New Chiral Auxiliaries For The [3+2]-Cycloaddition Of Nonstabilised Azomethine Ylides

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A thesis submitted in partial fulfilment of the degree of Doctor of Philosophy

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Abstract

The [3+2]-cycloaddition reaction of nonstabilised azomethine ylides to alkenes is a valuable synthetic method for the assembly of functionalised pyrrolidines. However, there are only a few examples of such cycloadditions being successfully performed with an unstabilised azomethine ylide that has been tethered to a removable chiral auxiliary. Most of the reactions studied so far have exhibited only modest levels of diastereoselectivity (ca. 60 % d.e.), and in every case, destruction of the chiral auxiliary has proven necessary before the newly fashioned chiral pyrrolidine cycloadduct could be liberated.

In the first part of this thesis, the potential utility of optically pure 1,1-dialkylhydrazines as chiral auxiliaries for nonstabilised azomethine ylide cycloadditions to alkenes has been investigated. While the preparation of several chiral 1,1-dialkylhydrazines was carried out successfully, the formation of the *N*-amino azomethine ylide precursors from these hydrazines failed, occasionally giving interesting unwanted and unexpected by-products.

The second part of this thesis focuses on the evaluation of several new chiral auxiliaries as stereochemical control elements for 1,3-dipolar cycloadditions of azomethine ylides to alkenes. This work failed with some auxiliaries and was partially successful with others. The successful [3+2]-cycloaddition reactions were all performed with dimethyl fumarate as the dipolarophile, but afforded little or no stereoselectivity. The cleavage of the newly-created pyrrolidine systems from these auxiliaries under various conditions also proved to be unsuccessful.

During this work a new method for the preparation of 1,1-dialkylhydrazines by the reduction of *N*-nitroso precursors was discovered. The potential utility of this method has been evaluated, and the results are discussed in Chapter 4.

Contents

Abbreviations

Ac	acetate
AD	Asymmetric Dihydroxylation
Anal.	analytical
Ar	aromatic
approx.	approximately
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Calc.	calculated
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulphoxide
DIBAL-H	diisobutylaluminium hydride
ds	diastereofacial selectivity
dt	doublet of a triplet
e.e.	enantiomeric excess
Et	ethyl
et al.	*et alia* (Latin)
Equiv.	equivalents
EWG	electron withdrawing group
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
FT-IR	Fourier Transform Infra Red
g.	gram(s)
h	hour(s)
HR-MS	High Resolution Mass Spectroscopy
Hünig's base	*N,N*-diisopropyl-*N*-ethylamine
I.R.	Infra Red

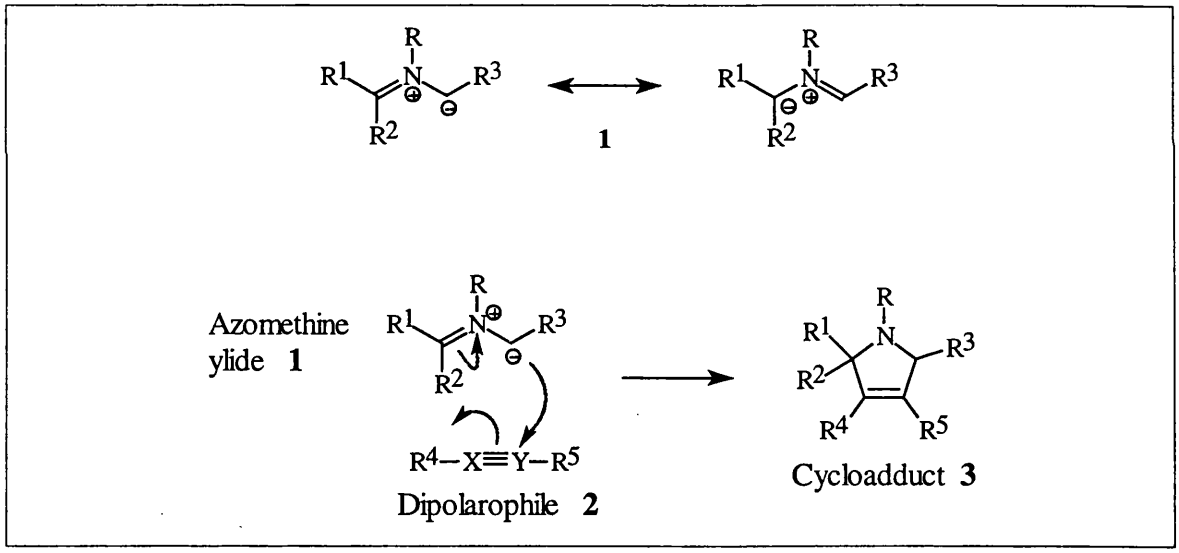
LDA	lithium diisopropylamide
m	multiplet
M	molar
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Ms	mesyl, methanesulfonyl-
mg	milligram(s)
MHz	megahertz
min.	minutes
ml	millilitres
M. Pt.	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
n.m.r.	nuclear magnetic resonance
OTf	*O*-triflate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
q	quartet
quat	quaternary
Rochelle's salt	potassium sodium tartrate monohydrate
r.t.	room temperature
t	triplet
t-/tert	tertiary
TBAF	tetra-*n*-butylammonium fluoride
THF	tetrahydrofuran
TES	triethylsilyl
TLC	Thin Layer Chromatography/Chromatogram
TMEDA	tetramethylethylenediamine
Ts	tosylate, *para*-toluenesulfonyl
Wilkinson's catalyst	$(PPh_3)_3RhCl$
Z	benzyloxycarbonyl

Chapter 1

A general survey of azomethine ylide [3+2]-cycloaddition reactions in organic chemistry

1.0 Introduction

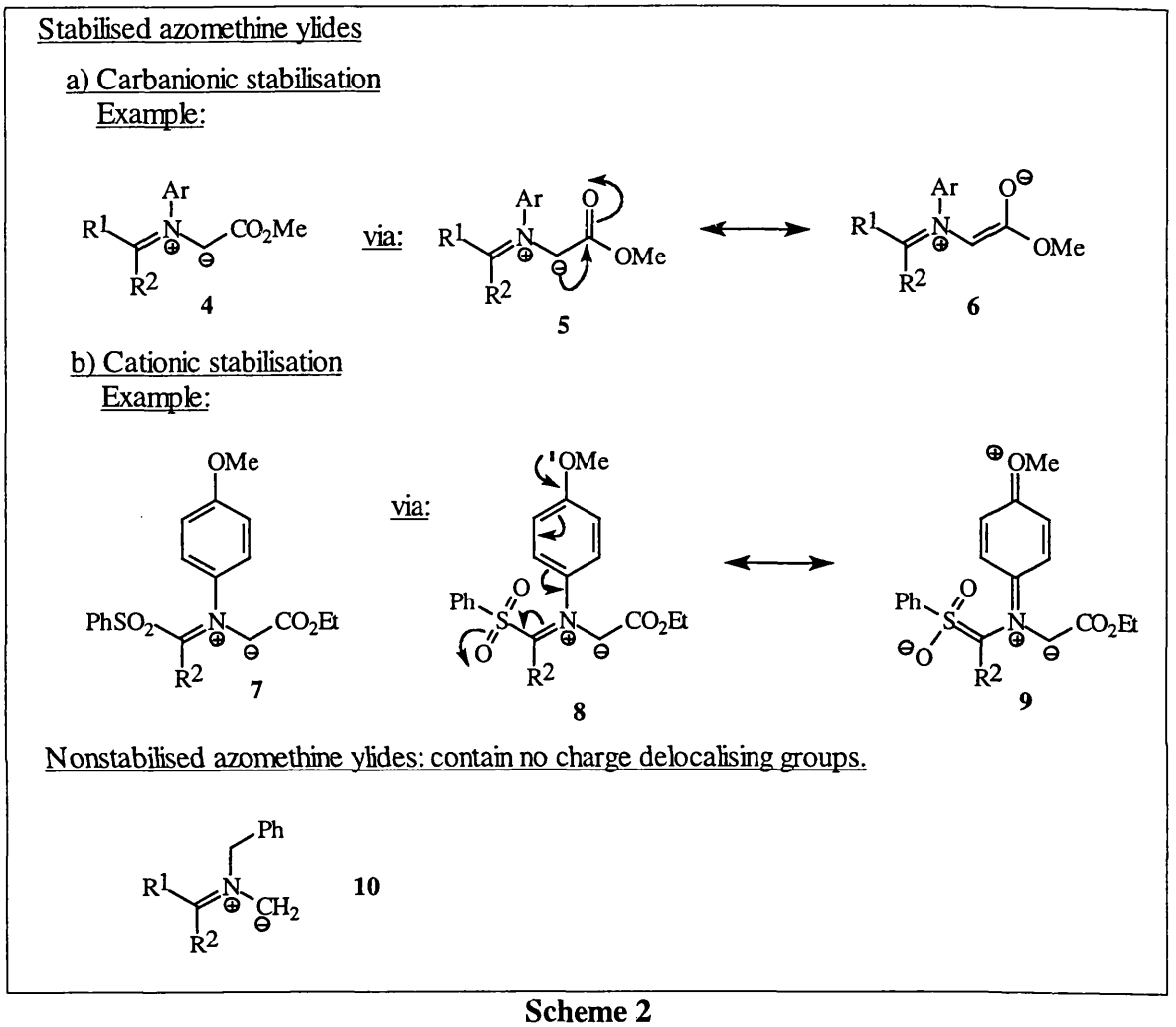
Azomethine ylides [1] are 1,3-dipoles that bear an iminium ion directly adjacent to a carbanionic centre; they are fleeting, transient intermediates of variable stability (**Scheme 1**).



Scheme 1

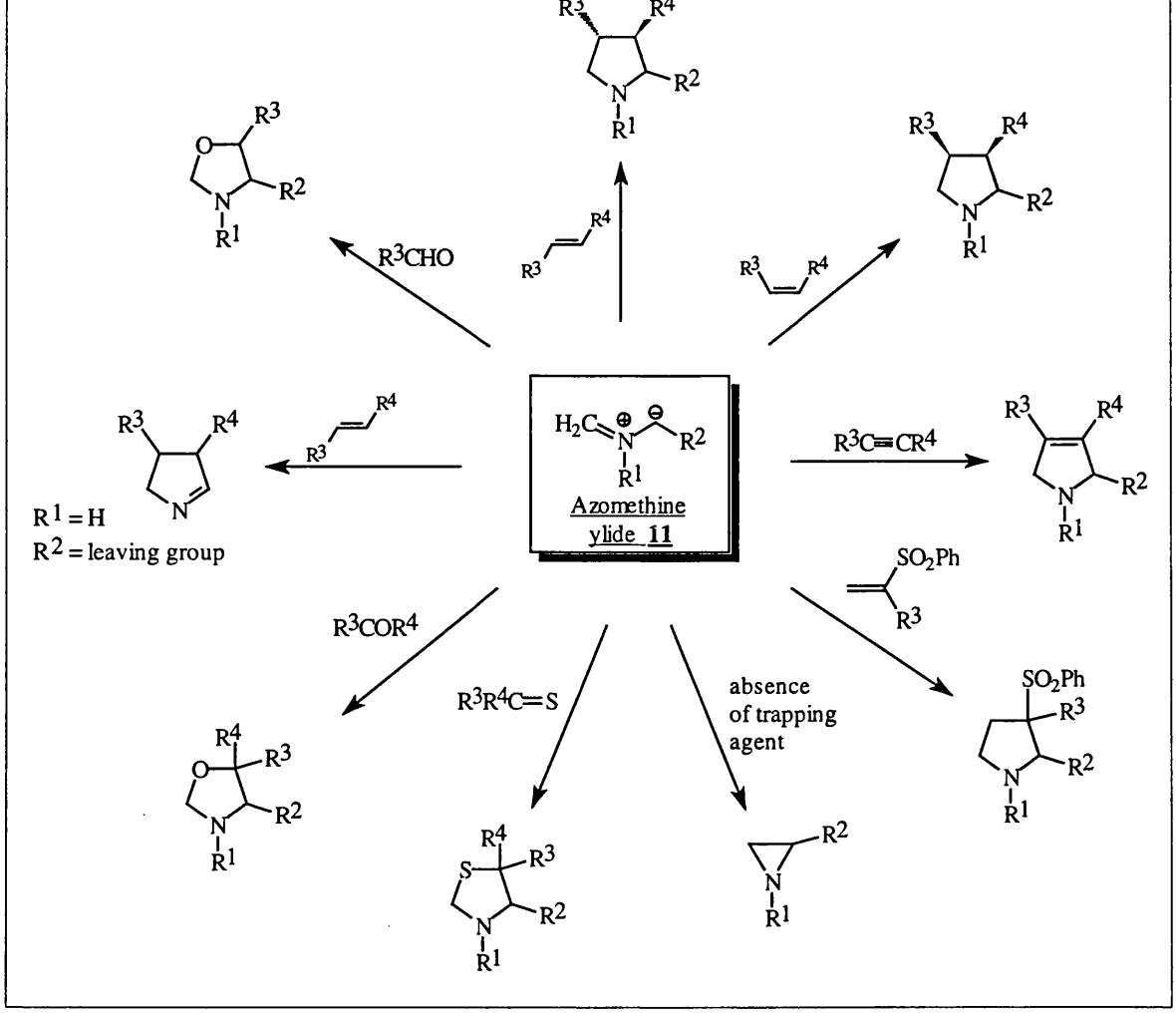
The [3+2]-cycloaddition reactions of azomethine ylides are [π4s+π2s] reactions and proceed through a 6π-electron 'aromatic' transition state. The 4π-electron component, the azomethine ylide **1**, contains only three atoms. Cycloaddition to a double or triple bond, termed the dipolarophile **2**, leads to a five-membered heterocyclic compound **3**.

There are two types of azomethine ylides: (1) stabilised azomethine ylides and, (2) nonstabilised azomethine ylides. The former contains at least one substituent capable of delocalising the negative or positive charge; the latter contains no such stabilising group (see for example **Scheme 2**).



Scheme 2

Cycloaddition reactions of azomethine ylides are generally performed with olefinic or acetylenic dipolarophiles, leading respectively to the formation of pyrrolidines and 2,5-dihydropyrroles, the latter being convertible into pyrroles. However, several other dipolarophiles can also be utilised to generate a host of various cycloadducts. Azomethine ylides have been trapped in an intramolecular fashion with tethered dipolarophiles. **Scheme 3** indicates briefly some of the cycloadducts which can be formed from azomethine ylides.



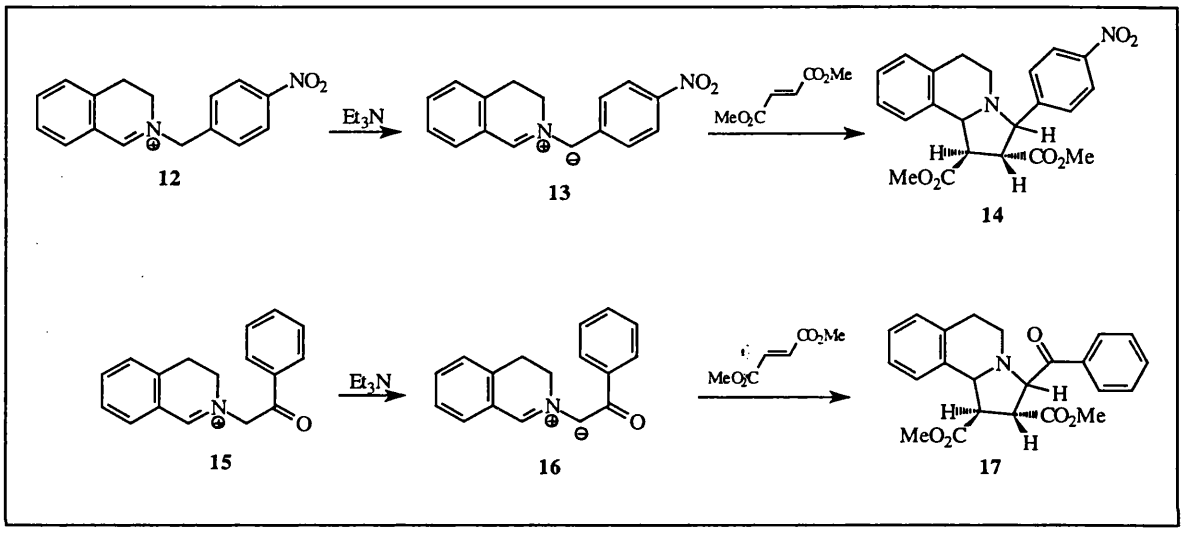
Scheme 3

When two chiral centres are created in the cycloaddition of azomethine ylides, one arising from each reactant, diastereomeric (*cis* and *trans*) products may be formed and it is not always easy to predict the stereochemical course of such reactions. Frequently mixtures of diastereomers are obtained. At most, four geometrical isomers are possible for these transient intermediates. Their cycloadditions to olefin or acetylene dipolarophiles give rise to the formation of two sets of carbon-carbon bonds in a single step.

Before we present a detailed discussion of the synthetic applications of azomethine ylides, a brief history of these transient species will be given.

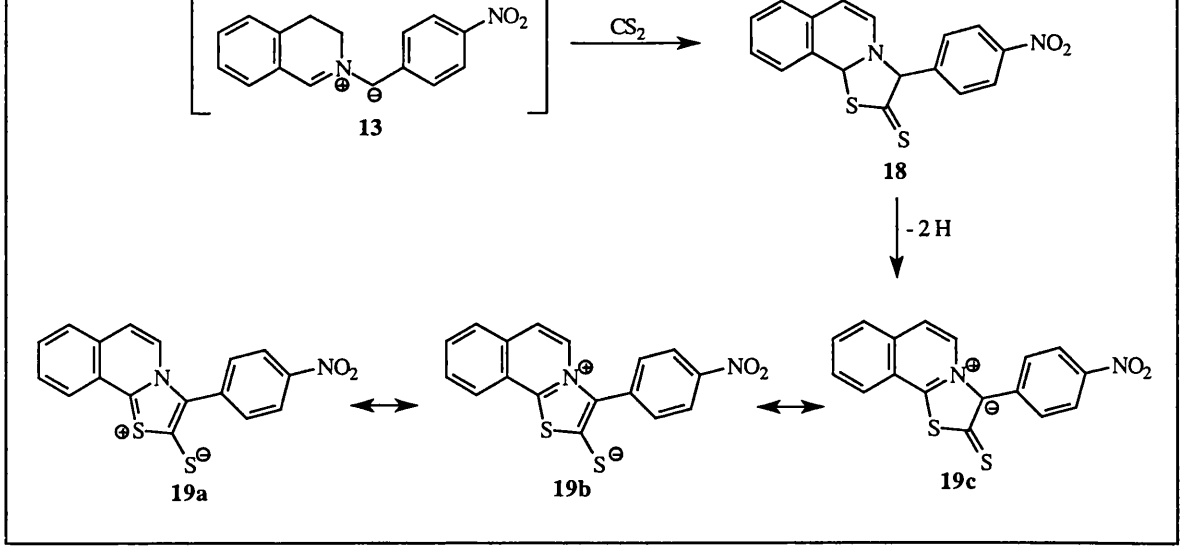
1.1 Historical aspects of azomethine ylide chemistry

One of the first recorded examples of an azomethine ylide engaging in a 1,3-dipolar cycloaddition was in 1959 when an iminium ion was deprotonated with base in the presence of dimethyl fumarate.[2] The azomethine ylides **13** and **16** were produced in equilibrium when *N*-*p*-nitrobenzyl- or *N*-phenacyl-3,4-dihydroisoquinolinium salts were treated with triethylamine. *In situ* cycloadditions to dimethyl fumarate afforded the cycloadducts **14** and **17** in 69 % and 73 % yields (**Scheme 4**).



Scheme 4

Since 1,3-dipolar cycloaddition reactions were first discovered in the late 1950s, an increasing number of papers have dealt with additions of azomethine ylides. One of the first was Kröhnke's report on the formation of **18** from *N*-benzylisoquinolinium salt **13** and carbon disulphide in alkaline medium.[3] This was followed by the spontaneous dehydrogenation of the initial cycloadduct to give the coppery red thiazole-type mesoionic compounds **19a-c** (**Scheme 5**).



Scheme 5

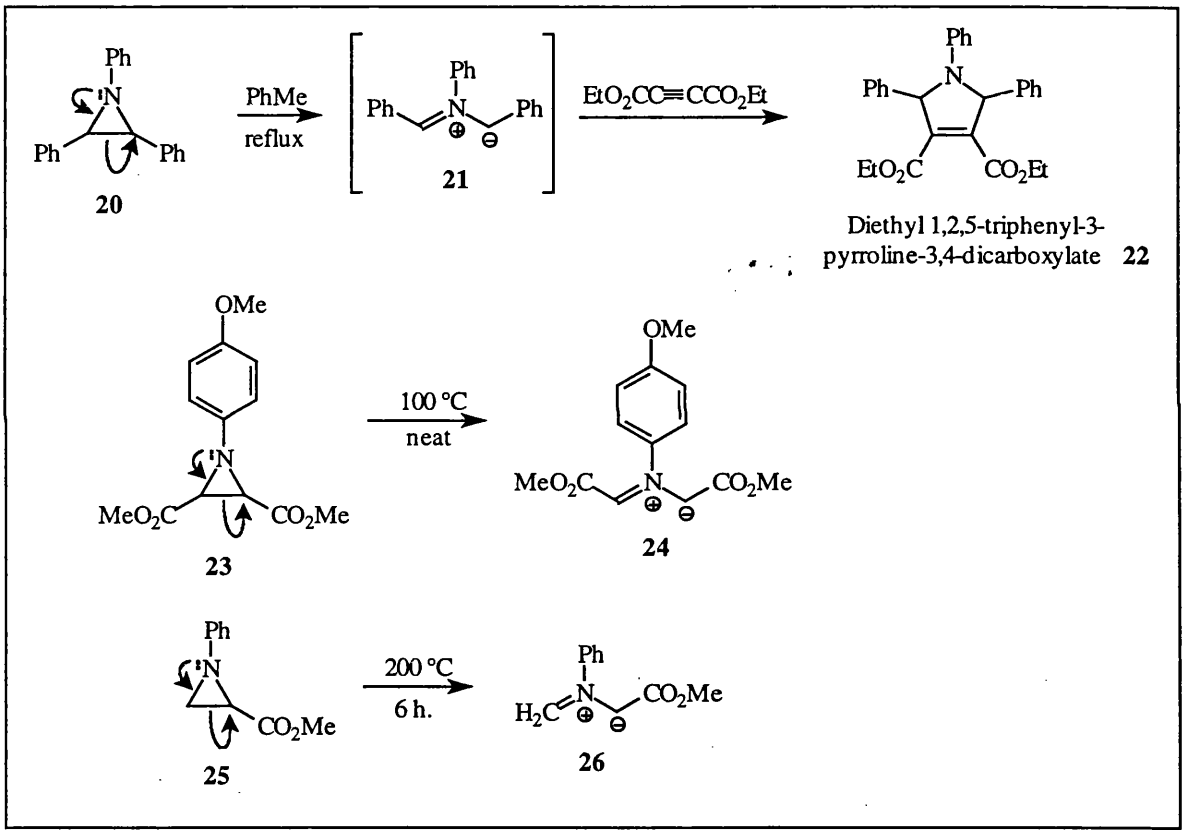
It was not until 1978, however, that the chemistry of azomethine ylide 1,3-dipoles was intensely and systematically studied. Ever since that time much valuable information on their reactivity has accumulated. The two pioneering works in this area are those of Vedejs *et al.*[4] and Grigg *et al.*[5] Vedejs demonstrated that nonstabilised azomethine ylides (viz. ylides bearing no ylide-stabilising substituents) could be smoothly generated if an appropriate method was employed. He also showed that in some cases such ylides can have considerable stability and be highly reactive towards a variety of dipolarophiles. On the other hand, stabilised azomethine ylides (viz. ylides bearing a stabilising substituent on the carbon or nitrogen atom) can be smoothly generated, usually by simple treatment of base. These azomethine ylides are thus stabilised through resonance and can react with a variety of dipolarophiles. In the following section, the main synthetic methods for generating both stabilised and nonstabilised azomethine ylides will be discussed.

1.2 The generation of azomethine ylides with achiral alkenes and alkynes

1.2.1 The aziridine route to azomethine ylides

The thermal ring-opening of aziridines is a convenient method for generating azomethine ylides that are stabilised by at least one electron-delocalising substituent.

The first example of such a reaction was reported by Heine and Peavy in 1965.[7] These workers found that when 1,2,3-triphenylaziridine **20** (of unspecified stereochemistry) was heated at reflux in toluene in the presence of diethyl acetylenecarboxylate, the azomethine ylide **21** was formed and that this reactive species could be trapped to give diethyl 1,2,5-triphenyl-3-pyrroline-3,4-dicarboxylate **22** in quantitative yield (**Scheme 6**). Aziridine rings open particularly readily if their carbon atoms are attached to electron-delocalising substituent(s), as the electron-rich ylide centre in the azomethine ylide is stabilised by such substituents. Thus, aziridines bearing two ester moieties on the carbon form ylides **24** at only 100 °C. Aziridines with only one ester activating group on the ring require higher temperatures (200 °C) to undergo ring opening to generate azomethine ylide **26**.[7]

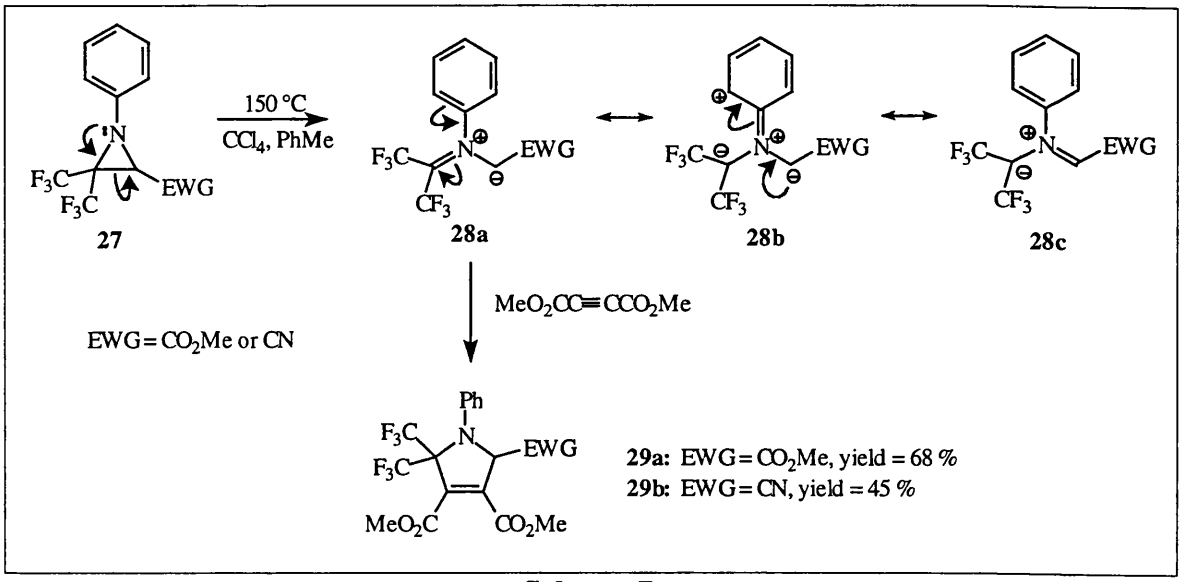


Scheme 6

The aziridine route is rarely used to generate non-stabilised azomethine ylides. This mode of generation is therefore quite restricted.

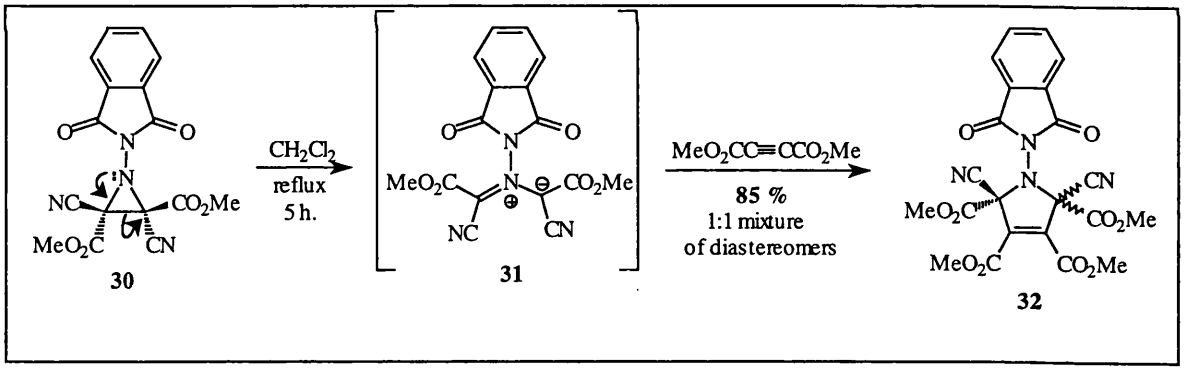
The thermolysis of 1,1-bis(trifluoromethyl)aziridines provides good access to trifluoromethyl-substituted stabilised azomethine ylides **28a** (See **Scheme 7**).[8] This

phenyl ring. The dipolarophile was then trapped as the pyrroline product **29a,b**.



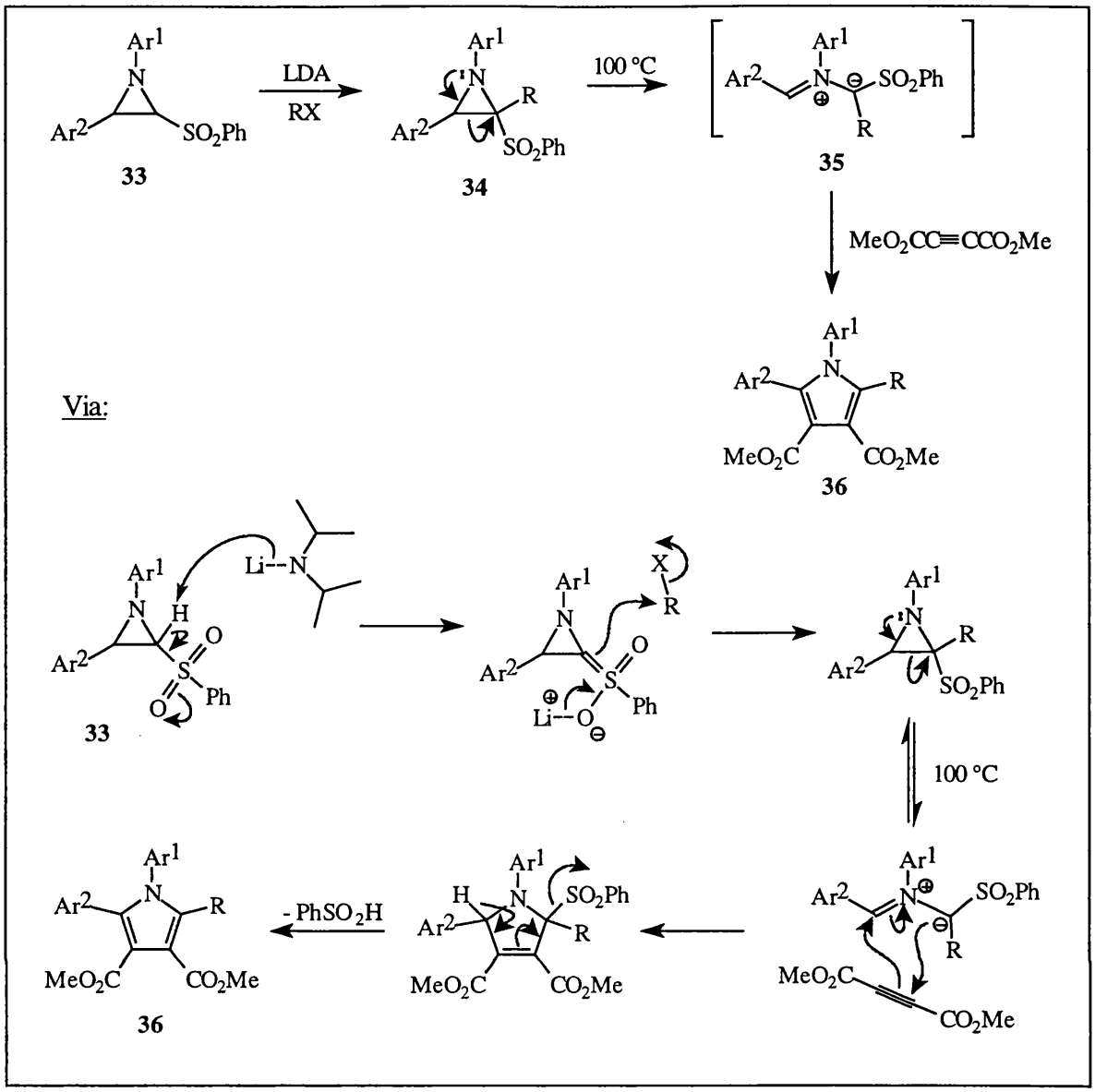
Scheme 7

The generation of azomethine ylides with a heteroatom substituent on nitrogen has been demonstrated by the thermolysis of 1-phthalimidoaziridines. This leads to the formation of stabilised *N*-aminoazomethine ylides **31** (**Scheme 8**).[9]



Scheme 8

A sulfonyl substituent at the carbon of aziridines allows a stabilised ring anion to be generated with base to allow an alkyl moiety to be introduced at this carbon. As the ring is activated by the sulfonyl group, alkylated aziridines undergo a ready ring opening leading to stabilised sulfonyl-substituted azomethine ylides **35** (**Scheme 9**). These readily engage in cycloadditions with dimethyl acetylenedicarboxylate, the sulfonyl group eventually being eliminated to afford the pyrrole derivative **36**.[10]

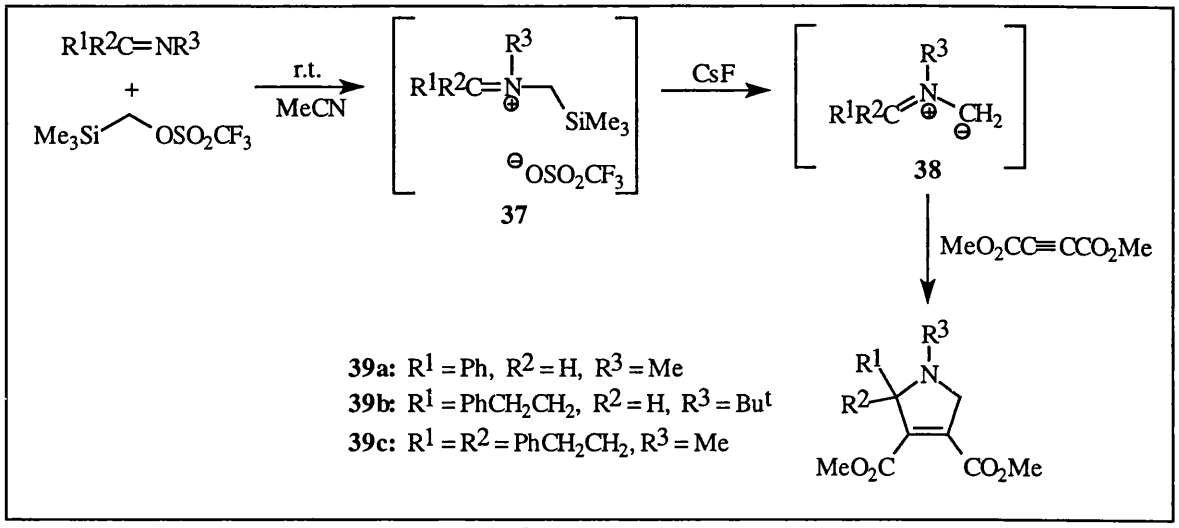


Scheme 9

1.2.2 The desilylation route to azomethine ylides

In 1979 Vedejs and Martinez [4] reported a new method for forming nitrogen, sulphur and phosphorus ylides, which consisted of initial alkylation of amines, imines, sulphides and phosphines with trimethylsilylmethyl triflate, and subsequent desilylation of the resulting salts with fluoride ion. For the generation of azomethine ylides, an imine is treated with the triflate in acetonitrile at room temperature to form the corresponding iminium triflate **37** and the subsequent desilylation is carried out *in situ* with CsF. The azomethine ylides **38** are also usually trapped *in situ* with an appropriate

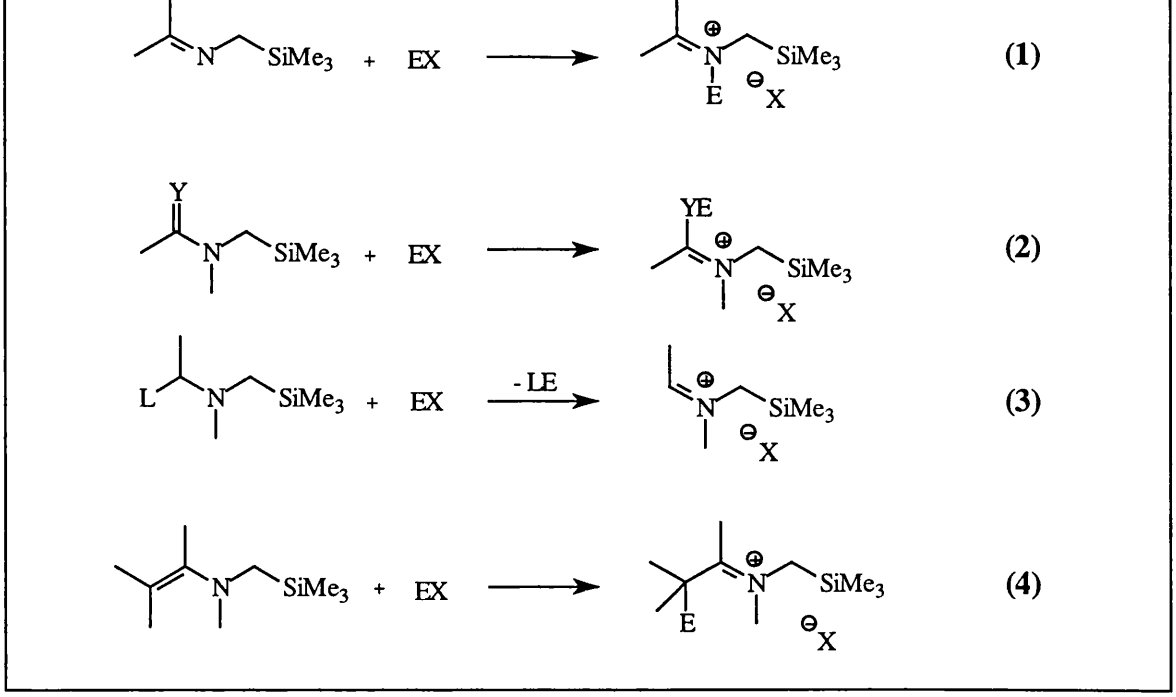
ylides (**Scheme 10**).



Scheme 10

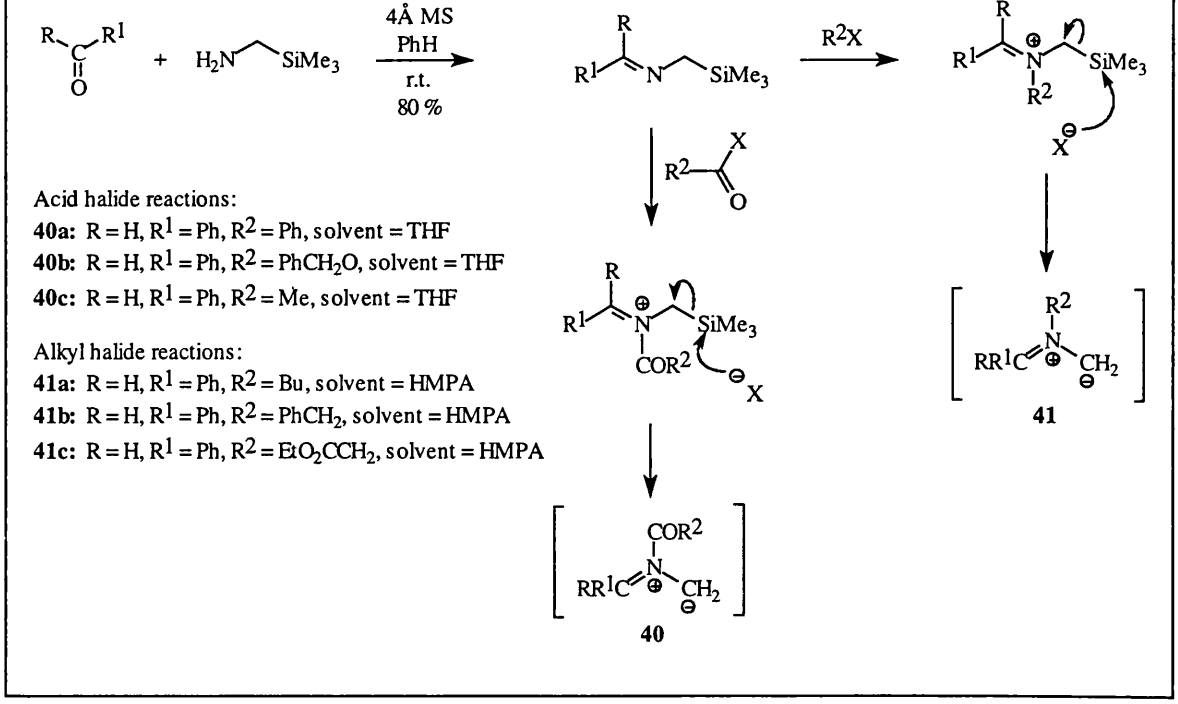
N-Silylmethylation can also be performed with other alkylating agents, such as trimethylsilylmethyl chloride, bromide or iodide. However, the resulting iminium salts desilylate immediately after they have formed due to attack of the silyl substituent by the halide counteranions. This leads to serious decomposition of the requisite iminium ion intermediates. The key step used to unveil the azomethine ylide is fluoride ion treatment which is selectively nucleophilic to a silicon atom.

There are several other preparative methods for obtaining *N*-silylmethyliminium salts; the key intermediates of the Vedejs-Martinez method (**Scheme 11**). These include; (1): the quaternisation of *N*-silylmethylimines by the addition of an electrophile (EX) to the imine nitrogen; (2): the quaternisation of *N*-silylmethylamides or related derivatives by the addition of an electrophile to a heteroatom other than the amide nitrogen; (3): the quaternisation of *N*-silylmethyl hemiacetal derivatives by the elimination of a leaving group (L) from an adjacent carbon; and (4): the quaternisation of *N*-silylmethylenamines by the addition of an electrophile to the enamine unit.



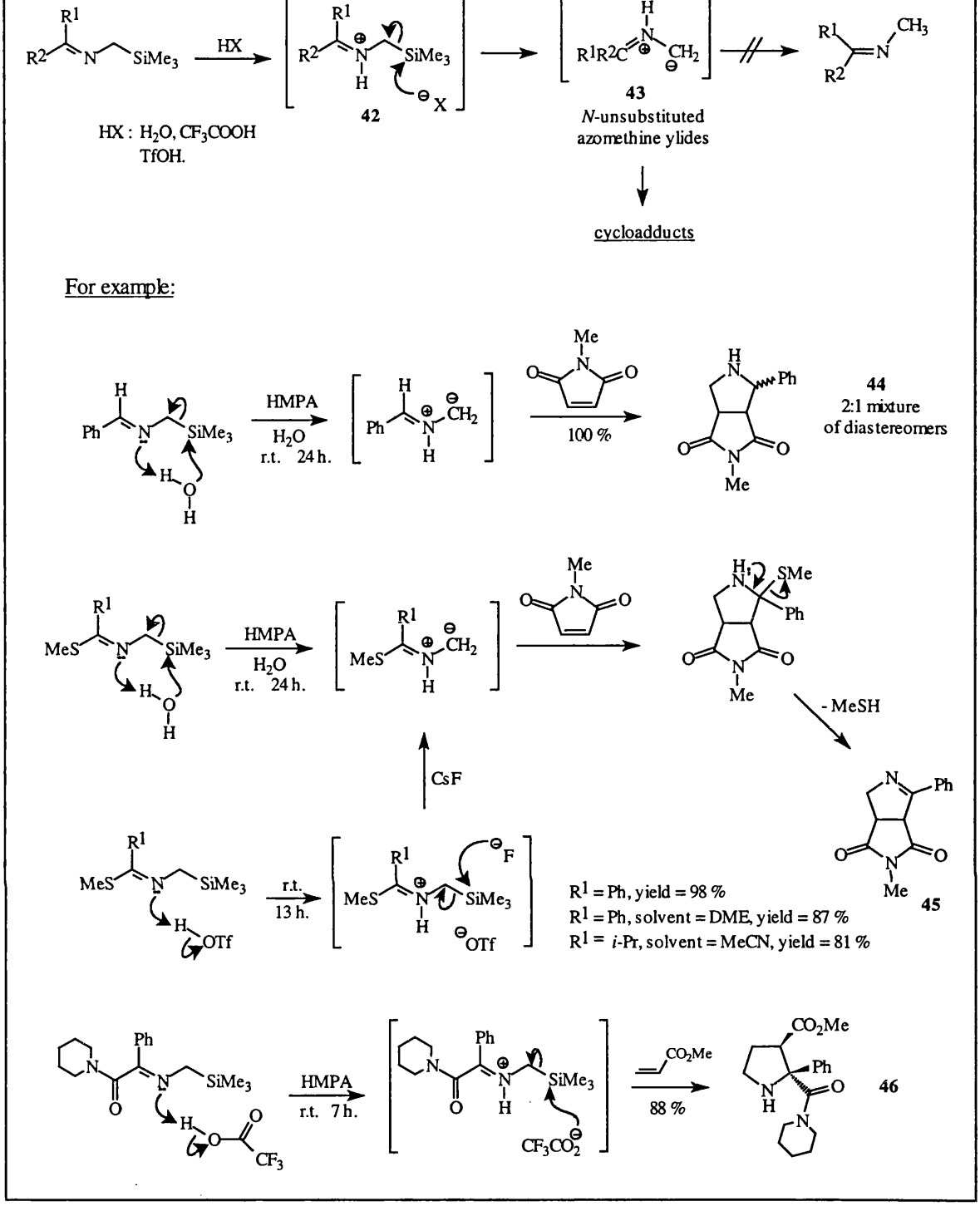
Scheme 11

The quaternisation of *N*-silylmethylimines, according to Eq. (1) (**Scheme 11**), is usually performed with electrophiles such as acid halides [11-14] and alkyl halides;[15-17] this generates *N*-acyl azomethine ylides **40** or *N*-alkyl azomethine ylides **41** respectively (**Scheme 12**). As the silyl moiety of the intermediary *N*-silylmethyliminium salts is more easily desilylated than that of the starting imines, the quaternisation and desilylation steps need not be separated. An acyl or alkyl halide is simply added to the *N*-silylmethylimine in the presence of a dipolarophile. Desilylation of the resultant iminium salts takes place spontaneously by the attack of counter halide anion, X^-. Thus, the quaternisation of *N*-silylmethylimines according to Eq. (1), can be carried out in a simple one-pot procedure.



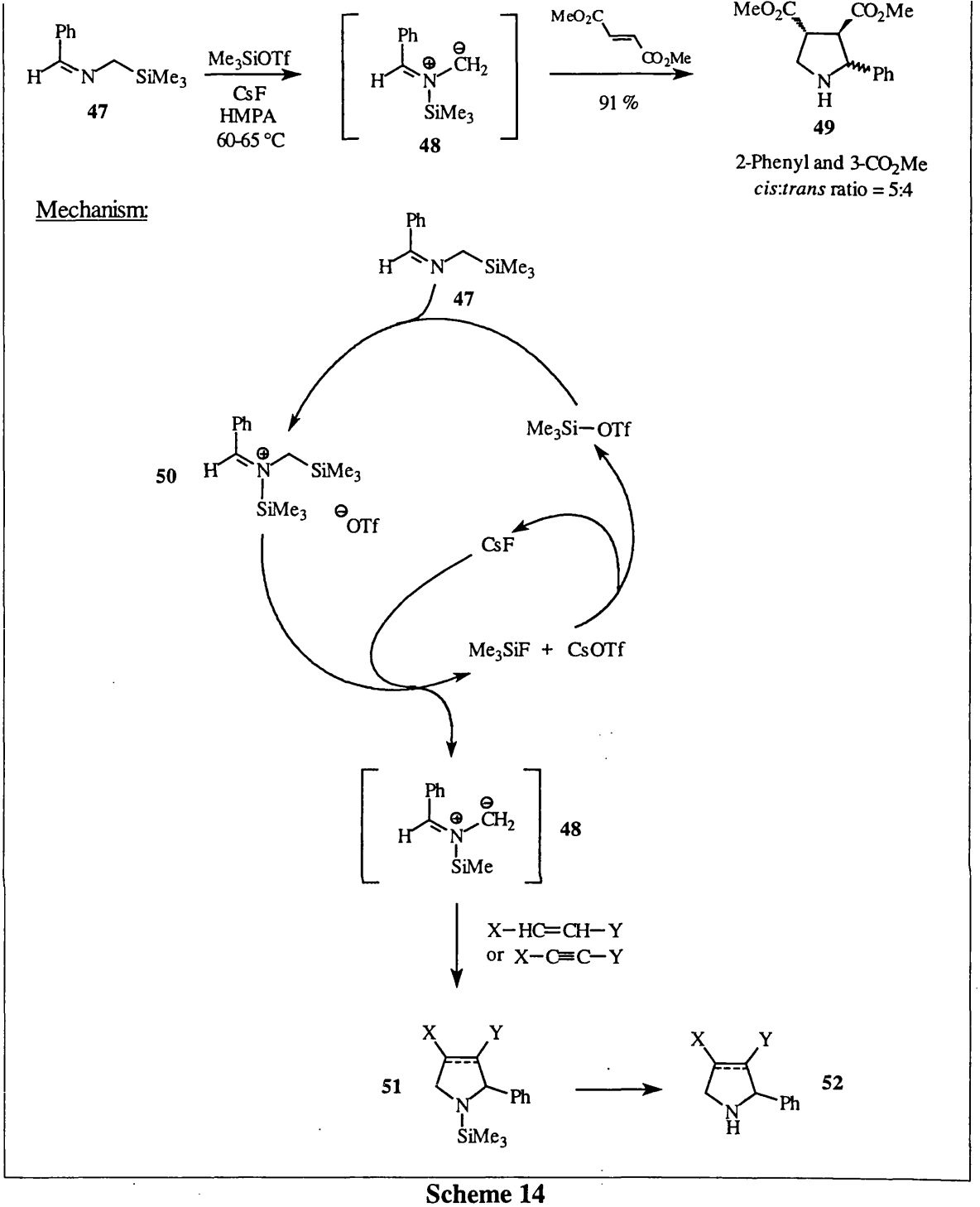
Scheme 12

It is also pertinent to mention that the process of *N*-protonation of *N*-silylmethylimines and subsequent desilylation works well for generating *N*-unsubstituted azomethine ylides. *N*-Protonated iminium intermediates **42** are first formed, and desilylation by the counter ion (X^-) then leads to the formation of the *N*-unsubstituted azomethine ylide **43** (**Scheme 13**). This method works satisfactorily for generating nonstabilised *N*-unsubstituted azomethine ylides. Although *N*-unsubstituted azomethine ylides are capable of isomerising irreversibly to the corresponding *N*-methylimine tautomers, these unusual azomethine ylides show remarkable stability and can often be captured by activated dipolarophiles in high yields. Water,[18-20] TFA,[16,18,21] and triflic acid with CsF [20] are commonly used for the *N*-protonation and desilylation process. The remarkable stability of *N*-unsubstituted azomethine ylides **43**, especially under the highly acidic conditions employed for desilylation, is quite surprising since acids also catalyse the irreversible conversion of ylides to their *N*-methylimine tautomers.



Scheme 13

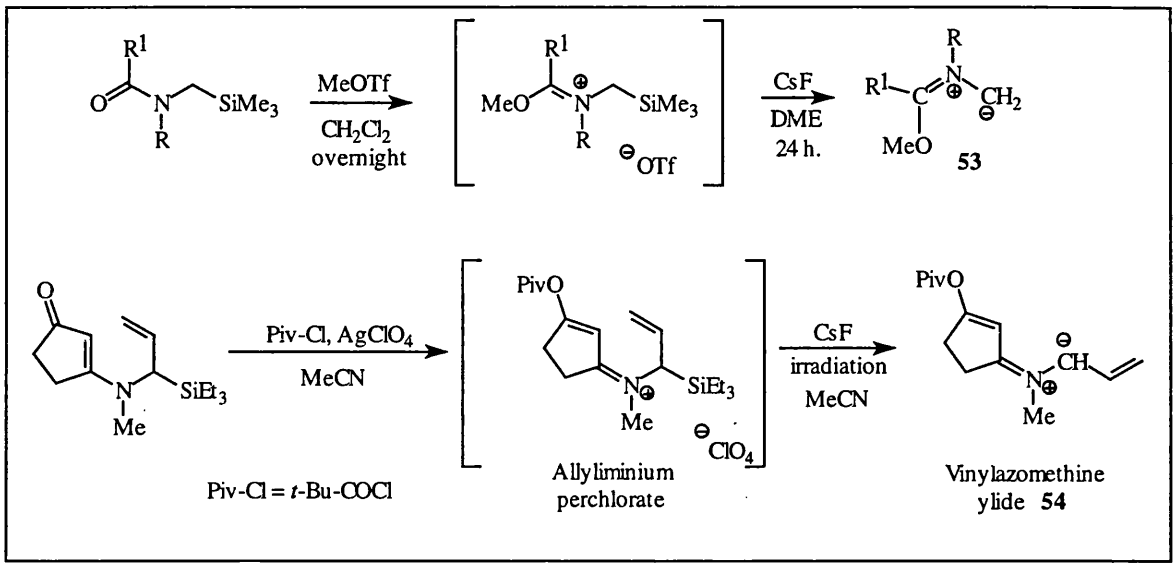
N-Silylation with catalytic trimethylsilyl triflate forms *N*-silylated iminium triflates **50**, which are subsequently desilylated *in situ* with fluoride ion to generate *N*-silylated azomethine ylides **48**.[18,22,23] The mechanism of this method of azomethine ylide generation has been proposed by Achiwa *et al.*[23] (**Scheme 14**).



Scheme 14

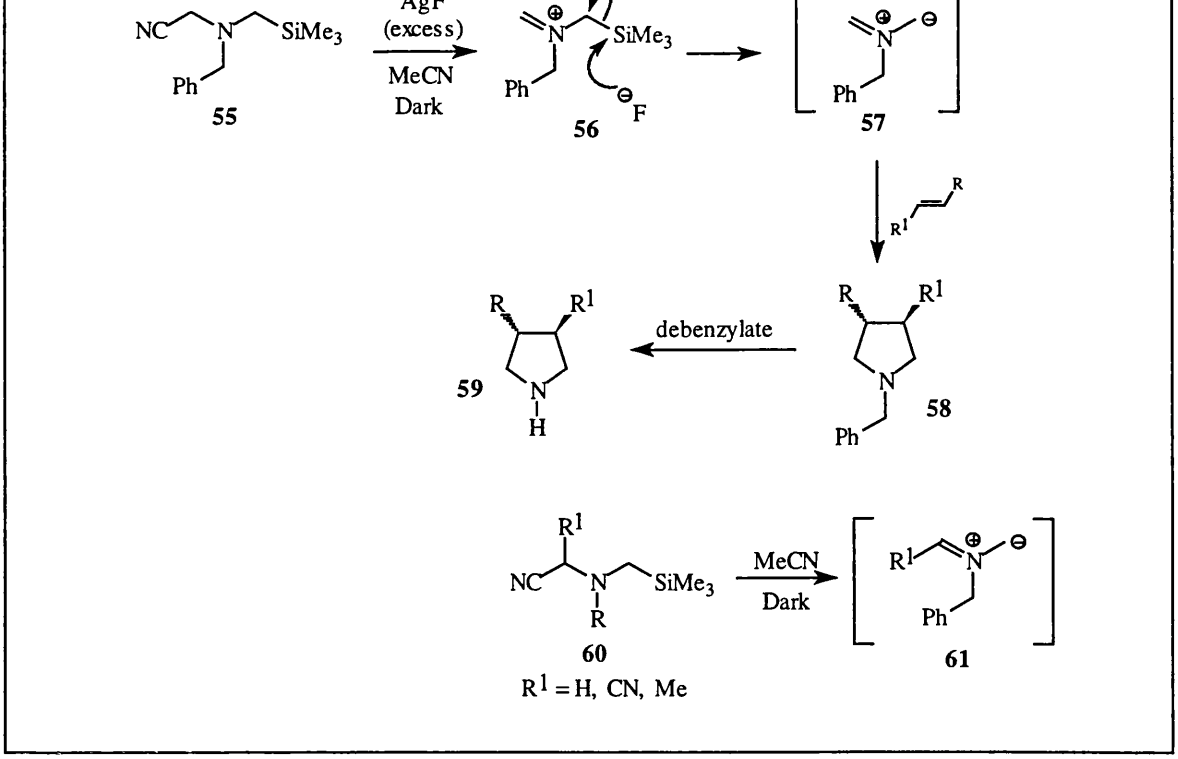
This reaction involves the cycloaddition of an ylide **48** formed from the intermediary *N*-trimethylsilylmethyliminium salt **50**, which was derived from **47** in the presence of a catalytic amount of trimethylsilyl triflate. The generated ylide **48** then reacted with olefinic or acetylenic dipolarophiles to form the *N*-trimethylsilyl-substituted pyrrolidine **51** which were transformed into *N*-unsubstituted cycloadducts **52**. The reaction is further accelerated catalytically by the addition of CsF, which aids in the fission of the silicon-carbon bond.

Another convenient entry into *N*-silylmethyliminium salts entails either acylating, silylating or alkylating *N*-silylmethylamides or derivatives on the amide oxygen [Eq. (2) in **Scheme 11**]. *O*-Alkylation of *N*-silylmethylamides with methyl triflate [24-26] or *O*-acylation [27] of *N*-silylmethyl-enaminones leads to *N*-(1-silylalkyl)iminium salt intermediates respectively. Fluoride-induced desilylation can then be used to generate the azomethine ylide, for example **53** and **54** (**Scheme 15**).



Scheme 15

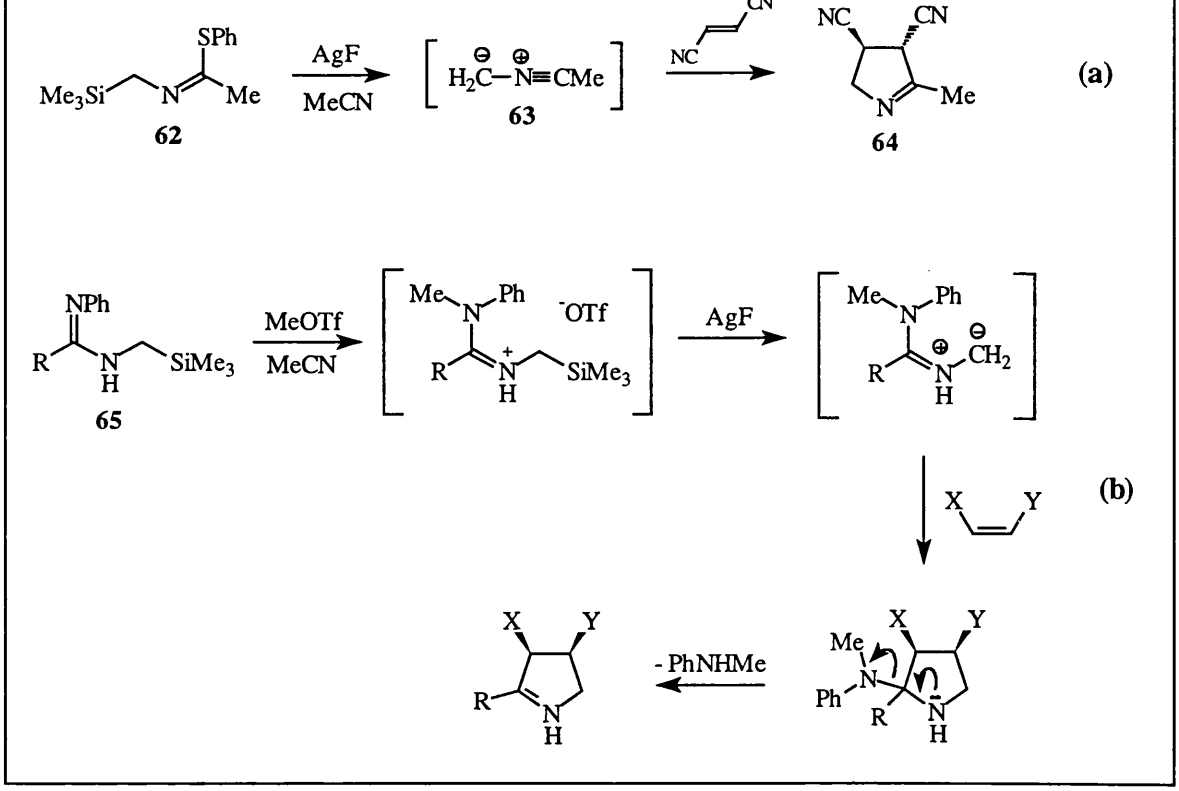
A third variant for forming *N*-silylmethyliminium salts is through the expulsion of an α-leaving group (L) from *N*-silylmethylamines [Eq. (3) in **Scheme 11**]. This has been reported by Padwa *et al.*[28] in 1983. It involves the silver fluoride-induced decyanation of *N*-benzyl-*N*-cyanomethyl(trimethylsilylmethyl)amine **55** to generate the *N*-silylmethyliminium intermediate **56** (**Scheme 16**). The fluoride ion then attacks the silyl moiety to bring about a spontaneous desilylation to generate the azomethine ylide **57**. This method is convenient for the preparation of *C*-unsubstituted azomethine ylides (**60**, R = H), although the type of α-substituent R^1 is rather limited (e.g. R^1 = Me, CN).[17,29-32] Subsequent debenzylation of the cycloadduct **58** (R^1 = H) provides compound **59**, a synthetic equivalent of a completely unsubstituted azomethine ylide.



Scheme 16

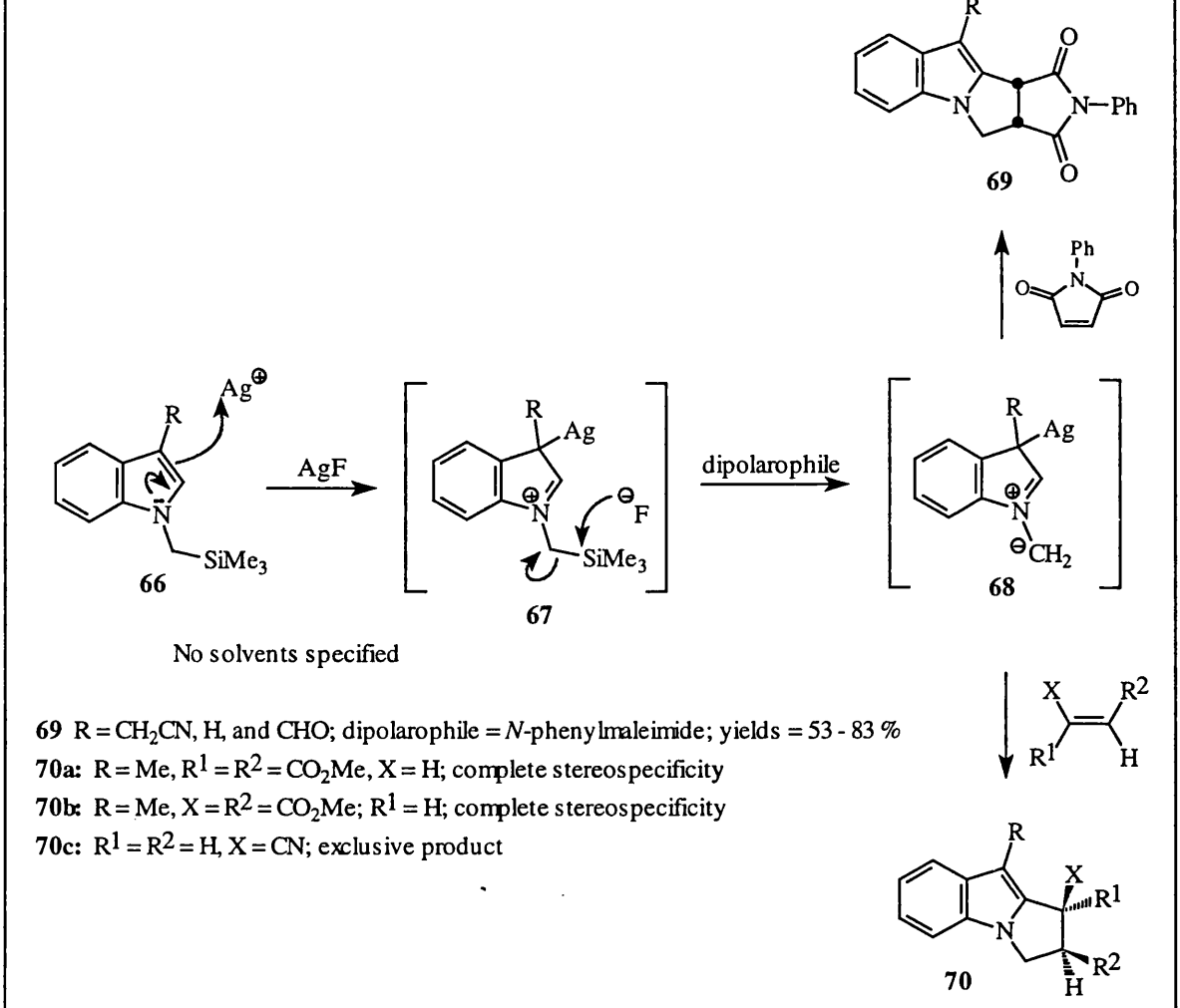
This desilylation of an α-silyl iminium salt is now the preferred method for generating azomethine ylides. The fluoride ion is thought to be the best "silaphile" for ylide generation, and CsF and AgF are usually the reagents of choice. Organic fluoride donors such as tetra-*n*-butylammonium fluoride are not satisfactory because they tend to contain water or the bifluoride (F_2H^-) ion, contaminants which can protonate basic ylides.[33-36] All naked fluoride sources tend to be highly hygroscopic, but CsF has the advantage that it can be vacuum-dried over a small Bunsen flame without significant decomposition.

Padwa *et al.*[37] have also used similar conditions to convert *N*-[(trimethylsilyl)methyl]-thioimidates **62** into nitrile ylides **63** [see **Scheme 17**, eq. (a)] in experiments that are related to those of Tsuge *et al.* [38] for amidines **65** [**Scheme 17**, eq. (b)].



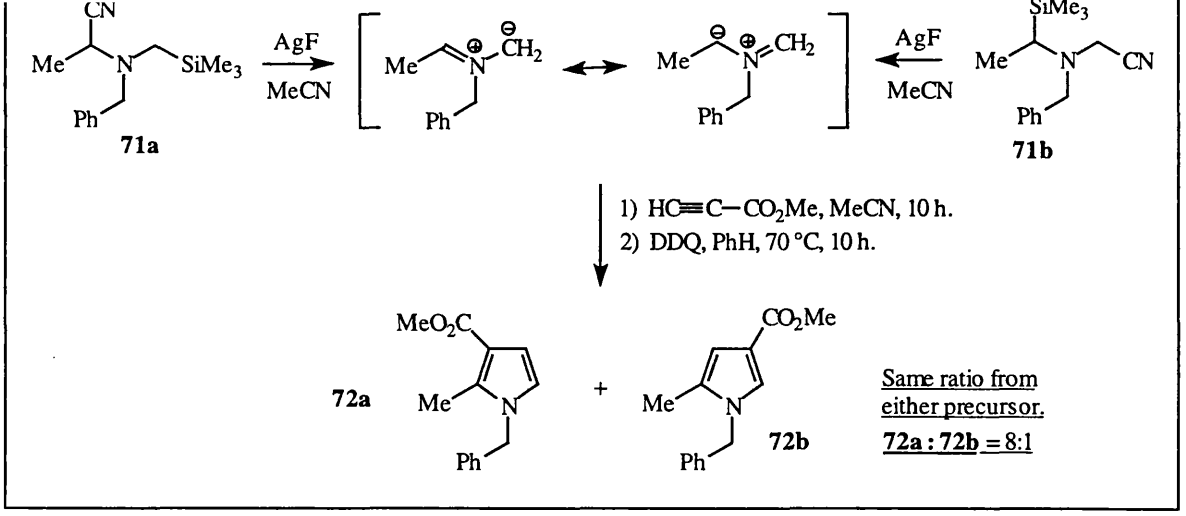
Scheme 17

Conceptually it would be possible to prepare *N*-silylmethyliminium salts by the addition of an electrophile to the β-carbon of *N*-silylmethylenamines [Eq. (4) in **Scheme 11**]. The reaction of 1-(trimethylsilylmethyl)indoles **66** with AgF is reported to be initiated by the addition of silver cation to the 3-position to form *N*-silylmethyliminium fluoride **67**, whose desilylation leads to azomethine ylides **68** (**Scheme 18**).[39] Not many examples of this reaction are known, and the narrow application of this method may arise from the lack of general methods for the preparation of *N*-silylmethylenamines.



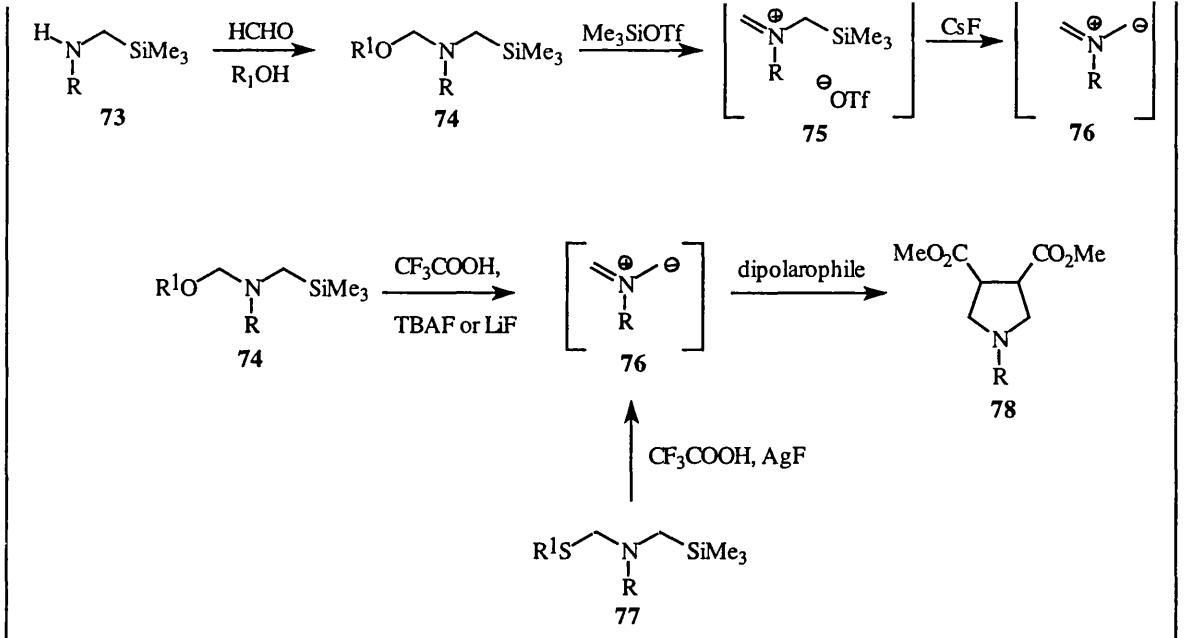
Scheme 18

Padwa *et al.* [30,40] have shown that the unsymmetrical azomethine ylide precursors **71a** and **71b** (**Scheme 19**) produce identical ratios of cycloaddition regioisomers with methyl propiolate, providing reasonable evidence for a common ylide intermediate. Similar conclusions were reached by Achiwa *et al.*[41] using deuterium-labelled ylide precursors. Overall, the evidence is reasonably firm, but not yet conclusive, that silicon-free ylides are intermediates in these experiments.



Scheme 19

N-Alkoxymethyl(trimethylsilylmethyl)amines **74** are convenient precursors of *C*-unsubstituted azomethine ylides **76**. These amines **74** are readily available from the reaction of *N*-alkylated silylmethylamines **73** with formaldehyde in alcoholic solvents (**Scheme 20**).[42] Treating these amines with trimethylsilyl triflate in MeCN or THF causes elimination of the alkoxy group, R^1O^-, to produce *N*-silylmethyliminium triflates **75**. Subsequent desilylation with CsF generates the corresponding *C*-unsubstituted azomethine ylides **76**. It will be noted that the alkoxy elimination and the subsequent desilylation of **75** can be induced by TFA,[41,43] TBAF,[41] or LiF.[44] *N*-(Alkylthiomethyl)(trimethylsilylmethyl)amines **77** also function as the precursors of *C*-unsubstituted azomethine ylides **76**. In these cases, TFA [41] and AgF are effective both for the elimination of alkylthio group, R_1S^-, and the desilylation.



3,4-(*trans*) **78a:** R = $PhCH_2$, R^1 = OMe, dipolarophile = dimethyl fumarate, catalyst = CF_3CO_2H, solvent = CH_2Cl_2, time = 3 h, yield = 97 %

3,4-(*trans*) **78b:** R = $PhCH_2$, R^1 = OMe, dipolarophile = dimethyl fumarate, catalyst = TBAF, solvent = DMF, time = 3 h, yield = 35 %

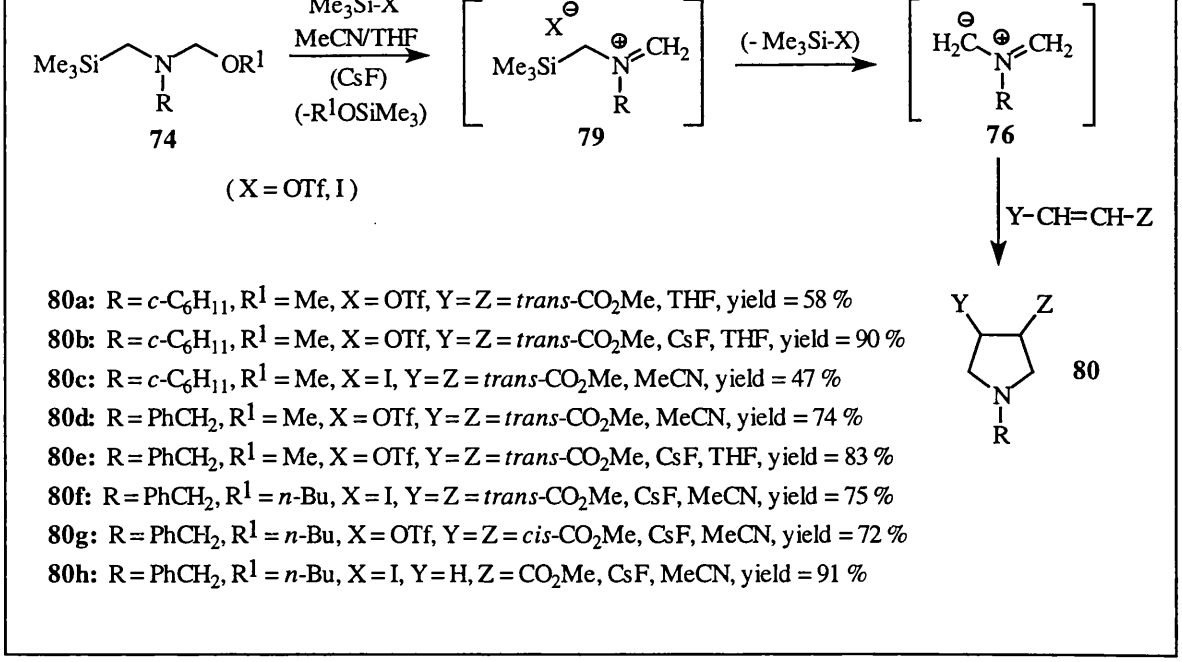
3,4-(*trans*) **78c:** R = $PhCH_2$, R^1 = OMe, dipolarophile = dimethyl fumarate, catalyst = LiF, solvent = MeCN, sonicate at 35 °C for 5 h, yield = 90 %

3,4-(*trans*) **78d:** R = $PhCH_2$, R^1 = OMe, dipolarophile = fumaronitrile, catalyst = LiF, solvent = MeCN, sonicate at 35 °C for 5 h, yield = 80 %

3,4-(*cis*) **78e:** R = $PhCH_2$, R^1 = OMe, dipolarophile = dimethyl maleate, catalyst = LiF, solvent = MeCN, sonicate at 35 °C for 5 h, yield = 90 %

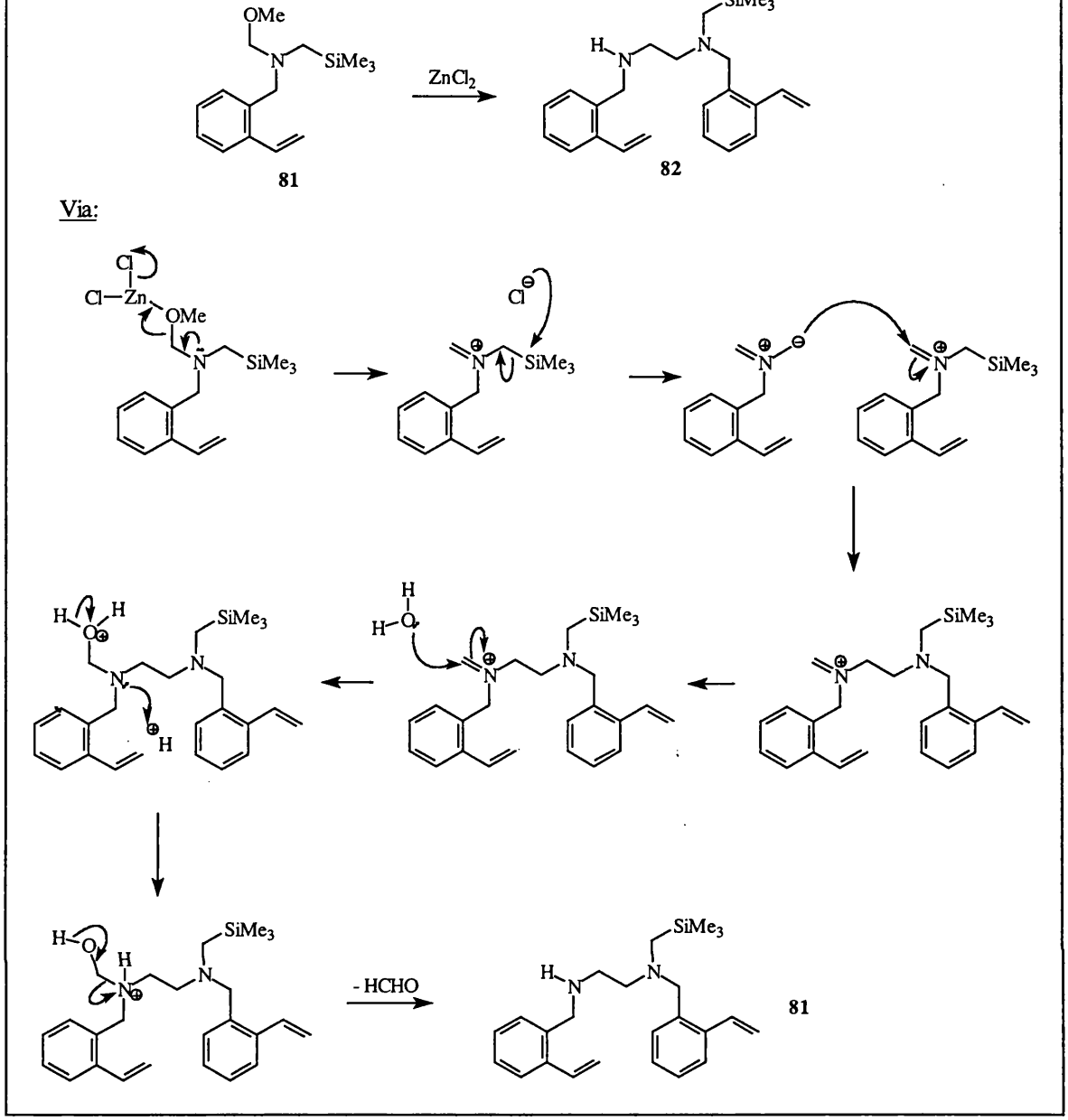
Scheme 20

Hosomi and Sakurai [42] have shown that nonstabilised azomethine ylides can be obtained from aminals **74** after treatment with catalytic trimethylsilyl triflate or trimethylsilyl iodide (**Scheme 21**). Optimal results were obtained by heating the aminal precursor, the dipolarophile, and the catalyst in a dipolar aprotic solvent such as MeCN. Although CsF was not a requirement for these reactions, it did usually enhance the yields.



Scheme 21

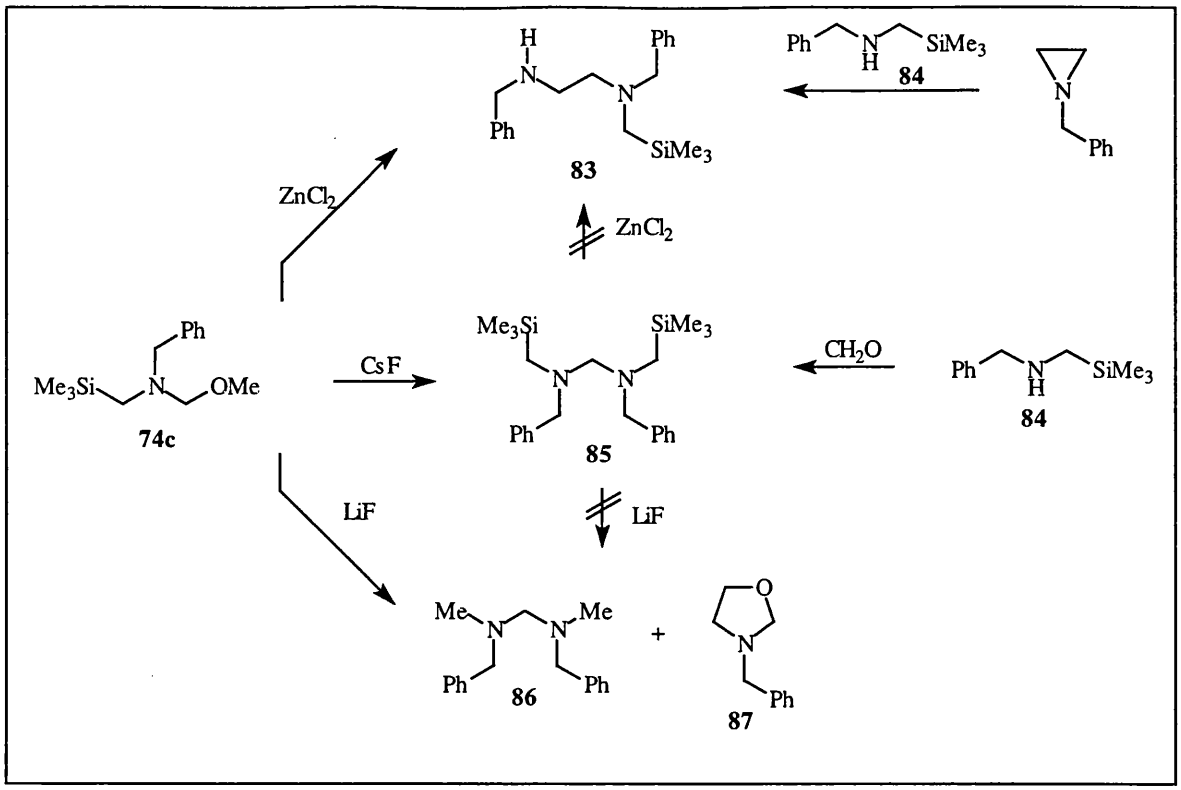
The intramolecular cycloaddition of *o*-vinylbenzyl methoxy amine **81** has been investigated using $ZnCl_2$ as a promoter, but this afforded only the monosilylated product **82** with no traces of the intramolecular cycloadduct in the crude reaction mixture (**Scheme 22**).[44]



Scheme 22

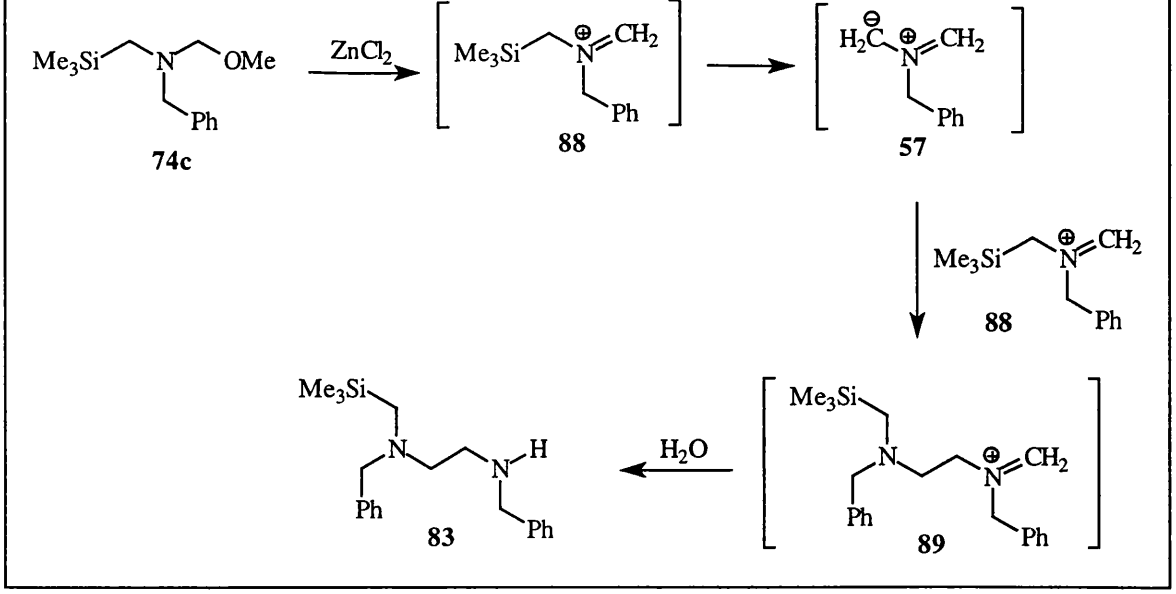
This result led to the examination of zinc chloride and methoxy silyl amine **74c** in the absence of a trapping agent. It was found that the reaction proceeded in an analogous fashion to that encountered with **81** and gave the monosilylated diamine **83** (**Scheme 23**). The identity of **83** was determined by its spectral properties and by comparison with an independently synthesised sample prepared by treating *N*-benzylaziridine with *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine **84**. An entirely different product was obtained, however, when **74c** was treated with CsF. The major product was identified as the disilylated diamine **85** by comparison with an authentic sample prepared by treating **84** with formaldehyde. A control experiment showed that **85** was not converted to **83** when treated with zinc chloride. The reaction of **74c** with lithium fluoride took

yet another course producing *N,N* -dimethyl-*N,N* -dibenzyldiaminomethane **86** and *N*-benzyloxazolidine **87**. Compound **85** did not produce **86** upon treatment with LiF.



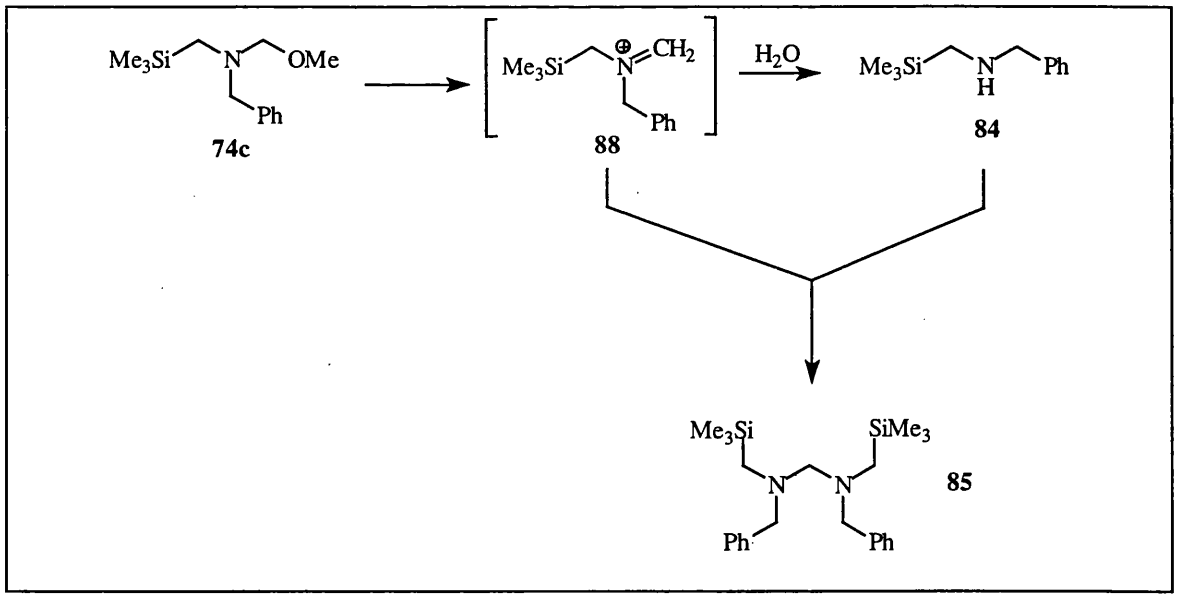
Scheme 23

α-Methoxy amines can be considered as latent forms of iminium ions due to their ability to lose the methoxy ion upon treatment with Lewis acids. Thus, the reaction of **74c** with zinc chloride can most reasonably be explained by assuming initial formation of an iminium ion **88** followed by a subsequent desilylation to generate the azomethine ylide **57** (see **Scheme 24**). In the absence of a trapping agent, the 1,3-dipole reacts with **88** to give a new iminium ion **89**, to afford the observed product **83** on hydrolytic work-up.



Scheme 24

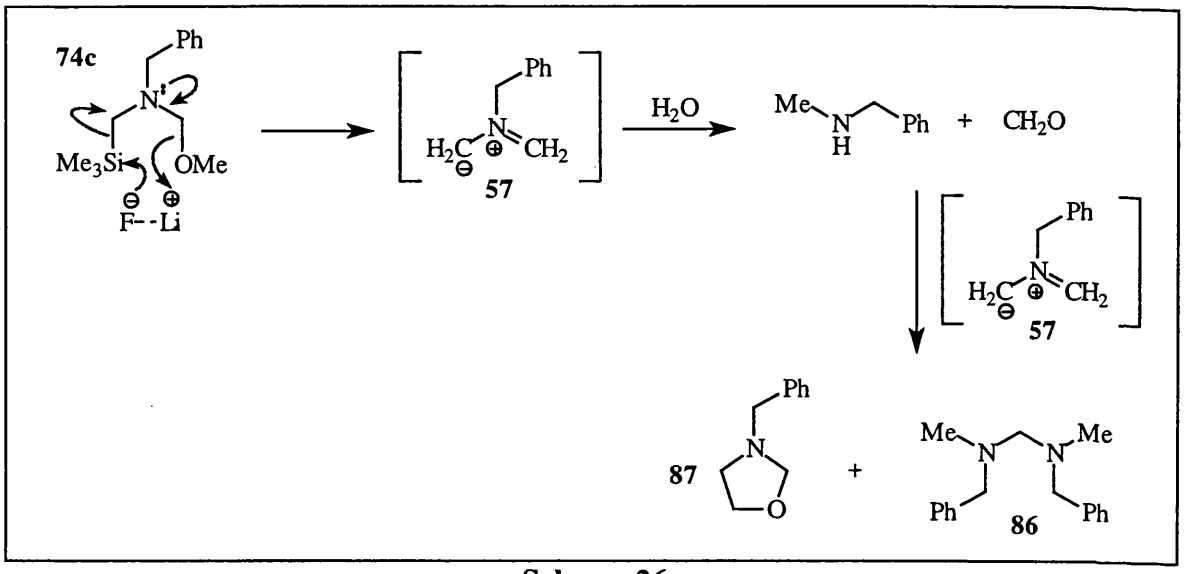
To rationalise the difference in product distribution when caesium fluoride was used as the desilylating agent, it was proposed that the initially formed iminium ion **88** underwent a prior hydrolysis to **84** and formaldehyde. It was believed that the caesium fluoride used contained a significant amount of water, which resulted in hydrolysis rather than desilylation of the ylide. Once the **84** was formed, it reacted with another equivalent of **88** to afford the disilylated diamine **85** (**Scheme 25**).



Scheme 25

In contrast to CsF, the reaction of **74c** with LiF gave no traces of the disilylated product **85**. Lithium fluoride has the advantage that it is relatively anhydrous and less

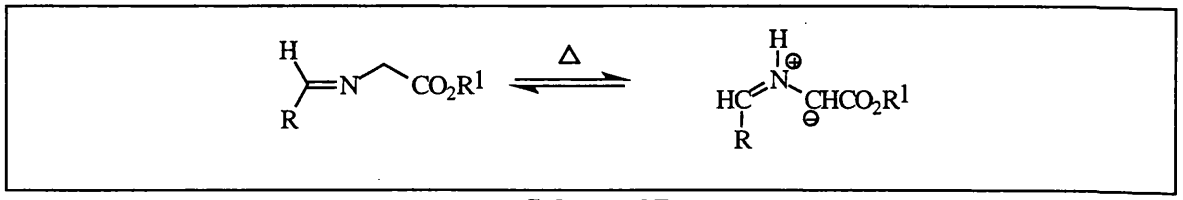
in solution and thereby suppressing the hydrolysis reaction. It was believed that the formation of the azomethine ylide **57** proceeded in a concerted fashion when LiF was used (see **Scheme 26**). In the absence of a trapping agent, the resultant dipole would eventually react with small amounts of water still present in solution to generate benzylmethylamine and formaldehyde. Both of these compounds, in turn, reacted further to give the observed products **86** and **87**.



Scheme 26

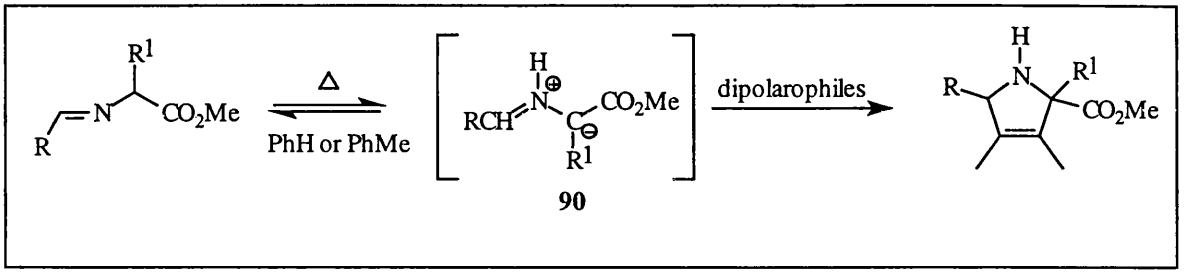
1.2.3 The tautomerisation route to azomethine ylides

α-Amino acid ester imines are highly acidic because the conjugate bases resulting from deprotonation are stabilised by both the imine and the ester moieties. Clearly, if the imine nitrogen then picks up the liberated proton, this formally generates a stabilised azomethine ylide potentially capable of undergoing cycloadditions to alkenes and alkynes (**Scheme 27**).



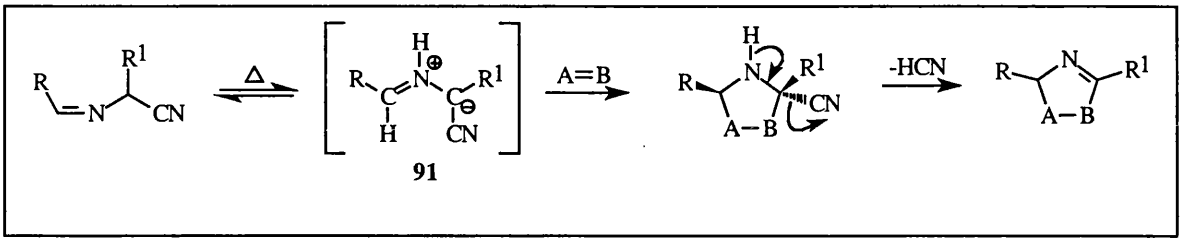
Scheme 27

as tautomers of imines was provided by Grigg *et al.*[45,46] When imines of α-amino acid esters were heated in benzene or toluene in the presence of a variety of dipolarophiles, pyrrolidine-2 or 3-pyrroline-2-carboxylates were isolated. This indicates that a thermal equilibrium exists between imine esters and azomethine ylides **90** (**Scheme 28**). This thermal method of generating *N*-unsubstituted azomethine ylides is frequently referred to as the *tautomerisation route* to azomethine ylides.



Scheme 28

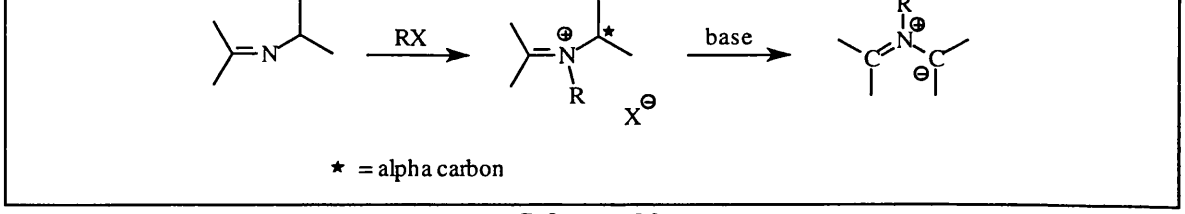
The imines of α-amino alkylnitriles undergo thermal tautomerisation to give the corresponding *N*-unsubstituted azomethine ylides **91** (**Scheme 29**).[5,47-49] Although cyano-stabilised azomethine ylides **91** have served as useful synthetic equivalents of the ester-stabilised azomethine ylides **90**, they can also be synthetic equivalents of nonstabilised nitrile ylides through a cycloaddition and HCN elimination sequence.[48,49]



Scheme 29

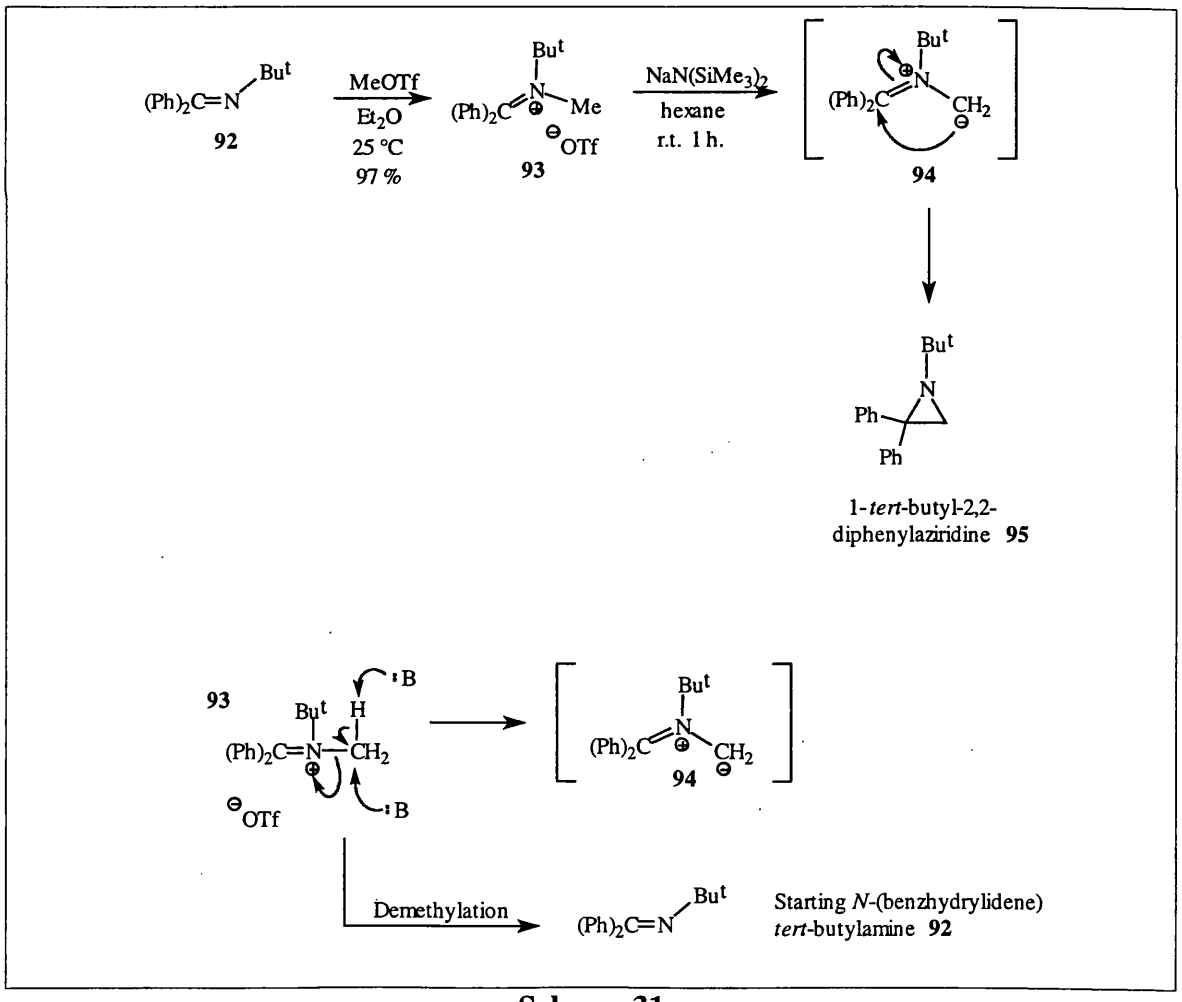
1.2.4 The deprotonation route to azomethine ylides

One of the most direct, yet difficult, methods for obtaining azomethine ylide 1,3-dipoles involves the sequence of imine *N*-alkylation followed by α-deprotonation (**Scheme 30**).



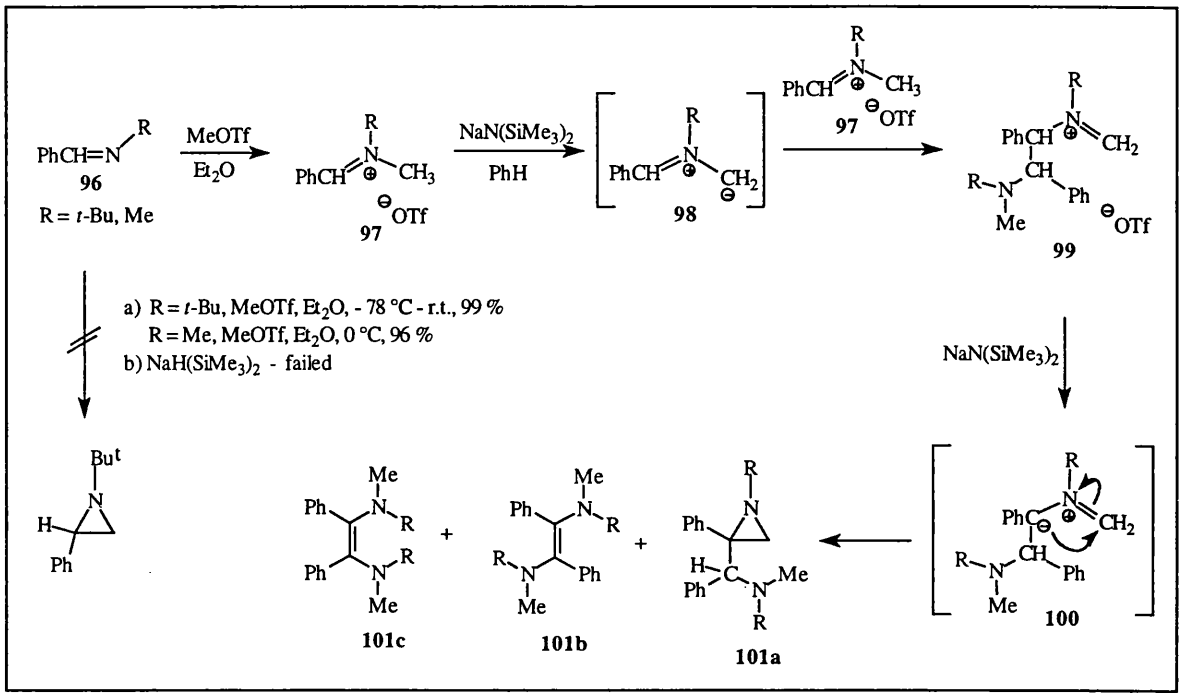
Scheme 30

This methodology was first introduced by Deyrup *et al.*[50] (**Scheme 31**) for the preparation of aziridines. *N*-Methylation of imines with methyl triflates affords labile *N*-methyliminium triflates **93** and **97**. Deprotonation of **93** is usually best performed with sodium hexamethyldisilazide to generate azomethine ylide **94**, which is captured without added dipolarophile in an intramolecular fashion as a cyclised isomer, 1-*tert*-butyl-2,2-diphenyl-aziridine **95**. Trapping of the intermediate azomethine ylide **94** with various dipolarophiles failed to prevent the formation of **95**. It should also be noted that deprotonation of **93** is usually accompanied by demethylation to provide the starting imine **92** even when a non-nucleophilic strong base is utilised.



Scheme 31

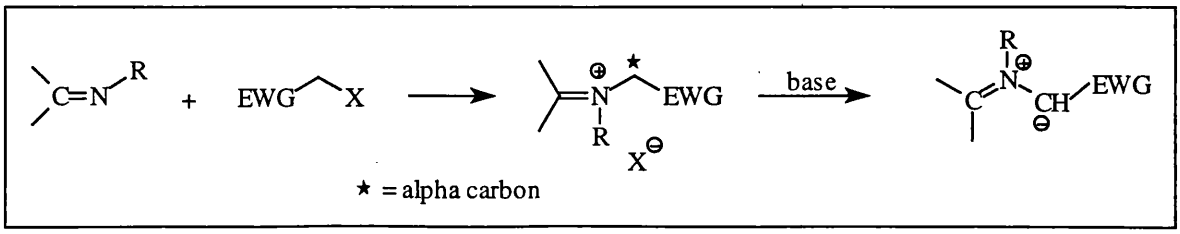
dimeric products **101a-c** arising from the substituted azomethine ylide **100**, which itself is formed from a nucleophilic addition of azomethine ylide **98** to the iminium salt **97** and subsequent deprotonation (**Scheme 32**).



Scheme 32

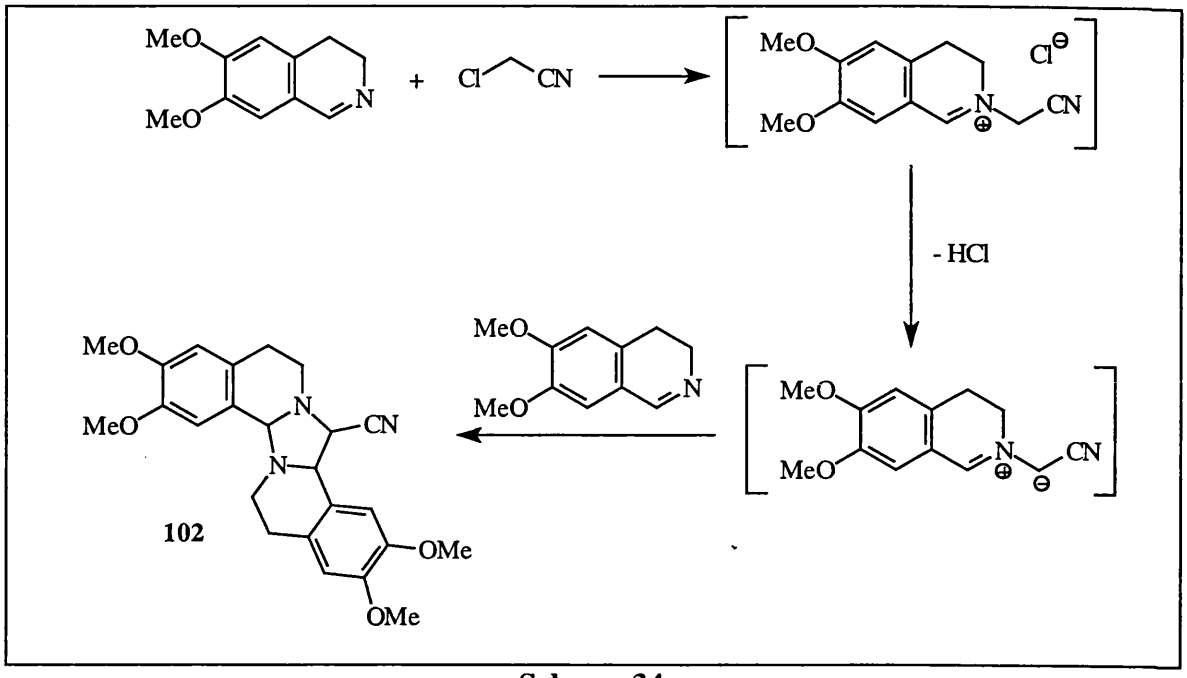
Although the *N*-alkylation and deprotection sequence pioneered by Deyrup is often referred to as the deprotonation route, it has to be concluded that this sequence (**Scheme 30**) does not provide a synthetically useful route to azomethine ylides for cycloaddition reactions. Modifications are required to remedy this situation.

If the acidity of the α-hydrogen of iminium intermediates were to be increased, α-deprotonation could be smoothly carried out with a weak base and this would avoid the undesired alkylation. In order to do this, an electron-withdrawing group (EWG) is required on the α carbon of the iminium salt. These ideas are depicted in **Scheme 33**.



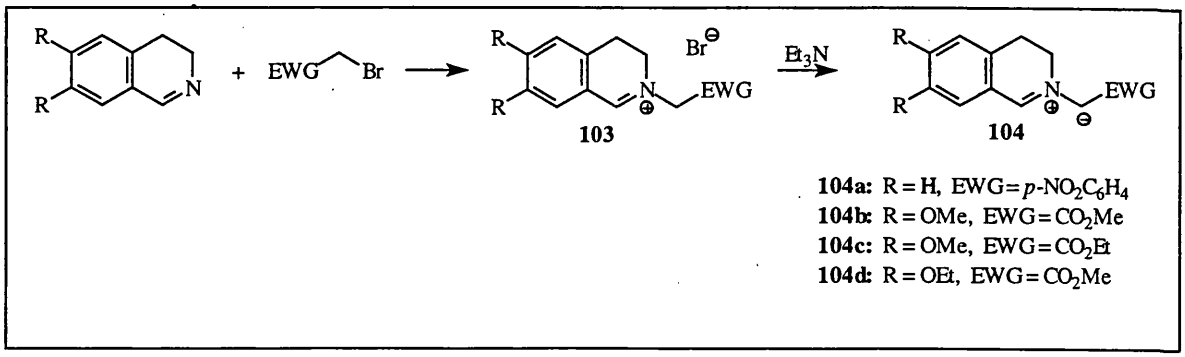
Scheme 33

If anion stabilisation by an EWG is extensive, the resulting iminium salts quickly lose the α-hydrogen under the alkylation conditions, which leads to a spontaneous generation of the azomethine ylide and cycloaddition to the starting imine. For example, in the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline with chloroacetonitrile, the cycloadduct **102** was formed by such a process (**Scheme 34**).[51]



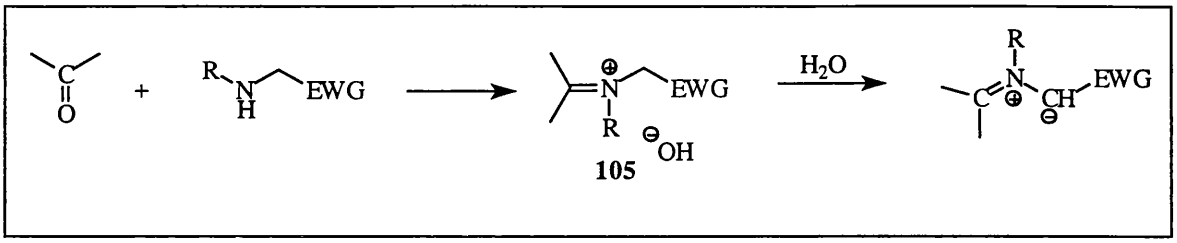
Scheme 34

Alkylating agents that carry an appropriate EWG such as *p*-nitrobenzyl bromide [2] and α-bromo-esters [52-54] have successfully been employed in the preparation of iminium precursors **103** (**Scheme 35**). Iminium salts **103** then form the azomethine ylides **104** upon treatment with triethylamine.



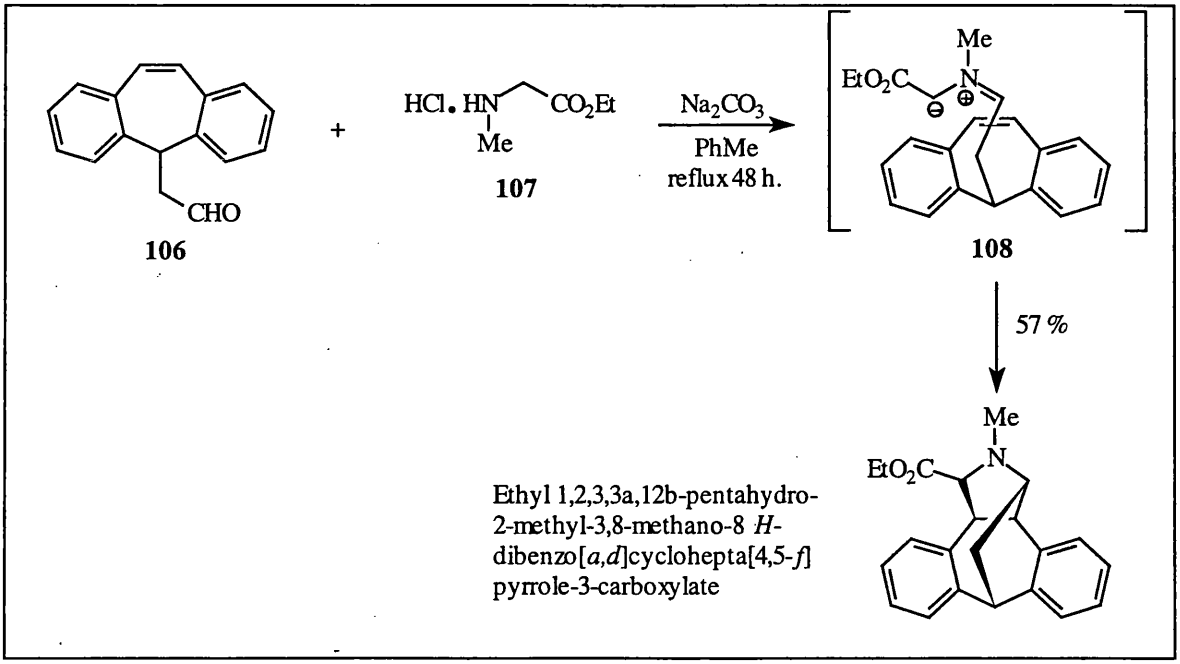
Scheme 35

is to condense *N*-substituted α-amino acid esters or derivatives (EWG = -CO_2R, -CN, etc.) with carbonyl compounds (**Scheme 36**). The intermediate iminium salts **105** are associated with a highly basic hydroxide counterion, which immediately deprotonates the α-hydrogen soon after **105** is formed. The stabilised azomethine ylides thus generated can then be smoothly trapped by added dipolarophiles.



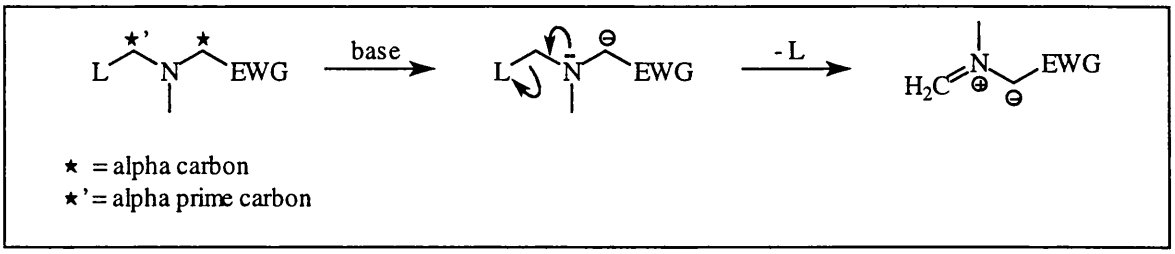
Scheme 36

Confalone *et al.*[55,56] have been advocates of the deprotonation method for the preparation of azomethine ylides. They condensed *N*-substituted α-amino esters with aldehydes to generate azomethine ylides (**Scheme 37**). Thus, 5-formylmethyldibenzo-[*a,d*]tropylidene **106** was heated with ethyl sarcosinate **107** under reflux in toluene. The water formed was continuously driven off with the aid of a Dean-Stark trap. The ester-stabilised azomethine ylide **108** so generated was trapped in an intramolecular fashion.



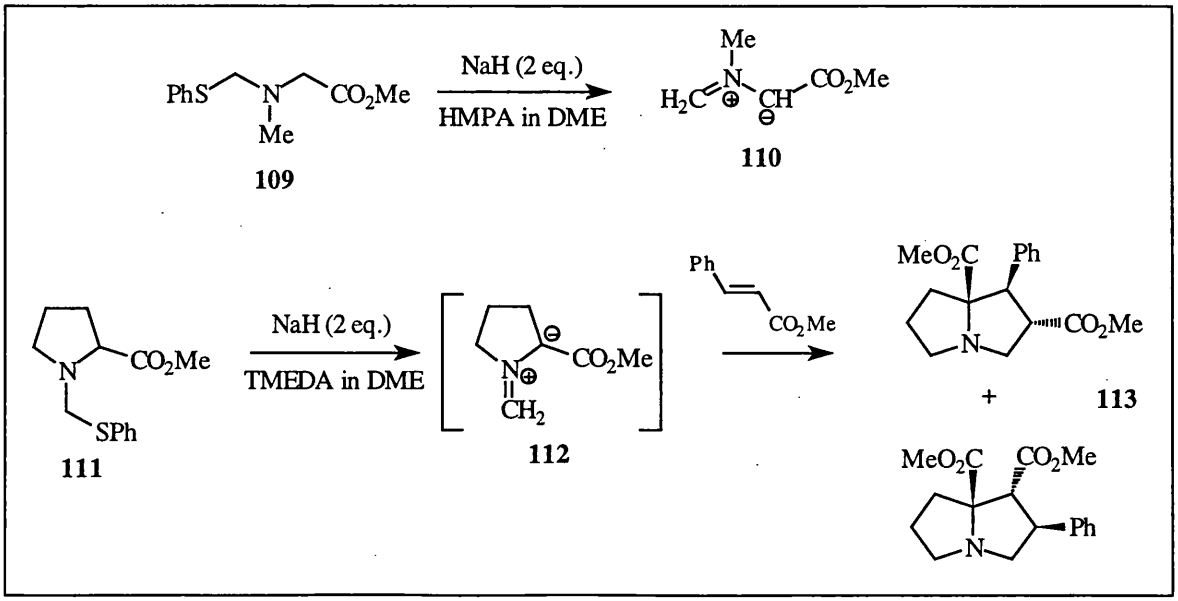
Scheme 37

Scheme 38 shows another variation of the deprotonation route to azomethine ylides involving amines bearing an α-electron-withdrawing and an α'-leaving group (L). This method is closely related to the modified version of the aforementioned desilylation route (**Scheme 11**).



Scheme 38

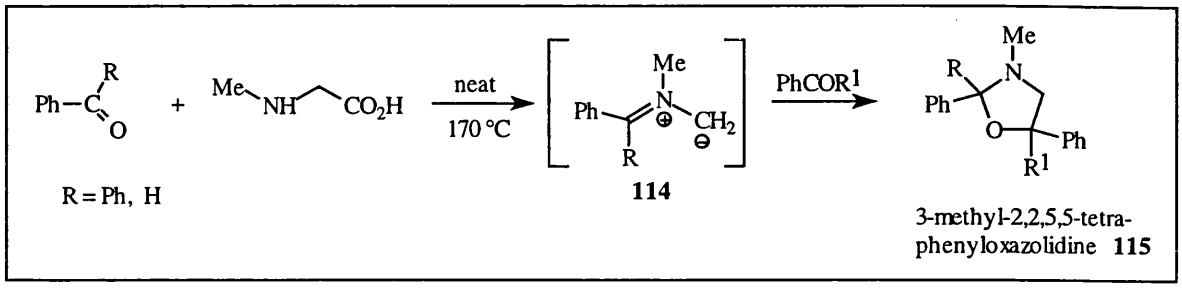
An example for the generation of stabilised azomethine ylides via the deprotonation method where the amine contains an α-electron-withdrawing and an α'-leaving group (L) has been reported by Achiwa *et al.*[57] Methyl *N*-(phenylthiomethyl)sarcosinate **109** was treated with NaH (two equivalents) in DME and HMPA to generate azomethine ylide **110** (**Scheme 39**). A cyclic ylide **112** was generated by a similar procedure using methyl *N*-(phenyl-thiomethyl)prolinate **111** which was trapped with a dipolarophile to afford the corresponding cycloadduct **113** as a 1:1 regioisomeric mixture.



Scheme 39

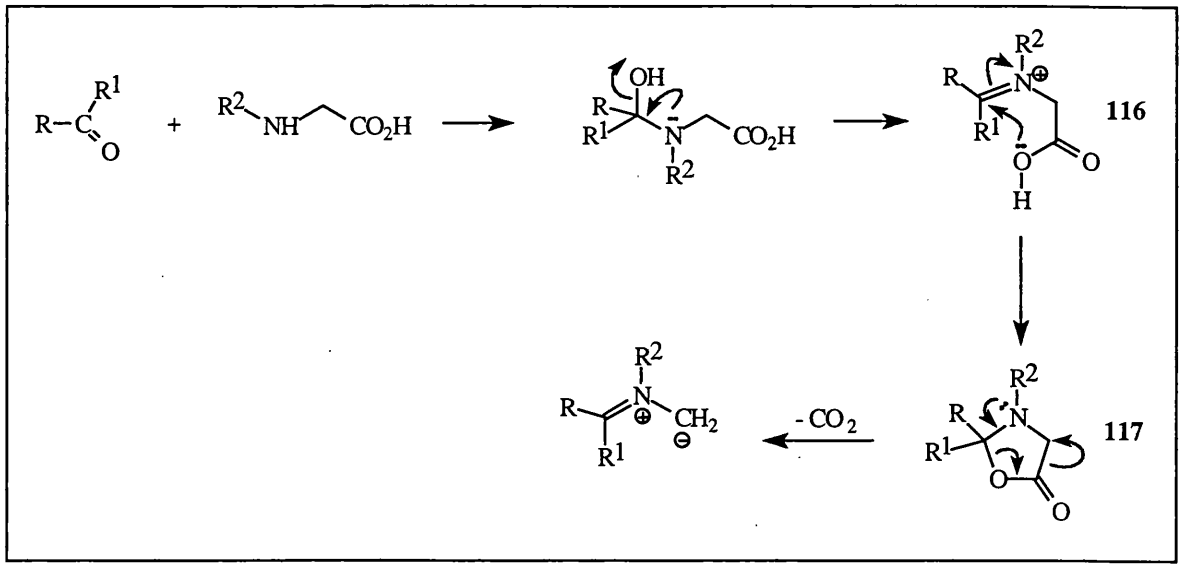
1.2.3 The decarboxylation route to azomethine ylides

During investigations on the carbonyl-assisted decarboxylation of *N*-alkylated α-amino acids, Rizzi [58] found that azomethine ylide intermediates are involved in the decarboxylative condensation. Heating sarcosine and benzophenone at 170 °C (or benzaldehyde at 150-170 °C) gave 3-methyl-2,2,5,5-tetraphenyloxazolidine **115**, which corresponds to the cycloadduct of azomethine ylide **114** to the carbonyl compound (**Scheme 40**).



Scheme 40

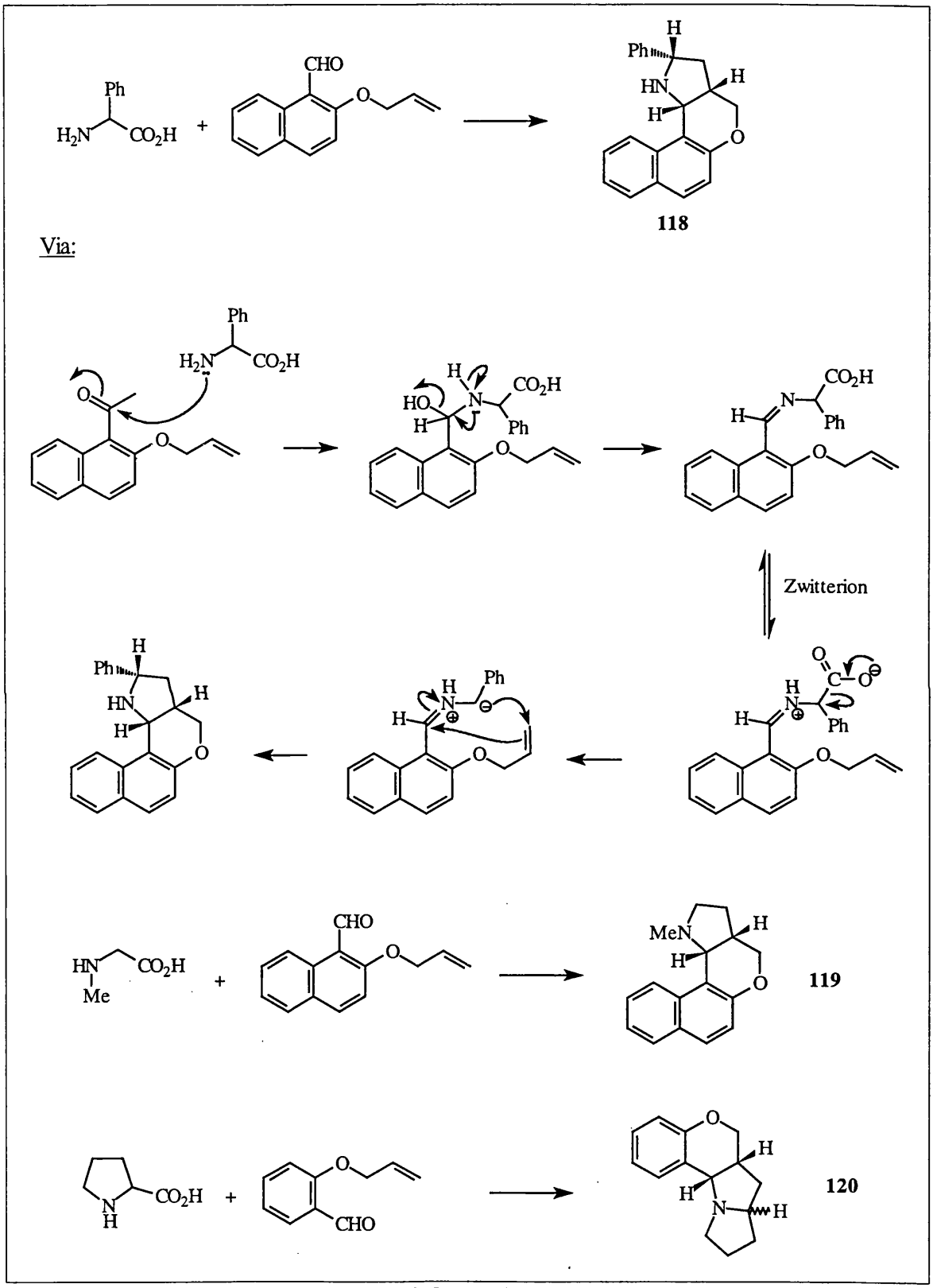
This sequence may involve the initial formation of iminium carboxylate **116** which then cyclises into the thermally labile 5-oxazolidinone intermediate **117**. This subsequently undergoes a facile thermal decarboxylation to generate the nonstabilised azomethine ylide (**Scheme 41**).



Scheme 41

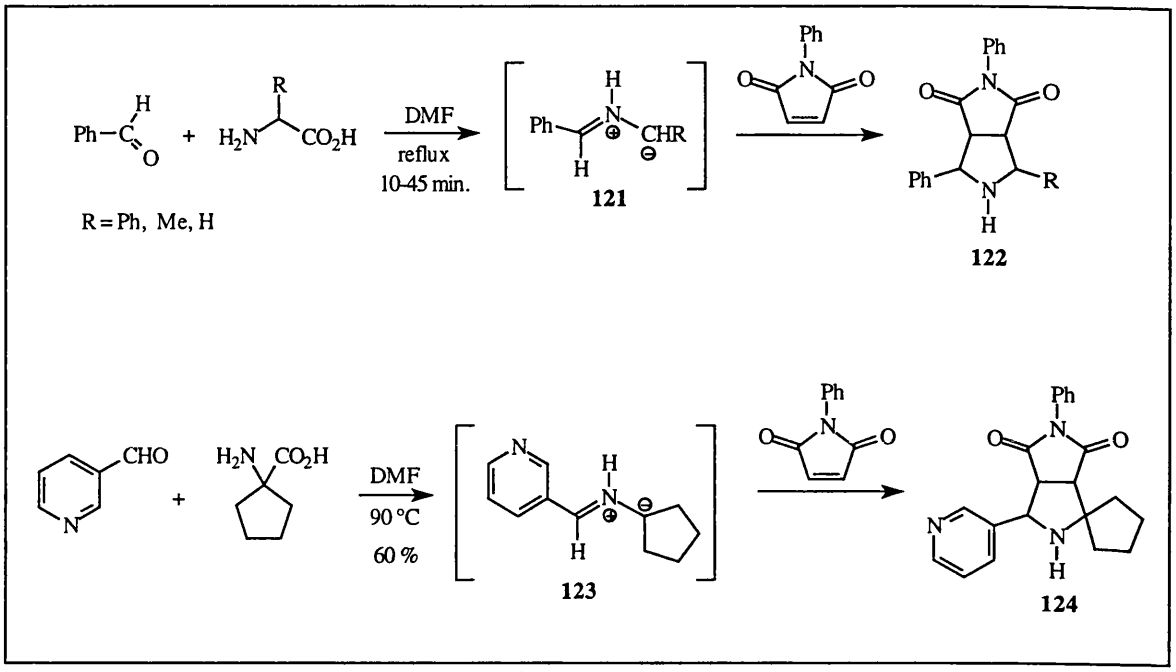
The generation of nonstabilised azomethine ylides by the decarboxylation route and internal trapping has also been investigated by Grigg *et al.*[59,60] They showed that

with *N*-substituted or *N*-unsubstituted α-amino acids in DMF for short periods of time, provided access to a variety of *cis*-fused cycloadducts, **118, 119** and **120** (**Scheme 42**).



Scheme 42

can be prepared from the decarboxylation procedure by heating benzaldehyde or pyridine-3-carbaldehyde and α-amino acids in boiling DMF. When *N*-phenylmaleimide was also present, mixtures of several stereoisomeric cycloadducts were obtained (**Scheme 43**).

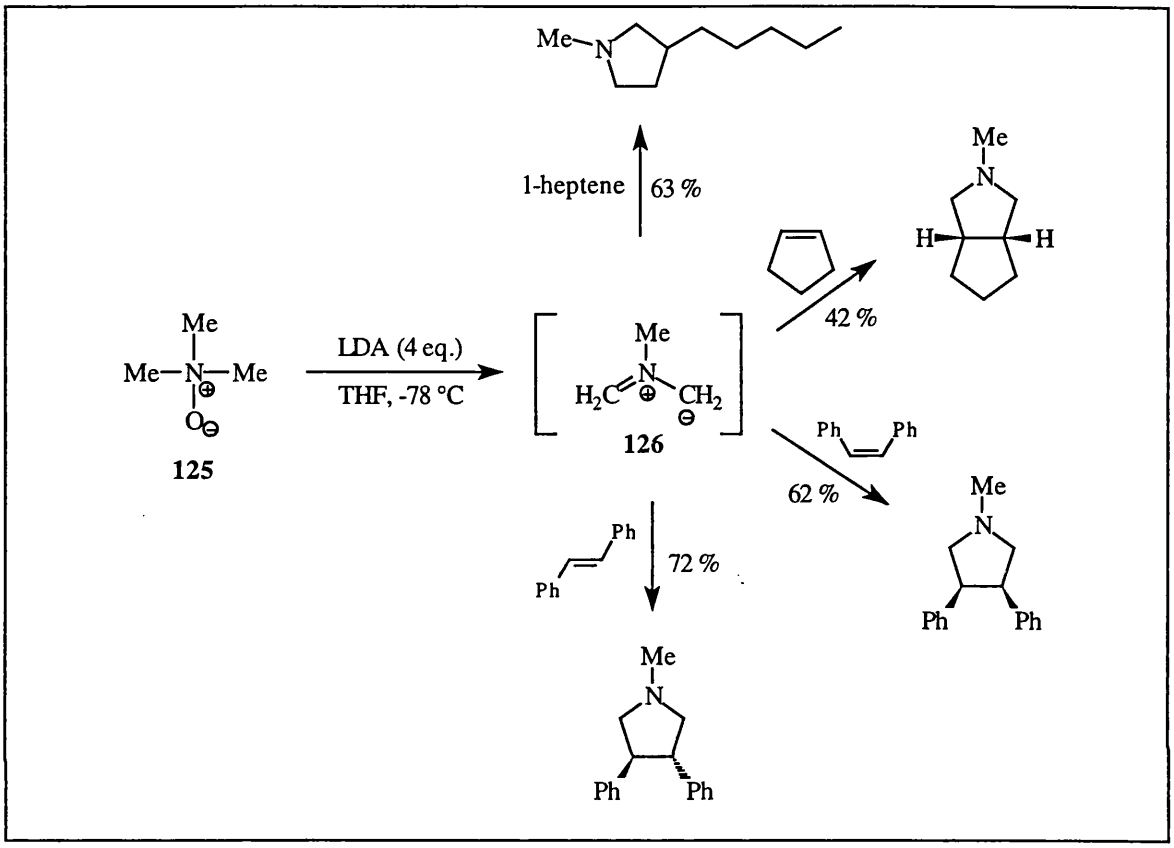


Scheme 43

1.2.6 The *N*-oxide route to azomethine ylides

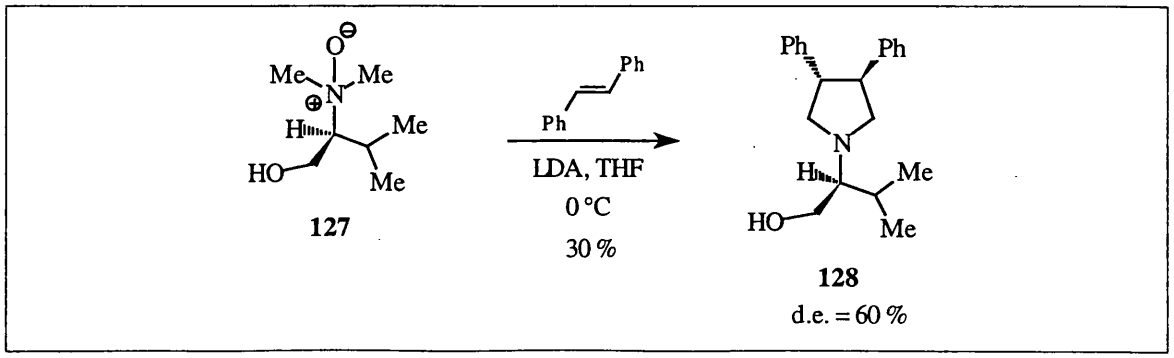
The extensive study of desilylation in the azomethine ylide area can be attributed to the scarcity of viable methods for generation of the nonstabilised members of this dipole family. Work by Roussi *et al.*[61-64] indicated that treatment of amine *N*-oxides with strong base can also produce nonstabilised azomethine intermediates. This method for azomethine ylide generation is commonly referred to as the *N-oxide route*. In contrast to the desilylation route, this method has permitted the successful [3+2] trapping of certain unactivated olefins, apparently, because there is no iminium species present to compete in dipole trapping. However, the strongly basic reaction conditions required obviously preclude the use of sensitive trapping agents, and serve to limit the applicability of the method.

°C generated the *C*-unsubstituted nonstabilised azomethine ylide **126** (**Scheme 44**). This ylide intermediate underwent smooth cycloaddition reactions to nonactivated olefinic dipolarophiles, such as 1-alkenes, cyclic alkenes, styrene, (*E*)- and (*Z*)-stilbene to give a variety of pyrrolidines.[61]



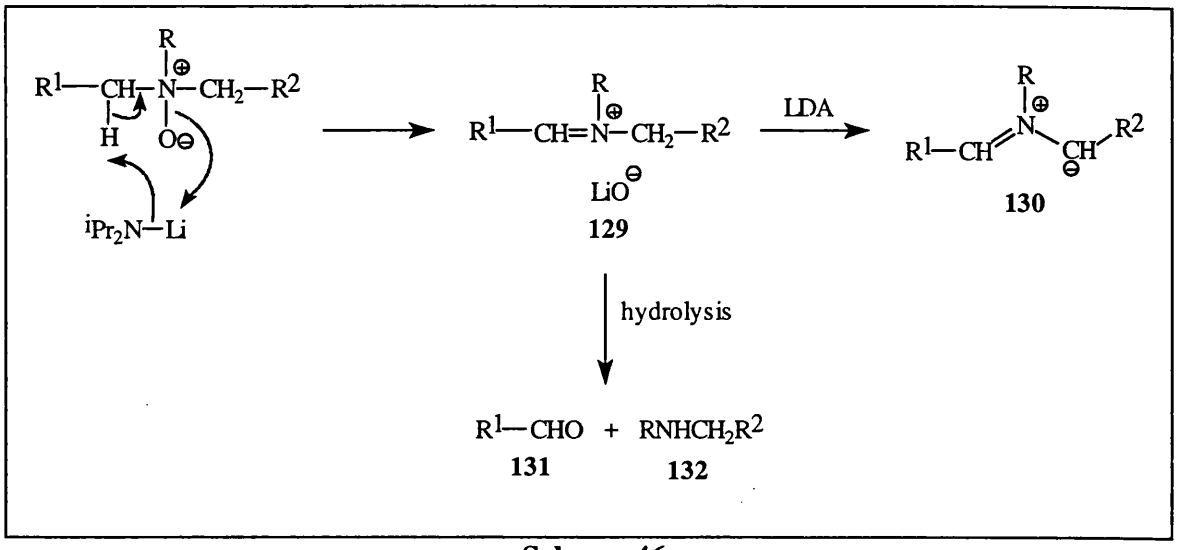
Scheme 44

Roussi *et al.*[65] have also harnessed this methodology for the preparation of chiral nonstabilised azomethine ylides. For example, deprotonation of amine *N*-oxide **127** with LDA followed by interception with (*E*)-stilbene, afforded a 4:1 mixture of diastereomeric adducts **128** (**Scheme 45**).



Scheme 45

The mechanism of azomethine ylide generation via the *N*-oxide route is illustrated in (**Scheme 46**). The tertiary amine *N*-oxide chelates to the Li^+ cation and the amine base then effects α-deprotonation. After elimination of LiO^-, an iminium ion **129** is generated. A second deprotonation of the iminium intermediate then creates the azomethine ylide **130**. Evidence for this mechanism has been provided by the examination of the products of hydrolysis, **131** and **132**, after base treatment.

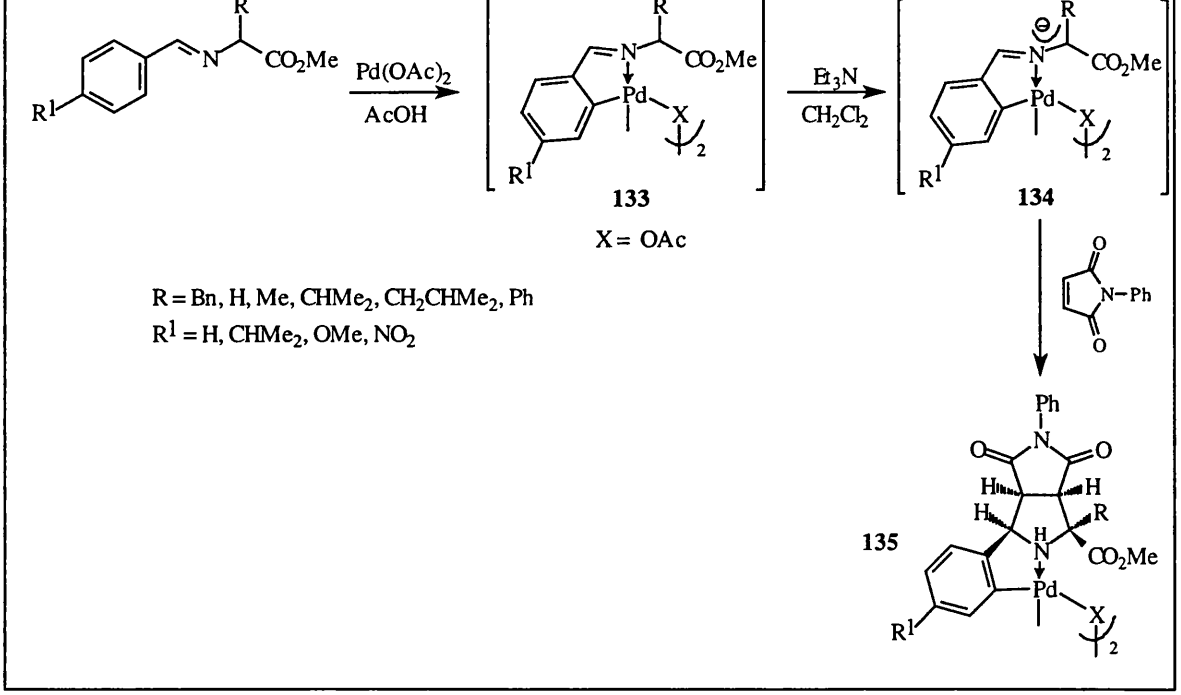


Scheme 46

Although the range of azomethine ylides that can be generated by the *N*-oxide route is quite restricted, the method does nevertheless give rise to useful pyrrolidines.

