1 equiv.) and a crystal of 4-dimethylaminopyridine. After 16 hours the solvent was removed and the residue purified by chromtatography on silica (0–20% EtOAc/petrol) to obtain the title *compound 83* as a colourless oil (1.01 g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, ArH), 4.80 (1H, br s, C≡CCH), 4.58-4.38 (2H, br m, NCH_2Ph), 2.17-2.05 (2H, m, CH_2C≡C), 1.95-1.78 (1H, m, CHCH(CH_3)$_2$), 1.48-1.17 (13H, m, alkyl and C(CH_3)$_3$), 1.03-0.95 (3H, m, CH_3), 0.95-0.81 (6H, m, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 146.7, 127.8, 127.0, 126.3, 85.9, 79.8, 77.6, 55.2, 48.1, 33.2, 30.6, 28.2, 27.4, 21.8, 19.34, 19.21, 18.3, 13.5; ν_{max} (neat) /cm^{-1} 2962, 2932, 2873, 1692; m/z (ESI) 236.1 [M+H]$^+$;

HRMS (ESI) found 366.2389 $[M+Na]^+$, $C_{22}H_{33}NNaO_2$ requires 366.2404. Appendix page 370.

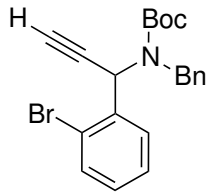
tert-Butyl benzyl(1-(thiophen-2-yl)prop-2-yn-1-yl)carbamate



84

Prepared according to general method **E** using 2-thiophenecarboxaldehyde (0.93 mL, 10.0 mmol, 1 equiv.), benzylamine (1.22 mL, 10.0 mmol, 1 equiv.), sodium acetylide (18% in light mineral oil, 9 mL, 30 mmol, 3 equiv.) and $BF_3 \cdot THF$ (3.10 mL, 30 mmol, 3 equiv.) in THF (20 mL) to obtain the crude intermediate amine (0.72 g, 32%). The crude amine was then dissolved in DCM (5 mL) and triethylamine (0.46 mL, 3.3 mmmol, 1.1 equiv). Boc_2O (0.72 g, 3.3 mmol, 1.1 equiv.) was added as a solution in DCM (5 mL) and the reaction stirred for 16 hours. The solvent was then removed under reduced pressure and the residue purified by chromatography on silica (0–20% EtOAc/petrol) to obtain the *product* **84** as a pale yellow oil (0.88 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (7H, app. dt, J 14.8 and 7.0, ArH), 6.93 (1H, t, J 4.2), 6.64 (1H, s), 4.42 (2H, s, NCH_2Ph), 2.50 (1H, dd, J 2.5 and 1.0, HC≡CCH), 1.37 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 141.6, 127.9 (2C), 127.1(2C), 126.7, 126.5, 125.9, 81.0, 80.1, 74.3, 48.0, 47.6 (rotameric), 28.2; ν_{max} (neat) /cm^{-1} 3296, 3031, 2977, 2931, 1687; m/z (ESI) $[M+H]^+$; HRMS (ESI) found 350.1169 $[M+Na]^+$, $C_{19}H_{21}NNaO_2S$ requires 350.1185. Appendix page 371.

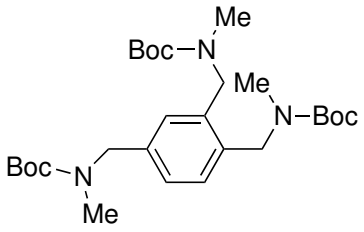
N-tert-Butyl benzyl(1-(2-bromophenyl)prop-2-yn-1-yl)carbamate



85

Prepared according to general procedure **E** using benzylamine (1.1 mL, 20 mmol, 1 equiv.), 2-bromobenzaldehyde (2.33 mL, 20 mmol, 1 equiv.), sodium acetylide (18% in light mineral oil, 18 mL, 60 mmol, 3 equiv.) $BF_3 \cdot THF$ (6.2 mL, 60 mmol, 3 equiv.) in THF (50 mL). The crude product was purified by chromatography on silica (0-30% EtOAc/petrol) to obtain the free amine colourless oil (3.59 g, 60%). The oil was dissolved in DCM (20 mL) with triethylamine (1.7 mL, 12 mmol, 1 equiv.). Boc_2O (2.62 g, 12 mmol, 2 equiv.) was added and the reaction stirred at room temperature for 16 hours. 2-Ethanolamine (3 mL) was added and the reaction stirred for 30 minutes. The reaction was then washed with water (3 × 50 mL), brine (30 mL), dried ($MgSO_4$), and the concentrated under reduced pressure. The residue was then purified by chromatography on silica (0–10% EtOAc/petrol) to obtain the pure *product* **85** as a colourless viscous oil (1.56 g, 38%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80-7.79 (1H, m, Ar*H*), 7.44 (1H, d, *J* 7.1, Ar*H*), 7.28 (1H, t, *J* 7.6, Ar*H*), 7.18-7.08 (6H, m, Ar*H*), 6.51 (1H, br s, HC≡CC*H*Ar), 4.33 (2H, m, NCH_2Ph), 2.56 (1H, d, *J* 1.8, *H*C≡CCH), 1.47 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 138.7 (rotameric), 135.8, 133.3, 130.7 (rotameric), 129.9, 127.8, 127.32, 127.19, 126.4, 124.5, 80.8, 80.5, 75.0, 52.1 (rotameric), 47.8, 28.4; ν_{max} (neat) /cm^{-1} 3298, 2977, 2931, 1692, 1157; *m/z* (ESI) 823.2 [2M+Na]$^+$; HRMS (ESI) found 422.0724 [M+Na]$^+$, $C_{21}H_{22}^{79}BrNNaO_2$ requires 422.0726. Appendix page 372.

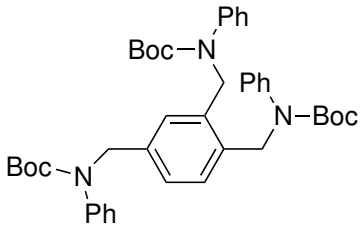
Tri-*tert*-butyl (benzene-1,2,4-triyltris(methylene))-tris(methylcarbamate)



87

Prepared according to general method **B** using *tert*-butyl methyl(prop-2-ynyl)carbamate **67** (25 mg, 0.15 mmol, 1 equiv.), [Rh(dppe)(nbd)]ClO_4 (7 mg, 10 mol %) in 1,2-DCE (0.6 mL) without addition of the aldehyde. After 1 hour the reaction was cooled to room temperature. Et_2O (5 mL) was added and the reaction filtered through a pad of silica (Et_2O) to obtain the *product 87* (25 mg, quant.). ^{1}H NMR (500 MHz, DMSO−d_6) δ 7.14-7.09 (2H, m, ArH), 6.96-6.94 (1H, m, ArH), 4.39 (4H, br s, 2 × NCH_2Ph), 4.36 (2H, br s, NCH_2Ph), 2.75 (3H, br s, NCH_3), 2.73 (6H, br s, 2 × NCH_3), 1.41 (27H, m, 3 × C(CH_3)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6) δ 155.2 (3C), 126.08, 126.06, 126.04, 125.0, 124.76, 124.73, 78.9 (2C), 78.8, 51.7, 51.6, 50.8, 48.5, 33.9, 28.1, 28.0 (2C); ν_{max} (neat) /cm^{-1} 2975, 2930, 1692; m/z (ESI) 530.2 [M+Na]$^+$; HRMS (ESI) found 530.3228 [M+Na]$^+$, $C_{27}H_{45}N_3NaO_6$ requires 530.3206. Appendix page 354.

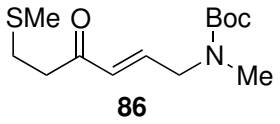
Tri-*tert*-butyl (benzene-1,2,4-triyltris(methylene))-tris(phenylcarbamate)



88

Prepared according to general method **D** using *tert*-Butyl phenyl(prop-2-ynyl)-carbamate **69** (58 mg, 0.25 mmol, 1 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and DPEphos (12.4 mg, 10 %) without the aldehyde in 1,2-DCE (1.5 mL). After 16 hour the reaction was cooled. Et_2O (5 mL) was added and the reaction filtered through a pad of silica (Et_2O) and the solvent removed under reduced pressure. The crude product was then purified by chromatography on silica (5–30% EtOAc/petrol to obtain the *product* **88** as a colourless oil (42 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-6.99 (18H, m, ArH), 4.78-4.74 (6H, m, 3 × NCH_2Ph), 1.38 (18 H, br s, 2 × C(CH_3)$_3$), 1.37 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.73, 154.62, 154.56, 142.60, 142.55, 142.2, 128.5, 126.55, 126.50, 126.47, 126.36, 125.84, 125.79, 80.56, 80.43 (2C), 53.67, 53.60, 53.57, 50.73, 50.55, 28.26 (2C), 28.23; ν_{max} (neat) /cm^{-1} 2976.6, 2930.6, 1693.5; m/z (ESI) 716.4 [M+Na]$^+$; HRMS (ESI) found 716.3673 [M+Na]$^+$, $C_{42}H_{51}N_3NaO_6$ requires 716.3670. Appendix page 355.

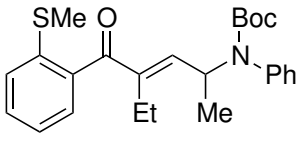
(*E*)-*tert*-Butyl methyl(6-(methylthio)-4-oxohex-2-enyl)carbamate



86

Prepared according to general procedure **D** using methylthiopropionaldehyde (15 μL, 0.15 mmol, 1 equiv), *tert*-butyl methyl(prop-2-ynyl)carbamate (51 mg, 0.3 mmol, 2 equiv.), $[Rh(cod)_2]BF_4$ (6.2 mg, 10 mol %) and dppb (6.4 mg, 10 mol %) in 1,2-DCE (0.6 mL). After 16 hours, the reaction gave the title *compound* **86** as a yellow oil (21 mg, 52%) after chromatography on silica (5–40% Et_2O/Petrol). ^{1}H NMR (500 MHz, DMSO−d_6, 120 °C) δ 6.72 (1H, dt, J 16.0, C(O)CH=C*H*CH_2), 6.13 (1H, d, J 16.0, C(O)C*H*=CH), 3.98 (2H, m, CH=CHC*H*$_2$N), 2.88-2.70 (4H, m, SC*H*$_2$C*H*$_2$), 2.82 (3H, s, NC*H*$_3$), 2.08 (3H, s, SC*H*$_3$), 1.43 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6, 120 °C) δ 198.6, 155.8, 142.7, 130.8, 79.9, 55.4, 50.3, 35.0, 29.0, 28.9, 15.8; ν_{max} (neat) /cm^{-1} 2974, 2918, 1689, 1633, 1390; m/z (ESI) 296.1 $[M+Na]^+$; HRMS (ESI) found 296.1285 $[M+Na]^+$, $C_{13}H_{23}NNaO_3S$ requires 296.1291. Appendix page 315.

(*E*)-*tert*-Butyl (4-(2-(methylthio)benzoyl)hex-3-en-2-yl)-(phenyl)carbamate

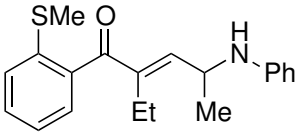


89a

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **73** (246 mg, 0.90 mmol, 2

equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title compound as a pale yellow crystals (157 mg, 82%, 4.7:1) after chromatography on silica (5–40% Et_2O/Petrol). Mpt 76–79 °C; **89a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.12 (7H, m, Ar*H*), 6.99 (2H, app d, *J* 7.5, Ar*H*), 5.99-5.96 (1H, m, C(O)CEt=C*H*CHCH$_3$), 5.30-5.14 (1H, m, CEt=CHC*H*CH$_3$), 2.63-2.55 (2H, m, CH$_3$C*H*$_2$C=C), 2.39 (3H, s, SC*H*$_3$), 1.36 (9H, s, C(C*H*$_3$)$_3$), 1.22 (3H, d, *J* 6.9, CHC*H*$_3$), 1.14 (3H, t, *J* 7.6, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 154.5, 145.2, 143.1, 139.2, 137.6, 130.2, 129.5, 128.7, 128.5, 128.2, 127.4, 127.1, 124.5, 80.4, 51.7, 28.3, 20.0, 19.7, 17.0, 13.8; ν_{max} (neat) $/cm^{-1}$ 2969, 2928, 2876, 1689, 1647; m/z (ESI) 426.3 [M+H]$^+$; m/z HRMS (ESI) found 448.1906 [M+Na]$^+$, $C_{25}H_{31}NNaO_3S$ requires 448.1917. Appendix page 323.

(*E*)-2-Ethyl-1-(2-(methylthio)phenyl)-4-(phenylamino)pent-2-en-1-one

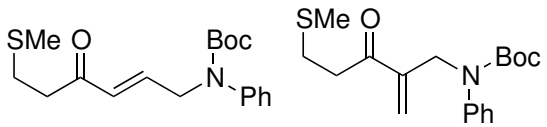


93

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **92** (156 mg, 0.90 mmol, 2 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in propylene carbonate (3.0 mL). After 16 hours, the reaction gave the title **compound** *93* as a colourless crystals (146 mg, 87%) after chromatography on silica (5–40% Et_2O/Petrol). Mpt 76–79 °C; Mpt 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (2H, m, Ar*H*), 7.20-7.13 (3H, m, Ar*H*), 7.10-7.06 (1H, m, Ar*H*), 6.73 (1H, tt, *J* 7.3 and 1.0), 6.58-6.54 (2H, m) 5.97 (1H, d, *J* 8.6, C(O)C=C*H*CH), 4.45-4.38

(1H, m, CEt=CHCHCH$_3$), 3.59 (1H, br. s, NH), 2.64 (2H, qd, J 7.6 and 2.2, CH=CH_2CH$_3$), 2.37 (3H, s, SCH_3), 1.37 (3H, d, J 6.7, CHCH_3), 1.21 (3H, t, J 7.5, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.6, 150.3, 147.2, 142.8, 139.0, 138.0, 130.3, 129.3, 129.1, 127.3, 124.6, 118.1, 113.7, 48.1, 21.3, 19.8, 16.9, 13.5; ν_{max} (neat) /cm^{-1} 3851, 3361, 3056, 2971, 2925, 2867, 2359, 1739, 1632, 1600, 739; m/z (ESI) 326.3 [M+H]$^+$; m/z HRMS (FI) found 325.1506 [M]$^+$, $C_{20}H_{23}NOS$ requires 325.1500. Appendix page 322.

Data for compounds from table 4.7: (E)-*tert*-Butyl (6-(methylthio)-4-oxohex-2-en-1-yl)(phenyl)carbamate) and *tert*-butyl (2-methylene-5-(methylthio)-3-oxopentyl)-(phenyl)carbamate

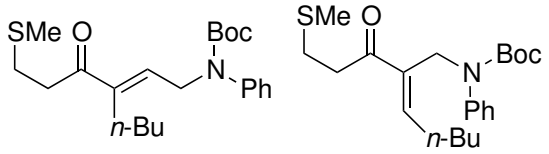


a **b**

Prepared according to general procedure **D**, without hydrogenation, using 3-methylthiopropionaldehyde (23 μL, 0.23 mmol, 1 equiv), alkyne **69** (58 mg, 0.25 mmol, 1.1 equiv.), [Rh(nbd)$_2$]BF$_4$ (8.6 mg, 10 mol %) and dppm (8.8 mg, 10 mol %) in 1,2-DCE (1.5 mL). After 5 hours, the reaction gave the title *compound* **a** (23 mg, 30%) after chromatography on silica (0–30% Et$_2$O/Petrol). **a**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27-7.23 (2H, m, ArH), 7.14-7.11 (3H, m, ArH), 6.79 (1H, dt, J 16.0 and 5.2, CH=CHCH$_2$), 6.14 (1H, dt, J 16.0 and 1.5, C(O)CH=CHCH$_2$), 4.34 (2H, dd, J 5.2 and 1.5, CH=CHCH_2), 2.78 (2H, m, CH$_2$CH_2C(O)), 2.69 (2H, m, SCH_2CH$_2$C(O)), 2.04 (3H, s, CH_3S), 1.37 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.0, 154.3, 142.6, 142.4, 130.0, 128.8, 126.2, 126.1, 81.0, 51.5, 40.2, 28.3, 28.2, 15.8; ν_{max} (neat) /cm^{-1} 3337, 3062, 2977, 2931, 1698; m/z (ESI) 358.2 [M+Na]$^+$; m/z HRMS

(ESI) found 358.1439 $[M+Na]^+$, $C_{18}H_{25}NNaO_3S$ requires 358.1447. Appendix page 331. **b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.23 (2H, m, Ar*H*), 7.14-7.06 (3H, m, Ar*H*), 6.11 (1H, app. m, H_ACH_B), 5.87 (1H, app. t, *J* 1.8, H_AC*H_B*), 4.45 (2H, t, *J* 1.5, CH_2N), 2.95-2.92 (2H, m, CH_2CH$_2$), 2.68 (2H, m, CH$_2$CH_2), 2.04 (3H, s, CH_3S), 1.37 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 154.5, 144.2, 142.7, 128.6, 125.8, 125.7, 124.1, 80.8, 50.2, 38.0, 28.4, 28.3, 15.9; *m*/*z* (ESI) 358.2 $[M+Na]^+$. Appendix page 335.

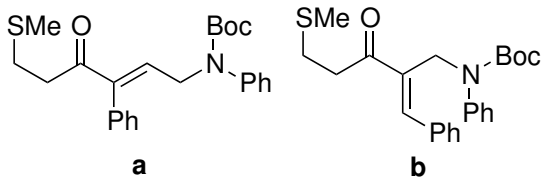
Data for compounds from table 4.7: (*E*)-*tert*-Butyl (3-(3-(methylthio)propanoyl)hept-2-en-1-yl)-(phenyl)carbamate , a and (*E*)-*tert*-butyl (2-(3-(methylthio)propanoyl)hept-2-en-1-yl)(phenyl)carbamate, b



Prepared according to general procedure **D**, without hydrogenation, using 3-methylthiopropionaldehyde (23 μL, 0.23 mmol, 1 equiv), alkyne **71** (72 mg, 0.25 mmol, 1.1 equiv.), [Rh(nbd)$_2$]BF$_4$ (8.6 mg, 10 mol %) and dppm (8.8 mg, 10 mol %) in 1,2-DCE (1.5 mL). After 5 hours, the reaction gave the title *compounds* as an inseparable mixture of *isomers* (17 mg, ~1:1.2 **a**:**b**, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) **a** and **b**: δ 7.38-7.03 (18 H, m, Ar*H*), 6.95-6.98 (2H, m, Ar*H*), 6.51 (2H, m, **a**: C(O)C=C*H* and **b**: C=C*H*CH$_2$), 4.59 (2H, s, **b** C=CCH_2N), 4.41 (2H, d, *J* 6.1, **a** C(O)C=CHCH_2N), 2.84 (2H, t, *J* 7.2, alkyl), 2.62-2.69 (6 H, m, alkyl), 2.46-2.51 (3H, m, alkyl), 2.11-2.16 (4H, m, **a**: C=CCH_2CH$_2$ and **b**: C=CHCH_2CH$_2$), 2.04 (3H, s, **a**: SCH_3), 1.98 (3H, s, **b**: SCH_3), 1.37 (9H, s, **b**: C(CH_3)$_3$), 1.34 (9H, s, **b**: C(CH_3)$_3$), 1.27-1.11 (8H, m,

alkyl), 0.85-0.74 (6H, m, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) **a** and **b**: δ 199.4, 199.0, 159.0, 154.5, 146.7, 142.7, 138.3, 137.2, 129.6, 128.9, 128.4, 127.8, 126.5, 126.3, 114.2, 109.8, 83.4, 80.6, 48.4, 43.0, 40.2, 37.7, 37.6, 31.1, 30.7, 29.0, 28.8, 28.6, 28.3, 28.0, 26.8, 25.7, 22.8, 22.5, 15.8, 13.8; ν_{max} (neat) $/cm^{-1}$ 2959, 2929, 2872, 1694; m/z HRMS (FI) found 391.2181 $[M+]^+$, $C_{22}H_{33}NO_3S$ requires 391.2181. Appendix page 332.

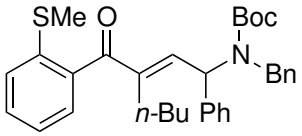
Data for compounds from table 4.7: (E)-*tert*-Butyl (6-(methylthio)-4-oxo-3-phenylhex-2-en-1-yl)-(phenyl)carbamate, a and (E)-*tert*-butyl (2-benzylidene-5-(methylthio)-3-oxopentyl) (phenyl)carbamate, b



Prepared according to general procedure **D**, without hydrogenation, using 3-methylthiopropionaldehyde (23 μL, 0.23 mmol, 1 equiv), alkyne **75** (77 mg, 0.25 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and dppm (8.8 mg, 10 mol %) in 1,2-DCE (1.5 mL). After 5 hours, the reaction gave the title *compounds* a partially separable mixture of isomers (51 mg, 2:1 **a**:**b**, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) **a**: δ 7.40-7.28 (4H, m, ArH), 7.22-7.07 (3H, m, ArH), 6.91 (2H, o t, J 6.3, C(O)C=CHCH_2N and ArH), 4.25 (2H, d, J 6.3, C=CHCH_2N), 2.82-2.79 (2H, m, SCH_2CH_2C(O)), 2.73-2.70 (2H, m, SCH_2CH_2C(O)), 2.06 (3H, s, SCH_3), 1.43 (9H, s, C(CH_3)$_3$); **b**: δ 7.39-7.37 (4H, m, ArH), 7.27-7.25 (3H, m, ArH), 7.19-7.11 (2H, m, ArH), 6.83 (2H, app d, J 7.5, PhCH=CC(O)CH_2N and ArH), 4.92 (2H, s, C(O)CCH_2N), 2.83 (2H, t, J 7.5, SCH_2CH_2C(O)), 2.65 (2H, t, J 7.5, SCH_2CH_2C(O)), 2.10 (3H, s,

SCH_3), 1.40 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) **a**: δ 199.8, 154.4, 141.9, 139.0, 129.4z, 129.1, 129.0, 128.8, 128.4, 127.9, 126.7, 80.9, 48.9, 48.3, 39.5, 28.3, 15.8; **b**: δ 199.8, 154.6, 141.4, 140.5, 136.9, 134.5, 129.4, 128.5, 128.2, 127.7, 126.2, 80.5, 43.5, 38.2, 30.9, 28.3, 15.8; ν_{max} (neat) /cm^{-1} 3061, 2977, 2929, 1691; m/z (ESI) 434.2 [M+Na]$^+$; m/z HRMS (ESI) found 434.1745 [M+Na]$^+$, $C_{24}H_{29}NNaO_3S$ requires 434.1760. Appendix page 333 and page 334.

(*E*)-*tert*-Butyl (3-(2-(methylthio)benzoyl)-1-phenylhept-2-en-1-yl)(phenyl)carbamate

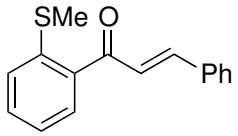


95

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **94** (352 mg, 0.90 mmol, 2 equiv.), [Rh(nbd)$_2$]BF_4 (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 36 hours, the reaction gave the title *compound* **95** (212 mg, 87%) as a yellow oil after chromatography on silica (0–35% Et_2O/Petrol). ^{1}H NMR (500 MHz, DMSO−d_6, 93 °C) δ 7.44 (2H, *d*, J 3.2, Ar*H*), 7.34 (2H, t, *J* 7.3, Ar*H*), 7.26 (4H, dt, *J* 14.3 and 7.7, Ar*H*), 7.19 (3H, t, *J* 8.9, Ar*H*), 7.11 (2H, d, *J* 7.3, Ar*H*), 7.02 (1H, d, *J* 7.4, Ar*H*), 6.44 (1H, d, *J* 9.2, C(O)C=C*H*CH), 5.86-5.84 (1H, m, C=CHC*H*), 4.50 (1H, d, *J* 15.9, NCH_AH$_B$Ph), 4.30 (1H, d, *J* 15.9, NCH$_A$$H_B$Ph), 2.42 (3H, s, SC$H_3$), 2.34-2.25 (2H, m, CH_2CH_2C=C), 1.36-1.23 (4H, m, alkyl), 1.23 (9H, s, C(CH_3)$_3$), 0.82 (3H, br t, *J* 6.7, CH_3CH$_2$); ^{13}C NMR (125 MHz, DMSO−d_6, 93 °C) δ 198.8, 155.6, 143.90, 143.8, 140.5, 140.3, 139.4, 137.1, 130.9, 129.2, 129.0, 128.6, 128.24, 128.20, 128.0, 127.7, 127.6, 125.7, 80.6, 58.7, 50.5, 31.1, 28.6, 26.1,

23.1, 17.2, 14.3; ν_{max} (neat) /cm^{-1} 2958, 2928, 2871, 1688, 1656; m/z (ESI) 1081.64 [2M+Na]$^+$; m/z HRMS (ESI) found 552.2546 [M+Na]$^+$, $C_{33}H_{39}NNaO_3S$ requires 552.2543. Appendix page 341.

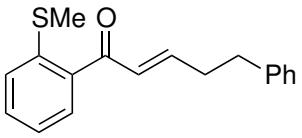
(*E*)-1-(2-(Methylthio)phenyl)-3-phenylprop-2-en-1-one



96

Prepared according to general method **D**, without hydrogenation, using 2-methylthiobenzaldehyde (97 μL, 0.75 mmol, 1 equiv.), phenyl acetylene (90 μL, 0.83 mmol, 1.1 equiv.), [Rh(nbd)$_2$]BF$_4$ (14 mg, 0.037 mmol, 5 mol %) and dppe (15 mg, 0.037 mmol, 5 mol %) in propylene carbonate (2.5 mL), to give the title *compound* **96** (160 mg, 84%, 11:1 **a**:**b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, dd, J 7.7 and 0.7, Ar*H*), 7.64 (1H, d, J 15.9, C(O)CH=C*H*), 7.50-7.45 (3H, m, Ar*H*), 7.41 (4H, m, Ar*H*), 7.33 (1H, d, J 15.9, C(O)C*H*=CH), 7.24 (1H, t, J 7.34, Ar*H*), 2.46 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 145.3, 140.6, 137.2, 134.8, 131.6, 130.6, 129.5, 129.0, 128.5, 126.2, 124.8, 124.2, 16.5; ν_{max} (neat) /cm^{-1} 3059, 2912, 1655, 1598, 1208, 750; m/z (ESI) 531 [2M+Na]$^+$; HRMS (ESI) found 277.0657 [M+Na]$^+$, $C_{16}H_{14}NaOS$ requires 277.0658. Appendix page 342.

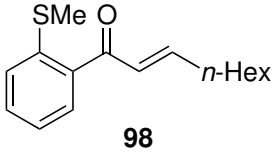
((*E*)-1-(2-(Methylthio)phenyl)-5-phenylpent-2-en-1-one



97

Prepared according to general method **D**, without hydrogenation, using 2-methylthiobenzaldehyde (97 μL, 0.75 mmol, 1 equiv.), 4-phenyl-1-butyne (122 μL, 0.83 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (14 mg, 0.037 mmol, 5 mol %) and dppe (15 mg, 0.037 mmol, 5 mol %) in propylene carbonate (2.5 mL), to give the *linear* **97** (149 mg, 70%) and *branched* isomer (51 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, d, J 7.7, ArH), 7.46-7.41 (1H, m, ArH), 7.36-7.29 (3H, m, ArH), 7.24-7.16 (4H, m, ArH), 6.91 (1H, dt, J 15.5 and 6.8, C(O)CH=CHCH$_2$), 6.67 (1H, d, J 15.5, C(O)CH=CH), 2.83 (2H, t, J 7.7, CH$_2$CH_2Ph), 2.61 (2H, m, CH=CHCH_2CH$_2$), 2.43 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 149.4, 140.8, 140.5, 136.8, 131.4, 129.5, 129.2, 128.5, 128.4, 126.2, 126.1, 124.0, 34.5, 34.4, 16.4; ν_{max} (neat) /cm^{-1} 3060, 3026, 2920, 2856, 1661, 1615, 1300, 748; m/z (ESI) 305 [M+Na]$^+$; HRMS (ESI) found 305.0972 [M+Na]$^+$, $C_{18}H_{18}NaOS$ requires 305.0971. Appendix page 343.

(*E*)-1-(2-(Methylthiophenyl)non-2-en-1-one

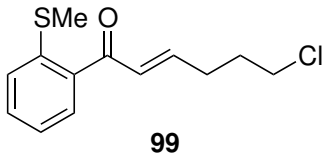


98

Prepared according to general method **D**, without hydrogenation, using 2-methylthiobenzaldehyde (97 μL, 0.75 mmol, 1 equiv.), 1-octyne (122 μL, 0.83 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (14 mg, 0.037 mmol, 5 mol %) and dppe (15 mg, 0.037 mmol,

5 mol %) in propylene carbonate (2.5 mL), to give the *linear* **98** (169 mg, 83%) and *branched* isomer (36 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J 7.7, ArH), 7.43-7.39 (1H, m, ArH), 7.32 (1H, d, J 8.0, ArH), 7.19-7.15 (1H, m, ArH), 6.90-6.83 (1H, m, C(O)CH=CH), 6.63 (1H, d, J 15.6, (O)CH=CH), 2.41 (3H, s, SCH_3), 2.26 (2H, app. q, J 7.2, CH=CHCH_2), 1.51-1.44 (2H, m, $CHCH_2CH_2CH_2$), 1.36-1.28 (6H, m, alkyl), 0.87 (3H, t, J 6.6, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 151.1, 140.2, 137.1, 131.2, 129.3, 128.5, 126.1, 124.0, 32.8, 31.6, 28.9, 28.0, 22.5, 16.4, 14.1; ν_{max} (neat) $/cm^{-1}$ 2955, 2926, 2856, 1661, 1615; m/z (ESI) 263.1 $[M+H]^+$; HRMS (ESI) found 285.1280 $[M+Na]^+$, $C_{16}H_{22}NaOS$ requires 285.1284. Appendix page 344

(*E*)-6-Chloro-1-(2-(methylthio)phenyl)hex-2-en-1-one

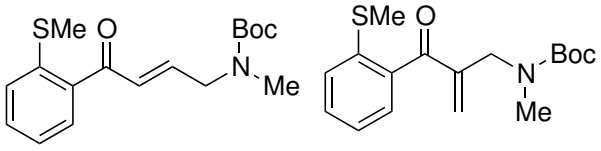


99

Prepared according to general method **D**, without hydrogenation, using 2-methylthiobenzaldehyde (97 μL, 0.75 mmol, 1 equiv.), 5-chloropentyne (87 μL, 0.83 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (14 mg, 0.037 mmol, 5 mol %) and dppe (15 mg, 0.037 mmol, 5 mol %) in propylene carbonate (2.5 mL, 0.3M), to give the *linear* **99** (126 mg, 66%) and branched isomer (63 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, J 7.7, ArH), 7.46-7.43 (1H, m, ArH), 7.34 (1H, d, J 8.0), 7.22-7.18 (1H, m, ArH), 6.85 (1H, dt, J 15.5 and 6.8, C(O)CH=CH), 6.72 (1H, d, J 15.6, C(O)CH=CH), 3.57 (2H, t, J 6.4, CH_2CH_2Cl), 2.50-2.44 (2H, m, CH=CHCH_2), 2.44 (3H, s, SCH_3), 2.01-1.94 (2H, m, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 148.1, 140.6, 136.7, 131.5, 129.5, 129.4, 126.1, 124.0, 44.1, 30.7, 29.7, 16.4; ν_{max} (neat) $/cm^{-1}$ 3059, 2957, 2020, 1662, 1616, 1298, 755, 740; m/z (ESI) 277 $[M+Na]^+$; HRMS (ESI)

found 277.0424 $[M+Na]^+$, $C_{13}H_{15}{}^{35}ClNaOS$ requires 277.0424. Appendix page 345

(*E*)-*tert*-butyl methyl(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate and tert-butyl methyl(2-(2-(methylthio)benzoyl) allyl)carbamate

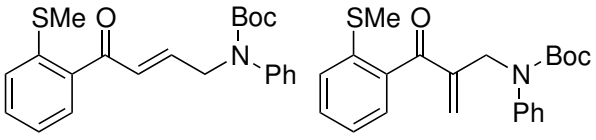


100a **100b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **xxx** (113 mg, 0.90 mmol, 1.5 equiv.), $[Rh(ndb)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compounds* **100a** (68 mg, 47%) and **100b** (67 mg, 46%) as yellow oils after chromatography on silica (0–20% Et_2O/Petrol). **100a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, dd, J 7.7 and 1.3, ArH), 7.37 (1H, app t, J 7.2, ArH), 7.27 (1H, d, J 7.9, ArH), 7.14-7.10 (1H, m, ArH), 6.66 (2H, m, CH=CH), 3.98 (2H, br s, C=CHCH_2N), 2.81 (3H, br s, NCH_3), 2.36 (3H s, SCH_3), 1.38 (9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4 (rotameric), 155.5 (rotameric), 144.4, 140.9, 131.7, 129.6, 128.7 (rotameric) ,127.8 (rotameric), 126.1, 124.0, 80.0, 50.1 (d, J 66.0, rotamer) 34.5, 28.4, 16.4; ν_{max} (neat) /cm^{-1} 2972, 2922, 1689, 1619, 1389, 1365; m/z (ESI) 344.2 $[M+Na]^+$; HRMS (ESI) found 344.1296 $[M+Na]^+$, $C_{17}H_{23}NNaO_3S$ requires 344.1291. Appendix page 316. **100b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (3H, m, ArH), 7.14-7.09 (1H, m, ArH), 5.80-5.76 (1H, m, C=CH_AH$_B$), 5.59 (1H, C=CH$_A$$H_B$), 4.18 (2H, br. s, CC$H_2$N), 2.86 (3H, br. s, NC$H_3$), 2.36 (3H, s, SC$H_3$), 1.39 (9H, br. s, C(C$H_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 155.9, 144.7, 138.1, 131.0, 129.1, 128.4, 128.0,

127.6, 124.6, 79.8, 63.5, 34.9, 28.4, 17.1; ν_{max} (neat) /cm^{-1} 2973.5, 2924, 1693, 1655, 1480, 1456, 1390, 1146; m/z (ESI) 344.2 $[M+Na]^+$. Appendix page 327.

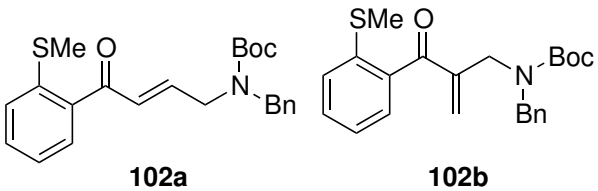
(*E*)-*tert*-butyl (4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)-(phenyl)carbamate



101a **101b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **69** (207 mg, 0.90 mmol, 2 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compounds* **101** as a yellow oil (148 mg, 86%, 1.1:1 **a**:**b**) after chromatography on silica (0–35% EtOAc/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) **a**: δ 7.47 (1H, dd, J 7.7 and 1.4, ArH), 7.38-7.7.34 (1H, m, ArH), 7.27-7.22 (3H, m, ArH), 7.19-7.15 (2H, m, ArH), 7.13-7.06 (2H, m, ArH), 6.82 (1H, dt, J 15.6 and 4.9, C(O)CH=CHCH$_2$), 6.71 (1H, dt, J 15.6 and 1.4, C(O)CH=CHCH$_2$), 4.39 (2H, dd, J 4.9 and 1.4, CH=CHCH_2), 2.34 (3H, s, SCH_3), 1.37 (9H, br. s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) **a**: δ 192.3, 154.3, 144.7, 142.5, 141.0, 136.2, 131.7, 129.8, 128.8, 128.6, 126.13, 126.10, 126.06, 124.0, 81.0, 51.7, 28.3, 16.4; ^{1}H NMR (400 MHz, $CDCl_3$) **b** 7.36-7.19 (7H, m, ArH), 7.12-7.07 (2H, m, ArH), 5.95 (1H, t, J 1.6, C=CH_AH$_B$), 5.64 (1H, t, J 1.2, C=CCH$_A$$H_B$), 4.64 (2H, s, C=CC$H_2$), 2.32 (3H, s, SC$H_3$), 1.39 (9H, s, C(C$H_3$)$_3$); ν_{max} (neat) /cm^{-1} 3054, 2976, 2926, 1694, 1380, 1366, 1150; m/z (ESI) 384.2 $[M+H]^+$; m/z HRMS (ESI) found 406.1433 $[M+Na]^+$, $C_{22}H_{25}NNaO_3S$ requires 406.1447. Appendix page 338 and 339.

(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate and *tert*-butyl benzyl(2-(2-(methylthio)benzoyl)allyl)carbamate

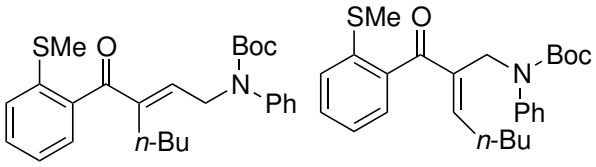


102a **102b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **68** (352 mg, 0.90 mmol, 2 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compounds* **102a** (106 mg, 59%) and **102b** (63 mg, 35%) as yellow oils after chromatography on silica (0–20% Et_2O/Petrol). **102a** ^{1}H NMR (500 MHz, DMSO−d_6, 90 °C) δ 7.51 (1H, ddd, J 8.0, 7.1 and 1.4, ArH), 7.47-7.43 (2H, m, ArH), 7.35-7.32 (2H, m, ArH), 7.28-7.25 (4H, m, ArH), 6.58 (1H, d, J 15.8, C(O)CH=CH), 6.53 (1H, dt, J 6.4 and 4.0, C(O)CH=CHCH$_2$), 4.44 (2H, s, NCH_2Ph), 4.04 (2H, br d, J 4.8, CH=CHCH_2N)), 2.42 (3H, s, SCH_3), 1.43 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6, 90 °C) δ 193.5, 155.7, 145.7, 139.7, 139.2, 138.3, 132.2, 130.0, 129.6, 129.2, 128.4, 127.96, 127.87, 125.3, 80.4, 51.4, 49.0, 28.9, 16.9; ν_{max} (neat) /cm^{-1} 2976, 2925, 1688,1619; m/z (ESI) 420.2 [M+Na]$^+$; HRMS (ESI) found 420.1595 [M+Na]$^+$, $C_{23}H_{27}NNaO_3S$ requires 420.1604. Appendix page 317. **102b** ^{1}H NMR (500 MHz, DMSO−d_6, 90 °C) δ 7.50 (2H, dt, J 3.1 and 1.6, ArH), 7.36 (1H, t, J 7.4, ArH), 7.31-7.27 (4H, m, ArH), 5.86 (1H, s, C=CH_AH$_B$), 5.59 (1H, s, C=CH$_A$$H_B$), 4.46 (2H, s, NC$H_2$Ph), 4.16 (2H, s, CC$H_2$N), 2.43 (3H, s, SC$H_3$), 1.44 (9H, s, C(C$H_3$)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6, 90 °C) δ 198.0, 155.9, 145.4, 139.21, 139.17, 138.2, 131.7, 129.37, 129.25, 128.8, 128.30, 128.26, 127.9, 125.7, 80.3, 51.1, 47.3, 28.9, 17.4; ν_{max} (neat)

/cm^{-1} 2975, 2924, 2854, 1693, 1661; m/z (ESI) 420.2 $[M+Na]^+$; HRMS (ESI) found 420.1602 $[M+Na]^+$, $C_{23}H_{27}NNaO_3S$ requires 420.1604. Appendix page 318.

(*E*)-*tert*-Butyl (3-(2-(methylthio)benzoyl)hept-2-en-1-yl)-(phenyl)carbamate and (*E*)-*tert*-butyl (2-(2-(methylthio)benzoyl)hept-2-en-1-yl)(phenyl)carbamate

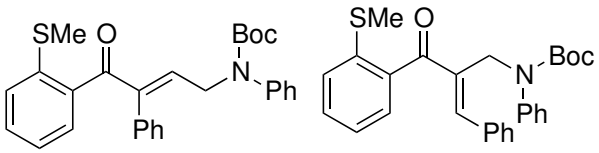


103a **103b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), alkyne **71** (258 mg, 0.90 mmol, 2 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave an inseparable mixture of the title *compounds* **103a** and **103b** as a yellow oil (166 mg, 84%, 1:1.2 **a**:**b**) after chromatography on silica (0–35% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) **a** and **b**: δ 7.42-7.38 (2H, m, Ar*H*), 7.36-7.28 (7H, m, Ar*H*), 7.24-7.13 (7H, m, Ar*H*), 7.02 (1H, ddd, *J* 7.5, 7.2 and 1.3, Ar*H*), 6.62 (1H, dd, *J* 7.6 and 1.2, Ar*H*), 6.20 (2H, app t, *J* 7.4, **a**: C(O)CH=C*H*CH_2N and **b**: C=C*H*CH_2CH_2), 4.88 (2H, s, **b**: C=CCH_2N), 4.51 (2H, d, *J* 6.2, **a**: C(O)CH=CHCH_2N), 2.43 (3H, s, **a**: SCH_3), 2.39 (3H, s, **b**: SCH_3), 2.32-2.30 (4H, m, CH_2CH_2), 1.47 (9H, br s, **b**: C(CH_3)$_3$), 1.41 (9H, s, **a**: C(CH_3)$_3$), 1.37-1.30 (8H, m, alkyl), 0.93-0.88 (6H, m, **a** and **b**, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) **a** and **b**: δ 198.2, 197.1, 154.5, 154.3, 151.9, 142.9, 141.3, 138.8, 138.6, 138.1, 138.0, 137.6, 130.4, 129.2, 128.82, 128.76, 128.6, 128.5, 127.6, 127.3, 126.7, 126.5, 126.2, 126.1, 125.7, 124.4, 124.0, 80.8, 80.3, 48.5, 43.0, 30.9, 30.6, 28.9, 28.3, 28.2, 25.9, 22.9, 22.6, 16.9, 16.7, 13.92, 13.87; ν_{max} (neat) /cm^{-1} 3062,

3041, 957, 2925, 2871, 2860, 1630, 1651; m/z (ESI) 901.5 $[2M+Na]^+$; m/z HRMS (ESI) found 462.2061 $[M+Na]^+$, $C_{26}H_{33}NNaO_3S$ requires 462.2073. Appendix page 340.

(E)-*tert*-Butyl (4-(2-(methylthio)phenyl)-4-oxo-3-phenylbut-2-en-1-yl)(phenyl)carbamate and (E)-*tert*-butyl (2-(2-(methylthio)benzoyl)-3-phenylallyl)(phenyl)carbamate

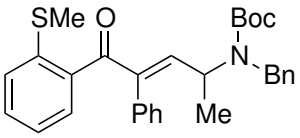


104a **104b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (29 μL, 0.23 mmol, 1 equiv), alkyne **74** (77 mg, 0.25 mmol, 1.1 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and dppm (8.8 mg, 10 mol %) in 1,2-DCE (1.5 mL). After 5 hours, the reaction gave title *compounds* **104a** and **104b** as a inseparable mixture (90 mg, 85%, 1.1:1 **a**:**b**) after chromatography on silica (0–35% Et_2O/Petrol). ^{1}H NMR (500 MHz, $CDCl_3$) **a**: δ 7.42-7.25 (7H, m, ArH), 7.21-7.11 (4H, m, ArH), 7.07-6.97 (3H, m, ArH), 6.41 (1H, t, J 6.2, C(O)C=CH), 4.40 (2H, d, J 6.2, C=CHCH_2N), 2.43 (3H, s, SCH_3), 1.38 (9H, s, C(CH_3)$_3$); **b**: δ 7.42-7.25 (7H, m, ArH), 7.21-7.11 (4H, m, ArH), 7.07-6.97 (3H, m, ArH), 6.61 (1H, app d, J 7.6, PhCH=CCH_2), 5.12 (2H, s, PhCH=CCH_2), 2.41 (3H, s, SCH_3), 1.44 (9H, app d, J 19.7, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) **a** and **b**: δ 197.5, 197.0, 154.6, 154.2, 145.6, 137.3, 134.2, 130.8, 129.7, 129.4, 128.7, 128.5, 128.2, 128.0, 127.6, 127.3, 126.5, 126.1, 124.5, 123.9, 80.8, 80.5, 48.9 (rotameric), 43.7, 28.3, 28.2,17.0, 16.5; ν_{max} (neat) /cm^{-1} 3060, 2977, 2925, 1692, 1652; m/z (ESI) 941.3 $[2M+Na]^+$; m/z HRMS (ESI) found 482.1757 $[M+Na]^+$, $C_{28}H_{29}NNaO_3S$ requires 482.1760. Appendix page

330.

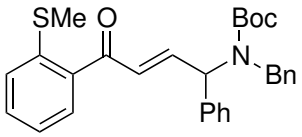
(*E*)-*tert*-Butyl benzyl(5-(2-(methylthio)phenyl)-5-oxo-4-phenylpent-3-en-2-yl)carbamate



105

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (30 μL, 0.23 mmol, 1 equiv), alkyne **81** (117 mg, 0.35 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and DPEphos (12.4, 10 mol %) in 1,2-DCE (1.5 mL). After 16 hours, the reaction gave the title *compound* **105** (60 mg, 54%) as a yellow oil after chromatography on silica (0–20% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (5H, m, Ar*H*), 7.28-7.17 (7H, m, Ar*H*), 7.03-7.01 (2H, m, Ar*H*), 6.58 (1H, d, *J* 9.3, C(O)C=C*H*), 4.42 (1H, d, *J* 15.6, NCH_AH$_B$Ph), 4.27 (1H, br s, C=CHC*H*CH_3), 4.10 (1H, d, *J* 15.6, NC$H_A H_B$Ph), 2.44 (3H, s), 1.35 (9H, s, C(CH_3)), 1.16 (3H, d, *J* 6.9, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 155.2, 146.2, 146.1, 142.3, 138.7, 134.6, 130.6, 129.4, 128.9, 128.4, 128.3, 127.9, 127.8, 127.5, 127.1, 125.0, 80.2, 63.4, 51.9, 49.8, 28.3, 28.2, 17.2; ν_{max} (neat) /cm^{-1} 3059, 2974, 2925, 1686, 1660; m/z (ESI) 510.2 $[M+Na]^+$; HRMS (ESI) found 510.2068 $[M+Na]^+$, $C_{30}H_{33}NNaO_3S$ requires 510.2073. Appendix page 324.

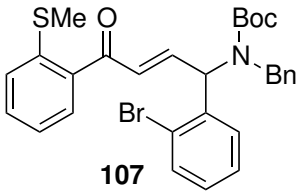
(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)phenyl)-4-oxo-1-phenylbut-2-en-1-yl)carbamate



106a

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (30 μL, 0.23 mmol, 1 equiv), alkyne **81** (112 mg, 0.35 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and DPEphos (12.4, 10 mol %) in 1,2-DCE (1.5 mL). After 16 hours, the reaction gave the title *compound* **106a** (96mg, 88%) as a bright yellow oil after chromatography on silica (0–20% Et_2O/Petrol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-6.95 (15H, m, Ar*H* and C(O)CH=C*H*), 6.59-6.53 (1H, br app d, *J* 16.6, C(O)C*H*=CH), 5.74 (1H, br s, CH=CHC*H*Ph), 4.35 (2H, br s, NCH_2Ph), 2.36 (3H, s, SCH_3), 1.29 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 155.7, 146.1, 140.8, 138.5, 136.3, 131.6, 129.88, 129.71, 129.51, 128.8, 128.6, 128.3, 127.8, 127.09, 126.95, 126.2, 124.0, 80.8, 61.3, 28.3, 27.6, 16.4; ν_{max} (neat) /cm^{-1} 3062, 3030, 2977, 2925, 1689; *m*/*z* (ESI) 969.5 [2M+Na]$^+$; HRMS (ESI) found 496.1906 [M+Na]$^+$, $C_{29}H_{31}NNaO_3S$ requires 496.1917. Appendix page 325.

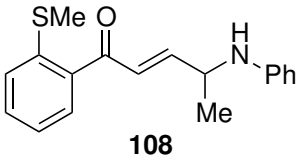
(*E*)-*tert*-Butyl benzyl(1-(2-bromophenyl)-4-(2-(methylthio)-phenyl)-4-oxobut-2-en-1-yl)carbamate



107

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (30 μL, 0.23 mmol, 1 equiv.), alkyne **85** (140 mg, 0.35 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (8.6 mg, 10 mol %) and DPEphos (12.4, 10 mol %) in 1,2-DCE (1.5 mL). After 16 hours, the reaction gave the title *compound* **107** (94mg, 74%) as a yellow oil after chromatography on silica (5% acetone/45% DCM/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.42 (3H, m, ArH), 7.35-7.25 (4H, m, ArH), 7.18-7.07 (7H, m, ArH), 7.06-6.98 (4H, m, ArH and C(O)CH=CHCH), 6.64 (1H, dd, J 15.6 and 1.7, C(O)CH=CHCH), 6.20 (1H, br s, C(O)CH=CHCH), 4.59-4.55 (1H, m, NCH_AH$_B$Ph), 4.24 (1H, d, J 15.8, NCH$_A$$H_B$Ph), 2.44 (3H, s, SC$H_3$), 1.48 (9H, s, C(C$H_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1 (rotameric), 155.6 (rotameric), 145.6, 141.1, 138.4, 137.4, 136.1, 133.2, 131.8, 130.3 (rotameric), 129.9, 129.7, 129.0 (rotameric), 128.0, 127.6, 127.4 (rotameric), 126.7, 126.1, 125.5, 124.0, 80.8, 61.1 (rotameric), 48.5, 28.4, 16.4; ν_{max} (neat) /cm^{-1} 2976, 2926, 1691, 1620; m/z (ESI) 574.2 [M+Na]$^+$; HRMS (ESI) found 574.1010 [M+Na]$^+$, $C_{29}H_{30}^{79}BrNNaO_3S$ requires 574.1022. Appendix page 319.

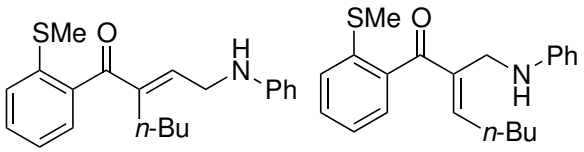
(*E*)-1-(2-(methylthio)phenyl)-4-(phenylamino)-pent-2-en-1-one



108

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.), alkyne **77** (130 mg, 0.90 mmol, 2 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25, 10 mol %) in 1,2-DCE (1.5 mL). After 16 hours, the reaction gave the title *compound* **108** (86mg, 29%) as a yellow oil after chromatography on silica (0–20% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (1H, m, Ar*H*), 7.35-7.31 (1H, m, Ar*H*), 7.24-7.22 (1H, m, Ar*H*), 7.11-7.04 (3H, m, Ar*H*), 6.82-6.73 (2H, m, Ar*H*), 6.66-6.61 (1H, app tt, *J* 7.3 and 1.0, C(O)CH=C*H*CH), 6.52 (1H, app dd, *J* 8.6 and *J* 1.0, C(O)C*H*=CHCH), 4.11 (1H, qd, *J* 6.7 and 3.7, CH=CHC*H*CH_3), 3.66 (1H, br s, N*H*), 2.32 (3H, s, SC*H*$_3$), 1.32 (3H, d, *J* 6.8, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 151.2, 146.8, 140.8, 136.6, 131.6, 129.8, 129.3, 127.1, 126.1, 124.0, 117.9, 113.4, 50.5, 21.2, 16.5; ν_{max} (neat) /cm^{-1} 3396, 3054, 2971, 2919, 2860, 1598, 1497; m/z (ESI) 298.2 $[M+H]^+$; HRMS (ESI) found 319.1001 $[M+Na]^+$, $C_{19}H_{18}NNaOS$ requires 319.1007. Appendix page 320.

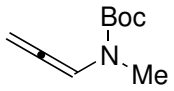
(*E*)-1-(2-(Methylthio)phenyl)-2-(2-(phenylamino)ethylidene)-hexan-1-one and (*E*)-1-(2-(methylthio)phenyl)-2-((phenylamino)methyl)hept-2-en-1-one



109a **109b**

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv), *N*-(hept-2-yn-1-yl)aniline (126 mg, 0.67 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (1.5 mL). After 16 hours, the reaction gave an inseparable mixture of isomers **109a** and **109b** (104 mg, 2.8:1, 68%) as a pale yellow oil after chromatography on silica (0–35% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) **a**: δ 7.39-7.31 (2H, m, Ar*H*), 7.26-7.13 (4H, m, Ar*H*), 6.77-6.73 (1H, m, Ar*H*), 6.59 (2H, d, *J* 7.7, Ar*H*), 6.21 (1H, t, *J* 6.0, C(O)C=C*H*), 4.01 (2H, d, *J* 6.0, C=CHCH_2), 3.89 (1H, br s, NH), 2.56 (2H, t, *J* 7.6, CH_2CH_2), 2.42 (3H, s, SCH_3), 1.57-1.33 (4H, m, alkyl), 0.98 (3H, t, *J* 7.2, CH_3); **b**: δ 7.39-7.31 (2H, m, Ar*H*), 7.26-7.13 (4H, m, Ar*H*), 6.77-6.73 (1H, m, Ar*H*), 6.69 (2H, d, *J* 7.7, Ar*H*), 6.33 (1H, t, *J* 7.6), 4.18 (2H, s, C=CCH_2N), 3.89 (1H, br s, N*H*), 2.44-2.37 (2H, o m, C=CCH_2CH_2), 2.41 (3H, s, SCH_3), 1.57-1.33 (4H, m, alkyl), 0.91 (3H, t, *J* 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ **a** and **b**: 198.8, 198.2, 151.0, 148.2, 147.6, 144.6 (2C), 143.3, 139.2, 138.9, 137.8, 137.7, 130.5, 130.4, 129.3 (2C), 129.1, 128.8, 127.5, 127.2, 124.7, 124.6, 118.0, 117.8, 113.8, 113.0, 42.7, 39.8, 31.0, 30.8, 29.1, 26.2, 23.0, 22.5, 17.1, 16.9, 14.0, 13.9; ν_{max} (neat) $/cm^{-1}$ 3339, 3056, 2956, 2925, 2870, 1646, 1599; m/z HRMS (FI) found 339.1773 $[M]^+$, $C_2H_{25}NOS$ requires 339.1657. Appendix page 321.

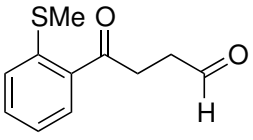
tert-Butyl methyl(propa-1,2-dien-1-yl)carbamate



111

Prepared according to a literature procedure.[165] *tert*-Butyl methyl(prop-2-ynyl)carbamate **67** (0.82 g, 4.8 mmol, 1 equiv.) was stirred with *t*-BuOK (107 mg, 0.96 mmol, 20 mol %) in THF (50 mL) for 16 hours. Et_2O (50 mL) was added, the reaction filtered and the solvent removed under reduced pressure to yield the *allenamide* **111** as a colourless oil (0.62 g, 76%) that was used without further purification. ^{1}H 400 MHz, $CDCl_3$) δ 7.11 (1H, app br d, J 65.8, $H_2C{=}C{=}CH$), 5.34 (2H, br s, $H_2C{=}C{=}C$), 2.89 (3H, s, NCH_3), 1.48 (9H, br d, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (rotameric), 153.1, 101.4, 86.7 (rotameric), 80.9, 31.6 (rotameric), 28.3; ν_{max} (neat) /cm^{-1} 2977, 2933, 1695, 1141; HRMS (FI) found 169.1105 $[M]^+$, $C_9H_{15}NO_2$ requires 169.1103. Appendix page 385.

4-(2-(methylthio)phenyl)-4-oxobutanal

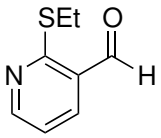


112

Prepared according to general procedure **D** using 2-methylthiobenzaldehyde (25 μL, 0.20 mmol, 1 equiv.), allenamide **111** (50 mg, 0.30 mmol, 1.5 equiv.), $Rh(nbd)_2]BF_4$ (7.5 mg, 10 mol %) and DPEphos (10.8 mg, 10 mol %) in 1,2-DCE (1.3 mL). The product *1,4-dicarbonyl* was obtained as a yellow powder (24 mg, 57%) after chromatography on silica (0–25% Et_2O/petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s, CHO), 7.84 (1H, dd, J 7.8 and 1.1, ArH), 7.44-7.38 (1H, m, ArH), 7.26 (1H, d,

J 8.1, ArH), 7.13 (1H, t, J 7.5, ArH), 3.24 (2H, t, J 6.3, CH_2CH_2CHO), 2.86 (2H, t, J 6.3, CH_2CH_2CHO), 2.35 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 198.7, 142.7, 133.7, 132.5, 130.3, 125.1, 123.5, 37.8, 32.4, 15.9; ν_{max} (neat) $/cm^{-1}$ 3423, 3060, 2976, 2920, 2849, 2727, 1716, 1671; HRMS (FI) found 208.0560 $[M]^+$, $C_{11}H_{12}O_2S$ requires 208.0558. Appendix page 386.

7.2.6 General method F for the preparation of thioether-substituted aldhydes, as exemplified by 2-ethylthionicotinaldehyde

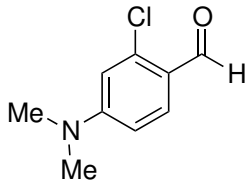


113

Sodium hydride (60% in mineral oil, 3.1 g, 78 mmol, 1.1 equiv.) in THF (85 mL) was stirred at 0 °C in a flask fitted with a bleach scubber. Ethanethiol (5.7 mL, 78 mmol, 1.1 equiv) was added dropwise over 10 minutes and the reaction stirred for a further 1 hour. 2-Chloro-3-pyridinecarboxaldehyde (10.0 g, 71 mmol, 1 equiv.) in THF (15 mL) was added dropwise to the slurry of sodium ethanethiolate. After the addition the reaction is allowed to warm to room temperature over 2 hours. The reaction was then cooled to 10 °C and saturated $NH_4Cl_{(aq)}$ (20 mL) added and the reaction purged with nitrogen for 5 minutes. The reaction was then extracted with Et_2O (3 × 75 mL). The combined organic extracts were then washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then distilled (106-113 °C, 1 mbar) and oil then further purified by chromatography on silica (0-40% EtOAc/petrol) to obtain the pure *product* **113** as a pale yellow oil (9.13 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (1H, s, CHO), 8.53 (1H, dd, J

4.7 and 1.5, ArH), 7.94 (1H, dd, J 7.6 and 1.6, ArH), 7.09 (1H, dd, J 7.6 and 4.8, ArH), 3.21 (2H, q, J 7.4, CH_2CH$_3$), 1.33 (3H, t, J 7.4, CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 190.0, 162.4, 153.1, 139.3, 128.4, 118.8, 24.0, 14.2; ν_{max} (neat) /cm^{-1} 3359, 3123, 3044, 2971, 2869, 2729, 1689; m/z (ESI) 357.1 [2M+Na]$^+$; HRMS (ESI) found 357.0690 [2M+Na]$^+$, $C_{16}H_{18}N_2NaO_2S_2$ requires 257.0702. Appendix page 388.

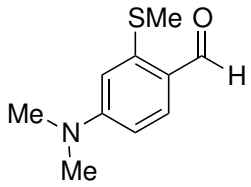
2-Chloro-4-(dimethylamino)benzaldehyde



115

Prepared according to a patented procedure.[196] Dimethyl-3-chloroaniline (5.00 g, 32.0 mmol, 1 equiv.), hexamethylenetetramine (5.63 g, 40.2 mmol, 1.3 equiv.) and paraformaldehyde (1.93 g, 64.3 mmol formaldehyde equiv., 2.0 equiv.) in acetic acid (9.2 mL, 161 mmol, 5 equiv.) was heated to 100 °C for 2 hours. The mixture was cooled to room temperature and poured into ice cold HCl(aq) (3%, 140 mL, 116.6 mmol, 3.6 equiv.). The product was filtered and washed with further cold water (2 × 40 mL) and dried under vacuum to obtain the pure product **115** as white crystals (2.16 g, 38%). Mpt 50–55 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.20 (1H, s, CHO), 7.79-7.82 (1H, m, ArH), 6.57-6.60 (2H, m, ArH), 3.08 (6H, s, N(CH_3)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.1, 154.4, 140.2, 130.8, 121.1, 111.4, 110.1, 40.1; ν_{max} (neat) /cm^{-1} 2886, 2651, 1694, 1591; m/z HRMS (FI) found 184.0524 [M]$^+$, $C_9H_{10}ClNO$ requires 184.0524. Appendix page 396.

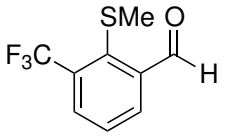
4-(Dimethylamino)-2-(methylthio)benzaldehyde



116

Sodium methanethiolate (451 mg, 6.4 mmol, 1.2 equiv.) was stirred in DMF (30 mL), at 0 °C. A solution of 2-chloro-4-(dimethylamino)benzaldehyde (1.00 g, 5.4 mmol, 1 equiv.) in DMF (5 mL) was added dropwise. After stirring for 5 minutes the reaction was warmed to 40 °C for 3 hours. The reaction was cooled to room temperature and poured over ice (50 g). The cream precipitate was filtered out and washed with further ice cold water (2 × 20 mL) to obtain the *aldehyde* **116** as an off white powder (0.81 g, 76%). Mpt 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (1H, s, C*H*O), 7.61 (1H, d, *J* 8.7), 6.47 (1H, dd, *J* 8.7 and 2.4, Ar*H*), 6.39 (1H, d, *J* 2.0, Ar*H*), 3.08 (6H, s, N(CH_3)$_2$), 2.44 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 153.5, 145.1, 135.5, 122.1, 107.5, 106.9, 40.0, 15.4; ν_{max} (neat) /cm^{-1} 2915, 2825, 2725, 1658, 1577; m/z (ESI) 218.1 [M+Na]$^+$; m/z HRMS (ESI) found 218.0613 [M+Na]$^+$, $C_{10}H_{13}NNaOS$ requires 218.0610. Appendix page 397.

2-(Methylthio)-3-(trifluoromethyl)benzaldehyde

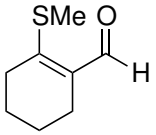


117

Prepared as for aldehyde **116**, using sodium methanethiolate (378 mg, 5.4 mmol, 1.2 equiv.), 2-chloro-3-trifluoromethylbenzaldehyde (936 mg, 4.5 mmol, 1 equiv.) in DMF (10 mL) at 90 °C for 16 hours. The product was purified by chromatography

on silica (10% EtOAc/petrol) to obtain the pure product **117** as yellow crystals (0.36 g, 36%). Mpt 35–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (1H, d, J 0.50, C*H*O), 8.09 (1H, dd, J 7.8 and 1.0, Ar*H*), 7.95 (1H, dd, J 7.8 and 1.0, Ar*H*), 7.59 (1H, t, J 7.8, Ar*H*), 2.41 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 139.8, 139.4, 135.2 (q, J 33.5), 132.1, 131.6 (q, J 5.6), 129.2, 123.2 (q, J 274.0); ^{31}P NMR (376 MHz, $CDCl_3$) δ -59.5; 23.0 (CH3); m/z (ESI) 219.0 $[M\text{-}H]^-$. Data consistent with literature.[173]

2-(Methylthio)cyclohex-1-enecarbaldehyde



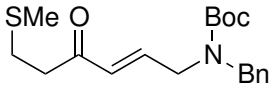
119

Prepared according to a literature method.[173,197] Potassium tribromide (14.4 mL, 153 mmol, 3 equiv.) was added dropwise to a solution of DMF (12.9 mL, 168 mmol, 3.3 equiv.) in chloroform (80 mL) at 0 °C. The mixture was stirred for 60 minutes and then cyclohexanone (5.3 mL, 51 mmol, 1 equiv.) in chloroform (10 mL) was added dropwise. After a further 8 hours, the mixture was poured into ice cold water (300 mL). The mixture was neutralised ($NaHCO_{3\,(s)}$) and the layers separated. The aqueous was extracted with DCM (3 × 40 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then purified by chromatography on silica (10% EtOAc/petrol) to obtain 2-bromo-cyclohex-1-enecarbaldehyde **118** as a yellow oil (2.45 g, 25%), which was used immediately.

2-(Methylthio)cyclohex-1-enecarbaldehyde **119** was then prepared as for aldehyde **116**, using sodium methanethiolate (1.00 g, 14.3 mmol, 1.1 equiv.), bromo-enone

118 (2.45 g, 13.0 mmol, 1 equiv.) in DMF (30 mL) at 0 °C. After addition of the vinyl bromide, the reaction was stirred for 30 minutes and then allowed to warm to room temperature over 16 hours. Water (30 mL) was added dropwise and the reaction stirred for 20 minutes. The mixture was then extracted with Et_2O (3 × 30 mL). The combined extracts were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude crystalline solid was then re-crystallised twice (acetone/water) to obtain the pure aldehyde **119** as pale yellow needles (1.52 g, 75%). Mpt 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (1H, s, C*H*O), 2.47 (2H, tt, *J* 6.2 and 2.0, alkyl), 2.28 (3H, s, SCH_3), 2.21 (2H, tt, *J* 6.2 and 2.0 Hz, alkyl), 1.72-1.63 (2H, m, alkyl), 1.60-1.52 (2H, m, alkyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 189.5, 157.0, 134.8, 30.7, 23.9, 22.9, 21.2, 14.0; *m*/*z* (ESI) 179.0 [M+Na]$^+$. Data consistent with literature.[173]

(*E*)-*tert*-Butyl benzyl(6-(methylthio)-4-oxohex-2-en-1 -yl)carbamate

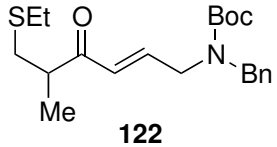


120

Prepared according to general procedure **D**, without hydrogenation, using 2-methylthiopropionaldehyde (45 μL, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compound* **120** (87 mg, 55%) as a colourless oil after chromatography on silica (0–35% Et_2O/Petrol). ^{1}H NMR (250 MHz, DMSO−d_6, 90 °C) vδ 7.36-7.24 (5H, m), 6.68 (1H, dt, *J* 16.0 and 5.3, C(O)CH=C*H*), 6.08 (1H, dt, *J* 16.0 and 1.5, C(O)C*H*=CH), 4.43 (2H, s, NCH_2Ph), 3.99 (2H, dd, *J* 5.4 and 1.5, CHCH_2N), 2.80-2.85 (2H, m, $SCH_2CH_2C(O)$),

2.64-2.70 (2H, m, SCH_2CH$_2$C(O)), 2.08 (3 H, s, SCH_3), 1.44 (9H, s, C(CH_3)$_3$); ^{13}C NMR (63 MHz, DMSO−d$_6$, 90 °C) δ 198.7, 159.8, 143.1, 139.2, 130.7, 129.2, 128.4, 128.0, 80.4, 63.7, 51.2, 48.7, 28.9, 28.7, 15.8; ν_{max} (neat) /cm^{-1} 3411, 2976, 2919, 1689, 1634; m/z (ESI) 372.2 [M+Na]$^+$; HRMS (ESI) found 372.1593 [M+Na]$^+$, $C_{19}H_{27}NNaO_3S$ requires 372.1604. Appendix page 389.

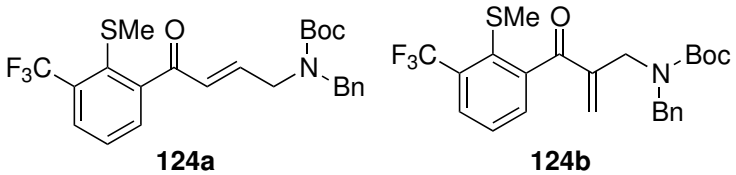
(*E*)-*tert*-Butyl benzyl(6-(ethylthio)-5-methyl-4-oxohex-2-en-1-yl)carbamate



122

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **121** (59 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), [Rh(nbd)$_2$]BF$_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compound* **122** (157 mg, 93%) as a orange oil after chromatography on silica (0–30% EtOAc/Petrol). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.25 (5H, m, ArH), 6.67 (1H, dt, J 15.9 and 5.3, C(O)CH=CH), 6.18 (1H, dt, J 15.9 and 1.4, C(O)CH=CH), 4.43 (2H, s, NCH_2Ph), 3.99 (2H, dd, J 5.3 and 1.3, CH=CHCH_2), 3.04-2.92 (1H, m, SCH$_2$CHC(O)), 2.77 (1H, dd, J 13.1 and 7.0, SCH_AH$_B$CHC(O)), 2.55-2.46 (3H, o m, SCH_2CH$_3$ and SCH$_A$$H_B$CHC(O)), 1.44 (9H, s, C(CH_3)$_3$), 1.19 (3H, t, J 7.3, CH$_2$CH_3), 1.08 (3H, d, J 6.9, CHCH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.9, 155.7, 143.0, 139.2, 129.5, 129.2, 128.4, 128.0, 80.3, 51.3, 48.8, 44.5, 34.8, 28.9, 26.7, 17.1, 15.5; ν_{max} (neat) /cm^{-1} 2975, 2930, 1692, 1631, 1161, 1122; m/z (ESI) 400.2 [M+Na]$^+$; m/z HRMS (FI) found 377.2015 [M]$^+$, $C_{21}H_{31}NO_3S$ requires 377.2025. Appendix page 390.

(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)-3-(trifluoromethyl)-phenyl)-4-oxobut-2-en-1-yl)carbamate and *tert*-Butyl benzyl(2-(2-(methylthio)-3-(trifluoromethyl)benzoyl)allyl)carbamate

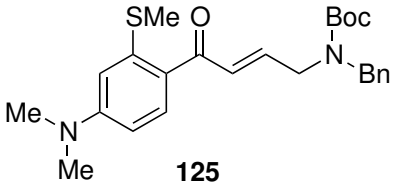


124a **124b**

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **116** (99 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave a partially separable mixture of *isomers* **124a** and **124b** (85 mg, 2.4:1, 41%) as a yellow oil after chromatography on silica (0–30% EtOAc/Petrol). **124a** ^{1}H NMR (500 MHz, DMSO−d_6, 90 °C) δ 7.90 (1H, d, J 7.9, ArH), 7.68 (1H, t, J 7.8, ArH), 7.48 (1H, d, J 7.6, ArH), 7.32-7.22 (5H, m, ArH), 6.42-6.39 (1H, m, C(O)CH=CH), 6.30 (1H, dt, J 16.0 and 5.1, C(O)CH=CH), 4.41 (2H, s, NCH_2Ph), 4.03 (3H, d, J 5.1, CH=CHCH_2N), 2.27 (3H, s, SCH_3), 1.40 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6, 90 °C) δ 195.2, 155.6, 149.5, 147.7, 139.1, 131.9, 131.7, 130.4, 129.2, 128.8 (1C, q, J 5.7, CF_3) 128.4, 128.0, 80.4, 51.5, 48.9, 28.9, 22.5; ^{19}F NMR (470 MHz, DMSO−d_6) δ 58.5; ν_{max} (neat) /cm^{-1} 2977, 2930, 1693, 1665, 1162, 1133; m/z (ESI) 488.2 [M+Na]$^+$; m/z HRMS (ESI) found 488.1465 [M+Na]$^+$, $C_{24}H_{26}F_3NNaO_3S$ requires 488.1478. Appendix page 394. **124b** ^{1}H NMR (500 MHz, DMSO−d_6, 90 °C) δ 7.92 (1H, d, J 7.9, ArH), 7.73-7.70 (1H, m, ArH), 7.55 (1H, d, J 7.6, ArH), 7.39-7.28 (5H, m, ArH), 5.95 (1H, s, C(O)C=CH_AH$_B$), 5.57 (1H, s, C(O)C=CH$_A$$H_B$), 4.47 (2H, s, NC$H_2$Ph), 4.20 (2H, s, C=CC$H_2$N), 2.27 (3H, s, SC$H_3$), 1.44 (9H, s, C(C$H_3$)$_3$); ^{13}C NMR (125 MHz, DMSO−d_6, 90 °C) δ 195.7, 154.6, 147.9, 144.2, 137.8, 133.2 (1C, q, J 29.0, CF_3), 130.7, 130.4, 129.2, 128.7, 127.9, 126.9, 126.6, 124.1, 121.9, 79.0, 49.7,

45.4, 27.6, 21.3; ^{19}F NMR (470 MHz, DMSO−d_6) δ 58.5; ν_{max} (neat) /cm^{-1} 2979, 2931, 1695, 1667, 1160, 1129; m/z (ESI) 488.2 $[M+Na]^+$; m/z HRMS (ESI) found 488.1467 $[M+Na]^+$, $C_{24}H_{26}F_3NNaO_3S$ requires 488.1478. Appendix page 395.

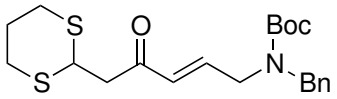
(*E*)-*tert*-Butyl benzyl(4-(4-(dimethylamino)-2-(methylthio) phenyl)-4-oxobut-2-en-1-yl)carbamate



125

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **125** (99 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the *product* **125** (128 mg, 4.3:1, 65%) as a yellow oil after chromatography on silica (0.5% NEt_3/45–65% Et_2O/Petrol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (1H, m, Ar*H*), 7.35-7.23 (5H, m, Ar*H*), 6.83-6.78 (2H, m, C(O)C*H*=C*H*), 6.47 (1H, d, *J* 2.3, Ar*H*), 6.42 (1H, dd, *J* 8.9 and 2.3, Ar*H*), 4.51-4.44 (2H, m), 4.07-3.96 (2H, m), 3.09 (6H, s, N(CH_3)$_2$), 2.43 (3H, s, SCH_3), 1.49 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8 (rotameric), 155.6 (rotameric), 152.5, 146.1 (rotameric), 140.8 (rotameric), 137.9 (rotameric), 132.9 (rotameric), 128.6, 128.4, 128.0, 127.3 (rotameric), 126.7, 122.7, 106.4, 80.2, 49.9 (rotameric), 47.4 (rotameric), 40.0, 28.4, 15.9; ν_{max} (neat) /cm^{-1} 2975, 2931, 2865, 1694, 1619; m/z (ESI) 441.2 $[M+H]^+$; m/z HRMS (ESI) found 463.2012 $[M+Na]^+$, $C_{25}H_{32}N_2NaO_3S$ requires 463.2026. Appendix page 398.

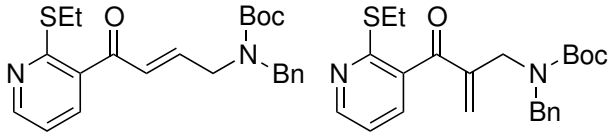
(*E*)-*tert*-butyl (5-(1,3-dithian-2-yl)-4-oxopent-2-en-1-yl)(benzyl)-carbamate



127

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **126** (73 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the title *compound* **127** (162 mg, 89%) as a colourless gum after chromatography on silica (0–30% EtOAc/Petrol). ^{1}H NMR (500 MHz, DMSO−d_6, 90 °C) δ 7.37-7.33 (2H, m, Ar*H*), 7.29-7.26 (3H, m, Ar*H*), 6.70 (1H, dt, *J* 16.0 and 5.4, C(O)CH=C*H*CH$_2$), 6.11 (1H, dt, *J* 16.0 and 1.1, C(O)C*H*=CHCH$_2$), 4.43 (1H, o t, *J* 7.0, S$_2$C*H*CH$_2$), 4.42 (2H, s, NCH_2Ph), 3.98 (2H, dd, *J* 5.4 and 1.1, C(O)CH=CHCH_2N), 2.95 (2H, d, *J* 7.0, CHCH_2C(O)), 2.89-2.86 (4H, m, SCH_2CH$_A$H$_B$CH_2S), 2.06-2.00 (1H, m, SCH$_2$CH_AH$_B$CH$_2$S), 1.78 (1H, dtt, *J* 13.7, 9.1 and 4.6, SCH$_2$CH$_A$$H_BCH_2$S), 1.43 (9H, s, C(C$H_3$)$_3$); ^{13}C NMR (125 MHz,DMSO−d_6, 90 °C) δ 195.9, 155.7, 143.8, 139.1, 130.7, 129.2, 128.4, 128.0, 80.4, 51.2, 48.7, 46.4, 41.5, 29.5, 28.9, 25.9; ν_{max} (neat) /cm^{-1} 2975, 2930, 1689, 1632; *m*/*z* (ESI) 430.2 [M+Na]$^+$; *m*/*z* HRMS (ESI) found 430.1473 [M+Na]$^+$, $C_{21}H_{29}NNaOS_2$ requires 430.1481. Appendix page 391.

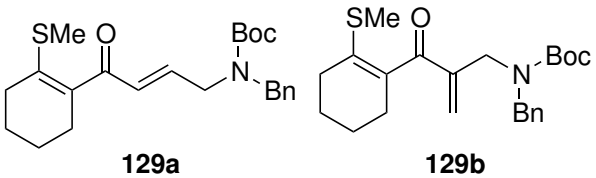
(*E*)-*tert*-Butyl benzyl(4-(2-(ethylthio)pyridin-3-yl)-4-oxobut-2-en-1-yl)carbamate and *tert*-butyl benzyl(2-(2-(ethylthio)-nicotinoyl)allyl)carbamate



128a **128b**

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **113** (75 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave an inseparable mixture of *isomers* **128a** and **128b** (162 mg, 1.7:1, 87%) as a colourless gum after chromatography on silica (0–30% EtOAc/Petrol). ^{1}H NMR (200 MHz, $CDCl_3$) **a** and **b**: δ 8.55-8.50 (1H, m, ArH), 8.53 (1H, m, ArH), 7.73-7.69 (1H, m, ArH), 7.73-7.69 (1H, m, ArH), 7.33-7.22 (10 H, mC), 8.53 (1 H, ddd, J 4.9, 3.5 and 1.6, F), 7.69-7.73 (1 H, mG), 7.22-7.33 (10 H, mH), 7.04 (2 H, dd, J 7.8 and 4.7, I), 6.79 (1H, dt, J 15.7 and 4.6, **a**: C(O)CH=CHCH$_2$N), 6.65 (1H, d, J 15.7, C(O)CH=CH), 5.93 (1H, app d, J 14.5, **b**: C=CH_AH$_B$), 5.67 (1H, s, **b**: C=CH$_A$$H_B$), 4.49 (3H, br s, NCH$_2$N), 4.21-4.17 (2H, m, **b**: C=CCH_2N), 4.07-3.99 (2H, m, **a**: CH=CHCH_2N), 3.26-3.14 (4H, m, SCH_2CH$_3$), 1.49 (18H, br s, C(CH_3)$_3$), 1.39-1.32 (6H, m, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) **a**: δ 190.8, 155.6, 151.2, 150.8, 145.2, 144.3, 137.7, 136.9, 128.7, 128.6, 128.0, 127.5, 118.0, 80.5, 50.4, 47.5, 28.4, 24.6, 14.2, 14.1; ν_{max} (neat) /cm^{-1} 3033, 2975, 2930, 1690; m/z (ESI) 435.2 [M+Na]$^+$; m/z HRMS (ESI) found 435.1707 [M+Na]$^+$, $C_{23}H_{28}N_2NaO_3S$ requires 435.1713. Appendix page 392.

(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)cyclohex-1-en-1-yl)-4-oxobut-2-en-1-yl)carbamate and (*tert*-butyl benzyl(2-(2-(methylthio)cyclohex-1-enecarbonyl)-allyl)carbamate)carbamate



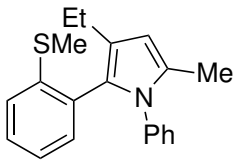
129a **129b**

Prepared according to general method **D**, without hydrogenation, using aldehyde **119** (70 mg, 0.45 mmol) alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.). After 16 hours, the reaction gave an partially separable mixture of *isomers* **129a** and **129b** (180 mg, 1.7:1, 99%) as a yellow oil after chromatography on silica (1% triethylamine/0-25% Et_2O/petrol). **a** ^{1}H NMR (400 MHz, $CDCl_3$) δ) 7.33-7.22 (5H, m, Ar*H*), 6.71-6.67 (1H, m, C(O)CH=C*H*), 6.41-6.38 (1H, m, C(O)C*H*=CH), 4.46-4.41 (2H, m, CH=CHCH_2N), 4.01-3.90 (2H, m, NCH_2Ph), 2.43 (2H, d, *J* 5.9, CH_2CH$_2$), 2.33 (2H, t, *J* 5.9, CH_2CH$_2$), 2.22 (3H, s, SCH_3), 1.74-1.64 (4H, m), 1.47 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 154.1, 154.0, 141.9, 141.8, 137.8, 128.4, 128.1, 128.0, 127.4, 80.3, 49.9, 47.5, 29.8, 28.4, 28.2, 23.0, 21.9, 14.9; ν_{max} (neat) /cm^{-1} 3063, 3030, 2975, 2930, 2863, 1692, 1619; *m*/*z* (ESI) 825.4 [M+Na]$^+$; *m*/*z* HRMS (ESI) found 424.1905 [M+Na]$^+$, $C_{23}H_{31}NNaO_3S$ requires 424.1917. Appendix page 336. **b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, Ar*H*), 5.93 (1H, s, C=CH_AH$_B$), 5.79 (1H, app d, *J* 38.1, C=CH$_A$$H_B$), 4.45 (2H, app d, *J* 13.3), 4.11 (2H, app d, *J* 32.0), 2.35-2.32 (2H, m, CH_2CH$_2$), 2.26-2.21 (2H, m, CH_2CH$_2$), 2.12 (3H, s, SCH_3), 1.79-1.67 (4H, m, alkyl), 1.47 (9H, s, C(CH_3)$_3$). Appendix page 337.

7.2.7 General Procedure G for synthesis of synthesis of pyrroles by telescoped hydroacylation-cyclisation

$[Rh(nbd_2)]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in a microwave tube were dissolved in 1,2-DCE (2 mL) at room temperature and stirred for 5 minutes. The aldehyde (1 equiv.) and alkyne (1.1 equiv.) were dissolved in 1,2-DCE (1 mL) then added to the solution of catalyst. The mixtured was immersed in an oil bath or heating block at 70 °C. After 16 hours, the reaction was cooled to room temperature and Et_2O (3–4 solvent volumes) was added. The mixture was filtered and concentrated under reduced pressure. The residue was then dissolved in EtOH (1 mL) and water (1 mL) and heated in a microwave to 170 °C for 1 hour. The reaction mixture was then directly loaded onto a column of base washed silica and purified by chromatography (0.5% NEt_3/petrol) to obtain the pyrrole product.

3-Ethyl-5-methyl-2-(2-(methylthio)phenyl)-1-phenyl-1H-pyrrole

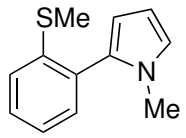


110

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **73** (136 mg, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **110** as a colourless gum (57 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.13 (6H, m, ArH), 7.06 (1H, d, J 7.7, ArH), 7.02 (1H, dd, J 7.5 and 1.5, ArH), 6.94 (1H, td, J 7.4 and 1.0, ArH), 6.07 (1H, s, ArH), 2.40 (1H, dq, J 14.8 and 7.5, $CH_AH_BCH_3$), 2.34 (3H, s, SCH_3), 2.29 (1H, m, $CH_AH_BCH_3$), 2.16 (3H, s, $ArCH_3$), 1.16 (3H, t,

J 7.5, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 138.9, 132.5, 131.9, 129.3, 128.2, 128.1, 128.0, 127.5, 126.7, 124.8, 123.6, 123.5, 106.7, 19.5, 15.29, 15.25, 13.3; ^{1}H NMR (400 MHz, DMSO−d_6) δ 7.25 (2H, td, J 7.8 and 1.2, ArH), 7.21-7.16 (2H, m, ArH), 7.11 (3H, dd, J 7.2 and 1.7, ArH), 6.95-6.90 (2H, m, ArH), 5.93 (1H, d, J 0.8, ArH), 2.30 (3H, s, SCH_3), 2.26-2.08 (2H, m, CH_2CH$_3$), 2.03 (3H, d, J 0.8, ArCH_3), 1.02 (3H, t, J 7.5); ^{13}C NMR (100 MHz, DMSO−d_6) δ 141.8, 139.4, 133.0, 131.9, 129.3, 129.2, 129.1, 128.5, 127.7, 127.7, 124.6, 124.3, 124.3, 107.9, 20.1, 16.0, 15.2, 13.8; ν_{max} (neat) /cm^{-1}3060, 2971, 2925, 2870, 1667; m/z HRMS (FI) found 307.1396 [M]$^+$, $C_{20}H_{21}NS$ requires 307.1395. Appendix page 383.

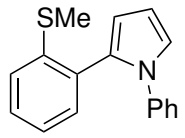
1-Methyl-2-(2-(methylthio)phenyl)-1H-pyrrole



131

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **67** (94 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **131** (45 mg, 50%) as a colourless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (1H, m, ArH), 7.16-7.13 (2H, m, ArH), 7.09-7.05 (1H, m, ArH), 6.64 (1H, dd, J 2.6 and 1.9, ArH), 6.14 (1H, dd, J 3.5 and 2.6, ArH), 6.07 (1H, dd, J 3.5 and 1.9, ArH), 3.35 (3H, s, NCH_3), 2.28 (3H, s, SCH_3); ^{1}H NMR (250 MHz, DMSO−d_6) δ 7.40 (1H, dd, J 8.4 and 4.1, ArH), 7.31 (1H, d, J 7.9, ArH), 7.20 (2H, d, J 3.9, ArH), 6.83 (1H, t, J 2.2, ArH), 6.07 (1H, dd, J 3.5 and 2.7, ArH), 6.02 (1H, dd, J 3.5 and 1.8, ArH), 3.39 (3 H, s, NCH_3), 2.38 (3H, s, SCH_3). ^{13}C NMR (63 MHz, DMSO−d_6) δ 140.9, 132.0, 131.8, 131.7, 129.5, 124.9, 124.8, 123.4, 109.8, 107.8, 34.8, 15.2; ν_{max} (neat) /cm^{-1} 2925, 2856; m/z HRMS (FI) found 203.0768 [M]$^+$, $C_{12}H_{13}NS$ requires 203.0769. Appendix page 379.

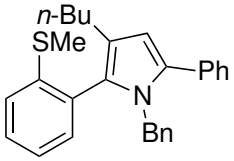
1-Phenyl-2-(2-(methylthio)phenyl)-1H-pyrrole



133

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **69** (127 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **133** (57 mg, 48%) pale yellow solid. Mpt 94–98 °C; ^{1}H NMR (500 MHz, DMSO−d_6) δ 7.33-7.21 (5H, m, ArH), 7.15-7.09 (3H, m, ArH), 7.00 (2H, dtd, J 13.6, 7.0 and 1.6, ArH), 6.32 (2H, t, J 1.3, ArH), 2.31 (3H, s, SCH_3); ^{13}C NMR (63 MHz, DMSO−d_6) δ 140.6, 140.3, 132.15, 132.00, 131.0, 129.8, 129.2, 127.1, 125.33, 125.27, 124.7, 123.8, 112.8, 109.7, 15.5; ν_{max} (neat) /cm^{-1} 3057, 2979, 2919, 1499; m/z HRMS (FI) found 265.0924 $[M]^+$, $C_{17}H_{15}NS$ requires 265.0925. Appendix page 380.

1-Benzyl-3-butyl-2-(2-(methylthio)phenyl)-5-phenyl-1H-pyrrole

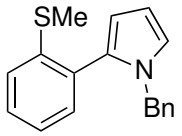


134

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **94** (187 mg, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **134** as a colourless gum (91 mg, 49%). ^{1}H NMR (250 MHz, DMSO−d_6, 90 °C) δ 7.36-7.30 (7H, m, ArH), 7.10-6.97 (5H, m, ArH), 6.65-6.61 (2H, m, ArH), 6.22 (1H, s, ArH), 5.09 (1H, d, J 16.7, NCH_AHH_BPh), 4.80 (1H, d, J 16.7, NCH$_A$$H_B$Ph), 2.35 (3H, s, SC$H_3$), 2.34-2.17 (2H, m, C$H_2CH_2$), 1.54-1.38 (2H, m, alkyl), 1.37-1.20

(2H, m, alkyl), 0.81 (3H, t, J 7.2, CH_2CH_3); ^{13}C NMR (63 MHz, DMSO−d_6, 90 °C) δ 141.9, 140.0, 135.0, 134.5, 133.0, 131.7, 131.1, 129.5 (2C), 129.2, 128.7, 127.42, 127.34, 126.7, 125.6, 124.7, 123.7, 110.4, 48.9, 33.3, 26.5, 22.6, 15.5, 14.4; ν_{max} (neat) /cm^{-1} 3060, 3028, 2956, 2926, 2870, 2857; m/z HRMS (FI) found 411.2034 $[M]^+$, $C_{28}H_{29}NS$ requires 411.2021. Appendix page 381.

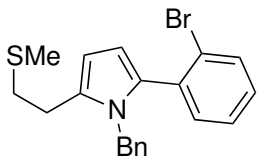
1-Benzyl-2-(2-(methylthio)phenyl)-1H-pyrrole



135

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **68** (129 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **135** as a colourless gum (61 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, ddd, J 8.0, 7.1 and 1.7, ArH), 7.28 (1H, dd, J 7.9 and 1.0, ArH), 7.24-7.18 (3H, m, ArH), 7.12-7.05 (2H, m, ArH), 6.89-6.86 (3H, m, ArH), 6.14 (1H, dd, J 3.5 and 2.8, ArH), 6.05 (1H, dd, J 3.5 and 1.8, ArH), 4.92 (2H, s, NCH_2Ph), 2.35 (3H, s, SCH_3); ^{13}C NMR (125 MHz, DMSO−d_6) δ 140.0, 138.8, 131.4, 130.90, 130.75, 128.7, 128.2, 127.0, 126.6, 124.1, 123.9, 122.0, 109.4, 107.7, 50.0, 14.4; ν_{max} (neat) /cm^{-1} 3060, 2980, 2920, 1662; m/z HRMS (ESI) found 279.1087 [M+]$^+$, $C_{18}H_{17}NS$ requires 279.1087. Appendix page 382.

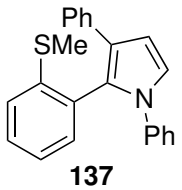
1-Benzyl-2-(2-bromophenyl)-5-(2-(methylthio)ethyl)-1*H*-pyrrole



136

Prepared according to general procedure **G** using 3-methylthiopropionaldehyde (45 μL, 0.45 mmol, 1 equiv.) and alkyne **85** (200 mg, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **136** (45 mg, 50%) as a colourless gum (71 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (1H, m, Ar*H*), 7.28-7.14 (6H, m, Ar*H*), 6.82-6.79 (2H, m, Ar*H*), 6.20 (1H, d, *J* 3.5, Ar*H*), 6.14-6.13 (1H, m, Ar*H*), 4.98 (2H, s, NCH_2Ph), 2.80-2.74 (2H, m, SCH_2CH$_2$), 2.71-2.68 (2H, m, SCH$_2$CH_2), 2.03 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 134.7, 133.1, 132.7 (2C), 132.3, 129.3, 128.8, 128.5, 127.1 (2C), 125.8, 108.9, 106.4, 47.9, 33.5, 27.2, 15.7; ν_{max} (neat) /cm^{-1} 3061, 3029, 2916, 2854; *m*/*z* (ESI) 408.1 [M+Na]$^+$; HRMS (FI) found 385.0502 [M]$^+$,$C_{20}H_{20}^{79}BrNS$ requires 385.0500. Appendix page 377.

2-(2-(Methylthio)phenyl)-1,3-diphenyl-1*H*-pyrrole

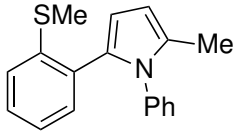


137

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **75** (154 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **137** as colourless crystals (37 mg, 24%). Mpt 140–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (2H, m, Ar*H*), 7.23-7.14 (9H, m, Ar*H*), 7.12-7.09 (2H, m, Ar*H*), 7.05-7.03 (2H, m, Ar*H*), 6.66 (1H, d, *J* 3.0, Ar*H*), 2.21 (3H, s, SCH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.4, 140.1, 136.1, 132.7, 131.6, 128.8, 128.5, 128.1, 127.0, 126.4, 125.42, 125.32, 125.0, 124.4, 122.6, 111.3, 108.8, 15.5; ν_{max} (neat) $/cm^{-1}$ 3056, 2969, 2920; m/z (ESI) 364.1 $[M+Na]^+$; HRMS (ESI) found 364.1129 $[M+Na]^+$, $C_{23}H_{19}NNaS$ requires 364.1130. Appendix page 375.

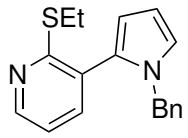
2-Methyl-5-(2-(methylthio)phenyl)-1-phenyl-1*H*-pyrrole



138

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **77** (94 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **138** as a colourless gum (27 mg, 21%). ^{1}H NMR (300 MHz, DMSO−d_6) δ 7.34-7.23 (3H, m, Ar*H*), 7.17-7.10 (4H, m, Ar*H*), 6.92-6.83 (2H, m, Ar*H*), 6.16 (1H, d, *J* 3.4, Ar*H*), 6.03 (1H, dd, *J* 3.4 and 0.8, Ar*H*), 2.31 (3H, s, SCH_3), 2.08 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO−d_6) δ 139.5, 138.2, 131.5, 131.2, 130.2, 129.4, 128.6, 127.82, 127.80, 127.1, 123.9, 123.4, 109.9, 107.0, 14.7, 13.0; ν_{max} (neat) $/cm^{-1}$ 3055, 2976, 2919, 2853; m/z HRMS (FI) found 279.1089 $[M]^+$, $C_{18}H_{17}NS$ requires 279.1082. Appendix page 376.

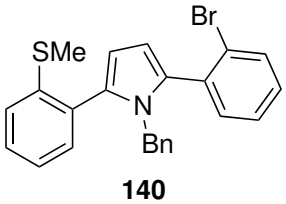
3-(1-Benzyl-1*H*-pyrrol-2-yl)-2-(ethylthio)pyridine



139

Prepared according to general procedure **G** using aldehyde **113** (75 mg, 0.45 mmol, 1 equiv.) and alkyne **68** (123 mg, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **139** as a colourless gum (38 mg, 29%). ^{1}H NMR (500 MHz, DMSO−d_6) δ 8.41 (1H, dd, J 4.8 and 1.8, ArH), 7.36-7.33 (1H, m, ArH), 7.22-7.16 (3H, m, ArH), 7.05 (1H, dd, J 7.5 and 4.8, ArH), 6.97 (1H, dd, J 2.7 and 1.8, ArH), 6.85-6.83 (2H, m, ArH), 6.16 (1H, dd, J 3.5 and 2.8, ArH), 6.14 (1H, dd, J 3.5 and 1.8, ArH), 4.96 (2H, s, NCH_2Ph), 3.04 (2H, q, J 7.3, SCH_2CH$_3$), 1.21 (3H, t, J 7.3, SCH$_2$CH_3); ^{13}C NMR (125 MHz, DMSO−d_6) δ 159.1, 148.4 (2C), 138.6, 138.3, 128.3, 127.1, 126.5 (2C), 123.1, 118.7, 110.5, 107.9, 50.2, 23.5, 14.5; ν_{max} (neat) /cm^{-1} 3031, 2968, 2926, 2869; m/z (ESI) 295.1 [M+H]$^+$; HRMS (ESI) found 295.1263 [M+H]$^+$, $C_{18}H_{19}N_2S$ requires 295.1263.
Appendix page 373

1-Benzyl-2-(2-bromophenyl)-5-(2-(methylthio)phenyl)-1*H*-pyrrole

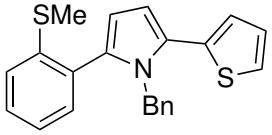


140

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **85** (200 mg, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **140** as a white crystalline solid (86 mg, 44%). Mpt 97–99 °C; ^{1}H NMR (400 MHz, DMSO−d_6) δ 7.67 (1H, dd, J 7.8 and 1.4, ArH), 7.36-7.20 (5H, m, ArH), 7.08 (2H,

dd, J 6.4 and 1.4, ArH), 7.03 (3H, td, J 3.0 and 1.5, ArH), 6.48 (2H, td, J 3.8 and 1.7, ArH), 6.24 (1H, d, J 3.5, ArH), 6.20 (1H, d, J 3.5, ArH), 4.83 (2H, s, NCH_2), 2.37 (3H, s, SCH_3); ^{13}C NMR (100 MHz, DMSO−d_6) δ 140.7, 139.2, 134.9, 133.90, 133.81, 133.54, 133.36, 132.4, 131.6, 130.7, 129.7, 128.8, 128.3, 127.5, 126.6, 125.26, 125.11, 124.8, 110.8, 110.4, 49.1, 15.4; ν_{max} (neat) /cm^{-1} 3062, 3031, 2945, 2918; m/z (ESI)456.1, 458.1 [M+Na]$^+$; HRMS (FI) found 433.0527 [M]$^+$, $C_{24}H_{20}{}^{79}BrNS$ requires 433.0500. Appendix page 374.

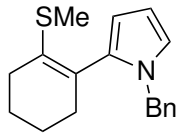
1-Benzyl-2-(2-(methylthio)phenyl)-5-(thiophen-2-yl)-1H-pyrrole



141

Prepared according to general procedure **G** using 2-methylthiobenzaldehyde (58 μL, 0.45 mmol, 1 equiv.) and alkyne **84** (219 μL, 0.67 mmol, 1.5 equiv.) to obtain *pyrrole* **141** as a yellow oil (13 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 7.43 (1H, app ddd, J 5.2, 1.1 and 0.5, ArH), 7.37-7.31 (2H, m, ArH), 7.29-7.26 (1H, m, ArH), 7.18-7.04 (4H, m, ArH), 7.01-6.98 (1H, m, ArH), 6.92-6.91 (1H, m, ArH), 6.71-6.69 (2H, m, ArH), 6.44 (1H, d, J 3.6, ArH), 6.20 (1H, d, J 3.7, ArH), 5.11 (2H, s, NCH_2Ph), 2.37 (3H, s, SCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.5, 134.5, 132.1, 129.9, 129.6, 129.24, 129.11, 128.8, 128.5, 127.6, 126.4, 126.2, 125.7, 125.1, 124.8, 111.11, 110.96, 48.7, 15.3; ν_{max} (neat) /cm^{-1} 3061, 3029, 2919; m/z HRMS (FI) found 361.0984 [M]$^+$, $C_{22}H_{19}NS_2$ requires 361.0959. Appendix page 387.

