Studies towards the synthesis of Roseophilin

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Contents

Abstract

The pigment Roseophilin is a novel antibiotic with a topologically unique skeleton incorporating an *ansa*-bridged 1-azafulvene core and an extended conjugated heterocyclic chromophore comprising furan and pyrrole moieties. Chapter one discusses the nature of this and related products and summarises the major contributions made towards their synthesis. Chapter two discusses the possible approaches to this complex natural product and outlines the proposed research. The proposed macrocyclisation step, the Nicholas reaction, is reviewed in the following chapter.

The approach to the macrotricyclic core of Roseophilin is discussed in the ensuing chapters. Chapter four presents the initial strategy in which the [*b*]-fused pyrrole ring is constructed, by means of an aldol reaction onto a cyclopentanone frame.

A second strategy in which the [*b*]-fused pyrrole ring is approached *via* a 1,4-dicarbonyl compound, involving the synthesis and use of molybdenum electrophiles is discussed in chapter five.

A third and highly convergent strategy is presented in chapter six. This approach starts from pyrrole and makes use of the nucleophilicity of the heteroaromatic ring. The progress made in the approach to the macrotricyclic core is discussed. The building blocks for the isopropylsubstituted cyclopentanone ring are introduced *via* a Knoevenagel condensationon 3-formylpyrrole and subsequent copper(I)-catalysed 1,4-addition. The reactive handle for the intramolecular macrocyclisation is introduced by a Sonogashira reaction at the 5-position of pyrrole. Finally the macrocyclisation studies, conclusions and perspectives are presented.

Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the result of my own investigations. Where work of other investigators has been used, this has been fully acknowledged in the text.

Louise Lea

Abbreviations

Ac	acetyl
AIBN	2,2'-azo*bis*isobutylnitrile
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
bp	boiling point
Bu	n-butyl
^{i}Bu	*iso*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CIPE	complex induced proximity effect
Cp	cyclopentadienyl
CSA	camphor sulfonic acid
Cy	cyclohexyl
dbmp	2,6-di-*tert*-butyl-4-methylpyridine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DHP	dihydropyran
DIBALH	diisobutylaluminium hydride
DMAP	dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
IR	infrared
KHMDS	potassium *bis*(trimethylsilyl)amide
L	unspecified ligand
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
LTMP	lithium tetramethylpiperidide
M	unspecified metal
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mp	melting point
Ms	methanesulfonyl
NaHMDS	sodium *bis*(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	N-methylmorpholine-N-oxide
NMM	4-methylmorpholine
NMR	nuclear magnetic resonance

Nu	nucleophile
o/n	overnight
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium toluene-4-sulfonate
Pr	propyl
^{i}Pr	*iso*-propyl
PTSA	*para*-toluenesulfonic acid
Py	pyridine
RCM	ring closing metathesis
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethyldiamine
TMS	trimethylsilane
Tr	triphenylmethyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet

Acknowledgements

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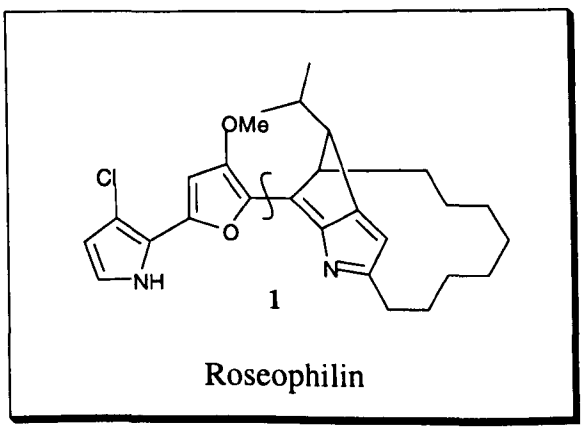
Finally I would like to thank the staff and students of the Department of Chemistry, particularly those of the Raphael lab 1997-2000, for their humour and enthusiasm in helping to make the experience so much fun.

To Jason

1.0 Roseophilin

The pigment Roseophilin **1** was isolated from *Streptomyces griseoviridis* by Seto et al. in 1992.[1] It is a novel antibiotic with a topologique unique skeleton incorporating an *ansa*-bridged 1-azafulvene core and an extended conjugated heterocyclic chromophore comprising furan and pyrrole moieties.



1

Roseophilin

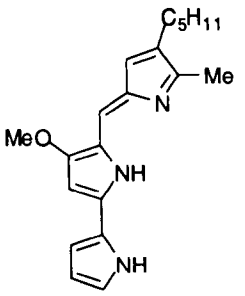
Roseophilin exhibits very promising cytotoxicity in *vitro* towards K562 human erythroid leukaemia (IC_{50} 0.15 μg/mL) and KB human epidermoid carcinoma (IC_{50} 0.40 μg/mL) cell lines.[1] The cytotoxicity is believed to originate from the conjugated heterocyclic ring system which may intercalate with DNA. These preliminary reports render Roseophilin a new lead structure in the search for anti-cancer agents while the intricate macrotricyclic core offers an attractive target for total synthesis.

1.1 The "Prodiginine" antibiotics

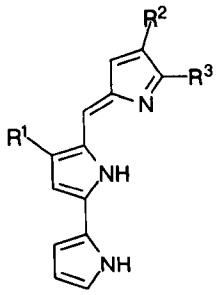
Roseophilin is a close structural relative to the "prodiginine" antibiotics of which the parent compound Prodigiosin **2** was first reported in 1934 (Figure 1). The "prodiginine"

antibiotics, produced by a retricted group of eubacteria and actinomyces, possess a deeply red-coloured characteristic pyrrolylpyrromethene chromophore. The red apparence of *Serratia marescens* and related bacteria, due to the production of prodigiosin-type metabolites, forms the basis of the 'bleeding host' which occurred rater frequently during the middle ages.[2] Although numerous reports on the antimicrobial, cytotoxic and antimalarial activity of these compounds can be found in the literature, clinical applications have been prevented by their fairly high toxicity.[3,4] However, a recent report showed that some members of this series, in particular Undecylprodigiosin **5** and Streptorubin B **11** inhibit T-cell proliferation at doses which are not cytotoxic.[5-7] Undecylprodigiosin **5** appears to exert its immunomodulating properties with a mechanism of action which is distinctly different from that of Cyclosporin A, FK506 and Rapamycin.[8] Since the availability of agents acting at different stages along the T-cell activation pathway may improve therapeutic results, the prodigines constitute important lead compounds in the search for supplemetary drugs to prevent allograft rejection.

Synthetic approaches to Prodigiosin[9] and related antibiotics[10-14] have been dominated by the work of Wasserman et al. More recently the synthesis of the biologically promising Undecylprodigiosin[15] and Streptorubin B[16] have been achieved.

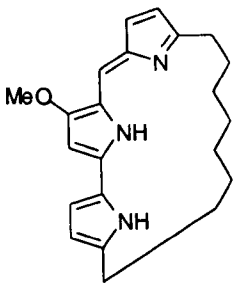


2 Prodiogiosin

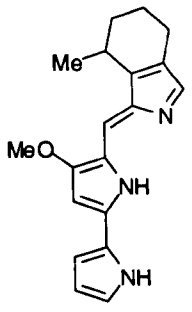


	R^1	R^2	R^3
3	H	H	H
4	OH	C_5H_{11}	Me
5	OMe	H	$C_{11}H_{23}$
6	OMe	H	C_9H_{19}

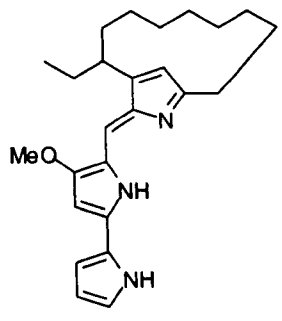
3 Prodiogiosene
4 Norprodigiosin
5 Undecylprodigiosin
6 Nonylprodigiosin



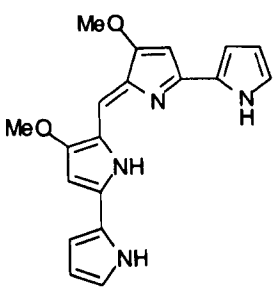
7 Cyclic nonylprodigiosin



8 Cycloprodigiosin



9 Metacycloprodigiosin



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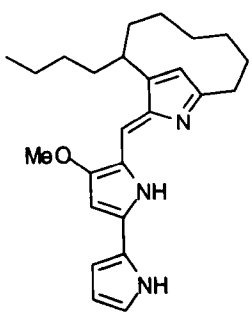


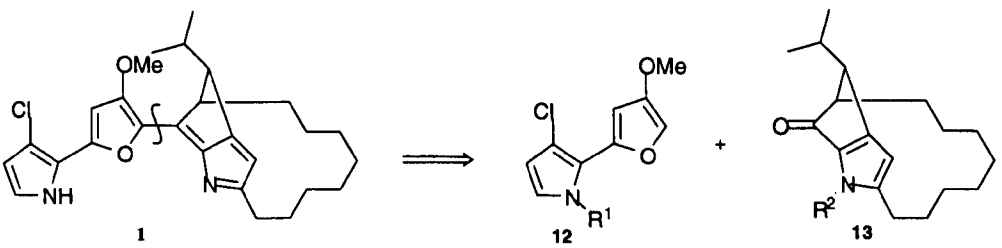
11 Streptorubin B

Figure 1 - The "prodigine" antibiotics

The structural similarities in the *meta*-bridged heterocyclic entities of azafulvenes **5** and **11** and Roseophilin are apparent, which reinforces the theory that Roseophilin is a new lead structure in the search for anti-cancer agents.

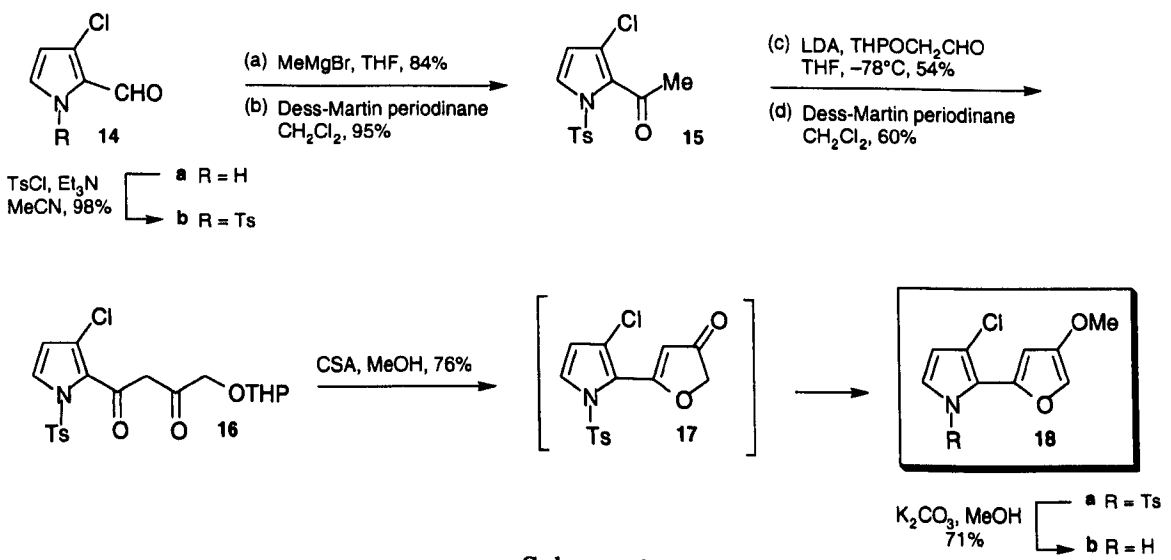
1.2 Synthetic approaches to Roseophilin

Considerable efforts have been directed towards the synthesis of Roseophilin **1** since its structure was first disclosed in 1992. As Roseophilin **1** incorporates an azafulvene chromophore it may be formed by the condensation of a ketopyrrole fragment **13** with the appropriately substituted heterocyclic side chain **12** (Scheme 1). Model reactions carried out by Terashima et al. corroborate the viability of this approach.[17] Acid-catalysed reactions of **12** (R^1 = Ts) with simple 2-acyclpyrroles lead to the desired chromophore, albeit in rather low yields.



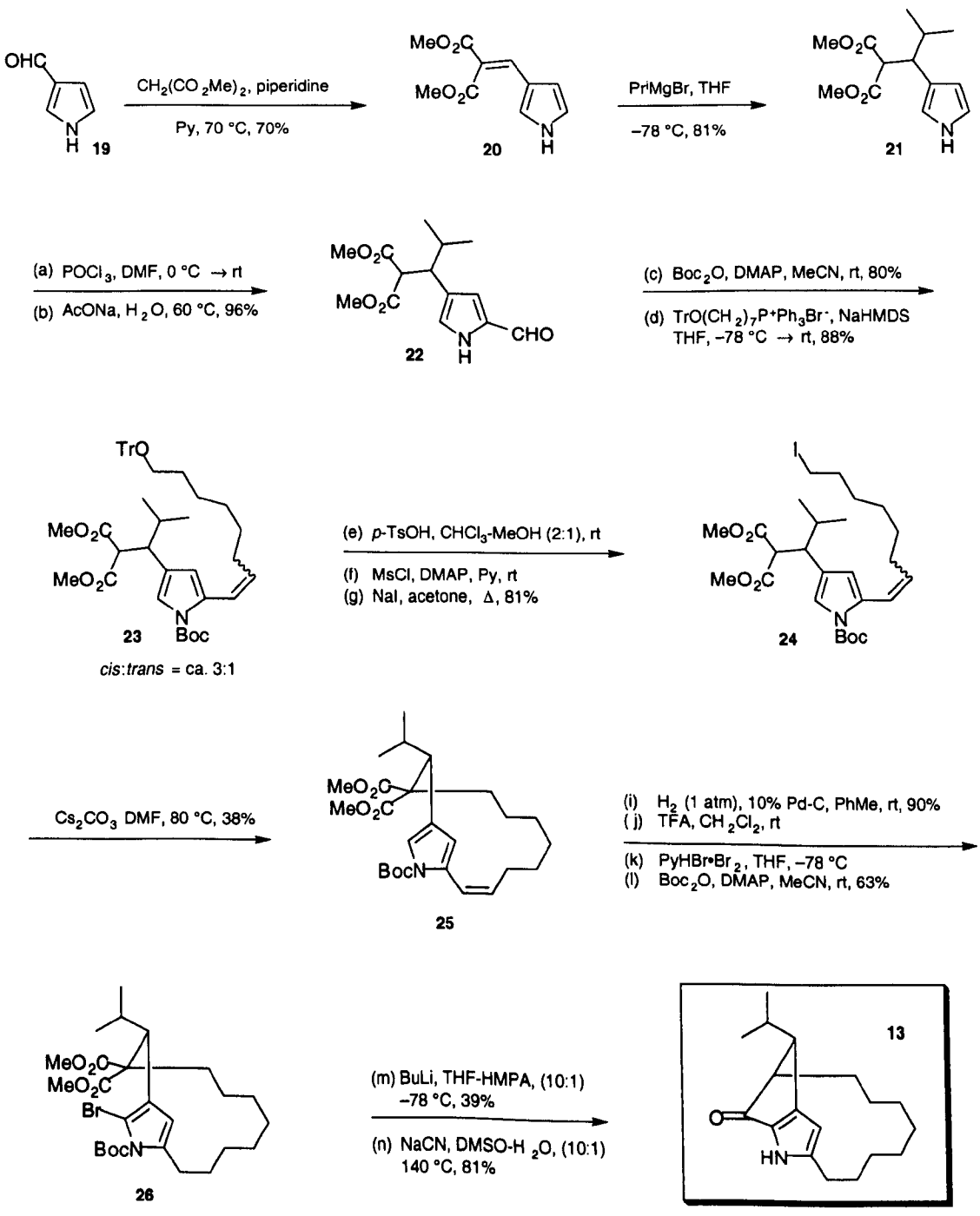
Scheme 1

Terashima's elegant approach to the conjugated heterobiaryl moiety **12**, the first published approach to **1**, is outlined below (Scheme 2).[17]



Scheme 2

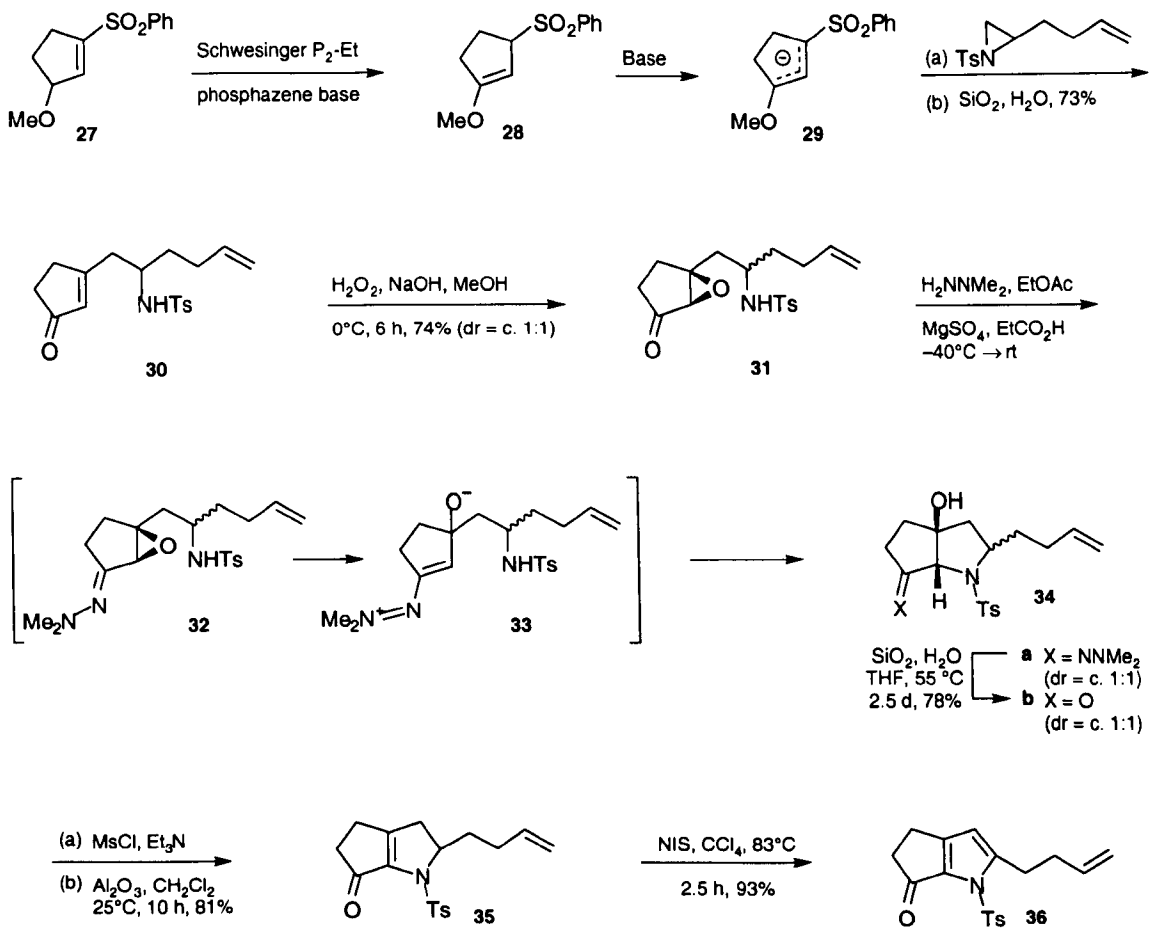
Terashima's subsequent approach to the racemic macrotricyclic core **13** of Roseophilin (Scheme 3) published in 1998 constituted a formal total synthesis of **1**.[18] The synthesis starts from pyrrole and relies on the nucleophilicity of the "π-excessive" heterocycle to introduce functionality to the ring *via* Vilsmeier formylation at the 3- and 2-position respectively.



Scheme 3

A notable aspect of this synthesis is the introduction of a *cis* double bond α to the pyrrole in order to bring the reactive sites into closer proximity for the macrocyclisation. The linear side chain was incorporated *via* Wittig olefination which yielded a 3 :1 preference of the desired *cis* isomer. Terashima found this mixture of Wittig products to be "hardly separable" and they were carried through without separation. The macrocyclisation was achieved in moderate yield under diluted conditions (5 mM) to give the *cis*-olefinic macrocycle as the sole product. When the dihydroderivative of **24** was used in the macrocyclisation only 21% yield of the cyclised product was obtained. This observation supports the theory that the *cis* olefin plays an important role in the macrocyclisation. Lithiation of **26** achieved the second cyclisation step to give the cyclopentanone ring in mediocre yield with concomitant cleavage of the Boc protecting group. Subsequent decarboxylation under Krapcho conditions conclude the synthesis to give the macrotricyclic core of Roseophilin **13** (R^2 = H).

Fuchs et al. disclosed their novel annulation method for the construction of bicyclic ketopyrroles as the first approach to the ketopyrrole moiety of Roseophilin **1** in 1996 (Scheme 4).[19] They hoped to extend this strategy to the racemic synthesis of the macrotricyclic core of Roseophilin **12**, introducing the isopropyl substitutent before isomerisation to the allylic isomer with Schwesinger's base and effecting the macrocyclisation by Grubb's ring closing metathesis (RCM).

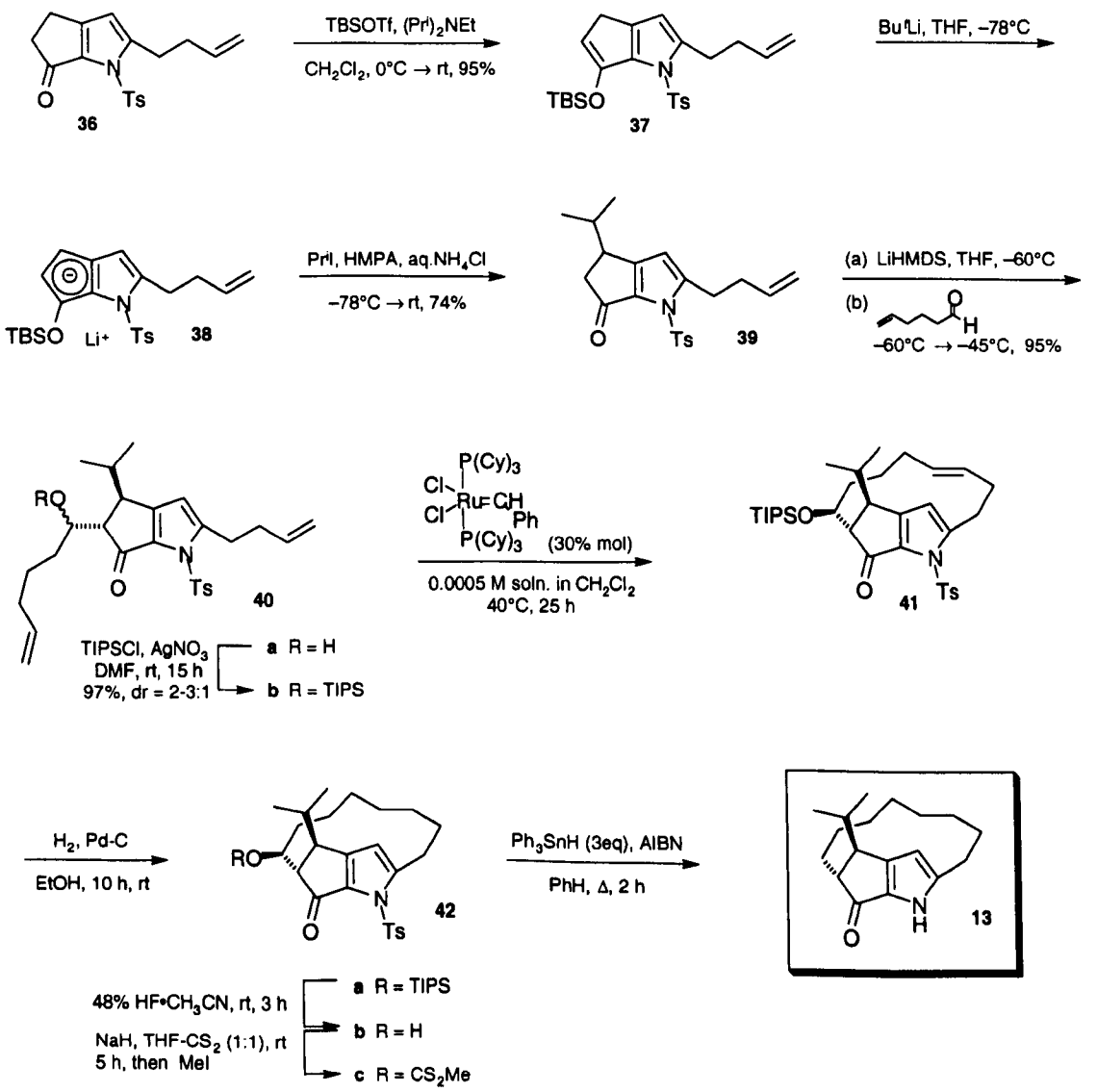


Scheme 4

However in a subsequent publication, they failed to construct the desired allylic isomer of the isopropyl substituted vinyl sulfone and could only generate a 3 :1 equilibrium mixture in which the desired (labile and inseperable) allyl sulfone constitued the minor component.[20]

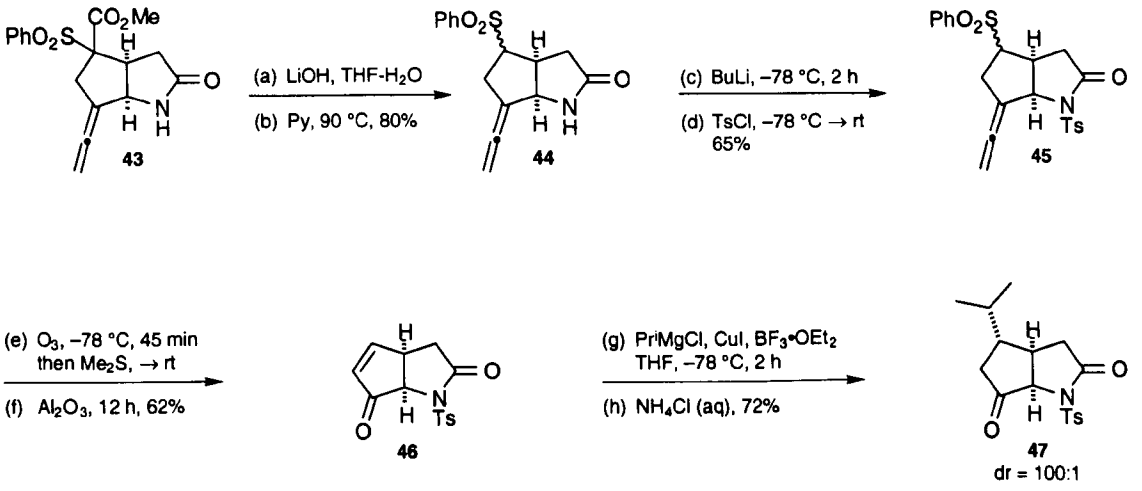
An alternative route to the correctly substituted ketopyrrole was promptly effected in order to test the feasibility of the RCM (Scheme 5).[20] Aldol condensation of 5-hexenal with the ketopyrrole moiety **39** yielded a 2-3 :1 mixture of unassigned diastereomers. Fuchs had planned to remove the undesired hydroxyl substituent before the RCM step. However this resulted in unwanted side reactions yielding dimeric products, a result of intermolecular RCM, and none of the desired *ansa*-bridged compound.

Studies of the molecular mechanics of the substrates revealed that the bulkier triisopropylsilyl derivative has a global minimum with the hexenyl side chain in much closer proximity to the requisite butenyl moiety making it a far better substrate for RCM. In the event, treatment of a 0.5 mM solution of the (2-3 :1) mixture of unassigned diastereoisomers of **41** with Grubb's catalyst afforded the *ansa*-bridged silylether as a single diastereoisomer in 60% yield. Radical based removal of the xanthate furnished racemic **13** (R^2 = H) as a single diastereomer.



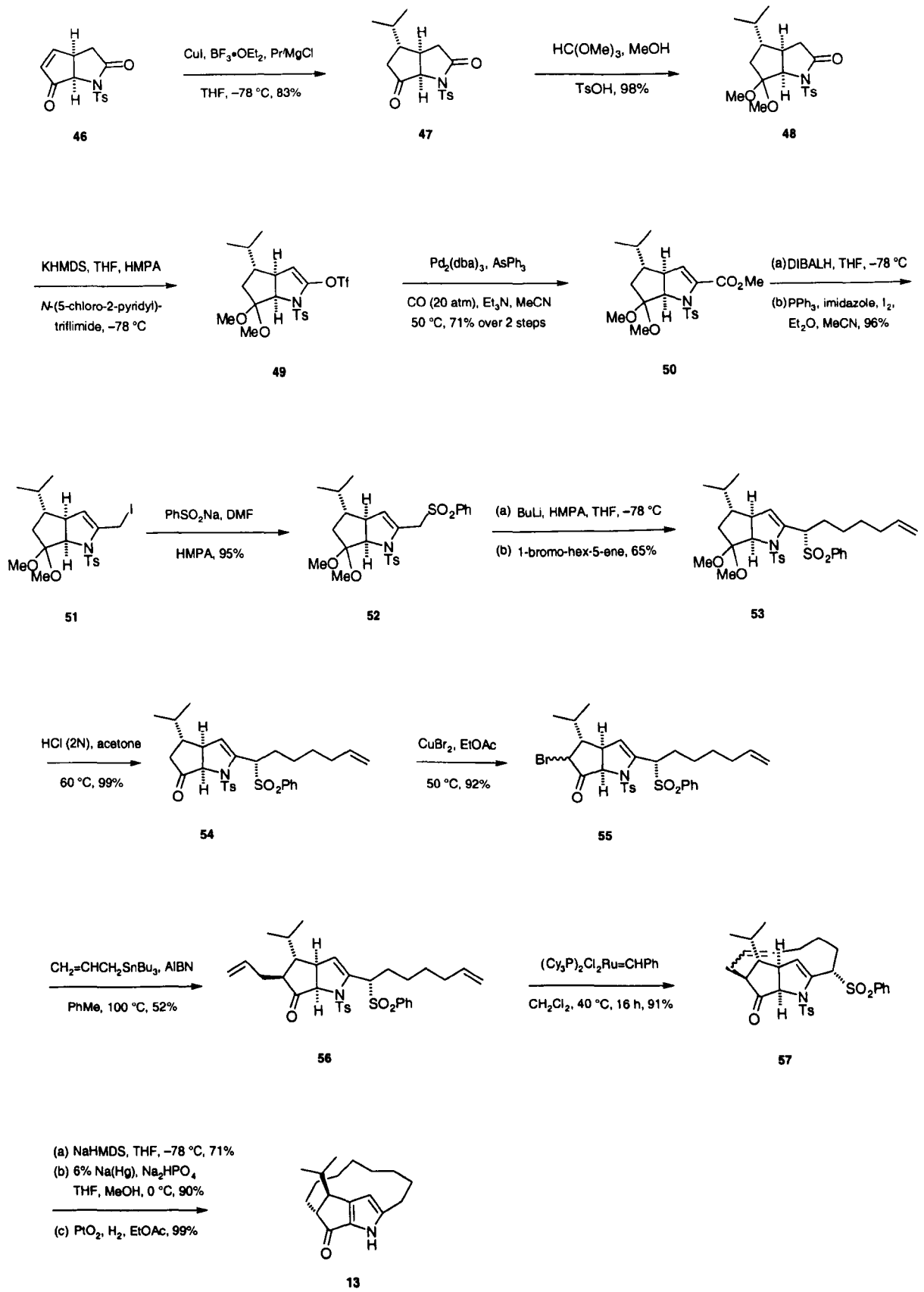
Scheme 5

The first and only enantioselective approach to the macrotricyclic core of Roseophilin **13** has been disclosed by Hiemstra et al. (Scheme 6).[21] Enantiopure **47** is proposed as an intermediate for a projected synthesis of **13**. The approach relies on the steric hindrance of the *cis*-fused rings to effect a diastereoselective Michael addition to the cyclopentane **47**.



Scheme 6

In a recent communication Hiemstra et al. have reported the completion of the macrocyclic core of Roseophilin, which constitutes a formal total synthesis of the natural product (Scheme 7).[22] The macrocyclisation was achieved by RCM in excellent yield. The phenyl sulfone of **52** which is incorporated as a reactive handle for alkylation also populates reactive conformers in the macrocyclisation (Thorpe-Ingold effect). The synthesis is versatile allowing for either enantiomer of the natural product to be formed. The route may also be adapted to produce analogues, particularly in modifying the length of the *ansa* bridge by alkylation of the sulfone of **53** with various alkyl halides.

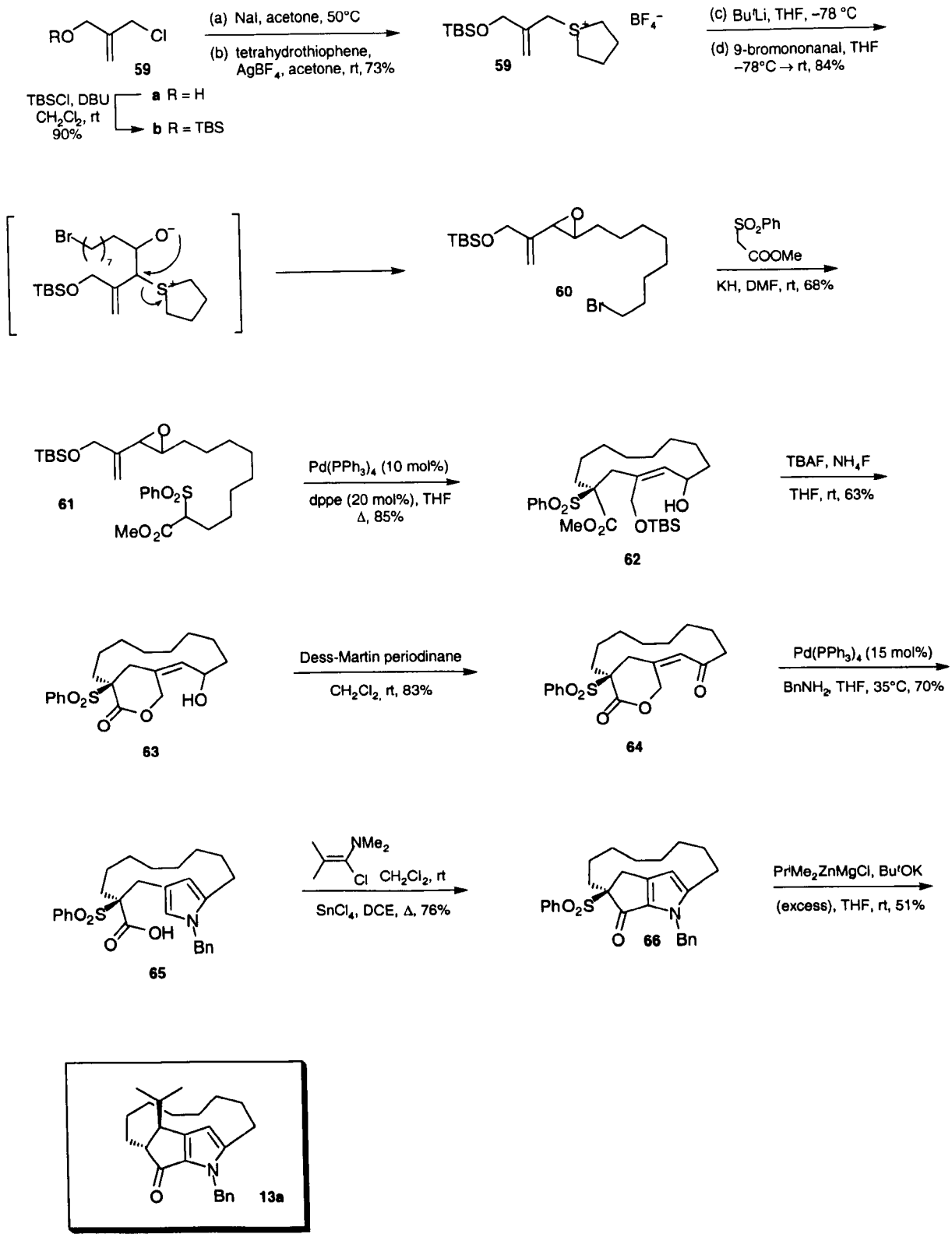


Scheme 7

Of all the approaches to Roseophilin Fürstner et al. have enjoyed the greatest success. They were the first in 1997 to disclose a complete synthesis of the *N*-benzyl protected

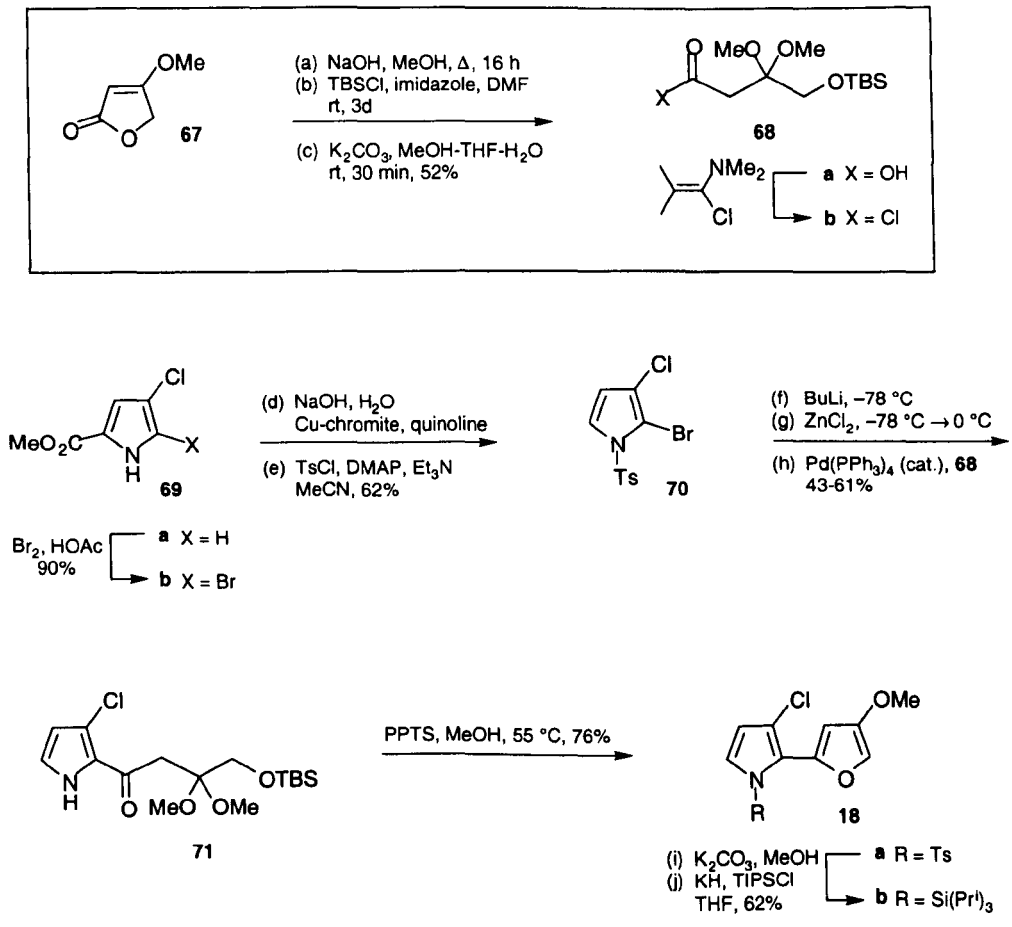
macrotricyclic core **13a** (R^2 = Bn) (Scheme 8).[23] **13a** was obtained by means of a novel palladium-catalysed manifold for the formation of *ansa*-pyrroles which proceeds *via* the key intermediates, vinyl oxirane **60** and allyl lactone **64**.

Fürstner's plan was to introduce the macro cyclisation step early in the synthesis, setting a framework upon which to construct the ketopyrrole moiety. Their synthesis relies on the subtle differences in reactivity between the two allylic precursors **60** and **64** in the palladium-catalysed substitution reactions. The first, driven by the release of ring strain in the regioselective opening of the vinyl oxirane **60**, and the second, with nucleophilic benzylamine delivering the desired pyrrole encoded in the 1,4-dioxygen functionality of the substrate. The subsequent Michael addition of the isopropyl unit occurred diastereoselectively yielding the racemic *N*-benzyl protected macrotricyclic core.



Scheme 8

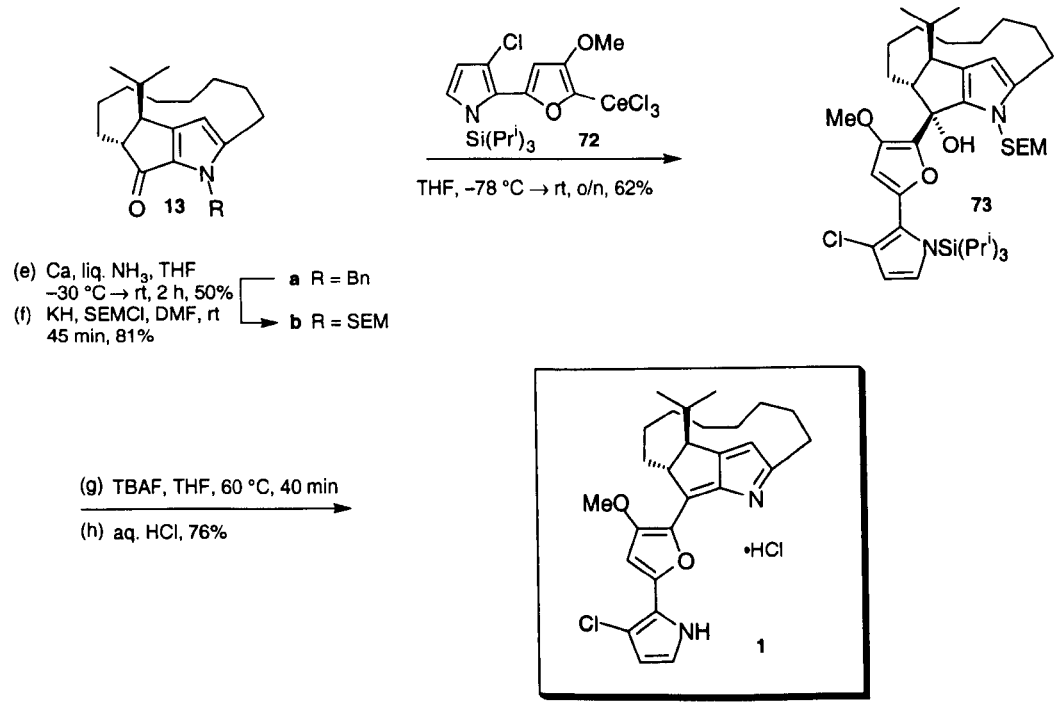
In their ensuing paper Fürstner et al. disclosed their approach to the *N*-protected heterocyclic moieties **18a** and **18b** (Scheme 9) and completion of the synthesis, the first and only total synthesis of Roseophilin **1** (Scheme 10).[24]



Scheme 9

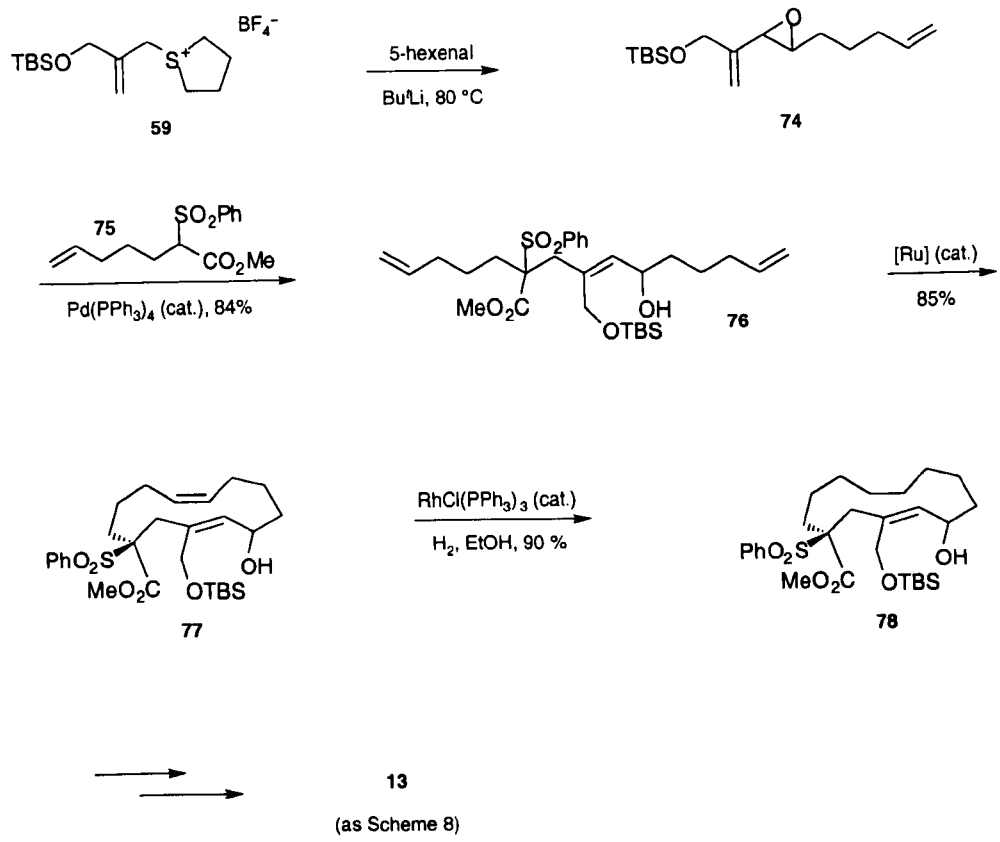
Fürstner had expected an acid-catalysed condensation of **18a** with the ketopyrrole derivative to form the desired azafulvene chromophore as suggested by Fuchs' model studies. However, these conditions failed in the total synthesis of Roseophilin itself since no reaction with the sterically encumbered ketone was observed, while the heterocyclic side chain decomposed over long reaction times or more forcing conditions. Fürstner's alternative was to generate the highly nucleophilic organocerium derivative **72** (Scheme 10) despite Terashima's failure to couple lithiated **18a**. Lithiation and transmetallation of *N*-TIPS protected **18b** gave exclusively the organocerium derivative **72** which coupled readily with the *N*-SEM protected macrotricyclic core **13b** to give **73**. No coupling between **72** and the potassium salt of **13** (R^2 = H) could be achieved. The enantiomeric

mixture of Roseophilin hydrochloride was seperated by chiral HPLC to provide samples of (+)- and (–)-**1** for further biological evaluation.



Scheme 10

Fürstner has recently published a second generation approach to Roseophilin, based on key macrocyclic intermediate **13**, which is concise and high-yielding but, most importantly, is flexible allowing access to a number of chromophore analogues.[25] The second approach retains the palladium-catalysed strategy but incorporates RCM to introduce the macrocycle (Scheme 11).



Scheme 11

Various analogues of **1** were synthesised by this method including deschlorodesmethoxyroseophilin **79** and the simplified targets **80-82** (Figure 2).

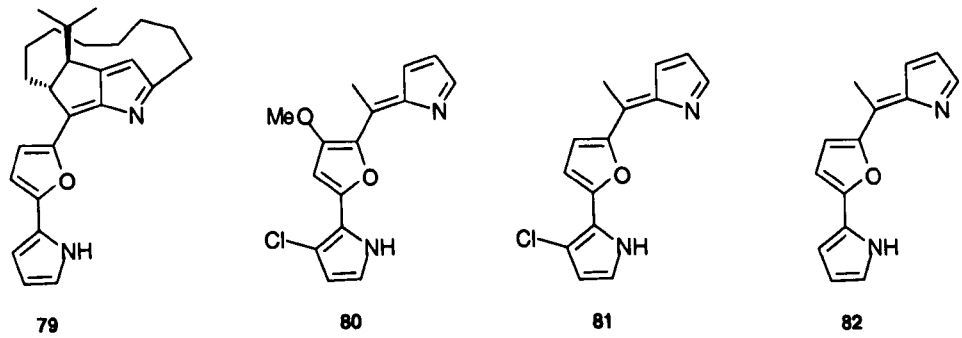
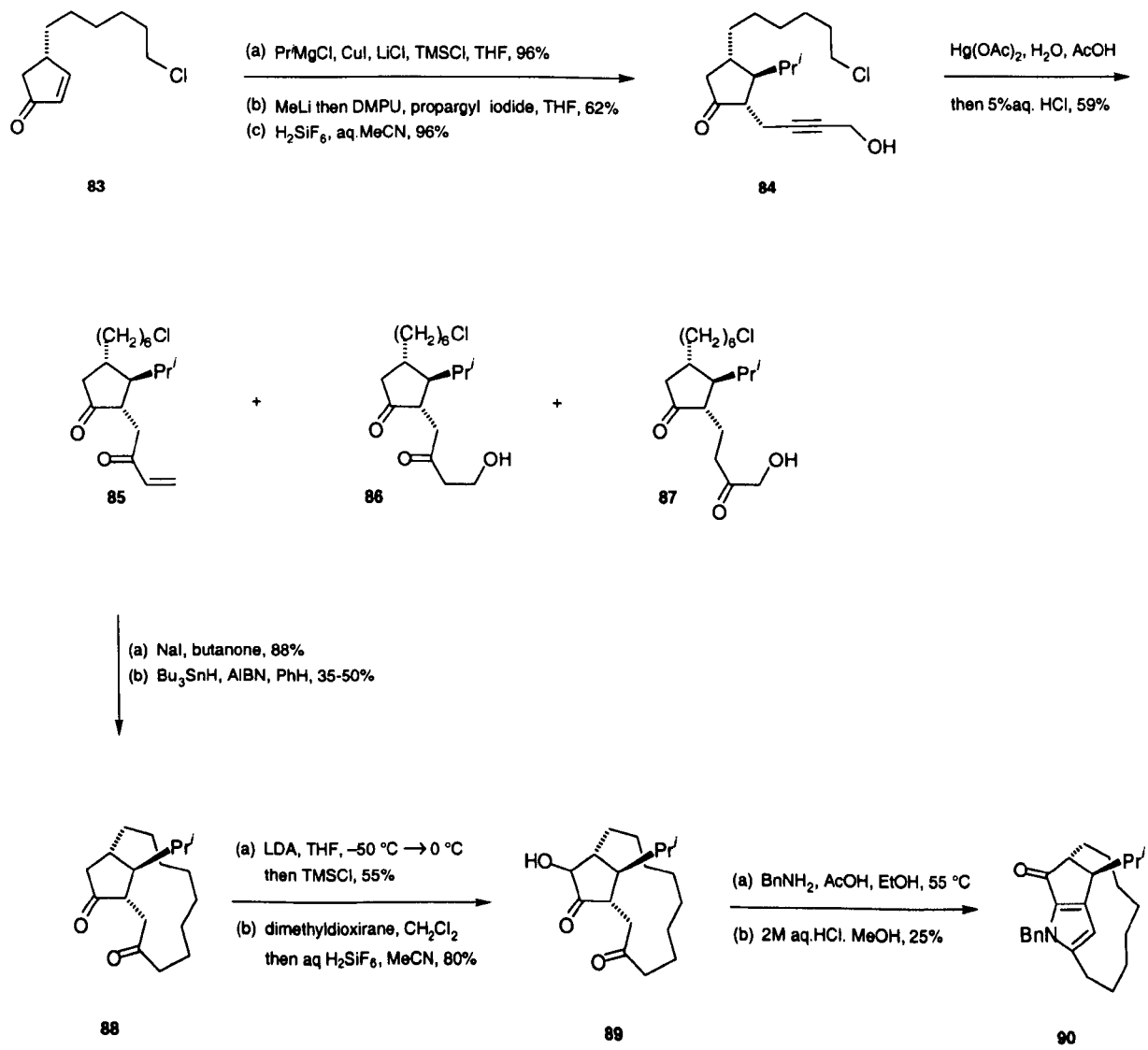


Figure 2

The most recently reported approach is that of Robertson et al. (Scheme 12).[26] Their strategy starts from the cyclopentenone derivative **83** and involves a radical macrocyclisation to adduct **88**. Selective monosilylation in the 5-membered ring with LDA

and chlorotrimethylsilane proved to be a challenging task. Only under equlibrating conditions was monosilylation achieved with a mixture (3-4 :1) of the kinetic enol ether and the undesired thermodynamic enol ether to give **89**. The pyrrole ring of **90** was formed *via* a Paal-Knorr synthesis in the final step with the presumed advantage that the energetic drive towards aromaticity would override the ring strain inherent in the formation of the tricyclic product. Pyrrole formation was accompanied by unexpected oxidation to afford **90**, the spectroscopic of which exactly matched that reported by Fürstner for his ketopyrrole.



Scheme 12

The syntheses of Roseophilin **1** described above are varied in their approach. Interestingly none of the routes are without problem, the unique structure of the macrotricyclic core has been proved to be a formidable challenge. Our approach to this intriguing natural product is discussed in the following chapters.

2.0 Proposed research

2.1 Approaches to Roseophilin

In our approach to the synthesis of Roseophilin we have considered three strategies to the macrocyclic core :

(a) From the macrocycle, a strategy in which the pyrrole and its [*b*]-fused cyclopentanone moiety is constructed onto the ready formed macrocycle, an approach already exploited by Fürstner et al.[24, 25] The advantage of this method is that the macrocycle may be formed without the strain inherent in the planar bicyclic system. The disadvantage is that there is little scope for stereoselectivity in the synthesis and characterisation of intermediates is complicated.

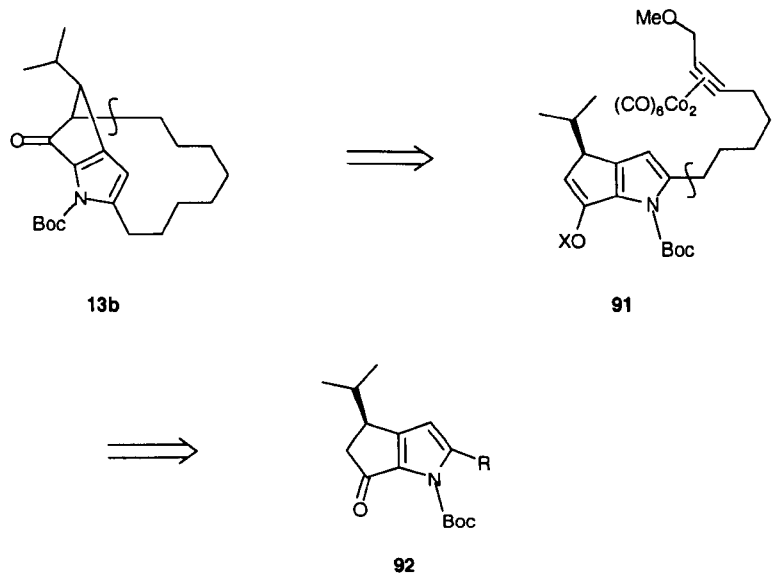
(b) From a cyclopentanone derivative. A strategy, which was used by Fuchs et al., has the advantage that cyclopentenones are cheap and readily available. The functionality inherent in the starting material provides a handle for derivitisation allowing swift access to fairly complex intermediates. This approach provides scope for the introduction of stereoselectivity, as demonstrated by Hiemstra et al. in their recent synthesis.[22] Another possibility is an asymmetric 1,4-conjugate addition to a cyclopentenone derivative.

(c) From a pyrrole derivative. The strategy reported by Terashima et al.[18] utilises the nucleophilic nature of the electron-rich pyrrole ring in order to construct the remaining rings. Pyrrole itself is a cheap and readily available starting material ; however, a disadvantage here is that pyrrole and its derivatives are readily oxidised in air

(characterised by the darkening of the compound) and undergo polymerisation in acidic conditions (characterised by the red colour).

Our proposed synthesis focuses on the macrocyclic core of Roseophilin **13b**, which may be disconnected as shown (Scheme 13) to give the structure **91**: the enolate of the bicyclic ketopyrrole; and an eight carbon side chain incorporating a cobalt-stabilised propargyl cation at the site of disconnection. The transformation from **91** to **13b** is possible by means of an intramolecular Nicholas reaction[27] (the coupling of a cobalt stabilised propargyl cation and a suitable nucleophile, see Chapter 3).

The Nicholas reaction is a high yielding process and is particularly useful in the synthesis of macrocycles, as demonstrated by Schreiber et al. in their preparations of highly strained substituted cylooctynes.[28] The dicobalt complexed alkyne is sterically demanding and there is ample precedent to suggest that the ring closure will be diastereoselective, *anti* to the isopropyl moiety.[29] The Nicholas reaction and the subsequent decomplexation proceed under mild conditions which renders the reaction suitable for inclusion in the final stages of a natural product synthesis. Removal of the resulting alkyne functionality by hydrogenation would then yield the nitrogen protected macrocyclic core **13b**.



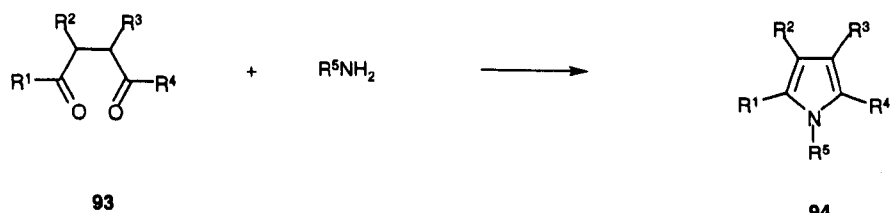
13b 91 92

Scheme 13

We chose to approach the pyrrole bicycloalkanone **92** from cyclopentenone and to construct the heterocycle onto this framework.

2.2 Pyrrole synthesis

There are many methods available for the synthesis of substituted pyrroles **94** and there are several reviews on the subject.[30-35] The most famous pyrrole synthesis is perhaps the Knorr-Paal synthesis from a 1,4-dicarbonyl presursor **93** (Scheme 14).[36-39]

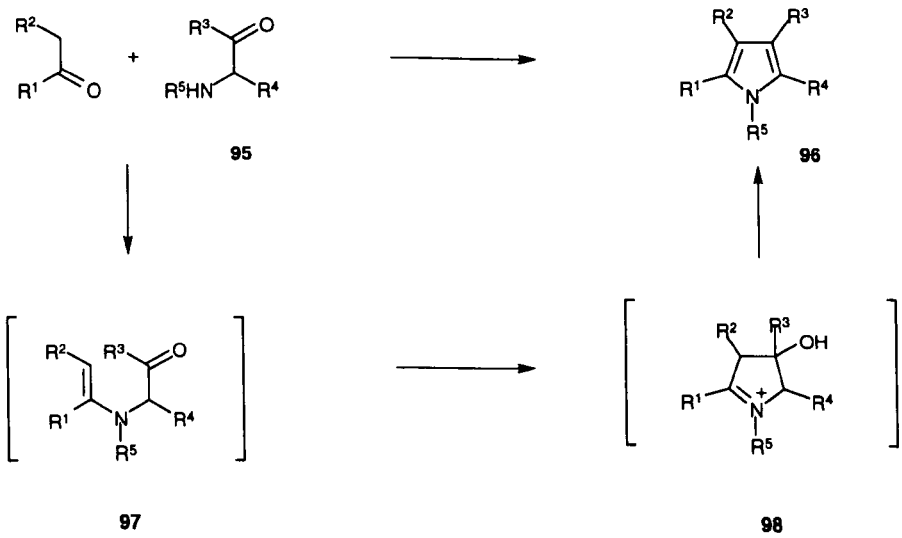


93 94

Scheme 14

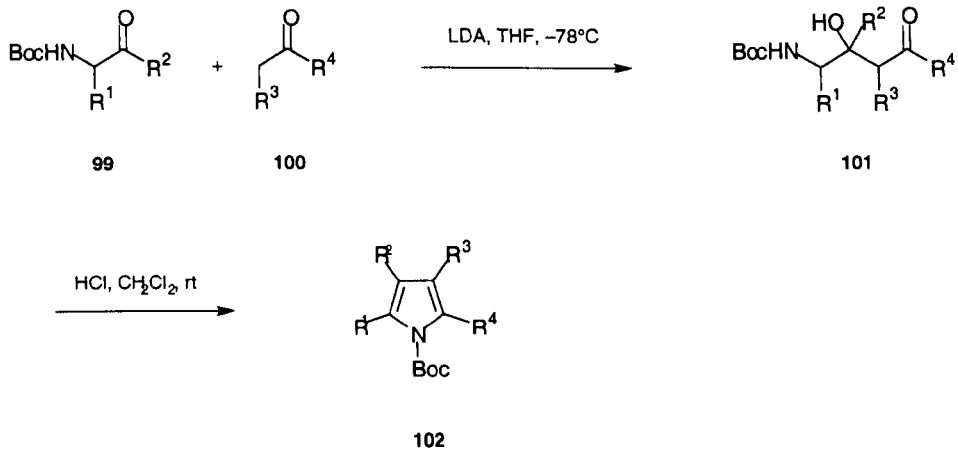
Sterically crowded *N*,2,5-trisubstituted pyrroles may be synthesised in good yields by an appropriate modification of the Knorr-Paal condensation.[40] For moderately sterically crowded compounds a water scavenging technique is used (azeotropic distillation of water with benzene) and for severely sterically crowded compounds a titanium(IV) chloride catalyst has been used.

