Synthesis of a new class of homochiral amines and novel bio-active tropanes

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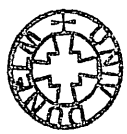
Mustafa Tavasli, B.Ed. (Hons), M.Sc.

Ph.D. Thesis



University of Durham, Department of Chemistry

September 1999

To my family…

Declaration

The work contained in the thesis was carried out in the Department of Chemistry at the University of Durham between October 1996 and September 1999. All the work is the author's individual contribution, unless otherwise indicated and it has not previously been submitted for a degree either in this or any other university.

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Abstract

Synthesis of a New Class of Homochiral Amines and Novel Bio-active Tropanes

Mustafa Tavasli, B.Ed. (Hons), M.Sc.

This thesis describes two main programmes: the synthesis of a new class of homochiral amines and the synthesis of ketone analogues of 3α-esterified tropane alkaloids.

In chapter one, a scaled-up synthesis of (*S*)-α-(diphenylmethyl)pyrrolidine **1** is described. The key hydrogenation step of the oxazolidinone intermediate **2** was extended to the synthesis of the other chiral amines **70**, **73**, **76**, **79** and **82**. Hydrogenation of the oxazolidinones proceeded in good yields (71 - 87 %) and was not susceptible to racemisation. Thus, a convenient route from amino acid ester hydrochlorides (*S*)-valine **65**, (*S*)-phenylalanine **66**, (*S*)-alanine **67**, (*S*)-isoleucine **68** and (*S*)-leucine **69** allowed a range of novel chiral amines to be prepared.

In chapters two and three, a new route to ketone analogues of tropane esters is described. In chapter two, results of an attempt to prepare ketone **110** are outlined. Ketone **110** is an analogue of the tropane alkaloid littorine **101**, where the bridging ester O atom is replaced by a CH_2 group. The first approach to ketone **110** involved the Wittig reaction of acetylmethylenephosphorane **118** and the Horner-Wadsworth-Emmons reaction of diethylbenzoylmethanephosphonate **122** with tropinone **116**. Tropinone **116** was found to be particularly unreactive in both cases. The second approach to ketone **110** involved the coupling reactions of both N-troc-3α-tosyloxymethyltropane **170** and N-troc-3α-iodomethyltropane **185** with 2-phenylacetyl-1,3-dithiane **147** and 1,3-ditihiane **142**. These were also unreactive and as a result the synthesis of ketone **110** remains unresolved.

In chapter three, the synthesis of other ketone analogues of naturally occurring 3α-esterified tropane alkaloids is described. A six-step route to the ketones was devised and in this route the Grignard reactions of tropan-3-ylacetaldehyde **227** emerged as the key to the success of the strategy. Three ketone analogues **218**, **219** and **220** of tropate esters were successfully prepared. Ketone **220**, the analogue of apoatropine **201**, was found to be a muscarinic acetylcholine receptor antagonist (EC_{50} $1.9x10^{-7}$ M) in guinea-pig ileum, showing a 500-fold less activity than atropine **202**. However the activity is still within the clinical range.

Acknowledgements

I would like to thank my supervisor, Prof. David O'Hagan, for his unlimited support, encouragement and help throughout this work.

I would also like to thank Dr. Robert F. Halliwell, not only allowing us to do the biological testing in his lab, but also making them a priority. In this respect, Graham R. Foxon deserves a special thank you, both for setting up the required apparatus to a working condition from scratch and for bringing me up to the standard to run the biological tests myself.

I also wish to thank my colleagues in the GC50, especially to those individuals who were brave enough to stand up to the smell of dimethyl sulphide. A big thank you goes to Dr. Alan Kenwright for his effort to sort out the problems associated with *endo* and *exo* isomers.

Finally thanks to my sponsor Kocatepe University of Afyon, Turkiye, for the YÖK scholarship.

CONTENTS

ABBRIVATIONS

CSA	Chiral solvating agent
CDA	Chiral derivatizing agent
e.e.	Enantiomeric excess
Xc	Chiral auxiliary
LDA	Lithium diisopropylamide
E^+	Electrophile
SAMP	(*S*)-1-Amino-2-(methoxymethyl)pyrrolidine
RAMP	(*R*)-1-Amino-2-(methoxymethyl)pyrrolidine
MOMO	Methoxymethoxy
HAL	Homochiral amine ligand
HLAB	Homochiral lithiumamide base
CLSR	Chiral lanthanide shift reagent
HMPA	Hexamethylphosphoric triamide
BOC	*tert*-Butoxycarbonyl
Ac	Acetyl
DME	1,2-Dimethoxyethane
Trisyl azide	2,4,6-Triisopropylbenzenesulfonyl azide
atm.	Atmosphere
p.s.i	Pounds per square inches
NMR	Nuclear magnetic resonance
HETCOR	Heteronuclear correlated
DEPT	Distortionless enhancement by polarisation transfer
HMBC	Heteronuclear multiple bond correlation
D	Deuterium
T	Tritium
HWE	Horner-Wadswoth-Emmons
THF	Tetrahydrofuran
DMF	Dimethylformamide
Ts	Tosyl
THP	Tetrahydropyranyl
PPTS	Pyridinium *p*-toluenesulfonate
DMSO	Dimethylsulfoxide

Sia_2BH	Disiamylborane
9-BBN	9-Borabicyclo[3.3.1]nonane
TrocCl	2,2,2-Trichloroethyl chloroformate
$LiAlH_4$	Lithium aluminium hydride
BMS	Borane-methyl sulfide
t.l.c.	Thin layer chromatography
DNA	Deoxyribonucleicacid
DIBAL-H	Diisobutylaluminum hydride
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
NOESY	Nuclear overhauser enhancement spectrum
mAChR	Muscarinic acetylcholine receptor
ACh	Acetylcholine
IC_{50}	Inhibition concentration required for half maximal response
EC_{50}	Effective concentration required for half maximal response
μM	Micromolar
nM	Nanomolar
τ	Torsion angle
CSD	Cambridge Crystallographic database
νmax	Maximum absorption
EI	Electron ionisation
CI	Chemical ionisation

CHAPTER ONE

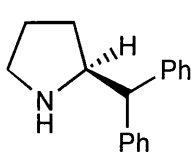
Synthesis of a New Class of Homochiral Amines

CHAPTER ONE

1.1 General introduction

The development of enantioselective carbon-carbon (C-C) bond forming reactions[1] is an important activity for many leading researchers in academia, and the pharmaceutical and chemical industries. As a result of this interest many enantiomerically enriched compounds have been produced. In this respect, a great deal of enantioselective C-C bond forming reactions was carried out by using homochiral amine auxiliaries,[2,3] ligands[4,5] and bases.[6,7] The use of homochiral amines has not been limited to these areas, however they have also found applications as chiral resolving agents[8] in the determination of enantiomeric excess (e.e) of the end products, as well as in the combinatorial synthesis[9].

In this research programme, the scaled synthesis of (*S*)-α-(diphenylmethyl)pyrrolidine **1** is demonstrated and the key step, hydrogenation of oxazolidinone **2**, is extended to the syntheses of more general (*S*)-α-(diphenylmethyl)-α-alkyl-methylamines **3**. Homochiral amines such as **3** will open access to a series of chiral amines. At the outset, it is appropriate to review briefly the current status of homochiral amines in asymmetric synthesis.



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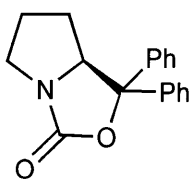

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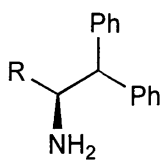
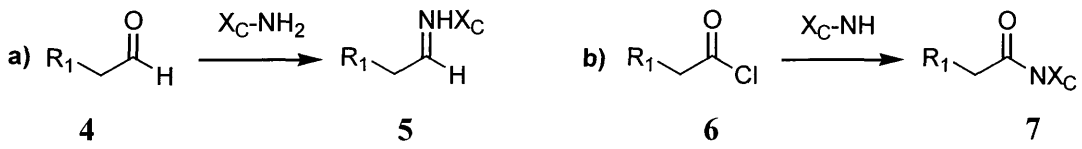


3

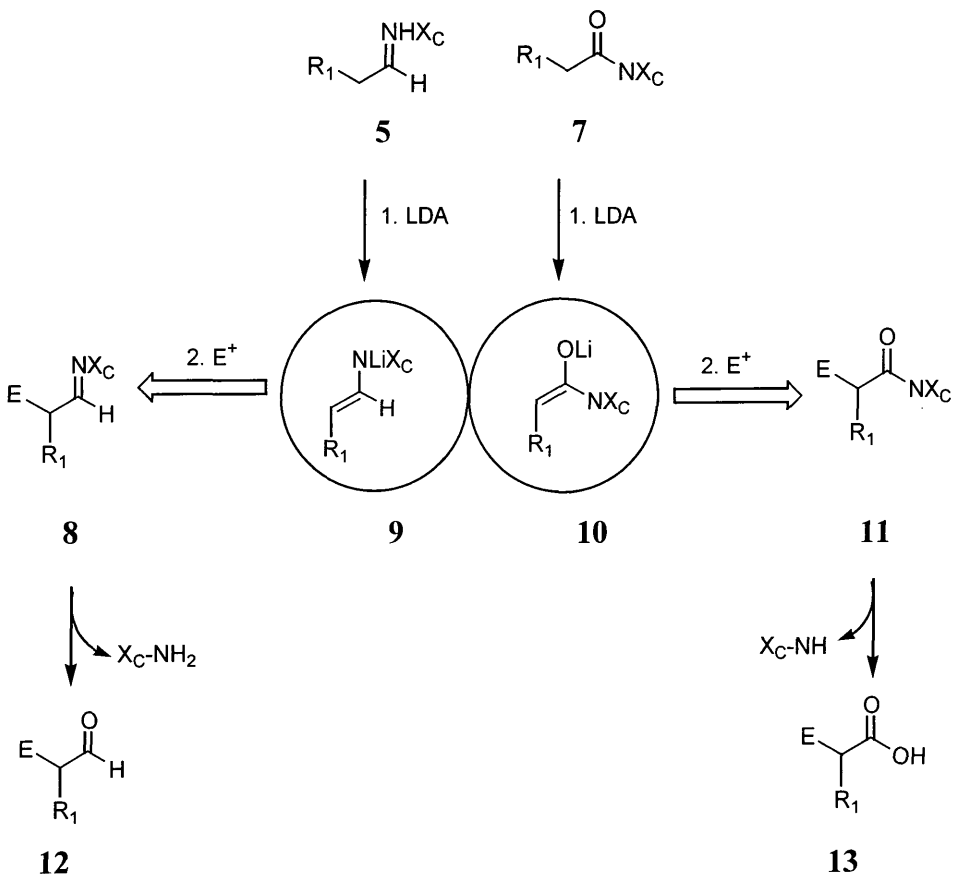
1.1.1 Amines as chiral auxiliaries

Chirality transfer with chiral auxiliaries usually occurs in cases where achiral substrates are covalently bond to chiral auxiliaries[10]. In the case of chiral amine auxiliaries (X_C-NH_2 or X_C-NH), this covalent bond could be generated *via* a formation of imines **5** from achiral aldehydes **4** (or ketones) (**Scheme 1a**), or *via* a formation of amides **7** from a carboxylic acid derivatives, such as acid chloride **6** (**Scheme 1b**).



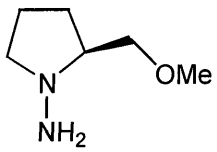
Scheme 1

The carbanions **9** and **10** then generated from **5** and **7** with lithium amide bases such as lithium diisopropyl amide (LDA) can react with one of the following electrophiles (E^+): alkyl halides, carboxylic acid derivatives, and aldehydes (or ketones). These reactions, depending on the electrophile used, are known as alkylations, acylations and aldol reactions and generate diastereoisomers **8** and **11**. Chiral primary and secondary amine auxiliaries (X_C-NH_2 and X_C-NH) are finally removed from the system, affording enantiomerically enriched chiral products **12** and **13**. The set of chemical operations[11] discussed above is depicted in **Scheme 2**.

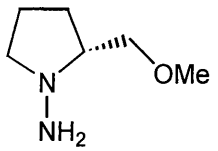


Scheme 2

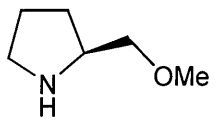
Transformation of achiral aldehydes (or ketones) into their corresponding chiral derivatives are widely achieved by chiral hydrazine auxiliaries[2] (X_C-NH-NH_2), such as (*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine **14**. These auxiliaries were developed by Enders[2] from (*S*)- or (*R*)-2-methoxymethylpyrrolidine **15**, and are known as SAMP-**14** or RAMP-**14**.



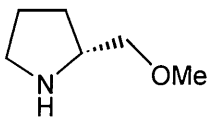
SAMP-**14**



RAMP-**14**

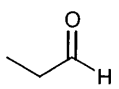


(*S*)-**15**



(*R*)-**15**

A more recent application[12] of SAMP-**14** was reported in the total synthesis of epothilone A, where propionaldehyde **16**, after coupling with SAMP-**14**, was transformed into one of the building blocks **17**. In this transformation, alkylation of the SAMP derivative **18** with 4-iodo-1-benzyloxybutane was the key step, and proceeded in good yield (92 %) and in excellent e.e. (98 %) to give **19**. Ozonolysis of **19** finally produced the target molecule **17**.



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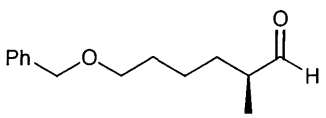

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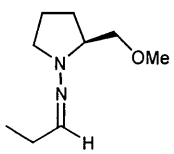

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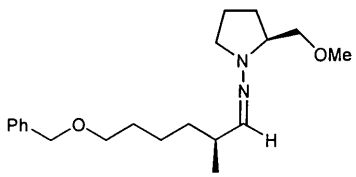
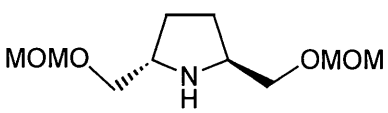


19

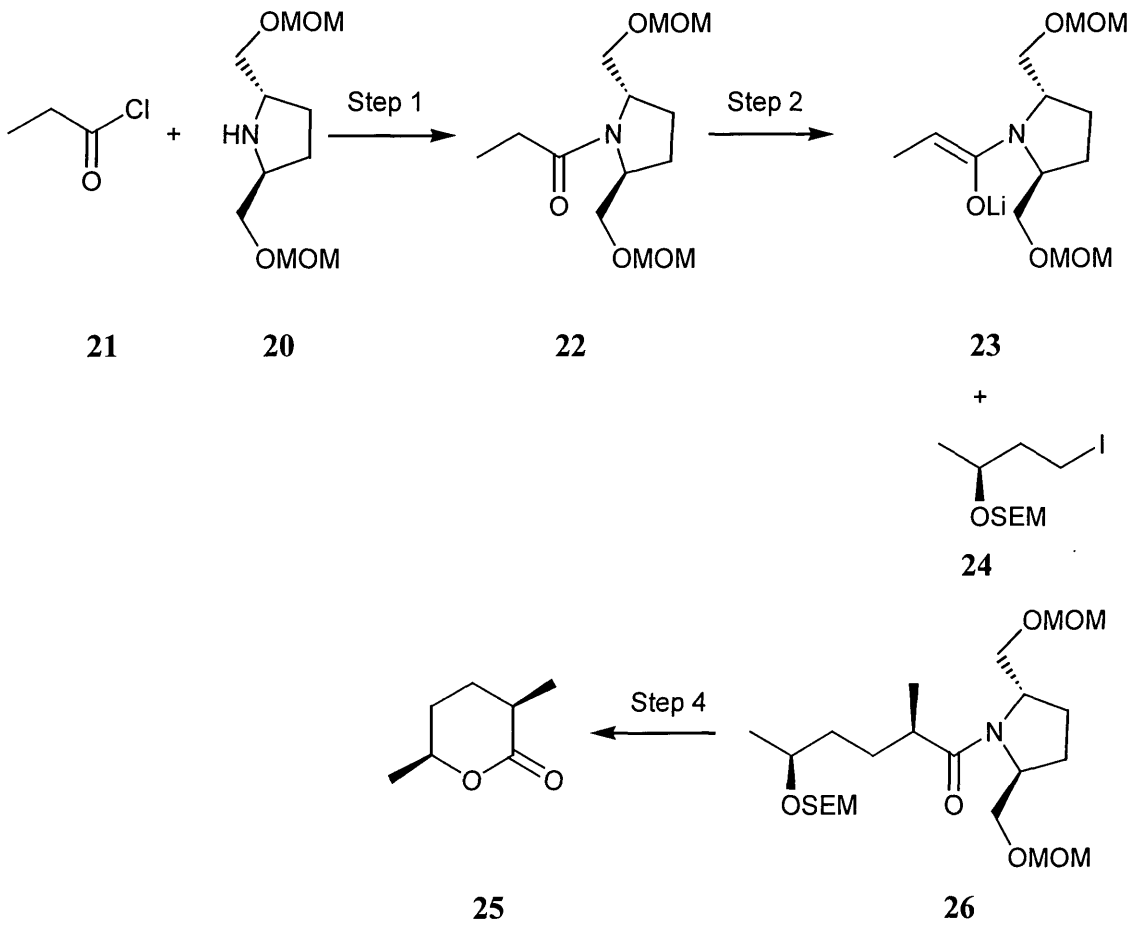
On the other hand, transformation of achiral carboxylic acid derivatives are accessible using C2-symmetric amines[3], such as (2R,5R)-2,5-bis-(methoxymethoxymethyl)-pyrrolidine[13] **20**, where MOMO is acronym for methoxymethoxy.



20

Such a transformation is illustrated in the synthesis[14] of (2*R*,5*S*)-2-methyl-5-hexanolide **25**, a sex pheromone of the carpenter bee. In this synthesis, propionyl chloride **21** was

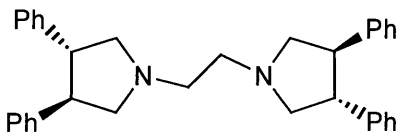
first coupled with **20** to give the corresponding amide **22** (**Step 1**), which was then lithiated under standard conditions (LDA, THF, -78 °C) (**Step 2**). Treatment of the lithiated amide **23** with the iodide **24** (**Step 3**), followed by acid-catalysed hydrolysis (**step 4**), generated the target molecule **25**, as shown in **Scheme 3**.



Scheme 3

1.1.2 Amines as chiral ligands

Chiral ligands have played a key role in the development of asymmetric bond forming reactions[15]. In this respect, chiral amines, in particular chiral diamines[5], such as **27**, **29** and **28** feature prominently. The chiral environment is usually introduced *via* coordination to metals *via* N atom[16]. Metal complexes of homochiral amine ligands (HALs) such as organometallics[17] (RM), Grignard reagents[18] (RMgX) and osmium tetraoxide[19] (OsO_4) are well studied.



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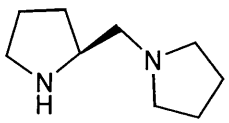

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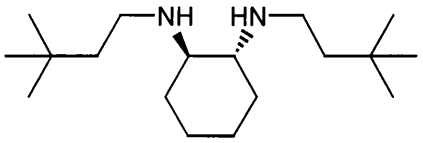
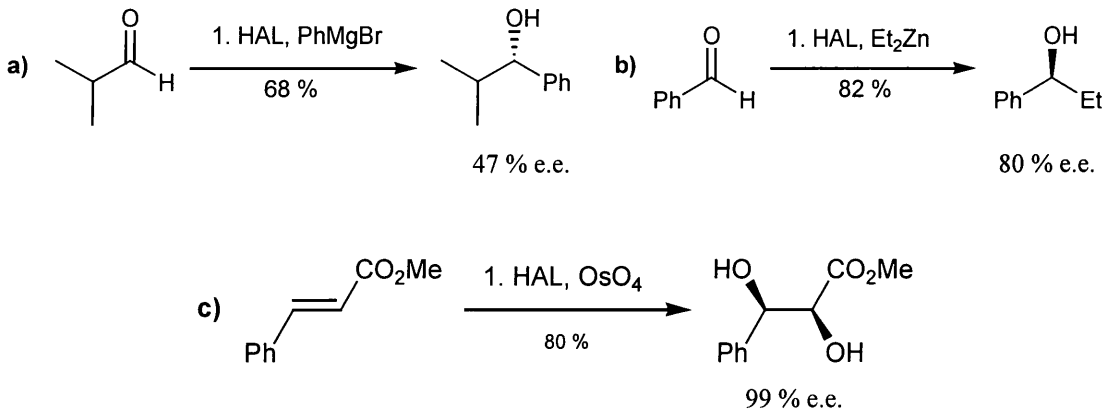


29

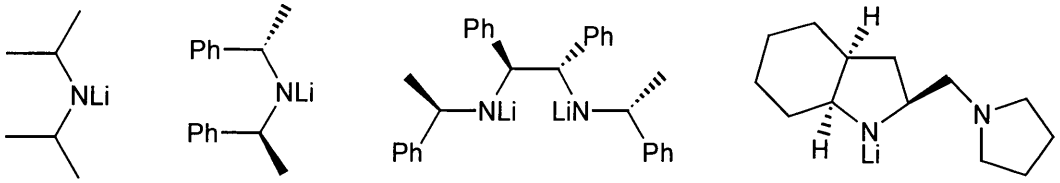
For instance, the use of **27** was reported by Nakajima[18] *et al.* in the enantioselective 1,2-addition reaction of phenylmagnesium bromide to isobutanal (**Scheme 4a**). Ligand **28** was reported by Asami[17] and Inoue for the enantioselective 1,2-addition of diethylzinc to benzaldehyde (**Scheme 4b**) and **29** was reported by Hanessian[20] *et al.* in enantioselective OsO_4-mediated *cis*-dihydroxylation of alkenes (**Scheme 4c**). These reactions clearly illustrate the value of HALs. However, in order to maximise enantioselectivity, structural tuning is still a challenge in the design and synthesis of new chiral ligands[21].



Scheme 4

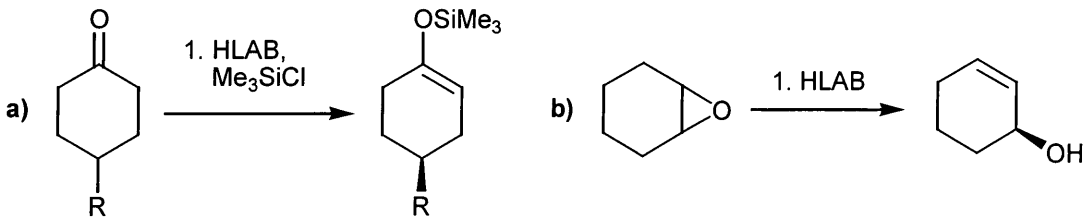
1.1.3 Amines as chiral bases

Lithium amide bases[22] such as lithium diisopropylamide (LDA) have established an important position in organic synthesis, and are widely used as strong bases with low nucleophilicity. With the discovery of lithium di[(*S*)-1-phenylethyl]amide (*S,S*)-**30** or its antipode (*R,R*)-**30** by Whitesell[23] and Felman, the use of homochiral lithium amide bases[7] (HLAB), such as **31**, *(S)*-**32** has attracted considerable attention in connection with recent progress in asymmetric synthesis.



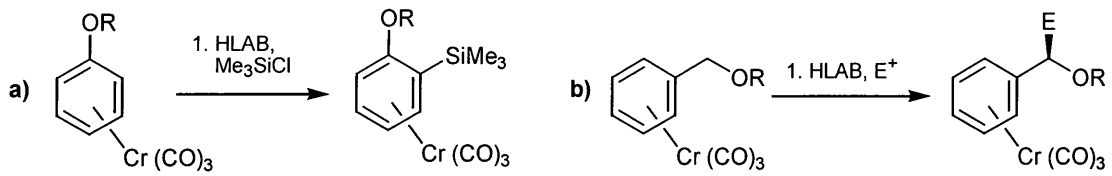
LDA (*S,S*)-**30** **31** (*S*)-**32**

Interests[7] in this area have focused primarily on two asymmetric reactions: the enantioselctive deprotonation of cyclic ketones (**Scheme 6a**) and the enantioselective rearrangement of epoxides to allylic alcohols (**Scheme 6b**).



Scheme 5

More recent studies[7] have however shifted towards asymmetric aromatic and benzylic functionalisation of tricarbonyl(η^6-arene)chromium complexes, as depicted in **Scheme 6a** and **Scheme 6b** respectively.

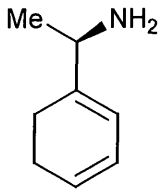


Scheme 6

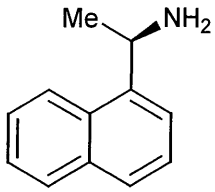
1.1.4 Amines as chiral resolving agents

Asymmetric synthesis is not complete without analysing the end product, in where enantiomeric excess (e.e.) of the isomer and the configuration of new stereogenic centre has to be determined. To date, NMR spectroscopy is one of the most straightforward methods used[24]. It relies on the fact that diastereotopic nuclei are, in principle, anisochronous and should have a different chemical shifts and different coupling constants[25]. Conversion of enantiomers into a diastereoisomeric mixture / complex is

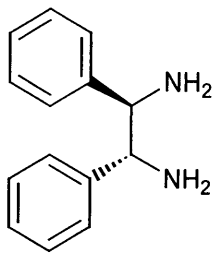
therefore necessary, and this is usually achieved by one of the following methods[26]: chiral lanthanide shift reagents (CLSRs), chiral derivatizing agents (CDAs) and chiral sovating agents (CSAs). The use of CSAs[27], which make *in situ* NMR analysis possible by inducing anisochrony either through the formation of ion pairing or hydrogen bonding, emerges as an efficient method for the determination of the e.e. of the isomer and the configuration of new stereogenic centre. In this respect, the most widely employed CSAs are (*R*)-amines[28,29] **33** and **34** (or their antipodes (*S*)-**33** and (*S*)-**34**). Other amines, such as[30,31] (*R*,*R*)-**35** are also known. Although the use of amines as CSAs has had wide applications, they are mainly dedicated to the analysis[27] of asymmetric carboxylic acids and alcohols.



(*R*)-**33**



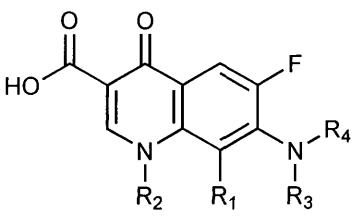
(*R*)-**34**



(*R*,*R*)-**35**

1.1.5 Amines in combinatorial synthesis

In drug discovery, various amines (R_3R_4NH) have been used to develop a range of quinolones[32], such as **36**, a potent antibacterial agent. Amines (R_1R_2NH) have been employed to mimic transition states or intermediates of enzyme catalysed reactions[33], such as peptide isosteres **37** and **38**. In both cases, the type of amines used was however not disclosed.



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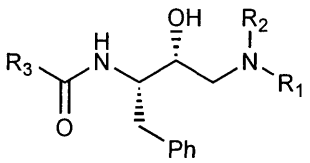

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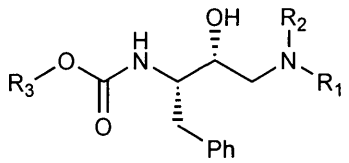

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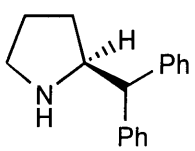
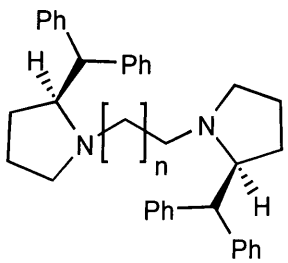
1.2 (*S*)-α-(Diphenylmethyl)pyrrolidine 1 - Scale up

1.2.1 Introduction

A new and straightforward route to (*S*)-α-(diphenylmethyl)pyrrolidine **1** was developed in Durham as part of my MSc[34] programme. This improved significantly on a previous synthesis[35]. Amine **1** was used in Durham to prepare[36] the diamines **39** and **40**, as potential bidentate ligands for asymmetric chemistry.



1



39 (n= 1); **40** (n= 2)

The chemistry of **1** and its applications were explored in a preliminary way[34]. In particular, **1** was investigated as a chiral auxiliary in asymmetric alkylation reactions and as a chiral solvating agent (CSA) for ^{1}H NMR analysis of the enantiomeric purity of chiral carboxylic acids and alcohols. Asymmetric alkylations were carried on N-phenylacetamide **41** and N-propionamide **42** under standard deprotonation conditions (LDA, THF, -78 °C) with benzylbromide ($PhCH_2Br$) and methyl iodide (CH_3I), in the presence and absence of HMPA. The results are summarised in **Table 1**. From these results, it was concluded that **1** is not a good chiral auxiliary.

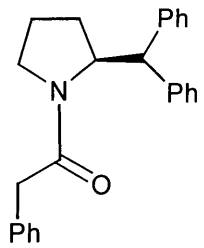
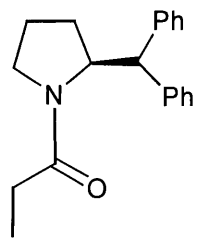
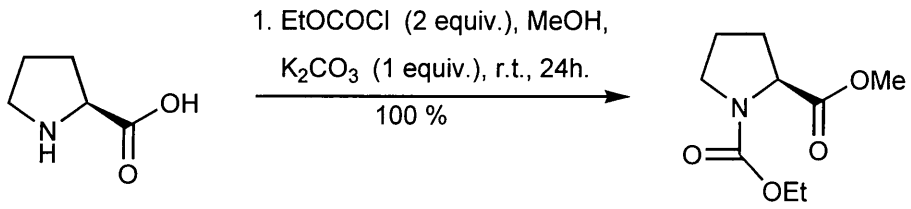
Entry	Substrate	Alkyl halide	Additive	Diastereoisomer ratio
1	 **41**	CH_3I	None	1.1 : 1.0
		CH_3I	HMPA	1.5 : 1.0
2	 **42**	$PhCH_2Br$	None	1.1 : 1.0
		$PhCH_2Br$	HMPA	2.1 : 1.0

Table 1: Asymmetric alkylation of amide derivatives **41** and **42** in the presence and absence of HMPA.

Although **1** did not emerge as a good chiral auxiliary, it proved to be an excellent CSA for ^1H NMR analysis of the enantiomeric purity of chiral carboxylic acids[36]. To promote the application of **1** and make it available to the wider-research community, it became necessary to scale up the preparation of **1**. At the outset, the objective was to prepare a 60 g batch of **1**, a three fold increase in scale. This required the preparation of amide ester **44** in large quantities as the first step in the synthesis of **1**.

1.2.2 Synthesis of (*S*)-α-(diphenylmethyl)pyrrolidine 1

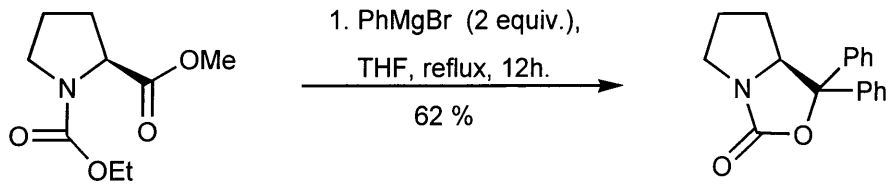
Following the literature method described by Kanth[37] and Periasamy, and with our previous experience, amide ester **44** was readily prepared by the reaction of (*S*)-proline **43** with ethyl chloroformate in the presence of K_2CO_3 and MeOH, as depicted in **Scheme 7**. This reaction began with 90 grams of (*S*)-proline **43** and gave 157 grams of the amide ester **44** as a clear oil. The conversion was essentially 100 %, which made for an excellent first step in the synthesis of **1**.



43 **44**

Scheme 7

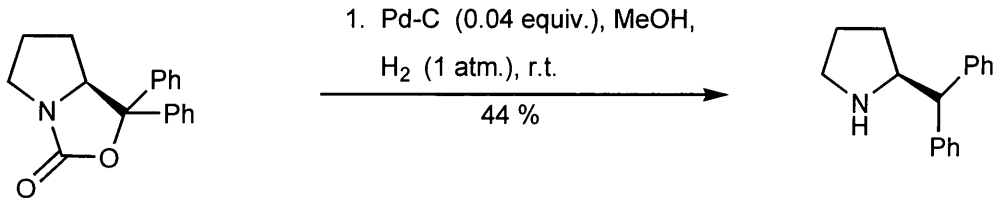
The second step involved the Grignard reaction of the amide ester **44** with phenylmagnesium bromide. Cyclisation to oxazolidinone **2** occurred *in situ*, as illustrated in **Scheme 8**. Contemporaneously, this cyclisation was also reported by Deleunay[38] and Le Corre. This provided 133 grams of oxazolidinone **2** as a white solid. The compound **2** was purified by re-crystallisation from ethyl acetate in a moderate (62 %) yield.



44 **2**

Scheme 8

The final step in the synthesis of **1** was the hydrogenation of oxazolidinone **2** with palladium on activated carbon in MeOH, as shown in **Scheme 9**. This process successfully generated pyrrolidine **1**, by formally removing the elements of CO_2 from oxazolidinone **2**. Pyrrolidine **1** is an oil, but distillation gave an impure product. However, re-crystallisation of its HCl salt from isopropyl alcohol proved an excellent method for purification and gave a nice white crystalline solid. After basification and extraction into dichloromethane, 50 grams of pyrrolidine **1** was obtained as an oil in moderate yield (44 %). This material was pure by ^{1}H and ^{13}C NMR, GC and elemental analysis.



2 **1**

Scheme 9

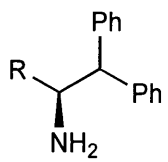
1.2.3 Discussion

By following the three-step route, a 50 g batch of pyrrolidine **1** was successfully prepared. This was made available to the Aldrich Chemical Company (Cat. No: 46,718-9) and pyrrolidine **1** is now commercially available to the wider research community. We hope that many research groups world-wide will now start to explore the chemistry of **1**.

1.3 Homochiral primary amines from amino acids

1.3.1 Introduction

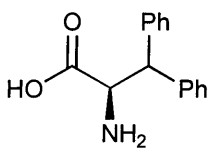
New chiral building blocks, especially enantiomerically pure are required by pharmaceutical and agrochemical industries, in particular to service the recent growth in combinatorial chemistry, which is now dominating drug discovery. In this respect, the conversion of amino acids into chiral amines such as (*S*)-α-(diphenylmethyl)-α-alkyl-methylamines **3**, provide an interesting range of novel compounds. Amines with the general structure **3** are potentially available by extending the chemistry of (*S*)-proline / (*S*)-α-(diphenylmethyl)pyrrolidine and starting from a more general range of α-amino acids.



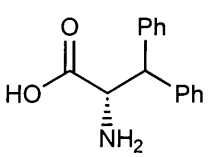
3

Increasingly attention has been focused on the synthesis of (*R*)- or (*S*)-α-(diphenylmethyl)glycine[39,40,41,42,43] **45**, which fulfil general structure **3** and have

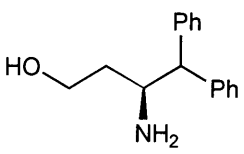
found applications in the preparation of bioactive peptides.[44,45] Another example is the preparation of (*S*)-α-(diphenylmethyl)-α-(2-hydroxyethy)-methylamine[46] **46**, which also fulfil general structure **3** and has found application in the preparation of **47**[47], a potential receptor for carboxylic acids and reagent/catalyst.



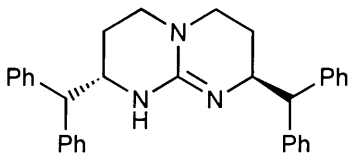
(*R*)-**45**



(*S*)-**45**

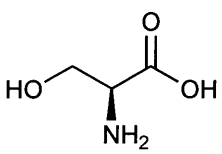


(*S*)-**46**

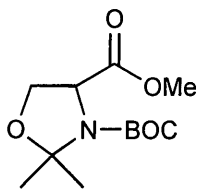


47

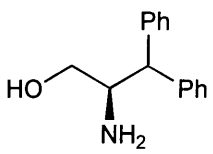
The syntheses of **45** and **46** involved either the modification of enantiomerically pure amino acids or the use of asymmetric reactions. With the former approach, the synthesis of (*R*)-**45** began with the preparation of the fully protected oxazolidine ester[48] **49** from (*S*)-serine **48**. This was then followed by the Grignard addition to the ester moiety and catalytic dehydroxylation ($Pd(OH)_2$-C, HCO_2H; NaOH, MeOH-H_2O) to give amino alcohol[41] **50**. This generated the required diphenylmethyl group. Then BOC protection of the amino group, Jones oxidation (CrO_3, H_2SO_4, acetone) of the alcohol to the corresponding carboxylic acid and then removal of the BOC group finally yielded (*R*)-**45** in enantiomerically pure form.



(*S*)-**48**



49



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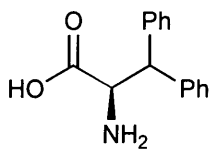
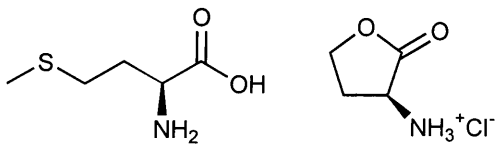


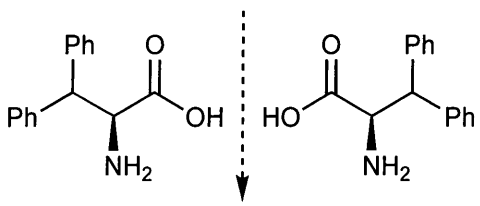
(*R*)-**45**

The synthesis of (*S*)-**46** began by transforming (*S*)-methionine **51**, into **52**. This was followed by a Grignard reaction to give amino-diol **53**, where the primary OH and NH_2 groups were protected as N-Ac (acetyl) and O-Ac, respectively. The Ac-protected **53** was then subjected to a range of hydrogenolysis conditions, but only application of Ram and Spicer's catalytic transfer method[49] (10 % Pd-C, $NH_4^+HCO_2^-$, AcOH) successfully gave **54**, generating the required diphenylmethyl group. Removal of the N-Ac and O-Ac protecting groups from **54** finally yielded (*S*)-**46** in enantiomerically pure form.



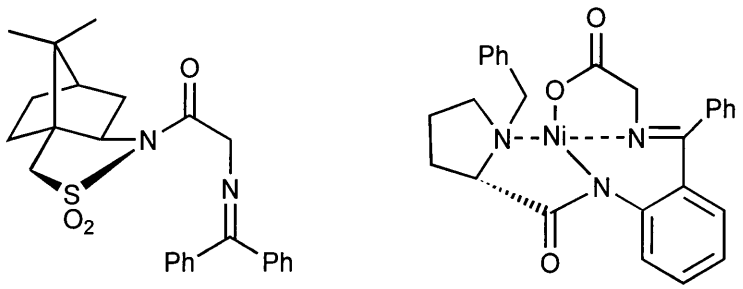
(*S*)-**51** **52** **53** (*S*)-**54**

With later approaches, chiral auxiliaries were employed, where either stereoselective introduction of the diphenylmethyl group or the amino group was achieved. As enolate alkylation of Schiff bases derived from glycine is well defined and frequently used in the synthesis of a variety of optically active amino acids[50], the same approach was adopted in the synthesis of **45**, to introduce the required diphenylmethyl group either in (*S*) or (*R*) form. The following two examples are illustrative.



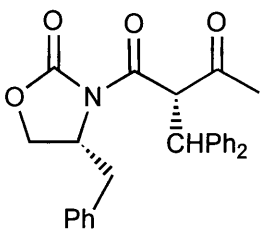
(*S*)-**45** (*R*) -**45**

Alkylation[39] of the sultam-derived N-(diphenylmethylene)glycine amide **55** with bromodiphenylmethane (Ph_2CHBr) provided the desired diphenylmethyl group in good yield (68 %) and in excellent diastereoisomeric excess (d.e.) (> 95 %). Subsequent hydrolysis of the ketimine and cleavage of the sultam group finally yielded (*S*)-**45**. Alkylation[43] of the nickel (II) complex-derived glycine **56** with Ph_2CHBr generated the desired diphenylmethyl group in good yield (68 %) and in excellent d.e. (90 %). Subsequent decomposition of the complex and separation of Ni (II) ions yielded (*S*)-**45**, when the (*S*)-proline containing complex was used.

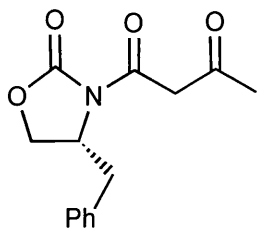


55 (*S*)-**56**

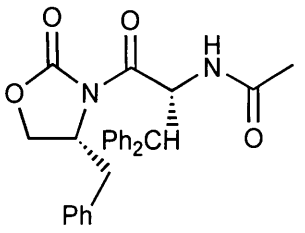
In addition to the enolate alkylation of Schiff bases derived from glycine, a Schmidt rearrangement was also deployed in the synthesis of **45**. The requisite β-ketocarboximide substrate, (*4R,2'R*)-**57** was prepared from the alkylation[42] of the (*4R*)-acetoacetimide **58** with Ph_2CHBr. In this reaction, the desired diphenylmethyl group was generated in the (*R*) form, but in low yield (41 %) and in modest d.e. (64 %). The Schmidt rearrangement (NaN_3, H_2SO_4, DME) proceeded then with retention of configuration providing (*4R,2'R*)-acetamide **59** in good yield (85 %). Subsequent cleavage of the oxazolidinone group and hydrolysis of the acetamide group yielded (*R*)-**45**. However, alkylation of (*4S*)-**58** provided (*S*)-**45**.



(*4R,2'R*)-**57**

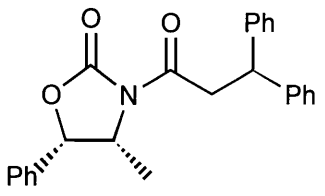


(*4R*)-**58**

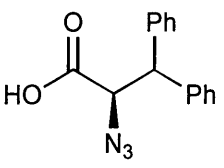


(*4R,2'R*)-**59**

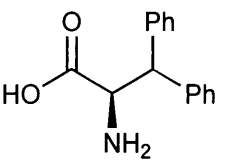
The three examples reported above involve the stereoselective introduction of the diphenylmethyl group *via* alkylation of chiral enolates. A conceptually different approach was also reported for the synthesis of (*R*)- and (*S*)-**45**. This involved the stereoselective introduction of the amino group *via* a direct azidation[40] of (*4R,5S*)-diphenylpropionimide **60** with trisyl azide. The azidation proceeded in excellent yield (94 %) and in complete stereocontrol to give a single diastereoisomer. Subsequent cleavage produced (*R*)-azido acid **61**. Hydrogenation of **61** furnished the final product, (*R*)-**45**. By the azidation of (*4S,5R*)-**60**, (*S*)-azido acid **61** was also produced in enantiomerically pure form.



(*4R,5S*)-**60**



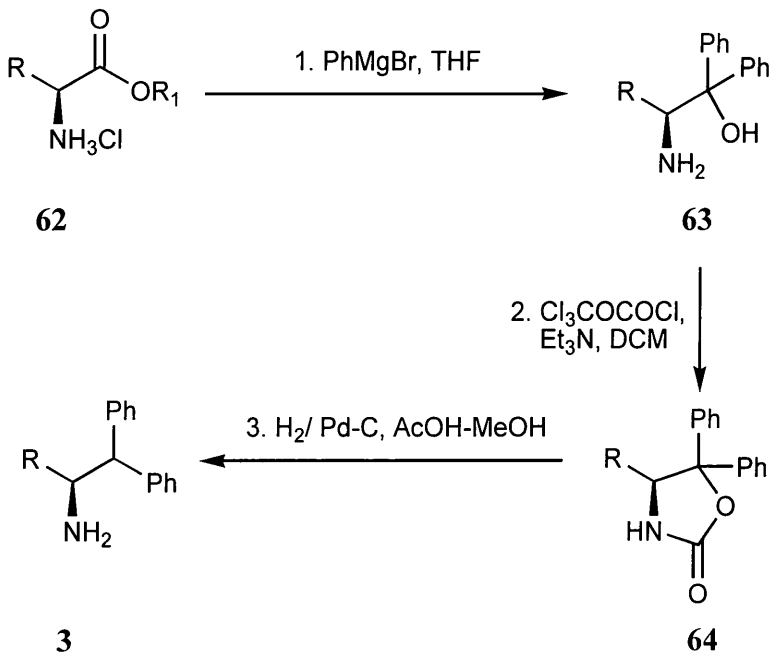
(*R*)-**61**



(*R*)-**45**

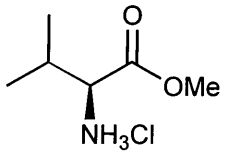
There was no standard procedure available to transform the amino acid carboxylate into the corresponding diphenylmethyl group. However, following the success of the

synthesis of pyrrolidine **1** from (*S*)-proline **43**, it was decided to explore a similar strategy for the synthesis of other chiral amines from primary amino acids. Catalytic hydrogenation of a range of 5,5-diphenyl-2-oxazolidinones represented by **64** had the potential to deliver the new series of amines **3**. For this purpose, the route outlined in **Scheme 10** was proposed, and addressed.

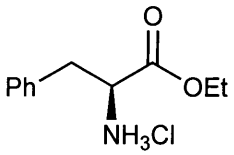


Scheme 10

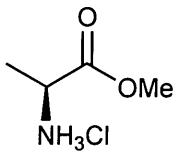
The first step in the syntheses of (*S*)-α-(diphenylmethyl)alkyl amines **3** required the preparation of amino alcohols **63**, by straightforward Grignard reaction of the corresponding amino acid ester hydrochlorides **62** with phenylmagnesium bromide. Of course, the presence of the ammonium chloride demands at least 5 equivalents of Grignard reagent. If the amino alcohols **63** are then converted to the oxazolidinones **64**, hydrogenation would generate the required amines **3**. For simplicity, (*S*)-amino acid ester hydrochlorides without extra functional groups on their side chains were chosen as starting materials in these reactions. The amino acid ester hydrochlorides **65-69** of (*S*)-valine, (*S*)-phenylalanine, (*S*)-alanine, (*S*)-isoleucine and (*S*)-leucine were therefore chosen and are depicted in **Figure 1**.



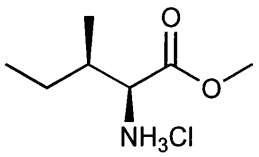
65



66



67



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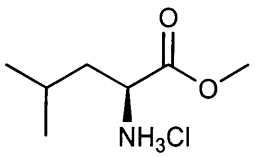


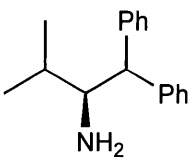
69

Figure 1: (*S*)-Amino acid ester hydrochlorides **65-69**, chosen for the transformation.

Preparation of the amino alcohols **63** from **65-69** and their cyclisation to the oxazolidinones **64** is well known and has already been described in the literature. The only exception was the oxazolidinone derived from (*S*)-isoleucine **68**. It was anticipated that the hydrogenation would be straightforward following our previous experience in the synthesis of pyrrolidine **1**, however that remained to be tested.

1.3.2 Synthesis of (*S*)-α-(diphenylmethyl)-α-alkyl-methylamine 3

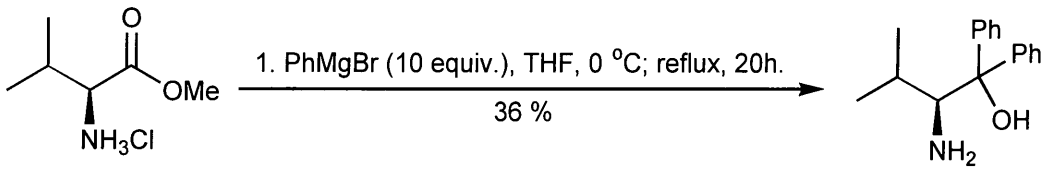
(*S*)-Valine methyl ester hydrochloride **65** was chosen as the first starting material among the five amino acid ester hydrochlorides. This transformation would generate amine **70**. The first step in this transformation began with the preparation of the corresponding amino alcohol **71**.



70

Amino alcohol **71** has been prepared by Itsuno[51] *et al.* from the reaction of (*S*)-valine methyl ester hydrochloride **65** with an 8-fold excess of phenylmagnesium bromide (PhMgBr) in 56 % yield, and by Gawley[52] and Zhang with a 5-fold excess of PhMgBr in 44 % yield. Very recently, a free amine of (*S*)-valine methyl ester rather than its hydrochloride salt was employed by Hintermann and Seebach[53], thus reducing the

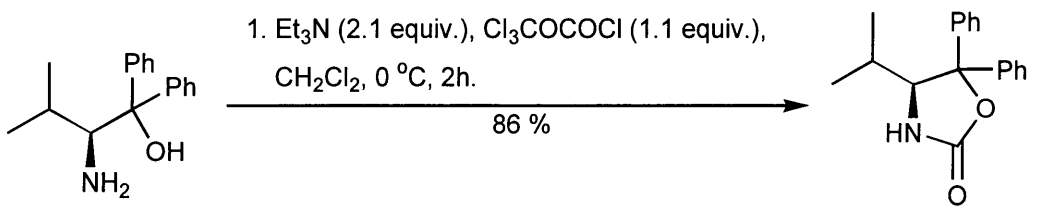
excess of PhMgBr to only 3-fold. The yield was 50 %. In our case, amino alcohol **71** was prepared by the addition of (*S*)-valine methyl ester hydrochloride **65** to a 10-fold excess of PhMgBr in THF, as depicted in **Scheme 11**.



65 **71**

Scheme 11

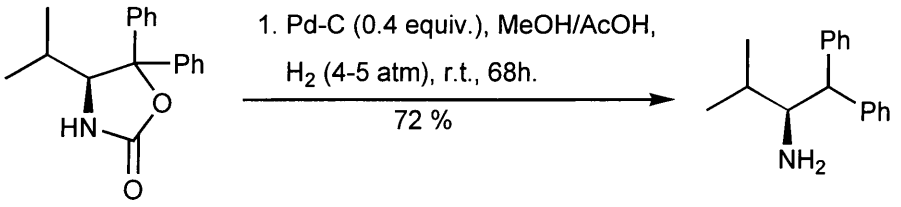
After work-up, amino alcohol **71** was found to be contaminated with a large amount of biphenyl as an impurity. By dissolving the HCl salt of amino alcohol **71** in methanol, the majority of this impurity was immediately precipitated out as a white solid. Further purification by column chromatography gave amino alcohol **71** as a white solid in moderate yield (36 %). Following the method described by Akiba[54] *et al.*, reaction of this amino alcohol **71** with diphosgene ($Cl_3COCOCl$), in the presence of triethylamine (Et_3N) gave then the corresponding oxazolidinone **72** as a white solid in good yield (86 %). This is summarised in **Scheme 12**.



71 **72**

Scheme 12

As an alternative to diphosgene, the following reagents were also reported: tri-phosgene [$(Cl_3CO)_2CO$] by Gibson[55] *et al.*, ethyl chloroformate (EtOCOCl) by Hintermann and Seebach[53] and phosgene (Cl_2CO) by Gawley and Zhang[52]. Cyclisation of amino alcohol **71** with these reagents proceeded in 73 %, 91 % and 95 % yields, respectively. Oxazolidinone **72** was then subjected to hydrogenation with a catalytic amount of palladium on activated carbon, in a mixture of AcOH and MeOH, as illustrated in **Scheme 13**.

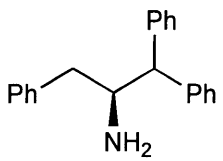


72 **70**

Scheme 13

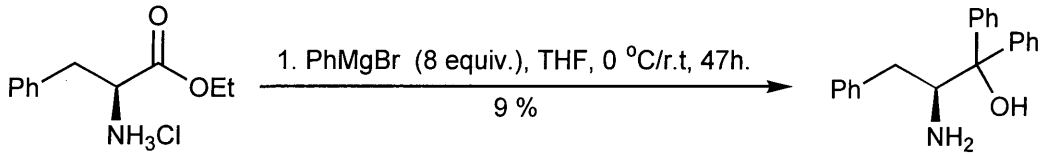
As anticipated, the hydrogenation was successful and gave the first amine **70** of the series as a white crystalline solid, in good yield (72 %). The amine **70** was re-crystallised from petroleum ether. ^{1}H NMR analysis of **70** indicated a doublet of doublets (3.46 ppm, J= 10.5 and 2.4 Hz) for the proton at the stereogenic centre and a doublet (3.70 ppm, J= 10.5 Hz) for the CH of the diphenylmethyl group. The Heteronuclear Correlated (HETCOR) spectrum of **70** proved necessary for the assignment of the ^{13}C NMR signals. Thus, the peak at 58.1 ppm was assigned to the CH of the diphenylmethyl group and the peak at 58.9 ppm assigned to the carbon atom at the stereogenic centre. In the event, (*S*)-valine methyl ester **65** was successfully transformed into novel amine **70**.

(*S*)-Phenylalanine ethyl ester hydrochloride **66** was chosen as the next amino acid to be studied, to generate amine **73**. Again the first step in this transformation commenced with the synthesis of the corresponding amino alcohol **74**.



73

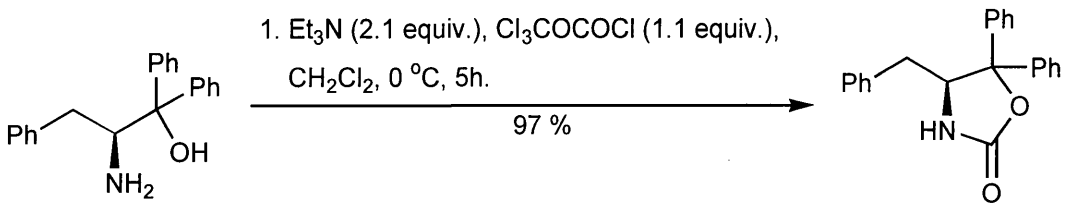
Amino alcohol **74** was prepared by the portionwise addition of (*S*)-phenylalanine ethyl ester hydrochloride **66** to PhMgBr, as depicted in **Scheme 14**. However, this time an 8-fold excess of Grignard reagent was used following the literature method reported by Itsuno[56] *et al.*



66 **74**

Scheme 14

Biphenyl was again a significant by-product, however since biphenyl is a neutral impurity, the basicity of the amino alcohols was exploited in its purification. The reaction mixture was therefore treated with hydrochloric acid. Upon work-up, amino alcohol **74** was isolated as a single product, but in low yield (9 %). However, this can clearly be improved and the reaction has been reported by Itsuno[56] *et al.* in a 53 % yield. Further purification, if required, was possible by re-crystallisation of the free amine from a mixture of ethyl acetate and diethyl ether, which gave a white crystalline solid. Suprisingly, two disparate yields (26 and 63 %) were reported by Weber[57] *et al.* and Dammast[58] and Reißig for this reaction, carried out under the same conditions (diethyl ether and 5-fold excess of PhMgBr). A moderate yield (50 %) was also reported by Hintermann and Seebach[53], in where the free base of **66** was subjected to the Grignard reaction with a 3-fold excess of PhMgBr. Improvement of the yield in our hands was not pursued as our focus was on the final hydrogenation step. Amino alcohol **74** was then submitted to the cyclisation reaction with diphosgene ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 15**.

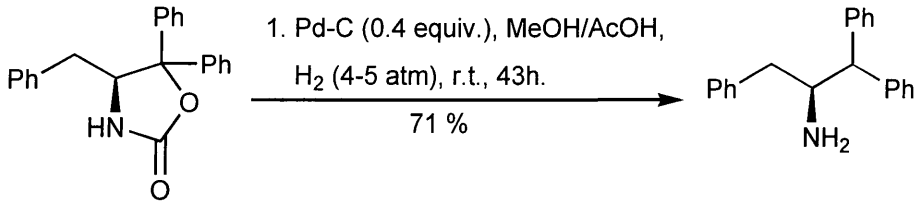


74 **75**

Scheme 15

This generated oxazolidinone **75** as a white solid in excellent yield (97 %). The cyclisation procedure described by Akiba[54] *et al.* this time proved superior to the one used by Hintermann and Seebach[53]. For the final step, oxazolidinone **75** was subjected to the hydrogenation reaction with a catalytic amount of palladium on activated carbon

in a mixture of AcOH and MeOH, as illustrated in **Scheme 16**.

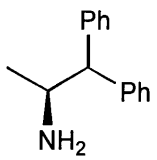


75 **73**

Scheme 16

This successfully generated the second amine **73**, which was purified by column chromatography and obtained as a light-brown solid in good yield (71 %). The ^{1}H NMR spectrum of **73** displayed a doublet (3.71 ppm, J= 9.9 Hz) for the CH of the diphenylmethyl group and a doublet of doublets of doublets (3.81 ppm, J= 9.9, 9.6, 2.7 Hz) for the proton at the stereogenic centre. The HETCOR spectrum of **73** proved necessary for the assignment of the ^{13}C NMR signals. From this, the peak at 59.7 ppm was assigned to the CH of the diphenylmethyl group and the peak at 55.7 ppm assigned to the carbon atom at the stereogenic centre.

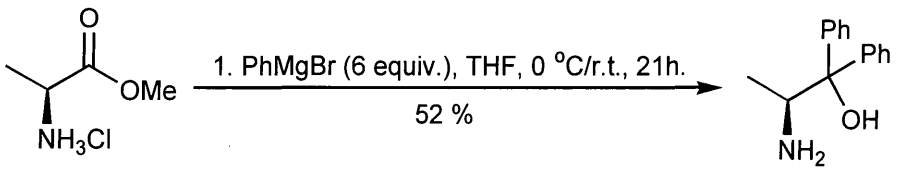
It emerged at this stage that a limitation of the route is the syntheses of the amino alcohols **71** and **74**, which suffer from moderate to poor yields. This appears to be due to biphenyl formation, and the separation of this by-product in an effective way is an important issue. None-the-less, the synthesis of the third amine **76** was pursued, which began with the preparation of amino alcohol **77**.



76

Amino alcohol **77** has already been prepared in 40-60 % yield by Itsuno[51] *et al.*, in 57 % yield by Weber[57] *et al.* and in 45 % yield by Dammast and Reißig[58] from (*S*)-alanine methyl ester hydrochloride **67**. In these reactions, 8-fold[51] and 5-fold[57,58] excesses of phenylmagnesium bromides were used. In our case, the amino alcohol was also

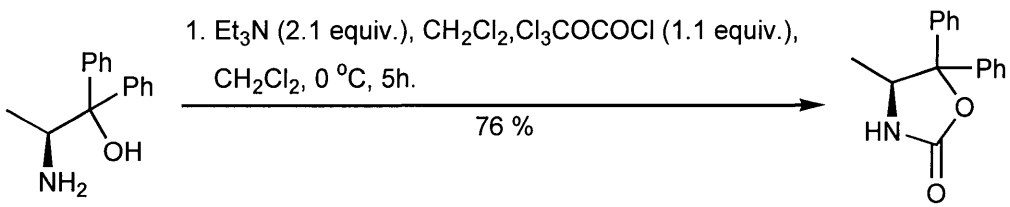
prepared from **67**, after reacting with a 6-fold excess of PhMgBr, as depicted in **Scheme 17**.