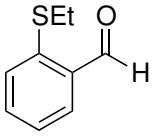
1-Benzyl-2-(2-(methylthio)cyclohex-1-en-1-yl)-1H-pyrrole



142

Prepared according to general procedure **G** using aldehyde **119** (70 mg, 0.45 mmol, 1 equiv.) and alkyne **68** (129 μL, 0.50 mmol, 1.1 equiv.) to obtain *pyrrole* **142** as a colourless oil (46 mg, 36%). ^{1}H NMR (200 MHz, DMSO−d_6) δ 7.36-7.24 (3H, m, Ar*H*), 7.09-7.04 (2H, m, Ar*H*), 6.79 (1H, dd, *J* 2.7 and 1.8, Ar*H*), 6.01 (1H, dd, *J* 3.5 and 2.7, Ar*H*), 5.81 (1H, dd, *J* 3.5 and 1.8, Ar*H*), 4.99 (2H, s, NCH_2Ph), 2.32-2.26 (2H, m, CH_2CH$_2$), 2.11 (3H, s, SCH_3), 1.84-1.78 (2H, m, CH_2CH$_2$), 1.61-1.44 (4H, m, alkyl); ^{13}C NMR (125 MHz, DMSO−d_6) δ 139.1, 133.3, 133.2, 128.2, 127.14, 127.07, 125.9, 121.0, 107.22, 107.16, 50.5, 33.2, 28.5, 22.6, 22.2, 13.0; ν_{max} (neat) /cm^{-1} 2926, 2856, 2831; *m*/*z* HRMS (FI) found 283.1389 [M]$^+$, $C_{18}H_{21}NS$ requires 283.1395. Appendix page 378.

2-(Ethylthio)benzaldehyde

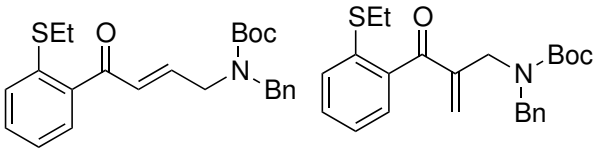


114

Sodium ethanethiolate (0.50 g, 6.0 mmol, 1.2 equiv.) was stirred in DMF (10 mL) at 0 °C. 2-Chlorobenzaldehyde (0.93 g, 5.0 mmol, 1.0 equiv.) in DMF (3 mL) was added dropwise over 10 minutes. The reaction was then heated to 45 °C for 1 hour. The reaction was cooled to 5 °C and water (20 mL) added. The mixture was extracted using Et_2O (3 × 20 mL). The organic layers were then washed with water (20 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated under reduced pressure.

The crude oil was purified by chromatography on silica (5-20% EtOAc/petrol) to obtain the pure *product* **114** as a yellow oil (0.67 g, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.30 (1H, s, C*H*O), 7.76 (1H, dd, *J* 7.6 and 1.3, Ar*H*), 7.45 (1H, td, *J* 7.5 and 1.5, Ar*H*), 7.35 (1H, d, *J* 7.9, Ar*H*), 7.27-7.19 (1H, m, Ar*H*), 2.92 (2H, q, *J* 7.4, SCH_2CH$_3$), 1.30 (3H, t, *J* 7.4, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 141.9, 133.87, 133.79, 132.1, 127.9, 125.1, 27.1, 13.6; ν_{max} (neat) /cm^{-1} 3060, 2971, 2929, 2736, 1738, 1689, 1194; m/z (ESI) 335.1 $[2M+Na]^+$; m/z HRMS (ESI) found 189.0341 $[M]^+$, $C_9H_{10}NaOS$ requires 189.0345. Appendix page 399.

Data for compounds from table 5.3: (*E*)-*tert*-Butyl benzyl(4-(2-(ethylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate and *tert*-Butyl benzyl(2-(2-(ethylthio)benzoyl)allyl)carbamate

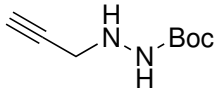


a **b**

Prepared according to general procedure **D**, without hydrogenation, using aldehyde **114** (75 mg, 0.45 mmol, 1 equiv), alkyne **68** (221 mg, 0.90 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (17 mg, 10 mol %) and DPEphos (25 mg, 10 mol %) in 1,2-DCE (3.0 mL). After 16 hours, the reaction gave the *isomers* **a** and **b** (167 mg, 1.6:1, 90%) as a yellow oil after chromatography on silica (5–20% Et_2O/Petrol). **a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (3H, dd, *J* 17.8 and 5.5, Ar*H*), 7.34-7.20 (6H, m, Ar*H*), 6.68-6.59 (2H, m, C(O)C*H*=C*H*), 4.49-4.45 (2H, m, NH_2Ph), 4.07-3.95 (2H, m, CH=CHCH_2), 2.92 (2H, q, *J* 7.4, SCH_2CH$_3$), 1.50 (9H, s, C(CH_3)$_3$), 1.32 (3H, t, *J* 7.4, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 155.6 (rotameric), 144.8, 138.0 (rotameric), 131.1, 129.8, 129.2, 128.9, 128.6, 128.5, 128.2, 128.0, 127.4, 124.8, 80.4

(rotameric), 50.2 (rotameric), 47.4 (rotameric), 28.4, 27.6, 13.7; ν_{max} (neat) $/cm^{-1}$ 3030, 2974, 1691, 1621; m/z HRMS (FI) found 411.1871[M]$^+$, $C_{24}H_{29}NO_3S$ requires 411.1868. Appendix page 400. **b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.26 (12H, m, ArH), 5.91 (1H, app d, J 51.5, C=CH_AH$_B$), 5.65 (1H, app d, J 6.4, C=CH$_A H_B$), 4.52 (2H, app d, J 15.7, NCH_2Ph), 4.23 (2H, app d, J 37.5, C=CCH_2N), 2.88 (2H, q, J 7.4, SCH_2CH$_3$), 1.51-1.44 (9H, m, C(CH_3)$_3$), 1.26 (3H, t, J 7.4, SCH$_2$C$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ; ν_{max} (neat) $/cm^{-1}$ 3030, 2975, 2930, 1692, 1662; m/z HRMS (FI) found 411.1870 [M]$^+$, $C_{24}H_{29}NO_3S$ requires 411.1868. Appendix page 401.

tert-Butyl 2-(prop-2-yn-1-yl)hydrazinecarboxylate

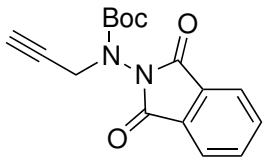


143

Prepared by a modified literature procedure.[175] *tert*-Butyl carbazate (8.00 g, 60.6 mmol, 3 equiv.) and finely powdered K_2CO_3 (2.80 g, 20.3 mmol, 1.0 equiv.) was stirred in a mixture of THF/DMF (9:1, 52 mL) at room temperature. Propargyl bromide (80% in PhMe, 2.25 mL, 20.2 mmol, 1.0 equiv.) in a mixture of THF/DMF (9:1, 8 mL) was added over 2 hours by syringe pump. After 44 hours, the reaction mixture was concentrated. DCM (50 mL) and water (75 mL) were added and the layers separated. The aqueous layer was extracted with DCM (2 × 25 mL). The combined organic extracts were washed with water (50 mL), brine (25 mL) then dried ($MgSO_4$) and then concentrated under reduced pressure to yield the crude product as a yellow oil. The oil was dissolved in Et_2O (50 mL) and HCl (1 M in Et_2O, 50 mL). The white crystalline salt was filtered out (7.93 g) and dissolved in water (30 mL). A saturated solution of $Na_2CO_{3\,(aq)}$ was added until pH 9-10

was achieved. The aqueous solution was extracted with DCM (3 × 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by chromatography on silica (5-40% Et_2O/petrol) to obtain the pure product **143** as a white crystalline solid (2.46 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, br s, NHN*H*Boc), 4.08 (1H, br s, N*H*NHBoc), 3.62 (2H, m, HC≡CCH_2), 2.24-2.23 (1H, m, *H*C≡CCH$_2$), 1.46 (9H, app d, *J* 1.5, rotameric, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 80.9, 79.9, 72.3, 41.2, 28.3; ν_{max} (neat) /cm^{-1} 3319, 3287, 3244, 2988, 1699, 1545, 1160; *m*/*z* (ESI) 193.1 [M+Na]$^+$; HRMS (ESI) found 193.0950 [M+Na]$^+$, $C_8H_{14}N_2NaO_2$ requires 193.0947. Data consistent with literature.[175] Appendix page 402.

tert-Butyl-(1,3-dioxoisoindolin-2-yl-1-yl)carbamate

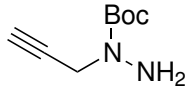


144

N-(*tert*-Butyoxycarbonyl)aminophthalimide (0.65 g, 2.5 mmol, 1 equiv.) and K_2CO_3 (1.38 g, 10.0 mmol, 4 equiv.) were stirred in MeCN (20 mL) at room temperature. Propargyl bromide (80% in PhMe, 0.55 mL, 5.0 mmol, 2 equiv.) was added and the reaction heated to 90 °C for 4 hours. The reaction was cooled to room temperature and filtered. The filtrate was concentrated under vacuum to an oil that crystallised on standing. The *product* **144** was recrystallised (Et_2O/hexane) to obtain white crystals (0.54 g, 72%) mpt 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-8.00 (4H, m, Ar*H*), 4.46 (2H, d, *J* 2.4, HC≡CCH_2), 3.05 (1H, b d, *J* 33.6, rotameric, *H*C≡C), 1.38 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 153.1, 136.3 (2C), 130.2, 124.6, 83.5, 78.4, 76.5, 28.5; ν_{max} (neat) /cm^{-1} 3261, 1796, 1715, 1364,1251; *m*/*z*

HRMS (ESI) found 323.1001 $[M+Na]^+$, $C_{16}H_{16}N_2NaO_4$ requires 323.1002. Appendix page 404.

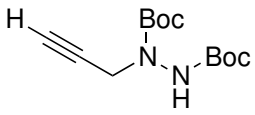
tert-Butyl 1-(prop-2-yn-1-yl)hydrazinecarboxylate



145

tert-butyl-(1,3-dioxoisoindolin-2-yl-1-yl)carbamate (400 mg, 1.33 mmol, 1 equiv.) was dissolved in THF (10 mL) at room temperature. Methyl hydrazine (0.14 mL, 2.66 mmol, 2 equiv.) was added and a precipitate forms over 36 hours. Ethyl acetate (10 mL) was added and the reaction filtered. The filtrate was concentrated under reduced pressure to yield a colourless oil and a yellow residue. The colourless oil was triturated out with minimal Et_2O and concentrated once more to obtain the pure *product* **145** (90 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (2H, d, J 2.4, HC≡CCH_2), 4.06 (2H, br s, NH_2), 2.19 (1H, t, J 2.4, HC≡CCH$_2$), 1.41 (9H, br s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 81.3, 79.2, 71.4, 40.8, 28.2; ν_{max} (neat) $/cm^{-1}$ 3340, 2979, 2934, 2118. 1694, 1391, 1367; m/z HRMS (ESI) found 193.0944 $[M+Na]^+$, $C_8H_{14}N_2NaO_2$ requires 193.0947. Appendix page 405.

Di-*tert*-butyl 1-(prop-2-yn-1-yl)hydrazine-1,2-dicarboxylate

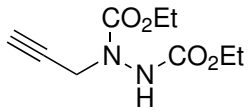


146

Prepared according to a modified literature procedure.[198] Sodium hydride (60% in mineral oil, 0.34 g, 8.6 mmol, 1 equiv.) was stirred in a mixture of THF/DMF (9:1, 20

mL) at 0 °C. Di-*tert*-butyl hydrazine-1,2-dicarboxylate (3.00 g, 12.9 mmol, 1.5 equiv.) was dissolved in THF/DMF (9:1, 5 mL) and added dropwise to the sodium hydride suspension. After stirring for 30 minutes, propargyl bromide (80% in PhMe, 0.96 mL, 8.6 mmol, 1 equiv.) was added as a solution in THF/DMF (9:1, 10 mL) over 1.5 hours using a syringe pump. The reaction was allowed to warm to room temperature and stirred for 20 hours. Brine (10 mL) was added dropwise to the reaction, which was then extracted using EtOAc (30 mL). The organic layer was washed with water (3 × 25 mL), brine (15 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-20% Et_2O/petrol) to obtain the *product* **146** as a white crystalline solid (0.99 g, 43%). Mpt 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (0.75H, br s, N*H*), 6.19 (0.25H, br s, N*H*), 4.26 (2H, br s, HC≡CCH_2), 2.23 (1H, t, J 2.4, HC≡CCH$_2$), 1.47 (9H br s, C(CH_3)$_3$), 1.465 (9H, br s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.6, 81.7, 81.6, 78.8, 72.1, 45.7, 28.31, 28.27; ν_{max} (neat) /cm^{-1} 3310, 3292, 2983, 2938, 1730, 1689. Data consistent with literature.[198] Appendix page 407.

Diethyl 1-(prop-2-yn-1-yl)hydrazine-1,2-dicarboxylate

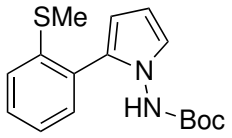


147

Prepared as for *tert*-butyl-(1,3-dioxoisoindolin-2-yl-1-yl)carbamate using propargyl bromide (80% in PhMe, 3.5 mmol, 1 equiv.), K_2CO_3 (0.48 g, 3.5 mmol, 1 equiv.) and diethyl 1,2-hydrazinedicarboxylate (1.20 g, 5.2 mmol, 1.5 equiv.) in MeCN (20 ml) at 90 °C for 4 hours. Purified by chromatography on silica (5-30% Et_2O/petrol) to obtain the *product* **147** as a colourless oil (0.60 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (0.8H, br s, N*H*), 6.58 (0.2H, br s, N*H*), 4.33 (2H, br s, HC≡CCH_2), 4.21

(4H, q, J 7.1, 2 × OCH_2CH$_3$), 2.28 (1H, td, J 2.5 and 0.4, HC≡CCH_2), 1.28 (6H, t, J 7.1, 2 × OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.5, 153.3, 72.6, 63.0, 62.2 (2C), 40.2, 14.4 (2C); ν_{max} (neat) /cm^{-1} 3291, 2984, 1705, 1262, 1214; m/z HRMS (ESI) found 237.0850 [M+Na]$^+$, $C_9H_{14}N_2NaO_4$ requires 237.0846. Appendix page 408.

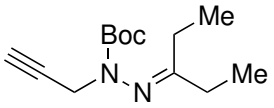
tert-Butyl (2-(2-(methylthio)phenyl)-1H-pyrrol-1-yl)carbamate



148

Prepared according to general procedure **D** using 2-methylthiobenzaldehyde (30 μL, 0.23 mmol, 1 equiv), alkyne **143** (41 mg, 0.24 mmol, 1.04 equiv.), [Rh(nbd)$_2$]BF$_4$ (8.5 mg, 10 mol %) and dcpm (9.4 mg, 10 mol %) in 3-pentanone (2.5 mL). After 20 hours, the reaction gave the title compound as a pale yellow oil (63 mg, 90%) after filtration through a pad of silica (1% triethylamine/hexane followed by 15% acetone/hexane). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (1H, br s, NH), 7.37-7.32 (2H, m, ArH), 7.25 (1H, d, J 7.5, ArH), 7.17 (1H, td, J 7.4 and 1.2, ArH), 6.82 (1H, d, J 0.3, ArH), 6.20 (2H, t, J 4.1, ArH), 2.40 (3H, s, SCH_3), 1.25 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.8, 138.6, 132.3, 132.1, 130.5, 129.3, 128.8, 125.0, 122.9, 108.3, 106.7, 81.6, 41.1, 27.8, 15.2 ν_{max} (neat) /cm^{-1} 3302, 2979, 2923, 1727, 1158; m/z (ESI) 327.12 [M+Na]$^+$; HRMS (ESI) found 327.1130 [M+Na]$^+$, $C_{16}H_{20}N_2NaO_2S$ requires 327.1138. Appendix page 403.

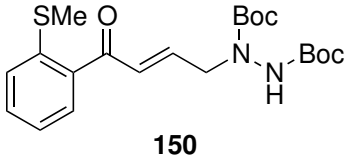
tert-Butyl 2-(pentan-3-ylidene)-1-(prop-2-yn-1-yl)hydrazine-carboxylate



149

tert-Butyl 1-(prop-2-yn-1-yl)hydrazinecarboxylate (39 mg, 0.23 mmol, 1 equiv) was stirred in 3-pentanone (3.0 mL, 28.4 mmol, 123 equiv.), *p*-TSA $\cdot$ H_2O (a crystal) and $MgSO_4$ (approximately 0.5 g). After 16 hours, the reaction was filtered and the filtrate concentrated under reduced pressure to yield the *product* **149** as a colourless oil (50 mg, 91%) containing trace amounts of *p*-TSA $\cdot$ H_2O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (2H, d, J 2.2, major rotamer, HC≡CCH_2), 2.32-2.46 (4H, m, 2 × CH_2CH$_3$), 2.16 (1H, dt, J 2.4 and 1.2, major rotamer, HC≡CCH$_2$), 1.43 (9H, d, J 1.7, major rotamer, C(CH_3)$_3$), 1.11 (6 H, dtd, J 34.2, 7.6 and 1.8, 2 × CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 153.8, 81.3, 79.2, 71.5, 39.4, 28.2, 24.1, 11.3, 10.4; ν_{max} (neat) /cm^{-1} 3256, 2976, 2937, 1692, 1366, 1156; m/z HRMS (ESI) found 261.1566 [M+Na]$^+$, $C_{13}H_{22}N_2NaO_2$ requires 261.1573. Appendix page 406.

(*E*)-di-*tert*-Butyl 1-(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)hydrazine-1,2-dicarboxylate

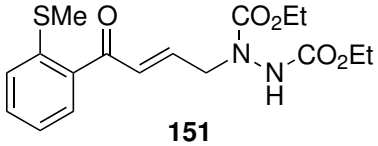


150

Prepared according to general procedure **D** using 2-methylthiobenzaldehyde (30 μL, 0.23 mmol, 1 equiv), alkyne **146** (65 mg, 0.24 mmol, 1.04 equiv.), [Rh(nbd)$_2$]BF$_4$

(8.5 mg, 10 mol %) and dcpm (9.4 mg, 10 mol %) in 3-pentanone (2.5 mL). After 10 minutes, the reaction was concentrated and purified by filtration through a pad of silica (10% EtOAc/hexane followed by 20% EtOAc/hexane) to obtain the title *compound* **150** (55 mg, 40%, ∼6.5:1 **a**:**b**) ^{1}H NMR (400 MHz, $CDCl_3$) **a**: δ 7.64-7.62 (1H, m, Ar*H*), 7.44 (1H, t, *J* 7.5, Ar*H*), 7.34 (1H, d, *J* 8.1, Ar*H*), 7.19 (1H, t, *J* 7.5, Ar*H*), 6.78 (2H, br s, C(O)C*H*=C*H*), 4.31 (2H, br s, CH=CHCH_2N), 2.43 (3H, s, SCH_3), 1.45 (18H, s, 2 × C(CH_3)$_3$) **b**: δ 7.64-7.62 (1H, m, Ar*H*), 7.44 (1H, t, *J* 7.5, Ar*H*), 7.34 (1H, d, *J* 8.1, Ar*H*), 7.19 (1H, t, *J* 7.5, Ar*H*) , 6.45-6.56 (3 H, mF), 6.26-6.30 (1H, m, C=CH_AH$_B$), 6.06 (1H, app d, J 44.9, 1H, m, C=CH_AH$_B$), 5.69 (1H, s, C=CH$_A$$H_B$), 4.47 (2H, br s, CC$H_2$N), 2.42 (3H, s, SC$H_3$), 1.45 (18H, s, C(C$H_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) **a** δ 192.6 (rotameric), 155.1 (2C), 143.5, 140.9, 136.2, 131.7, 129.9 (rotameric), 126.0, 123.9, 81.7 (rotameric), 81.4 (rotameric), 50.8 (rotameric), 28.1, 16.3; ν_{max} (neat) /cm^{-1} 3314, 2978, 2930, 1707, 1667; *m*/*z* HRMS (ESI) found [M+Na]$^+$, requires . Appendix page 409.

(*E*)-diethyl 1-(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)hydrazine-1,2-dicarboxylate



151

Prepared according to general procedure **D** using 2-methylthiobenzaldehyde (60 μL, 0.46 mmol, 1 equiv), alkyne **147** (103 mg, 0.24 mmol, 1.04 equiv.), [Rh(nbd)$_2$]BF_4 (17 mg, 10 mol %) and dcpm (19 mg, 10 mol %) in 3-pentanone (2.5 mL). After 10 minutes, the reaction was concentrated and purified by filtration through a pad of silica (10% EtOAc/hexane followed by 20% EtOAc/hexane) to obtain the title *compound* **151** (51 mg, 30%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* 7.0,

ArH), 7.46-7.43 (1H, m, ArH), 7.34 (1H, d, J 7.9, ArH), 7.21-7.18 (1H, m, ArH), 6.81 (2H, br s, C(O)CH=CH), 4.37 (2H, br s, CH=CHCH_2N), 4.18 (4H, q, J 7.1, OCH_2CH$_3$), 2.43 (3 H, s, SCH_3), 1.28-1.23 (6H, m, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 156.0, 142.5, 141.0, 136.0, 131.8, 129.9, 126.0, 124.0, 62.9, 62.2, 51.6 (rotameric), 30.3, 16.3, 14.5, 14.4; ν_{max} (neat) $/cm^{-1}$ 3294, 2982, 2922, 1709, 1666, 1620; m/z (ESI) 365.1 [M-H]$^-$;m/z HRMS (ESI) found 389.1137 [M+Na]$^+$, $C_{17}H_{22}N_2NaO_5S$ requires 389.1142. Appendix page 410.

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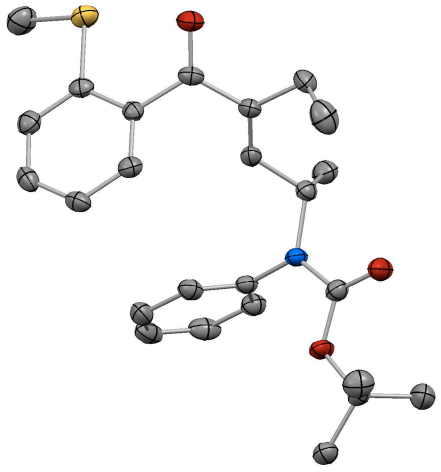
Chapter 8

Appendix

8.1 X-ray Crystallographic Data

8.1.1 (*E*)-*tert*-Butyl (4-(2-(methylthio)benzoyl)hex-3-en-2-yl)-(phenyl)carbamate, 89



Scheme 8.1: X-ray crystal structure of γ-amino enone **89**

Table 1. Crystal data and structure refinement for 001py10.

Identification code	001py10
Empirical formula	C25 H31 N O3 S
Formula weight	425.57
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 7.8873(2) A alpha = 90 deg. b = 34.1606(7) A beta = 110.6031(10) deg. c = 9.1299(2) A gamma = 90 deg.
Volume	2302.58(9) A^3
Z, Calculated density	4, 1.228 Mg/m^3
Absorption coefficient	0.166 mm^-1
F(000)	912
Crystal size	0.48 x 0.28 x 0.12 mm
Theta range for data collection	5.10 to 25.03 deg.
Limiting indices	-9<=h<=9, -39<=k<=40, -10<=l<=10
Reflections collected / unique	7226 / 3997 [R(int) = 0.0682]
Completeness to theta = 25.03	98.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0 and 0.907
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3997 / 0 / 277
Goodness-of-fit on F^2	0.964
Final R indices [I>2sigma(I)]	R1 = 0.0473, wR2 = 0.0772
R indices (all data)	R1 = 0.1310, wR2 = 0.0966
Extinction coefficient	0
Largest diff. peak and hole	0.203 and -0.306 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 001py10.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	-318(1)	2034(1)	8938(1)	38(1)
N(1)	1053(2)	822(1)	3172(2)	26(1)
O(1)	-546(2)	787(1)	550(2)	38(1)
O(2)	2511(2)	698(1)	1541(2)	33(1)
O(3)	-2579(2)	2023(1)	5680(2)	36(1)
C(1)	879(3)	770(1)	1641(3)	28(1)
C(2)	-613(3)	895(1)	3537(3)	25(1)
C(3)	-433(3)	1262(1)	4488(3)	26(1)
C(4)	-1662(3)	1545(1)	4249(3)	24(1)
C(5)	-1318(3)	1866(1)	5425(3)	25(1)
C(6)	-1087(3)	549(1)	4370(3)	35(1)
C(7)	-3463(3)	1547(1)	2911(3)	32(1)
C(8)	-3280(3)	1684(1)	1387(3)	47(1)
C(9)	2685(3)	629(1)	-2(2)	27(1)
C(10)	2125(3)	989(1)	-1024(3)	41(1)
C(11)	1629(3)	268(1)	-767(3)	40(1)
C(12)	4705(3)	557(1)	466(3)	34(1)
C(13)	2772(3)	790(1)	4437(3)	24(1)
C(14)	3365(3)	431(1)	5129(3)	30(1)
C(15)	4986(3)	406(1)	6378(3)	36(1)
C(16)	6015(3)	736(1)	6939(3)	38(1)
C(17)	5439(3)	1092(1)	6241(3)	35(1)
C(18)	3822(3)	1120(1)	4983(3)	29(1)
C(19)	590(3)	1994(1)	6291(3)	22(1)
C(20)	1183(3)	2083(1)	7904(3)	26(1)
C(21)	2972(3)	2201(1)	8629(3)	31(1)
C(22)	4137(3)	2229(1)	7800(3)	31(1)
C(23)	3549(3)	2149(1)	6221(3)	30(1)
C(24)	1781(3)	2033(1)	5485(3)	26(1)
C(25)	1217(3)	1996(1)	10938(3)	45(1)

Table 3. Bond lengths [A] and angles [deg] for 001py10.

S(1)-C(20)	1.763(2)
S(1)-C(25)	1.806(2)
N(1)-C(1)	1.367(3)
N(1)-C(13)	1.443(3)
N(1)-C(2)	1.486(2)
O(1)-C(1)	1.212(2)
O(2)-C(1)	1.345(3)
O(2)-C(9)	1.482(2)
O(3)-C(5)	1.223(2)
C(2)-C(3)	1.504(3)
C(2)-C(6)	1.522(3)
C(3)-C(4)	1.331(3)
C(4)-C(5)	1.492(3)
C(4)-C(7)	1.513(3)
C(5)-C(19)	1.498(3)
C(7)-C(8)	1.523(3)
C(9)-C(10)	1.512(3)
C(9)-C(11)	1.515(3)
C(9)-C(12)	1.517(3)
C(13)-C(14)	1.382(3)
C(13)-C(18)	1.384(3)
C(14)-C(15)	1.384(3)
C(15)-C(16)	1.380(3)
C(16)-C(17)	1.373(3)
C(17)-C(18)	1.387(3)
C(19)-C(24)	1.389(3)
C(19)-C(20)	1.412(3)
C(20)-C(21)	1.390(3)
C(21)-C(22)	1.384(3)
C(22)-C(23)	1.377(3)
C(23)-C(24)	1.377(3)

C(20)-S(1)-C(25)	102.16(11)
C(1)-N(1)-C(13)	122.44(18)
C(1)-N(1)-C(2)	118.19(18)
C(13)-N(1)-C(2)	119.30(16)
C(1)-O(2)-C(9)	120.33(17)
O(1)-C(1)-O(2)	125.8(2)
O(1)-C(1)-N(1)	124.3(2)
O(2)-C(1)-N(1)	109.8(2)
N(1)-C(2)-C(3)	110.94(19)
N(1)-C(2)-C(6)	111.95(19)
C(3)-C(2)-C(6)	110.49(18)
C(4)-C(3)-C(2)	126.5(2)
C(3)-C(4)-C(5)	118.5(2)
C(3)-C(4)-C(7)	124.0(2)
C(5)-C(4)-C(7)	117.4(2)
O(3)-C(5)-C(4)	120.4(2)
O(3)-C(5)-C(19)	120.3(2)
C(4)-C(5)-C(19)	119.4(2)
C(4)-C(7)-C(8)	112.02(19)
O(2)-C(9)-C(10)	110.65(19)
O(2)-C(9)-C(11)	110.34(18)
C(10)-C(9)-C(11)	112.6(2)
O(2)-C(9)-C(12)	101.38(16)
C(10)-C(9)-C(12)	110.9(2)
C(11)-C(9)-C(12)	110.5(2)
C(14)-C(13)-C(18)	119.6(2)
C(14)-C(13)-N(1)	120.4(2)
C(18)-C(13)-N(1)	120.0(2)
C(13)-C(14)-C(15)	119.9(3)

C(16)-C(15)-C(14)	120.4(3)
C(17)-C(16)-C(15)	119.8(2)
C(16)-C(17)-C(18)	120.1(3)
C(13)-C(18)-C(17)	120.1(2)
C(24)-C(19)-C(20)	119.6(2)
C(24)-C(19)-C(5)	119.3(2)
C(20)-C(19)-C(5)	121.09(19)
C(21)-C(20)-C(19)	117.9(2)
C(21)-C(20)-S(1)	122.20(18)
C(19)-C(20)-S(1)	119.92(17)
C(22)-C(21)-C(20)	121.1(2)
C(23)-C(22)-C(21)	121.0(2)
C(24)-C(23)-C(22)	118.6(2)
C(23)-C(24)-C(19)	121.8(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 001py10.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

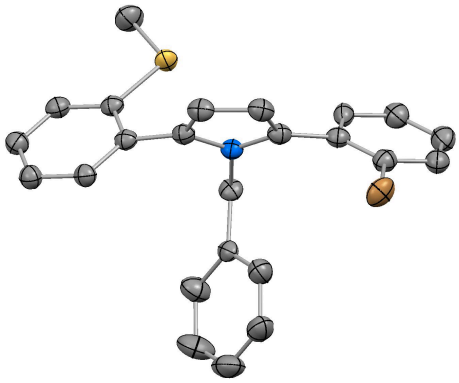
	U11	U22	U33	U23	U13	U12
S(1)	36(1)	51(1)	34(1)	-6(1)	20(1)	-1(1)
N(1)	20(1)	39(1)	20(1)	-3(1)	8(1)	5(1)
O(1)	26(1)	62(1)	23(1)	-6(1)	5(1)	6(1)
O(2)	25(1)	57(1)	20(1)	-6(1)	10(1)	6(1)
O(3)	27(1)	39(1)	45(1)	-5(1)	18(1)	4(1)
C(1)	29(2)	32(2)	25(2)	-3(1)	11(1)	2(1)
C(2)	19(1)	33(2)	22(1)	-1(1)	6(1)	3(1)
C(3)	22(1)	34(2)	22(1)	-4(1)	10(1)	-4(1)
C(4)	20(1)	28(2)	27(1)	-1(1)	11(1)	0(1)
C(5)	24(2)	27(2)	28(1)	6(1)	14(1)	4(1)
C(6)	36(2)	34(2)	40(2)	-5(1)	19(1)	0(1)
C(7)	21(1)	37(2)	34(2)	-4(1)	6(1)	0(1)
C(8)	41(2)	52(2)	40(2)	12(2)	4(1)	-3(2)
C(9)	28(2)	35(2)	19(1)	-2(1)	11(1)	1(1)
C(10)	46(2)	44(2)	37(2)	8(2)	17(1)	5(2)
C(11)	37(2)	43(2)	42(2)	-11(2)	17(1)	-7(2)
C(12)	31(2)	46(2)	30(2)	-5(1)	15(1)	0(1)
C(13)	21(1)	32(2)	21(1)	0(1)	11(1)	4(1)
C(14)	29(2)	37(2)	26(2)	1(1)	11(1)	5(1)
C(15)	33(2)	48(2)	30(2)	14(2)	14(1)	16(2)
C(16)	23(2)	71(2)	21(2)	1(2)	8(1)	6(2)
C(17)	26(2)	48(2)	32(2)	-8(2)	11(1)	-6(2)
C(18)	26(2)	34(2)	29(2)	2(1)	14(1)	1(1)
C(19)	21(1)	20(2)	26(1)	0(1)	8(1)	2(1)
C(20)	27(2)	23(2)	30(2)	1(1)	13(1)	5(1)
C(21)	33(2)	28(2)	31(2)	-2(1)	12(1)	2(1)
C(22)	22(1)	28(2)	37(2)	0(1)	5(1)	-3(1)
C(23)	23(2)	32(2)	37(2)	2(1)	14(1)	0(1)
C(24)	28(1)	27(2)	26(1)	1(1)	12(1)	4(1)
C(25)	49(2)	57(2)	31(2)	1(2)	18(1)	2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 001py10.

	x	y	z	U(eq)
H(2)	-1638	934	2524	30
H(3)	669	1296	5345	31
H(6A)	-1166	310	3751	53
H(6B)	-2254	596	4494	53
H(6C)	-145	516	5403	53
H(7A)	-4313	1722	3177	38
H(7B)	-3980	1279	2767	38
H(8A)	-2805	1952	1515	71
H(8B)	-4470	1678	550	71
H(8C)	-2447	1510	1115	71
H(10A)	810	1023	-1352	62
H(10B)	2468	957	-1950	62
H(10C)	2734	1220	-433	62
H(11A)	1967	49	-29	59
H(11B)	1907	202	-1702	59
H(11C)	328	320	-1065	59
H(12A)	5369	793	961	52
H(12B)	4994	493	-467	52
H(12C)	5058	338	1206	52
H(14)	2662	203	4748	36
H(15)	5392	159	6852	44
H(16)	7119	718	7805	46
H(17)	6149	1320	6621	42
H(18)	3434	1366	4496	34
H(21)	3403	2263	9713	37
H(22)	5360	2305	8328	37
H(23)	4347	2174	5652	36
H(24)	1364	1977	4396	31
H(25A)	2098	1787	11019	67
H(25B)	530	1935	11619	67
H(25C)	1855	2245	11262	67

Table 6. Torsion angles [deg] for 001py10.

8.1.2 1-Benzyl-2-(2-bromophenyl)-5-(2-(methylthio)phenyl)-1*H*-pyrrole, 140



Scheme 8.2: X-ray crystal structure of pyrrole **140**

Table 1. Crystal data and structure refinement for 005py10.

Identification code	005py10
Empirical formula	C24 H20 Br N S
Formula weight	434.38
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 35.5681(7) A alpha = 90 deg. b = 7.3083(2) A beta = 111.3180(9) deg. c = 16.5335(4) A gamma = 90 deg.
Volume	4003.69(17) A^3
Z, Calculated density	8, 1.441 Mg/m^3
Absorption coefficient	2.166 mm^-1
F(000)	1776
Crystal size	0.2 x 0.2 x 0.08 mm
Theta range for data collection	5.13 to 25.03 deg.
Limiting indices	-41<=h<=42, -7<=k<=8, -19<=l<=19
Reflections collected / unique	6283 / 3520 [R(int) = 0.0196]
Completeness to theta = 25.03	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0 and 0.853

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 005py10.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	1415(1)	3284(4)	3376(2)	26(1)
C(1)	1644(1)	3776(4)	2889(2)	27(1)
C(2)	1722(1)	5609(5)	3010(2)	32(1)
C(3)	1537(1)	6263(5)	3585(2)	32(1)
C(4)	1352(1)	4810(4)	3807(2)	29(1)
C(5)	1182(1)	1573(4)	3228(2)	30(1)
C(6)	789(1)	1671(5)	2453(2)	29(1)
C(7)	659(1)	149(6)	1926(3)	47(1)
C(8)	281(2)	151(7)	1253(3)	64(1)
C(9)	38(1)	1662(7)	1102(3)	56(1)
C(10)	165(1)	3179(7)	1613(3)	48(1)
C(11)	538(1)	3191(6)	2288(2)	41(1)
C(12)	1798(1)	2390(5)	2424(1)	27(1)
C(13)	2079(1)	1123(3)	2918(1)	28(1)
C(14)	2246(1)	-133(4)	2513(1)	32(1)
C(15)	2132(1)	-121(4)	1615(1)	34(1)
C(16)	1850(1)	1145(4)	1121(1)	33(1)
C(17)	1683(1)	2401(6)	1526(1)	30(1)
S(1)	2218(1)	1213(2)	4066(1)	31(1)
C(24)	2625(1)	-396(6)	4450(3)	45(1)
C(112)	1822(11)	2320(40)	2510(7)	29(2)
C(113)	2108(4)	952(16)	2849(7)	29(2)
C(114)	2223(8)	-160(40)	2296(8)	30(2)
C(115)	2052(9)	100(40)	1403(8)	31(2)
C(116)	1766(9)	1470(40)	1064(7)	32(2)
C(117)	1651(13)	2580(50)	1617(8)	31(2)
Br(11)	2340(2)	607(7)	4063(3)	44(1)
C(18)	1164(1)	4607(4)	4495(2)	30(1)
C(19)	858(1)	5739(3)	4542(1)	34(1)
C(20)	706(1)	5489(4)	5198(2)	37(1)
C(21)	858(1)	4106(5)	5806(2)	40(1)
C(22)	1164(1)	2973(4)	5760(2)	39(1)
C(23)	1316(1)	3224(5)	5104(2)	32(1)
Br(1)	635(1)	7652(1)	3738(1)	44(1)
C(118)	1240(8)	4400(40)	4592(15)	32(2)
C(119)	912(4)	5550(20)	4466(7)	34(2)
C(120)	677(6)	5340(40)	4972(15)	37(2)
C(121)	769(8)	3990(40)	5605(17)	38(2)
C(122)	1097(9)	2840(40)	5731(15)	36(2)
C(123)	1332(10)	3040(40)	5224(18)	31(2)
S(11)	792(3)	7283(13)	3659(5)	31(1)
C(124)	363(8)	8300(50)	3810(30)	45(1)

Table 3. Bond lengths [A] and angles [deg] for 005py10.

N(1)-C(4)	1.385(4)
N(1)-C(1)	1.386(4)
N(1)-C(5)	1.471(4)
C(1)-C(2)	1.368(5)
C(1)-C(112)	1.488(9)
C(1)-C(12)	1.490(4)
C(2)-C(3)	1.422(5)
C(3)-C(4)	1.369(5)
C(4)-C(118)	1.520(10)
C(4)-C(18)	1.522(4)
C(5)-C(6)	1.516(4)
C(6)-C(7)	1.385(5)
C(6)-C(11)	1.388(5)
C(7)-C(8)	1.397(6)
C(8)-C(9)	1.370(7)
C(9)-C(10)	1.367(7)
C(10)-C(11)	1.390(5)
C(12)-C(13)	1.3900
C(12)-C(17)	1.3900
C(13)-C(14)	1.3900
C(13)-S(1)	1.7806(19)
C(14)-C(15)	1.3900
C(15)-C(16)	1.3900
C(16)-C(17)	1.3900
S(1)-C(24)	1.792(4)
C(112)-C(113)	1.3900
C(112)-C(117)	1.3900
C(113)-C(114)	1.3900
C(113)-Br(11)	1.889(10)
C(114)-C(115)	1.3900
C(115)-C(116)	1.3900
C(116)-C(117)	1.3900
C(18)-C(19)	1.3900
C(18)-C(23)	1.3900
C(19)-C(20)	1.3900
C(19)-Br(1)	1.893(2)
C(20)-C(21)	1.3900
C(21)-C(22)	1.3900
C(22)-C(23)	1.3900
C(118)-C(119)	1.3900
C(118)-C(123)	1.3900
C(119)-C(120)	1.3900
C(119)-S(11)	1.777(10)
C(120)-C(121)	1.3900
C(121)-C(122)	1.3900
C(122)-C(123)	1.3900
S(11)-C(124)	1.796(11)

C(4)-N(1)-C(1)	109.3(3)
C(4)-N(1)-C(5)	125.7(3)
C(1)-N(1)-C(5)	122.6(3)
C(2)-C(1)-N(1)	107.5(3)
C(2)-C(1)-C(112)	131.8(19)
N(1)-C(1)-C(112)	119.3(17)
C(2)-C(1)-C(12)	130.4(3)
N(1)-C(1)-C(12)	121.8(3)
C(112)-C(1)-C(12)	5.6(5)
C(1)-C(2)-C(3)	108.0(3)
C(4)-C(3)-C(2)	107.7(3)
C(3)-C(4)-N(1)	107.6(3)
C(3)-C(4)-C(118)	133.3(14)

N(1)-C(4)-C(118)	114.9(11)
C(3)-C(4)-C(18)	131.5(3)
N(1)-C(4)-C(18)	120.2(3)
C(118)-C(4)-C(18)	11.3(7)
N(1)-C(5)-C(6)	113.0(3)
C(7)-C(6)-C(11)	118.4(3)
C(7)-C(6)-C(5)	119.2(3)
C(11)-C(6)-C(5)	122.2(3)
C(6)-C(7)-C(8)	120.3(4)
C(9)-C(8)-C(7)	120.4(4)
C(10)-C(9)-C(8)	119.8(4)
C(9)-C(10)-C(11)	120.4(4)
C(6)-C(11)-C(10)	120.7(4)
C(13)-C(12)-C(17)	120.0
C(13)-C(12)-C(1)	118.10(18)
C(17)-C(12)-C(1)	121.80(18)
C(12)-C(13)-C(14)	120.0
C(12)-C(13)-S(1)	117.56(12)
C(14)-C(13)-S(1)	122.43(12)
C(15)-C(14)-C(13)	120.0
C(14)-C(15)-C(16)	120.0
C(17)-C(16)-C(15)	120.0
C(16)-C(17)-C(12)	120.0
C(13)-S(1)-C(24)	103.24(17)
C(113)-C(112)-C(117)	120.0
C(113)-C(112)-C(1)	134.8(6)
C(117)-C(112)-C(1)	105.2(6)
C(112)-C(113)-C(114)	120.0
C(112)-C(113)-Br(11)	119.9(4)
C(114)-C(113)-Br(11)	120.1(4)
C(115)-C(114)-C(113)	120.0
C(114)-C(115)-C(116)	120.0
C(117)-C(116)-C(115)	120.0
C(116)-C(117)-C(112)	120.0
C(19)-C(18)-C(23)	120.0
C(19)-C(18)-C(4)	123.23(18)
C(23)-C(18)-C(4)	116.77(18)
C(18)-C(19)-C(20)	120.0
C(18)-C(19)-Br(1)	122.57(13)
C(20)-C(19)-Br(1)	117.43(13)
C(21)-C(20)-C(19)	120.0
C(20)-C(21)-C(22)	120.0
C(21)-C(22)-C(23)	120.0
C(22)-C(23)-C(18)	120.0
C(119)-C(118)-C(123)	120.0
C(119)-C(118)-C(4)	102.6(7)
C(123)-C(118)-C(4)	136.0(7)
C(118)-C(119)-C(120)	120.0
C(118)-C(119)-S(11)	120.3(4)
C(120)-C(119)-S(11)	119.7(4)
C(121)-C(120)-C(119)	120.0
C(120)-C(121)-C(122)	120.0
C(123)-C(122)-C(121)	120.0
C(122)-C(123)-C(118)	120.0
C(119)-S(11)-C(124)	100.1(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 005py10.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	26(1)	23(1)	27(1)	0(1)	9(1)	-3(1)
C(1)	26(2)	29(2)	25(2)	3(1)	7(1)	-1(1)
C(2)	33(2)	28(2)	32(2)	6(1)	9(1)	-5(1)
C(3)	34(2)	26(2)	33(2)	1(1)	7(1)	-1(1)
C(4)	27(2)	26(2)	30(2)	0(1)	7(1)	0(1)
C(5)	32(2)	25(2)	34(2)	0(1)	14(1)	-8(1)
C(6)	27(2)	36(2)	26(2)	0(1)	13(1)	-8(1)
C(7)	50(2)	40(2)	43(2)	-8(2)	8(2)	-1(2)
C(8)	62(3)	62(3)	50(3)	-14(2)	-1(2)	-17(2)
C(9)	38(2)	76(3)	42(2)	0(2)	1(2)	-9(2)
C(10)	34(2)	66(3)	41(2)	4(2)	11(2)	9(2)
C(11)	40(2)	44(2)	37(2)	-5(2)	13(2)	2(2)
C(12)	26(1)	27(1)	28(1)	2(1)	10(1)	-4(1)
C(13)	25(1)	28(1)	30(1)	2(1)	10(1)	-4(1)
C(14)	28(1)	31(2)	35(2)	1(1)	10(1)	-2(1)
C(15)	33(2)	33(2)	36(2)	-2(1)	13(1)	-1(1)
C(16)	34(2)	35(2)	31(1)	0(1)	13(1)	-1(1)
C(17)	31(2)	32(2)	29(1)	2(1)	11(1)	-1(1)
S(1)	28(1)	34(1)	26(1)	2(1)	5(1)	10(1)
C(24)	40(2)	44(2)	45(2)	5(2)	9(2)	12(2)
C(112)	28(2)	29(2)	29(2)	1(2)	11(2)	-3(2)
C(113)	27(2)	29(2)	30(2)	1(2)	9(2)	-2(2)
C(114)	28(2)	30(2)	31(2)	0(2)	11(2)	-2(2)
C(115)	32(3)	32(3)	31(3)	0(2)	12(2)	-1(2)
C(116)	32(3)	33(3)	31(3)	2(2)	11(2)	-1(2)
C(117)	30(2)	31(2)	30(2)	1(2)	11(2)	-2(2)
Br(11)	39(1)	34(1)	61(1)	10(1)	20(1)	11(1)
C(18)	28(2)	28(2)	31(2)	-2(1)	8(1)	-4(1)
C(19)	31(1)	31(2)	37(2)	-3(1)	11(1)	-2(1)
C(20)	36(2)	39(2)	40(2)	-6(2)	16(1)	-5(1)
C(21)	40(2)	42(2)	39(2)	-3(2)	18(1)	-6(2)
C(22)	42(2)	39(2)	38(2)	0(1)	16(1)	-5(2)
C(23)	32(1)	33(2)	36(2)	-10(1)	19(1)	-7(1)
Br(1)	39(1)	34(1)	61(1)	10(1)	20(1)	11(1)
C(118)	31(2)	32(2)	35(2)	-5(2)	14(2)	-3(2)
C(119)	33(2)	34(2)	36(2)	-3(2)	12(2)	-3(2)
C(120)	36(2)	37(2)	38(2)	-3(2)	14(2)	-3(2)
C(121)	38(2)	39(2)	38(2)	-3(2)	16(2)	-4(2)
C(122)	37(2)	37(2)	36(2)	-3(2)	16(2)	-5(2)
C(123)	33(2)	32(2)	33(2)	-3(2)	16(2)	-5(2)
S(11)	28(1)	34(1)	26(1)	2(1)	5(1)	10(1)
C(124)	40(2)	44(2)	45(2)	5(2)	9(2)	12(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 005py10.

	x	y	z	U(eq)
H(2)	1873	6319	2754	38
H(3)	1542	7488	3780	39
H(5A)	1122	1281	3753	35
H(5B)	1348	566	3136	35
H(7)	826	-902	2022	57
H(8)	194	-902	897	77
H(9)	-219	1656	645	67
H(10)	-3	4231	1506	57
H(11)	622	4251	2641	49
H(14)	2439	-999	2851	38
H(15)	2246	-979	1338	41
H(16)	1772	1153	507	40
H(17)	1491	3267	1189	37
H(24A)	2526	-1618	4230	67
H(24B)	2730	-413	5087	67
H(24C)	2840	-37	4245	67
H(114)	2418	-1091	2529	36
H(115)	2131	-655	1025	38
H(116)	1650	1648	453	38
H(117)	1456	3514	1385	37
H(20)	497	6263	5230	45
H(21)	754	3934	6254	48
H(22)	1268	2028	6176	47
H(23)	1525	2450	5072	38
H(120)	453	6129	4886	45
H(121)	609	3849	5951	46
H(122)	1160	1912	6163	43
H(123)	1556	2256	5311	37
H(12A)	182	7340	3866	67
H(12B)	219	9084	3315	67
H(12C)	455	9044	4344	67

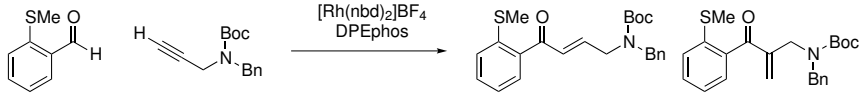
Table 6. Torsion angles [deg] for 005py10.

8.2 Design of Experiments Data

The following data were gathered for the design of experiments screens in chapter 5. The design was made using Stat-Ease, Inc, Design-Expert® (Version 7.1.3). The experiment running order was randomised to standardise the experimental errors arising from non-specific and environmental effects.

The reactions were carried out using 0.1 mmol of 2-(methylthio)benzaldehyde and the alkyne **68** was scaled accordingly. Three stock mixtures of the starting materials were made (containing 2:1, 1:1.25, and 1:2 of aldehyde:alkyne). To carry out the reaction, the rhodium source and ligand were weighed into microwave vials which were then purged with nitrogen. The appropriate amount of solvent (e.g. 0.2, 0.85, or 1.50 mL) was added and the catalyst dissolved by stirring and sonication (under 20 seconds). The mixture of starting materials was then injected by micro syringe and the vial placed in a preheated aluminium heating block or oil bath set at the appropriate temperature. The temperature was verified by a thermometer placed in a dummy microwave vial containing solvent and a stirrer. At the end of the reaction time, the reaction was cooled and Et_2O (15 mL) added to precipitate the catalyst. The mixture was then filtered and the solvents removed under reduced pressure and the resulting residue analysed by ^{1}H NMR Spectroscopy on a DPX400 spectrometer.

8.2.1 Initial Resolution IV Design and Results



Run	Solvent	Volume mL	Equiv. rel. aldehyde	Temp. °C	Cat. %	Time hours	Conv. %	Lin:bra
1	Acetone	0.20	0.50	20.00	2.00	1.00	0	–
2	DCE	1.50	2.00	55.00	20.00	16.00	100	1.90
3	DCE	0.85	1.25	37.50	11.00	8.50	20	1.66
4	DCE	0.85	1.25	37.50	11.00	8.50	19	2.07
5	DCE	0.20	0.50	55.00	2.00	16.00	9	1.07
6	DCE	0.20	2.00	55.00	20.00	1.00	25	1.49
7	Acetone	1.50	0.50	55.00	20.00	1.00	24	2.76
8	DCE	1.50	0.50	55.00	2.00	1.00	3	1.63
9	Acetone	0.20	2.00	55.00	2.00	1.00	0	–
10	Acetone	0.85	1.25	37.50	11.00	8.50	25	1.79
11	DCE	1.50	0.50	20.00	20.00	16.00	55	4.92
12	Acetone	0.20	0.50	55.00	20.00	16.00	63	0.62
13	Acetone	0.85	1.25	37.50	11.00	8.50	30	1.98
14	DCE	1.50	2.00	20.00	2.00	1.00	0	–
15	Acetone	0.85	1.25	37.50	11.00	8.50	22	2.54
16	Acetone	0.20	2.00	20.00	20.00	16.00	16	3.63
17	DCE	0.20	0.50	20.00	20.00	1.00	7	7.83
18	DCE	0.20	2.00	20.00	2.00	16.00	4	6.33
19	Acetone	1.50	0.50	20.00	2.00	16.00	2	> 20
20	Acetone	1.50	2.00	20.00	20.00	1.00	8	12.50
21	DCE	0.85	1.25	37.50	11.00	8.50	25	2.68
22	Acetone	1.50	2.00	55.00	2.00	16.00	23	1.4

Table 8.1: Initial DoE Screen

8.2.2 Diagnostics for Resolution IV Design, Conversion

Use your mouse to right click on individual cells for definitions.
Response 1 Conversion
Hierarchical Terms Added after Manual Regression
B

ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	11738.17	11	1067.11	45.51	< 0.0001	significant
A-Solvent vol	517.56	1	517.56	22.07	0.0015	
B-equiv	10.56	1	10.56	0.45	0.5210	
C-Temp	1501.56	1	1501.56	64.04	< 0.0001	
D-Cat loading	4128.06	1	4128.06	176.05	< 0.0001	
E-Time	2626.56	1	2626.56	112.02	< 0.0001	
F-Solvent	280.56	1	280.56	11.97	0.0086	
AB	410.06	1	410.06	17.49	0.0031	
AD	232.56	1	232.56	9.92	0.0136	
AE	451.56	1	451.56	19.26	0.0023	
AF	1139.06	1	1139.06	48.58	0.0001	
BF	588.06	1	588.06	25.08	0.0010	
Curvature	199.52	2	99.76	4.25	0.0551	not significant
Residual	187.58	8	23.45			
Lack of Fit	134.25	4	33.56	2.52	0.1965	not significant
Pure Error	53.33	4	13.33			
Cor Total	12125.27	21				

The Model F-value of 45.51 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, C, D, E, F, AB, AD, AE, AF, BF are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy model reduction may improve your model.

The "Curvature F-value" of 4.25 implies there is curvature (as measured by difference between the average of the center points and the average of the factorial points) in the design space There is only a 5.51% chance that a "Curvature F-value" this large could occur due to noise.

The "Lack of Fit F-value" of 2.52 implies the Lack of Fit is not significant relative to the error. There is a 19.65% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Std. Dev.	4.84	R-Squared	0.9843
Mean	21.82	Adj R-Squared	0.9626
C.V. %	22.19	Pred R-Squared	0.8098
PRESS	2268.00	Adeq Precision	26.017

The "Pred R-Squared" of 0.8098 is in reasonable agreement with the "Adj R-Squared" of 0.9626.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Y ratio of 26.017 indicates an adequate signal. This model can be used to navigate the design

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	21.19	1	1.21	18.40	23.98	
A-Solvent vol	5.69	1	1.21	2.90	8.48	1.00
B-equiv	0.81	1	1.21	-1.98	3.60	1.00
C-Temp	9.69	1	1.21	6.90	12.48	1.00

D-Cat loading	16.06	1	1.21	13.27	18.85	1.00
E-Time	12.81	1	1.21	10.02	15.60	1.00
F-Solvent	4.19	1	1.21	1.40	6.98	1.38
AB	5.06	1	1.21	2.27	7.85	1.00
AD	3.81	1	1.21	1.02	6.60	1.00
AE	5.31	1	1.21	2.52	8.10	1.00
AF	8.44	1	1.21	5.65	11.23	1.00
BF	6.06	1	1.21	3.27	8.85	1.00
Ctr Pt F[1]	8.67	1	3.28	1.11	16.23	1.19
Ctr Pt F[2]	-4.04	1	3.28	-11.60	3.52	

Final Equation in Terms of Coded Factors:

```
Conversion   =
+21.19
+5.69    * A
+0.81    * B
+9.69    * C
+16.06   * D
+12.81   * E
+4.19    * F
+5.06    * A * B
+3.81    * A * D
+5.31    * A * E
+8.44    * A * F
+6.06    * B * F
```

Final Equation in Terms of Actual Factors:

```
Solvent Acetone
Conversion   =
-0.56502
-33.64316    * Solvent vol
-15.82692    * equiv
+0.55357     * Temp
+1.23077     * Cat loading
+0.78205     * Time
+10.38462    * Solvent vol * equiv
+0.65171     * Solvent vol * Cat loading
+1.08974     * Solvent vol * Time

Solvent DCE
Conversion   =
-34.46566
-7.68162     * Solvent vol
+0.33974     * equiv
+0.55357     * Temp
+1.23077     * Cat loading
+0.78205     * Time
+10.38462    * Solvent vol * equiv
+0.65171     * Solvent vol * Cat loading
+1.08974     * Solvent vol * Time
```

The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.
In the Diagnostics Node, Select Case Statistics from the View Menu.

Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:
1) Normal probability plot of the studentized residuals to check for normality of residual

8.2.3 Diagnostics for Resolution IV Design, Selectivity

Use your mouse to right click on individual cells for definitions.
Response 2 Linear xs
Hierarchical Terms Added after Manual Regression
BF

ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	437.33	15	29.16	140.35	0.0001	significant
A-Solvent vol	36.42	1	36.42	175.33	0.0002	
B-equiv	8.38	1	8.38	40.35	0.0031	
C-Temp	122.88	1	122.88	591.51	< 0.0001	
D-Cat loading	1.70	1	1.70	8.20	0.0458	
E-Time	11.66	1	11.66	56.14	0.0017	
F-Solvent	15.48	1	15.48	74.54	0.0010	
AB	14.90	1	14.90	71.72	0.0011	
AC	14.29	1	14.29	68.78	0.0012	
AD	3.17	1	3.17	15.25	0.0175	
AE	5.06	1	5.06	24.37	0.0078	
AF	103.43	1	103.43	497.89	< 0.0001	
BD	21.07	1	21.07	101.42	0.0005	
BF	9.000E-004	1	9.000E-004	4.332E-003	0.9507	
ABD	78.94	1	78.94	380.02	< 0.0001	
ABF	4.31	1	4.31	20.73	0.0104	
Curvature	22.00	2	11.00	52.94	0.0013	significant
Pure Error	0.83	4	0.21			
Cor Total	460.16	21				

The Model F-value of 140.35 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, C, D, E, F, AB, AC, AD, AE, AF, BD, ABD, ABF are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy model reduction may improve your model.

The "Curvature F-value" of 52.94 implies there is significant curvature (as measured by difference between the average of the center points and the average of the factorial points) the design space. There is only a 0.13% chance that a "Curvature F-value" this large could occur due to noise.

Std. Dev.	0.46	R-Squared	0.9981
Mean	3.58	Adj R-Squared	0.9910
C.V. %	12.72	Pred R-Squared	N/A
PRESS	N/A	Adeq Precision	48.512

Case(s) with leverage of 1.0000: Pred R-Squared and PRESS statistic not defined

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Y ratio of 48.512 indicates an adequate signal. This model can be used to navigate the design

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	4.13	1	0.11	3.81	4.45	
A-Solvent vol	1.51	1	0.11	1.19	1.83	1.00
B-equiv	-0.72	1	0.11	-1.04	-0.41	1.00
C-Temp	-2.77	1	0.11	-3.09	-2.45	1.00
D-Cat loading	0.33	1	0.11	9.890E-003	0.64	1.00
E-Time	0.85	1	0.11	0.54	1.17	1.00

F-Solvent	-0.98	1	0.11	-1.30	-0.67	1.38
AB	-0.97	1	0.11	-1.28	-0.65	1.00
AC	-0.95	1	0.11	-1.26	-0.63	1.00
AD	-0.45	1	0.11	-0.76	-0.13	1.00
AE	0.56	1	0.11	0.25	0.88	1.00
AF	-2.54	1	0.11	-2.86	-2.23	1.00
BD	1.15	1	0.11	0.83	1.46	1.00
BF	7.500E-003	1	0.11	-0.31	0.32	1.00
ABD	2.22	1	0.11	1.90	2.54	1.00
ABF	0.52	1	0.11	0.20	0.84	1.00
Ctr Pt F[1]	-3.01	1	0.31	-3.87	-2.15	1.19
Ctr Pt F[2]	-1.01	1	0.31	-1.87	-0.15	

Final Equation in Terms of Coded Factors:

```
Linear xs    =
+4.13
+1.51    * A
-0.72    * B
-2.77    * C
+0.33    * D
+0.85    * E
-0.98    * F
-0.97    * A * B
-0.95    * A * C
-0.45    * A * D
+0.56    * A * E
-2.54    * A * F
+1.15    * B * D
+7.500E-003  * B * F
+2.22    * A * B * D
+0.52    * A * B * F
```

Final Equation in Terms of Actual Factors:

```
Solvent Acetone
Linear xs    =
-3.73221
+19.96973    * Solvent vol
+4.47566     * equiv
-0.087742    * Temp
+0.42632     * Cat loading
+0.015756    * Time
-8.61254     * Solvent vol * equiv
-0.083077    * Solvent vol * Temp
-0.70890     * Solvent vol * Cat loading
+0.11538     * Solvent vol * Time
-0.26033     * equiv * Cat loading
+0.50627     * Solvent vol * equiv * Cat loading

Solvent DCE
Linear xs    =
+3.18612
+9.48640     * Solvent vol
+2.68668     * equiv
-0.087742    * Temp
+0.42632     * Cat loading
+0.015756    * Time
-6.48433     * Solvent vol * equiv
```

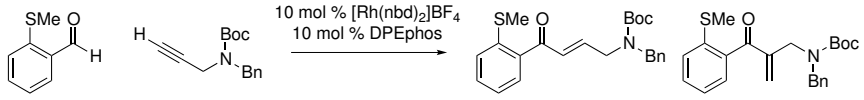
```
-0.083077     * Solvent vol * Temp
-0.70890      * Solvent vol * Cat loading
+0.11538      * Solvent vol * Time
-0.26033      * equiv * Cat loading
+0.50627      * Solvent vol * equiv * Cat loading


 The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.
 In the Diagnostics Node, Select Case Statistics from the View Menu.

Proceed to Diagnostic Plots (the next icon in progression).  Be sure to look at the:
   1) Normal probability plot of the studentized residuals to check for normality of residual
   2) Studentized residuals versus predicted values to check for constant error.
   3) Externally Studentized Residuals to look for outliers, i.e., influential values.
   4) Box-Cox plot for power transformations.

If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon
```

8.2.4 Focused Resolution V Screen and Results



Run	Solvent	Volume mL	Equiv. rel. aldehyde	Temp. °C	Conv. %	Lin:bra
1	DCE	2.50	2.00	80.0	60	2.18
2	3-pentanone	1.35	1.25	67.5	57	1.98
3	DCE	1.35	1.25	67.5	78	2.18
4	DCE	0.20	2.00	80.0	91	1.43
5	3-pentanone	0.20	2.00	80.0	65	1.60
6	3-pentanone	2.50	2.00	55.0	60	2.34
7	3-pentanone	1.35	1.25	67.5	65	1.79
8	DCE	1.35	1.25	67.5	65	1.85
9	DCE	1.35	1.25	67.5	57	2.85
10	3-pentanone	0.20	0.50	55.0	78	1.88
11	3-pentanone	0.20	0.50	80.0	78	0.70
12	DCE	0.20	2.00	55.0	58	1.95
13	3-pentanone	2.50	2.00	80.0	84	1.59
14	3-pentanone	2.50	0.50	55.0	95	2.61
15	3-pentanone	2.50	0.50	80.0	95	1.26
16	DCE	0.20	0.50	55.0	95	1.36
17	DCE	0.20	0.50	80.0	80	0.46
18	3-pentanone	1.35	1.25	67.5	63	1.63
19	3-pentanone	0.20	2.00	55.0	21	2.36
20	DCE	2.50	2.00	55.0	35	2.22
21	DCE	2.50	0.50	55.0	95	1.87
22	DCE	2.50	0.50	80.0	95	1.38

Table 8.2: Initial DoE Screen

8.2.5 Diagnostics for Resolution V Design, Conversion

Use your mouse to right click on individual cells for definitions.
Response 1 Yield/conversion
ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	7544.73	9	838.30	17.75	< 0.0001	significant
A-Solvent	68.06	1	68.06	1.44	0.2576	
B-Solvent Volume	175.56	1	175.56	3.72	0.0827	
C-Equiv	3510.56	1	3510.56	74.34	< 0.0001	
D-Temp	770.06	1	770.06	16.31	0.0024	
AB	1072.56	1	1072.56	22.71	0.0008	
AC	1.56	1	1.56	0.033	0.8593	
BC	126.56	1	126.56	2.68	0.1326	
CD	1242.56	1	1242.56	26.31	0.0004	
ABC	540.56	1	540.56	11.45	0.0070	
Curvature	428.16	2	214.08	4.53	0.0397	significant
Residual	472.21	10	47.22			
Lack of Fit	212.88	6	35.48	0.55	0.7574	not significant
Pure Error	259.33	4	64.83			
Cor Total	8445.09	21				

The Model F-value of 17.75 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case C, D, AB, CD, ABC are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The "Curvature F-value" of 4.53 implies there is significant curvature (as measured by difference between the average of the center points and the average of the factorial points) in the design space. There is only a 3.97% chance that a "Curvature F-value" this large could occur due to noise.

The "Lack of Fit F-value" of 0.55 implies the Lack of Fit is not significant relative to the pu error. There is a 75.74% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Std. Dev.	6.87	R-Squared	0.9411
Mean	71.36	Adj R-Squared	0.8881
C.V. %	9.63	Pred R-Squared	0.7384
PRESS	2097.28	Adeq Precision	13.719

The "Pred R-Squared" of 0.7384 is in reasonable agreement with the "Adj R-Squared" of 0.8881.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. You ratio of 13.719 indicates an adequate signal. This model can be used to navigate the design sp

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	74.06	1	1.72	70.23	77.89	
A-Solvent	-2.06	1	1.72	-5.89	1.77	1.37
B-Solvent Volume	3.31	1	1.72	-0.52	7.14	1.00
C-Equiv	-14.81	1	1.72	-18.64	-10.98	1.00
D-Temp	6.94	1	1.72	3.11	10.77	1.00
AB	8.19	1	1.72	4.36	12.02	1.00
AC	0.31	1	1.72	-3.52	4.14	1.00
BC	-2.81	1	1.72	-6.64	1.02	1.00
CD	8.81	1	1.72	4.98	12.64	1.00
ABC	5.81	1	1.72	1.98	9.64	1.00
Ctr Pt A[1]	-9.46	1	4.65	-19.82	0.91	1.19
Ctr Pt A[2]	-10.33	1	4.65	-20.70	0.032	

Final Equation in Terms of Coded Factors:

```
Yield/conversion     =
+74.06
-2.06    * A
+3.31    * B
-14.81   * C
+6.94    * D
+8.19    * A * B
+0.31    * A * C
-2.81    * B * C
+8.81    * C * D
+5.81    * A * B * C
```

Final Equation in Terms of Actual Factors:

```
Solvent DCE
Yield/conversion     =
+132.03116
+8.26087     * Solvent Volume
-70.11667    * Equiv
-0.62000     * Temp
-10.00000    * Solvent Volume * Equiv
+0.94000     * Equiv * Temp

Solvent pentanone
Yield/conversion     =
+130.38623
+5.65217     * Solvent Volume
-87.47899    * Equiv
-0.62000     * Temp
+3.47826     * Solvent Volume * Equiv
+0.94000     * Equiv * Temp
```

The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.
In the Diagnostics Node, Select Case Statistics from the View Menu.

Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:
1) Normal probability plot of the studentized residuals to check for normality of residuals.
2) Studentized residuals versus predicted values to check for constant error.
3) Externally Studentized Residuals to look for outliers, i.e., influential values.
4) Box-Cox plot for power transformations.

If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon.

8.2.6 Diagnostics for Resolution V Design, Selectivity

Use your mouse to right click on individual cells for definitions.
Response 2 Linear xs
ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	4.18	3	1.39	11.99	0.0002	significant
B-Solvent Volume	0.86	1	0.86	7.40	0.0145	
C-Equiv	1.08	1	1.08	9.26	0.0073	
D-Temp	2.24	1	2.24	19.30	0.0004	
Curvature	0.63	1	0.63	5.44	0.0322	significant
Residual	1.98	17	0.12			
Lack of Fit	1.44	13	0.11	0.82	0.6508	not significant
Pure Error	0.54	4	0.13			
Cor Total	6.79	21				

The Model F-value of 11.99 implies the model is significant. There is only a 0.02% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case B, C, D are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy model reduction may improve your model.

The "Curvature F-value" of 5.44 implies there is significant curvature (as measured by difference between the average of the center points and the average of the factorial points) the design space. There is only a 3.22% chance that a "Curvature F-value" this large could occur due to noise.

The "Lack of Fit F-value" of 0.82 implies the Lack of Fit is not significant relative to the error. There is a 65.08% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Std. Dev.	0.34	R-Squared	0.6790
Mean	1.80	Adj R-Squared	0.6224
C.V. %	18.90	Pred R-Squared	0.4740
PRESS	3.24	Adeq Precision	10.653

The "Pred R-Squared" of 0.4740 is in reasonable agreement with the "Adj R-Squared" of 0.6224.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Y ratio of 10.653 indicates an adequate signal. This model can be used to navigate the design

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	1.70	1	0.085	1.52	1.88	
B-Solvent Volume	0.23	1	0.085	0.052	0.41	1.00
C-Equiv	0.26	1	0.085	0.080	0.44	1.00
D-Temp	-0.37	1	0.085	-0.55	-0.19	1.00
Center Point	0.38	1	0.16	0.036	0.72	1.00

Final Equation in Terms of Coded Factors:

Linear xs =
+1.70
+0.23 * B
+0.26 * C
-0.37 * D

Final Equation in Terms of Actual Factors:

```
Linear xs    =
+3.01651
+0.20163     * Solvent Volume
+0.34583     * Equiv
-0.029950    * Temp
```

The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.
In the Diagnostics Node, Select Case Statistics from the View Menu.

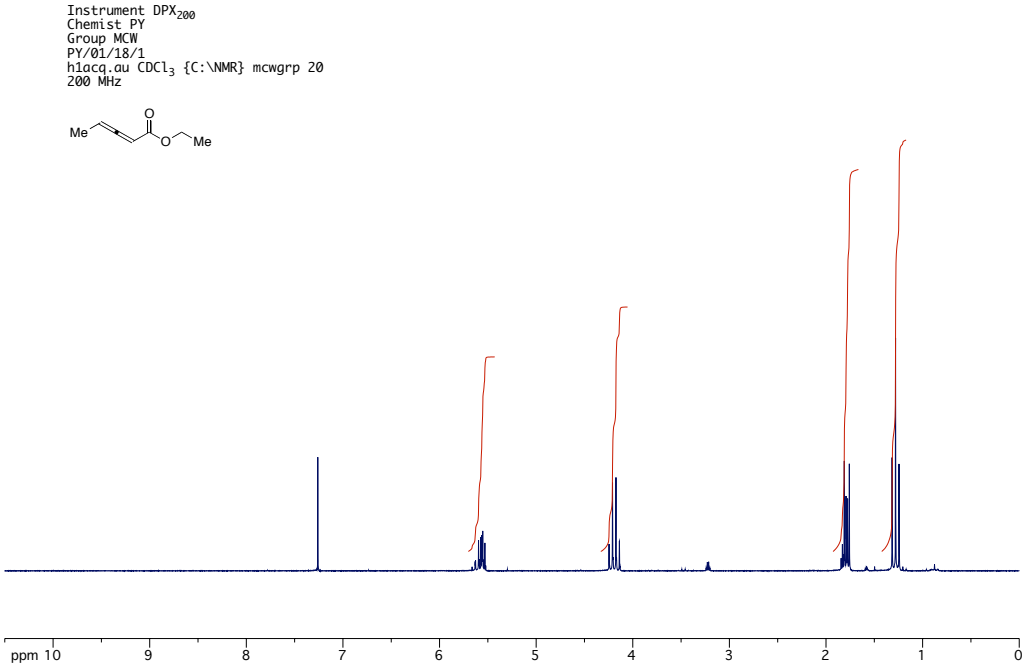
Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:

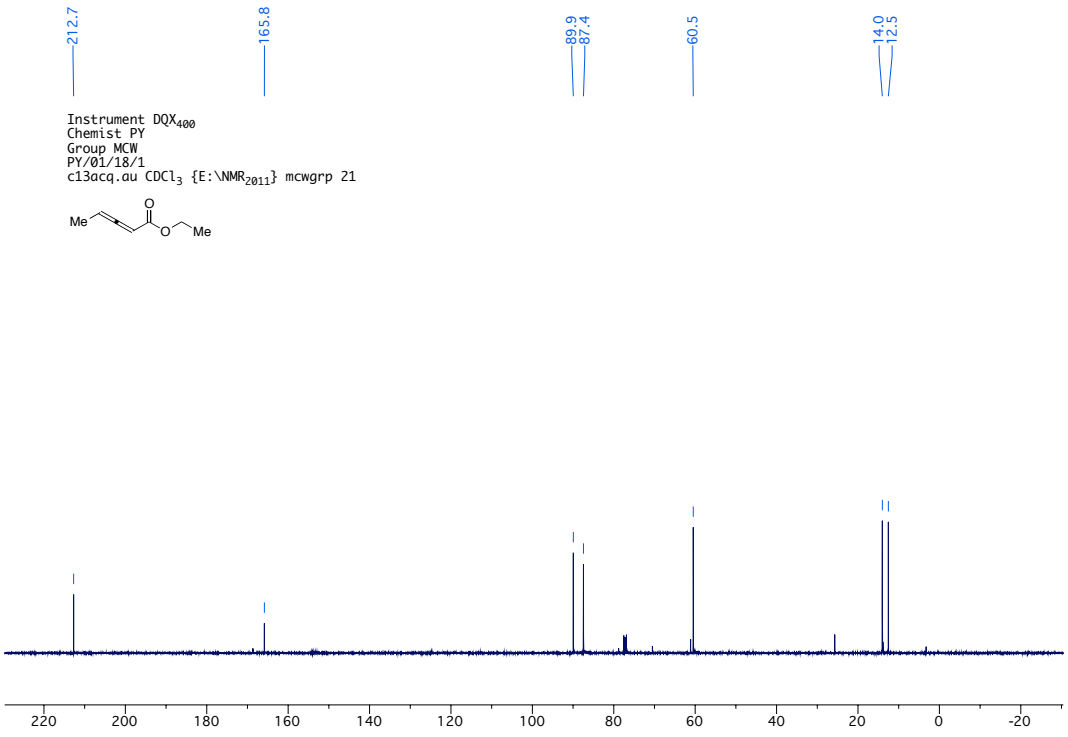
1) Normal probability plot of the studentized residuals to check for normality of residual
2) Studentized residuals versus predicted values to check for constant error.
3) Externally Studentized Residuals to look for outliers, i.e., influential values.
4) Box-Cox plot for power transformations.

If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon

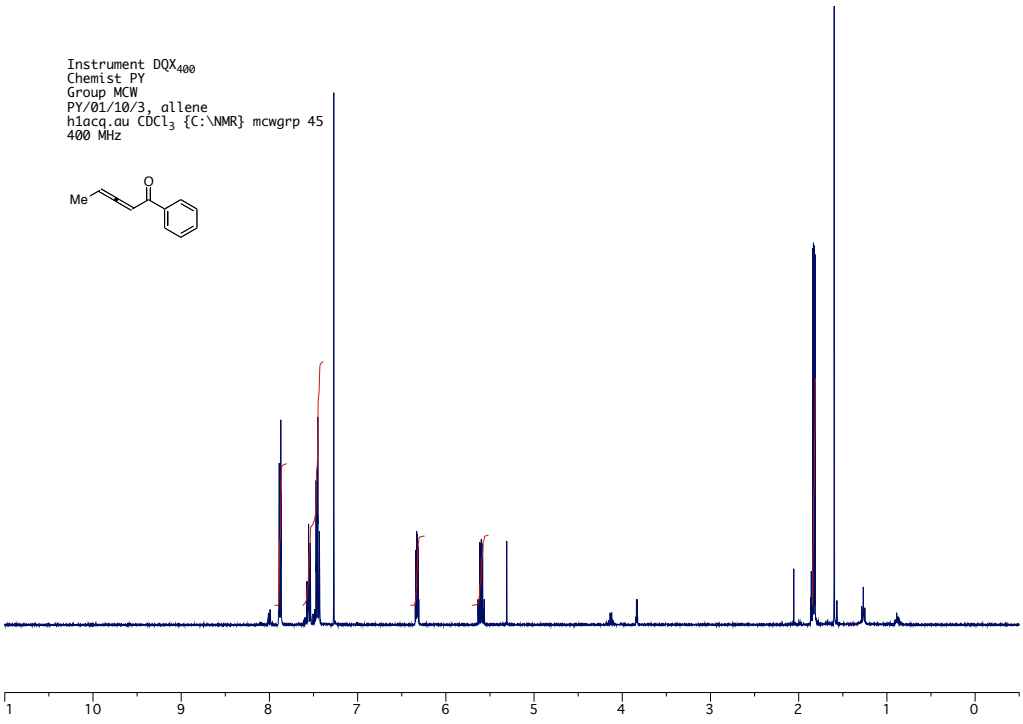
8.3 NMR data for reported compounds

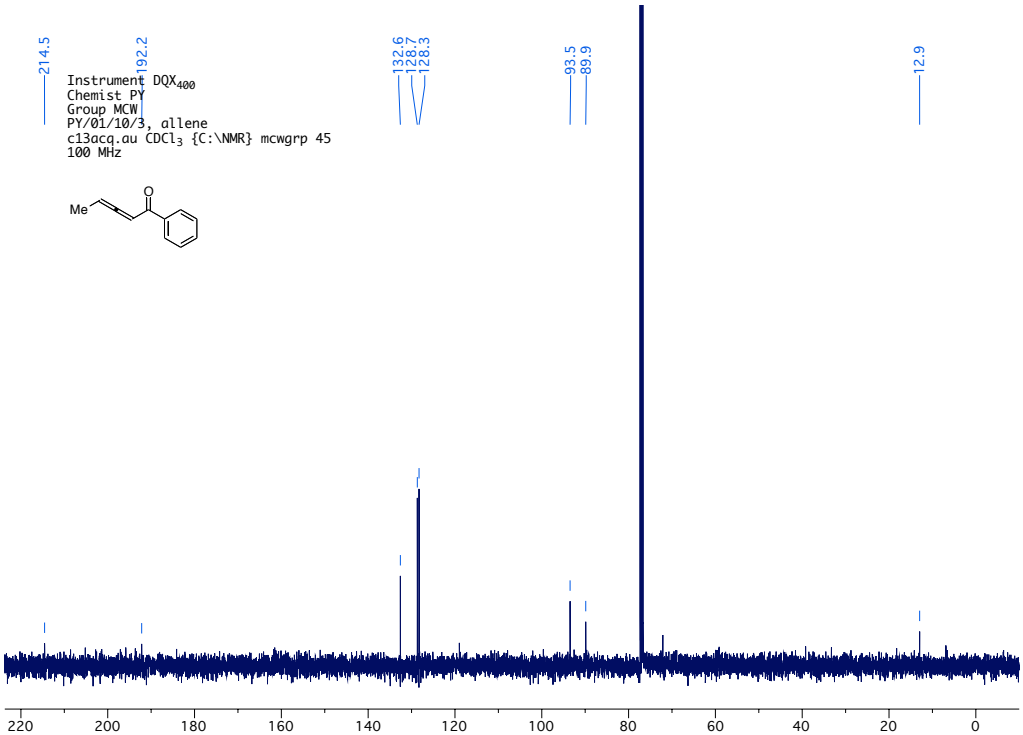
1-Phenylpenta-2,3-dien-1-one, experimental page 116



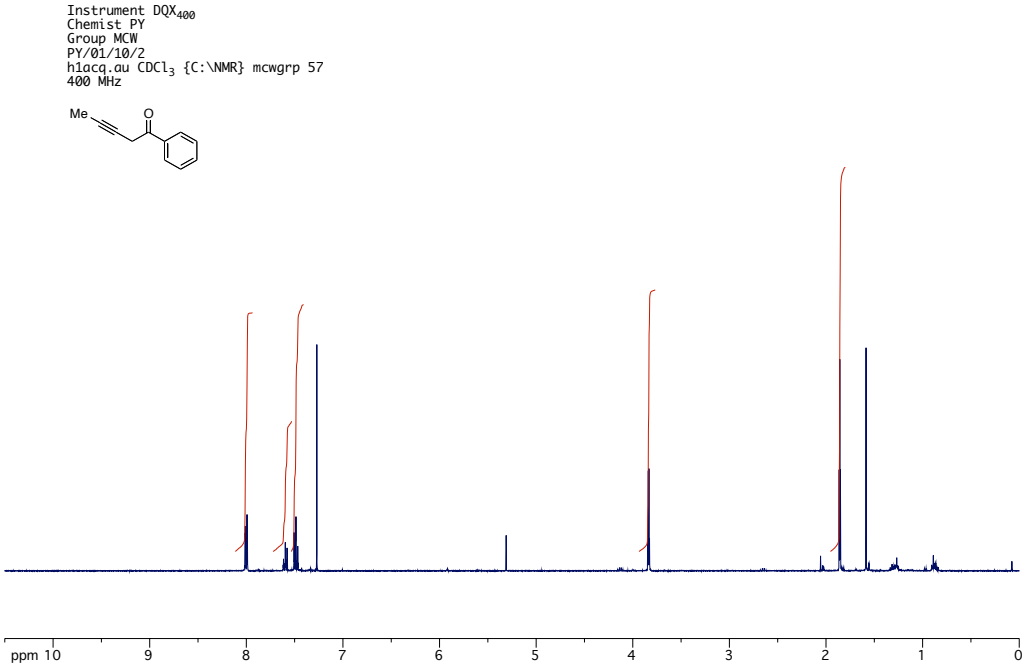


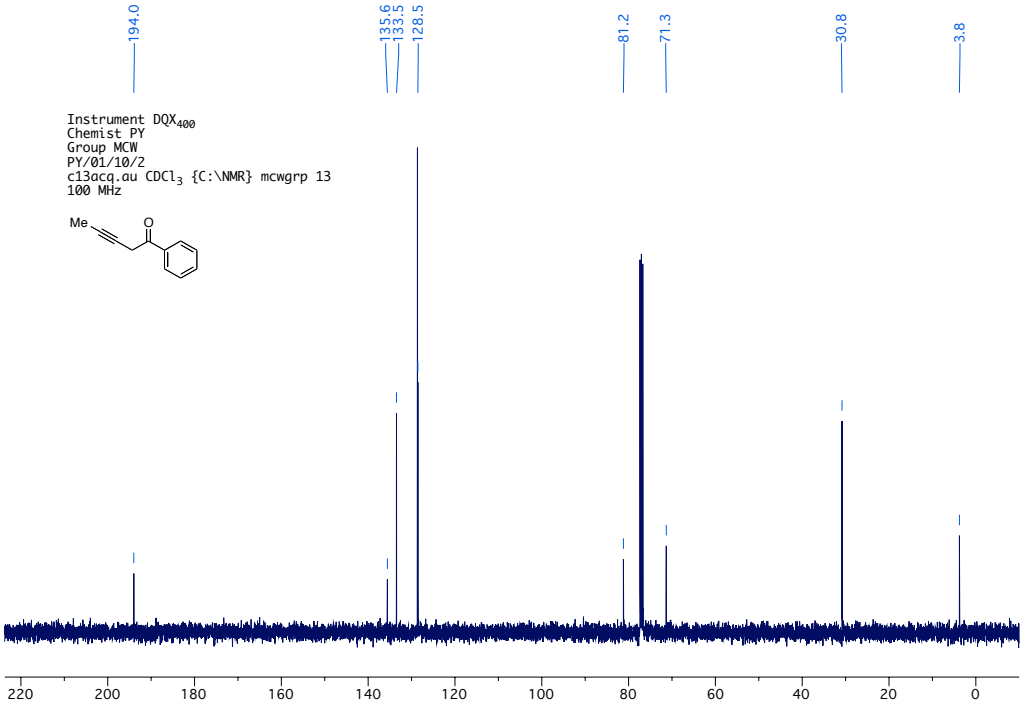
1-Phenylpenta-2,3-dien-1-one, experimental page 117



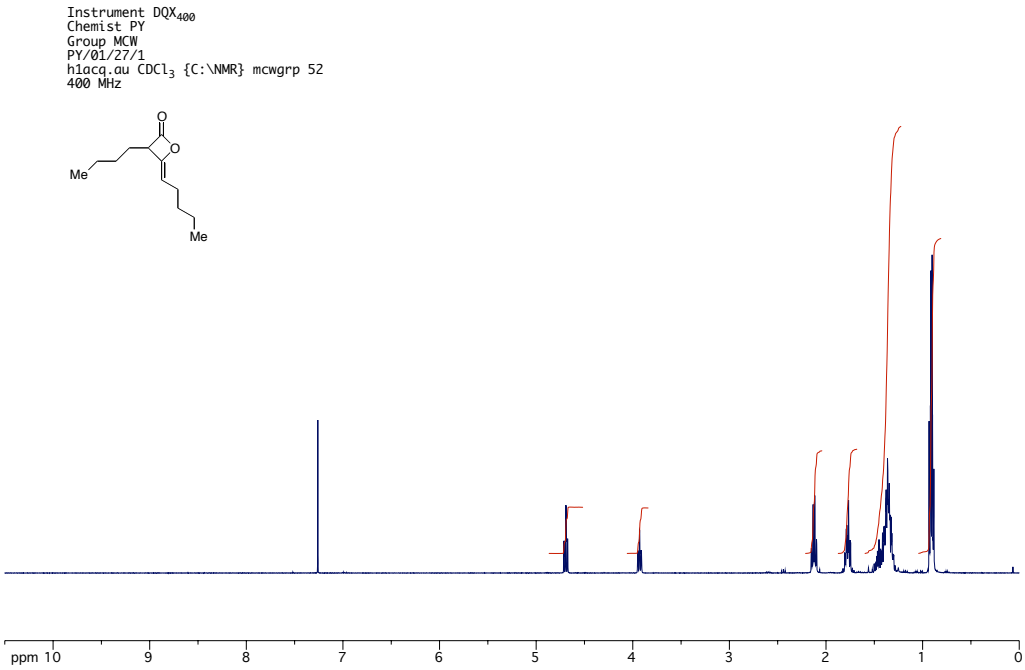


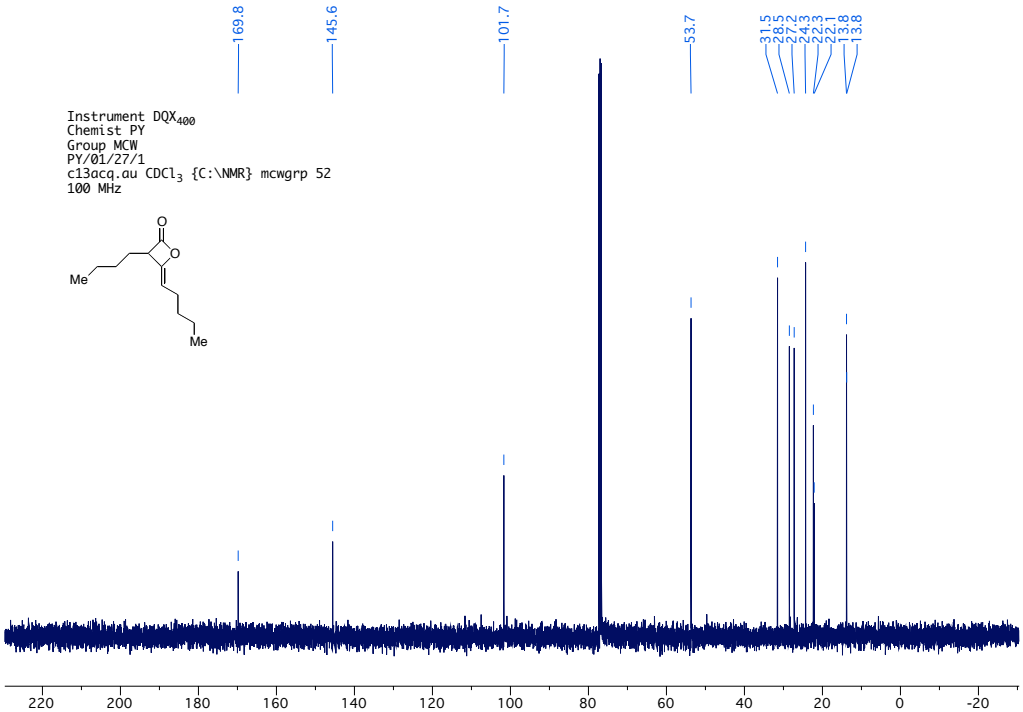
1-Phenylpent-3-yn-1-one, experimental page 118



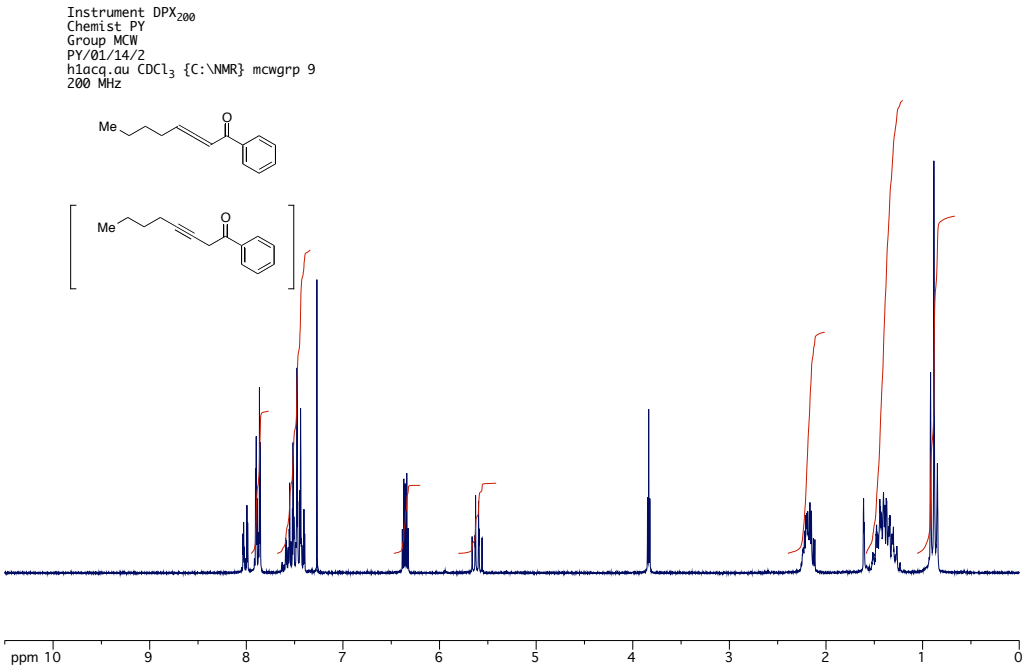


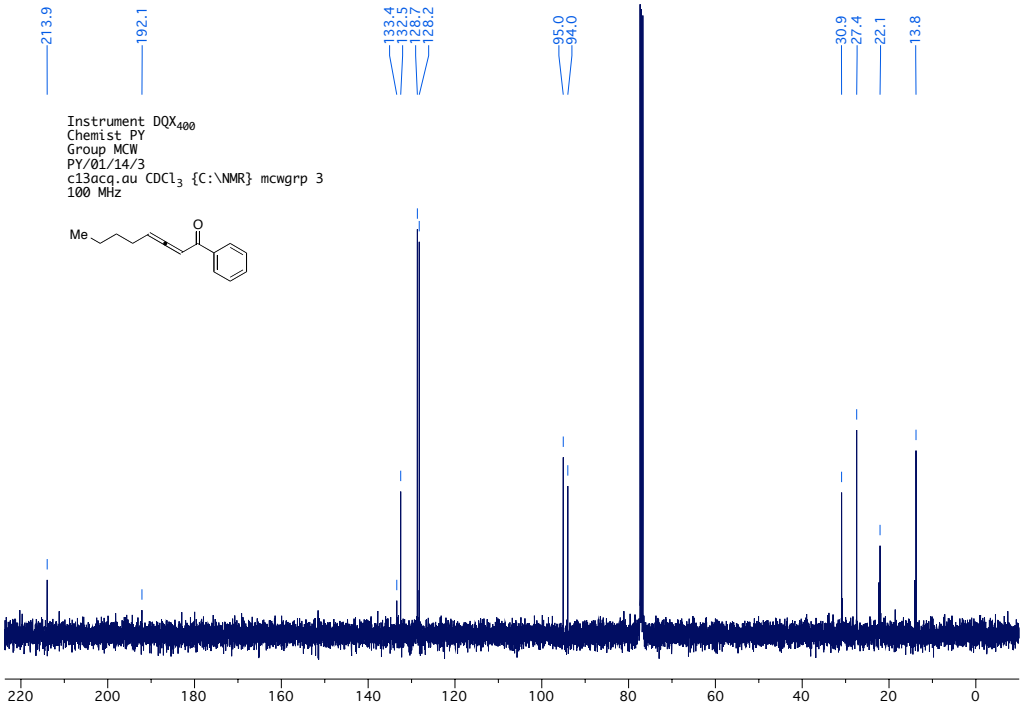
(Z)-3-butyl-4-pentylideneoxetan-2-one, experimental page 118



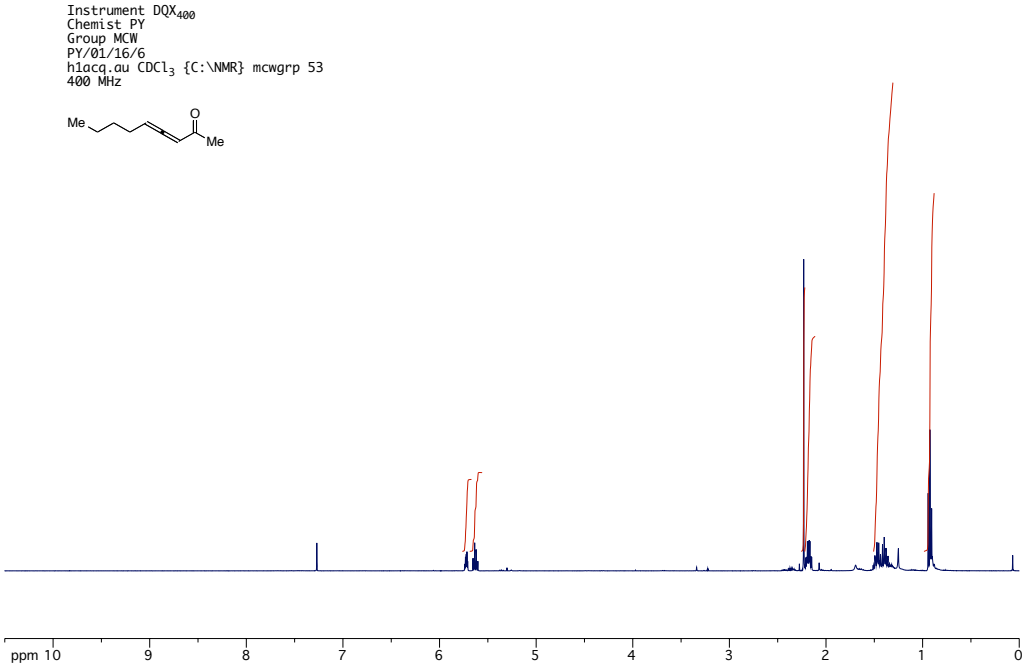


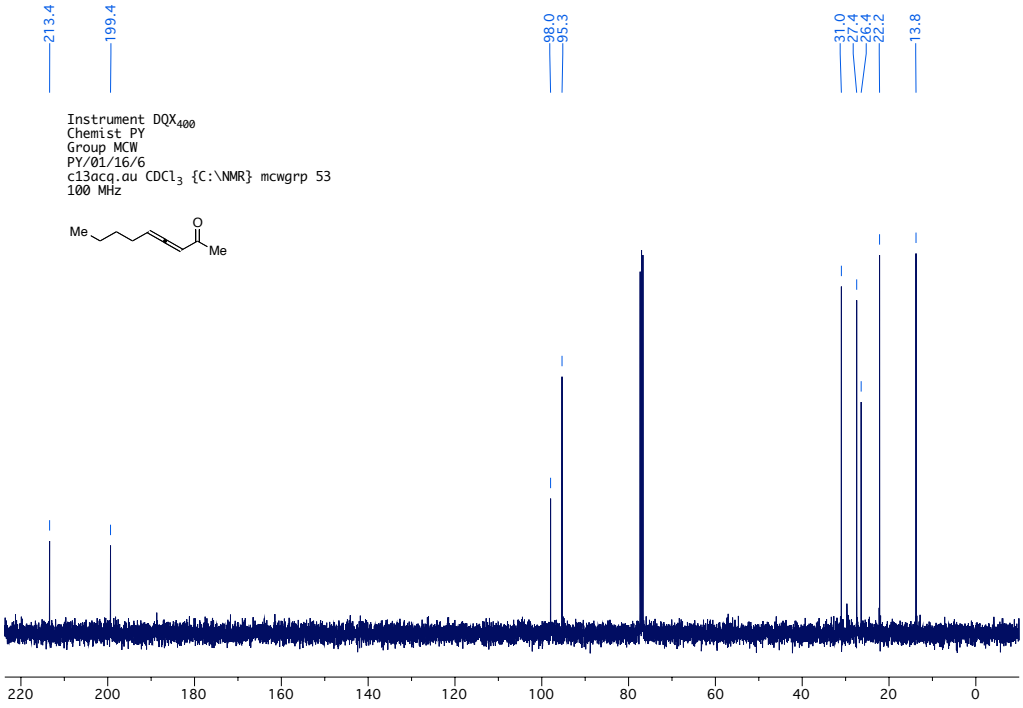
1-phenylocta-2,3-dien-1-one, experimental page 119



