New Methodology

For The Synthesis

of

Homochiral Unsaturated Amines

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of the requirements for the degree of
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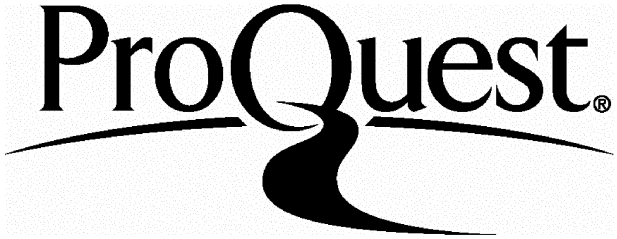

"Abandon all hope ye who enter here..."

Dante *"The Inferno"*

Declaration

I, Alastair Rae, hereby state that the following is entirely my own work and has not been submitted for any other degree or examination.

Alastair Rae

February 1998

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Abbreviations

The following abbreviations have been used in this thesis:

Ac	Acetyl
APCI	Atmospheric pressure chemical ionisation
Boc	*tert*-Butoxycarbonyl
BTMSA	(Bis)trimethylsilylacetylene
Cbz	Benzyloxycarbonyl
COSY	Correlation spectroscopy
Cyhex	Cyclohexyl
DCM	Dichloromethane
d.e.	Diastereomeric excess
DEAD	Diethylazodicarboxylate
DIBALH	Diisobutyl aluminium hydride
DIEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DQF	Digitally quantum filtered
e.e.	Enantiomeric excess
EI	Electron impact
eq.	Equivalents
FAB	Fast atom bombardment
GABA-T	γ-Amino butyric acid transaminase
HPLC	High performance liquid chromatography
I.R.	Infra-red

LDA	Lithium diisopropylamide
Moc	Methoxycarbonyl
MTPA	Methoxytrifluoromethylphenylacetyl
Ms	Methanesulfonyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
PCC	Pyridinium chloro chromate
Pht	Phthalimido
PPTS	Pyridinium para-toluenesulfonate
py.	Pyridine
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

Abstract

New methodology for the synthesis of chiral propargyl amines is described.

A chiral (*N*)-Boc-1,3-amino alcohol, derived by the homologation of (*L*)-alanine with diazomethane, has been synthesised and this was then used, *via* reaction with a series of diethyl acetals, in the synthesis of chiral 1,3-tetrahydrooxazines (aminals).

The structure of the aminals was determined, by both solution NMR and X-ray crystallographic methods, to exist as a twist chair structure with unusual conformational properties.

The aminals were then functionalised with the Grignard reagent of (trimethylsilyl)acetylene, in the presence of boron trifluoride diethyl etherate, to give novel, ring opened, unsaturated amino alcohols.

The subsequent unmasking of the required amines was then carried out by oxidation and subsequent retro-Michael elimination. The degree of chiral induction was determined *via* the Moshers amide method, and ranged from moderate to excellent.

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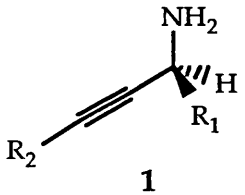
Chapter 1: Introduction

1.1 Aim

The aim of this work is the development of a new methodology for the synthesis of unsaturated homochiral amines, particularly propargyl amines (**1**).

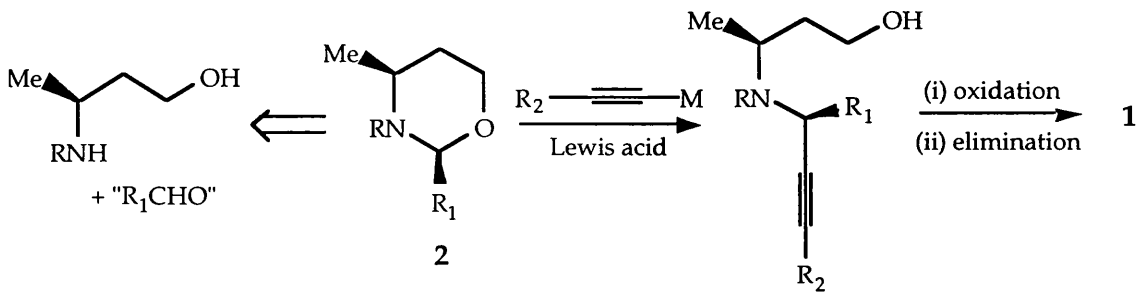


1

These compounds are of vital importance, both as therapeutic agents[1] and as chiral building blocks in synthesis.[2]

This work is centred around the synthesis and functionalisation of chiral 1,3 tetrahydrooxazines (aminals) (**2**). These are recognised to come from the condensation of a chiral 1,3-amino alcohol with an aldehyde or equivalent. If functionalised with unsaturated nucleophiles, e.g. an acetylide, under the direction of a Lewis acid, a new chiral centre should be created as part of a fully protected (tertiary) amine. Removal of the protecting groups and the chiral auxiliary will reveal the required amine (Figure 1).

Figure 1



The 4-methyl, along with the nitrogen protecting group and the 2-(R_1) substituent should be sufficient to provide a conformational "lock" on the aminal ring. This should hold all of the ring substituents in a defined relationship to each other.

The nature of the nitrogen protecting group is important, as it must be removable under conditions which will not damage the acetylene, but must also be stable under all the reaction conditions employed. For these reasons, the *tert*-butoxycarbonyl (Boc) group is considered to be the most favoured, as it is stable to mild acidic conditions required for aminal synthesis and to the Lewis acidic conditions for ring opening.[3]

In truth the "chiral auxiliary" does not strictly meet the criteria to be an auxiliary, i.e. it is not recovered after the synthesis. However, as it fulfils the other function of an auxiliary, i.e. it imparts chirality to the final product, it will be referred to as such for the purposes of this work.

1.2 Methodology for the Production of Propargyl Amines

There is little existing methodology for the production of chiral propargyl amines, especially those containing non-proteinogenic or sensitive side chains.

There are four main categories;

(1) the Gilbert method,

(2) the Corey-Fuchs method,

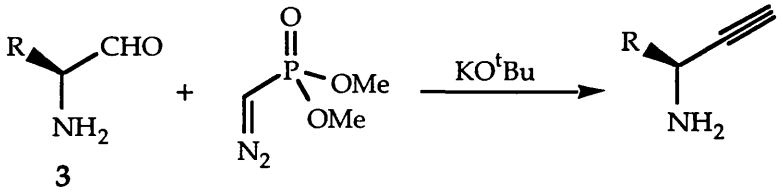
(3) conversion of chiral propargyl alcohols to their amine analogues,

(4) other methods.

1.2.1 The Gilbert Method

This is a relatively mild method of producing chiral propargyl amines and involves the reaction of a chiral α-amino aldehyde (**3**) with diazomethyl phosphonates (Figure 2).[4]

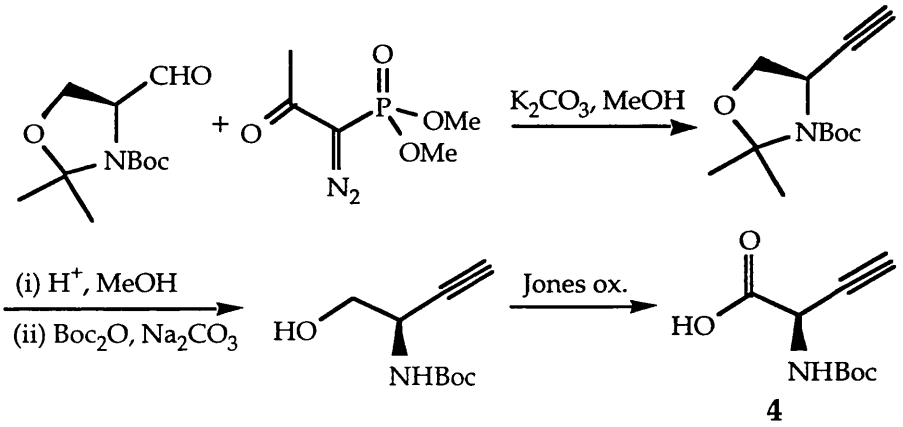
Figure 2



This method has been shown to proceed with no loss of stereochemical integrity from the chiral aldehyde.[5, 6]

The mild conditions associated with it make the Gilbert method useful in the production of sensitive substrates. An example of this is Meffre's synthesis of the easily racemised (*D*)-(*N*)-Boc-ethynyl glycine (**4**)(Figure 3).[7]

Figure 3

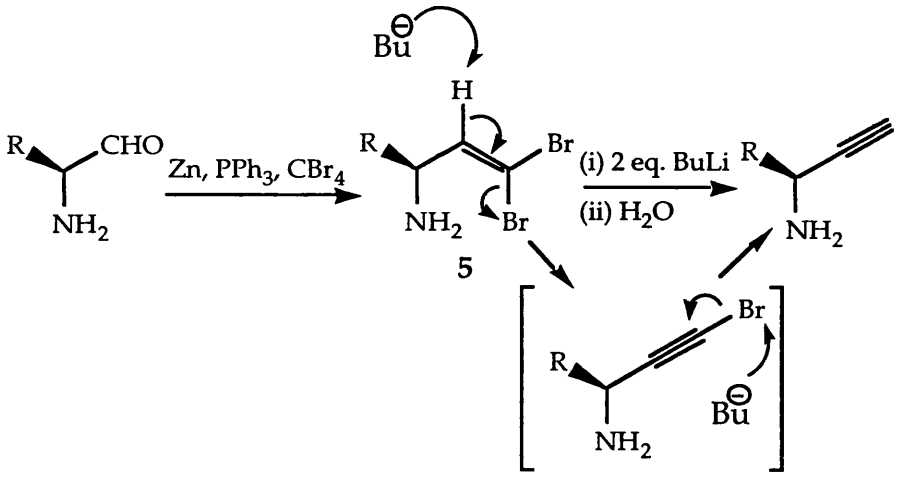


The main drawback of this method, however, is its reliance on a chiral α-amino aldehyde as a starting material. As these are most readily available from the corresponding amino acid, economic syntheses are limited to using only starting materials from the chiral pool.

1.2.2 The Corey-Fuchs Method

The use of the PPh_3/CBr_4 system for the synthesis of 1,1-dibromoalkenes was originally developed by McKelvie.[8] This was then further developed by Corey to allow the conversion of the bromoalkene to the terminal alkyne.[9] As with the Gilbert method it utilises chiral α-amino aldehydes, which are converted to their γ-dibromoalkene derivatives (**5**) with zinc, triphenylphosphine and carbon tetrabromide. The dibromoalkenes are then treated with butyllithium which gives, *via* an elimination/lithiation mechanism, the required propargyl amine (Figure 4).

Figure 4



This procedure has been used in the synthesis of functionalised (*E*)-allylic amines and is shown to proceed with retention of stereochemistry.[2]

This method again is limited to the use of proteinogenic α-amino acids as readily available starting materials. It can also be problematic, with numerous by-products and low yields being reported,[7] especially when using sensitive or highly functionalised substrates. Some of these problems can be avoided using the modified method of Chuche,[10] which employs

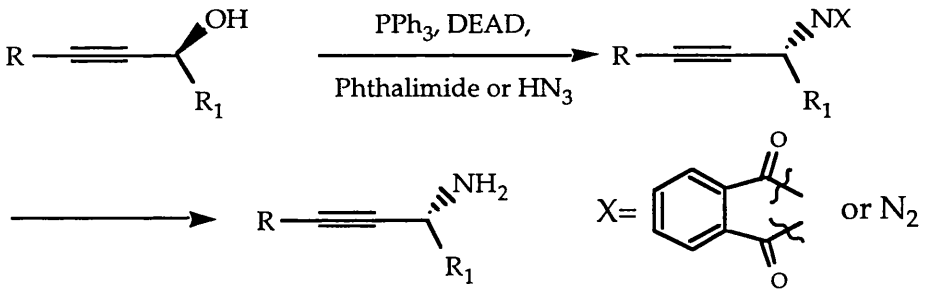
triethylamine during the conversion of the aldehyde to the alkene, presumably complexing out the known reactive dibromotriphenylphosphine impurity. A less nucleophilic base such as sodium hexamethyldisilazane can be employed in the elimination stage to give the bromoalkyne in high yield.

1.2.3 The Conversion of Chiral Propargyl Alcohols to their Amine Analogues

There are two things which make this method attractive to the synthetic chemist; (1) the large number of methods available for the synthesis of optically pure propargyl alcohols, and (2) the Mitsunobu reaction.[11]

The Mitsunobu reaction is important as it allows facile introduction of the amino functionality, with high confidence in the stereochemical integrity of the chiral centre. In the vast majority of cases exclusive S_N2 displacement of the alcohol is observed, causing inversion of the stereocentre (Figure 5).

Figure 5

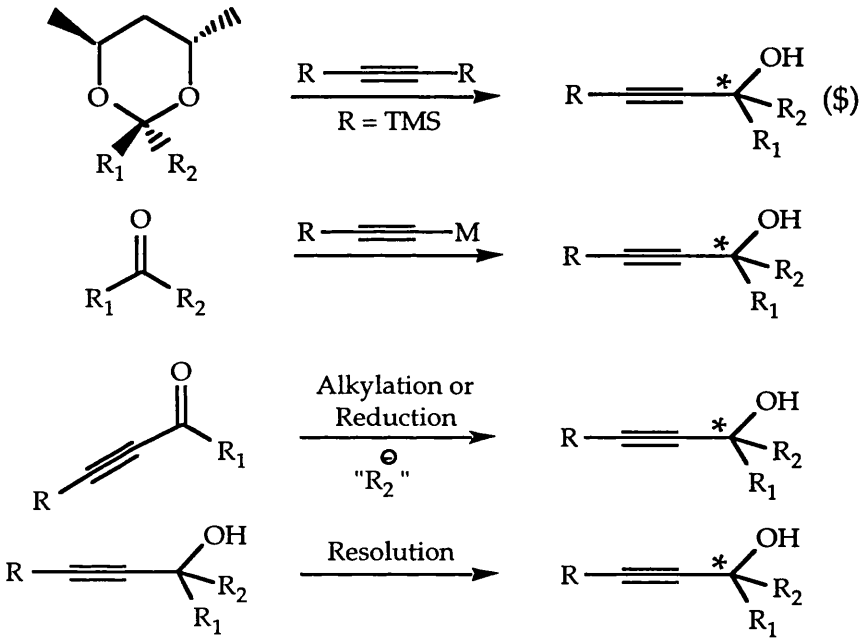


The amino functionality may, of course, be introduced in other ways, e.g. by mesylation of the alcohol followed by displacement with sodium azide.

It has been observed that both methods can lead to elimination, instead of phthalimide/azide insertion, to give ene-yne products[1, 12]

There are many ways of producing optically active alcohols described in the literature, many of which are applicable to propargyl alcohols. This may be *via* the ring opening of chiral acetals,[13] asymmetric nucleophilic addition to an aldehyde or ketone,[14] asymmetric reduction of an acetylenic ketone (by enzymatic or chemical methods)[1, 15, 16] or by resolution of a racemic alcohol by enzymatic means.[17] This is demonstrated in Figure 6.

Figure 6

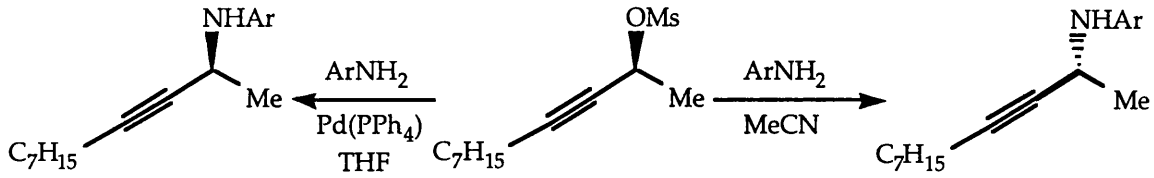


R_1 = alkyl, aryl
R_2 = alkyl, aryl or H
($) = further steps required to give chiral alcohol

In a similar vein, Marshall has shown that both enantiomers of a range of aromatic propargyl amines can be accessed from a single enantiomer of a propargyl alcohol.[18] The alcohol is converted to the mesylate derivative, and reaction with various anilines, in the presence of palladium(*tetrakis*-triphenylphosphine), gives the amine product with retention of

stereochemistry. Reaction in the absence of palladium, gives the more conventional product with inversion of stereochemistry (Figure 7).

Figure 7

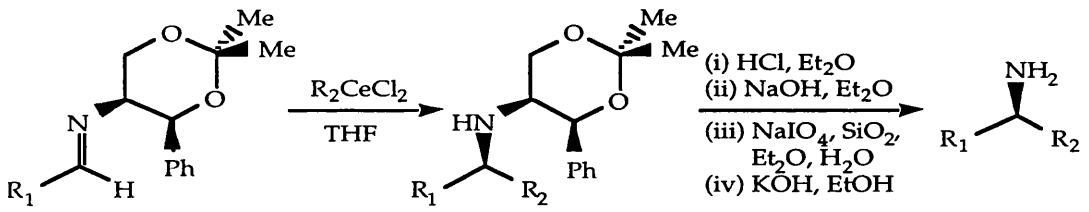


The main disadvantage of the above method is that it is not generally applicable as the aryl group cannot be easily removed without damaging the acetylene.

1.2.4 Other Methods

Enders has described the addition of alkylcerium reagents to chiral alkynyl- and alkenyl-imines in high diastereoselectivity.[19] The amines are then freed from the chiral auxiliary *via* a complex series of steps (Figure 8).

Figure 8



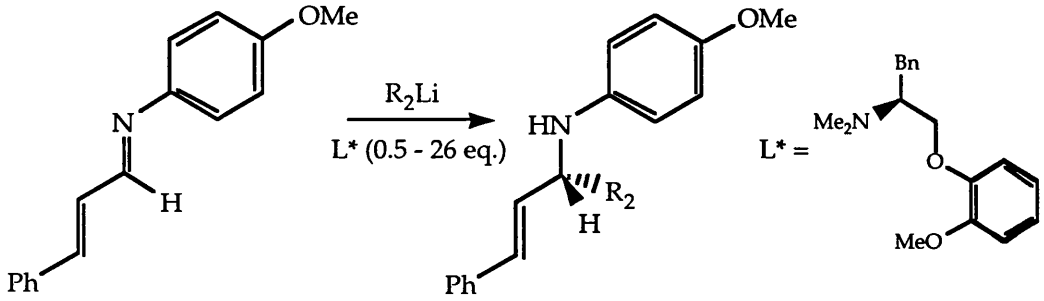
d.e. = 86-98%

R_1 = PhCH=CH, PhC≡C, $^tBuC{\equiv}C$; R_2 = Me, Et, Bu, Allyl, $TBDMSO(CH_2)_3$

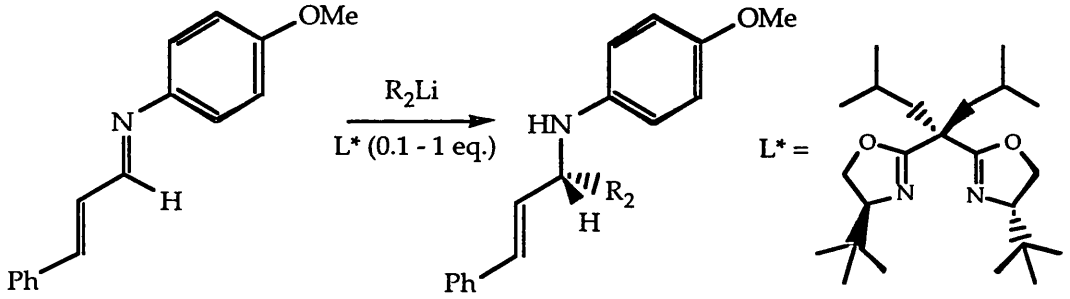
Tomioka showed that alkyl lithiums could add stereoselectively to vinyl imines, in the presence of a chiral ligand, to produce chiral allyl amines in good e.e. (up to 90 %).[20] Similarly, Denmark has carried out essentially the same transformation using a different chiral ligand (also in good e.e. (up to 85 %)).[21] Both tranformations are shown in Figure 9.

Figure 9

Tomioka

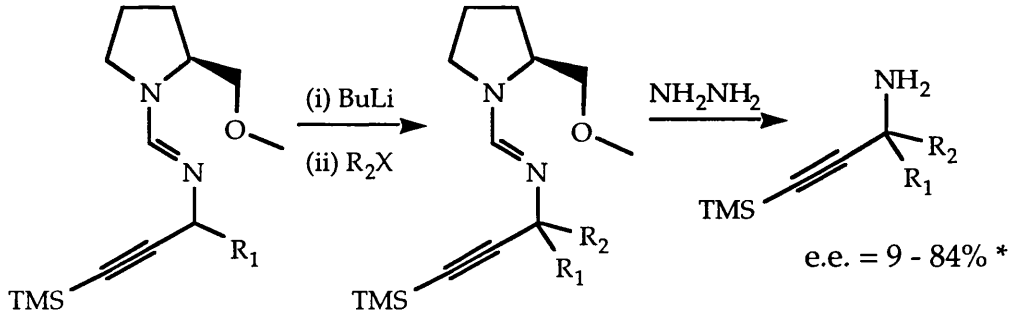


Denmark



Also available is the methodology of Kolb and Barth which allows the stereoselective alkylation of chiral α-imino propargylic anions to give chiral propargyl amines in good yield and moderate stereoselectivity (Figure 10).[22]

Figure 10

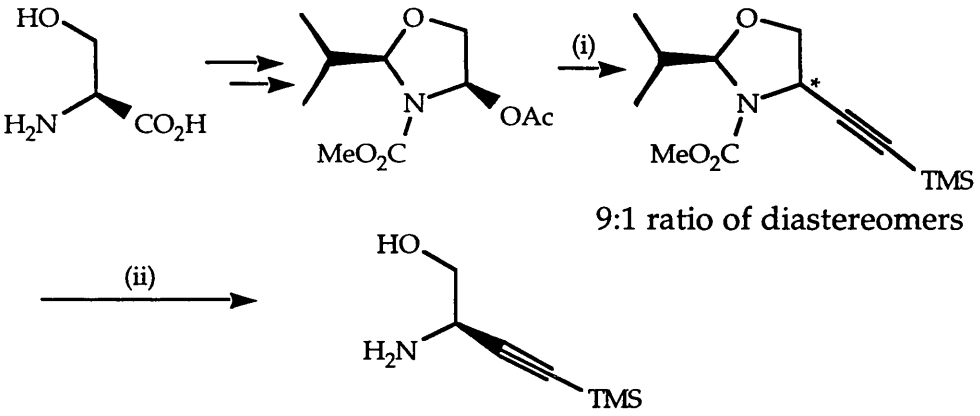


* measured after conversion to
the corresponding amino acid

The final example in this miscellaneous list is the work of Seebach.[23] In work not dissimilar to that of this thesis, he desribes the addition of bistrimethylsilylacetylene to 4-acetoxy-1,3-oxazolidines derived from (*L*)-

serine. Chromatography followed by treatment of the product of this with concentrated HCl gives the required amine, essentially optically pure (Figure 11).

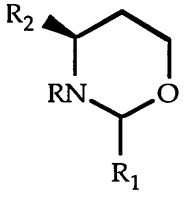
Figure 11



(i) TMS-C≡C-TMS, $TiCl_4$, (ii) (a) Column Chromatography, (b) 6M HCl

1.3 The Use of Chiral 1,3-Oxazines and 1,3-Oxazolidines as Templates for Chiral Amine Synthesis

The use of chiral 1,3-oxazines (6) and 1,3-oxazolidines (7) as precursors to chiral *saturated* amines is well documented in the literature and it is therefore crucial that these be discussed in detail.



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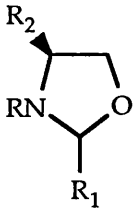

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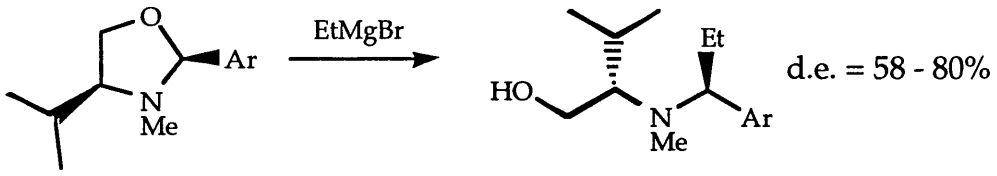
1.3.1 Chiral 1,3-Oxazolidines

The work of Takahashi and Higashiyama has provided the most in-depth study of the reactions of 1,3-oxazolidines with organometallics, in particular Grignard reagents. They demonstrated that chiral 2-substituted 1,3-oxazolidines, derived by the condensation of (*S*)-valinol and an aryl

aldehyde, undergo stereoselective ring opening at the 2-position upon treatment with Grignard reagents to give 1, 3-amino alcohols (Figure 12).[24]

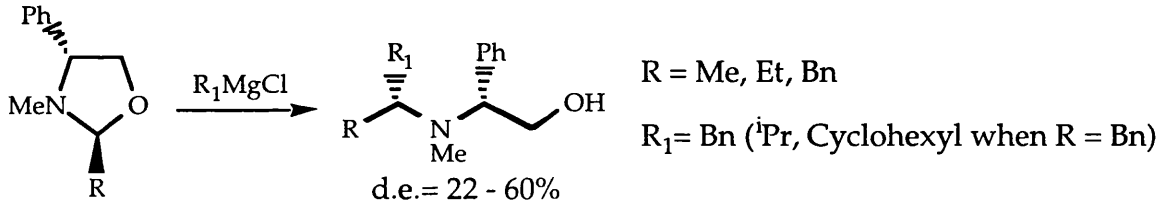
Figure 12



The absolute stereochemistries of the products were assigned by circular dichroism.

They went on to explore the further use of 1,3-oxazolidines derived from (*R*)-phenylglycinol, again in reactions with benzyl magnesium chloride.[25] Here they reported that the Grignard reagent adds in a *syn*-fashion with respect to the phenyl group of the chiral auxiliary in moderate to good diastereoselectivity (Figure 13).

Figure 13

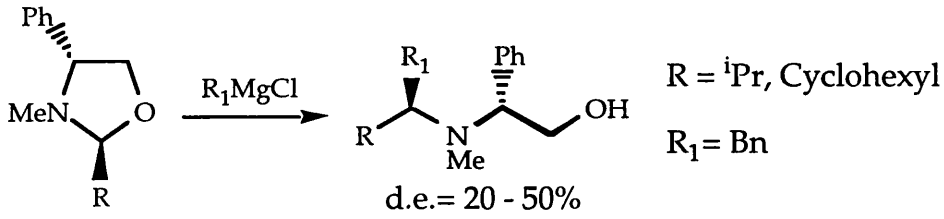


The configuration of the methyl derivative was determined by removal of the chiral auxiliary by hydrogenolysis followed by conversion of the amine to its hydrochloride salt. The optical rotation of this was then compared to that of an authentic sample.

Two conflicting results were reported, however, for the reactions of the isopropyl and cyclohexyl derivatives. These were shown to proceed in an *anti-* addition fashion producing the opposite diastereomer at the "ring

opening" stage (Figure 14). The configuration of the cyclohexyl derivative was determined by X-ray crystallography.

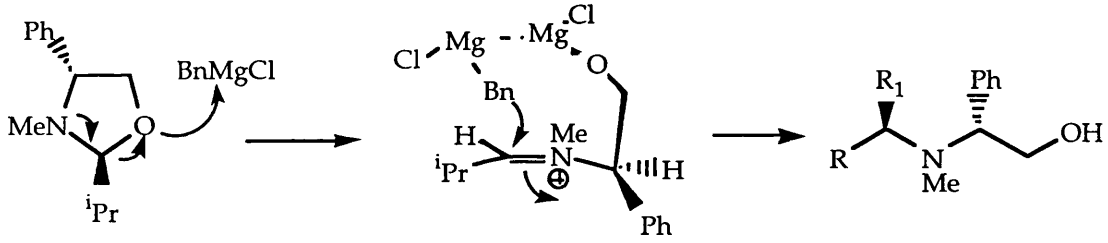
Figure 14



While the majority of derivatives required only one equivalent of Grignard reagent to proceed to completion, the isopropyl and cyclohexyl derivatives required at least 2 equivalents.

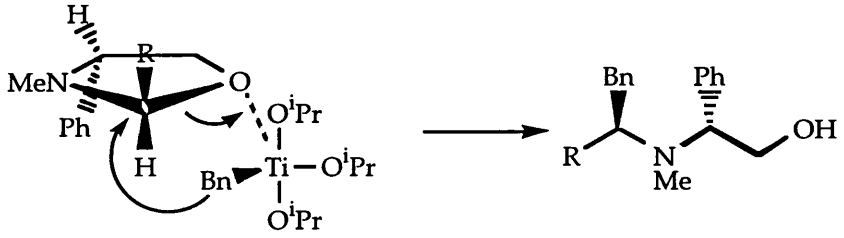
This led to the postulation of an open chain mechanism (in the case of the isopropyl and cyclohexyl derivatives) involving attack of the nucleophile on an iminium tautomer of the oxazolidine (Figure 15).

Figure 15



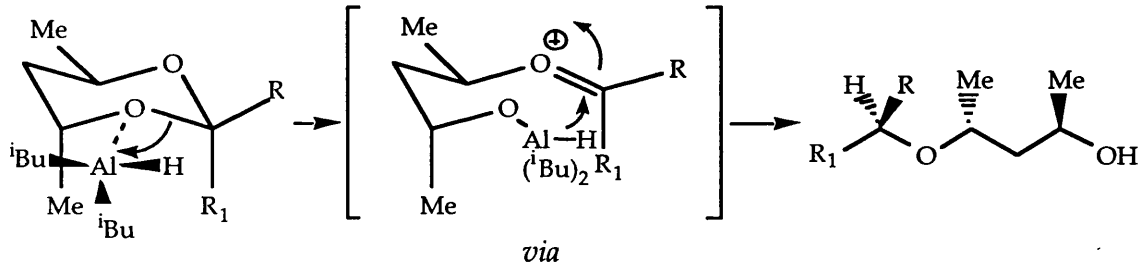
The methodology was extended to encompass titanium nucleophiles, which were shown to produce ring opened oxazolidines of an opposite stereochemistry to that of the corresponding Grignard addition.[26] The proposed mechanism is shown in Figure 16 and postulates that oxygen/titanium co-ordination first occurs, followed by delivery of the nucleophile to the N-face of the ring.

Figure 16



Analogy was drawn to the aluminium hydride cleavage of chiral 1,3-dioxane acetals described by Yamamoto.[27] Here the aluminium reagent co-ordinates to one of the ring oxygens, weakening the C-O bond, and relieves the 1,3-diaxial ring strain between R_1 and the axial methyl. Hydride is then delivered from the *same* face (Figure 17).

Figure 17

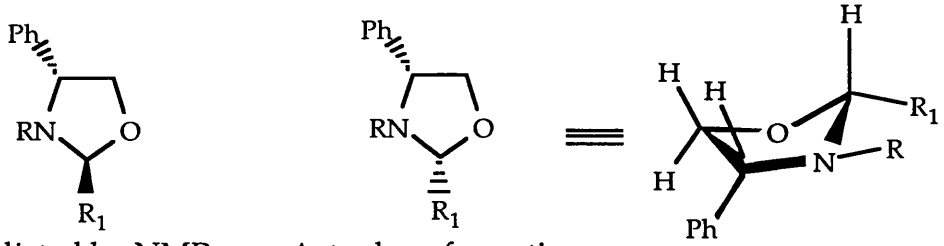


via

This apparent disparity in the face of attack brought into question the assignment of the structure of the 1,3-oxazolidines, which had been assigned as *trans* by NMR studies.[25] X-Ray crystallography later showed that the conformation was in fact *cis* (Figure 18).[28]

This clears up the disparity between the Takahashi and Yamamoto work. A more detailed study of structure, and its effect on mechanism, will be discussed later.

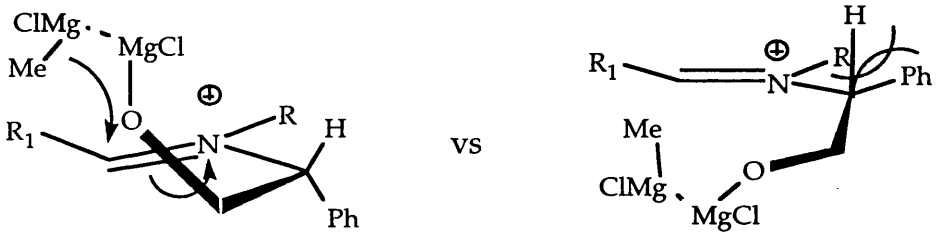
Figure 18



Predicted by NMR Actual conformation from x-ray studies

A marked increase in diastereoselectivity for addition of Grignard reagents was noticed when the bulkiness of the nitrogen protecting group was increased in the order Me < Bn < ^{i}Pr.[28] This gave further credence to the proposed mechanism of attack, whereby the phenyl of the auxiliary and N-protecting group are orientated to minimise steric interactions (Figure 19).

Figure 19

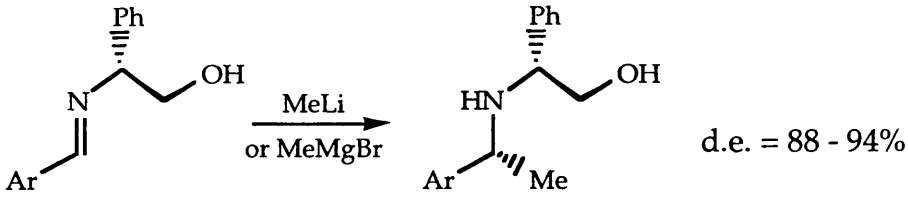


Favoured transition state due to minimal steric interactions

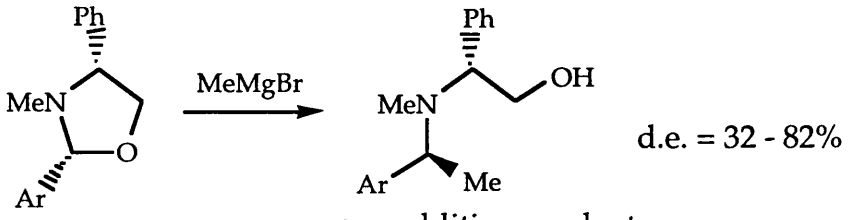
Disfavoured transition state due to steric clash of R and Ph

Further investigation of the mechanism of substitution was attempted by comparison of the alkylation of chiral aromatic imines with the alkylation of chiral 1,3-oxazolidines.[29] It was shown that (*R*)-phenylglycinol derived imines can be alkylated with MeLi or MeMgBr[30] to give major products of an opposite stereochemistry from that of the reaction of the (*R*)-(N)-methylphenylglycinol derived oxazolidines with MeMgBr (Figure 20).

Figure 20



anti-addition product

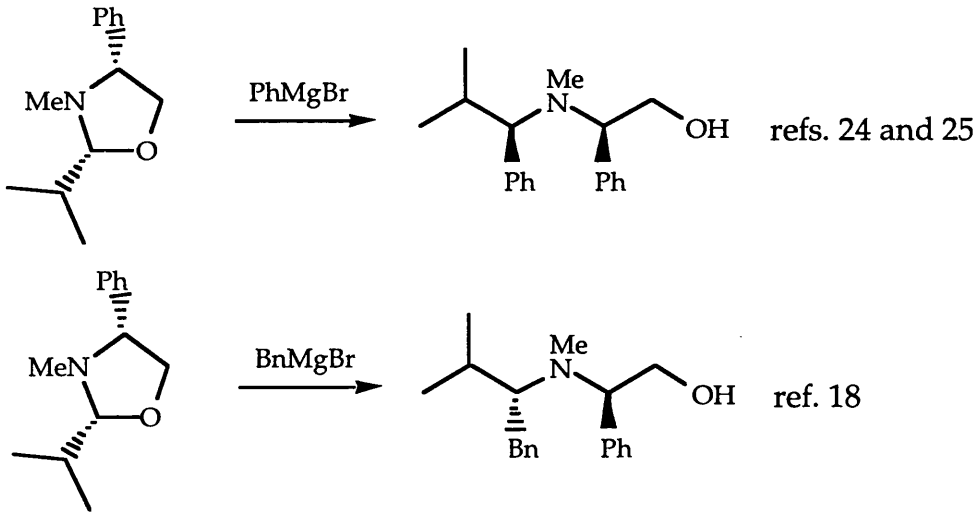


syn-addition product

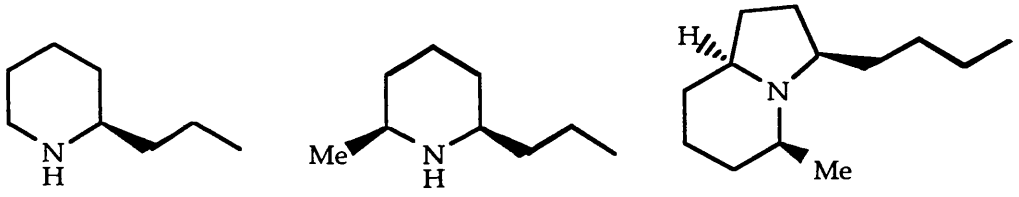
This methodology can be extended to the analogous aliphatic imines and oxazolidines, which can also be alkylated with organometallics to yield opposite stereochemistries from a single enantiomer of an auxiliary.[31] To avoid potential side reactions in the imine series, alkyl cerium ($RCeCl_2$) reagents were used in preference to the more basic lithium and Grignard reagents.

Interestingly, the conflicting result of the earlier oxazolidine work is not repeated here,[25] with the isopropyl derivative being functionalised in the expected manner with PhMgBr whereas when BnMgBr was used (in the earlier work) the opposite stereochemistry was observed (Figure 21). This new result was also observed in other Grignard reagent additions to oxazolidines.[32] No explaination of the disparity was given.

Figure 21



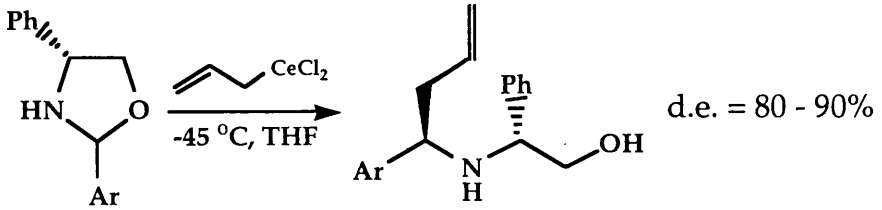
The methodology described has been utilised in the synthesis of a number of heterocyclic natural products. The piperidine containing compounds (-)-coniine (**8**) and (-)-dihydropinidine (**9**) were obtained in high d.e.,[33] as was the indolizidine (+)-monomorine (**10**).[34]



8 **9** **10**

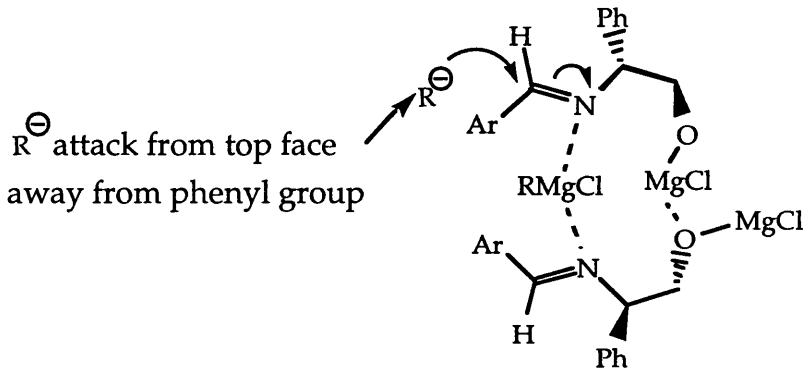
Another, smaller, but no less significant contribution to this methodology has come from Pridgen. He was the first to describe the synthesis of homoallyl amines *via* the reaction of aryl 1,3-oxazolidines with allylcerium chloride in good to excellent yields (70 - 90%) (Figure 22).[35]

Figure 22



The mechanism of addition was presumed to be *via* the imine tautomer due to its predominance in solution state equilibria of non-(N)-alkylated 1,3-oxazolidines.[36] The high order of the transition state was assumed because of the excess (2.5 to 3 equivalents) of alkylating reagent required to effect clean addition (Figure 23).[37]

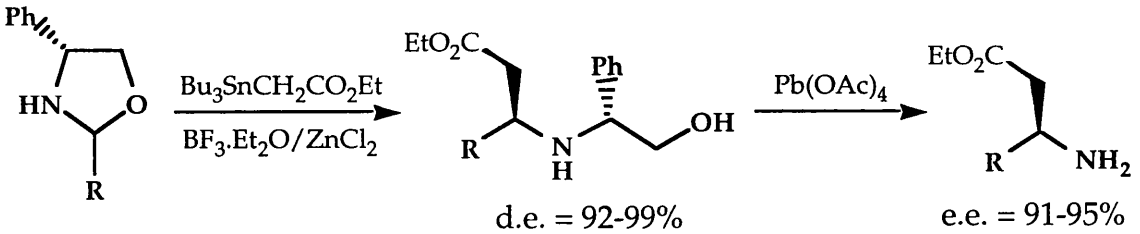
Figure 23



The greatest diastereoselectivity was observed for cerium mediated additions.

Other organometallics have been utilised to similar effect. The addition of ethyl tributylstannylacetate, under Lewis acidic conditions, to a range of alkyl and aryl 1,3-oxazolidines leads to β-amino esters (after oxidative removal of the auxiliary side chain) (Figure 24).[38]

Figure 24

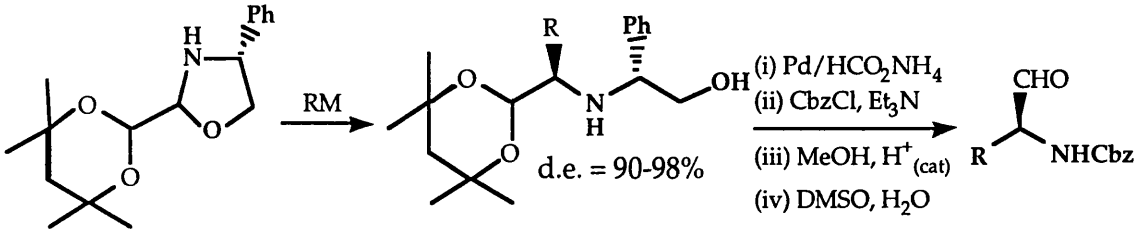


d.e. = 92-99% e.e. = 91-95%

Two other interesting reactions were also observed by Pridgen. One was the addition of Grignard reagents, alkyl lithiums and alkyl cerium reagents to

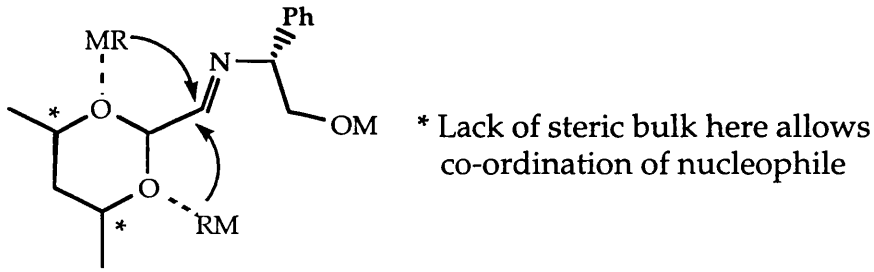
1,3-oxazolidines with side chains containing acetals.[39] The auxiliary was then removed and the acetal hydrolysed to give a range of α-amino aldehydes (Figure 25).

Figure 25



Low diastereoselectivity was observed with less hindered acetals, presumably due to competing chelation of the organometallic to the acetal oxygens followed by nucleophilic attack, which could occur from either face (Figure 26).