67 **77**

Scheme 17

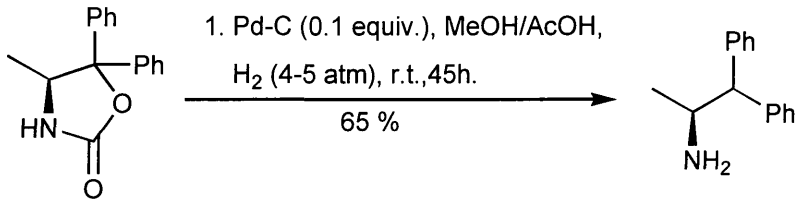
Upon work-up, amino alcohol **77** was recovered but, as expected, was contaminated with biphenyl. However, this time, purification by dry-flash column chromatography proved relatively straightforward and was more successful in comparison to the previous methods investigated so far. This gave amino alcohol **77** as a white solid in a yield of 52 %, which was satisfactory and competitive with previous reports. With amino alcohol **77** in hand, it was subjected to cyclisation with diphosgene ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 18**. The same transformation, but with the *racemic*-amino alcohol **77** has been reported by Hassner[59] and Reuss. However, in that case phosgene (Cl_2CO) was employed in the cyclisation step, according to the method described by Newman[60] and Kutner. The yield was not reported.



77 **78**

Scheme 18

Upon work-up, the corresponding oxazolidinone **78** was recovered as a white solid in good yield (76 %). Finally, oxazolidinone **78** was subjected to hydrogenation with a catalytic amount of palladium on activated carbon as before (**Scheme 19**).

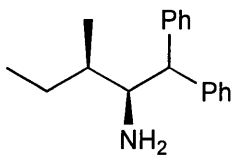


78 **76**

Scheme 19

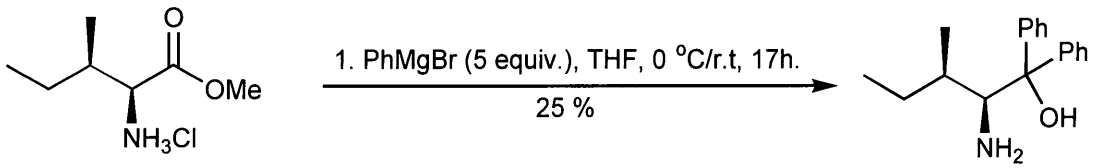
This generated amine **76**, which was purified over dry-flash column chromatography and obtained as a white solid in moderate yield (65 %). The ^{1}H NMR spectrum of **76** illustrated a doublet (3.55 ppm, J= 9.0 Hz) for the CH of the diphenylmethyl group and a doublet of quartets (3.73 ppm, J= 9.0 Hz) for the proton at the stereogenic centre. The HETCOR spectrum of **76** proved diagnostic for the assignment of the ^{13}C NMR signals. As a result, the peak at 50.3 ppm was assigned to the CH of the diphenylmethyl group and the peak at 62.4 ppm was assigned to the carbon atom at the stereogenic centre.

With the syntheses of three chiral amines **70**, **73** and **76**, the consistency of the new method has been established. To extend the range of amines further, it was anticipated that conversion of two other amino acid esters, namely (*S*)-isoleucine and (*S*)-leucine methyl ester hydrochlorides **68** and **69**, would be amenable to the method, as they have no complicating functional groups in their side chains. Thus the synthesis of amino alcohol **80** was addressed as the first step towards amine **79**.



79

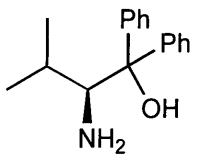
Amino alcohol **80** has already been prepared by Itsuno[51] *et al.* from (*S*)-isoleucine methyl ester hydrochloride **68** in 40-60 % yield. In this reaction, direct addition of **68** to the Grignard was used. In our case, amino alcohol **80** was prepared by inverse addition and with a 5-fold excess of phenylmagnesium bromide, as depicted in **Scheme 20**.



68 **80**

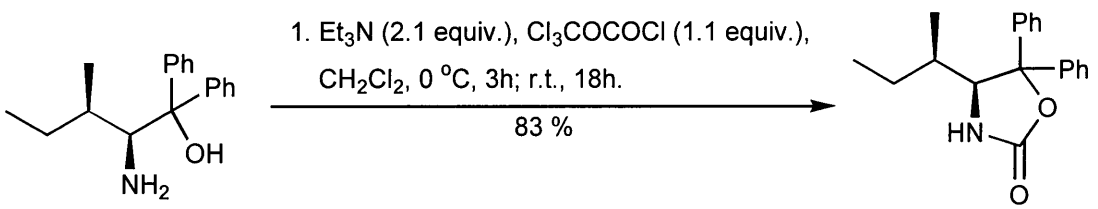
Scheme 20

After usual work-up, biphenyl as a neutral impurity was readily separated from the amino alcohol **80** by treatment of the crude product with concentrated HCl. After basification and extraction into ethyl acetate, **80** was isolated, but was contaminated with the unreacted amino ester from the starting material **68**. The crude product was however used directly for the next step without further purification. Only a small amount of this product was purified by dry-flash column chromatography and amino alcohol **80** was obtained as a white solid in low yield (25 %). The application of inverse addition in the synthesis of other amino alcohols, such as **71** by Delair[61] *et al.* resulted also in poor yields (~17 %).



71

With the amino alcohol **80** (60 %) in hand, it was converted to oxazolidinone **81**. This required treatment of **80** with diphosgene ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 21**.

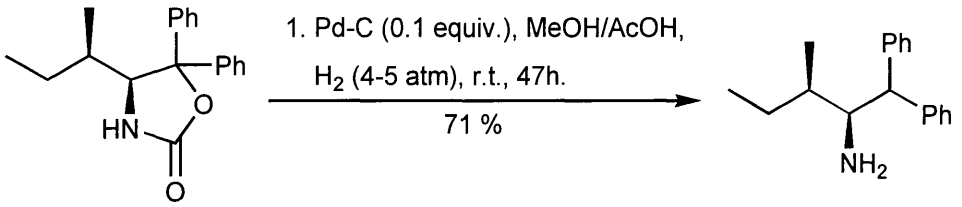


80 **81**

Scheme 21

Despite the fact that the 40 % impurity was present, the cyclisation proceeded without any complications. Upon work-up, the impurity was readily separated from

oxazolidinone **81**, as the solubility of the oxazolidinones was poor in common organic solvents. Thus, oxazolidinone **81** was obtained as a light-brown solid in good yield (83 %). This novel compound was a single diastereoisomer as judged by ^{1}H and ^{13}C NMR analysis. Oxazolidinone **81** was finally subjected to hydrogenation under the standard conditions, as illustrated in **Scheme 22**.

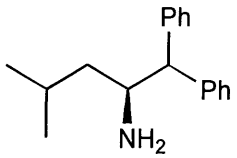


81 **79**

Scheme 22

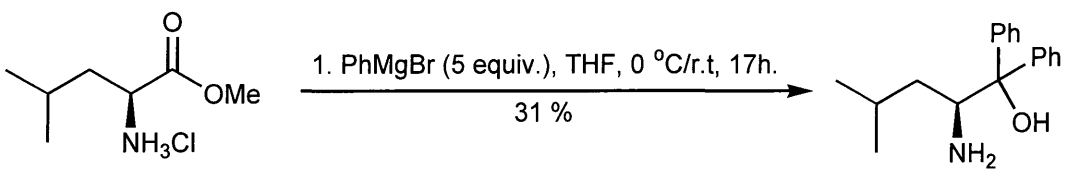
Amine **79** was obtained as a white solid in good yield (71 %), after purification by dry-flash column chromatography. The ^{1}H NMR spectrum of **79** displayed a doublet of doublets (3.50 ppm, J= 10.5 and 2.4 Hz) for the proton at the stereogenic centre and a doublet (3.87 ppm, J= 10.5 Hz) for the CH of the diphenylmethyl group. In order to assign the rest of the ^{1}H NMR signals, a Distortionless Enhacement by Polarization Transfer (DEPT) spectrum of **79**, where methine (CH), methylene (CH_2) and methyl (CH_3) carbons are distinguished, proved necessary. From this, it became clear that the multiplets at 1.00-1.20 and 1.50-1.70 ppm were due to the protons of the CH_2 group, hence the multiplet at 1.28-1.44 ppm was assigned to the proton of the CH next to the methyl group. With the DEPT analysis of **79** in hand, the ^{13}C NMR signals were also readily assigned. For example, the peak at 56.4 ppm was assigned to the CH of the diphenylmethyl group and the peak at 58.4 ppm assigned to the carbon at the C-N stereogenic centre.

The final transformation of the series started with (*S*)-leucine methyl ester hydrochloride **69**, to generate the corresponding amine **82**. The first step in this transformation began with the synthesis of amino alcohol **83**.



82

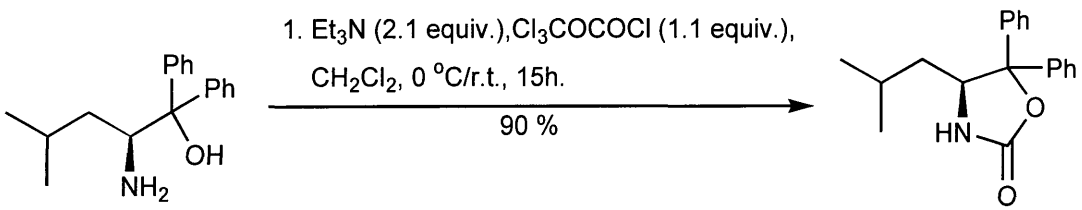
Preparation of **83** was first reported by Itsuno[51] *et al.* by the direct addition of (*S*)-leucine methyl ester hydrochloride **69** to an 8-fold excess of phenylmagnesium bromide. In our case, inverse addition, but with a 5-fold excess of Grignard reagent, was used.



69 **83**

Scheme 23

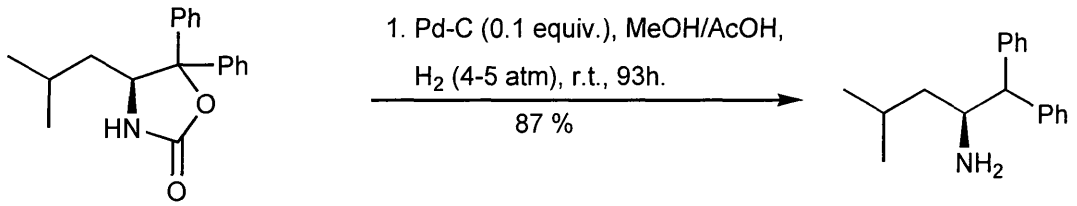
After usual work-up, treatment of the crude product with concentrated HCl allowed separation of biphenyl from the amino alcohol **83**. After basification and extraction into ethyl acetate, a crude product was obtained as a pale-yellow solid, but was contaminated with the amino ester derived from the starting material **69**. None-the-less, the crude product was used directly for the next step without further purification. Only a small amount of this product was purified by dry-flash column chromatography and amino alcohol **83** was isolated as a white solid in low yield (31 %). With amino alcohol **83** (65 %) in hand, it was submitted to cyclisation with diphosgene ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 24**.



83 **84**

Scheme 24

The cyclisation again proceeded without any complications and upon work-up, the impurity was readily separated from oxazolidinone **84**. Thus, the corresponding oxazolidinone **84** was obtained as a white solid and in excellent yield (90 %). Oxazolidinone **84** was then subjected to hydrogenation, as illustrated in **Scheme 25**.



84 **82**

Scheme 25

Upon work-up, this generated our final amine **82** of the series as a white solid and in good yield (87 %). The ^{1}H NMR spectrum of **82** was readily assigned, but in contrast to the previous examples, the proton at the stereogenic centre and the CH of the diphenylmethyl group overlapped at 3.6 ppm to give a multiplet. The DEPT and the Heteronuclear Multiple Bond Correlation (HMBC) spectra of **82** proved necessary for the assignment of the ^{13}C NMR signals. With the DEPT analysis of **82**, it became clear that the CH_2 group unexpectedly shifted to higher frequency giving a signal at 45.2 ppm, whereas the the CH of the isobutyl group shifted to lower frequency at 25.2 ppm. Assigment of the carbon signals at 52.1 and 61.2 ppm was possible on the basis of the HMBC spectrum, which shows correlation between two- or three-bond distant proton and carbon atoms. Since the carbon signal at 61.2 ppm shows correlation to the aromatic (Ph) protons, this must be the diphenylmethyl (Ph_2CH) carbon, and therefore the carbon signal at 52.1 ppm must be the carbon atom at the stereogenic centre ($CHNH_2$). The HMBC spectrum of **82** is depicted in **Figure 2**.

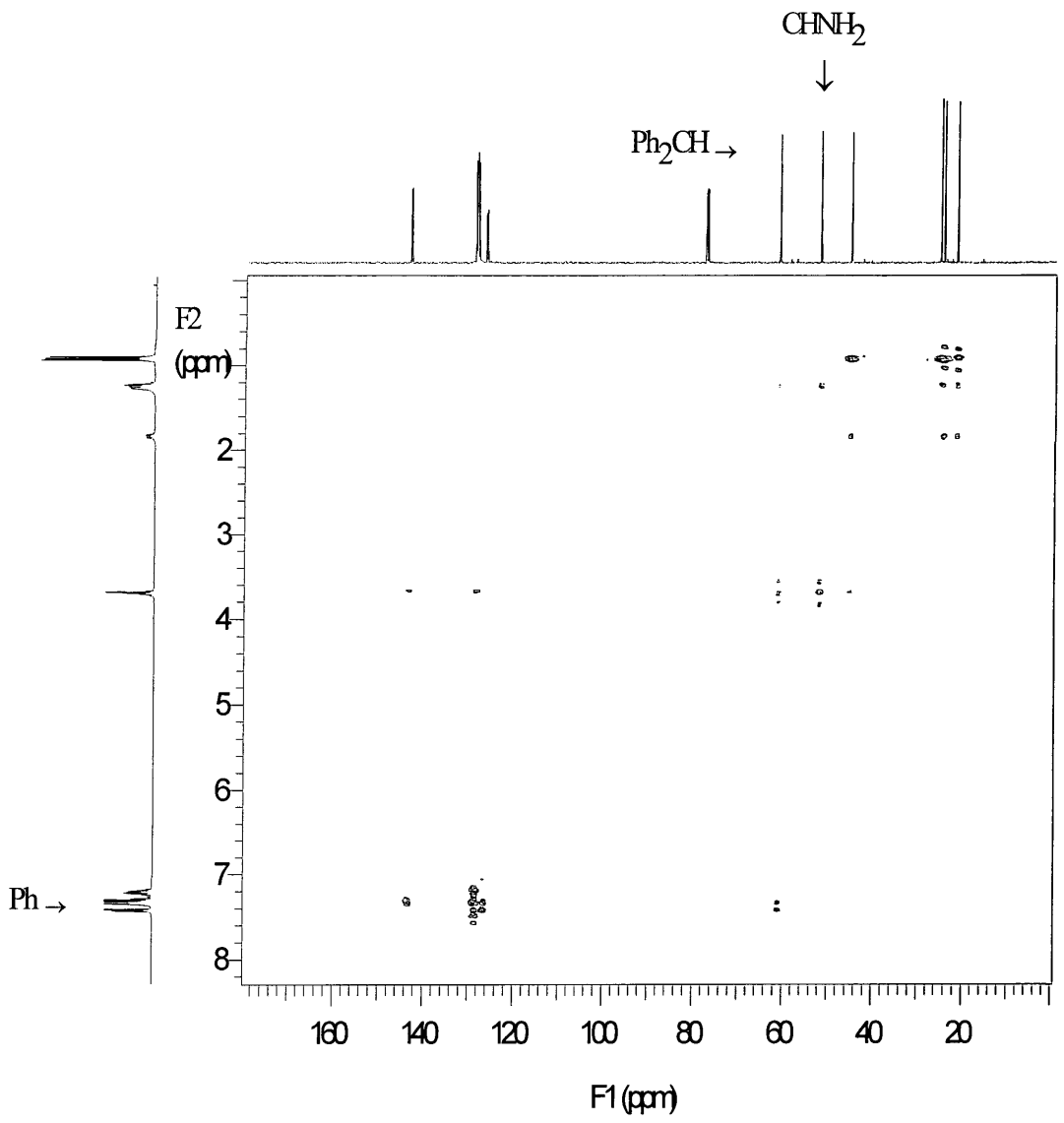
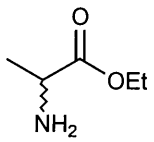


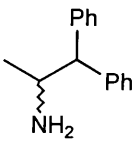
Figure 2: The HMBC spectrum of **82**.

1.3.3 Enantiomeric excess of (*S*)-α-(diphenylmethyl)-α-alkyl-methylamines 3

Determination of the enantiomeric purity of the novel chiral amines became necessary to demonstrate that the stereogenic centre had not racemised to any extent during the three-step synthesis. This therefore required a synthesis of one of the amines as a *racemate*, to provide a control. For this purpose, (*SR*)-alanine ethyl ester hydrochloride **85** was chosen as a starting material. Following the previously established route, (*SR*)-**85** was converted to the *(SR)*-α-(diphenylmethyl)-α-methyl-methylamine **76**.

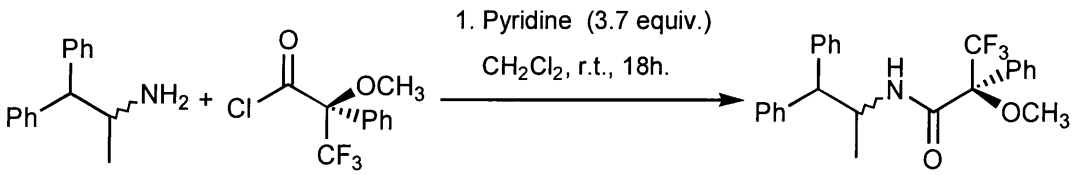


(*SR*)-**85**



(*SR*)-**76**

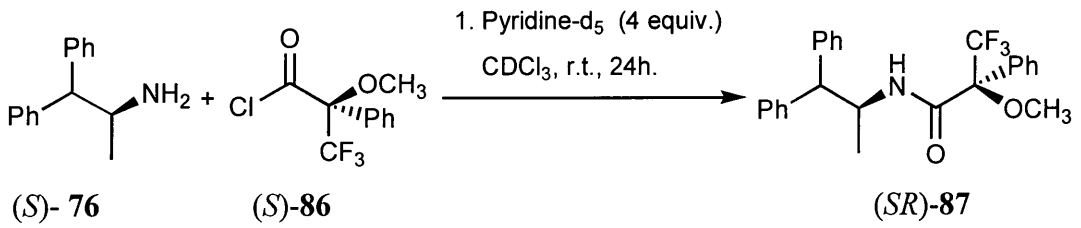
The non-equivalence of the CF_3 group in diastereoisomers of α-methoxy-α-trifluoro-methylphenylacetyl (Mosher) derivatives is often observable by ^{19}F-NMR, and such esters and amides are widely employed for enantiomeric excess (e.e.) determinations[62]. Therefore, the *racemic* amine **76** was converted to the corresponding diastereoisomeric (*SR*)- and (*RR*)-amides **87** with one equivalent of (*S*)-Mosher's acid chloride **86**, as depicted in **Scheme 26**, by a modification of the published procedure[62]. As a result of this reaction, the stereogenic centre of **86** is inverted from (*S*) to (*R*) by replacement of the Cl atom with the amide N atom.



(*SR*)-**76** (*S*)-**86** (*SR*)- and (*RR*)-**87**

Scheme 26

The reaction was monitored by ^{19}F NMR spectroscopy and after 5h, the fluorine peak at -72.4 ppm had disappeared, suggesting that all of the Mosher's acid chloride (*S*)-**86** was consumed. After purification by chromatography, both ^{19}F and ^{1}H NMR analysis of (*SR*)- and (*RR*)-**87** displayed two separate signals (**Table 2**, **Entry 1**) for the diastereotopic CF_3 (-69.3 and -70.0 ppm) and OCH_3 (3.02 and 2.84 ppm) groups. The chemical shift differences (Δδ) between the diastereoisomers for these groups were measured at 0.2 and 0.19 ppm, respectively. Such differences give base-line separations and allow precise integration of the fluorine and proton signals. The diastereoisomeric ratio of (SR)-**87** / (RR)-**87** was determined as 1.1:1. This small deviation from the expected 1:1 ratio probably arises from isomer separation on purification. The pure amine, (*S*)-**76** was then converted to the diastereoisomeric amide, (*SR*)-**87**, as illustrated in **Scheme 27**. In view of the small kinetic bias observed with the racemate, the (*S*)-**76** was reacted with a 1.4 equivalent of Mosher's acid chloride (*S*)-**86**, to ensure a complete conversion.



(*S*)- **76** (*S*)-**86** (*SR*)-**87**

Scheme 27

The reaction was monitored by ^{19}F and ^{1}H NMR and the peak at -70.0 ppm was assigned to the CF_3 group in the resulting amide (*SR*)-**87**, whereas the peak at -71.9 ppm was assigned to the product of some hydrolysis (Mosher's acid). Comparison of both the ^{1}H- and ^{19}F-NMR spectra (**Table 2**) of the racemate- and (*S*)-amine- derived Mosher's amides **87** shows very clearly that in the latter case a single diastereoisomer is formed, and by implication that the starting amine **76** was optically pure.

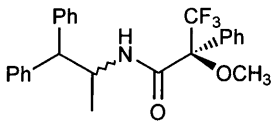
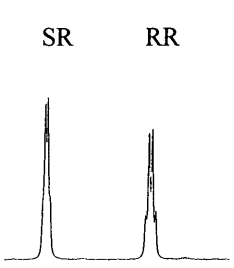
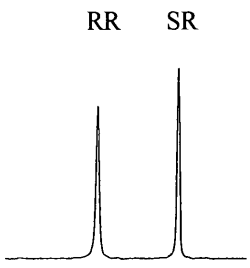
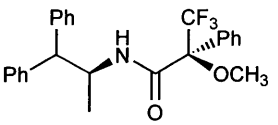
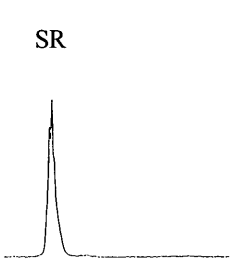
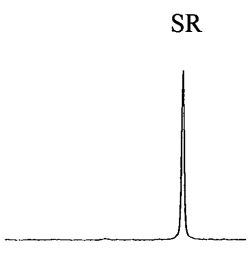
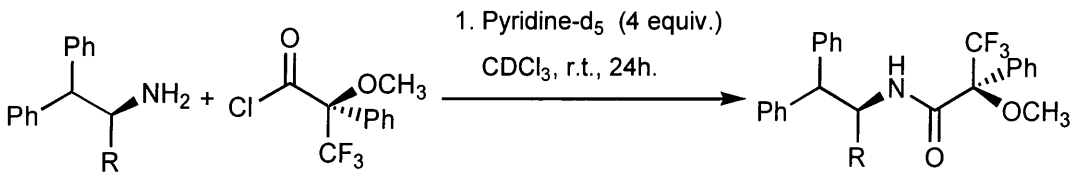
Entry	Compounds	δ_H of OCH_3 (ppm)	δ_F of CF_3 (ppm)
1	 (*SR*) and (*RR*)-**87**		
2	 (*SR*)-**87**		

Table 2: Selected regions of the ^{1}H-NMR (OCH_3: 3.10, 2.70 ppm) and ^{19}F-NMR (CF_3: -68, -73 ppm) spectra of the (*R*)-Mosher's amide **87**, prepared either from racemic (*SR*)-**76** or pure (*S*)-**76**.

All of the remaining amines, (*S*)-**3** (R= isopropyl **70**, benzyl **73**, *sec*-butyl **79** and isobutyl **82**) were also converted to their respective Mosher's amide derivatives **88-91**, as shown in **Scheme 28**. In all cases the resulting amides *(SR)*-**88-91** were subjected to ^{1}H and ^{19}F NMR analyses, and the spectra indicated that all were single diastereoisomers, consistent with their origin from enantiomerically pure amines. The relevant sections of the ^{1}H and ^{19}F NMR spectra are shown in **Table 3**.



(*S*)-**3** (*S*)-**86** (SR)-**88-91**

Scheme 28

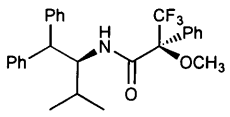
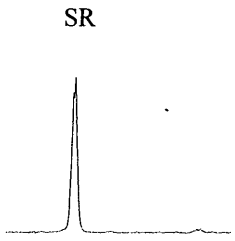
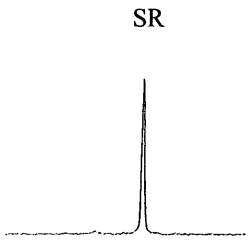
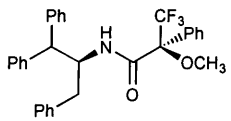
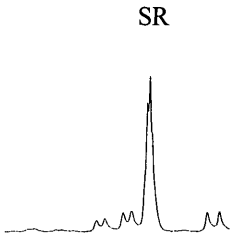
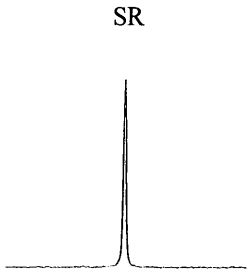
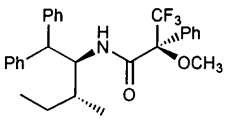
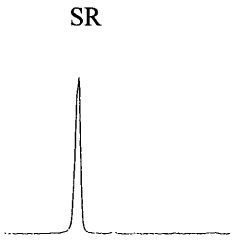
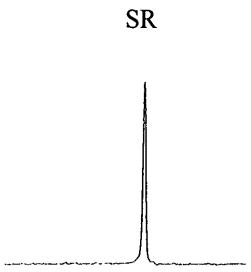
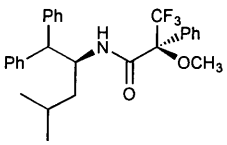
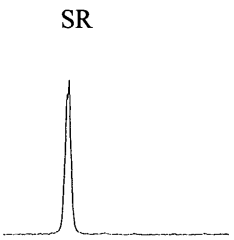
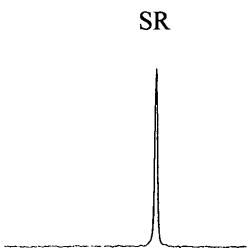
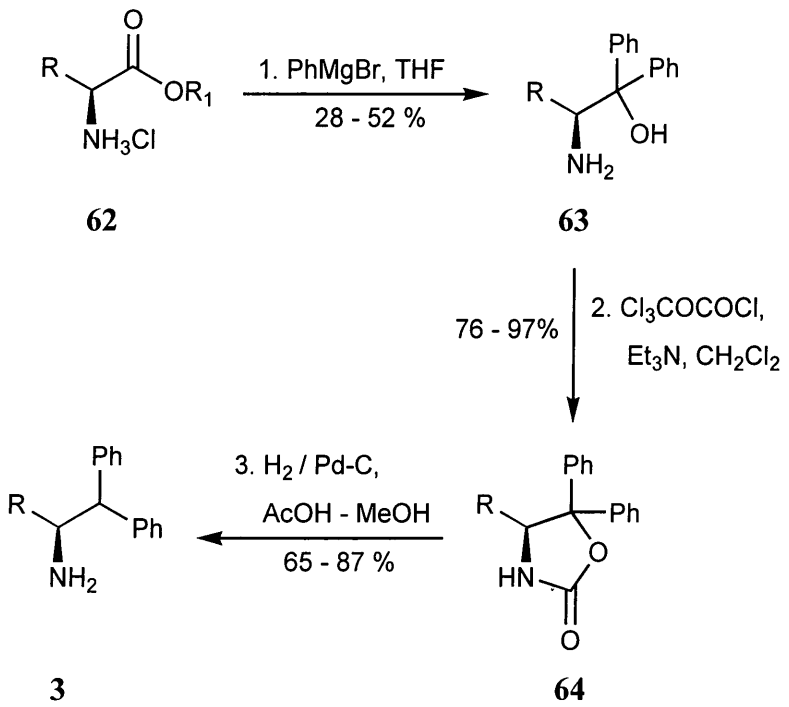
Entry	Compounds	δ_H of OCH_3 (ppm)	δ_F of CF_3 (ppm)
1	 (*SR*)-**88**	 SR 2.98 ppm	 SR -69.6 ppm
2	 (SR)-**89**	 SR 2.84 ppm	 SR -69.5 ppm
3	 (*SR*)-**90**	 SR 2.97 ppm	 SR -69.6 ppm
4	 (*SR*)-**91**	 SR 2.98 ppm	 SR -69.7 ppm

Table 3: Selected regions of the ^{1}H-NMR (OCH_3: 3.10, 2.70 ppm) and ^{19}F-NMR (CF_3: -68, -73 ppm) spectra of the (*R*)-Mosher's amides **88-91**, prepared from the (*S*)-**3**.

1.3.4 Discussion

A three-step route, as depicted in **Scheme 29**, has been developed to transform amino acid esters **62** into the novel chiral amines **3**. This transformation is amenable to some variety and potentially allows one to choose different starting amino acid esters **62** to generate different amines **3**.



Scheme 29

The first step in the route involved preparation of amino alcohols **63** either by direct or inverse addition of the corresponding amino acid ester hydrochlorides **62** to the Grignard reagent. A summary of the conditions for all of the amino alcohols prepared is shown in **Table 4**. The yields for the Grignard reactions varied between (9 %) and (52 %), according to the addition, hydrolysis and purification methods. Hydrolysis with HCl gave the lowest yield (9 %). The two lowest yields (25 % and 31 %) were obtained from the inverse addition of the amino acid esters. Recrystallisation of amino alcohol as an HCl salt was partially successful in the separation of the biphenyl impurity, but further purification by chromatography was still required. This gave the second best recovery, but still in low yield (36 %). Hydrolysis with saturated NH_4Cl and purification with dry-flash column chromatography led to a better recovery (52 %). Excess of Grignard reagents at more than 6-fold seemed to have little effect on the conversion, and purification became more difficult due to increased biphenyl formation. From these

observations, it can be concluded that a 6-fold excess of Grignard reagent, direct addition of amino acid esters, hydrolysis with saturated NH_4Cl and purification by dry-flash chromatography are key elements in the successful amino alcohol synthesis.

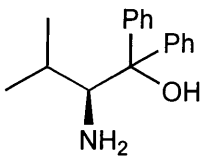
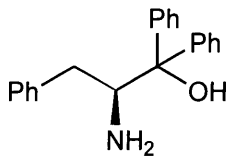
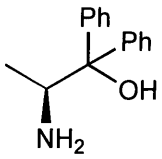
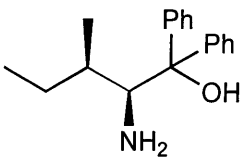
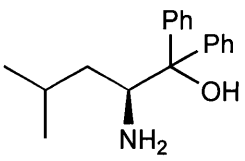
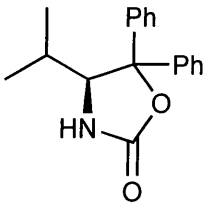
Amino alcohol	PhMgBr (equiv.)	Addition	Hydrolysis	Purification	Yield (%)
 **71**	10	direct	NH_4Cl	recrystallisation and chromatography	36
 **74**	8	direct	HCl	recystallisation	9
 **77**	6	direct	NH_4Cl	chromatography	52
 **80**	5	inverse	NH_4Cl	chromatography	31
 **83**	5	inverse	NH_4Cl	chromatography	25

Table 4: Synthesis of the amino alcohols **71**, **74**, **77**, **80** and **83** under different conditions.

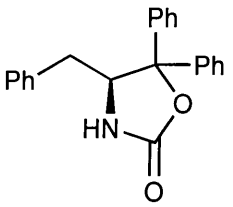
The second step in the route required the preparation of the oxazolidinones **72**, **75**, **78**, **81** and **84**, with the general structure **64** (see **Figure 3**). This was readily achieved by cyclisation of the amino alcohols **63** with diphosgene, in the presence of triethylamine

in good to excellent yields (76 - 97 %). The solubility of the oxazolidinones **64** was poor in common organic solvents and this assisted their purification. It was observed that the solubility improved with the larger alkyl groups on the 4 position. For instance, **81** and **84** were soluble in dichloromethane or chloroform, whereas with **72**, **75** and **78** were insoluble, except in dimethyl sulphoxide (DMSO).



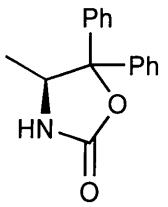
72

(Yield: 86 %)



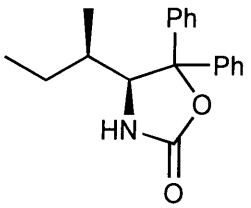
75

(Yield: 97 %)



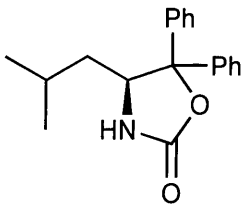
78

(Yield: 76 %)



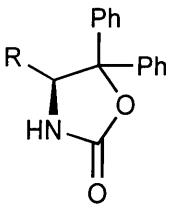
81

(Yield: 83 %)



84

(Yield: 90 %)



64

Figure 3: The oxazolidinones **72**, **75**, **78**, **81** and **84** prepared in this transformation and their general structure **64**.

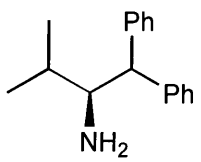
The final step in the route was hydrogenation of the oxazolidinones **64** over palladium on activated carbon. In this hydrogenation, a mixture of acetic acid and methanol was used as a solvent, where the oxazolidinones **64** formed either a solution or a suspension. The hydrogenation was carried out at 4-5 atm by using a Parr hydrogenator. Upon concentration, the crude amines were treated with hydrochloric acid, to disassociate amine-acetate salts formed during the hydrogenation, followed by basification and extraction into dichloromethane. Purification of the amines was achieved by one of the following:

i) Re-crystallisation, as was the case for amine **70**.

ii) Column chromatography, as was the case for amines **73** and **76**.

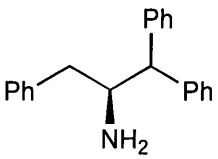
iii) Washing the acidic solution with diethyl ether, as was the case for amines **79** and **82**.

The yields varied between 65 % and 87 %. The resultant amines **70**, **73**, **76**, **79** and **82**, represented by the general structure **3** are depicted in **Figure 4**.



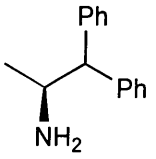
70

(Yield: 72 %)



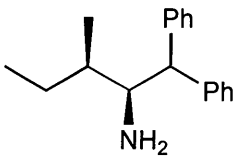
73

(Yield: 71 %)



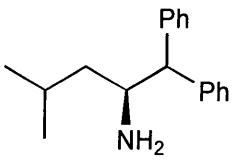
76

(Yield: 65 %)



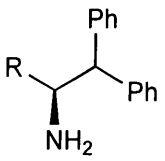
79

(Yield: 71 %)



82

(Yield: 87 %)



3

Figure 4: The novel homochiral amines **70**, **73**, **76**, **79** and **82** prepared from the three-step route and their general structure **3**.

The presence of a single stereoisomer for the resultant amines in each case was demonstrated by the reaction of (*S*)-Mosher's acid chloride with the (*S*)-amines **3**. In all cases ^{1}H and ^{19}F NMR analysis of the resultant stereoisomers indicated that the synthetic sequence followed for the preparation of the novel amines is not susceptible to racemisation, certainly not at a detectable level.

CHAPTER TWO

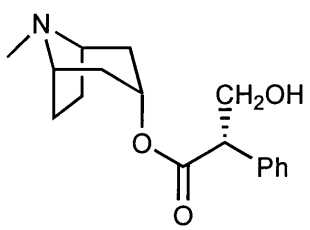
Towards the Synthesis of Ketone Analogue of Littorine

CHAPTER TWO

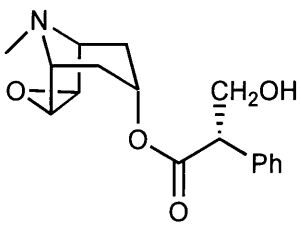
2.1 General introduction

2.1.1 Biosynthesis of tropane alkaloids hyoscyamine and scopolamine

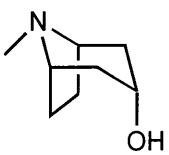
Hyoscyamine **92** and its epoxidised derivative scopolamine **93** are secondary metabolites of the Solenacae family of plants and have been widely used in the clinic[63]. They are esters of tropine **94** and (*S*)-tropic acid **95**. The biosynthetic origin of the tropine moiety **94** and (*S*)-tropic acid **95** have been the focus of much interest for many years[64].



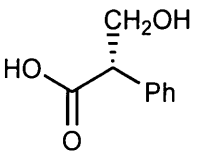
92



93

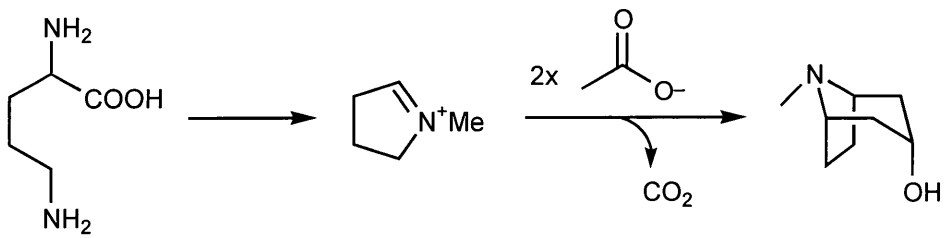


94



95

The biosynthesis of tropine **94** has been substantially settled as is shown **Scheme 30**. It has been confirmed that the amino acid ornithine **96** is incorporated into N-methylpyrrolidium **97**. However, points of detail on the condensation of two acetyl groups with **97** remain to be resolved.



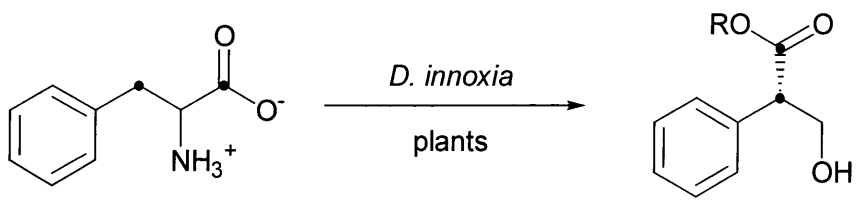
96 **97** **94**

Scheme 30

2.1.2 Biosynthetic origin of (*S*)-tropic acid 95

The biosynthetic origin of the (*S*)-tropic acid **95** is still a subject of discussion and investigations.[65,66] In the 60s, Leete[67] suggested that (*S*)-phenylalanine **98** was a direct

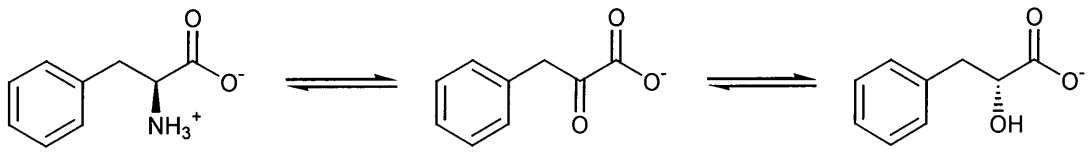
precursor of (*S*)-tropic acid **95**. In a definitive experiment fifteen years later Leete[68] demonstrated in *Datura innoxia* plants that (*RS*)-phenyl[1,3-$^{13}C_2$]alanine **98** was incorporated into the tropate moiety of hyoscyamine **92**, in where the two ^{13}C isotopes became contiguous by an intramolecular rearrangement, as shown in **Scheme 31**.



(*RS*)-[1,3-$^{13}C_2$]-**98** [1,2-$^{13}C_2$]-**92**

Scheme 31

Although (*S*)-phenylalanine **98** is a good precursor of (*S*)-tropic acid **95**, the true substrate for the rearangement and the stereochemical course to (*S*)-tropic acid **95** has recently been re-evaluated. Feeding experiments[69,70] with ^{14}C-labelled phenylpyruvate **99** and phenyllactate **100** indicated that the two compounds become similarly incorporated into the tropic acid moiety of the alkaloids. This observation can be explained if phenylalanine **98**, phenylpyruvate **99** and phenyllactate **100** interconvert *in vivo*, as depicted in **Scheme 32**.

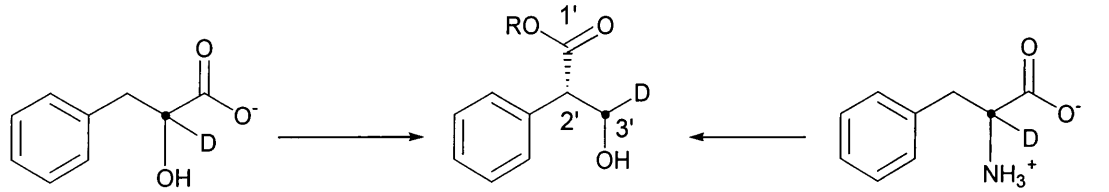


98 **99** **100**

Scheme 32

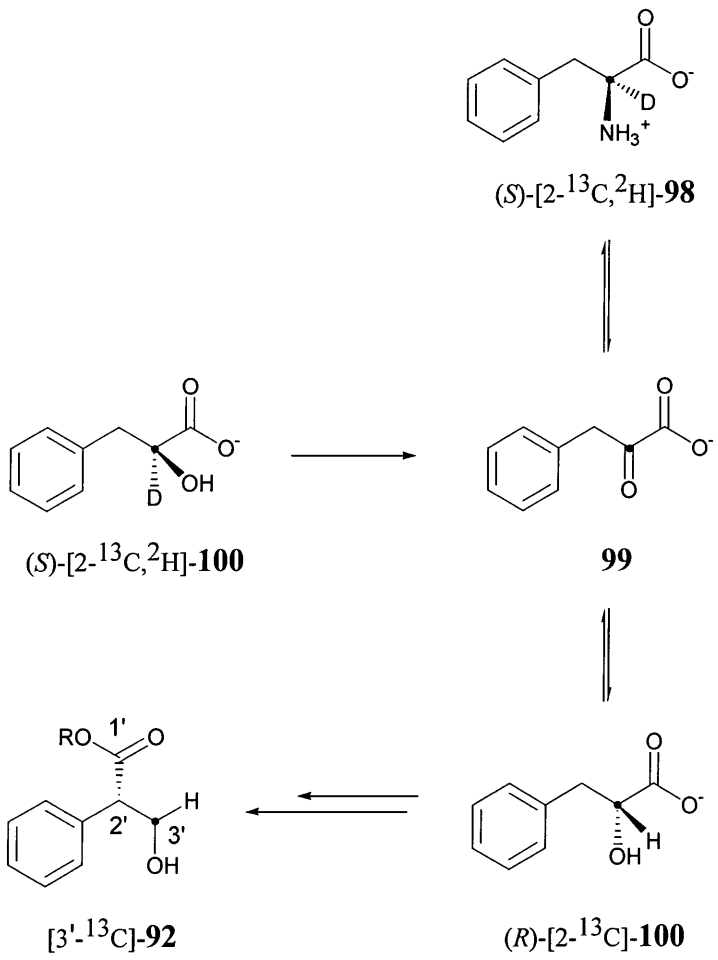
The importance of phenyllactate **100** as a precursor to (*S*)-tropic acid **95** was shown by two different research groups[71,72] after feeding (*RS*)-phenyl[1,3-$^{13}C_2$]lactate **100** to transformed root cultures of *Datura stramonium*. The observed spin-spin coupling of the two ^{13}C nuclei in the extracted hyosyamine **92** and scoplamine **93** confirmed the intramolecular rearrangement shown by Leete[68]. It remained to be confirmed however which was the most direct precursor of the three. Therefore, a series of feeding experiments[66,73] was carried out in Durham by supplementing *Datura stramonium* root

cultures with the following labelled compounds: *racemic*, and resolved (*R*)- and (*S*)-phenyl[2-^{13}C,^{2}H]alanines **98** and *racemic* phenyl[2-^{13}C,^{2}H]lactate **100**. All of the feeding experiments with racemic phenyl[2-^{13}C,^{2}H]alanine **98**, the (*R*)-isomer, and racemic phenyl[2-^{13}C,^{2}H]lactate **100** resulted in a substantial retention of ^{2}H (D, deuteruim) and ^{13}C isotopes, at C3' of hyoscyamine **92 (Scheme 33)**. On the other hand feeding with the (*S*)-phenyl[2-^{13}C,^{2}H]alanine **98** resulted in a complete lost of D isotope, at C3' of hyoscyamine **92 (Scheme 34)**. These results clearly indicate that (*R*)-phenyllactate **100** is the stereosiomer used during the biosynthesis.



(*RS*)-[2-^{13}C,^{2}H]-**100** [3'-^{13}C,^{2}H]-**92** (*RS*)- or (*R*)-[2-^{13}C,^{2}H]-**98**

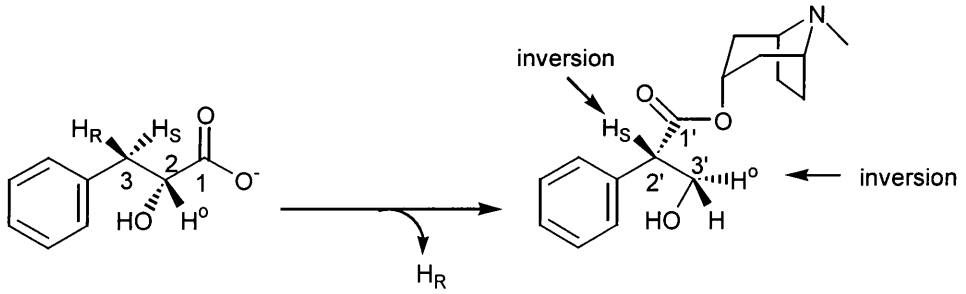
Scheme 33



Scheme 34

2.1.3 Stereochemistry of the rearrangement

During the rearrangement of phenyllactate **100** to hyoscyamine **92**, two bonds (C1-C2 and C3-H_R) of **100** are broken, and C1 migrated to C3 to form a new bond of the tropate moiety (C1'-C2') of **92**. However H_R of **100** is removed and the origin of the new C3'-H bond of the tropate moiety is unknown. Feeding experiments[74] with radiolabelled phenyl[2-^{3}H]lactate **100** showed that the tritium (T) isotope was retained at the 3'-*pro-S* position (H^o) in the resultant hyoscyamine **92**, whereas feeding[75] (2*R*,3*R*)- and (2*R*,3*S*)-[3-^{2}H]phenyllactates **100** only the deuterium (D) isotope at the 3*S* position (C3-H_S) of **100** retained. This hydrogen becomes configurationally inverted in the resultant hyoscyamine **92** (C2'- H_S). These experiments clearly demonstrate that inversion of configuration occurred at both bond-breaking and -forming centres. The overall stereochemical course of the rearrangement is summarised in **Scheme 35**.

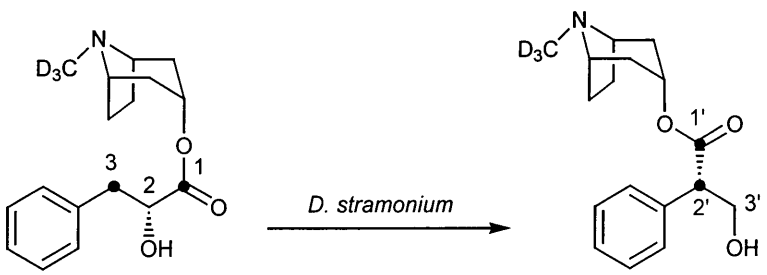


100 **92**

Scheme 35

2.1.4 Littorine 101 is a direct precursor to hyoscyamine 92

In tropane alkaloid forming plants, littorine **101**, the tropine ester of (*R*)-phenyllactate **100**, was also co-produced with hyoscyamine **92** and scopolamine **93**. Therefore, it appeared reasonable that (*R*)-phenyllactate **100** can couple to tropine **94** in *Datura stramonium* to give littorine **101**. This then is the true substrate for the putative isomerase enzyme. The role of littorine **101** as a direct precursor of hyoscyamine **92** was established in an experiment[76] using isotopically labelled littorine **101**, where three ^{2}H (D) nuclei incorporated into N-CH_3 of the tropine moiety and two ^{13}C nuclei incorporated into C1 and C3 position of phenyllactoyl moiety. A high level of ^{13}C spin-spin coupling, observed by NMR, unequivocally demonstrated that littorine **101** can rearrange *in vivo* to hyoscaymine **92**, as shown in **Scheme 36**.



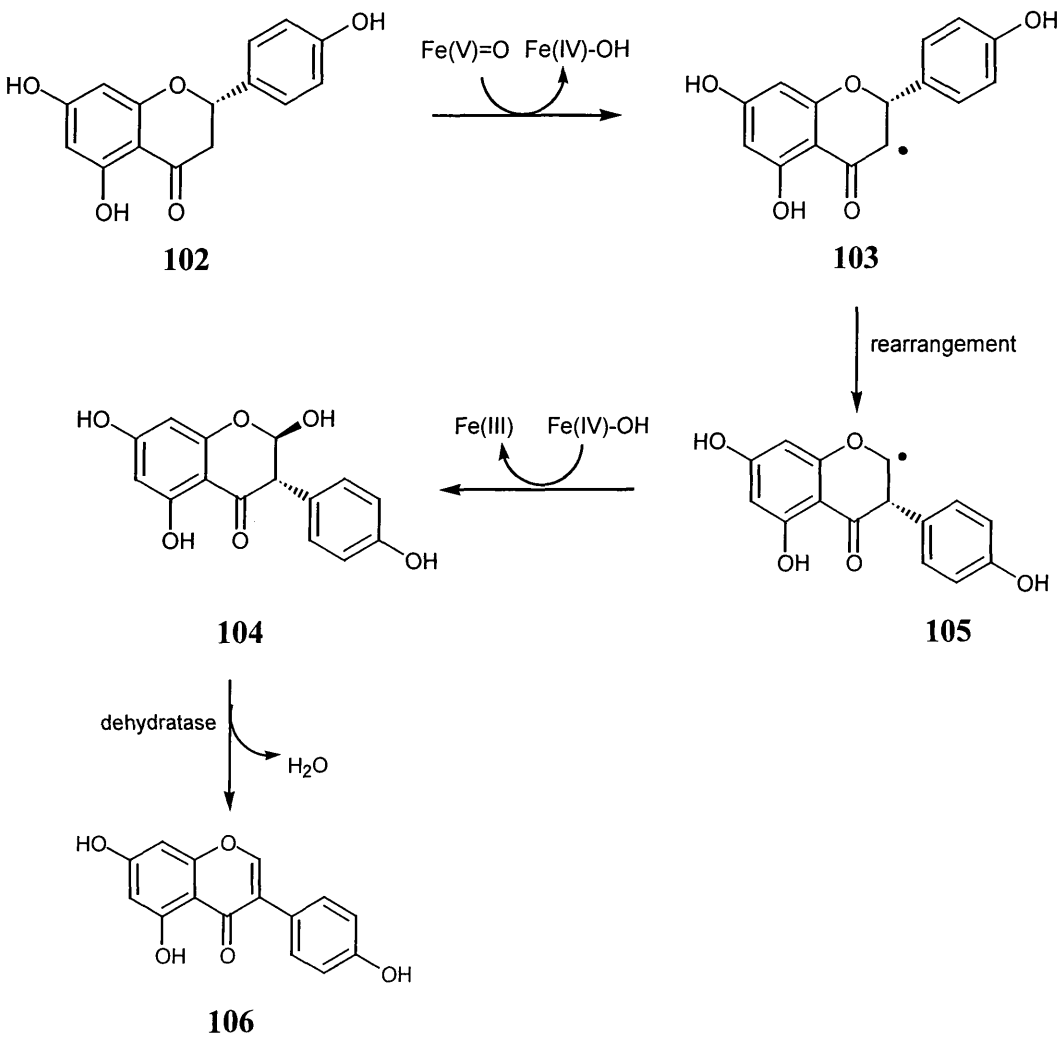
101 **92**

Scheme 36

2.1.5 Mechanistic hypothesis

It is interesting to note that a considerable number of biosynthetic rearrangement reactions are reasonably explained as cytochrome P_{450}-mediated reactions, such as

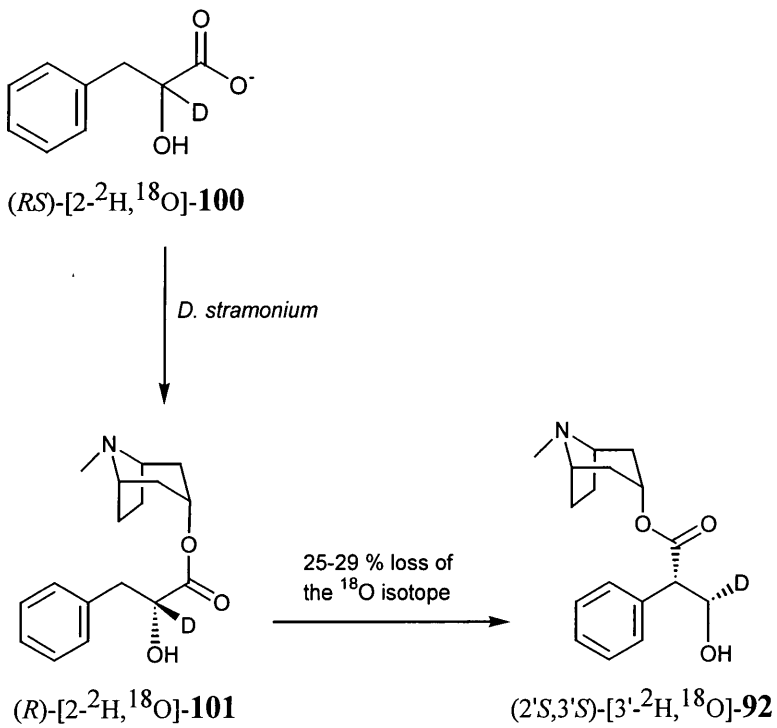
formation[77] of 2,7,4'-trihydroxyisoflavanone **104** from flavanone **102**, as depicted **Scheme 37**. In P_{450}-mediated reactions[78] the initially formed Fe(III)-O-O$^{\bullet}$ species is converted into Fe(III)-O-OH and then heterolysis of the oxygen-oxygen bond gives the oxo-derivative for which a number of structures are possible; for example Fe(IV)=O, (+·)Fe(IV)=O and Fe(IV)-O$^{\bullet}$. For example, in the case of 2,7,4'-trihydroxyisoflavanone **104** formation, one of these species, e.g. iron-oxo [Fe(V)=O], appears to initiate the abstraction of hydrogen to generate a substrate radical **103**. Rearrangement to a product radical **105**, followed by oxygen rebound, where the rearranged radical is quenched by an hydroxyl radical from Fe(IV)-OH, gave 2,7,4'-trihydroxyisoflavanone **104**. This intermediate was isolable and the new hydroxyl group was labelled from ^{18}O. A dehydratase then acts to produce the final product, daidzein **106**.



102 **103** **104** **105** **106**

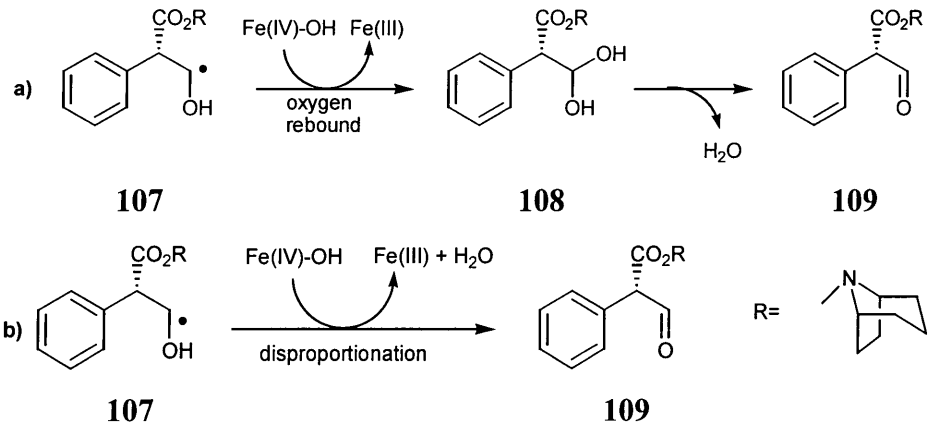
Scheme 37

The recent stereochemical conclusions[75], and in particular the absence of a vicinal interchange process (i.e. the proton (H_R) at C3 of phenyllactate **100** was lost and not relocated at the 3'-pro-R site of hyoscyamine **92**, see **Scheme 35**, p. 44) have led to the suggestion that a haem-thiolate enzyme, cytochrome P_{450} may be responsible for the rearrangement. This hypothesis has gained support by the observation[79] that the P_{450} inhibitor, chlortrimazole inhibited the conversion of littorine **101** to hyosyamine **92** in roots of *Datura stramonium*. The possibility of an oxygen-rebound was also investigated by a feeding experiment[80], where racemic (*RS*)-phenyl[2-^{2}H,^{18}O]lactate was supplemented to transformed root cultures of *Datura stramonium*, as illustrated in **Scheme 38**. It was shown that both ^{18}O and ^{2}H (D, deuterium) isotopes were incorporated into littorine **101**. However during the rearrangement of littorine **101** to hyoscyamine **92**, 25-29 % of the ^{18}O isotope was lost.



Scheme 38

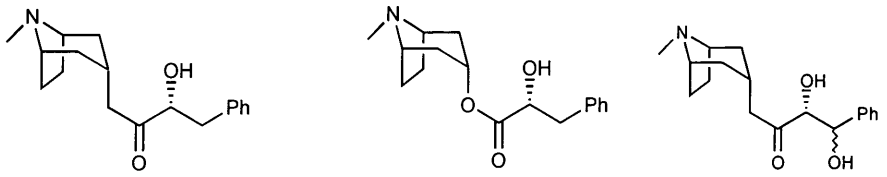
The high retention of the ^{18}O isotope (71-75 %) can be rationalised if a diol hydrate **108**, formed by oxygen-rebound from product radical **107**, collapses to an aldehyde **109** in a stereospecific manner (**Scheme 39a**) or disproportionation of the Fe(IV)-OH and the product radical **107** occurs to give an aldehyde **109** directly (**Scheme 39b**).



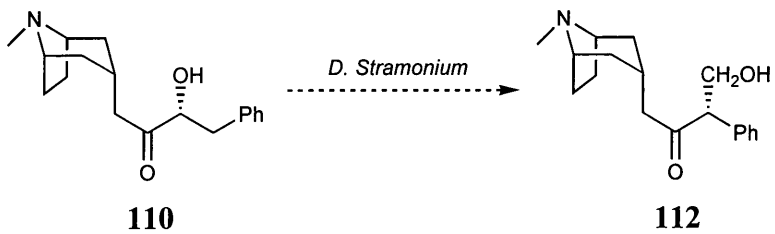
Scheme 39

2.1.6 Aim and objectives

In this research programme, **110** became a target molecule. This is an analogue of littorine **101**, where the bridging O atom has been replaced by a CH_2 group. If prepared and fed to cell free extracts *of Datura stramonium*, it may give a shunt product, which might reveal some detail of the process. For example, if an oxygen rebound process is operating, then diol **111** may be generated.



More interesting, of course, would be to observe a rearrangement of ketone **110** to **112**, as depicted in **Scheme 40**, however this would require a considerable flexibility of the enzyme and this was not anticipated as a realistic outcome.