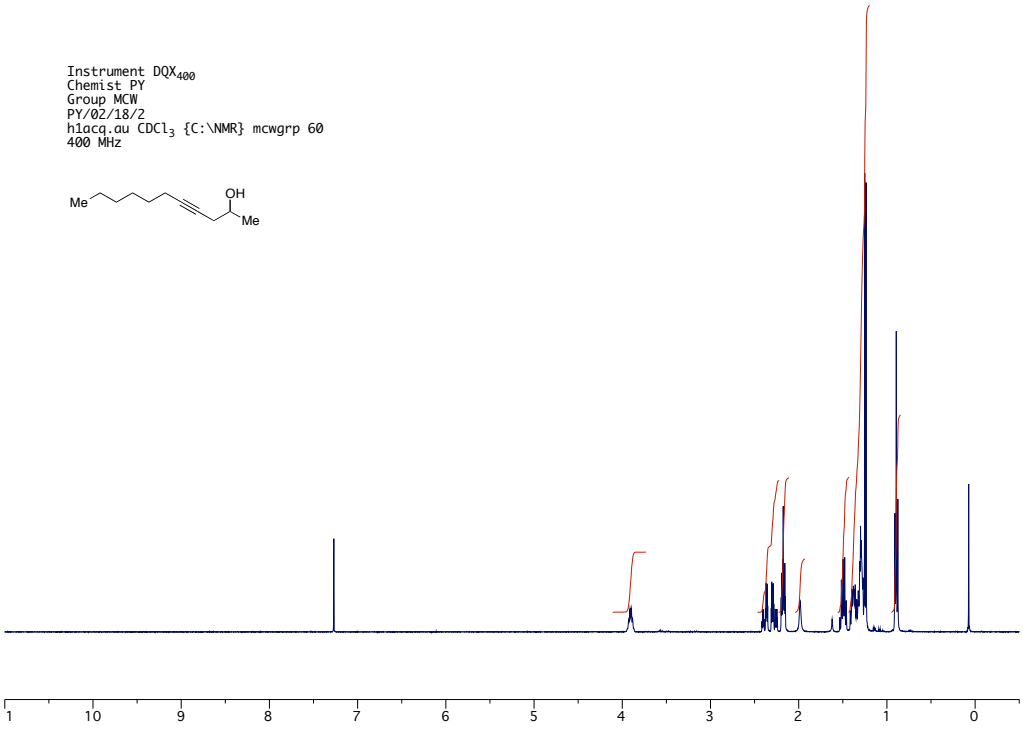


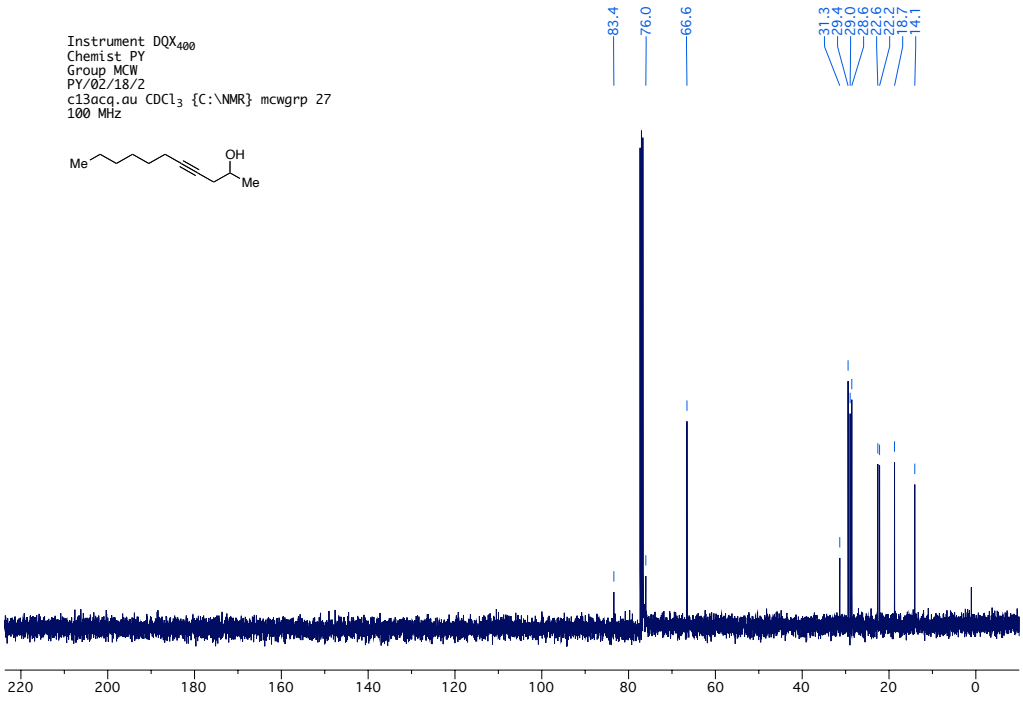
Nona-3,4-dien-2-one, experimental page 120



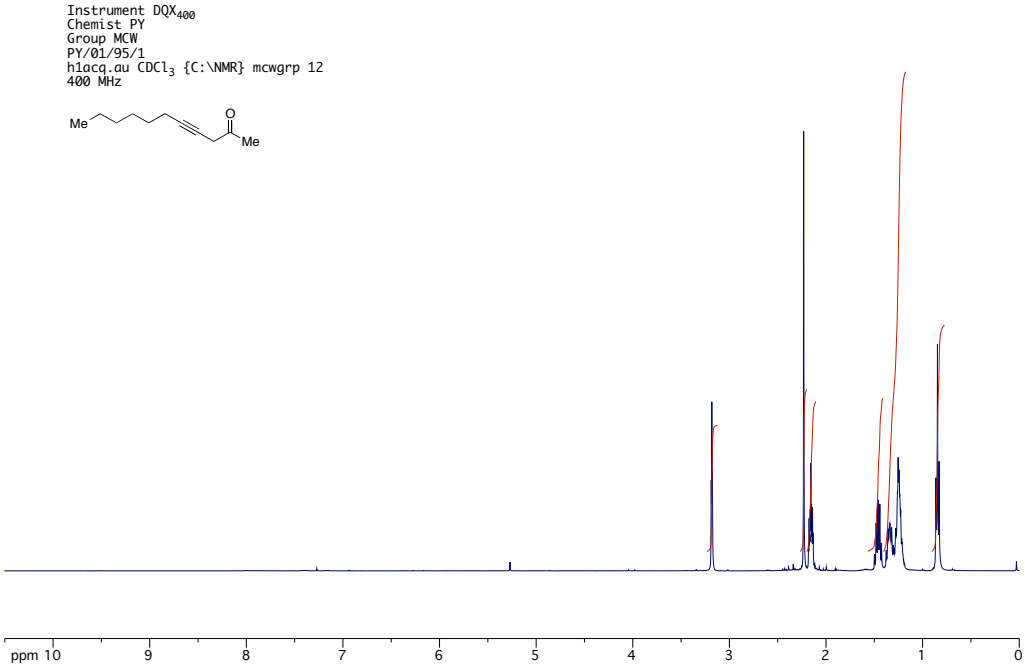


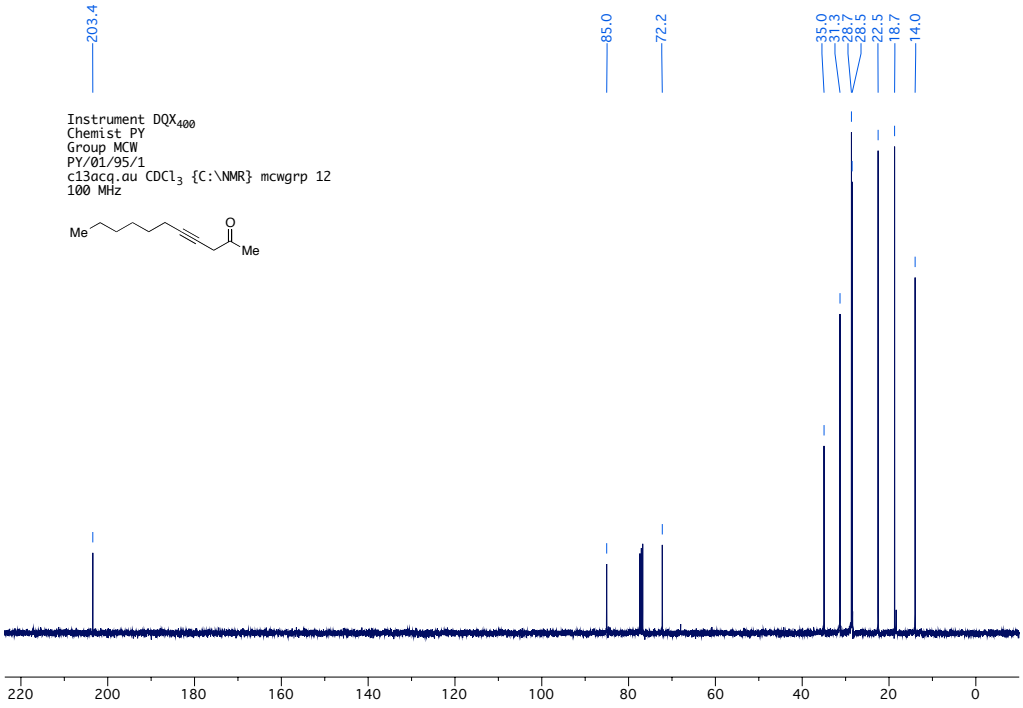
4-Undecyn-2-ol, experimental page 121



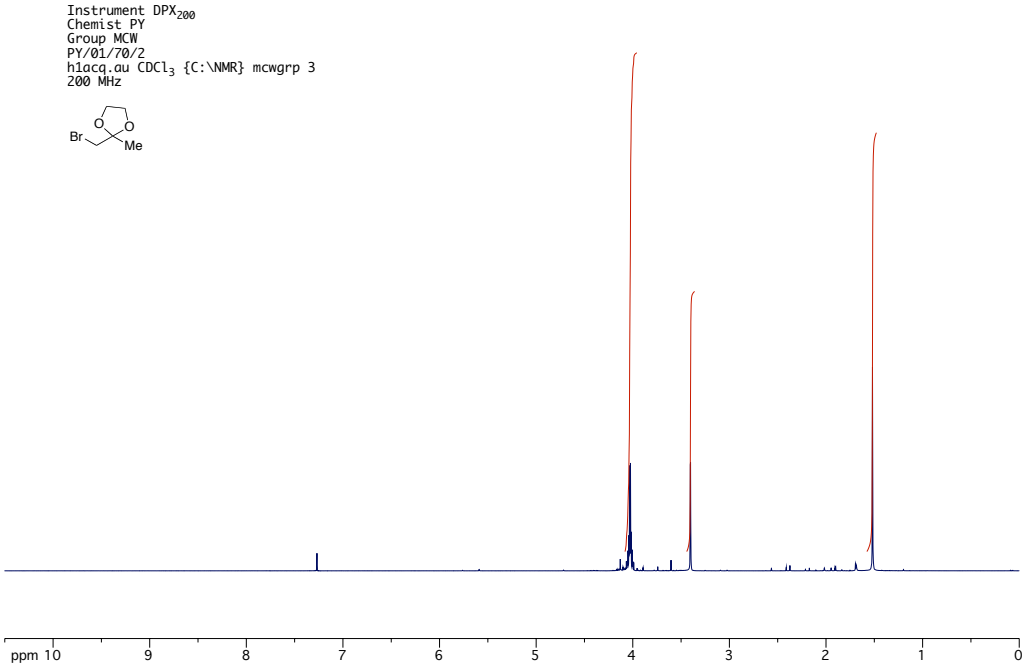


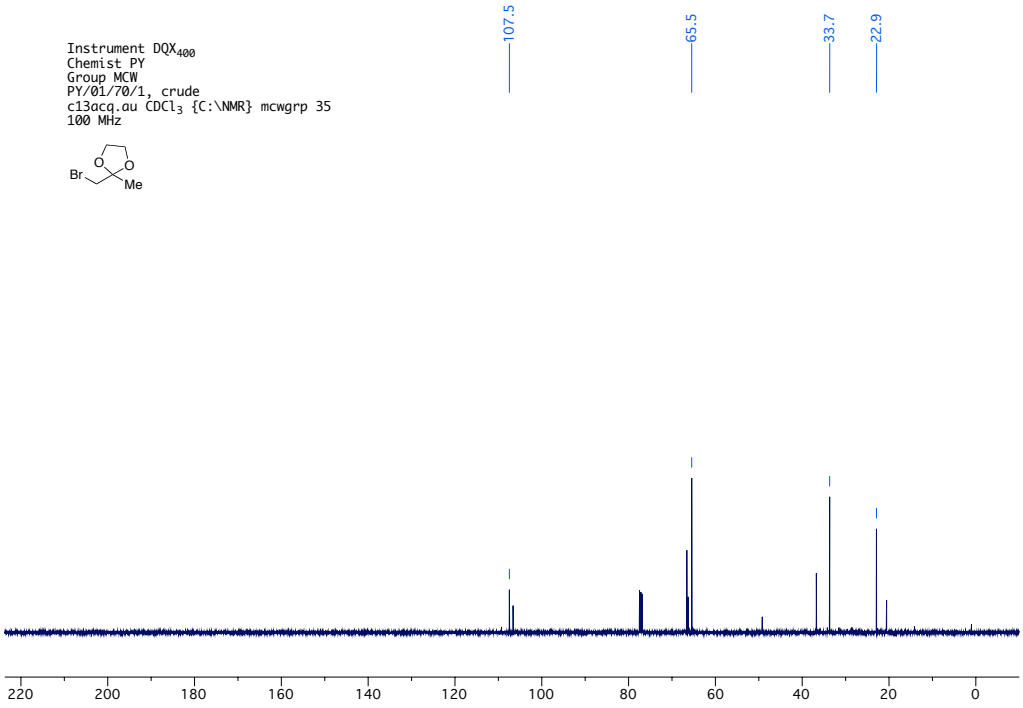
4-Undecyn-2-one, experimental page 122



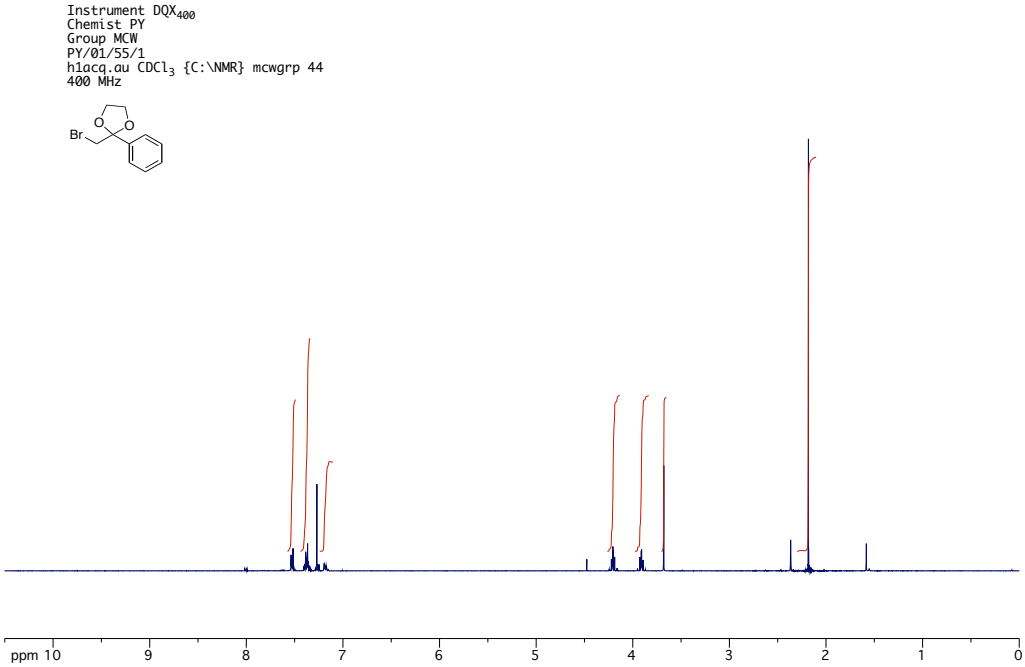


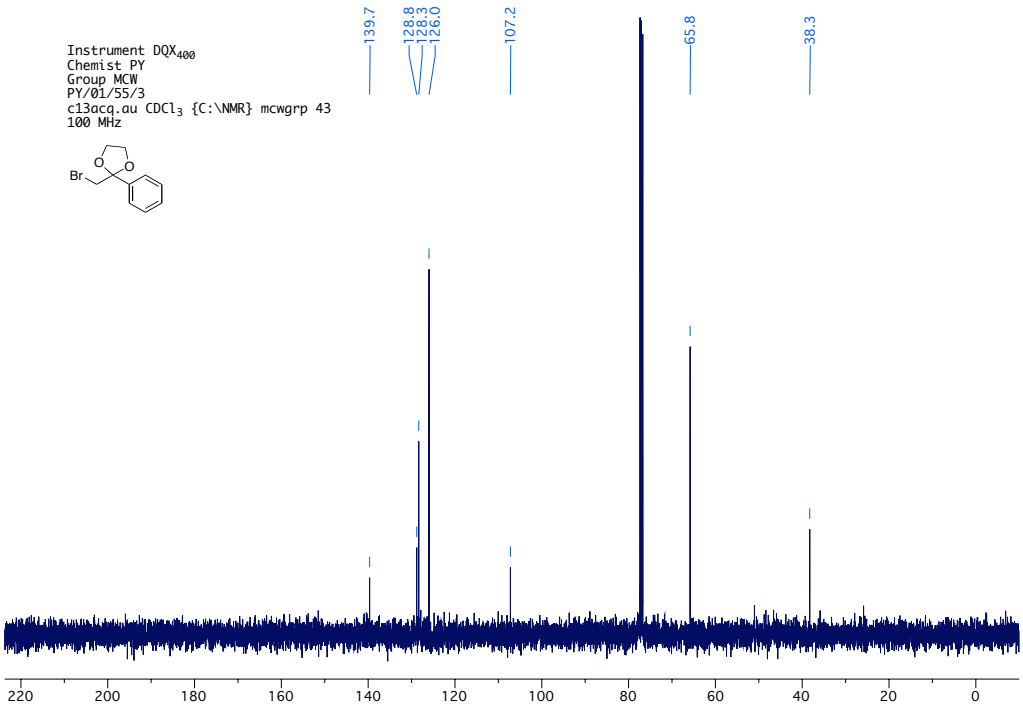
2-Methyl-2-bromomethyl-1,3-dioxolane, experimental page 123



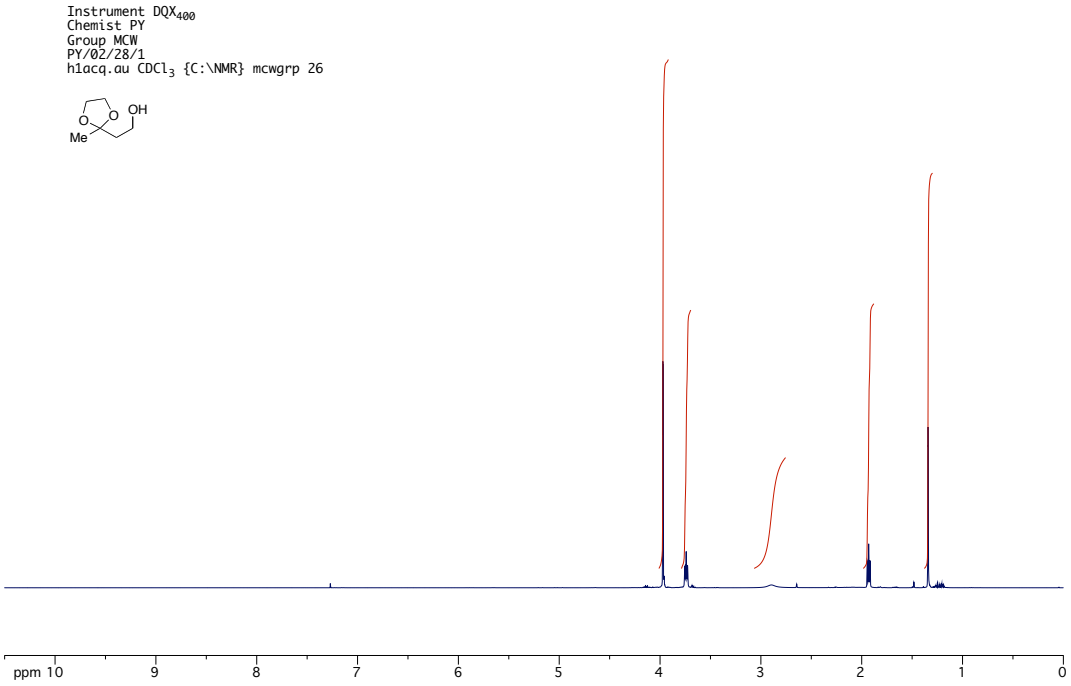


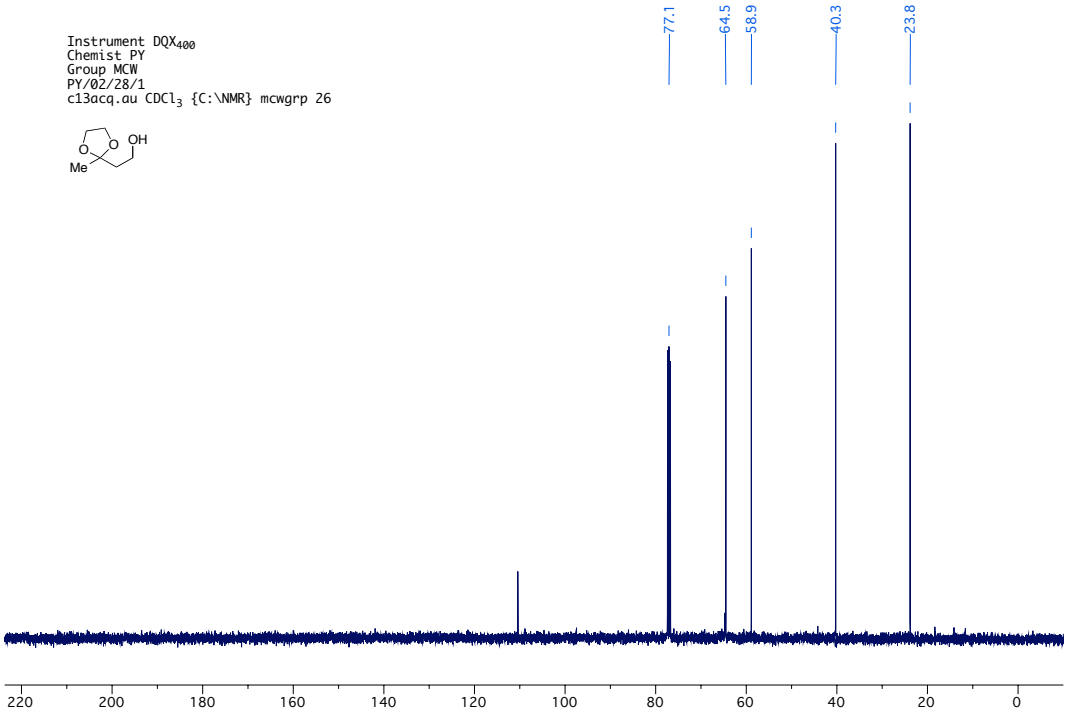
2-Phenyl-2-bromomethyl-1,3-dioxolane, experimental page 124



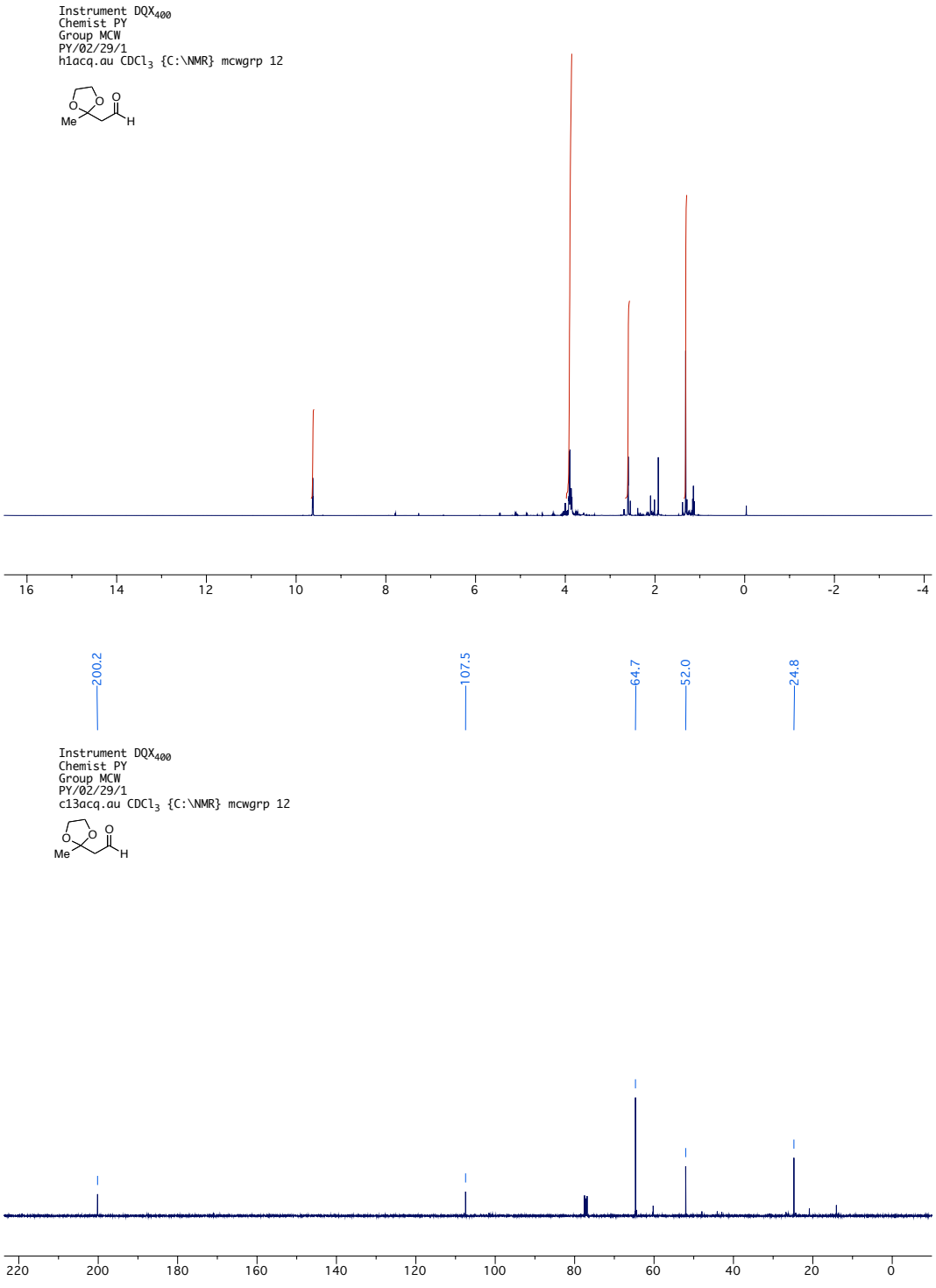


2-(2-Methyl-1,3-dioxalan-2-yl)ethanol, experimental page 126

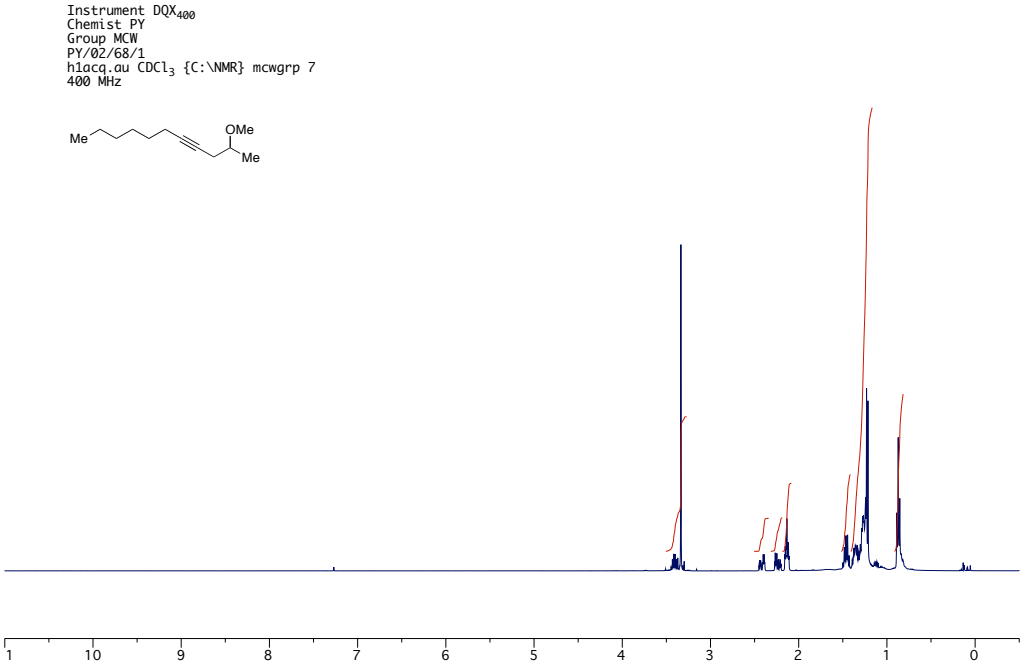


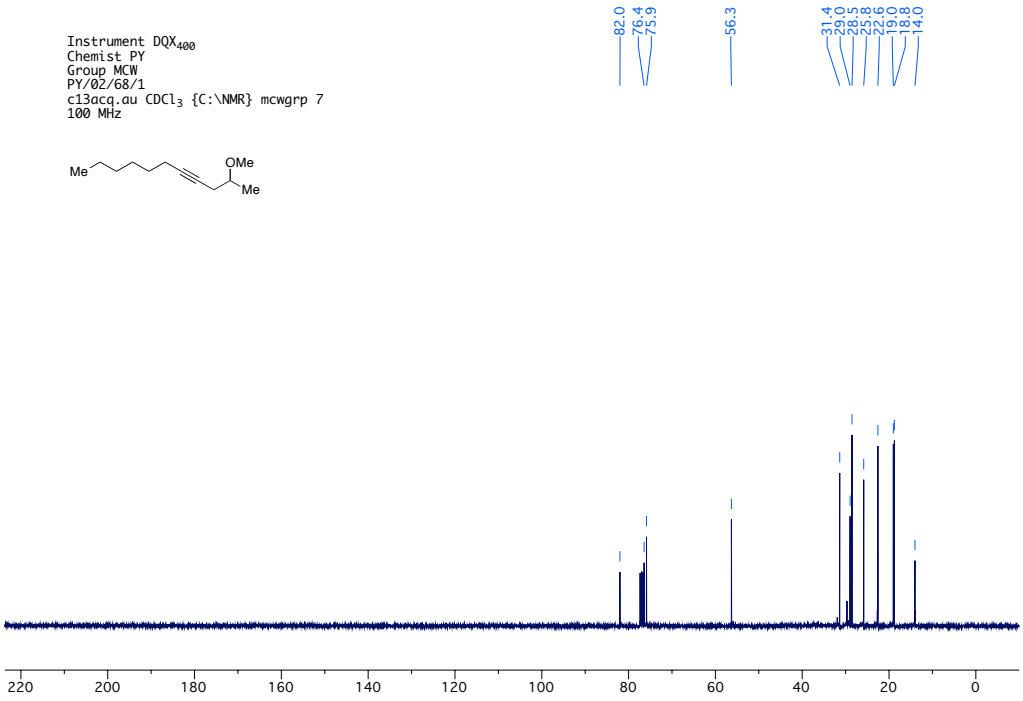


2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde, experimental page 127

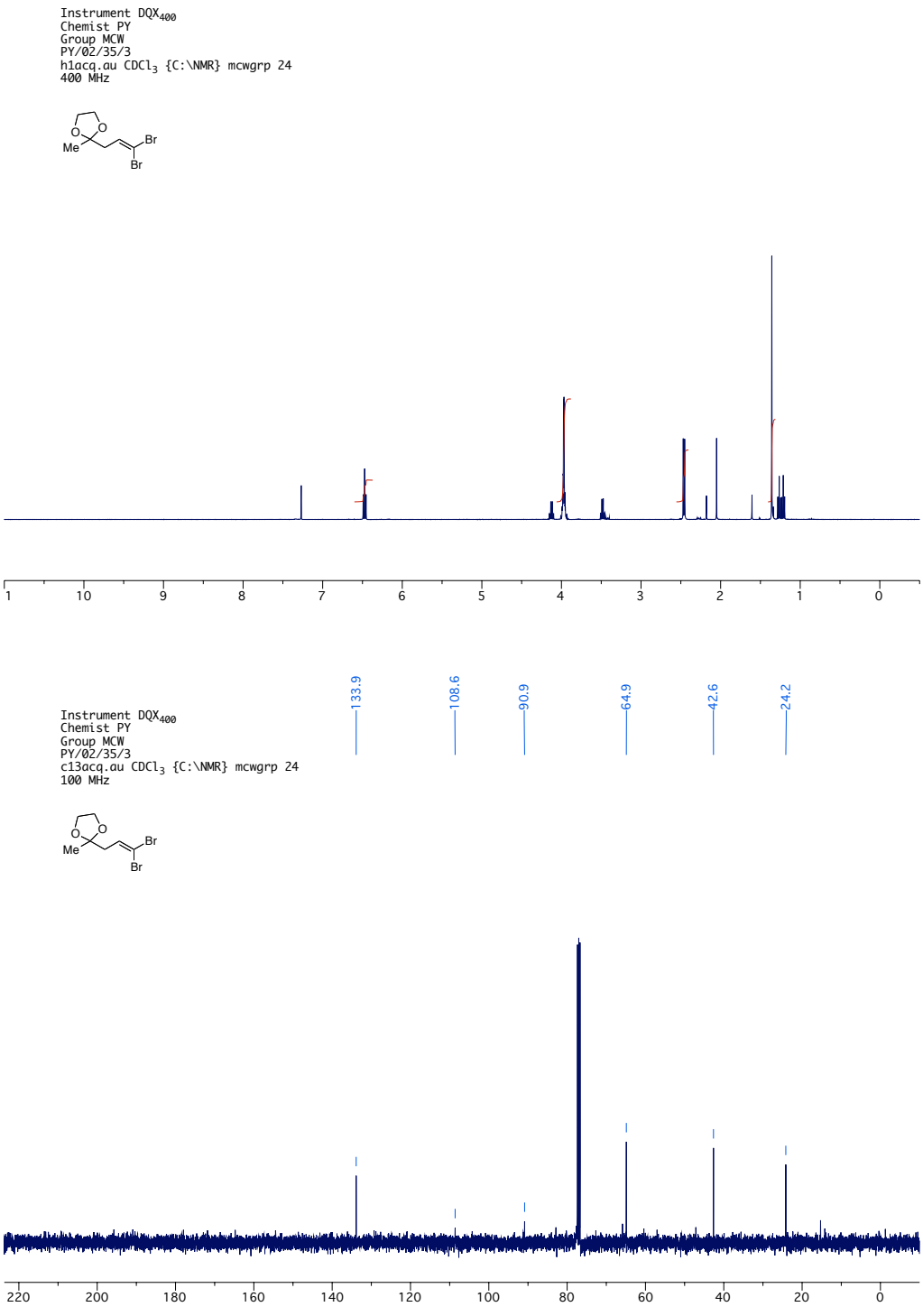


2-Methoxyundec-4-yne, experimental page 137

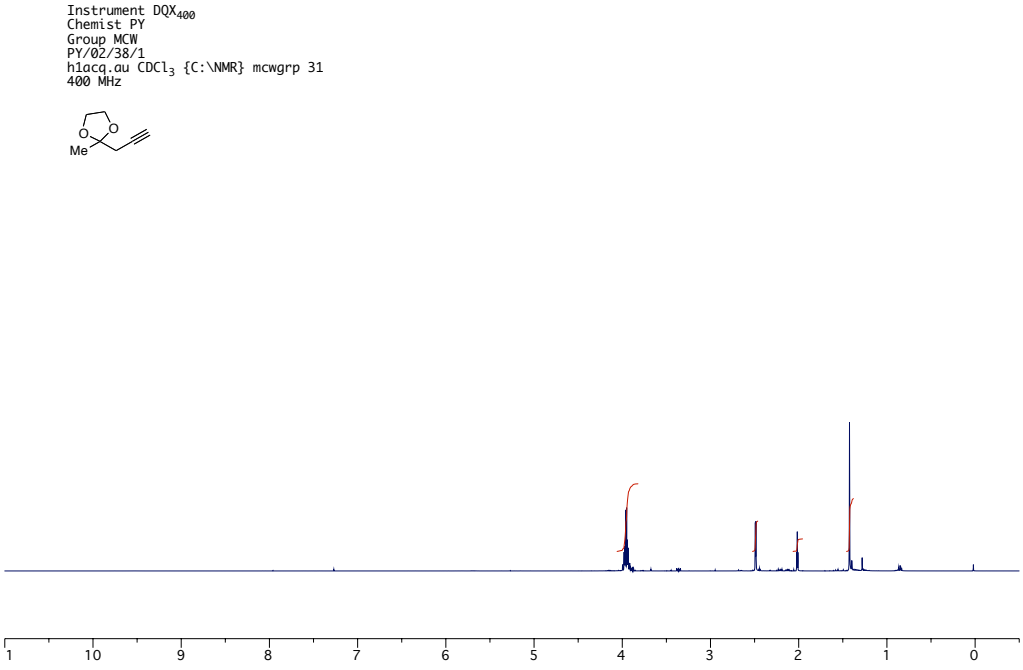


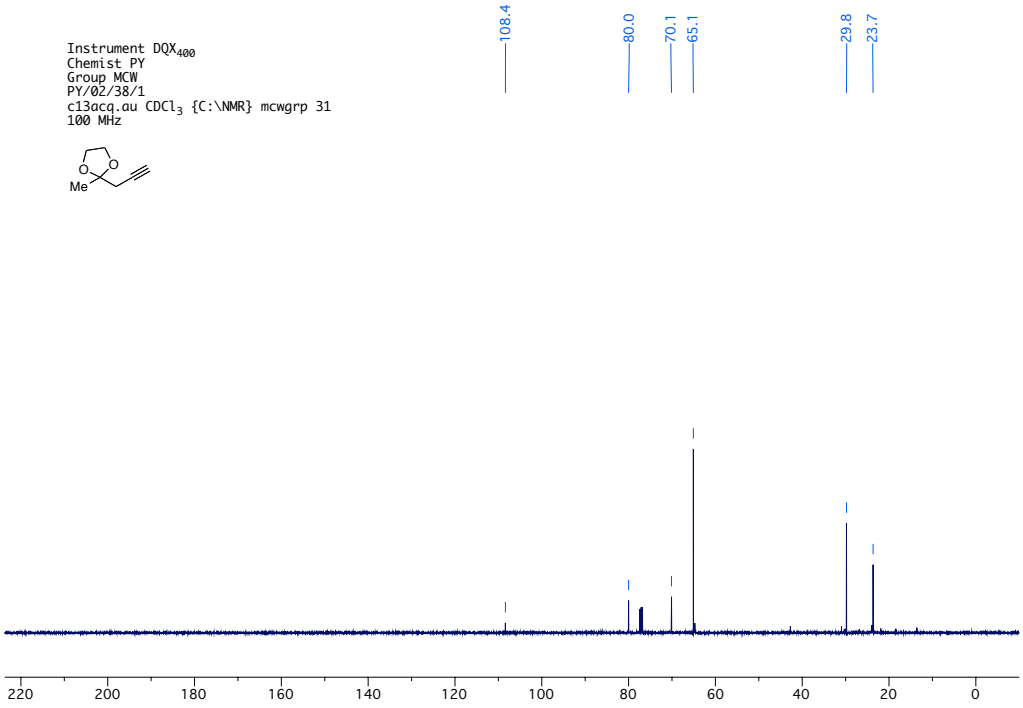


2-(3,3-dibromoallyl)-2-methyl-1,3-dioxalane, experimental page 127

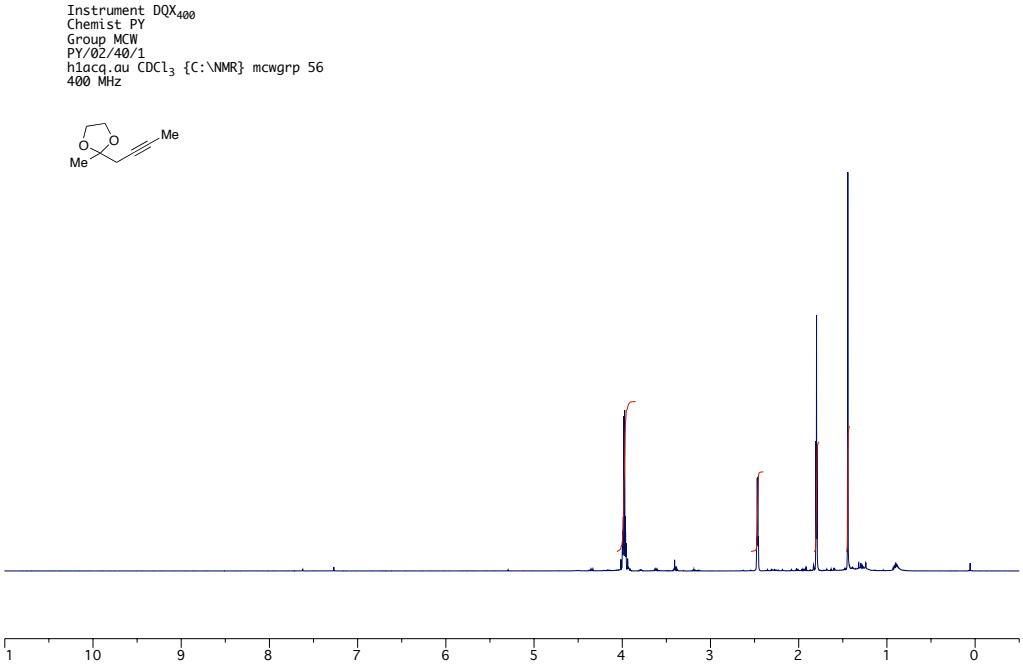


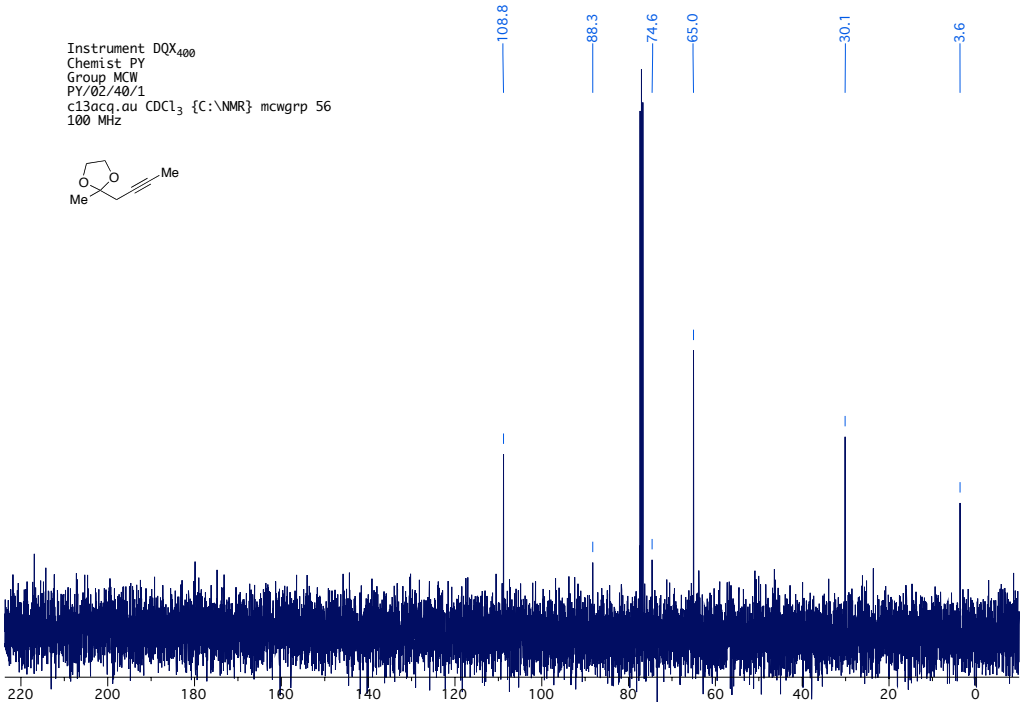
2-methyl-2-(2-propynyl)-1,3-dioxolane, experimental page 128



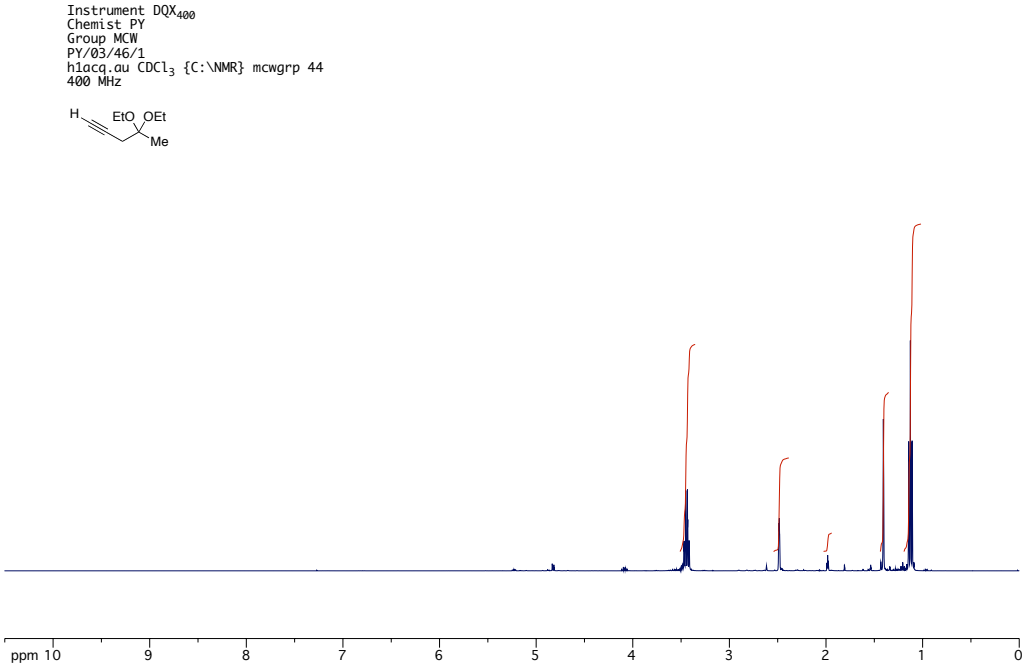


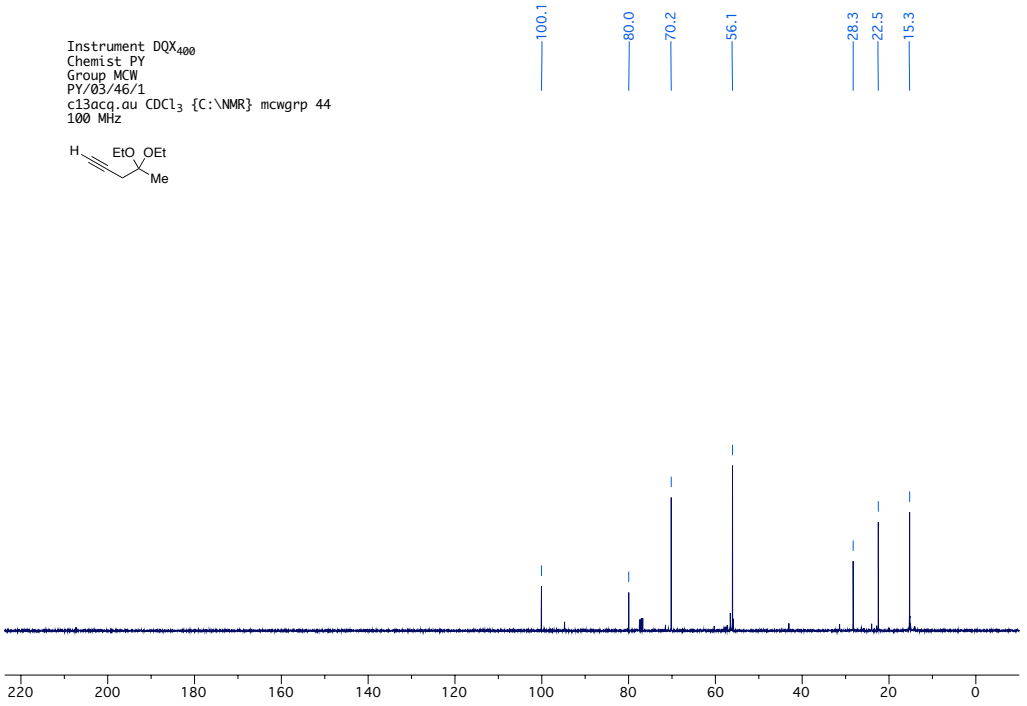
2-(2-butynyl)-2-methyl-1,3-dioxolane, experimental page 129



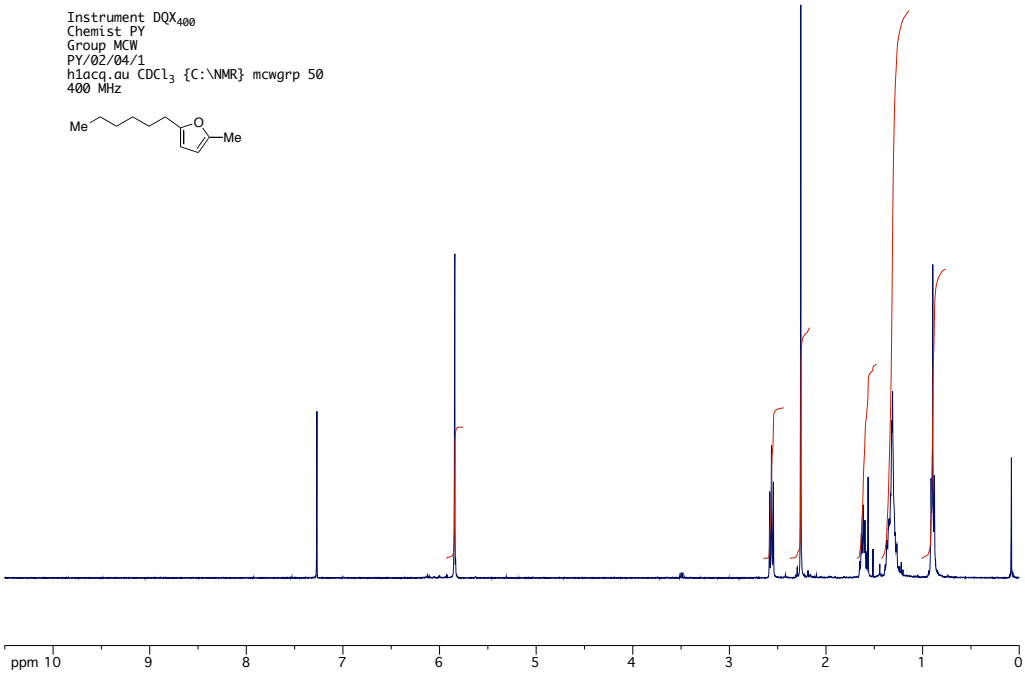


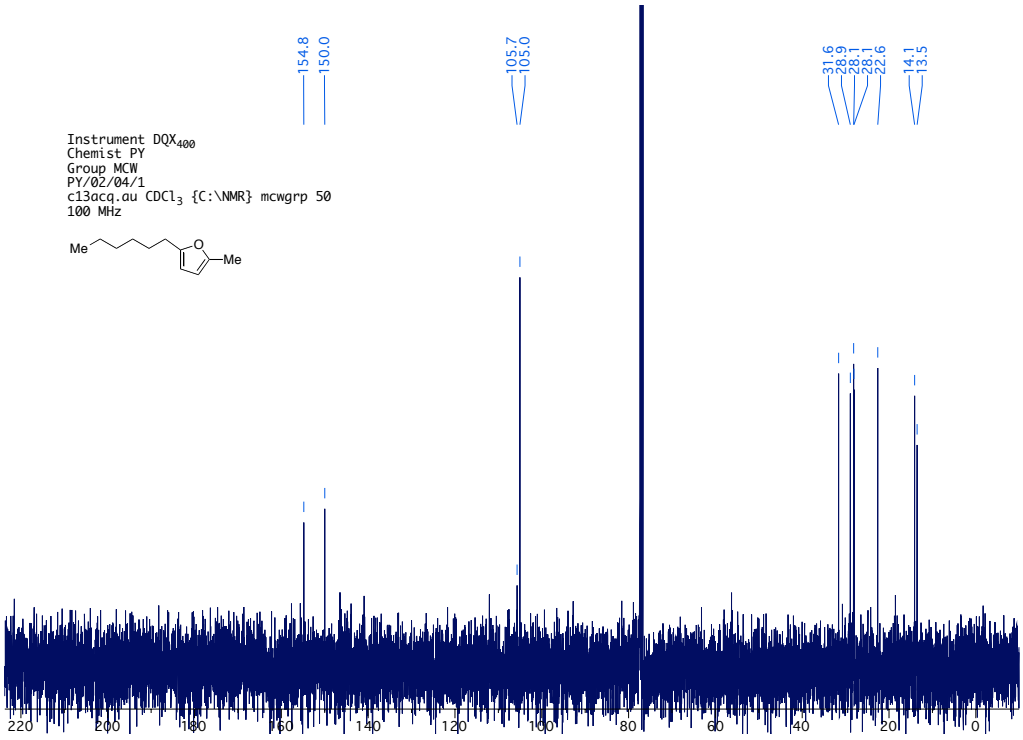
4,4-Diethoxy-pent-1-yne, experimental page 125



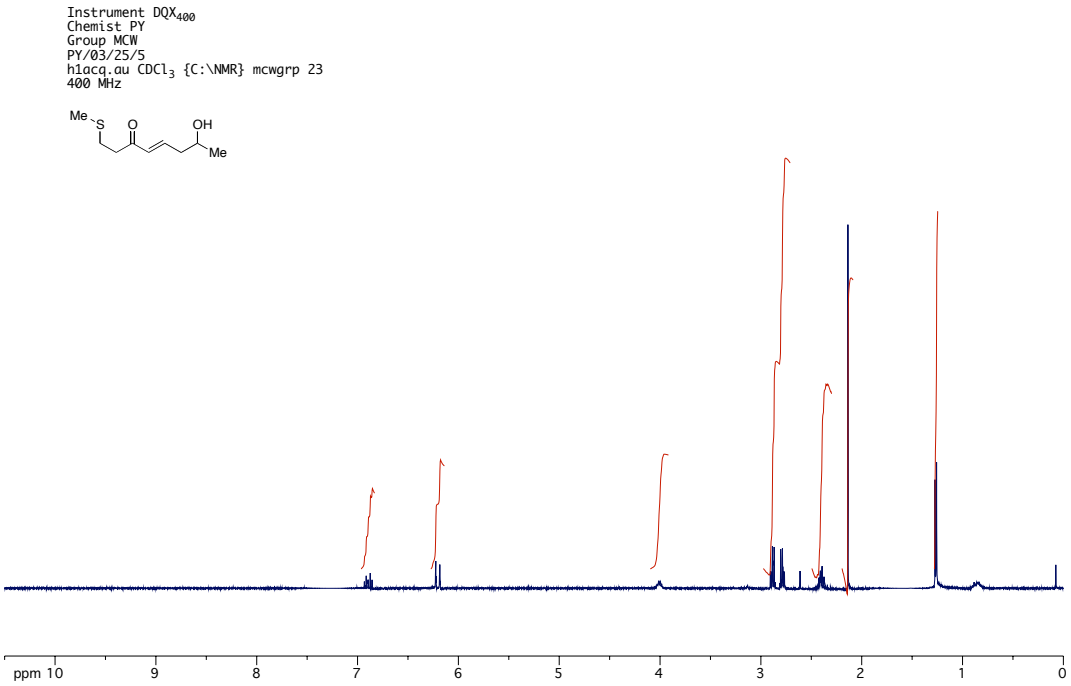


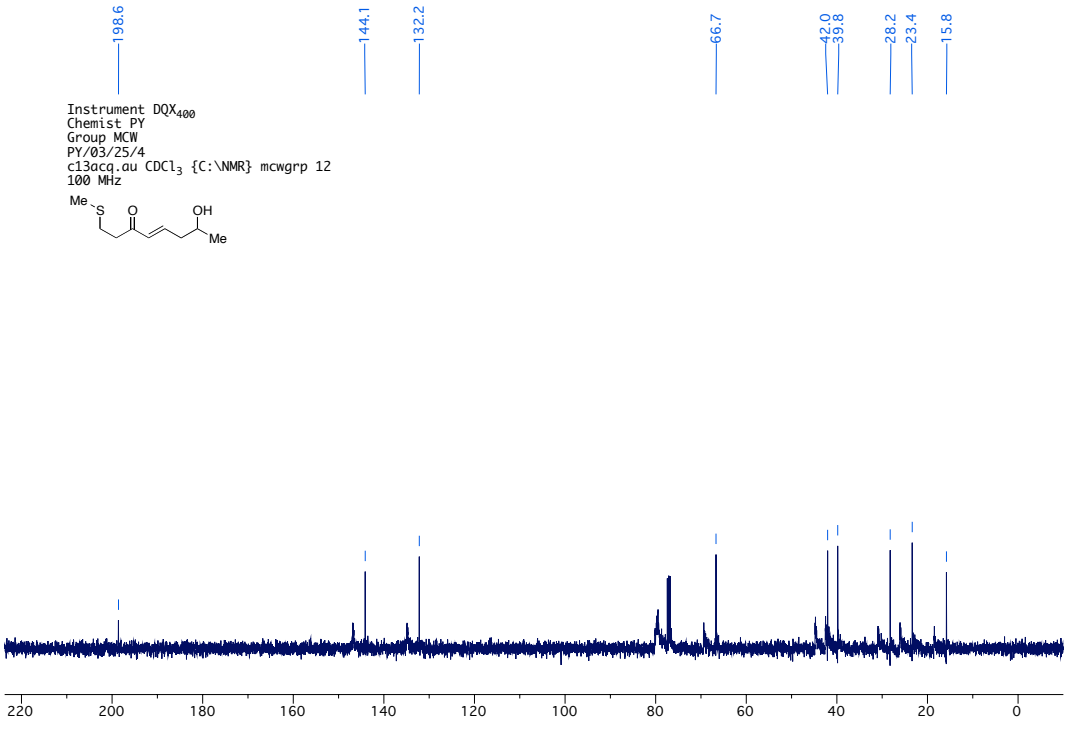
2-Hexyl-5-methylfuran, experimental page 131



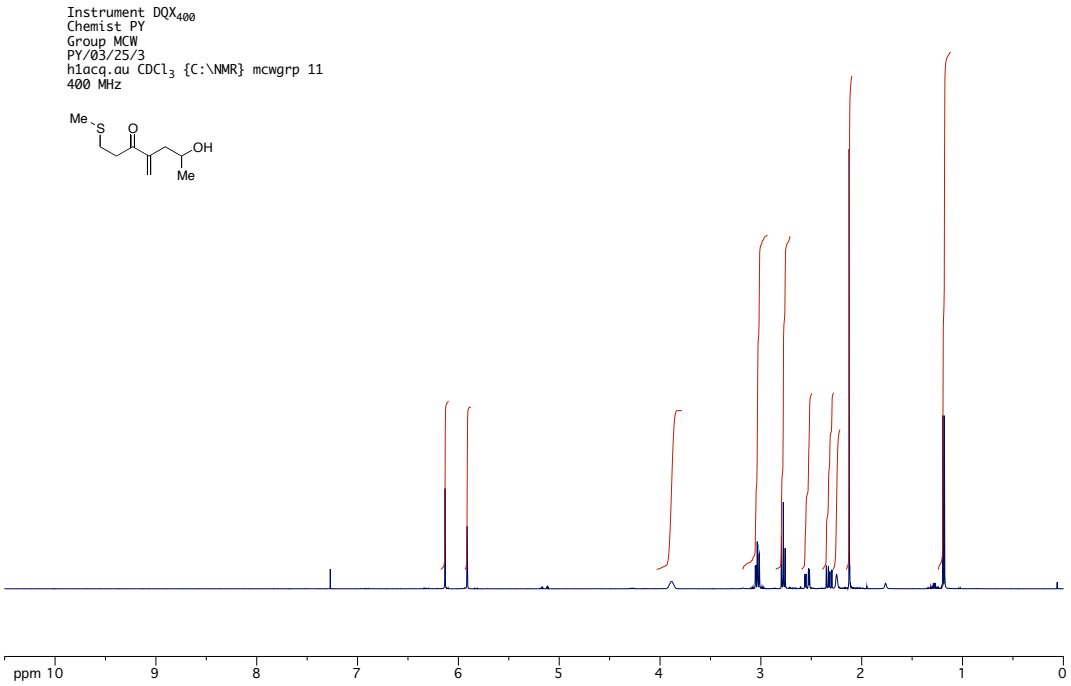


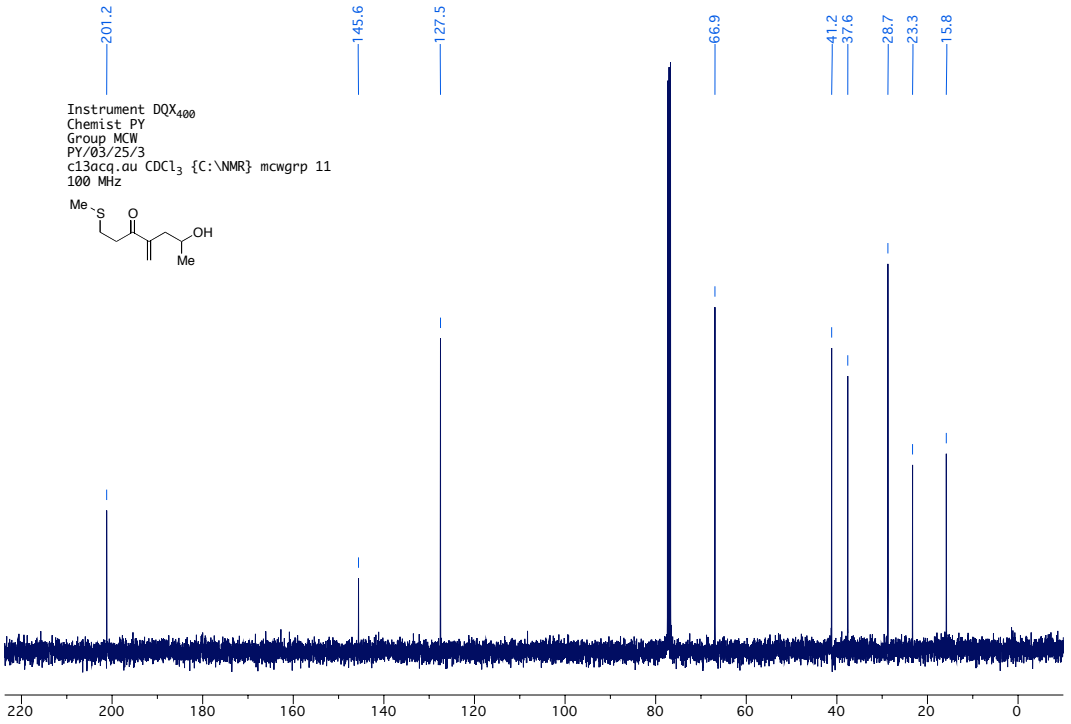
(*E*)-7-Hydroxy-1-(methylthio)4-octen-3-one, experimental page 131



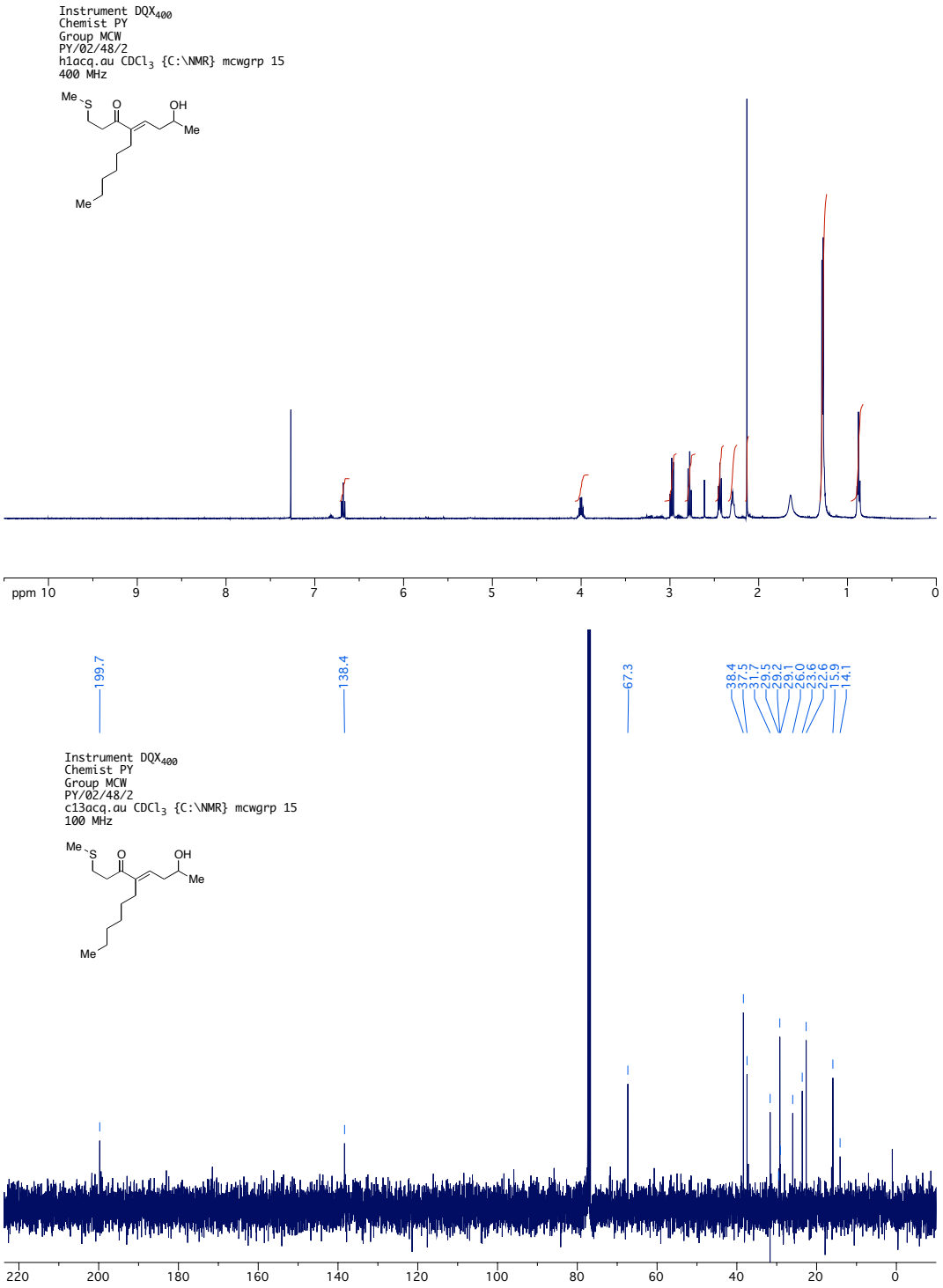


6-Hydroxy-4-methylene-1-(methylthio)heptan-3-one, experimental page 131

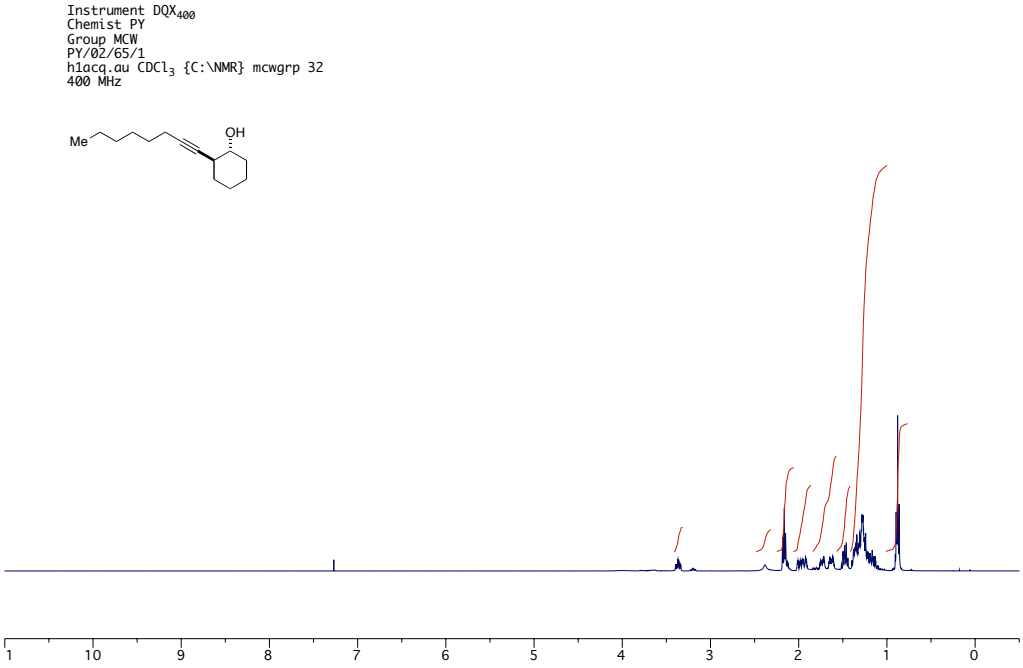


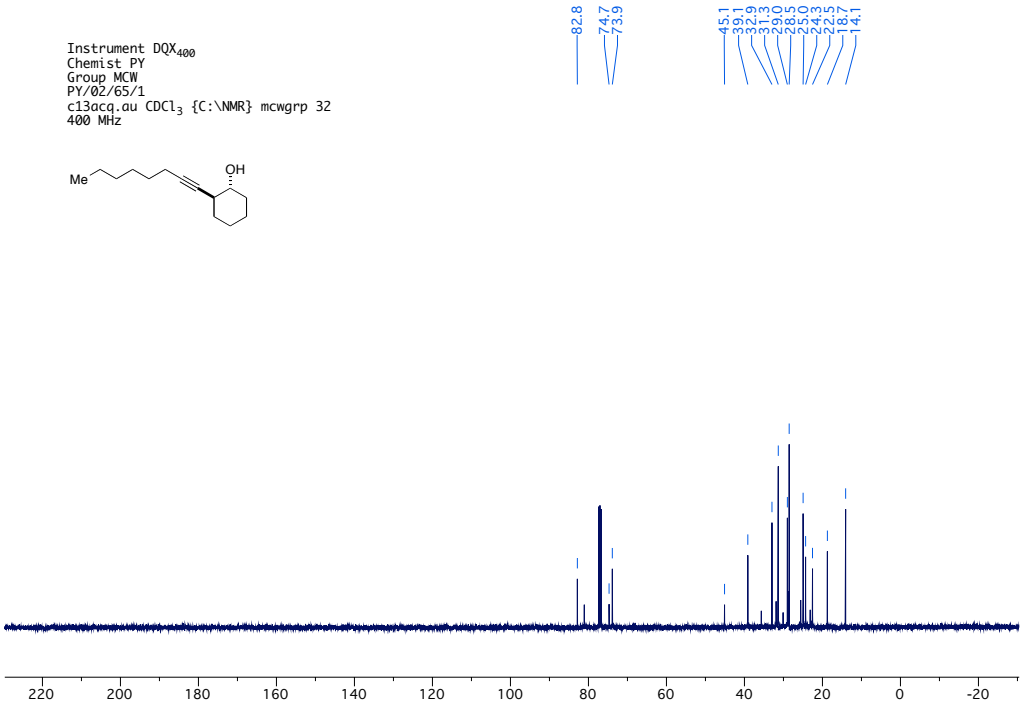


(*E*)-4-(3-Hydroxybutylidene)-1-(methylthio)decan-3-one, experimental page 133

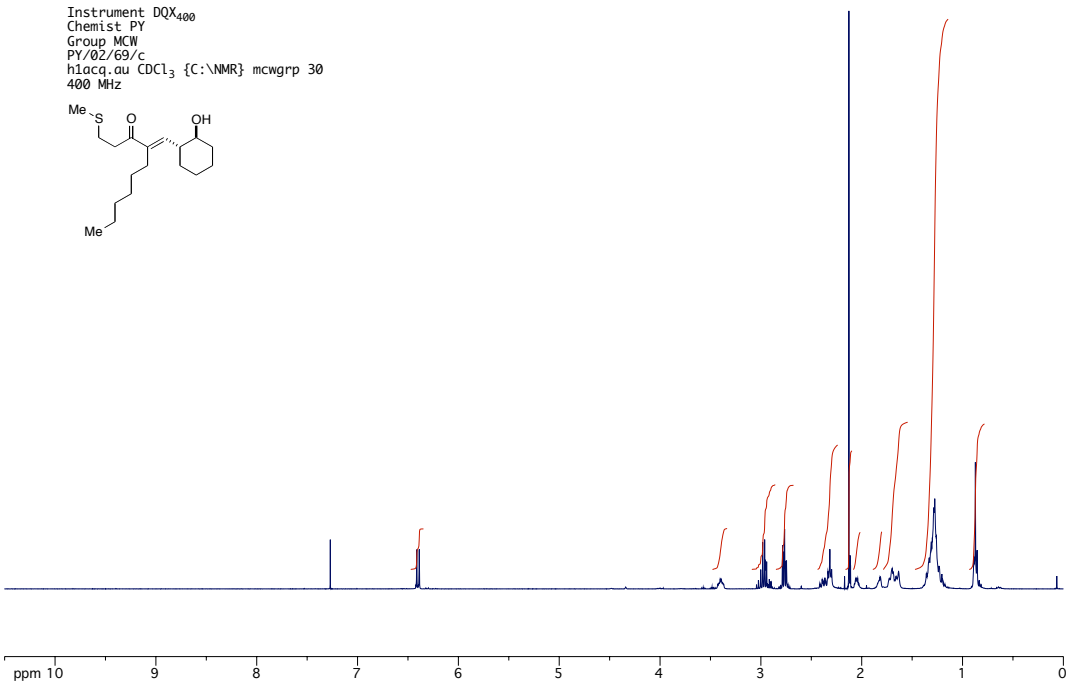


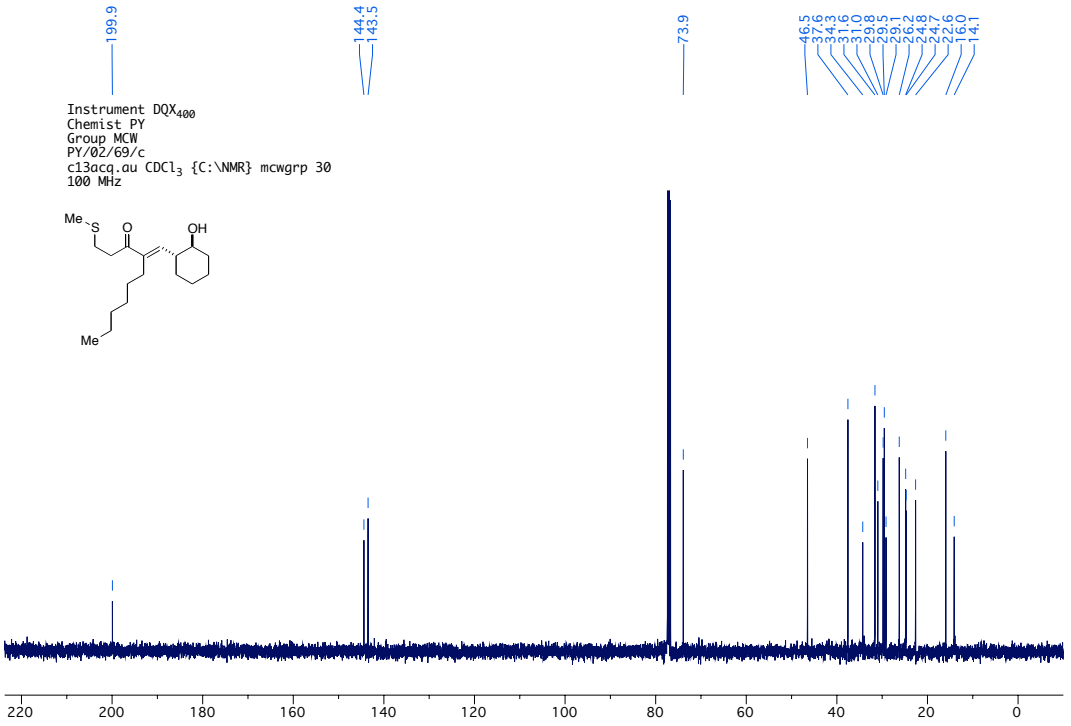
trans-2-(1-Octynyl)cyclohexanol, experimental page 123



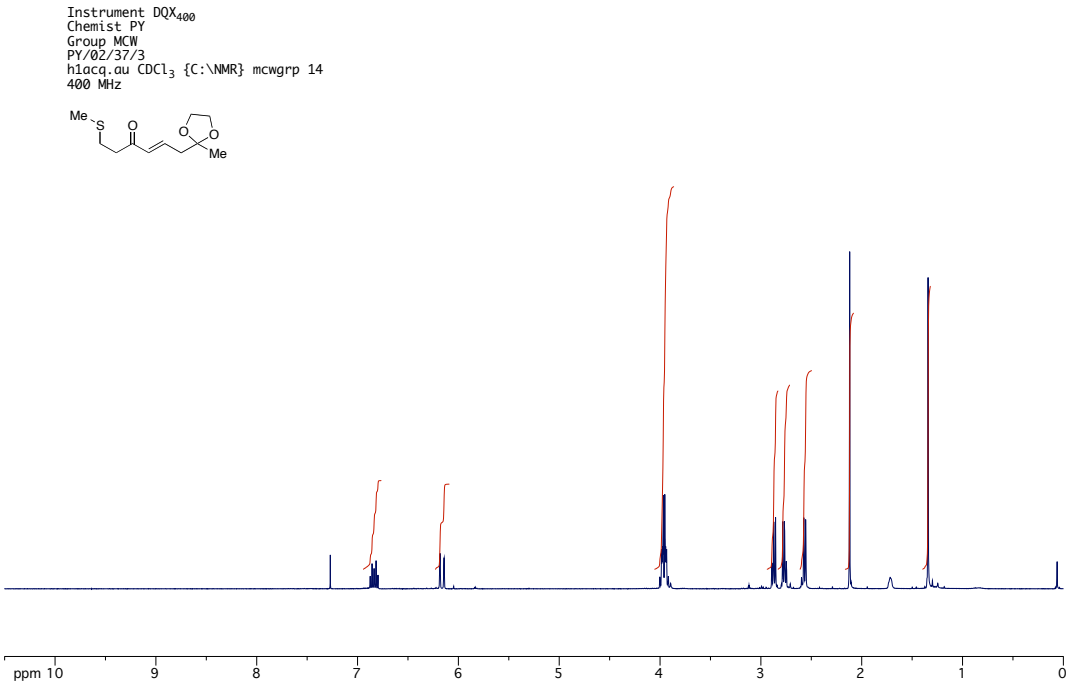


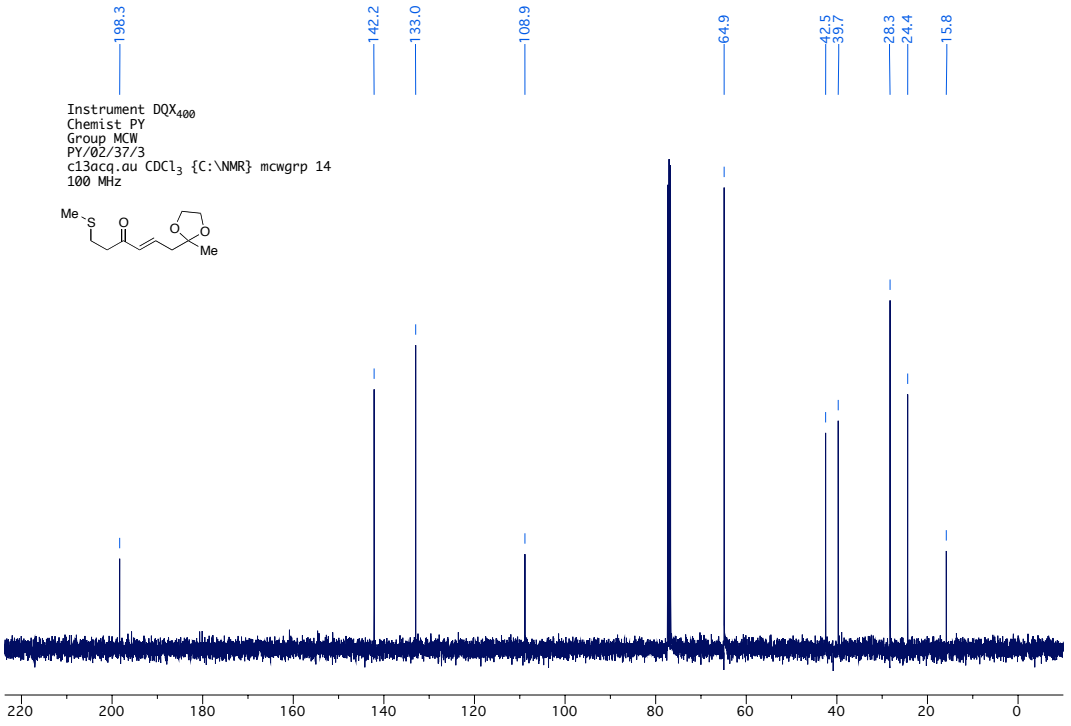
(*E*)-4-((2-Hydroxycyclohexyl)methylene)-1-(methylthio)decan-3-one, experimental page 134



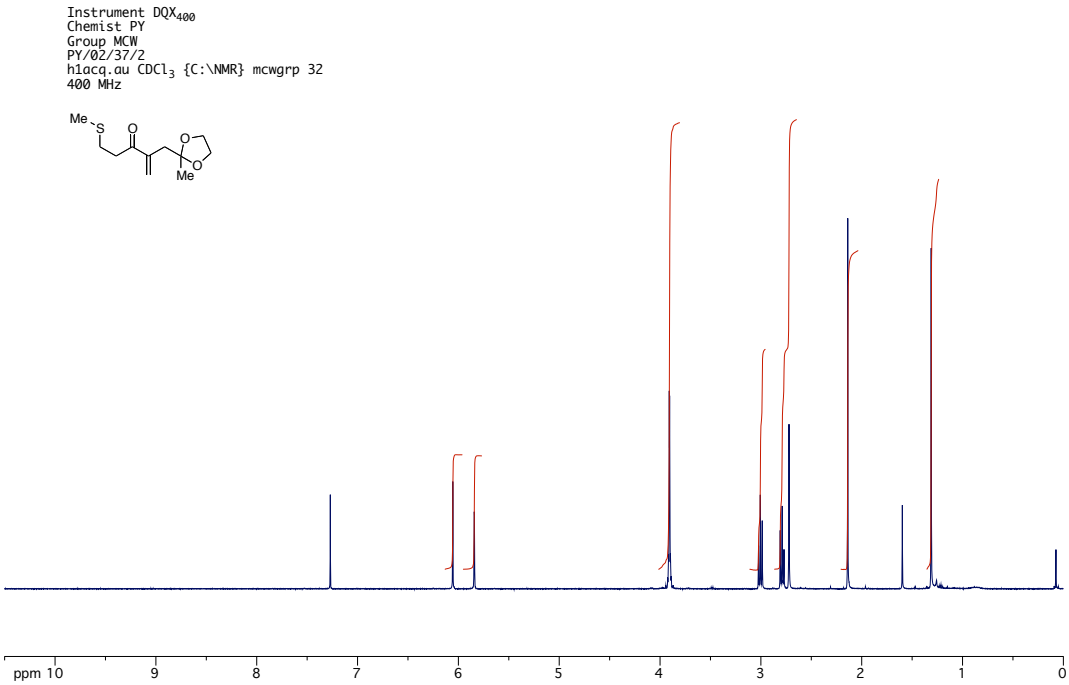


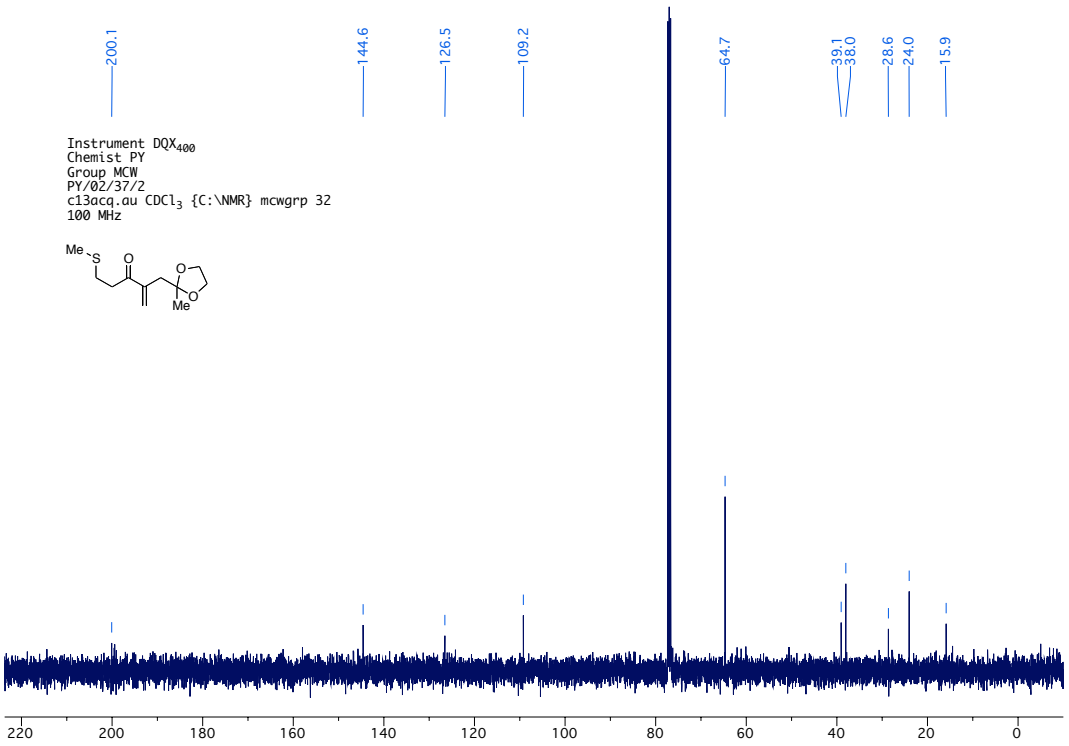
(*E*)-6-(2-Methyl-1,3-dioxolan-2-yl)-1-(methylthio)hex-4-en-3-one, experimental page 135



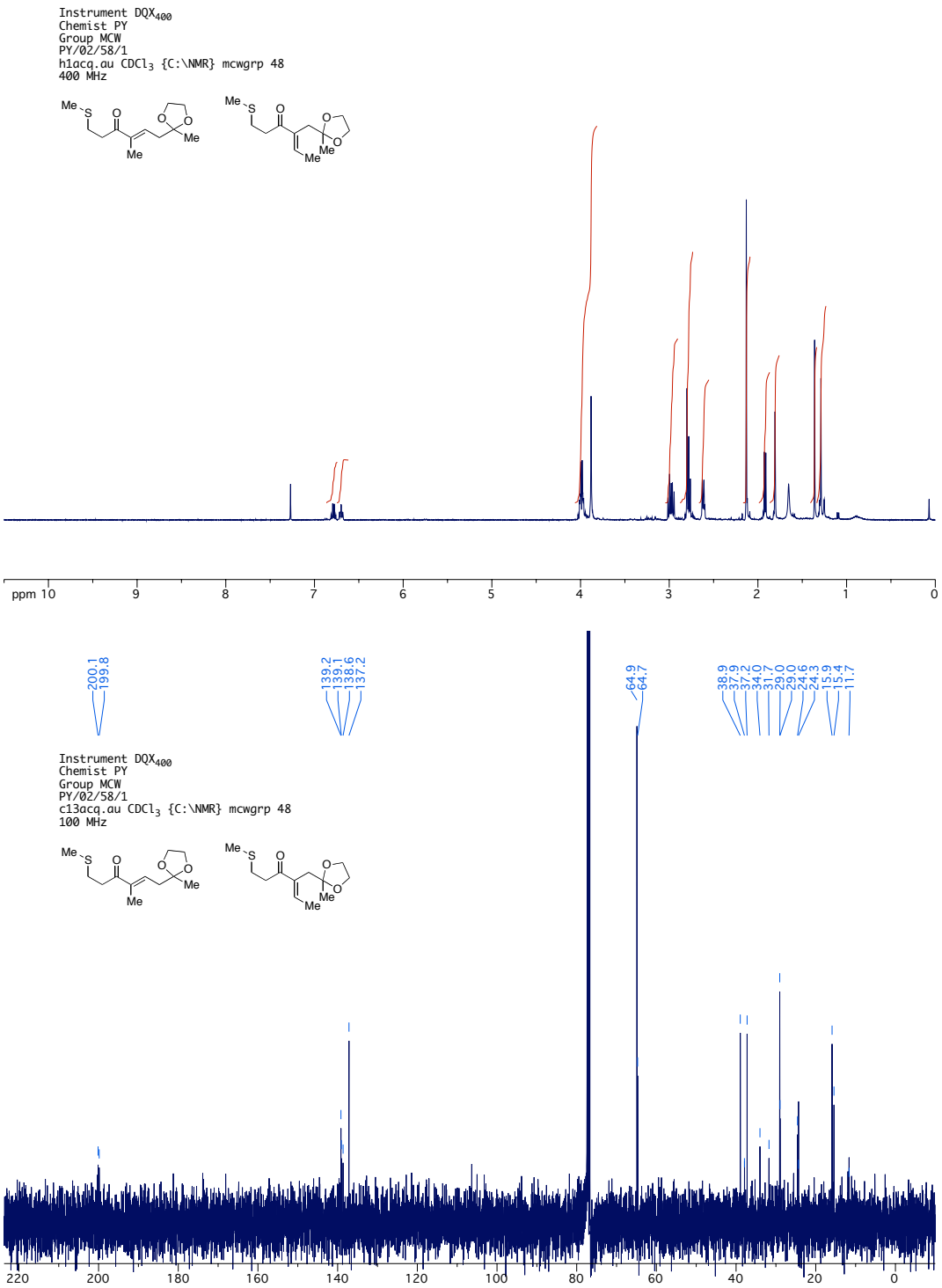


2-((2-methyl-1,3-dioxolan-2-yl)methyl)-5-(methylthio)pent-1-en-3-one, experimental page 135

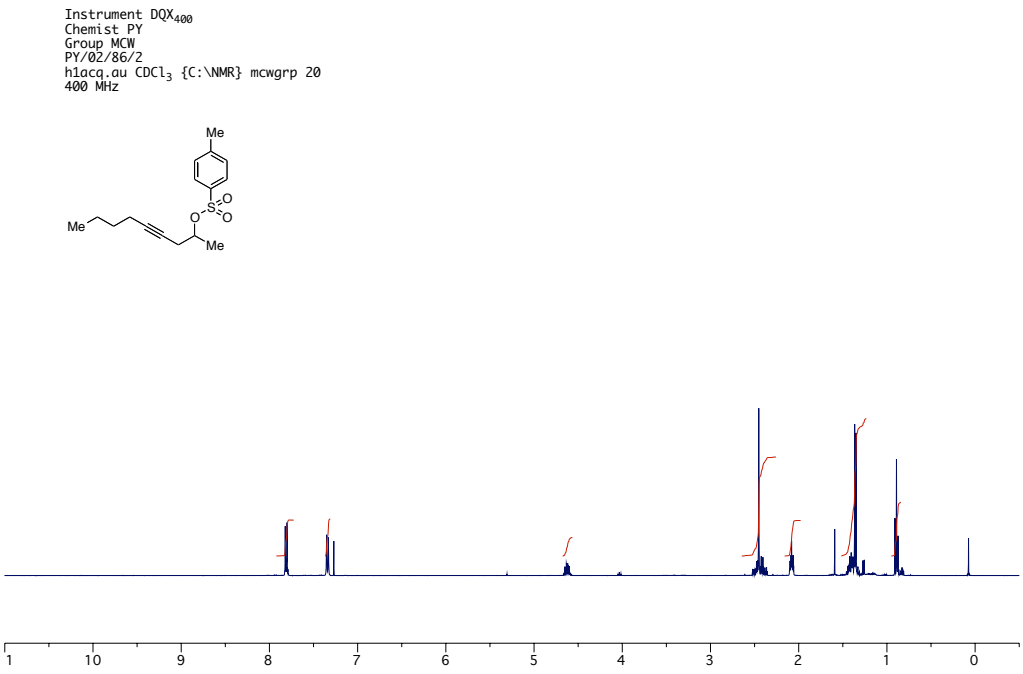


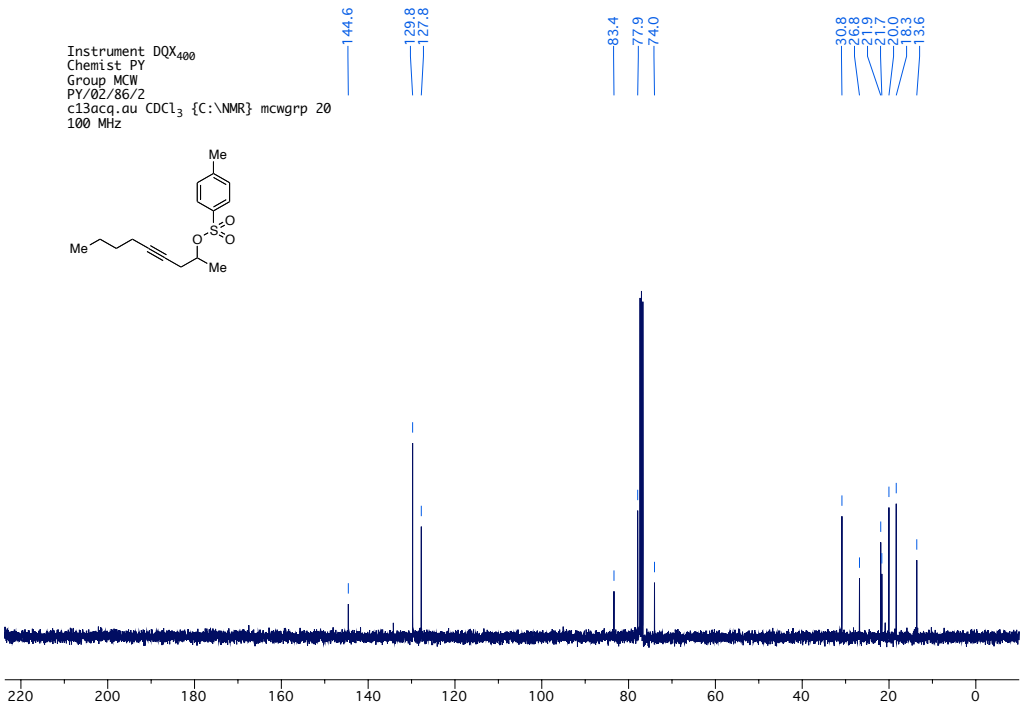


(*E*)-4-Methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-(methylthio)hex-4-en-3-one and (*E*)-4-((2-methyl-1,3-dioxolan-2-yl)methyl)-1-(methylthio)-4-hexen-3-one, experimental page 136

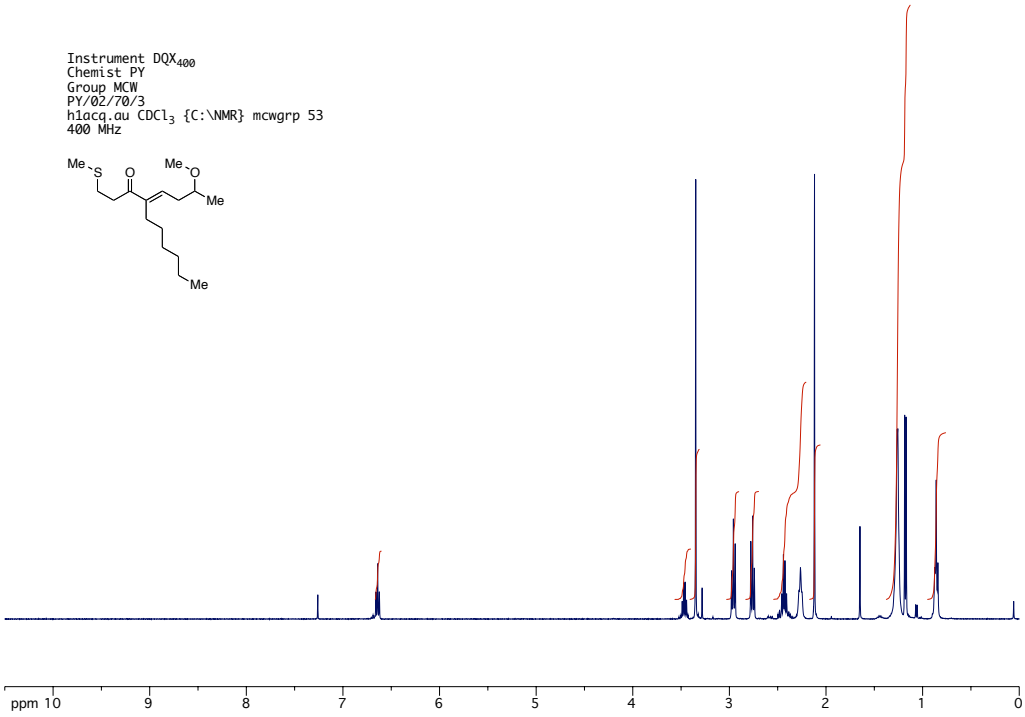


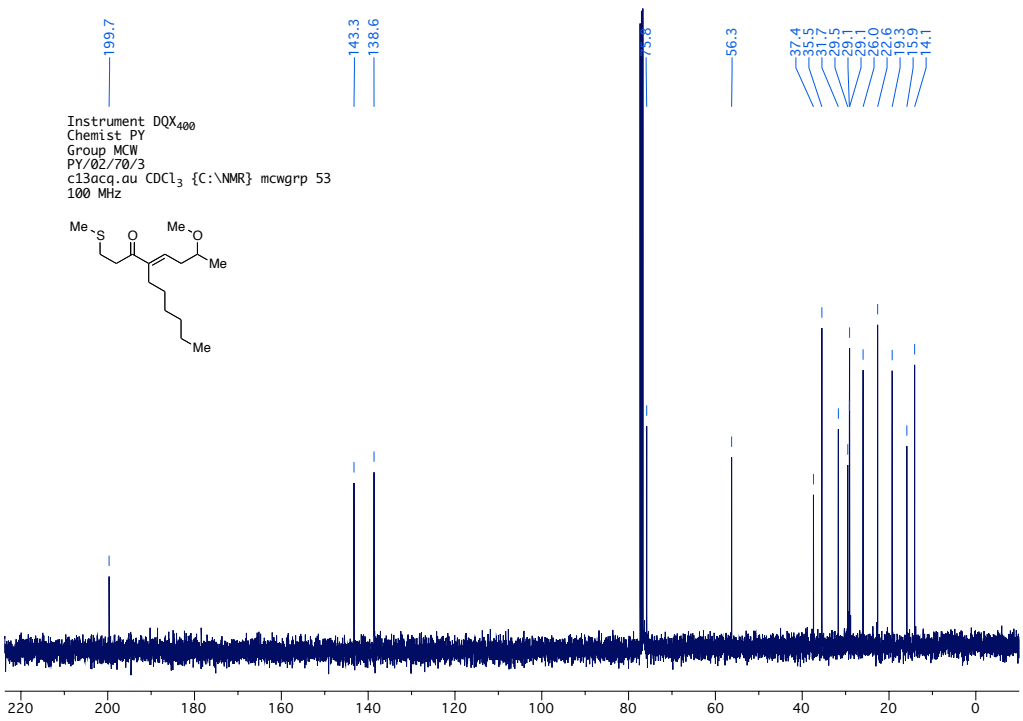
4-Nonyn-2-yl 4-methylbenzenesulphonate, experimental page 141