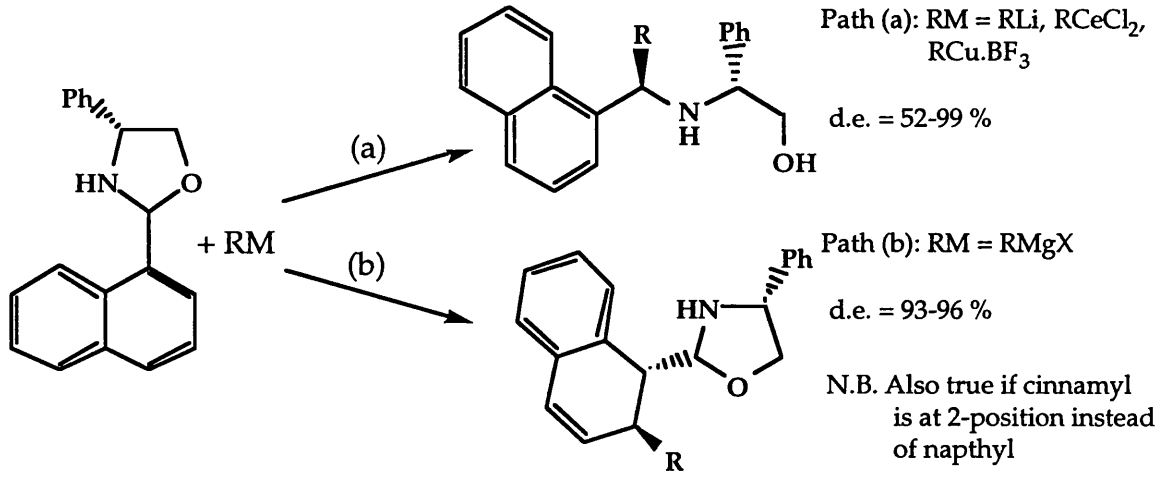
Figure 26



This is an important result as very little has been published about additions to oxazolidines with functionalised side chains and opens up the possibility of further elaboration to synthetically useful products.

Also interesting is the report of the selectivity of Grignard reagents over other organometallics (including organocopper reagents) to add to 2-naphthyl- and 2-cinnamyl-1,3-oxazolidines in a 1,4-manner, instead of the expected 1,2-addition (Figure 27).[40]

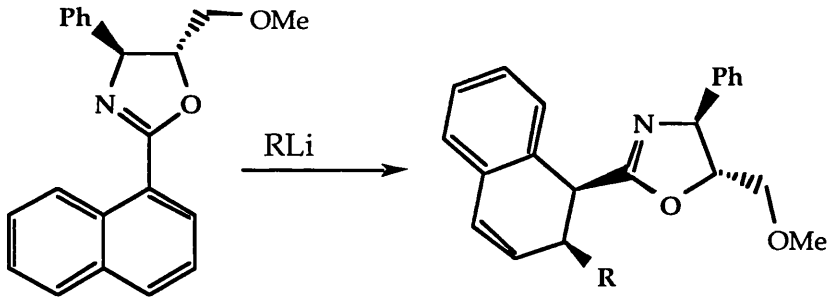
Figure 27



This is unusual as copper is known to promote the 1,4-addition of Grignard reagents to α,β-unsaturated systems, whereas Grignard reagents alone usually give a mixture of 1,2- and 1,4-addition products.[41a]

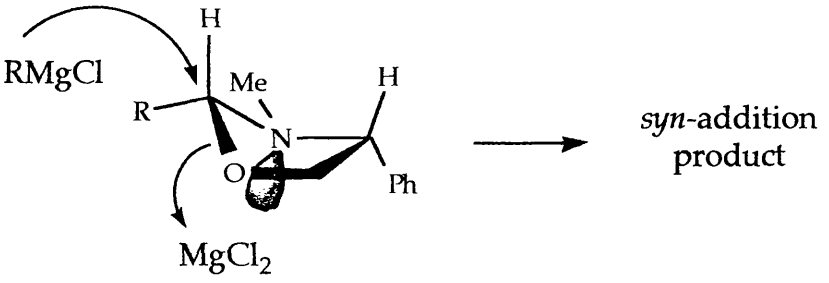
The preference of 1,4-addition over 1,2- has also been described by Meyers in the addition of organolithiums to 1,3-oxazolines (Figure 28).[42]

Figure 28



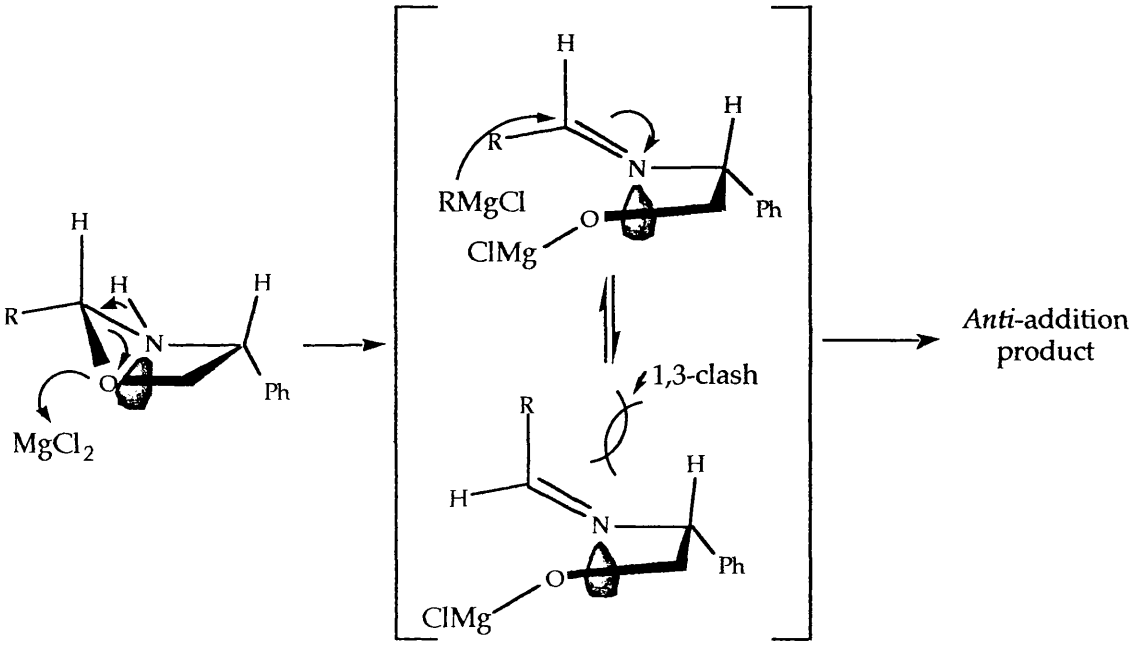
All of the research of Pridgen exhibits *anti*-addition to 1,3-oxazolidines, whereas the earlier work of Takahashi shows only *syn*-addition. The only difference between the two is Takahashi's use of an alkyl group on the oxazolidine nitrogen. This will stabilise the oxazolidine in solution with nucleophilic attack taking place in an S_N2 - like fashion (Figure 29).

Figure 29



The lack of an nitrogen protecting group favours the imine tautomer (especially in polar media) and can, because of 1,3-allylic strain, allow the formation of a transition state similar to Figure 30.

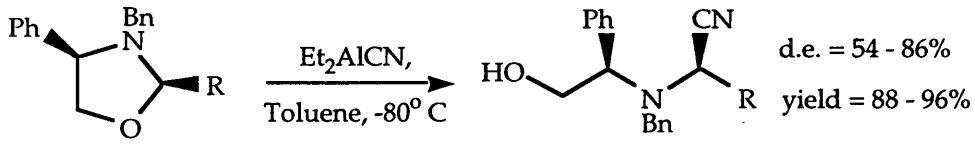
Figure 30



A contribution to the study of 1,3-oxazolidine ring opening has also been made by the group of Pedrosa. They have described the reaction of (N)-benzyl-2-(*R*)-1,3-oxazolidines with diethylaluminium cyanide.[43] This proceeds to give the *syn*-addition product (Figure 31), an unexpected result when considering the analogous chiral acetal work.[27] The resulting nitriles were hydrolysed with ethanolic hydrogen chloride and the auxiliary

removed by hydrogenation to give α-amino esters in good e.e.. The enantiomeric products were obtained from the (*S*)-oxazolidines.

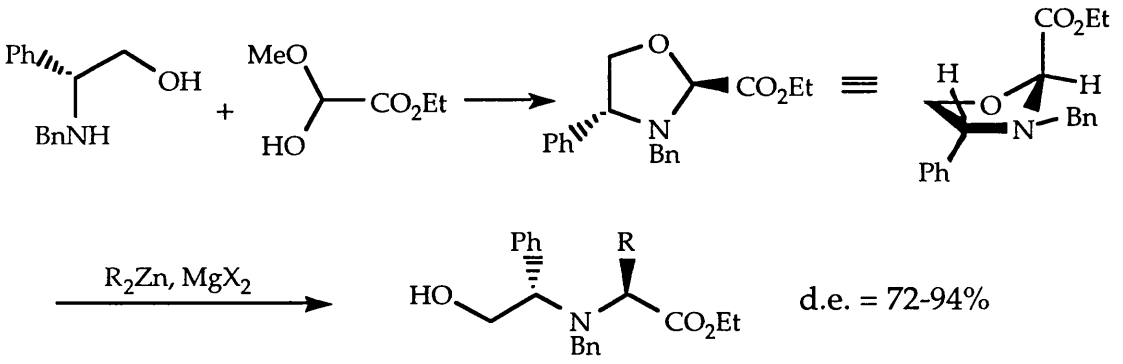
Figure 31



The homologous β-amino esters were obtained by reaction of the same chiral 1,3-oxazolidines with Reformatsky reagents. Again the *syn*-adduct was formed with high diastereoselectivity.[44]

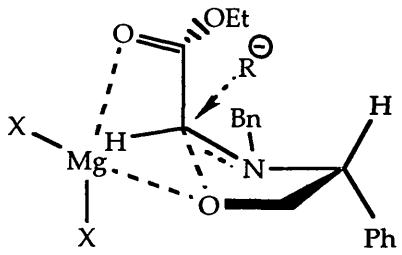
Pedrosa has also described a chiral glycine synthon based on a chiral oxazolidine derived from (N)-benzyl-(*R*)-phenylglycinol and (methyl)ethyl glyoxalate.[45] The oxazolidine adopts the unusual 2,4-*trans* conformation, as confirmed by X-ray crystallography (presumably due to steric crowding). Reaction of the synthon with dialkylzincs in the presence of magnesium halides gives the *syn*-adduct with excellent diastereoselectivity (Figure 32). The diastereomeric excess is further improved by chromatography.

Figure 32



The mechanism is presumed to be *via* Lewis acid chelation to the O-face followed by S_N2 attack at the N-face (Figure 33).

Figure 33

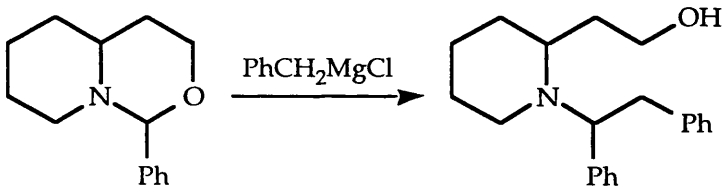


1.3.2 Chiral 1,3-Oxazines

In contrast to the 1,3-oxazolidines, there has been little work on their 6 membered relations, the 1,3-oxazines. As a more specific sub-set of this there is even less work on the reactions of chiral 1,3-oxazines.

The first use of 1,3-oxazines in synthesis was reported by Goodson and Christopher in the synthesis of racemic tertiary propanolamines (Figure 34).[46]

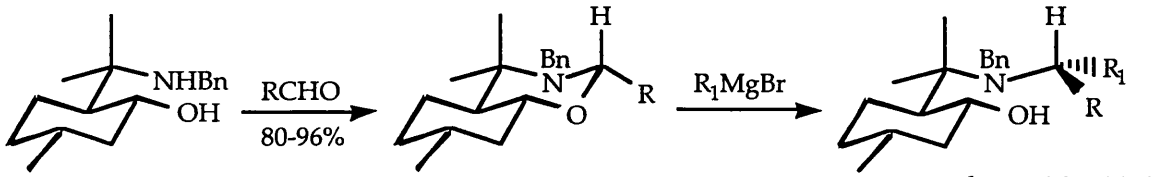
Figure 34



Pedrosa has described the synthesis of racemic *tert*-aminopropanol derivatives by the face-selective ring opening of achiral 1,3-tetrahydrooxazines by Grignard reagents in excellent yields.[47] The reductive cleavage with $LiAlH_4$ and the ring opening by Reformatsky reagents of these achiral 1,3-oxazines has also been reported in high yield.[48] Racemic propargyl propanolamines have been synthesised by the ring opening of 1,3-oxazines with alkynylboron reagents.[49]

Ring opening of chiral 1,3-oxazines has been limited to the reactions of Grignard and organoaluminium reagents. Highly conformationally stable perhydro-1,3-oxazines derived from (+)-pulegone (**11**) were shown to react with Grignard reagents in good yields and high e.e. (Figure 35).[50]

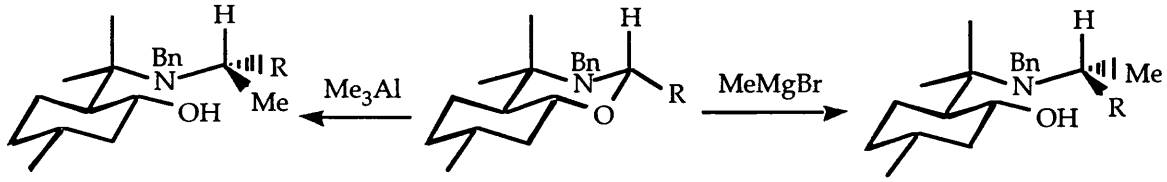
Figure 35



11

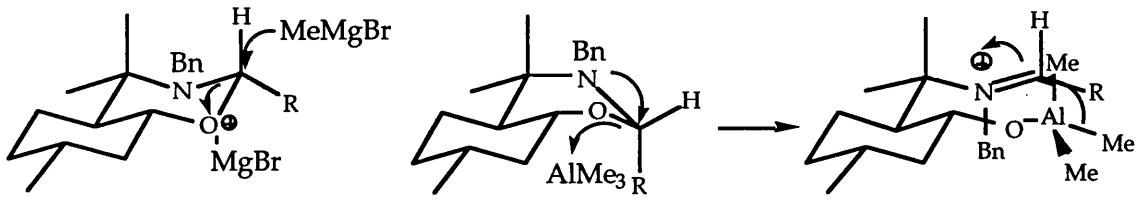
In a comparative study, the reactions of similar 1,3-oxazines with both Grignard and aluminium reagents have been observed.[51] These are shown to give diastereomeric ring opened products (Figure 36).

Figure 36



It was found that aluminium reagents gave the best d.e.'s and yields, although the majority of the Grignard reagents used in the study were hindered, cycloalkyl derivatives. As would be expected by analogy with acetal chemistry[27] the sense of the ring opening with aluminium reagents is reversed from that of Grignard reagents. This again indicates the type of mechanism shown in Figure 37.

Figure 37



Grignard Mechanism Aluminium mechanism

1.3.3 Summary

In summary it is observed that (N)-alkylation of chiral 1,3-oxazolidines produces different results (in ring opening with Grignard reagents) to the un-alkylated derivatives, i.e. a *syn*- versus *anti*-addition with respect to the 4-position of the oxazolidine ring.

The analogous chiral imines also produce *anti*-adducts which, along with the predominance of the imine tautomer in polar solvents, strengthens the case for an imine intermediate to be involved in the ring opening of the unprotected oxazolidines.

The requirement for a minimum of two equivalents of Grignard reagent to be involved for ring opening to proceed to completion (in the majority of cases) suggests that $MgBr_2$ is formed (*via* the Schlenk equilibrium) which then co-ordinates to the ring oxygen. The nucleophile can then be delivered onto the most favoured face of the intermediate imine/iminium ion.

In theory, 1,3-oxazine ring opening would appear to be much simpler. The sense of ring opening and the diastereoselectivity are dependent upon the type and steric bulk of the nucleophile. Grignard reagents attack from the "N-face" to give the *syn*-adduct, whereas organoaluminium reagents attack from the "O-face" to give the *anti*-adduct. The greater diastereoselectivity of

the aluminium reagents may be explained by a closed ring transition state where the face selectivity is chelation controlled. Grignard reagents, however can be seen to proceed *via* a more open iminium ion transition state in which the face selectivity is less specific due to the lack of both chelation and rigidity in the transition state.

1.4 The Synthesis of Chiral β-Amino Acids

The use of a chiral β-amino alcohol, derived from the corresponding acid, as a chiral auxiliary in this work prompts the need to briefly review the synthesis of these compounds.

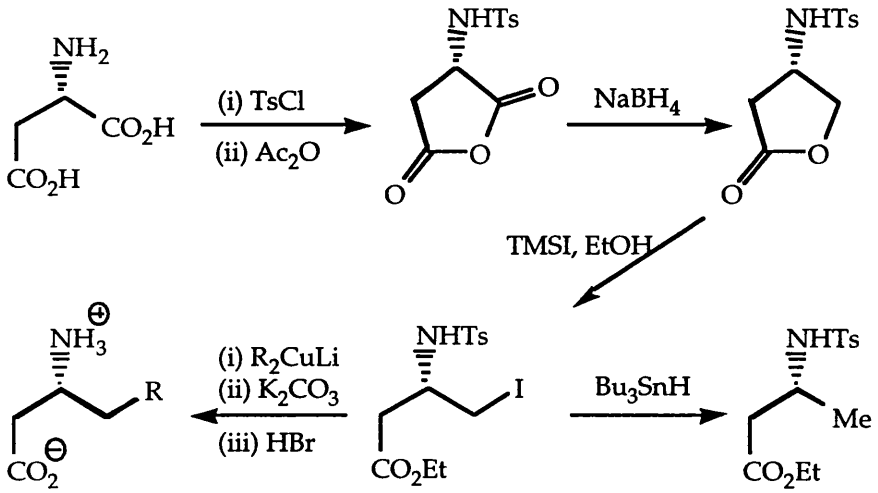
The pharmacological properties of β-amino acids and the related β-lactams has prompted much interest in the development of novel synthetic methodologies for this class of compound. The field was recently reviewed by Cole[52] and Cardillo.[53] To comprehensively review this area would be to repeat the existing literature. Therefore, only a brief overview of the available methodologies will be given.

1.4.1 Synthetic Methods

The Arndt-Eistert synthesis can be used in the synthesis of β-amino acids *via* the synthesis and rearrangement of chiral diazoketones derived from α-amino acids. This process has been shown to proceed with retention of chirality.[54] The reduction of an α-amino acid followed by tosylation of the resulting alcohol and displacement with sodium cyanide leads to α-amino nitriles. Hydrolysis of the nitrile leads to the required acid.[55] Aziridines can also be functionalised in a similar manner, both with cyanide and with

dithiane.[56] Jefford has developed a synthesis of alkyl β-amino acids from aspartic acid (Figure 38).[57]

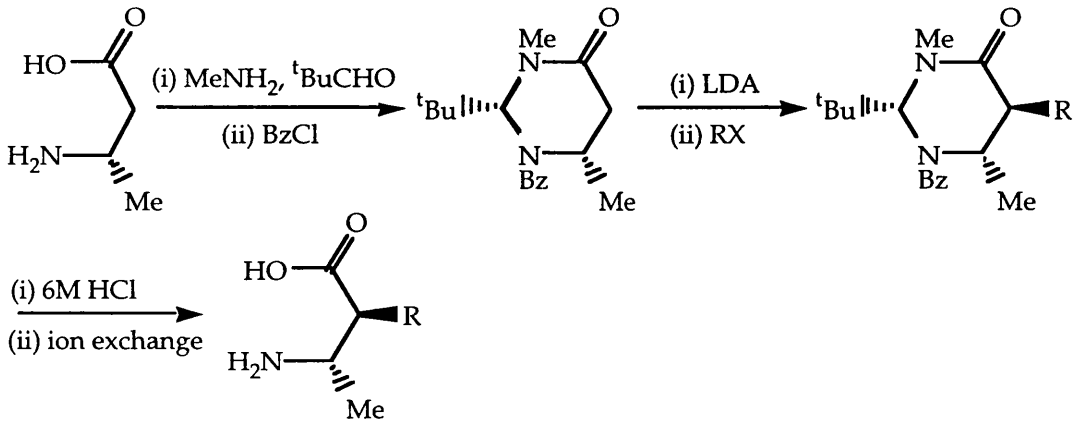
Figure 38



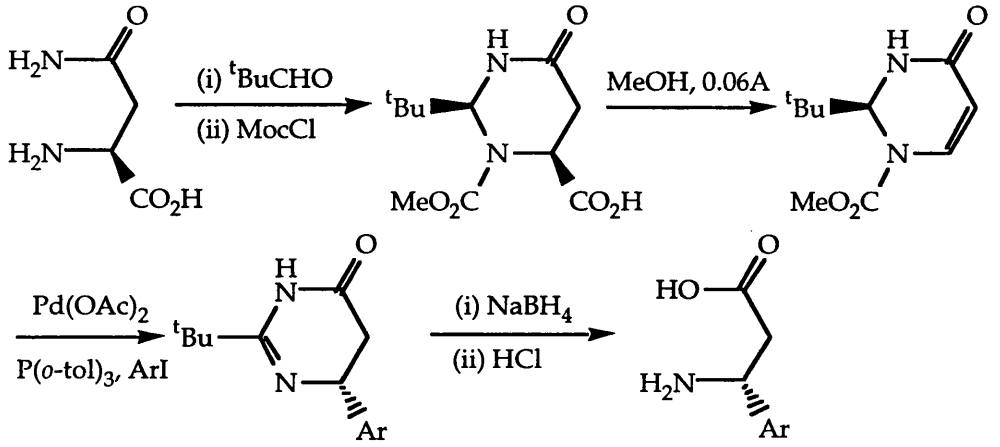
Seebach[58] and Konopelski[59] have used 2-*tert*-butylperhydropyrimidin-4-ones derived from β-aminobutyric acid and asparagine to produce almost enantiopure α-β-alkyl and β-alkyl amino acids (Figure 39).

Figure 39

Seebach



Konopelsky



Michael additions of chiral amine bases to acrylates has also been studied in great detail,[60] as have nucleophilic additions to imines[61] and, as already mentioned, chiral 1,3-oxazolidines.[38, 44]

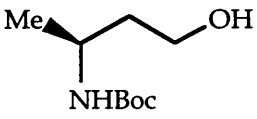
1.4.2 Enzymatic Methods

Very little work has been published on the area of asymmetric synthesis of β-amino acids by enzymatic means. Initial studies in the are were carried out in 1964, with the resolution of β-aminohydrocinnamic acid and β-aminobutanoic acid by chymotrypsin[62] and in 1977 with penicillin G acylase.[63] Further work with the later enzyme was carried out in 1995 by Soloshonok *et. al.* to produce virtually enantiopure β-aryl amino acids.[64] Gotor has described the resolution of ethyl-(±)-3-aminobuyrate with *Candida antarctica* lipase in good e.e..[65]

Chapter 2: Results and Discussion

2.1 Synthesis of the Chiral Auxiliary

The auxiliary that was intended for use in this work was (N)-Boc-3-(*S*)-aminobutan-1-ol (**12**). This can be envisaged to come from the corresponding butyric acid (**13**) *via* a simple reduction.



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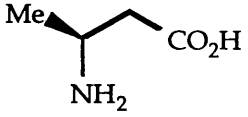
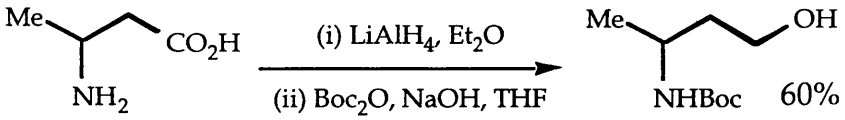


13

As there is no readily available supply of the material, a synthetic methodology towards this had to be devised.

It is necessary to note that all preliminary work on this project was carried out on racemic material. Racemic **12** (rac-**12**) was initially obtained by reduction of racemic **13** (rac-**13**) with $LiAlH_4$, then Boc protection in a rather low yielding procedure (Figure 40).[66]

Figure 40



rac-13 **rac-12**

It was later found that the Meyers procedure for the reduction and (N)-protection of amino acids was more effective.[67] This involves the direct reduction of the amino acid with $NaBH_4$ in the presence of iodine, followed by Boc protection of the crude amino alcohol in excellent yield.

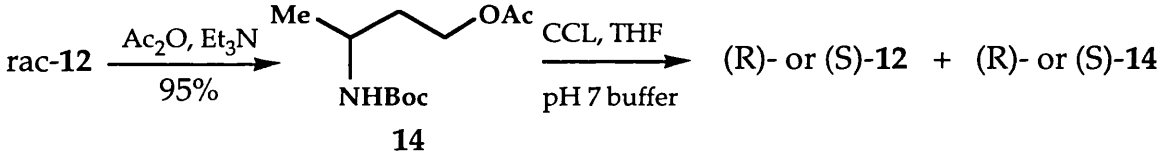
Whilst attempting to find a simple route to chiral **12**, rac-**12** was used to carry out further investigations into oxazine synthesis.

2.1.1 Enzymatic Resolution of Rac-12 or Rac-13

It was thought that an enzymatic resolution of either rac-**12** or rac-**13** would prove to be the most convenient and cost effective method of producing **12**, mainly due to the relatively low cost of the acid and the catalytic nature of all such procedures.

Initial enzyme work centred around the resolution of rac-**12** *via* conversion to the O-acyl compound (**14**) and then treating this with *Candida cylindricea* lipase (CCL) (Figure 41). HPLC of the (*R*)-Moshers ester derivative[68] of the racemic alcohol gave a reliable baseline separation of the two diastereomers and hence allowed an estimate of the e.e. of the resolution. Initial results indicated that some resolution had taken place (1.7:1 ratio of enantiomers). Unfortunately subsequent attempts to repeat this result failed.

Figure 41



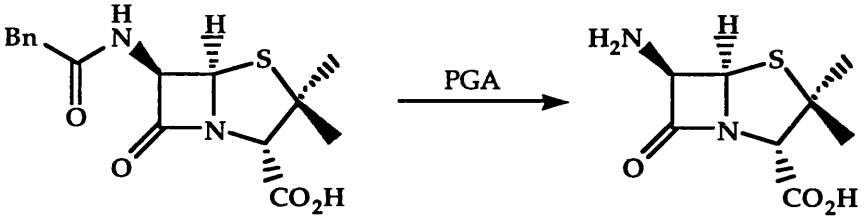
14 was also treated with porcine liver esterase (PLE). This resulted in very small quantities of **12** being produced with assay of the product indicating that this was a 2:1 mixture of diastereomers. The enzyme *Subtilisin* Carlsberg was also used but failed to give any of **12** whatsoever.

The failure of CCL, PLE and *Subtilisin* Carlsberg to resolve **14** to an appreciable amount is possibly due to the site of enzyme action being situated 3 atoms away from the chiral centre leading to poor stereocontrol.

With this in mind it was decided to examine transformations at the nitrogen, i.e. one atom away from the chiral centre, in the hope that better control could be exercised.

Penicillin-G-amidase (PGA) is used in the industrial production of 7-aminopenicillanic acid (**15**) from penicillin-G (**16**) (Figure 42)[69] and has been used in the resolution of aryl β-amino acids *via* their phenylacetamides.[64]

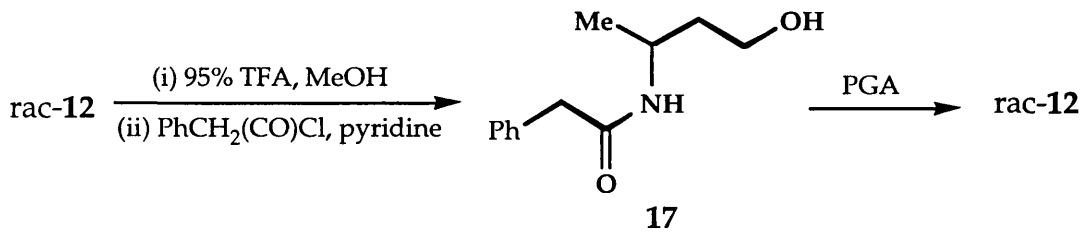
Figure 42



16 **15**

(N)-Phenylacyl-3-aminobutan-1-ol (**17**) was synthesised and was treated with PGA-450[70] at 30°C overnight (Figure 43). This led to complete cleavage of the amide and no resolution was observed. It was hoped that a shorter reaction time and/or lower temperature would have given a more selective reaction and further investigation of this route was attempted. However, difficulty arose in the quantitative analysis of this and the route was abandoned.

Figure 43



17

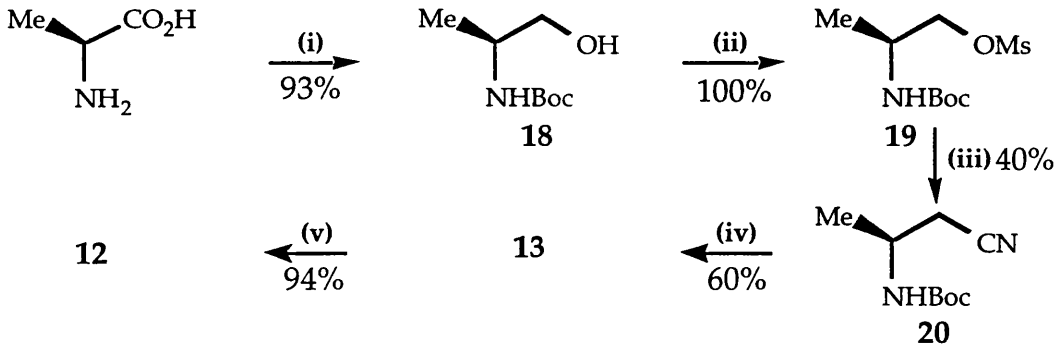
It was becoming increasingly clear that an enzymatic resolution to give **12** was not going to be an easy task. Due to the constraints of time and the need

for chiral material, synthetic methods for the production of **12** were investigated.

2.1.2 Synthetic Routes to the Chiral Auxiliary

Work which had already been carried out in the group[66] allowed the synthesis of **12** from (*L*)-alanine *via* a 1 carbon homologation with NaCN (Figure 44). Alanine was firstly reduced and Boc protected, using the method of Meyers, to give **18**. The alaninol was then mesylated (**19**) and this was displaced with cyanide in hot DMF to give nitrile **20** in moderate yield. Most attempts to hydrolyse/reduce the nitrile, whilst maintaining Boc protection of the nitrogen, failed. These included aqueous base and DIBAL. Finally, heating the nitrile in concentrated hydrochloric acid at reflux, provided the required acid. Nitrogen reprotection gave **13**. Reduction of the isobutyl mixed anhydride of **13** furnished **12** in overall disappointing yield.

Figure 44



(i) (a)$NaBH_4$/Iodine, Δ, THF; (b) Boc_2O, NaOH; (ii) MsCl, Et_3N, O °C; (iii) NaCN, DMF, 60 °C; (iv) (a) 10M HCl, Δ; (b) Boc_2O, NaOH; (v) (a) $^iBuO(CO)Cl$, Et_3N, THF, O °C; (b) $NaBH_4$, H_2O, O °C

This sequence was relatively simple and was used to provide initial supplies of the auxiliary. There are however two main disadvantages in using this route:

(i) there are seven synthetic steps and the overall yield is low (ca. 25%),

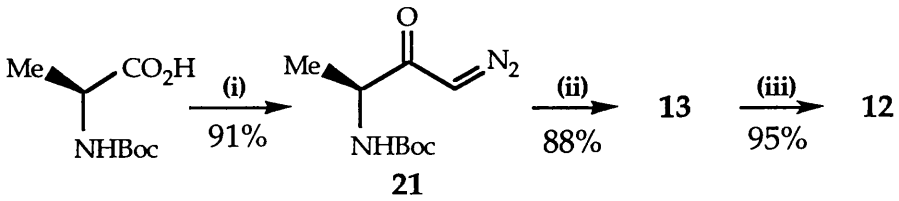
(ii) the route uses 7.5 equivalents of the highly dangerous cyanide.

The low yield of the cyanide insertion may be attributed to side reactions including of the neighbouring group effect of carbamate nitrogen which can cause displacement of the mesylate to give the aziridine. Some evidence for the formation of this was found.[66] The fact that the substitution is taking place in a β-branched substrate will also deactivate C-1 towards nucleophilic attack. Given these problems an alternative route was sought.

The Arndt-Eistert homologation of amino acids with diazomethane followed by Wolff rearrangement had been attempted previously in the group, though with little success.[71]

Treatment of the isobutyl mixed anhydride of (*L*)-N-(Boc)-alanine with diazomethane gave the diazoketone **21** in excellent yield. Subsequent treatment of this with either silver (I) oxide or silver (I) acetate in water, gave **13** in good yield. Mixed anhydride reduction with $NaBH_4$ gave **12** in excellent overall yield (76 %) (Figure 45).

Figure 45



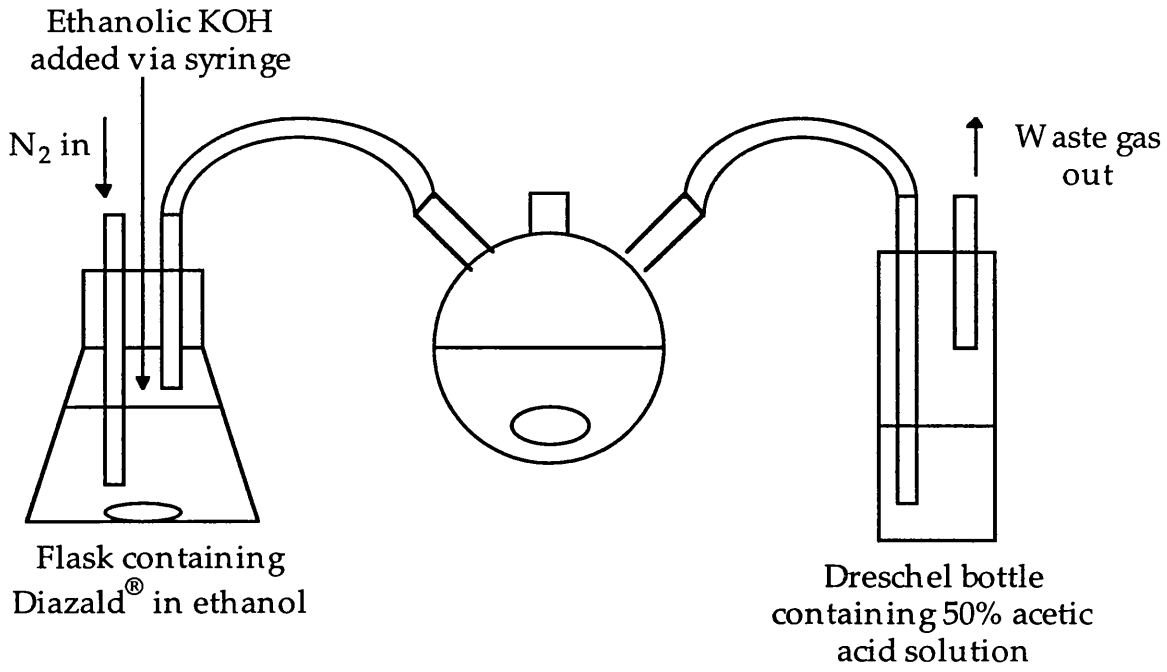
(i) (a) $^{i}BuO(CO)Cl$, Et_3N, THF, O°C; (b) CH_2N_2; (ii) AgOAc or Ag_2O;
(iii) (a) $^{i}BuO(CO)Cl$, Et_3N, O °C; (b) $NaBH_4$, H_2O, O°C

This proved to be a much more effective method of producing **12**, with each step being high yielding giving a good overall yield. Having fewer steps meant that the synthesis could be carried out quickly giving rapid access to the chiral auxiliary.

One problem in the synthesis of **21** is the reaction must be performed under anhydrous conditions, or significant quantities of (N)-Boc-(*L*)-alanine methyl ester are isolated. The normal method of diazomethane production, where the diazomethane is distilled in an ethereal solution does not combat this problem (obviously conventional methods of drying the highly unstable solution are unacceptable). An alternative method was found which generates diazomethane as a gas which is passed through the solution on a stream of nitrogen.[72] This method ensures that the diazomethane is dry and is much safer than the original method with the overall concentration of this highly toxic and explosive substance kept low at all times during the reaction by virtue of its consumption being synchronous with its generation. An acetic acid scrubber connected to the gas outlet ensures that all waste gas is neutralised (Figure 46).

Attempts to effect Wolff rearrangement of **21** with light proved to be unsuccessful, probably due to the use of the wrong wavelength of light (a study of the literature indicated that 700 Watt quartz lamp should be used[73]). However this would be a far more economic and environmentally friendly solution than the use of silver salts if the appropriate equipment were available.

Figure 46



All tubing *must* be either fire polished glass or 2mm bore Portex® plastic tube. Stirrer bars should have rough edges smoothed with a knife before use.

Having made sufficient quantities of **12** it was possible to continue with the synthetic sequence.

2.2 Synthesis of Chiral 1,3-Tetrahydrooxazines

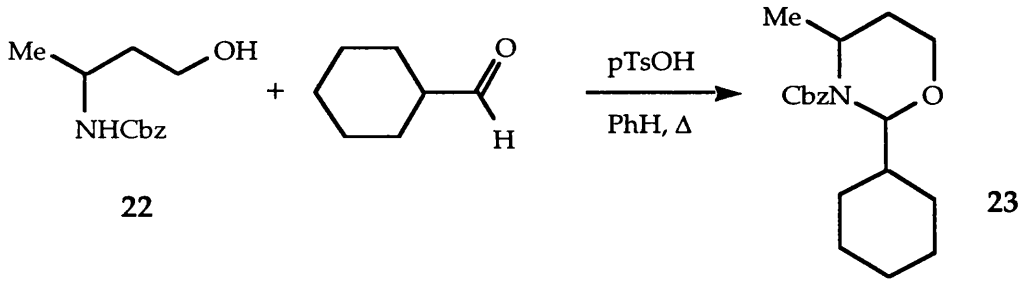
In parallel to the development of a route to **12**, preliminary work on the synthesis of the aminal rings was carried out using the readily available rac-**12**.[66] This allowed for the rapid development of the methodology.

Attempts to synthesise aminals in a manner analogous to that for acetals, i.e. direct condensation of an aldehyde with rac-**12** under acid catalysis, failed. Simple refluxing of the two compounds with PPTS in benzene, under Dean Stark conditions to remove any water formed in the reaction, gave only starting material. Similarly the use of other methods of dehydration, e.g. 4Å molecular sieves or magnesium sulphate, the use of stronger acid, e.g.

pTsOH, or the use of a solvent of higher boiling point such as toluene, all failed to give significant amounts of product.[50] When stronger acid or toluene as solvent were used, significant quantities of 3-amino butanol were recovered due to the lability of the Boc group under these extreme conditions.

A small quantity of (N)-Cbz-3-aminobutanol (**22**) was synthesised by substituting CbzCl for Boc_2O in step (ii) of Figure 35. When **22** and cyclohexanecarboxaldehyde were subjected to reflux in benzene with pTsOH, under Dean Stark conditions, a good yield of the corresponding aminal (**23**) was obtained (Figure 47).

Figure 47

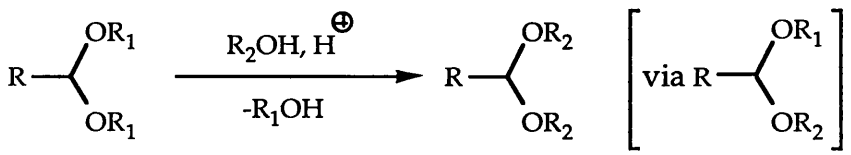


22 **23**

This was proof that, in principle, aminals could be synthesised in this manner although **23** would be of little use as the Cbz group could not be removed without damage to an acetylene moiety introduced in a future ring opening step.

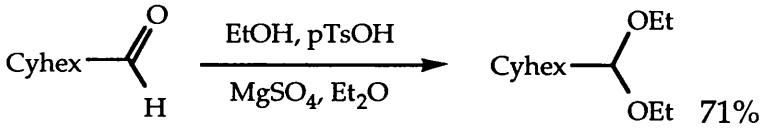
It was then decided to investigate the possible utility of a "transacetalisation" reaction to see if this would allow access to a range of aminals.[74] This has been shown to allow the preparation of mixed acetals from symmetric acetals (Figure 48).

Figure 48



To this end the diethyl acetal of cyclohexanecarboxaldehyde (**24a**) was prepared by stirring it in the presence of catalytic pTsOH with an excess of dry ethanol, using $MgSO_4$ as a dehydrating agent. 4Å molecular sieves can also be used but are less convenient from an experimental viewpoint (Figure 49).

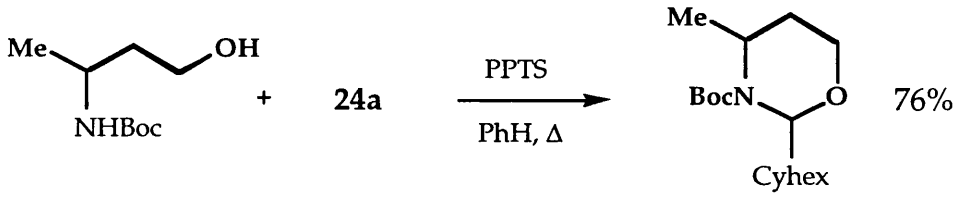
Figure 49



24a

Rac-**12** and **24a** were then heated at reflux in benzene, under Dean Stark conditions, with catalytic PPTS and gave a good yield of the racemic aminal (rac-**25a**) (Figure 50).

Figure 50



The success of the "transacetalisation" in the face of the failure of the direct method may be rooted in the fact that there are differing mechanisms of formation of aminals from the different substrates.

In the case of attack on the carbonyl, it has been shown that protonation of the carbonyl oxygen is the first step, generating a hydroxy carbocation.[41b]

This would then be attacked by either the oxygen or the nitrogen of the amino alcohol, losing water to generate a hemi acetal/aminal. The process would then repeat itself to give the aminal (Figure 51).

In the acetal case, the first step will be protonation of oxygen followed by elimination of a molecule of ethanol, in a step analogous to the acid catalysed hydrolysis of acetals.[75] This will give the ethereal carbocation which is more stable than the hydroxy carbocation in Figure 45 by virtue of resonance effects.[41c] After addition of the amino alcohol the process would be repeated to give the required aminal (Figure 52).

Figure 51

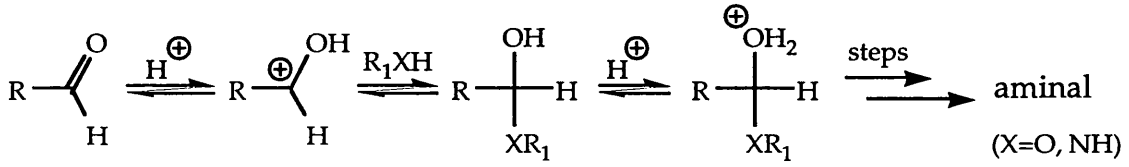
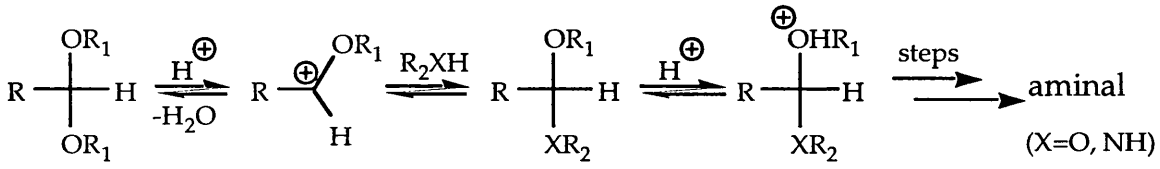


Figure 52



An acetal oxygen is approximately three to four times more basic than that of a carbonyl oxygen making its protonation under mild acid conditions more favourable.[41d] This could explain why the transacetalisation process is facile compared to the reaction with the aldehyde.