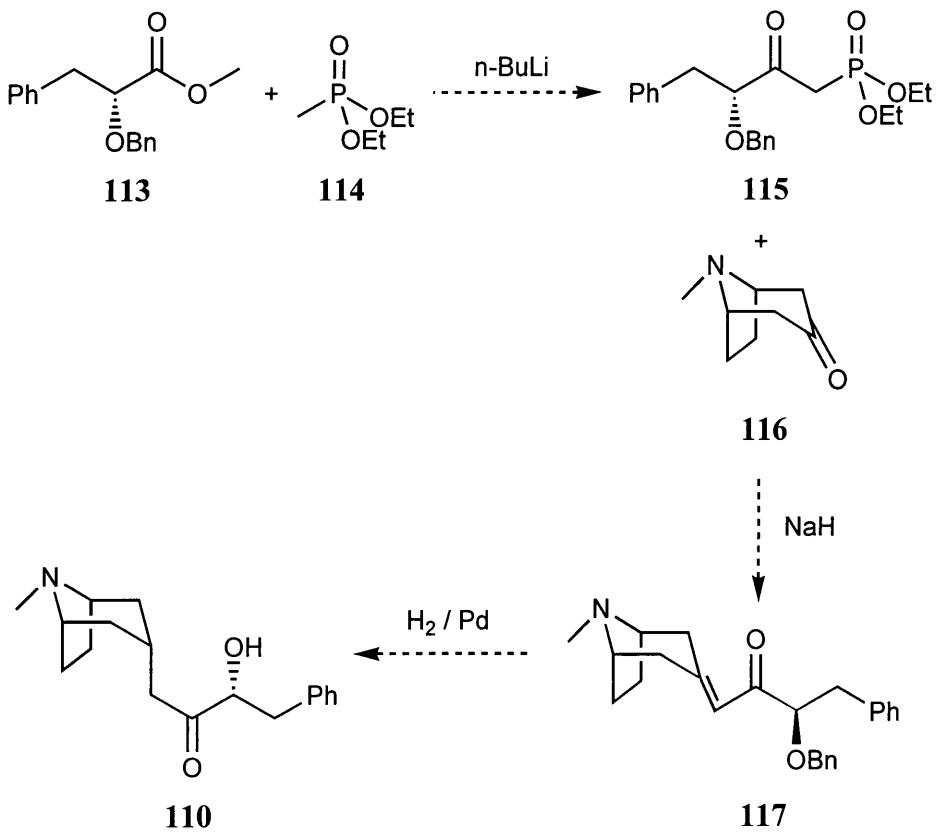


Scheme 40

2.2 Wittig and HWE reactions of tropinone

2.2.1 Introduction

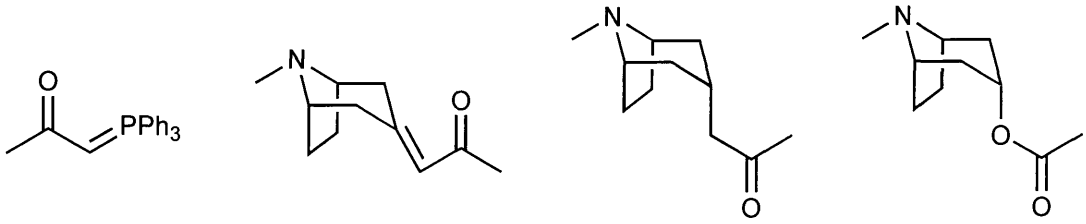
In order to prepare the required target we initiated the synthetic route to ketone **110** as shown in **Scheme 41**. The first step in this route involved preparation of β-ketophosphonate **115,** as analogues compounds have commonly been used for the preparation of α,β-unsaturated ketones *via* the Horner-Wadsworth-Emmons (HWE) reactions[81]. It was anticipated that the desired β-ketophosphonate **115** could be prepared from the reaction of the lithium salt of diethyl methylphosphonate[82] **114** with carboxylic acid ester **113**. We envisaged that the HWE reaction of tropinone **116** with **115** would be the key step in this route, leading to the formation of α,β-unsaturated ketone **117**. Finally double bond reduction was anticipated to afford the *endo* isomer as the predominant product.



Scheme 41

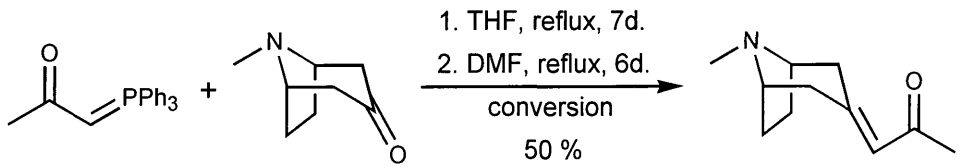
2.2.2 Attempted synthesis of (tropane-3-ylidine) ketones 119 and 123

It was judged appropriate to establish the protocol on a model system. Therefore, acetylmethylenephosphorane[83] **118** was chosen as a model reagent. This was attractive, as hydrogenation of **119** would give ketone **120**, the CH_2 analogue of the tropane alkaloid acetoxytropane[84] **121**.



118 **119** **120** **121**

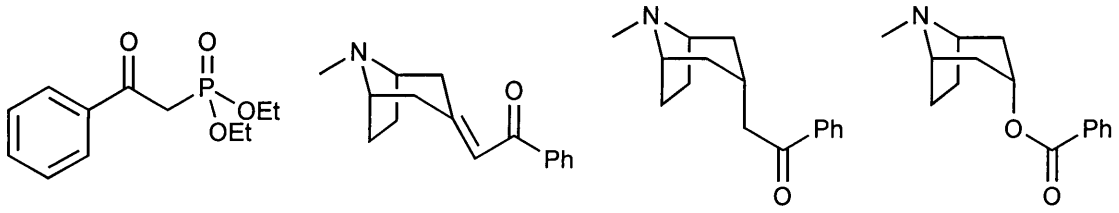
Phosphorane **118** was subjected to the Wittig reaction with tropinone **116** under two sets of conditions, as summarised in **Scheme 42**. The ^{31}P NMR analysis of the reaction mixture in THF (reflux, 7 days) did not show any traces of triphenylphosphine oxide, however the reaction mixture in DMF (reflux, 6 days) displayed the characteristic peak at 24 ppm in the ^{31}P NMR spectrum. This suggested a conversion of almost 50 %, however, neither the desired product **119** nor the starting material **116** could be recovered from the reaction.



118 **116** **119**

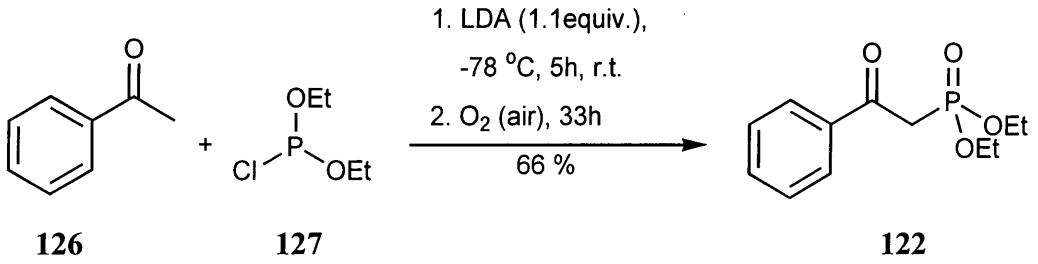
Scheme 42

In view of the failed Wittig reaction between tropinone **116** and phosphorane **118,** diethyl benzoylmethanephosphonate **122** was considered as an alternative model compound. This HWE reaction, if followed by hydrogenation, would generate ketone **123**, the CH_2 analogue of the tropane alkaloid benzoyloxytropane[84,85] **125**.



122 **123** **124** **125**

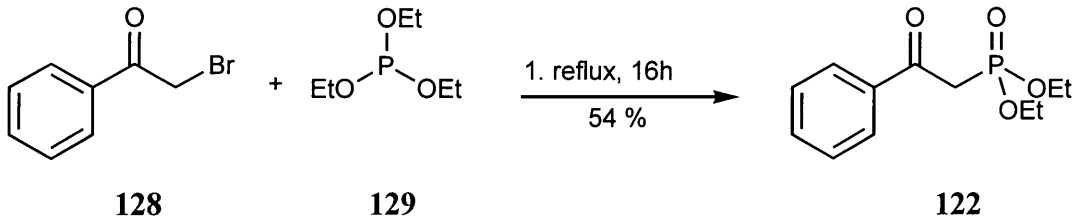
Phosphonate **122** was prepared from the reaction of acetophenone **126** with diethyl chlorophosphite **127**, following a literature method[86], as depicted in **Scheme 43**. This required the formation of the lithium enolate of acetophenone **126** at -78 °C, followed by addition of diethyl chlorophosphite **127**. Upon work-up, the resulting product was subjected to air oxidation and gave the desired phosphonate **122**, in moderate yield (66 %).



126 **127** **122**

Scheme 43

An alternative approach to phosphonate **122** was investigated in parallel and followed the method described by Dawson[87] and Burger, in which bromoacetophenone **128** and triethyl phosphite **129** are heated together, as shown in **Scheme 44**.

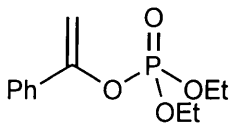


128 **129** **122**

Scheme 44

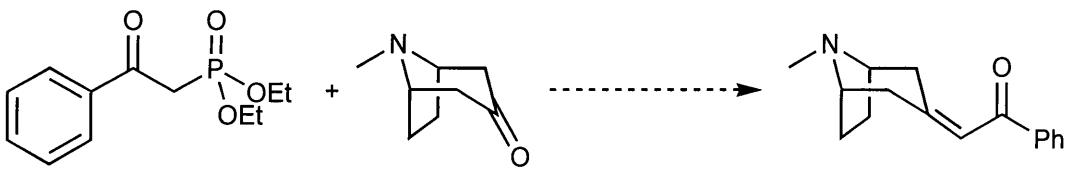
Although this proved to be a straightforward route, a side product (probably unavoidable Perkow product **130**) was also generated, which made purification difficult.

Only after three subsequent distillations and column chromatography (eluting with a 1:1 mixture of ethyl acetate and hexane), a fairly pure sample of phosphonate **122** was obtained in 54 % yield.



130

Phophonate **122** was treated with tropinone **116** under various conditions and these are summarised in **Scheme 45** and **Table 5**. In the end this reaction was unsuccessful.



122 **116** **123**

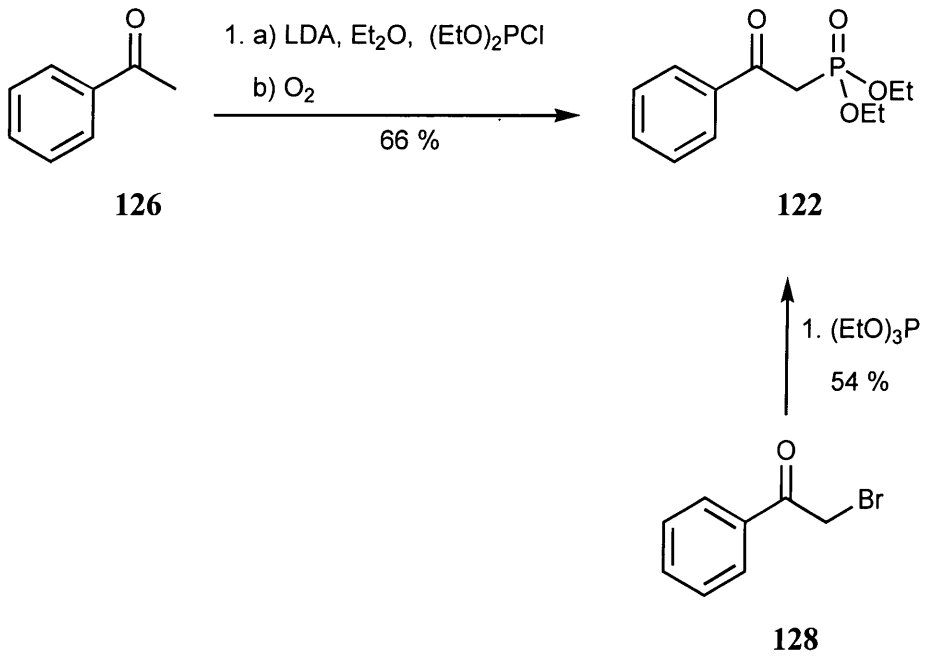
Scheme 45

Entry	Base	Solvent	Time	Reference
1	NaH	THF	r.t., 3d	[88]
2	NaH	THF	r.t., 4d	[89]
3	NaH	Et_2O	r.t., 22h; reflux, 6d	[90]
4	KOtBu	DMF	r.t., 25h; reflux, 7d	[91]
5	n-BuLi	DME	-78 °C to r.t., 1h; reflux, 8d	[92]
6	LDA	THF	-78 °C, 2h; r.t., 16h; reflux, 4d	[93]

Table 5: The attempted HWE reaction of tropinone **116** with phophonate **122** under different conditions.

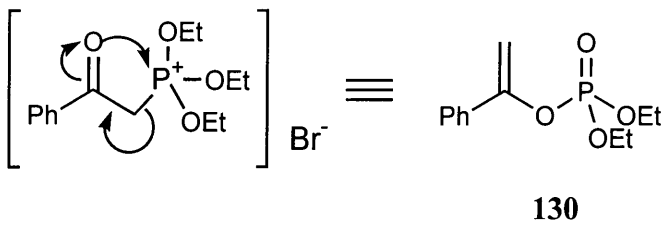
2.2.3 Discussion

Starting from either acetophenone **126** or bromoacetophenone **128**, model β-ketophosphonate **122** was readily prepared in good (66 %) to moderate (54 %) yields respectively, as depicted in **Scheme 46**.



Scheme 46

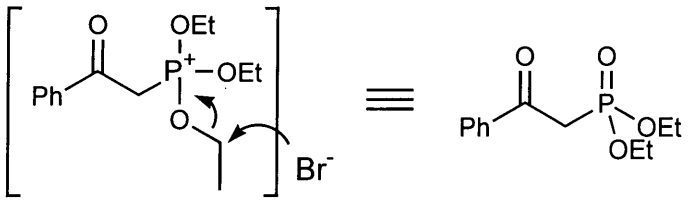
Preparation of phosphonate **122** from **128** represents a classical Arbuzov reaction and proved a straightforward route to β-ketophosphonate **122**. However, it is known that[94,95] this route quite commonly suffers from an un-avoidable Perkow reaction, which generates vinyl phosphate **130** *via* the nucleophilic attack of the carbonyl oxygen on to the phosphorus atom, as shown in **Figure 5**.



130

Figure 5: Formation of vinyl phosphate **130** by an avoidable Perkow reaction.

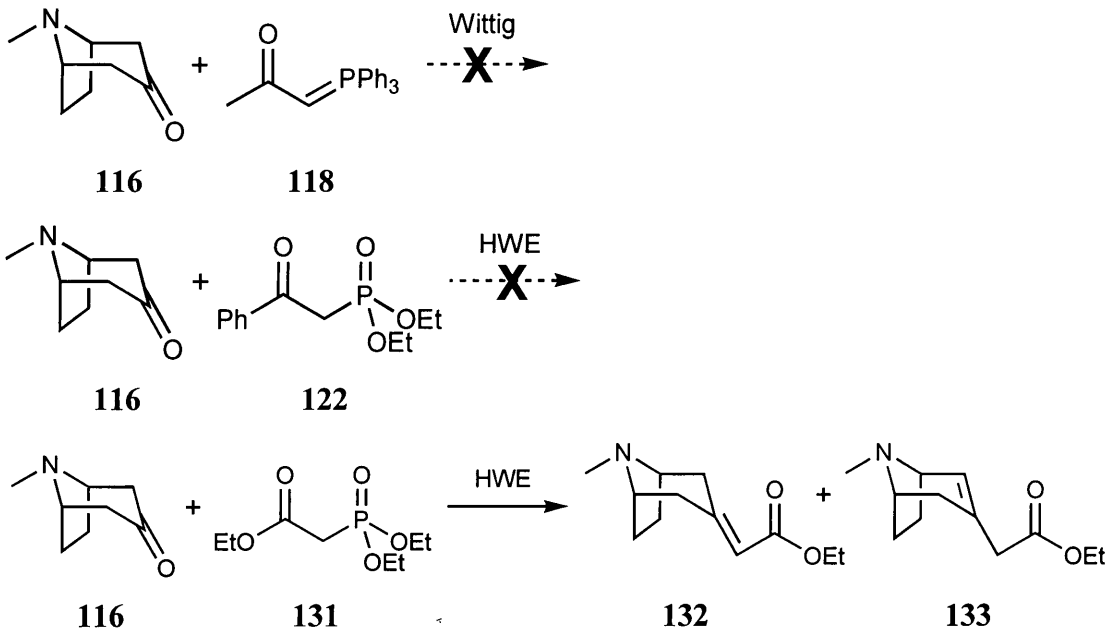
Formation of phosphonate **122** by an Arbuzov reaction occurs *via* the elimination of ethyl bromide as illustrated in **Figure 6** and is dependant upon the halide used and the reaction temperature[96]. High temperatures and less electronegative halogens usually favour phosphonate formation[97]. From our experience, column chromatography is a reasonable method for the separation of the Arbuzov product **122** from the Perkow product **130**.



122

Figure 6: Formation of phosphonate **122** by an Arbuzov reaction.

Tropinone **116** was found to be particularly unreactive both for the Wittig reaction of acetylmethylenephosphorane **118** and for the HWE reaction of diethyl benzoylmethane-phosphonate **122**. This is perhaps due to a combination of steric effects associated with nucleophilic approach to the ketone of the tropinone ring, and the relative decrease in the nucleophilicity of phosphorane[98] **118** and phosphonate **122**, when compared to triethyl phosphonoacetate **131**. Unlike phosphorane **118** and phosphonate **122**, the anion[98] derived from phosphonate ester **131** is more strongly nucleophilic and was reported[88] to react with tropinone **116** to give both α,β-unsaturated ester **132** and β,γ-unsaturated ester **133**, as depicted in **Scheme 47**.



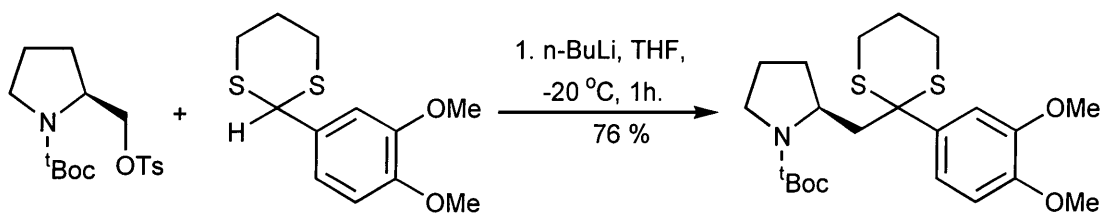
Scheme 47

This failure has led us to develop another potential route to ketone **110**, and this is discussed in the following section.

2.3 Coupling reactions: thioacetal and tropane precursors

2.3.1 Introduction

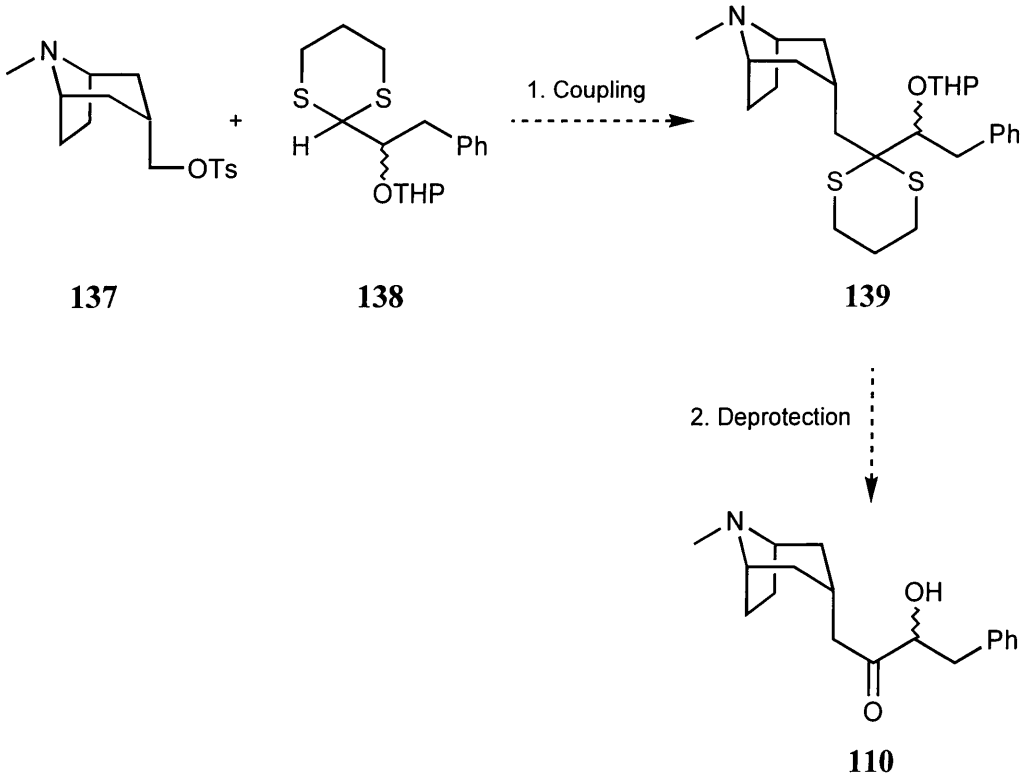
It is well known that lithiated 1,3-dithiane species show high nucleophilicity towards alkyl halides and arene sulfonates derived from primary alcohols[99]. The following example is illustrative[100]: (2*S*)-N-(t-Butoxycarbonyl)-O-tosylprolinol **134** reacted smoothly with the 2-(3,4-dimethoxyphenyl)-1,3-dithiane **135**, in spite of this relatively hindered primary centre to generate the substituted product **136** in good yield (76 %), as shown in **Scheme 48**.



134 **135** **136**

Scheme 48

In order to prepare ketone **110**, we proposed a coupling reaction between 3α-tosyloxymethyltropane **137** and thioacetal **138** to generate thioacetal **139**. The final step in the synthesis would only require the removal of the protecting groups from **139** as illustrated in **Scheme 49**. The synthesis of tropane **137** and thioacetal **138** are discussed in the following sections.



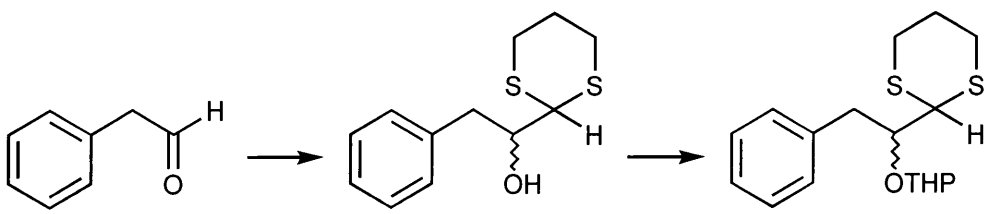
137 138 139 110

Scheme 49

2.3.2 Thioacetal precursor synthesis

2.3.2.1 Introduction

Starting from phenylacetaldehyde **140**, it was anticipated that the synthesis of thioacetal **138** would be straightforward. The first step in the synthesis of **138** required the preparation of **141**. Such compounds have already been reported in the literature[101] and are successfully prepared by the reaction of aldehydes with 2-lithio-1,3-dithianes. Protection of the hydroxyl group with THP was expected to give thioacetal **138**, as depicted in **Scheme 50**.

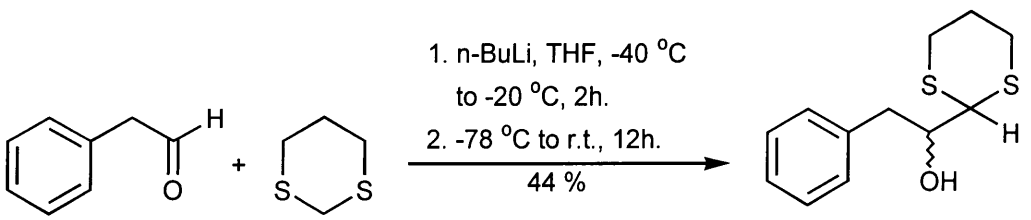


140 141 138

Scheme 50

2.3.2.2 Synthesis of thioacetal 138

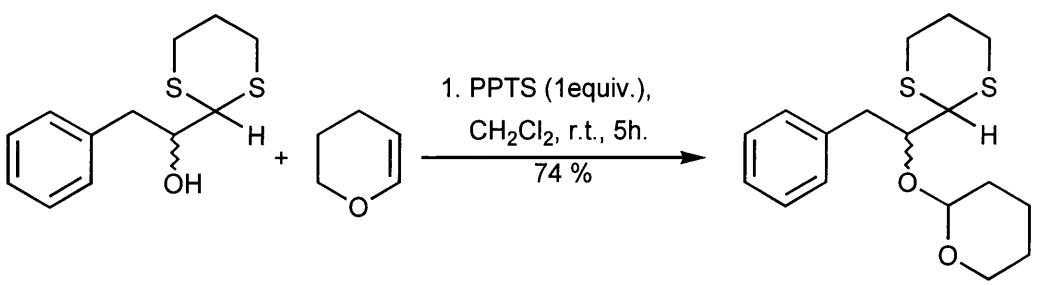
In the event, compound **141** was readily prepared by the reaction of phenylacetaldehyde **140** with the anion of 1,3-dithiane **142** at -78 °C, as depicted in **Scheme 51**. According to the method described by Corey and Seebach[102], the anion was generated with n-butyllithium between -20 and -40 °C in THF. Compound **141** was purified over silica gel and obtained as a light-brown liquid in moderate yield (44%). The reverse addition of the dithiane anion was also explored in the hope of improving the yield. However, this offered no improvement (42%).



140 **142** **141**

Scheme 51

Protection of the hydroxyl group of **141** as a tetrahydropyranyl (THP) ether followed the method described by Miyashita[103] *et al.* (1977). Thus treatment of **141** with 3,4-dihydro-2H-pyran **143** in pyridinium *p*-toluenesulfonate (PPTS) was carried out, as shown in **Scheme 52**. Thioacetal **138** was, as expected, a mixture of two diastereoisomers and was purified over silica gel. However, presence of some starting material (as an almost 1:1 mixture) could be still detected by ^{1}H and ^{13}C NMR, and GC-MS. This may be a disadvantage of the silica gel purification

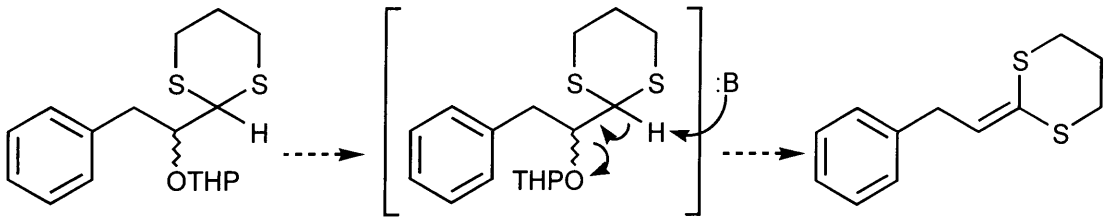


141 **143** **138**

Scheme 52

2.3.2.3 Potential problem of thioacetal 138, and its replacement by thioacetal 147

It was anticipated that thioacetal **138**, when treated with a base, might generate the corresponding 2-phenylethylidine-1,3-dithiane **144**, following the mechanism shown in **Scheme 53**. It has already been reported that[104] 2-(tetrahydrofuran-2-yl)-1,3-dithiane **145** gave the corresponding unsaturated alcohol **146**, when treated with a strong base such as n-BuLi or LDA, as depicted in **Figure 7**.



138 **144**

Scheme 53

145 **146**

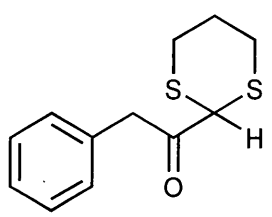
Figure 7: Decomposition of the thioacetal **145** to the coresponding unsaturated alcohol **146** upon treatment with a strong base.

Therefore it became necessary to design an alternative thioacetal compound, in which the following criteria are met:

i) Stabilisation of anion when treated with a base

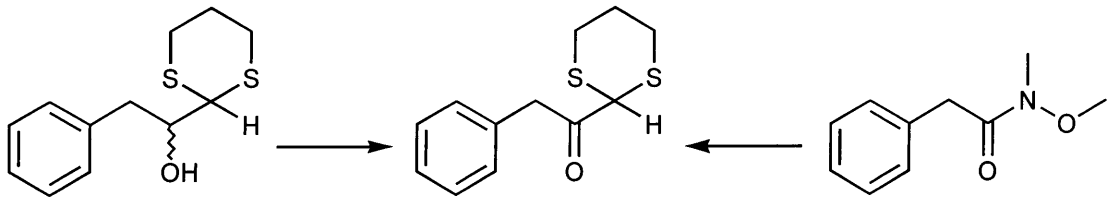
ii) Generation of an hydroxyl group after the coupling reaction.

It was judged that 2-phenylacetyl-1,3-dithiane **147** would be ideal for this purpose.



147

Addition of 2-lithio-1,3-dithianes to aldehydes, followed by Swern oxidation is reported as a general method for the preparation of 2-acyl-1,3-dithianes[105]. Alternatively, N-methoxy-N-methyl amides[106] proved to be efficient in the acylation of 2-lithio-1,3-dithianes and gave the corresponding 2-acyl-1,3-dithianes in high yields ranging from 80 to 95 %. However, acylation of 2-lithio-1,3-dithianes with esters[105] and acid chlorides[107] commonly resulted in double alkylations and deprotonations[101]. Therefore, it was anticipated that the target molecule **147** could be readily prepared either by the Swern oxidation of **141** or by the reaction of 2-lithio-1,3-dithianes with N-methoxy-N-methyl amide **148**, as illustrated in **Scheme 54**. Preparation of amide **148** has already been described in the literature[108,109,110] in good to excellent yields (69-100%).

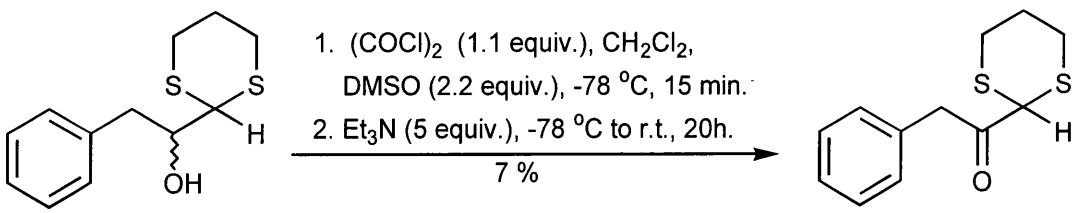


141 **147** **148**

Scheme 54

2.3.2.4 Synthesis of alternative thioacetal 147

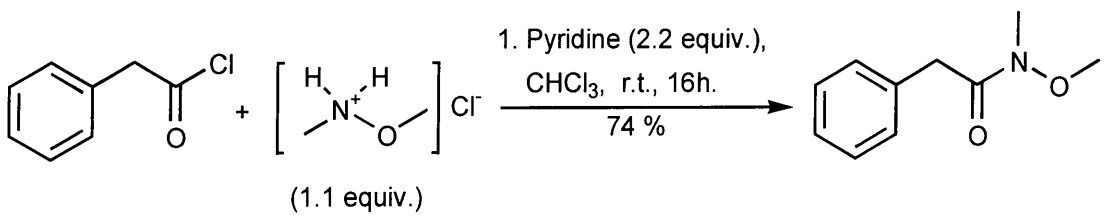
With **141** in hand, Swern oxidation[111] was initially investigated. The Swern oxidation required the activation of dimethylsulfoxide (DMSO) by oxalyl chloride [$(COCl)_2$] at low temperature (-78 °C), followed by the addition of **141** and triethylamine (Et_3N), as shown in **Scheme 55**. The target thioacetal compound **147** was purified over silica gel and obtained as a white solid in low yield (7 %).



141 **147**

Scheme 55

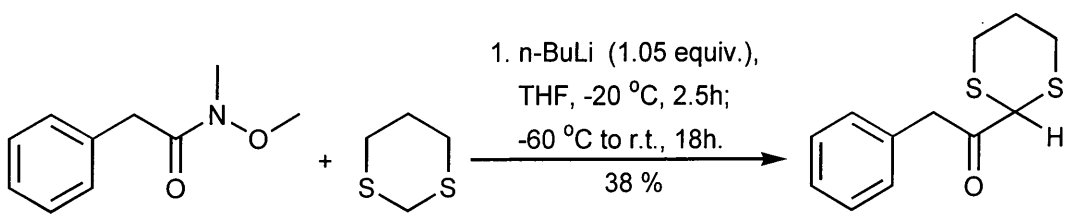
This conversion was unsatisfactory and therefore an alternative method was explored begining with the synthesis of amide **148**. Following the method described by Sibous[109] and Tipping, amide **148** was readily prepared from the reaction of phenylacetyl chloride **149** with N-methoxy-N-methylamine hydrochloride **150** in the presence of pyridine, as depicted in **Scheme 56**. Amide **148** was purified by distillation and obtained in good yield (74%), an improvement on the previous synthesis.



149 **150** **148**

Scheme 56

Amide **148** was then subjected to the condensation reaction with the anion derived from 1,3-dithiane **142**, as depicted in **Scheme 57**. The resultant thioacetal **147** was this time purified over neutral alumina and isolated as a white solid in fairly low yield (19 %). However, with the use of excess of amide **148**, compound **147** could be recovered in 38 % yield.

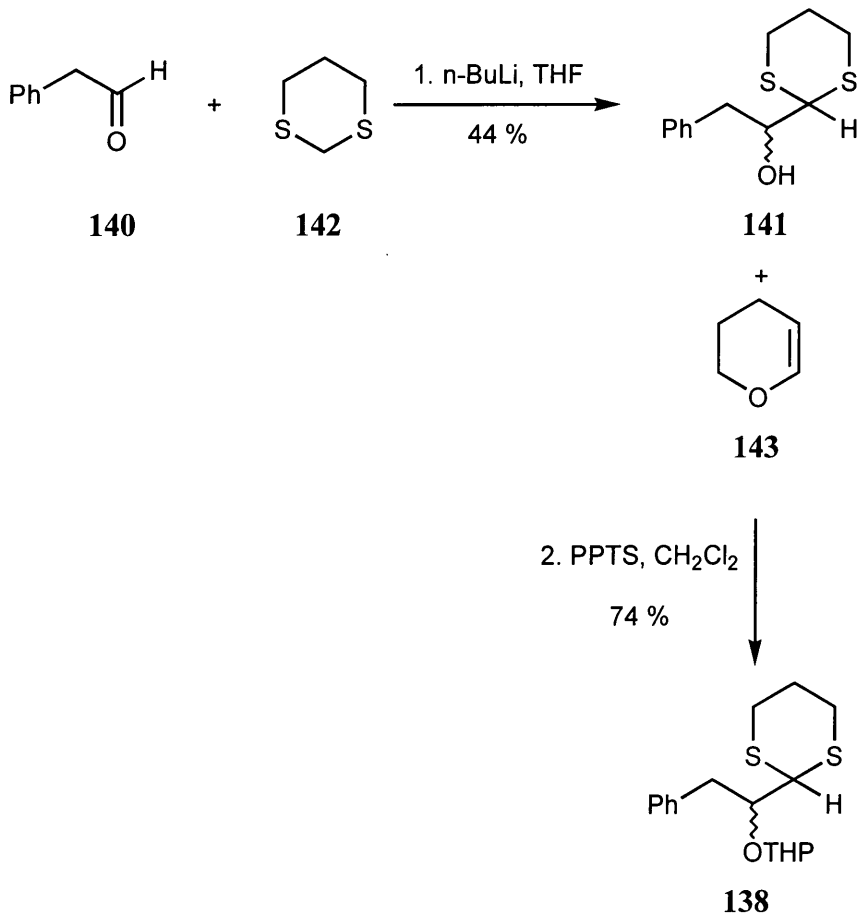


148 **142** **147**

Scheme 57

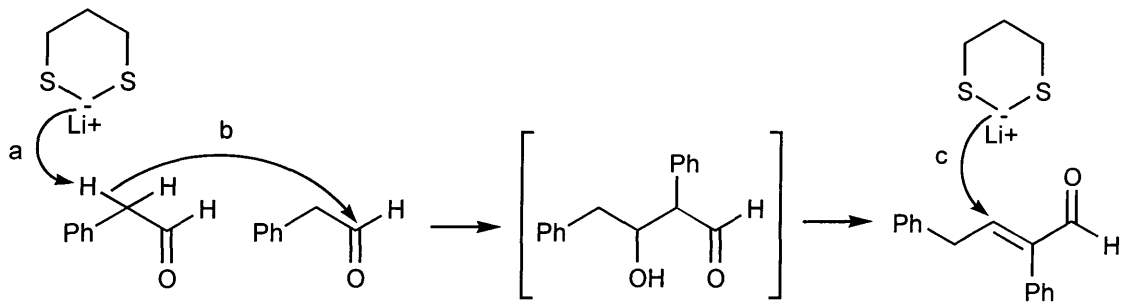
2.3.2.5 Discussion

Thioacetal **138**, required for the coupling reaction, was prepared starting from phenylacetaldehyde **140**, as depicted in **Scheme 58**.



Scheme 58

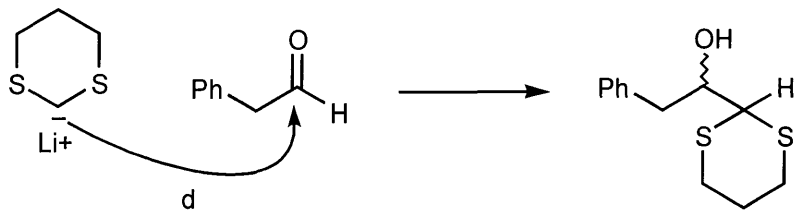
The moderate yield (44 %) for the first step may be explained by the mechanism[112] shown below. If the dithiane anion abstracts one of the α-protons from aldehyde **140** (path a), this anion would attack another aldehyde **140** (path b), leading to the formation of the aldol product **151**. Dehydration of **151** would then give the α,β-unsaturated aldehyde **152**, which is also liable to Michael attack (path c). These are shown in **Scheme 59**.



140 **140** **151** **152**

Scheme 59

If the dithiane anion attack occurs as depicted in **Scheme 60** (path d), then compound **141** could be generated from aldehyde **140**. Inverse addition[105], which keeps the concentration of highly reactive dithiane anion low with respect to the aldehyde[113], is generally known to increase the yield by circumventing side-product formations. However, this did not have a demonstrable effect in our hands. A chiral centre in a molecule makes prochiral centres throughout the molecule non-equivalent[114]. Therefore, carbons adjacent to the sulphur atom in **141** became resolved, but could not be assigned unambiguously in the ^{13}C NMR spectra.



140 **141**

Scheme 60

The THP oxygen undergoes an α-cleavage in mass spectroscopy, as illustrated in **Figure 8**. This is an important process in identifying the presence of a THP ether and produces a peak at 85 amu, which often dominates the spectrum[115]. In our case the peak at 85 amu was therefore attributed to the formation of **138**. The preparation of this compound however still requires optimisation.

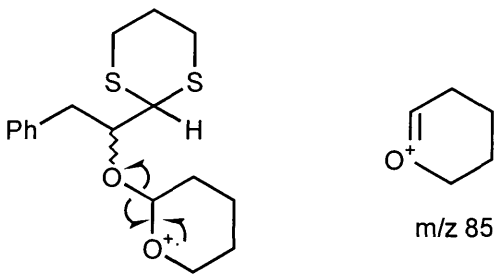
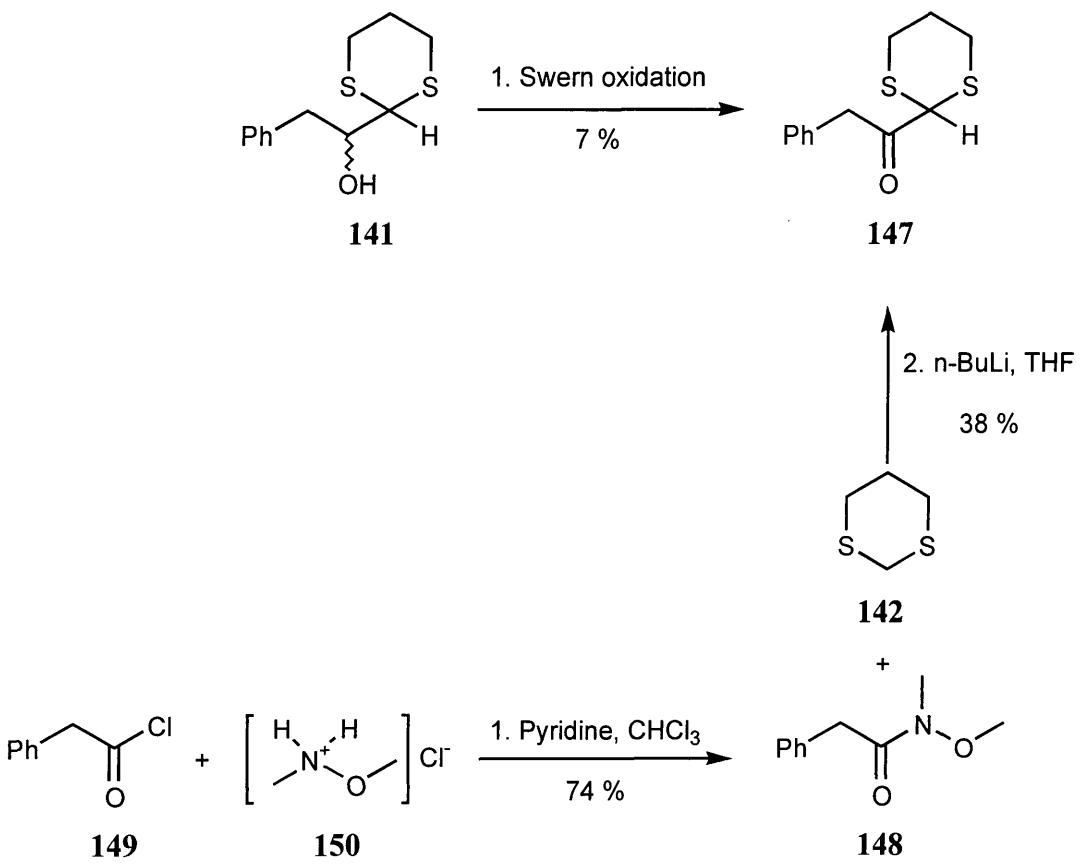


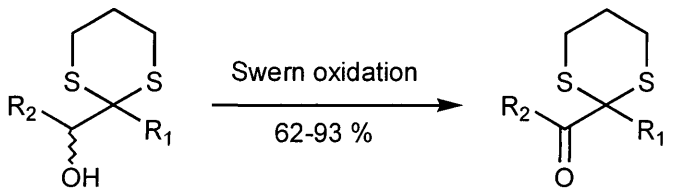
Figure 8: An α-cleavage of THP oxygen of **138** in mass spectroscopy and the corresponding ion at 85 amu.

Thioacetal **147**, an alternative substrate to THP protected thioacetal **138**, was also prepared successfully either from **141** or starting from phenylacetylchloride **149**, as illustrated in **Scheme 61**.



Scheme 61

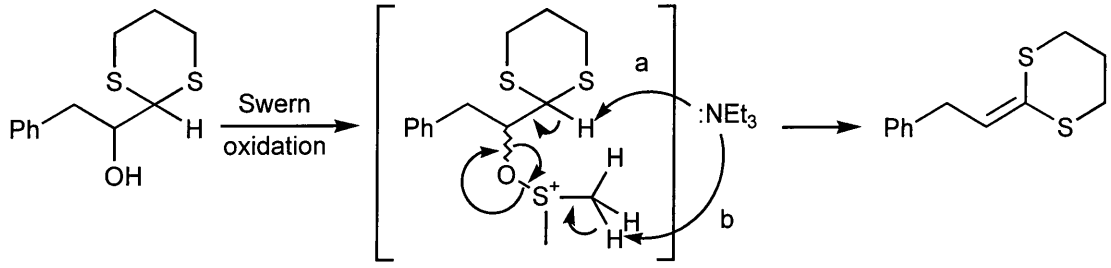
The Swern oxidation of **141** gave a disappointingly low yield (7 %), despite other successful Swern oxidations of e.g. 2-(1'-hydroxyalkyl)-2-alkyl-1,3-dithianes[116] **153** to 2-acyl-2-alkyl-1,3-dithiane **154** in high yields (62-93 %), as depicted in **Scheme 62**.



153 **154**

Scheme 62

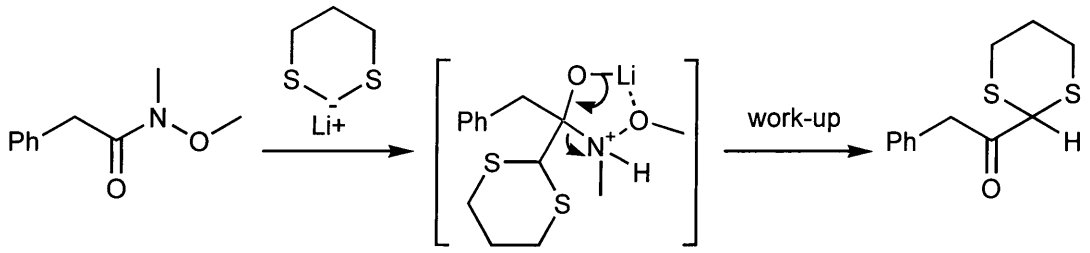
It became apparent from the above reaction that the low yield (7 %) was due to the presence of the acidic proton at the C2 position of thioacetal **141**. On addition of triethylamine (Et_3N), this proton (path a) was probably abstracted faster than the proton of the sulfoxonium salt (path b) and thus led to the formation of 2-phenylethylidine-1,3-dithiane **144** in an elimination reaction, as depicted in **Scheme 63**.



141 **144**

Scheme 63

Amide **148** was readily prepared from phenylacetyl chloride **149** in good yield (74 %) and then was indeed successfully employed in the synthesis of thioacetal **147**, however the yield was still low (38 %). This improvement was possibly due to the methoxyl oxygen[109], which is capable of coordinating to Li metal, as shown in **Scheme 64**. This may suppress carbonyl formation until aqueous work-up, and prevent any side product formation and thus furnish thioacetal **147** as suggested by Seebach[117] and Corey.



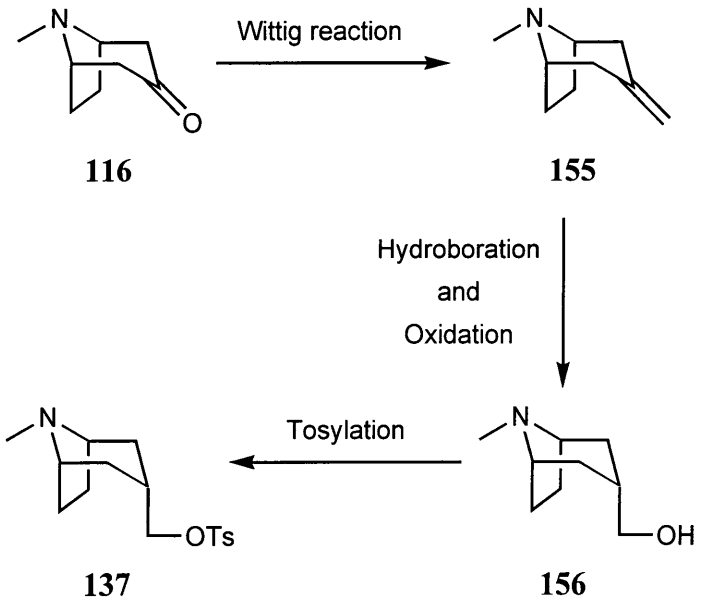
148 **147**

Scheme 64

2.3.3 Functionalised tropane precursor synthesis

2.3.3.1 Introduction

Starting from tropinone **116**, it was anticipated that 3α-tosyloxymethyltropane **137** could be prepared, following the route described by Murr[118] *et al.* This route, in the first instance, requires the preparation of 3-methylenetropane **155** by Wittig reaction of **116**. Hydroboration of **155** with disiamylborane (Sia_2BH), followed by oxidation with alkaline hydrogen peroxide was expected to give 3α-hydroxymethyltropane **156**. Treatment of **156** with n-butyllithium and the addition of p-toluenesulfonyl chloride would then generate the tosyl compound **137**, as depicted in **Scheme 65**.

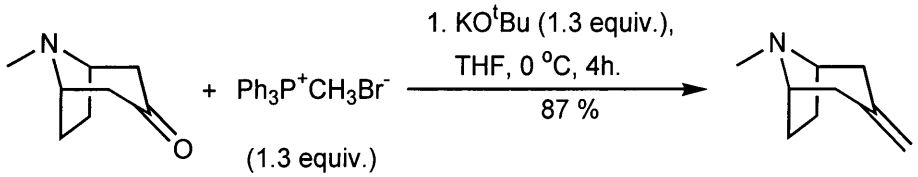


116 **155** **156** **137**

Scheme 65

2.3.3.2 Attempted synthesis of 3α-tosyloxymethyltropane 137

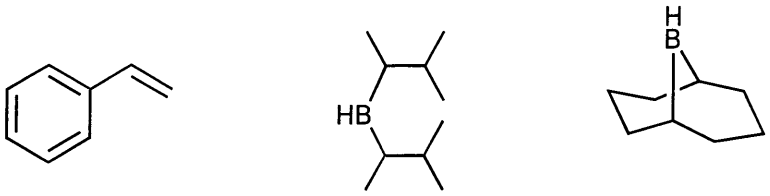
In the event, 3-methylenetropane **155** was readily prepared, following the method described by Murr[118] *et al.* This required the addition of tropinone **116** to a solution of methylenetriphenylphosphine, which was generated from a mixture of methyltriphenylphosphonium bromide **157** and potassium *tert*-butoxide in THF (**Scheme 66**). Compound **155** was purified by distillation and isolated as oil in good yield (87 %).



116 **157** **155**

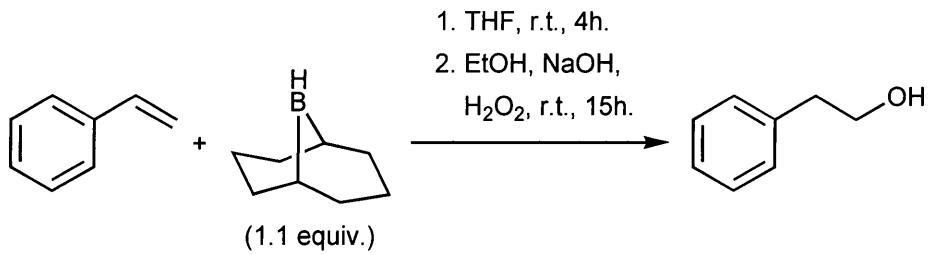
Scheme 66

The next step required hydroboration and it was necessary to establish the hydroboration protocol on a model system. Therefore, styrene **158** was selected and subjected to hydroboration with disiamylborane[119] (Sia_2BH) **159** and 9-borabicyclo[3.3.1]nonane[120] (9-BBN) **160**.



158 Sia_2BH **159** 9-BBN **160**

When Sia_2BH **159** was used, no reaction was observed at all. Fortunately, the use of 9-BBN **160** successfully generated 2-phenylethyl alcohol **161**, as depicted in **Scheme 67**. The various conditions are summarised in **Table 6**.



(1.1 equiv.)

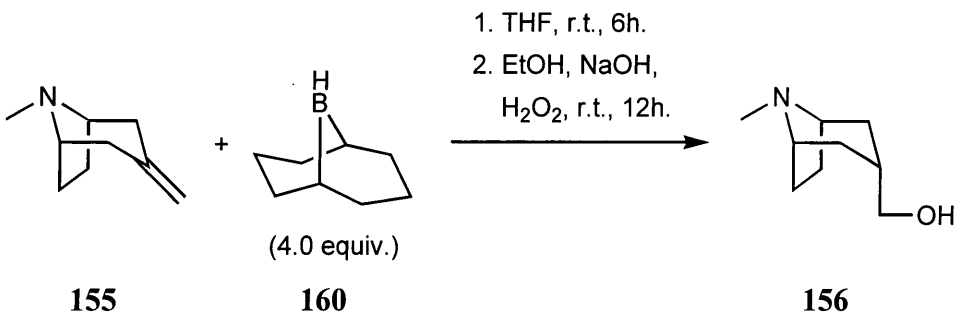
158 **160** **161**

Scheme 67

Entry	olefin	hydroborating agent	NaOH	H_2O_2	Reaction
1	**158** (10.00 mmol)	Sia_2BH **159** (12.00 mmol)	5 ml, 3 M	5 ml, 27.5 %	No
2	**158** (3.00 mmol)	Sia_2BH **159** (3.38 mmol)	1 ml, 6 M	2 ml, 27.5 %	No
3	**158** (8.73 mmol)	9-BBN **160** (9.60 mmol)	2 ml, 6 M	5 ml, 27.5 %	YES

Table 6: Hydroboration and oxidation of styrene **158** under different conditions.

After the modest but promising result of the hydroboration of styrene **158**, 3-methylenetropane **155** was then subjected to hydroboration with 9-BBN[120] **160** and Sia_2BH[119] **159**. No reaction could be achieved with Sia_2BH **159** under a variety of different conditions. Some success was achieved however, when compound **155** was treated with a four-fold excess of 9-BBN **160**, as shown in **Scheme 68**.



155 **160** **156**

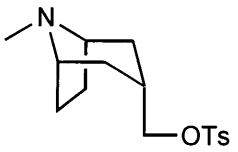
Scheme 68

In the event, neither **155** nor **156** could be isolated. Attempted distillation of the reaction mixture almost certainly lead to loss of the desired alcohol **156**, leaving only the *cis*-1,5-cyclooctanediol, an alcohol generated from the oxidation of 9-BBN **160**. This reaction needs further investigation. In addition, compound **155** was also subjected to hydroboration with BH_3.THF, following the method described by Lyle[121] *et al.* However, despite some effort no reaction was observed. The various conditions are summarised in **Table 7**.

Entry	olefin	hydroborating agent	NaOH	H_2O_2	Reaction
1	**155** (3.24 mmol)	Sia_2BH **159** (1.24 equiv.)	2 ml, 3 M	2 ml, 27.5 %	No
2	**155** (2.00 mmol)	9-BBN **160** (2.00 equiv.)	2 ml, 3 M	2 ml, 27.5 %	No
3	**155** (3.00 mmol)	Sia_2BH **159** (4.00 equiv.)	4 ml, 3 M	8 ml, 27.5 %	No
4	**155** (2.00 mmol)	9-BBN **160** (4.00 equiv.)	2 ml, 6 M	5 ml, 27.5 %	YES
5	**155** (2.00 mmol)	BH_3.THF (1.80 equiv.)	1 ml, 9M	3 ml, 27.5 %	No

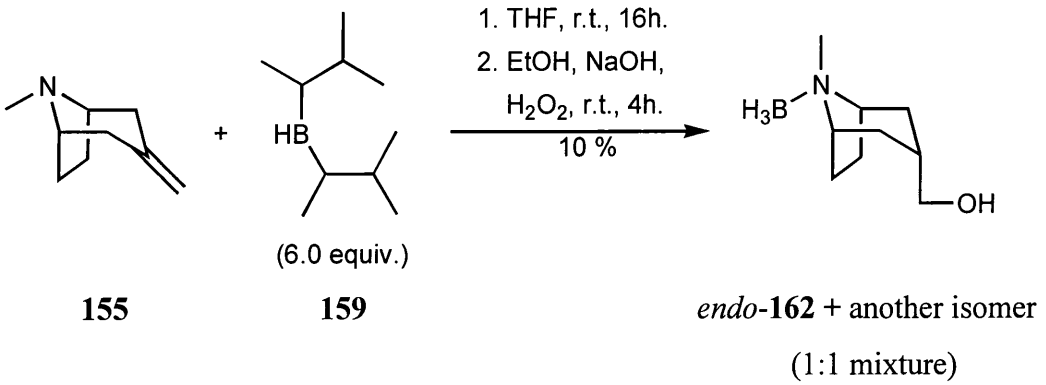
Table 7: Hydroboration and oxidation of 3-methylenetropane **155** under different conditions.

In order to proceed with the synthesis of the target electrophile **137**, hydroboration of 3-methylenetropane **155** was re-investigated under two different sets of conditions.



137

In the first case, **155** was subjected to hydroboration by *in situ* preparation of Sia_2BH **159** following the literature method described by Brown[119] and Zweifel, as shown in **Scheme 69**. The reaction generated a product, which emerged to be a 1:1 mixture of stereoisomers, as determined from the ^1H NMR spectrum, showing a set of doublets at δ 3.63 and 3.58 ppm for the methylene protons of CH_2OH moiety for each stereoisomer. The ^{13}C NMR spectrum, shown in **Figure 9**, also indicated that the stereoisomers were present in a 1:1 ratio. One of the isomer was later revealed to be the *endo* BH_3-N complex **162** (see **Figure 11**, p. 62). The product mixture was purified by chromatography and isolated as viscous oil. The yield of this reaction was however disappointingly low (10%).



155 **159** *endo*-**162** + another isomer (1:1 mixture)

Scheme 69

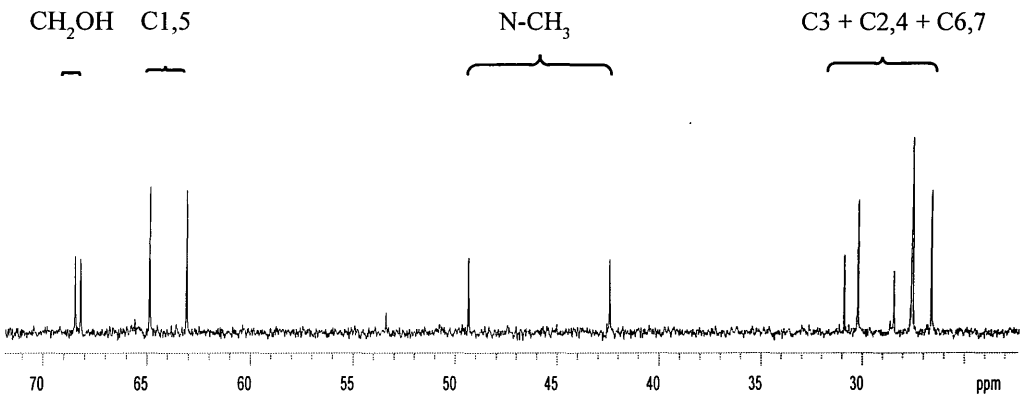
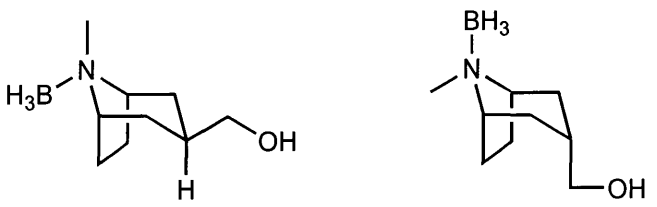


Figure 9: The ^{13}C NMR spectrum of *endo*-**162**, showing the presence of another isomer in a 1:1 ratio.