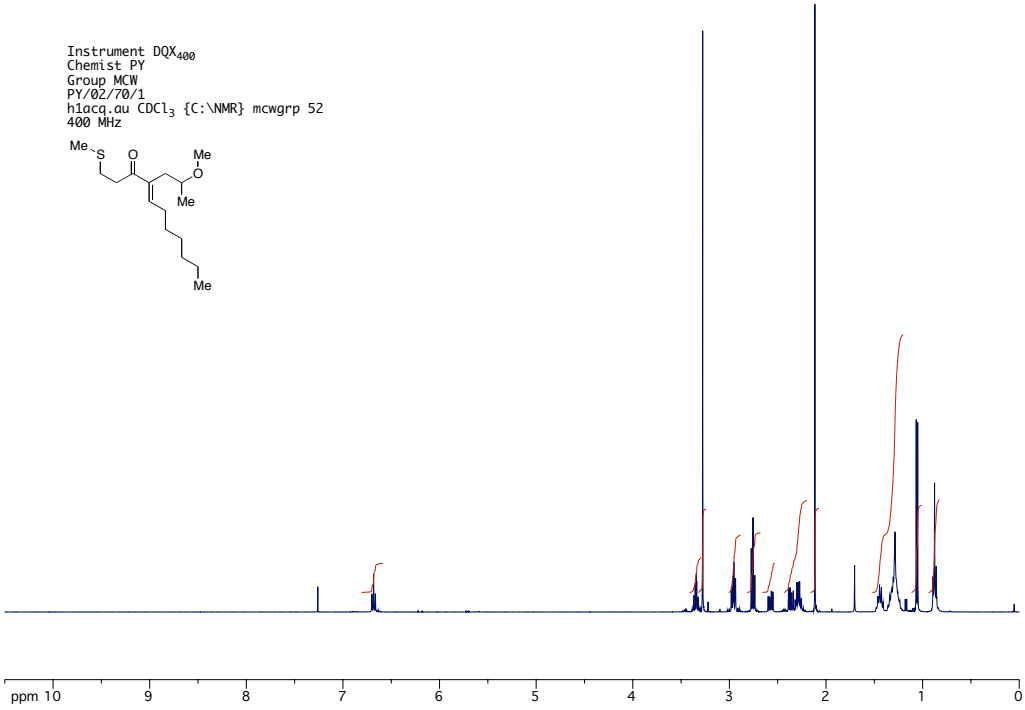


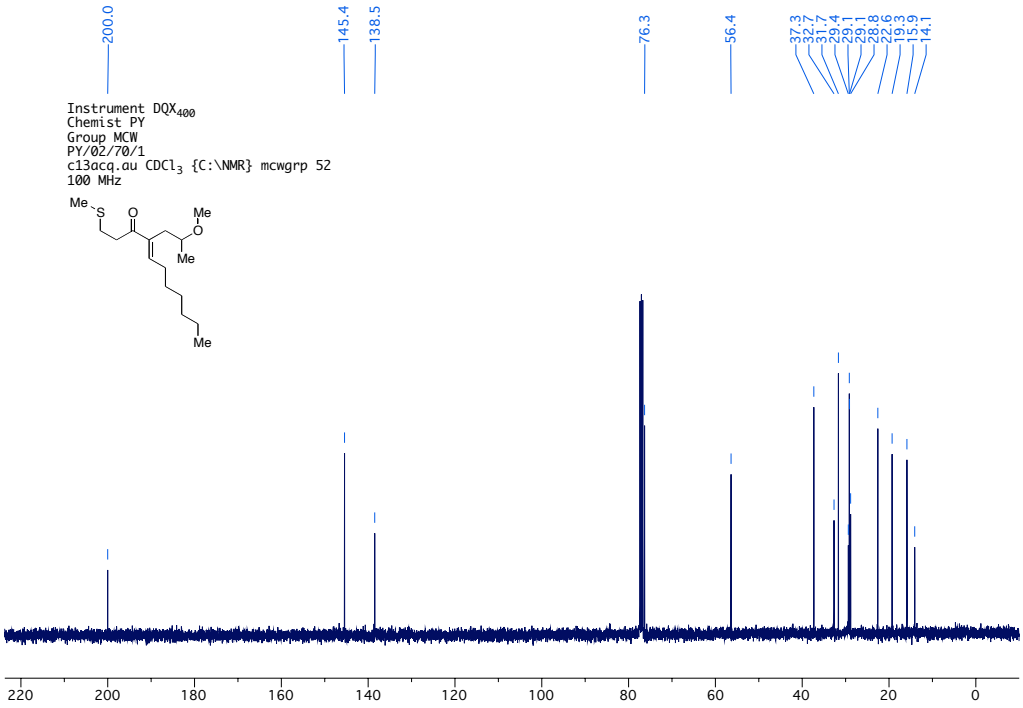
(*E*)-4-(3-methoxybutylidene)-1-(methylthio)decan-3-one, experimental page 138



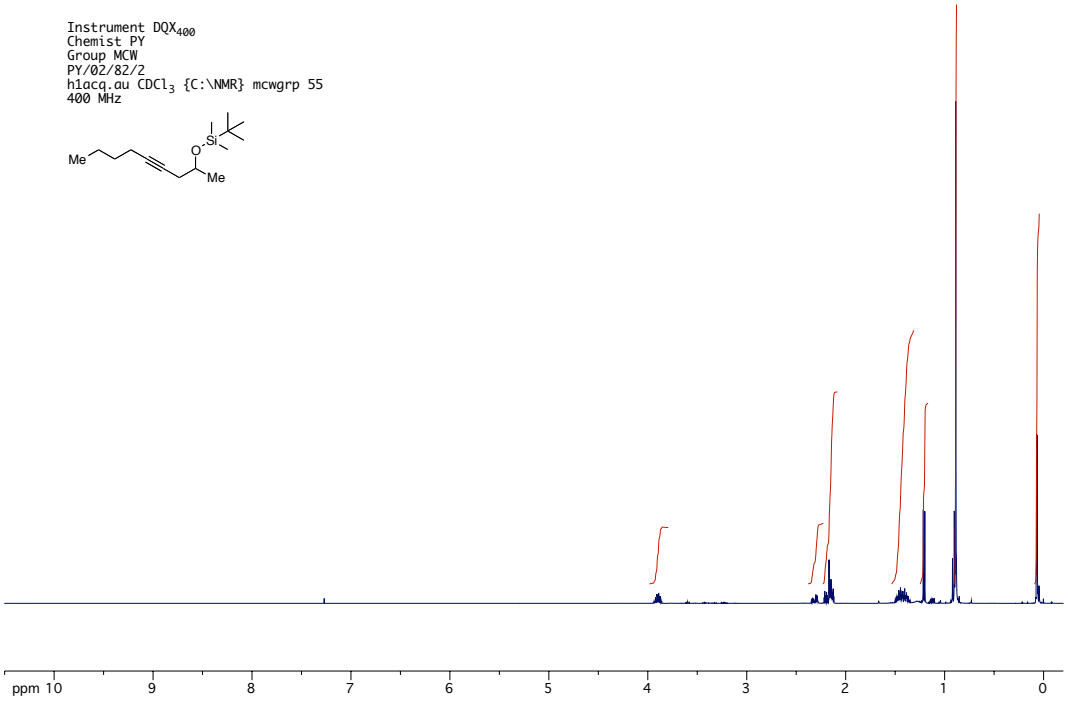


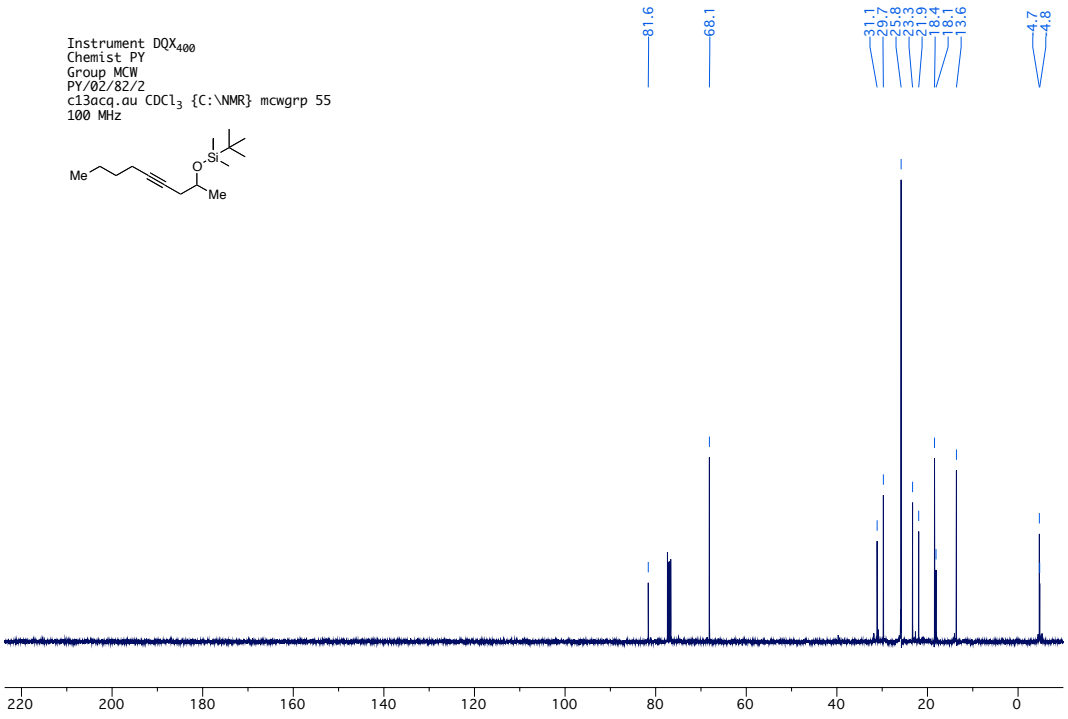
(*E*)-4-(2-methoxypropyl)-1-(methylthio)undec-4-en-3-one, experimental page 138



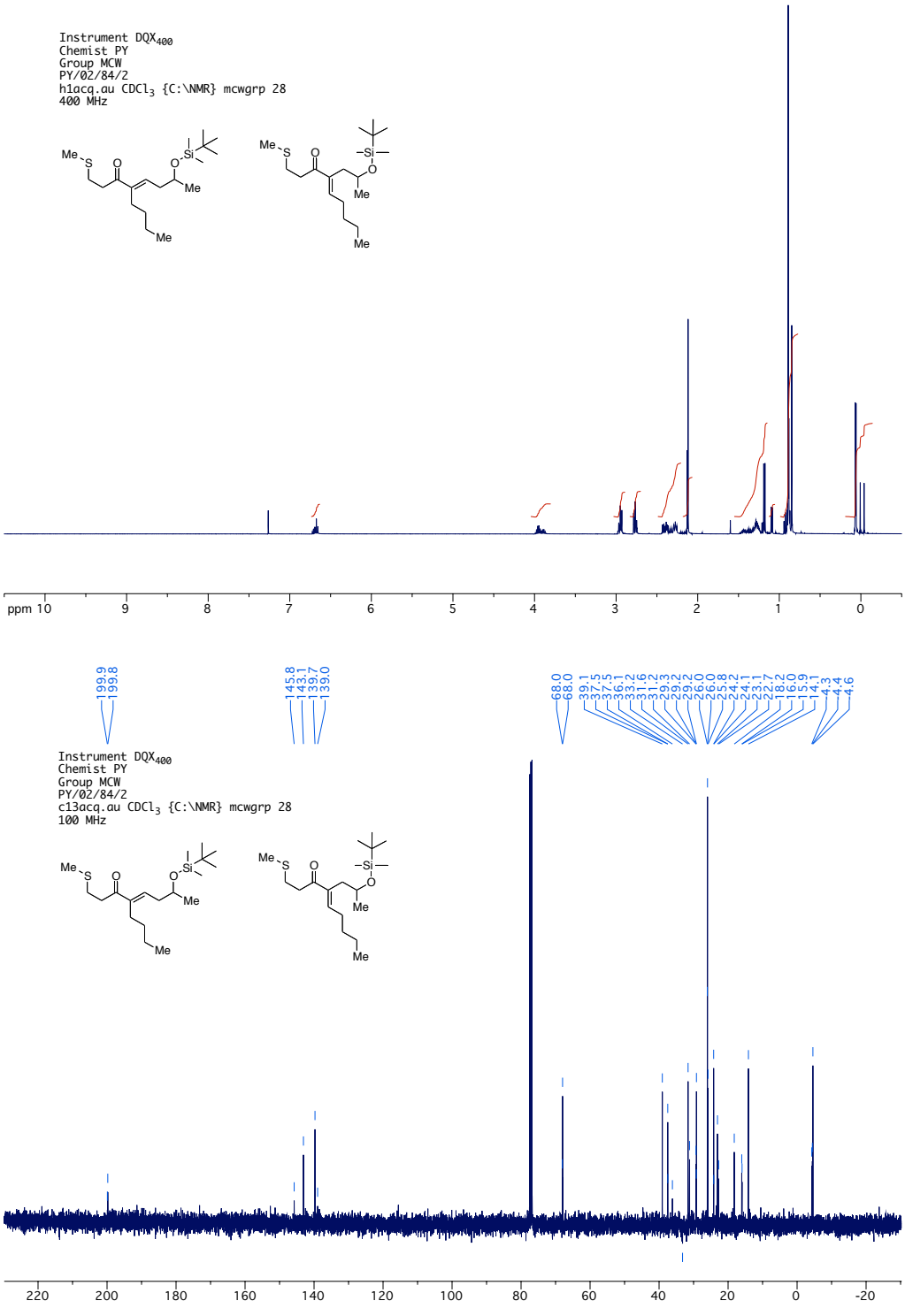


tert-Butyldimethylsilyloxy(4-nonyl-2-ol), experimental page 139

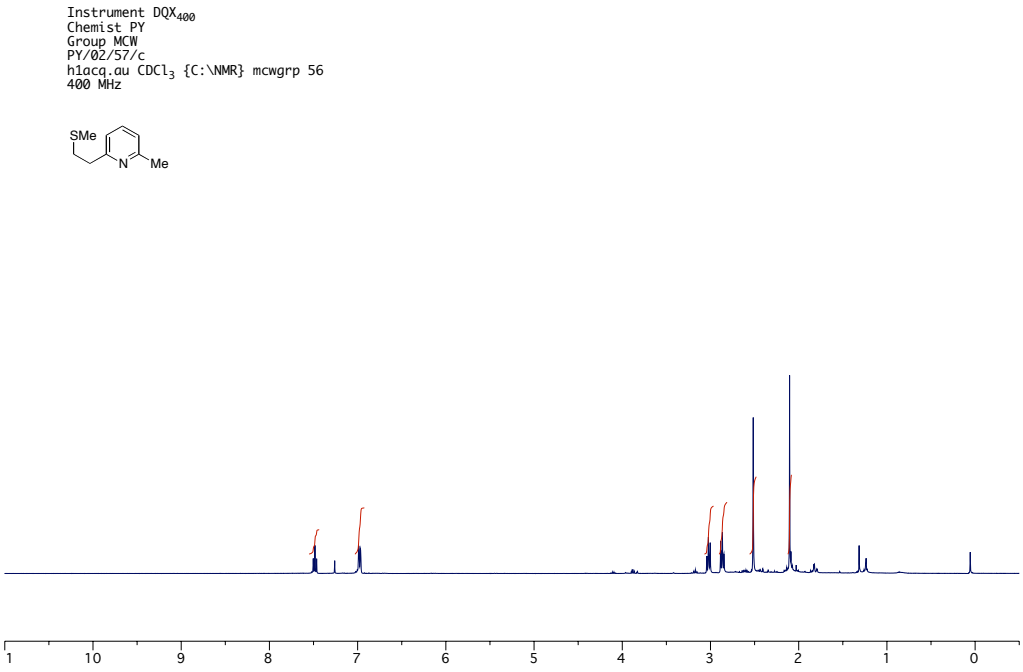


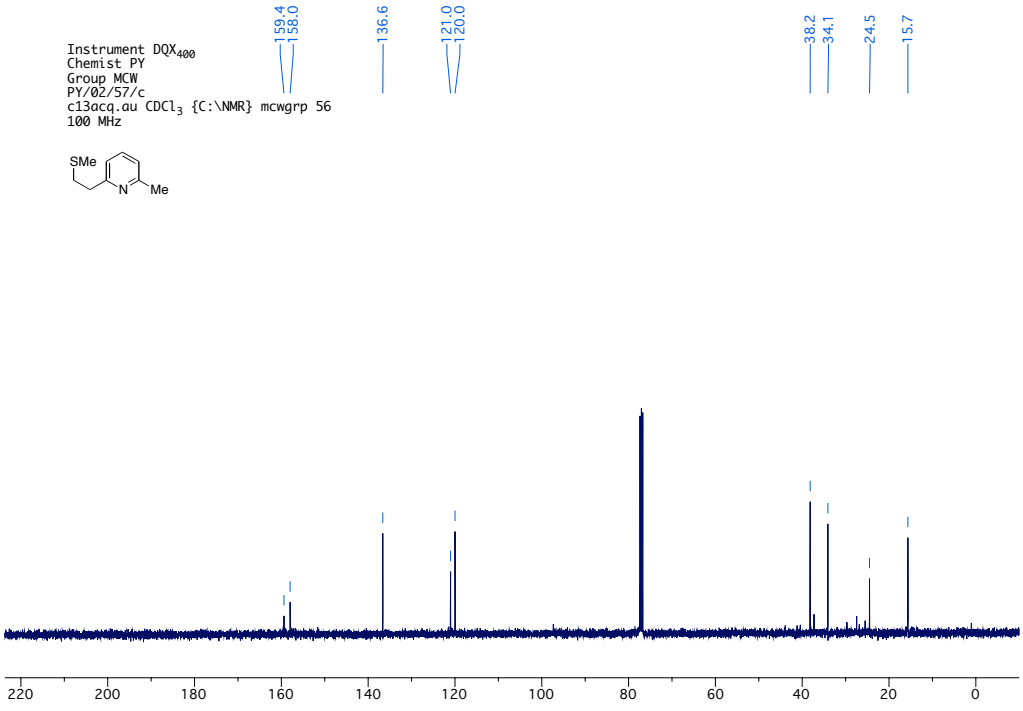


(*E*)-4-butyl-7-(tert-butyldimethylsilyloxy)-1-(methylthio)oct-4-en-3-one and (*E*)-4-(2-(tert-butyldimethylsilyloxy)propyl)-1-(methylthio)-non-4-en-3-one, experimental page 140

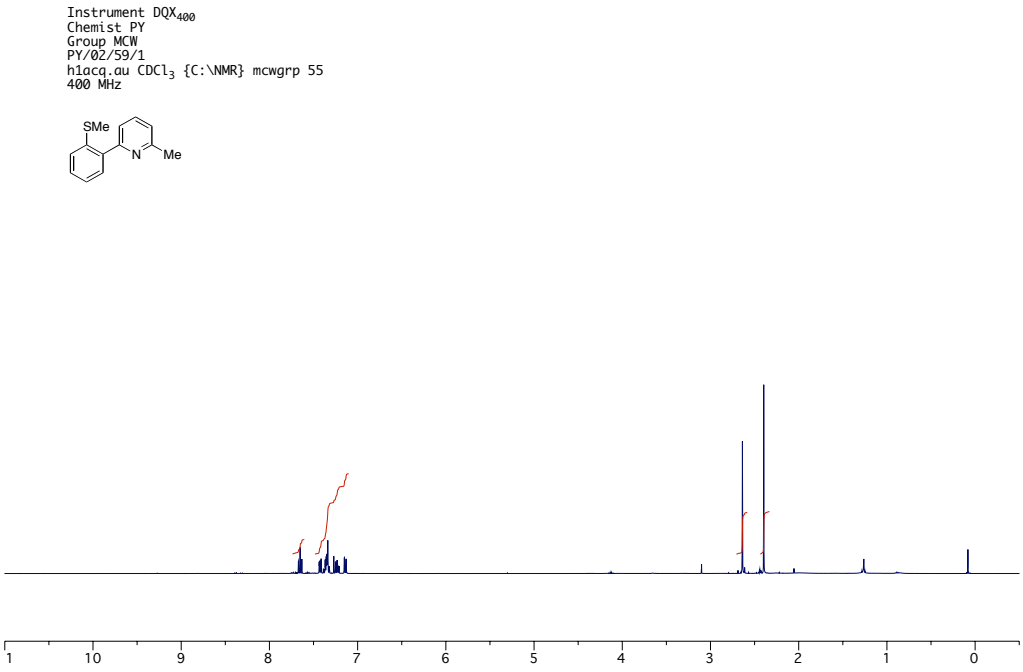


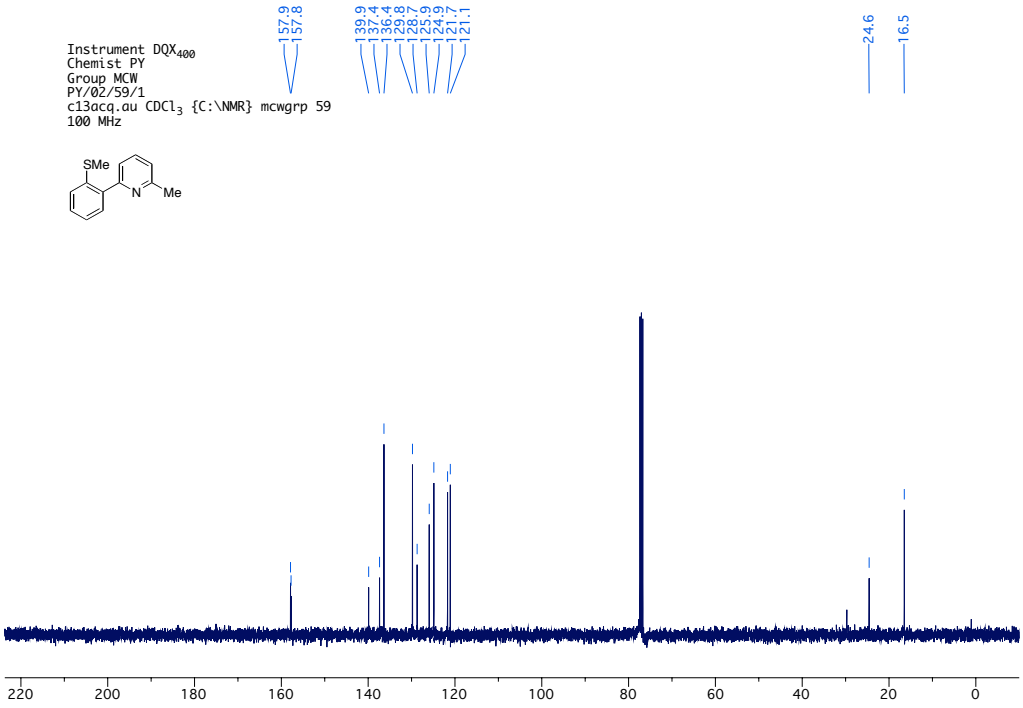
2-methyl-6-(2-(methylthio)ethyl)pyridine, experimental page 145



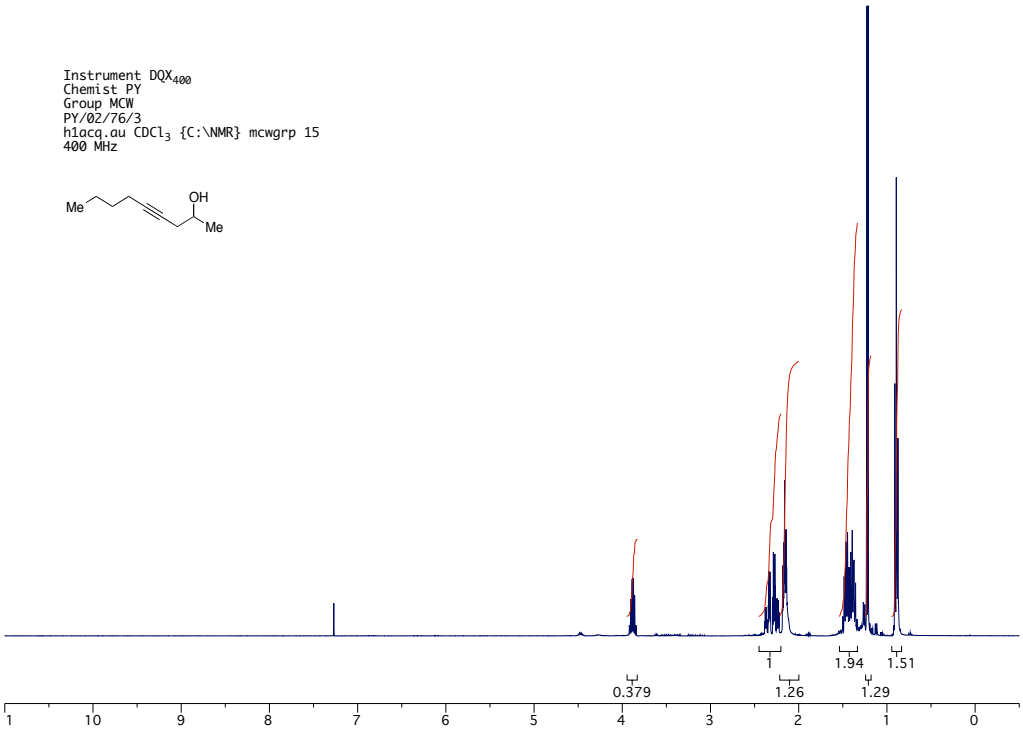


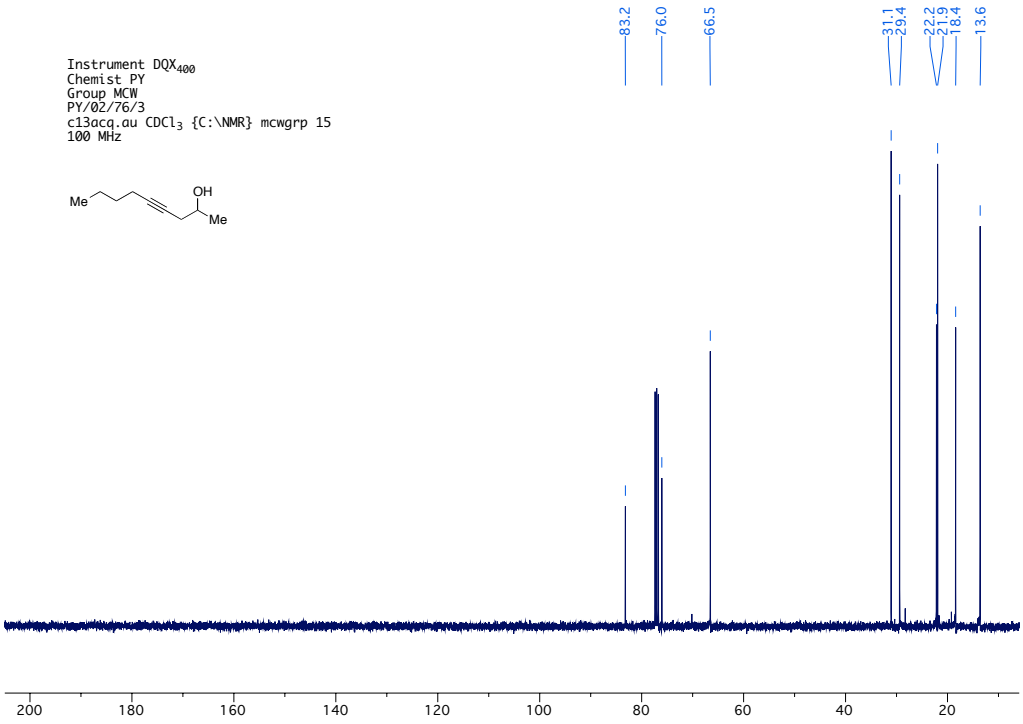
2-methyl-6-(2-(methylthio)phenyl)pyridine, experimental page 146





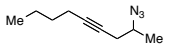
4-nonyn-2-ol, experimental page 120

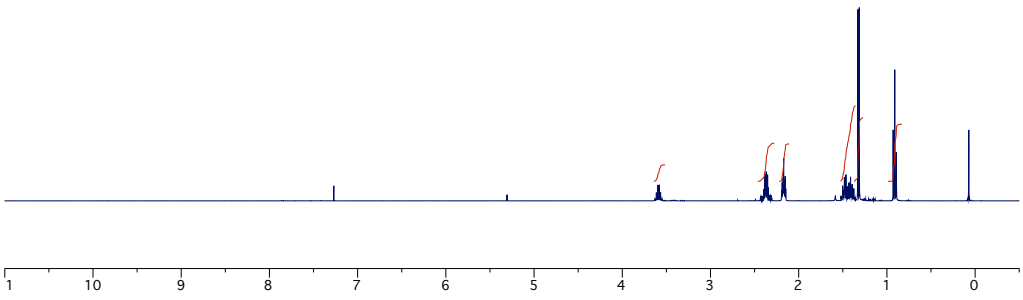




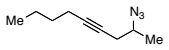
4-Azidonon-4-yne, experimental page 141

Instrument DQX$_{400}$
Chemist PY
Group MCW
PY/02/89/c
h1acq.au $CDCl_3$ {C:\NMR} mcwgrp 30
400 MHz

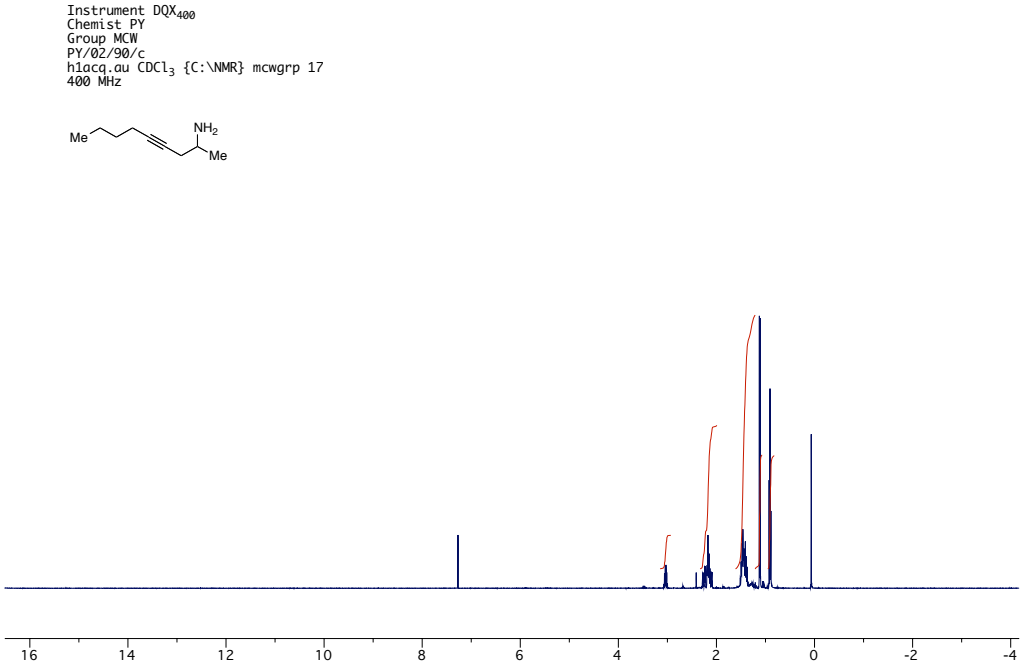


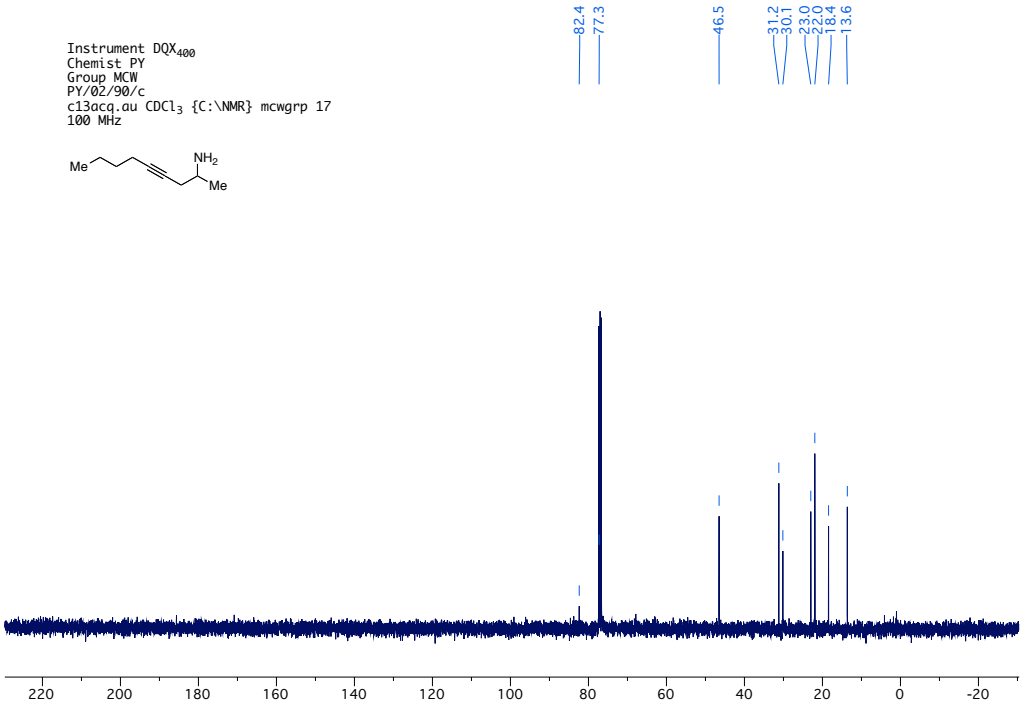


Instrument DQX$_{400}$
Chemist PY
Group MCW
PY/02/89/c
c13acq.au $CDCl_3$ {C:\NMR} mcwgrp 30
100 MHz

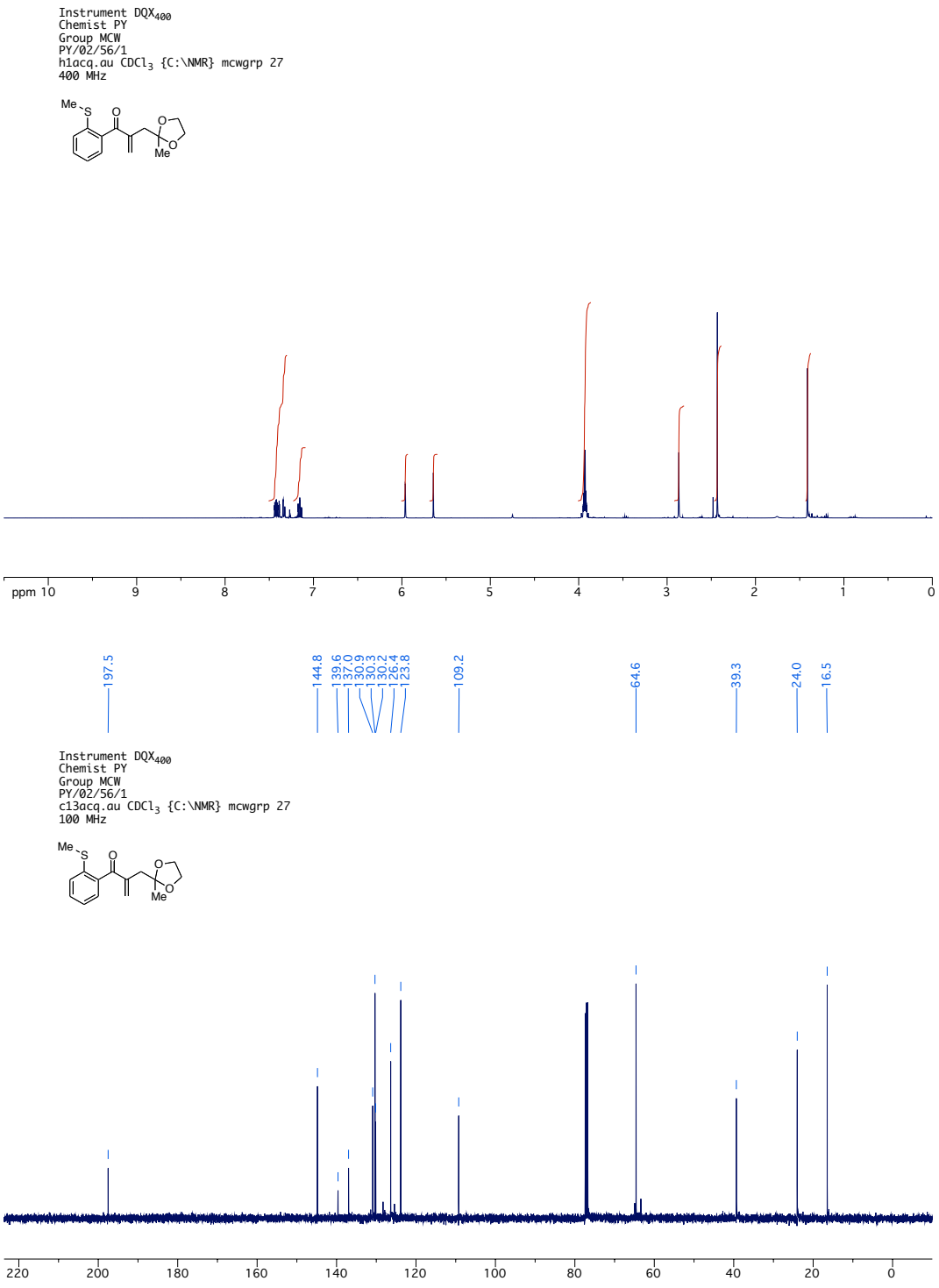


4-Nonyn-2-amine, experimental page 142

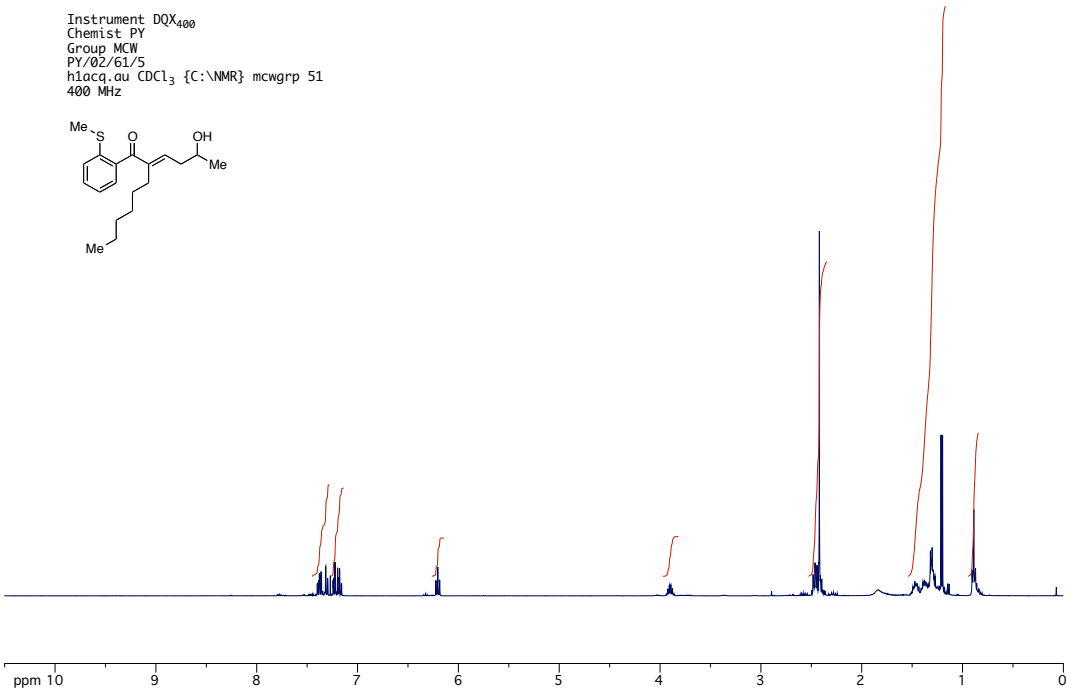


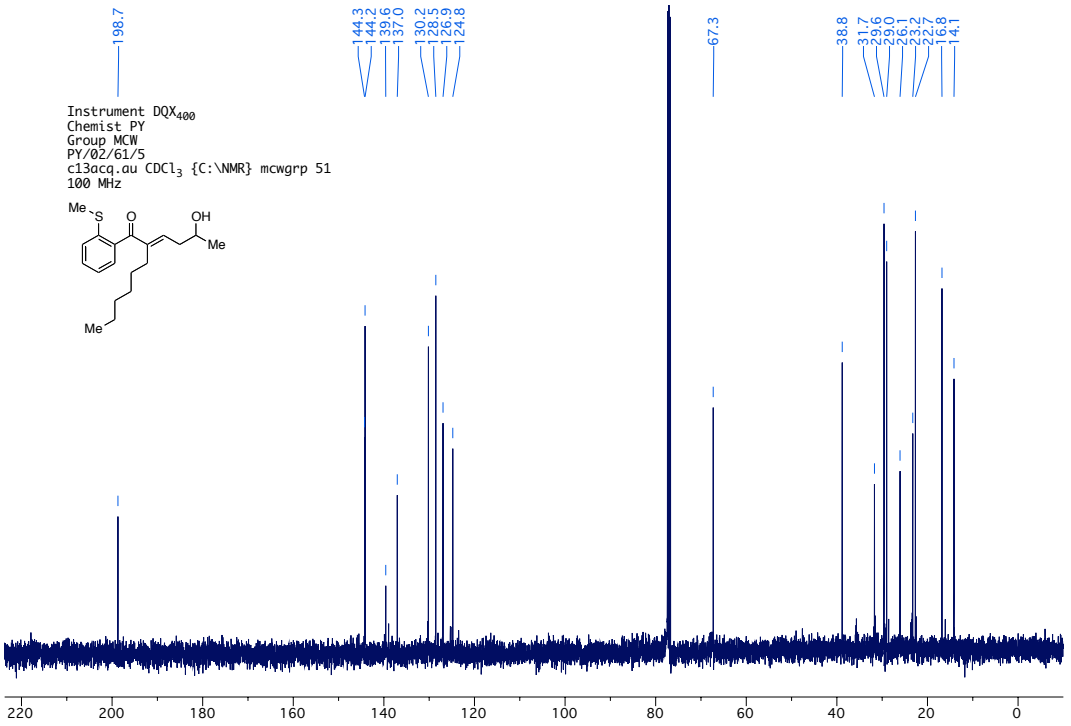


2-((2-methyl-1,3-dioxolan-2-yl)methyl)-1-(2-(methylthio)phenyl)-2-propen-1-one, experimental page 143

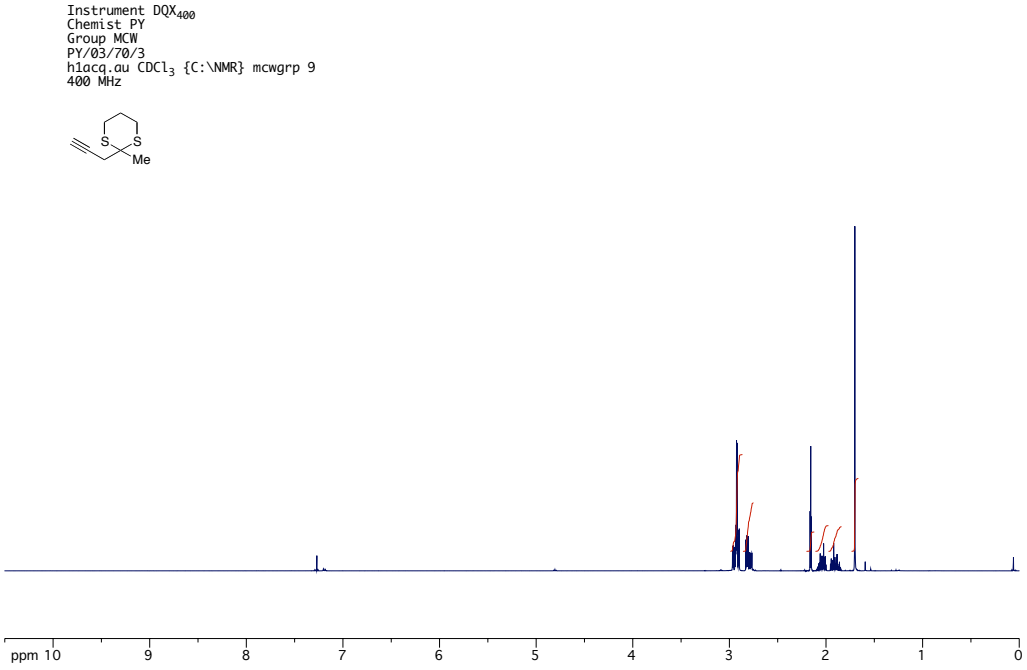


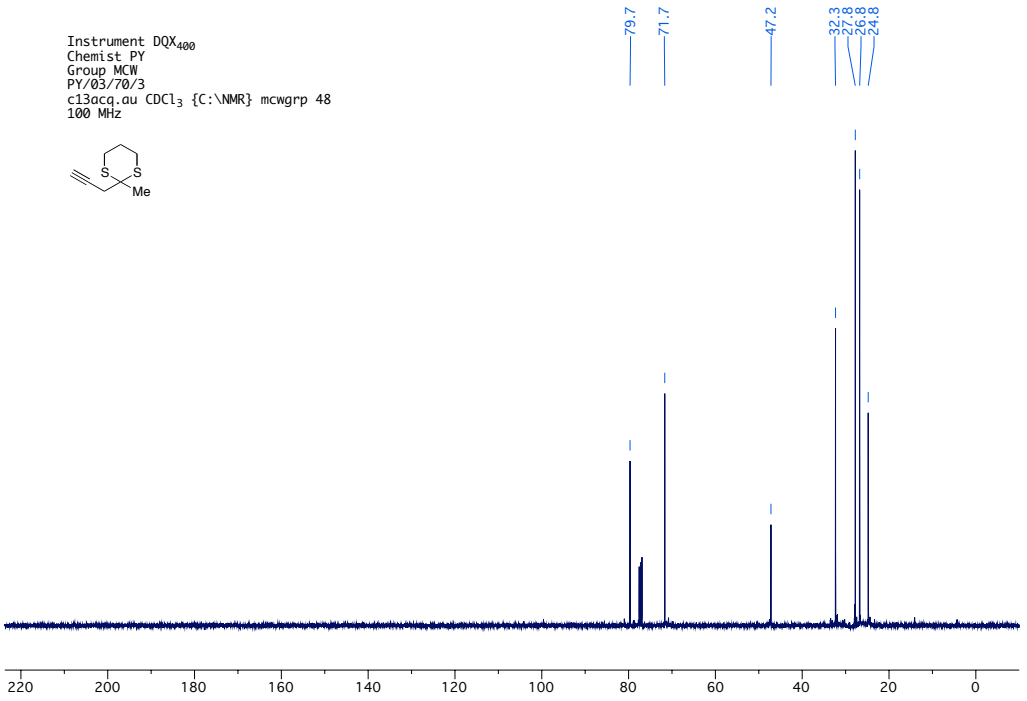
(*E*)-2-(3-Hydroxybutylidene)-1-(2-(methylthio)phenyl)octan-1-one, experimental page 144



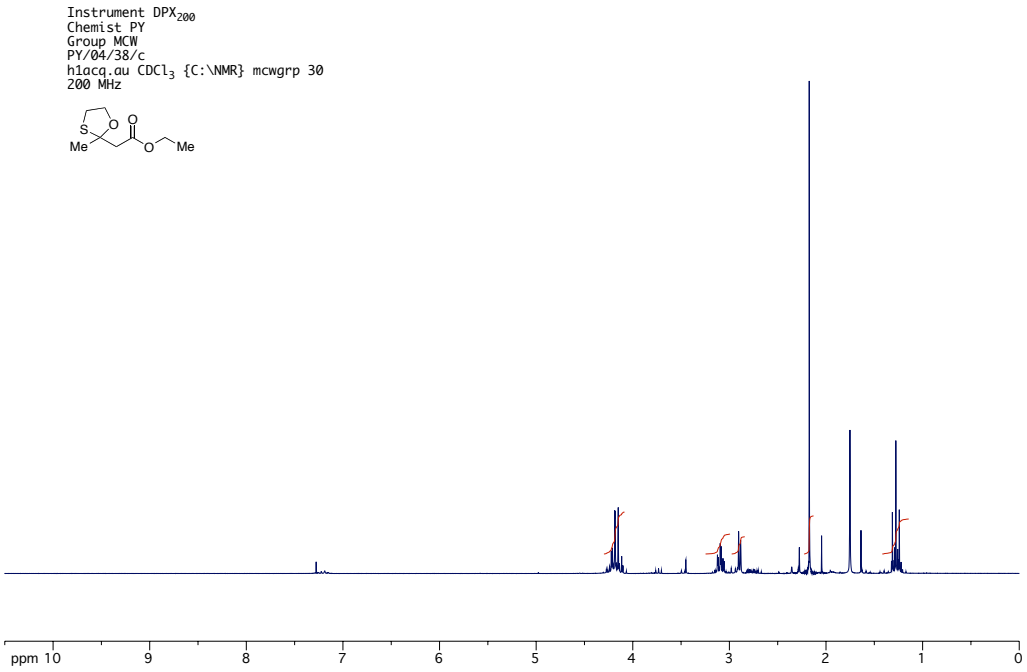


2-Methyl-2-propyn-2-yl-1,3-dithiane, experimental page 146

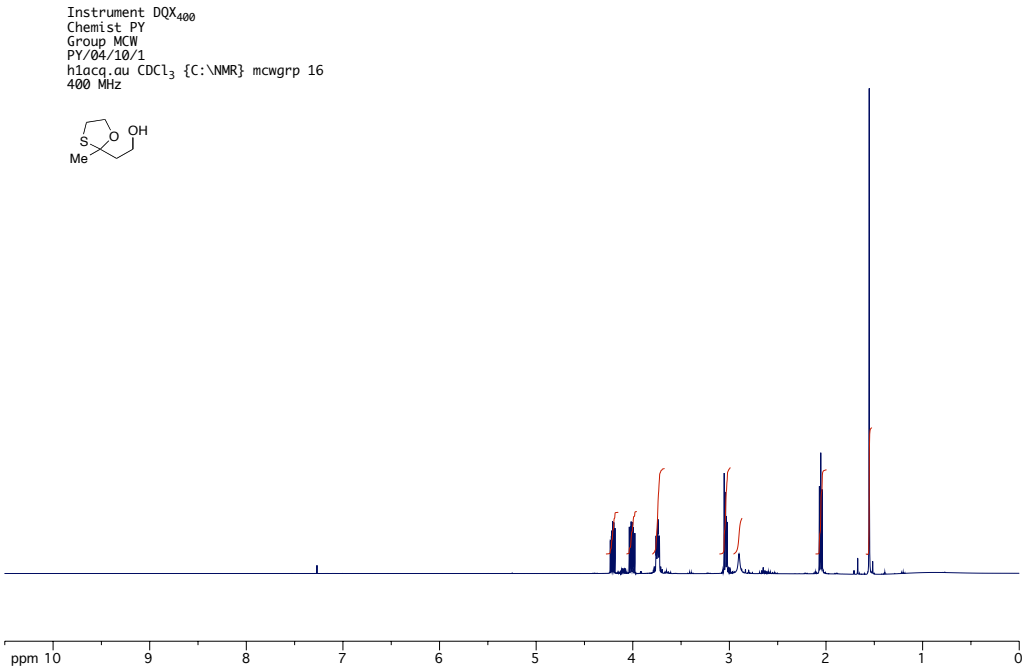




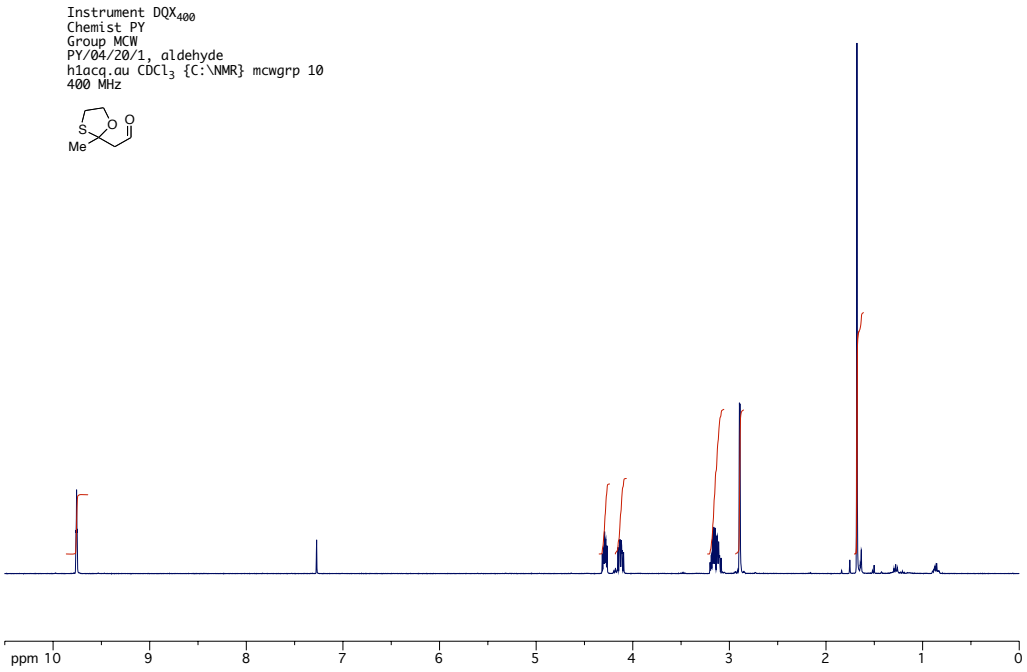
Ethyl 2-(2-methyl-1,3-oxathiolan-2-yl)acetate, experimental page 147

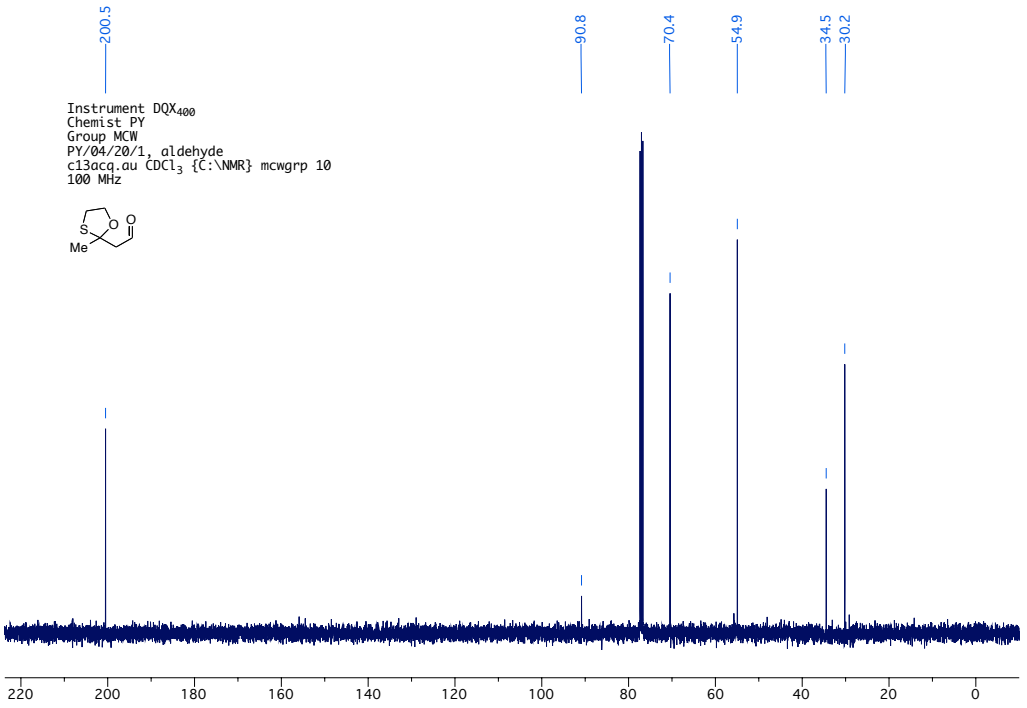


2-(2-Methyl-1,3-oxathionan-2-yl)ethanol, experimental page 148

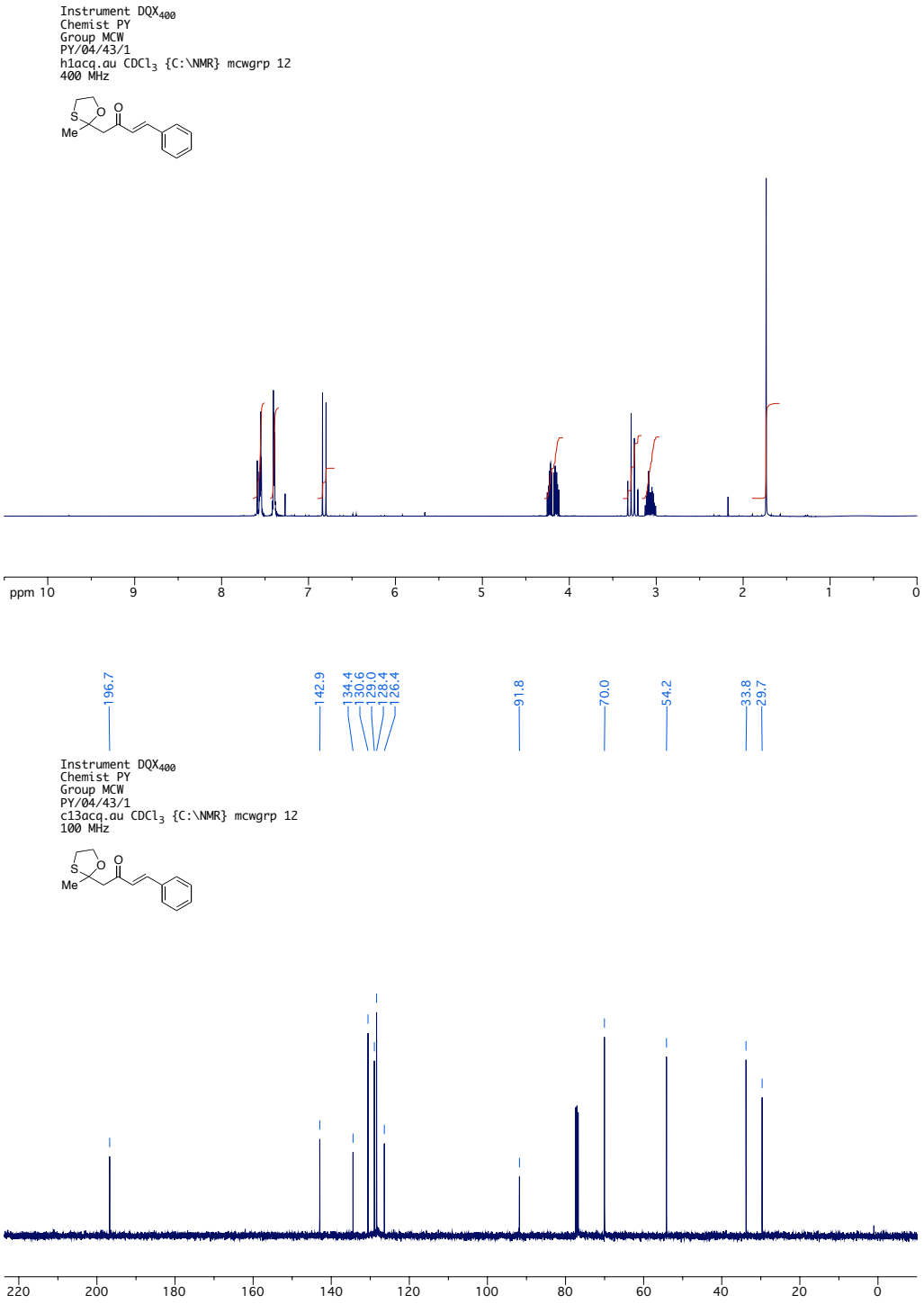


2-(2-methyl-1,3-oxathiolan-2-yl)acetaldehyde, experimental page 149

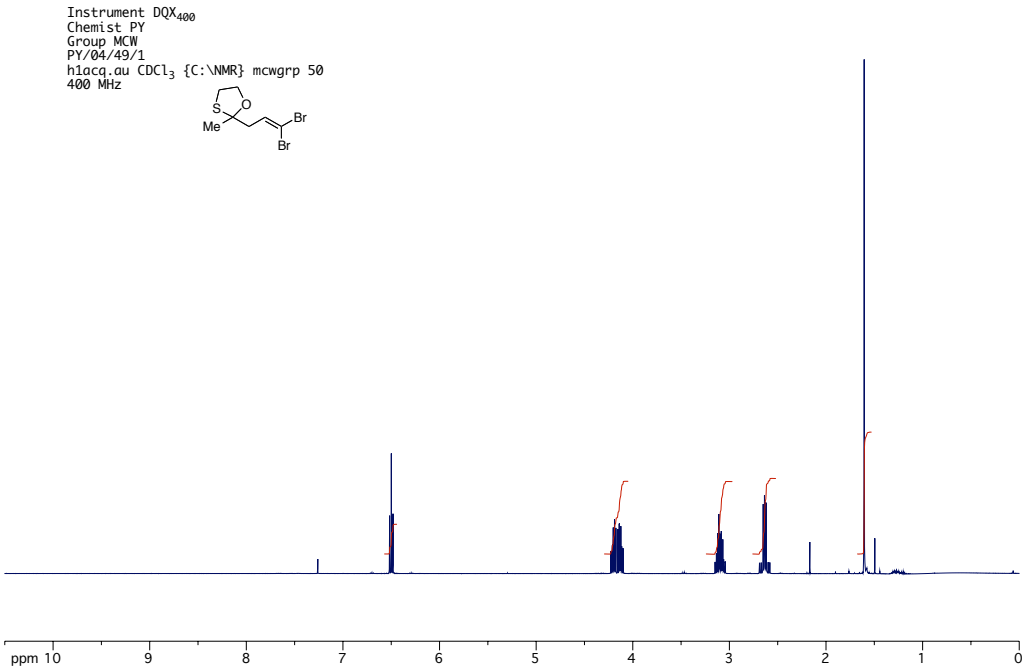


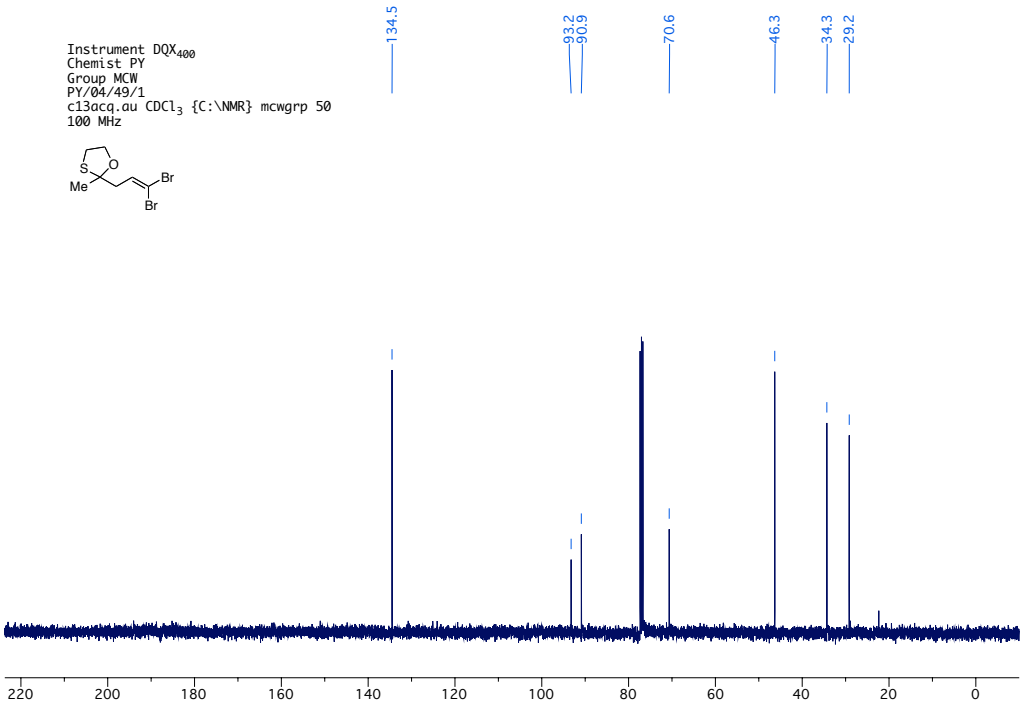


2-(2-methyl-1,3-oxathiolan-2-yl)acetaldehyde, experimental page 152

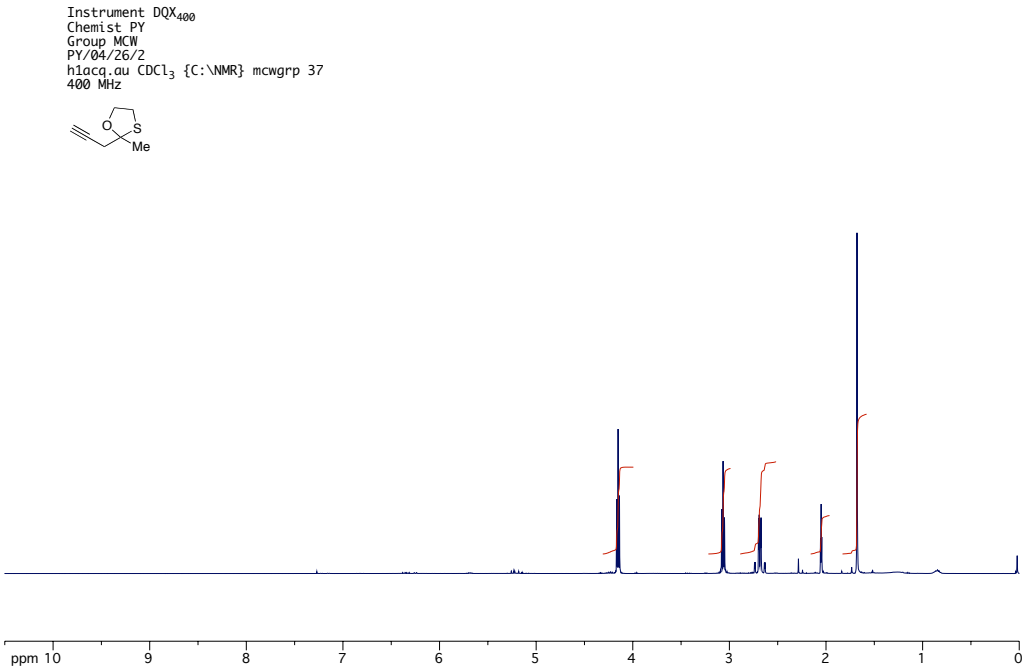


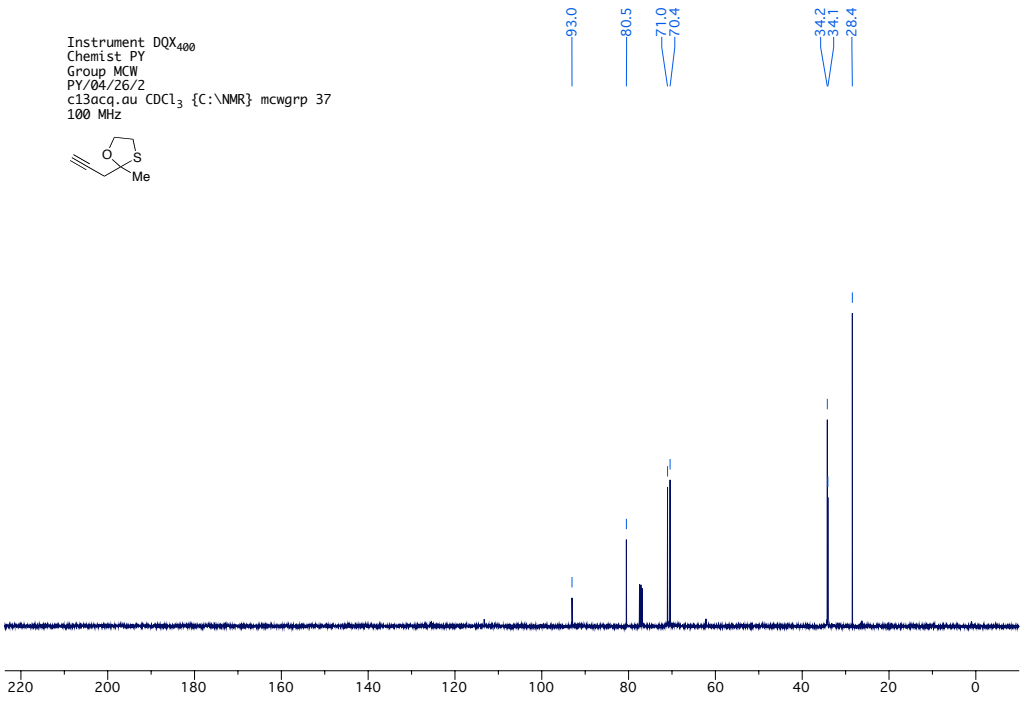
2-(3,3-dibromoallyl)-2-methyl-1,3-oxathiolane, experimental page 150



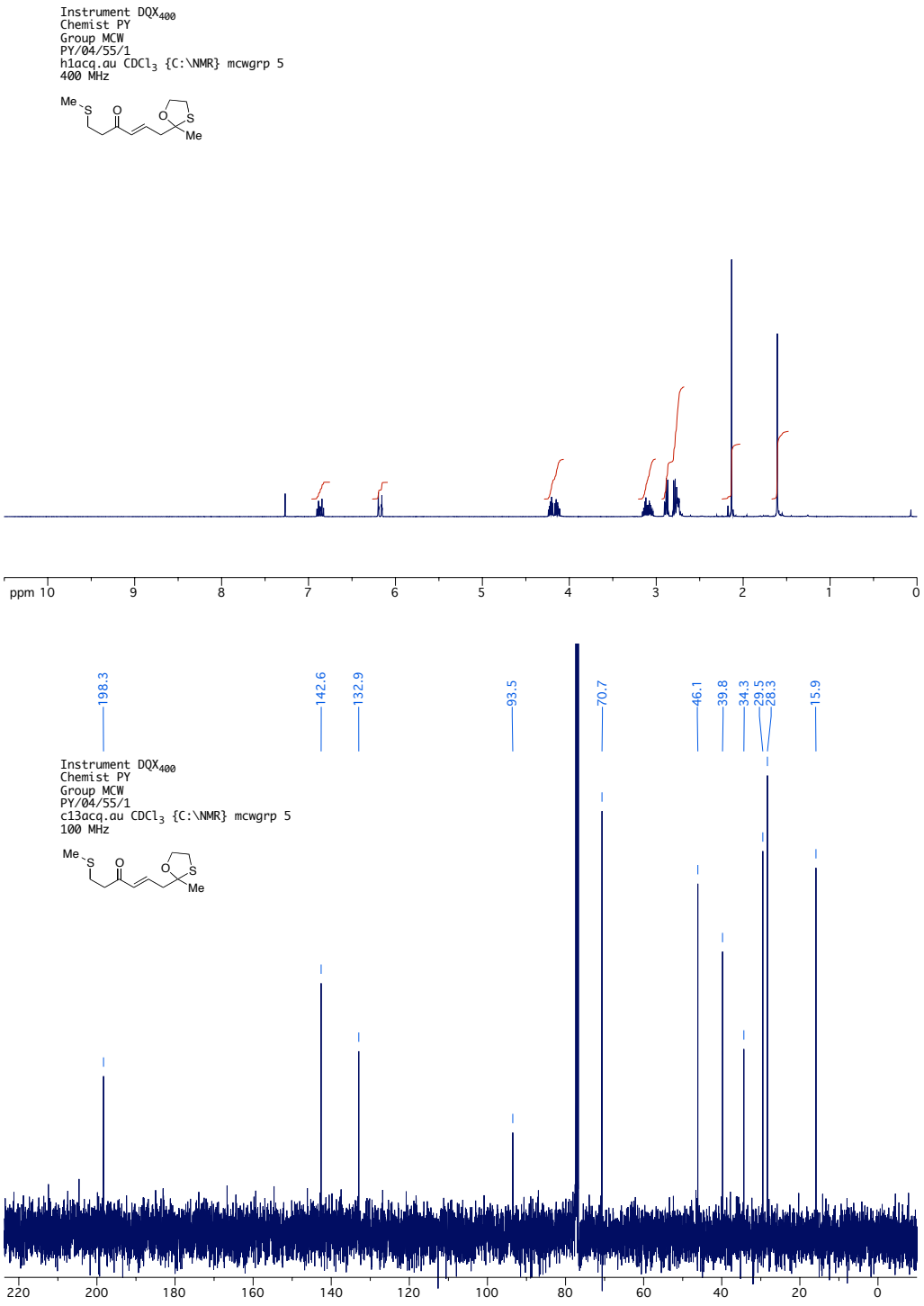


2-methyl-2-(prop-2-ynyl)-1,3-oxathiolane, experimental page 150

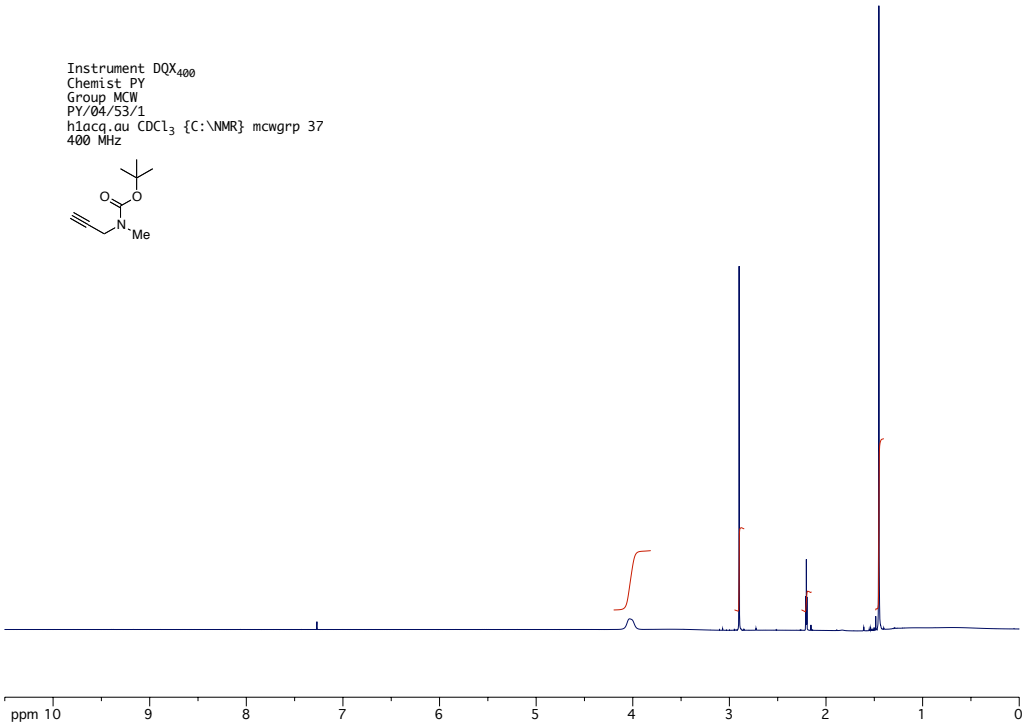


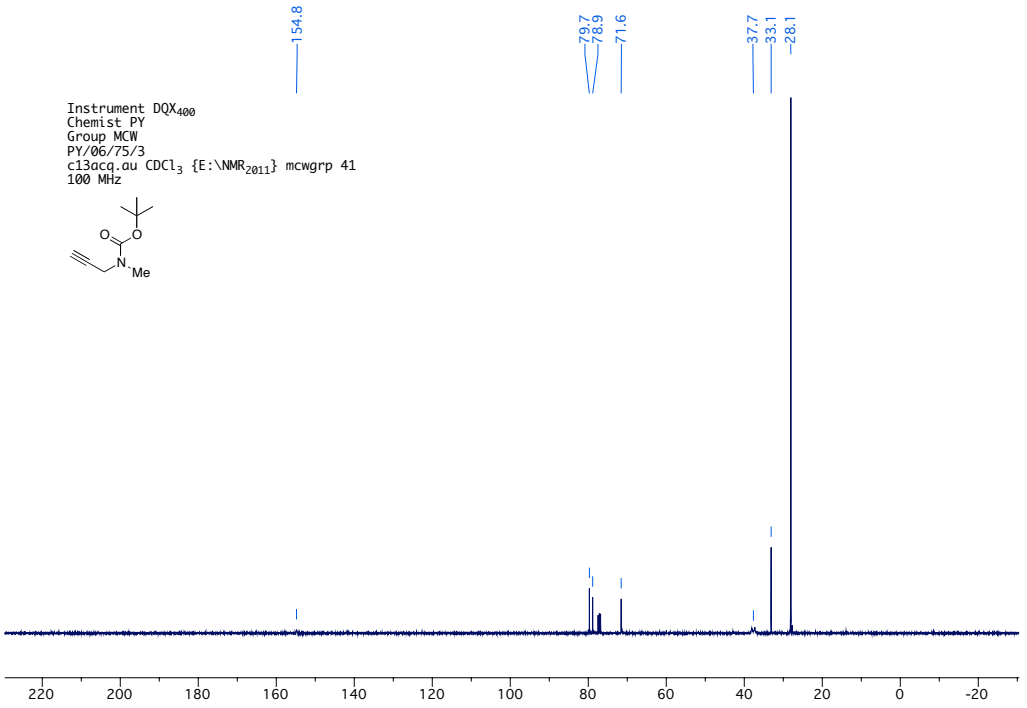


(*E*)-6-(2-methyl-1,3-oxathiolan-2-yl)-1-(methylthio)hex-4-en-3-one, experimental page 153

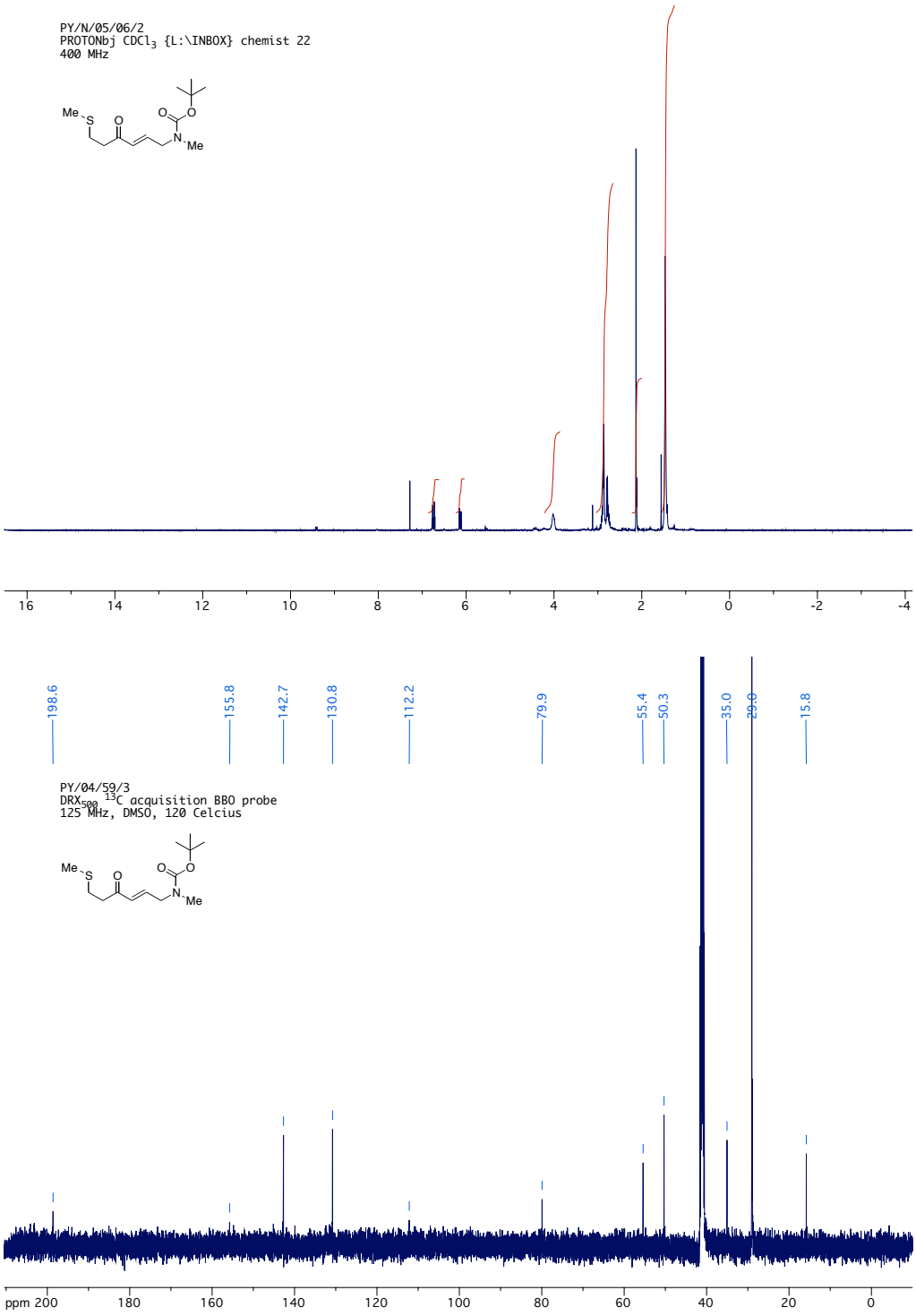


tert-butyl methyl(prop-2-ynyl)carbamate, experimental page 153

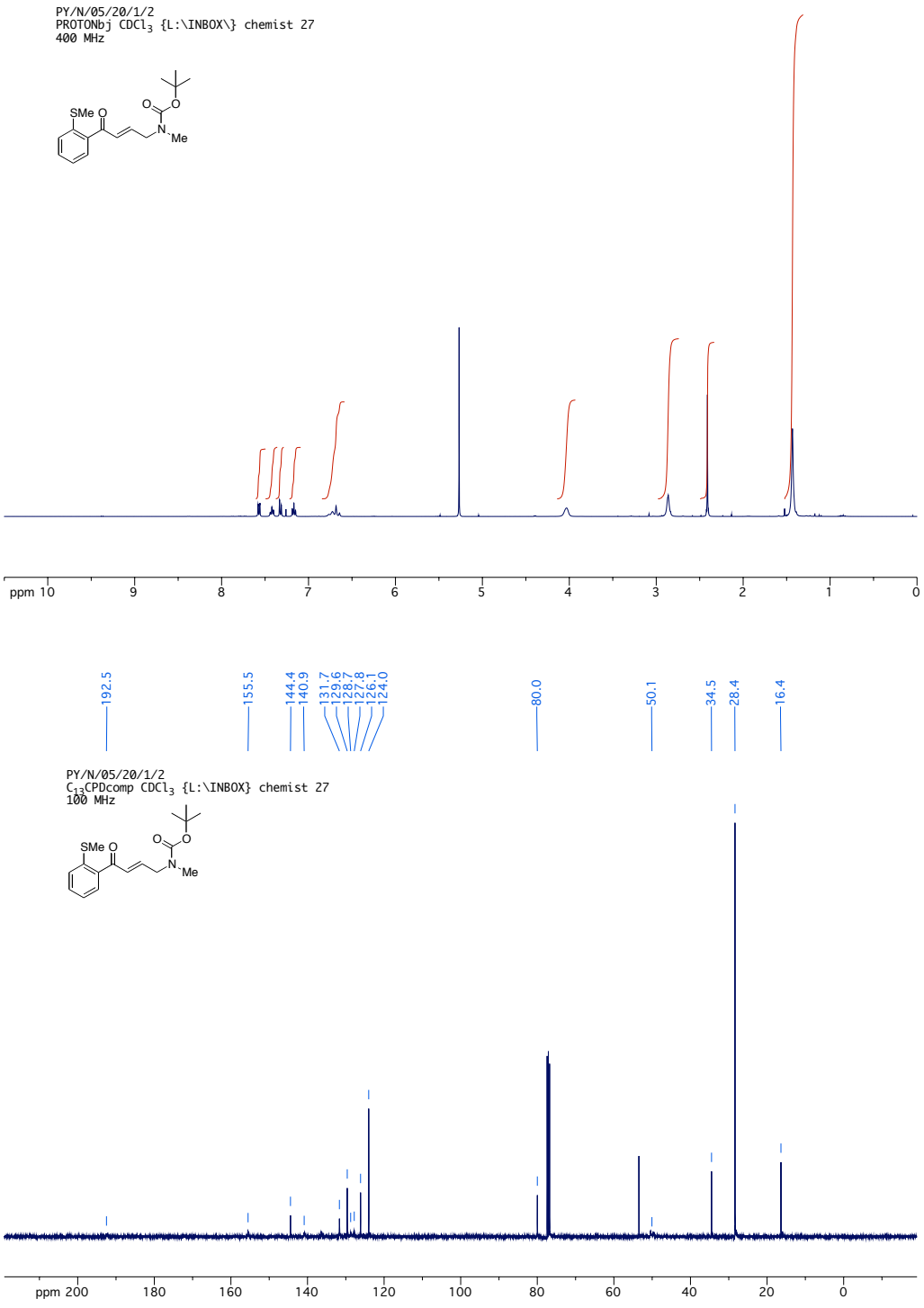




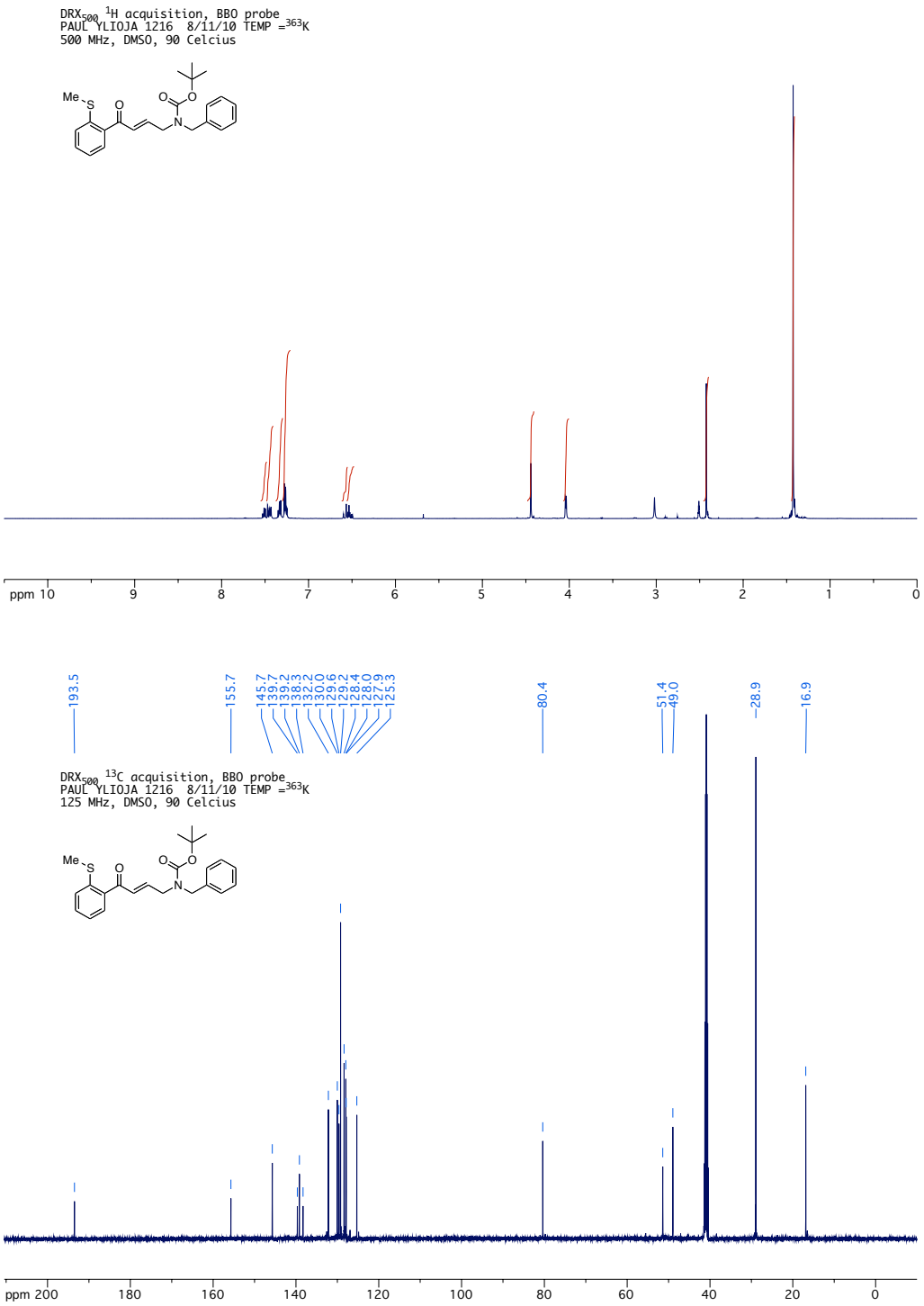
(*E*)-tert-butyl methyl(6-(methylthio)-4-oxohex-2-enyl)carbamate, experimental page 177



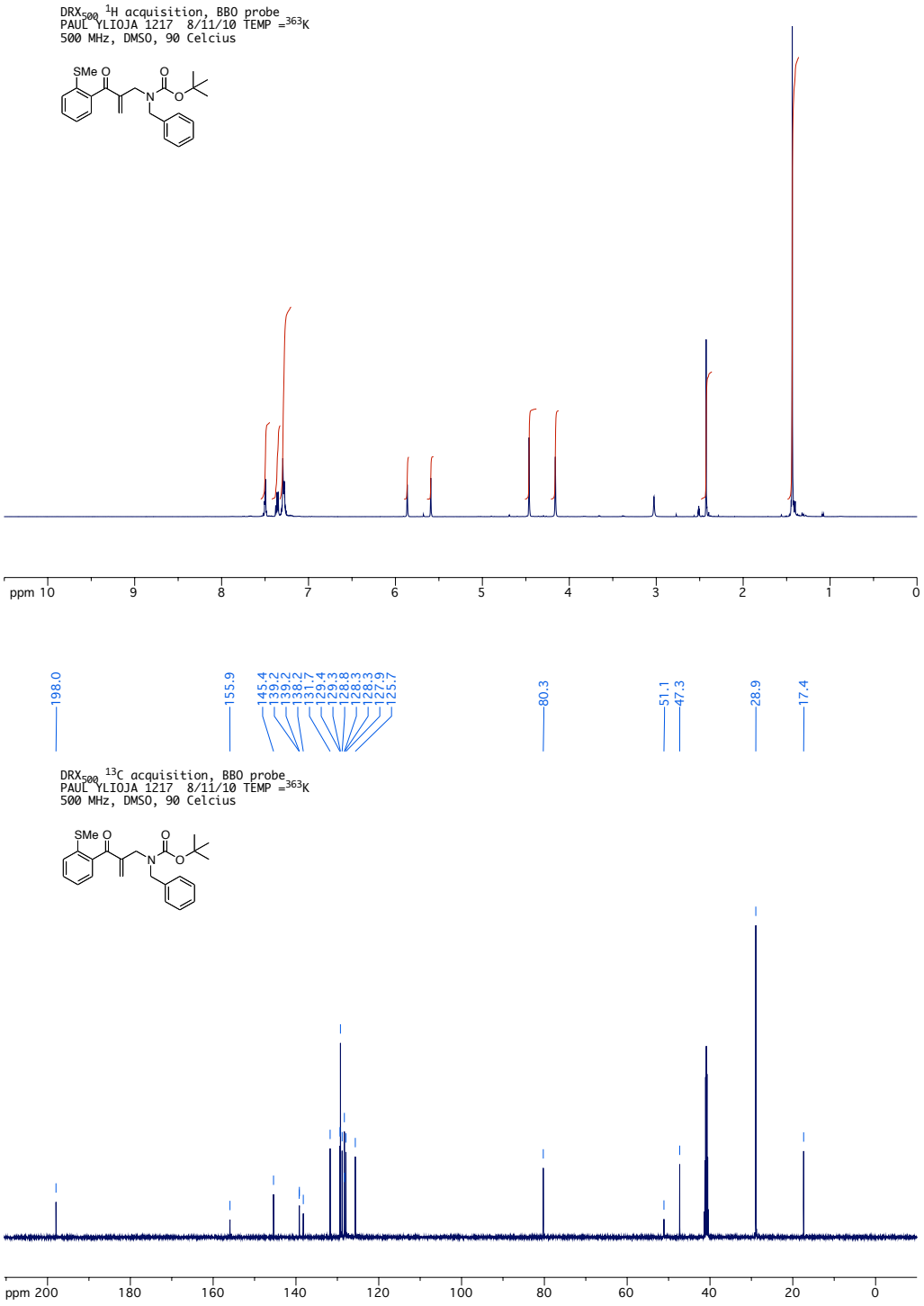
(*E*)-*tert*-butyl methyl(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 186



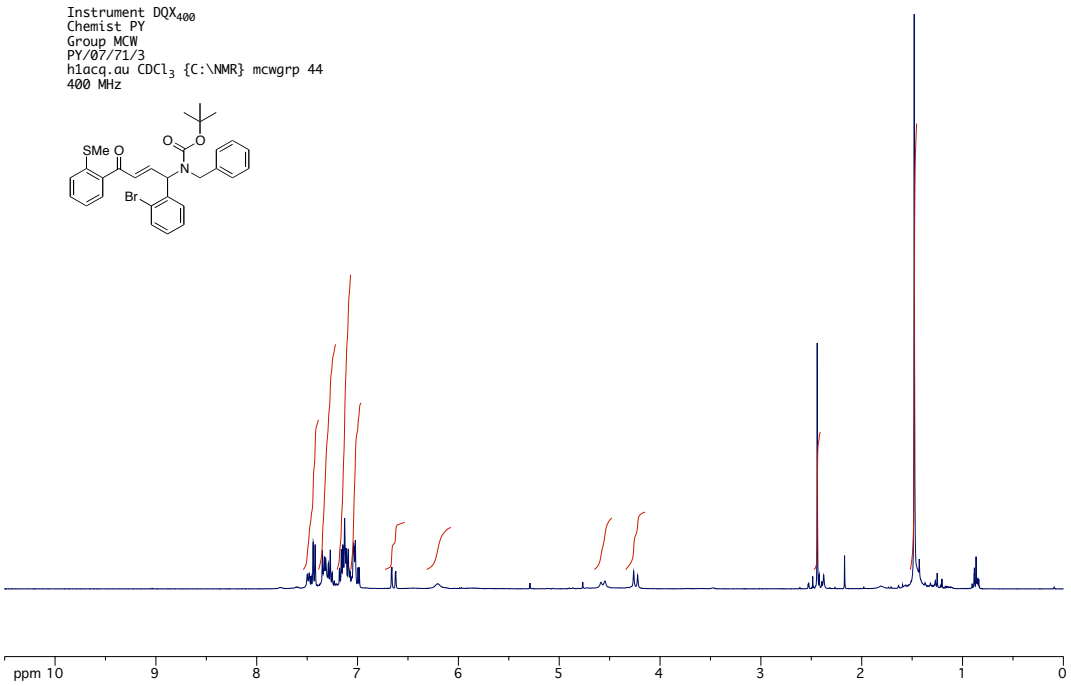
(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 188

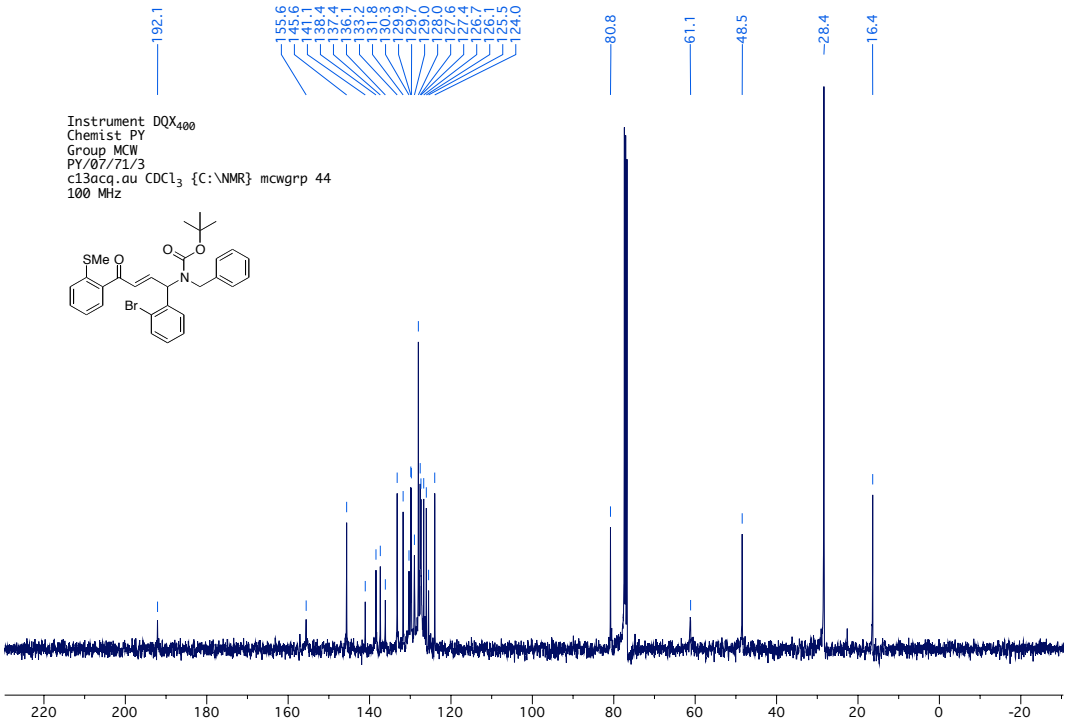


tert-Butyl benzyl(2-(2-(methylthio)benzoyl)allyl)carbamate, experimental page ??