Pyrroles may also be generated from amino carbonyl compounds **95**, the Knorr method (Scheme 15).[41-43] These condensations may involve enamine intermediates **97** and in some cases such species have been isolated.[44]



Scheme 15

The pyrrole synthesis we have in mind for the construction of the heterocyclic moiety of bicycloalkanone **92** is a novel method recently published by Cushman et al. (Scheme 16).[45]

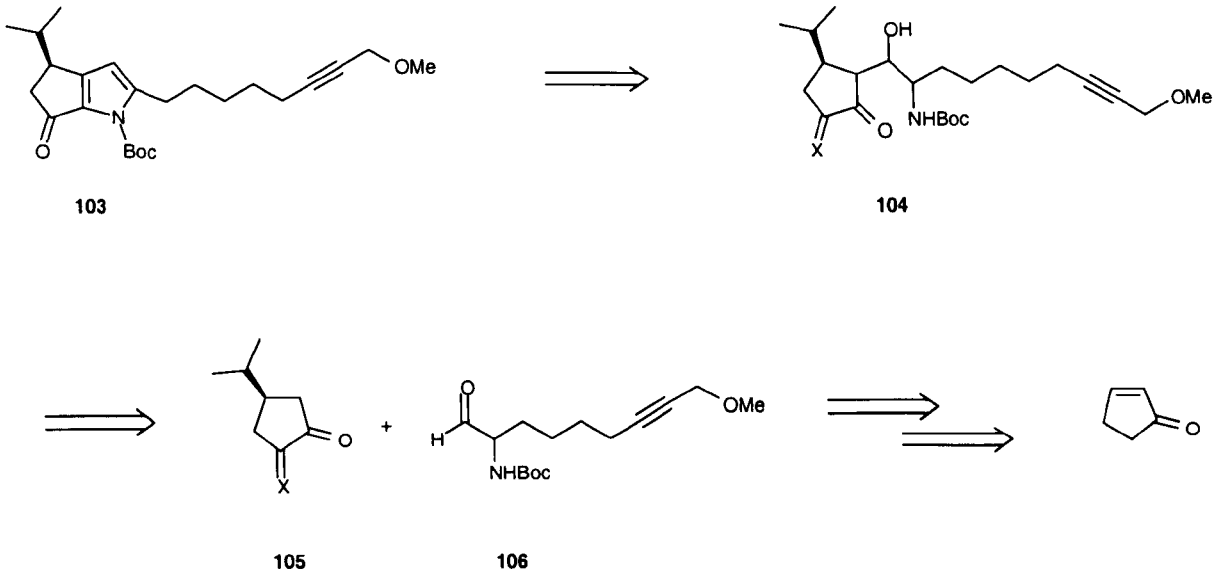


Scheme 16

Boc-α-amino aldehydes (**99**, R^2 = H) or ketones (**99**, $R^2 = CH_3$) are reacted with the lithium enolates derived from ketones **100** to afford, after protonation, aldol intermediates **101** which then cyclise to the desired pyrroles **102** under mild acidic conditions. Although this method is not ideal (reported yields are poor, 5% to 42% for the systems applied), the overall route is relatively short and has the advantage that the substituted pyrroles and fused pyrroles have been obtained from inexpensive and readily available starting materials.

2.3 Retrosynthetic analysis

Our approach to the pyrrole bicycloalkanone **92** is outlined below (Scheme 17). The aldol reaction, discussed previously, between the cyclopentanone derivative **105** (where X is a masked ketone moiety and the isopropyl unit is to be introduced *via* a 1,4-conjugate addition) and the appropriately substituted α-aminoaldehyde **106** allows access to adduct **104** which should undergo cyclisation and aromatisation to give the pyrrole **103** under acidic conditions.



Scheme 17

The strategy will initially be investigated with a model system. We have not, at this stage, considered how the masked ketone moiety X will be introduced, but its inclusion will be discussed in the ensuing chapters.

3.0 The Nicholas Reaction

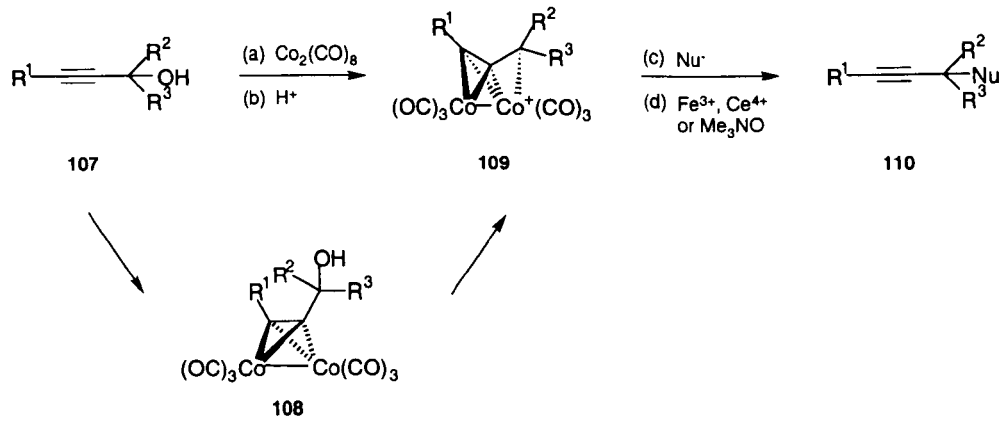
The dramatically enhanced stability of carbocations flanked by π-coordinated organic moieties is a phenomenon that sparked much interest and some controversy in the fledgling field of organotransition-metal chemistry.[46, 47] This effect is manifested in many ways:

(1) (Benzyl chloride)-$Cr(CO)_3$ undergoes hydrolysis 10^5 times faster that benzyl chloride itself.[48]

(2) The PK_{R^+} values (reflecting thermodynamic stabilities of carbocations) of α-ferrocenyl carbocations rival those of the remarkably stable aromatic cyclopropenium ions.[49]

(3) Several metal-stabilised carbocations are isolable as highly crystalline shelf-stable salts suitable for X-ray structure determination.[50, 51]

Propargylic cations were first shown to be stabilised by coordination to the dicobalt hexacarbonyl group **107** by Nicholas et al. who were investigating the use of the dicobalt hexacarbonyl unit as a protecting group for the C–C triple bond (Scheme 18).[52] Subsequently Nicholas et al. found that these complexes can serve as electrophilic propargyl synthons because of their reactivity to a wide variety of hetero- and carbon-centred nucleophiles.[27] Attack occurs exclusively at the propargylic carbon thus avoiding the allenic by-products which plague the reactions of classical propargyl electrophiles.[53] Although other attempts had been made to overcome the propargyl/allenyl problem e.g. using carbanions derived from 1-trialkylsilylpropyne,[54, 55] until the advent of the Nicholas reaction no successful method of broad generality was available.



Scheme 18

Although other mono- and polynuclear metal complexes of propargyl cations are known, including those flanked by α–$(C_4H_3)Fe(CO)_3$,[50] –$(C_5H_4)Cr(CO)_2NO$,[56] –$C[Co_3(CO)_9]$[57] and –$(RCC)M_2(CO)_4(C_2H_5)_2$ (M = Mo, W)[58] groups, it is the dinuclear complexes which have generated the most interest. While most of the interest in the above mentioned systems centres on the mode of stabilisation provided by the metal, the more reactive $Co_2(CO)_8$ complexes have provided a richer and more useful reaction chemistry.

3.1 Dinuclear (μ-propargylium) complexes

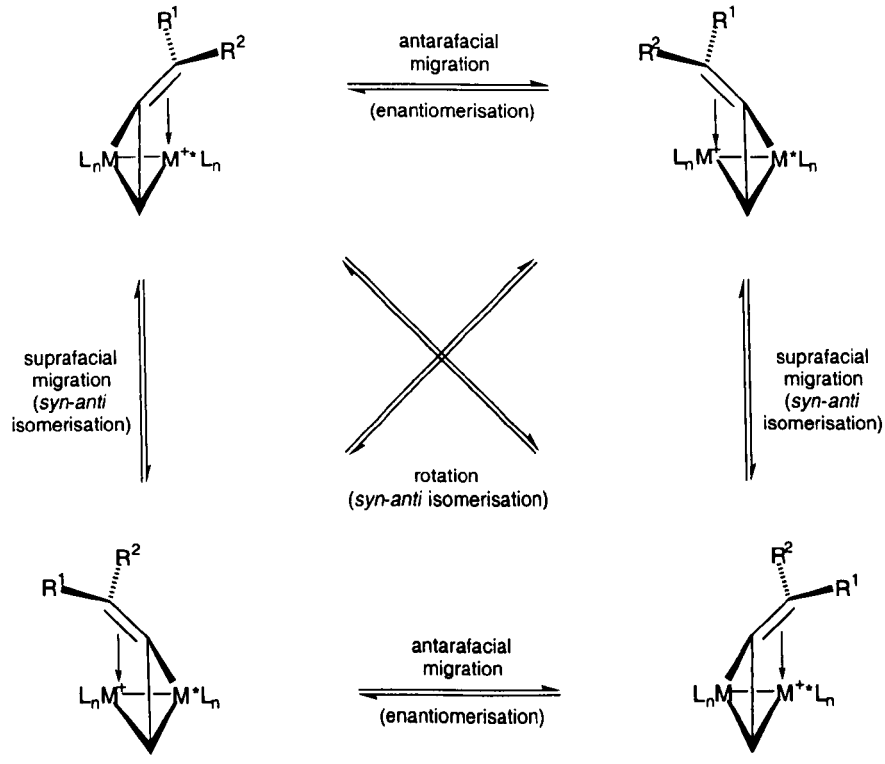
3.1.1 Preparation

The cationic cobalt complexes are obtained as dark red solids on protonation of the corresponding [(propargyl alcohol)$Co_2(CO)_6$] complexes[59] which, in turn, are derived from alkyne complexation with dicobalt octacarbonyl.[60] In the solid state the salts are stable in dry air for long periods and can be stored indefinitely at 0 °C under nitrogen; in humid air or wet solvents the salts hydrolyse rapidly back to the propargyl alcohol precursors.[61] The more hydrolytically stable $Co_2(CO)_5(PPh_3)$ derivatives have been prepared analagously.

Besides protonation of the precursor alcohols, treatment of the alcohols or corresponding ethers, acetates, acetals or aldehydes with Lewis acids has been increasingly used for *in situ* generation of the cations.[62]

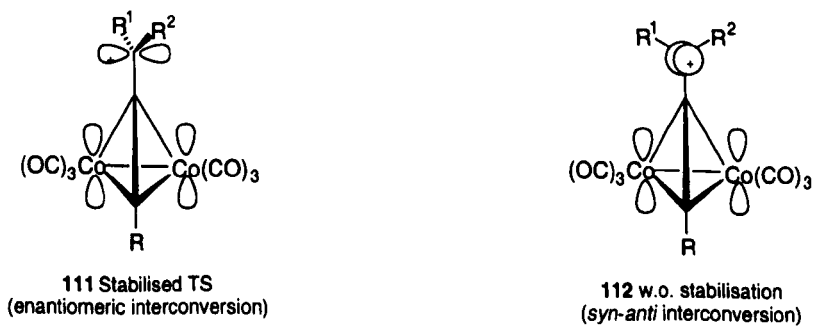
3.1.2 Structure

Experimental evidence has been presented that the Nicholas carbocation has fluxional properties that result in an interaction of the electron-deficient propargylic carbon with both cobalt tricarbonyl units resulting in effective charge delocalisation between the two metals atoms. IR data for the cation shows an increase in ν(CO) (40-60 cm^{-1}) relative to the neutral complexes[61] and significantly deshielded ^{13}C NMR resonances.[63] In a detailed variable-temperature NMR study Schreiber et al. identified two distinct fluxional process for the cobalt complexed cations,[64] a lower energy antarafacial migration of the alkylidene ligand from one metal to the other resulting in enantiomerisation and a higher energy *syn-anti* interconversion *via* either 180° rotation of the alkylidene ligand or a suprafacial migration (120° rotation with migration) (Scheme 19).



Scheme 19

The transition state of the enantiomerisation may resemble the upright structure **111** (Figure 3) which is capable of maintaining partial delocalisation of the carbon *p*-orbital into hybrid *d*-orbitals on the neighbouring cobalt atoms.[65, 66] The increased energetic requirements for achieving diastereoisomerisation (*syn-anti*-interconversion) may be associated with the requirement for achieving the rotated upright structure **112** which localises the charge on carbon.



111 Stabilised TS
(enantiomeric interconversion)

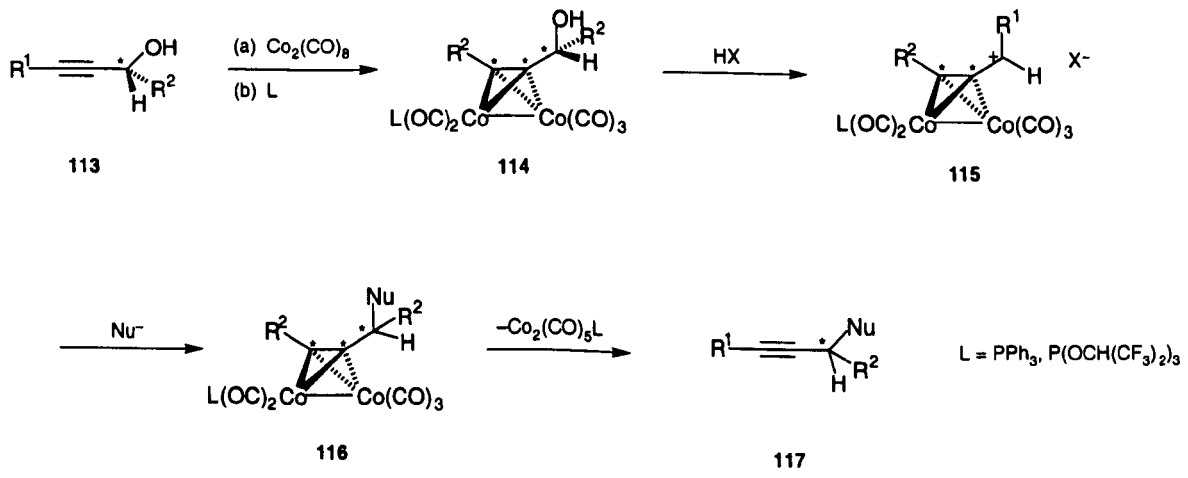
112 w.o. stabilisation
(*syn-anti* interconversion)

Figure 3

3.2 Stereochemistry

The dynamic behaviour of cobalt cations, especially secondary systems, has relevance to the stereochemistry of the propargylic substitution reaction. If the Lewis acid mediated alkylation reaction passes through a static cobalt cation then retention of stereochemistry would result and this is the normal outcome of alkylation reactions which proceed through the mononuclear metal-stabilised carbocation intermediates such as the benzylic substitution reaction of chromium arene tricarbonyl compexes.[67]

Nicholas et al. found that dicobalt complexes of chiral propargyl alcohols react with triphenylphosphine with a high degree of stereoselectivity to give diastereoisomers which exhibit considerable configurational stability (Scheme 20).[29] The chiral cluster cations (e.g. **115**, L = PR_3) are more conformationally rigid than the parent hexacarbonyl complexes ; however, they exhibit a greatly diminished electrophilicity which is reflected in their failure to react with mild, synthetically relevant carbon nucleophiles (e.g. silyl enol ethers and allyl silanes).[68]

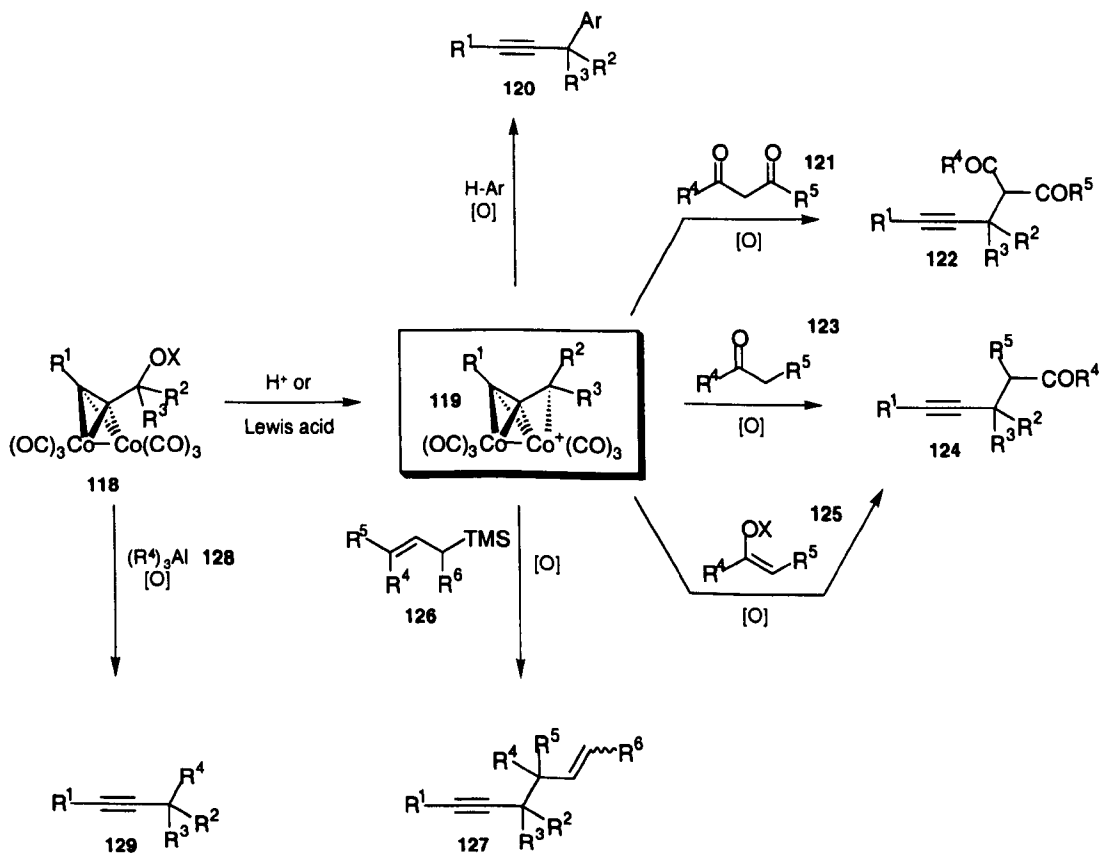


Scheme 20

In the search for more highly electrophilic complexes which maintain stereocontrol, incorporation of the relatively bulky, weakly σ-donating, strongly π-accepting $P(OCH(CF_3))_3$ ligand has been described by Nicholas et al.[69] These complexes coupled readily and diastereoselectively with mild carbon nucleophiles. Importantly when derived from enantioenriched propargyl alcohols, such chirality transfer reactions occur with significant diastereoselectivity and virtually complete enantioselectivity.

3.3 Nucleophiles

The reactions of the parent cationic cobalt complexes (isolated or generated *in situ*) have been explored with a wide variety of carbon-centred nucleophiles (Scheme 21).[53, 70]



Scheme 21

3.3.1 Aromatics

Electron-rich aromatic systems including anisole, phenol, *N*,*N*-dimethylaniline and 1,2,4-trimethoxybenzene react at room temperature or below with complexes to produce, after demetallation, good to excellent yields of C-propargylated aromatic derivatives **120** (Scheme 21).[71] Pauson et al. have demonstrated that heteroaromatic substrates including substituted furans and thiophenes may also be alkylated efficiently at the 2-position.[72] Such reactions have been successfully used in the synthesis of prostaglandin derivatives.

3.3.2 β-Dicarbonyls

β-Diketones and β-ketoesters **121** will react freely (–78 °C → 0 °C) *via* attack on the electron-rich double bond of the enol tautomer affording mono-C-propargylated products **122** in good yields.[73] This selectivity reflects the ready reversibility of the coupling reaction, C-alkylation being thermodynamically favoured. The steric bulk of the complex is noteworthy, more conventional alkylation reactions of β-dicarbonyls suffer from dialkylation, O-alkylation and allenic by-product formation.[74, 75]

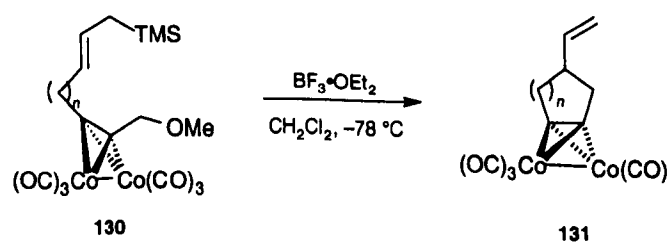
3.3.3 Ketones and enol derivatives

Nicholas et al. made the surprising discovery during an NMR experiment in d_6-acetone that acetone itself and other ketones with α-hydrogens **123** readily reacts with the cationic salts at temperatures <0 °C to give excellent yields of α-(propargyl)$Co_2(CO)_6$ derivatives **124**.[76]

The regioselectivity of these reactions with unsymmetrical ketones is striking: attack by the cationic complexes occurs exclusively (>95%) at the more substituted α–carbon. This observation coupled with the ready alkylation of β-dicarbonyls (above) is consistent with a mechanism involving attack by the electrophilic complexes on the more substituted (and more prevalent[77]) enol tautomer. In order to obtain useful rates and high yields without a large excess of ketone it is advantageous to use stoichiometric quantities of the corresponding enol acetates or trimethylsilyl enol ethers **125**. In this way it is possible to control the regioselectivity *via* the kinetic or thermodynamic enol derivative.

3.3.4 Allyl silanes

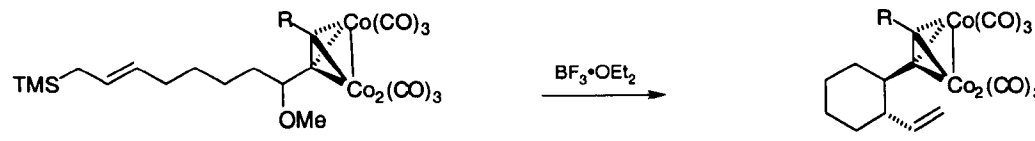
A final class of π-nucleophiles that couple efficiently with the propargyl complexes are allylsilanes **126**.[78] A reaction which provides a novel and regiocontrolled route to 1,5-enynes **127** (useful intermediates in terpenoid synthesis). As is characteristic of allyl silane/electrophile reactions, the new carbon-carbon bond is formed specifically γ to the silicon ; even quaternary centres can be generated in this way with little or no competing elimination. Schreiber et *al* have successfully developed an intramolecular variant of the reaction (Scheme 22).[28]



130 131

Scheme 22

The endocyclic version produces the novel cycloalkyne complexes **131** (n = 2-4). The existence of such strained cycloalkyne derivatives is made possible by the severely bent geometry of the coordinated alkynes **130**,[79, 80] which suggests a similar bending in the intermediate cationic complexes. An example of the exocyclic version proceeds with complete *anti* stereocontrol attesting once again to the powerful stereodirecting effect of the complex (Scheme 23).



132 **133**

Scheme 23

3.3.5 Organometallic nucleophiles

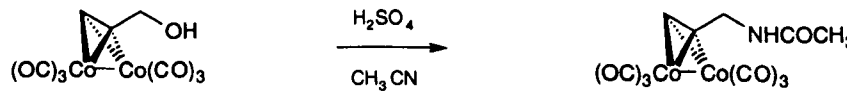
Nicholas et al. have screened several organometallic nucleophiles in order to develop a reliable propargyl-hydrocarbon coupling. Reaction of organoaluminium reagents, R_3Al **128**, with the complexes of propargyl acetates are the most effective system to date.[81] The reactions with trialkylaluminiums proceed rapidly even at –78 °C, giving moderate to excellent yields depending on the nature of the R group (Me>Et>Pr>>Bu^i). The methodology permits reasonably efficient generation of tertiary and quaternary propargyl centres **129** and hence is superior to classical acetylide/alkyl halide routes in such cases. The facility of such reactions is ascribable to the special ability of the aluminium reagents to function as Lewis acids[82] coupled with the ability of the organocobalt unit to release electron density to the developing carbcationic centre.

3.3.6 Miscellaneous nucleophiles

Several non-carbon nucleophiles have been combined with the cationic cobalt complexes and perhaps the most important among such nucleophiles is the hydride ion.[83] Nicholas et al found that tertiary propargyl alcohols could be converted to the corresponding secondary alkyl acetylenes *via* treatment of their dicobalt complexes with $NaBH_4$-TFA followed by demetallation in a one-pot sequence. A method which offers an attractive alternative to the direct acetylide-*sec*-alkyl halide coupling which is particularly inefficient.[84]

Oxygen-centered nucleophiles (OH^-, RO^- from H_2O and ROH) have been used extensively by Smit et al. to 'trap' the cations generated by addition of electrophiles to 1,3-enyne cobalt derivatives.[85, 86]

An interesting albeit isolated and unoptimised example of *N*-propargylation by the dicobalt stabilised cations comes from their inclusion in the Ritter reaction with acetonitrile (Scheme 24).[87] This reaction could, in general, afford a practical route to propargyl amines and amides which have important use as monoamine oxidase inhibitors and sedatives.[88]

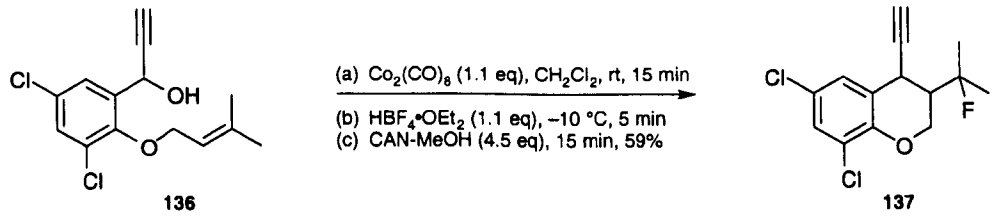


134 135

Scheme 24

3.4 The intramolecular Nicholas reaction

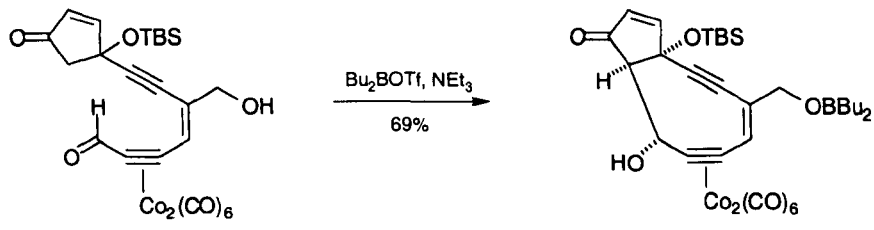
The intramolecular Nicholas reaction is a powerful tool in natural product synthesis. Diastereoselectivity is a key issue in the intramolecular alkylations as the steric bulk of the dicobalt complex forces its approach *anti-* to any other substituents on the forming ring. An aspect exploited by Tyrell et al. in their one-pot diastereoselective synthesis of benzopyrans **137** (Scheme 25),[89] is the first reported Nicholas reaction with a trisubstituted alkene **136**. The reaction proceeds *via* two successive cations, intramolecular cyclisation on the propargyl cation takes place to afford a second cation which is quenched by a fluoride ion to give **137**.



Scheme 25

Another important issue in the intramolecular alkylations is the exceptional reactivity of the dicobalt stabilised cations towards nucleophiles, facilitating the formation of macrocycles and highly strained rings. The 'superelectrophilicity' is exemplified in the preparation of cyclooctynes.[28] The formation of 8-membered rings by direct cyclisation of acyclic precursors is often a low-yielding process, primarily as a result of unfavourable torsional strain and transannular interactions engendered in the cyclisation process. However, low-temperature treatment of acyclic cationic cobalt acetylene complexes with Lewis acid has yielded, by intramolecular cyclisation, substituted cobalt-complexed cycloctynes in >90% yields.[90]

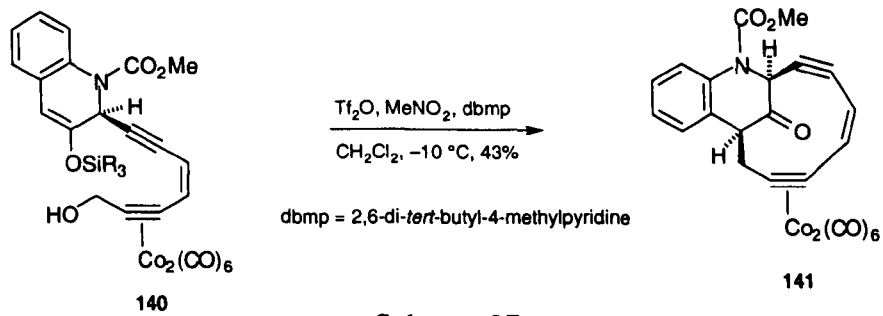
Intramolecular Nicholas reactions have found wide application in approaches to the synthesis of the conformationally strained enediyne anticancer antibiotics. Magnus et al. have explored the synthesis of the neocarzinostatin chromophore (Scheme 30).[91]



138 139

Scheme 26

Magnus et al. also reported the synthesis of the core tetrahydroquinoline enediyne structure of dynemicin using intramolecular silyl enol ether alkylation (Scheme 27).[92]

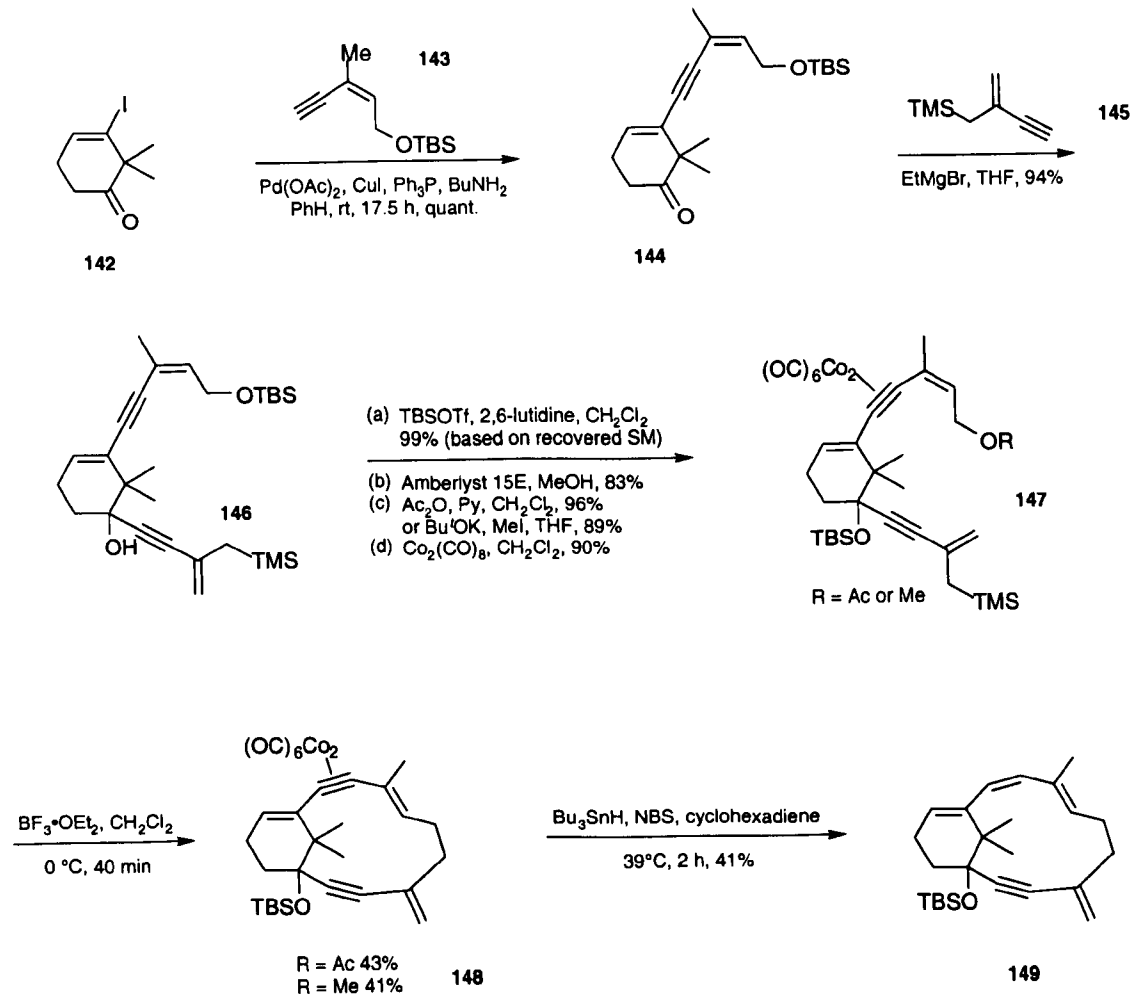


140 141

Scheme 27

Isobe et al. utilised a modification of the intramolecular Nicholas reaction in their approach to the recently isolated bicyclic taxoid diterpoids which have been proposed as the biosynthetic precursors of the taxanes (Scheme 28).[93] In their approach the acetylene cobalt complex serves two purposes: firstly the stabilisation of the conjugated allyl cation (generated *in situ* from **147**); and secondly its significant steric bulk is exploited in macrocyclisation *via* the Thorpe-Ingold effect, bringing the reactive sites closer together. The highly strained 12-membered ring of **148** was thus constructed in reasonable yield. Conventional oxidative decomplexation of **148** could not be achieved, presumably due to

the increased ring size generated by the free acetylene. Reductive decomplexation using NBS as a radical initiator achieved the *cis* double bond and the desired diterpene taxoid skeleton **149**.

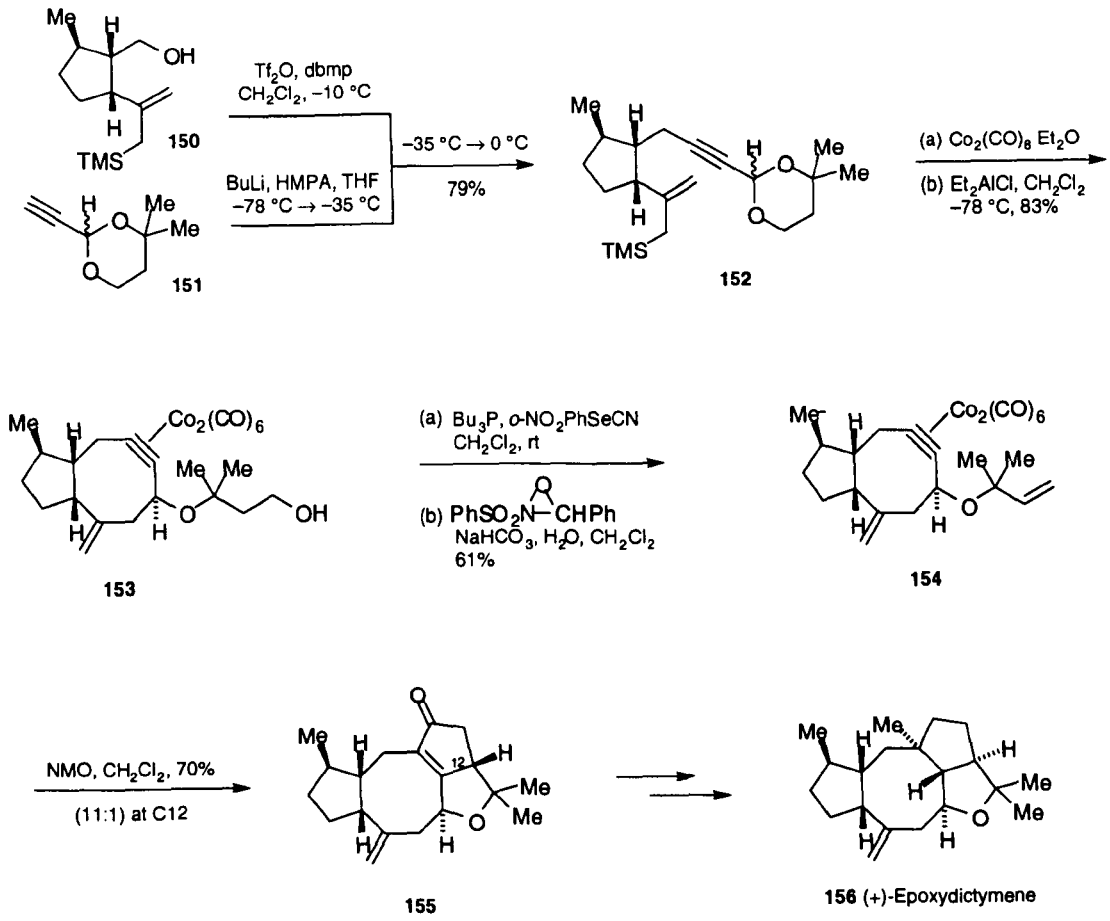


Scheme 28

3.4.1 Tandem cobalt-promoted alkylation/cyclisation

The abililty of the dicobalt acetylenic complex to stabilise adjacent cationic centres and to promote (2+2+2) cyclisations with olefins (Pauson-Khand reaction) have been cleverly combined to provide a powerful annulation methodology for constructing complex

cyclopentenoid derivatives. Schreiber et al exploited the methodology in their approach to (+)-Epoxydictymene (Scheme 29) achieving high yields in both the key cyclisations.[90]



Scheme 29

3.5 Summary

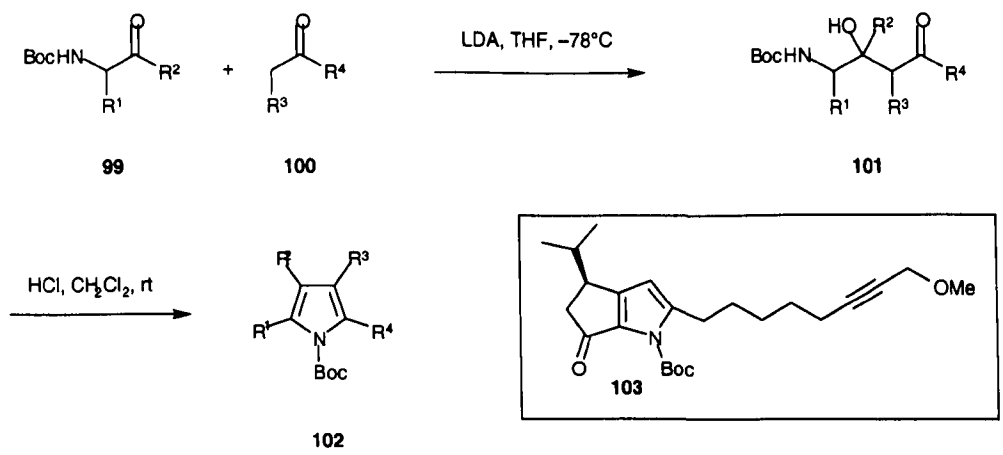
The Nicholas reaction involving stabilisation of an adjacent cationic centre by a dicobalt complexed acetylene, and its ready coupling with a wide variety of nucleophiles, is a powerful tool in natural product synthesis. The potent reactivity of the propargyl cation towards nucleophiles makes the methodology of prime importance in the synthesis of macrocycles and highly strained structures. The cobalt complexes are easy to prepare and

although moisture sensitive, may be isolated and stored in dry air for long periods. The more reactive cationic complexes may be generated *in situ* with protic or Lewis acids. The reaction is technically simple, requiring only mild nucleophiles, and tends to be high yielding with a high degree of diastereospecificity derived from the steric bulk of the complexed acetylene.

4.0 First approach to the bicycloalkanone 103

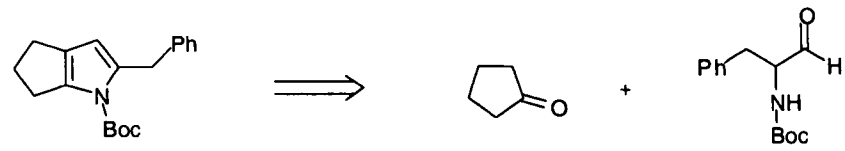
4.1 The Cushman aldol approach

There are many methods for the synthesis of substituted pyrroles and fused pyrroles such as **103**. However, a new pyrrole synthesis recently published by Cushman et al.[45] (Scheme 30), is an encouraging starting point for the synthesis of the fused pyrrole ring system of **103**.



Scheme 30

Studies towards the construction of the bicycloalkanone **103** began on a model system **157**, devoid of the bulky isopropyl group and the ketone functionality. Incorporating the α-benzyl substituent on the pyrrole moiety imparted UV absorbtiuits making it easier to follow the reaction by TLC (Scheme 31).

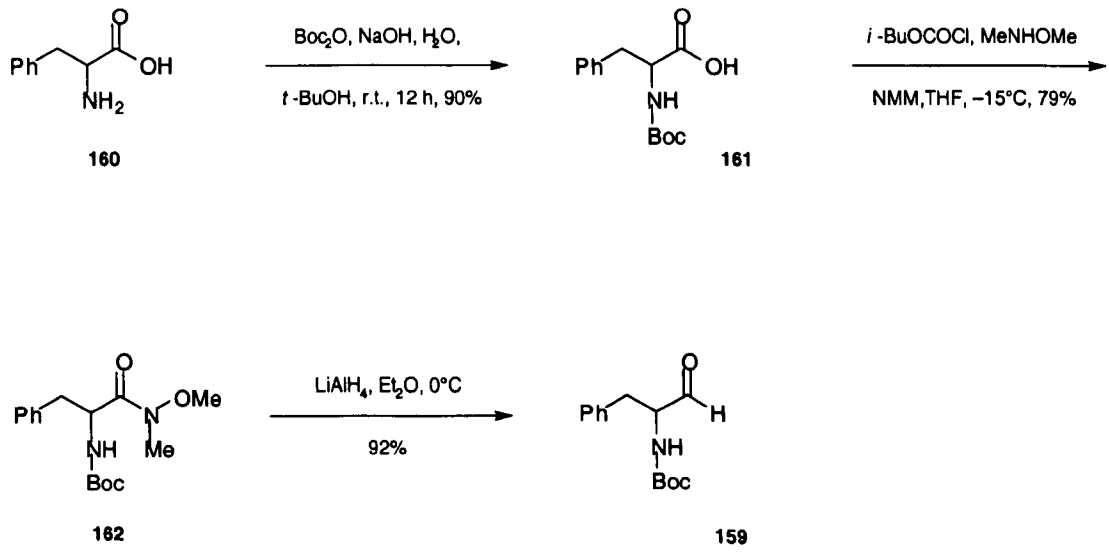


157 158 159

Scheme 31

4.1.1 Synthesis of Boc-DL-phenylalanal 159

The first step in the synthesis of **157** was the formation of Boc-DL-phenylalanal **159** from the α-amino acid, DL-phenylalanine **160** (Scheme 32).



160 161 162 159

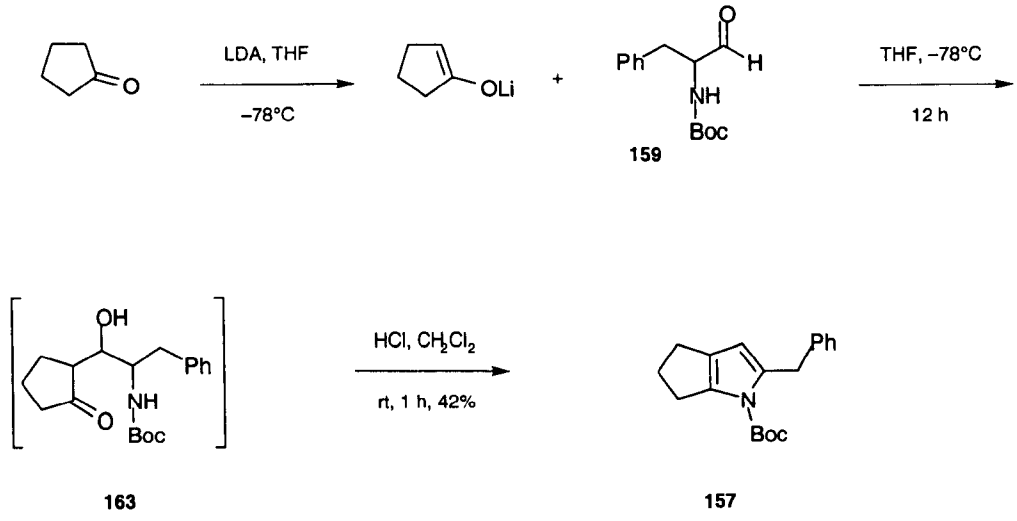
Scheme 32

As the chirality of the α-amino aldehyde is of no consequence, it is lost in the formation of the fused pyrrole, a racemic mixture of the amino acid was used as the starting material and **159** was prepared in three steps, in a 65% yield. Boc-amino protection of the crystalline α-amino acid **160** was achieved under Schotlen-Baumann conditions, according

to a literature procedure, in 90% yield.[94] The formation of the Weinreb amide intermediate **161** from Boc-α-amino acids used by Cushman, and indeed used widely in the literature, is carried out in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) and N,O-dimethylhydroxylamine hydrochloride. This method has the disadvantage that hexamethylphosphoric triamide (HMPA), a cancer suspect agent, is produced as a by product and so an alternative method utilising isobutyl chloroformate, according to a literature communication,[95] was employed to give **162** as a crystalline solid in 79% yield. Subsequent reduction of **162** to the crystalline α-amino aldehyde **159** was acheived with lithium aluminium hydride in 92% yield.

4.1.2 Aldol reaction

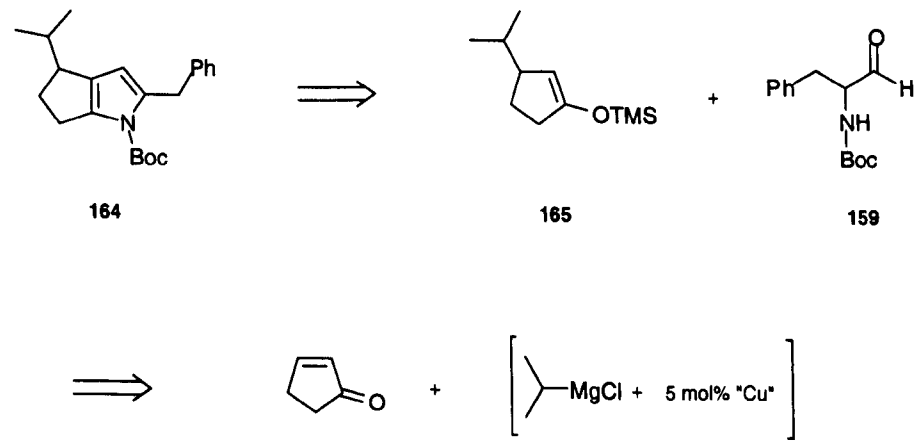
Initial attempts to form the fused pyrrole system **157** (Scheme 33) yielded the desired compound in two steps from cyclopentanone and Boc-DL-phenylalanal **159**, in 18% yield as a colourless oil, which decomposed slowly in air to a give brown residue. Efforts to optimise the reaction acheived a maximum 42% yield over the two steps. The problem lies in the first step, which affords low yields of the diastereomeric aldol product **163** with several products apparent by TLC. The aldol product was isolated as a mixture of both diastereoisomers and rotamers and due to the inherent difficulties in characterisation was used immediately in the next step. Separation of the by products by flash column chromatography yielded several cylopentanone derivatives originating from self condensation with the lithium enolate. The aldehyde **159** was also recovered in part. Cyclisation of the aldol product **163** to the fused pyrrole **157** was achieved in quantitative yield. Despite several attempts to prevent homocondensation by slow addition of cyclopentenone to the organolithium the yield could not be improved beyond 42%.



Scheme 33

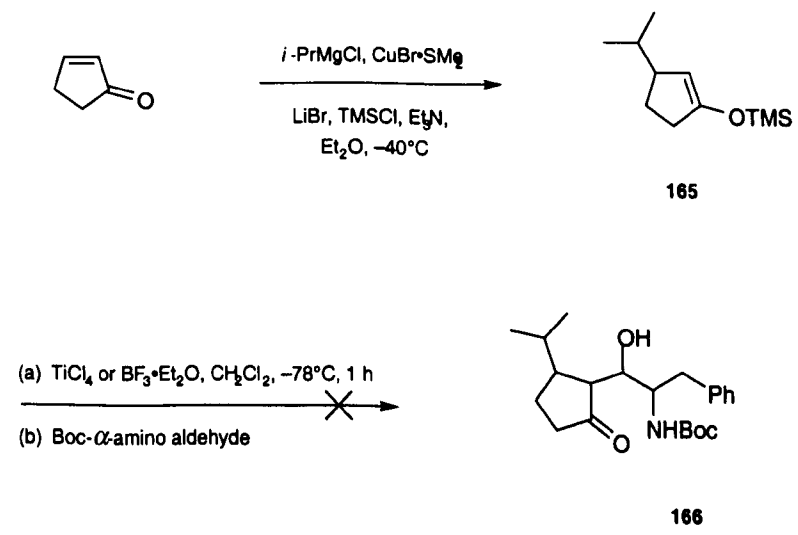
4.2 Mukaiyama aldol approach

The problems encountered in the formation of the lithium enolate from cyclopentanone prompted an alternative approach to the aldol product: a Mukaiyama aldol reaction[96] between the enol silane **165** (Scheme 34) and **159**.



Scheme 34

It was anticipated that the enol ether **165** could be formed regiospecifically from a copper-mediated, chlorotrimethylsilane-accelerated, 1,4-addition of isopropylmagnesium chloride, which would trap the enol silane in one synthetic step.[97] Cyclisation of the aldol product, which may occur under the acidic conditions of the Mukaiyama reaction, would then afford **164** in a one pot reaction. Formation of **165**, however, was not straightforward. Attempts at synthesis on a small scale (1.0 mmol) proved problematic due to the lability of the product; desilylation to the corresponding ketone occurs rapidly in the presence of moisture. Although anhydrous reaction conditions and base washed glassware was used, synthesis of **165** on a small scale resulted in a 1:1 mixture of the ketone to the silyl enol ether, as shown by NMR. A larger scale reaction (10.0 mmol) yielded the desired product **165** as a yellow oil, which was pure by NMR standard. However attempts at further purification of **165** by distillation, including flash distillation techniques, resulted in partial desilylation to a 3:1 mixture of the ketone to the enol silane. **165**, which is stable for several days when stored under nitrogen at –30°C, was attained in 96% yield (Scheme 35), and was used without purification in the next step.



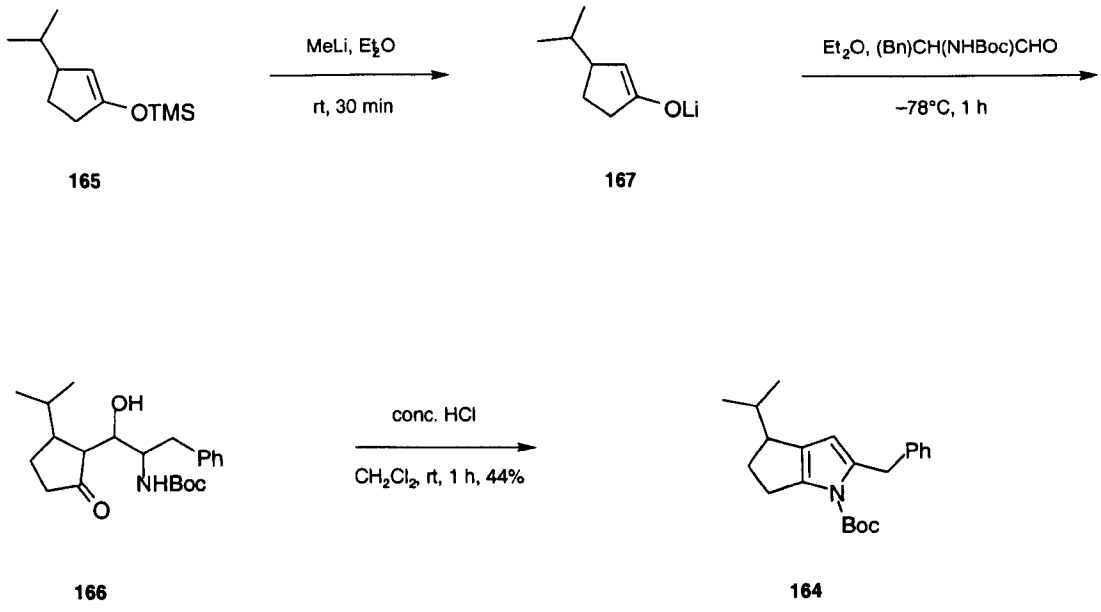
Scheme 35

The Mukaiyama aldol reaction, carried out in the prescence of two equivalents of the aldehyde **159** and three equivalents of Lewis acid, proved unsuccessful and neither the desired aldol product **166** nor the fused pyrrole **164** were isolated. Several products were apparent by TLC, however flash column chromatography did not yield the desired product. Although the aldehyde **159** was stable to the Lewis acid, it was not recovered from the reaction mixture. Thinking that it may be possible that the desired compound was present but hidden in an inseparable mixture of cycloalkanones, the reaction was carried out firstly on a larger scale, in an effort to ameliorate the isolation of the desired product; secondly, with just one equivalent of the enol silane **165**, an attempt to reduce homocondensation of excess starting material and simplify the TLC; and thirdly, with variation in the number of equivalents of Lewis acid, bearing in mind that unlike common aldehyde substrates, the *N*-Boc-α-amino aldehyde contains four heteroatoms all of which may coordinate to the Lewis acid. However, the desired product was not apparent by TLC and flash column chromatography again afforded only products of homocondensation. Variation in Lewis acid did not yield the desired product. Finally the reaction was carried out in the presence of molecular sieves according to a recent literature precendent in which α-amino aldehydes undergo aldol reaction in high yield in the presence of simple silyl ketene acetals and molecular sieves.[98] Again no positive result was gained and the reaction was abandoned.

4.3 Progression of the Cushman pyrrole synthesis

It has been established that the crossed aldol reaction of the lithium enolate of cyclopentanone and amino aldehyde **159** is successful, albeit impeded by unwanted homocondensation reactions. It is therefore reasonable to assume that the lithium enolate **167**, which may be formed regioselectively and without unwanted homocondensation

according to a procedure by House et al.,[99] (Scheme 36) would undergo aldol reaction with **159** to yield, after aromatisation, the desired isopropyl substituted bicyclic pyrrole **164**.



Scheme 36

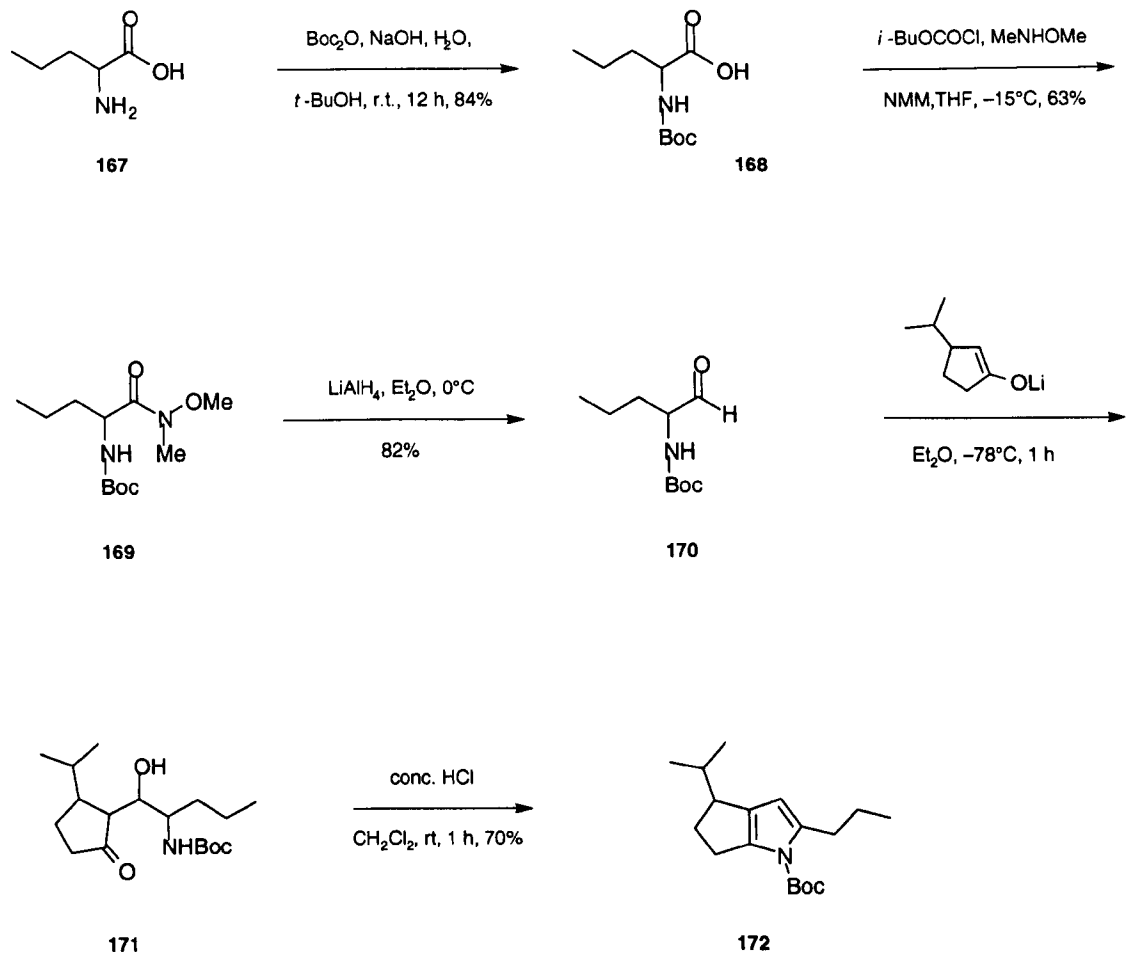
Initial attempts at the aldol reaction following the original publication by Cushman, in which the reaction was allowed to proceed overnight as the temperature rose from –78°C to room temperature, were disappointing. Several products were isolated by chromatography, all the result of unwanted side reactions. The desired compound **166** was not present. However on successive attempts, when the experiment was followed rigorously by TLC, it became apparent that the aldol reaction goes to completion after just one hour. The desired pyrrole **164** was formed in 44% yield over three steps from **165**. With an adequate model system for the synthesis of the isopropyl substituted [*b*]-fused bicycloalkanone in hand we turned our attention to the introduction of the ketone functionality.

4.3.1 Introduction of the carbonyl moiety

4.3.1.1 Directed metallation approach

We considered two approaches to the introduction of the ketone functionality at this stage: firstly, introduction of the carbonyl substituent after formation of the pyrrole, making use of the functionality within the fused pyrrole system itself; and secondly, to construct the pyrrole from the correctly substituted cyclopentanone derivative. We believed that a pseudo benzylic oxidation would not be possible in this case, assuming the pyrrole moiety is capable of behaving as a pseudo benzylic compound, there are three sites on which oxidation may occur. In our opinion the site favoured would be the undesired tertiary centre, α to the isopropyl unit.

The pyrrole ring is aromatic and electron rich and protons α to this ring can therefore be considered to be pseudo benzylic by nature. If a regioselective metallation of the pyrrole system could be effected then the ketone functionality could be introduced directly by use of an electrophilic oxygen species, such as a Franklin-Davis oxaziridine. However **164** is not a suitable substrate for metallation due to the benzyl substituent at the 2 position, which creates a labile proton at the diaryl substituted centre, so an alternative **172** was constructed from DL-Norvalinal **167** in 70% yield (Scheme 37).



Scheme 37

There are three pseudo benzylic positions on **172** (Figure 4) which may be labile to metallation. It was expected that protons H^1 and H^2 may be more labile than H^3 due to ring strain, and that abstraction of H^2 may be favoured over H^1 with use of a Boc-directed metallation, known formally as the **C**omplex **I**nduced **P**roximity **E**ffect (**CIPE**).

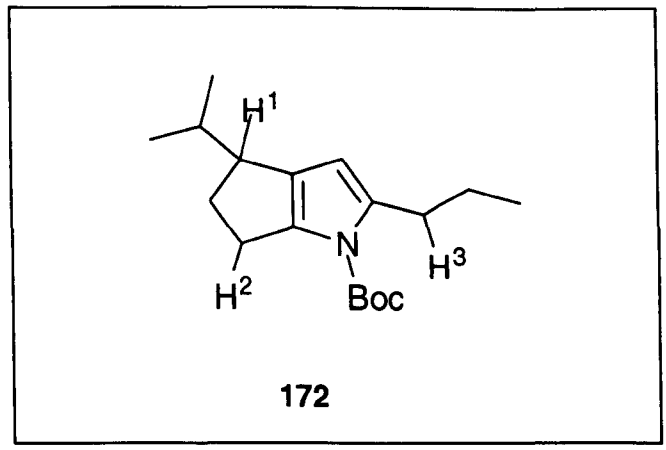
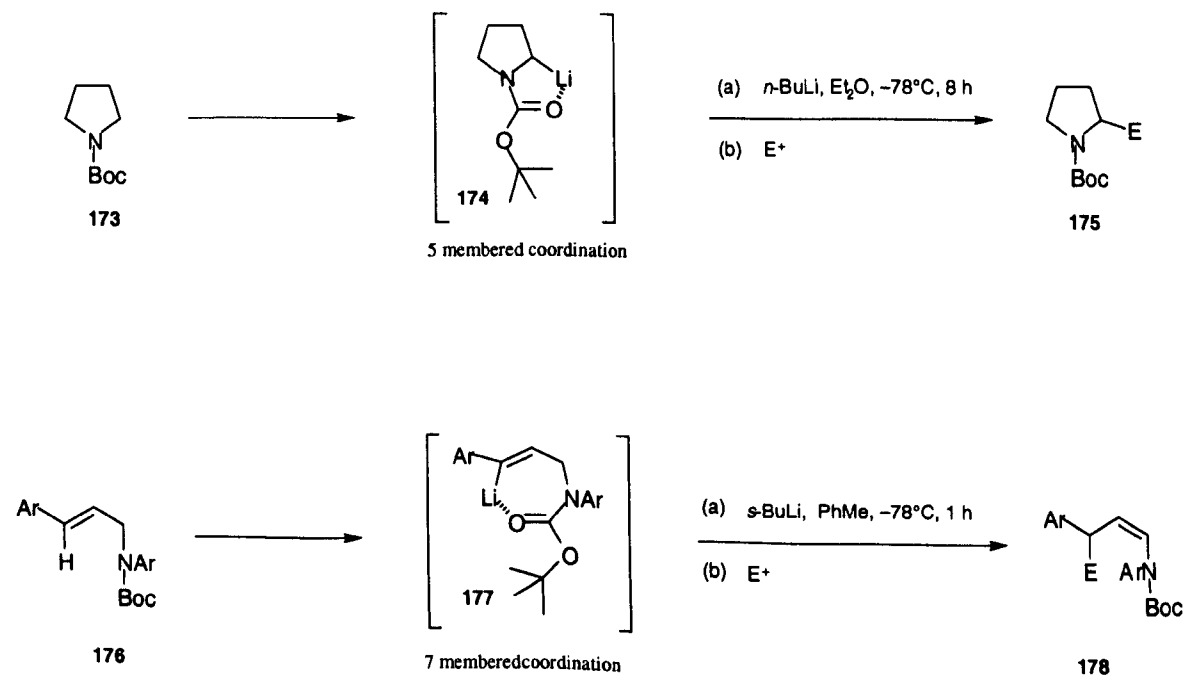


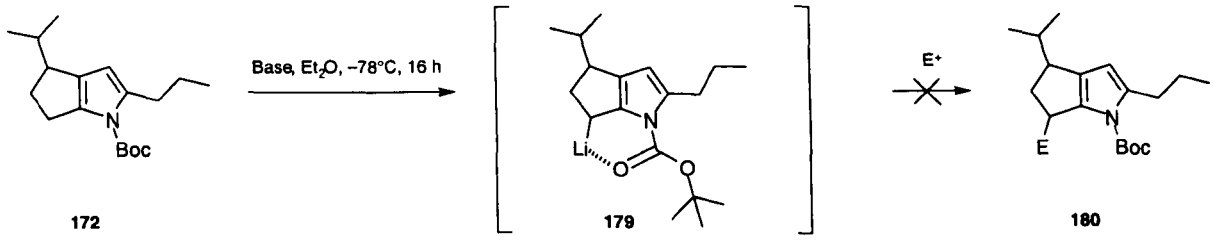
Figure 4

Such metallations have been carried out on a variety of substrates, where regioselectivity is controlled by a cyclic intermediate generated by coordination of an amide oxygen to the metal centre. Scheme 38 gives two examples, the first by Beak at al. is a 5-membered coordination compound **174**[100] and the second, a 7-membered coordination compound **177**[101] ring transition states have been reported (Scheme 38).