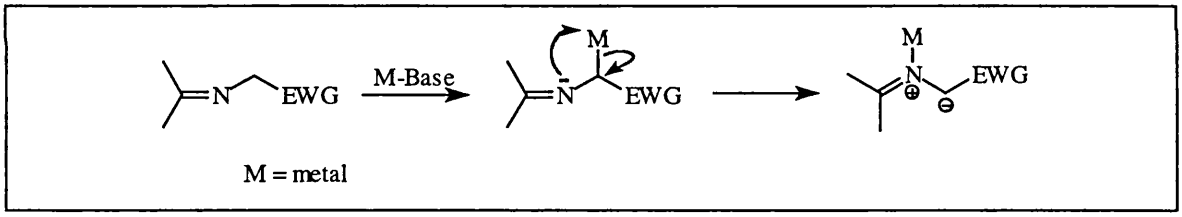
1.2.7 The *N*-metallation route to azomethine ylides

Another route to stabilised azomethine ylides is via the *N*-metallation of imines derived from α-amino acids or esters. This can be seen when *N*-(*p*-substituted benzylidene) imines of α-amino esters are converted into the *o*-palladated dimeric complexes **133** by treatment with palladium acetate in hot acetic acid.[66] The complexes **133** are readily deprotonated with triethylamine in CH_2Cl_2 to generate red solutions of *N*-metallated azomethine ylides **134**, which are captured with *N*-phenylmaleimide as an *endo*-selective dimeric cycloadduct **135** (**Scheme 47**).



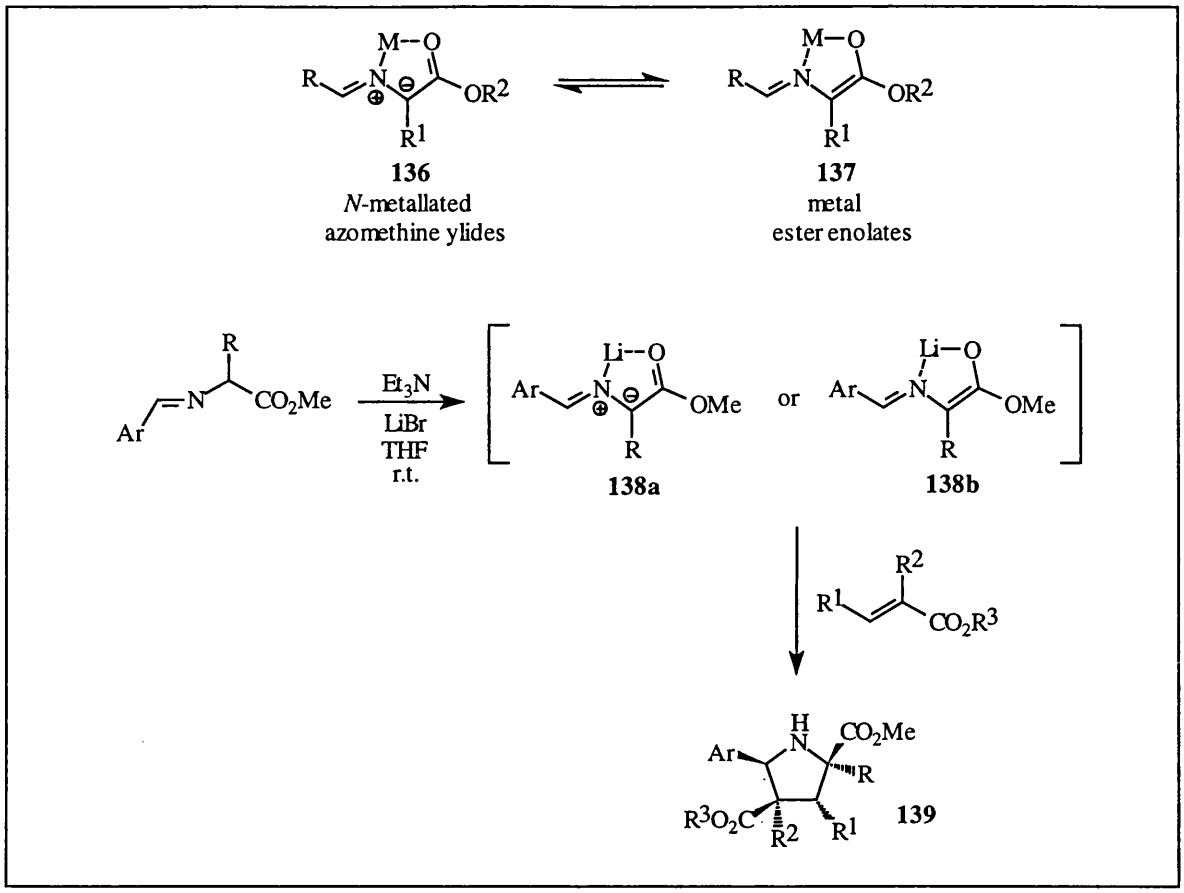
Scheme 47

α-Metallation of the imines bearing an electron-withdrawing α-substituent will generate the α-metallated imines. A 1,2-metal migration follows and the *N*-metallated azomethine ylide is generated (**Scheme 48**).



Scheme 48

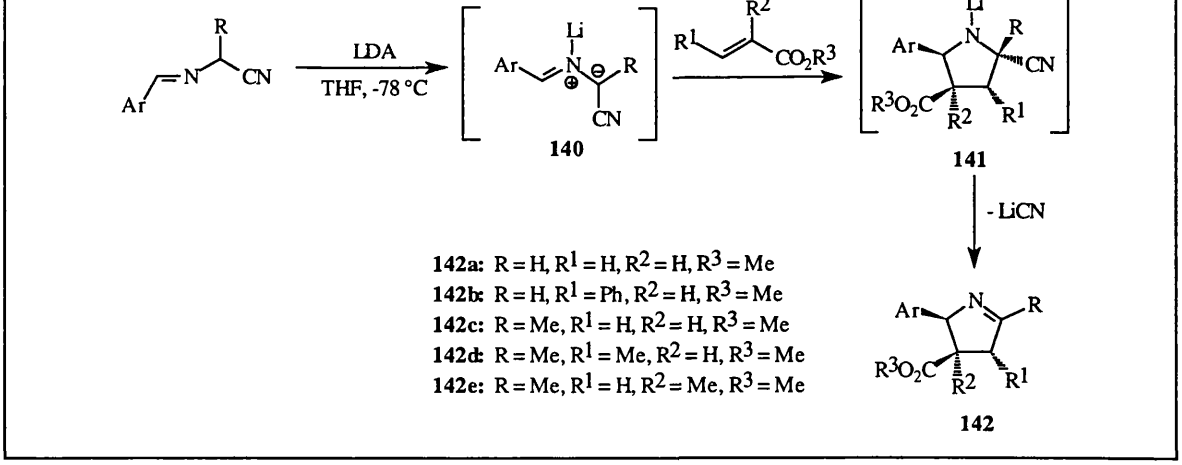
N-Metallated azomethine ylides **136** of ester-stabilised types are tautomeric to the metal ester enolates **137** of chelate-stabilised types. The only structural difference is which heteroatom between the imine nitrogen and the ester carbonyl oxygen is connected with the metal (M) by a covalent bond. In the presence of lithium bromide in THF, the imines of α-amino esters can be deprotonated with triethylamine at room temperature to generate highly reactive 1,3-dipoles **138a,b** which exist either in an *N*-lithiated azomethine ylide structure **138a** or in a chelated lithium enolate form **138b** (**Scheme 49**).[67]



Scheme 49

The cycloaddition trapping of **138a,b** can be carried out, without any trouble because of the weakly basic conditions, with a variety of olefins such as maleimides, maleates, fumarates, acrylates, crotonates, methacrylates and vinyl ketones. The corresponding cycloadducts **139** are obtained in a highly regio- and stereoselective fashion.

The imines of α-aminonitriles can be lithiated with LDA at -78 °C in THF. The anionic intermediates **140** generated are captured in a regio- and stereoselective, and stereospecific cycloaddition with a number of olefins to furnish 4,5-cis-1-pyrrolines **142a-e** after elimination of lithium cyanide (**Scheme 50**).[68]



Scheme 50

Unlike the *N*-metallated species **138a** and **138b** derived from the imines of α-amino esters or amides, the lithium is presumably sitting on the imine nitrogen so that **140** can be classified as an *N*-metallated azomethine ylide. In the cycloaddition step, the chelation of the lithium metal to the carbonyl oxygen of dipolarophiles is again important for the high regio- and stereoselectivities.

1.2.8 General summary of the methods for the generation of azomethine ylides for cycloaddition reactions

The various possible methods for the generation of azomethine ylides, either stabilised or nonstabilised, considered in this section are summarised briefly in **Table 1** below.

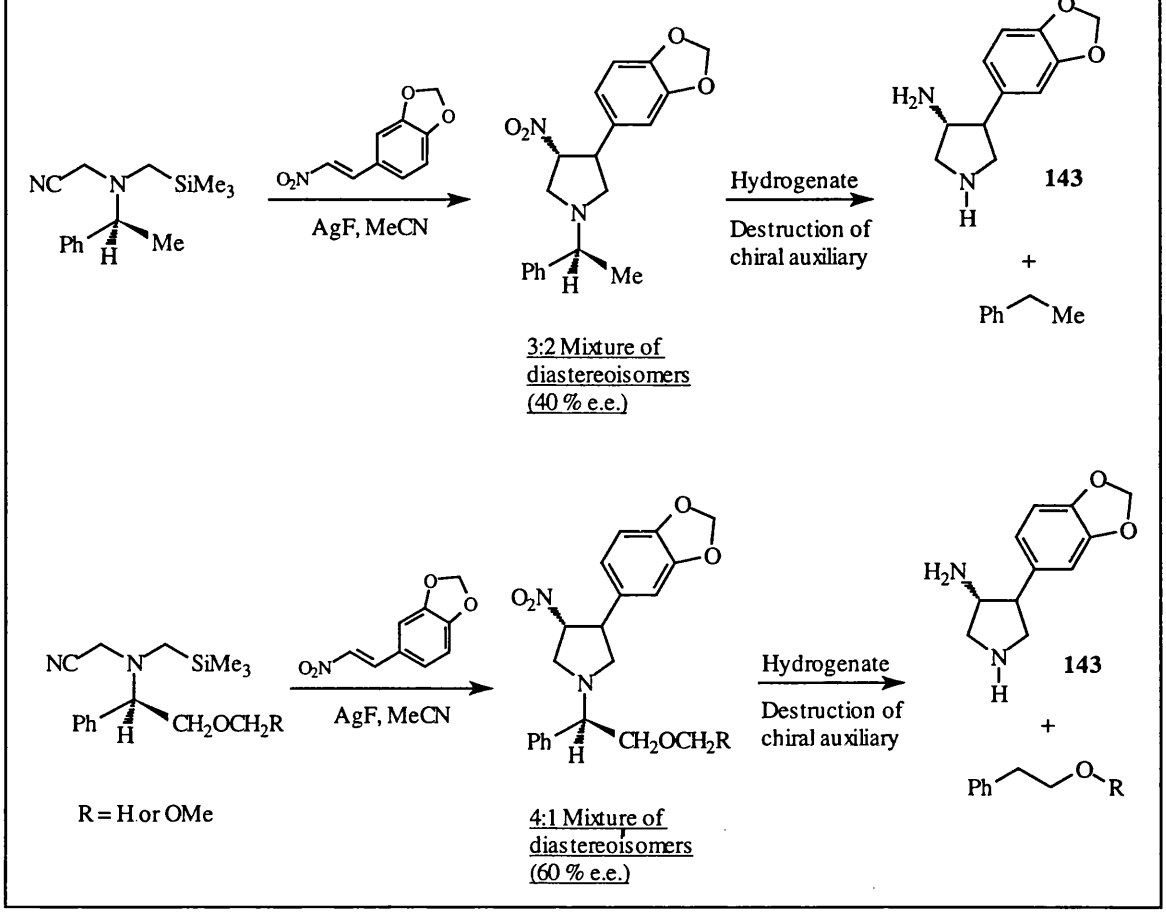
	Azomethine ylide generated	
Method of generation	Stabilised	Nonstabilised
Aziridine route	Yes	No
Desilylation route	No	Yes
Tautomerisation route	Yes	No
Decarboxylation route	Yes	Yes
N-oxide route	No	Yes
Deprotonation route	Yes	Yes
N-Metallation route	Yes	No

Table 1 Summary of the azomethine ylides generated via various methods

1.3 Asymmetric induction in the reactions of azomethine ylides with alkenes

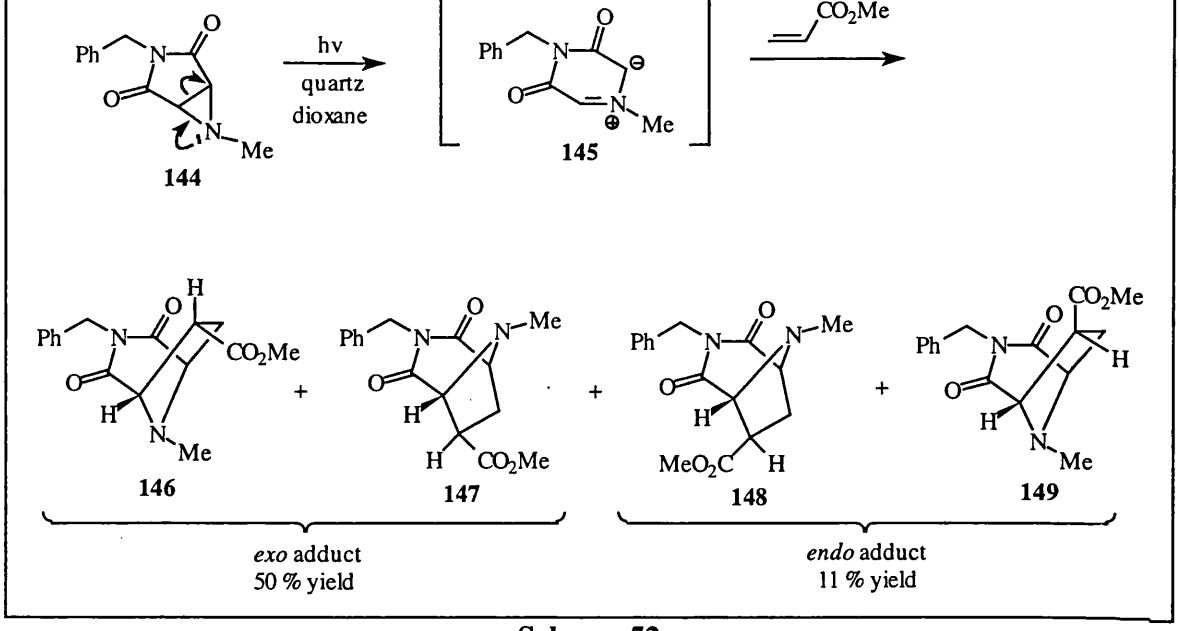
There are five issues which need to be considered when evaluating the utility of a general chiral auxiliary for the cycloaddition reactions of azomethine ylides in asymmetric synthesis: (1) availability of the auxiliary, (2) diastereofacial selectivity, (3) *endo*/*exo* selectivity, (4) geometry of the 1,3-disubstituted ylides, and (5) auxiliary removal/recovery. Suffice it is to say that none of the chiral systems reported so far appears to satisfy all of these requirements. Particularly noteworthy is the fact that all of the known systems require destructive removal of a chiral auxiliary attached to nitrogen.

At present, there are only a few successful examples of asymmetric 1,3-dipolar cycloadditions where an unstabilised azomethine ylide has been tethered to a removable chiral auxiliary.[40] Most of the reactions that have so far been investigated have, at best, exhibited only modest levels of stereocontrol (ca. 60 % d.e.), and in every case, destruction of the chiral auxiliary has been necessary before the newly fashioned pyrrolidine cycloadduct could be liberated (**Scheme 51**). One could envisage that the resultant cycloadduct could be removed via hydrogenation to afford, as in the case of **Scheme 51**, the amino-pyrrolidine **143**.

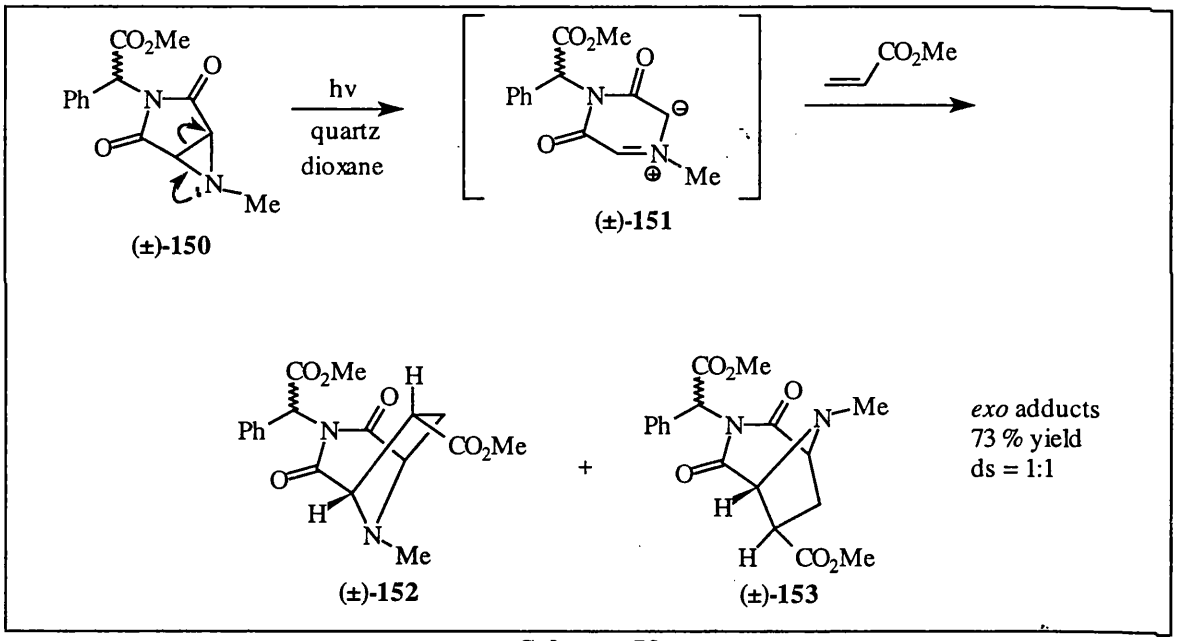


Scheme 51

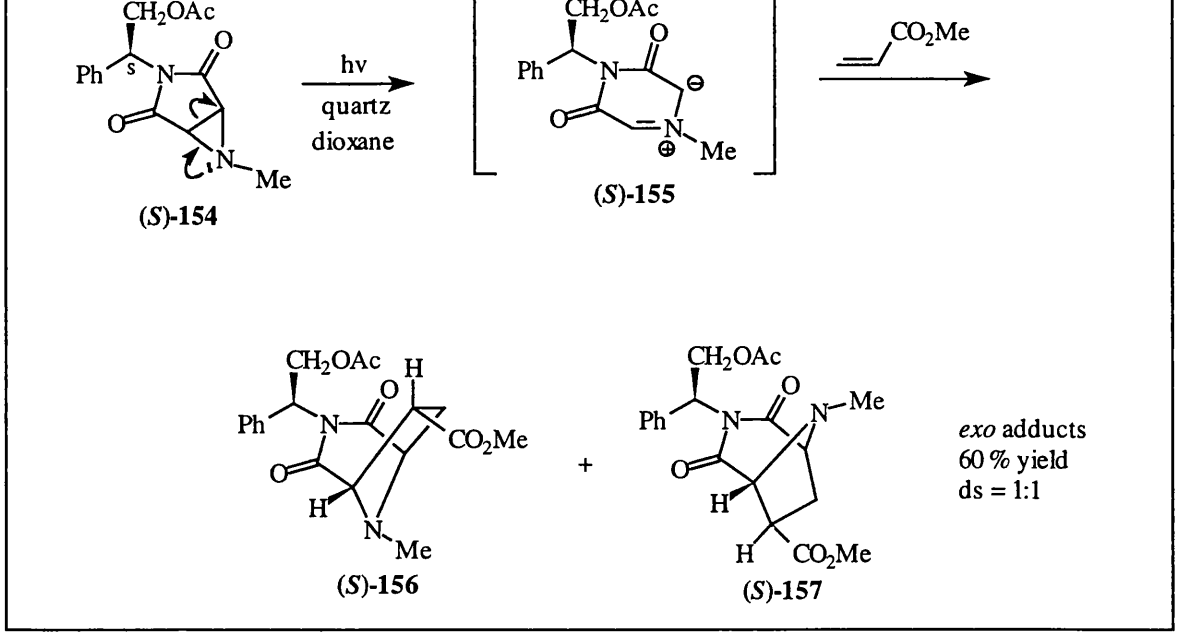
Garner *et al.*[69,70] have reported excellent diastereofacial selectivity in the 1,3-dipolar cycloaddition reactions of photochemically-generated achiral azomethine ylides **145/151** and chiral azomethine ylides **155/182** with various achiral and chiral dipolarophiles (**Scheme 52-61**). This work was initiated from previous studies where no chirality was present in the electron-withdrawing group substituted dipolarophiles for the cycloaddition reactions of azomethine ylides **145/151/155** (**Scheme 52-55**, **Table 2**, entries 1-4). In the cases indicated in **Schemes 52-55** clean cycloadditions resulted, but all cycloadducts contained a 1:1 mixture of diastereomers.



Scheme 52

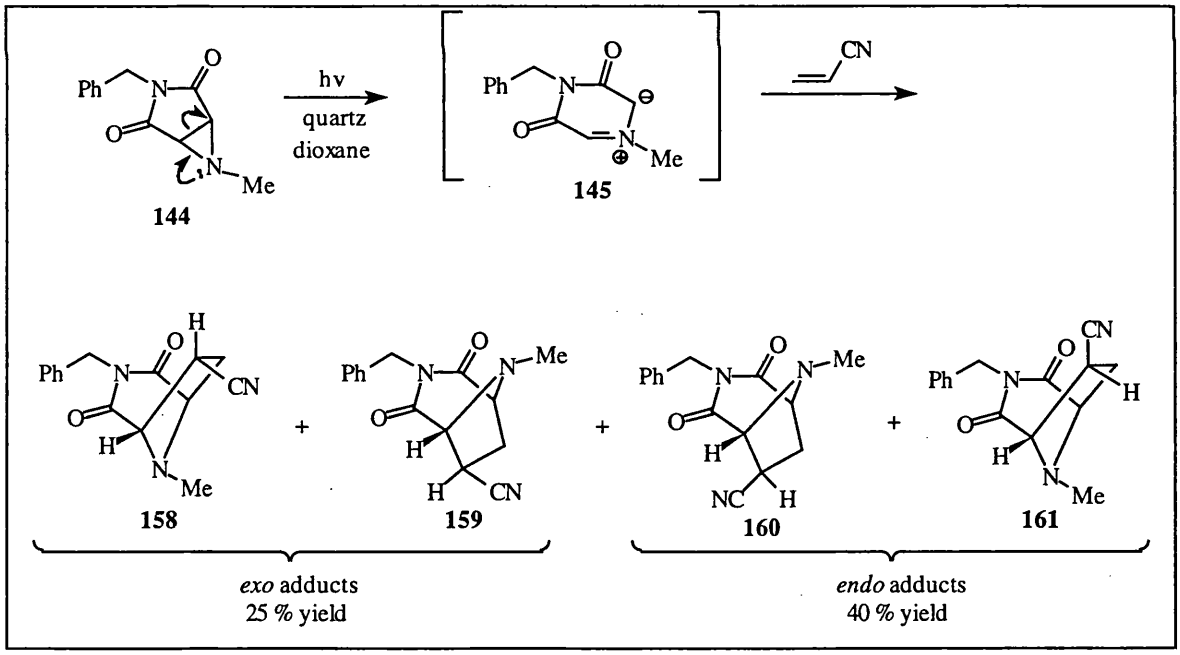


Scheme 53



Scheme 54

With methyl acrylate (**Schemes 52-54**), the preferential formation of the *exo* adducts **146/147**, **152/153**, abd **156/157** were observed, though small amounts of the *endo* adducts **148/149** could be detected in the case of the benzylic unsubstituted substrate **144**.

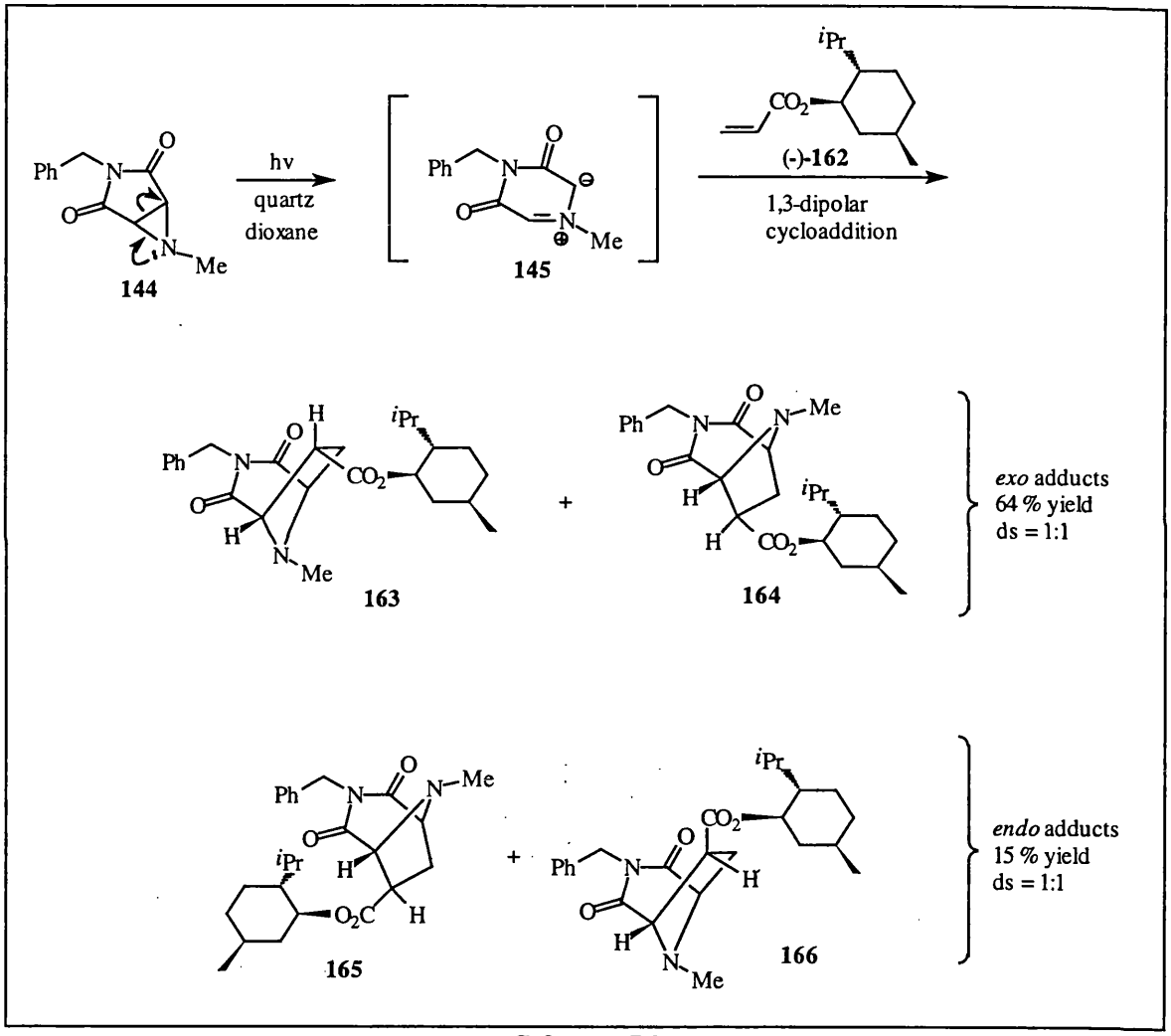


Scheme 55

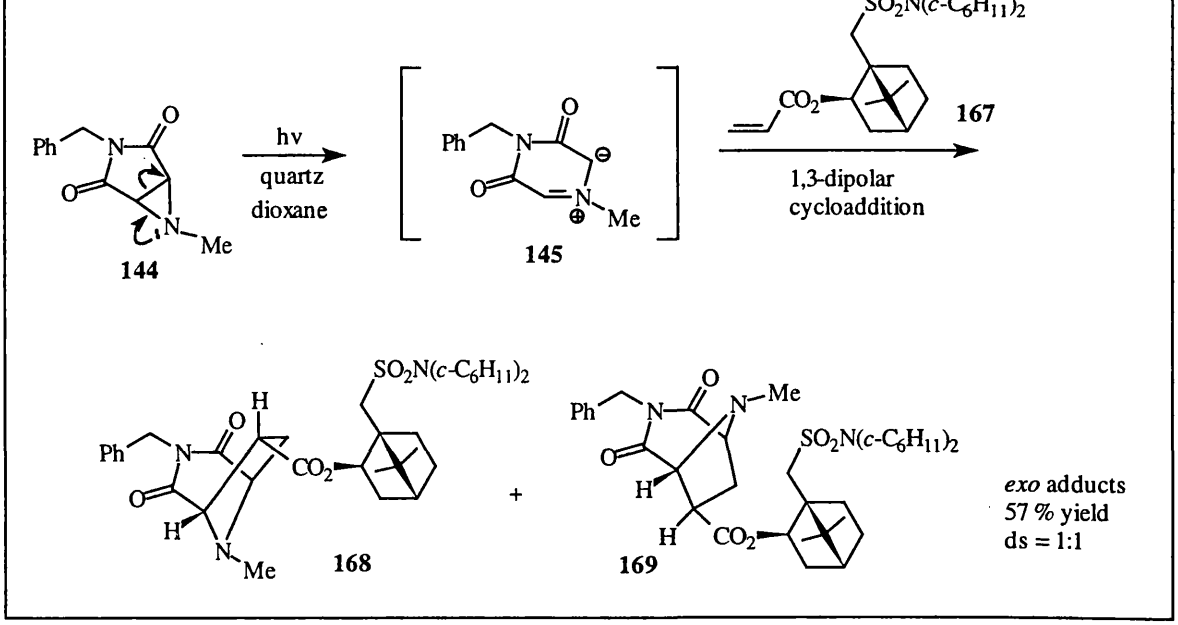
Trapping the azomethine ylide with acrylonitrile as the dipolarophile, however, favoured the *endo* adducts **160/161** over the *exo* adducts **158/159**. The diastereomeric

chromatography and were analysed as mixtures using ^{1}H n.m.r. data.

Chiral acrylates **162** and **167**, derived from menthol and 10-[dicyclohexyl-(sulfonylamido)]isoborneol, respectively, were then utilised (**Table 2**, entries 5-6) as the dipolarophiles. They also underwent clean cycloaddition reactions to the photochemically generated azomethine ylide **145** but no facial selectivity was observed. Again the predominant products were the *exo* cycloadducts **163/164** and **168/169**.



Scheme 56



Scheme 57

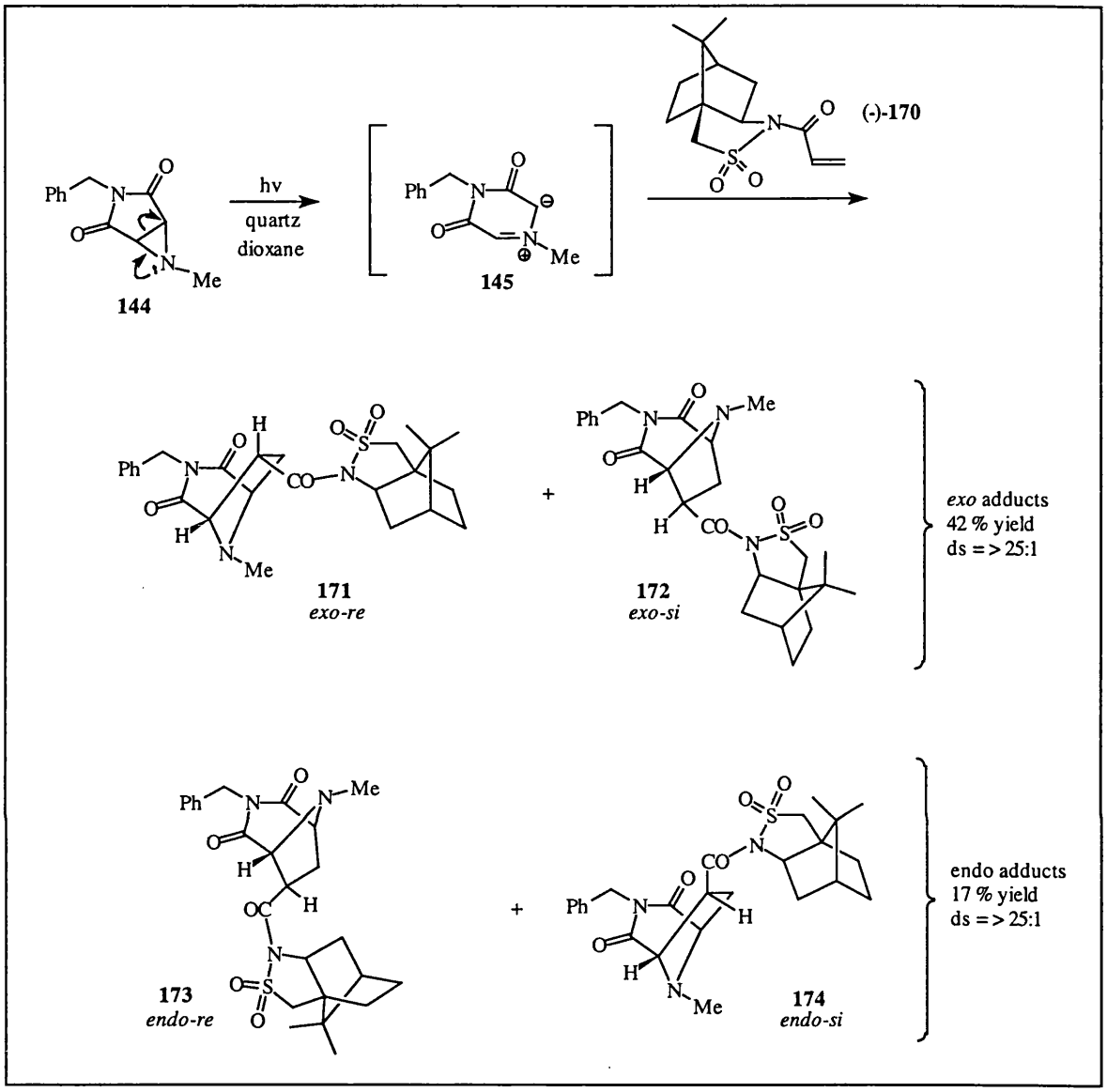
The above results are summarised in **Table 2** below.

entry	aziridine	dipolarophile	*exo* adducts	% yield	ratio (ds)	*endo* adducts	% yield	ratio (ds)
1	**144**	**methyl acrylate**	**146/147**	50	-	**148/149**	11	-
2	(±)-**150**	**methyl acrylate**	(±)-**152**/(±)-**153**	73	1:1	-	-	-
3	(*S*)**154**	**methyl acrylate**	(*S*)-**156**/(*S*)-**157**	60	1:1	-	-	-
4	**144**	**acrylo-nitrile**	**158/159**	25	-	**160/161**	40	-
5	**144**	(-)-**162**	**163/164**	64	1:1	**165/166**	15	1:1
6	**144**	(-)-**167**	**168/169**	57	1:1	-	-	-

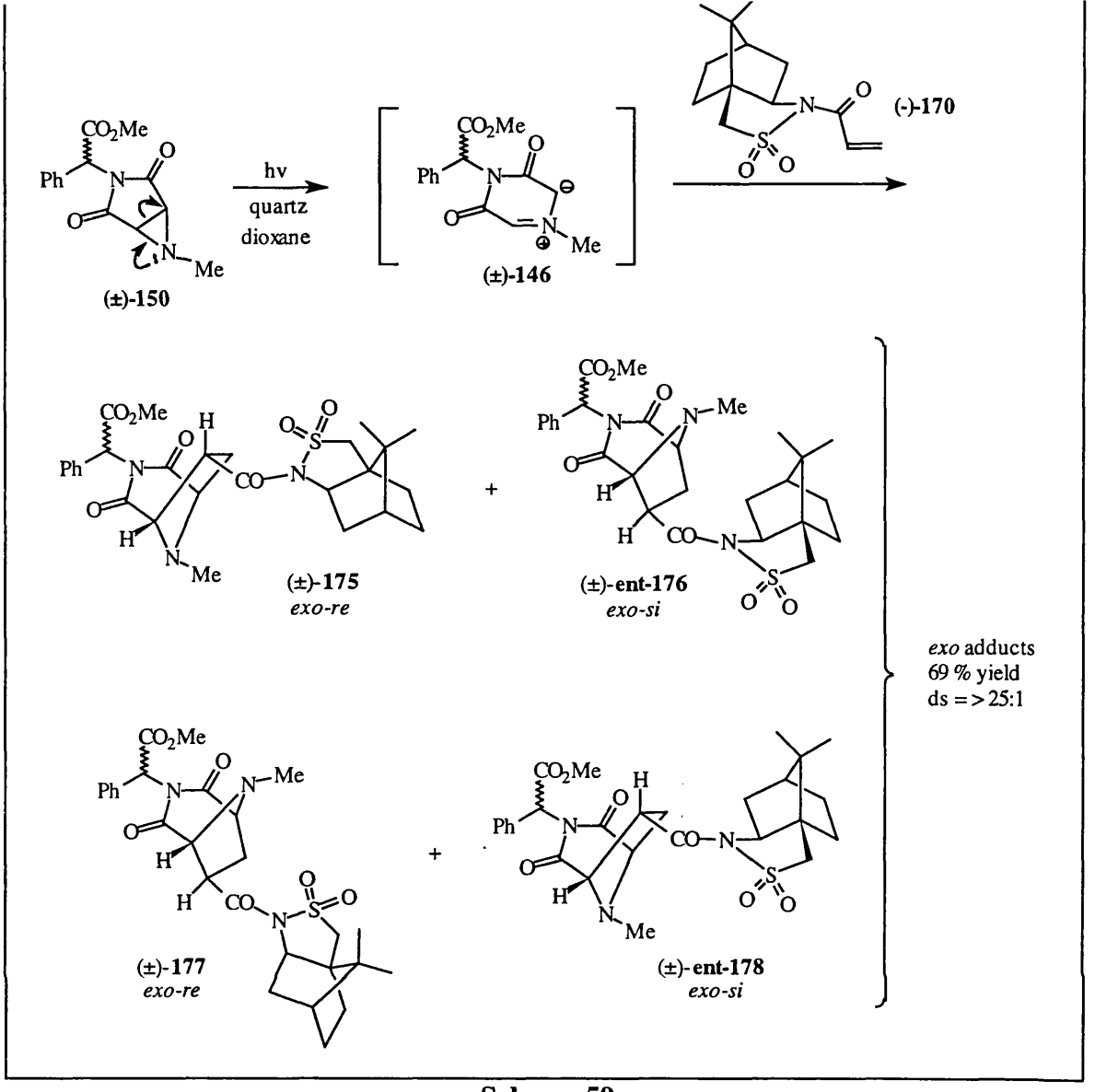
Table 2 1,3-Dipolar cycloadditions with acrylate and acrylonitrile dipolarophiles

Oppolzer's acryloyl camphorsultam **(-)-170** [71] was then used as the chiral dipolarophile (**Scheme 58-61**). When the photolysis of the aziridines **144**/(±)-**150**/(*S*)-**154**/(*S*)-**181** was conducted with solid chiral sultam added in 0.2-equivalent portions

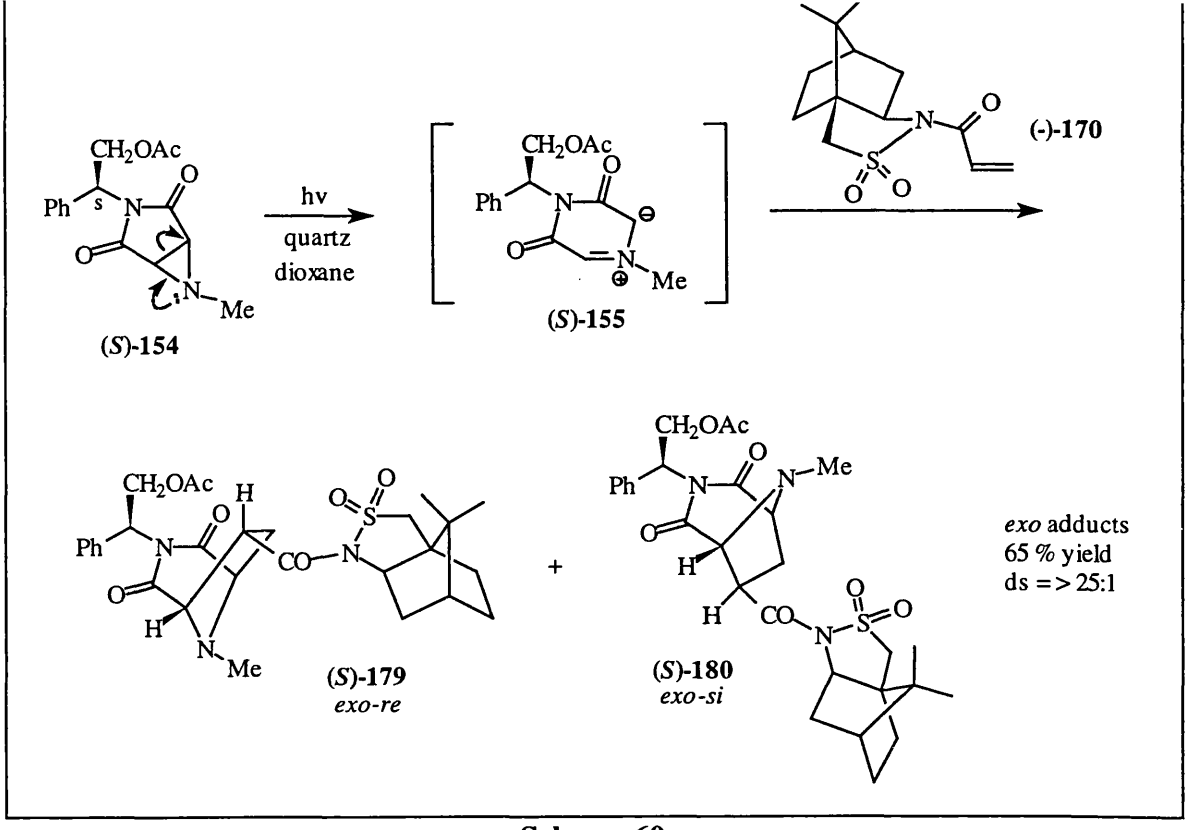
in isolated yields in the range 42–69 % based on recovered aziridine (**Schemes 58-61, Table 3**).



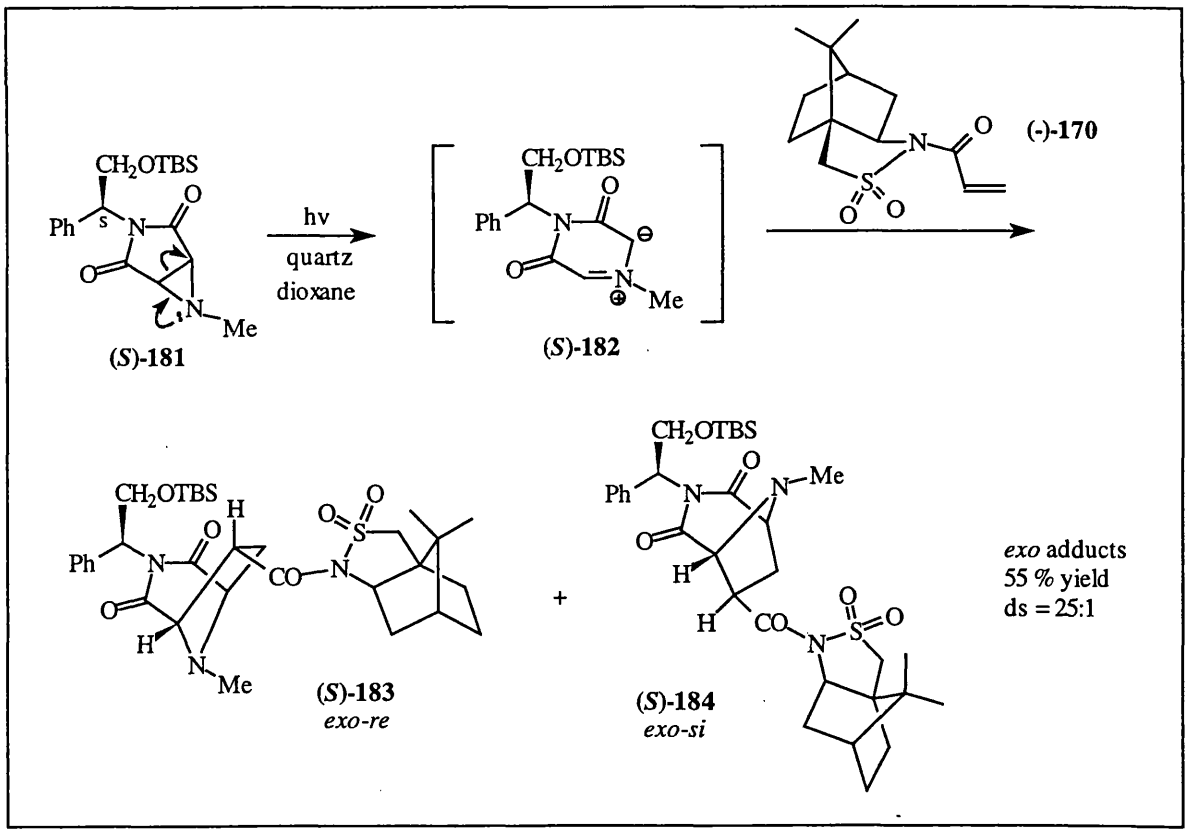
Scheme 58


hv
quartz
dioxane
(±)-150
(±)-146
(-)-170
(±)-175
exo-re
(±)-ent-176
exo-si
(±)-177
exo-re
(±)-ent-178
exo-si
exo adducts
69 % yield
ds = > 25:1

Scheme 59



Scheme 60



Scheme 61

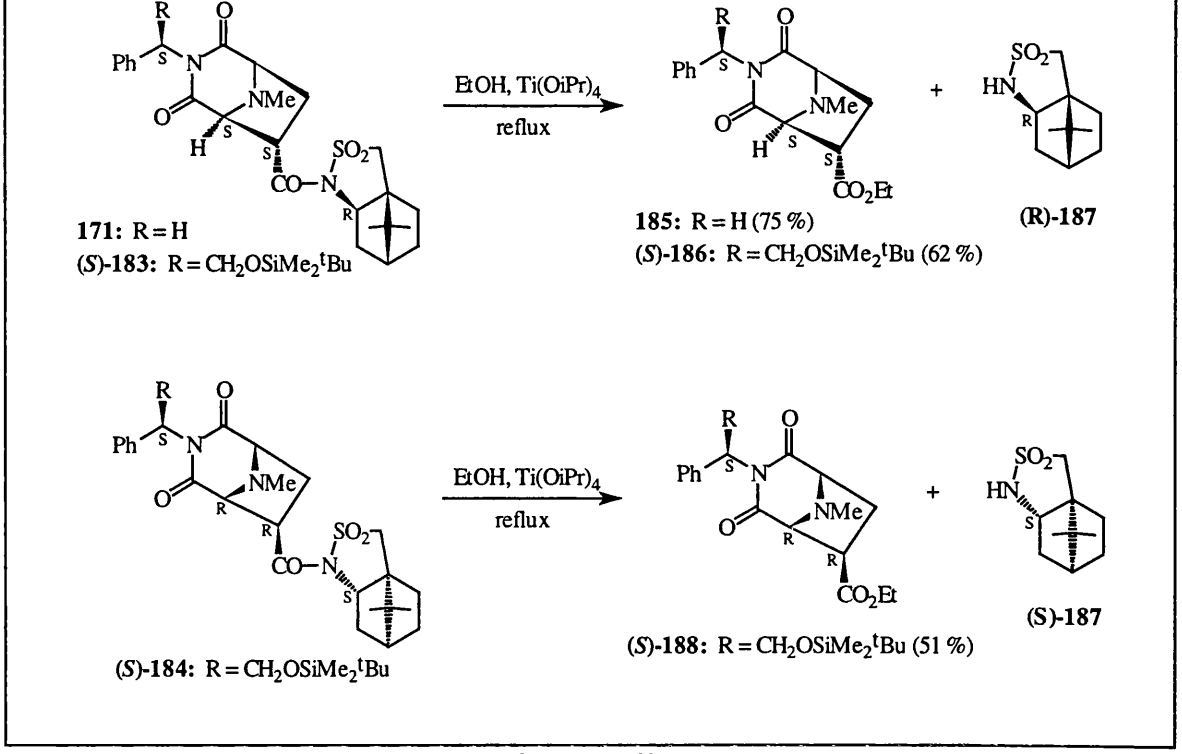
These result are summarised in **Table 3** below.

entry	aziridine	dipolarophile	*exo* adducts	% yield	ratio (ds)	*endo* adducts	Yield %	ratio (ds)
1	**144**	(-)-**170**	**171/172**	42	>25:1	**173/174**	17	>25:1
2	(±)-**150**	(-)-**170**	**175 + ent-176 /177 + ent-178**	69	>25:1	-	-	-
3	(*S*)-**154**	(-)-**170**	(*S*)-**179 /** (*S*)-**180c**	65	>25:1	-	-	-
4	(*S*)-**181**	(-)-**170**	(*S*)-**183 /** (*S*)-**184**	55	>25:1	-	-	-

Table 3 1,3-Dipolar cycloaddition reactions with chiral acryloyl sultam dipolarophiles

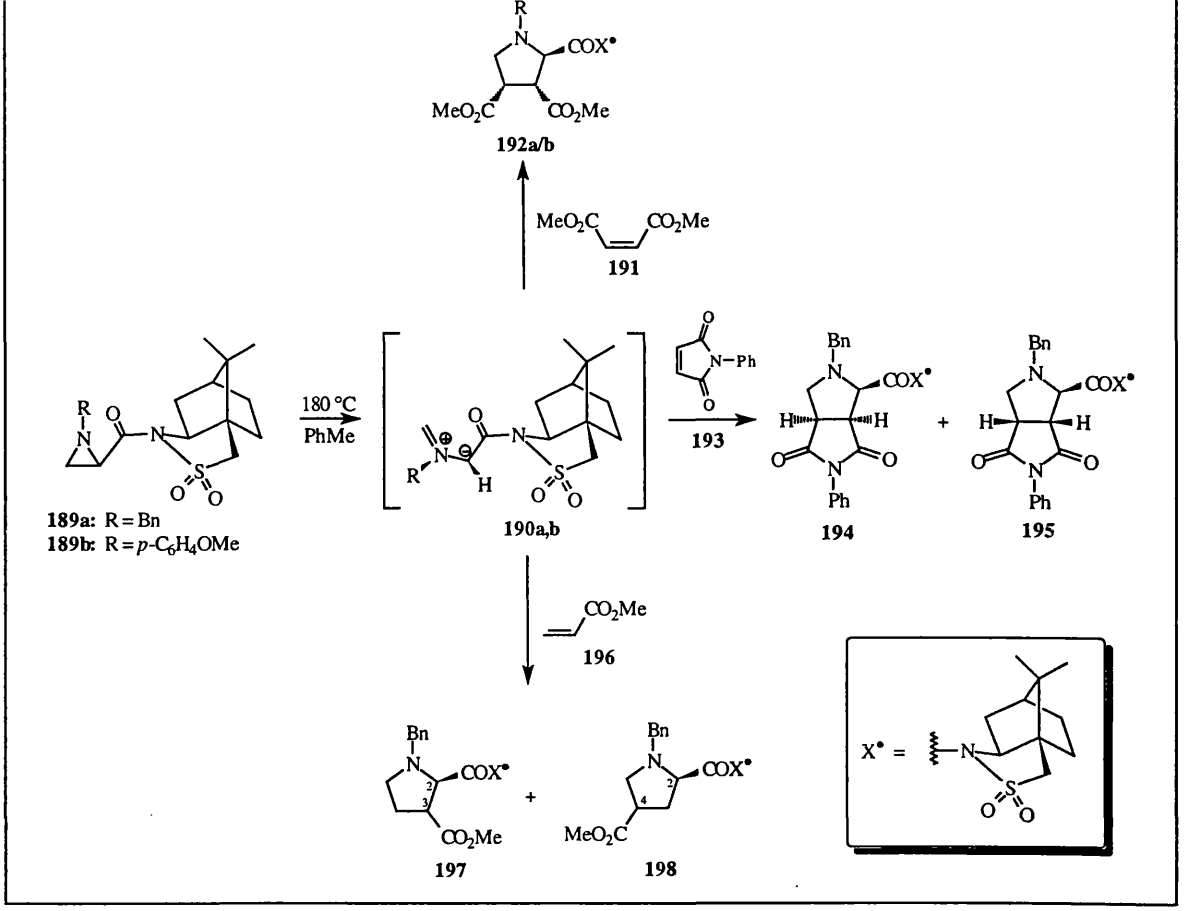
With the benzylamine-derived aziridine **144** and (-)-**170**, two products identified as *exo-re* adduct **171** and *endo-re* adduct **173** were obtained in a ratio of 2.4:1. Only traces of what was believed to be the diastereomeric *exo-si* **172** and *endo-si* **174** addition products were detected in unresolved samples of **171** and **173**, respectively. The dipolarophile facial selectivity associated with all cycloadditions employing **(-)-170** was uniformly excellent (ds > 25:1) as determined by crude ^{1}H n.m.r. analysis.

The cycloadducts could be converted to their corresponding ethyl esters in good yield and the chiral sultam auxiliary efficiently recovered by means of titanium(IV)-mediated alcoholysis (**Scheme 62**).[72] Thus, exposure of adducts **171/(*S*)-183** and (*S*)-**184** to 5-8 equivalent of $Ti(O^iPr)_4$ in refluxing ethanol led to the isolation of the corresponding ethyl esters **185/(*S*)-186** and (*S*)-**188** in 61-75 % yield along with 70-90 % of the reusable sultam **187**.



Scheme 62

Garner *et al.*[73] has also successfully utilised Oppolzer's camphor sultam in the search towards a general chiral auxiliary for the cycloaddition reactions of azomethine ylides **190ab** and **200** (**Schemes 63 and 64**).



Scheme 63

Thermolysis of aziridines **189a/b** in the presence of the dipolarophiles indicated in **Table 4** afforded the 1,3-dipolar cycloadducts via the stabilised *N*-substituted azomethine ylides **190a/b**.

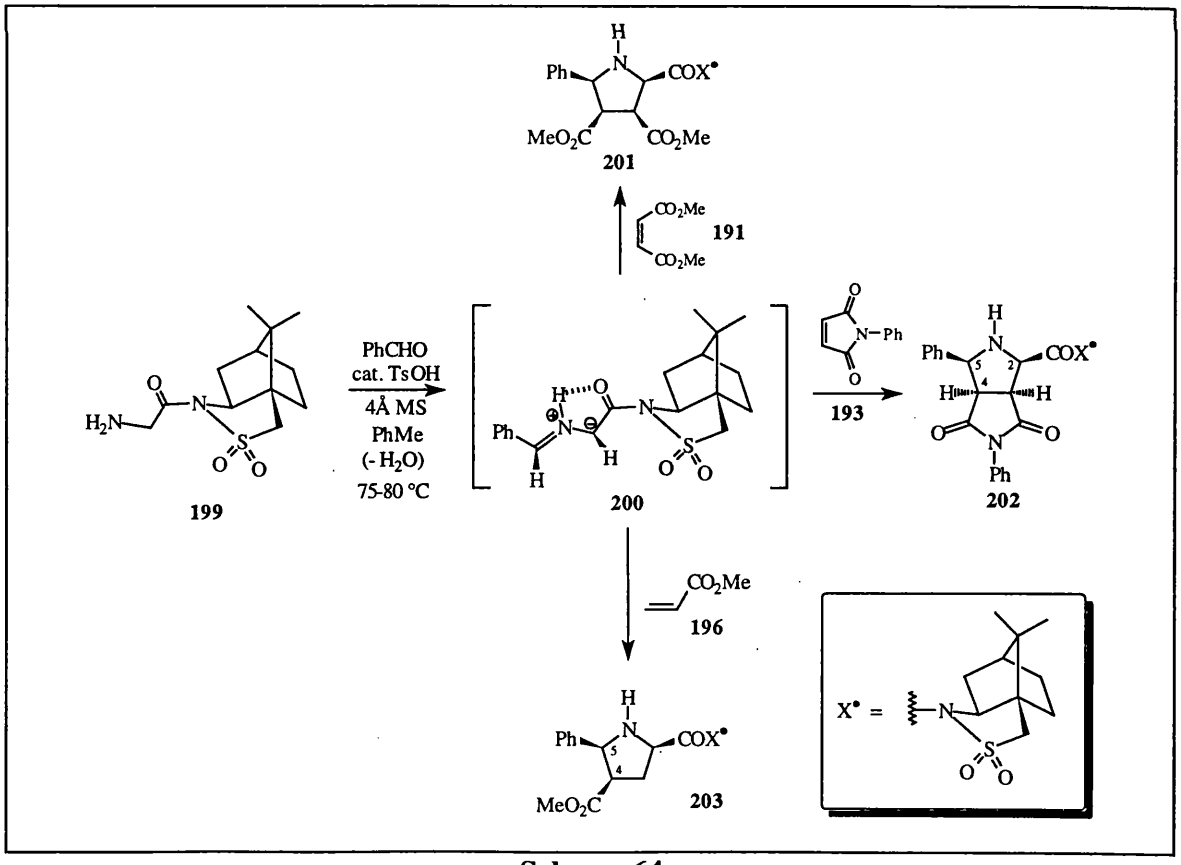
entry	azomethine ylide	dipolarophile	major cycloadduct(s)	facial selectivity [a]	combined yield (%) [b]
1	**190a**	**191**	**192a**	9:1	60
2	**190b**	**191**	**192b**	11:1	82
3	**190a**	**193**	**194/195** (1.8:1)	10:1	73[c]
4	**190a**	**196**	**197/198** (2:1)	[d]	92
5	**200**	**191**	**201**	6:1	57[c]
6	**200**	**193**	**202**	7:1	84
7	**200**	**196**	**203**	5:1	53[c]

Table 4 Auxiliary-controlled 1,3-dipolar cycloadditions of azomethine ylides

[a] Kinetic diastereomer ratios were determined from the crude ^{1}H n.m.r. spectrum spectra; [b] The combined (total) yield of cycloadducts after flash chromatography on silica gel; [c] Between 5 and 7 % of other minor cycloadducts were also formed; [d] The minor facial diastereomers could not be detected.

When dimethyl maleate **191** was used as the dipolarophile, cycloadducts **192a** and **192b** were obtained as the major products (entries 1 and 2, **Table 4**) which conforms to exclusive *endo* cycloaddition to the *Z*-ylide **190a/b**. While cycloadditions to *N*-phenylmaleimide **193** occurred in good chemical yield, the *endo* selectivity was considerably eroded (**194/195** = 1.8:1) with this dipolarophile (entry 3). Cycloaddition to the unsymmetrical dipolarophile, methyl acrylate **196**, led to the formation of regioisomers **197** and **198** in a ratio of 2:1 (entry 4). However, the observed diastereofacial selectivity (ds = 6:1 to 11:1) was on the order of that usually associated with Oppolzer's sultam auxiliary.

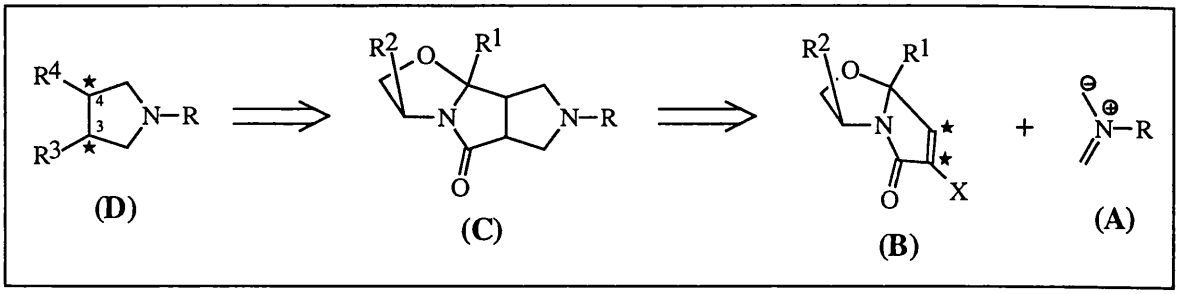
Dipolar cycloadditions of the NH azomethine ylide **200**, generated via the imine tautomerisation route, were also investigated by these workers (**Scheme 64**). Thus, the glycyl sultam **199** was condensed with benzaldehyde to give an intermediate imine (not shown) that underwent acid-catalysed tautomerisation to the 3-phenyl substituted azomethine ylide **200** which could be trapped with the same dipolarophiles **191**, **193** and **196** (entries 5-7, **Table 4**). In each case, the major product was that configuration in which all pyrrolidine substituents were *cis* to one another, resulting from an *endo* approach of the dipolarophile to the *E,E*-ylide **200**.



Scheme 64

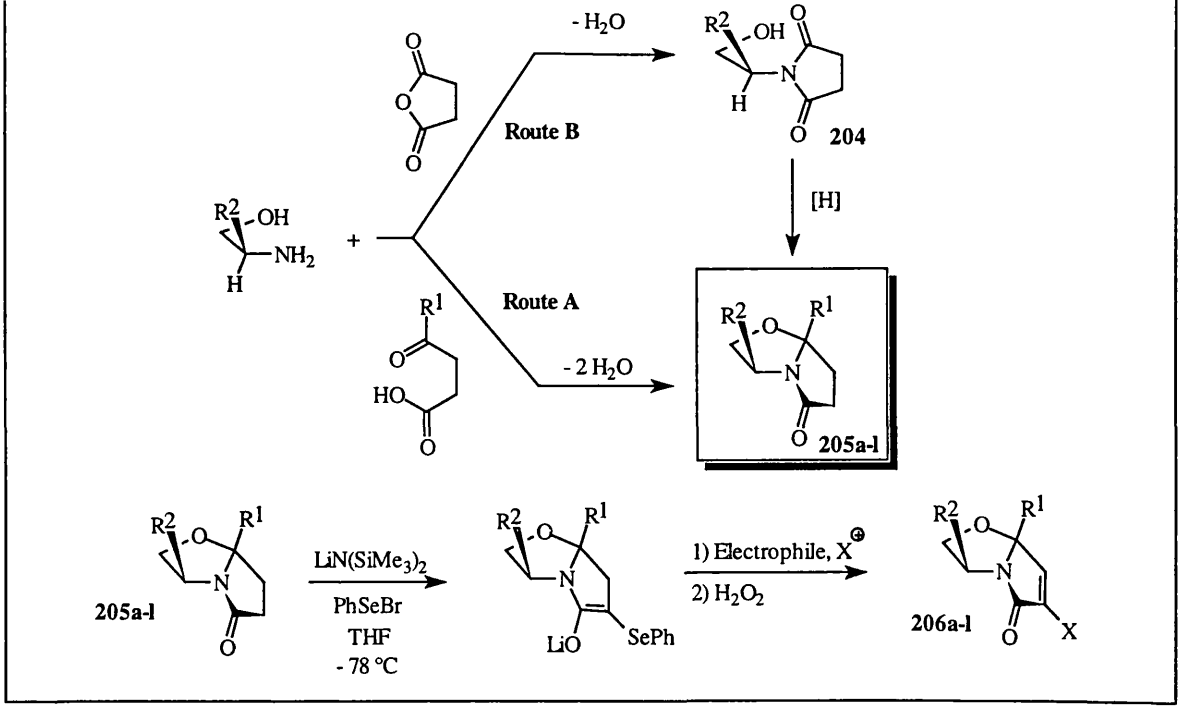
As with **190a/b**, the diastereofacial selectivity associated with ylide **200** was uniformly good (ds = 5-7:1). These results thus demonstrate that a reusable chiral auxiliary can be successfully incorporated into an azomethine ylide for the purpose of stereocontrol.

Meyers *et al.*[74,75] have employed a chiral dipole (**A**) and a chiral dipolarophile (**B**) for the enhancement of diastereoselection in azomethine ylide cycloadditions (**Scheme 65**).



Scheme 65

The preparation of these bicyclic chiral dipolarophile precursors followed two general routes (**Scheme 66**). When the angular substituent (R^1) on the bicyclic lactam **205** was an alkyl or aryl substituent, **Route A** was employed, which involved the cyclo-condensation reaction between a chiral amino-alcohol [76] and a keto-acid. Alternatively, **Route B** was used for the preparation of the lactams **205** where R^1 = H. In this process, condensation of an amino-alcohol (R^2 = ^{i}Pr, Ph) with succinimide gave an intermediate chiral imide **204**. Partial reduction of the imide to give an intermediate hydroxy lactam, followed by acid-catalysed ring closure, afforded the desired hydrogen bicyclic lactam **205** (R = H).



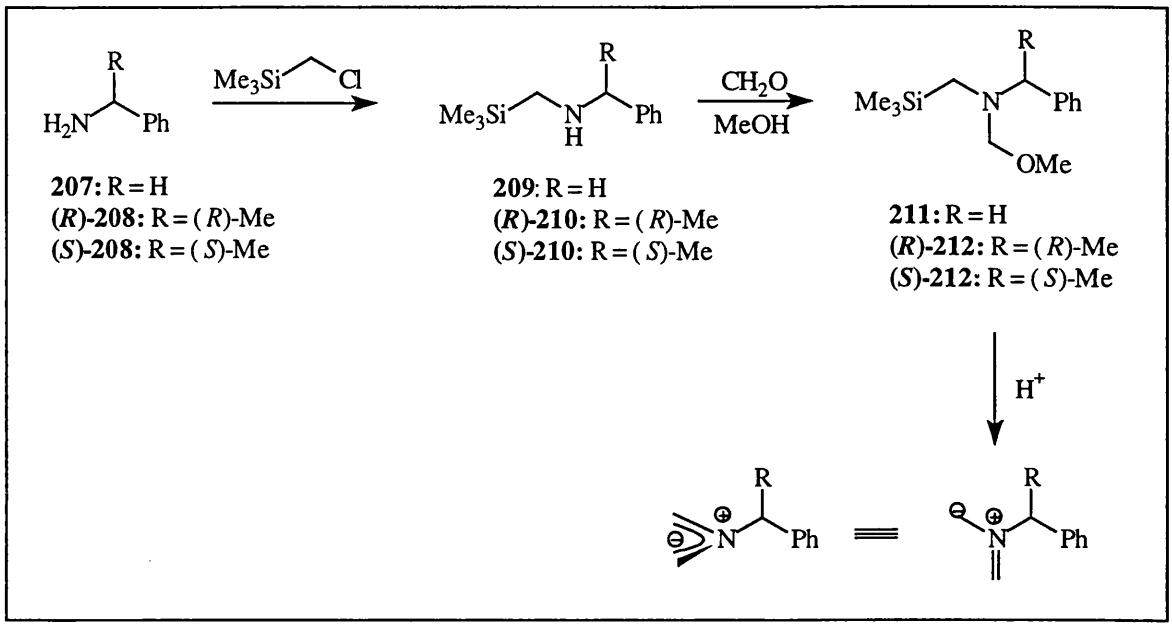
Scheme 66

Sequential treatment of the saturated lactams **205a-l** with base (2.0 equivalents) followed by the addition of phenylselenenyl bromide (1.0 equivalent) afforded α-selenenyl enolates that were quenched by a variety of electrophiles. The required unsaturated lactams **206a-l** were obtained in good yields after oxidation as shown in **Table 5**.

lactam	R^1	R^2	X	electrophile	% yield
206a	Me	*i*-Pr	H	NH_4Cl	82
206b	Me	Ph	H	NH_4Cl	82
206c	H	Ph	H	NH_4Cl	78
206d	Me	*i*-Pr	CO_2Me	$ClCO_2Me$	66
206e	Me	*i*-Pr	CO_2t-Bu	Boc_2O	43
206f	H	Ph	Cl	*p*-$TolSO_2Cl$	71
206g	H	Ph	Br	$(BrCCl_2)_2$	84
206h	H	Ph	I	NIS	55
206i	Me	Ph	Br	$(BrCCl_2)_2$	75
206j	Me	H	H	NH_4Cl	17
206k	Me	*i*-Pr	Me	MeI	77
206l	Ph	*i*-Pr	CO_2Me	$ClCO_2Me$	69

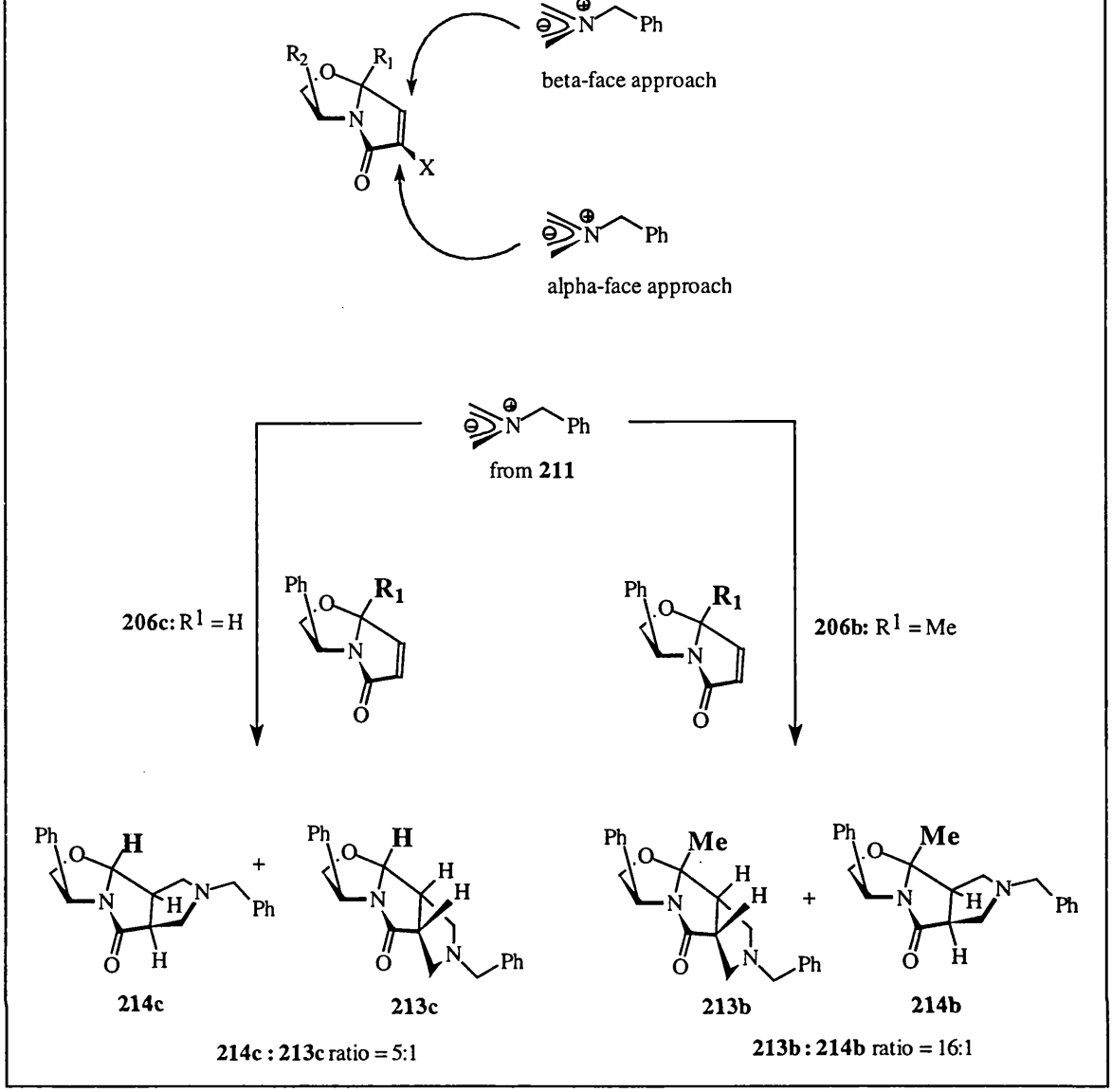
Table 5 Preparation of chiral dipolarophiles 206a-l from bicyclic lactams 205a-l

The achiral and chiral azomethine ylide precursors **211**, (*R*)-**212** and (*S*)-**212**, were derived from benzylamine and enantiomerically pure (*R*) and (*S*) α-methylbenzylamines according to Padwa *et al.*[44] (**Scheme 67**).



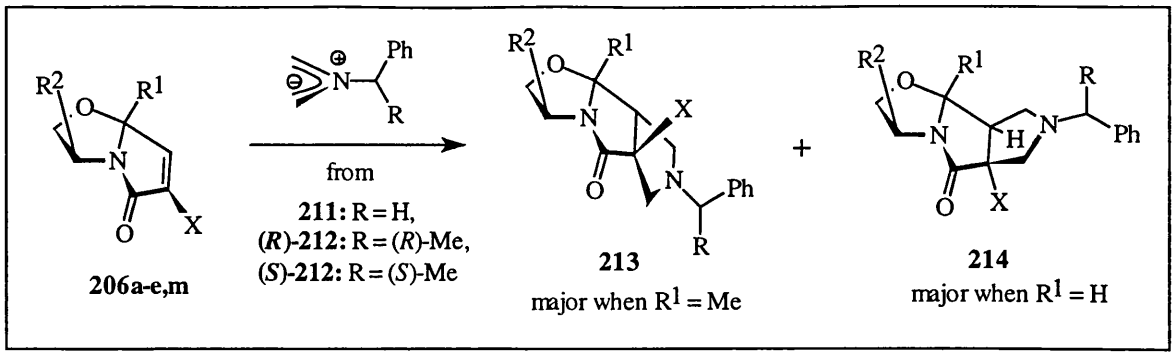
Scheme 67

The role of the substituent (R^1) attached to the angular carbon is what determines the overall direction of cycloaddition. Predominant approach of the achiral dipole to the "bottom" or α-face is seen when the angular substituent is large (R^1 = Me) whereas predominant approach to the β-face occurs when the angular substituent is small (R^1 = H) (**Scheme 68**). Thus, reaction of 2 equivalents of achiral dipole precursor **211** with angular methyl lactam **206b** afforded a 16:1 mixture of cycloadduct **213b** along with the minor isomer **214b** in quantitative yield. In contrast, reaction of precursor **211** with the angular hydrogen lactam **206c** afforded only a 5:1 mixture of cycloadducts with **214c** predominating as a result of preferential approach of the dipole to the "top" or β-face of **206c**.



Scheme 68

The double asymmetric synthesis of the tricyclic cycloadducts was then explored (**Scheme 69**). Optimum parameters for the Meyers cycloadditions for the generation of the azomethine ylide precursors (***R***)-**212** and (***S***)-**212** were under the Achiwa conditions (CF_3CO_2H in CH_2Cl_2).[18] **Table 6** summarises the results of the addition to chiral lactams **206a-e,l** by achiral **211** and chiral dipole precursors (***R***)-**212** and (***S***)-**212**. In cases where the α-substituent, X, was hydrogen (entries 1-3), it was observed that the π-facial selectivities were insensitive to the configuration at the benzylic carbon of the dipole. In contrast, where X was larger then hydrogen (entries 4-6, X = CO_2Me or CO_2t-Bu), significantly enhanced selectivity was observed for cycloadditions with the dipole precursor (***R***)-**212**, compared to the ratios provided by the achiral precursor **211** and the dipole precursor (***S***)-**212**.



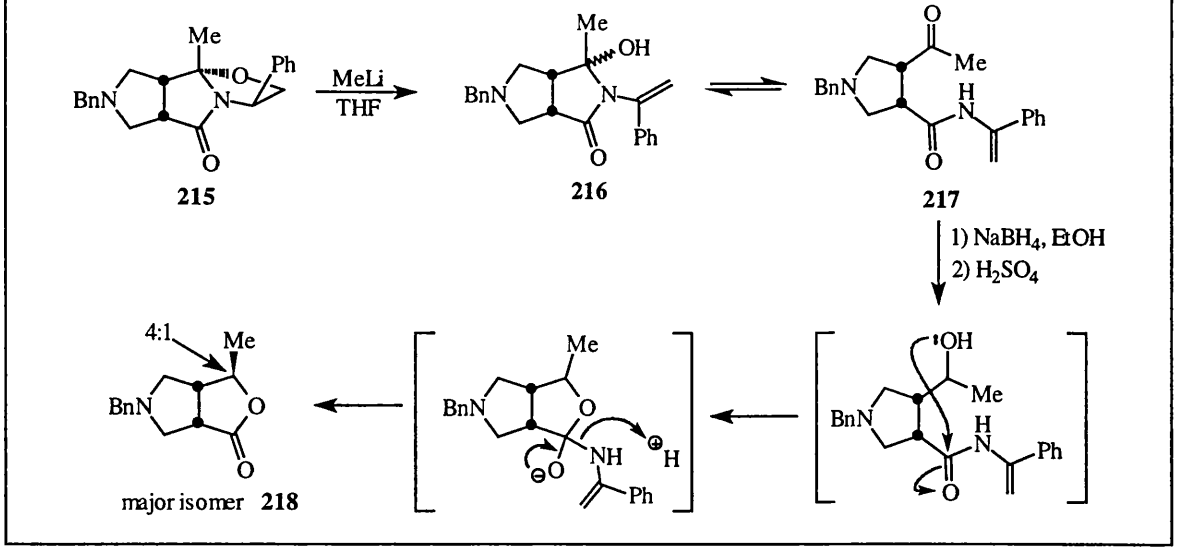
Scheme 69

	lactam **206**				ylide from **211**	ylide from **(*R*)-212**	ylide from **(*S*)-212**
entry	R^2	R^1	X	Lactam	(A)-213:214[a]	(*R*)-213:214[a]	(*S*)-213:214[a]
1	*i*-Pr	Me	H	**206a**	91:9	94:6	91:9
2	Ph	Me	H	**206b**	94:6	91:9	92:8
3	Ph	H	H	**206c**	17:83	19:81	16:84
4	*i*-Pr	Me	CO_2Me	**206d**	71:29	87:13	59:41
5	*i*-Pr	Me	CO_2t-Bu	**206e**	72:28	92:8	51:49
6	*i*-Pr	Ph	CO_2Me	**206l**	74:26	87:13	69:31

Table 6 Effect of structure on facial selectivity

[a] **(A)-213:214** refers to adducts derived from the *N*-benzyl (achiral) ylide; **(*R*)-213:214** and **(*S*)-213:214** refer to adducts from the *R* and *S* α-benzylamine ylides, respectively.

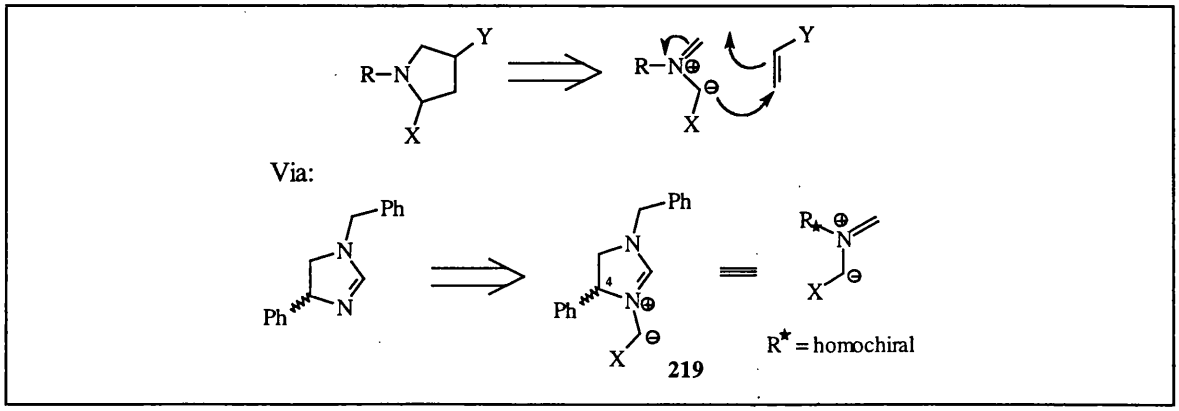
An example of the synthetic utility of tricyclic lactams is shown in **Scheme 70**. Compound **215** was observed to give non-racemic bicyclic hydroxylactams **216** as a consequence of benzylic proton abstraction by MeLi, followed by oxazolidine C-O bond cleavage. Conversion of **216** to a 4:1 mixture of bicyclic lactones was carried out by $NaBH_4$ reduction of its tautomer **217** followed by acid treatment [77,78] in 51 % overall yield from **215**. The major lactone **218** (*R*) was shown to be 93.7 % e.e. by chiral stationary HPLC analysis.



Scheme 70

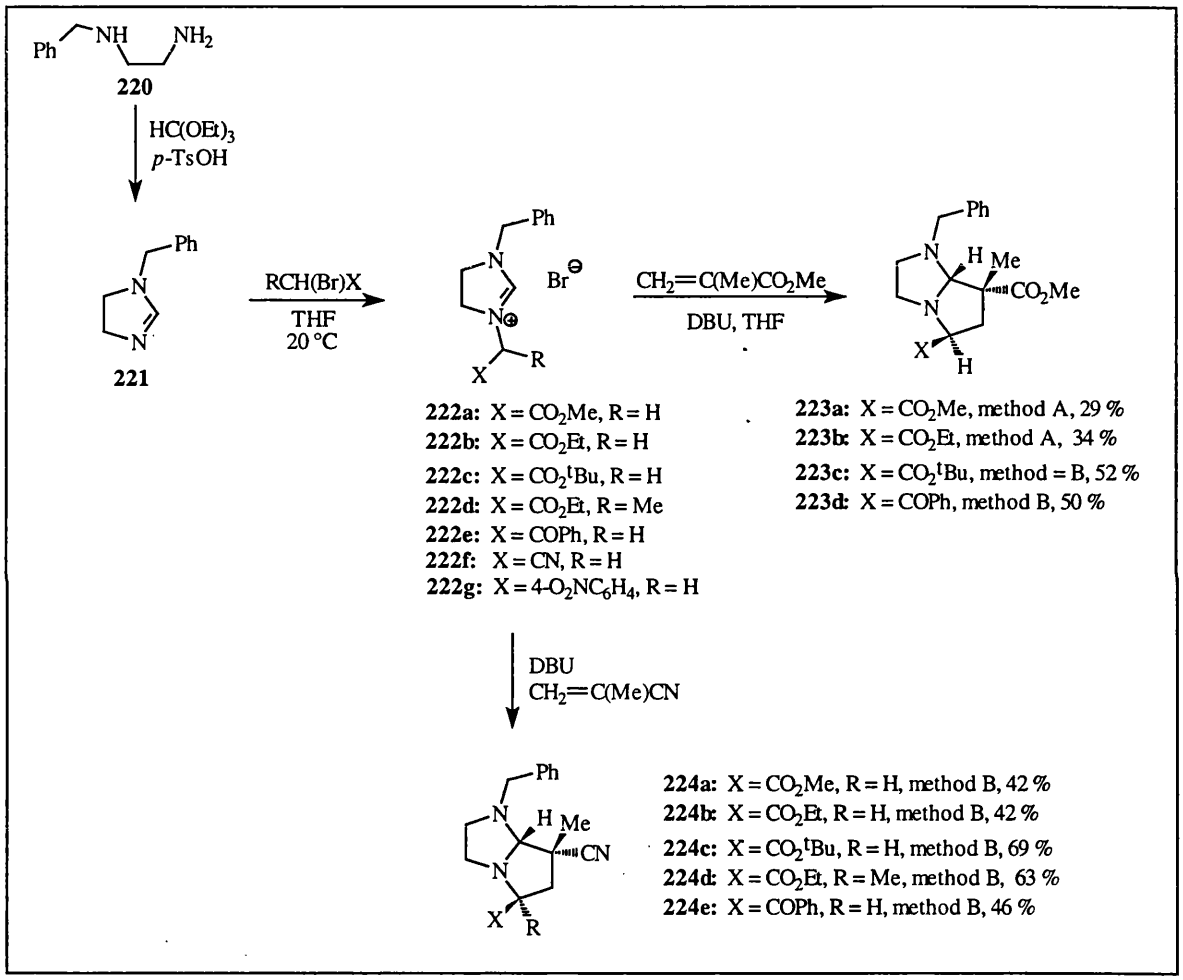
These results give an brief insight into the stereoselectivities attainable when cycloaddition reactions are performed with both chiral dipoles and chiral dipolarophiles. Choosing the correct template on which to base the cycloaddition reactions of azomethine ylides is therefore of great importance if any reasonable diastereoselectivity is to be obtained.

Jones *et al.*[79] have also developed a very powerful methodology for controlling the facial selectivity of ylides of stabilised azomethine ylide additions. Their method is especially useful since it allows 2,4-*trans*-disubstituted prolines to be constructed. These are a particularly difficult class of compounds to prepare, yet the Jones method now provides easy access to them. Jones made use of the conformationally restrained auxiliary of homochiral stabilised 4-phenyl-imidazolinium ylides **219**, available as either enantiomer, by virtue of the heterocyclic ring (**Scheme 71**).



Scheme 71

This work developed from earlier work in the Jones group whereby amidines were utilised as a source of azomethine ylides.[80] The substrate chosen was 1-benzyl-2-imidazoline **221** which was prepared from *N*-benzyl-1,2-diaminoethane **220** and triethyl orthoformate (4 mol equiv.) in the presence of *p*-TsOH (0.05 mol equiv.) in 72 % yield. Compound **221** was then quaternised in THF with the α-haloesters methyl, ethyl, and *tert*-butyl bromoacetate, and ethyl 2-bromopropionate, as well as with 2-bromoacetophenone, bromoacetonitrile, and 4-nitrobenzyl bromide to furnish the salts **222a-g** (**Scheme 72**).

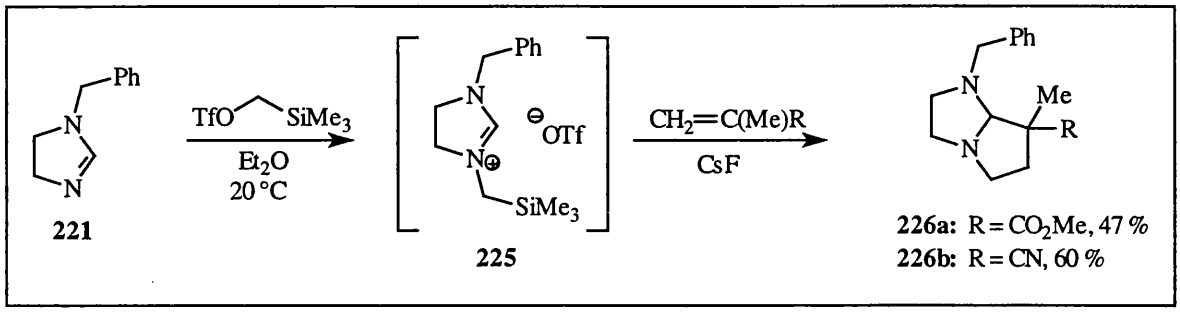


Scheme 72

Two methods were used for ylide formation and the subsequent cycloaddition: (A) dropwise addition of DBU to a slurry of freshly prepared **222** in excess dipolarophile; and (B) very slow (over < 4 h) addition of DBU to a solution of **222** and dipolarophile in THF at reflux. Hence, using methyl methacrylate as dipolarophile, the cycloadducts **223a-c** were prepared regiospecifically; using methacrylonitrile as dipolarophile afforded **224a-d**. Similarly, **222e** led to **223d** and **224e** using methyl methacrylate and

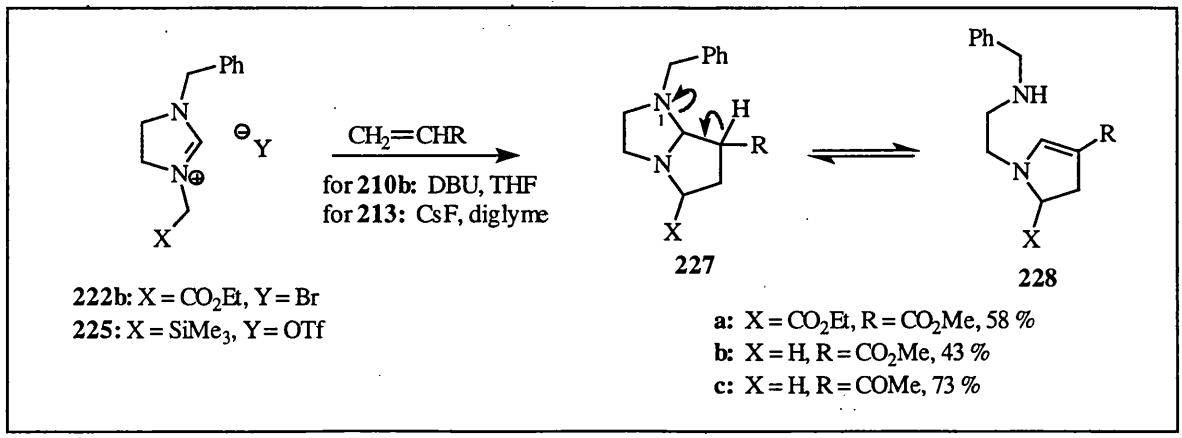
methacrylonitrile, respectively. No cycloadducts were isolated from **222f** and **222g**. The cycloadducts, **223** and **224**, all consisted of a single diastereoisomer.

The cycloadditions were also performed with nonstabilised imidazolinium azomethine ylides prepared according to the desilylation method of Vedejs.[26] Imidazoline **221** was converted to **225**, which was added directly in diglyme to a slurry of excess CsF and dipolarophile in diglyme (**Scheme 73**). With methyl methacrylate and methyacrylonitrile, **226a** and **226b** were prepared as 1:1 and 2:1 mixtures of diastereomers, respectively.



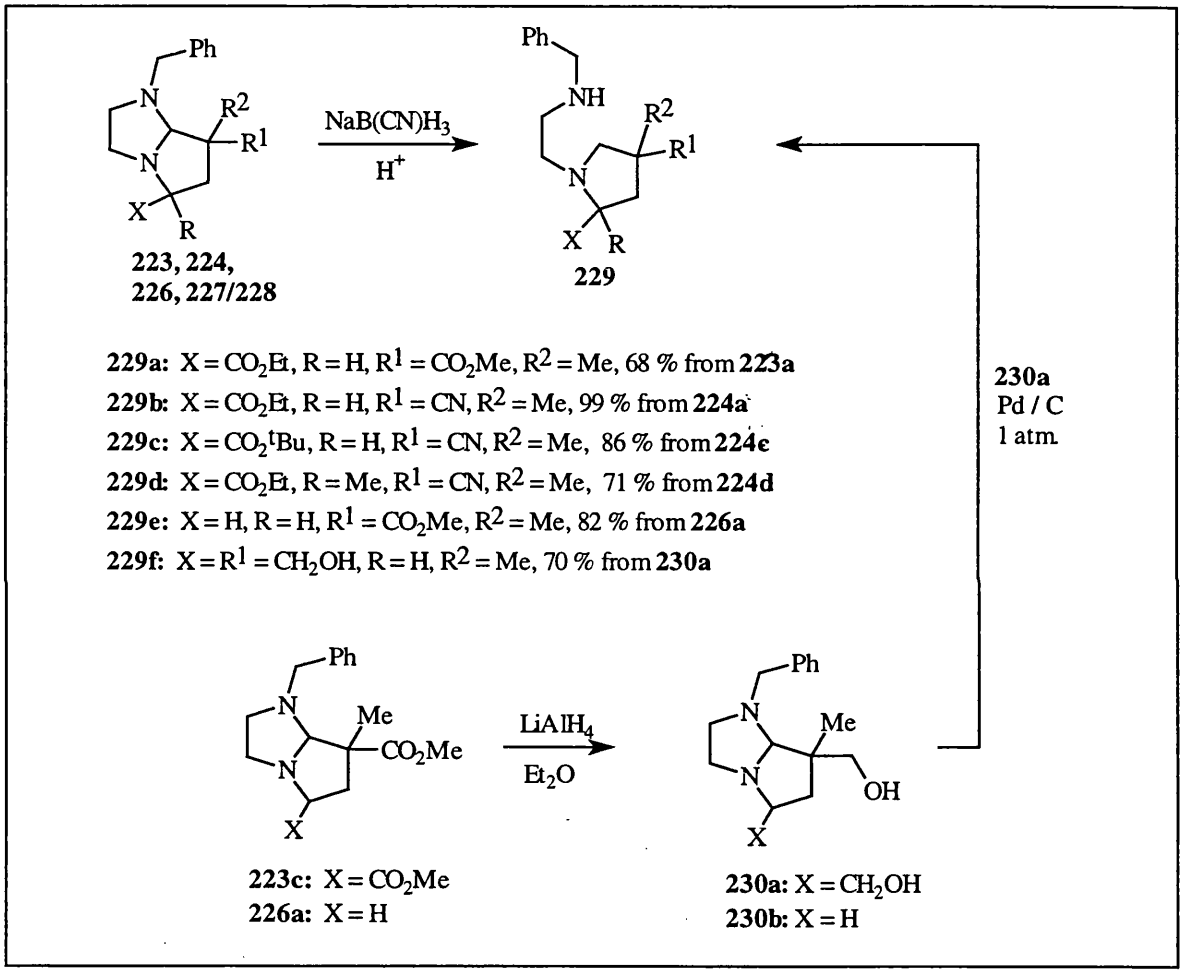
Scheme 73

All of the dipolarophiles used in **Scheme 72** and **Scheme 73** were substituted α- to the activating group. When dipolarophiles lacking these α-substituents were utilised, a ring-opening elimination was observed in equilibrium with the bicyclic adducts after purification by flash chromatography. Salt **222b** with methyl acrylate and DBU gave a mixture of **227a** and the dihydropyrrole **228a** (**Scheme 74**). Likewise, **225** with methyl acrylate (CsF, diglyme) gave a mixture of **227b** and **228b**, and with but-3-en-2-one a mixture of **227c** and **228c**.



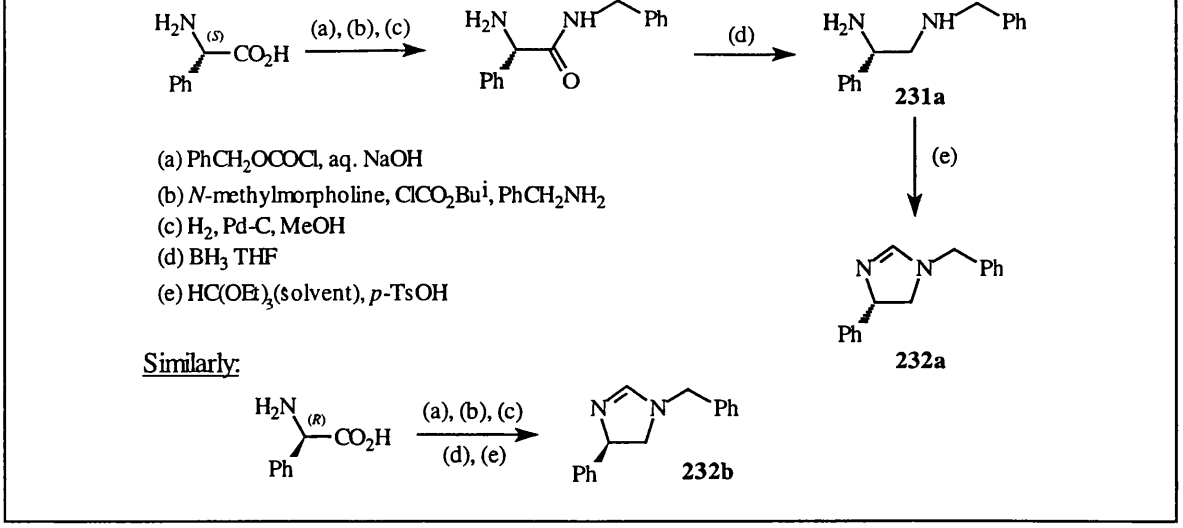
Scheme 74

This equilibrium could be established under acidic conditions via protonation at N-1. Thus reduction under acidic conditions using $NaB(CN)H_3$ converted the appropriate pyrroloimidazoles **223**, **224**, **226** and **227/228** into the substituted pyrrolidines **229a-e** in high yields as single stereoisomers (**Scheme 75**). This ring-opening step could be avoided by using $LiAlH_4$ in Et_2O (**Scheme 75**). Treating **223c** with $LiAlH_4$ afforded the diol **230a** as did similar treatment of **226a** to give **230b** (still as a 1:1 diastereomeric mixture). Hydrogenation of **230a** (1 atm., Pd/C) afforded the pyrrolidine diol **229f** in 70 %.



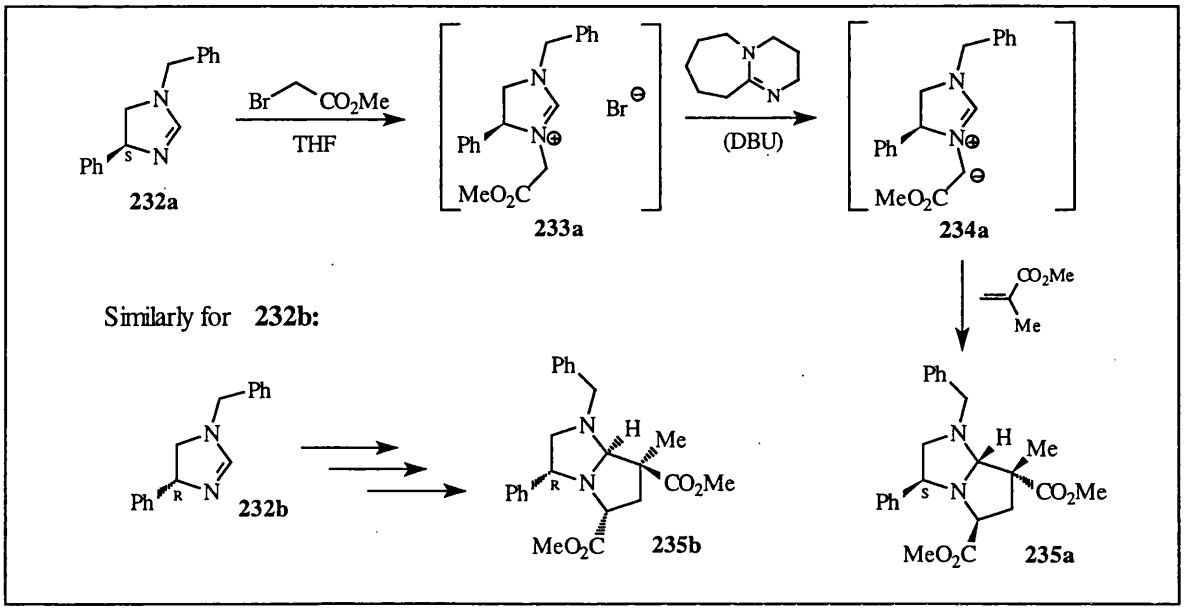
Scheme 75

These workers then extended this work to the cycloadditions of homochiral ylides as indicated in **Scheme 71** earlier. The precursors to the ylides **219** were the imidazolines **232a,b**. These were prepared by the action of refluxing triethyl orthoformate (as solvent) with a catalytic amount of *p*-TsOH with the homochiral diamines **231a,b**. These diamines **231a,b** were prepared from (*S*)- or (*R*)-phenylglycine (**Scheme 76**).[81]



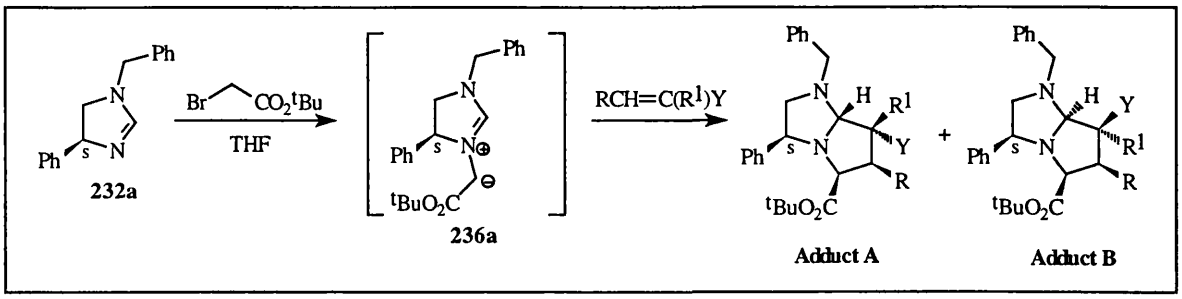
Scheme 76

The quaternisation of the imidazolines **232** with various halides proved to be a very slow process. The cycloadditions of the imidazolinium ylides **234a,b** to various dipolarophiles were therefore performed *in situ* by the addition of dipolarophile (3 mol equiv.) to a solution of imidazolines **232a,b** in THF. The solution was heated at reflux for 1h, after which time 1 mol equiv. of DBU was added dropwise over 4 h. The reaction mixture was then heated for a further 2 h at reflux. Isolation provided the hexahydropyrrolo[1,2-*a*]imidazole cycloadducts **235a,b**. Using methyl bromoacetate as alkylating agent and methyl methacrylate as dipolarophile furnished cycloadducts **235a** from (***S***)-imidazoline **232a** and **235b** from (***R***)-imidazoline **232b**, both as single enantiomers (**Scheme 77**).



Scheme 77

Several other cycloadducts based on this technique were also prepared using *tert*-butyl bromoacetate as the alkylating agent. These results are indicated in **Scheme 78** (showing the use of **232a**) and **Table 7**



Scheme 78

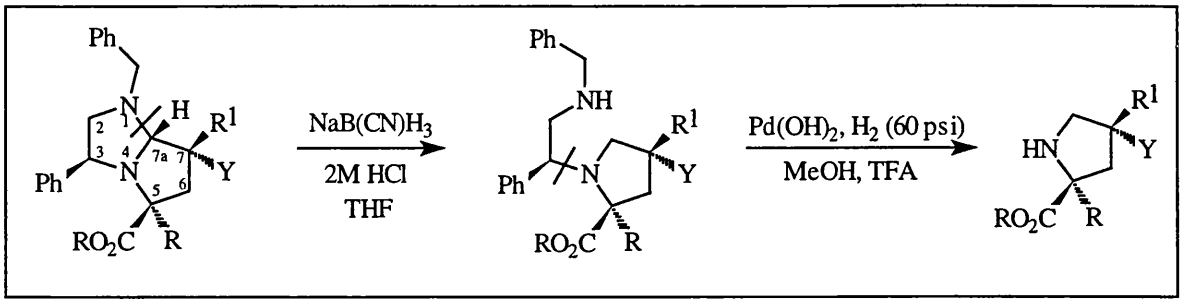
Dipolarophile			Adduct A		Adduct B	
R	R^1	Y	(*S*) enantiomer **232a** / yield (%)	(*R*) enantiomer **232b** / yield (%)	(*S*) enantiomer **232a**/ yield (%)	(*R*) enantiomer **232b**/ yield (%)
H	Me	CO_2Me	**237** (61)	**238** (62)	-	-
H	Me	CN	**239** (27)	**240** (22)	**241** (4)	**242** (3)
H	H	CO_2Me	**243** (65)	**244** (63)	-	-
H	H	$CO_2{}^tBu$	**245** (59)	**246** (49)	**247** (3)	**248** (2)
Me	H	CO_2Me	**249** (46)	**250** (26)	-	-
H	H	SO_2Ph	**251** (33)	-	-	-
H	H	COMe	**252** (71)	-	-	-

Table 7 Cycloadducts derived from (*S*)/(*R*)-4-*tert*-butyl imidazolinium ylides 234a,b with various dipolarophiles

Cycloadducts **237** and **238** were produced using methyl methacrylate as dipolarophile from (*S*)- and (*R*)-imidazoline **232a,b** respectively in comparative yields. Methacrylonitrile (R = H, R^1 = Me, Y = CN) afforded the corresponding adducts **239** and **240** as the major diastereoisomers from **232a** and **232b,** respectively. However, minor *exo* addition also occurred affording **241** and **242** indicating the smaller size of the CN group. Diastereomeric ratios were (*endo*:*exo* 7:1) **239** with **241** and (*endo*:*exo* 8:1) with **240** and **242**. Methyl and *tert*-butyl acrylates furnished cycloadducts **243** and **244**, and **245** and **246**, respectively. With *tert*-butyl acrylate (R = H, R^1 = H, Y = $CO_2{}^tBu$) a minor amount of the *exo* isomer was formed (**245**:**247** *endo*:*exo* = 20:1, and **246**:**248** *endo*:*exo* 25:1). Methyl (*E*)-crotonate, afforded sole *endo* adducts **249** and **250**

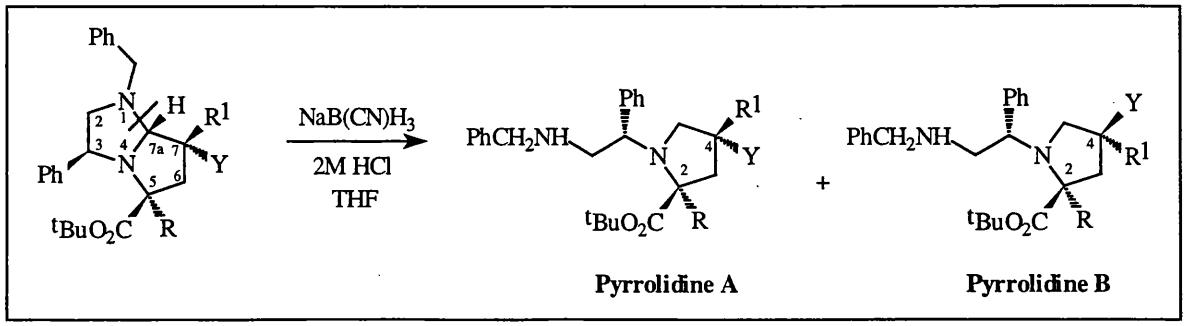
from **232a** and **232b**, respectively. Phenyl vinyl sulphone furnished **251** from **232a** and methyl vinyl ketone gave **252**, both as single diastereomers.

Removal of the chiral template was found to be most efficiently performed by a two step reductive sequence (**Scheme 79**). The initial step was the cleavage of the C(7a)-N(1) bond using $NaB(CN)H_3$ in acidic media as discussed previously. This was then followed by the removal of the benzylic *N*-substituent by hydrogenolysis over Pearlman's catalyst, $Pd(OH)_2$.



Scheme 79

Thus *tert*-butyloxycarbonyl cycloadducts **237**, **239**, **243**, **245** and **249** were reduced with [$NaB(CN)H_3$, 2M HCl, THF] to the *N*-substituted pyrrolidines **A** and **B** (**Scheme 80**, **Table 8**). These pyrrolidines could then be hydrogenated crude without the need for purification. One difficulty encountered was the partial epimerisation at C-4 for pyrroloimidazoles mono-substituted at C-7 (R^1 = H). Epimer ratios in favour of the 2,4-*trans* isomers were obtained when a large excess (10 mol equiv.) of acid followed by rapid addition of exactly one equiv. of $NaB(CN)H_3$ was used. Hence, reduction of **243** produced a 5:1 *trans*:*cis* mixture of C-4 epimers **255** and **256** respectively, whilst adduct **245** from *tert*-butyl acrylate afforded **257** and **258** in an isomer ratio of 3:1 in favour of *trans*. These epimer mixtures were used crude in the hydrogenolysis step.

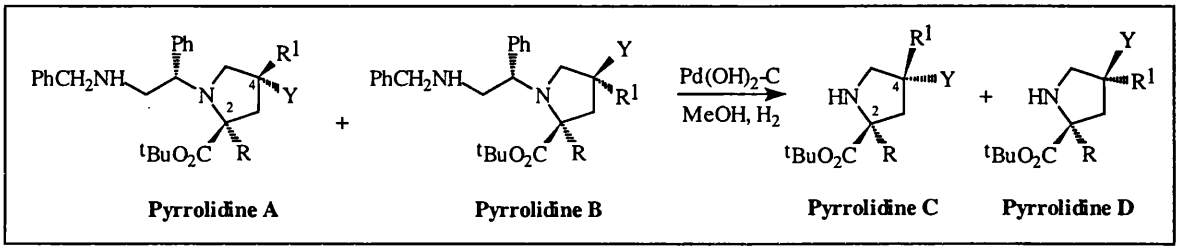


Scheme 80

	Pyrroloimidazole			Pyrrolidine A		Pyrrolidine B	
label	R	R^1	Y	label	yield (%)	label	yield (%)
237	H	Me	CO_2Me	**253**	73	-	-
239	H	Me	CN	**254**	80	-	-
243	H	H	CO_2Me	**255**	83	**256**	17
245	H	H	$CO_2{}^tBu$	**257**	72	**258**	24
249	Me	Me	CO_2Me	**259**	99	-	-

Table 8 Cleavage of the C(7a)-N(1) bond using $NaB(CN)H_3$

Cleavage of the benzylic C-N bond in **253-259** by hydrogenolysis over Pearlman's catalyst, $Pd(OH)_2$, using H_2 (60 psi), MeOH and 1 mol equiv. of CF_3CO_2H, as standard conditions afforded the pyrrolidines **260-266** (**Scheme 81**, **Table 9**).



Scheme 81

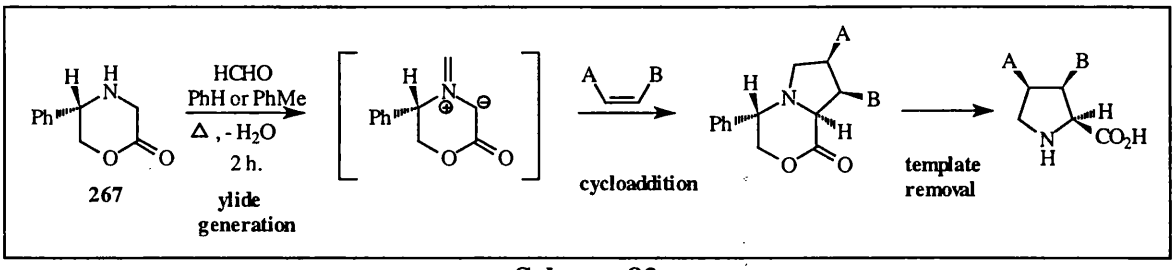
	Pyrrolidine			Pyrrolidines (yield, %)		
R	R^1	Y	A	B	C	D
H	Me	CO_2Me	**253**		**260** (90)	
H	Me	CN	**254**		**261** (30)	
H	H	CO_2Me	**255**	**256**	**262** (24)	**263** (31)
H	H	$CO_2{}^tBu$	**257**	**258**	**264** (57)	**265** (5)
Me	Me	CO_2Me	**259**		**266** (61)	

Table 9 Hydrogenolysis using $Pd(OH)_2$

Hydrogenolysis of the crude epimer mixtures **255-258** afforded epimeric pyrrolidines **262-265**. It is interesting to note that a considerable improvement in epimer ratio was observed in one of the products **264** and **265** when compared to the starting material. These pyrrolidine epimers could easily be separated by flash chromatography. An enantioselective route to homochiral hexahydropyrrolo[1,2-*a*]-imidazoles has thus been developed via the 1,3-dipolar cycloaddition of stabilised azomethine ylides. Although

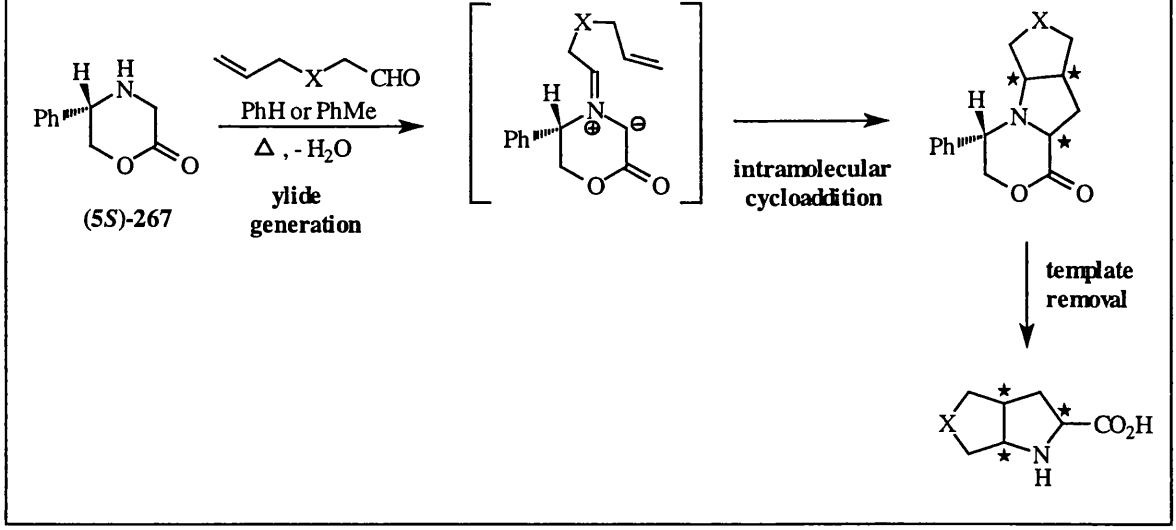
the chiral template is destroyed in the removal from the newly formed pyrrolidine cycloadducts, this method does show that homochiral pyrrolidine-containing compounds can be easily prepared via stabilised azomethine ylide cycloaddition reactions.

Harwood *et al.*[82] have demonstrated that homochiral 5-phenylmorpholine-2-one template **267** reacts with aldehydes to generate azomethine ylides capable of undergoing intermolecular cycloadditions with electron deficient alkenes (**Scheme 82**).[83-85] Subsequent removal of the chiral template permits the construction of proline derivatives.



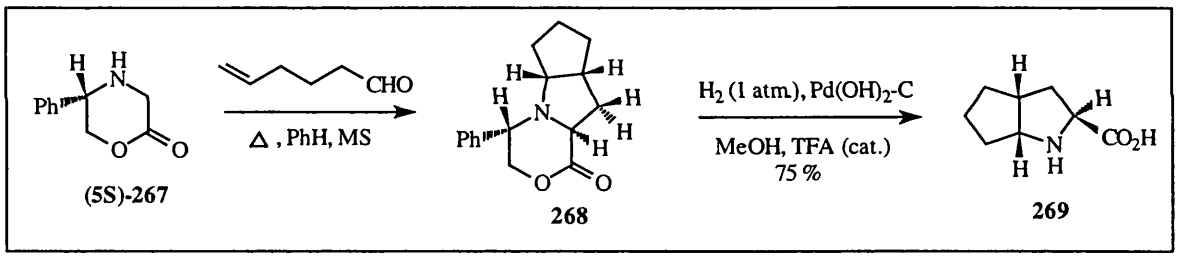
Scheme 82

These chiral compounds can be easily prepared from readily available starting material in a one-step procedure from phenylglycinol according to Dellaria *et al.*[86] [phenylglycinol, $^{i}Pr_2NEt$ (2.5 equiv.), $BrCH_2CO_2Ph$ (1.1 equiv.), MeCN, r.t., 15-18 h]. These workers have extended this work into the intramolecular cycloaddition reaction using aldehydes possessing appropriately positioned unsaturation. Combining ylide generation with an intramolecular [3+2]-cycloaddition provided the diastereocontrolled construction of several stereocentres and rapid access to proline derivatives (**Scheme 83**).



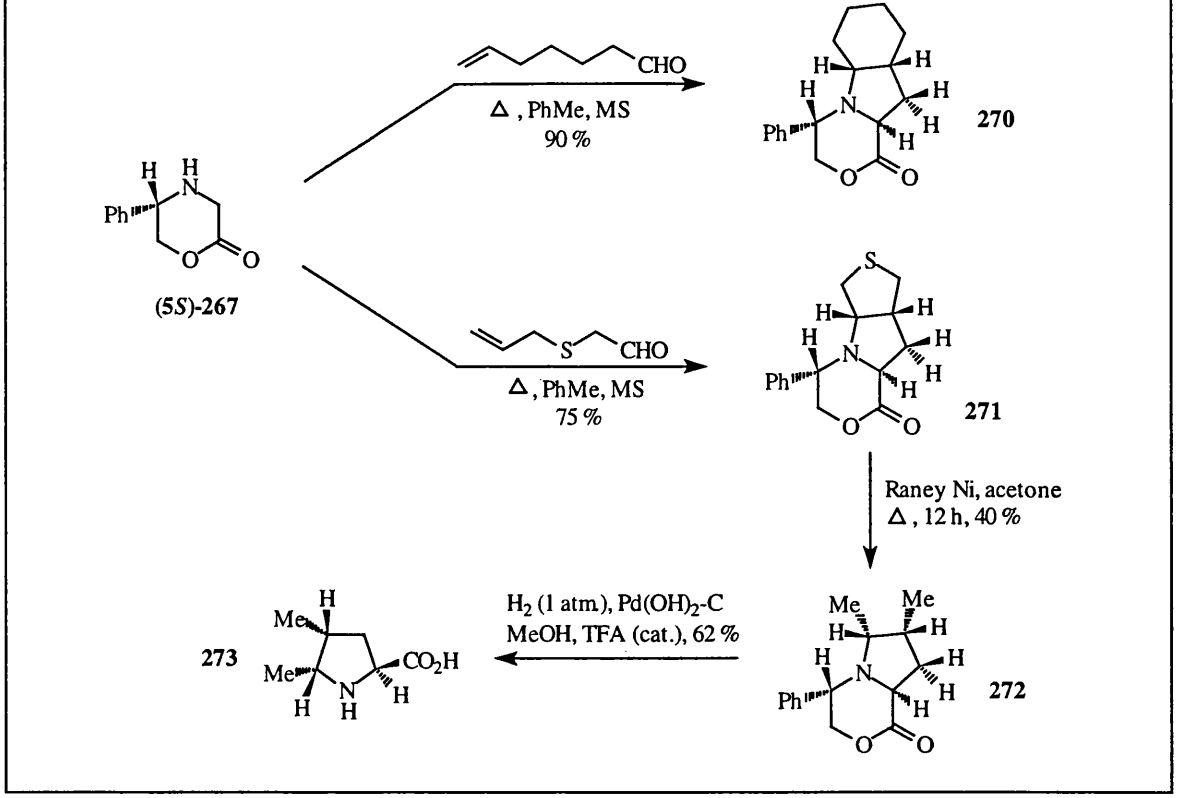
Scheme 83

Treating (**5*S***)-**267** with 5-hexenal (2.5 equiv.) in PhH at reflux and removing the water using molecular sieves in a Soxhlet extractor furnished **268** as a single cycloadduct within 3 h in 95 % yield. Removal of the template under hydrogenolytic conditions, afforded (**1*R*,3*S*,5*S***)-**269** in 75 % recrystallised yield (**Scheme 84**).



Scheme 84

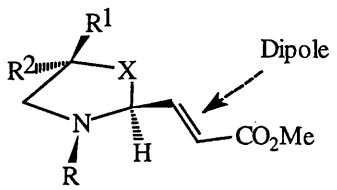
Using 6-heptenal (1.1 equiv.) with (**5*S***)-**267** in refluxing PhMe for 12 h led to **270** as a single cycloadduct in 90 % yield after recrystallisation from Et_2O (**Scheme 85**). Similarly, using 3-thia-5-hexenal (1.1 equiv.) in PhMe at reflux for 48 h gave the single cycloadduct **271** which was isolated in 75 % recrystallised yield. Reductive cleavage of the thioether linkage in **271** was achieved by heating a solution of **271** in acetone at reflux with excess Raney nickel for 12 h to afford **272** in 40 % isolated yield. Hydrogenolytic degradation of the morpholin-2-one framework was carried out using Pearlman's catalyst as previously described to leave (**1*S*,4*R*,5*R***)-**273** in 62 % yield.



Scheme 85

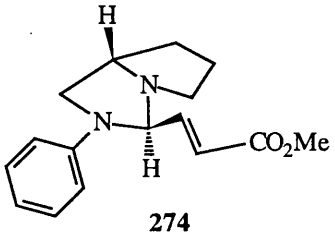
Thus, the process of generating chiral ylides capable of undergoing diastereocontrolled dipolar cycloaddition permits rapid access to both bicyclic and monocyclic 4-5-disubstituted derivatives of proline with high enantiocontrol over the new asymmetric centres generated.

Kanemasa *et al.*[87] were the first to present an example of a highly efficient asymmetric 1,3-dipolar cycloaddition of azomethine ylides, where reactive *N*-metallated azomethine ylides and an α,β-unsaturated ester with a chiral perhydropyrrolo[1,2-*c*]imidazol-3-yl moiety at the β-position have been employed. These workers expected that α,β-unsaturated carbonyl compounds bearing a 2-pyrrolidinyl chiral controller, or heteroanalog (X = heteroatom) could serve effectively as chiral dipolarophiles since the approach of dipole from one side of the olefin face would be sterically hindered by the extruding *N*-substituent, R.



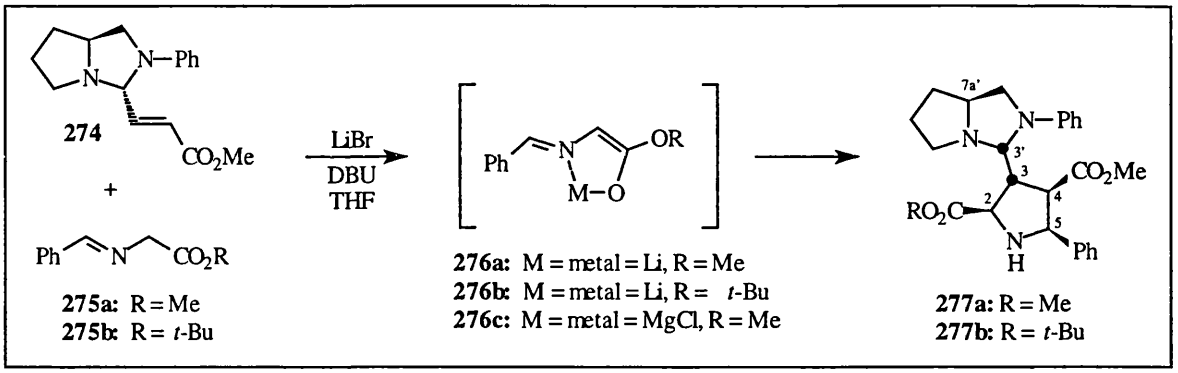
Chiral dipolarophiles

For example:



274

The reaction of methyl (benzylideneamino)acetate **275a** with methyl (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazole-3-(*E*)-propenoate **274** smoothly took place at -78 °C for 5 h in THF in the presence of LiBr (1.5 equiv.) to furnish 82 % yield of cycloadduct **277a** as a single diastereomer (**Scheme 86**, **Table 10**, entry 1). This proceeded through the lithiated azomethine ylide **276a** and indicated the occurrence of the exclusive diastereoface-selective cycloaddition between **275a** and **276a**.



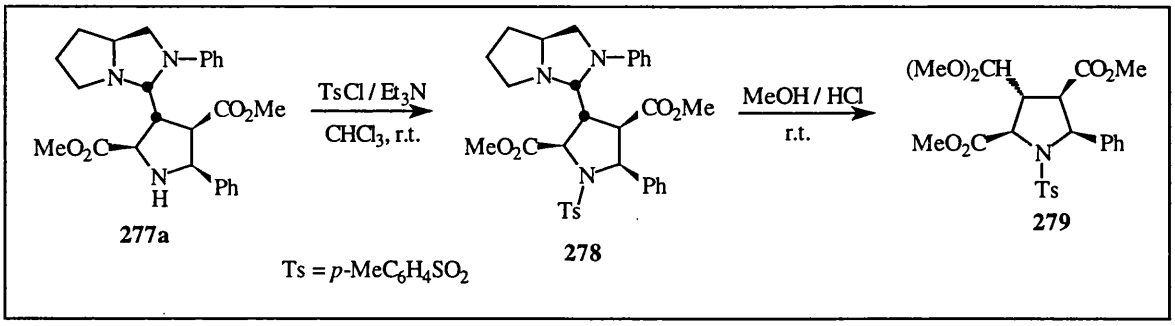
Scheme 86

entry	base	imine	ylide type	reaction conditions		product	yield %	isomer ratio
				temp./°C	time /h			
1	LiBr / DBU	**275a**	**276a**	-78	5	**277a**	82	single
2	LiBr / Et_3N	**275a**	**276a**	r.t.	24	**277a**	79	single
3	LiBr / Et_3N	**275a**	**276a**	40	30	**277a**	63	single
4	LiBr / Et_3N	**275a**	**276a**	60	30	-	-	-
5	LDA	**275a**	**276a**	-78	24	-	-	-
6	LiBr / DBU	**275b**	**276b**	-78	5	**277b**	100	single
7	LiBr / Et_3N	**275b**	**276b**	r.t.	24	**277b**	96	single
8	*t*-BuMgCl	**275a**	**276c**	-78	42	**277a**	30	single

Table 10 Asymmetric 1,3-dipolar cycloaddition reactions of *N*-metallated azomethine ylides 276a-c with chiral olefin 274

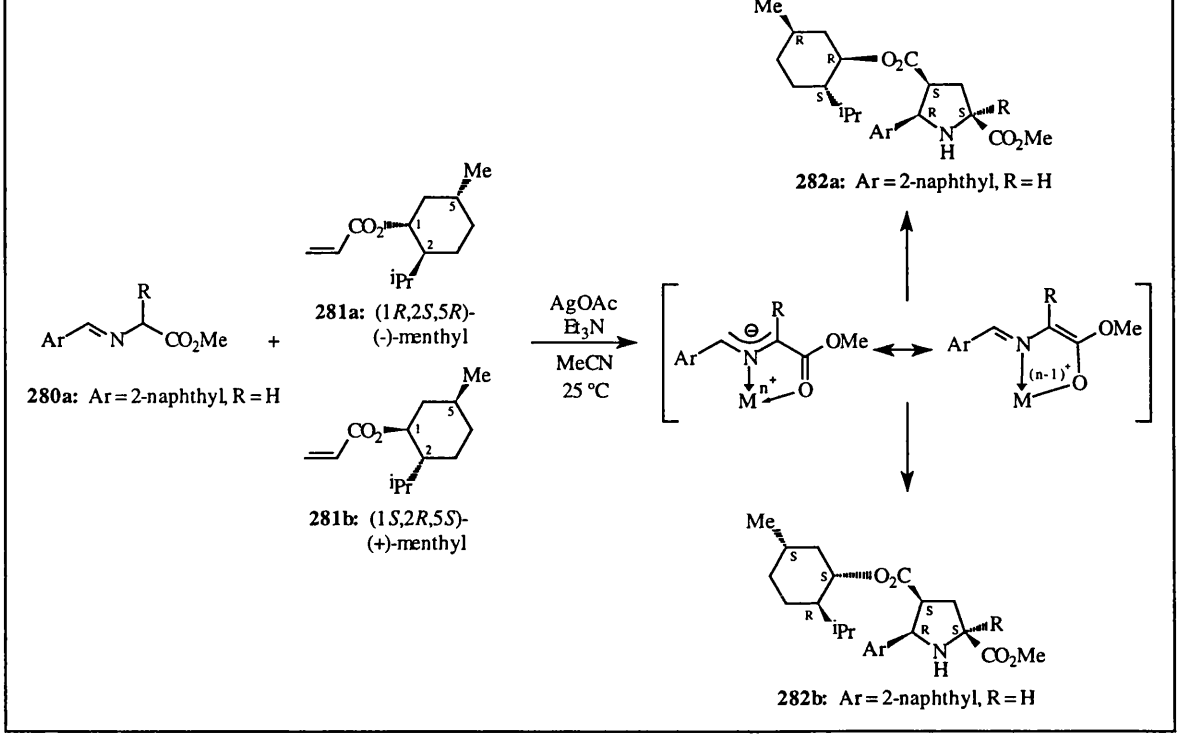
The absolute diastereoselective formation of **277a** was not affected in the reaction at room temperature (**277a**: 79 %, entry 2), where the ylide **276a** (M = Li) was generated by treating **275a** with LiBr and Et_3N. Performing the same reaction at 40 °C also had no effect in the diastereofacial selectivity (entry 3). However, the same reaction carried out at 60 °C by using LiBr /Et_3N (entry 4) or at -78 °C by using LDA (entry 5) led to the formation of complex mixtures. In the case of *tert*-butyl ester **275b**, 100 % yield of the single diastereomer **277b** was obtained using LiBr and DBU at -78 °C via the azomethine ylide **276b** (entry 6). Similarly, 96 % yield of **277b** was obtained at room temperature using LiBr and Et_3N (entry 7). *N*-Magnesioazomethine ylide **276c** (M = MgCl), generated from **275a** and *tert*-butylmagnesium chloride at -78 °C, slowly reacted with **274** at -78 °C to furnish 30 % yield of **277a** as a single diastereomer (entry 8).

Removal of the heterocyclic chiral controller from **277a** was performed by a sequence of *N*-tosylation and acetal exchange reaction (**Scheme 87**). Thus, cycloadduct **277a** was allowed to react with *p*-toluenesulfonyl chloride and Et_3N in $CHCl_3$ at room temperature to give tosylate **278** in 66 % yield. Compound **278** was then treated with MeOH saturated with HCl at room temperature resulting in the formation of polyfunctionalised 2,4-pyrrolidinedicarboxylate **279**.



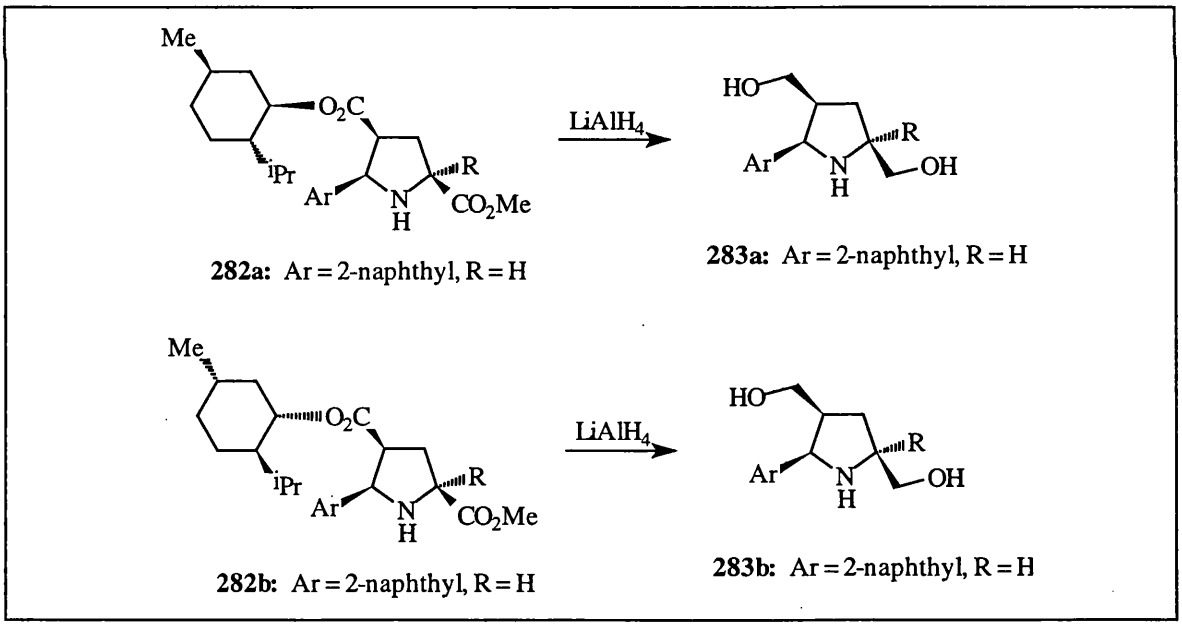
Scheme 87

Grigg *et al.*[88] have also achieved complete asymmetric induction in the cycloaddition reactions of homochiral dipolarophiles with a range of imines of α-amino esters in the presence of metal salts. These workers initially studied the cycloaddition of **280a** with **281a** and **281b** in the presence of silver acetate (1.5 mol) and triethylamine (1 mol) (**Scheme 88**). In each case, a single diastereomer of **282a** and **282b** was obtained in approx. 50 %.



Scheme 88

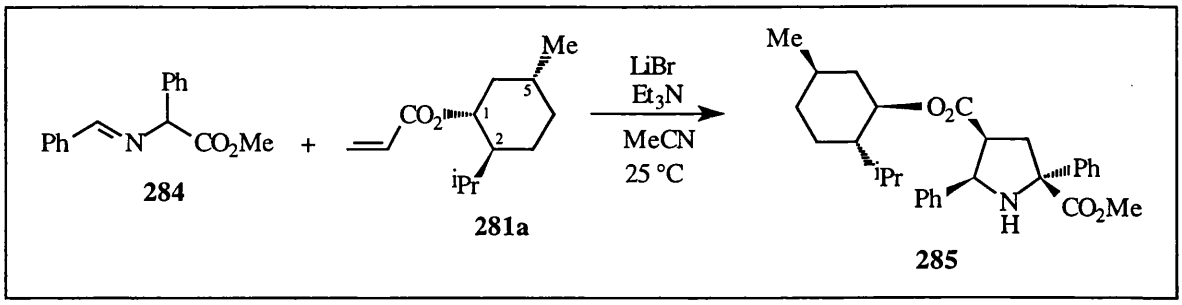
The chiral menthyl template was easily removed from these products by reduction with $LiAlH_4$ as indicated in **Scheme 89**.



Scheme 89

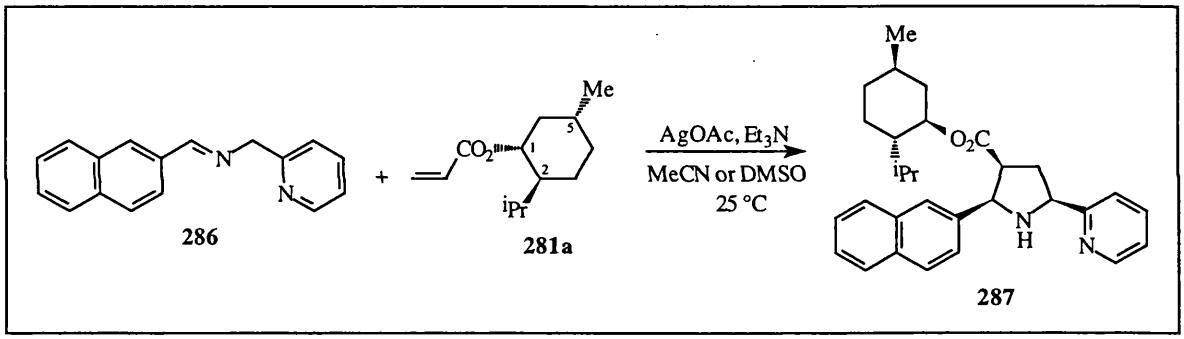
Previous work by Grigg *et al.*[89] has also shown that the lithium bromide catalysed cycloaddition of the phenylglycine imine **284** to menthyl acrylate **281a** occurs

in quantitative yield. When **284** was reacted with **281a** in the presence of lithium bromide (1.5 mol) and Et_3N (1 mol) clean cycloaddition occurred to give **285** as a single diastereomer (**Scheme 90**).



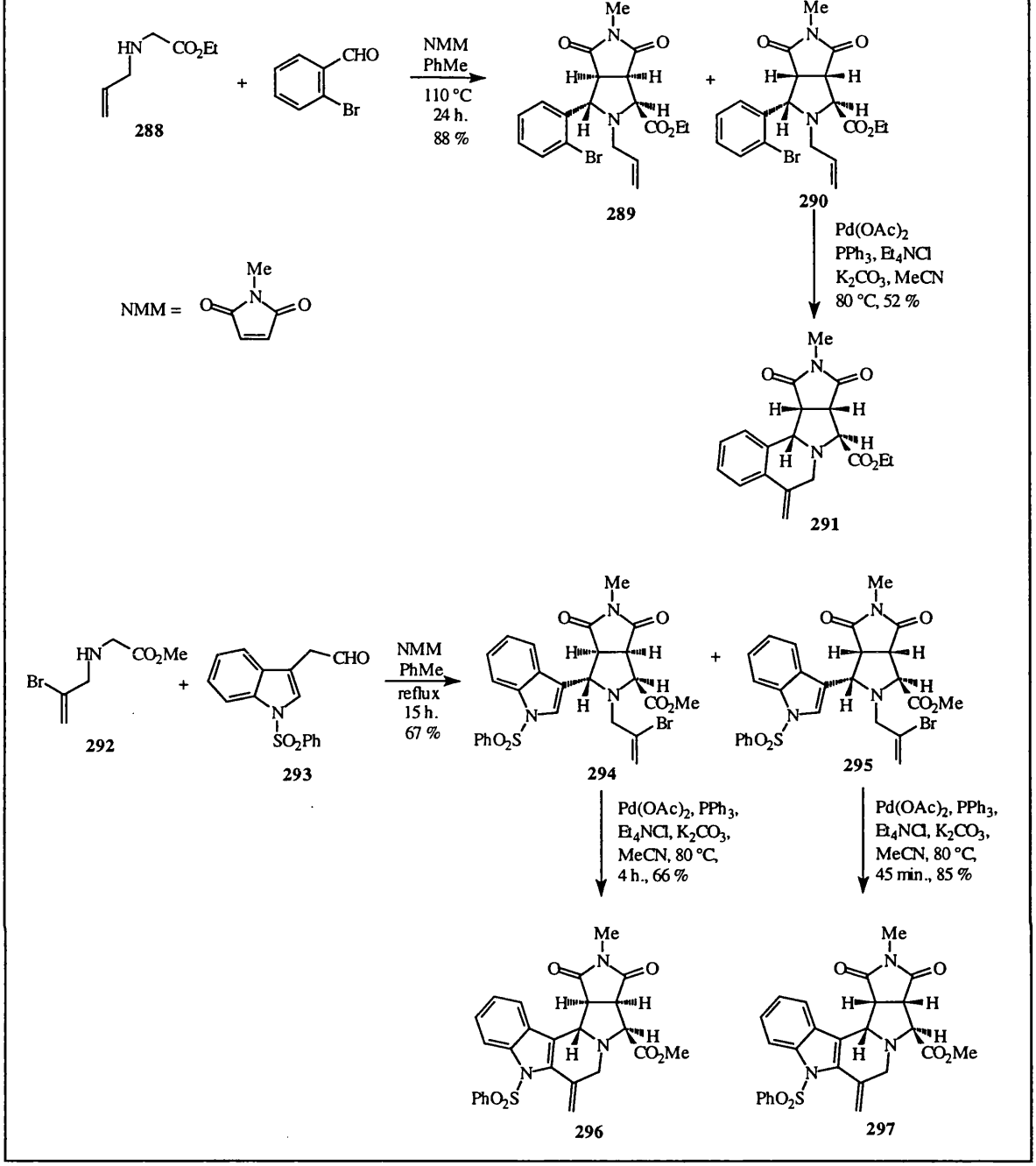
Scheme 90

Similarly, imine **286** reacts with **281a** [AgOAc (1 mol), Et_3N (1 mol), 25 °C] in either MeCN (12 h) or DMSO (6 h) to give the homochiral cycloadduct **287** in 70 % yield (**Scheme 91**) showing that other potentially chelating imines also undergo the asymmetric cycloaddition reaction.