At this time a supply of non-racemic **12** was available, so a range of diethyl acetals were synthesised as described above (**24b-g**) and were converted to their chiral aminal derivatives (**25a-g**) (Table 1).

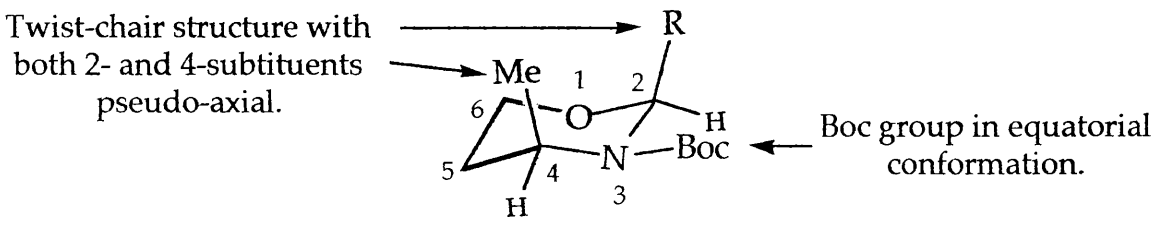
Table 1

R	acetal	aminal	Aminal Yield (%)
cyclohexyl	**24a**	**25a**	76
hexyl	**24b**	**25b**	83
propyl	**24c**	**25c**	69
^{i}propyl	**24d**	**25d**	55
5-(TIPSoxy)-pentyl	**24e**	**25e**	63
3-(TIPSoxy)-propyl	**24f**	**25f**	74
benzyl	**24g**	**25g**	51

The exceptions were **24e** and **24f** which was synthesised by refluxing in dry ethanol with catalytic PPTS, under Dean Stark conditions, to give an excellent yield of the acetal.

^{1}H NMR of the aminals appeared to suggest a mixture of diastereoisomers at the 2-position, but further investigation by both X-ray crystallography and further NMR studies did not support this assumption. This will be discussed in greater detail in Chapter 3. At this point it is sufficient to say that the 2,4-diaxial configuration was assigned to **25a-g** (Figure 53).

Figure 53

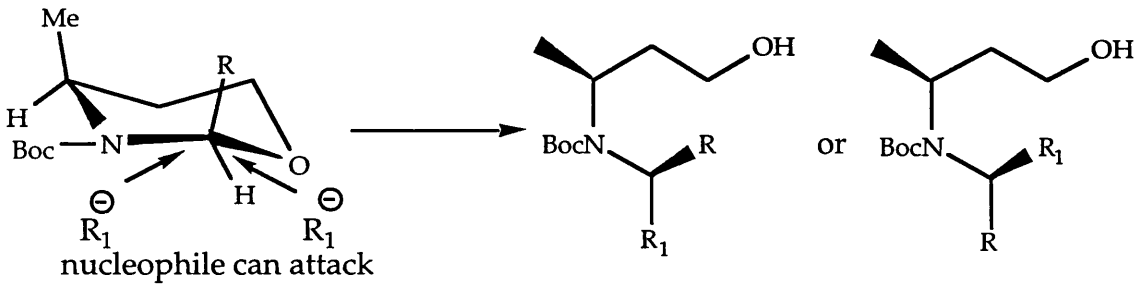


2.3 Ring Opening of 1,3-tetrahydrooxazines with Acetylenic Nucleophiles

This is the key step in the methodology; the one in which the new chiral centre will be established. Although a new chiral centre is set up at the 2-position during the synthesis of the aminals, the mechanism of attack at this position will be the deciding factor in the overall stereoselectivity.

For example, the nucleophile may attack from either the N- or O- face (in the absence of any control from the Lewis acid or steric effects) to give either diastereomer of the ring opened compound (Figure 54).

Figure 54



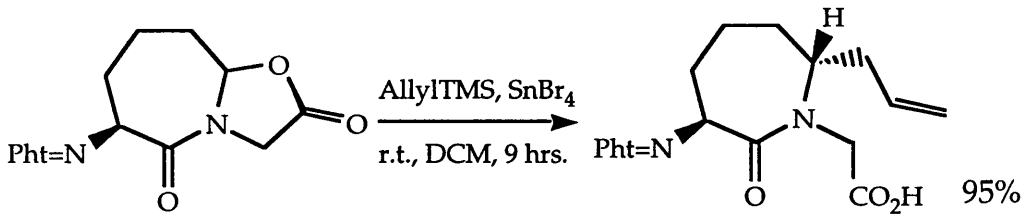
As with the synthesis of the aminals, the ring opening reactions were first carried out on racemic material.

Ring opening reactions of aminal rac-**25a** were attempted with bis(trimethylsilyl)acetylene (which has been used as a nucleophile in the ring opening of acetals by Johnson[13]). The Lewis acid in this case was $TiCl_4$, which was also thought to be useful in the ring opening of aminals.[66]

Initial experiments indicated that rac-**25a** was being consumed in a very short time (< 5 minutes by TLC), but even after 1 hour of reaction none of the required product could be isolated. Work up gave a high recovery of

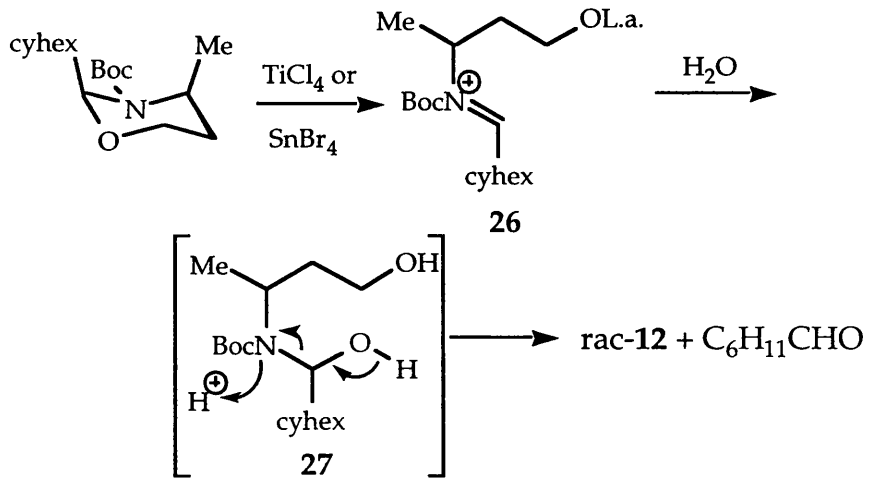
starting aldehyde and rac-**12**. A similar result was observed when the reaction was carried out with $SnBr_4$. This Lewis acid had been used by Robl in his synthesis of azepinone analogues, where allylsilane addition to bicyclic oxazolidinones gave the desired homoallyl amines (Figure 55).[76]

Figure 55



Both results can be rationalised by envisaging complexation of the aminal to the Lewis acid giving iminium ion **26**. If the nucleophile used was not strong enough to react with **26** the no further reaction would be observed until the aqueous work up, whereupon **26** would react with the added water. This would give the "hemi-aminal" **27** which would then collapse to give the observed products (Figure 56).

Figure 56

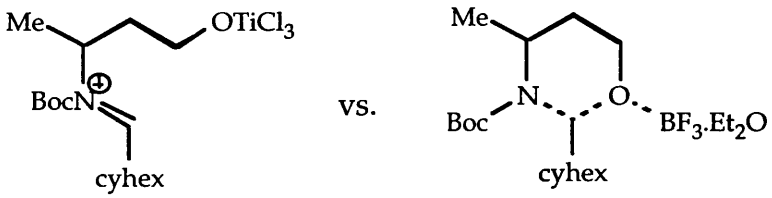


It was obvious from this that bis(trimethylsilyl)acetylene was not nucleophilic enough to attack the Lewis acid complexed aminal. It was then

decided to employ a softer Lewis acid perhaps coupled with a more reactive nucleophile.

In subsequent reactions $BF_3.Et_2O$ was used along with (trimethylsilyl)acetylene, the rationale being that the aminal would not be so tightly bound to the Lewis acid, perhaps promoting an S_N2-type attack on an oxazine system still bearing chair-like characteristics (**28**) as opposed to the more open chain iminium system which is more likely from the stronger $TiCl_4$ or $SnBr_4$ (**26**) (Figure 57).

Figure 57



26 **28**

Initially this produced a small amount of a product which, by crude NMR, could have been the required compound. This proved very difficult to isolate however and no proof as to its identity could be found. Subsequent reactions gave no indication of any reaction whatsoever.

Many other nucleophile / Lewis acid combinations (most of which had been used in similar reactions of aminals or acetals) were tried in an attempt to prepare some ring opened material. However, these had little or no success and are detailed in Table 2, with references where appropriate.

Table 2

Aminal	Nucleophile	Lewis acid	Yield/%	Reference
rac-**25a**	TMSC≡CLi	$TiCl_4$	5	–
rac-**25a**	TMSC≡CLi	$BF_3.Et_2O$	0#	49
rac-**25a**	TMSC≡CH	$SnCl_4$	0#	77
rac-**25a**	$(TMSC{\equiv}C)^-(AlMe_3Li)^+$	–	0*	78
rac-**25a**	$TMSC{\equiv}CSnMe_3$	$BF_3.Et_2O$	0*	79

* starting material was recovered

\# starting material was consumed

The failure of entry 2 to provide some of the ring opened product was surprising when considering the work of Wu, who suggests that alkynyl lithiums, in the presence of $BF_3.Et_2O$, will give a moderate yield of the ring opened material.[49]

Grignard reagents were then turned to as nucleophiles, as these have been shown by Pedrosa to ring open aminals in this manner.[50, 51] This reaction has been shown to require a second equivalent of Grignard reagent presumably acting as a Lewis acid.

The Grignard reagent derived from (trimethylsilyl)acetylene was used but initially proved to be unsuccessful with no ring opened product observed, even at elevated temperatures (in the previous work by Pedrosa only room temperature was needed). A more detailed examination of the literature indicated that Grignard reagent cleavage of both acetals and aminals were

assisted by the addition of a Lewis acid catalyst.[80] Further experiments were then carried out using a variety of Lewis acids as detailed in Table 3.

Table 3

Aminal	Nucleophile	Lewis acid	Yield/%	Reference
rac-**25a**	TMSC≡CMgBr	$TiCl_4$	10	–
rac-**25a**	"	$MgBr_2.Et_2O$	0*	–
rac-**25a**	"	$Ti(O^iPr)_4$	0*	–
rac-**25a**	"	$TiCl_2(O^iPr)_2$	0*	81

* starting material was recovered

However, when $BF_3.Et_2O$ was used (in THF at elevated temperature), the racemic ring opened compound rac-**29a** was isolated in good yield. Attempts to optimise this reaction gave no overall improvement to the original yield (Table 4).

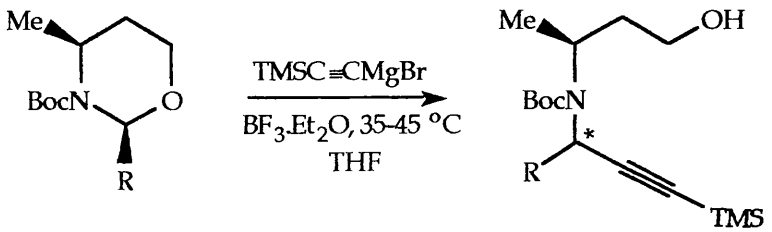
Table 4

rac-**25a**	$RMgX^{(a)}$	$BF_3.Et_2O$	Vol. of THF	Time/mins	Yield/%
0.5 mmol	2.00 mmol	1.25 mmol	2.5 ml	60	(63)
0.5 mmol	2.52 mmol	0.9 mmol	3 ml	120	(47)
0.5 mmol	2.25 mmol	1 mmol	3 ml	60	(47)
0.5 mmol	1.53 mmol	1.5 mmol	2 ml	45	(39)
0.5 mmol	2.00 mmol	0.9 mmol	2.5ml	60	(36)

(a) R = TMSC≡C.

For the reaction to proceed, it was necessary for the temperature to be between 35 - 45°C. Below 35°C no reaction could be observed. However, above 45°C significant amounts of unidentifiable by-products were isolated. Having established conditions under which alkynylation would occur satisfactorily, aminals **25a-f** were carried forward to the corresponding ring opened derivatives **29a-f** (Figure 58). The results of these transformations are summarised in Table 5.

Figure 58



25a-e **29a-e**

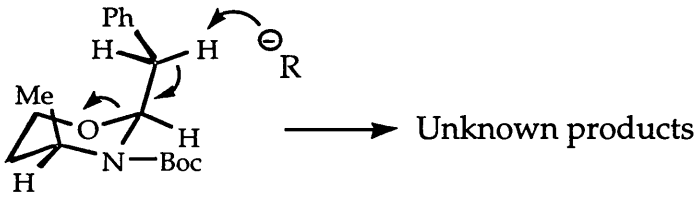
Table 5

R	Aminal	Alcohol	Yield/%
cyclohexyl	**25a**	**29a**	65
hexyl	**25b**	**29b**	63
propyl	**25c**	**29c**	63
^{i}propyl	**25d**	**29d**	48
5-(TIPSoxy)-pentyl	**25e**	**29e**	55
3-(TIPSoxy)-propyl	**25f**	**29f**	46
benzyl	**25g**	**29g**	0

Surprisingly the 2-benzyl aminal (**25g**) failed to give any of the required product, despite TLC indicating its consumption during the course of the

reaction. This may be due to the basic Grignard reagent removing one of the acidic benzylic protons of **25f**, leading to elimination to give unknown by-products (Figure 59). This problem is probably enhanced by the relatively high temperatures required for the reaction.

Figure 59

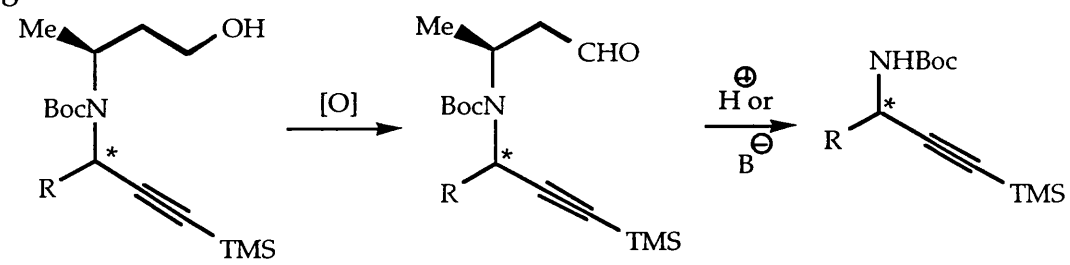


It was also impossible to make any estimate of the diastereoselectivity at this stage as the ^{1}H NMR of all the ring opened compounds were unresolved. HPLC would probably have allowed this to be estimated but this was not considered at the time. Additionally, there would have been a necessity to make the corresponding racemic mixture of ring opened compounds for comparison.

2.5 Removal of the Chiral Auxiliary to give Chiral Propargyl Amines

It was envisaged that removal of the chiral auxiliary could be effected by oxidation of the ring opened alcohol to the aldehyde followed by an acid or base driven "retro-Michael" type β-elimination to reveal the required amine (Figure 60).

Figure 60



This, although seemingly trivial, was one of the most difficult steps in the synthesis. Having already introduced the acetylenic moiety, it is now important that the chiral auxiliary can be removed without damaging both it and the new chiral centre. Admittedly it will be difficult to judge whether the conditions employed here have any effect on the chiral centre as there is no accurate assessment of the optical purity of the ring opening step.

It would also be beneficial if the Boc protecting group could be retained, as unprotected propargyl amines have been shown to be unstable and prone to decomposition.[7]

Taking all the above criteria into account, it was desirable that strongly oxidising, basic or acidic conditions should be avoided if possible.

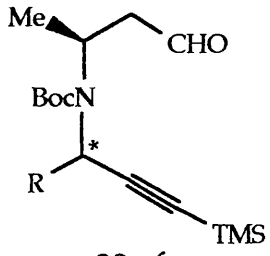
2.5.1 Oxidation of the Alcohols to Aldehydes

PCC oxidation[82] of the alcohol rac-**29a** was attempted and was seen to be partially successful by ^{1}H NMR of the crude reaction mixture. Purification of the aldehyde proved to be difficult however so other methods were investigated which might provide a higher degree of conversion.

Swern oxidation[83] failed to give any of the aldehyde, indeed significant decomposition of the alcohol was observed. It is thought that reaction of the alcohol with oxalyl chloride may have occurred leading to the breakdown that was observed.

The little used Parikh/Doering variant of the Swern,[84] using sulphur trioxide/pyridine complex, as an activator of the DMSO, instead of oxalyl chloride, was next attempted but only starting material was recovered. However, using the modified procedure of Baker and Castro[85] smooth

conversion of the alcohol to the aldehyde rac-**30a** was observed. The aldehyde was obtained in high yield and purity (based on TLC and NMR analysis of the crude). This procedure was subsequently used to convert the chiral alcohols **29a-f** to the corresponding aldehydes **30a-f** (Table 6). The aldehydes were used without further purification, indeed attempting to do so led to vastly reduced yields with no improvement in purity.



30a-f

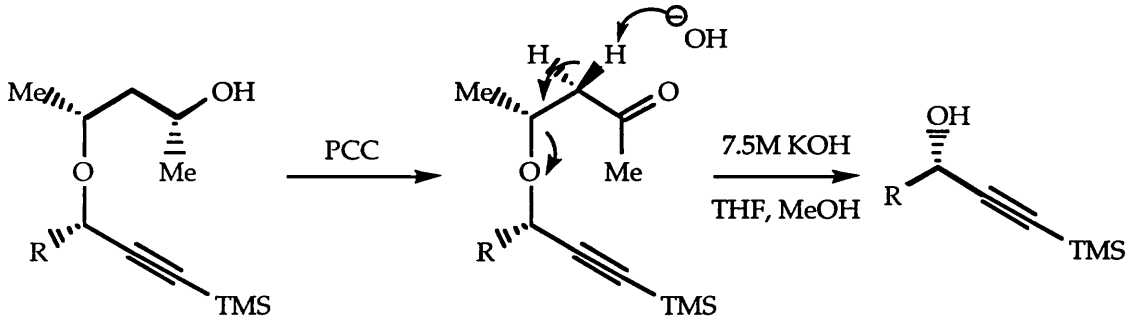
Table 6

R	Alcohol	Aldehyde	Yield/%
cyclohexyl	**29a**	**30a**	99
hexyl	**29b**	**30b**	95
propyl	**29c**	**30c**	71
^{i}propyl	**29d**	**30d**	84
5-(TIPSoxy)-pentyl	**29e**	**30e**	89
3-(TIPSoxy)-propyl	**29f**	**30f**	100

2.5.2 Attempted Removal of the Auxiliary under Basic conditions

The pioneering work by Johnson into chiral acetal chemistry indicated that the analogous propargyl alcohols may be accessed from propargyl ether **31** *via* oxidation of the alcohol to the ketone **32** followed by a base driven retro-Michael reaction to give the required alcohol **33** (Figure 61).[13]

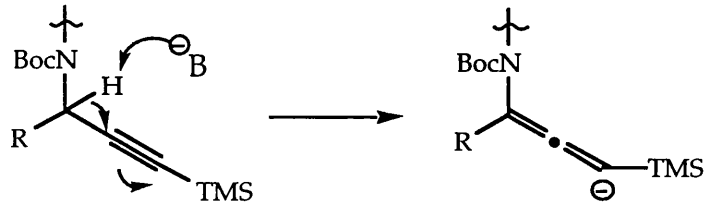
Figure 61



31 **32** **33**

If this method could be applied to the work in hand then it would have the real advantage of leaving both the Boc group and the acetylene intact. The strongly basic conditions gave some cause for concern, however, given the highly acidic nature of the proton at the new chiral centre. The reactivity of this site would be enhanced by the ability of the TMS group on the acetylene to stabilise any intermediate negative charge (Figure 62).

Figure 62



Acidic proton subject to basic attack

α-Negative charge stabilised by silicon

With this in mind, it was decided that a less basic medium would be employed in an attempt to prepare the chiral amines.

Triethylamine and rac-**30a** were stirred together for twenty four hours but no reaction was observed.

Further work was carried out using basic ion-exchange resin but it too failed to yield any product with only rac-**30a** being recovered.

It was obvious that stronger base was required so the rac-**30a** was stirred in dilute aqueous NaOH and THF. TLC indicated that the aldehyde had been consumed after 1 hour but subsequent work up and NMR gave only starting material in quantitative yield. This result was been reproduced a number of times and could possibly be rationalised by Figure 62 (above).

Upon work-up the "allenium" ion would rearrange back to the acetylene.

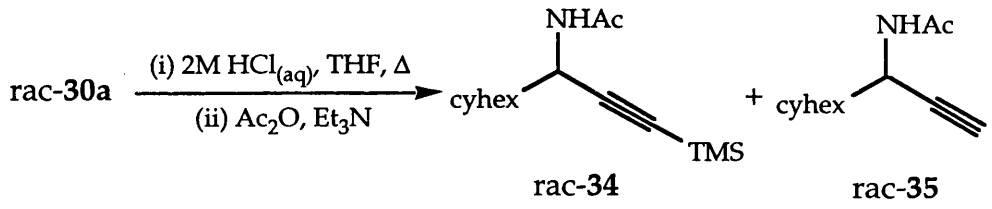
2.5.3 Attempted Removal of the Auxiliary under Acidic conditions

Given the failure of base to produce the required product it was decided to attempt the cleavage under acidic conditions. This had the disadvantage that the acid labile Boc group may be removed but it was hoped that a mild enough method would be found allowing retention of the protecting groups.

Treatment of rac-**30a** with piperidium acetate in refluxing benzene[86] gave no reaction, even after 24 hours. A similar result was observed with acidic ion exchange resin.

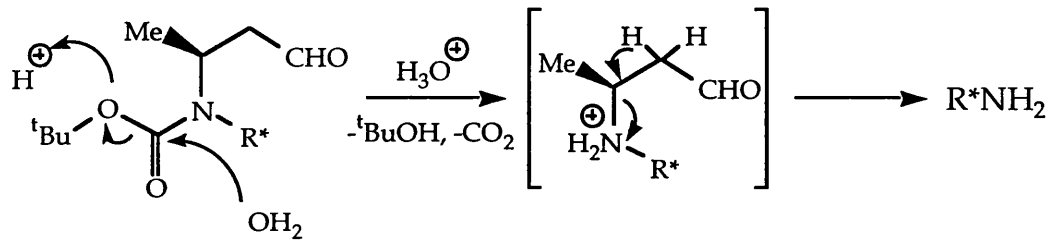
The reaction of rac-**30a** with aqueous 2M HCl in THF at reflux for 3 hours allowed smooth cleavage of the auxiliary. Initial identification of the product was difficult, with both the NMR and mass spectrum giving inconclusive results. However, in situ acylation of the product with acetic anhydride gave rise to the required N-acyl-amine rac-**34** in 60% yield with a small quantity of the de-silylated product rac-**35** also being isolated (12%) (Figure 63). The isolation of rac-**35** was unexpected as the cleavage of silicon-carbon bonds is usually achieved with either fluoride ion or non-aqueous basic conditions.

Figure 63



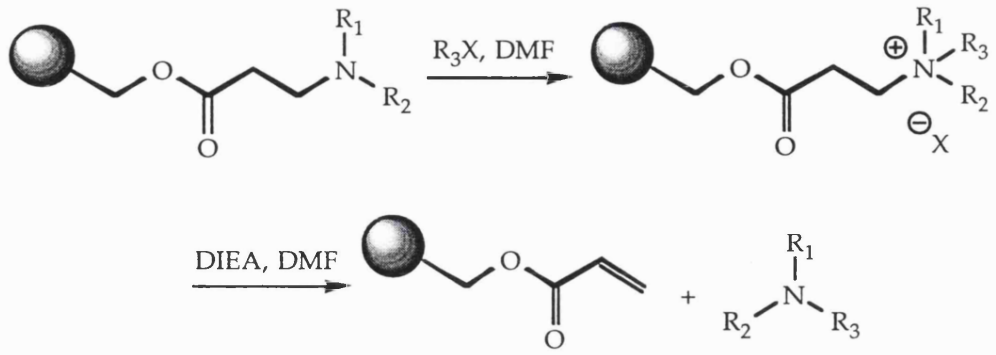
Removal of the Boc group to give the protonated, quaternised secondary amine may be the first step in the removal of the auxiliary under these conditions. Subsequent β-elimination would then follow (Figure 64).

Figure 64



This is a variant of the Hoffman elimination which can be more generally applied to elimination in systems containing quaternary ammonium salts. This has been demonstrated in a recent paper by Brown *et al.* who describe a solid-phase synthesis of tertiary amines.[87] Resin-bound β-amino esters were quaternised and then underwent facile β-elimination under basic conditions to remove the amine from the resin (Figure 65).

Figure 65



The chiral aldehydes **30a-f** were then subjected to the same conditions, substituting Boc_2O for Ac_2O, to provide the required (N)-Boc chiral amines **36a-f**. Fortunately none of the de-silylated material has been observed in these reactions.

The e.e.'s of **36a-f** were measured by removal of the Boc group and conversion to the (*S*)-Moshers amides **37a-f**. The ^{19}F NMR of these were taken and the e.e.'s measured from the respective integrals of the major and minor CF_3 peaks.

For comparison, the racemic amide rac-**37b** was synthesised from heptanal by ethynylation with TMSC≡CMgBr to give the propargyl alcohol rac-**38**. Mitsunobu displacement of the alcohol with phthalimide gave rac-**39**. Treatment of this with hydrazine hydrate in refluxing ethanol affording the propargyl amine which was immediately converted to its Moshers amide derivative with (*S*)-MTPA-Cl (Figure 66).

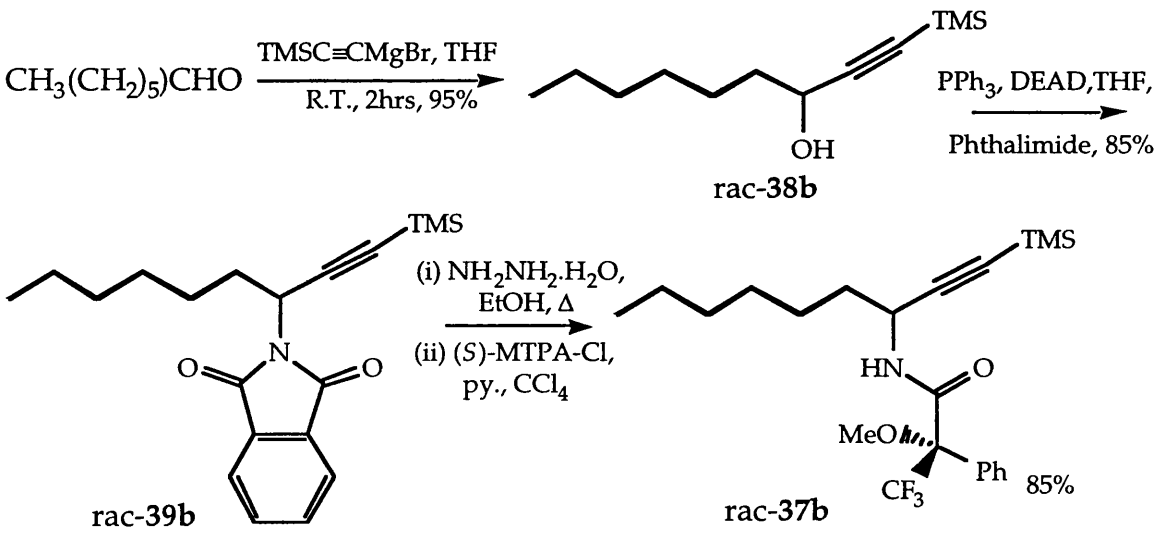
The chemical shift and integrals of the racemic CF_3 peaks were compared to those of the chiral compound to confirm assignment of the e.e..

The results of the auxiliary removal with the e.e. of the products are given in Table 7.

Table 7

R	aldehyde	Boc amine	Yield/%	Moshers amide	e.e./%
cyclohexyl	**30a**	**36a**	70	**37a**	40
hexyl	**30b**	**36b**	68	**37b**	60
propyl	**30c**	**36c**	65	**37c**	64
^{i}propyl	**30d**	**36d**	71	**37d**	86
5-(TIPSoxy)pentyl	**30e**	**36e**	35	**37e**	95
3-(TIPSoxy)propyl	**30f**	**36f**	77	**37f**	52

Figure 66



It is reasonable to assume that, in some cases at least, there are different mechanisms operating at the ring opening stage. This would explain the lower diastereoselectivity in some cases.

In order to establish a possible mechanism of ring opening then two things must be investigated in greater detail. These are;

(a) to firmly establish the overall conformation of the aminal ring and the substituents,

(b) determination of the absolute stereochemistry of the new chiral centre and hence the major diastereomer of ring opening. This will best be done by either X-ray crystallographic studies or correlation by synthesis of amines **36a-f** to a known compound or compounds.

Both of these points will be addressed in Chapters 3 and 4 respectively.

Chapter 3: Conformational Studies on 1,3-Tetrahydrooxazines

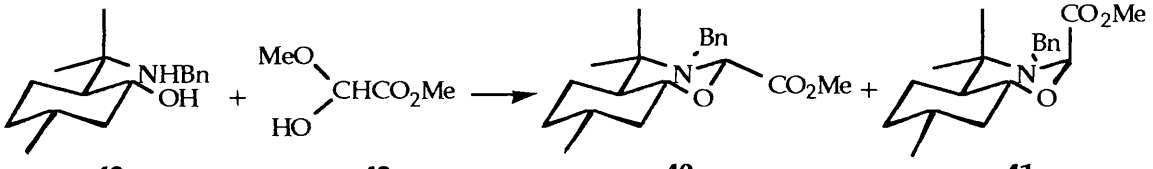
3.1 Conformational Analysisof 1,3-Oxazine Systems

There have been a number of conformational studies carried out on 1,3-oxazine systems (both by NMR and X-ray crystallography). These provide an insight as to some of the factors which may control the conformation of the aminal systems synthesised in this work. In the light of this, it will be necessary to review this area.

3.1.1 NMR Studies on 1,3-Oxazines

Eliel[88] has synthesised the oxazine esters **40** and **41** by the condensation of amino alcohol **42** and the methyl hemi-acetal of methyl glyoxalate **43** (Figure 67).

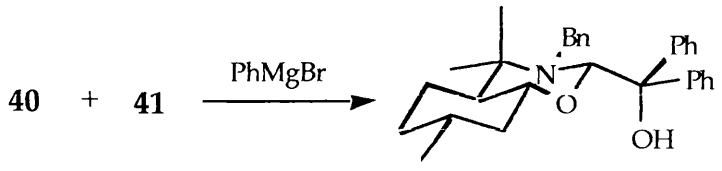
Figure 67



42 **43** **40** **41**

Oxazines **40** and **41** are obtained from the reaction as a mixture of diastereomers but can be separated by column chromatography. Compound **41** appears to be unstable however as when a mixture of **40** and **41** are treated with excess PhMgBr only the *equatorial* product **44** is isolated (Figure 68).

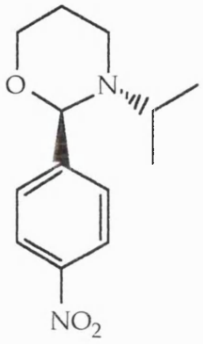
Figure 68



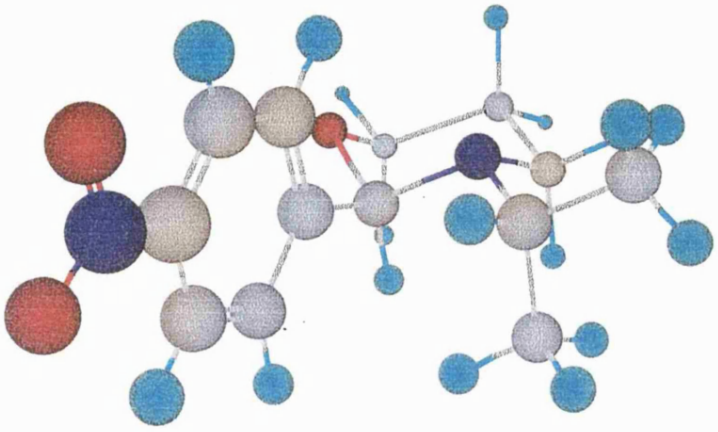
44

3.1.2 X-Ray Crystallographic Studies

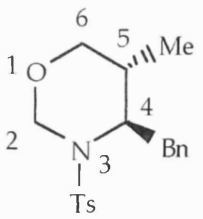
Shoja and Saba[89] synthesised oxazine **45** and established that the prefered structure was that of a chair with the adjacent substituents in a *trans* di-equatorial conformation.



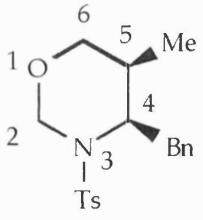
45



As a reminder that often NMR data alone cannot be entirely reliable, Burgess showed that the *trans* and *cis* oxazines **46** and **47** adopt very different conformations than would otherwise have been assigned from the NMR data.[90] The H^4/H^5 ^1H coupling constants were measured as <0.5 Hz and 4.6 Hz respectively. Normally this would suggest that **47** should have the *trans* relationship with a smaller than expected di-axial coupling constant being observed.



46

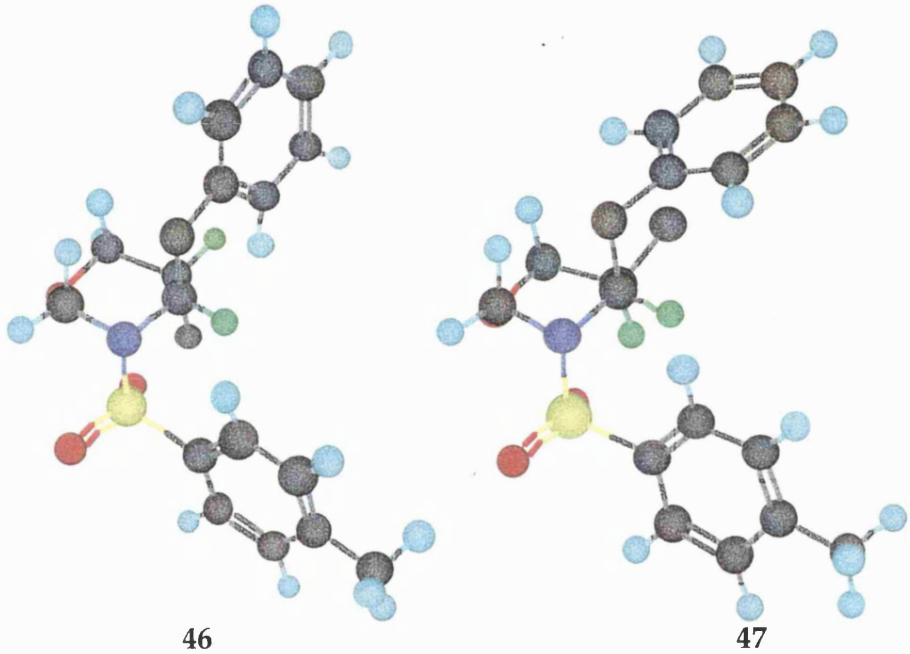


47

Crystallography reveals however that the strain imposed by the 1,2 relationship of the benzyl and tosyl groups causes them to adopt a di-axial arrangement, forcing the methyl group of **46** also to adopt an axial

conformation. This explains the very small H^4/H^5 ^1H coupling constant which was observed for this compound. The measured dihedral angle was 80° which corresponds to a coupling constant of 0 Hz, as predicted by the Karplus equation. The equivalent angle in **47** was 50°, which corresponds to 3.2 Hz. Representations of the structures are shown in Figure 69 with H^4 and H^5 indicated in green. The protons of the methyl group and the benzylic carbon have been removed for clarity.

Figure 69

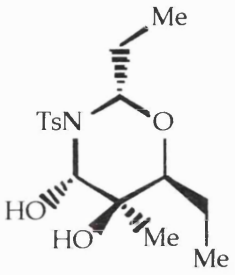


46 **47**

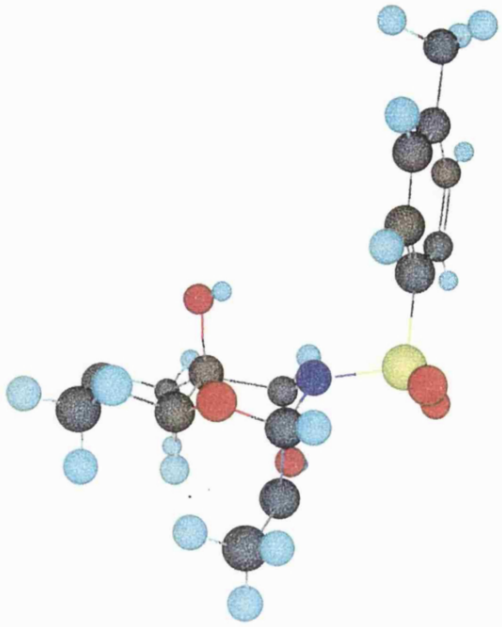
Perhaps the most interesting piece of work, from the point of view of the this discussion, was the work carried out by Weinreb.[91]

Crystallography showed that oxazine **48** has a 2,4-di-axial arrangement with the tosyl group on the nitrogen in an equatorial conformation. Admittedly, this structure is somewhat complicated by the presence of additional substitution at the 5- and 6-positions. However, as **48** was synthesised from **49** by epoxidation then ring opening, it is clear that all the substituents prefer to orientate themselves in a manner which is contrary to the expected

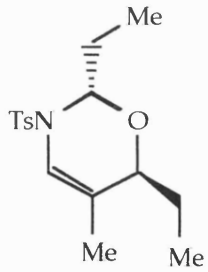
thermodynamically prefered all-equatorial conformation but which allows a minimal number of steric clashes.



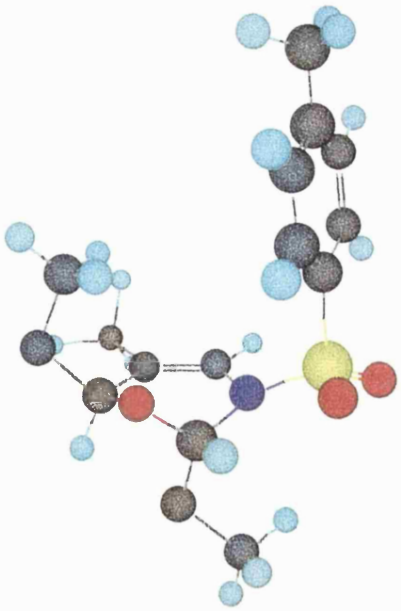
48



The structure of **49** is also interesting and shows a single stereoisomer with a 2,6-*trans* configuration with the steric clashes of the C^2 and N-tosyl groups minimised. The structure is described by Wienreb as having a "flattened sofa" configuration!



49



There are many factors which control the configuration of 1,3-oxazine systems. Substituent size is obviously important as in the case of **46** and **47**, where the desire to minimise steric interactions would appear to be the controlling factor. The conformation of the nitrogen substituent is controlled by electronic effects as well as steric effects. If the nitrogen lone pair can be delocalised into the substituent, e.g. **46** and **48**, then the nitrogen will be almost planar. Steric effects will the determine the overall conformation, i.e. whether the substiuent will be axial or equatorial. If there is only one adjacent substituent then a 1,2 di-axial arrangement will probably be observed (**46**). However if the nitrogen has three adjacent substituents, as in **48**, then an axial-equatorial-axial conformation will be observed.

3.2 Structural Studies on Tetrahydrooxazines 25g and 25a

3.2.1 Absolute Ring Conformation

The absolute configuration of position 2 and the absolute conformation of the tetrahydrooxazines described in this thesis is inherently interesting due to the 2-, 3-, 4-substitution pattern these compounds possess. The most simple method of determining the absolute structure is via X-ray crystallography which will allow the solid state structure to be defined. Additionally, NMR studies can give a great deal of information about the solution phase structure of the aminal ring. This should provide a more realistic view of the conformation of the aminal ring during a reaction.

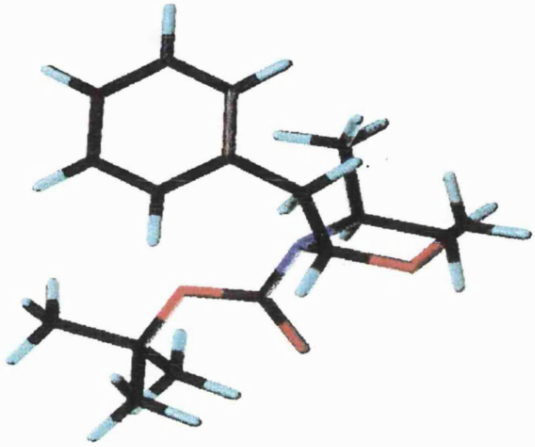
3.2.1.1 NMR studies

Oxazine **25g** (where R = benzyl) was studied extensively using both 1-dimensional and 2-dimensional NMR techniques. 2-D COSY experiments allowed the overall chemical structure to be accurately assigned and these

were followed by NOESY experiments which, after modelling and minimisation using SYBYL®, gave the solution phase conformation.

This was shown to have a flattened and twisted chair structure with the benzyl and methyl groups in pseudo-axial conformations. The Boc group adopts an equatorial conformation (Figure 70).

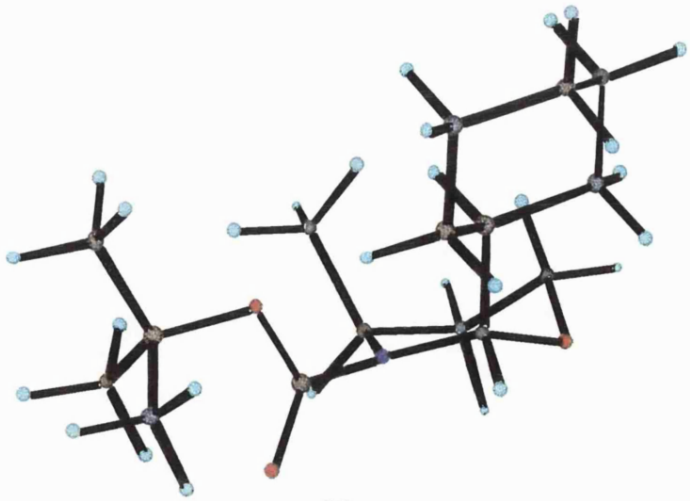
Figure 70



25g

Analysis of **25a** indicated a similar structure, which is shown in Figure 71 as a three dimensional model based on the NMR results. The data for both these structures is presented in Appendix 1.