Scheme 38

In our case metallation would lead to a 6 membered coordination compound **179**, which although suffering from ring strain imparted from the [*b*]-fused 5 membered rings, was not predicted to be unfavourable (Scheme 39). Metallation was attempted with LDA, *n*-BuLi, *s*-BuLi and *t*-BuLi, both with and without the presence of TMEDA, but in all cases no deuteration was observed after a D_2O quench. Likewise derivitisation with simple electrophiles e.g. iodomethane, benzaldehyde was not possible. In the presence of TMEDA the Boc protecting group was partially cleaved.

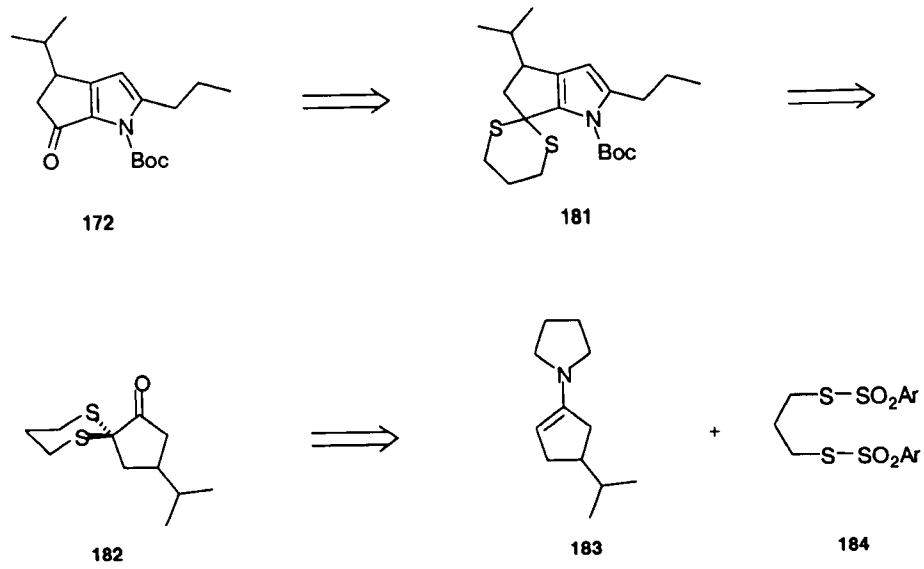


172 179 180

Scheme 39

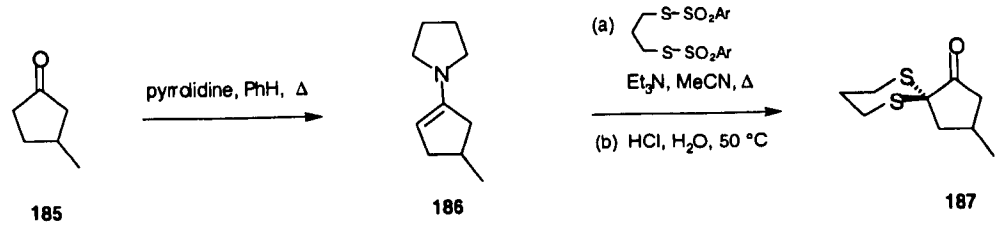
4.3.1.2 Incorporation of a dithioacetal as a masked ketone functionality

Construction of the pyrrole with the ketone functionality in place was next attempted by the incorporation of a dithioacetal alpha to the existing ketone, a strategy which not only introduced a protected carbonyl substituent but also ensured formation of the desired thermodynamic enolate (Scheme 40).



Scheme 40

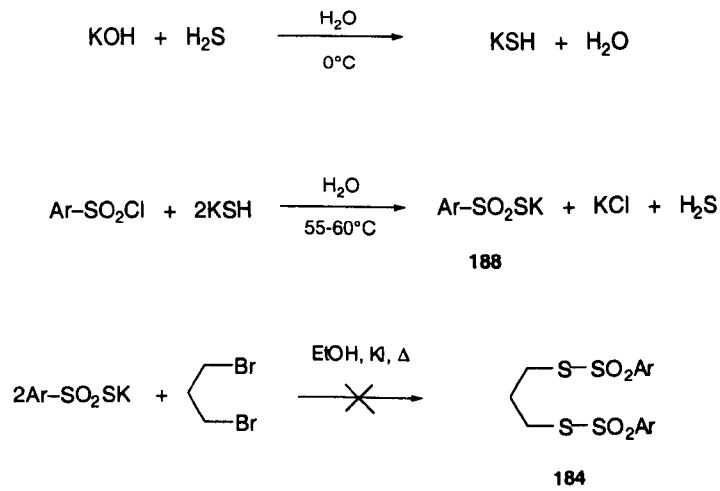
Initial work in this area was carried out by R.B.Woodward et al.[102] and application of this method to **187** is outlined below (Scheme 41).



Scheme 41

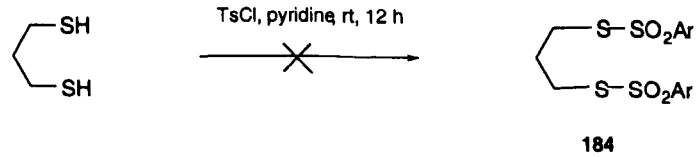
The requisite dithiotosylate **184** has been little used in the 26 years since the initial publication[103] due to the difficulties involved in its preparation. The method published in Organic Syntheses[104] (Scheme 42) reported low yields and warned of the problem of potassium *p*-toluene sulfinate formation, the presence of which cleaves the acid (and base) labile sulfur-sulfur bond. The synthesis of potassium thiotosylate **188**, was attempted several times: the first few attempts yielding potassium *p*-toluenesulfinate (identifiable by melting point); later attempts gave the correct melting point but did not give the

dithiotosylate **184** when refluxed with dibromopropane. Similar failure attended the use of commercially available potassium thiotosylate. The problem at this stage is again the lability of the sulfur-sulfur bond which is readily cleaved on formation of the dithiotosylate to give a polymeric mixture of alkyl thiotosylates. An alternative route route to **184** was required.



Scheme 42

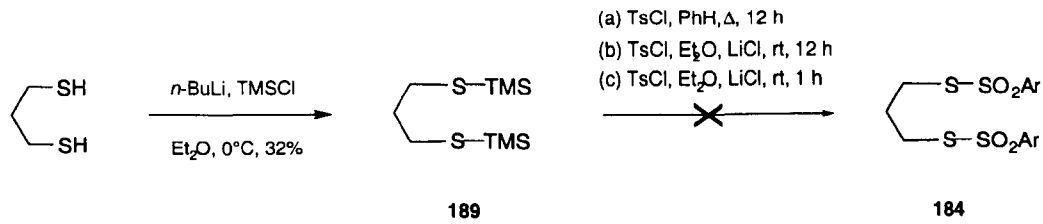
An approach to **184** from propanedithiol according to a literature publication (Scheme 43),[105] afforded a very low yield of the desired product (<5% by NMR) in an inseparable mixture of polymers.



Scheme 43

Another route *via* the bistrimethylsilylthiol ether **189** purported to make use of the weak sulfur-silicon bond. It was expected that the trimethylsilyl group would cleave in the presence of chloride ions, facilitating an S_N2 reaction with tosyl chloride, to yield **184**

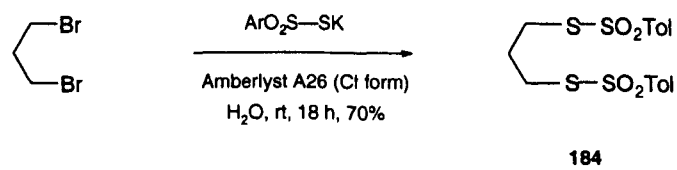
(Scheme 44). The bis-trimethylsilylthiol ether **189** was prepared according to a literature procedure[106] and the reaction was initially carried out in toluene at reflux yielding only products of polymerisation. In an effort to avoid over reaction the experiment was repeated at rt with a catalytic amount of lithium chloride, only to give the same disappointing results as before.



189 **184**

Scheme 44

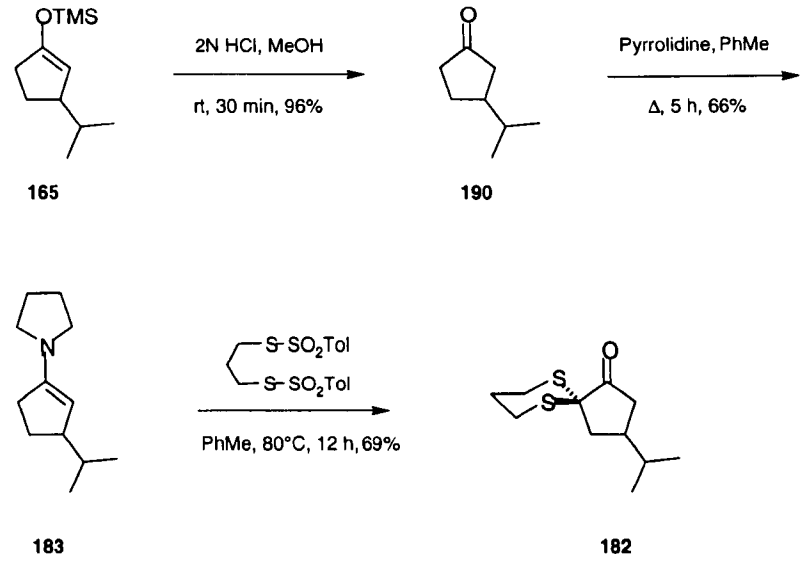
Takano [107] reported a method based on Woodward's synthesis using Amberlyst resin as a solid support on which to construct the thiotosylates in order to prevent polymerisation. Trimethylene dithiotosylate was assembled accordingly, in 70% yield, from 1,3-dibromopropane (Scheme 45).



184

Scheme 45

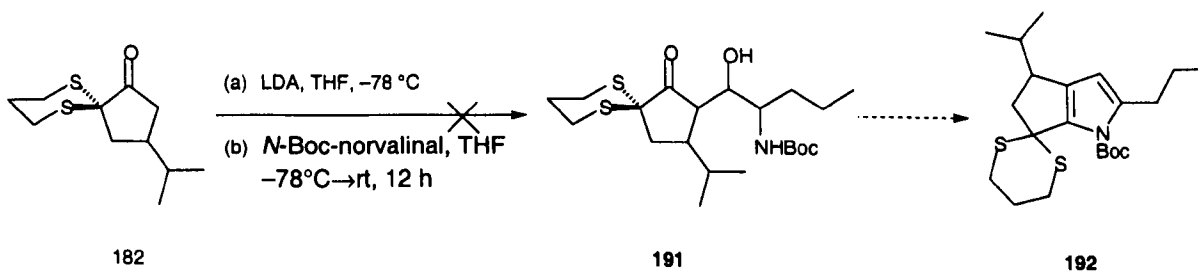
The subsequent formation of the dithioacetal to give a monoprotected α-diketone **182**, was achieved in 69% yield according to an Organic Syntheses procedure,[102] from the corresponding enamine **183** (Scheme 46).



Scheme 46

4.3.2 Aldol reaction

Attempts to perform the Cushman pyrrole synthesis using the masked α-diketone **182** failed to return any of the desired pyrrole **192**. The problem lay in the failure of the first step, the aldol condensation.



Scheme 47

Several different bases were investigated (Table 1) both with and without the presence of TMEDA as an additive. In each case the enolate was quenched with the α-aminoaldehyde **170** and a simple aliphatic aldehyde, *n*-hexanal.

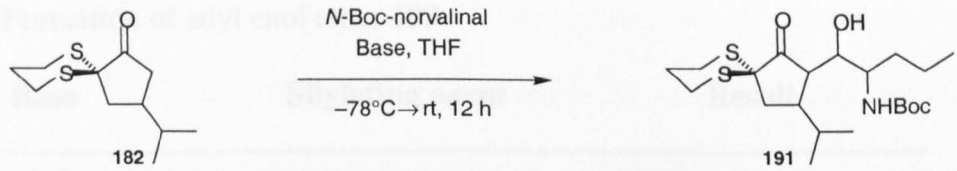


Table 1 : Cushman aldol reaction

Base	Aldehyde	Additive	Result
LDA	**170**	-	**182** recovered
"	"	TMEDA	"
"	*n*-hexanal	-	"
LIHMDS	**170**	-	**182** recovered
"	"	TMEDA	"
"	*n*-hexanal	-	"
KHMDS	**170**	-	**182** recovered
"	"	TMEDA	"
"	*n*-hexanal	-	"
NaHMDS	**170**	-	**182** recovered
"	"	TMEDA	"
"	*n*-hexanal	-	"
n-BuLi	**170**	-	**182** recovered
"	"	TMEDA	"
"	*n*-hexanal	-	"

No aldol reaction occurred with **170** under any of the condtions investigated. The ketone **182** was recovered quantitavely in all cases. In order to establish that the problem was not arising from the α-aminoaldehyde **170** the aldol reaction was attempted under the same conditions with *n*-hexanal, with the same result. An alternative strategy *via* an enol silane intermediate **193** was investigated (Table 2). Isolation and desilylation of **193** would establish whether or not the issue is the deprotonation of the sterically hindered ketone **182** or reaction between the enolate formed and the aldehyde.

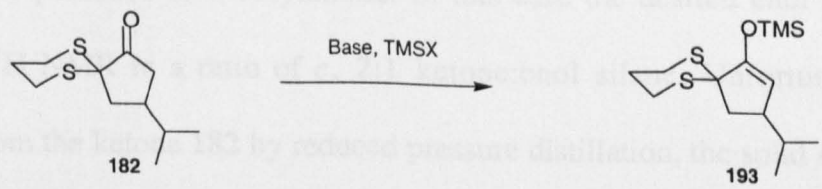


Table 2 : Formation of silyl enol ether **193**

Base	Silylating agent	Result
LDA[a]	TMSCl	**182** recovered
LiHMDS[a]	TMSCl	**182** recovered
KHMDS[a]	TMSCl	**182** recovered
NaHMDS[a]	TMSCl	**182** recovered
Et_3N[b]	TMSOTf (1.1 eq)	33%
"	TMSOTf (2.0 eq)	50%
"	TMSOTf (3.0 eq)	66%
"	TMSOTf (4.0 eq)	80%
"	TMSOTf (5.0 eq)	100%

[a] THF, –78 °C→ rt, 12 h

[b] Et_2O, rt, 4 h

Formation of the silyl enol ether **193** was not straightforward. Treatment of **182** with LDA in the presence of TMSCl yielded no reaction, the same result was apparent with LiHMDS and KHMDS. A more reactive system was clearly required and so **182** was treated with TMSOTf in the presence of triethylamine. In this case the desired enol silane **193** was observed by ^{1}H NMR in a ratio of *c.* 2:1 ketone:enol silane. Unfortunately **193** was inseparable from the ketone **182** by reduced pressure distillation, the solid starting material

co-distilling with the product. An increase in the number of equivalents of the silylating agent drastically improves the ratio of enol silane:ketone. Thus **193** was prepared in quantitative yield, in the presence of 5 equivalents of TMSOTf.

The enol silane **193** was purified by reduced pressure distillation ; however, it was extremely labile and underwent partial hydrolysis to the ketone in *c.* 48 hours, despite being stored in base-washed glassware, under nitrogen at –30°C. Contrary to expectations **193** was stable to rapid flash column chromatography on base-washed silica with a basic eluent.

Treatment of the silyl enol ether **193** with methyllithium according to a procedure by House et al.[99] yielded the desired lithium enolate **194** but it failed to react with the α-aminoaldehyde **170** and did not furnish the sought after aldol adduct. This reaction was attempted under a range of reaction conditions (Table 3) without success. Again there was no reaction between the substrate and *n*-hexanal, indicating that the problem was indeed arising from the sterically hindered enolate **194**.

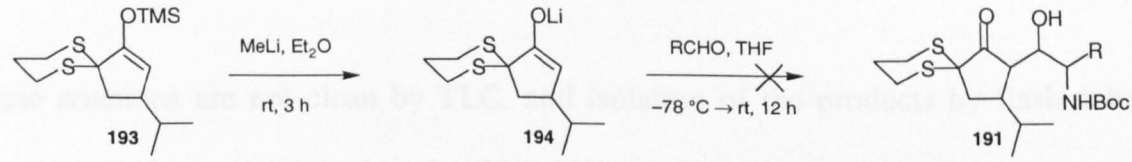


Table 3 : Cushman aldol reaction

Aldehyde	Reaction Conditions	Result
170	Et_2O, –78 °C, 1 h	**182** recovered
170	Et_2O, –78 °C → rt, 12 h	**182** recovered
170	THF, –78 °C → rt, 12 h	**182** recovered
n-hexanal	Et_2O, –78 °C → rt, 12 h	**182** recovered
n-hexanal	THF, –78 °C → rt, 12 h	**182** recovered

The Mukaiyama directed aldol reaction between enol silane **193** and the aldehyde **170** was next attempted using $TiCl_4$ and BF_3•OEt_2 as Lewis acids but once again, the ketone **182** was recovered, always in ≥90% yield; and again there was no reaction between the substrate and *n*-hexanal.

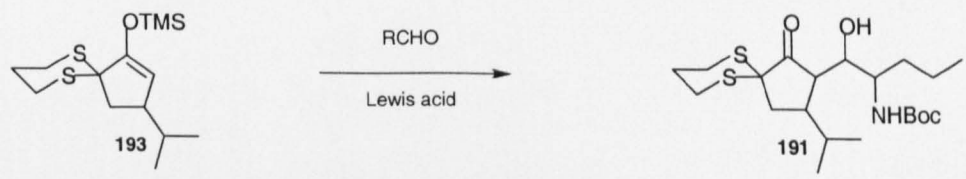


Table 4 : Mukaiyama aldol reaction

Lewis Acid	No of equivalents	Aldehyde	Result
$TiCl_4$	3	**170**	**182** recovered
"	4	"	"
"	5	"	"
"	10	"	"
"	3	*n*-hexanal	"
$BF•Et_2O$	3	**170**	"
"	4	"	"
"	5	"	"
"	10	"	"
"	3	*n*-hexanal	"

These reactions are not clean by TLC, and isolation of the products by flash column chromatography returned the ketone **182** (≥90% yield) and several minor products in very small amounts (≤ 1%) which are unidentifiable by ^{1}H NMR. The aldehyde **170** is not recovered even on greatly increasing the polarity of the eluent. A possible explanation for the lack of reactivity is that the enolate **194** and enol silane **193** are simply too hindered to act as a nucleophile ; alternatively, the aldol reaction may be reversible with the equilibrium lying on the side of the starting materials. In order to stabilise the aldol adducts, a number of metal enolates were investigated using oxyphilic metals such as magnesium,[108] boron,[109] aluminium,[110] tin,[111] titanium,[112] zirconium[113] and zinc[114]) (Table 5).

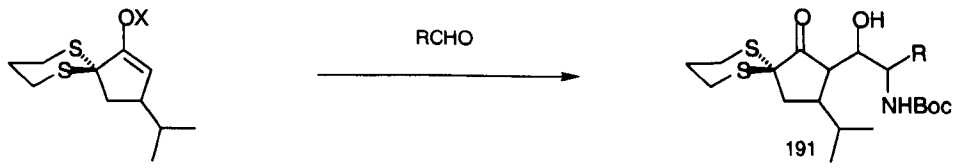


Table 5 : Variation in enolate

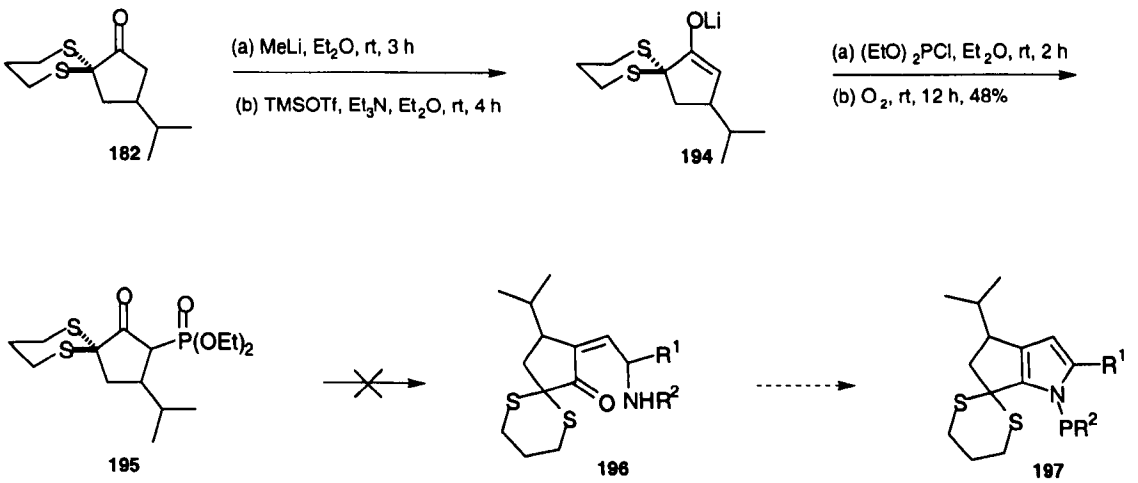
X	Reaction Conditions	Aldehyde	Result
Li	(a) **193**, MeLi, Et_2O, rt, 4 h (b) RCHO, Et_2O, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
Mg	(a) **194**, $MgBr_2$, Et_2O, –78 °C, 3 h (b) RCHO, Et_2O, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
B	(a) **182**, Bu_2BOTf, $EtNPr^i_2$, CH_2Cl_2, –90 °C, 1 h (b) RCHO, CH_2Cl_2, –90 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
Al	(a) **182**, $AlMe_3$, PhMe, Δ, 4 h (b) RCHO, PhMe, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
Sn	(a) **182**, SnOTf, 1-Et-piperidine, CH_2Cl_2, –78 °C, 3 h (b) RCHO, CH_2Cl_2, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
Ti	(a) **193**, $TiCl_4$, CH_2Cl_2, –78 °C, 1 h (b) RCHO, CH_2Cl_2, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "
Zr	(a) **194**, Cp_2ZrCl_2, Et_2O, –90 °C, 3 h (b) RCHO, Et_2O, –90 °C→ rt, 12 h	**170** *n*-hexanal	**182** recovered "
Zn	(a) **194**, $ZnCl_2$, Et_2O, –78 °C→ 0 °C, 30 min (b) RCHO, Et_2O, –78 °C → rt, 12 h	**170** *n*-hexanal	**182** recovered "

In none of the cases examined was any evidence for the formation of the desired aldol adduct obtained with either α-aminoaldehyde **170** or *n*-hexanal. Once again the only product obtained from the reaction was the cyclopentanone **182**. At this point, work on the aldol approach was abandoned.

5.0 New approaches to 103

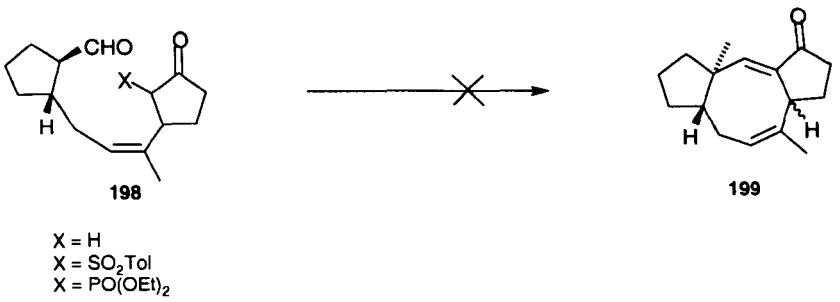
5.1 Wittig approach

The exhaustion of approaches to the aldol reaction of α-ketothioacetal **182** and the appropriate α-amino aldehyde in studies towards the ketopyrrole fragment **103** (as discussed in the previous chapter), required a new approach to **103**. The first to be considered was a Wittig reaction of the phosphorus ylide generated from ketone **182** and an α-amino aldehyde. Such a reaction would set up a very similar structure to the Cushman aldol adduct **191** and allow acid catalysed ring closure, as before, to give the desired pyrrole **197** (Scheme 48).



Scheme 48

Although the phosphorus ylide was generated, according to a literature procedure,[115] Wittig reaction between the ylide and an aldehyde did not occur. It appears that again the reaction centre is too hindered, a conclusion also reached by Snider et al. in their attempted intramolecular Wittig reaction of a similar, though less hindered substrate (Scheme 49).[115]



X = H
X = SO_2Tol
X = $PO(OEt)_2$

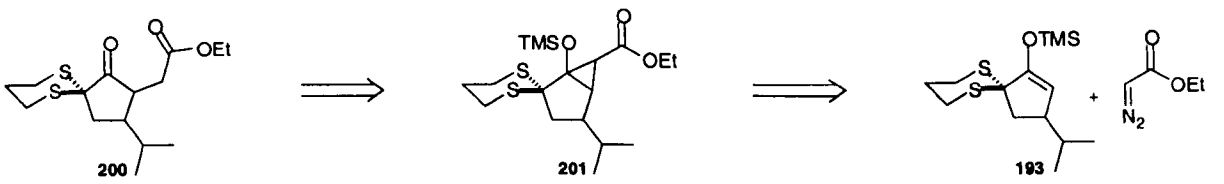
Scheme 49

There are many published methods for the synthesis of pyrroles, the most general being the Paal-Knorr synthesis : reaction of a 1,4-dicarbonyl compound with ammonia or a primary amine.[36-39] This is a very straightforward synthesis and is limited only by the accessibility of the 1,4-dicarbonyl precursors. Hence the following approaches centre on the synthesis of the appropriate 1,4-dicarbonyl compound from the ketone **182**.

5.2 *Via* 1,4-dicarbonyl precursors

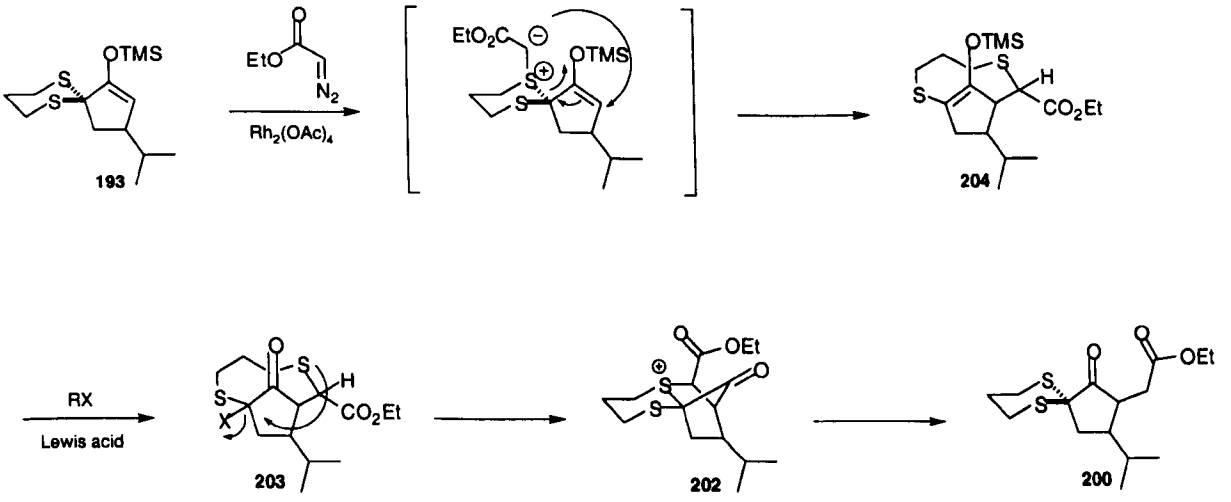
5.2.1 Carbene approach

The carbene mediated cyclopropanation of olefins and enol ethers is well established. The reaction is classically copper-catalysed[116] although more recently rhodium catalysis has been used allowing much milder reaction conditions and giving improved yields.[117] Reaction of silyl enol ether **193** with ethyl diazoacetate in the presence of the rhodium acetate dimer should yield the 1,4-dicarbonyl compound **200** after desilylation of the intermediate cyclopropane **201** (Scheme 50).



Scheme 50

However in the case of enol silane **193** the reaction is complicated by the presence of the thioacetal. Sulfur is an electron donor and so may itself react with the carbene to produce a sulfur ylide. This is not necessarily a disaster as there is ample literature precedent (see Example 1) to suggest that, by a series of rearrangements of the sulfur ylide, the 1,4-dicarbonyl compound **200** may still be accessible (Scheme 51).[118]

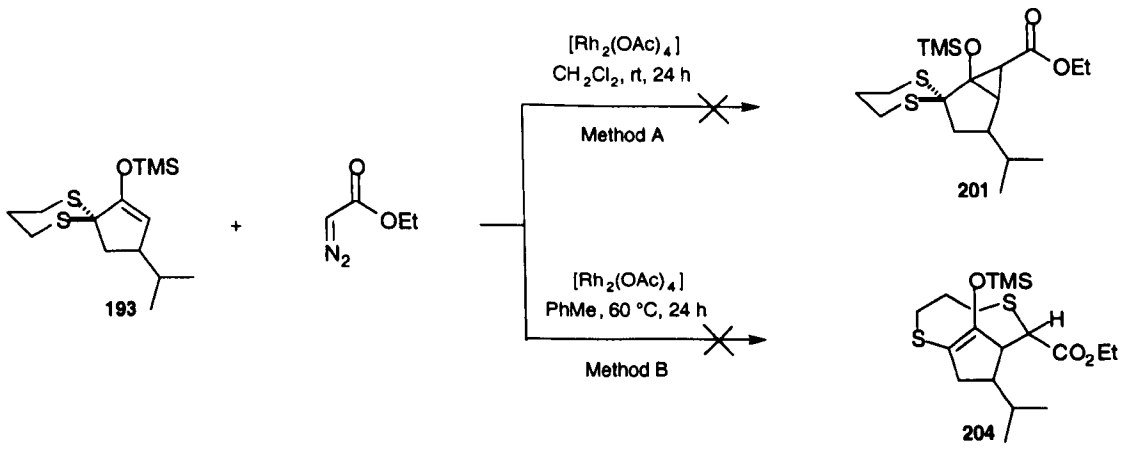


Scheme 51

Ando and co-workers have thoroughly investigated the formation and rearrangements of ylides derived from reactions of diazo compounds with organic sulfides in thermal, photochemical and catalytic processes.[118] Three major pathways for sulfur ylide rearrangement have been identified: intramolecular elimination, [1,2]-rearrangement and [2,3]-sigmatropic rearrangement. With allyl sulfides the [2,3]-sigmatropic rearrangement is

the major reaction pathway to give a 9-membered ring containing a *trans* double bond **204**. Desilylation and incorporation of a leaving group alpha to the carbonyl would allow the 6-membered thioacetal to reform giving an unstable 5-membered ring which could easily be cleaved to yield the desired 1,4-dicarbonyl compound **200**.

Generation of the sulfur ylide from reaction of diazo compounds with allyl sulfides requires much harsher conditions than cyclopropanation of olefins or enol silanes. It was therefore possible to attempt the reaction on substrate **193** in two ways: firstly by treating it as an enol silane with a view to cyclopropanation, Method A;[117] and secondly as an allyl sulfide with a view to the [2,3]-sigmatropic shift (Scheme 52), Method B.[119]

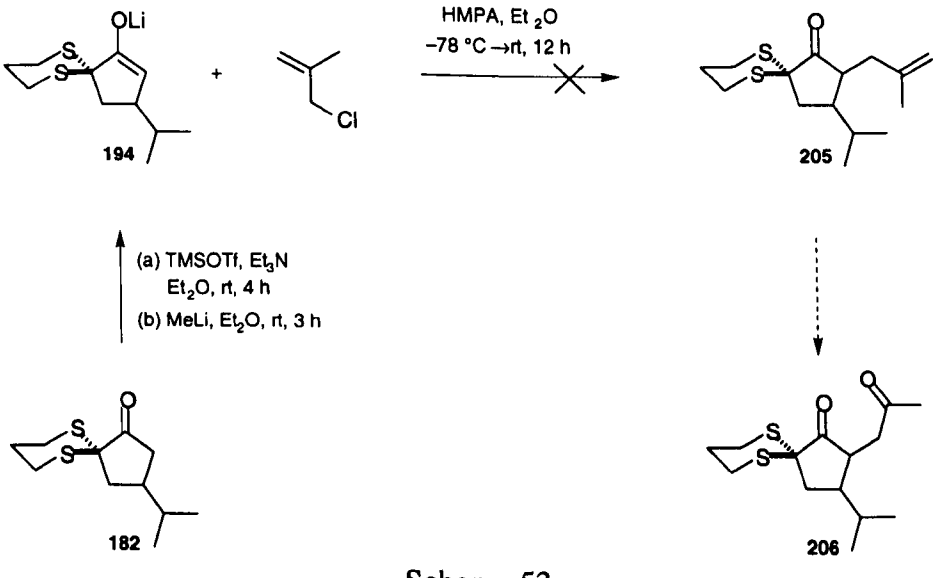


Scheme 52

Unfortunately after extensive attempts at both methods the desired reaction did not occur because the silyl enol ether **193** was not stable enough to withstand the reaction conditions.

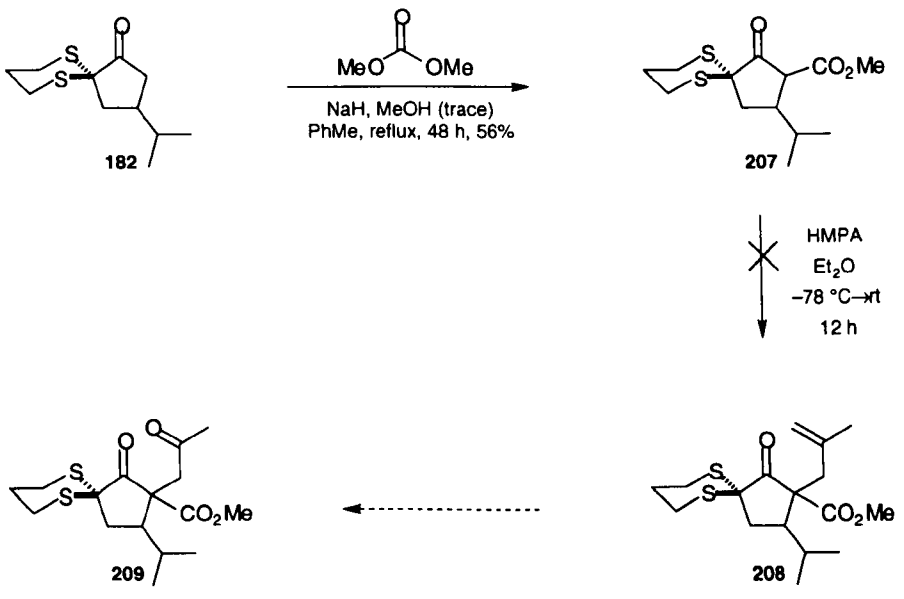
5.2.2 Allylation

The subsequent approach to the desired 1,4-dicarbonyl compound was attempted allylation alpha to the carbonyl group of ketone **182**. Allylic electrophiles allow for more forcing reaction conditions and once incorporated it was predicted that the olefin may be cleaved either under oxidative conditions of with palladium catalysis (Wacker-Tsuji reaction) to yield the desired 1,4-dicarbonyl compound. It was appreciated that this approach is not ideal and that the presence of the dithioacetal is likely to cause problems in the oxidative cleavage required to unleash the second carbonyl group. Accordingly the lithium enolate **194** was treated with methallyl chloride in the presence of HMPA (Scheme 53) only to yield the starting material.



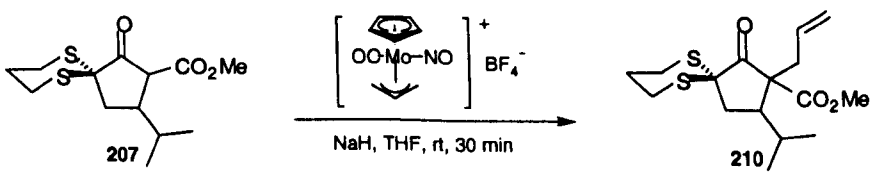
Scheme 53

In an attempt to increase the nucleophilicity of the enolate the β-ketoester **207** was prepared (Scheme 54).



Scheme 54

The attempted allylation of **207**, after extensive efforts, failed. Finally a last ditch attempt at allylation was made with a cationic (π-allyl)molybdenum complex.[120] Such complexes are of current interest within the Kocienski group[121] and we believed that by virtue of its cationic nature, the complex would be highly electrophilic. Addition of the cationic complex to the anion generated by deprotonation of **207** with sodium hydride yielded the desired α-allyl compound **210** in 90% yield (Scheme 55), proving that the cationic complex is indeed a 'super-electrophile'.

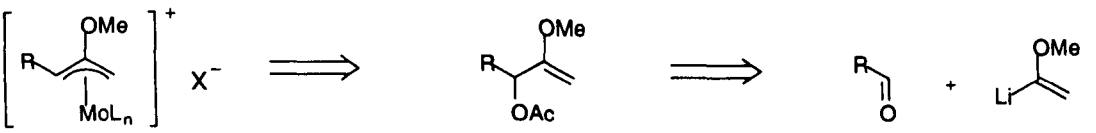


Scheme 55

This result, we felt, could not be ignored and so the best method of exploiting this success was carefully considered.

5.3 Molybdenum electrophile approach

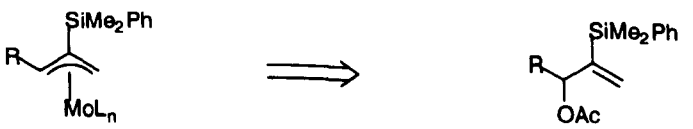
To utilise the (π-allyl)molybdenum electrophiles in the approach to the ketopyrrole fragment **103** would involve subsequent oxidative cleavage, as discussed earlier, in order to achieve the 1,4-dicarbonyl compound. These derivatisation steps in the presence of the thioacetal may prove problematic. An alternative approach is to derivatise the electrophile in order to create the pyrrole precursor in the addition step. There are several ways in which this may be achieved. The molybdenum chemistry may be used to introduce functionality e.g. a (π-allyl)molybdenum complex of an enol ether **211** (Scheme 56) would introduce an oxygen substituent as an enol ether which may then be hydrolysed under mild conditions to give the desired 1,4-dicarbonyl compound.



211 **212**

Scheme 56

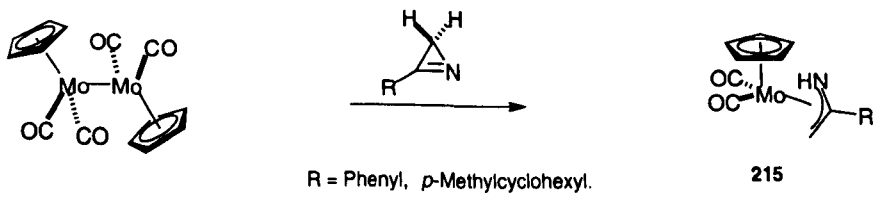
Very little is known about oxygen-functionalised molybdenum complexes but **211** is likely to be extremely air-sensitive and as a result difficult to handle. Another option is to create a (π-allyl)molybdenum complex **213** from a vinyl silane **214** (Scheme 57) which should render the complexes easier to handle.



213 **214**

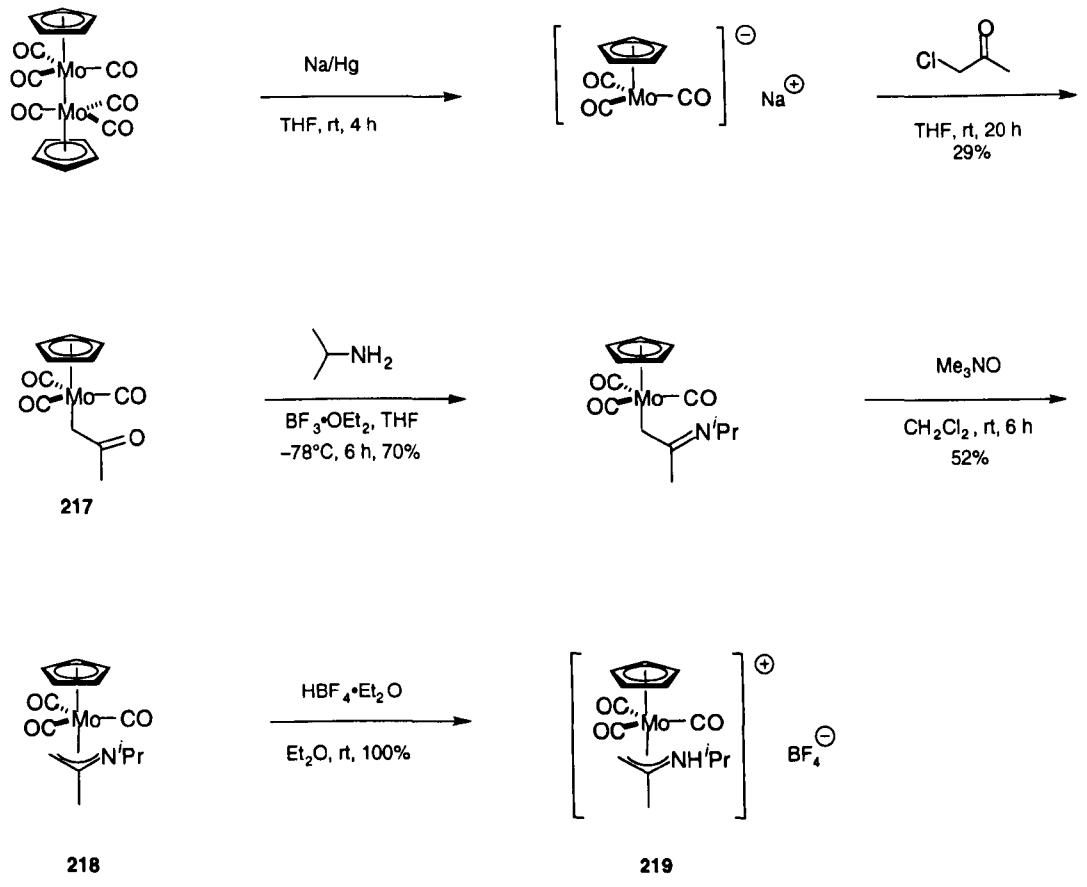
Scheme 57

A Fleming-Tamao oxidation after addition would furnish the desired 1,4-dicarbonyl. Furthermore if a a (π-allyl)molybdenum complex could be generated from an imine to give an η^3-bonded azaallyl complex **215** then the nitrogen functionality could be introduced in the addition step and subsequent ring closure would form the desired pyrrole. An expedient literature search revealed that such (π-azaallyl)molybdenum complexes are, albeit recent, features in the literature. Although the complexes have not been employed for organic synthesis the structure have been assigned conclusively by x-ray crystallography. There are 3 literature preparations of (π-azaallyl)molybdenum complexes, the earliest dating from 1985 and involving the ring-opening of 2-substituted aziridines (Scheme 58).[122]



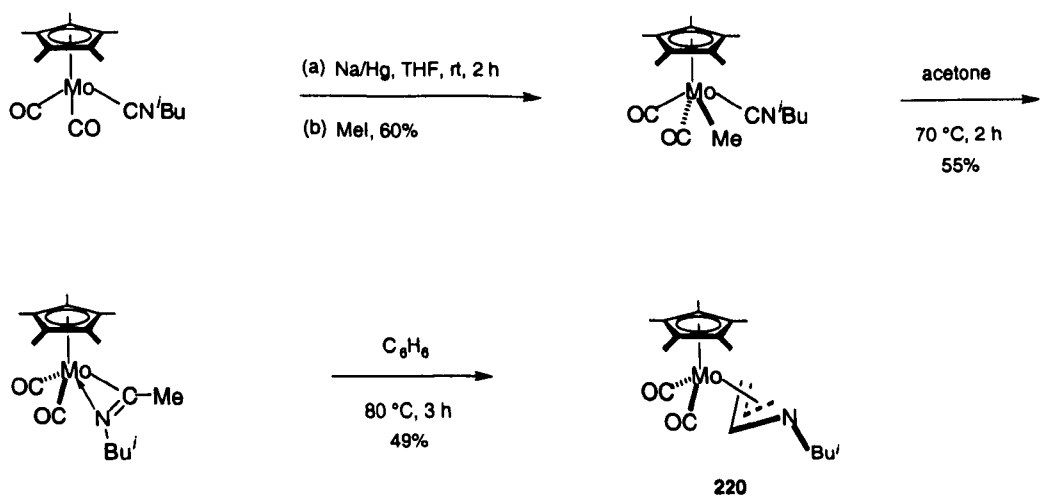
Scheme 58

However Green and co-workers did not provide full characterisation details for their complexes and have failed to publish since. The second method and the one of choice involves the condensation of an amine with η^1-molybdenum bound ketone complexes **217** to give the desired η^3-bonded azaallyl complex **218** (Scheme 59).[123]



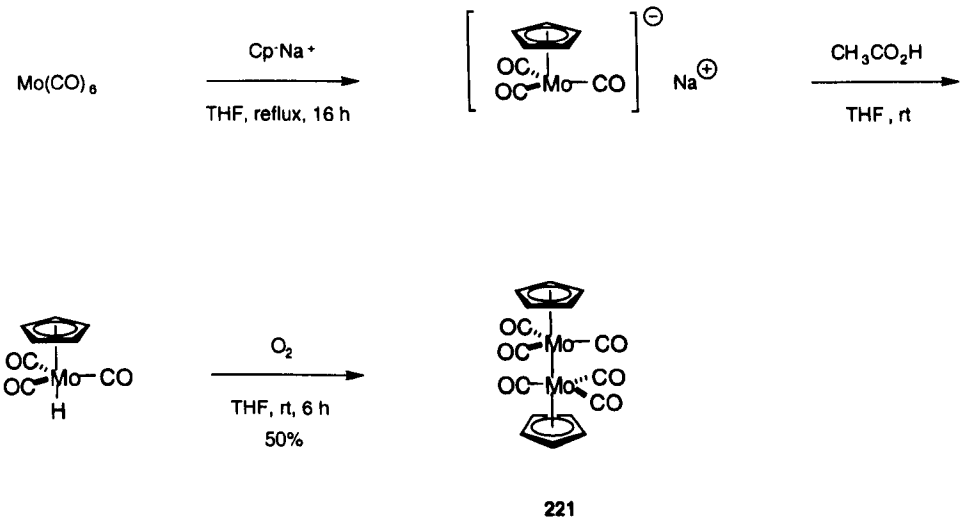
Scheme 59

The third and most recent method involves the rearrangement of a methyl molybdenum complex containing isocyanide ligands to give the complex **220** (Scheme 60).[124]



Scheme 60

Correspondingly the synthesis of the complex **218** was attempted according to the literature method. The molybdenum dimer **221** was obtained by reaction of sodium cyclopentadienide with molydenum hexacarbonyl (Scheme 61). A literature search revealed that Heathcock et al. Have achieved similar success in the synthesis of the η^1-molybdenum bound ketone *via* a one-pot reaction[125] in which chloroacetone is simply added to the sodium salt generated from reaction of sodium cyclopentadienide with molybdenum hexacarbonyl. This method is not recommended in the original publication due to the presence of excess cyclopentadiene in the reaction mixture making product isolation difficult. However the one-pot procedure appreciably decreases reaction time and the outcome is not significantly compromised.



Scheme 61

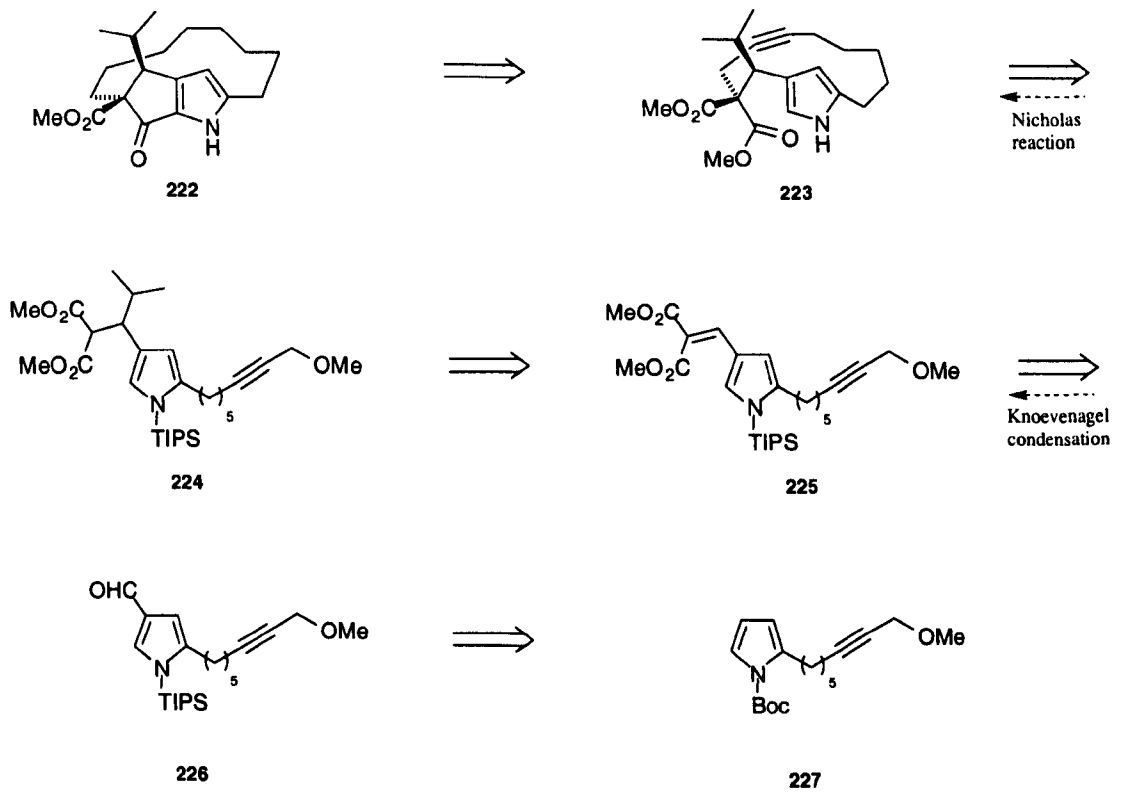
Handling of such air-sensitive compounds is not trivial and progress was initially slow with extensive, if not complete, decomposition suffered in the early stages. Improvement in experimental technique allowed some advancement but after much time and effort decomposition of the molybdenum complexes was still a major problem. The synthesis of the desired complex was achieved, albeit in low yield, with the product and intermediates

decomposing rapidly after isolation. Reactions were followed by ^{1}H NMR spectroscopy, the cyclopentadienyl moiety giving a characteristic signal for each product, but isolation and characterisation of each of the complexes was impossible. Decomposition occurred in the NMR tube before the spectra could be recorded. Several attempts at reaction between the β-ketothioacetal and the azaallyl complex **219** failed, quite possibly as a result of decomposition of the complex. Eventually after much consideration the molybdenum electrophile approach was abandoned. From our experience the simple complexes are difficult to prepare and handle, synthesis of a functionalised complex as required for our purposes may prove impractical and much time had already been lost.

6.0 Approach from a pyrrolyl precursor

6.1 Retrosynthetic analysis

As discussed in Chapter 2 several approaches may be applied to Roseophilin and finally we decided to tackle the synthesis from a pyrrolyl precursor. Our proposed synthesis (Scheme 62) starts from *N*-Boc-pyrrole and makes use of the high nucleophilicity of the heteroaromatic ring. Molecular modelling studies predicted that formation of the macrocyclic ring before the construction of the cyclopentanone ring should allow more scope for the approach of the electrophile due to the system being less rigid.



Scheme 62

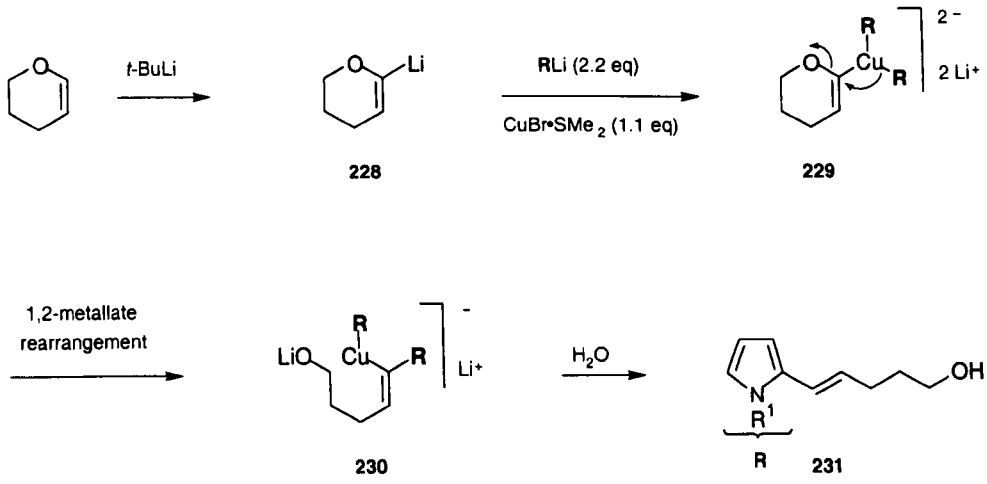
With the intramolecular Nicholas reaction still in mind for the closure of the macrocycle, we envisaged a malonate derivative **224** as an expedient nucleophile. The vinylic malonic ester of **225** may be introduced *via* a Knoevenagel condensation[126] on the 3-formylpyrrole

226. Introduction of the isopropyl substituent could then be effected by a copper-catalysed conjugate addition of isopropylmagnesium halide and perhaps eventually an enantioselective conjugate addition. Ring closure and subsequent reduction of the alkyne then yields fragment **222**. Structure **224** has the advantage that the malonate may be generated under mild conditions, necessary in the presence of the propargylic cation.

6.2 Approaches to the precursor to macrocyclisation

6.2.1 1,2-Metallate rearrangement

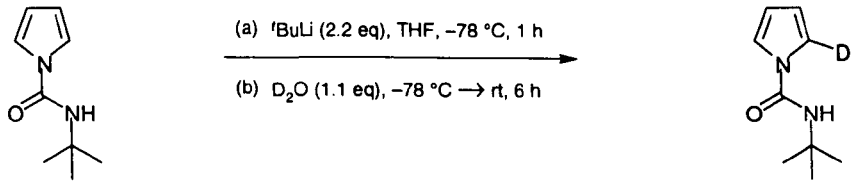
The starting point of the synthesis is the *N*-protected-2-substituted pyrrole **227**. A novel synthesis of 2-substituted pyrroles presented itself to us in the form of a 1,2-metallate rearrangement, a reaction well documented by Kocienski et al. (Scheme 63).[127] Reaction of the 6-lithio-2,3-dihydropyran **228** with lithium di-*N*-protected-pyrrolylcuprate (generated *in situ*) would yield a higher order cuprate **229** which, according to precedent, should undergo a 1,2-alkyl migration to give a 2-substituted pyrrole **231** provided the that the pyrrolyl moiety behaves as a transferrable ligand. The terminal hydroxyl unit thus generated would allow for futher functionality to be introduced.



Scheme 63

6.2.1.1 *N*-Boc-2-lithiopyrrole

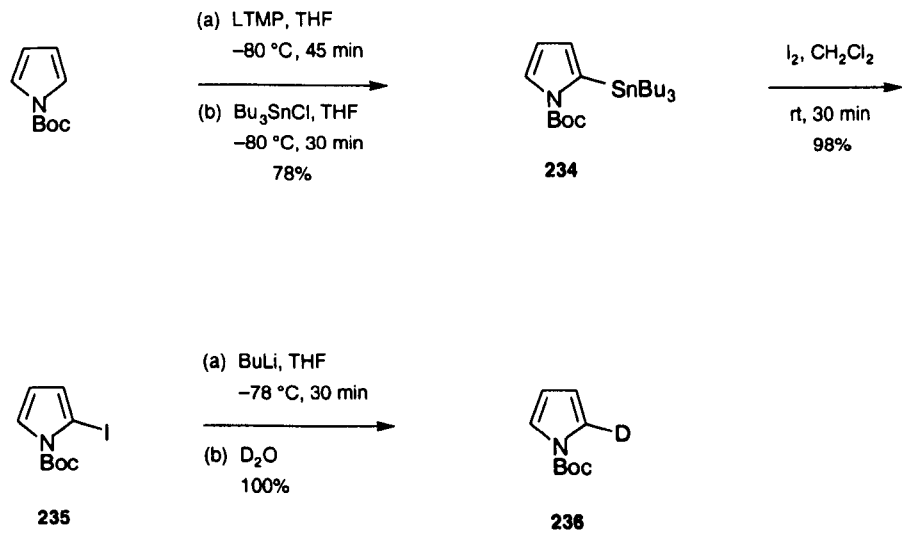
In order to effect the aforementioned 1,2-metallate rearrangement, a reliable and clean preparation of *N*-Boc-2-lithiopyrrole was required. The direct metal-hydrogen exchange of the α-hydrogens of the pyrrole itself is not possible due to the presence of the acidic proton on the pyrrole nitrogen. *N*-Boc-pyrrole is an ideal substrate as the protecting group both directs α-lithiation and prevents the formation of the dianion. However the relatively expensive hindered base, lithium tetramethylpiperidide (LTMP) is required rather than butyllithium to prevent cleaving of the carbamate protecting group. There are few established and reliable alternatives : direct lithium-halogen exchange between *N*-Boc-2-bromopyrrole (derived from pyrrole and 1,3-dibromo-5,5-dimethylhydantoin)[128] is the first ; a more recent method reported by Snieckus et al.[129] is the direct and regiospecific α-lithiation of *N*-(*tert*-butylcarbamoyl)pyrrole **232** with *t*-BuLi. The latter requires 2 equivalents of the organometallic and creates the dianion with the carbamoyl nitrogen being lithiated first (Scheme 64).



232 233

Scheme 64

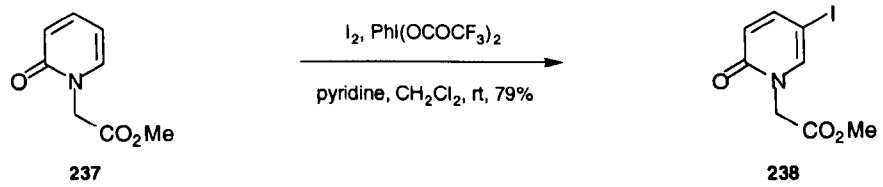
A straightforward approch in our case seemed to be the synthesis of the 2-stannylpyrrole **234** with subsequent transmetallation with *n*-BuLi (Scheme 65). The stannane was formed with ease but transmetallation could not be achieved. Treatment of **234** with iodine however yielded the 2-iodopyrrole **235** which was amenable to lithium-halogen exchange with *n*-BuLi as demonstrated by a D_2O quench.



235 234 236

Scheme 64

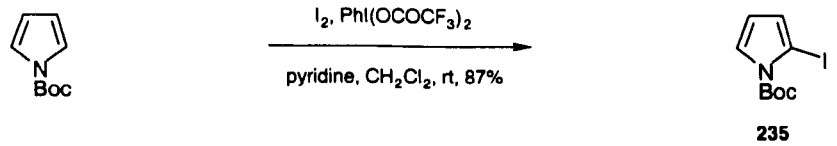
A more expedient route to the desired 2-iodopyrrole **235** was achieved in one step from *N*-Boc-pyrrole, according to a recently published procedure for the iodination of electron deficient aromatic systems with bis(trifluoroacetoxy)iodobenzene (Scheme 65).[130]



237 238

Scheme 64

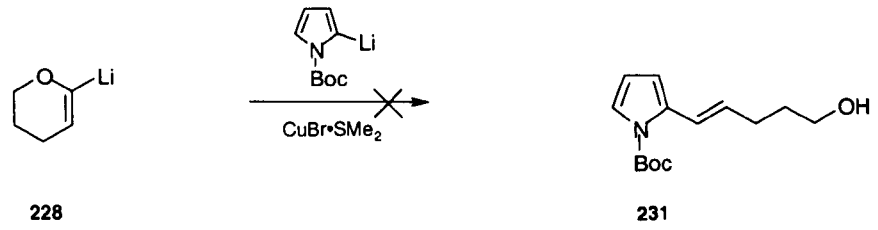
Pyrrole, which is not an electron deficient system, was not included in this report but we felt that the Boc protecting group, which is electron withdrawing and has a stabilising effect on pyrrole, may render it a suitable substrate. There are few established routes to the formation of 2-halo-pyrroles, regioselective mono-halogenation cannot be achieved by treatment of pyrrole with most halogenating agents. Instead, a non-regioselective mixture of mono-, di, tri- and even tetrahalopyrroles are formed. *N*-Boc-pyrrole was a suitable substrate for the reaction and so a novel, direct access, to the desired *N*-Boc-2-iodopyrrole was generated (Scheme 65).