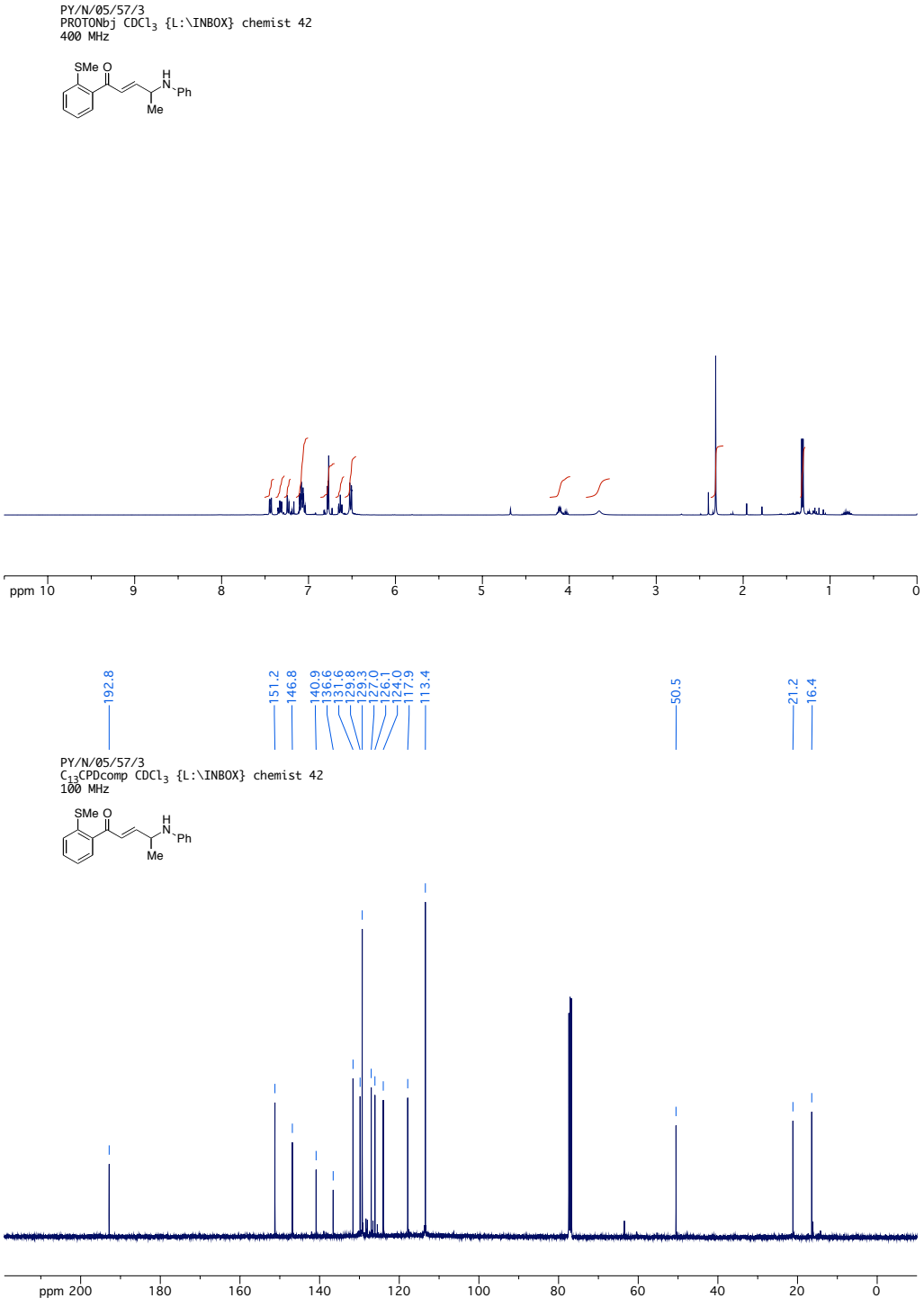


(*E*)-*tert*-Butyl benzyl(1-(2-bromophenyl)-4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 193

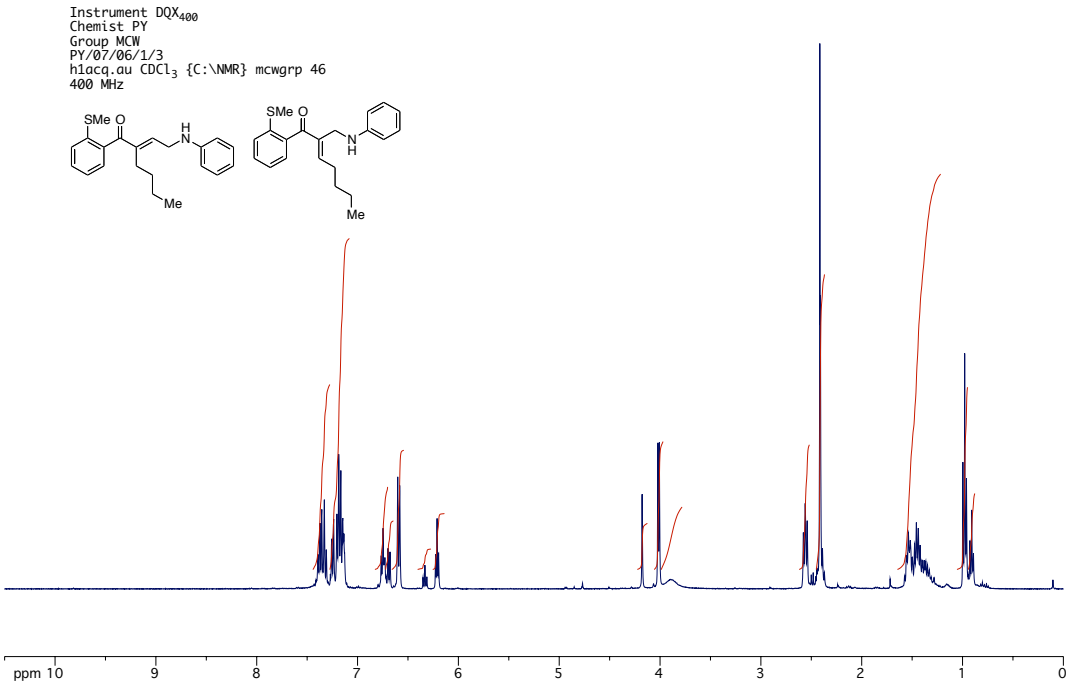


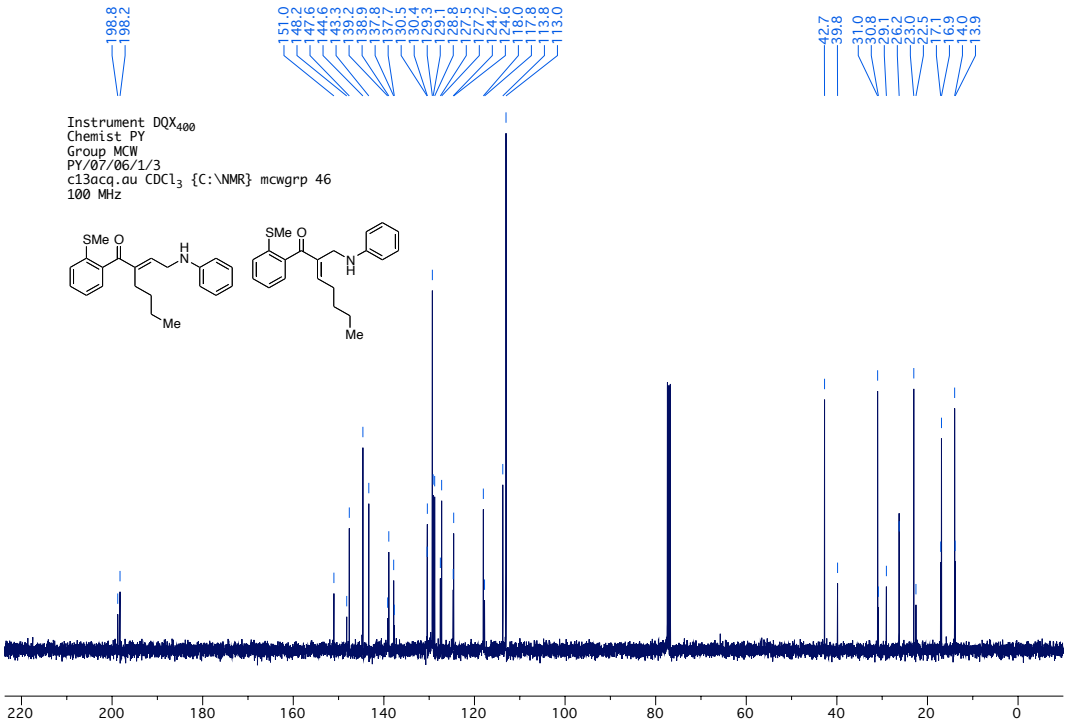


(*E*)-*tert*-Butyl methyl(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 194

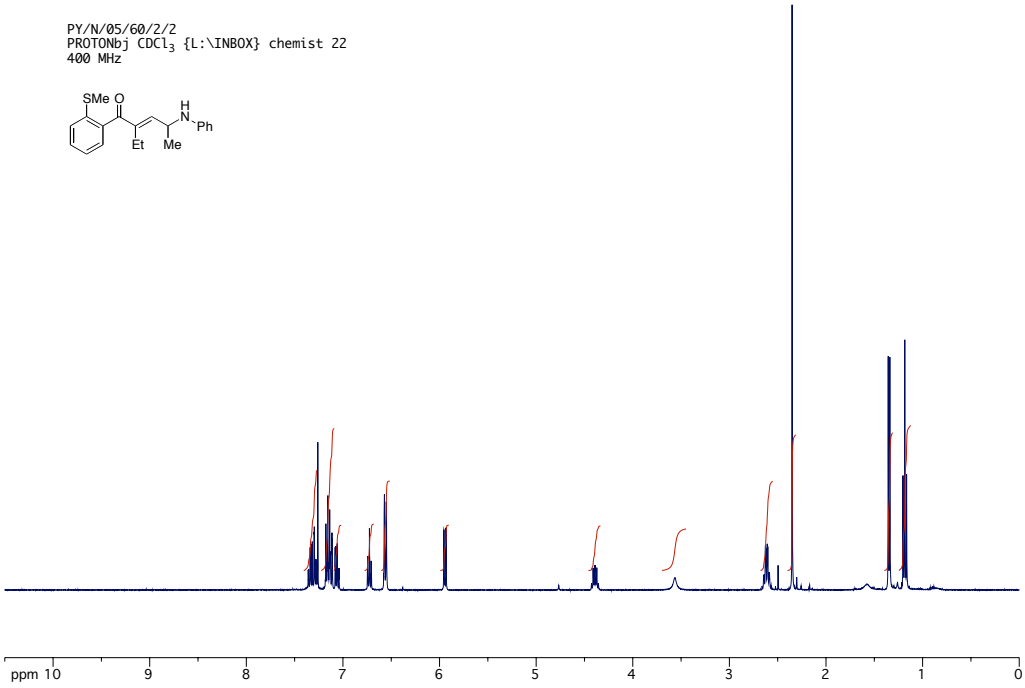


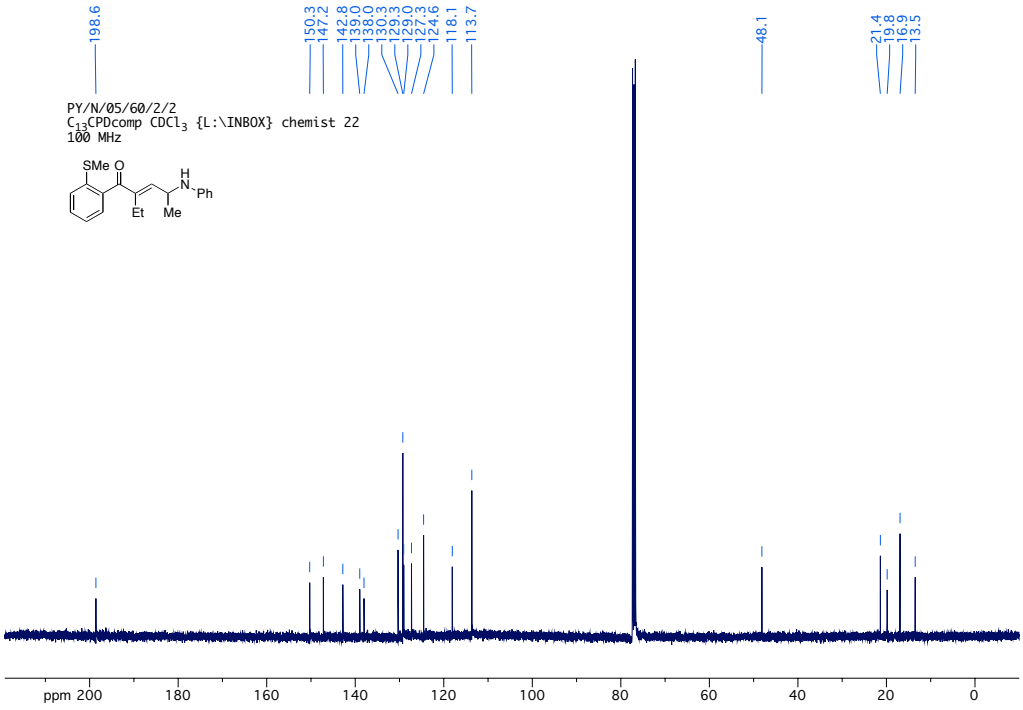
(*E*)-1-(2-(methylthio)phenyl)-2-(2-(phenylamino)ethylidene)hexan-1-one and (*E*)-1-(2-(methylthio)phenyl)-2-((phenylamino)methyl)hept-2-en-1-one, experimental page 195





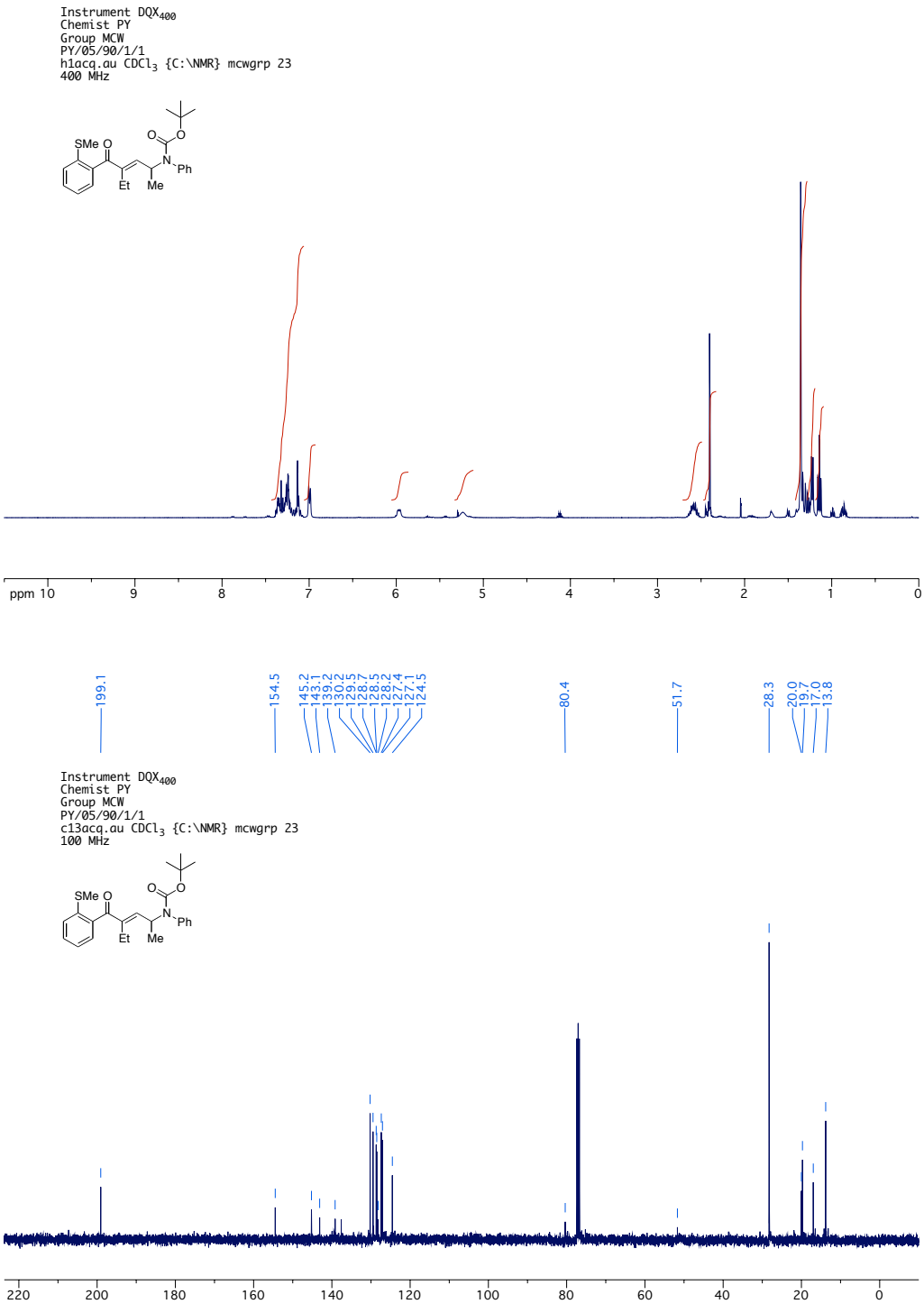
(*E*)-2-ethyl-1-(2-(methylthio)phenyl)-4-(phenylamino)pent-2-en-1-one, experimental page 178



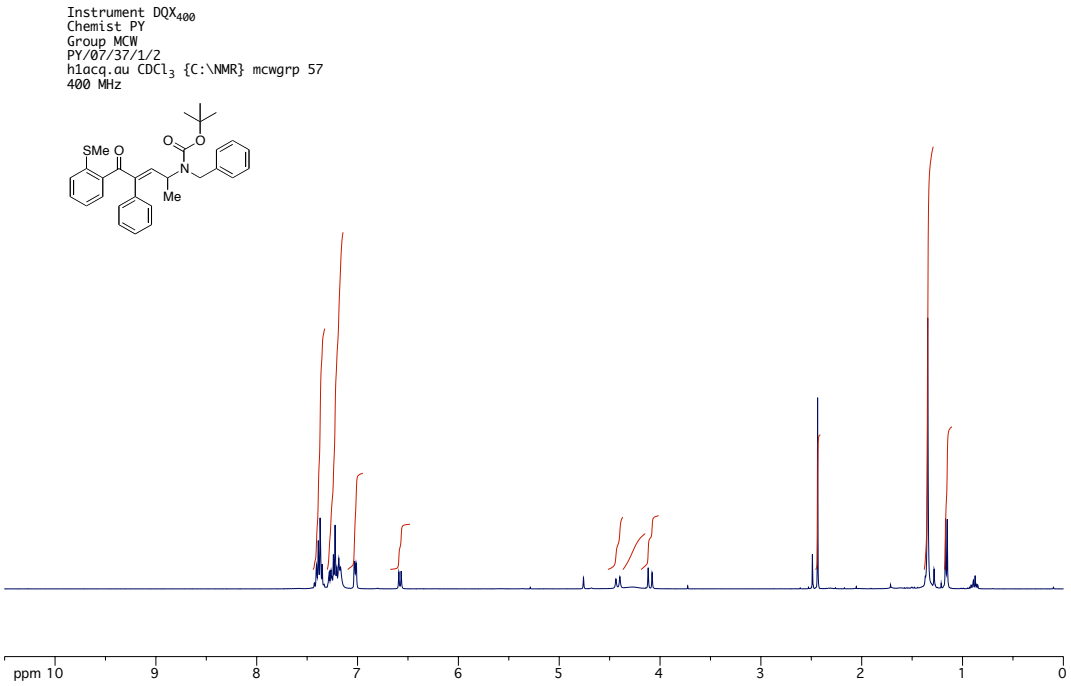


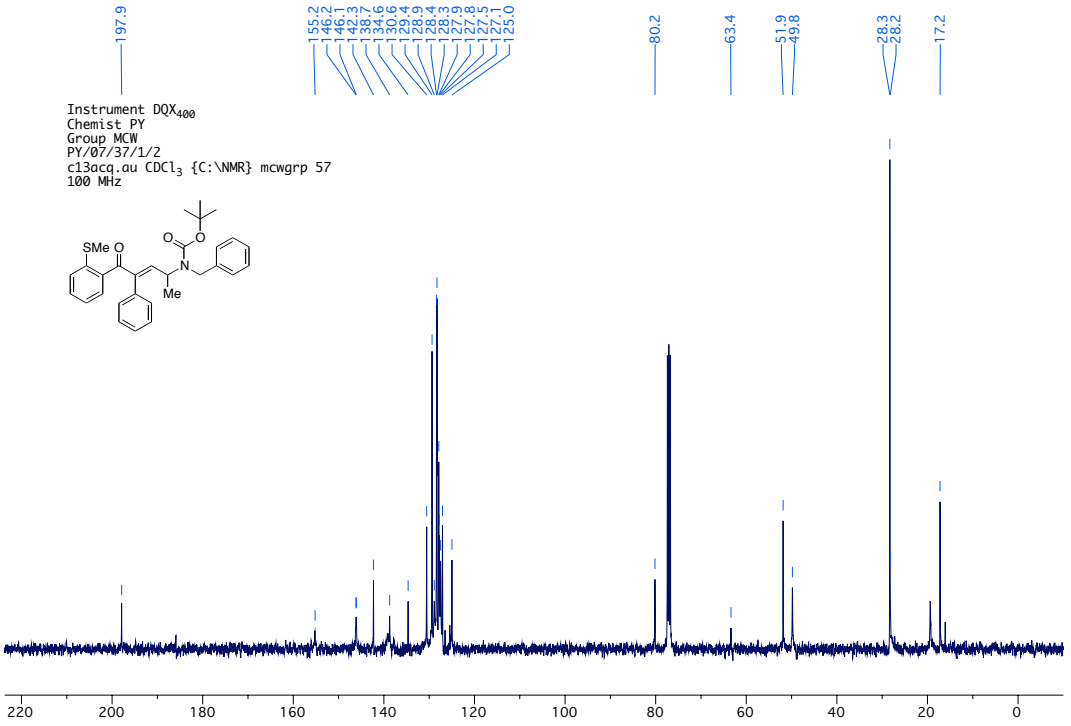
(*E*)-*tert*-butyl (4-(2-(methylthio)benzoyl)hex-3-en-2-yl)(phenyl)carbamat

experimental page 177

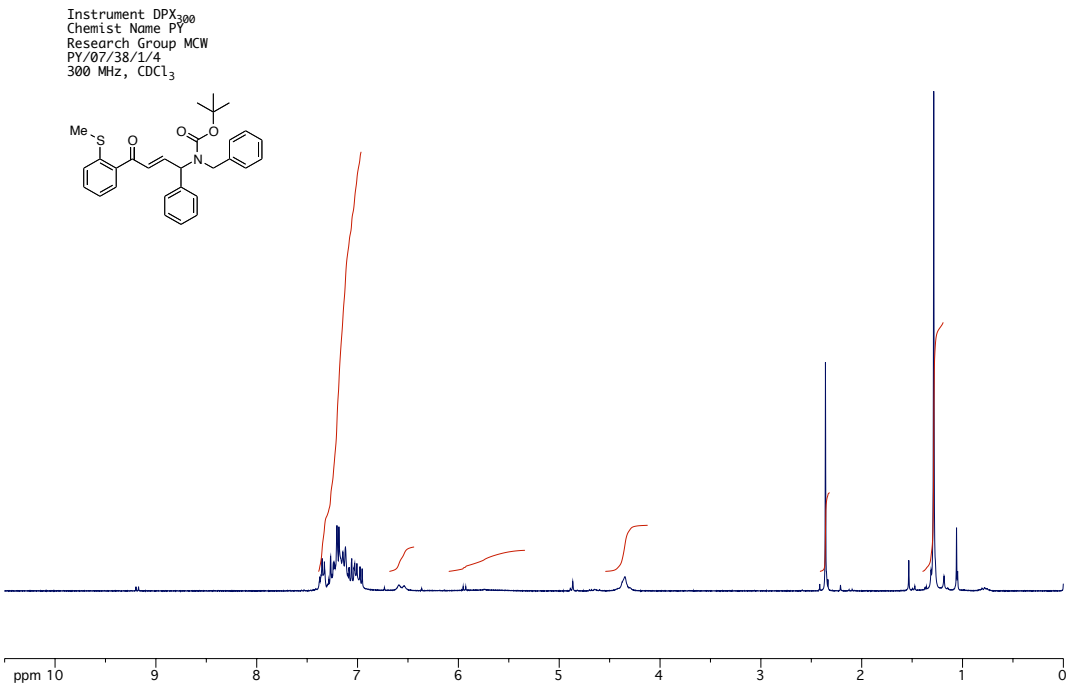


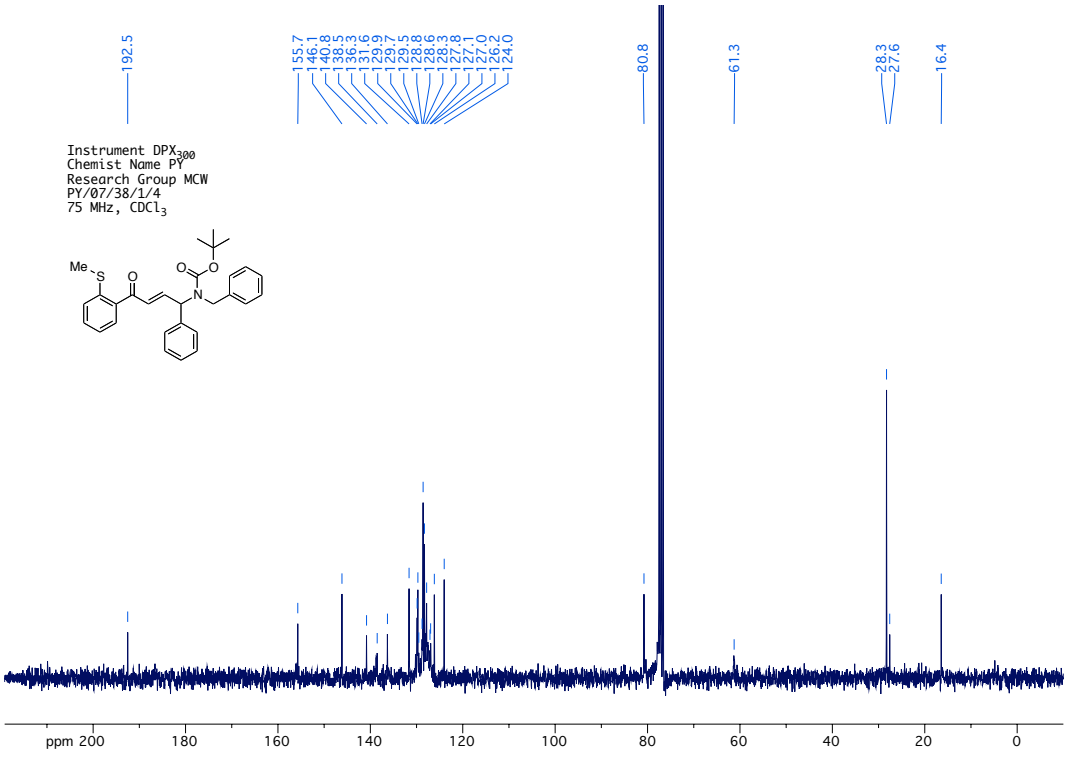
(*E*)-*tert*-Butyl benzyl(5-(2-(methylthio)phenyl)-5-oxo-4-phenylpent-3-en-2-yl)carbamate, experimental page 191



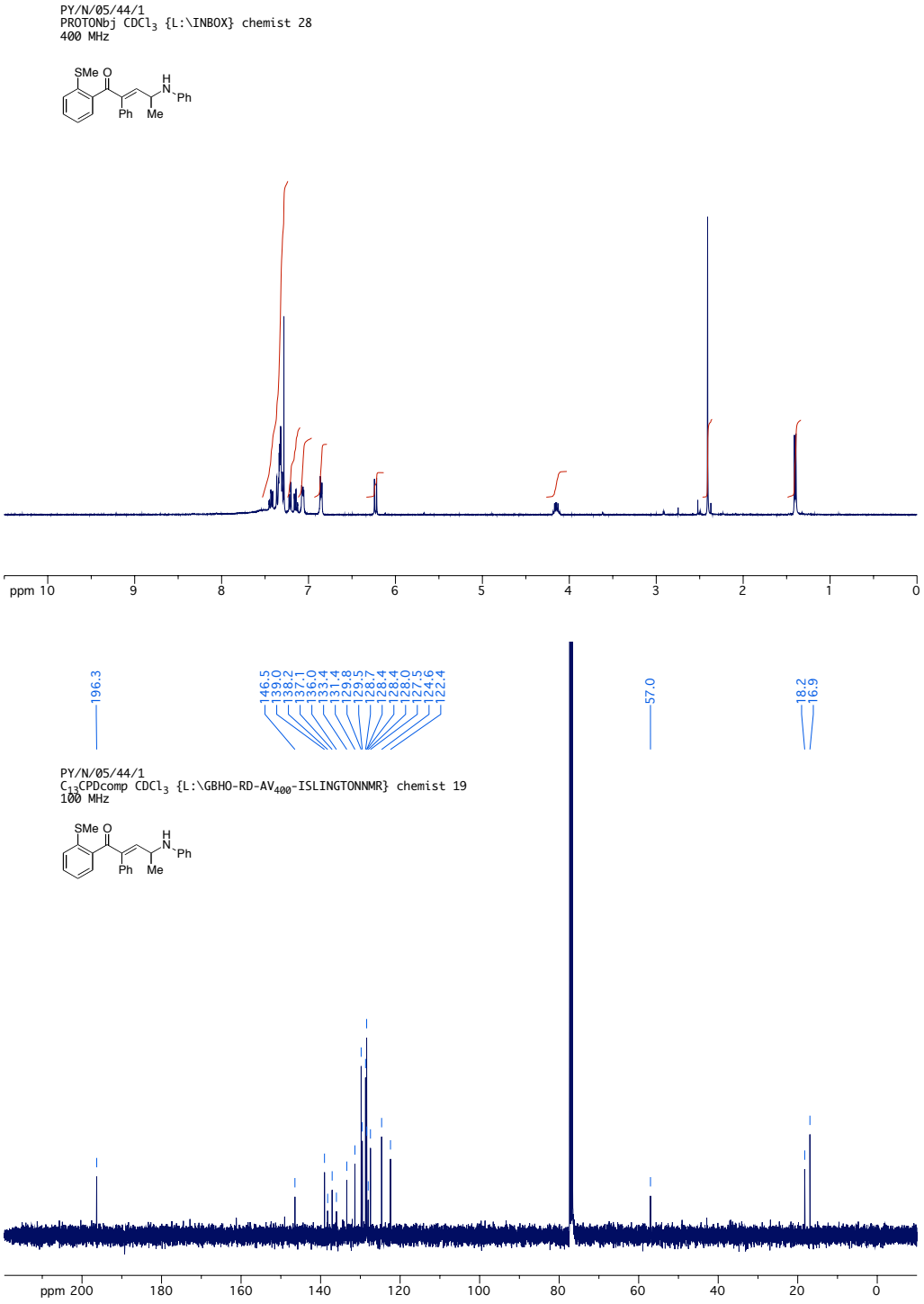


(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)phenyl)-4-oxo-1-phenylbut-2-en-1-yl)carbamate, experimental page 192



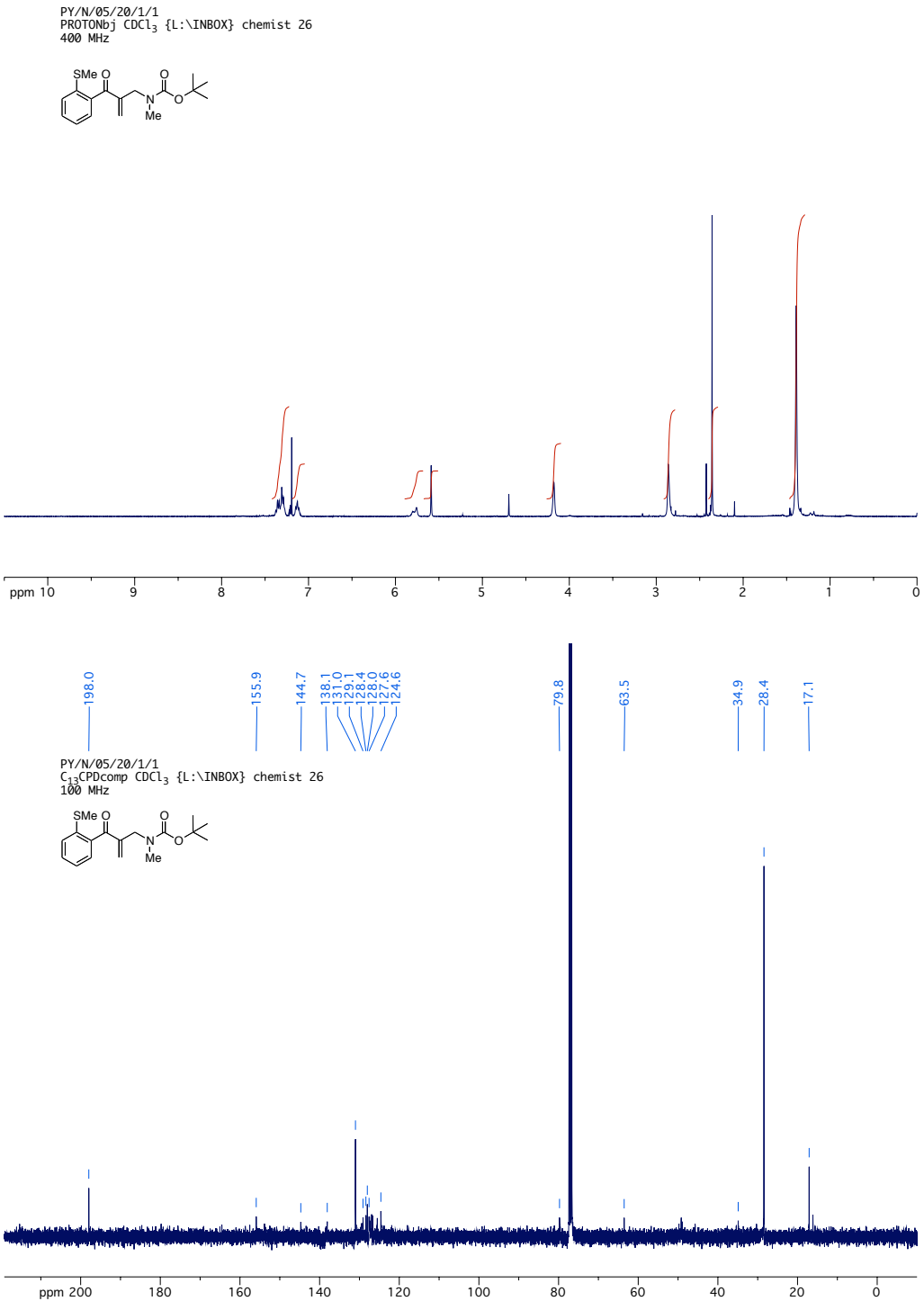


(E)-1-(2-(methylthio)phenyl)-2-phenyl-4-(phenylamino)pent-2-en-1-one, experimental page 191

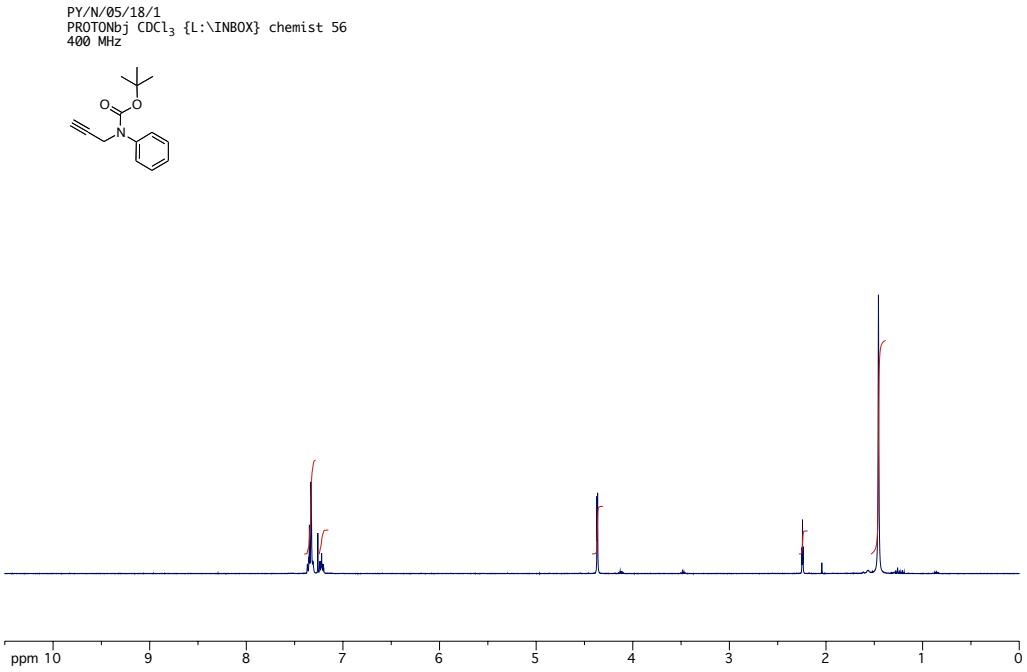


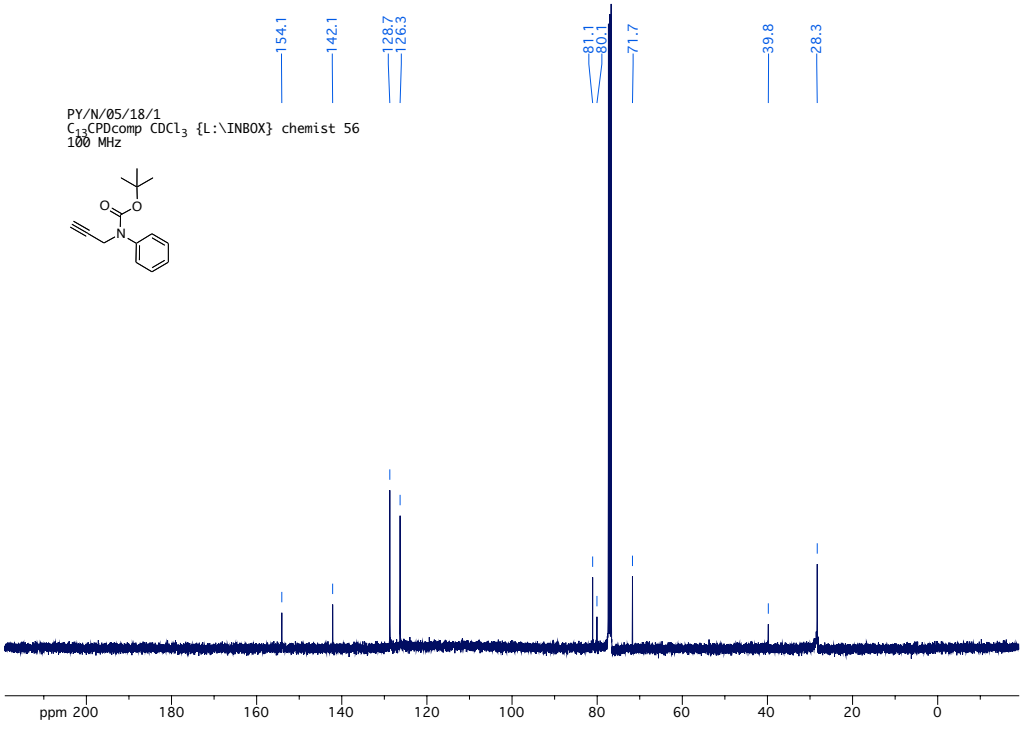
(*E*)-*tert*-butyl methyl(2-(2-(methylthio)benzoyl)allyl)carbamate)carbama

experimental page 186

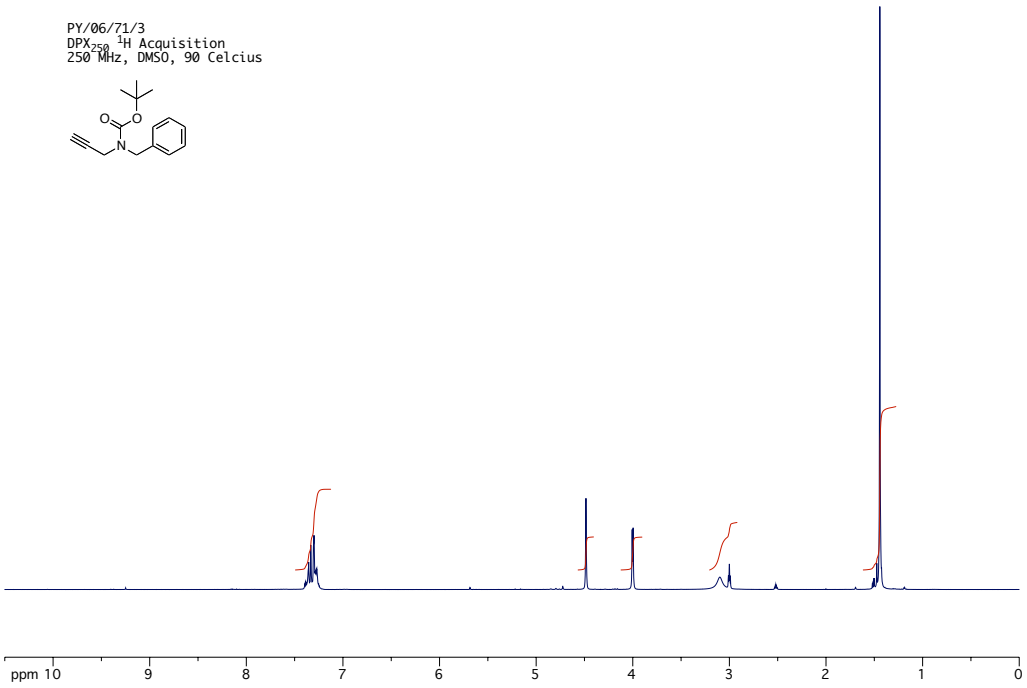


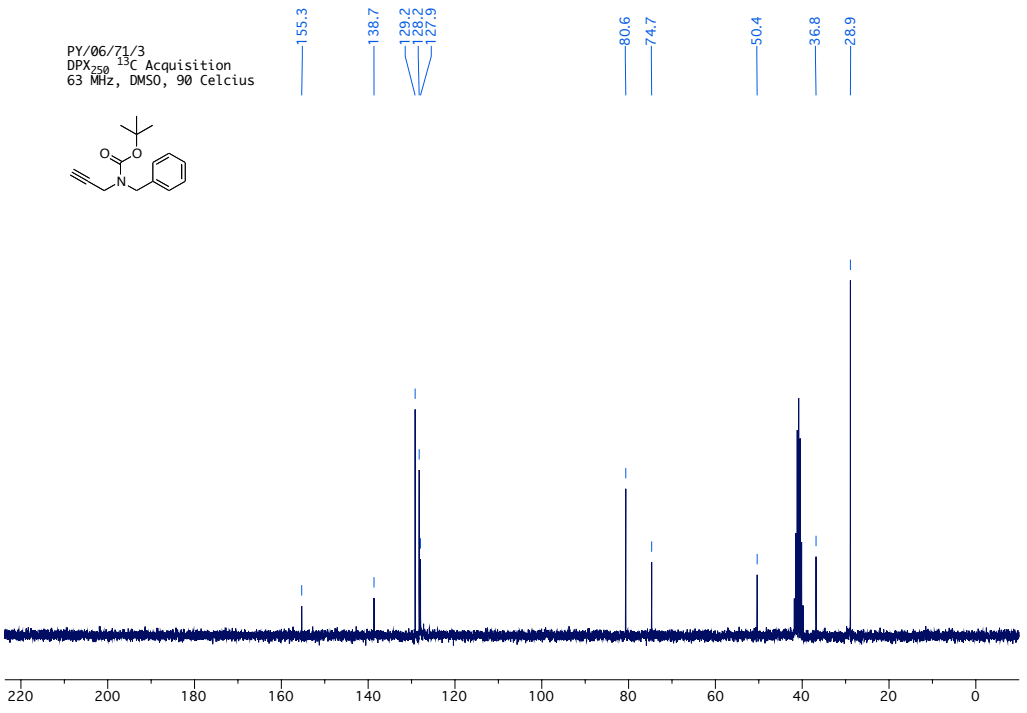
tert-butyl phenyl(prop-2-yn-1-yl)carbamate), experimental page 155



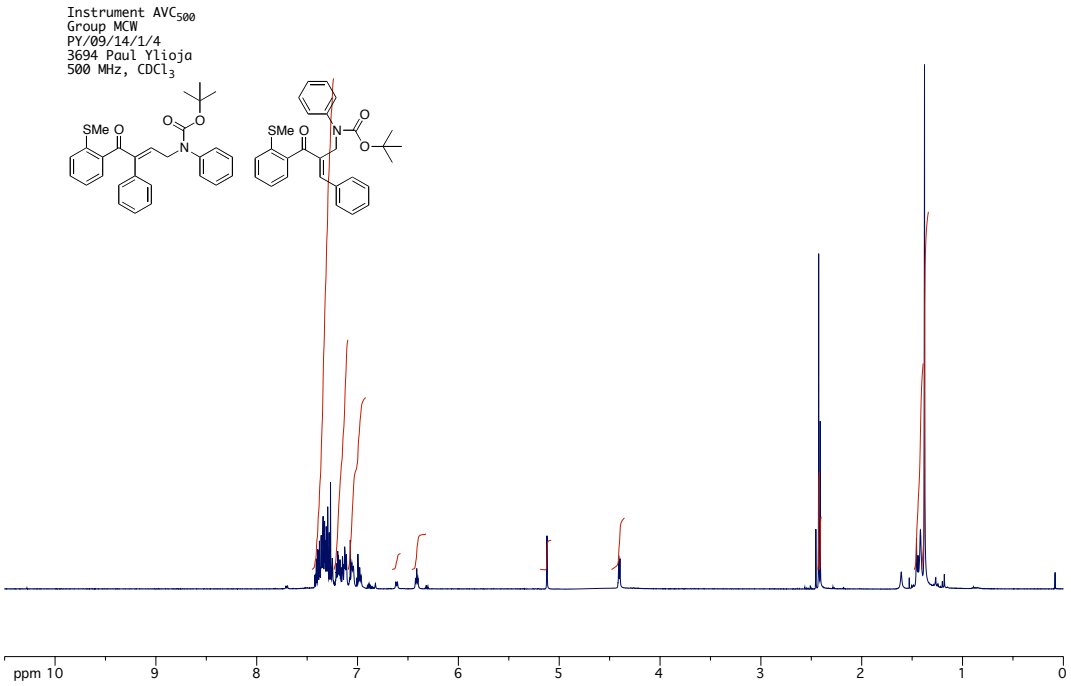


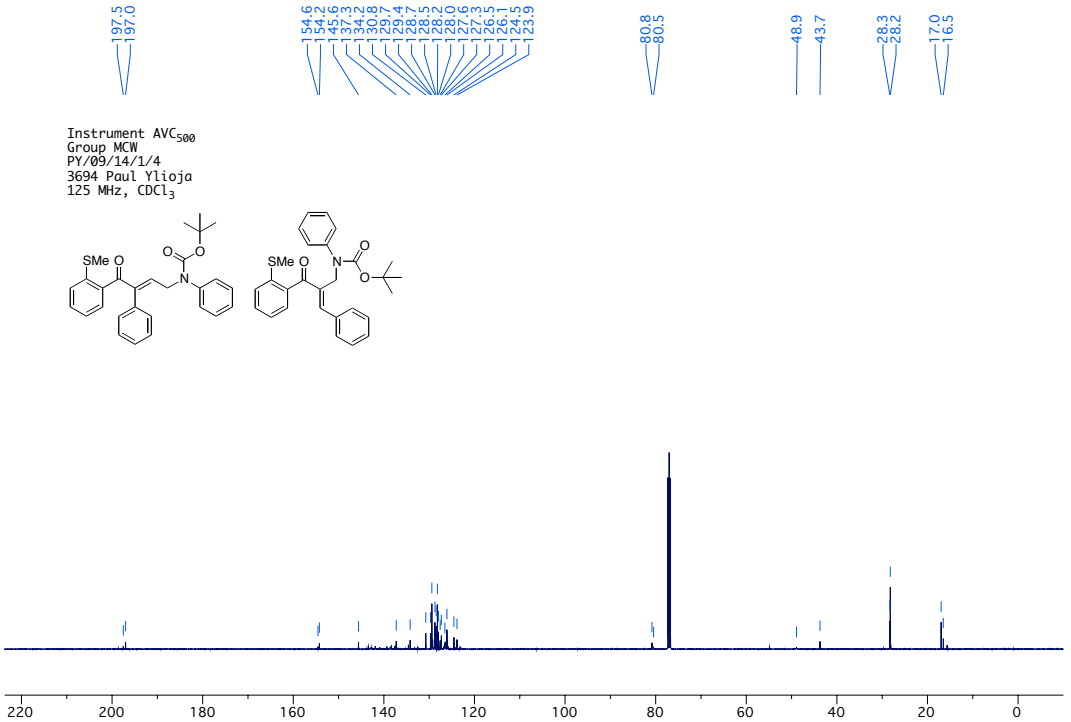
tert-butyl benzyl(prop-2-yn-1-yl)carbamate, experimental page 154



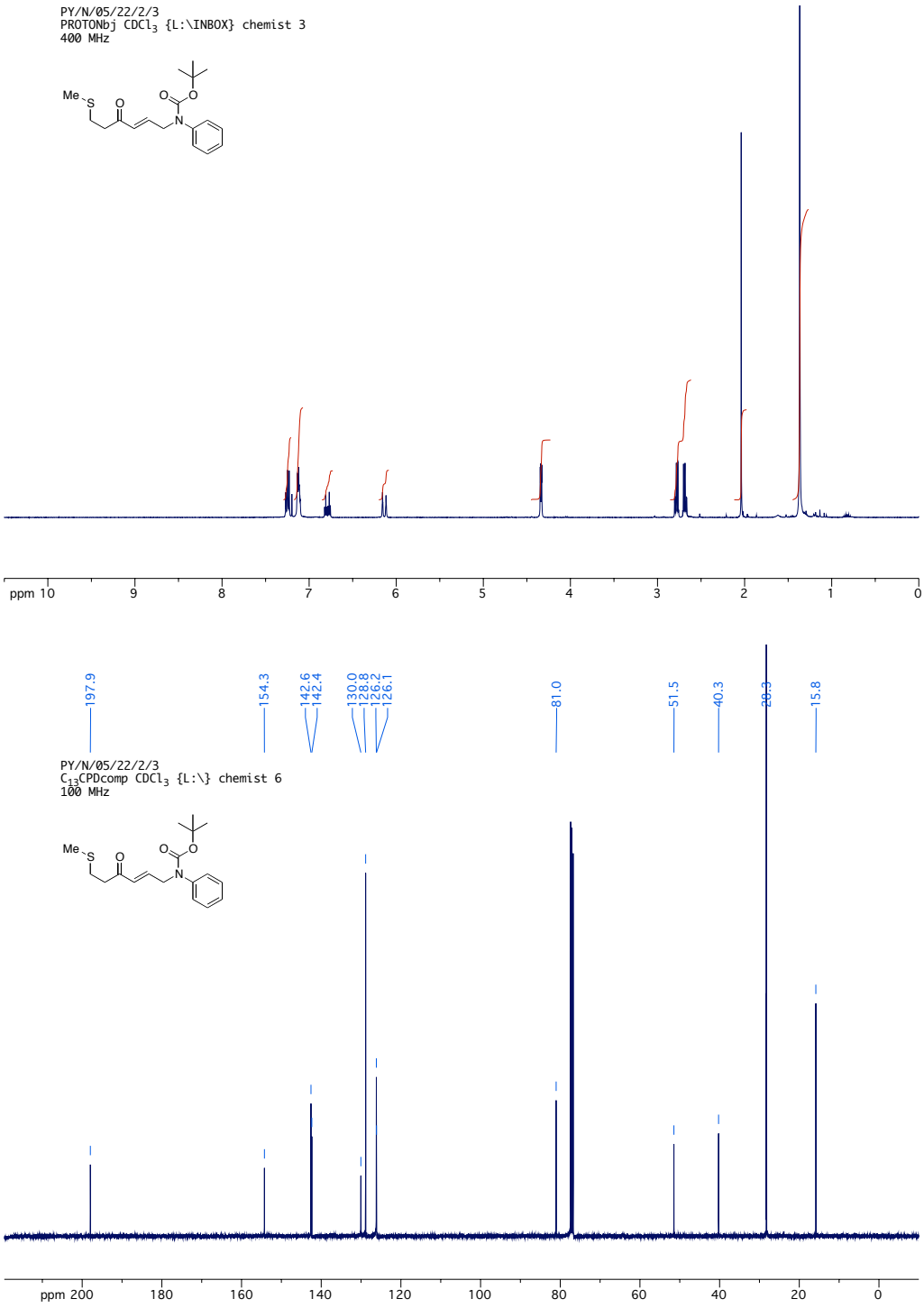


(*E*)-*tert*-Butyl (4-(2-(methylthio)phenyl)-4-oxo-3-phenylbut-2-en-1-yl)(phenyl)carbamate, experimental page 190

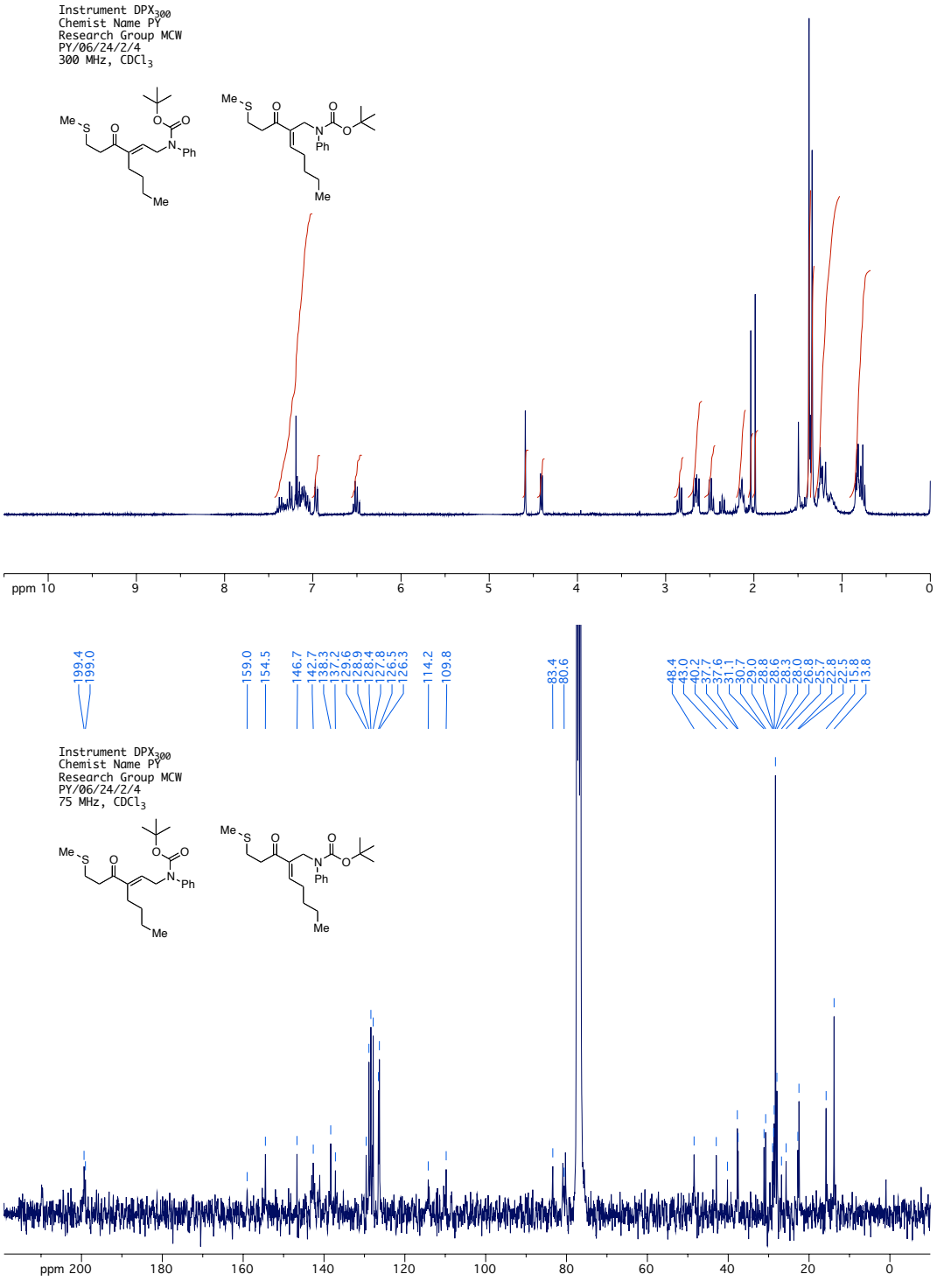




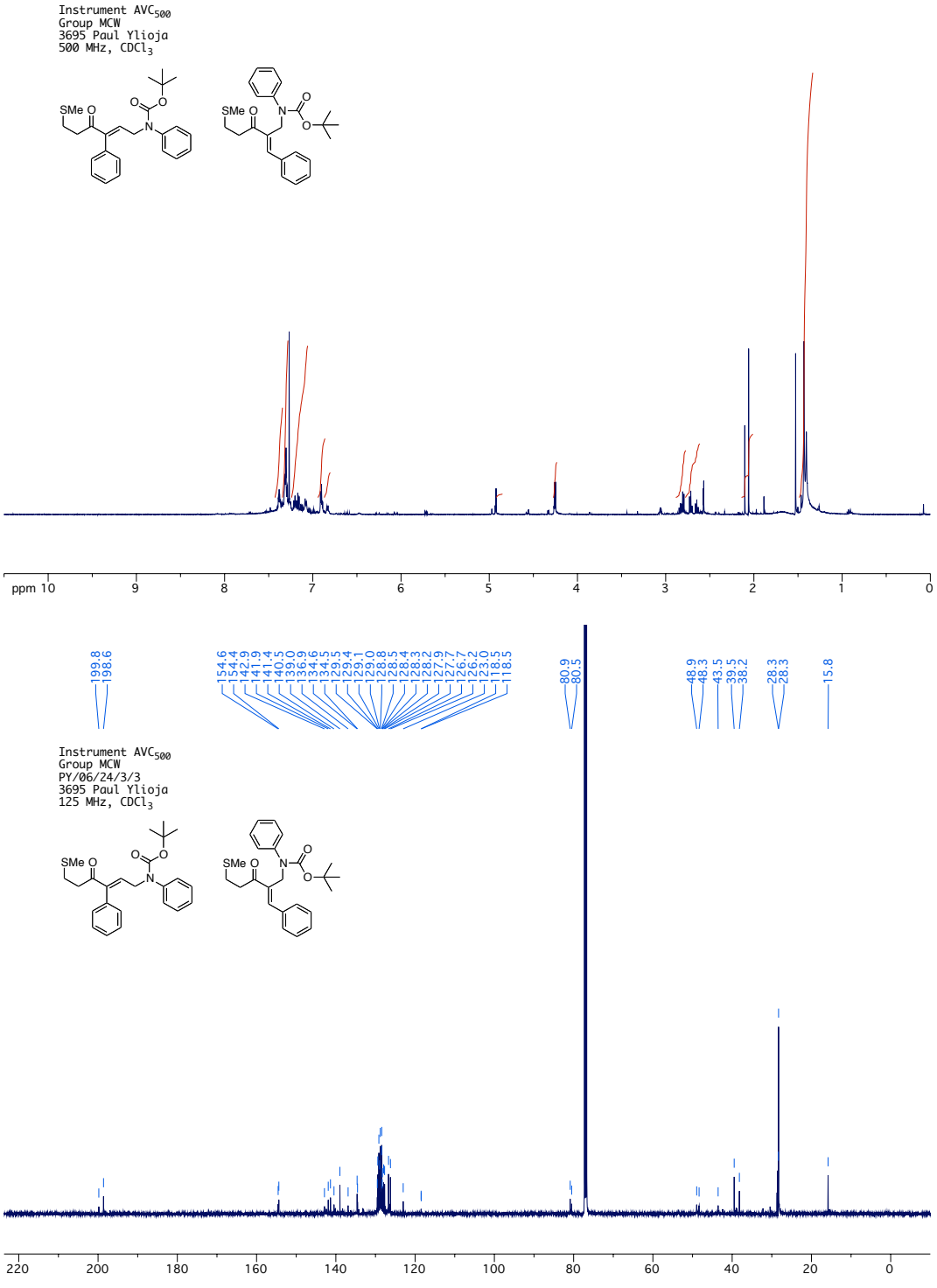
(*E*)-*tert*-butyl (6-(methylthio)-4-oxohex-2-en-1-yl)(phenyl)carbamate), experimental page 179



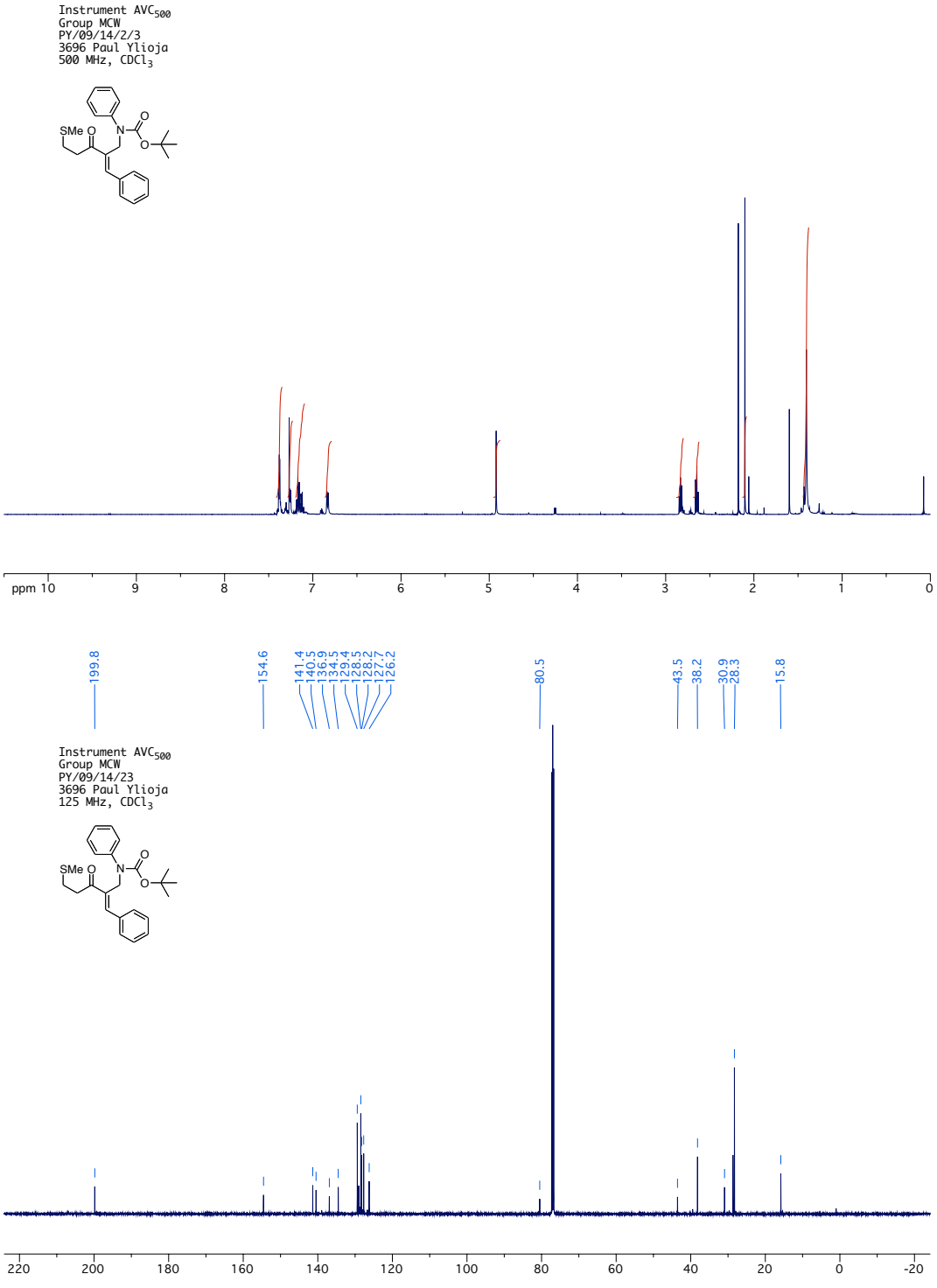
(*E*)-*tert*-Butyl (3-(3-(methylthio)propanoyl)hept-2-en-1-yl)-(phenyl)carbamate and (*E*)-*tert*-butyl (2-(3-(methylthio)propanoyl)hept-2-en-1-yl)(phenyl)carbamate, experimental page 180



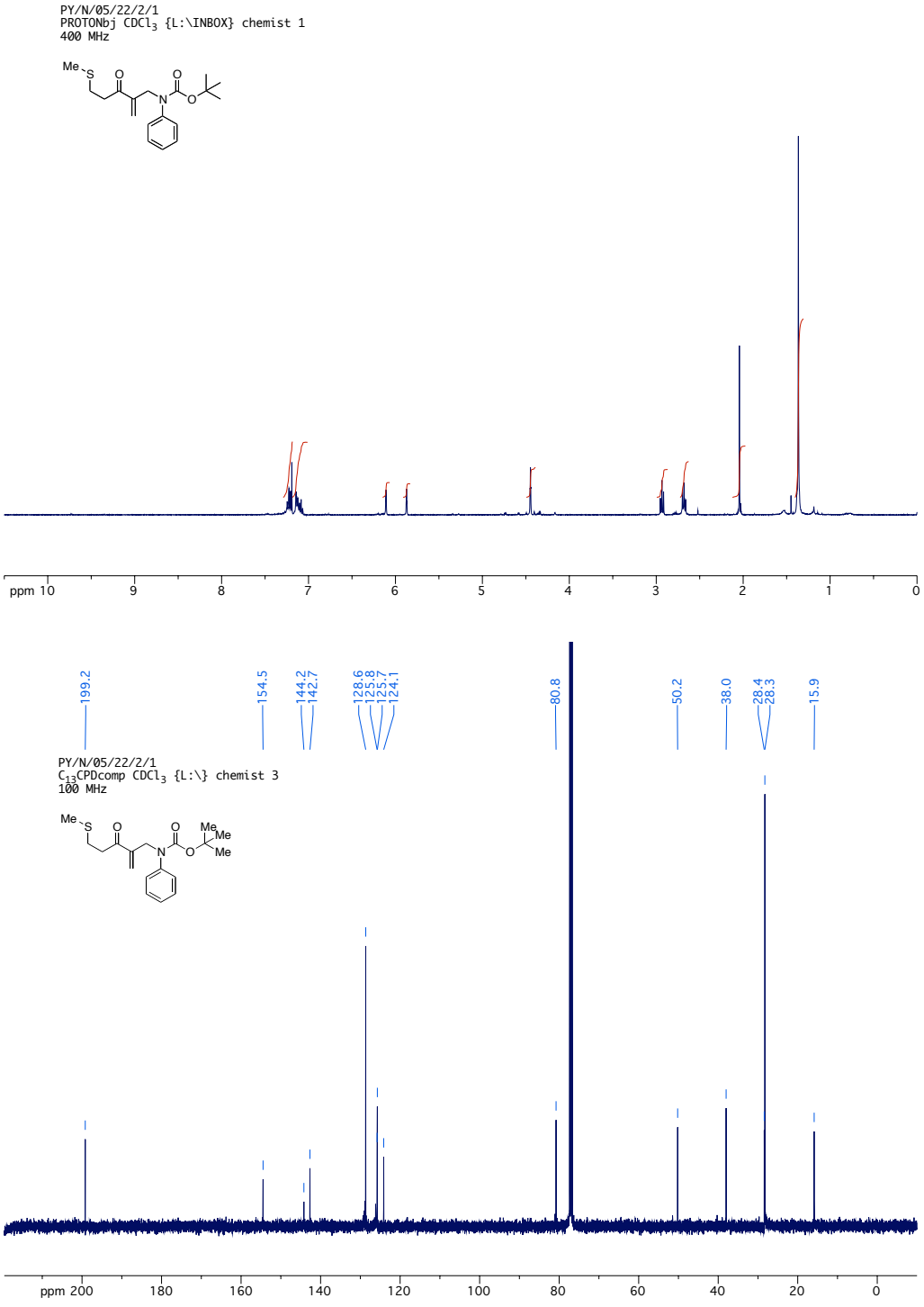
(*E*)-*tert*-Butyl (6-(methylthio)-4-oxo-3-phenylhex-2-en-1-yl)-(phenyl)carbamate, a and (*E*)-*tert*-butyl (2-benzylidene-5-(methylthio)-3-oxopentyl)(phenyl)carbamate, b, experimental page 181



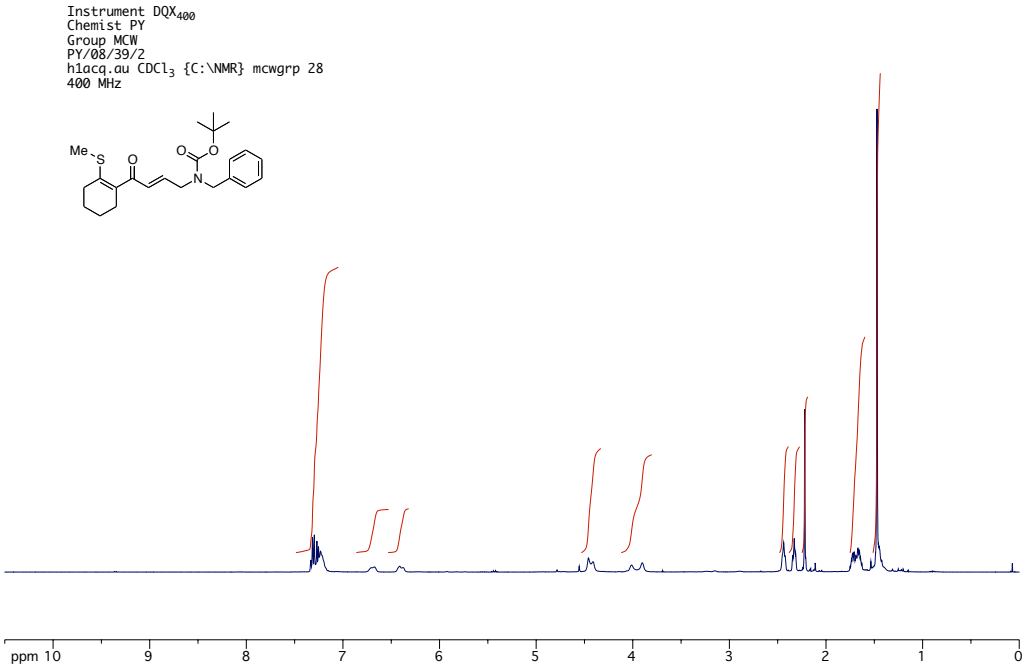
(*E*)-*tert*-Butyl (6-(methylthio)-4-oxo-3-phenylhex-2-en-1-yl)-(phenyl)carbamate, a and (*E*)-*tert*-butyl (2-benzylidene-5-(methylthio)-3-oxopentyl)(phenyl)carbamate, b, experimental page 181

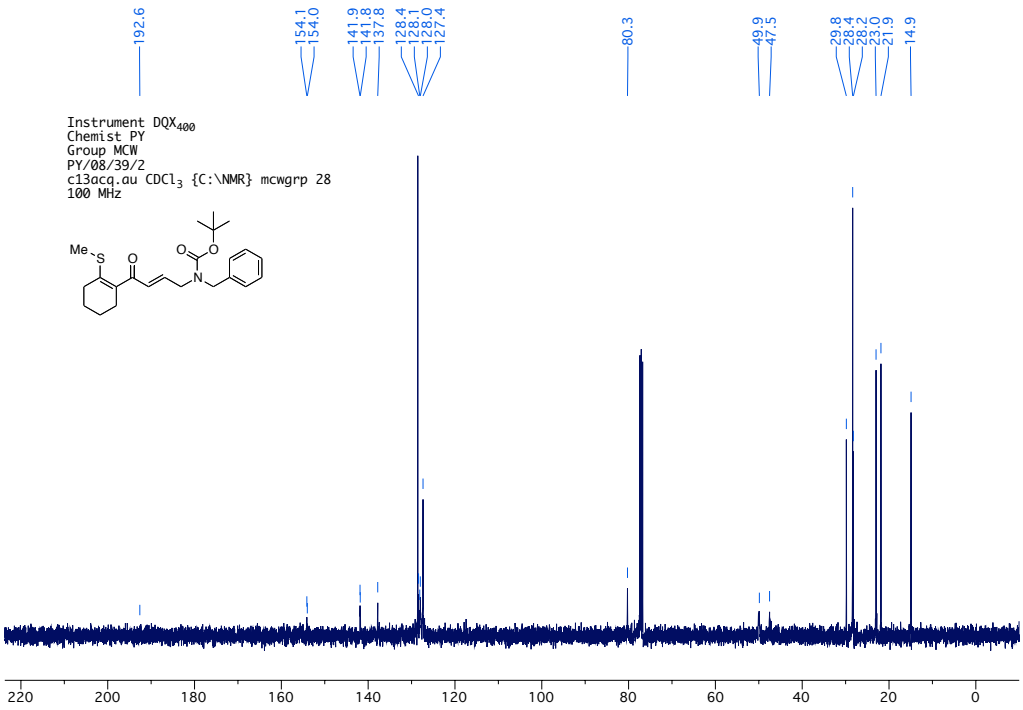


tert-butyl (2-methylene-5-(methylthio)-3-oxopentyl)(phenyl)carbamate, experimental page 179



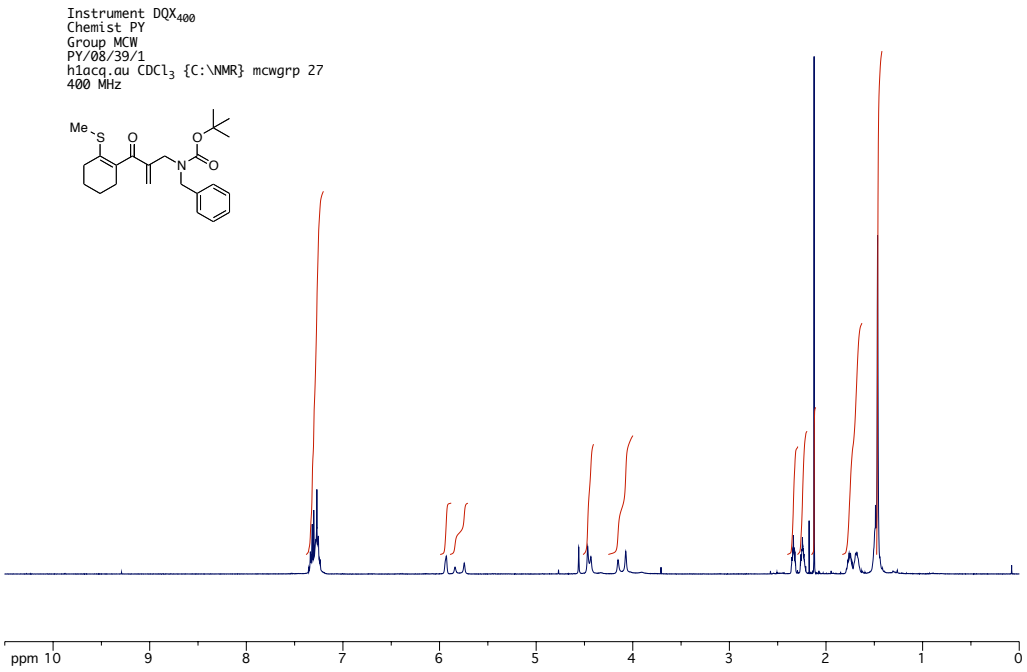
(*E*)-tert-butyl benzyl(4-(2-(methylthio)cyclohex-1-en-1-yl)-4-oxobut-2-en-1-yl)carbamate, experimental page 207





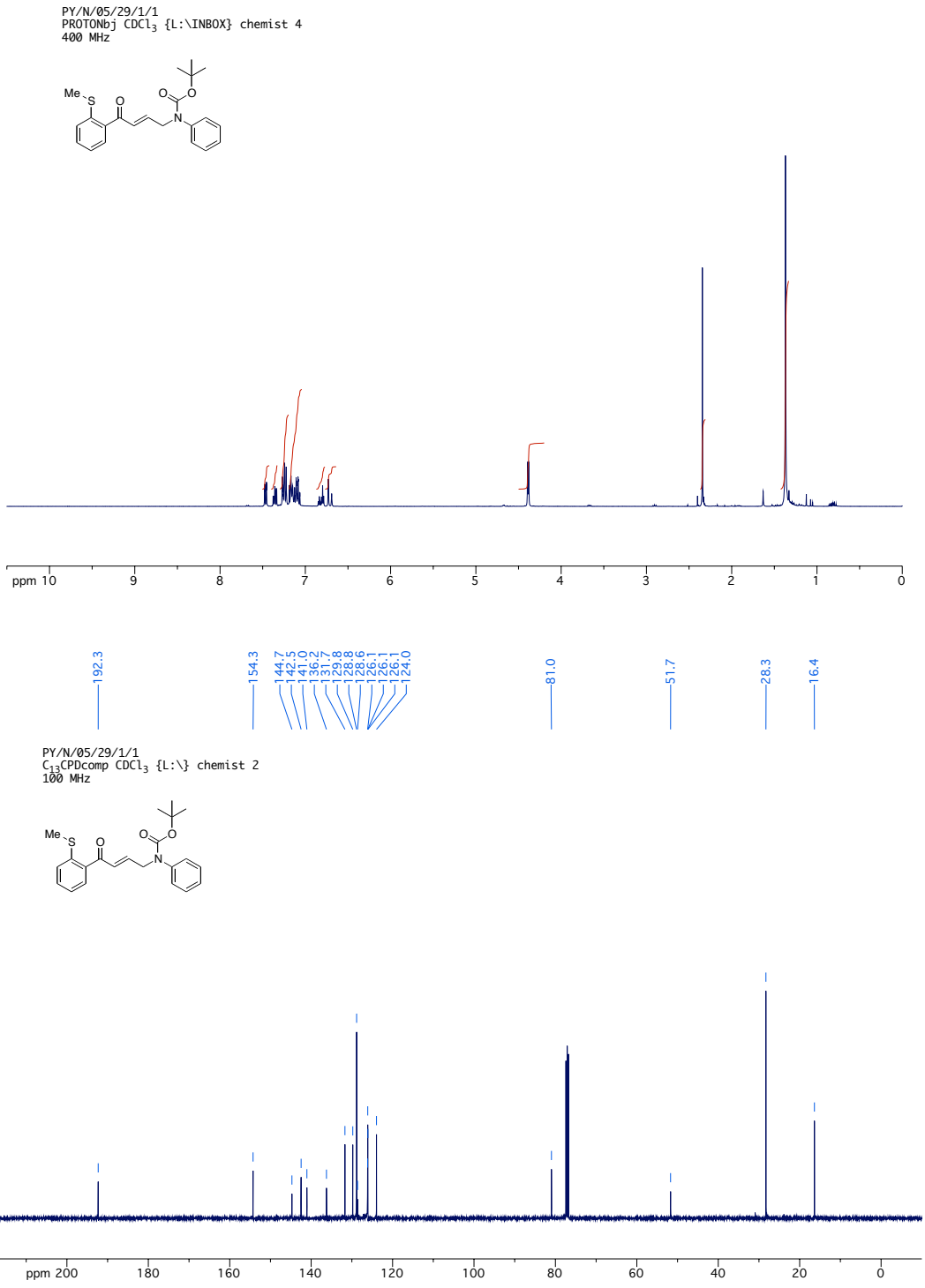
(*tert*-Butyl benzyl(2-(2-(methylthio)cyclohex-1-enecarbonyl)allyl)carbam

experimental page 207

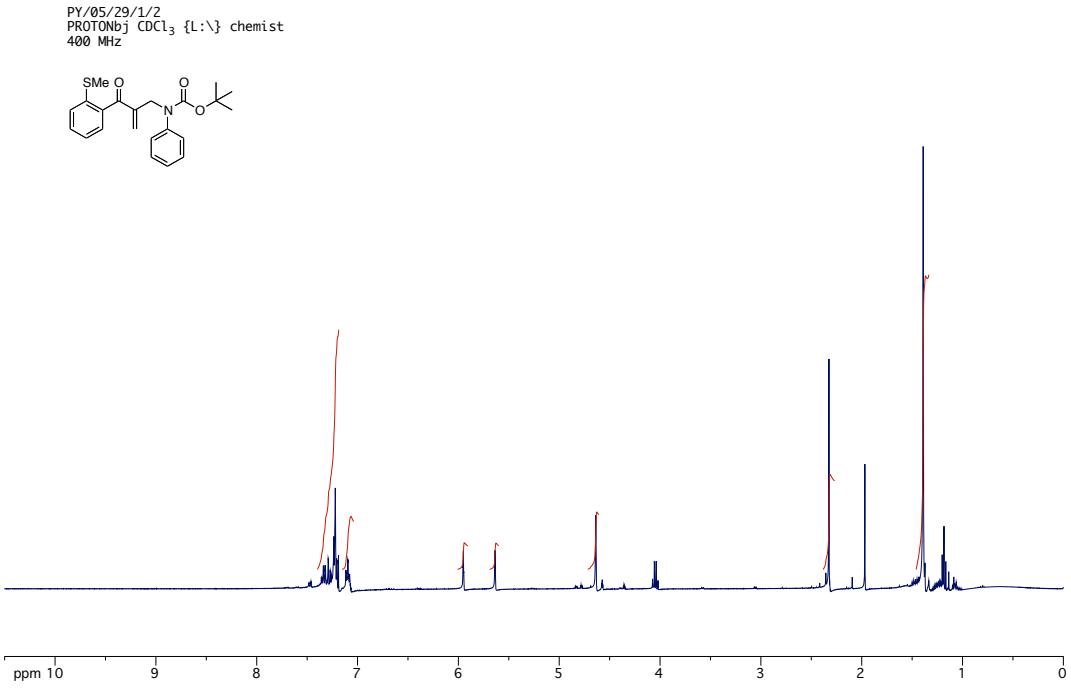


(*E*)-*tert*-Butyl (4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)(phenyl)carb

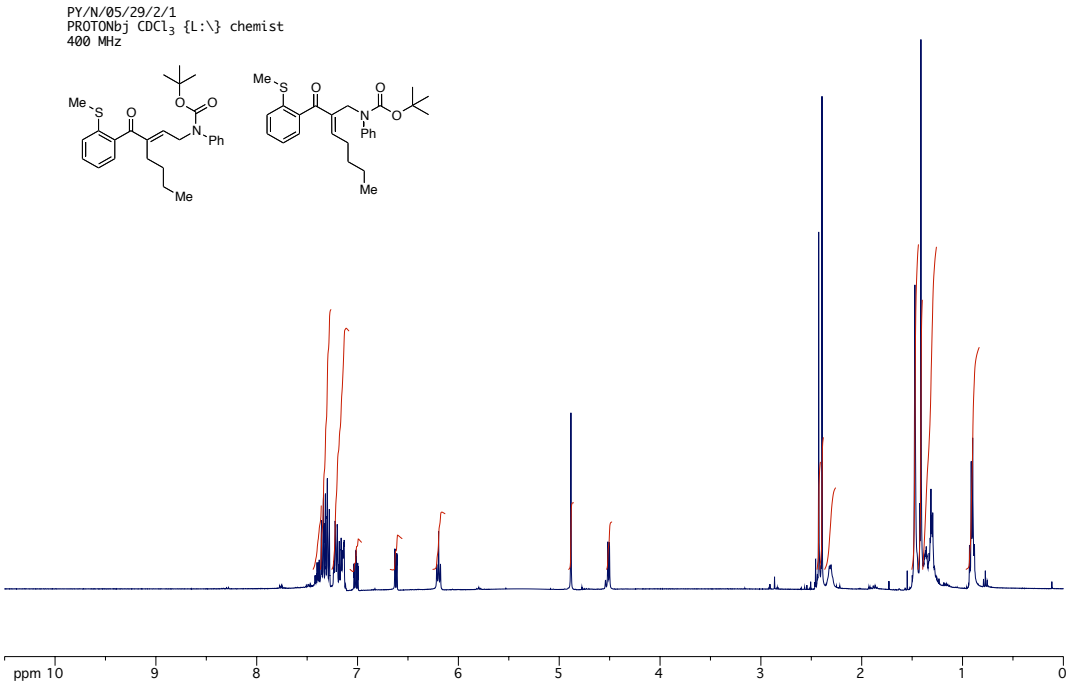
experimental page 187



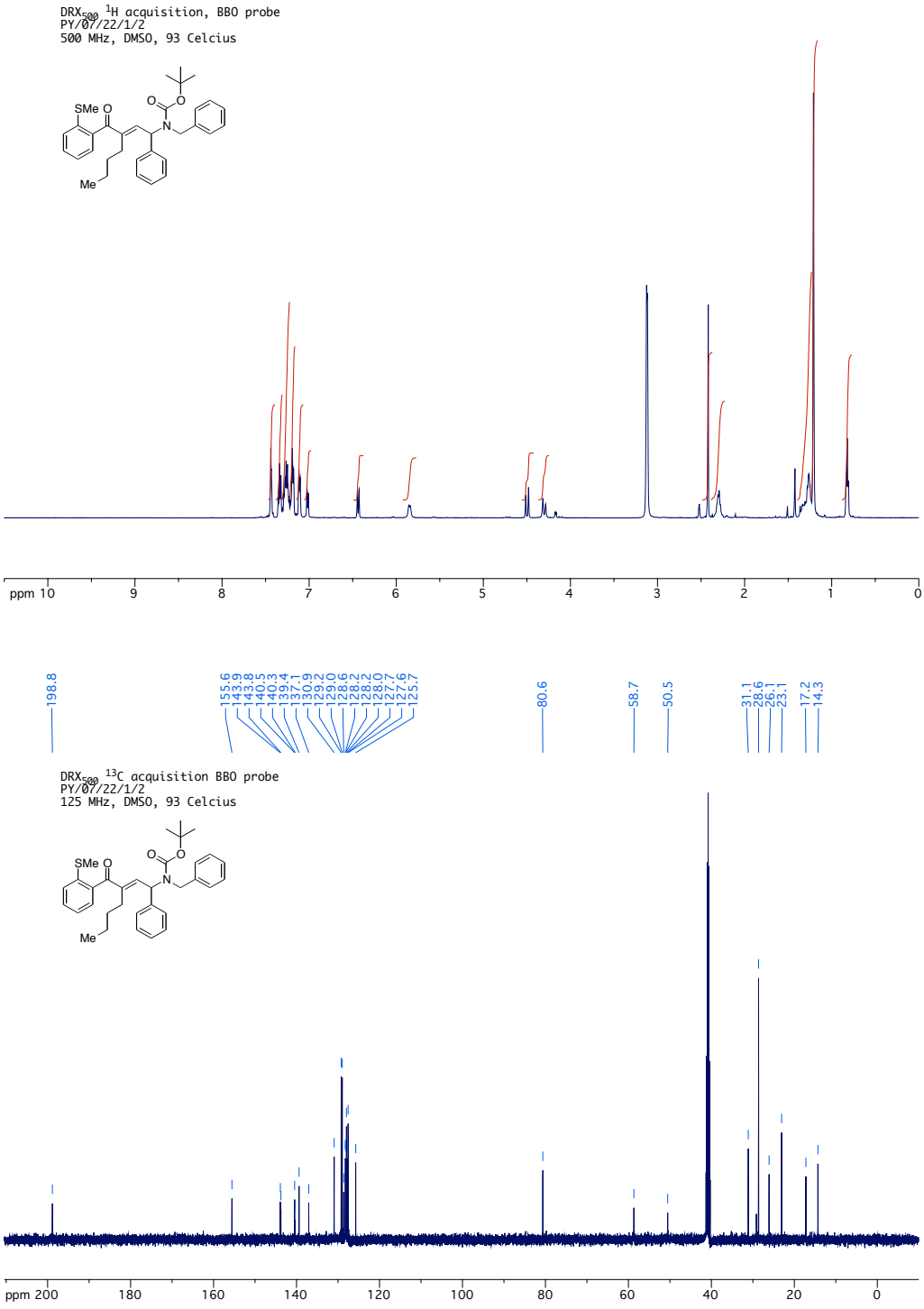
tert-Butyl (2-(2-(methylthio)benzoyl)allyl)(phenyl)carbamate, experimental page 187



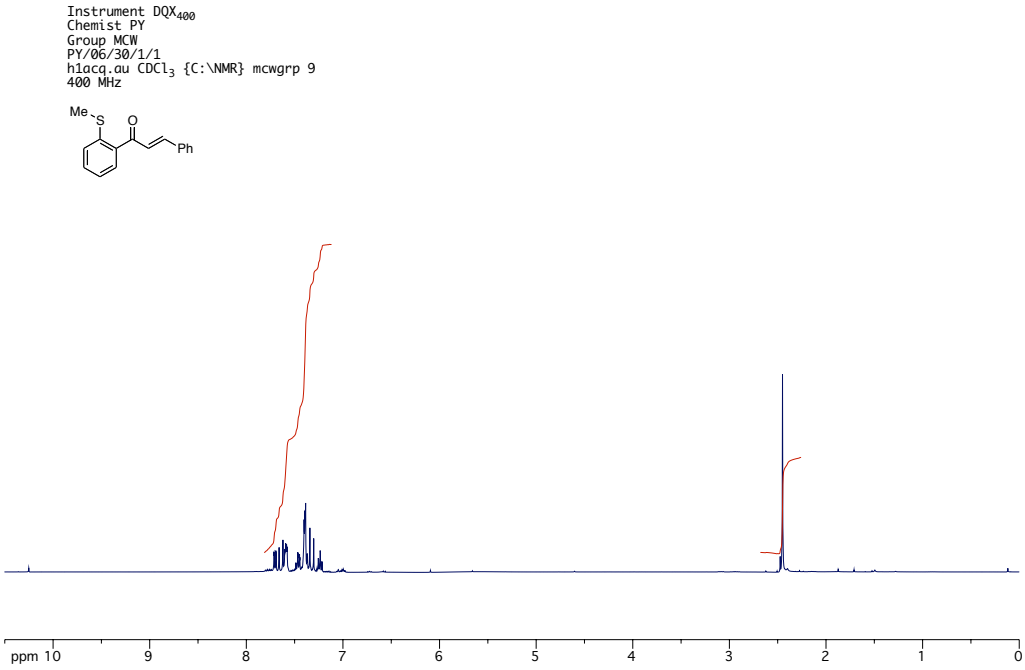
(*E*)-*tert*-Butyl (3-(2-(methylthio)benzoyl)hept-2-en-1-yl)-(phenyl)carbamate, experimental page 189

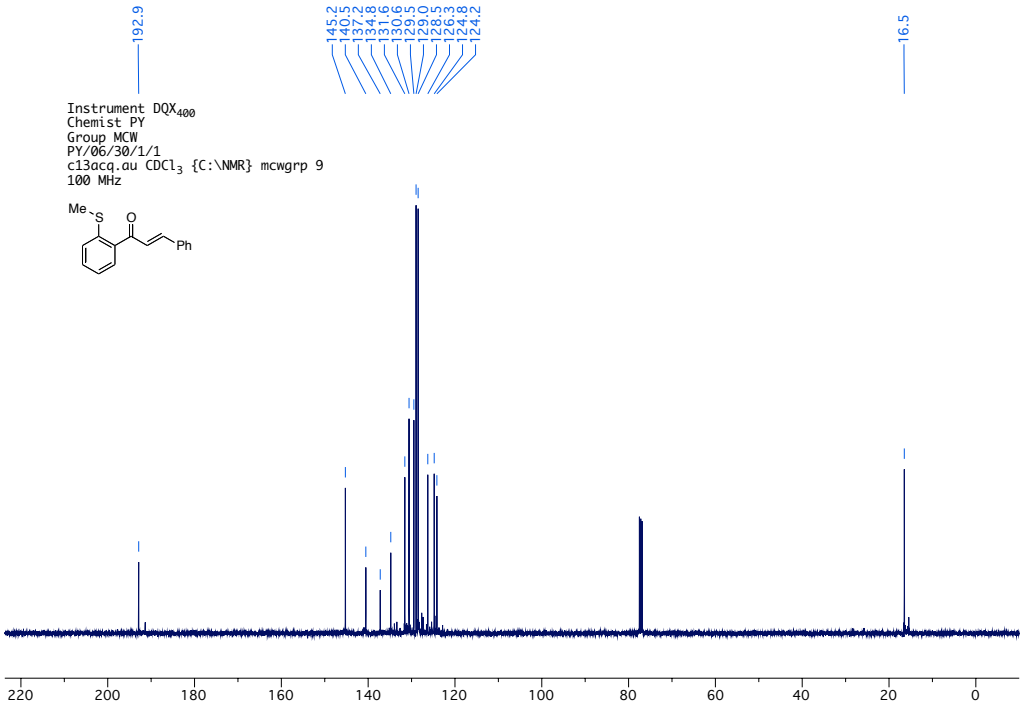


(*E*)-*tert*-Butyl (3-(2-(methylthio)benzoyl)-1-phenylhept-2-en-1-yl)(phenyl)carbamate, experimental page 182