Scheme 91

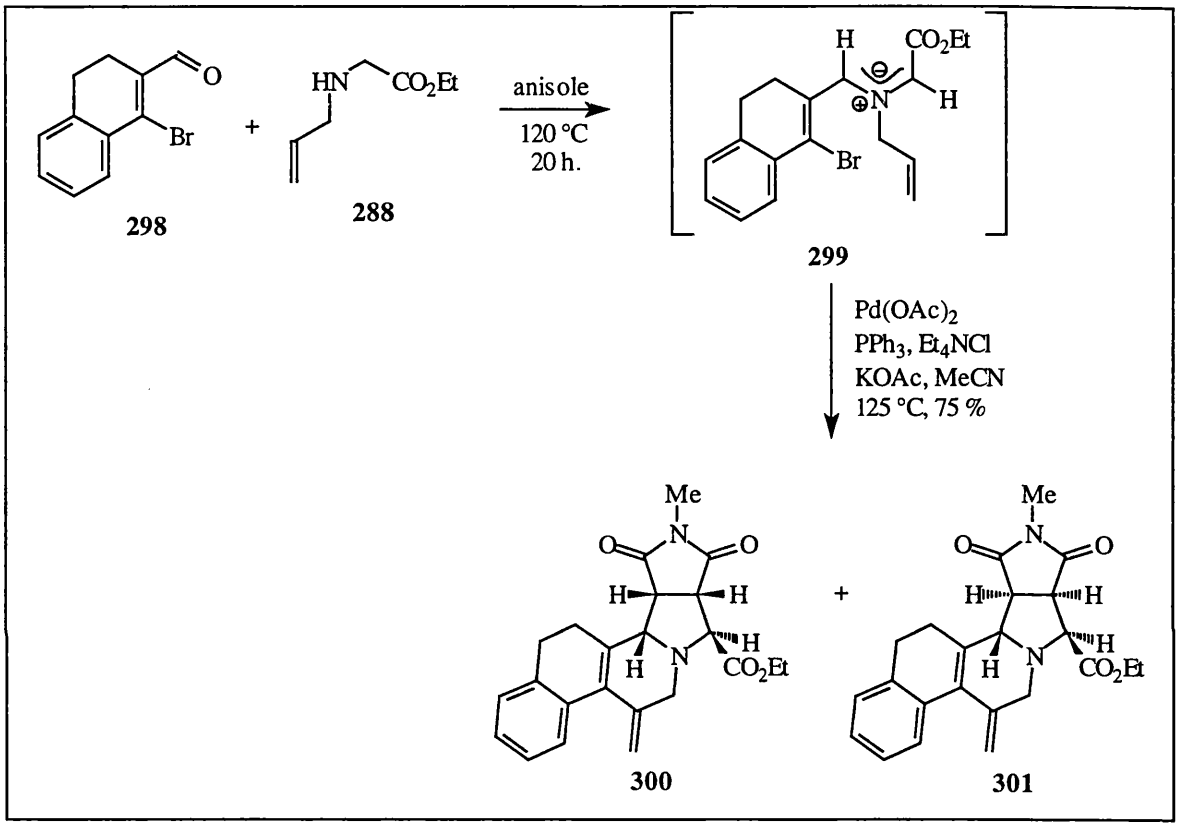
Grigg *et al.*[90] has successfully utilised a combination of a 1,3-dipolar cycloaddition of an *in situ* generated azomethine ylide followed by a palladium catalysed cyclisation to afford four new stereocentres and two new rings in a single step. The approach developed involves the condensation of an aldehyde with a secondary α-amino ester. Facile deprotonation of the intermediate iminium ion furnishes the required azomethine ylide.[91] The palladium catalysed cyclisation utilises an aryl or vinyl halide moiety and this can be located on either the aldehyde substrate or the α-amino ester. This can be seen in **Scheme 92**.



Scheme 92

Glycine ester **288** reacted with *o*-bromobenzaldehyde and *N*-methylmaleimide to give a 1:2.3 mixture of **289** and **290**, which was readily separated by flash chromatography. Isomer **290** cyclised in MeCN at 80 °C over 40 h using a catalytic system comprising 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, Et_4NCl (1 mol) and anhydrous K_2CO_3. Similarly, indole aldehyde **293** reacted with **292** and *N*-methylmaleimide in boiling PhMe over 15 h to give a 1:2 mixture of **294** and **295**. Again these isomers were separated by flash chromatography and cyclised separately under the same conditions.

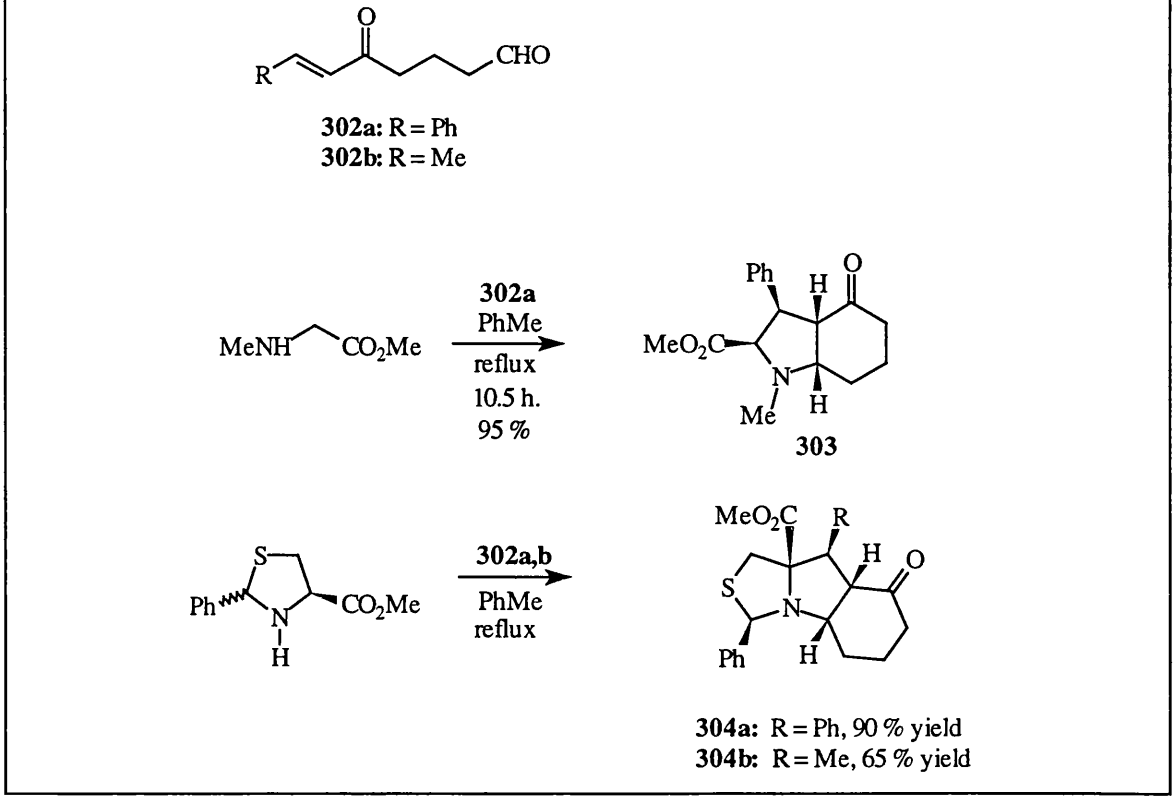
This procedure has successfully been carried out in a one-pot procedure. This was exemplified by the reaction of aldehyde **298** with **288** and *N*-methylmaleimide followed by addition of the catalyst system used previously, with KOAc (2 mol) replacing K_2CO_3 as base, raising the reaction temperature to 125 °C and continuing the heating for a further 4 h (**Scheme 93**). The product consisted of a 9.5:1 mixture of **300** and **301**, due to both *endo*- and *exo*-cycloaddition of NMM to the stereospecifically formed *trans*-dipole **299**.



298 288 299 300 301

Scheme 93

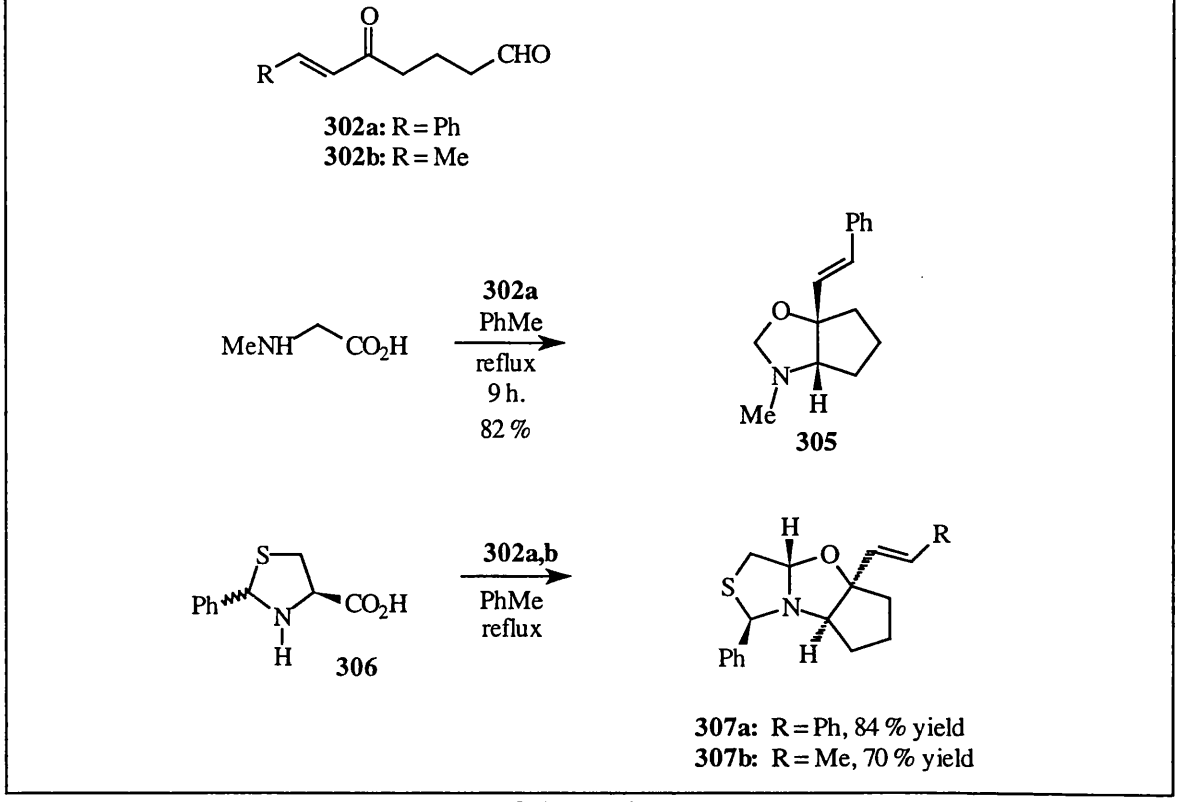
Kanemasa *et al.*[92] have obtained complete stereoselectivity in the intramolecular cycloadditions of azomethine ylides bearing a carbonyl-activated olefinic moiety, generated from α-amino acids or esters and 5-oxo-6-heptenals. The condensation of α-amino acids or derivatives with carbonyl compounds offers one of the most direct and convenient generation methods of azomethine ylides, both stabilised and nonstabilised. This method was extended to carbonyl compounds bearing an internal dipolarophilic moiety such as olefinic aldehydes **302a,b** (**Scheme 94**).



Scheme 94

Heating equimolar amounts of (*E*)-7-phenyl-5-oxo-6-heptenal **302a** and methyl sarcosinate, under reflux in PhMe with continuous removal of water by aid of a Dean-Stark trap, afforded the internal cycloadduct **303** as a single stereoisomer in 95 % yield. Similarly, cycloadducts **304a,b** were obtained again as single stereoisomers in 90 % and 65 % yields, respectively, in the reactions of **302a** and (*E*)-5-oxo-6-octenal (**302b**) with methyl 2-phenyl-4-thiazolidine-carboxylate under the equivalent conditions.

In contrast to the ester-stabilised ylides, the intramolecular cycloadditions of nonstabilised azomethine ylides generated by the decarboxylative condensation of α-amino acids, instead of α-amino esters, with olefinic aldehydes **302** selectively produced isomeric internal cycloadducts (**Scheme 95**).

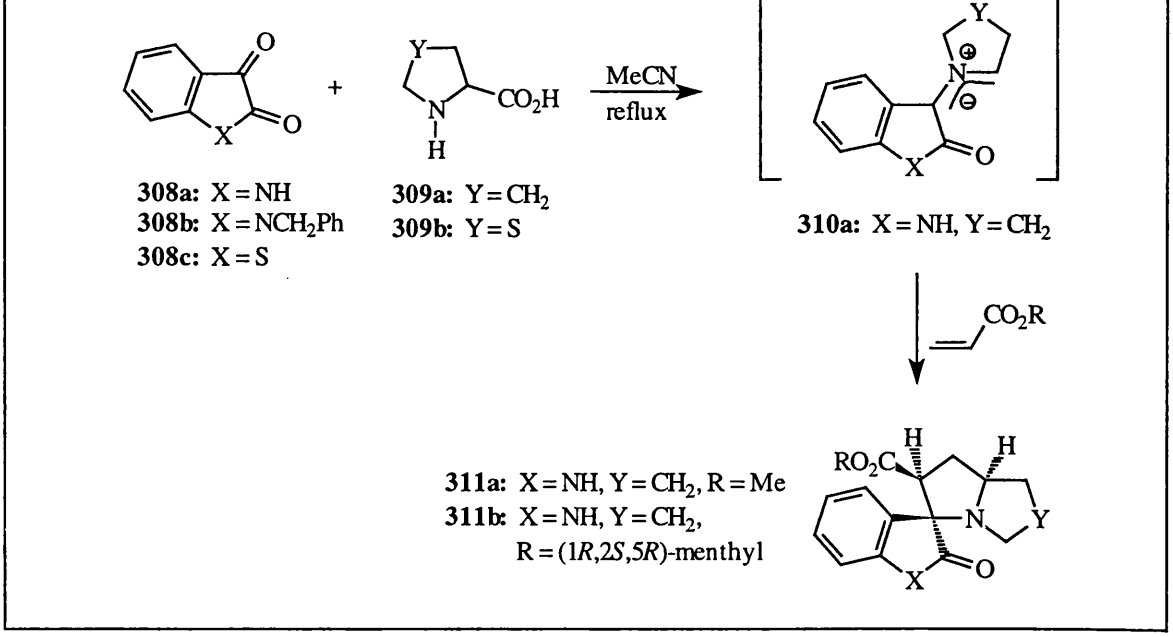


Scheme 95

Thus, the reaction of sarcosine with **302a** under reflux in PhMe for 9 h afforded **305**, the internal adduct to the carbonyl group, in 82 % yield as a single stereoisomer. Similarly, reactions of **306** with **302a,b** produced **307a,b** also as single stereoisomers in 84 and 70 % yields, respectively.

It was thus shown that ester-stabilised azomethine ylides undergo smooth cycloadditions at the olefinic moiety, while the nonstabilised azomethine ylides react at the carbonyl moiety, both in an exclusively selective fashion.

Grigg *et al.*[93] have also reported the use of azomethine ylides produced by the decarboxylation of iminium species derived from cyclic secondary α-amino acids and isatin (**Scheme 96**).



308a: X = NH
308b: X = NCH_2Ph
308c: X = S

309a: Y = CH_2
309b: Y = S

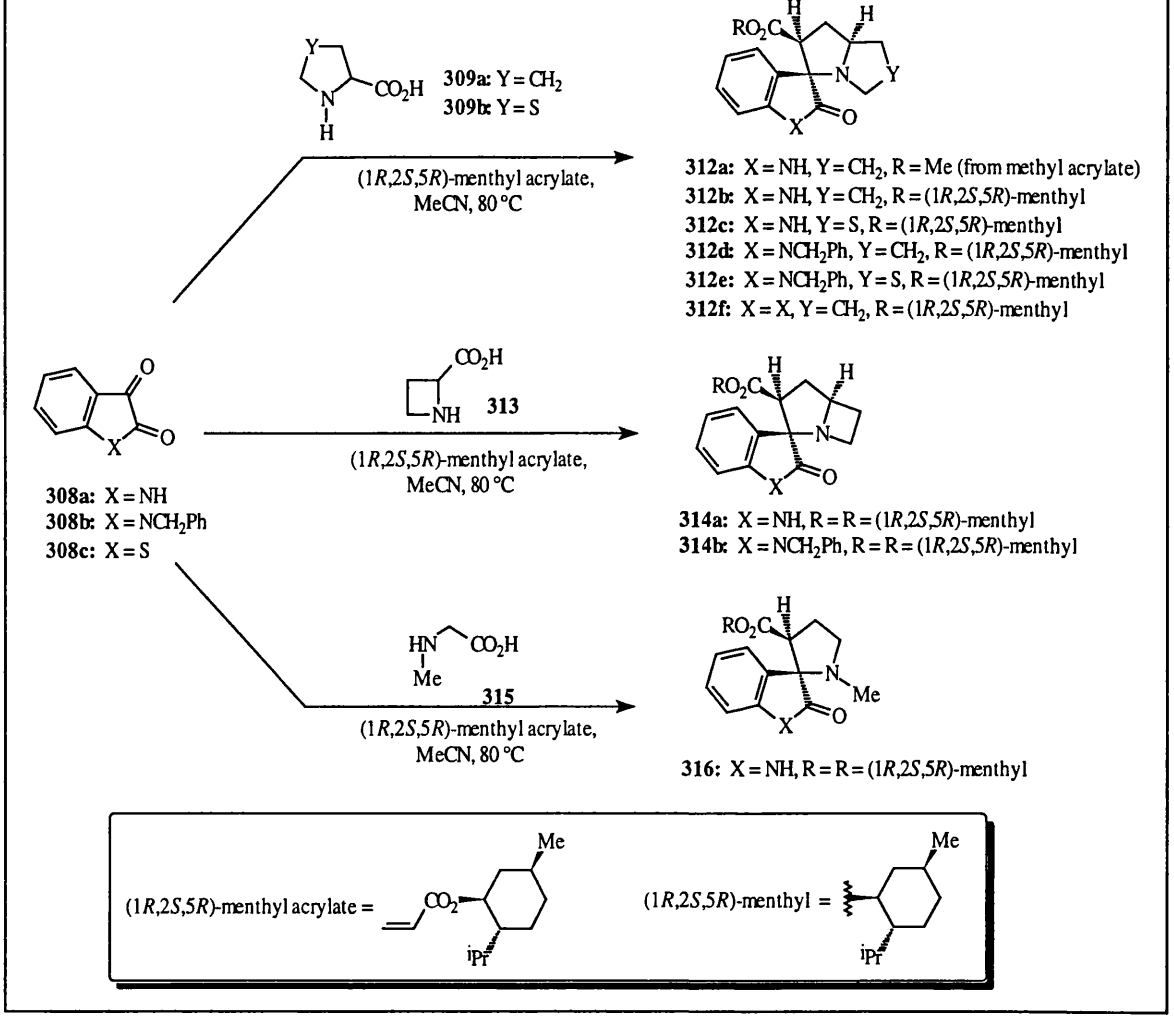
310a: X = NH, Y = CH_2

311a: X = NH, Y = CH_2, R = Me
311b: X = NH, Y = CH_2, R = (1*R*,2*S*,5*R*)-menthyl

Scheme 96

Isatin **308a**, proline **309a** and methyl acrylate reacted regio- and stereospecifically in boiling MeCN to furnish a single cycloadduct **311a** in good yield via the azomethine ylide **310a**. Repeating the reaction with (1*R*,2*S*,5*R*)-menthyl acrylate as the dipolarophile afforded a 9:1 mixture of diastereomers **311b**. The (1*R*,2*S*,5*R*)-stereochemistry of the major isomer **311b** was established by a single crystal X-ray structure determination.

A series of related cycloadditions was also carried out using the dicarbonyl compounds **308a-c**, α-amino acids **309a,b**, **313**, and menthyl acrylate. These reactions occurred in moderate to good yield with diastereomer ratios in the range 67-80 % for the cyclic secondary α-amino acids. A single acyclic secondary α-amino acid **315** was also studied proceeding in 60 % d.e. (**Scheme 97, Table 11**).



Scheme 97

carbonyl compound	amino acid	major isomer	reaction conditions		% d.e.[b]
			time (h)	yield (%)[a]	
308a	**309a**	**312b**	4.5	85	80
308a	**309b**	**312c**	20	77	82
309b	**309a**	**312d**	5.5	79	72
308b	**309b**	**312e**	20	76	76
308c	**309a**	**312f**	23	59	67
308a	**313**	**314a**	42	52	74
308b	**313**	**314b**	50	46	72
308a	**315**	**316**	27	65	60

Table 11 Chiral induction in the cycloaddition of 308a-c with secondary α-amino acids and (1*R*,2*S*,5*R*)-menthyl acrylate

[a.] Combined isolated yield of both isomers; [b.] Based on integration of the menthyl Me signals in the n.m.r. spectrum

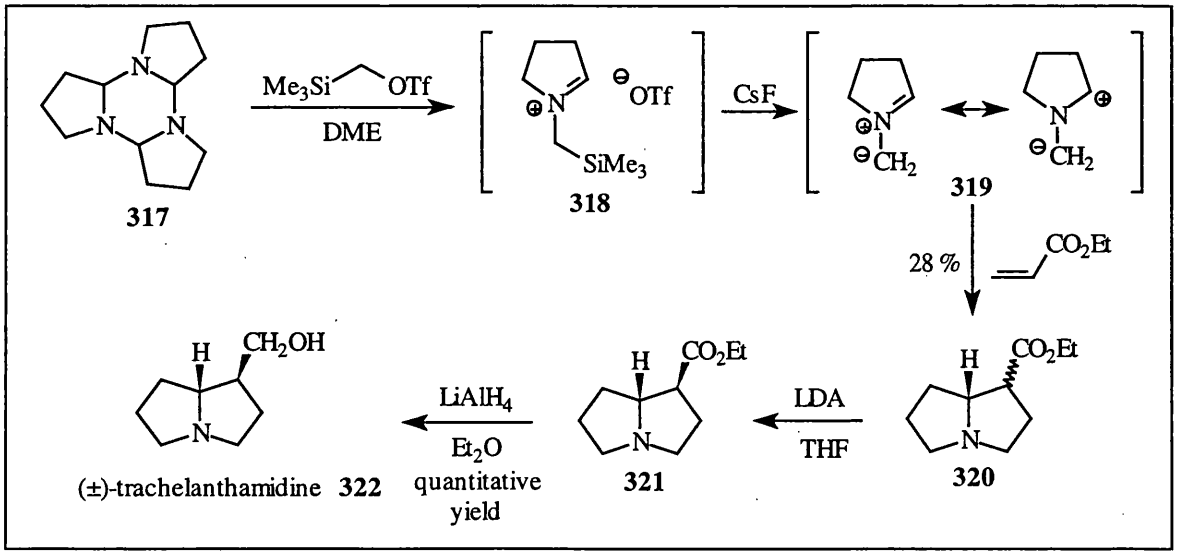
Thus it was been shown that the cycloaddition of stabilised azomethine ylides prepared from the decarboxylation route can react with menthyl acrylate in good to moderate diastereomeric ratios.

It has been shown in the above discussion that high to complete asymmetric induction can be achieve in the 1,3-dipolar cycloaddition reactions of certain stabilised and nonstabilised azomethine ylides with appropriate dipolarophiles. Various methods have been used to effect this high chiral induction into the subsequent cycloadducts, and so it is perhaps appropriate to illustrate the use of azomethine ylides for the preparation of natural products. This will be discussed briefly in the following section.

1.4 Natural products via the [3+2]-cycloaddition reactions of azomethine ylides

Pyrrolidine rings are frequently encountered structural units in many synthetically challenging alkaloids. The 1,3-dipolar cycloadditions of nonstabilised and stabilised azomethine ylides have been utilised extensively for the construction of the pyrrolidine skeleta of a number of natural products, primarily alkaloids. Some examples of how the various methods for the generation of these intermediates have been incorporated into the synthesis of some of these alkaloids are indicated in the following section.

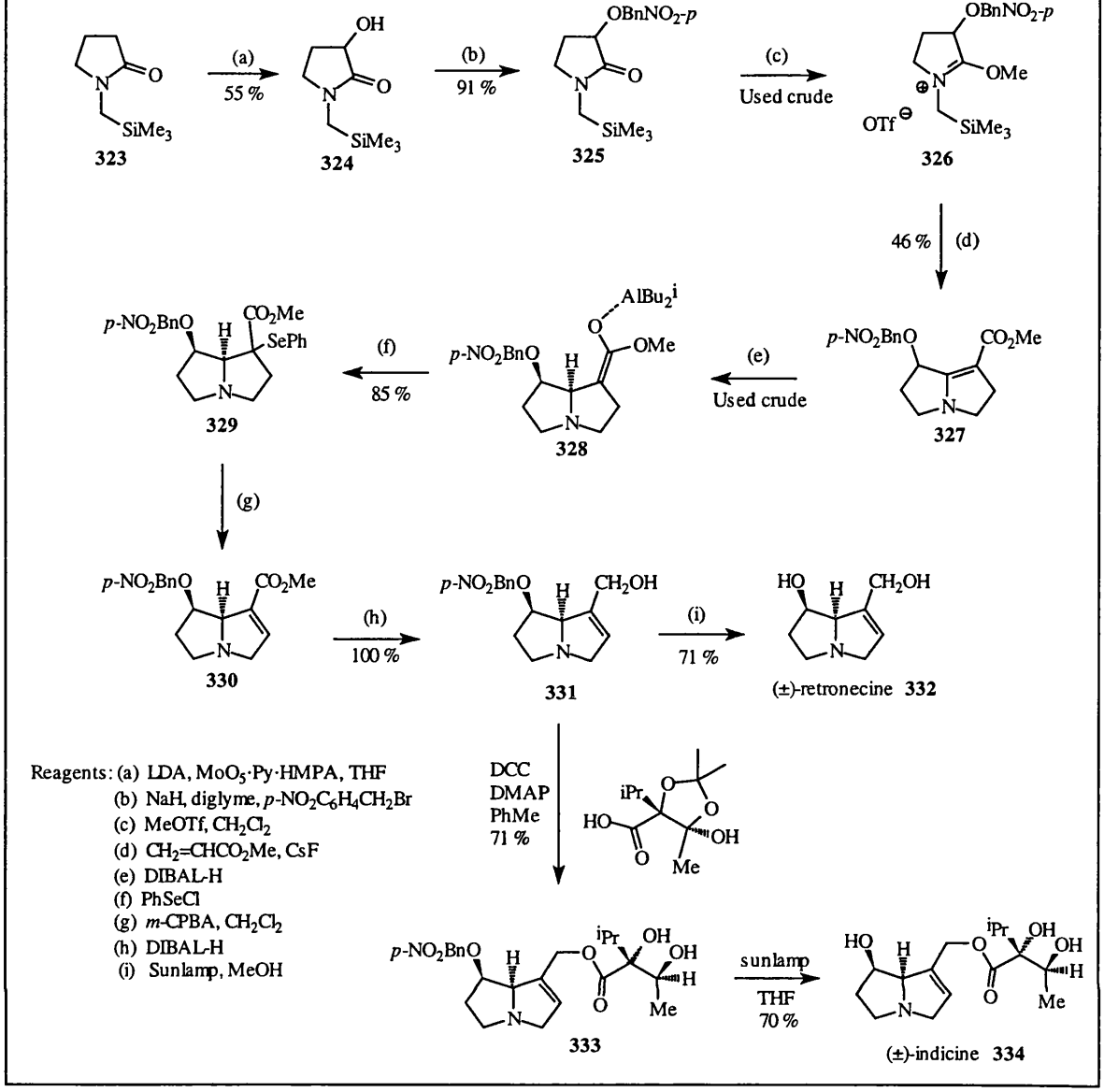
For the synthesis of (±)-trachelanthamidine **322,** Achiwa *et al.*[94] have reported a short route that utilised the nonstabilised azomethine ylide **319** (**Scheme 98**). They reacted **317** with trimethylsilylmethyl triflate to obtain iminium salt **318** which underwent desilylation with F^- to give an ylide **319** that reacted with ethyl acrylate to produce ethyl pyrrolizidine-1-carboxylate **320** as a mixture of stereoisomers. After the epimerisation of **320** with LDA, the ester moiety of **321** was reduced with $LiAlH_4$ in ether to provide (±)-trachelanthamidine **322**.



317 318 319 320 321 (±)-trachelanthamidine 322

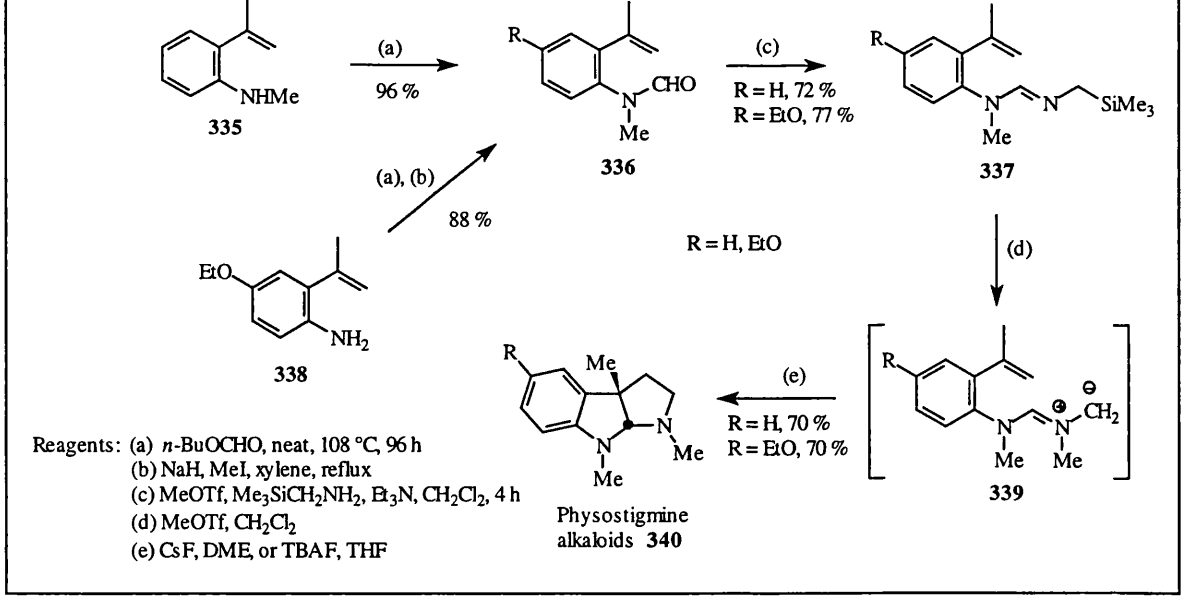
Scheme 98

Retronecine also belongs to the pyrrolizidine family of alkaloids. It was synthesised by Vedejs *et al.*[26] using an azomethine ylide cycloaddition reaction as the key step for the pyrrolizidine ring construction (**Scheme 99**). *N*-Silylmethylpyrrolidine-2-one **323** was α-deprotonated with LDA and treated with MoO_5•Py•HMPA (MoOPH) to give 3-hydroxy-2-pyrrolidinone **324**. The 3-OH group was then protected as a photosensitive *p*-nitrobenzyl ether **325**. The carbonyl at the 2-position was then *O*-methylated with methyl triflate to form the *N*-(silylmethyl)imidate salt **326** as the azomethine ylide precursor. Desilylation with fluoride ion and subsequent cycloaddition to methyl acrylate produced 1,7*a*-dehydropyrrolizidine-1-carboxylate **327** after the elimination of methanol from the initial cycloadduct. The stereoselective 1,4-reduction of **327** with DIBAL-H followed by the phenylselenylation of the aluminium enolate **328** afforded the selenide **329** in a single step. An oxidation and elimination sequence then gave rise to the 1,2-dehydropyrrolizidine-1-carboxylate **330**. Reduction of the ester group in **330** with DIBAL-H and subsequent deprotection (sunlamp in MeOH) afforded (±)-retronecine **332**. (±)-Indicine **334**, a monoester of retronecine, was directly derived from the mono *O*-protected alcohol **331** after *O*-acylation with trachelanthic acid acetonide followed by photolytic deprotection.



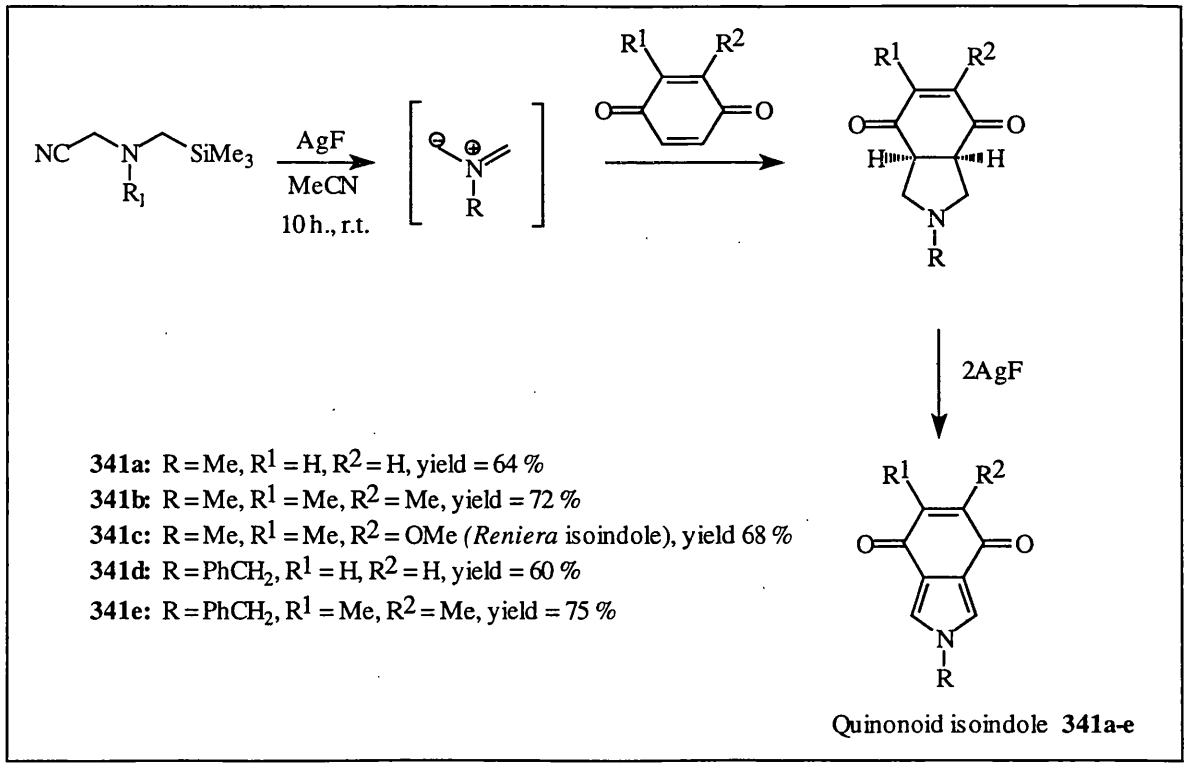
Scheme 99

Livinghouse *et al.*[12,14,17] have discovered a new method for generating of amidinium ylides and have applied this to the synthesis of physostigmine alkaloids **340** (**Scheme 100**). *N*-Formylation of *N*-methyl-2-isopropenylaniline **335** was followed by *O*-methylation with methyl triflate, and subsequent treatment with trimethylsilylmethylamine led to amidine **337**. Amidine **337** was *N*-methylated with methyl triflate at 25 °C in CH_2Cl_2 and the resulting formamidinium salt treated with CsF or TBAF to generate the azomethine ylide **339**. Internal trapping by intramolecular cycloaddition of **339** gave physostigmine alkaloids such as deoxyseroline **340** (R = H) and (±)-eserethole **340** (R = OEt).



Scheme 100

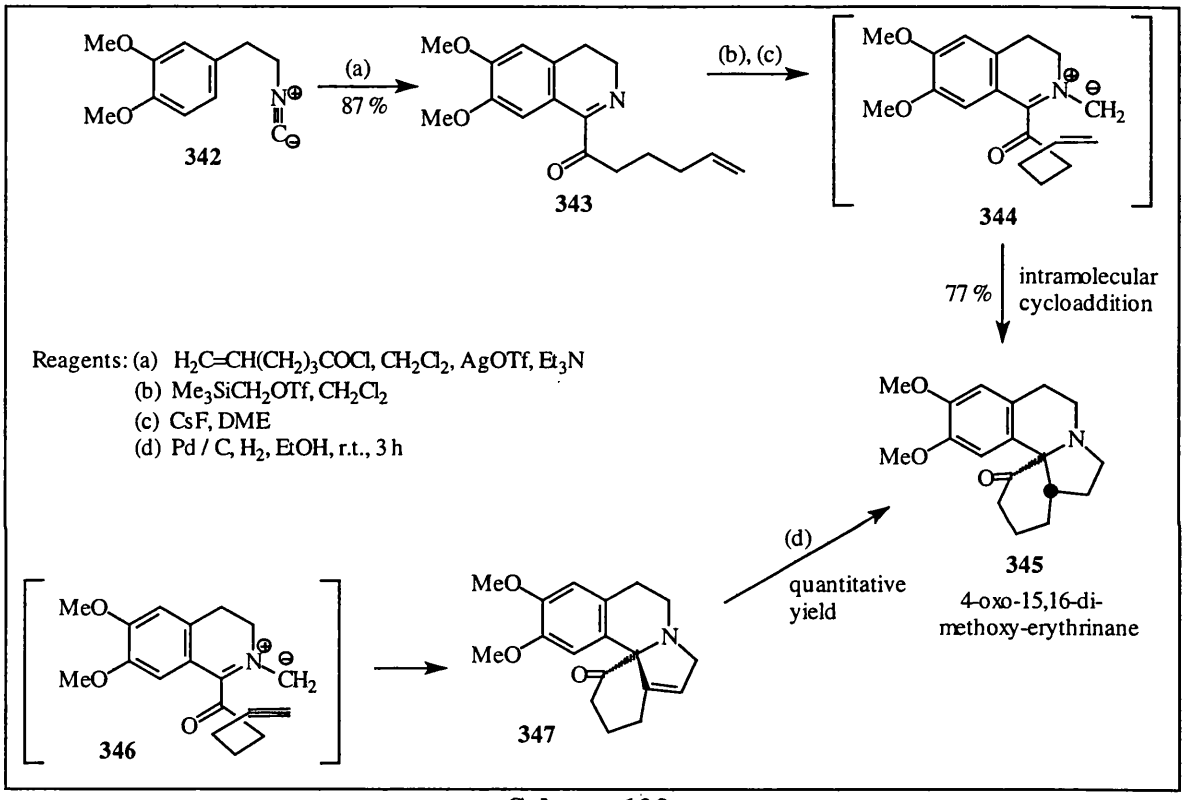
Padwa *et al.*[29] have employed nonstabilised azomethine ylides for the synthesis of the *Reniera* isoindoles **341** (**Scheme 101**). Treatment of the *N*-methyl-α-[(cyanomethyl)amino]-silane with five equivalents of AgF in the presence of the appropriately substituted quinone gave the natural product **341c** directly in 68 % yield. Excess AgF was required to oxidise the intermediate cycloadduct.



341a: R = Me, R^1 = H, R^2 = H, yield = 64 %
341b: R = Me, R^1 = Me, R^2 = Me, yield = 72 %
341c: R = Me, R^1 = Me, R^2 = OMe (*Reniera* isoindole), yield 68 %
341d: R = $PhCH_2$, R^1 = H, R^2 = H, yield = 60 %
341e: R = $PhCH_2$, R^1 = Me, R^2 = Me, yield = 75 %

Scheme 101

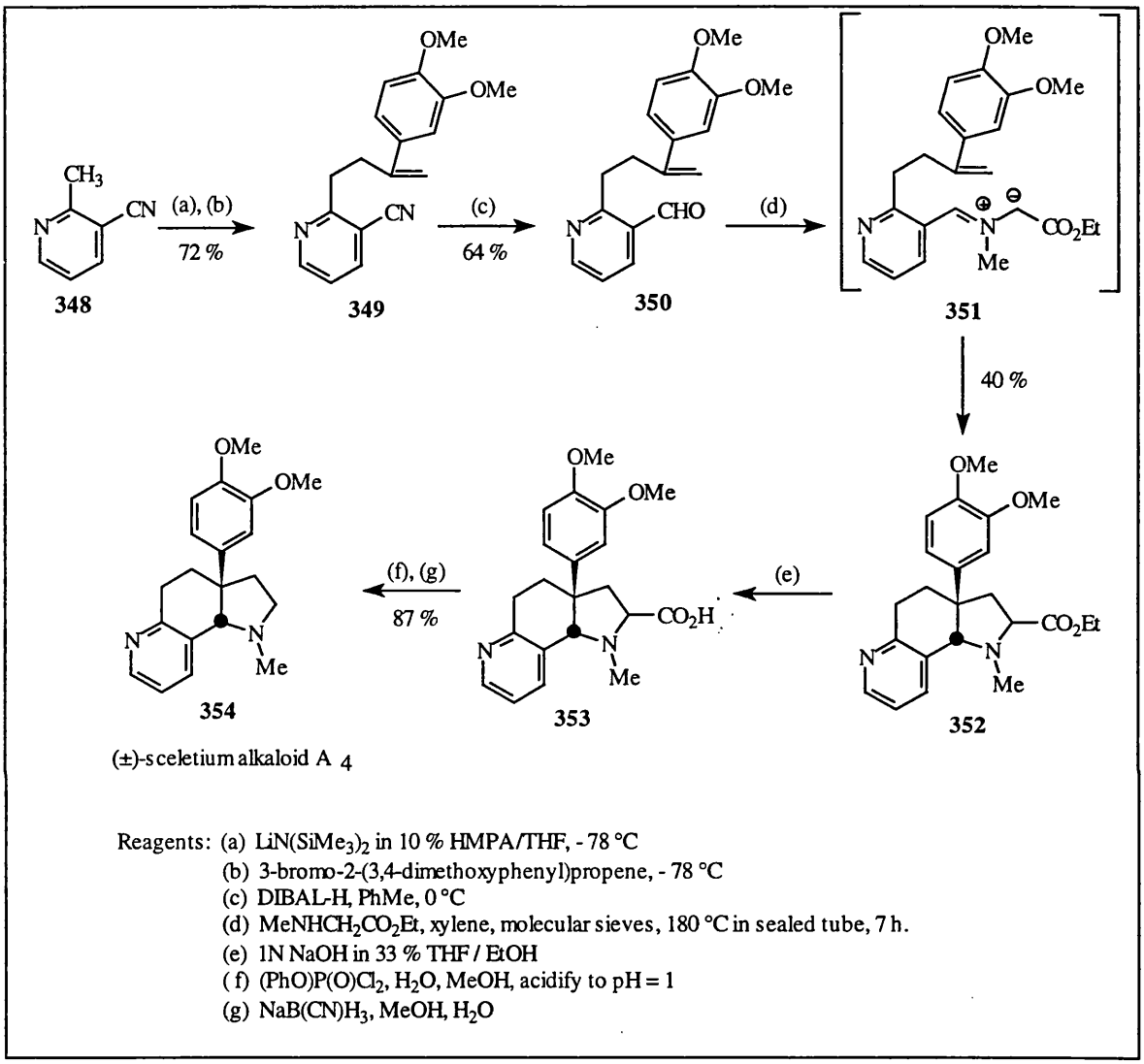
This desilylation route has also been used effectively by Livinghouse *et al.*[95] to construct the skeleton of the *Erythrina* alkaloids (**Scheme 102**). Thus, reaction of 2-(3,4-dimethoxy-phenyl)ethylisonitrile **342** with 5-hexenoyl chloride and subsequent cyclisation in the presence of silver triflate afforded the 3,3-dihydroisoindole **343**. *N*-Silylmethylation with trimethyl-silylmethyl triflate and desilylation with fluoride generated the azomethine ylide **344**, whose intramolecular cycloaddition gave 4-oxo-15,16-dimethoxyerythrinane **345**. The latter could also be obtained from the azomethine ylide **346** after catalytic hydrogenation of the cycloadduct **347**.



Scheme 102

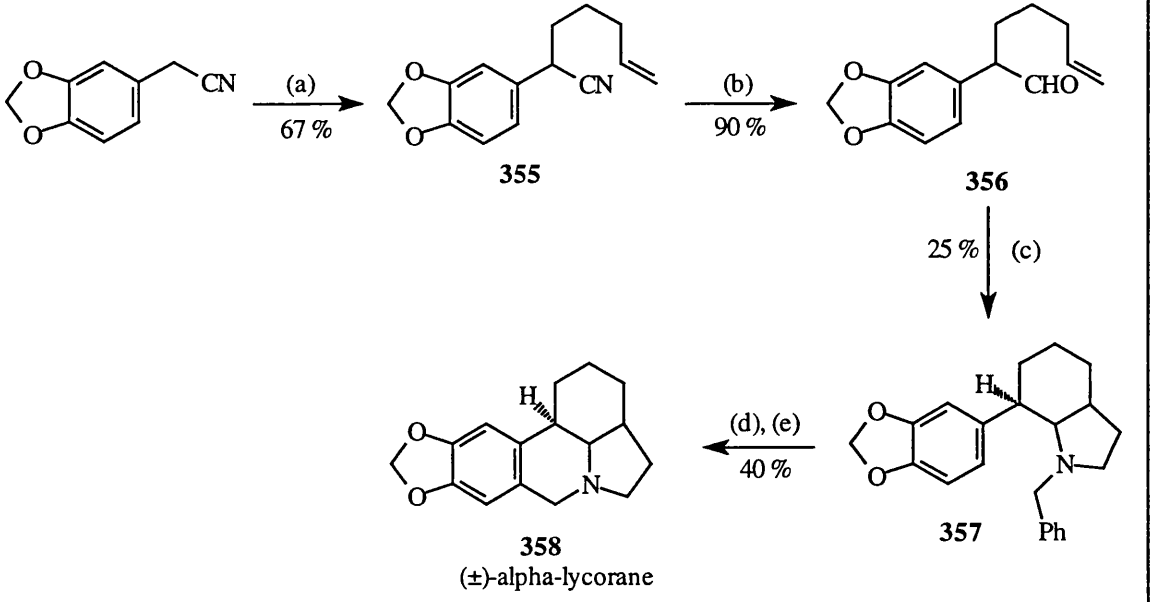
Confalone *et al.*[56] have successfully exploited an intramolecular azomethine ylide cycloaddition in their synthesis of the *Sceletium* alkaloid A_4 **354** (**Scheme 103**). Deprotonation of 3-cyano-2-methylpyridine **348** with lithium hexamethyldisilazide and subsequent alkylation with 3-bromo-2-(3,4-dimethoxyphenyl)propene provided **349**. DIBAL-H reduction of this nitrile led to aldehyde **350** which was required for azomethine ylide generation by the deprotonation route. Heating **350** and ethyl sarcosinate at 180 °C in a sealed tube generated azomethine ylide **351**, whose cycloaddition gave rise to cycloadduct **352**. Hydrolysis of the ester moiety to the

carboxylic acid **353** with NaOH in THF/MeOH was followed by decarboxylation and reduction. Acid **353** was then heated with phenyl dichlorophosphate at 100 °C and the resulting iminium product reduced with $NaB(CN)H_3$ to provide (±)-*Sceletium* alkaloid A_4 **354**.



Scheme 103

Confalone *et al.*[96] have synthesised lycorane skeletal by intramolecular cycloadditions of azomethine ylides generated by decarboxylation (**Scheme 104**). Thus 3,4-(methylenedioxy)-phenylacetonitrile was deprotonated with LDA and an alkylation performed with 5-bromo-1-pentene in HMPA/THF to afford **355**. The latter was then reduced to aldehyde **356**. Heating **356** with *N*-benzylglycine in toluene furnished a single cycloadduct **357**. Debenzylation of **357** by catalytic hydrogenation followed by a cyclisation with formaldehyde provided (±)-α-lycorane **358**.



Reagents: (a) LDA, HMPA/THF, 5-bromo-1-pentene
(b) DIBAL-H, PhMe
(c) *N*-benzylglycine + $HN(SiMe_3)_2$, PhMe
(d) HCO_2H / MeOH, 10 % Pd / C
(e) HCHO, H^+

Scheme 104

1.5 Closing remarks

The chemistry of azomethine ylide 1,3-dipoles has undergone a renaissance since 1978. Methods for generating azomethine ylides, which were limited before then to the aziridine route and the deprotonation route, have since been greatly extended. Initially, it was believed that only azomethine ylides stabilised by at least one electron-withdrawing substituent could be generated smoothly, but this long-held view has now been revised. Nonstabilised azomethine ylides bearing no ylide-stabilising substituent are accessible, and they are stable enough to be utilised in cycloaddition reactions to various dipolarophiles. The desilylation route is particularly effective for this purpose. *N*-Unsubstituted or even *N*-metallated ylides and the tautomers of the corresponding imines or α-metallated imines, have been shown accessible both through the desilylation and the tautomerisation routes. Cycloadditions of these ylides has provided *N*-unsubstituted cycloadducts. Nonstabilised azomethine ylides generated by the *N*-oxide route have also been shown to be exceptionally reactive, undergoing cycloadditions to nonactivated olefin dipolarophiles. Again, this can be seen to be a

major breakthrough. Finally, technology has now evolved for performing asymmetric azomethine ylide cycloadditions, and no doubt, this will prove useful for the future synthesis of many naturally occurring pyrrolidines in homochiral form.

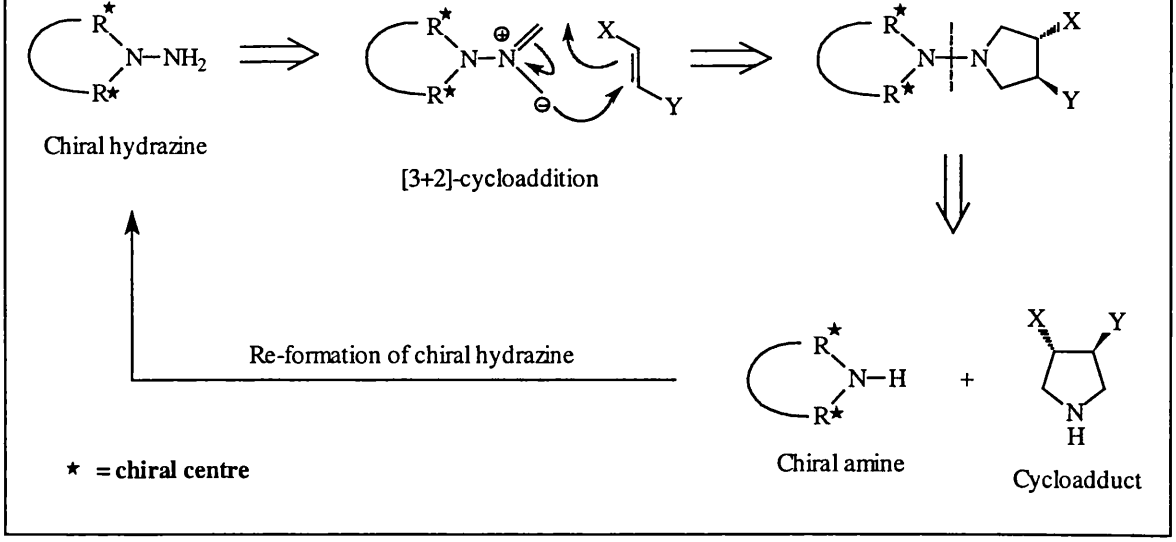
Chapter 2

Evaluation of a new chiral auxiliary for nitrogen in the asymmetric [3+2]-cycloaddition of nonstabilised azomethine ylides

2.0 Introduction

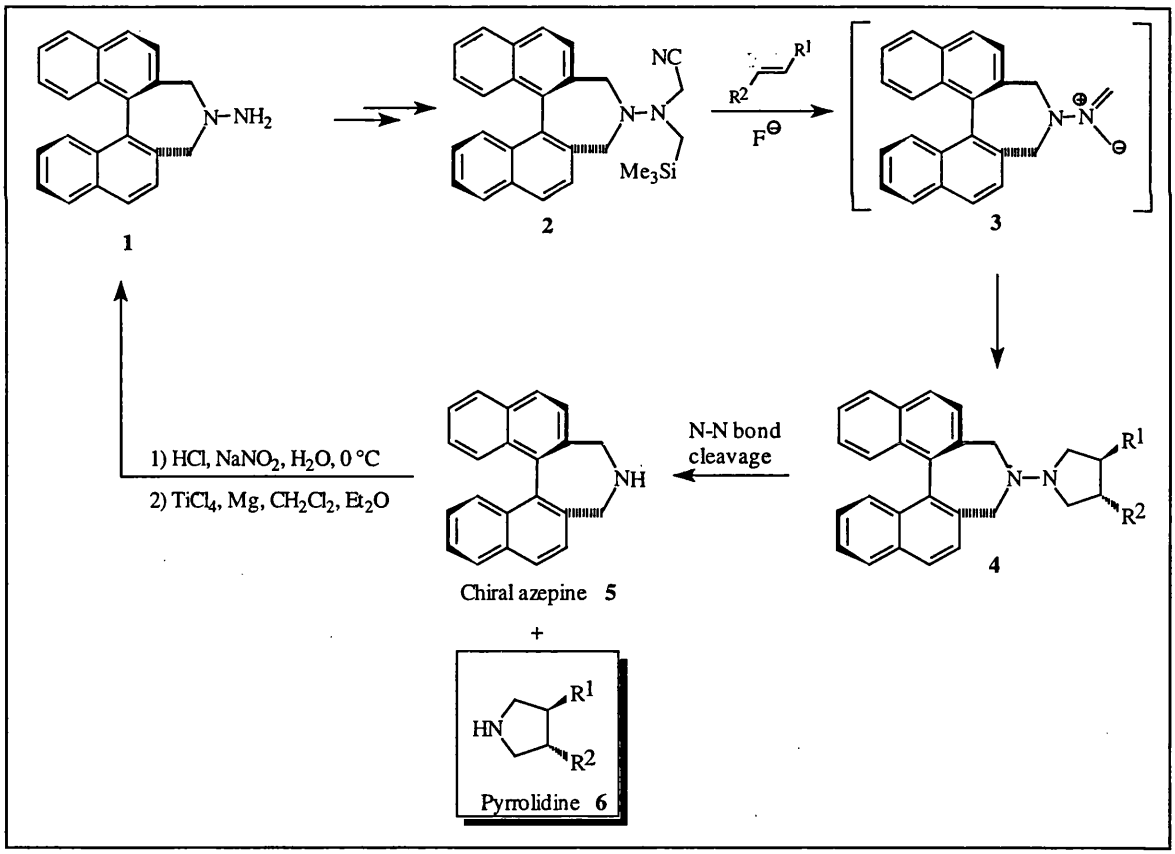
The control of stereochemistry at carbon centres adjacent to nitrogen has never been an easy task.[97] A popular strategy for this purpose, is to utilise chiral auxiliaries containing benzylic C-N bonds. These can be cleaved from the product amines by catalytic hydrogenolysis.[40] A drawback of such auxiliaries, however, is that they cannot be recovered after cleavage, which makes their use sacrificial and prohibitively expensive on an industrial scale.

One class of chiral auxiliary for nitrogen that would have the potential for recovery after use would be chiral hydrazines. Again, these should be removable from the chiral product by hydrogenolysis, but this time, it would be the N-N bond that is suffering cleavage.[98] After separation of the product from such a chiral auxiliary, the latter should be capable of being recycled by *N*-nitrosation and reduction.[99] In this project, our aim was to design, develop and evaluate a new chiral hydrazine with a view to inducing high stereocontrol in the asymmetric [3+2]-cycloadditions between non-stabilised azomethine ylides and alkenes. Our ultimate aim was to develop a new strategy for building homochiral pyrrolidine systems. Our idea is illustrated in **Scheme 1**.



Scheme 1

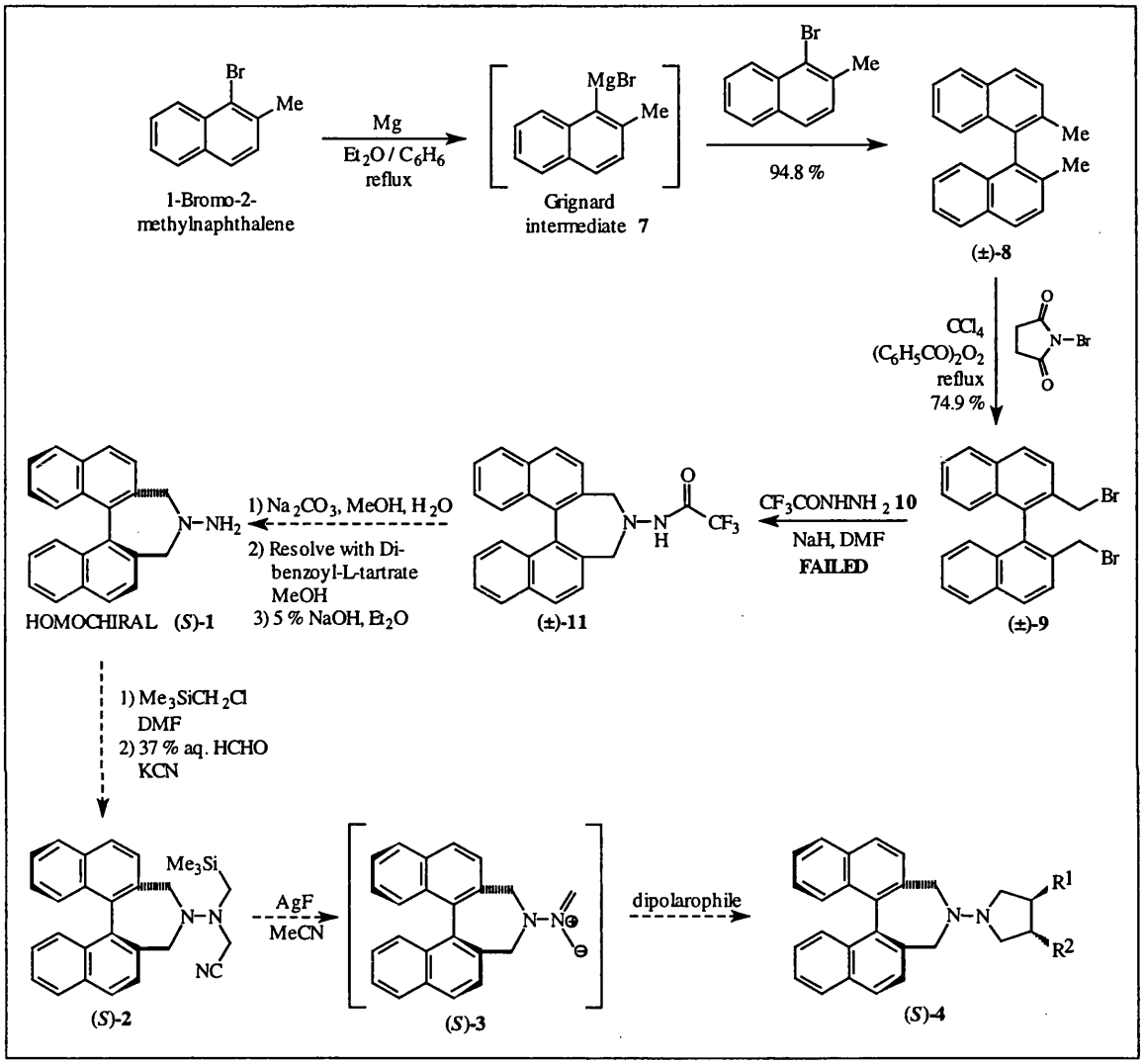
The chiral auxiliary we intended to prepare and investigate was compound **1** as indicated in **Scheme 2**.



Scheme 2

2.1 Initial preparation of cycloaddition precursor **2**

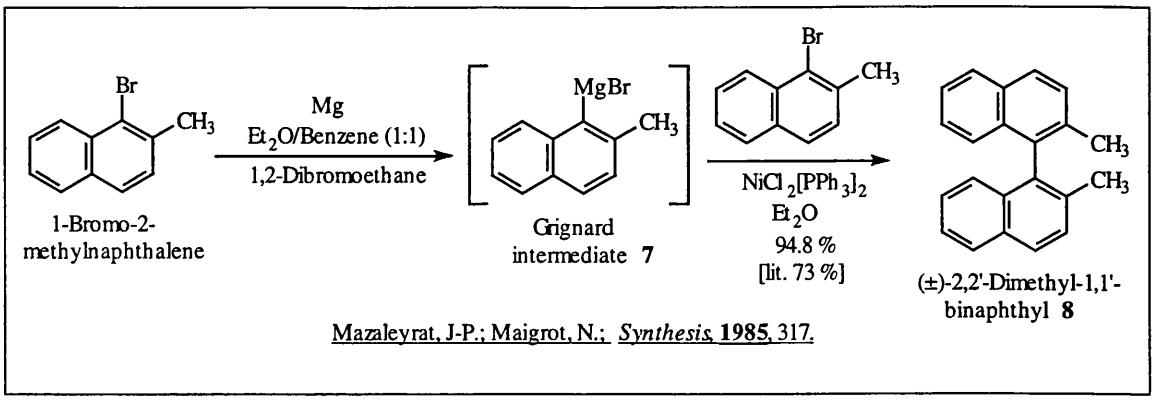
The first strategy we investigated for obtaining **1** is depicted in **Scheme 3**. It will now be discussed step by step.



Scheme 3

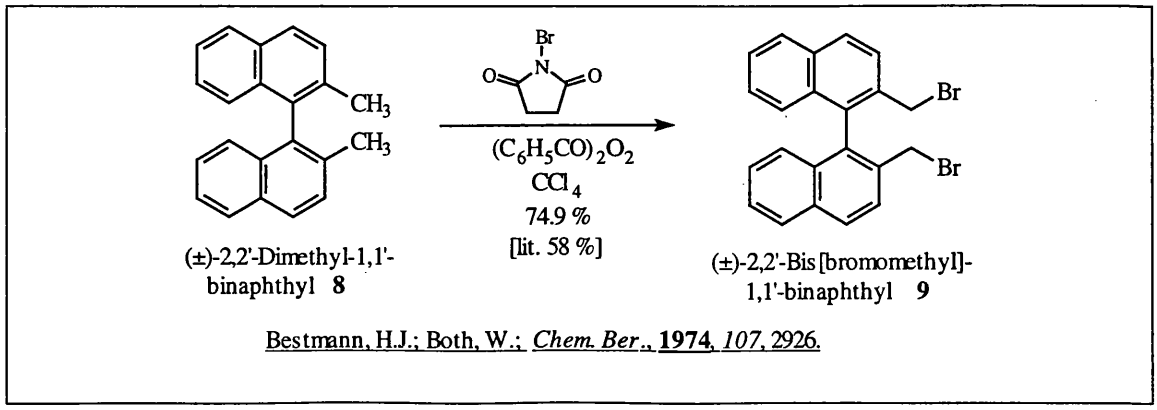
The first reaction carried out in this route was the preparation of (±)-**8**, as indicated in **Scheme 4**. For this, the procedure of Mazaleyrat *et al.*[100] was followed. This used the Grignard intermediate (±)-**7** for a Ni(0)-catalysed cross-coupling reaction with 1-bromo-2-methylnaphthalene. Bis[triphenylphosphine] dichloronickel was the catalyst of choice, it yielding (±)-**8** as a clear oil in yields up to 94.8 %. The 400 MHz ^{1}H n.m.r. spectrum of (±)-**8** in $CDCl_3$ showed the two methyl groups as a singlet at δ 2.15. These groups also gave rise to a single peak at δ 20.0 in the 100 MHz ^{13}C n.m.r.

spectrum in $CDCl_3$. The mass spectrum (HRMS, FAB, MNOBA matrix) showed the correct $(M+H)^+$ peak at *m/e* 283.1487 indicating an empirical formula of $C_{22}H_{19}$.



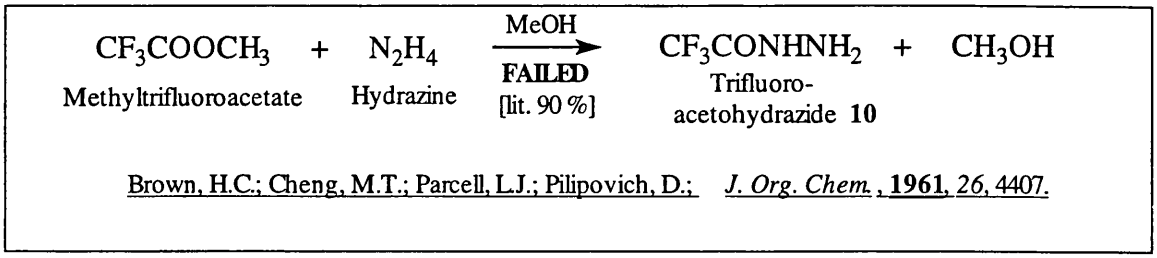
Scheme 4

Dibromide (±)-**9** had previously been prepared from **8** by Bestmann *et al.*[101] by refluxing it with *N*-bromosuccinimide in carbon tetrachloride (**Scheme 5**). Benzoyl peroxide was used as the initiator for this reaction. The crude (±)-2,2'-bis[bromomethyl]-1,1'-binaphthyl **9** was obtained as a yellow solid in 75 % yield. It was sufficiently pure for use in subsequent reactions. The 400 MHz ^1H n.m.r. spectrum of crude **9** in $CDCl_3$ indicated that the correct compound had been prepared. Its four benzylic protons were seen as a singlet at δ 4.30. This was a shift of 2.15 ppm downfield from that of the dimethyl compound (±)-**8**. Such an effect would be expected for **9** due to the electron-withdrawing effect of the two bromide groups. The same effect was seen in the 100 MHz ^{13}C n.m.r. spectrum of **9** which showed a singlet for the two methine groups at δ 32.6. These carbons had been shifted downfield by 12.6 ppm by bromination. The HRMS (FAB, NMOBA matrix) mass spectrum also backed up our assignment by showing an M^+ ion at *m/e* 439.9598 which corresponded to a empirical formula of $C_{22}H_{16}{}^{79}Br_2$.



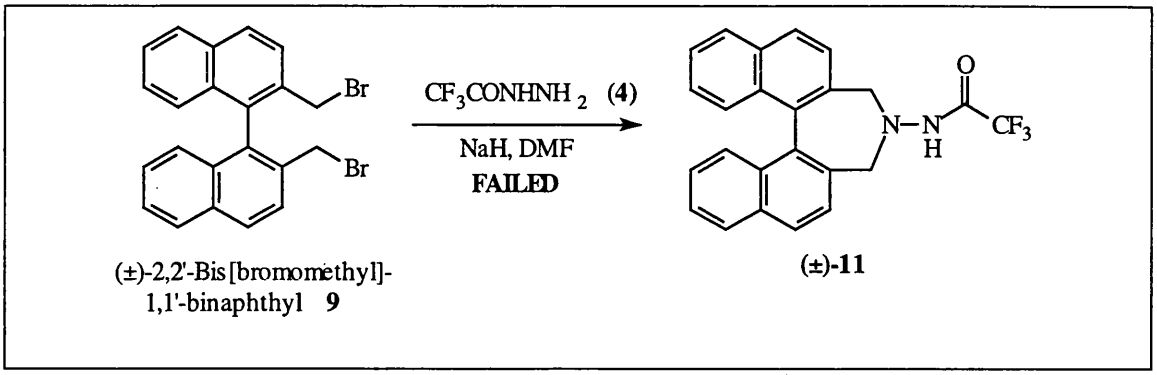
Scheme 5

To prepare hydrazine derivative (±)-**11**, we needed to make trifluoroacetylhydrazide **10**. Its synthesis had been described previously by Pilipovich and Parcell *et al.*[102] and involved reacting methyl trifluoroacetate with hydrazine in methanol as indicated in **Scheme 6**.



Scheme 6

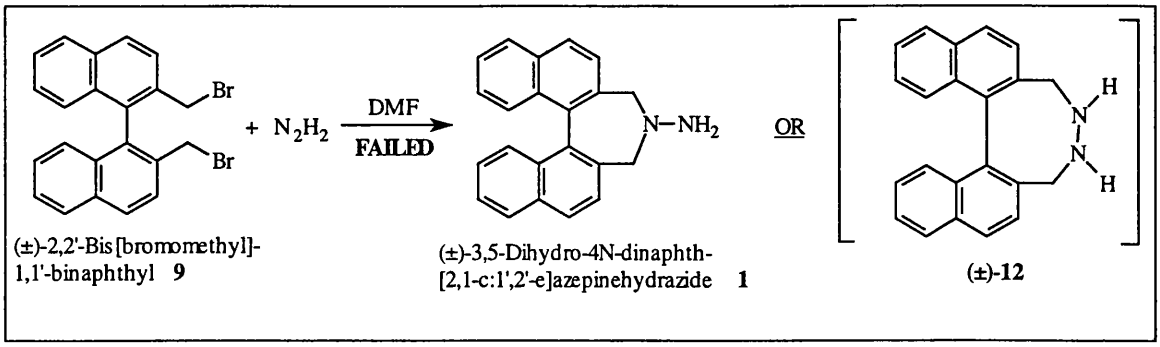
The preparation of **10** was carried out under nitrogen and the purification of the resulting white solid attempted by sublimation. This was, however, unsuccessful. The crude compound was therefore recrystallised from diethyl ether to obtain a white powdery solid in 86 % yield. A small sample of this crude material was reacted with the dibromide (±)-**9** and sodium hydride in DMF in an attempt to prepare the cyclised product (±)-**11** as indicated in **Scheme 7**. 400 MHz ^{1}H n.m.r. analysis of the product indicated that **11** could not be obtained and this route was therefore abandoned. Mass spectroscopy further indicated that the reaction for the preparation of **10** had been unsuccessful.



Scheme 7

A slightly different method for the preparation of the 1,1-substituted hydrazine derivative (±)-**1** was therefore investigated as indicated in **Scheme 8**. This entailed reaction of the dibromide (±)-**9** with hydrazine in DMF in order to give the 7-membered

ring system of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1**. However, no reaction was observed.



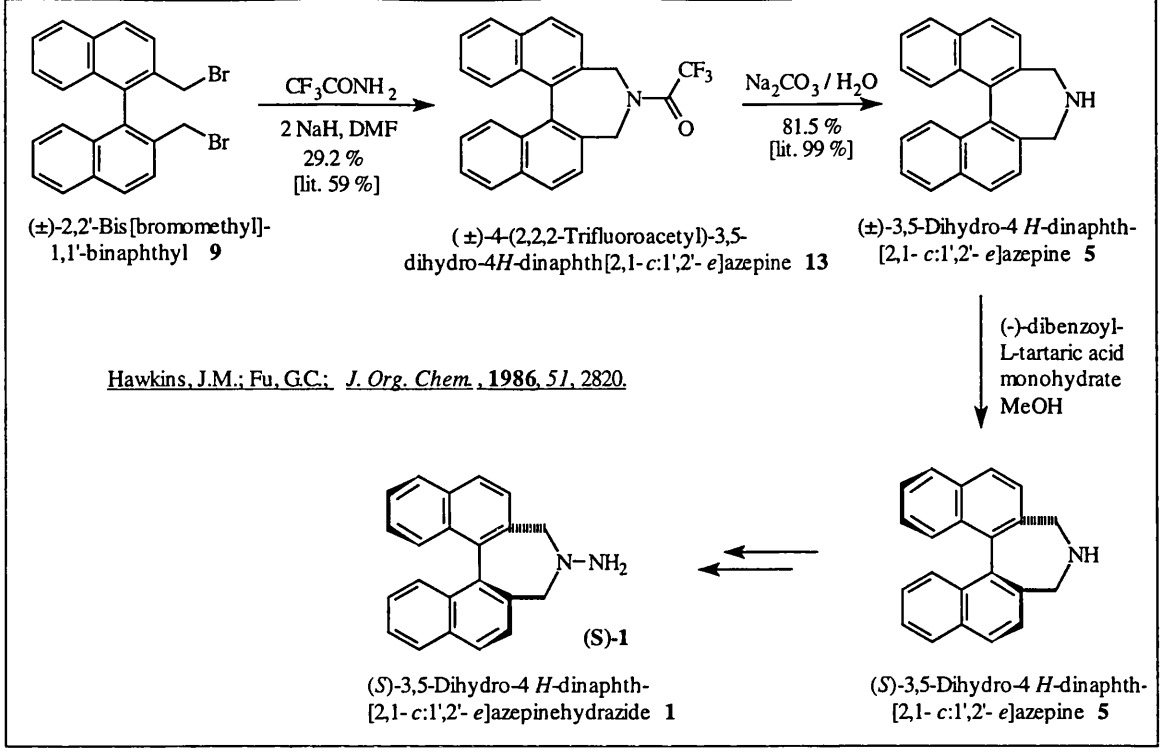
Scheme 8

2.2 Alternative preparation towards the cycloaddition precursor **2**

Due to the difficulties and failures encountered in the above reactions we decided to focus upon the preparation of hydrazine **1** from **5**.

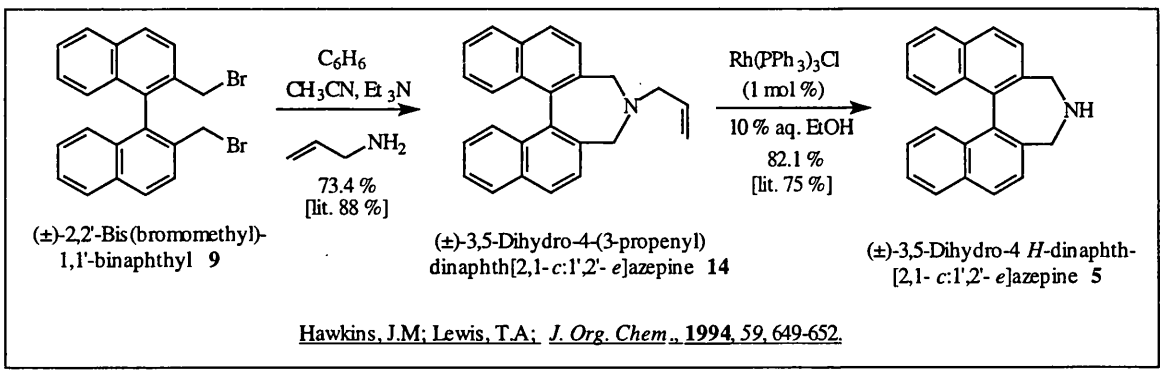
2.2.1 Preparation of hydrazine **1**

The approach by Hawkins *et al.*[103] was adopted. It was decided to prepare the 7-membered cyclic amine, (±)-4-(2,2,2-trifluoroacetyl)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **13** according to this method, by reacting the dibromide (±)-**9** with 2,2,2-trifluoroacetamide. This was then to be reacted with sodium carbonate in water to yield (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** which would furnish both enantiomers after resolution from dibenzoyltartaric acid monohydrate in MeOH (**Scheme 9**). The homochiral free amine, (***S***)- or (***R***)-**5** would then be converted to the hydrazine (±)-**1** via nitrosation and reduction.



Scheme 9

The initial step, the preparation of (±)-**13**, was successfully carried out, but in much lower yield than that reported (max. 29.2 %). Repeated reactions did not increase the yields. However, the procedure was continued, and (±)-**5** was prepared in high yield (82 %) by treatment with aqueous base. An improved preparation of amine **5** was later found, again by Hawkins *et al.*[104] which appeared applicable to the larger scale preparation of (±)-**5**. This method is outlined in **Scheme 10**.



Scheme 10

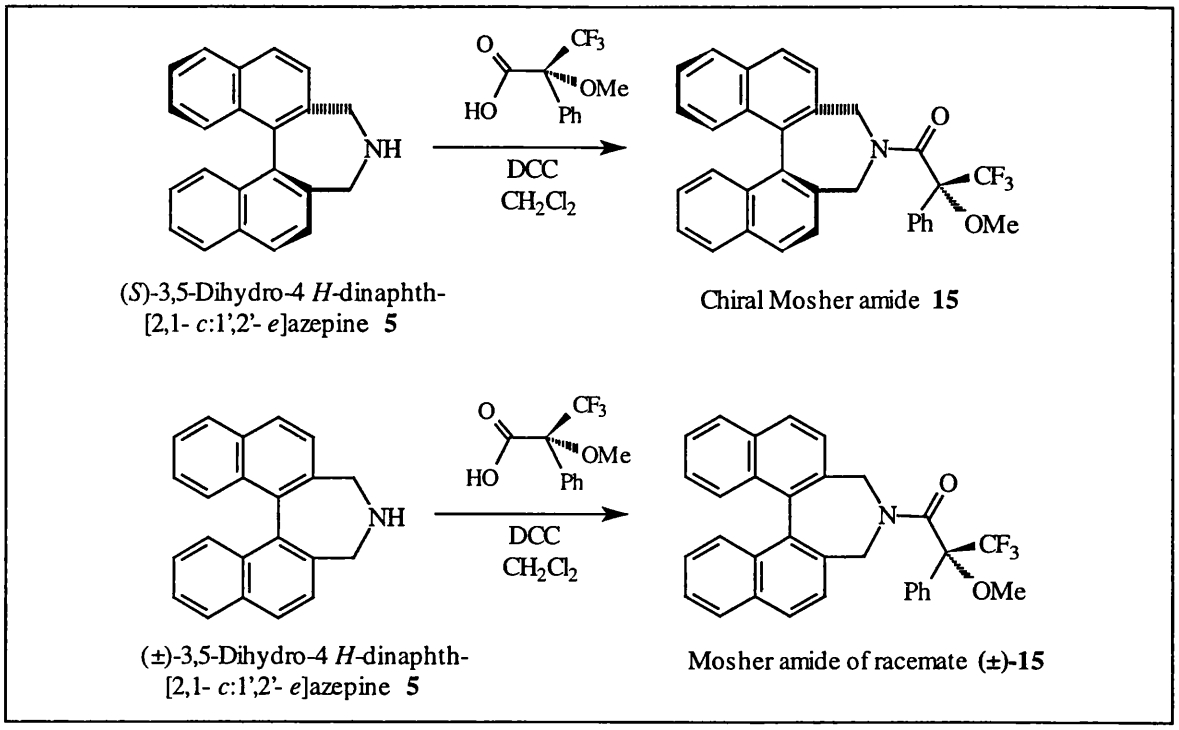
The initial step entailed slowly adding a solution of allylamine in acetonitrile to a stirred solution of dibromide (±)-**9** in warm benzene, triethylamine, and acetonitrile under nitrogen. After work-up, a crude brown product was obtained as a foam, which was purified by flash chromatography, eluting with hexanes:EtOAc (5:1). This afforded

the propenyl compound (±)-**14** as a yellow-brown solid in 73 % yield. The HRMS of (±)-**14** (FAB, MNOBA matrix) contained a molecular ion at *m/e* 336.1752 which indicated an empirical formula of $C_{25}H_{22}N$. The two sets of benzylic protons resonated as doublets at δ 3.21 (J_{HH} = 12.4 Hz) and δ 3.78 (J_{HH} = 12.4 Hz). The allylic methylenes resonated as a triplet at δ 3.16 (J_{HH} = 7.0 Hz). The terminal alkene protons appeared as a multiplet at δ 5.25-5.33, while the -CH= proton resonated as a multiplet further downfield between δ 6.00-6.10.

Compound (±)-**14** was then heated in 10 % aqueous ethanol to dissolve the amine and prior to reflux temperature, a catalytic amount (1 mol %) of tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) was added. This mixture was then heated at reflux. The reaction was driven to completion by the continuous azeotropic removal of propanal. After removal of the solvents and crystallisation from toluene:hexanes, compound (±)-**5** was isolated in 82 % yield. The 400 MHz ^{1}H n.m.r. spectrum of **5** in $CDCl_3$ showed the presence of the two benzylic -CH_2- groups as doublets at δ 3.53 (J_{HH} = 12.4 Hz) and δ 3.85 (J_{HH} = 12.4 Hz). The -NH- group was observed as a broad singlet at ca. δ 2.1. The 100 MHz ^{13}C n.m.r. spectrum of (±)-**5** in $CDCl_3$ also contained all the aromatic carbon peaks (four quaternary and six non-quaternary peaks), as well as the two -CH_2- groups next to the aromatic rings. The latter gave rise to a single resonance at δ 48.7.

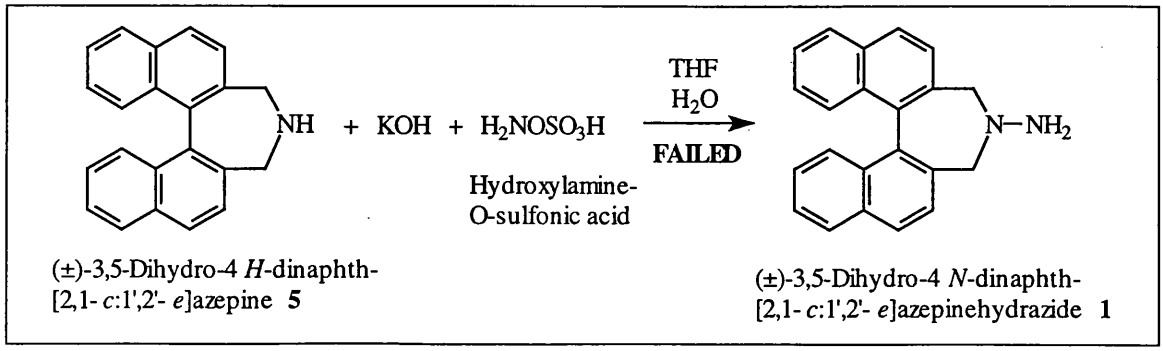
The resolution of (±)-**5** was successfully carried out according to the procedure reported by Hawkins *et al.*[103] A solution of the racemic mixture of (±)-**5** in MeOH was slowly added to a solution of (-)-dibenzoyl-L-tartaric acid monohydrate in MeOH at room temperature. The needles formed over approx. 3 days at -20 °. Treatment of a solution of the needles in Et_2O with a 5 % aqueous NaOH solution gave (*S*)-**5** as a white solidified foam. The formation of Mosher amide (*S*)-**15** was then investigated. The latter was obtained by reacting the Mosher acid, (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, with the azepine (*S*)-**5** and DCC in CH_2Cl_2. The 400 MHz ^{1}H n.m.r. spectrum of the isolated Mosher amide (*S*)-**15** indicated an e.e. of 100 % by comparison with the 400 MHz ^{1}H n.m.r. spectrum Mosher amide of the racemate (±)-**15** (**Scheme 11**). The atmospheric pressure chemical ionisation of (*S*)-**15** also gave the required $(M+H)^+$ mass of *m/e* 512.3 giving an empirical formula of $C_{32}H_{24}F_3NO_2$.

The corresponding (*R*)-**5** isomer was obtained after concentrating the mother liquor and performing a similar aqueous base treatment, as for the (*S*)-**5** isomer.



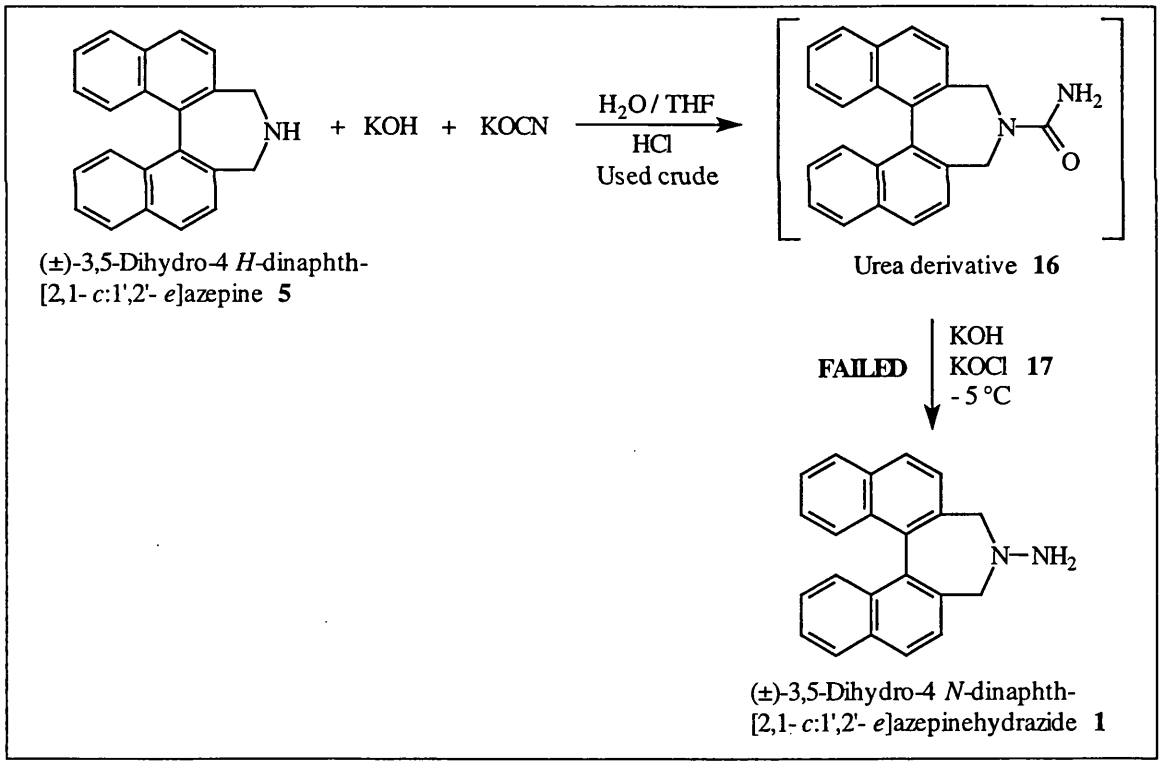
Scheme 11

Having demonstrated that the Hawkins resolution was successful, we next elected to evaluate the subsequent chemistry with racemic (±)-**1**. Once this chemistry had been figured out, the chiral compound would be brought forward in order to evaluate the level of stereocontrol this auxiliary could exert in the azomethine ylide cycloaddition reactions. However, at this point problems were encountered. The formation of the N-N bond when preparing (±)-**1** from the azepine (±)-**5** proved rather problematic. One method investigated utilised hydroxylamine-*O*-sulfonic acid [106] as indicated in **Scheme 12**. The reaction was carried out on a moderate scale (100 mg), but afforded an extremely low yield (7 mg) of suspected product (±)-**1**.



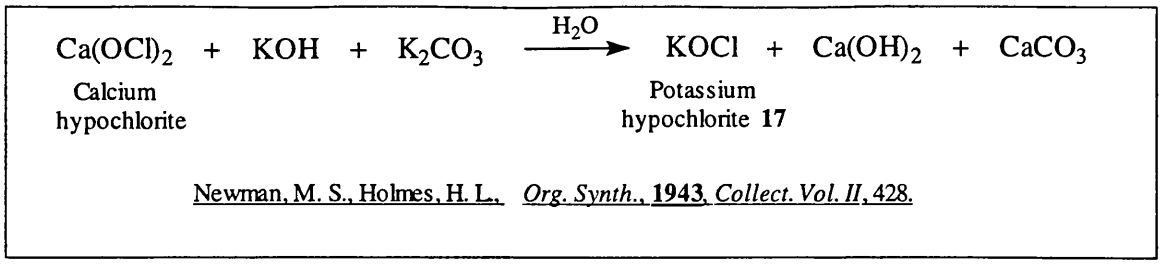
Scheme 12

Another protocol evaluated for preparing the hydrazine (±)-**1** utilised a method introduced by Enders *et al.*[106] This involved preparing the crude urea derivative (±)-**16** (**Scheme 13**). Thus, the azepine (±)-**5** was dissolved in water containing a small volume of THF in order to ensure solubilization, and potassium cyanate was then added in the presence of potassium hydroxide. The resulting crude urea (±)-**16** was then reacted *in situ* with more potassium hydroxide and a freshly prepared solution of potassium hypochlorite **17** of known molarity.[107] The resulting product was then decarboxylated by the addition of hydrochloric acid, and the product isolated as a yellow foam. Flash chromatography in hexanes and ethyl acetate afforded only 189 mg (approx. 19 % overall yield) of a white crystalline solid that was initially suspected to be (±)-**1**. The mass spectrum (HRMS) of this material, however, gave rise to a molecular ion that had the incorrect molecular mass. The 400 MHz ^{1}H n.m.r. spectrum of this product also showed that the reaction had been unsuccessful. As a result, the method was abandoned at this stage.



Scheme 13

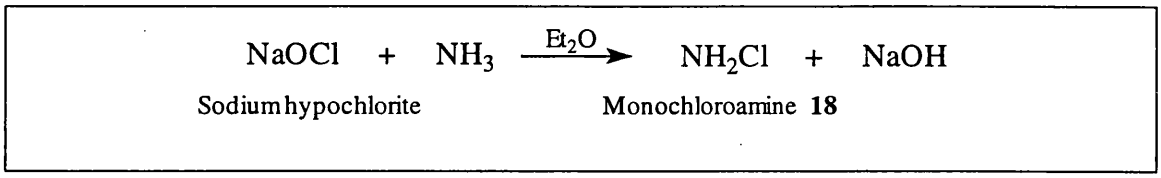
The optimised preparation of the aqueous potassium hypochlorite solution **17** is a modification of an Organic Synthesis procedure.[108] The general reaction is shown in **Scheme 14**.



Newman, M. S., Holmes, H. L., *Org. Synth.*, **1943**, *Collect. Vol. II*, 428.

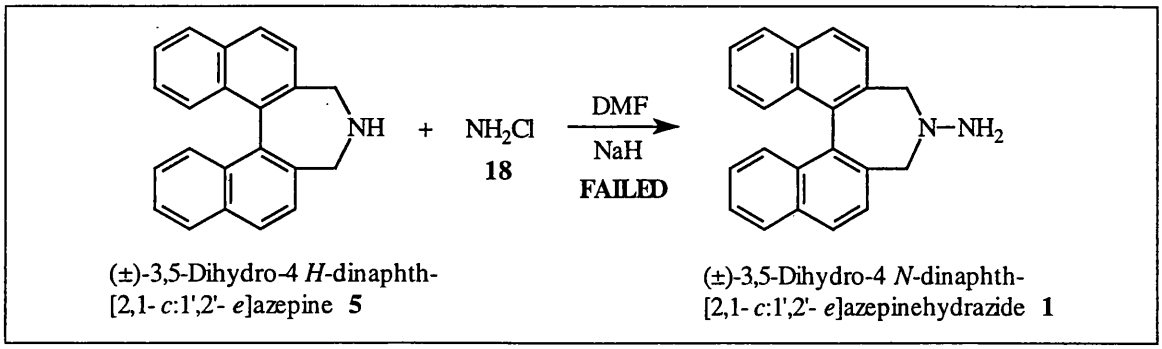
Scheme 14

Monochloramine has also previously been used to prepare hydrazine derivatives [109,110,] in reasonable to excellent yield, and it therefore seemed like a reagent worth evaluating for the N-N bond formation. An ethereal solution of monochloramine **18** was prepared by reacting sodium hypochlorite, NaOCl, with an equimolar solution of ammonia (**Scheme 15**).[109] The product **18** was extracted into ether and the molarity of the solution determined by iodometric titration (1 ml 0.1 N $Na_2S_2O_3$ = 2.57 mg NH_2Cl).



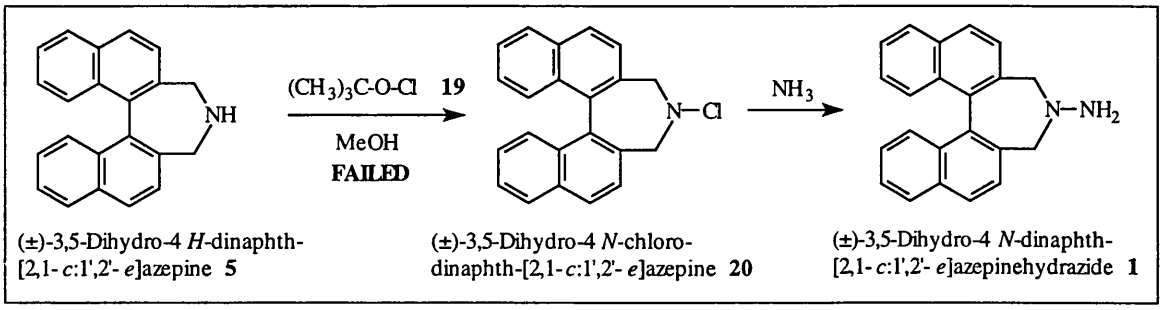
Scheme 15

The monochloramine solution was then reacted with the azepine (±)-**5** in the presence of sodium hydride in DMF as indicated in **Scheme 16**.[110] Flash chromatography of the crude residue obtained by aqueous work-up afforded a yellow clear oil in a mere 8 % yield. The 400 MHz ^1H n.m.r. spectrum of this product showed it to be the wrong compound and this method was therefore abandoned.



Scheme 16

Another tactic for obtaining (±)-**1** attempted the preparation of the *N*-chloro derivative (±)-**20** from (±)-**5**; the method of Altenkirk *et al.*[111] was followed. Compound **20** would then be reacted with ammonia to yield the required hydrazine derivative (±)-**1** as indicated in **Scheme 17**.



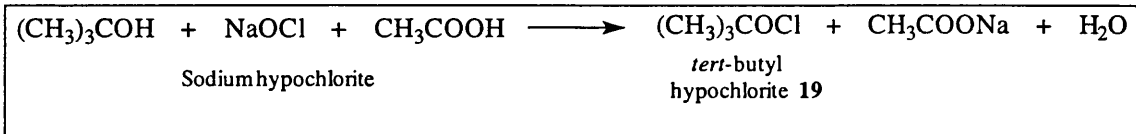
(±)-3,5-Dihydro-4 *H*-dinaphth-[2,1-*c*:1',2'-*e*]azepine **5**

(±)-3,5-Dihydro-4 *N*-chloro-dinaphth-[2,1-*c*:1',2'-*e*]azepine **20**

(±)-3,5-Dihydro-4 *N*-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **1**

Scheme 17

The initial step, the preparation of (±)-**20**, utilised *tert*-butyl hypochlorite **19** as the chlorinating agent. This was prepared according to Mintz *et al.*[112] as shown below.

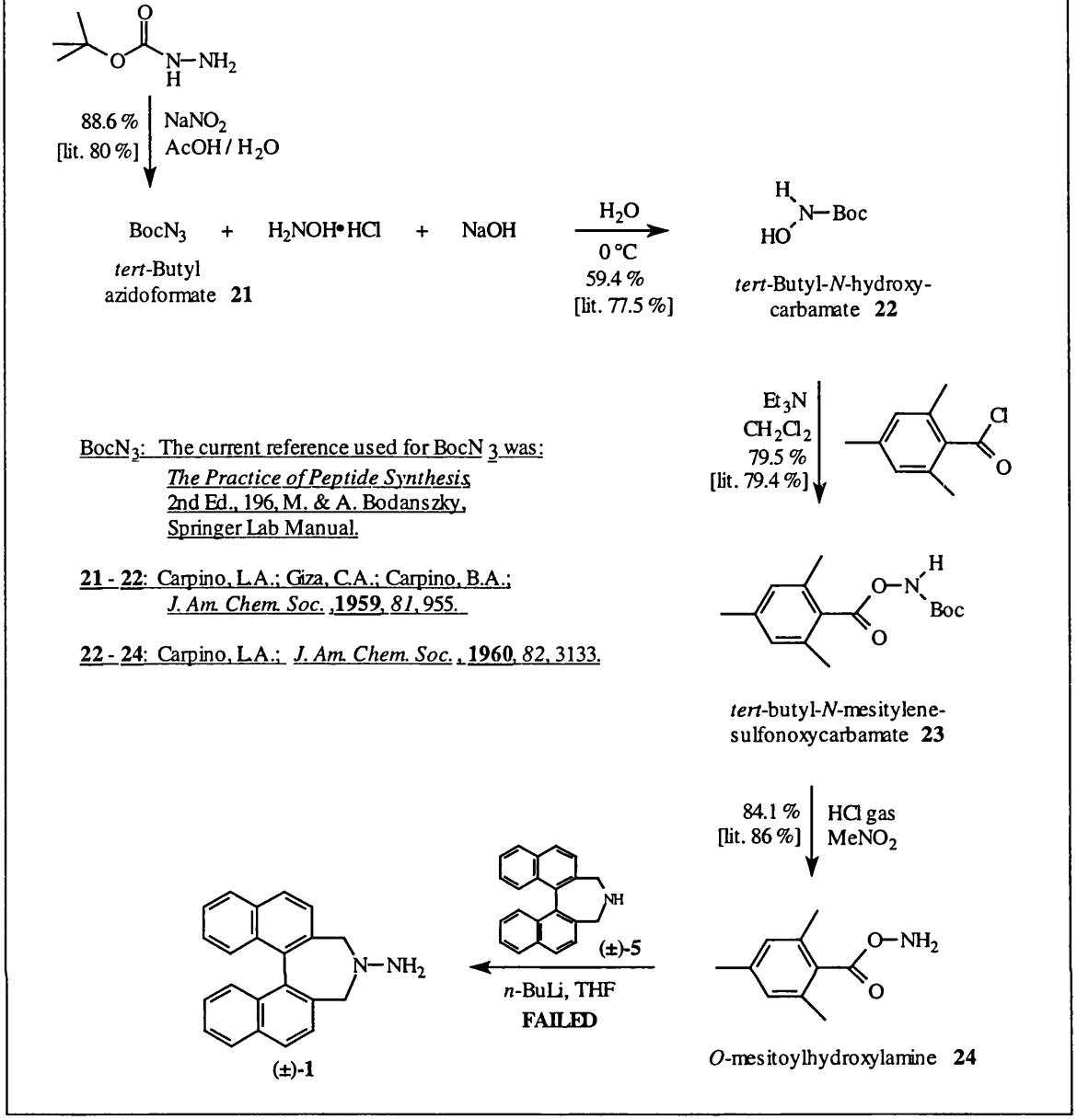


Mintz, M.J.; Walling, C.; *Org. Synth.*, **Vol. 49**, 9.

Scheme 18

The *tert*-butyl hypochlorite solution was reacted with (±)-**5** dissolved in methanol and the crude yellow product (220 mg, 99 %) isolated. The 400 MHz ^{1}H n.m.r. spectrum of this product indicated that the peaks for the two -CH_2- groups in (±)-**20** were absent. As a result, this approach was not investigated further.

Another method investigated for the preparation of hydrazine **1** entailed reacting its lithio derivative with amine **24** (**Scheme 19**).



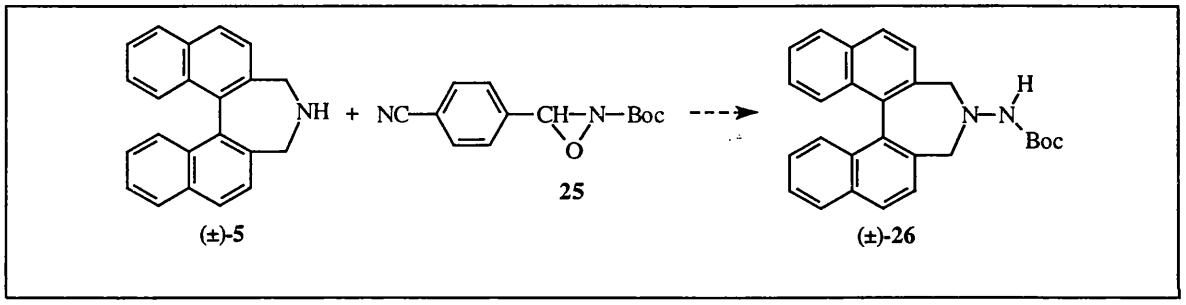
Scheme 19

The preparation of **24** required four steps. The initial step was the preparation of *tert*-butyl azidoformate **21**, following a procedure reported by Carpino *et al.*[113] Sodium nitrite was slowly added at 0 °C to a solution of *tert*-butyl carbazate in a mixture of acetic acid and water. Work-up afforded the required $BocN_3$ as a yellow oil in 89 % yield which was used without purification. The 400 MHz ^1H n.m.r. spectrum of the crude product showed the *tert*-butyl methyl protons as a singlet at δ 1.52 and the 100 MHz ^{13}C n.m.r. spectrum indicated these at δ 27.6. The quaternary *tert*-butyl carbon appeared at δ 84.6 while the carbonyl group was found at δ 155.7. As a final proof, the I.R. spectrum revealed a characteristic $-N_3$ peak at 2133 cm^{-1} as well as the C=O stretch at 1730 cm^{-1}. The next step, the preparation of *tert*-butyl *N*-hydroxycarbamate **22**, also worked well.[113] The *tert*-butyl azidoformate **21** was added to a cold solution of

hydroxylamine hydrochloride in water. To this mixture was then slowly added a cold solution of NaOH and the mixture stirred for 60 min. After work-up, the required compound crystallised under a vacuum in 59 % yield. The 400 MHz ^{1}H n.m.r. spectrum indicated the correct compound had been formed with the *tert*-butyl methyl protons giving rise to a singlet at δ 1.37 and the -NH and -OH overlapping as a broad singlet at δ 7.58. The 100 MHz ^{13}C n.m.r. spectrum showed the *tert*-butyl methyl groups were present at δ 28.0 while the quaternary *tert*-butyl carbon appeared at δ 81.7, with the carbonyl group being located at δ 158.8. Finally, the HRMS mass spectrum showed the correct $(M+H)^+$ ion for $C_5H_{12}NO_3$ at *m/e* 134.0817. The desired amine **24** had also previously been prepared by Carpino [114] and the next two steps again proceeded in good yield. To a mixture of **22** and Et_3N in CH_2Cl_2 at 0-4 °C was added a solution of mesitoyl chloride in CH_2Cl_2. After work-up a yellow/brown oil was obtained which crystallised after standing. Recrystallisation from hexane furnished the required secondary amine **23** as block-like yellow crystals in 79 % yield. The 400 MHz ^{1}H n.m.r. spectrum indicated the correct compound had been formed with the *tert*-butyl methyl protons giving rise to a singlet at δ 1.51. The two *ortho* methyl groups resonated as a singlet at δ 2.35 while the *para* substituted methyl group appeared as a singlet at δ 2.26. The remaining two protons on the aromatic ring gave a singlet at δ 6.85. The 100 MHz ^{13}C n.m.r. spectrum indicated the presence of two C=O groups at δ 155.6 and δ 169.1 which again corroborated the proposed structure. The I.R. spectrum also showed two sharp peaks at 1774 cm^{-1} and 1728 cm^{-1}, corresponding to the two C=O stretching absorptions for the compound. The HRMS mass spectrum also gave the correct $(M+H)^+$ ion at *m/e* 280.1549 which indicated an empirical formula of $C_{15}H_{22}NO_4$. The Boc group was removed by passing a stream of anhydrous HCl through a solution of *tert*-butyl *N*-mesitylenesulfonoxycarbamate **23** in $MeNO_2$ with stirring. The solution was left to stand, and after work-up, a colourless oil was obtained in 84 % yield. This oil solidified on standing at room temperature. The 400 MHz ^{1}H n.m.r. spectrum showed the absence of the Boc group. The two *ortho* methyl groups now gave rise to a singlet at δ 2.29 with the *para* substituted methyl group appearing at δ 2.26. The remaining protons on the aromatic ring again appeared as a singlet at δ 6.80. The 100 MHz ^{13}C n.m.r. spectrum now only showed the presence of one C=O group at δ 176.0. The HRMS mass spectrum also contained a peak with the correct $(M-ONH_2)^+$ mass of $C_{10}H_{11}O$ at *m/e* 147.0810. The preparation of (±)-**1** was then attempted using this freshly prepared compound. To a solution of (±)-**5** in THF was added dropwise *n*-BuLi

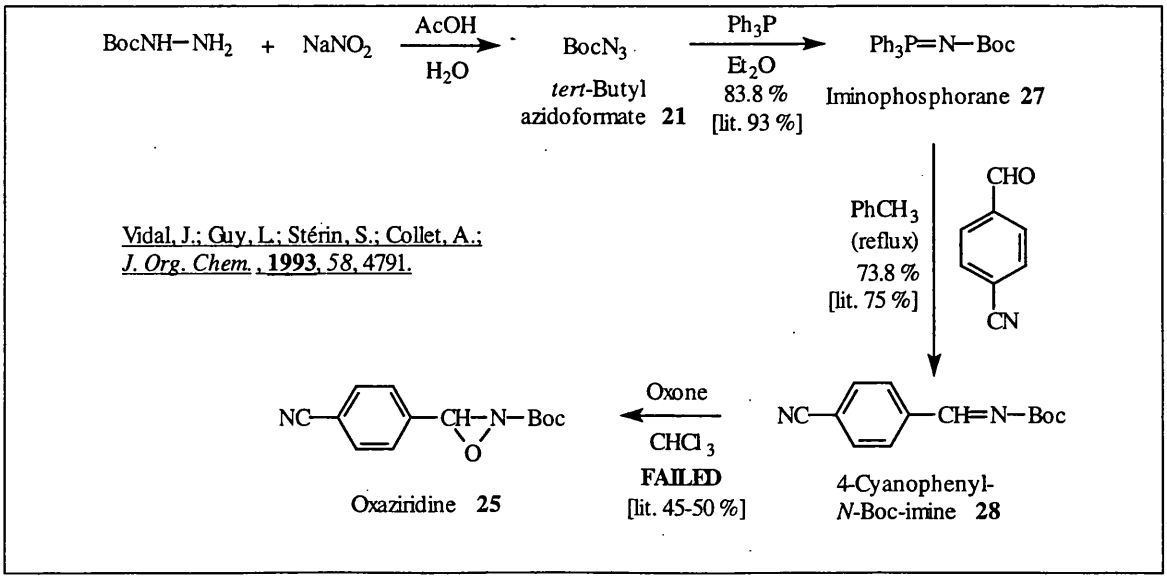
at -78 °C. The solution was stirred for 15 min. before a solution of *O*-mesitoylhydroxylamine **24** in THF was added. However, at -78 °C, no reaction was observed. Warming the reaction mixture to room temperature had no effect, and so the method was abandoned.

Recently, there has been a significant amount of interest in electrophilic aminations with oxaziridines.[115] Electrophilic amination is an important synthetic process,[116-120] and from a practical point of view, the development of new reagents that allow the direct transfer of a *N*-protected group to nucleophilic centres is of great practical interest. Thus, after it was reported that oxaziridine **25** [115] transfers its *N*-Boc fragment to a variety of N- and C-nucleophiles under very mild conditions, we decided to apply this reagent to our azepine (±)-**5** with the hope that the required target hydrazine (±)-**1** would also be prepared in this manner (**Scheme 20**).



Scheme 20

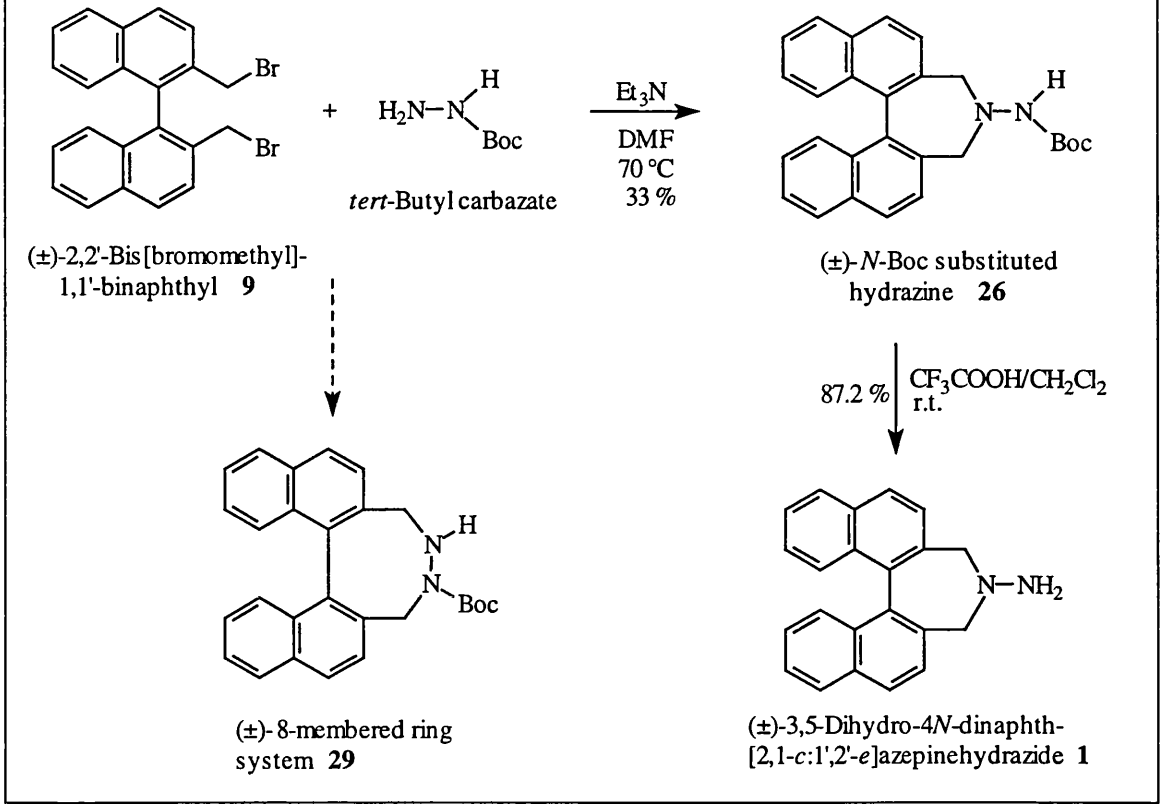
The general pathway for preparing oxaziridine **25** is depicted in **Scheme 21.**



Scheme 21

tert-Butyl azidoformate **21** was converted (**Scheme 19**) into iminophosphorane **27** by the reaction with triphenylphosphine in Et_2O at room temperature.[115] A high yield (84 %) of pure white crystals was obtained after 30 min. The ^1H and ^{13}C n.m.r. spectra both showed the product to be pure. This was further reinforced by the I.R. spectrum which showed the expected C=O stretch at 1621 cm^{-1} as well as the HRMS mass spectrum which gave the required $(M+H)^+$ mass of *m/e* 378.1623 corresponding to an empirical formula of $C_{23}H_{25}NO_2P$. The 4-cyanophenyl-*N*-Boc-imine **28** was prepared by refluxing **27** with 4-cyanobenzaldehyde in toluene overnight. After removal of triphenylphosphine oxide and rapid flash chromatography in Et_2O:hexanes, the required *N*-Boc-imine **28** was isolated in 74 % yield. The 400 MHz ^1H n.m.r. spectrum showed the *tert*-butyl methyl groups at δ 1.60 with the two aromatic protons each giving rise to a doublet - one at δ 7.77 (J_{HH} 8.4 Hz) and the other at δ 8.01 ppm (J_{HH} 8.4 Hz). The remaining -CH=N proton was found as a singlet at δ 8.83. The HRMS also showed the correct $(M+H)^+$ ion at *m/e* 231.1134 which corresponded to an empirical formula of $C_{13}H_{15}N_2O_2$. The oxidation of this compound was attempted with K_2CO_3 and Oxone in H_2O. However, the required compound was not isolated. It may have decomposed during the flash chromatography process as part of its purification or simply not have been formed in the reaction mixture. No further attempts were made to prepare this compound since we had now thought of a more expedient route to (±)-**26**, which involved only one reaction between (±)-**9** and *tert*-butyl carbazate, which thereby reduced the total number of steps that would now be required.

This new method for the preparation of (±)-**26** entailed reacting *tert*-butyl carbazate with dibromide (±)-**9** [121-123], in the presence of triethylamine in DMF. The resultant Boc protected hydrazine derivative (±)-**26** would then be deprotected to furnish the required hydrazine (±)-1 (**Scheme 22**).

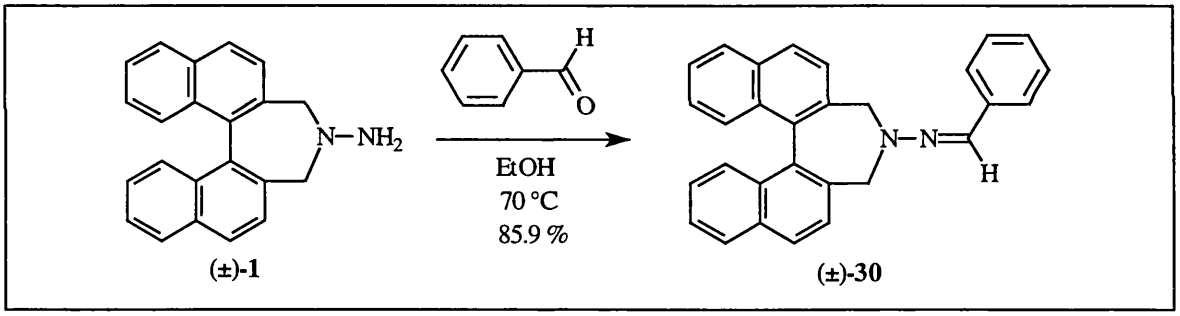


Scheme 22

When a solution of *tert*-butyl carbazate in dry DMF containing triethylamine was stirred with (±)-**9** overnight, conventional work-up afforded a pure white powder after recrystallisation from Et_2O in only 33 % yield. Repeated variations of the reaction did not increase the yield significantly. The ^1H and ^{13}C n.m.r. spectra showed that the pure required product had been obtained. The HRMS mass spectrum (FAB, MNOBA matrix) revealed an $(M+H)^+$ ion at *m/e* 411.2073. Due to the symmetry of the 7-membered ring system , the two $-CH_2-$ groups next to the naphthalene rings were expected to be equivalent and give the two typical AB splitting. This was found to be the case (δ 3.44, J_{HH} 12.4 Hz; δ 3.96, J_{HH} 12.4 Hz). The 8-membered ring system **29** would not be symmetric, and had it been formed, the two $-CH_2-$ groups would therefore be expected to show rather more complex splitting patterns. The 100 MHz ^{13}C n.m.r. spectrum also showed the presence of the Boc group in (±)-**26**. The quaternary peak for the *tert*-butyl group was clearly visible at δ 80.3, as was the C=O group at δ 154.3. The remaining peaks also clearly showed the symmetry of the molecule. The two $-CH_2-$ groups next to the aromatic rings were seen as a single peak at δ 58.9, in addition to the required four quaternary and six non-quaternary aromatic peaks. Thus we believe that we have successfully prepared our hydrazine precursor (±)-**26**.

The cleavage of the Boc group was easily carried out in a 1:1 mixture of CF_3CO_3H and CH_2Cl_2. Addition of (±)-**26** to the mixture gave a clear yellow solution which, after work-up, and neutralisation with aqueous potassium carbonate, afforded the free hydrazine (±)-**1** as a white powder in 87.0 % yield after recrystallisation from Et_2O. The 400 MHz ^1H n.m.r. spectrum showed the presence of the two -CH_2- groups next to the aromatic rings as doublets at δ 3.34 (J_{HH} = 12.4 Hz) and δ 3.89 (J_{HH} = 12.4 Hz) which are rather different to the doublets shown by the azepine (±)-**5**. The -NH_2 group was also found as a very broad and flat signal at ca. δ 2.96. The 100 MHz ^{13}C n.m.r. spectrum now showed that the two -CH_2- groups next to the aromatic rings had been shifted to δ 61.6, a shift of 12.9 ppm downfield compared to the azepine (±)-**5** where they appeared at δ 48.7. The HRMS mass spectrum (FAB, MNOBA matrix) also supported our assignment, it giving the expected $(M+H)^+$ peak at *m/e* 311.1548 which was indicative of an empirical formula of $C_{22}H_{19}N_2$.

In order to confirm that the hydrazine had been formed, the hydrazone (±)-**30** from benzaldehyde was prepared. This is shown in **Scheme 23**.

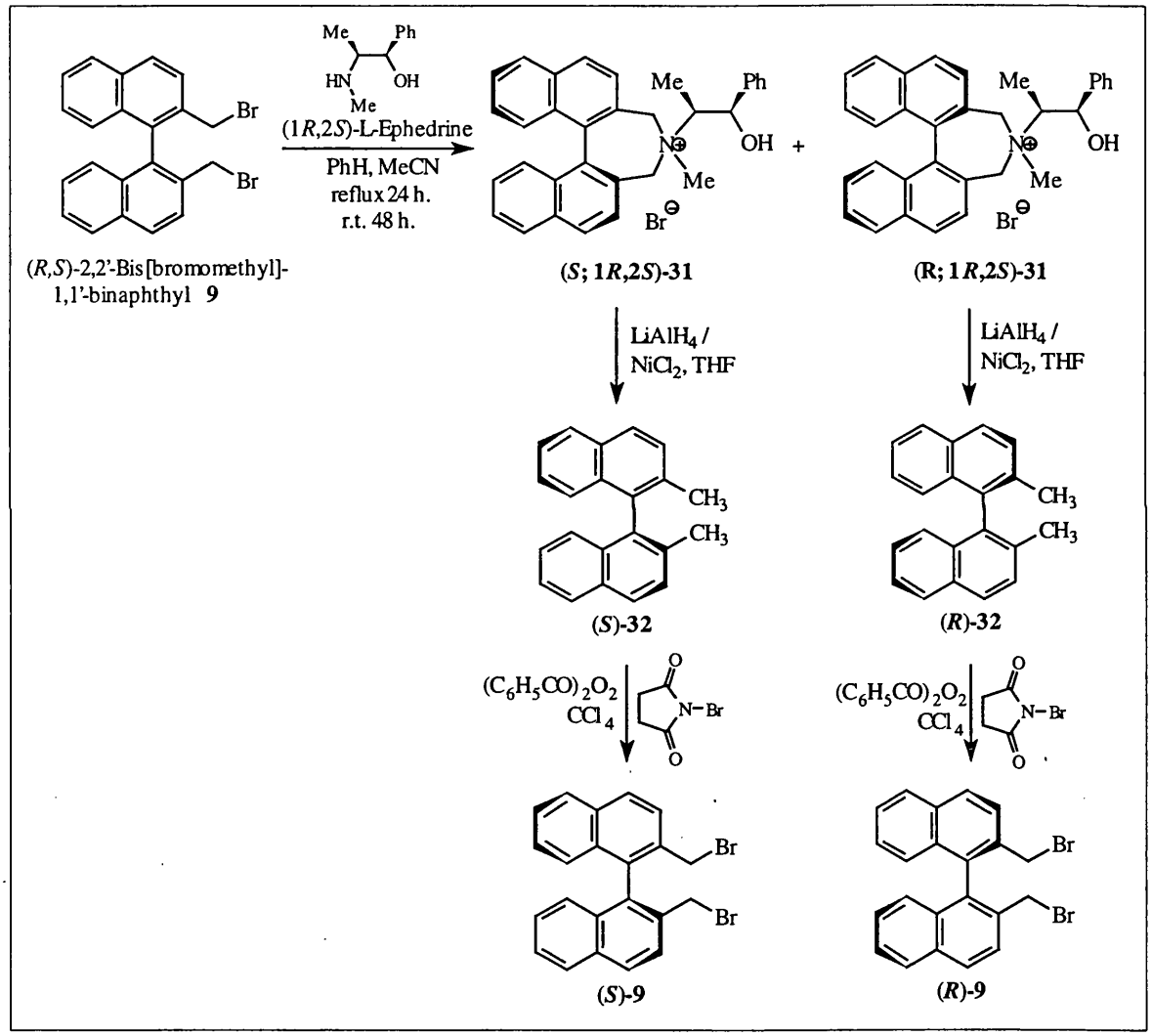


Scheme 23

Benzaldehyde was added to a mixture of (±)-**1** in EtOH and the reaction mixture stirred at 70 °C for 15 min. after which filtration of the mixture gave the required hydrazone in 86 % yield. The 400 MHz ^1H n.m.r. spectrum clearly showed that the hydrazone had been formed. The two -CH_2- groups next to the aromatic rings had now shifted downfield to δ 3.79 (doublet, J_{HH} 12.4 Hz) and δ 4.60 (doublet, J_{HH} 12.4 Hz) when compared with the hydrazine **1** (δ 3.34, 3.89). The =CH- group was observed as a singlet at δ 7.38 and the phenyl group as a multiplet in the range δ 7.20-7.34. The 100 MHz ^{13}C n.m.r. spectrum now showed the two -CH_2- groups next to the naphthyl rings at δ 56.5, which is a shift of 5.1 ppm upfield from the pure hydrazine. The remaining peaks expected were all observed. The HRMS mass spectrum (FAB, MNOBA matrix)

also showed the required (M)$^+$ ion at *m/e* 398.1783 indicating that (±)-**30** had a formula of $C_{29}H_{22}N_2$.

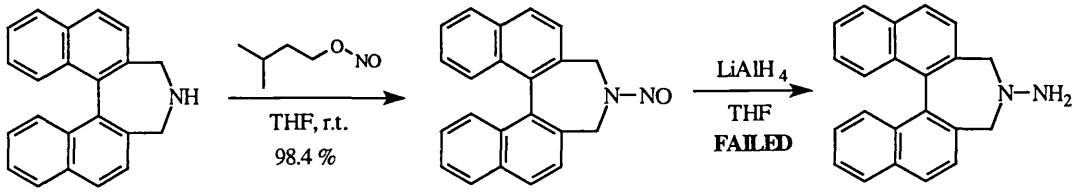
One problem associated with this method was that of separating the two enantiomers from one another. Fortunately, Mazaleyrat *et al.*[100] had provided a solution for overcoming this problem (**Scheme 24**). These workers had prepared (±)-**9** (**Scheme 5**) and resolved it with (L)-ephedrine. This led to the separable quaternary salts (***S***)-**31** and (***R***)-**31**, which after reduction with $LiAlH_4$ in the presence of $NiCl_2$ afforded enantiomerically pure (***S***)-**32** and (***R***)-**32**, as well as recovered (L)-ephedrine.



Scheme 24

However, because of the low yield encountered in the preparation of the *N*-Boc hydrazine (±)-**26** via this pathway it was decided, at this point, to attempt another method for preparing (±)-**1**. Hosono *et al.*[124] had successfully utilised isoamyl nitrite to transform a secondary amine into the corresponding *N*-nitroso compound, and had then

reduced it to the substituted hydrazine with excess $LiAlH_4$ in high yields. We believed this methodology might prove useful for the preparation of our hydrazine (±)-**1** as shown in **Scheme 25**.



(±)-3,5-Dihydro-4 *H*-dinaphth-[2,1-*c*:1',2'-*e*]azepine **5**

(±)-3,5-Dihydro-4 *N*-nitroso-dinaphth-[2,1-*c*:1',2'-*e*]azepine **33**

(±)-3,5-Dihydro-4 *N*-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **1**

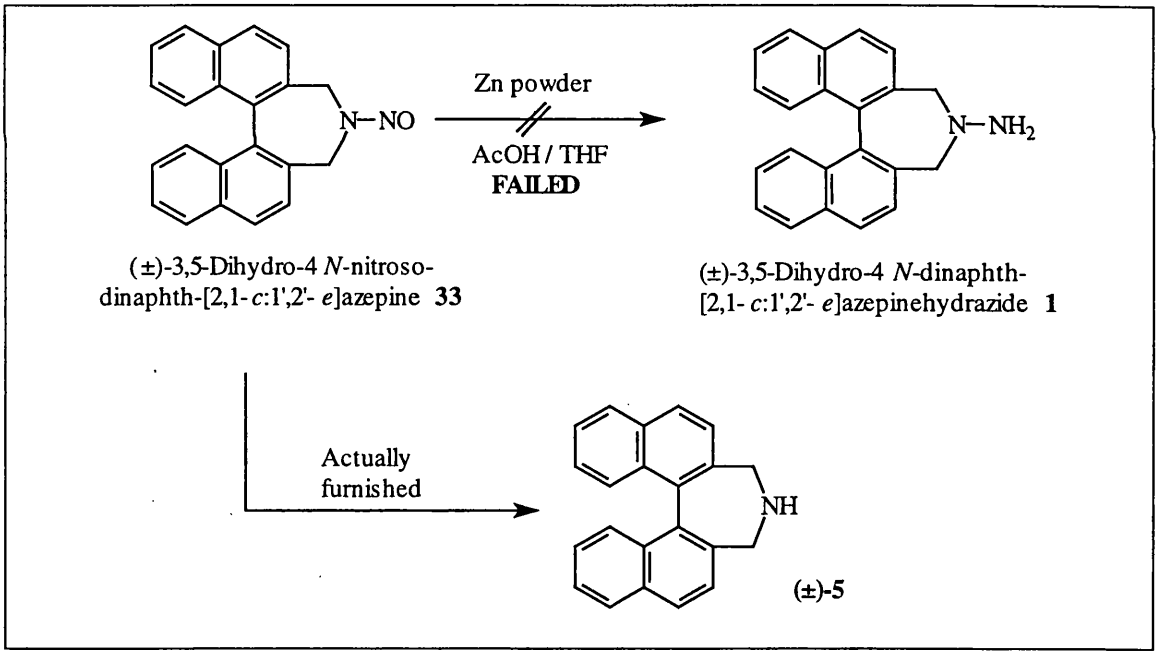
Scheme 25

The first step, the preparation of the *N*-nitroso-azepine (±)-**33**, proceeded successfully in THF with 5.2 equivalents of isoamyl nitrite in up to 98 % yields. Off white-yellow crystals were isolated after flash chromatography in a hexanes:EtOAc mixture (5:1). The 400 MHz ^{1}H n.m.r. spectrum did indeed indicate that the nitroso compound had been formed. Two doublets for the -CH_2- groups were found at δ 3.62 (J_{HH} = 14.4 Hz) and δ 4.70 (J_{HH} = 14.4 Hz). Due to the presence of the -N=O group, these two doublets each corresponded to a single proton only. The remaining two protons were found further downfield as a doublet of doublet at δ 5.66 (J_{HH} = 14.4 Hz, J_{HH} = 14.4 Hz). The remaining aromatic protons were found in the ranges δ 7.26-7.30 (2H, multiplet), δ 7.40 (2H , triplet, J_{HH} 9.4 Hz), δ 7.48-7.53 (3H, multiplet), δ 7.66 (1H, doublet, J_{HH} 8.0 Hz) and δ 7.95-8.01 (4H, multiplet). The 100 MHz ^{13}C n.m.r. spectrum also showed the unsymmetrical character of the compound. The two -CH_2- groups now appeared as a singlet each at δ 47.1 and δ 54.3. Each aromatic carbon atom was also observed, of which eight were quaternary and 12 were non-quaternary carbon peaks. This spectral evidence was also supported by the HRMS mass spectrum (FAB, MNOBA matrix) which showed the molecular mass of (±)-**33** (M^+) at *m/e* 324.1263, indicating a molecular formula of $C_{22}H_{16}N_2O$. The elemental analysis calculated for $C_{22}H_{16}N_2O$ also afforded the required result of C = 81.08; H = 5.03 and N = 5.49.

The reduction of the nitroso compound (±)-**33** was attempted by the method of Hosono *et al.*[124] Unfortunately the reaction was unsuccessful. After work-up, several products were present according to TLC analysis. Several solvent systems were investigated, but separation proved impossible via both flash chromatography and

recrystallisation. The $LiAlH_4$ reduction method was not followed further since the amount of side reactions would ultimately lead to a very low and unacceptable yield of required product.

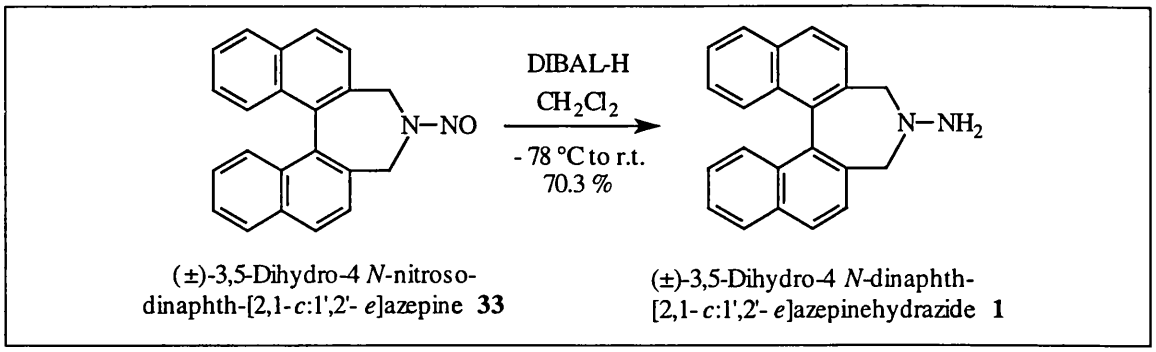
The reduction of *N*-nitroso groups, and the preparation of substituted hydrazines, have also been investigated in great detail by Corey *et al.*[125] Other *N*-nitroso reductions have also been investigated in the literature. Johnstone *et al.*[99] looked at the reduction of *N*-nitrosamines to *N,N*-disubstituted hydrazines by a low-valent titanium reagent. Lunn *et al.*[126] also utilised aqueous $TiCl_3$ reductions and compared the method to other reagents commonly utilised in these reductions. Not withstanding these reports it was, however, decided to attempt the reduction of (±)-**33** using zinc powder following the method of Schmidt *et al.*[127] (**Scheme 26**). The reaction was carried out in acetic acid and THF with 10 equivalent of zinc dust and appeared to proceed very cleanly over about 3 hours. The zinc salts were filtered off by suction through Celite, and flash chromatography in a CH_2Cl_2:MeOH (10:1) mixture afforded the suspected hydrazine in 81 % yield.



Scheme 26

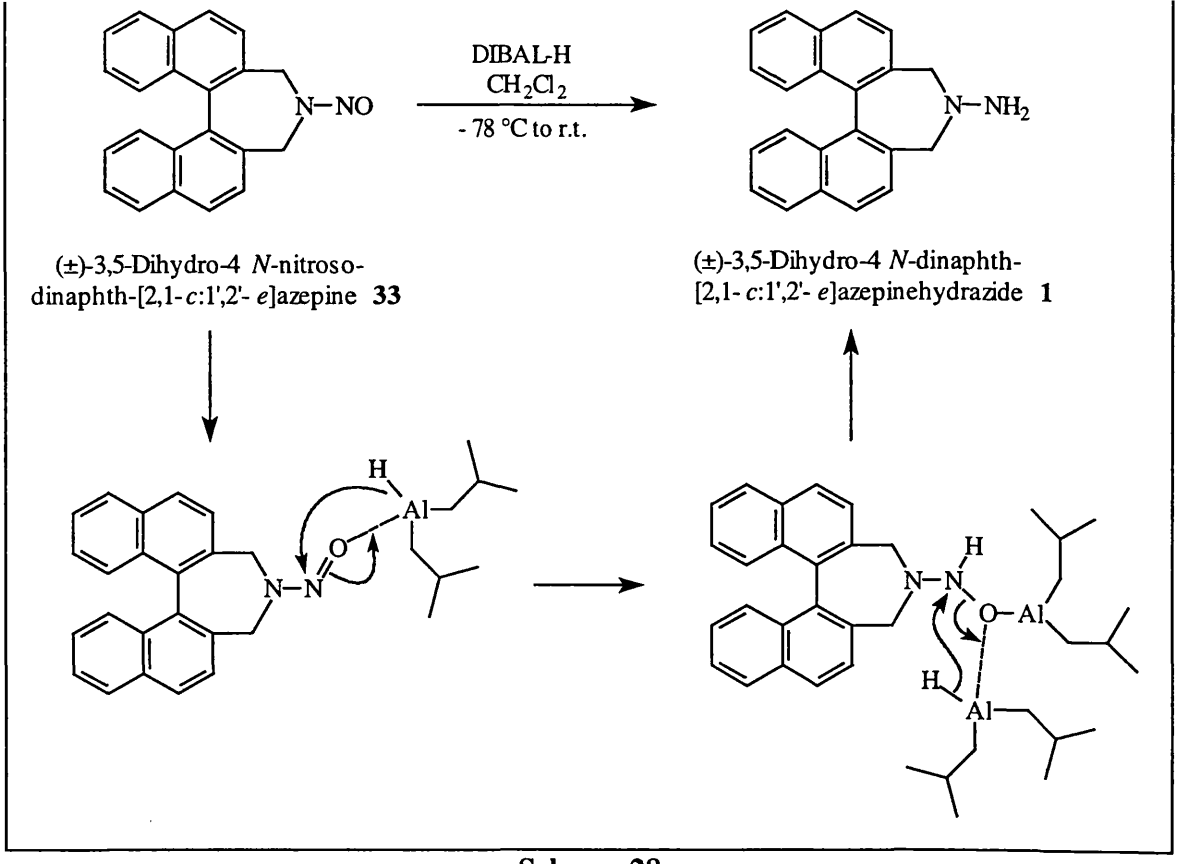
The 400 MHz ^1H n.m.r. spectrum of the isolated product appeared to be identical to that of (±)-**5** and this was further supported by the FAB mass spectrum. The zinc had thus cleaved the N-N bond and it was possible that the required hydrazine (±)-**1** had been prepared, but that it had then broken down under the reaction conditions.

Since the *N*-nitroso derivative of the azepine could easily be prepared in high yield (98 %), we felt that the reduction of this compound deserved more attention. Lithium aluminium hydride appeared to be too powerful a reducing agent and some other reducing agent would have to be found. It was postulated that the N=O group might react like a C=O group and therefore be reduced by diisobutylaluminium hydride to afford the required hydrazine as shown in **Scheme 27.**



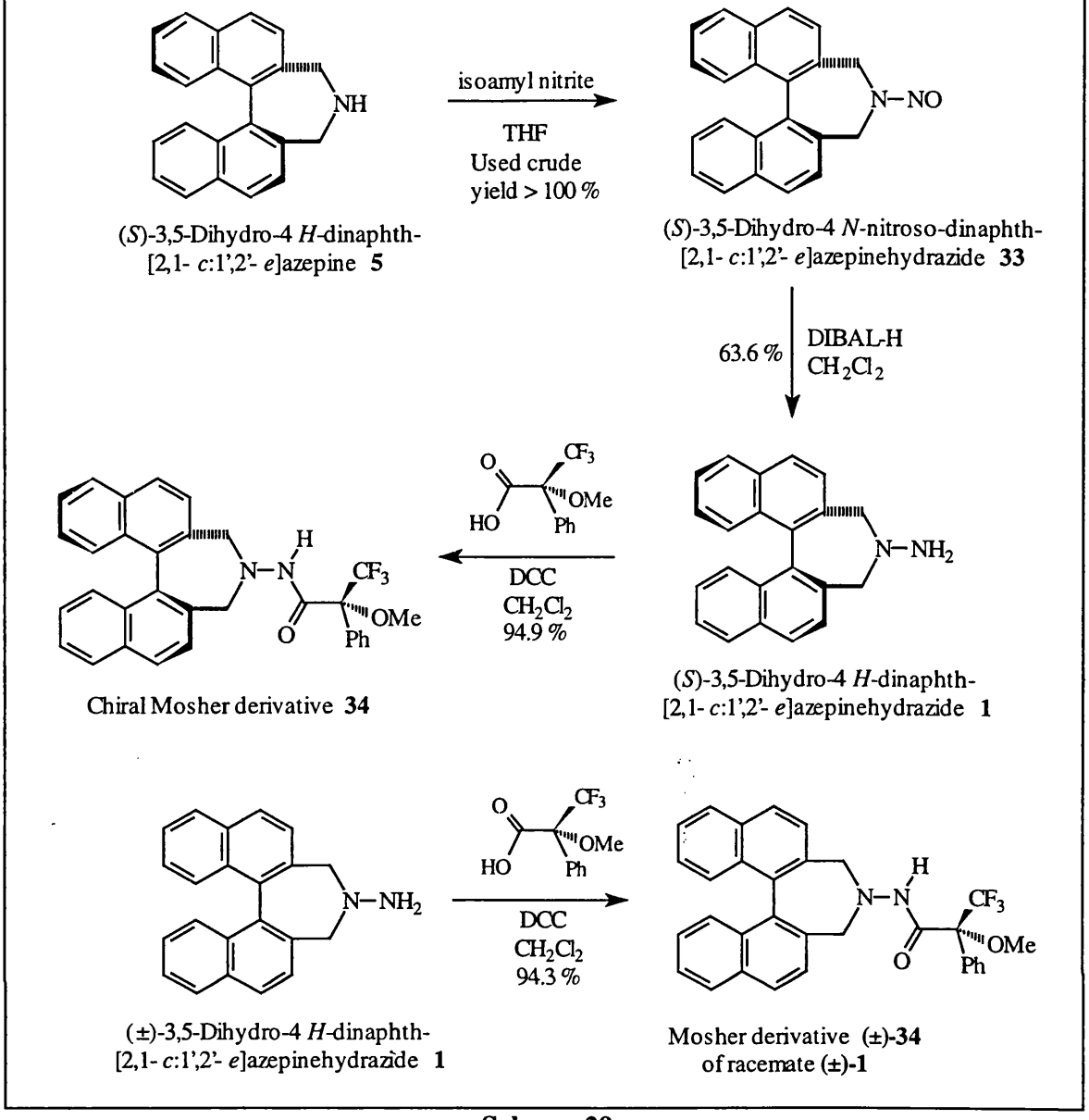
Scheme 27

A solution of DIBAL-H in toluene was added slowly to a solution of (±)-**33** in CH_2Cl_2 at -78 °C. The reaction mixture was stirred at this temperature for approx. 2 h after which it proved necessary to allow the solution to warm to room temperature for anything up to 65 h. Work-up with a 10 % aqueous Rochelle's salt solution followed by flash chromatography using a CH_2Cl_2:MeOH, 50:1, mixture as eluent afforded the required hydrazine (±)-**1** as a white solidified foam in up to 70 % yield. To the best of our knowledge, this was the first example of a *N*-nitroso reduction being successfully performed with diisobutylaluminium hydride to afford a 1,1-disubstituted hydrazine. The ^1H and ^{13}C n.m.r. spectra showed identical spectra to those prepared via the Boc deprotection method in **Scheme 22.** The HRMS mass spectrum (FAB, MNOBA matrix) also backed up this evidence by giving the required $(M+H)^+$ ion at *m/e* 311.1548 indicating a formula of $C_{22}H_{19}N_2$. The mechanism is believed to be as follows (**Scheme 28**).



Scheme 28

Since we were able to successfully prepare hydrazine (±)-**1** via this novel reduction method, it was decided to establish whether the chiral hydrazine **1** could be prepared in a similar manner. The chiral amine (*S*)-**5** was chosen, from which the *N*-nitroso compound (*S*)-**33** was prepared using isoamyl nitrite in THF (**Scheme 29**). This was then used crude for the reduction with DIBAL-H in CH_2Cl_2. The chiral hydrazine (**S**)-**1** was then converted to the Mosher derivative **34** by reaction with the Mosher acid, (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, and DCC in CH_2Cl_2 which successfully afforded chiral **34** as brown oil in 95 % yield. The FAB-MS (FAB, MNOBA matrix) of chiral **34** corroborated the structure by showing the required $(M+H)^+$ ion at *m/e* 527 indicating an empirical formula of $C_{32}H_{25}F_3N_2O_2$. Similarly, the racemic hydrazine (±)-**1** was converted to the Mosher derivative (±)-**34**. A comparison of the two 400 MHz ^1H n.m.r. spectra and the 470 MHz ^{19}F n.m.r. spectrum of chiral **34** quickly revealed that the 100 % e.e. had been retained in the hydrazine (*S*)-**1**.

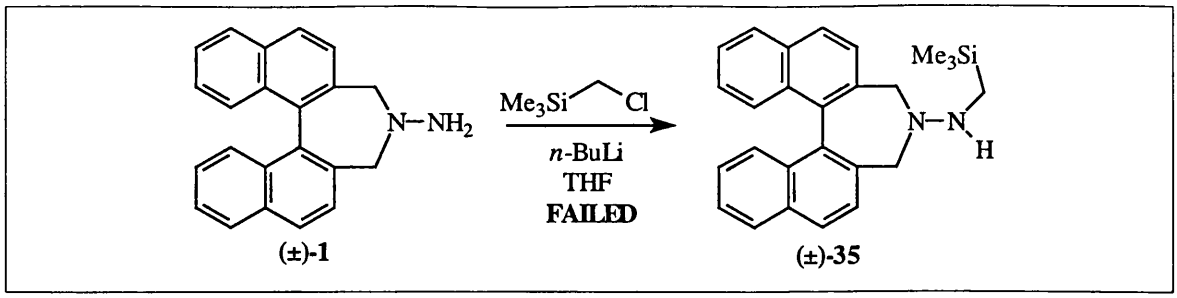


Scheme 29

Having successfully isolated our required hydrazine (±)-**1**, we were now in a position to attempt the preparation of the cycloaddition precursor (±)-**2**. The following section will discuss the preparation of this precursor.

2.2.2 Attempted preparation of the hydrazine cycloaddition precursor **2**

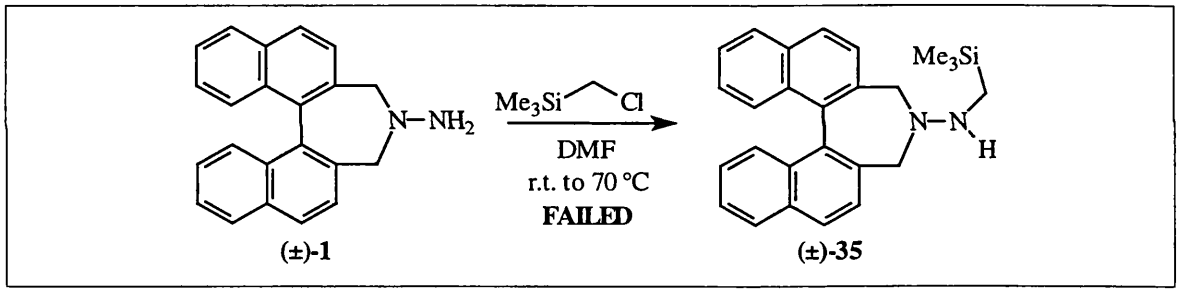
Our obtention of hydrazine (±)-**1** now put us in a position to attempt the preparation of our ylide precursors for the cycloadditions indicated previously in **Scheme 2**. The reaction of (±)-**1** with (chloromethyl)trimethylsilane and various strong bases failed to produce (±)-**35** under a variety of conditions investigated.