Figure 71



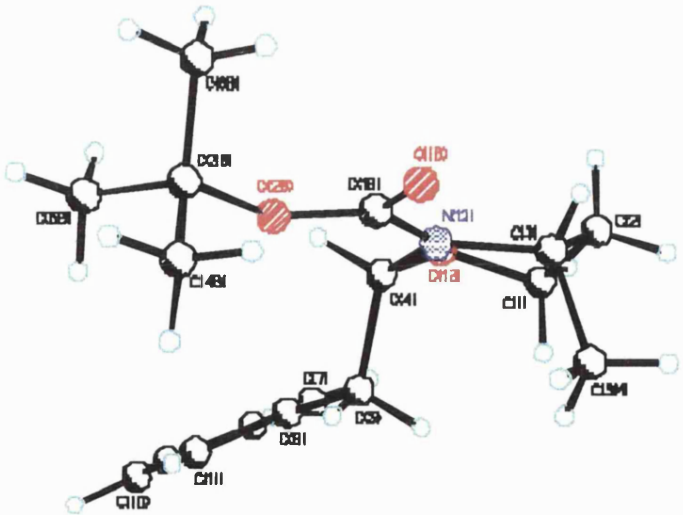
25a

3.2.1.2 X-Ray Crystallographic studies

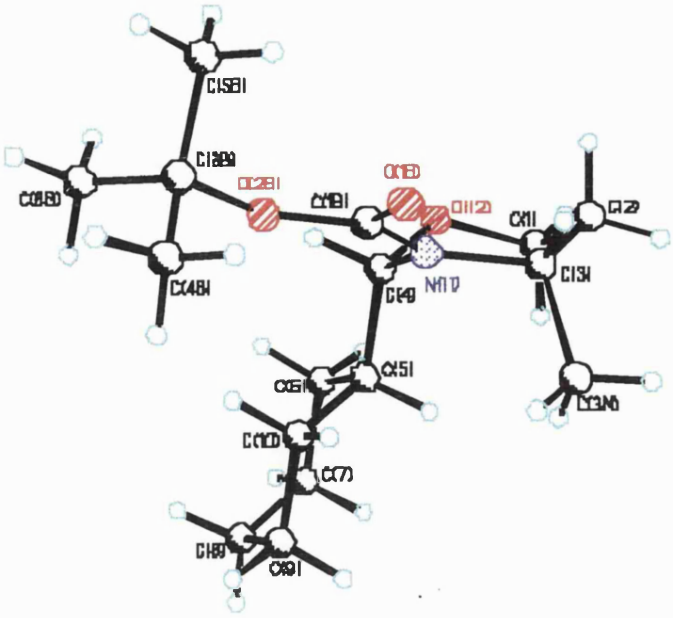
Crystals of both **25g** and **25a** were grown and then studied by X-ray crystallography. As in the NMR studies, a 2,4-diaxial arrangement is shown between the benzyl/cyclohexyl groups and the methyl group. The Boc group again adopts an equatorial conformation. The X-ray structures are shown in Figure 72. The data for both of these structures is shown in Appendix 2.

The absolute configuration given by these experiments is quite logical from a steric point of view. All three ring substituents adopt conformations which allow a minimal number of steric interactions, certainly fewer than would be observed from the theoretically expected all- equatorial conformation. These results are consistent with the pattern indicated in section 3.1.2 where three neighbouring substituents give rise to an aminal with an axial-equatorial-axial conformation with an essentially planar nitrogen.

Figure 72



25g



25a

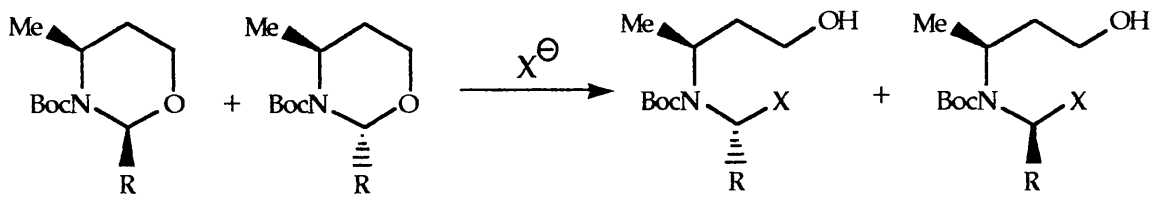
3.2.2 Ring Configuration at Position 2

More important than the absolute structure however, is that the configuration at position 2 of the aminal ring be known accurately, along with the ratio of any diastereomers which may occur at this position (Figure 73).

Figure 73

As has already been stated in chapter two, this stereochemistry at position 2 will have a pronounced effect upon the diastereoselectivity of the ring opening reaction. Consider for example, an aminal with a 1 : 1 ratio of axial : equatorial conformers. If attack occurs from one face only, e.g. the N-face (as was hoped) then the ring opened product will be a 1 : 1 mixture of diastereomers (Figure 74).

Figure 74



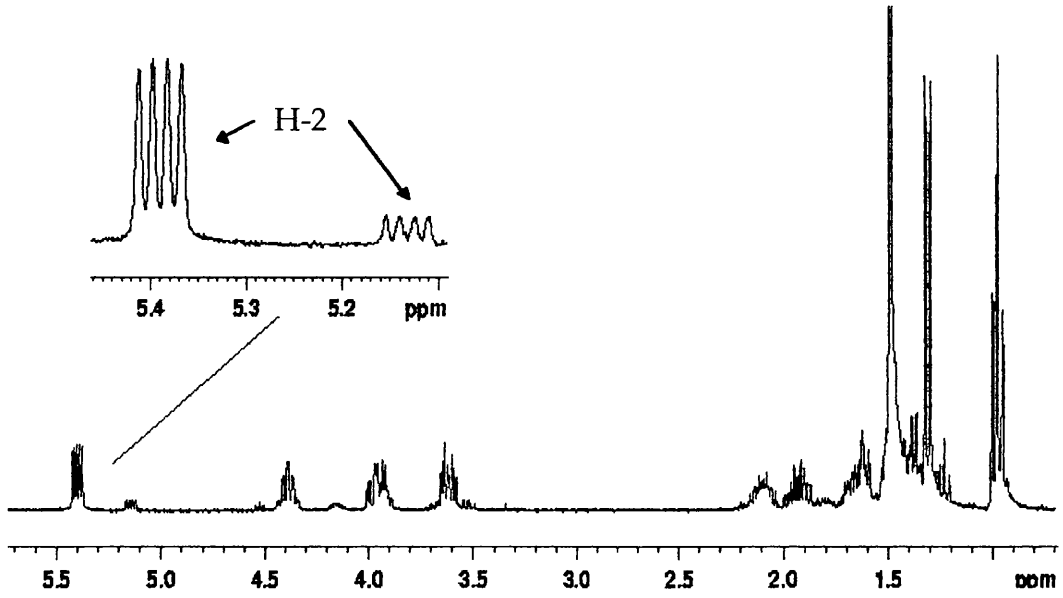
It is also critical that the configuration of the major and minor isomers be known (i.e. whether the axial or equatorial isomer is prevailant) if any meaningful discussion is to be had on the mechanism of ring opening.

3.2.2.1 NMR studies

One dimensional ^{1}H NMR studies of aminals **25a-f** indicated clearly that there are two distinct signals observable for H-2. These are observed in varying ratios. The ^{1}H NMR of the n-propyl derivative **25c** is shown in Figure 75, with the H-2 signal shown as the expanded area.

Figure 75

25c

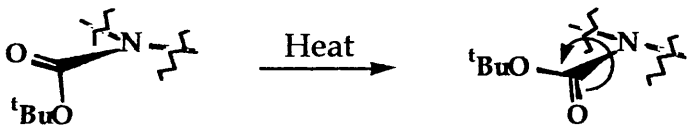


Initially it was assumed that this indicated a mixture of diastereomers at the 2-position. However, irradiation of both the major and minor peaks gave

similar NOE's indicating that they are for the *same* diastereoisomer (see Appendix 1, Spectra 9 and 10).

It was suggested[92] that the two observed signals may be due to rotamers of the Boc group (Figure 76) where one configuration is separated from the other by some form of energy barrier.

Figure 76



This phenomenon should be detectable *via* variable temperature ^{1}H NMR whereby heating should cause either an increase in the population of one form or a coalesence of the two signals as free rotation of the Boc group occurs at a higher energy. The later phenomenon is observable in the variable temperature ^{1}H NMR of DMF where a coalesence of the two methyl signals is observed at higher temperatures.[93]

Experiments were conducted both in d-6 DMSO and in d-8 toluene with heating up to 105°C. Even after 20 minutes at this temperature however, no coalescence could be observed. It was impossible to increase the temperature due to the thermal lability of the Boc group.[3]

3.3 Conclusion

Having established that the aminal ring probably has only one diastereomer, and taking in to account the reduced diastereoselectivity after the ring opening step, it is logical that there must be at least two different

mechanisms for ring opening. This is necessary to explain the variable isomer ratios of the final amine products.

At this stage it was desirable that some form of correlation must be found to allow the dominant mechanism to be determined.

Chapter 4: Determination of the Mechanism of Aminal Ring Opening

In order to establish possible mechanisms by which ring opening could have occurred, it was necessary to assign the dominant absolute stereochemistry in the amines **36a-f**.

Two possible methods were envisaged for this purpose;

(i) preparation of a chiral crystalline derivative,

(ii) correlation of one or more of the amines to a chiral literature compound of known optical rotation.

4.1 Attempts to Produce Crystalline Derivatives

This was the preferred option to determine the dominant stereochemistry of the **36a-f** and was thought to be accessible at either of two points;

(i) produce a crystalline derivative of one of the ring opened compounds **29a-f**. These already have a defined chiral centre and should allow facile determination of the absolute stereochemistry.

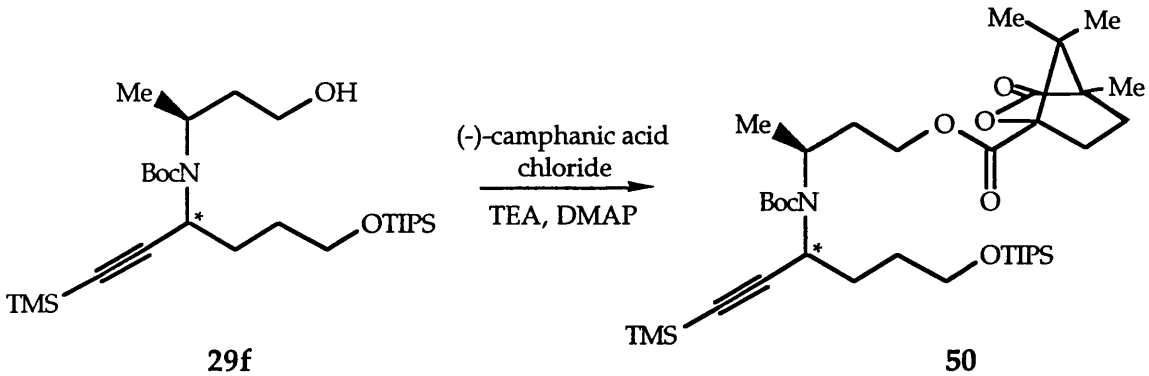
(ii) produce a crystalline derivative of one of **36a-f** with a pre-defined chiral centre,

4.1.1 Synthesis of Crystalline Derivatives of Alcohols 29a-f

It was thought that the synthesis of a bulky ester of one of the ring opened alcohols **29a-f** would lead to a crystalline compound. To this end the (-)-camphanate ester (**50**) of **29f** was synthesised by coupling with (-)-camphanic acid chloride in the presence of Et_3N and DMAP (Figure 77). This unfortunately did not provide a crystalline material. The lack of crystallinity

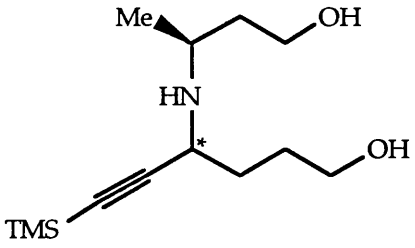
was probably due to the bulky silyl protecting groups and attempts were made to remove these using HF.pyridine complex in THF. This merely led to decomposition of **50**.

Figure 77



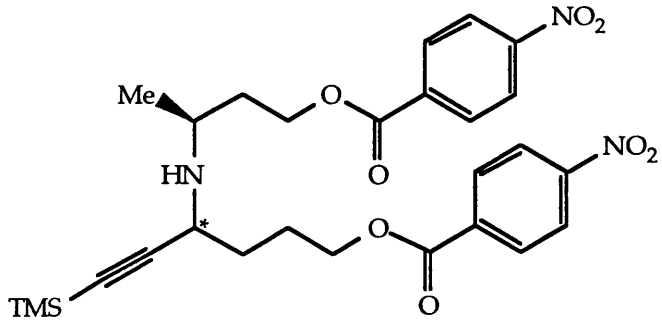
29f **50**

Following the same rationale that the TIPS ether (and possibly the Boc group) were the cause of the crystallinity problem, these groups were removed by treating **29f** with dilute hydrochloric acid. The resulting diol (**51**) was indeed a solid but gave only fine needles of a quality not high enough for diffraction studies. Many attempts were made to produce higher quality crystals but these were unsuccessful.



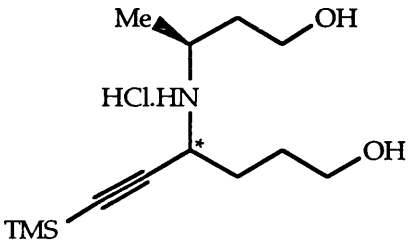
51

Treatment of **51** with p-nitrobenzoyl chloride in pyridine gave **52**, which was shown to be the diester by NMR. This gave a brown solid which failed to produce crystalline material.



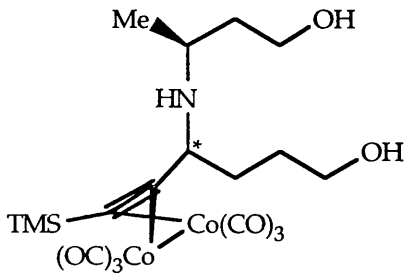
52

Compound **51** was treated with HCl in dry ether to produce the hydrochloride salt **53**. Again fine needles were formed which were of insufficient quality for diffraction.



53

It was suggested that the cobalt (0) carbonyl/acetylene complex of **51** (**54**) might be a more crystalline solid.[94] This complex was synthesised but was, rather surprisingly, found to be an oil.

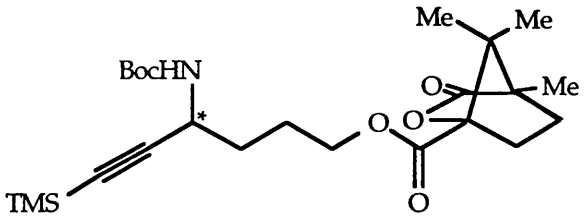


54

Similarly, the $Co(CO)_6$ complex of **29a** was prepared but failed to give crystals of sufficient quality to merit further study.

4.1.2 Synthesis of Chiral Derivatives of Amines 36a-f

This area was not explored in great detail due to constraints in the amount of available material. However the (-)-camphanate ester of **36f** was synthesised (**55**) but did not yield any solid material.



55

4.2 Correlation of Amines 36a-e to Literature Compounds

Due to the lack of success in finding a crystalline derivative it was decided to explore the possibility of correlating one or two of the amines **36a-f** to a known literature compound. Comparison of the optical rotation of the synthetic material with that of the literature compound will then give an indication of which diastereomer was formed preferentially during the ring opening reaction.

This correlation study would also provide an extended use for the methodology by showing its application in synthesis.

The synthetic strategy was split into two parts;

(i) the correlation of the alkyl amines, i.e. **36a-d**,

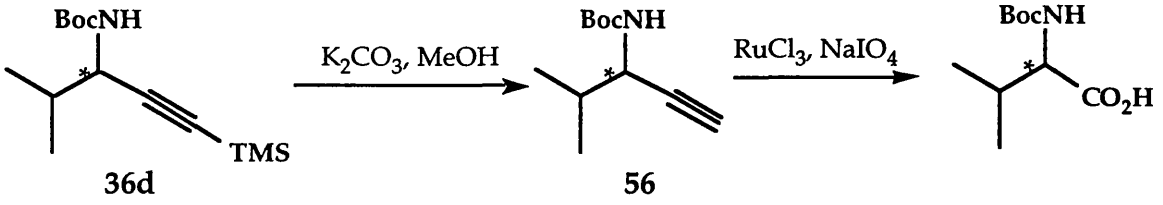
(ii) the correlation of the amino alcohols **36e-f**.

The choice of two different correlation strategies is due to the possibility that a separate mechanism may be in operation for the different type of substrate.

4.2.1 Attempted Correlation of the Amine 36d to (N)-Boc-Valine

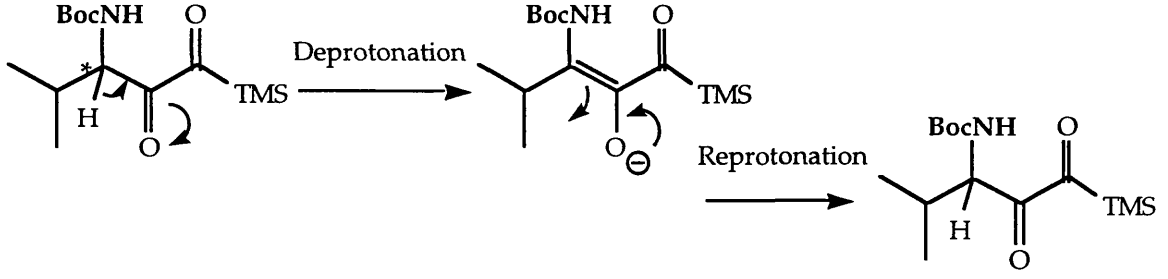
It was decided that the best correlation of one of the alkyl amines would be to a known amino acid derivative due to their wide availability and high stability. To this end a two step scheme was devised for the conversion of **36d** to (N)-Boc-valine. This is shown in Figure 78.

Figure 78



The scheme involves the removal of the TMS group with K_2CO_3 in anhydrous methanol[95] to give **56** then oxidative cleavage of the acetylene with RuO_4[96] to give the required acid. It is possible to cleave TMS protected acetylenes to acids directly[97] but the intermediate diketone is rather long lived (ca. 1 hour) and this could lead to racemisation of the chiral centre (Figure 79).

Figure 79

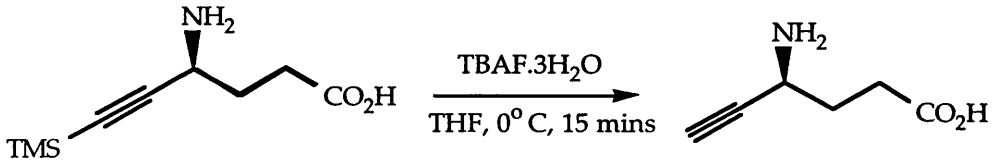


Initially the scheme was shown to work reasonably well, but difficulty ensued when trying to measure the optical rotation of the synthesised Boc-valine. The literature value for this compound is measured in glacial acetic acid. These conditions, in this case at least, proved to give irreproducible

and inaccurate optical data. The strongly acidic conditions caused significant cleavage of the Boc group and some decomposition of the sample.

Another cause for concern was that the strongly basic conditions for the synthesis of **56** could be scrambling the chiral centre so it was decided to carry out this step with TBAF instead. TBAF had been shown previously to affect a similar transformation in the production of GABA-T inhibitors with no sign of racemisation (Figure 80).[98]

Figure 80



In this case, however, significant racemisation was seen to have taken place as the resulting Boc-valine had very little optical rotatory power.[#] This route was discontinued until a reliable synthesis of **56** could be found.

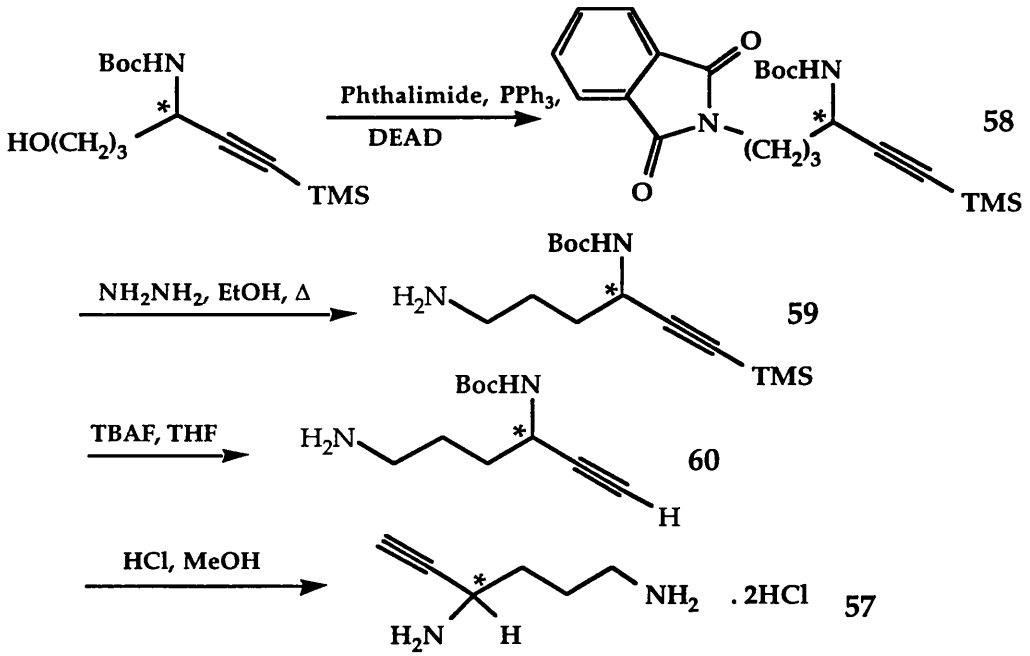
4.2.2 Attempted Correlation of Amino Alcohol 36f to an Inhibitor of Ornithine Decarboxylase

A synthetic sequence whereby **36f** could converted to the ornithine decarboxylase inhibitor **57** (Figure 81) was devised. Both enantiomers of **57** had previously been synthesised by Casara.[99]

This was run concurrently with the valine correlation described above and hence the problems associated with the removal of the TMS group from the acetylene were unknown for most of this time.

[#] The measurement was taken in methanol and compared to that of an authentic sample.

Figure 81



The steps for introduction and deprotection of the second amino group were both facile and reasonably high yielding (*via* Mitsunobu displacement of the alcohol with phthalimide followed by cleavage of the phthalimide group with hydrazine hydrate). However, the removal of the TMS and Boc groups were both very low yielding, giving insufficient quantities of the highly unstable **57** to measure an accurate optical rotation.

Unsurprisingly the value eventually obtained was very low when compared with that of the literature and merely confirmed the, by now apparent, problems with the silyl deprotection.

The route was abandoned due to the problems associated with it and the limited time available to produce the necessary result.

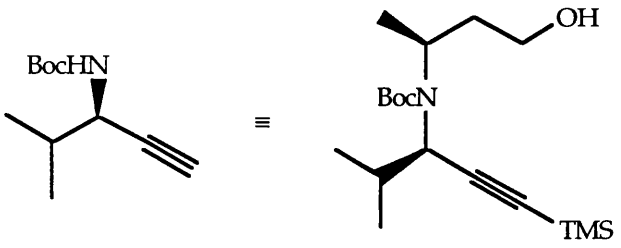
4.2.3 Correlation of 36d to Compound 56

After the disappointing results from the initial attempts at correlation, a literature value for the optical rotation of (*S*)-**56** was found.[2] This value was for the enantiomer derived from natural (*L*)-valine. Further investigation revealed work by Seebach[23] that stated TMS groups could be removed from chiral propargyl amines with concentrated HCl giving no loss of stereochemical integrity.

Heating **36d** to 100°C in 6M HCl for two hours, followed by reprotection with Boc gave **56** in low yield. Although the quantity of **56** obtained was small, there was sufficient material to provide an optical rotation (α_D = 24.00°, c = 0.25; $CHCl_3$, Lit.: α_D = -45.3° (c = 1.04),[2] -57.9° (c = 1.026);[100] both $CHCl_3$).

This indicated that the predominant enantiomer was the (*R*)- form and corresponds to diastereomer (*1R, 1'S*)-**29d** at the ring opened stage (Figure 82).

Figure 82



(*R*)-**56** (1*R*, 1'*S*)-**29d**

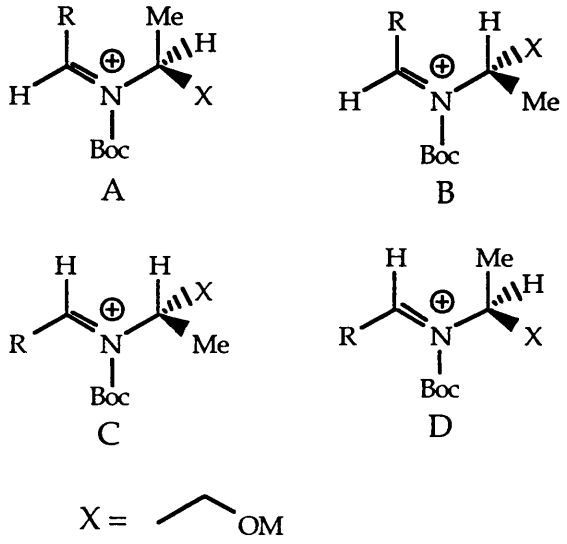
4.3 Mechanism of Ring Opening

As a reliable determination of the major isomer obtained from the ring opening stage has been established it is now valid that a mechanism for this

should be proposed. This is probably best done by considering the transition state of the ring opening reaction (ROR).

If the transition state is considered to exist in an iminium form (as proposed by Pedrosa; see Chapter 2)[51] then clearly 1,3-allylic strain will play a part in deciding the most stable conformation of the reaction intermediate.[101] Using these principles, there are a number of possible conformers; the four most probable are shown in Figure 83.

Figure 83

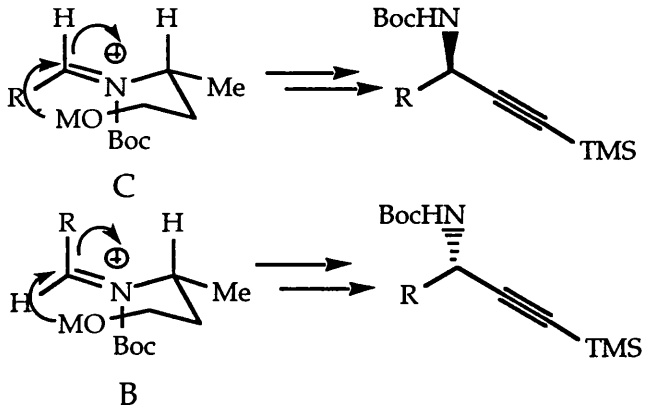


In each pair of conformers, B and C will be the most favoured (due to minimised 1,3-strain), with C likely to have the lowest energy of all.

In addition, as the presence of one equivalent of $BF_3.Et_2O$ is essential for ring opening to occur, it is likely that the reacting species is either an alkynyl boron, e.g. M = $TMSC{\equiv}CBF_2$, or an alkynyl boronate, e.g. M = $TMSC{\equiv}CBF_3^-$ $MgBr^+$. This would therefore lead us to consider some form of chelation mechanism, where the incoming nucleophile would be delivered by the oxygen to the iminium ion.

If this were the case then conformer C would furnish the observed major diastereomer, whilst B would give the minor diastereomer (Figure 84).

Figure 84



The other two conformers, A and D, would also give us the major and minor products respectively, though D is likely to be the most stable of the two, possibly leading to the observed reduction in diastereoselectivity.

A mechanism where $BF_3.Et_2O$ alone is acting as the Lewis acid and then directing the nucleophile by chelation is unlikely due to saturation of borons' co-ordination sphere, making co-ordination by it difficult.

Chapter 5: Experimental

Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification. THF and Et_2O were distilled from sodium/benzophenone. Benzene was distilled from sodium. DCM was distilled from P_2O_5 and stored over 4 Å molecular sieves. DMSO, DMF, TEA and pyridine were distilled from CaH_2 and stored over 4 Å molecular sieves. Methanol and ethanol were distilled from magnesium and iodine. Hexane is described as the fraction boiling between 67 - 70 °C unless otherwise stated. Diazald® is the commercial name for N-methyl-N-nitroso-p-toluenesulphonamide supplied by the Aldrich Chemical company.

CCL was a gift from Biocatalysts Limited. PLE was obtained from Sigma where 1 unit will hydrolyse 10 μmole of ethyl butyrate to ethanol and butyric acid per minute at pH8.0 at 25 °C. *Subtilisin* Carlsberg was obtained from Sigma. PGA-450 is a commercial form of the enzyme penicillin G amidase and was a gift from Boehringer Mannheim (Industrial Division).

NMR spectra were recorded on Varian XL-200, Varian VX-400, Bruker AC 250, Bruker AC 300, Bruker AM 360 and Bruker AMX 500 spectrometers operating at 200, 250, 300, 400 and 500 MHz for ^1H; 100, 75 and 90 MHz for ^{13}C and at 392 and 325.8 MHz for ^{19}F. Chemical shift (δ) values are measured in parts per million relative to the residual (undeuterated) solvent peak as an internal standard for ^1H and ^{13}C and relative to $CFCl_3$ for ^{19}F. J (coupling) values are measured in Hertz. Multiplicities (for ^1H) are

shown as; s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, dd = doublet of doublets, m = complex multiplet, bs = broad singlet, bm = broad multiplet.

Nominal and high resolution mass spectra were taken on VG ZAB-SE spectrometer with sources for FAB and EI^+. Some nominal mass spectra were also measured on a VG Quattro mass spectrometer with sources for EI^+ and APCI. These are indicated in the text.

I.R. spectra were recorded on a Perkin-Elmer 1600 FT-I.R. spectrometer and are for solutions in $CHCl_3$ unless otherwise stated.

Optical rotations of chiral compounds were measured on a JASCO 600 spectrophotometer and an Optical Activity POLAAR 2000 polarimeter using sucrose as a standard. All rotations were taken as solutions in $CHCl_3$ unless otherwise stated. All literature rotations should be assumed to be in $CHCl_3$ unless otherwise stated.

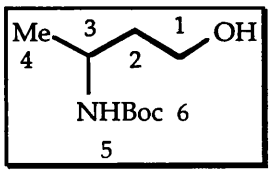
Melting points were taken on an Electrothermal 9100 instrument and are uncorrected.

CHN analysis were carried out on a Perkin Elmer 2400 CHN Elemental Analyzer.

Column chromatography refers to flash chromatography as described by Still[102], and was carried out with distilled solvents. Silica gel was purchased from BDH (particle size 40 -> 63 μm). Aluminium oxide (neutral, Brockman grade 1, 100 - 125 mesh) was purchased from Fluka.

The names of all new compounds are indicated in italics. Literature compound names are given in normal text.

(±)-3-*N*-(*tert*-Butoxycarbonyl)-aminobutan-1-ol (rac-**12**)[103]



(a) Reduction of rac-**13** using $LiAlH_4$

To a suspension of $LiAlH_4$ (1.46 eq.; 30 mmol ; 1.194 g) in dry THF, (50 ml) was added 3-aminobutanoic acid (20.6 mmol; 2.134 g). The mixture was heated under reflux for 2 hours and then allowed to cool, followed by an alkaline quench (NaOH, 0.57 M, 14 ml). The mixture was then made basic (NaOH, 2 M, 20 ml). Water (10 ml) and Boc_2O (1.25 eq.; 25 mmol; 5.450 g) added and mixture was stirred for 24 hours. It was then poured into water (50 ml) and extracted with DCM (3 x 75 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous yellow oil. Column chromatography (silica gel; 1:1 EtOAc : hexane; R_F = 0.25) yielded rac-**12** (2.339 g; 60 %) as a white solid (m.pt.= 44.5 - 45.7 °C) Lit. = 59 - 60°C.

^1H NMR (200 MHz) ($CDCl_3$); δ 1.18 (d, J = 7.2, H-4, 3H), 1.41 (s, H-6, 9H), 1.72-1.79 (m, H-2, 2H), 3.59 (dd, J = 7.2, 3.6, H-1, 2H), 3.73-3.80 (bs, H-3, 1H), 4.52 (bs, H-5, 1H), O*H* missing.

^{13}C NMR (100 MHz) ($CDCl_3$); δ 21.47, 28.32, 40.75, 43.03, 58.92, 79.72, *C*=O missing.

mass spectrum (FAB); m/z 212 (81%), 190 (9%), 134 (100%).

$C_9H_{19}O_3NNa$: requires 212.1263 found 212.1260.

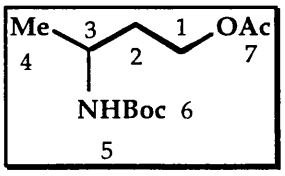
I.R. (nujol mull); υ_{max} (cm^{-1}) 3400, 3175, 1700.

CHN; requires C=57.15, H=10.12, N=7.01; found C=57.14, H=10.23, N=7.15.

(b) Reduction of rac-**13** using $NaBH_4$[67]

To a suspension of 3-aminobutanoic acid (20.6 mmol; 2.134 g) in dry THF (60 ml) was added $NaBH_4$ (2.4 eq.; 49.4 mmol; 1.860 g), followed by a solution of iodine (2.1eq.; 42.8 mmol; 5.43 g) in THF (14.2 ml). The mixture was heated under reflux for 18 hours and then allowed to cool, followed by the dropwise addition of methanol (50 ml). The solvent was removed *in vacuo* and the resultant residue was dissolved in aqueous NaOH (2 M; 20 ml), water (30 ml) and ethanol (5 ml). Boc_2O (1.46 eq.; 30 mmol; 6.540 g) was then added and the mixture stirred for 24 hours. It was then poured into water (50 ml) and extracted with DCM (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous yellow oil. Column chromatography (silica gel; 1:1 EtOAc : hexane; R_F = 0.25) yielded rac-**12** (3.572 g; 95 %) as a white solid (m.pt. = 44.5 - 45.7 °C).
All analytical data were identical to those produced by method (a).

3-N-(tert-*Butoxycarbonyl)-aminobutylethanoate* (**14**)



To a solution of rac-**12** (3.3 mmol; 0.638 g) in dry DCM (15 ml), under N_2 was added acetic anhydride (0.59 ml) and Et_3N (0.92 ml). After two days the

reaction mixture was washed with water (3 x 10 ml) and dried over Na_2SO_4. The solvents were removed *in vacuo* to give a clear oil. Column chromatography (silica gel, 50 % EtOAc in hexane; R_F = 0.5) gave the title compound as a viscous oil (0.736 g; 97 %).

^1H NMR (200 MHz) ($CDCl_3$); δ 1.15 (d, J = 7.2, H-4, 3H), 1.41 (s, H-6, 9H), 1.72-1.79 (q, J = 6.8, H-2, 2H), 2.04 (s, H-7, 3H), 3.73-3.80 (m, H-3, 1H), 4.10 (t, J = 7.0, H-1, 2H), 4.30-4.40 (bs, H-5, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 20.90, 21.16, 28.31, 35.73, 45.71, 61.56, 79.14, 155.16, 171.54.

mass spectrum (FAB); m/z 232 (M+1), 190 (M-Ac).

Attempted enzymatic resolution of **14** to give optically pure **12**

(a) using CCL

14 (0.52 mmol; 0.120 g) was dissolved in 1 : 1 acetone : pH7 buffer[104] (3 ml) and a catalytic amount of CCL was added. After 3 days the mixture was poured into water (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous oil. Column chromatography (silica gel, 50 % EtOAc in hexane, R_F = 0.25) gave **12** as a crystalline solid (0.035 g; 71 % based on 50 % conversion).

$[\alpha]_D$ (c = 17.5 mg ml^{-1}) = + 2.74° (lit. + 10.2° c = 5 mg ml^{-1}).[105]

(b) using PLE

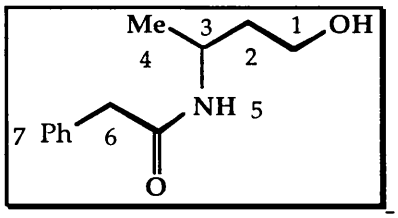
To a solution of **14** (1 mmol; 0.231 g) in THF (0.1 ml) and buffer[104] (pH=7.6; 0.4 ml) was added PLE (10 units; 2.5 µl) and the mixture was stirred for 17 hours. Attempts were made to follow the reaction by normal phase HPLC but this proved inconsistent. The mixture was extracted with DCM (3 x 2 ml) and the organics were dried over Na_2SO_4. The solvent was removed *in vacuo* to give a yellow oil. Column chromatography (silica gel, 50 % EtOAc in hexane) gave **12** (0.179 g) and **14** (0.010 g).

$[\alpha]_D$ (c = 51 mg ml^{-1}) = + 2.88°.

(c) using *Subtilisin* Carlsberg

14 (0.52 mmol; 0.120 g) was dissolved in 1 : 1 acetone : pH7 buffer[104] (3 ml) and a catalytic amount of *Subtilisin* Carlsberg was added. After 3 days the mixture was poured into water (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous oil which was shown to be identical to **14**.

(±)-3-N-(Phenylacetamido)-butan-1-ol (**17**)



To a solution of rac-**12** (5 mmol; 0.945 g) in MeOH (2 ml) at 0 °C was added trifluoroacetic acid (15 ml). After TLC indicated the consumption of rac-**12** (1

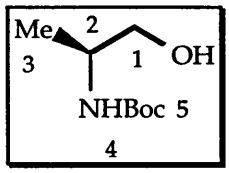
hour), Et_2O was added (50 ml) and the solvents were removed *in vacuo*. The addition of ether/evaporation was repeated twice and the residue was then taken up in $CHCl_3$ (5 ml) and cooled to 0 °C. Pyridine (2 eq.; 10 mmol; 0.8 ml) and then phenylacetyl chloride (1.2 eq.; 6 mmol; 0.8 ml) were added dropwise. The mixture was stirred for 1 hour after which the mixture was poured into saturated $NaHCO_3$ solution (10 ml) and washed with water (5 ml) and brine (5 ml). The organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil. Column chromatography (silica gel, 50 % EtOAc in hexane, R_F = 0.25) gave **17** as a clear oil (0.404 g, 39 %).

^1H NMR (200 MHz) ($CDCl_3$); δ 1.05 (d, J = 6.5, H-4, 3H), 1.55-1.82 (m, H-2, 2H), 3.52 (d, J = 8.2, H-6, 2H), 4.97-5.23 (m, H-1,-3, 4H), 5.45-5.53 (bs, H-5, 1H), 7.23-7.41 (m, H-7, 5H), O*H* missing.

Attempted resolution of **17** with PGA-450 to give optically pure 3-amino butan-1-ol

To a solution of **17** (0.5 mmol; 0.104 g) in methanol (2 ml) and buffer[104] (pH7.6; 6.6 ml) was added PGA-450 (10 units; 0.075 g). The mixture was stirred at 30 °C for 17 hours after which the enzyme was filtered and washed with methanol (5 ml). The solvents were removed *in vacuo* to give only rac-3-amino butan-1-ol (0.04 g).

2-(*S*)-*N*-(*tert*-Butoxycarbonyl)-alaninol (**18**)[66]

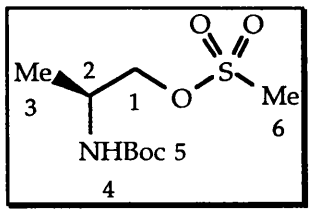


To a suspension of (*S*)-alanine (100 mmol; 8.91 g) in dry THF (250 ml), was added $NaBH_4$ (2.45 eq.; 245 mmol; 9.3 g), followed by a solution of iodine (2 eq.; 200mmol; 25.3 g) in THF (75 ml). The mixture was heated under reflux for 18 hours and then allowed to cool, followed by a methanol quench (100 ml). The solvent was removed *in vacuo* and the resultant residue was dissolved in aqueous NaOH (2 M : 100 ml), water (50 ml) and THF (50 ml). Boc_2O (1 eq.; 100 mmol; 21.8 g) was then added and the mixture stirred for 24 hours. It was then poured into water (100 ml) and extracted with DCM (3 x 200 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give **18** as a white solid (15.15 g, 87 %) (m. pt. = 57 - 58°C, Lit. = 59 - 60°C).

^1H NMR (200 MHz) ($CDCl_3$); δ 1.14 (d, J = 7.1, H-3, 3H), 1.42 (s, H-5, 9H), 3.50 (dd, J = 11.5, 4.5, H-1, 2H), 3.67-3.83 (m, H-2, 1H), 4.55 (bs, H-4, 1H).

The analytical data were identical to the literature.

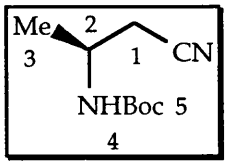
2-(*S*)-*N*-(*tert*-Butoxycarbonyl)-1-(*O*)-(methane sulfonyl)-alaninol (**19**)[66]



To a solution of **18** (87 mmol; 15.15 g) in DCM (150 ml) was added TEA (3eq.; 261 mmol; 36.4 ml) at 0 °C. Mesyl chloride (2 eq.; 174 mmol; 13.5 ml) was added over 10 minutes and the mixture was stirred for 1 hour, during which time a yellow precipitate was seen to form. The mixture was poured into saturated NH_4Cl solution (200 ml) and washed with saturated $NaHCO_3$ solution (200 ml). The solvents were removed *in vacuo* to give **19** as a yellow-orange solid which was used without further purification (21.8 g, 99 %).

^1H NMR (200 MHz) ($CDCl_3$); δ 1.21 (d, J = 7.2, H-3, 3H), 1.43 (s, H-5, 9H), 3.02 (s, H-6, 3H), 3.92-4.05 (bs, H-2, 1H), 4.15 (d, J = 7.0, H-2, 2H), 4.55 (bs, H-4, 1H). The analytical data were identical to the literature.

2-(*S*)-*N*-(*tert*-Butoxycarbonyl)-aminopropionitrile (**20**)[66]



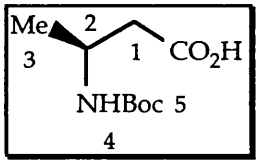
NaCN (7.5 eq.; 650 mmol; 31.98 g) was suspended in a solution of **19** (87 mmol; 21.8 g) in DMF (200 ml), under mechanical stirring. This was heated to 55 °C for 75 minutes. The mixture was cooled to room temperature and

diluted with Et_2O (150 ml). The resultant slurry was filtered under suction through an alumina plug, which was washed with Et_2O (700 ml). The solvents were removed *in vacuo* to give a viscous oil (13.87 g). Column chromatography (silica gel; 30 % EtOAc in hexane) gave a solid (10 g), which was recrystallised from an ether/hexane mixture to give **20** as a white solid (6 g; 38 %) (m. pt. = 67 - 68°C, Lit. = 67 - 69°C).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.30 (d, J = 7.2, H-3, 3H), 1.43 (s, H-5, 9H), 2.54 (d, J = 7.0, H-1, 2H), 3.92-4.05 (bs, H-2, 1H), 4.55 (bs, H-4, 1H).

The analytical data were identical to the literature.

3-(*S*)-*N*-(*tert*-Butoxycarbonyl)-aminobutyric acid (**13**)[106]

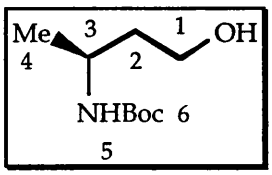


Nitrile **20** (32 mmol; 6 g) was dissolved in concentrated HCl (50 ml) and heated at reflux for 5 hours. The solution was made basic with NaOH solution (5 M; 120 ml) and the water was removed *in vacuo*. The residue was dissolved in NaOH solution (2 M; 30 ml), water (15 ml) and ^{t}BuOH (5 ml). Boc_2O (1.5 eq.; 48 mmol; 10.46 g) was added and the mixture was stirred overnight. The solution was then cooled to 0 °C and acidified with HCl solution to ca. pH=5. The mixture was extracted with $CHCl_3$ (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give the title compound as a white solid (2.01 g; 32 %) (m. pt. = 70 - 71°C, Lit. 76 - 78°C).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.24 (d, J = 6.8, H-3, 3H), 1.43 (s, H-5, 9H), 2.55 (t, J = 5.1, H-1, 2H), 4.05 (bs, H-2, 1H), 4.93 (bs, H-4, 1H), CO_2H missing.

The analytical data were identical to the literature.