235

Scheme 65

Unfortunately the 1,2-metallate rearrangement with *N*-Boc-2-lithiopyrrole was not achieved (Scheme 66). The reaction was quenched after 24 h with D_2O which proved the presence of the pyrrolyl anion. As the pyrrolyl cuprate **229** has not previously been described it is possible that it may be a non-transferrable ligand, in which case the reaction has no further pertinence to our approach.



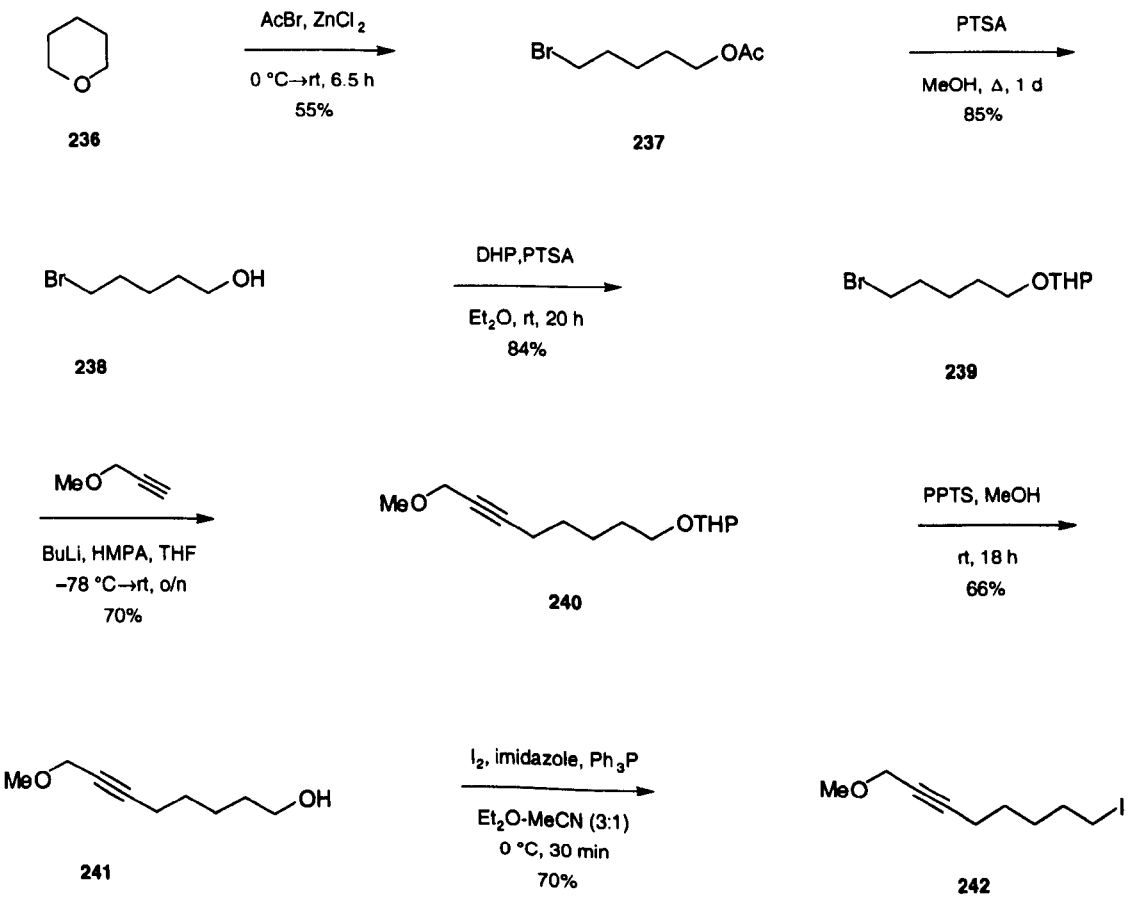
228 231

Scheme 66

6.2.2 Anionic S_N2 reaction

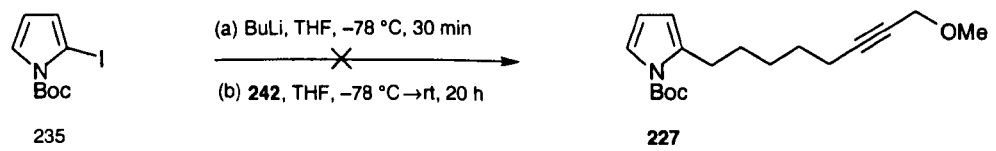
6.2.2.1 Synthesis of the side chain 242

The next advance in our approach was the synthesis of the side chain (Scheme 67) with the aim of introducing it to the *N*-Boc-2-lithiopyrrole *via* the iodide **235**.



Scheme 67

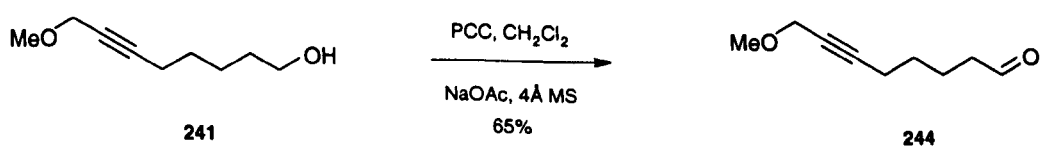
The iodide **242** was assembled in 6 steps from tetrahydropyran **236**.[131] Opening of the 6-membered ring and subsequent protecting group manipulation yielded the THP protected 5-bromopentanol **239** which was easily coupled with methyl propargyl ether according to a standard protocol.[131] Deprotection and iodination of the liberated alcohol furnished **242**. Unfortunately **242** afforded no reaction with the pyrrolyl anion, although encorporating a good leaving group it isn't a reactive enough electrophile for the coupling required (Scheme 67).



235 **227**

Scheme 67

A Suzuki coupling between the pyrrole and **242** was considered at this stage however, although such cross-couplings may be achieved between 9-aryl-9-BBN derivatives and iodoalkanes bearing β-hydrogens, the yields are reported to be poor.[132] The aldehyde **244**, available by a sodium acetate buffered oxidation of **241** is a better choice of electrophile (Scheme 68).

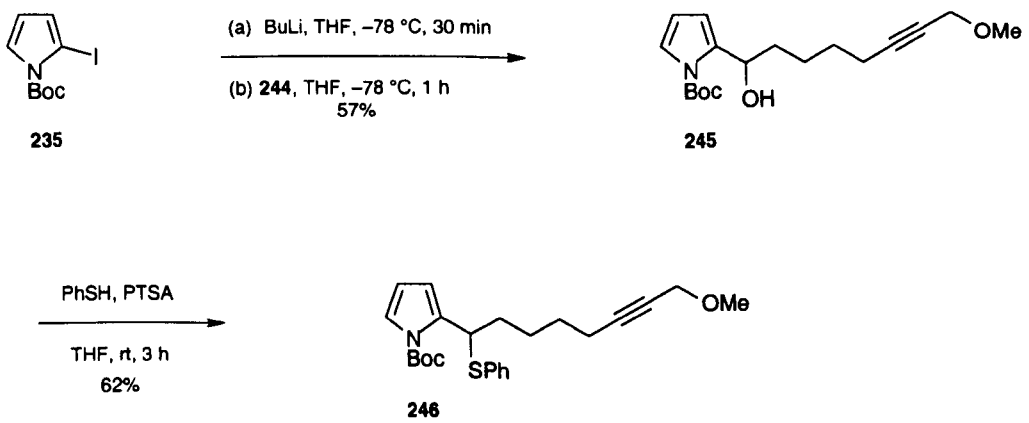


241 **244**

Scheme 68

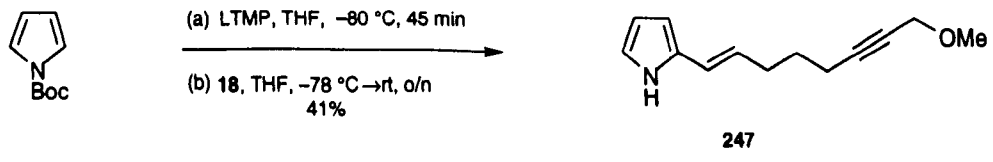
Coupling was successful and the adduct **245** was isolated in moderate yield (Scheme 69). Although the yield based on recovered starting material was near enough quantitative, the reaction could not be optimised further. Surprisingly the α-pyrrolyl hydroxyl moiety of the

N-Boc-protected **245** is not prone to elimination as may be expected and so we were faced with the choice of an elimination, which may be possible by treatment with TFA and triethylsilane provided the pyrrole is stable under those conditions, or derivitisation to a thioether which could be removed simultaneously with the reduction of the alkyne after macrocyclisation. The thioether has the added advantage that by virtue of its steric bulk it may promote the macrocyclisation by forcing the reactive sites together. The thioether **246** was therefore contrived, according to a literature procedure (Scheme 69).[133]



Scheme 69

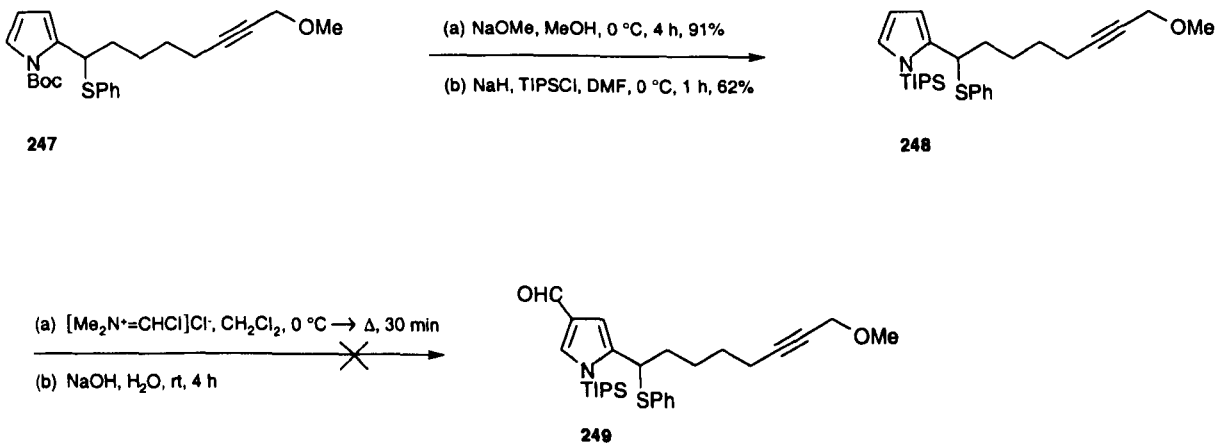
It is interesting to note that coupling of the aldehyde **244** with *N*-Boc-2-lithiopyrrole, formed directly with LTMP, gave a different result. The reaction which was much slower, requiring 12 h at rt, caused Boc cleavage and elimination of the hydroxyl moiety to afford the undesired α-vinylpyrrole **247** (Scheme 70).



Scheme 70

6.2.3 β-pyrrole formylation

Formylation of pyrrole at the β position, as proposed in our retrosynthetic analysis, requires some consideration. It has long been known that pyrrole undergoes predominant or exclusive kinetic electrophilic substitution at the α (2 or 5) position. A very effective strategy has been developed for the synthesis of 3-substituted pyrroles based on the use of the triisopropylsilyl (TIPS) moiety as a sterically demanding nitrogen substituent to obstruct the attack of electrophilic reagents at the α positions.[134] The *N*-TIPS-2-substituted pyrrole **248** was duly prepared (Scheme 71), but formylation of this intermediate under Vilsmeier-Haack conditions to give **249** did not occur.



Scheme 71

The substrate was not stable to the reaction conditions, forming an intractable black tar.

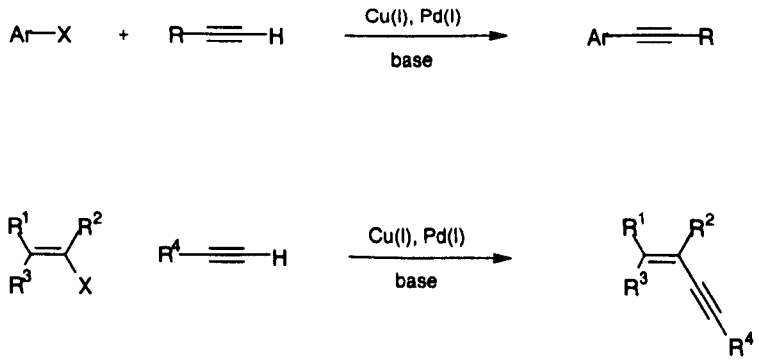
6.2.4 Sonogashira approach

We were reluctant to change our approach greatly at this stage, and since 3-formylation of unsubstituted *N*-TIPS-pyrrole is an established reaction, only a minor reorganisation of our

current strategy would offer an expedient solution to the problem in hand. However, regioselective introduction of the propargylic side chain opposite to the β-substituent already present now poses a problem. With the functionality introduced at the 3-position it would be impossible to regioselectively lithiate and couple the requisite anion with the aldehyde **244**. A solution to this previously unconsidered complication would be to use *N*-Boc-2-iodopyrrole **235**, already a feature of our strategy, and perform a Sonogashira reaction.

6.2.4.1 The Sonogashira Reaction

The Sonogashira reaction is a copper-palladium co-catalysed coupling of terminal alkynes with aromatic and vinyl halides (Scheme 72).[135] It is typically a technically simple, efficient and high yielding reaction which tolerates a wide variety of functional groups.



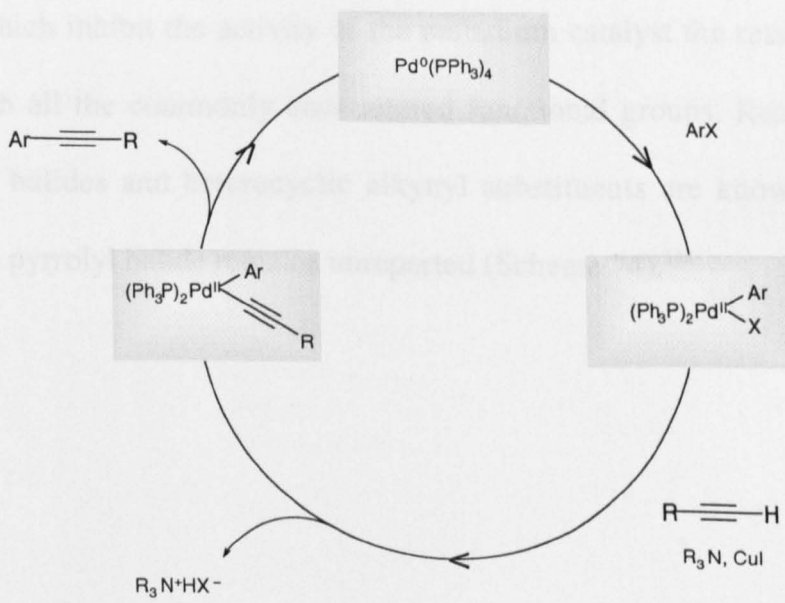
Scheme 72

The reaction was developed in 1975 by Sonogashira[136] at the same time as both Heck and Cassar reported a similar process which did not involve copper catalysis but required more forcing conditions.[137] The reaction can in fact be envisaged as an extension of the well-used Heck palladium catalysed arylation of alkenes. Prior to 1975 the only method

available for coupling alkynes and iodoarenes was the Stephens-Castro reaction, involving a preformed copper acetylide reacting in pyridine at high temperatures. The Sonogashira process is a major advance as it allows a wide range of substrates to couple under very mild conditions.

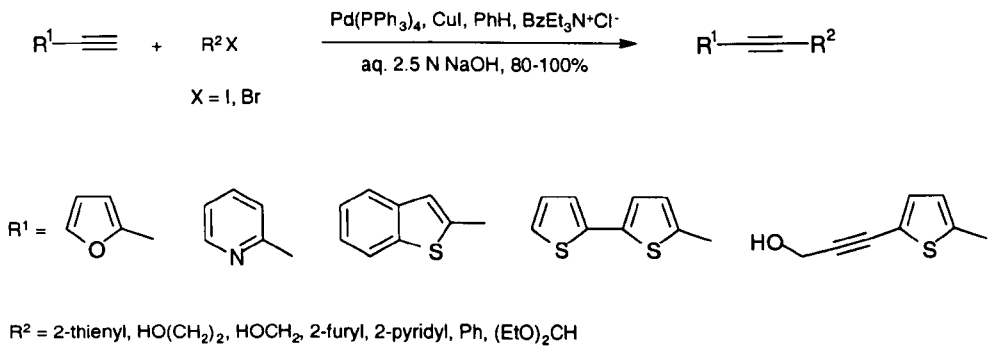
Mechanism

The Sonogashira reaction almost certainly follows the normal oxidative addition-reductive elimination process common to palladium-catalysed carbon-carbon bond forming reactions (Scheme 73). The exact mechanism of the reaction however is not known and in particular the role of the copper catalyst remains unclear. The oxidative addition of the aryl halide to the palladium(0) species is the rate determining step of the reaction. Substrates bearing electron-withdrawing groups *ortho* or *para* to the halide will therefore react more readily as the more electron deficient aryl halides will undergo oxidative addition more rapidly. The reaction does proceed without the copper(I) co-catalyst but only under more forcing conditions and not for less active substrates.



Scheme 73

The most commonly used form of the Sonogashira reaction couples an aromatic iodide with a terminal alkyne. However, other substrates such as aromatic bromides, chlorides and vinyl halides have been reported. Both Pd(II) and Pd(0) have been used but Pd(II) catalysts benefit from greater long-term stability than the palladium(0) species. Samples of $PdCl_2(PPh_3)_2$ which have been stored under normal laboratory conditions for several years still prove effective in the reaction whereas $Pd(PPh_3)_4$, although it may be freshly prepared, rapidly deteriorates unless stored under carefully controlled conditions. The amount of copper and palladium catalysts used is generally of the order of 2 mol% of each with respect to the halide and alkyne. This ratio is likely to lead to product formation within an acceptable time period but is not necessarily optimum. In large scale preparations (>100 g) catalyst ratios as low as 0.5 mol% have proved effective. Sonogashira's initial procedure used diethylamine as both base and solvent and this medium continues to be used. There appears to be no particular advantage of diethylamine over many of the commonly used organic bases, several of which have been successfully used in the reaction. The Sonogashira reaction is one of the most functionally tolerant reactions available for carbon-carbon bond formation. Although it may be possible to find unique combinations of functionality which inhibit the activity of the palladium catalyst the reaction is generally compatible with all the commonly encountered functional groups. Reactions with both heteroaromatic halides and heterocyclic alkynyl substituents are known although their coupling with a pyrrolyl halide remains unreported (Scheme 74).[138]

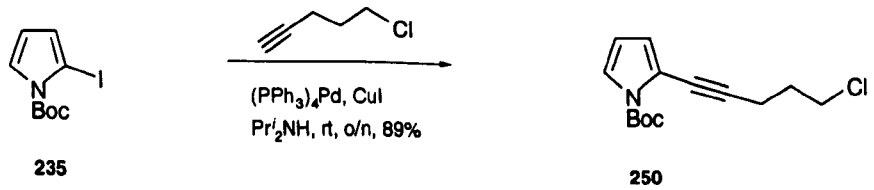


Scheme 74

Some limitations in the nature of the alkyne exist, in particular those alkynes which are conjugated to electron withdrawing groups and short-chain alkynyl amines in which the amino groups can undergo palladium-catalysed addition to the triple bond to give cyclic imines.[139] As may be expected from such an efficient and functionally tolerant process, there are many applications of the Sonogashira reaction in the approach to natural products.[140-146] The reaction is particularly useful in the synthesis of the enediyne antibiotics.[147]

6.4.2.2 Model studies

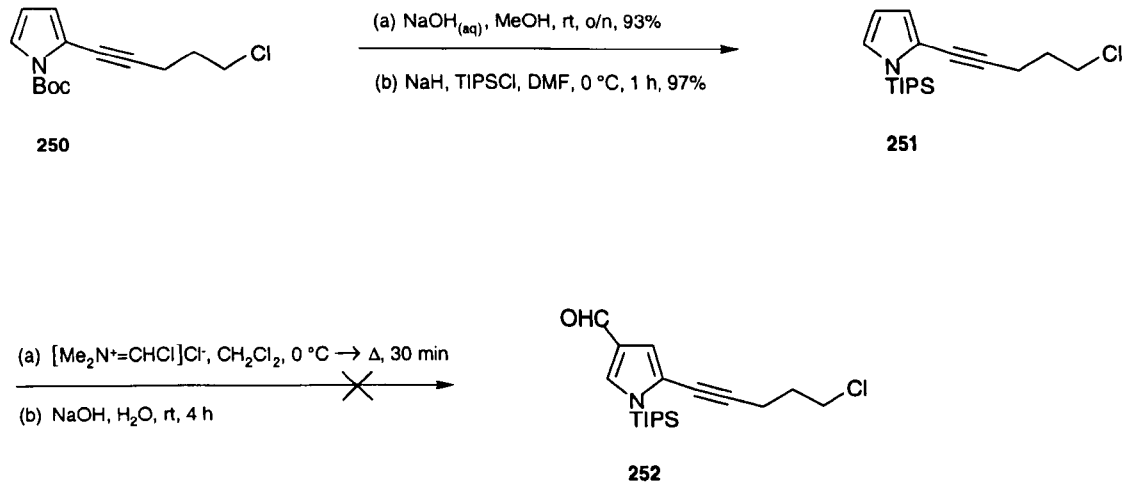
Model studies on *N*-Boc-2-iodopyrrole **235** with 5-chloropentyne yielded the adduct **250** in 89% yield (Scheme 75).



235 **250**

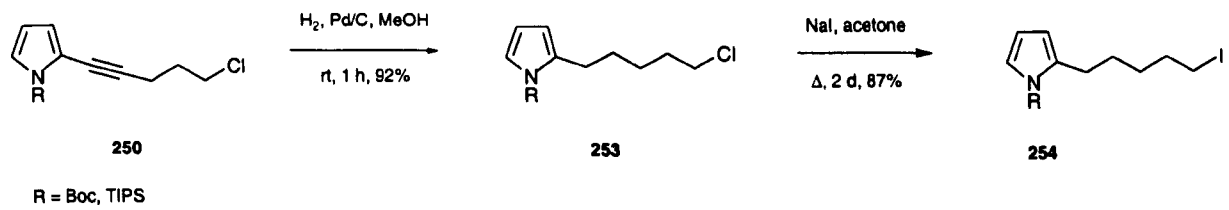
Scheme 75

As suspected 3-formylation of the *N*-TIPS-pyrrole **251** (Scheme 76) at this stage was not possible, the reaction yielding a black tar as before.

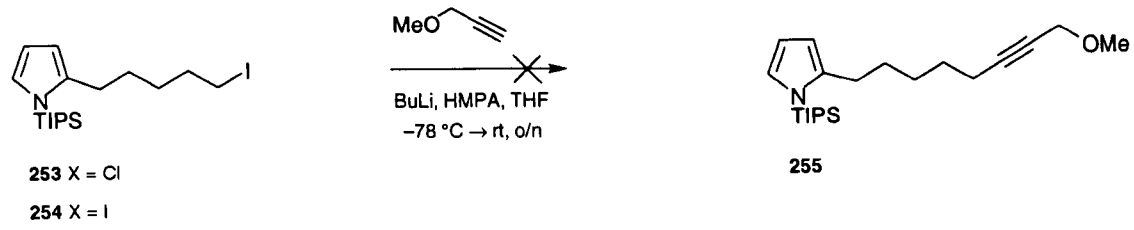


Scheme 76

Reduction of the internal alkyne of **250** was achieved readily (Scheme 77) ; however treatment of **253** with the lithium anion of methyl propargyl ether, according to a procedure published by Nicolaou et al.,[148] did not lead to displacement of the chloride or the corresponding iodide **254** (Scheme 78).



Scheme 77



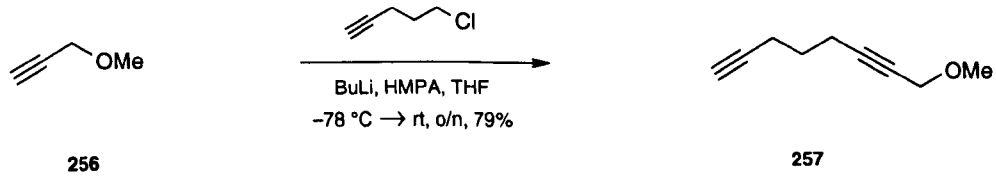
253 X = Cl

254 X = I

255

Scheme 78

Perplexed by these results we attempted the reaction between 5-chloropentyne and the alkynyl anion, which furnished the desired diyne **257** in a 79% yield (Scheme 79).



256

257

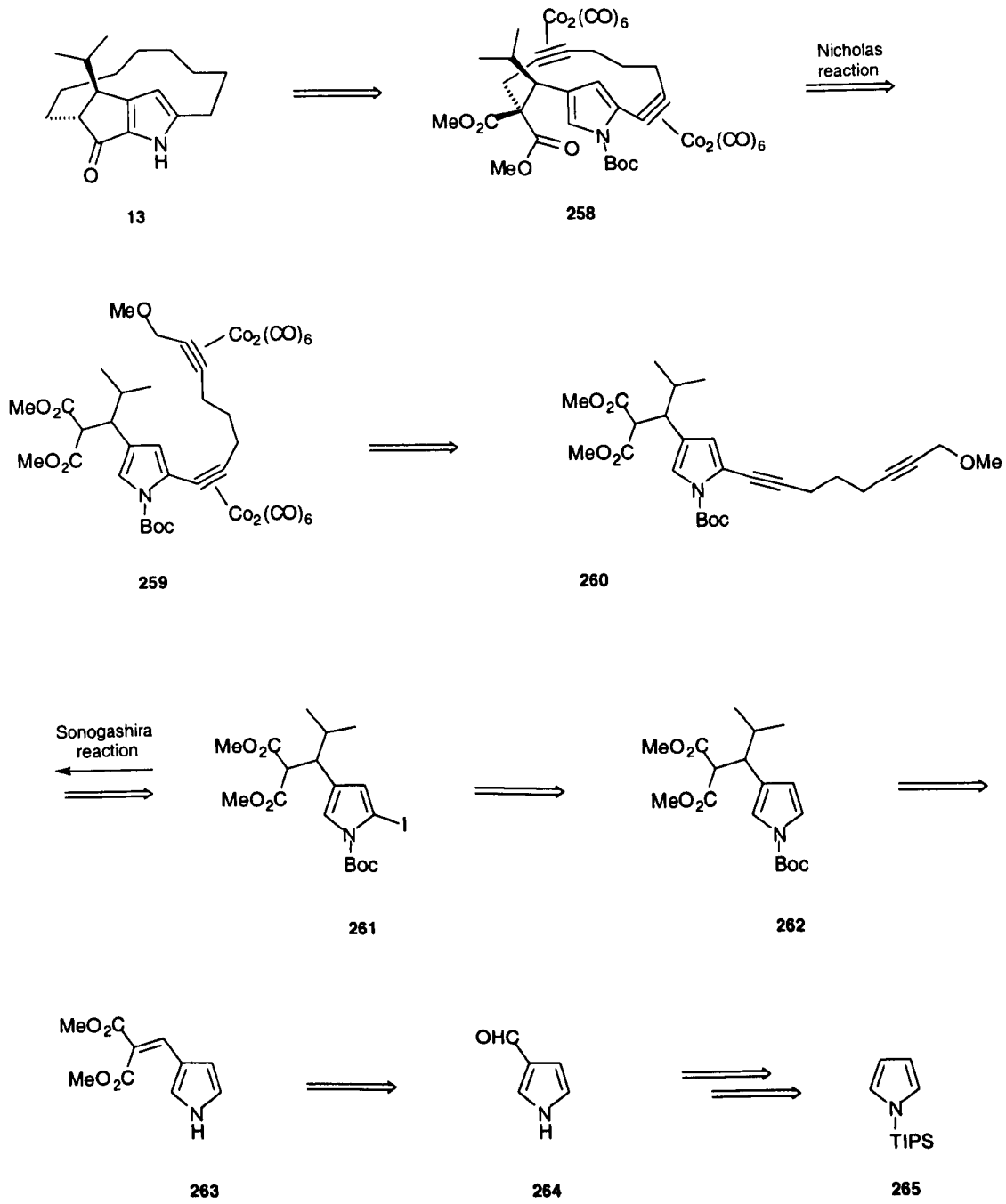
Scheme 79

Evidently the method is not at fault and the pyrrole moiety is the root of the problem. The reaction was attempted several times with an increased number of equivalents of the anion with no improvement in result. In all cases the pyrrole **254** was recovered quantitatively.

Although 3-formylation of **245** may well be achieved, it is futile if we cannot introduce the propargyl unit, essential for the proposed macrocyclic ring closure. The only option left is to effect the formylation at the outset and to introduce the dialkyne **257** without reduction of the extraneous triple bond (a regioselective reduction of the electron rich internal alkyne of this system was attempted without success).

6.2.4.3 Retrosynthetic analysis

The Nicholas reaction, proposed for macrocyclisation would form a highly strained 13-membered ring, however the presence of the second alkyne may be favourable in this case (Scheme 80). The dicobalt complex of both alkynes imparts an sp^2 character to the sp centres and distorts the triple bond,[79, 80, 149] bringing the reactive sites together (Scheme 80). The Nicholas reaction (as discussed in chapter 3) is particularly effective in the formation of macrocycles and strained rings due to the propargyl cation stablised by the dicobalt complex. Thanks to the steric bulk of the dicobalt complexes the reaction benefits from a high degree of diastereoselectivity, favouring the desired *anti* conformation. Decomplexation of **258** , usually carried out under oxidative conditions, and subsequent reduction of the alkynyl moieties should provide **13** after decarboxylation.



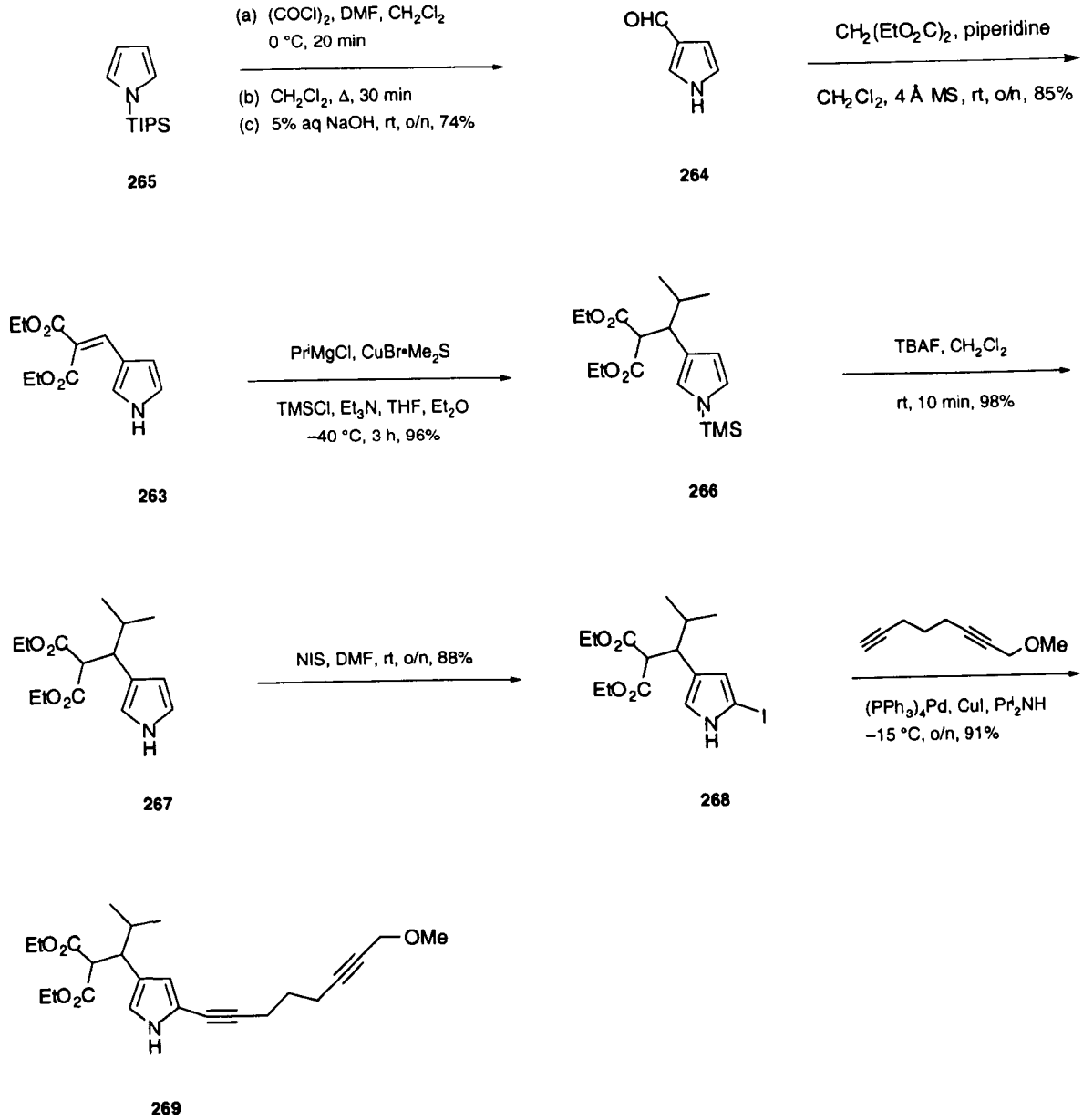
Scheme 80

The Sonogashira reaction, as discussed previously, is a highly specific, mild process and is expected to be high yielding. The second ring closure, to form the cyclopentenone ring of **13** is predicted to be facile. Gentle warming of intermediate **258** in the presence of a mild base may effect cyclisation. If more forcing conditions are required, lithiation of the 2-position of the pyrrole and subsequent transmetallation to a nucleophilic organocerium derivative should prove effective.

The advantage in this synthesis is the brevity and flexibility of the approach. The cyclisations may be carried out in the order shown above or reversed in order to minimise ring strain and thus optimise the macrocyclisation step. A possible disadvantage is in the choice of a pyrrolyl starting material. Pyrrole is highly nucleophilic and prone both to oxidation on exposure to air and polymerisation in the presence of electrophilic substitutents. However with the appropriate use of protecting groups (the bulky TIPS group to shield the reactive 2-position and electron-withdrawing Boc groups to reduce the nucleophilicity of the ring) these disadvantages should be alleviated.

6.2.4.4 Synthesis of the Nicholas precursor

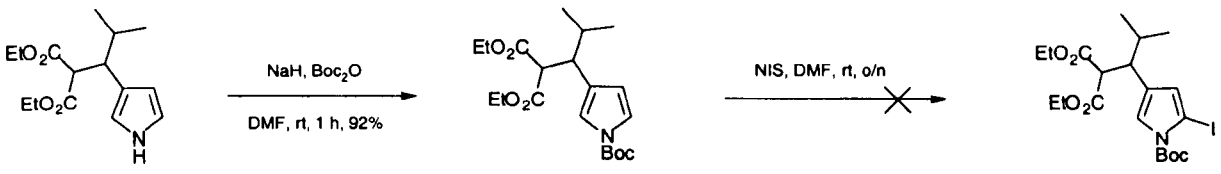
Synthesis of the Nicholas precursor was achieved in 6 steps from *N*-TIPS-pyrrole in a 45% overall yield (Scheme 81).



Scheme 81

Introduction of the isopropyl moiety *via* a copper (I) catalysed 1,4-conjugate addition, accelerated by chlorotrimethylsilane, resulted in the *N*-silyl derivative **266**. Despite the lability of the nitrogen-silicon bond **266** was resistant to treatment with aqueous hydrochloric acid. The unwanted trimethylsilyl moiety was readily removed with TBAF. α-Iodination of the pyrrole ring of **267** was achieved efficiently and regioselectively with *N*-iodosuccinamide. Treatment of **267** with bis(trifluoroacetoxy)iodobenzene, a method we had effectively used in the synthesis of *N*-Boc-2-iodopyrrole, was unsuccessful in this case due to the increased electron density of the unprotected pyrrole ring. *N*-Boc protection of

intermediate **269** allowed for some iodination with bis(trifluoroacetoxy)iodobenzene but the reaction was not clean amd required lengthy purification. Attempted iodination of the *N*-Boc protected intermediate **270** with *N*-iodosuccinamide was unsuccessful, in this case the electron withdrawing effect of the protecting group rendered the pyrrole ring inactive to substitution (Scheme 82).



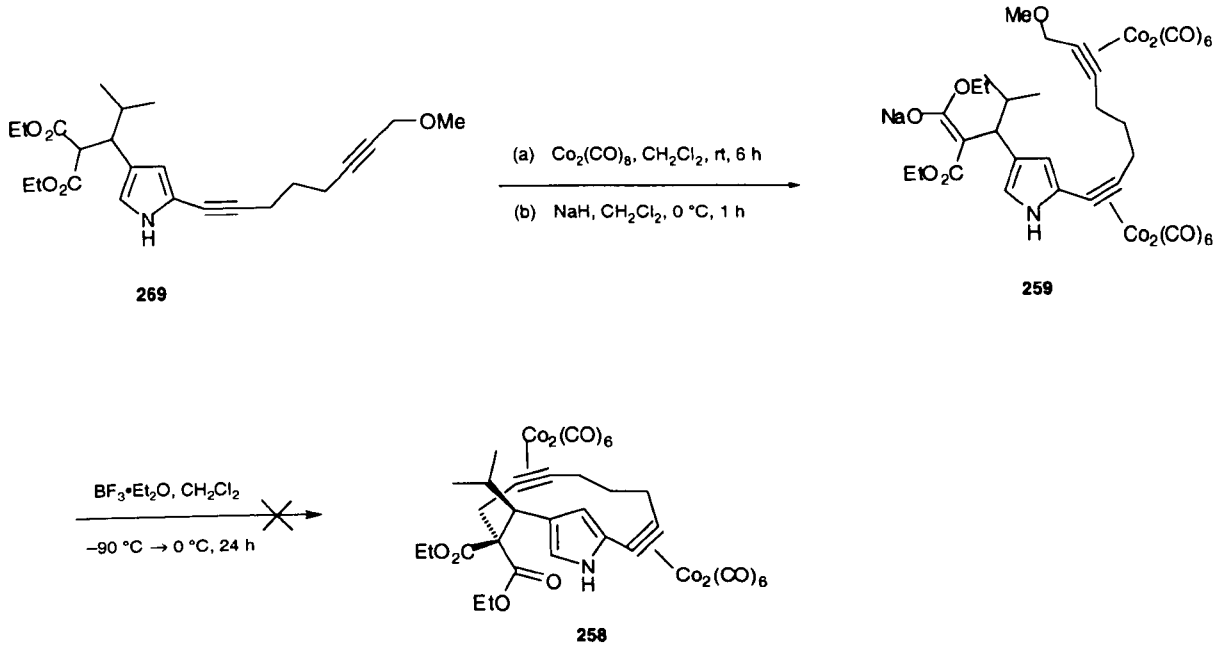
267 **270** **271**

Scheme 82

6.3 The Nicholas reaction

6.3.1 Macrocyclisation

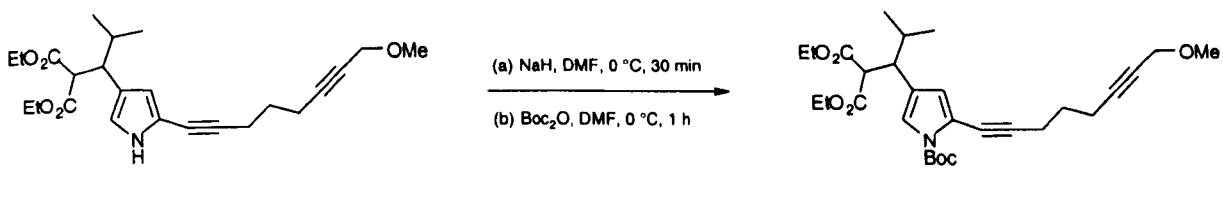
Dicomplexation of **269** with dicobaltoctacarbonyl was achieved cleanly, by TLC. The complex itself was a rich brown colour. Removal of the malonate proton was effected *in situ* with sodium hydride. However addition of the Lewis acid even at low temperature (–90 °C) initiated degradation of the intermediate to produce a highly polar intractable black tar (Scheme 83).



269 259 258

Scheme 83

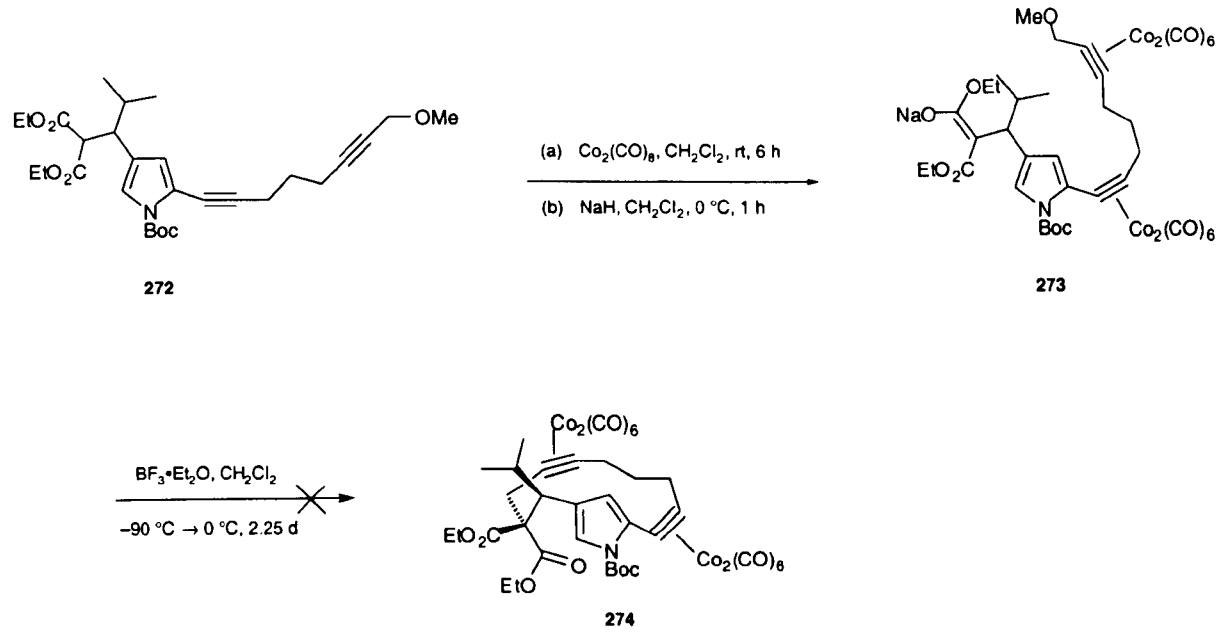
The pyrrole ring is electron rich and we believed its presence α to the internal dicobalt-alkyne complex must have a destabilising effect. In order to alleviate the problem we introduced electron withdrawing Boc protection as a means of stabilising the complex (Scheme 84).



269 272

Scheme 84

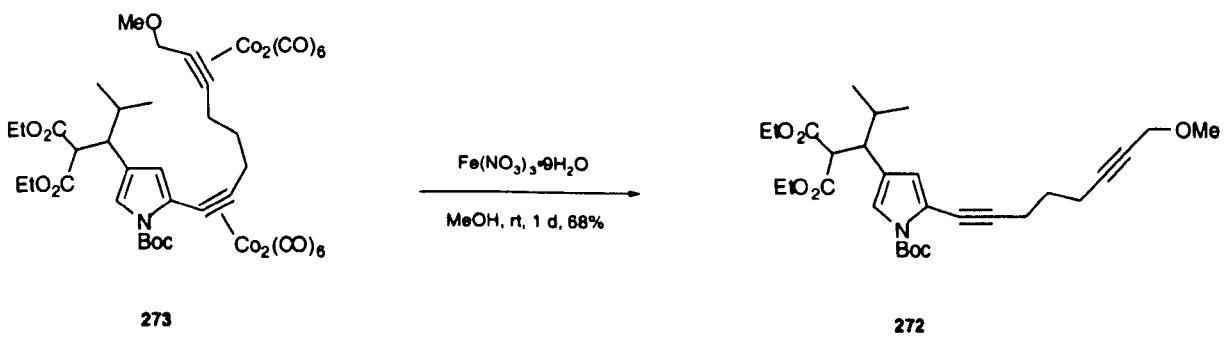
The *N*-Boc protected intermediate **272** underwent dicomplexation with dicobaltoctacarbonyl, again quantitatively by TLC, the complex **273** this time being a deep red colour (Scheme 85).



272 273 274

Scheme 85

On introduction of the Lewis acid at –90 °C **273** remained, at least partially, visible by TLC. After 6 h at –90 °C with no reaction the reaction mixture was gradually warmed to rt, however even after 2 days at rt there had been no cyclisation. Refluxing the reaction mixture caused decomposition of the complex. The dicomplexed *N*-Boc substrate **273** was recovered in 68% yield, decomplexation with ceric ammonium nitrate yielded **272** (Scheme 86). All subsequent attempts produced the same result.

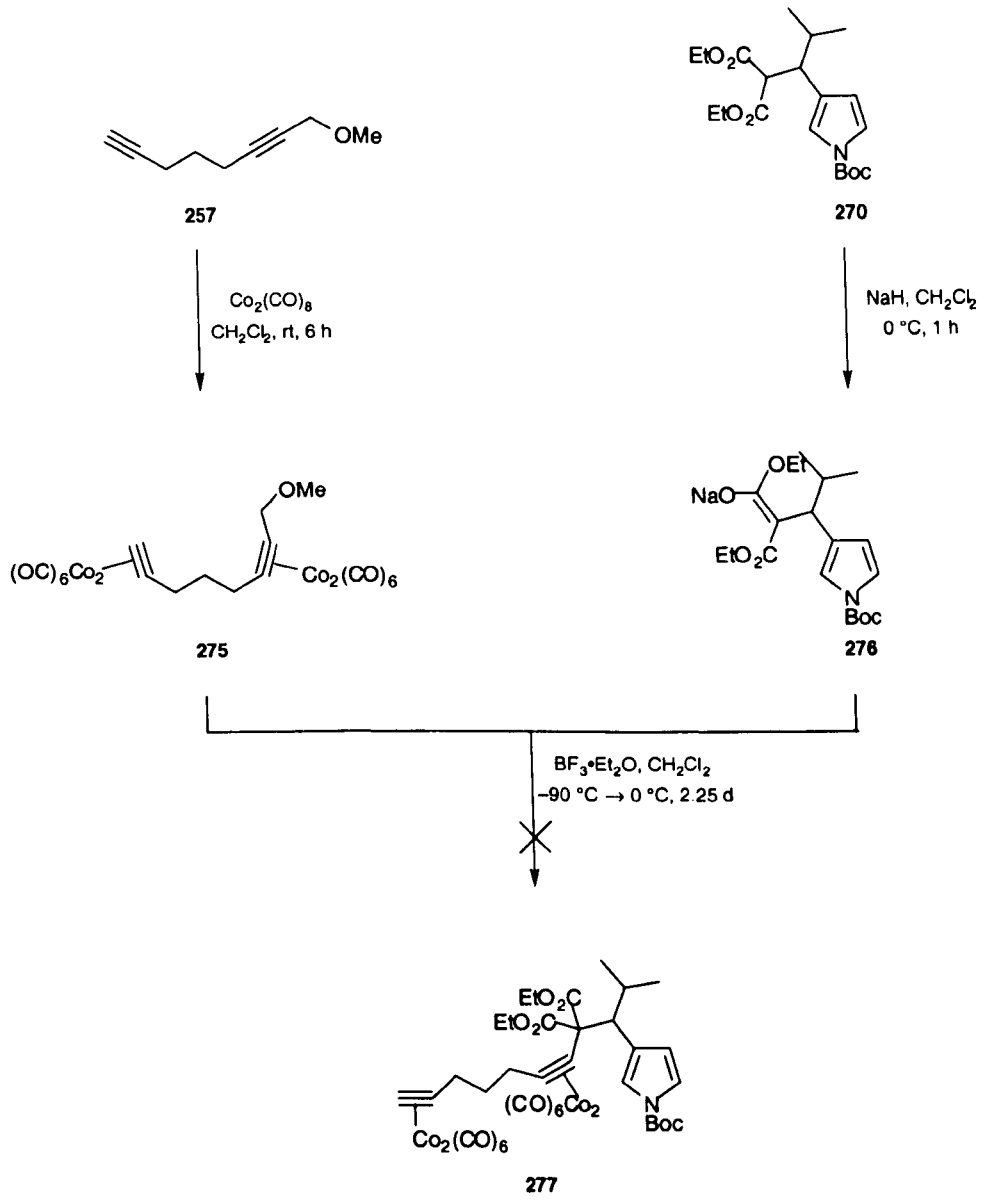


273 272

Scheme 86

6.3.2 Nicholas Coupling

Although the substrate is, at least partially, stable to the reaction conditions it is evidently not amenable to cyclisation. It is possible that the ring would be too highly strained and that the reaction is therefore not thermodynamically possible, alternatively the tertiary nucleophilic centre may be too hindered to allow the approach of the sterically demanding dicobalt complex. The latter theory may be explored by attempted coupling of the free diyne **257** with the pyrrole intermediate **270** (Scheme 87). Treatment of the diyne **257** with dicobalt octacarbonyl yielded the dicomplexed intermediate **275**, which was bright red in colour. The Lewis acid was added at –90 °C and the mixture was stirred at this temperature for 10 min before addition of the preformed anion **276**. The reaction mixture was held at –90 °C for 6 h at which point no reaction had occured by TLC and the mixture was gradually warmed to rt and held there for 2 days. Still no reaction had occurred, the dicobalt complex **275** was recovered along with the unreacted pyrrole **270**.



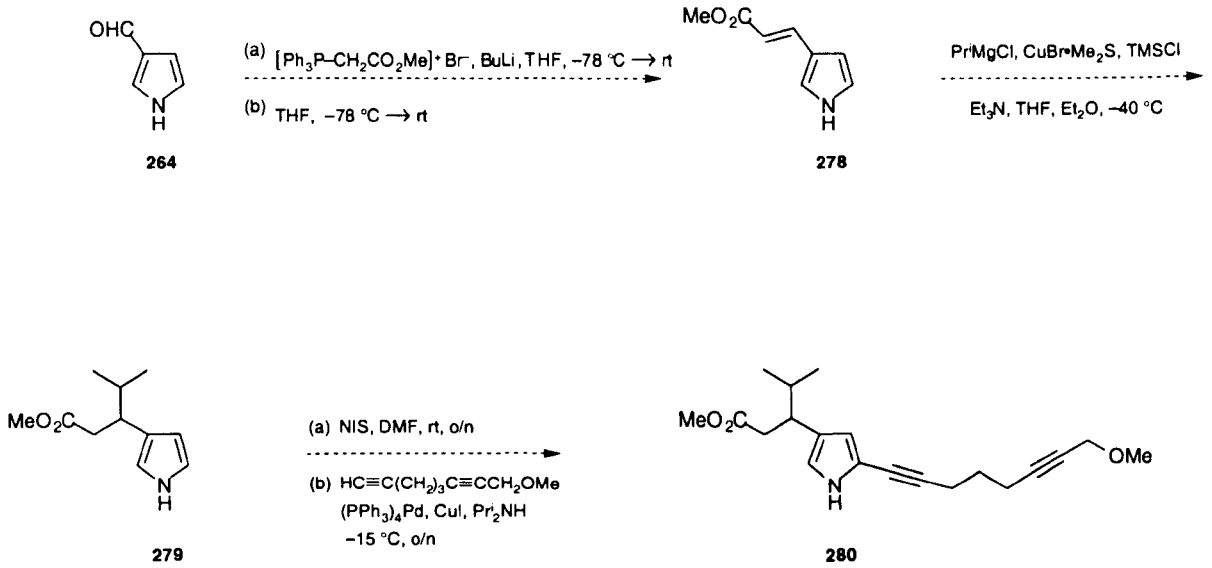
Scheme 87

It is unfortunate that the key step of our strategy was incorporated at the end of our synthesis. The trials faced along the route to the key step allowed us precious little time for modification and the strategy was eventually unsuccessful.

7.0 Conclusions and perspectives

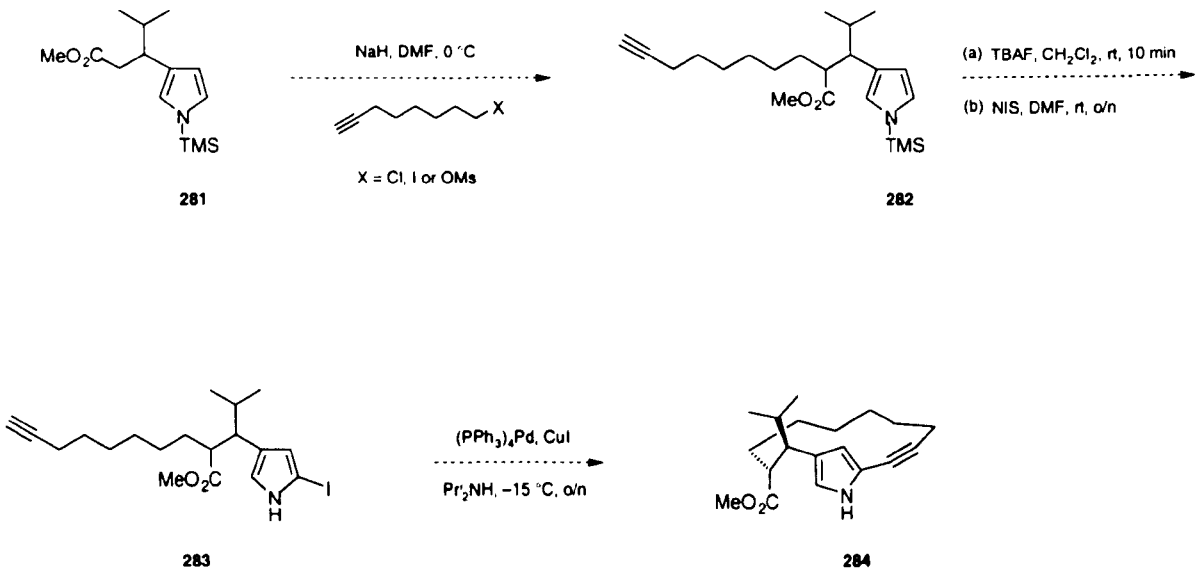
Our approach to Roseophilin has been unsuccessful thus far. None of our attempts to use the Nicholas reaction for the macrocyclisation worked. It is unclear as to whether the problem arises from the ring strain created in the cyclisation or the steric hindrance of the malonate nucleophile. Literature precedent strongly suggests that the coupling between a propargyl cation and malonate or enolate derivative is favourable (as discussed in Chapter 3) and I still feel that this choice for macrocyclisation was not misguided. Despite the lack of precedent for the dicobalt complex α to the *N*-Boc-protected pyrrole, it has been demonstrated that this complex is stable to the reaction conditions. Furthermore the use of a sterically demanding moiety at this position, which has long been a feature of our strategy, has recently been shown to enhance macrocyclisation by Hiemstra et al.[22]

One possible modification of our synthesis uses a Wittig reaction rather than a Knoevenagel condensation to give the vinyl pyrrole **278** (Scheme 88). The Nicholas precursor **280** now incorporates a secondary nucleophilic centre, which may allow approach of the sterically demanding dicobalt stabilised propargyl cation.



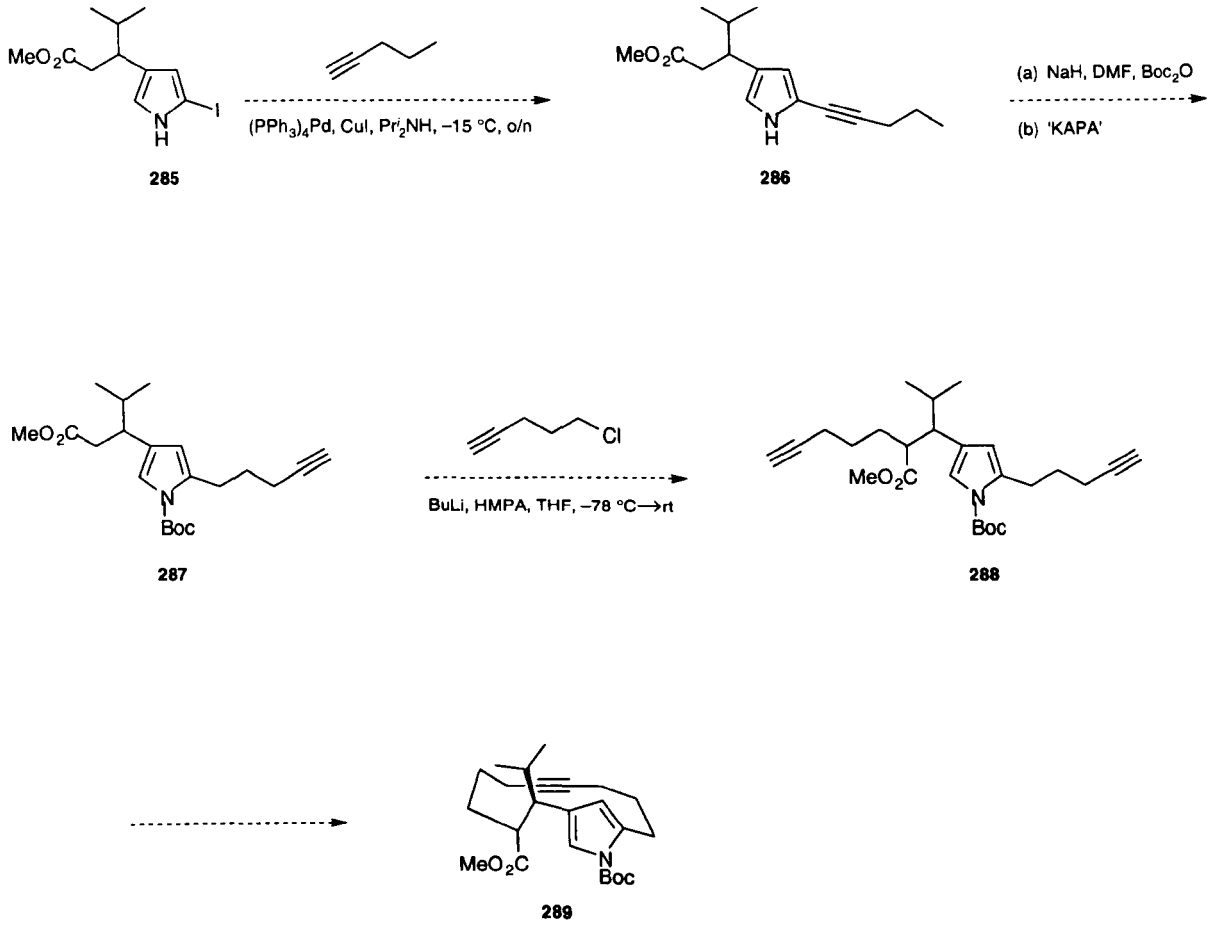
Scheme 88

One of the main advantages of our approach, and indeed something we tried to maintain in all our approaches, is the brevity and flexibility of the strategy. The synthesis of our Nicholas precursor **269** is rapid and high yielding, an advantage which allows for modification even in the final stages of the approach. If the Nicholas reaction proves unsuccessful an alternative method of macrocyclisation may be considered. As the Sonogashira reaction has been so successful in this approach, it may be possible to effect the macrocyclisation *via* this method (Scheme 89). Coupling of 1-halooct-7-yne, synthesised in two steps by a potassium zipper reaction and halogenation from the commercially available 2-octyn-1-ol, with the enolate moiety of **281** would allow the expedient construction of the macrocyclisation precursor **283**. α Pyrrole iodination with *N*-iodosuccinamide followed by an intramolecular Sonogashira reaction would then yield the macrocycle **284**.



Scheme 89

Completion of the synthesis according to the strategy discussed in the previous chapter would give the macrotricyclic core. A third and perhaps more ambitious modification to our route, deviating only slightly from the previous suggestion, would be to effect the Sonogashira reaction of **285** with propyne and perform a potassium zipper reaction to give the terminal alkyne **287** (Scheme 90). Coupling of commercially available 5-chloropentyne (or its corresponding iodide) to the enolate of **287** would give intermediate **288**, which is suitable for an alkynyl metathesis reaction, as recently described by Fürstner et al., to give the macrocyclic intermediate **289**.



285 286 287 288 289

Scheme 90

Experimental

General procedures

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon or nitrogen. Organic extracts were dried over $MgSO_4$ unless otherwise specified and evaporated at electric pump (5-10 mmHg) or water pump (20 mmHg) pressure using a Büchi rotary evaporator. Distillations in which the bath temperature is record were perfromed with a Kugelrohr apparutus.

Where appropriate, solvents and reagents were purified and dried by standard methods, *i.e.* by distillation from the usual dring agent prior to use : diethyl ether (ether) and THF were distilled from sodium/benzophenone and used fresh. Pentane, cyclohexane, dichloromethane, DMF and toluene were distilled from calcium hydride and either used fresh or stored over 4 Å molecular sieves under nitrogen. Methanol was distilled from the corresponding magnesium alkoxide. Piperidine, pyridine, pyrrole and triethylamine were distilled from calcium hydride and stored over KOH under nitrogen. Commercial organometallics were used as supplied, alkyllithium lithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrozone and Grignard reagents were titrated against 2-propanol in the presence of 1,10-phenanthroline indicator. All other reagents were purified according to literature procedures.[150]

All reactions were magnetically stirred and were monitored by TLC using Machery-Nagel Düren Alugram Sil G/UV_{254} precoated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm) then with ethanolic phosphomolybdic acid or

anisaldehyde with heating. Flash chromatography was performed on Merck silica gel 60 (0.04-0.063 mm, 230-400 mesh), unless otherwise stated, and run under low pressure.

Melting points were measured on a Griffin electrochemical apparatus and are uncorrected.

IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm^{-1} and are defined as strong (s), medium (m) or weak (w). Broad absorptions are designated (br).

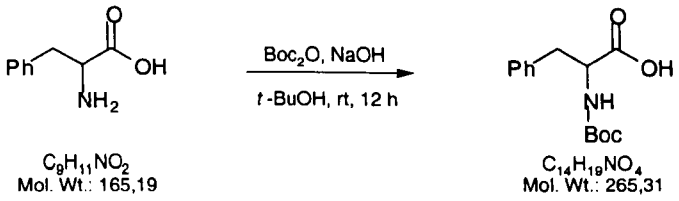
Proton NMR spectra were recorded in Fourier Transform mode on a Jeol JNX-Gx-270 (270 MHz), Bruker AC 300 (300 MHz), Bruker AM 360 (360 MHz) or Bruker AM 400 (400 MHz) spectrometer in either chlorofrom-*d* or benzene-d_6. Chemical shifts are reported in ppm relative to the residual $CHCl_3$ (δ = 7.27 ppm) or benzene ((δ = 7.20 ppm). Multiplicities are described using the following abbreviations : (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quin) quintuplet, (m) multiplet.

Carbon-13 NMR spectra were recorded on a Jeol JNX-GX-270 (68 MHz), Bruker AC 300 (75 MHz), Bruker AM 360 (90 MHz) or Bruker AM 400 (100 MHz) spectrometer in either chlorofrom-*d* (δ = 77.2 ppm)or benzene-d_6 (δ = 128.7 ppm). Chemical shifts are reported in ppm relative to the solvent. Multiplicites were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique with secondary pulses at 90° and 135°. C-H coupling is indicated by an integer 0-3 in parenthesis following the ^{13}C chemical shift value denoting the number of coupled protons.

Mass spectre were run on a VG 70-250.SE or JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in

parentheses, by the peak intensity relative to the base peak (100%). All compounds submitted for mass spectral analysis were purified by either distillation or column chormatograpy and estimated to be at least 95% pure by NMR and TLC.

N-(*tert*-Butoxycarbonyl)-DL-phenylalanine (161)

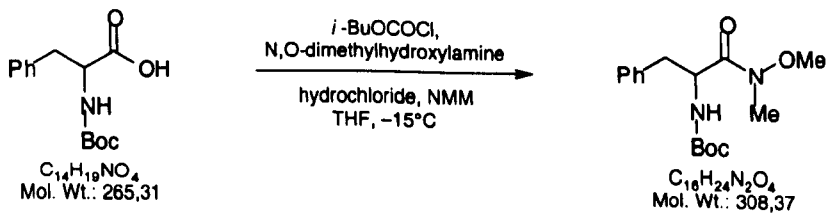


$C_9H_{11}NO_2$
Mol. Wt.: 165,19

$C_{14}H_{19}NO_4$
Mol. Wt.: 265,31

H_2O (10mL) was added to a solution of DL-phenylalanine (1.00 g, 6.05 mmol) and sodium hydroxide (0.27 g, 6.66 mmol) in *tert*-butanol (8 mL) and the mixture was stirred at rt for 10 min. Di-*tert*-butyl-dicarbonate (1.32 g, 6.66 mmol) was added dropwise and the cloudy solution was stirred at rt for 12 h. The reaction mixture was then acidified to pH 1 with aqueous HCl (1N, 10 mL), the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by recrystallisation from ethyl acetate to obtain the pure *N*-(*tert*-butoxycarbonyl)-DL-phenylalanine (1.44 g, 5.45 mmol, 90%) as a white crystalline solid, mp 85-88°C (Lit. mp 87-88°C).[94] Spectroscopic data is in accordance with literature values.[94]

N-(*tert*-Butoxycarbonyl)-DL-phenylalanine, *N*-methoxy-*N*-methylamide (162)



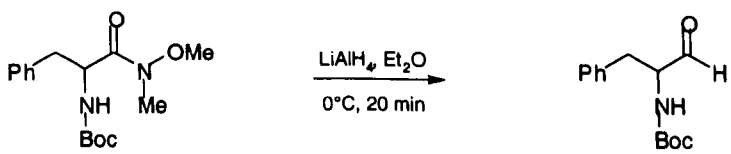
$C_{14}H_{19}NO_4$
Mol. Wt.: 265,31

$C_{16}H_{24}N_2O_4$
Mol. Wt.: 308,37

N-Methyl morpholine (2.60 mL, 23.50 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-DL-phenylalanine (1.39 g, 5.24 mmol) in THF (20 mL) at –15°C,

followed by isobutyl chloroformate (1.0 mL, 7.86 mmol), to give a precipitate. After 15 min *N,O*-dimethylhydroxylamine hydrochloride (0.77 g, 7.86 mmol) was added and stirring was continued at –15°C for 1 min before the cloudy solution was warmed to rt and stirred for a further 20 min. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by recrystallisation from ethyl acetate to give *N*-(*tert*-butoxycarbonyl)-DL-phenylalanine, *N*-methoxy-*N*-methylamide (1.28 g, 4.14 mmol, 79%) as a white crystalline solid, mp 133-136°C (Lit. mp : none given). Spectroscopic data is in accordance with literature values.[95]

_N_-(*tert* -Butoxycarbonyl)-DL-phenylalanal (159)



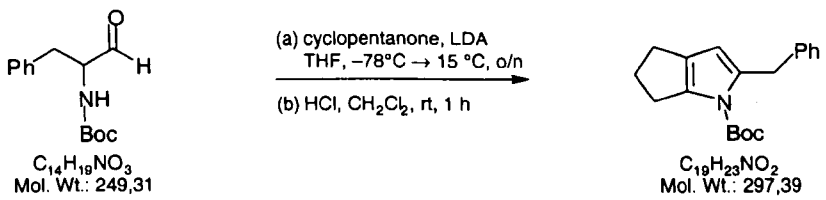
$C_{16}H_{24}N_2O_4$
Mol. Wt.: 308,37

$C_{14}H_{19}NO_3$
Mol. Wt.: 249,31

Lithium aluminium hydride (138 mg, 3.65 mmol) was added to a stirred solution of *N*-(*tert*-butoxycarbonyl)-DL-phenylalanine *N*-methoxy-*N*-methylamide (900 mg, 2.90 mmol) in Et_2O (20 mL) at 0°C. Reduction was complete in 20 min. The reaction mixture was hydrolysed with a solution of $KHSO_4$ (690 mg, 5.00 mmol) in H_2O (20 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-EtOAc (1:1)) to give *N*-(*tert* -butoxycarbonyl)-DL-phenylalanal (665 mg, 2.67 mmol, 92%) as a white

waxy solid, mp 84-87°C (Lit. mp 86°C).[95] Spectroscopic data is in accordance with literature values.[95]

_N_-(*tert*-Butoxycarbonyl)-2-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (157)



$C_{14}H_{19}NO_3$
Mol. Wt.: 249,31

$C_{19}H_{23}NO_2$
Mol. Wt.: 297,39

Cyclopentanone (0.07 mL, 0.80 mmol) was added to a freshly prepared solution of LDA in THF (5 mL) at –78°C and the mixture was stirred at –78°C for 1.5 h. *N*-(*tert*-butoxycarbonyl)-DL-phenylalanal (100 mg, 0.40 mmol) in THF (2 mL and 2 x 1 mL rinses), at –78°C was transferred *via* cannula to the reaction vessel. Stirring was continued at –78°C and the reaction mixture was allowed to warm to +15°C overnight. H_2O (10 mL) was then added, followed by Et_2O (10 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to yield a diastereomeric mixture of aldol products (152 mg). The aldol products were dissolved in CH_2Cl_2 (5 mL) and one drop of conc. HCl was added. The yellow solution became orange and was stirred for 1 h at rt before being diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-EtOAc (95:5)) to give the *N*-(*tert*-butoxycarbonyl)-2-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (50 mg, 0.52 mmol, 42%) as a brown oil.

IR (thin film): ν = 2931 (w), 2857 (w), 1738 (s), 1603 (s), 1494 (m), 1454 (m), 1368 (m), 1335 (w), 1168 (m), 1117 (w), cm^{-1}.

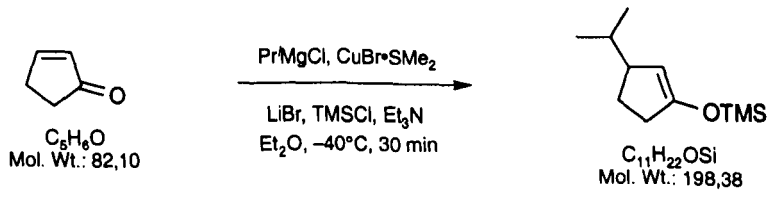
^1H NMR (300MHz, $CDCl_3$): δ = 7.15-7.35 (5H, m, Ar), 5.62 (1H, s, C**H**=C(Bn)NBoc), 4.24 (2H, s, C**H**$_2$Ph), 2.95 (2H, br t, J = 7.0 Hz, C**H**$_2$C(R)NBoc), 2.55 (2H, br t, J = 7.0 Hz, C**H**$_2$C=C(R)NBoc), 2.35 (2H, quin, J = 7.0 Hz, C**H**$_2$CH$_2$C(R)NBoc), 1.53 (9H, s, Boc).

^{13}C NMR (75MHz, $CDCl_3$): δ = 149.85 (0), 140.23 (0), 139.97 (0), 138.50 (0), 137.77 (1), 134.42 (0), 128.37 (1), 126.12 (1), 121.53 (1), 113.32 (1), 109.05 (1), 83.02 (0), 36.02 (2), 29.30 (2), 28.07 (3 (3C)), 27.86 (2), 25.42 (2).

LRMS (CI mode, isobutane): m/z = 297 [$(M + H)^+$ 87%], 207 (43), 197 (100), 91 (21), 57 (100).

HRMS (CI mode, isobutane): found $(M + H)^+$ 298.1805. $C_{19}H_{24}NO_2$ requires 2981.1808.

3-Isopropyl-cyclopenten-1-yloxy-trimethylsilane (165)



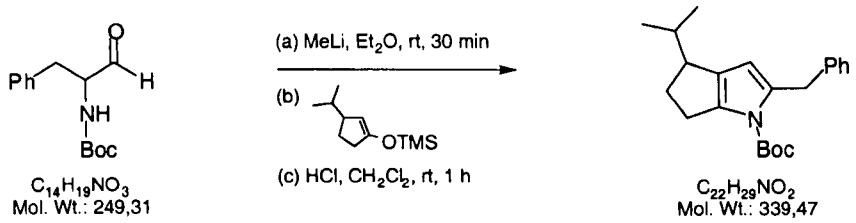
Anhydrous LiBr (2.08 g, 23.95 mmol) and CuBr•SMe_2 (123 mg, 0.60 mmol, 5 mol%) were added to the reaction vessel while still hot and the flask was refilled with nitrogen through

several vacuum cycles. Et_2O (30 mL) was added and the reaction mixture was cooled to –40°C. Isopropylmagnesiumchloride (0.76 M solution in THF, 18.80 mL, 14.28 mmol) was added, followed by a mixture of chlorotrimethylsilane (3.03 mL, 23.87 mmol), distilled from a small amount of *N,N*-dimethylaniline, and 2-cyclopenten-1-one (1.00 mL, 11.94 mmol) in Et_2O (5 mL and 2 x 2 mL rinses) at –40°C, which was added dropwise over 15 min. The brown solution was stirred for a further 15 min at –40°C, then warmed to 0°C and triethylamine (3.50 mL, 25.11 mmol) was added to give a precipitate. The mixture was poured onto a an ice cold saturated solution of NH_4Cl (3.00 g) in H_2O (20 mL), the aqueous phase was separated and extracted with Et_2O (3 x 10mL). The organic phases were combined, washed with aqueous NH_4Cl until the aqueous phase reached a pH of 7. The extract was dried over $MgSO_4$ and carefully concentrated *in vacuo*. The 3-isopropyl-cyclopenten-1-yloxy-trimethylsilane (2.27 g, 11.46 mmol, 96%) was used in the next step, without purification.

^{1}H NMR (200MHz, $CDCl_3$): δ = 4.62 (1H, dd, J_1 = 3.7, J_2 = 3.3 Hz, C**H**=COTMS); 2.42-2.38 (1H, m, C**H**Pr^i);. 2.28-2.18 (2H, m, C**H**$_2$COTMS); 2.01-1.67 (1H, m, C**H**$(CH_3)_2$); 1.57-1.40 (2H, m, C**H**$_2$CHPr^i); 0.85 (3H, d, J = 3.3 Hz, CH(CH_3)C**H**$_3$); 0.82 (3H, d, J = 3.3 Hz, CH(CH_3)C**H**$_3$); 0.20 (9H, s, OTMS).

^{13}C NMR (50MHz, $CDCl_3$): δ = 154.88 (0), 105.47 (1), 48.89 (2), 33.58 (2), 33.46 (2), 25.53 (2), 20.06 (3), 19.93 (3), 0.00 (3 (3C)).

_N_-(*tert*-Butoxycarbonyl)-2-benzyl-4-isopropyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (164)



$C_{14}H_{19}NO_3$
Mol. Wt.: 249,31

$C_{22}H_{29}NO_2$
Mol. Wt.: 339,47

Methyllithium (1.62 M solution in Et_2O, 0.5 mL, 0.81 mmol) was added to a solution of 3-isopropyl-cyclopenten-1-yloxy-trimethylsilane (154 mg, 0.80 mmol) in Et_2O (5 mL) at –78°C. The reaction mixture was allowed to warm to rt and was kept stirring at rt for 1 h, before being cooled to –78°C again. *N*-(*tert*-Butoxycarbonyl)-DL-phenylalanal (100 mg, 0.40 mmol) in Et_2O (2 mL and 2 x 1 mL rinses) at –78 °C was transferred *via* cannula to the reaction vessel and the reaction was followed by TLC as the mixture was allowed to warm to rt. The reaction was quenched at –40°C after 1 h by transferral *via* cannula to a flask of rapidly stirred ice cold H_2O (10 mL). Et_2O (10 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-EtOAc (95:5)) to yield a diastereomeric mixture of aldol products (82 mg). The aldol products were dissolved in CH_2Cl_2 (5 mL) and one drop of conc. HCl was added. The yellow solution became orange and was stirred for 1 h at rt before being diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-EtOAc (95:5)) to give *N*-(*tert*-butoxycarbonyl)-2-benzyl-4-isopropyl-1,4,5,6-tetrahydrocyclopenta[*b*] pyrrole (60 mg, 0.18 mmol, 44%) as a pale yellow oil.

IR (thin film): ν = 3028 (w), 2956 (s), 2870 (s), 1738 (s), 1370 (m), 1334 (w), 1322 (w), 1174 (m), 1118 (m) cm^{-1}.

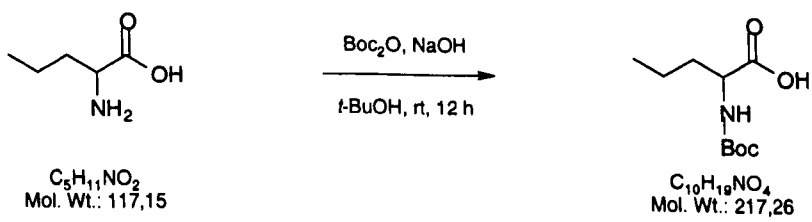
^{1}H NMR (360MHz, $CDCl_3$): δ = 7.31-7.12 (5H, m, Ar); 5.64 (1H, t, J = 1.0 Hz, C**H**=C(Bn)NBoc); 4.24 (1H, d, J = 15.8 Hz, PhC**H**$_a$H$_b$); 4.19 (1H, d, J = 15.8 Hz, PhCH$_a$**H**$_b$); 2.97-2.76 (2H, m, C**H**$_2$CHPr^i); 2.73-2.65 (1H, m, C**H**$_a$H$_b$CNBoc); 2.48-2.34 (1H, m, CH$_a$**H**$_b$CNBoc); 2.08-1.93 (1H, m, C**H**Pr^i); 1.64 (1H, dq, J_1 = 2.5 Hz J_2 = 1.24 Hz, C**H**(CH$_3$)$_2$); 1.49 (9H, s, Boc); 0.90 (3H, d, J = 6.8Hz, CH(CH$_3$)C**H**$_3$); 0.88 (3H, d, J = 6.8Hz, CH(CH$_3$)C**H**$_3$).

^{13}C NMR (91MHz, $CDCl_3$): δ = 149.90 (0), 140.33 (0), 138.45 (0), 137.04 (0), 130.56 (0), 129.01 (1 (2C)), 128.35 (1 (2C)), 126.06 (1), 109.77 (1), 83.01 (0), 45.97 (1), 35.95 (2), 33.41 (1), 32.34 (2), 28.88 (2), 28.16 (3 (3C)), 20.64 (3). 20.38 (3).

LRMS (CI mode, isobutane): m/z = 340 [(M + H)$^+$, 72%], 339 (9), 297 (12), 251 (42), 240 (100), 91 (27), 57 (100), 43 (8).

HRMS (CI mode, isobutane): found (M + H)$^+$ 340.2779. $C_{22}H_{30}NO_2$ requires 340.2277.

_N_-[(1,1-Dimethylethoxy)carbonyl]-2-aminopentanoic acid (168)



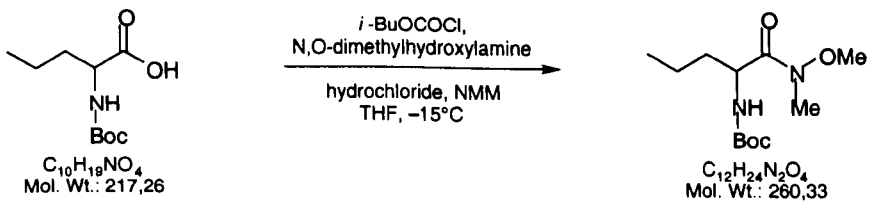
$C_5H_{11}NO_2$
Mol. Wt.: 117,15

$C_{10}H_{19}NO_4$
Mol. Wt.: 217,26

H_2O (25 mL) was added to a solution of DL-norvaline (3.00 g, 25.61 mmol) and sodium hydroxide (1.13 g, 28.25 mmol) in *tert*-butanol (25 mL) and the mixture was stirred at rt for 10 min. Di-*tert* -butyldicarbonate (6.71 g, 30.74 mmol) was added dropwise and the

cloudy solution was stirred at rt for 12 h. The reaction mixture was then acidified to pH 1 with aqueous HCl (1N), the aqueous phase was separated and extracted with Et_2O (3 x 30 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by recrystallisation from EtOAc to obtain the pure *N*-[(1,1-dimethylethoxy)carbonyl]-2-aminopentanoic acid (4.64 g, 21.36 mmol, 84%) as a white crystalline solid, mp 81 - 83 °C (Lit. mp : none given). Spectroscopic data is in accordance with literature values.[151]

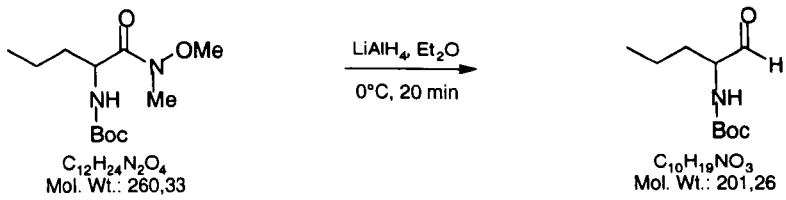
Carbamic acid-[1[(methoxymethylamino)carbonyl]-2-propyl]-1,1-dimethylethyl ester (169)



N-Methyl morpholine (10.0 mL, 90.95 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-DL-norvaline (4.39 g, 20.21 mmol) in THF (40 mL) at –15°C, followed by isobutyl chloroformate (3.93 mL, 30.3 mmol), to give a precipitate. After 15 min *N,O*-dimethylhydroxylamine hydrochloride (2.96 g, 30.34 mmol) was added and stirring was continued at –15°C for 1 min before the cloudy solution was warmed to rt and stirred for a further 20 min. The reaction mixture was then quenched with saturated $NaHCO_3$ (20 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 20 mL). The organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by recrystallisation from Et_2O to give carbamic acid-[1[(methoxymethylamino)carbonyl]-2-propyl]-1,1-dimethylethyl ester (3.32

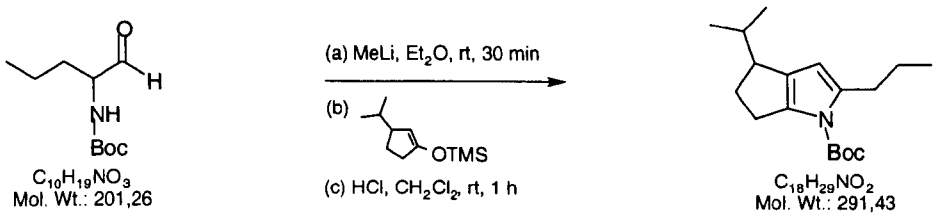
g, 12.75 mmol, 63%) as a white crystalline solid, mp 107 - 108 °C (Lit. mp none given). Spectroscopic data is in accordance with literature values.[152]

2-(1,1-Dimethylethoxycarbonylamino)pentanal (170)



Lithium aluminium hydride (584 mg, 15.39 mmol) was added to a stirred solution of *N*-(*tert*-butoxycarbonyl)-DL-norvaline, *N*-methoxy-*N*-methylamide (3.19 g, 12.25 mmol) in Et_2O (50 mL) at 0 °C. Reduction was complete in 20 min. The reaction mixture was hydrolysed with a solution of $KHSO_4$ (2.92 g, 21.44 mmol) in H_2O (20 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 20 mL). The organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-EtOAc (1:1)) to give the 2-(1,1-dimethylethoxycarbonylamino)pentanal (2.02 g, 10.04 mmol, 82%) as a colourless oil. Spectroscopic data is in accordance with literature values.[152]

N-[(1,1-Dimethylethoxy)carbonyl]-2-propyl-4-isopropyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (172)



Methyllithium (1.48 M solution in Et_2O, 1.09 mL, 1.62 mmol) was added to a solution of 3-isopropyl-cyclopenten-1-yloxy-trimethylsilane (317 mg, 1.60 mmol) in Et_2O (5 mL) at –78°C. The reaction mixture was allowed to warm to rt and was kept stirring at rt for 3 h, before being cooled to –78°C again. *N*-(*tert*-Butoxycarbonyl)-DL-norvalinal (161 mg, 0.80 mmol) in Et_2O (2 mL and 2 x 1 mL rinses), at –78°C was transferred *via* cannula to the reaction vessel and reaction was followed by TLC as the mixture was allowed to warm towards rt. The reaction was quenched at –40°C after 1 h by transferral *via* cannula to a flask of rapidly stirred ice cold H_2O (10 mL). Et_2O (10 mL) was added and the aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by chromatography (SiO_2; hexanes-Et2O (95:5)) to yield a diastereomeric mixture of aldol products (224 mg). The aldol products were dissolved in CH_2Cl_2 (5 mL) and one drop of conc. HCl was added. The yellow solution became orange and was stirred for 1 h at rt before being diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and purified by SiO_2; hexanes-Et2O (95:5)) to give *N*-[(1,1-dimethylethoxy)carbonyl]-2-propyl-4-isopropyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (170 mg, 0.56 mmol, 70%) as a colourless oil.

IR (thin film): ν = 2960 (w), 2870 (w), 2324 (s), 2070(s), 1740 (s), 1652 (s), 1528 (m), 1458 (m), 1428 (m), 1370 (m), 1336 (w), 1252 (w), 1176 (m), 1122 (w), 1016 (w), 800 (m), 660 (m) cm^{-1}.

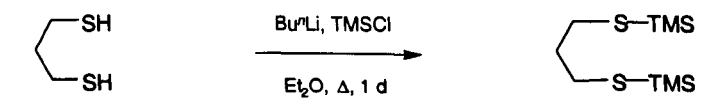
^{1}H NMR (360MHz, $CDCl_3$): δ = 5.84 (1H, t, J = 1.0 Hz C**H**=C(Pr)NBoc), 2.97-2.75 (4H, m, 2(C**H**$_2$CNBoc)), 2.74-2.67 (1H, m, C**H**Pr^i), 2.41 (1H, dt, J_1 = 8.6 Hz, J_2 = 7.2 Hz, C**H**$_a$H$_b$CHPr^i), 2.06-1.94 (1H, m, CH$_a$**H**$_b$CHPr^i), 1.70-1.63 (3H, m, C**H**(CH$_3$)$_2$), 1.59 (9H, s, Boc), 1.00 (3H, t, J = 7.4 Hz, CH$_2$C**H**$_3$), 0.96 (3H, d, J = 6.7 Hz, CH(CH$_3$)C**H**$_3$), 0.93 (3H, d, J = 6.7 Hz, CH(CH$_3$)C**H**$_3$).

^{13}C NMR (91MHz, $CDCl_3$): δ = 149.90 (0), 138.99 (0), 130.74 (0), 130.33 (0), 107.55 (1), 82.55 (0), 45.85 (1), 33.36 (1), 32.32 (2), 31.75 (2), 28.80 (2), 28.09 (3, (3C)), 22.38 (2), 20.58 (3), 20.21 (3) 13.97 (3).

LRMS (CI mode, isobutane): 292 [(M + H)$^+$, 72%], 249 (59), 192 (100), 57 (42), 43 (18).

HRMS (CI mode, isobutane): found 292.2276. $C_{18}H_{30}NO_2$ requires 292.2277.

1,3-Propanedithio-bis(trimethylsilylane) (189)



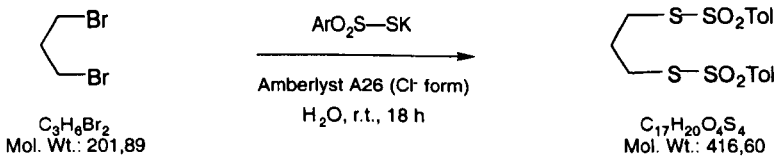
$C_3H_8S_2$
Mol. Wt.: 108,23

$C_9H_{24}S_2Si_2$
Mol. Wt.: 252,59

To a solution of 1,3-propanedithiol (5.0 mL, 0.05 mol) in Et_2O (100 mL) at 0°C, was added *n*-BuLi (2.31 M in hexanes, 43.3 mL, 0.05 mol) dropwise over a 0.5 h period. The reaction mixture was allowed to warm to rt and chlorotrimethylsilane (13 mL, 0.10 mol) was added over a 0.5 h period with efficient stirring. After a 24 h reflux period, filtration under N_2 and distillation (bp = 75°C (0.02mmHg)) afforded 4.01 g (15.88 mmol, 32%) of

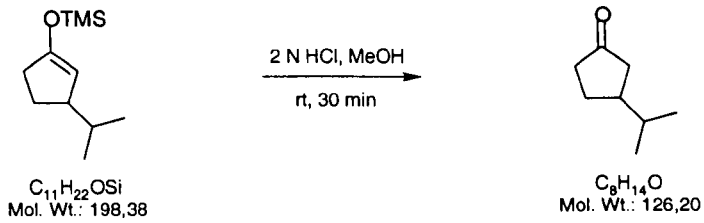
the desired 1,3-propanedithio-bis-(trimethylsilylane) as a colourless oil.Spectroscopic data is in accordance with literature values.[106]

p-Toluenesulfonothioic acid, 4-methyl-*S*, *S'*-1,3-propanediyl ester (184)



Amberlyst resin A26 (Cl^- form) (14.34 g) was added to a solution of *p*-toluene thiosulfonic acid potassium salt (5.00 g, 22.09 mmol) in water (20 mL) at rt, and the mixture was stirred at rt for 18 h. The loaded resin was subsequently removed from the solvent by filtration and was washed thoroughly with H_2O, then acetone and allowed to dry in air. The dry resin was mixed with anhydrous toluene (20 mL) and 1,3-dibromopropane (11.04 mmol) was added. The reaction mixture was stirred at 80°C, under a N_2 atmosphere for 20 h. The resin was removed by filtration and the filtrate was concentrated *in vacuo* to yield the desired *p*-toluenesulfonothioic acid, 4-methyl-*S*, *S'*-1,3-propanediyl ester practically pure. The product was purified further by recrystallisation from EtOH, to yield a white crystalline solid (3.24 g, 7.78 mmol, 68%), mp 66-67°C (Lit. mp 63.5-65 °C).[104] Spectroscopic data is in accordance with literature values.[104]

3-Isopropylcyclopentanone (190)

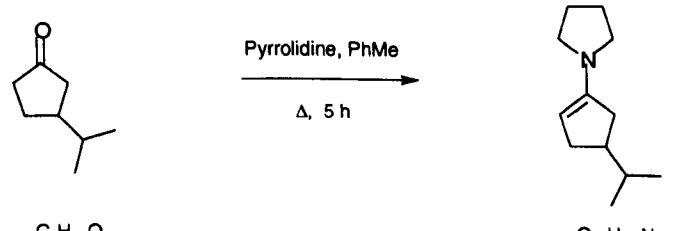


$C_{11}H_{22}OSi$
Mol. Wt.: 198,38

$C_8H_{14}O$
Mol. Wt.: 126,20

Aqueous HCl (2 N, 2mL) was added to a solution of 3-isopropyl-cyclopenten-1-yloxy-trimethylsilane (1.58 g, 7.96 mmol) in MeOH (20 mL) and the mixture was stirred at rt for 30 min. The solution was poured onto a saturated $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 x 20 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by distillation (bp = 65°C (9.0 mmHg)) to yield the desired 3-isopropylcyclopentanone as a pale yellow oil (0.964 g, 7.64 mmol, 96%). Spectroscopic data is in accordance with literature values.[153]

3-Isopropyl-1-pyrrolidino-cyclopentene (183)



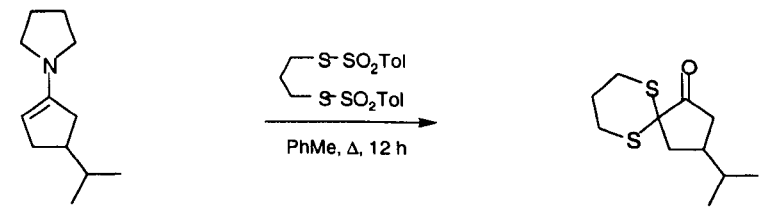
$C_8H_{14}O$
Mol. Wt.: 126,20

$C_{12}H_{21}N$
Mol. Wt.: 179,30

A solution of 3-isopropylcyclopentanone (1.27 g, 10.06 mmol) and pyrrolidine (1.10 mL, 13.18 mmol) in toluene (30 mL) was refluxed in a Dean-Stark apparatus until the separation of H_2O ceased (5 h). The excess pyrrolidine and toluene were removed from the reaction mixture *in vacuo*. The resulting residue was stored at –30°C and distilled immediately before use in the next step, yielding the 3-isopropyl-1-pyrrolidino-cyclopentene as a colourless oil (1.20 g, 6.69 mmol, 66%), which decomposed rapidly

after distillation and was therefore used immediately without characterisation in the next step.

3-Isopropyl-5, 5-(trimethylenedithio)cyclopentanone (182)



$C_{12}H_{21}N$
Mol. Wt.: 179,30

$C_{11}H_{18}OS_2$
Mol. Wt.: 230,39

A solution of freshly distilled 3-isopropyl-1-pyrrolidino-cyclopentene (250 mg, 1.39 mmol), *p*-toluenesulfonothioic acid, 4-methyl-,*S*, *S'*-1,3-propanediyl ester (581 mg, 1.39 mmol) and triethylamine (0.41 mL, 2.94 mmol) in anhydrous acetonitrile (10 mL) was refluxed for 12 h under a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue was treated with aqueous HCl (0.1 N, 7 mL) for 30 min at 50°C. The mixture was cooled to rt and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL) until the aqueous layer remained basic, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to yield a yellow residue from which 3-isopropyl-5, 5-(trimethylenedithio)cyclopentanone was isolated by chromatography (SiO_2; hexanes-Et_2O (95:5)) as a white solid. The product was further purified by recrystallisation from pentane to give white crystals (222 mg, 0.96 mmol, 69%), mp 56-58°C.

IR (nujol mull): ν = 2966 (m br), 2890 (m br), 2848 (m), 2670 (m), 1732 (s), 1460 (m br), 1376(m br), 1306 (m), 1144 (w), 954 (w), 906 (w), 726 (w), 580 (w) cm^{-1}.

^{1}H NMR (360MHz, $CDCl_3$) δ = 3.88 (1H, dt, J_1 = 13.40 Hz, J_2 = 2.67 Hz, C**H**$_a$H$_b$S), 3.13 (1H, dt, J_1 = 13.5 Hz, J_2 = 2.66 Hz, C**H**$_a$H$_b$S), 2.74 - 2.61 (1H, m, C**H**$_a$H$_b$CS$_2$), 2.54 (1H, td, J_1 = 13.30 Hz, J_2 = 2.68 Hz, CH$_a$**H**$_b$S), 2.46 (1H, td, J_1 = 13.70 Hz, J_2 = 2.12 Hz, CH$_a$**H**$_b$S), 2.23 - 1.99 (4H, m, C**H**$_2$C=O, CH$_a$**H**$_b$CS$_2$, C**H**$_a$H$_b$CH$_2$S), 1.86 (1H, d quin, J_1 = 13.83 Hz, J_2 = 2.69 Hz, CH$_a$**H**$_b$CH$_2$S), 1.65 - 1.58 (1H, m, C**H**Pr^i), 1.46 - 1.34 (1H, m, CH(CH$_3$)C**H**$_3$), 0.89 (6H, d, J = 6.63 Hz, CH(CH$_3$)C**H**$_3$).

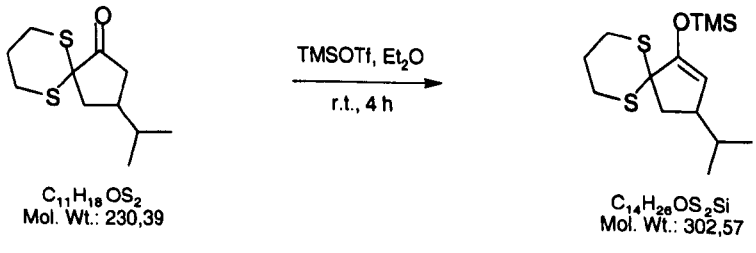
^{13}C NMR (91MHz, $CDCl_3$): δ = 224.40 (0), 50.08 (0), 43.36 (2), 41.11 (2), 39.14 (1), 33.71 (1), 26.59 (2), 26.07 (2), 24,90 (2), 21.05 (3), 20.19 (3).

LRMS (EI mode): *m/z* = 230 (M^+, 59%), 159 (32), 132 (100) 91(19).

HRMS (EI mode): found 230.0799. $C_{11}H_{18}OS_2$ requires 230.0799.

Combustion analysis: found C, 57.33; H, 7.89. Analysis calculated for $C_{11}H_{18}OS_2$: C, 57.34; H, 7.87.

3-Isopropyl-5, 5-(trimethylenedithio)cyclopentan-1-yloxy-trimethylsilane (193)



$C_{11}H_{18}OS_2$
Mol. Wt.: 230,39

$C_{14}H_{26}OS_2Si$
Mol. Wt.: 302,57

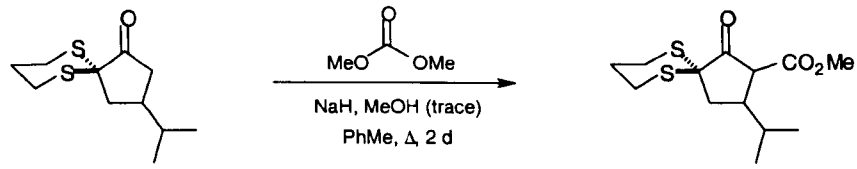
Trimethylsilyltriflate (0.79 mL, 4.35 mmol) was added dropwise to a solution of 3-isopropyl-5, 5-(trimethylenedithio)cyclopentanone (200 mg, 0.87 mmol) and triethylamine (0.20 mL, 1.42 mmol) in Et_2O (8 mL) at 0°C. The reaction mixture was allowed to warm to rt and was stirred under N_2 for 4 h. Triethylamine (1 mL, 7.10 mmol) was added, the mixture was diluted with pentane (10 mL) and poured onto a layer of pentane (20 mL) over a saturated solution of $NaHCO_3$ (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O-Et_3N (94:5:1)) to yield 3-isopropyl-5, 5-(trimethylenedithio)cyclopentan-1-yloxy-trimethylsilane (249 mg, 0.82 mmol, 94%) as a colourless oil.

IR (thin film): ν = 1636 (s), 1422 (m br), 1268 (m), 1254 (m), 1230 (m), 1072 (w), 868 (w), 634 (w) cm^{-1}.

^1H NMR (360MHz, $CDCl_3$): δ = 4.52 (1H, d, J = 2.06 Hz, **CH**OTMS), 3.49 (1H, td, J_1 = 12.46 Hz, J_2= 2.92 Hz, CH_aH_bS), 3.37 (1H, td, J_1= 12.37 Hz, J_2= 2.82 Hz, CH_aH_bS), 2.75-2.64 (2H, m, CH_2S_2), 2.47 (1H, dt, J_1= 13.91 Hz, J_2= 2.08 Hz, CH_aH_bS), 2.31 (1H, dt, J_1= 13.93 Hz, J_2 = 2.38 Hz, CH_aH_bS), 2.13-2.06 (1H, m, **CH**Pr^i), 1.95-1.82 (1H, m, $CH_aH_bCH_2S$), 1.77 (1H, m, $CH_aH_bCH_2S$), 1.34-1.18 (1H, m, **CH**$(CH_3)_2$), 0.86 (3H, d, J = 6.72 Hz, $CH(CH_3)CH_3$), 0.84 (3H, d, J = 6.68 Hz, $CH(CH_3)CH_3$), 0.29 (9H, s, TMS)

^{13}C NMR (91MHz, $CDCl_3$): δ = 159.85 (0), 102.59 (1), 54.44 (0), 45.95 (1), 44.07 (2), 33.09 (1), 28.86 (2), 28.60 (2), 24.93 (2), 20.48 (3), 20.17 (3), 0.20 (3 (3C)).

2-Carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (207)



$C_{11}H_{18}OS_2$
Mol. Wt.: 230.39

$C_{13}H_{20}O_3S_2$
Mol. Wt.: 288.43

Sodium hydride (50% in mineral oil, 40 mg, 0.79 mmol) was washed several times by decantation with pentane. A solution of 3-isopropyl-5, 5-(trimethylenedithio)cyclopentan-1-yloxy-trimethylsilane (50 mg, 0.22 mmol) in toluene (2 mL) was intoduced, dimethyl dicarbonate (0.2 mL, 2.36 mmol) and methanol (10 μL) were added. The mixture was stirred under reflux for 20 h, cooled to rt and poured into aqueous acetic acid (10 mL). The mixture was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution (10 mL), and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the resulting solid was purified by recrystallisation from pentane to yield the desired 2-carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (35 mg, 0.12 mmol, 56%) as a white, crystalline solid, mp 89-91 °C.

IR (nujol mull): ν = 2943 (m, br), 2919 (m, br), 1747 (s), 1739 (s), 1432 (m, br), 1218 (m), 1205 (m), 1077 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.82 (1H, td, J_1 = 13.38, J_2 = 2.60 Hz, CH_aH_bS), 3.80 (3H, s, OCH_3), 3.21 (1H, d, J = 10.91 Hz, $CHCO_2CH_3$), 3.11 (1H, td, J_1 = 13.03, J_2 = 2.31 Hz, CH_aH_bS), 2.68 (1H, dddd, J_1 = 14.75, J_2 = 7.89, J_3 = 3.74, J_4 = 1.10 Hz, $CH_aH_bCS_2$), 2.56 (1H, dt, J_1 = 14.77, J_2 = 3.37 Hz, CH_aH_bS), 2.50 (1H, dt, J_1 = 13.76, J_2 = 3.36 Hz, CH_aH_bS), 2.23 (1H, dd, J_1 = 10.47, J_2 = 7.15 Hz, $CHPr^i$), 2.22-2.16 (1H, m, $CH_aH_bCS_2$), 1.90 (1H, qt, J_1 = 13.96, J_2 = 3.11 Hz, $CH_aH_bCH_2S$), 1.66 (1H, dd, J_1 = 13.50, J_2 = 12.48

Hz, $CH_aH_bCH_2S$), 1.58 (1H, dqq, J_1 = 7.62, J_2 = 6.83, J_3 = 6.75 Hz, $CH(CH_3)_2$), 0.92 (3H, d, J = 6.70 Hz, $CH(CH_3)CH_3$), 0.90 (3H, d, J = 6.75 Hz, $CH(CH_3)CH_3$).

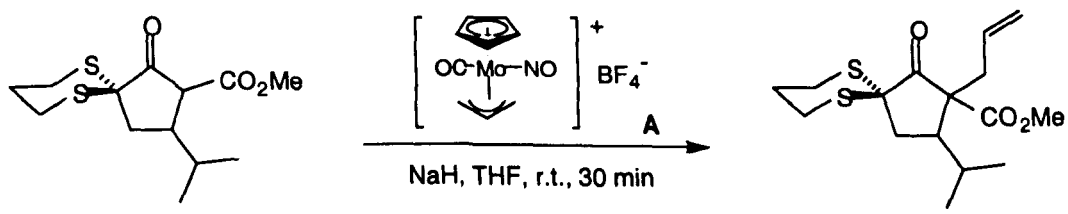
^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.64 (0), 169.65 (0), 58.11 (3), 52.82 (1), 50.80 (0), 42.46 (1), 40.89 (2), 32.95 (1), 26.91 (2), 26.52 (2), 24.84 (2), 20.83 (3), 19.80 (3).

LRMS (EI mode): m/z = 288 (18%), 257 (4), 134 (9), 132 (100), 97 (5).

HRMS (EI mode): found 288.0853. $C_{13}H_{20}O_3S_2$ requires 288.0854.

Combustion analysis: found C, 54.16; H, 7.01. Analysis calculated for $C_{13}H_{20}O_3S_2$: C, 54.13; H, 6.99.

2-Allyl-2-carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (210)



$C_{13}H_{20}O_3S_2$
Mol. Wt.: 288,42

$C_{16}H_{24}O_3S_2$
Mol. Wt.: 328,49

Sodium hydride (50% in mineral oil, 6 mg, 0.094 mmol) was washed several times by decantation with pentane. A solution of desired 2-carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (25 mg, 0.085 mmol) in THF (5 mL) was added and the mixture was stirred at rt for 1 h. The cationic molybdenum complex **A** (100 mg, 0.38 mmol) was added in one portion and the mixture was stirred at rt for 20 min. The mixture

was then poured into H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined extracts were washed with H_2O (5 mL), dried over $MgSO_4$ to give a yellow oil (59 mg). The crude product was dissolved in acetone (5mL), sodium acetate (96 mg, 1.2 mmol) and ceric ammonium nitrate (104 mg, 0.19 mmol) were added and the mixture was stirred at rt for 1 h before being poured into H_2O and extracted with Et_2O (3 x 10 mL). The combined extracts were washed with H_2O (5 mL), dried over $MgSO_4$ to give 2-allyl-2-carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone as a yellow oil (27.4 mg, 0.077 mmol, 90%).

IR (thin film): ν = 3823 (w), 3651 (w), 2945 (m, br), 2923 (m, br), 1745 (s), 1740 (s), 1431 (m, br), 1221 (m), 1202 (m), 1078 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 (1H, dddd, J_1 = 17.65, J_2 = 9.48, J_3 = 7.60, J_4 = 5.20 Hz, CH=CH2), 5.03 (2H, dt, J_1 = 13.82 Hz, J_2 = 1,26 Hz, C=CHaHb), 3.88 (1H, td J_1 = 13 80 Hz, J_2 = 2.67 Hz, CH_aH_bS), 3.66 (3H, s, CO_2CH_3), 2.98 (1H, td J_1 = 13 64 Hz, J_2 = 2.68 Hz, CH_aH_bS), 2.90 (1H, ddt, J_1 = 14.60 Hz, J_2 = 5.28, J_3 = 1.64 Hz, $CH_aH_bCS_2$), 2.63 (1H, dd, J_1 = 14.60 Hz, J_2 = 5.12 Hz, $CHPr^i$), 2.71-2.63 (2H, m, CH_2–CH=CH_2), 2.37-2.20 (4H, m, $CH_aH_bCS_2$, CH_aH_bS, CH_2CH_2S), 1.82 (1H, qd J_1 = 13 83 Hz, J_2 = 2.69 Hz, CH_aH_bS), 1.21-1.12 (1H, m, $CH(CH_3)CH_3$), 1.00 (6H d J = 6.66 Hz, $CH(CH_3)CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.30 (0), 171.30 (0), 133.88 (1), 118.80 (2), 64.28 (0), 52.43 (3), 50.29 (0), 45.55 (1), 41.64 (2), 38.68 (2), 31.00 (1), 27.03 (2), 26.16 (2), 24.92 (2), 22.00 (3), 21.49 (3).

LRMS (EI mode): 328 (M^+, 18%), 132 (100).

HRMS (EI mode): found 328.1165. $C_{16}H_{24}O_3S_2$ requires 328.1167.

2-Allyl-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (210a)

$C_{16}H_{24}O_3S_2$
Mol. Wt.: 328,49

$C_{14}H_{22}OS_2$
Mol. Wt.: 270,45

Finely powdered sodium cyanide (3.7 mg, 0.76 mmol) was added to a solution of 2-allyl-2-carbomethoxy-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (25 mg, 0.76 mmol) in anhydrous DMSO and the mixture was heated to 160 °C for 2 h with vigorous stirring. The cooled reaction mixture was poured onto H_2O (2 mL) at 0 °C and extracted with hexanes (3 x 5 mL). The extracts were washed thouroughly with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Kugelrohr distillation of the residue yielded 2-allyl-3-isopropyl-5,5-(trimethylenedithio)-cyclopentanone (19.0 mg, 0.70 mmol, 92%) as a colourless oil.

IR (thin film): ν = 3826 (w), 3653 (w), 2942 (m, br), 2919 (m, br), 1737 (s), 1430 (m, br), 1215 (m), 1192 (m), 1064 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.79 (1H, dddd, J_1 = 16.97, J_2 = 10.05, J_3 = 7.43, J_4 = 6.86 Hz, C**H**=CH_2), 5.07 (1H, d, J = 16.97 Hz, CH=C**H**$_a$H$_b$), 5.03 (2H, d, J = 9.94 Hz, CH=CH$_a$**H**$_b$), 3.91 (1H, td, J_1 = 13.46, J_2 = 2.56, C**H**$_a$H$_b$S), 3.20 (1H, td J_1 = 13 69 Hz, J_2 = 2.31 Hz, CH$_a$**H**$_b$S), 2.59-2.41 (4H, m, 2(CH$_a$**H**$_b$S), C**H**$_2$CS$_2$), 2.30-2.17 (2H, m, C**H**$_2$CH=CH$_2$), 2.10-1.99 (2H, m, C**H**C(O), C**H**Pr^i), 1.91-1.80 (2H, m, C**H**$_a$H$_b$CH$_2$S,

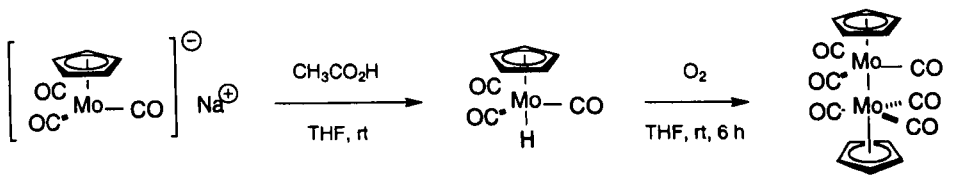
$CH(CH_3)_2$), 1.33 (1H, d, J = 19.31 Hz, $CH_aH_bCH_2S$), 0.96 (3H, d, J = 6.85 Hz, $CH(CH_3)CH_3$), 0.86 (3H, d, J = 6.81 Hz, $CH(CH_3)CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.22 (0), 135.48 (1), 116.90 (2), 50.15 (1), 49.48 (0), 42.19 (1), 38.78 (2), 34.50 (2), 29.67 (1), 27.09 (2), 26.24 (2), 25.12 (2), 21.35 (3), 17.69 (3).

LRMS (EI mode): 270 (M^+, 30%), 227 (4), 199 (5), 187 (5), 132 (100), 41 (5).

HRMS (EI mode): found 270.1111. $C_{14}H_{22}OS_2$ requires 270.1112.

η^5-Cyclopentadienylmolybdenum tricarbonyl dimer $[CpMo(CO)_3]_2$

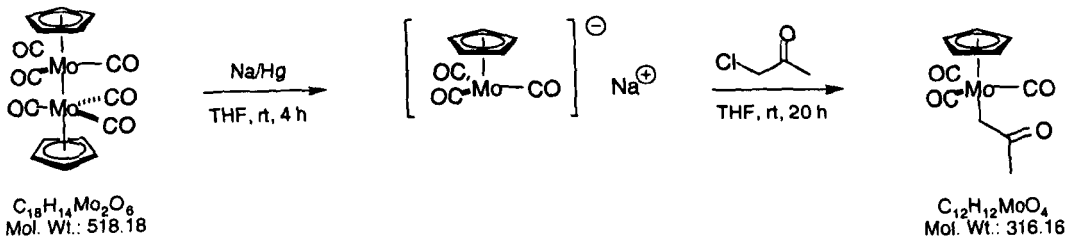


$C_{18}H_{14}Mo_2O_6$
Mol. Wt.: 518.18

Freshly cracked cyclopentadiene (270 mg, 4.2 mmol) was added to sodium sand (96 mg, 4.2 mmol) in THF (20 mL) and this mixture was sonicated for *ca.* 4 h until all the sodium had reacted. The resulting solution of cyclopentadienyl sodium was transferred *via* cannula under positive pressure to a solution of molybdenum hexacarbonyl (1 g, 3.8 mmol) in THF (15 mL) and the mixture was stirred at the minimum temperature necessary for reflux for 16 h. The yellow solution of the anion $[CpMo(CO)3]^-Na^+$ was cooled to rt and any lost solvent was replaced. Glacial acetic acid (0.65 mL) was added and the reaction mixture

was vortexed under a rapid stream of air for 5 h. The solvent was removed *in vacuo* and the red-purple dimer $[CpMo(CO)_3]_2$ was extracted from the residue with hot (80 °C) toluene (5 x 30 mL) until the extracts remained colourless. The extracts were filtered and the volatiles were removed *in vacuo* to yield red-purple crystals (585 mg, 1.2 mmol, 63%) which are sufficiently pure for use in the next step. Spectroscopic data is in accordance with literature values.[125]

η^5-Cyclopentadienyl(2-oxopropyl)tricarbonyl molybdenum [$CpMo(CO)_3(\eta^1$-$CH_2COMe)$] (217) (Method A)



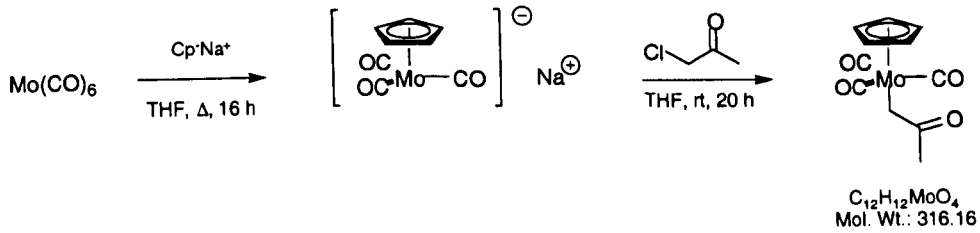
$C_{18}H_{14}Mo_2O_6$
Mol. Wt.: 518.18

$C_{12}H_{12}MoO_4$
Mol. Wt.: 316.16

A solution of the molybdenum dimer $[CpMo(CO)_3]_2$ (500 mg, 1.0 mmol) in THF (35 mL) was stirred at rt with a 30% excess of sodium metal as 5% Na/Hg amalgam (1.3 mmol) for 12 h until the red-purple colour of the dimer became the yellow colour of the anion $[CpMo(CO)_3]^-Na^+$. The solution was decanted from excess amalgam *via* cannula under positive pressure and freshly distilled chloroacetone (0.16 mL, 2.1 mmol) was added to give a red solution. The reaction mixture was stirred at rt for 20 h after which NaCl had precipitated. The solvent was removed *in vacuo* and the resulting red-brown residue was dried under high vacuum. The residue was extracted with CH_2Cl_2 (30 mL), filtered under N_2 and the solvent was again removed *in vacuo*. The residue remaining was extracted with pentane (3 x 20 mL) to leave a dry powdery solid, the extracts were filtered under N_2 and

the volatiles were removed *in vacuo* to yield the acetone complex [$CpMo(CO)_3(\eta^1$-$CH_2COMe)$] as a red solid (17 mg, 0.056 mmol, 11.2% after substantial decomposition). Reaction was followed by ^1H NMR which clearly showed the cyclopentadiene signal characteristic of the required product. However the isolated product could not be characterised due to extensive and rapid decomposition. The isolated product was used immediately in the subsequent reaction.

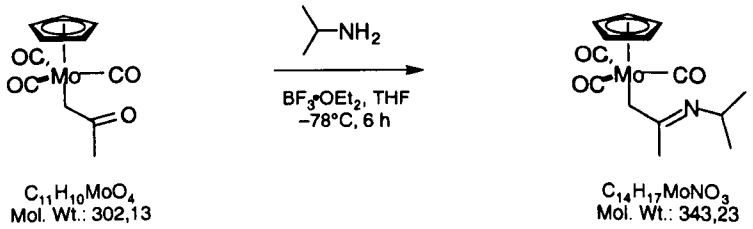
η^5-Cyclopentadienyl(2-oxopropyl)tricarbonyl molybdenum [$CpMo(CO)_3(\eta^1$-$CH_2COMe)$] (217) (Method B)



Freshly cracked cyclopentadiene (932 mg, 14.1 mmol) was added to sodium sand (324 mg, 14.1 mmol) in THF (70 mL) and this mixture was sonicated for c. 4 h until all the sodium had reacted. The resulting solution of cyclopentadienyl sodium was transferred via cannula under positive pressure to a solution of molybdenum hexacarbonyl (3.00 g, 11.3 mmol) in THF (50 mL) and the mixture was stirred at the minimum temperature necessary for reflux for 16 h. The reaction mixture was cooled to rt and freshly distilled chloroacetone (1.2 mL, 14.5 mmol) was added. The resulting red solution was stirred at rt for 20 h after which NaCl had precipitated. The solvent was removed in vacuo and the resulting red-brown residue was dried under high vacuum. The residue remaining was extracted with pentane (3 x 100 mL) to leave a dry powdery solid, the extracts were filtered under N_2 and the volatiles were removed in vacuo to yield the η^1-acetone complex [$CpMo(CO)_3(\eta^1$-

$CH_2COMe)$] as a red solid (486 mg, 1.54 mmol, 13.6% after substantial decomposition). Reaction was followed by ^1H NMR which clearly showed the cyclopentadiene signal characteristic of the required product. However the isolated product could not be characterised due to extensive and rapid decomposition. The isolated product was used immediately in the subsequent reaction.

η^5-Cyclopentadienyl-η^1-(N-isopropyl-2-iminopropyl)-tricarbonyl molybdenum [$CpMo(CO)_3(\eta^1$-$CH_2CMe{=}NCHMe_2)$] (Method A)

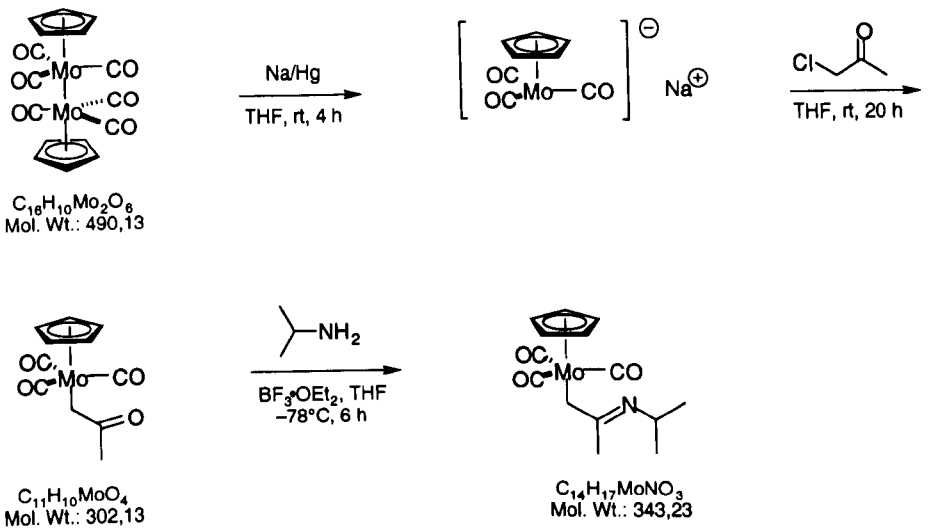


$C_{11}H_{10}MoO_4$
Mol. Wt.: 302,13

$C_{14}H_{17}MoNO_3$
Mol. Wt.: 343,23

BF_3•OEt_2 (0.21 mL, 1.54 mmol) was added to a solution of [$CpMo(CO)_3(\eta^1$-$CH_2COMe)$] (485 mg, 1.54 mmol) in THF (10 mL) at –78 °C. To this red stirred solution was added isopropylamine (0.14 mL, 1.54 mmol) and the solution became yellow. The mixture was stirred at –78 °C for 6 h. The solvent was removed *in vacuo* and the red-brown residue was purified by flash column chromatography under N_2 (Al_2O_3; hexanes-anhydrous Et_2O, (1:1)). After elution of the first red-purple band of $[CpMo(CO)_3]_2$ a yellow band was collected and evaporated to dryness to yield the η^1-imine complex [$CpMo(CO)_3(\eta^1$-$CH_2CMe{=}NCHMe_2)$] as a yellow solid (213 mg, 0.63 mmol, 38% after partial decomposition). Reaction was followed by ^1H NMR which clearly showed the cyclopentadiene signal characteristic of the required product. However the isolated product could not be characterised due to extensive and rapid decomposition. The isolated product was used immediately in the subsequent reaction.

η^5-Cyclopentadienyl-η^1-(*N*-isopropyl-2-iminopropyl)-tricarbonyl molybdenum [CpMo(CO)3(η^1-$CH_2CMe{=}NCHMe_2$)] (Method B)



$C_{16}H_{10}Mo_2O_6$
Mol. Wt.: 490,13

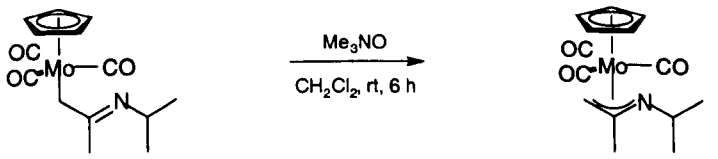
$C_{11}H_{10}MoO_4$
Mol. Wt.: 302,13

$C_{14}H_{17}MoNO_3$
Mol. Wt.: 343,23

Freshly cracked cyclopentadiene (621 mg, 9.4 mmol) was added to sodium sand (216 mg, 9.4 mmol) in THF (50 mL) and this mixture was sonicated for *c.* 4 h until all the sodium had reacted. The resulting solution of cyclopentadienyl sodium was transferred *via* cannula under positive pressure to a solution of molybdenum hexacarbonyl (2.00 g, 7.5 mmol) in THF (30 mL) and the mixture was stirred at the minimum temperature necessary for reflux for 16 h. The reaction mixture was cooled to rt and freshly distilled chloroacetone (0.77 mL, 9.7 mmol) was added. The resulting red solution was stirred at rt for 20 h after which time NaCl had precipitated. The reaction mixture was cooled to –78 °C and BF_3•OEt_2 (1.05 mL, 8.3 mmol) was added. To this red stirred solution was added isopropylamine (0.70 mL, 8.3 mmol), the solution became yellow and the mixture was stirred at –78 °C for 6 h. The solvent was removed *in vacuo* and the red-brown residue was purified by flash column chromatography under N_2 (Al_2O_3 hexanes-Et_2O (1:1)). After elution of the first red-purple band of $[CpMo(CO)_3]_2$ and a second red band of an unknown complex, a yellow band was

collected and evaporated to dryness to yield the η^1-imine complex [$CpMo(CO)_3(\eta^1$-$CH_2CMe{=}NCHMe_2)$] as a yellow solid (77 mg, 0.23 mmol, 30.7% after substantial decomposition). Reaction was followed by ^1H NMR which clearly showed the cyclopentadiene signal characteristic of the required product. However the isolated product could not be characterised due to extensive and rapid decomposition. The isolated product was used immediately in the subsequent reaction.

η^5-Cyclopentadienyl-η^3-(*N*-isopropyl-2-methylazaallyl) tricarbonyl molybdenum (218) [$CpMo(CO)_2(\eta^3$-$CH_2CMeNCHMe_2)$]

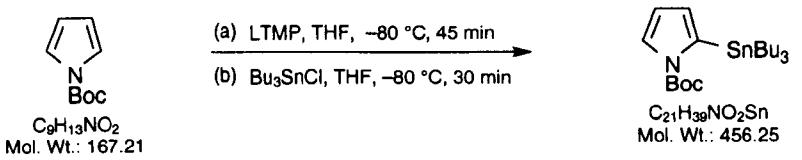


$C_{14}H_{17}MoNO_3$
Mol. Wt.: 343,23

$C_{14}H_{17}MoNO_3$
Mol. Wt.: 343,23

Trimethylamine-*N*-oxide (17 mg, 0.23 mmol) was added to a stirred solution of [$CpMo(CO)_3(\eta^1$-$CH_2CMe{=}NCHMe_2)$] (77 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) at rt and the mixture was stirred for 6 h. The solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography under N_2 (Al_2O_3 hexanes-Et_2O (1:1)). A brown band was collected and evaporated to dryness to yield a dark brown solid. Recrystallisation from CH_2Cl_2-hexanes yielded block-shaped brown crystals of [$CpMo(CO)_2(\eta^3$-$CH_2CMeNCHMe_2)$] (44.2 mg, 0.13 mmol, 56%). Reaction was followed by ^1H NMR which clearly showed the cyclopentadiene signal characteristic of the required product. However the isolated product could not be characterised due to extensive and rapid decomposition. The isolated product was used immediately in the subsequent reaction.