Scheme 30

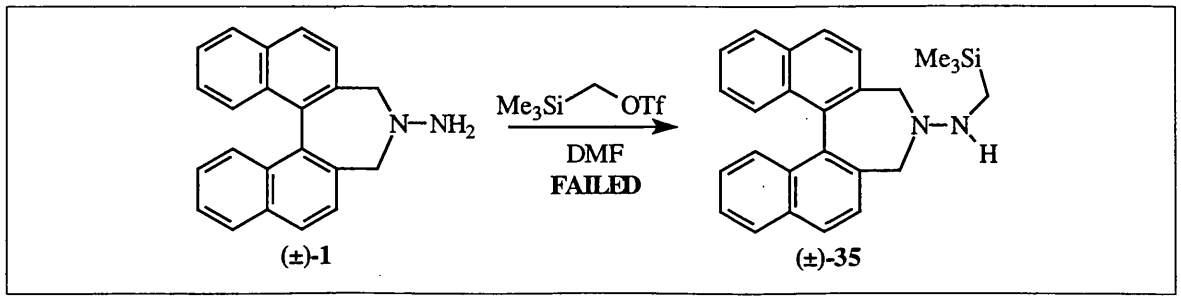
For example, when a stirred solution of (±)-**1** in THF at -78 °C was treated with *n*-BuLi for 20 min., and (chloromethyl)trimethylsilane added no reaction occurred after warming to room temperature for 24 h (**Scheme 30**).

Likewise when a solution of (±)-**1** in DMF at room temperature was added dropwise to (chloromethyl)trimethylsilane at room temperature, again no reaction occurred even after 20 h. Heating at 90 °C for 24 h again had no beneficial effect (**Scheme 31**).



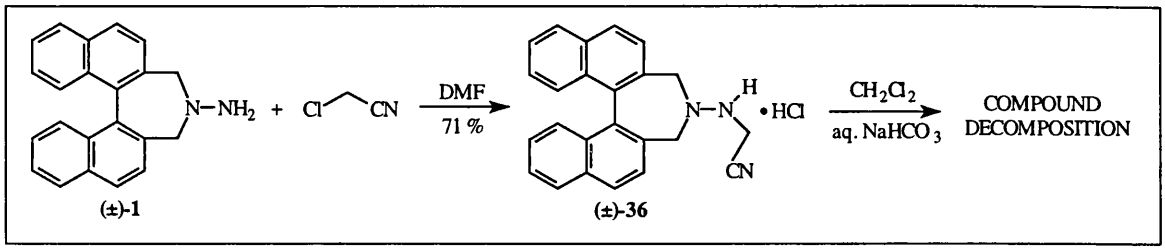
Scheme 31

The use of trimethylsilylmethyl triflate as indicated in **Scheme 32** was similarly unsuccessful.



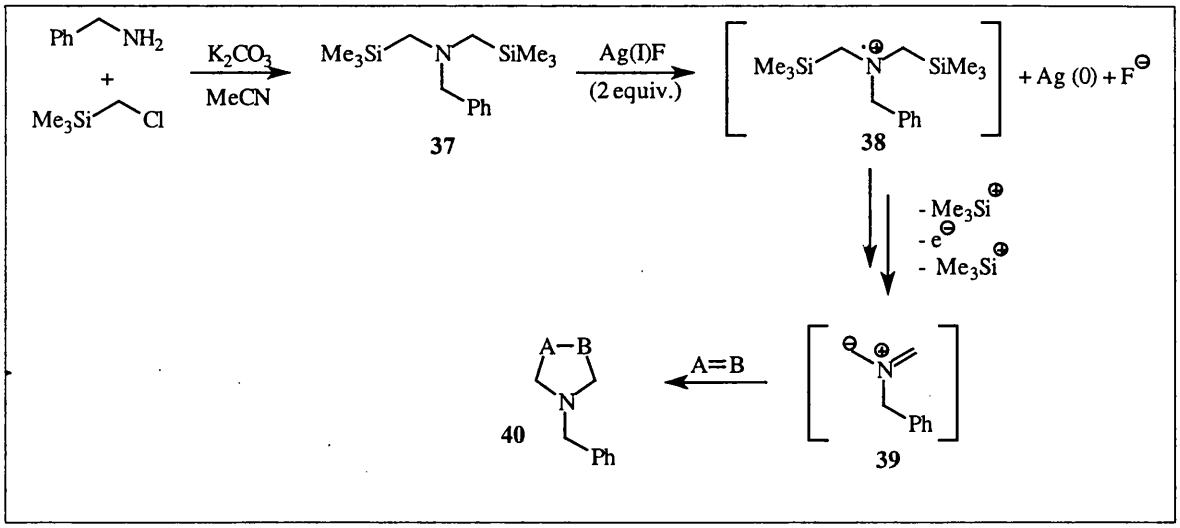
Scheme 32

In view of these failures, we decided to prepare (±)-**36**. The reaction of (±)-**1** with chloroacetonitrile (0.83 equiv.) in DMF at room temperature, appeared to give the hydrochloride salt (±)-**36** in 71 % yield as shown in **Scheme 33**. The 400 MHz ^{1}H n.m.r. spectrum of the salt suggested it was pure and so it was treated with aqueous sodium bicarbonate in order to afford the free hydrazine derivative. However, numerous products were now present and no further purification was carried out.



Scheme 33

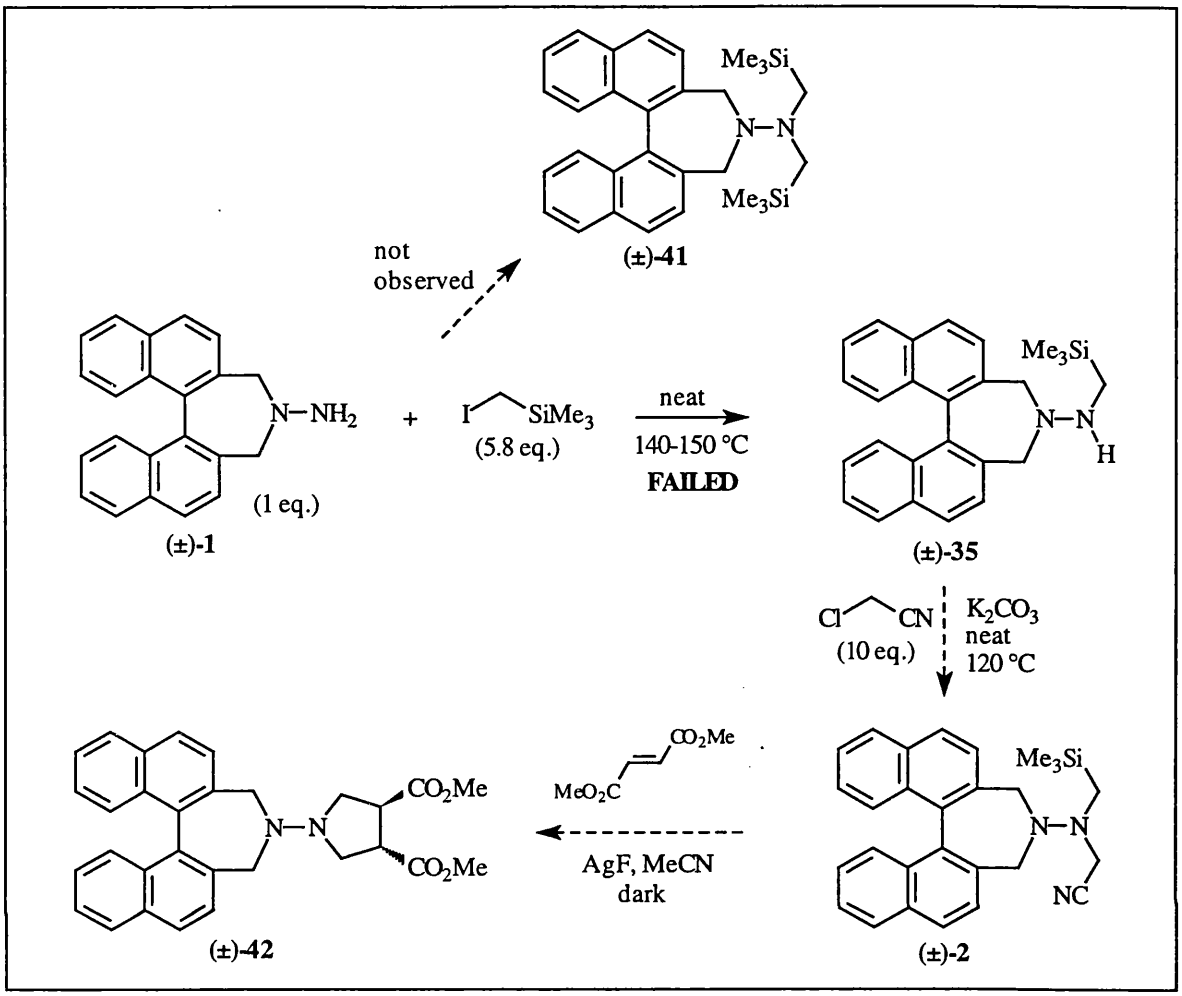
Pandey *et al.*[128] have reported an efficient strategy for generating nonstabilised ylides via the sequential double desilylation method. They made use of bis(*N,N*-trimethylsilylmethyl)benzylamine **37** in MeCN with AgF as a one electron oxidant. Trapping of the resultant azomethine ylide **39** with a suitable dipolarophile afforded the required cycloadduct **40** (**Scheme 34**).



Scheme 34

In order to prepare compound (±)-**41** it was decided to react (±)-**1** with (iodomethyl)trimethylsilane in excess. (Iodomethyl)trimethylsilane was used since it was envisaged that this would give a faster reaction, I^- being a better leaving group than

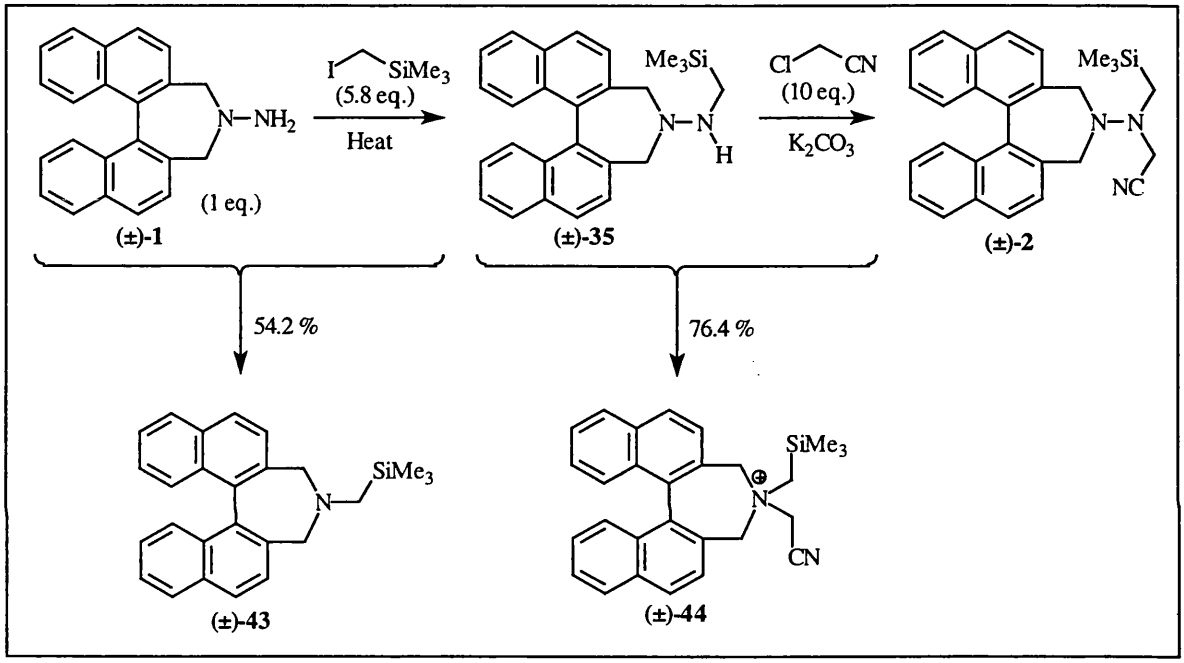
Cl. The first method attempted utilised 5.8 equiv. of neat (iodomethyl)trimethylsilane with no base as indicated in **Scheme 35**.



Scheme 35

The solid hydrazine (±)-**1** was heated to 140-150 °C in neat (iodomethyl)trimethylsilane. At approx. 60 °C the hydrazine dissolved and the mixture turned a clear yellow. At approx. 100 °C, a white precipitate was observed which was believed to be the hydroiodide salt of the required product. Work-up gave what appeared to be compound (±)-**35** as shown by 400 MHz ^{1}H n.m.r. spectroscopy only. No bis(Me$_3$Si-methyl)hydrazine (±)-**41** was observed. Suspected (±)-**35** was then treated with neat chloroacetonitrile and K_2CO_3 as the base. According to the n.m.r. data the correct compound (±)-**2** was isolated. The cycloaddition of (±)-**2** to dimethyl fumarate was then attempted to afford (±)-**42** using AgF in acetonitrile. The 400 MHz ^{1}H n.m.r. spectrum of the product, however, indicated it was not successful. It was therefore decided to await the results of the HRMS mass spectra of the previous two compounds [suspected (±)-**35** and (±)-**2**] before repeating any reactions and wasting

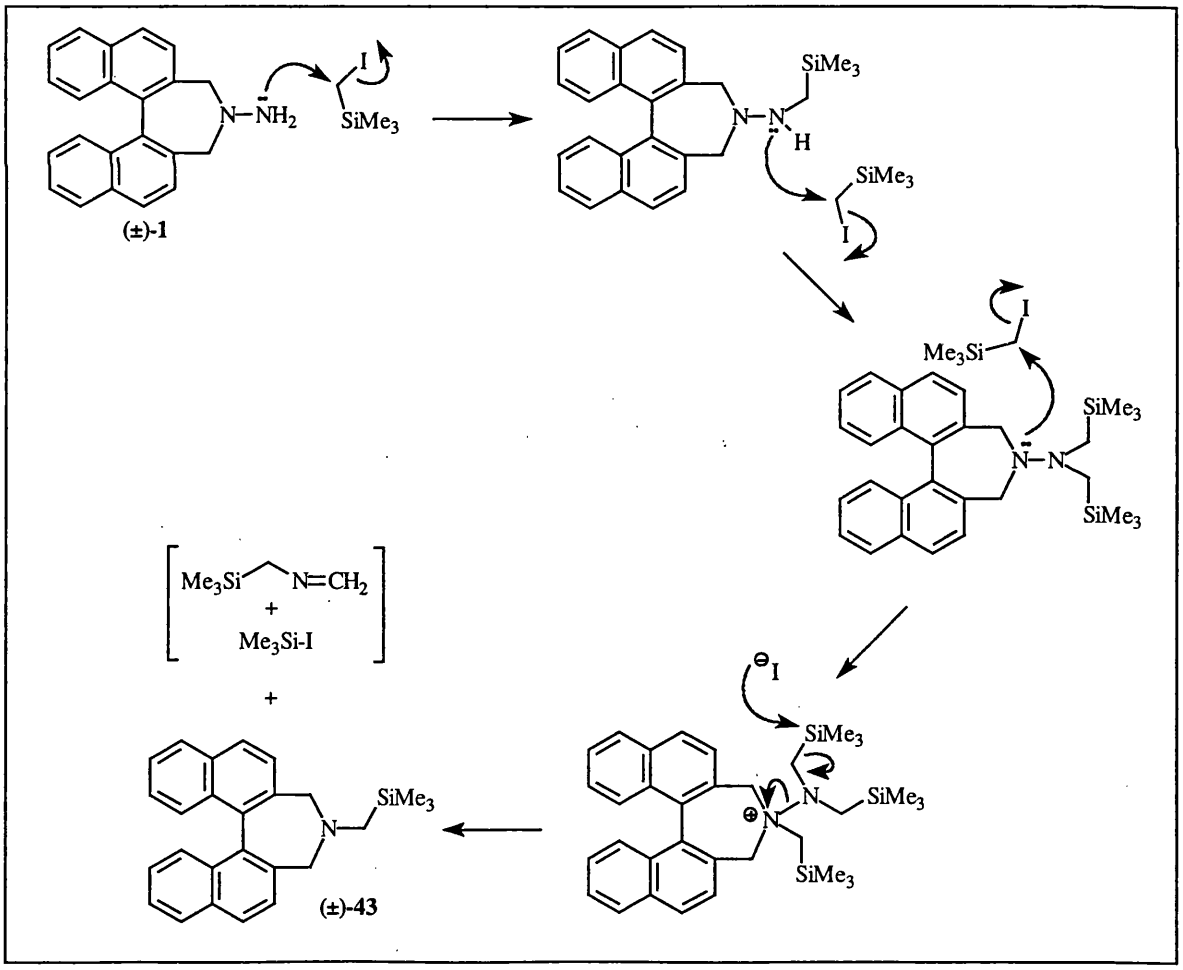
more starting materials. The HRMS mass spectra (FAB, MNOBA matrix) were a bit surprising. The treatment of (±)-**1** with neat (iodomethyl)-trimethylsilane at 140 °C afforded a compound that had a $(M+H)^+$ mass of *m/e* 382 which indicated a formula of $C_{26}H_{28}NSi$. This suggested that the tertiary amine (±)-**43** had been formed. Furthermore, when this tertiary amine had been treated with neat chloroacetonitrile with K_2CO_3 as the base, the quarternary salt (±)-**44** had been formed. This salt had a HRMS mass spectrum (FAB, MNOBA matrix) containing a peak at *m/e* 421.1974 which corresponded to $C_{28}H_{29}N_2Si$ $(M)^+$ and provided further evidence of its identity. These results are shown more clearly in **Scheme 36.**



Scheme 36

It transpired that the 400 MHz ^1H n.m.r. spectrum of the tertiary amine (±)-**43** had originally been incorrectly interpreted as the substituted hydrazine (±)-**35** as it showed the Me_3Si group as a singlet at δ 0.16. Each proton of the $-CH_2-$ group next to the Me_3Si group was observed as doublets at δ 2.05 (J_{HH} 14.4 Hz) and δ 2.31 (J_{HH} 14.4 Hz) and the two $-CH_2-$ groups next to the aromatic rings were each seen as doublets at δ 3.28 (J_{HH} 12.0 Hz) and δ 3.68 (J_{HH} 12.0 Hz). Had (±)-**35** been formed, a similar ^1H n.m.r. spectrum would have been observed and the free NH may not have been seen. The 100 MHz ^{13}C n.m.r. spectrum of this tertiary amine also showed the required peaks. The Me_3Si group was found at δ -0.8 with the $-CH_2-$ group next to the aromatic rings at δ 47.6 and the $-CH_2-$ next to the Me_3Si group at δ 58.9. The 400 MHz ^1H n.m.r.

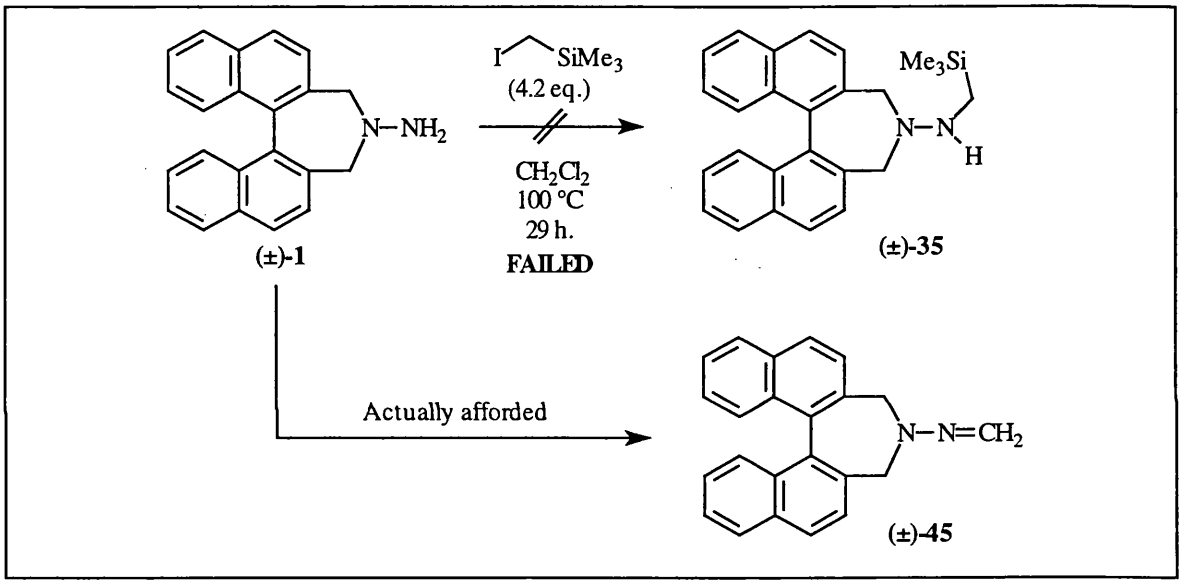
spectrum for the quaternary amine salt (±)-**44** indicated the non-symmetry of the molecule and the Me_3Si group was found at δ 0.49 and each non-aromatic proton as a doublet. These doublets were found at δ 3.08 (J_{HH} 14.4 Hz), δ 3.33 (J_{HH} 14.4 Hz), δ 3.64 (J_{HH} 12.4 Hz), δ 3.99 (J_{HH} 12.4 Hz), δ 4.73 (J_{HH} 12.4 Hz), δ 4.86 (J_{HH} 17.6 Hz), δ 5.84 (J_{HH} 12.4 Hz) and δ 6.28 (J_{HH} 17.6 Hz). The 100 MHz ^{13}C n.m.r. spectrum also showed six peaks for the non-aromatic part of the molecule. The Me_3Si group was found at δ -0.4 and the -CN group at δ 111.8. The aromatic rings also showed the required number of eight quaternary and 12 non-quaternary carbon atoms. A possible mechanism for the formation of (±)-**43** is indicated in **Scheme 37** below. It is believed that the terminal $-NH_2$ initially reacts with two molecules of (iodomethyl)-trimethylsilane. The remaining N atom then reacts with one equivalent of (iodomethyl)-trimethylsilane to give the corresponding salt. I^-, which is now in excess in the reaction mixture, then attacks the silyl group of one of the terminal $-N-CH_2-SiMe_3$ groups. This then cleaves the N-N bond in order to afford the required tertiary amine (±)-**43** with the elimination of $Me_3SiCH_2N{=}CH_2$ and Me_3Si-I.



Scheme 37

The compound prepared from the attempted cycloaddition remains unidentified. The HRMS mass spectrum (FAB, MNOBA matrix) gave what appeared to be the $(M+H)^+$ peak at *m/e* 349. The other major peak appears to correspond to $C_{22}H_{17}$ $(M+H)^+$ at *m/e* 281. This is believed to be the two aromatic rings, the two $-CH_2-$ and the N atom. The 400 MHz ^1H n.m.r. spectrum also shows the 12 aromatic protons, as well as a singlet at δ 3.64 (3 protons) which could be assigned to a CO_2Me group.

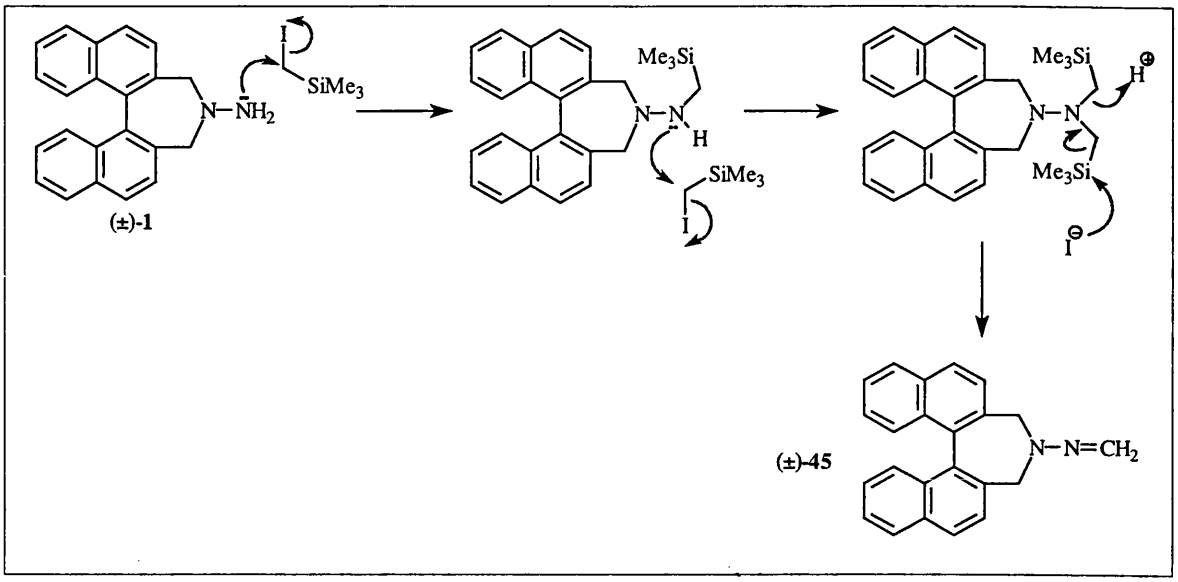
It was decided to attempt slightly 'softer' conditions by adding a solvent to the reactions of chloroacetonitrile or (iodomethyl)trimethylsilane with our hydrazine. The first of these methods is shown in **Scheme 38**.



Scheme 38

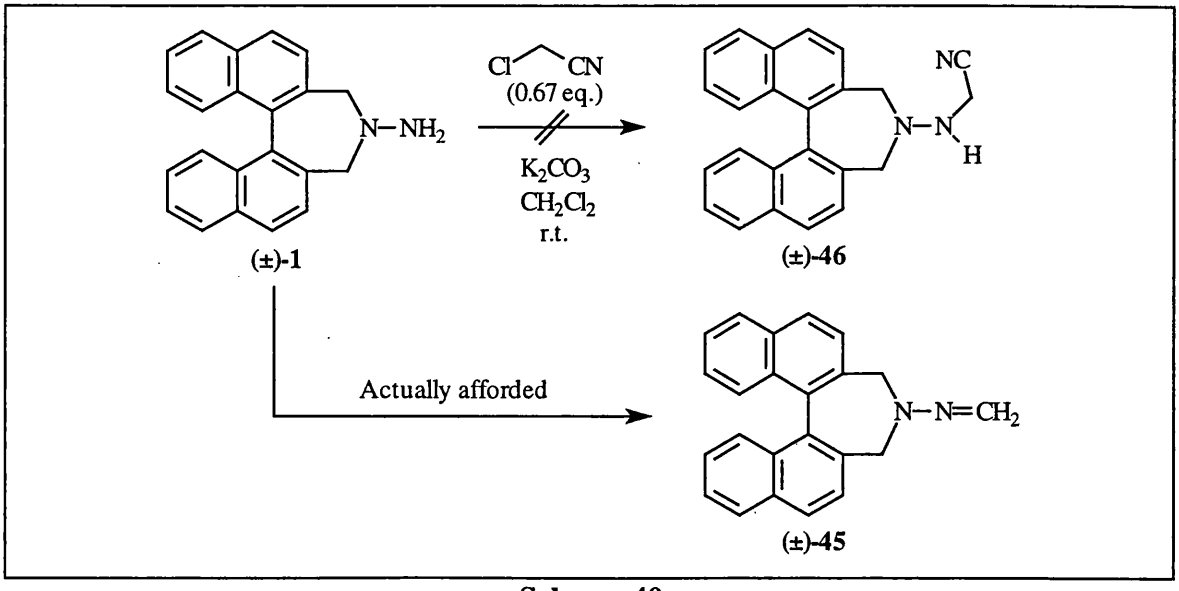
To a solution of (±)-**1** in CH_2Cl_2 (2 ml) was added (iodomethyl)trimethylsilane and the reaction mixture stirred at 100 °C for 29 h in the dark. Basic work-up afforded a yellow solid which was subjected to flash chromatography (CH_2Cl_2/MeOH, 50:1) to afford the major product as a yellow solid. The n.m.r. data seemed to indicate that hydrazone (±)-**45** had formed (**Scheme 38**). The 400 MHz ^1H n.m.r. spectrum showed the two $-CH_2-$ next to the aromatic rings as doublets at δ 3.64 (J_{HH} 12.4 Hz) and δ 4.43 (J_{HH} 12.4 Hz). The $-N=CH_2$ protons appeared as two doublets in the characteristic positions of δ 6.17 (J_{HH} 10.4 Hz) and δ 6.27 (J_{HH} 10.4 Hz). This evidence was further backed up by the HRMS mass spectrum which gave a $(M+H)^+$ peak at *m/e* 323.1548 corresponding to a formula of $C_{23}H_{19}N_2$. The mechanism for this reaction can be envisaged as indicated in

Scheme 39. The hydrazine reacts with two equivalents of (iodomethyl)-trimethylsilane, to form the bis(Me_3Si)-substituted hydrazine derivative which under the acidic reaction conditions (HI) and relatively high temperature, is attacked by I^- resulting in a desilylation and subsequent formation of the hydrazone by loss of Me_4Si and Me_3Si-I.



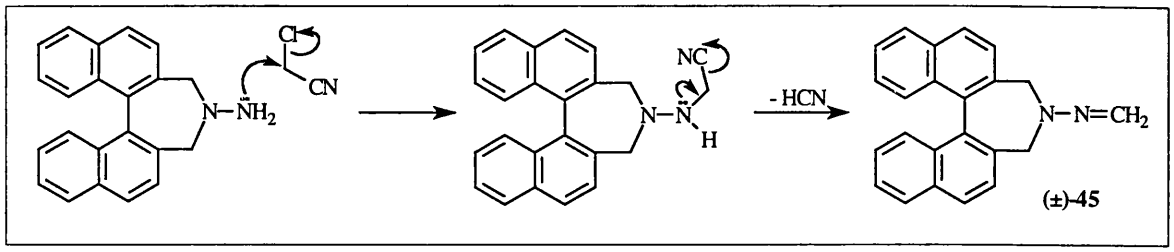
Scheme 39

The second method involved reacting (±)-**1** with chloroacetonitrile using K_2CO_3 as the base. This is indicated in **Scheme 40** below.



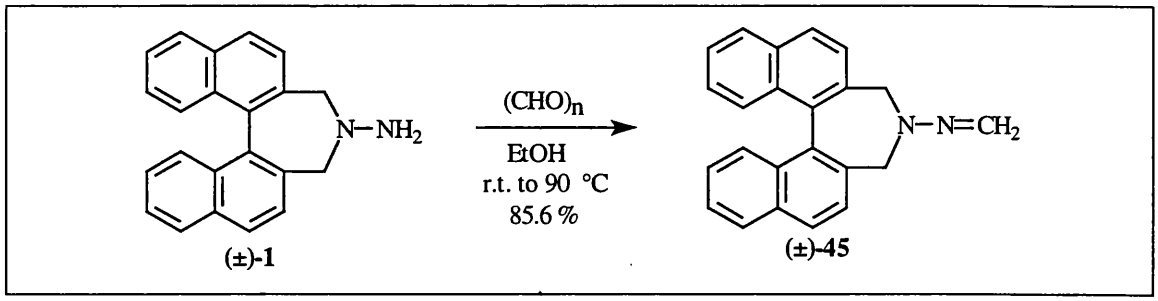
Scheme 40

Likewise when a solution of (±)-**1** and solid K_2CO_3 in CH_2Cl_2 was added chloroacetonitrile (0.67 equiv.) and the reaction mixture stirred at room temperature for 1 h. Filtration of the salts and work-up furnished a white solid. Flash chromatography (CH_2Cl_2/MeOH, 50:1) afforded the major product as a solidified foam. The 400 MHz ^{1}H n.m.r. spectrum gave identical results to the previous hydrazone (±)-**45**. This was further backed up by the high resolution mass spectrum. The mechanism is believed to be as follows (**Scheme 41**):



Scheme 41

In order to prove that the hydrazone had been formed in the last two reactions, it was decided to make this deliberately by reacting (±)-**1** with *para*-formaldehyde following a protocol first described by Enders *et al.*[129] This is indicated in **Scheme 42.**



Scheme 42

To a solution of (±)-**1** in EtOH at room temperature was added *para*-formaldehyde and the solution stirred at 90 °C for 4 h. Flash chromatography (hexanes:EtOAc, 5:1) gave the required hydrazone (±)-**45** as a yellow solidified foam in 86 % yield. This compound had identical properties to the two identical hydrazones prepared via the (iodomethyl)trimethylsilane and chloroacetonitrile methods.

2.3 Remarks

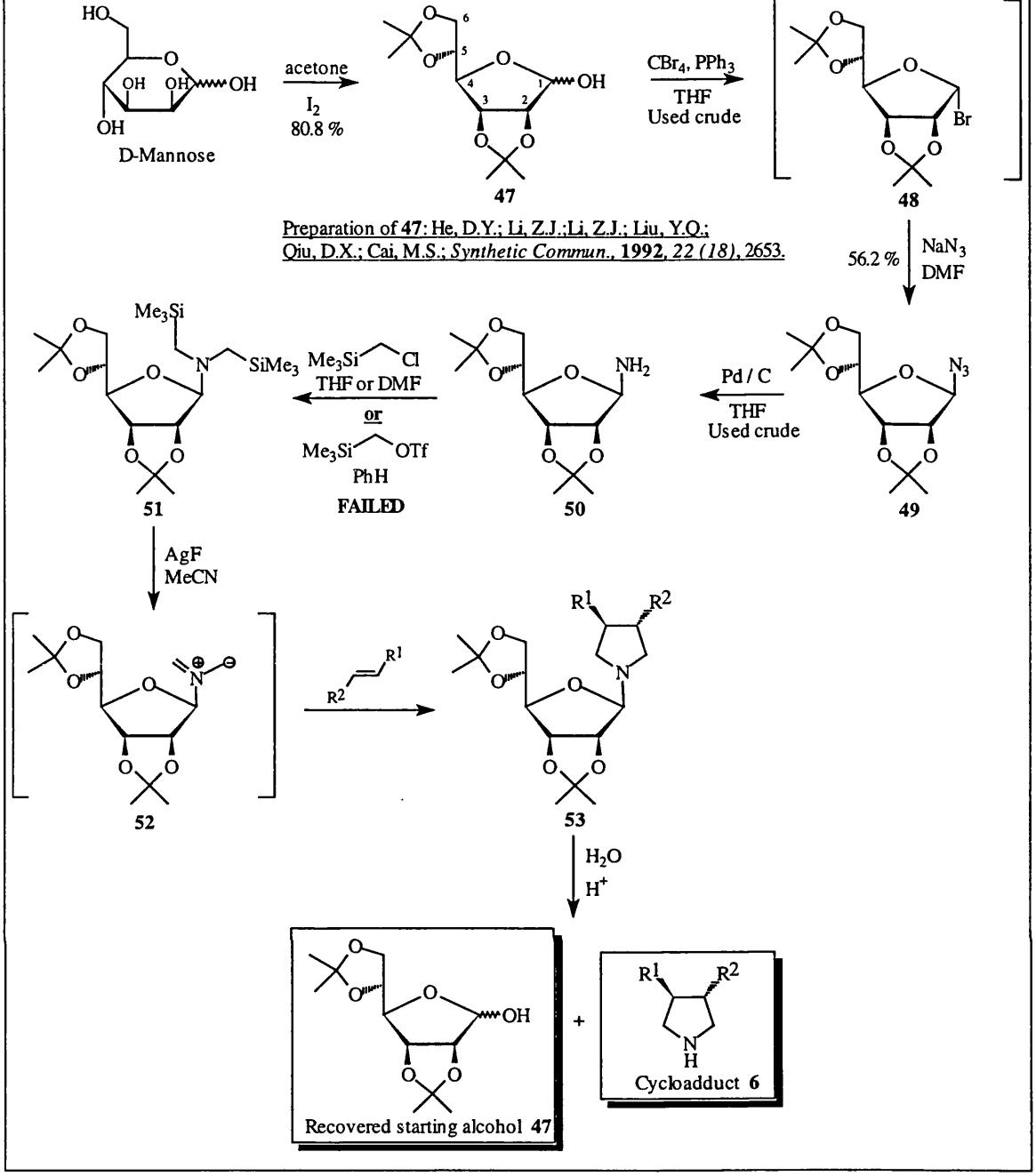
Due to these surprising results, it was decided to move away from the use of this chiral hydrazine as an auxiliary for the [3+2]-cycloaddition of nonstabilised azomethine ylides. Several attempts had been made to prepare the 1,3-dipole but unfortunately, all were unsuccessful. The evaluation of other auxiliaries therefore looked necessary. Some of these are discussed in Chapter 3.

Chapter 3

An attempt at introducing new chiral auxiliaries for the [3+2]-cycloaddition reactions of nonstabilised azomethine ylides

3.1 Investigations into the use of a mannose based auxiliary for the [3+2]-cycloadditions of azomethine ylides

Given all these previous disappointments, we decided to pursue an alternative method for the preparation of ylide precursors, that would make use of derivatives of D-mannose. Our general strategy is outlined in **Scheme 43**. Initially, D-mannose would be converted to **47**,[130] and this then transformed to amine **50**, by initially converting **47** to the bromide **48**, reacting this with NaN_3 and then hydrogenating the azide **49** over palladium on carbon to furnish the required amine **50**. Treatment of **50** with either (chloromethyl)trimethylsilane or trimethylsilylmethyl triflate should then furnish the precursor **51** needed for the cycloaddition chemistry. Addition of silver fluoride in the presence of an appropriately substituted olefin should afford the 1,3-dipolar cycloaddition product **53**. Exposure of **53** to aqueous acid was then envisaged for cleaving off the newly formed pyrrolidine cycloadduct **6** as well regenerating the starting material **47**.

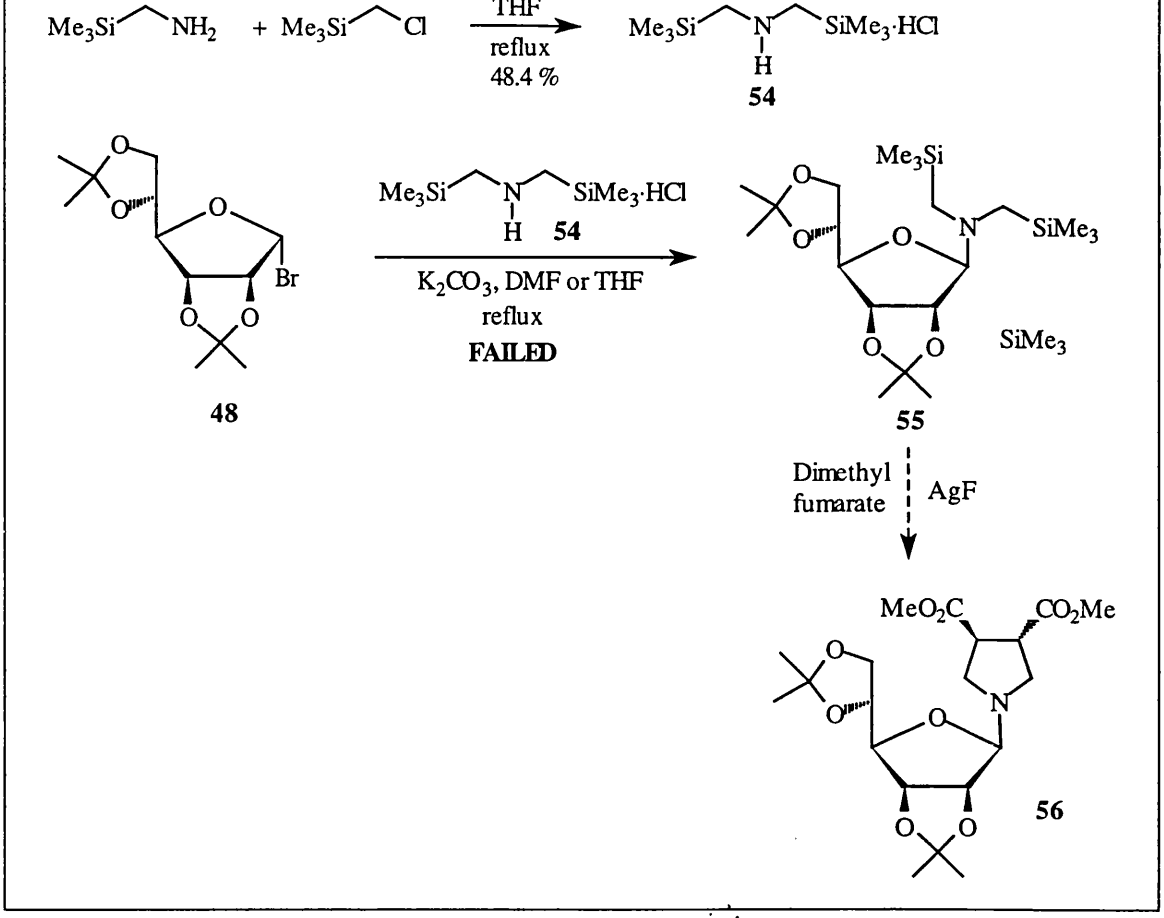


Scheme 43

The conversion of D-mannose (20 g) into **47** proceeded very cleanly and in up to 81 % yield. The 400 MHz ^{1}H n.m.r. spectrum showed the four required methyl groups as singlets at δ 1.29, 1.34, 1.42 and 1.43. The C-1 proton resonated as a doublet at δ 5.33 and had a coupling constant of J_{HH} 2.8 Hz. The 100 MHz ^{13}C n.m.r. spectrum also confirmed that the correct compound had been obtained. The four methyl groups were found at δ 24.4, 24.8, 25.8 and 26.8. The two quaternary carbons were found at δ 109.1 and δ 112.6 ppm and C-1 was observed at δ 101.1. The HRMS mass spectrum (FAB, MNOBA matrix) contained a peak for $C_{12}H_{20}O_6Na$ $(M+Na)^+$ at *m/e* 261.1338. Finally, the I.R. spectrum gave the characteristic broad -OH band at 3437 cm^{-1}. Alcohol **47** was

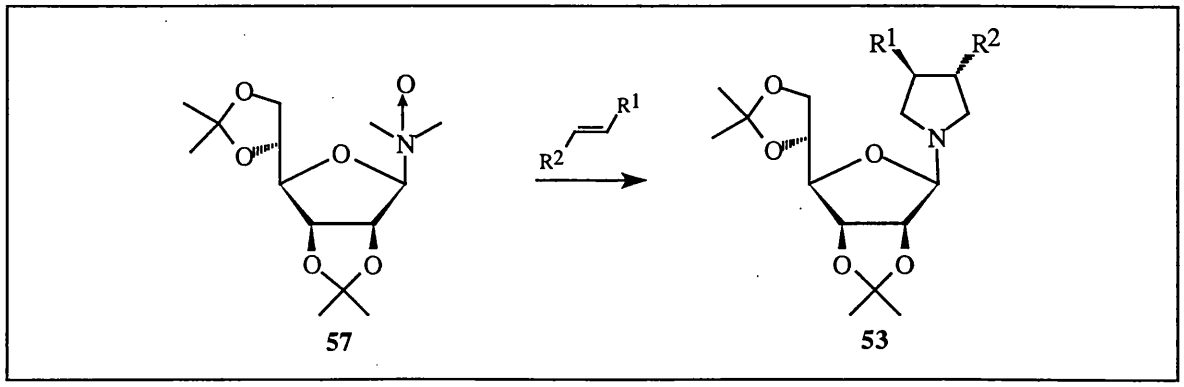
then dissolved in distilled THF and cooled to 0 °C. Triphenylphosphine and carbon tetrabromide were added and the reaction mixture stirred for approx. 1 h at room temperature. A white precipitate of triphenylphosphine oxide was immediately observed which was removed by thorough suction filtration. Concentration of the filtrate gave the crude bromide **48**, which was taken forwards to the next step without further purification. The 400 MHz ^{1}H n.m.r. spectrum of the crude material showed the four required methyl groups as singlets at δ 1.32, 1.39, 1.47 and 1.47. The C-1 proton was now observed as a singlet at δ 5.45, a shift of 0.21 ppm downfield from the alcohol. The observation of a singlet at C-1 also indicates that only one isomer had been formed. The 100 MHz ^{13}C n.m.r. spectrum also showed the correct compound. The four methyl groups were found at δ 24.6, 25.1, 25.9 and 26.9. The two quaternary acetal carbons could be seen at δ 109.4 and δ 113.2 and C-1 was observed at δ 95.5, a shift of 5.64 ppm upfield of the alcohol **47**. The crude bromide was immediately treated with sodium azide (20 equivalents) to afford the crude azide. Flash chromatography in hexanes:EtOAc afforded the pure azide **49** as a clear yellow oil in 56 % yield. Unreacted bromide **48** was also isolated from the column. The 100 MHz ^{13}C n.m.r. spectrum of **49** showed the four methyl groups were found at δ 24.3, 25.1, 25.2 and 26.9. The two quaternary carbons were found at δ 109.3 and δ 113.6 and C-1 was observed at δ 89.1, a further shift of 6.40 ppm upfield from bromide **48**. As a final proof of structure, the I.R. spectrum of **49** indicated the characteristic $-N_3$ peak at 2123 cm^{-1}. The reduction of the azide with 5 mol% palladium on carbon and hydrogen in THF was then carried out. The reaction proceeded very cleanly and leaving the crude amine **50** as a clear oil which was used immediately without further purification. The amine **50** was then reacted with (chloromethyl)trimethylsilane in either DMF or THF, but both of these methods proved unsuccessful. Treating a solution of **50** in benzene with trimethylsilylmethyl triflate was likewise unfruitful.

Our attempts to modify the above chemistry to obtain the bis-Me_3Si sugar **55** from the reaction of **54** with bromide **48** failed (**Scheme 44**). TLC indicated no reaction occurred. The method was abandoned at this point.



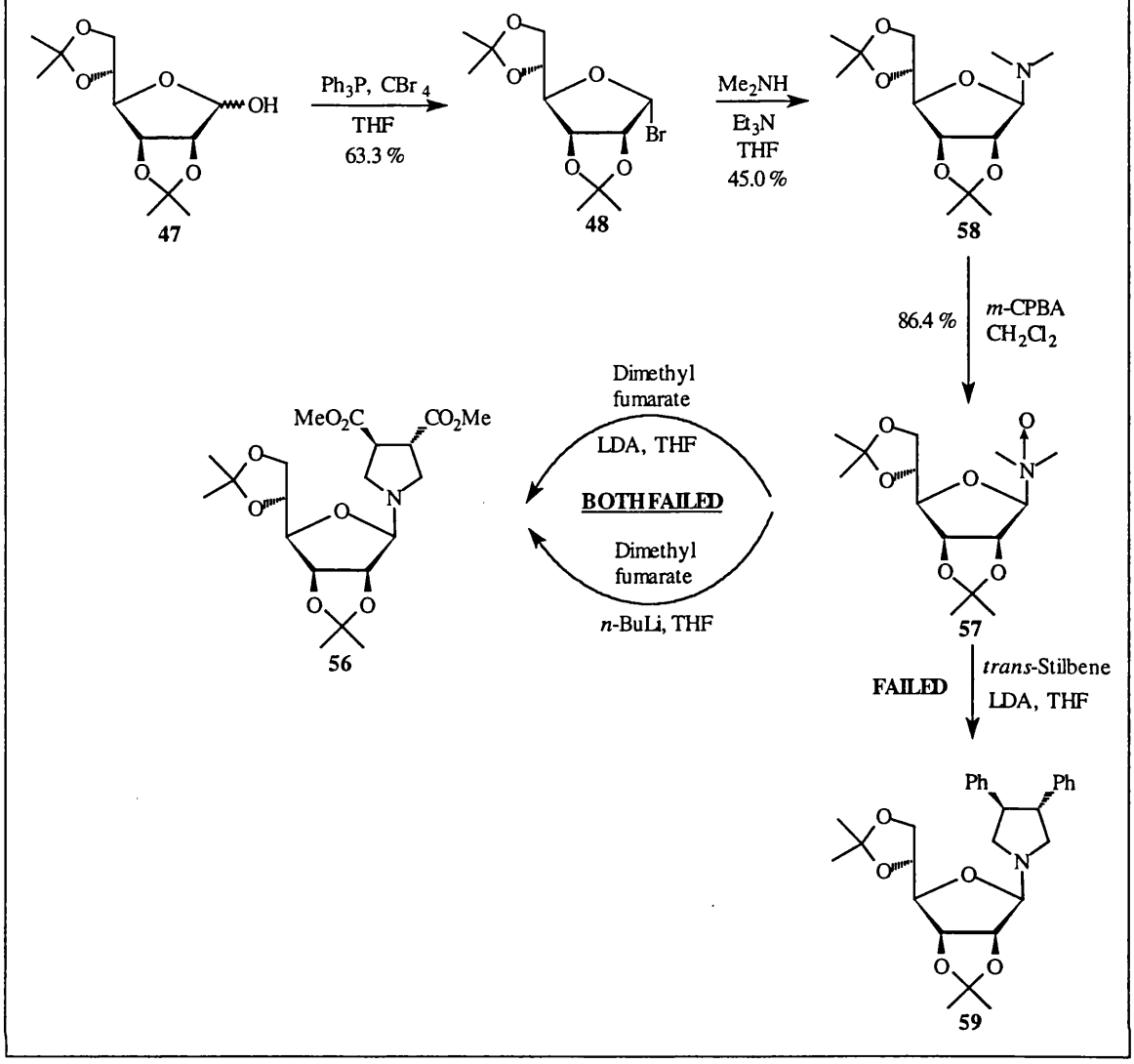
Scheme 44

Another strategy attempted, modified the chemistry of Roussi *et al.*[131] These workers have investigated the base-mediated deprotonation of amino-sugar *N*-oxides to obtain azomethine ylides, and used them to prepare pyrrolidines via [3+2]-cycloaddition with stilbene. It was envisaged that this method could also be utilised with our sugar-based auxiliary as indicated in **Scheme 45**.



Scheme 45

Alcohol **47** was converted to bromide **48** in the same manner as previously. The bromide was this time subjected to flash chromatography (hexanes/EtOAc, 5:1) and was obtained in 63 % yield. Compound **48** was then reacted with dimethylamine in the presence of Et_3N in THF to furnish **58** in 45 % yield (**Scheme 46**). The 400 MHz ^1H n.m.r. spectrum showed the four required sugar methyl groups as singlets at δ 1.32, 1.35, 1.42 and 1.46. The two newly-introduced methyl groups were observed as a singlet further downfield as expected at δ 2.22. The 100 MHz ^{13}C n.m.r. spectrum also showed the correct compound. The four acetal methyl groups were found at δ 24.7, 25.2, 26.1 and 26.9. The two *N*-methyl groups were seen at δ 40.8 with C-1 being observed at δ 101.0, a shift of 5.54 ppm downfield from bromide **48**. The HRMS mass spectrum also showed a peak of *m/e* 288.1811 which corresponded to an $(M+H)^+$ ion with empirical formula $C_{14}H_{26}NO_5$. Treating the sugar amine **58** with *m*-CPBA in CH_2Cl_2 afforded the *N*-oxide **57** in 86 % yield. The 100 MHz ^{13}C n.m.r. spectrum showed the four methyl groups at δ 24.3, 25.2, 26.0 and 26.7. The two methyl groups next to the N atom were now seen as two different signals at δ 55.1 and δ 55.7 with C-1 being observed at δ 105.8, a shift of 4.81 ppm downfield from the tertiary amine **58**. The FAB-MS mass spectrum also showed a peak for the correct mass of *m/e* 304.2 for an $(M+H)^+$ ion indicating an empirical formula of $C_{14}H_{26}NO_6$. The *N*-oxide was then treated with LDA and a suitable dipolarophile (dimethyl fumarate and *trans*-stilbene were both tried) in order to yield the required sugar-pyrrolidines **56** and **59**. However, both methods failed. Use of *n*-BuLi in the same manner also met with failure and so this method was subsequently abandoned.

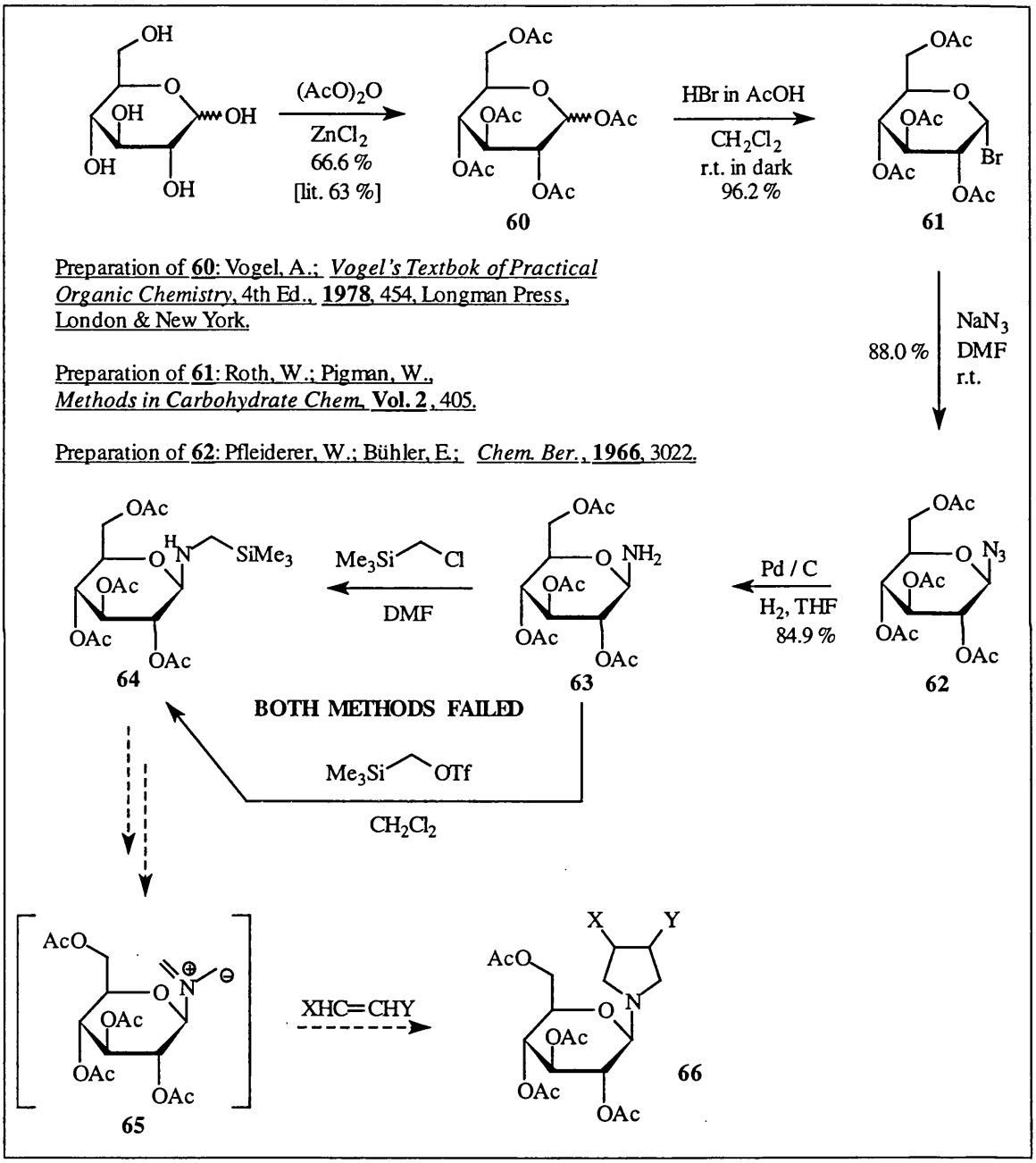


Scheme 46

Due to the fact that no major progress was made in the synthesis of the azomethine ylide precursors using this method, it was decided to evaluate yet another chiral auxiliary. This was to be based on D-glucose and is discussed in the following section.

3.2 An attempt at the use of D-glucose as a chiral auxiliary for azomethine ylide [3+2]-cycloadditions

Our next plan was to establish whether the azomethine ylide **65** could be prepared (**Scheme 47**).

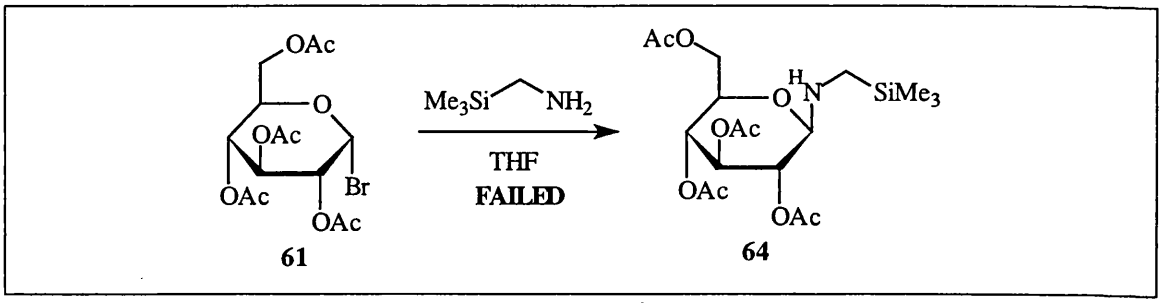


Scheme 47

Our initial effort was directed at preparing amine **63**. This was synthesised according to **Scheme 47** by acetylation of D-(+)-glucose [132] followed by bromination to afford commercially available bromide **61**.[133] Treatment with sodium azide afforded

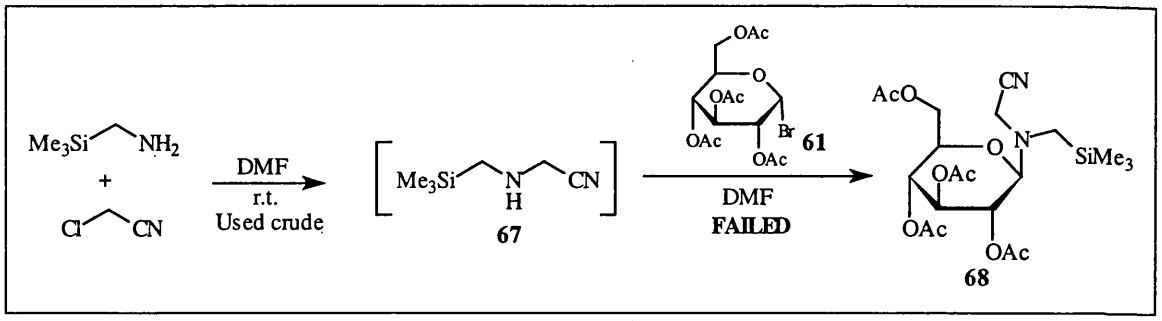
azide **62** [151] which was converted to amine **63** by hydrogenation. The reaction of amine **63** with (chloromethyl)trimethylsilane in DMF, was expected to yield the required secondary amine **64**. However, no reaction was observed when this reaction was attempted and the amine was recovered. The reaction was repeated using trimethylsilylmethyl triflate in CH_2Cl_2, but again the required compound was not formed.

The reaction of bromide **61** with trimethylsilylmethyl amine in THF was also investigated **(Scheme 48)**. However, this method also proved unsuccessful.



Scheme 48

Another procedure was also attempted as indicated in **Scheme 49**. This was based on preparing *N*-cyanomethyl-*N*-trimethylsilylmethylamine **67**, from trimethylsilylmethyl amine and chloroacetonitrile in DMF at room temperature. The product was not isolated, but was reacted further *in situ* by addition of **61**. However, no reaction was observed and the method was abandoned.



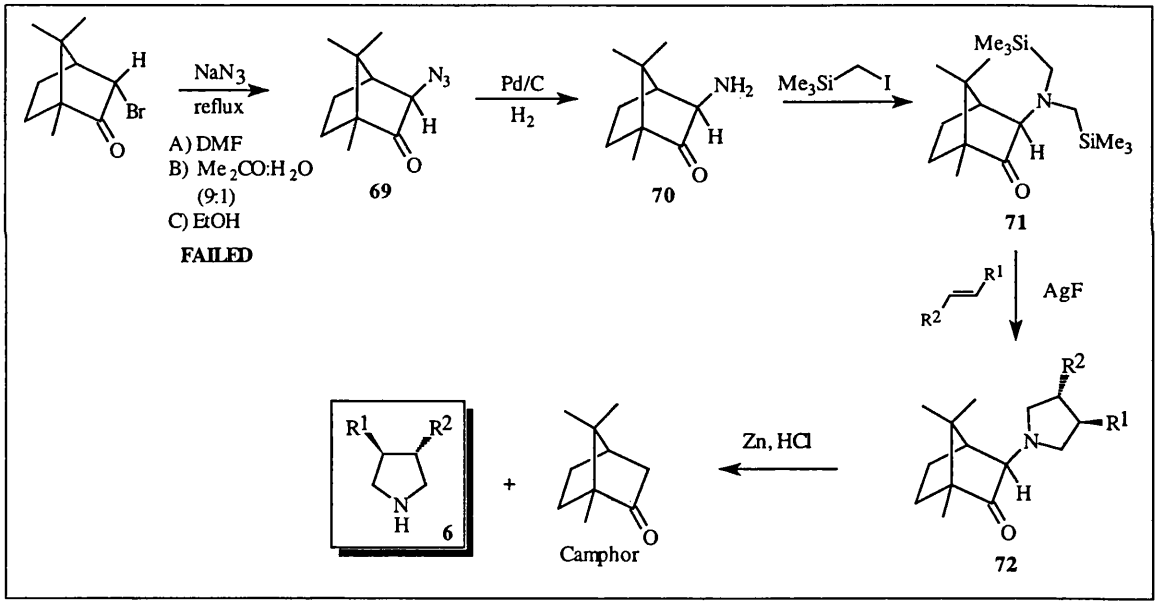
Scheme 49

Again, we were unsuccessful in the preparation of the required ylide precursors. The method was abandoned at this stage for another, more promising route based on camphor which will be discussed in the next section.

3.3 Evaluation of a novel camphor-derived auxiliary in the [3+2]-cycloaddition reaction of nonstabilised azomethine ylides

3.3.1 [(1*R*)]-*endo*-(+)-3-Bromocamphor as starting material

In this approach, commercially available [(1*R*)]-*endo*-(+)-3-bromocamphor was to be treated with sodium azide to give the *exo*-3-camphor azide **69** which would then be reduced to the amine **70**. Treatment of amine **70** with two equivalents of (iodomethyl)trimethylsilane would then give the bis(Me_3Si methyl) camphor **71** which would be treated with a suitable dipolarophile and AgF, to form the cycloaddition product **72**. Zinc dust and HCl was envisaged for cleaving off the auxiliary to obtain the pyrrolidine derivative **6** and camphor (**Scheme 50**).

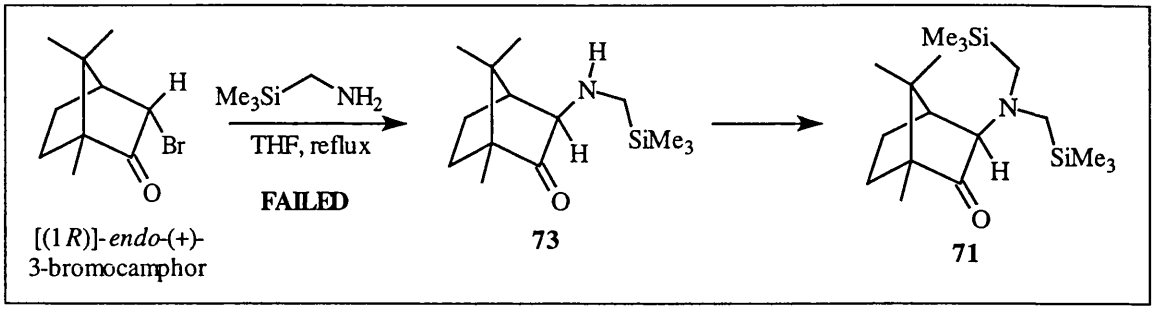


Scheme 50

Our initial attention focussed on replacing the bromide in [(1*R*)]-*endo*-(+)-3-bromocamphor with azide ion. NaN_3 (20 equivalents) was added to a solution of 3-bromocamphor in DMF and the mixture heated to 140 °C. After 22 h TLC showed that there was no reaction and the reaction was therefore abandoned. The reaction was repeated on two further occasions with two different solvents but in each case no reaction was observed. It is likely that the top methyl group of the camphor makes the

bromide too sterically hindered for the S_N2 reaction to take place. The method was abandoned at this point.

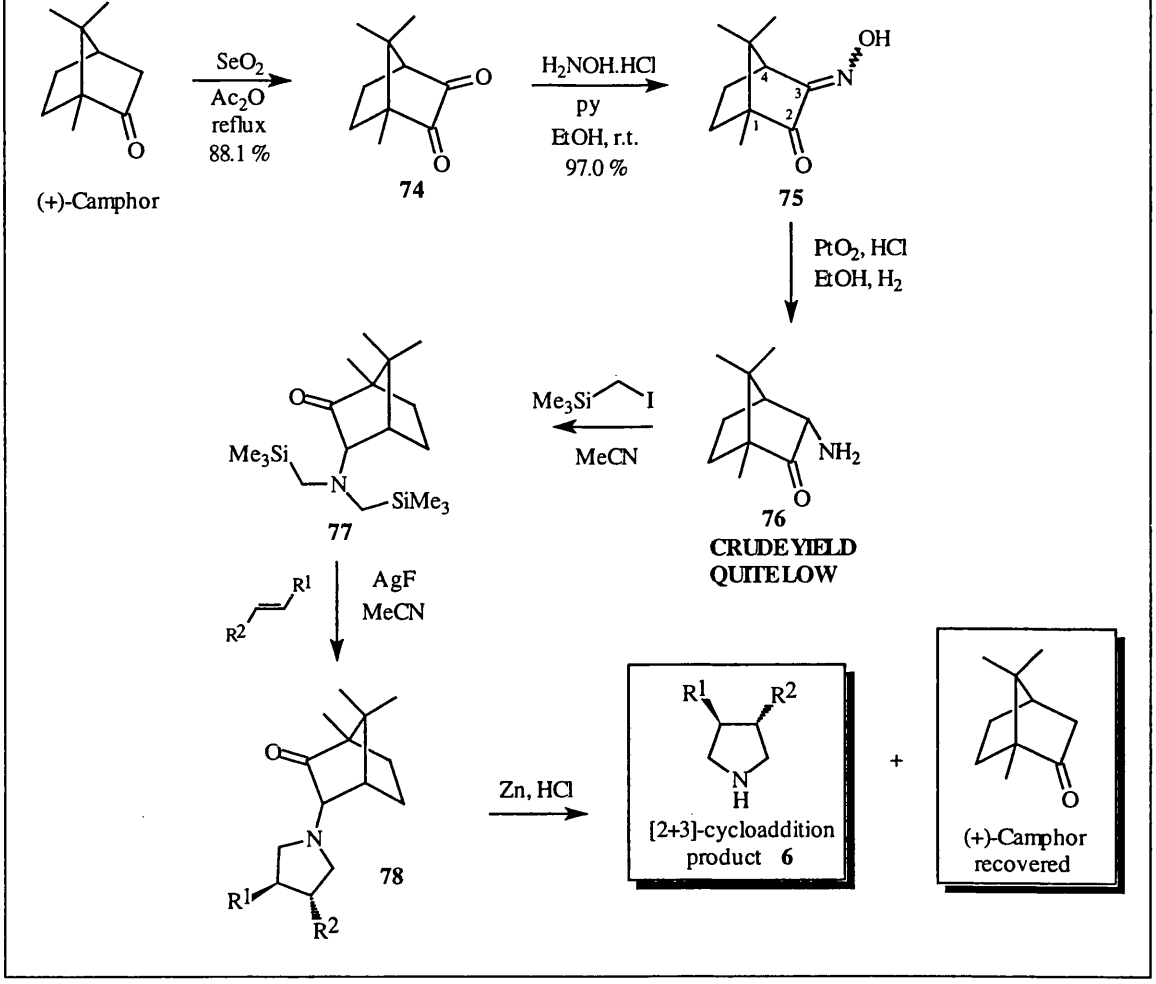
It was also decided to react the *endo*-3-bromocamphor with trimethylsilylmethyl amine as shown in **Scheme 51**. However, again, no reaction was found to take place. Again, this indicated that the camphor framework was too bulky to allow the Me_3Si methyl group to be attached the *exo* side of camphor.



Scheme 51

3.3.2 The utilisation of a camphor-amine **76**

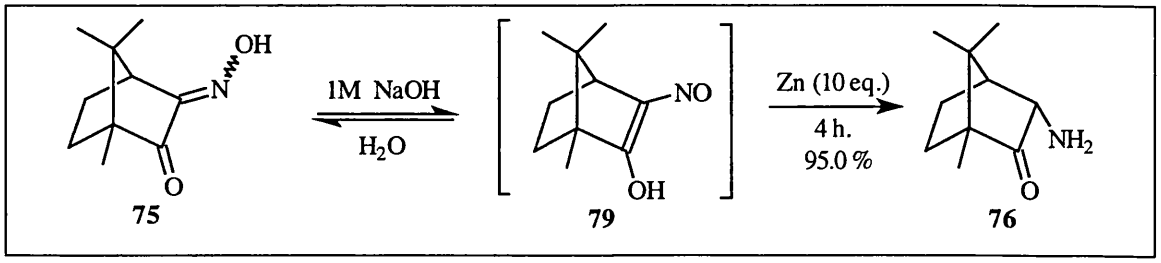
After a further analysis of the problem it was envisaged that the *endo*-camphor amine **76** might be successfully used to prepare the cycloaddition precursor **77** as there was less bulk around the amine group (**Scheme 52**).



Scheme 52

(+)-Camphorquinone-3-oxime **75** is commercially available but is relatively expensive. It was decided therefore to prepare this starting from the much cheaper (+)-camphor itself. (+)-Camphorquinone **74** was prepared by the oxidation of (+)-camphor with SeO_2 in acetic anhydride.[135] This proceeded in 88 % yield and furnished **74** as light crystals. The carbonyl at position 3 was then converted to (+)-camphorquinone-3-oxime **75** [136] in 97 % yield by treatment with hydroxylamine hydrochloride and pyridine in absolute ethanol. The 400 MHz ^{1}H n.m.r. spectrum showed the C-4 proton as a doublet at δ 3.20 (J_{HH} 4.8 Hz) and also showed that a mixture of *syn*:*anti* isomers around the N-OH bond was present in a ratio of approx. 5:1. This was further seen in the 100 MHz ^{13}C n.m.r. spectrum where two peaks were observed for the carbonyl group at δ 204.3 and δ 203.5 as well as two for the oxime carbon at δ 159.4 and δ 156.0. A further 16 carbon peaks were also observed as required. The HRMS mass spectrum (FAB, MNOBA matrix) also showed an $(M+H)^+$ ion at *m/e* 182.118 indicating an empirical formula of $C_{10}H_{16}NO_2$. The I.R. spectrum contained the characteristic imine C=O stretch at 1740 cm^{-1} as well as the C=N stretch at 1642 cm^{-1}. The reduction of the

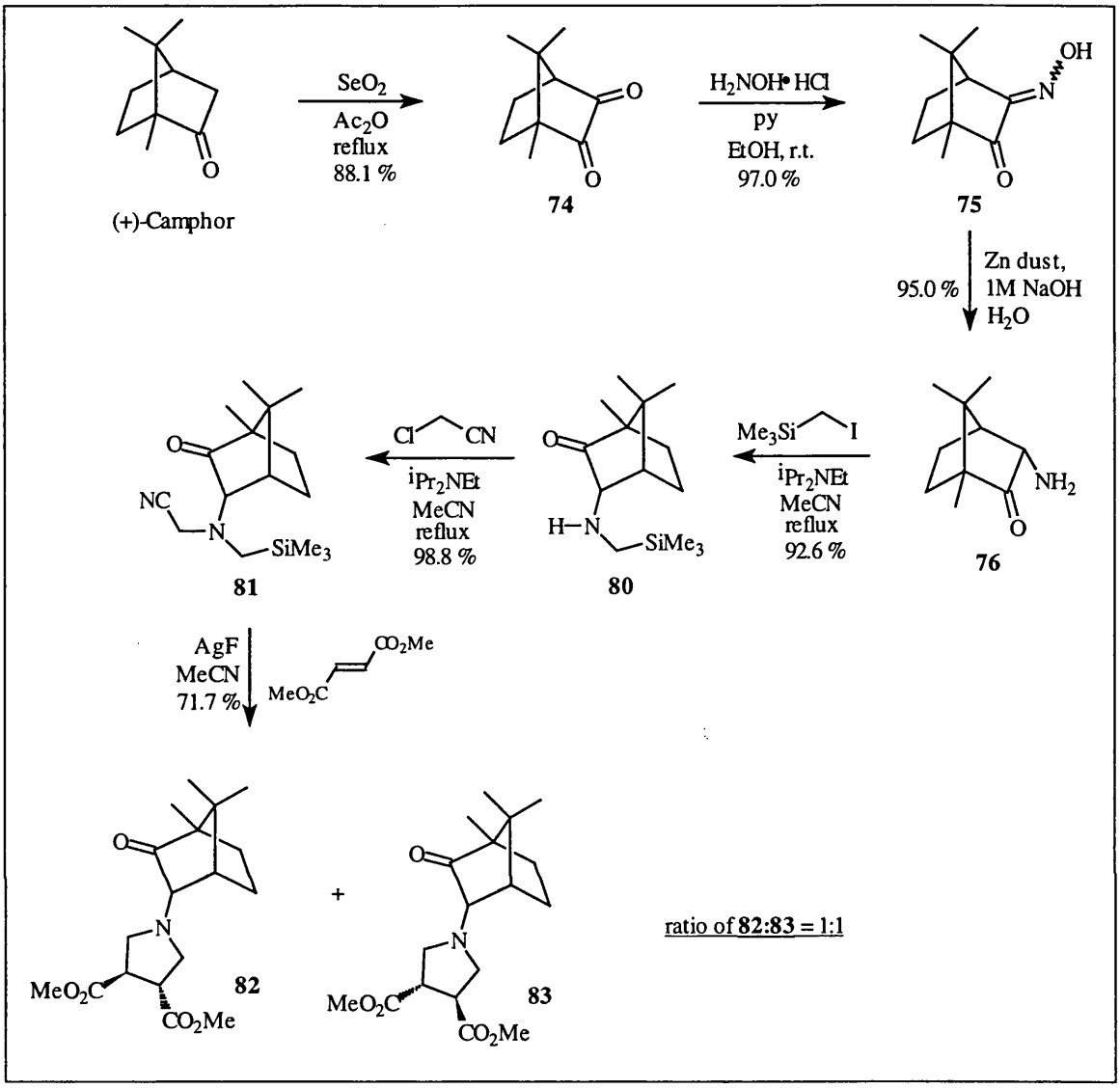
oxime using PtO_2 and HCl in EtOH under hydrogen according to Beckett *et al.*[137] gave an unacceptable yield of crude product amine **76**. Palladium on carbon in a mixture of HCl and EtOH has also been utilised to prepare amine **76**,[138] but it was decided to used the procedure suggested by Duden *et al.*[139] This uses the fact that under basic conditions the oxime **75** is in equilibrium with the nitroso compound **79** as shown in **Scheme 53**. The equilibrium was shifted to the right by treating the oxime **75** with 1M aqueous NaOH solution followed by immediate addition of 10 equivalents of zinc dust in order to reduce the nitroso group to the primary amine **76**. This proceeded smoothly over 4 hours in 95 % yield.



Scheme 53

Amine **76** was then treated with 1.47 equivalents of (iodomethyl)trimethylsilane in the presence of 1.52 equivalents of Hünig's base in MeCN and the reaction mixture stirred at reflux for 22 h. Aqueous work-up furnished crude (1*R*)-*endo*-(+)-3-(*N*-trimethylsilylmethyl)camphor amine **80** as a clear yellow oil in 93 % crude yield. It was found that this compound could be used crude for the subsequent reaction with a yield loss of approx. 10 %. The 400 MHz ^{1}H n.m.r. spectrum showed the Me_3Si group present at δ 0.05 as well as the -CH_2- next to the Me_3Si group as two non-equivalent doublets at δ 1.88 (J_{HH} 13.4 Hz) and δ 1.94 (J_{HH} 13.4 Hz). The NH group was observed as a broad singlet at δ 1.38. The 100 MHz ^{13}C n.m.r. spectrum showed the Me_3Si group at δ -2.7, the C=O group at δ 219.3 and the signal from C-3 at δ 68.5. The FAB-MS mass spectrum (MNOBA matrix) for $C_{14}H_{28}NOSi$ further contained a correct $(M+H)^+$ peak at *m/e* 254.3. The secondary amine **80** was treated with Hünig's base (1.64 equivalents) and chloroacetonitrile (1.63 equivalents) in MeCN to afford (1*R*)-*endo*-(+)-3-(*N*-cyanomethy-*N*-trimethylsilyl methyl)camphor amine **81** as a clear oil in up to 99 % yield. The 400 MHz ^{1}H n.m.r. spectrum showed the two newly-introduced -CH_2- next to the -CN group as two doublets at δ 4.38 (J_{HH} 17.4 Hz) and δ 3.44 (J_{HH} 17.4 Hz). The 100 MHz ^{13}C n.m.r. spectrum indicated the presence of the new -C≡N group at δ 115.0. The HRMS mass spectrum (FAB, MNOBA matrix) also gave the correct

(M+H)$^+$ peak at *m/e* 293.2049 which corresponded to a formula of $C_{16}H_{29}N_2OSi$. (See **Scheme 54** for the general pathway taken).



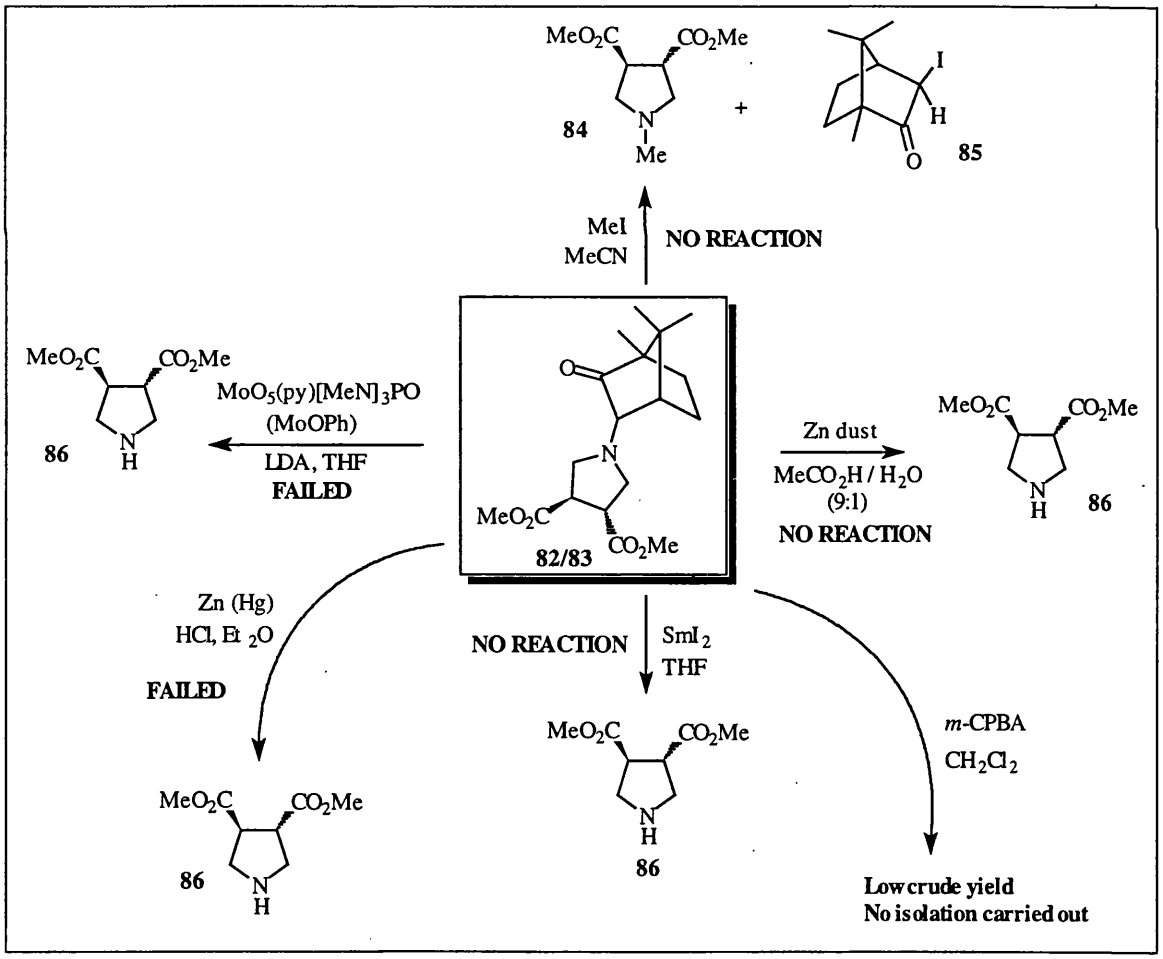
Scheme 54

The cycloaddition of **81** with dimethyl fumarate (2 equivalents) and AgF (1.7 equivalents) in MeCN was then performed. The mixture was stirred in the dark for up to six days and the product purified by flash chromatography eluting with hexanes:EtOAc, 10:1. This successfully afforded the required cycloadducts **82** and **83** in up to 72 % yield based on recovered unreacted starting material. The 400 MHz ^{1}H n.m.r. spectrum confirmed that the cycloaddition had been successful, but it showed that a 1:1 mixture of diastereoisomers had been formed. Specifically, in the 400 MHz ^{1}H n.m.r. spectrum of **82** and **83** there were two methyl ester singlets present in similar ratio at δ 3.67 and δ 3.68. The 100 MHz ^{13}C n.m.r. spectrum also showed three C=O groups, one from the camphor at δ 216.3, and the other two from the two methyl ester

groups on the pyrrolidine ring at δ 173.9 and δ 173.8. The HRMS mass spectrum (FAB, MNOBA matrix) of **82** and **83** for $(M+H)^+$ contained an ion at *m/e* 338.1967 as one would expect for a compound of empirical formula $C_{18}H_{28}NO_5$. The I.R. spectrum also showed the usual ester C=O peak at 1741 cm^{-1}.

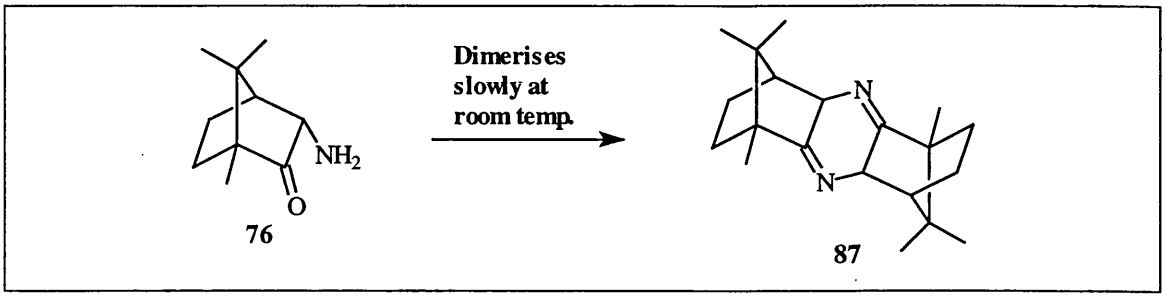
3.3.3 Attempted removal of the pyrrolidine moiety

Although our cycloaddition reaction was not stereoselective, we decided to attempt cleavage of the pyrrolidine ring. Various conditions were attempted as shown in **Scheme 55**. These include (a) the use of MoOPH and LDA in THF,[140] (b) iodomethane in MeCN, (c) zinc dust in a mixture of acetone and water, (d) amalgamated zinc [141] in Et_2O and HCl, (e) SmI_2 in THF and, (f) *m*-CPBA in CH_2Cl_2. However, none of them were successful.



Scheme 55

Another problem encountered in the camphor strategy (**Scheme 54**) was the dimerisation of the amine **76** at room temperature to afford the di-imine **87** as indicated in **Scheme 56** and mentioned briefly by Duden *et al.*[139] When **87** was left at room temperature for up to 96 h an orange paste forms. Flash chromatography in hexanes:EtOAc, 12:1, affords **87** as a light yellow solid with a melting point of 106-108 °C. The 400 MHz ^{1}H n.m.r. spectrum indicated the two -CHN= protons at δ 3.60 as a triplet (2H, J_{HH} 1.2 Hz). The 100 MHz ^{13}C n.m.r. spectrum gave the C=N- peak at δ 187.2 as well as the two other quaternary carbon atoms at δ 54.1 and δ 47.1. The FAB-MS mass spectrum of **87** (FAB, MNOBA matrix) gave rise to an $(M+H)^+$ peak for $C_{20}H_{31}N_2$ at *m/e* 299.3. The I.R. spectrum also gave the imine stretch at 1650 cm^{-1}. Thus, the camphor amine therefore has to be used immediately if kept as the free amine.

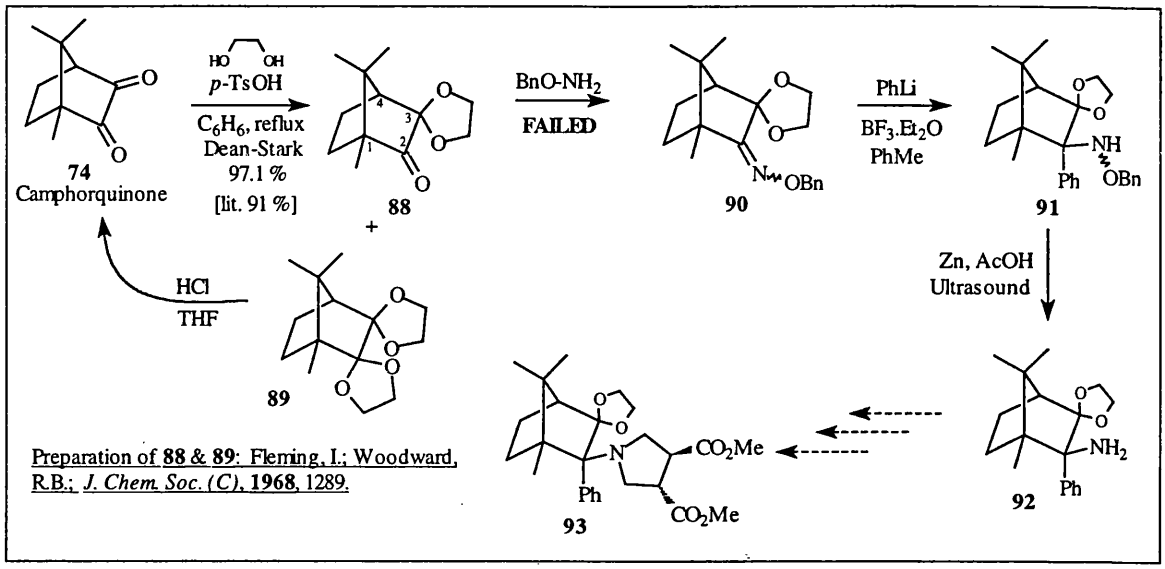


Scheme 56

3.3.4 Attempted introduction of a phenyl group into the auxiliary

Due to the C-N bond cleavage problems we thought it might be worthwhile introducing a phenyl ring on the 3-position of the camphor. If this were possible, we would then be able to cleave off the pyrrolidine ring by hydrogenolysis. However, this would mean re-designing the procedure already found to be partially successful. The new procedure attempted is indicated in **Scheme 57** below. It would start with the mono-protection of camphorquinone. The remaining ketone group in **88** would then be converted to the *O*-benzylated oxime **90**, which in turn would be treated with phenyllithium with the presence of boron trifluoroetherate according to the method of Moody *et al.*[142] If successful, this would yield the protected hydroxylamine **91**. Due to steric hindrance provided by the top methyl group, it was envisaged that the phenyl group would add mainly to the bottom side of the oxime to afford the *exo*-amino-*endo*-phenyl-camphor derivative **91**. Zinc, acetic acid and ultrasound would then be used to

cleave the N-O- bond to afford the free amine **92**. Working through similar processes as previously using (iodomethyl)trimethylsilane, chloroacetonitrile and the subsequent cycloaddition should afford the required cycloadduct **93**. Hydrogenation would then cleave off the pyrrolidine ring. It was also thought that the cycloaddition reaction would be more stereoselective due to steric hindrance from the top methyl group as well as the *endo*-phenyl group.

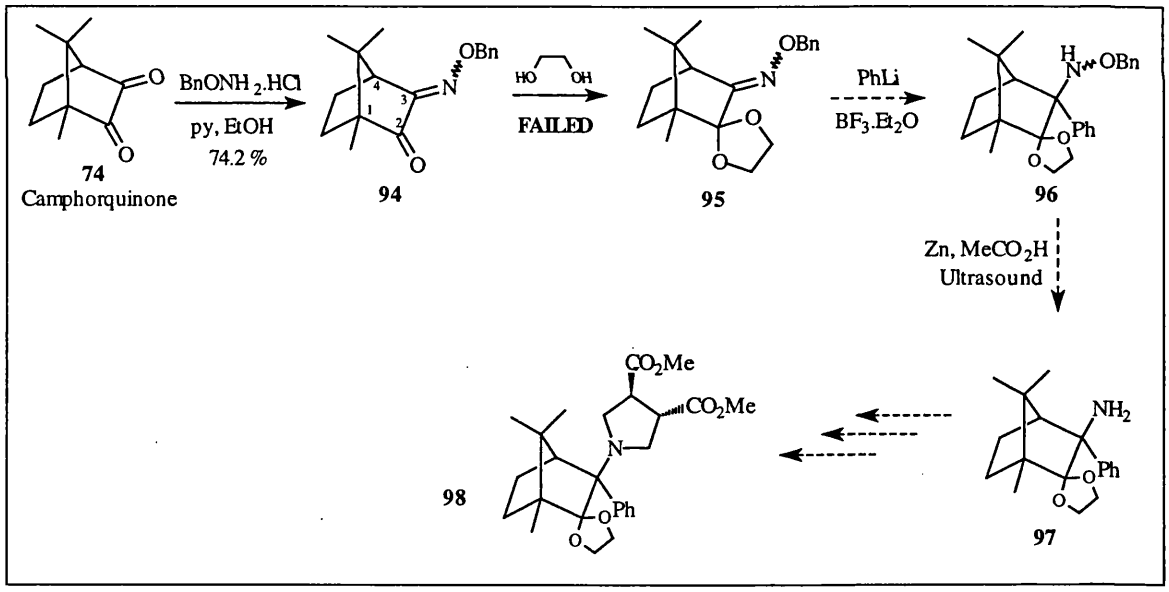


Scheme 57

The route commenced with a protection of camphorquinone **74** using ethylene glycol and *p*-TsOH in benzene under Dean-Stark conditions.[143] This successfully afforded [(1*R*)]-(+)-3,3-ethylenedioxycamphor **88** in up to 97 % based on recovered **74**. The 400 MHz ^{1}H n.m.r. spectrum of **88** showed the three methyl groups at δ 0.80, 0.88 and 0.92. The presence of the ethylenedioxy group was observed as three multiplets at δ 3.85-3.95 and δ 4.05-4.10 and δ 4.17-4.22. The 100 MHz ^{13}C n.m.r. spectrum showed one C=O signal only with the new quaternary C-3 peak at δ 106.8. The HRMS mass spectrum (FAB, MNOBA matrix) also gave the correct $(M+H)^+$ peak at *m/e* 211.1334 indicating a formula of $C_{12}H_{19}O_3$ and the I.R. spectrum gave the C=O stretch at 1754 cm^{-1}. The 400 MHz ^{1}H n.m.r. for the 2,2,3,3-diethylenedioxycamphor **89** by-product showed the three methyl groups at δ 0.60, 0.68 and 0.98. The diethylenedioxy group was found as multiplets in the range δ 3.55-3.79. The C-4 proton was observed as a double triplet at δ 1.15 (J_{HH} 12.4 Hz, 1.2 Hz). The 100 MHz ^{13}C n.m.r. spectrum of **89** showed the absence of any carbonyl groups as did the I.R. spectrum. The HRMS mass spectrum (FAB, MNOBA matrix) also gave the required $(M+H)^+$ ion of *m/e* 255.1596 which

corresponded to $C_{14}H_{23}O_4$. The next step of treating **88** with *O*-benzyl-hydroxylamine hydrochloride in EtOH and pyridine failed. The reaction was also attempted using free *O*-benzylhydroxylamine in pyridine, but this also failed. As a last attempt, the reaction was repeated with *O*-benzylhydroxylamine and *p*-TsOH in benzene set up in a Dean-Stark apparatus. Again this was unsuccessful and so the method was abandoned at this point. It is possible that the ketone was simply too sterically hindered and the formation of the oxime **90** is impossible via this method.

We then decided to attempt the reverse of the process shown above. This is indicated in **Scheme 58** below. The first step would be the formation of [(1*R*)]-(+)-*O*-benzylhydroxyl-camphorquinone-3-oxime **94** followed by the protection of the remaining ketone using ethylene glycol to afford **95**. Again the protocol of Moody *et al.*[142] would be used in order to afford what would be expected to be mainly the *exo*-amine **97**. Working through the same procedure as described above (**Scheme 57**) would generate the *exo*-cycloadduct **98**. Hydrogenation should again cleave off the pyrrolidine ring.

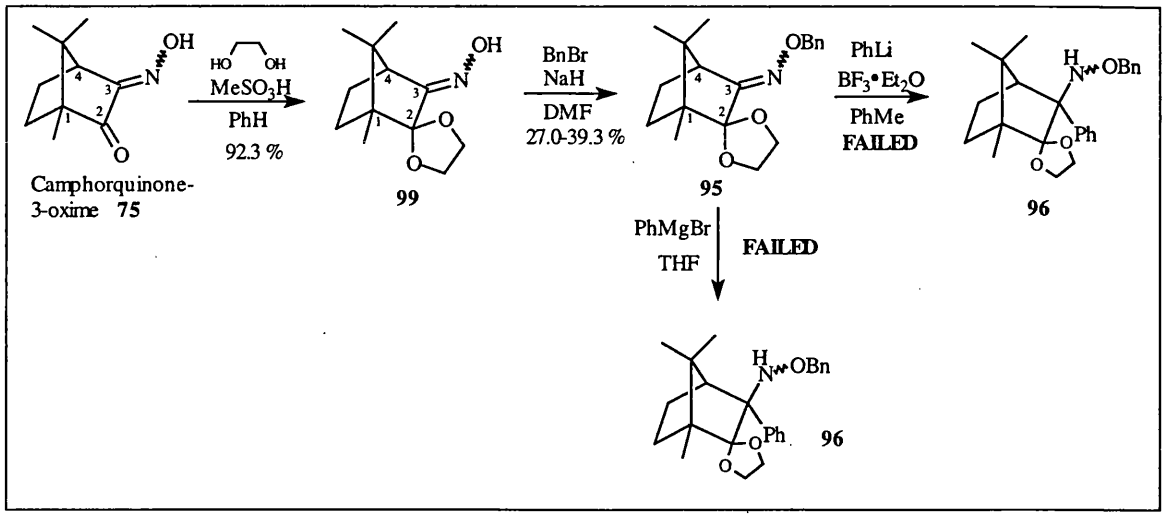


Scheme 58

The initial step, the preparation of **94** was carried out as in the preparation of camphorquinone-3-oxime **75**. Camphorquinone **74** was treated with pyridine and *O*-benzylhydroxylamine hydrochloride in absolute EtOH. This afforded the required *O*-benzylated oxime **94** as a clear liquid in 74 % yield. The 400 MHz ^{1}H n.m.r. indicated a

mixture of *syn* and *anti* isomers around the N-O bond of approx. 2.8:1 as shown by the two C-4 proton doublets from the major isomer at δ 3.17 (J_{HH} 4.4 Hz) and the minor isomer at δ 2.60 (J_{HH} 4.4 Hz). The 100 MHz ^{13}C n.m.r. spectrum also showed the presence of two isomers; it revealed two C=O groups at δ 203.9 and δ 197.9, two oxime -C=N- peaks at δ 159.2 and δ 156.4 as well as two peaks for the benzyl -CH_2- group at δ 77.2 and δ 77.2. In like fashion, the I.R. spectrum contained the expected C=O peak at 1748 cm^{-1} and the oxime -C=N- peak at 1634 cm^{-1}. Finally, the HRMS mass spectrum (FAB, MNOBA matrix) corroborated an empirical formula of $C_{17}H_{22}NO_2$ for **94**; it contained the correct $(M+H)^+$ peak at *m/e* 272.1651. Again, however, problems were encountered in the protection of the carbonyl group. The first method attempted used a mixture of ketone **94**, ethylene glycol and *p*-TsOH in benzene in a Dean-Stark apparatus, but this proved to be unsuccessful. The second method used the same setup, but $MeSO_3H$ was used in preference to *p*-TsOH. Since no reaction was observed, the approach was abandoned.

We then postulated that the presence of the benzyl group on the oxime **94** might be preventing us from protecting this remaining carbonyl group, and it was therefore decided to attempt the protection using camphorquinone-3-oxime **75** as indicated in **Scheme 59**.

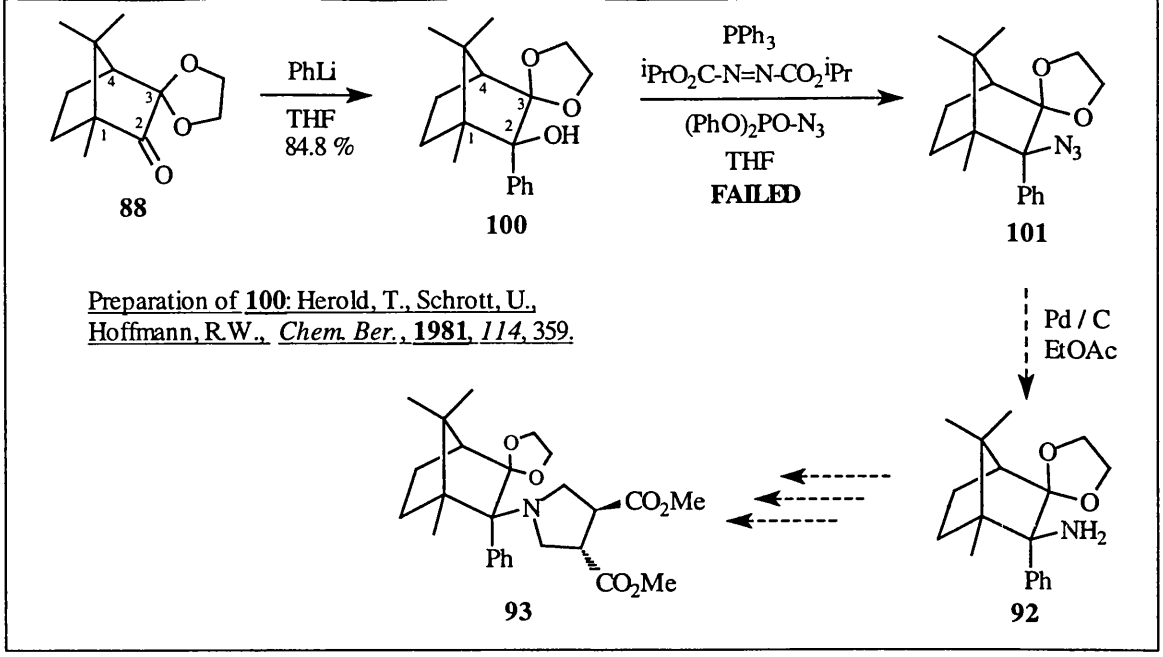


Scheme 59

The initial attempt failed using *p*-TsOH in neat ethane-1,2-diol in a similar manner to Lester *et al.*[144] The ketone protection using ethane-1,2-diol and a catalytic amount of $MeSO_3H$ in benzene was then attempted. To a solution of **75** in benzene was added

$MeSO_3H$ and ethane-1,2-diol and the mixture stirred at gentle reflux for 24 h. Aqueous work-up and flash chromatography using a mixture of hexanes/EtOAc, 2:1, furnished 2,2-ethylenedioxy-camphorquinone-3-oxime **99** as a clear yellow oil in 92 % yield. The 400 MHz ^{1}H n.m.r. spectrum suggested that only one isomer now existed around the =N-O- bond. The expected three methyl groups were located at δ 0.92, 1.06 and 1.09. The C-4 proton was observed as a triplet at δ 2.71 (J_{HH} 9.6 Hz) and the -OH group as a broad singlet at δ 2.89. The ethyleneoxy group gave rise to a triplet at δ 3.66 (2H, J_{HH} 4.8 Hz) and a multiplet in the range of δ 4.01-4.10. The 100 MHz ^{13}C n.m.r. spectrum also showed the formation of one isomer only. The oxime -C=N-OH peak was observed at δ 174.9 with no other minor peak for the other isomer in this region. The I.R. spectrum gave the usual oxime stretch at 1724 cm^{-1} and the HRMS mass spectrum (FAB, MNOBA matrix) for **99** contained the expected $(M+H)^+$ ion at *m/e* 226.1443 indicating an empirical formula of $C_{12}H_{20}NO_3$. The -OH group was then protected as the required -OBn oxime **95** using benzyl bromide and sodium hydride in DMF in 27-39 % yield. The 400 MHz ^{1}H n.m.r. spectrum of the product showed the benzyl -CH_2- at δ 4.53 with the C-4 proton being observed as a triplet at δ 2.79 (J_{HH} 9.8 Hz). The ethyleneoxy group resulted in three multiplets being present at δ 3.62-3.68, δ 4.16-4.26 and δ 4.27-4.35. Treatment of this *O*-benzylated oxime **95** with phenyllithium and BF_3•Et_2O in toluene gave no reaction. Treating **95** with PhLi in THF at -78 °C without BF_3•Et_2O also failed. Since Cativiela *et al.*[145] had added vinyl magnesium bromide to a -C=N- double bond in an imine to afford the corresponding secondary amine, we speculated that this method might be applicable to our oxime. However, the reaction of **95** with phenyl magnesium bromide in THF was also unsuccessful.

Due to these results, it was decided to attempt the preparation of alcohol **100** as shown in **Scheme 60**. Converting this to the azide **101**, and hydrogenation would furnish the amine **92** from which the cycloadduct **93** could be prepared. The only problem we perceived was that of steric hindrance from the top methyl group as found earlier with [(1*R*)]-*endo*-(+)-3-bromocamphor (**Scheme 50**).

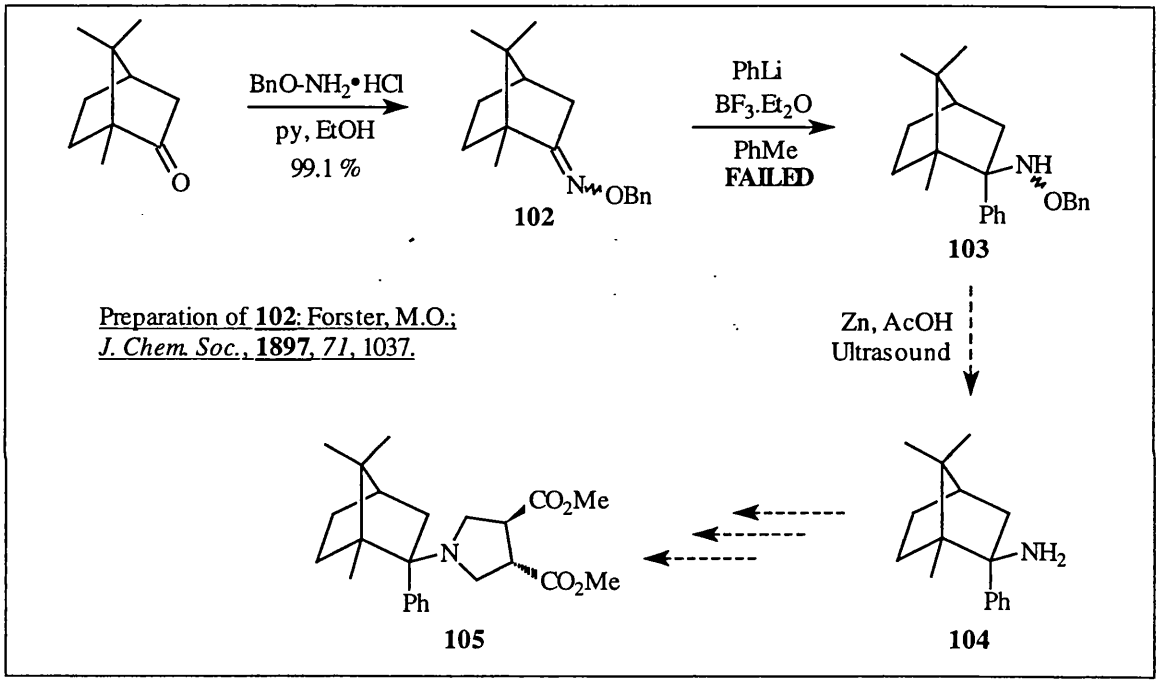


Scheme 60

The preparation of **100** was achieved by following the protocol of Herold *et al.*[146] Alcohol **100** was obtained in 85 % yield by treating **88** with phenyl lithium in THF at -78 °C and stirring at room temperature for 4 h. Aqueous work-up and flash chromatography afforded the alcohol as a clear oil. The 400 MHz ^{1}H n.m.r. spectrum showed the three methyl groups at δ 0.73, 0.94 and 1.33 with the ethylenedioxy group as two multiplets between δ 3.19-3.25 (1H) and δ 3.77-3.88 (3H). The C-4 proton appeared as a doublet at δ 1.86 (J_{HH} 4.8 Hz) and the -OH was observed as a singlet at δ 3.46. The 100 MHz ^{13}C n.m.r. spectrum gave no C=O signal as expected and showed the required number of aromatic peaks at δ 141.0, 129.4, 126.4 and 126.2. The quaternary C-3 peak was also found at δ 116.8 which is a shift of 10.05 ppm downfield compared to the C-3 peak observed for [(1*R*)]-(+)-3,3-ethylenedioxycamphor **88.** The new C-2 quaternary carbon was observed at δ 84.5. The I.R. spectrum indicated the required -OH peak at 3516 cm^{-1}. The final piece of structural evidence was supplied by the HRMS mass spectrum (FAB, MNOBA matrix) for **100** which gave rise to an $(M)^+$ ion at *m/e* 288.1725 corroborating a formula of $C_{18}H_{24}O_3$. The direct conversion of the alcohol **100** to the azide **101** was carried out according to Bose *et al.*[147] using commercially available diphenylphosphoryl azide.[148] Triphenylphosphine and diisopropyl azodicarboxylate was added to a solution of **100** in THF while stirring at room temperature. This was followed by the slow addition of diphenylphosphoryl azide. After stirring at room temperature for 3 days the mixture was concentrated, but

TLC showed no reaction and the method was abandoned. It thus appears that the -OH group is too sterically hindered for it to be activated and displaced by the azide ion.

It was also decided to prepare (1*R*)-(+)-*O*-hydroxybenzyl-camphorquinone-2-oxime **102** [149] and then exploit the Moody phenyllithium/oxime addition reaction as mentioned earlier (**Scheme 61**). Zinc dust, acetic acid and ultra sound would then give the amine **104** which could be treated with (iodomethyl)trimethylsilane, chloroacetonitrile and then AgF and a suitable dipolarophile to give the cycloadduct **105**.

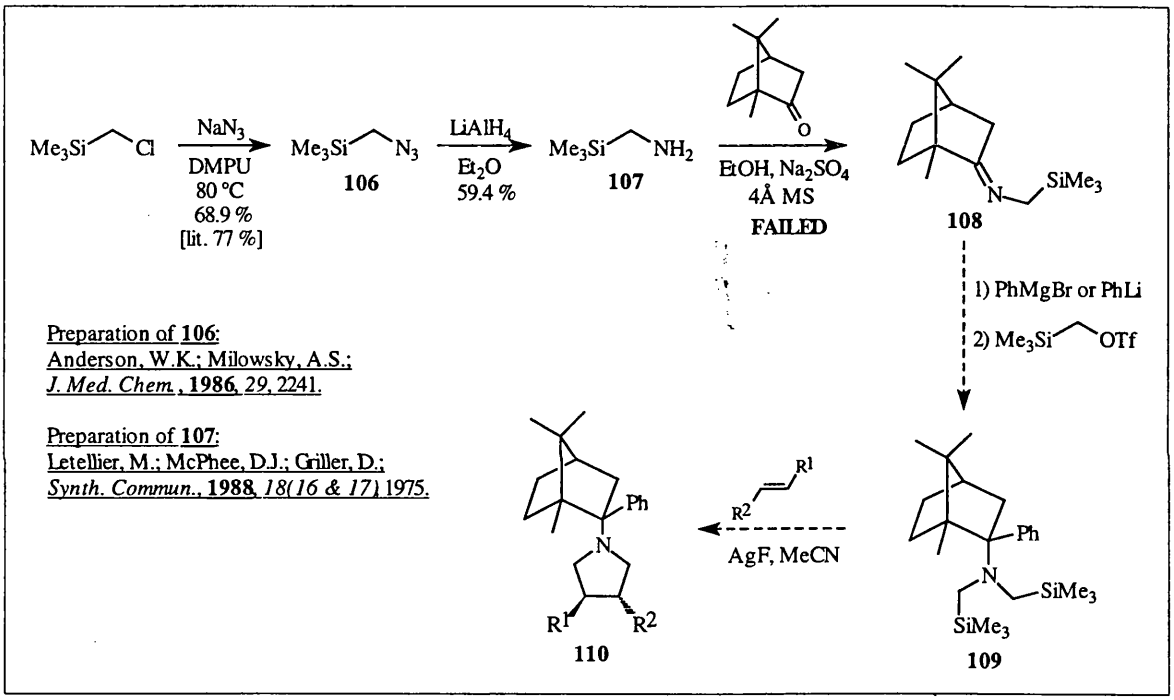


Scheme 61

The preparation of **102** was successfully carried out in 99 % yield by treating (+)-camphor with *O*-benzylhydroxylamine hydrochloride in pyridine and ethanol. The 400 MHz ^{1}H n.m.r. spectrum showed the formation of one isomer only. The benzyl -CH_2- was seen as a singlet at δ 5.15 with the three methyl groups at δ 0.82, 0.96 and 1.10. The 100 MHz ^{13}C n.m.r. spectrum also indicated only one isomer and there was no C=O group present. The benzylic -CH_2- group was observed at δ 75.0, with the phenyl group carbons found at δ 138.4, 128.0, 127.6 and 127.2. The quaternary oxime C=N-OR peak was found in its characteristic place of δ 169.4. The I.R. spectrum also gave the usual weak oxime -C=N- stretch at 1664 cm^{-1} and the HRMS mass spectrum (FAB, MNOBA matrix) also gave the expected $(M+H)^+$ ion at *m/e* 258.1858 corresponding to a formula

$C_{17}H_{24}NO$. Treating **102** with phenyl lithium and $BF_3 \cdot Et_2O$ in toluene gave numerous products as observed by TLC and no isolation attempts were carried out.

Another method based on [(1*R*)]-(+)-camphor as the starting material is indicated in **Scheme 62** below. This started with the formation of the imine **108**. This was then to be reacted with PhMgBr as of Cativiela *et al.*[145] or with PhLi followed by reaction with trimethylsilylmethyl triflate to afford the bis-(*N,N*-trimethylsilylmethyl) amine derivative **109** on which the cycloaddition with a suitable dipolarophile would be carried out.



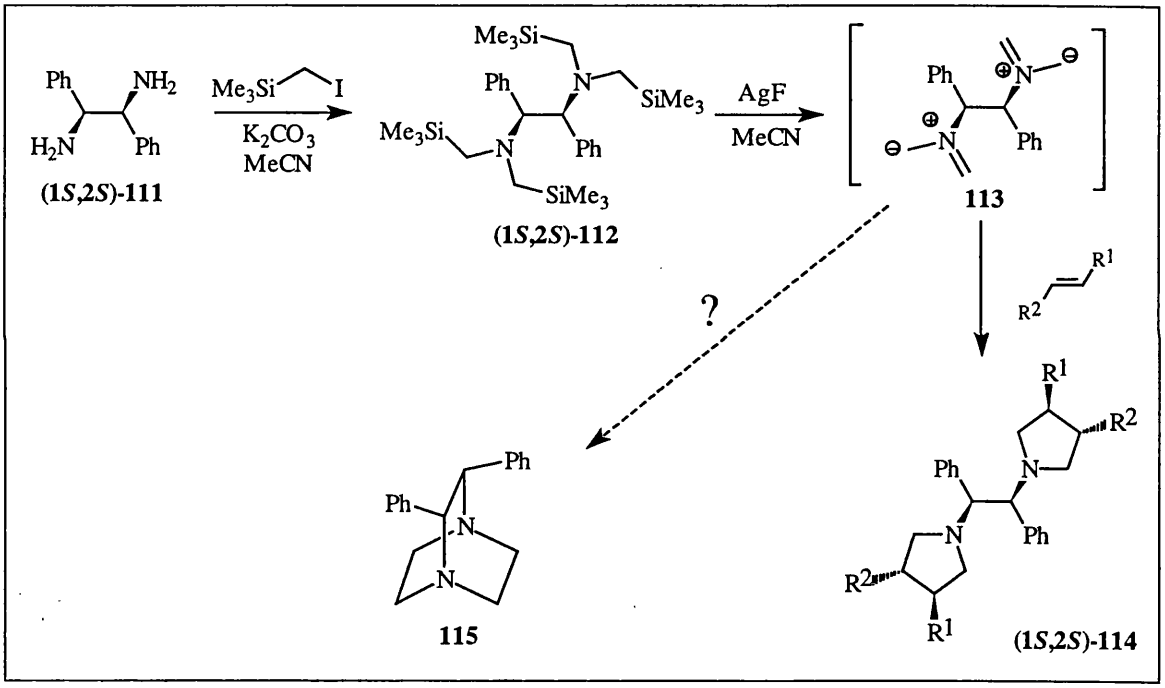
Scheme 62

Trimethylsilylmethyl amine is commercially available and has been used previously in this project, but it is extremely expensive. It was therefore decided to prepare this compound. This started with the preparation of trimethylsilylmethyl azide **106** according to Anderson *et al.*[150] The azide was then reduced to trimethylsilylmethyl amine **107** according to Letellier *et al.*[151] The reaction of camphor with trimethylsilylmethyl amine in absolute EtOH proved to be unsuccessful. Repeating the reaction and adding Na_2SO_4 and 4Å activated molecular sieves to the mixture also proved to be unsuccessful.

Due to the problems already encountered in this camphor based sequence of reactions, we abandoned further development of this approach at this stage. It was felt more advantageous to pursue another line of investigation, namely the preparation of a precursor for the double [3+2]-cycloaddition of azomethine ylides.

3.4 Attempting the preparation of a double [3+2]-cycloaddition precursor based on (1*S*,2*S*)-(-)-1,2-diamino-1,2-diphenylethane

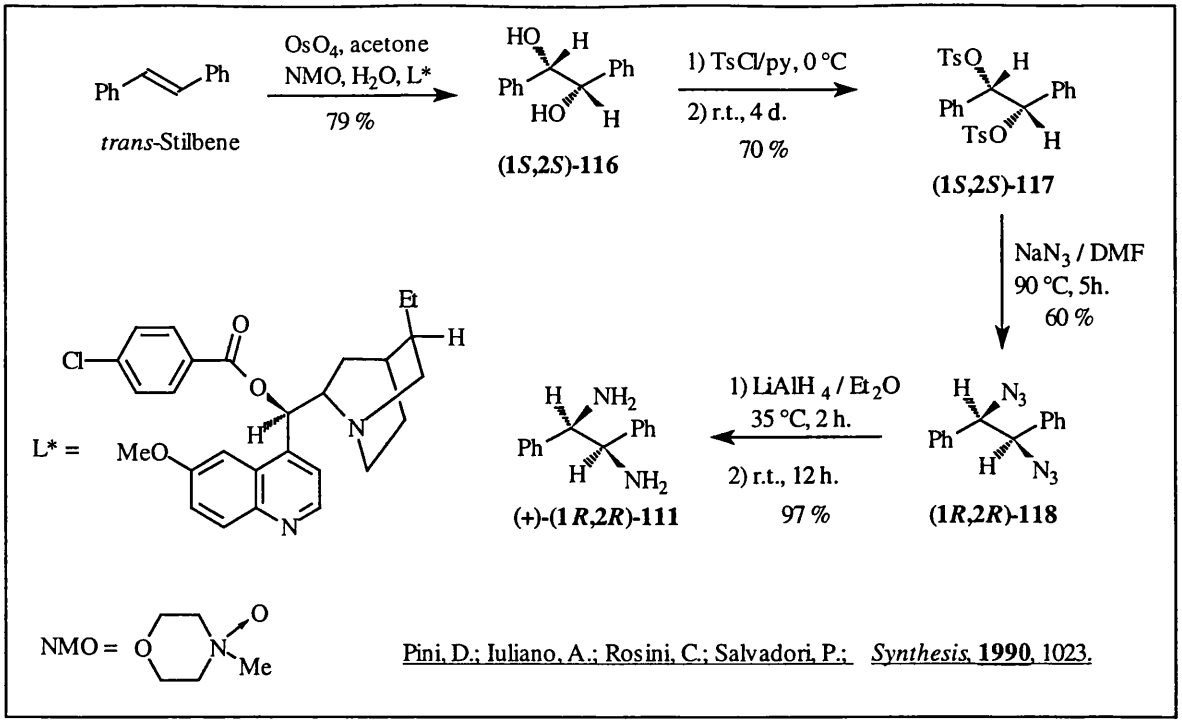
Another chiral auxiliary we evaluated was based on (1*S*,2*S*)-(-)-1,2-diamino-1,2-diphenylethane **111** and the strategy shown in **Scheme 63**. It was envisaged that the diamine **111** could be converted to **112** by addition of (iodomethyl)trimethylsilane in the presence of a suitable base. Treatment of this precursor with AgF and a suitable dipolarophile would afford the bis(pyrrolidine) cycloadduct **114**. However, the di-ylide **113** may also cyclise *in-situ,* thus affording the bicyclo[2,2,2]-system **115** which may show great future potential as a chiral base.



Scheme 63

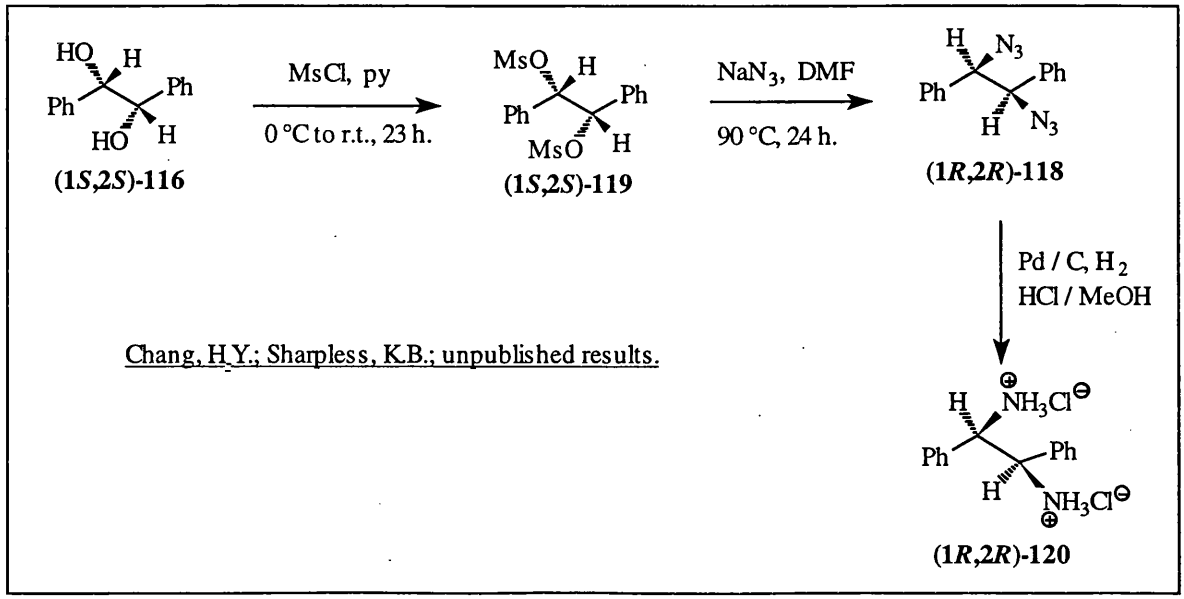
3.4.1 Preparation of (1*S*,2*S*)-(-)-1,2-diamino-1,2-diphenylethane **111**

(1*S*,2*S*)-(-)-1,2-Diamino-1,2-diphenylethane **111** is commercially available, but is rather expensive. It was therefore decided to prepare this compound. Previous routes to optically pure stilbenediamine have entailed resolution of the racemic diamine.[152] Salvadori *et al.*[153] has developed a four-step procedure for preparing stilbenediamine using *trans*-stilbene as the starting material (**Scheme 64**).



Scheme 64

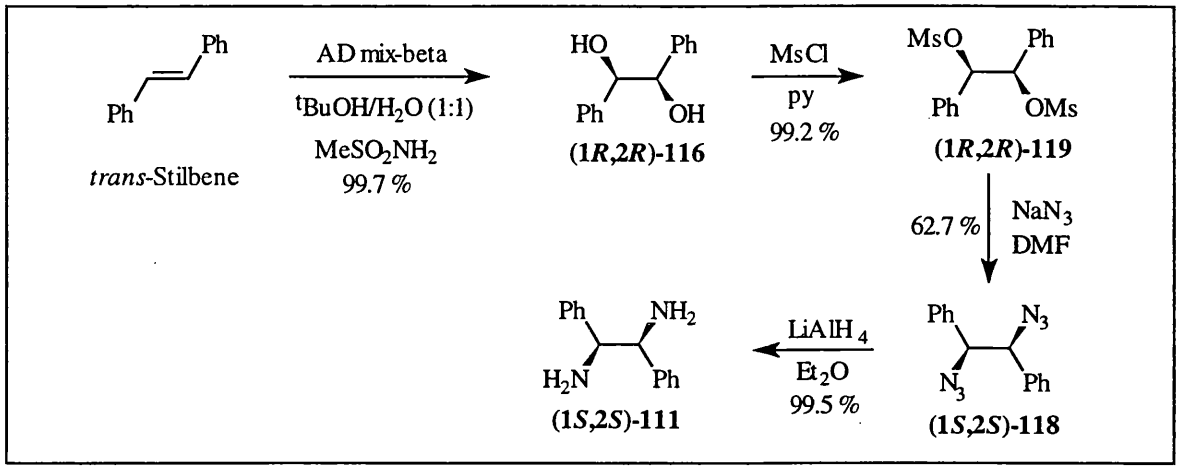
The asymmetric catalytic *cis*-dihydroxylation of *trans*-stilbene to obtain enantiomerically pure diol **(*S,S*)-116** has been achieved using OsO_4, acetone, NMO/H_2O and dihydroquinine *p*-chlorobenzoate as the ligand (Sharpless method).[154] After conversion to the bis-*p*-toluenesulfonate **(*S,S*)-117**, double displacement with NaN_3 followed by reduction, provides enantiomerically pure (+)-(*R,R*)-stilbenediamine **(*R,R*)-111** in 32 % overall yield. More recently, Chang has developed a route to the bishydrochloride salt **(*R,R*)-120** of (*R,R*)-stilbenediamine [155] **(Scheme 65)**.



Scheme 65

The last two procedures offer advantages over earlier resolution-based methods, since they use only readily available starting materials and either enantiomer can be obtained through proper choice of ligand for the AD step. In addition, the method may be adapted for the preparation of other enantiomerically pure diamines, provided the corresponding alkenes contain no functional groups which are incompatible with osmium tetroxide.

Our method for the preparation of stilbene diamine **111** combines the work of Salvadori and Chang. It is indicated below (**Scheme 66**).

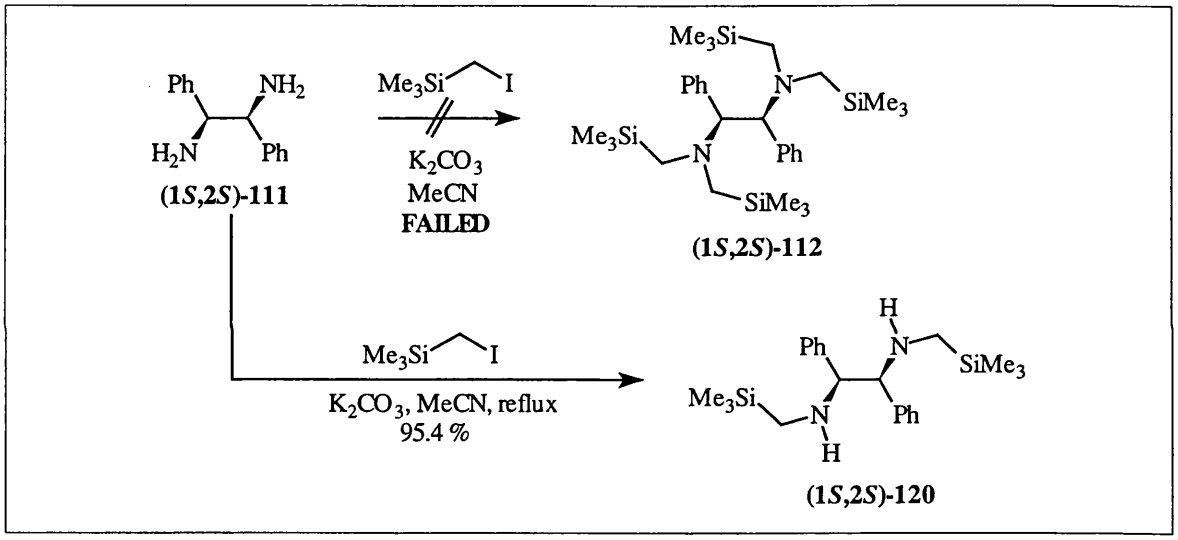


Scheme 66

The procedure started with the preparation of enantiomerically pure stilbenediol from *trans*-stilbene. We used the Sharpless AD method using AD-mix-β.[155] This proceeded cleanly to give (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediol (**1*R*,2*R*)-116** in quantitative yield. Reacting the diol **(1*R*,2*R*)-116** with mesyl chloride in pyridine at room temperature for 3 h afforded (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-dimesyloxyethane **(1*R*,2*R*)-119** in up to quantitative yield. Treatment with sodium azide in DMF at 90 °C for 7 h gave (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-diazide **(1*S*,2*S*)-118** in 63 % yield, which on reduction using $LiAlH_4$ gave (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-diamine **(1*S*,2*S*)-111** in quantitative yield. The 400 MHz ^1H n.m.r. spectrum of **(1*S*,2*S*)-111** showed the two $-NH_2$ groups as a singlet at δ 1.58 and the two methines next to the aromatic rings resonated as a singlet at δ 4.08. The 100 MHz ^{13}C n.m.r. spectrum showed the methines next to the aromatic rings at δ 61.8. The HRMS mass spectrum (FAB, MNOBA matrix) of **(1*S*,2*S*)-111** showed the correct $(M+H)^+$ peak at *m/e* 213.1392 indicating an empirical formula of $C_{14}H_{17}N_2$.

3.4.2 Attempted preparation of the cycloaddition precursors **112/120**

The reaction of diamine **(1*S*,2*S*)-111** with four equivalents of (iodomethyl)-trimethylsilane in acetonitrile with potassium carbonate as the base did not replace all four amine protons. Only two were replaced, one on each amine, as shown by the symmetry indicated in the n.m.r. data. The reaction was successfully repeated in up to 95 % yield using 2.41 equivalents of (iodomethyl)trimethylsilane and 3 equivalents of base to give (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-(*N*',*N*''-bis-trimethylsilylmethyl)-diamine **(1*S*,2*S*)-120** as a clear yellow oil which solidified on standing at room temperature (**Scheme 67**).

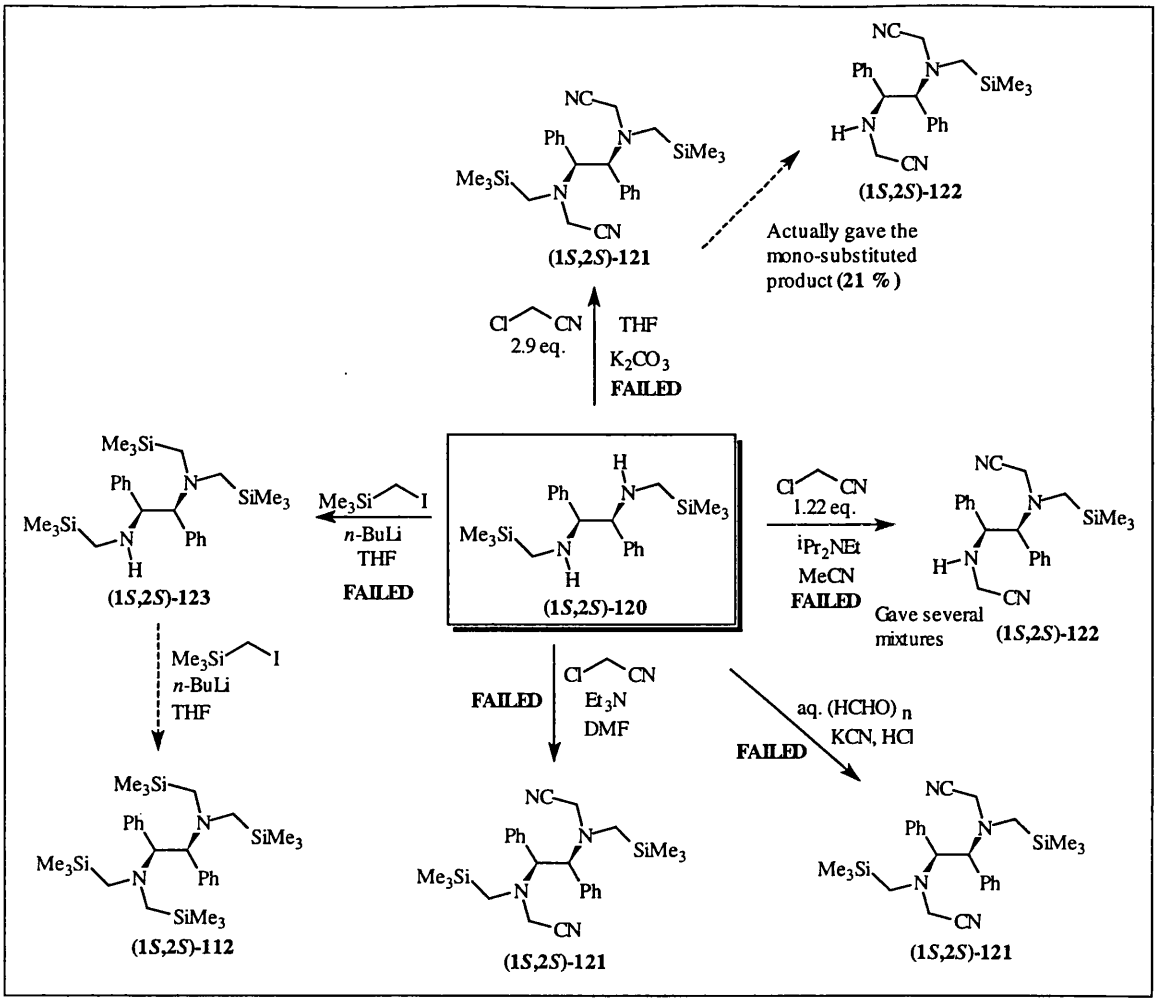


Scheme 67

The 400 MHz ^{1}H n.m.r. spectrum of **(1*S*,2*S*)-120** showed the two Me_3Si groups as a singlet at δ 0.01 with each of the -CH_2- protons next to the Me_3Si group giving rise to a doublet each at δ 1.75 (J_{HH} 13.6 Hz) and δ 1.87 (J_{HH} 13.6 Hz). The two -NH- groups were observed as a broad singlet at δ 1.89 with the remaining two methine protons next to the aromatic rings being seen as a singlet at δ 3.45. This is a shift of 0.63 ppm upfield as compared to the diamine **(1*S*,2*S*)-111**. The 100 MHz ^{13}C n.m.r. spectrum showed the newly-introduced Me_3Si groups and the -CH_2- groups as singlets at δ -2.6 and δ 37.7 respectively. The two methine groups were now observed in the ^{13}C n.m.r. spectrum at δ 73.4, a shift of 11.6 ppm downfield from the same group in the diamine **(1*S*,2*S*)-111**. The HRMS mass spectrum (FAB, MNOBA matrix) of **(1*S*,2*S*)-120** was

also correct, it showing an $(M+H)^+$ ion at *m/e* 385.2495 corresponding to a formula of $C_{22}H_{37}N_2Si_2$.

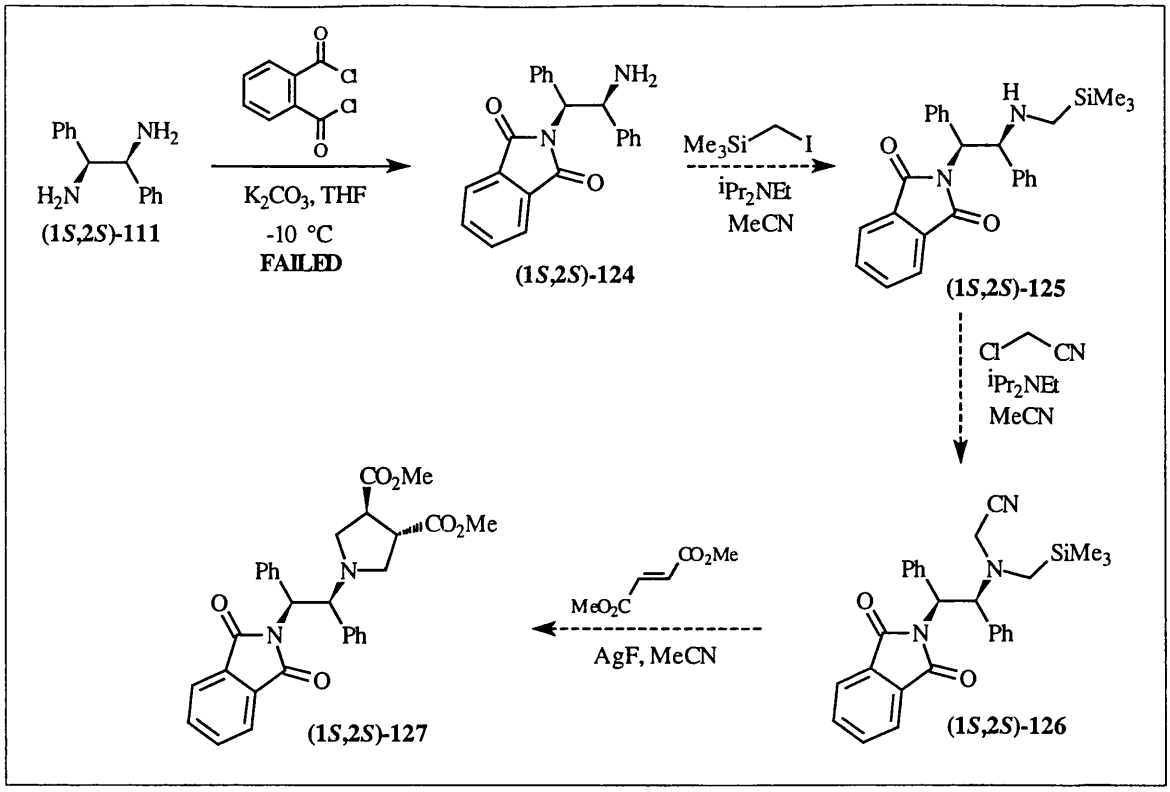
The next step was then to attach the cyanomethyl group to each of the two remaining secondary amine groups. It was expected that this would be done with chloroacetonitrile with a suitable base, but what appeared to be a trivial process proved to be rather problematic. Several methods were attempted with various conditions as shown in **Scheme 68**. The first attempt used 2.9 equivalents of chloroacetonitrile in THF using potassium carbonate as the base. Heating the mixture to 80 °C for approx. 20 hours resulted in an unacceptable low yield of the compound where only one CH_2-CN group had been attached to the amine **(1*S*,2*S*)-122**. Further heating had no effect on the yield. The base was then changed to Et_3N and the solvent to DMF and the reaction mixture stirred over the weekend at 100 °C. However, this was also found to be unsuccessful. A solution of **(1*S*,2*S*)-120** in MeCN was also treated with Hünig's base and chloroacetonitrile. Again, the solution was stirred at gentle reflux for approx. 3 days after which time the reaction failed to give the required compound. Compound **(1*S*,2*S*)-120** was also reacted with one equivalent of *n*-BuLi in THF at -78 °C to which was added (iodomethyl)trimethylsilane (2.7 equivalent). However, this also failed to provide the required compound **(1*S*,2*S*)-123**. As a final attempt, it was decided to utilise the method of Padwa *et al.*[40] This treated **(1*S*,2*S*)-120** with aqueous formaldehyde, potassium cyanide and HCl in THF. However, this also failed. It is possible that the two lone pairs of electrons on the remaining amine groups are too sterically hindered for these reactions to take place. As a result, the method was abandoned at this stage.



Scheme 68

Due to the unsuccessful efforts just described, it was decided to attempt protection of one of the amine groups, and then to work through the cycloaddition sequence again in order to possibly increase the yields and stereoselectivities.

We initially decided to attempt mono-protection with phthaloyl chloride. This is shown in **Scheme 69**. The reaction was carried out in THF with potassium carbonate as the base, but after 27 hours at room temperature no reaction was observed. Heating the reaction had no effect either, and the reaction was abandoned.

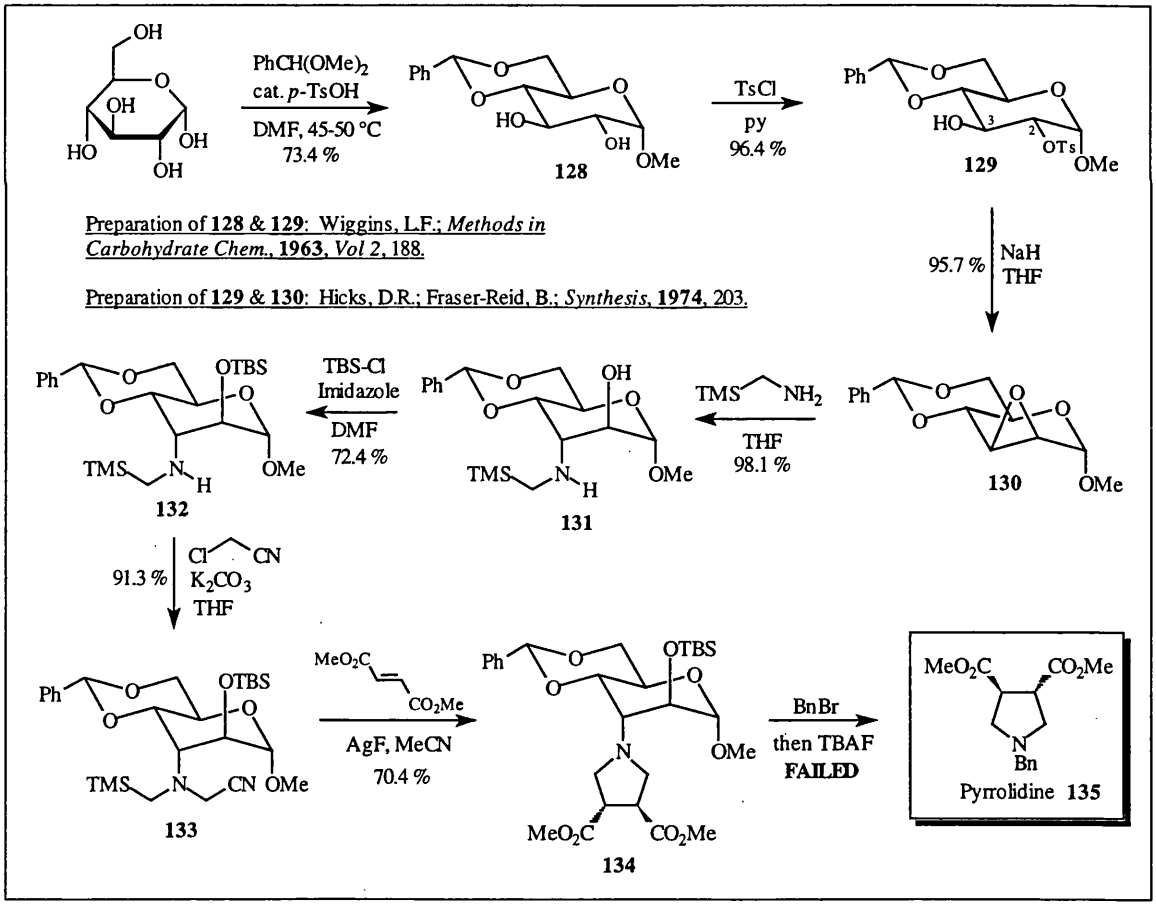


Scheme 69

Again we were unfortunate not to prepare the required precursors for the [3+2]-cycloaddition reactions. Due to the above results, it was decided to attempt another carbohydrate-based system, with the hope that more success would be achieved. The new method is discussed in the following section.

3.5 Investigation into the [3+2]-cycloaddition precursor using methyl α-D-glucopyranoside as the starting material

Our new plan centered around the preparation of azomethine ylide precursor **133** from methyl-α-D-glucopyranoside. This approach is detailed in **Scheme 70**. The 4,6-acetal **128** would be prepared from benzaldehyde dimethyl acetal and this then mono-tosylated by treatment with tosyl chloride in pyridine. The mono-tosylated compound **129** would then be converted to the epoxide **130** which would then be ring-opened with trimethylsilylmethyl amine. Protection of the hydroxyl group in **131** and chloroacetonitrile treatment was then expected to yield the cycloaddition precursor **133**. Upon treatment with silver fluoride and a suitable dipolarophile it was hoped that the pyrrolidine cycloadduct **134** would result. After ammonium salt formation treatment with TBAF would cleave off the required pyrrolidine compound **135** while at the same time recovering the epoxide **130** which could be re-introduced into the same process.