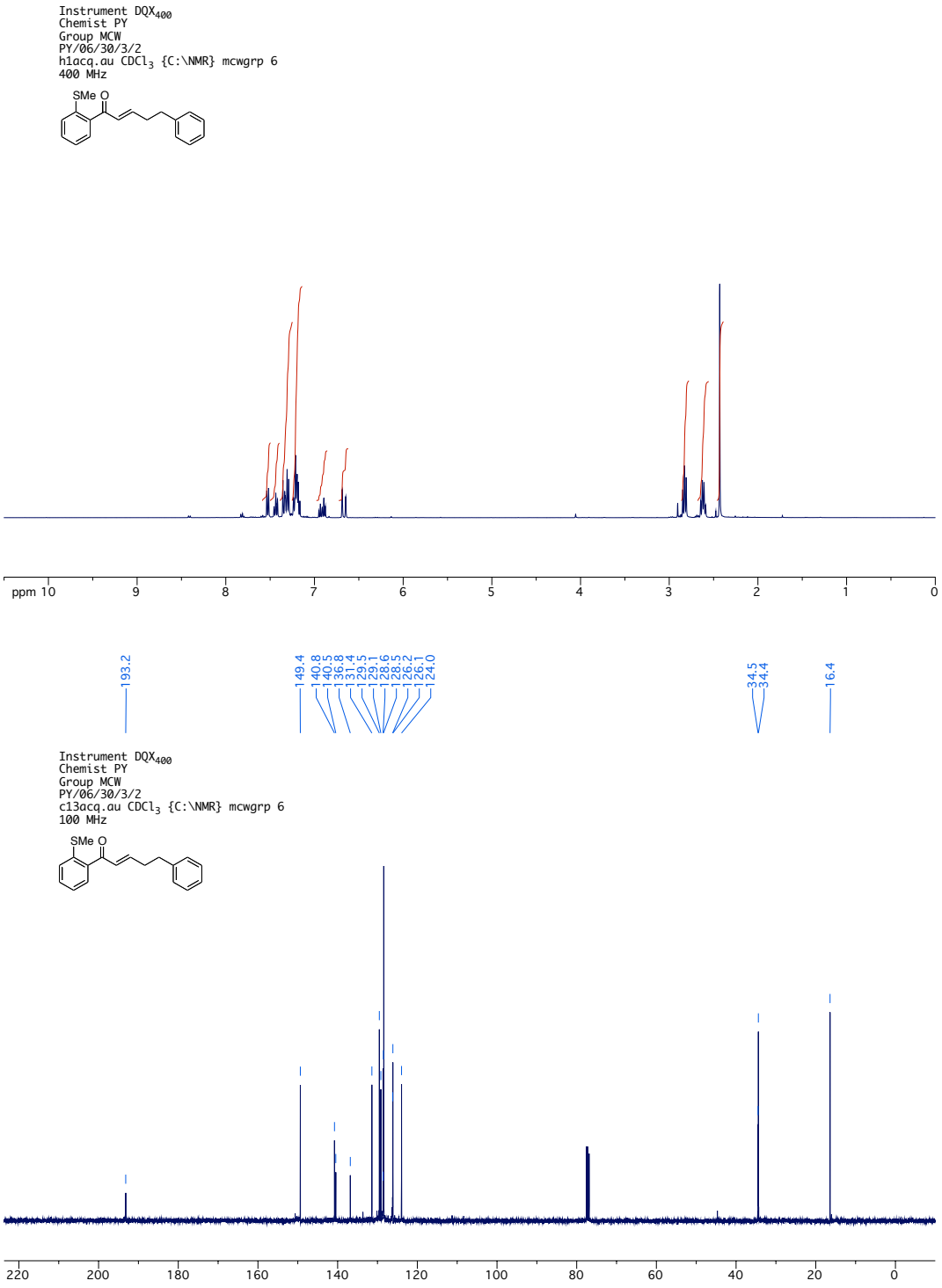


(E)-1-(2-(methylthio)phenyl)-3-phenylprop-2-en-1-one, experimental page 183

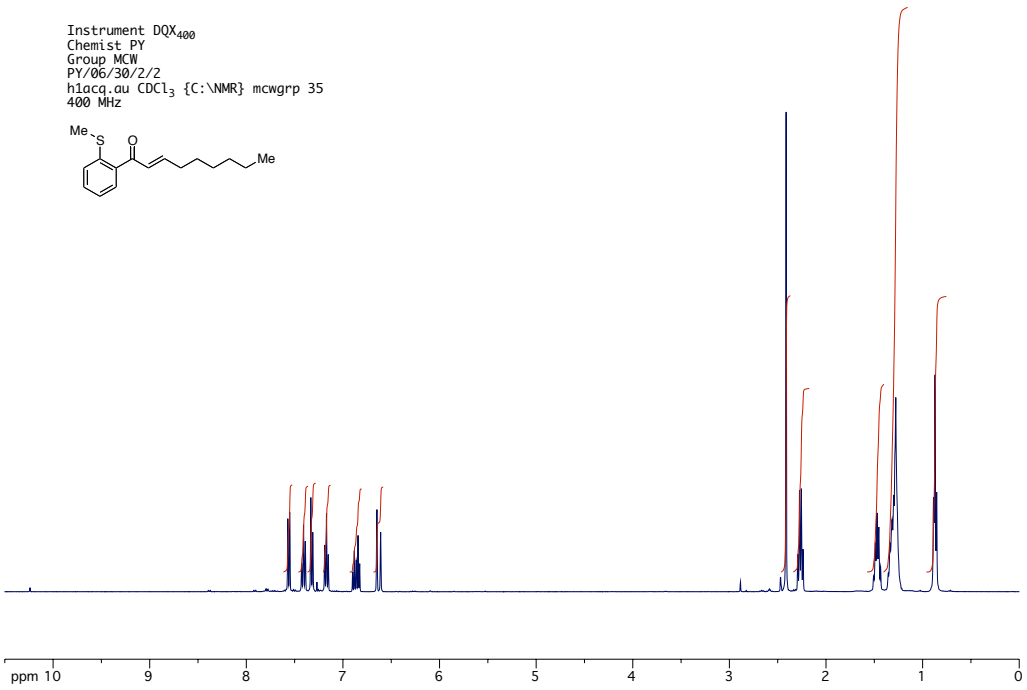


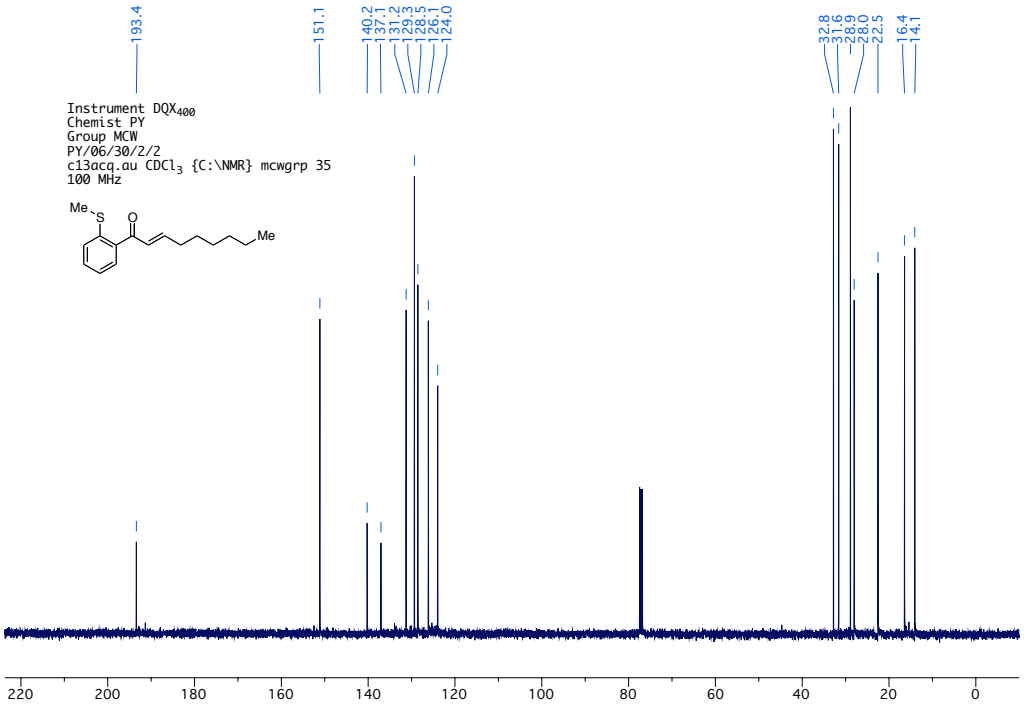


((*E*)-1-(2-(Methylthio)phenyl)-5-phenylpent-2-en-1-one, experimental page 183

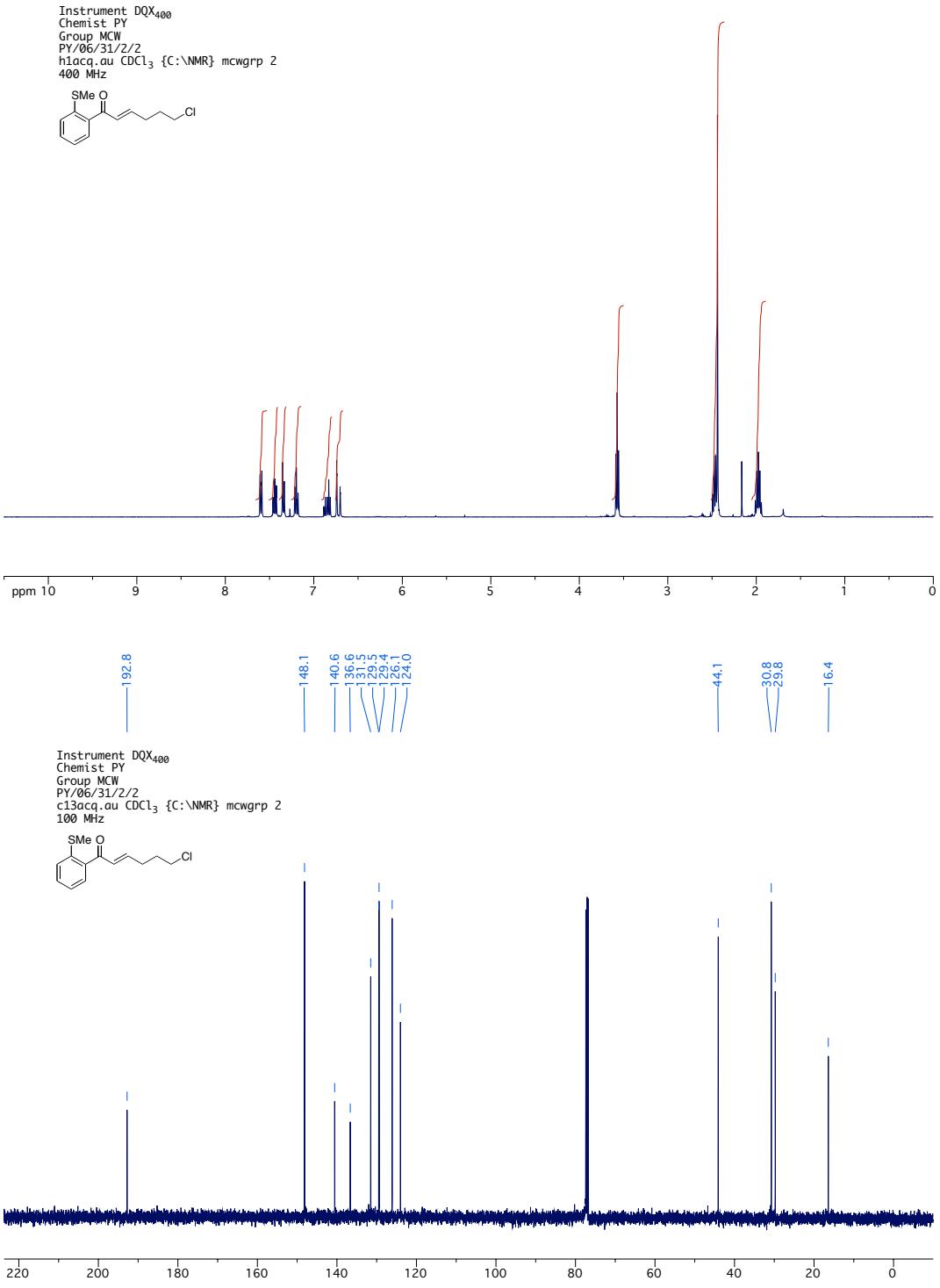


(E)-1-(2-(methylthiophenyl)non-2-en-1-one, experimental page 184

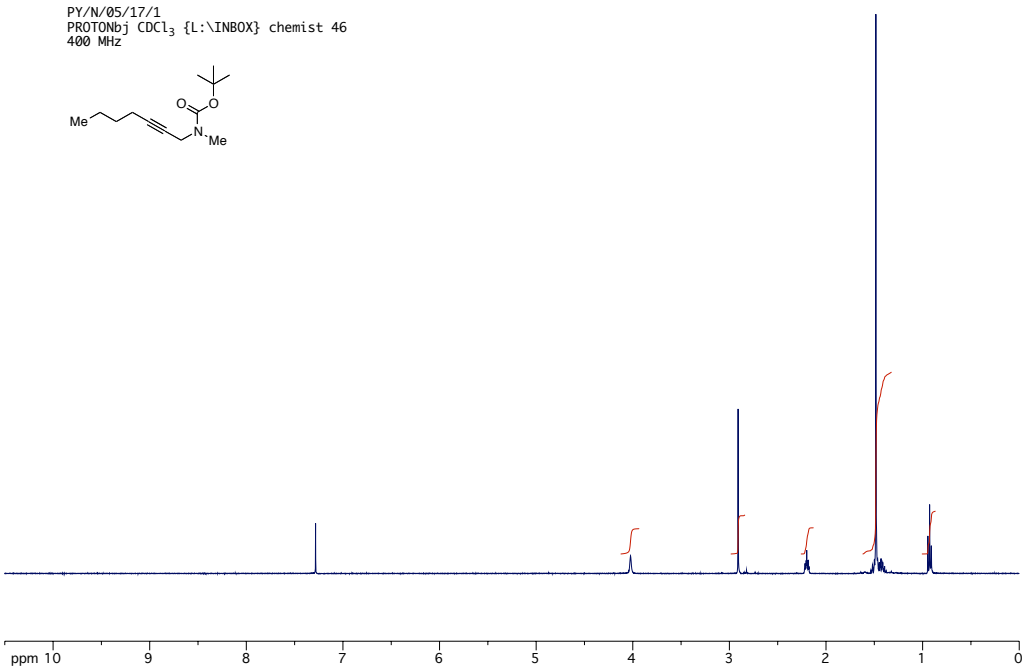


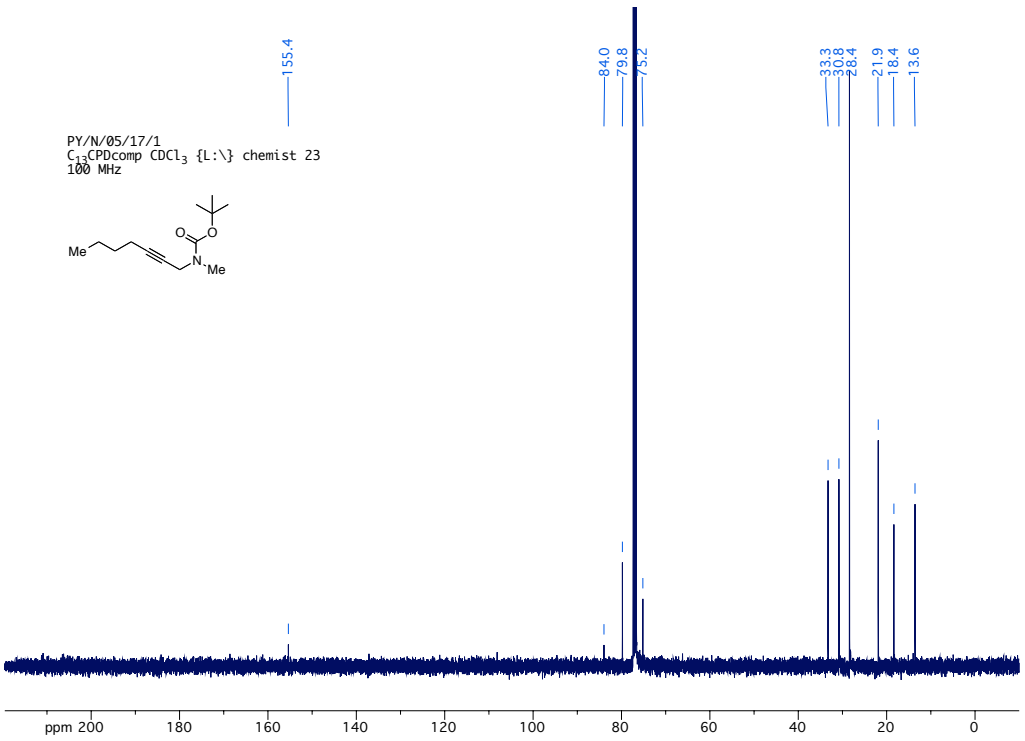


(E)-6-Chloro-1-(2-(methylthio)phenyl)hex-2-en-1-one, experimental page 184

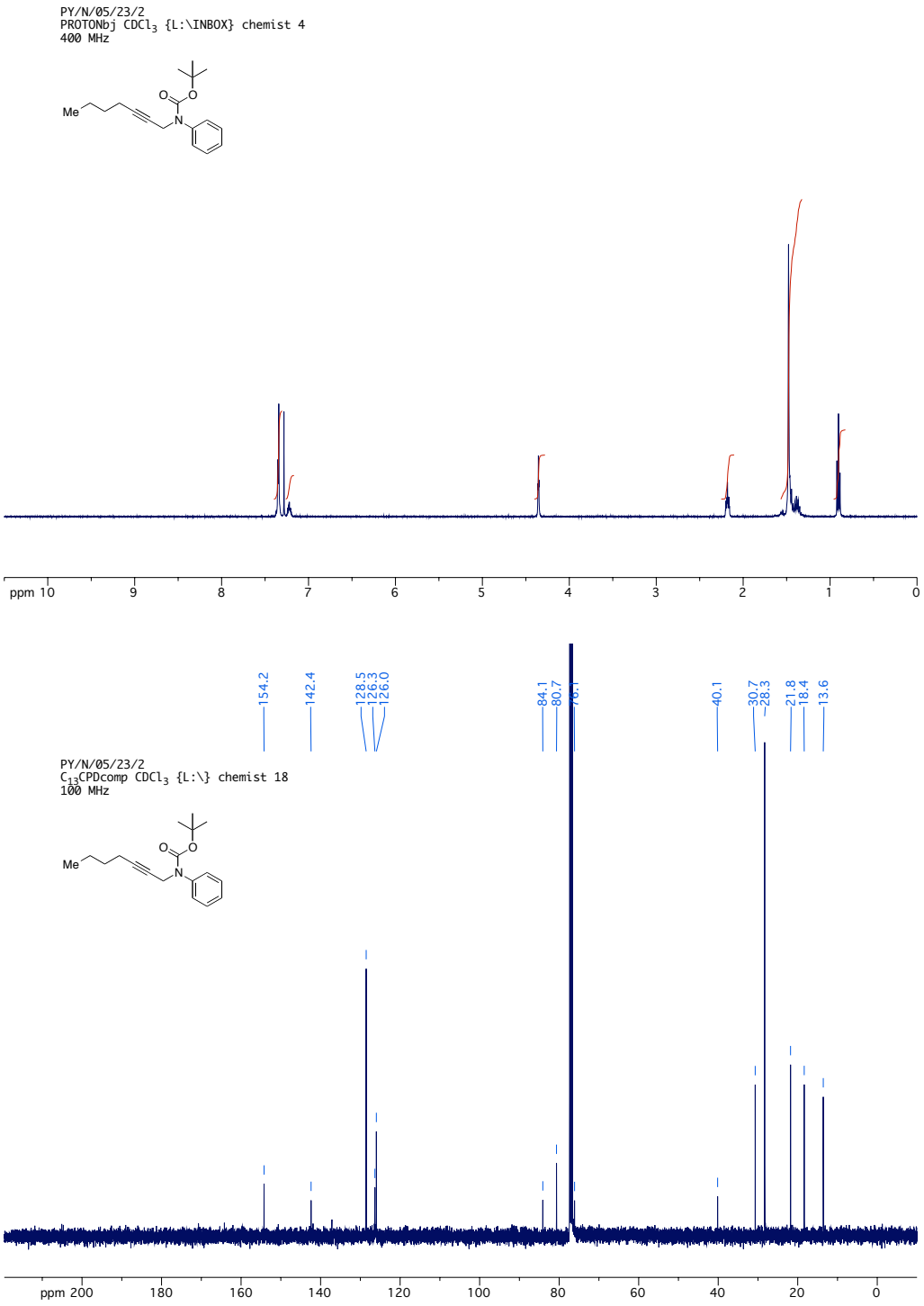


tert-butyl hept-2-yn-1-yl(methyl)carbamate, experimental page 156

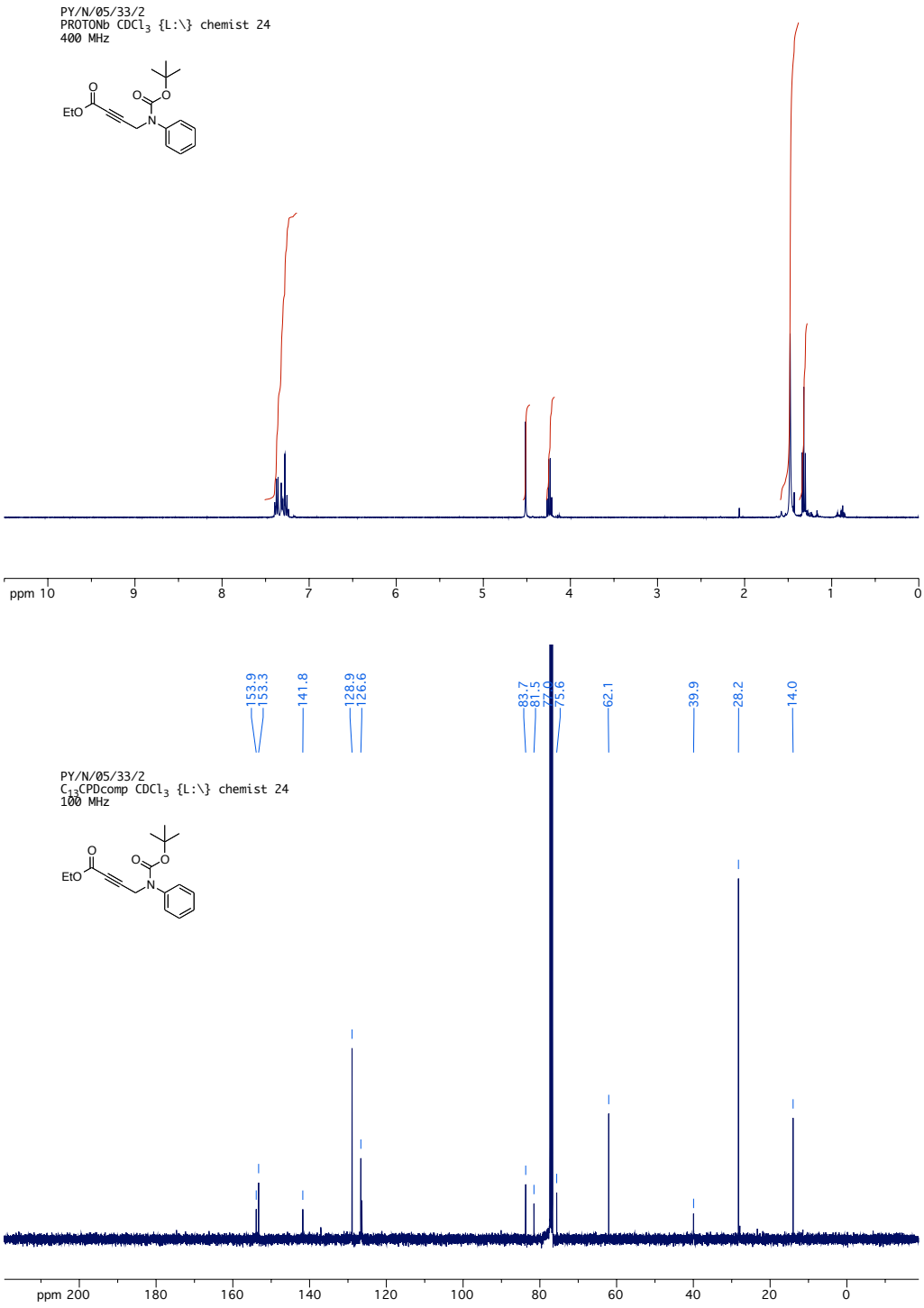




(*E*)-*tert*-butyl hept-2-yn-1-yl(phenyl)carbamate, experimental page 157

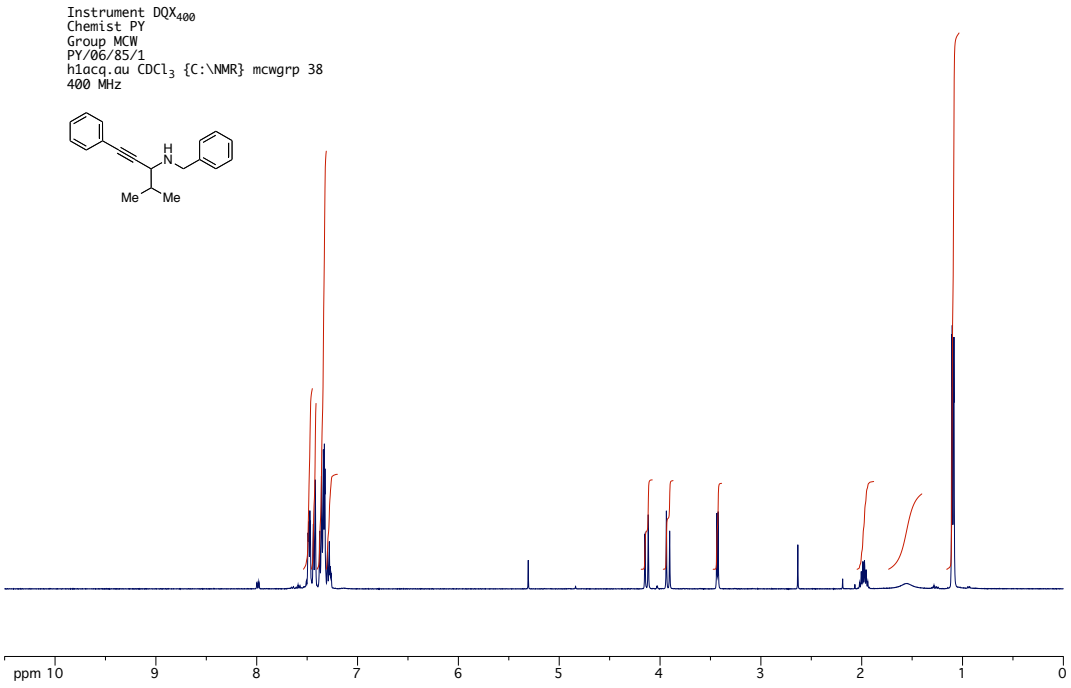


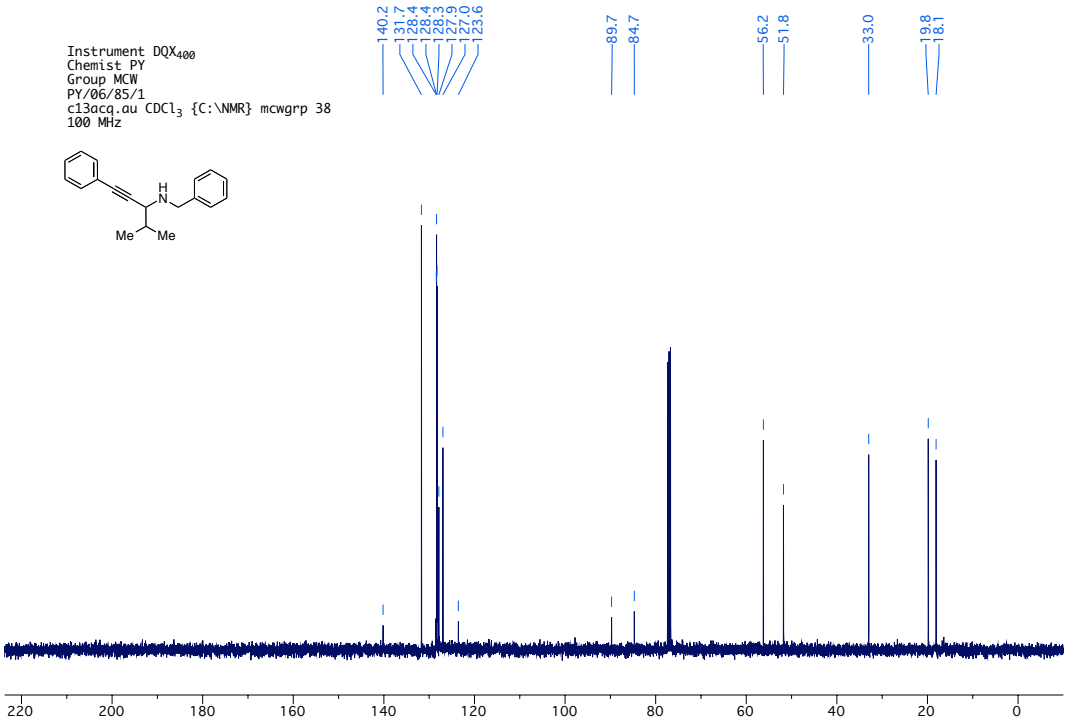
Ethyl 4-((*tert*-butoxycarbonyl)(phenyl)amino)but-2-ynoate, experimental page 157



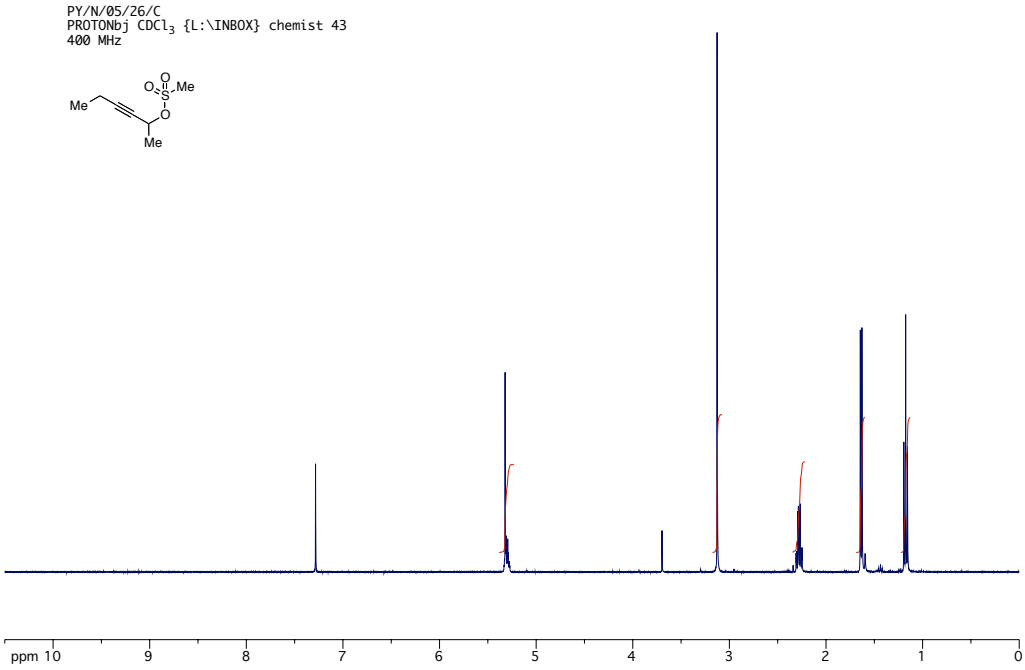
N-Benzyl-4-methyl-1-phenylpent-1-yn-3-amine, experimental

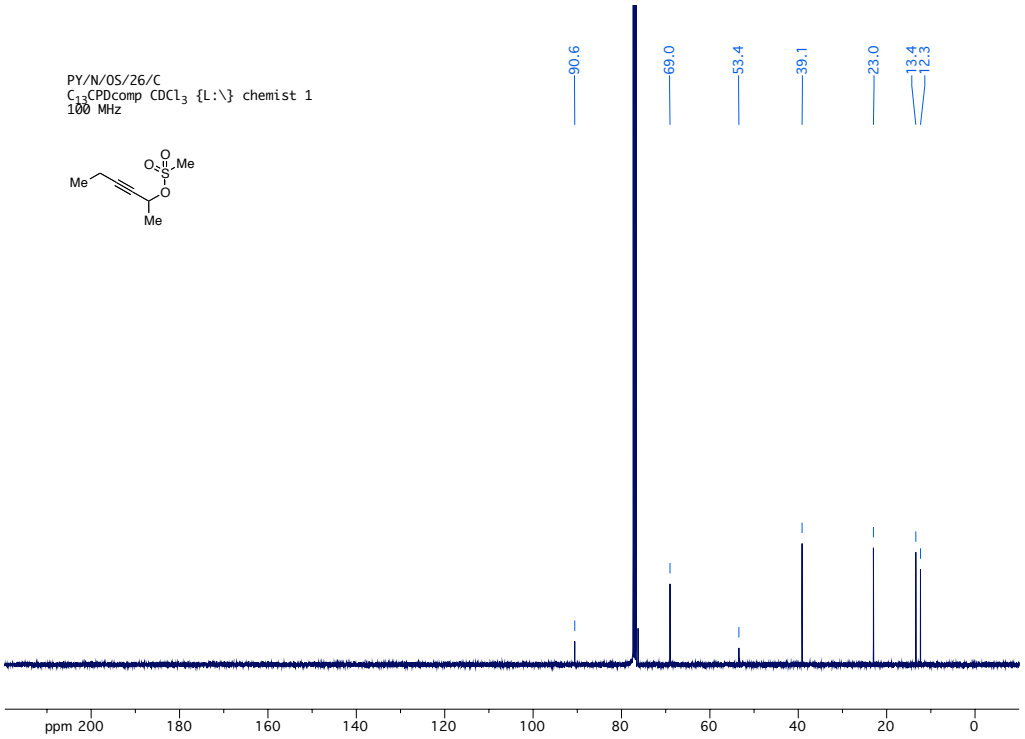
page 163



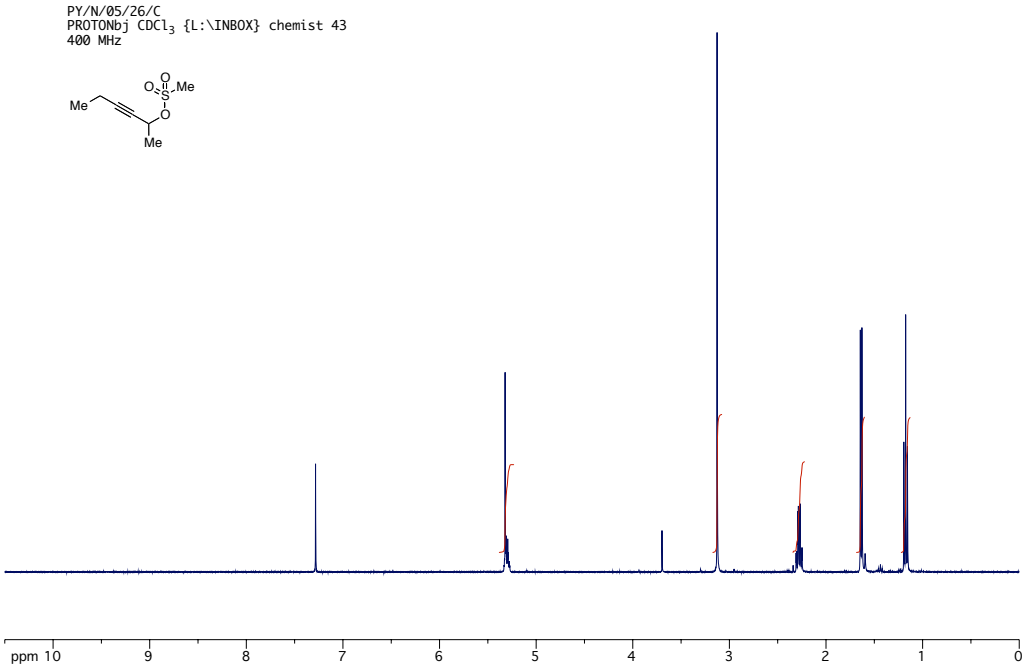


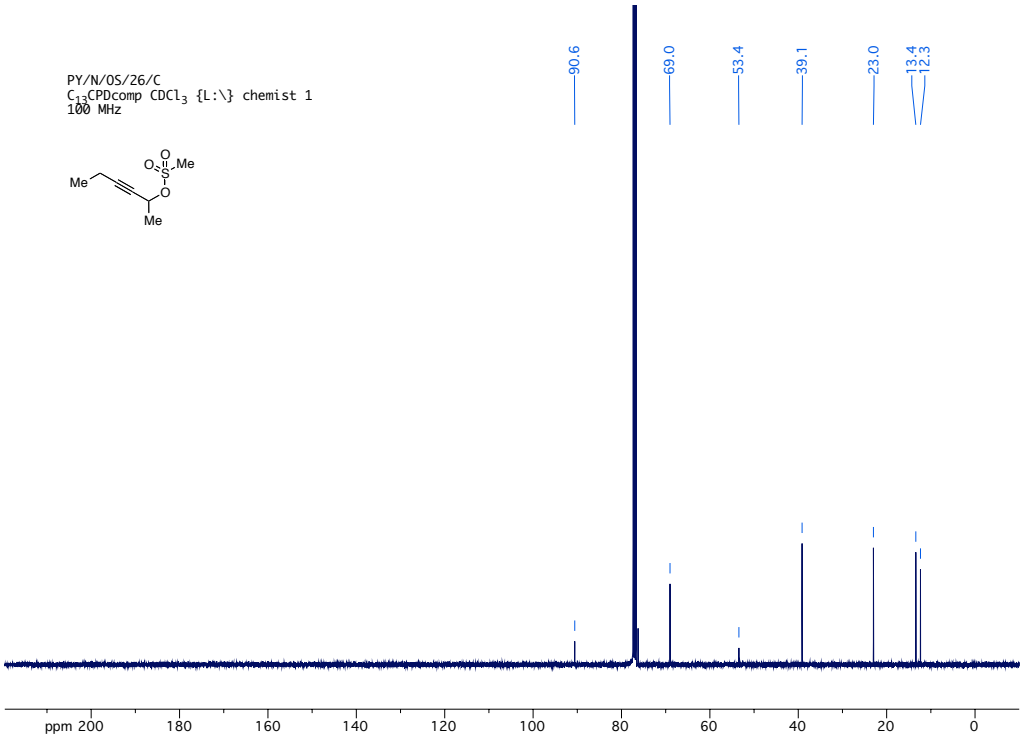
(*E*)-*tert*-Butyl hept-2-yn-1-yl(phenyl)carbamate, experimental page 158



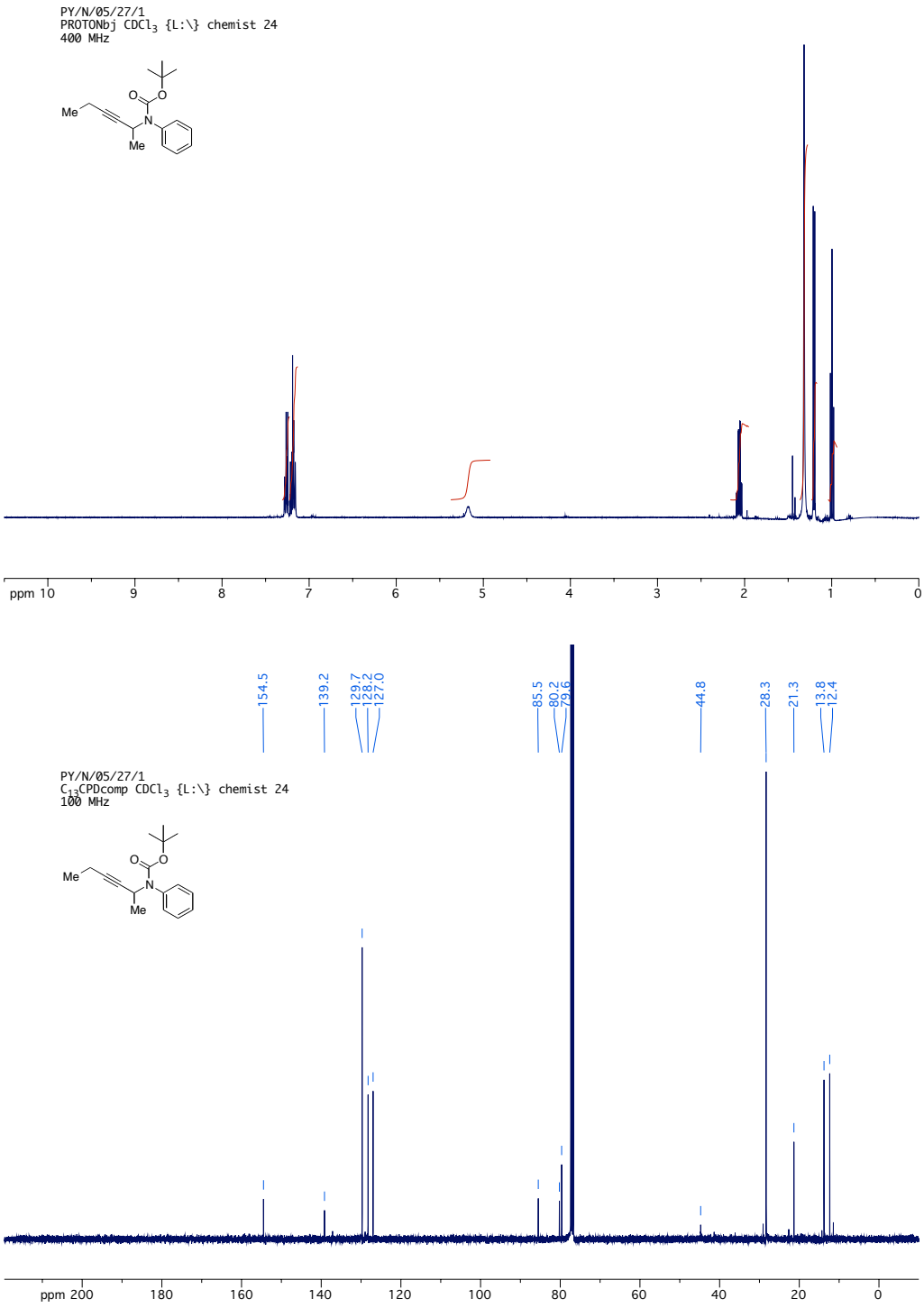


(*E*)-*tert*-Butyl hept-2-yn-1-yl(phenyl)carbamate, experimental page 158

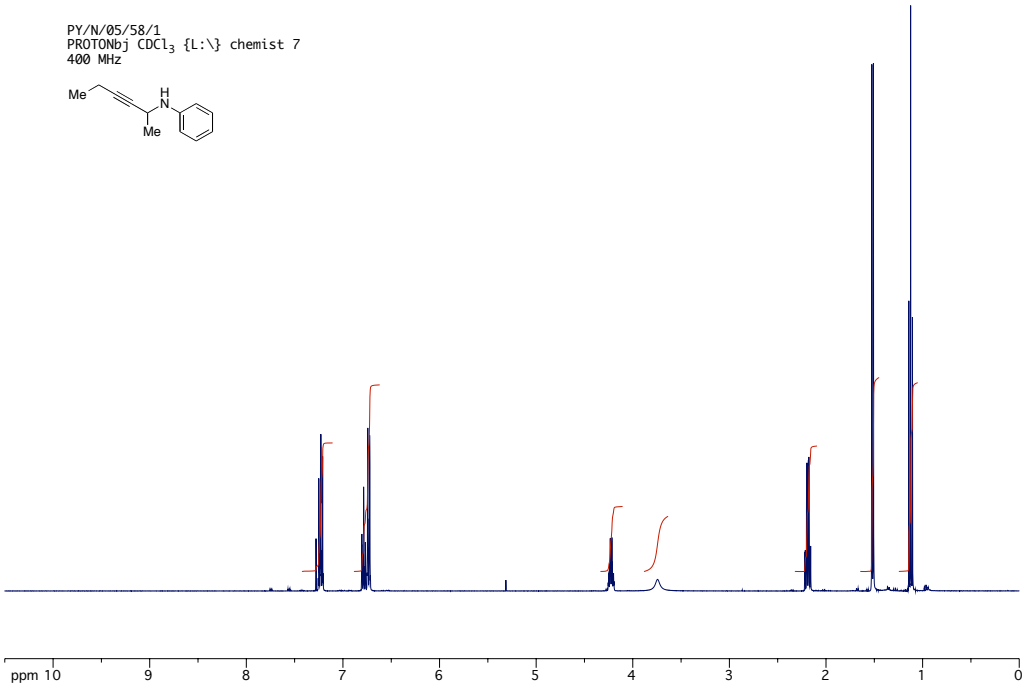


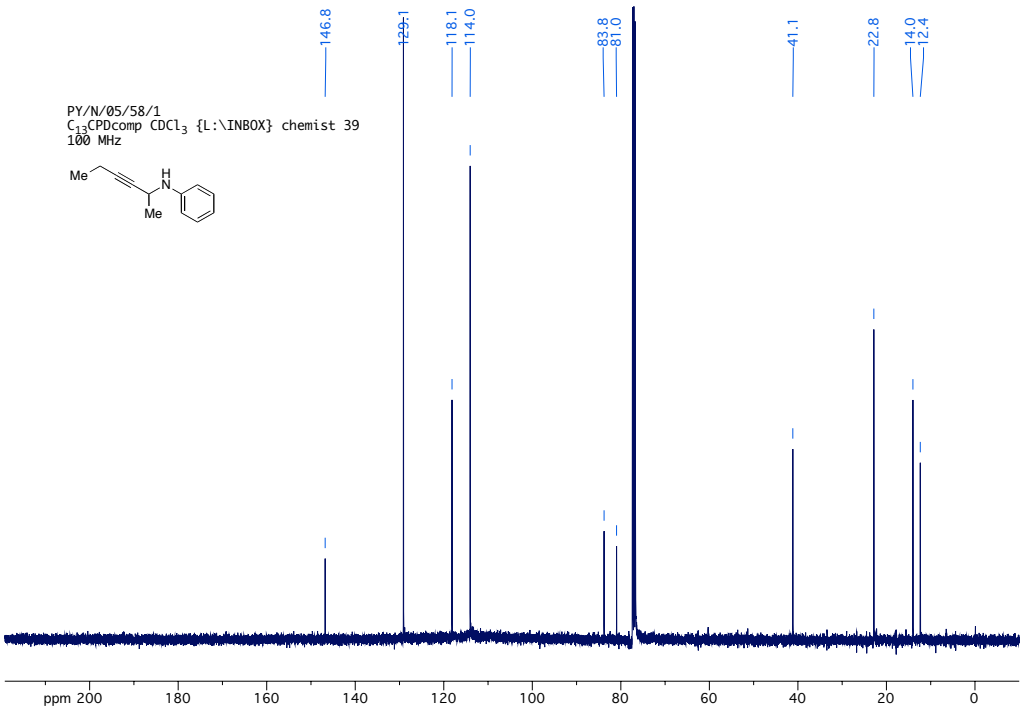


(*E*)-*tert*-Butyl hex-3-yn-2-yl(phenyl)carbamate, experimental page 159

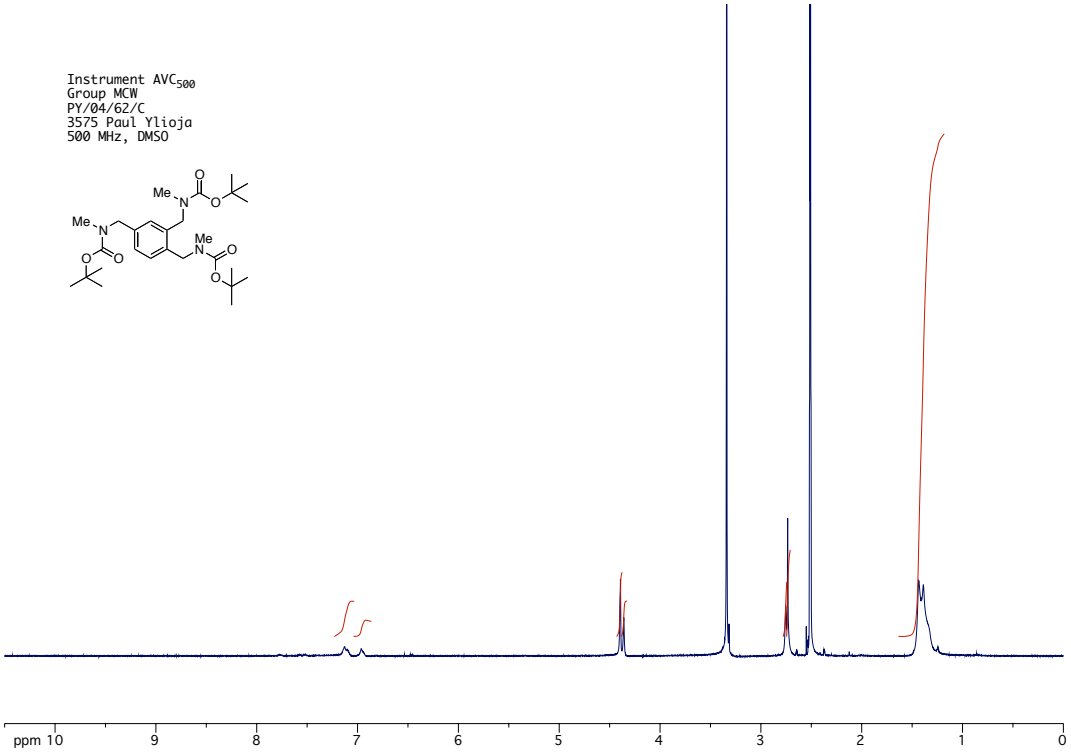


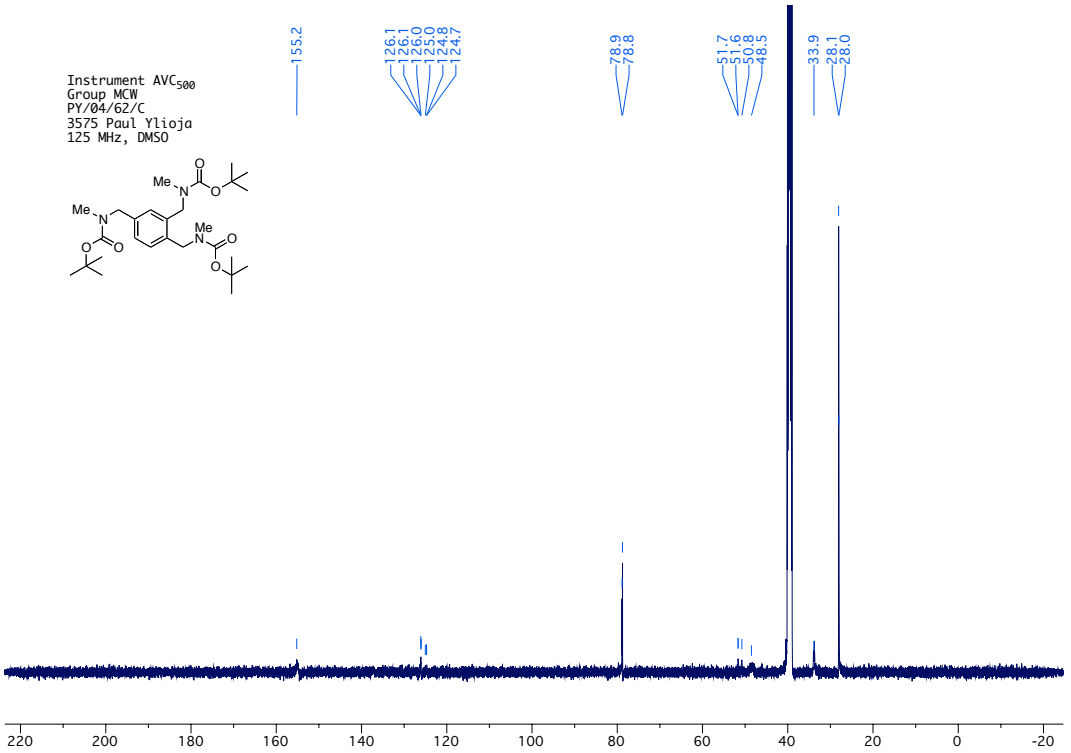
N-(Hex-3-yn-2-yl)aniline, experimental page 160



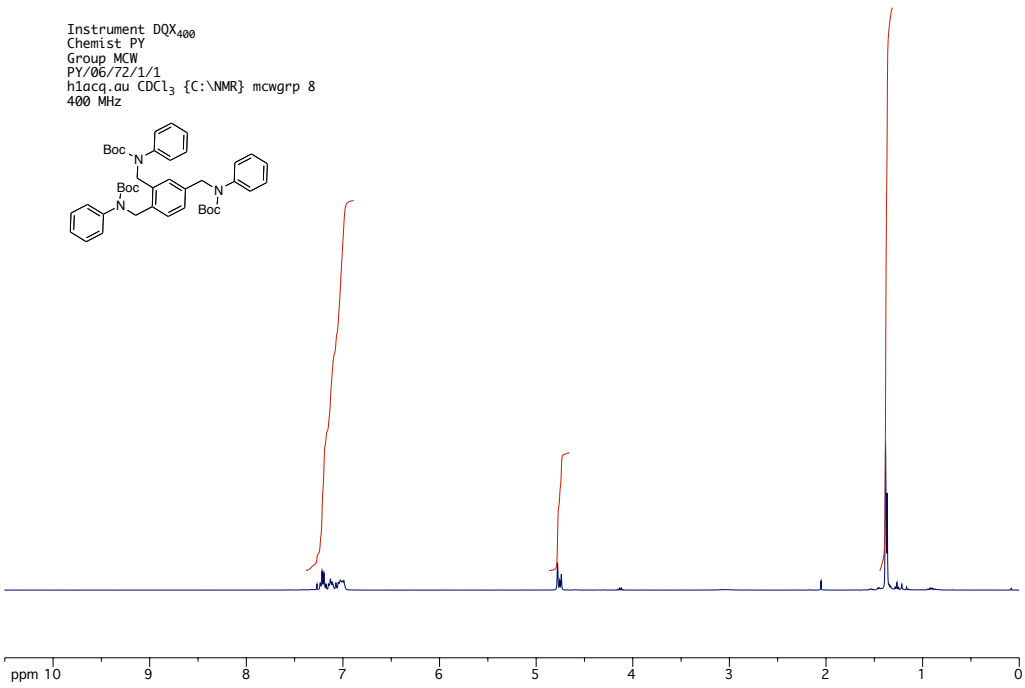


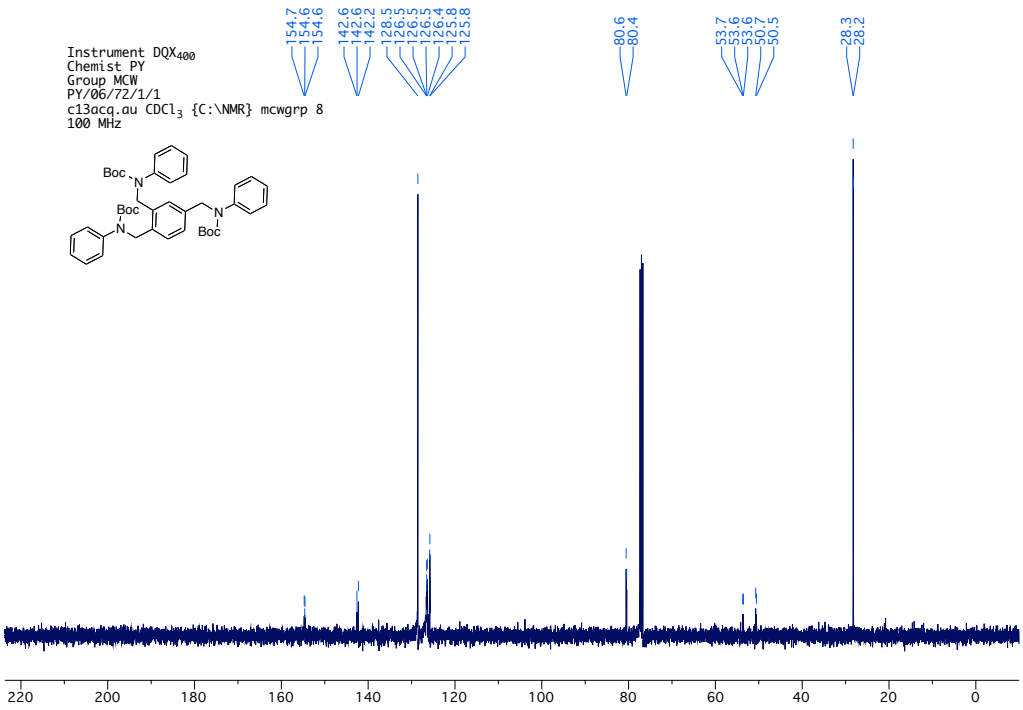
tri-*tert*-Butyl (benzene-1,2,4-triyltris(methylene))-tris(methylcarbamate), experimental page 175



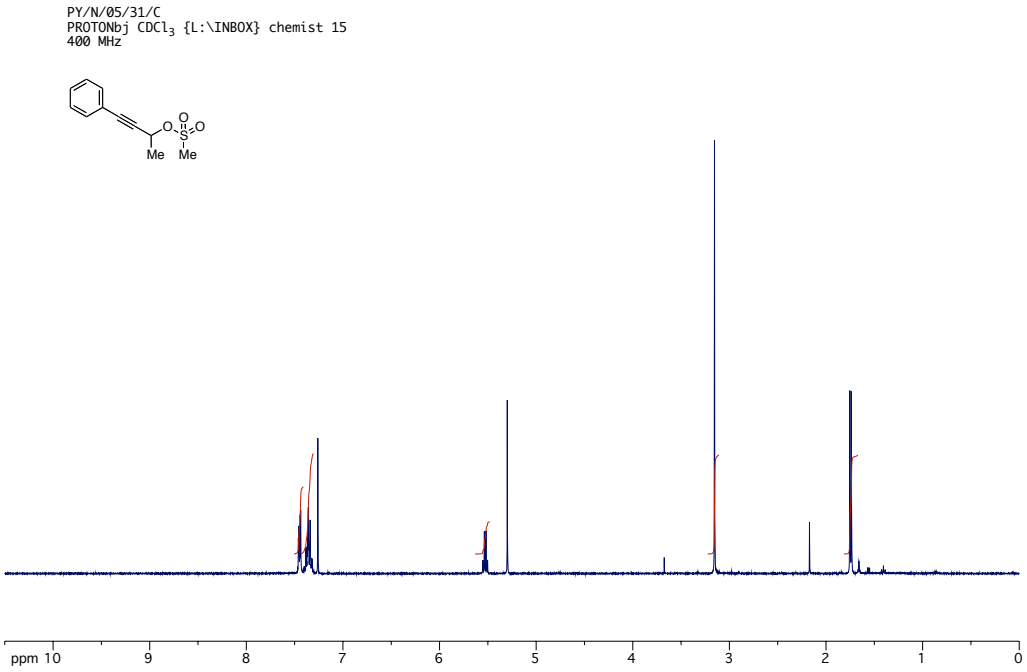


tri-*tert*-Butyl (benzene-1,2,4-triyltris(methylene))-tris(phenylcarbamate), experimental page 176

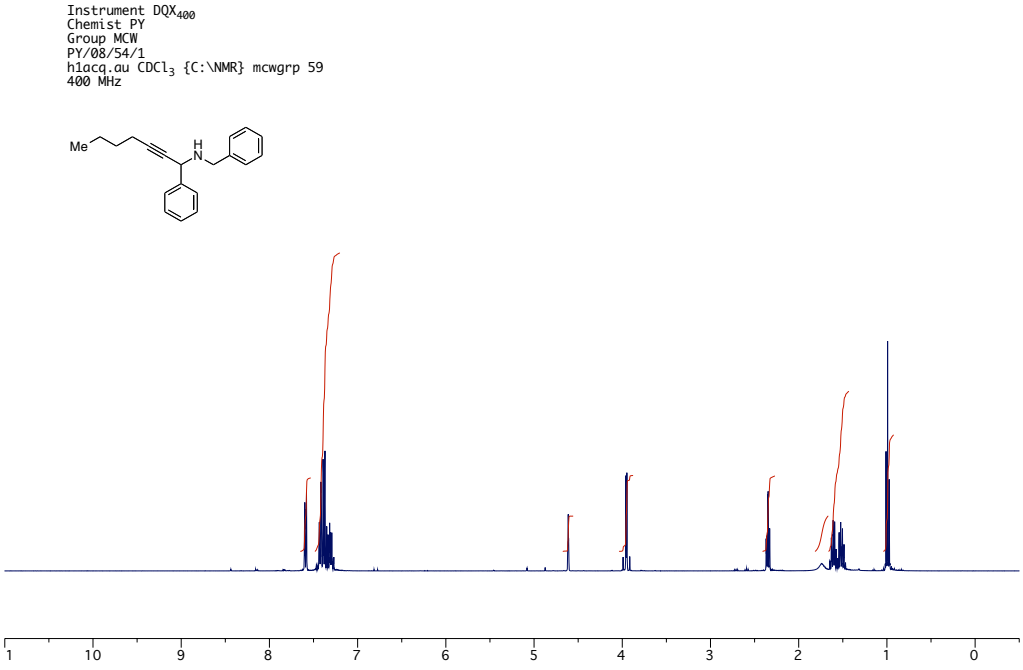


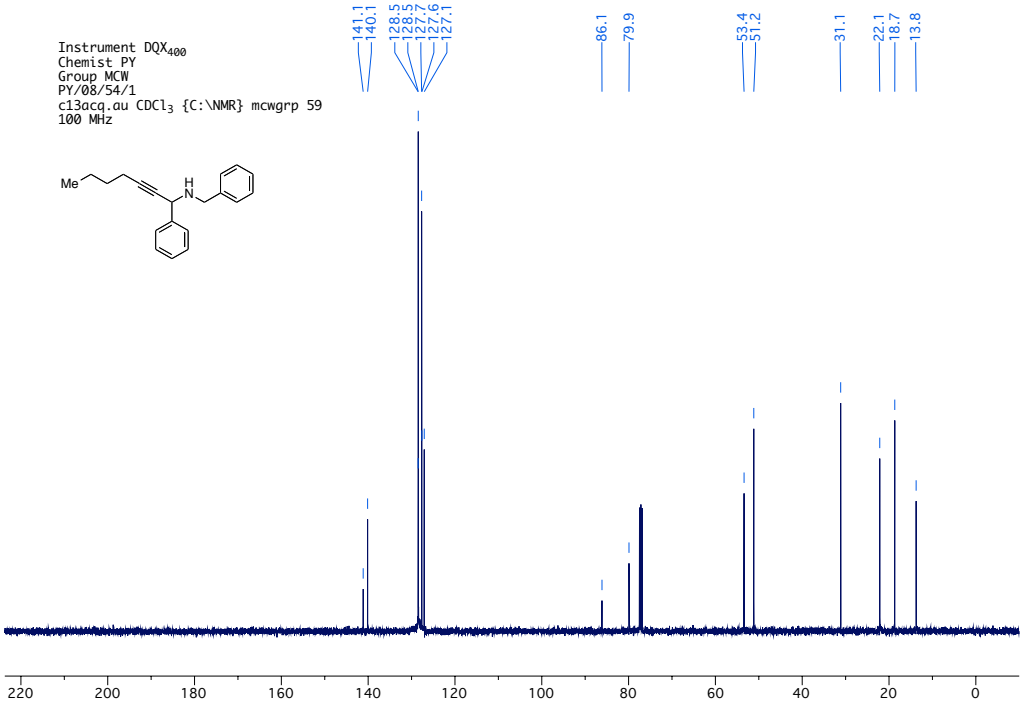


4-Phenylbut-3-yn-2-yl methanesulfonate, experimental page ??

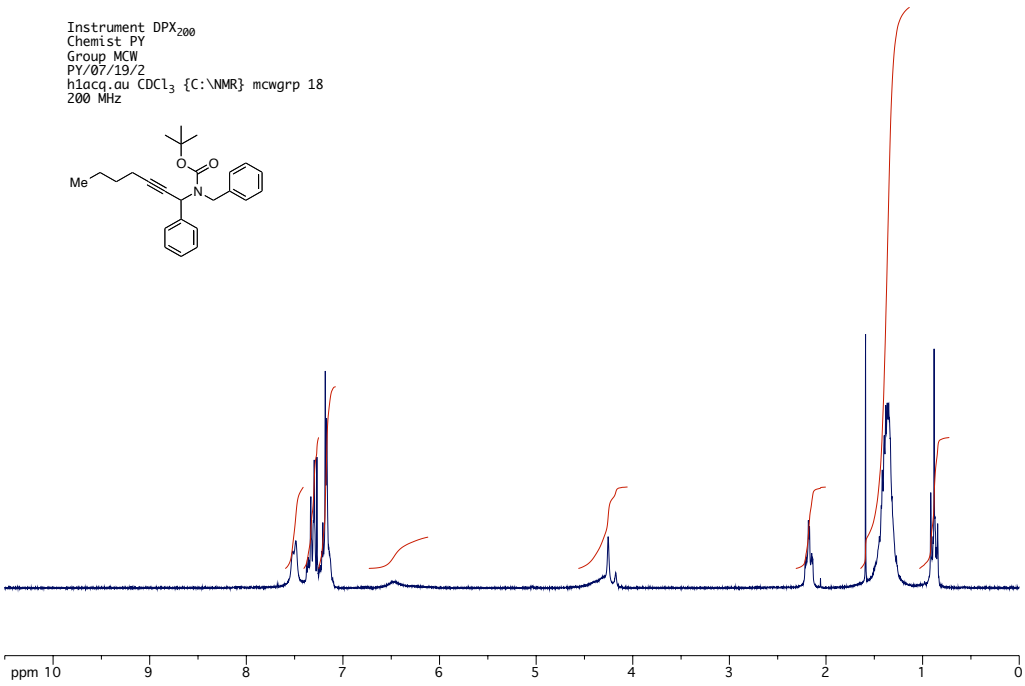


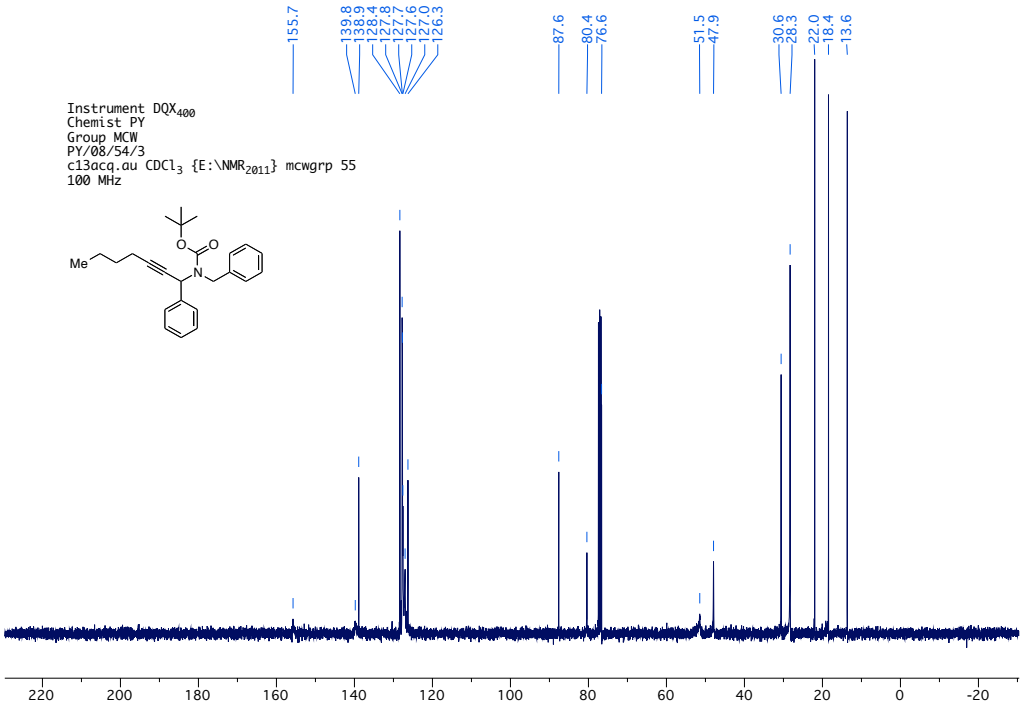
N-benzyl-1-phenylhept-2-yn-1-amine, experimental page 165



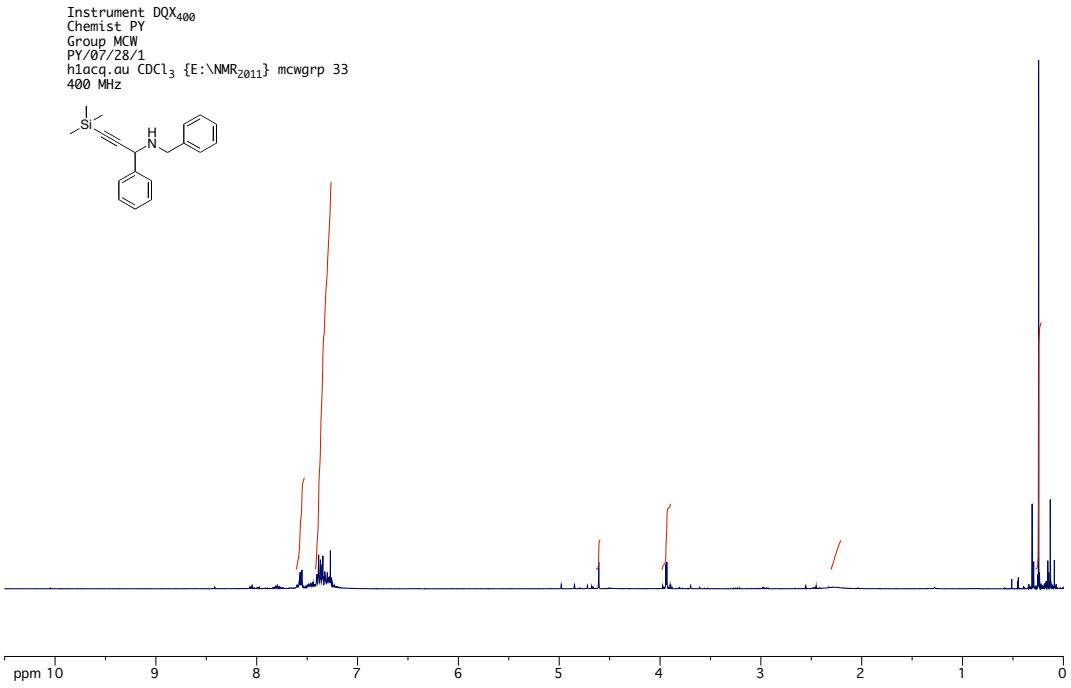


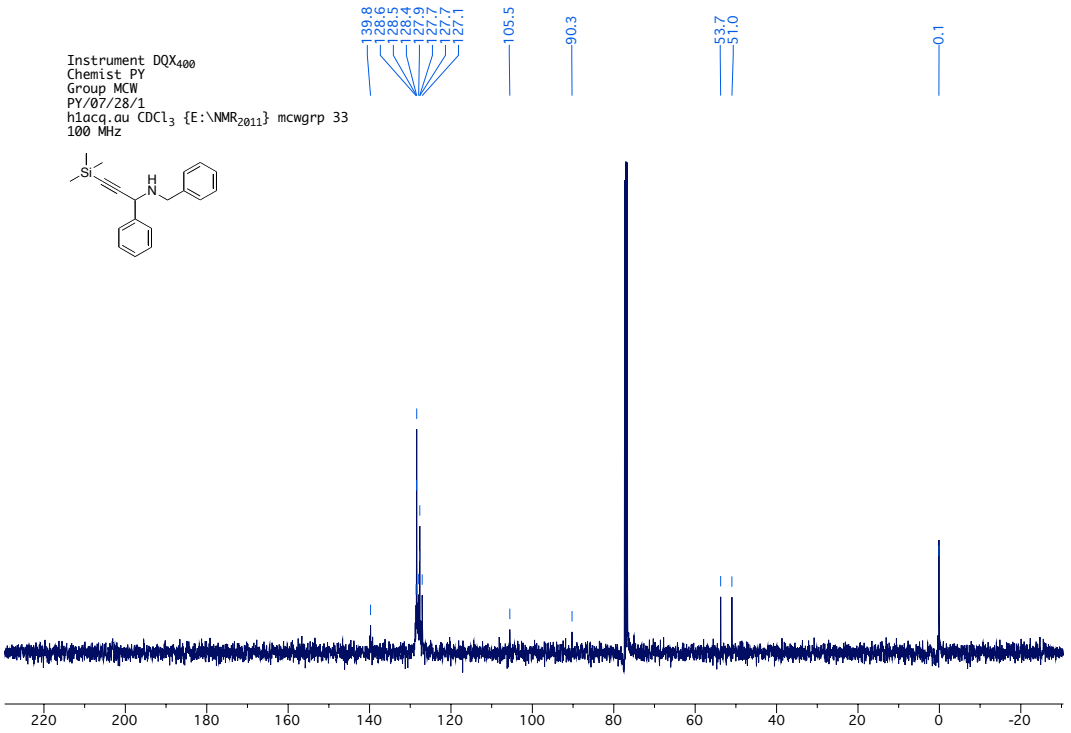
tert-butyl benzyl(1-phenylhept-2-yn-1-yl)carbamate, experimental page 166



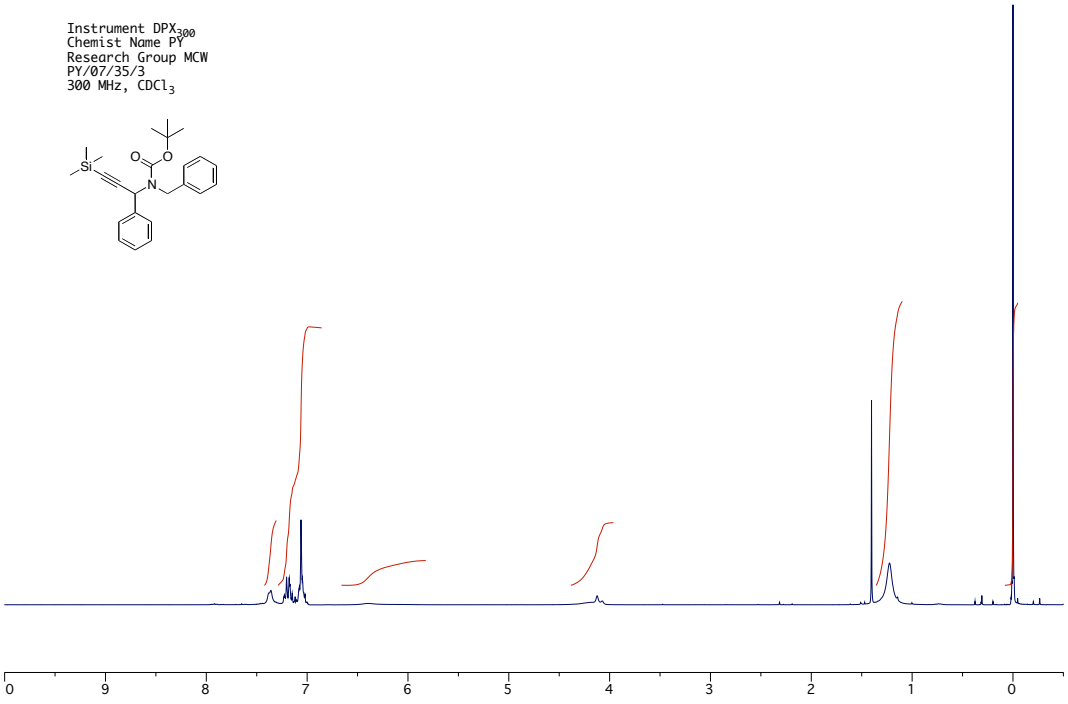


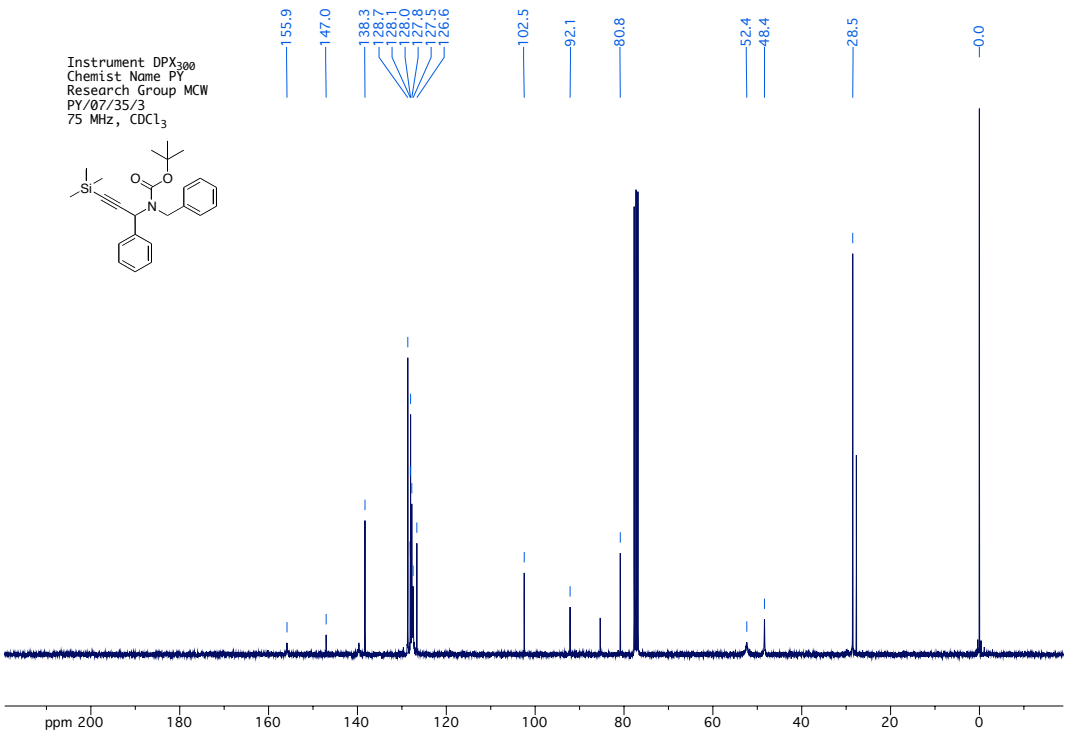
N-Benzyl-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-amine, experimental page 167



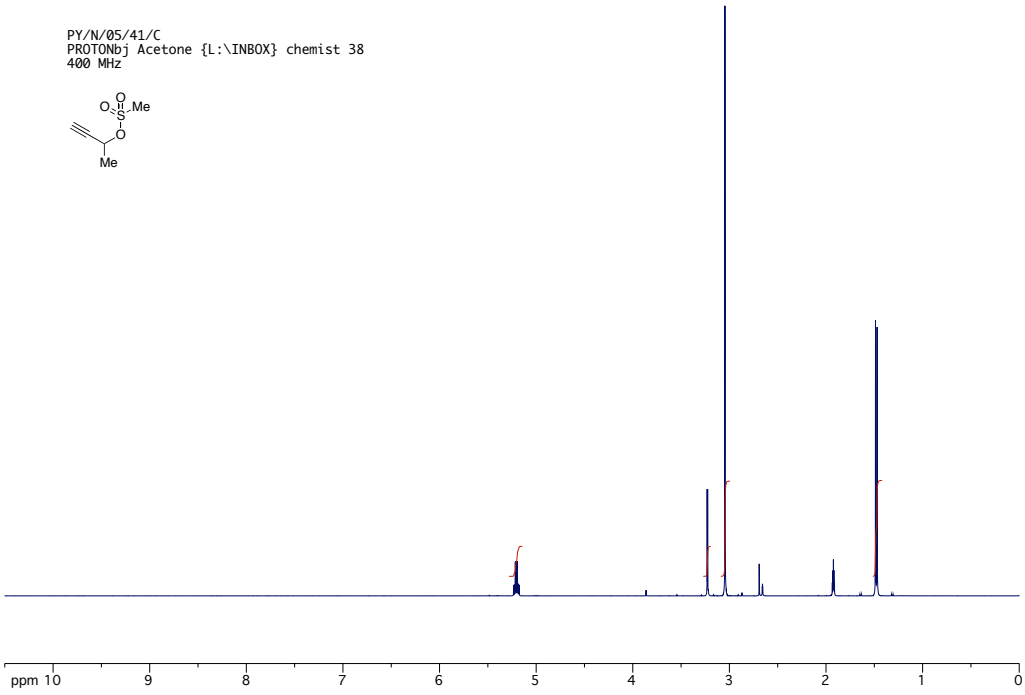


tert-Butyl phenyl(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)-carbamate, experimental page 167

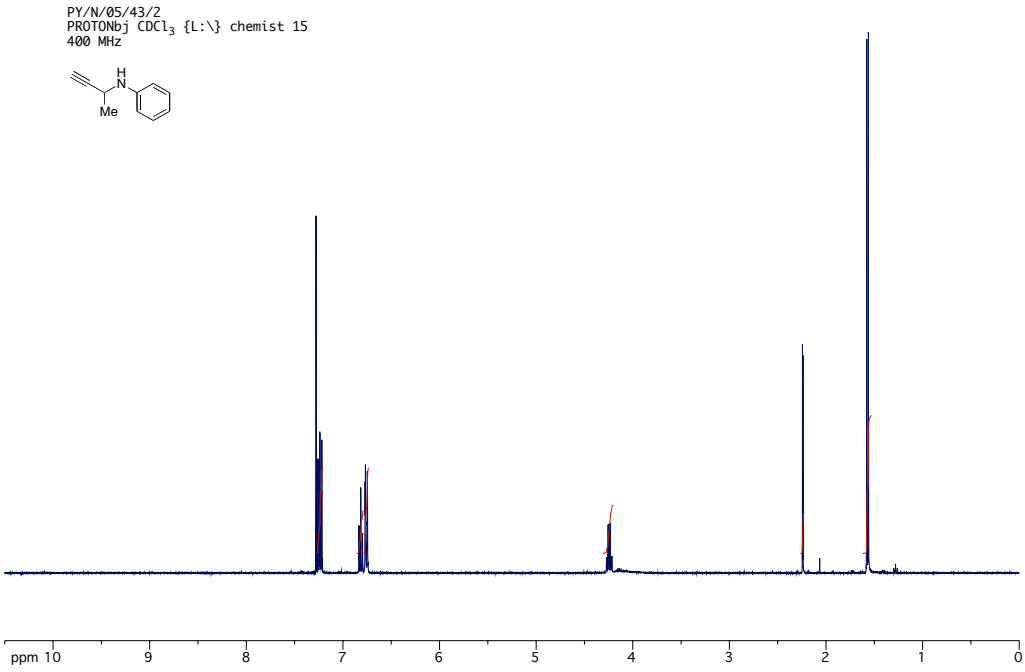


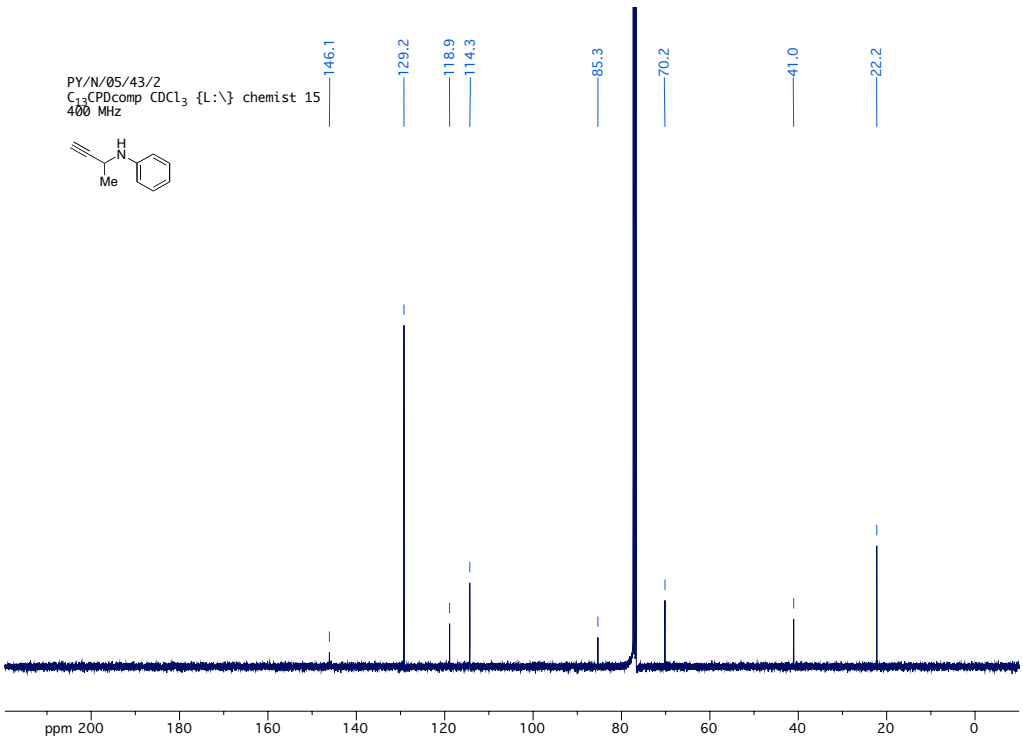


but-3-yn-2-yl methanesulfonate, experimental page 162

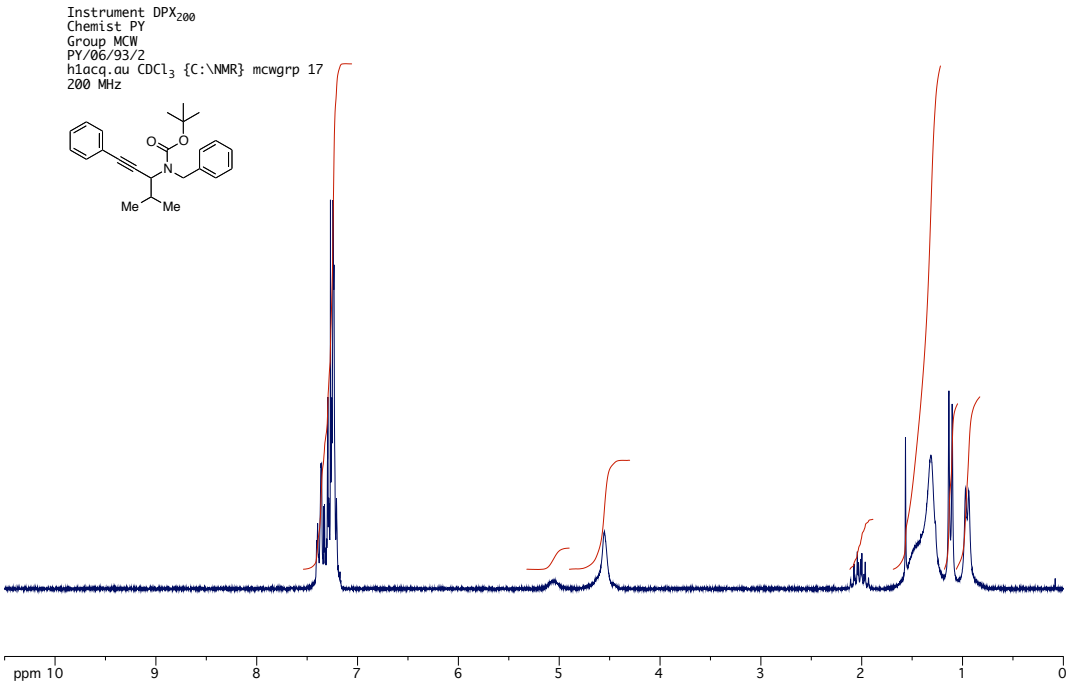


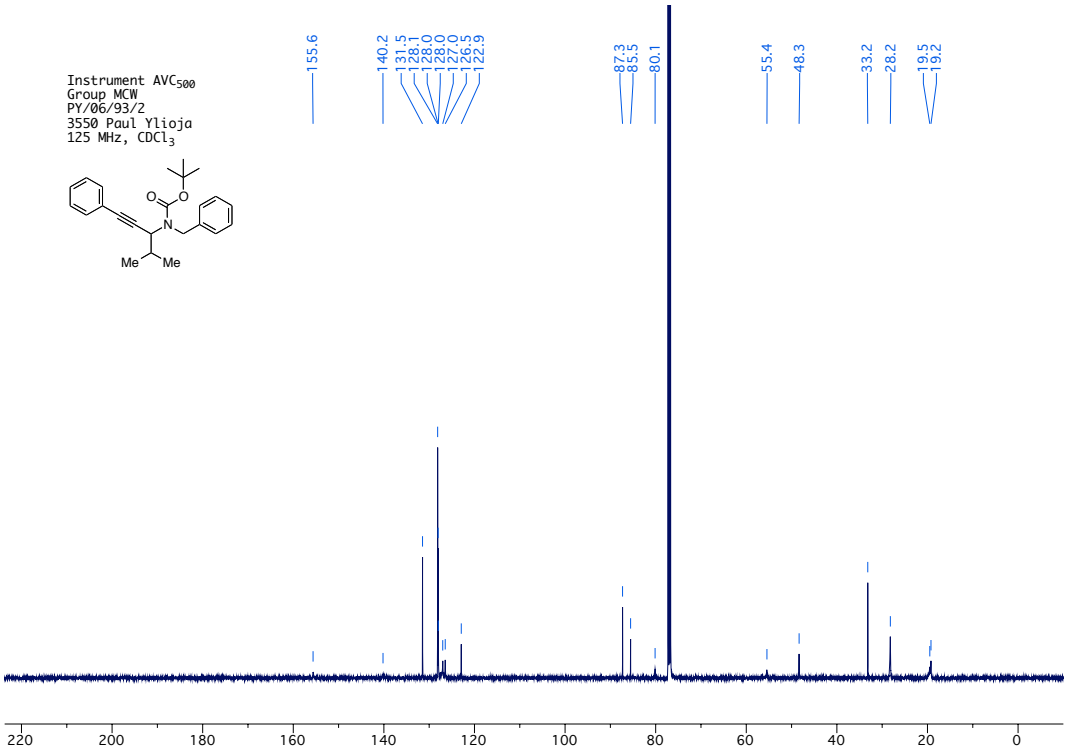
N-(But-3-yn-2-yl)aniline, experimental page 162



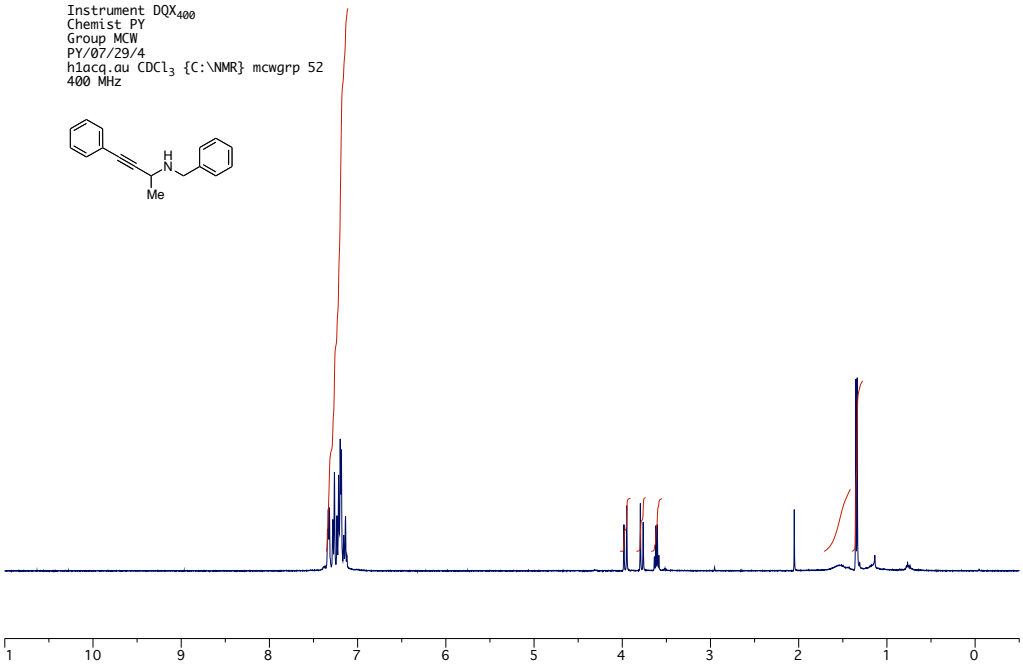


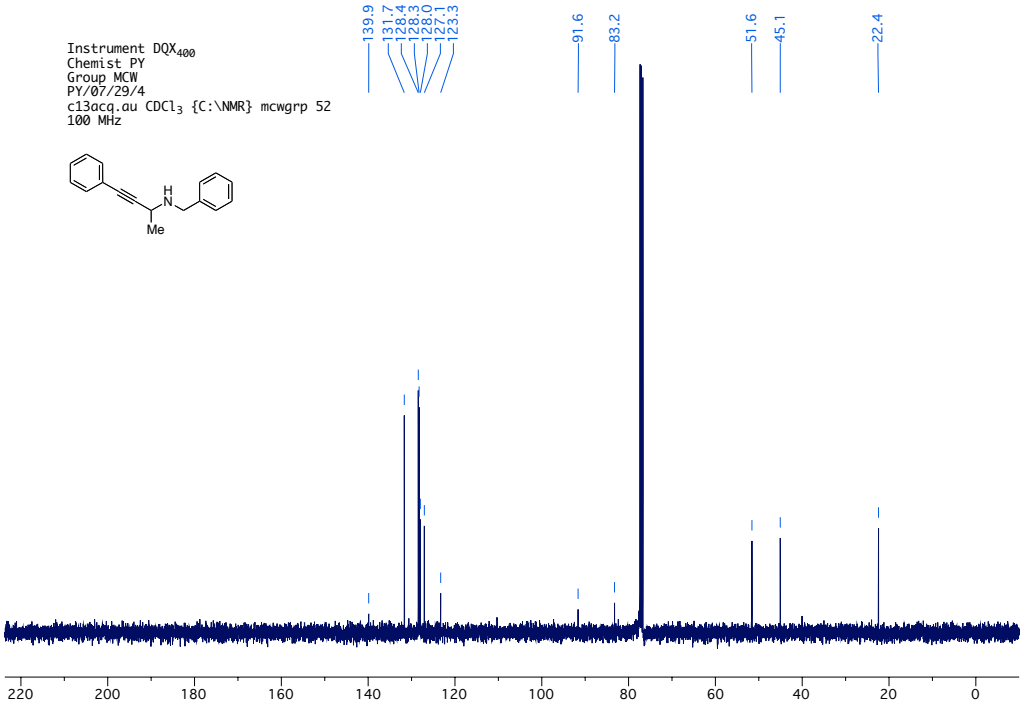
tert-Butyl benzyl(4-methyl-1-phenylpent-1-yn-3-yl)carbamate, experimental page 164