N-(*tert*-Butoxycarbonyl)-2-(tributylstannyl)pyrrole (234)



To a solution of 2,2,6,6,-tetramethylpiperidine (4.5 mL, 26.7 mmol) in THF (50 mL) at –80 °C was added *n*-butyllithium (2.3 M in hexanes, 11.5 mL, 26.7 mmol). The reaction mixture was stirred for 10 min at –80 °C, the cooling bath was replaced with an ice bath and the mixture was stirred for a further 1 h at 0 °C before being recooled to –80 °C. *N*-(*tert*-Butoxycarbonyl)pyrrole (4.2 mL, 25.4 mmol) was added and the mixture was stirred at –80 °C for 45 min. Tributyltin chloride (7.5 mL, 27.6 mmol) was added dropwise and the mixture was stirred at –80 °C for 30 min. The mixture was diluted with H_2O (5 mL) and warmed to rt. The organic phase was diluted with Et_2O (100 mL) and washed with sat. NH_4Cl (30 mL), brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O (9:1)) to yield *N*-(*tert*-butoxycarbonyl)-2-(tributylstannyl)pyrrole (9.49 g, 20.8 mmol, 78%) as a colourless oil which yellows on exposure to air.

IR (thin film): ν = 2956 (s, br), 2822 (s, br), 2871 (m, br), 2853 (m, br), 1729 (s), 1386 (s), 1340 (s), 1157 (s), 978 (m), 853 (w), 725 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (1H, dd, J_1 = 3.02, J_2 = 1.34 Hz, C**H**NBoc), 6.71 (1H, dd, J_1 = 2.96, J_2 = 1.28 Hz, C**H**=C(SnBu$_3$)NBoc), 6.46 (1H, t, J = 3.01 Hz, C**H**=CHNBoc), 1.90-1.74 (6H, m, 3(SnC**H**$_2$C**H**$_2$C**H**$_2$C**H**$_3$)), 1.52 (6H, sext. J = 7.41 Hz,

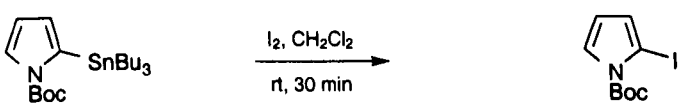
3($SnCH_2CH_2CH_2CH_3$)), 1.41 (9H, s, Boc), 1.46-1.28 (6H, m, 3($SnCH_2CH_2CH_2CH_3$)), 1.05 (9H, t, J = 7.35 Hz, 3($SnCH_2CH_2CH_2CH_3$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.59 (0), 134.66 (0), 124.11 (1), 123.99 (1), 113.90 (1), 83.28 (0), 30.05 (2 (3C)), 28.14 (3 (3C)), 28.04 (2 (3C)), 14.33 (3 (3C)), 11.85 (2 (3C)).

LRMS (CI mode, isobutane): m/z = 458.2 [$(M + H)^+$, 43%], 400 (100), 344 (64), 291 (40), 168 (8).

HRMS (CI mode, isobutane): found [$(M + H)^+$, ^{116}Sn] 454.2073 (Err –0.8 ppm); [$(M + H)^+$, ^{118}Sn] 456.2075 (Err –0.1 ppm); [$(M + H)^+$, ^{119}Sn] 457.2120 (Err 6.0 ppm); [$(M + H)^+$, ^{120}Sn] 458.2089 (Err 1.7 ppm). $C_{21}H_{39}NO_2Sn$ requires 456.2082.

N-(*tert*-Butoxycarbonyl)-2-iodopyrrole (235)



$C_{21}H_{39}NO_2Sn$
Mol. Wt.: 456.25

$C_9H_{12}INO_2$
Mol. Wt.: 293.10

Freshly sublimed iodine (556 mg, 2.19 mmol) was added to a solution of N-(*tert*-butoxycarbonyl)-2-(tributylstannyl)pyrrole (1.00 g, 2.19 mmol) in CH_2Cl_2 (10 mL) at rt under N_2. The mixture was stirred for 30 min until the iodine colour discharged. The reaction mixture was poured onto H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL), the solvent was removed *in vacuo* and the resulting residue was purified by flash column

chromatography (Al_2O_3; hexanes-Et_2O (9:1)) to yield *N*-(*tert*-butoxycarbonyl)-2-iodopyrrole (629 mg, 2.15 mmol, 98%) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 2980 (br), 1752 (s), 1458 (w), 1430 (m), 1370 (m), 1322 (s), 1285 (m), 1153 (s), 1051 (m), 976 (m) cm^{-1}.

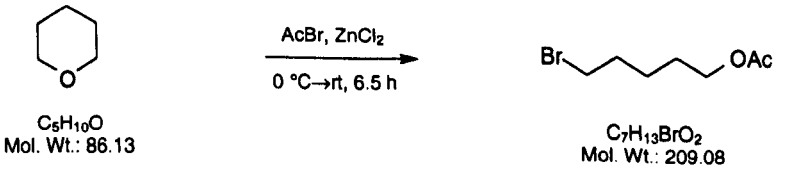
^1H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.45 (1H, m, C**H**NBoc), 6.56-6.54 (1H, m, C**H**=C(I)NBoc), 6.02-6.00 (1H, m, C**H**=CHCNBoc), 1.37 (9H, s, Boc).

^{13}C NMR (91MHz, $CDCl_3$): δ = 148.02 (0), 126.29 (1), 125.51 (1), 114.24 (1), 84.65 (0), 64.01 (0), 28.06 (3 (3C)).

LRMS (CI mode, isobutane): *m/z* = 294 [$(M + H)^+$, 100%], 293 (38), 238 (65), 237 (15), 193 (22), 109 (6).

HRMS (CI mode, isobutane): found $(M + H)^+$, 293.9994. $C_9H_{12}INO_2$ requires 293.9992

5-Bromopentyl acetate (237)



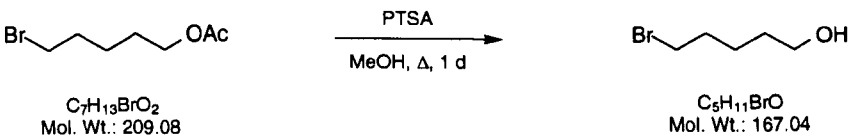
$C_5H_{10}O$
Mol. Wt.: 86.13

$C_7H_{13}BrO_2$
Mol. Wt.: 209.08

Acetyl bromide (5 mL, 67.6 mmol) was added rapidly to an ice-cold mixture of tetrahydropyran (5.42 mL, 55.5 mmol) and anhydrous $ZnCl_2$ (59 mg, 0.43 mmol),

maintaining the internal temperature of the reaction between 25 and 30 °C. The mixture was stirred at 0 °C for 30 min and at rt for 6 h. The product was purified by distillation (bp 110-115 °C (15 mmHg)) to yield 5-bromopentyl acetate (6.4 g, 30.6 mmol, 55%) as a colourless oil. Spectroscopic data is in accordance with literature values.[131]

5-Bromopentanol (238)

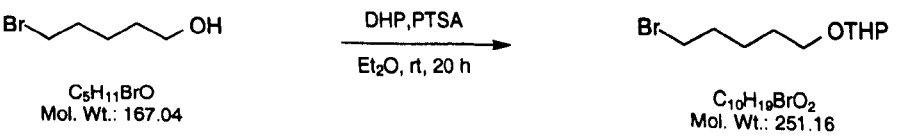


$C_7H_{13}BrO_2$
Mol. Wt.: 209.08

$C_5H_{11}BrO$
Mol. Wt.: 167.04

5-Bromopentyl acetate (6.0 g, 28.7 mmol) was refluxed for 1 d with PTSA (150 mg, 0.79 mmol) in MeOH (50 mL). The reaction mixture was cooled to rt and poured onto saturated $NaHCO_3$ solution (20 mL) and extracted with Et_2O (3 x 30 mL). The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by distillation (bp 45-50 °C (0.5 mmHg)) to yield 5-bromopentanol (4.1 g, 24.4 mmol, 85%) as a colourless oil. Spectroscopic data is in accordance with literature values.[154]

5-Bromo-1-(tetrahydropyran-2-yloxy)pentane (239)

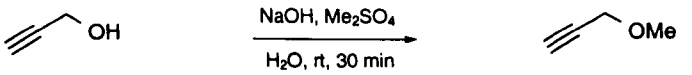


$C_5H_{11}BrO$
Mol. Wt.: 167.04

$C_{10}H_{19}BrO_2$
Mol. Wt.: 251.16

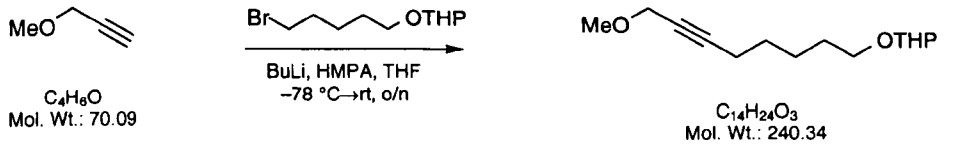
To a solution of 5-Bromopentanol (4.0 g, 23.9 mmol) in Et_2O (400 mL) was added a catalytic amount of PTSA and dihydropyran (2.18 mL, 23.9 mmol). The reaction mixture was stirred at rt for 20 h, then poured onto sat. $NaHCO_3$ (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by distillation (bp 80-100 °C (0.1 mmHg)) to yield 5-bromo-1-(tetrahydropyran-2-yloxy)pentane (5.04 g, 20.1 mmol, 84%) as a colourless oil. Spectroscopic data is in accordance with literature values.[155]

Methyl propargyl ether



Dimethyl sulfate (183 mL, 1.94 mol) was added to a propargyl alcohol (100 mL, 1.72 mol) and in H_2O (60 mL) at 0 °C. To this solution a 50% aqueous NaOH solution (190 mL) was added carefully to maintain the internal temperature between 10 and 15 °C. Once the addition was complete the mixture was stirred at rt for 30 min. The organic layer was separated, dried over $NaSO_4$ and distilled (bp 61-63 °C (760 mmHg)) to yield methyl propargyl ether (119.35 g, 1.70 mmol, 99%). Spectroscopic data is in accordance with literature values.[156]

1-Methoxy-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-2-yne (240)



C_4H_6O
Mol. Wt.: 70.09

$C_{14}H_{24}O_3$
Mol. Wt.: 240.34

To a solution of methyl propargyl ether (1.94 mL, 23.0 mmol) in THF (50 mL) at –78 °C was added *n*-butyllithium (2.2 M in hexanes, 11.0 mL, 24.1 mmol), followed, after 10 min by HMPA (5.6 mL, 32.2 mmol) and 5-bromo-1-(tetrahydropyran-2-yloxy)pentane (4.93 g, 20.5 mmol). The reaction was allowed to warm to rt and stirred at rt overnight. The reaction mixture was poured onto sat. NH_4Cl (15 mL) and Et_2O (30 mL) and was further extracted with Et_2O (3 x 30 mL). The combined organic phases were washed successively with aqueous HCl (1N, 15 mL), sat. $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et2O (1:1)) to yield the pure 1-methoxy-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-2-yne (3.5 g, 14.5 mmol, 70%) as a colourless oil.

IR (thin film): ν = 2939 (s), 2864 (s), 2820 (s), 2294 (w), 2228 (w), 2217 (w), 1452 (m), 1355 (m), 1121 (m), 906 (m) cm^{-1}.

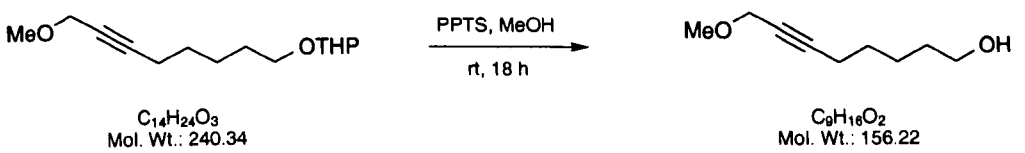
^1H NMR (400 MHz, $CDCl_3$): δ = 4.57 (1H, dd, J_1 = 4.45, J_2 = 4.41 Hz, $\mathbf{CHO_2}$), 4.07 (2H, t, J = 2.12 Hz, $\mathbf{CH_2}OCH_3$), 3.85 (1H, dt, J_1 = 9.41, J_2 = 7.40, Hz, $\mathbf{CH_aH_b}OCHOR$), 3.74 (1H, dt, J_1 = 9.64, J_2 = 6.73 Hz, $CH_a\mathbf{H_b}OCHOR$), 3.52-3.46 (1H, m $\mathbf{CH_aH_b}OTHP$), 3.41-3.36 (1H, m, $CH_a\mathbf{H_b}OTHP$), 3.36 (3H, s, $OC\mathbf{H_3}$), 2.24 (2H, tt, J_1 = 8.68, J_2 = 2.03 Hz, $\mathbf{CH_2}C{\equiv}C$), 1.84-1.78 (1H, M, $\mathbf{CH_aH_b}O_2$), 1.73-1.67 (1H, m, $CH_a\mathbf{H_b}O_2$), 1.64-1.42 (10H, m, $(\mathbf{CH_2})_3CH_2OTHP$, $\mathbf{CH_2}CH_2CHO_2R$, $\mathbf{CH_2}CH_2OCH(R)O$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.99 (1), 87.10 (0), 75.97 (0), 67.53 (2), 62.46 (2), 60.34 (2), 57.50 (3), 30.90 (2), 29.40 (2), 28.61 (2), 28.26 (2), 25.67 (2), 19.80 (2), 18.84 (2).

LRMS (CI mode, isobutane): *m/z* = 241 [$(M + H)^+$, 100%], 209 (9), 157 (100), 85 (36).

HRMS (CI mode, isobutane): found $(M + H)^+$, 241.1806. $C_{14}H_{25}O_3$ requires 241.1804.

8-Methoxyoct-6-yn-1-ol (241)



$C_{14}H_{24}O_3$
Mol. Wt.: 240.34

$C_9H_{16}O_2$
Mol. Wt.: 156.22

To solution of 1-methoxy-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-2-yne (3.3 g, 13.7 mmol) in MeOH (50 mL) was added a solution of PPTS (3.02 mmol) in MeOH (15 mL) formed *in situ* from pyridine (0.25 mL, 3.02 mmol) and PTSA (574 mg, 3.02 mmol) and the resulting mixture was stirred at rt for 18 h. The solution was concentrated *in vacuo* and dissolved in ethyl acetate (100 mL). The organic solution was washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (1:1)) to yield the pure 8-methoxyoct-6-yn-1-ol (1.42 g, 9.09 mmol, 66 %) as a colourless oil.

IR (thin film): ν = 3408 (br), 2837 (s), 2861 (s), 2279 (w), 2229 (w), 1655 (w), 1451 (m), 1095 (s), 904 (w) cm^{-1}.

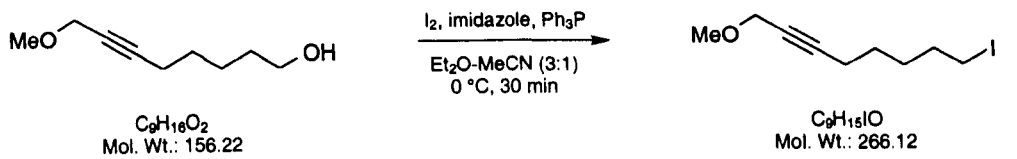
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (2H, t, J = 2.14 Hz, CH_2OCH_3), 3.60 (2H, t, J = 6.51 Hz, CH_2OH), 3.33 (3H, s, OCH_3), 2.22 (2H, tt, J_1 = 6.88, J_2 = 2.11 Hz, $CH_2C{\equiv}C$), 1.96 (1H, s, OH), 1.59-1.49 (4 H, m, 2 x CH_2), 1.47-1.39 (2H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.01 (0), 75.95 (0), 62.71 (2), 60.29 (2), 57.47 (3), 32.29 (2), 28.46 (2), 25.10 (2), 18.79 (2).

LRMS (CI mode, isobutane): m/z = 157 [$(M + H)^+$, 100%], 125 (17), 107 (8), 81 (13), 69 (22).

HRMS (CI mode, isobutane): found $(M + H)^+$, 157.1228. $C_9H_{16}O_2$ requires 157.1229.

1-Iodo-8-methoxyoct-6-yne (242)



$C_9H_{16}O_2$
Mol. Wt.: 156.22

$C_9H_{15}IO$
Mol. Wt.: 266.12

To a solution of 8-methoxyoct-2-yn-1-ol (390 mg, 2.5 mmol) in Et_2O-MeCN (3:1) (20 mL) at 0 °C was added freshly sublimed iodine (950 mg, 3.74 mmol), imidazole (570 mg, 7.5 mmol) and triphenylphosphine (982 mg, 3.74 mmol) and the mixture was stirred at 0 °C under N_2 for 30 min. The reaction mixture was diluted with H_2O (10 mL) and filtered through a plug of celite. The remaining aqueous layer was separated and extracted with Et_2O (3 x 30 mL) and the combined organic phases were washed with aqueous sodium thiosulfate (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2; hexanes-Et2O (2:1))

to yield the pure 1-iodo-8-methoxyoct-6-yne (465 mg, 1.75 mmol, 70%) as a colourless oil.

IR (thin film): ν = 2985 (m), 2935 (s), 2858 (m), 2819 (m), 1596 (w), 1449 (m), 1095 (s), 906 (m) cm^{-1}.

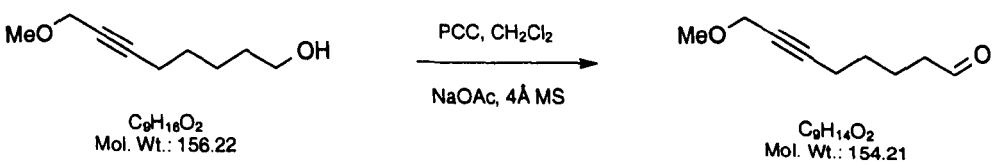
^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (2H, t, J = 2.14 Hz, CH_2OCH_3), 3.37 (3H, s, OCH_3), 3.19 (2H, t, J = 7.01 Hz, CH_2I), 2.25 (2H, tt, J_1 = 6.75, J_2 = 2.07 Hz, $CH_2C{\equiv}C$), 1.85 (2H, pent., J = 7.10 Hz, CH_2), 1.59-1.49 (4 H, m, 2 x CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.71 (0), 77.52 (0), 60.36 (2), 57.63 (3), 33.17 (2), 29.85 (2), 27.66 (2), 18.76 (2), 6.80 (2).

LRMS (CI mode, isobutane): m/z = 533 [$(2M + H)^+$, 16%], 267 [$(M + H)^+$, 100%], 235 (94), 107 (9).

HRMS (CI mode, isobutane): found $(M + H)^+$, 267.0245. $C_9H_{16}IO$ requires 267.0247.

8-Methoxyoct-6-yn-1-al (244)



$C_9H_{16}O_2$
Mol. Wt.: 156.22

$C_9H_{14}O_2$
Mol. Wt.: 154.21

Pyridinium chlorochromate (2.07 g, 9.60 mmol) and sodium acetate (157 mg, 1.92 mmol) and 4Å molecular sieves were suspended in CH_2Cl_2 (8.5 mL) and 1-methoxyoct-2-yn-1-ol

(1.00 g, 6.40 mmol) was added in one portion with magnetic stirring. After 2 h the reaction was diluted with Et_2O (20 mL) and the supernatent was decanted from the black gum. The insoluble residue was washed with Et_2O (3 x 20 mL). The combined organic layers were filtered through a plug of silica, eluted with Et_2O (250 mL) and the solvent was removed *in vacuo* . The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (2:1)) to yield the pure 8-methoxyoct-6-yn-1-al (643 mg, 4.17 mmol, 65%) as a colourless oil.

IR (thin film): ν = 2938 (s), 2822 (m), 2723 (w), 2361 (w), 2344 (w), 2277 (w), 2230 (w), 1724 (s), 1359 (m), 1187 (m), 1096 (s), 905 (m) cm^{-1}.

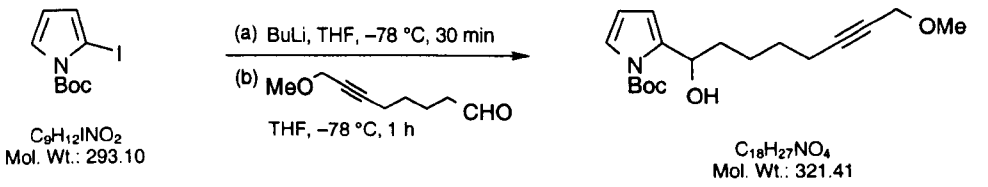
^1H NMR (400 MHz, $CDCl_3$): δ = 9.78 (1H, t, J = 2.00 Hz, C**H**O), 4.07 (2H, t, J = 2.15 Hz, CH_2OCH_3), 3.37 (3H, s, OCH_3), 2.47 (2H, dt, J_1 = 1.64, J_2 = 7.25 Hz, $C_{22}CHO$), 2.27 (2H, tt, J_1 = 6.98, J_2 = 2.15 Hz, $CH_2C{\equiv}C$), 1.56 (2H, pent., J = 7.45 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.38 (1), 86.36 (0), 76.48 (0), 60.31 (2), 57.60 (3), 43.48 (2), 28.09 (2), 21.36 (2), 18.61 (2).

LRMS (CI mode, isobutane): m/z = 155 [$(M + H)^+$, 100%], 123 (38), 95 (24), 75 (57).

HRMS (CI mode, isobutane): found $(M + H)^+$, 155.1073. $C_9H_{15}O_2$ requires 155.1074.

_N_-(*tert*-Butoxycarbonyl)-2-(8-methoxy-1-hydroxy-6-octynyl)pyrrole (245)



$C_9H_{12}INO_2$
Mol. Wt.: 293.10

$C_{18}H_{27}NO_4$
Mol. Wt.: 321.41

To a solution of *N*-(*tert*-butoxycarbonyl)-2-iodopyrrole (189 mg, 0.713 mmol) in THF (10 ml) at –78 °C was added *n*-BuLi (2.3 M in hexanes, 0.31 mL, 0.713 mmol) and the mixture was stirred for 30 min at –78 °C. The preformed lithium reagent was added *via* a cooled (CO_2) cannula to a solution of 8-methoxyoct-6-yn-1-al (100 mg, 0.649 mmol) in THF (10 mL) also at –78 °C. The resulting mixture was stirred at low temperature for 1 h until all the aldehyde had been consumed (as judged by TLC). H_2O (1 mL) was added and the mixture was allowed to warm to rt. The organic phase was diluted with Et_2O (30 mL), washed with sat. NH_4Cl (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography (alumina, hexanes-Et2O (9:1)) to yield [*N*-(*tert*-butoxycarbonyl)pyrrol-2-yl]-1-(8-methoxy)oct-6-yn-1-ol (119 mg, 0.37 mmol, 57 %) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 3485 (br), 2979 (m), 2935 (s), 2862 (m), 2821 (m), 2274 (w), 2215 (w), 1736 (s), 1336 (m), 1125 (m), 1095 (m) cm^{-1}.

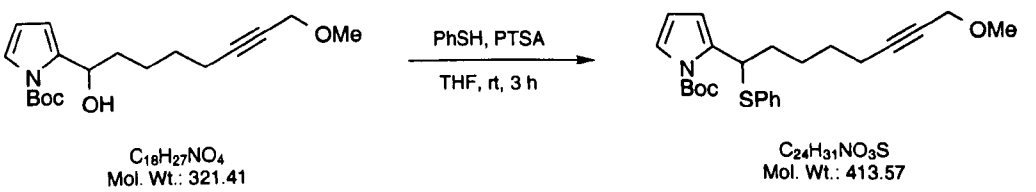
^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (1H, dd J_1 = 3.32, J_2 = 3.33 Hz, **CH**NBoc), 6.20-6.19 (1H, m, **CH**=CHNBoc), 6.11 (1H, t, J = 3.35 Hz, **CH**=C(R)NBoc), 4.85 (1H, dt, J_1 = 5.54, J_2 = 8.04, Hz, **CH**OH), 4.06 (2H, dd, J_1 = 4.11, J_2 = 4.31 Hz, CH_2OCH_3), 4.01 (1H, d, J = 5.43, **OH**), 3.35 (3H, s, OCH_3), 2.28 (2H, dd, J_1 = 6.84, J_2 = 6.74 Hz, $CH_2C{\equiv}C$), 1.99 (2H, m, CH_2), 1.74-1.42 (4H, m, 2 xCH_2), 1.66 (9H, s, Boc).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.51, 138.40, 122.10, 111.61, 110.45, 87.19, 84.73, 66.48, 60.40, 57.57, 34.16, 33.97, 28.72, 28.18 (3C), 25.88, 18.91.

LRMS (EI mode): *m/z* = 321 (100%), 140 (62), 96 (100), 57 (94).

HRMS (EI mode): found 321.1938. $C_{18}H_{27}NO_4$ requires 321.1940.

_N_-(*tert*-Butoxycarbonyl)-2-(8-methoxy-1-phenylthio-6-octynyl)pyrrole (246)



$C_{18}H_{27}NO_4$
Mol. Wt.: 321.41

$C_{24}H_{31}NO_3S$
Mol. Wt.: 413.57

To a stirred solution of *N*-(*tert*-butoxycarbonyl)-2-(8-methoxy-1-hydroxy-6-octynyl)pyrrole (26 mg, 0.081 mmol) and thiophenol (8.3 μL, 0.081 mmol) in THF (3 mL) was added a catalytic amount of PTSA and the mixture was stirred at rt for 3 h. The reaction was poured into H_2O (5 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with H_2O (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (2:1)) to yield the pure [*N*-(*tert*-butoxycarbonyl)pyrrol-2-yl]-8-(1-methoxy-8-phenylsulfyl)oct-2-yne (20.8 mg, 0.05 mmol, 62%) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 3449 (br), 2979 (m), 2934 (s), 2860 (m), 2820 (m), 2280 (w), 2240 (w), 1740 (s), 1483 (w), 1322 (m) 1121 (m) cm^{-1}.

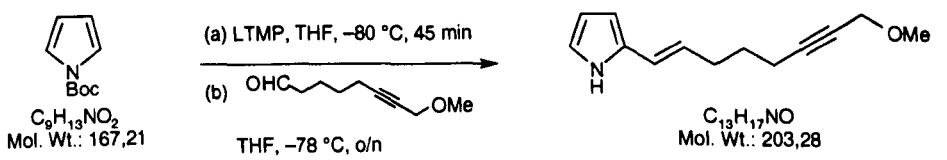
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16-7.12 (6H, m, Ar-**H** (5H) and C**H**NBoc), 6.04 (1H, t, J = 3.35 Hz, C**H**=CHNBoc), 5.994-5.986 (1H, m, C**H**=C(R)NBoc), 5.07 (1H, br m, C**H**SPh), 4.09-4.07 (2H, br m, CH_2OCH_3), 3.36 (3H, s, OCH_3), 2.22-2.19 (2H, br m, $CH_2C{\equiv}C$), 1.87-1.73 (2H, m, CH_2CHSPh), 1.67-1.56 (4H, m, 2 xCH_2), 1.61 (9H, s, Boc).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 135.70, 134.30, 128.57 (2C), 127.65, 122.06, 112.61, 109.88 (2C), 87.05, 83.98, 77.51, 76.11, 60.37, 57.57, 34.12, 28.47, 28.21 (3C), 26.75, 18.81.

LRMS (EI mode): m/z = 313 (53%), 204 (49), 172 (100), 130 (13), 57 (55).

HRMS (EI mode): found $(M - Boc + H)^+$, 313.1497. $C_{19}H_{23}NOS$ requires 313.1500.

(*E*)-2-(8-methoxyoct-6-yn-1-enyl)-1H-pyrrole (247)



To a solution of 2,2,6,6,-tetramethylpiperidine (104 μL, 0.62 mmol) in THF (3 mL) at –80 °C was added n-butyllithium (2.3 M in hexanes, 270 μL, 0.62 mmol). The reaction mixture was stirred for 10 min at –80 °C the cooling bath was replaced with an ice bath and the mixture was stirred for a further 1 h and was recooled to –80 °C. N-(tert-butoxycarbonyl)pyrrole (98 μL, 0.59 mmol) was added and the mixture was stirred at –80 °C for 45 min. The preformed lithium reagent was added via a cooled (CO_2) cannula to a

solution of 8-methoxyoct-6-yn-1-al (100 μL, 0.64 mmol) in THF (2 mL) also at –78 °C and the reaction was allowed to warm to rt and stirred overnight.. The mixture was diluted with H_2O (0.1 mL) and warmed to rt. The organic phase was diluted with Et_2O (10 mL) and washed with sat. NH_4Cl (5 mL), brine (5 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O (2:1)) to yield 1*H*-pyrrol-2-yl-1-(8-methoxy)oct-1-ene-6-yne (49 mg, 0.24 mmol, 41%) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 3388 (br), 2934 (s), 2857 (m), 2291 (w), 2210 (w), 1736 (m), 1451 (m), 1094 (s) cm^{-1}.

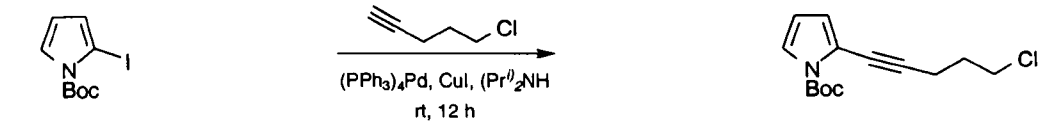
^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (1 H, br s, N**H**), 6.73-6.71 (1H, m, C**H**NH), 6.29 (1H, d, J = 16.1 Hz, pyrrole-C**H**=CH), 6.18 (1H, m, C**H**=CHNH), 6.16 (1H, br s, C**H**=C(R)NH), 5.78 (1H, dt, J_1 = 15.95, J_2 = 7.05 Hz, pyrrole-CH=C**H**), 4.16 (2H, t, J = 2.14, CH_2OCH_3), 3.48 (3H, s, OCH_3), 2.33-2.24 (4H, m, $CH_2C{\equiv}C$ and CH_2), 1.68 (2H, pent., J = 7.16 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.84 (0), 124.66 (1), 121.50 (1), 118.08 (1), 109.44 (1), 107.09 (1), 87.00 (0), 76.30 (0), 60.39 (2), 57.58 (3), 32.06 (2), 28.56 (2), 18.30 (2).

LRMS (EI mode): *m/z* = 203 (38%), 170 (78), 158 (100), 143 (88), 106 (94), 80 (56).

HRMS (EI mode): found 203.1311. $C_{13}H_{17}NO$ requires 203.1310.

_N_-(*tert*-Butoxycarbonyl)-2-(5-chloropent-1-ynyl)pyrrole (250)



$C_9H_{12}INO_2$
Mol. Wt.: 293.10

$C_{14}H_{18}ClNO_2$
Mol. Wt.: 267.75

To a solution of *N*-(*tert*-butoxycarbonyl)-2-iodopyrrole (1 g, 3.41 mmol) in freshly distilled diisopropylamine (5 mL) at rt was added copper(I) iodide (6.5 mg, 3.41μmol, 1 mol%) and tetrakispalladium(0)triphenylphosphine (40 mg, 3.41μmol, 1 mol%) to give a yellow suspension. The reaction mixture was cooled to 0 °C and 5-chloropentyne (0.54 mL, 4.09 mmol) was added with rapid stirring whereupon a colour change from yellow to dark brown was observed. The mixture was allowed to warm to rt and was stirred under nitrogen for 12 h. The resulting black suspension was diluted with diethyl ether (20 mL) and filtered through celite. The filtrate was evaporated *in vacuo* to yield a dark brown oil, which was purified by flash column chromatography (SiO_2; hexanes-Et_2O (9:1)) to yield the pure *N*-(*tert*-butoxycarbonyl)-2-(5-chloropent-1-ynyl)pyrrole (813 mg, 3.03 mmol, 89%) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 2926 (br), 1739 (s), 1664 (w), 1458 (w), 1401 (m), 1370 (m), 1317 (s), 1259 (w), 1139 (s) cm^{-1}.

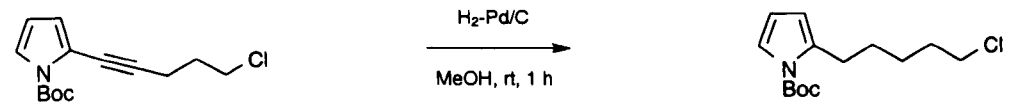
^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (1H, dd, J_1 = 3.32, J_2 = 1.72 Hz, **CH**NBoc), 6.44 (1H, dd, J_1 = 3.41, J_2 = 1.71 Hz, **CH**=C(R)NBoc), 6.12 (1H, t, J = 3.37 Hz, **CH**=CHNBoc), 3.73 (2H, t, J = 6.38 Hz, CH_2Cl), 2.64 (2H, t, J = 6.81 Hz, C≡C**CH**$_2$), 2.06 (2H, pent., J = 6.57 Hz, CH_2CH_2Cl), 1.61 (9H, s, Boc).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.56 (0), 122.06 (1), 120.18 (1), 115.64 (0), 110.89 (1), 91.80 (0), 84.14 (0), 73.81 (0), 43.91 (2), 31.58 (2), 28.15 (3 (3C)), 17.42 (2).

LRMS (CI mode, isobutane): 269 [$(M + H)^+$, 100%], 254 (18), 214 (30), 212 (92), 168 (11).

HRMS (CI mode, isobutane): found $(M + H)^+$, 268.1103. $C_{14}H_{19}ClNO_2$ requires 268.1105.

_N_-(*tert*-Butoxycarbonyl)-2-(5-chloropentyl)pyrrole (253a)



$C_{14}H_{18}ClNO_2$
Mol. Wt.: 267.75

$C_{14}H_{22}ClNO_2$
Mol. Wt.: 271.78

Palladium 10% activated on charcoal (0.23 mmol, 5 mol%) was added in one portion to a solution of *N*-(*tert*-butoxycarbonyl)-2-(5-chloropent-1-ynyl)pyrrole (1.23 g, 4.59 mmol) in methanol (15 mL) at rt. The reaction vessel was evacuated at water pump pressure, *via* a KOH drying tube, and flushed with hydrogen through several vacuum cycles. The resulting black suspension was stirred under an atmosphere of hydrogen at rt for 1 hour. The reaction mixture was filtered through a plug of celite and the filtrate was evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (9:1)) to yield a colourless oil, *N*-(*tert*-butoxycarbonyl)-2-(5-chloropentyl)pyrrole, (1.15 g, 4.22 mmol, 92%).

IR (thin film): ν = 2979 (br), 2936 (br), 2863 (br), 1740 (s), 1492 (m), 1408 (m), 1370 (m), 1332 (s), 1256 (m), 1169 (m), 1121 (s), 772 (s) cm^{-1}.

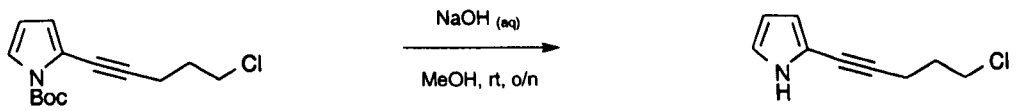
^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (1H, dd, J_1 = 3.35, J_2 = 1.78 Hz, C**H**NBoc), 6.08 (1H, t, J = 3.31 Hz, C**H**=CHNBoc), 5.97-5.95 (1H, m br, C**H**=C(R)NBoc), 3.55 (2H, t, J = 6.77 Hz, CH_2Cl), 2.87 (2H, t, J = 7.56 Hz, Pyrrole–CH_2), 1.83 (2H, pent., J 7.12 Hz, CH_2CH_2Cl), 1.70-1.49 (4H, m, 2(CH_2)), 1.60 (9H, s, Boc).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.68 (0), 136.15 (0), 121.03 (1), 111.06 (1), 110.05 (1), 83.44 (0), 45.19 (2), 32.66 (2), 28.83 (2), 28.36 (2), 28.22 (3 (3C)), 26.82 (2).

LRMS (EI mode): 271 (M^+ 21%), 215 (53), 171 (23), 136 (20), 124 (28), 80 (62), 57 (100).

HRMS (EI mode): found 217.1338. $C_{14}H_{22}ClNO_2$ requires 271.1339.

2-(5-Chloropent-1-ynyl)-1*H*-pyrrole (250a)



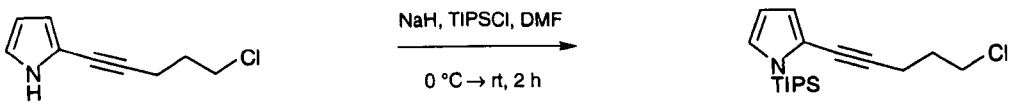
$C_{14}H_{18}ClNO_2$
Mol. Wt.: 267.75

$C_9H_{10}ClN$
Mol. Wt.: 167.63

Aqueous sodium hydroxide (1 N, 10 mL) was added to a solution of *N*-(*tert*-butoxycarbonyl)-2-(5-chloropent-1-ynyl)pyrrole (1.0 g, 3.68 mmol) in methanol (10 mL). The reaction mixture was stirred at rt overnight. The resulting solution was diluted with hexanes (20 mL) and the organic layer was separated from the aqueous. The aqueous phase

was extracted with 95:5 hexanes-Et_2O (3 x 20 mL). The combined organic phases were evaporated *in vacuo* to yield a yellow oil which was purified by flash column chromatography (Al_2O_3, hexanes-Et_2O (3:1)). The desired 2-(5-chloropent-1-ynyl)-1*H*-pyrrole was isolated as a colourless oil (574 mg, 3.42 mmol, 93%) which blackened rapidly on exposure to air. The product was used immediately in the subsequent step without characterisation.

_N_-(Triisopropylsilyl)-2-(5-chloropent-1-ynyl)pyrrole (251)



$C_9H_{10}ClN$
Mol. Wt.: 167,64

$C_{18}H_{30}ClNSi$
Mol. Wt.: 323.98

2-(5-Chloropent-1-ynyl)-1*H*-pyrrole (3.7 g, 22.1 mmol) in anhydrous DMF (5 mL) was added dropwise at 0 °C to an efficiently stirred suspension of sodium hydride (883 mg of a 60% dispersion in mineral oil, 22.1 mmol) in anhydrous DMF (10 mL). After 1 h, when hydrogen evolution had ceased, triisopropylsilylchloride (7.08 mL, 33.2 mmol) was added dropwise and stirring was continued at 0 °C for a further 45 min. The reaction mixture was quenched by careful addition of H_2O (1 mL) and was then partitioned between diethyl ether (50 mL) and H_2O (10 mL). The organic phase was removed and washed with H_2O (3 x 20 mL), dried over sodium sulfate, filtered and reduced *in vacuo*. The colourless residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (95:5)) to yield the desired *N*-(triisopropylsilyl)-2-(5-chloropent-1-ynyl)pyrrole (6.93 g, 21.43 mmol, 97%).

IR (thin film): ν = 2947 (br), 2868 (s), 1463 (m), 1446 (m), 1294 (m), 1173 (s), 1147 (s), 1060 (s), 1020 (m), 883 (m), 725 (m) cm^{-1}.

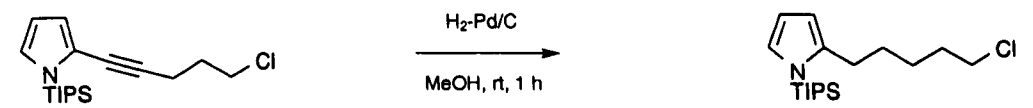
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (1H, dd, J_1 = 2.72, J_2 = 1.40 Hz, **CH**NTIPS), 6.54 (1H, dd, J_1 = 3.25, J_2 = 1.32 Hz, **CH**=C(R)NTIPS), 6.20 (1H, t, J = 3.05 Hz, **CH**=CHNTIPS), 3.69 (2H, t, J = 6.37 Hz, $\mathbf{CH_2}$Cl), 2.61 (2H, t, J = 6.79 Hz, C≡C$\mathbf{CH_2}$), 2.02 (2H, pent., J = 6.59 Hz, $\mathbf{CH_2}CH_2Cl$), 1.70 (3H, sept., J = 7.58 Hz, 3(**CH**$(CH_3)_2$)), 1.15 (18H, d, J = 7.55 Hz, 3(CH($\mathbf{CH_3}$)$_2$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.52 (1), 119.05 (1), 118.64 (0), 110.22 (1), 89.44 (0), 77.07 (0), 43.90 (2), 31.50 (2), 18.29 (3 (6C)), 17.29 (2), 13.18 (1 (3C)).

LRMS (EI mode): *m/z* = 323 (M^+ 100%), 261 (29), 252 (50), 246 (18), 219 (16), 177 (12), 59 (12).

HRMS (EI mode): found 323.1834. $C_{18}H_{30}ClNSi$ requires 323.1836.

_N_-(Triisopropylsilyl)-2-(5-chloropentyl)pyrrole (253b)



$C_{18}H_{30}ClNSi$
Mol. Wt.: 323.98

$C_{18}H_{34}ClNSi$
Mol. Wt.: 328.01

Palladium 10% activated on charcoal (0.54 mmol, 5 mol%) was added in one portion to a solution of *N*-(triisopropylsilyl)-2-(5-chloropent-1-ynyl)pyrrole (3.5 g, 10.8 mmol) in methanol (30 mL) at rt. The reaction vessel was evacuated at water pump pressure, *via* a KOH drying tube, and flushed with hydrogen through several vacuum cycles. The

resulting black suspension was stirred under an atmosphere of hydrogen at rt for 1 hour. The reaction mixture was filtered through a plug of celite and the filtrate was evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, hexanes-Et_2O (95:5)) to yield *N*-(triisopropylsilyl)-2-(5-chloropentyl)pyrrole (3.33 g, 10.2 mmol, 94%) as a colourless oil.

IR (thin film): ν = 2947 (br), 2868 (s), 1736 (w), 1465 (m), 1415 (w), 1320 (w), 1256 (w), 1158 (m), 1065 (m), 1018 (m), 997 (w), 923 (w), 883 (s), 711 (m) cm^{-1}.

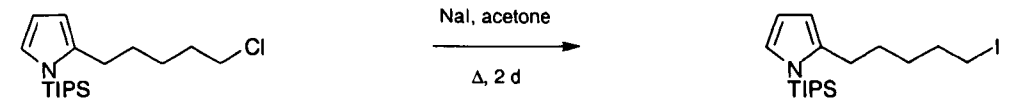
^1H NMR (400 MHz, $CDCl_3$): δ = 6.76-6.75 (1H, m br, C**H**NTIPS), 6.21 (1H, t, *J* = 3.00 Hz, C**H**=CHNTIPS), 6.09 (1H, m br, C**H**=C(R)NTIPS), 3.58 (2H, t, *J* = 6.69 Hz, CH_2Cl), 2.64 (2H, t, *J* = 7.68 Hz, pyrrole-CH_2), 1.89-1.73 (4H, m, 2(CH_2)), 1.62-1.45 (5H, m, CH_2, 3(C**H**(CH_3)$_2$)), 1.14 (18H, d, *J* = 7.55 Hz, 3(CH(CH_3)$_2$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.37 (0), 124.53 (1), 109.38 (1), 108.40 (1), 45.20 (2), 32.81 (2), 29.16 (2), 28.58 (2), 27.27 (2), 18.40 (3 (6C)), 13.40 (1 (3C)).

LRMS (EI mode): *m/z* = 327 (M^+ 100%), 292 (25), 284 (25), 250 (29), 228 (82), 222 (64), 194 (20), 93 (18), 59 (29).

HRMS (EI mode): found 327.2150. $C_{18}H_{34}ClNSi$ requires 327.2149.

N-(Triisopropylsilyl)-2-(5-iodopentyl)pyrrole (254)



$C_{18}H_{34}ClNSi$
Mol. Wt.: 328.01

$C_{18}H_{34}INSi$
Mol. Wt.: 419.46

To a solution of sodium iodide (1.03 g, 6.86 mmol) in anhydrous acetone (50 mL) was added *N*-(triisopropylsilyl)-2-(5-chloropentyl)pyrrole (1.5 g, 4.57 mmol) and the resulting solution was refluxed for 2 days. The solution was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (60 mL) and was washed with aqueous sodium thiosulfate (0.5 M, 20 mL). The aqueous layer was separated and extracted further with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O (97:3)) to yield the pure *N*-(triisopropylsilyl)-2-(5-iodopentyl)pyrrole (1.67 g, 3.98 mmol, 87%).

IR (thin film): ν = 2947 (br), 2868 (s), 1466 (s), 1415 (m), 1385 (w), 1260 (m), 1242 (w), 1202 (w), 1066 (s), 1018 (m), 883 (s), 785 (w), 711 (s) cm^{-1}.

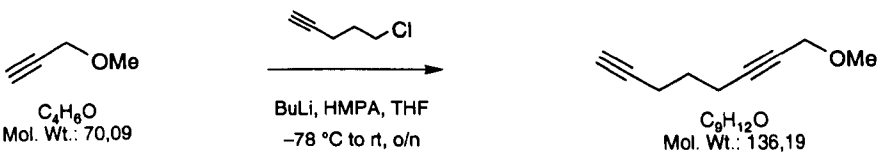
^1H NMR (400 MHz, $CDCl_3$): δ = 6.88 (1H, m br, **CH**NTIPS), 6.58 (1H, t, J = 2.99 Hz, **CH**=CHNTIPS), 6.37 (1H, m br, **CH**=C(R)NTIPS), 2.82 (2H, t, J = 7.02 Hz, CH_2I), 2.68 (2H, t, J = 7.71 Hz, pyrrole-CH_2), 1.72-1.57 (4H, m, 2(CH_2)), 1.49-1.29 (5H, m, CH_2, 3(**CH**$(CH_3)_2$)), 1.15 (18H, d, J = 7.49 Hz, 3(CH(CH_3)$_2$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.08 (0), 124.74 (1), 110.81 (1), 109.87 (1), 34.18 (2), 31.12 (2), 29.70 (2), 28.85 (2), 18.30 (3 (6C)), 13.85 (1 (3C)), 6.93 (2).

LRMS (EI mode): 419 (M^+, 100%), 376 (18), 320 (36), 292 (45), 250 (34), 236 (53), 222 (41), 205 (26), 84 (97), 59 (18).

HRMS (EI mode): found 419.1504. $C_{18}H_{34}INSi$ requires 419.1505.

8-Methoxyoct-1,6-diyne (257)



C_4H_6O
Mol. Wt.: 70,09

$C_9H_{12}O$
Mol. Wt.: 136,19

To a solution of methyl propargyl ether (1.94 mL, 23.0 mmol) in THF (50 mL) at –78 °C was added n-BuLi (2.2 M in hexanes, 11.0 mL, 24.1 mmol), followed, after 10 min by HMPA (5.6 mL, 32.2 mmol) and 5-chloropentyne (2.15 mL, 20.5 mmol). The reaction was allowed to warm to rt and stirred at rt overnight. The reaction mixture was poured onto sat. NH_4Cl (15 mL) and Et_2O (30 mL) and was further extracted with Et_2O (3 x 30 mL). The combined organic phases were washed successively with aqueous HCl (1N, 15 mL), saturated NaHCO3 solution (15 mL) and brine (15 mL), dried over MgSO4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (1:1)) to yield the pure 8-methoxyoct-1,6-diyne (2.21 g, 16.2 mmol, 79%) as a colourless oil.

IR (thin film): ν = 3295 (br), 2936 (br), 2846 (m), 2821 (m), 1452 (m), 1434 (m), 1378 (w), 1358 (m), 1187 (m), 1148 (w), 1130 (m), 1095 (s), 906 (m) cm^{-1}.

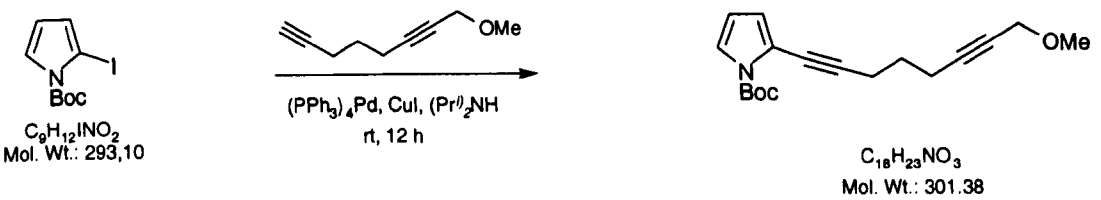
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (2H, t, J = 2.14 Hz, $\mathbf{CH_2}OCH_3$), 3.37 (3H, s, $O\mathbf{CH_3}$), 2.37 (2H, tt, J_1 = 7.03, J_2 = 2.14 Hz, $\mathbf{CH_2}C(CCH_2OCH_3)$), 2.33 (2H, td, J_1 = 7.06, J_2 = 2.64 Hz, $HC{\equiv}C\mathbf{CH_2}$), 1.97 (1H, t, J = 2.63 Hz, $\mathbf{H}C(CCH_2)$), 1.75 (2H, pent., J = 7.02 Hz, $HC(CCH_2\mathbf{CH_2})$.

^{13}C NMR (400 MHz, $CDCl_3$): δ = 85.98 (0), 83.62 (0), 76.68 (1), 69.03 (0), 60.34 (2), 57.63 (3), 27.63 (2), 17.96 (2), 17.22 (2).

LRMS (CI mode, isobutane): m/z = 137 [$(M + H)^+$, 100%], 136 (69), 105 (63), 91 (13), 79 (17), 69 (37), 67 (21).

HRMS (CI mode, isobutane): found 137.0963. $C_9H_{13}O$ requires 137.0967.

_N_-(*tert*-Butoxycarbonyl)-2-(8-methoxyoct-1,6-diynyl)pyrrole



$C_9H_{12}INO_2$
Mol. Wt.: 293,10

$C_{18}H_{23}NO_3$
Mol. Wt.: 301.38

To a solution of *N*-(*tert*-butoxycarbonyl)-2-iodopyrrole (2.24 g, 7.65 mmol) in freshly distilled diisopropylamine (10 mL) at rt was added copper(I) iodide (14.6 mg, 7.65 μmol, 1 mol%) and tetrakispalladium(0)triphenylphosphine (90 mg, 7.65 μmol, 1 mol%) to give a yellow suspension. The reaction mixture was cooled to 0 °C and 8-methoxyoct-1,6-diyne (2.69 g, 9.18 mmol) was added with rapid stirring, a colour change from yellow to dark brown was observed. The mixture was allowed to warm to rt and was stirred under N_2 for

12 h. The resulting black suspension was diluted with Et_2O (20 mL) and filtered through celite. The filtrate was evaporated *in vacuo* to yield a dark brown oil, which was purified by flash column chromatography (SiO_2; hexanes-Et_2O (1:1)) to yield the pure *N*-(*tert*-butoxycarbonyl)-2-(8-methoxyoct-1,6-diynyl)pyrrole (2.12 mg, 7.04 mmol, 92%) as a colourless oil which darkens on exposure to air.

IR (thin film): ν = 2981 (w), 2935 (m), 2868 (w), 1736 (s), 1467 (w), 1401 (w), 1370 (m), 1336 (s), 1317 (s), 1258 (w), 1140 (s), 1095 (m), 1071 (w), 906 (w), 847 (w), 732 (m) cm^{-1}.

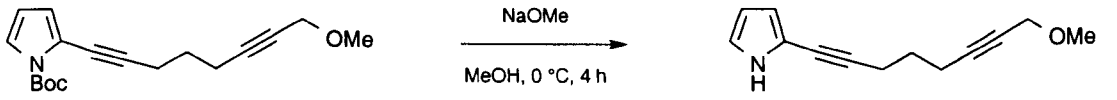
^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (1H, dd, J_1 = 3.29, J_2 = 1.72 Hz, C**H**NBoc), 6.44 (1H, dd, J_1 = 3.38, J_2 = 1.69 Hz, C**H**=C(R)NBoc), 6.12 (1H, t, J = 3.37 Hz, C**H**=CHNBoc), 4.09 (2H, t, J = 2.13 Hz, CH_2OCH_3), 3.38 (3H, s, OCH_3), 2.57 (2H, t, J = 7.06 Hz, pyrrole-C≡CCH_2), 2.43 (2H, tt, J_1 = 7.05, J_2 = 2.08 Hz, $CH_2C{\equiv}CCH_2OCH_3$), 1.83 (2H, pent., J = 7.01 Hz, $CH_2CH_2C{\equiv}C$), 1.61 (9H, s, Boc).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.62 (0), 121.99 (1), 120.15 (1), 115.79 (0), 110.92 (1), 92.76 (0), 82.30 (0), 84.12 (0), 76.81 (0), 73.48 (0), 60.37 (2), 57.62 (3), 28.19 (3 (3C)), 27.92 (2), 19.20 (2), 18.20 (2).

LRMS (CI mode, ammonia): *m/z* = 319 [$(M + NH_4)^+$, 13%], 263 (13), 246 (17), 214 (7), 202 (39), 170 (36), 144 (4).

HRMS (CI mode, isobutane): found $(M + H)^+$, 302.1758. $C_{18}H_{24}NO_3$ requires 302.1757.

2-(8-Methoxyoct-1,6-diynyl)-1*H*-pyrrole



$C_{18}H_{23}NO_3$
Mol. Wt.: 301.38

$C_{13}H_{15}NO$
Mol. Wt.: 201.26

To a dry 25 mL round bottom flask equipped with a stirrer bar and reflux condenser was added anhydrous methanol (10 mL) and sodium pieces (100 mg, 4.17 mmol. The mixture was stirred at reflux for 1 h before being cooled to 0 °C. *N*-(*tert*-butoxycarbonyl)-2-(8-methoxyoct-1,6-diynyl)pyrrole (1.0 g, 3.31 mmol) in anhydrous methanol (2.5 mL) was added dropwise under N_2. Once addition was complete the reaction mixture was allowed to warm to rt and was stirred at this temperature for 4 h. The reaction was quenched by careful addition of aqueous sodium hydroxide (1N, 5 mL), hexanes (20 mL) were added and the organic layer was separated from the aqueous. The aqueous phase was extracted with 95:5 hexanes-Et_2O (3 x 20 mL). The combined organic phases were evaporated *in vacuo* to yield a yellow oil which was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O (1:1)). The desired 2-(8-methoxyoct-1,6-diynyl)-1*H*-pyrrole was isolated as a colourless oil (633 mg, 3.14 mmol, 95%) which blackened rapidly on exposure to air.

IR (thin film): ν = 3399 (br), 3310 (br), 2989 (w), 2935 (m), 2904 (m), 2825 (m), 1556 (w), 1450 (m), 1430 (w), 1378 (w), 1359 (w), 1274 (w), 1187 (m), 1129 (m), 1093 (s), 1027 (w), 1002 (w), 901 (w), 804 (w), 728 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (1H, s br, **NH**), 6.70 (1H, ddd, J_1 = 2.72, J_2 = 2.68, J_3 = 1.44 Hz, **CH**NH), 6.37 (1H, ddd, J_1 = 3.65, J_2 = 2.49, J_3 = 1.20 Hz, **CH**=C(R)NH), 6.16 (1H, dt, J = 3.40, J_2 = 2.72 Hz, **CH**=CHNH), 4.10 (2H, t, J = 2.13 Hz, CH_2OCH_3),

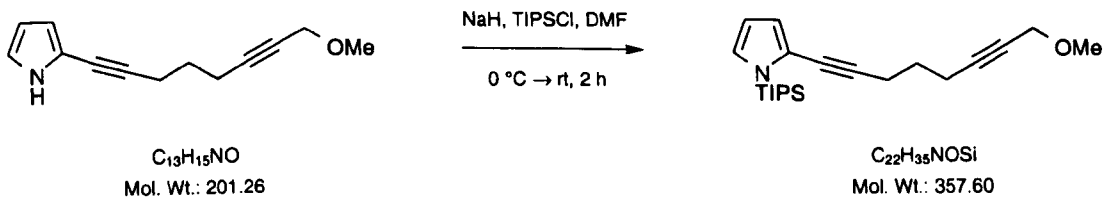
3.39 (3H, s, OCH_3), 2.54 (2H, t, J = 6.97 Hz, pyrrole-C≡CCH_2), 2.41 (2H, tt, J_1 = 6.98, J_2 = 2.15 Hz, $CH_2C{\equiv}CCH_2OCH_3$), 1.81 (2H, pent., J = 6.95 Hz, $CH_2CH_2C{\equiv}C$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.31 (0), 118.71 (1), 113.80(1), 109.09 (1), 89.95 (0), 86.25 (0), 76.66 (0), 73.77 (0), 60.39 (2), 57.66 (3), 27.85 (2), 18.88 (2), 18.20 (2).

LRMS (EI mode): m/z = 200 [(M – H)$^-$, 27%], 186 (42), 170 (100), 158 (78), 130 (54), 117 (35), 104 (51), 77 (20), 51 (12).

HRMS (EI mode): found (M – H)$^-$, 200.1075. $C_{13}H_{14}NO$ requires 200.1075.

N-(Triisopropylsilyl)-2-(8-methoxyoct-1,6-diynyl)pyrrole



$C_{13}H_{15}NO$
Mol. Wt.: 201.26

$C_{22}H_{35}NOSi$
Mol. Wt.: 357.60

2-(8-methoxyoct-1,6-diynyl)-1*H*-pyrrole (250 mg, 1.24 mmol) in anhydrous DMF (1 mL) was added dropwise at 0 °C to an efficiently stirred suspension of sodium hydride (50 mg of a 60% dispersion in mineral oil, 1.24 mmol) in anhydrous DMF (5 mL). After 1 h, when hydrogen evolution had ceased, triisopropylsilylchloride (0.40 mL, 1.86 mmol) was added dropwise and stirring was continued at 0 °C for a further 45 min. The reaction mixture was quenched by careful addition of H_2O (0.25 mL) and was then partitioned between diethyl ether (30 mL) and H_2O (10 mL). The organic phase was removed and washed with H_2O (3 x 10 mL), dried over sodium sulfate, filtered and reduced *in vacuo*. The colourless residue

was purified by flash column chromatography (SiO_2; hexanes-Et_2O (9:1)) to yield the desired *N*-(triisopropylsilyl)-2-(8-methoxyoct-1,6-diynyl)pyrrole (408 mg, 1.14 mmol, 92%).

IR (thin film): ν = 2946 (br), 2892 (w), 2867 (s), 1465 (m), 1449 (m), 1173 (m), 1147 (m), 1096 (s), 1060 (m), 1019 (m), 883 (m), 725 (m), 690 (m), 665 (s) cm^{-1}.

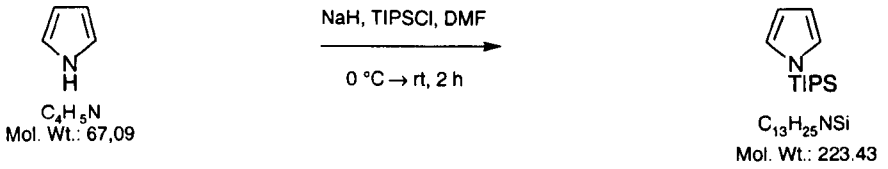
^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (1H, dd, J_1 = 3.24, J_2 = 1.30 Hz, C**H**NTIPS), 6.73 (1H, dd, J_1 = 2.75, J_2 = 1.36 Hz, C**H**=C(R)NTIPS), 6.35 (1H, t, J = 3.10 Hz, C**H**=CHNTIPS), 3.97 (2H, t, J = 2.15 Hz, C$\mathbf{H_2}$OCH$_3$), 3.24 (3H, s, OC$\mathbf{H_3}$), 2.35 (2H, t, J = 6.97 Hz, pyrrole-C≡CC$\mathbf{H_2}$), 2.20 (2H, tt, J_1 = 7.03, J_2 = 2.13 Hz, C$\mathbf{H_2}$C≡CCH$_2$OCH$_3$), 1.67 (3H, sept., J = 7.59 Hz, 3(C**H**(CH$_3$)$_2$)), 1.59 (2H, pent., J = 7.02 Hz, C$\mathbf{H_2}$CH$_2$C≡C), 1.16 (18H, d, 3(CH(C$\mathbf{H_3}$)$_2$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.03 (0), 128.16 (1), 120.17 (1), 119.87 (0), 111.34 (1), 90.81 (0), 86.11 (0), 77.85 (0), 60.50 (2), 57.32 (3), 28.41 (2), 19.35 (2), 18.67 (3 (6C)), 18.31 (2), 13.32 (1 (3C)).

LRMS (EI mode): *m/z* = 357 (M^+, 8%), 342 (9), 312 (40), 235 (100), 224 (34), 207 (25), 193 (12), 137 (12), 115 (17), 84 (16), 59 (16).

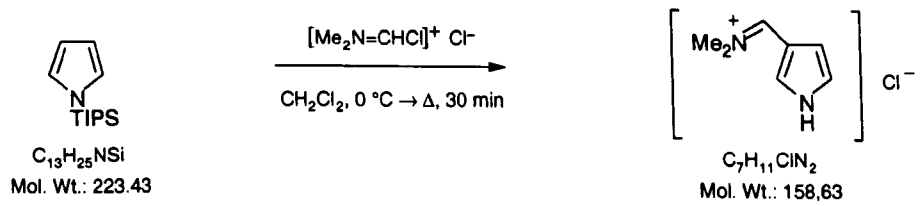
HRMS (EI mode): found 357.2489. $C_{22}H_{35}NOSi$ requires 257.2488.