Scheme 70

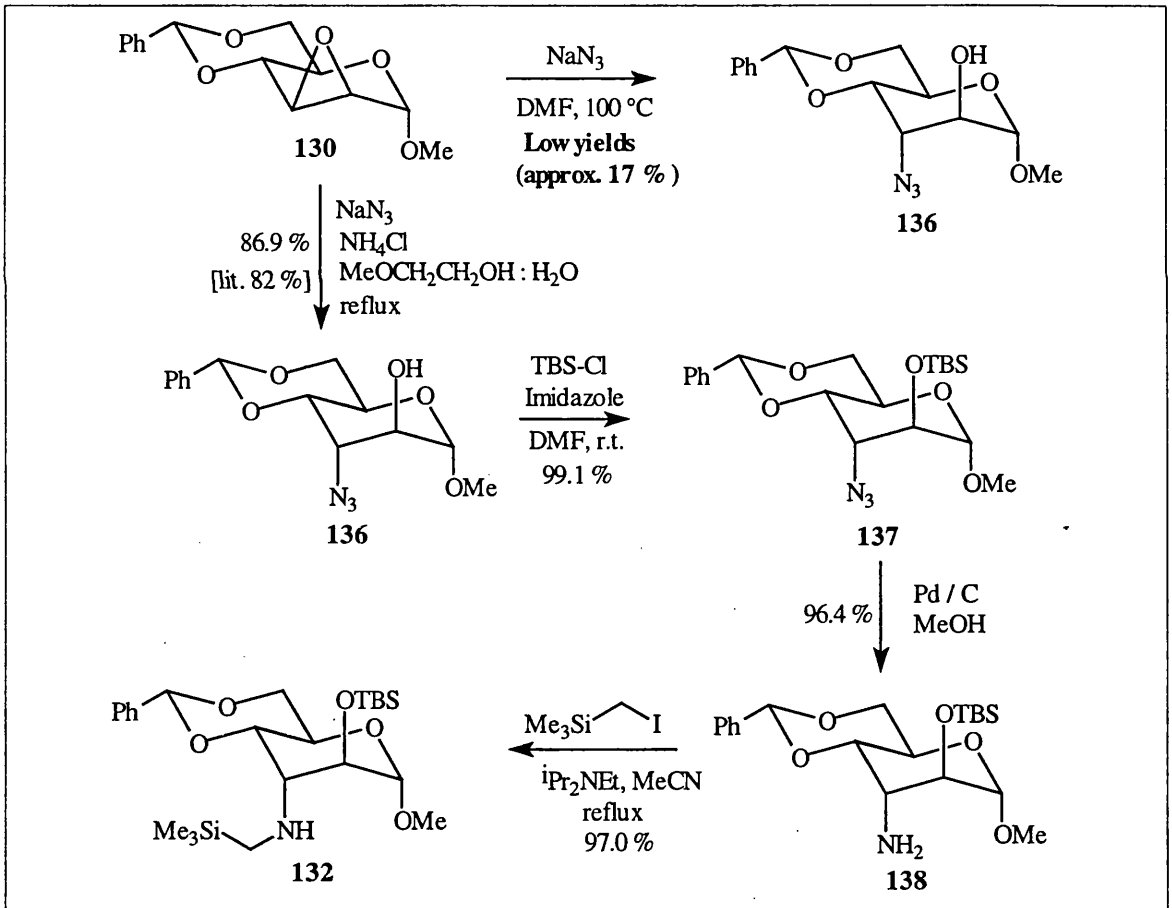
3.5.1 Preparation of the cycloaddition precursor **133**

Commercially available (+)-(4,6-*O*-benzylidene)-methyl-α-D-glucopyranoside **128** was reacted with tosyl chloride in pyridine to obtain known (+)-(4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl)-methyl-α-D-glucopyranoside **129** in 96 % yield.[156] Taking advantage of this *trans*-diequatorial arrangement between the hydroxyl group at C-3 and tosylate at C-2, **130** was successfully generated in 96 % yield by treatment of tosylate **129** with sodium hydride in THF at reflux for 23 hours (**Scheme 70**).[157] The 400 MHz ^{1}H n.m.r. spectrum displayed a multiplet at δ 7.35-7.50 which integrated to five protons. In addition to this, the singlet from the methyl group on the tosylate was absent The C-5 benzylidene proton was found as a singlet at δ 5.55 with the methoxy singlet at δ 3.45. The 100 MHz ^{13}C n.m.r. spectrum now only showed the presence of four aromatic signals from the phenyl group; the remaining four peaks from the tosylate group were absent as was the signal from the *para*-substituted methyl group. Further proof of the structure was provided by the HRMS mass spectrum (FAB, MNOBA matrix) which displayed a $(M+H)^+$ peak at *m/e* 265.1076 indicating a formula of $C_{14}H_{17}O_5$. The I.R. spectrum also showed the absence of hydroxyl groups.

Epoxide ring opening with previously prepared trimethylsilylmethyl amine **107** in THF at gentle reflux for 4 days afforded the *trans*-diaxial methyl 3-(trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside **131** as a clear oil in 98 % yield. Treatment of this secondary amine with imidazole and *tert*-butyldimethylsilyl chloride in DMF at room temperature for 4 days afforded methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132** as a clear yellow oil in 72 % yield. The 400 MHz ^{1}H n.m.r. spectrum showed the Me_3Si group at δ 0.02 with the two TBS-methyl groups as two singlets at δ 0.09 and δ 0.10, and the *tert*-butyl group at δ 0.90. The two -CH_2- protons next to the Me_3Si group were each found as doublets at δ 2.11 (J_{HH} 12.8 Hz) and δ 2.22 (J_{HH} 12.8 ppm) with the methoxy group at δ 3.33. The benzylidene proton was observed as a singlet at δ 5.57 while the aromatic section afforded a multiplet at δ 7.32-7.48. The 100 MHz ^{13}C n.m.r. spectrum indicated the Me_3Si group at δ -2.7 and the new -CH_2- group at δ 38.0. Further evidence supporting the identity of amine **132** was also provided by the HRMS mass spectrum (FAB MNOBA matrix) which showed

an $(M+H)^+$ ion at *m/e* 482.2758 which corresponded to an empirical formula of $C_{24}H_{44}NO_5Si_2$.

One problem we felt we had to be overcome in the above synthesis, was the use of trimethylsilylmethyl amine. While the epoxide ring opening proceeded well, it required a large excess of this reagent as expected for an S_N2 reaction. Trimethylsilylmethyl amine **107** had been prepared earlier, but this required two steps, including a distillation under vacuum. It was therefore decided to open the epoxide **130** with sodium azide followed by TBS protection of the alcohol **136** formed. The azide **137** could then be reduced using palladium on carbon, and the resulting amine **138** treated with (iodomethyl)trimethylsilane. This would result in the same number of steps as the previous method (preparation of trimethylsilylmethyl azide **106** → secondary amine **132**) and is indicated in **Scheme 71**.



Scheme 71

The epoxide ring opening was initially carried out in DMF at 100 °C for 46 h, but this gave an unacceptable yield of azide **136** in 17 %. It was then discovered that this ring opening had previously been carried out using sodium azide and ammonium chloride in a mix of 2-methoxyethanol and water.[158] Sodium azide and NH_4Cl was added to a solution of **130** in a mixture of 2-methoxyethanol and water and the solution stirred at gentle reflux for 5 h. Aqueous work-up followed by flash chromatography in hexanes/EtOAc, 5:1→3:1, gave methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside **136** as a white solid in 87 % yield. The 400 MHz ^1H n.m.r. spectrum showed the methoxy group at δ 3.40 and the benzylidene proton at δ 5.59. Proof that the azide had been formed came from the I.R. spectrum which showed the characteristic $-N_3$ peak at 2105 cm^{-1}. The HRMS mass spectrum (FAB MNOBA matrix) gave the correct $(M+Na)^+$ mass at *m/e* 330.1066 corresponding to a formula of $C_{14}H_{17}N_3O_5Na$.

The hydroxy group in **136** was then protected as the TBS- compound **137** using imidazole and TBS-Cl in DMF over 24 h. This proceeded in a virtually quantitative yield (99 %) after flash chromatography using hexanes:EtOAc, 8:1→5:1, as the eluent. The 400 MHz ^1H n.m.r. spectrum showed the newly-introduced *tert*-butyl group at δ 0.90 and the two TBS-methyl groups at δ 0.10 and δ 0.11. The -OMe group was observed at δ 3.39. The I.R. spectrum also showed the absence of the -OH group. The HRMS mass spectrum of **137** (FAB MNOBA matrix) indicated an empirical formula of $C_{20}H_{32}N_3O_5Si$ since there was a $(M+H)^+$ mass at *m/e* 422.2111. Hydrogenation of the azide group was carried out in methanol using palladium on carbon (10 % Pd/C) as a catalyst. Purification by flash chromatography (hexanes/EtOAc, 3:1→1:1) afforded methyl 3-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyl-dimethylsilyl)-3-deoxy-α-D-altropyranoside **138** as a clear yellow oil in 96 % yield. The 400 MHz ^1H n.m.r. spectrum revealed the two protons corresponding to the NH_2 as a very broad singlet at approx. δ 1.62 and the -OMe group was observed at δ 3.34. The HRMS mass spectrum (FAB MNOBA matrix) for **138** showed a peak with the correct $(M+H)^+$ mass of 396.2206 indicating an empirical formula of $C_{20}H_{34}NO_5Si$.

Amine **138** was then stirred at gentle reflux for 16 h with Hünig's base and (iodomethyl)-trimethylsilane in acetonitrile. Flash chromatography furnished **132** as a clear yellow oil in of 97 % yield. The 400 MHz ^1H and 100 MHz ^{13}C n.m.r. spectra were identical to those obtained previously using trimethylsilylmethyl amine to open up

the epoxide ring and they clearly showed that the $-CH_2-SiMe_3$ moiety had been introduced. The next step was the attachment of the $-CH_2-CN$ group. This was done by reacting **132** with chloroacetonitrile and Hünig's base in MeCN. Stirring the reaction mixture at reflux for 3-4 days afforded the required cycloaddition precursor **133** the as a clear oil in 91 % yield. The 400 MHz ^1H n.m.r. spectrum indicated the presence of the $-CH_2-CN$ protons as a doublet of a doublet at δ 3.97 (J_{HH} 3.9 Hz, 16.0 Hz) and the two doublets from the $-CH_2-$ protons next to the Me_3Si group were now observed at δ 2.40 (J_{HH} 14.4 Hz) and δ 2.63 (J_{HH} 14.4 Hz). The newly-introduced $-CH_2CN$ segment was also apparent in the 100 MHz ^{13}C n.m.r. spectrum. The CN group resonated at its characteristic position of δ 116.2 while the $-CH_2-$ was observed at δ 44.7. The structure was proved further by the HRMS mass spectrum (FAB, MNOBA matrix) which contained a $(M+H)^+$ peak at *m/e* 521.2867.

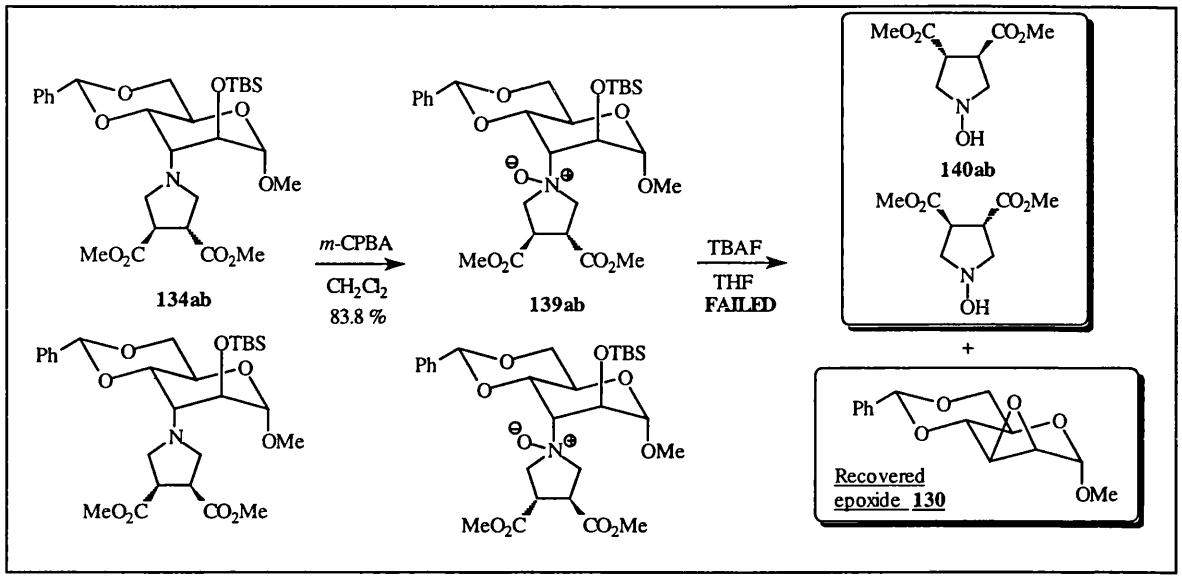
3.5.2 Cycloaddition of azomethine ylide precursor **133**

We were now in a position to attempt the desired cycloaddition. Dimethyl fumarate was chosen as the initial dipolarophile. A mixture of **133**, dimethyl fumarate and AgF in MeCN was stirred in the dark at room temperature for 5 days. This afforded the required cycloadduct **134** as a clear oil in 70 % yield. The 400 MHz ^1H n.m.r. spectrum showed two peaks corresponding to the benzylidene proton, with an approximate 2:1 integral ratio. This indicated poor stereoselectivity in the cycloaddition. The structure assigned to **134a/134b** was supported by its I.R. spectrum which showed the required ester C=O peak at 1739 cm^{-1}. The HRMS mass spectrum of **134a/134b** (FAB, MNOBA matrix) contained the required $(M+H)^+$ peak at *m/e* 566.2785.

3.5.3 Attempted removal of the pyrrolidine section from the cycloadduct **134ab**

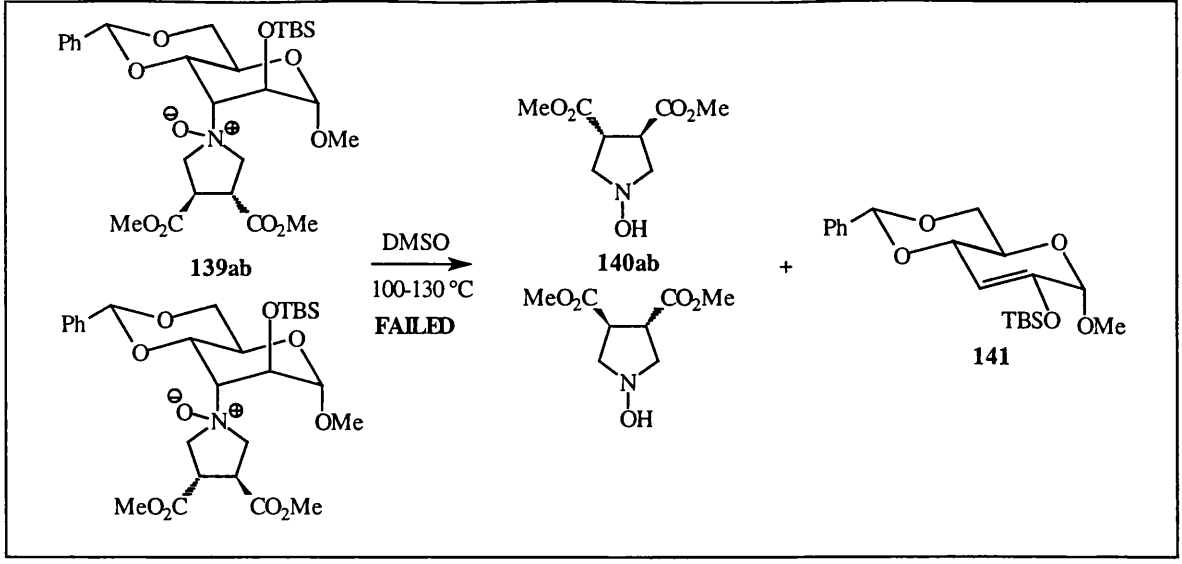
Although the cycloaddition appeared to show little stereoselectivity, it was decided to attempt the C-N bond cleavage to see if this was possible. While at first sight this appears to be a trivial task, it transpired that it was rather troublesome. An

initial attempt was made to form the sugar-*N*-oxides **139ab** by treating the sugar-cycloadduct **134ab** with *m*-CPBA in dichloromethane. The *N*-oxide was successfully formed (HRMS data only) in 84 % yield. It was then thought that treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF would afford the pyrrolidine *N*-hydroxides **140ab** as well as recovered sugar epoxide **130** which could be reused in the synthesis as indicated in **Scheme 72**. However, no reaction was observed after the TBAF stage and the method was abandoned. Similarly, HF in MeCN and water also failed.



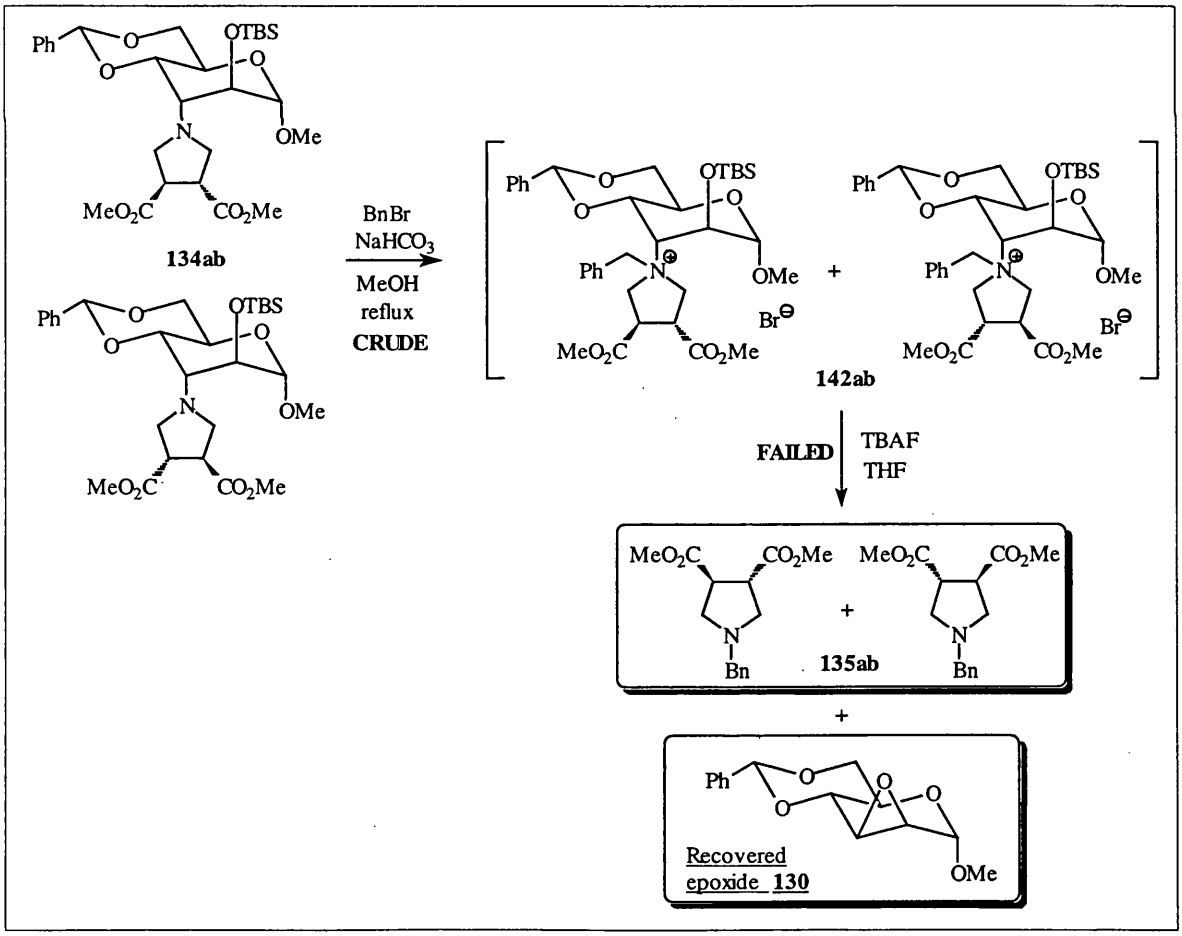
Scheme 72

Another method of C-N bond cleavage attempted was via a Cope elimination. The *N*-oxides **139ab** were heated to 100 °C in DMSO, but no reaction was observed after 15 h. Raising the reaction temperature to 130 °C for a further 16 h had no effect and the method was therefore abandoned. The expected pathway is shown in **Scheme 73** below.



Scheme 73

Another method attempted utilises the protocol suggested by Roussi *et al.*[159] and is shown in **Scheme 74** below. This involves the initial formation of the benzylated salts **142ab** in methanol and this could then be treated crude which TBAF to afford the required benzylated pyrrolidines **135ab** as well as recovered sugar epoxide **130**.



Scheme 74

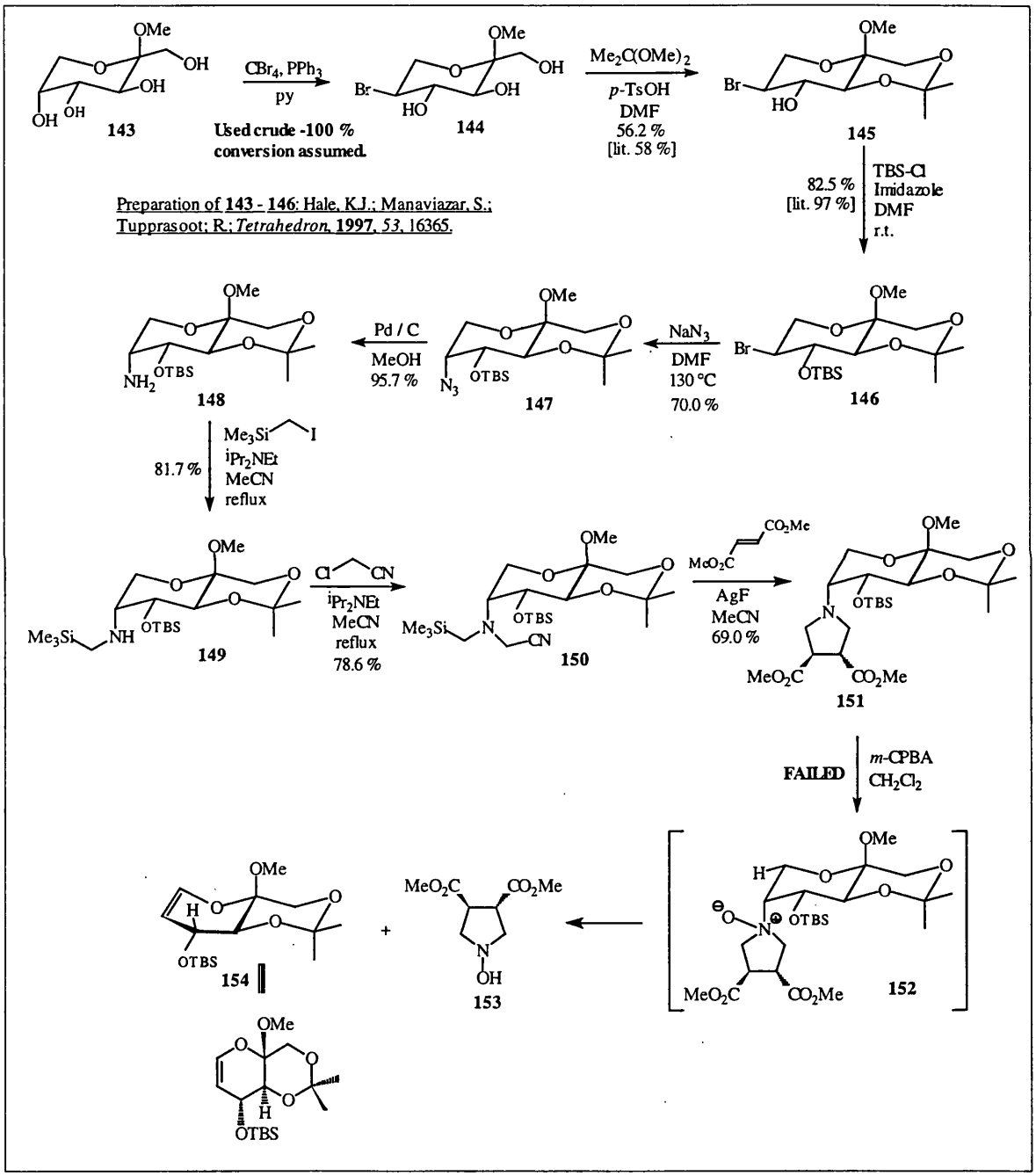
To a solution of the sugar cycloadduct **134ab** in MeOH at room temperature was added $NaHCO_3$ and benzyl bromide. The reaction mixture was stirred under nitrogen for 1h, then heated to gentle reflux for 4 h after which time TLC indicated the absence of the sugar cycloadduct and the presence of a new product suspected to be the benzylated salt. The reaction mixture was cooled to 0 °C and TBAF was added. However, after 16 h at room temperature TLC showed no formation of epoxide **130** and pyrrolidine **135** when compared to samples prepared previously. The method was abandoned at this stage.

3.5.4 Remarks

More success was achieved using this carbohydrate method. The precursor for the [3+2]-cycloadditions was successfully prepared and the cycloaddition also proceeded. Even though the cycloaddition gave a mixture of isomeric products, attempts were made to cleave off the newly formed pyrrolidine adduct. However, this proved to be unsuccessful. Having now tasted some success with the methyl-α-D-glucopyranoside-based system, it was decided to investigate the utility of the fructopyranoside-auxiliary shown in the next section.

3.6 Utilising methyl β-D-fructopyranoside as the chiral auxiliary for azomethine ylide [3+2]-cycloaddition reactions

The new chiral controller to be investigated was **150**; its synthesis is indicated in **Scheme 75** below.



Scheme 75

3.6.1 The preparation of the amine **148**

Methyl β-D-fructopyranoside **143** [160] had been prepared earlier in the group as part of another project and the initial bromination step was carried out with carbon tetrabromide and triphenylphosphine in pyridine. The majority of the triphenylphosphine oxide was removed by flash chromatography and the compound **144** used as obtained. The protection of the two hydroxyl groups proceeded in 56 % yield (assuming 100 % for the bromination step).[161] The remaining hydroxyl group was protected as the TBS group by treating a stirred solution of **145** and imidazole in DMF with TBS-Cl. Bromide **146** was then treated with 20 equivalents of sodium azide in DMF and the reaction mixture stirred under nitrogen at 130 °C for 42 h. Aqueous work-up and flash chromatography (hexanes/EtOAc, 25:1→8:1) gave methyl 5-azido-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **147** as a clear yellow oil in 70 % yield. The I.R. spectrum showed the characteristic $-N_3$ peak at 2104 cm^{-1}. The azide was then hydrogenated using palladium on carbon in MeOH to afford methyl 5-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148** as a clear yellow oil in 96 % yield. The 400 MHz ^1H n.m.r. spectrum showed the $-NH_2$ group as a broad singlet at δ 1.57 with the methoxy group at δ 3.24 and the two isopropylidene methyl groups at δ 1.43 and δ 1.39. The TBS group was also clearly present, with the *tert*-butyl group at δ 0.84 and the two methyl groups at δ 0.04 and δ 0.03. The I.R. spectrum showed the absence of the $-N_3$ group as required. As final evidence for the correct structure, the HRMS mass spectrum of **148** (FAB, MNOBA matrix) showed the required $(M+H)^+$ peak at *m/e* 348.2206 indicating a compound with empirical formula $C_{16}H_{34}NO_5Si$.

3.6.2 The preparation of the cycloaddition precursor **150**

A solution of the amine **148** in MeCN was heated at reflux for 20 h with (iodomethyl)trimethylsilane and Hünig's base. Aqueous work-up and flash chromatography (hexanes/EtOAc, 8:1) afforded methyl 5-(*N*-trimethylsilylmethyl)-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149** as a clear oil in 82 % yield. The 400 MHz ^1H n.m.r. spectrum clearly showed the new $-CH_2SiMe_3$ group. The Me_3Si group was seen as a singlet at δ

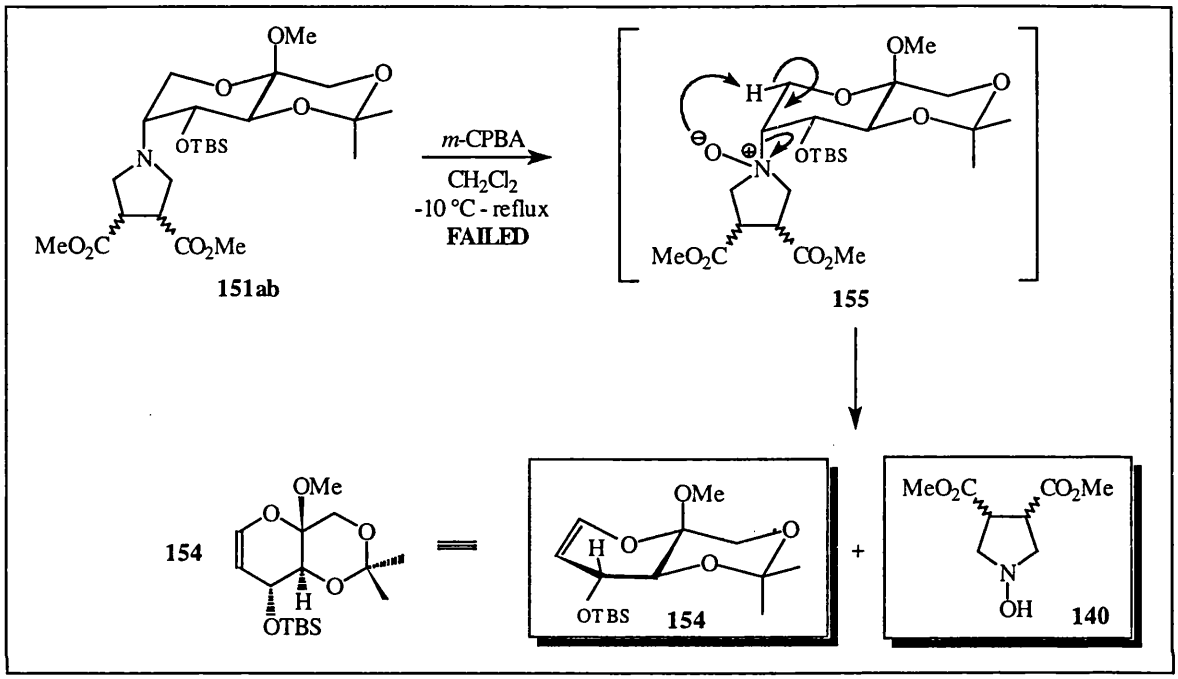
0.03 and the two -CH_2- protons were each observed as doublets at δ 1.61 (J_{HH} 12.8 Hz) and δ 2.25 (J_{HH} 12.8 Hz). The integral of NH group was observed at approx. δ 1.78 although the baseline appeared to be virtually flat. The 100 MHz ^{13}C n.m.r. spectrum also showed the presence of the Me_3Si group at δ -2.4 with the -CH_2- group at δ 38.0. This secondary amine **149** was treated with Hünig's base and chloroacetonitrile in MeCN and heated at reflux for 25 h. Aqueous work-up and flash chromatography afforded methyl 5-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-iso-propylidene-β-D-fructopyranoside **150** as a clear yellow oil in 79 % yield. The 400 MHz ^1H n.m.r. spectrum showed the new -CH_2CN group buried inside a multiplet at δ 4.14-4.19. The two doublets from the -CH_2- group next to the Me_3Si group were now observed further upfield at δ 2.37 (J_{HH} 14.4 Hz) and δ 2.58 (J_{HH} 14.4 Hz) as expected due to the introduction of the electron-withdrawing -CN group. The 100 MHz ^{13}C n.m.r. spectrum showed the -CN signal in its characteristic position at δ 116.3 with the new CH_2- group at δ 44.8. The I.R. spectrum of **150** showed the CN group as a weak peak at 2229 cm^{-1} while the HRMS mass spectrum indicated an empirical formula of $C_{22}H_{45}N_2O_5Si_2$ by giving the required $(M+H)^+$ ion at *m/e* 473.2867.

3.6.3 Cycloaddition of **150**

The cycloaddition was then attempted using dimethyl fumarate as the dipolarophile. Dimethyl fumarate and AgF was added to a solution of **150** in MeCN. The reaction mixture was stirred at room temperature in the dark for approx. 9 h before it was filtered through a pad of Celite. Concentration of the filtrate followed by flash chromatography in hexanes:EtOAc, 10:1, gave the desired pyrrolidine adduct **151** as a clear oil in 69 % yield. The 400 MHz ^1H n.m.r. spectrum showed that a 1:1 mixture of isomers had formed, indicating that the reaction was non-stereospecific. The methoxy groups gave rise to two peaks of the same intensity at δ 3.31 and δ 3.21. The I.R. spectrum showed the presence of the ester groups by giving the required ester C=O stretch at 1738 cm^{-1}. The HRMS mass spectrum (FAB, MNOBA matrix) of **151ab** contained an $(M+H)^+$ ion at *m/e* 518.2785 as one would expect for $C_{24}H_{44}NO_9Si$.

3.6.4 The attempted removal of the pyrrolidine system from the sugar moiety

C-N bond cleavage was next attempted. It was hoped that *syn*-elimination (**Scheme 76**) [162] would occur, to provide a route to the required *N*-hydroxy-pyrrolidine **140** as well as the glycal **154**.



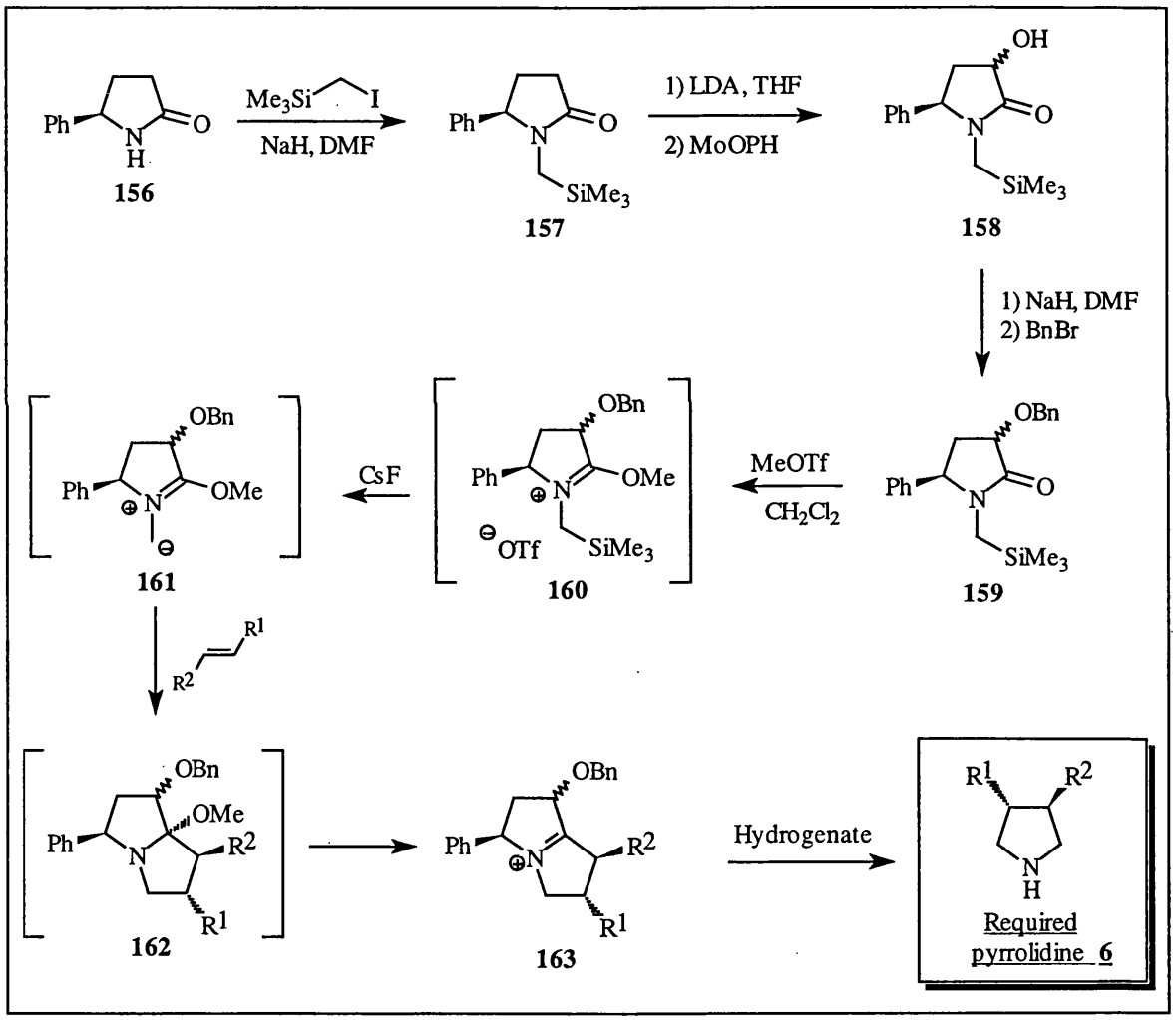
Scheme 76

To the sugar cycloadduct **151ab** in CH_2Cl_2 at -10 °C was added in one portion *m*-CPBA (1.2 equivalents) and the mixture stirred at room temperature for 79 h after which time the TLC showed no reaction. A further 3.6 equivalents of *m*-CPBA was therefore added and the reaction mixture heated to gentle reflux for 1½ h. TLC again showed no reaction and the method was therefore abandoned at this stage since no stereoselectivity was shown in the cycloaddition.

3.7 Attempting the preparation of a 1,3-azomethine ylide dipole precursor based on (*R*)-5-phenyl-2-pyrrolidinone **156**

3.7.1 Introduction

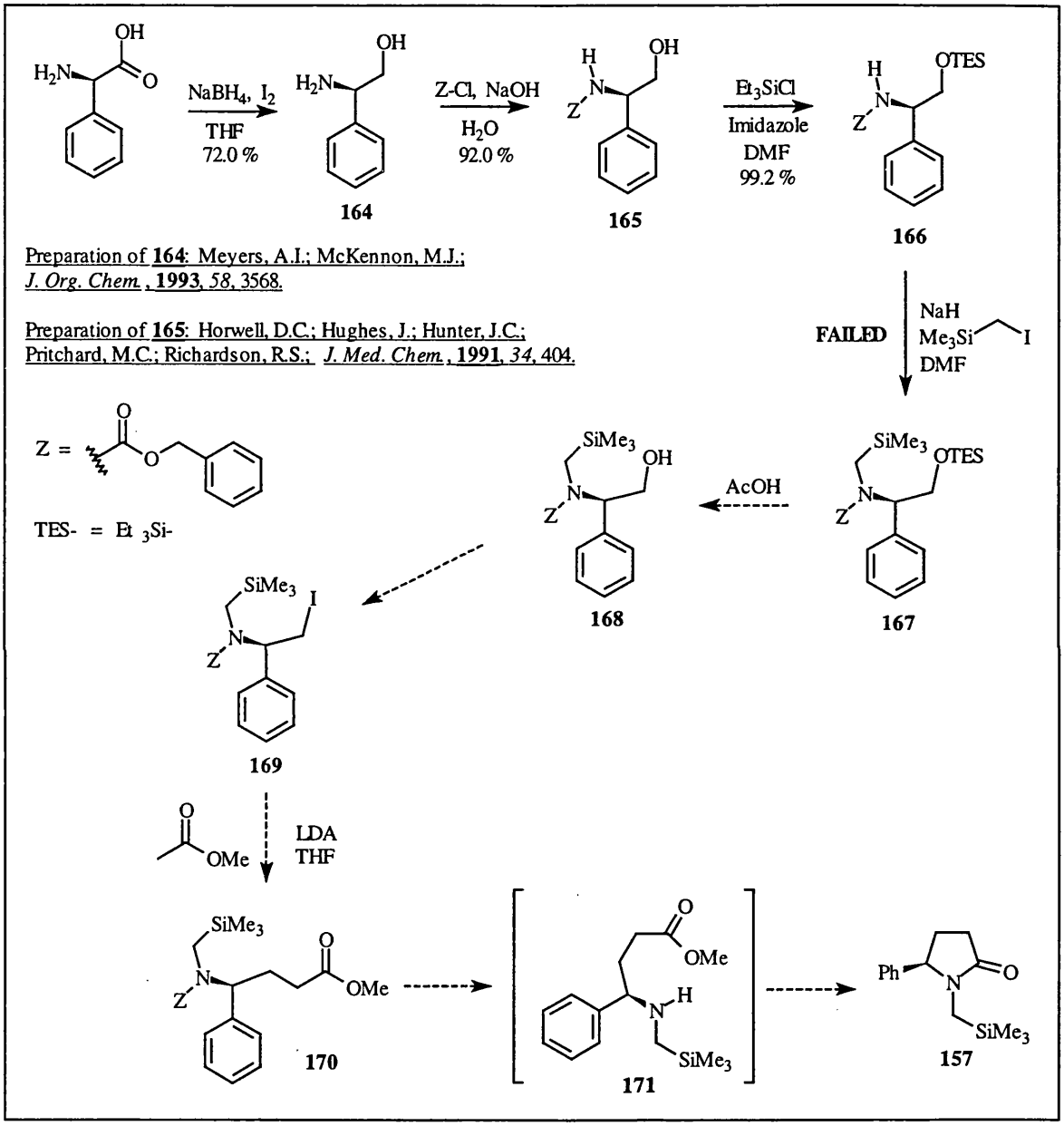
Due to the stereoselectivities of our cycloaddition reactions, we next elected to fashion an azomethine ylide that would not be able to undergo free rotation about the C-N axis. We favoured the creation of a dipole such as **161** which we envisaged we could prepare from the lactam **156** (**Scheme 77**).



Scheme 77

3.7.2 Preparation of the (*R*)-5-phenyl-2-pyrrolidinone derivative **157**

The initial step in this sequence was the preparation of (*R*)-5-phenyl-2-pyrrolidinone **156**. We decided to attempt the preparation of chiral (*R*)-5-phenyl-2-pyrrolidinone **156** or its derivative **157** as indicated in **Scheme 78** below.

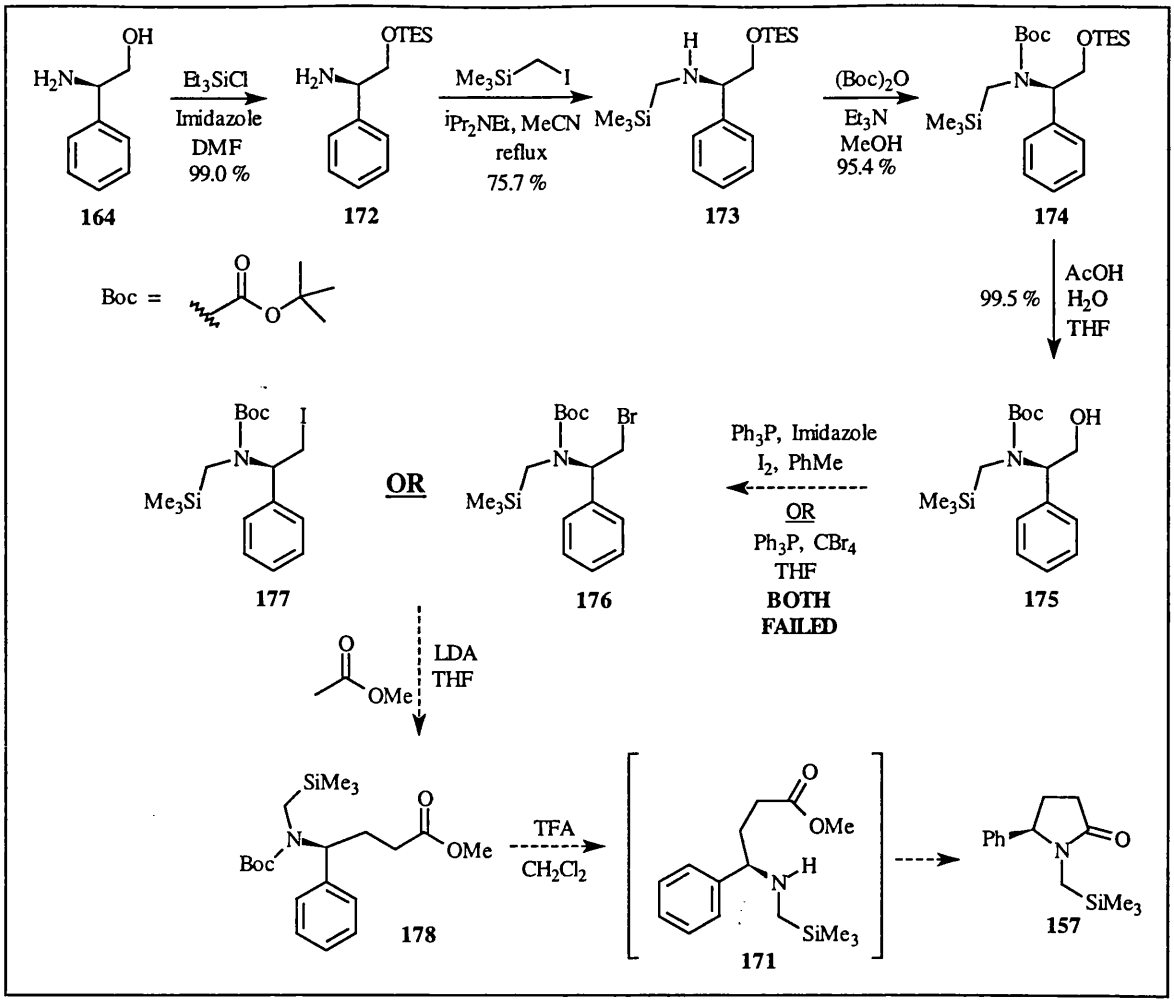


Scheme 78

The preparation started with commercially available D-(-)-α-phenylglycine. This was reduced to D-(-)-α-phenylglycinol **164** in 72 % yield according to the general method suggested by Meyers *et al.*[76] using $NaBH_4$ and I_2 in THF. The amino group was then mono-protected with the benzyloxycarbonyl group (Z) using Z-Cl in NaOH and water

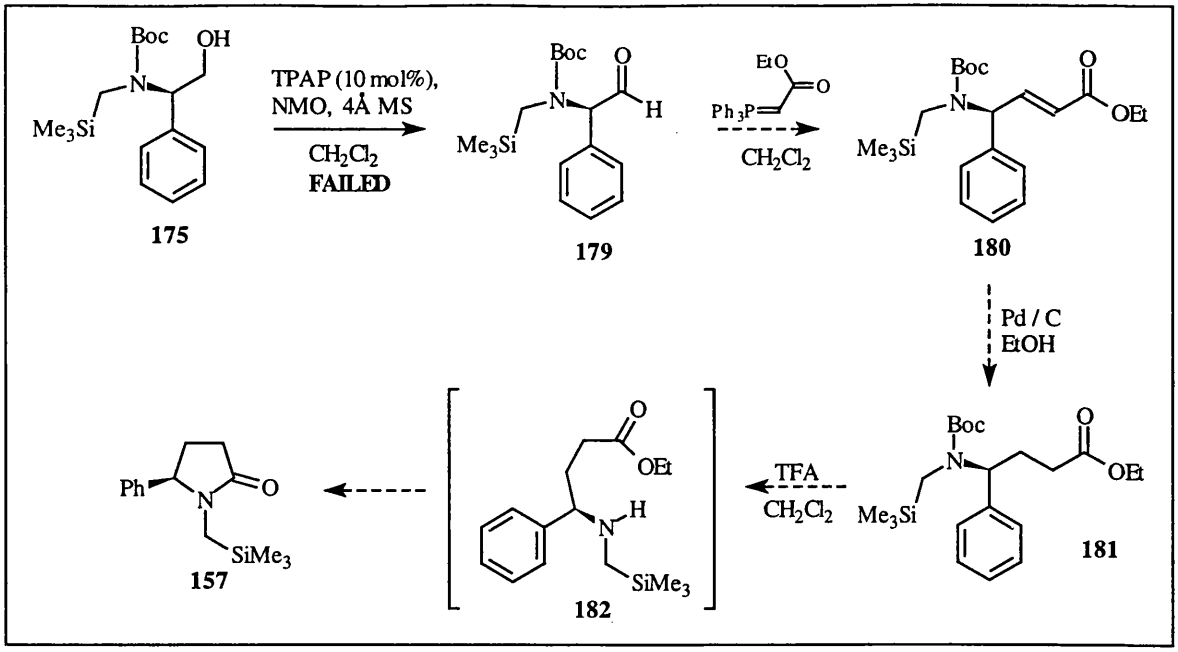
in 92 % yield using a similar method to Horwell *et al.*[163] The 400 MHz ^{1}H n.m.r. spectrum showed rotamers were present as seen by the broadening of the peaks, but the integration was correct. The 100 MHz ^{13}C n.m.r. spectrum showed that the benzyl -CH_2- group had been introduced, it showing a peak at δ 69.0 as well as the C=O group at δ 156.5. Two quaternary aromatic carbon signals were also observed at δ 139.1 and δ 136.2. The I.R. spectrum showed the presence of the C=O group at 1685 cm^{-1} while the HRMS mass spectrum (FAB, MNOBA matrix) contained an $(M+H)^+$ ion at *m/e* 272.1287. The alcohol group of this Z-protected secondary amine **165** was then protected with triethylsilyl chloride using imidazole and DMF to afford D-(-)-α-*O*-triethylsilyl-*N*-Z-phenylglycinol **166** as a clear liquid in 99 % yield. The 100 ^{13}C n.m.r. spectrum showed the presence of the new TES group by giving rise to two signals at δ 4.1 and δ 6.5. The HRMS mass spectrum (FAB, MNOBA matrix) also contained the correct $(M+H)^+$ peak at *m/e* 386.2151. The preparation of D-(-)-α-*O*-triethylsilyl-*N*-(trimethysilylmethyl)-*N*-Z-phenylglycinol **167** was attempted using NaH and (iodomethyl)-trimethylsilane in DMF, but failed. Repeated attempts using NaH in THF and DMSO also failed. *n*-BuLi in THF was attempted without success. It is possible that the amine group is too sterically hindered for the reaction to take place. Had this been successful, the TES group would have been removed using acetic acid to leave the free alcohol **168**, which then would have been converted to the iodo-compound **169**, and this alkylated with the enolate of methyl acetate to obtain ester **170**. Removal of the Z-group would furnish (*R*)-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157** *in situ*.

Another attempted preparation of (*R*)-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157** is indicated in **Scheme 79**. Again, this began with **164**. The hydroxyl group was protected with the TES group and the free amine **172** treated with (iodomethyl)trimethylsilane to afford the secondary amine **173**. Treatment with di-*tert*-butyl-dicarbonate, (Boc_2O), followed by acetic acid then furnished the tertiary aminol **175**. This was unable to be converted to either the bromide **176** or iodide **177**. Hence this approach was also abandoned.



Scheme 79

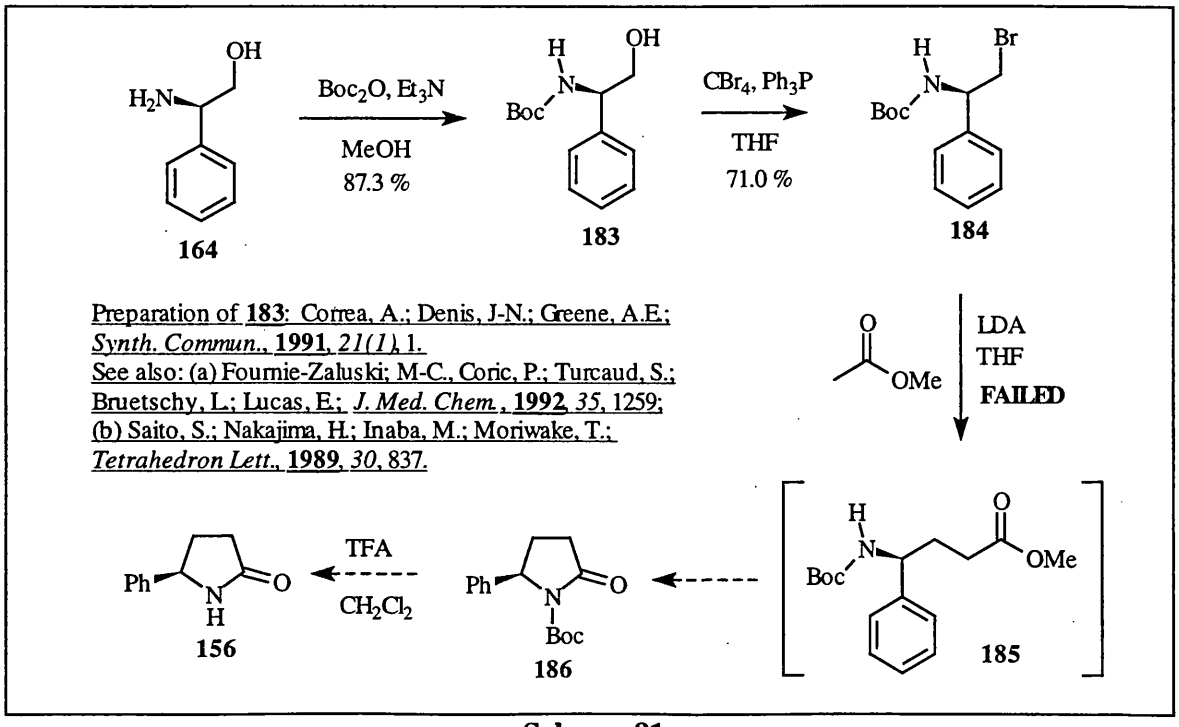
Since we could prepare the aminol **175** in high yield, we felt that its utility deserved a little further investigating (**Scheme 80**). Treating this alcohol **175** with TPAP, NMO and 4Å molecular sieves in CH_2Cl_2 should oxidise it to the aldehyde **179**. This could then be treated with the commercially available Wittig reagent in CH_2Cl_2 to afford the alkene **180** which upon hydrogenation should furnish ester **181**. Removal of the Boc group using TFA in CH_2Cl_2 should hopefully furnish **157**.



Scheme 80

The above method was unfortunately unsuccessful at the initial oxidation stage. The method was abandoned at this stage.

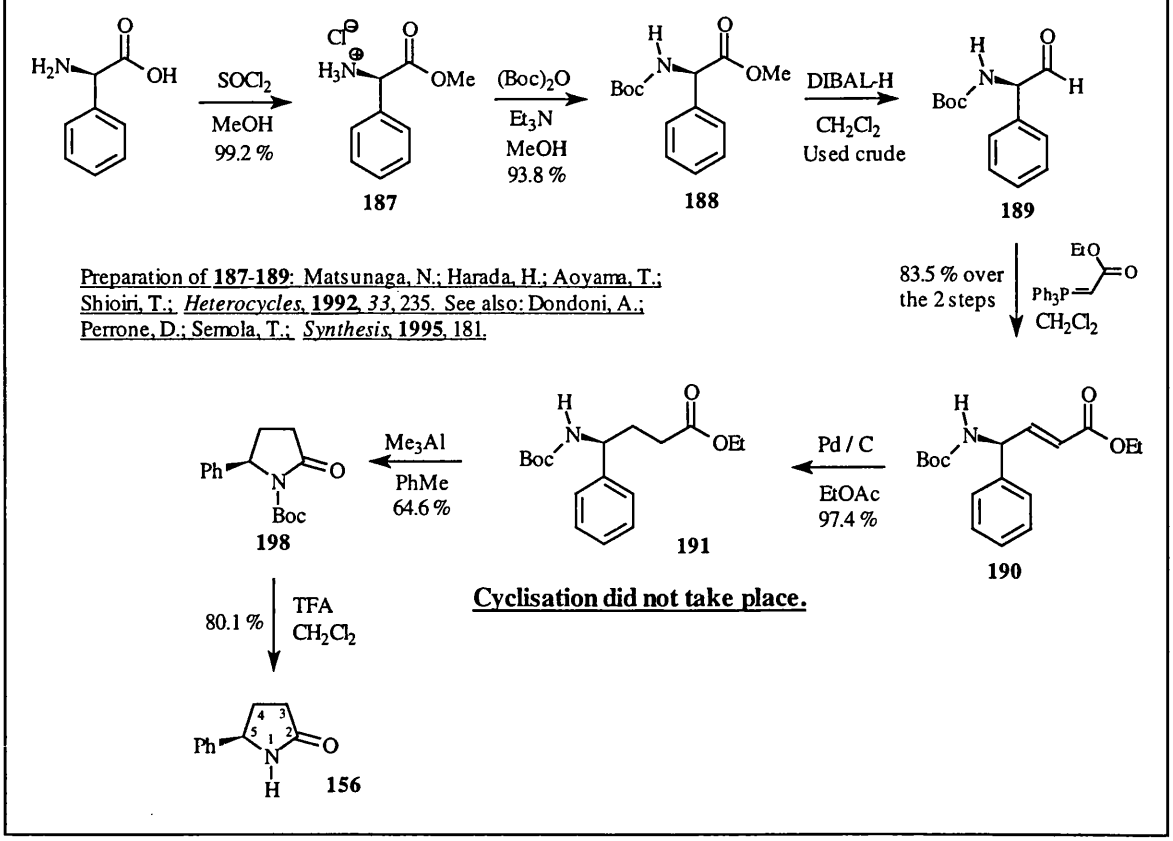
We next investigated the preparation of the *N*-Boc protected phenylglycinol **183** [164] which was converted to the bromide **184** under the usual reaction conditions. We envisaged that this could then be subjected to the enolate chemistry described previously. **Scheme 81** below shows those ideas more fully.



Scheme 81

The preparation of **183** proceeded successfully in 87 % yield by treating alcohol **164** with Et_3N and di-*tert*-butyl-dicarbonate in MeOH at room temperature for 5 min. The I.R. spectrum showed the presence of the C=O peak at 1671 cm^{-1} and the HRMS mass spectrum for (FAB, NMOBA matrix) $C_{13}H_{20}NO_3$ showed the required $(M+H)^+$ ion at *m/e* 238.1443. A solution of this aminol **183** in THF was then treated with triphenylphosphine followed by carbon tetrabromide. The mixture was stirred at room temperature for 5 hours, the $Ph_3P=O$ removed by suction filtration and the filtrate concentrated *in vacuo* affording the crude bromide **184** as a brown oil. Flash chromatography (hexanes:EtOAc, 16:1→8:1) furnished **184** as a white solid in 71 % yield. Again the 400 MHz ^1H n.m.r. spectrum gave rise to rotamers, but the integration proved to be correct. The structural assignment was backed up by the HRMS mass spectrum for **184** (FAB, MNOBA matrix) which gave the correct $(M)^+$ ion at *m/e* 300.0599. We were now in a position to attempt the enolate chemistry. To a stirred solution of LDA (1 equiv.) in THF at -78 °C was added methyl acetate and the resultant mixture stirred at -78 °C for 10 min. A solution of **184** in THF was then added and the solution stirred at -78 °C for 10 min. then room temperature for 50 min. after which time TLC indicated that no more bromide was present. Aqueous work-up followed by flash chromatography (hexanes:EtOAc, 10:1) gave the major product of which the 400 MHz ^1H n.m.r. spectrum showed to be the incorrect compound. No attempt was made to identify this compound and the method was abandoned at this stage.

The next attempted preparation of **156** is shown in **Scheme 82** below. Reaction of **187** [165] with triethylamine followed by di-*tert*-butyl-dicarbonate afforded the Boc protected amino ester **188**. Diisobutylaluminium hydride reduction then furnished aldehyde **189** which was then subjected to a Wittig reaction to obtain alkene **190**. Hydrogenation of the alkene to the saturated ester **191** followed by the Me_3Al induced cyclisation [166] then afforded the *N*-Boc-lactam **186** in 65 % yield. Deprotection was performed using trifluoroacetic acid to furnish **156**.

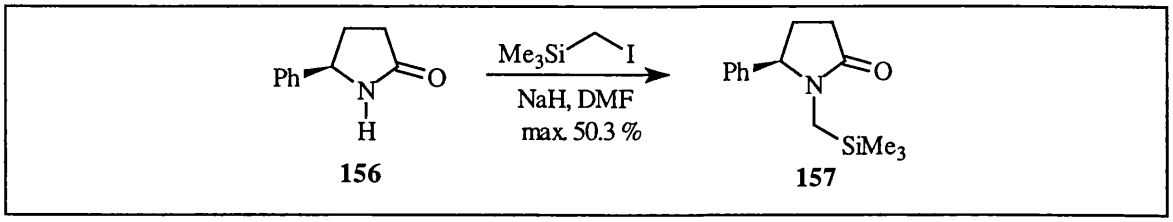


Scheme 82

The Boc group was successfully removed by treating a solution of (***R***)-**186** in CH_2Cl_2 with trifluoroacetic acid for 5 min. Flash chromatography (hexanes/EtOAc, 1:1) delivered (***R***)-**156** as a light brown solid in 80 % yield. The 400 MHz ^1H n.m.r. spectrum showed the absence of the Boc group. The NH group was found as a broad singlet at δ 6.42 with a triplet corresponding to one of the C-3 protons at δ 4.73 (J_{HH} 7.2 Hz). The 100 MHz ^{13}C n.m.r. spectrum showed the ring C=O at δ 178.9 with C-5 at δ 58.1. The I.R. spectrum also showed the C=O peak at 1682 cm^{-1} and the HRMS mass spectrum (FAB MNOBA matrix) showed an $(M+H)^+$ ion at *m/e* 162.0914.

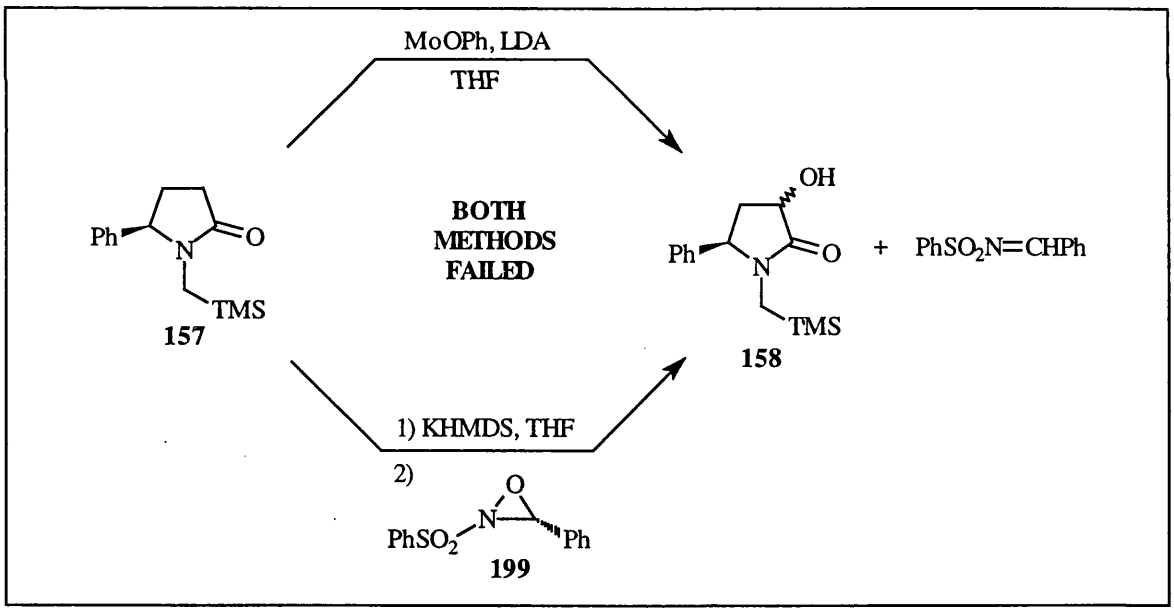
The attachment of the trimethylsilylmethyl group to (***R***)-**156** proved rather troublesome. Sodium hydride (100 %, washed with hexane) was found to give the best result of 50 % as shown in **Scheme 83**. Repeated reactions using identical conditions only afforded yields of up to 30 % of (*R*)-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**. Potassium hydride (washed with hexane) and *n*-BuLi were also used as the base, but these did not increase the yields. The 400 MHz ^1H n.m.r. spectrum clearly showed the newly-introduced trimethylsilyl methyl group. The two -CH_2- protons were observed as two doublets at δ 2.05 (J_{HH} 15.2 Hz) and δ 3.18 (J_{HH} 15.2 Hz) with the $SiMe_3$ group at δ 0.01. The 100 MHz ^{13}C n.m.r. spectrum also confirmed the

structure as it showed the $SiMe_3$ group at δ -1.39 and the new $-CH_2-$ group at δ 32.5. The HRMS mass spectrum (FAB MNOBA matrix) for an empirical formula of $C_{14}H_{22}NOSi$ gave final structure proof as it gave the required $(M+H)^+$ peak at *m/e* 248.1471.



Scheme 83

Even though these yields were not impressive it was decided to attempt the oxidation using MoOPH and LDA according to **Scheme 84**. A solution of **(*R*)-157** in THF was added to a solution of LDA in THF at -78 °C. This was followed by the addition of solid MoOPH. However, TLC indicated no reaction, even at room temperature, and the method was abandoned. Another mild oxidation reagent investigated was benzenesulfonyl-3-phenyloxaziridine **199** (**Scheme 84**).[167]



Scheme 84

When a solution of the enolate derived from **(*R*)-157** in THF was added to a solution of benzene-sulfonyl-3-phenyloxaziridine **199** in THF at -78 °C no reaction took place at -78 °C or room temperature and the method was therefore abandoned.

3.7.3 Conclusions

Several methods have been investigated for the preparation of (*R*)-5-phenyl-2-pyrrolidinone **156** and its derivative, (*R*)-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**. These two compounds were successfully prepared via the Wittig method followed by cyclisation using trimethylaluminium in acceptable yields. The attachment of the trimethylsilyl moiety proceeded in moderate to low yields only and the two oxidation methods used for the introduction of the hydroxyl group were both unsuccessful. We have, however, been successful in preparing chiral 5-phenyl-2-pyrrolidinone which may prove useful for other synthetic applications.

Chapter 4

Evaluation of the scope of the *N*-nitroso reduction with diisobutylaluminium hydride

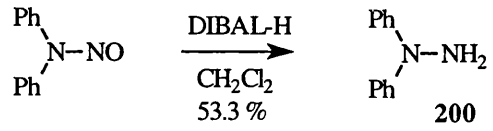
4.0 Introduction

The reduction of *N*-nitroso compounds to hydrazines is widely known and is most frequently carried out using zinc dust or lithium aluminium hydride.[168] However, in some cases these two methods are only partially successful or fail completely, as was the case with our binaphthyl system. In our case we envisaged that the -NO group could act rather like a carbonyl group and therefore be reduced with DIBAL-H. As shown previously, this was indeed found to be the case. Since there were no previous examples of this reduction in the literature, we decided to investigate the scope of this method a little further. Various other *N*-nitroso compounds, both aromatic and aliphatic, were prepared from the secondary amines, and their reduction with DIBAL-H investigated. Isoamyl nitrite in THF was always used for *N*-nitrosation, and the resultant *N*-nitroso compounds were then subjected to DIBAL-H reduction in CH_2Cl_2 to give the corresponding hydrazine derivatives. In most cases, the equivalents of isoamyl nitrite and DIBAL-H was kept in the range 5-5.3. The DIBAL-H used was a 1.5M solution in toluene and was slowly added at -78 °C. The reaction mixtures usually had to be stirred at room temperature for longer periods of time, and the isolated yields were not always impressive. Our results did, however, show that the method is reasonably successful. Below are the compounds attempted.

4.1 Preparation of *N*-amino-diphenylamine **200**

The first example selected for study was commercially available *N*-nitroso-diphenylamine (**Scheme 85**). Approx. two equivalents of DIBAL-H were required for

this reduction. Extra reagent usually resulted in other by-products being formed in the reaction mixture. Aqueous work-up and flash chromatography (hexanes/EtOAc, 60:1→45:1) afforded the *N*-amino-diphenylamine **200** as a purple oil which solidified in the freezer in 53 % yield. The 400 MHz ^{1}H n.m.r. spectrum gave the NH_2 as a singlet at δ 4.14 while the 10 aromatic protons were found as a multiplet in the range δ 6.96-7.31. The 100 MHz ^{13}C n.m.r. spectrum also only indicated four aromatic peaks as required and the HRMS (FAB, MNOBA matrix) for $C_{12}H_{12}N_2$ $(M)^+$ gave rise to a peak at *m/e* 184.1006.

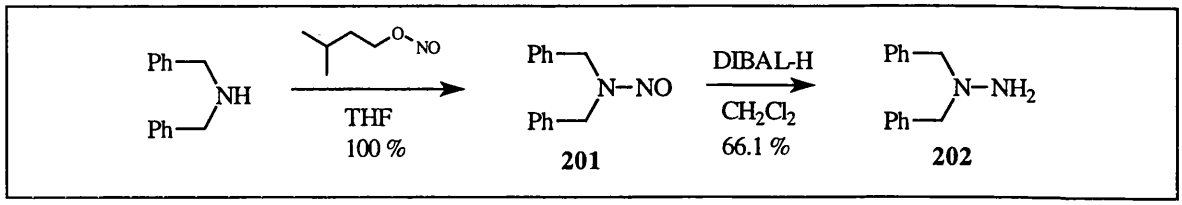


Scheme 85

4.2 Preparation of *N*-amino-dibenzylamine **202**

The second compound chosen was based on dibenzylamine as indicated in **Scheme 86**. To a stirred solution of dibenzylamine in THF was added isoamyl nitrite (approx. 5.1 equiv.) at room temperature and the solution stirred under nitrogen for 23 h. The solvent and excess isoamyl nitrite were removed *in vacuo* leaving yellow/orange paste which was subjected to flash chromatography (hexanes:EtOAc, 8:1) to afford pure *N*-nitroso-dibenzylamine **201** as a clear yellow oil in a quantitative yield; the latter solidified on standing at room temperature. The 400 MHz ^{1}H n.m.r. spectrum indicated the non-symmetrical character by showing the two -CH_2- as two singlets at δ 4.64 and δ 5.18. The remaining 10 aromatic protons were observed as a multiplet in the range δ 7.02-7.37. The 100 MHz ^{13}C n.m.r. spectrum also showed the two -CH_2- as two singlets at δ 44.8 and δ 54.9. Eight aromatic peaks were observed as expected of which two were quaternary signals. As final proof, the HRMS (FAB, MNOBA matrix) of **201** gave rise to a $(M+H)^+$ ion at *m/e* 227.1189 corresponding to $C_{14}H_{15}N_2O$. The reduction step required 5.1 equivalents of DIBAL-H in CH_2Cl_2. After being stirred at -78 °C for 2h, the reaction mixture was then allowed to stir at room temperature for approx. 74 h before being worked-up. *N*-Amino-dibenzylamine **202** was obtained as a in 66 % yield; it solidified upon standing at room temperature. The 400 MHz ^{1}H n.m.r. spectrum now showed the NH_2 group as a broad singlet at δ 2.90, with the benzyl -CH_2- appearing as a

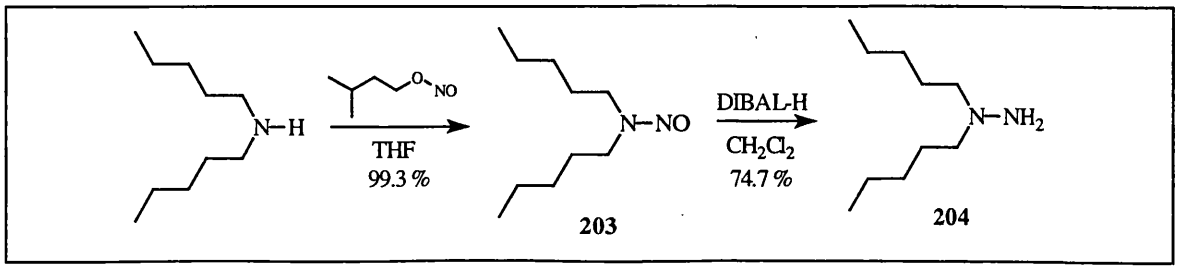
singlet at δ 3.78. The aromatic protons were observed as a multiplet in the range δ 7.30-7.45. The 100 MHz ^{13}C n.m.r. spectrum showed the required four phenyl signals, as well as the two benzylic -CH_2- groups at δ = 64.8. The HRMS (FAB, MNOBA matrix) contained an $(M)^+$ ion at *m/e* 212.1321 which indicated a molecular formula of $C_{14}H_{16}N_2$.



Scheme 86

4.3 Preparation of *N*-amino-dipentylamine **204**

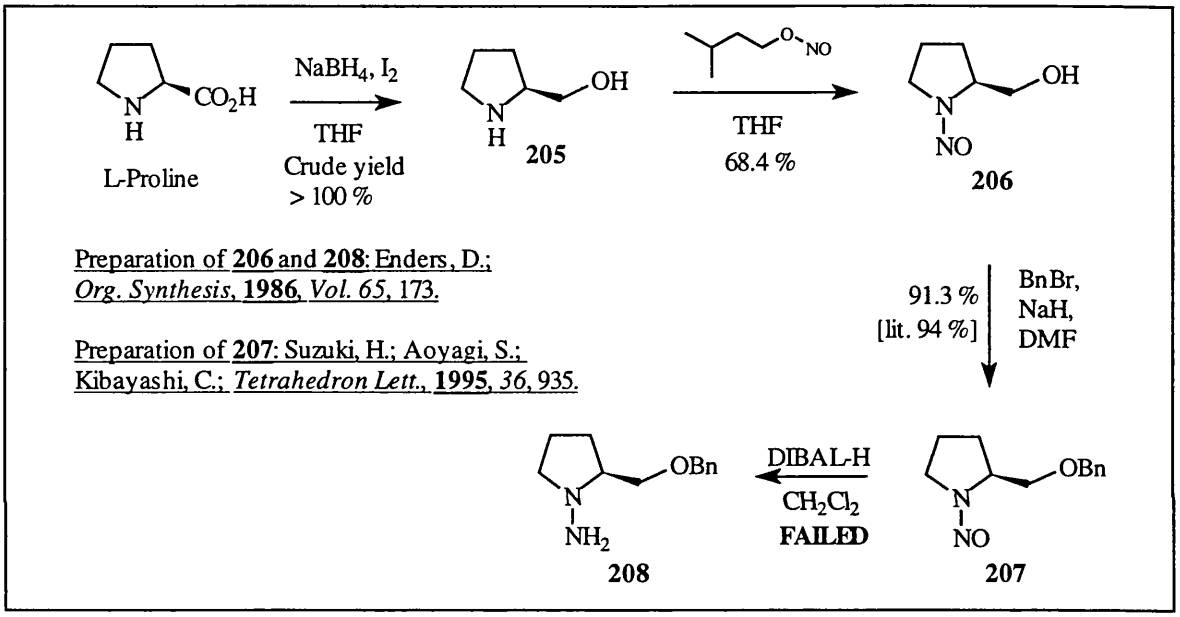
The third example chosen was dipentylamine (**Scheme 87**). To a stirred solution of dipentylamine in THF was added isoamyl nitrite (5 equivalents) at room temperature and the solution stirred under nitrogen for 20 h. The solvent and excess isoamyl nitrite was removed *in vacuo* leaving a clear yellow liquid. Flash chromatography (hexanes:EtOAc, 8:1) afforded pure *N*-nitroso-dipentylamine **203** as a clear yellow liquid in 99 % yield. The 400 MHz ^1H n.m.r. spectrum showed the correct compound had been formed. The 100 Hz ^{13}C n.m.r. spectrum also indicated the required 10 signals. The HRMS (FAB, MNOBA matrix) was also correct for $C_{10}H_{23}N_2O$ $(M+H)^+$ giving rise to a peak at *m/e* 187.1813. The reduction also proceeded well and in a reasonable yield, but required 5.2 equivalents of DIBAL-H and a reaction time of four days at room temperature before reaction completion. *N*-Amino-dipentylamine **204** was obtained as a clear liquid after flash chromatography in 75 % yield. The ^{13}C n.m.r. spectrum showed the required five signals. The HR-MS mass spectrum (FAB, MNOBA matrix) for **204** gave a $(M-NH_2)^+$ peak at *m/e* 156 indicating a formula of $C_{10}H_{24}N_2$.



Scheme 87

4.4 Attempted preparation of (*S*)-*N*-amino-*O*-benzylprolinol **208**

L-Prolinol **205** was reacted with isoamyl nitrite at room temperature to give pure (*L*)-*N*-nitroso prolinol **206** as an orange oil in 68 % yield after flash chromatography (**Scheme 88**).[106,169] The hydroxyl group was then benzylated by treatment with NaH and benzyl bromide according to Suzuki *et al.*[170] This furnished pure (*L*)-*O*-benzyl-*N*-nitroso prolinol **207** as an orange/yellow oil in 91 % yield. The reduction using DIBAL-H was, however, unsuccessful.

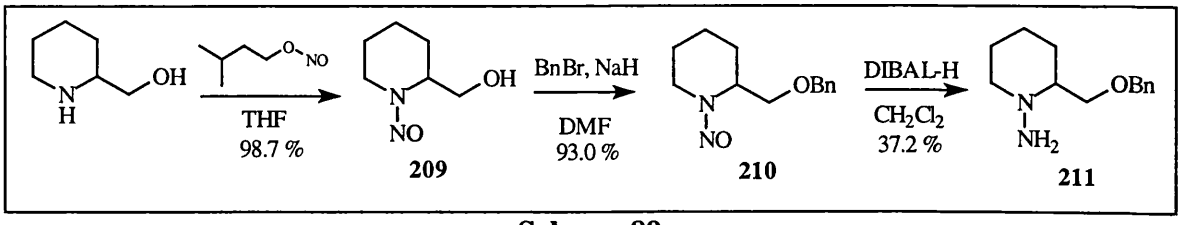


Scheme 88

4.5 Preparation of *N*-amino-*O*-benzyl-2-hydroxymethyl piperidine **211**

The fifth compound selected for study was based on (±)-2-piperidinemethanol (**Scheme 89**). When treated with isoamyl nitrite (5.1 equivalents) at room for 65 h, pure (±)-*N*-nitroso-2-piperidinemethanol **209** was isolated as a clear yellow liquid in 99 % yield. The HRMS (FAB, MNOBA matrix) confirmed the correct structure for **209**, it containing an $(M+H)^+$ ion at *m/e* 145.0972. Again, the hydroxyl group was blocked to afford pure (±)-*O*-benzyl-*N*-nitroso-2-piperidinemethanol **210** as a clear yellow oil in 93 % yield. As previously, the reduction step was carried out with 5.3 equivalents of DIBAL-H and afforded *N*-amino-*O*-benzyl-2-hydroxymethyl piperidine **211** as a clear yellow oil in 37 % yield. The 100 MHz ^{13}C n.m.r. spectrum of **211** indicated four

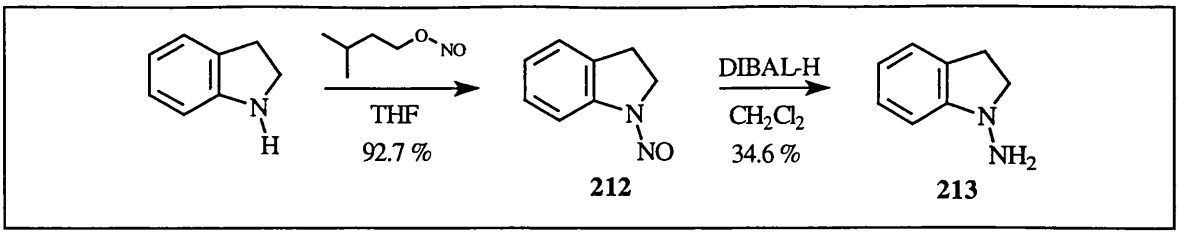
aromatic signals of which one was a quaternary carbon. Seven other non-aromatic signals were also obtained. The HRMS mass spectrum (FAB, MNOBA matrix) showed a peak that corresponded to an $(M+H)^+$ ion at *m/e* 221.1654.



Scheme 89

4.6 Preparation of *N*-amino-indoline **213**

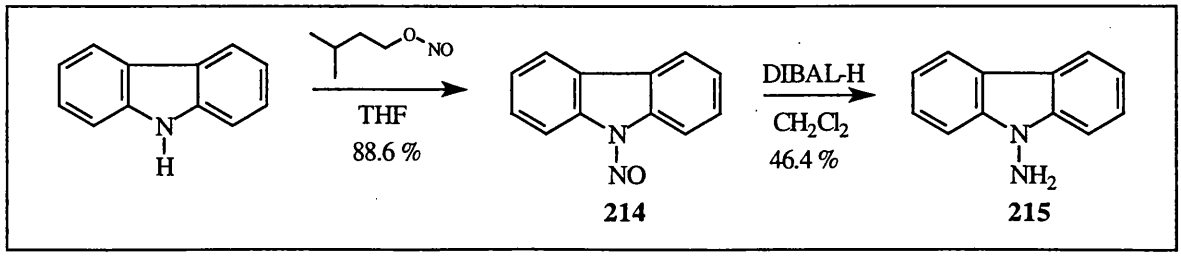
The sixth amine chosen was indoline (**Scheme 90**). To a stirred solution of indoline in THF was added isoamyl nitrite (5.1 equivalents) at room temperature and the solution stirred under nitrogen for 50 min. Work-up and crystallisation from Et_2O afforded pure *N*-nitroso-indoline **212** as flaky brown crystals in 93 % yield. The 400 MHz ^1H n.m.r. spectrum showed the two non-aromatic $-CH_2-$ groups as triplets at δ 3.20 (2H, J_{HH} 7.6 Hz, J_{HH} 8.0 Hz) and δ 3.49 (2H, J_{HH} 7.6 Hz, J_{HH} 8.0 Hz). The four aromatic protons were in turn observed as multiplets at δ 7.21-7.24, δ 7.29-7.33 and δ 7.81-7.83. The 100 MHz ^{13}C n.m.r. spectrum indicated two quaternary carbon signals at δ 132.0 and δ 140.8 with the remaining four aromatic carbon signals at δ 112.1, 126.1, 127.0 and 128.2. The two non-aromatic carbon peaks were observed at δ 26.0 and δ 46.1. The HRMS (FAB, MNOBA matrix) exhibited the required $(M+H)^+$ ion at *m/e* 149.0720. The reduction required 4.1 equivalents of DIBAL-H at room temperature for 49 h. Flash chromatography furnished *N*-amino-indoline **213** as a brown oil in 35 % yield. The 400 MHz ^1H n.m.r. spectrum showed the NH_2 as a broad singlet at δ 3.56 with the two non-aromatic $-CH_2-$ groups being observable as triplets at δ 2.91 (2H, J_{HH} 8.0 Hz) and δ 3.36 (2H, J_{HH} 8.0 Hz). The four aromatic protons appeared as two multiplets between δ 6.79-6.84 (2H) and δ 7.10-7.18 (2H). The 100 MHz ^{13}C n.m.r. spectrum also indicated two non-aromatic signals at δ 27.9 and δ 60.9. The six benzenoid carbon signals were also observed, of which two were quaternary at δ 128.7 and δ 154.5. Final structure proof was provided by the HRMS (FAB, MNOBA matrix) which contained an ion at *m/e* 134.0842.



Scheme 90

4.7 Preparation of *N*-amino carbazole **215**

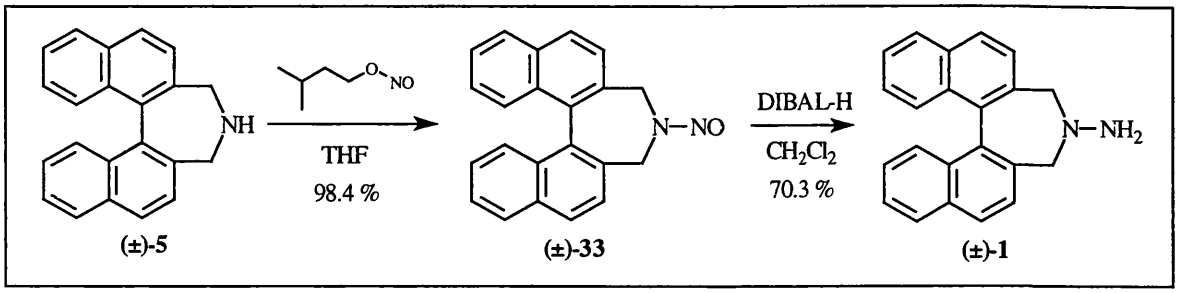
Scheme 91 shows the eighth example, based on carbazole. Isoamyl nitrite (5 equivalents) was added to a solution of carbazole in THF at room temperature and the solution stirred under nitrogen for 28 h. Flash chromatography (hexanes:CH_2Cl_2, 5:1) afforded pure *N*-nitroso carbazole **214** as bright yellow fluffy crystals in 89 % yield. The 400 MHz ^{1}H n.m.r. spectrum showed the eight aromatic protons as multiplets at δ 7.41-7.55 (4H), δ 7.86-7.91 (2H), δ 8.19-8.21 (1H) and δ 8.52-8.55 (1H). Again the 100 MHz ^{13}C n.m.r. spectrum indicated the non-symmetrical character of the compound. All 12 carbon signals were observed of which four were quaternary signals. The HRMS (FAB, MNOBA matrix) contained an $(M+H)^+$ ion of the correct mass (*m/e* 197.0712) while the elemental analysis calculated for $C_{12}H_8N_2O$ gave the required result of C = 73.09; H = 4.11 and N = 13.24. The reduction step used 5.3 equivalents of DIBAL-H and took 6 h at room temperature to afford *N*-amino carbazole **215** as a light brown crystalline solid in 46 % yield. The 400 MHz ^{1}H n.m.r. spectrum now showed the NH_2 group as a broad singlet at δ 4.52, and the remaining aromatic protons were observed as multiplets at δ 7.21-7.26 (2H), δ 7.45-7.52 (4H) and δ 8.04-8.06 (2H). The 100 MHz ^{13}C n.m.r. spectrum showed the required six aromatic signals of which two were quaternary at δ 120.8 and 141.3. Finally, the HRMS (FAB, MNOBA matrix) for **215** indicated the correct measured mass of 182.0850 for the $(M)^+$ ion.



Scheme 91

4.8 Preparation of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**

The eighth and final example to be included in this DIBAL-H reduction method was based on the previously prepared azepine (±)-**5** as indicated in **Scheme 92**. The results of these two preparative procedures have already been discussed in Chapter 2.



Scheme 92

4.9 Remarks

Several examples of the reduction of *N*-nitroso compounds with DIBAL-H have been provided. A summary of the yields is indicated in **Table 12**. The preparation of the *N*-nitroso compounds was achieved in excellent yield using excess isoamyl nitrite in THF (89 - 100 %). The subsequent DIBAL-H reductions of the *N*-nitroso compounds varied in yields (35 - 70 %). Our results do, however, indicate that the method is applicable to a range of substrates. Only one of our examples (the pyrrolidine derivative) failed to give a successful DIBAL-H reduction.

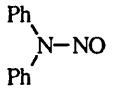
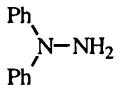
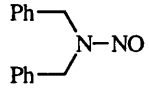
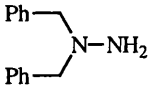
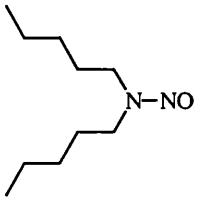
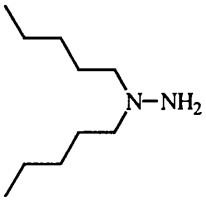
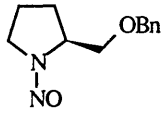
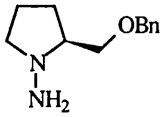
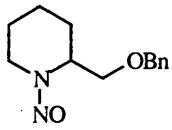
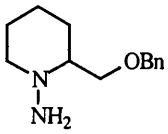
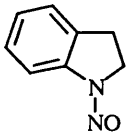
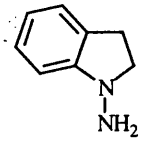
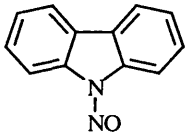
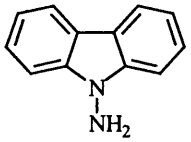
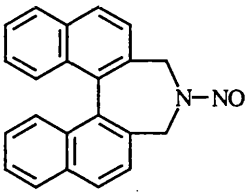
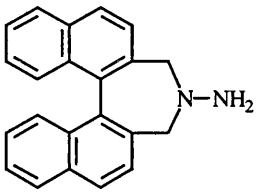
Compound	Yield %	Compound	Yield %
	Commercially available		53
	100		66
	99		75
	---		FAILED
	---		37
	93		35
	89		46
	98		70

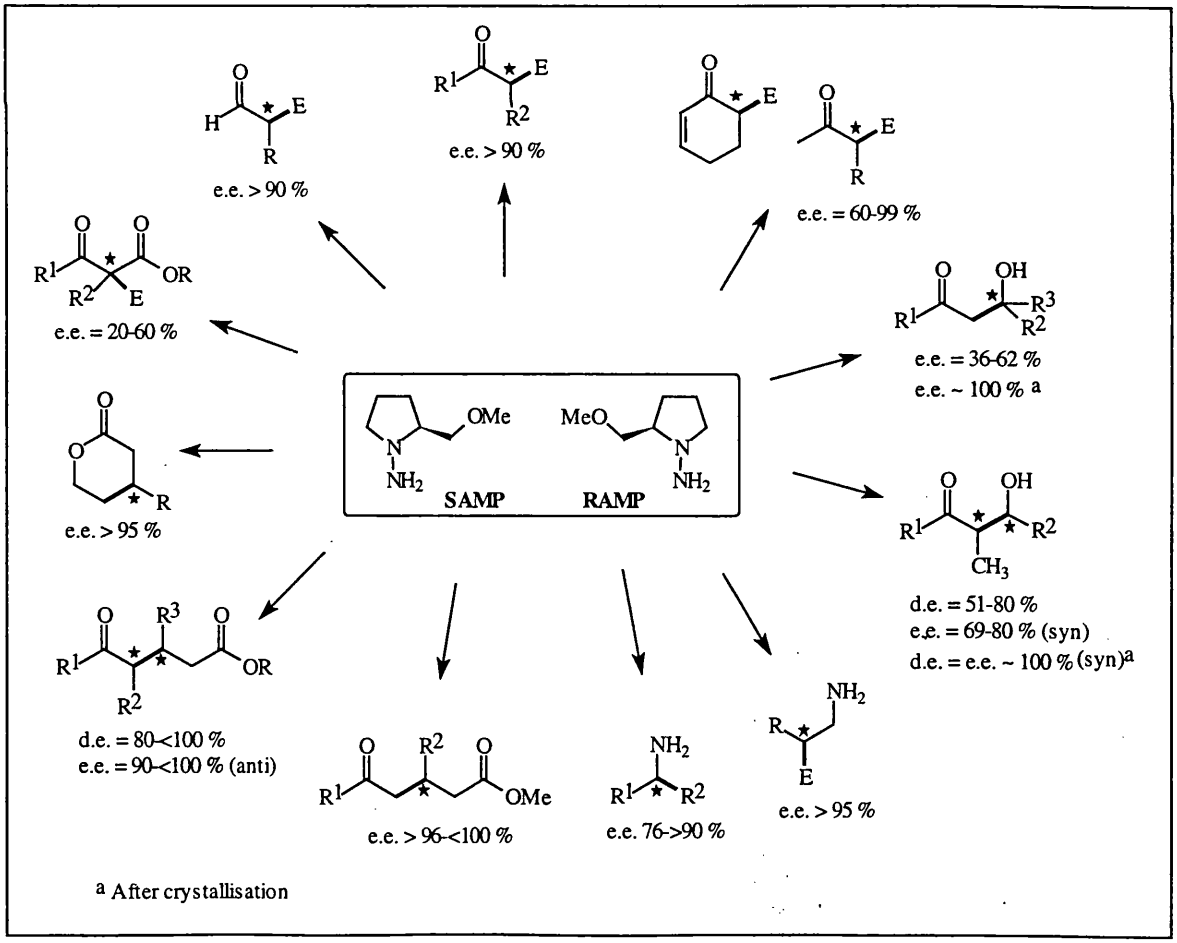
Table 12 Reduction of *N*-nitroso compounds using DIBAL-H

Concluding Remarks

For this project various methods for the preparation of precursors for the [3+2]-cycloaddition reactions of nonstabilised azomethine ylides have been prepared. Unfortunately, the initial objective of utilising a chiral hydrazine **1** as one such precursor was found to be unsuccessful, though this work led to the first practical synthesis of racemic and homochiral (*R*)- and (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1** in good yield starting from inexpensive, readily available starting materials.

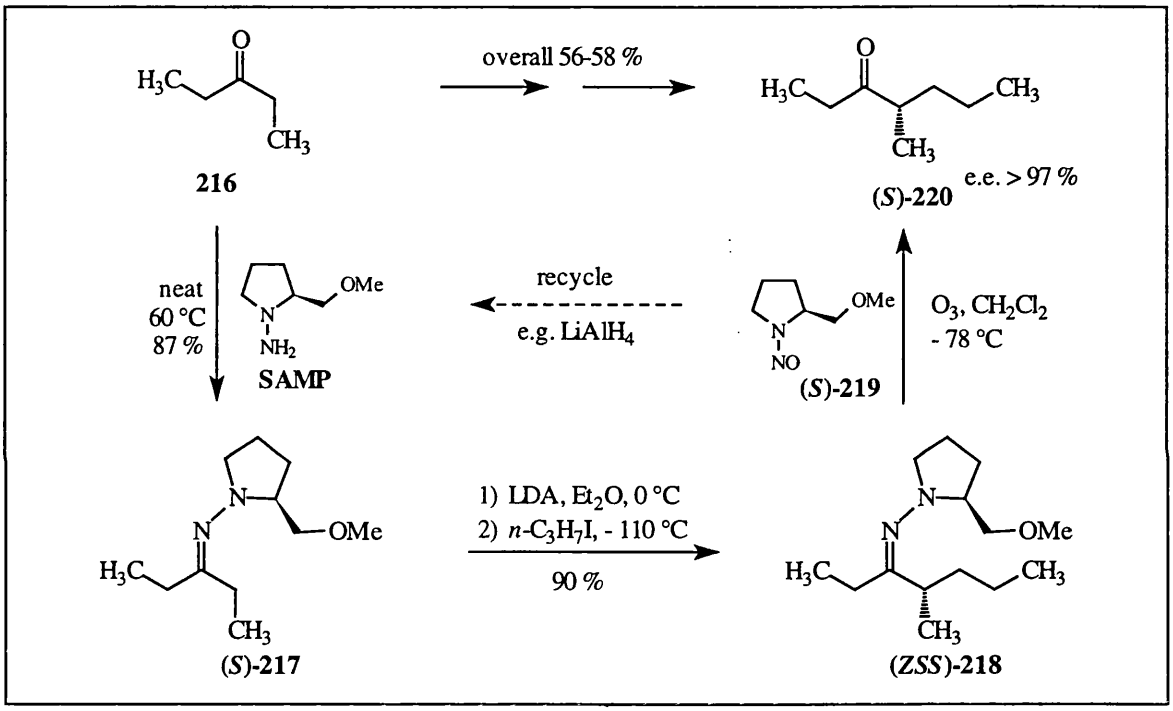
We hope that this chiral hydrazine may prove to be an efficient competitor to Enders' expensive SAMP [(*S*)-1-amino-2-(methoxymethyl)pyrrolidine] and RAMP [(*R*)-1-amino-2-(methoxymethyl)pyrrolidine] hydrazines.

Enders *et al.*[171] have successfully synthesised several optically active carbonyl compounds and amines using this SAMP-hydrazine method (**Scheme 93**).



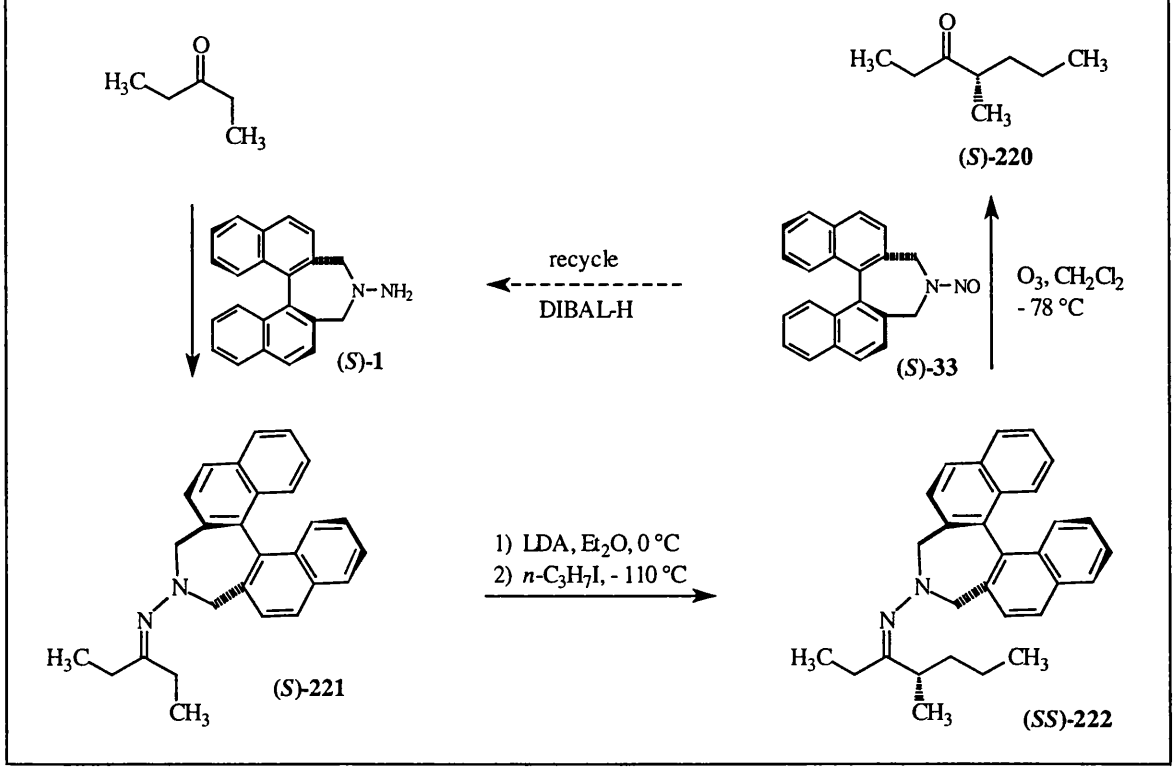
Scheme 93

One example is the preparation of (*S*)-(+)-4-methyl-3-heptanone via a three-step procedure starting from the conformationally flexible, acyclic ketone **216** → **(*S*)-220** and this proceeded with virtually complete asymmetric induction (**Scheme 94**). This demonstrated complete stereochemical control of the three critical operations: metallation, alkylation, and cleavage. The SAMP-hydrazone was deprotonated using lithium diisopropylamide, and then alkylated with propyl iodide to afford **(*ZSS*)-218.** Oxidative cleavage by ozonolysis furnished the optically active carbonyl compound **(*S*)-220** as well as the corresponding *N*-nitroso derivative **(*S*)-219**. The chiral auxiliary SAMP could be recycled with $LiAlH_4$-reduction of **(*S*)-219**.



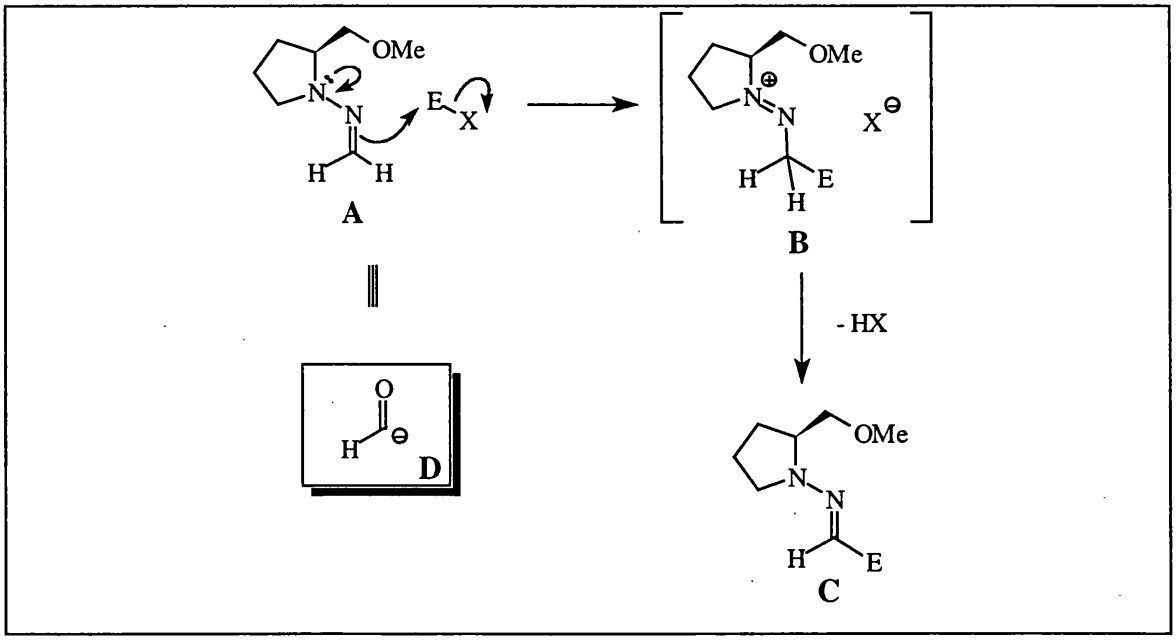
Scheme 94

We envisage that our hydrazine **1** could be equally or more efficiently utilised than SAMP or RAMP (**Scheme 95**).



Scheme 95

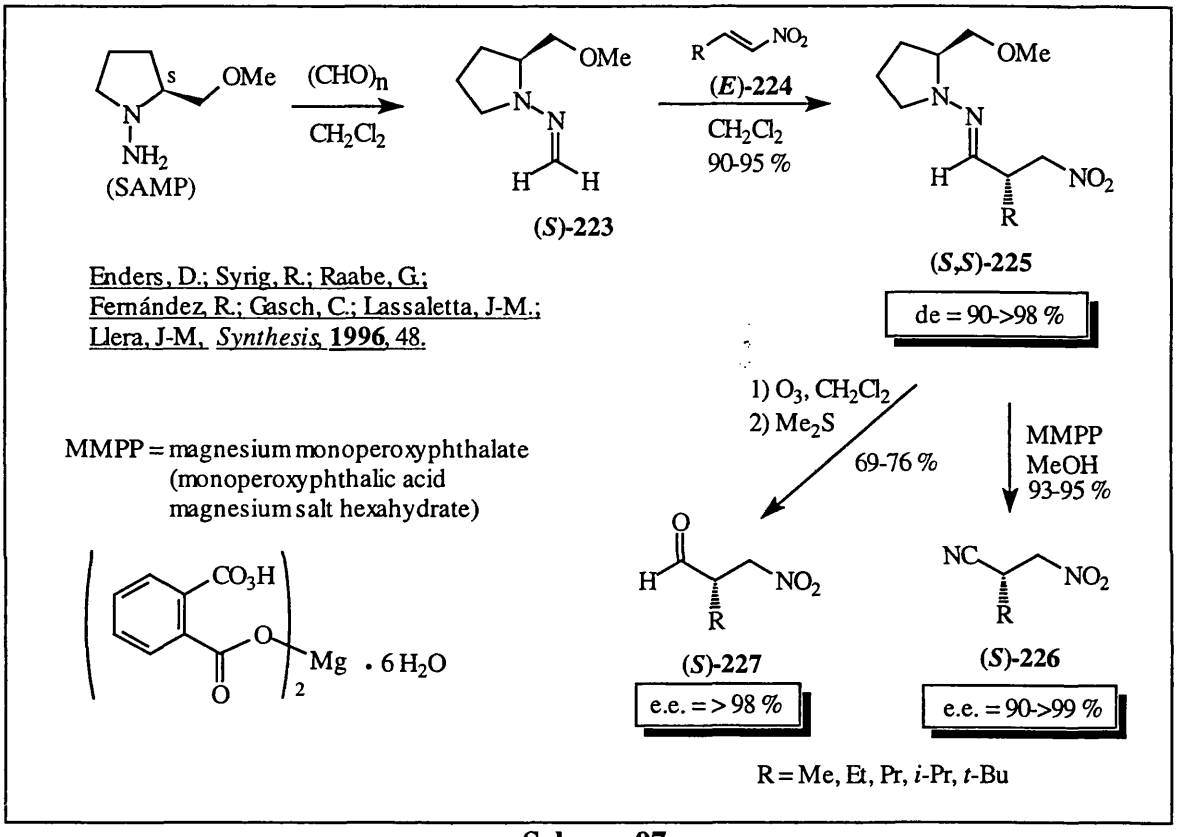
Enders *et al.*[129] have also investigated the formaldehyde SAMP-hydrazone **A** for its aza-enamine reactivity towards electrophiles (**A** → **B** → **C**) and its ability to function as a chiral equivalent of the formyl anion **D** (**Scheme 96**).



Scheme 96

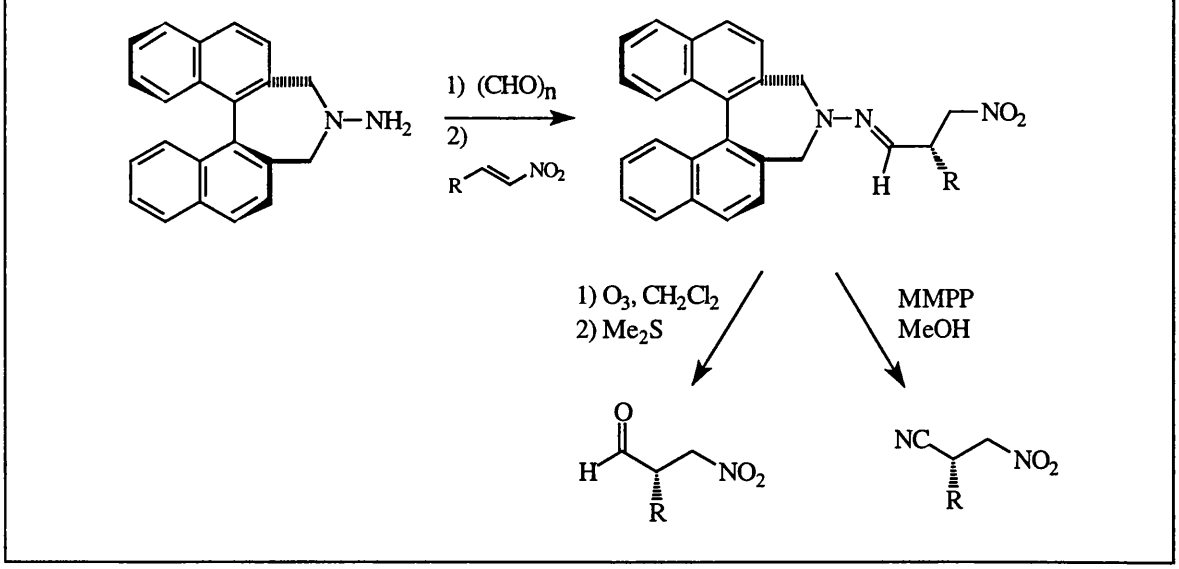
They reported their optimal conditions for the conjugate nucleophilic formylation and cyanation of nitroalkenes employing formaldehyde SAMP-hydrazone **A** as a chiral

formyl anion and cyanide equivalent (**Scheme 97**). Stirring the formaldehyde SAMP-hydrazone (*S*)-**223** with aliphatic nitroalkenes (*E*)-**224** under neutral conditions afforded the Michael addition products (*S,S*)-**225** exclusively as the (*E*)-configured, α-substituted β-nitroaldehyde SAMP-hydrazones after flash chromatography. Oxidative transformation of the aldehyde hydrazones **225** with magnesium monoperoxyphthalate (MMPP) in MeOH led to the corresponding α-substituted β-nitro nitriles (*S*)-**226**. The corresponding α-substituted β-nitroaldehydes (*S*)-**227** were obtained by ozonolysis followed by reductive work-up.



Scheme 97

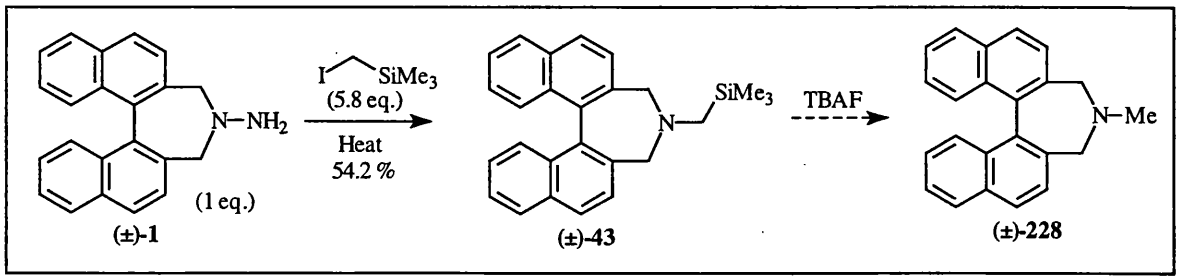
Again, we believe that our chiral hydrazine **1** could also be used in a similar manner, and due to the steric bulk of the two naphthalene ring systems may give equally high enantiomeric excesses in the Michael additions reactions (**Scheme 98**).



Scheme 98

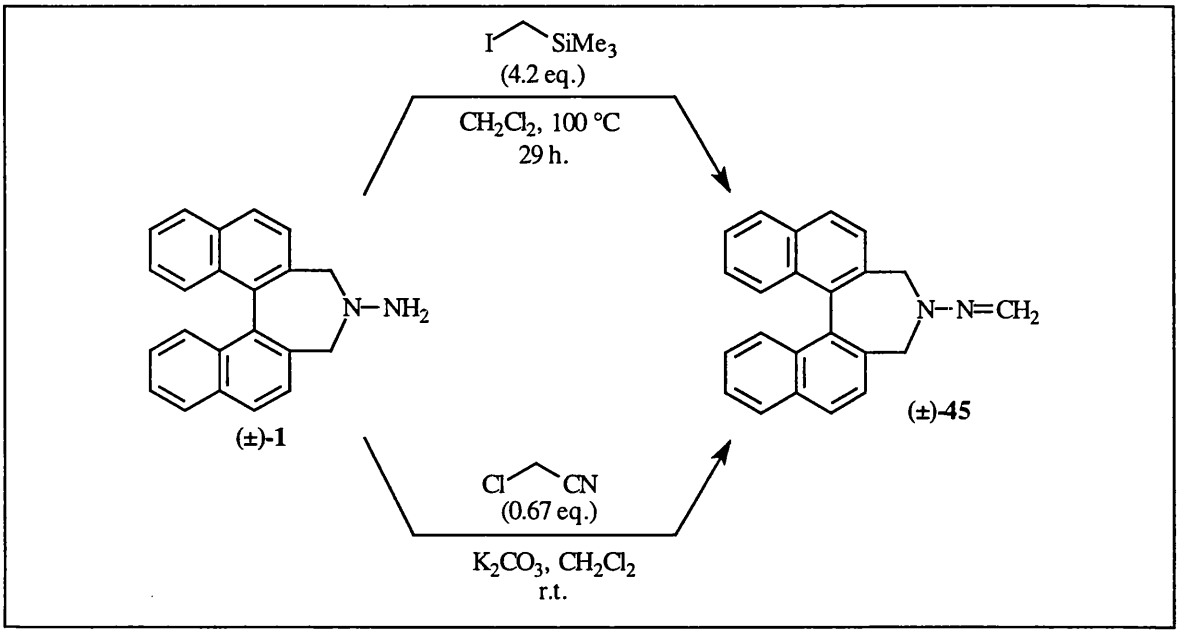
During the course of the preparation of hydrazine **1**, several interesting reactions were observed. The reduction of 3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33** was found to be highly efficient using DIBAL-H. To our knowledge, this was the first example of a *N*-nitroso reduction with DIBAL-H. This led to an evaluation of the scope of this reduction method with various *N*-nitroso compounds, prepared in turn from the corresponding secondary amines with isoamyl nitrite.

Another potentially useful reaction was the surprising cleavage of the N-N bond using neat excess (iodomethyl)trimethylsilane (**Scheme 99**). This generated the tertiary amine (±)-**43** which is a novel method for this kind of N-N bond cleavage and may provide an efficient way into *N*-methylated compounds (±)-**228**.



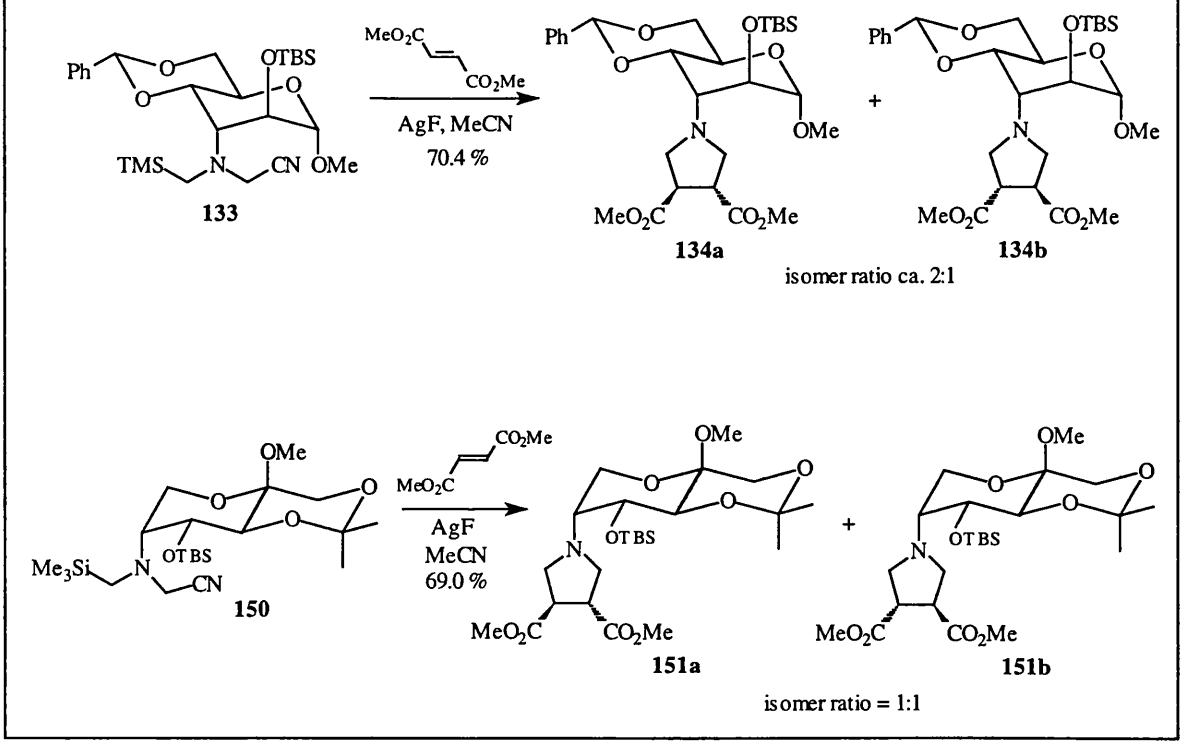
Scheme 99

Treatment of **1** with (iodomethyl)trimethylsilane or chloroacetonitrile in CH_2Cl_2 surprisingly afforded the hydrazone (±)-**45** (**Scheme 100**). This was proved by the deliberate preparation of (±)-**45** by treating **1** with *para*-formaldehyde in CH_2Cl_2.



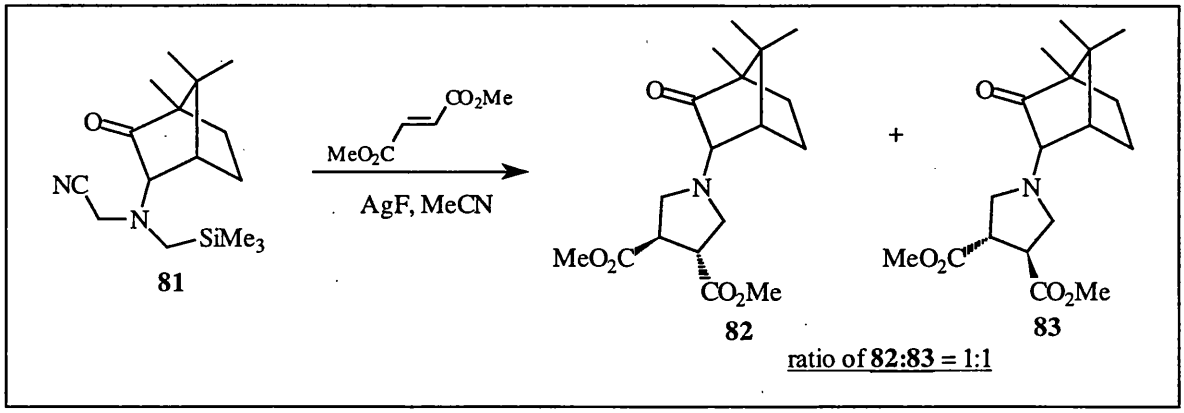
Scheme 100

The preparation of a variety of chiral auxiliaries for the [3+2]-cycloaddition reactions of azomethine ylides was also attempted with varied success. Two carbohydrate auxiliaries, mannose and D-glucose, were found to be completely unsuccessful. The remaining two carbohydrate auxiliaries, methyl-α-D-glucopyranoside and methyl β-D-fructopyranoside, were more successful (**Scheme 101**). In both cases, the required cycloaddition precursors were prepared and the azomethine ylides generated. These were successfully captured with dimethyl fumarate, but unfortunately, the best stereoselectivity achieved was a mixture of 2:1. In both cases, the newly-formed pyrrolidine moiety could not be cleaved from the chiral auxiliary.



Scheme 101

Camphor was also used as the chiral auxiliary for our attempted 1,3-dipolar cycloadditions. The azomethine ylide was successfully generated and trapped with dimethyl fumarate (**Scheme 102**). Again, however, the reaction was non-stereospecific. Similarly, the pyrrolidine moiety could not be removed from the camphor auxiliary. The attempted introduction of a phenyl group and the subsequent preparation of the cycloaddition precursor under various conditions also failed.



Scheme 102

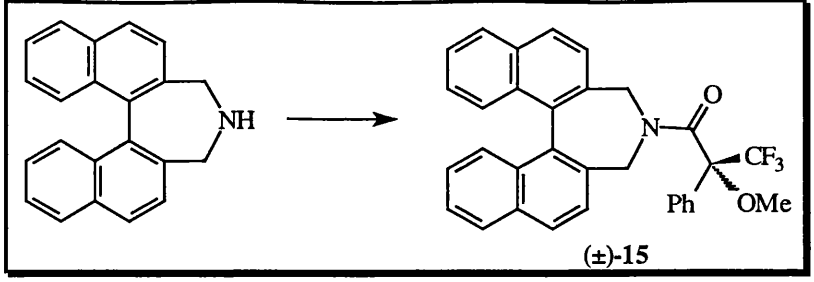
We also successfully prepared (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-diamine **(1*S*,2*S*)-111** which was converted to (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-(*N'*,*N''*-bis-trimethylsilylmethyl)-diamine **(1*S*,2*S*)-120**. However, preparing an azomethine ylide precursor from this compound was meet with failure.

As a final attempt, we attempted the preparation of a 'fixed' azomethine ylide which would offer no free rotation around the C-N bond, and therefore result in poor stereoselectivity in the resulting pyrrolidine unit. This work was based on (*R*)-5-phenyl-2-pyrrolidinone **156** which had, to our knowledge, only been prepared in racemic form followed by resolution or separation of each enantiomer by chiral chromatography. We successfully prepared this compound **156** as well as its derivative, (*R*)-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**, in reasonable yield. The introduction of a hydroxyl group at C-3 was unsuccessful, and the method was abandoned.

The chemistry of [3+2]-cycloaddition reactions of nonstabilised azomethine ylides to various dipolarophiles is an area of increasing interest. However, due to the difficulties in obtaining good to high stereoselectivities in their reactions, there are few successful examples available. We have attempted various chiral auxiliaries, some of which had the potential of being recycled into the same procedure, but we were constantly faced with either complete failure or with cycloadducts having poor stereoselectivities. This work does indicate the problems encountered with this type of cycloaddition reactions, and the project has been abandoned at this point.

Experimental

All reactions were carried out under an inert atmosphere of nitrogen with freshly distilled solvents unless otherwise stated. All solvents were reagent grade. DMPU was dried over excess 4Å molecular sieves that had been activated by prolonged heating (1h) with a Bunsen burner while under high vacuum (0.01 mmHg). DMPU was stored and used under an atmosphere of dry nitrogen and employed without further purification. CH_2Cl_2, toluene, benzene, $^iPr_2NH$ and Et_3N were freshly distilled from calcium hydride under nitrogen. THF and Et_2O were freshly distilled from sodium metal under dry nitrogen. Flash chromatography was carried out according to Still *et al.*[172] with Sorbsil C60 40/60A (230-400 mesh) silica gel. Precoated silica gel plates (250 mM) with a fluorescent indicator (E. Merck Kieselgel 60 F_{254}) were used for analytical Thin Layer Chromatography. ^1H and ^{13}C n.m.r. spectra were carried out on a Varian VXR-400 Series NMR spectrometer (400 MHz) or a JEOL 300 Series Spectrometer (300 MHz). Chemical shifts in the ^1H n.m.r. that are recorded in deuterochloroform ($CDCl_3$) are reported in δ-values relative to the residual traces of $CHCl_3$ set at δ 7.24 ppm. Chemical shifts in the ^{13}C n.m.r. spectra recorded in $CDCl_3$ are recorded in δ values relative to the residual $CHCl_3$ peak at δ 77.0 ppm. Residual traces of DMSO in DMSO-d_6 were set at 2.5 ppm for ^1H n.m.r. spectra and 39.5 ppm for ^{13}C n.m.r. spectra. All infra red spectra were recorded on a Perkin Elmer 1605 Series FT-IR Spectrophotometer and values shown are in wave numbers (cm^{-1}). All melting points were determined on a Reichert Hotstage Microscope, No. 242 274, (20-230 °C range) and are uncorrected. High-resolution mass spectra were measured by the ULIRS Mass Spectrometry Service Centre at the London School of Pharmacy on a VG analytical ZAB-SE mass spectrometer. Combustion microanalyses were performed by the Microanalytical Laboratory of University College London. The preparation of known compounds following existing experimental procedures are not included in this part of the report. The procedures followed can be found referenced in the aforementioned text with the relevant chemical and physical data.



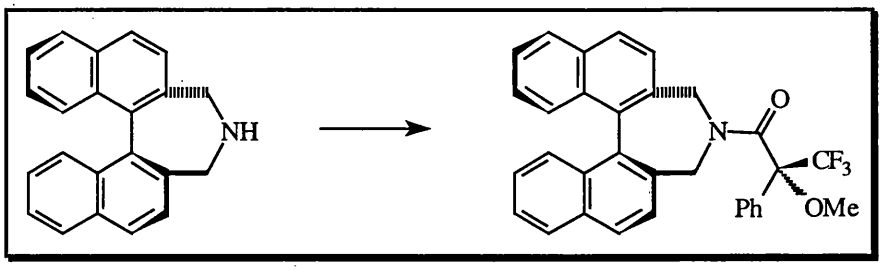
(±)-15

Mosher amide of racemate (±)-**15**

A mixture of (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** (75 mg, 0.25 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (62 mg, 0.27 mmol) and DCC (54 mg, 0.26 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature under N_2 for 5 days. The reaction mixture was then diluted with EtOAc, quenched with 5 % aqueous AcOH, the aqueous layer discarded and the organic layer washed once with water. This was then dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving an oil which was subjected to flash chromatography (hexanes/EtOAc, 3:1) affording the Mosher amide (±)-**15** as a clear oil.

Yield: 117 mg, 90.0 %.

δ_H (400 MHz, $CDCl_3$) 2.76 (1H, d, J_{HH} 13.2 Hz), 3.57 (1H, d, J_{HH} 13.5 Hz), 3.57 (3H, s, OMe), 3.62 (1H, d, J_{HH} 13.5 Hz), 3.83 (3H, s, OMe), 4.76 (1H, d, J_{HH} 13.2 Hz), 4.80 (1H, d, J_{HH} 12.0 Hz), 5.46 (1H, d, J_{HH} 13.7 Hz), 5.54 (1H, d, J_{HH} 8.4 Hz), 5.72 (1H, d, J_{HH} 13.5 Hz), 7.14-7.34 (6H, m), 7.38-7.70 (18H , m), 7.82 (2H, d, J_{HH} 8.2 Hz), 7.91-7.99 (8H, m).



Chiral Mosher amide **15**

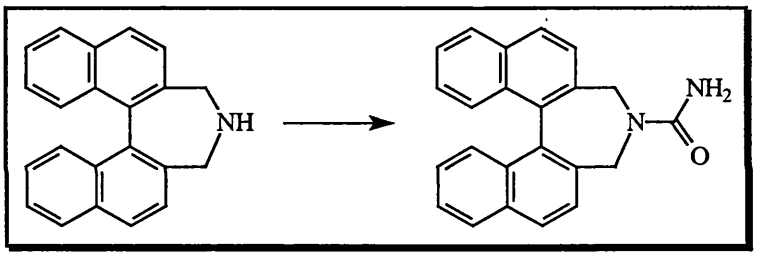
A mixture of (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** (98 mg, 0.33 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (79 mg, 0.34 mmol) and DCC

(70 mg, 0.34 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature under N_2 for 5 days. The reaction mixture was then diluted with EtOAc, quenched with 5 % aqueous AcOH, the aqueous layer discarded and the organic layer washed once with water. This was then dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving an oil which was subjected to flash chromatography (hexanes/EtOAc, 3:1) affording the chiral Mosher amide **15** as a clear oil.

Yield: 58 mg, 34.1 %.

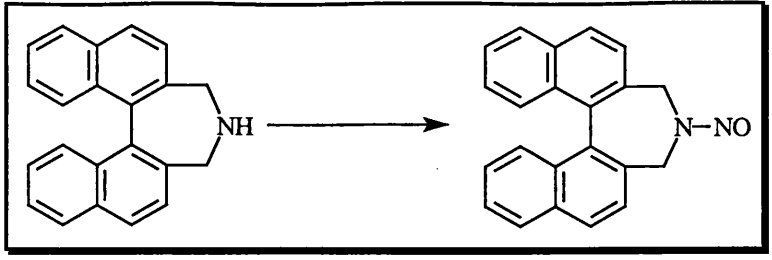
Atmospheric Pressure Chemical Ionisation for $C_{32}H_{25}F_3NO_2$ $(M+H)^+$: 512.3.

δ_H (400 MHz, $CDCl_3$) 2.76 (1H, d, J_{HH} 13.2 Hz), 3.57 (1H, d, J_{HH} 13.1 Hz), 3.84 (3H, s, OMe), 4.80 (1H, d, J_{HH} 13.1 Hz), 5.73 (1H, d, J_{HH} 13.1 Hz), 7.14-7.28 (6H, m), 7.40-7.56 (6H, m), 7.68 (1H, d, J_{HH} 8.3 Hz), 7.91-7.99 (4H, m).



(±)-Urea derivative **16**

A solution of (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** (1.00 g, 3.39 mmol) in THF (3 ml) was added at room temperature with stirring to H_2O (10 ml, H_2O initially at pH = 3.0 adjusted with dilute HCl). To this white solution was added KOCN (330 mg, 4.06 mmol) in H_2O (1 ml) in one portion, and the solution was then allowed to stir overnight at 50 °C in order to yield the crude urea derivative which was used *in situ*.



(±)-3,5-Dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33**

To a solution of (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** (5.00 g, 16.93 mmol) in dry THF (50 ml) was added isoamyl nitrite (12.0 ml, 89.32 mmol) while stirring at room temperature under nitrogen. The solution was stirred for approx. 21 h before the solvent and excess reagents were removed *in vacuo*. Rapid flash chromatography (hexanes/EtOAc, 3:1) afforded the *N*-nitroso compound as an off white/yellow solid.

Yield: 5.40 g, 98.4 %.

M. Pt.: 195-197 °C.

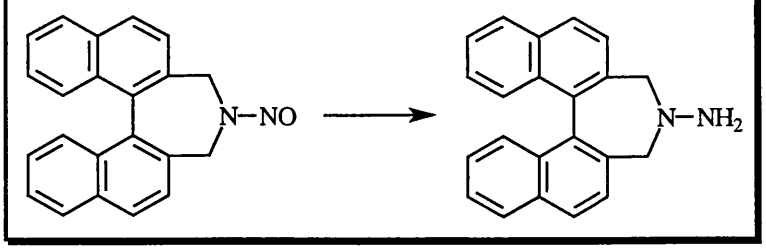
HR-MS (FAB, MNOBA matrix) for $C_{22}H_{17}N_2O$ $(M+H)^+$: required mass: 325.1341; measured mass: 325.1346.

Anal. calculated for $C_{22}H_{16}N_2O$: Calculated: C, 81.46; H, 4.97; C, 8.64: Found: C, 81.08, H, 5.03; N, 5.49.

δ_H (400 MHz, $CDCl_3$) 3.62 (1H, d, J_{HH} 15.2 Hz), 4.70 (1H, d, J_{HH} 13.2 Hz), 5.66 (2H, dd, J_{HH} 18.4 Hz, 14.4 Hz), 7.26-7.30 (2H, m), 7.40 (2H , t, J_{HH} 9.4 Hz), 7.48-7.53 (3H, m), 7.66 (1H, d, J_{HH} 8.0 Hz), 7.95-8.01 (4H, m).

δ_C (100 MHz, $CDCl_3$) 47.0, 54.3, 126.3, 126.4, 126.5, 127.2, 127.4, 127.5, 128.3, 128.4, 129.4, 129.7, 130.2, 131.2, 131.5, 131.5, 133.3, 133.5, 134.2, 135.7. **Two peaks not seen due to overlap.**

I.R. (KBr, 16 scans): 3051, 1593, 1504, 1429, 1343, 1318, 1233, 1116, 1066, 972, 868, 818, 751, 621, 530.



(±)-3,5-Dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1**

To a stirred solution of (±)-3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33** (5.20 g, 16.03 mmol) in CH_2Cl_2 (50 ml) cooled to -78 °C was dropwise added DIBAL-H (60.0 ml, 90.00 mmol, 1.5 M solution in toluene) and the resultant mixture stirred at -78 °C for 2 h. The reaction mixture was then allowed to stir at room temperature for 65 h before being slowly poured into a mixture of 10 % aqueous Rochelle's salt solution (60 g in 600 ml) and CH_2Cl_2 (600 ml). The solution was stirred vigorously for 1½ h at room temperature, the CH_2Cl_2 layer extracted, and the aqueous layer extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a light yellow solid. Flash chromatography (CH_2Cl_2/MeOH, 50:1 → 25:1, CH_2Cl_2 load) furnished the hydrazine as a light yellow solid.

Yield: 3.50 g, 70.3 %.

M. Pt.: 155-159 °C.

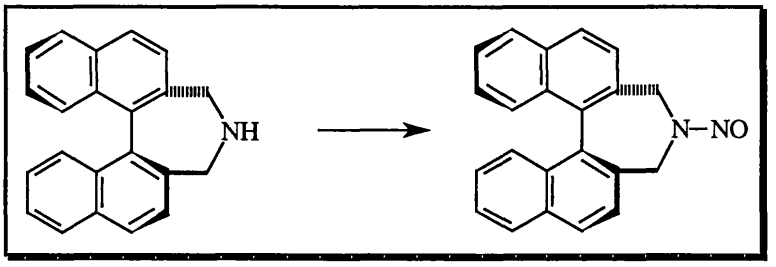
HR-MS (FAB, MNOBA matrix) for $C_{22}H_{19}N_2$ $(M+H)^+$: required mass: 311.1548; measured mass: 311.1556.

Anal. calculated for $C_{22}H_{18}N_2$: Calculated: C, 85.13; H, 5.85; N, 9.02: Found: C, 81.88; H, 5.61; C, 8.41.

δ_H (400 MHz, $CDCl_3$) 2.96 (2H, br s, NH_2), 3.34 (2H, d, J_{HH} 12.4 Hz), 3.89 (2H, d, J_{HH} 12.4 Hz), 7.23-7.28 (2H, m), 7.46 (4H , t, J_{HH} 7.6 Hz), 7.60 (2H, d, J_{HH} 8.4 Hz), 7.93-7.96 (4H, m).

δ_C (100 MHz, $CDCl_3$) 61.6, 125.6, 125.9, 127.5, 127.5, 128.3, 128.5, 131.5, 132.8, 133.3, 135.0.

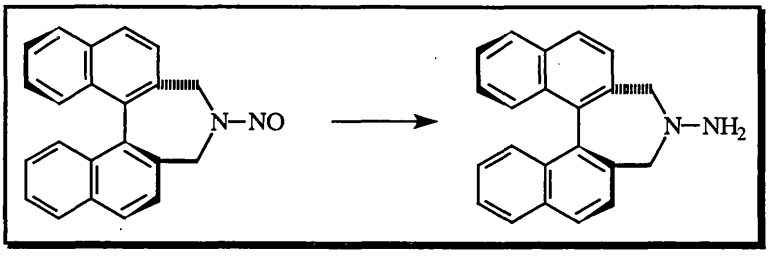
I.R. (KBr, 16 scans): 3320, 3048, 2934, 1592, 1504, 1461, 1365, 1326, 1238, 1140, 1056, 1026, 996, 959, 925, 869, 819, 786, 754, 623, 591, 567, 537, 468.



(*S*)-3,5-Dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33**

To a solution of (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **5** (500 mg, 1.69 mmol) in dry THF (10 ml) was added isoamyl nitrite (1.30 ml, 9.68 mmol) while stirring at room temperature under nitrogen. The solution was stirred at room temperature for 19 h before the solvent and excess reagents were removed *in vacuo*. Rapid flash chromatography (hexanes/EtOAc, 3:1) afforded the *N*-nitroso compound as an off white/yellow solid which was used without further analysis for the subsequent DIBAL-H reduction.

Yield: 625 mg, > 100 %.



(*S*)-3,5-Dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1**

To a stirred solution of (*S*)-3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33** (549 mg, 1.69 mmol, 100 % conversion assumed) in CH_2Cl_2 (6 ml) cooled to -78 °C was dropwise added DIBAL-H (6.0 ml, 9.0 mmol, 1.5 M solution in toluene) and the resultant mixture stirred at -78 °C for 1 h. The reaction mixture was then allowed to stir at room temperature for 44 h before being slowly poured into a mixture of 10 %

aqueous Rochelle's salt solution (6 g in 60 ml) and CH_2Cl_2 (70 ml). The solution was stirred vigorously for 1 h at room temperature, the CH_2Cl_2 layer extracted, and the aqueous layer extracted two times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a brown oil. Flash chromatography (CH_2Cl_2/MeOH, 50:1 → 30:1, CH_2Cl_2 load) furnished the hydrazine as a light brown solidified foam.

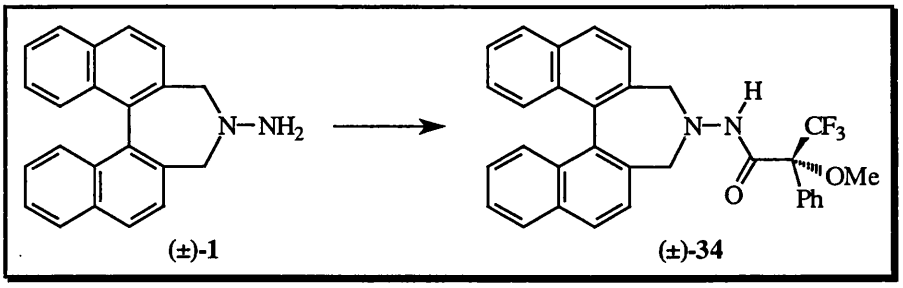
Yield: 334 mg, 63.6 %.

FAB-MS (FAB, MNOBA matrix) for $C_{22}H_{19}N_2$ $(M+H)^+$: 311.

Atmospheric Pressure Chemical Ionisation for $C_{22}H_{19}N_2$ $(M+H)^+$: 311.1

δ_H (400 MHz, $CDCl_3$) 2.74 (2H, br s, NH_2), 3.35 (2H, d, J_{HH} 12.4 Hz), 3.89 (2H, d, J_{HH} 12.4 Hz), 7.24-7.28 (2H, m), 7.42-7.48 (4H , m), 7.60 (2H, d, J_{HH} 8.4 Hz), 7.93-7.97 (4H, m).

δ_C (100 MHz, $CDCl_3$) 61.6, 125.6, 125.9, 127.5, 127.5, 128.3, 128.5, 131.5, 132.8, 133.3, 135.0.



(±)-1 (±)-34

Mosher derivative (±)-**34** of racemate (±)-**1**

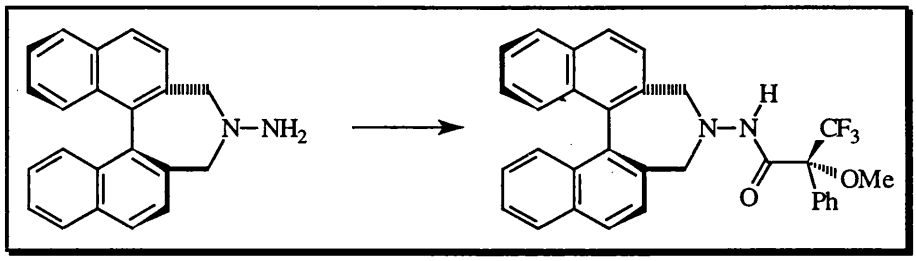
A mixture of (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1** (114 mg, 0.37 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (86 mg, 0.37 mmol) and DCC (75 mg, 0.36 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature under N_2 for 4 days. The reaction mixture was then diluted with EtOAc, quenched with 5 % aqueous AcOH, the aqueous layer discarded and the organic layer washed once with water. This was then dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving

an oil which was subjected to flash chromatography (hexanes/EtOAc, 3:1) affording the racemic Mosher derivative (±)-**34** as a light brown solid.

Yield: 182 mg, 94.3 %.

δ_H (400 MHz, $CDCl_3$) 3.34 (3H, d, J_{HF} 1.2 Hz, OMe), 3.44 (2H, d, J_{HH} 13.2 Hz), 3.46 (2H, d, J_{HF} 1.2 Hz, OMe), 3.51 (2H, d, J_{HH} 12.4 Hz), 3.89 (2H, d, J_{HH} 12.4 Hz), 3.99 (2H, d, J_{HH} 12.4 Hz), 7.18 (2H, d, J_{HH} 8.4 Hz), 7.24-7.30 (4H , m), 7.36-7.59 (16H, m), 7.67-7.69 (2H, m), 7.85 (2H, d, J_{HH} 8.4 Hz), 7.92-8.00 (8H, m).

δ_F (470 MHz, $CDCl_3$): - 69.53, -69.60.



Chiral Mosher derivative **34**

A mixture of (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1** (93 mg, 0.30 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (67 mg, 0.29 mmol) and DCC (62 mg, 0.30 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature under N_2 for 4 days. The reaction mixture was then diluted with EtOAc, quenched with 5 % aqueous AcOH, the aqueous layer discarded and the organic layer washed once with water. This was then dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving an oil which was subjected to flash chromatography (hexanes/EtOAc, 3:1) affording the Mosher derivative **34** as a brown oil.

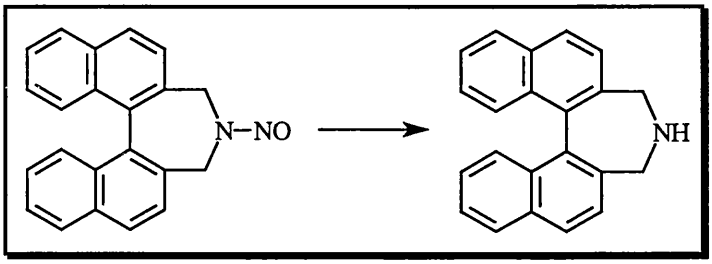
Yield: 150 mg, 94.9 %.

FAB-MS (FAB, MNOBA matrix) for $C_{32}H_{26}F_3N_2O_2$ $(M+H)^+$: 527.

δ_H (400 MHz, $CDCl_3$) 3.44 (2H, d, J_{HH} 12.4 Hz), 3.90 (2H, d, J_{HH} 12.4 Hz), 3.46 (3H, d, J_{HF} 1.6 Hz, OMe), 7.18 (2H, d, J_{HH} 8.0 Hz), 7.24-7.28 (2H , m), 7.42 (2H, d, J_{HH} 8.4

Hz), 7.45-7.49 (2H, m), 7.52-7.55 (3H, m), 7.67-7.69 (2H, m), 7.85 (2H, d, J_{HH} 8.0 Hz), 7.93 (2H, d, J_{HH} 8.0 Hz).