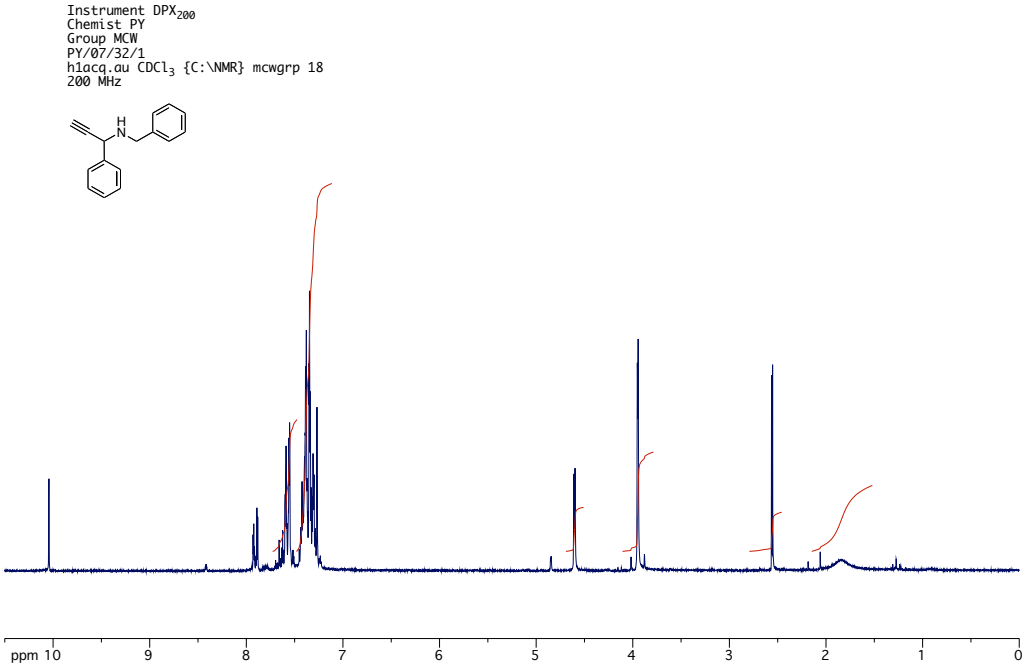


N-Benzyl-4-phenylbut-3-yn-2-amine, experimental page 169

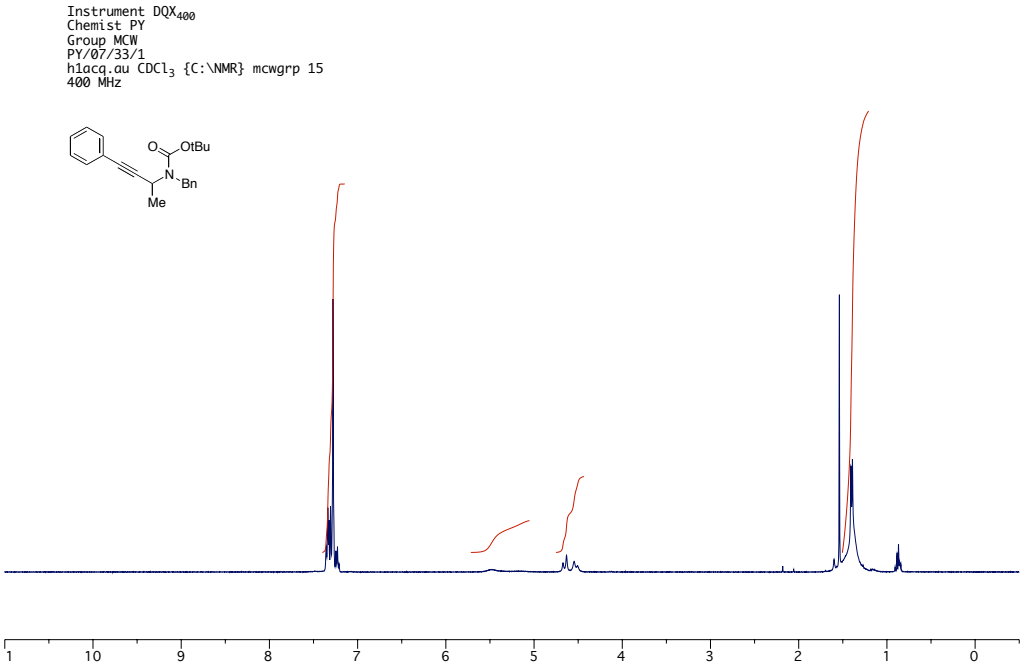


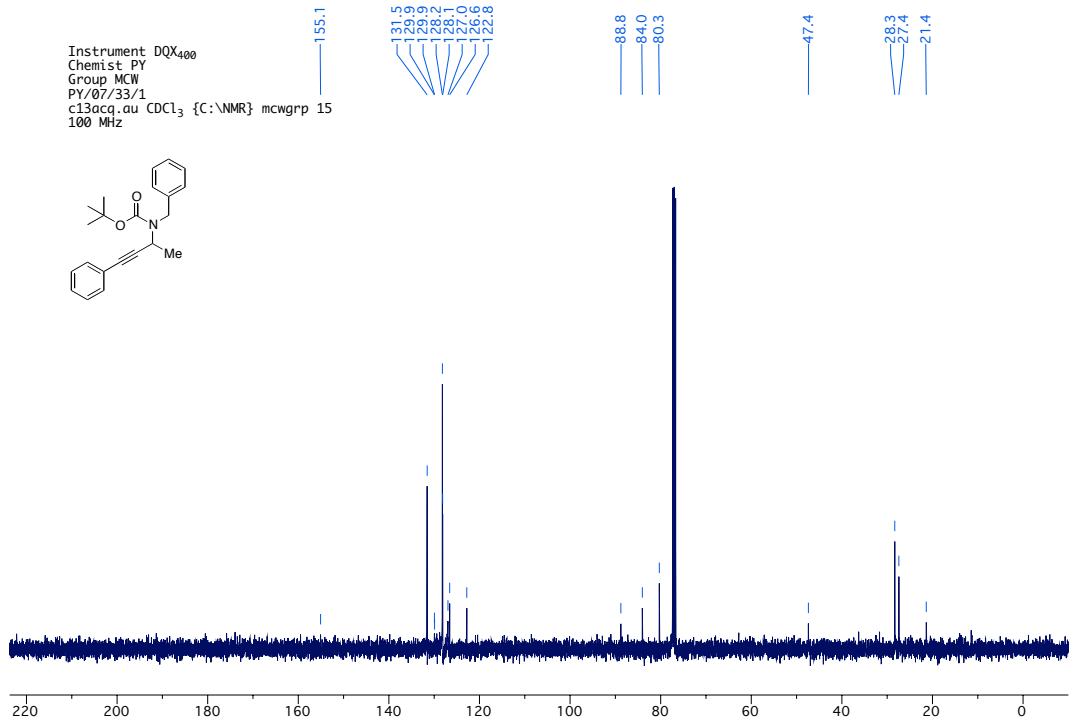


N-Benzyl-1-phenylprop-2-yn-1-amine, experimental page 170

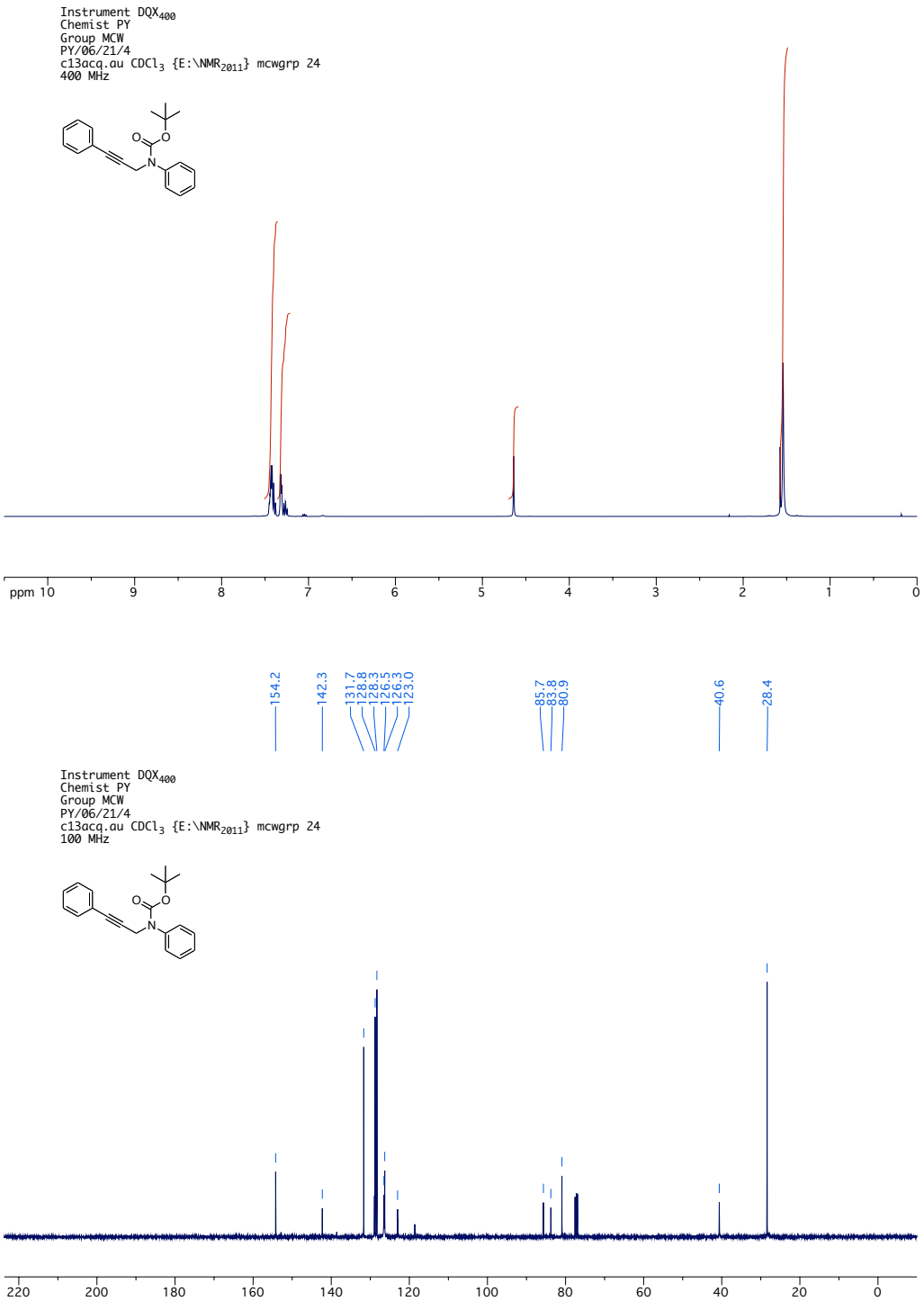


tert-Butyl benzyl(4-phenylbut-3-yn-2-yl)carbamate, experimental page 169

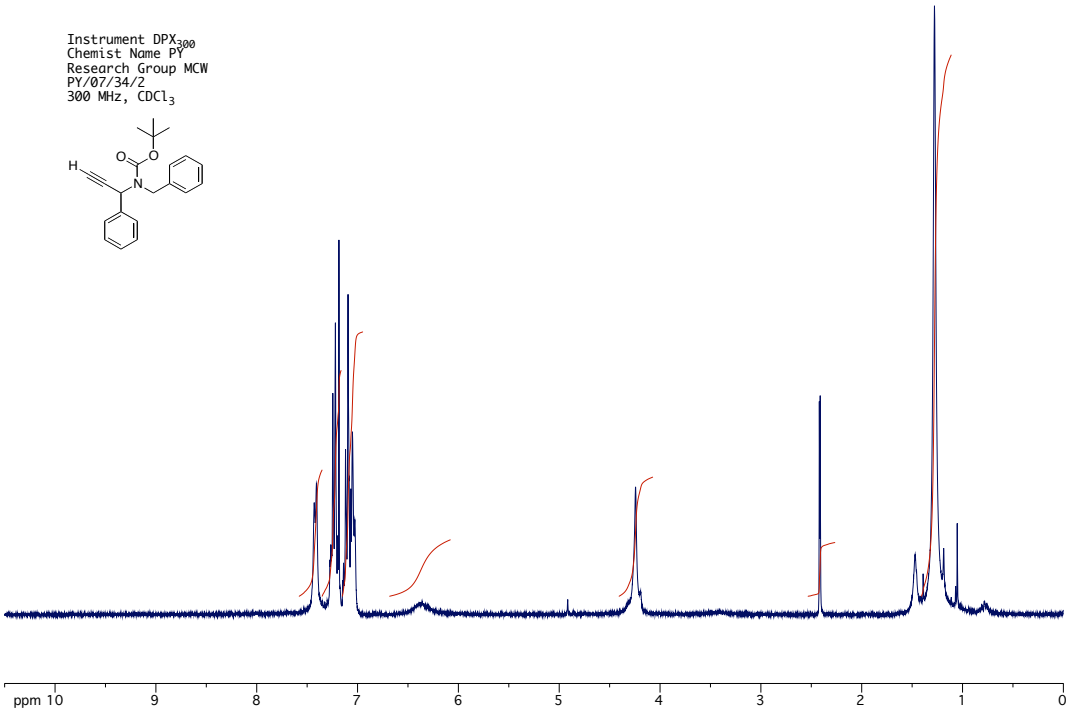


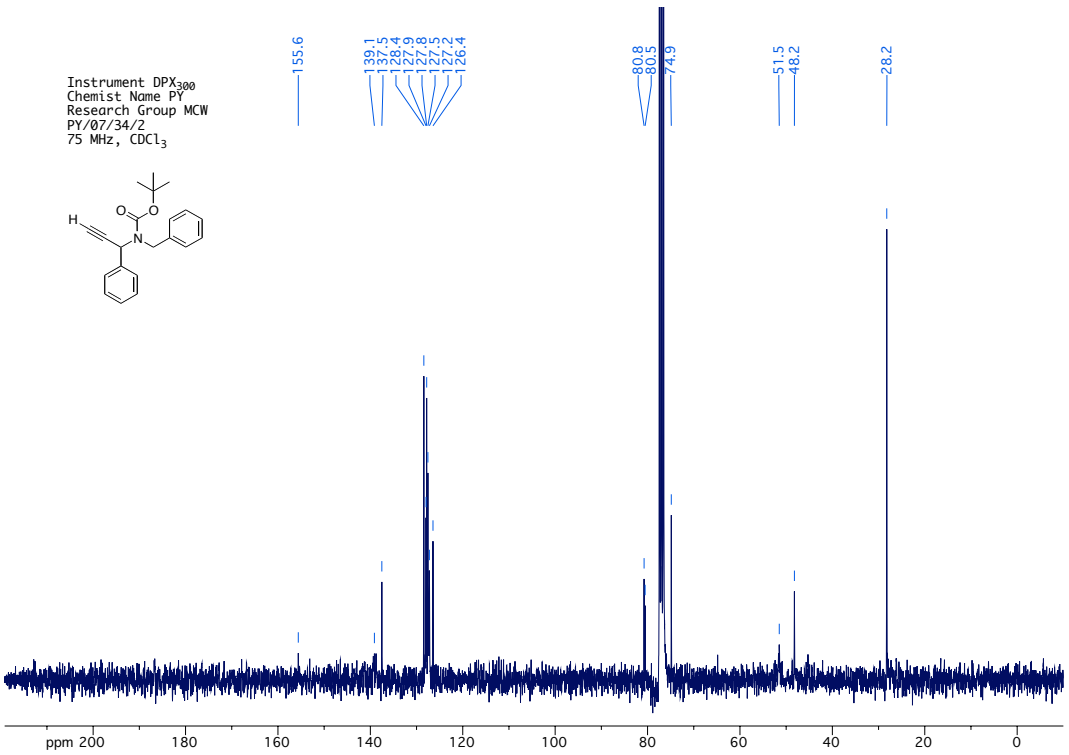


tert-Butyl phenyl(4-phenylbut-3-yn-2-yl)carbamate, experimental page 161

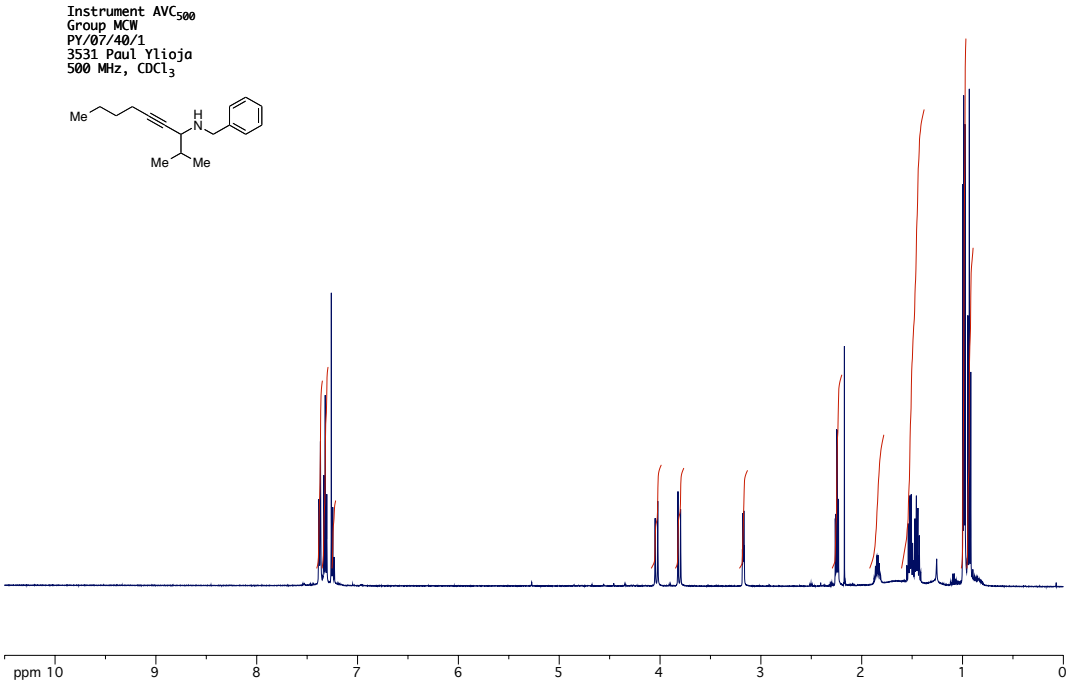


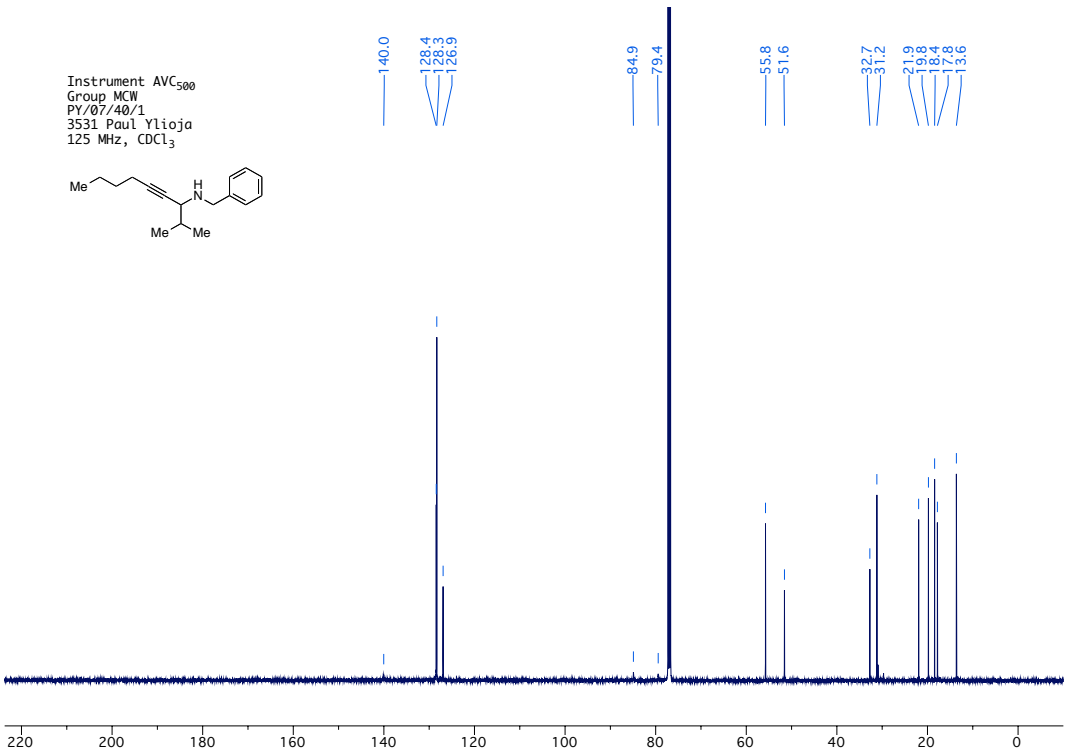
tert-Butyl benzyl(1-phenylprop-2-yn-1-yl)carbamate, experimental page 169



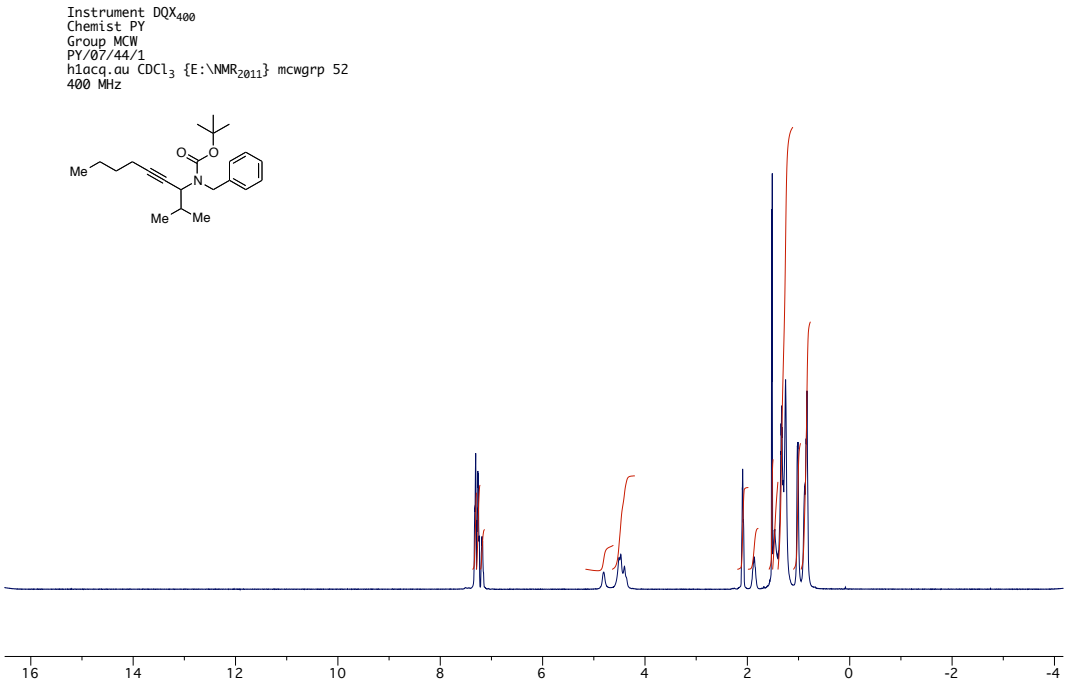


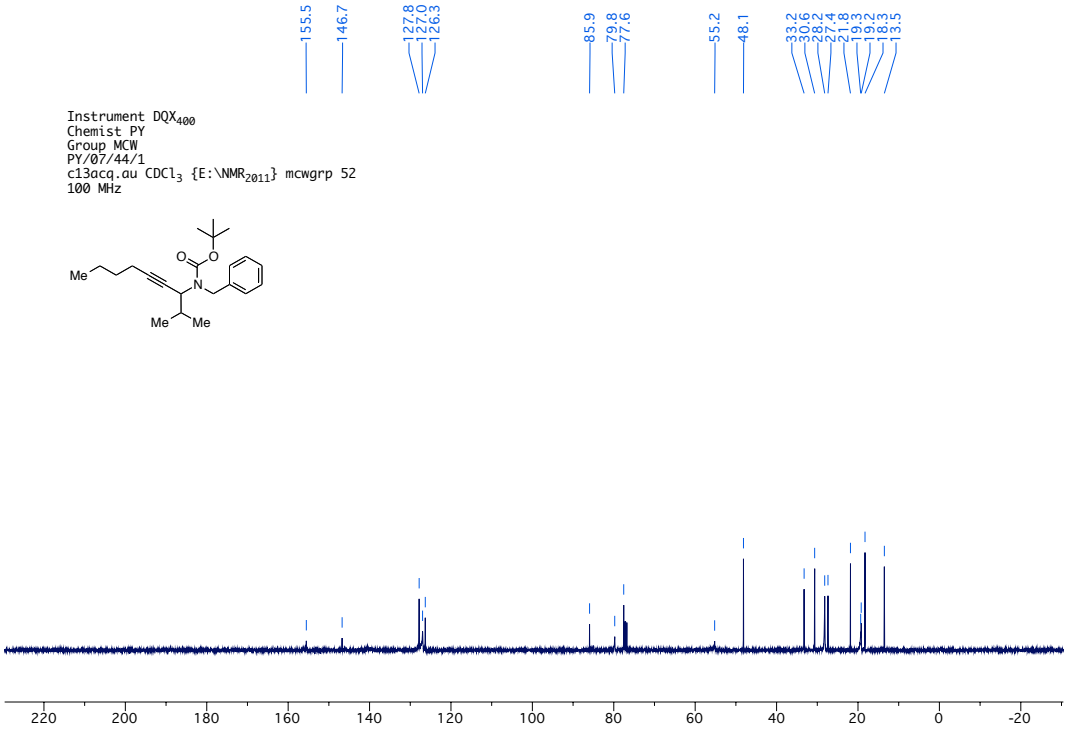
N-Benzyl-2-methylnon-4-yn-3-amine, experimental page 171



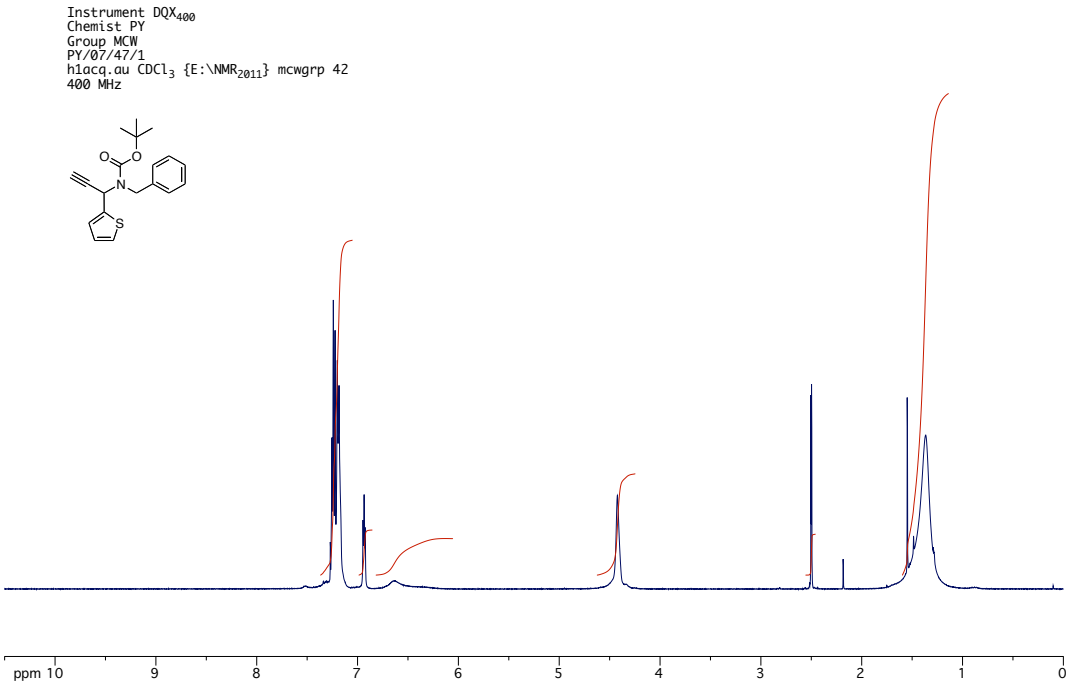


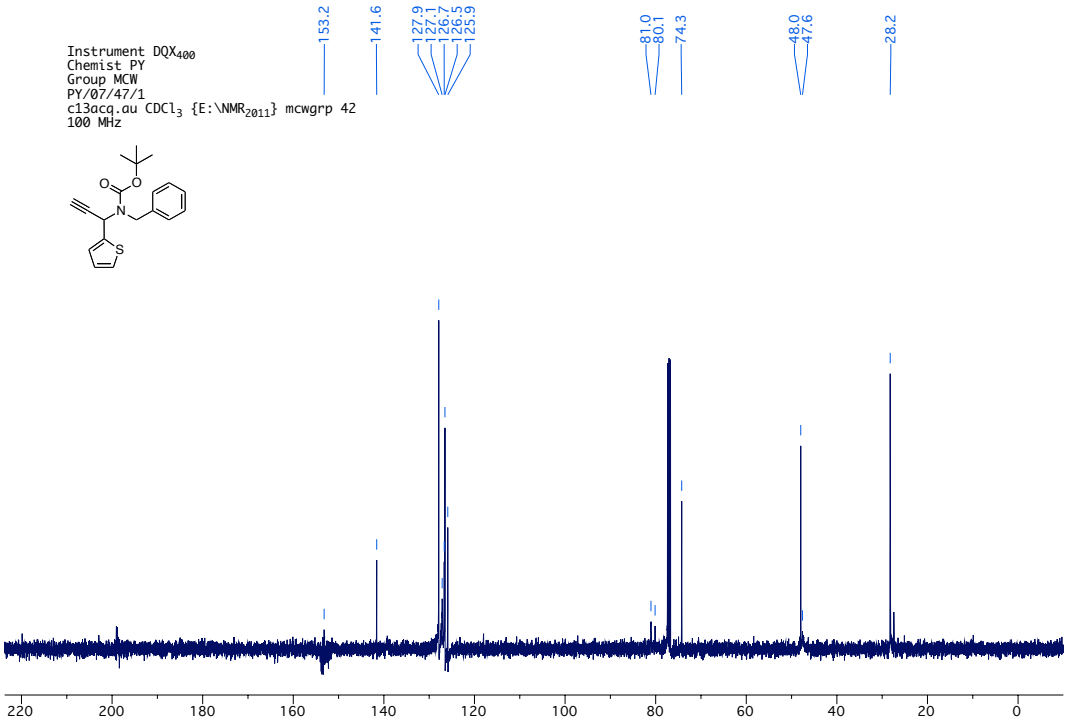
tert-Butyl benzyl(2-methylnon-4-yn-3-yl)carbamate, experimental page 172



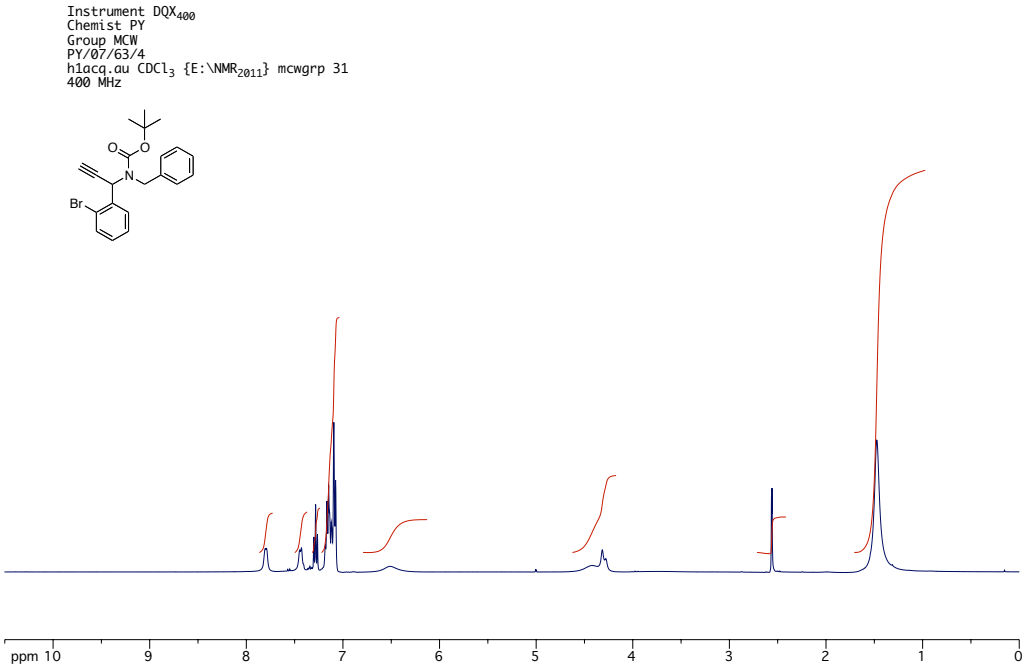


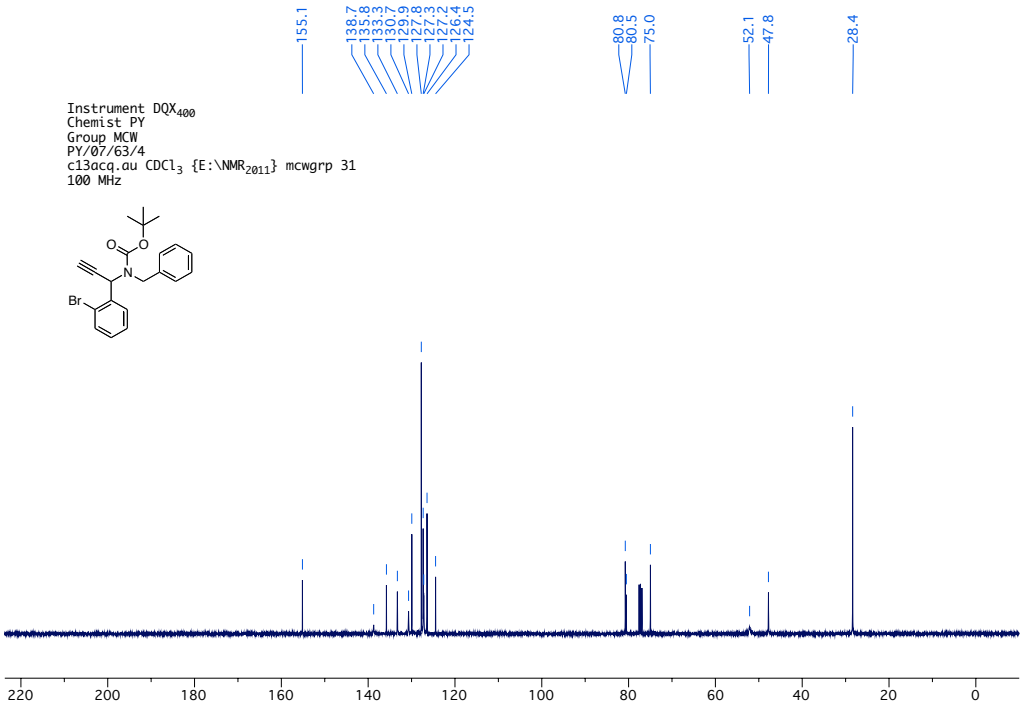
tert-Butyl benzyl(1-(thiophen-2-yl)prop-2-yn-1-yl)carbamate, experimental page 173



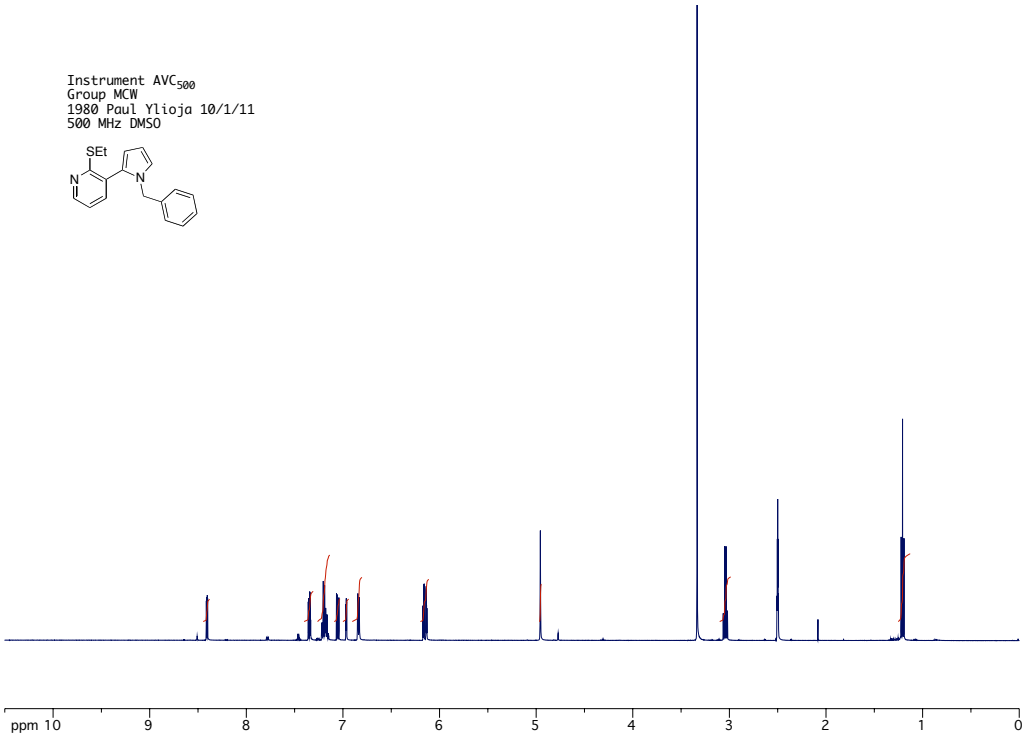


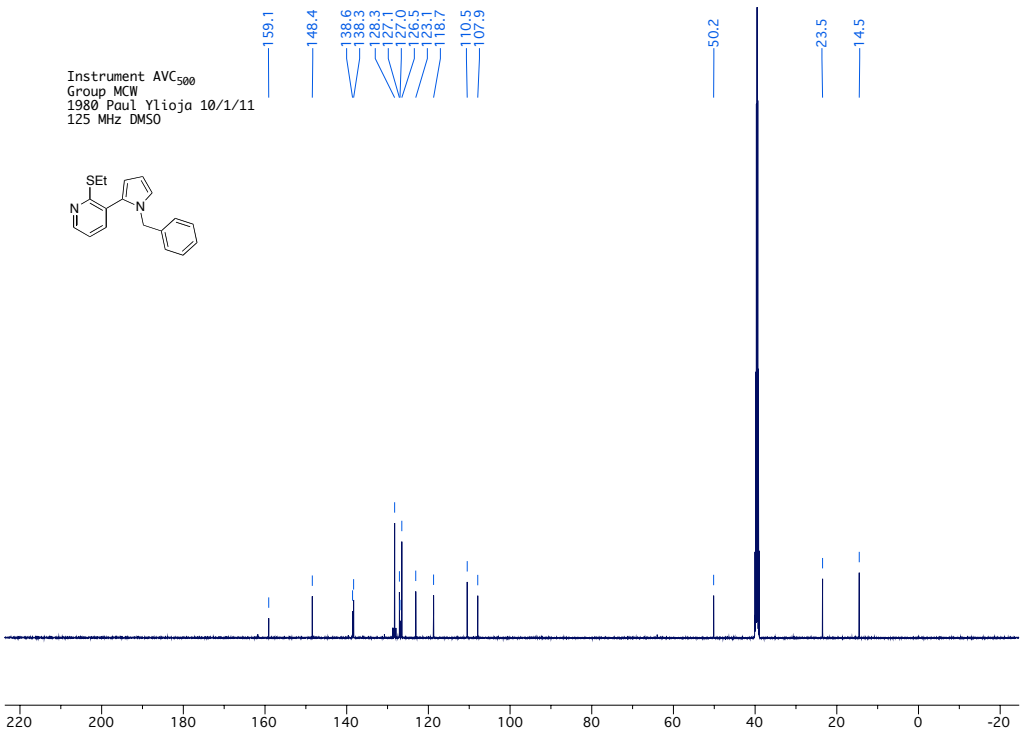
3-(1-benzyl-1*H*-pyrrol-2-yl)-2-(ethylthio)pyridine, experimental page 174



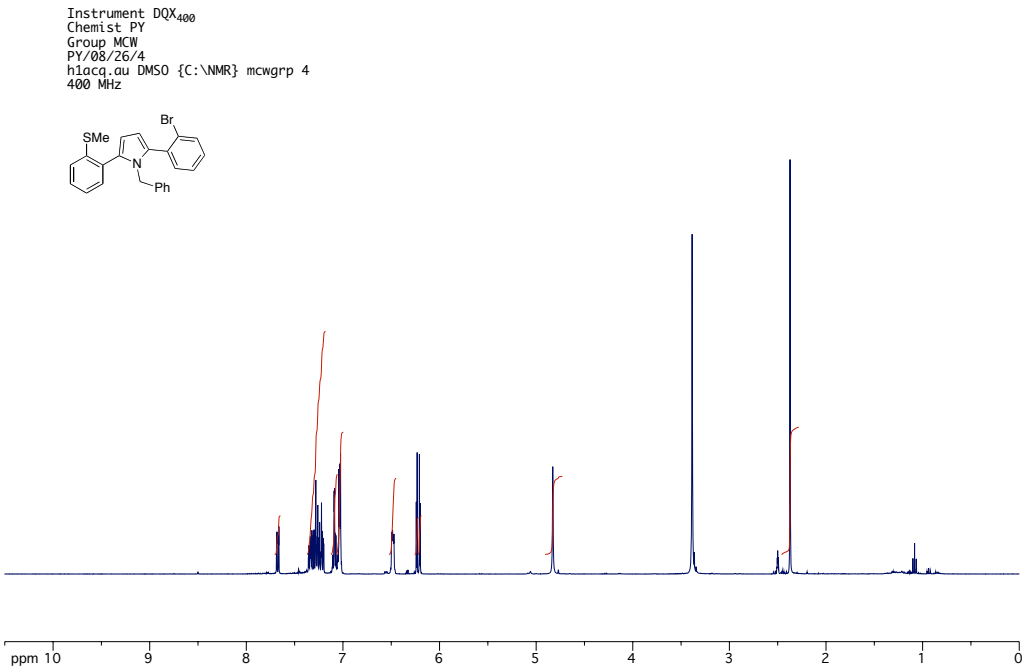


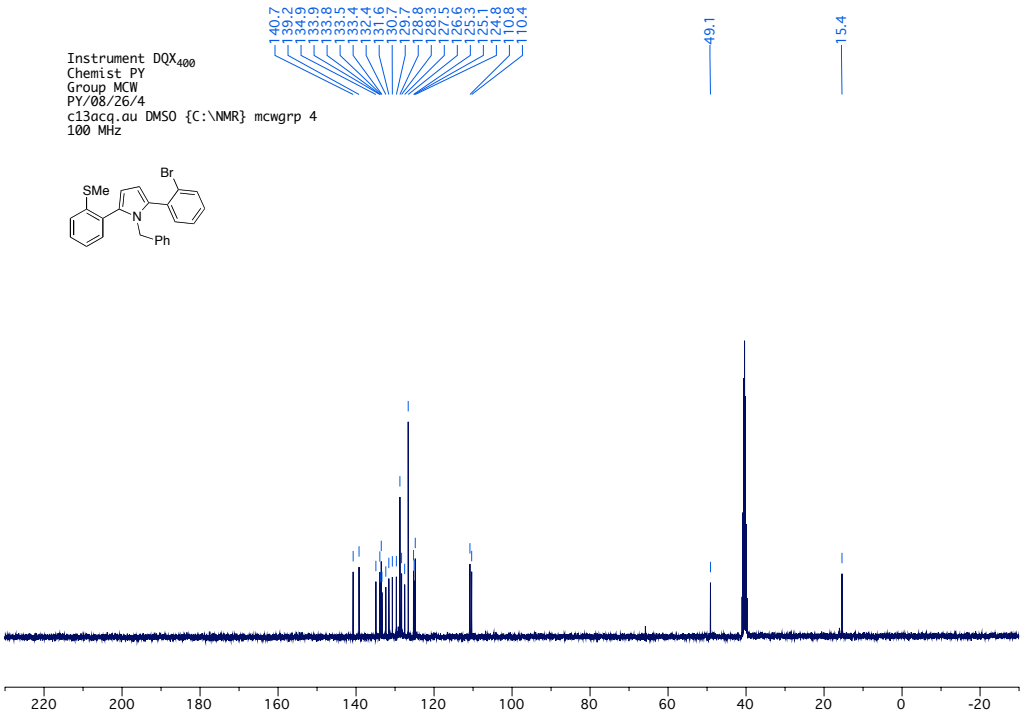
3-(1-benzyl-1*H*-pyrrol-2-yl)-2-(ethylthio)pyridine, experimental page 214



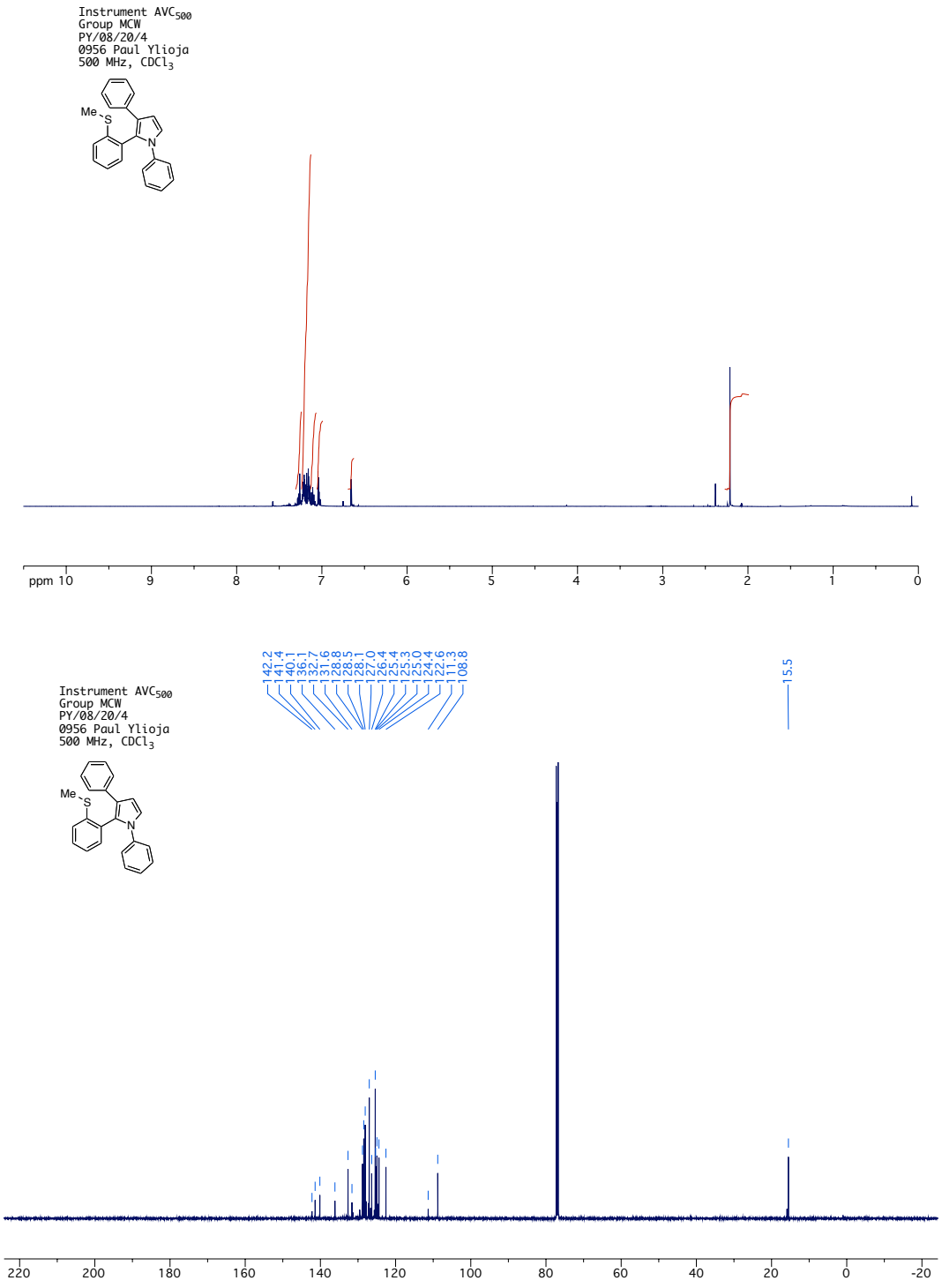


1-benzyl-2-(2-bromophenyl)-5-(2-(methylthio)phenyl)-1*H*-pyrrole, experimental page 214

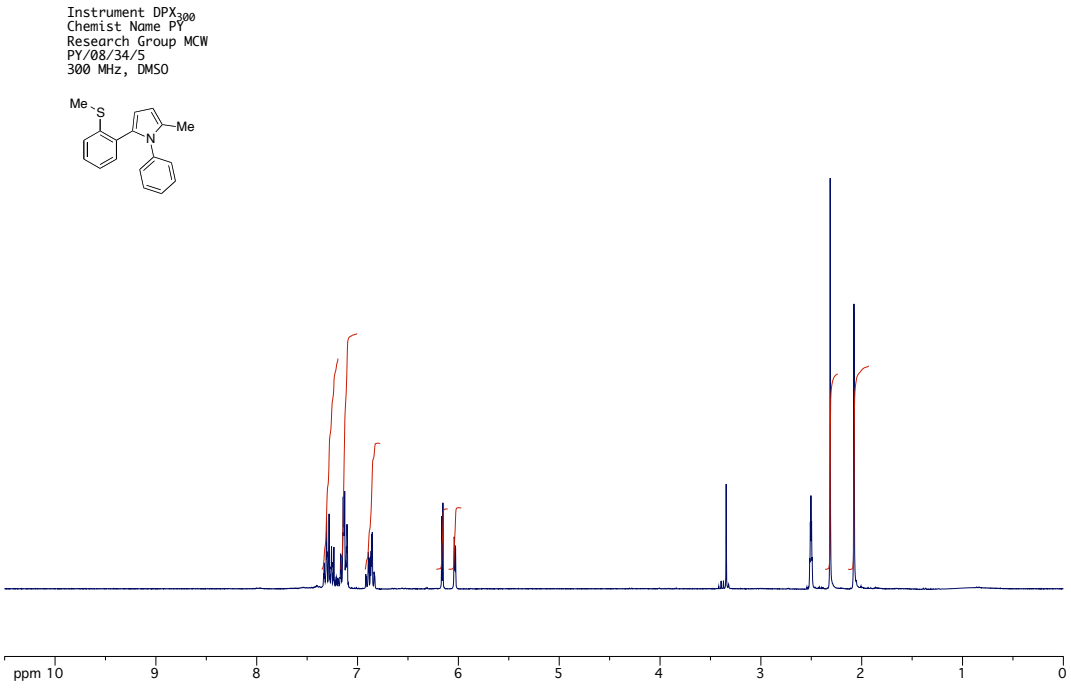


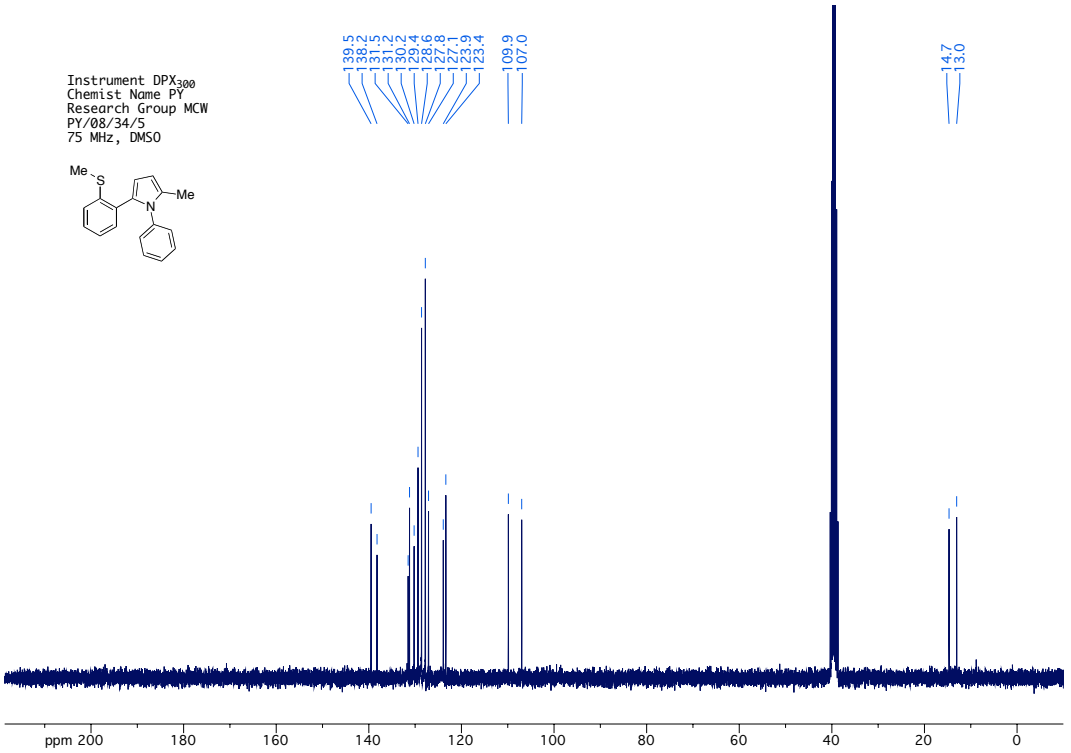


2-(2-(methylthio)phenyl)-1,3-diphenyl-1*H*-pyrrole, experimental page 212

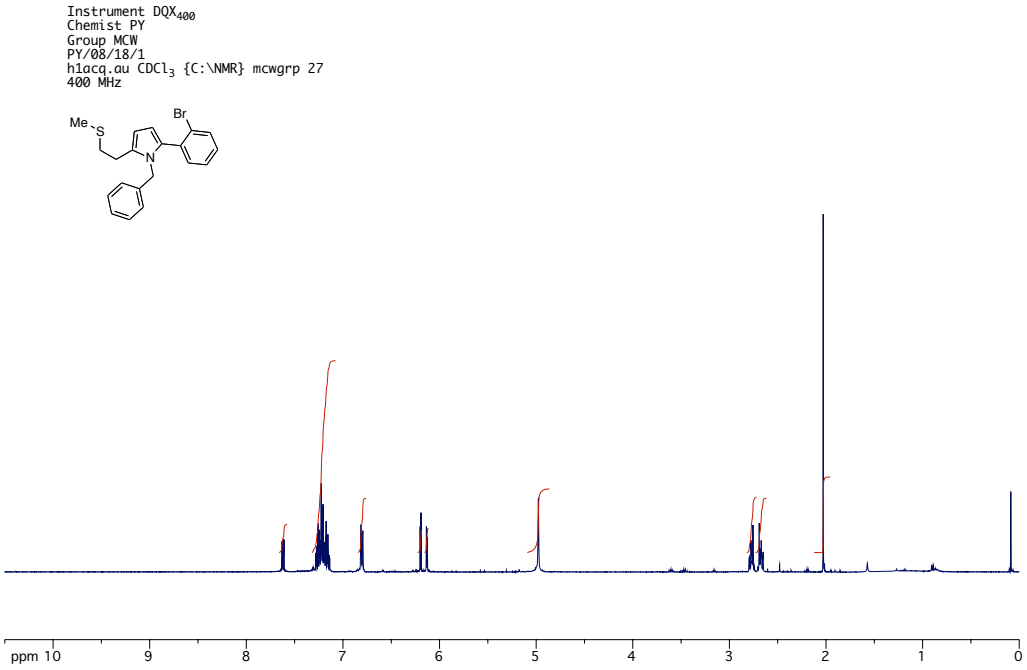


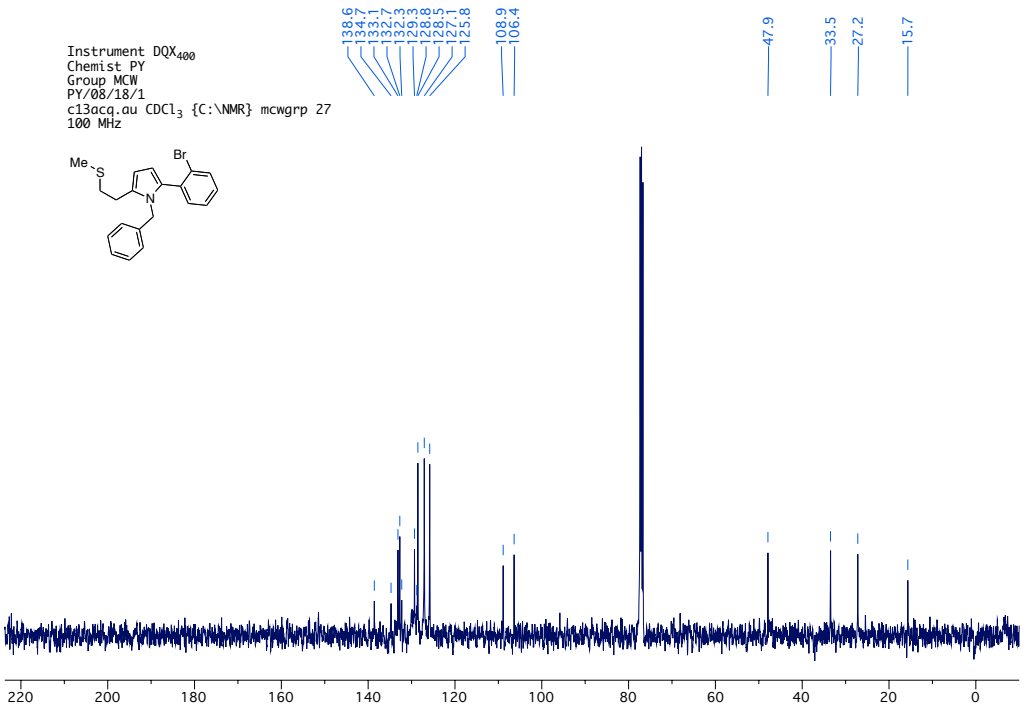
2-Methyl-5-(2-(methylthio)phenyl)-1-phenyl-1*H*-pyrrole, experimental page 213



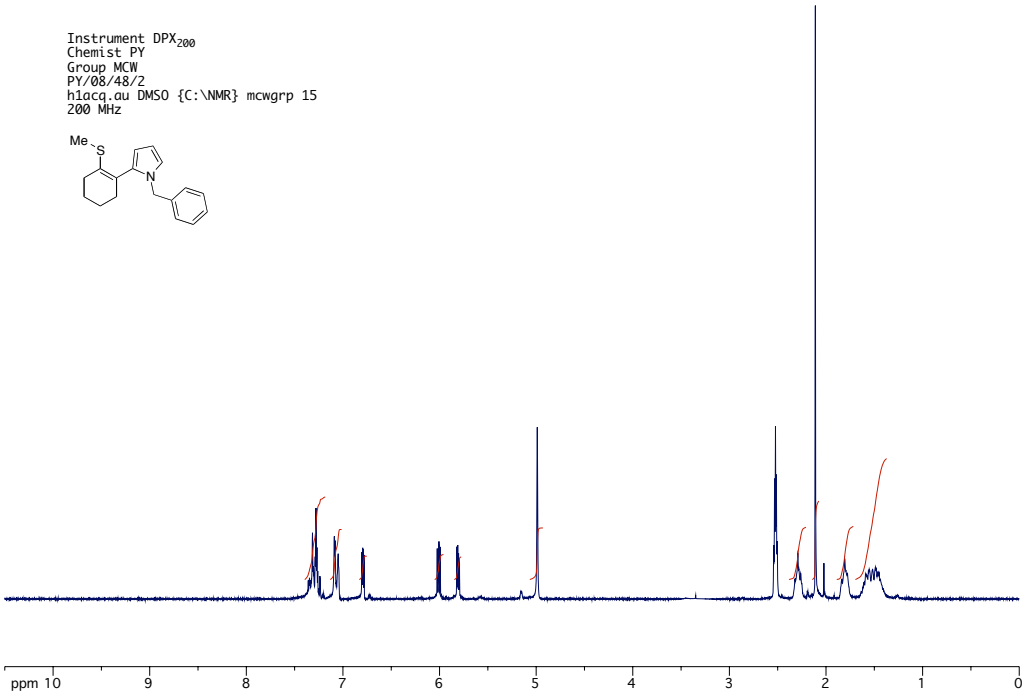


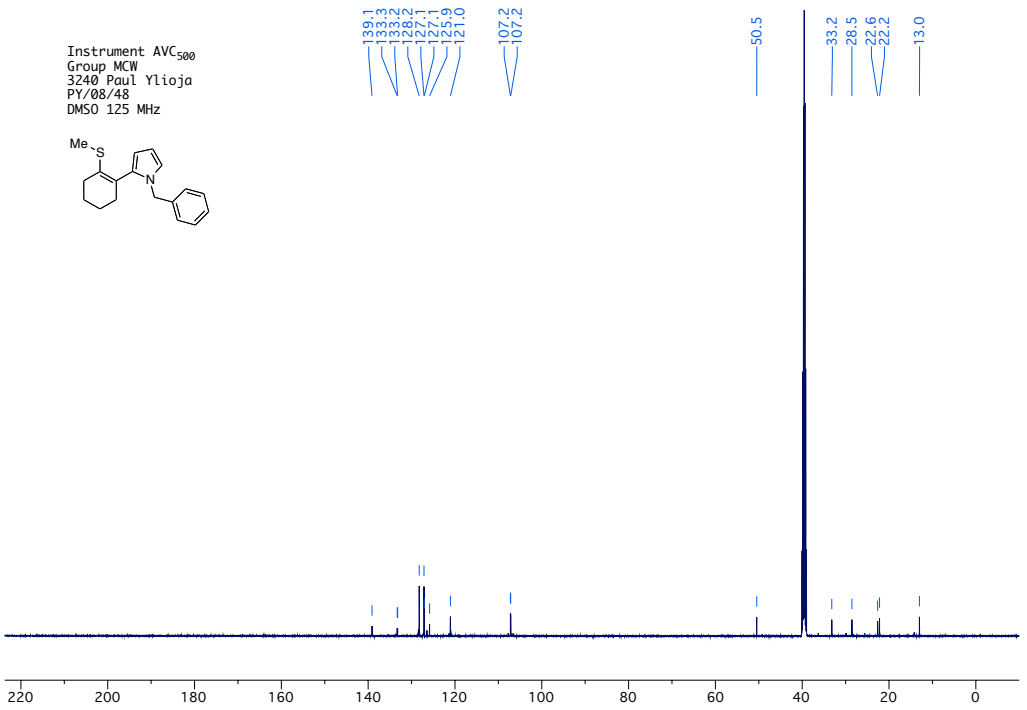
1-benzyl-2-(2-bromophenyl)-5-(2-(methylthio)ethyl)-1*H*-pyrrole, experimental page 212



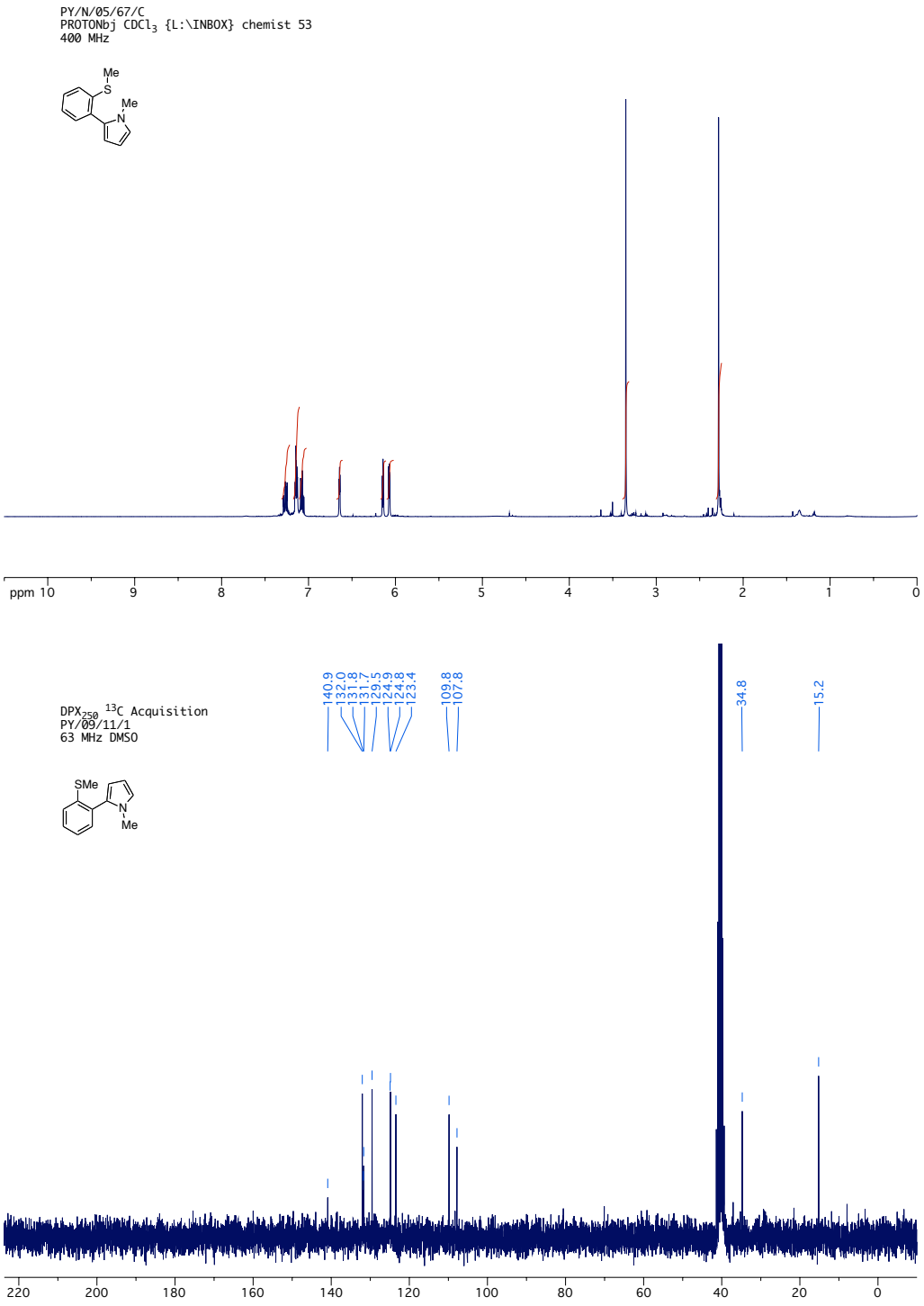


1-benzyl-2-(2-(methylthio)cyclohex-1-en-1-yl)-1H-pyrrole, experimental page 216

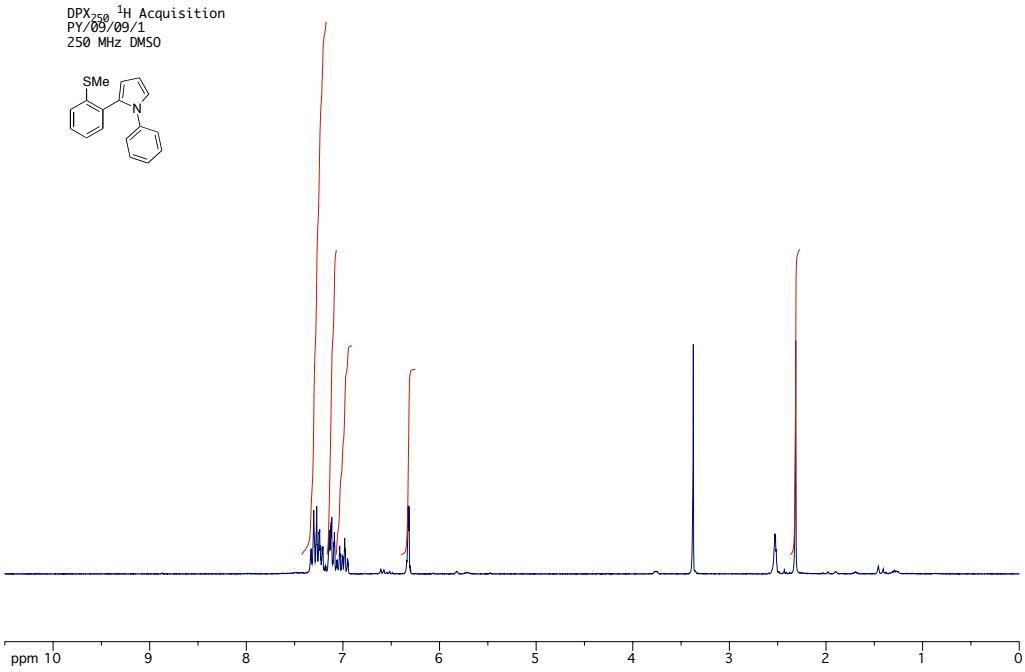


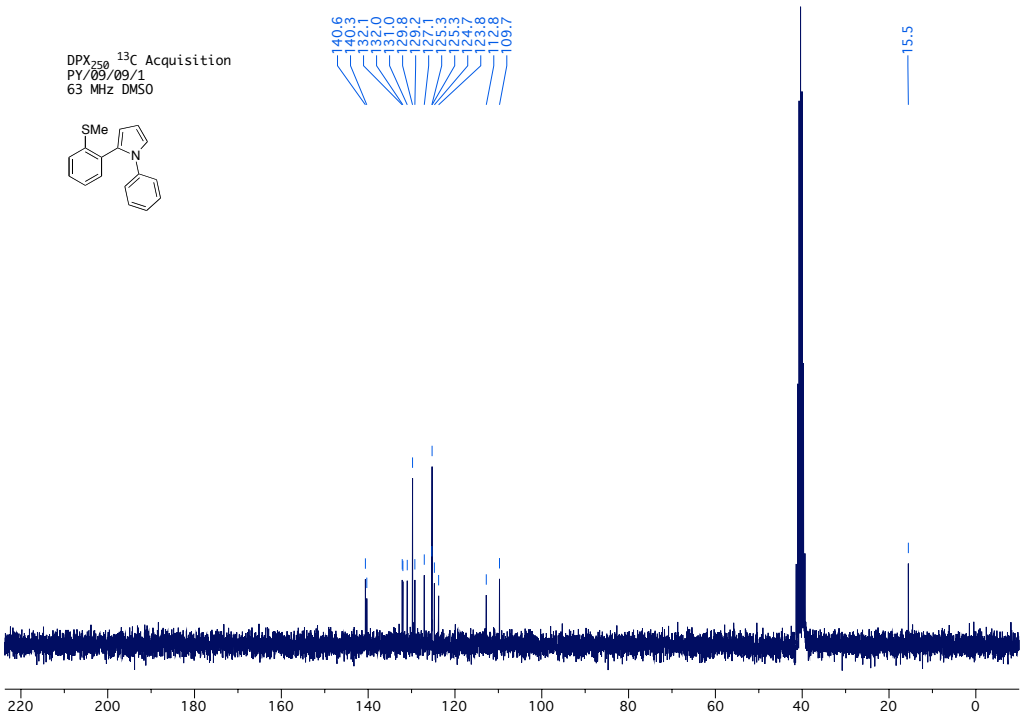


1-methyl-2-(2-(methylthio)phenyl)-1H-pyrrole, experimental page 209

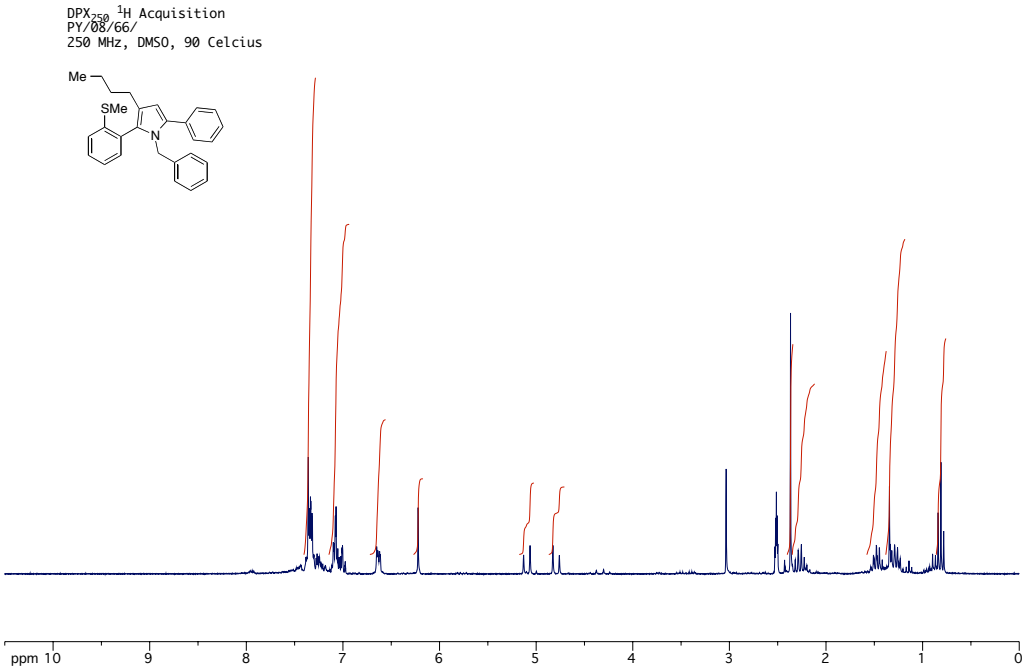


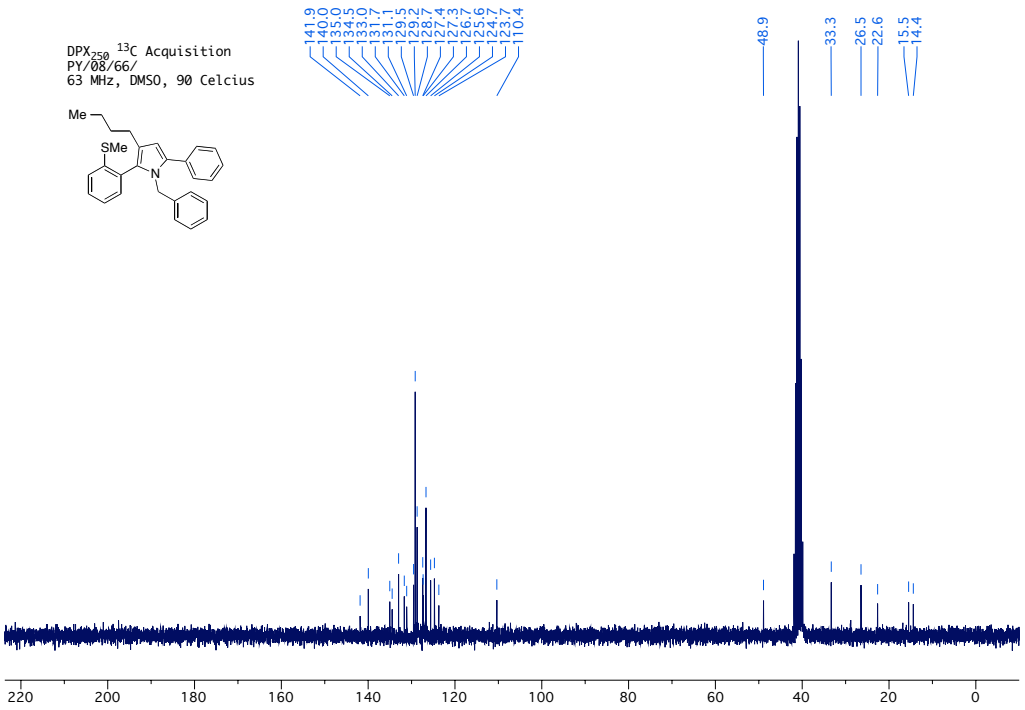
1-Phenyl-2-(2-(methylthio)phenyl)-1H-pyrrole, experimental page 210



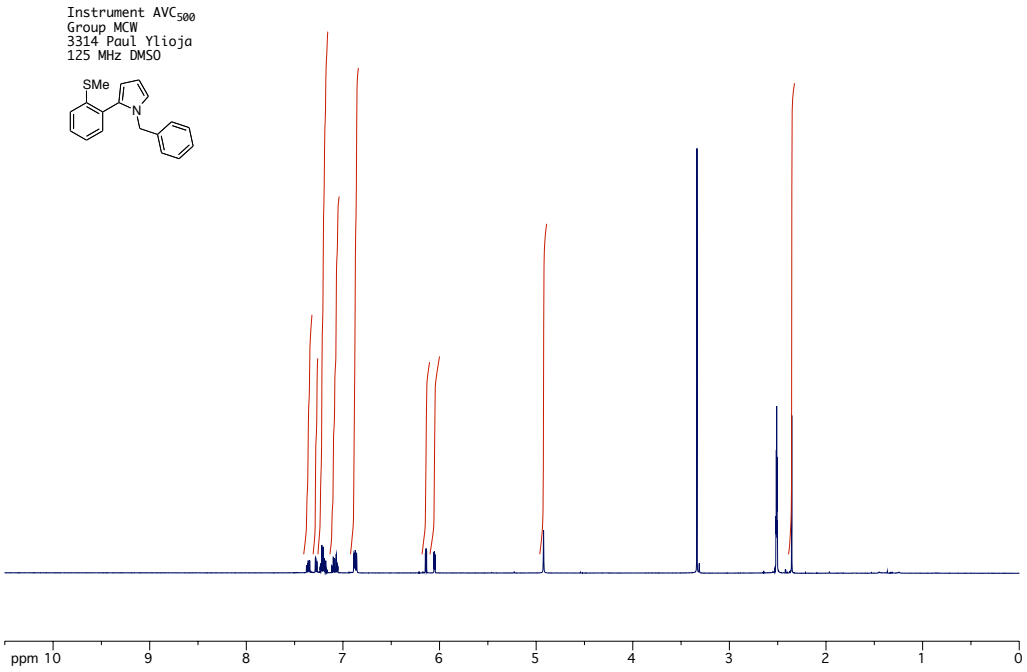


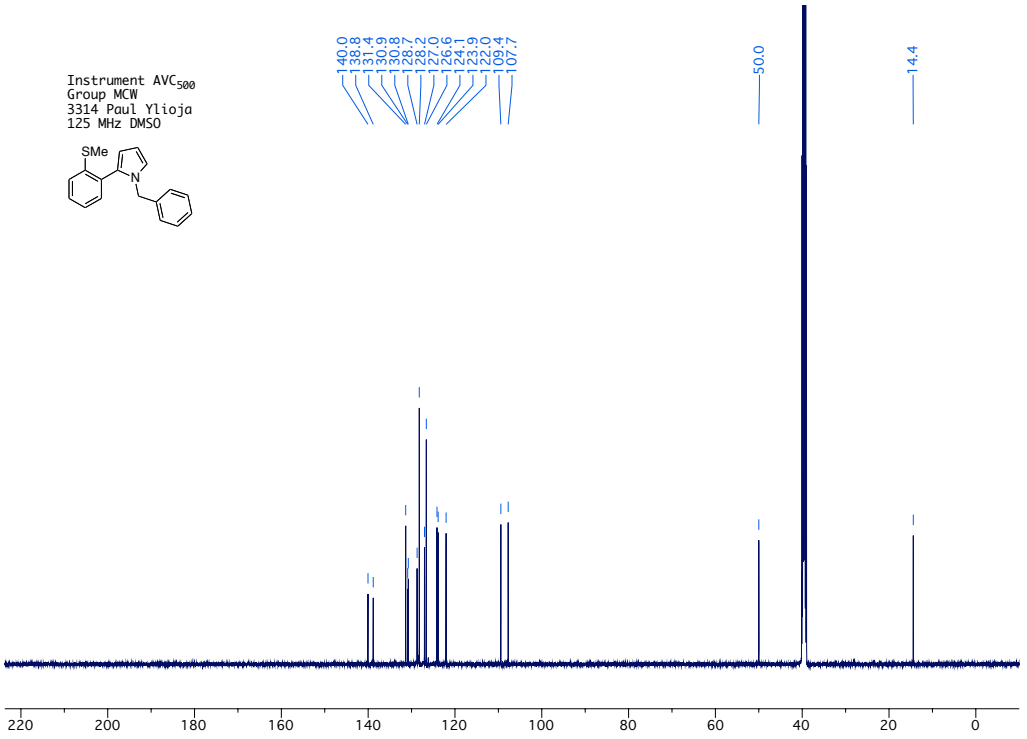
1-benzyl-3-butyl-2-(2-(methylthio)phenyl)-5-phenyl-1H-pyrrole, experimental page 210



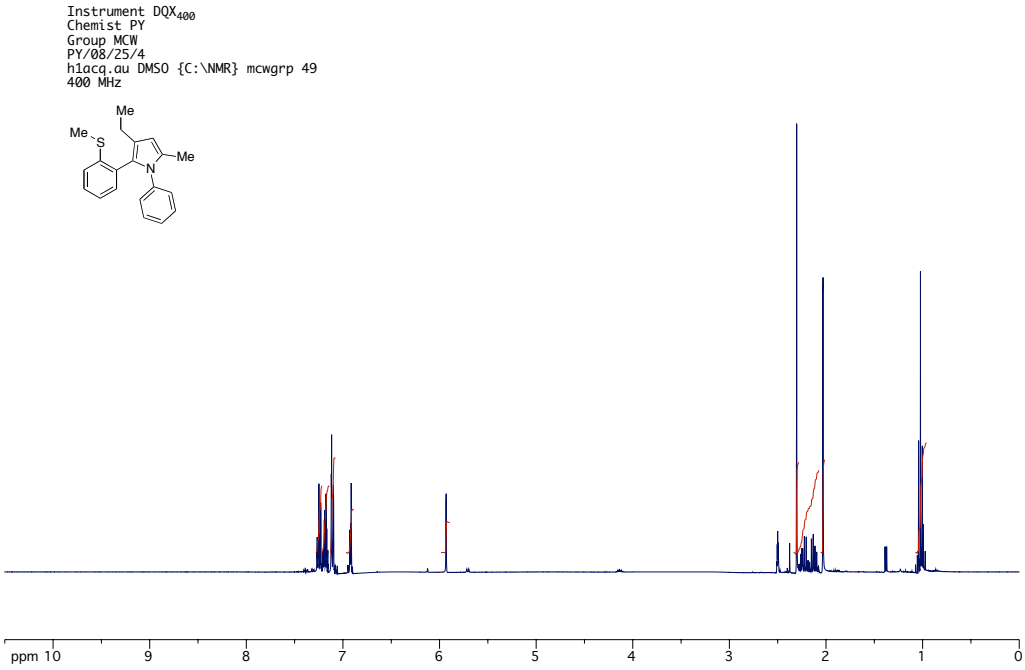


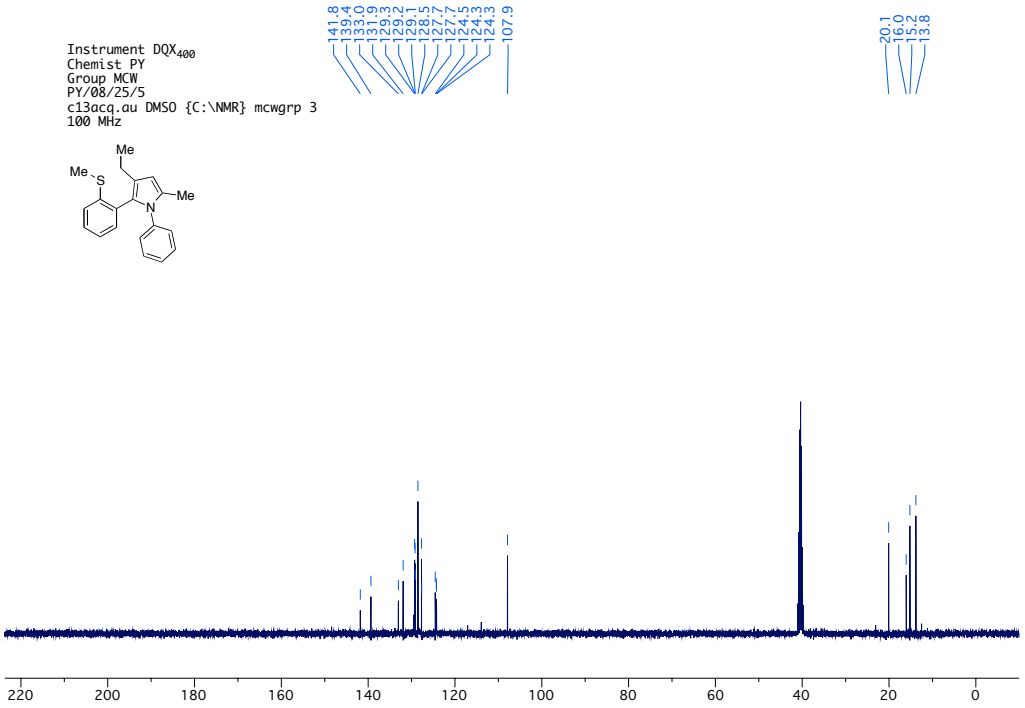
1-benzyl-2-(2-(methylthio)phenyl)-1H-pyrrole, experimental page 211



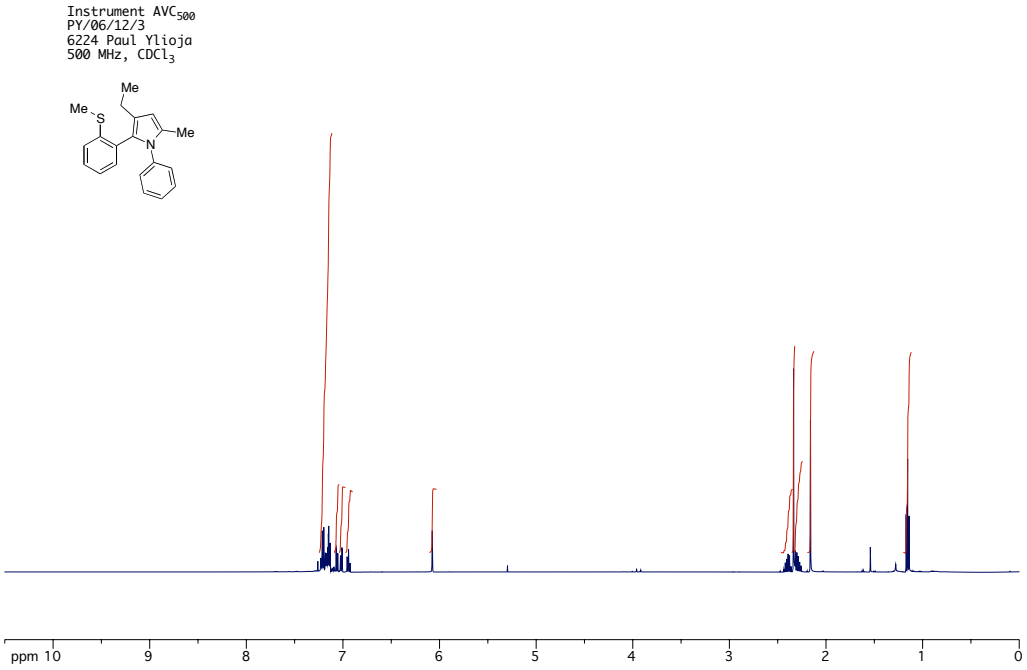


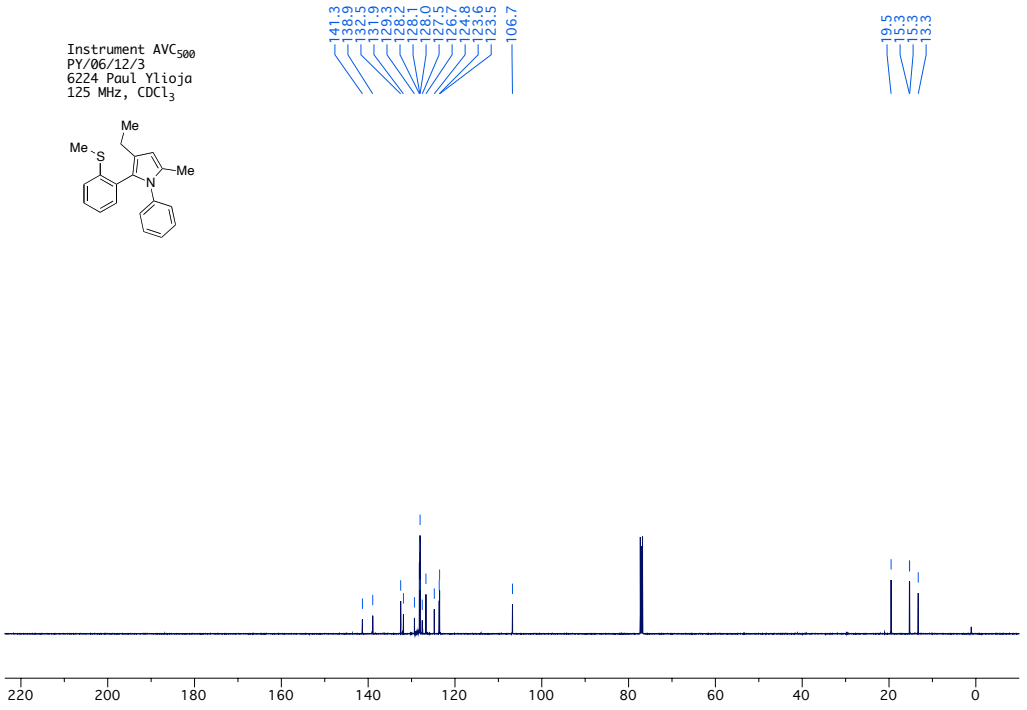
3-Ethyl-5-methyl-2-(2-(methylthio)phenyl)-1-phenyl-1H-pyrrole, experimental page 208



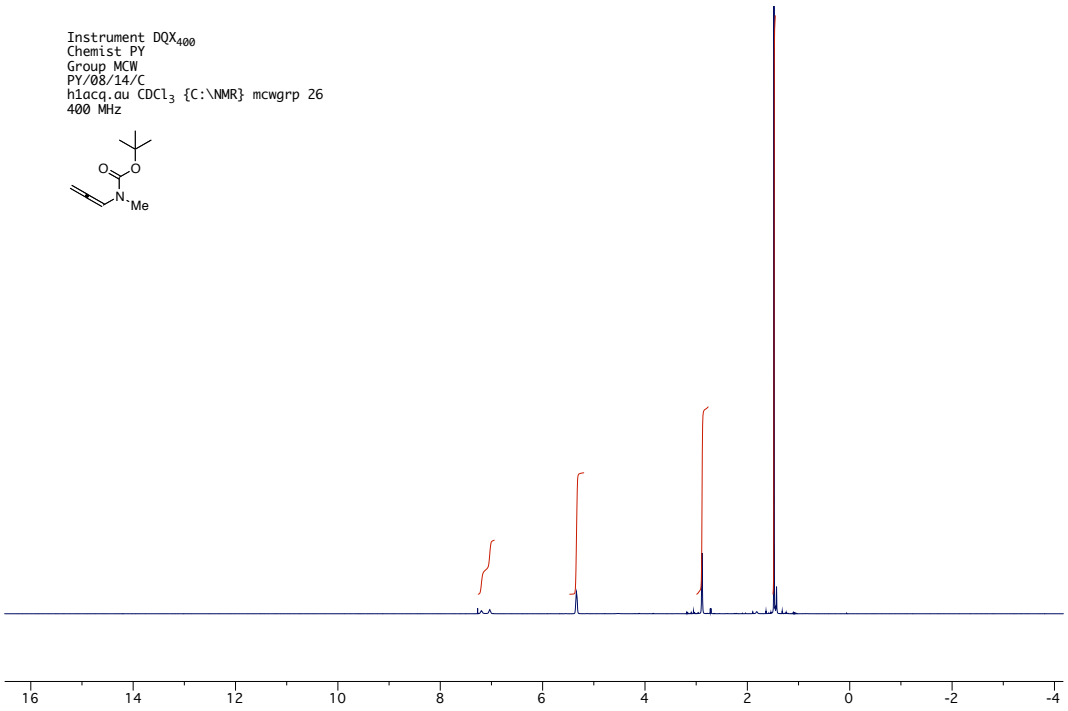


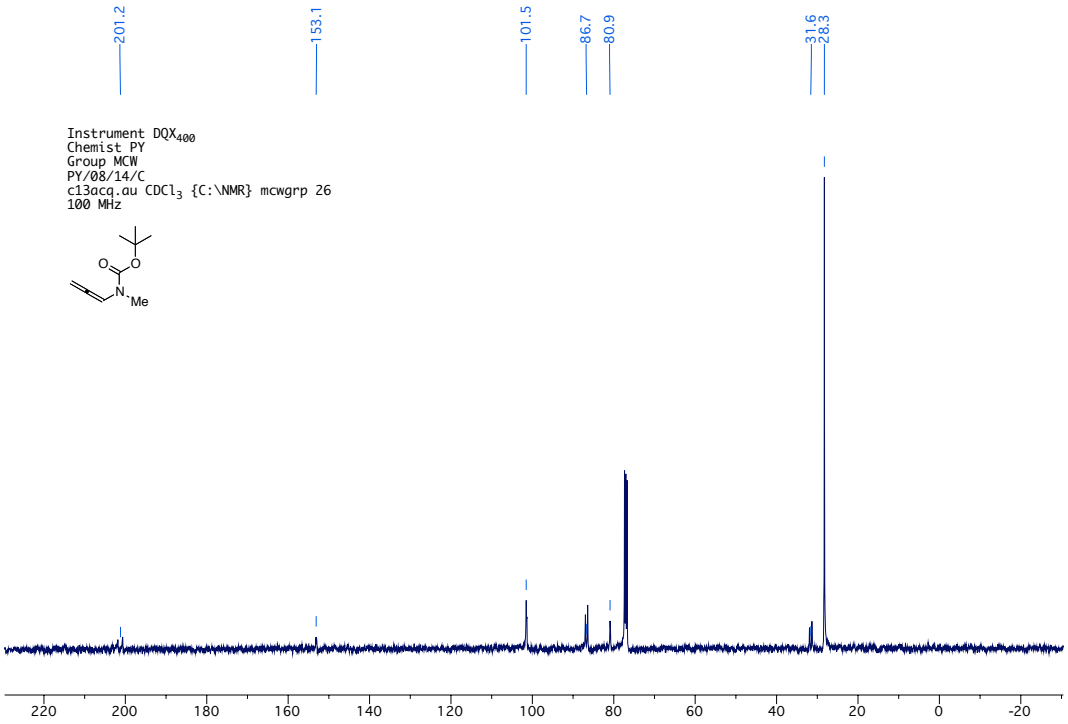
3-Ethyl-5-methyl-2-(2-(methylthio)phenyl)-1-phenyl-1H-pyrrole, experimental page 208



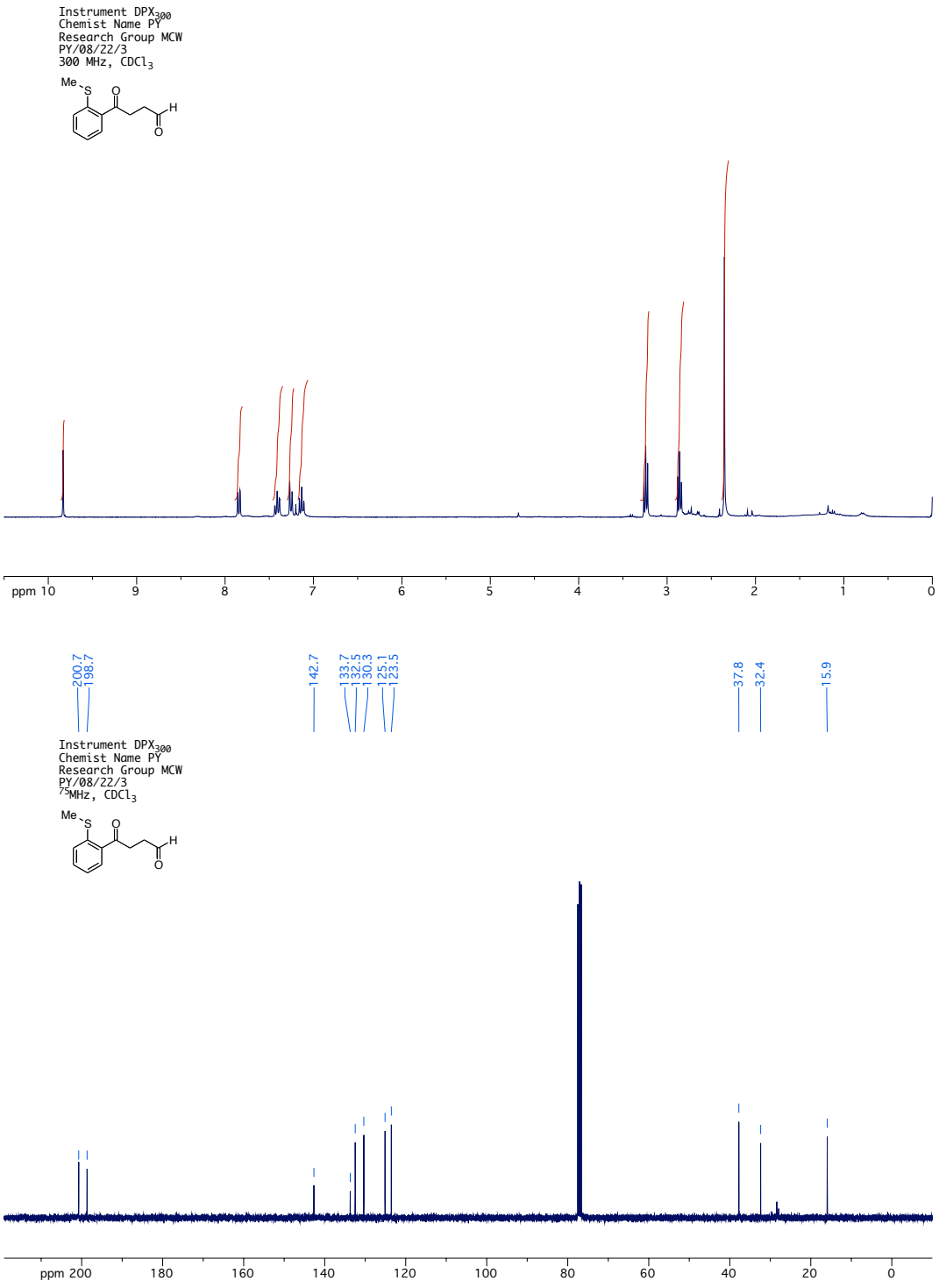


tert-Butyl methyl(propa-1,2-dien-1-yl)carbamate, experimental page 196

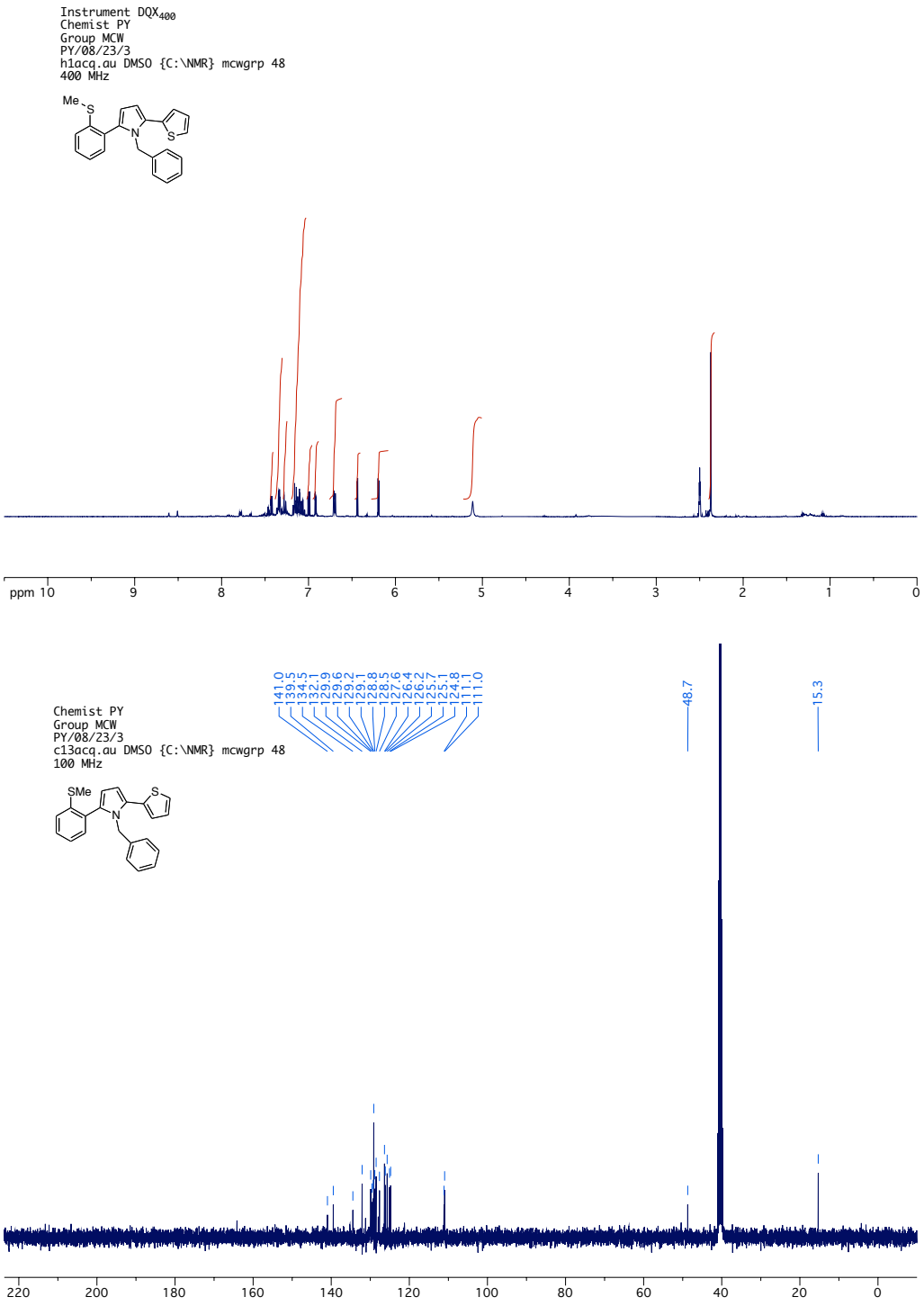




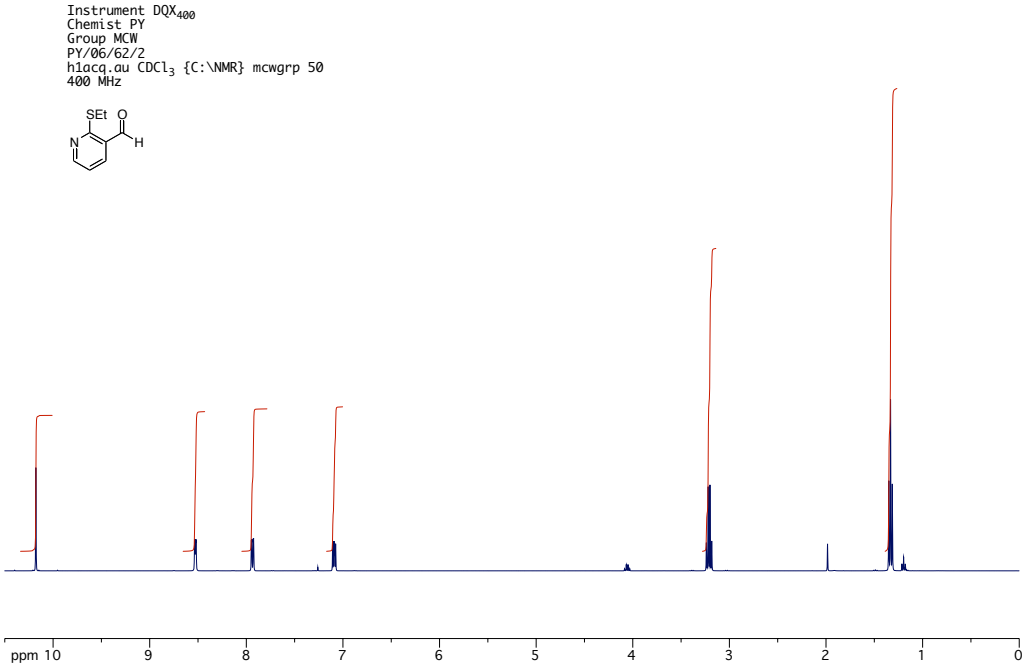
4-(2-(methylthio)phenyl)-4-oxobutanal, experimental page 196