Another isomer, present as a 1:1 mixture with *endo*-**162** can have two potential origins: either it is an *exo* isomer **162** as a result of the hydroboration or it is a diastereomeric *endo* BH_3 complex **162** with a different BH_3 configuration at nitrogen, as depicted in **Figure 10**.



exo-**162** *endo*-**162**

(BH_3 is in *ax* position)

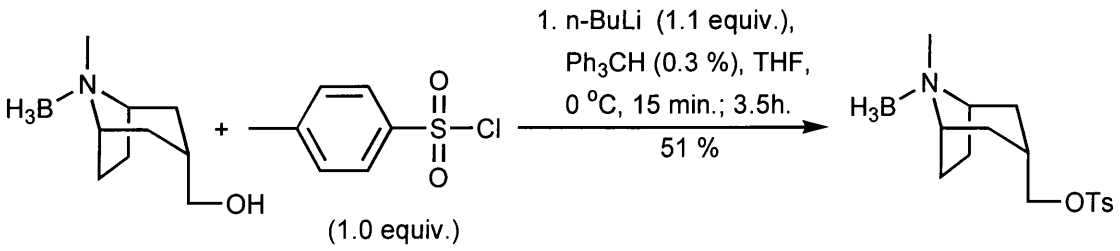
Figure 10: Structures of the two possible isomers present as a 1:1 mixture with *endo*-**162** (BH_3 is in *eq* position).

When Sia_2BH **159** (4.6 equiv.) was used, the yield did not significantly increase (12 %). In an attempt to improve the yield, reverse addition of the reagents was explored, with Sia_2BH **159** (5.0 equiv.). However, no hydroboration was observed at all in this case. To optimise the reaction conditions and to increase the isomer ratio, 3-methylenetropane **155** was also submitted to hydroboration by *in situ* preparation of 9-BBN **160**, under three different sets of conditions (**Table 8**). However, in each case no hydroboration product was observed.

Entry	Hydroborating agent (equiv.)	Quenching agent (ml)	6M NaOH (ml)	28 % H_2O_2 (ml)	Yield (%)
1	Sia_2BH (4.6)	MeOH (5.0)	20	40	12
2	Sia_2BH(5.0)	H_2O (1.0)	7	14	-
3	Sia_2BH (6.0)	EtOH (7.0)	5	8	10
4	9-BBN (2.2)	MeOH (0.5)	3	6	-
5	9-BBN (3.3)	MeOH (1.0)	5	10	-
6	9-BBN (4.4)	MeOH (1.5)	7	14	-

Table 8: Optimised hydroboration and oxidation conditions of 3-methylenetropane **155**.

With N-borane-3α-hydroxymethyltropane **162** in hand, the compound **162** was subjected to tosylation, following the method described by Murr[118] *et al.* (1991). The method first requires generation of the alkoxide with n-butyllithium in the presence of a catalytic amount of triphenylmethane (Ph_3CH), and then addition of tosyl chloride **163**, as shown in **Scheme 70**. The reaction generated a tosyl compound **164** was also a 1:1 mixture of two stereoisomers.



162 **163** *endo*-**164** + another isomer (1:1 mixture)

Scheme 70

One isomer was successfully purified by chromatography and isolated as a white solid. A suitable crystal of this isomer was obtained by re-crystallisation from petroleum ether and was submitted for X-ray analysis. Surprisingly, at the time, the isomer was revealed to be a BH_3-N complex and its tosyloxymethyl group was indeed had the *endo* configuration, as required for the target stereoisomer. The X-ray structure of the isomer is illustrated in **Figure 11**. It was concluded in retrospect that one of the mixtures in the

product alochol **162** obtained from the hydroboration reaction was also a BH_3-N complex with an *endo* hydroxymethyl configuration.

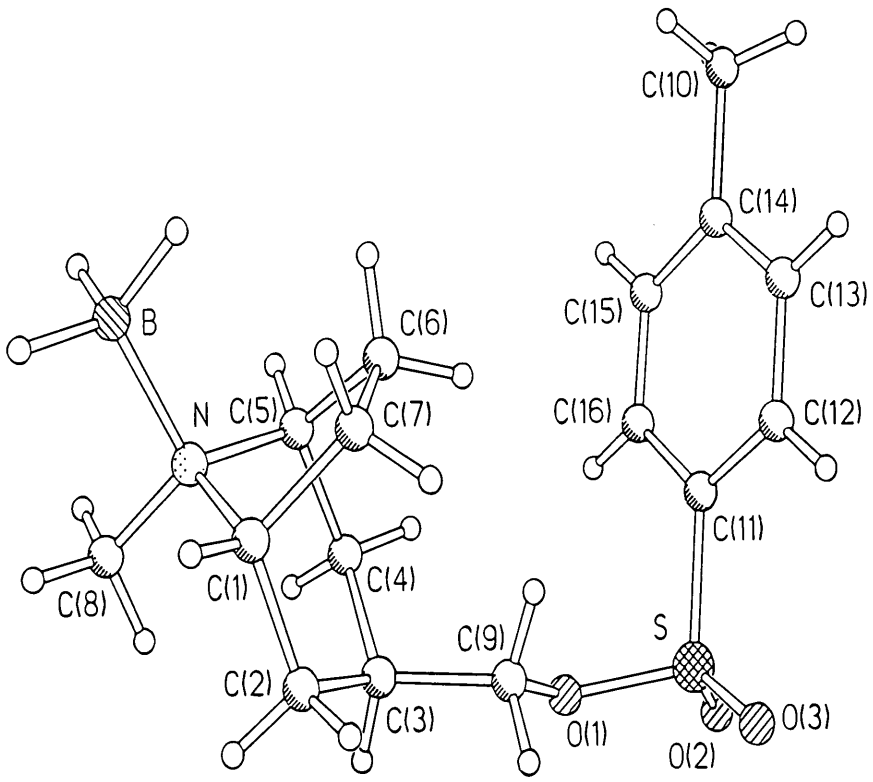
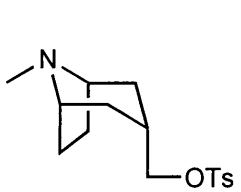


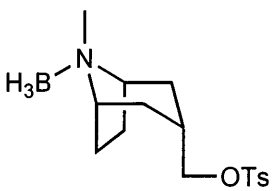
Figure 11: The X-ray crystal structure of the *endo* BH_3-N complex **164**.

2.3.3.3 Synthesis of N-Troc-3α-tosyloxymethyltropane 137

The preparation of 3α-tosyloxymethyltropane **137** was unsuccessful in our hands due to complex **164**, which formed between diborane and the nitrogen of the tropane ring.



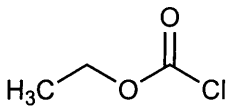
137



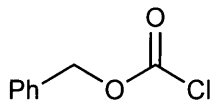
164

To succeed it became necessary to deactivate the N-methyl group. This can be achieved by urethane formation by reaction with ethyl chloroformate **165**, benzyl chloroformate **166** or 2,2,2-trichloroethyl chloroformate (TrocCl) **167**. This strategy has been known

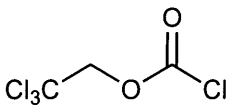
for some time in the alkaloid field[122] and among these urethanes TrocCl **167** is reported to be a valuable protecting group for tropane nitrogen[123].



165

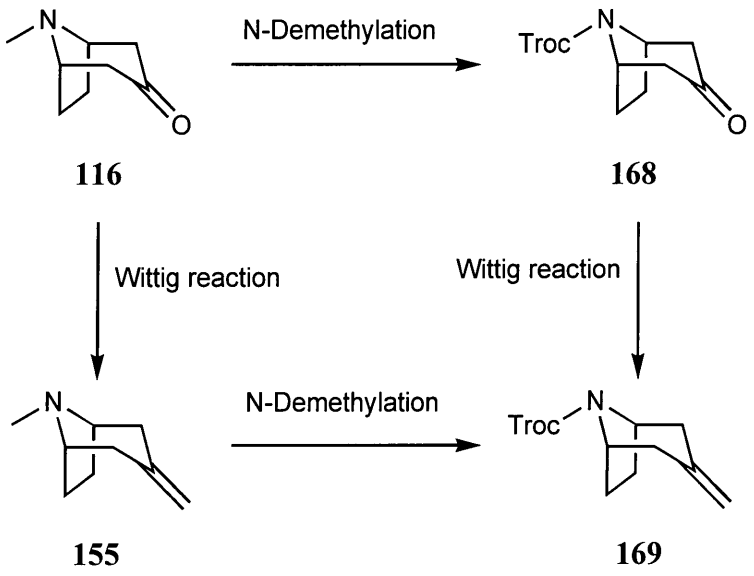


166



TrocCl **167**

It was anticipated that either the N-methyl group of tropinone **116** or 3-methylenetropane **155** could be deactivated in this way, as depicted in **Scheme 27**, to generate **168** or **169**. Such a reaction of **116** with TrocCl **167** has already been described by Montzka[123] *et al.*

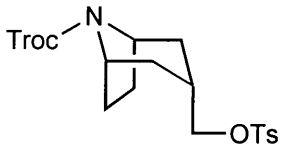


116 **168**

155 **169**

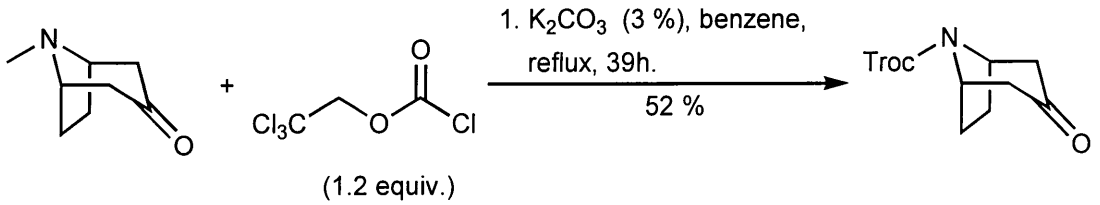
Scheme 71

The required urethane electrophile, in this case, N-Troc-3α-tosyloxymethyltropane **170** should be readily prepared, following the same route described for 3α-tosyloxymethyltropane **137**. After hydroboration-oxidation, re-conversion of Troc into the necessary N-methyl group should be readily achieved by a $LiAlH_4$ reduction. During the synthesis of scopine, pseudoscopine and epoxytropanes, a similar conversion by Justice[124,125] and Malpass has already been reported.



170

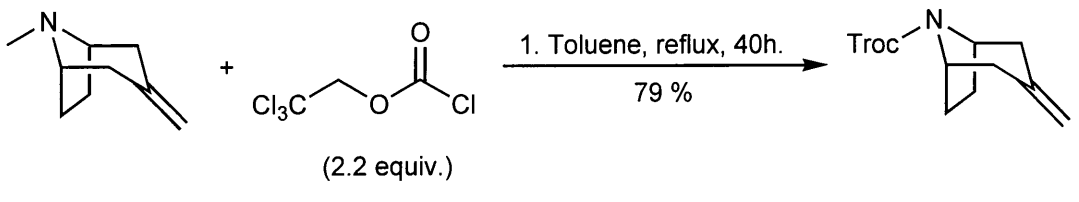
First, N-demethylation of tropinone **116** was carried out following the method described by Montzka[123] *et al.* This involved the reaction of **116** with 20% excess of TrocCl **167** in refluxing benzene with a catalytic amount of K_2CO_3, as shown in **Scheme 72**. Compound **168** was purified by column chromatography and isolated as a white amorphous solid in a moderate yield (52%).



116 TrocCl **167** **168**

Scheme 72

Next, N-demethylation of 3-methylenetropane **155** with TrocCl **167** was explored. The reaction was carried out in refluxing toluene, following the method described by He[126] and Brossi, as shown in **Scheme 73**. The absence of a catalytic amount of K_2CO_3 differs from the previous method. Again compound **169** was purified by column chromatography and was isolated as clear oil in good yield (79%). This compound solidified on standing.

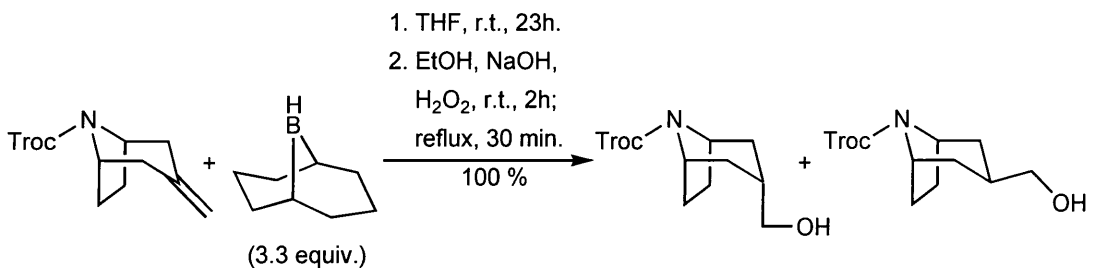


155 TrocCl **167** **169**

Scheme 73

Compound **169** was then submitted to hydroboration by *in situ* preparation of 9-BBN **160** following the literature methods[120,127], as shown in **Scheme 74**. The resultant alcohol

171 was purified by chromatography and isolated as viscous oil in excellent yield (100 %). However, compound **171** was a mixture of two isomers with an *endo/exo* ratio of ~3:1, as determined from ^{1}H NMR spectrum.

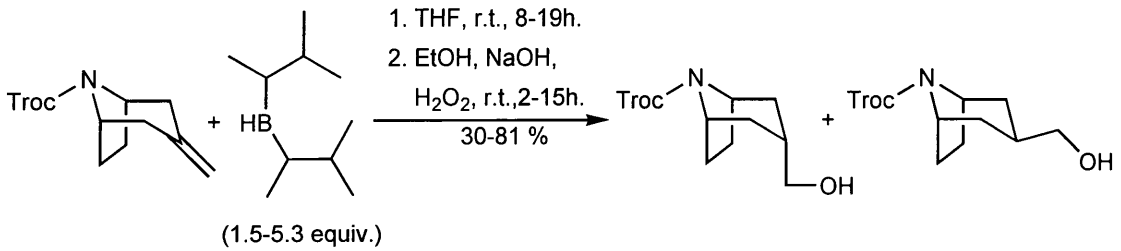


169 **160** *endo*-**171** / *exo*-**171**

(3 : 1)

Scheme 74

The ^{13}C NMR spectrum of **171** showed a peak at δ 67.4 ppm for the *endo* and δ 67.6 ppm for the *exo* carbon resonances of -CH_2OH moiety. In an attempt to increase the isomer ratio in the favour of the *endo* product, compound **169** was also subjected to hydroboration by *in situ* preparation of more bulky Sia_2BH[119] **159**, as depicted in **Scheme 75**, using a variety of different conditions (see **Table 9**, p. 66).



169 **159** *endo*-**171** / *exo*-**171**

(18 -73 : 1)

Scheme 75

The resultant compound **171** was purified by chromatography and isolated as oil in up to 81 % yield. Compound **171** was also a mixture of two isomers, and this time the *endo/exo* isomer ratio, which was determined by ^{1}H NMR analysis, increased substantially, varying from 18:1 to 73:1 in different experiments in favour of the *endo* isomer. These experiments are summarised in **Table 9**.

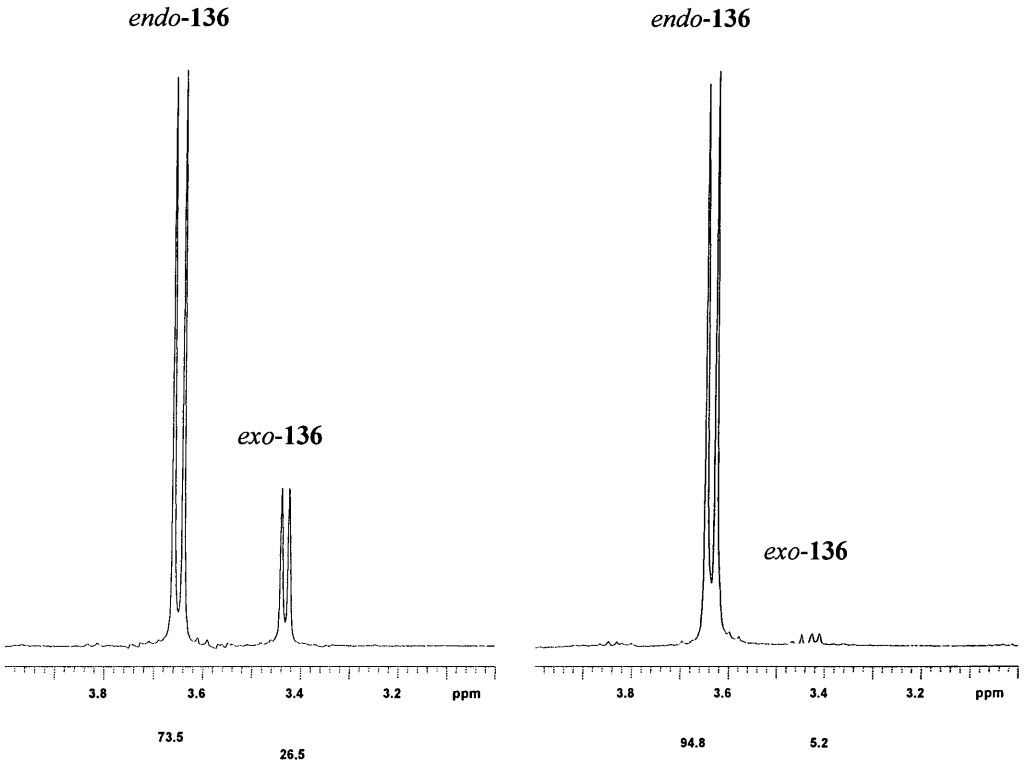
Entry	Hydroborating agent (equiv.)	Quenching agent (ml)	6M NaOH (ml)	28 % H_2O_2 (ml)	Yield (%)	isomer ratio (*endo*/*exo*)
1	Sia_2BH[a] (1.5)	H_2O (0.5)	3	6	30	18:1
2	Sia_2BH[a] (3.0)	H_2O (1.0)	4	8	38	21:1
3	Sia_2BH[a] (3.5)	H_2O (0.5)	4	8	68	43:1
4	Sia_2BH[a] (5.3)	H_2O (2.0)	2	2	81	73:1

a) prepared readily by treating a mixture of 2-methyl-2-butene and sodium borohydride either in THF or diglyme (entry 4) with boron trifluoride diethyl etherate at -10 to 0 °C.

Table 9: Optimised conditions of hydroboration and oxidation of N-Troc-3-methylenetropane **169**.

Compound **169** was finally subjected to hydroboration with Sia_2BH **159** (8.0 equiv.), a reagent which was prepared from borane-THF complex (1.0 M solution in THF) and 2-methyl-2-butane (2.0M solution in THF) using a kit supplied by the Aldrich Chemical Company. However, no hydroboration reaction was observed at all.

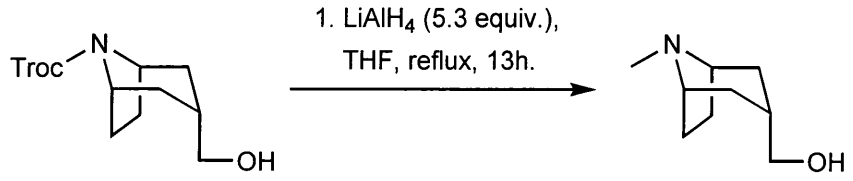
Thus, it was demonstrated that the more bulky alkyl groups on the Sia_2BH **159**, when compared to the 9-BBN **160**, increase the isomer ratio substantially. A typical set of ^1H NMR spectra for **171**, showing the *endo* (δ 3.65 ppm) and *exo* (δ 3.43 ppm) methylene resonances of $-CH_2OH$ moiety, are shown in **Figure 12** for 9-BBN and Sia_2BH.



9-BBN (as **Scheme 74**, p. 65) Sia_2BH (**entry 1**, **Table 9**, p. 66)

Figure 12: Typical ^1H NMR spectra for **171**, showing the *endo* and *exo* methylene resonances of the CH_2OH moiety.

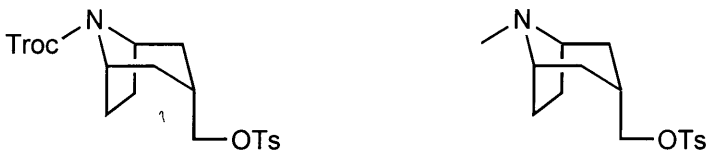
Reduction of the Troc group was required now to reconvert the protecting group into an N-methyl group and provide the required 3α-hydroxymethyltropane **156**. Therefore compound **171** was subjected to reduction by $LiAlH_4$ in refluxing THF following the method described by Justice[124,125] and Malpass, as illustrated in **Scheme 76**. The ^1H NMR analysis of the crude material did not indicate the presence of the carbamate moiety (4.50-5.00 ppm) and were now two methyl singlets at 2.22 and 2.23 ppm. Although the ^1H NMR analysis was encouraging, t.l.c. analysis of the crude material indicated a complex mixture.



171 **156**

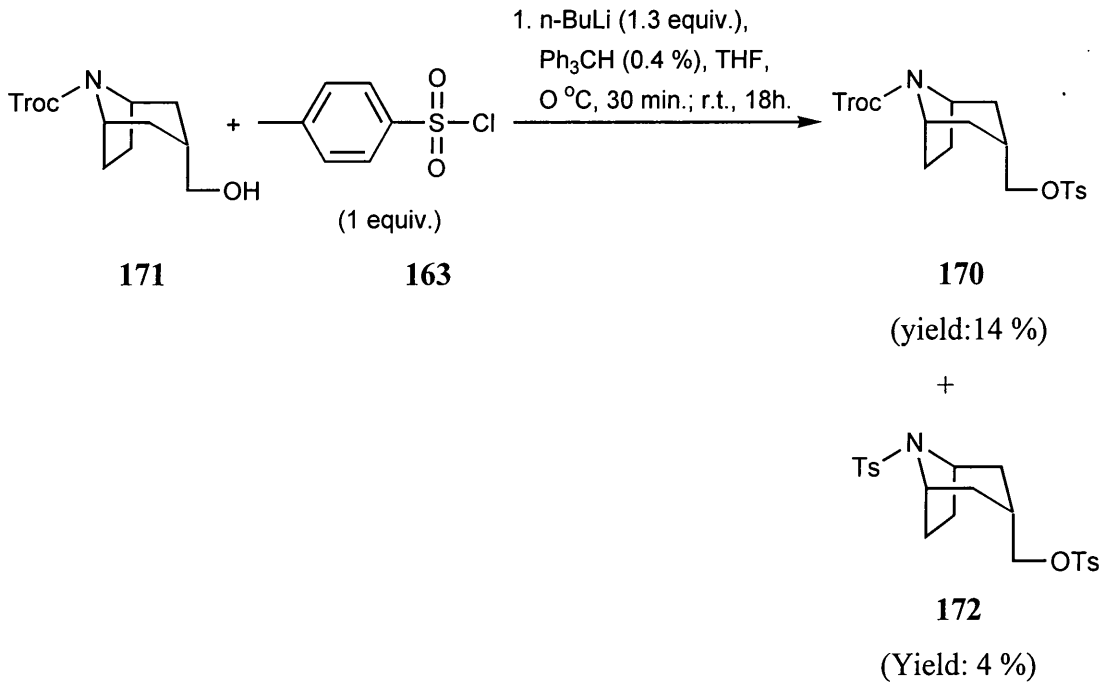
Scheme 76

In view of this, N-Troc-3α-tosyloxymethyltropane **170** emerged as an alternative electrophile to 3α-tosyloxymethyltropane **137** for the coupling reaction. It was anticipated that synthesis of **170** should be straightforward, following the tosylation method described by Murr[118] *et al.*



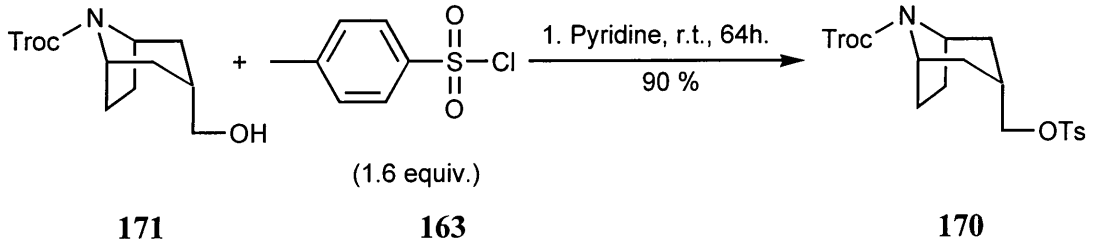
170 **137**

To develop this strategy, compound **171** was treated with p-toluenesulfonyl chloride **163**, in the presence of n-BuLi and a catalytic amount of triphenylmethane (Ph_3CH), as depicted in **Scheme 77**. After purification over silica gel, tosylate **170** was isolated in low yield (14 %), but N-tosylamide **172** was also isolated as a by-product in low yield (4 %).



Scheme 77

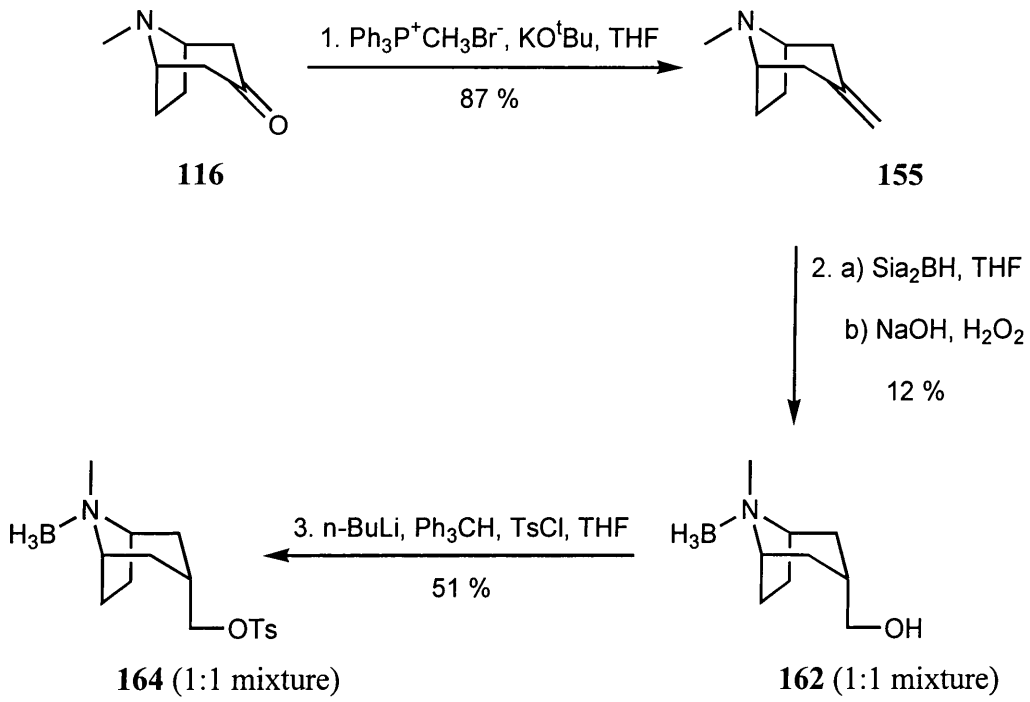
This low yield (14 %) was disappointing and therefore the method described by Prisbe[128] *et al.* was explored, as shown in **Scheme 78**. This required treatment of **171** with tosyl chloride **163** in the presence of the much milder base, pyridine. Following the work-up described by Furniss[129] *et al.* involving purification over neutral alumina, tosylate **170** was this time isolated as a white solid and in excellent yield (90%).



Scheme 78

2.3.3.4 Discussion

Tosyloxymethyltropane, required for the coupling reaction, could only be prepared as its BH_3 complex **164**, as shown in **Scheme 79**.



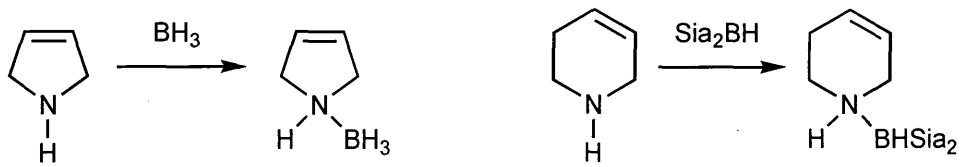
116 **155**

164 (1:1 mixture) **162** (1:1 mixture)

Scheme 79

The first step involved the preparation of 3-methylenetropane **155** from tropinone **116** in excellent yield (87 %), but the next step, hydroboration of **155** proved to be very difficult and generated **162** as a 1:1 mixture in a disappointingly low yield (12 %). The final step was the tosylation of **162**, which proceeded in only moderate yield (51 %) to give the final product **164**. The X-ray crystal structure analysis of **164** offered a method not only for assigning the stereochemistry of **164**, but also for assigning the stereochemistry of the alcohol **162**. Clearly as compound **164** had the tosyloxymethyl group in the *endo* configuration, this tells us retrospectively that alcohol **162** must also have possessed the *endo* configuration.

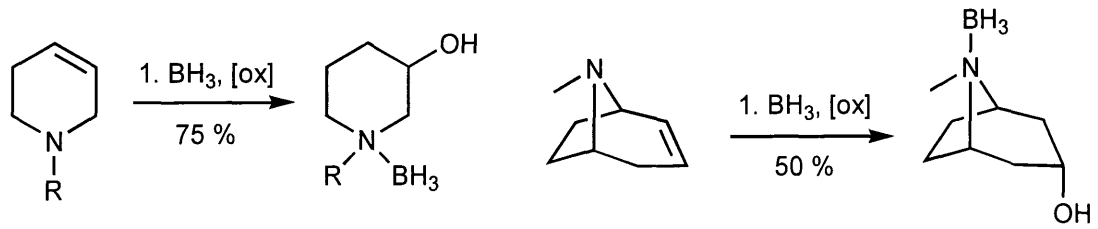
A review of the literature reveals that[121,130] unsaturated amines, such as 2,4-dihydropyrroline **173** and 1,2,3,6-tetrahydro-pyridine **175**, on treatment with an excess of borane-methyl sulfide (BMS) or disiamylborane (Sia_2BH), gave BH_3-N complexes **174** and **176**, leaving the double bond intact, as depicted in **Scheme 80**.



173 **174** **175** **176**

Scheme 80

On the other hand, N-alkyl-1,2,3,6-tetrahydropyridine[130,121] **177** and 2-tropidine **179** behaved differently and not only formed BH_3-N complexes, but also underwent hydroboration with an excess of diborane. Upon oxidation, the corresponding amino alcohols **178** and **180** were obtained as BH_3-N complexes in moderate to good yields, as shown in **Scheme 81**. Formation of BH_3-N complex **162** was therefore consistent with these results during BH_3 and *in situ* prepared Sia_2BH reactions.



177 **178** **179** **180**

Scheme 81

All of the tropanes **155**, **162** and **164**, which have been examined by mass spectroscopy, exhibit a metastable peak at 82 amu. This is almost a characteristic peak for tropane alkaloids and can be rationalised in the following manner[131]. First, removal of one of the non-bonding electrons from nitrogen forms the molecular ion (f), which is then cleaved homolytically between C1 and C2. Initial generation of radical ion (g) involves hydrogen transfer from C-6, affording (h), which on decomposition generates metastable ion (i), as illustrated in **Figure 13**.

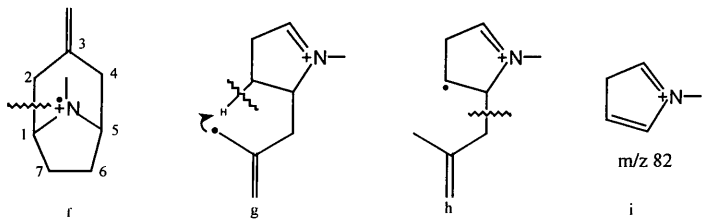
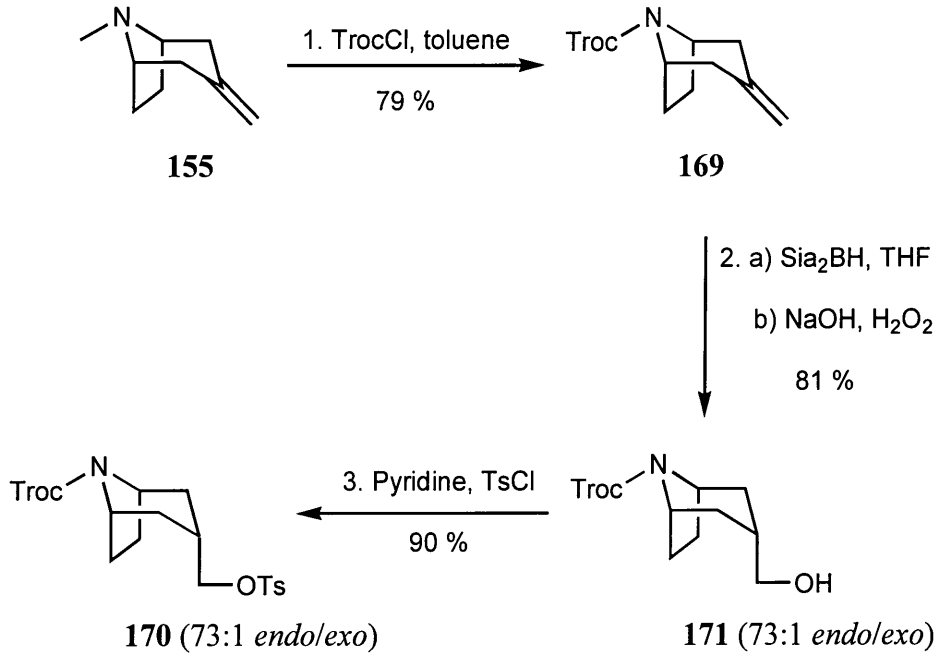


Figure 13: Formation of the characteristic metastable peak at 82 amu for the tropane alkaloids **155**, **162** and **164**.

N-Troc-3α-tosyloxymethyltropane **170** has been developed as an alternative substrate to the N-BH_3 complex **164** and was readily prepared starting from 3-methylenetropane **155**, as depicted in **Scheme 82**.

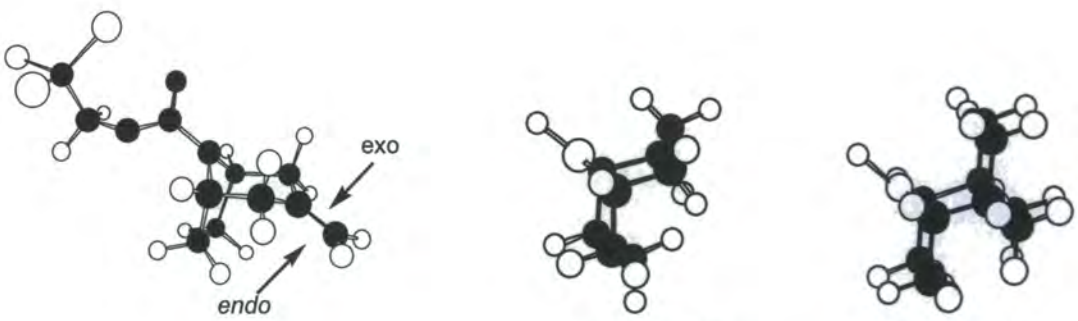


Scheme 82

The first step involved demethylation of **155** and proceeded in good yield (79 %) to give **169**. This was followed by hydroboration of **169** and the alcohol **171** was successfully generated as an almost single *endo* isomer and also in excellent yield (81 %). The final step was the tosylation of **171**, which yielded the required tosyl product **170** in excellent yield (90 %).

In hydroboration reactions[132], the availability of the double bond and the size of the alkyl group on the borane generally influence the stereoselectivity. The *endo*-face of the

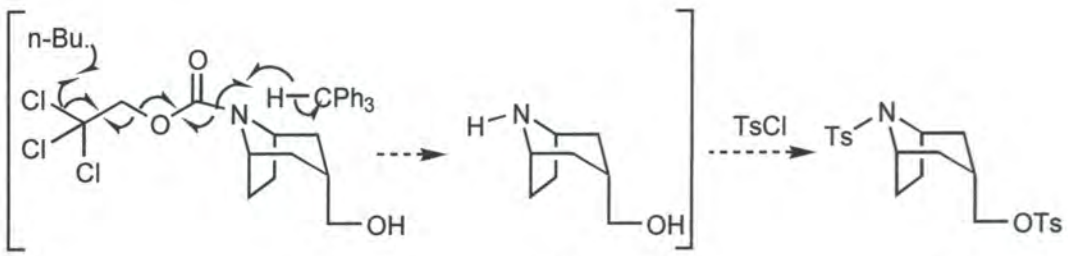
double bond in **169** is less available than the *exo*-face, due to transannular interactions with the hydrogen atoms attached to C6 and C7. Sia_2BH **159** is a bulkier reagent than 9-BBN **160**, as shown in **Figure 14**. Therefore, hydroboration of **169** with Sia_2BH **159** took place exclusively from the *exo*-face of the double bond giving the required *endo* isomer, as a major product. However, hydroboration of **169** with 9-BBN **160** was less selective and gave only a 3:1 mixture in favour of the *endo* isomer.



169 9-BBN **160** Sia_2BH **159**

Figure 14: The 3D molecular modelling of N-Troc-3-methylenetropane **169**, 9-BBN **160** and Sia_2BH **159**.

When n-BuLi rather than pyridine was used as a base in the tosylation of **171**, the yield was disappointingly low (14 %). This may be due to a competing radical process, where n-BuLi initiates the formation of pseudotropane **181** and then its ultimate conversion to N-tosylamide **172**, as illustrated in **Scheme 83**. Isolation of N-tosylamide **172** as a by-product may support the hypothesis suggested above.



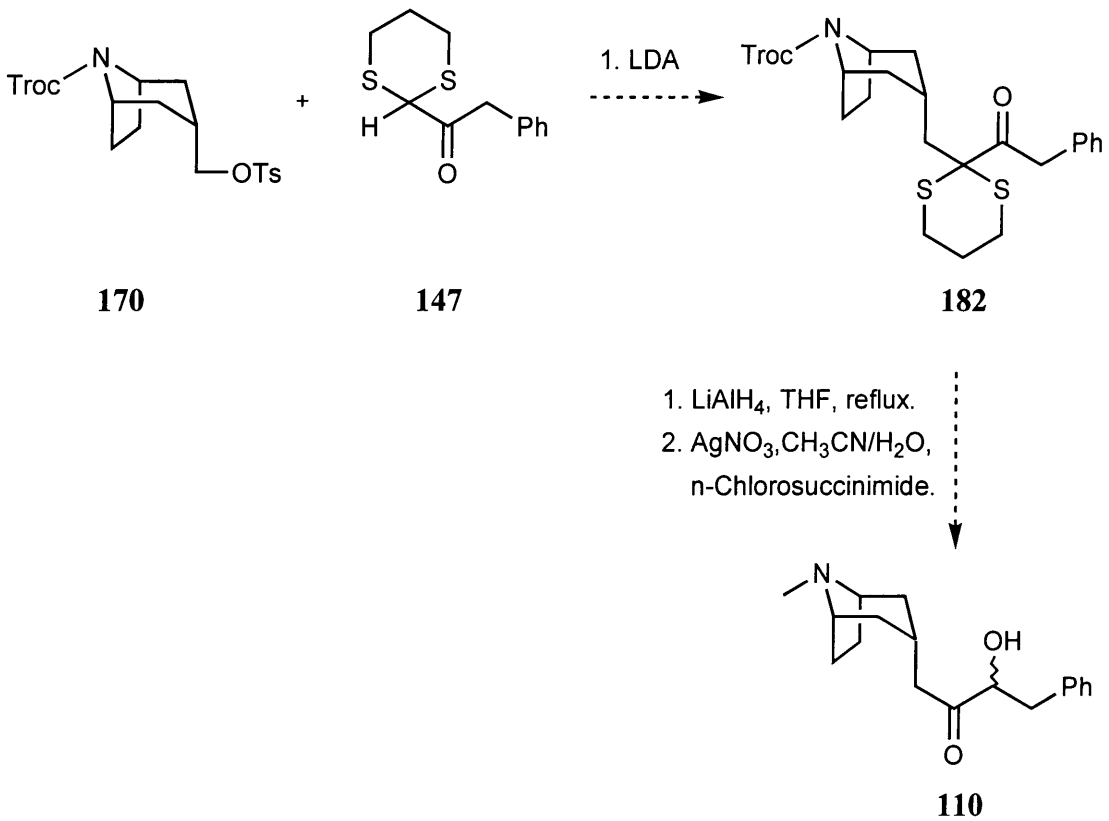
181 **172**

Scheme 83

2.3.4 Coupling reactions

2.3.4.1 Introduction

N-Troc-3α-Tosyloxymethyltropane **170** is a potential substrate now for the coupling reaction with 2-phenylacyl-1,3-dithiane **147** and offers a route for the synthesis of ketone **110**, as outlined in **Scheme 84**. It was envisaged that the key step in this route would involve the synthesis of **182**. The final steps would then require reduction of the Troc group to an N-methyl tropane and reduction of the carbonyl group to a hydroxyl group. Removal of 1,3-dithiane would finally generate the target molecule **110**.



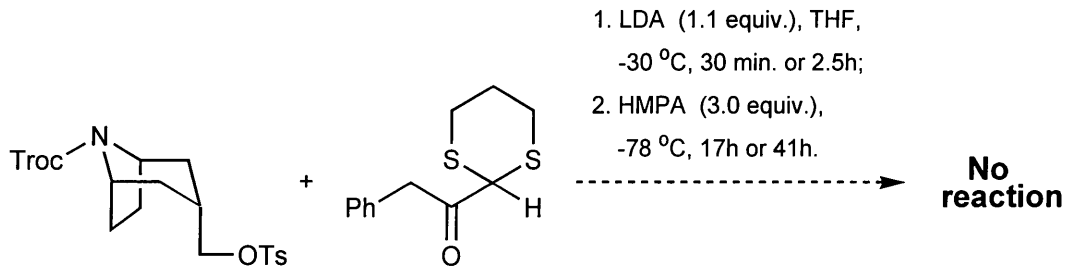
170 **147** **182** **110**

Scheme 84

2.3.4.2 Attempted synthesis of key intermediate 182 *via* tosylate 170

Following the literature method[133], compound **170** was subjected to a coupling reaction with the carbanion derived from thioacetal **147**. The reaction was carried out in the presence of hexamethylphosphoric triamide (HMPA) under two different sets of conditions, as illustrated in **Scheme 85**. In the first instance, the carbanion was generated at -78 °C by *in situ* preparation of LDA and was then stirred for 2.5 h at

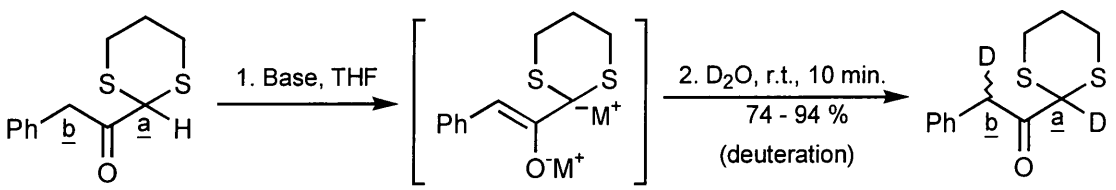
-30 °C, prior to the addition of **170**. In the second case, the carbanion was generated using commercially available LDA and then stirred for 30 min at -30 °C, prior to the addition of **170**. In both reactions an excess of **170** was added to the carbanion at –78 °C and then the reaction mixture was left to stir overnight (17 h) or 41 h. However, in both cases no reaction was observed.



170 **147**

Scheme 85

In order to ensure that the lithiation of thioacetal **147** had taken place, a deuterium exchange reactions was carried out as suggested by Seebach[117] and Corey. This required generation of the anion from thioacetal **147**, followed by the addition of an excess of D_2O, as illustrated in **Scheme 86**. Upon work-up, the ^1H NMR analysis of the crude material revealed that not only had the thioacetal proton (a) become labelled with isotope, but that one of the methylene protons (b) adjacent to the carbonyl group was also substantially exchanged. The level of deuterium incorporation into both sites (a and b) in **183** was determined by the integration of the ^1H NMR signals for the thioacetal methine (a) and the methylene protons (b) relative to the methylene protons adjacent to the sulphur atom. The reaction conditions and the incorporation results are summarised in **Table 10**.



147 **183**

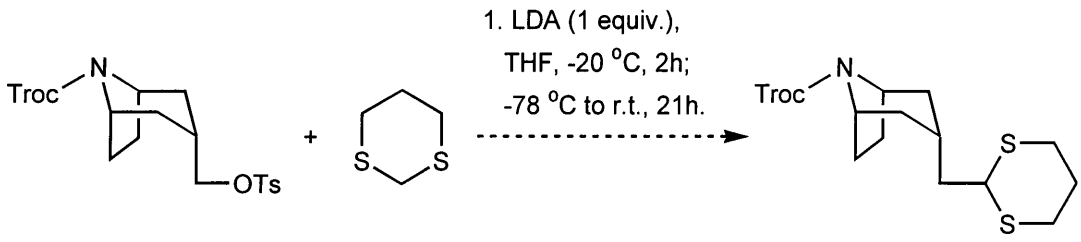
Scheme 86

entry	Base (equiv.)	Reaction temp., time	Deuterated 183 at a (%)	Deuterated 183 at b (%)
1	LDA[a] (1.1)	-78/ 0 °C, 3h	76	74
2	LDA[b] (1.1)	-30 °C, 0.5h	83	86
3	NaH (2.7)	r.t., 15 min.	94	92

a) *In situ* Prepared by the addition of n-BuLi (1.6 M solution in hexanes) into the solution of diisopropylamine in THF at –78 °C **b)** Commercially available

Table 10: Generation of the deuterated thioacetal **183** by deuterium exchange reaction of thioacetal **147** under different conditions.

After this failure, the coupling reaction of **170** with 1,3-dithiane **142** was also investigated. Following the method described by Page[105] *et al.*, dithiane **142** was first lithiated with lithium diisopropylamine (LDA) in THF between -30 and -20 °C. The anion was then reacted with **170** between -78 °C and r.t., as shown in **Scheme 87**. The reaction was monitored by t.l.c. (3:7 AcOEt/Petrol) and a single new spot was observed. Purification over silica gel (1:4 ethyl acetate/petrol) gave a milk-white amorphous solid. However, characterisation of this product by the ^{1}H NMR analysis was inconsistent with the desired product **184**.



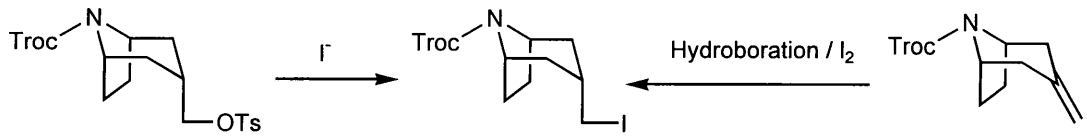
170 **142** **184**

Scheme 87

2.3.4.3 Synthesis of N-Troc-3α-iodomethyltropane 185

In view of the failed reactions of N-Troc-3α-tosyloxymethyltropane **170** with 2-phenylacetyl-1,3-dithiane **147** and 1,3-dithiane **142**, and also in view of the fact that primary iodides are reported to react readily with 1,3-dithiane **142**, N-Troc-3α-iodomethyltropane **185** was considered as an alternative electrophile. It was anticipated that this could be achieved either by nucleophilic substitution of tosylate **170** with NaI

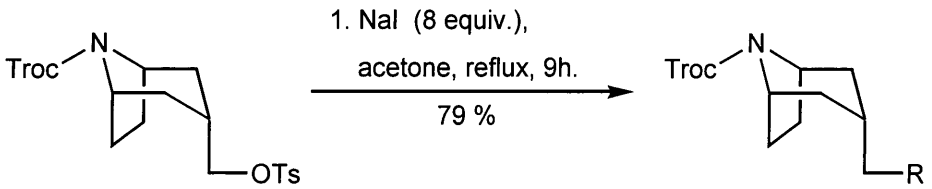
or by hydroboration / iodination of **169**, as depicted in **Scheme 88**.



170 **185** **169**

Scheme 88

Nucleophilic displacement of tosylate **170** with NaI was investigated in the first instance. Following the literature method described by Byon[134] *et al.*, tosylate **170** was treated with NaI in refluxing acetone, as shown in **Scheme 89**. When wet acetone was used, hydroxide (OH^-) displacement occurred and gave predominantly N-Troc-3α-hydroxymethyltropane **171**. However, in freshly distilled and dry acetone, this reaction was suppressed and only iodide (I^-) displacement took place, generating the required product **185**, which was purified by chromatography and isolated as an oil in good yield (79 %).



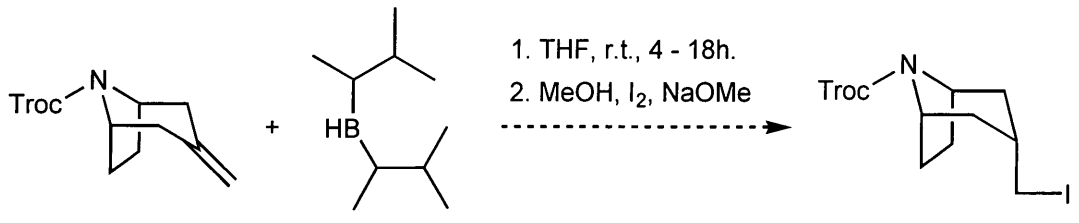
170

171 R= OH

185 R= I

Scheme 89

Since organoboranes give very rapid reactions with iodine under the influence of NaOH[135] or NaOMe[136], this has emerged as a straightforward method for the transformation of terminal olefins into primary iodides[135]. Accordingly the hydroboration-iodination of N-Troc-3-methylenetropane **169** was also investigated. This required hydroboration of **169** with Sia_2BH **159**, followed by iodination under two sets of conditions, as illustrated in **Scheme 90**. The ^1H NMR analysis of the crude material did not indicate any residual double bond. However, the title compound could never be isolated. The conditions are summarised in **Table 11**.



(3 - 5 equiv.)

169 **159** **185**

Scheme 90

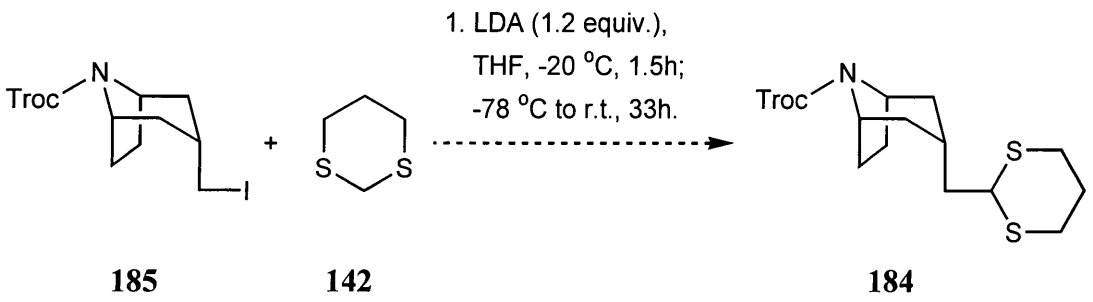
Entry	Hydroborating agent (equiv.)	Quenching agent (ml)	3M NaOH in MeOH, ml	I_2 (equiv.)	Reaction
1	Sia_2BH[a] **159** (3)	MeOH (1.0)	3	3	Yes
2	Sia_2BH[a] **159** (5)	MeOH (1.5)	6	5	Yes

a) *In situ* prepared by treating a mixture of 2-methyl-2-butene and $NaBH_4$ in THF with $BF_3.OEt_2$ at -10 to 0 °C.

Table 11: Hydroboration and iodination of N-Troc-3-methylenetropane **169** under different conditions.

2.3.4.4 Attempted synthesis of key intermediate 182 *via* iodide 185

With N-Troc-3α-iodomethyltropane **185** in hand, it was subjected to a coupling reaction with the anion generated from 1,3-dithiane **142** and LDA, following the method described by Page[105] *et al.*, as shown in **Scheme 91**. The reaction was monitored by t.l.c. (2:8 Petrol / CH_2Cl_2) and two new spots were observed. However, purification by column chromatography over silica gel (0.5:9 ethyl acetate/petrol) did not afford the desired compound **184**.

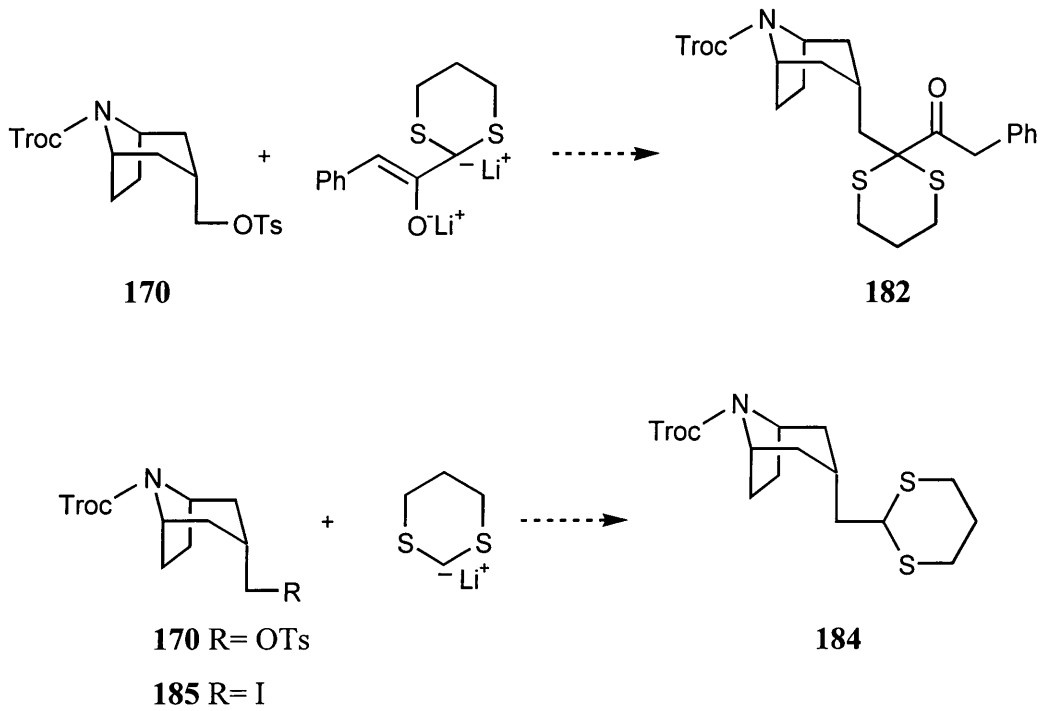


185 **142** **184**

Scheme 91

2.3.4.5 Discussion

N-Troc-3α-Tosyloxymethyltropane **170** failed to react with 2-lithiated-2-phenylacetyl-1,3-dithiane. More surprisingly, both N-Troc-3α-tosyloxymethyltropane **170** and N-Troc-3α-iodomethyltropane **185** also failed to react with 2-lithiated-1,3-dithiane, as depicted in **Scheme 92**.



170 **182**

170 R= OTs

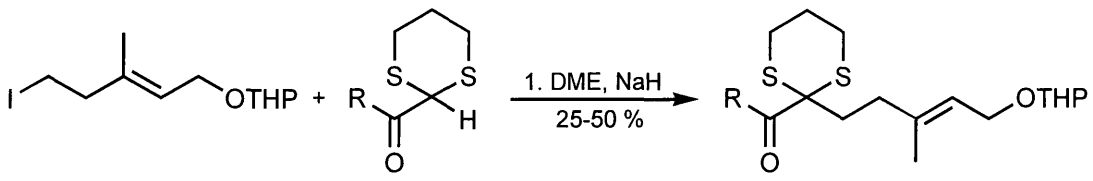
185 R= I

184

Scheme 92

The most reasonable explanation as to why the coupling reactions of N-Troc-3α-tosyloxy- and iodo- methyltropanes **170** and **185** were unsuccessful in our hands is the steric hindrance due to C6 and C7 of the tropane ring, and consequently a lack of susceptibility of the tosyl group of **170** and iodo group of **185** to nucleophilic attack.

A review of the literature indicates that[137] coupling reactions of 2-acyl-1,3-dithianes with alkyl iodides are adversely influenced by the increased size of substituents at the 2-position of 1,3-dithianes, consistent with our observations. For instance, the iodide **186** reacted with the acyldithiane **187** [R: $CH_2CH_2CH=C(CH_3)_2$] within 96 h and gave **188** in low yield (25 %). However, the iodide **186** reacted with the 2-acetyl-1,3-dithiane **189** [R: CH_3] within 3h and gave **190** in moderate yield (50 %), as depicted **Scheme 93**.

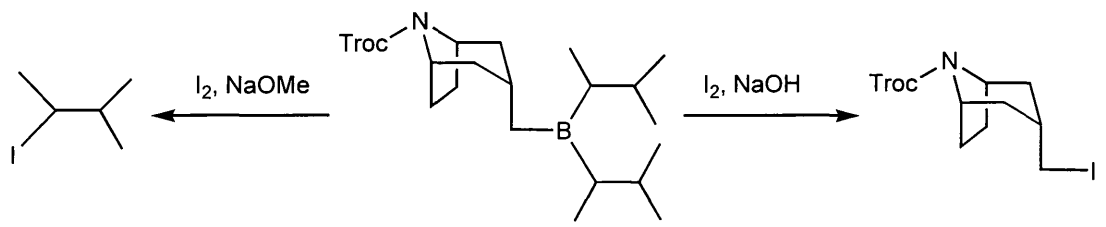


186 **187** **188** R: $CH_2CH_2CH=C(CH_3)_2$

189 **190** R: CH_3

Scheme 93

It is not clear at present that why N-Troc-3α-iodomethyltropane **185**, obtained by a hydroboration-I_2 reaction, could not be isolated, apart from suggesting that[136,138] the use of NaOMe as a base led to the conversion of the two *sec*-siamyl groups of borane **192**, in preference to the primary group, into the corresponding iodide **191** (**Scheme 94**). As suggested by Brown[135] *et al.*, the choice of base, such as NaOH, may circumvent the formation of **191**, by producing only the desired iodide **185**, since the primary group will react in preference to the *sec*-siamyl groups in the borane **192** (**Scheme 94**).



191 **192** **185**

Scheme 94

CHAPTER THREE

Ketone Analogues of 3α-Esterified

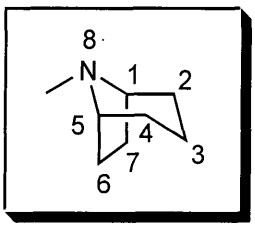
Tropane Alkaloids

CHAPTER THREE

3. 1 General introduction

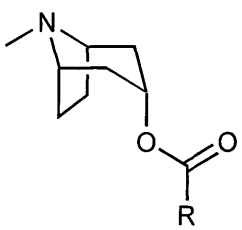
3.1.1 3α-Esterified tropane alkaloids

The tropane alkaloids[139] have a common bridged heterocyclic system containing the 8-methyl-8-aza-bicyclo[3.2.1]octane ring **193** as shown below. These alkaloids are not only found in the plant family Solanaceae, but also in other plant families, such as Convolvulaceae, Erythroxylaceae, Proteaceae and Rhizophoraceae. In addition, the presence of tropane alkaloids has occasionally been identified in the plant families Brassicaceae (Cruciferae), Euphorbiaceae and Olacaceae. This class of natural products displays interesting and diverse pharmacological activities, such as parasympatholitic, anaesthetic and anticholinergic effects[140].

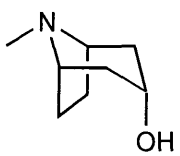


193

The largest group of tropanes[139] are the 3α-monosubstituted tropane alkaloids **194**, which are derived by esterification of the alcohol tropine (3α-hydroxytropane) **94** with a carboxylic acid. The carboxylic acid moiety of these naturally occurring alkaloids can be quite diverse and range from aliphatic to aromatic acids. Some of the naturally occurring ones are summarised in **Table 12**.