3-(*S*)-*N*-(*tert*-Butoxycarbonyl)-aminobutan-1-ol (**12**)[106]

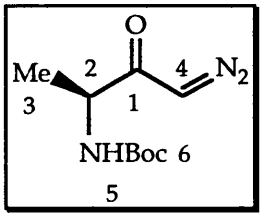


To a solution of acid (10 mmol; 2.01g) in THF (30 ml) at 0 °C was added TEA (1 eq.; 10 mmol; 1.39 ml) and isobutyl chloroformate (1.1 eq.; 11 mmol; 1.42 ml) dropwise. The mixture was stirred for 1 hour and the cold solution was filtered into an ice cooled flask with the solid being washed with dry THF (20 ml). The filtered solution was then added slowly, by cannula, to an ice cooled solution of $NaBH_4$ (3 eq.; 30 mmol; 1.13 g) in water (5 ml). the mixture was stirred for 1 hour and was then concentrated *in vacuo*. EtOAc (15 ml) was added and then organics were washed with saturated $NaHCO_3$ solution (10 ml), brine (10 ml) and then dried over Na_2SO_4. The solvent was removed *in vacuo* to give **12** as a white crystalline solid (1.137 g; 60 %).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.18 (d, J = 7.20, H-4, 3H), 1.41 (s, H-6, 9H), 1.72-1.79 (m, H-2, 2H), 3.59 (dd, J = 7.2, 3.6, H-1, 2H), 3.73-3.80 (bs, H-3, 1H), 4.52 (bs, H-5, 1H), O*H* missing.

The analytical data were identical to the literature.

2-(*S*)-*N*-(tert-Butoxycarbonyl)-amino-4-diazomethylpropanone (**21**)[107]



The following procedure was modified from the literature.[108]

To a solution of (*S*)-*N*-(Boc) alanine (10 mmol; 1.87 g) in THF (30 ml) at 0°C, was added TEA (1 eq.; 10 mmol; 1.39 ml) and isobutyl chloroformate (1 eq.; 10 mmol; 1.29 ml) dropwise. The white suspension was left to stir for 30 minutes. Diazomethane (2 eq.; 20 mmol; 0.84 g) was generated and added in the manner described in Chapter 2 by adding ethanolic KOH solution (3.6 g in ethanol (95 %; 8.5 ml)) to Diazald® (mmol; 6.42 g) in ethanol (99 %, 40 ml) dropwise over 10 minutes. The resulting yellow suspension was stirred for a further 3 hours allowing it to come to room temperature. The solution was concentrated *in vacuo* and then diluted with Et_2O (20 ml). The ethereal mixture was washed with water (20 ml), $NaHCO_3$ solution (20 ml) and brine (20 ml). The organics were then dried over Na_2SO_4 and the solvent was removed *in vacuo* to give the crude product as a yellow solid. This was recrystallised from hexane/ethyl acetate to give **21** as a yellow crystalline solid (1.92 g; 91 %) (m. pt. = 96.5 - 98 °C).

^1H NMR (360 MHz) ($CDCl_3$); δ 1.32 (d, J = 7.2, H-3, 3H), 1.43 (s, H-6, 9H), 4.11-4.32 (m, H-2, 1H), 5.05 (bs, H-5, 1H), 5.40 (bs, H-4, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 18.31, 28.25, 53.17, 79.88, 155.10, 194.41, $CH=N_2$ missing.

mass spectrum (FAB); m/z 236 (45%), 214 (74%), 158 (100%).

$C_9H_{16}N_3O_3$ requires 214.1192, found 214.1180.

I.R.; υ_{max} (cm^{-1}) 3148, 2974, 2246, 1707, 1641.

$[\alpha]_D$ (c = 9.55 mg ml^{-1}) = - 71.73°.

3-(*S*)-*N*-(*tert*-Butoxycarbonyl)-aminobutyric acid(**13**)[107]

Procedure (a)[54]

Ag_2O (0.4 eq.; 0.8 mmol; 0.2 g), Na_2CO_3 (0.45 eq.; 0.9 mmol; 0.2 g) and $Na_2S_2O_3$ (0.4 eq.; 0.8 mmol; 0.2 g) was dissolved in water (20 ml) and heated to 80 °C. **21** (2 mmol; 0.440 g) in dioxane (10 ml) was added at a rate sufficient to maintain a constant temperature. During this time further Ag_2O (3 x 0.1 g) was added. After all nitrogen evolution had ceased (ca. 20 minutes). the mixture was left to stir for 30 minutes after which it was diluted with water (10 ml), filtered, cooled to O °C and extracted with Et_2O (40 ml). The aqueous layer was again cooled in ice, acidified with ice cold HCl solution (1 M; ca. pH = 4) and then extracted with EtOAc (3 x 25 ml). The organics were then dried over Na_2SO_4 and the solvent was removed *in vacuo* to give the title compound as a white solid (0.338 g; 84 %) (m. pt. = 70 - 71 °C).

^1H NMR (360 MHz) ($CDCl_3$); δ 1.24 (d, J = 6.8, 3H), 1.43 (s, 9H), 2.55 (t, J = 5.1, 2H), 4.05 (bs, 1H), 4.93 (bs, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 20.30, 28.24, 40.52, 79.49, 155.15, 176.53.

mass spectrum (FAB), m/z 226 (M+Na), 204 (M+1), 104 (M-Boc).

$C_9H_{17}NO_4Na$ requires 226.1055, found 226.2050.

I.R.($CHCl_3$); υ_{max} (cm^{-1}) 3610, 3435, 3015, 1812, 1707.

$[\alpha]_D$ (c = 20.0 mg ml^{-1}) = -12.70°.

CHN; requires C = 53.19, H = 8.43, N = 6.89; found C = 53.23, H = 8.42, N = 6.85.

Procedure (b)[109]

21 (15 mmol; 3.15 g) was dissolved in THF : water solution (1:1; 150 ml) and AgOAc (0.4 eq.; 6 mmol; 1 g) was added. Nitrogen was given off and the mixture turned black. After 1 hour saturated $NaHCO_3$ solution was added (50 ml) and the mixture was extracted with Et_2O (100 ml). The aqueous layer was cooled to 0 °C, acidified with HCl (1 M; ca. pH = 4) and extracted with $CHCl_3$ (3 x 100 ml). The organics were then dried over Na_2SO_4 and the solvent was removed *in vacuo* to give the title compound as a white solid (2.306 g; 88 %).

The analytical data were identical to the literature and to those obtained from procedure (a).

3-(*S*)-*N*-(*tert*-Butoxycarbonyl)-aminobutan-1-ol (**12**)

13 was reduced to **12** by conversion to its mixed anhydride with isobutyl chloroformate followed by reduction with sodium borohydride as detailed above (95 %). The optical purity of the **12** was found to be greater than 99 % by HPLC of its *O*-(*S*)-Moshers ester (silica column, 10 % ethyl acetate in

hexane, RT = 7.15 minutes (100 %), (*S*)-Moshers ester of rac-**12**, RT_1 = 6.64 minutes (52 %), RT_2 = 7.16 minutes (48 %), 260 nm).

^1H NMR (360 MHz) ($CDCl_3$); δ 1.18 (d, J = 7.2, 3H), 1.21-1.37 (m, 2H), 1.41 (s, 9H), 1.72-1.79 (m, 2H), 3.59 (dd, J = 7.2, 3.6, 2H), 3.73-3.80 (bs, 1H), 4.52 (bs, 1H), O*H* missing.

^{13}C NMR (90 MHz) ($CDCl_3$); δ 21.47, 28.32, 40.75, 43.03, 58.92, 79.72, *C*=O missing.

mass spectrum (FAB); m/z 212 (81%), 190 (9%), 134 (100%).

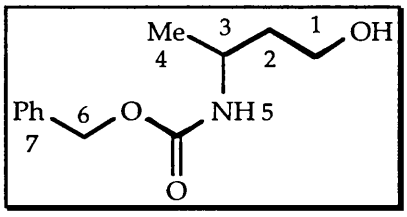
$C_9H_{19}O_3NNa$: requires 212.1263 found 212.1260.

I.R. (nujol mull); υ_{max} (cm^{-1}) 3400, 3175, 1700.

$[\alpha]_D$ (c=17mg ml^{-1}) = + 9.00°.

CHN; requires C=57.15, H=10.12, N=7.01; found C=57.17, H=10.35, N=7.23.

(±)-3-*N*-(Benzyloxycarbonyl)amino butan-1-ol (**22**)[66]



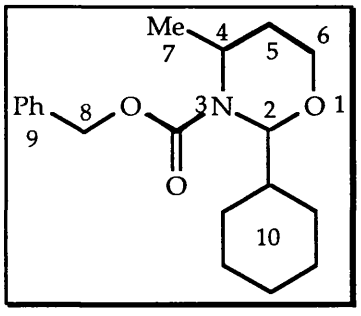
To a suspension of 3-amino butanoic acid (5 mmol; 0.533 g) in dry THF (10 ml), $NaBH_4$ (2.5 eq.; 12.5 mmol; 0.465 g) was added, followed by a solution of iodine (2.1 eq.; 10.5 mmol; 1.357 g) in THF (5 ml). The mixture was heated under reflux for 18 hours and then allowed to cool, followed by a methanol quench (20 ml). The solvent was removed *in vacuo* and the resultant

residue was dissolved in aqueous NaOH (2 M; 10 ml) and THF (5 ml). The mixture was cooled to 0 °C and benzyl chloroformate (1.3 eq.; 6.5 mmol; 1.11 g) was added over 30 minutes whilst the pH was kept at ~10. After a further 30 minutes the mixture was neutralised and extracted with EtOAc (3 x 60 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous brown oil. Column chromatography (silica gel; 1:1 EtOAc : hexane; R_F = 0.25) yielded a viscous clear oil which crystallised on standing (0.574 g; 52 %).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.22 (d, J = 6.6, H-4, 3H), 1.36-1.43 (m, H-2, 1H), 1.79-1.86 (m, H-2, 1H), 3.03 (dd, J = 11.2, 5.8, O-**H**, 1H), 3.64 (t, J = 7.0, H-1, 2H), 3.94-3.98 (m, H-3, 1H), 4.71 (bs, H-5, 1H), 5.11 (s, H-6, 2H), 7.31-7.40 (m, H-7, 5H).

The analytical data obtained were identical to the literature.

N-(Benzyloxycarbonyl)-2(*S* *)-cyclohexyl-4(*S* *)-methyl-1,3-tetrahydrooxazine (**23**)[66]



22 (2.05 mmol; 0.46 g), cyclohexanecarboxaldehyde (1 eq.; 2.05 mmol; 0.25 ml) and a trace of pTsOH were heated in dry benzene (10 ml) under reflux for 1 hour. The mixture was poured into $NaHCO_3$ (30 ml) and extracted with

EtOAc (3 x 25 ml) The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a pale yellow oil. Column chromatography (silica gel, 15 % EtOAc in hexane; R_F = 0.28) gave **23** as a clear viscous oil (0.303 g; 50 %)

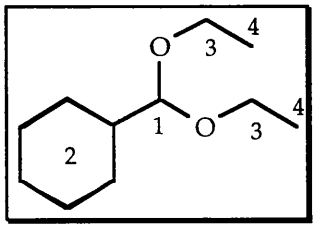
^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.31 (d, J = 7.2, H-7, 3H), 1.50-1.82 (m, H-10, 11H), 1.92-2.13 (m, H-5, 2H), 3.61(m, J = 11.9, 4.3, H-6, 1H), 3.91 (m, J = 11.2, 3.24, H-6, 1H), 4.42 (m, J = 7.20, 3.00, H-4, 1H), 5.12 (s, H-8, 2H), 5.23 (d, J = 10.80, H-2, 1H), 7.30-7.40 (m, H-9, 5H).

All other data were identical to the literature.

General procedure for the synthesis of diethyl acetals (**24a-f**)

To a stirred solution of aldehyde (10 mmol) in dry Et_2O (20 ml) was added $MgSO_4$, pTsOH (cat.) and dry ethanol (4 eq.; 40 mmol; 3.4 ml). The solution stirred overnight, filtered (the filtrate being washed with Et_2O (3 x 10 ml)) and then poured into saturated aqueous $NaHCO_3$ solution (30 ml). The organic layer was washed with water (3 x 30 ml) and dried over Na_2SO_4. The solvents were removed *in vacuo* to give the required acetal.

Cyclohexanecarboxaldehyde diethyl acetal (**24a**)[110]

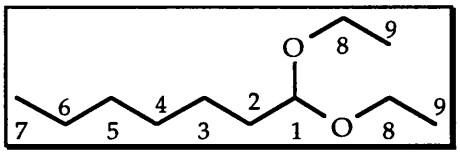


Yield = 71 % (clear oil).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.20 (t, J = 7.0, H-4, 6H), 1.35-1.80 (m, H-2, 11H), 3.42-3.74 (m, H-3, 4H), 4.12 (d, J = 7.2, H-1, 1H).

The analytical data were identical to the literature.

Heptaldehyde diethyl acetal (**24b**)[111]

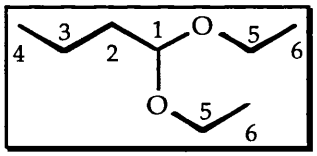


yield = 67 % (clear oil).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.88 (t, J = 6.8, H-7, 3H), 1.20 (t, J = 7.0, H-9, 6H), 1.30 (m, H-3,-4,-5,-6, 8H), 1.59 (m, H-2, 2H), 3.43-3.71 (m, H-8, 4H), 4.48 (t, J = 5.8, H-1, 1H).

The analytical data were identical to the literature.

Butyraldehyde diethyl acetal (**24c**)[112]



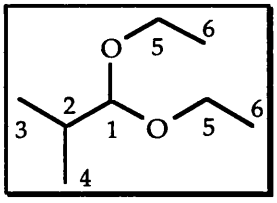
The procedure used was identical to the general procedure except that the solvents were removed by fractional distillation due to the volatility of the product.

yield = 66 % (clear oil).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.93 (t, J = 7.2, H-4, 3H), 1.20 (t, J = 7.0, H-6, 6H), 1.31-1.46 (m, H-3, 2H), 1.55-1.64 (m, H-2, 2H), 3.43-3.70 (m, H-5, 4H), 4.49 (t, J = 5.0, H-1, 1H).

The analytical data were identical to the literature.

^{iso}Butyraldehyde diethyl acetal (**24d**)[113]

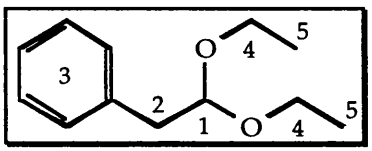


yield = 71 % (clear oil).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.93 (d, J = 6.7, H-3,-4, 6H), 1.22 (t, J = 7.0, H-6, 6H), 1.89 (sep, J = 6.7, H-2, 1H), 3.46-3.74 (m, H-5, 4H), 4.11 (d, J = 6.8, H-1, 1H).

The analytical data were identical to the literature.

Phenylacetaldehyde diethyl acetal (**24g**)[114]

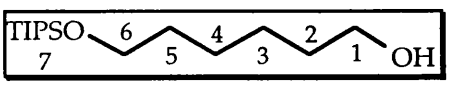


yield = 86 % (clear oil.)

^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.17 (t, J = 7.0, H-5, 6H), 2.92 (d, J = 5.8, H-2, 2H), 3.38-3.73 (m, H-4, 4H), 4.64 (t, J = 5.8, H-1, 1H), 7.21-7.40 (m, H-3, 5H).

The analytical data were identical to the literature.

6-(Triisopropylsilyloxy)hexan-1-ol



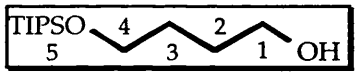
To a solution of hexan-1,6-diol (18.3 mmol; 2.16 g) in THF (33 ml) was added NaH (18.3 mmol; 0.729 g). After 1 hour triisopropylchlorosilane (18.3 mmol;

3.9 ml) was added and the mixture was stirred for a further hour. The mixture was poured into Et_2O (30 ml) and washed with washed with $NaHCO_3$ solution (30 ml) and brine (30 ml). The organics were then dried over Na_2SO_4 and the solvent was removed *in vacuo* to give a clear oil. Column chromatography (silica gel; 20 % EtOAc in hexane; R_F = 0.24) gave the title compound as a clear viscous oil (1.98 g; 42 %).

^1H NMR (300 MHz) ($CDCl_3$); δ 1.04 (s, H-7, 21H), 1.34-1.42 (m, H-3,-4, 4H), 1.51-1.62 (m, H-2,-5, 4H), 3.64 (q, J = 7.2, H-1,-6, 4H).

mass spectrum ($APCI^+$); m/z 275 (M+1).

4-(Triisopropylsilyloxy)butan-1-ol[115]



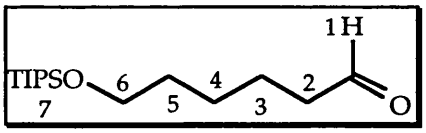
The above procedure was applied to butan-1,4-diol to give the title compound.

Yield = 88 % (clear viscous oil).

^1H NMR (300 MHz) ($CDCl_3$); δ 1.13 (s, H-5, 21H); 1.70-1.81 (m, H-2,-3, 4H); 3.72 (t, J = 5.8, H-4, 2H); 3.81 (t, J = 5.5, H-1, 2H).

The analytical data were identical to the literature.

6-(Triisopropylsilyloxy)hexanal

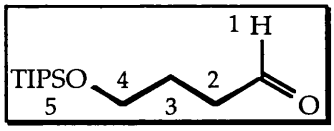


To a solution of 6-triisopropylsilyloxyhexan-1-ol (1.94 mmol; 0.5 g) in THF (1.5 ml), DMSO (13 ml) and TEA (1.94 ml) were added. SO_3.pyridine complex (5.82 mmol; 0.77 g) was added over 10 minutes. The reaction was stirred for 45 minutes after which it was cooled to 0 °C, acidified with HCl (1 M; ca. pH = 4) and extracted with EtOAc : hexane (1: 1; 3 x 20 ml). The organics were washed with water (40 ml) and dried over Na_2SO_4. The solvents were removed *in vacuo* to give a clear oil. Column chromatography (alumina; 15 % EtOAc in hexane; R_F = 0.6) gave the title compound as a clear viscous oil (0.454 g; 91 %).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.04 (s, H-7, 21H), 1.31-1.62 (m, H-3,-4,-5, 6H), 2.44 (m, J = 7.2, 1.8, H-2, 2H), 3.68 (t, J = 6.2, H-6, 2H), 9.76 (t, J = 1.8, H-1, 1H).

mass spectrum ($APCI^+$); m/z 273 (M+1).

4-(Triisopropylsilyloxy)butanal[115]



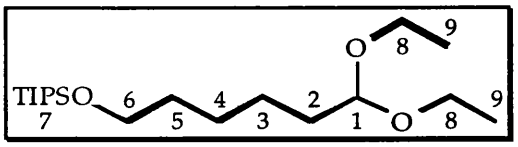
The above procedure was applied to 4-triisopropylsilyloxybutan-1-ol to give the title compound.

Yield = 100 % (clear viscous oil).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.04 (s, H-5, 21H); 1.88 (pent., J = 7.0, H-3, 2H); 2.55 (m, J = 7.2, 1.8, H-2, 2H); 3.74 (t, J = 6.0, H-4, 2H); 9.81 (t, J = 1.7, H-1, 1H).

The analytical data were identical to the literature.

6-(Triisopropylsilyloxy)hexanal diethyl acetal (**24e**)



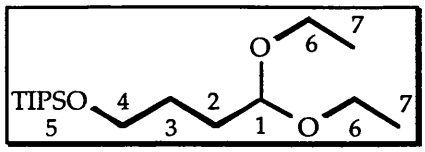
To a solution of 6-triisopropylsilyloxyhexanal (1.5 mmol; 0.385 g) in dry ethanol (30 ml) was added a trace amount of PPTS. The mixture was heated under Dean-Stark conditions for 1 hour. The solution was then cooled and poured into saturated $NaHCO_3$ solution (20 ml) and then concentrated *in vacuo*. The residue was taken up in water and extracted with DCM (2 x 30 ml). The organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give the title compound as a clear oil (0.264 g; 53 %) (b. pt. = 42°C @ 10 mm Hg).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.07 (s, H-7, 21H), 1.22 (t, J = 7.1, H-9, 6H), 1.36-1.42 (m, H-3,-4, 4H), 1.55-1.65 (m, H-2,-5, 4H), 3.45-3.56 (m, H-8, 2H), 3.60-3.79 (m, H-6,-8, 4H), 4.45 (t, J = 5.8, H-1, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 11.94, 15.25, 17.93, 24.53, 25.66, 32.88, 33.58, 60.77, 63.26, 102.86.

mass spectrum (ES^+); m/z 301 (M-OEt, 80%), 273 (M-73, 100%).

4-(Triisopropylsilyloxy)butanal diethyl acetal (**24f**)



The above procedure was applied to 4-triisopropylsilyloxybutanal to give the title compound.

Yield = 72 % (clear oil).

B. pt. = 69 °C @ 7 mm Hg.

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.05 (s, H-5, 21H); 1.20 (t, J = 7.1, H-7, 6H); 1.57-1.62 (m, H-3, 2H); 1.66-1.80 (m, H-2, 2H), 3.44-3.52 (m, H-6, 2H); 3.60-3.66 (m, H-6, 2H); 3.69 (t, J = 6.2, H-4, 2H), 4.51 (t, J = 5.8, H-1, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 11.92, 15.25, 17.93, 28.15, 29.92, 60.75, 63.03, 102.81.

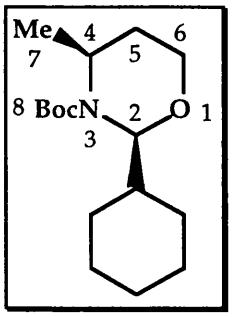
mass spectrum ($APCI^+$); m/z 318 (M), 317 (M-1), 316 (M-2).

General procedure for the synthesis of N-(*tert*-butoxycarbonyl)-2-(*S*)-alkyl-4-(*S*)-methyl-1,3-tetrahydrooxazines (**25a-f**)

12 (1.247 g : 6.6 mmol), diethyl acetal (**24a-f**) (1 equivalent) and a trace of PPTS were heated in dry benzene (50 ml) under reflux for 2 hours. The mixture was cooled to room temperature, washed with $NaHCO_3$ (50 ml), water (2 x 20 ml) and brine (20 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a pale yellow oil. Column chromatography gave the required compound (for the eluent and stationary phase, see the R_F value for each compound).

N-(tert-*Butoxycarbonyl)-2-(S)-cyclohexyl-4-(S)-methyl-1,3-tetrahydrooxazine*

(25a)



yield = 76 % (white crystalline solid).

R_F = 0.50 (silica gel, 20 % EtOAc in hexane).

M.pt. = 47.1 - 48.5 °C.

^{1}H NMR (360 MHz) ($CDCl_3$); δ 1.31 (d, J = 7.2, H-8, 3H), 1.45 (s, H-9, 9H), 1.50-1.82 (m, cyhex, 11H), 1.92-2.13 (m, H-5, 2H), 3.61 (m, H-6, 1H), 3.91 (m, H-6, 1H), 4.42 (m, H-4, 1H), 5.18 (d, J = 10.8, H-2, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 20.78, 25.82, 26.25, 28.29, 28.36, 29.63, 40.90, 43.83, 56.20, 79.67, 85.43, 154.29.

mass spectrum (FAB); m/z 284 (22%), 200 (21%), 184 (100%).

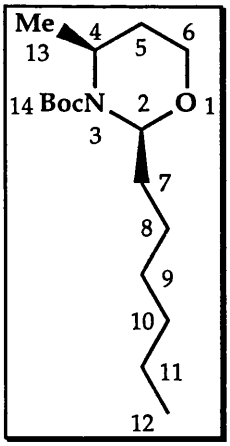
$C_{16}H_{30}NO_3$ requires 284.2226 found 284.2220.

I.R.; υ_{max} (cm^{-1}) 2985, 1695, 1177.

$[\alpha]_D$ (c = 45 mg ml^{-1}) = + 2.71°.

CHN requires C=68.05, H=9.99, N=4.96; found C=67.76, H=10.23, N=4.98.

N-(tert-*Butoxycarbonyl*)-2-(S)-*hexyl*-4-(S)-*methyl*-*tetrahydro*-1,3-*oxazine* (**25b**)



Yield = 83 % (viscous oil).

R_F = 0.48 (alumina, 10 % EtOAc in hexane).

^{1}H NMR (360 MHz) ($CDCl_3$); δ 0.87 (t, J = 6.9, H-12, 3H), 1.28 (d, J = 7.0, H-13, 3H), 1.30-1.38 (m, H-8,-9,-10,-11, 8H), 1.44 (s, H-14, 9H), 1.62-1.70 (m, H-7, 2H), 1.82-1.92 (m, H-5, 1H), 2.00-2.13 (m, H-5, 1H), 3.58 (m, H-6, 1H), 3.92 (m, H-6, 1H), 4.35 (m, H-4, 1H), 5.34 (dd, J = 9.0, 4.7, H-2, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 13.93, 21.49, 22.52, 25.68, 28.41, 28.91, 29.46, 31.76, 33.76, 43.58, 56.37, 79.62, 82.75, 153.59.

mass spectrum (FAB); m/z 286 (21%), 200 (20%), 186 (100%).

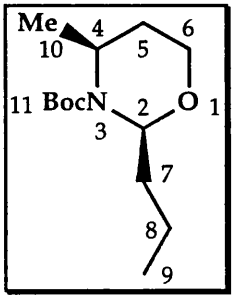
$C_{16}H_{32}NO_3$ requires 286.2382, found 286.2370.

I.R.; υ_{max} (cm^{-1}) 2929, 2865, 1695, 1177.

$[\alpha]_D$ (c = 15.4 mg ml^{-1}) = + 7.53°.

N-(tert-*Butoxycarbonyl)-2-(S)-propyl-4-(S)-methyl-1,3-tetrahydrooxazine*

(25c)



Yield = 69 % (viscous oil).

R_F = 0.48 (alumina, 10 % EtOAc in hexane).

^1H NMR (360 MHz) ($CDCl_3$); δ 0.95 (t, J = 7.2, H-9, 3H), 1.28 (d, J = 6.8, H-10, 3H), 1.32-1.41 (m, H-8, 2H), 1.46 (s, H-11, 9H), 1.58-1.68 (m, H-7, 2H), 1.85-1.92 (m, H-5, 1H), 2.00-2.08 (m, H-5, 1H), 3.58 (m, H-6, 1H), 3.92 (m, H-6, 1H), 4.35 (m, H-4, 1H), 5.36 (dd, J = 9.0, 4.3, H-2, 1H).

^{13}C NMR (90 MHz) ($CDCl_3$); δ 13.77, 18.96, 21.52, 28.45, 29.50, 35.99, 43.62, 56.40, 79.68, 82.52, 153.63.

mass spectrum (FAB); m/z 244 (15%), 144 (100%).

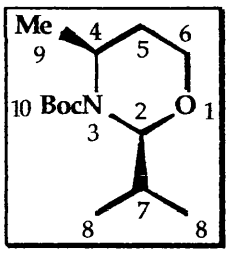
$C_{13}H_{25}NO_3$ requires 244.1913 found 244.1920.

I.R.; υ_{max} (cm^{-1}) 2966, 2873, 1695, 1177.

$[\alpha]_D$ (c = 100 mg ml^{-1}) = + 7.77°.

N-(tert-Butoxycarbonyl)-2-(S)-isopropyl-4-(S)-methyl-1,3-tetrahydrooxazine

(25d)



Yield = 55 % (viscous oil).

R_F = 0.35 (alumina, 10 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.90 (d, J = 6.7, H-8, 3H), 1.00 (d, J = 6.5, H-8, 3H), 1.32 (d, J = 7.0, H-9, 3H), 1.48 (s, H-10, 9H), 1.60-1.62 (m, H-7, 1H), 2.03-2.12 (m, H-5, 1H), 2.29-2.39 (m, H-5, 1H), 3.62 (m, H-6, 1H), 3.93 (m, H-6, 1H), 4.45 (m, H-4, 1H), 5.11 (d, J = 10.2, H-2, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 18.45, 19.20, 20.75, 28.28, 29.50, 31.26, 43.76, 56.10, 79.69, 86.11, *C*=O missing.

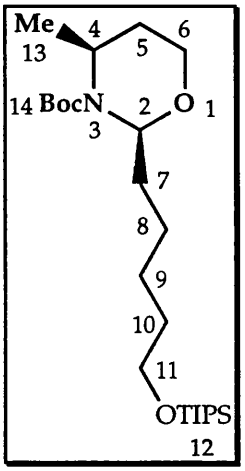
mass spectrum (FAB); m/z 244 (9%), 144 (15%), 116 (100%).

$C_{13}H_{26}NO_3$ requires 244.1913, found 244.1900.

I.R.; υ_{max} (cm^{-1}) 2972, 2874, 1694, 1176.

$[\alpha]_D$ (c = 6.85 mg ml^{-1}) = + 31.82°.

N-(tert-Butoxycarbonyl)-2-(S)-(11-triisopropyloxy)pentyl-4-(S)-methyl-tetrahydro-1,3-oxazine (**25e**)



Yield = 63 % (viscous oil).

R_F = 0.52 (alumina, 10 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.04 (s, H-12, 21H), 1.24 (d, J = 7.2, H-13, 3H), 1.35-1.43 (m, H-8,-9, 4H), 1.42 (s, H-14, 9H), 1.52-1.57 (m, H-10, 2H), 1.62-1.70 (m, H-7, 2H), 1.86-1.95 (m, H-5, 1H), 2.01-2.16 (m, H-5, 1H), 3.60 (m, H-6, 1H), 3.64 (t, J = 6.5, H-11, 2H), 3.91 (m, H-6, 1H), 4.31 (m, H-4, 1H), 5.34 (dd, J = 9.0, 4.3, H-2, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 11.96, 17.99, 21.49, 25.50, 25.62, 28.42, 29.43, 32.97, 33.90, 43.57, 56.36, 63.26, 82.74, 153.59, $SiCH(CH_3)_2$ missing.

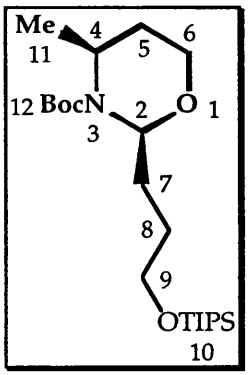
mass spectrum (FAB); m/z 444 (4%), 344 (100%).

$C_{24}H_{50}NO_4Si$ requires 444.3509 found 444.3500.

I.R.; υ_{max} (cm^{-1}) 2939, 2866, 1695, 1176, 1105.

$[\alpha]_D$ (c = 76 mg ml^{-1}) = + 1.37°.

N-(tert-*Butoxycarbonyl)-2-(S)-(9-triisopropyloxy)propyl-4-(S)-methyl-tetrahydro-1,3-oxazine* (25f)



Yield = 74 % (viscous oil).

R_F = 0.65 (alumina, 10 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 1.08 (s, H-10, 21H); 1.30 (d, J = 7.0, H-11, 3H); 1.48 (s, H-12, 9H); 1.59 -1.84 (m, H-5,-7,-8, 5H); 2.00-2.15 (m, H-5, 1H); 3.61 (m, H-6, 1H); 3.74 (t, J = 6.1, H-9, 2H); 3.96 (m, H-6, 1H); 4.38 (m, H-4, 1H) 5.40 (dd, J = 9.0, 4.8, H-2, 1H)

^{13}C NMR (75 MHz) ($CDCl_3$); δ 11.86, 17.90, 21.26, 28.30, 29.30, 30.22, 43.50, 53.30, 56.06, 62.89, 79.62, 82.58, 153.48.

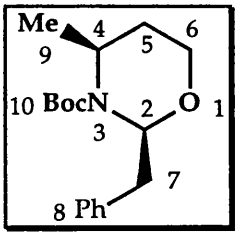
mass spectrum (FAB); m/z 416 (7%), 316 (100%).

$C_{22}H_{46}NO_4Si$ requires 416.3196; found 416.3180.

I.R.; υ_{max} (cm^{-1}) 2942, 2866, 1695, 1175, 1105.

$[\alpha]_D$ (c = 5 mg ml^{-1}) = - 0.78°.

N-(tert-*Butoxycarbonyl)-2(S)-benzyl-4(S)-methyl-1,3-tetrahydrooxazine* (**25g**)



Yield = 51 % (white crystalline solid)

R_F = 0.33 (alumina, 4 % EtOAc in Toluene)

m.pt. = 62.8 - 64.0 °C

^{1}H NMR (250 MHz) ($CDCl_3$); δ 1.37 (d, J= 7.0, H-9, 3H), 1.44 (s, H-10, 9H), 1.48-1.56 (m, H-5, 1H), 2.07-2.17 (m, H-5, 1H), 2.96 (dd, J = 13.7, 3.8, H-7, 1H), 3.17 (dd, J = 13.7, 9.0, H-7, 1H), 3.62 (m, H-6, 1H), 4.07 (m, H-6, 1H), 4.43 (m, H-4, 1H), 5.51 (dd, J = 9.0, 3.8, H-2, 1H), 7.20-7.35 (m, H-8, 5H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 21.80, 28.33, 29.30, 40.30, 43.50, 56.86, 57.50, 79.89, 84.17, 126.31, 128.26, 129.22, 137.75, C=O missing.

mass spectrum (FAB); m/z 292 (6%), 200 (10%), 192 (100%).

I.R.; υ_{max} (cm^{-1}) 2995, 1694, 1176.

$[\alpha]_D$ (c = 2.1 mg ml^{-1}) = + 35.71°.

CHN requires C = 70.07, H = 8.65, N = 4.81; found C = 69.95, H = 8.44, N = 4.79.

Attempted ring opening of rac-**25a** with BTMSA in the presence of $TiCl_4$

To a stirred solution of **25a** (0.5 mmol; 0.141 g) and bis(trimethylsilyl)acetylene (6 eq.; 3 mmol; 0.511 g) in dry DCM (10 ml), under N_2, at -78 °C, was added $TiCl_4$ in DCM (1.75 eq.; 0.875 mmol; 0.875 ml). After 20 minutes the reaction was quenched (1:1 MeOH : DCM, 10 ml) and

the clear solution was warmed to room temperature. The mixture was washed with HCl (1 M; 10 ml) and water (2 x 15 ml). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a clear oil. Column chromatography (silica gel, 2 % EtOAc in toluene) gave rac-**12** (70 mg; 74 % recovery). This was repeated a further two times.

Attempted ring opening of **25a** with BTMSA in the presence of $SnBr_4$

To a stirred solution of **25a** (0.5 mmol; 0.141 g) and bistrimethylsilylacetylene (6 eq.; 3 mmol; 0.511 g) in dry DCM (10 ml), under N_2, at -78 °C, was added $SnBr_4$ in DCM (1.75 eq.; 0.875 mmol; 0.875 ml). After 20 minutes the reaction was quenched (1:1 MeOH : DCM, 10 ml) and the clear solution was warmed to room temperature. The mixture was washed with HCl (1M; 10 ml) and water (2 x 15 ml). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a clear oil. Column chromatography (silica gel, 2 % EtOAc in toluene) gave rac-**12** (63 mg; 69 % recovery). This was repeated a further two times.

Attempted ring opening of **25a** with (trimethylsilyl)acetylene in the presence of $BF_3.Et_2O$

To a stirred solution of **25a** (0.25 mmol; 65 mg) and trimethylsilylacetylene (8 eq.; 2 mmol; 0.196 g) in dry DCM (10 ml), under N_2, at -78 °C, was added boron trifluoride etherate (2 eq.; 0.5 mmol; 0.071 ml). After 1 hour no reaction was evident, although ^1H NMR of the crude reaction mixture

indicated the formation of some of the required compound. An attempt was made to isolate this but this proved unsuccessful. This reaction was repeated at -20 °C, 0 °C and 20 °C, but no reaction was observed.

Attempted ring opening of **25a** with the Grignard reagent of (trimethylsilyl)acetylene

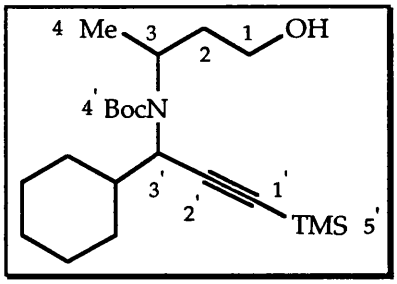
To a stirred suspension of EtMgBr (3M in THF; 1.6 mmol; 0.53 ml) in dry THF (1 ml) at 0 °C, under N_2, was added trimethylsilylacetylene (4.1 eq.; 1.6 mmol; 0.22 ml) over 2 -3 minutes. A brown precipitate was formed which dissolved on heating to 30 °C. After 15 minutes a solution of **25a** (0.39 mmol; 0.111 g) in dry THF (3 ml) was added and the mixture was refluxed overnight. The reaction was quenched with saturated NH_4Cl solution (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a pale yellow oil. Column chromatography gave unreacted **25a** and a white crystalline solid (20 mg). Analysis by NMR and mass spectrometry failed to reveal the identify the solid. This reaction was repeated a further two times.

Attempted ring opening of **25a** with the Grignard reagent of (trimethylsilyl)acetylene in the presence of $TiCl_4$

To a stirred solution of **25a** (0.5 mmol; 130 mg) and $TiCl_4$ (1M in DCM; 2 eq.; 1 mmol; 1 ml) in dry THF (2 ml) at 0 °C, under N_2, was added a pre-prepared solution of the Grignard reagent of (trimethylsilyl)acetylene (3.04 eq.; 1.52 mmol) in THF (1.5 ml) over 10 minutes. The resulting brown solution turned black over 10 minutes. After 3 hours the reaction was quenched with

saturated NH_4Cl solution (5 ml) and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a black gum. This proved to be unidentifiable by ^1H NMR.

N-(tert-*Butoxycarbonyl*)-N-(*1(R*)-3-trimethylsilyl-1-cyclohexyl-prop-2-ynyl*)-*3-(S*)-amino butan-1-ol* (rac-**29a**)



To a stirred solution of EtMgBr (3 M in THF; 4 eq., 2.4 mmol; 0.79 ml) in dry THF (2.5 ml) at 0 °C, under N_2 was added trimethylsilylacetylene (4.03 eq.; 2.42 mmol; 0.237 g; 0.33 ml). A brown precipitate was formed which dissolved on heating to 30 °C. After fifteen minutes a solution of **25a** (0.6 mmol; 0.155 g) in THF (0.5 ml) was added, followed by $BF_3.Et_2O$ (1.17 eq.; 0.7 mmol; 0.1 ml). After 45 minutes the reaction was quenched with saturated NH_4Cl solution (5 ml) and extracted with EtOAc (3 x 25 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous brown oil. This was purified by column chromatography (silica gel, 20 % EtOAc in hexane; R_F = 0.20) to give rac-**29a** as a viscous brown oil (0.121 g; 63 %).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.18 (s, H-5′, 9H), 1.10-1.20 (m, cyhex, 3H), 1.21-1.30 (m, cyhex, 2H), 1.38 (d, J = 6.8, H-4, 3H), 1.47 (s, H-4′, 9H), 1.61-1.81 (m, cyhex, 6H), 1.98-2.12 (m, H-2,-3, 3H), 3.52-3.74 (m, H-1,-3′, 3H), O*H* missing.

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0.40, 20.25, 26.98, 29.20, 30.76, 42.36, 50.16, 55.53, 59.53, 60.37, 61.29, 80.74, 81.35, 104.54, 156.28.

mass spectrum (FAB); m/z 404 (50%), 382 (35%), 326 (97%), 282 (100%).

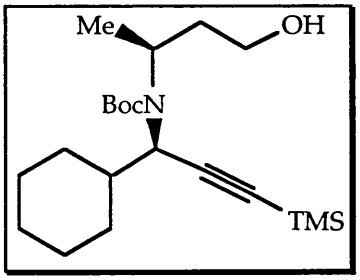
$C_{21}H_{40}NO_3Si$ requires 382.2777, found 382.2760.

I.R.; υ_{max} (cm^{-1}) 3620, 3020, 2153, 1677, 1271.

General procedure for chiral ring opened alcohols (**29a-f**)

The procedure was the same as for rac-**29a**.

N-(tert-Butoxycarbonyl)-N-(1(R)-3-trimethylsilyl-1-cyclohexyl-prop-2-ynyl)-3(S)-amino butan-1-ol (**29a**)



Yield = 65 % (viscous yellow oil).

R_F = 0.20 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.18 (s, 9H), 1.10-1.20 (m, 3H), 1.21-1.30 (m, 2H), 1.38 (d, J = 6.8, 3H), 1.47 (s, 9H), 1.61-1.81 (m, 6H), 1.98-2.12 (m, 3H), 3.52-3.74 (m, 3H), O*H* missing.

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0.40, 20.25, 26.98, 29.20, 30.76, 42.36, 50.16, 55.53, 59.53, 60.37, 61.29, 80.74, 81.35, 104.54, 156.28.

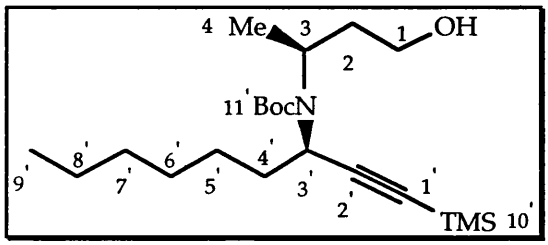
mass spectrum (FAB); m/z 404 (54%), 382 (33%), 326 (94%), 282 (100%).

$C_{21}H_{40}NO_3Si$ requires 382.2777, found 382.2760.

I.R.; υ_{max} (cm^{-1}) 3620, 3020, 2153, 1677, 1271.

$[\alpha]_D$ (c = 4.89 mg ml^{-1}) = + 28.20°.

N-(tert-*Butoxycarbonyl*)-3'-N-(1(R)-3-trimethylsilyl-1-hexyl-prop-2-ynyl)-3(S)-amino butan-1-ol (**29b**)



Yield = 63 % (viscous yellow oil).

R_F = 0.23 (silica gel, 20 % EtOAc in hexane).

^1H NMR (300 MHz) ($CDCl_3$); δ 0.13 (s, H-10', 9H), 0.87 (m, H-9', 3H), 1.19-1.30 (m, H-4' -> H-8', 10H), 1.28 (d, J = 6.8, H-4, 3H), 1.45 (s, H-11', 9H), 1.48-1.95 (m, H-2,-3, 3H), 3.59-3.76 (m, H-1,-3', 3H), O*H* missing.

^{13}C NMR (90 MHz) ($CDCl_3$); δ -0.22, 13.92, 19.05, 22.39, 26.40, 28.39, 31.58, 35.13, 37.02, 47.39, 48.29, 58.63, 59.41, 80.13, 80.65, 105.16, 155.39.

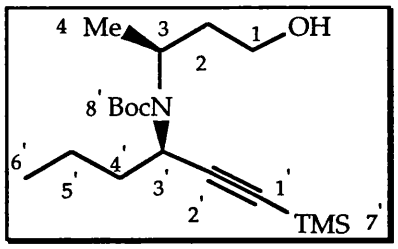
mass spectrum (ES^+); m/z 384 (10%), 328 (100%), 284 (16%).

$C_{21}H_{42}NO_3Si$ requires 384.2934, found 384.2950 (FAB).

I.R.; υ_{max} (cm^{-1}) 3456, 2960, 2930, 2172, 1682, 1250.

$[\alpha]_D$ (c = 3.98 mg ml^{-1}) = + 23.40°.

N-(tert-*Butoxycarbonyl)-3'-N-(1(R)-3-trimethylsilyl-1-propyl-prop-2-ynyl)-3(S)-amino butan-1-ol* (**29c**)



Yield = 63 % (viscous yellow oil).

R_F = 0.21 (silica gel, 20 % EtOAc in hexane).

^1H NMR (250 MHz) ($CDCl_3$); δ 0.10 (s, H-7', 9H), 0.89 (t, J = 7.2, H-6', 3H), 1.25-1.67 (m, H-4',-5', 4H), 1.28 (d, J = 6.8, H-4, 3H), 1.70-1.95 (m, H-2,-3, 3H), 3.49-3.65 (m, H-1,-3', 3H), O*H* missing.

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0, 13.79, 19.27, 19.91, 28.31, 28.61, 32.51, 37.60, 48.53, 60.50, 80.37, 105.33, 155.67, 1 x C≡C missing.