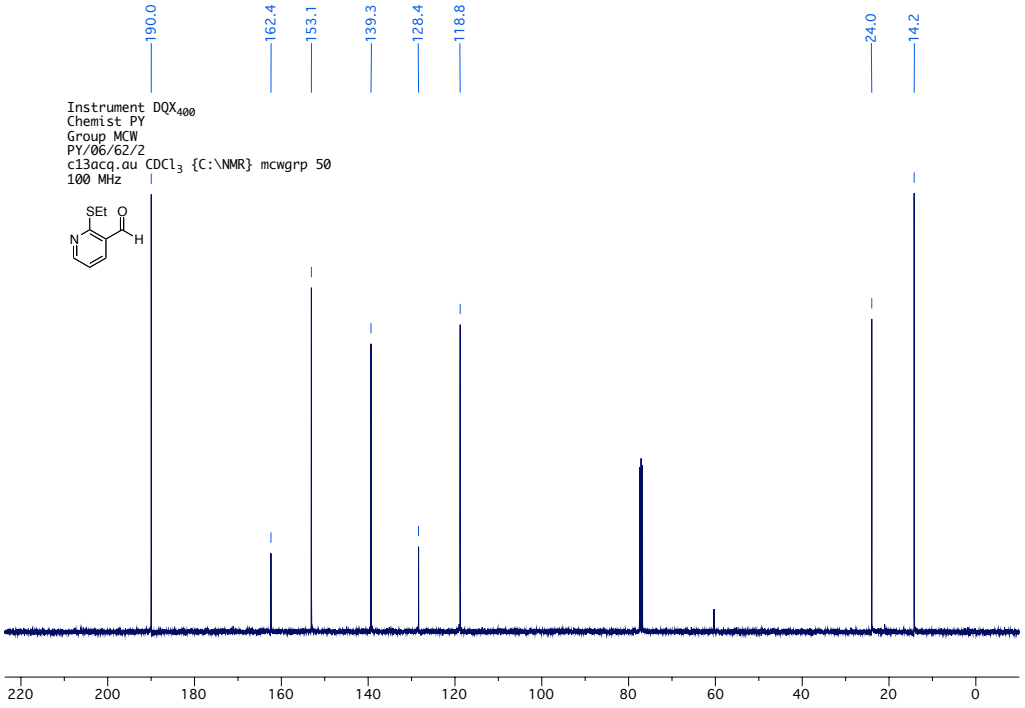


1-benzyl-2-(2-(methylthio)phenyl)-5-(thiophen-2-yl)-1H-pyrrole, experimental page 215

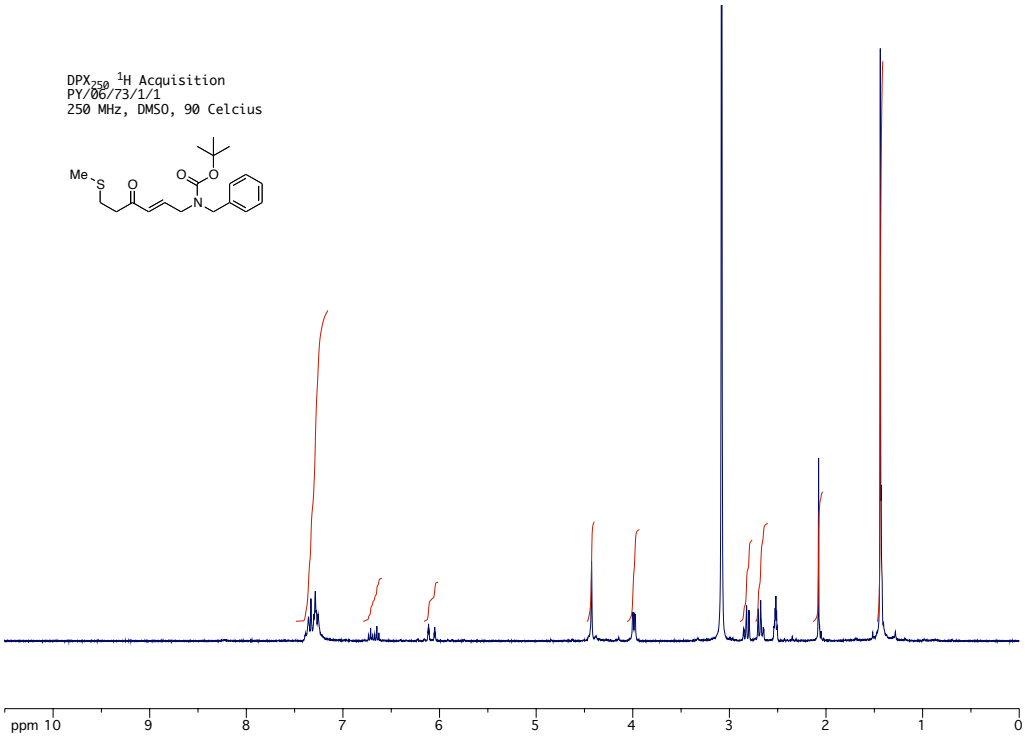


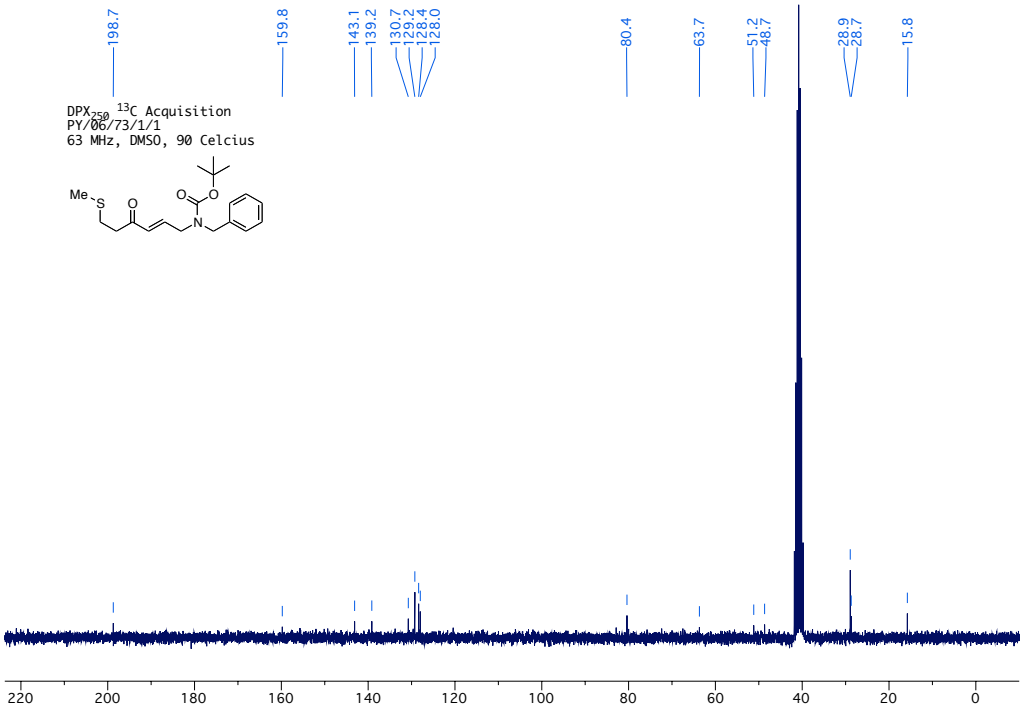
2-Ethylthionicotinaldehyde, experimental page 197



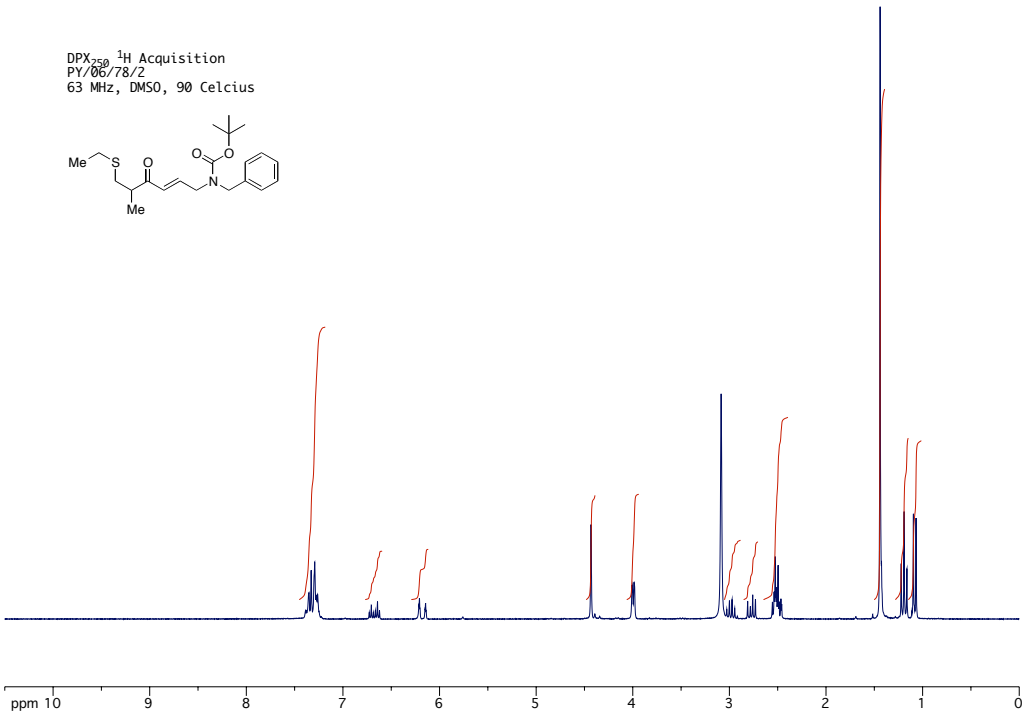


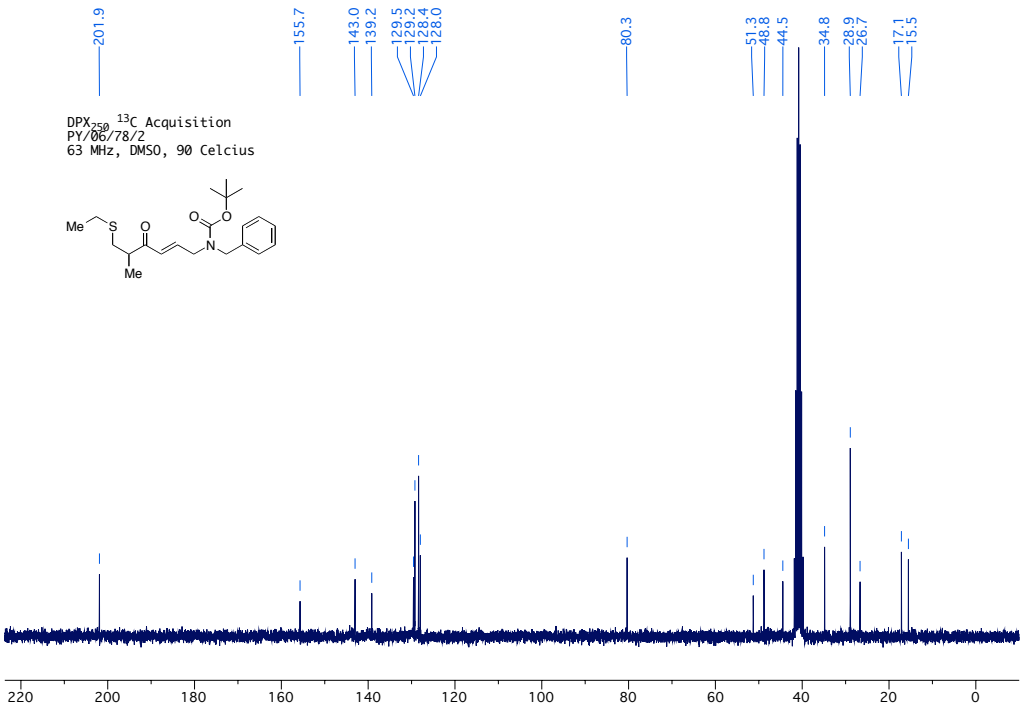
(*E*)-*tert*-Butyl benzyl(6-(methylthio)-4-oxohex-2-en-1-yl)carbamate, experimental page 201



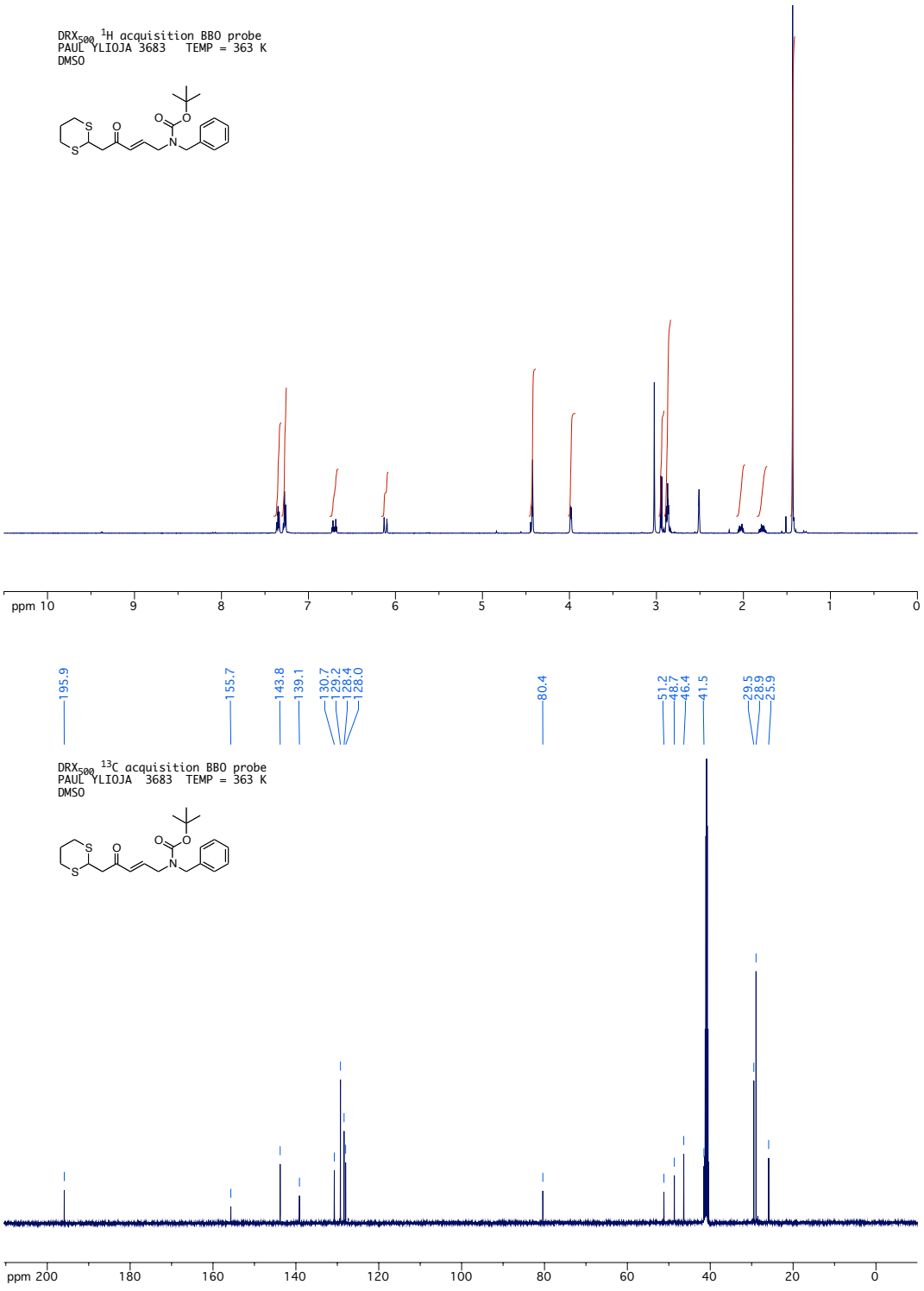


(*E*)-*tert*-Butyl benzyl(6-(ethylthio)-5-methyl-4-oxohex-2-en-1-yl)carbamate, experimental page 202

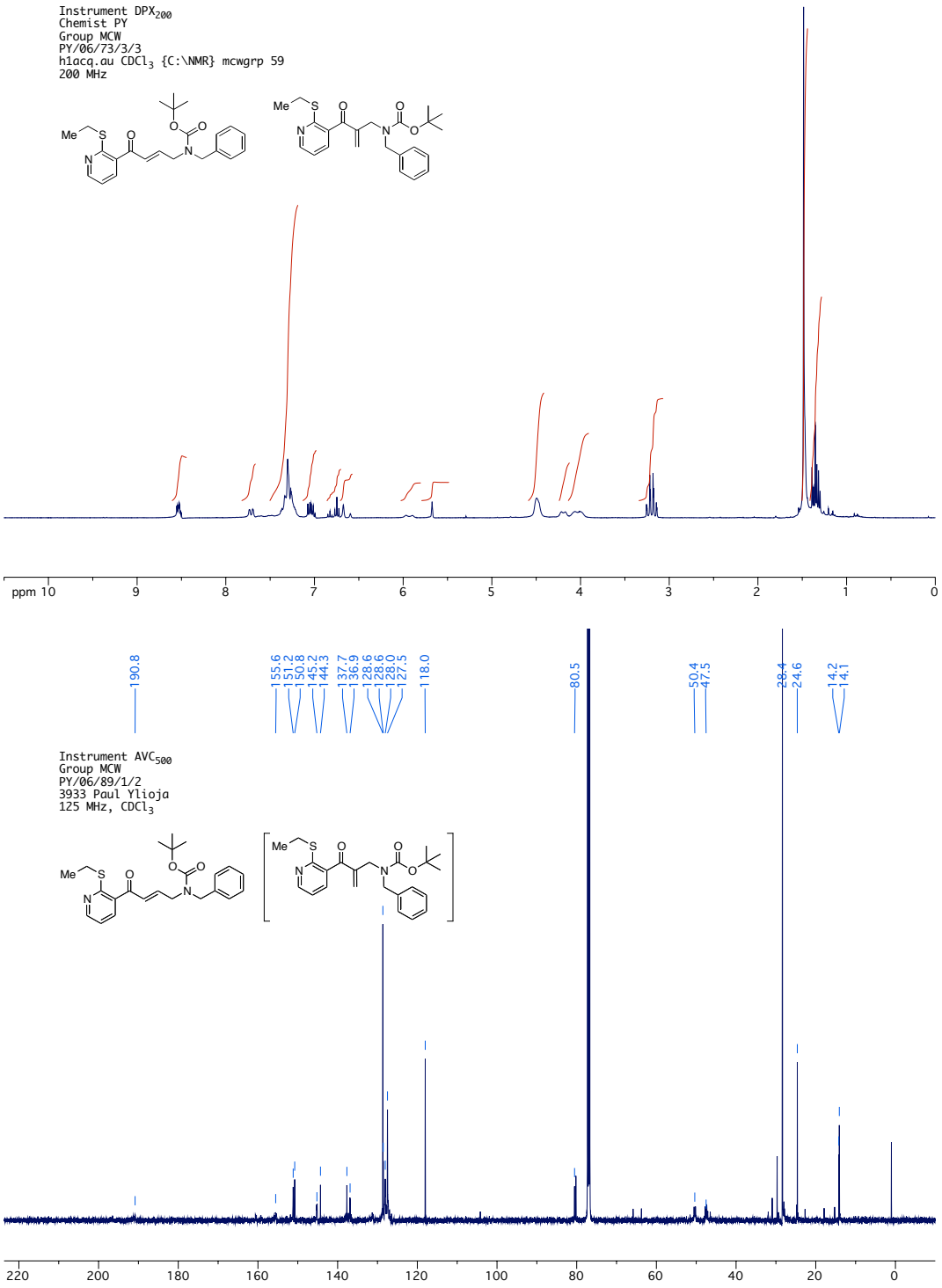




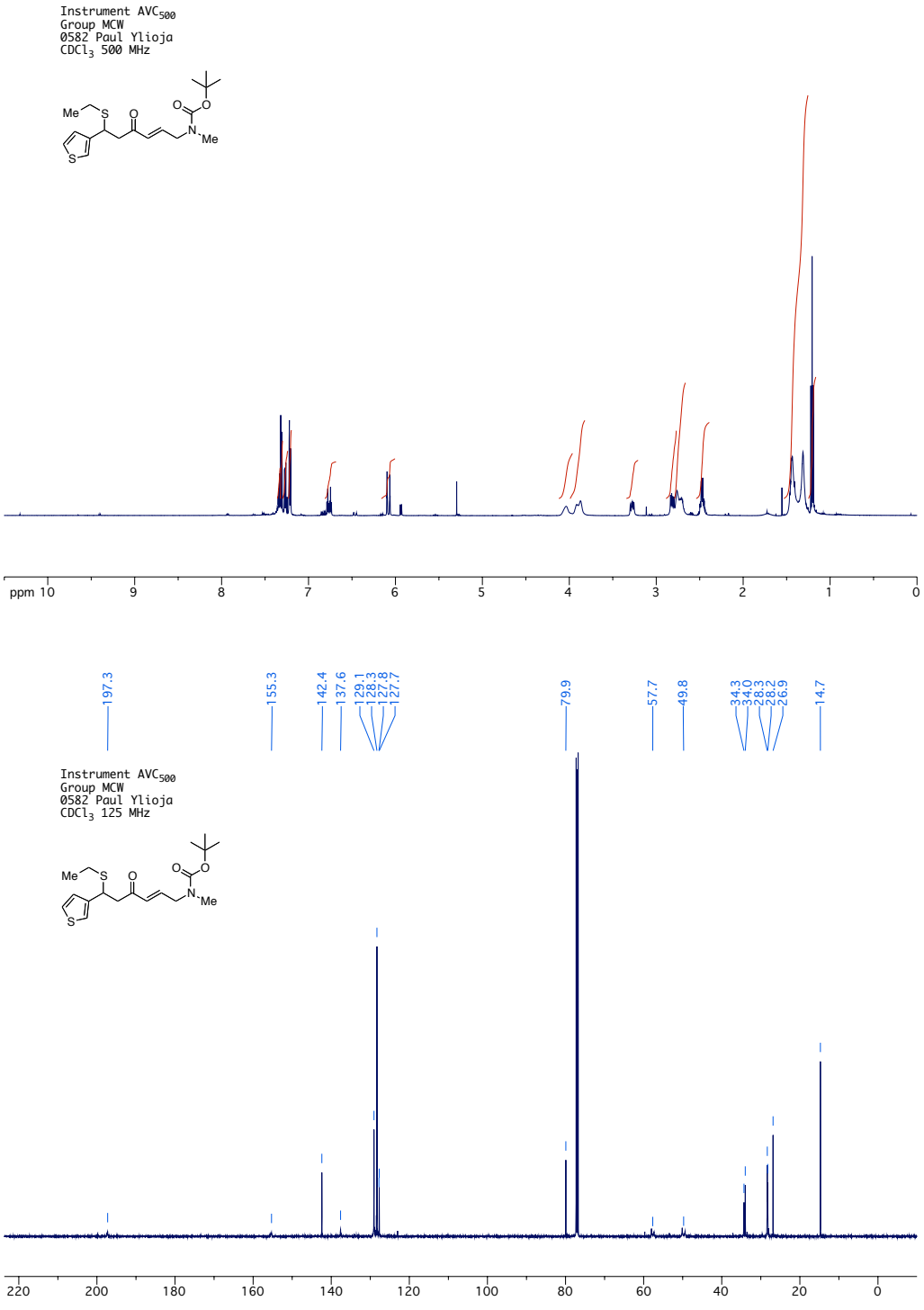
(*E*)-*tert*-butyl (5-(1,3-dithian-2-yl)-4-oxopent-2-en-1-yl)(benzyl)-carbamate, experimental page 205



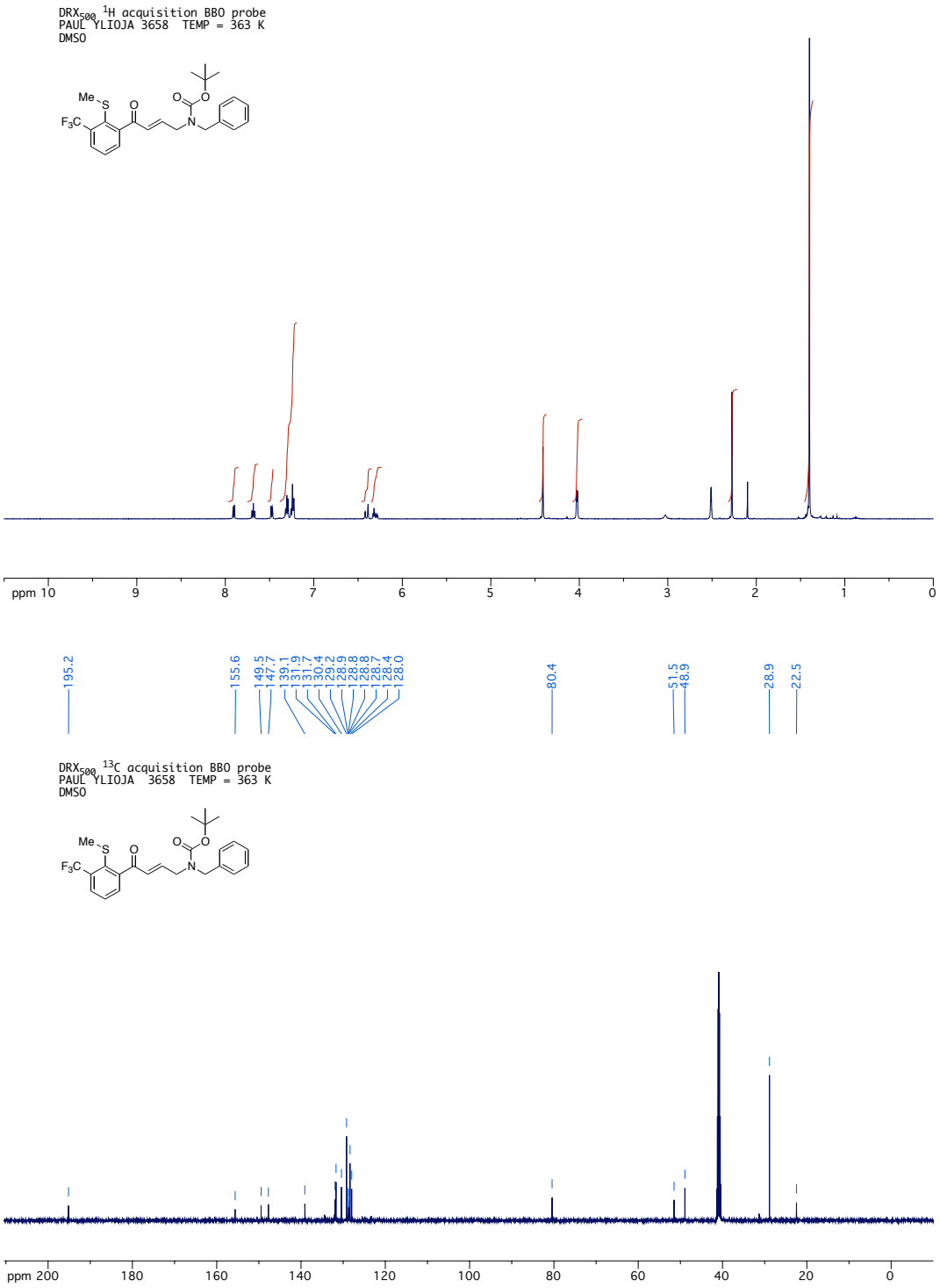
(*E*)-*tert*-Butyl benzyl(4-(2-(ethylthio)pyridin-3-yl)-4-oxobut-2-en-1-yl)carbamate, experimental page 206



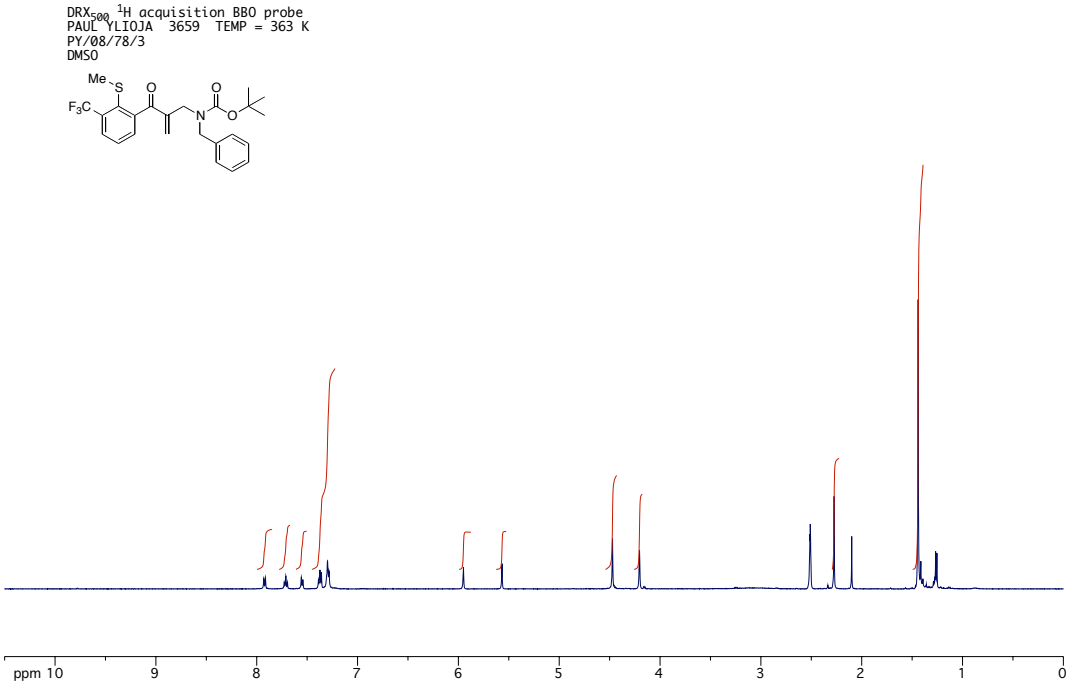
2-chloro-4-(dimethylamino)benzaldehyde, experimental page ??

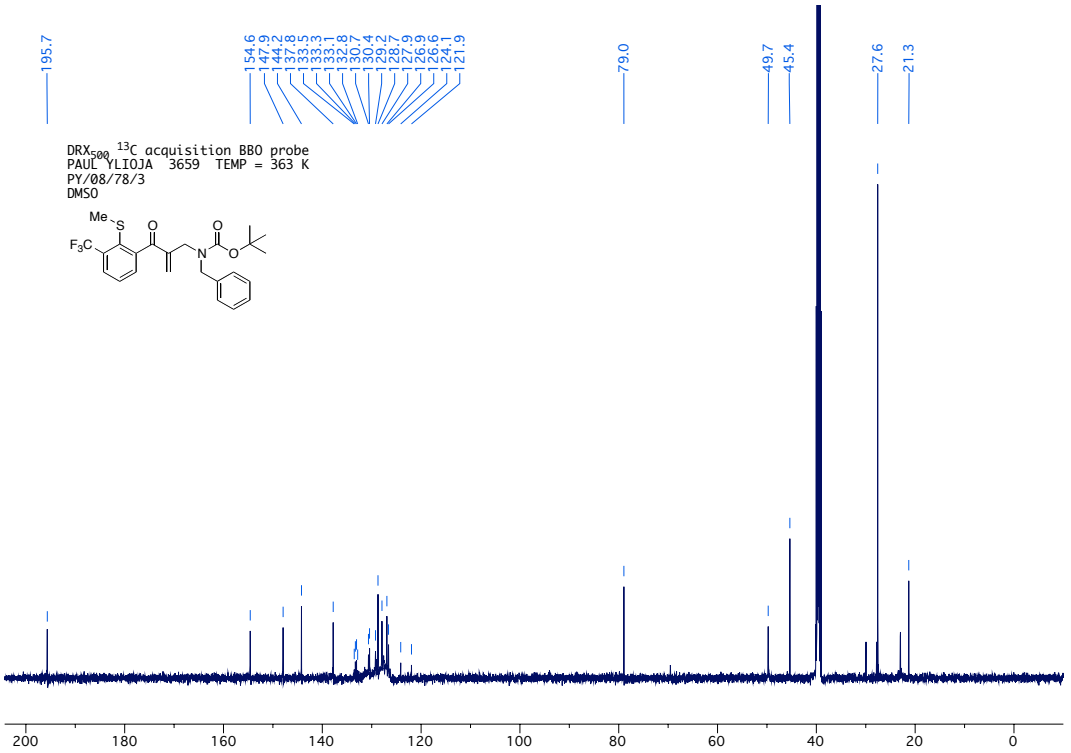


(*E*)-*tert*-Butyl benzyl(4-(2-(methylthio)-3-(trifluoromethyl)-phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 203

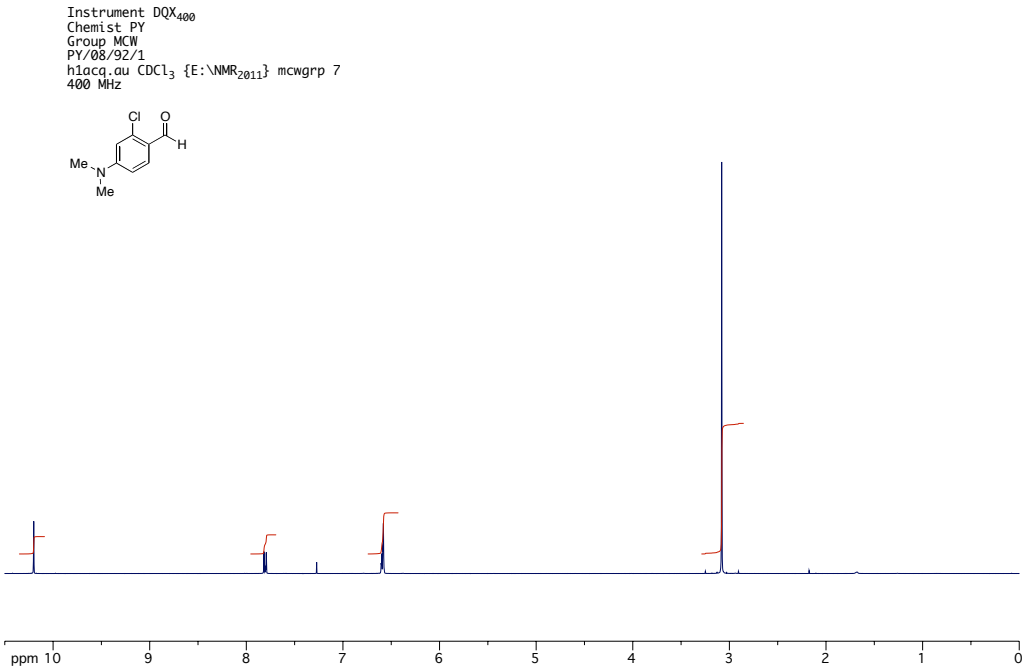


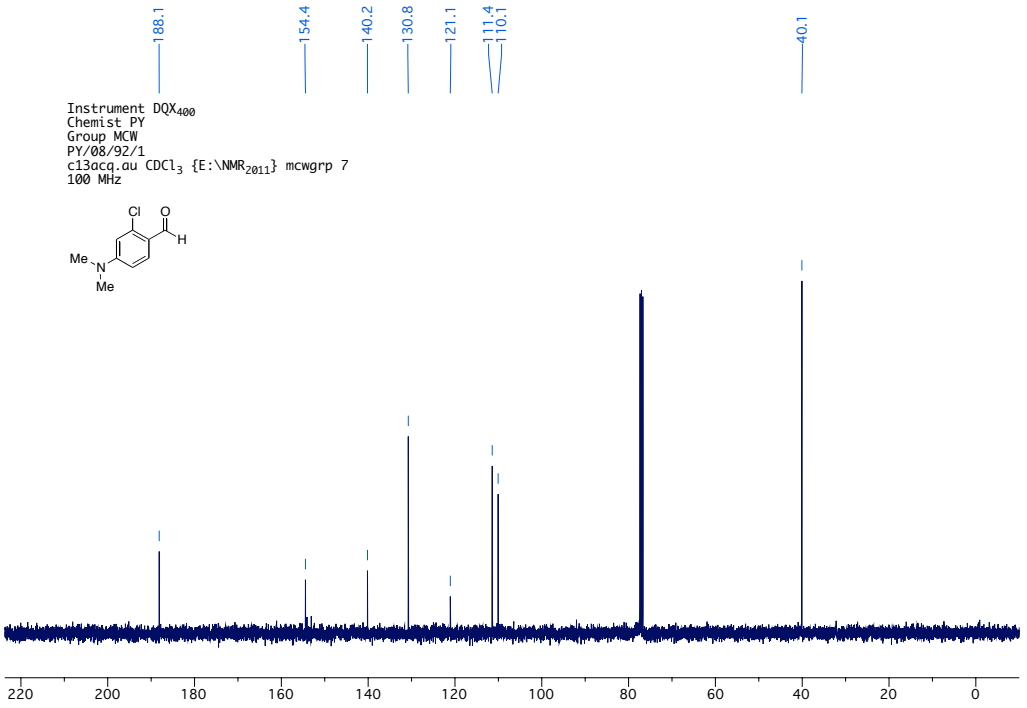
tert-Butyl benzyl(2-(2-(methylthio)-3-(trifluoromethyl)benzoyl)allyl)carbamate, experimental page 203





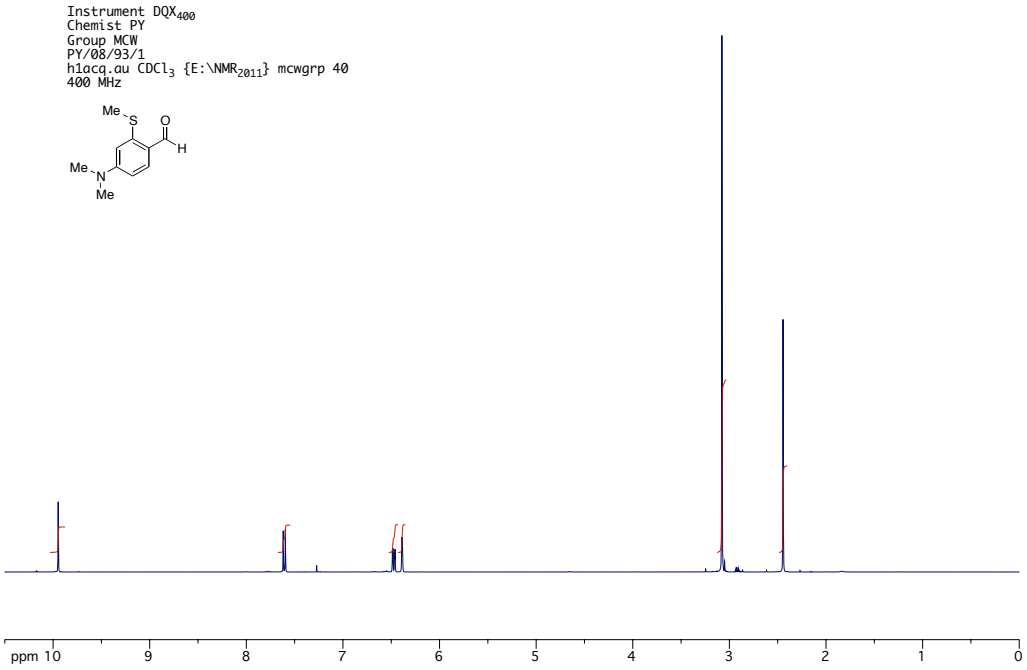
2-chloro-4-(dimethylamino)benzaldehyde, experimental page 198

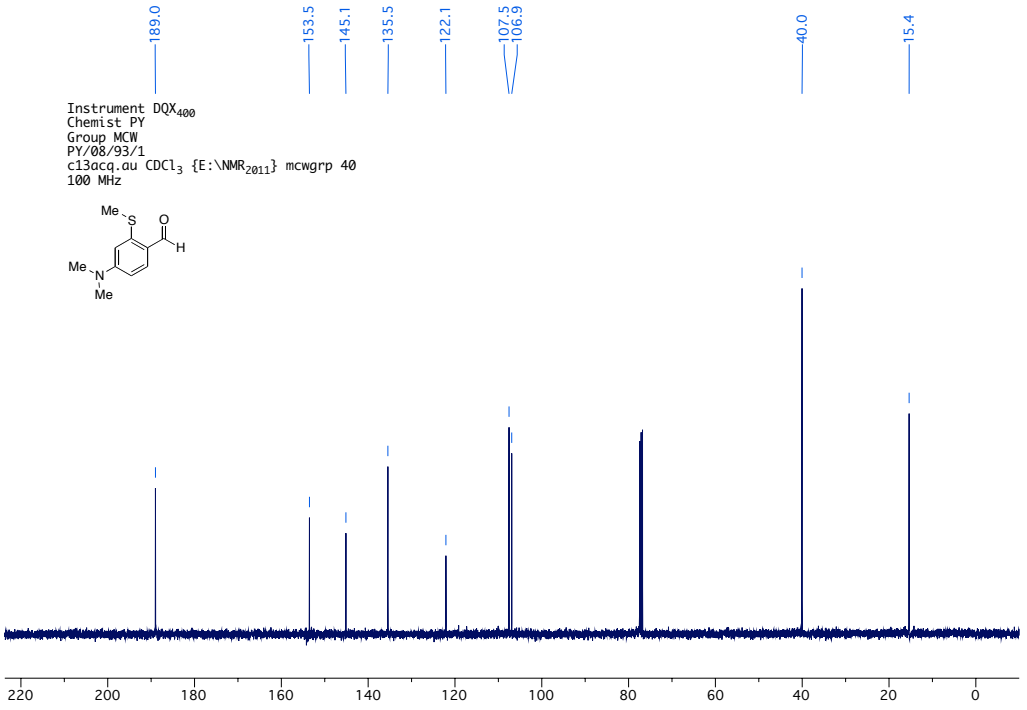




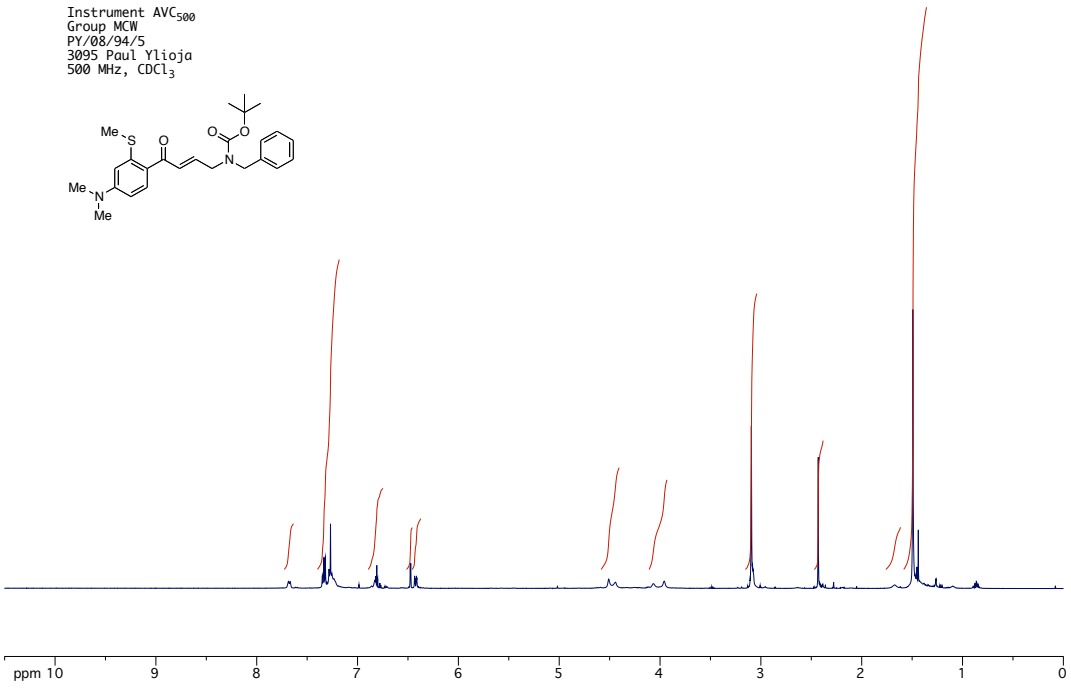
4-(dimethylamino)-2-(methylthio)benzaldehyde, experimental

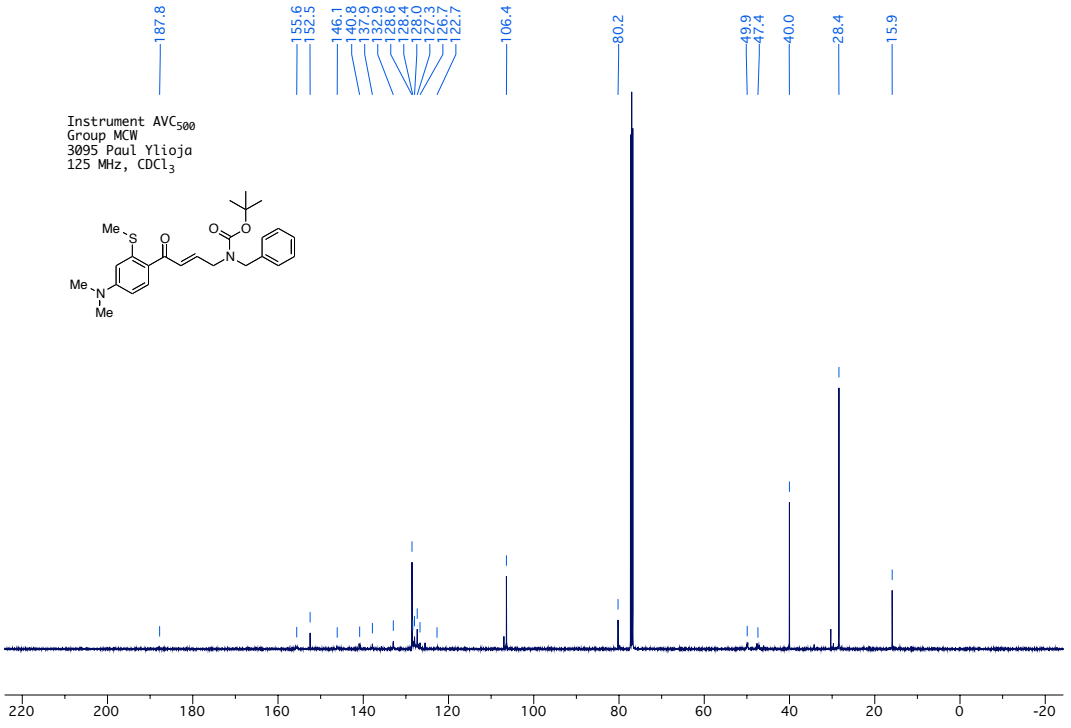
page 199



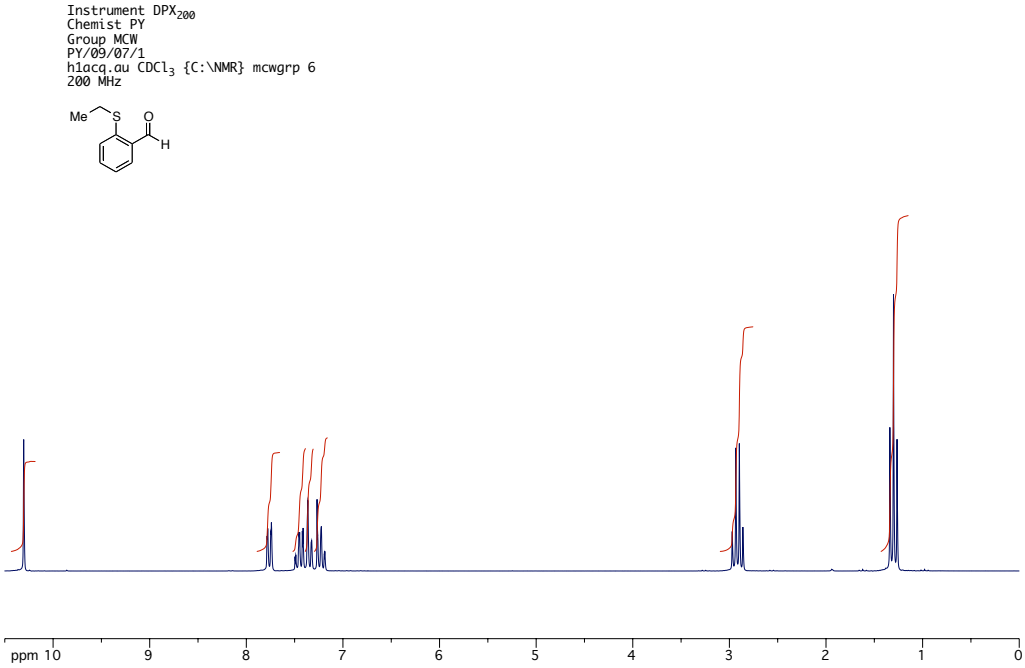


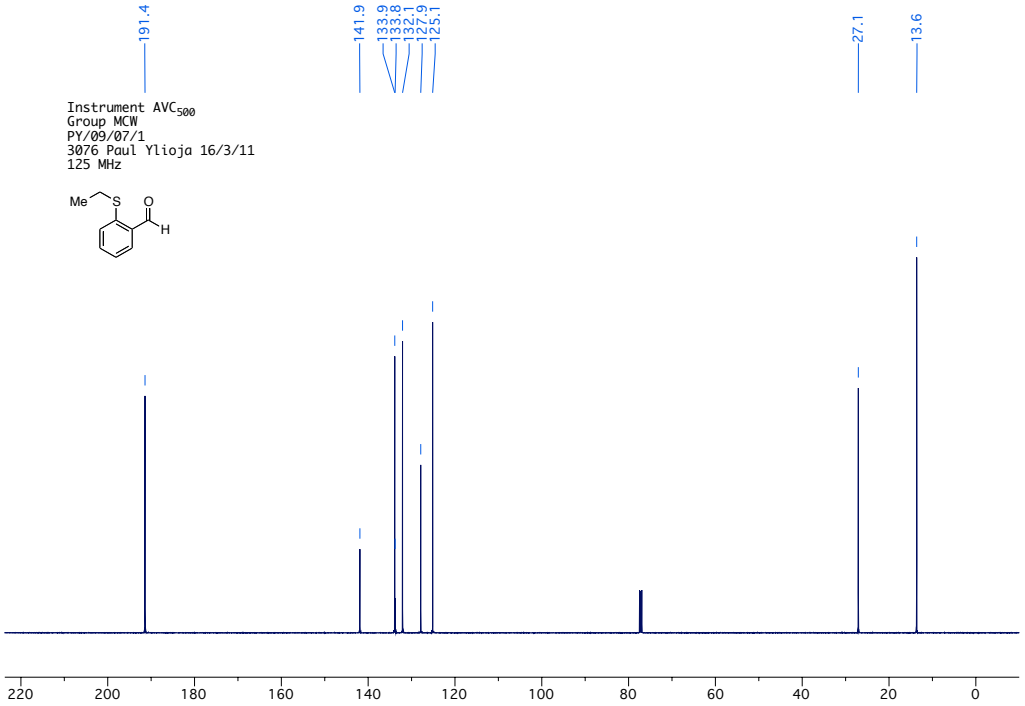
4-(dimethylamino)-2-(methylthio)benzaldehyde, experimental page 199



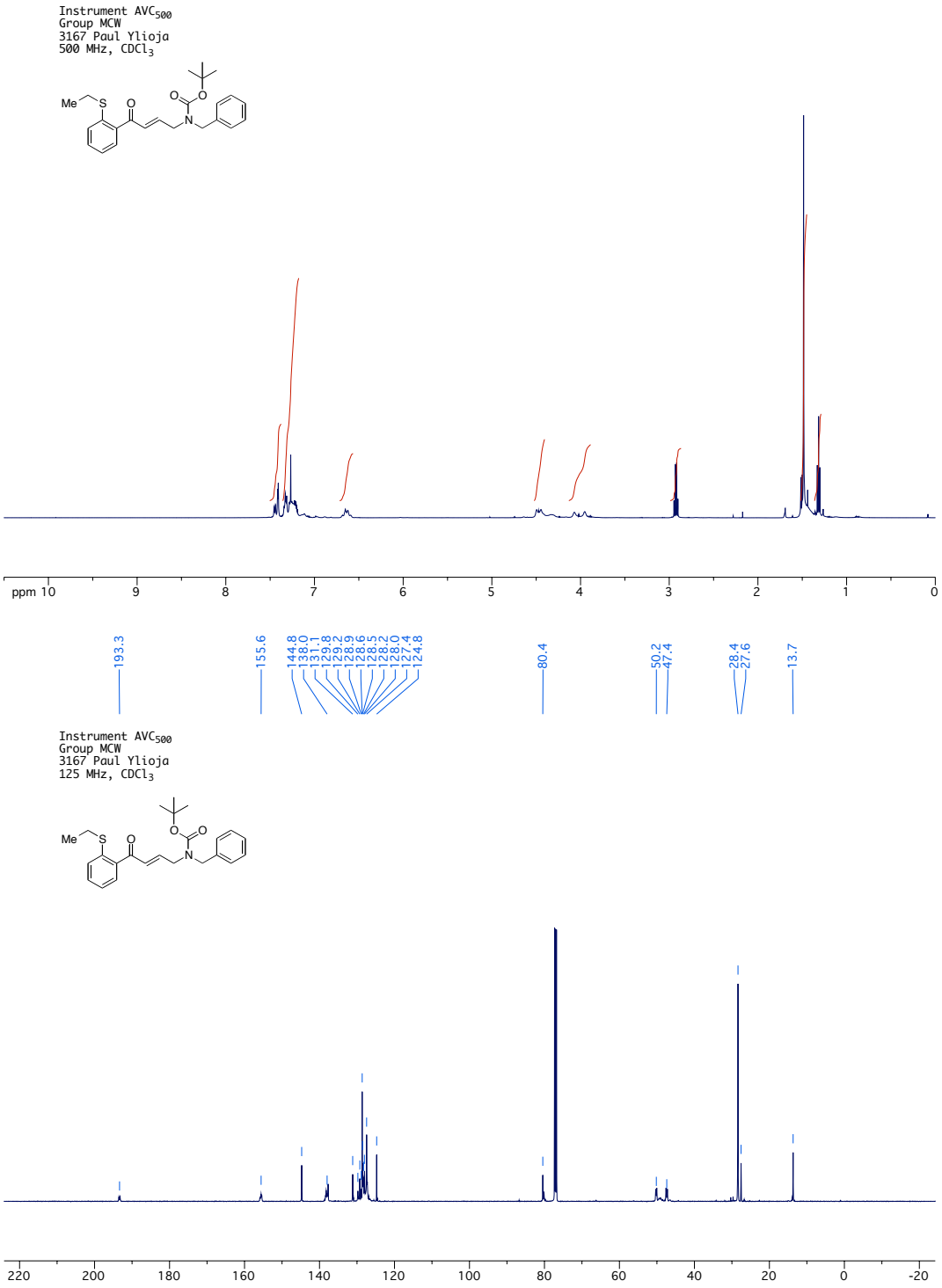


2-(Ethylthio)benzaldehyde, experimental page 216

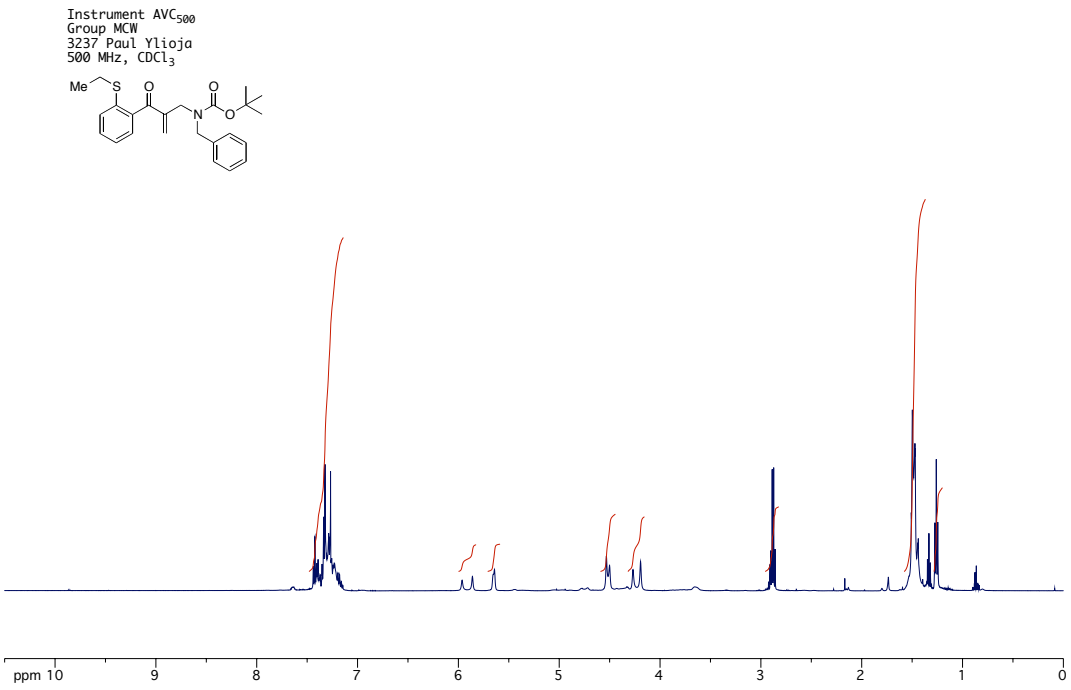




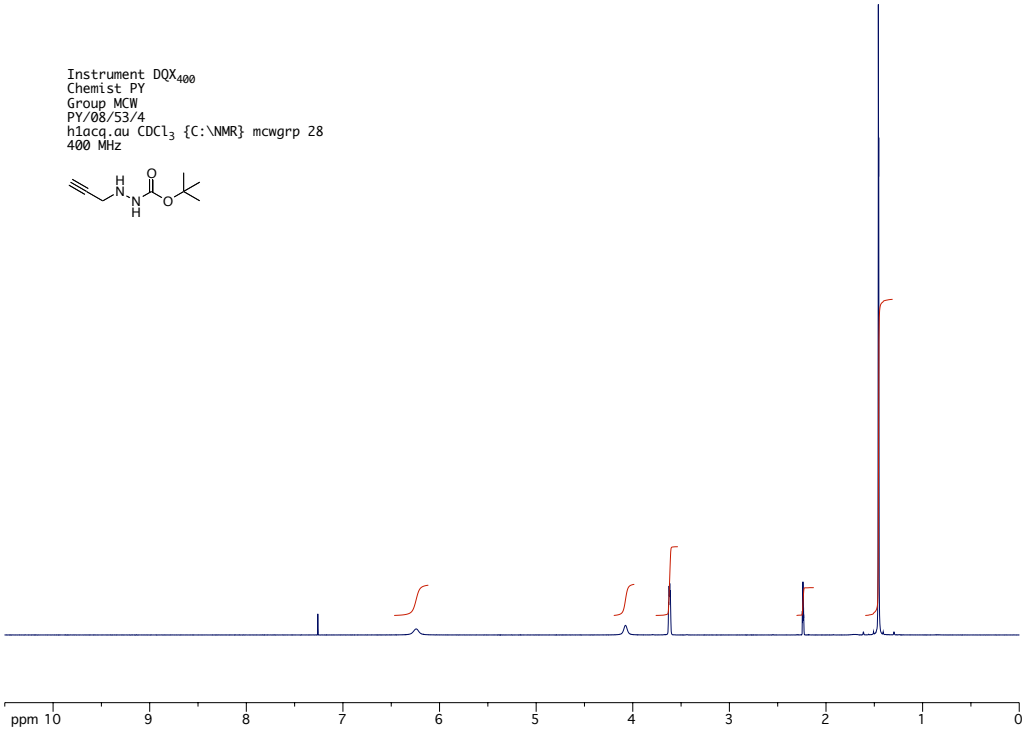
(*E*)-*tert*-Butyl benzyl(4-(2-(ethylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 217

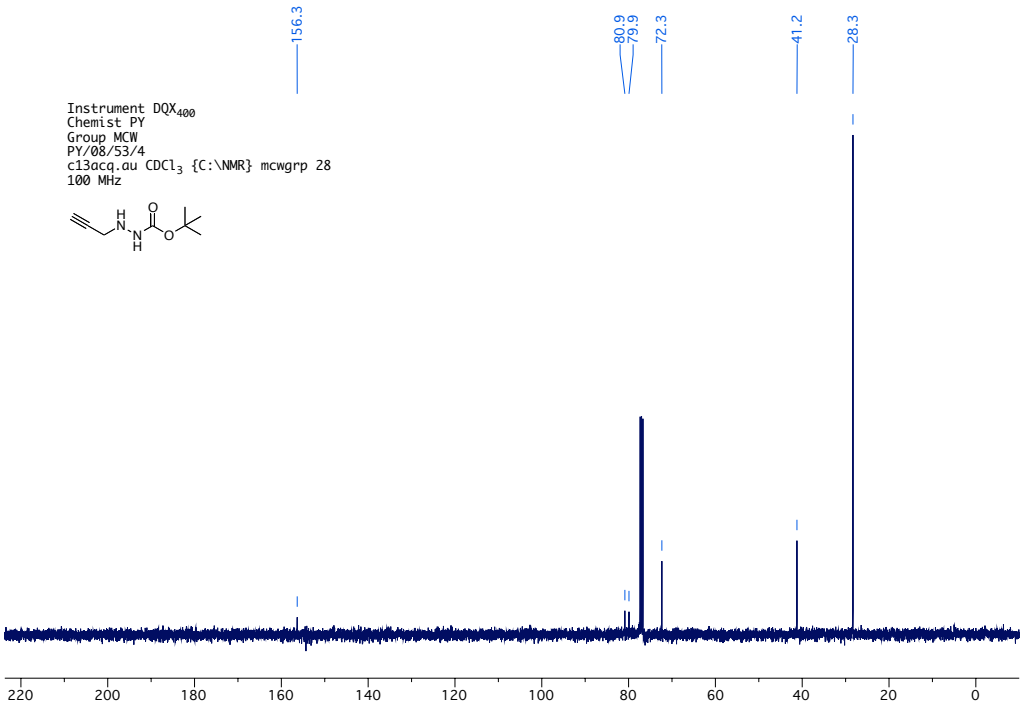


(*E*)-*tert*-Butyl benzyl(4-(2-(ethylthio)phenyl)-4-oxobut-2-en-1-yl)carbamate, experimental page 217

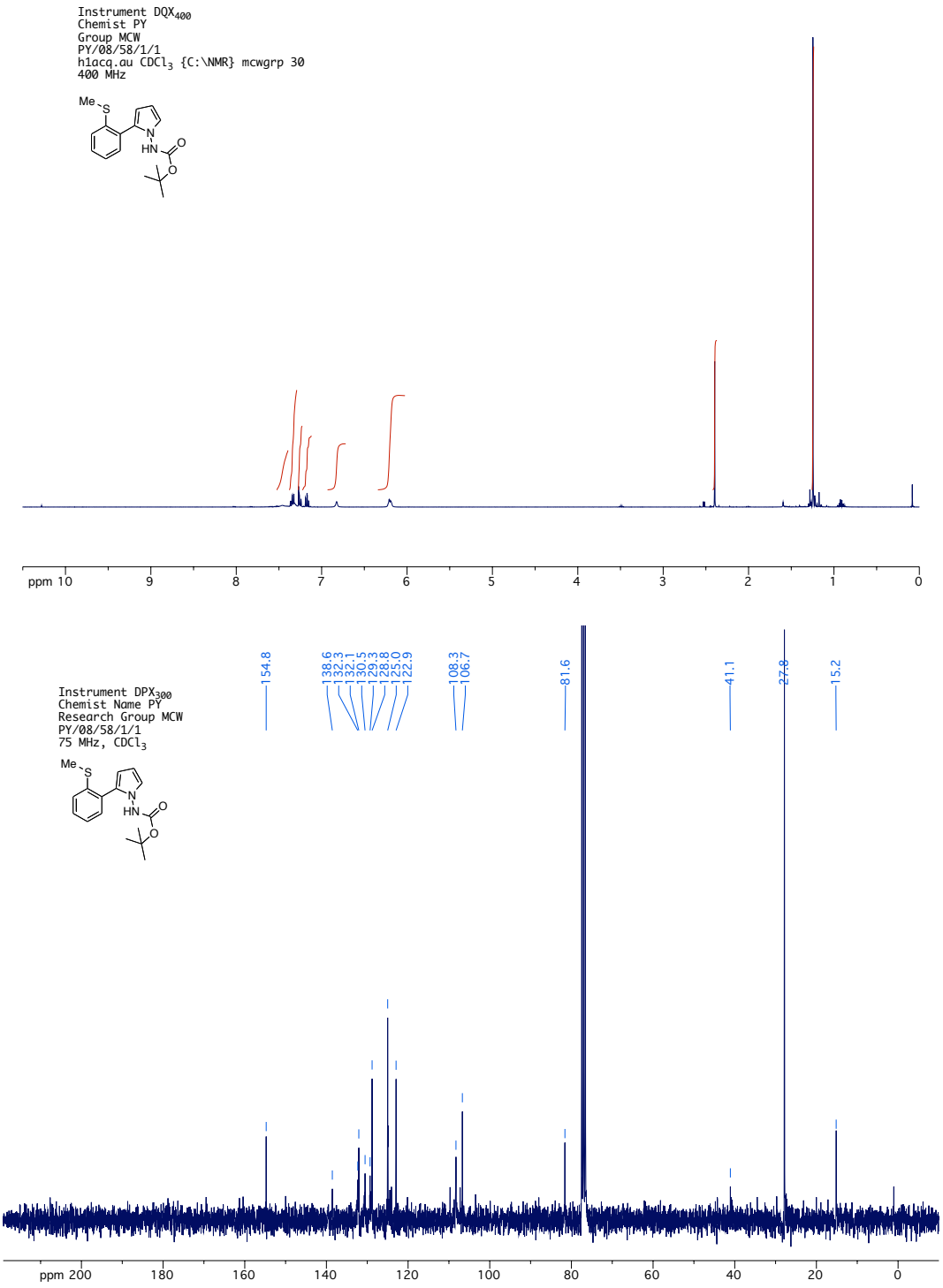


Tert-butyl 2-(prop-2-yn-1-yl)hydrazinecarboxylate, experimental page 218

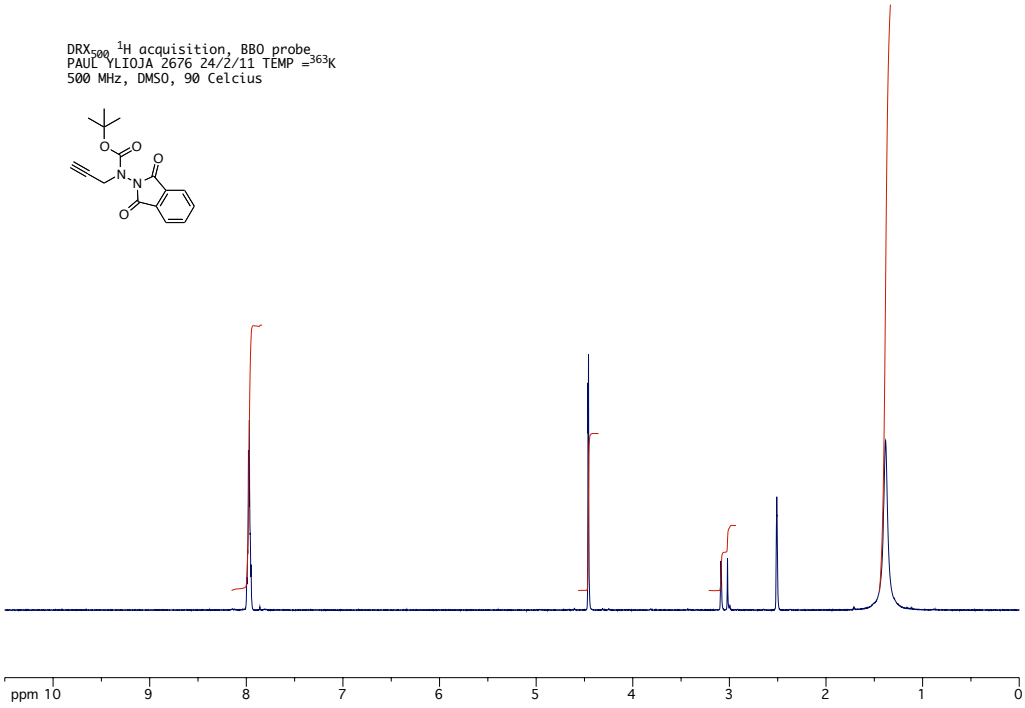


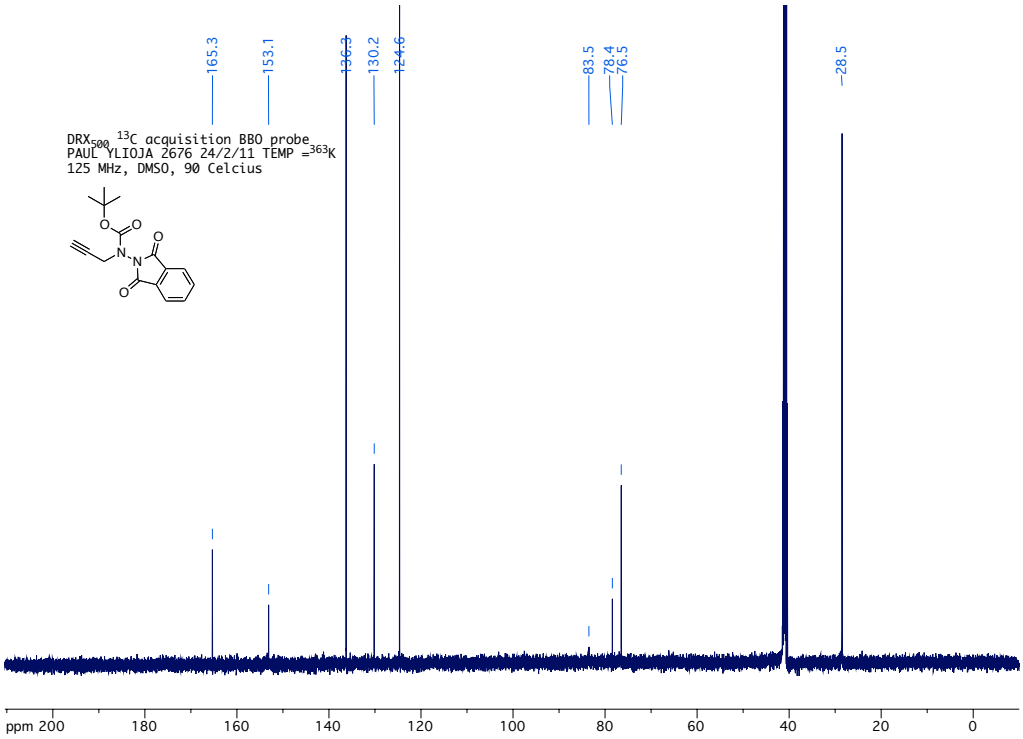


Tert-butyl (2-(2-(methylthio)phenyl)-1H-pyrrol-1-yl)carbamate, experimental page 222

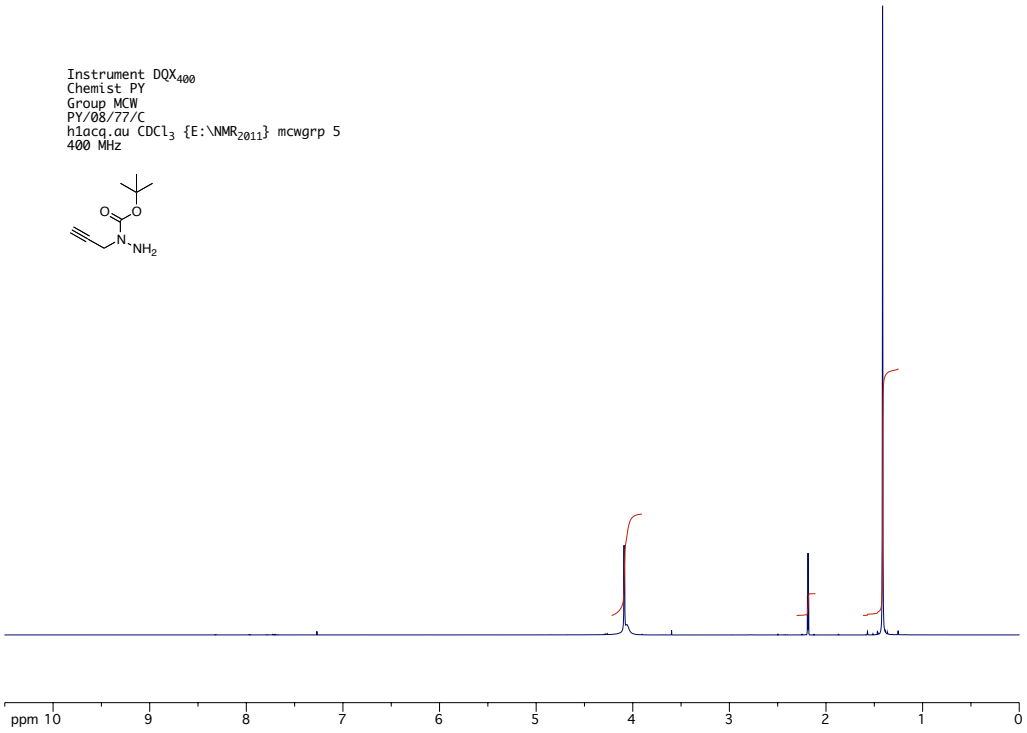


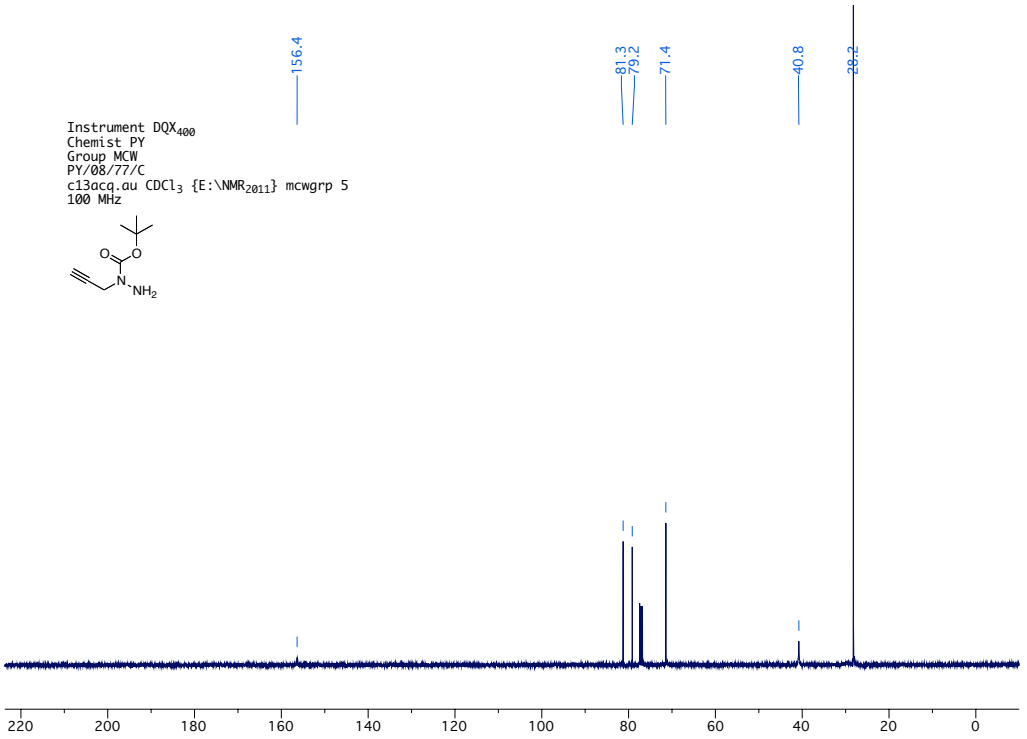
Tert-butyl-(1,3-dioxoisoindolin-2-yl-1-yl)carbamate, experimental page 219



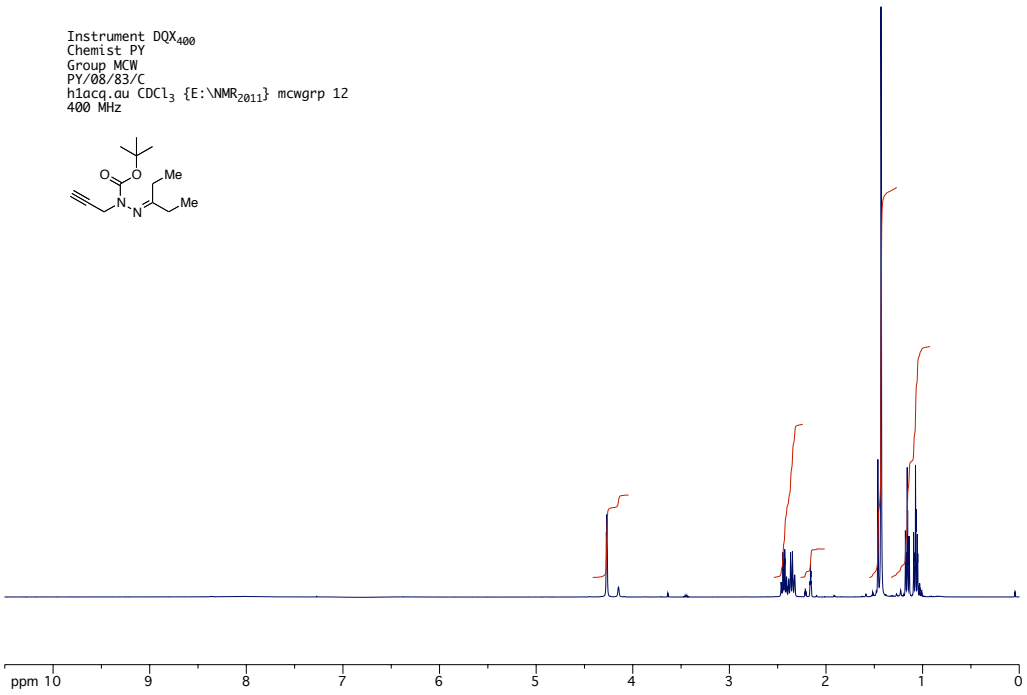


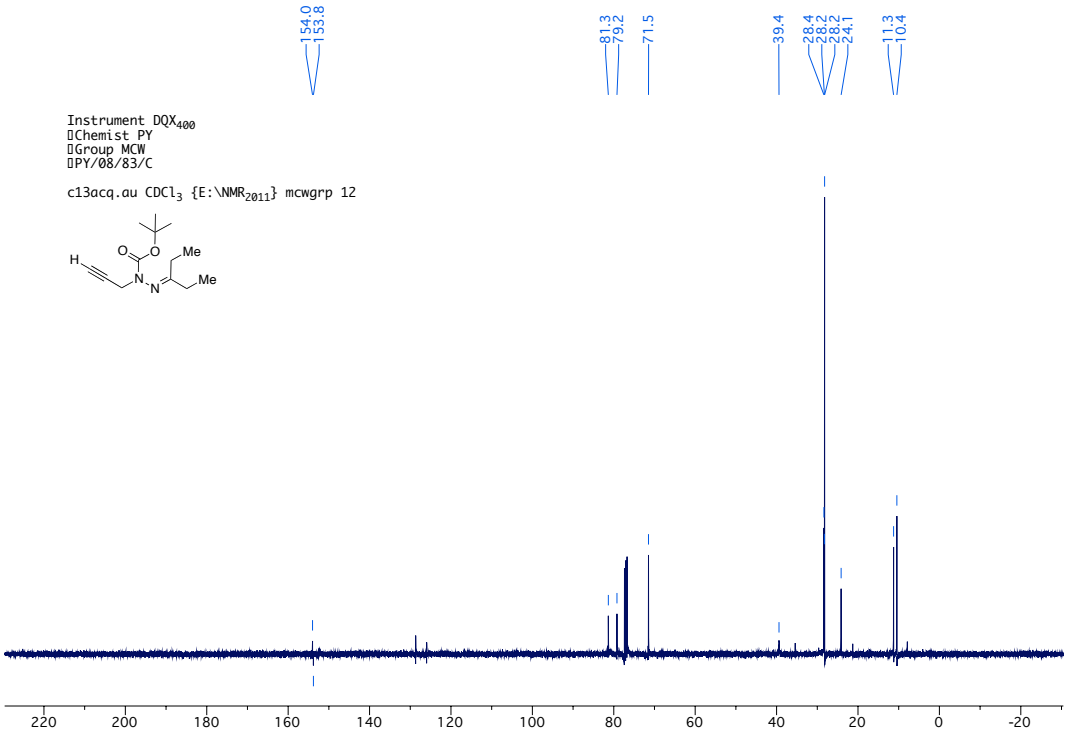
Tert-butyl 1-(prop-2-yn-1-yl)hydrazinecarboxylate, experimental page 220



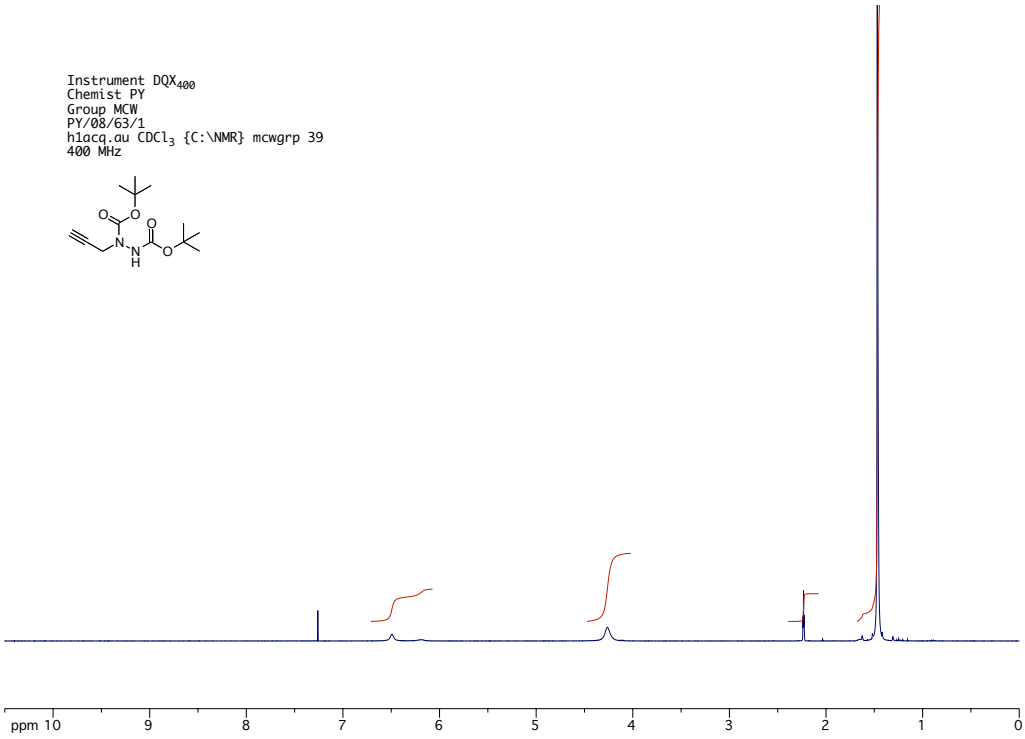


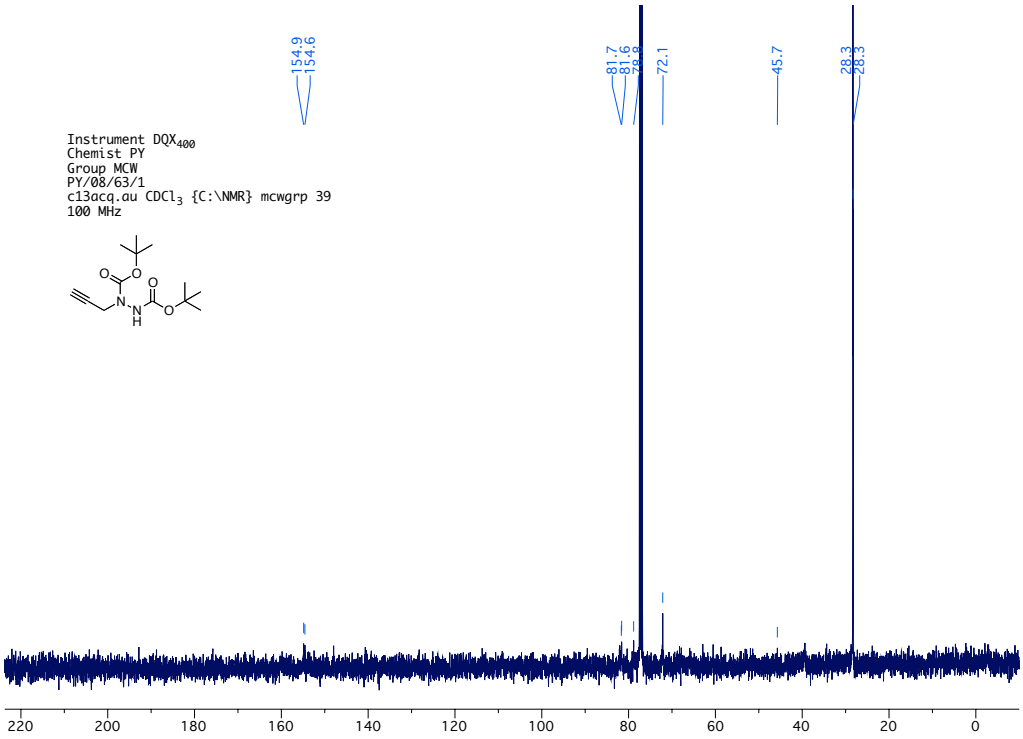
Tert-butyl 2-(pentan-3-ylidene)-1-(prop-2-yn-1-yl)hydrazinecarboxylate, experimental page 223



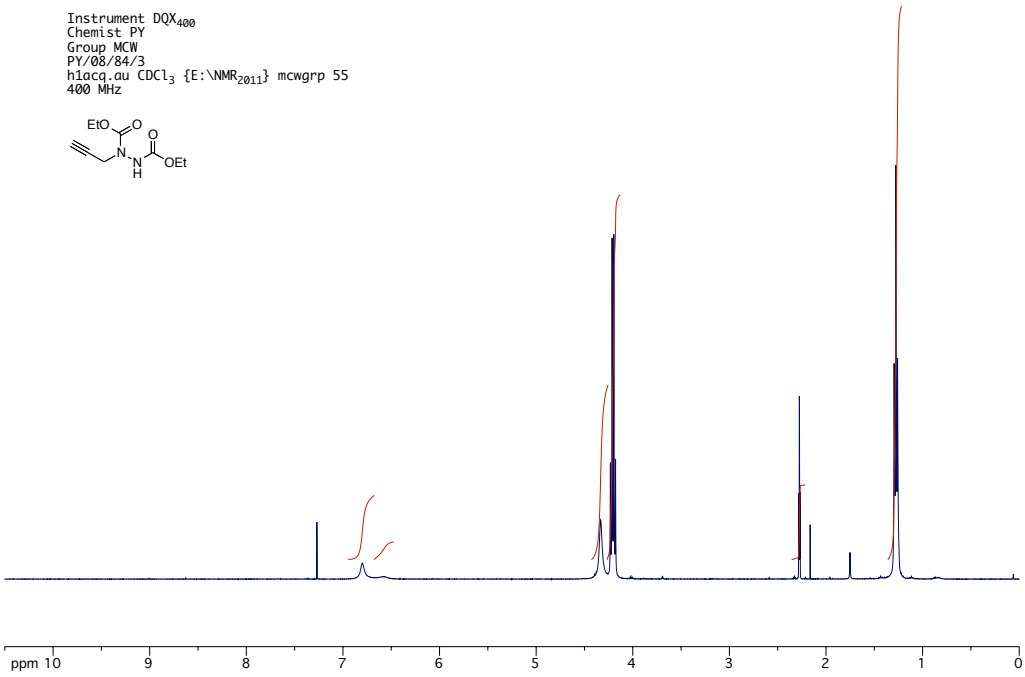


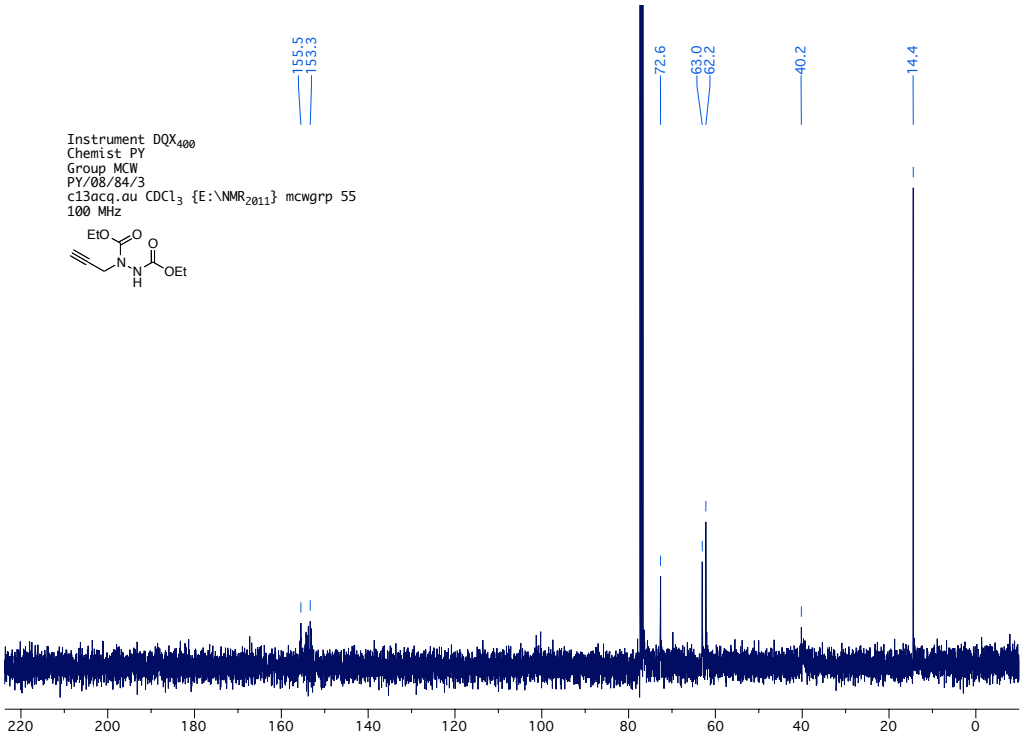
Di-*tert*-butyl 1-(prop-2-yn-1-yl)hydrazine-1,2-dicarboxylate, experimental page 220



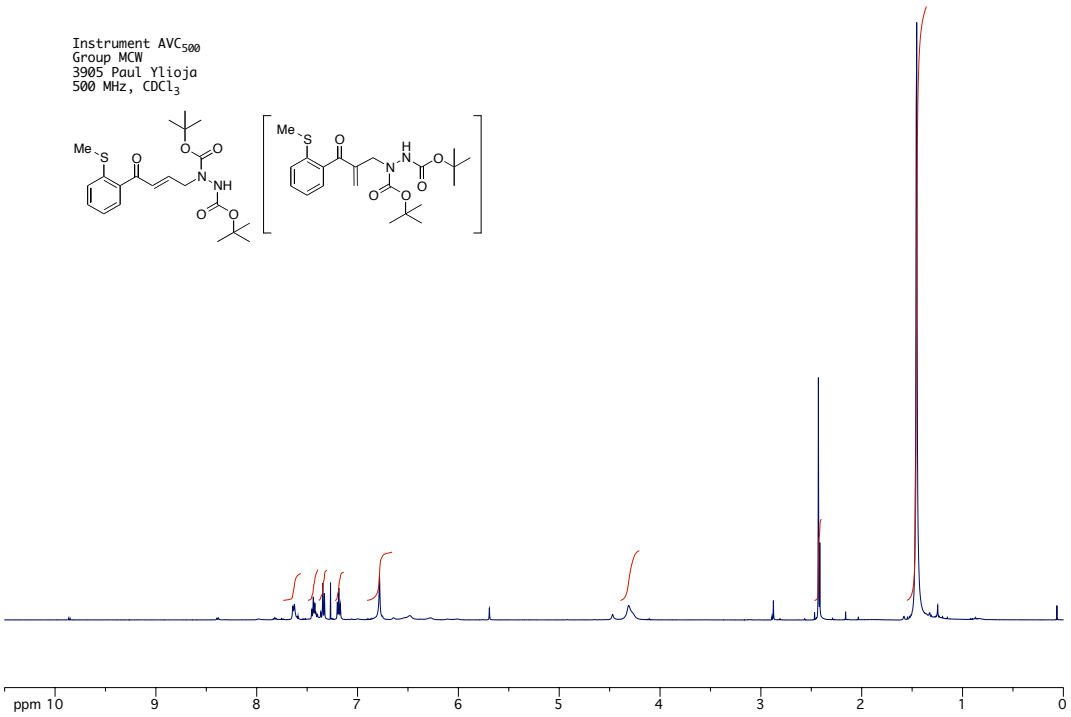


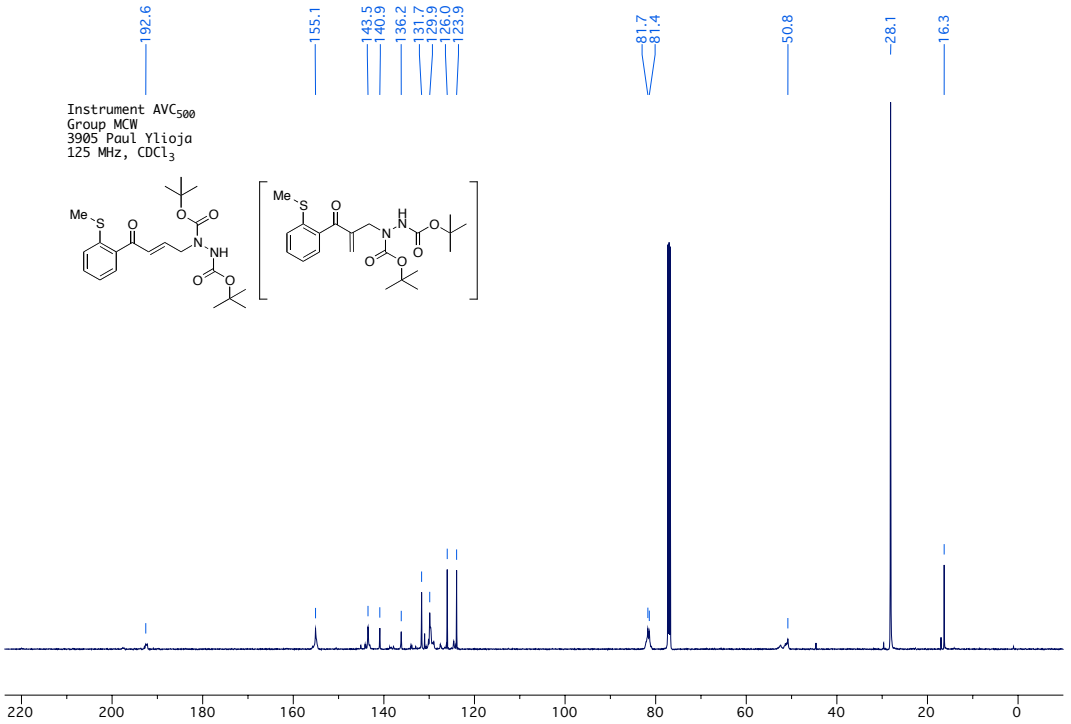
Diethyl 1-(prop-2-yn-1-yl)hydrazine-1,2-dicarboxylate, experimental page 221





(*E*)-di-*tert*-Butyl 1-(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)hydrazine-1,2-dicarboxylate, experimental page 223





(*E*)-diethyl 1-(4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl)hydrazine-1,2-dicarboxylate, experimental page 224