194



94

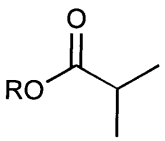
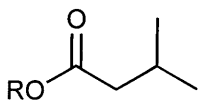
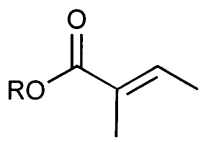
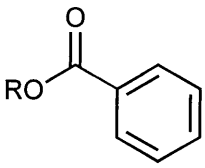
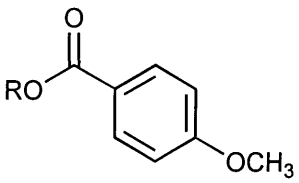
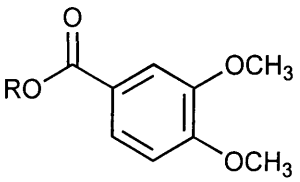
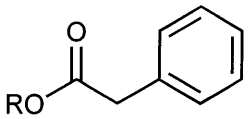
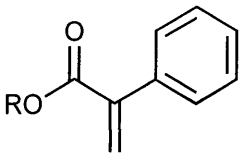
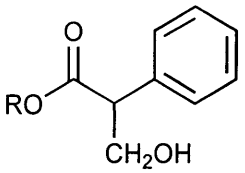
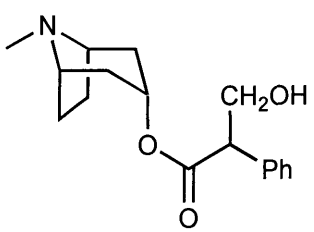
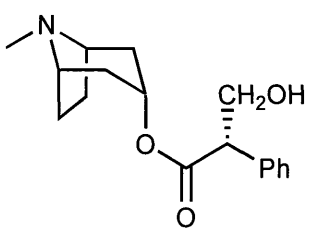
R= Tropine **94**		
		
195[84,141]	**196**[142]	**197**[143]
		
125[84,85]	**198**[144]	**199**[145]
		
200[142]	**201**[141, 143]	**202**[143]

Table 12: Some of the known carboxylic acid moieties of the naturally occurring tropane alkaloids **200**, **125** and **203-204**.

Among these acids, the *(RS)*- and *(S)*-tropic acid esters[139] atropine **202** and hyoscyamine **92**, respectively are widely occurring tropane alkaloids found in the plant family Solanaceae, especially in *Hyoscyamus niger*, *Atropa belladonna* and *Datura stramonium*. These alkaloids were the first of the parasympatholytics[63] to be identified, i.e. muscarinic receptor antagonists.

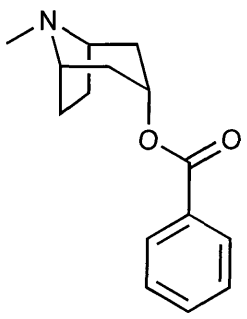


202

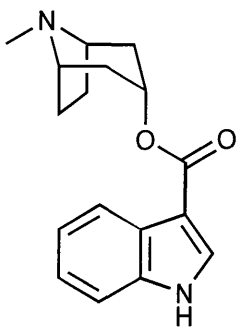


92

The benzoic acid ester **125**, benzolyoxytropane is found in the plant families Rhizophoraceae[84] and Erythroxylaceae[85] and inhibits 5-hydroxytryptamine (5-HT_3)-induced bradycardia in urethane-anesthetized rats[146]. 5-Hydroxytryptamine is a neurotransmitter, which operates within the central and peripheral nervous systems and its deficiency is associated with depression. Benzoyloxytropane **125** has approximately 100-fold less affinity to the 5-HT_3 receptors than those well-known 5-HT_3 receptor ligands[147], such as tropisetron **205**, a synthetic 3α-monosubstituted tropane alkaloid. The synthetic tropane alkaloid, MDL-72222 **206** has also been developed. This compound is amongst the most commonly used 5-HT_3 receptor ligands[146,147] in the treatment of depression.



125



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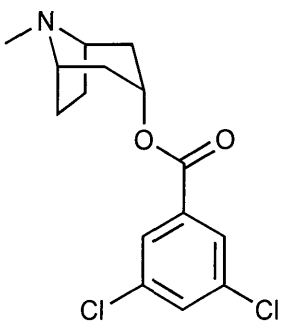
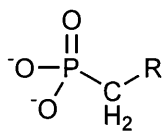


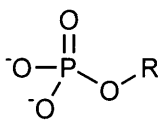
206

3.1.2 CH_2 for O replacement

In this programme analogues of tropane alkaloids have been prepared where the O atom is replaced by a CH_2 group. This follows other successes of this strategy, for example phosphonic acids[148] **207** can function as analogues of natural phosphates **208** and renders them stable to phosphatase activity.



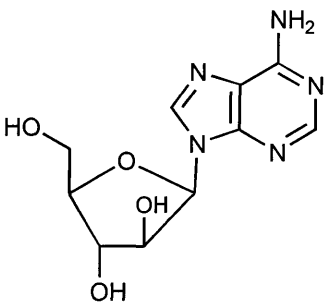
207



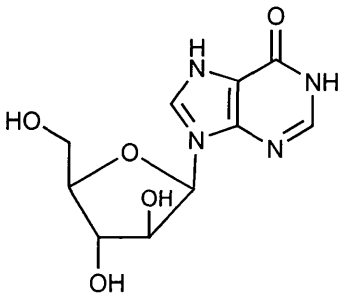
208

Vidarabine (9-β-D-arabinofuranosyladenine) **209** is an antitumour agent and shows a broad-spectrum activity against DNA viruses. As a result, it is clinically used for the treatment of herpes encephalitis and herpes keratitis[149]. However, it suffers from rapid

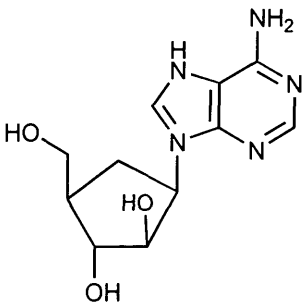
in vivo deamination to the corresponding 9-β-D-arabinofuranosylhypoxanthine **210** by adenosine deaminase. In order to suppress this problem, compound **211**, known as cyclaridine was prepared, in which the ring ether oxygen of **209** was replaced by a CH_2 group. This was reported to be resistant to adenosine deaminase and displays substantial anti herpes activity.



209

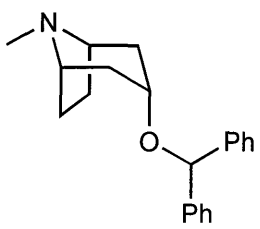


210

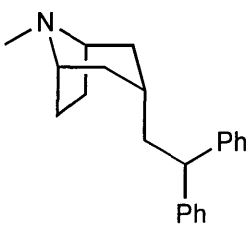


211

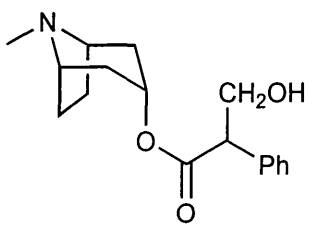
Benztropine **212**, a tropane ether is a parasympatholytic agent used clinically as an anti-Parkinson's disease drug. When the bridging ether oxygen was replaced by a CH_2 moiety[150], the corresponding 2-(tropan-3-yl)-1,1-diphenylethane **213** was found to be more active than atropine **202** and as active as benztropine **212** in the *in vitro* assays. This is the only example of such a modification in tropane alkaloids analogue synthesis.



212



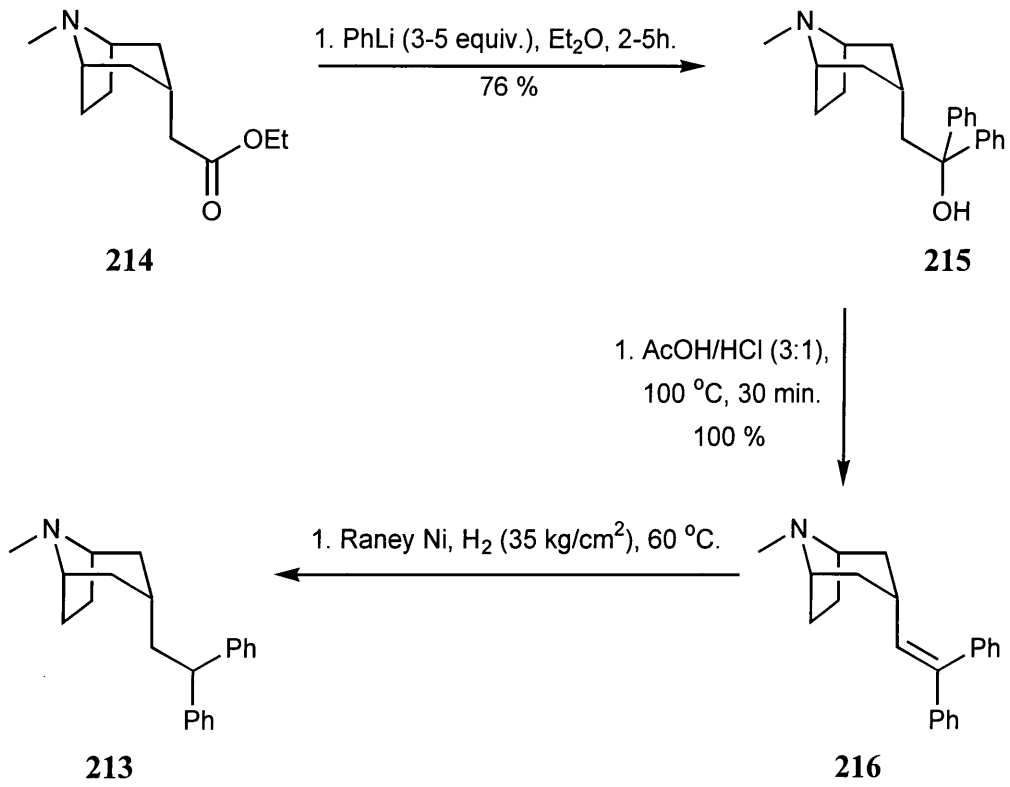
213



202

Tropane alkane **213** was prepared from ethyl (tropan-3-yl)acetate **214** in three steps[150], as shown in **Scheme 95**. The first step involved reaction of tropane ester **214** with phenyl lithium to give the corresponding 2-(tropane-3-yl)-1,1-diphenylethanol **215** in good yield (76 %). Alcohol **215** was then heated in a mixture of HCl and AcOH to give the corresponding olefin 2-(tropane-3-yl)-1,1-diphenylethene **216** in quantitative yield (100 %). Hydrogenation of tropane alkene **216** under strenuous conditions (Raney Ni / 60 °C / 35 kg/cm_2 H_2) finally generated tropane alkane **213**, however, the yield was not

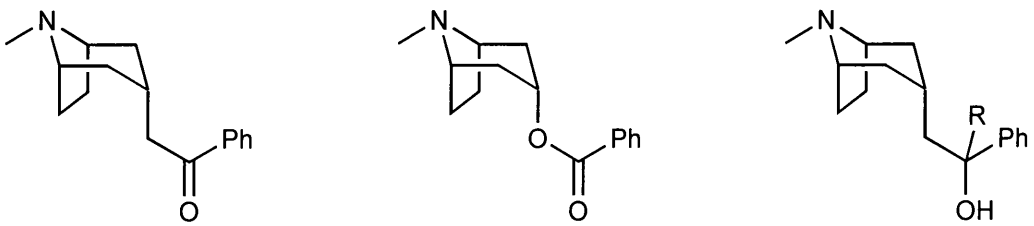
reported for the final step.



Scheme 95

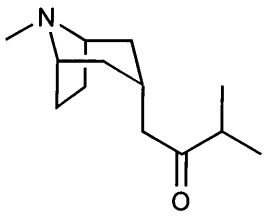
3. 2 Ketone analogues of 3α-esterified tropane alkaloids

Ketone **124** is a CH_2 analogue of benzoyloxytropane **125** and was first prepared by Zirkle[150] *et al.* in 1962 as an intermediate in the synthesis of 3-substituted tropane derivatives, mainly with the general structure **217**. More recently, it was reported that[146] ketone **124** was as good inhibitor of 5-HT_3 receptor as benzoyloxytropane **125**.

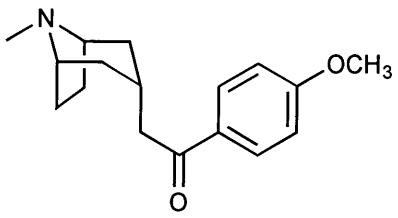


A literature survey has shown that ketone **124** is the only known CH_2 analogue of the naturally occurring 3α-substituted tropane alkaloids and it was decided to devise a route

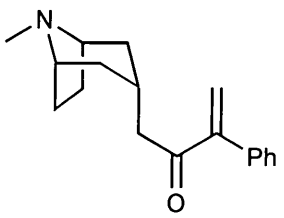
that would allow the synthesis of more such analogues of tropane ester natural products. At the outset, the ketones **218**, **219** and **220** were selected as target compounds for this study. In each case the corresponding esters **195**, **198** and **201** have all been identified in various plants.



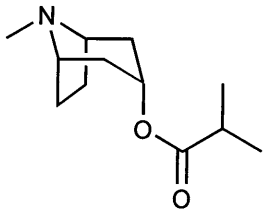
218



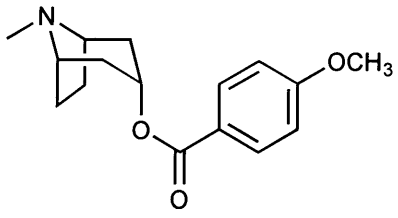
219



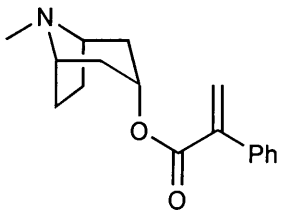
220



195[84,141]

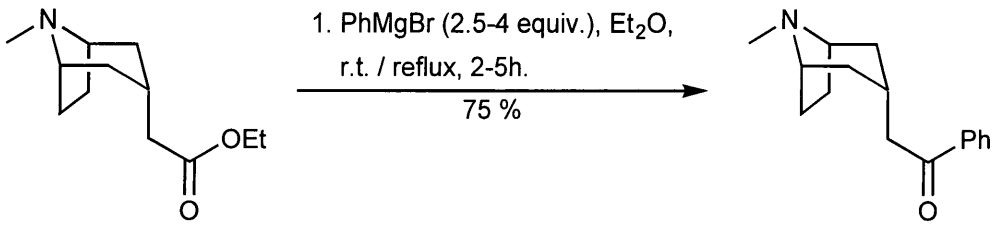


198[144]



201[141,143]

Since ketone[150] **124** was prepared from the Grignard reaction of ester **214** with phenylmagnesium bromide, as depicted in **Scheme 96** and isolated as a major product in good yield (75 %), it was envisaged that an analogous strategy would provide an appropriate route for the synthesis of ketones **218-220**.

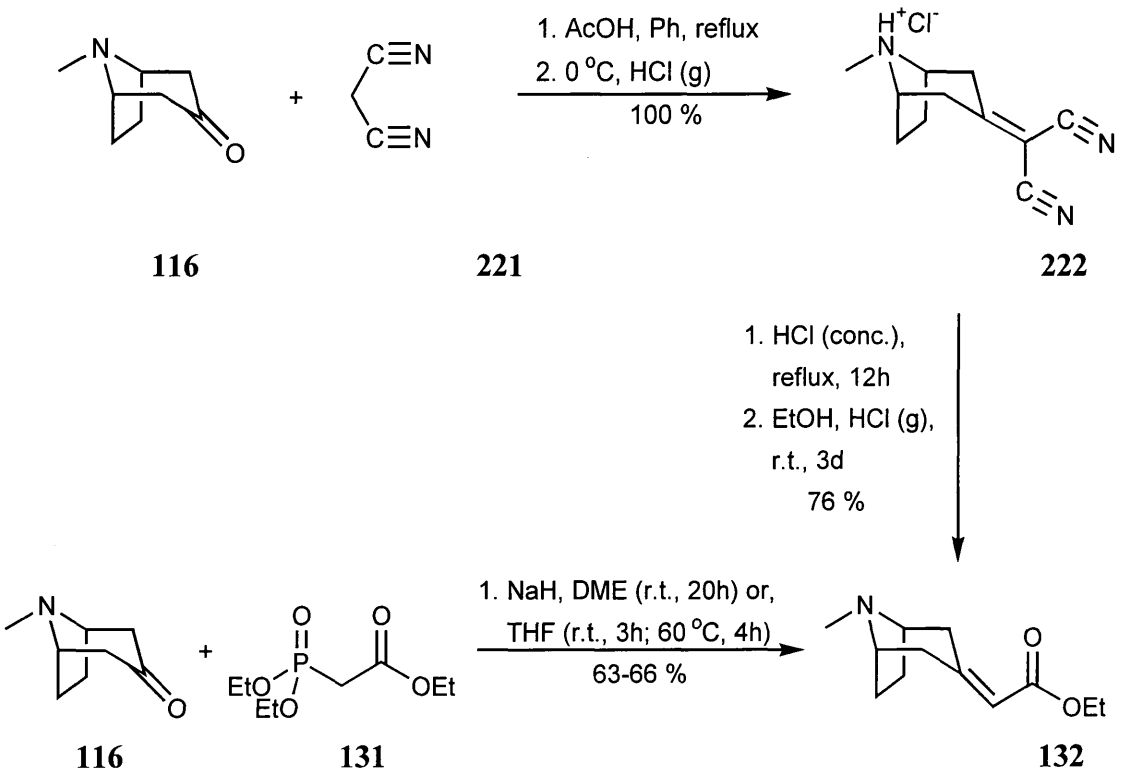


214 **124**

Scheme 96

Preparation of the key starting ester, ethyl (tropan-3-yl)acetate **214** by two different methods[151,88] has been reported, both starting from tropinone **116**. The method of

Zirkle[151] *et al.* began with a Knoevenagel condensation of tropinone **116** with malononitrile **221** to generate the corresponding (tropan-3-ylidine)malononitrile **222** as an HCl salt in excellent yield (100 %). Acid-catalysed hydrolysis of **222**, followed by decarboxylation and esterification gave ethyl (tropan-3-ylidine)acetate **132** in good yield (76 %). An alternative method reported by Calvert[88] and Hobson differs only in the synthesis of **132**. This route used a Horner-Emmons reaction between tropinone **116** and triethyl phosphonoacetate **131** to genearte **132** in moderate yield (63 %). These approaches to **132** are shown in **Scheme 97**.

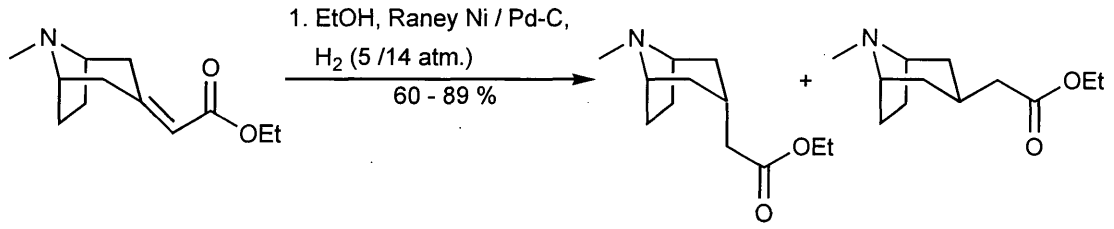


116 **221** **222**

116 **131** **132**

Scheme 97

The final step to ester **214**, as illustrated in **Scheme 98**, involved the catalytic hydrogenation of **132**. Raney nickel was used as a catalyst and the hydrogenation was carried out under 5 atm. or 60 p.s.i pressure to generate **214** in excellent yield (89 %), but as a mixture of stereoisomers. The *endo* (α) form was the predominant isomer of the hydrogenation reaction, and was isolated as a single isomer, after recrystallisation of its picrate salt.



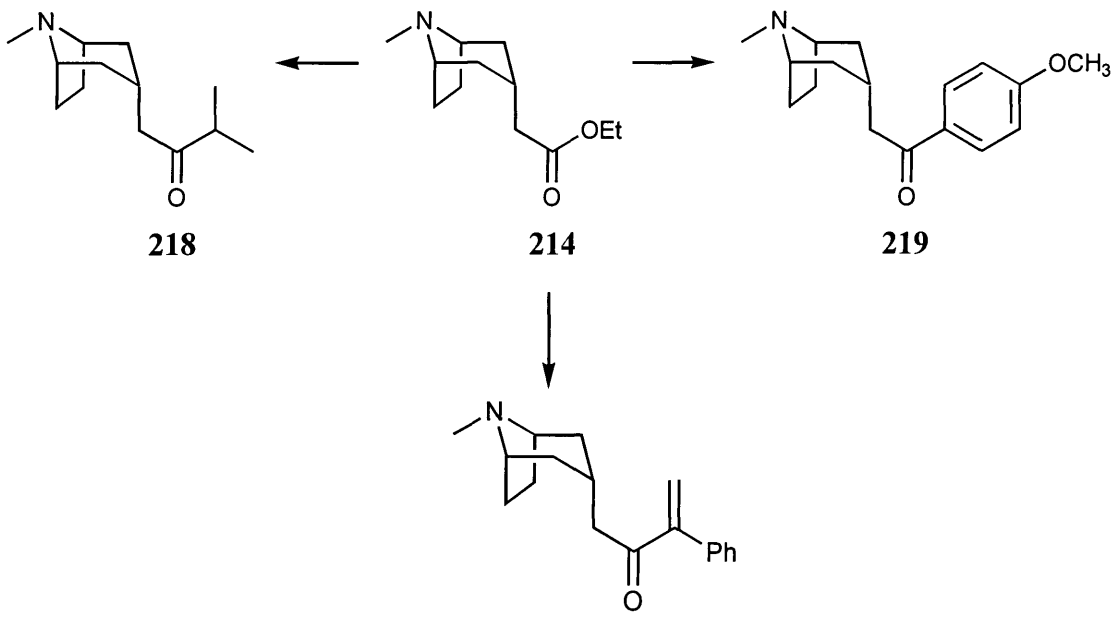
132 *endo*-**214** *exo*-**214**

Scheme 98

A modification of Calvert[88] and Hobson's method to **214** has recently been reported by Kato[152] *et al.* The Horner-Emmons reaction of tropinone **116** was carried out in THF rather than in 1,2-dimethoxyethane (DME) and the hydrogenation used palladium on activated carbon under 14 atm. pressure. The yield of Horner-Emmons reaction was improved slightly, however hydrogenation yield was reported to be only 60 %.

3.2.1 Attempted synthesis of ketone analogues from ester 214

At the outset a Grignard reaction of ester **214** was chosen as a method to the ketone analogues **218-220**, as outlined in **Scheme 99**. Thus the programme began with the synthesis of ester **214**.

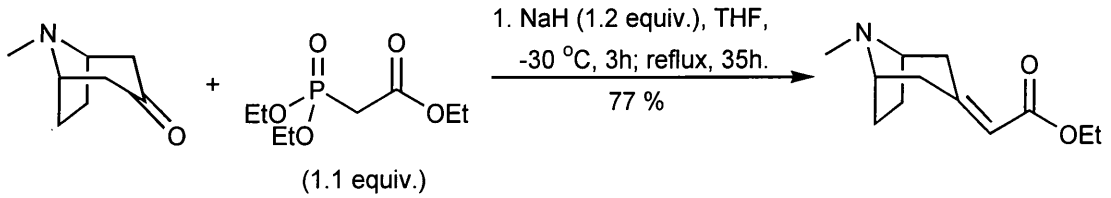


218 **214** **219**

220

Scheme 99

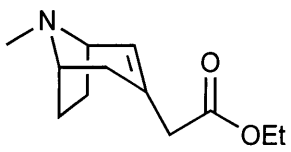
Calvert[88] and Hobson's method was chosen to prepare **214**. The first step in this route, as discussed before, involved the Horner-Emmons reaction of tropinone **116** with triethyl phosphonoacetate. Deprotonation of triethyl phosphonoacetate **131** was mediated at - 78 °C with NaH, followed by the addition of tropinone **116**, as shown in **Scheme 100**.



116 **131** **132**

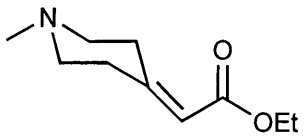
Scheme 100

After distillation, the α,β-unsaturated ester **132** was obtained as an oil in 77 % yield, an improvement on the reported[88,152] yields (63 % and 66 %). As expected, ester **132** was contaminated with the β,γ-unsaturated ester **133** about 11 % (8:1 ratio). This was clearly evident by ^{13}C NMR analysis of ester **132**. Separation of the two isomers was not necessary, as ester **132** was used directly as a mixture with **133** for hydrogenation.

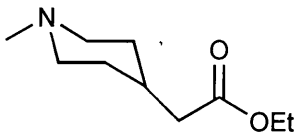


133

Under three sets of conditions i) 1 atm - 23 h, ii) 3-4 atm - 96 h and iii) 20 atm - 21 h, hydrogenation over palladium on activated carbon failed to give **214**, and only the starting esters **132** and **133** were recovered, after filtration of the catalyst. This was unexpected, since hydrogenation of conjugated double bonds under these conditions is common[153]. For instance, it was reported that[154] ethyl (4-piperidine-3-ylidine)acetate **223** in ethanol was successfully hydrogenated over palladium on activated carbon to the corresponding ethyl (4-piperidine-3-yl)acetate **224** in excellent yield (90 %).

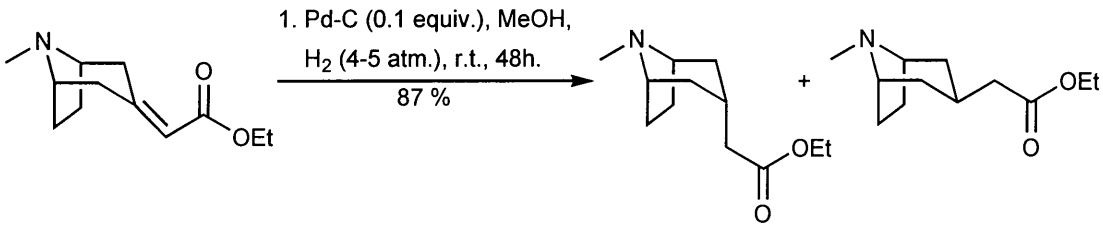


223



224

Since the core structure of **223** is present in **132**, the focus turned towards purification of the starting ester **132** (+ 11 % of **133**). Ester **132** (+ 11 % of **133**) was treated with HCl and then the aqueous layer was washed with diethyl ether, made basic with NaOH and extracted back into diethyl ether. Hydrogenation then proceeded smoothly over palladium on activated carbon even under 4-5 atm., and the reaction was complete within 22h, as depicted in **Scheme 101**. Thus it is concluded that the initial reaction product contained an impurity which rendered catalytic hydrogenation problematic.



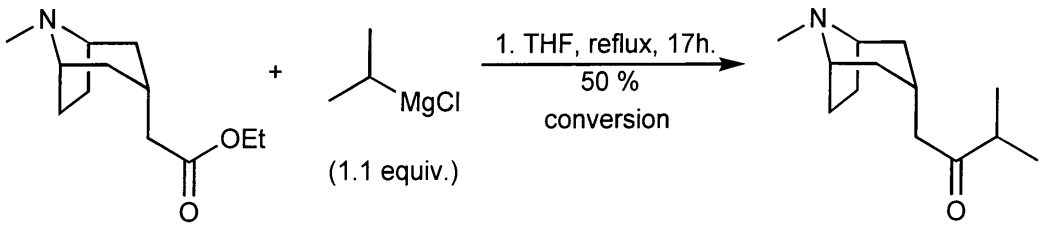
132 (+ 11 % of **133**) *endo*-**214** / *exo*-**214** (5:1)

Scheme 101

This hydrogenation was carried out under 14 atm. pressure of hydrogen for 14h by Kato[152] *et al.* and from this, ester **214** was obtained as a mixture of stereoisomers, but the ratio was not reported. The *endo* form was the predominant isomer of the hydrogenation reaction and isolated as a single stereoisomer in moderate yield (60 %), after purification over neutral alumina. In our case, ester **214** was also a mixture of stereoisomers and obtained as clear oil in excellent yield (87 %), after distillation. The *endo*/*exo* isomer ratio was determined to be 5:1 from the ^{13}C NMR spectrum.

With ester **214** in hand, albeit as a mixture of stereoisomers, it was first subjected to a Grignard reaction with 1.1 equivalents of isopropylmagnesium chloride **225** in THF, as depicted in **Scheme 102**. In contrast to the method described by Zirkle[150] *et al.*, in where 2.5-4 equivalents of Grignard reagent was reported, only a slight excess of the Grignard reagent was used in order to prevent the overaddition to the product ketone **218**. The ^{1}H

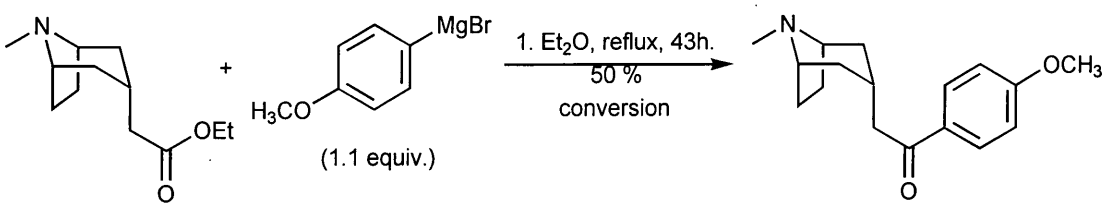
NMR analysis of the crude material indicated that ketone **218** had formed, but approximately 50 % of the starting material **214** still remained. We did not attempt to separate the two compounds, since the conversion was about 50 %.



214 (5:1 *endo / exo*) **225** **218** (5:1 *endo / exo*)

Scheme 102

Further investigation was pursued by submitting compound **214** to the Grignard reaction again with 1.1 equivalents of 4-methoxyphenylmagnesium bromide **226** in refluxing diethyl ether, as illustrated in **Scheme 103**. Following the literature methods[155,156], the Grignard reagent **226** was readily prepared in diethyl ether from the reaction of 4-bromoanisole with magnesium turnings in the presence of iodine crystals. Ketone **219** was generated, but ^{1}H NMR again indicated an approximate 50 % conversion of **214**.

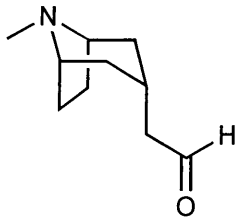


214 (5:1 *endo / exo*) **226** **219** (5:1 *endo / exo*)

Scheme 103

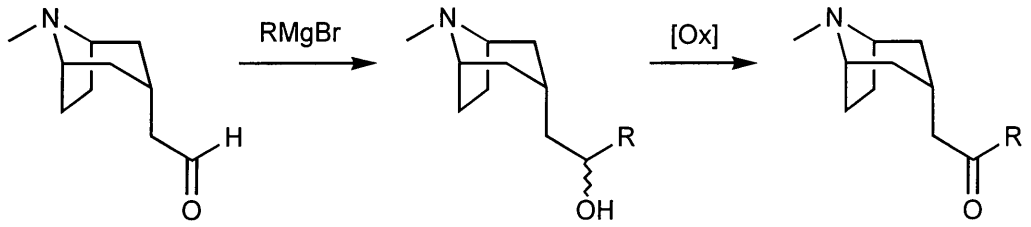
3.2.2 Ketone analogues from aldehyde 227

The low levels of conversion of the Grignard reactions with tropane ester **214**, under even prolonged reaction conditions, prompted an alternative substrate to be explored in order to develop a satisfactory route. An ideal replacement for this was judged to be tropane aldehyde **227**.



227

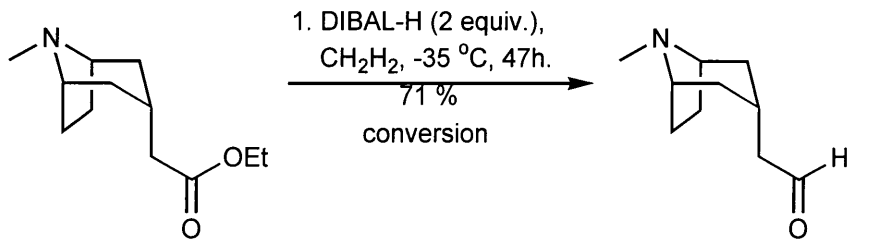
It was anticipated that aldehyde **227** could be prepared by the DIBAL-H reduction of ester **214**, following the method described by Baasov[157] and Sheves. This would then be amenable to Grignard reaction to generate a secondary alcohol **228**, which could be oxidised to ketone **229**, as shown in **Scheme 104**.



227 **228** **229**

Scheme 104

Accordingly, ester **214** was subjected to DIBAL-H reduction in dichloromethane (**Scheme 105**), under different conditions (**Table 13**, p. 95). The reaction temperature was varied from -78 °C to room temperature (25 °C) and in each case (**Entry 1-4**) was monitored by ^{1}H NMR spectroscopy. However, the formation of aldehyde **227** was observed only between -60 °C to -40 °C (**Entry 2** and **3**). The same reaction was again carried out at almost identical temperatures (**Entry 5** and **6**), but with 2 equivalents of DIBAL-H. This time the reaction was much more successful generating aldehyde **227** at -35 °C and in a 71 % conversion (**Entry 6**).



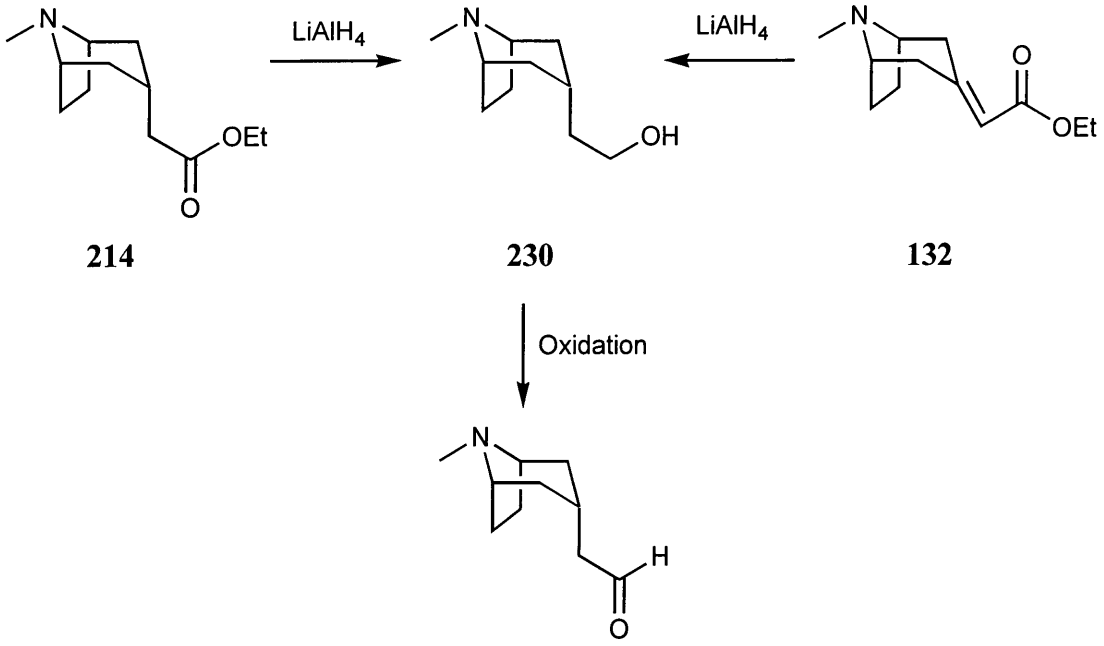
214 (5:1 *endo* / *exo*) **227** (5:1 *endo* / *exo*)

Scheme 105

Entry	Time (h)	Temperature (°C)	DIBAL-H (equiv.)	Aldehyde (%)
1	1.5	-78	3	-
2	2.5	-60	3	9
3	4	-40	3	50
4	1	25	3	-
5	14	-55	2	-
6	47	-35	2	71

Table 13: The DIBAL-H reduction of ester **214** under different conditions.

Although the conversion was good (71 %), aldehyde **227** could not be purified, as it decomposed on silica gel and activated neutral aluminium oxide. Therefore, an alternative route to aldehyde **227** was investigated. This required oxidation of tropane alcohol **230**, as depicted in **Scheme 106**. Since many methods are available for the oxidation[158] of primary alcohols to aldehydes, it was anticipated that this should be straightforward. Alcohol **230** could be directly prepared either by $LiAlH_4$ reduction of saturated ester **214** or reduction of the unsaturated ester **132**.

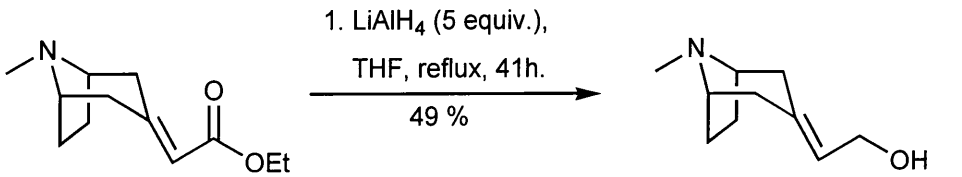


214 **230** **132**

227

Scheme 106

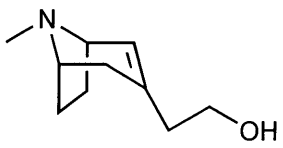
The $LiAlH_4$ reduction of **132** was explored in the first instance. This was carried out by reacting ester **132** with $LiAlH_4$ in refluxing THF, as illustrated in **Scheme 107**. In contrast to the method described by Dutta[159] *et al.*, ester **132** was added to the slurry of $LiAlH_4$ at -60 °C and allowed to warm to room temperature prior to reflux.



132 (+ 11 % of **133**) **231** (+ 11 % of **232**)

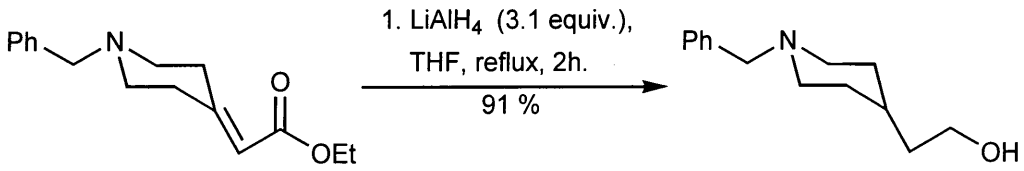
Scheme 107

After a tedious work-up, due to the gelatinous nature of the reaction mixture after the addition of NaOH solution, distillation afforded allylic alcohol **231** as a white solid in moderate yield (49 %). Allylic alcohol **231** was contaminated with about 11 % of the *endo*-cyclic unsaturated alcohol **232** (8:1 ratio), as anticipated.



232

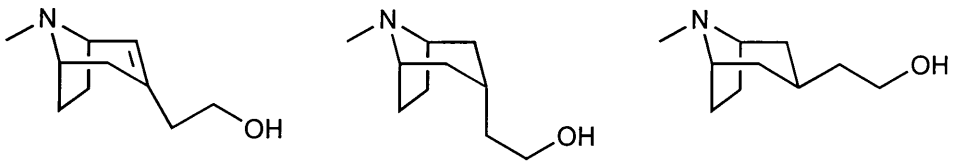
Since $LiAlH_4$ reductions of α-β-unsaturated carbonyl compounds are accompanied, to an appreciable extent, by carbon-carbon double bond reductions[160], isolation of allylic alcohol **231** was however a surprise. For instance, it was reported that[159] $LiAlH_4$ reduction of ethyl (N-benzyl-piperidine-3-ylidine)acetate **233** gave the corresponding saturated alcohol, (N-benzyl-piperidine-3-ylidine)ethanol **234** in excellent yield (91 %), as depicted in **Scheme 108**.



233 **234**

Scheme 108

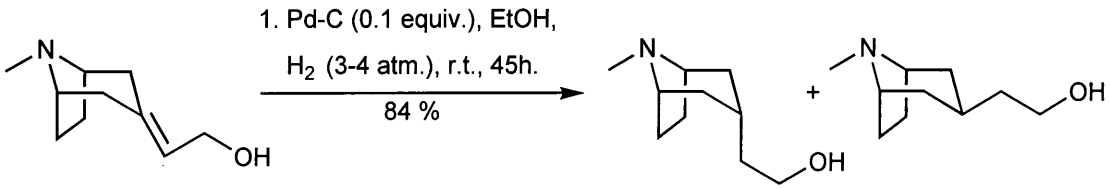
Therefore the reaction was conducted by the addition of ester **132** to the slurry of $LiAlH_4$ at 0 °C and then followed by reflux (24 h). This time, some of the allylic alcohol **231** was further reduced to give the saturated alcohol **230**. So the product mixture containing allylic alcohol **231** was eventually contaminated with the saturated *endo* and *exo* alcohol **230**, as well as with the *endo*-cyclic unsaturated alcohol **232**. These contaminants are shown in **Figure 15** and it was clearly evident from the ^1H NMR spectrum that the contamination was about 50 % of the product mixture.



232 *endo*-**230** *exo*-**230**

Figure 15: The *endo*-cyclic unsaturated alcohol **232** and the saturated *endo* and *exo* alcohols **230**, contaminants of allylic alcohol **231**.

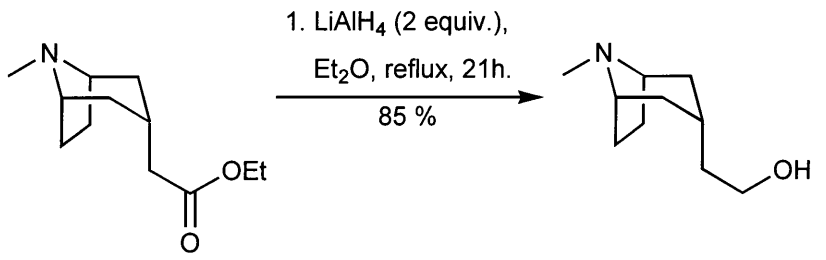
Following the literature methods previously described by Zirkle[151] *et al.* and Kato[152] *et al.*, allylic alcohol **231** (with 11 % of **232**) was then subjected to hydrogenation with a catalytic amount of palladium on activated carbon, but under 1 atm. pressure of hydrogen. This resulted in a reaction product of **230**, as shown in **Scheme 109**. The optimal conditions for this hydrogenation was 3-4 atm. pressure and the double bond was efficiently reduced to the saturated alcohol **230**. Alcohol **230** was purified by distillation and obtained as a clear oil in excellent yield (84 %). The ^{13}C NMR revealed that alcohol **230** was a mixture of *endo* (88 %) and *exo* (12 %) isomers, in the ratio of 7:1.



231 (+ 11 % of **232**) *endo*-**230** / *exo*-**230** (7:1)

Scheme 109

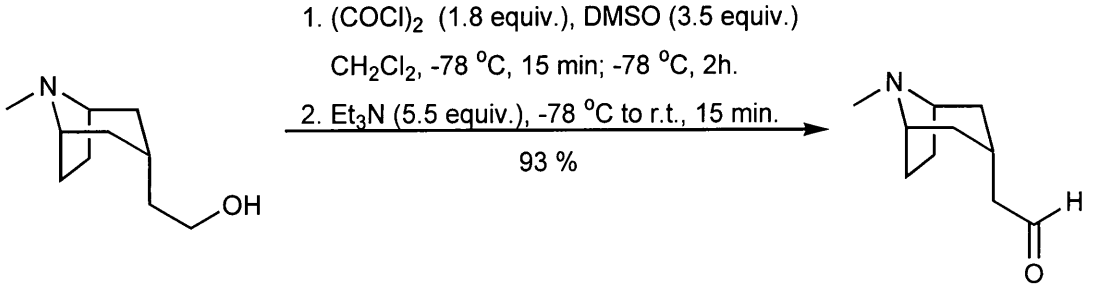
With saturated ester **214** in hand, its $LiAlH_4$ reduction to the corresponding alcohol **230** was also explored. The $LiAlH_4$ reduction of **214** was carried out in refluxing diethyl ether, as illustrated in **Scheme 110**. In the event this proved straightforward and upon work-up by the hydrolysis method described by Micolovic[161] and Mihailovic, alcohol **230** was obtained as a clear oil and in good yield (85 %). In comparison to the $LiAlH_4$ reduction of unsaturated ester **132**, the $LiAlH_4$ reduction of saturated ester **214** progressed much more smoothly.



214 (5:1 *endo / exo*) **230** (5:1 *endo / exo*)

Scheme 110

With alcohol **230** (5:1 *endo / exo*) in hand, it was subjected to various oxidation protocols with pyridinium chlorochromate[162] (PCC) and pyridinium dichromate[163] (PDC), however all failed to give the necessary aldehyde **227**. However, following the method described by Gilligan[164] *et al.*, the Swern oxidation of **230** proved very successful and gave aldehyde **227** in excellent yield (93 %). As described by Mancuso[165] *et al.*, the reaction first involves the activation of dimethyl sulfoxide (DMSO) by the addition of oxalyl chloride [$(COCl)_2$] at low temperature (-78 °C to -60 °C). This is followed by the addition of alcohol **230** and triethylamine (Et_3N), as depicted in **Scheme 111**.



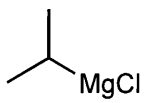
230 (5:1 *endo / exo*) **227** (5:1 *endo / exo*)

Scheme 111

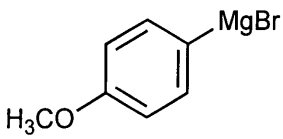
Longer reaction times (e.g. 24h or 45h) led to the formation of some unidentified side products. However, short reaction times (max 30 min.), upon work-up, gave aldehyde **227** as a light-brown oil in excellent yield (93 %) and in this case aldehyde **227** was sufficiently clean to be used directly in the next step. It is noteworthy that when the aqueous layer was at pH 9-10, aldehyde **227** was always isolated as its HCl salt and in low yields. However, with the aqueous layer at pH 10-11, aldehyde **227** was isolated as

a free amine and in excellent yield (93 %). The isomer ratio was calculated to be 5:1 from the integration of aldehydic protons in the ^{1}H NMR spectrum. This ratio was consistent with the isomer ratio of the starting material.

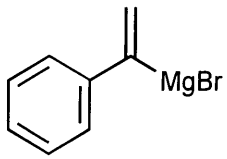
With aldehyde **227** in hand, a series of Grignard reactions were explored. These involved reactions with isopropylmagnesium chloride **225**, 4-methoxyphenyl-magnesium bromide **226** and α-phenylvinylmagnesium bromide **235**. In all of the three Grignard reactions studied, the literature method described by Gilligan[164] *et al.* was followed, with only slight modifications to optimise the reactions conditions.



225

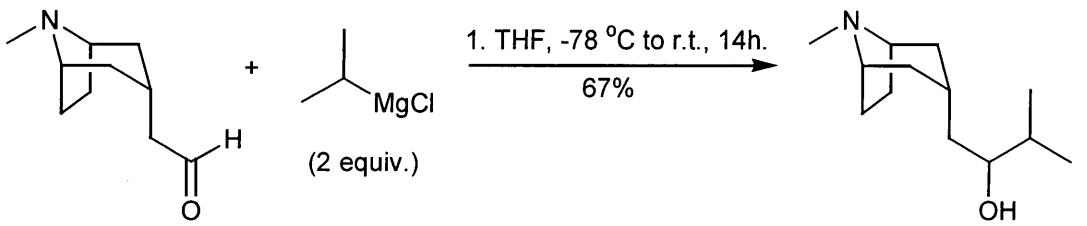


226



235

Aldehyde **227** was first reacted[164] with the commercially available Grignard reagent **225**, as depicted in **Scheme 112**, under different conditions (see **Table 14**, p. 102). At the outset, the reaction was carried out in THF and at low to high temperature for 14 hours (**Table 14**: **Entry 1**). In the event, alcohol **236** was obtained as a mixture of *endo* and *exo* isomers in good yield (67 %). This was clearly evident by the ^{13}C NMR spectrum of alcohol **236**, in which two sets of signals were displayed in a 5:1 ratio for each carbon, as illustrated in **Figure 16**. This ratio reflects the ratio of the starting aldehyde **227**. The reaction was then repeated in THF and at room temperature for a longer time period (**Table 14**: **Entry 2**). On work-up, the extraction was carried out with the aqueous layer at pH 9-10, instead of pH at 10-11, and alcohol **236** was obtained as its HCl salt, but in low yield (12 %).



227 (5:1 *endo / exo*) **225** **236** (5:1 *endo / exo*)

Scheme 112

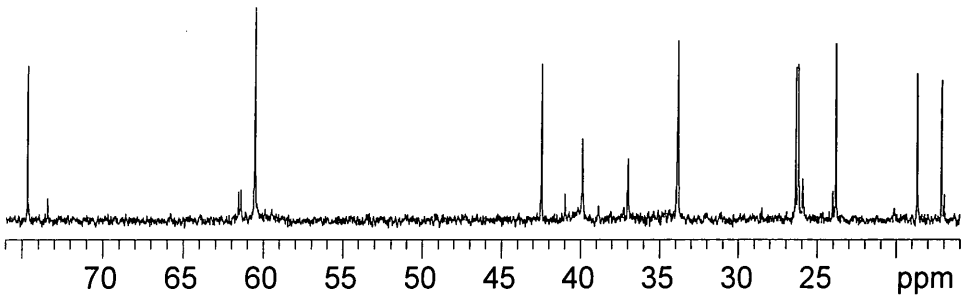


Figure 16: The ^{13}C NMR spectrum of alcohol **236** obtained from the Grignard reaction of aldehyde **227** with isopropylmagnesium chloride **225** at room temperature, showing a 5:1 isomer ratio.

The reaction was finally conducted in diethyl ether and at low temperature for a short time (**Table 14: Entry 3**). After the usual work-up, alcohol **236** was isolated as a clear oil, but was contaminated with the unreacted aldehyde **227**. Alcohol **236** was readily separated from residual unreacted aldehyde **227** during work-up with the aqueous layer at pH 9-10 and extraction into dichloromethane. From this, alcohol **236** was obtained as an almost *endo* isomer, but in low yield (16 %). This was evident by the ^{13}C NMR spectrum shown in **Figure 17**.

Entry	Excess of Grignard (equiv.)	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)
1	2	THF	-78/r.t.	14	67
2	2	THF	r.t.	21	12
3	1.5	Et_2O	-70/-10	1.5	16

Table 14: The Grignard reaction of aldehyde **227** with isopropylmagnesium chloride **225** under different conditions.

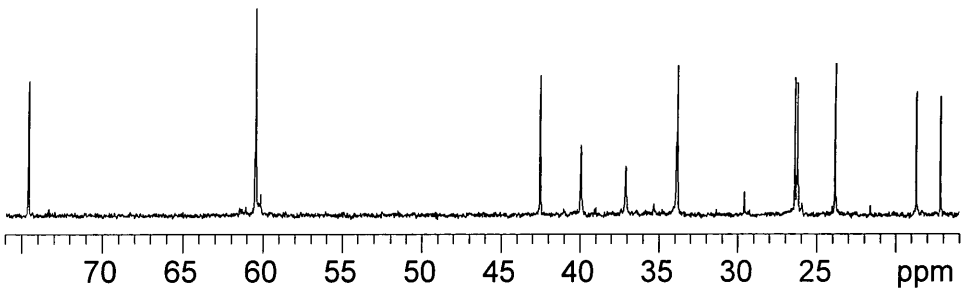
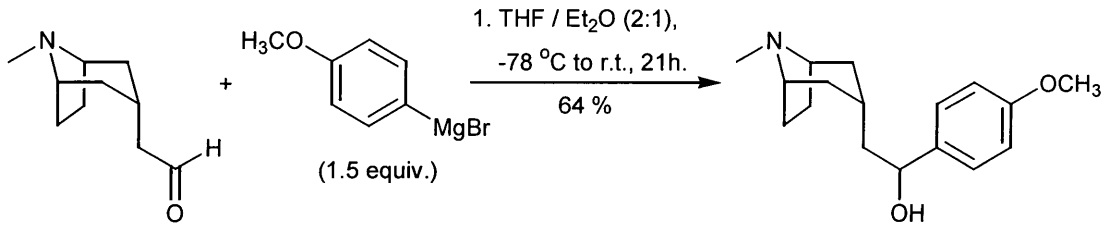


Figure 17: The ^{13}C NMR spectrum of alcohol **236** obtained from the Grignard reaction of aldehyde **227** with isopropylmagnesium chloride **225** at low temperature, showing a predominant *endo* isomer.

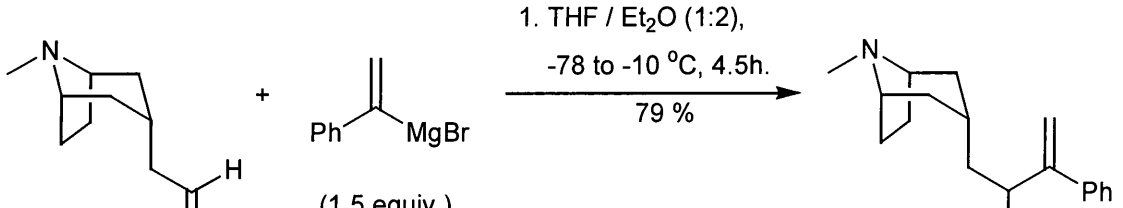
Aldehyde **227** was next subjected to a Grignard reaction[164] with 4-methoxyphenyl-magnesium bromide **226**, as illustrated in **Scheme 113**. At the outset, the reaction was carried out in a 2:1 mixture of THF / diethyl ether, and at low (-78 °C) to high temperature (r.t.), for an extended time period (21 h). From this, alcohol **237** was obtained as a mixture of *endo* and *exo* isomers again in the ratio of 5:1 and in good yield (64 %). The reaction was then conducted in diethyl ether at low temperature (-70 °C to -20 °C) for a shorter time (1.5 h) and this gave alcohol **237** as an almost *endo* isomer, but in low yield (13 %).



227 (5:1 *endo / exo*) **226** **237** (5:1 *endo / exo*)

Scheme 113

It emerges that product alcohols can be obtained as predominantly single *endo* isomers at low temperatures with short reaction times, where conversions are also low. This indicates some level of kinetic discrimination during the reaction. To explore this further, α-phenylvinylmagnesium bromide **235**, the last Grignard reagent studied in this series, was first prepared in diethyl ether from the reaction of α-bromostyrene and magnesium turnings, according to the method of Normant[156], where a trace of iodine was used. Following the method described by Gilligan[164] *et al.*, 1.5 equivalents of the Grignard reagent **235** was then reacted with aldehyde **227**, as shown in **Scheme 114,** with different reaction times (see **Table 15**, p. 104).



227 (5:1 *endo / exo*) **235** **238** (5:1 *endo / exo*)

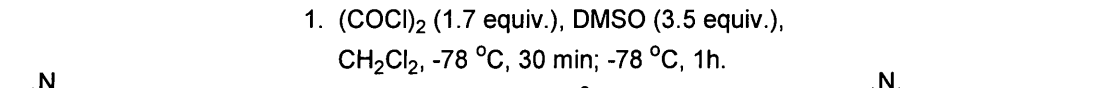
Scheme 114

With a short reaction time (**Table 15, Entry 1**) again only an *endo* isomer of alcohol **238** was obtained in a low yield (19 %). As the reaction time was increased (**Table 15, Entry 2**), the yield increased and the isomer ratio was now 11.5:1.0, indicating some reaction of the minor *exo* isomer. Extending the reaction time to 4.5h (**Entry 3**) resulted in complete reaction to give the alcohol **238** in excellent yield (79 %), and now in a ratio of 5:1, which reflects that of the starting aldehyde **227**.

Entry	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Isomer ratio (*endo* / *exo*)
1	Et_2O	-60/0	1.5	19	endo
2	THF/Et_2O (2:1)	-78/-60	3	38	11.5/1.0
3	THF/Et_2O (1:2)	-78/-10	4.5	79	5.1/1.0

Table 15: The Grignard reaction of aldehyde **227** with α-phenylvinylmagnesium bromide **235** under different conditions.

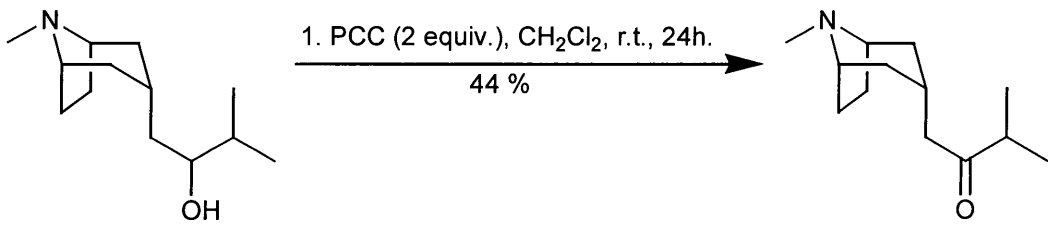
In order to complete the synthesis of the target ketone analogues, it became necessary to oxidise the corresponding alcohols **236**, **237** and **238**, either as a mixture of *endo* and *exo* isomers or as an *endo* isomer. Alcohol **236** was chosen as the first substrate and following the method described by Gilligan[164] *et al.*, it was subjected to the Swern oxidation, as a mixture of *endo* and *exo* isomers. During the Swern oxidation, dimethyl sulfoxide (DMSO) was activated first by the addition of oxalyl chloride $[COCl)_2]$ at -60 / -70 °C, and was then followed by subsequent reaction with alcohol **236** and triethylamine (Et_3N), as depicted in **Scheme 115**.



236 (5:1 *endo* / *exo*) **218** (5:1 *endo* / *exo*)

Scheme 115

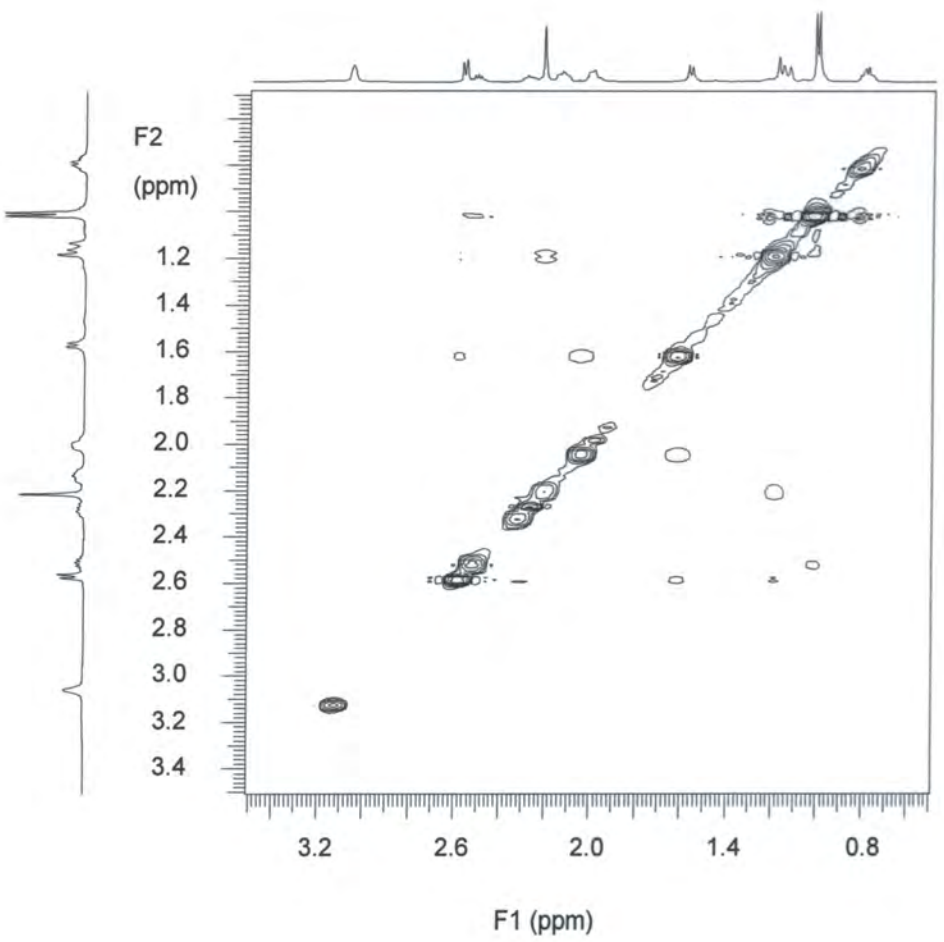
Although the Swern oxidation was very successful in generating ketone **218** (5:1 *endo/exo*), there was a general drawback due to the unpleasant smell of dimethyl sulphide. Therefore oxidation of alcohol **236** to the corresponding ketone **218** was also explored using the pyrridinium chlorochromate (PCC) adsorbed on to alumina. This method was described by Cheng[166] *et al.* and proved straightforward, as it only required stirring alcohol **236** and PCC in dichloromethane. The reaction is depicted in **Scheme 116**.