δ_F (470 MHz, $CDCl_3$): - 69.60 ppm. Racemic Mosher derivative (±)-**34** prepared as above using (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1** gave δ_F (470 MHz, $CDCl_3$): - 69.53 ppm and - 69.60 ppm, indicating 100 % e.e.

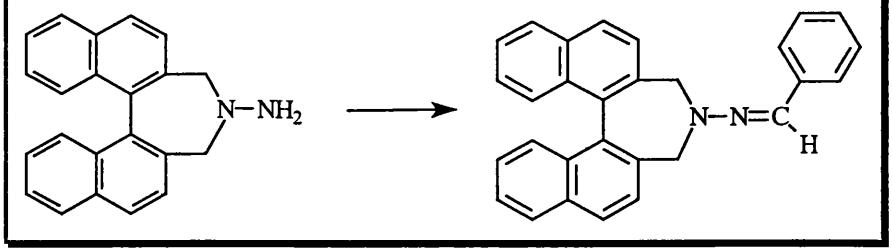


(±)-3,5-Dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **5**

To a vigorously stirred solution under nitrogen of Zn dust (2.07 g, 31.66 mmol) in AcOH (50 ml) was added a solution of (±)-3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]azepine **33** (1029 mg, 3.17 mmol) dissolved in THF (10 ml) and AcOH (10 ml) dropwise via a syringe at 0 °C. The resultant solution was stirred at room temperature for 3 h before the solution was diluted with THF (30 ml) and filtered through Celite. The filtrate was concentrated *in vacuo* affording a clear yellow oil. Flash chromatography in CH_2Cl_2:MeOH (10:1) afforded (±)-3,5-dihydro-4*H*-dinaphth[2,1-c:1',2'-e]azepine **5**. This evidence was backed up by the mass spectrum (FAB-MS) which showed the same molecular mass.

Yield of azepine: 800 mg, 85.6 %.

The spectral data matched that of (±)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine 5 prepared by Hawkins (see text, page 102, Scheme 10).



Hydrazone (±)-**30**

To a solution of (±)-3,5-dihydro-4*N*-dinapth[2,1-*c*;1',2'-*e*]azepinehydrazide **1** (100 mg, 0.32 mmol) in EtOH (2 ml) at room temperature was added benzaldehyde (0.05 ml, 0.49 mmol) and the solution stirred at 70 °C for 15 min. after which the product was seen as a white precipitate. The reaction mixture was cooled to room temperature, the product filtered off under suction, washed well with EtOH and dried in the air.

Yield: 110 mg, 85.9 %.

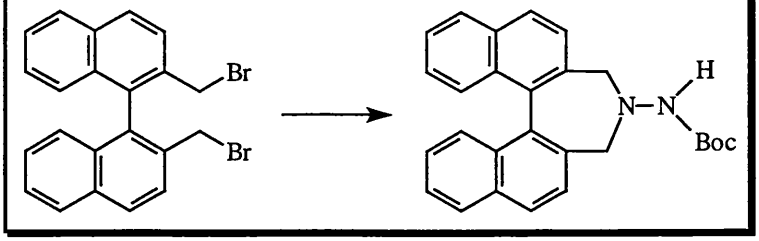
M. Pt.: 194-195 °C.

HR-MS for (FAB, MNOBA matrix) $C_{29}H_{22}N_2$ $(M)^+$: required mass: 398.1783; measured mass: 398.1757.

δ_H (400 MHz, $CDCl_3$): 3.79 (2H, d, J_{HH} 12.4 Hz), 4.60 (2H, d, J_{HH} 12.4 Hz), 7.20-7.34 (5H, m), 7.38 (1H, s), 7.44-7.51 (4H, m), 7.56-7.58 (2H, m), 7.61 (2H, d, J_{HH} 8.4 Hz), 7.93 (4H, d, J_{HH} 8.0 Hz).

δ_C (100 MHz, $CDCl_3$: 56.5, 125.7, 125.8, 125.9, 127.4, 127.5, 127.6, 128.3, 128.4, 128.7, 131.4, 133.2, 133.4, 134.7, 134.8, 136.7.

I.R. (KBr, 16 scans): 3056, 2938, 1578, 1504, 1459, 1429, 1364, 1326, 1232, 1138, 1088, 1049, 1002, 963, 883, 824, 756, 598, 532.



(±)-3,5-Dihydro-4*N*-(*N*'-Boc amino)-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **26**

To a stirred room temperature solution of *tert*-butyl carbazate (3.60 g, 27.24 mmol) in dry DMF (45 ml) was added (±)-2,2'-bis[bromomethyl]-1,1'-binaphthyl **9** (10.0 g, 22.72 mmol) and Et_3N (16.09 g, 0.159 mol) under nitrogen. The solution was heated at 70 °C for 20 hours. The white precipitate was removed by suction filtration, the filtrate diluted with water (60 ml), and the product extracted into Et_2O several times. The combined ether layers were washed with brine (2 x 100 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* affording a light brown solid. Recrystallisation from Et_2O afforded a white crystalline solid.

Yield: 3.05 g, 32.7 %.

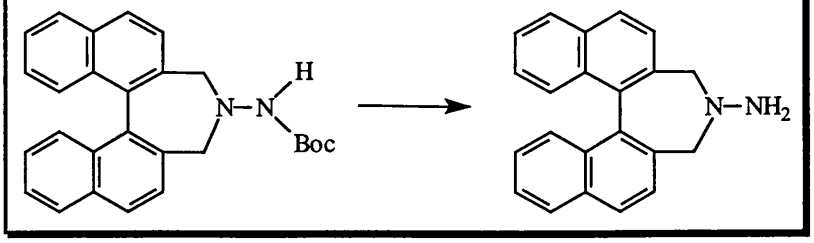
M. Pt.: 185-187 °C.

HR-MS for (FAB, MNOBA matrix) $C_{27}H_{27}N_2O_2$ $(M+H)^+$: required mass: 411.2073; measured mass: 411.2080.

δ_H (400 MHz, $CDCl_3$): 1.48 (9H, s, 3 x CH_3), 3.44 (2H, d, J_{HH} 12.4 Hz), 3.96 (2H, d, J_{HH} 12.4 Hz), 5.48 (1H, s, -NH), 7.23-7.27 (2H, m), 7.43-7.47 (4H, m), 7.60 (2H, d, J_{HH} 8.0 Hz), 7.95 (4H, t, J_{HH} 8.0 Hz).

δ_C (100 MHz, $CDCl_3$): 28.4, 58.9, 80.3, 125.7, 126.0, 127.4, 127.6, 128.3, 128.6, 131.4 (quat-C), 132.2 (quat-C), 133.3 (quat-C), 135.1 (quat-C), 154.3 (C=O).

I.R. (KBr, 16 scans): 3182, 3044, 2974, 2933, 1728, 1702, 1542, 1505, 1389, 1366, 1271, 1246, 1172, 1135, 1095, 1045, 1025, 817, 751.



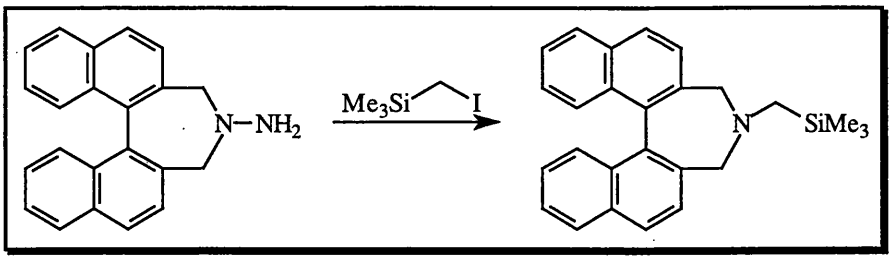
(±)-3,5-Dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **1**

A solution of (±)-3,5-dihydro-4*N*-(*N*'-Boc amino)-dinaphth[2,1-*c*:1',2'-*e*]azepine-hydrazide **26** (300 mg, 0.73 mmol) in a 1:1 mixture of CH_2Cl_2/AcOH (10 ml) was stirred at room temperature for 1 hour and the solvents removed *in vacuo*. Excess AcOH was removed by the co-evaporation with toluene (2 x 10 ml), and the product was then dissolved in CH_2Cl_2 (5 ml) and washed with K_2CO_3 (1 g dissolved in 5 ml H_2O). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving an off-white/yellow foam. Crystallisation from Et_2O afforded a white powder.

Yield: 198 mg, 87.2 %.

HR-MS for (FAB, MNOBA matrix) $C_{22}H_{19}N_2$ $(M+H)^+$: required mass: 311.1548; measured mass: 311.1540.

The spectral data matched that of the hydrazine prepared via *N*-nitroso reduction (see page 200).



(±)-3,5-Dihydro-4*N*-(trimethylsilylmethyl)-dinaphth[2,1-*c*:1',2'-*e*]azepine **43**

To (±)-3,5-dihydro-4*N*-dinapth[2,1-*c*;1',2'-*e*]azepinehydrazide **1** (300 mg, 0.97 mmol) was added (iodomethyl)trimethyl silane (1.00 ml, 6.73 mmol). The resultant solution was heated to 140-150 °C for 3 h, cooled to room temperature, Et_3N (0.40 ml, 2.87

mmol) added, and heated to gentle reflux for 30 min. The cooled solution was then diluted with CH_2Cl_2, quenched with water and extracted four times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* giving a black/brown solid. Flash chromatography (CH_2Cl_2/MeOH, 25:1) furnished the tertiary amine (±)-**43** as a brown solidified foam.

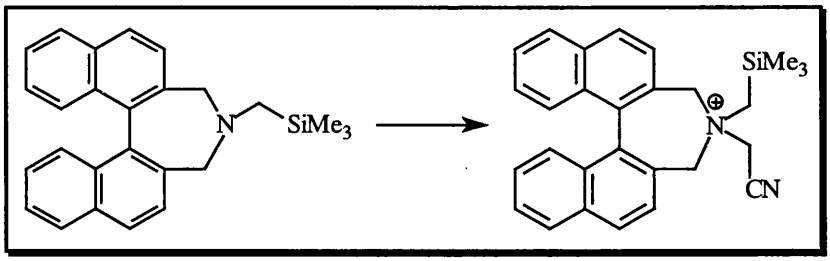
Yield: 200 mg, 54.2 %.

FAB-MS for (FAB, MNOBA matrix) $C_{26}H_{28}NSi$ $(M+H)^+$: Found: 382.

δ_H (400 MHz, $CDCl_3$): 0.16 (9H, s, Me_3Si), 2.05 (1H, d, J_{HH} 14.4 Hz), 2.31 (1H, d, J_{HH} 14.4 Hz), 3.28 (2H, d, J_{HH} 12.0 Hz), 3.68 (2H, d, J_{HH} 12.0 Hz), 7.24-7.28 (2H, m), 7.44-7.48 (4H, m), 7.58 (2H, d, J_{HH} 8.0 Hz), 7.93-7.97 (4H, m).

δ_C (100 MHz, $CDCl_3$: -0.8, 47.6, 58.9, 125.6, 125.9, 127.5, 128.0, 128.3, 128.4, 131.3, 133.3, 135.0. **One quat-C overlaps the other.**

I.R. (neat, 16 scans): 3047, 2948, 2891, 2788, 1593, 1508, 1460, 1364, 1247, 1094, 1027, 853, 816, 751, 624, 535.



(±)-3,5-Dihydro-4*N*-(trimethylsilylmethyl)-4*N*-(cyanomethyl)-dinaphth-[2,1-*c*:1',2'-*e*]azepine **44**

To the tertiary amine **43** (100 mg, 0.262 mmol) and solid K_2CO_3 (348 mg, 2.52 mmol) under nitrogen was added chloroacetonitrile (0.50 ml, 7.90 mmol) at room temperature. The reaction mixture was stirred at 120 °C for 1 h, cooled to room temperature, diluted with CH_2Cl_2 and the solid precipitate removed by suction filtration. The filtrate was concentrated *in vacuo* leaving a brown oil which was subjected to flash chromatography (CH_2Cl_2/MeOH, 25:1) affording the quarternary amine as a light brown solid.

Yield: 84 mg, 76.4 %.

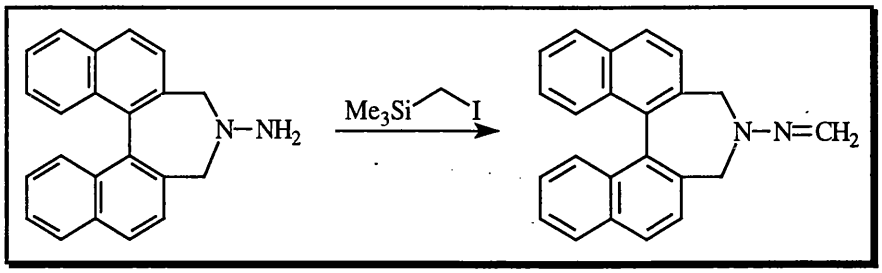
M. Pt.: 148-155 °C.

HR-MS for (FAB, MNOBA matrix) $C_{28}H_{29}N_2Si$ $(M)^+$: 421.1974.

δ_H (400 MHz, $CDCl_3$): 0.49 (9H, s, Me_3Si), 3.08 (1H, d, J_{HH} 14.4 Hz), 3.33 (1H, d, J_{HH} 14.4 Hz), 3.64 (1H, d, J_{HH} 12.4 Hz), 3.99 (1H, d, J_{HH} 12.4 Hz), 4.73 (1H, d, J_{HH} 12.4 Hz), 4.86 (1H, d, J_{HH} 17.6 Hz), 5.84 (1H, d, J_{HH} 12.4 Hz), 6.28 (1H, d, J_{HH} 17.6 Hz), 7.31-7.40 (3H, m), 7.47 (1H, d, J_{HH} 8.4 Hz), 7.56-7.63 (2H, m), 7.70 (1H, d, J_{HH} 8.4 Hz), 8.00 (1H, d, J_{HH} 8.4 Hz), 8.05 (1H, d, J_{HH} 8.4 Hz), 8.14 (2H, t, J_{HH} 9.2 Hz), 8.58 (1H, d, J_{HH} 8.4 Hz).

δ_C (100 MHz, $CDCl_3$: -0.4, 50.1, 56.1, 66.0, 68.5, 111.8, 125.2, 126.5, 127.2, 127.3, 127.3, 127.6, 127.8, 127.8, 128.1, 128.4, 128.6, 128.9, 130.5, 130.9, 131.1, 131.3, 134.6, 134.7, 136.3, 137.2.

I.R. (KBr, 16 scans): 2925, 2898, 1596, 1509, 1458, 1437, 1364, 1256, 1030, 851, 753, 660, 625.



Hydrazone (±)-**45**

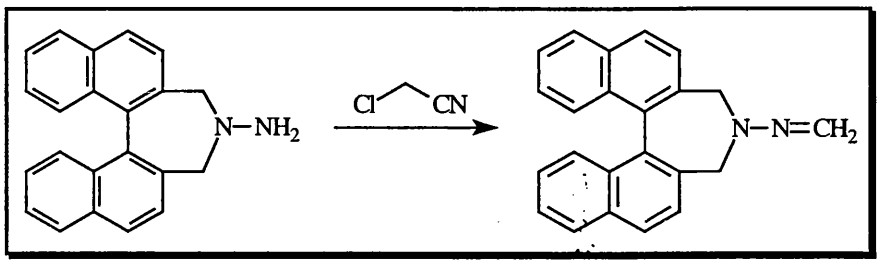
To a solution of (±)-3,5-dihydro-4*N*-dinapth[2,1-*c*;1',2'-*e*]azepinehydrazide **1** (100 mg, 0.32 mmol) in CH_2Cl_2 (2 ml) was added (iodomethyl)trimethylsilane (0.20 ml, 1.35 mmol) while stirring under nitrogen. The reaction mixture was stirred at 100 °C for 29 h in the dark, diluted with CH_2Cl_2, then treated with a 10 % aqueous KOH solution (10 ml) and then extracted twice with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving a yellow solid. Flash

chromatography (CH_2Cl_2/MeOH, 50:1) afforded hydrazone (±)-**45** as the major product as a yellow solid.

Yield: 24 mg, 23.1 %.

HR-MS for (FAB, MNOBA matrix) $C_{23}H_{19}N_2$ $(M+H)^+$: required mass: 323.1548; measured mass: 323.1560.

The spectral data matched that of the deliberately prepared hydrazone using *para*-formaldehyde (see page 211).



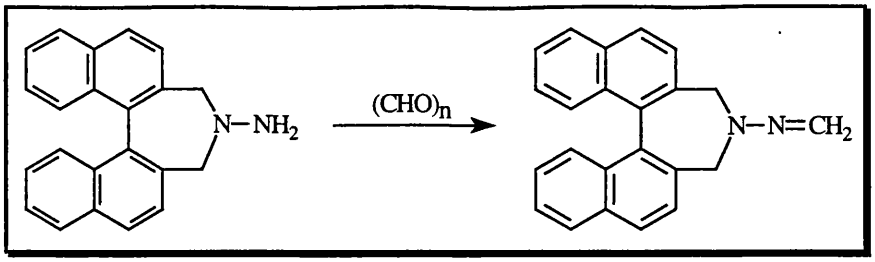
Hydrazone (±)-**45**

Alternative procedure.

To a solution of (±)-3,5-dihydro-4*N*-dinapth[2,1-*c*;1',2'-*e*]azepinehydrazide **1** (736 mg, 2.37 mmol) and solid K_2CO_3 (655 mg, 4.74 mmol) in CH_2Cl_2 (4 ml) was added chloroacetonitrile (0.10 ml, 1.58 mmol) while stirring under nitrogen. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2, the precipitate filtered off under suction and the precipitate washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated *in vacuo* leaving a white solid. Flash chromatography (CH_2Cl_2/MeOH, 50:1) afforded the major product as a foam which was still slightly impure. The ^1H n.m.r. spectrum indicated the formation of hydrazone (±)-**45** as compared to the previous preparation.

HR-MS for (FAB, MNOBA matrix) $C_{23}H_{19}N_2$ $(M+H)^+$: required mass: 323.1548; measured mass: 323.1560.

The spectral data matched that of the deliberately prepared hydrazone using *para*-formaldehyde (see page 211).



Hydrazone (±)-**45**

Deliberate preparation:

To a solution of (±)-3,5-dihydro-4*N*-dinapth[2,1-*c*;1',2'-*e*]azepinehydrazide **1** (100 mg, 0.32 mmol) in EtOH (2 ml) at room temperature was added *para*-formaldehyde (12 mg, 0.39 mmol) and the solution stirred at 90 °C for 4 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted 3 times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator leaving a brown foam. Flash chromatography (hexanes:EtOAc, 5:1) gave a yellow solidified foam.

Yield: 89 mg, 85.6 %.

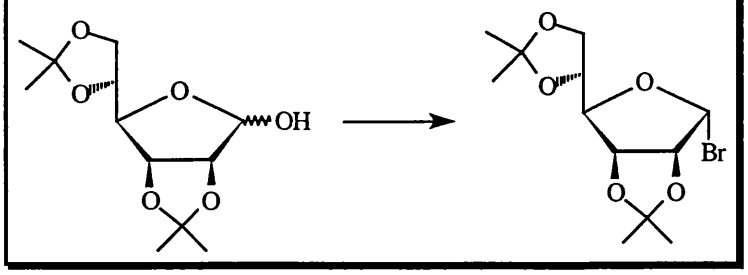
M. Pt.: 168-171 °C.

HR-MS for (FAB, MNOBA matrix) $C_{23}H_{19}N_2$ $(M+H)^+$: required mass: 323.1548; measured mass: 323.1560.

δ_H (400 MHz, $CDCl_3$): 3.65 (2H, d, J_{HH} 12.4 Hz), 4.44 (2H, d, J_{HH} 12.4 Hz), 6.18 (1H, d, J_{HH} 10.4 Hz), 6.27 (1H, d, J_{HH} 10.8 Hz), 7.24-7.28 (2H, m), 7.45-7.48 (4H, m), 7.58 (2H, d, J_{HH} 8.4 Hz), 7.95 (4H, d, J_{HH} 8.4 Hz).

δ_C (100 MHz, $CDCl_3$): 55.7, 124.4, 125.7, 125.9, 127.4, 128.3, 128.7, 131.4, 133.1, 133.2, 134.7. **One peak overlapping the other.**

I.R. (neat, 16 scans): 3056, 2938, 1578, 1504, 1459, 1429, 1364, 1326, 1232, 1138, 1088, 1049, 1002, 963, 883, 824, 756, 598, 532.

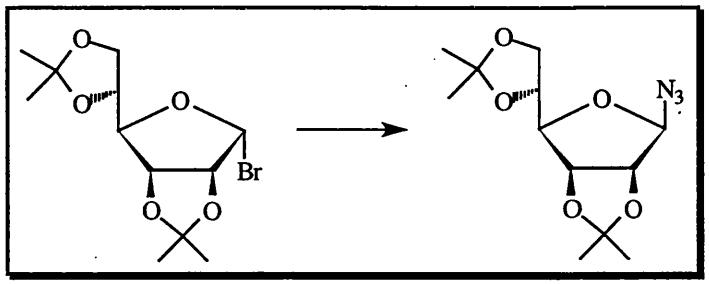


2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl bromide **48**

To a stirred solution of alcohol **47** (4.45 g, 17.10 mmol) in THF (80 ml) cooled to 0 °C (external temperature, ice-salt bath) was added triphenylphosphine (13.45 g, 51.28 mmol) and carbon tetrabromide (17.01 g, 51.29 mmol) and the solution stirred at room temperature for 1 hour. The white triphenylphosphine oxide which precipitated out was filtered off under suction and the filter cake washed thoroughly with THF. The solvent was removed on a rotary evaporator leaving a crude clear oil which was used immediately for the next reaction.

δ_H (400 MHz, $CDCl_3$): 1.32 (3H, s), 1.39 (3H, s), 1.47 (6H, s, 2 x $-CH_3$), 4.02-4.14 (3H, m), 4.40-4.48 (2H, m), 4.79 (1H, dd, J_{HH} 3.66 Hz, 6.0 Hz), 5.45 (1H, s).

δ_C (100 MHz, $CDCl_3$): 24.6, 25.1, 25.9, 26.9, 66.8, 72.8, 79.5, 81.9, 85.0, 95.5, 109.4 (quat-C), 113.2 (quat-C).



2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl azide **49**

To a stirred room temperature solution of the crude bromide **48** (6.21 g, 19.22 mmol, 100 % conversion assumed) in dry DMF (40 ml) was added sodium azide (23.82 g, 366.41 mol). The resulting solution was stirred at room temperature overnight before being diluted with brine (50 ml). The product was extracted into Et_2O (3 x 50 ml), and the combined organic layers were washed with brine (100 ml), dried over $MgSO_4$,

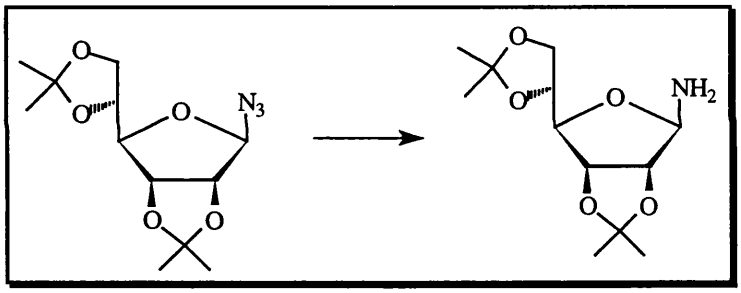
filtered and concentrated *in vacuo* leaving a yellow oil as crude product. Flash chromatography (hexanes:EtOAc, 18:1) afforded the required azide as a clear light brown oil.

Yield: 3.08 g, 56.2 %.

δ_H (400 MHz, $CDCl_3$): 1.33 (3H, s), 1.35 (3H, s), 1.41 (3H, s), 1.52 (3H, s), 3.56 (1H, dd, J_{HH} 3.6 Hz, 7.6 Hz), 4.04-4.11 (2H, m), 4.37 (1H, d, J_{HH} 3.6 Hz), 4.40-4.44 (1H, m), 4.64 (1H, dd, J_{HH} 3.6 Hz, 6.0 Hz), 4.74 (1H, dd, J_{HH} 3.6 Hz, 6.0 Hz).

δ_C (100 MHz, $CDCl_3$): 24.3, 25.1, 25.2, 26.9, 66.7, 72.8, 78.5, 79.5, 81.1, 89.1, 109.3 (quat-C), 113.6 (quat-C).

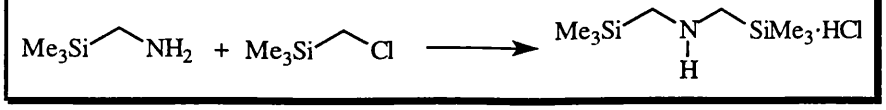
I.R. (neat, 16 scans): 2987, 2938, 2362, 2123 ($-N_3$), 1736, 1458, 1378, 1271, 1211, 1163, 1117, 1071, 998, 846, 771.



2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl amine **50**

To a stirred solution of azide **49** (210 mg, 0.74 mmol) in dry THF (10 ml) at room temperature was added palladium on carbon (39 mg, 0.037 mmol, 5 mol %, contains 10 % Pd in carbon). The solution was stirred at room temperature under a hydrogen atmosphere for 4 hours. The solution was then filtered by suction and the solvent removed on the rotary evaporator leaving the product as a clear oil which was used immediately for the next reaction without further purification.

Yield (crude): 210 mg, > 100 %.

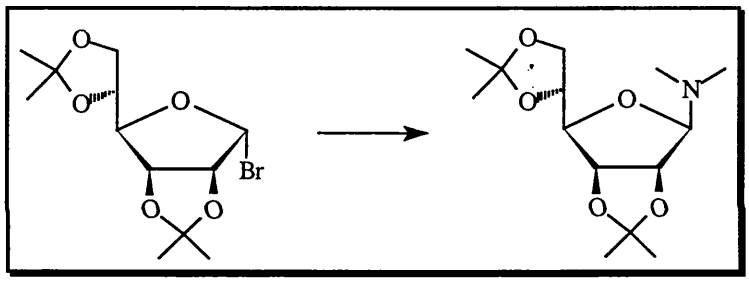


(*N*-Trimethylsilylmethyl) trimethylsilylmethylamine **54**

To a solution of trimethylsilylmethyl amine (1.00 ml, 7.46 mmol) in THF (5 ml) at room temperature was added (chloromethyl)trimethylsilane (0.60 ml, 4.30 mmol) and the reaction mixture stirred at gentle reflux for 4 days. The grey/white precipitate was then filtered off under suction filtration leaving a white solid which was used crude for the subsequent reaction.

Yield: 470 mg, 48.4 %.

FAB-MS for (FAB, MNOBA matrix) $C_8H_{24}NSi_2Cl$ $(M\text{-}Cl)^+$: 190.



2,3:5,6-Di-*O*-isopropylidene-*N*,*N*-dimethyl-β-D-mannofuranosyl amine **58**

To a solution of sugar bromide **48** (3.50 g, 10.83 mmol) in THF (5 ml) stirring under nitrogen at room temperature was added Et_3N (1.45 g, 2.0 ml, 14.35 mmol) and dimethylamine (7.0 ml, 14.00 mmol, 2M solution in THF). The reaction mixture was then stirred in the dark for 24 hours, diluted with water and extracted three times with diethyl ether. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear oil. Flash chromatography (hexanes:EtOAc, 10:1 → EtOAc) afforded the amine as a clear oil (1.40 g, 45 %) which solidified on standing.

Yield: 1.40, 45.0 %.

M. Pt.: 67-70 °C.

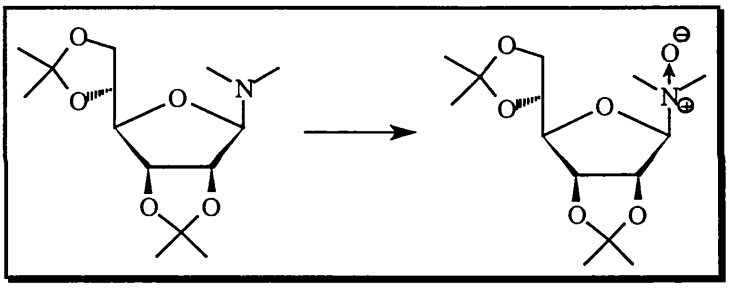
$[\alpha]_D^{20} = +7.1°$ (*c* 0.218, MeOH).

HR-MS (FAB, MNOBA matrix) for $C_{14}H_{26}NO_5$ $(M+H)^+$: required mass: 288.1811; measured mass: 288.1804.

δ_H (400 MHz, $CDCl_3$): 1.32 (3H, s), 1.35 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 2.22 (6H, s, NMe_2), 3.92 (1H, dd, J_{HH} 3.6 Hz, 8.0 Hz), 4.00-4.11 (3H, m), 3.34-3.36 (1H, m), 4.66 (1H, d, J_{HH} 6.0 Hz), 4.77 (1H, dd, J_{HH} 3.6 Hz, 6.0 Hz).

δ_C (100 MHz, $CDCl_3$): 24.7, 25.2, 26.1, 26.9, 40.8, 67.0, 73.4, 80.6, 81.7, 83.8, 101.0, 109.2, 112.6.

I.R. (KBr, 16 scans): 3439, 2979, 2940, 2877, 2805, 1455, 1376, 1286, 1257, 1207, 1153, 1120, 1059, 1020, 976, 948, 921, 895, 844, 798, 745, 683, 584, 515.



2,3:5,6-Di-*O*-isopropylidene-*N*,*N*-dimethyl-β-D-mannofuranosylamine-*N*-oxide **57**

To the tertiary amine prepared above **58** (1.00 g, 3.48 mmol) in CH_2Cl_2 (8 ml) at -10 °C was added in one portion *meta*-chloroperbenzoic acid (1.32 g, 3.83 mmol, 56-88 %, 50% assumed). The mixture was stirred at 0 °C for 10 minutes after which the crude reaction mixture was rapidly flashed chromatographed (CH_2Cl_2:MeOH, 5:1 → 1:1) affording the pure *N*-oxide as an off white-yellow solid.

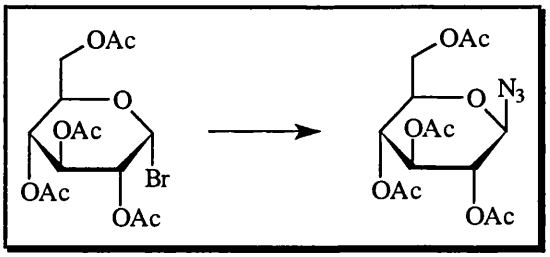
Yield: 921 mg, 86.4 %.

FAB-MS (FAB, MNOBA matrix) for $C_{14}H_{26}NO_6$ $(M+H)^+$: required mass: 304.1760; measured mass: 304.1748.

δ_H (300 MHz, $CDCl_3$): 1.33 (6H, s, 2 x Me), 1.40 (3H, s), 1.45 (3H, s), 3.07 (3H, s), 3.12 (3H, s), 4.02-4.08 (2H, m), 4.29-4.32 (1H, m), 4.69 (1H, s), 4.92-4.96 (2H, m), 5.43 (1H, d, J_{HH} 5.7 Hz).

δ_C (75 MHz, $CDCl_3$): 24.3, 25.2, 26.0, 26.7, 55.1, 55.7, 66.6, 73.3, 80.9, 82.0, 86.7, 105.8, 109.4, 113.0.

I.R. (neat, 16 scans): 3380, 2988, 1659, 1456, 1381, 1262, 1210, 1161, 1125, 1069, 970, 947, 895, 846, 796.



1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranosyl azide **62**

To a stirred solution of α-bromide **61** (9.00 g, 21.89 mmol) in dry DMF (100 ml) at room temperature was added sodium azide (28.46 g, 0.438 mol, 20 equivalents). The solution was stirred at room temperature for 15 hours. The reaction mixture was then quenched with brine (100 ml) and the product extracted into Et_2O (2 x 300 ml). The product crystallised in Et_2O, the crystalline product remaining in the aqueous phase was therefore extracted into EtOAc (2 x 300 ml). The combined organic layers were washed with brine (2 x 300 ml), water (2 x 200 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* affording pure white crystals.

Yield: 7.19 g, 88.0 %.

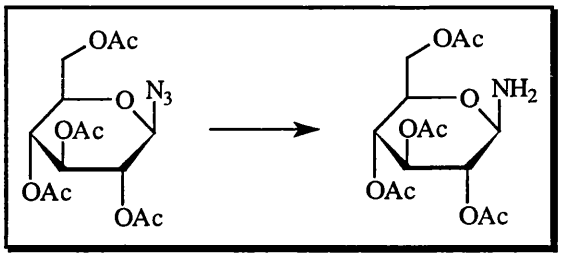
M. Pt.: 127-128 °C.

HR-MS for (FAB, MNOBA matrix) $C_{14}H_{19}N_3O_9Na$ $(M+Na)^+$: required mass: 396.1019; measured mass: 396.1010.

δ_H (400 MHz, $CDCl_3$): 1.92 (3H, s), 1.94 (3H, s), 1.98 (3H, s), 2.01 (3H, s), 3.71-3.75 (1H, m), 4.07 (1H, dd, J_{HH} 2.4 Hz, 12.4 Hz), 4.19 (1H, dd, J_{HH} 4.8 Hz, 12.4 Hz), 4.58 (1H, d, J_{HH} 9.2 Hz), 4.86 (1H, t, J_{HH} 9.4 Hz), 5.01 (1H, t, J_{HH} 9.8 Hz), 5.14 (1H, t, J_{HH} 9.6 Hz).

δ_C (100 MHz, $CDCl_3$): 20.3, 20.5, 61.5, 67.7, 70.4, 72.4, 73.8, 87.6, 169.0 (C=O), 169.1 (C=O), 169.9 (C=O), 170.4 (C=O). **Two Me peaks overlapping.**

I.R. (KBr, 16 scans): 2970, 2910, 2119, 1756, 1439, 1374, 1311, 1241, 1214, 1121, 1059, 1038, 976, 951, 907, 878, 712, 674, 644, 607, 556, 482.



1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranosyl amine **63**

To a stirred solution of β-azide **62** (1.30 g, 3.48 mmol) in dry THF (15 ml) at room temperature was added palladium on carbon (185 mg, 0.174 mmol, contains 10 % Pd on carbon). The solution was stirred at room temperature under a hydrogen atmosphere for 5 hours. The solution was then filtered by suction in air and the solution diluted with water (20 ml). The product was extracted into Et_2O (3 x 25 ml) and the combined Et_2O layers washed with brine (50 ml), the organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo* affording pure white crystals which required no further purification.

Yield: 1026 mg, 84.9 %.

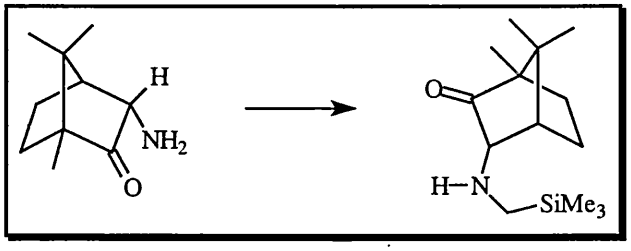
M. Pt.: 120-122 °C.

HR-MS for (FAB, MNOBA matrix) $C_{14}H_{19}O_9$ $(M\text{-}NH_2)^+$: required mass: 331.1029; measured mass: 331.1013.

δ_H (400 MHz, $CDCl_3$): 1.94 (2H, br s, $-NH_2$), 2.02 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 3.68-3.72 (1H, m), 4.11 (1H, dd, J_{HH} 2.4 Hz, 12.4 Hz), 4.21 (1H, d, J_{HH} 8.8 Hz), 4.23 (1H, dd, J_{HH} 4.8 Hz, 12.4 Hz), 4.84 (1H, t, J_{HH} 9.2 Hz), 5.05 (1H, t, J_{HH} 9.6 Hz), 5.25 (1H, t, J_{HH} 9.6 Hz).

δ_C (100 MHz, $CDCl_3$): 20.6, 20.7, 20.7, 62.2, 68.7, 71.9, 72.6, 73.1, 84.9, 169.5 (C=O), 170.1 (C=O), 170.6 (C=O). **One Me and one C=O peak overlapping.**

I.R. (KBr, 16 scans): 3457, 3405, 3332, 2973, 2934, 1732, 1636, 1443, 1373, 1236, 1133, 1095, 1036, 978, 911, 886, 844, 775, 705, 676, 600, 561, 546, 511.



(1*R*)-*endo*-3-(*N*-Trimethylsilyl methyl)camphor amine **80**

To a solution of (1*R*)-*endo*-3-camphor amine **76** (11.50 g, 68.76 mmol) in dry acetonitrile (50 ml) was added *N,N*-diisopropyl-*N*-ethylamine (18.0 ml, 0.104 mol) and (iodomethyl)-trimethylsilane (15.0 ml, 0.101 mol). The reaction mixture was stirred under N_2 at reflux for 22 hours. The reaction mixture was then cooled to room temperature, quenched with water, and extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear yellow oil which could be used crude for the subsequent reaction with only about 10 % reduction in yield as when compared to the pure product.

Yield (crude): 16.20 g, 92.9 %.

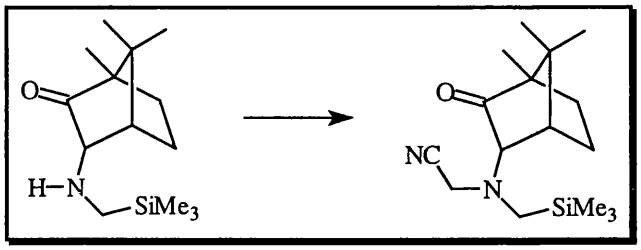
FAB-MS (MNOBA matrix) for $C_{14}H_{28}NOSi$ $(M+H)^+$: 254.3.

δ_H (400 MHz, $CDCl_3$): 0.05 (9H, s, Me_3Si), 0.85 (3H, s), 0.88 (3H, s), 0.98 (3H, s), 1.23-1.30 (1H, m), 1.38 (1H, NH), 1.52-1.62 (2H, m), 1.81-1.85 (1H, m), 1.88 (1H, d,

J_{HH} 13.4 Hz), 1.94 (1H, d, J_{HH} 13.4 Hz), 2.14 (1H, t, J_{HH} 4.4 Hz), 3.18 (1H, d, J_{HH} 4.8 Hz).

δ_C (100 MHz, $CDCl_3$): -2.7, 9.5, 18.4, 19.5, 19.8, 32.0, 38.7, 44.0, 46.5, 58.5, 68.5, 219.3.

I.R. (neat, 16 scans): 2957, 2873, 2772, 1746, 1453, 1392, 1317, 1248, 1129, 1047, 1007, 869, 698.



(1*R*)-(+)-*endo*-3-(*N*-Cyanomethyl-*N*-trimethylsilylmethyl)camphor amine **81**

To a solution of (1*R*)-*endo*-3-(*N*-trimethylsilylmethyl)camphor amine **80** (4.93 g, 19.45 mmol) in acetonitrile (50 ml) was added *N,N*-diisopropyl-*N*-ethylamine (5.50 ml, 31.79 mmol) and chloroacetonitrile (2.00 ml, 31.60 mmol) and the resultant reaction mixture stirred at gentle reflux for approx. 90 h. The reaction mixture was then cooled to room temperature, quenched with water, and extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving a brown oil. Flash chromatography (hexanes/CH_2Cl_2, 1:1) afforded the required tertiary amine as a clear yellow oil.

Yield: 5.60 g, 98.8 %.

$[\alpha]_D^{20}$ = + 62.2° (*c* 0.238, MeOH).

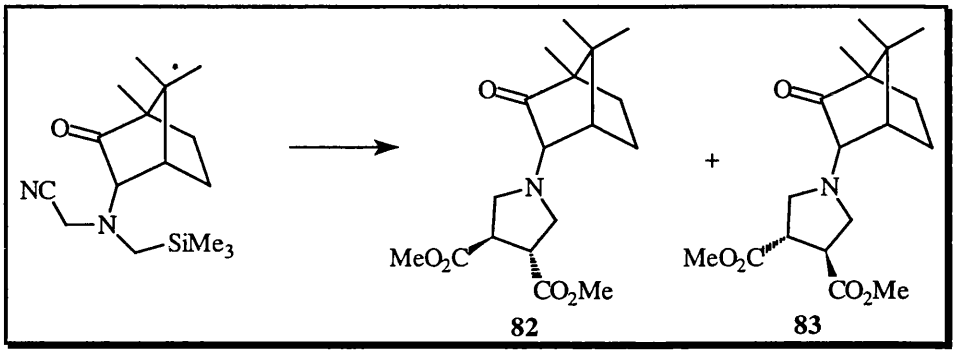
HR-MS (FAB, MNOBA matrix) for $C_{16}H_{29}N_2OSi$ $(M+H)^+$: required mass: 293.2049; measured mass: 293.2060.

δ_H (400 MHz, $CDCl_3$): 0.05 (9H, s, Me_3Si), 0.81 (3H, s), 0.84 (3H, s), 0.92 (3H, s), 1.36 (1H, t, J_{HH} 9.0 Hz), 1.58-1.69 (2H, m), 1.76 (1H, t, J_{HH} 8.6 Hz), 2.02 (1H, dd, J_{HH} 1.8

Hz, 14.6 Hz), 2.19 (1H, t, J_{HH} 4.2 Hz), 2.31 (1H, d, J_{HH} 14.8 Hz), 2.90 (1H, d, J_{HH} 4.4 Hz), 3.44 (1H, d, J_{HH} 17.4 Hz), 4.38 (1H, d, J_{HH} 17.4 Hz).

δ_C (100 MHz, $CDCl_3$): -1.6, 9.7, 19.1, 19.3, 19.9, 30.8, 43.1, 43.4, 43.8, 47.2, 59.2, 68.3, 115.0, 216.5.

I.R. (neat, 16 scans): 2959, 1740, 1426, 1251, 1040, 855, 759.



(1*R*)-(+)-(*trans*-3,4-Dicarbomethoxy)-*N*-(*endo*-3-camphor)pyrrolidine **82+83**

To a solution of tertiary amine **81** (4.22 g, 14.43 mmol) in acetonitrile (50 ml) was added dimethyl fumarate (4.16 g, 28.86 mmol) and silver (I) fluoride (3.17 g, 24.99 mmol) while stirring under nitrogen in the dark. The reaction mixture was stirred in the dark for 6 days, filtered through a pad of Celite, washed thoroughly with CH_2Cl_2 and concentrated *in vacuo* leaving a brown solid. This was flash chromatographed (hexanes:EtOAc, 10:1) affording the cycloadduct as a clear yellow oil. Unreacted starting amine **81**, 630 mg, was also recovered.

Yield from flash chromatography: 2.97 g, 61.0 %.
Yield based on recovered starting material is thus 71.7 %.

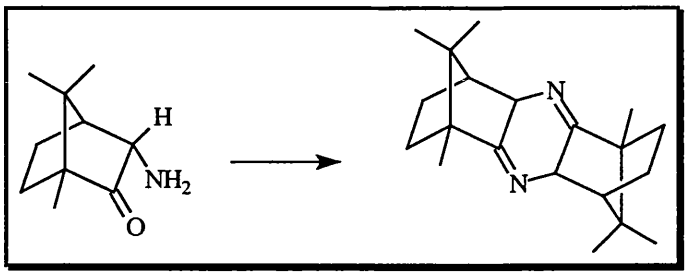
$[\alpha]_D^{20}$ = + 33.4° (*c* 0.394, MeOH).

HR-MS (FAB, MNOBA matrix) for $C_{18}H_{28}NO_5$ $(M+H)^+$: required mass: 338.1967; measured mass: 338.1950.

δ_H (400 MHz, $CDCl_3$): 0.95 (3H, s), 0.84 (3H, s), 0.95 (3H, s), 1.34-1.38 (1H, m), 1.57-1.65 (2H, m), 1.86-1.91 (1H, m), 2.06-2.09 (1H, m), 2.55 (1H, t, J_{HH} 5.0 Hz), 2.79 (1H, dd, J_{HH} 5.6 Hz, 9.2 Hz), 2.93-2.96 (1H, m), 3.06 (1H, t, J_{HH} 8.6 Hz), 3.31-3.39 (2H, m), 3.60-3.65 (1H, m), 3.67 (3H, s), 3.68 (3H, s).

δ_C (100 MHz, $CDCl_3$): 9.6, 19.2, 19.5, 19.6, 19.8, 30.8, 30.9, 44.6, 44.8, 47.7, 52.2, 55.9, 56.0, 69.3, 69.4, 173.8 (C=O), 173.9 (C=O), 216.3 (C=O).

I.R. (neat, 16 scans): 2957, 2870, 2801, 1741, 1438, 1376, 1312, 1206, 1176, 1039, 1008, 756.



1,6,11,11,12,12-Hexamethyl-1,2,3,4,4a,6,7,8,9,9a-decahydro-1,4;6,9-dimethano-phenazine **87**

The camphor amine **76** was left standing at room temperature for 24 - 96 hours, after which time virtually all camphor amine had dimerised to an orange paste. Flash chromatography (hexanes:EtOAc, 12:1) gave the dimer as a pure light yellow solid.

M.Pt.: 106-108 °C.

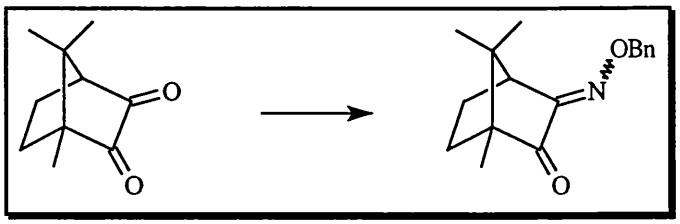
$[\alpha]_D^{20}$ = - 247.0° (*c* 0.2, MeOH).

FAB-MS (FAB, MNOBA matrix) for $C_{20}H_{31}N_2$ $(M+H)^+$: required mass: 299.2487; measured mass: 299.2498.

δ_H (400 MHz, $CDCl_3$): 0.91 (6H, s), 0.94-0.96 (2H, m), 0.99 (6H, s), 1.06 (6H, s), 1.50-1.56 (2H, m), 1.60-1.65 (2H, m), 1.76 (2H, dt, J_{HH} 11.6 Hz), 2.43 (2H, br s), 3.60 (2H, t, J_{HH} 1.2 Hz).

δ_C (100 MHz, $CDCl_3$) 11.0, 19.0, 20.0, 36.7, 47.1, 48.8, 54.1, 65.5, 187.2. **One peak overlaps the other.**

I.R. (neat, 16 scans): 2958, 2869, 1747, 1650, 1474, 1447, 1371, 1327, 1292, 1268, 1227, 1155, 1110, 1048, 1011, 903, 748, 630, 481.



(1*R*)-Camphorquinone-3-*O*-benzyl-oxime **94**

To a solution of (1*R*)-camphorquinone **74** (1.00 g, 6.02 mmol) in absolute EtOH (10 ml) was added pyridine (0.7 ml, 8.65 mmol) and *O*-benzylhydroxylamine hydrochloride (1056 mg, 6.62 mmol) and the solution stirred at room temperature for 4 hours. The reaction mixture was then quenched with water and extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated on rotary affording a yellow solid which was subjected to flash chromatography (hexanes:EtOAc, 25:1) to leave a clear liquid. ^{1}H n.m.r. indicated a mixture of *syn/anti* isomers of 2.8:1.

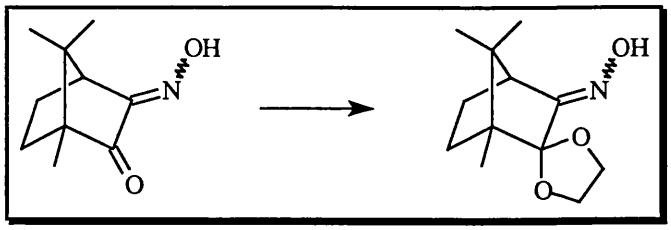
Yield: 1.21 g, 74.2 %.

HR-MS (FAB, MNOBA matrix) for $C_{17}H_{22}NO_2$ $(M+H)^+$: required mass: 272.1651; measured mass: 272.1655.

δ_H (400 MHz, $CDCl_3$, major isomer only): 0.84 (3H, s), 0.94 (3H, s), 1.00 (3H, s), 1.45-1.57 (2H, m), 1.69-1.78 (1H, m), 1.94-2.03 (1H, m). 3.17 (1H, d, J_{HH} 4.4 Hz), 5.24 (2H, s), 7.24-7.34 (5H, m).

δ_C (100 MHz, $CDCl_3$, mixture of *syn/anti* isomers): 8.9, 9.0, 17.5, 18.0, 20.4, 20.6, 23.8, 25.1, 29.7, 30.6, 44.7, 45.3, 47.2, 50.4, 58.4, 59.4, 77.2, 77.2, 127.5, 127.6, 128.0, 128.0, 128.2, 128.3, 136.8, 137.5, 156.4, 159.2, 197.9 (C=O), 203.9 (C=O).

I.R. (neat, 16 scans): 3032, 2960, 2873, 1748, 1634, 1497, 1454, 1393, 1372, 1323, 1108, 1036, 997, 969, 920, 885, 846, 736, 698.



(1*R*)-2,2-Ethylenedioxy-camphorquinone-3-oxime **99**

To a stirred solution of (1*R*)-camphorquinone-3-oxime **75** (4.60 g, 25.38 mmol) in benzene (50 ml) at room temperature was added $MeSO_3H$ (0.16 ml, 2.47 mmol) and ethane-1,2-diol (7.00 ml, 0.126 mol) and the mixture stirred at gentle reflux for 24 h. The cooled reaction mixture was then treated with an aqueous solution of K_2CO_3 until pH ~ 8, the solution then extracted with CH_2Cl_2, the combined extracts dried over $MgSO_4$, filtered and concentrated affording a clear yellow oil. Flash chromatography (hexanes/EtOAc, 2:1) furnished the required product as a clear yellow oil.

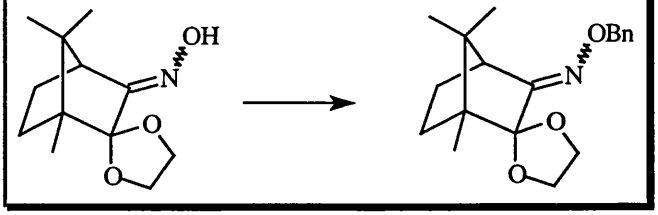
Yield: 5.28 g, 92.3 %.

HR-MS (FAB, MNOBA matrix) for $C_{12}H_{20}NO_3$ $(M+H)^+$: required mass: 226.1443; measured mass: 226.1434.

δ_H (400 MHz, $CDCl_3$): 0.92 (3H, s), 1.06 (3H, s), 1.09 (3H, s), 1.43-1.50 (1H, m), 1.79-1.89 (1H, m), 1.95-2.05 (1H, m). 2.47-2.55 (1H, m), 2.71 (1H, t, J_{HH} 9.6 Hz), 2.89 (1H, s, OH), 3.66 (2H, t, J_{HH} 4.8 Hz), 4.01-4.10 (2H, m).

δ_C (100 MHz, $CDCl_3$): 21.3, 21.9, 24.4, 32.4, 39.2, 46.3, 54.2, 60.2, 65.8, 120.6, 174.9. **One peak overlapping the other**.

I.R. (neat, 16 scans): 3487, 2969, 2886, 2239, 1724, 1460, 1382, 1316, 1270, 1210, 1161, 1117, 1081, 1029, 888.

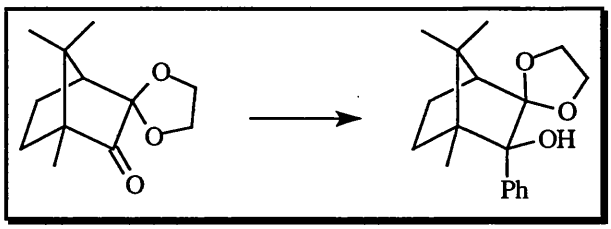


(1*R*)-2,2-Ethylenedioxy-camphorquinone-3-*O*-benzyl oxime **95**

To a solution of (1*R*)-2,2-ethylenedioxy-camphorquinone-3-oxime **99** (100 mg, 0.44 mmol) in DMF (2 ml) at room temperature was added in one portion NaH (20 mg, 0.49 mmol, 60 % dispersion in oil) and the mixture stirred under nitrogen for 15 min. Benzyl bromide (0.06 ml, 0.50 mmol) was then added and the reaction mixture stirred at room temperature for 2 h. The mixture was quenched with water, extracted twice with EtOAc, the combined organic extracts washed four times with water, twice with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving a clear yellow liquid. Flash chromatography (hexanes/EtOAc, 10:1) gave a clear oil.

Yield: 55 mg, 39.3 %.

δ_H (400 MHz, $CDCl_3$): 1.03 (3H, s), 1.17 (3H, s), 1.19 (3H, s), 1.53-1.60 (1H, m), 1.91-2.01 (1H, m), 2.02-2.13 (1H, m), 2.61-2.66 (1H, m), 2.79 (1H, t, J_{HH} 9.8 Hz), 3.62-3.68 (2H, m), 4.16-4.26 (1H, m), 4.27-4.35 (1H, m), 4.53 (2H, s), 7.25-7.36 (5H, m).



(1*R*)-2-*exo*-Hydroxy-2-*endo*-phenyl-3,3-ethylenedioxycamphor **100**

To a solution of (1*R*)-3,3-ethylenedioxycamphor **88** (928 mg, 4.41 mmol) in THF (20 ml) was added phenyllithium (4.50 ml, 8.10 mmol, 1.8M solution in cyclohexane:diethyl ether, 70:30) while stirring under nitrogen at -78 °C. The resultant reaction mixture was warmed slowly to room temperature, and stirred for 4 hours before being slowly quenched with water and extracted three times CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated on the rotary evaporator

leaving a dark brown oil. Flash chromatography (hexanes:CH_2Cl_2, 4:1) afforded the alcohol as a clear oil

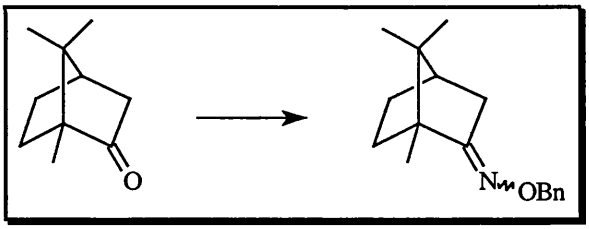
Yield: 1.08 g, 84.8 %.

HR-MS (FAB, MNOBA matrix) for $C_{18}H_{24}O_3$ $(M)^+$: required mass: 288.1725; measured mass: 288.1721.

δ_H (400 MHz, $CDCl_3$): 0.73 (3H, s), 0.94 (3H, s), 1.15-1.23 (1H, m), 1.33 (3H, s), 1.40-1.47 (1H, m), 1.68-1.77 (1H, m), 1.86 (1H, d, J_{HH} 4.8 Hz), 1.97-2.03 (1H, m), 3.19-3.25 (1H, m), 3.46 (1H, s, OH), 3.77-3.88 (3H, m), 7.19-7.30 (3H, m), 7.78-7.80 (2H, m).

δ_C (100 MHz, $CDCl_3$): 10.0, 21.1, 22.3, 22.8, 30.1, 47.0, 53.8, 54.7, 63.92, 64.8, 84.5, 116.8, 126.2, 126.4, 129.4, 141.0.

I.R. (neat, 16 scans): 3516, 3054, 2954, 2897, 1488, 1392, 1368, 1306, 1207, 1148, 1126, 1102, 1045, 1021, 952, 849, 811, 757, 714.



(1*R*)-Camphor-2-*O*-benzyl oxime **102**

To a solution of (1*R*)-(+)-camphor (2.00 g, 13.14 mmol) in absolute EtOH (10 ml) was added pyridine (1.30 ml, 16.07 mmol) and *O*-benzylhydroxylamine hydrochloride (2.52 g, 15.79 mmol) and the solution stirred at gentle reflux for 24 hours. The reaction mixture was then diluted with water and extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated on rotary affording a brown oil. Flash chromatography (hexanes:CH_2Cl_2, 4:1) gave the product as a clear oil.

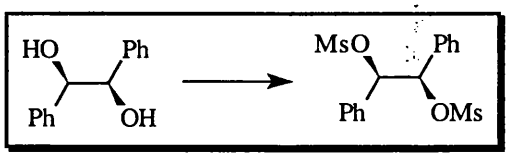
Yield: 3.35, 99.1 %.

HR-MS (FAB, MNOBA matrix) for $C_{17}H_{24}NO$ $(M+H)^+$: required mass: 258.1858; measured mass: 258.1870.

δ_H (400 MHz, $CDCl_3$): 0.82 (3H, s), 0.96 (3H, s), 1.10 (3H, s), 1.24-1.30 (1H, m), 1.49-1.55 (1H, m), 1.71-1.79 (1H, m), 1.83-1.92 (2H, m), 2.10 (1H, d, J_{HH} 18.0 Hz), 2.58 (1H, dt, J_{HH} 3.6 Hz), 5.15 (2H, s), 7.29-7.43 (5H, m).

δ_C (100 MHz, $CDCl_3$): 11.1, 18.4, 19.3, 27.1, 32.6, 33.8, 43.5, 47.9, 51.5, 75.0, 127.2, 127.6, 128.0, 138.4 (quat-C), 169.4 (C=O).

I.R. (neat, 16 scans): 3031, 2958, 2873, 1664 (w), 1497, 1453, 1428, 1389, 1368, 1200, 1116, 1082, 1016, 914, 826, 730, 697.



(1*R*,2*R*)-(-)-1,2-Diphenyl-1,2-dimesyloxyethane **119**

To a solution of (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediol **116** (11.0 g, 51.34 mmol) in pyridine (50 ml) at 0 °C was added in one-portion MsCl (11.0 ml, 0.142 mol) and the reaction mixture stirred at room temperature for 3 h. The mixture was then diluted with ice-water, extracted twice with CH_2Cl_2, the combined extracts dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving a light brown solid which required no further purification.

Yield: 18.86 g; 99.2 %.

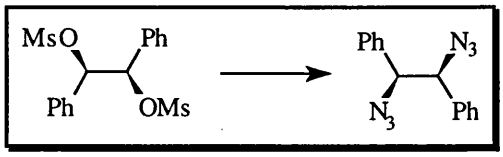
M. Pt.: 88-90 °C.

HR-MS (FAB, MNOBA matrix) for $C_{16}H_{18}O_6S_2Na$ $(M+Na)^+$: required mass: 393.0443 ; measured mass: 393.0430.

δ_H (400 MHz, $CDCl_3$): 2.79 (6H, s, 2 x Me), 5.75 (2H, s), 7.14-7.23 (10H, m)

δ_C (100 MHz, $CDCl_3$): 39.1, 84.1, 127.4, 128.7, 129.5, 133.3 (quat-C).

I.R. (KBr, 16 scans): 3032, 2988, 2938, 1500, 1460, 1412, 1363, 1175, 980, 930, 883, 816, 773, 737, 697, 625, 604, 529, 482.



(1*S*,2*S*)-(+)-1,2-Diphenylethane-1,2-diazide **118**

A solution of (1*R*,2*R*)-(-)-1,2-diphenyl-1,2-dimesyloxyethane **119** (3.80 g, 10.26 mmol) and NaN_3 (1.87 g, 28.76 mmol) in DMF (50 ml) was heated to 90 °C for 7 h. The mixture was cooled to room temperature, quenched with water (50 ml) and extracted 5 times with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* leaving a clear brown oil. Flash chromatography (hexanes:CH_2Cl_2, 5:1) afforded a clear yellow oil.

Yield: 1.70 g; 62.7 %.

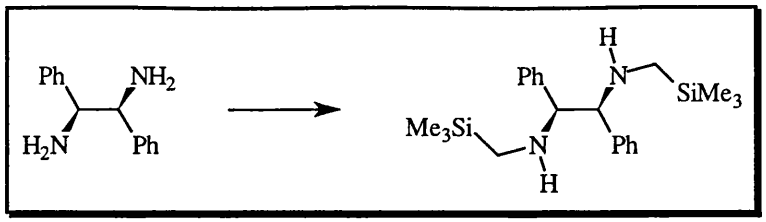
$[\alpha]_D^{20}$ = + 156.5° (*c* 0.1, $CHCl_3$) (Lit.: + 157°, *c* 1.05, $CHCl_3$).[153]

HR-MS (FAB, MNOBA matrix) for $C_{14}H_{13}N_6$ $(M+H)^+$: required mass: 265.1202 ; measured mass: 265.1212.

δ_H (400 MHz, $CDCl_3$): 4.65 (2H, s), 7.06-7.08 (4H, m), 7.22-7.26 (6H, m).

δ_C (100 MHz, $CDCl_3$): 70.6, 127.5, 128.4, 128.5, 135.6.

I.R. (neat, 16 scans): 3064, 3033, 2105, 1493, 1454, 1250, 1076, 853, 764, 699.



(1*S*,2*S*)-(-)-1,2-Diphenylethane-1,2-bis(*N'*,*N''*-trimethylsilyl methyl)diamine **120**

To a solution of (1*S*,2*S*)-(-)-1,2-diamino-1,2-diphenylethane **111** (3.85 g, 18.13 mmol) and anhydrous solid K_2CO_3 (7.52 g, 54.41 mmol) in acetonitrile (60 ml) was added (iodomethyl) trimethylsilane (6.50 ml, 43.74 mmol) and the reaction mixture stirred at 100 °C for 68 hours. The cooled reaction mixture was then filtered and concentrated *in vacuo* leaving a yellow solid. Flash chromatography (hexanes:EtOAc, 50:1 → 20:1) gave a clear yellow oil which solidified on standing at room temperature.

Yield: 6.66 g; 95.4 %.

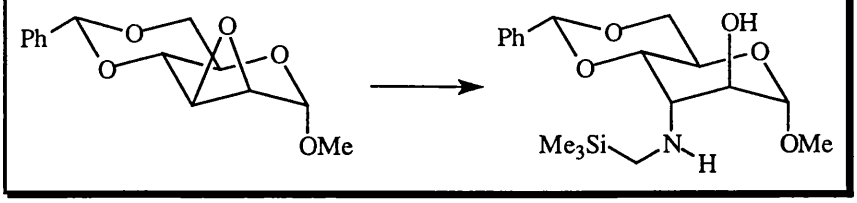
$[\alpha]_D^{20} = -7.1°$ (*c* 0.218, MeOH).

HR-MS (FAB, MNOBA matrix) for $C_{22}H_{37}N_2Si_2$ $(M+H)^+$: required mass: 385.2495; measured mass: 385.2481.

δ_H (400 MHz, $CDCl_3$): 0.01 (18H, s, 2 x Me_3Si), 1.75 (2H, d, J_{HH} 13.6 Hz), 1.87 (2H, d, J_{HH} 13.6 Hz), 1.89 (2H, br s, 2 x NH), 3.45 (2H, s), 6.94-6.96 (4H, m), 7.08-7.11 (6H, m).

δ_C (100 MHz, $CDCl_3$): -2.6, 37.7, 73.4, 126.5, 127.7, 128.0, 141.7 (quat-C).

I.R. (neat, 16 scans): 3324, 3065, 3026, 2954, 2895, 2764, 1454, 1250, 1190, 1103, 862, 759, 698, 572.

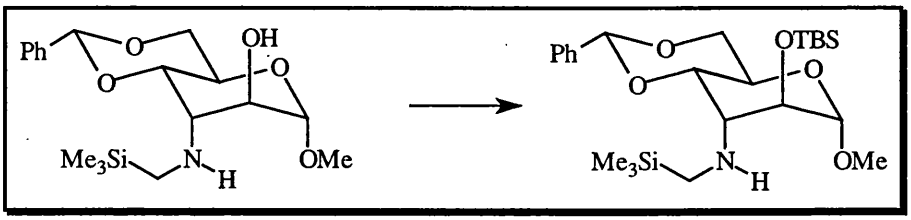


Methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside **131**

To a solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside **130** (1000 mg, 3.78 mmol) in THF (30 ml) was added trimethylsilylmethyl amine (5.00 ml, 37.29 mmol). The reaction mixture was stirred under nitrogen at gentle reflux for 4 days after which TLC indicated no reaction. DMF (30 ml) was then added and the mixture heated a reflux for a further 4 days. The cooled reaction mixture was quenched with water and extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear oil. Flash chromatography (CH_2Cl_2:MeOH, 25:1) gave a clear oil.

Yield: 1364 mg; 98.1 %.

δ_H (400 MHz, $CDCl_3$): -0.01 (9H, s, Me_3Si), 2.18 (2H, d, J_{HH} 0.8 Hz), 3.06-3.07 (1H, m), 3.33 (3H, s, OMe), 3.74 (1H, t, J_{HH} 10.2 Hz), 3.99 (1H, dd, J_{HH} 0.8 Hz, 2.8 Hz), 4.04 (1H, dd, J_{HH} 4.0 Hz, 9,6 Hz), 4.14-4.16 (1H, m), 4.24 (1H, dd, J_{HH} 5.0 Hz, 10.2 Hz), 4.57 (1H, s), 5.53 (1H, s), 7.30-7.45 (5H, m).



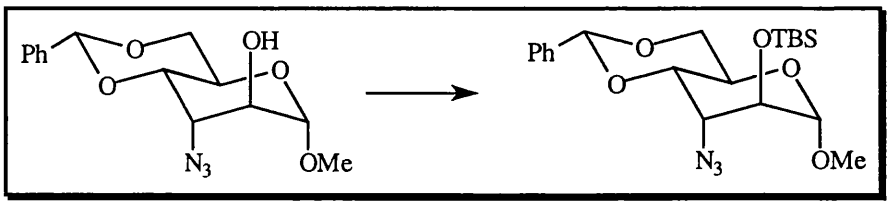
Methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132**

To a stirred solution of alcohol **131** (1364 mg, 3.71 mmol) in DMF (10 ml) was added imidazole (1.27 g, 18.65 mmol) and TBS-Cl (2.82 g, 18.71 mmol) at room temperature. The reaction mixture was stirred for 4 days, quenched with water and extracted twice with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated

in vacuo leaving a brown oil. Flash chromatography (hexanes:EtOAc, 5:1) afforded a clear yellow oil.

Yield: 1.30 g, 72.6 %.

The spectral data matched that of the same amine derivative prepared via the epoxide ring-opening using NaN_3 in water and 2-methoxyethanol (see page 232).



(+)-Methyl 3-azido-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **137**

To a stirred solution of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside **136** (18.78 g, 61.11 mmol) in DMF (200 ml) was added imidazole (12.48 g, 0.183 mol) and *tert*-butyldimethylsilyl chloride (27.63 g, 0.183 mol) at room temperature. The reaction mixture was stirred under nitrogen at room temperature for 24 h, quenched with water and extracted three times with EtOAc. The combined extracts were washed once with brine, twice with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear oil. Flash chromatography (hexanes:EtOAc, 8:1→5:1) afforded a clear yellow oil.

Yield: 25.52 g; 99.1 %.

$[\alpha]_D^{20} = +12.5°$ (*c* 0.28, MeOH).

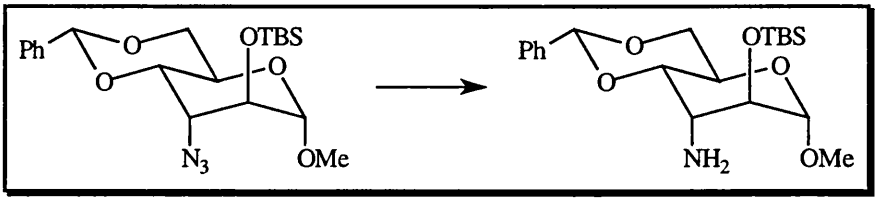
HR-MS for (FAB MNOBA matrix) for $C_{20}H_{32}N_3O_5Si$: $(M+H)^+$: actual: 422.2111; measured: 422.2130.

δ_H (400 MHz, $CDCl_3$): 0.10 (3H, s, Me), 0.11 (3H, s, Me), 0.90 (9H, s, ^tBu), 3.39 (3H, s, OMe), 3.79 (1H, t, J_{HH} 10.0 Hz), 3.87 (1H, d, J_{HH} 2.0 Hz), 3.91 (1H, d, J_{HH} 3.2 Hz),

4.12 (1H, dd, J_{HH} 3.6 Hz, 9.6 Hz), 4.20 (1H, dd, J_{HH} 3.6 Hz, 10.0 Hz), 4.26 (1H, dd, J_{HH} 3.6 Hz, 10.0 Hz), 4.43 (1H, s), 5.61 (1H, s), 7.35-7.50 (5H, m).

δ_C (100 MHz, $CDCl_3$): -5.0, 18.0, 25.7, 55.7, 58.8, 60.9, 69.2, 70.6, 76.0, 101.8, 102.3, 126.2, 128.4, 129.2, 137.1 (quat-C).

I.R. (neat, 16 scans): 3068, 3038, 2929, 2858, 2216, 2107, 1471, 1404, 1381, 1362, 1343, 1324, 1299, 1260, 1218, 1195, 1106, 1047, 1007, 966, 939, 913, 839, 779, 699, 674, 647, 614.



Methyl 3-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **138**

To a solution of methyl 3-azido-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **137** (43.00 g, 0.102 mol) in methanol (300 ml) was slowly added palladium on carbon (10.85 g, 10 mol%, 10 % Pd on C) and the reaction mixture stirred under H_2 for 24 h. The reaction mixture was then filtered through a pad of Celite, the pad washed thoroughly with CH_2Cl_2 and the combined filtrate concentrated *in vacuo* leaving a black oil which was subjected to flash chromatography (hexanes/EtOAc, 3:1→1:1) affording a clear yellow oil.

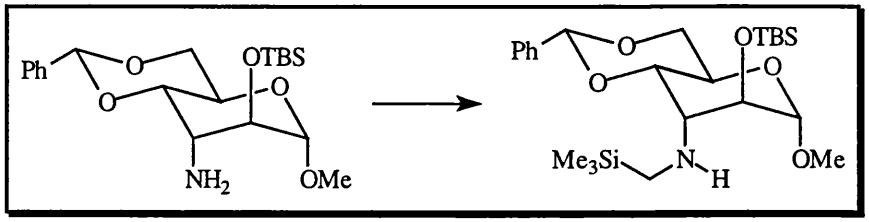
Yield: 39.70 g; 98.4 %.

HR-MS for (FAB MNOBA matrix) for $C_{20}H_{34}NO_5Si$: $(M+H)^+$: actual: 396.2206; measured: 396.2202.

δ_H (400 MHz, $CDCl_3$): 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s, ^tBu), 1.62 (2H, br s, -NH_2), 3.18 (1H, t, J_{HH} 2.8 Hz), 3.34 (3H, s, OMe), 3.80 (1H, t, J_{HH} 10.0 Hz), 3.88 (1H, t, J_{HH} 1.2 Hz), 3.95 (1H, dd, J_{HH} 4.0 Hz, 3.6 Hz), 4.01 (1H, dd, J_{HH} 4.8 Hz, 5.2 Hz), 4.27 (1H, dd, J_{HH} 4.8 Hz, 10.0 Hz), 4.45 (1H, s), 5.62 (1H,s), 7.30-7.48 (5H, m).

δ_C (100 MHz, $CDCl_3$): -5.2, -5.1, 17.8, 25.6, 53.1, 55.1, 57.7, 69.2, 71.9, 76.8, 101.7, 102.4, 126.0, 128.1, 128.9, 137.4 (quat-C).

I.R. (neat, 16 scans): 3395, 2930, 2858, 1592, 1465, 1395, 1312, 1256, 1216, 1126, 1050, 1008, 981, 842, 755, 698.



Methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132**

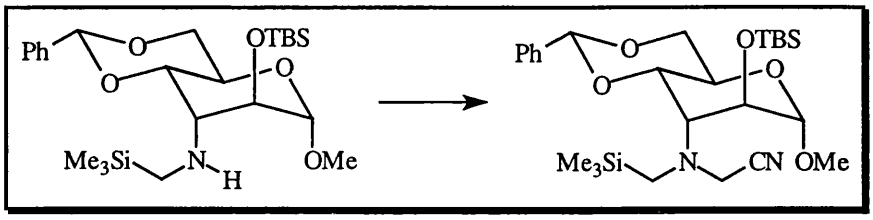
To a stirred solution of methyl 3-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **138** (21.57 g, 54.53 mmol) in MeCN (100 ml) was added *N,N*-diisopropyl-*N*-ethylamine (16.0 ml, 91.73 mmol) and (iodomethyl)trimethylsilane (13.0 ml, 87.49 mmol) at room temperature. The reaction mixture was stirred at gentle reflux for 16 h, cooled to room temperature, diluted with water and extracted four times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a an oil. Flash chromatography (hexanes/EtOAc, 10:1, CH_2Cl_2 load) afforded the required amine as a clear yellow oil. Yield: 25.48 g, 97.0 %.

HR-MS for (FAB MNOBA matrix) for $C_{24}H_{44}NO_5Si_2$: $(M+H)^+$: actual: 482.2758; measured: 482.2740.

δ_H (400 MHz, $CDCl_3$): 0.02 (9H, s, Me_3Si), 0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s, ^tBu), 1.58 (1H, br s, NH), 2.11 (1H, d, J_{HH} 12.8 Hz), 2.22 (1H, d, J_{HH} 12.8 Hz), 2.96 (1H, t, J_{HH} 3.0 Hz), 3.33 (1H, s, OMe), 3.75 (1H, t, J_{HH} 10.2 Hz), 3.97 (1H, d, J_{HH} 2.8 Hz), 4.02 (1H, dd, J_{HH} 4.0 Hz, 10.0 Hz), 4.15-4.17 (1H, m), 4.25 (1H, dd, J_{HH} 5.2 Hz, 10.0 Hz), 4.44 (1H, s), 5.57 (1H, s), 7.32-7.36 (3H, m), 7.46-7.48 (2H, m).

δ_C (100 MHz, $CDCl_3$): -4.9, -4.9, -2.7, 18.1, 25.8, 38.0, 55.1, 58.7, 62.7, 69.4, 69.6, 77.2, 102.2, 102.7, 126.3, 128.3, 129.0, 137.9.

I.R. (neat, 16 scans): 3353, 2953, 2931, 2858, 1467, 1381, 1251, 1140, 1104, 1050, 918, 854, 757, 697, 665.



Methyl 3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **133**

To a stirred solution of methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132** (25.48 g, 52.89 mmol) in MeCN (200 ml) was added *N,N*-diisopropyl-*N*-ethylamine (47.00 ml, 0.269 mol) and chloroacetonitrile (17.00 ml, 0.269 mol) at room temperature. The reaction mixture was stirred at gentle reflux for 86 h, cooled to room temperature, diluted with water and extracted 5 times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a black oil. Flash chromatography (hexanes/EtOAc, 30:1) afforded the required tertiary amine as a clear yellow oil.

Yield: 25.15 g; 91.3 %.

HR-MS (FAB, MNOBA matrix) for $C_{26}H_{45}N_2O_5Si_2$ $(M+H)^+$: required mass: 521.2867; measured mass: 521.2883.

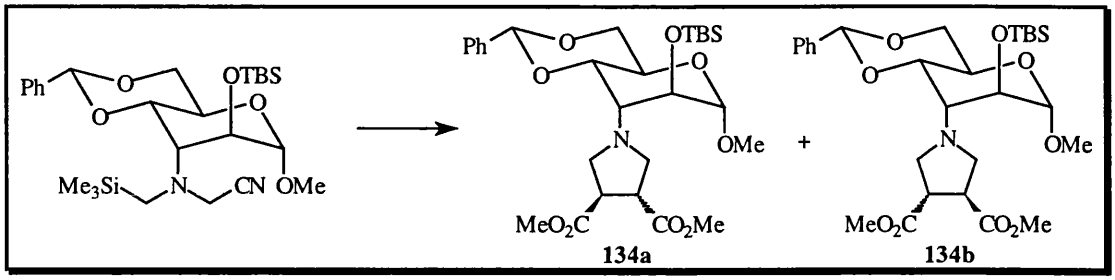
Anal. calculated for $C_{26}H_{44}N_2O_5Si_2$: Calculated: C, 59.96; H, 8.52; N, 5.38: Found: C, 57.90; H, 8.19; N, 5.13.

δ_H (400 MHz, $CDCl_3$): 0.04 (9H, s, Me_3Si), 0.14 (3H, s), 0.18 (3H, s), 0.93 (9H, s, ^tBu), 2.40 (1H, d, J_{HH} 14.4 Hz), 2.63 (1H, d, J_{HH} 14.4 Hz), 3.00 (1H, s), 3.34 (3H, s), 3.73 (1H, dt, J_{HH} 1.6 Hz, 8.2 Hz), 3.97 (2H, dd, J_{HH} 3.9 Hz, 16.0 Hz), 4.19 (2H, dd, J_{HH} 1.6

Hz, 17.6 Hz), 4.29 (2H, dd, J_{HH} 2.2 Hz, 10.4 Hz), 4.40 (1H, s), 5.49 (1H, s), 7.32-7.47 (5H, m).

δ_C (100 MHz, $CDCl_3$): -5.0, -4.7, -1.6, 17.9, 25.7, 44.7, 45.5, 54.9, 58.6, 64.8, 69.1, 69.4, 78.5, 101.3, 102.1, 116.2, 126.0, 128.1, 128.9, 137.6 (quat-C).

I.R. (neat, 16 scans): 3067, 3037, 2954, 2858, 2781, 1465, 1376, 1314, 1254, 1219, 1193, 1096, 910, 837, 777, 697.



Methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)pyrrolidine-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **134ab**

To a solution of methyl 3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **133** (5.20 g, 9.98 mmol) in MeCN (50 ml) was added dimethyl fumarate (4.32 g, 29.97 mmol) and AgF (3.80 g, 29.25 mmol) and the solution stirred at room temperature in the dark for 5 days. The reaction mixture was filtered through a pad of Celite, the pad washed thoroughly with CH_2Cl_2 and the filtrate concentrated *in vacuo* leaving a brown solid. Flash chromatography (hexanes/EtOAc, 20:1→10:1) afforded the cycloadduct as a clear oil.

Yield: 3.98 g; 70.4 %.

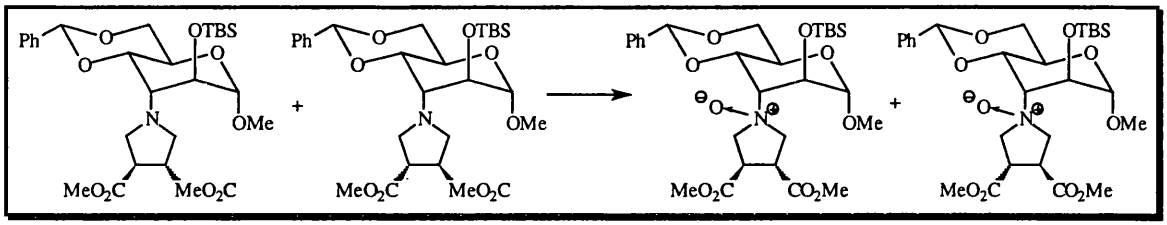
HR-MS (FAB, MNOBA matrix) for $C_{28}H_{44}NO_9Si$ $(M+H)^+$: required mass: 566.2785; measured mass: 566.2760.

δ_H (400 MHz, $CDCl_3$, mixture of isomers): 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 2.69 (1H, br s), 2.97 (1H, dd, J_{HH} 5.2 Hz, 8.8 Hz), 3.09 (1H, t, J_{HH} 8.6 Hz), 3.15 (1H, t, J_{HH} 7.4 Hz), 3.29 (1H, s), 3.31 (1H, s), 3.34-3.39 (2H, m), 3.67 (6H, s), 3.68 (3H, s), 4.06

(1H, dd, J_{HH} 2.0 Hz, 13.2 Hz), 4.12 (1H, dt, J_{HH} 9.4 Hz, 2.8 Hz), 4.20-4.33 (2H, m), 4.37 (1H, s), 5.46 (1H, d, J_{HH} 3.2 Hz), 7.29-7.36 (3H, m), 7.43-7.46 (2H, m).

δ_C (100 MHz, $CDCl_3$, mixture of isomers): -5.1, -5.0, 17.9, 25.6, 44.5, 44.7, 51.97, 54.9, 55.1, 56.4, 56.4, 58.9, 59.0, 65.1, 69.3, 69.4, 70.2, 70.3, 77.2, 77.9, 77.9, 101.6, 102.4, 102.5, 126.1, 126.3, 128.1, 128.8, 128.9, 137.7, 137.8, 173.9. **Peak overlapping present.**

I.R. (neat, 16 scans): 2953, 2931, 2896, 2857, 1739, 1463, 1437, 1405, 1381, 1362, 1311, 1256, 1196, 1174, 1132, 1104, 1050, 1012, 992, 918, 840, 778, 757, 699, 667.

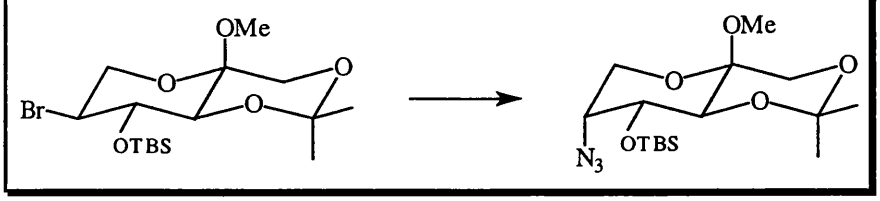


Methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)pyrrolidine-*N*-oxide-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **139ab**

To the cycloadduct prepared above **134ab** (235 mg, 0.42 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added in one portion *meta*-chloroperbenzoic acid (172 mg, 0.50 mmol, 56-88 %, 50% assumed). The mixture was then stirred at room temperature for 2 h. The crude reaction mixture was then diluted with CH_2Cl_2, treated with 10 % aqueous $NaHCO_3$ (10 ml) and extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear oil. Flash chromatography (CH_2Cl_2:MeOH, 50:1) afforded the *N*-oxide **139** as a clear oil which was used immediately.

Yield: 202 mg, 83.5 %.

HR-MS for (FAB, MNOBA matrix) $C_{28}H_{44}NO_{10}Si$, $(M+H)^+$: required mass: 582.2735; measured mass: 582.2720.



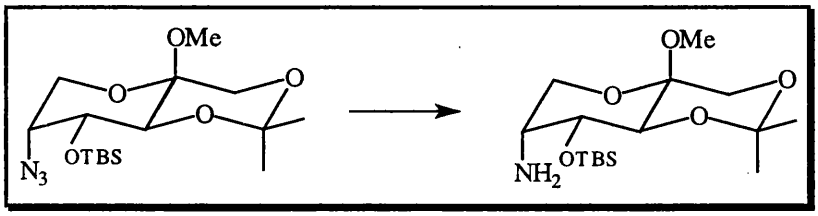
Methyl 5-azido-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **147**

A mixture of methyl 5-bromo-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-α-D-fructopyranoside **146** (8.40 g, 20.42 mmol) and sodium azide (27.50 g, 0.423 mol) in DMF (80 ml) was stirred under nitrogen at 130 °C for 42 h after which the cooled reaction mixture was quenched with water and extracted with CH_2Cl_2 (5 x). The combined extracts were washed twice with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear yellow/orange liquid. Flash chromatography (hexanes/EtOAc, 25:1→8:1) gave the azide as a clear yellow oil.

Yield: 5.34 g; 70.0 %.

HR-MS (FAB, MNOBA matrix) for $C_{16}H_{31}N_3O_5Si$ $(M\text{-}OMe)^+$: 342.

I.R. (neat, 16 scans): 2991, 2932, 2857, 2104, 1467, 1375, 1333, 1256, 1189, 1153, 1113, 1057, 951, 922, 880, 841, 780, 724, 672.



Methyl 5-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148**

To a solution of methyl 5-azido-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **147** (400 mg, 1.07 mmol) in methanol (10 ml) was added palladium on carbon (114 mg, 10 mol%, 10 % Pd on C) and the reaction mixture stirred under H_2 for 6 h. The reaction mixture was then filtered through a pad

of Celite, the pad washed thoroughly with MeOH and the filtrate concentrated *in vacuo* leaving a light green oil. Flash chromatography (CH_2Cl_2:MeOH, 40:1) afforded the amine as a clear yellow oil.

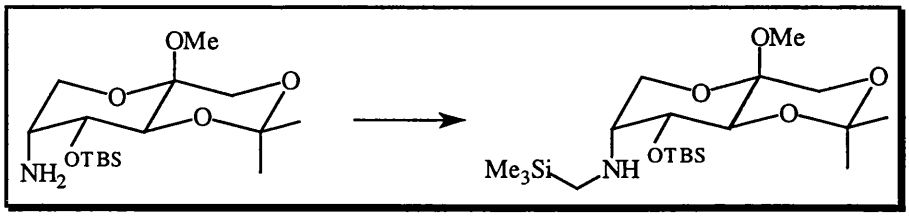
Yield: 356 mg; 95.7 %.

HR-MS for (FAB, MNOBA matrix) $C_{16}H_{34}NO_5Si$, $(M+H)^+$: required mass: 348.2206; measured mass: 348.2220.

δ_H (400 MHz, $CDCl_3$): 0.03 (3H, s, Me), 0.04 (3H, s, Me), 0.84 (9H, s, ^tBu), 1.39 (3H, s, Me), 1.43 (3H, s, Me), 1.57 (2H, broad s, NH_2), 3.08 (1H, broad m), 3.24 (3H, s, OMe), 3.55 (2H, m), 3.81-3.87 (3H, m), 4.02 (1H, dd, J_{HH} 4.8 Hz, 9.6 Hz).

δ_C (100 MHz, $CDCl_3$): -5.0, -4.4, 18.1, 18.9, 25.7, 29.1, 47.9, 53.1, 60.9, 64.1, 67.7, 71.8, 94.0, 100.0.

I.R. (neat, 16 scans): 2990, 2933, 2889, 2858, 1590, 1466, 1376, 1286, 1256, 1194, 1140, 1102, 1054, 948, 922, 865, 939, 780, 730, 671.



Methyl 5-(*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149**

To a stirred solution of methyl 5-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148** (320 mg, 0.92 mmol) in MeCN (5 ml) was added *N,N*-diisopropyl-*N*-ethylamine (0.30 ml, 1.72 mmol) and (iodomethyl)-trimethylsilane (0.25 ml, 1.68 mmol) at room temperature. The reaction mixture was stirred at gentle reflux for 20 h, cooled to room temperature, quenched with water and extracted 3 times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a brown oil. Flash chromatography (hexanes/EtOAc, 8:1, CH_2Cl_2 load) afforded the required secondary amine as a clear oil.

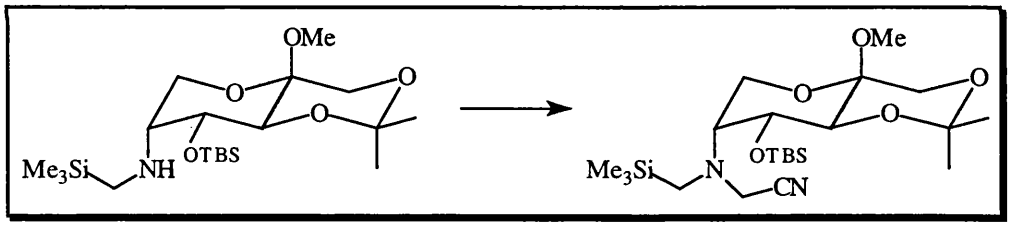
Yield: 326 mg; 81.7 %.

HR-MS for (FAB, MNOBA matrix) $C_{20}H_{44}NO_5Si_2$, $(M+H)^+$: required mass: 434.2758; measured mass: 434.2740.

δ_H (400 MHz, $CDCl_3$): 0.03 (9H, s, Me_3Si), 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s, ^tBu), 1.39 (3H, s), 1.43 (3H, s), 1.61 (1H, d, J_{HH} 12.8 Hz), 2.25 (1H, d, J_{HH} 12.8 Hz), 2.64 (1H, d, J_{HH} 4.8 Hz), 3.24 (3H, s, OMe), 3.56 (1H, d, J_{HH} 12.0 Hz), 3.57 (1H, d, J_{HH} 12.4 Hz), 3.74 (1H, d, J_{HH} 12.0 Hz), 3.83 (1H, d, J_{HH} 12.0 Hz), 4.05 (1H, d, J_{HH} 10.0 Hz), 4.14 (1H, dd, J_{HH} 4.8 Hz, 9.6 Hz).

δ_C (100 MHz, $CDCl_3$): -4.8, -4.4, -2.4, 18.1, 19.0, 25.8, 29.1, 38.0, 47.7, 59.7, 60.9, 64.6, 67.8, 71.9, 93.9, 99.9.

I.R. (neat, 16 scans): 3341, 2953, 2889, 2857, 2800, 2758, 1468, 1374, 1288, 1253, 1192, 1142, 1104, 1056, 929, 861, 780, 730, 670.



Methyl 5-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150**

To a stirred solution of methyl 5-(*N*-trimethylsilylmethyl)-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149** (274 mg, 0.63 mmol) in MeCN (4 ml) was added *N,N*-diisopropyl-*N*-ethylamine (0.30 ml, 1.72 mmol) and chloroacetonitrile (0.10 ml, 1.58 mmol) at room temperature. The reaction mixture was stirred at 100-110 °C for 25 h, cooled to room temperature, diluted with water and extracted 5 times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a brown oil. Flash chromatography (hexanes/EtOAc, 10:1, CH_2Cl_2 load) afforded the required secondary amine as a clear yellow oil.

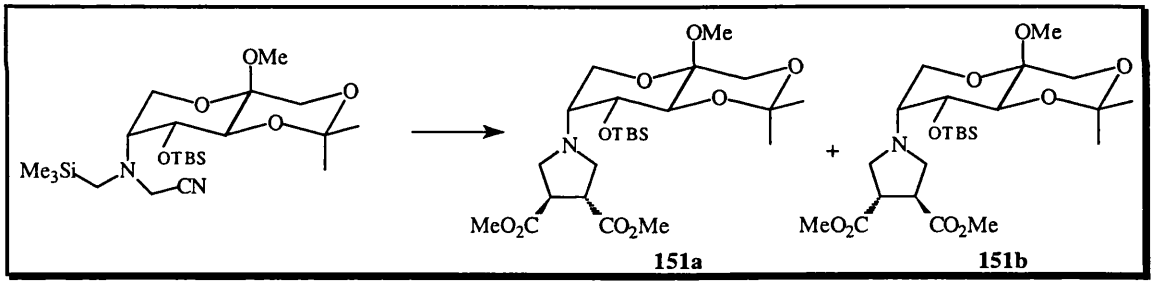
Yield: 235 mg; 78.6 %.

HR-MS for (FAB, MNOBA matrix) $C_{22}H_{45}N_2O_5Si_2$, $(M+H)^+$: required mass: 473.2867; measured mass: 473.2890.

δ_H (400 MHz, $CDCl_3$): 0.06 (3H, s), 0.09 (3H, s), 0.09 (9H, s, Me_3Si), 0.86 (9H, s, ^tBu), 1.39 (3H, s), 1.42 (3H, s), 2.37 (1H, d, J_{HH} 14.4 Hz), 2.58 (1H, d, J_{HH} 14.4 Hz), 2.81 (1H, d, J_{HH} 2.0 Hz), 3.22 (3H, s, OMe), 3.45 (1H, d, J_{HH} 12.0 Hz), 3.69 (1H, d, J_{HH} 17.2 Hz), 3.76 (1H, dd, J_{HH} 6.0 Hz, 13.2 Hz), 3.84 (1H, d, J_{HH} 12.4 Hz), 3.86 (1H, dd, J_{HH} 1.8 Hz, 13.4 Hz), 4.14-4.19 (3H, m).

δ_C (100 MHz, $CDCl_3$): -4.8, -4.4, -1.5, 18.3, 18.7, 25.9, 29.1, 43.6, 44.8, 48.0, 60.8, 61.0, 64.1, 70.4, 71.9, 94.0, 99.9, 116.3.

I.R. (neat, 16 scans): 2992, 2954, 2897, 2857, 2774, 2229, 1468, 1434, 1380, 1287, 1252, 1192, 1142, 1103, 1159, 948, 917, 856, 779, 760, 671.



Methyl 5-*N*-(*trans*-3,4-dicarbomethoxypyrrolidine)-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **151ab**

To a solution of methyl 5-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150** (180 mg, 0.38 mmol) in acetonitrile (4 ml) was added dimethyl fumarate (165 mg, 1.14 mmol) followed by AgF (145 mg, 1.14 mmol). The reaction mixture was stirred at room temperature under N_2 in the dark for approx. 9 h before it was filtered through a pad of Celite. The pad was washed thoroughly with CH_2Cl_2 and the filtrate concentrated *in vacuo* affording a brown crystalline solid. Flash chromatography (hexanes:EtOAc, 10:1, CH_2Cl_2 load) gave the desired pyrrolidine adducts as a clear oil.

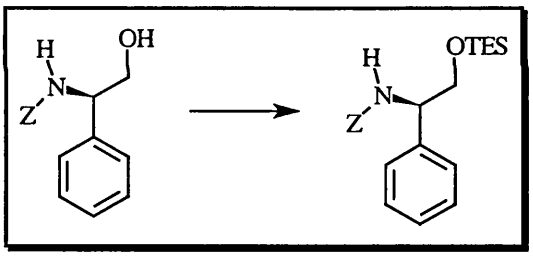
Yield: 136 mg; 69.0 %.

HR-MS for (FAB, MNOBA matrix) $C_{24}H_{44}NO_9Si$, $(M+H)^+$: required mass: 518.2785; measured mass: 518.2770.

δ_H (400 MHz, $CDCl_3$): 0.04 (6H, s), 0.84 (9H, s), 1.38 (3H, s), 1.42 (3H, s), 2.51 (1H, br s), 2.90 (1H, dd, J_{HH} 5.6 Hz, 8.8 Hz), 2.99 (1H, t, J_{HH} 8.4 Hz), 3.18-3.19 (1H, m), 3.21 (3H, s, OMe), 3.27-3.38 (3H, m), 3.51 (1H, dd, J_{HH} 2.4 Hz, 12.0 Hz), 3.61-3.65 (1H, m), 3.67 (3H, s, Me), 3.68 (3H, s, Me), 3.70-3.72 (1H, m), 3.81 (1H, dd, J_{HH} 4.6 Hz, 12.2 Hz), 4.10-4.20 (2H, m).

δ_C (100 MHz, $CDCl_3$): -4.4, -4.4, 18.9, 25.8, 29.1, 44.6, 44.7, 47.8, 52.1, 52.1, 55.8, 55.9, 61.0, 61.9, 64.9, 65.0, 70.0, 71.8, 94.2, 99.9, 174.1, 174.2.

I.R. (neat, 16 scans): 2992, 2953, 2895, 2856, 2801, 1738, 1592, 1463, 1437, 1380, 1312, 1287, 1254, 1193, 1148, 1106, 1059, 951, 921, 865, 838, 780, 736, 672.



N-(Benzyloxy)carbonyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **166**

To a solution of *N*-(benzyloxy)carbonyl-D-(-)-α-phenylglycinol **165** (5.00 g, 18.43 mmol) and imidazole (2.51 g, 36.87 mmol) in DMF (50 ml) at room temperature was added chloro triethylsilane (5.00 ml, 29.79 mmol). The reaction mixture was stirred under nitrogen for 30 min., then quenched with water and extracted twice with EtOAc. The combined extracts were washed with water (5 x) dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear liquid. Flash chromatography (hexanes:EtOAc, 20:1→10:1) afforded the protected alcohol as a clear liquid.

Yield: 7.05 g; 99.2 %.

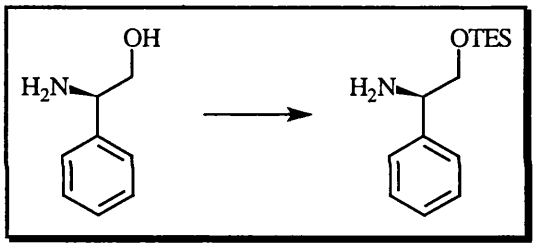
$[\alpha]_D^{20}$ = - 12.4° (*c* 0.210, MeOH).

HR-MS for (FAB, MNOBA matrix) $C_{22}H_{32}NO_3Si$, $(M+H)^+$: required mass: 386.2151; measured mass: 386.2139.

δ_H (400 MHz, $CDCl_3$): 0.55 (6H, q, J_{HH} 7.8 Hz), 0.91 (9H, t, J_{HH} 8.0 Hz), 3.77-3.79 (1H, broad m), 3.93 (1H, dd, J_{HH} 4.2 Hz, 10.2 Hz), 4.83 (1H, br s), 5.07-5.17 (2H, m), 5.70 (1H, br s), 7.24-7.34 (10H, m).

δ_C (100 MHz, $CDCl_3$): 4.1, 6.5, 56.5, 66.0, 66.6, 126.6, 127.2, 127.7, 127.9, 128.2, 128.3, 136.4, 140.3, 155.9 (C=O).

I.R. (neat, 16 scans): 3443, 3332, 3064, 3032, 2955, 2910, 2878, 1710, 1501, 1459, 1412, 1381, 1337, 1284, 1236, 1108, 1011, 912, 856, 744, 699.



O-Triethylsilyl-D-(-)-α-phenylglycinol **172**

To a solution of D-(-)-α-phenylglycinol **164** (5.00 g, 36.45 mmol) and imidazole (3.72 g, 54.64 mmol) in DMF (100 ml) under N_2 at room temperature was added chloro triethylsilane (6.12 ml, 36.49 mmol). The reaction mixture was stirred for 10 min. then quenched with water and extracted twice with EtOAc. The combined organic extracts were washed three times with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear liquid which required no further purification.

Yield: 9.07 g; 99.0 %.

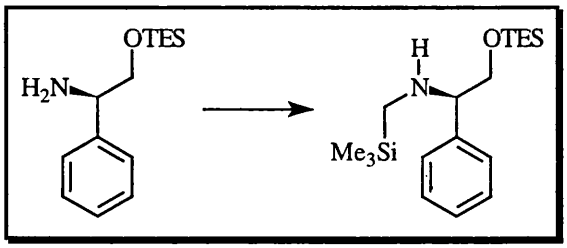
$[\alpha]_D^{20}$ = - 14.1° (*c* 0.22, MeOH).

HR-MS for (FAB, MNOBA matrix) $C_{14}H_{26}NOSi$, (M+H)$^+$: required mass: 252.1784; measured mass: 252.1799.

δ_H (400 MHz, $CDCl_3$): 0.57 (6H, q, J_{HH} 7.8 Hz), 0.93 (9H, t, J_{HH} 7.8 Hz), 1.72 (2H, broad s, NH_2), 3.49 (1H, dd, J_{HH} 8.8 Hz, 9.6 Hz), 3.70 (1H, dd, J_{HH} 3.8 Hz, 9.6 Hz), 4.06 (1H, dd, J_{HH} 3.8 Hz, 8.6 Hz), 7.24-7.37 (5H, m).

δ_C (100 MHz, $CDCl_3$): 4.4, 6.8, 57.7, 69.3, 126.9, 127.3, 128.3, 142.6.

I.R. (neat, 16 scans): 3385, 3028, 2954, 2910, 2878, 1458, 1414, 1240, 1088, 1011, 847, 741, 701.



N-Trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **173**

To a solution of *O*-triethylsilyl-D-(-)-α-phenylglycinol **172** (7.70 g, 30.62 mmol) in MeCN (100 ml) at room temperature was added Hünig's base (9.70 ml, 55.61 mmol) followed by (iodomethyl)trimethylsilane (7.30 ml, 49.13 mmol). The resultant clear mixture was stirred at gentle reflux for 29 h. The reaction mixture was then cooled to room temperature, diluted with water, extracted with EtOAc (4 x), and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo* affording a brown solid. Flash chromatography (hexanes:EtOAc, 100:1 → 50:1) gave a clear yellow oil.

Yield: 7.83 g; 75.7 %.

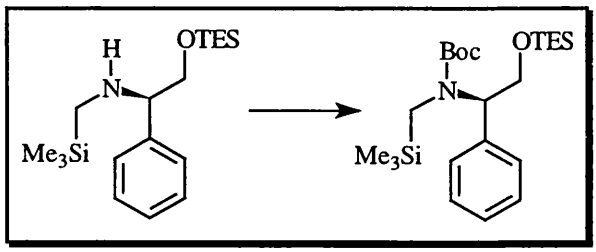
$[\alpha]_D^{20}$ = - 42.0° (*c* 0.212, MeOH).

HR-MS for (FAB, MNOBA matrix) $C_{18}H_{36}NOSi_2$, (M+H)$^+$: required mass: 338.2335; measured mass: 338.2324.

δ_H (400 MHz, $CDCl_3$): 0.03 (9H, s, Me_3Si), 0.61 (6H, q, J_{HH} 8.0 Hz), 0.97 (9H, t, J_{HH} 7.8 Hz), 1.81 (1H, d, J_{HH} 13.6 Hz), 1.89 (1H, broad s, NH), 1.94 (1H, d, J_{HH} 13.6 Hz), 3.47-3.51 (1H, m), 3.64-3.69 (2H, m), 7.24-7.37 (5H, m).

δ_C (100 MHz, $CDCl_3$): -2.7, 4.4, 6.7, 37.7, 68.3, 69.2, 127.1, 127.9, 128.2, 141.2.

I.R. (neat, 16 scans): 3342, 3063, 3027, 2955, 2910, 2878, 2771, 1458, 1415, 1378, 1350, 1248, 1188, 1108, 1079, 1010, 972, 858, 781, 745, 701, 668.



N-tert-Butoxycarbonyl-*N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **174**

To a solution of *N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **173** (432 mg, 1.28 mmol) in MeOH (10 ml) was added Et_3N (0.18 ml, 1.29 mmol) and di-*tert*-butyl dicarbonate, (Boc_2O), (335 mg, 1.53 mmol) and the mixture stirred at room temperature for 47 h. The reaction mixture was then quenched with water, extracted four times with EtOAc and the combined extracts dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a clear yellow oil. Flash chromatography (hexanes:CH_2Cl_2, 2:1, CH_2Cl_2 load) gave the required tertiary amine as a clear yellow oil.

Yield: 534 mg; 95.4 %.

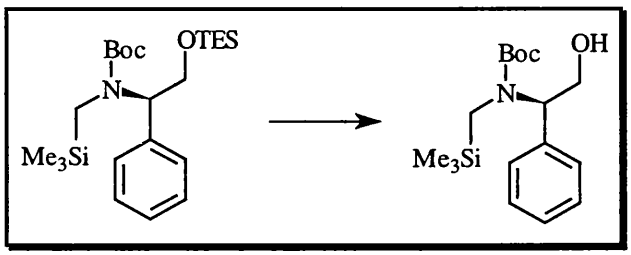
$[\alpha]_D^{20}$ = - 40.6° (*c* 0.212, MeOH).

HR-MS for (FAB, MNOBA matrix) $C_{23}H_{44}NO_3Si_2$, $(M+H)^+$: required mass: 438.2860; measured mass: 438.2879.

δ_H (400 MHz, $CDCl_3$): -0.07 (9H,br s, Me_3Si), 0.63 (6H, q, J_{HH} 8.0 Hz), 0.97 (9H, t, J_{HH} 8.0 Hz), 1.48 (9H, s, ^tBu), 2.43-2.56 (1H, broad m), 4.04-4.08 (1H, broad m), 5.15-5.16 (1H, broad m), 7.23-7.32 (5H, m).

δ_C (100 MHz, $CDCl_3$): -1.1, 4.4, 6.8, 28.5, 35.0, 61.3, 62.5, 79.2, 127.3, 127.7, 128.5, 139.3, 156.0.

I.R. (neat, 16 scans): 3063, 2956, 2879, 1692, 1445, 1392, 1366, 1346, 1244, 1160, 1105, 1054, 1010, 852, 748, 699.



N-tert-Butoxycarbonyl-*N*-trimethylsilylmethyl-D-(-)-α-phenylglycinol **175**

To a solution of *N-tert*-butoxycarbonyl-*N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenyl-glycinol **174** (1.00 g, 2.28 mmol) in THF (1.66 ml) was added water (5 ml) and AcOH (10 ml) and the mixture stirred at room temperature for 10 min. The reaction mixture was then concentrated *in vacuo* leaving a clear liquid which was subjected to flash chromatography (hexanes/EtOAc, 3:1, CH_2Cl_2 load) which afforded the free alcohol as a clear oil.

Yield: 735 mg; 99.5 %.

$[\alpha]_D^{20}$ = - 60.3° (*c* 0.116, MeOH).

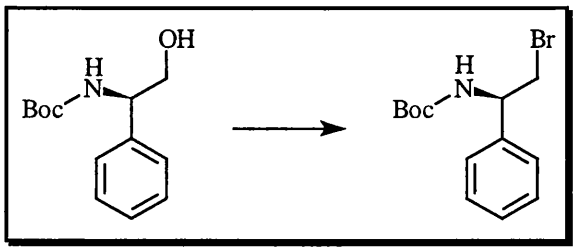
HR-MS for (FAB, MNOBA matrix) $C_{17}H_{30}NO_3Si$, $(M+H)^+$: required mass: 324.1995; measured mass: 324.1989.

Anal. calculated for $C_{17}H_{29}NO_3Si$: Calculated: C, 63.12; H, 9.04; N, 4.33: Found: C, 61.08; H, 8.96; N, 4.07.

δ_H (400 MHz, $CDCl_3$): -0.08 (9H, br s, Me_3Si), 1.48 (9H, br s, Bu), 2.31-2.37 (2H, broad m), 4.02-4.08 (2H, broad m), 4.90-4.92 (1H, broad s), 7.24-7.35 (5H, m).

δ_C (100 MHz, $CDCl_3$): -1.4, 28.3, 28.5, 37.0, 63.4, 80.2, 127.7, 127.8, 128.6, 137.9.

I.R. (neat, 16 scans): 3430 (b), 2974, 2898, 1666, 1448, 1393, 1366, 1345, 1245, 1156, 1104, 1077, 1029, 984, 852, 763, 699.



D-(-)-α-(1-Bromoethyl)-*N*-(*tert*-butoxycarbonyl)benzylamine **184**

To a solution of D-(-)-α-*N*-(*tert*-butoxycarbonyl)phenylglycinol **183** (13.30 g, 56.05 mmol) and triphenylphosphine (44.10 g, 0.168 mol) in dry THF (250 ml) at 0 °C was added carbon tetrabromide (55.76 g, 0.168 mol) in one portion. A white precipitate of $Ph_3P{=}O$ was seen almost immediately. The reaction mixture was stirred at 0 °C for 5 min. then room temperature for 5 h. The mixture was then diluted with Et_2O, the white $Ph_3P{=}O$ filtered off under suction, the filter cake washed twice with Et_2O, and the filtrate concentrated *in vacuo* affording a brown oil. Flash chromatography (hexanes:EtOAc, 16:1→8:1, CH_2Cl_2 load) gave the bromide as a white solid.
Yield: 11.95 g; 71.0 %.

$[\alpha]_D^{20}$ = - 59.0° (*c* 0.2, MeOH).

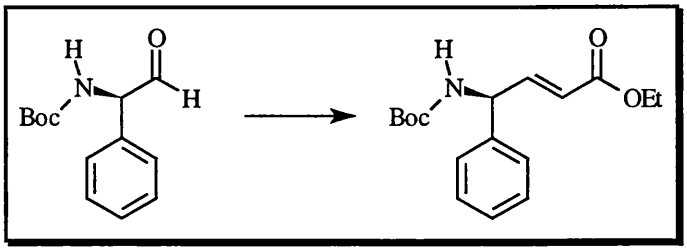
M. Pt.: 112-114 °C.

HR-MS for (FAB, MNOBA matrix) $C_{13}H_{18}NO_2Br$, $(M)^+$: required mass: 300.0599; measured mass: 300.0580.

δ_H (400 MHz, $CDCl_3$): 1.42 (9H, s, ^tBu), 3.66 (2H, br s), 4.99 (1H, br s), 5.27 (1H, br s), 7.26-7.36 (5H, m).

δ_C (100 MHz, $CDCl_3$): 28.2, 37.1, 54.7, 80.0, 126.3, 127.9, 128.6, 139.3, 154.9.

I.R. (KBr, 16 scans): 3360, 2984, 2940, 1691, 1525, 1451, 1426, 1391, 1354, 1286, 1251, 1167, 1047, 1025, 883, 761, 701, 648, 514.



(*R*)-(-)-α-4-*tert*-Butoxycarbonylamino-4-phenyl-(*E*)-but-2-enoic acid ethyl ester **190**

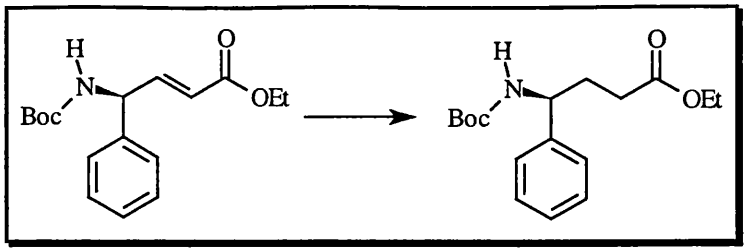
To a solution of crude aldehyde **189** (982 mg crude, quantitative yield assumed of 887 mg, 3.77 mmol) in CH_2Cl_2 (8 ml) was added in one portion $Ph_3P{=}CHCO_2Et$ (1313 mg, 3.77 mmol) at room temperature and the reaction mixture stirred under nitrogen for 45 min. The reaction mixture was then concentrated *in vacuo* leaving a clear yellow oil. This was subjected to flash chromatography (hexanes/EtOAc,10:1, CH_2Cl_2 load) affording a clear oil which solidified on standing at room temperature.

Yield: 771 mg; 67.0 %. (Overall yield of the two steps is 83.5 %).

Chemical Ionisation for $C_{17}H_{23}NO_4Na$, $(M+Na)^+$: measured mass = 328.

δ_H (300 MHz, $CDCl_3$): 1.26 (3H, t, J_{HH} 7.1 Hz), 1.42 (9H, s, ^tBu), 4.18 (2H, q, J_{HH} 6.6 Hz), 4.87 (1H, broad s), 5.42 (1H, broad s), 5.96 (1H, dd, J_{HH} 15.6 Hz, 1.7 Hz), 7.03 (1H, dd, J_{HH} 15.6 Hz, 5.1 Hz), 7.23-7.35 (5H, m).

I.R. (neat, 16 scans): 3348, 2979, 2933, 1717, 1656, 1510, 1497, 1455, 1392, 1367, 1248, 1167, 1144, 982, 866, 756, 699.



(*R*)-(-)-α-4-*tert*-Butoxycarbonylamino-4-phenyl-butanoic acid ethyl ester **191**

To a solution of alkene **190** (19.47 g, 63.76 mmol) in EtOAc (300 ml) was added Pd/C (679 mg, 10 mol%, 10 % Pd on C) and the solution flushed with hydrogen. The resultant black reaction mixture was stirred at room temperature for 6 h and then filtered through a pad of Celite. The pad was washed thoroughly with EtOAc and the filtrate concentrated *in vacuo* leaving a white solid which was sufficiently pure for the next reaction.

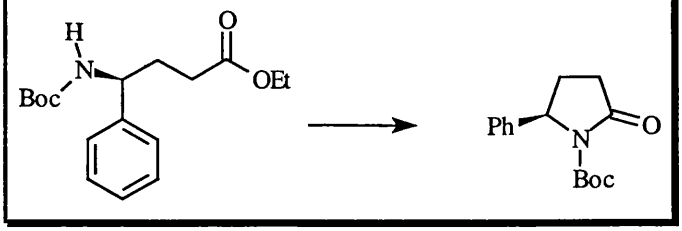
Yield: 19.10 g; 97.4 %.

HR-MS for (FAB MNOBA matrix): $C_{17}H_{26}NO_4$, $(M+H)^+$: actual: 308.1862; measured: 308.1865.

δ_H (300 MHz, $CDCl_3$): 1.20 (3H, t, J_{HH} 7.2 Hz, Me), 1.37 (9H, s, ^{t}Bu), 2.04 (2H, br s), 2.26-2.31 (2H, m), 4.07 (2H, q, J_{HH} 7.2 Hz), 4.62 (1H, br s), 5.56 (1H, br s), 7.20-7.30 (5H, m).

δ_C (100 MHz, $CDCl_3$): 14.1, 28.2, 31.2, 31.6, 54.4, 60.4, 79.3, 126.2, 127.2, 128.5, 142.2 (quat-C), 155.1 (C=O), 173.1 (C=O).

I.R. (KBr, 16 scans): 3389, 2977, 2936, 1730, 1689, 1512, 1457, 1389, 1369, 1288, 1244, 1210, 1158, 1094, 1028, 997, 868, 831, 756, 701,574, 533.



(*R*)-(-)-α-*N*-*tert*-Butoxycarbonyl-5-phenyl-2-pyrrolidinone **186**

To a solution of crude saturated ester **191** (19.10 g, 62.14 mmol) in dry PhMe (250 ml) at -10 °C under nitrogen was slowly added Me_3Al (38.00 ml, 76.00 mmol, 2M in hexanes) over 5 min. The reaction mixture was then allowed to warm to room temperature and stirred for 45 min. before being diluted with CH_2Cl_2. The mixture cooled to 0 °C and then slowly quenched with a 10 % aqueous Rochelle's salt solution (38 g in 380 ml), stirred vigorously at room temperature for 1h, and the organic layer separated. The aqueous layer was extracted three times with EtOAc, the combined organic extracts dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a white solid. Flash chromatography (hexanes/EtOAc, 8:1→4:1, CH_2Cl_2 load) gave the required lactam as a white solid.

Yield: 10.49 g; 64.6 %.

M.Pt.: 105-109 °C.

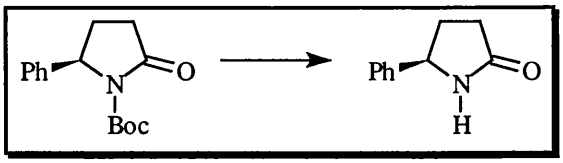
HR-MS for (FAB MNOBA matrix) $C_{15}H_{19}NO_3Na$, $(M+Na)^+$: required mass: 284.1253; measured mass: 284.1263.

Anal. calculated for $C_{15}H_{19}NO_3$: Calculated: C, 68.94; H, 7.33; N, 5.36: Found: C, 68.66; H, 7.29; N, 5.31.

δ_H (400 MHz, $CDCl_3$): 1.23 (9H, s, ^tBu), 3.07-4.04 (1H, m), 2.41-2.51 (2H, m), 2.62-2.68 (1H, m), 5.09-5.12 (1H, m), 7.17-7.34 (5H, m).

δ_C (100 MHz, $CDCl_3$): 27.4, 27.6, 31.2, 61.6, 82.8 (quat-C), 125.0, 127.5, 128.7, 142.5 (quat-C), 149.5 (C=O), 174.8 (C=O).

I.R. (KBr, 16 scans): 3343, 3073, 3034, 2977, 2936, 1764, 1696, 1603, 1480, 1296, 1151, 1053, 1003, 963, 913, 848, 785, 756, 703,600, 569, 532, 457.



(*R*)-α-5-Phenyl-2-pyrrolidinone **156**

To a solution of the *N*-Boc protected lactam **186** (6.19 g, 23.69 mmol) in CH_2Cl_2 (50 ml) at room temperature was added in one portion trifluoroacetic acid (50 ml). The reaction mixture was stirred for 5 min. after which the mixture was concentrated *in vacuo*. Any traces of trifluoroacetic acid were removed by twice co-evaporation with toluene leaving a green oil. Flash chromatography (hexanes/EtOAc, 1:1, CH_2Cl_2 load) afforded the lactam as a light brown solid.

Yield: 3.06 g; 80.1 %.

M.Pt.: 89-91 °C.

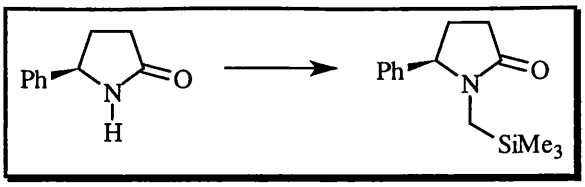
HR-MS for (FAB MNOBA matrix) for $C_{10}H_{12}NO$, $(M+H)^+$: required mass: 162.0914; measured mass: 162.0919.

Anal. calculated for $C_{10}H_{11}NO$: Calculated: C, 74.51, H, 6.88, N, 8.69: Found: C, 71.39; H, 6.55; N, 8.24.

δ_H (400 MHz, $CDCl_3$): 1.91-1.99 (1H, m), 2.34-2.59 (3H, m), 4.73 (1H, t, J_{HH} 7.2 Hz), 6.42 (1H, NH), 7.26-7.36 (5H, m).

δ_C (100 MHz, $CDCl_3$): 30.3, 31.2, 58.1, 125.5, 127.8, 128.8, 142.4 (quat-C), 178.9 (C=O).

I.R. (KBr, 16 scans): 3455, 3189, 3088, 1682, 1491, 1458, 1384, 1349, 1263, 1205, 1147, 1096, 1027, 940, 898, 759, 702, 593, 534, 475.



(*R*)-α-*N*-(Trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**

To NaH (25 mg, 0.63 mmol, 60 % dispersion in oil) was added distilled hexane (4 ml) under nitrogen and the solution stirred well. The NaH was allowed to settle and the hexane and oil removed via syringe. The above process was repeated twice before DMF (5 ml) was added to the powdered NaH. The lactam **156** (100 mg, 0.62 mmol) was then added in one portion and the reaction mixture stirred at room temperature for 70 min. (Iodomethyl)trimethylsilane (0.10 ml, 0.67 mmol) was then added and the solution stirred under nitrogen at room temperature for 19 h. The reaction mixture was then quenched with water, extracted twice with EtOAc, extracted twice with CH_2Cl_2, the combined extracts dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a brown oil. Flash chromatography (hexanes/EtOAc, 1:1, CH_2Cl_2 load) gave the required product as a clear brown oil.

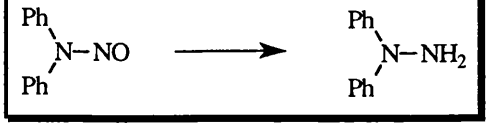
Yield: 77 mg; 50.3 %.

HR-MS for (FAB MNOBA matrix) for $C_{14}H_{22}NOSi$, $(M+H)^+$: required mass: 248.1471; measured mass: 248.1484.

δ_H (400 MHz, $CDCl_3$): 0.01 (9H, s, Me_3Si), 1.81-1.86 (1H, m), 2.05 (1H, d, J_{HH} 15.2 Hz), 2.39-2.52 (3H, m), 3.18 (1H, d, J_{HH} 15.2 Hz), 4.54 (1H, t, J_{HH} 6.4 Hz), 7.12-7.37 (5H, m).

δ_C (100 MHz, $CDCl_3$): -1.4, 28.6, 29.7, 32.5, 64.5,126.4, 127.9, 129.0, 141.2 (quat-C), 174.4 (C=O).

I.R. (KBr, 16 scans): 3456, 3030, 2953, 2894, 1682, 1492, 1458, 1419, 1361, 1249, 1150, 1080, 1029, 852, 762, 702.



N-Amino-diphenylamine **200**

To a stirred solution of commercially available *N*-nitroso-diphenylamine (5.00 g, 25.22 mmol) in CH_2Cl_2 (50 ml) cooled to -78 °C was dropwise added DIBAL-H (35.00 ml, 52.50 mmol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 2 h 20 min. after which time DIBAL-H (15.0 ml, 22.50 mmol) was added at -78 °C. The reaction mixture was then allowed to stir at -78 °C for approx. 3 h and then room temperature for 15 h before being diluted with CH_2Cl_2 (100 ml). With cooling (ice bath) and very vigorous stirring, the reaction mixture was treated with a 10 % aqueous Rochelle's salt solution (35 g in 350 ml) and the emulsion stirred for 60 min. at room temperature. The mixture was then extracted with CH_2Cl_2, the combined CH_2Cl_2 extracts dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a brown oil. Flash chromatography (hexanes/EtOAc, 60:1→45:1) afforded the hydrazine as a purple oil which solidified in the freezer.

Yield: 2.48 g; 53.3 %.

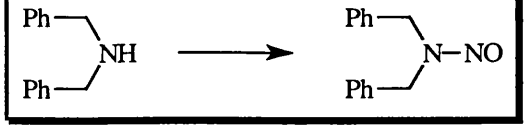
M. Pt.: 34-36 °C. (Lit.: 34.5 °C).[173]

HR-MS (FAB, MNOBA matrix) for $C_{12}H_{12}N_2$ $(M)^+$: required mass: 184.1000 ; measured mass: 184.1006.

δ_H (400 MHz, $CDCl_3$) 4.14 (2H, s, $-NH_2$), 6.96-7.00 (2H, m), 7.19-7.22 (4H, m), 7.26-7.31 (4H, m).

δ_C (100 MHz, $CDCl_3$): 119.4, 121.9, 129.0, 149.2 (quat-C).

I.R. (KBr, 16 scans): 3339, 3019, 1588, 1491, 1315, 1253, 1168, 1102, 1074, 860, 830, 748, 693, 609, 507.



N-Nitroso-dibenzylamine **201**

To a stirred solution of dibenzylamine (10.00 g, 9.75 ml, 50.69 mmol) in THF (60 ml) was added isoamyl nitrite (35.00 ml, 0.261 mol) at room temperature and the solution stirred under nitrogen for 23 h. The solvent and excess isoamyl nitrite was removed *in vacuo* leaving yellow/orange paste. Flash chromatography (hexanes:EtOAc, 8:1, CH_2Cl_2 load) afforded the pure *N*-nitroso compound as a clear yellow oil which solidified on standing at room temperature.

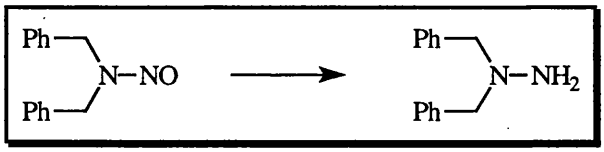
Yield: 11.47 g; 100 %.

HR-MS (FAB, MNOBA matrix) for $C_{14}H_{15}N_2O$ $(M+H)^+$: required mass: 227.1184 ; measured mass: 227.1189.

δ_H (400 MHz, $CDCl_3$): 4.64 (2H, s, $-CH_2-$), 5.18 (2H, s, $-CH_2-$), 7.02-7.04 (2H, m), 7.22-7.24 (2H, m), 7.26-7.30 (4H, m), 7.34-7.37 (2H, m).

δ_C (100 MHz, $CDCl_3$): 44.8, 54.9, 127.8, 128.3, 128.4, 128.5, 128.8, 129.0, 133.8 (quat-C), 134.4 (quat-C).

I.R. (KBr, 16 scans): 3443, 3083, 3082, 3027, 2978, 1494, 1428, 1352, 1316, 1267, 1173, 1125, 1070, 1025, 955, 932, 820, 763, 741, 696, 604, 490.



N-Amino-dibenzylamine **202**

To a stirred solution of *N*-nitrosodibenzylamine **201** (5.00 g, 22.10 mmol) in CH_2Cl_2 (75 ml) cooled to -78 °C was dropwise added DIBAL-H (75.0 ml, 0.113 mmol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 2 h. The

reaction mixture was then allowed to stir at room temperature for approx. 74 h before being slowly poured into a mixture of 10 % aqueous Rochelle's salt solution (75 g in 750 ml) and CH_2Cl_2 (700 ml). The solution was stirred vigorously for 90 min. at room temperature and then extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a clear oil. Flash chromatography (hexanes/EtOAc, 10:1→5:1, CH_2Cl_2 load) furnished the hydrazine as a clear oil which solidified on standing at room temperature.

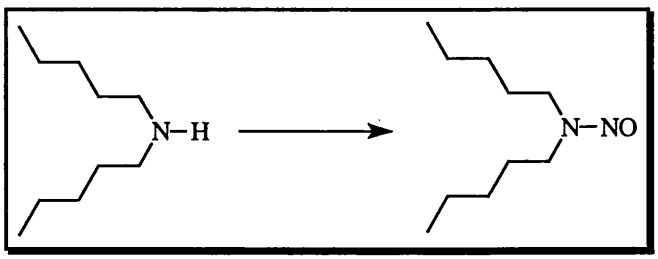
Yield: 3.10 g; 66.1 %.

HR-MS (FAB, MNOBA matrix) for $C_{14}H_{16}N_2$ $(M)^+$: required mass: 212.1313; measured mass: 212.1321.

δ_H (400 MHz, $CDCl_3$): 2.90 (2H, br s, $-NH_2$), 3.78 (4H, s, 2 x $-CH_2-$), 7.30-7.45 (10H, m).

δ_C (100 MHz, $CDCl_3$): 64.8, 127.1, 128.3, 129.0, 137.8 (quat-C).

I.R. (KBr, 16 scans): 3329, 3116, 3059, 3027, 2924, 2800, 1601, 1492, 1451, 1376, 1218, 1071, 997, 948, 909, 842, 748, 696, 621, 511.



N-Nitroso-dipentylamine **203**

To a stirred solution of dipentylamine (10.00 g, 12.87 ml, 63.57 mmol) in THF (50 ml) was added isoamyl nitrite (43.00 ml, 0.320 mol) at room temperature and the solution stirred under nitrogen for 20 h. The solvent and excess isoamyl nitrite was removed *in vacuo* leaving a clear yellow liquid. Flash chromatography (hexanes:EtOAc, 8:1, CH_2Cl_2 load) afforded the pure *N*-nitroso compound as a clear yellow liquid.

Yield: 11.76 g, 99.5 %.

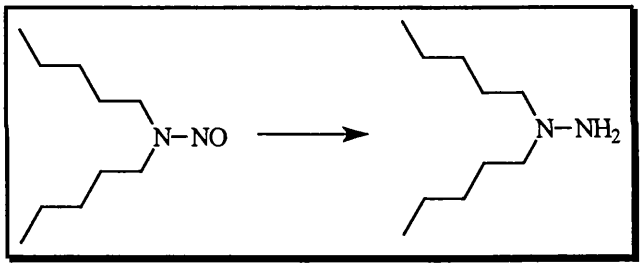
HR-MS (FAB, MNOBA matrix) for $C_{10}H_{23}N_2O$ $(M+H)^+$: required mass: 187.1810; measured mass: 187.1813.

Anal. calculated for $C_{10}H_{22}N_2O$: Calculated: C, 64.47; H, 11.90; N, 15.04: Found: C, 64.68; H, 12.19; N, 15.06.

δ_H (400 MHz, $CDCl_3$): 0.83 (3H, t, J_{HH} 7.2 Hz, $-CH_3$), 0.86 (3H, t, J_{HH} 7.0 Hz, $-CH_3$), 1.16-1.35 (8H, m), 1.40-1.47 (2H, pentet), 1.66-1.73 (2H, pentet), 3.48 (2H, t, J_{HH} 7.6 Hz), 4.01 (2H, t, J_{HH} 7.2 Hz).

δ_C (100 MHz, $CDCl_3$): 13.8, 13.8, 22.1, 22.2, 25.6, 27.9, 28.6, 29.2, 43.6, 52.2.

I.R. (neat, 16 scans): 2958, 2933, 2866, 1459, 1359, 1256, 1172, 1085, 986, 860, 731.



N-Amino-dipentylamine **204**

To a stirred solution of *N*-nitrosodipentylamine **203** (4.00 g, 21.47 mmol) in CH_2Cl_2 (60 ml) cooled to -78 °C was dropwise added DIBAL-H (75.0 ml, 0.113 mol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 60 min. The reaction mixture was then allowed to stir at room temperature for 4 days before being slowly poured into a mixture of 10 % aqueous Rochelle's salt solution (75 g in 750 ml) and CH_2Cl_2 (500 ml). The solution was stirred vigorously for 2 h at room temperature, the CH_2Cl_2 layer extracted, and the aqueous layer extracted once with CH_2Cl_2 and twice with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a clear liquid. Flash chromatography (hexanes/Et_2O, 5:1, hexane load) furnished the hydrazine as a clear liquid.

Yield: 2.76 g; 74.6 %.

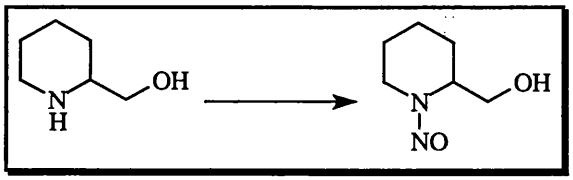
HR-MS (FAB, MNOBA matrix) for $C_{10}H_{24}N_2$ $(M\text{-}NH_2)^+$: 156.

Anal. calculated for $C_{10}H_{24}N_2$: Calculated: C, 69.70; H, 14.04; N, 16.25: Found: C, 70.75, H, 14.05; N, 14.55.

δ_H (400 MHz, $CDCl_3$): 0.87 (6H, t, J_{HH} 7.0, 2 x $-CH_3$), 1.21-1.34 (8H, m, 4 x $-CH_2-$), 1.47-1.55 (4H, pentet, 2 x $-CH_2-$), 2.42 (4H, t, J_{HH} 7.6 Hz, 2 x $-CH_2-$).

δ_C (100 MHz, $CDCl_3$): 14.1, 22.7, 26.9, 29.6, 61.7.

I.R. (neat, 16 scans): 2956, 2930, 2860, 2806, 1593, 1510, 1462, 1377, 1322, 1250, 1215, 1084, 942, 887, 849, 818, 730.



(±)-*N*-Nitroso-2-piperidinemethanol **209**

To a stirred solution of (±)-2-piperidinemethanol (5.00 g, 43.41 mmol) in THF (50 ml) was added isoamyl nitrite (30.00 ml, 0.223 mol) at room temperature and the solution stirred under nitrogen for 64½ h. The solvent and excess isoamyl nitrite was then removed *in vacuo* leaving a clear yellow oil. Flash chromatography (hexanes:EtOAc, 3:1→1:1, CH_2Cl_2 load) afforded the pure *N*-nitroso compound as a clear yellow liquid which was used immediately.

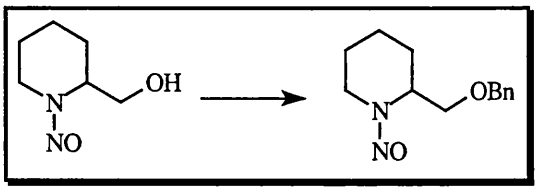
Yield: 6.18 g; 98.7 %.

HR-MS (FAB, MNOBA matrix) for $C_6H_{13}N_2O_2$ $(M+H)^+$: required mass: 145.0977; measured mass: 145.0972.

Anal. calculated for $C_6H_{12}N_2O_2$: Calculated: C, 49.99; H, 8.39; N, 19.43. Found: C, 48.69, H, 8.67; N, 18.91.

δ_C (100 MHz, $CDCl_3$): 19.6, 21.6, 24.5, 25.6, 27.6, 38.5, 48.0, 49.4, 60.1, 62.0, 62.3. **One peak overlaps the each other.**

I.R. (neat, 16 scans): 3399, 2945, 2867, 1430, 1366, 1272, 1206, 1160, 1134, 1104, 1059, 1002, 953.



(±)-*O*-Benzyl-*N*-nitroso-2-piperidinemethanol **210**

To a solution of NaH (2.00 g, 50.00 mmol, 60 % dispersion in oil) in DMF (25.0 ml) was slowly added a solution of (±)-*N*-nitroso-2-piperidinemethanol **209** (5.55 g, 38.50 mmol) in DMF (25.0 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 1 h and benzyl bromide (6.00 ml, 50.44 mmol) was then added dropwise. The mixture was stirred for 4½ h and was then cooled to 0 °C, slowly quenched with H_2O and extracted three times with EtOAc. The combined organic extracts were washed twice with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* affording the required compound as a clear yellow oil. Flash chromatography (hexanes/EtOAc, 5:1, CH_2Cl_2 load) gave the pure *N*-nitroso product as a clear yellow oil which was used immediately.

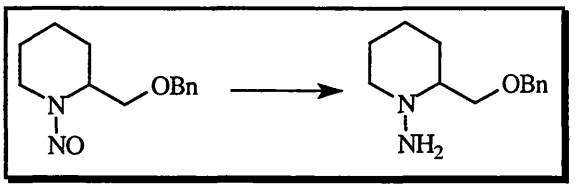
Yield: 8.39 g; 93.0 %.

HR-MS (FAB, MNOBA matrix) for $C_{13}H_{19}N_2O_2$ $(M+H)^+$: required mass: 235.1447; measured mass: 235.1450.

Anal. calculated for $C_{13}H_{18}N_2O_2$: Calculated: C, 66.64; H, 7.74; N, 11.96; Found: C, 66.65, H, 7.62; N, 11.99.

δ_C (100 MHz, $CDCl_3$, mixture of isomers): 19.9, 20.9, 24.4, 25.2, 25.7, 27.6, 37.3, 46.3, 48.2, 58.8, 67.5, 68.9, 72.9, 73.0, 127.5, 127.5, 127.6, 127.7, 128.3, 128.3, 137.6, 137.7.

I.R. (neat, 16 scans): 3030, 2942, 2863, 1433, 1363, 1295, 1250, 1204, 1168, 1106, 1008, 741, 699.



(±)-*N*-Amino-*O*-benzyl-2-hydroxymethyl piperidine **211**

To a stirred solution of (±)-*O*-benzyl-2-hydroxymethyl-*N*-nitrosopiperidine **210** (5.00 g, 21.34 mmol) in CH_2Cl_2 (60 ml) cooled to -78 °C was dropwise added DIBAL-H (75.0 ml, 0.113 mol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 60 min. The reaction mixture was then allowed to stir for six days at room temperature before being diluted with CH_2Cl_2 (700 ml). With cooling (ice bath) and very vigorous stirring, the reaction mixture was treated with a 10 % aqueous Rochelle's salt solution (75 g in 750 ml). Stirring was continued for 60 min. at room temperature and the mixture extracted twice with EtOAc. The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving a clear yellow oil. Flash chromatography (CH_2Cl_2/MeOH, 50:1 → 30:1) afforded a clear yellow oil.

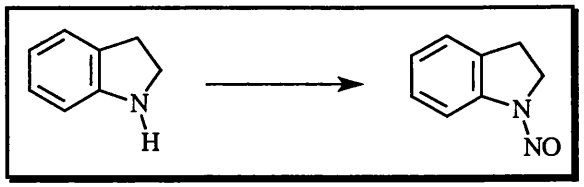
Yield: 1.75 g; 37.2 %.

HR-MS (FAB, MNOBA matrix) for $C_{13}H_{21}N_2O$ $(M+H)^+$: required mass: 221.1654; measured mass: 221.1669.

δ_H (400 MHz, $CDCl_3$, mixture of isomers): 1.10-1.24 (2H, m), 1.26-1.42 (2H, m), 1.43-1.71 (8H, m), 2.07-2.13 (4H, m), 2.95 (4H, br s, 2 x NH_2), 3.09-3.12 (2H, m), 3.50 (2H, dd, J_{HH} 4.6 Hz, 9.6 Hz), 3.65 (2H, dd, J_{HH} 4.8 Hz, 9.6 Hz), 4.49 (4H, 2 x s), 7.21-7.33 (10H, m).

δ_C (100 MHz, $CDCl_3$): 25.5, 25.7, 29.2, 60.8, 67.0, 75.2, 75.4, 127.5, 127.6, 128.2, 138.2.

I.R. (neat, 16 scans): 3337, 3086, 3062, 3030, 2931, 2855, 2792, 1602, 1496, 1450, 1369, 1312, 1263, 1205, 1108, 1026, 1006, 961, 906, 867, 824, 739, 699.



N-Nitroso-indoline **212**

To a stirred solution of indoline (6.04 ml, 53.88 mmol) in THF (40 ml) was added isoamyl nitrite (37.00 ml, 0.275 mol) at room temperature and the solution stirred under nitrogen for 50 min. The solvent and excess isoamyl nitrite was removed *in vacuo* leaving a dark brown oil. Crystallisation from Et_2O afforded the pure *N*-nitroso compound as flaky brown crystals.

Yield: 7.40 g; 92.7 %.

M.Pt.: 87-91 °C.

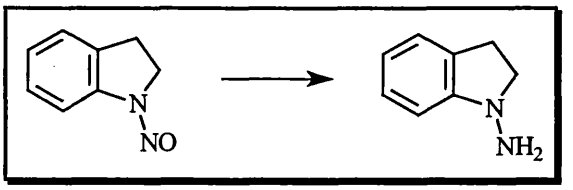
HR-MS (FAB, MNOBA matrix) for $C_8H_9N_2O$ $(M+H)^+$: required mass: 149.0715; measured mass: 149.0720.

Anal. calculated for $C_8H_8N_2O$: Calculated: C, 64.85; H, 5.44; N, 18.91: Found: C, 61.91, H, 5.06; N, 18.05.

δ_H (400 MHz, $CDCl_3$): 3.20 (2H, t, J_{HH} 7.8 Hz), 3.49 (2H, t, J_{HH} 7.8 Hz), 7.21-7.24 (1H, m), 7.29-7.33 (2H, m), 7.81-7.83 (1H, m).

δ_C (100 MHz, $CDCl_3$): 26.0, 46.1, 112.1, 126.1, 127.0, 128.2, 132.0 (quat-C), 140.8 (quat-C).

I.R. (KBr, 16 scans): 3050, 2941,1484, 1456, 1390, 1299, 1260, 1210, 1172, 1096, 1042, 984, 940, 821, 796, 759, 695.



N-Amino-indoline **213**

To a stirred solution of *N*-nitrosoindoline **212** (4.00 g, 27.00 mmol) in CH_2Cl_2 (70 ml) cooled to -78 °C was dropwise added DIBAL-H (75.00 ml, 0.113 mol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 2 h. The reaction mixture was then allowed to stir at room temperature for 49 h before being slowly poured into a mixture of 10 % aqueous Rochelle's salt solution (75 g in 750 ml) and CH_2Cl_2 (700 ml). The solution was stirred vigorously for 1 h at room temperature, the CH_2Cl_2 layer extracted, and the aqueous layer extracted once with CH_2Cl_2 and twice with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a brown oil. Flash chromatography (hexanes/EtOAc, 5:1, CH_2Cl_2 load) furnished the hydrazine as a brown oil.

Yield: 1.25 g; 34.5 %.

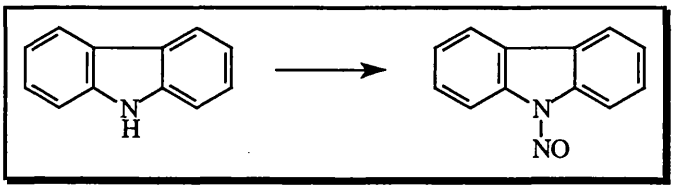
HR-MS (FAB, MNOBA matrix) for $C_8H_{10}N_2$ $(M)^+$: required mass: 134.0844; measured mass: 134.0842.

Anal. calculated for $C_8H_{10}N_2$: Calculated: C, 71.61; H, 7.51; N, 20.88: Found: C, 71.26, H, 7.66; N, 19.49.

δ_H (400 MHz, $CDCl_3$): 2.91 (2H, t, J_{HH} 8.0 Hz), 3.36 (2H, t, J_{HH} 8.0 Hz), 3.56 (2H, br s, NH_2), 6.79-6.84 (2H, m), 7.10-7.18 (2H, m).

δ_C (100 MHz, $CDCl_3$): 27.9, 60.9, 109.7, 120.0, 124.4, 127.3, 128.7, 154.5.

I.R. (neat, 16 scans): 3333, 3046, 2954, 2845, 1604, 1478, 1460, 1330, 1251, 1157, 1080, 1015, 922, 860, 753, 718.



N-Nitroso carbazole **214**

To a stirred solution of carbazole (5.00 g, 29.90 mmol) in THF (40 ml) was added isoamyl nitrite (20.00 ml, 0.149 mol) at room temperature and the solution stirred under nitrogen for 28 h. The solvent and excess isoamyl nitrite was removed *in vacuo* leaving a green solid. Flash chromatography (hexanes:CH_2Cl_2, 5:1) afforded the pure *N*-nitroso compound as bright yellow fluffy crystals.

Yield: 5.73 g; 97.6 %.

M. Pt.: 79-81 °C.

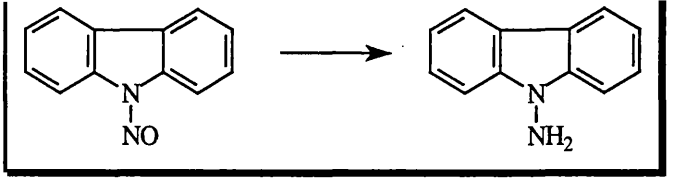
HR-MS (FAB, MNOBA matrix) for $C_{12}H_9N_2O$ $(M+H)^+$: required mass: 197.0715; measured mass: 197.0712.

Anal. calculated for $C_{12}H_8N_2O$: Calculated: C, 73.46; H, 4.11; N, 14.28; Found: C, 73.09, H, 4.11; N, 13.24.

δ_H (400 MHz, $CDCl_3$): 7.41-7.55 (4H, m), 7.86-7.91 (2H, m), 8.19-8.21 (1H, m), 8.52-8.55 (1H, m).

δ_C (100 MHz, $CDCl_3$): 112.3, 116.5, 119.9, 120.4, 124.8 (quat-C), 125.3 (quat-C), 126.2, 127.4, 128.1, 128.6, 132.7 (quat-C), 138.5 (quat-C).

I.R. (KBr, 16 scans): 1470, 1429, 1311, 1248, 1203, 1149, 1122, 1058, 972, 932, 747, 716, 565.