_N_-(Triisopropylsilyl)pyrrole (265)



Pyrrole (10 mL, 144 mmol) was added dropwise at 0 °C to a mechanically stirred suspension of sodium hydride (6.34 g of a 60% dispersion in mineral oil) in anhydrous DMF (100 mL). After 2 h, when hydrogen evolution had ceased, triisopropylsilylchloride (30.6 mL, 144 mmol) was added dropwise and stirring at 0°C was continued for 1 h. The reaction mixture was partitioned between H_2O (50 mL) and Et_2O (150 mL). The organic phase was separated and washed with H_2O (3 x 50 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The residue was purified by distillation (b.p. 78 °C, (0.4 mmHg)) to yield *N*-(triisopropylsilyl)pyrrole (31.21 g, 139.68 mmol, 97%) as a colourless oil. Spectroscopic data is in accordance with literature values.[157]

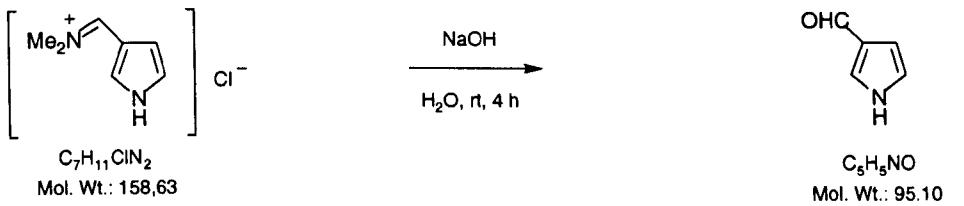
3-(Dimethyliminomethylenyl)-1*H*-pyrrolyl chloride



A solution of anhydrous DMF (9.95 mL, 129 mmol) in anhydrous CH_2Cl_2 (20 mL) was added to a stirred solution of oxalyl chloride (9.99 mL, 118 mmol) in CH_2Cl_2 (500 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 20 min. A solution of *N*-(triisopropylsilyl)pyrrole (25.0 g, 112 mmol) in anhydrous CH_2Cl_2 (20 mL) was added rapidly to the stirred suspension of the Vilsmeier-Haack reagent at 0 °C. The mixture was immediately placed in an oil bath preheated to 60 °C and the solid went into solution

briefly before a precipitate formed again. The mixture was heated at reflux for 30 min before being cooled to 0 °C again. The precipitate was collected by filtration and washed several times with anhydrous Et_2O before exposure to air. The solid was dried *in vacuo* and used immediately in the next step.

3-Formyl-1*H*-pyrrole (264)

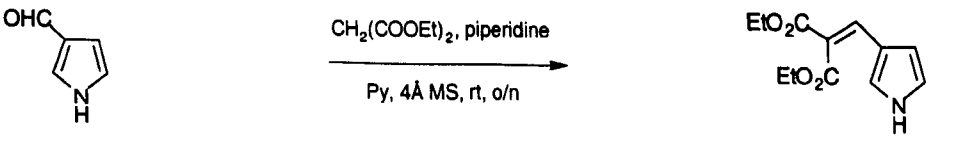


$C_7H_{11}ClN_2$
Mol. Wt.: 158,63

C_5H_5NO
Mol. Wt.: 95.10

The iminium salt (assumed 112 mmol) was added to a 5% aqueous NaOH solution (500 mL) and was stirred at rt for 4 h. The solution was exhaustively extracted with CH_2Cl_2, dried over K_2CO_3 and reduced *in vacuo*. The residue was purified by distillation (bp 132-137 °C, 1 mmHg) to yield the desired 3-formyl-1*H*-pyrrole (7.88 g, 82.9 mmol, 74%) as a white solid, mp 67-68 °C (Lit. mp 68 °C).[158] Spectroscopic data is in accordance with literature values.[159]

2-(1*H*-Pyrrol-3-ylmethylene)malonic acid, diethyl ester (263)

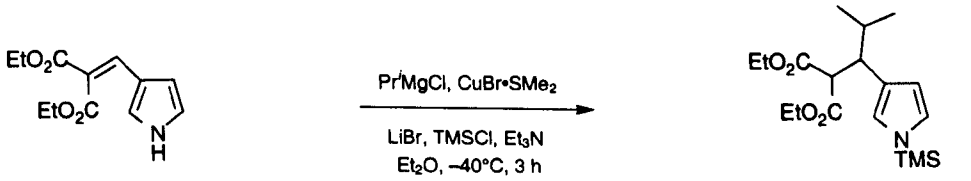


C_5H_5NO
Mol. Wt.: 95.10

$C_{12}H_{15}NO_4$
Mol. Wt.: 237.25

To a solution of diethyl malonate (3.51 mL, 23.12 mmol) and anhydrous piperidine (4.16 mL, 42.06 mmol) in anhydrous pyridine (10 mL) at rt was added powdered 4 Å molecular sieves (500 mg) and 3-formyl-1*H*-pyrrole (2.00g, 21.03 mmol). The reaction mixture was stirred at rt overnight. The mixture was filtered through celite and reduced *in vacuo*, *via* an HCl trap. The residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O-Et_3N (34:65:1)) to yield the pure 2-(1*H*-Pyrrol-3-ylmethylene)malonic acid, diethyl ester (4.24 g, 17.88 mmol, 85%) as a white solid, mp 62-64 °C (Lit mp 62-63°C).[160] Spectroscopic data is in accordance with literature values.[126]

2-(*N*-(Trimethylsilyl)-1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (266)



$C_{12}H_{15}NO_4$
Mol. Wt.: 237.25

$C_{18}H_{31}NO_4Si$
Mol. Wt.: 353.53

Anhydrous LiBr (2.50 g, 28.73 mmol) and CuBr•SMe2 (146 mg, 0.72 mmol, 5 mol%) were added to a flame dried 200 mL 3-necked round bottomed flask whilst still hot and the flask was evacuated and purged with nitrogen through several vacuum cycles. Et_2O (40 mL) was added and the reaction mixture was cooled to –40 °C (internal temperature). Isopropylmagnesium chloride (1.67 M solution in THF, 10.28 mL, 17.17 mmol) was added dropwise, followed by slow addition of a mixture of chlorotrimethylsilane (3.64 mL, 28.73 mmol), distilled from a small amount of *N*,*N*-diethylaniline to remove traces of HCl, and 2-(1*H*-pyrrol-3-ylmethylene)malonic acid, diethyl ester (3.38 g, 14.25 mmol) in Et_2O (10 mL and 2 x 2.5 mL rinses) to keep the internal temperature at –40 °C. Once addition was

complete the brown solution was stirred for a further 15 min at –40 °C before being allowed to warm to 0 °C. Triethylamine (4.17 mL, 30.17 mmol) was added and a precipitate was formed. The mixture was poured onto an ice cold solution of sat. NH_4Cl (25 mL) and the aqueous phase was separated and extracted with Et_2O (3 x 20 mL). The organic phases were combined, washed with aqueous HCl (1 N, 25 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (1:1)) to yield the pure 2-(*N*-(trimethylsilyl)-1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (4.84 g, 13.68 mmol, 96%) as a colourless oil.

IR (thin film): ν = 2961 (br), 2874 (w), 1758 (s), 1732 (s), 1481 (m), 1466 (w), 1368 (w), 1258 (s), 1176 (m), 1154 (m), 1134 (m), 1103 (s), 1035 (m), 973 (w), 844 (s), 784 (w), 762 (w), 706 (w) cm^{-1}.

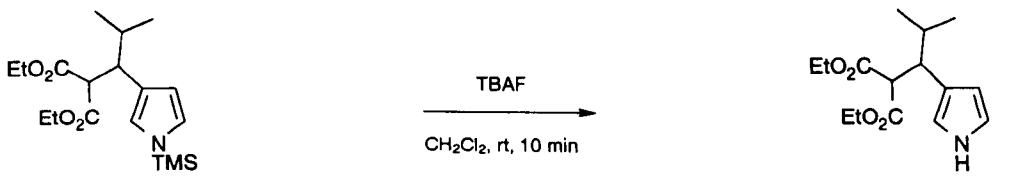
^1H NMR (400 MHz, $CDCl_3$): δ = 6.49-6.48 (2H, m, 2(C**H**NTMS)), 6.39-6.38 (1H, m br, C**H**=CHNTMS), 4.20 (1H, dd, J_1 = 11.20, J_2 = 3.72 Hz, pyrrole-C**H**), 4.12-3.99 (2H, m, OCH_2), 3.97-3.82 (3H, m, OCH_2, $CH(CO_2Et)_2$), 2.28-2.20 (1H, m, $CH(CH_3)CH_3$), 1.02 (6H, d, J = 6.60 Hz, $CH(CH_3)CH_3$), 1.00 (3H, t, J = 7.00 Hz, $COCH_2CH_3$), 0.83 (3H, t, J = 7.08 Hz, $COCH_2CH_3$), 0.10 (9H, s, TMS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.68 (0), 168.98 (0), 123.93 (0), 123.02 (1 (2C)), 113.65 (1), 61.75 (2), 61.36 (2), 57.83 (1), 45.19 (1), 30.89 (1), 22.82 (3), 18.45 (3), 14.75 (3), 14.47 (3), 0.00 (3 (3C)).

LRMS (CI mode, isobutane): *m/z* = 354 [$(M + H)^+$, 100%], 353 (18), 310 (5), 194 (17).

HRMS (CI mode, isobutane): found $(M + H)^+$, 354.2098. $C_{18}H_{32}NO_4Si$ requires 354.2101.

2-(1*H*-Pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (267)



$C_{18}H_{31}NO_4Si$
Mol. Wt.: 353.53

$C_{15}H_{23}NO_4$
Mol. Wt.: 281.35

TBAF (1.79 g, 5.65 mmol) was added in one portion to a solution of 2-(*N*-(trimethylsilyl)-1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (2.00g, 5.65 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at rt for 10 min. At this time the reaction was complete by TLC and the reaction mixtire was diluted with Et_2O (50 mL) and poured onto H_2O (30 mL). The aqueous phase was separated and extracted further with Et_2O (3 x 10 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O (1:1)) to yield the pure 2-(1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (1.56 g, 5.54 mmol, 98%) as a colourless oil which blackens rapidly on exposure to air.

IR (thin film): ν = 3406 (br), 2963 (br), 1746 (s), 1730 (s), 1466 (w), 1447 (m), 1369 (m), 1264 (m), 1228 (m), 1178 (m), 1152 (m), 1097 (w), 1073 (w), 1033 (m), 666 (w) cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.00 (1H, s br, NH), 6.31-6.29 (2H, m br, 2(CHNH)), 6.17-6.16 (1H, m br, CH=CHNH), 4.15 (1H, d, J = 11.32 Hz, $CH(CO_2Et)_2$), 4.08-4.05

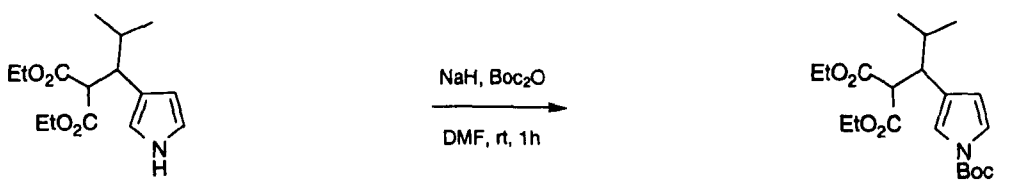
(2H, m, OCH_2), 3.96-3.83 (2H, m, OCH_2,), 3.81 (1H, dd, J_1 = 11.32, J_2 = 4.16 Hz, pyrrole-CH), 2.23-2.15 (1H, m, $CH(CH_3)CH_3$), 0.97 (3H, t, J = 6.52 Hz, $COCH_2CH_3$), 0.96 (6H, d, J = 6.28 Hz, $CH(CH_3)CH_3$), 0.83 (3H, t, J = 7.04 Hz, $COCH_2CH_3$).

^{13}C NMR (100 MHz, C_6D_6): δ = 169.69 (0), 168.99 (0), 120.53 (0), 117.84 (1), 117.59 (1), 110.42 (1), 61.75 (2), 61.40 (2), 57.86 (1), 45.10 (1), 30.83 (1), 22.77 (3), 18.28 (3), 14.73 (3), 14.46 (3).

LRMS (CI mode, isobutane): m/z = 282 [$(M + H)^+$, 100%], 281 (39), 238 (8), 236 (5), 194 (19), 164 (8), 162 (8), 122 (86), 120 (7).

HRMS (CI mode, isobutane): found $(M + H)^+$, 282.1704. $C_{15}H_{24}NO_4$ requires 282.1706.

2-(*N*-(*tert*-Butoxycarbonyl)-1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (270)



$C_{15}H_{23}NO_4$
Mol. Wt.: 281.35

$C_{20}H_{31}NO_6$
Mol. Wt.: 381.46

2-(1*H*-Pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (1 g, 3.55 mmol) in anhydrous DMF (2 mL) was added dropwise to an efficiently stirred suspension of sodium hydride (142 mg of a 60% dispersion in mineral oil, 3.55 mmol) in anhydrous DMF (5 mL) at 0 °C. After 1 h, when hydrogen evolution had ceased, di-*tert*-butyldicarbonate (1.16 g, 5.33 mmol) was added dropwise and stirring was continued at 0 °C for a further 45 min. The

reaction mixture was quenched by careful addition of H_2O (1 mL) and was partitioned between Et_2O (30 mL) and H_2O (4 mL). The organic phase was removed and washed with H_2O (3 x 5 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The colourless residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (2:1)) to yield 2-(*N*-(*tert*-butoxycarbonyl)-1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (1.25 g, 3.27 mmol, 92%) as a colourless oil which darkens gradually on exposure to air.

IR (thin film): ν = 2979 (br), 1740 (vs), 1460 (w), 1370 (m), 1345 (m), 1323 (m), 1251 (m), 1159 (s), 1033 (m), 973 (m) cm^{-1}.

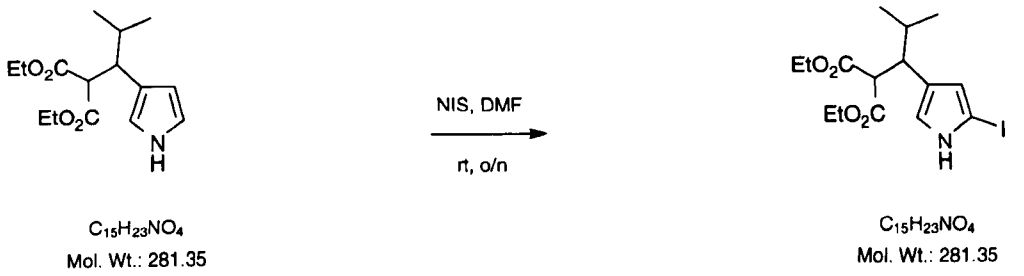
^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (1H, t br, J = 2.24 Hz, C**H**NBoc), 6.99 (1H, s br, C**H**NBoc), 6.07 (1H, dd, J_1 = 3.24, J_2 = 1.72 Hz, C**H**=CHNBoc), 4.26-4.18 (2H, m, OC**H**$_2$), 4.02 (2H, q, J_1 = 7.12 Hz, OC**H**$_2$), 3.77 (1H, d, J = 11.16 Hz, C**H**$(CO_2Et)_2$), 3.29 (1H, dd, J_1 = 11.16, J_2 = 4.40 Hz, pyrrole-C**H**), 1.92-1.87 (1H, m, C**H**$(CH_3)_2$), 1.58 (9H, s, Boc), 1.30 (3H, t, J = 6.88 Hz, $COCH_2C\mathbf{H}_3$), 1.09 (3H, t, J = 7.08 Hz, $COCH_2C\mathbf{H}_3$), 0.87 (3H, d, J = 6.76 Hz, $CH(CH_3)C\mathbf{H}_3$), 0.83 (3H, d, J = 6.80 Hz, $CH(CH_3)C\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.48 (0), 174.41 (0), 168.93 (0), 124.08 (0), 119.46 (1), 118.69 (1), 113.69 (1), 84.05 (0), 61.62 (2), 60.13 (2), 56.11 (1), 44.09 (1), 29.68 (1), 28.20 (3 (3C)), 21.89 (3), 17.61 (3), 17.61 (3), 14.26 (3).

LRMS (CI mode, isobutane): m/z = 382 [$(M + H)^+$, 100%], 381 (22), 333 (18), 326 (57), 284 (7), 282 (5), 222 (24), 208 (4), 166 (5), 122 (8).

HRMS (CI mode, isobutane): found $(M + H)^+$, 382.2231. $C_{20}H_{32}NO_6$ requires 382.2230.

2-(2-Iodo-1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (268)

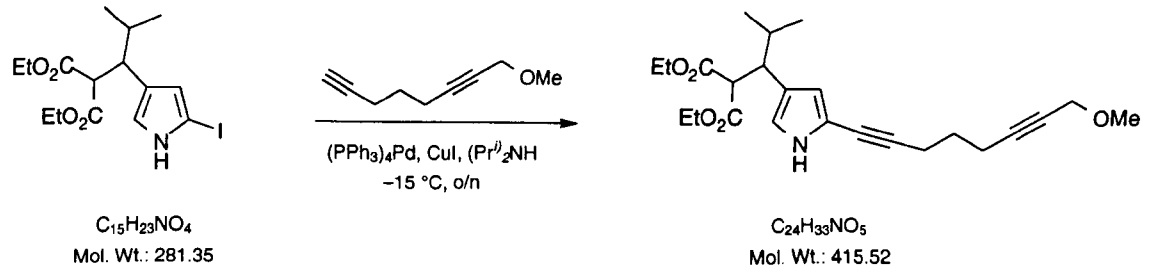


$C_{15}H_{23}NO_4$
Mol. Wt.: 281.35

$C_{15}H_{23}NO_4$
Mol. Wt.: 281.35

To a solution of 2-(1*H*-pyrrol-3-yl-1-isobutyl)malonic acid, diethyl ester (1.91 g, 6.75 mmol) in THF (10 mL) was added *N*-iodosuccinimide (1.65 g, 7.12 mmol) and the reaction mixture was stirred at rt overnight. Triethylamine (0.05 mL, 0.35 mmol) and Et_2O (20 mL) were added and the mixture was poured onto H_2O (10 mL). The aqueous phase was separated and extracted further with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, flitered and reduced *in vacuo*. The residue was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O-Et_3N (65:34:1)) to yield the pure 2-(2-iodo-1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (1.67 g, 5.96 mmol, 88%) which blackened rapidly in the presence of air and was used immediately in the following step.

2-(2-(8-Methoxyoct-1,6-diynyl)1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (269)



$C_{15}H_{23}NO_4$
Mol. Wt.: 281.35

$C_{24}H_{33}NO_5$
Mol. Wt.: 415.52

To a solution of 2-(2-iodo-1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (1.67 g, 5.96 mmol) in freshly distilled diisopropylamine (7.5 mL) at 0 °C was added copper (I) iodide (57 mg, 0.23 mmol, 5 mol%) and tetrakispalladium(0)triphenylphosphine (345 mg, 0.23 mmol, 5 mol%) to give a yellow suspension. 8-Methoxyoct-1,6-diyne (894 mg, 6.54 mmol) was added with rapid stirring and a colour change from yellow to black was observed. The reaction mixture was stirred at 0 °C under nitrogen overnight. The resulting black suspension was diluted with Et_2O (20 mL) and filtered through celite. The filtrate was reduced *in vacuo* to yield a black oil which was purified by flash column chromatography (Al_2O_3; hexanes-Et_2O-Et_3N (50:49:1)) to yield the pure 2-(2-(8-methoxyoct-1,6-diynyl)1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (2.25 g, 5.42 mmol, 91%) as a colourless oil which blackens readily on exposure to air.

IR (thin film): ν = 3377 (br), 2977 (br), 1759 (s), 1729 (s), 1466 (w), 1369 (m), 1264 (m), 1132 (m), 1095 (s), 1030 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (1H, s, br, N**H**), 6.48 (1H, dd, J_1 = 2.16, J_2 = 1.75 Hz, C**H**NH), 6.18 (1H, d, J = 1.68 Hz, CHC(R)CNH), 4.26-4.17 (2H, m, OCH_2CH_3), 4.09 (2H, t, J = 2.47 Hz, CH_2OCH_3), 3.99 (2H, q, J = 7.08 Hz, OCH_2CH_3), 3.75 (1H, d, J = 11.38 Hz, $CH(CO_2Et)_2$), 3.38 (3H, s, OCH_3), 3.21 (1H, dd, J_1 = 11.35, J_2 = 4.19 Hz, pyrrole-C**H**), 2.51 (2H, t, J = 6.95 Hz, pyrrole-C≡CCH_2), 2.39 (2H, tt, J_1 = 6.95, J_2 = 2.08 Hz, $CH_2C{\equiv}CCH_2OCH_3$), 1.89-1.77 (1H, m, $CH(CH_3)_2$), 1.79 (2H, pent., J = 6.99 Hz,

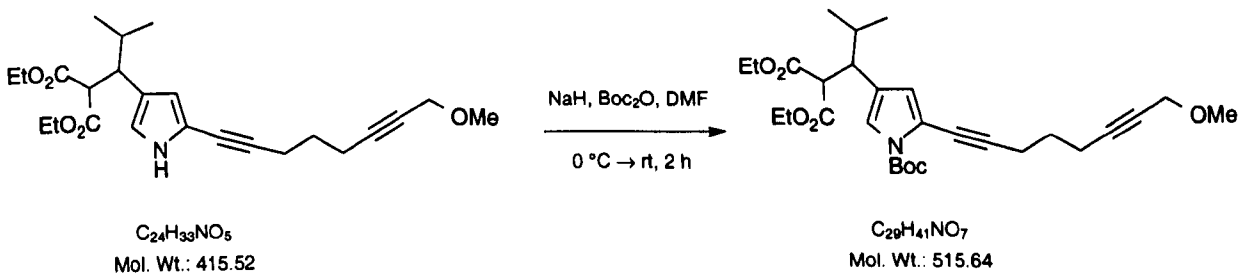
$CH_2CH_2C{\equiv}CCH_2OCH_3$), 1.28 (3H, t, J = 7.13 Hz, OCH_2CH_3), 1.06 (3H, t, J = 7.14 Hz, OCH_2CH_3), 0.85 (3H, d, J = 6.78 Hz, $CH(CH_3)CH_3$), 0.80 (3H, d, J = 6.75 Hz, $CH(CH_3)CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.06 (0), 168.49 (0), 120.44 (0), 118.09 (1), 114.99 (1), 112.67 (0), 89.74 (0), 86.22 (0), 73.99 (0), 66.04 (0), 61.52 (2), 61.19 (2), 60.39 (2), 57.66 (3), 56.51 (3), 44.19 (1), 29.70 (1), 27.86 (2), 21.90 (3), 18.89 (2), 18.21 (2), 17.40 (3), 14.26 (3), 13.97 (3).

LRMS (CI mode, isobutane): m/z = 416 [$(M + H)^+$, 100%], 415 (13), 384 (11), 312 (5), 256 (13), 240 (4), 161 (3).

HRMS (CI mode, isobutane): found $(M + H)^+$, 416.2438. $C_{24}H_{34}NO_5$ requires 416.2438.

2-(2-(8-Methoxyoct-1,6-diynyl)*N-tert*-butoxycarbonyl-1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (272)



$C_{24}H_{33}NO_5$
Mol. Wt.: 415.52

$C_{29}H_{41}NO_7$
Mol. Wt.: 515.64

2-(2-(8-Methoxyoct-1,6-diynyl)1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (1.50 g, 3.61 mmol) in anhydrous DMF (2 mL) was added dropwise to an efficiently stirred suspension of sodium hydride (144 mg of a 60% dispersion in mineral oil, 3.61 mmol) in anhydrous DMF (5 mL) at 0 °C. After 1 h, when hydrogen evolution had ceased, di-*tert*-

butyldicarbonate (1.18 g, 5.42 mmol) was added dropwise and stirring was continued at 0 °C for a further 45 min. The reaction mixture was quenched by careful addition of H_2O (1 mL) and was partitioned between Et_2O (30 mL) and H_2O (4 mL). The organic phase was removed and washed with H_2O (3 x 5 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The colourless residue was purified by flash column chromatography (SiO_2; hexanes-Et_2O (2:1)) to yield 2-(2-(8-methoxyoct-1,6-diynyl)*N*-*tert*-butoxycarbonyl-1*H*-pyrrol-4-yl-1-isobutyl)malonic acid, diethyl ester (1.64 g, 3.18 mmol, 88%) as a colourless oil which yellows in the presence of air.

IR (thin film): ν = 3437 (br), 2961 (br), 2934 (m), 1755 (s), 1735 (s), 1638 (w), 1465 (w), 1398 (w), 1369 (m), 1331 (m), 1258 (m), 1154 (s), 1132 (s), 1096 (m), 1032 (w), 905 (w), 847 (w), 768 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (1H, d, J = 1.84 Hz, C**H**NH), 6.32 (1H, d, J = 1.84 Hz, C**H**C(R)CNH), 4.26-4.18 (2H, m, OC**H**$_2$CH$_3$), 4.09 (2H, t, J = 2.12 Hz, C**H**$_2$OCH$_3$), 4.03 (2H, q, J = 7.08 Hz, OC**H**$_2$CH$_3$), 3.73 (1H, d, J = 11.12 Hz, C**H**(CO$_2$Et)$_2$), 3.38 (3H, s, OC**H**$_3$), 3.22 (1H, dd, J_1 = 11.16, J_2 = 4.48 Hz, pyrrole-C**H**), 2.55 (2H, t, J = 7.08 Hz, pyrrole-C≡CC**H**$_2$), 2.42 (2H, tt, J_1 = 7.04, J_2 = 2.08 Hz, C**H**$_2$C≡CCH$_2$OCH$_3$), 1.89-1.80 (1H, m, C**H**(CH$_3$)$_2$), 1.82 (2H, pent., J = 7.04 Hz, C**H**$_2$CH$_2$C≡CCH$_2$OCH$_3$), 1.60 (9H, s, Boc), 1.28 (3H, t, J = 7.12 Hz, OCH$_2$C**H**$_3$), 1.11 (3H, t, J = 7.12 Hz, OCH$_2$C**H**$_3$), 0.86 (3H, d, J = 6.72 Hz, CH(CH$_3$)C**H**$_3$), 0.81 (3H, d, J = 6.80 Hz, CH(CH$_3$)C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.74 (0), 168.13 (0), 148.37 (0), 122.57 (0), 121.55 (1), 120.66 (1), 115.43 (0), 93.07 (0), 86.59 (0), 84.03 (0), 77.39 (0), 73.92 (0), 61.65 (2), 61.37 (2), 60.37 (2), 56.60 (3), 55.87 (1), 43.88 (1), 29.58 (1), 28.19 (3 (3C)), 27.91 (2), 21.84 (3), 19.18 (2), 18.21 (2), 17.59 (3), 14.25 (3), 14.01 (3).

LRMS (CI mode, isobutane): *m/z* = 516 [$(M + H)^+$, 91%], 460 (78), 416 (100), 384 (36), 312 (15), 268 (15), 256 (20), 224 (18), 161 (7).

HRMS (CI mode, isobutane): found $(M + H)^+$, 516.2961. $C_{29}H_{42}NO_7$ requires 516.2962.

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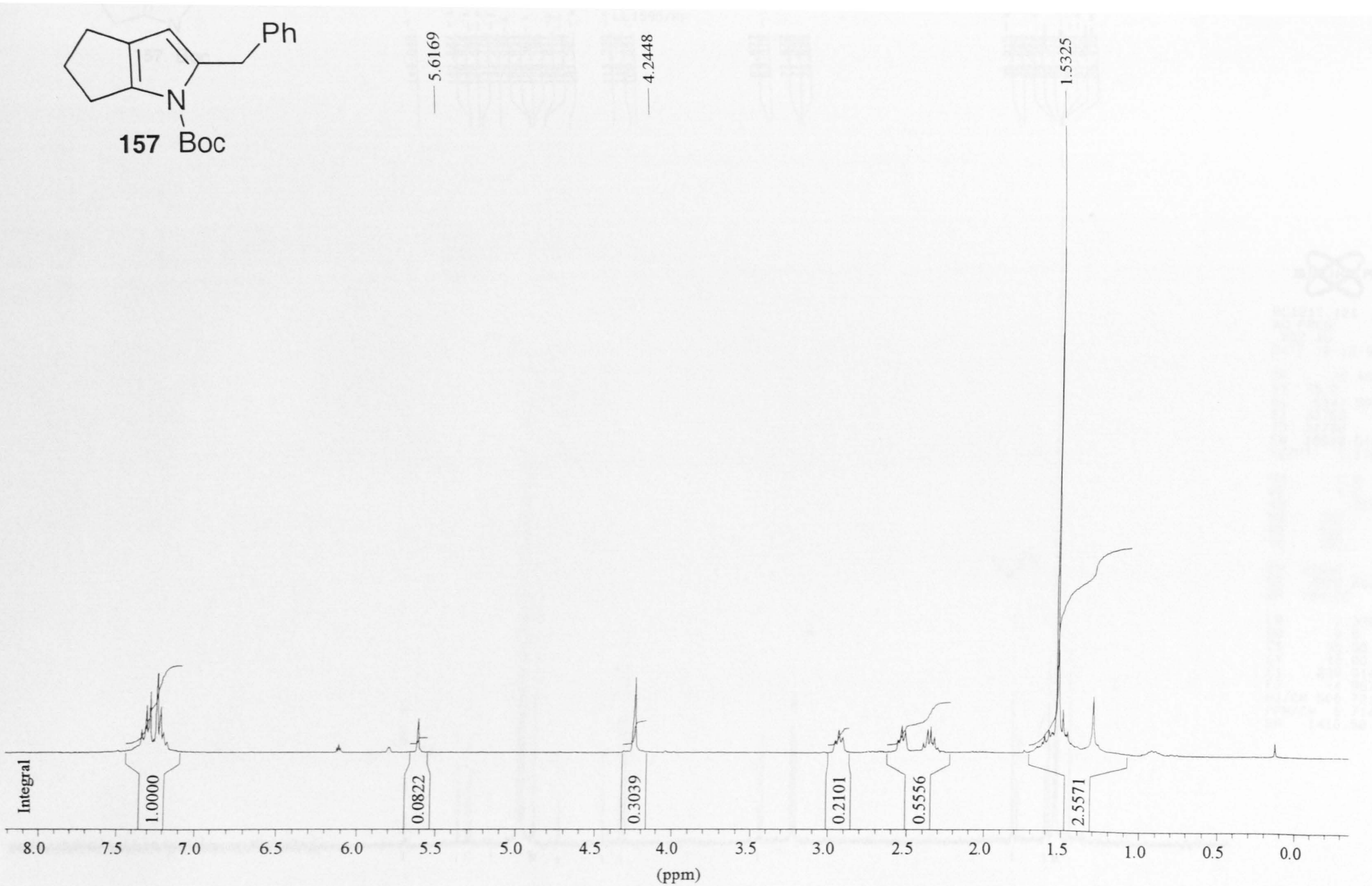
Appendix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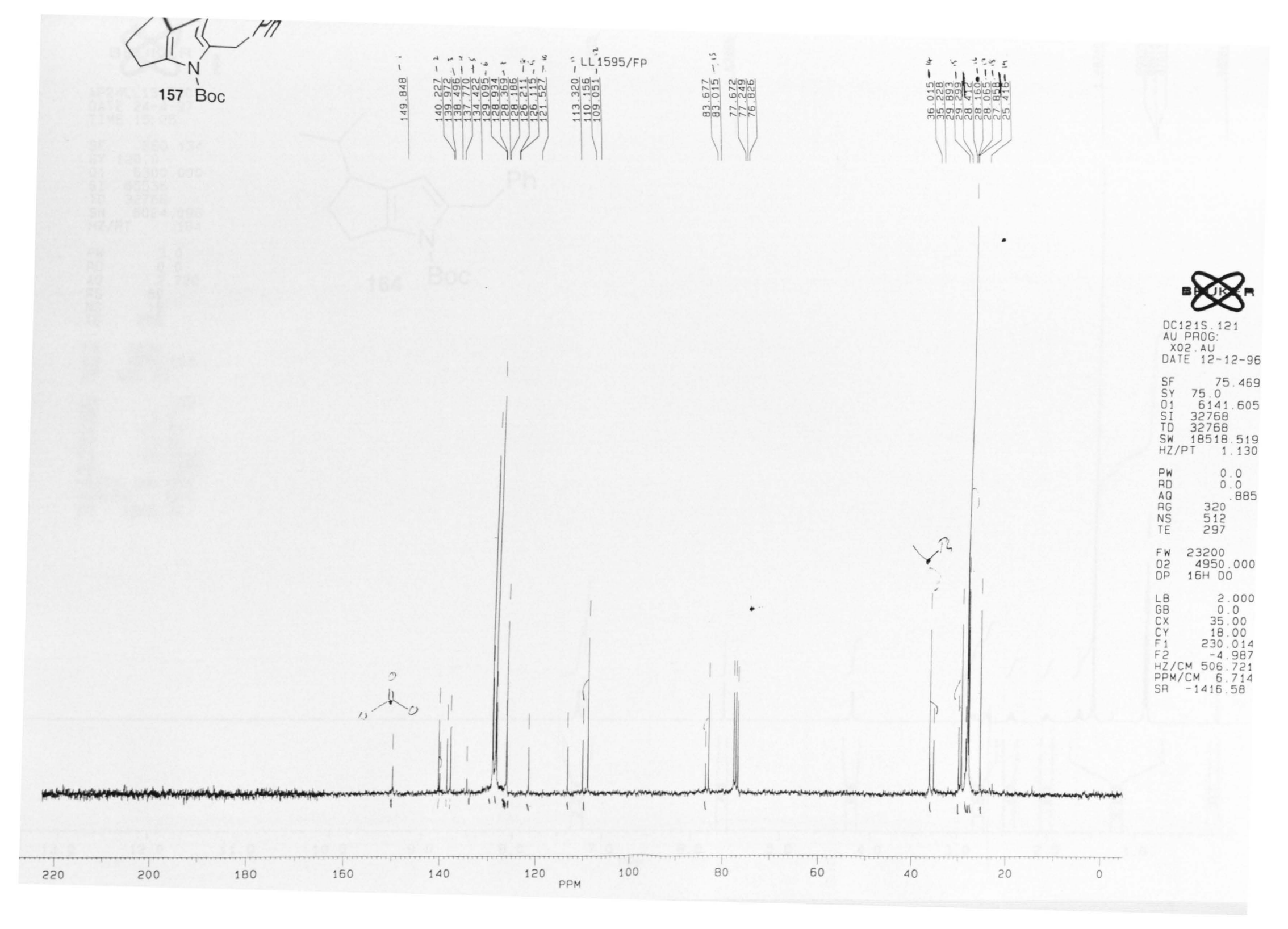
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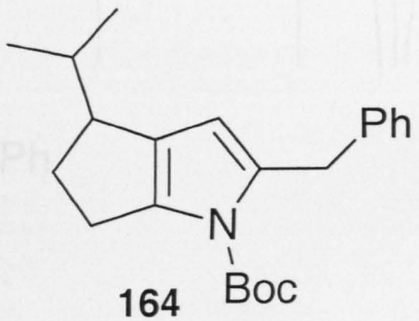

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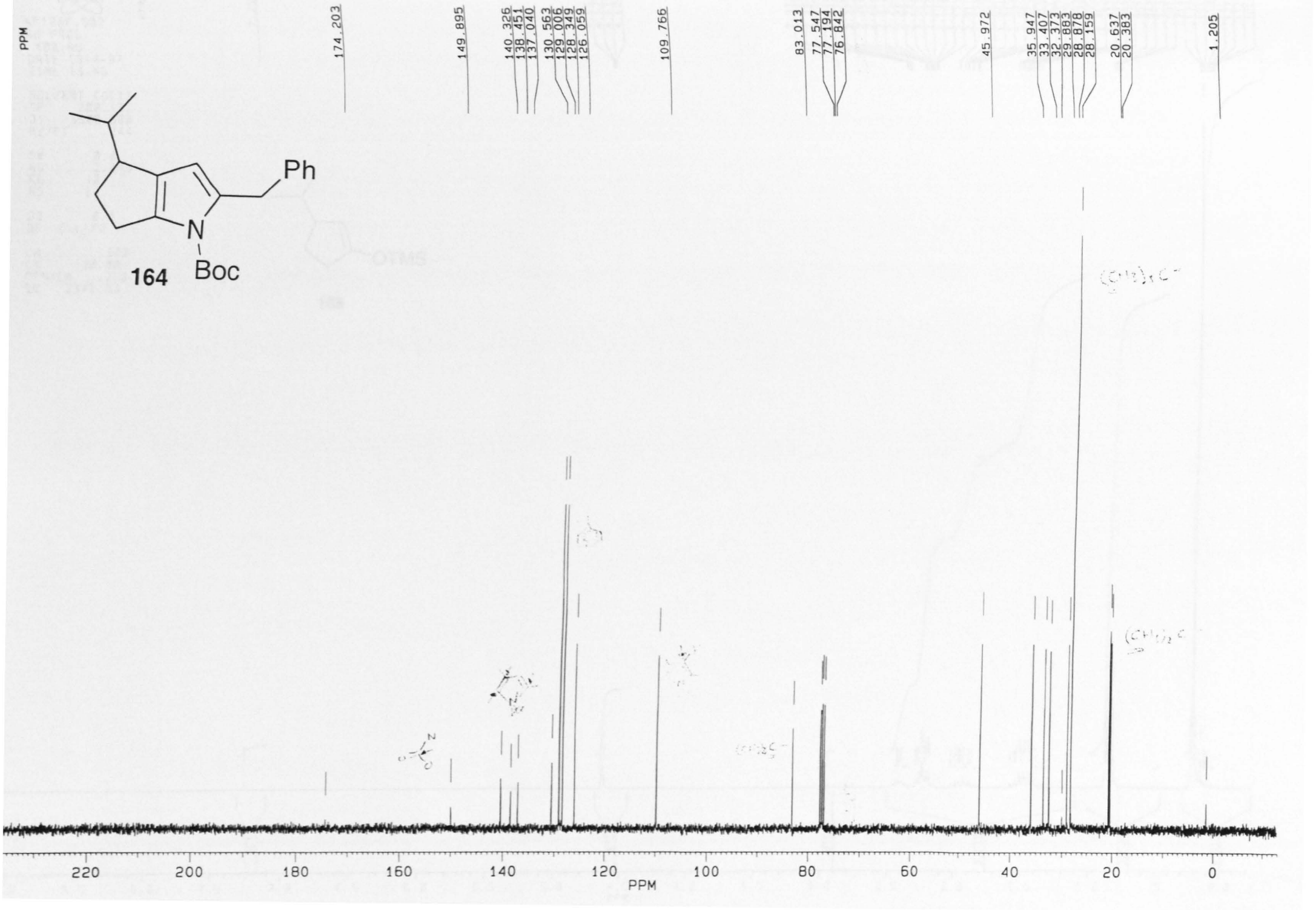

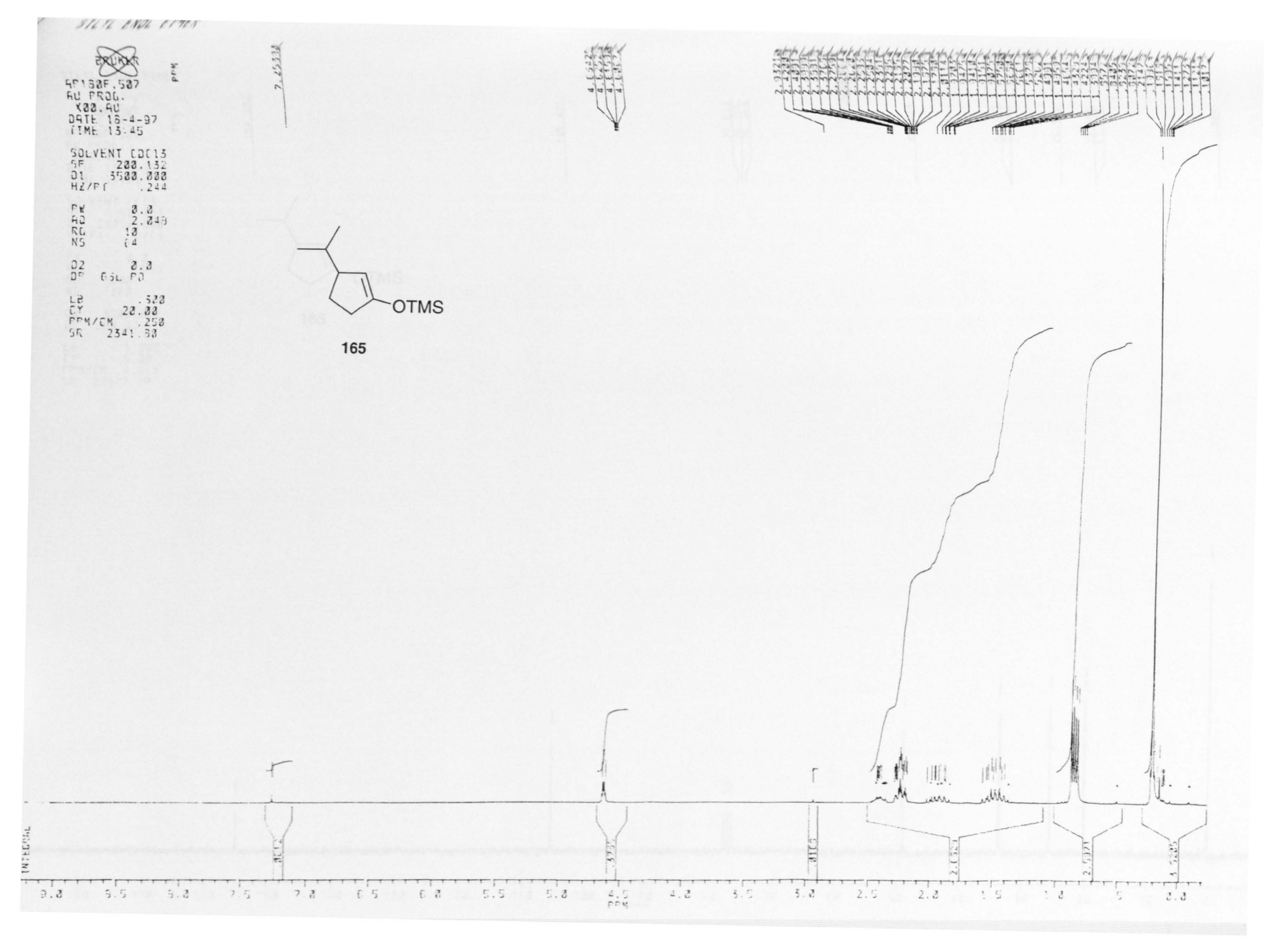
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SILYL ENOL ETHER

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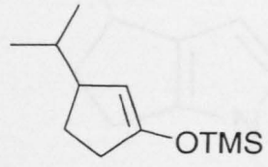

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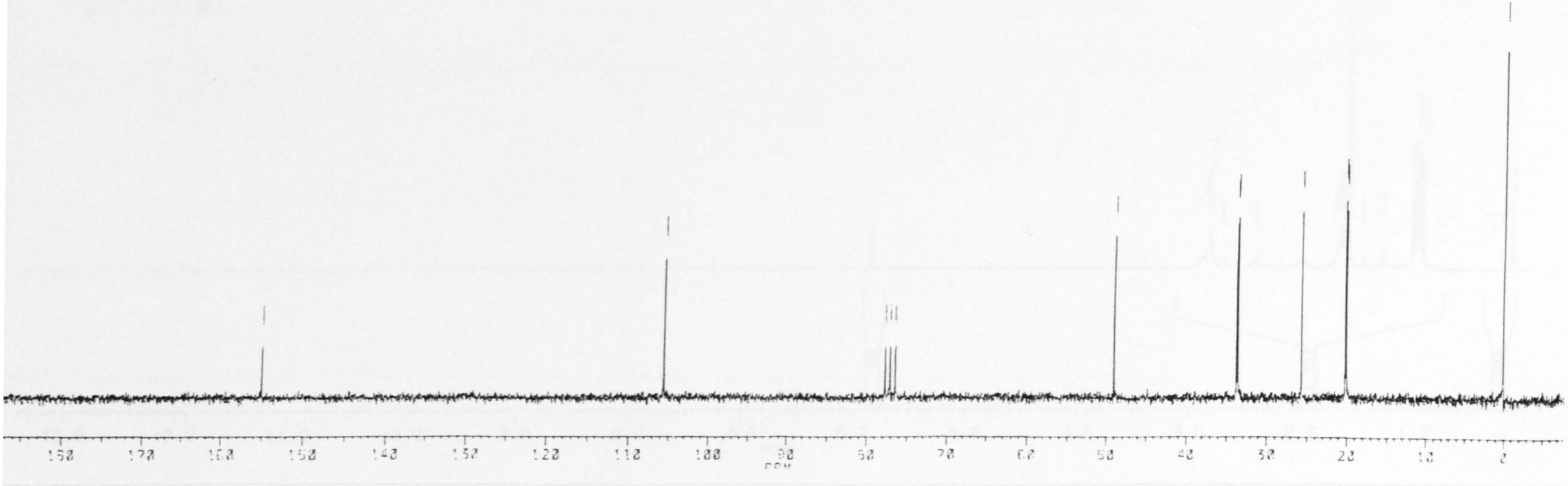

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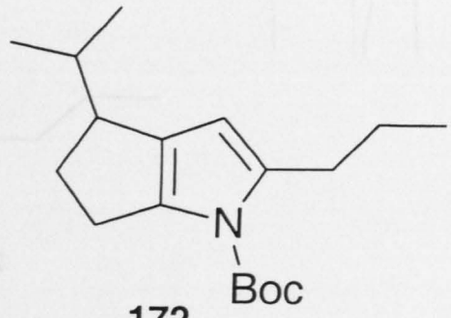

172

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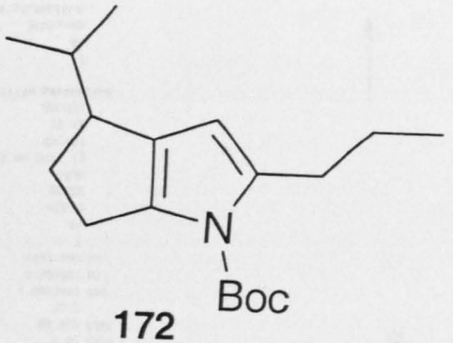

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User - L. Lea

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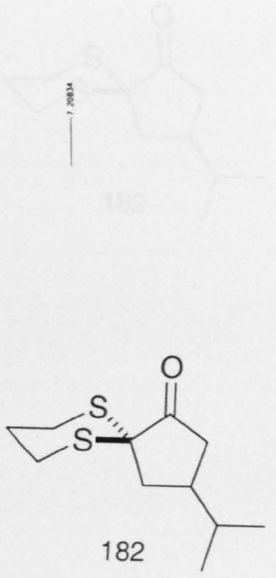

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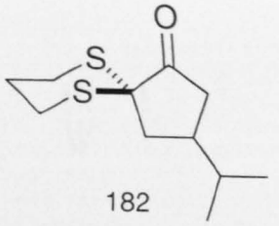
User - L. Lee



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User - Lea
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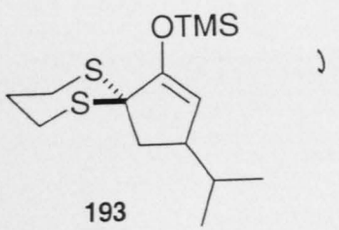

193

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User - L. Lee

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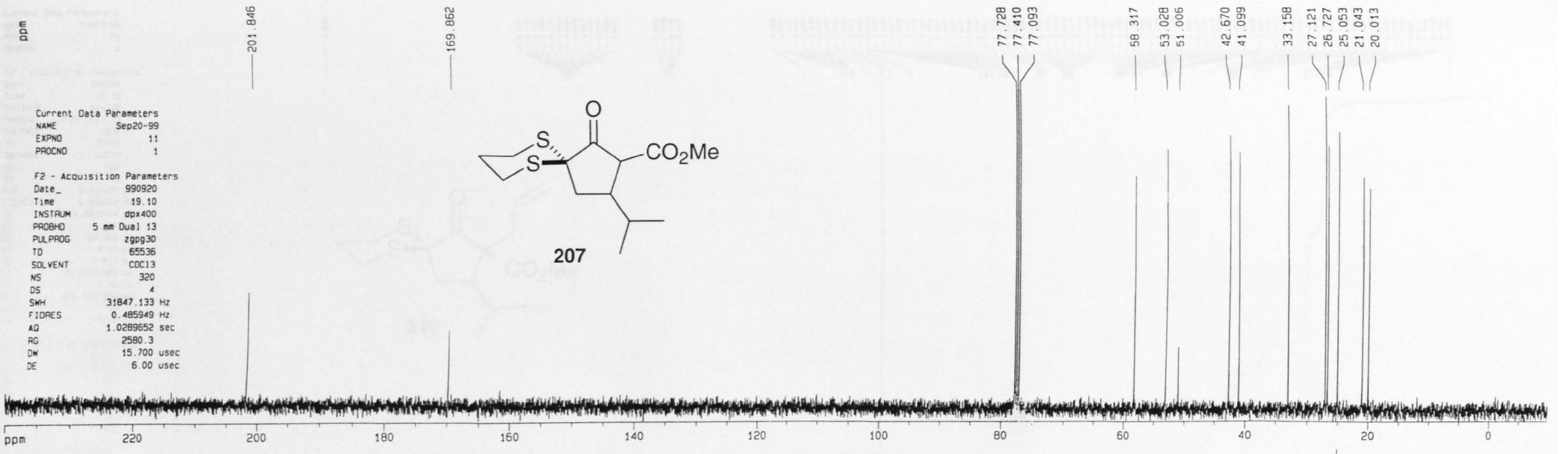

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1D NMR plot parameters
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F2 -1006.13 Hz
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User - L. Lea
E

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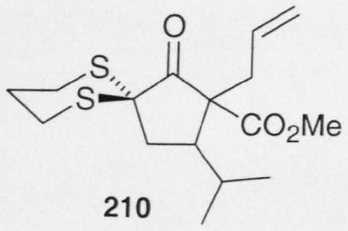

210

User - L. Lee

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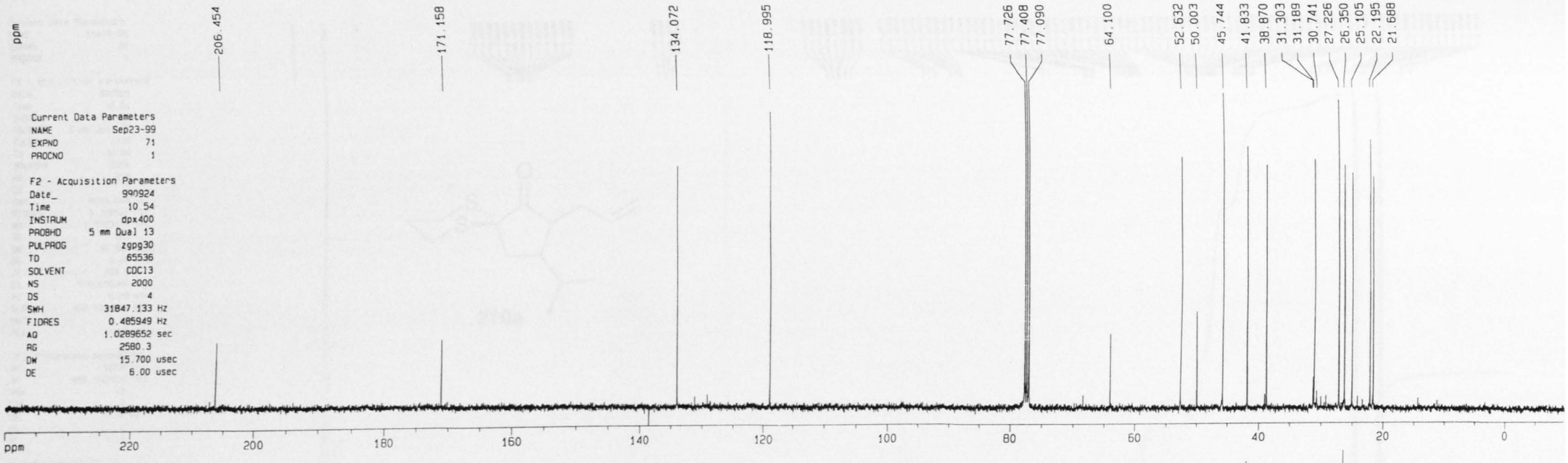

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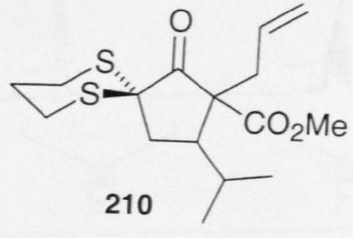
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm



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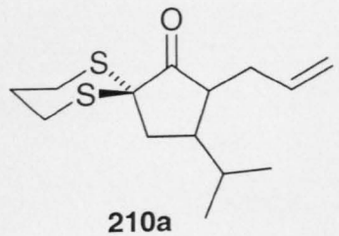
User - L. Lea
TACET 2

Current Data Parameters
NAME Sep29-99
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 990929
Time 18.51
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 256
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

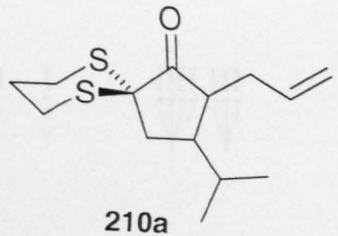
1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



210a

User - L. Lee

TACET 2



210a

ppm

209.775

136.240
128.640
128.399
128.280
128.159
117.088

50.659
50.021
42.600
39.570
34.845
32.132
30.053
27.337
27.051
26.605
25.619
21.393
20.750
17.783

Current Data Parameters
NAME Sep29-99
EXPNO 21
PROCNO 1

F2 - Acquisition Parameters
Date_ 990929
Time 19.26
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT C606
NS 2000
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec

ppm 220 200 180 160 140 120 100 80 60 40 20 0

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127069 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78925 Hz/cm

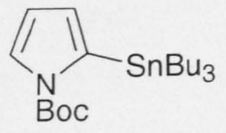
User - L. Lea

Current Data Parameters
NAME Sep28-99
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 990928
Time 22.36
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 90.5
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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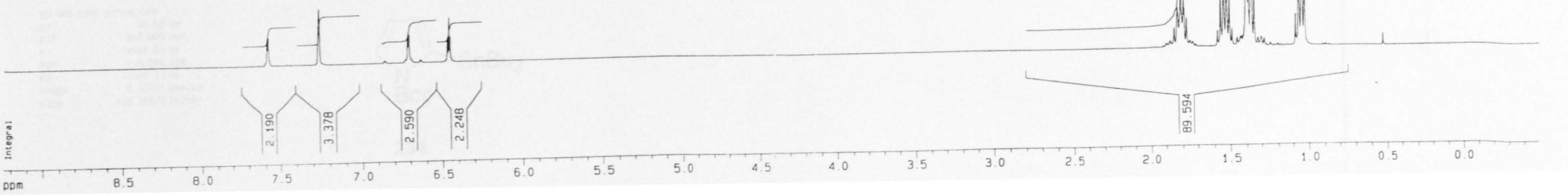
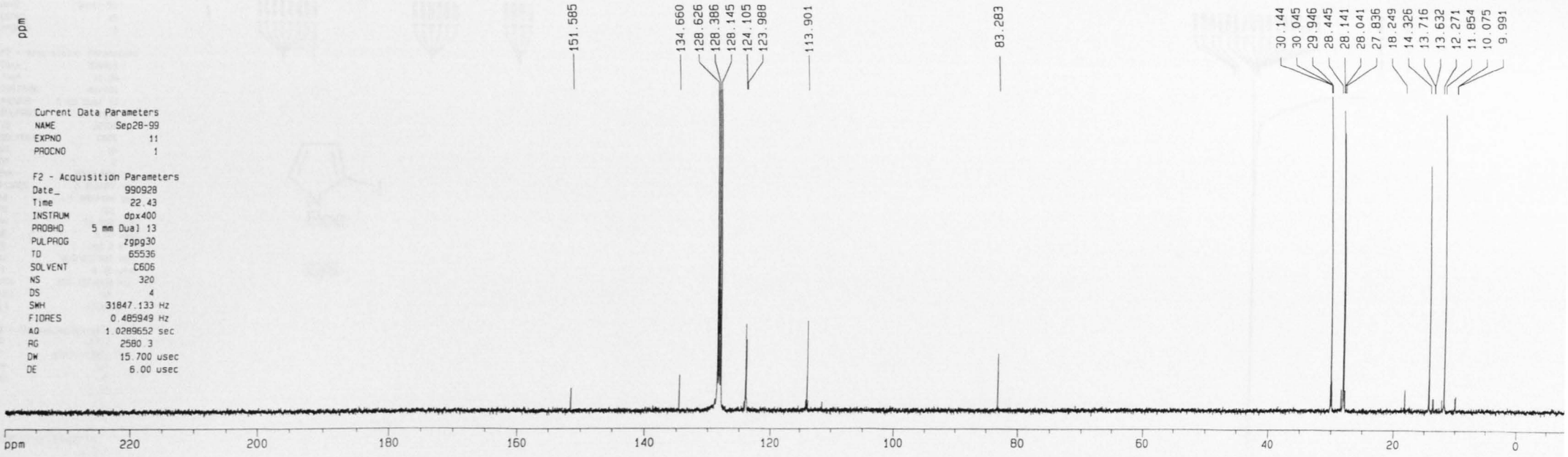


User - L. Lee



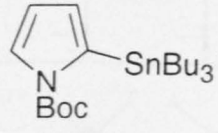
Current Data Parameters
NAME Sep28-99
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 990928
Time 22.43
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127069 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78925 Hz/cm



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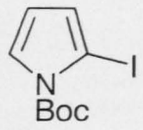
User - L. Lea
A

Current Data Parameters
NAME Sep17-99
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 12.58
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

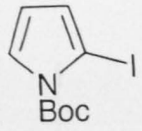
1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



235

User - L. Lee

A



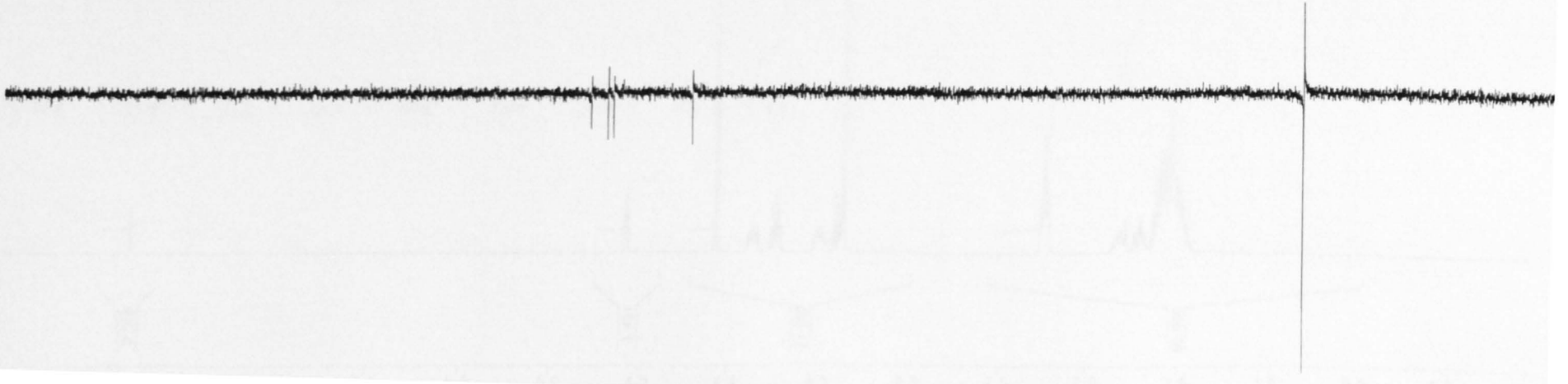
235

Current Data Parameters
NAME Sep17-99
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.05
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec
TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127069 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78925 Hz/cm



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Current Data Parameters

NAME	Dec10-98
EXPNO	30
PROCNO	1

F2 - Acquisition Parameters

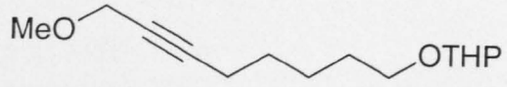
Date_	981210
Time	17.05
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99998 Hz/cm



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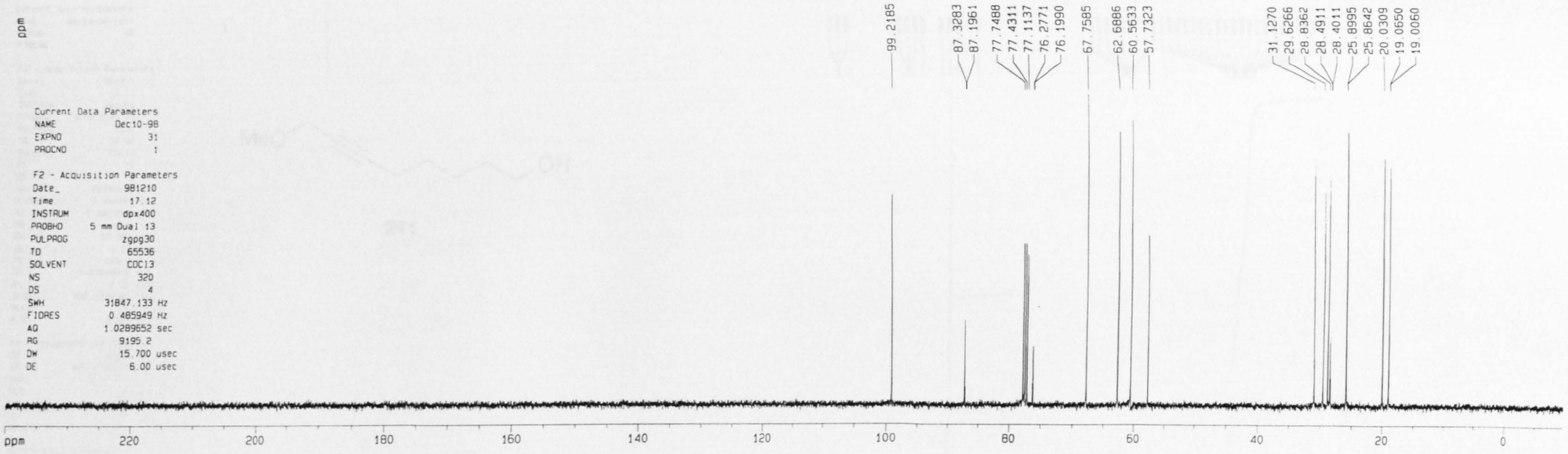