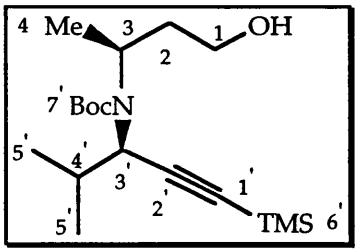
mass spectrum (ES^+); m/z 342 (9%), 286(100%), 242 (94%).

$C_{18}H_{36}NO_3Si$ requires 342.2464, found 342.2450 (FAB).

I.R.; υ_{max} (cm^{-1}) 3456, 2963, 2934, 2171, 1682, 1251.

$[\alpha]_D$ (c = 4.55 mg ml^{-1}) = + 37.40°.

N-(tert-*Butoxycarbonyl)-3'*-N-*(1(R)-3-trimethylsilyl-1-(1-methylethyl)-prop-2-ynyl)-3(S)-amino butan-1-ol* (**29d**)



Yield = 48% (viscous yellow oil).

R_F = 0.23 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.09 (s, H-6', 9H), 0.84 (d, J = 6.6, H-5', 3H), 0.98-1.01 (m, H-5', 3H), 1.28 (d, J = 6.7, H-4, 3H), 1.42 (s, H-7', 9H), 1.81-2.18 (m, H-4',-2, 3H), 3.41-3.85 (m, H-3',-1,-3, 4H), O*H* missing.

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.30, 19.44, 19.69, 20.74, 28.32, 32.21, 37.13, 47.55, 55.73, 58.61, 79.80, 84.84, 105.64, 155.56.

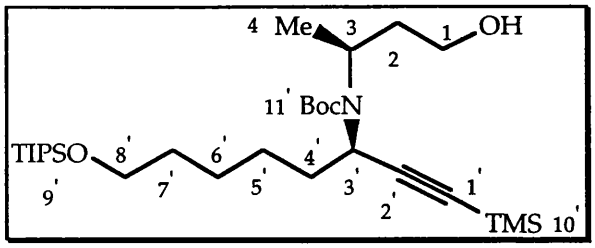
mass spectrum (FAB); m/z 364 (25%), 342 (40%), 241 (70%), 198 (100%).

$C_{18}H_{35}NO_3Si$ requires 342.2464, found 342.2450.

I.R.; υ_{max} (cm^{-1}) 3456, 2967, 2172, 1682, 1250.

$[\alpha]_D$ (c = 5.5 mg ml^{-1}) = + 16.85°.

N-(tert-*Butoxycarbonyl)-3'*-N-*(1*(R)-*3-trimethylsilyl-1-(5-triisopropylsilyloxy pentyl)-prop-2-ynyl)-3*(S)-*amino butan-1-ol* (**29e**)



Yield = 55% (viscous yellow oil).

R_F = 0.23 (silica gel, 20% EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.12 (s, H-10', 9H), 1.03 (s, H-9', 21H), 1.10-1.59 (m, H-4' -> -7', 8H), 1.30 (d, J = 6.8, H-4, 3H), 1.44 (s, H-11', 9H), 1.60-2.05 (m, H-2,-3, 3H), 3.52-3.74 (m, H-1,-3', 3H), 3.64 (t, H-8', 2H), 4.12 (bs, OH, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.18, 11.92, 17.94, 19.05, 25.27, 25.33, 26.40, 28.44, 32.82, 35.28, 47.44, 48.34, 63.16, 80.20, 105.15, 155.43, either 1 x C≡C or ^{t}BuCO missing.

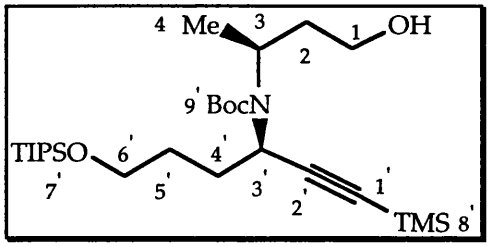
mass spectrum (FAB); m/z 564 (12%), 442 (100%).

$C_{29}H_{59}NO_4Si_2Na$ requires 564.3880, found 564.3860.

I.R.; υ_{max} (cm^{-1}) 3457, 2940, 2866, 2172, 1682, 1250, 1113.

$[\alpha]_D$ (c = 3.89 mg ml^{-1}) = + 15.70°.

N-(tert-*Butoxycarbonyl)-3'*-N-*(1(R)-3-trimethylsilyl-1-(3-triisopropylsilyloxy propyl)-prop-2-ynyl)-3(S)-amino butan-1-ol* (**29f**)



Yield = 46 % (yellow oil).

R_F = 0.27 (silica gel; 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.19 (s, H-8', 9H); 1.14 (s, H-7', 21H); 1.28-1.35 (m, H-5', 2H); 1.33 (d, J = 6.8, H-4, 3H); 1.52 (s, H-9', 9H); 1.57-1.81 (m, H-4', 2H); 1.98-2.01 (m, H-2,-3, 3H); 3.57-3.67 (m, H-1, 2H); 3.70-3.81 (m, H-6',-3', 3H), O*H* missing.

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.18, 11.92, 17.94, 19.05, 26.40, 28.44, 32.82, 35.28, 47.44, 48.34, 62.77, 80.15, 104.95, 155.48, either 1 x C≡C or ^{t}BuCO missing.

mass spectrum (FAB); m/z 536 (11%), 414 (100%).

$C_{27}H_{55}NO_4Si_2Na$ requires 536.3567; found 536.3580.

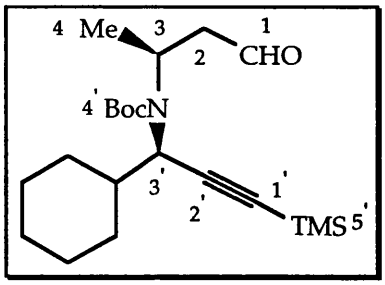
I.R.; υ_{max} (cm^{-1}) 3471, 2943, 2867, 2172, 1693, 1250, 1114.

$[\alpha]_D$ (c = 7.5 mg ml^{-1}) = + 16.9°.

General procedure for aldehydes **30a-f**

Alcohols **29a-e** were converted to their aldehyde derivatives by activated DMSO oxidation using the procedure of Baker and Castro[85] already described for 6-Triisopropylsilyloxyhexanal.

N-(tert-*Butoxycarbonyl*)-N-*(1(R)-3-trimethylsilyl-1-cyclohexyl-prop-2-ynyl)-3(S)-amino butan-1-al* (**30a**)

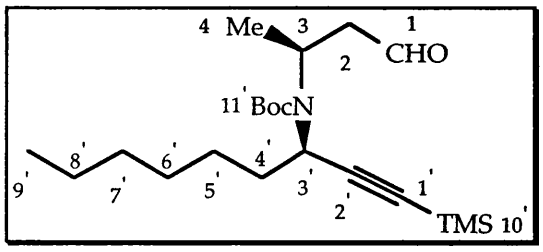


Yield = 99 % (viscous yellow oil).

R_F = 0.49 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.18 (s, H-5', 9H), 1.10-1.20 (m, cyhex, 3H), 1.21-1.30 (m, cyhex, 2H), 1.38 (d, J = 7.2, H-4, 3H), 1.47 (s, H-4', 9H), 1.61-1.81 (m, cyhex, 6H), 1.98-2.12 (m, H-2,-3, 3H), 3.52-3.74 (m, H-3', 1H), 9.70 (s, H-1, 1H)

N-(tert-*Butoxycarbonyl*)-N-*(1(R)-3-trimethylsilyl-1-hexyl-prop-2-ynyl)-3(S)-amino butan-1-al* (**30b**)

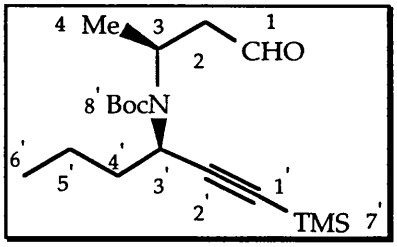


Yield = 95 % (viscous yellow oil).

R_F = 0.48 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.13 (s, H-10', 9H), 0.87 (m, H-9', 3H), 1.16-1.32 (m, H-4' -> -8', 10H), 1.37 (d, J = 6.5, H-4, 3H), 1.46 (s, H-11', 9H), 1.48-1.95 (m, H-2,-3, 3H), 3.59-3.76 (m, H-3', 1H), 9.74 (s, H-1, 1H)

N-(tert-*Butoxycarbonyl*)-3'-N-(1(R)-3-*trimethylsilyl*-1-*propyl*-prop-2-*ynyl*)-3(S)-*amino butan*-1-*al* (**30c**)

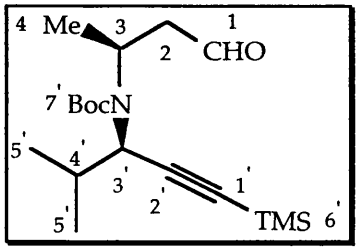


Yield = 71 % (viscous yellow oil).

R_F = 0.49 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.17 (s, H-7', 9H), 0.92 (t, J = 7.0, H-6', 3H), 1.25-1.35 (m, H-5', 2H), 1.39 (d, J = 6.0, H-4, 3H), 1.48 (s, H-8', 9H), 1.57-1.62 (m, H-4',-2,-3, 5H), 4.04-4.17 (m, H-3', 1H), 9.75 (s, H-1, 1H).

N-(tert-*Butoxycarbonyl*)-3'-N-(1(R)-3-*trimethylsilyl*-1-(1-*methylethyl*)-prop-2-*ynyl*)-3(S)-*amino butan*-1-*al* (**30d**)

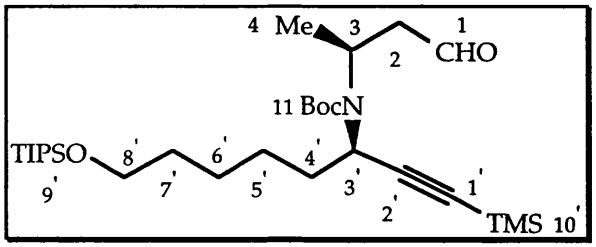


Yield = 84 % (viscous yellow oil).

R_F = 0.50 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.19 (s, H-6', 9H), 0.87-0.99 (m, H-5', 3H), 1.01-1.08 (m, H-5', 3H), 1.42 (d, J = 7.3, H-4, 3H), 1.47 (s, H-7', 9H), 1.49-1.62 (m, H-2,-4', 3H), 1.79-1.95 (m, H-3, 1H), 4.07-4.15 (m, H-3', 1H), 9.79 (t, J = 1.4, H-1, 1H).

N-(tert-*Butoxycarbonyl*)-3'-N-(1(R)-3-*trimethylsilyl*-1-(5-*triisopropylsilyloxy pentyl*)-prop-2-*ynyl*)-3(S)-*amino butan*-1-*al* (**30e**)

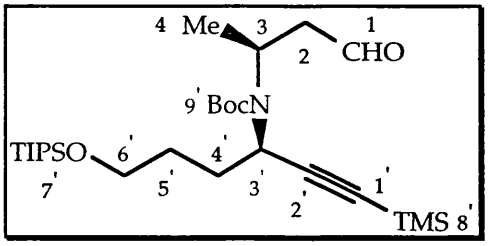


Yield = 89 % (viscous yellow oil).

R_F = 0.52 (silica gel, 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.10 (s, H-10', 9H), 0.89 (s, H-9', 21H), 1.24-1.28 (m, H-5' -> -7', 6H), 1.30 (d, J = 6.8, H-4, 3H), 1.41 (s, H-11', 9H), 1.45-1.58 (m, H-4',-2,-3, 5H), 3.59 (t, J = 6.5, H-8', 2H), 3.99-4.04 (m, H-3', 1H), 9.67 (t, J = 1.7, H-1, 1H).

N-(tert-*Butoxycarbonyl*)-3'-N-(1(R)-3-*trimethylsilyl*-1-(3-*triisopropylsilyloxy propyl*)-prop-2-*ynyl*)-3(S)-*amino butan*-1-*ol* (**30f**)



Yield = 100 % (yellow oil).

R_F = 0.50 (silica gel; 20 % EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.21 (s, H-8', 9H), 1.14 (s, H-7', 21H), 1.25-1.30 (m, H-5', 2H), 1.39 (d, J = 7.0, H-4, 3H), 1.52 (s, H-9', 9H), 1.57-1.81 (m, H-4', 2H), 1.98-2.01 (m, H-2,-3, 3H), 3.68 (t, J = 6.6, H-6', 2H), 4.08-4.20 (m, H-3', 1H), 9.72 (s, H-1, 1H).

Attempted synthesis of N-(tert-*butoxycarbonyl)-3-(trimethylsilyl)-1-cyclohexyl-prop-2-yn-1-amine*

To a solution of rac-**30a** (0.5 mmol; 0.190 g) in THF (0.1 ml) was added NaOH (2 M; 0.4 ml). The mixture was stirred for 1.5 hours, by which time the aldehyde appeared to be consumed by TLC. The mixture was then extracted with $CHCl_3$ (3x4 ml), the organics dried over Na_2SO_4 and the solvents removed *in vacuo* to give a yellow oil (0.180 g). This was shown to be starting material by ^1H NMR.

Attempted synthesis of N-(tert-*butoxycarbonyl)-3-(trimethylsilyl)-1-cyclohexyl-prop-2-yn-1-amine*

A solution of rac-**30a** (0.079 mmol; 0.030 g) in MeOH (0.3 ml) was stirred over basic resin (Amberlite IRA 904) for 2 days. No reaction was observed and the starting material was recovered.

Attempted synthesis of N-(tert-*butoxycarbonyl)-3-(trimethylsilyl)-1-cyclohexyl-prop-2-yn-1-amine*

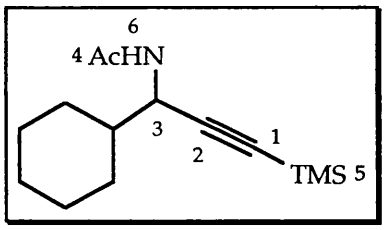
Rac-**30a** (0.079 mmol; 0.030 g) and piperidium acetate (0.01 mmol, 0.0015 g) were dissolved in benzene (1 ml) and the mixture was heated to reflux for 24 hours. No reaction was observed and the starting material was recovered.

N-*(Acetimido)-3-(trimethylsilyl)-3-cyclohexyl-prop-2-yn-1-amine* (rac-**34**)

To a solution of rac-**30a** (0.079 mmol; 0.030 g) in THF (0.5 ml) was added HCl (2 M; 1.5 ml) and the solution was heated at reflux for 3 hours whereupon a

brown precipitate was seen to form and TLC indicated the complete consumption of starting material. The solvents were removed *in vacuo* to give a white solid. This was dissolved in $CHCl_3$ (1 ml) and Et_3N (2.53 eq.; 0.2 mmol; 0.028 ml). Ac_2O (3.09 eq.; 0.24 mmol; 0.022 ml) was added and the mixture stirred for 2 hours. The mixture was poured into water (2 ml) and extracted with $CHCl_3$ (3 x 2 ml). The organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil. Column chromatography (silica gel, 45 % EtOAc in hexane) gave two spots; a yellow oil (rac-**34**, 0.012 g, 60 %, R_F = 0.37) and a white solid (N-*(acetimido)-3-cyclohexyl-prop-1-yneamine*, rac-**35**, 0.002 g, 12 %, R_F = 0.23).

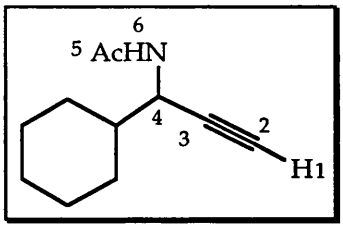
Rac-**34**



^{1}H NMR (200 MHz) ($CDCl_3$); δ 0.05 (s, H-5, 9H), 1.40-1.78 (m, cyhex, 11H), 1.95 (s, H-4, 3H), 4.60 (dd, J = 9.2, 6.3, H-3, 1H), 5.60 (bd, J = 8.2, H-7, 1H).

mass spectrum (FAB); m/z 252 (M+1).

Rac-35



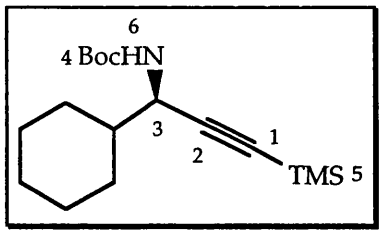
^{1}H NMR (200 MHz) ($CDCl_3$); δ 1.40-1.78 (m, cyhex, 11H), 1.95 (s, H-5, 3H), 2.20 (d, J = 2.8, H-1, 1H), 4.60 (m, H-4, 1H), 5.6 (m, H-6, 1H).

mass spectrum (FAB); m/z 180 (M+1).

General procedure for the conversion of aldehydes **30a-e** into (*R*)-*N*-(*tert*-butoxycarbonyl)-amines **36a-f**

To a solution of aldehyde (0.079 mmol) in THF (0.5 ml) was added HCl (2 M; 1.5 ml) and the solution was heated at reflux for 3 hours whereupon a brown precipitate was seen to form and TLC indicated the complete consumption of starting material. The solvents were removed *in vacuo* to give an off-white solid. This was dissolved in DCM (1 ml) and cooled to 0°C. Et_3N (2.53 eq.; 0.2 mmol; 0.028 ml) was added followed by a solution of Boc_2O (3.01 eq.; 0.24 mmol; 0.022 ml) in DCM (0.5 ml). The mixture was stirred overnight whereupon it was poured into water (2 ml) and extracted with $CHCl_3$ (3 x 2 ml). The organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil. Column chromatography gave the required product.

(R)-N-(tert-Butoxycarbonyl)-3-(trimethylsilyl)-1-cyclohexyl-prop-2-yn-1-amine (**36a**)



Yield = 70 %.

R_F = 0.52 (silica gel; 20 %EtOAc in hexane)

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.17 (s, H-5, 9H); 1.00-1.41 (m, cyhex, 6H); 1.46 (s, H-4, 9H); 1.62-1.93 (m, cyhex, 5H); 4.35 (bs, H-3, 1H); 4.72 (bs, H-6, 1H).

mass spectrum (FAB); m/z 332, 308.

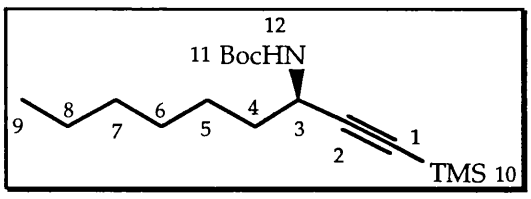
$C_{17}H_{30}NO_2Si$ requires 308.2046, found 308.2030.

$C_{17}H_{31}NO_2SiNa$ requires 332.2022, found 332.2010.

I.R.; υ_{max} (cm^{-1}) 3619, 3020, 2931, 2171, 1679, 1215.

$[\alpha]_D$ (c = 2.9 mg ml^{-1}) = + 35.86°.

(R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)-non-1-yn-3-amine (**36b**)



Yield = 68 %.

R_F = 0.53 (silica gel; 20 % EtOAc in hexane)

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.18 (s, H-10, 9H), 0.92 (t, J = 7.0, H-9, 3H), 1.23-1.40 (m, H-7,-8, 4H), 1.49 (s, H-11, 9H), 1.58-1.62 (m, H-4 -> -6, 6H), 4.41 (bs, H-3, 1H), 4.70 (bs, H-12, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0, 13.70, 14.11, 18.93, 22.58, 25.55, 28.43, 28.20, 29.76, 31.74, 36.47, 80.05, 87.50, 105.82, 154.70

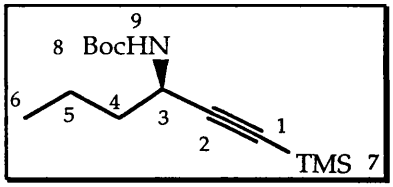
mass spectrum (FAB); m/z 312 (10%), 256 (100%).

$C_{17}H_{34}NO_2Si$ requires 312.2359, found 312.2370.

I.R.; υ_{max} (cm^{-1}) 3448, 2961, 2929, 2254, 1708, 1250.

$[\alpha]_D$ (c = 5 mg ml^{-1}) = + 23.00°.

(R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)-hex-1-yn-3-amine (**36c**)



Yield = 65 %.

R_F = 0.50 (silica gel; 20%EtOAc in hexane)

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.18 (s, H-7, 9H), 0.97 (t, J = 7.0, H-6, 3H), 1.23-1.36 (m, H-5, 2H), 1.45 (s, H-8, 9H), 1.58-1.65 (m, H-4, 2H), 4.40 (bs, H-3, 1H), 4.70 (bs, H-9, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0, 13.70, 18.93, 28.43, 31.75, 67.16, 105.76, 154.68

^{t}BuCO and 1x C≡C missing.

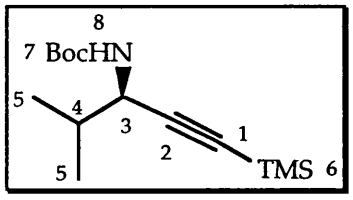
mass spectrum (FAB); m/z 270 (9%), 256 (80%), 214 (100%).

$C_{14}H_{28}NO_2Si$ requires 270.1889, found 270.1870.

I.R.; υ_{max} (cm^{-1}) 3448, 2963, 2931, 2254, 1708, 1250.

$[\alpha]_D$ (c = 4.7 mg ml^{-1}) = + 25.20°.

(R)-N-(tert-Butoxycarbonyl)-1-(trimethylsilyl)-1-(4-methyl)-pent-1-yn-3-amine **(36d)**



Yield = 71 %.

R_F = 0.50 (silica gel; 20 %EtOAc in hexane)

^1H NMR (300 MHz) ($CDCl_3$); δ 0.14 (s, H-6, 9H), 0.95 (d, J = 6.9, H-5, 6H), 1.44 (s, H-7, 9H), 1.87 (m, J = 6.6, H-4, 1H), 4.29 (bs, H-3, 1H), 4.77 (bs, H-8, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.19, 17.31, 18.60, 28.23, 33.03, 49.24, 80.05, 88.14, 103.81, 154.80.

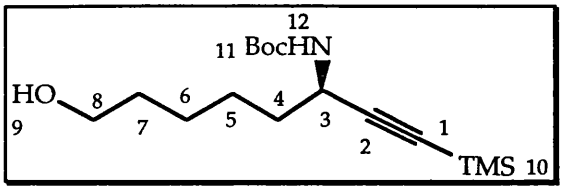
mass spectrum (FAB); m/z 270 (14%), 214 (100%), 170 (75%).

$C_{14}H_{28}NO_2Si$ requires 270.1889, found 270.1880.

I.R.; υ_{max} (cm^{-1}) 3448, 2963, 2930, 2254, 1708, 1250.

$[\alpha]_D$ (c = 5.15 mg ml^{-1}) = + 18.60°.

(R)-N-(tert-Butoxycarbonyl)-6-amino-8-trimethylsilyl-oct-7-yn-ol **(36e)**



Yield = 35 %.

R_F = 0.27 (silica gel; 20 %EtOAc in hexane).

^1H NMR (300 MHz) ($CDCl_3$); δ 0.16 (s, H-10, 9H), 1.41 (s, H-11, 9H), 1.49-1.70 (m, H-5,-6,-7, 6H), 1.78-1.82 (m, H-4, 2H), 3.50 (bs, H-9, 1H), 3.58 (t, J = 6.5, H-8, 2H), 4.34 (bs, H-3, 1H), 4.92 (bd, J = 8.2, H-12, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 0.16, 25.10, 28.28, 32.45, 36.04, 36.36 43.32, 62.56, 70.89, 105.32, 154.82, ^{t}BuCO missing.

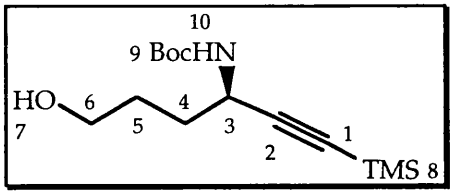
mass spectrum (FAB); m/z 336 (16%), 314 (15%), 258 (100%), 214 (30%).

$C_{16}H_{32}NO_3Si$ requires 314.2151, found 314.2140.

I.R.; υ_{max} (cm^{-1}) 3620, 3450, 2961, 2929, 2254, 1708, 1250.

$[\alpha]_D$ (c = 1.2 mg ml^{-1}) = + 36.70°.

(R)-N-(tert-Butoxycarbonyl)-4-amino-6-trimethylsilyl-hex-5-yn-ol **(36f)**



Yield = 77 %.

R_F = 0.25 (silica gel; 20%EtOAc in hexane)

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.14 (s, H-8, 9H), 1.44 (s, H-9, 9H), 1.60-1.80 (m, H-5,-4, 4H), 2.10 (bs, H-7, 1H), 3.61-3.78 (m, H-6, 2H), 4.43 (bs, H-3, 1H), 4.88 (bd, J = 6.2, H-10, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.40, 27.64, 32.44, 47.50, 64.33, 66.38, 81.70, 104.57, 154.58, ^{t}BuCO missing.

mass spectrum (FAB); m/z 308 (20%), 286 (25%), 230 (100%), 186 (30%).

$C_{14}H_{28}NO_3Si$ requires 286.1838; found 286.1850.

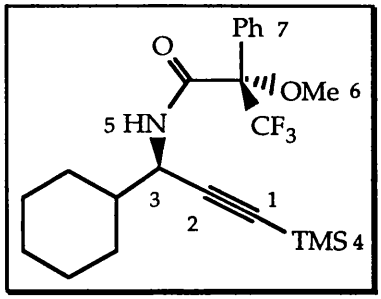
I.R.; υ_{max} (cm^{-1}) 3621, 3448, 2961, 2929, 2254, 1708, 1250.

$[\alpha]_D$ (c = 62 mg ml^{-1}) = + 11.70°.

General procedure for the conversion of **36a-e** to Moshers amides **37a-e**

To a solution of (*N*)-Boc-amine (**36a-e**) (1 mmol) in wet methanol (0.7 ml) was added trifluoroacetic acid (7 ml). The mixture was stirred until no starting material was detectable by TLC. Et_2O (10 ml) was added and the solvents were removed *in vacuo* to give an off-white solid. The solid was dissolved in DCM (3 ml) and the solution was cooled to 0°C. Pyridine (6 ml) was added followed by (*S*)-methoxytrifluoromethylphenylacetyl chloride (1.4 eq; 1.4 mmol; 0.240 ml). The mixture was stirred for 1 hour, poured into saturated Na_2HCO_3 solution (5 ml) and then extracted with DCM (3 x 5 ml). The organics were dried over Na_2SO_4 and the solvents removed to give the crude products **37a-e**.

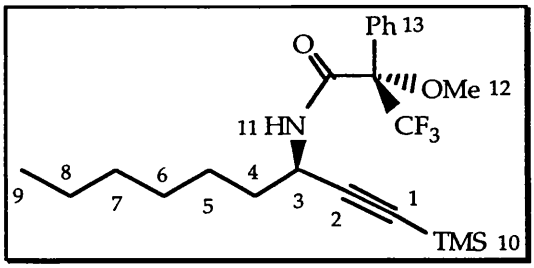
N-((S)-MTPA)-3-(Trimethylsilyl)-1(R)-cyclohexyl-prop-2-yn-amine (37a)



^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.14 (s, H-4, 9H), 1.40-1.78 (m, cyhex, 11H), 3.56 (s, H-6, 3H), 4.78 (m, H-3, 1H), 7.38-7.48 (m, H-7, 5H).

^{19}F NMR (325.8 MHz) ($CDCl_3$); δ -69.13 (60 %), -69.19 (40 %).

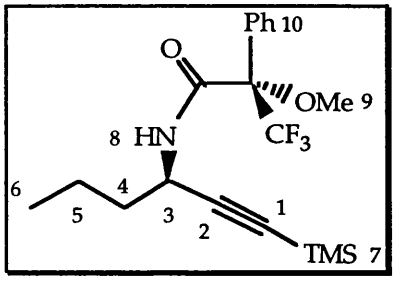
N-((S)-MTPA)-1-(Trimethylsilyl)-non-1-yn-3(R)-amine (37b)



^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.14 (s, H-10, 9H), 0.84-0.94 (m, H-9, 3H), 1.20-1.38 (m, H-6,-7,-8, 6H), 1.53-1.72 (m, H-4,-5, 4H), 3.56 (s, H-12, 3H), 4.80 (m, H-3, 1H), 7.41-7.52 (m, H-13, 5H).

^{19}F NMR (325.8 MHz) ($CDCl_3$); δ -69.07 (80 %), -69.22 (20 %).

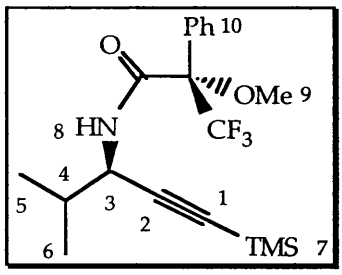
N-((S)-MTPA)-1-(Trimethylsilyl)-hex-1-yn-3(R)-amine (**37c**)



^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.15 (s, H-7, 9H), 0.89-0.98 (m, H-6, 3H), 1.44-1.65 (m, H-4,-5, 4H), 3.56 (s, H-9, 3H), 4.80 (m, H-3, 1H), 7.31-7.44 (m, H-10, 5H).

^{19}F NMR (325.8 MHz) ($CDCl_3$); δ -69.07 (82 %), -69.22 (18 %).

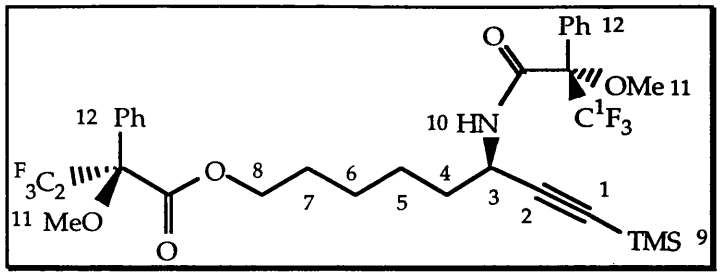
N-((S)-MTPA)-1-(Trimethylsilyl)-4-methyl-pent-1-yn-3(R)-amine (**37d**)



^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.21 (s, H-6, 9H), 1.01 (d, J = 7.0, H-5, 6H), 2.01 (m, H-4, 1H), 3.62 (bs, H-8, 3H), 4.66 (dd, J = 10.5, 8.0, H-3, 1H), 7.35-7.69 (m, H-9, 5H).

^{19}F NMR (392 MHz) ($CDCl_3$); δ -76.29 (93 %), -76.32 (7 %).

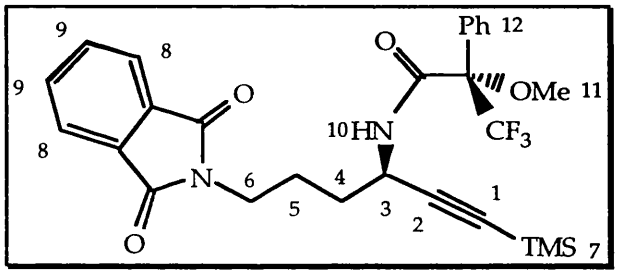
(N, O)-(Bis-(S)-MTPA)-6-amino-8-(trimethylsilyl)-oct-7-yn-1-ol (**37e**)



^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.18 (s, H-9, 9H), 1.47-1.53 (m, H-4,-5,-6, 6H), 1.65-1.82 (m, H-7, 2H), 3.66 (bs, H-11, 6H), 4.35 (t, J = 8.0, H-8, 2H), 4.76 (m, H-3, 1H), 7.30-7.67 (m, H-12, 10H).

^{19}F NMR (392 MHz) ($CDCl_3$); δ {-75.20 (95 %), -75.26 (5 %)} (C^1F_3), -75.88 (100%) (C^2F_3).

N-((S)-MTPA)-1-(Trimethylsilyl)-6-phthalimido-hex-1-yn-3-amine (**37f**)

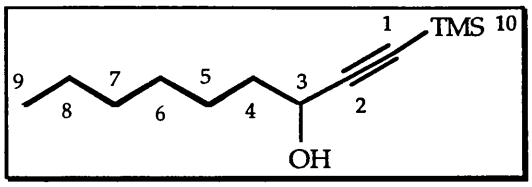


The same procedure as was used for **36a-e** was applied to **58** (*vide infra*) to give the required amide.

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.18 (s, H-7, 9H), 1.65-1.97 (m, H-4,-5, 4H), 3.10-3.15 (m, H-6, 2H), 3.74 (bs, H-11, 3H), 4.18 (m, H-3, 1H), 7.30-7.47 (m, H-12, 5H), 7.50-7.60 (m, H-9, 2H), 7.81-7.90 (m, H-8, 2H).

^{19}F NMR (392 MHz) ($CDCl_3$); δ -69.33 (76 %), -69. 45 (24 %).

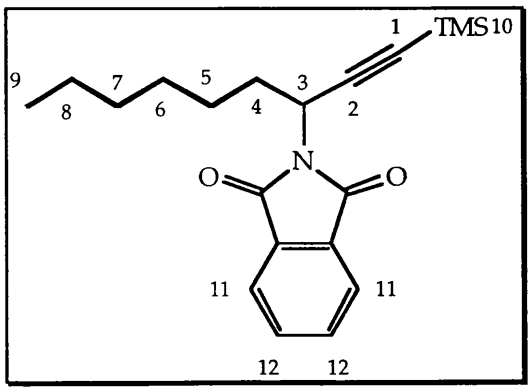
1-Trimethylsilyl-non-1-yn-3-ol (rac-**38b**)



To a stirred solution of EtMgBr (1M in THF; 12 mmol; 12 ml) at 0 °C, was added trimethylsilylacetylene (2 eq.; 12 mmol; 1.96 ml). A brown precipitate was formed which dissolved on heating to 30 °C. A solution of heptanal (6 mmol; 0.84 ml) in THF (6 ml) was then added dropwise. After 1 hour the reaction was quenched with saturated NH_4Cl solution (15 ml) and extracted with EtOAc (3 x 25 ml). The combined organic layers were dried over Na_2SO_4 and the solvents removed *in vacuo* to give a viscous brown oil. This was purified by column chromatography (silica gel, 50 % EtOAc in hexane; R_F = 0.43) to give rac-**38b** as a viscous brown oil (1.25 g : 98 %).

^{1}H NMR (360 MHz) ($CDCl_3$); δ 0.20 (s, H-10, 9H), 0.72 (t, J = 6.5, H-9, 3H), 1.10-1.18 (m, H-6,-7,-8, 6H), 1.21-1.32 (m, H-5, 2H), 1.45-1.55 (m, H-4, 2H), 4.18 (t, J = 6.5, H-3, 1H).

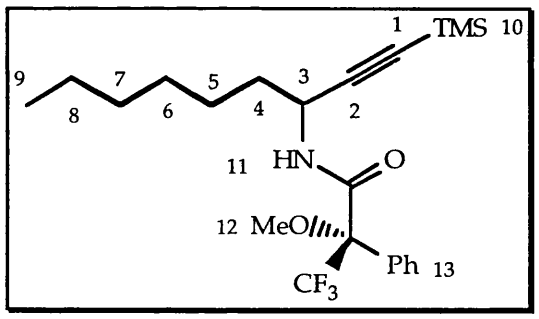
1-Trimethylsilyl-3-phthalimido-non-1-yne (rac-**39b**)



To a solution of rac-**38b** (5 mmol; 1.06 g), triphenylphosphine (1.1 eq.; 5.5 mmol; 1.44 g) and phthalimide (1.1 eq.; 5.5 mmol; 0.82 g) in THF (25 ml) was added diethylazodicarboxylate (1.12 eq.; 5.6 mmol; 0.87 ml) dropwise over 5 minutes. The mixture was stirred overnight (16 hours) and then the solvents were removed *in vacuo*. Column chromatography (silica gel; 50 % EtOAc in hexane; R_F = 0.49) gave the title compound as a pale yellow oil (1.45 g; 85 %).

^{1}H NMR (360 MHz) ($CDCl_3$); δ 0.15 (s, H-10, 9H), 0.71 (t, J = 6.8, H-9, 3H), 1.03-1.34 (m, H-5 -> H-8, 8H), 1.80-2.01 (m, H-4, 2H), 4.86 (t, J = 7.9, H-3, 1H), 7.41-7.62 (m, H-12, 2H), 7.67-7.72 (m, H-11, 2H).

N-((S)-MTPA)-1-(Trimethylsilyl)-non-1-yn-3-amine (rac-**37b**)



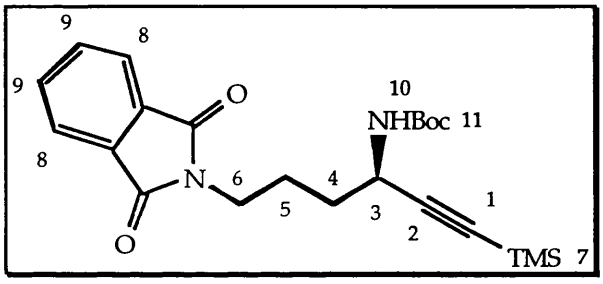
A solution of rac-**39b** (0.1 mmol; 0.0247 g) in ethanol (1.6 ml) and hydrazine hydrate (25 eq.; 2.5 mmol; 0.072 ml) was heated at reflux for 3 hours after which time the solvent was removed *in vacuo*. The residue was dissolved in DCM (0.3 ml) and the solution was cooled to 0 °C. Pyridine (0.6 ml) was added followed by (*S*)-methoxytrifluoromethylphenylacetyl chloride (1.1 eq.; 0.11 mmol; 0.020 ml). The mixture was stirred for 1 hour, poured into saturated Na_2HCO_3 solution (1 ml) and then extracted with DCM (3 x 2 ml).

The organics were dried over Na_2SO_4 and the solvents removed to give the crude rac-**37b**.

^{1}H NMR (250 MHz) ($CDCl_3$); δ 0.14 (s, H-10, 9H), 0.84-0.94 (m, H-9, 3H), 1.20-1.38 (m, H-6,-7,-8, 6H), 1.53-1.72 (m, H-4,-5, 4H), 3.56 (s, H-12, 3H), 4.80 (m, H-3, 1H), 7.41-7.52 (m, H-13, 5H).

^{19}F NMR (325.8 MHz) ($CDCl_3$); δ -69.06 (50 %), -69.22 (50 %).

N-(tert-*Butoxycarbonyl)-1-(trimethylsilyl)-6-phthalimido-hex-1-yn-3-amine* (58)



To a solution of **36f** (0.5 mmol; 0.135 g), triphenylphosphine (1.1 eq.; 0.55 mmol; 0.150 g) and phthalimide (1.1 eq.; 0.55 mmol; 0.082 g) in THF (5 ml) was added diethylazodicarboxylate (1.32 eq.; 0.66 mmol; 0.11 ml) dropwise over 5 minutes. The mixture was stirred overnight (16 hours) and then the solvents were removed *in vacuo*. Column chromatography (silica gel; 50 % EtOAc in hexane; R_F = 0.68) gave the title compound as a pale yellow solid (0.122 g; 60 %).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.14 (s, H-7, 9H); 1.43 (s, H-11, 9H); 1.63-1.75 (m, H-4, 2H); 1.78-1.87 (m, H-5, 2H); 3.73 (t, J = 7.0, H-6, 2H); 4.10 (m, H-3, 1H); 4.49 (bs, H-10, 1H); 7.72 (m, H-9, 2H); 7.84 (m, H-8, 2H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.20, 24.86, 28.28, 33.62, 37.51, 43.28, 79.83, 87.93, 104.69, 123.15, 132.10, 133.83, 154.63, 168.24.

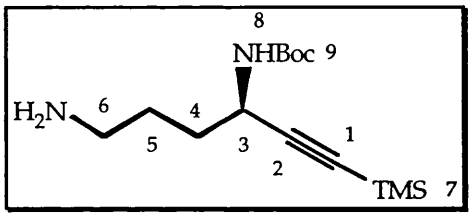
mass spectrum (FAB); m/z 437 (25%), 415 (21%), 359 (71%), 315 (83%), 307 (100%).

$C_{22}H_{30}N_2O_4SiNa$ requires 437.1873; found 437.1860.

I.R.; υ_{max} (cm^{-1}) 3619, 3020, 2400, 1711, 1216.

$[\alpha]_D$ (c = 39 mg ml^{-1}) = + 12.69°.

3-N-(tert-Butoxycarbonyl)-6-diamino-1-(trimethylsilyl)-hex-1-yne (**59**)



A solution of **58** (0.3 mmol; 0.122 g) in ethanol (2 ml) and hydrazine hydrate (26.7 eq; 8 mmol; 0.23 ml) was heated at reflux for 4 hours after which time the solvent was removed *in vacuo*. The residue was triturated with $CHCl_3$ and filtered. The triturant was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; 50 % MeOH in $CHCl_3$; R_F = 0.44) to give the title compound as a yellow viscous oil (0.070 g; 83 %).

^1H NMR (300 MHz) ($CDCl_3$); δ 0.15 (s, H-7, 9H); 1.44 (s, H-9, 9H); 1.50-1.73 (m, H-4,-5, 4H); 2.73 (t, J = 6.5, H-6, 2H); 4.41 (bs, H-3, 1H); 4.92 (bs, H-8, 1H).

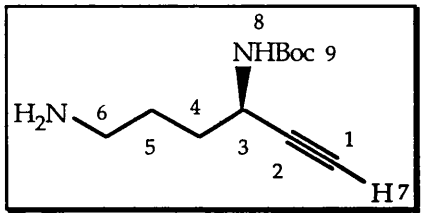
^{13}C NMR (75 MHz) ($CDCl_3$); δ -0.22, 28.23, 29.48, 33.66, 41.54, 43.28, 79.65, 82.25, 87.75, 154.69.

mass spectrum (FAB); m/z 285 (M+1).

I.R.; υ_{max} (cm^{-1}) 3671, 3624, 3448, 2961, 2929, 2254, 1708, 1250.

$[\alpha]_D$ (c = 18.5 mg ml^{-1}) = + 21.24°.

3-N-(tert-*Butoxycarbonyl)-6-diamino-hex-1-yne* **(60)**



To a solution of **59** (0.13 mmol; 0.037 g) in wet THF (1 ml) at 0°C, was added dropwise TBAF (1M in THF; 1.5 eq.; 0.195 mmol; 0.195 ml). After 30 minutes the mixture was poured into water and was extracted with Et_2O (3 x 2 ml). The organics were dried over Na_2SO_4 and the solvents removed *in vacuo* to give the title compound as a pale yellow oil (0.0093 g; 34 %).

R_F = 0.61 (25% MeOH in $CHCl_3$).

^1H NMR (300 MHz) ($CDCl_3$); δ 1.47 (s, H-9, 9H), 1.51-1.80 (m, H-4,-5, 4H), 2.29 (d, J = 2.3, H-7, 1H), 2.65-2.75 (m, H-6, 2H), 4.45 (bs, H-3, 1H), 4.98 (bs, H-8, 1H).

^{13}C NMR (75 MHz) ($CDCl_3$); δ 19.61, 23.95, 28.23, 33.38, 42.49, 58.73, 70.97, 83.32, 147.51.

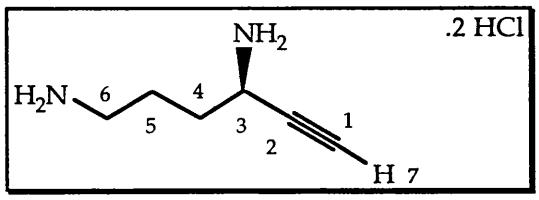
mass spectrum (FAB); m/z 213 (24%), 154 (29%), 133 (100%).

$C_{11}H_{21}N_2O_2$ requires 213.1603; found 213.1620

I.R.; υ_{max} (cm^{-1}) 3671, 3624, 3448, 3302, 3019, 2976, 2254, 1708.

$[\alpha]_D$ (c = 4.65 mg ml^{-1}) = + 8.17°.