N-Amino carbazole **215**

To a stirred solution of *N*-nitrosocarbazole **214** (4.00 g, 20.39 mmol) in CH_2Cl_2 (60 ml) cooled to -78 °C was dropwise added DIBAL-H (70.00 ml, 0.105 mol, 1.5 M solution in toluene) and the resultant clear yellow mixture stirred at -78 °C for 2 h. The reaction mixture was then allowed to stir at room temperature for 6 h before being slowly poured into a mixture of 10 % aqueous Rochelle's salt solution (70 g in 700 ml) and CH_2Cl_2 (700 ml). The solution was stirred vigorously for 1 h at room temperature, the CH_2Cl_2 layer extracted, and the aqueous layer extracted twice with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a brown solid. Flash chromatography (hexanes/CH_2Cl_2, 20:1→1:1, CH_2Cl_2 load) furnished the hydrazine as a light brown crystalline solid.

Yield: 1.72 g; 46.4 %.

M. Pt.: 149-151 °C.

HR-MS (FAB, MNOBA matrix) for $C_{12}H_{10}N_2$ $(M)^+$: required mass: 182.0844; measured mass: 182.0850.

Anal. calculated for $C_{12}H_{10}N_2$: Calculated: C, 79.10; H, 5.53; N, 15.37: Found: C, 78.10, H, 5.43; N, 15.16.

δ_H (400 MHz, $CDCl_3$): 4.52 (2H, br s, $-NH_2$), 7.21-7.26 (2H, m), 7.45-7.52 (4H, m), 8.04-8.06 (2H, m).

δ_C (100 MHz, $CDCl_3$): 108.2, 119.3, 120.1, 120.8 (quat-C), 125.8, 141.3 (quat-C).

I.R. (KBr, 16 scans): 3333, 3265, 3051, 1604, 1478, 1450, 1317, 1232, 1150, 934, 855, 748, 723.

Bibliography

1 For a good review, see: Tsuge, O.; Kanemasa, S.; *Advances in Heterocyclic Chemistry*, **1989**, *45*, 232.

2 Huisgen, R.; Grashey, R.; Steingruber, E.; *Tetrahedron Lett.,* 1963, 1441.

3 Kröhnke, F.; Steuernagel, H.; *Angew. Chem.*, **1961**, *73*, 26.

4 Vedejs, E.; Martinez, G.R.; *J. Am. Chem. Soc.*, **1979**, *101*, 6452.

5 Grigg, R.; Kemp, J.; *Tetrahedron Lett.*, **1978**, 2823.

6 Heine, H.W.; Peavy, R.; *Tetrahedron Lett.*, **1965**, 3123.

7 Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H.; *Tetrahedron Lett.*, **1966**, 397.

8 Saunier, Y.N.; Danion-Bougot, R.; Danion, D.; Carriè, R.; *Tetrahedron*, **1976**, *32*, 1995.

9 Charrier, J.; Foucaud, A.; Person, H.; Loukakou, E.; *J. Org. Chem.*, **1983**, *48*, 481.

10 Reutrakul, V.; Prapansiri, V.; Panyachotipun, C.; *Tetrahedron Lett.*, **1984**, *25*, 1949.

11 Achiwa, K.; Sekiya, M.; *Chem. Lett.*, **1981**, 1213.

12 Livinghouse, T.; Smith, R.; *J. Chem. Soc., Chem. Commun.*, **1983**, 210.

13 Achiwa, K.; Motoyama, T.; Sekiya, M.; *Chem. Pharm. Bull.*, **1983**, *31*, 3939.

14 Smith, R.; Livinghouse, T.; *J. Org. Chem.*, **1983**, *48*, 1554.

15 Achiwa, K.; Imai, N.; Inaoka, T.; Sekiya, M.; *Chem. Pharm. Bull.*, **1984**, *32*, 2878.

16 Imai, N.; Terao, Y.; Achiwa, K.; *Heterocycles*, **1985**, *23*, 1107.

17 Smith, R.; Livinghouse, T.; *Tetrahedron*, **1985**, *41*, 3559.

18 Achiwa, K.; Imai, N.; Motoyama, T.; Sekiya, M.; *Chem. Lett.*, **1984**, 2041.

19 Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K.; *Heterocycles*, **1985**, *23*, 2489.

20 Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K.; *J. Org. Chem.*, **1987**, *52*, 2523.

21 Imai, N.; Tokiwa, Y.; Akahori, Y.; Achiwa, K.; *Chem. Lett.*, **1986**, 1113.

22 Achiwa, K.; Sekiya, M.; *Tetrahedron Lett.*, **1982**, *23*, 2589.

23 Achiwa, K.; Sugiyama, K.; Sekiya, M.; *Chem. Pharm. Bull.*, **1985**, *33*, 1975.

24 Vedejs, E.; Martinez, G.R.; *J. Am. Chem. Soc.*, **1980**, *102*, 7993.

25 Vedejs, E.; West, F.G.; *J. Org. Chem.*, **1983**, *48*, 4773.

Vedejs, E.; Larsen, S.; West, F.G.; *J. Org. Chem.*, **1985**, *50*, 2170.

27 Chen, S.; Ullrich, J.W.; Mariano, P.S.; *J. Am. Chem. Soc.*, **1983**, *105*, 6160.

28 Padwa, A.; Chen, Y.Y.; *Tetrahedron Lett.*, **1983**, *24*, 3447.

29 Parker, K.A.; Cohen, I.S.; Padwa, A.; Dent, W.; *Tetrahedron Lett.*, **1984**, *25*, 4917.

30 Padwa, A.; Chen, Y.Y.; Dent, W.; Nimmesgern, H.; *J. Org. Chem.*, **1985**, *50*, 4006.

31 Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M.K.; Wong, G.S.K.; *Chem. Ber.*, **1986**, *119*, 813.

32 Padwa, A.; Eisenbarth, P.; Venkatramanan, M.K.; Wong, G.S.K.; *J. Org. Chem.*, **1987**, *52*, 2427.

33 Yakobson, G.G.; Akhmetova, N.E.; *Synthesis*, **1983**, 169.

34 Cox, D.P.; Terpinski, J.; Lawrynowicz, W.; *J. Org. Chem.*, **1984**, *49*, 3216.

35 Vorbruggen, H.; Krolikiewicz, K.; *Tetrahedron Lett.*, **1984**, *25*, 1259.

36 Sharma, R.K.; Fry, J.L.; *J. Org. Chem.*, **1983**, *48*, 2112.

37 Turro, N.J.; Cha, Y.; Gould, I.R.; Padwa, A.; Grasdaska, J.R.; Tomas, M.; *J. Org. Chem.*, **1985**, *50*, 4415.

38 Tsuge, O.; Kanemasa, S.; Matsuda, K.; *Chem. Lett.*, **1985**, 1411.

39 Padwa, A.; Gasdaska, J.R.; *J. Am. Chem. Soc.*, **1986**, *108*, 1104.

40 Padwa, A.; Chen, Y.Y.; Chiacchio, V.; Dent, W.; *Tetrahedron*, **1985**, *41*, 3529.

41 Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K.; *Chem. Pharm. Bull.*, **1985**, *33*, 896.

42 Hosomi, A.; Sakata, Y.; Sakirai, H.; *Chem. Lett.*, **1984**, 1117.

43 Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K.; *Chem. Pharm. Bull.*, **1985**, *33*, 2762.

44 Padwa, A.; Dent, W.; *J. Org. Chem.*, **1987**, *52*, 235.

45 Grigg, R.; Kemp, J.; *J. Chem. Soc., Chem. Commun.*, **1977**, 125.

46 Grigg, R.; Kemp, J.; *J. Chem. Soc., Chem. Commun.*, **1978**, 109.

47 Tsuge, O.; Ueno, K.; *Heterocycles*, **1982**, *19*, 1411.

48 Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K.; *Chem. Lett.*, **1985**, 1601.

49 Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K.; *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 1809.

50 Deyrup, J.A.; Szabo, W.A.; *J. Org. Chem.*, **1975**, *40*, 2048.

51 Bende, Z.; Simon, K.; Tóth, G.; Töke, L.; Weber, L.; *Justus Liebigs Ann. Chem.*, **1982**, 924.

Chem., **1982**, 2146.

53 Tóth, G.; Frank, J.; Bende, Z.; Weber, L.; Simon, K.; *J. Chem. Soc., Perkin I*, **1983**, 1961.

54 Bende, Z.; Töke, L.; Weber, L.; Tóth, G.; Janke, F.; Csonka, G.; *Tetrahedron*, **1984**, *40*, 369.

55 Confalone, P.N.; Huie, E.M.; *J. Org. Chem.*, **1983**, 2994.

56 Confalone, P.N.; Huie, E.M.; *J. Am. Chem. Soc.*, **1984**, *106*, 7175.

57 Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M.; *Tetrahedron Lett.*, **1984**, *25*, 1579.

58 Rizzi, G.P.; *J. Org. Chem.*, **1970**, *35*, 2069.

59 Grigg, R.; Thianpatnagul, S.; *J. Chem. Soc., Chem. Commun.*, **1984**, 180.

60 Grigg, R.; Thianpatnagul, S.; *J. Chem. Soc., Chem. Commun.*, **1984**, 182.

61 Beugelmans, R.; Negron, G.; Roussi, G.; *J. Chem. Soc., Chem. Commun.*; **1983**, 31.

62 Beugelmans, R.; Benadijila-Iguertsira, L.; Chastanet, J.; Negron, G.; Roussi, G.; *Can. J. Chem.*, **1985**, *63*, 725.

63 Chastanet, J.; G.; Roussi, G.; *Heterocycles*, **1985**, *23*, 653.

64 Chastanet, J.; Roussi, G.; *J. Org. Chem.*, **1985**, *50*, 2910.

65 Roussi, G.; Negron, G.; Zhang, J.; *Heterocycles*, **1992**, *34*, 293.

66 Grigg, R.; Devlin, J.; *J. Chem. Soc., Chem. Commun.*,**1986**, 631.

67 Tsuge, O.; Kanemasa, S.; Yoshioka, M.; *J. Org. Chem.*, **1988**, *53*, 1384.

68 Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K.; *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 3359.

69 Garner, P.; Ho, W.B.; *J. Org. Chem.*, **1990**, *55*, 3973.

70 Garner, P.; Ho, W.B.; Grandhee, S.K.; Youngs, W.J.; Kennedy, V.O.; *J. Org. Chem.*, **1991**, *56*, 5893.

71 Preparation of camphorsultam, **170**: Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C.; *Tetrahedron*, **1986**, *42*, 4035. For a comprehensive review of camphor-derived chiral auxiliaries, see: Oppolzer, W.; *Tetrahedron*, **1987**, *43*, 1969. (The original article contains printing errors; a corrected version was reprinted in the Errata secton of: *Tetrahedron*, **1987**, *43*, Issue 18).

72 Seebach, D.; Hungerbühler, F.; Schnurrenberger, P.; Weidmann, B.; Züger, M.; *Synthesis*, **1982**, 138.

73 Garner, P.; Dogan, O.; *J. Org. Chem.*, **1994**, *59*, 4.

74 Fray, A.H.; Meyers, A.I.; *J. Org. Chem.*, **1996**, *61*, 3362.

[76] Meyers, A.I.; McKennon, M.J.; *J. Org. Chem.*, **1993**, *58*, 3568.

[77] Makaiyama, T.; Yamashita, H.; Asami, M.; *Chem. Lett.*, **1983**, 385.

[78] Speckamp, W.N.; deBoer, J.J.J.; *Tetrahedron Lett.*, **1975**, *46*, 4039.

[79] Jones, R.C.F.; Howard, K.J.; Snaith, J.; *Tetrahedron Lett.*, **1996**, *37*, 1707. See also: Jones, R.C.F.; Howard, K.J.; Snaith, J.; *Tetrahedron Lett.*, **1996**, *37*, 1711.

[80] Jones, R.C.F.; Nichols, J.R.; Cox, M.T.; *Tetrahedron Lett.*, **1990**, *31*, 2333.

[81] Jones, R.C.F.; Turner, I.; Howard, K.J.; *Tetrahedron Lett.*, **1993**, *34*, 6329.

[82] Harwood, L.M.; Lilley, I.A.; *Tetrahedron Lett.*, **1993**, *34*, 537.

[83] Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.; *Tetrahedron: Asymmetry*, **1991**, *2*, 169

[84] Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.; *Tetrahedron: Asymmetry*, **1991**, *2*, 997.

[85] Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.; Wong, L.F.; *Tetrahedron: Asymmetry*, **1991**, *2*, 1343.

[86] Dallaria, J.F.Jr.; Santarsiero, B.D.; *J. Org. Chem.*, **1989**, *54*, 3916.

[87] Kanemase, S.; Yamamoto, H.; *Tetrahedron Lett.*, **1990**, *31*, 3633. See also: Kanemase, S.; Yamamoto, H.; Wada, E.; Sakurai, T.; Urushido, K.; *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 2857.

[88] Barr, D.A.; Dorrity, M.; Grigg, R.; Malone, J.F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P.; *Tetrahedron Lett.*, **1990**, *31*, 6569.

[89] Barr, D.A.; Grigg, R.; Gunaratne, H.Q.N.; Kemp, J.; McMeekin, P.; Sridharan, V.; *Tetrahedron*, **1988**, *44*, 557.

[90] Grigg, R.; Coulter, T.; *Tetrahedron Lett.*, **1991**, *32*, 1359.

[91] Grigg, R.; Duffy, L.M.; Dorrity, M.J.; Malone, J.F.; Rajviroongit, S.; Thornton-Pett, M.; *Tetrahedron*, **1990**, *46*, 2213.

[92] Kanemasa, S.; Doi, K.; Wada, E.; *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 2866.

[93] Coulter, T.; Grigg, R.; Malone, J.F.; Sridharan, V.; *Tetrahedron Lett.*, **1991**, *32*, 5417.

[94] Terao, N.; Imai, N.; Achiwa, K.; Sekiya, M.; *Chem. Pharm. Bull.*, **1982**, *30*, 3167.

[95] Westling, M.; Smith, R.; Livinghouse, T.; *J. Org. Chem.*, **1986**, *51*, 1159.

[96] Wang, C.J.; Ripka, W.C.; Confalone, P.N.; *Tetrahedron Lett.*, **1984**, *25*, 4613.

[97] Hawkins, J.M.; Lewis, T.A.; *J. Org. Chem.*, **1992**, *57*, 2114.

Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F.; *Tetrahedron*, **1988**, *44*, 5525.

[99] Entwistle, I.D.; Johnstone, R.A.W.; Wilby, A.H.; *Tetrahedron*, **1982**, *38*, 419.

[100] Mazaleyrat, J-P.; Maigrot, N.; *Synthesis*, **1985**, 317.

[101] Bestmann, H.J.; Both, W.; *Chem. Ber.*, **1974**, *107*, 2926.

[102] Brown, H.C.; Cheng, M.T.; Parcell, L.J.; Pilipovich, D.; *J. Org. Chem.*, **1961**, *26*, 4407.

[103] Hawkins, J.M.; Fu, G.C.; *J. Org. Chem.*, **1986**, *51*, 2820.

[104] Hawkins, J.M.; Lewis, T.A.; *J. Org. Chem.*, **1994**, *59*, 649.

[105] Gösl, R.; Meuwsen, A.; *Chem. Ber.*, **1959**, 2521.

[106] Enders, D.; Fey, P.; Kipphardt, H.; *Org. Synth.*, **1986**, *65*, 173.

[107] Claxton, G.P.; Allen, L.; Grisar, J.M.; *Org. Synth.*, **1976**, *56*, 118.

[108] Newman, M.S.; Holmes, H. L.; *Org. Synth., Collect.*, **1943**, *Vol. II*, 428.

[109] Theilacker, W.; Wegner, E.; *Angew. Chem.*, **1960**, *72*, 127. And references therein.

[110] Metlesics, W.; Tavares, R.F.; Sternbach, L.H.; *J. Org. Chem.*, **1965**, *30*, 1311.

[111] Altenkirk, B.; Israelstam, S.S.; *J. Org. Chem.*, **1962**, *27*, 4532.

[112] Mintz, M.J.; Walling, C.; *Org. Synth.*, **Vol. 49**, 9.

[113] Carpino, L.A.; Giza, C.A.; Carpino, B.A.; *J. Am. Chem. Soc.*,**1959**, *81*, 955. The current reference used was: *The Practice of Peptide Synthesis*, 2nd Ed., 196, M. & A. Bodanszky, Springer Lab Manual. CARE: Extreme care MUST be taken when preparing this compound - see *Org. Synth.*, **Vol. 57**, 122.

[114] Carpino, L.A.; *J. Am. Chem. Soc.*, **1960**, *82*, 3133.

[115] Vidal, J.; Guy, L.; Stérin, S.; Collet, A.; *J. Org. Chem.*, **1993**, *58*, 4791.

[116] Vidal, J.; Damestoy, S.; Collet, A.; *Tetrahedron. Lett.*, **1995**, *36*, 1439.

[117] Vidal, J.; Drouin, J.; Collet, A.; *J. Chem. Soc., Chem. Commun.*, **1991**, 435.

[118] Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M.; *J. Am. Chem. Soc.*, **1992**, *114*, 5900.

[119] Genêt, J-P.; Mallart, S.; Greck, C.; Piveteau, E.; *Tetrahedron Lett.*, **1991**, *32*, 2359.

[120] Andreae, S.; Schmitz, E.; *Synthesis*, **1991**, 327.

[121] Carpino, L.A.; Göwecke, S.; *J. Org. Chem.*, **1964**, *29*, 2820.

[122] Carpino, L.A.; Santilli, A.A.; Murray, R.W.; *J. Am. Chem. Soc.*, **1959**, *82*, 2728.

[123] Carpino, L.A.; *J. Am. Chem. Soc.*, **1957**, *79*, 4427.

Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K.; Terada, Y.; *Tetrahedron*, **1994**, *50*, 13335.

125 Corey, E.J.; McCaully, R.J.; Sachdev, H.S.; *J. Am. Chem. Soc.*, **1970**, *92*, 2476. See also: Corey, E.J.; Sachdev, H.S.; Gougoutas, J.Z.; Saenger, W.; *J. Am. Chem. Soc.*, **1970**, *92*, 2488.

126 Lunn, G.; Sansone, E.B.; Keefer, L.K.; *J. Org. Chem.*, **1984**, *49*, 3470.

127 Schmidt, U.; Braun, C.; Sutoris, H.; *Synthesis*, **1996**, 223.

128 Pandey, G.; Lakshmaiah, G.; *Tetrahedron Lett.*, **1993**, *34*, 4861. See also (a) Pandey, G.; Lakshmaiah, G.; Kumaraswamy, G.; *J. Chem. Soc., Chem. Commun.*,**1992**, 1313; (b) Pandey, G.; *Synlett.*, **1991**, 546.

129 Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J-M.; Llera, J-M.; *Synthesis*, **1996**, 48.

130 He, D.Y.; Li, Z.J.; Li, Z.J., Liu, Y.Q.; Qiu, D.X.; Cai, M.S.; *Synthetic Commun.*, **1992**, *22(18)*, 2653. See also: (a) Asakura, J-i.; Matsubara, Y.; Yoshihara, M.; *J. Carbohydrate Chem.*, **1996**, *15(2)*, 231; (b) Schmidt, O.T.; *Methods in Carbohydrate Chem.*, 1963, *Vol 2*, 319.

131 Roussi, G.; Chastanet, J.; Fathallah, H.; Negron, G.; *Heterocycles*, **1992**, *34*, 1565.

132 Vogel, A., *Vogel's Textbook of Practical Organic Chemistry*, 4th Ed., **1978**, 454, Longman Press, London & New York.

133 Roth, W., Pigman, W., *Methods in Carbohydrate Chem.*, **Vol 2**, 405.

134 Pfleiderer, W.; Bühler, E.; *Chem. Ber.*, **1966**, 3022.

135 Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M.; *Helv. Chimica Acta.*, **1985**, *68*, 2100.

136 Forster, M.O.; Rao, K.A.N.; *J. Chem. Soc.*, **1926**, 2670.

137 Beckett, A.H.; Lan, N.T.; McDough, G.R.; *Tetrahedron*, **1969**, *25*, 5689.

138 Cooper, G.H.; Chittenden, R.A.; *J. Chem. Soc. (C)*, **1970**, 49.

139 Duden, P.; Pritzkow, W.; *Chem. Ber.*, **1899**, *32*, 1538.

140 Vedejs, E.; Larsen, S.; *Org. Synth.*, **Vol. 64**, 127.

141 Sarda, P.; Elphimoff-Felkin, I.; *Org. Synth.*, **Vol. 56**, 101.

142 Moody, C.J.; Lightfoot, A.P.; Gallagher, P.T.; *Synlett.*, **1997**, 659.

143 Fleming, I.; Woodward, R.B.; *J. Chem. Soc. (C)*, **1968**, 1289.

144 Lester, M.G.; Petrow, V.; Stephenson, O.; *Tetrahedron*, **1965**, *21*, 771.

145 Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M.D.; Gálvez, J.; *Synthesis*, **1997**, 747.

146 Herold, T.; Schrott, U.; Hoffmann, R.W.; *Chem. Ber.*, **1981**, *114*, 359.

147 Lal, B.; Pramanik, B.N.; Manhas, M.S.; Bose, A.K.; *Tetrahedron Lett.*, **1977**, *23*, 1977.

148 (a) Schoiri, T.; Ninomiya, K.; Yamada, S.; *J. Am. Chem. Soc.*, **1972**, *94*, 6203; (b) Yamada, S.; Kota, N.I.; Shiori, T.; *J. Am. Chem. Soc.*, **1975**, *97*, 7174; (c) Jackson, A.G.; Kenner, G.W.; Moore, G.A.; Ramage, R.; Thorpe, W.D.; *Tetrahedron Lett.*, **1976**, 3627.

149 Forster, M.O.; *J. Chem. Soc.*, **1897**, *71*, 1037.

150 Anderson, W.K.; Milowsky, A.S.; *J. Med. Chem.*, **1986**, *29*, 2241. See also: Tsuge, O.; Kanemasa, S.; Matsuda, K.; *Chem. Lett.*, **1983**, 1131.

151 Letellier, M.; McPhee, D.J.; Griller, D.; *Synthetic Commun.*, **1988**, *18(16 & 17)*, 1975.

152 Corey, E.J.; Pikul, S.; *Org. Synth.*, **Vol. 71**, 22.

153 Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P.; *Synthesis*, **1990**, 1023.

154 Jacobsen, E.N.; Markó, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B.; *J. Am. Chem. Soc.*, **1988**, *110*, 1968. See also: McKee, B.H.; Gilheany, D.G.; Sharpless, K.B.; *Org. Synth.*, **Vol. 70**, 47.

155 Chang, H-Y.; Sharpless, K.B.; *unpublished results.* For the general scheme see: Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B.; *Chem. Rev.*, **1994**, *94*, 2483.

156 Wiggins, L.F.; *Methods in Carbohydrate Chem.*, **1963**, *Vol 2*, 188.

157 Hicks, D.R.; Fraser-Reid, B.; *Synthesis*, **1974**, 203.

158 Izawa, T.; Nishimura, Y.; Kondo, S.; *Carbohydrate Research*, **1991**, *211*, 137. See also: Guthrie, R.D.; Murphy, D.; *J. Org. Chem.*, **1963**, 5288.

159 Roussi, G.; Zhang, J.; *Tetrahedron Lett.*, **1988**, *29*, 3481.

160 Chan, J.Y.C.; Cheong, P.P.L.; Hough, L.; Richardson, A.C.; *J. Chem. Soc., Perkin Trans. I*, **1985**, 1447.

161 Hale, K.J.; Manaviazar, S.; Tupprasoot, R.; *Tetrahedron*, **1997**, *53*, 16365.

162 Sharpless, K.B.; Lauer, R.F.; *J. Am. Chem. Soc.*, **1973**, *95*, 2697.

163 Horwell, D.C.; Hughes, J.; Hunter, J.C.; Pritchard, M.C.; Richardson, R.S.; *J. Med. Chem.*, **1991**, *34*, 404.

Correa, A.; Denis, J-N.; Greene, A.E.; *Synth. Commun.*, **1991**, *21(1)*, 1. See also: (a) Fournie-Zaluski; M-C., Coric, P.; Turcaud, S.; Bruetschy, L.; Lucas, E.; *J. Med. Chem.*, **1992**, *35*, 1259; (b) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T.; *Tetrahedron Lett.*,**1989**, *30*, 837.

165 Matsunaga, N.; Harada, H.; Aoyama, T.; Shioiri, T.; *Heterocycles*, **1992**, *33*, 235. See also: Dondoni, A.; Perrone, D.; Semola, T.; *Synthesis*, **1995**, 181.

166 Taschner, M.J.; Huang, Y.; El-Alali, A.; Chen, L.; Youngs, W.J.; *Tetrahedron Lett.*, **1992**, *33*, 2765.

167 Davis, F.A.; Stringer, O.D.; *J. Org. Chem.*, **1982**, *47*, 1774.

168 Zimmer, H.; Audrieth, L.F.; Zimmer, M.; Rowe, R.A.; *J. Am. Chem. Soc.*, **1955**, *77*, 790.

169 Enders, D.; *Asymmetric Synthesis*, **1984**, *Vol. 3*, Academic Press, page 275.

170 Suzuki, H.; Aoyagi, S.; Kibayashi, C.; *Tetrahedron Lett.*, **1995**, *36*, 935.

171 Enders, D.; Kipphardt, H.; Fey, P.; *Org. Synth.*, **1987**, *65*, 183.

172 Still, W.C.; Kahn, A.; Mitra, A.; *J. Org. Chem.*, **1978**, *43*, 2923.

173 Kalamar, J.; Lazar, M.; Horak, F.; Legrady, S.; *Chem. Abs.*, **1968**, *69*, 86668h.

Appendix

The following section shows the ^{1}H and ^{13}C n.m.r. spectra obtained. The data for those not shown can be found in the relevant references mentioned in the preceeding text.

Figure 1	^{1}H n.m.r. spectrum of Mosher amide of racemate of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepine (±)-**15**
Figure 2	^{1}H n.m.r. spectrum of chiral Mosher amide of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepine **15**
Figure 3	^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-nitroso-dinaphth-[2,1-*c*:1',2'-*e*]azepine **33**
Figure 4	^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-nitroso-dinaphth-[2,1-*c*:1',2'-*e*]azepine **33**
Figure 5	^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **1**
Figure 6	^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **1**
Figure 7	^{1}H n.m.r. spectrum of (*S*)-3,5-dihydro-4*N*-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **1**
Figure 8	^{13}C n.m.r. spectrum of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**
Figure 9	^{1}H n.m.r. spectrum of Mosher derivative (±)-**34** of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide (±)-**1**
Figure 10	^{1}H n.m.r. spectrum of chiral Mosher compound of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **34**
Figure 11	^{19}F n.m.r. spectra of Mosher derivative (±)-**34** of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide (±)-**1** and chiral Mosher compound of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **34**
Figure 12	^{1}H n.m.r. spectrum of hydrazone **30**
Figure 13	^{13}C n.m.r. spectrum of hydrazone **30**

Figure 66	^{1}H n.m.r. spectrum of methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)pyrrolidine-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **134ab**
Figure 67	^{13}C n.m.r. spectrum of methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)-pyrrolidine-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **134ab**
Figure 68	^{1}H n.m.r. spectrum of methyl 5-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148**
Figure 69	^{13}C n.m.r. spectrum of methyl 5-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148**
Figure 70	^{1}H n.m.r. spectrum of methyl 5-(*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149**
Figure 71	^{13}C n.m.r. spectrum of methyl 5-(*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149**
Figure 72	^{1}H n.m.r. spectrum of methyl 5-(*N*-cyanomethyl-*N*-trimethylsilyl-methyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150**
Figure 73	^{13}C n.m.r. spectrum of methyl 5-(*N*-cyanomethyl-*N*-trimethylsilyl-methyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150**
Figure 74	^{1}H n.m.r. spectrum of methyl 5-*N*-(*trans*-3,4-dicarbomethoxypyrrolidine)-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructo-pyranoside **151ab**
Figure 75	^{13}C n.m.r. spectrum of methyl 5-*N*-(*trans*-3,4-dicarbomethoxy-pyrrolidine)-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **151ab**
Figure 76	^{1}H n.m.r. spectrum of *N*-(benzyloxy)carbonyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **166**
Figure 77	^{13}C n.m.r. spectrum of *N*-(benzyloxy)carbonyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **166**
Figure 78	^{1}H n.m.r. spectrum of *O*-triethylsilyl-D-(-)-α-phenylglycinol **172**

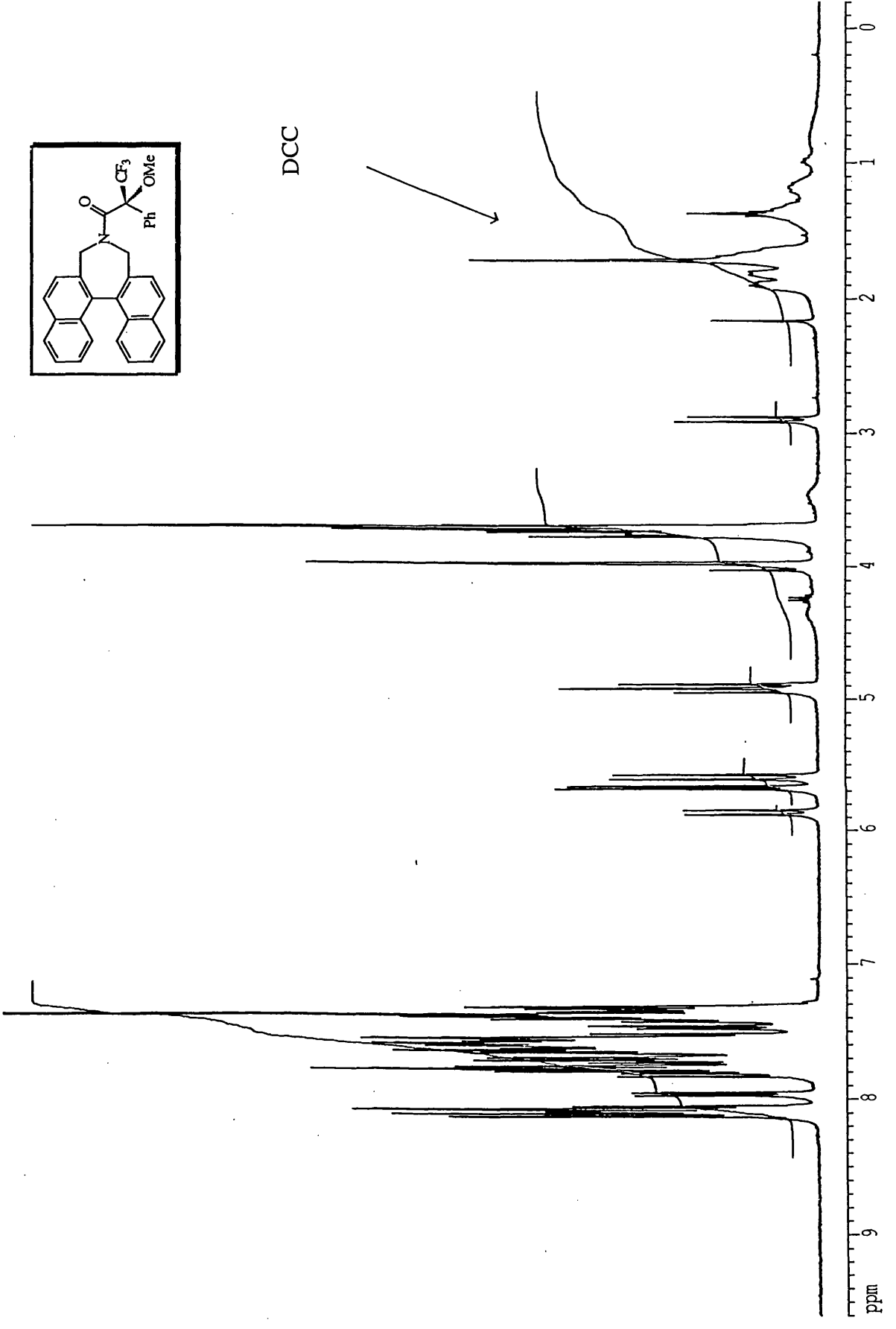


Figure 1 ^{1}H n.m.r. spectrum of racemic Mosher amide of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepine (±)-**15**

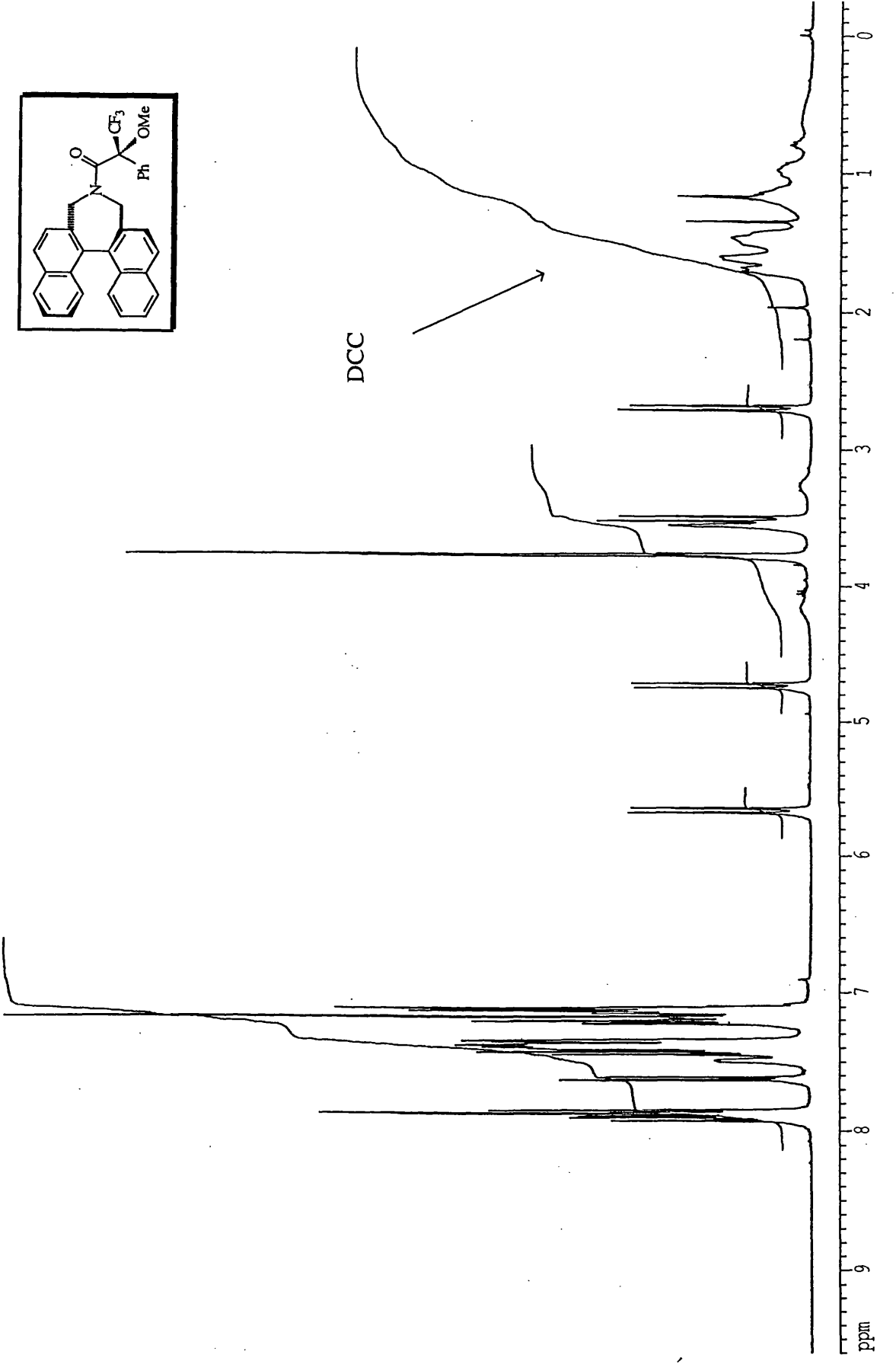


Figure 2 ^{1}H n.m.r. spectrum of chiral Mosher amide of (*S*)-3,5-dihydro-4*N*-dinaphth-[2,1-*c*:1',2'-*e*]azepine **15**

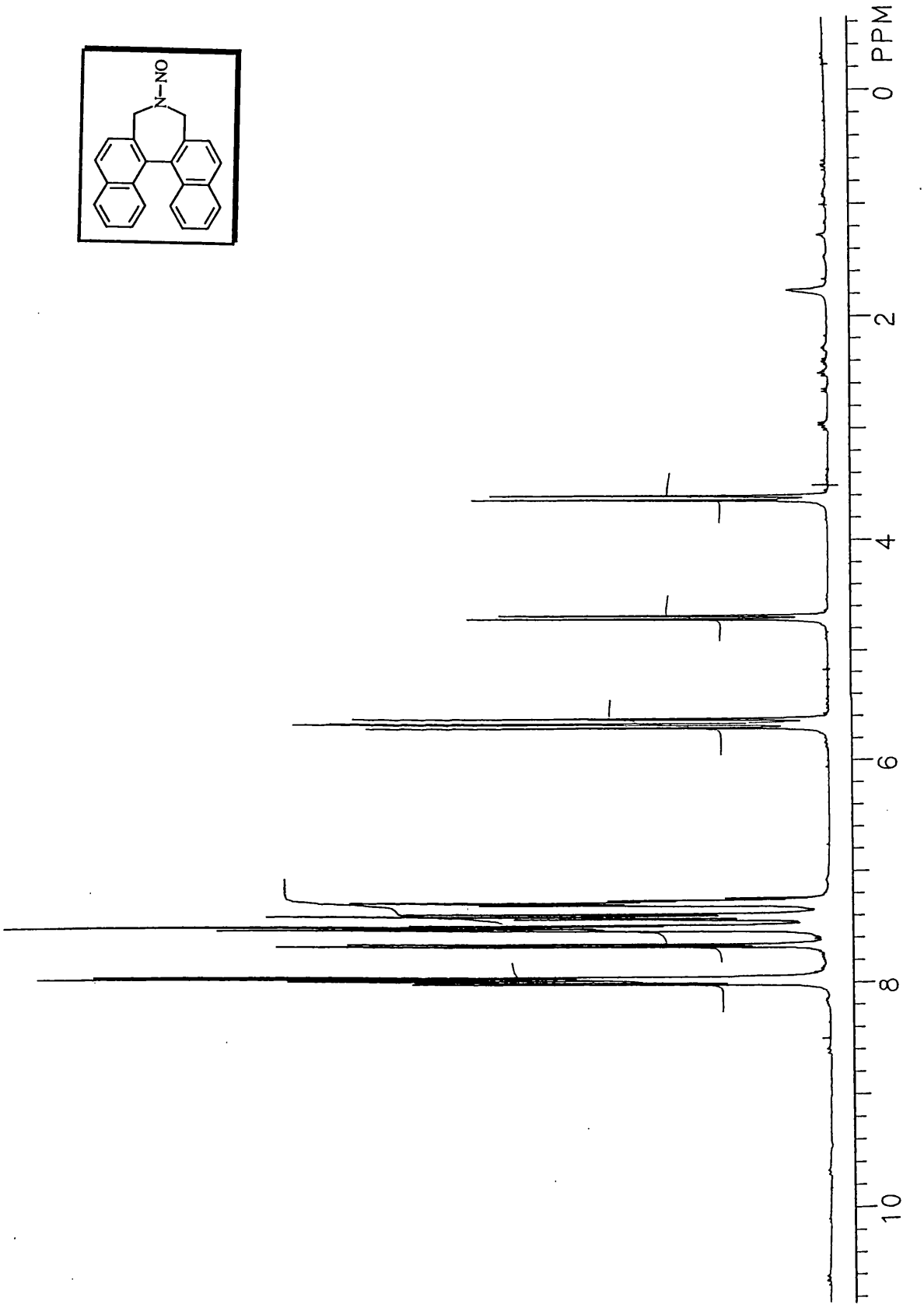


Figure 3 ^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]-azepine **33**

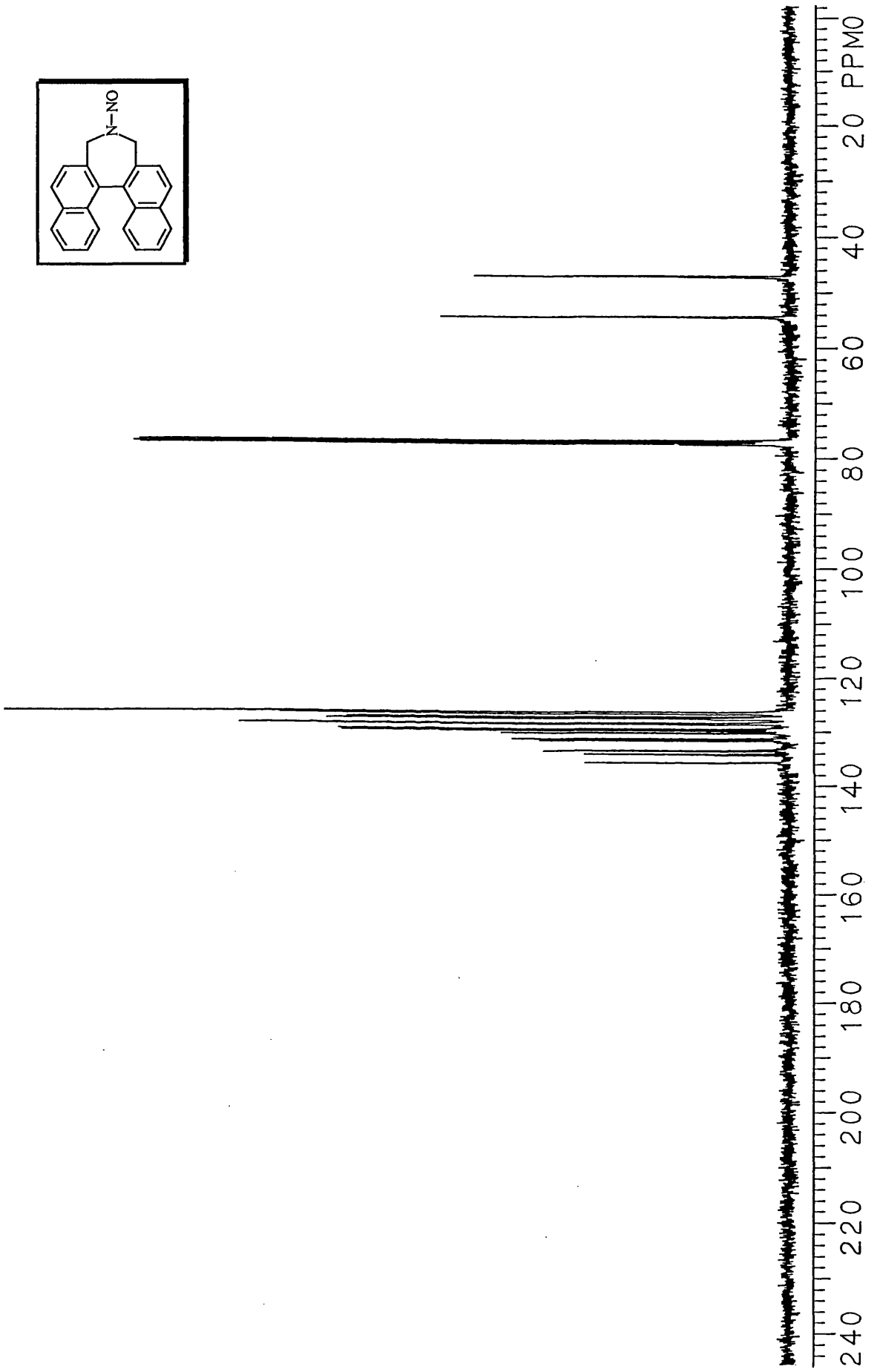


Figure 4 ^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-nitroso-dinaphth[2,1-*c*:1',2'-*e*]-azepine **33**

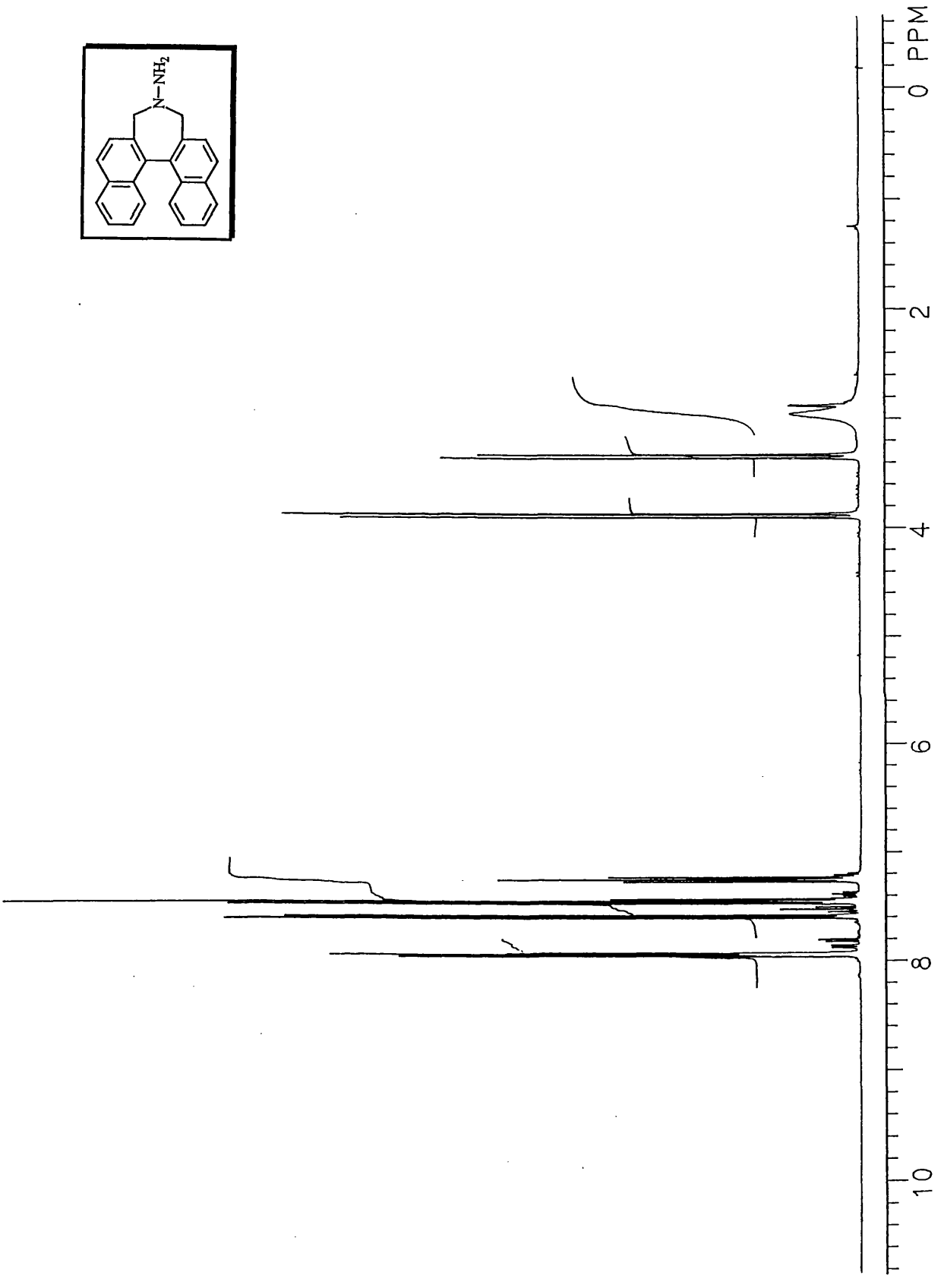


Figure 5 ^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**

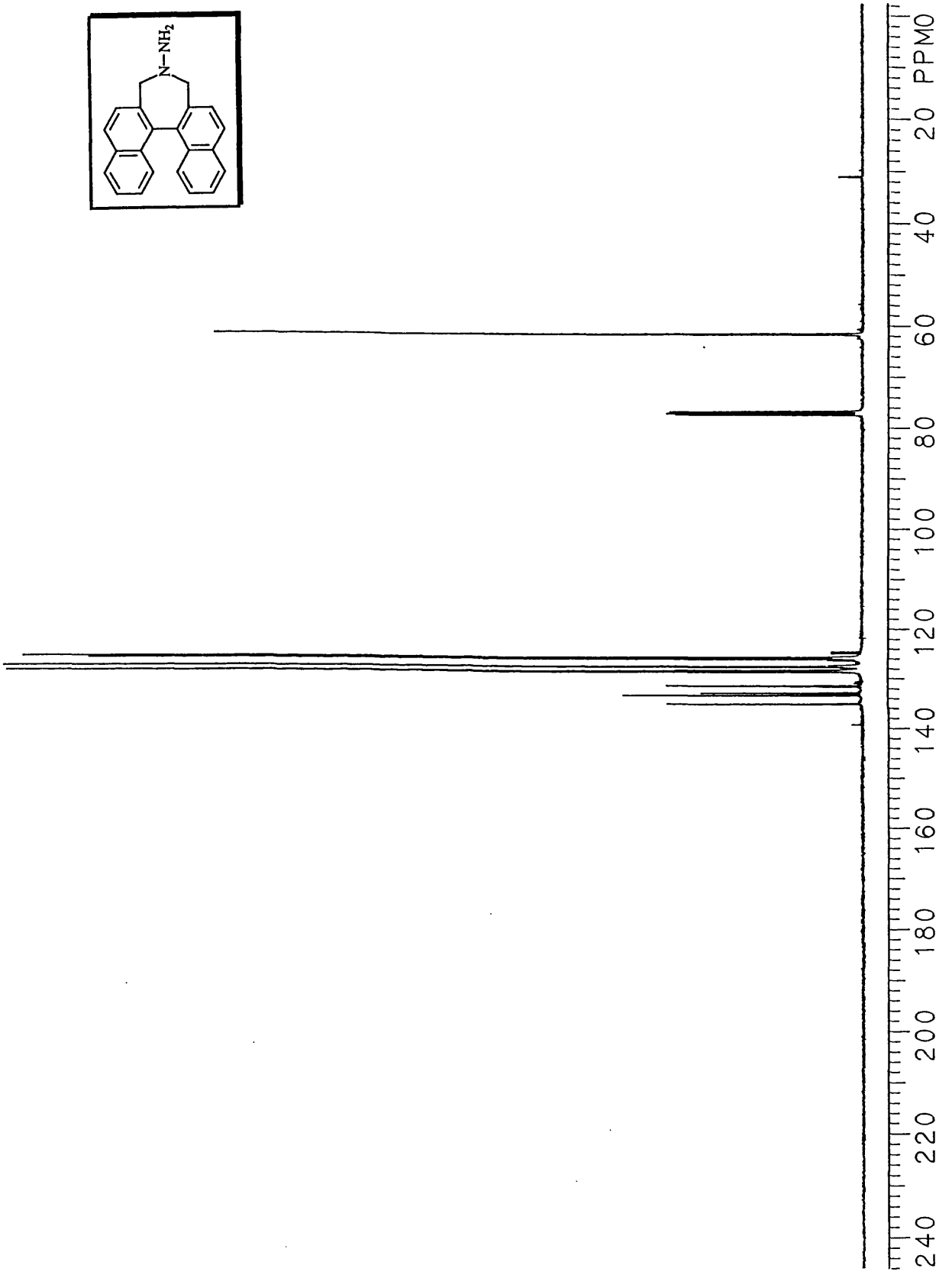


Figure 6 ^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**

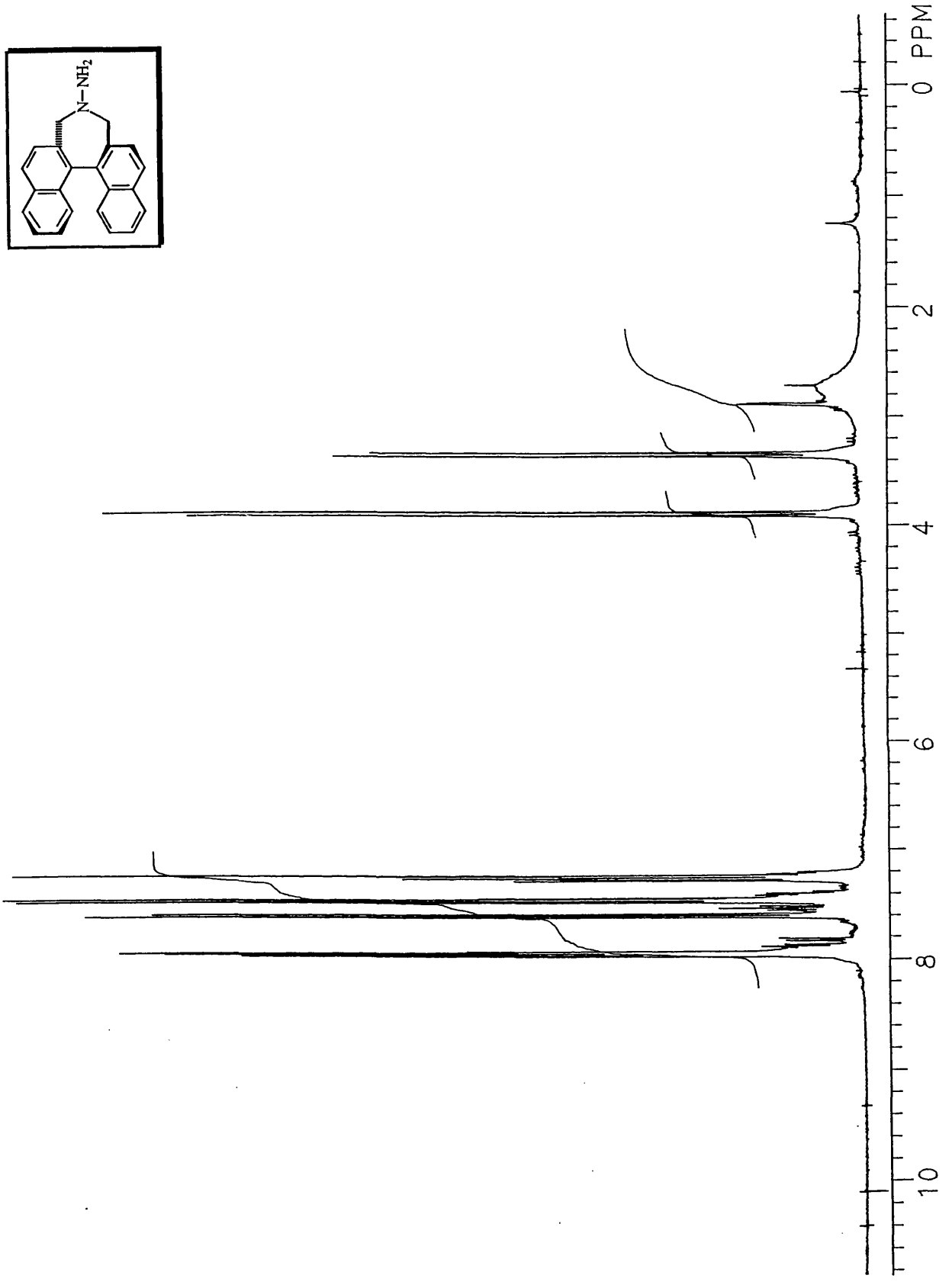


Figure 7 ^{1}H n.m.r. spectrum of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**

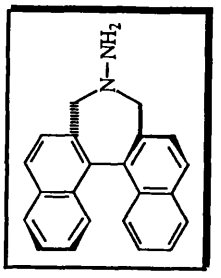


Figure 8 ^{13}C n.m.r. spectrum of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]-azepinehydrazide **1**

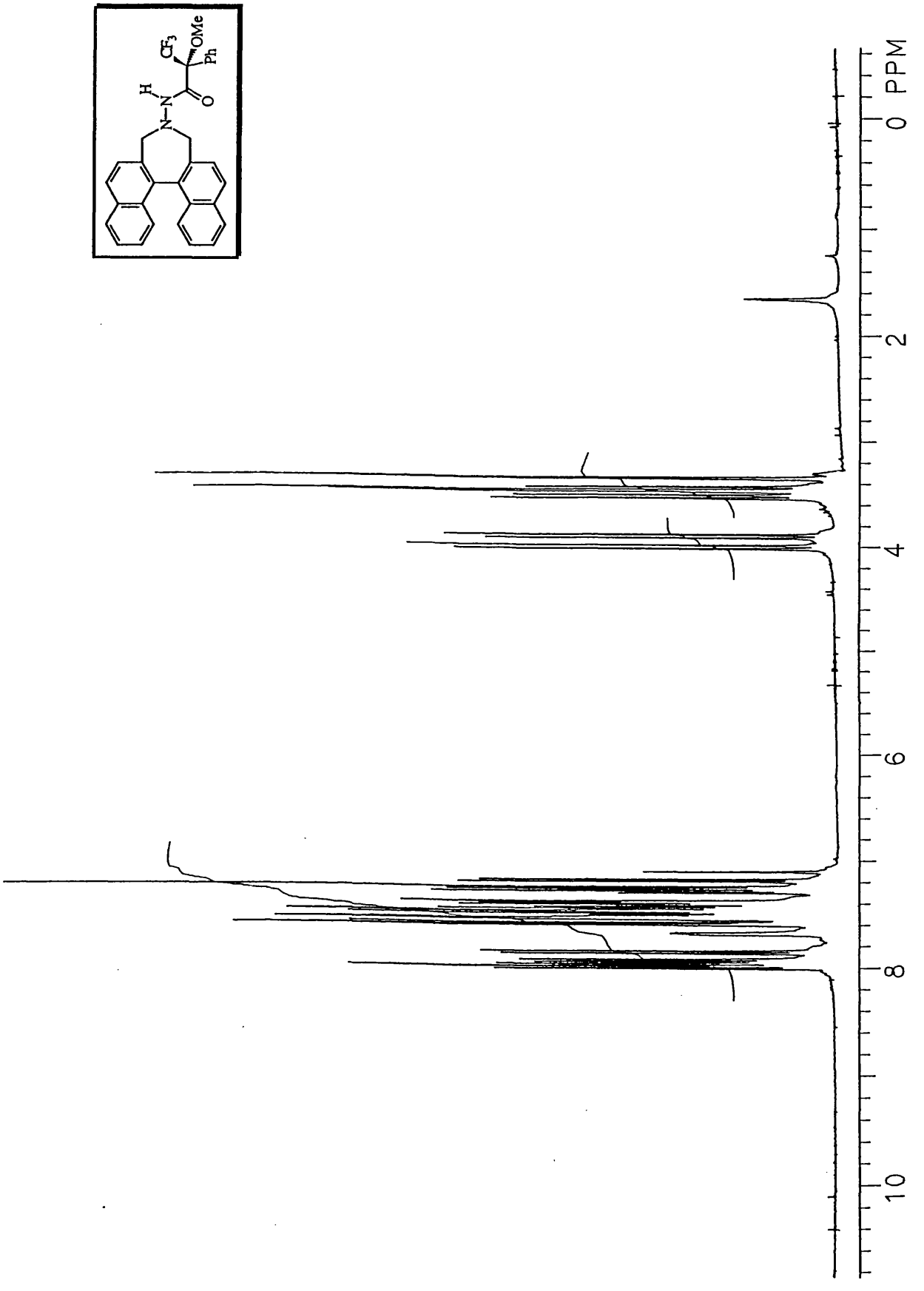
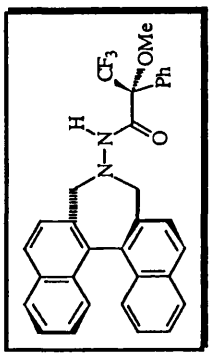


Figure 9 ^{1}H n.m.r. spectrum of Mosher derivative (±)-**34** of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide (±)-**1**



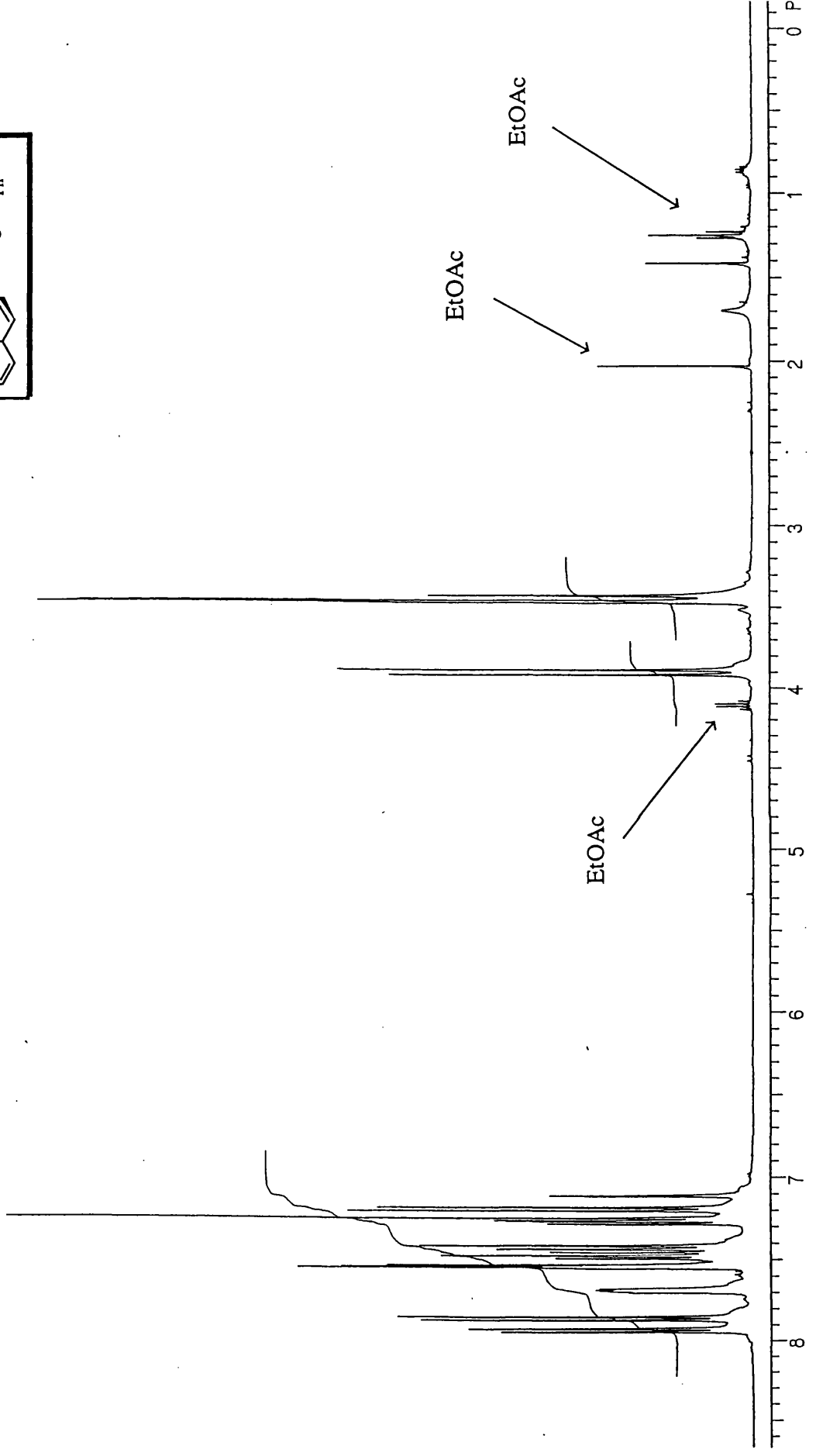


Figure 10 ^{1}H n.m.r. spectrum of chiral Mosher compound of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **34**

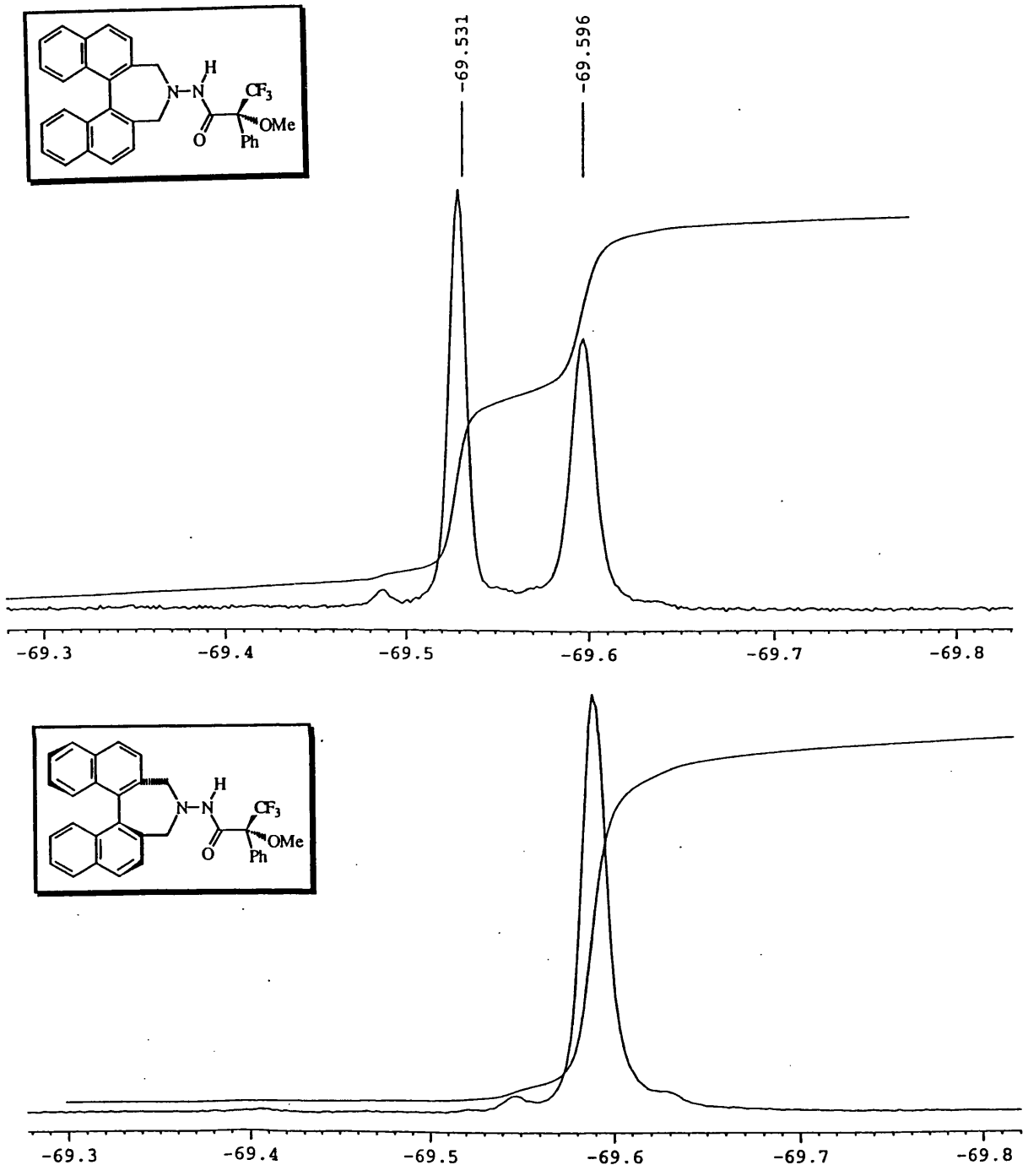


Figure 11 ^{19}F n.m.r. spectra of Mosher derivative (±)-**34** of (±)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide (±)-**1** and chiral Mosher compound of (*S*)-3,5-dihydro-4*N*-dinaphth[2,1-*c*:1',2'-*e*]azepinehydrazide **34**

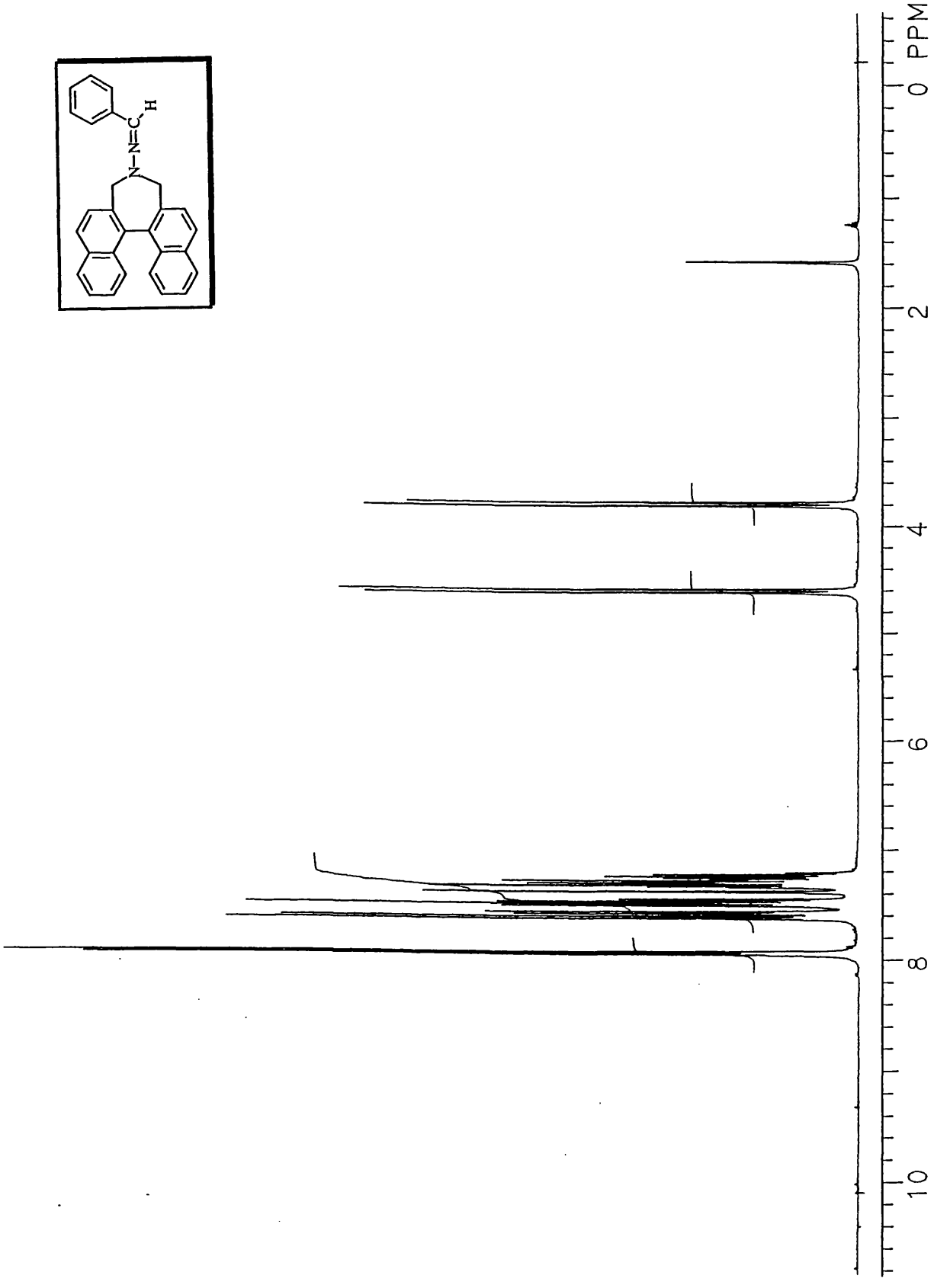


Figure 12 ^{1}H n.m.r. spectrum of hydrazone **30**

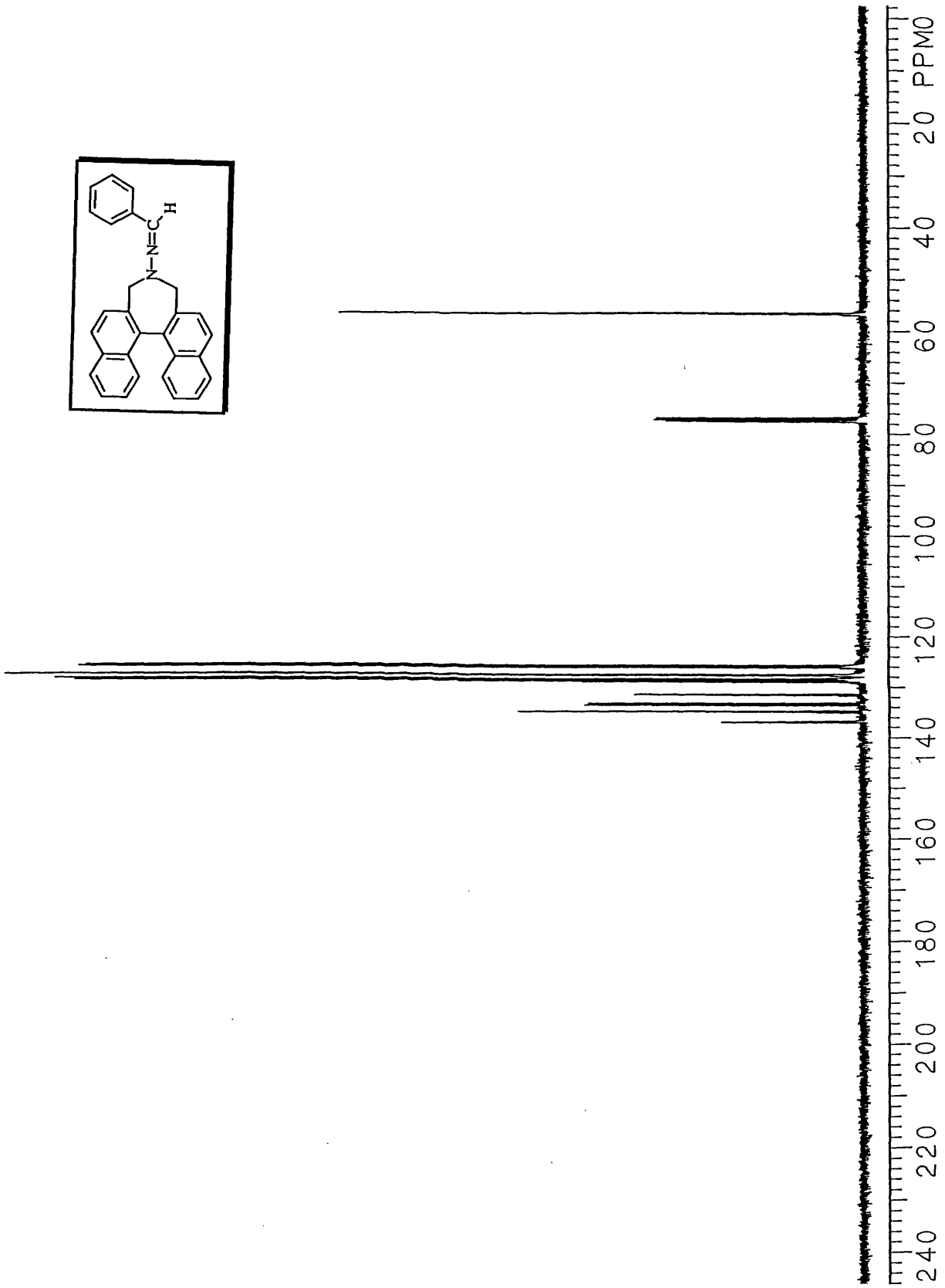


Figure 13 ^{13}C n.m.r. spectrum of hydrazone **30**

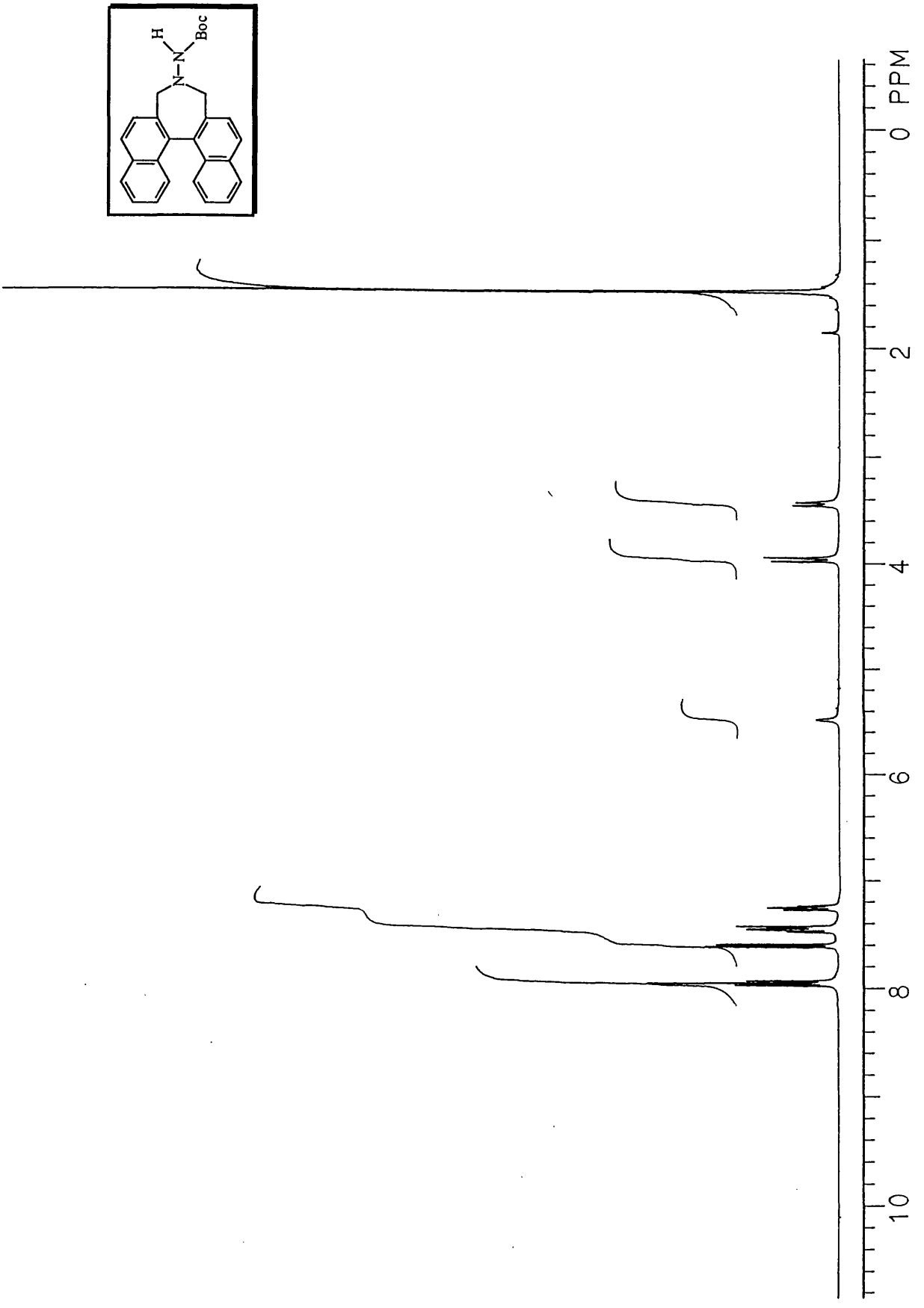


Figure 14 ^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(*N*'-Boc amino)-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **26**

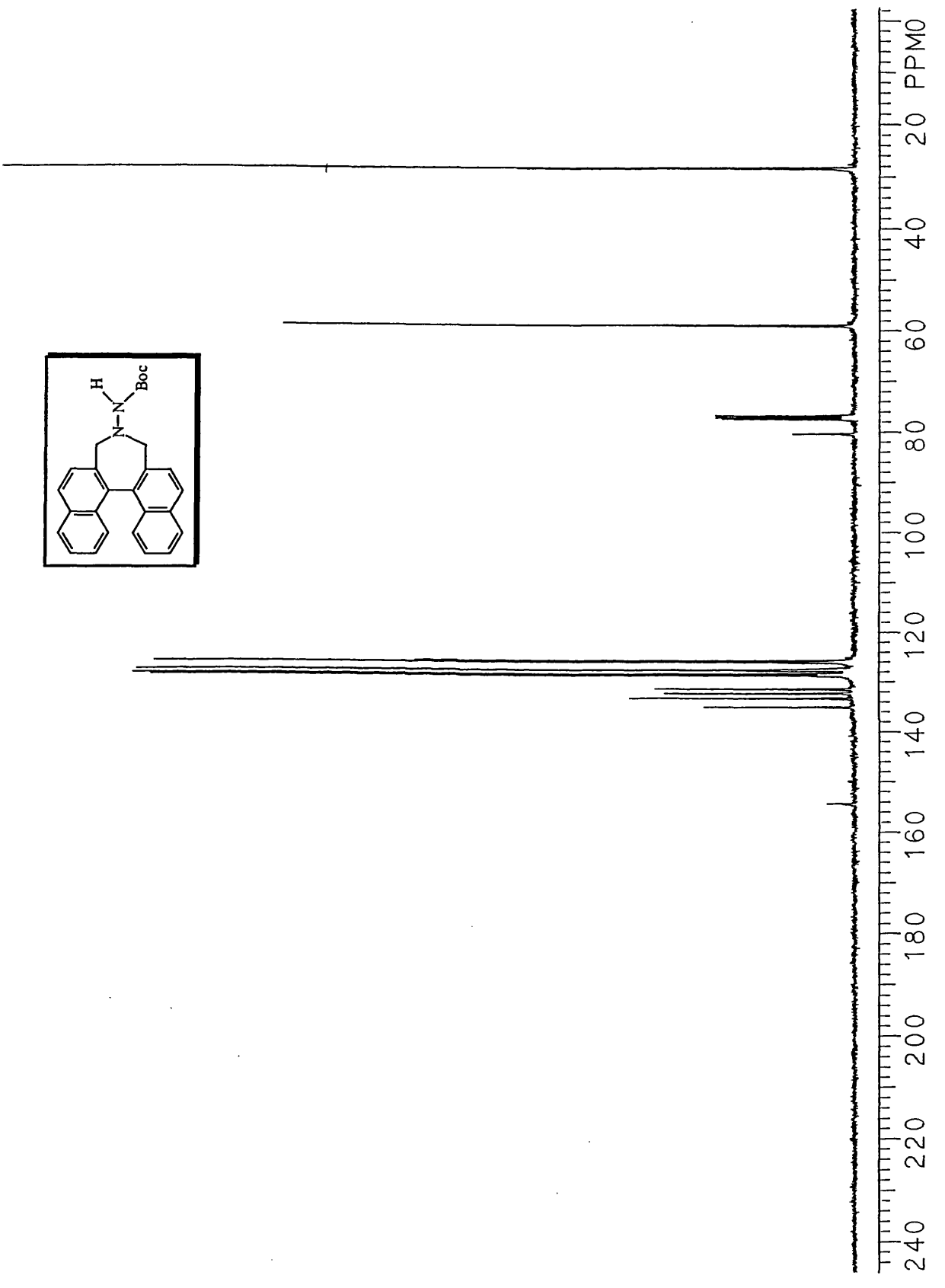


Figure 15 ^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(*N'*-Boc amino)-dinaphth-[2,1-*c*:1',2'-*e*]azepinehydrazide **26**

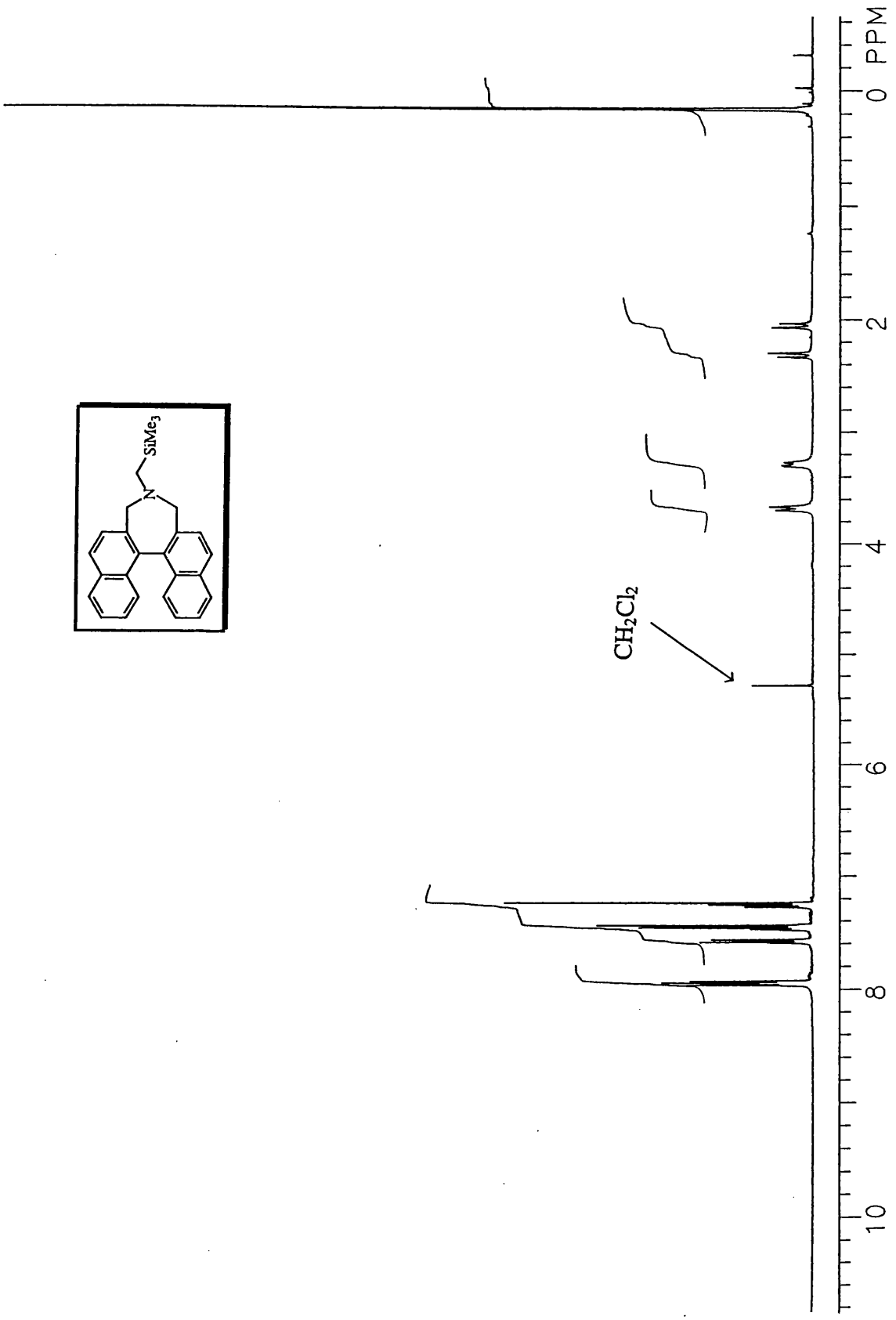


Figure 16 ^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(trimethylsilylmethyl)-dinaphth-[2,1-*c*:1',2'-*e*]azepine **43**

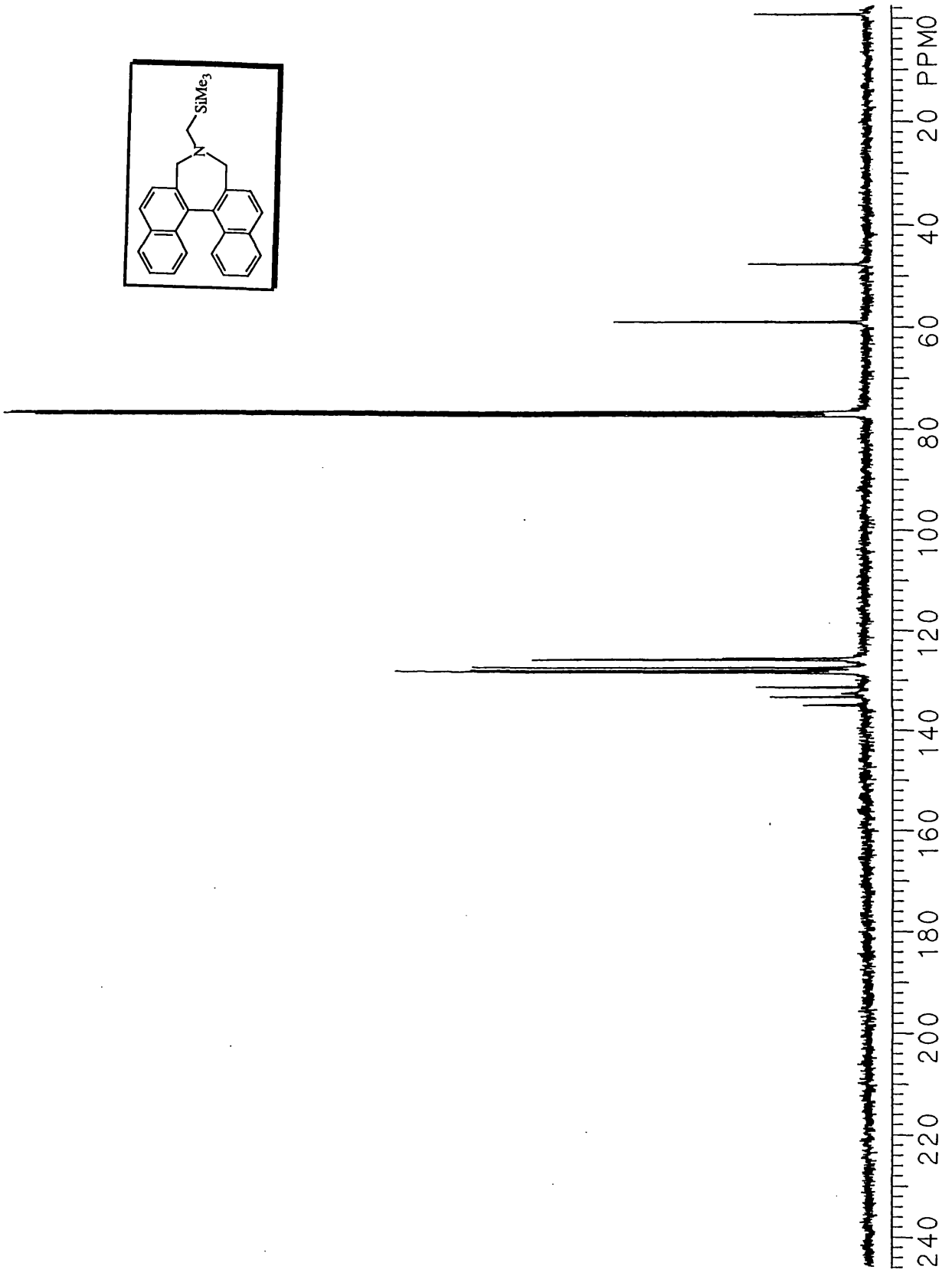


Figure 17 ^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(trimethylsilylmethyl)-dinaphth-[2,1-*c*:1',2'-*e*]azepine **43**

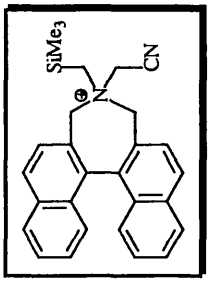


Figure 18 ^{1}H n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(trimethylsilylmethyl)-4*N*-(cyanomethyl)dinaphth[2,1-*c*:1',2'-*e*]azepine **44**

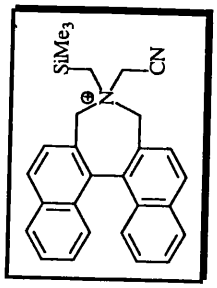


Figure 19 ^{13}C n.m.r. spectrum of (±)-3,5-dihydro-4*N*-(trimethylsilylmethyl)-4*N*-(cyanomethyl)-dinaphth[2,1-*c*:1',2'-*e*]azepine **44**

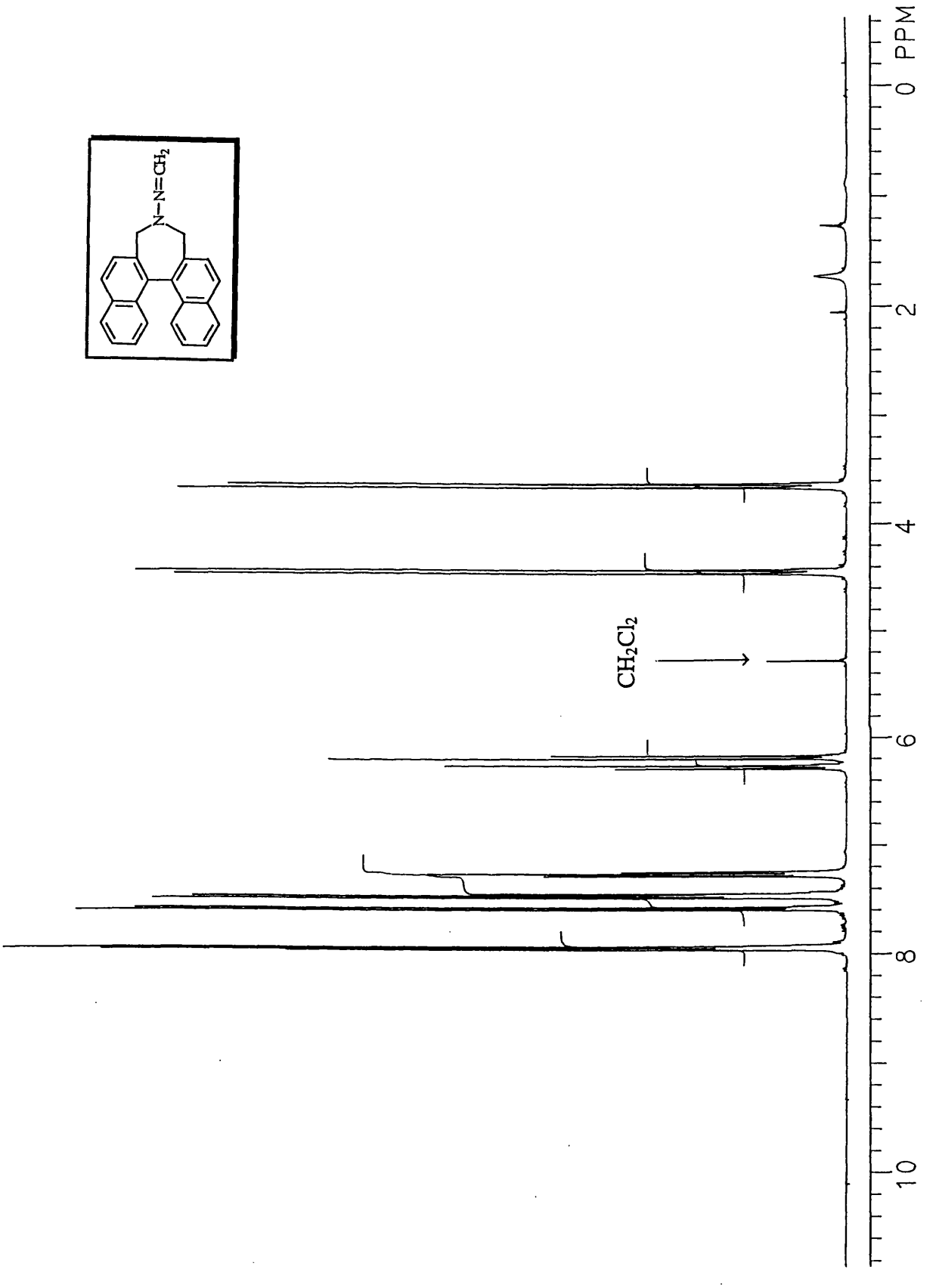


Figure 20 ^{1}H n.m.r. spectrum of hydrazone (±)-**45**

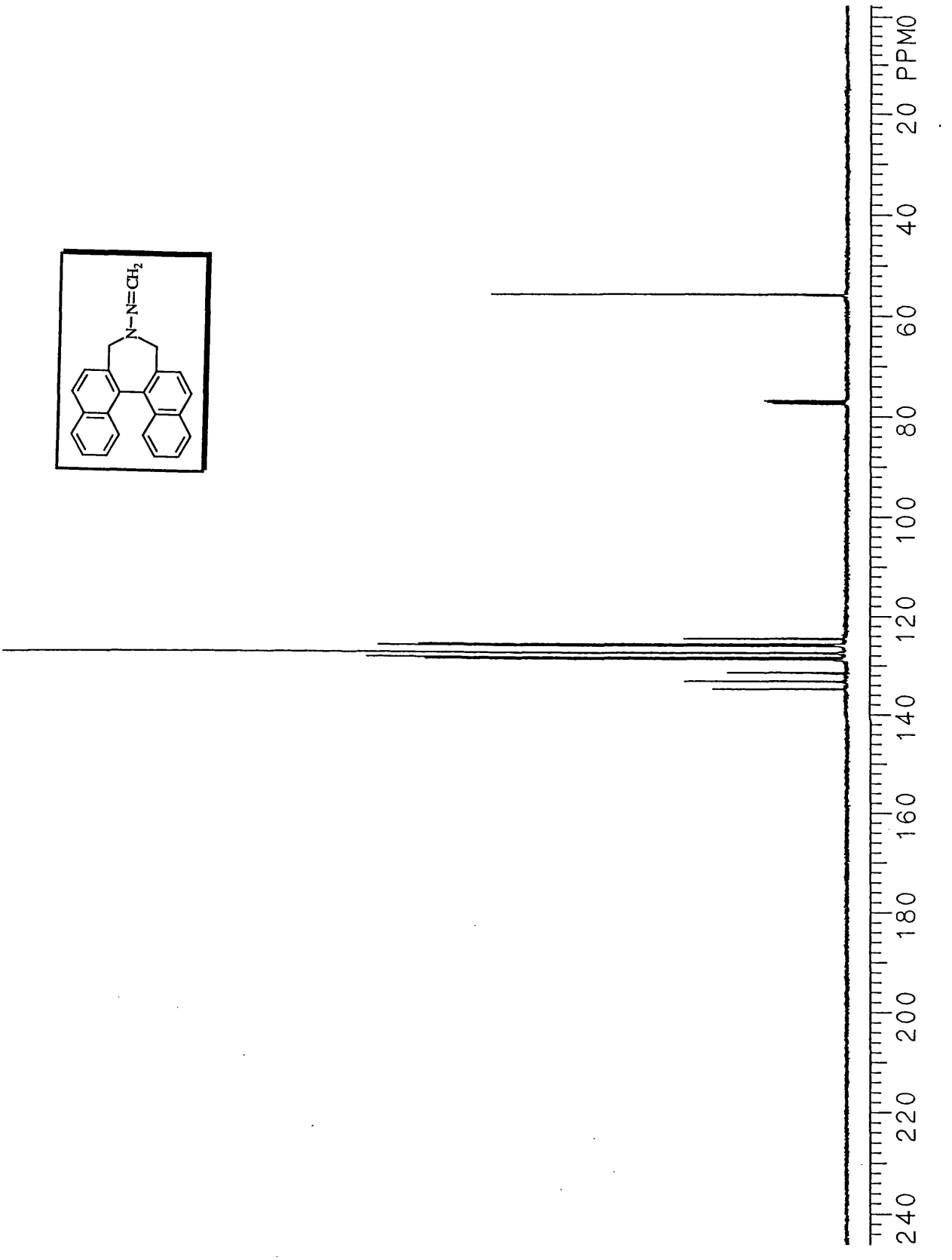


Figure 21 ^{13}C n.m.r. spectrum of hydrazone (±)-**45**

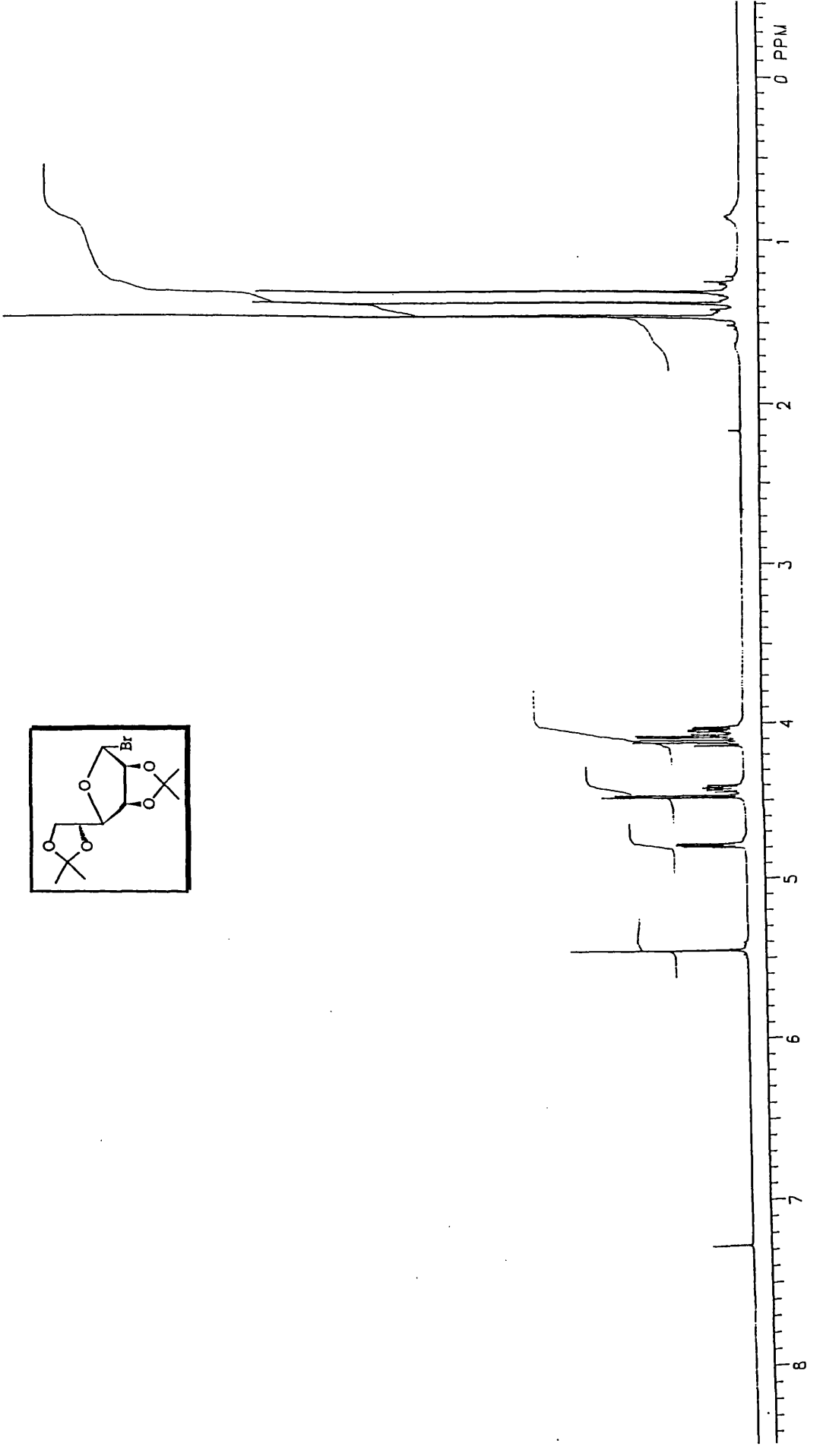


Figure 22 ^{1}H n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl bromide **48**

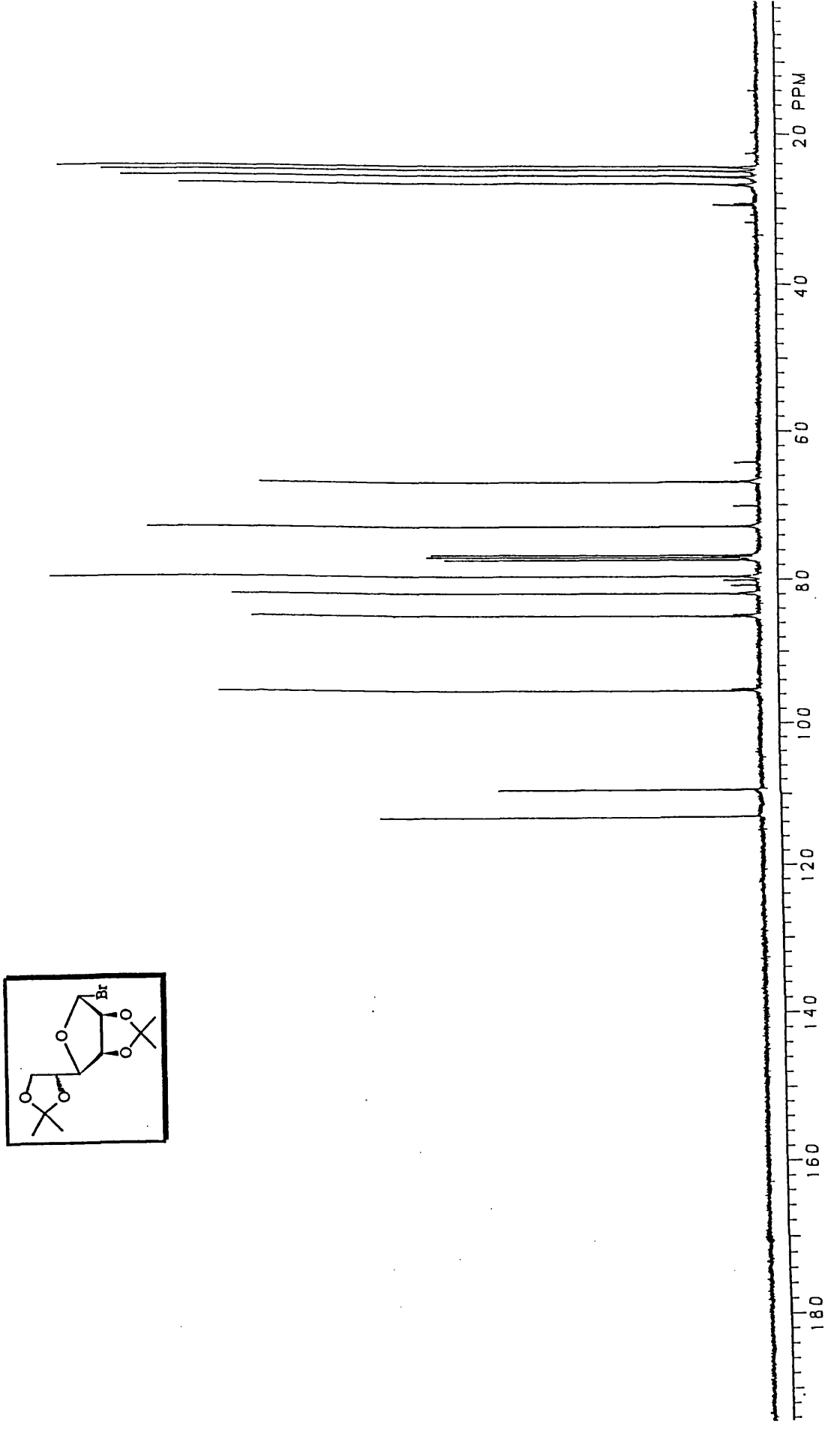


Figure 23 ^{13}C n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl bromide **48**

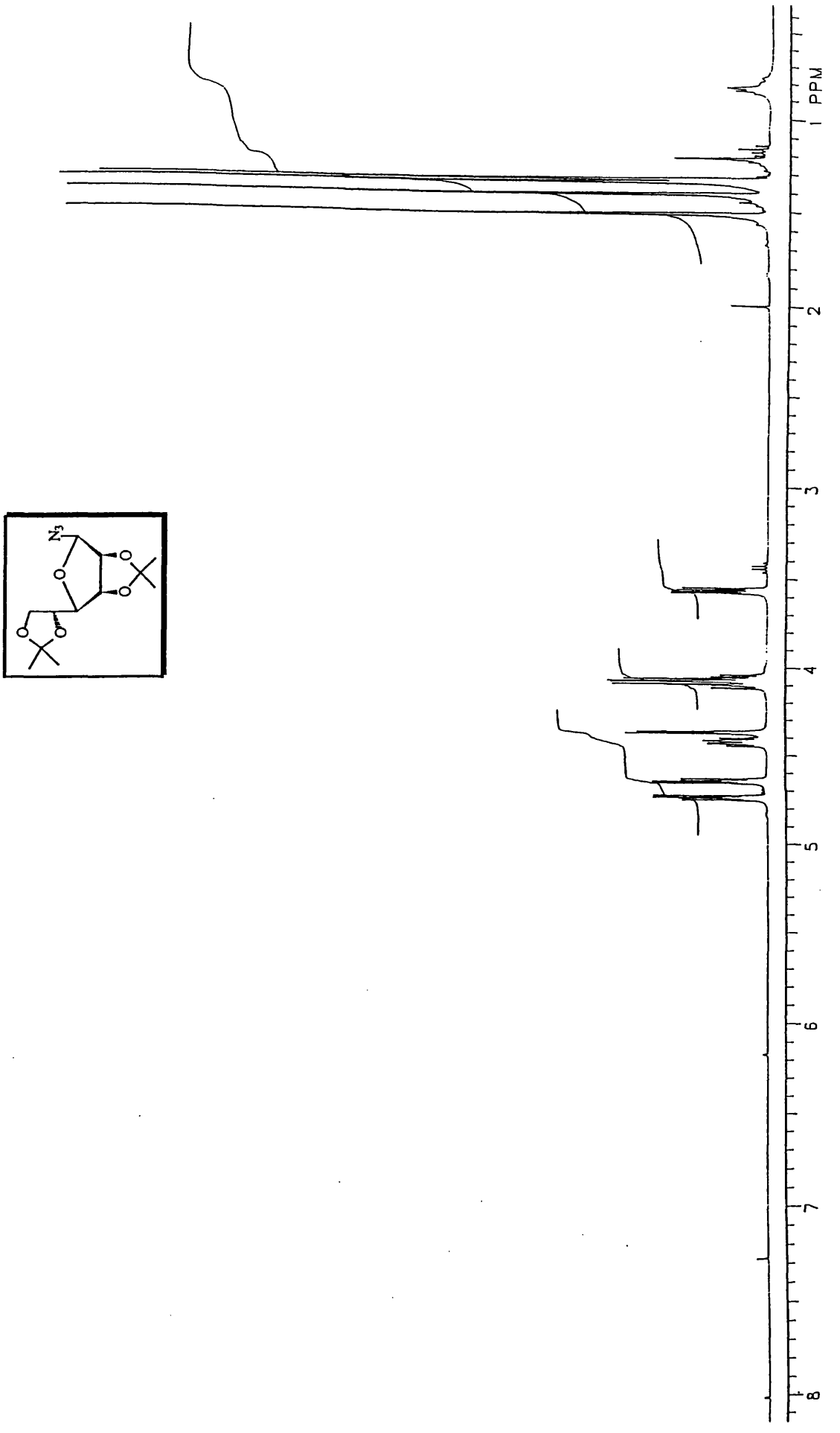


Figure 24 ^{1}H n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl azide **49**

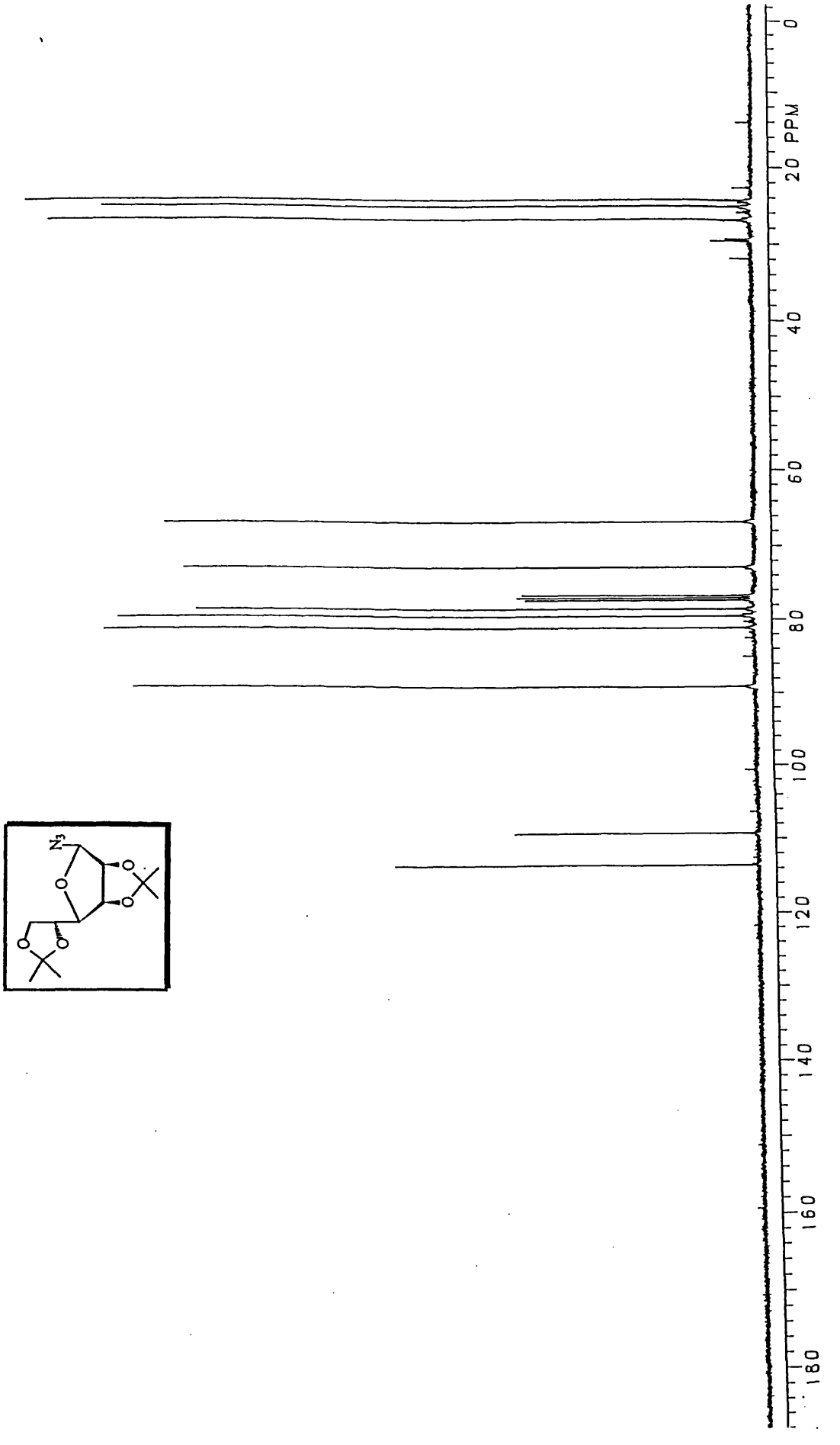


Figure 25 ^{13}C n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl azide **49**

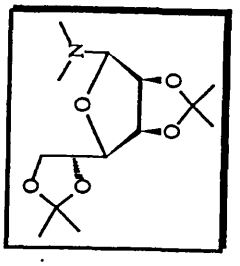
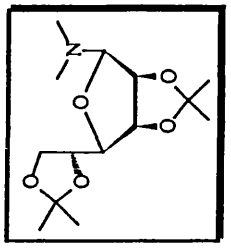


Figure 26 ^{1}H n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-*N,N*-dimethyl-β-D-mannofuranosyl amine **58**



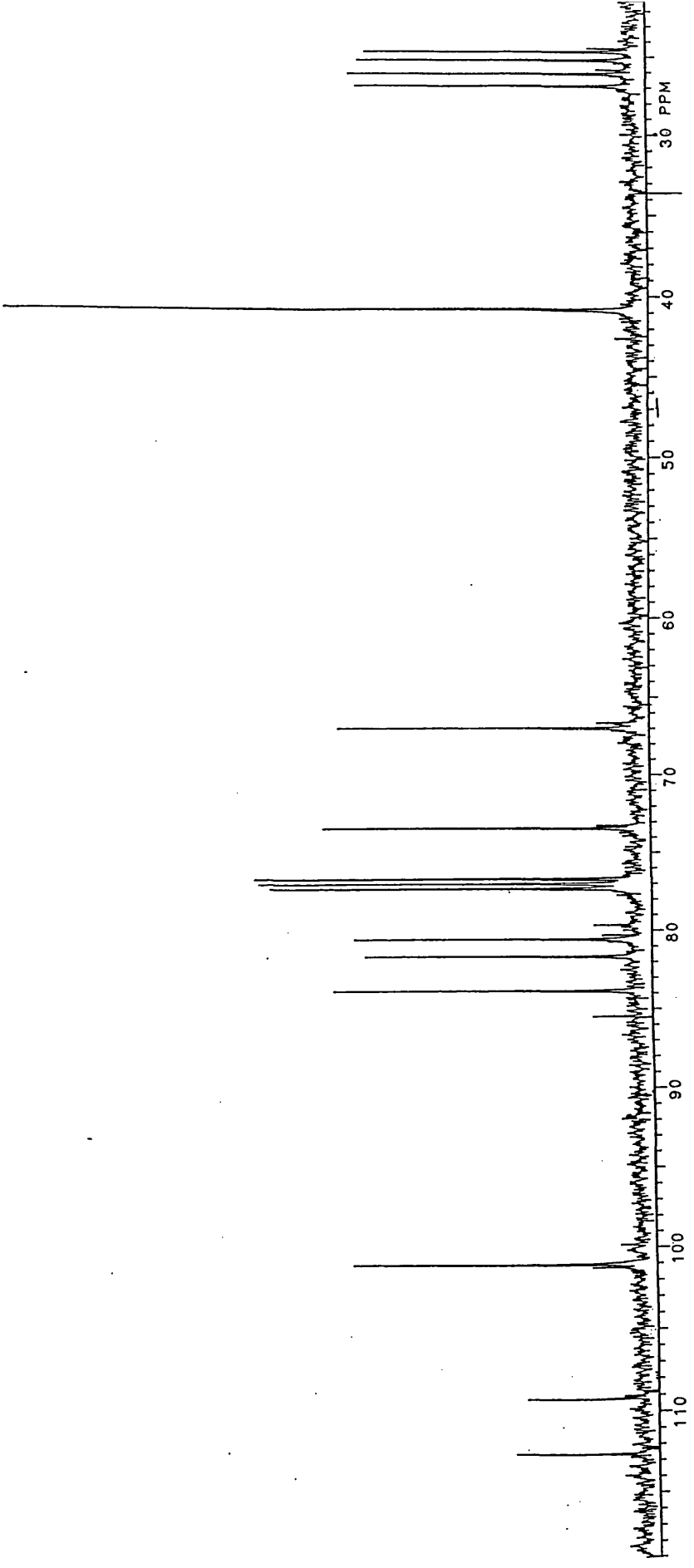


Figure 27 ^{13}C n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-*N,N*-dimethyl-β-D-mannofuranosyl amine **58**

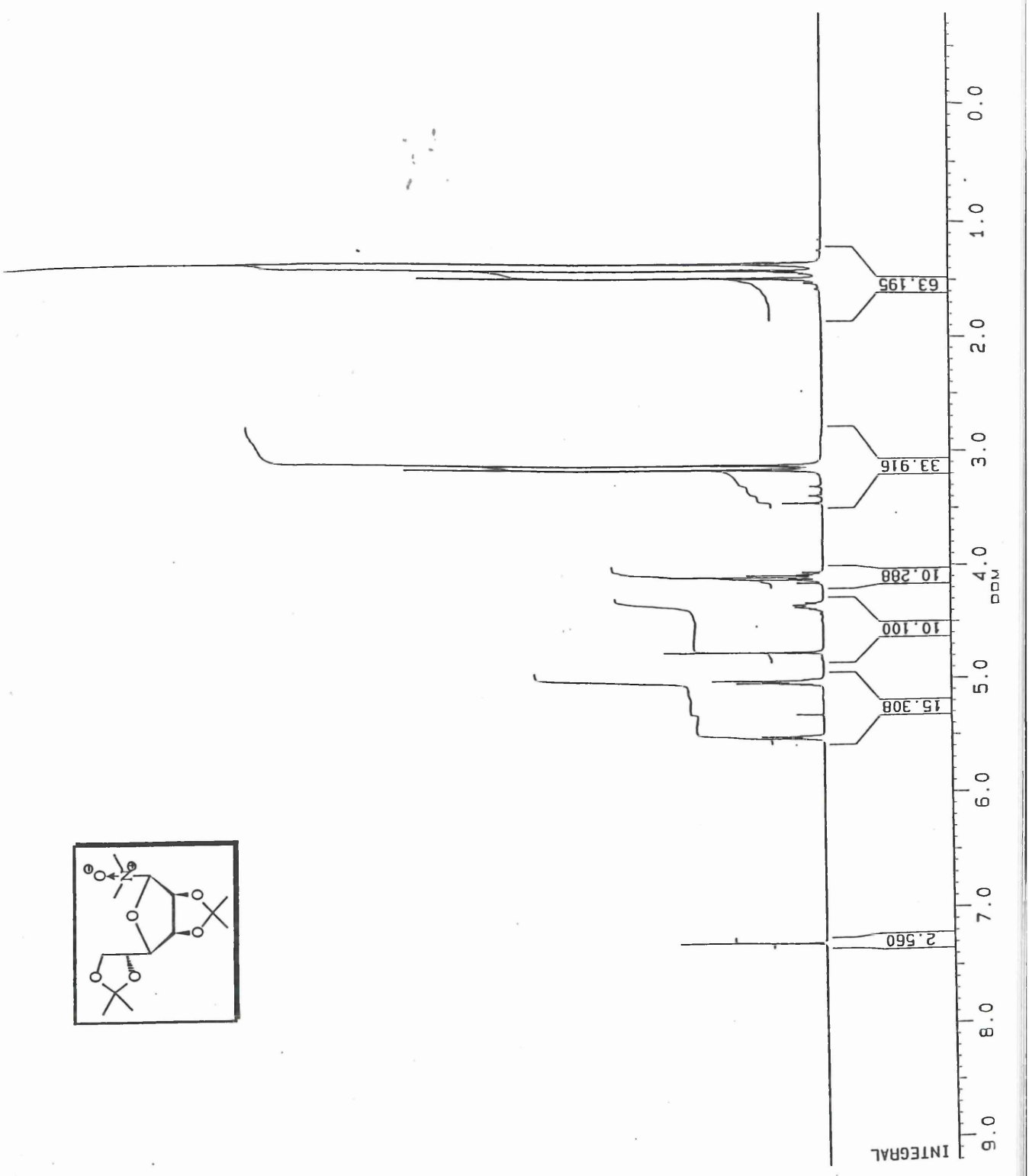


Figure 28 ^{1}H n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-*N,N*-dimethyl-β-D-mannofuranosyl amine-*N*-oxide 57

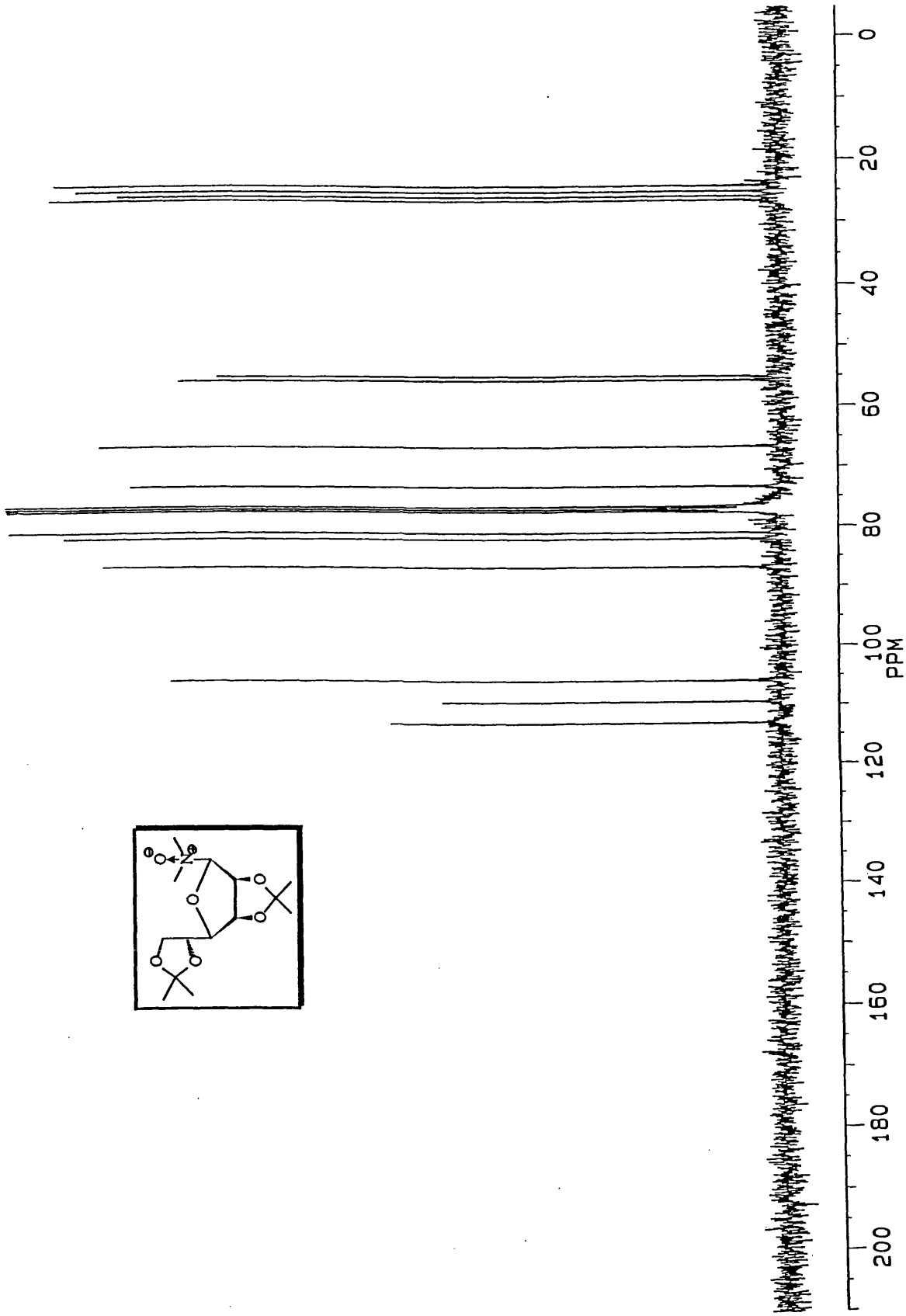


Figure 29 ^{13}C n.m.r. spectrum of 2,3:5,6-di-*O*-isopropylidene-*N,N*-dimethyl-*β*-D-mannofuranosyl amine-*N*-oxide **57**

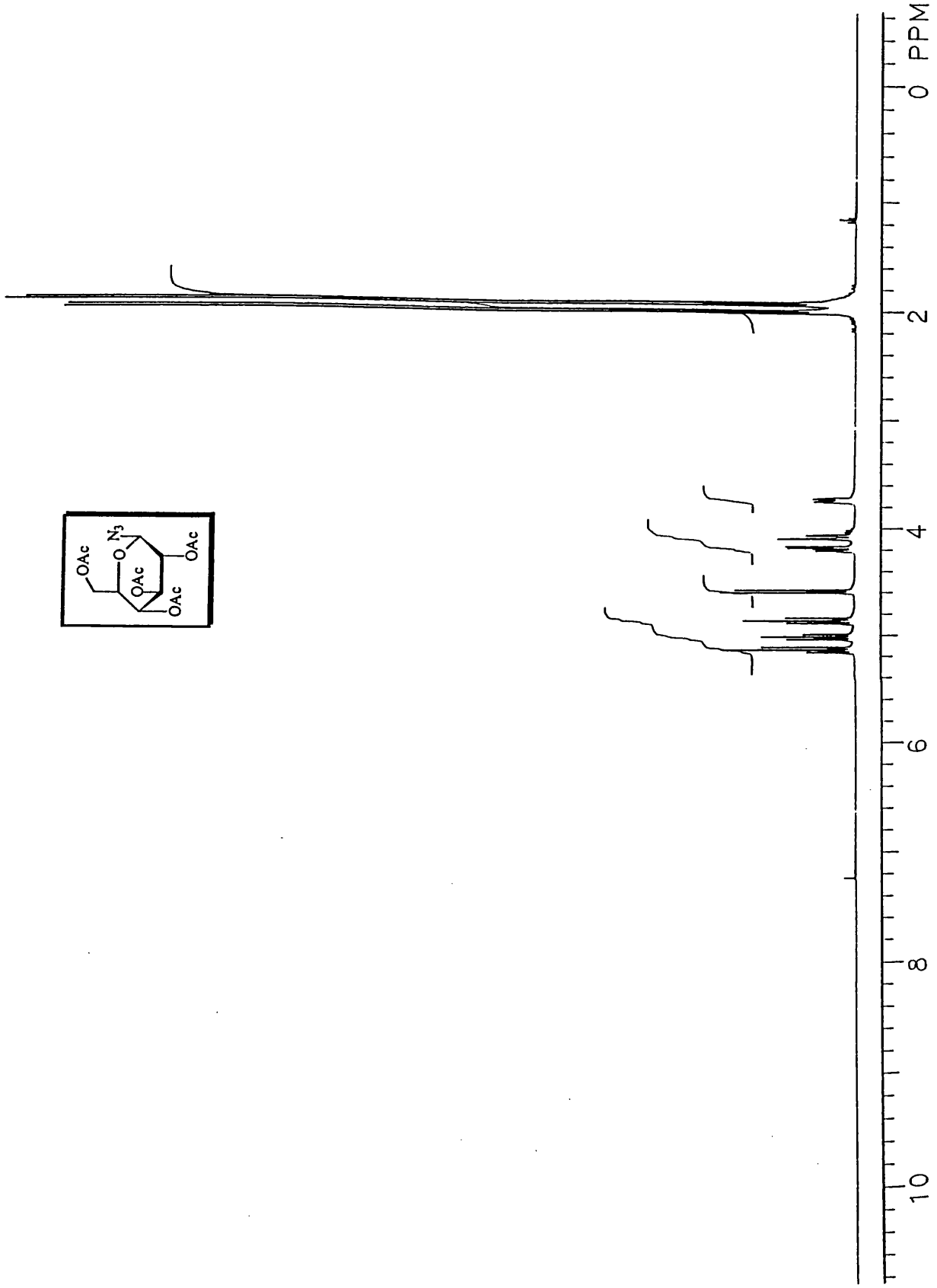


Figure 30 ^{1}H n.m.r. spectrum of 1,2,3,4,6-penta-*O*-acetyl-*β*-D-glucopyranosyl azide **62**

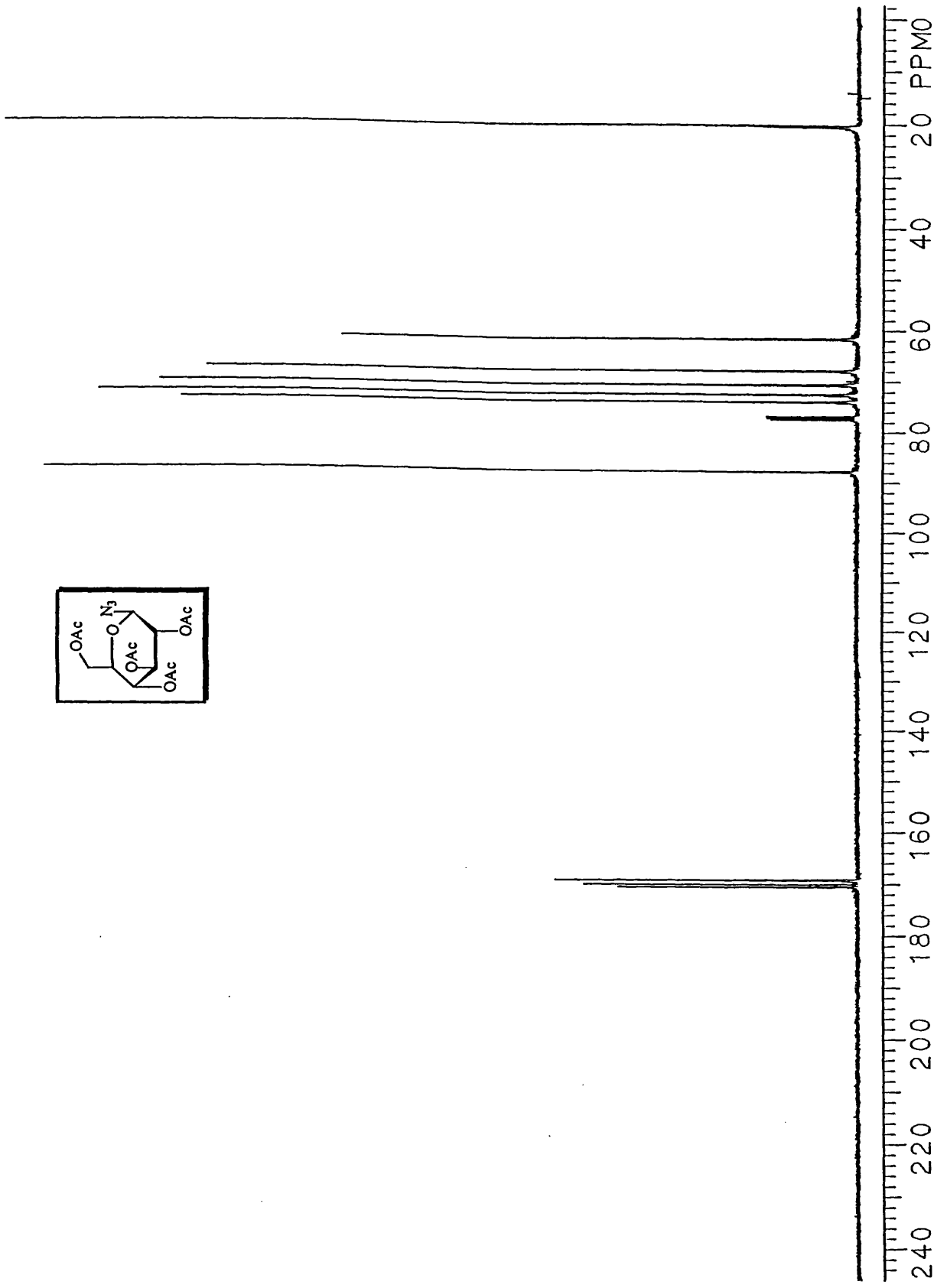


Figure 31 ^{13}C n.m.r. spectrum of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl azide **62**

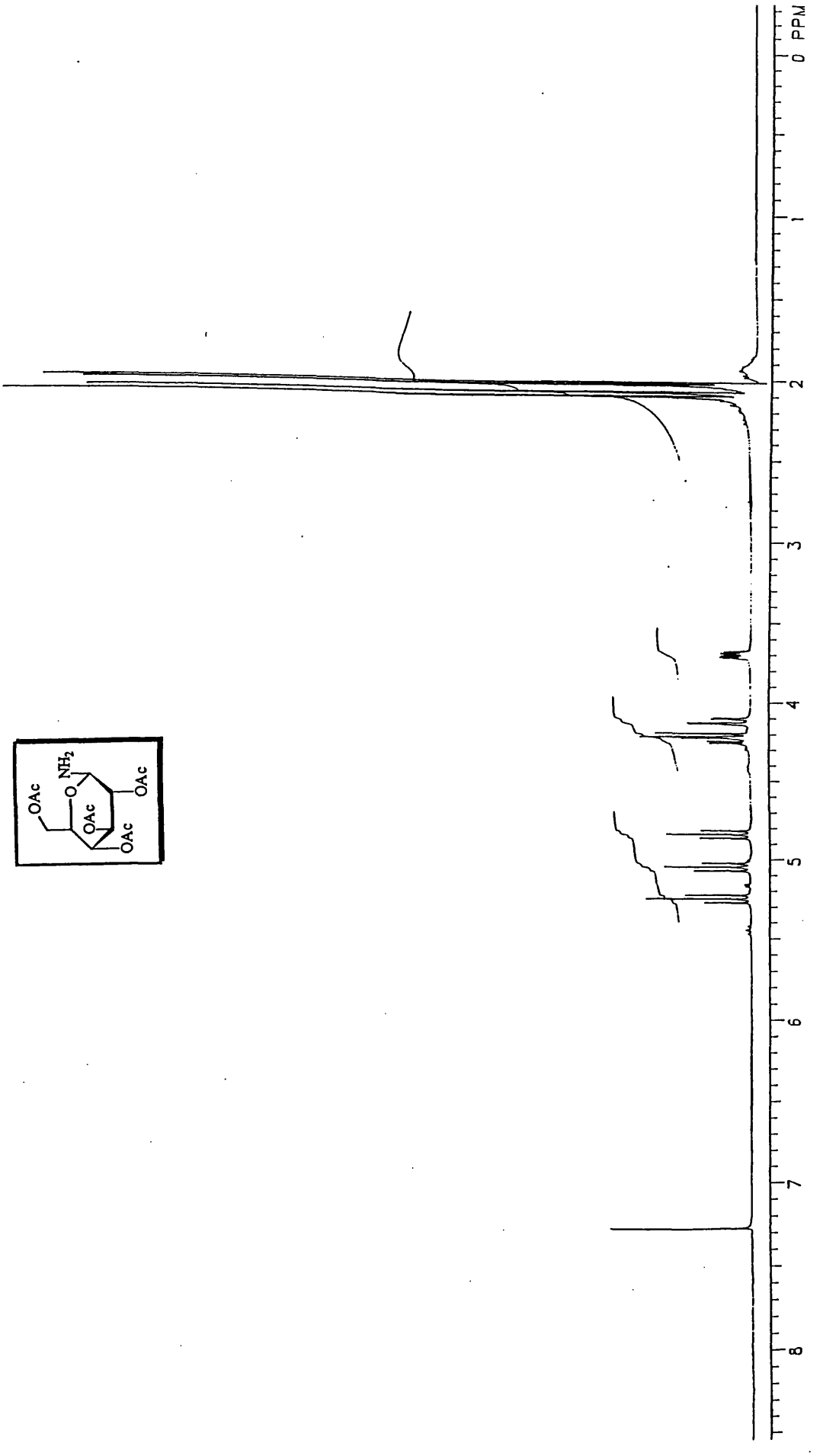


Figure 32 ^{1}H n.m.r. spectrum of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl amine **63**

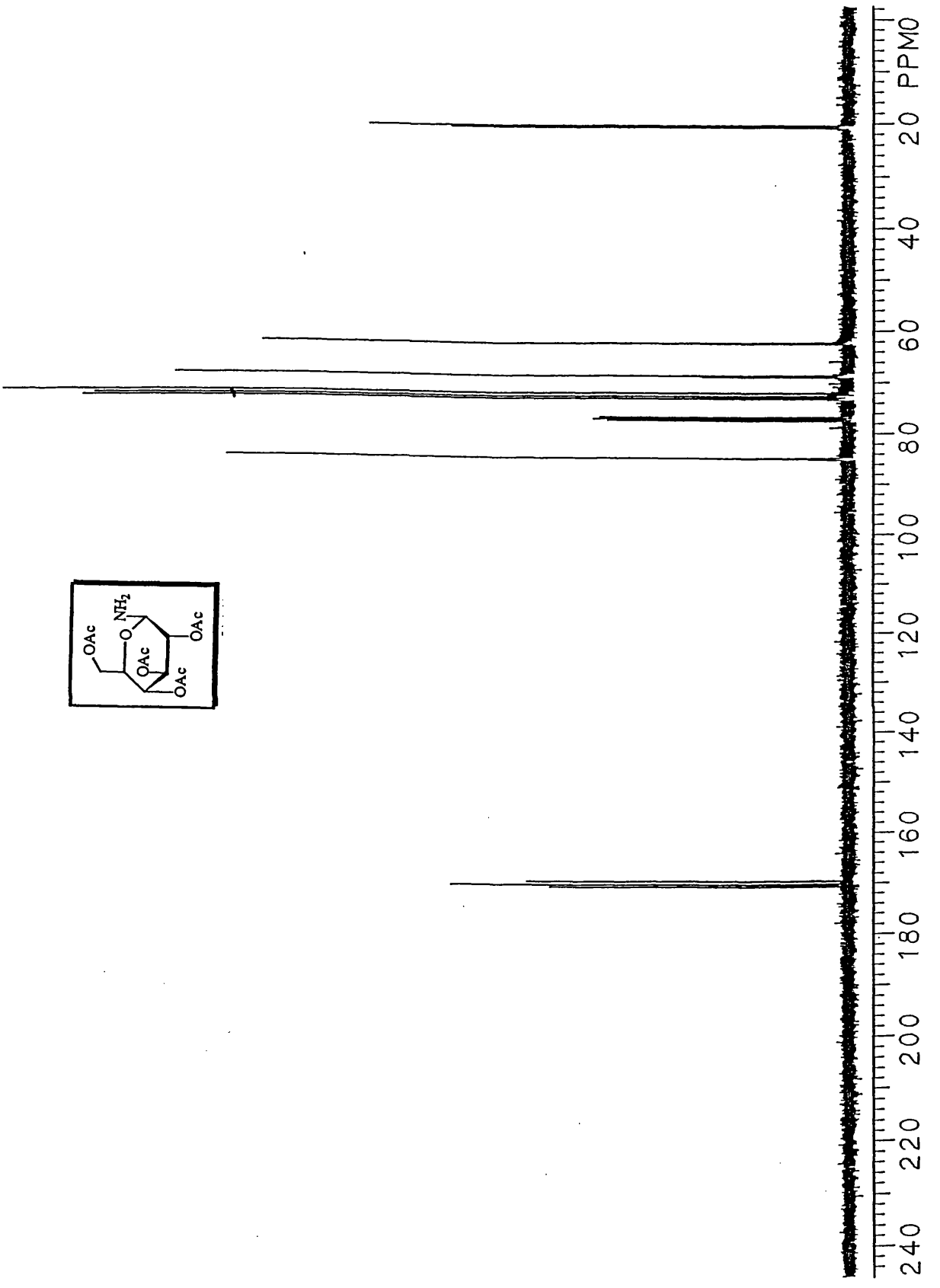


Figure 33 ^{13}C n.m.r. spectrum of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl amine **63**