236 (5:1 *endo* / *exo*) **218** (5:1 *endo* / *exo*)

Scheme 116

The PCC adsorbed on alumina clearly prevented the black-tar formation, found in the unsupported reaction and thus aided the separation of the majority of PCC from the medium by filtration. However, isolation of ketone **218** from the traces of PCC still required further work-up. From this, the first ketone analogue **218** was obtained as a pale-yellow oil, as a mixture of *endo* / *exo* isomers (5:1). The reaction was conducted with an *endo* isomer of alcohol **236**, obtained after low conversion in the Grignard reaction and from this product ketone **218** was obtained as an *endo* isomer. The 2D ^{1}H NMR Nuclear Overhauser Enhancement Spectrum (NOESY) of product ketone **218**, obtained from this experiment, showed a strong interaction between the C9 protons and those attached to the *endo*-C6,7 protons. There are weak interactions as well between the C9 protons and *eq*-C2,4 and the C9 protons and the C-3 proton. From this it is concluded that the ketone **218** was indeed the *endo* isomer, and in retrospect, alcohol **236** must also be the *endo* isomer as well. The NOESY spectrum of ketone **218** and the relevant proton interactions are illustrated in **Figure 18**.



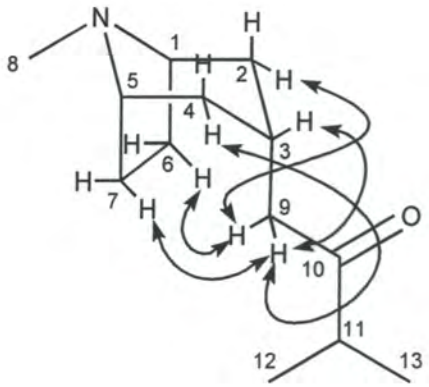
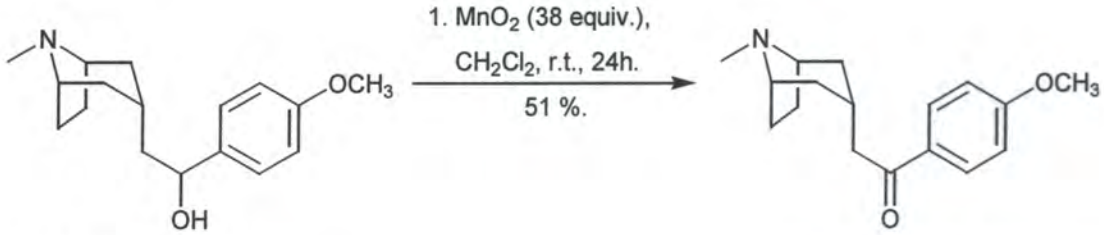


Figure 18: The NOESY spectrum of ketone **218** and the relevant proton interactions.

Since manganese dioxide (MnO_2) is a well known and mild oxidising agent[167], particularly for the oxidation of allylic and benzylic alcohols, it was anticipated that oxidation of alcohols **237** and **238** to the corresponding ketones **220** and **219** would be

readily achieved with MnO_2. In this respect, benzylic alcohol **237** (5:1 *endo/exo*) was subjected to oxidation with activated MnO_2 in dichloromethane, as shown in **Scheme 117**. In this reaction, the MnO_2 supported on activated carbon was used, and its activity was further increased, following the method described by Carpino[168]. This required heating at 80 °C for a few days in an oven.



237 (5:1 *endo / exo*) **219** (5:1 *endo / exo*)

Scheme 117

After filtration of the MnO_2, ketone **219** was obtained as a light-brown oil in moderate yield (51 %) with an isomer ratio of 5:1. The reaction was also conducted for the single *endo* isomer of alcohol **237**, and from this reaction ketone **219** was obtained as a single isomer. Ketone **219**, as its HCl salt was re-crystallised from a mixture of diethyl ether and ethanol. This allowed us to obtain an X-ray structure of ketone **219** from a suitable crystal. The resultant X-ray structure is depicted in **Figure 19** and clearly shows that ketone **219** is an *endo* isomer.

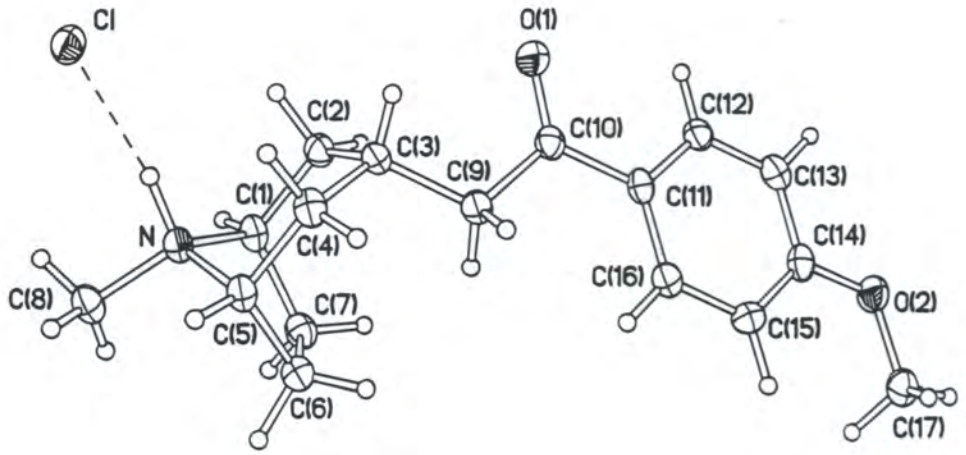
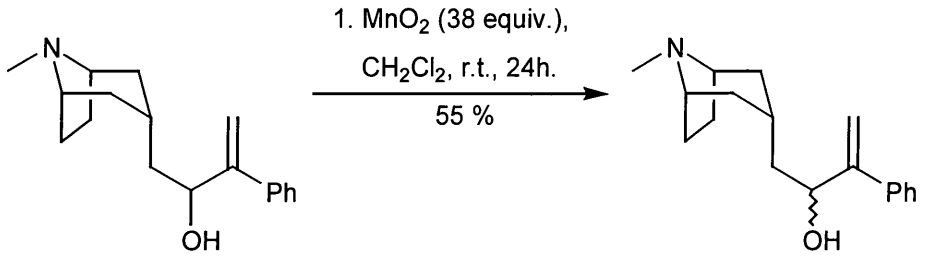


Figure 19: The X-ray structure of the *endo* ketone **219**.

Allylic alcohol **238** was then submitted to a similar oxidation with activated MnO_2 in dichloromethane, as shown in **Scheme 118**. After filtration, this gave the final ketone **220** of the series, as a light-brown oil again in moderate yield (55 %). These reactions could be followed conveniently by ^1H NMR spectroscopy. If the MnO_2 was used without activation, the reaction was generally incomplete, even when the reaction time was increased.

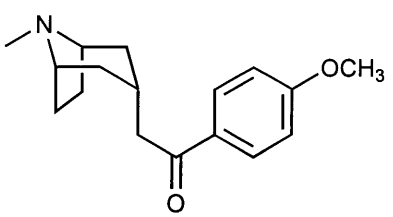


238 (5:1 *endo / exo*) **220** (5:1 *endo / exo*)

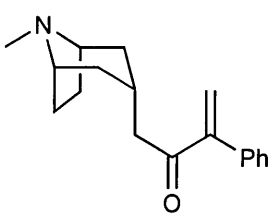
Scheme 118

3.2.3 Biological testing

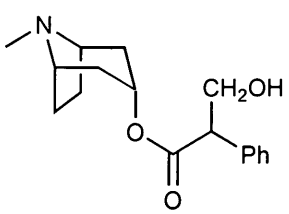
To assess the potential biological effects of the structural changes imposed by the CH_2 replacement, the muscarinic acetylcholine receptor (mAChR) antagonist activity of the ketone analogues **219** and **220** were determined using a *in vitro* guinea-pig ileum preparation. The results were compared with the mAChR antagonist atropine **202**. Biological tests were carried out in the laboratory of Dr. Robert F. Halliwell by Graham R. Foxon and myself at the Department of Biological Sciences in the University of Durham. The isolated guinea-pig ileum contains heterogeneous populations of muscarinic receptors[169], and is a well established pharmaceutical assay for the investigation of mAChR acting drugs[170].



219 (5:1 *endo / exo*)

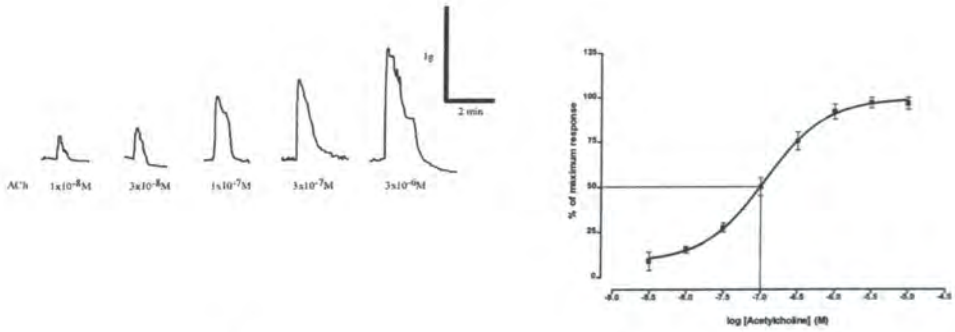


220 (5:1 *endo / exo*)



202

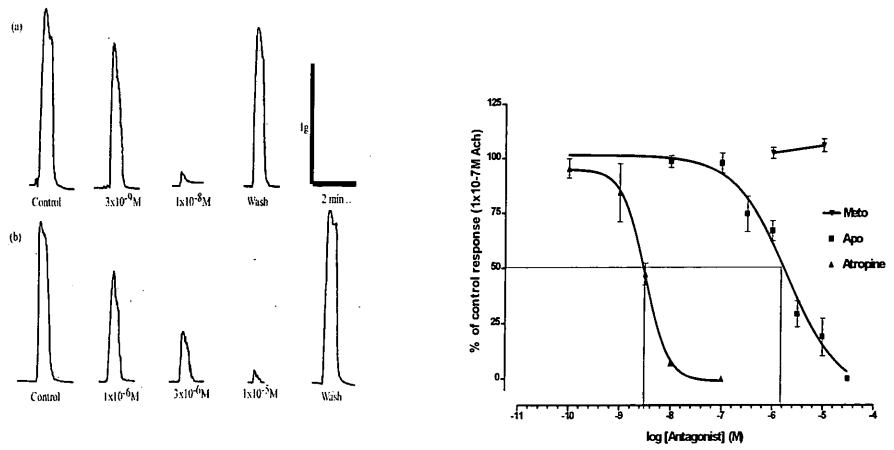
Addition of ACh (3 nM-10 μM) evoked a concentration-dependant contraction of the quinea-pig ileum, as depicted in **Figure 20a**. The EC_{50} value for ACh from **Figure 20b** was determined to be $1.15x10^{-7} \pm 0.0086$ M (n= 6). After a concentration response curve (CRC) was correlated, addition of 0.1 μM ACh yielded reproducible responses.



a b

Figure 20: a) The actual chart recorder traces of ACh-evoked responses from one of the 6 experiments; **b)** The concentration-response data plotted from an avarage of 6 experiments. The EC_{50} value for ACh was found to be $1.15x10^{-7} \pm 0.0086$ M (n= 6).

Atropine **202** (0.1 nM-0.1 μM) concentration-dependently inhibited the control ACh (0.1 μM) response, as illustrated in **Figure 21a**, demonstrating antagonist activity. The IC_{50} value for atropine from **Figure 21c** was determined to be $3.15x10^{-9} \pm 0.085$ M (n= 3), which was very close to those of the IC_{50} values (2 nM) reported by other research groups[171,172]. Ketone **220** similarly inhibited the control ACh (0.1 μM) response in a concentration dependant manner, as shown in **Figure 21b**. The IC_{50} value for ketone **220** from **Figure 21c** was determined to be $1.9x10^{-6} \pm 0.235$ M (n= 4). The inhibitory effects of atropine **202** and ketone **220** were reversible upon washing, but the reversibility of ketone **220** was much quicker than atropine **202**, suggesting less strong binding. A preliminary test with ketone **219** showed no inhibition of the control ACh (0.1 μM) response.

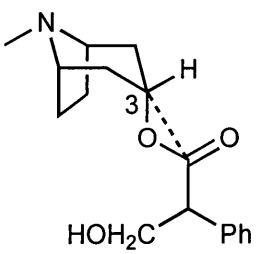


c

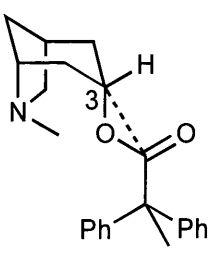
Figure 21: The actual chart recorder traces of ACh (0.1 μM)-evoked responses in the absence and presence of atropine **202 (a)** and ketone **220 (b)**; **c)** The concentration-inhibition data plotted from an avarage of 3 and 4 experiments for atropine **202** and ketone **220**, respectively. The EC_{50} values for atropine **202** and ketone **220** were $3.15x10^{-9} \pm 0.085$ M (n= 3) and $1.9x10^{-6} \pm 0.235$ M (n=4), respectively.

3.2.4 Conformation of ketones *versus* esters

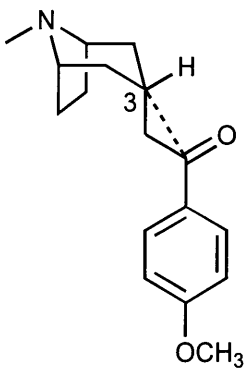
The three-dimensional structure of the muscarinic receptors is yet to be determined. Information on how muscarinic antagonists interact with these receptors comes from a comparison of the X-ray structures of both highly active and less active individual antagonists[172]. In this respect, the X-ray structure of atropine[173] **202** has played a crucial role in the correlation of the structural features of other known antagonists, such as azaprophen[174] **239**. In our case, the X-ray structure of ketone **219** was compared with those[174] of atropine **202** and azaprophen **239**.



202



239



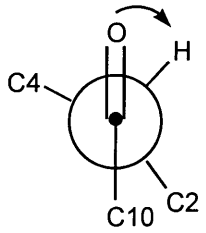
219

It was revealed that the replacement of the bridging ester O atom by a CH_2 group did not have a significant effect on:

i) the distance between the N atom and the carbonyl O atom. For **219** this was calculated to be 5.45 °A. The same N-O distance was 5.29 Å for atropine **202** and 5.41 Å for azaprophen **239**.

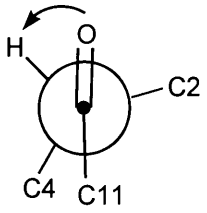
ii) the torsion angle (τ) between the secondary alcohol C(3)-H bond and the carbonyl C=O bond. For **219** this was calculated to be -34°. The same τ was 33° for atropine **202** and 30° for azaprophen **239**.

Atropine **202** and azaprophen **239**



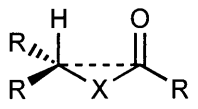
O=C-----C—H : 30 - 33°

ketone **219**



O=C-----C—H : - 34°

To gain a more informed conclusion on whether such tropane ketones can be convincing analogues of tropane esters for biological studies, it became desirable to get a wider picture on how the carbonyl C=O bond and the secondary alcohol C-H bond orientate in X-ray structures of other esters and ketones. The relationship between the C=O bond and the C-H bond is described by the torsion angle H-C···C=O (τ), as depicted in **Figure 22**.



O=C-----C—H (τ)

X= O, CH_2

Figure 22

For this purpose, a survey of the current (April 1999) release of the Cambridge Crystallographic Database[175] (CSD) was carried out by Dr. Andrei S. Batsanov (Durham University), for related structures and the τ values determined. The results, which are

summarised in Table **Table 16**, clearly show that the conformation of ketone **219** (τ= -34°) is similar to the mean value for fragments in both **Entry 2** and **Entry 3**. This study is really very revealing, and indicates that the replacement of O by a CH_2 group in going from tropane esters to ketones does not introduce a dramatic conformational change. Thus the ketones are anticipated to produce good biological mimics of these tropane esters.

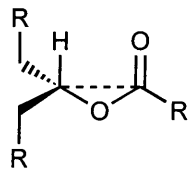
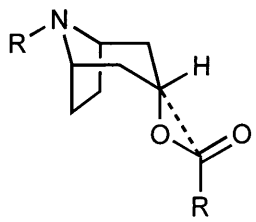
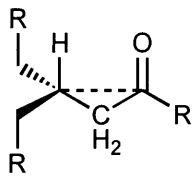
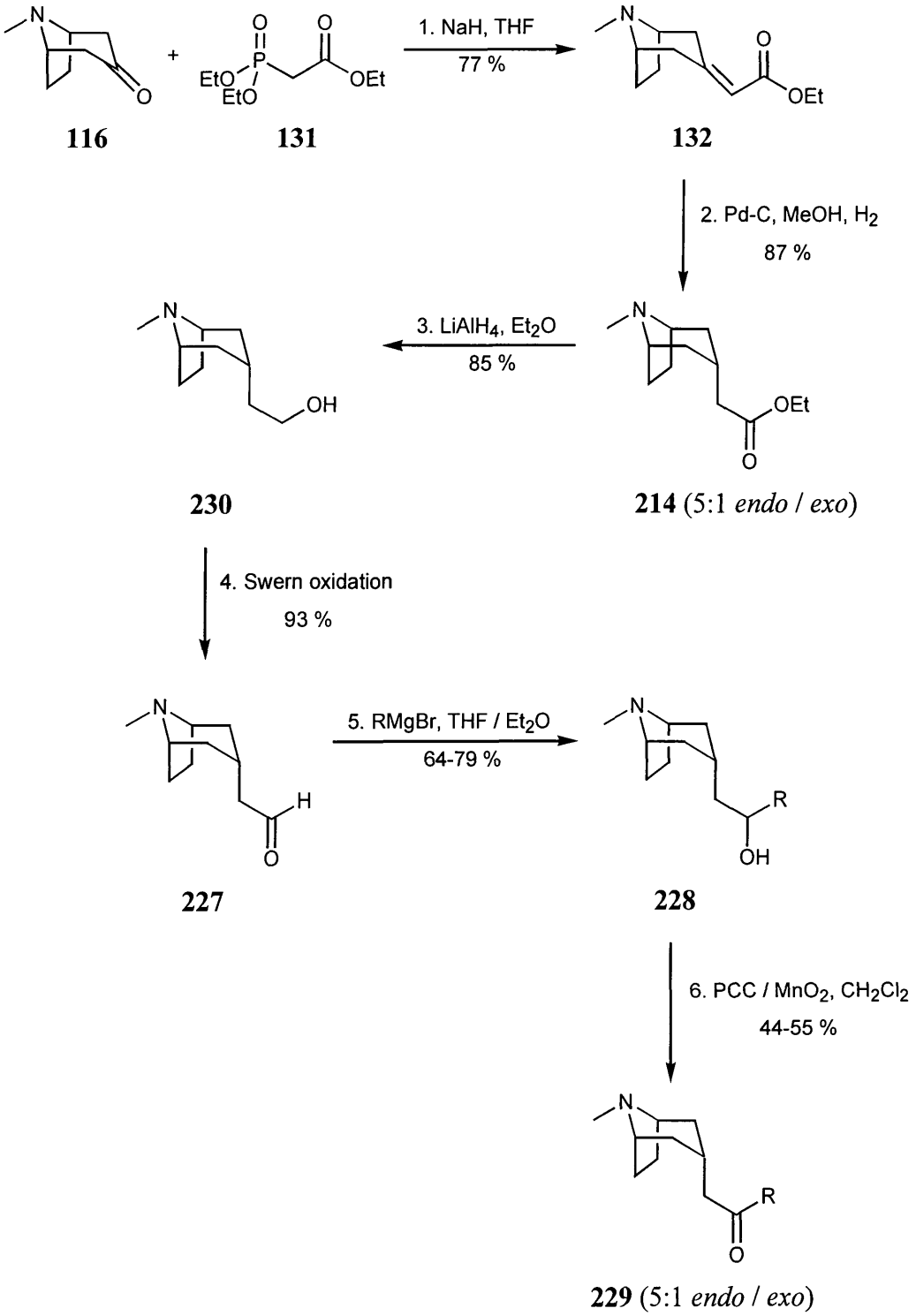
Entry	Type of fragment	Number of compounds	Torsion angle (τ) extremes	Mean value of (τ)
1		221	1-56 (18-42, 82 %)	30-32
2		12	20-48	36
3		14	34-49	41

Table 16: Torsion angles H-C·····C=O (τ) in esters of secondary alcohols (**Entry 1**), tropane esters (**Entry 2**) and ketones (**Entry 3**).

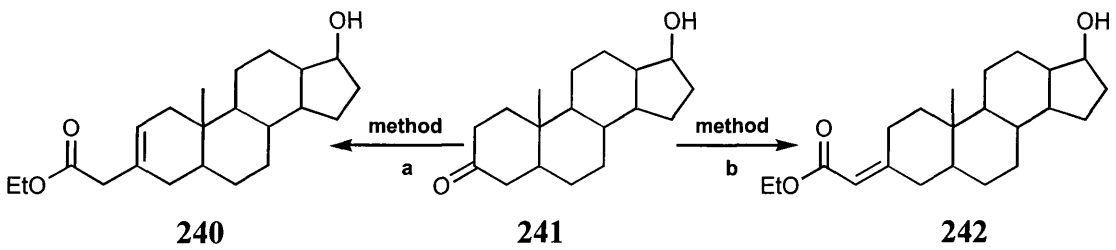
3.2.5 Discussion

In this research programme a six-step route has been developed from tropinone **116** to ketones **229**, as depicted in **Scheme 119**.



Scheme 119

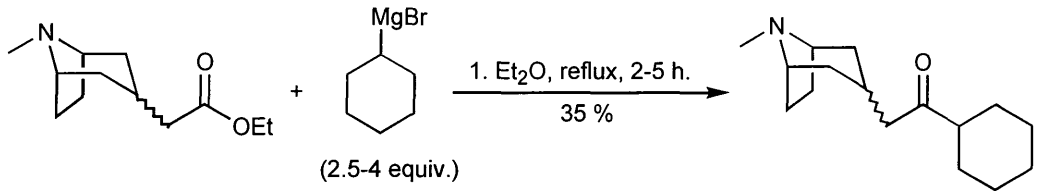
For the first step, the HWE reaction of tropinone **116** with triethyl phosphonoacetate **131** proceeded smoothly and generated the α,β-unsaturated ester **132** as the major product. The yield was good (77 %), however this was contaminated with the β,γ-unsaturated ester **133** as a minor product. Similar observations were also noted in other literature reactions of cyclic ketones[176] with triethyl phosphonoacetate **131**. For instance, the reaction of dihydrotestosterone **241** with triethyl phosphonoacetate **131** in the presence of 2 equivalents of NaH at 80 °C (**method a**) was reported to give the β,γ-unsaturated ester **240** in quantitative yield. However, the same reaction, in the presence of 1 equivalent of NaH (**method b**), gave exclusively the α,β-unsaturated ester **242** as the *trans* isomer, as illustrated in **Scheme 120**.



240 **241** **242**

Scheme 120

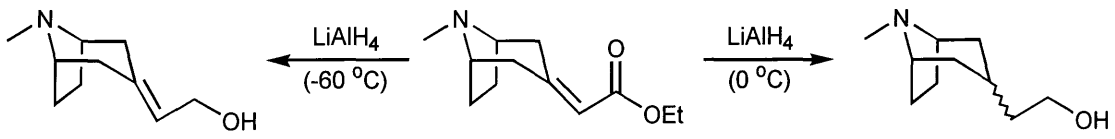
For the second step, successful hydrogenation of the α,β-unsaturated ester **132** was only achieved after the esters **132** and **133** was treated with HCl and the aqueous layer was washed with diethyl ether. Thus hydrogenation gave the saturated ester **214** in excellent yield (87 %). The Grignard reactions of ester **214** with isopropylmagnesium chloride and 4-methoxyphenyl-magnesium bromide proved unsatisfactory, as the conversion was only about 50 %. Unsatisfactory results were also reported by Zirkle[151] *et al.* in the Grignard reaction of ester **214** with cyclohexymagnesium bromide **243** (2.5-4 equivalents). For instance, when the reaction was carried out at room temperature, the corresponding ketone **244** was obtained in an optimised yield of 35 %, as shown in **Scheme 121**.



214 **243** **244**

Scheme 121

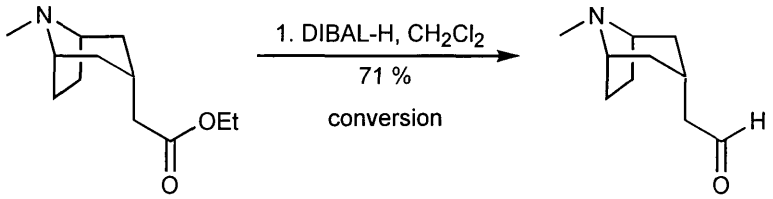
For the third step, $LiAlH_4$ reduction of the saturated ester **214** was successful in generating alcohol **230** in good yield (85 %). The attempted synthesis of alcohol **230** by $LiAlH_4$ reduction of the α,β-unsaturated ester **132** resulted in generating either allylic alcohol **231** or a 1:1 mixture of allylic and saturated alcohols **231** and **230**. However, when the α,β-unsaturated ester **132** was added to the slurry of $LiAlH_4$ at -60 °C, allylic alcohol **231** was the only product isolated. This proved to be a very subtle reaction. At 0 °C, partial addition of the hydride to the C=C double bond also occurred to generate alcohol **230**, as depicted in **Scheme 122**.



231 **132** **230**

Scheme 122

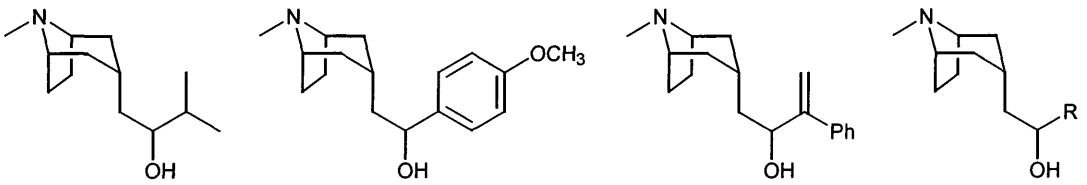
For the fourth step, aldehyde **227** was obtained by Swern oxidation of alcohol **230** in excellent yield (93%). As depicted in **Scheme 123**, attempted synthesis of aldehyde **227** from the direct DIBAL-H reduction of saturated ester **214** was unsuccessful. The conversion was about 71 %, but the separation of aldehyde **227** from ester **214** could not be achieved, as it decomposed on silica and on neutral alumina.



214 **227**

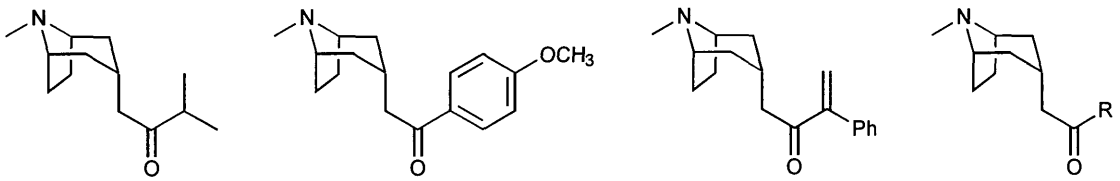
Scheme 123

For the fifth step, Grignard reactions of aldehyde **227** generated secondary alcohols **236**, **237** and **238**, with the general structure **228**, in good yields (64-79 %). At low temperature and with short reaction time, the alcohols **228** were isolated as predominantly *endo* isomers. However, the yields were low (13-19 %).



236 **237** **238** **228**

For the final step, oxidation of alcohols **228** either by MnO_2 or PCC gave the corresponding ketones **218**, **219** and **220**, with the general structure **229**, in moderate yields (44-55 %). It was concluded both from NOE spectrum of **218** and X-ray structure of **219** that ketones were predominantly *endo* isomers and it follows that the alcohols must also be the *endo* isomers.



218 **219** **220** **229**

It was shown that ketone **220** is a novel muscarinic acetylcholine receptor (mAChR) antagonist, which is 500-fold less potent than atropine, but 33-fold more potent than pirenzepine[171,172] in the inhibition of the ACh-induced contraction of guinea-pig ileum. Pirenzepine is a mAChR antagonist, which reduces gastric acid and pepsin secretion and was once popular for the treatment of peptic ulcers[177].

CHAPTER FOUR

Experimental

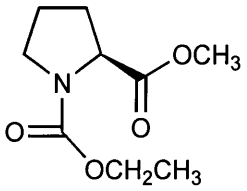
CHAPTER FOUR

4.1 General experimental

^{1}H-, ^{13}C-, ^{19}F- and ^{31}P-NMR spectra were recorded on the following spectrometers: A Varian Gemini-200, operating at 199.977 MHz for the proton and at 50 MHz for the carbon. A Bruker AC-250, operating at 250.133 MHz for the proton and 62.257 MHz for the carbon. A Varian VXR-400 (S), operating at 399.952 MHz for the proton and 100.577 MHz for the carbon. The chemical shifts are δ (ppm) units and quoted relative to tetramethylsilane (TMS) in chloroform-*d* ($CDCl_3$), followed by the number of hydrogens, multiplicity, and assigment. Infrared (ir) spectra were recorded on a Perkin-Elmer F. T. 170X spectrometer. Band positions are recorded as their wavenumber (cm^{-1}) and given as maximum absorption (ν_{max}). Mass spectra (ms) were recorded on a VG Analytical 7070E organic mass spectrometer, operating at 70eV. Peaks are reported as m/e ratios, followed by relative intensities in parentheses. All melting points (m.p.) were determined in Pyrex capillaries, using a digital Gallenkamp melting point apparatus and are uncorrected. Optical rotations, $[\alpha]_D^{25}$ were measured on an Optical Activity Ltd. AA-10 Automatic Polarimeter and are recorded in units of $10^{-1}deg.cm^2g^{-1}$. Flash Chromatography was carried out using Fluka silica gel-60 (35-70 μm), or Beckman activated neutral aluminium oxide. X-Ray crystal data was collected on a Siemens R3m/v diffractometer. All solvents were dried and distilled prior to use unless otherwise stated. Solvents were dried from the following reagents under a nitrogen atmosphere: Tetrahydrofuran (THF) and diethyl ether were dried first by standing over sodium wire and then heated at reflux over sodium and benzophenone until the mixture develops the deep purple colour of the sodium benzophenone ketyl. Dichloromethane (DCM), chloroform (wash with water to remove EtOH, dry over KCO_3) and toluene distilled first to discard wet forerun and then heated at reflux over calcium hydride. Methanol (MeOH) and ethanol (EtOH) were heated under reflux over magnesium alkoxide. Acetone was dried first over $MgSO_4$, and then heated under reflux over phosphorus pentoxide. Petrol refers to petroleum ether (40-60 °C) and ether refers to diethyl ether. Non-aqueous reactions were carried out under a nitrogen atmosphere. In general chemicals were used as received from suppliers (Aldrich, Sigma and Jannsen).

4.2 Experimental for chapter one

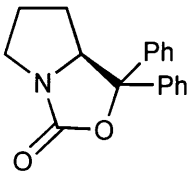
4.2.1 (*S*)-N-Ethoxycarbonyl-2-(methoxycarbonyl)pyrrolidine[37] 44



44

Ethyl chloroformate (178 g, 1.6 mol) was added dropwise to a suspension of (*S*)-proline **43** (90 g, 0.78 mol) and Na_2CO_3 (87 g, 0.82 mol) in MeOH (800 ml) at 0 °C. After addition was complete, the solution was stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue partitioned between water and $CHCl_3$. Organic products were extracted into $CHCl_3$ (8x100 ml) and the combined extracts were washed with brine (3x100 ml) and dried over $MgSO_4$. Concentration gave the title compound **44** (157 g, 100%) as a clear oil. δ_H 1.00-1.25 (2H, m, C4), 1.70-2.00 (2H, m, C3), 2.00-2.30 (3H, m, $C\underline{H}_3CH_2O$), 3.25-3.50 (2H, m, C5), 3.60 (3H, s, CH_3O), 3.95-4.15 (H, m, CH), 4.15-4.35 (2H, q, $CH_3C\underline{H}_2O$). δ_C 14.6 ($\underline{C}H_3CH_2O$), 23.4 and 24.3 (C4), 29.8 and 30.8 (C3), 46.2 and 46.6 (C5), 52.0 and 52.1 (OCH_3), 58.7 and 58.9 (C2), 61.1 and 61.2 ($O\underline{C}H_2CH_3$), 154.5 and 155.0 (N-C=O), 173.2 and 173.3 (C=O). **$C_9H_{15}NO_4$.** Calculated C 53.70, H 7.52, N 6.96; Found C 53.41, H 7.50, N 7.61. **ν_{max} (cm^{-1}):** 2981, 2956, 2882, 1749 and 1703 (C=0), 1419, 1382, 1349, 1201, 1174, 1121, 1090. **m/z (EI)** 201 (M^+, 5 %), 142 (100 %), 70 (91 %), 41 (46 %).

4.2.2 (*S*)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane[38] 2

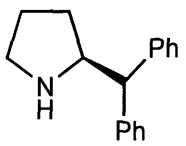


2

A solution of (*S*)-N-ethoxycarbonyl-2-(methoxycarbonyl)pyrrolidine **44** (157 g, 0.78 mol) in THF (300 ml) was added dropwise to a 1 M solution of PhMgBr (284 g, 1.6 mol) in THF at 0 °C. The reaction mixture was heated under reflux for 48 h, and then

an ice-cold saturated solution of NH_4Cl (2000 ml) was added. Organic products were extracted into ethyl acetate (20x100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave a crude product as a pale-yellow solid, which was re-crystallised from ethyl acetate. This gave the title compound **2** (133 g, 61 %) as a white amorphous solid. m.p. 148.3-148.5 °C (lit 148-149 °C). $[\alpha]_D^{25}$ = -271° (c, 1.00 in CH_2Cl_2) (lit[38]: -241.6 (c, 0.002, MeOH). δ_H 1.00-1.25 (1H, p, C4), 1.65-2.05 (3H, m, C3 and C4), 3.15-3.35 (1H, m, C5), 3.65-3.80 (1H, m, C5), 4.50-4.65 (1H, dd, CH), 7.20-7.45 (8H, m, Ar-H), 7.45-7.60 (2H, d, Ar-H). δ_C 24.9 (C4), 29.0 (C3), 46.0 (C5), 69.2 (CH), 85.8 (C), 125.4, 125.9, 127.7, 128.3, 128.5, 140.2, 143.3 (Ar), 160.4 (N-C=O). **$C_{18}H_{17}NO_2$.** Calculated C 77.38, H 6.14, N 5.02; Found C 77.25, H 6.16, N 4.94. **ν_{max} (cm^{-1}):** 2979, 2905, 1751 (C=O), 1447, 1387, 1345, 1248, 1227, 1056, 1005. **m/z (EI)** 279 (M^+, 13 %), 182 (45 %), 105 (100 %), 77 (32 %); **(CI)** 280 (MH^+, 9 %), 236 (16 %), 70 (2 %).

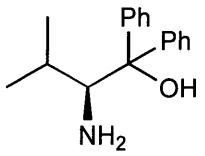
4.2.3 (*S*)-α-(Diphenylmethyl)pyrrolidine 1



1

A 20 g of palladium (10 %) on activated carbon was added to a solution of (*5S*)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane **2** (133 g, 0.48 mol) in MeOH (900 ml) at room temperature. The mixture was stirred until the hydrogenation was complete, as judged by the consumption of hydrogen gas by volume. Filtration of the catalyst and removal of the solvent gave a residue, which was re-crystallised from isopropyl alcohol as an HCl salt. After basification with NaOH and extraction into ethyl acetate (6x100 ml), concentration yielded the title compound **1** (50 g, 44 %) as an oil. **$[\alpha]_D^{25}$** = -7.8° (c, 2.05 in $CHCl_3$) (lit[35]: -7.8 (c, 2.11 in $CHCl_3$). δ_H 1.51-1.62 (1H, m, C4), 1.83-2.00 (3H, m, C3 and C4), 2.28 (1H, s, NH), 2.92-2.98 (1H, m, C5), 3.10-3.19 (1H, m, C5), 3.82-4.01 (2H, m, CH). δ_C 24.8 (C4), 30.6 (C3), 46.2 (C5), 58.5 ($CHPh_2$), 62.3 (CH), 126.4, 128.3, 128.7, 143.7 (Ar). **$C_{17}H_{20}NCl$ (HCl salt).** Calculated C 74.69, H 7.38, N 5.13, Cl 12.80; Found C 74.65, H 7.62, N 4.98, Cl 12.71. **ν_{max} (cm^{-1}):** 3405 (NH). **m/z (EI)** 237 (M^+, 0.3 %), 167 (35 %), 70 (100 %); **(CI)** 238 (MH^+, 100 %), 70 (22 %).

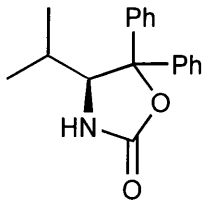
4.2.4 (*S*)-2-Amino-1,1-diphenyl-3-methylbutan-1-ol[51,52,53] 71



71

(*S*)-Valine methyl ester hydrochloride **65** (9.9 g, 59.1 mmol) was added portionwise to a 1 M solution of phenylmagnesium bromide (108.8 g, 0.6 mol) in THF at 0 °C and heated at reflux for 20h. After quenching with an ice-cold saturated solution of NH_4Cl, the organic layer was separated, washed with brine and concentrated. The resulting solid was treated with HCl (2 M, 100 ml) and then evaporated to dryness. A large amount of biphenyl impurity precipitated out as a white solid when the amine-hydrochloride salt was dissolved in hot MeOH and allowed to cool to room temperature. After filtration, the filtrate was made basic with KOH (1 M) and the organics were extracted into diethyl ether (4x100 ml). Combined extracts were dried over $MgSO_4$ and concentrated to obtain a crude product as a light brown solid. Purification over silica gel, eluting with a 1:4 and 1:1 mixture of ethyl acetate and petrol gave the title compound **71** (5.4 g, 36 %) as a white amorphous solid. **m.p.** 90-92 °C (lit[51,52] 94-95 °C). $[\alpha]_D^{25}$ = - 107.9° (c, 4.24 in $CHCl_3$) (lit[51]: - 127.7° (c, 0.64 in $CHCl_3$). δ_H 0.83 (6H, dd, J= 6.9 and 7.2 Hz, CH_3), 1.58-1.76 (1H, m, CH-Me_2), 0.40-2.80 (3H, NH_2 and OH), 3.76 (1H, s, CH-NH_2), 7.04-7.58 (10H, m, Ar). δ_C 16.3, 23.2 (CH_3), 28.1 (CH-Me_2), 60.4 (CH-NH_2), 79.9 (C), 125.7, 126.1, 126.5, 126.8, 128.2, 128.6, 145.1, 148.2 (Ar). **$C_{17}H_{21}NO$.** Calculated C 79.96, H 8.29, N 5.48; Found C 79.80, H 8.15, N 5.39. ν_{max} **(cm^{-1}):** 3383 (N-H), 3338 (O-H), 3021 (Ar C-H), 2962, 2926, 2873 (methyl C-H), 1594, 1490, 1447 (Ar C=C), 1382, 1366 (methyl C-H). **m/e (CI)** 256 (MH^+, 14 %), 72 (100 %).

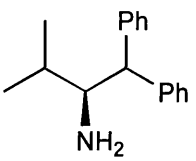
4.2.5 (*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone[52,53,55] 72



72

Trichloromethyl chloroformate (2.7 g, 13.7 mmol) was added to a mixture of (*S*)-2-amino-1,1-diphenyl-3-methylbutan-1-ol **71** (3.2 g, 12.4 mmol) and triethylamine (2.7 g, 26.5 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2h at the same temperature and then poured into a brine solution (250 ml). The aqueous layer was made basic with NaOH pellets and the organics were extracted into AcOEt (5x200 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated. The resulting crude product was washed with diethyl ether to obtain the title compound **72** (3.0 g, 86 %) as a white amorphous solid. **m.p.** 250-251 °C (lit[52] 250-251 °C; lit[53] 250-252 °C). $[\alpha]_D^{25}$ = - 201.6° (c, 2.52 in DMSO) (lit[53]: - 259.4° (c, 0.32 in $CHCl_3$). δ_H (DMSO-d_6) 0.51 (3H, d, J= 6.6 Hz, CH_3), 0.92 (3H, d, J= 7.2 Hz, CH_3), 1.76-1.94 (1H, m, CH-Me_2), 4.46 (1H, s, CH-NHCO), 7.24-7.72 (10H, m, Ar-H), 8.14 (1H, s, NH). δ_C (DMSO-d_6) 15.2, 20.9 (CH_3), 29.8 (CH-Me_2), 64.9 (CH-NH), 88.4 (C), 125.8, 126.2, 127.9, 128.4, 128.8, 129.1, 140.5, 146.1 (Ar), 158.1 (C=O). **Accurate mass (CI):** Found 282.149210; Calculated for (MH^+) $C_{18}H_{20}NO_2$ 282.149404 (0.7 ppm). ν_{max} **(cm^{-1}):** 3295 (N-H), 2956, 2927, 2867 (methyl C-H), 1765, 1746 (C=O), 1596, 1490, 1451 (Ar C=C), 1251 (C-O). **m/e (CI)** 299 (MNH_4^+, 8 %), 282 (MH^+, 25 %), 238 (96 %), 223 (100 %), 72 (100 %).

4.2.6 (*S*)-α-(Diphenylmethyl)-α-isopropyl-methylamine 70

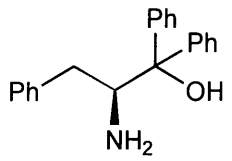


70

A solution of (*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **72** (2.9 g, 10.3 mmol) in MeOH/AcOH and a 10 % Pd (435 mg, 4.1 mmol) on activated carbon was shaken for 68h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was

treated with HCl (2 M, 50 ml), stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organic compounds were then extracted into AcOEt (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. Re-crystallisation from petroleum ether gave the title compound **70** (1.8 g, 72 %) as a light-brown crystals. **m.p.** 71-72 °C. $[\alpha]_D^{25}$ = - 4.2° (c, 10.98 in $CHCl_3$). δ_H 0.78 (3H, d, J= 6.6 Hz, CH_3), 0.91 (3H, d, J= 7.2 Hz, CH_3), 1.26 (2H, broad s, NH_2), 1.54-1.72 (1H, m, $CHMe_2$), 3.45 (1H, dd, J= 10.5 and 2.4 Hz, CH-NH_2), 3.70 (1H, d, J= 10.5 Hz, CH-Ph_2), 7.00-7.40 (10H, m, Ar-H). δ_C 14.2, 21.5 (CH_3), 28.9 (CH-Me_2), 58.1 (CH-Ph_2), 58.9 (CH-NH_2), 126.5, 126.7, 128.2, 128.5, 128.8, 129.0, 143.5 (Ar). **$C_{17}H_{21}N$.** Calculated C 85.30, H 8.84, N 5.85; Found C 85.12, H 8.91, N 5.96. **ν_{max} (cm^{-1}):** 3361 (N-H), 3065, 3022 (Ar C-H), 2956, 2926, 2867 (methyl C-H), 1596, 1493, 1450 (Ar C=C). **m/e (CI)** 240 (MH^+, 8 %), 72 (100 %).

4.2.7 (*S*)-2-Amino-1,1,3-triphenylpropan-1-ol[53,56-58] 74

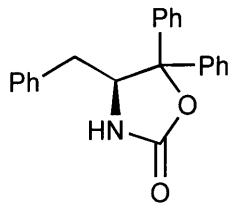


74

(*S*)-Phenylalanine ethyl ester hydrochloride **66** (9.9 g, 43.1 mmol) was added portionwise to a 1 M solution of phenylmagnesium bromide (63.5 g, 0.35 mol) in THF at 0 °C and stirred for 20h at room temperature. After quenching with ice-cold concentrated HCl, the aqueous layer was separated and evaporated to dryness. The resulting solid was washed with diethyl ether and AcOEt to obtain an amine-HCl salt as a white gummy solid. Upon basification with 1 M NaOH, organic products were extracted into diethyl ether and AcOEt, dried over $MgSO_4$, and concentrated to obtain a crude product. Re-crystallisation from a mixture of AcOEt and diethyl ether gave the title compound **74** (1.2 g, 9 %) as a white crystals. **m.p.** 141-142 °C (lit[51] 144-145 °C; lit[57] 143-144 °C). $[\alpha]_D^{25}$ = - 88.4° (c, 1.81 in $CHCl_3$) (lit[51]: - 88.5° (c, 0.604 in $CHCl_3$); lit[57]: - 94.3° (c, 2.30 in $CHCl_3$). δ_H 1.00-1.80 (3H, broad s, NH_2 and OH), 2.38 (1H, dd, J= 10.8 and 13.8 Hz, CH_2), 2.58 (1H, dd, J= 2.4 and 13.8 Hz, CH_2), 4.11 (1H, dd, J= 2.4 and 10.8 Hz, CH), 7.06-7.62 (15H, m, Ar-H). δ_C 36.9 (CH_2), 58.4 (CH), 78.7 (C), 125.6, 126.0, 126.6, 126.7, 126.9, 128.4, 128.7, 128.8, 129.3, 139.8, 144.5, 147.0 (Ar).

Accurate mass (CI): Found 304.171134; Calculated for (MH^+) $C_{21}H_{22}NO$ 304.170140 (- 3.3 ppm). ν_{max} **(cm^{-1}):** 3365 (N-H), 3320 (O-H), 3058, 3020 (Ar C-H), 2966, 2936 (methylene C-H), 1599, 1493, 1451(Ar C=C). **m/e (CI)** 304 (MH^+, 30 %), 271 (100 %).

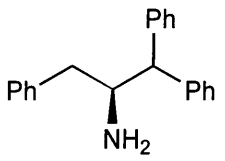
4.2.8 (*S*)-4-Benzyl-5,5-diphenyl -2-oxazolidinone[53] 75



75

Trichloromethyl chloroformate (718 mg, 3.6 mmol) was added to a mixture of (*S*)-2-amino-1,1,3-triphenylpropan-1-ol **74** (1.0 g, 3.3 mmol) and triethylamine (710 mg, 7.0 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature and then poured into a brine solution (150 ml). The aqueous layer was made basic with powdered K_2CO_3 and organic products were extracted into CH_2Cl_2 (3x50 ml). Combined extracts were dried over $MgSO_4/K_2CO_3$ and concentrated. The resulting crude product was washed with diethyl ether to obtain the title compound **75** (1.1 g, 97 %) as a white amorphous solid. **m.p.** 259-261 °C (lit[53] 255-257 °C). $[\alpha]_D^{25}$ = - 241.9° (c, 2.11 in DMSO) (lit[53]: - 281.5 ° (c, 0.63 in $CHCl_3$). δ_H **(CD_3COOD)** 2.18 (1H, dd, J= 10.8 and 13.8 Hz, CH_2), 2.52 (1H, dd, J= 3.6 and 13.8 Hz, CH_2), 4.67 (1H, dd, J= 3.6 and 10.8 Hz, CH), 6.90-7.60 (15H, m, Ar-H). δ_C **(CD_3COOD)** 44.2 (CH_2), 50.5 (CH), 94.1 (C), 130.5, 130.9, 131.5, 132.6, 132.8, 133.0, 133.1, 133.3, 133.4, 141.1, 143.4, 146.5 (Ar), 163.7 (C=O). **Accurate mass (CI):** Found 330.147890; Calculated for (MH^+) $C_{22}H_{20}NO_2$ 330.149404 (4.6 ppm). ν_{max} **(cm^{-1}):** 3248, 3174 (N-H), 3062, 3028 (Ar C-H), 2938, 2905 (methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). **m/e (CI)** 330 (MH^+, 5 %), 347 (MNH_4^+, 6 %), 196 (100 %).

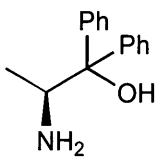
4.2.9 (*S*)-α-(Diphenylmethyl)-α-benzyl-methylamine 73



73

A solution of (*S*)-4-benzyl-5,5-diphenyl-2-oxazolidinone **75** (940 mg, 2.8 mmol) in MeOH/AcOH and a 10 % Pd (121 mg, 1.1 mmol) on activated carbon was shaken for 43h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl, stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organics were then extracted into CH_2Cl_2 (4x 50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. Purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petroleum ether, gave the title compound **73** (584 mg, 71 %) as a light-brown amorphous solid. **m.p.** 71-72 °C. $[\alpha]_D^{25}$ = -8.0° (c, 10.46 in $CHCl_3$). δ_H 1.21 (2H, broad s, NH_2), 2.29 (1H, dd, J= 9.6 and 13.5 Hz, CH_2), 2.79 (1H, d, J= 13.2 Hz, CH_2), 3.71 (1H, d, J= 9.9 Hz, CH-Ph_2), 3.81 (1H, dt, J= 2.7, 9.6 Hz, CH-NH_2), 7.06-7.33 (15H, m, Ar-H). δ_C 41.9 (CH_2), 55.7 (CH-NH_2), 59.7 (CH-Ph_2), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8, 129.1, 139.7, 142.6, 143.1 (Ar). **Accurate mass (CI):** Found 288.175856; Calculated for (MH^+) $C_{21}H_{22}N$ 288.175225 (-2.2 ppm). ν_{max} **(cm^{-1}):** 3383 (N-H), 3082, 3059, 3025 (Ar C-H), 2936, 2912 (methylene C-H), 1595, 1493, 1450 (Ar C=C). **m/e (CI)** 288 (MH^+, 100 %).

4.2.10 (*S*)-2-Amino-1,1-diphenylpropan-1-ol[51,57,58] 77

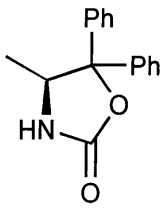


77

(*S*)-Alanine methyl ester hydrochloride **67** (9.9 g, 70.9 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (78.0 g, 0.4mol) in THF at 0 °C and then heated under reflux for 21h. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl, and stirred for 1h. After filtration, the organic

layer was separated and the aqueous layer was extracted with AcOEt (3x100 ml). Combined extracts were dried over $K_2CO_3/MgSO_4$ and concentrated to obtain a crude product. Purification over silica gel by means of dry-flash column chromatography (eluting first with CH_2Cl_2 and then with a mixture of AcOEt and petrol, increasing from 20 % up to 100 %) gave the title compound **77** (8.5 g, 52 %) as a white amorphous solid. **m.p.** 100-101 °C (lit[51,57] 100-102 °C). $[\alpha]_D^{25}$ = - 85.6° (c, 3.62 in $CHCl_3$) (lit[51]: - 82.4° (c, 0.814 in $CHCl_3$; lit[57]: - 85.9° (c, 2.77 in $CHCl_3$). δ_H 0.94 (3H, d, J= 6.3 Hz, CH_3), 1.00-1.50 (2H, broad s, NH_2), 4.15 (1H, q, J= 6.3 Hz, CH), 4.18-4.36 (1H, broad s, OH), 7.10-7.66 (10H, m, Ar-H). δ_C 17.4 (CH_3), 52.1 (CH), 78.7 (C), 125.7, 126.1, 126.6, 126.9, 128.2, 128.7, 145.0, 147.2 (Ar). **$C_{15}H_{17}NO$.** Calculated C 79.26, H 7.54, N 6.16; Found C 79.30, H 7.66, N 6.27. ν_{max} **(cm^{-1}):** 3432 (O-H), 3389, 3324 (N-H), 3025 (Ar C-H), 2987, 2902 (methyl C-H), 1593, 1487, 1447 (Ar C=C). **m/e (CI)** 228 (MH^+, 100 %).

4.2.11 (*S*)-4-Methyl-5,5-diphenyl-2-oxazolidinone 78

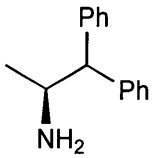


78

Trichloromethyl chloroformate (6.4 g, 32.2 mmol) was added to a mixture of (*S*)-2-amino-1,1-diphenylpropan-1-ol **77** (6.6 g, 29.3 mmol) and triethylamine (6.3 g, 62.3 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature, poured into a brine solution (150 ml), and diluted with more CH_2Cl_2. After filtration, the organic layer was separated and the aqueous layer was extracted once with a 1:1 mixture of CH_2Cl_2 and AcOEt. The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated. The resulting crude product was washed with diethyl ether, water, AcOEt and diethyl ether again, to obtain the title compound **78** (5.7 g, 76 %) as a white amorphous solid. **m.p.** 264-266 °C. $[\alpha]_D^{25}$= -279.7° (c, 4.14 in DMSO). δ_H 0.82 (3H, d, J= 6.3 Hz, CH_3), 4.65 (1H, q, J= 6.0 Hz, CH), 7.10-7.70 (10H, m, Ar-H), 7.93 (1H, broad s, NH). δ_C 19.6 (CH_3), 55.9 (CH), 85.6 (C), 126.3, 126.4, 128.1, 128.6, 128.8, 129.1, 140.6, 144.2 (Ar), 157.6 (C=O). **Accurate mass (CI):** Found 254.116639; Calculated for (MH^+) $C_{16}H_{16}NO_2$ 254.118104 (5.8 ppm). ν_{max} **(cm^{-1}):** 3255, 3152 (N-H),

3059, 3027 (Ar C-H), 2987, 2970, 2905 (methyl C-H), 1745, 1726 (C=O), 1493, 1447 (Ar C=C), 1243 (C-O). **m/e (CI)** 254 (MH^+, 9 %), 271 (MNH_4^+, 55 %), 52 (100 %).

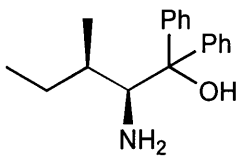
4.2.12 (*S*)-α-(Diphenylmethyl)-α-methyl-methylamine 76



76

A suspension of (*S*)-4-methyl-5,5-diphenyl-2-oxazolidinone **78** (3.5 g, 13.9 mmol) in MeOH/AcOH and a 10 % Pd (148 mg, 1.4 mmol) on activated carbon was shaken for 45h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl (2 M, 100 ml), stirred overnight at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3. Organic compounds were then extracted into diethyl ether (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. Purification over silica gel by means of dry-flash column chromatography (eluting first with AcOEt and then with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %) gave the title compound **76** (1.9 g, 65 %) as a white amorphous solid. **m.p.** 76-77 °C. $[\alpha]_D^{25}$ = - 19.3 (c, 10.76 in $CHCl_3$). δ_H 1.04 (3H, d, J= 6.3 Hz, CH_3), 1.31 (2H, s, NH_2), 3.55 (1H, d, J= 9.9 Hz, CH-Ph_2), 3.66-3.80 (1H, m, CH-NH_2), 7.10-7.40 (10H, m, Ar-H). δ_C 22.4 (CH_3), 50.3 (CH-NH_2), 62.4 (CH-Ph_2), 126.5, 126.8, 128.2, 128.5, 128.7, 129.0, 143.3, 143.7 (α-Ar). **$C_{15}H_{17}N$.** Calculated C 85.26, H 8.11, N 6.63; Found C 85.10, H 8.08, N 6.36. ν_{max} **(cm^{-1}):** 3344 (N-H), 3083, 3027 (Ar C-H), 2976, 2958 (methylene C-H), 1597, 1493, 1449 (Ar C=C). **m/e (CI)** 212 (MH^+, 100 %).

4.2.13 (*2S,3R*)-2-Amino-1,1-diphenyl-3-methylpentan-1-ol[51] 80

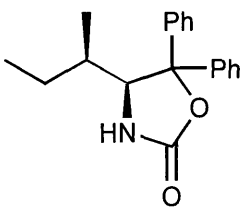


80

A 1 M solution of phenylmagnesium bromide (49.0 g, 0.27 mol) in THF was added dropwise to (*S*)-isoleucine methyl ester hydrochloride **68** (9.8 g, 54.0 mmol) at 0 °C and

then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (150 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight, diluted with water until partition occured. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x75 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (6.1 g, 42 %) as a pale yellow solid. This contaminated with the amino ester derived from the starting material, however was used for the next step without further purification. A small amount of the crude product (1.1 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, increasing from 40 % up to 80 %. From this, a pure amino alcohol **80** (654 mg, 60 %) was obtained as a white amorphous solid. **m.p.** 128-129 °C (lit[51] 135-136 °C). $[\alpha]_D^{25}$ = - 128.17° (c, 4.26 in $CHCl_3$) (lit[51]: - 124.1° (c, 1.23 in $CHCl_3$)). δ_H 0.72 (3H, t, J= 7.2 Hz, CH_3), 0.94 (3H, d, J= 6.9 Hz, CH_3), 0.80-1.10 (1H, m, CH_2), 1.40-1.60 (1H, m, CH), 1.76-1.94 (1H, m, CH_2), 0.60-2.10 (3H, OH and NH_2), 3.85 (1H, d, J= 1.5 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H). δ_C 12.1 (CH_3-CH_2), 18.7 (CH_3-CH), 22.5 (CH_2), 34.8 (CH-Me), 60.9 (CH-NH_2), 79.6 (C), 125.5, 125.9, 126.1, 126.5, 127.8, 128.2, 144.9, 147.9 (Ar). ν_{max} **(cm^{-1}):** 3343, 3279 (N-H and O-H), 3085, 3023 (Ar C-H), 2959, 2926, 2873 (methyl and methylene C-H), 1589, 1491, 1447 (Ar C=C). **m/e** 270 (MH^+, 4 %), 252 (20 %), 86 (100 %).