Hex-1-yn-3,6-diamine dihydrochloride (57)[99]



60 (0.044mmol; 0.0093g) was dissolved in MeOH (0.5ml) and aqueous HCl (2M, 0.5 ml) was added. The mixture was heated at reflux until no starting material was observed by TLC. The solvents were removed *in vacuo* to give crude product as a yellow solid which was purified by recrystallisation from ether/ethanol to give a (d) as a white solid (0.003 g; 37 %).

^{1}H NMR (300 MHz) (MeOH); δ 1.91-2.01 (m, H-4,-5, 4H); 3.01-3.15 (m, H-6, 2H); 3.21 (d, J = 1.99, H-7, 1H); 4.12-4.27 (m, H-3, 1H).

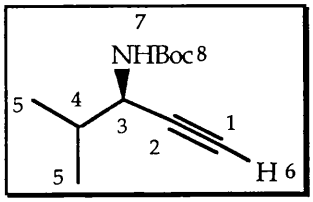
^{13}C NMR (75 MHz) (MeOH); δ 24.64, 31.48, 39.91, 63.48, 78.43, 1 carbon missing (either C-4 or C-5).

mass spectrum (FAB); m/z 113 (M+H).

$C_6H_{13}N_2$ requires 113.1079; found 113.1083.

$[\alpha]_D$ (c = 1.5 mg ml^{-1}; H_2O) = -2.67° (lit. = -20.2°; c = 0.41).[99]

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-pent-1-yn-3-amine (56)[2]



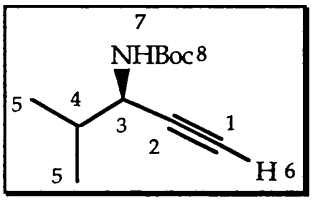
36d (0.63 mmol; 0.170) was treated with TBAF (1M in THF; 2 eq.; 1.26 mmol; 1.26 ml) in wet THF (5ml) as for **60** to give **56** as a clear oil (0.109 g; 88 %).

R_F = 0.45 (20% EtOAc in hexane).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.98 (d, J = 6.8, H-5, 1H); 1.44 (s, H-8, 9H); 1.89 (m, H-4, 1H); 2.25 (d, J = 2.4, H-6, 1H); 4.31 (bs, H-3, 1H); 4.78 (bs, H-7, 1H).

All other data were identical to that of the literature.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-pent-1-yn-3-amine (56)[2]



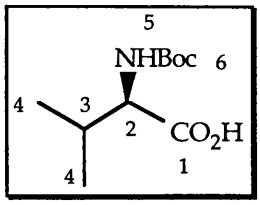
36d (0.011 mmol; 0.0029 g) was suspended in aqueous HCl (6 N; 1 ml) and heated at 100 °C for 2 hours. The solvent was removed *in vacuo* and the white residue was dissolved in DCM (0.4 ml). TEA (0.5 ml) was added followed by a solution of Boc_2O (3 eq.; 0.033 mmol; 0.0072g) in DCM (0.1 ml). The mixture was stirred for 24 hours after which the solvents were removed *in vacuo*. The residue was purified by column chromatography (silica gel; 20 % EtOAc in Hexane; R_F = 0.45) to give the title compound as a clear oil (0.005 g, 23 %).

^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.98 (d, J = 6.8, H-5, 1H); 1.44 (s, H-8, 9H); 1.89 (m, H-4, 1H); 2.25 (d, J = 2.4, H-6, 1H); 4.31 (bs, H-3, 1H); 4.78 (bs, H-7, 1H).

$[\alpha]_D$ (c = 0.25 mg ml^{-1}) = + 24.00° (lit. = - 45.3°; c = 1.04).[2]

All other data were identical to that of the literature.

N-(*tert*-butoxycarbonyl)-valine[116]

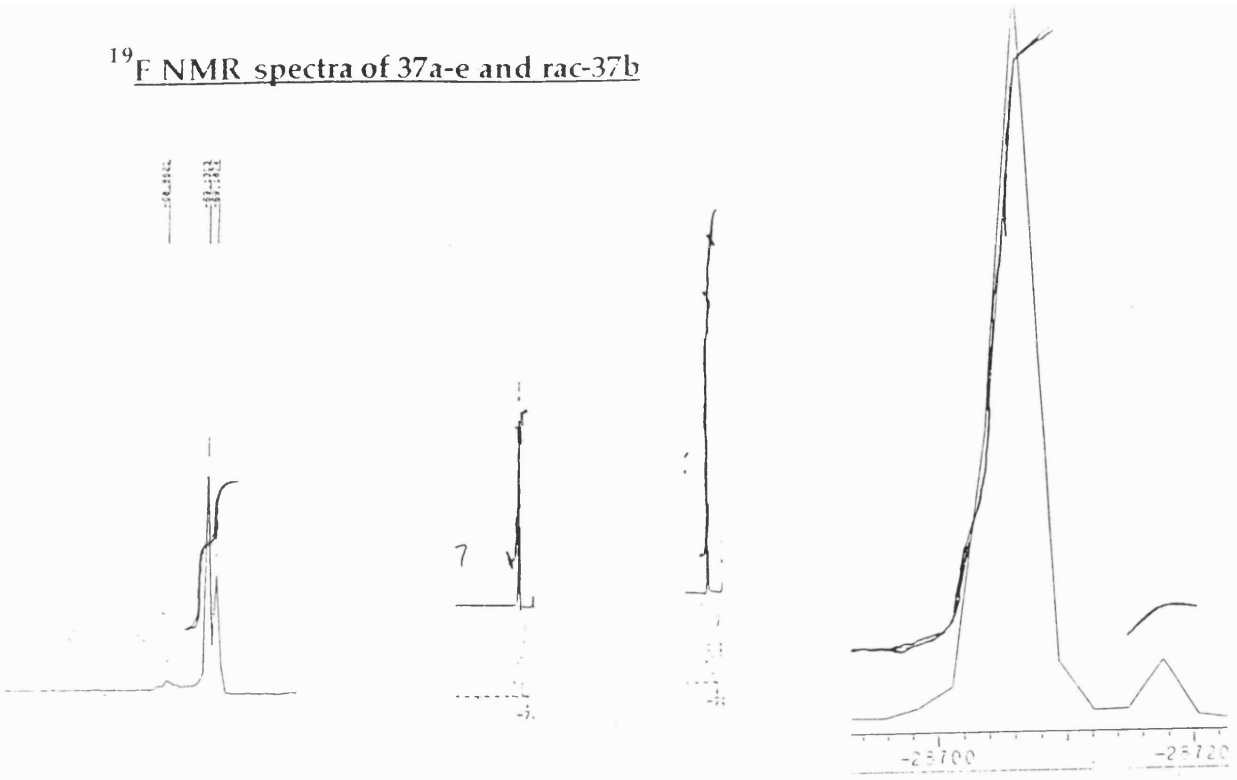


To a solution of **56** (0.28 mmol; 0.055 g) in CCl_4: CH_3CN: H_2O (1 : 1 : 1.4) (1.15 ml: 1.15 ml: 1.64 ml) was added $NaIO_4$ (4.1 eq.; 1.15 mmol; 0.247 g) and $RuCl_3$ (0.23 eq.; 0.0066 mmol; 0.00137 g). The mixture was stirred for 45 minutes and then filtered through Celite®. The filtrate was made basic with aqueous saturated $NaHCO_3$ solution (4 ml) and extracted with ether (3 x 3 ml). The basic aqueous layers were cooled in an ice/water bath and then carefully acidified (pH3) with 1M aqueous HCl solution (3 ml). The acidic layer was extracted with $CHCl_3$ (3 x 3 ml), dried over Na_2SO_4 and then solvents were removed *in vacuo* to give the title compound as a clear oil (0.048 g; 79 %).

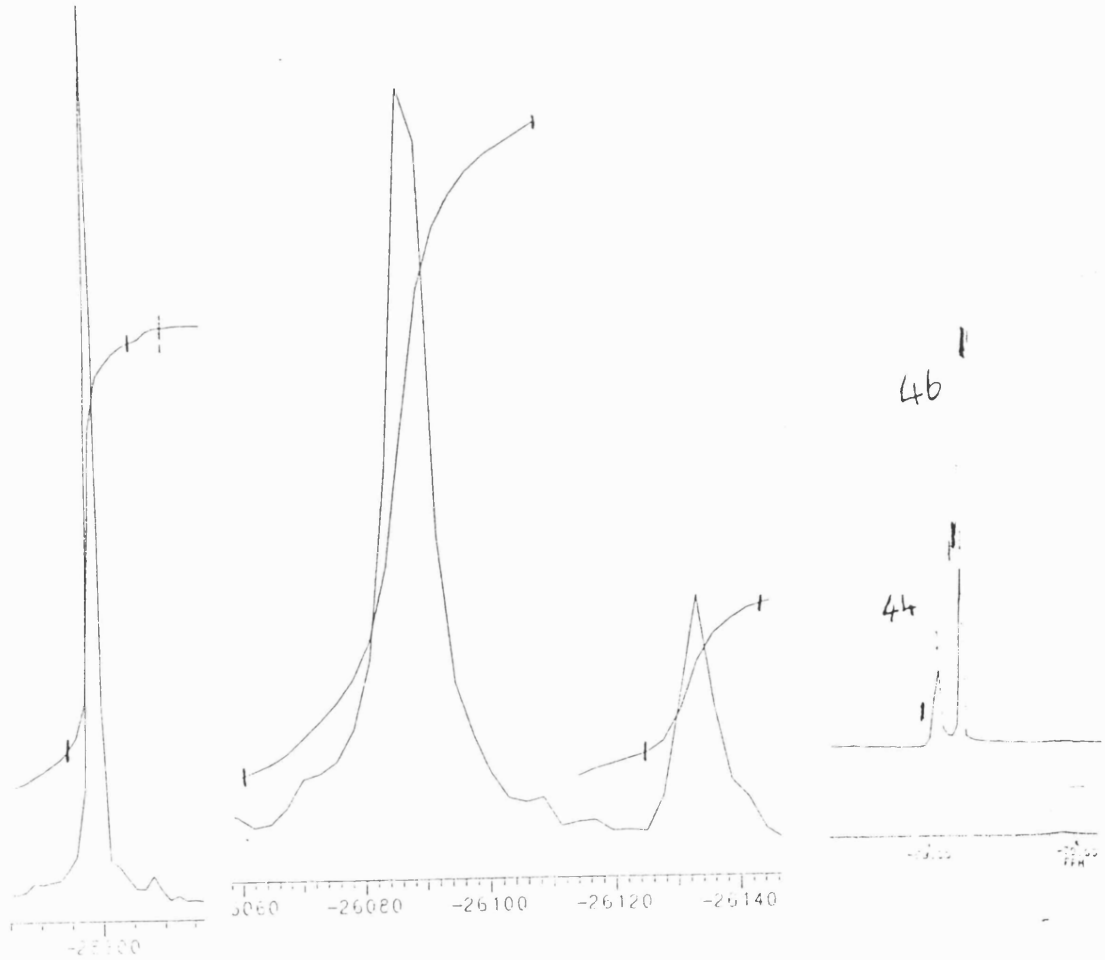
^{1}H NMR (300 MHz) ($CDCl_3$); δ 0.94 (d, J = 6.8, H-4, 3H); 1.01 (d, J = 6.8, H-4, 3H); 1.46 (s, H-6, 9H); 2.19-2.26 (m, H-3, 1H); 4.26 (dd, J = 8.8, 4.3, H-2, 1H); 5.09 (bd, J = 8.9, H-5, 1H); 8.34 (bs, 1H, CO_2**H**).

All other data were identical to that of the literature.

^{19}F NMR spectra of 37a-e and rac-37b



37a 37b 37c 37d



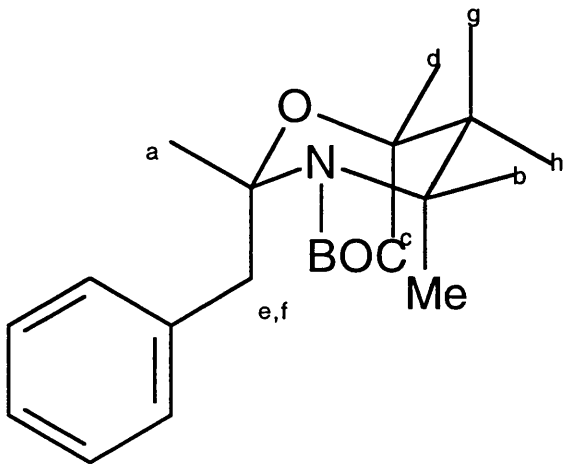
37e 37f rac-37b

Appendix 1: NMR Data

A.1.1 Solution Conformation of 25g by NMR Spectroscopy

Summary

The solution conformation for **25g** was was derived from COSY/NOESY data and found to be that of a twist chair.



25g

NMR

^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.37 (d, Me, 3H), 1.48 (s, BOC, 9H), 1.55 (m, Hh, 1H), 2.18 (m, Hg, 1H), 3.02 (dd, He or Hf, 1H), 3.21 (dd, He or Hf, 1H), 3.60 (dt, Hd, 1H), 4.05 (td, Hc, 1H), 4.42 (qd, Hb, 1H), 5.53 (dd, Ha, 1H), 7.28-7.19 (m, Ph, 5H).

Methodology

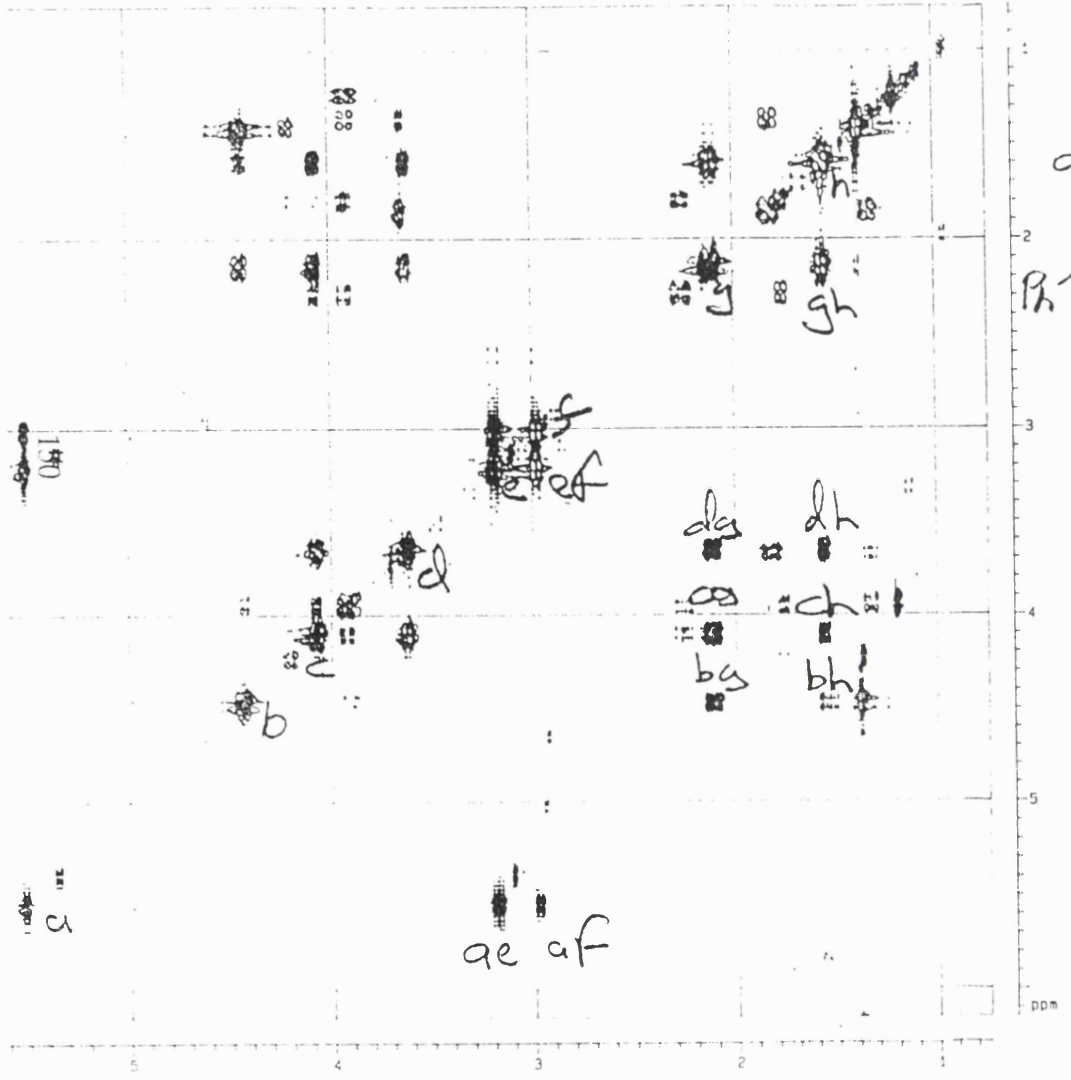
All experiments were performed on a Bruker AMX500 spectrometer. The ^{1}H 1D spectrum was assigned by analysis of a 2D-DQF-COSY. A NOESY experiment was then performed, and processed using SYBYL / TRIAD on a

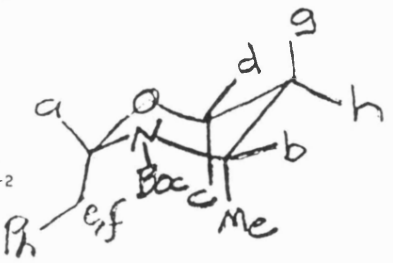
Silicon Graphics "Indigo" workstation to generate distance constraints for a unique solution conformation.

Results

COSY gave the following consistent spin system:- e/f - a, Me - b - g/h - c/d (Spectrum 1). Most NOEs observed could be satisfied by a chair conformation with both benzyl and methyl groups axial (Boc equatorial) (Spectra 2, 3 and 4). However, coupling constants and a small NOE (a - d), i.e. C2 to C4, gave evidence of distortion (Spectrum 5). NOE data was processed using SYBYL and TRIAD to generate 26 unique distance constraints. The result of molecular modelling with energy minimisation under these constraints was that **25g** existed as a twist chair in solution.

Spectrum 1





Current Data Parameters

NAME	88412_26
EXPNO	13
PROCNO	1

F2 - Acquisition Parameters

Date_	960827
Time	14.01
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	cosygpmftp
TD	4096
SOLVENT	CDCl3
NS	2
DS	8
SWH	6024.096 Hz
FIDRES	1.470727 Hz
AQ	0.3400180 sec
RG	16384
DW	83.000 usec
DE	118.57 usec
TE	300.0 K
P16	1000.00 usec
L21	100
P1	7.50 usec
D16	0.00010000 sec
NL1	1 dB
D1	1.29999995 sec
D0	0.0000030 sec
D20	0.0001000 sec
P2	0.0 usec
D13	0.0000040 sec
D27	0.0000000 sec
DE	118.57 usec
SFO1	500.1325006 MHz
NUCLEUS	1H
IN0	0.00008300 sec

F1 - Acquisition parameters

ND0	2
TD	512
SFO1	500.1333 MHz
FIDRES	11.765830 Hz
SW	12.045 ppm

F2 - Processing parameters

SI	2048
SF	500.1300073 MHz
WDW	QSINE
SSB	2.2
LB	0.00 Hz
GB	0
PC	1.40

F1 - Processing parameters

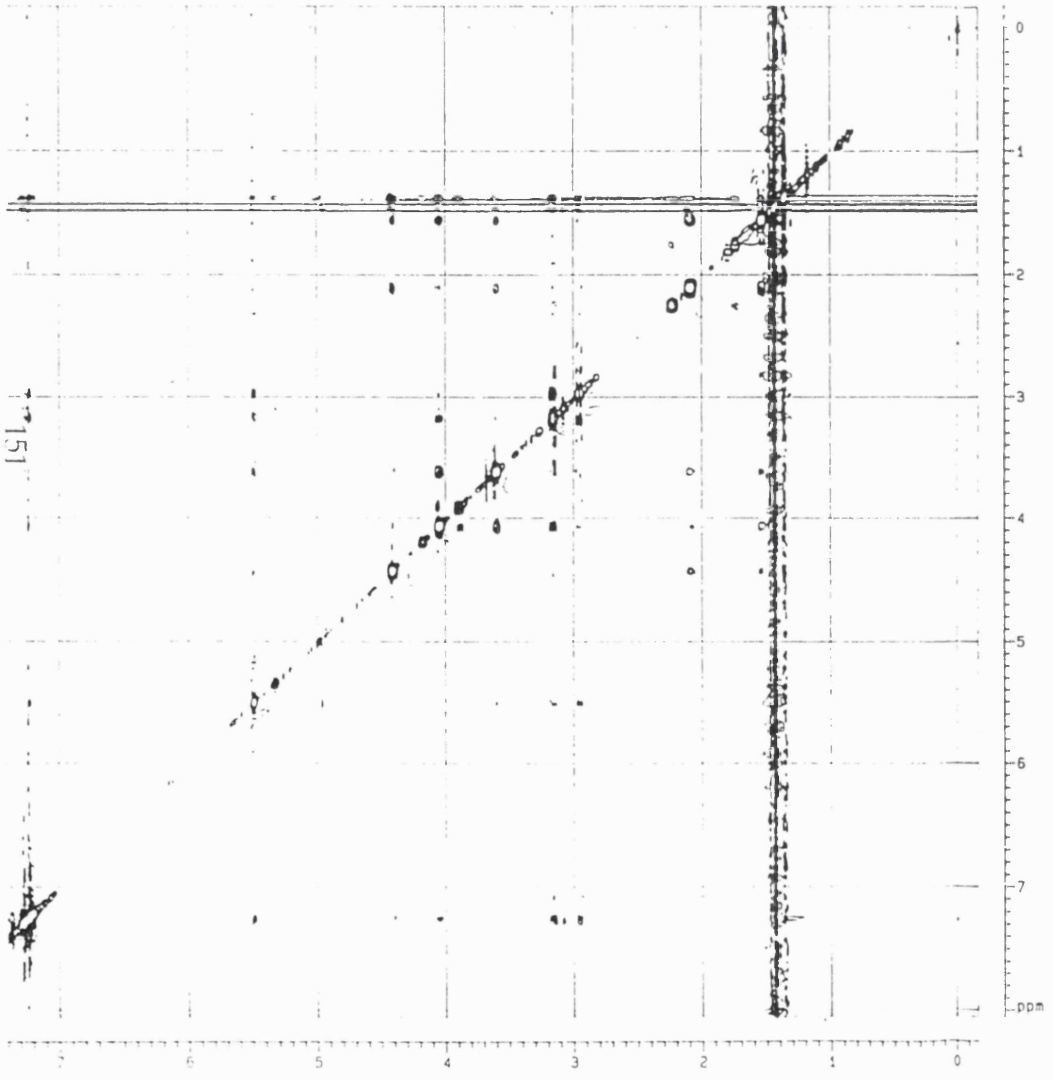
SI	512
MC2	TPPI
SF	500.1307478 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	20.00 cm
CX1	20.00 cm
F2PL0	5.944 ppm
F2L0	2972.81 Hz
F2PHI	0.733 ppm
F2HI	366.68 Hz
F1PL0	6.147 ppm
F1L0	3074.35 Hz
F1PHI	0.760 ppm
F1HI	379.97 Hz
F2PPMCM	0.26055 ppm/cm
F2HZCM	130.30638 Hz/cm
F1PPMCM	0.26937 ppm/cm
F1HZCM	134.71875 Hz/cm

Spectrum 2

A.Rae
CDCl3 300K
/8/96



a ⇒ e, F, (d), Ph
b ⇒ g, h, Me
c ⇒ d, e, h, Ph
d ⇒ e, g, h
e ⇒ f, Me
g ⇒ h
Me ⇒ Ph

Current Data Parameters

NAME	88412_26
EXPNO	12
PROCNO	1

F2 - Acquisition Parameters

Date_	960822
Time	16.21
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	noesytp2
TD	4096
SOLVENT	CDCl3
NS	48
DS	8
SWH	6250.000 Hz
FIDRES	1.525879 Hz
AQ	0.3277300 sec
RG	256
DW	80.000 usec
DE	114.29 usec
TE	300.0 K
PL1	1 dB
D1	1.29999995 sec
P1	7.50 usec
D0	0.0000030 sec
D9	0.50000000 sec
DE	114.29 usec
SFO1	500.1325006 MHz
NUCLEUS	1H
IN0	0.00008000 sec

F1 - Acquisition parameters

ND0	2
TD	512
SFO1	500.1333 MHz
FIDRES	12.207061 Hz
SW	12.497 ppm

F2 - Processing parameters

SI	2048
SF	500.1300217 MHz
WDW	QSINE
SSB	2.2
LB	0.00 Hz
GB	0
PC	2.00

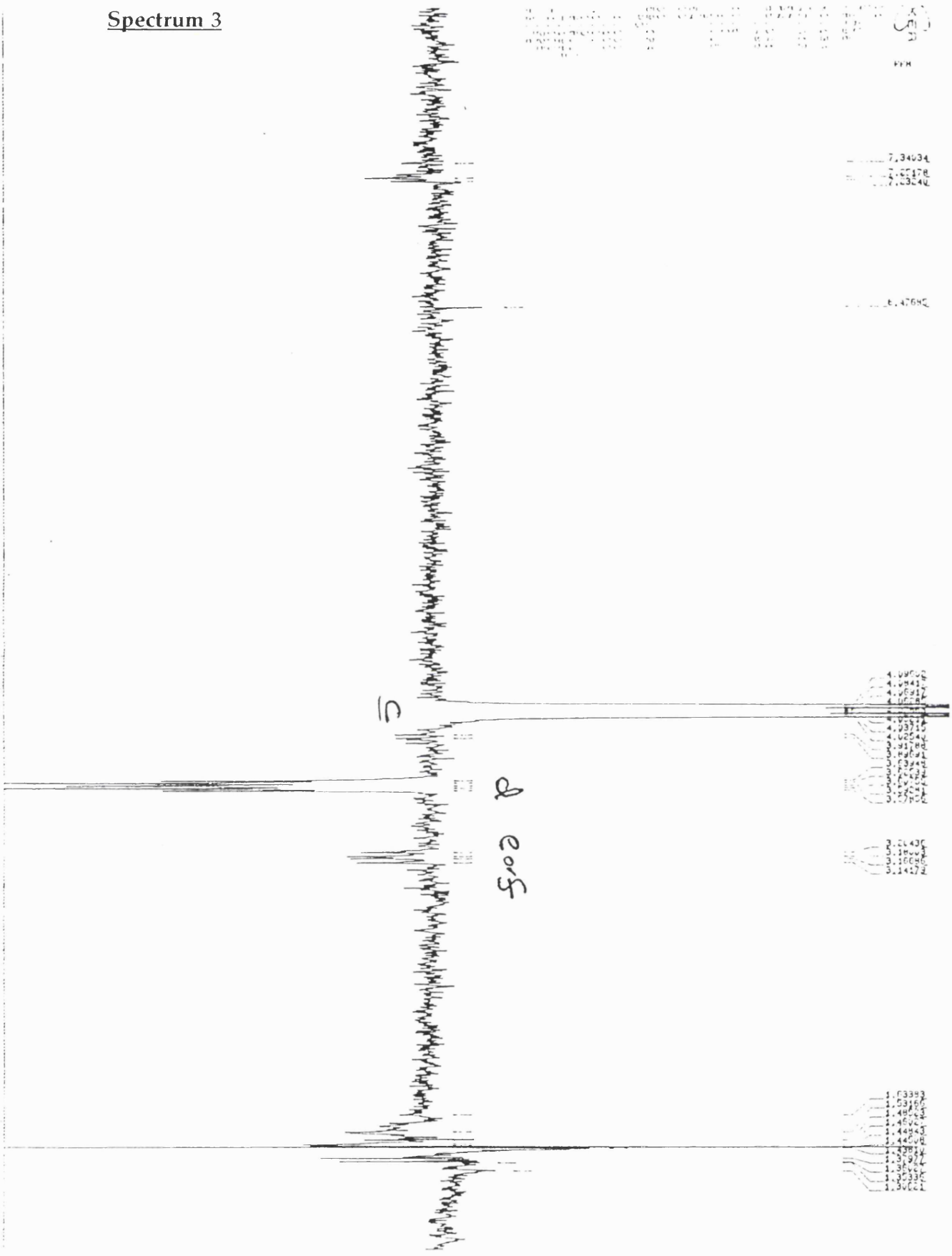
F1 - Processing parameters

SI	512
MC2	TPPI
SF	500.1307700 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

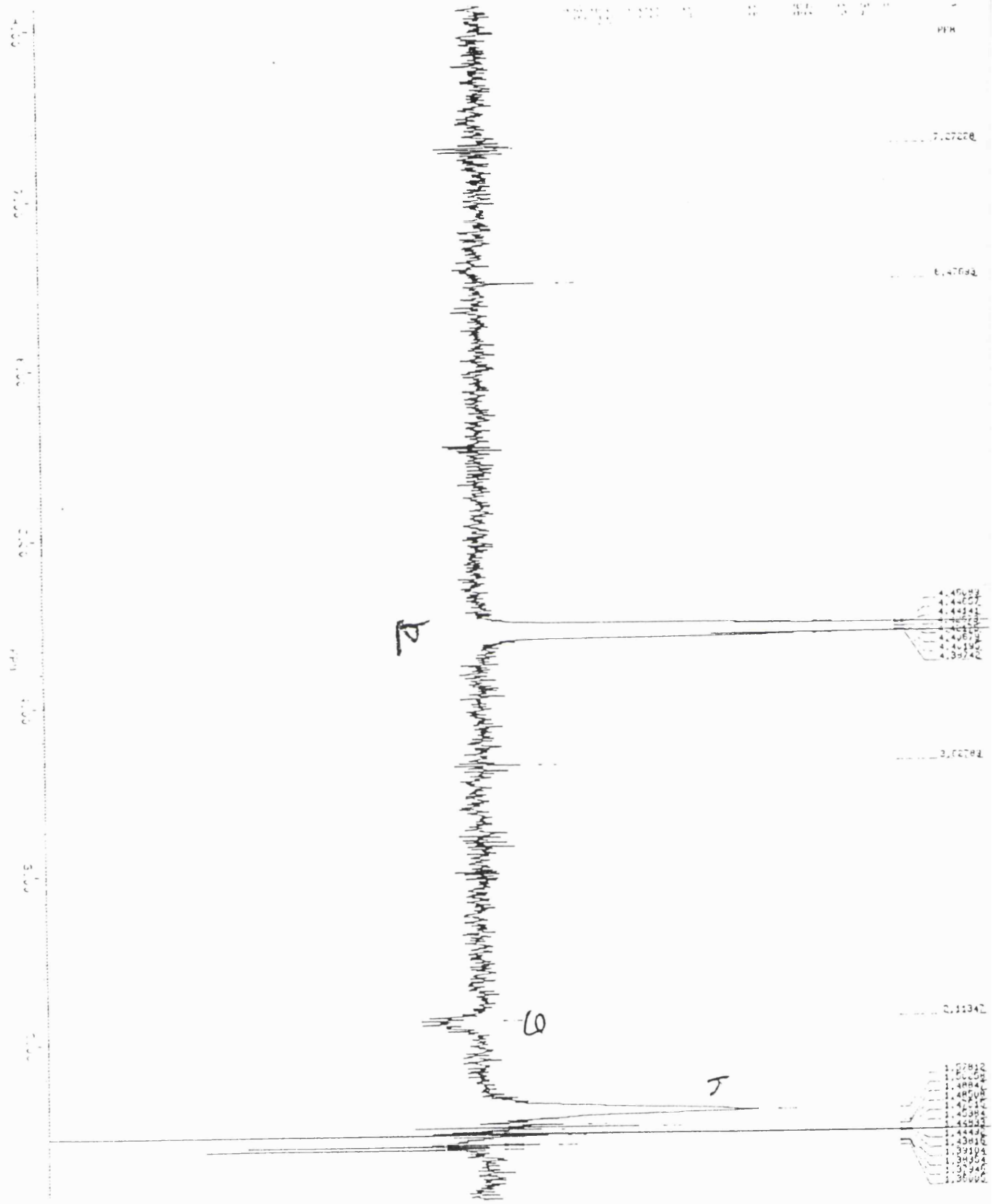
2D NMR plot parameters

CX2	20.00 cm
CY1	20.00 cm
F2P_0	8.050 ppm
F2_0	4026.22 Hz
F2P_1	-0.175 ppm
F2_1	-87.55 Hz
F1P_0	8.049 ppm
F1_0	4025.56 Hz
F1P_1	-0.176 ppm
F1_1	-88.21 Hz
F2PPMCM	0.41127 ppm/cm
F2HZCM	205.68855 Hz/cm
F1PPMCM	0.41127 ppm/cm
F1HZCM	205.68875 Hz/cm

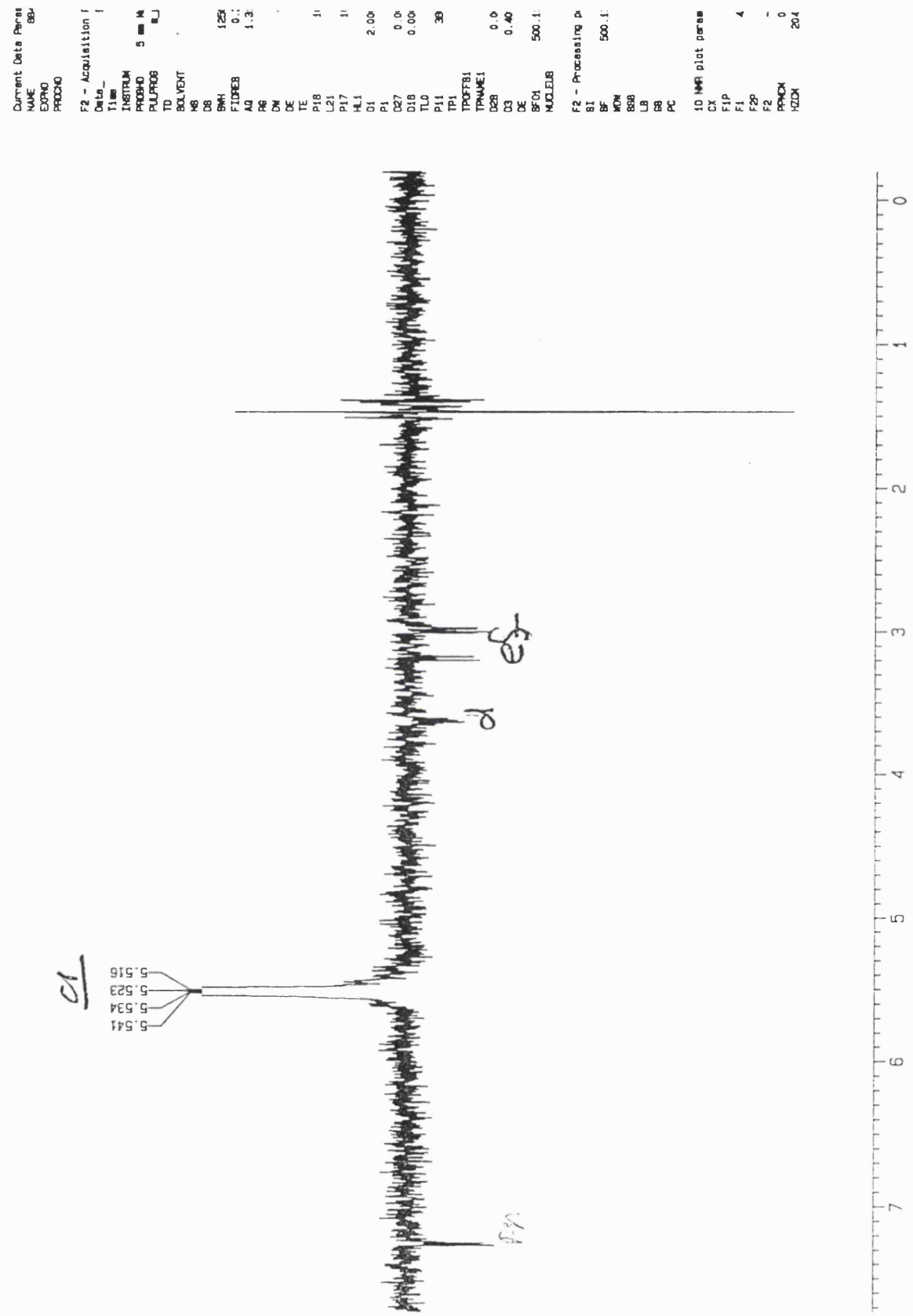
Spectrum 3



Spectrum 4



Spectrum 5



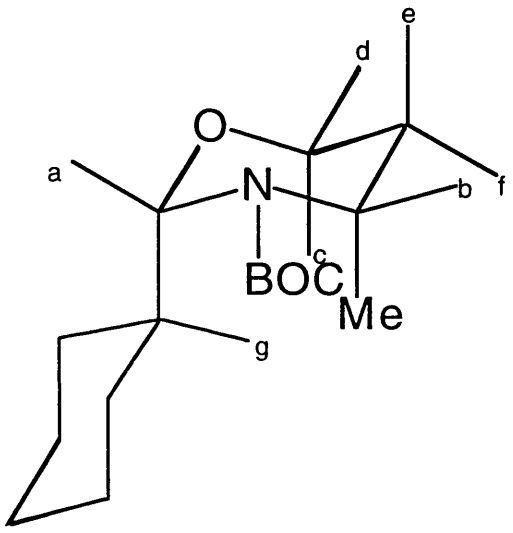
elected NOE
C)

A.1.2 Solution Conformation of 25a by NMR Spectroscopy

In order to establish if the major/minor peaks at position (a) were due to either rotatmers of the Boc group or a ratio of diastereoisomers, **25a** also underwent structural analysis by COSY/NOESY spectroscopy.

Summary

The solution conformation of **25a** was also found to be that of a twist chair, with both peaks corresponding to (a) giving identical NOE data.



25a

NMR

^{1}H NMR (500 MHz) ($CDCl_3$); δ 1.31 (d, Me, 3H), 1.45 (s, BOC, 9H), 1.50-1.82 (m, Cyclohexyl, 11H), 1.92-2.13 (m, He and Hf, 2H), 3.61 (dt, Hd, 1H), 3.91 (td, Hc, 1H), 4.42 (qd, Hb, 1H), 4.79(d, Ha-minor, 0.05H), 5.18 (d, Ha-major, 0.95H).

Methodology

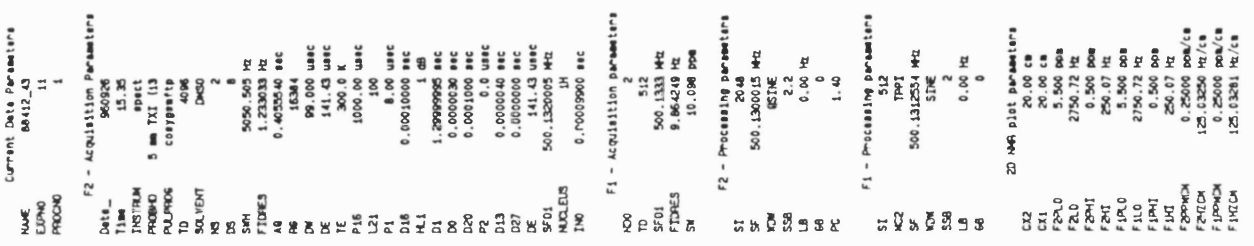
All experiments were performed on a Bruker AMX500 spectrometer. The ^{1}H 1D spectrum was assigned by analysis of a 2D-DQF-COSY. A NOESY experiment was then performed to establish the overall conformation.

Results

COSY gave the following consistent spin system:- g - a, Me - b - e/f - c/d (Spectrum 6). As in **25g** NOEs observed could be satisfied by a twist-chair conformation with both cyclohexyl and methyl groups axial (Boc equatorial) (Spectra 7 and 8).

NOE experiments on (a)-minor gave identical results to those for (a)-major (Spectrum 8) therefore it can be deduced that these peaks correspond to the same diastereoisomer (compare Spectra 9 and 10).