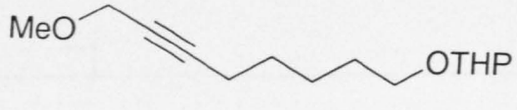
Current Data Parameters
NAME Dec10-98
EXPNO 31
PROCNO 1

F2 - Acquisition Parameters
Date_ 981210
Time 17.12
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 9195.2
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm



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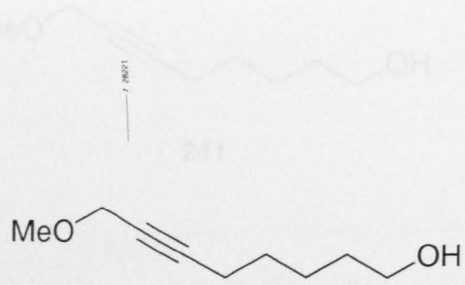
User - L. Lea

Current Data Parameters
NAME Dec10-98-1s14
EXPNO 40
PROCNO 1

F2 - Acquisition Parameters
Date_ 981210
Time 17.23
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 40.3
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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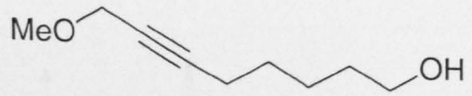
User - L. Leo



241

Current Data Parameters
NAME Dec10-98-jsl4
EXPNO 41
PROCNO 1

F2 - Acquisition Parameters
Date_ 981210
Time 17.30
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2298.8
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

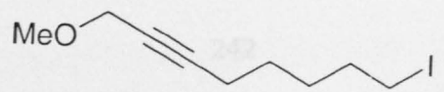
User - L. Lea

Current Data Parameters
NAME Dec10-98
EXPNO 50
PROCNO 1

F2 - Acquisition Parameters
Date_ 981210
Time 17.40
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 128
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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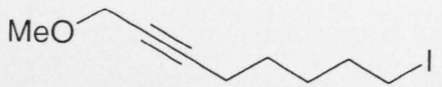
User - L. Lee



242

```
Current Data Parameters
NAME            Dec10-98
EXPNO                 51
PROCNO                 1

F2 - Acquisition Parameters
Date_           981210
Time            17.47
INSTRUM         dpx400
PROBHD     5 mm Dual 13
PULPROG         zgpg30
TD              65536
SOLVENT         CDCl3
NS              320
DS              4
SWH             31847.133 Hz
FIDRES          0.485949 Hz
AQ              1.0289652 sec
RG              5792.6
DW              15.700 usec
DE              6.00 usec
TE              298.0 K
D12             0.00002000 sec
PL13            18.00 dB
D1              0.01000000 sec
CPDPRG2         waltz16
PCPD2           80.00 usec
SFO2            400.1316005 MHz
NUC2            1H
PL2             -3.00 dB
PL12            16.00 dB
P1              6.90 usec
SFO1            100.6254245 MHz
NUC1            13C
PL1             -3.00 dB
D11             0.03000000 sec

F2 - Processing parameters
SI              32768
SF              100.6127290 MHz
WDW             EM
SSB             0
LB              1.00 Hz
GB              0
PC              2.00

1D NMR plot parameters
CX              39.50 cm
F1P             240.000 ppm
F1              24147.05 Hz
F2P             -10.000 ppm
F2              -1006.13 Hz
PPMCM           6.32911 ppm/cm
HZCM            636.78943 Hz/cm
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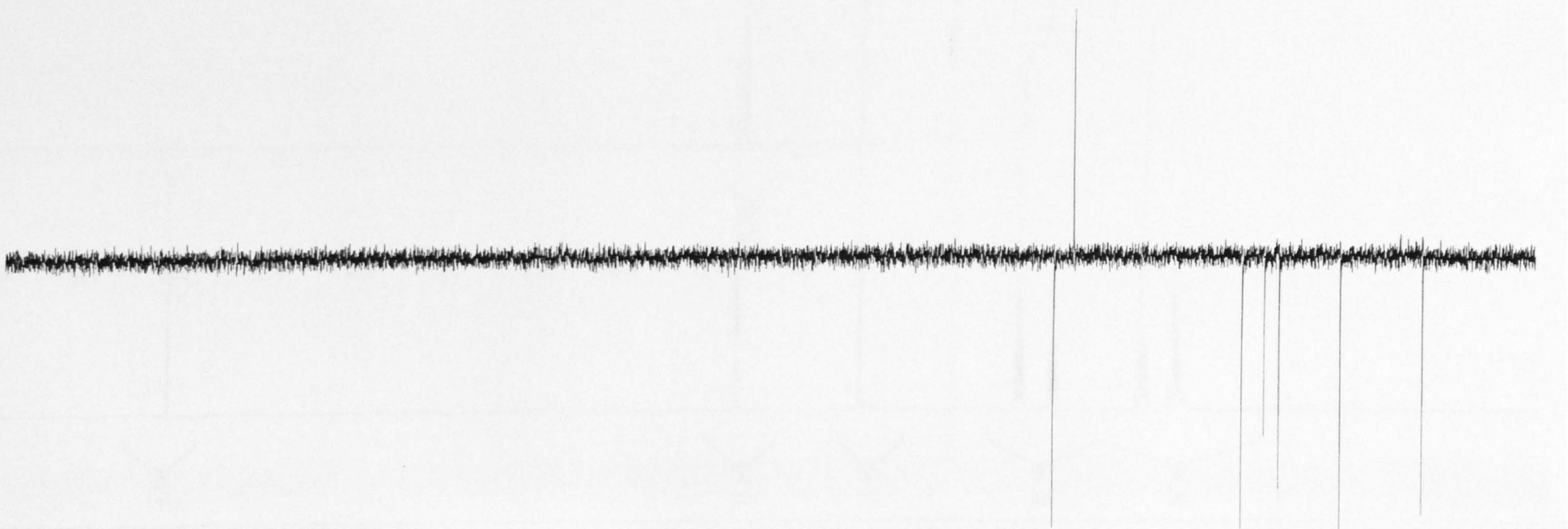


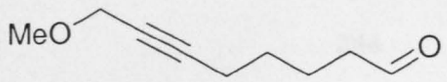
User - L. Lea
aldehyde

Current Data Parameters
NAME Dec11-98-1s11
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 981211
Time 16.48
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 406.4
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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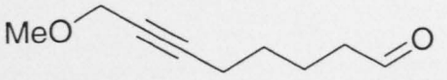
aldehyde



244

Current Data Parameters
NAME Dec11-98-1s11
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 981211
Time 17.17
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1600
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec
TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

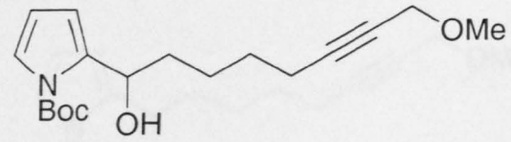
User - L. Lea
Hydroxyl adduct

Current Data Parameters
NAME Dec22-98-1s12
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 981222
Time 18.24
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

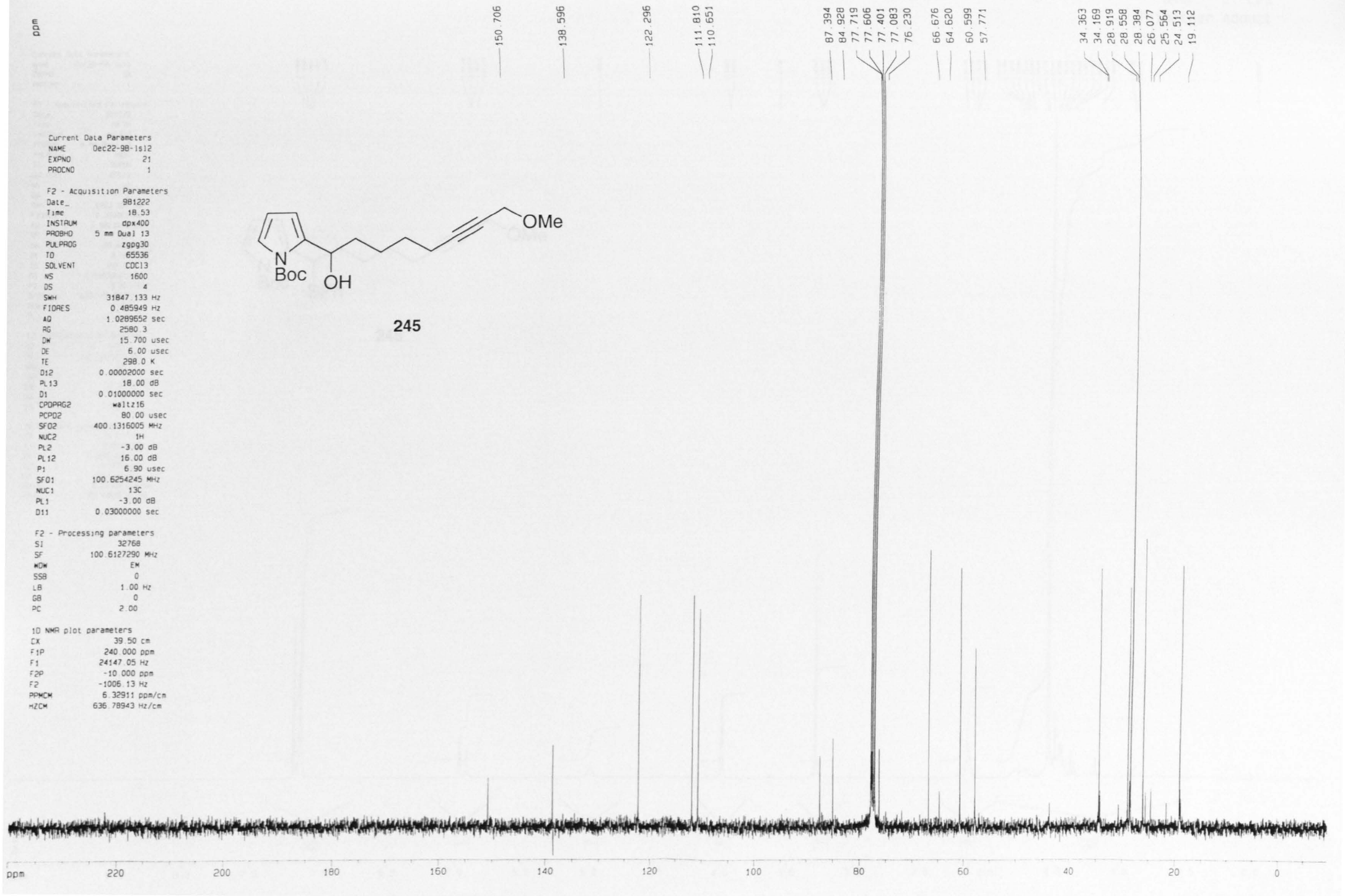
F2 - Processing parameters
SI 32768
SF 400.1300357 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99999 Hz/cm



245

Hydroxyl 3000Cl



245

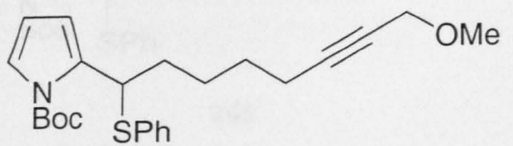
User - L. Lea
Thioether adduct

Current Data Parameters
NAME Dec22-98-1s13
EXPNO 30
PROCNO 1

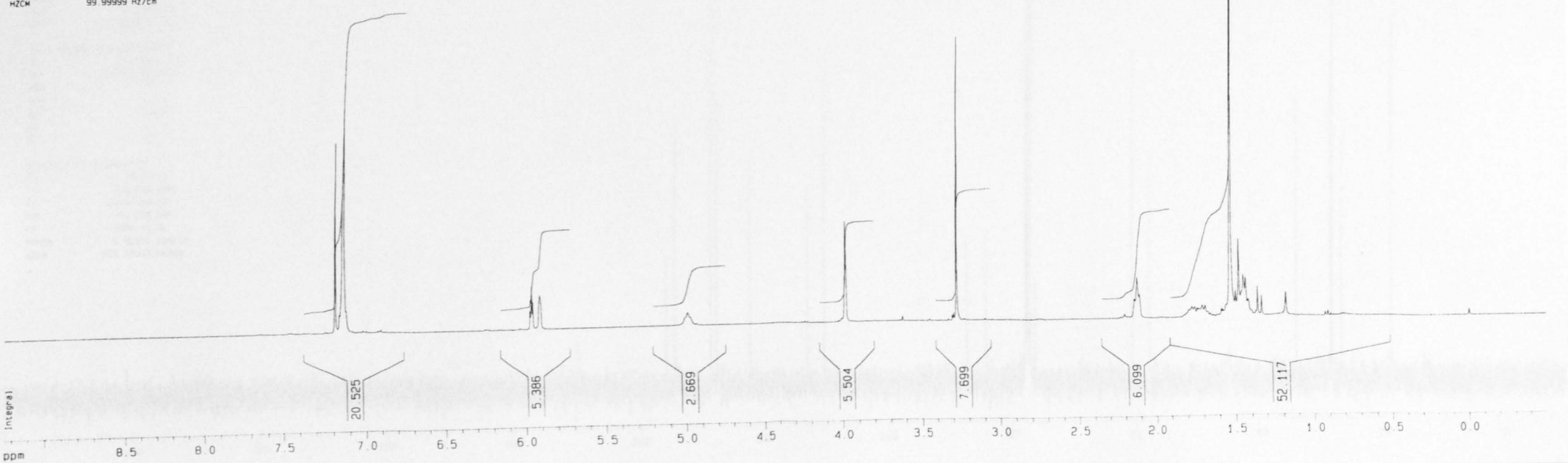
F2 - Acquisition Parameters
Date_ 981222
Time 18.59
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300375 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

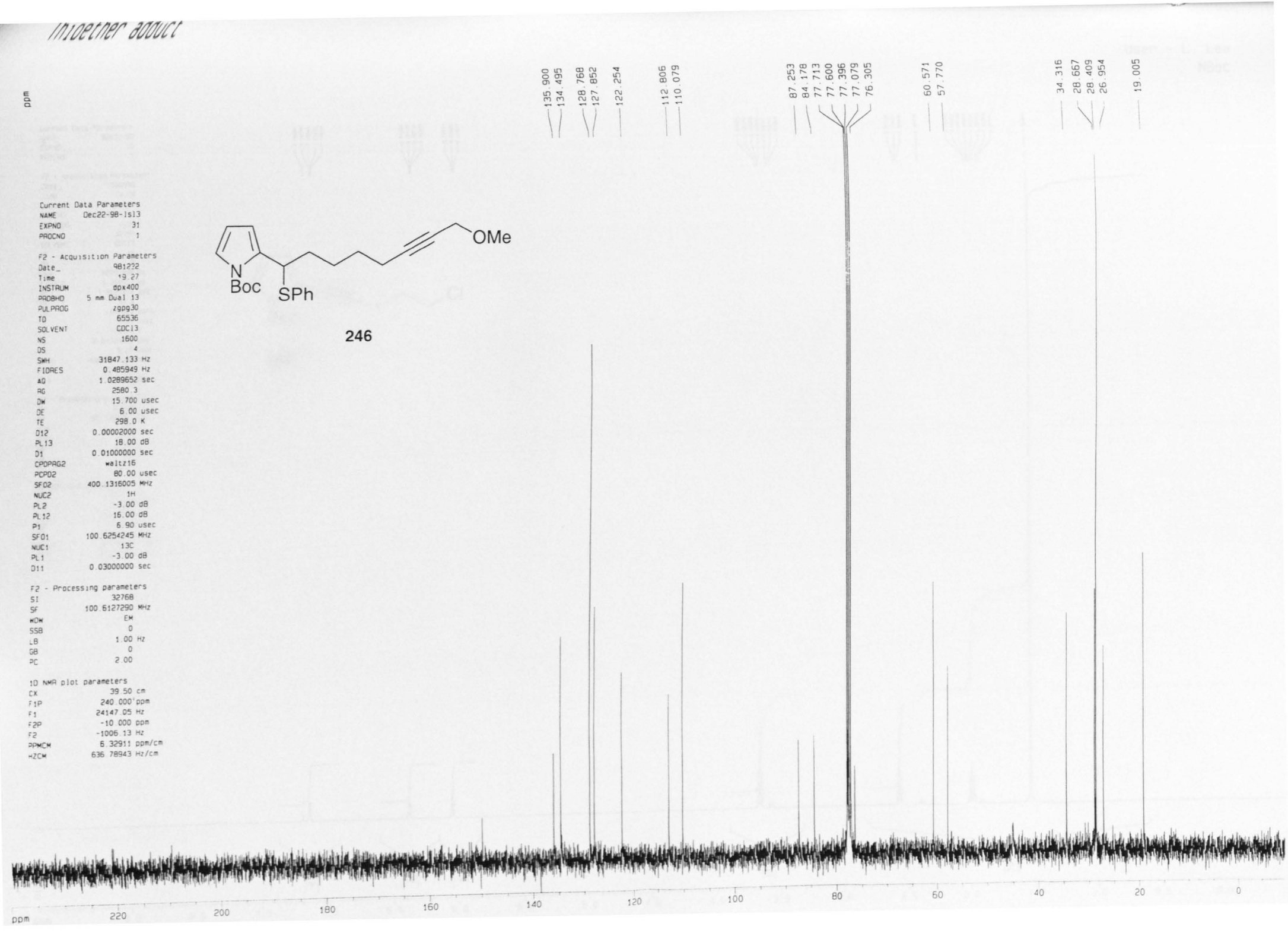
1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99999 Hz/cm



246



Thioether adduct



User - L. Lea
NBoc

Current Data Parameters

NAME	Sep30-99
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

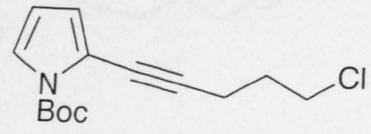
Date_	990930
Time	14.06
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	90.5
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300370 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

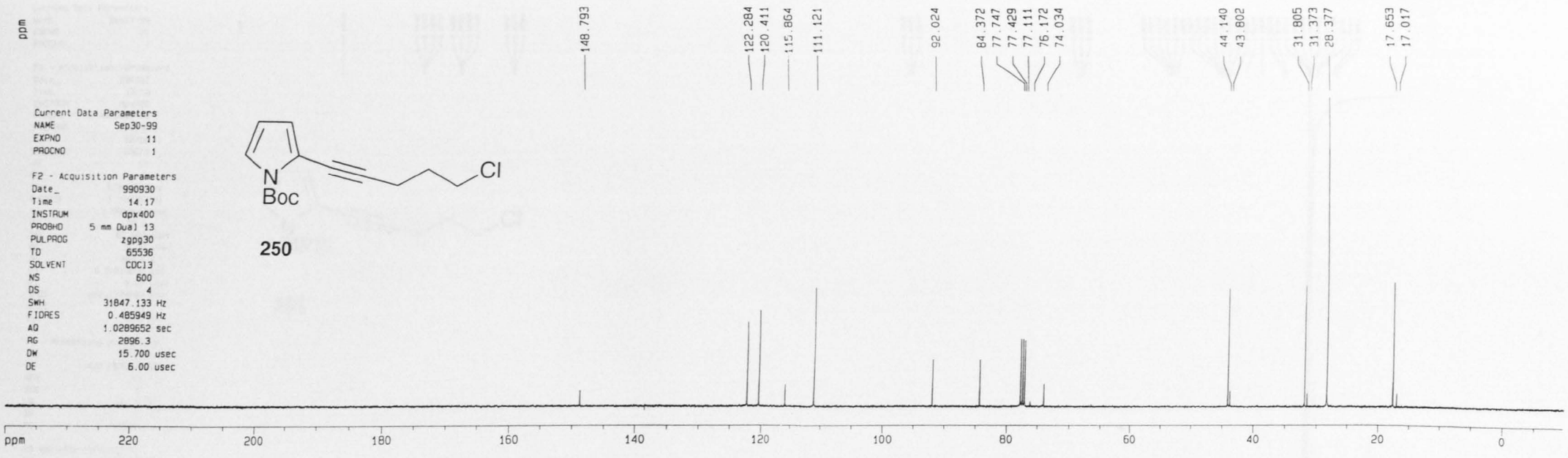
CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99999 Hz/cm



250

User - L. Lee

NBoc



Current Data Parameters
NAME Sep30-99
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 990930
Time 14.17
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 600
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2896.3
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

User - L. Lea

B

Current Data Parameters

NAME	Sep17-99
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

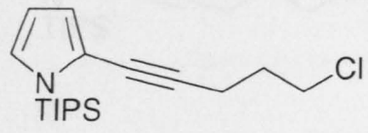
Date_	990917
Time	13.16
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	90.5
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99998 Hz/cm



251

User - L. Lee

B

251

ppm

126.728
119.255
118.849
110.428
89.645
77.721
77.405
77.279
77.087
44.103
31.702
18.499
17.490
13.038

Current Data Parameters
NAME Sep17-99
EXPNO 21
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.23
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec

ppm 220 200 180 160 140 120 100 80 60 40 20 0

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

User - L. Lea

Current Data Parameters

NAME	Sep23-99
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

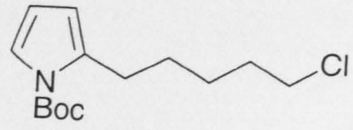
Date_	990923
Time	16.13
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	181
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99998 Hz/cm

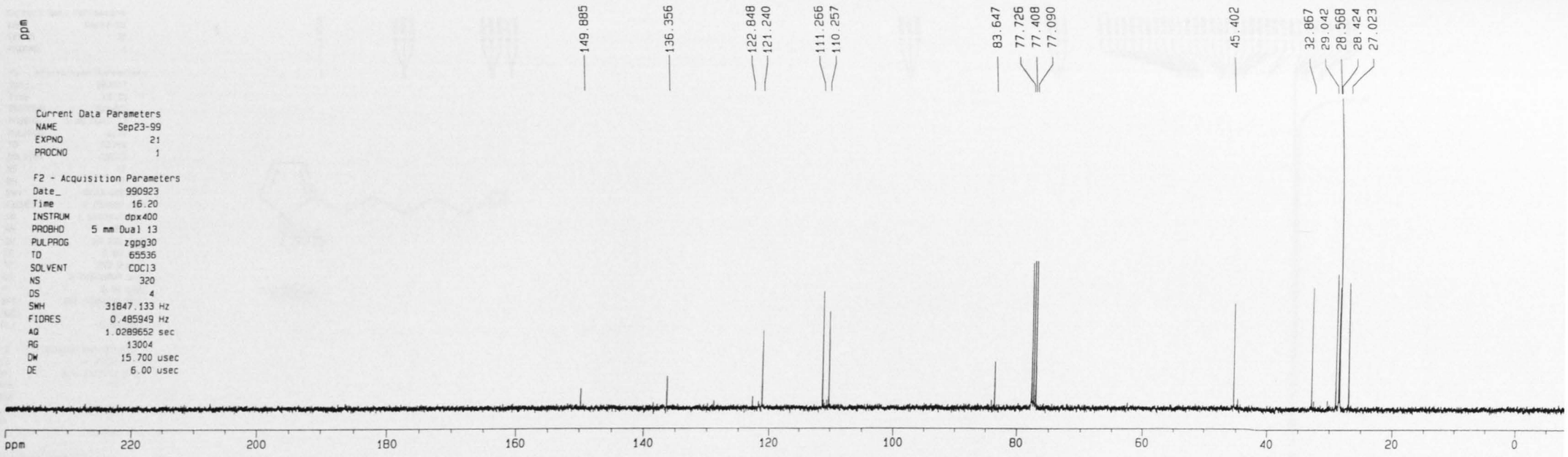


253a

Integral: 4.448 | 8.163 | 8.761 | 8.244 | 0.884 | 69.499

ppm: 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

User - L. Lee



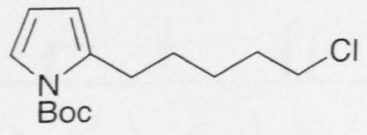
Current Data Parameters
NAME Sep23-99
EXPNO 21
PROCNO 1

F2 - Acquisition Parameters
Date_ 990923
Time 16.20
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 13004
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm



253a

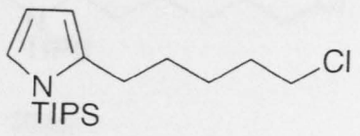
User - L. Lea
C

Current Data Parameters
NAME Sep17-99
EXPNO 30
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.33
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

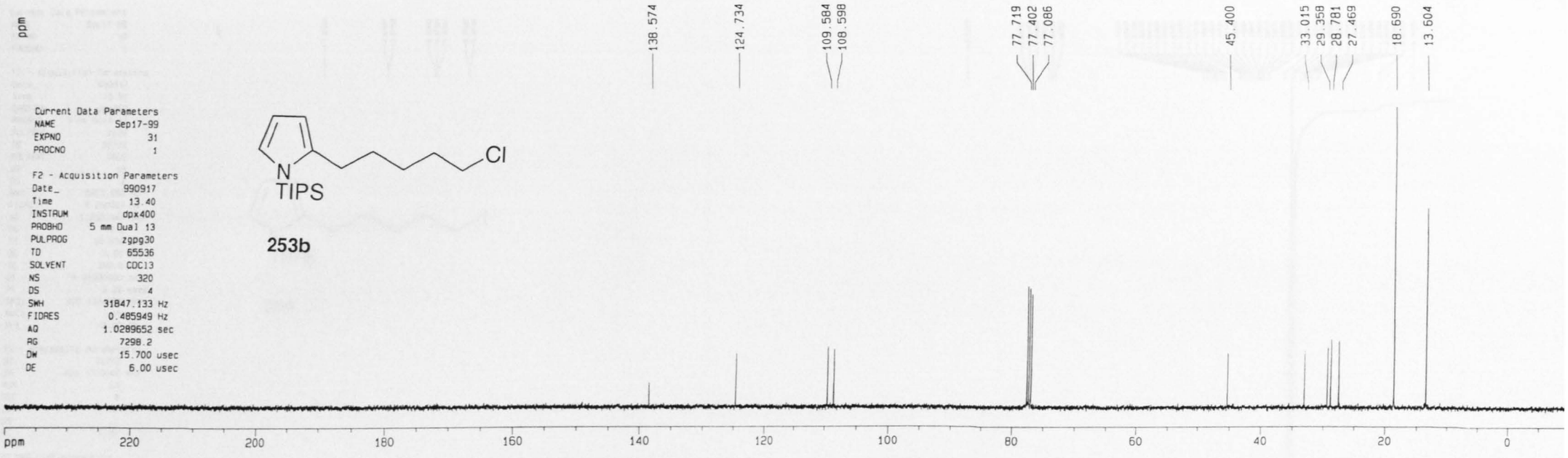
1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



253b

User - L. Lee

C



Current Data Parameters
NAME Sep17-99
EXPNO 31
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.40
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 7298.2
DW 15.700 usec
DE 6.00 usec

253b

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

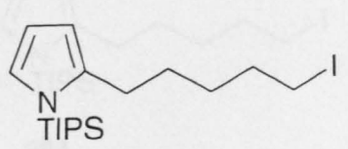
User - L. Lea
D

Current Data Parameters
NAME Sep17-99
EXPNO 40
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.51
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 40.3
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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User - L. Lee

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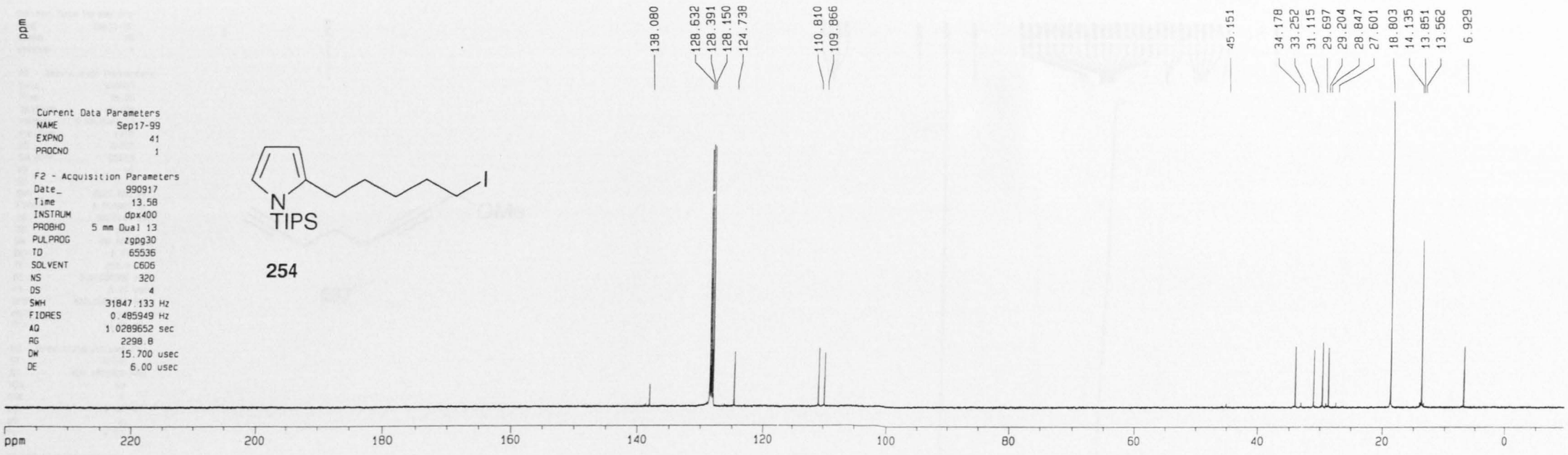


Current Data Parameters
NAME Sep17-99
EXPNO 41
PROCNO 1

F2 - Acquisition Parameters
Date_ 990917
Time 13.58
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2298.8
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SF02 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SF01 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127069 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78925 Hz/cm

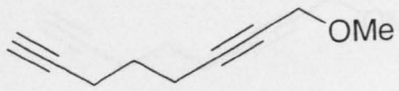
User - L. Lea

Current Data Parameters
NAME Sep23-99
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 990923
Time 15.56
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



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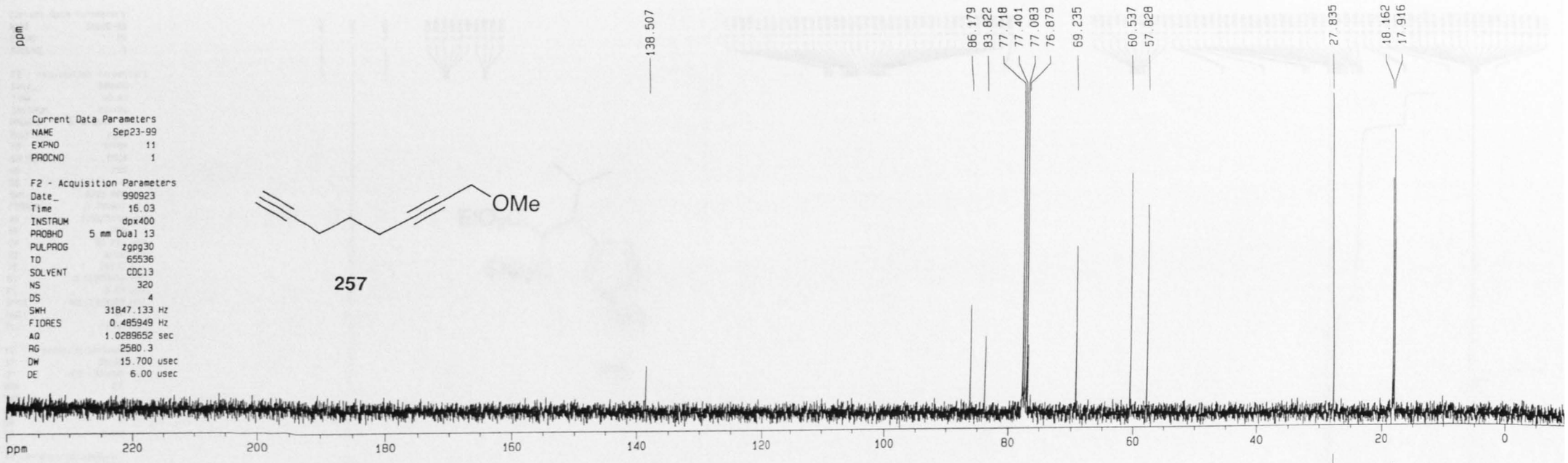


Current Data Parameters
NAME Sep23-99
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 990923
Time 16.03
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 320
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

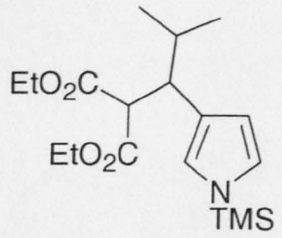
User - L. Lea
N-TMS

Current Data Parameters
NAME Sep25-99
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 990925
Time 20.07
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 256
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 256
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300695 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 100.00000 Hz/cm



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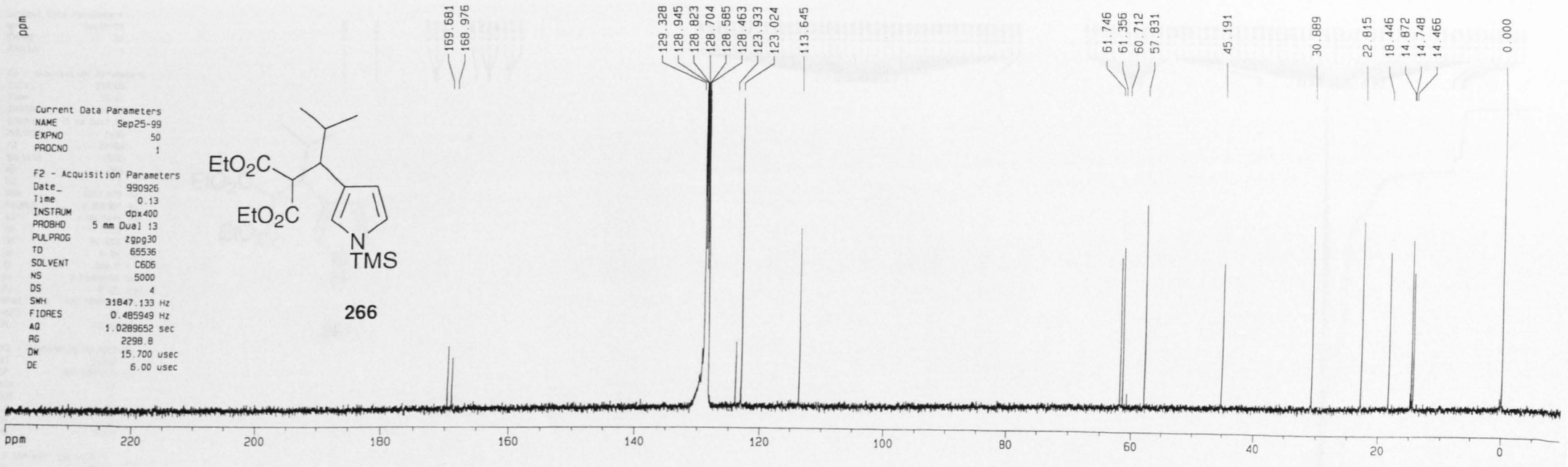
User - L. Leb

N-TMS



Current Data Parameters

NAME	Sep25-99
EXPNO	50
PROCNO	1

F2 - Acquisition Parameters

Date_	990926
Time	0.13
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zgpg30
TD	65536
SOLVENT	C6D6
NS	5000
DS	4
SWH	31847.133 Hz
FIDRES	0.485949 Hz
AQ	1.0289652 sec
RG	2298.8
DW	15.700 usec
DE	6.00 usec

266

TE	298.0 K
D12	0.00002000 sec
PL13	18.00 dB
D1	0.01000000 sec
CPDPRG2	waltz16
PCPD2	80.00 usec
SFO2	400.1316005 MHz
NUC2	1H
PL2	-3.00 dB
PL12	16.00 dB
P1	6.90 usec
SFO1	100.6254245 MHz
NUC1	13C
PL1	-3.00 dB
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	100.6126762 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	2.00

1D NMR plot parameters

CX	39.50 cm
F1P	240.000 ppm
F1	24147.04 Hz
F2P	-10.000 ppm
F2	-1006.13 Hz
PPMCM	6.32911 ppm/cm
HZCM	636.78906 Hz/cm

User - L. Lea

NH

Current Data Parameters

NAME	Sep26-99
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

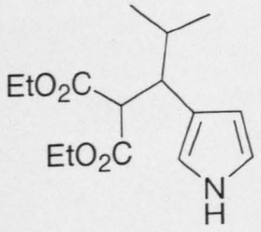
Date_	990926
Time	16.01
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	C606
NS	256
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	181
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SF01	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300658 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	100.00000 Hz/cm



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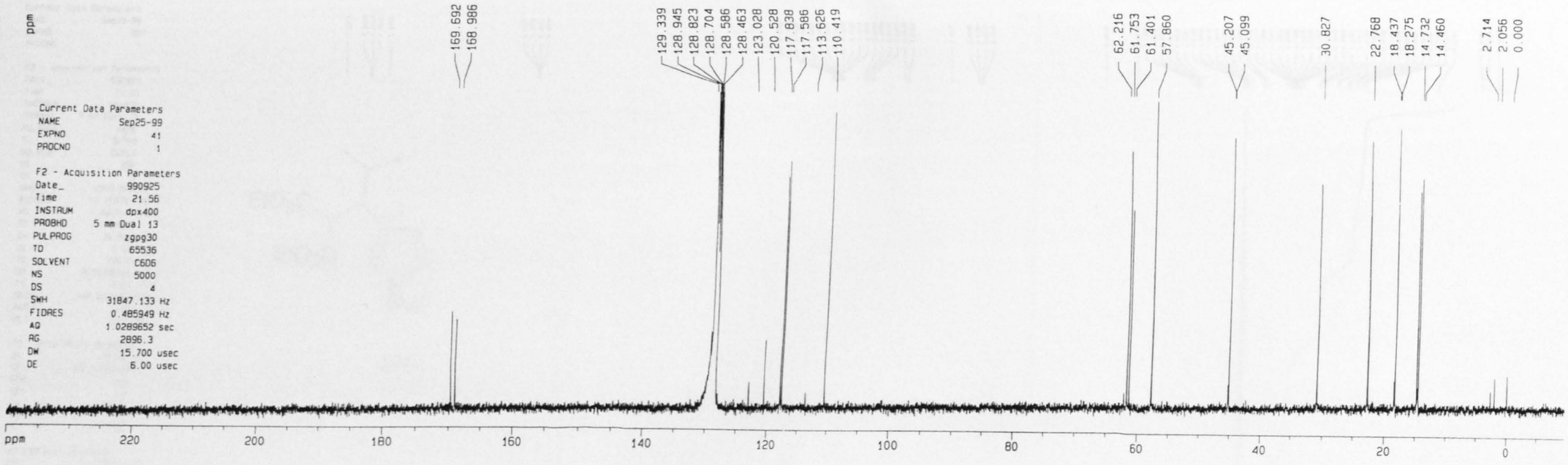
User - L. Lee

N-H



Current Data Parameters

NAME	Sep25-99
EXPNO	41
PROCNO	1

F2 - Acquisition Parameters

Date_	990925
Time	21.56
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zgpg30
TD	65536
SOLVENT	C6D6
NS	5000
DS	4
SWH	31847.133 Hz
FIDRES	0.485949 Hz
AQ	1.0289652 sec
RG	2896.3
DW	15.700 usec
DE	6.00 usec

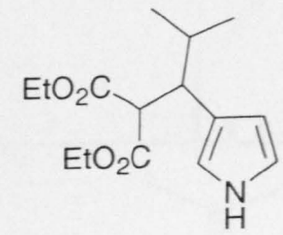
TE	298.0 K
D12	0.00002000 sec
PL13	18.00 dB
D1	0.01000000 sec
CPDPRG2	waltz16
PCPD2	80.00 usec
SFO2	400.1316005 MHz
NUC2	1H
PL2	-3.00 dB
PL12	16.00 dB
P1	6.90 usec
SFO1	100.6254245 MHz
NUC1	13C
PL1	-3.00 dB
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	100.6126763 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	2.00

1D NMR plot parameters

CX	39.50 cm
F1P	240.000 ppm
F1	24147.04 Hz
F2P	-10.000 ppm
F2	-1006.13 Hz
PPMCM	6.32911 ppm/cm
HZCM	636.78906 Hz/cm



User - L. Lea

F

Current Data Parameters

NAME	Sep23-99
EXPNO	80
PROCNO	1

F2 - Acquisition Parameters

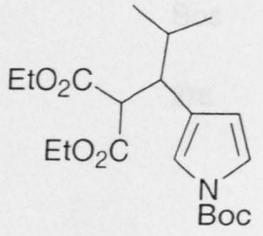
Date_	990924
Time	11.26
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	256
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	645.1
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300360 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99999 Hz/cm



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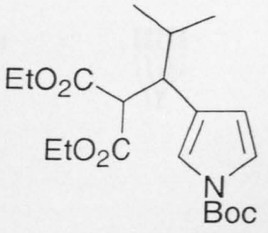
User - L. Lee

F



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Current Data Parameters
NAME Sep23-99
EXPNO 81
PROCNO 1

F2 - Acquisition Parameters
Date_ 990924
Time 12.02
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2000
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289552 sec
RG 4597.6
DW 15.700 usec
DE 6.50 usec
TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

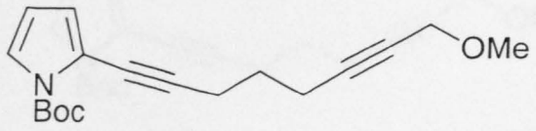
User - L. Lea
C

Current Data Parameters
NAME Sep23-99
EXPNO 50
PROCNO 1

F2 - Acquisition Parameters
Date_ 990924
Time 8.07
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 406.4
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

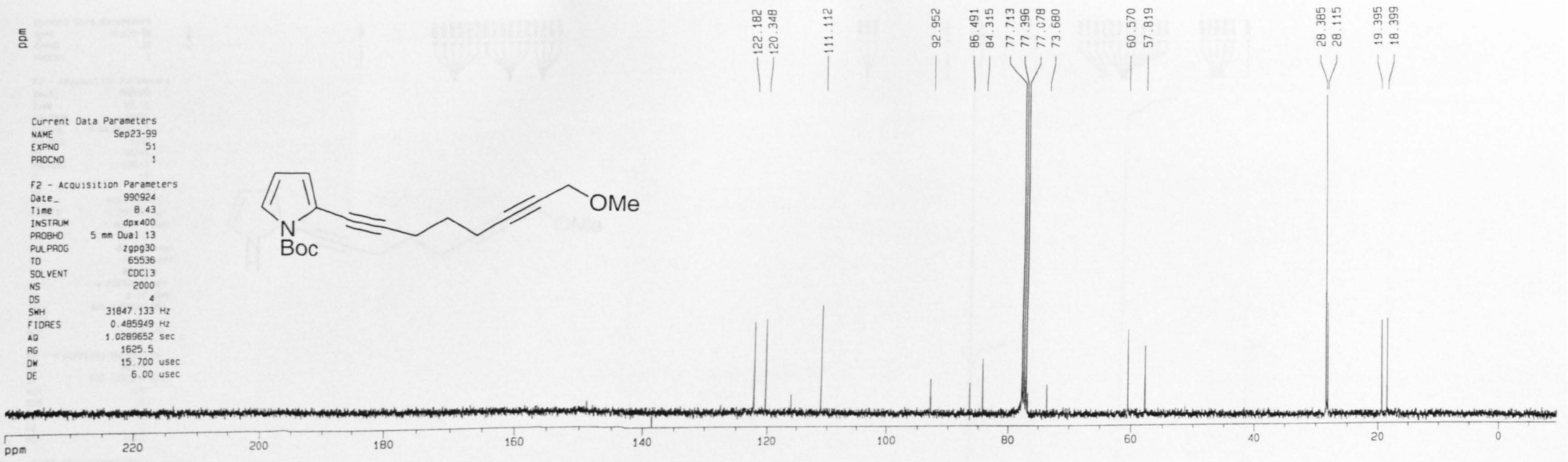
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



User - L. Lee

C



Current Data Parameters
NAME Sep23-99
EXPNO 51
PROCNO 1

F2 - Acquisition Parameters
Date_ 990924
Time 8.43
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2000
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 1625.5
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

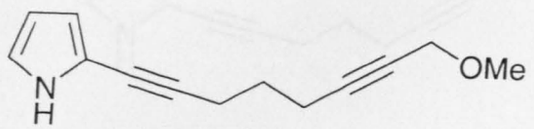
User - L. Lea

Current Data Parameters
NAME Sep20-99
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 990920
Time 19.21
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 322.5
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300372 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

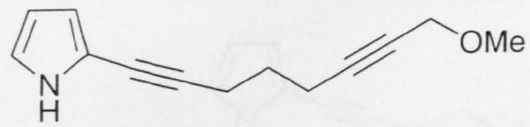
1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99999 Hz/cm



integral
5.673
1.608
5.712
5.427
5.645
12.454
18.108
26.935
18.008
0.431

ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

User - L. Leo



Current Data Parameters
NAME Sep20-99
EXPNO 21
PROCNO 1

F2 - Acquisition Parameters
Date_ 990920
Time 19.50
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1600
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 2580.3
DW 15.700 usec
DE 6.00 usec
TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SF02 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SF01 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78943 Hz/cm

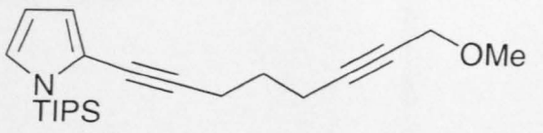
User - L. Lea
N-TIPS

Current Data Parameters
NAME Sep25-99
EXPNO 30
PROCNO 1

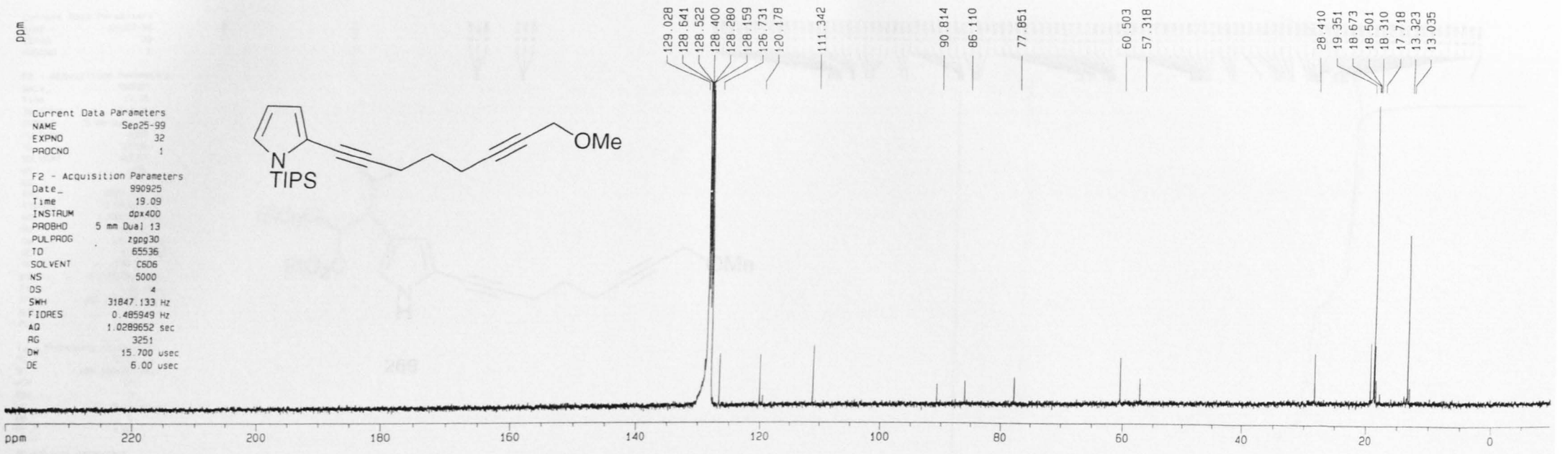
F2 - Acquisition Parameters
Date_ 990925
Time 17.41
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 256
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 322.5
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99998 Hz/cm



User - L. Lee
N-TIPS



Current Data Parameters
NAME Sep25-99
EXPNO 32
PROCNO 1

F2 - Acquisition Parameters
Date_ 990925
Time 19.09
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 5000
DS 4
SWH 31847.133 Hz
FIDRES 0.485949 Hz
AQ 1.0289652 sec
RG 3251
DW 15.700 usec
DE 6.00 usec

TE 298.0 K
D12 0.00002000 sec
PL13 18.00 dB
D1 0.01000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 400.1316005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 16.00 dB
P1 6.90 usec
SFO1 100.6254245 MHz
NUC1 13C
PL1 -3.00 dB
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 100.6127069 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 39.50 cm
F1P 240.000 ppm
F1 24147.05 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.32911 ppm/cm
HZCM 636.78925 Hz/cm

User - L. Lea

NH

Current Data Parameters

NAME	Sep27-99
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

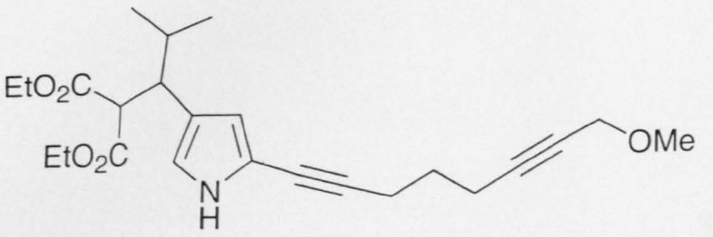
Date_	990927
Time	14.20
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	256
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	406.4
DW	60.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.01000000 sec
P1	9.20 usec
SFO1	400.1324689 MHz
NUC1	1H
PL1	-3.00 dB

F2 - Processing parameters

SI	32768
SF	400.1300355 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	4.00

1D NMR plot parameters

CX	39.01 cm
F1P	9.250 ppm
F1	3701.20 Hz
F2P	-0.500 ppm
F2	-200.06 Hz
PPMCM	0.24992 ppm/cm
HZCM	99.99999 Hz/cm



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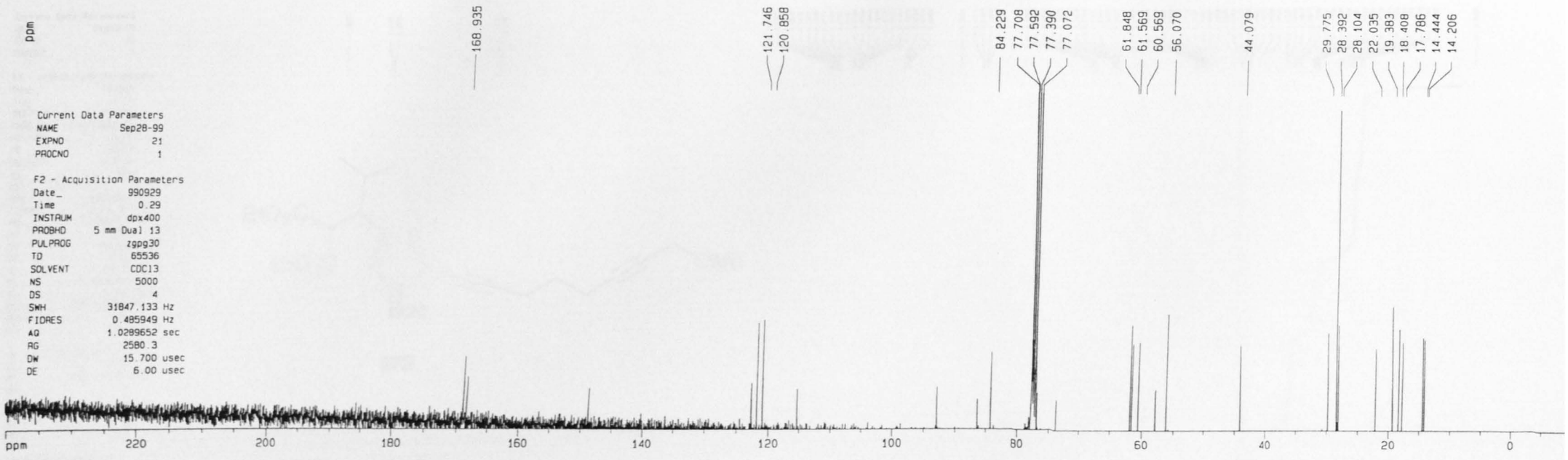
User - L. Lee

N-BOC



Current Data Parameters

NAME	Sep28-99
EXPNO	21
PROCNO	1

F2 - Acquisition Parameters

Date_	990929
Time	0.29
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	5000
DS	4
SWH	31847.133 Hz
FIDRES	0.485949 Hz
AQ	1.0289652 sec
RG	2580.3
DW	15.700 usec
DE	6.00 usec

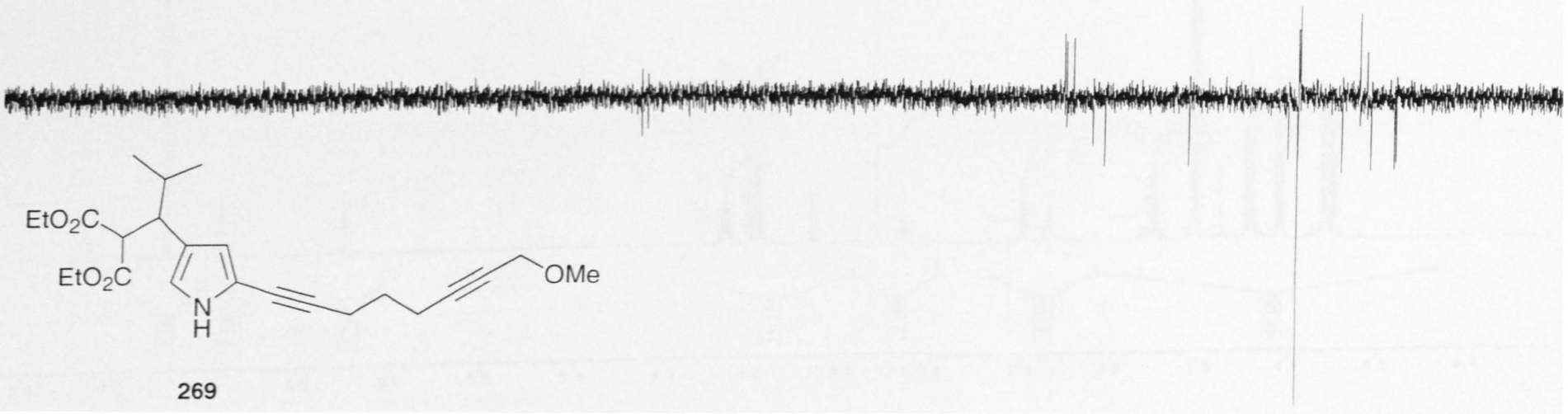
TE	298.0 K
D12	0.00002000 sec
PL13	18.00 dB
D1	0.01000000 sec
CPDPRG2	waltz16
PCPD2	80.00 usec
SFO2	400.1316005 MHz
NUC2	1H
PL2	-3.00 dB
PL12	16.00 dB
P1	6.90 usec
SFO1	100.6254245 MHz
NUC1	13C
PL1	-3.00 dB
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	2.00

1D NMR plot parameters

CX	39.50 cm
F1P	240.000 ppm
F1	24147.05 Hz
F2P	-10.000 ppm
F2	-1006.13 Hz
PPMCM	6.32911 ppm/cm
HZCM	636.78943 Hz/cm



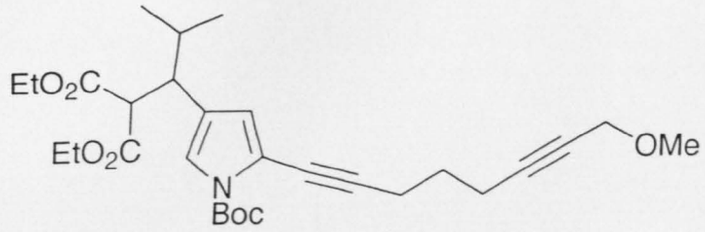
User - L. Lea
N-BOC

Current Data Parameters
NAME Sep28-99
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 990928
Time 23.01
INSTRUM dpx400
PROBHD 5 mm Dual 13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 256
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 512
DW 60.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.01000000 sec
P1 9.20 usec
SFO1 400.1324689 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 32768
SF 400.1300358 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 39.01 cm
F1P 9.250 ppm
F1 3701.20 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.24992 ppm/cm
HZCM 99.99999 Hz/cm



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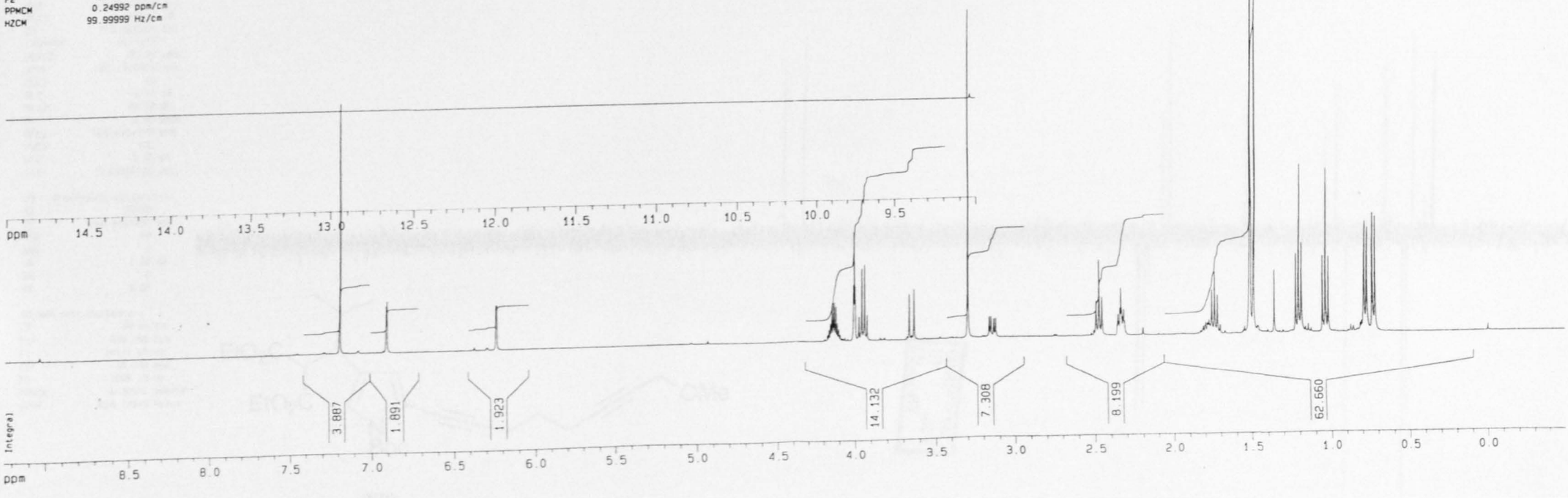
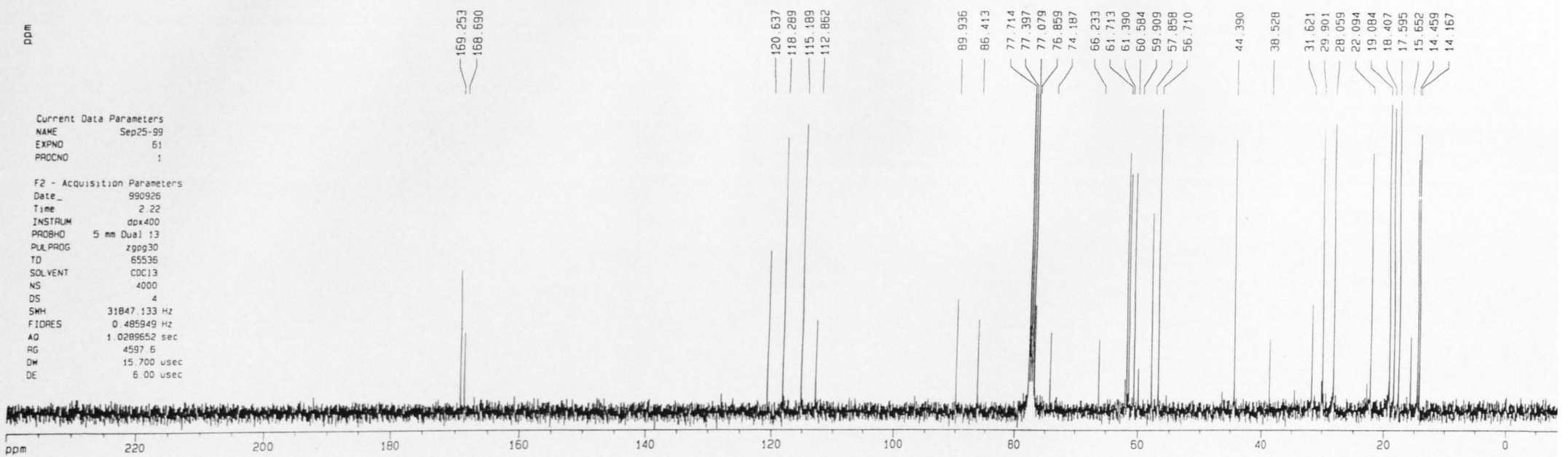


User - L. Lea
A



Current Data Parameters

NAME	Sep25-99
EXPNO	61
PROCNO	1

F2 - Acquisition Parameters

Date_	990926
Time	2.22
INSTRUM	dpx400
PROBHD	5 mm Dual 13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	4000
DS	4
SWH	31847.133 Hz
FIDRES	0.485949 Hz
AQ	1.0289652 sec
RG	4597.6
DW	15.700 usec
DE	6.00 usec

TE	298.0 K
D12	0.00002000 sec
PL13	18.00 dB
D1	0.01000000 sec
CPDPRG2	waltz16
PCPD2	80.00 usec
SFO2	400.1316005 MHz
NUC2	1H
PL2	-3.00 dB
PL12	16.00 dB
P1	6.90 usec
SFO1	100.6254245 MHz
NUC1	13C
PL1	-3.00 dB
D11	0.03000000 sec

F2 - Processing parameters

SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	2.00

1D NMR plot parameters

CX	39.50 cm
F1P	240.000 ppm
F1	24147.05 Hz
F2P	-10.000 ppm
F2	-1006.13 Hz
PPMCM	6.32911 ppm/cm
HZCM	636.78943 Hz/cm