4.2.14 (*S*)-4-[(R)-1-Methylpropyl]-5,5-diphenyl-2-oxazolidinone 81

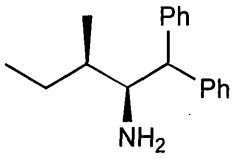


81

Trichloromethyl chloroformate (5.4 g, 27.3 mmol) was added to a mixture of (*S*)-2-amino-1,1-diphenyl-3-methylpentan-1-ol **80** (4.97 g of 60 %, 11.1 mmol) and

triethylamine (5.3 g, 52.0 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 3h at 0 °C, then allowed to warm to room temperature for 18h. The mixture was then washed with HCl (3x100 ml) and water (2x100 ml) and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **81** (2.7 g, 83 %) as a white amorphous solid. **m.p.** 221-223 °C. $[\alpha]_D^{25}$ = - 243.9° (c, 4.33 in $CHCl_3$). δ_H 0.41 (3H, t, J= 7.2 Hz, CH_3), 0.80 (3H, d, J= 6.9 Hz, CH_3), 0.80-0.96 (1H, m, CH_2), 1.18-1.32 (1H, m, CH-Me), 1.34-1.50 (1H, m, CH_2), 4.27 (1H, d, J= 3.6 Hz, CH-NH), 6.98 (1H, s, NH), 7.10-7.50 (10H, m, Ar-H). δ_C 11.3 (CH_3-CH_2), 17.2 (CH_3-CH), 22.7 (CH_2), 36.3 (CH-Me), 66.1 (CH-NH), 89.5 (C), 125.9, 126.5, 127.7, 128.0, 128.3, 128.6, 139.3, 144.0 (Ar), 159.1 (C=O). ν_{max} **(cm^{-1}):** 3281, 3162 (N-H), 3058 (Ar C-H), 2980, 2960, 2933, 2877 (methyl and methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). **m/e** 313 (MNH_4^+, 6 %), 296 (MH^+, 8 %), 237 (100 %).

4.2.15 (*S*)-α-(Diphenylmethyl)-α-[(*R*)-1-methylpropyl)-methylamine 79

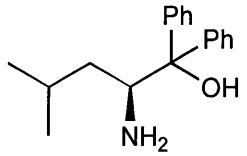


79

A suspension of (*S*)-4-*sec*-butyl-5,5-diphenyl-2-oxazolidinone **81** (2.3 g, 7.9 mmol) in MeOH/AcOH and a 10 % Pd (100 mg, 0.9 mmol) on activated carbon was shaken for 47h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and the aqueous layer was made basic with NaOH pellets. Organic compounds were then extracted into CH_2Cl_2 (5x100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave a crude product, which was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then with a mixture of AcOEt and petrol, ranging from 50 % up to 70 %. This afforded the title compound **79** (1.4 g, 71 %) as a white amorphous solid. **m.p.** 59-61 °C. $[\alpha]_D^{25}$ = -13.7° (c, 4.80 in $CHCl_3$). δ_H 0.76 (3H, t, J= 7.5 Hz, CH_3), 0.96 (3H, d, J= 6.9 Hz, CH_3), 1.00-1.18 (3H, broad s and m, NH_2 and

CH_2), 1.28-1.42 (1H, m, CH-Me), 1.50-1.70 (1H, m, CH_2), 3.50 (1H, dd, J= 10.5 and 2.40 Hz, CH-NH_2), 3.87 (1H, d, J= 10.5 Hz, CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 11.2 (CH_3-CH_2), 16.7 (CH_3-CH), 20.4 (CH_2), 34.8 (CH-Me), 56.4 (CH-Ph_2), 58.4 (CH-NH_2), 125.2, 125.4, 127.0, 127.4, 127.5, 127.7 (Ar). **Accurate mass (CI):** Found 254.189998; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (3.4 ppm). ν_{max} **(cm^{-1}):** 3355 (N-H), 3082, 3065, 3024 (Ar C-H), 2959, 2931, 2872 (methyl and methylene C-H), 1598, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

4.2.16 (*S*)-2-Amino-1,1-diphenyl-4-methylpentan-1-ol[51] 83

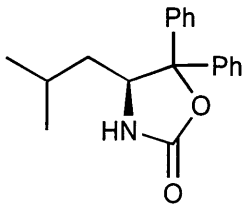


83

A 1 M solution of phenylmagnesium bromide (96.1 g, 0.53 mol) in THF was added dropwise at 0 °C to (*S*)-leucine methyl ester hydrochloride **69** (19.3 g, 0.11 mol) and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (400 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight and then diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x200 ml) and dried over $MgSO_4/K_2CO_3$. Concentration gave a crude product (13.7 g, 48 %) as a pale yellow solid. This contaminated with the amino ester of the unreacted starting material, however was used directly for the next step without further purification. A small amount of the crude product (1.31 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH_2Cl_2, then a mixture of AcOEt and petrol, increasing from 30 % up to 55 %. From this, a pure amino alcohol **83** (852 mg, 65 %) was obtained as a white amorphous solid. **m.p.** 131-132 °C (lit[51] 132-134 °C). $[\alpha]_D^{25}$ = -101.0° (c, 5.38 in $CHCl_3$) (lit[51]: -95.1° (c, 1.01 in $CHCl_3$)). δ_H 0.79 (6H, dd, J= 7.20 and 7.80 Hz, CH_3), 0.86-1.80 (6H), 3.89 (1H, J= 9.6 Hz, CH-NH_2), 7.00-7.70

(10H, m, Ar-H). δ_C 21.1, 23.8, 25.1, 39.2, 54.3, 78.9, 125.4, 125.6, 126.1, 126.4, 127.8, 128.2, 144.3, 147.0 (Ar). ν_{max} **(cm^{-1}):** 3337, 3268 (N-H and O-H), 3025 (Ar C-H), 2954, 2935, 2866 (methyl and methylene C-H), 1597, 1491, 1448 (Ar C=C). **m/e** 270 (MH^+, 5 %), 252 (M-OH, 11 %), 86 (100 %).

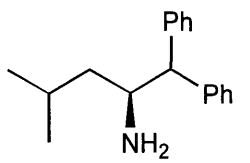
4.2.17 (*4S*)-4-Isobutyl-5,5-diphenyl-2-oxazolidinone 84



84

Trichloromethyl chloroformate (13.0 g, 65.8 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-4-methylpentan-1-ol **83** (12.4 g of 65 %, 29.9 mmol) and triethylamine (12.7 g, 125.5 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 15h, allowing to warm to room temperature. The mixture was then washed with HCl (3x200 ml) and water (2x200 ml), and dried over $MgSO_4$. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound **84** (7.9 g, 90 %) as a white solid. **m.p.** 212-214 °C. $[\alpha]_D^{25}$ = -286.1° (c, 4.32 in $CHCl_3$). δ_H 0.85 (3H, d, J= 6.6 Hz, CH_3), 0.91 (3H, d, J= 6.6 Hz, CH_3), 0.96-1.08 (2H, m, CH_2), 1.53-1.73 (1H, m, CH-Me_2), 4.57 (1H, dd, J= 10.5 and 3.60 Hz, CH-NH), 7.05 (1H, s, NH), 7.16-7.50 (10H, m, Ar-H). δ_C 20.8, 23.7, 24.9, 41.8, 58.8, 89.1, 125.9, 126.3, 127.6, 127.8, 128.1, 128.3, 139.3, 142.5 (Ar), 158.8 (C=O). ν_{max} **(cm^{-1}):** 3261, 3160 (N-H), 2955, 2869 (methyl and methylene C-H), 1752, 17235 (C=O), 1495, 1447 (Ar C=C), 1251 (C-O). **m/e** 313 (MNH_4^+, 12 %), 296 (MH^+, 15 %), 237 (100 %).

4.2.18 (*S*)-α-(Diphenylmethyl)-α-isobutyl-methylamine 82

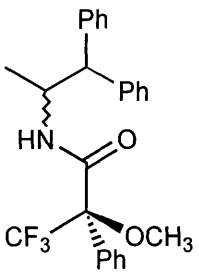


82

A suspension of (*S*)-4-isobutyl-5,5-diphenyl-2-oxazolidinone **84** (7.6 g, 25.6 mmol) in MeOH/AcOH and a 10 % Pd (282 mg, 2.6 mmol) on activated carbon was shaken for 93h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered

off over Hyflo Super Cell and solvents were evaporated under reduced pressure. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partitioned occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and then the aqueous layer was made basic with NaOH pellets. Organics were then extracted into CH_2Cl_2 (5x 100 ml) and the combined extracts were dried over $MgSO_4$. Concentration gave the title product **82** (5.7 g, 87 %) as a white amorphous solid. **m.p.** 46-48 °C. $[\alpha]_D^{25} = -31.6°$ (c, 4.12 in $CHCl_3$). δ_H 0.86 (6H, dt, J= 6.60 and 2.10 Hz, CH_3), 1.00-1.50 (4H, m and broad s, CH_2 and NH_2), 1.66-1.86 (1H, m, CH), 3.61 (2H, broad s, CH-NH_2 and CH-Ph_2), 7.10-7.40 (10H, m, Ar-H). δ_C 21.8 and 24.7 (CH_3), 25.5 (CH), 45.6 (CH_2), 52.4 (CH-NH_2), 61.6 (CH-Ph_2), 126.9, 127.1, 128.8, 129.0, 129.2, 129.4, 143.8, 144.0 (Ar). **Accurate mass (CI):** Found 254.190200; Calculated for (MH^+) $C_{18}H_{24}N$ 254.190875 (2.7 ppm). ν_{max} **(cm^{-1}):** 3368 (N-H), 3057, 3027 (Ar C-H), 2951, 2932, 2909, 2867 (methyl and methylene C-H), 1595, 1494, 1450 (Ar C=C). **m/e (CI)** 254 (MH^+, 100 %).

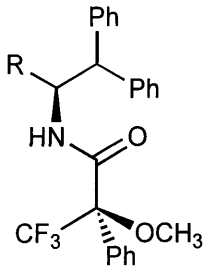
4.2.19 N-[(*SR*)-α,α-Diphenylmethylethyl](*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide 87



(*SR*+ *RR*)-**87**

A solution of pyridine-d_5 (56 mg, 0.70 mmol)) and (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride **86** (48 mg, 0.19 mmol) in CH_2Cl_2 (8 ml) was sequentially added to a solution of (*SR*)-α-(diphenylmethyl)-α-methyl-methylamine **76** (40 mg, 0.19 mmol) in CH_2Cl_2 (8 ml). The reaction mixture was stirred for 18h at room temperature and then washed with a 10 % HCl (2x15 ml) and water (3x15 ml). The organic layer was dried over $MgSO_4$ and was then concentrated to give a crude product. Purification over silica gel, eluting with CH_2Cl_2 gave the title compound **87** as a mixture of diastereomers. The product was only characterised, sufficiently to determine the stereochemical analysis. δ_F -70.0 (CF_3), -69.3 (CF_3). δ_H 2.84 (OCH_3), 3.02 (OCH_3).

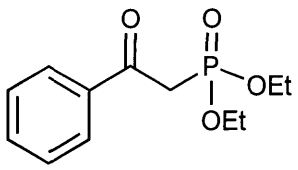
4.2.20 N-[(*S*)-α,α-Diphenylmethylalkyl](*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide



A solution of pyridine-d_5 (4 equiv.) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **86** (1.4 equiv.) in $CDCl_3$ (1.0 ml) was sequentially added *via* syringe into the sample bottle fitted with rubber septum and charged with the (*S*)-α-(diphenylmethyl)-α-alkyl-methylamine **3** (10 mg). The reaction mixture was then stirred for 24h at room temperature and analysed by both ^1H and ^{19}F NMR spectroscopy. The products were only characterised, sufficiently to determine the stereochemical analysis. (*SR*)-**87** (R= Me): δ_F -70.0 (CF_3). δ_H 3.02 (OCH_3). (*SR*)-**88** (R= *i*-Pr): δ_F -69.6 (CF_3). δ_H 2.99 (OCH_3). (*SR*)-**89** (R= Bn): δ_F -69.5 (CF_3). δ_H 2.84 (OCH_3). (*SR*)-**90** (R= sec-Bu): δ_F -69.6 (CF_3). δ_H 2.97 (OCH_3). (*SR*)-**91** (R= isobutyl): δ_F -69.7 (CF_3). δ_H 2.98 (OCH_3).

4.3 Experimental for chapter two

4.3.1 Diethyl benzoylmethanephosphonate 122



122

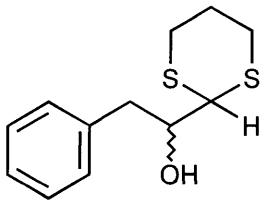
a) *Via* an Arbusov[87]

A mixture of bromoacetophenone **128** (6.0 g, 30.1 mmol) and triethyl phosphite **129** (5.0 g, 30.1 mmol) was heated under reflux at 165 °C for 16h. Purification by three sequential distillations (68-72 °C, 0.1-0.01 mm-Hg) and over silica gel (1:1 ethyl acetate/hexane) gave the title compound **122** (4.2 g, 54 %) as a clear oil. This product was contaminated, probably with **130** (1 %). δ_P 23.1. δ_H 1.27 (3H, dt, J= 7.2 and 0.4 Hz, 2x$\underline{CH_3}CH_2O$), 3.62 (2H, d, J= 22.8 Hz, CH_2P), 4.13 (2H, dq, J= 7.2 and 0.8 Hz, 2x$CH_3\underline{CH_2}O$), 7.47 (2H, t, J= 6.7 Hz, Ar-H), 7.58 (1H, t, J= 6.7 Hz, Ar-H), 8.00 (2H, d, J= 6.7 Hz, Ar-H). δ_C 16.1 ($\underline{C}H_3CH_2O$), 38.3 (d, J=130 Hz, CH_2P), 62.5 ($CH_3\underline{C}H_2O$), 128.5, 128.9, 133.5 and 136.4 (Ar), 191.79 (C=O). ν_{max} **(cm^{-1}):** 1681 (C=O), 1276 and 1254 (P=O), 1055 and 1026 (POEt). **m/e (EI)** 256 (M^+, 3 %), 105 (100 %).

b) Using LDA[86]

Diisopropylamine (0.9 g, 9.2 mmol) was added dropwise to a solution of n-butyllithium (0.6 g, 10.1 mmol) in hexanes at room temperature and was then diluted with diethyl ether (15 ml). The LDA solution was cooled to -78 °C, and then a solution of acetophenone **126** (1.0 g, 8.3 mmol) in diethyl ether (1 ml) was added and the mixture stirred for 1 h at this temperature. Diethyl chlorophosphite **127** (1.4 g, 9.2 mmol) was added at -78 °C and then the entire mixture was allowed to warm to room temperature over 5 h. The reaction was quenched with acetic acid (10 mmol) in diethyl ether (10 ml) and the mixture filtered through a Hyflo super cel. After concentration under reduced pressure, the residue was magnetically stirred for 33 h open to the air. Purification over silica gel (radial chromatography, 1:1 ethyl acetate/hexane) gave the title product **122** (1.4 g, 66 %) as clear oil. The spectral data are consistent with those of obtained by method a.

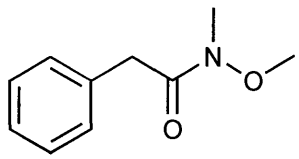
4.3.2 2-(1'-Hydroxy-2'-phenylethyl)-1,3-dithiane[102] 141



141

A 1.6 M solution of n-butyllithium (0.5 g, 7.8 mmol) in hexane was added dropwise to a 0.375 M solution of 1,3-dithiane **142** (0.9 g, 7.5 mmol) in THF. The mixture was stirred for 2 h at -40 to -10 °C, and then a solution of phenylacetaldehyde **140** (0.9 g, 7.5 mmol) in THF was added at -78 °C. The reaction was stirred for 12 h at -78 °C to room temperature and then diluted with water (100 ml). Organic compounds were extracted into pentane (4x40 ml), and then the organics were washed with water (3x50 ml), 7 % aqueous KOH (3x70 ml), and again water (3x50 ml). The organic extracts were dried over K_2CO_3, concentrated under reduced pressure, and then purified over silica gel, eluting with a 1:9 mixture of ethyl acetate and petrol. The title compound **141** (0.8 g, 44 %) was recovered as a light-brown liquid. δ_H 1.80-2.00 (1H, complex, CH_2), 2.00-2.20 (1H, complex, CH_2), 2.60-3.00 (6H, complex, CH_2Ph + CH_2-S + OH), 3.17 (1H, dd, J= 4.0 Hz, J=13.6 Hz, CH_2Ph), 3.88 (1H, d, J= 6.0 Hz, S-CH-S), 4.09 (1H, m, J= 4.4, 6.2, and 7.9 Hz, CH-OH), 7.20-7.40 (5H, complex, Ar-H). δ_C 25.5 (CH_2), 27.8 and 28.3 (S-CH-S), 39.9 (CH_2Ph), 51.2 (CH-OH), 73.2 (S-CH-S), 126.3, 128.2, 129.4 and 137.7 (Ar). **Accurate mass (EI):** Found 240.0643; calculated for (M^+) $C_{12}H_{16}OS_2$ 240.0643 (-0.2 ppm). ν_{max} **(cm^{-1}):** 3443 (OH). **m/e (EI)** 240 (M^+, 7 %), 119 (100%).

4.3.3 N-Methyl-N-methoxyphenylacetylamide[109] 148

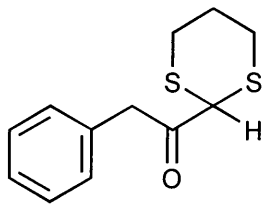


148

Neat phenylacetyl chloride **149** (5.0 g, 32.3 mmol) was added to a solution of N,O-dimethylhydroxylamine hydrochloride **150** (3.5 g, 35.5 mmol) in chloroform (70 ml). The mixture was cooled to 0 °C and pyridine (5.6 g, 71.0 mmol) was added dropwise.

The entire mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of ether (50 ml) and CH_2Cl_2 (50 ml) and then washed with saturated NH_4Cl (5x60 ml) and water (3x100 ml). The organic layer was dried over $MgSO_4$ and concentrated. Purification by distillation (b.p. 58-62 °C, 0.1-0.01 mm-Hg) gave the title compound **148** (4.3 g, 74 %) as a clear oil. δ_H 3.19 (3H, s, N- CH_3), 3.59 (3H, s, O-CH_3), 3.77 (2H, s, CH_2), 7.20-7.34 (5H, m, Ar). δ_C 32.1 (N- CH_3), 39.3 (O-CH_3), 61.1 (CH_2), 126.6, 128.4, 129.2, 134.8 (Ar), 172.3 (C=O). ν_{max} **(cm^{-1}):** 1663 (C=O). **m/e (EI)** 179 (M^+, 8 %), 91 (100 %).

4.3.4 2-Phenylacetyl-1,3-dithiane 147



147

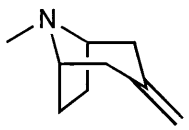
a) From acylation of 1,3-dithiane[106]

A 1.6 M solution of n-butyllithium (0.5 g, 7.3 mmol) in hexane was added dropwise at -60 °C to a solution of 1,3-dithiane **142** (0.8 g, 7.0 mmol) in THF (25 ml). The mixture was stirred for 2.5h at -20 °C, and then a solution of N-methyl-N-methoxyphenylacetylamide **148** (1.5 g, 8.4 mmol) in THF (5 ml) added at -60 °C. The reaction was stirred for 18h at -60 °C to room temperature and was then quenched with water (100 ml). Organic products were extracted into CH_2Cl_2 (4x50 ml) and the organic extract was washed with 1M HCl (4x70 ml), saturated $NaHCO_3$ and water (4x100 ml). Drying over $MgSO_4$ and concentration under reduced pressure gave a crude product as a pale-yellow solid. Purification over alumina (3:7 ethyl acetate/petrol) gave the title compound **147** (0.6 g, 38 %) as a white solid. **m.p.** 89-91 °C (Lit[107] 79-81 °C). δ_H 1.90-2.20 (2H, m), 2.50-2.60 (2H, m), 3.20-3.30 (2H, m), 3.96 (2H, s, CH_2Ph), 4.26 (1H, s, S-CH-S), 7.22-7.38 (5H, m, Ar). δ_C 25.1 (CH_2), 25.9 (CH_2-S), 45.3 and 46.8 (CH_2Ph and S-CH-S), 127.2, 128.7, 129.5 and 133.7 (Ar), 199.9 (C=O). **$C_{12}H_{14}OS_2$.** Calculated C, 60.47; H, 5.92; S, 26.90. **Found:** C, 60.03; H, 5.89. ν_{max} **(cm^{-1}):** 1709. **m/e (CI)** 256 ($M+NH_4^+$, 11 %), 239 ($M+H^+$, 2 %), 152 (100 %).

b) From Swern[111] oxidation of 141

A solution of methyl sulfoxide (1.3 g, 16.6 mmol) and **141** (1.8 g, 7.5 mmol) in CH_2Cl_2 (15 ml) were added dropwise at -78 °C to a solution of oxalyl chloride (1.1 g, 8.3 mmol) in CH_2Cl_2 (20 ml) every 15 min. After stirring for 15 min., Et_3N (3.8 g, 37.6 mmol) was added. The entire mixture was stirred for 20 h at -78 °C to room temperature and then quenched with distilled water (100 ml). Organic products were extracted into CH_2Cl_2 (1x50 ml) and the combined extracts were washed with diluted HCl (6x70 ml), saturated $NaHCO_3$ (2x100 ml) and distilled water (2x150 ml). Drying over $MgSO_4$ and concentration under reduced pressure gave a crude product. Purification over silica gel (1:6 AcOEt/petrol) afforded the title compound (0.1 g, 7 %) as a white solid. **m.p.** 89-91 °C (Lit[107] 79-81 °C). Spectroscopic data were identical to that in part (a).

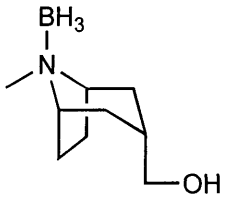
4.3.5 3-Methylenetropane[118] 155



155

A mixture of methyltriphenylphosphonium bromide **157** (3.4 g, 9.4 mmol) and potassium *tert*-butoxide (1.0 g, 9.1 mmol) in THF (20 ml) was stirred for 1 h at 0 °C, and then a solution of tropinone **116** (1.0 g, 7.2 mmol) in THF (5 ml) was added. The entire mixture was stirred for 3 h at 0 °C, quenched with 1M HCl solution and then THF was removed under reduced pressure. The mixture was diluted with water and the resultant triphenylphosphine oxide extracted into toluene (4x40 ml). The aqueous solution was then basified with 3M NaOH solution, and the desired product extracted into pentane (5x30 ml). Concentration of the combined organic extracts, after drying over $MgSO_4$, gave a crude product. Distillation (25 °C, 0.1-0.01 mm-Hg) gave the title compound **155** (0.7 g, 72 %) as a clear oil. δ_H 1.46 (2H, d, J= 8.1 Hz, *endo*-C6,7), 1.80-1.90 (2H, complex, *exo*-C6,7), 1.93 (2H, d, J=14.8 Hz, C2,4), 2.30 (3H, s, C8), 2.46 (2H, d, J=14.0 Hz, C2,4), 3.14 (2H, broad s, C1,5), 4.70 (2H, t, J= 2.2 Hz, C9). δ_C 26.3 (C6,7), 39.4 (C2,4), 40.1 (C8), 61.4, (C1,5), 111.6 (=CH_2), 143.1 (C3). ν_{max} **(cm^{-1}):** 3069 (=CH_2), 2792 (N-Me), 1644 (C=C). **m/e (EI)** 137 (M^+, 10 %), 82 (100 %).

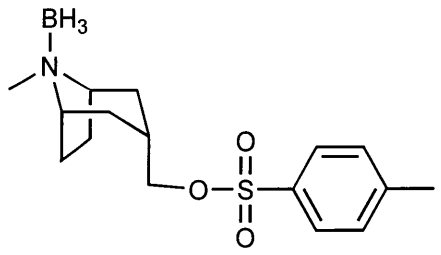
4.3.6 N-Trihydroborate-3α/β-hydroxymethyltropane[119] 162



162

Neat $BF_3.OEt_2$ (3.8 g, 26.7 mmol) was added dropwise to a mixture of $NaBH_4$ (0.8 mg, 20.0 mmol) and 2-methyl-2-butene (3.7 g, 53.4 mmol) in THF (10 ml) at -20 °C/ 0 °C. The reaction mixture was stirred at this temperature for an additional hour, and then a solution of 3-methylenetropane **155** (0.6 g, 4.5 mmol) in THF (5 ml) was added to this mixture. The entire reaction was further stirred for 16h at room temperature, and then oxidised at 0 °C with the subsequent addition of EtOH (2 ml), NaOH (5 ml, 6 M,) and H_2O_2 (8 ml, 30 %). The whole reaction was stirred for 4h at room temperature and then heated to 60 °C. After being diluted with water and ether, the mixture was filtered. The aqueous layer was saturated with solid K_2CO_3, and the organic products were extracted into ether (5x40 ml), combined and dried over $MgSO_4$. Concentration under reduced pressure and purification over silica gel (100 % ethyl acetate) gave the title compound **162** (70 mg, 10 %) as a pale yellow oil. This product was a 1:1 mixture of two stereoisomers. ***endo*-isomer:** δ_H 1.55 (2H, d, C6,7), 1.60 (2H, d, *ax*-C2,4), 1.90-2.10 (1H, complex, C3), 2.20-2.30 (2H, complex, C6,7), 2.60-2.65 (2H, complex, *eq*-C2,4), 2.70 (3H, s, N-CH_3), 3.30 (2H, broad s, C1,5), 3.63 (2H, d, J= 8.4 Hz, CH_2OH). δ_C 26.6 (C6,7), 27.6 (C2,4), 30.92 (C3), 42.4 (N-CH_3), 63.1 (C1,5), 68.2 (CH_2OH). ***exo*-isomer:** δ_H 1.45 (2H, d, *ax*-C2,4), 1.76 (2H, d, C6,7), 1.90-2.10 (1H, complex, C3), 2.20-2.30 (2H, complex, C6,7), 2.60 (3H, s, N-CH_3), 2.60-2.64 (2H, m, *exo*-6,7 of CH_2), 2.85 (2H, dt, *eq*-C2,4), 3.17 (2H, broad s, C1,5), 3.58 (2H, d, J= 8.9 Hz, CH_2OH). δ_C 28.5 (C6,7), 30.3 (C2,4), 30.3 (C3), 49.4 (N-CH_3), 64.9 (C1,5), 68.5 (CH_2OH). **Accurate mass (EI):** Found 155.1312; calculated for (M^+) $C_9H_{17}NO$ 155.1310 (- 1.4 ppm). ν_{max} **(cm^{-1}):** 3375 (OH). **m/e (EI)** 169 (M^+, 1 %), 155 (M-BH_3, 28 %), 82 (100 %).

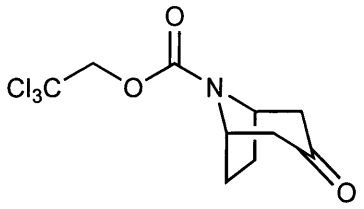
4.3.7 N-Trihydroborate-3α/β-tosyloxymethyltropane[118] 164



164

A 1.6M solution of n-BuLi (11 mg, 2.8 mmol) in hexane was added dropwise at 0 °C to a mixture of 3α/β-hydroxymethyltropane **162** (0.4 g, 2.6 mmol) and Ph_3CH (2 mg) in THF (10 ml). The reaction, which was slightly pink in colour, was stirred for 15 min., and then a solution of tosyl chloride **163** (0.5 g, 2.6 mmol) in THF (5 .0 ml) was added. The entire mixture was stirred for 3.5 h at 0 °C, diluted with diethyl ether (80 ml), and was then washed with brine (4x50 ml). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to give the product as a white solid. Purification over silica gel, eluting with ethyl acetate : petrol (5:15), gave some of the *endo*-isomer **164** (55 mg, 8 %) as a white amorphous solid, which was re-crystallised from petroleum ether. **m.p.** 113.8-116.5 °C. δ_H 1.30-1.50 (4H, m, *ax*-C2,4 and *endo*-C6,7), 2.10-2.30 (3H, complex, C3 and *exo*-C6,7), 2.45 (3H, s, *p*-CH_3-Ar), 2.50-2.60 (2H, complex, *eq*-C2,4), 2.65 (3H, s, N-CH_3), 3.25 (H, broad s, C1,5), 3.98 (H, d, J= 8.0 Hz, CH_2OH), 7.37 (2H, d, J= 8.0 Hz, Ar), 7.79 (2H, d, J= 8.0 Hz, Ar). δ_C 21.7 (*p*-CH_3-Ar), 24.3 (C3), 27.1 (C6,7) , 27.3 (C2,4), 42.4 (N-CH_3), 62.7 (C1,5), 74.0 (CH_2OH), 127.8, 130.0, 132.7, 145.2 and 151.0 (Ar). **Accurate mass (EI):** Found 309.1398; calculated for (M^+) $C_{16}H_{23}NO_3S$ 309.1399 (0.2 ppm). **m/e (EI)** 323 (M^+, 2 %), 309 (M-BH_3, 12 %), 82 (100 %). See X-ray structure in **Figure 11** (p. 71).

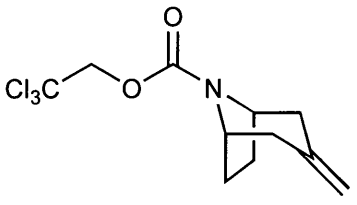
4.3.8 N-(2', 2', 2'-Trichloroethoxycarbonyl)tropinone[123] 168



168

2,2,2-Trichloroethyl chloroformate **167** (2.5 g, 12.0 mmol) was added to a mixture of potassium carbonate (42 mg, 0.3 mmol) and tropinone **116** (1.4 g, 10.0 mmol) in benzene (20 ml). The reaction mixture was heated at reflux for 38 h, and then the organic solvent was removed under reduced pressure. The residue was taken into ether (70 ml) and then the precipitate was filtered off. The whole was washed with a 3M HCl (2x40 ml) and water (2x40 ml), and then dried over $MgSO_4$. Concentration under reduced pressure gave oil, which was solidified on standing. Purification over silica gel (1:9 ethyl acetate/petrol) gave the title compound **168** (1.6 g, 52 %) as a milky-white solid. **m.p.** 78.8-80.1 °C (lit[123] 79-80 °C). δ_H 1.60-1.80 (2H, m, *endo*-C6,7), 2.00-2.20 (2H, m, *exo*-C6,7), 2.41 (2H, d, J= 16.0 Hz, *ax*-C2,4), 2.73 (2H, d, J= 16.4 Hz, *eq*-C2,4), 4.64 (2H, m, C1,5), 4.69 (1H, d, J= 12.0 Hz, CH_2O), 4.91 (1H, d, J= 12.0 Hz, CH_2O). δ_C 28.4 and 29.4 (C6,7), 48.6 and 49.2 (C2,4), 53.4 (C1,5), 74.72 (CH_2O), 95.6 (CCl_3), 151.6 (N-C=O), 207.23 (C=O). **$C_{10}H_{12}Cl_3NO_3$.** Calculated C, 39.96; H, 4.02; Cl, 35.39; N, 4.66. **Found:** C, 39.49; H, 3.98; N, 4.35. ν_{max} **(cm^{-1}):** 1706 (C=O). **m/e (CI)** 300 and 302 (MH^+, 8 and 8 %), 126 (100 %).

4.3.9 N-(2', 2', 2'-Trichloroethoxycarbonyl)-3-methylenetropane[126] 169

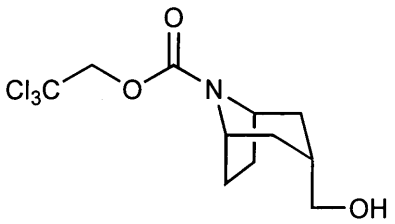


169

2,2,2-Trichloroethyl chloroformate **167** (1.4 g, 6.8 mmol) was added to a solution of 3-methylenetropane **155** (0.4 g, 3.1 mmol) in toluene (20 ml) at room temperature. The reaction mixture was heated under refluxed for 40h. Concentration under reduced pressure and then purification over silica gel (1:19 ethyl acetate/petrol) gave the title

compound **169** (0.7 g, 79 %) as a clear oil, which solidified on standing. **m.p.** 42-44 °C. δ_H 1.50-1.70 (2H, m, *endo*-C6,7), 1.80-2.00 (2H, m, *exo*-C6,7), 2.14 (2H, d, J=14.0 Hz, *ax*-C2,4), 2.52 (2H, d, J=14.0 Hz, *eq*-C2,4), 4.40 (2H, broad d, J=17.2 Hz, C1,5), 4.66 (1H, d, J=11.6 Hz, CH_2O), 4.80-5.00 (3H, m, CH_2O + $=CH_2$). δ_C 27.6 and 28.5 (C6,7), 40.6 and 41.3 (C2,4), 54.6 (C1,5), 74.6 (CH_2O), 95.9 (CCl_3), 114.2 ($=CH_2$), 141.3 (C3), 151.6 (NC=O). **Accurate mass (EI):** Found 297.0090; calculated for (M^+) $C_{11}H_{14}NO_2Cl_3$ 297.0090 (0.2 ppm). ν_{max} **(cm^{-1}):** 3073 ($=CH_2$), 1719 (C=O), 1646 (C=C). **m/e (EI)** 297, 299 and 301 (M^+, 28, 28 and 11 %), 68 (100 %).

4.3.10 N-(2', 2', 2'-Trichloroethoxycarbonyl)-3α/β-hydroxymethyltropane 171



171

a) Method using 9-BBN[120,127]

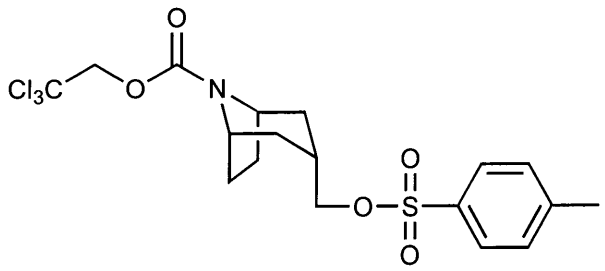
A 0.50 M solution of **169** (149 mg, 0.5 mmol) in THF (1.0 ml) was added dropwise to an *in situ* prepared 0.55 M solution of 9-BBN **160** (203 mg, 1.7 mmol) in THF (3 ml) at room temperature. The reaction mixture was stirred for 23 h, and then oxidised at 0 °C with the subsequent additions of MeOH (2 ml), 6.0 M NaOH (1 ml) and 30 % H_2O_2 (2 ml). The reaction mixture was further stirred for 2h at r.t., and then heated under reflux for 30 min. The aqueous layer was saturated with solid K_2CO_3 and organic products were extracted into ether (5x15 ml). Drying over $MgSO_4$ and concentration under reduced pressure gave a crude product. Purification over silica gel (1:4 and 2:3 ethyl acetate/petrol) yielded the title compound **171** (158 mg, 100 %) as a clear oil. This product was a 3:1 mixture of two stereoisomers. δ_H 1.40-1.60 (4H, complex, *ax*-C2,4), 1.60-1.80 (4H, complex, *endo*-C6,7), 1.80-2.30 (10H, complex, C3, *exo*-C6,7 and *eq*-C2,4), 3.43 (2H, d, J=6.4.0 Hz, *exo*-C11), 3.65 (2H, d, J=8.0 Hz, *endo*-CH_2OH), 4.20-4.50 (4H, broad dd, C1,5), 4.60-4.70 (2H, m, CH_2O), 4.80-4.90 (2H, m, CH_2O). ***endo*-isomer:** δ_C 28.6 and 29.3 (C6,7), 31.3 and 32.0 (C2,4), 31.7 (C3), 52.8 and 53.0 (C1,5), 67.4 (CH_2OH), 74.5 (CH_2O), 95.9 (CCl_3), 151.5 (NC=O). ***exo*-isomer:** δ_C 27.7 and 28.5 (C6,7), 31.2 (C3), 33.9 and 34.6 (C2,4), 53.7 and 53.8 (C1,5), 67.6 (CH_2OH), 74.5

(CH_2O), 95.9 (CCl_3), 151.5 (NC=O). **Accurate mass (EI):** Found 315.0172; calculated for (M^+) $C_{11}H_{16}NO_3Cl_3$ 315.0196 (7.5 ppm). ν_{max} **(cm^{-1}):** 3433 (OH), 1702 (C=O). **m/e (EI)** 315, 317 and 319 (M^+, 20, 19 and 7 %), 244 (100 %).

b) Method using disiamylborane[119]

Neat $BF_3.OEt_2$ (560 mg, 3.9 mmol) was added dropwise at -10 °C to a mixture of $NaBH_4$ (103 mg, 2.7 mmol) and 2-methyl-2-butene (516 mg, 7.3 mmol) in diglyme (4 ml). The semi-solid reaction mixture was stirred at this temperature for an additional hour, and then a solution of **169** (225 mg, 0.7 mmol) in diglyme (1 ml) was added. The reaction was further stirred for 12 h at r.t., and was then oxidised at 0 °C with the subsequent additions of water (2 ml), NaOH (2 ml, 6 M), and H_2O_2 (2 ml, 30 %). The reaction was stirred for an additional 2h at r.t. and heated to 60 °C. After being diluted with water and ether, the mixture was filtered. The aqueous layer was saturated with solid K_2CO_3, and then the organic products were extracted into diethyl ether (5x20 ml). The organic layer was washed with brine (7x20 ml) to remove excess diglyme. Drying over $MgSO_4$ and concentration under reduced pressure gave a residue, which was purified over silica gel (1:1 ethyl acetate/petrol) to give the product **171** (194 mg, 81 %) as a pale yellow oil. This product was a 77:1 mixture of two stereoisomers. ***endo*-isomer:** δ_H 1.40-1.60 (2H, m, *ax*-C2,4), 1.60-1.80 (2H, m, *endo*-C6,7), 1.80-2.10 (3H, complex, C3 and exo-C6,7), 2.10-2.30 (2H, m, *eq*-C2,4), 3.64 (2H, d, J= 8.0 Hz, CH_2OH), 4.30 (2H, broad d, C1,5), 4.66 (1H, d, J= 12.0 Hz, CH_2O), 4.82 (1H, d, J= 12.0 Hz, CH_2O). δ_C 28.6 and 29.3 (C6,7), 31.3 and 32.0 (C2,4), 31.7 (C3), 52.8 and 53.0 (C1,5), 67.39 (CH_2OH), 74.5 (CH_2O), 95.9 (CCl_3), 151.5 (NC=O). The *exo*-isomer cannot be assigned due to its low concentration in the mixture. The rest of the spectroscopic data were identical to that obtained by method a.

4.3.11 N-(2',2',2'-Trichloroethoxycarbonyl)-3α/β-tosyloxymethyltropane 170.



170

a) Method using n-butylithium[118]

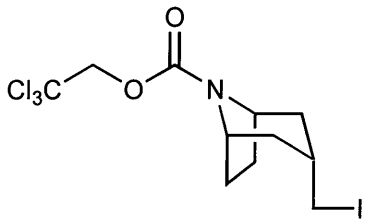
A 1.6 M solution of n-BuLi (154 mg, 2.4 mmol) in hexanes was added dropwise at 0 °C to a mixture **171** (604 mg, 1.9 mmol) and triphenylmethane (2 mg) in THF (8 ml). The reaction was stirred for 30 min., and then a solution of *p*-toluene-sulfonyl chloride **163** (364 mg, 1.9 mmol) in THF (6 ml) was added. The entire mixture was stirred for 18 h at 0 °C to r.t., diluted with ether (50 ml), and was then washed with brine (10x10 ml). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Purification over silica gel (1:4 and 1:1 ethyl acetate/petrol) gave a product, which was a mixture of two compounds. Further purification over silica gel afforded the title product **170** (123 mg, 14 %) as a liquid, which solidified on long standing. **m.p.** 80-81 °C. δ_H 1.40-1.60 (4H, complex, C6,7), 1.90-2.20 (5H, complex, C3 and C2,4), 2.45 (3H, s, *p*-CH_3-Ar), 4.03 (2H, d, J= 7.6 Hz, CH_2-OTs), 4.29 (2H, broad d, J= 20.8 Hz, C1,5), 4.64 (1H, d, J= 12.0 Hz, CH_2-O), 4.82 (1H, d, J= 12.4 Hz, CH_2-O), 7.35 (1H, d, J= 8.0 Hz, Ar), 7.78 (1H, d, J= 8.4 Hz, Ar). δ_C 21.7 (*p*- CH_3-Ar), 28.3 and 28.4 (C6,7), 29.1 (C3), 30.9 and 31.6 (C2,4), 52.5 and 52.6 (C1,5), 73.8 (CH_2-OTs), 74.5 (CH_2-O), 95.8 (CCl_3), 127.8, 129.9, 132.9 and 145.0 (Ar), 151.4 (NC=O). **$C_{18}H_{22}Cl_3NO_5S$.** Calculated C 45.92; H 4.71; N 2.97; Cl 22.59; S 6.81. **Found:** C 45.73; H 4.66; N 3.08. ν_{max} **(cm^{-1}):** 2966, 1713 (C=O), 1597, 1500 and 1417 (C=C), 1361, 1188 and 1176 (O=S=O). **m/e (EI)** 469, 471 and 473 (M^+, 11, 12 and 4 %), 91 (100 %).

b) Method using pyridine[128,129]

A solution of **171** (675 mg, 2.1 mmol) and p-toluenesulfonyl chloride **163** (650 mg, 3.4 mmol) in pyridine (15 ml) was stirred for 64 h at r.t. The reaction was poured into a mixture of crushed ice and CH_2Cl_2 and then organic product was extracted into CH_2Cl_2

(4x50 ml). The organic extracts were combined and washed with 3M HCl (3x50 ml), saturated $NaHCO_3$ (3x75 ml) and water (3x100 ml). Drying over $MgSO_4$ and concentration gave a golden yellow liquid. Purification over aluminium oxide (1:4 ethyl acetate/petrol) gave the title product **170** (0.9 g, 90 %) as a liquid, which was solidified on standing. The spectroscopic data were identical to that obtained by method a.

4.3.12 N-(2',2',2'-Trichloroethoxycarbonyl)-3α/β-iodomethyltropane 185

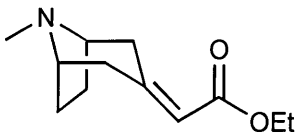


185

A solution of **170** (1.13 g, 2.39 mmol) and NaI (2.87 g, 19.13 mmol) in acetone (60 ml) was heated under reflux for 9h. After evaporation of the solvent, the residue was stirred with a 1:1 mixture of CH_2Cl_2 and petrol (250 ml). Purification over aluminum oxide (1:1 CH_2Cl_2/petrol) gave the title compound **185** (783 mg, 79 %) as a pale-yellow liquid. δ_H 1.40-1.80 (4H, complex, C6,7), 1.90-2.20 (5H, complex, C3 and C2,4), 4.03 (2H, d, J= 7.6 Hz, CH_2I), 3.36 (2H, d, J= 8 Hz, CH_2I), 4.30-4.50 (2H, broad d, C1,5), 4.62 (d, J= 12.4 Hz, CH_2O), 4.82 (1H, d, J= 12.4 Hz, CH_2O). δ_C 15.4 (CH_2I), 29.1 and 29.7 (C6,7), 31.8 (C3), 35.7 and 36.4 (C2,4), 52.5 and 52.6 (C1,5), 74.6 (CH_2O), 95.9 (CCl_3), 151.6 (C8). **Accurate mass (EI):** Found 424.9228; calculated for (M^+) $C_{11}H_{15}NO_2Cl_3I$ 424.9213 (- 3.5 ppm). ν_{max} **(cm^{-1}):** 2958, 1717 (C=O), 1419, 1119. **m/e (EI)** 425, 427 and 429 (M^+, 8, 7 and 3 %), 298 (100 %).

4.4 Experimental for chapter three

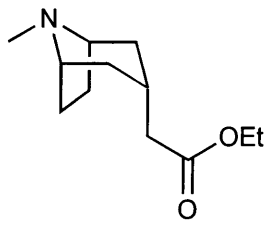
4.4.1 Ethyl (tropan-3'-ylidine)acetate[88,152] 132



132

Neat triethyl phosphonoacetate **131** (27.1 g, 0.121 mol) was added dropwise to a slurry of NaH (3.0 g, 0.125 mol) in THF (150 ml) at -30 °C. The mixture was stirred for 1 h and then a solution of tropinone **116** (15.0 g, 0.108 mol) in THF (100 ml) was added. The entire mixture was allowed to warm to room temperature for 2h and was then heated under reflux for 35h. The reaction mixture was quenched with water (50 ml) and concentrated to give a residue. The residue was partitioned between water (300 ml) and Et_2O (100 ml) and the organics were extracted into Et_2O (4x100 ml). The combined organic layers were treated with a 2 M HCl (150 ml) and were then washed with Et_2O (2x300 ml). Upon basification with a 2.5 M NaOH (130 ml), the title compound was extracted into Et_2O (4x100 ml), dried over $MgSO_4$ and concentrated to give the title compound **132** (17.4 g, 77 %) as a pale-yellow oil. The product was contaminated with 11 % of β,γ-unsaturated ester **133**. This was used directly for the next step without purification. δ_H 1.23 (3H, t, J= 7.2 Hz, $C\underline{H}_3CH_2O$), 1.46 (2H, broad dd, J= 8.8 and 2.4 Hz, *endo*-C6',7'), 1.88-1.98 (3H, m, *exo*-C6',7' and *ax*-C4'), 2.33 (3H, s, NCH_3), 2.30-2.40 (1H, broad d, *eq*-C2'), 2.65 (1H, broad d, J= 14.0 Hz, *eq*-C4'), 3.21 (2H, broad s, C1',5'), 3.46 (1H, broad d, J= 14.8 Hz, *ax*-C2'), 4.10 (2H, q, J=7.2 Hz, $CH_3C\underline{H}_2O$), 5.65 (1H, s, C=CH). δ_C 14.2 ($\underline{C}H_3CH_2O$), 26.7 and 26.9 (C6',7'), 38.8 (NCH_3), 35.0 and 41.6 (C2',4'), 59.5 ($CH_3\underline{C}H_2O$), 61.0 and 61.4 (C1',5'), 117.7 (=CH), 157.9 (C3'), 166.6 (C=O). ν_{max} **(cm^{-1}):** 2940, 2874, 2846, 2795 (N-Me), 1714 (C=O), 1643 (C=C), 1199, 1153, 1041. **m/z (CI)** 210 ($M+H^+$).

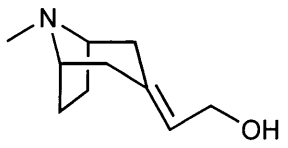
4.4.2 Ethyl (tropan-3'-yl)acetate[88,151,152] 214



214

A solution of ethyl (tropan-3'-ylidine)acetate **132** (16.4 g, 78.4 mmol) in MeOH (400 ml) and a 10 % palladium (834 mg, 7.8 mmol) on activated carbon was shaken for 51h under 4-5 atm. pressure of hydrogen at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate was concentrated to give a crude product. Purification by distillation (66 °C; 0.1-0.01 mm-Hg) gave the title compound **214** (15.3 g, 87 %) as a clear oil. The product was a mixture (5:1 *endo/exo*) and used directly for the next step. ***endo*-isomer:** δ_H 1.12 (3H, t, J= 6.9 Hz, $C\underline{H}_3CH_2O$), 1.17 (2H, broad d, J= 14.7 Hz, *eq*-C2',4'), 1.50 (2H, broad d, J= 8.4 Hz, *endo*-C6',7'), 1.88-1.96 (2H, m, *exo*-C6',7'), 1.97-2.09 (2H, m, *ax*-C2',4'), 2.10-2.20 (1H, m, C3'), 2.12 (3H, s, N-CH_3), 2.32 (2H, d, J= 8.1 Hz, $CH_2C{=}O$), 2.96 (2H, broad s, C1',5'), 3.99 (2H, q, J= 6.9 Hz, $CH_3C\underline{H}_2O$). ***endo*-isomer:** δ_C 14.4 ($\underline{C}H_3CH_2O$), 24.7 (C3'), 26.5 (C6',7'), 35.3 (C2',4'), 40.2 (N-CH_3), 43.2 ($\underline{C}H_2C{=}O$ and $CH_3\underline{C}H_2O$), 60.4 (C1',5'), 173.2 (C=O). ***exo*-isomer:** δ_H 1.11 (3H, t, J= 6.9 Hz, $C\underline{H}_3CH_2O$), 1.08-1.56 (4H), 1.84-2.20 (5H), 2.12 (3H, s, N-CH_3), 2.34 (2H, d, J= 8.1 Hz, $CH_2C{=}O$), 2.92-3.02 (2H, broad s, C1',5'), 3.97 (2H, q, J= 6.9 Hz, $CH_3C\underline{H}_2O$). ***exo*-isomer:** δ_C 14.4 ($\underline{C}H_3CH_2O$), 24.7 (C3'), 25.6 and 26.2 (C6',7'), 37.9 and 41.5 (C2',4'), 40.4 (N-CH_3), 42.9 ($CH_2C{=}O$ and $CH_3\underline{C}H_2O$), 60.3 and 61.3 (C1',5'), 172.8 (C=O). ν_{max} **(cm^{-1}):** 2932, 2796 (N-Me), 1735 (C=O), 1478, 1450, 1368, 1342, 1307, 1169, 1149, 1063, 1033. **m/z (EI)** 211 (M^+, 28 %), 124 (55 %), 96 (79 %), 82 (100 %), 42 (65 %).

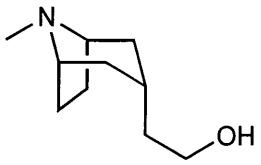
4.4.3 2-(Tropan-3'-ylidine)ethanol[159] 231



231

A solution of ethyl (tropan-3'-ylidine)acetate **132** (5.2 g, 24.9 mmol) in THF (55 ml) was added dropwise to a suspension of $LiAlH_4$ (4.7 g, 0.124 mol) in THF (75 ml) at –60 °C. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 41h. The reaction mixture was quenched with a 2.5 M NaOH (10 ml), diluted with Et_2O (50 ml) and then filtered through a sintered funnel. The filtrate was concentrated to give a residue, which was partitioned between brine and Et_2O. The organics were then extracted into Et_2O (6x50 ml). Combined extracts were dried over $MgSO_4$ and concentrated to give a crude material. This was purified by distillation (b.p. 68-72 °C; 0.1-0.01 mm-Hg) to yield the title compound **231** (2.0 g, 48 %) as a white crystalline solid. The product was contaminated with 11 % of *endo*-cyclic alcohol **232**. **m.p.** 55.5-57.5 °C. δ_H 1.36 (1H, broad d, J= 8.4 Hz, *endo*-C6',7'), 1.44 (1H, broad s, J= 9.3 Hz, *endo*-C6',7'), 1.80-1.90 (3H, m, *exo*-C6',7' and *ax*-C2',4'), 2.16-2.23 (2H, m, (*ax* + *eq*)-C2',4'), 2.28 (3H, s, N-CH_3), 2.49 (1H, broad s, J= 15.3 Hz, *eq*-C2',4'), 3.10 (2H, broad s, C1',5'), 3.64 (1H, broad s, OH), 4.08 (2H, d, J= 6.6 Hz, CH_2OH), 5.44 (1H, t, J= 6.9 Hz, C=CH). δ_C 26.5 and 26.8 (C6',7'), 39.9 (N-CH_3), 34.6 and 41.6 (C2',4'), 58.4 (CH_2OH), 61.4 and 61.8 (C1',5'), 126.4 (=CH), 136.6 (C3'). **$C_{10}H_{17}NO$.** Calculated C, 71.82; H, 10.25; N, 8.37. Found: C, 71.79; H, 10.31; N, 8.45. ν_{max} **(cm^{-1}):** 3161 (OH), 2940, 2797 (N-Me), 1669 and 1654 (C=CH). **m/z (EI)** 167 (M^+,17 %), 82 (100 %).

4.4.4 2-(Tropan-3'-yl)ethanol 230



230

a-) From the hydrogenation of 2-(tropan-3-ylidine)ethanol 231

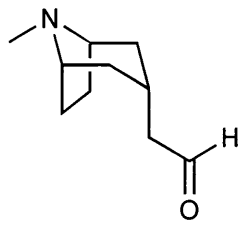
A solution of of 2-(tropan-3-ylidine)ethanol **231** (6.2 g, 36.9 mmol) in EtOH (150 ml) and a 10 % palladium (300 mg, 2.8 mmol) on activated carbon was shaken for 45h under 3-4 atm. pressure of hydrogen at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate was concentrated to give a crude product. Purification by distillation (76-78 °C; 0.1-0.01 mm-Hg) gave the title compound **230** (5.2 g, 84 %) as a clear oil and as a 7:1 *endo* / *exo* mixture. ***(endo+exo)*-isomer:** δ_H 1.29 (2H, broad d, J= 14.1 Hz, *eq*-C2',4'), 1.34-1.86 (7H), 1.61 (2H, broad d, J= 8.1 Hz, *endo*-C6',7'), 1.72 (2H, t, J= 6.6 Hz, $C\underline{H}_2CH_2OH$), 1.66-1.86 (1H, m, C3'), 1.90-2.04 (2H, m, *exo*-C6',7'), 2.04-2.16 (2H, m, *ax*-C2',4'), 2.21 (3H, s, N-CH_3), 2.78 (1H, broad s, OH), 3.06 (2H, broad s, C1',5'), 3.59 (2H, t, J= 6.6 Hz, CH_2OH). ***endo*-isomer:** δ_C 24.1 (C3'), 26.6 (C6',7'), 35.9 (C2',4'), 40.4 (N-CH_3), 41.7 ($\underline{C}H_2CH_2OH$), 60.7 (C1',5'), 61.7 (CH_2OH). ***exo*-isomer:** δ_C 24.5 (C3'), 26.3 (C6',7'), 38.5 (C2',4'), 40.0 (N-CH_3), 40.7 ($\underline{C}H_2CH_2OH$), 60.5 (CH_2OH), 61.5 (C1',5'). ν_{max} **(cm^{-1}):** 3201, 3161 (OH), 2967, 2927, 2886, 2851, 2797 (N-CH_3), 1473, 1342, 1026, 1011. **Accurate mass (EI):** Found 169.1470; Calculated for (M^+) $C_{10}H_{19}NO$ 169.1467 (-1.8 ppm). **m/z (EI)** 169 (M^+, 21 %), 96 (83 %), 82 (100 %).

b-) From the $LiAlH_4$ reduction of ethyl (tropan-3'-yl)acetate

A solution of ethyl (tropan-3'-yl)acetate **214** (12.4 g, 58.9 mmol) in Et_2O (50 ml) was added dropwise to a suspension of $LiAlH_4$ (4.5 g, 0.118 mol) in Et_2O (250 ml) at –60 °C. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 24h. The reaction mixture was sequentially quenched with water (4.8 ml), a 15 % NaOH (4.8 ml) and water (15 ml) to give a granular precipitate. The precipitate was filtered off through a sintered funnel and was then washed with Et_2O (2x50 ml). The combined filtrate was dried over $MgSO_4$ and concentrated to give the

title compound (8.5 g, 86 %) as a clear oil and as a 5:1 *endo/exo* mixture. The spectral data are consistent with those of obtained by method a.

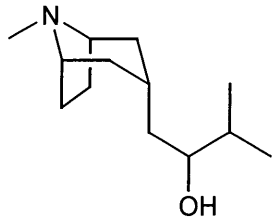
4.4.5 (Tropan-3'-yl)acetaldehyde 227



227

A solution of dimethyl sulfoxide (3.2g, 41.3 mmol) in CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (2.7 g, 21.2 mmol) in CH_2Cl_2 at -78 °C. After stirring for 15 min., a solution of 2-(tropan-3'-yl)ethanol **230** (2.0 g, 11.8 mmol) in CH_2Cl_2 was added. The mixture was stirred for 2h at -78 °C and was then quenched with triethylamine (6.6 g, 64.9 mmol). After stirring for 15 min at room temperature, 10 % NaOH solution was added to make the reaction mixture strongly basic. Organics were then extracted into CH_2Cl_2 (4x80 ml) and then the combined extracts were dried over $MgSO_4$ and concentrated to give the title compound **227** (1.84 g, 93 %) as a light-brown liquid and as a 5:1 *endo/exo* mixture. ***endo*-isomer:** δ_H 1.17 (2H, broad d, J= 14.4 Hz, *eq*-C2',4'), 1.52 (2H, broad d, J= 8.4 Hz, *endo*-C6',7'), 1.90-2.02 (2H, m, *exo*-C6',7'), 2.08-2.16 (2H, m, *ax*-C2',4'), 2.18 (3H, s, N-CH_3), 2.24-2.38 (1H, m, C3'), 2.48 (2H, dd, J= 7.8 and 2.0 Hz, CH_2CHO), 3.06 (2H, broad s, C1',5'), 9.54 (1H, t, J= 1.8 Hz, CHO). ***endo*-isomer:** δ_C 20.5 (C3'), 25.2 (C6',7'), 34.2 (C2',4'), 38.9 (N-CH_3), 51.4 (CH_2CHO), 59.4 (C1',5'), 201.6 (CHO). ***exo*-isomer:** δ_H 1.08-1.62 (4H), 1.90-2.38 (5H), 2.22 (3H, s, N-CH_3), 2.45-2.52 (2H, CH_2CHO), 3.14 (2H, broad s, C1',5'), 9.60 (1H, t, J= 1.8 Hz, CHO). ***exo*-isomer:** δ_C 21.7 (C3'), 24.8 (C6',7'), 36.4 (C2',4'), 39.1 (N-CH_3), 49.3 (CH_2CHO), 60.6 (C1',5'), 200.4 (CHO). ν_{max} **(cm^{-1}):** 2930, 2795 (N-CH_3), 1723 (C=O), 1450, 1339, 1231, 1129. **Accurate mass (EI):** Found 167.1311; Calculated for (M^+) $C_{10}H_{17}NO$ 167.1310 (-0.5 ppm). **m/z (EI)** 167 (M^+, 9 %), 124 (58 %), 96 (49 %), 83 (67 %), 82 (100 %), 42 (59 %).

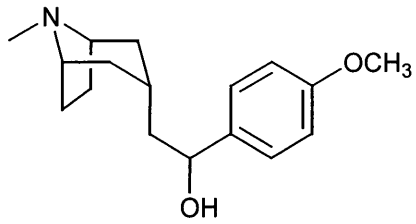
4.4.6 1-(Tropan-3'-yl)-3-methyl-2-butanol 236



236

A 2 M solution of isopropylmagnesium chloride (492 mg, 4.78 mmol) was added to a solution of (tropan-3'-yl)acetaldehyde **227** (400 mg, 2.39 mmol) in THF (30 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature for 14 h and was then concentrated under reduced pressure. The residue was diluted with saturated NH_4Cl and impurities were extracted into Et_2O (3x 30 ml). After the aqueous layer was made basic (pH 10-11) with NaOH pellets, organics were then extracted into CH_2Cl_2 (5x 40 ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over $MgSO_4$ and concentrated to give the title compound **236** (337 mg, 67 %) as a clear oil and as a 5:1 *endo/exo* mixture. δ_H 0.86 (6H, dd, J= 4.5 Hz, CH_3), 1.20-1.40 (3H, m), 1.50-1.70 (4H, m), 180-2.30 (6H, m), 2.22 (3H, s, NCH_3), 3.10 (2H, broad s, C1',5'), 3.40 (1H, m, CHOH). ***endo*-isomer:** δ_C 17.5 and 19.0 (CH_3), 24.1 (C3'), 26.5 and 26.7 (C6',7'), 34.2 and 37.4 (C2',4'), 40.3 (N-CH_3), 42.8 ($\underline{C}H_2CHOH$ + $\underline{C}HCHOH$), 60.8 (C1',5'), 74.9 (CHOH). ***exo*-isomer:** δ_C 17.3 and 18.9 (CH_3), 24.3 (C6',7'), 26.2 (C2',4'), 34.3, 37.4, 41.3 (N-CH3), 42.8 ($\underline{C}H_2CHOH$ + $\underline{C}HCHOH$), 61.7 and 61.9 (C1',5'), 73.7 (CHOH). **Accurate mass (EI):** Found 211.1936; Calculated for (M^+) $C_{13}H_{25}NO$ 211.1936 (0.07 ppm). ν_{max} **(cm^{-1}):** 3373 (O-H), 2958, 2928, 2797 (N-CH_3), 1470, 1451, 1338, 1230, 1131, 1063. **m/z (EI)** 211 (M^+, 3 %), 168 (3 %), 96 (64 %), 82 (100 %), 42 (74 %).