Spectrum 6



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PROCNO                       1

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Time                    15.25
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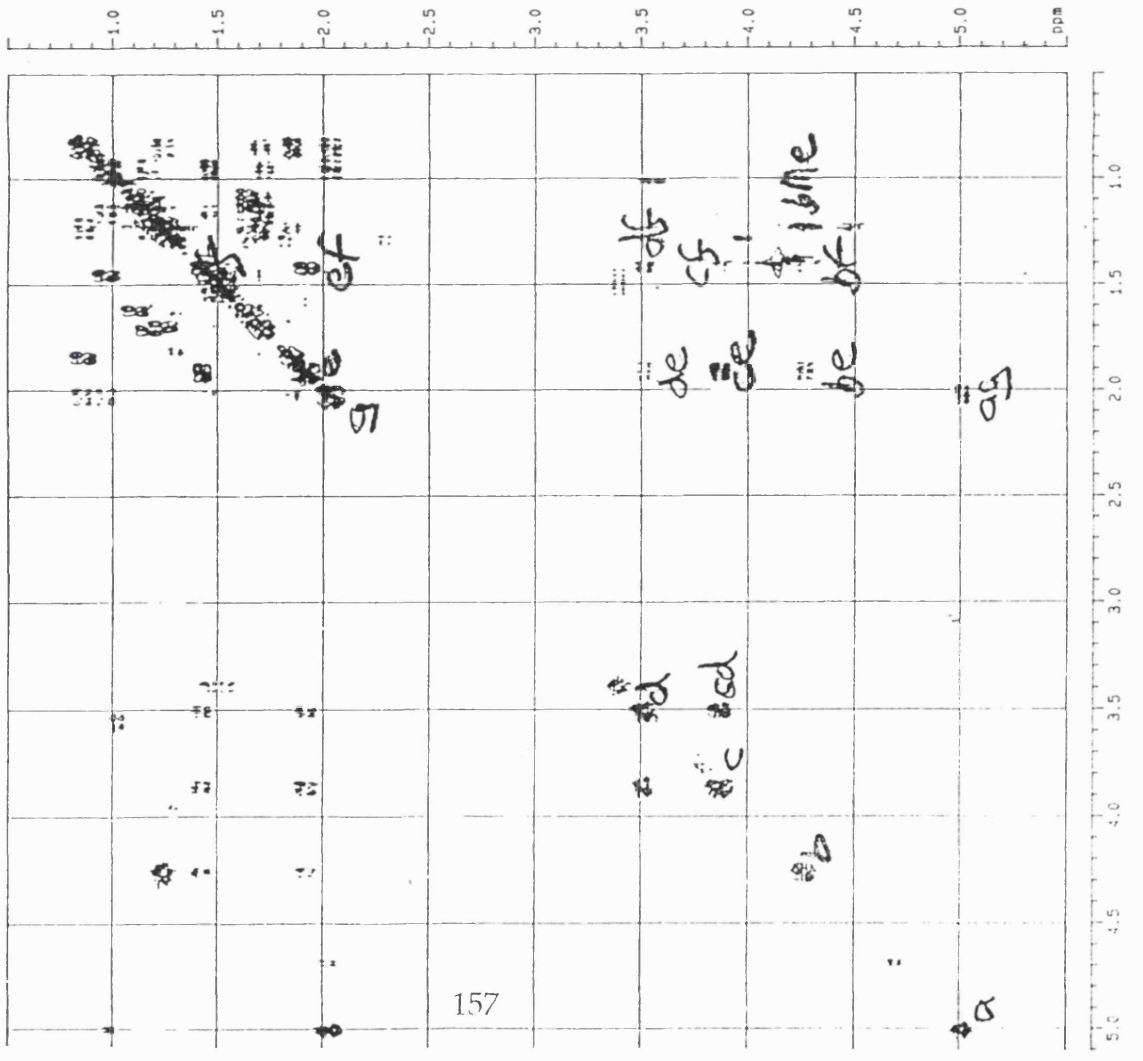
PULPROG                 cosygpmfqf
TD                        4096
SOLVENT                   CHCl3
NS                           2
DS                           8
SWH                   5050.505 Hz
FIDRES                1.233033 Hz
AQ                    0.4055540 sec
RG                       16384
DW                    99.000 usec
DE                    141.43 usec
TE                    300.0 K
P16                   1000.00 usec
L21                         100
P1                       8.00 usec
D16                   0.00010000 sec
HL1                          1 dB
D1                    1.29999995 sec
D0                    0.00000030 sec
D20                   0.00001000 sec
P2                       0.0 usec
D13                   0.00000040 sec
D27                   0.00000000 sec
DE                       141.43 usec
SFO1                  500.1320005 MHz
NUCLEUS                     1H
INO                   0.70003900 sec

F1 - Acquisition parameters
NDO                          2
TD                         512
SFO1                  500.1333 MHz
FIDRES                9.864249 Hz
SW                      10.098 ppm

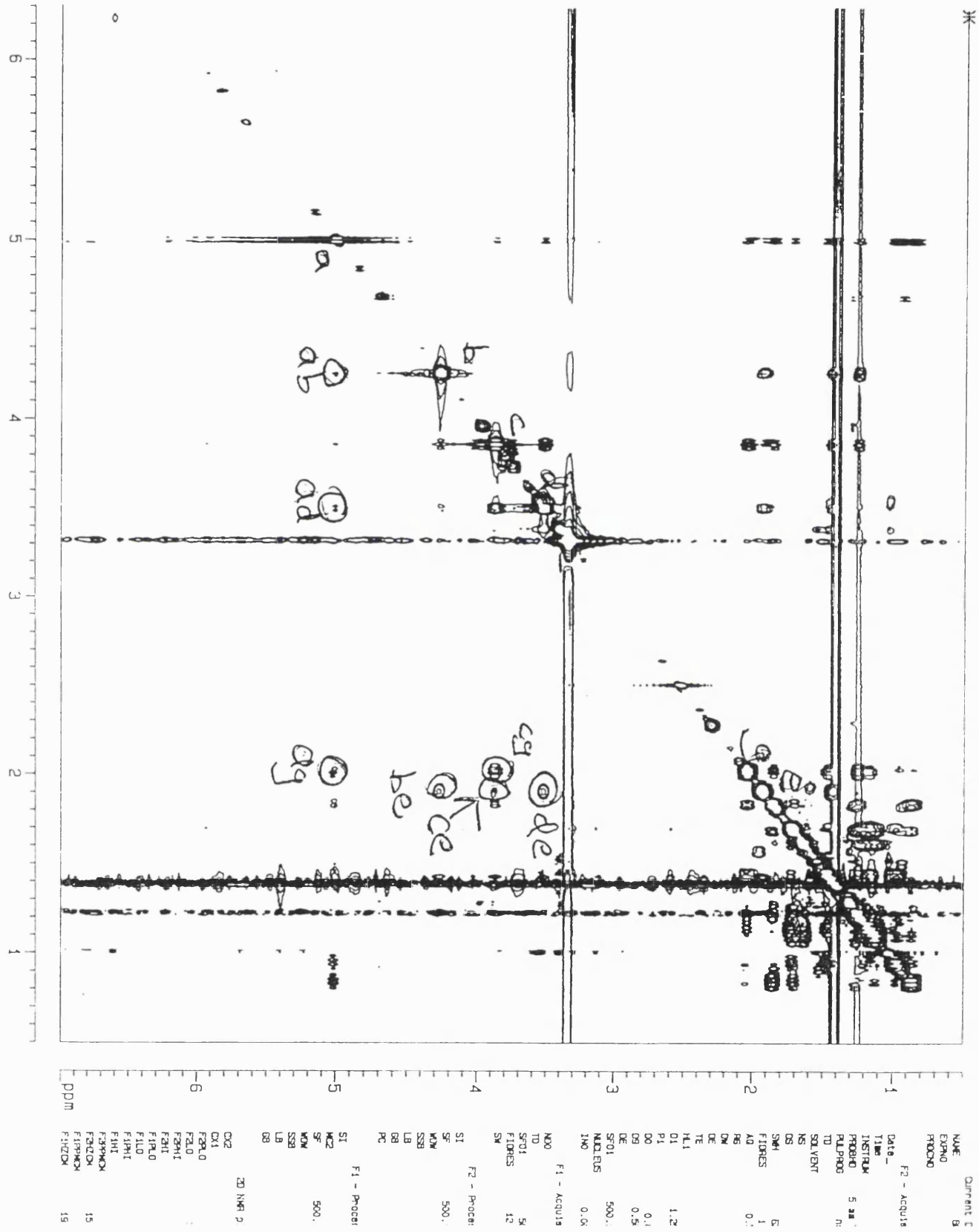
F2 - Processing parameters
SI                        2048
SF                    500.1300015 MHz
WDW                      QSINE
SSB                          2.2
LB                      0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                         512
                          TPPI
MC2
SF                    500.1312534 MHz
WDW                      SINE
SSB                          2
LB                      0.00 Hz
GB                           0

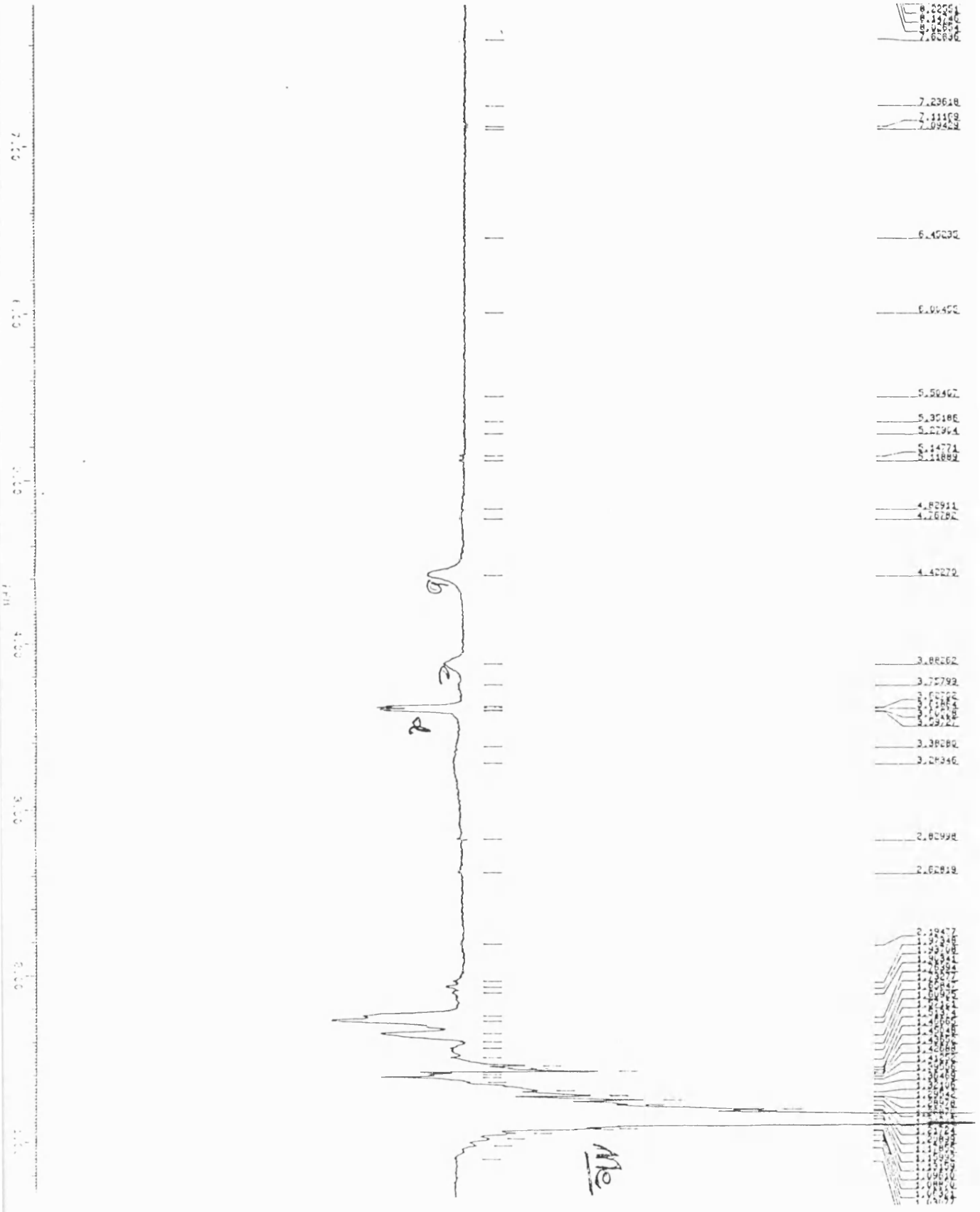
2D NMR plot parameters
CX2                      20.00 cm
CY1                      20.00 cm
F2PLO                 5.500 ppm
F2LO                  2750.72 Hz
F2PHI                 0.500 ppm
F2HI                  250.07 Hz
F1PLO                 5.500 ppm
F1LO                  2750.72 Hz
F1PHI                 0.500 ppm
F1HI                  250.07 Hz
F2PPMCM               0.25000 ppm/cm
F2HZCM                125.03250 Hz/cm
F1PPMCM               0.25000 ppm/cm
F1HZCM                125.03291 Hz/cm
```



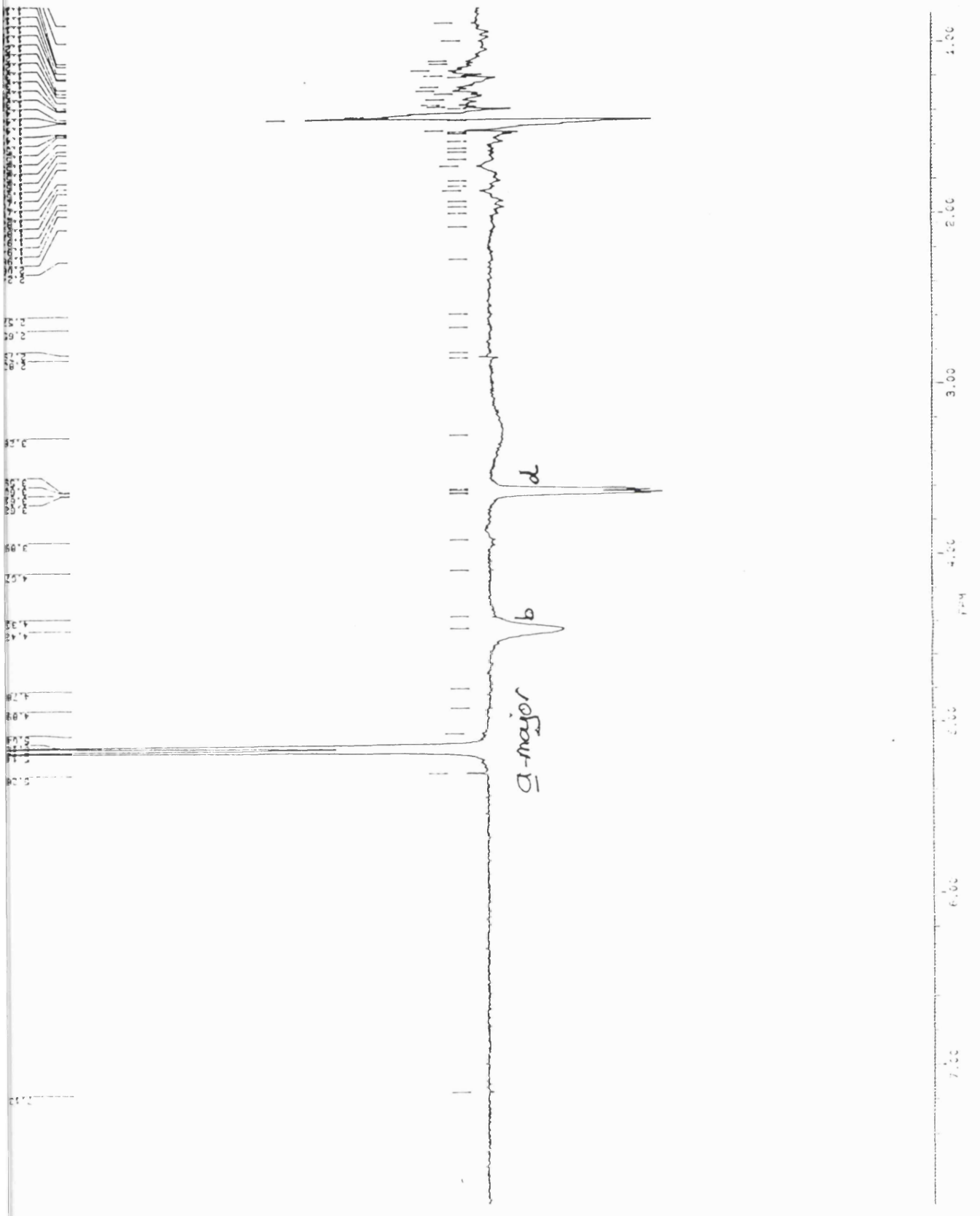
Spectrum 7



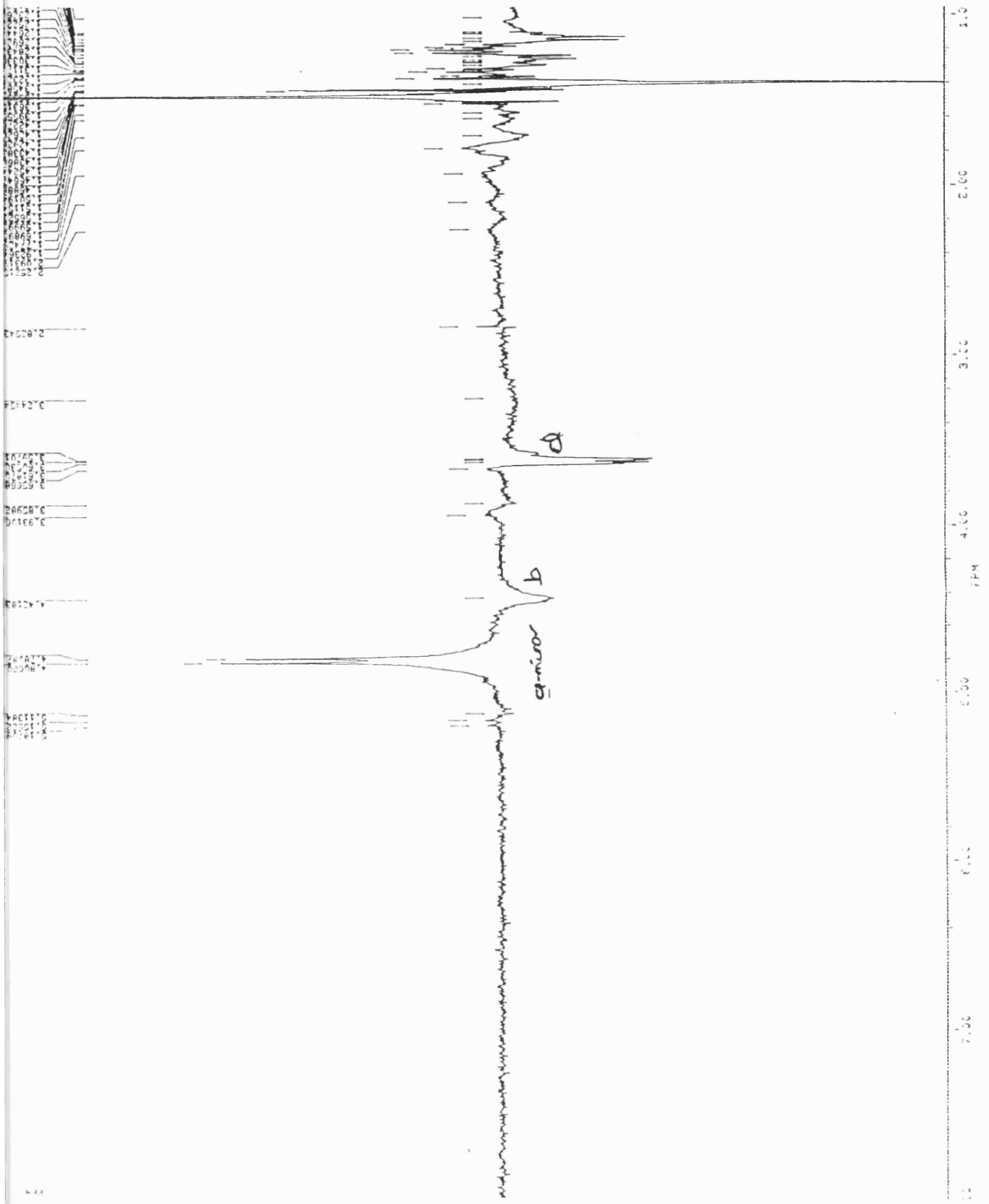
Spectrum 8



Spectrum 9

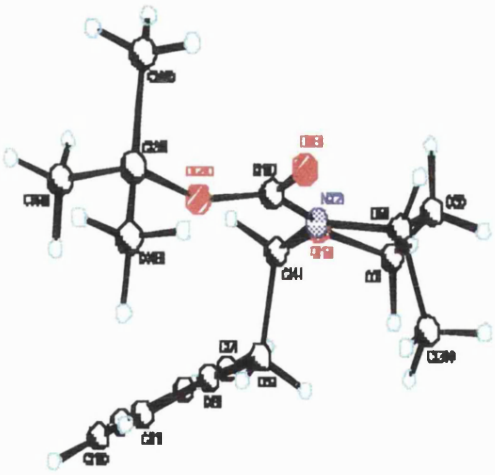


Spectrum 10

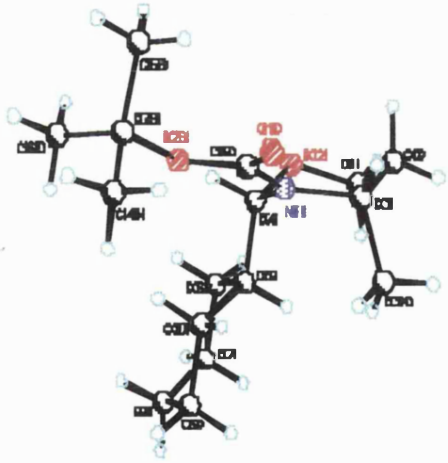


Appendix 2: X-ray Crystallography Data

Crystals of **25g** and **25a** were grown by evapouration from ethyl acetate/hexane mixtures. Data was collected in the range of $5 \leq 2\theta \leq 120°$ on a Stoe Stadi4 x-ray diffractometer equipped with an Oxford Cryosystems low temperature device[117] using ω-θ scans and on-line profile fitting.[118] The structure of both molecules was solved by direct methods (Shelxtl)[119] and refined against $F°$ with anisotropic displacement parameters for all non-H atoms, and H atoms placed in calculated positions. The structures were revealed to be a twist-chair with the methyl group from the auxiliary and the benzyl (**25g**) or cyclohexyl (**25a**) groups in pseudo-axial conformations.



25g



25a

Crystal data and structure refinement for 25g at 220(2) K.

Empirical formula	$C_{17}H_{25}NO_3$
Formula weight	291.38
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.0668(10) Å alpha = 90 deg. b = 11.952(3) Å beta = 90 deg. c = 23.096(9) Å gamma = 90 deg.
Volume	1674.7(8) $Å^3$
Z	4
Density (calculated)	1.156 Mg/m^3
Absorption coefficient	0.628 mm^{-1}
F(000)	632
Crystal description	Colourless column
Crystal size	0.43 x 0.12 x 0.08 mm
Theta range for data collection	3.83 to 60.09 deg.
Index ranges	-6<=h<=6, -9<=k<=13, -12<=l<=25
Reflections collected	1488
Independent reflections	1447 [R(int) = 0.0358]
Scan type	omega-theta
Data/restraints/parameters	1441/185/190 (Full-matrix least-squares on F^2)
Goodness-of-fit on F^2	1.012
Conventional R [F>4sigma(F)]	R1 = 0.0997 [552 data]
R indices (all data)	R1 = 0.2362, wR2 = 0.2847
Absolute structure parameter	0.7(18)
Final maximum delta/sigma	0.001
Weighting scheme	
calc w=1/[\s^2^(Fo^2^)+(0.1101P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.257 and -0.341 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **25g**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	5309(25)	1301(11)	2360(6)	49(4)
C(2)	5241(23)	2390(12)	2648(6)	53(4)
C(3)	2986(23)	2989(11)	2565(6)	43(3)
C(3M)	1270(22)	2506(12)	2988(5)	48(4)
C(4)	2746(24)	1881(10)	1606(6)	44(3)
C(5)	984(22)	962(11)	1706(6)	46(3)
C(6)	1063(23)	90(10)	1241(5)	30(3)
C(7)	2836(24)	-668(11)	1193(6)	44(3)
C(8)	2790(27)	-1475(12)	784(5)	50(4)
C(6)	1084(29)	-1639(13)	398(6)	62(4)
C(10)	-736(28)	-894(13)	455(6)	57(4)
C(11)	-687(28)	-69(13)	861(6)	57(4)
N(12)	2292(18)	2883(9)	1966(5)	40(2)
O(13)	4898(14)	1447(7)	1753(4)	44(2)
C(1B)	945(22)	3704(11)	1732(6)	37(3)
O(1B)	403(16)	4524(7)	2023(4)	52(3)
O(2B)	321(15)	3444(7)	1207(4)	46(2)
C(3B)	-1036(25)	4205(13)	864(6)	49(3)
C(4B)	-3328(23)	4384(16)	1161(7)	79(6)
C(5B)	-1235(33)	3616(16)	286(6)	104(7)
C(6B)	63(28)	5302(12)	789(7)	84(6)

Bond lengths [Å] and angles [deg] for **25g**.

C(1)-O(13)	1.434(14)
C(1)-C(2)	1.46(2)
C(2)-C(3)	1.56(2)
C(3)-N(12)	1.452(15)
C(3)-C(3M)	1.54(2)
C(4)-O(13)	1.45(2)
C(4)-N(12)	1.483(15)
C(4)-C(5)	1.55(2)
C(5)-C(6)	0.50(2)
C(6)-C(11)	1.39(2)
C(6)-C(7)	1.41(2)
C(7)-C(8)	1.35(2)
C(8)-C(9)	1.38(2)
C(9)-C(10)	1.42(2)
C(10)-C(11)	1.36(2)
N(12)-C(1B)	1.39(2)
C(1B)-O(1B)	1.233(14)
C(1B)-O(2B)	1.307(14)
O(2B)-C(3B)	1.46(2)
C(3B)-C(6B)	1.48(2)
C(3B)-C(5B)	1.51(2)
C(3B)-C(4B)	1.57(2)

O(13)-C(1)-C(2)	109.4(11)
C(1)-C(2)-C(3)	112.2(12)
N(12)-C(3)-C(3M)	112.0(11)
N(12)-C(3)-C(2)	109.4(12)
C(3M)-C(3)-C(2)	110.1(11)
O(13)-C(4)-N(12)	109.0(11)
O(13)-C(4)-C(5)	109.4(10)
N(12)-C(4)-C(5)	111.2(11)
C(6)-C(5)-C(4)	111.4(11)
C(11)-C(6)-C(7)	116.4(12)
C(11)-C(6)-C(5)	121.6(13)
C(7)-C(6)-C(5)	121.8(13)
C(8)-C(7)-C(6)	119.8(14)
C(7)-C(8)-C(9)	124.7(15)
C(8)-C(9)-C(10)	115.7(14)
C(11)-C(10)-C(9)	119.9(15)
C(10)-C(11)-C(6)	123.4(15)
C(1B)-N(12)-C(3)	118.7(11)
C(1B)-N(12)-C(4)	117.5(10)
C(3)-N(12)-C(4)	123.5(11)
C(1)-O(13)-C(4)	115.5(11)
O(1B)-C(1B)-O(2B)	128.1(13)
O(1B)-C(1B)-N(12)	120.5(12)
O(2B)-C(1B)-N(12)	111.4(12)

C(1B)-O(2B)-C(3B)	121.2(11)
O(2B)-C(3B)-C(6B)	111.2(12)
O(2B)-C(3B)-C(5B)	103.5(12)
C(6B)-C(3B)-C(5B)	110.1(15)
O(2B)-C(3B)-C(4B)	110.4(11)
C(6B)-C(3B)-C(4B)	109.3(14)
C(5B)-C(3B)-C(4B)	112.3(14)

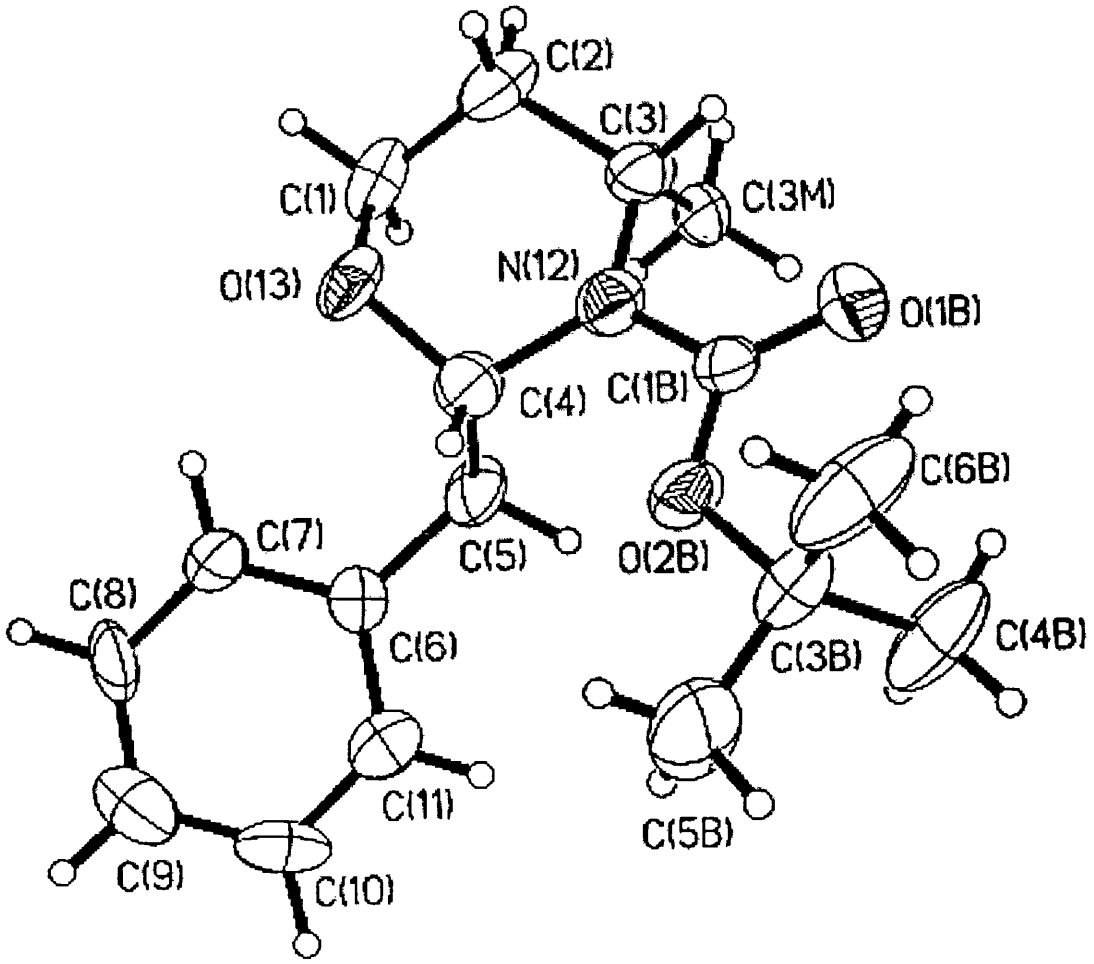
Anisotropic displacement parameters ($Å^2 \times 10^3$) for **25g**.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
C(1)	30(8)	50(8)	66(7)	14(7)	9(7)	12(7)
C(2)	28(7)	60(8)	71(8)	8(7)	-6(7)	-2(8)
C(3)	40(7)	34(8)	56(7)	0(6)	-15(6)	2(6)
C(3M)	40(8)	66(10)	37(6)	-23(8)	-3(7)	15(8)
C(4)	39(7)	30(6)	62(8)	-3(6)	-6(7)	-1(5)
C(5)	22(6)	43(7)	73(9)	-9(6)	8(8)	-4(6)
C(6)	38(7)	19(6)	34(6)	9(5)	3(6)	-2(5)
C(7)	35(7)	42(8)	55(8)	-7(6)	-11(7)	8(6)
C(8)	57(9)	57(9)	37(8)	-13(7)	16(7)	21(8)
C(9)	76(10)	59(9)	52(9)	-18(8)	5(8)	-14(8)
C(10)	66(9)	65(10)	40(8)	3(7)	-26(8)	-11(8)
C(11)	50(9)	64(9)	56(9)	-2(7)	-16(7)	15(8)
N(12)	35(6)	35(5)	48(5)	2(5)	-3(5)	-1(5)
O(13)	19(4)	41(5)	71(5)	6(5)	4(5)	-2(4)
C(1B)	28(7)	33(7)	50(7)	-5(6)	-9(6)	-1(6)
O(1B)	56(7)	40(5)	59(6)	-9(5)	-8(6)	8(5)
O(2B)	42(5)	41(5)	55(5)	4(4)	-16(5)	8(5)
C(3B)	32(7)	62(8)	53(8)	13(7)	-2(7)	11(7)
C(4B)	30(7)	124(15)	84(12)	37(12)	13(8)	18(8)
C(5B)	113(16)	132(14)	67(9)	-19(10)	-41(10)	71(14)
C(6B)	46(9)	80(9)	127(14)	61(10)	-19(12)	-5(9)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **25g**.

	x	y	z	U(eq)
H(1A)	6758(25)	956(11)	2417(6)	58
H(1B)	4192(25)	805(11)	2527(6)	58
H(2A)	6418(23)	2865(12)	2493(6)	64
H(2B)	5517(23)	2287(12)	3063(6)	64
H(3)	3183(23)	3794(11)	2653(6)	52
H(3M1)	-128(22)	2885(12)	2933(5)	72
H(3M2)	1771(22)	2617(12)	3383(5)	72
H(3M3)	1087(22)	1713(12)	2915(5)	72
H(4)	2737(24)	2100(10)	1193(6)	52
H(5A)	1235(22)	607(11)	2083(6)	55
H(5B)	-483(22)	1305(11)	1712(6)	55
H(7)	4046(24)	-612(11)	1446(6)	53
H(8)	4007(27)	-1959(12)	760(5)	60
H(9)	1120(29)	-2206(13)	116(6)	75
H(10)	-1969(28)	-972(13)	212(6)	68
H(11)	-1900(28)	418(13)	886(6)	68
H(4B1)	-4051(23)	3666(16)	1211(7)	119
H(4B2)	-4235(23)	4863(16)	920(7)	119
H(4B3)	-3118(23)	4732(16)	1537(7)	119
H(5B1)	-1956(33)	2899(16)	340(6)	156
H(5B2)	223(33)	3498(16)	125(6)	156
H(5B3)	-2098(33)	4072(16)	23(6)	156
H(6B1)	182(28)	5672(12)	1161(7)	126
H(6B2)	-798(28)	5763(12)	528(7)	126
H(6B3)	1524(28)	5189(12)	629(7)	126

Ortep Plot of 25g



Crystal data and structure refinement for 25a at 220(2) K.

Empirical formula	$C_{16}H_{29}NO_3$
Formula weight	283.40
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 10.1919(12) A alpha = 90 deg.
	b = 11.4054(9) A beta = 90 deg.
	c = 14.4730(14) A gamma = 90 deg.
Volume	1682.4(3) $Å^3$
Z	4
Density (calculated)	1.119 Mg/m^3
Absorption coefficient	0.604 mm^{-1}
F(000)	624
Crystal description	Colourless column
Crystal size	0.39 x 0.20 x 0.12 mm
Theta range for data collection	4.94 to 60.04 deg.
Index ranges	-11<=h<=11, -11<=k<=12, -11<=l<=16
Reflections collected	3744
Independent reflections	2336 [R(int) = 0.0321]
Scan type	omega-theta with learnt profile
Data / restraints / parameters	2330/0/186 (Full-matrix least-squares on F^2)
Goodness-of-fit on F^2	1.054
Conventional R [F>4sigma(F)]	R1 = 0.0374 [2018 data]
R indices (all data)	R1 = 0.0466, wR2 = 0.0888
Absolute structure parameter	-0.1(3)
Extinction coefficient	0.0179(7)
Final maximum delta/sigma	0.000
Weighting scheme	
calc w=1/[\s^2^(Fo^2^)+(0.0320P)^2^+0.2754P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.095 and -0.123 $e.Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **25a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	3791(2)	2028(3)	3416(2)	60(1)
C (2)	4568(3)	2026(3)	4298(2)	62(1)
C(3)	6019(3)	2281(2)	4133(2)	50(1)
C(4)	5636(2)	1479(2)	2513(2)	38(1)
C(5)	5695(2)	2533(2)	1858(1)	36(1)
C(6)	4816(2)	2321(2)	1020(2)	52(1)
C(7)	4873(3)	3345(3)	344(2)	60(1)
C(8)	6261(3)	3608(2)	42(2)	53(1)
C(9)	7151(2)	3811(2)	873(2)	46(1)
C(10)	7093(2)	2781(2)	1543(2)	41(1)
N(11)	6475(2)	1588(2)	3334(1)	40(1)
O(12)	4332(2)	1204(1)	2779(1)	48(1)
C(1B)	7654(2)	1053(2)	3405(2)	42(1)
O(1B)	8357(2)	1120(2)	4080(1)	64(1)
O(2B)	7959(1)	439(1)	2635(1)	43(1)
C(3B)	9183(2)	-238(2)	2584(2)	41(1)
C(4B)	10367(2)	551(2)	2670(2)	60(1)
C(5B)	9159(3)	-1195(2)	3310(2)	57(1)
C(6B)	9117(3)	-757(2)	1624(2)	53(1)

Bond lengths [Å] and angles [deg] for **25a**.

C(1)-O(12)	1.427(3)
C(1)-C(2)	1.502(4)
C(2)-C(3)	1.526(4)
C(3)-N(11)	1.476(3)
C(3)-C(3M)	1.526(4)
C(4)-O(12)	1.419(2)
C(4)-N(11)	1.469(3)
C(4)-C(5)	1.532(3)
C(5)-C(10)	1.523(3)
C(5)-C(6)	1.528(3)
C(6)-C(7)	1.524(3)
C(7)-C(8)	1.512(4)
C(8)-C(9)	1.524(3)
C(9)-C(10)	1.525(3)
N(11)-C(1B)	1.352(3)
C(1B)-O(1B)	1.214(3)
C(1B)-O(2B)	1.353(3)
O(2B)-C(3B)	1.468(3)
C(3B)-C(4B)	1.511(3)
C(3B)-C(6B)	1.512(3)
C(3B)-C(5B)	1.515(3)

O(12)-C(1)-C(2)	110.2(2)
C(1)-C(2)-C(3)	112.2(2)
N(11)-C(3)-C(3M)	112.9(2)
N(11)-C(3)-C(2)	109.0(2)
C(3M)-C(3)-C(2)	113.7(2)
O(12)-C(4)-N(11)	110.1(2)
O(12)-C(4)-C(5)	112.2(2)
N(11)-C(4)-C(5)	114.3(2)
C(10)-C(5)-C(6)	109.9(2)
C(10)-C(5)-C(4)	111.6(2)
C(6)-C(5)-C(4)	110.1(2)
C(7)-C(6)-C(5)	111.5(2)
C(8)-C(7)-C(6)	111.9(2)
C(7)-C(8)-C(9)	111.0(2)
C(8)-C(9)-C(10)	111.2(2)
C(5)-C(10)-C(9)	111.7(2)
C(1B)-N(11)-C(4)	122.7(2)
C(1B)-N(11)-C(3)	117.6(2)
C(4)-N(11)-C(3)	119.7(2)
C(4)-O(12)-C(1)	113.0(2)
O(1B)-C(1B)-N(11)	123.8(2)
O(1B)-C(1B)-O(2B)	124.1(2)
N(11)-C(1B)-O(2B)	112.1(2)
C(1B)-O(2B)-C(3B)	120.5(2)
O(2B)-C(3B)-C(4B)	111.2(2)

O(2B)-C(3B)-C(6B)	102.3(2)
C(4B)-C(3B)-C(6B)	110.1(2)
O(2B)-C(3B)-C(5B)	109.3(2)
C(4B)-C(3B)-C(5B)	112.6(2)
C(6B)-C(3B)-C(5B)	110.8(2)

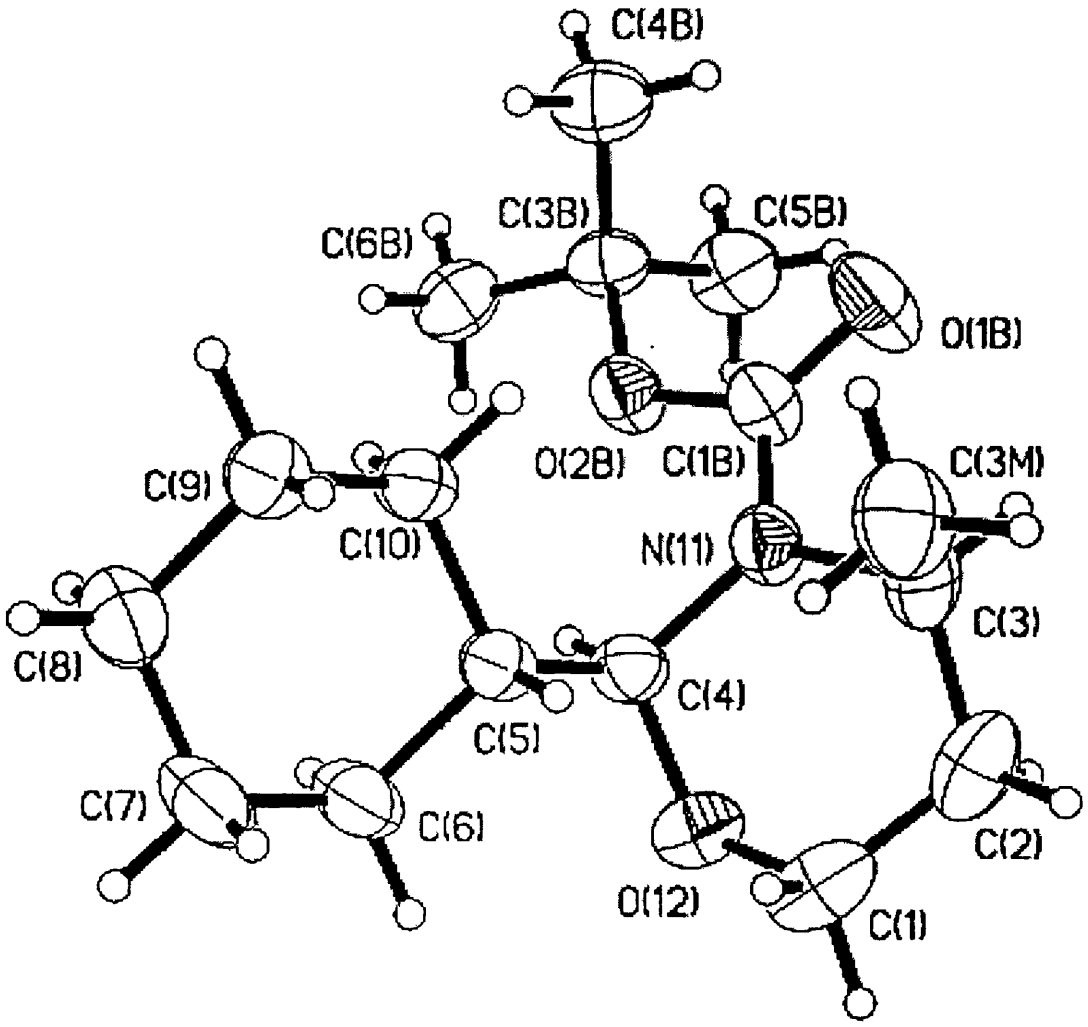
Anisotropic displacement parameters ($Å^2$ x 10^3) for **25a**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
C(1)	46(2)	55(2)	77(2)	5(2)	20(1)	3(1)
C(2)	70(2)	58(2)	56(2)	-4(1)	24(1)	10(2)
C(3)	65(2)	49(2)	36(1)	-9(1)	5(1)	9(1)
C(3M)	82(2)	58(2)	57(2)	-20(2)	2(2)	0(2)
C(4)	31(1)	41(1)	40(1)	-2(1)	-1(1)	4(1)
C(5)	32(1)	38(1)	37(1)	-2(1)	-4(1)	1(1)
C(6)	43(1)	60(2)	52(1)	9(1)	-16(1)	-9(1)
C(7)	57(2)	68(2)	53(2)	12(1)	-27(1)	-10(1)
C(8)	63(2)	52(2)	45(1)	5(1)	-8(1)	-4(1)
C(9)	45(1)	49(2)	45(1)	4(1)	-1(1)	-3(1)
C(10)	33(1)	46(1)	44(1)	4(1)	-3(1)	0(1)
N(11)	43(1)	44(1)	32(1)	-4(1)	-2(1)	9(1)
O(12)	38(1)	48(1)	57(1)	2(1)	6(1)	-2(1)
C(1B)	48(1)	45(1)	35(1)	-2(1)	-7(1)	4(1)
O(1B)	68(1)	77(1)	49(1)	-16(1)	-25(1)	20(1)
O(2B)	43(1)	48(1)	38(1)	-7(1)	-6(1)	14(1)
C(3B)	34(1)	35(1)	54(1)	3(1)	-1(1)	3(1)
C(4B)	51(2)	50(2)	79(2)	4(2)	-2(1)	-6(1)
C(5B)	56(2)	47(2)	67(2)	14(1)	1(1)	9(1)
C(6B)	50(2)	50(2)	60(2)	-4(1)	12(1)	4(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **25a**.

	x	y	z	U(eq)
H(1A)	2876(2)	1824(3)	3548(2)	71
H(1B)	3807(2)	2814(3)	3143(2)	71
H(2A)	4479(3)	1259(3)	4597(2)	74
H(2B)	4208(3)	2619(3)	4718(2)	74
H(3)	6500(3)	1988(2)	4681(2)	60
H(3M1)	5820(14)	3919(4)	3546(9)	98
H(3M2)	7261(5)	3681(3)	3912(13)	98
H(3M3)	6122(18)	3978(4)	4619(5)	98
H(4)	5967(2)	797(2)	2160(2)	45
H(5)	5364(2)	3231(2)	2192(1)	43
H(6A)	5096(2)	1603(2)	705(2)	62
H(6B)	3909(2)	2209(2)	1226(2)	62
H(7A)	4339(3)	3159(3)	-200(2)	71
H(7B)	4498(3)	4042(3)	638(2)	71
H(8A)	6264(3)	4308(2)	-351(2)	64
H(8B)	6599(3)	2950(2)	-323(2)	64
H(9A)	6880(2)	4529(2)	1193(2)	55
H(9B)	8056(2)	3918(2)	661(2)	55
H(10A)	7450(2)	2081(2)	1241(2)	49
H(10B)	7640(2)	2954(2)	2083(2)	49
H(4B1)	10405(10)	872(12)	3290(4)	90
H(4B2)	10300(9)	1185(9)	2226(9)	90
H(4B3)	11157(3)	101(4)	2550(12)	90
H(5B1)	9927(9)	-1689(9)	3240(8)	85
H(5B2)	8373(9)	-1665(9)	3234(8)	85
H(5B3)	9162(17)	-844(2)	3920(2)	85
H(6B1)	9883(9)	-1244(12)	1518(5)	80
H(6B2)	9097(17)	-130(2)	1171(2)	80
H(6B3)	8330(9)	-1229(12)	1566(4)	80

Ortep Plot of 25a



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