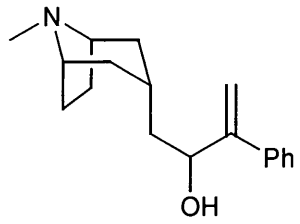
4.4.7 2-(Tropan-3'-yl)-1-*para*-methoxyphenyl-1-ethanol 237



237

A solution of 4-bromoanisole (673 mg, 3.60 mmol) in Et_2O (15 ml) was added dropwise to a suspension of magnesium turnings (96 mg, 3.96 mmol) and iodine crystals in Et_2O (5 ml) at room temperature. After addition was complete, the mixture was heated under reflux for 15 min and then cooled to ambient temperature. This Grignard reagent was added to a solution of (tropan-3'-yl)acetaldehyde **227** (200 mg, 1.20 mmol) in THF (20 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature for 21h and then concentrated. The residue was diluted with saturated NH_4Cl and impurities were extracted into Et_2O (3x30 ml). After the aqueous layer was made basic (pH 10-11) with NaOH pellets, organics were then extracted into CH_2Cl_2 (5x40 ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over $MgSO_4$ and concentrated to give the title compound **237** (210 mg, 64 %) as a pale-yellow viscous oil and as a 5:1 *endo/exo* mixture. δ_H 1.20-1.50, 1.60-2.30, 2.18 (3H, s, NCH_3), 3.10 (2H, broad s, C1',5') 3.74 (3H, s, OCH_3), 4.50 (1H, t, CHOH), 6.80 (2H, d, J= 8.7 Hz, Ar), 7.18 (2H, d, J= 8.7 Hz, Ar). *endo*-isomer: δ_C 24.1 (C3'), 26.5 and 26.6 (C6',7'), 34.7 and 36.0 (C2',4'), 39.6 (N-CH3), 48.4 ($\underline{C}H_2CHOH$), 55.4 (OCH_3), 60.5 (C1',5'), 72.3 (CHOH), 113.9, 127.3, 138.2 and 159.0 (Ar). *exo*-isomer: δ_C 24.5 (C3'), 26.3 (C6',7'), 37.7 and 38.5 (C2',4'), 39.6 (N-CH3), 46.7 ($\underline{C}H_2CHOH$), 53.6 (OCH_3), 61.4 and 61.5 (C1',5'), 71.0 (CHOH), 113.9, 127.1, 138.3 and 159.0 (Ar). **Accurate mass (EI):** Found 275.1882; Calculated for (M^+) $C_{17}H_{25}NO_2$ 275.1885 (1.2 ppm). ν_{max} **(cm^{-1}):** 3355 (O-H), 2931, 2836, 2801 ($N\text{-}CH_3$), 1610, 1585, 1510, 1451, 1338, 1245, 1075, 1037. **m/z (EI)** 275 (M, 23 %), 257 (8 %), 138 (78 %), 96 (73 %), 82 (100 %).

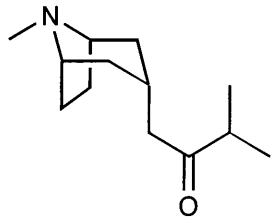
4.4.8 4-(Tropan-3'-yl)-2-phenyl-2-buten-3-ol 238



238

A solution of α-bromostyrene (657 mg, 3.59 mmol) in Et_2O (10 ml) was added dropwise to a suspension of magnesium turnings (96 mg, 3.95 mmol) and iodine crystals in Et_2O (5 ml) at room temperature. After addition was complete, the mixture was heated under reflux for 15 min and was then cooled to ambient temperature. This Grignard reagent was added to a solution of (tropan-3'-yl)acetaldehyde **227** (400 mg, 2.39 mmol) in THF (30 ml) at -78 °C. The reaction mixture was diluted with Et_2O (45 ml) and then stirred for 4.5 h between -78 °C and -10 °C. The reaction mixture was concentrated, the residue was diluted with saturated NH_4Cl and impurities were extracted into AcOEt (3x 40 ml). After the aqueous layer was made basic (pH 10-11) with NaOH pellets, organics were then extracted into CH_2Cl_2 (4x 50 ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over $MgSO_4$ and concentrated to give the title compound **238** (514 mg, 79 %) as a pale-yellow viscous oil and as a 5:1 *endo/exo* mixture. δ_H 1.10-1.50 (4H), 1.60-2.20 (7H), 2.09 (3H, s, NCH_3), 2.93 (2H, broad s, C1',5'), 3.95 (1H, broad s, OH), 4.46-4.58 (1H, m, CHOH), 5.18 (1H, s, $=CH_2$), 5.30 (1H, s, $=CH_2$), 7.14-7.34 (5H, m, Ar). *endo*-isomer: δ_C 24.3 (C3'), 26.3 and 26.4 (C6',7'), 34.3 and 37.0 (C2',4'), 40.2 ($N-CH_3$), 45.3 ($\underline{C}H_2CHOH$), 60.6 (C1',5'), 72.3 (CHOH), 112.3 ($=CH_2$), 127.1, 127.8, 128.6 and 140.3 (Ar), 153.0 (C=). *exo*-isomer: δ_C 24.5 (C3'), 26.3 (C6',7'), 28.0 and 30.3 (C2',4'), 40.6 ($N-CH_3$), 43.9 ($\underline{C}H_2CHOH$), 61.5 and 61.6 (C1',5'), 71.1 (CHOH), 112.3 ($=CH_2$), 127.0, 127.8, 128.6 and 140.2 (Ar), 153.2 (C=). **Accurate mass (EI):** Found 271.1936; Calculated for (M^+) $C_{18}H_{25}NO$ 271.1936 (0.05 ppm). ν_{max} **(cm^{-1}):** 3343 (O-H), 3079, 3055, 3028, 2923, 2855, 2800 ($N-CH_3$), 1627, 1597, 1492, 1450, 1338, 1122, 1071. **m/z (EI)** 271 (M^+, 13 %), 254 (61 %), 138 (41 %), 96 (93 %), 82 (100 %).

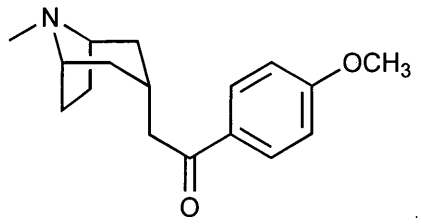
4.4.9 1-(Tropan-3'-yl)-3-methyl-2-butanone 218



218

A mixture of PCC (604 mg, 2.80 mmol) adsorbed on alumina and 1-(tropan-3'-yl)-3-methyl-2-butanol **236** (295 mg, 1.40 mmol) in CH_2Cl_2 (30 ml) was stirred for 24 h. The reaction was then diluted with ether (30 ml) and filtered through Hyflo Super Cell. Alumina was washed twice with a mixture of ether and CH_2Cl_2 (1:1) and the solution was concentrated to give a residue, which was made basic with 2.5 M NaOH solution. Organic were then extracted into AcOEt (3x 30 ml) and the combined extracts were dried over $MgSO_4$ and concentrated to give the title compound **218** (130 mg, 44 %) as a light-brown liquid and as a 5:1 *endo/exo* mixture. ***endo*-isomer:** δ_H 1.07 (3H, d, J= 6.9 Hz, $(CH_3)_2$-), 1.20 (2H, broad d, J= 14.1 Hz , *eq*-C2',4'), 1.61 (2H, broad d, J= 8.1 Hz, *endo*-C6',7'), 1.98-2.10 (2H, m, *exo*-C6',7'), 2.10-2.24 (2H, m, *ax*-C2',4'), 2.26 (3H, s, NCH_3), 2.28-2.42 (1H, m, C3'), 2.56 (1H, septet, J= 6.9 Hz, CHC=O), 2.62 (2H, d, J= 7.8 Hz, CH_2C=O), 3.10 (2H, broad s, C1',5'). ***endo*-isomer:** δ_C 17.2 (CH_3), 21.6 (C3'), 25.3 (C6',7'), 34.2 (C2',4'), 39.6 (N-CH_3), 48.2 (CH_2C=O and CHC=O), 59.3 (C1',5'), 213.1 (C=O). ***exo*-isomer:** δ_H 1.04 (6H, d, J= 6.9 Hz, CH_3), 1.13-1.70 (4H), 1.94-2.40 (5H), 2.26 (3H, s, NCH_3), 2.45-2.65 (2H), 3.06-3.16 (2H, broad s, C1',5'). ***exo*-isomer:** δ_C 17.0 (CH_3), 22.8 (C3'), 24.8 (C6',7'), 36.6 (C2',4'), 38.8 (N-CH_3), 45.9 (CH_2C=O and CHC=O), 60.5 (C1',5'), 213.1 (C=O). **Accurate mass (EI):** Found 209.1773; Calculated for (M^+) $C_{13}H_{23}NO$ 209.1780 (3.1 ppm). ν_{max} **(cm^{-1}):** 2960, 2930, 2795 (N-CH_3), 1710 (C=O), 1467, 1382, 1128, 1079, 1039. **m/z (EI)** 209 (M^+, 15 %), 138 (41 %),124 (52 %), 96 (68 %), 82 (100 %).

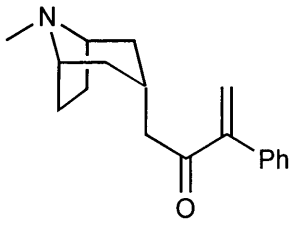
4.4.10 2-(Tropan-3'-yl)-1-*para*-methoxyphenyl-1-ethanone 219



219

Activated manganese dioxide (4.3 g, 49.4 mmol) was added to a solution of 2-(tropan-3'-yl)-1-*para*-methoxyphenyl-1-ethanol **237** (358 mg, 1.30 mmol) in CH_2Cl_2 (40 ml) and the mixture was stirred for 22h at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate concentrated to give the title compound **219** (181 mg, 51 %) as a light-brown liquid and as a 5:1 *endo/exo* mixture. ***endo*-isomer:** δ_H 1.27 (2H, broad d, J= 14.4 Hz, *eq*-C2',4'), 1.64 (2H, broad d, J= 8.4 Hz, *endo*-C6',7'), 1.90-2.06 (2H, m, *exo*-C6',7'), 2.08-2.18 (2H, m, *ax*-C2',4'), 2.19 (3H, s, NCH_3), 2.32-2.46 (1H, m, C3'), 3.00 (2H, d, J= 7.8 Hz, $CH_2C{=}O$), 3.05 (2H, broad s, C1',5'), 3.80 (3H, s, OCH_3), 6.86 (2H, d, J= 9.0 Hz, Ar), 7.84 (2H, d, J= 9.0 Hz, Ar). ***endo*-isomer:** δ_C 23.7 (C3'), 26.4 (C6',7'), 35.4 (C2',4'), 40.0 (N-CH3), 46.6 ($CH_2C{=}O$), 55.4 (OCH_3), 60.3 (C1',5'), 113.6, 130.2, 130.4 and 163.3 (Ar), 198.5 (C=O). ***exo*-isomer:** δ_H 1.36-1.70 (4H), 1.90-2.30 (5H), 2.20 (3H, s, NCH_3), 2.71 (2H, d, J= 6.6 Hz, $CH_2C{=}O$), 2.92 (2H, broad s, C1',5'), 3.80 (3H, s, OCH_3), 6.80-6.90 (2H, Ar), 7.80-7.90 (2H, Ar). ***exo*-isomer:** δ_C 24.8 (C3'), 25.8 (C6',7'), 38.1 (C2',4'), 40.3 (N-CH3), 44.6 ($CH_2C{=}O$), 55.3 (OCH_3), 61.4 (C1',5'), 113.6, 130.1, 130.5 and 163.3 (Ar), 198.3 (C=O). **Accurate mass (EI):** Found 273.1732; Calculated for (M^+) $C_{17}H_{23}NO_2$ 273.1729 (-1.1 ppm). ν_{max} **(cm^{-1}):** 2959, 2931, 2844, 2795 (N-CH_3), 1671 (C=O), 1599, 1575, 1509, 1260, 1169, 1029. **m/z (EI)** 273 (M^+, 11 %), 138 (77 %),124 (100 %), 96 (70 %), 82 (82 %). See X-ray structure in **Figure 19** (p. 116).

4.4.11 4-(Tropan-3'-yl)-2-phenyl-2-buten-3-one 220



220

Activated manganese dioxide (8.0 g, 92.0 mmol) was added to a solution of 4-(tropan-3'-yl)-2-phenyl-2-buten-3-ol **238** (657 mg, 2.4 mmol) in CH_2Cl_2 (25 ml) and the mixture was stirred for 24h at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate concentrated to give the title compound **220** (360 mg, 55 %) as a light-brown liquid and as a 5:1 *endo* / *exo* mixture. ***endo*-isomer:** δ_H 1.19 (2H, broad d, J= 14.4 Hz, *eq*-C2',4'), 1.51 (2H, broad d, J= 8.1 Hz, *endo*-C6',7'), 1.86-2.02 (2H, m, *exo*-C6',7'), 2.04-2.22 (2H, m, *ax*-C2',4'), 2.17 (3H, s, N-CH_3), 2.24-2.38 (1H, m, C3'), 2.81 (2H, d, J= 7.8 Hz, CH_2C=O), 3.02 (2H, broad s, C1',5'), 5.80 (1H, s, =CH_2), 5.97 (1H, s, =CH_2), 7.16-7.34 (5H, m, Ar). ***endo*-isomer:** δ_C 23.7 (C3'), 26.4 (C6',7'), 35.3 (C2',4'), 39.9 (N-CH_3), 48.1 (CH_2C=O), 60.2 (C1',5'), 123.8 (=CH_2), 127.2, 128.2, 128.3 and 137.1 (Ar), 149.6 (C=), 202.0 (C=O). ***exo*-isomer:** δ_H 1.12-1.66 (4H), 1.86-2.40 (5H), 2.16 (3H, s, N-CH_3), 2.52 (2H, d, J= 6.9 Hz, CH_2C=O), 2.96-3.10 (2H, broad s, C1',5'), 5.80 (1H, s, =CH_2), 5.99 (1H, s, =CH_2), 7.16-7.34 (5H, m, Ar). ***exo*-isomer:** δ_C 24.8 (C3'), 25.9 and 26.9 (C6',7'), 34.1 and 38.0 (C2',4'), 40.4 (N-CH_3), 46.2 (CH_2C=O), 59.7 and 61.2 (C1,5), 123.8 (=CH_2), 128.0, 128.1, 128.5 and 137.1 (Ar), 149.8 (C=), 201.6 (C=O). **Accurate mass (EI):** Found 269.1782; Calculated for (M^+) $C_{18}H_{23}NO$ 269.1780 (-1.0 ppm). ν_{max} **(cm^{-1}):** 2955, 2930, 2846, 2794 (N-CH_3), 1685 (C=O), 1493, 1446, 1130. **m/z (EI)** 269 (M^+, 6 %), 96 (85 %), 82 (100 %).

4.4.12 Biological testing

4.4.12.1 Drugs and solutions

Acetylcholine (ACh) chloride and atropine sulphate were purchased from Sigma and prepared daily as a 1 mM and 10 mM aqueous stock solutions, respectively. Ketone **220** was dissolved in 1.0 M HCl and then diluted with distilled water to prepare a 1 mM final stock solution. In these assays, the tissue was maintained in four 50 ml organ baths. Each organ bath was filled with a modified Tyrode solution, continuously oxygenated and maintained at 32 °C. The composition of modified Tyrode solution was as follow (mM): 136 NaCl, 2.62 KCl, 1.8 $MgCl_2.6H_2O$, 1.8 $CaCl_2.2H_2O$, 0.42 NaH_2PO_4, 11.9 $NaHCO_3$ and 5.5 glucose.

4.4.12.2 Tissue preparation[178]

Dunkin Hartley guinea-pigs (200-300 g) were rapidly killed by cervical dislocation. The abdomen was opened, a length of ileum was removed and kept in oxygenated Tyrode solution at room temperature. Small pieces of ileum (1.0-1.5 cm) was dissected and mounted longitudinally in an organ bath chamber, as shown in **Figure 1**. An initial load of 1 g was applied to each preparation and the ileum was allowed to equilibrate for at least 15 min before testing. After the equilibrium period, contractions of the muscle were induced by addition of ACh (3 nM-10 μM).

4.4.12.3 Determination of acetylcholine potency (EC_{50})

A non-cumulative concentration-response curve (CRC) for ACh was obtained with eight different concentrations of ACh, ranging from 3 nM to 10 μM (n=6; n= number of preparations involved in the experiment). ACh was added to the organ bath for 30 s and then the tissues were washed with fresh Tyrode solution. This was then repeated in a 4 min time cycle. The tissue responses were measured as changes in isometric tension displayed on a pen chart recorder (see **Figure 20a**). The responses were then calculated as a percentage of the maximum response obtained to ACh and plotted against the logarithm of the ACh concentration (see **Figure 20b**). The ACh potency was expressed as the 50 % effective concentration value (EC_{50}).

4.4.12.4 Determination of antagonist potency (IC_{50})

The tissues were incubated with antagonists for 3 min at increasing concentrations, ranging from 0.1 nM to 0.1 μM for atropine **202** and from 10 nM to 30 μM for ketone

220. Each incubation was followed by addition of 0.1 μM ACh for 30 s and then the tissues were washed with fresh Tyrode solution at least twice during the 4 min time cycle. The tissue responses to Ach in the presence of the drugs (see **Figure 21a** for atropine **202** and **Figure 21b** for ketone **220**) were measured and calculated as a percentage of the control response obtained to ACh in the absence of the antagonists. These data were plotted against the logarithm of the antagonist concentration (see **Figure 21c**). The antagonist potency was expressed as the 50% inhibitory concentration value (IC_{50}).

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APPENDIXES

APPENDIX

A.1 Publications, conferences and seminars

A.1.1 Papers published

A short synthesis of (S)-α-(diphenylmethyl)alkyl amines from amino acids, David O'Hagan and Mustafa Tavasli, *Tetrahedron: Asymm.*, **1999**, 10, 1189.

The synthesis, conformation and antimuscarinic properties of ketone analogues of tropane esters, Mustafa Tavasli, David O'Hagan, Andrei S. Batsanov, Graham R. Foxon, Robert F. Halliwell and Judith A. K. Howard, *J. Chem. Soc., Perkin Trans 1*, in press.

A.1.2 Research conferences attended

1996

December 16 The Royal Society of Chemistry, One-Day Postgraduate Symposium in Bioorganic Chemistry, University of Liverpool (Poster presentation).

1997

May 7 21st Century Heteocyclic Chemistry, University of Sunderland.

December 17 The Royal Society of Chemistry, Perkin Division, 26th Scottish Regional Meeting for the Reading of Original Papers, University of Strathclyde.

1998

April 6-9 The Royal Society of Chemistry, National Congress and Young Researchers Meeting, University of Durham.

1999

January 6 The Royal Society of Chemistry, Perkin Division, Bioorganic Group One-Day Postgraduate Symposium, University of Leicester.

May 5 The 2nd Sunderland Pre-grasmere Conference, Heterocycles as Synthetic Reagents: a Review Symposium, University of Sunderland.

August 1-6 17th International Congress of Heterocyclic chemistry, Institute of Organic Chemistry, Vienna University of Technology, Vienna, Austria (Poster presentation).

A.1.3 Colloquia, lectures and seminars from invited speakers

1996

October 14* Prof. A. R. Katritzky, University of Gainesville,University of Florida, USA: *Recent Advances in Benzotriazole Mediated Synthetic Methodology.*

October 16* Prof. Ojima, Guggenheim Fellow, State University of New York at Stony Brook: *Silylformylation and Silylcarbocyclisations in Organic Synthesis.*

October 22 Prof. B. J. Tighe, Department of Molecular Sciences and Chemistry, University of Aston: *Making Polymers for Biomedical Application - can we meet Nature's Challenge?*

October 29* Prof. D. M. Knight, Department of Philosophy, University of Durham: *The Purpose of Experiment - A Look at Davy and Faraday.*

November 13* Dr. G. Resnati, Milan: *Perfluorinated Oxaziridines - Mild Yet Powerful Oxidising Agents.*

November 18* Prof. G. A. Olah, University of Southern California, USA: *Crossing Conventional Lines in my Chemistry of the Elements.*

November 27 Dr. Richard Templer, Imperial College, London: *Molecular Tubes and Sponges.*

December 4 Prof. K. Muller-Dethlefs, York University: *Chemical Applications of Very High Resolution ZEKE Photoelectron Spectroscopy.*

December 11 Dr. Chris Richards, Cardiff University: *Sterochemical Games with Metallocenes.*

1997

January 15* Dr. V. K. Aggarwal, University of Sheffield: *Sulfur Mediated Asymmetric Synthesis.*

January 16 Dr. Sally Brooker, University of Otago, NZ: *Macrocycles- Exciting yet Controlled Thiolate Coordination Chemistry.*

January 21 Mr. D. Rudge, Zeneca Pharmaceuticals: *High Speed Automation of Chemical Reactions.*

January 22 Dr. Neil Cooley, BP Chemicals, Sunbury: *Synthesis and Properties of Alternating Polyketones.*

January 29 Dr. Julian Clarke, UMIST: *What can we learn about polymers and biopolymers from computer-generated nanosecond movie-clips?*

February 4 Dr. A. J. Banister, University of Durham: *From Runways to Non-metallic Metals - A New Chemistry Based on Sulphur.*

February 5 Dr. A. Haynes, University of Sheffield: *Mechanism in Homogeneous Catalytic Carbonylation.*

February 12 Dr. Geert-Jan Boons, University of Birmingham: *New Developments in Carbohydrate Chemistry.*

February 18 Prof. Sir James Black, Foundation/King's College London: *My Dialogues with Medicinal Chemists.*

February 25 Prof. A. G. Sykes, University of Newcastle: *The Synthesis, Structures and Properties of Blue Copper Proteins.*

February 26* Dr. Tony Ryan, UMIST: *Making Hairpins from Rings and Chains.*

March 4* Prof. C. W. Rees, Imperial College: *Some Very Heterocyclic Chemistry.*

March 5 Dr. J. Staunton FRS, Cambridge University: *Tinkering with biosynthesis - towards a new generation of antibiotics.*

October 8* Prof. E. Atkins, Department of Physics, University of Bristol: *Advances in the control of architecture for polyamides: from nylons to genetically engineered silks to monodisperse oligoamides.*

October 15* Dr. R. M. Ormerod, Department of Chemistry, Keele University: *Studying catalysts in action.*

October 21 Prof. A. F. Johnson, IRC, Leeds: *Reactive processing of polymers - science and technology.*

October 22 Prof. R. J. Puddephatt, University of Western Ontario: *Organoplatinum chemistry and catalysis.*

October 23 Prof. M. R. Bryce, University of Durham, Inaugural Lecture: *New Tetrathiafulvalene Derivatives in Molecular, Supramolecular and Macromolecular Chemistry: controlling the electronic properties of organic solids.*

October 29 Prof. R. Peacock, University of Glasgow: *Probing chirality with circular dichroism.*

November 5 Dr. M. Hii, Oxford University: *Studies of the Heck reaction.*

November 11 Prof. V. Gibson, Imperial College, London: *Metallocene polymerisation.*

November 19 Dr. G. Morris, Department of Chemistry, Manchester Univ.: *Pulsed field gradient NMR techniques: Good news for the Lazy and DOSY.*

November 20 Dr. L. Spiccia, Monash University, Melbourne, Australia: *Polynuclear metal complexes.*

November 26 Prof. R. W. Richards, University of Durham, Inaugural Lecture: *A random walk in polymer science.*

December 3 Prof. A. P. Davis, Department of Chemistry, Trinity College Dublin: *Steroid-based frameworks for supramolecular chemistry.*

December 10* Prof. M. Page, Department of Chemistry, University of Huddersfield: *The mechanism and inhibition of beta-lactamases.*

1998

January 20 Prof. J. Brooke, University of Lancaster: *What's in a formula? Some chemical controversies of the 19th century.*

January 27* Prof. R. Jordan, Dept. of Chemistry, Univ. of Iowa, USA: *Cationic transition metal and main group metal alkyl complexes in olefin polymerisation.*

January 28 Dr. S. Rannard, Courtaulds Coatings, Coventry: *The synthesis of dendrimers using highly selective chemical reactions.*

February 3* Dr. J. Beacham, ICI Technology: *The chemical industry in the 21st century.*

February 24 Prof. R. Ramage, University of Edinburgh: *The synthesis and folding of proteins.*

February 25 Dr. C. Jones, Swansea University: *Low coordination arsenic and antimony chemistry.*

March 4 Prof. T. C. B. McLeish, IRC of Polymer Science Technology, Leeds University: *The polymer physics of pyjama bottoms (or the novel rheological characterisation of long branching in entangled macromolecules).*

March 11 Prof. M. J. Cook, Dept of Chemistry, UEA: *How to make phthalocyanine films and what to do with them.*

March 17 Prof. V. Rotello, University of Massachusetts, Amherst: *The interplay of recognition & redox processes - from flavoenzymes to devices.*

March 18 Dr. J. Evans, Oxford University: *Materials, which contract on heating (from shrinking ceramics to bullet proof vests).*

October 7 Dr. S. Rimmer, Ctr Polymer, University of Lancaster: *New Polymer Colloids.*

October 23 Prof. J. C. Scaiano (RSC Endowed Lecture), Department of Chemistry, University of Ottawa, Canada: *In Search of Hypervalent Free Radicals.*

October 26 Dr. W. Peirs, University of Calgary, Alberta, Canada: *Reactions of the Highly Electrophilic Boranes HB(C6F5)2 and B(C6F5)3 with Zirconium and Tantalum Based Metallocenes.*

October 28 Prof. J. P. S. Badyal, Department of Chemistry, Inaugural Lecture, University of Durham: *Tailoring Solid Surfaces.*

November 10 Dr. J. S. O. Evans, Chemistry Department, University of Durham: *Shrinking Materials.*

November 11* Dr. M. Wills, Department of Chemistry, University of Warwick: *New Methodology for the Asymmetric Transfer Hydrogen of Ketones.*

November 12 Prof. S. Loeb, University of Windsor, Ontario, Canada: *From Macrocycles to Metallo-Supramolecular Chemistry.*

November 18* Dr. R. Cameron, Department of Materials Science & Metallurgy, Cambridge University: *Biodegradable Polymers.*

November 24 Dr. B. G. Davis, Department of Chemistry, University of Durham: *Sugars and Enzymes.*

December 2* Dr. M. Jaspers, Department of Chemistry, University of Aberdeen: *Bioactive Compounds Isolated from Marine Inverterates and Cyanobacteria.*

1999

January 19 Dr. J. Mann, University of Reading: *The Elusive Magic Bullet and Attempts to find it?*

January 27* Prof. K. Wade, Department of Chemistry, University of Durham: *Foresight or Hindsight? Some Borane Lessons and Loose Ends.*

February 3 Dr. C. Schofield, University of Oxford: *Studies on the Stereoelectronics of Enzyme Catalysis.*

February 17 Dr. B. Horrocks, Department of Chemistry, Newcastle University: *Microelectrode techniques for the Study of Enzymes and Nucleic Acids at Interfaces.*

February 24* Dr. A-K Duhme, University of York: *Bioinorganic Aspects of Molybdenum Transport in Nitrogen-Fixing Bacteria.*

March 3 Prof. B. Gilbert, Department of Chemistry, University of York: *Biomolecular Damage by Free Radicals: New Insights through ESR Spectroscopy.*

March 9 Dr. Michael Warhurst, Chemical Policy issues, Friends of the Earth: *Is the Chemical Industry Sustainable?*

March 17* Dr. J. Robertson, University of Oxford: *Recent Developments in the Synthesis of Heterocyclic Natural Products.*

A.2 Crystal structure data

A.2.1 N-Trihydroborate-3α-tosyloxymethyltropane 164

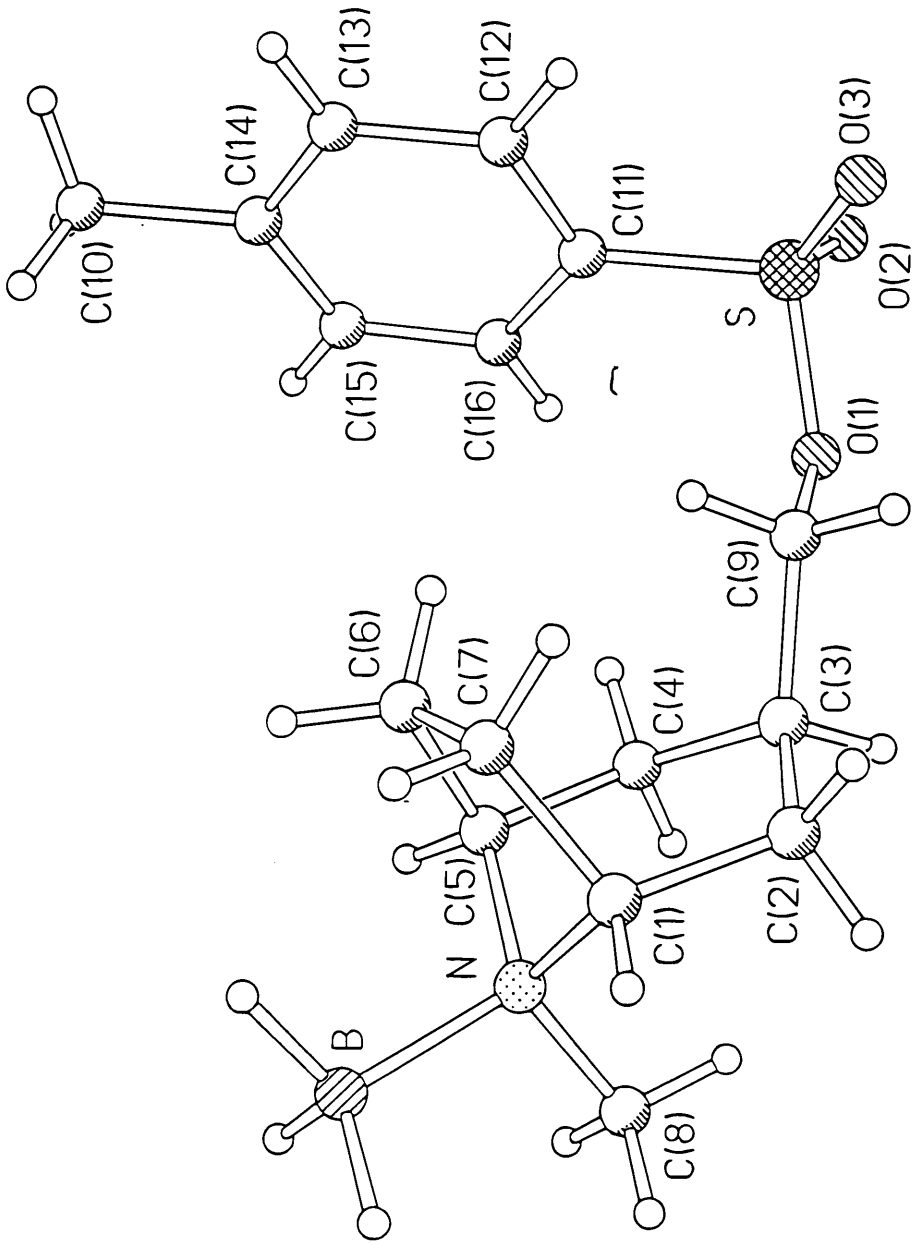

Table 1: Crystal data and structure refinement for N-trihydroborate-3α-tosyloxymethyltropane.

Identification code	97srv171	
Empirical formula	C16 H26 B N O3 S	
Formula weight	323.25	
Temperature	293(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 21.443(2) Å	α= 90°
	b = 7.9590(10) Å	β= 90°
	c = 10.224(2) Å	γ = 90°
Volume	1744.9(4) $Å^3$	
Z	4	
Density (calculated)	1.230 g/cm^3	
Absorption coefficient	1.731 mm^{-1}	
F(000)	696	
Crystal size	0.28 × 0.22 × 0.11 mm^3	
θ range for data collection	4.12 to 75.00°.	
Index ranges	$-16 \leq h \leq 26$, $-6 \leq k \leq 9$, $-8 \leq l \leq 12$	
Reflections collected	2243	
Independent reflections	2157 [R(int) = 0.0197]	
Reflections with I>2σ(I)	1613	
Absorption correction	Analytical	
Max. and min. transmission	0.837 and 0.726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2157 / 1 / 208	
Largest final shift/e.s.d. ratio	-0.001	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2σ(I)]	R_1 = 0.0431, wR_2 = 0.1026	
R indices (all data)	R_1 = 0.0657, wR_2 = 0.1154	
Absolute structure parameter	0.35(3)	
Extinction coefficient	0.00081(14)	
Largest diff. peak and hole	.206 and -.168 e.$Å^{-3}$	

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 97srv171. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S	6230(1)	4096(1)	4911(1)	52(1)
O(1)	5568(1)	4624(4)	4392(3)	55(1)
O(2)	6527(2)	3351(4)	3808(4)	66(1)
O(3)	6162(2)	3152(5)	6094(4)	65(1)
N	3988(2)	9398(4)	5051(4)	49(1)
C(1)	3977(2)	8095(6)	6114(5)	49(1)
C(2)	4024(2)	6322(6)	5566(6)	54(1)
C(3)	4580(2)	6017(6)	4633(5)	50(1)
C(4)	4783(2)	7622(6)	3904(5)	56(1)
C(5)	4665(2)	9258(6)	4631(5)	55(1)
C(6)	5006(2)	9343(7)	5936(5)	62(2)
C(7)	4546(3)	8577(7)	6921(5)	60(1)
C(8)	3543(3)	9034(7)	3959(6)	76(2)
C(9)	5105(2)	5163(6)	5362(5)	56(1)
C(10)	7495(3)	10692(7)	6108(7)	82(2)
C(11)	6586(2)	6013(6)	5268(5)	48(1)
C(12)	6851(2)	6273(7)	6478(5)	59(1)
C(13)	7151(3)	7806(7)	6730(6)	64(2)
C(14)	7180(2)	9020(8)	5810(6)	61(2)
C(15)	6919(2)	8745(7)	4600(6)	61(2)
C(16)	6628(2)	7257(7)	4310(5)	58(1)
B	3812(3)	11297(9)	5579(8)	75(2)

Table 3: Bond lengths [Å] and angles [°] for 97srv171.

S-O(2)	1.424(4)	C(8)-N-C(1)	113.3(4)
S-O(3)	1.432(4)	C(8)-N-C(5)	112.6(4)
S-O(1)	1.573(3)	C(1)-N-C(5)	99.7(3)
S-C(11)	1.745(5)	C(8)-N-B	106.0(4)
O(1)-C(9)	1.467(5)	C(1)-N-B	113.1(4)
N-C(8)	1.497(7)	C(5)-N-B	112.3(4)
N-C(1)	1.502(6)	N-C(1)-C(2)	111.9(4)
N-C(5)	1.518(6)	N-C(1)-C(7)	101.9(4)
N-B	1.649(8)	C(2)-C(1)-C(7)	112.3(4)
C(1)-C(2)	1.522(6)	C(1)-C(2)-C(3)	115.0(4)
C(1)-C(7)	1.523(7)	C(9)-C(3)-C(4)	113.6(4)
C(2)-C(3)	1.545(6)	C(9)-C(3)-C(2)	110.0(4)
C(3)-C(9)	1.513(6)	C(4)-C(3)-C(2)	112.7(4)
C(3)-C(4)	1.541(6)	C(5)-C(4)-C(3)	115.3(4)
C(4)-C(5)	1.520(6)	N-C(5)-C(4)	111.1(4)
C(5)-C(6)	1.523(7)	N-C(5)-C(6)	102.0(4)
C(6)-C(7)	1.536(7)	C(4)-C(5)-C(6)	112.7(4)
C(10)-C(14)	1.523(7)	C(5)-C(6)-C(7)	104.4(4)
C(11)-C(12)	1.376(7)	C(1)-C(7)-C(6)	105.0(4)
C(11)-C(16)	1.396(7)	O(1)-C(9)-C(3)	107.7(4)
C(12)-C(13)	1.403(7)	C(12)-C(11)-C(16)	119.9(5)
C(13)-C(14)	1.350(8)	C(12)-C(11)-S	120.0(4)
C(14)-C(15)	1.375(7)	C(16)-C(11)-S	120.1(4)
C(15)-C(16)	1.372(7)	C(11)-C(12)-C(13)	119.0(5)
O(2)-S-O(3)	119.8(2)	C(14)-C(13)-C(12)	121.0(5)
O(2)-S-O(1)	104.4(2)	C(13)-C(14)-C(15)	119.6(5)
O(3)-S-O(1)	109.4(2)	C(13)-C(14)-C(10)	120.4(6)
O(2)-S-C(11)	109.6(2)	C(15)-C(14)-C(10)	120.0(6)
O(3)-S-C(11)	109.0(2)	C(16)-C(15)-C(14)	121.2(5)
O(1)-S-C(11)	103.4(2)	C(15)-C(16)-C(11)	119.3(5)
C(9)-O(1)-S	117.5(3)		

Table 4: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 97srv171. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	49(1)	53(1)	53(1)	-6(1)	-2(1)	7(1)
O(1)	47(2)	63(2)	54(2)	-13(2)	-3(2)	4(2)
O(2)	62(2)	71(2)	63(2)	-22(2)	4(2)	7(2)
O(3)	67(2)	55(2)	72(3)	14(2)	1(2)	6(2)
N	50(2)	50(2)	47(3)	2(2)	-1(2)	3(2)
C(1)	48(3)	58(3)	41(3)	5(3)	2(2)	-5(2)
C(2)	43(2)	53(3)	67(3)	3(3)	-2(3)	-7(2)
C(3)	46(2)	56(3)	48(4)	-4(3)	-2(2)	-3(2)
C(4)	56(3)	69(3)	41(3)	0(3)	10(3)	3(3)
C(5)	62(3)	52(3)	50(4)	7(3)	11(3)	-6(2)
C(6)	54(3)	58(3)	73(4)	-12(3)	-4(3)	-7(3)
C(7)	61(3)	78(4)	40(3)	-1(3)	-1(3)	-1(3)
C(8)	64(3)	95(5)	68(4)	-1(4)	-15(3)	20(3)
C(9)	49(3)	58(3)	61(4)	5(3)	8(3)	7(2)
C(10)	55(3)	57(4)	136(6)	-23(4)	4(4)	-3(3)
C(11)	43(2)	51(3)	48(4)	-4(3)	-4(2)	4(2)
C(12)	59(3)	67(4)	50(3)	-7(3)	1(3)	6(3)
C(13)	68(4)	64(4)	60(4)	-16(3)	-17(3)	8(3)
C(14)	36(3)	64(4)	84(4)	-16(4)	0(3)	3(3)
C(15)	60(3)	60(3)	64(4)	8(3)	5(3)	-3(3)
C(16)	57(3)	68(4)	49(3)	-2(3)	-2(3)	0(3)
B	84(4)	59(4)	83(5)	0(4)	9(5)	19(4)

Table 5: Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^{3}$) for 97srv171.

	x	y	z	U(iso)
H(1)	3598(2)	8212(6)	6641(5)	59
H(21)	3641(2)	6071(6)	5100(6)	71
H(22)	4055(2)	5540(6)	6290(6)	71
H(3)	4436(2)	5223(6)	3966(5)	60
H(41)	5225(2)	7541(6)	3716(5)	72
H(42)	4564(2)	7666(6)	3074(5)	72
H(5)	4780(2)	10218(6)	4082(5)	66
H(61)	5103(2)	10496(7)	6165(5)	80
H(62)	5390(2)	8701(7)	5906(5)	80
H(71)	4726(3)	7594(7)	7338(5)	78
H(72)	4436(3)	9387(7)	7591(5)	78
H(81)	3609(12)	9823(32)	3263(17)	114(14)
H(82)	3122(3)	9131(48)	4271(11)	114(14)
H(83)	3612(12)	7914(19)	3641(26)	114(14)
H(91)	5293(2)	5937(6)	5980(5)	73
H(92)	4948(2)	4200(6)	5841(5)	73
H(101)	7187(4)	11483(19)	6402(43)	137(16)
H(102)	7693(18)	11112(28)	5332(13)	137(16)
H(103)	7802(15)	10534(14)	6780(32)	137(16)
H(12)	6829(2)	5447(7)	7120(5)	71
H(13)	7333(3)	7988(7)	7543(6)	77
H(15)	6940(2)	9585(7)	3969(6)	74
H(16)	6458(2)	7079(7)	3484(5)	70
H(1B)	4151(12)	11668(19)	6455(26)	77(9)
H(2B)	3286(12)	11315(13)	5954(28)	77(9)
H(3B)	3871(12)	12280(25)	4711(22)	77(9)

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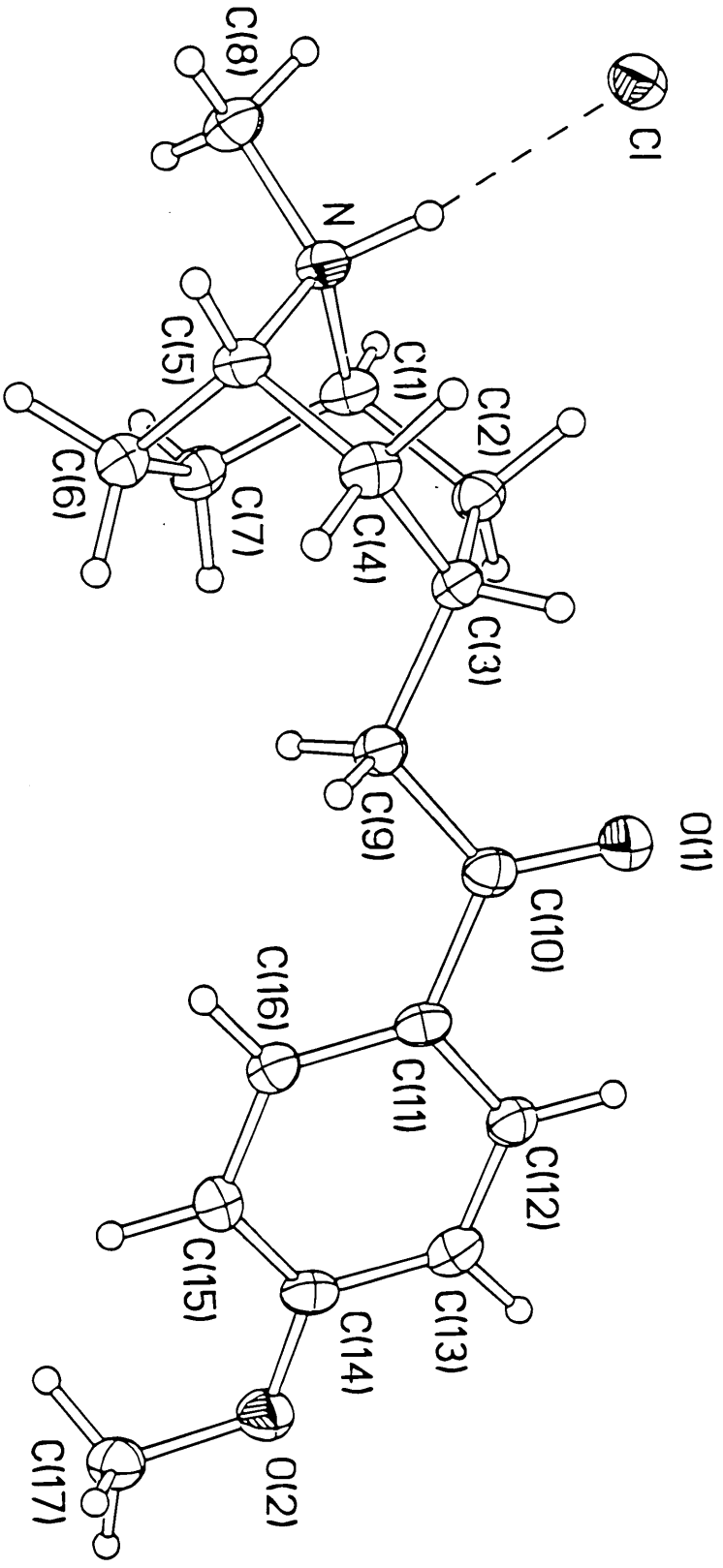

Table 1: Crystal data and structure refinement for 2-(Tropan-3-yl)-1-*para*-methoxyphenyl-1-ethanone.

Identification code	97srv170	
Empirical formula	$C_{17}H_{24}ClNO_2$	
Formula weight	309.82	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.341(1) Å	α= 90°
	b = 11.558(1) Å	β= 90°
	c = 21.415(4) Å	γ = 90°
Volume	1569.5(4) Å^3	
Z	4	
Density (calculated)	1.311 g/cm^3	
Absorption coefficient	0.248 mm^{-1}	
F(000)	664	
Crystal size	0.30 × 0.25 × 0.20 mm^3	
θ range for data collection	1.9 to 27.5°.	
Index ranges	$-8 \le h \le 8$, $-14 \le k \le 15$, $-23 \le l \le 27$	
Reflections collected	10962	
Independent reflections	3571 [R(int) = 0.0670]	
Reflections with I>2σ(I)	3099	
Completeness to θ = 27.5°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9521 and 0.9293	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3571 / 0 / 286	
Largest final shift/e.s.d. ratio	0.001	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2σ(I)]	R_1 = 0.0370, wR_2 = 0.0806	
R indices (all data)	R_1 = 0.0481, wR_2 = 0.0855	
Absolute structure parameter	-0.05(6)	
Largest diff. peak and hole	0.293 and -0.181 e.Å^{-3}	

Table 2: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 99srv170. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cl	13130.1(8)	6863.7(4)	3596.9(2)	263(1)
O(1)	6676(2)	6979(1)	1337(1)	299(3)
O(2)	-1360(2)	4822(1)	27(1)	272(3)
N	10065(3)	4855(1)	3431(1)	206(3)
C(1)	7921(3)	5402(2)	3303(1)	218(4)
C(2)	8168(4)	6166(2)	2723(1)	224(4)
C(3)	8986(3)	5530(2)	2133(1)	212(4)
C(4)	10648(3)	4606(2)	2311(1)	230(4)
C(5)	10183(3)	3955(2)	2917(1)	204(4)
C(6)	7986(4)	3389(2)	2950(1)	228(4)
C(7)	6510(3)	4332(2)	3217(1)	231(4)
C(8)	10308(4)	4360(2)	4070(1)	253(4)
C(9)	7217(3)	5049(2)	1717(1)	210(4)
C(10)	6085(3)	5974(2)	1336(1)	205(4)
C(11)	4199(3)	5611(2)	969(1)	205(4)
C(12)	2966(3)	6465(2)	678(1)	218(4)
C(13)	1134(3)	6180(2)	364(1)	241(4)
C(14)	500(3)	5023(2)	326(1)	222(4)
C(15)	1736(3)	4159(2)	599(1)	228(4)
C(16)	3572(3)	4457(2)	919(1)	215(4)
C(17)	-1993(4)	3628(2)	-37(1)	277(4)

Table 3: Bond lengths [Å] and angles [°] for 99srv170.

O(1)-C(10)	1.220(2)	C(6)-H(62)	1.01(2)
O(2)-C(14)	1.362(2)	C(7)-H(71)	0.97(3)
O(2)-C(17)	1.443(3)	C(7)-H(72)	0.99(3)
N-C(8)	1.491(3)	C(8)-H(81)	0.97(3)
N-C(5)	1.517(2)	C(8)-H(82)	0.85(3)
N-C(1)	1.524(3)	C(8)-H(83)	1.00(3)
N-H(1N)	1.02(3)	C(9)-C(10)	1.524(3)
C(1)-C(2)	1.531(3)	C(9)-H(92)	1.01(2)
C(1)-C(7)	1.537(3)	C(9)-H(92)	0.98(2)
C(1)-H(1)	0.98(2)	C(10)-C(11)	1.491(3)
C(2)-C(3)	1.552(3)	C(11)-C(16)	1.396(3)
C(2)-H(21)	1.01(2)	C(11)-C(12)	1.405(3)
C(2)-H(22)	0.98(3)	C(12)-C(13)	1.382(3)
C(3)-C(9)	1.536(3)	C(12)-H(12)	0.95(2)
C(3)-C(4)	1.549(3)	C(13)-C(14)	1.398(3)
C(3)-H(3)	0.92(2)	C(13)-H(13)	0.97(2)
C(4)-C(5)	1.529(3)	C(14)-C(15)	1.398(3)
C(4)-H(41)	1.03(3)	C(15)-C(16)	1.394(3)
C(4)-H(42)	0.97(3)	C(15)-H(15)	0.99(2)
C(5)-C(6)	1.541(3)	C(16)-H(16)	0.98(2)
C(5)-H(5)	0.96(2)	C(17)-H(171)	1.00(3)
C(6)-C(7)	1.547(3)	C(17)-H(172)	1.02(2)
C(6)-H(61)	1.01(2)	C(17)-H(173)	0.98(3)
C(14)-O(2)-C(17)	116.65(16)	N-C(1)-C(2)	107.08(16)
C(8)-N-C(5)	113.38(15)	N-C(1)-C(7)	101.96(15)
C(8)-N-C(1)	114.62(16)	C(2)-C(1)-C(7)	115.21(16)
C(5)-N-C(1)	101.42(14)	N-C(1)-H(1)	111.6(12)
C(8)-N-H(1N)	104.7(13)	C(2)-C(1)-H(1)	109.2(11)
C(5)-N-H(1N)	114.9(13)	C(7)-C(1)-H(1)	111.6(11)
C(1)-N-H(1N)	108.1(13)		
C(1)-C(2)-C(3)	114.97(16)	C(9)-C(3)-C(2)	113.55(17)
C(1)-C(2)-H(21)	104.7(13)	C(4)-C(3)-C(2)	110.67(16)
C(3)-C(2)-H(21)	109.5(12)	C(9)-C(3)-H(3)	103.8(14)
C(1)-C(2)-H(22)	106.9(14)	C(4)-C(3)-H(3)	109.8(14)
C(3)-C(2)-H(22)	112.9(13)	C(2)-C(3)-H(3)	105.6(14)
H(21)-C(2)-H(22)	107.3(18)	C(5)-C(4)-C(3)	114.70(17)
C(9)-C(3)-C(4)	112.97(17)		

Table 3: Bond lengths [Å] and angles [°] for 99srv170 (continued).

C(5)-C(4)-H(41)	108.1(15)	C(3)-C(4)-H(41)	109.5(14)
C(5)-C(4)-H(42)	108.8(13)	C(10)-C(9)-H(92)	108.8(13)
C(3)-C(4)-H(42)	107.3(14)	C(3)-C(9)-H(92)	112.6(13)
H(41)-C(4)-H(42)	108.2(19)	H(92)-C(9)-H(92)	103.9(18)
N-C(5)-C(4)	106.72(15)	O(1)-C(10)-C(11)	121.00(18)
N-C(5)-C(6)	102.34(16)	O(1)-C(10)-C(9)	121.44(17)
C(4)-C(5)-C(6)	114.96(17)	C(11)-C(10)-C(9)	117.55(16)
N-C(5)-H(5)	107.3(12)	C(16)-C(11)-C(12)	118.54(18)
C(4)-C(5)-H(5)	109.3(13)	C(16)-C(11)-C(10)	122.56(17)
C(6)-C(5)-H(5)	115.3(12)	C(12)-C(11)-C(10)	118.87(18)
C(5)-C(6)-C(7)	105.36(15)	C(13)-C(12)-C(11)	121.13(19)
C(5)-C(6)-H(61)	108.3(14)	C(13)-C(12)-H(12)	120.7(14)
C(7)-C(6)-H(61)	111.6(14)	C(11)-C(12)-H(12)	118.2(14)
C(5)-C(6)-H(62)	112.8(13)	C(12)-C(13)-C(14)	119.81(19)
C(7)-C(6)-H(62)	111.9(13)	C(12)-C(13)-H(13)	117.9(14)
H(61)-C(6)-H(62)	106.8(18)	C(14)-C(13)-H(13)	122.2(14)
C(1)-C(7)-C(6)	105.00(16)	O(2)-C(14)-C(15)	124.04(19)
C(1)-C(7)-H(71)	109.6(15)	O(2)-C(14)-C(13)	116.09(18)
C(6)-C(7)-H(71)	114.0(15)	C(15)-C(14)-C(13)	119.85(19)
C(1)-C(7)-H(72)	111.0(15)	C(16)-C(15)-C(14)	119.81(18)
C(6)-C(7)-H(72)	113.7(15)	C(16)-C(15)-H(15)	123.4(15)
H(71)-C(7)-H(72)	104(2)	C(14)-C(15)-H(15)	116.7(15)
N-C(8)-H(81)	108.2(15)	C(15)-C(16)-C(11)	120.82(18)
N-C(8)-H(82)	111.7(19)	C(15)-C(16)-H(16)	118.1(12)
H(81)-C(8)-H(82)	112(2)	C(11)-C(16)-H(16)	121.0(12)
N-C(8)-H(83)	107.4(14)	O(2)-C(17)-H(171)	112.3(14)
H(81)-C(8)-H(83)	105.4(19)	O(2)-C(17)-H(172)	103.5(13)
H(82)-C(8)-H(83)	112(2)	H(171)-C(17)-H(172)	109(2)
C(10)-C(9)-C(3)	113.61(16)	O(2)-C(17)-H(173)	110.6(14)
C(10)-C(9)-H(92)	108.1(13)	H(171)-C(17)-H(173)	108(2)
C(3)-C(9)-H(92)	109.2(13)	H(172)-C(17)-H(173)	113.0(18)

Table 4: Anisotropic displacement parameters ($Å^2 \times 10^4$) for 99srv170. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl	280(2)	238(2)	271(2)	-23(2)	-68(2)	-12(2)
O(1)	328(8)	252(7)	318(8)	46(6)	-107(7)	-46(6)
O(2)	246(7)	302(7)	268(7)	2(6)	-58(6)	4(6)
N	218(8)	226(8)	175(8)	3(6)	-30(6)	19(7)
C(1)	215(10)	257(9)	181(9)	-8(7)	-25(8)	58(8)
C(2)	257(10)	200(9)	216(9)	3(7)	-43(9)	24(9)
C(3)	220(9)	228(9)	188(9)	46(8)	-32(8)	-20(8)
C(4)	207(11)	285(11)	199(10)	7(8)	-2(7)	15(8)
C(5)	220(10)	219(9)	172(9)	-15(7)	-29(8)	42(8)
C(6)	250(10)	220(9)	214(9)	10(7)	-18(9)	-2(8)
C(7)	213(10)	276(10)	204(9)	31(8)	16(8)	13(8)
C(8)	302(11)	273(10)	185(9)	26(9)	-25(9)	35(10)
C(9)	223(10)	221(9)	186(9)	7(8)	-16(8)	9(8)
C(10)	213(9)	252(9)	149(9)	-5(7)	15(8)	-2(7)
C(11)	224(10)	264(9)	127(8)	-7(8)	3(7)	21(8)
C(12)	258(10)	221(9)	175(9)	9(7)	-2(9)	1(8)
C(13)	269(11)	264(10)	190(9)	29(8)	-7(8)	60(8)
C(14)	197(9)	313(10)	155(9)	-15(8)	0(7)	8(8)
C(15)	240(10)	204(9)	239(9)	-8(7)	-3(8)	-8(8)
C(16)	237(10)	224(9)	183(9)	4(8)	-2(7)	30(8)
C(17)	265(11)	312(10)	253(10)	10(9)	-46(10)	-19(10)

Table 5: Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 99srv170.

	x	y	z	U(iso)
H(1N)	1119(4)	549(2)	341(1)	29(6)
H(1)	745(3)	588(2)	365(1)	15(5)
H(21)	922(4)	678(2)	285(1)	22(5)
H(22)	681(4)	655(2)	266(1)	27(6)
H(3)	960(4)	609(2)	189(1)	19(5)
H(41)	1078(4)	401(2)	196(1)	39(7)
H(42)	1199(4)	500(2)	235(1)	25(6)
H(5)	1135(4)	345(2)	301(1)	18(5)
H(61)	807(4)	269(2)	324(1)	29(6)
H(62)	748(4)	310(2)	253(1)	30(6)
H(71)	587(4)	413(2)	361(1)	40(7)
H(72)	529(4)	451(2)	295(1)	35(6)
H(81)	1149(4)	382(2)	406(1)	30(6)
H(82)	918(5)	404(2)	420(1)	46(8)
H(83)	1076(4)	500(2)	435(1)	31(6)
H(92)	783(4)	446(2)	142(1)	30(6)
H(92)	617(4)	461(2)	195(1)	26(6)
H(12)	343(4)	725(2)	70(1)	23(6)
H(13)	34(4)	680(2)	17(1)	30(6)
H(15)	119(4)	336(2)	58(1)	30(6)
H(16)	437(3)	384(2)	112(1)	17(5)
H(171)	-208(4)	323(2)	37(1)	33(6)
H(172)	-347(4)	368(2)	-23(1)	25(6)
H(173)	-99(4)	320(2)	-30(1)	35(6)

Table 6: Torsion angles [°] for 99srv170.

C(8)-N-C(1)-C(2)	163.31(17)	C(4)-C(5)-C(6)-C(7)	-88.1(2)
C(5)-N-C(1)-C(2)	-74.15(17)	N-C(1)-C(7)-C(6)	-29.87(18)
C(8)-N-C(1)-C(7)	-75.32(19)	C(2)-C(1)-C(7)-C(6)	85.7(2)
C(5)-N-C(1)-C(7)	47.23(17)	C(5)-C(6)-C(7)-C(1)	1.8(2)
N-C(1)-C(2)-C(3)	57.0(2)	C(4)-C(3)-C(9)-C(10)	-157.61(16)
C(7)-C(1)-C(2)-C(3)	-55.6(2)	C(2)-C(3)-C(9)-C(10)	75.3(2)
C(1)-C(2)-C(3)-C(9)	91.2(2)	C(3)-C(9)-C(10)-O(1)	5.2(3)
C(1)-C(2)-C(3)-C(4)	-37.0(2)	C(3)-C(9)-C(10)-C(11)	-173.72(16)
C(9)-C(3)-C(4)-C(5)	-90.7(2)	O(1)-C(10)-C(11)-C(16)	175.05(19)
C(2)-C(3)-C(4)-C(5)	37.9(2)	C(9)-C(10)-C(11)-C(16)	-6.1(3)
C(8)-N-C(5)-C(4)	-161.54(17)	O(1)-C(10)-C(11)-C(12)	-6.9(3)
C(1)-N-C(5)-C(4)	75.07(18)	C(9)-C(10)-C(11)-C(12)	172.00(17)
C(8)-N-C(5)-C(6)	77.3(2)	C(10)-C(11)-C(12)-C(13)	-176.15(17)
C(1)-N-C(5)-C(6)	-46.04(17)	C(17)-O(2)-C(14)-C(15)	-3.7(3)
C(3)-C(4)-C(5)-N	-59.0(2)	C(17)-O(2)-C(14)-C(13)	177.70(18)
C(3)-C(4)-C(5)-C(6)	53.7(2)	C(12)-C(13)-C(14)-O(2)	177.83(17)
N-C(5)-C(6)-C(7)	27.11(18)	O(2)-C(14)-C(15)-C(16)	-177.19(17)

Table 7: Hydrogen bonds for 99srv170 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N-H(1N)...Cl	1.02(3)	2.05(3)	3.0481(18)	164.2(18)