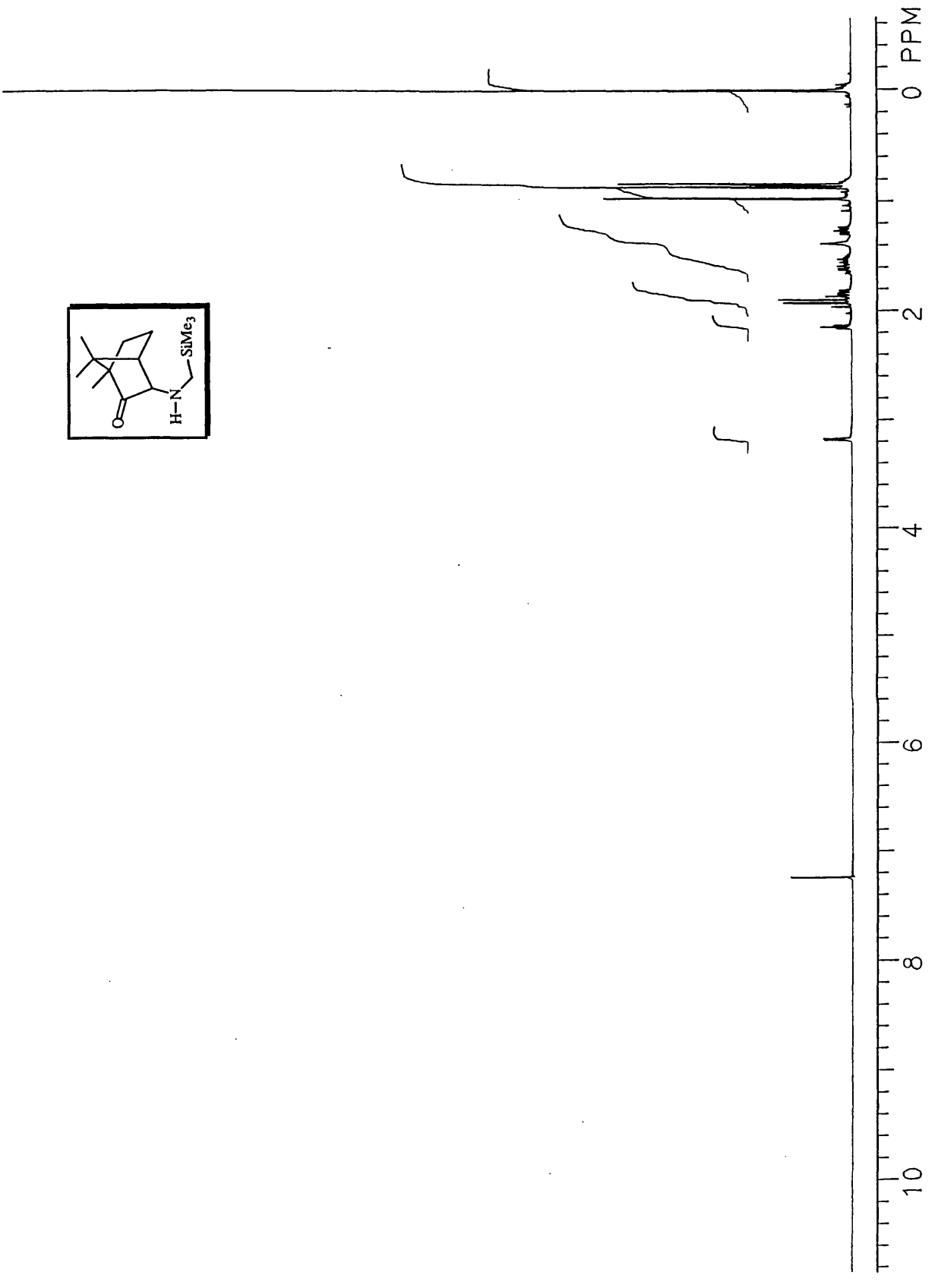


Figure 34 ^{1}H n.m.r. spectrum of (1*R*)-*endo*-3-(*N*-trimethylsilyl methyl)-camphor amine **80**

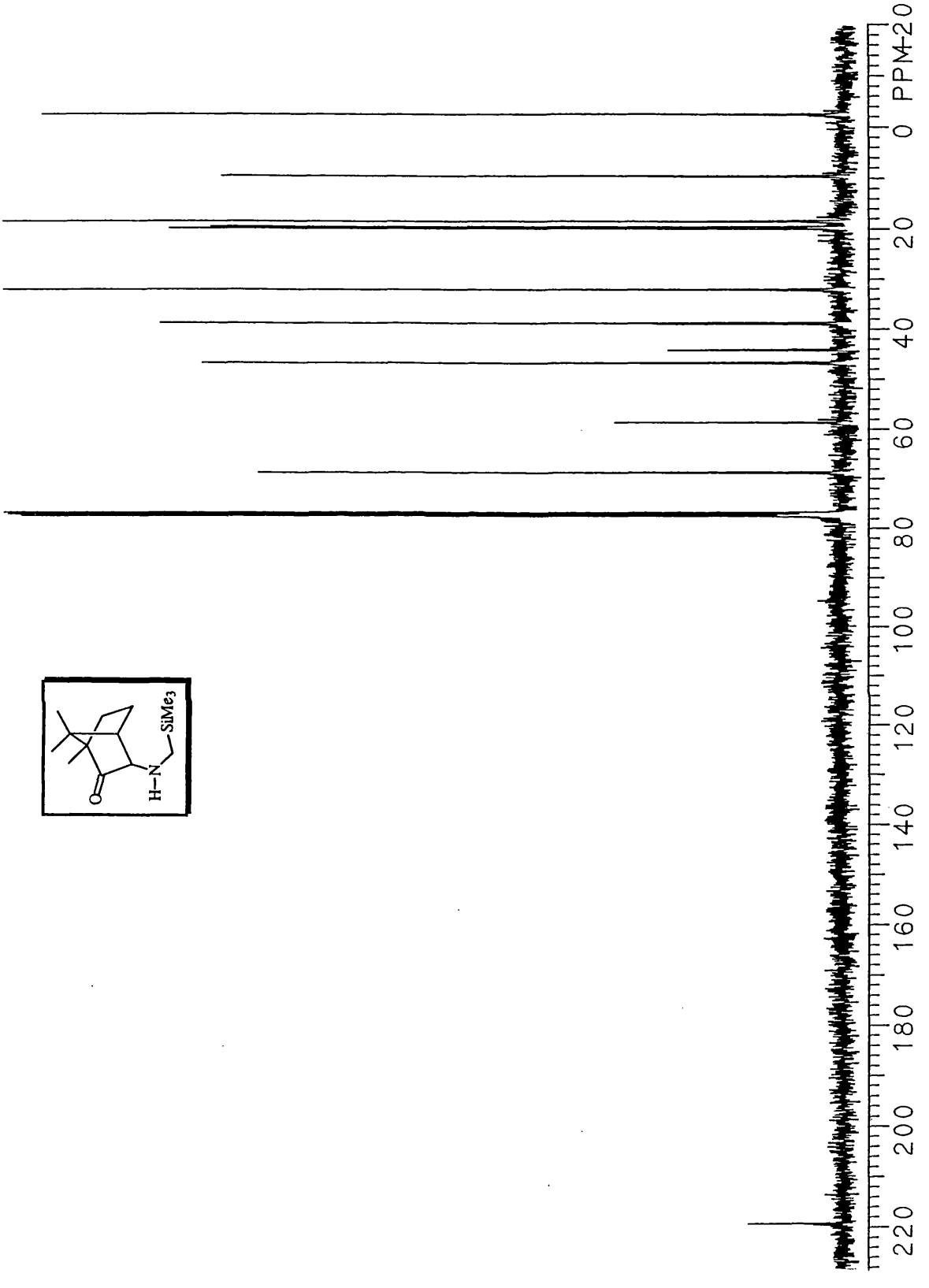


Figure 35 ^{13}C n.m.r. spectrum of (1*R*)-*endo*-3-(*N*-trimethylsilyl methyl)-camphor amine **80**

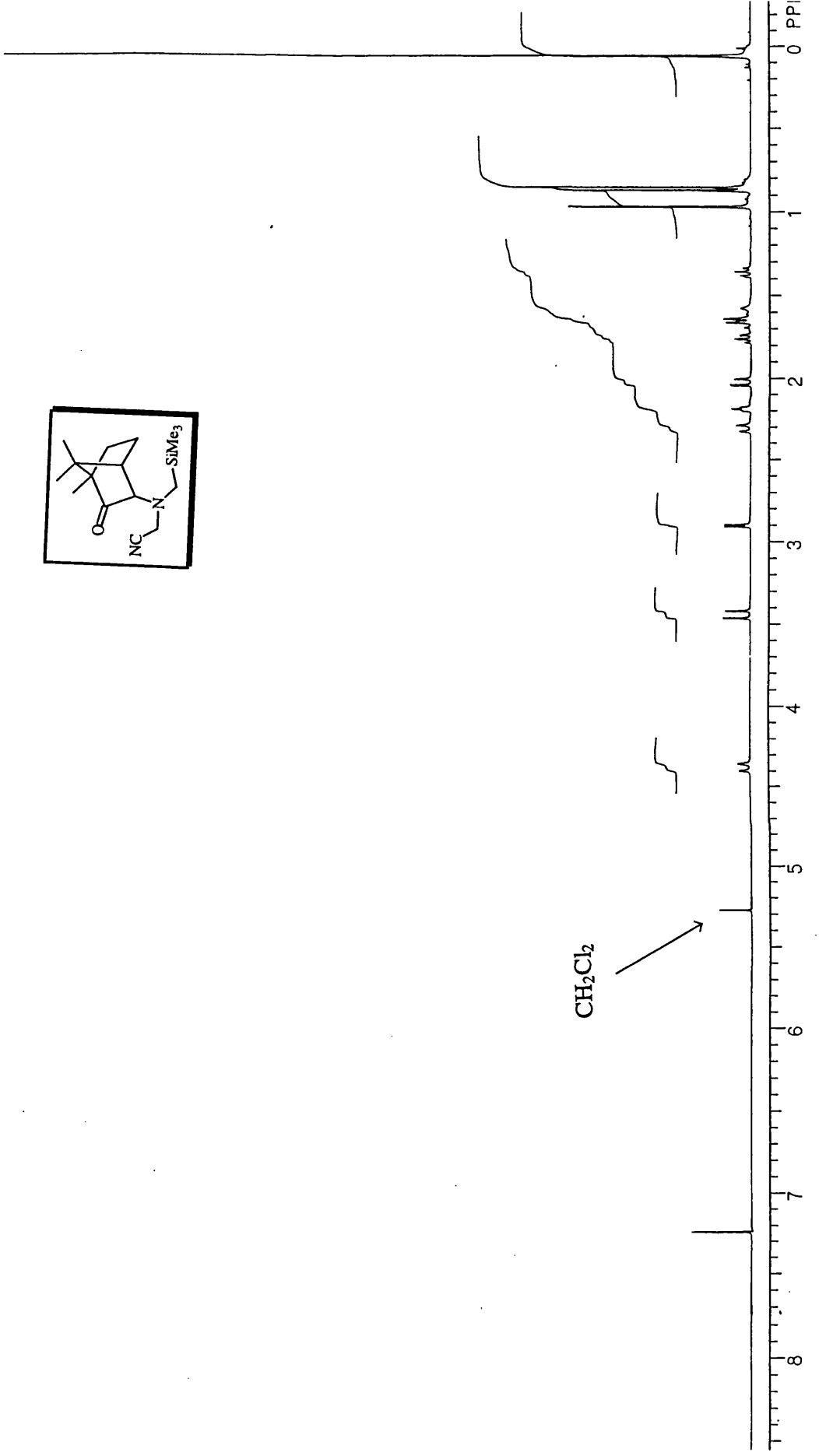


Figure 36 ^{1}H n.m.r. spectrum of (1*R*)-(+)-*endo*-3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)camphor amine **81**

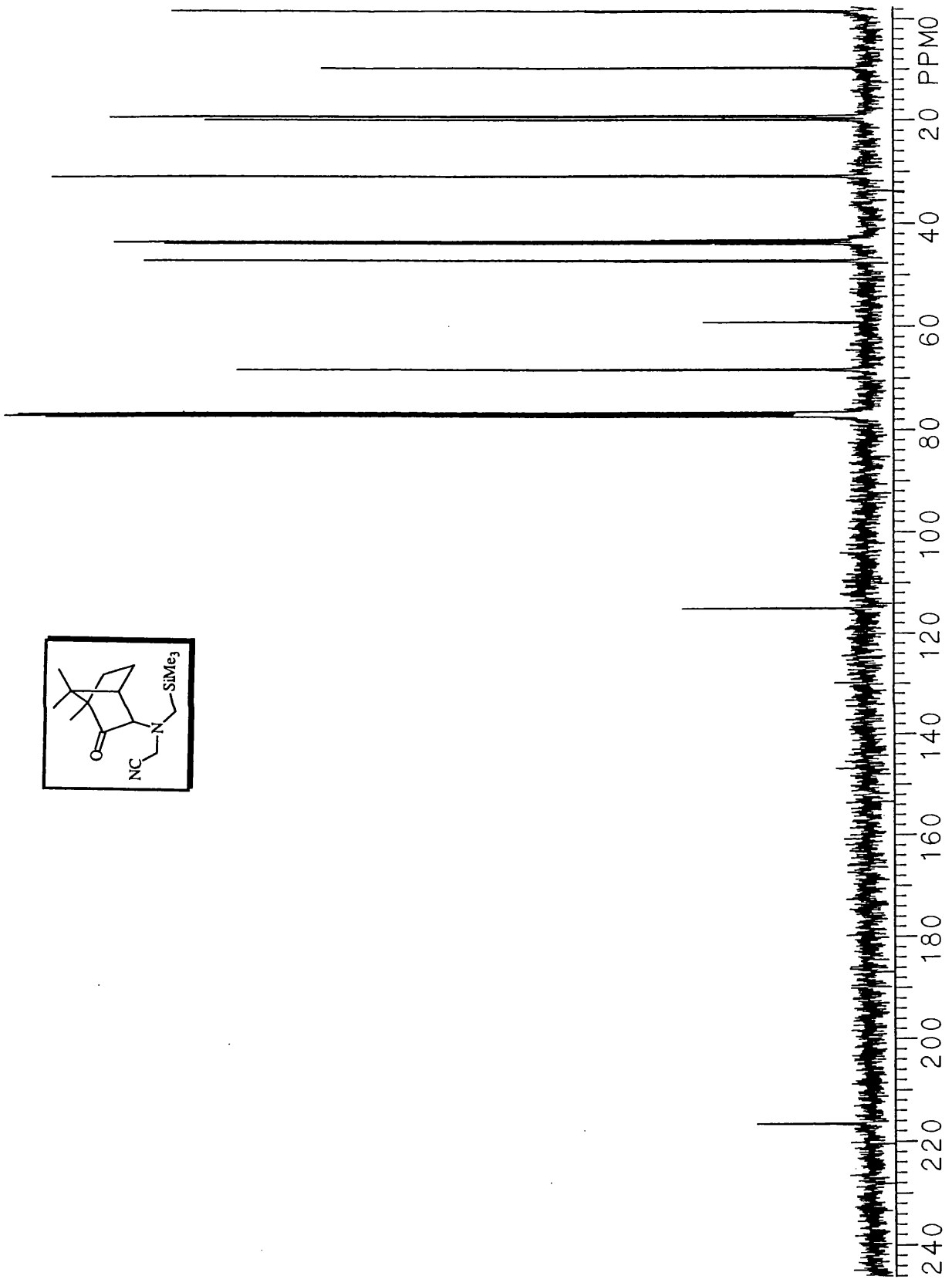


Figure 37 ^{13}C n.m.r. spectrum of (1*R*)-(+)-*endo*-3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)camphor amine **81**

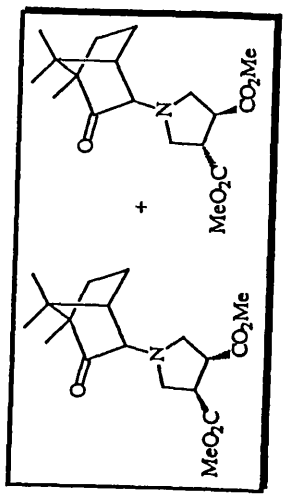


Figure 38 ^{1}H n.m.r. spectrum of (1*R*)-(+)-(*trans*-3,4-dicarbomethoxy)-*N*-(*endo*-3-camphor)pyrrolidine **82+83**

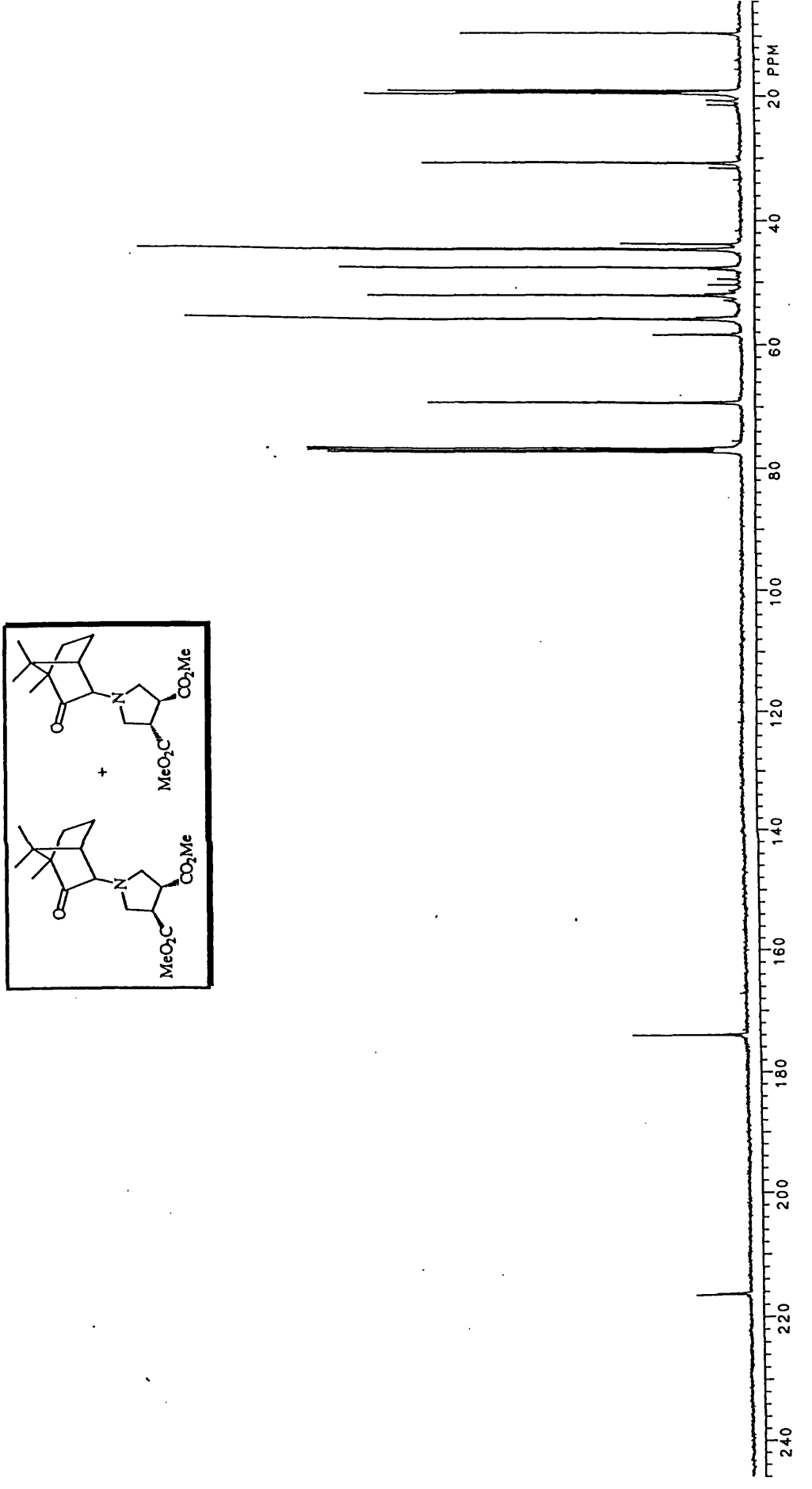


Figure 39 ^{13}C n.m.r. spectrum of (1*R*)-(+)-(*trans*-3,4-dicarbomethoxy)-*N*-(*endo*-3-camphor)pyrrolidine **82+83**

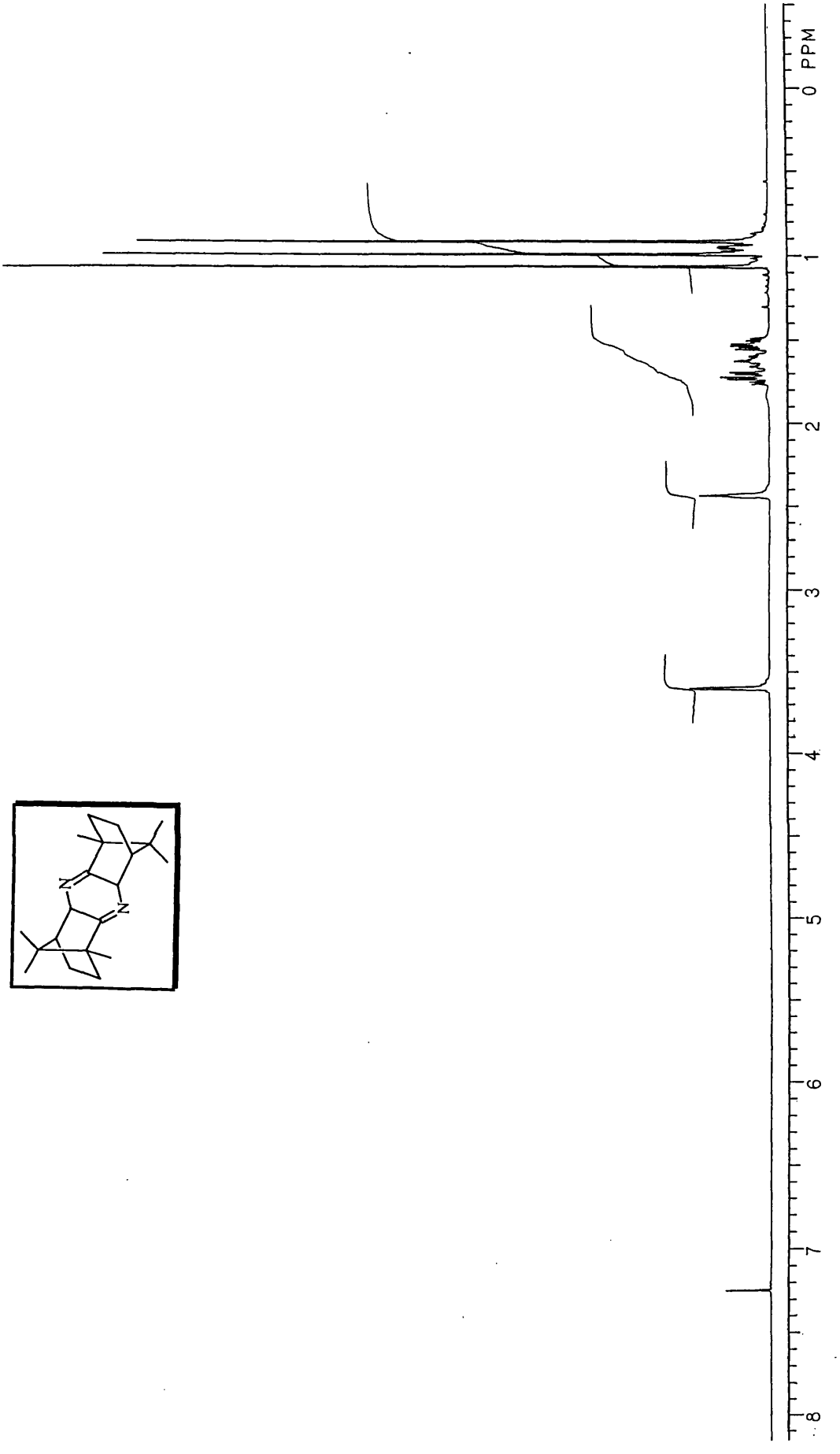


Figure 40 ^{1}H n.m.r. spectrum of 1,6,11,11,12,12-hexamethyl-1,2,3,4,4a,6,7,8,9,9a-decahydro-1,4;6,9-dimethano-phenazine **87**

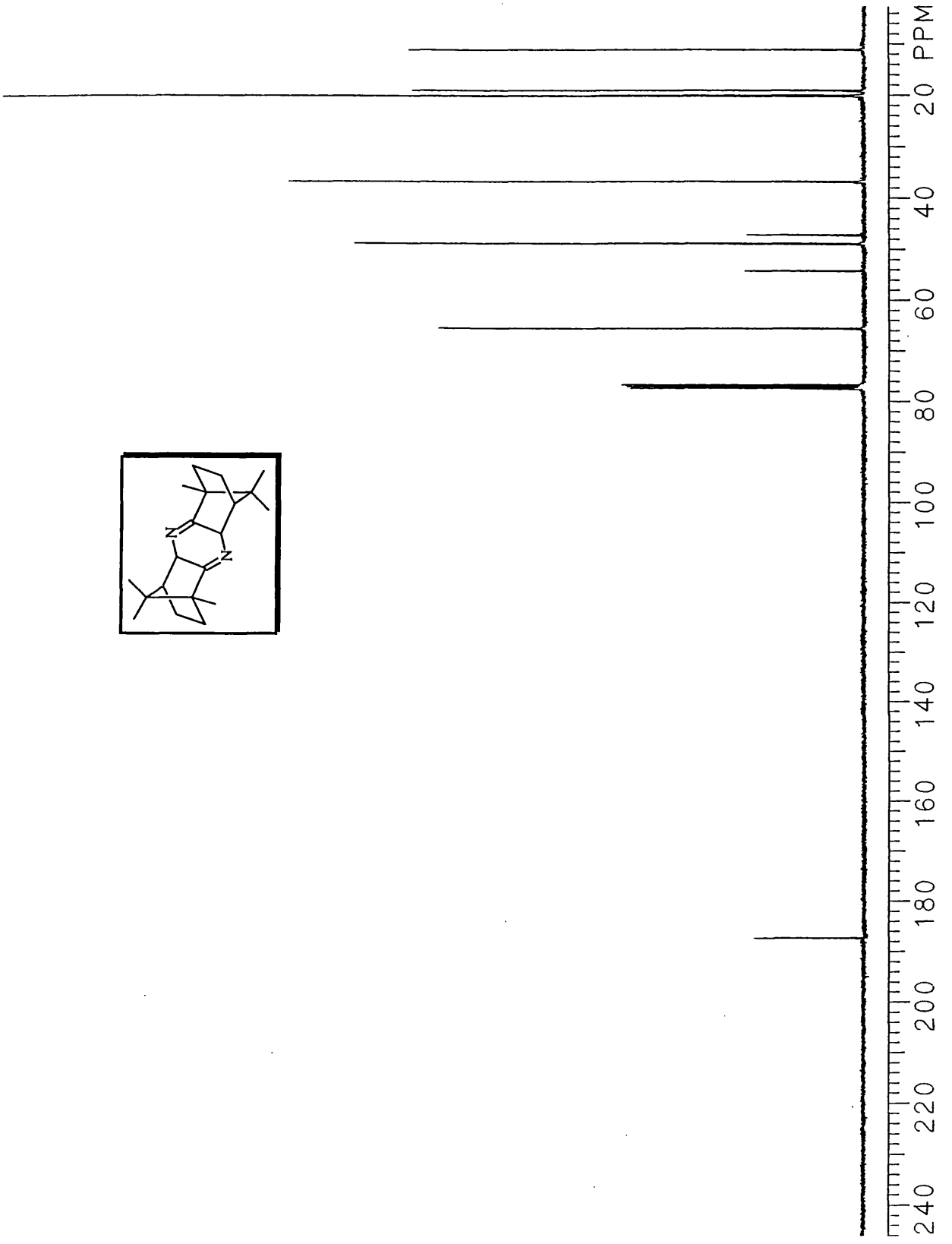


Figure 41 ^{13}C n.m.r. spectrum of 1,6,11,11,12,12-hexamethyl-1,2,3,4,4a,6,7,8,9,9a-decahydro-1,4;6,9-dimethano-phenazine **87**

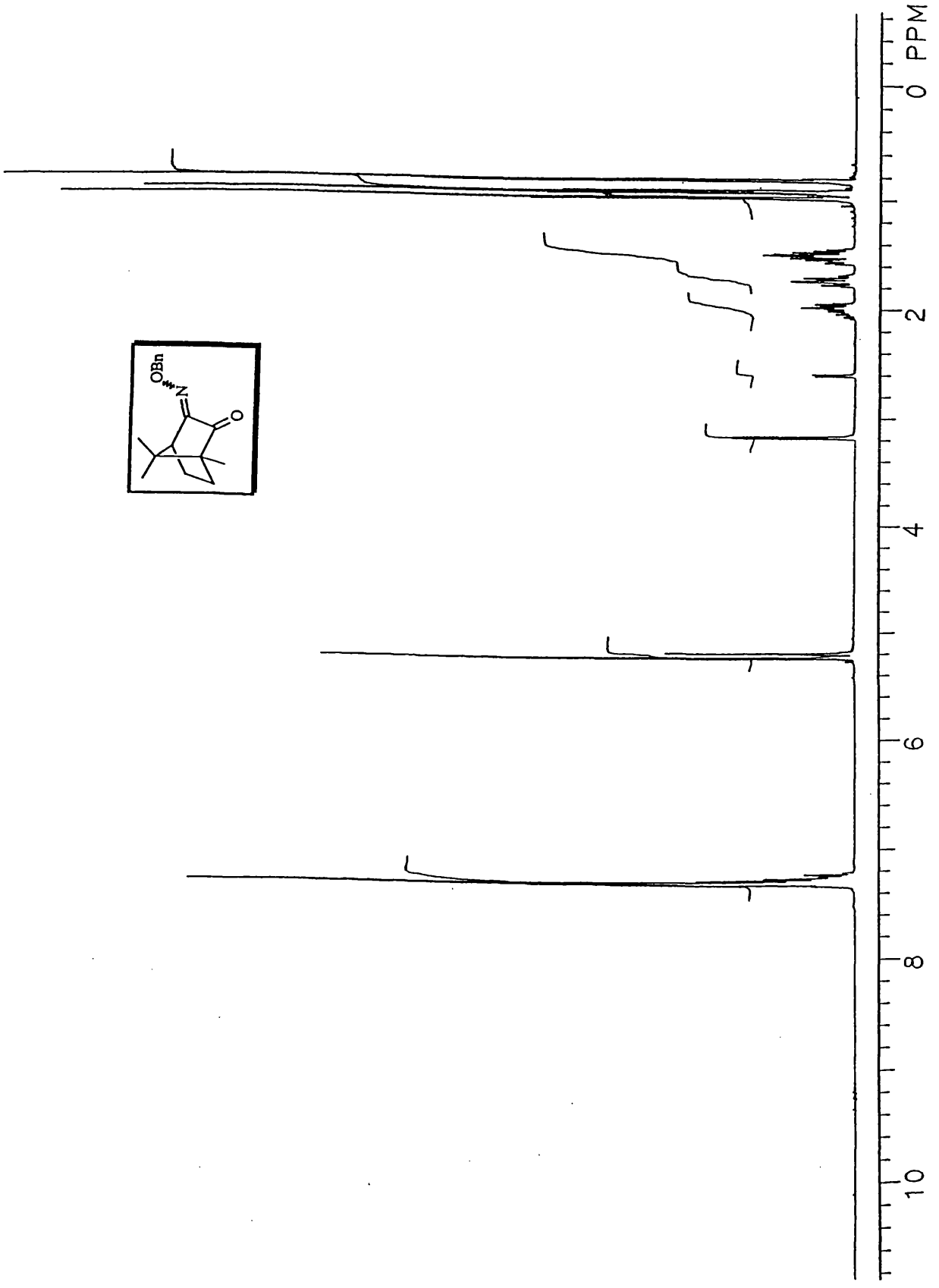


Figure 42 ^{1}H n.m.r. spectrum of (1*R*)-camphorquinone-3-*O*-benzyl-oxime **94**

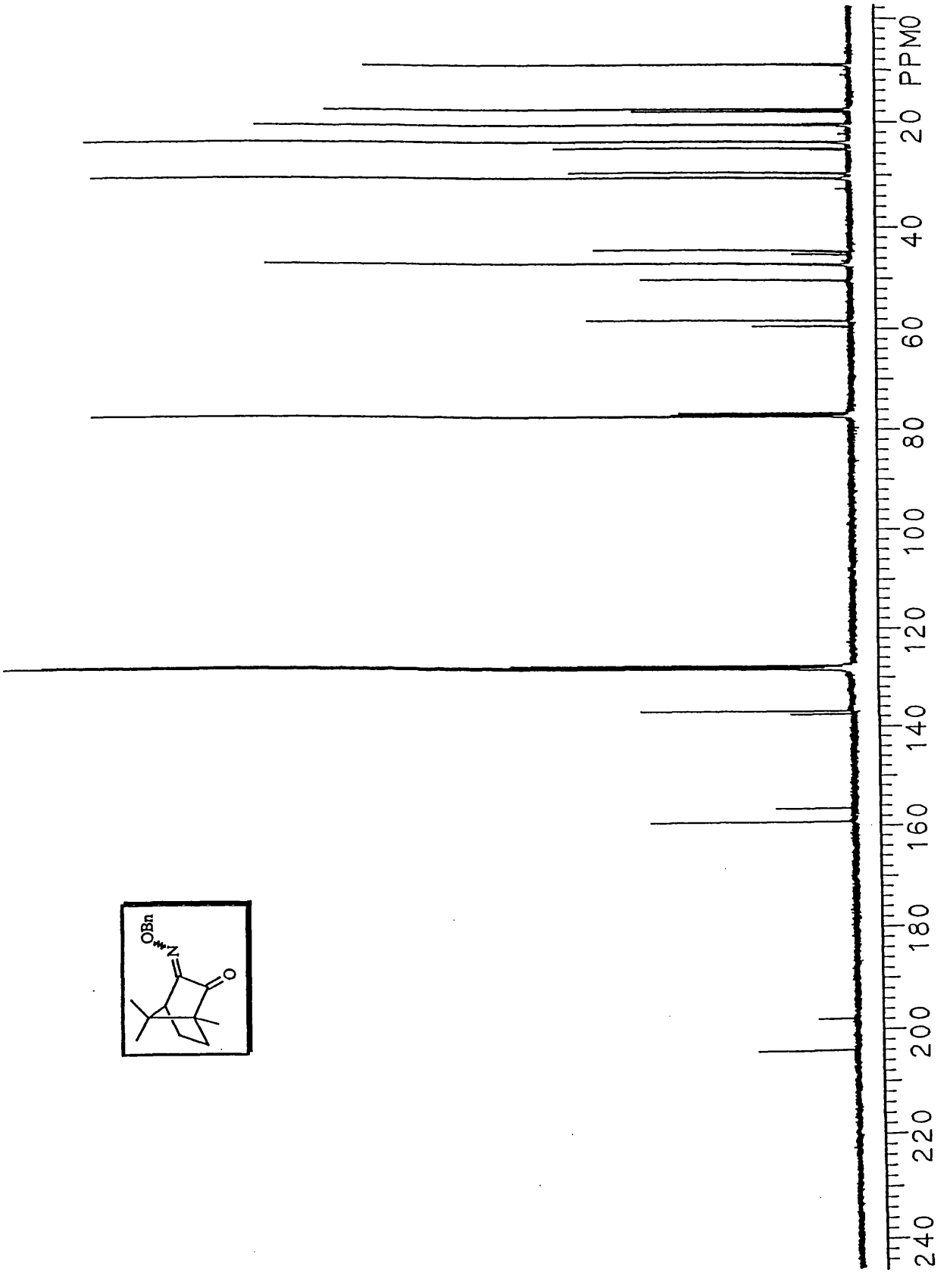


Figure 43 ^{13}C n.m.r. spectrum of (1*R*)-camphorquinone-3-*O*-benzyl-oxime **94**

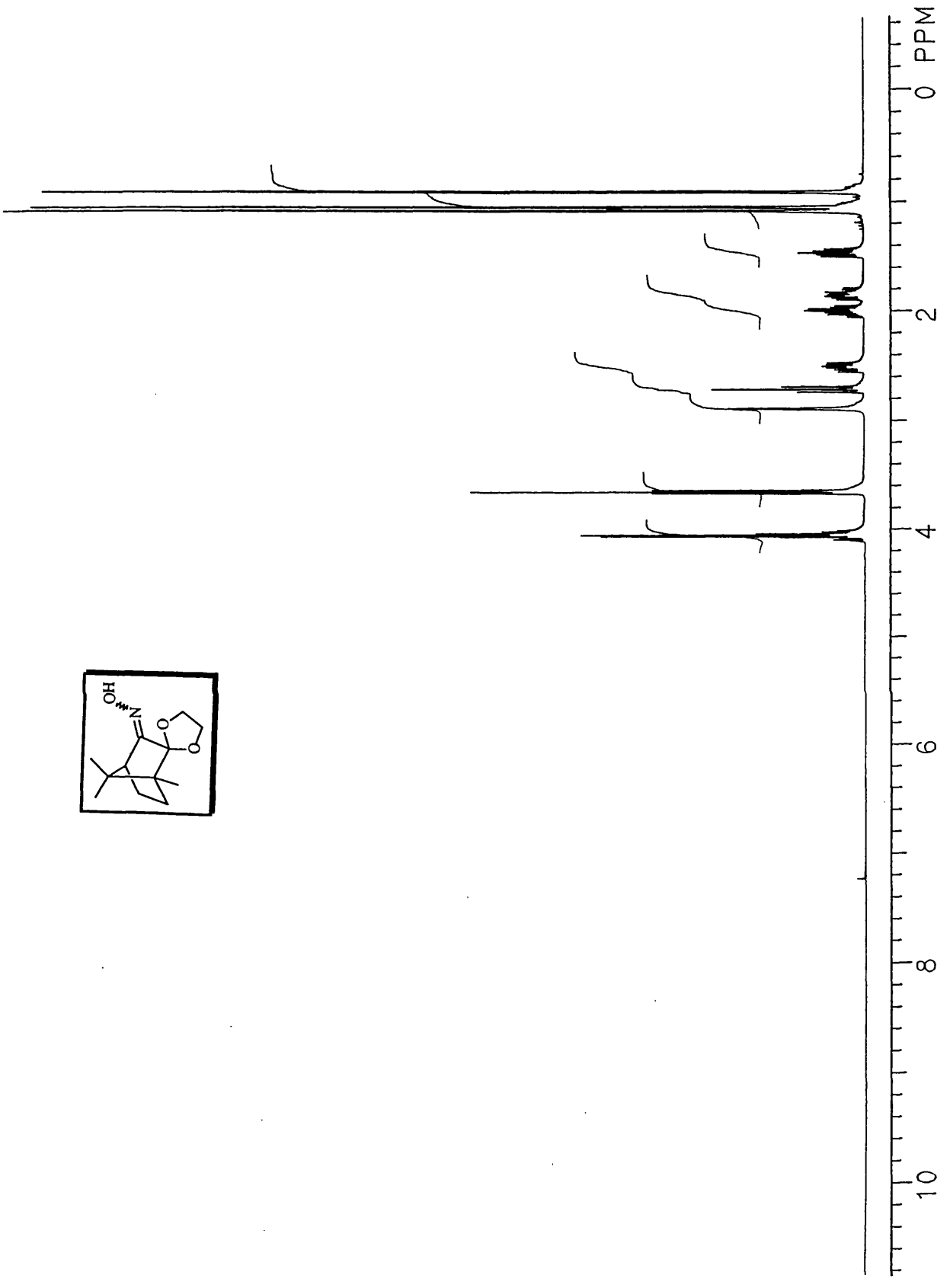


Figure 44 ^{1}H n.m.r. spectrum of (1*R*)-2,2-ethylenedioxy-camphorquinone-3-oxime **99**

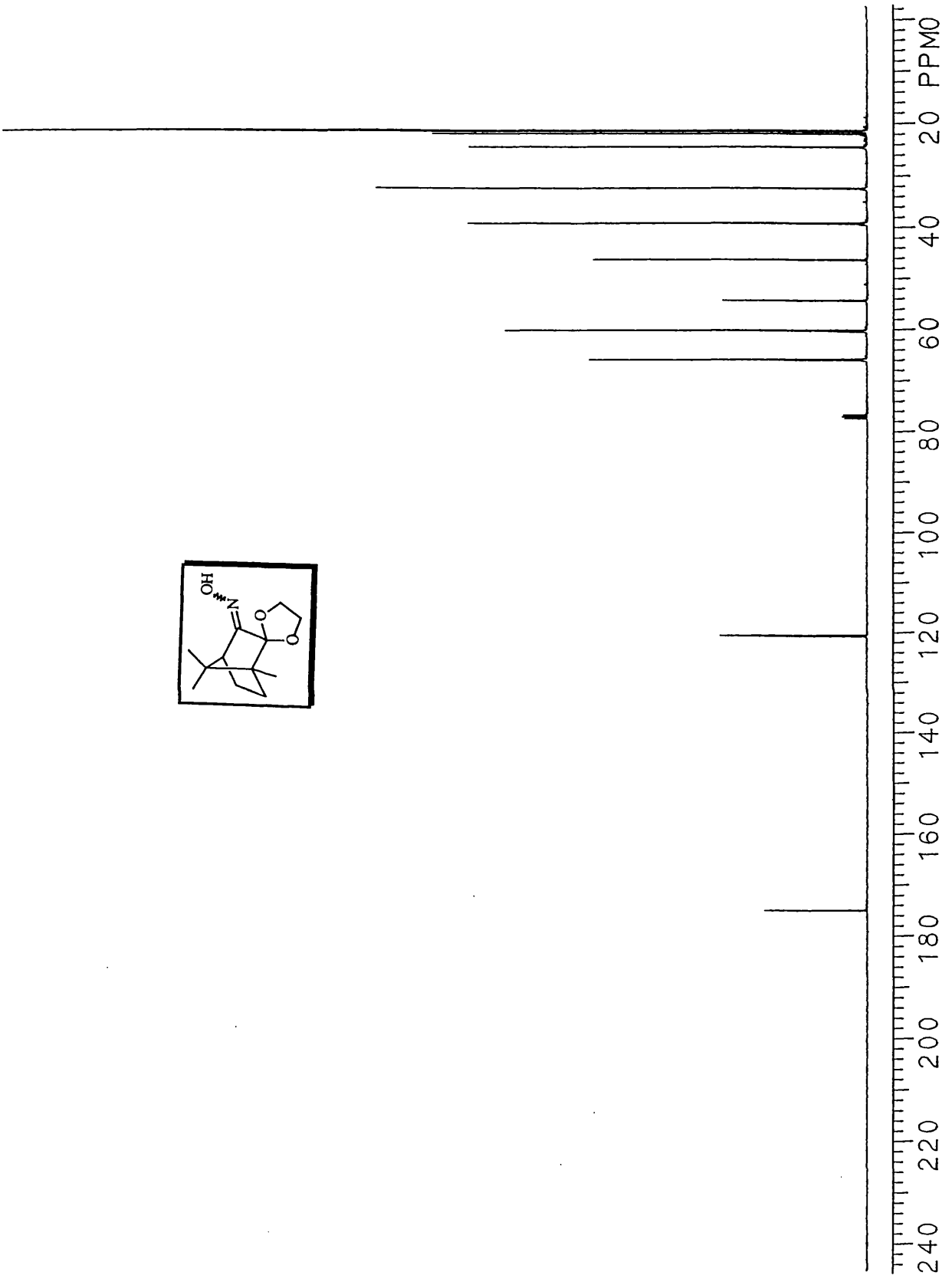


Figure 45 ^{13}C n.m.r. spectrum of (1*R*)-2,2-ethylenedioxy-camphorquinone-3-oxime **99**

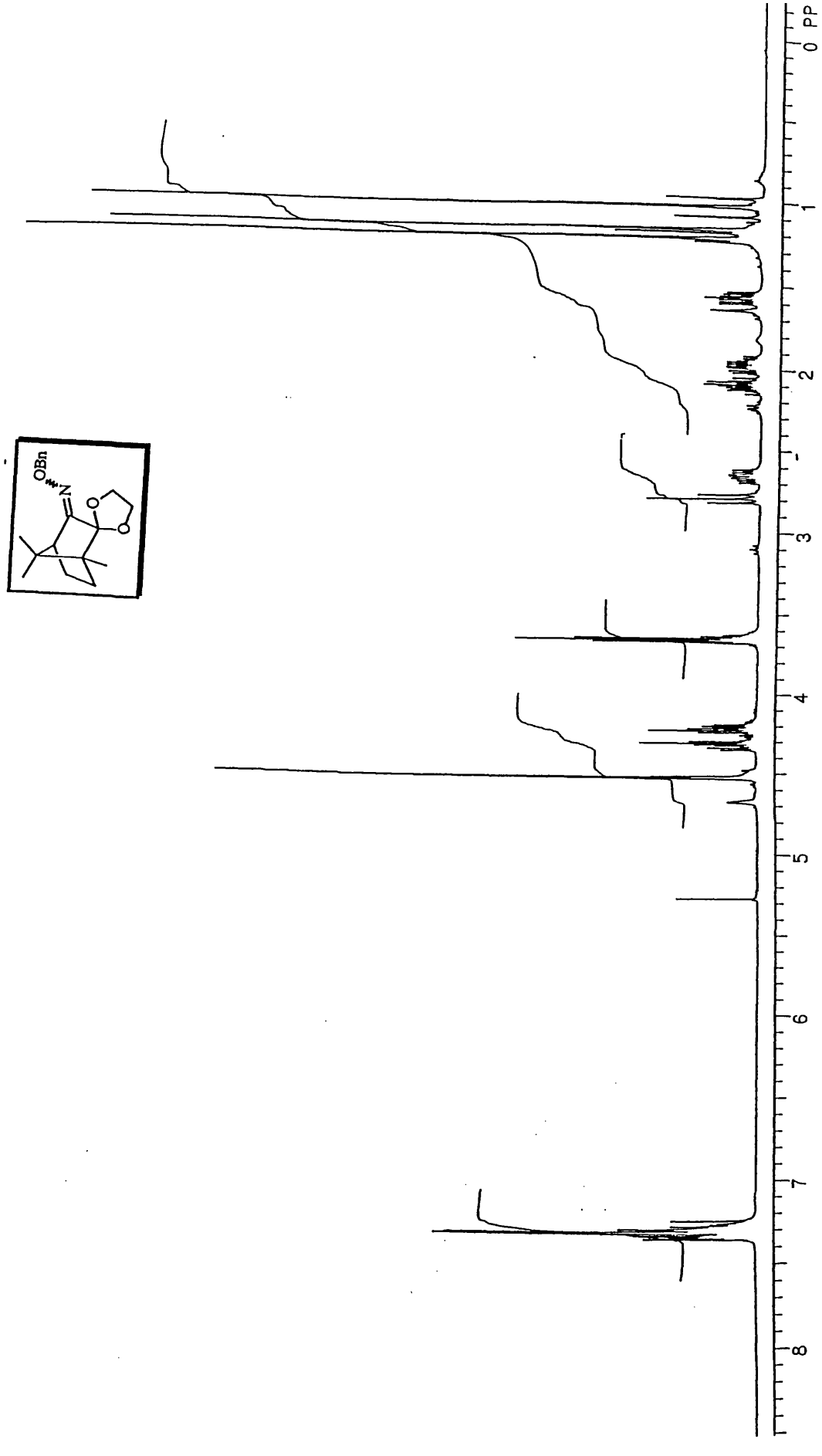


Figure 46 ^{1}H n.m.r. spectrum of (1*R*)-2,2-ethylenedioxy-camphorquinone-3-*O*-benzyl oxime **95**

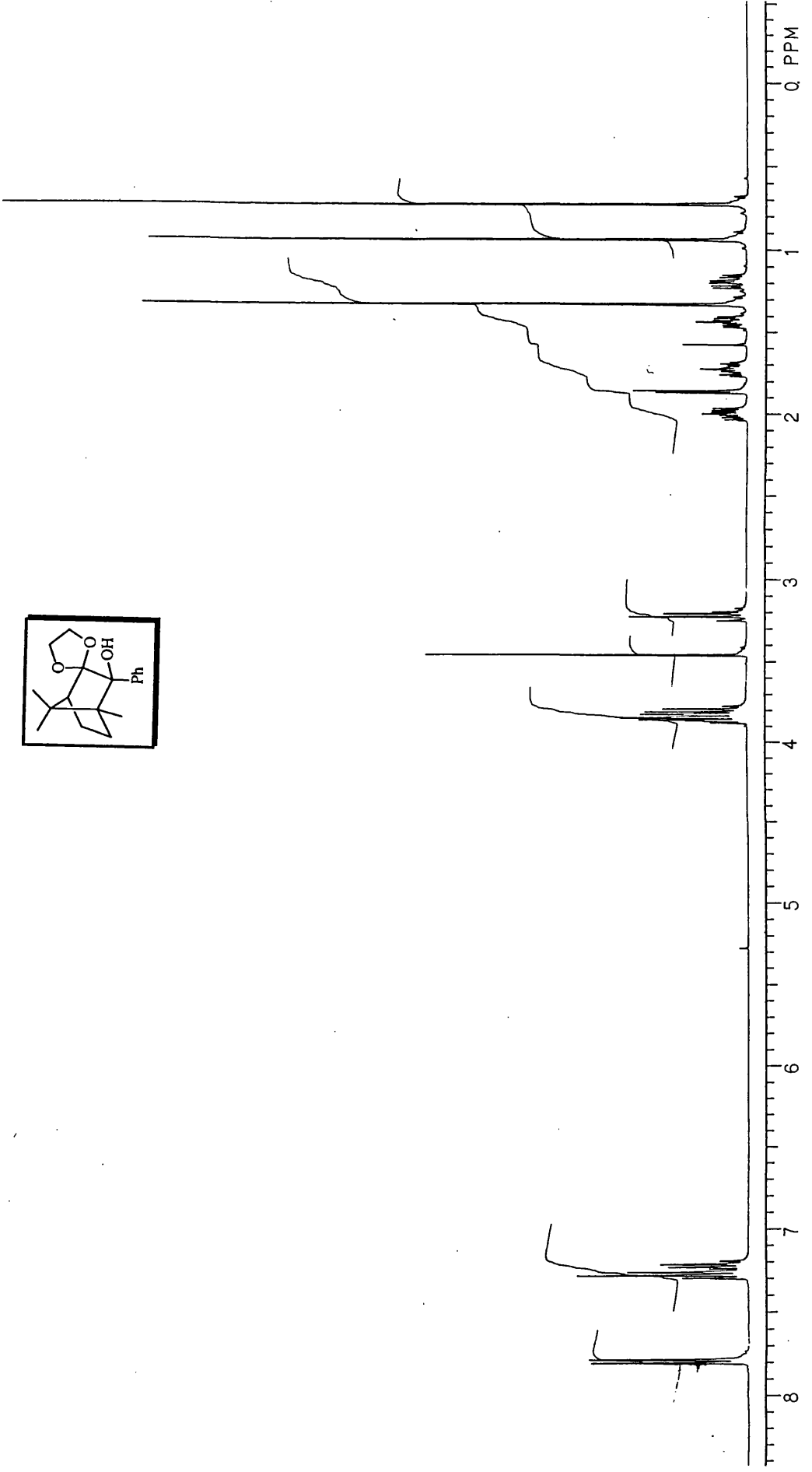


Figure 47 ^{1}H n.m.r. spectrum of (1*R*)-2-*exo*-hydroxy-2-*endo*-phenyl-3,3-ethylene-dioxycamphor **100**

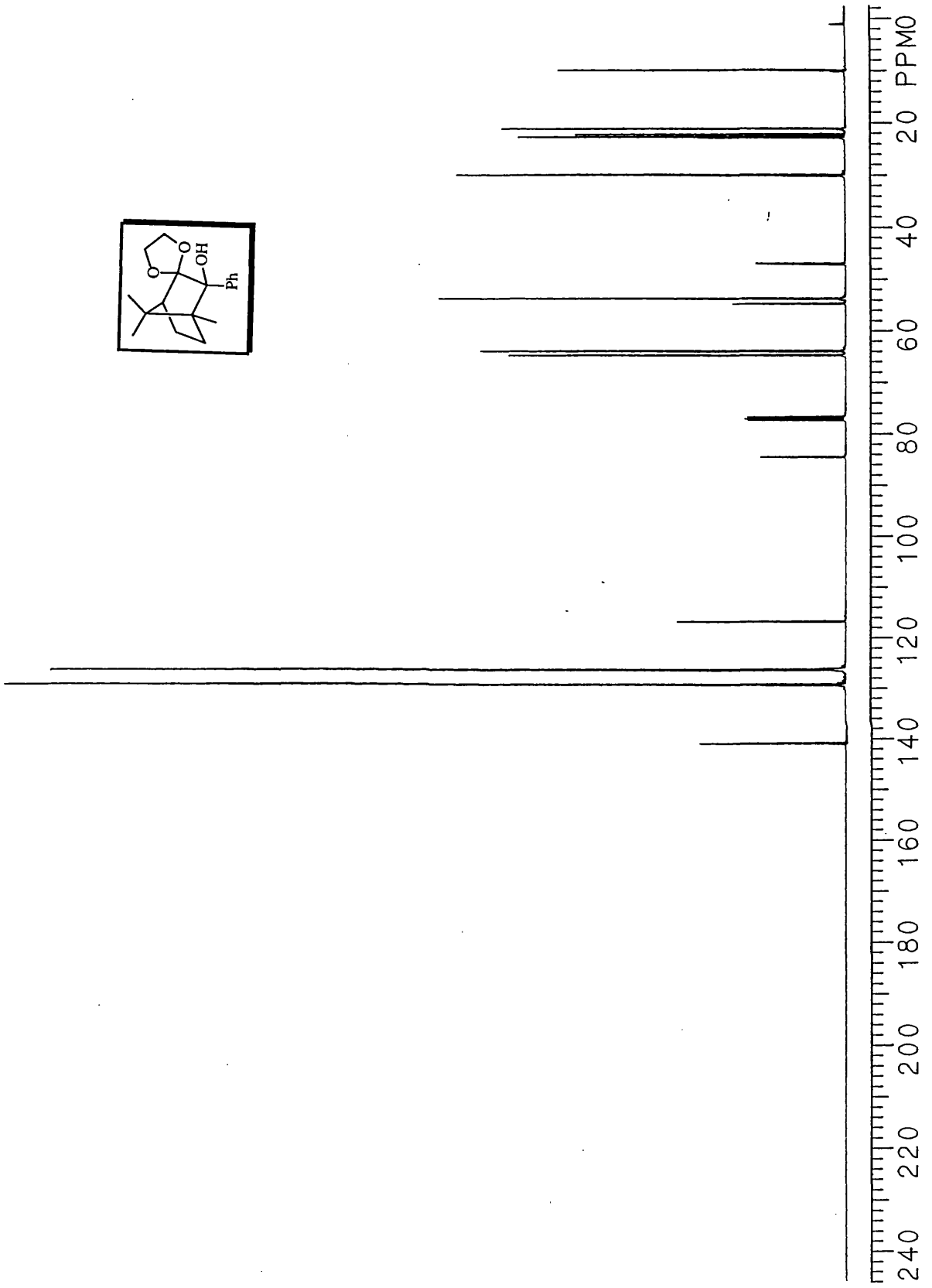


Figure 48 ^{13}C n.m.r. spectrum of (1*R*)-2-*exo*-hydroxy-2-*endo*-phenyl-3,3-ethylene-dioxycamphor **100**

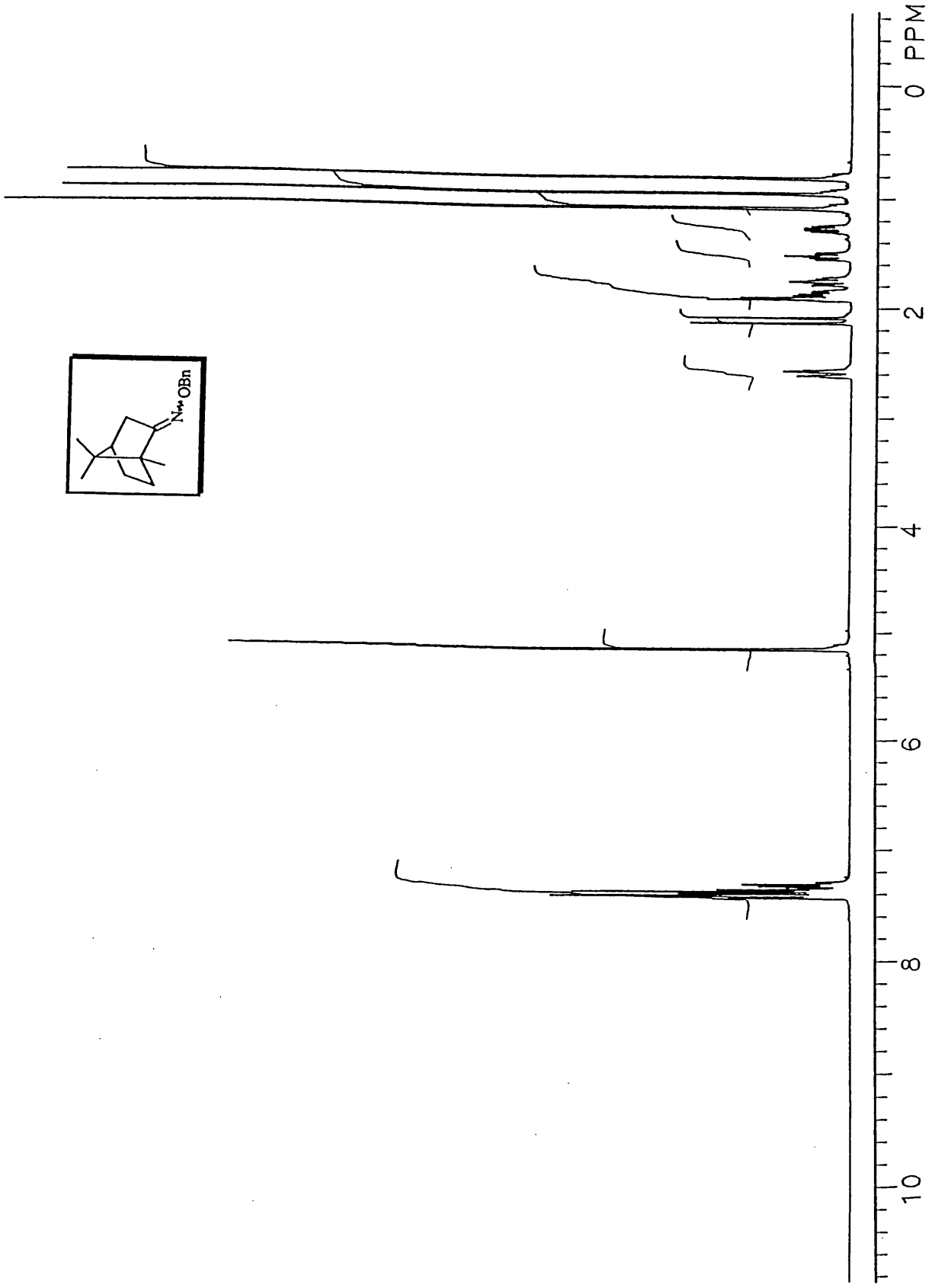


Figure 49 ^{1}H n.m.r. spectrum of (1*R*)-camphor-2-*O*-benzyl oxime **102**

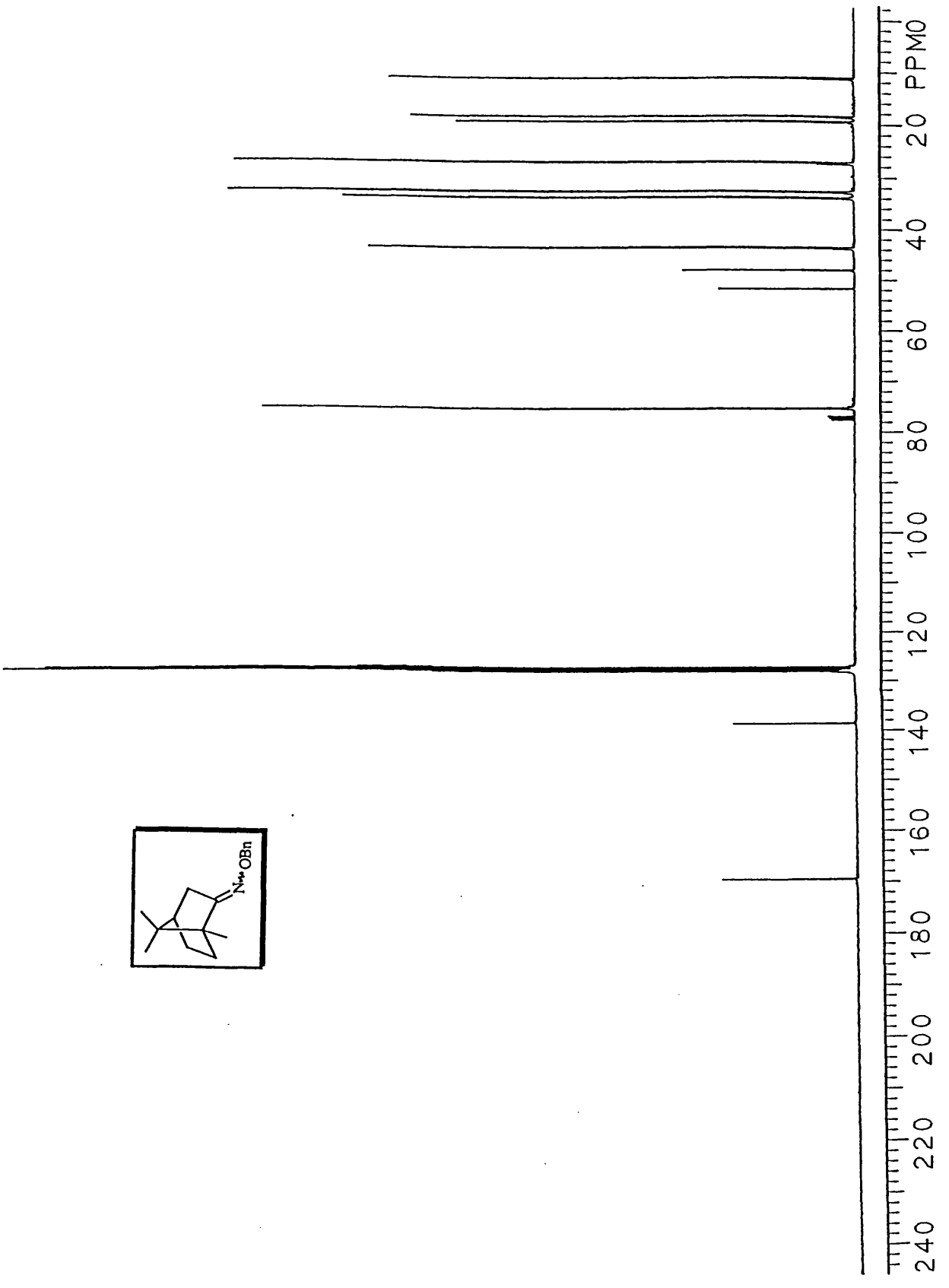


Figure 50 ^{13}C n.m.r. spectrum of (1*R*)-camphor-2-*O*-benzyl oxime **102**

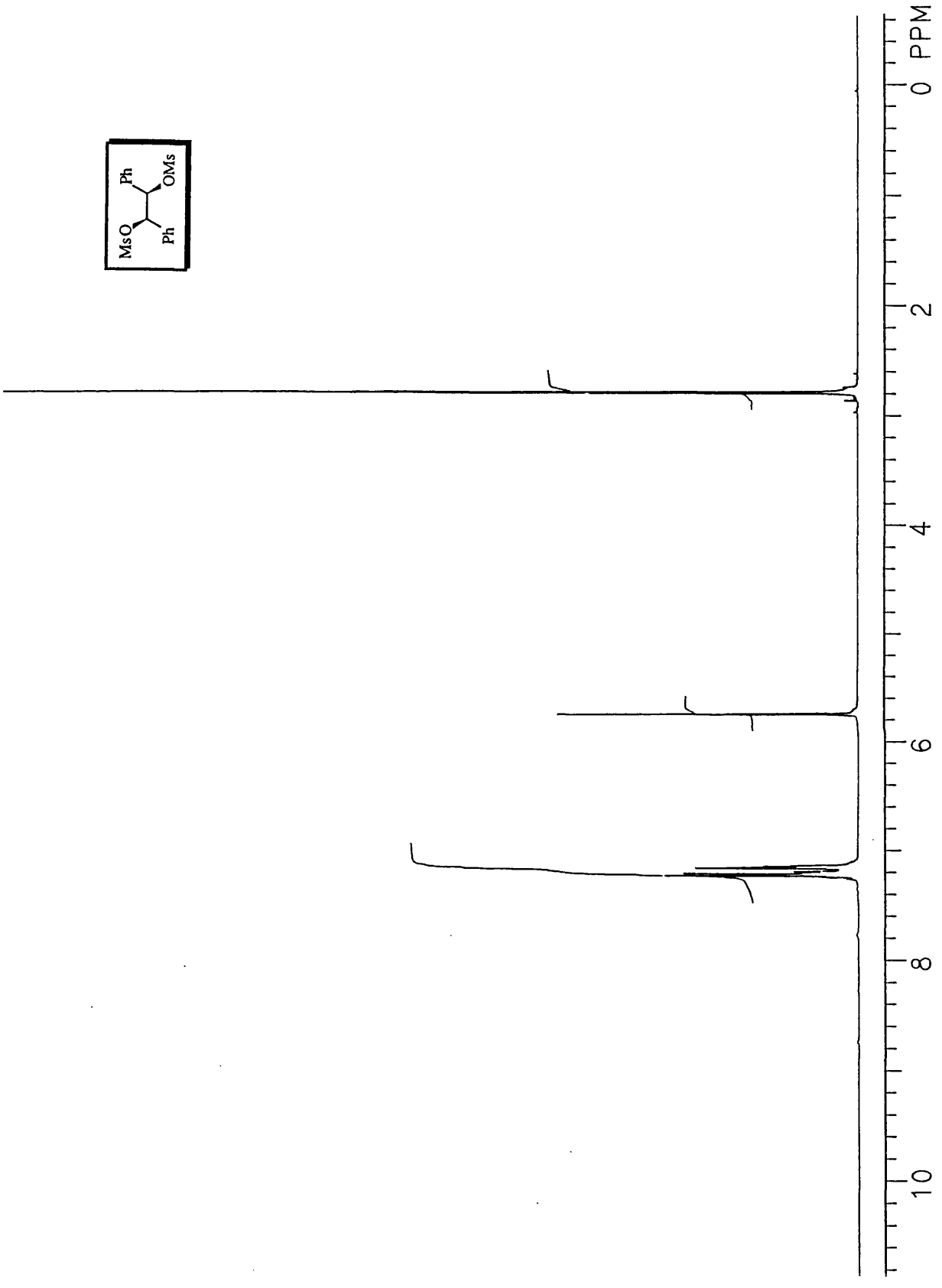


Figure 51 ^{1}H n.m.r. spectrum of (1*R*,2*R*)-(-)-1,2-diphenyl-1,2-dimesyloxyethane **119**

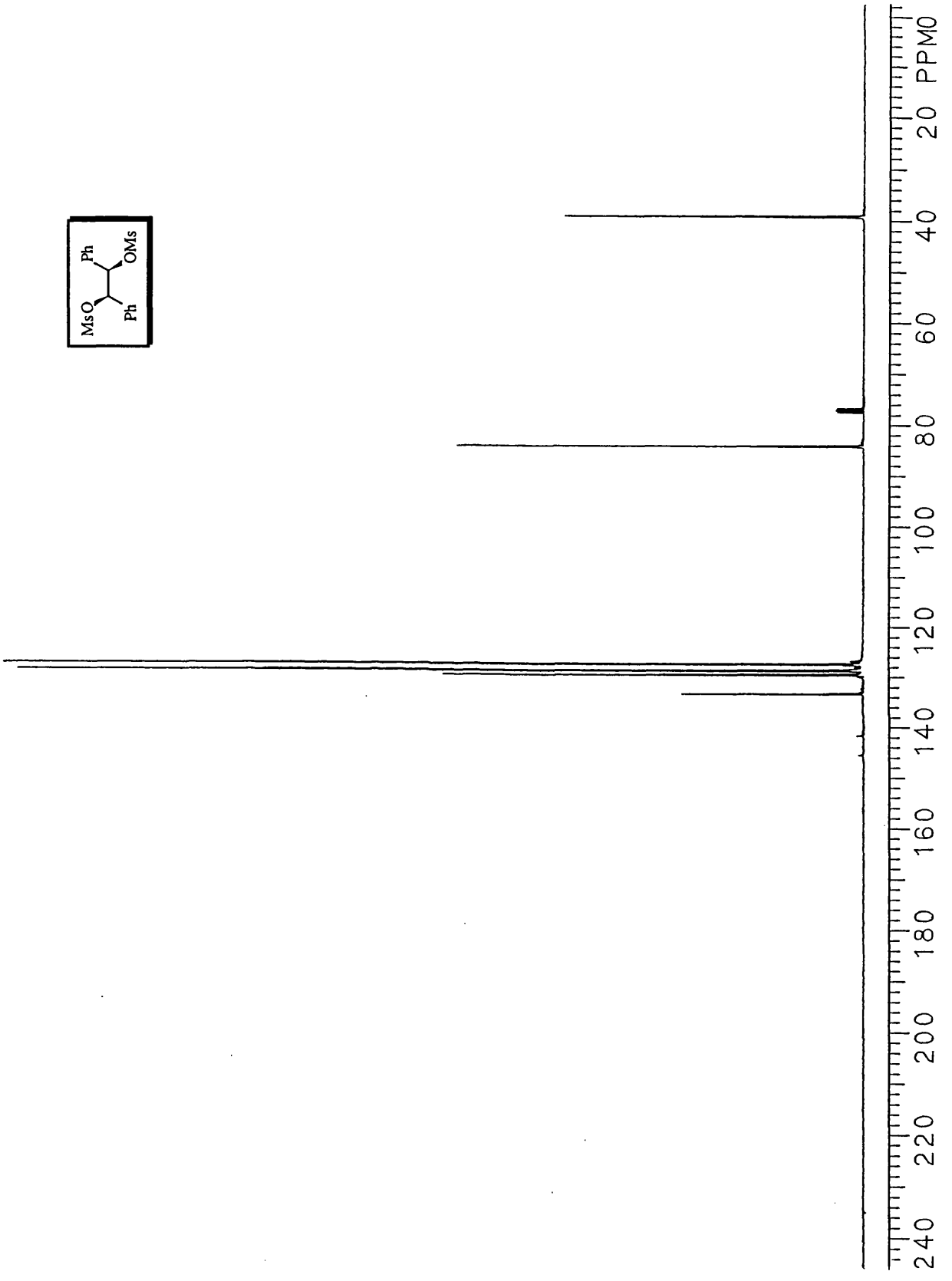


Figure 52 ^{13}C n.m.r. spectrum of (1*R*,2*R*)-(-)-1,2-diphenyl-1,2-dimesyloxyethane **119**

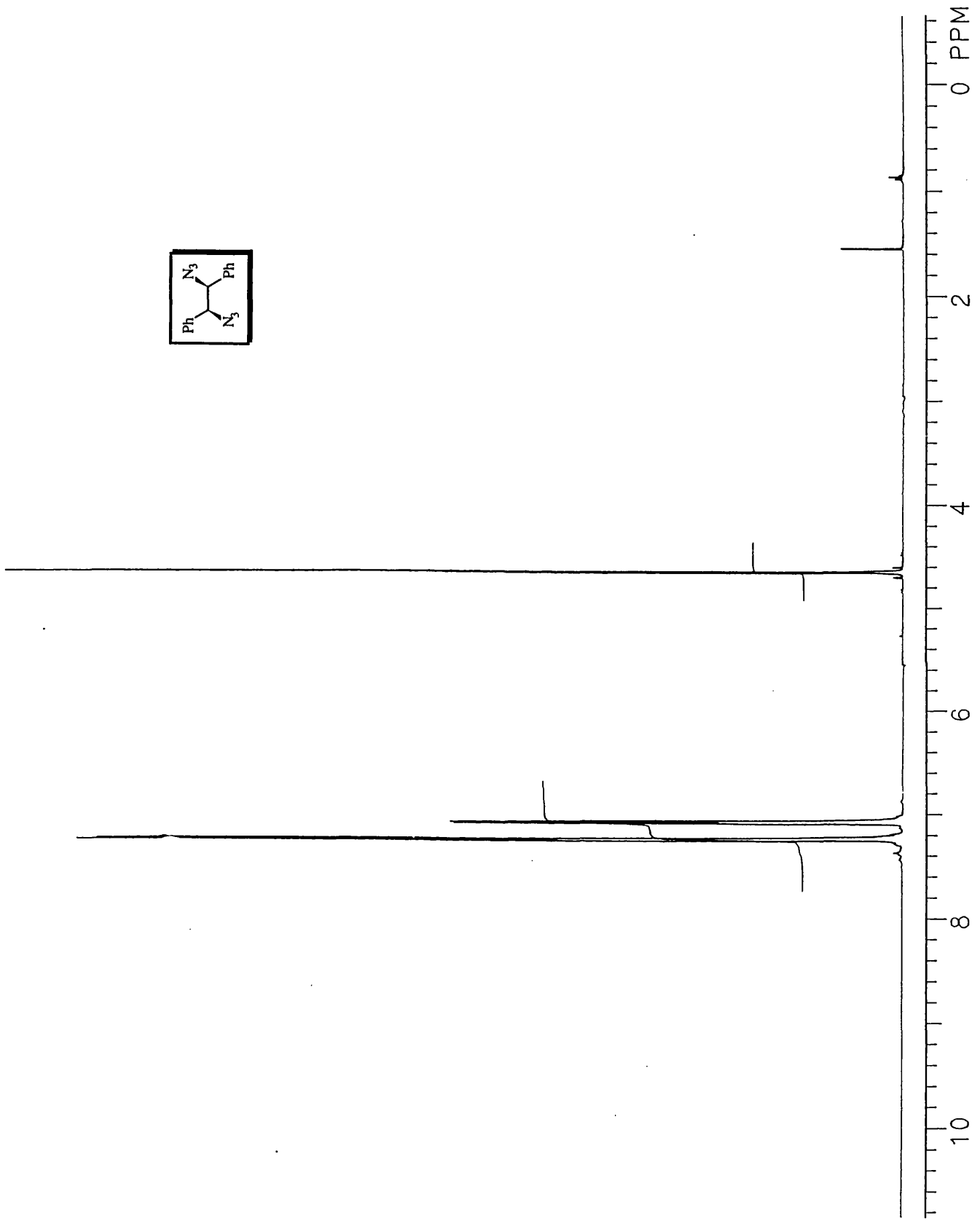


Figure 53 ^{1}H n.m.r. spectrum of (1*S*,2*S*)-(+)-1,2-diphenylethane-1,2-diazide **118**

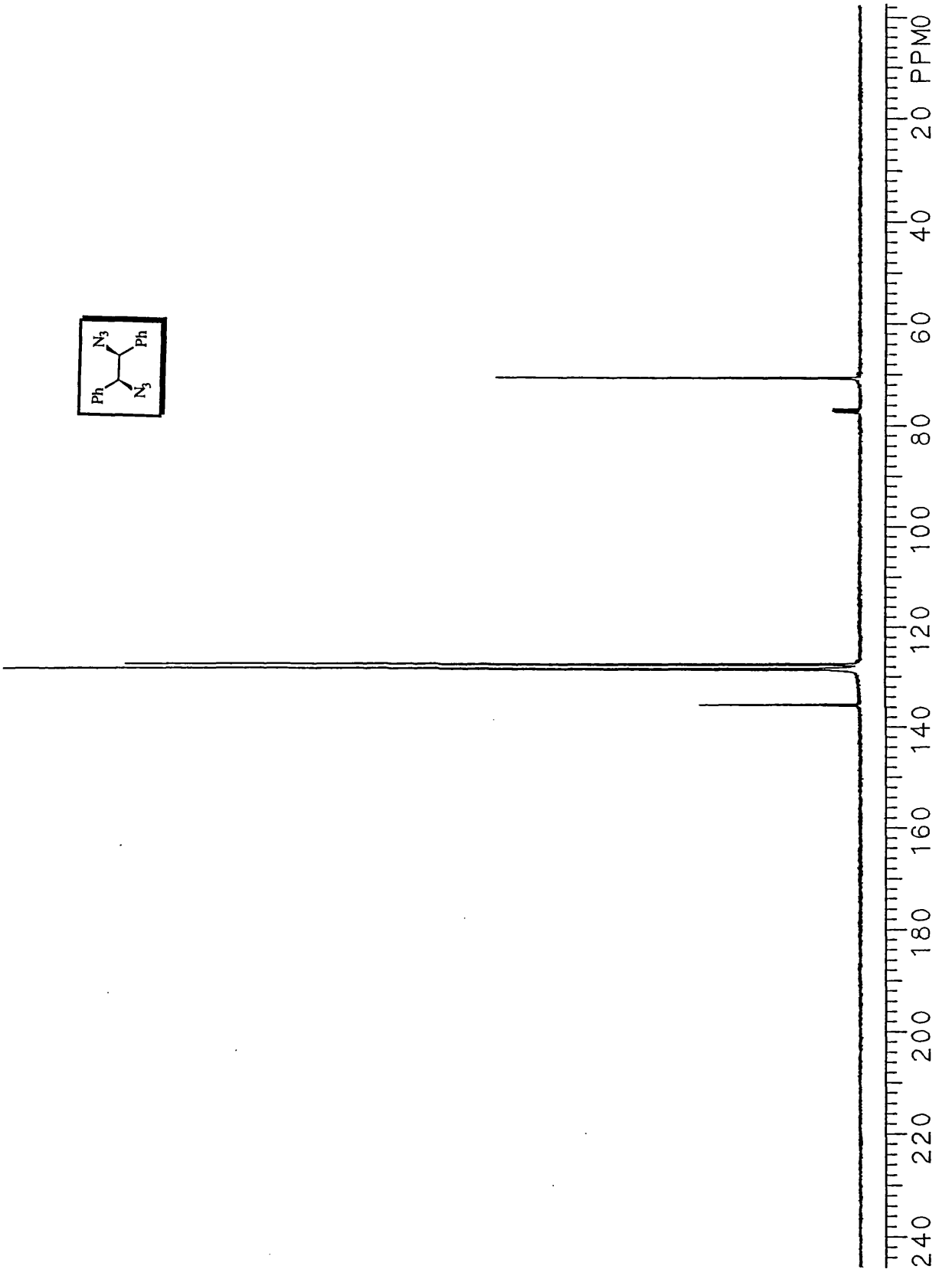


Figure 54 ^{13}C n.m.r. spectrum of (1*S*,2*S*)-(+)-1,2-diphenylethane-1,2-diazide **118**

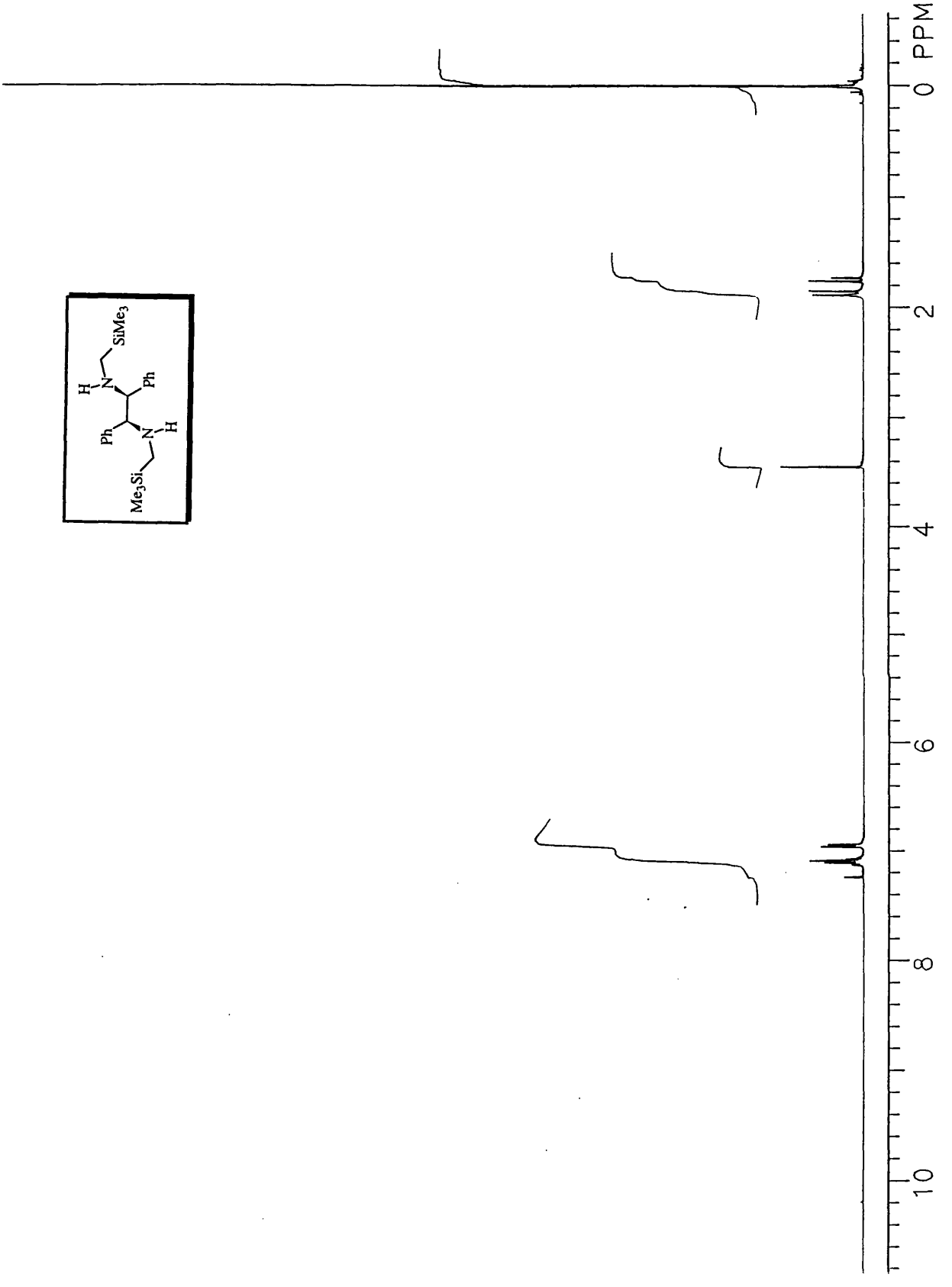


Figure 55 ^{1}H n.m.r. spectrum of (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-bis(*N*',*N*''-trimethylsilyl methyl)diamine **120**

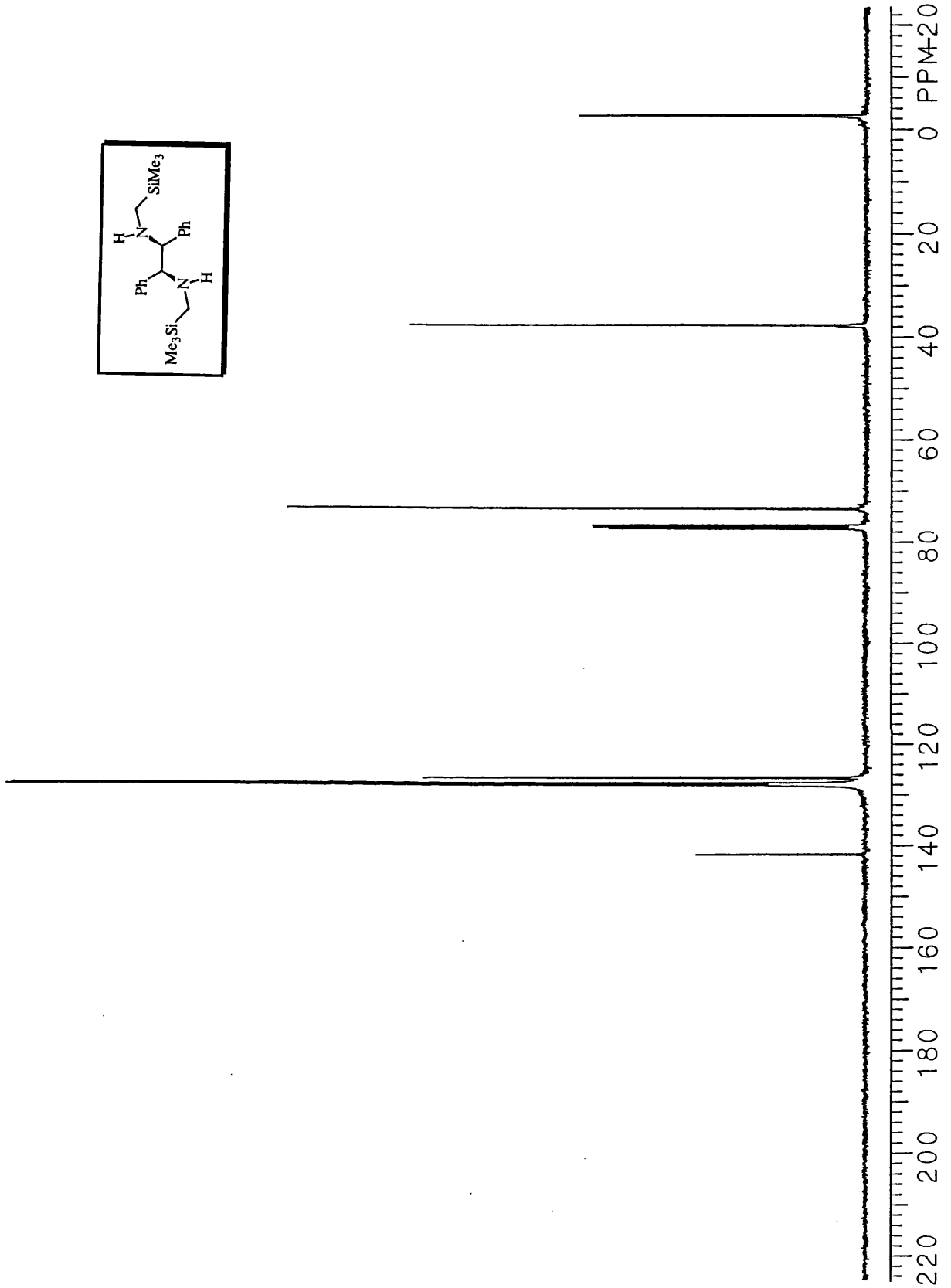


Figure 56 ^{13}C n.m.r. spectrum of (1*S*,2*S*)-(-)-1,2-diphenylethane-1,2-bis(*N'*,*N''*-trimethylsilylmethyl)diamine **120**

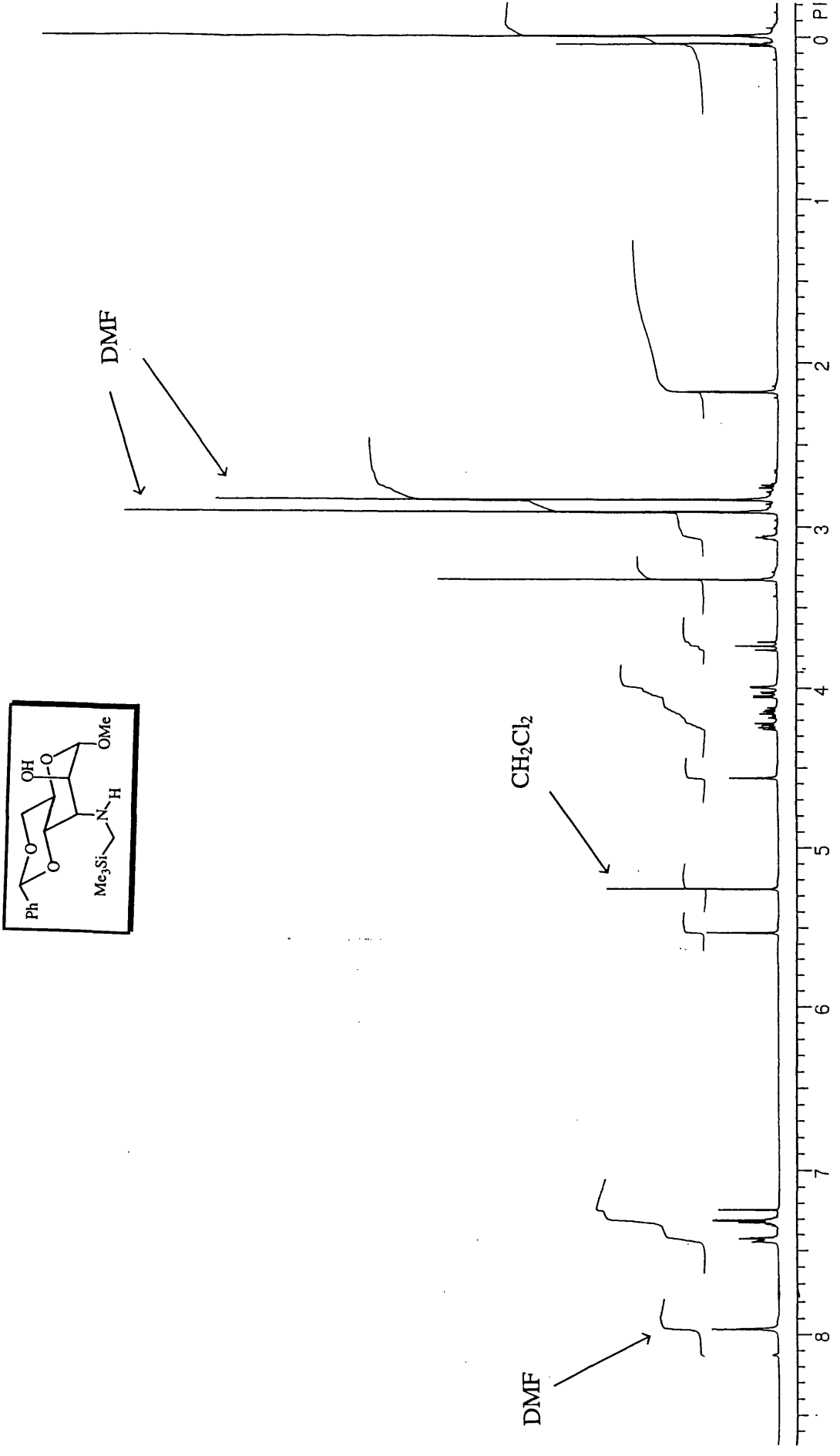


Figure 57 ^{1}H n.m.r. spectrum of methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside **131**

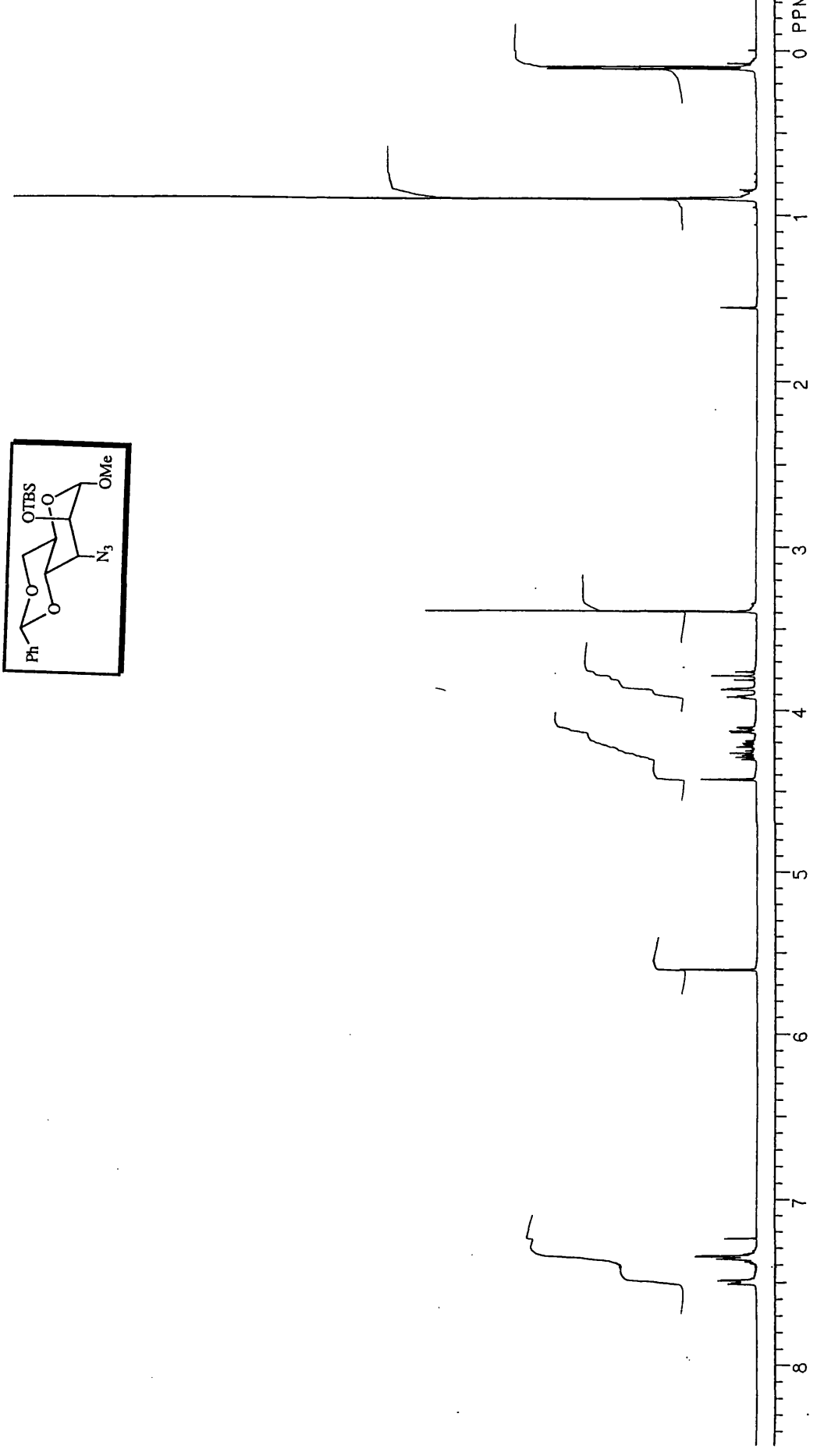


Figure 58 ^{1}H n.m.r. spectrum of (+)-methyl 3-azido-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **137**

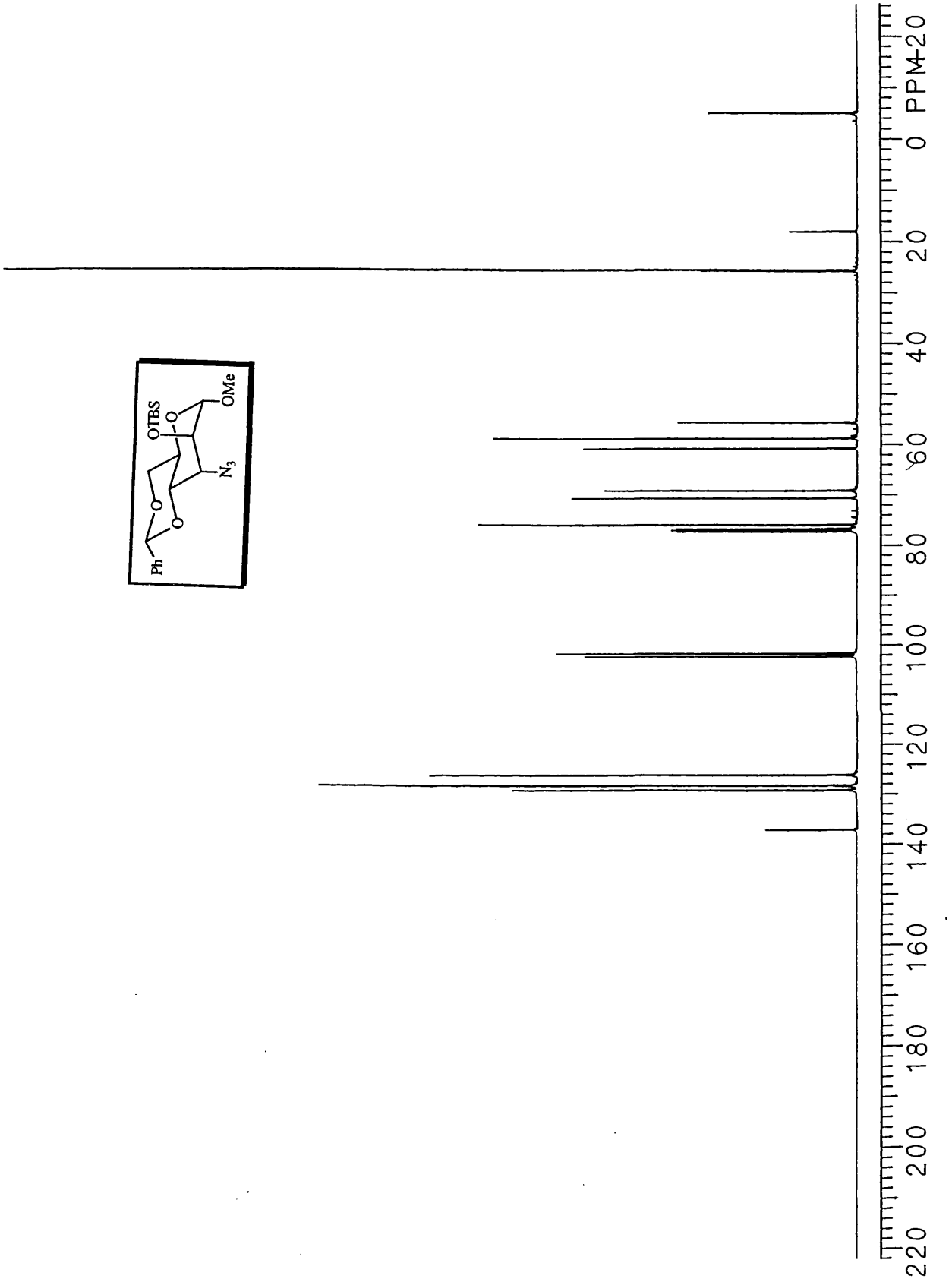


Figure 59 ^{13}C n.m.r. spectrum of (+)-methyl 3-azido-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-altropyranoside **137**

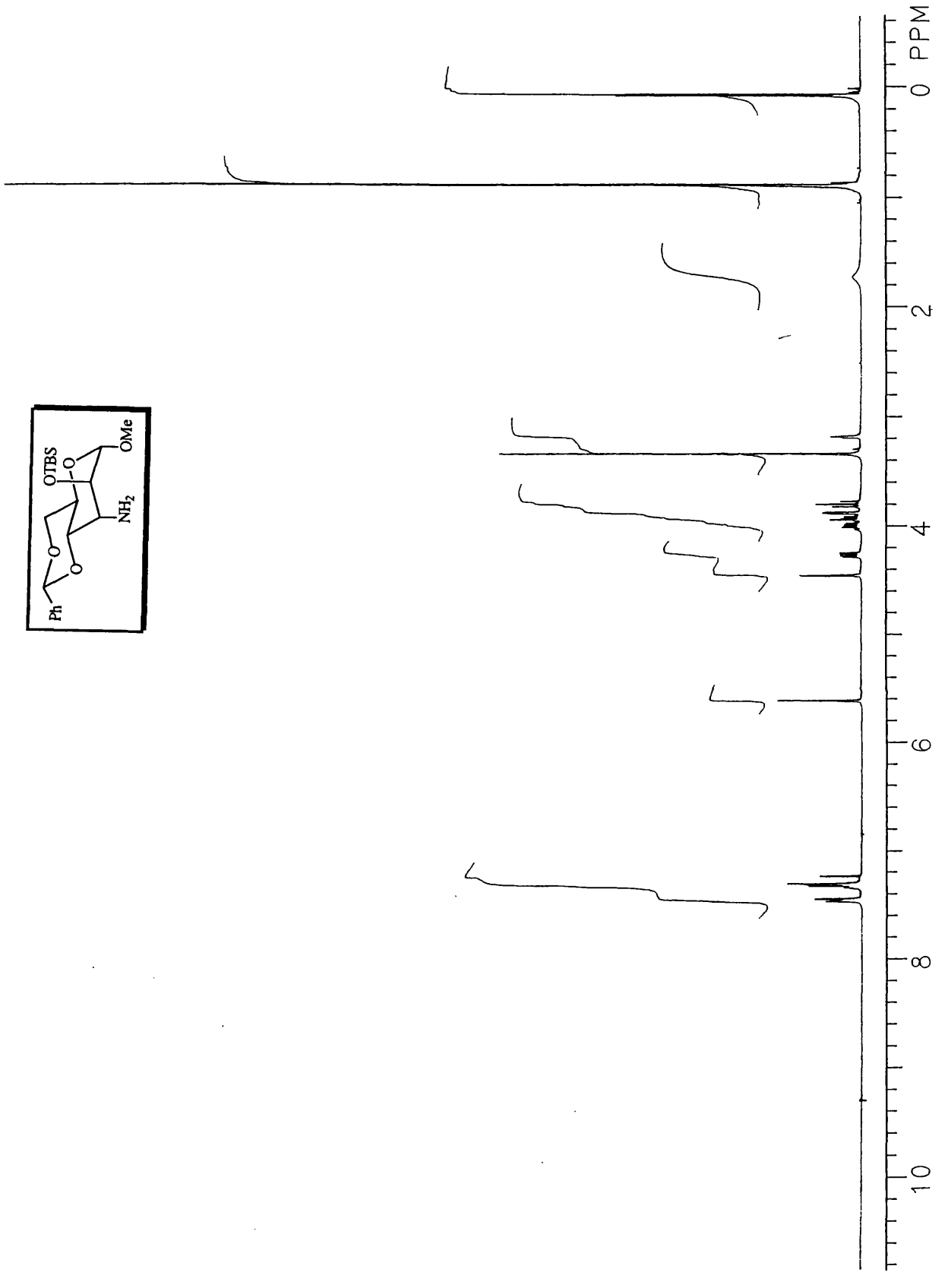


Figure 60 ^{1}H n.m.r. spectrum of methyl 3-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyl-dimethylsilyl)-3-deoxy-α-D-altropyranoside **138**

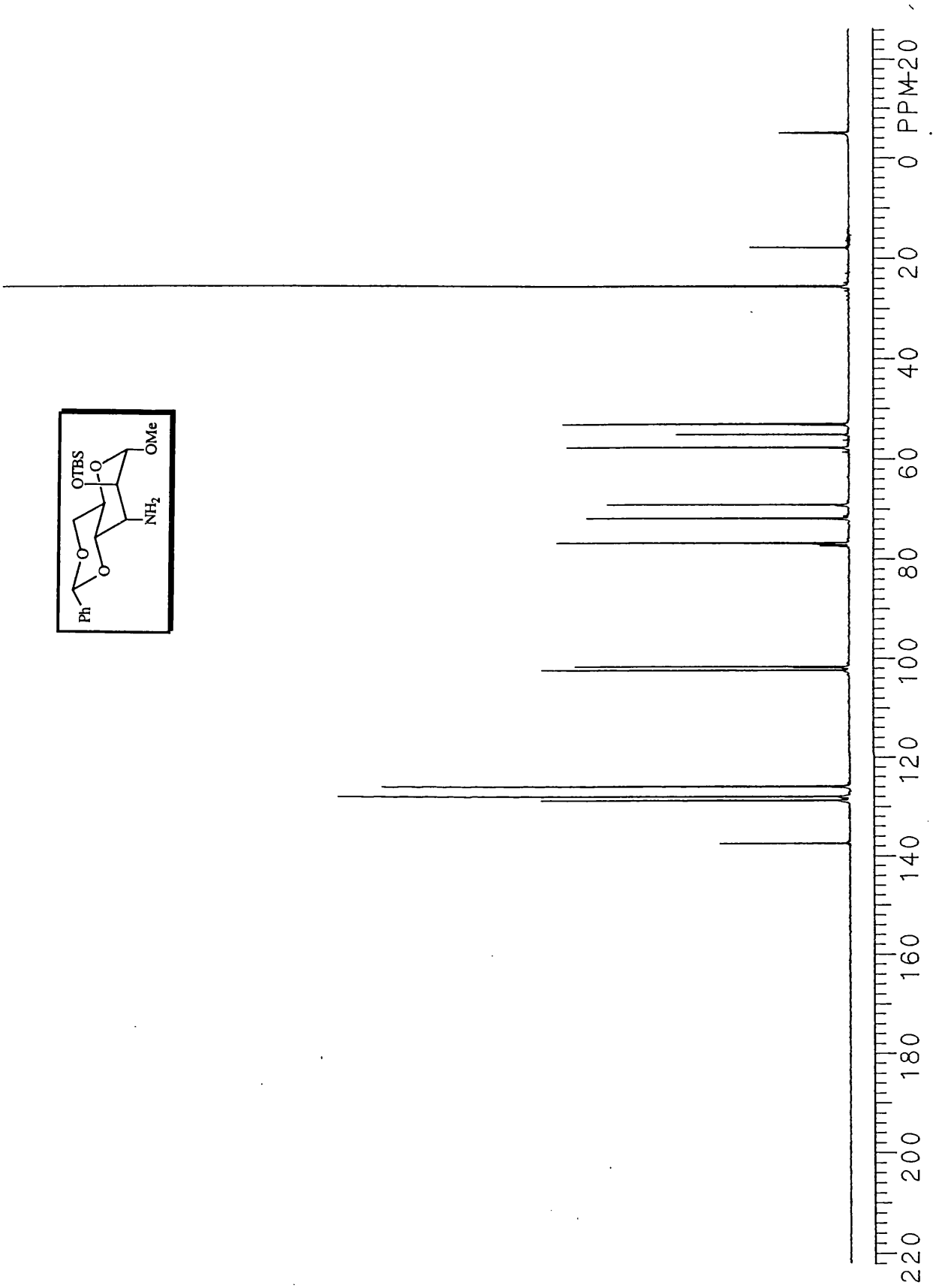


Figure 61 ^{13}C n.m.r. spectrum of methyl 3-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyl-dimethylsilyl)-3-deoxy-α-D-altropyranoside **138**

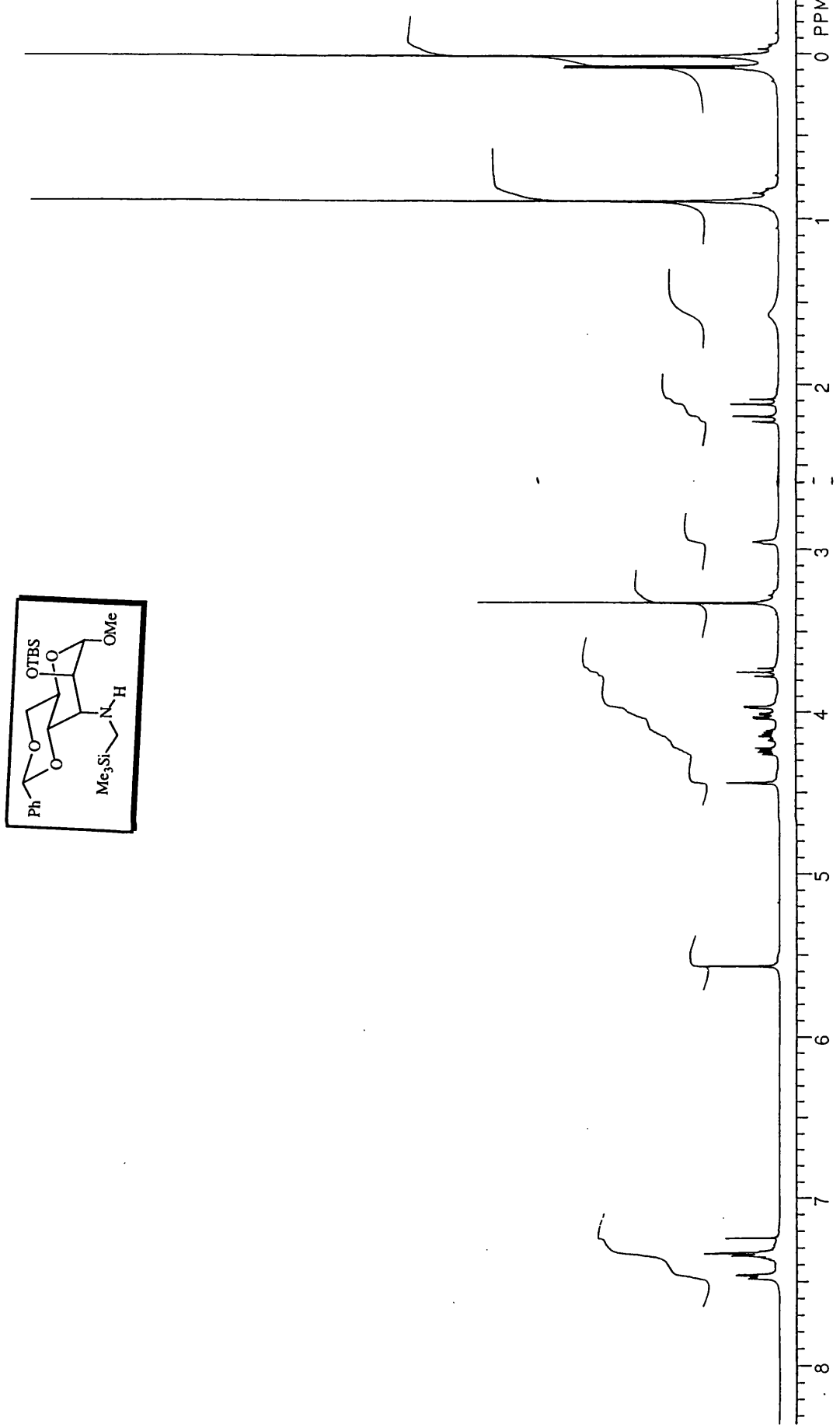


Figure 62 ^{1}H n.m.r. spectrum of methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132**

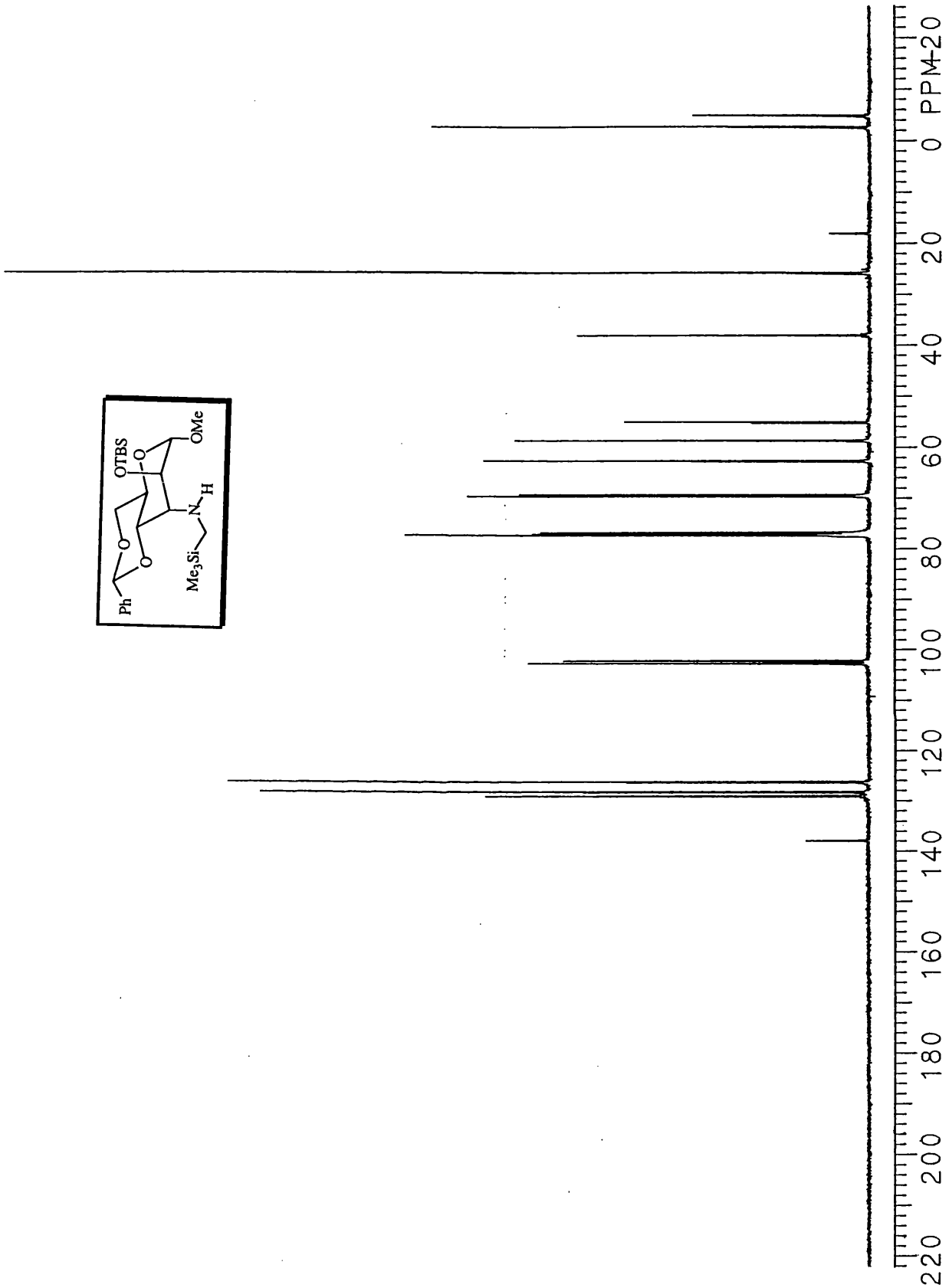


Figure 63 ^{13}C n.m.r. spectrum of methyl 3-(*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **132**

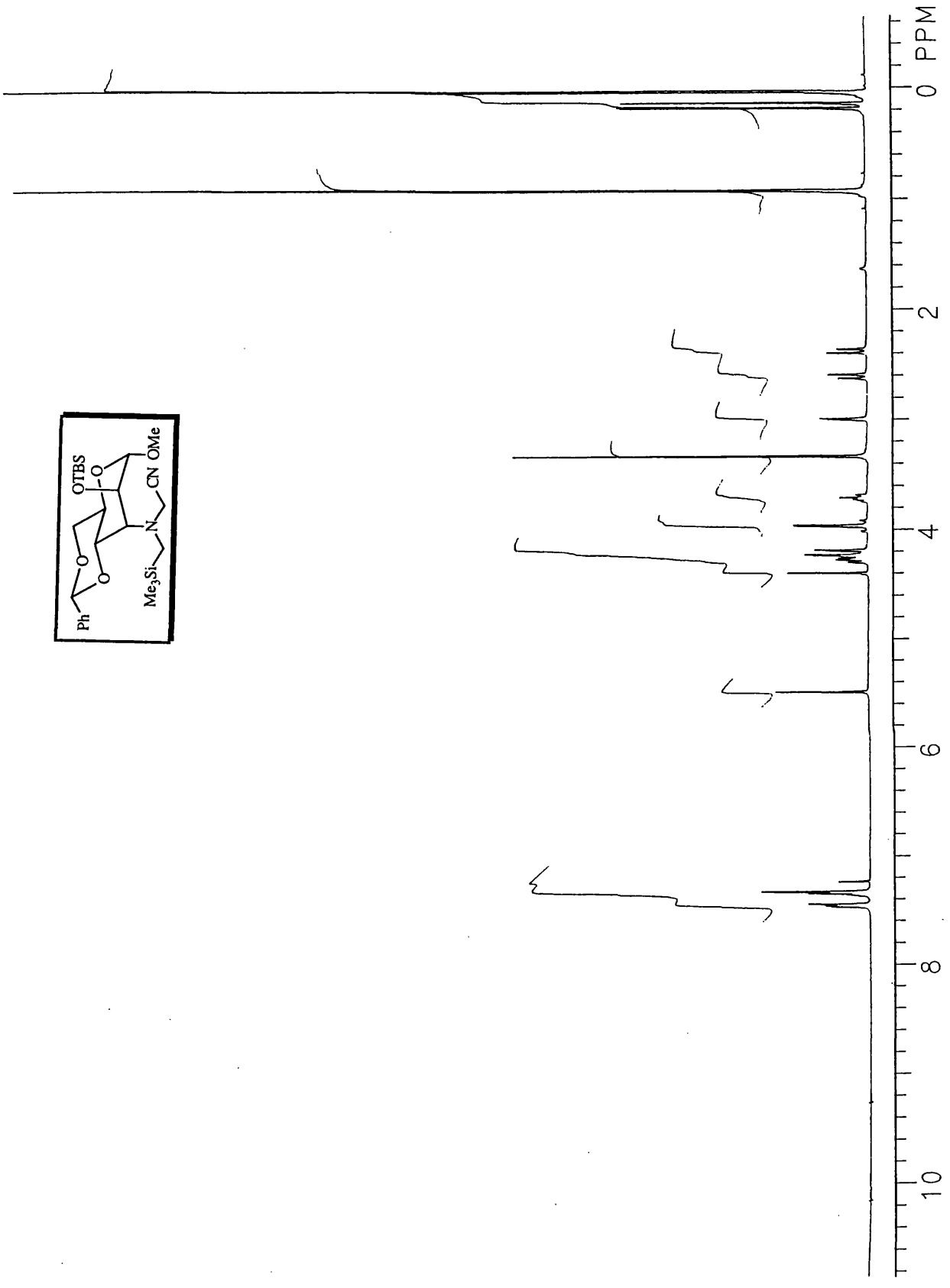


Figure 64 ^{1}H n.m.r. spectrum of methyl 3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **133**

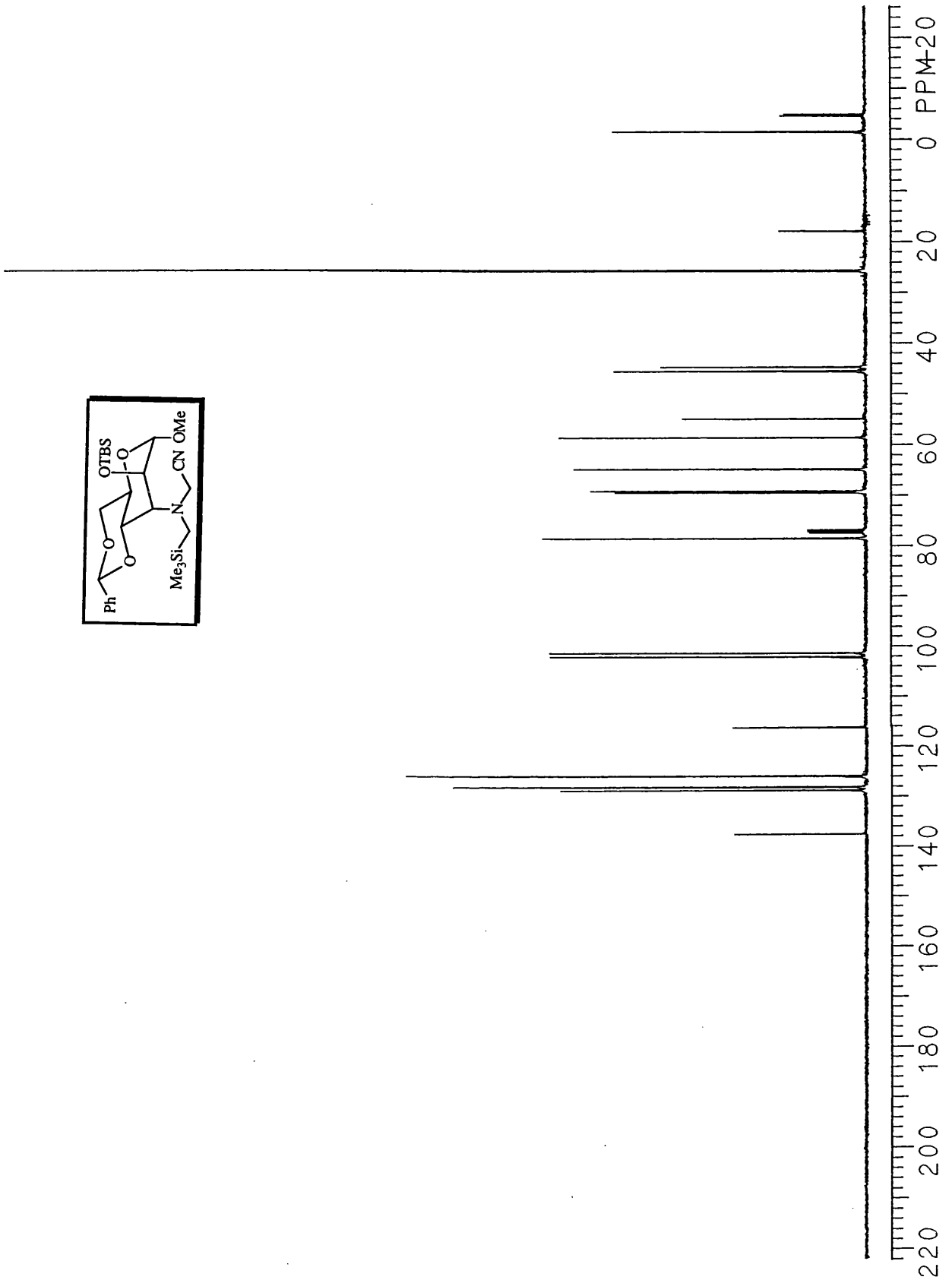


Figure 65 ^{13}C n.m.r. spectrum of methyl 3-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)-amino-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **133**

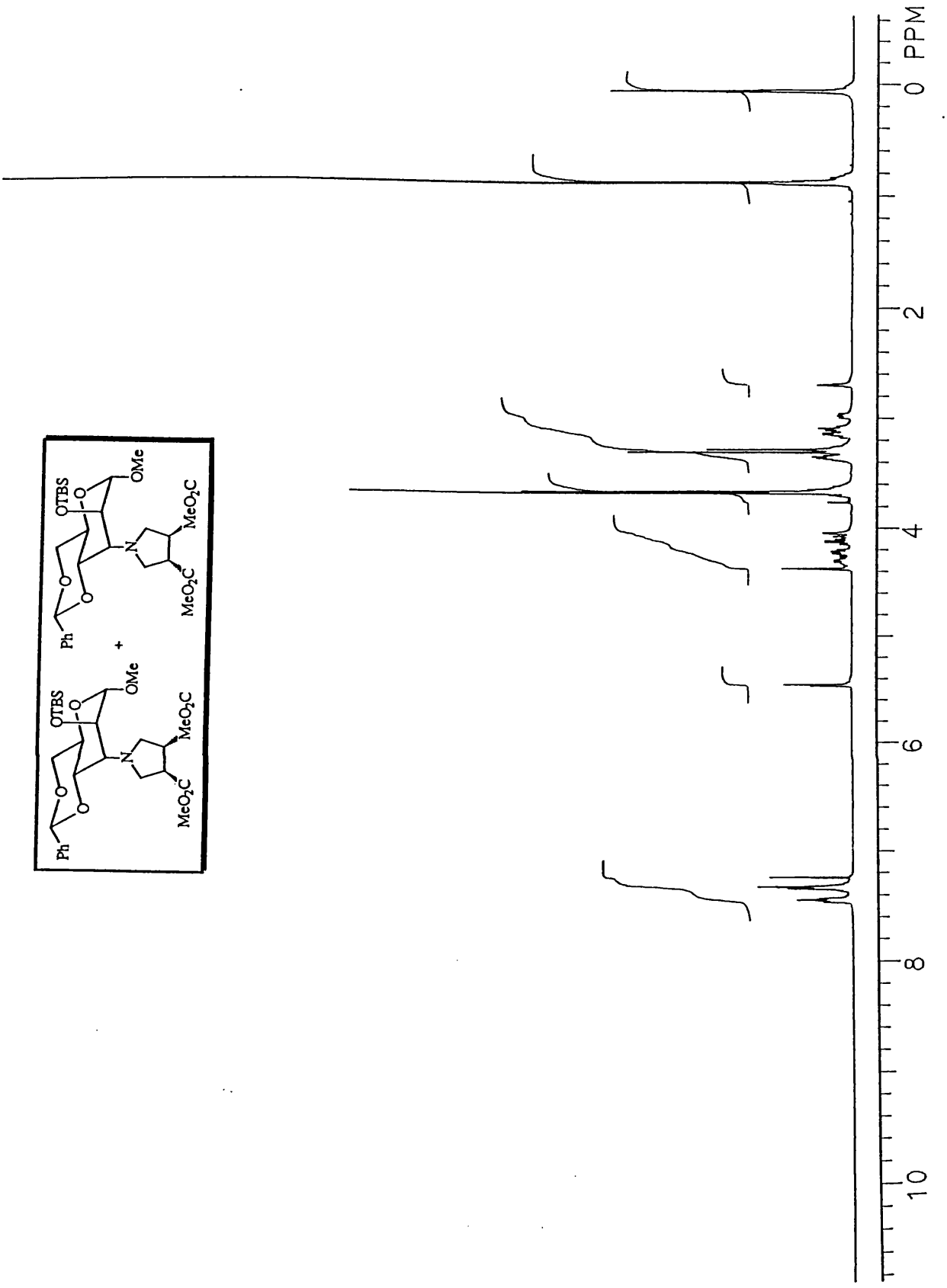


Figure 66 ^{1}H n.m.r. spectrum of methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)pyrrolidine-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **134ab**

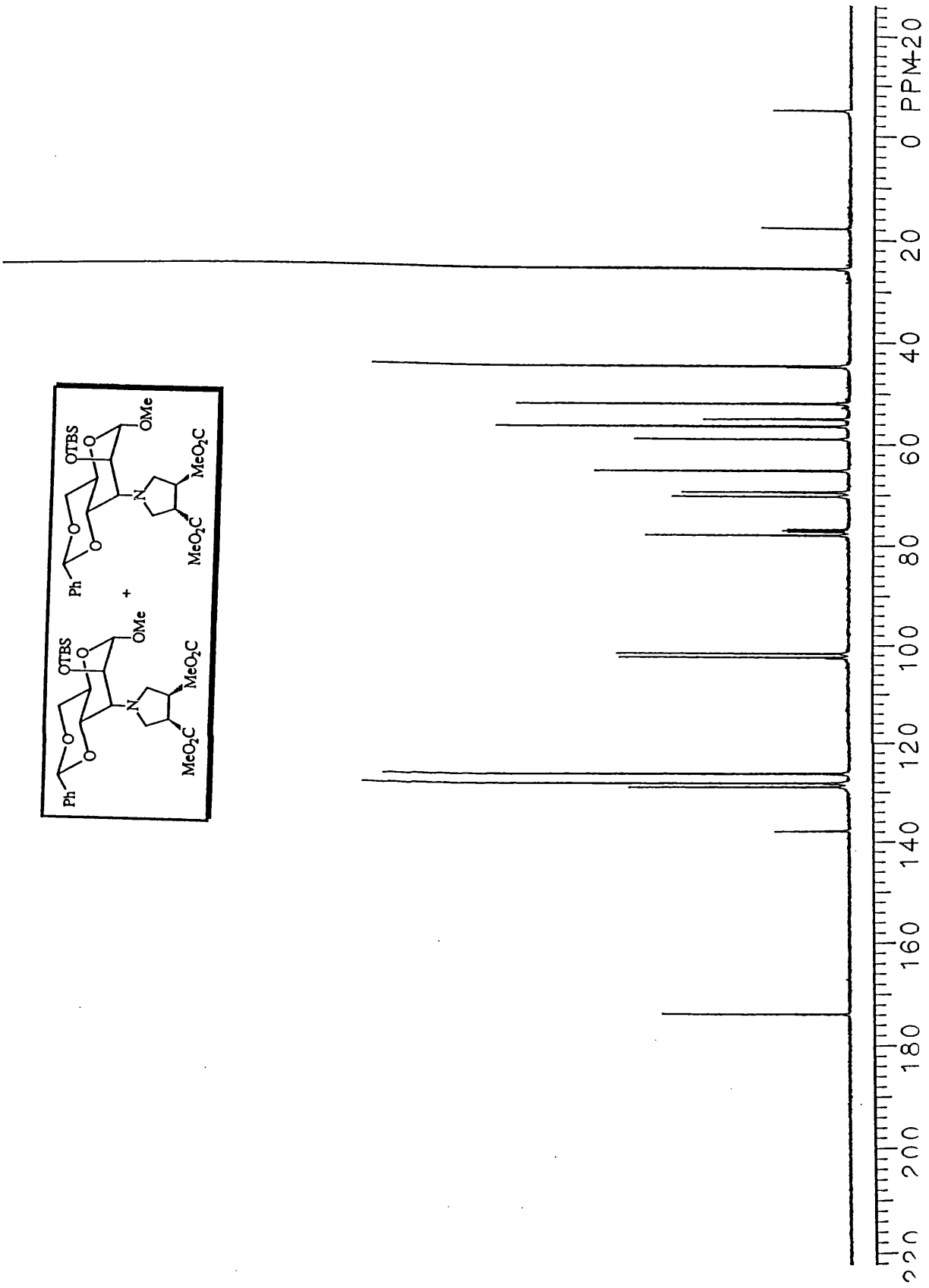


Figure 67 ^{13}C n.m.r. spectrum of methyl 3-*N*-(*trans*-3,4-dicarbomethoxy)pyrrolidine-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-deoxy-α-D-altropyranoside **134ab**

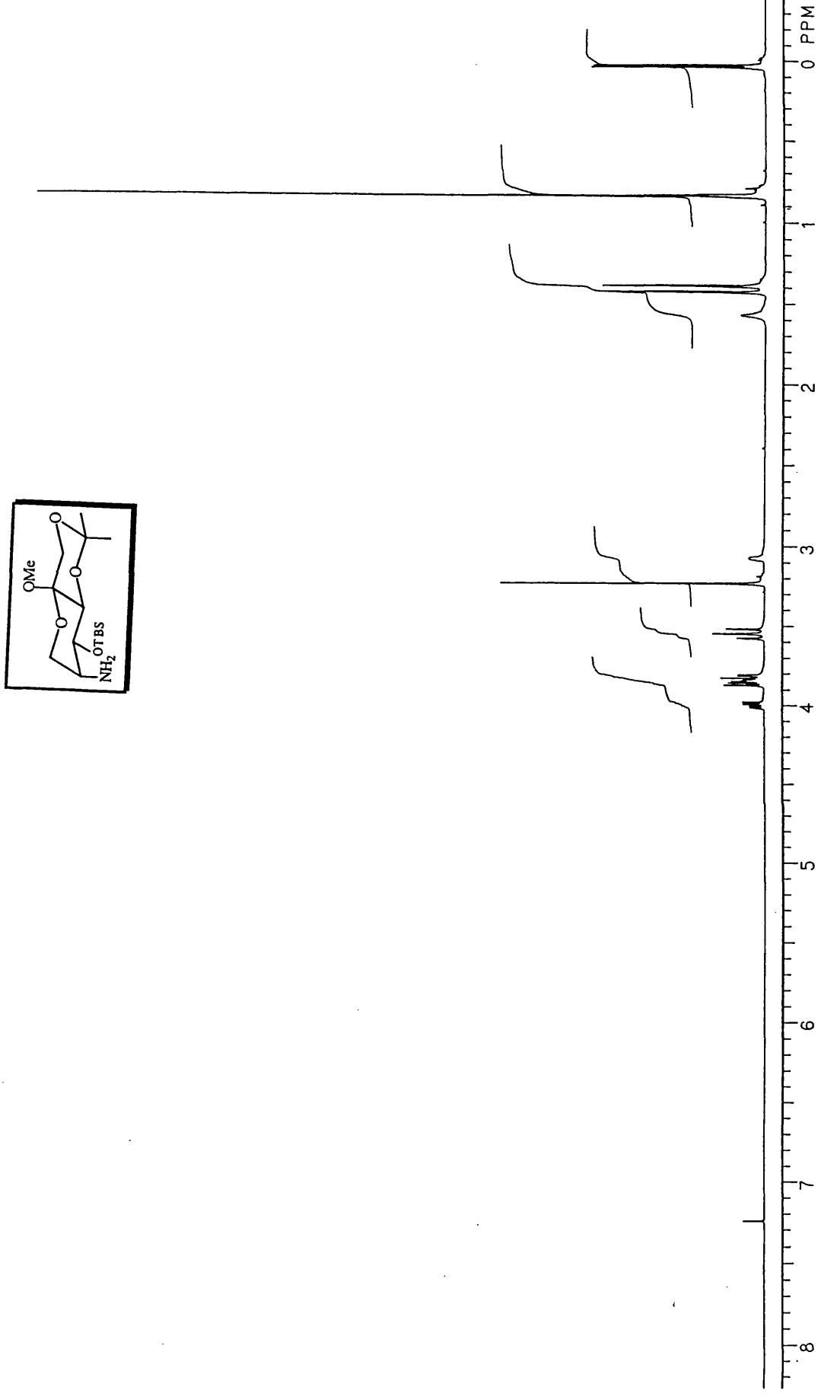


Figure 68 ^{1}H n.m.r. spectrum of methyl 5-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148**

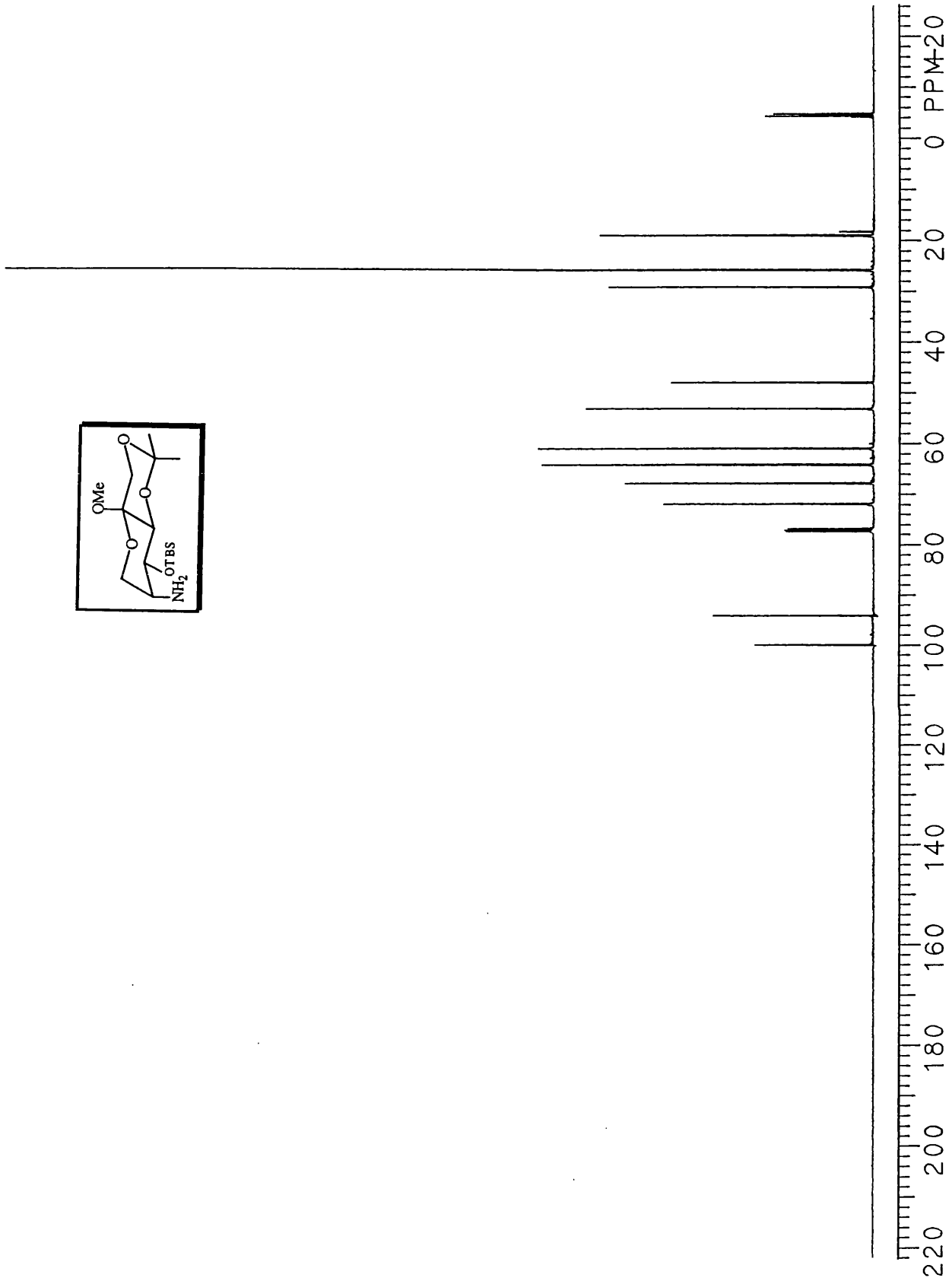


Figure 69 ^{13}C n.m.r. spectrum of methyl 5-amino-5-deoxy-4-*O*-*tert*-butyl-dimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **148**

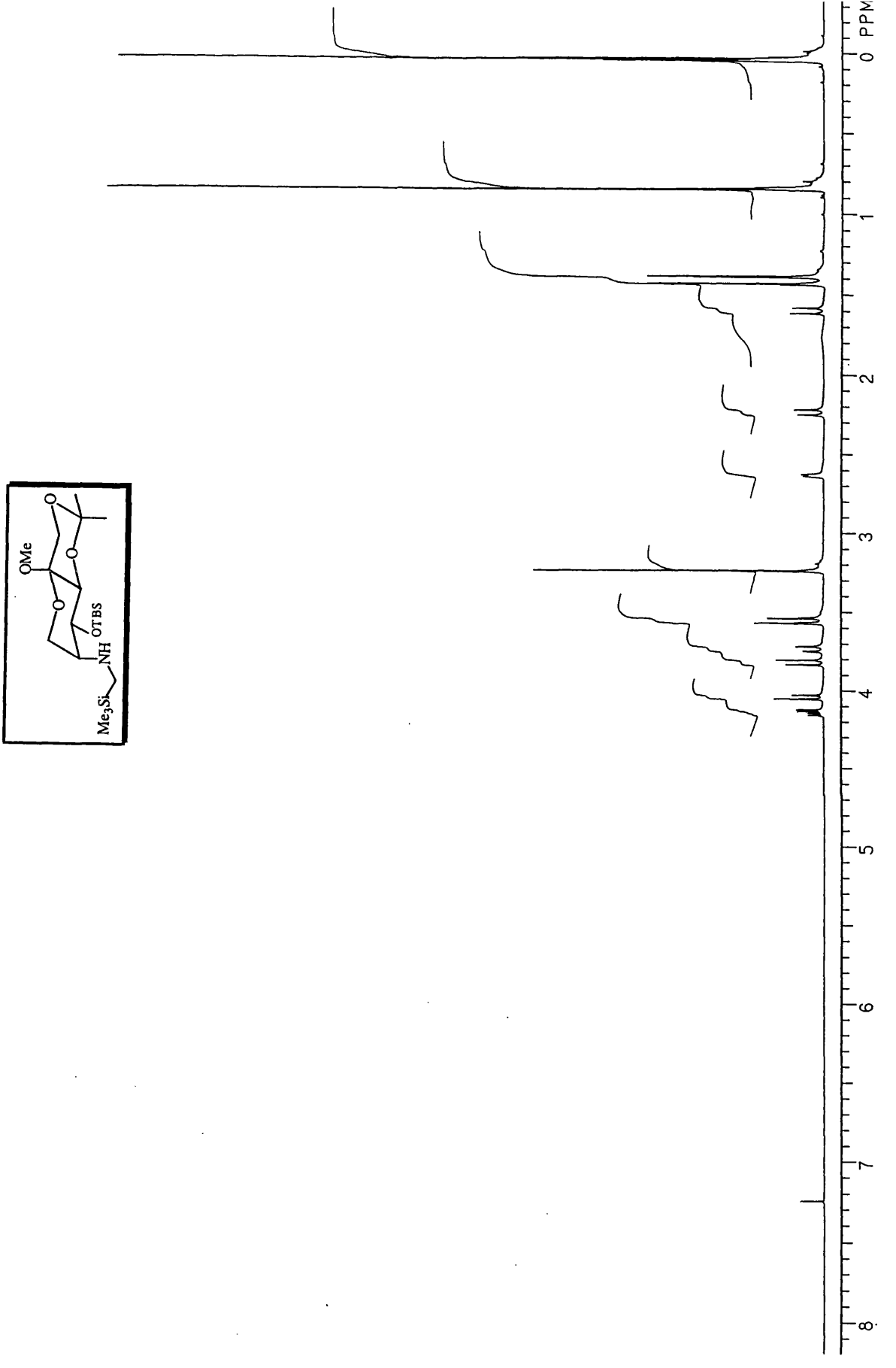


Figure 70 ^{1}H n.m.r. spectrum of methyl 5-(*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149**

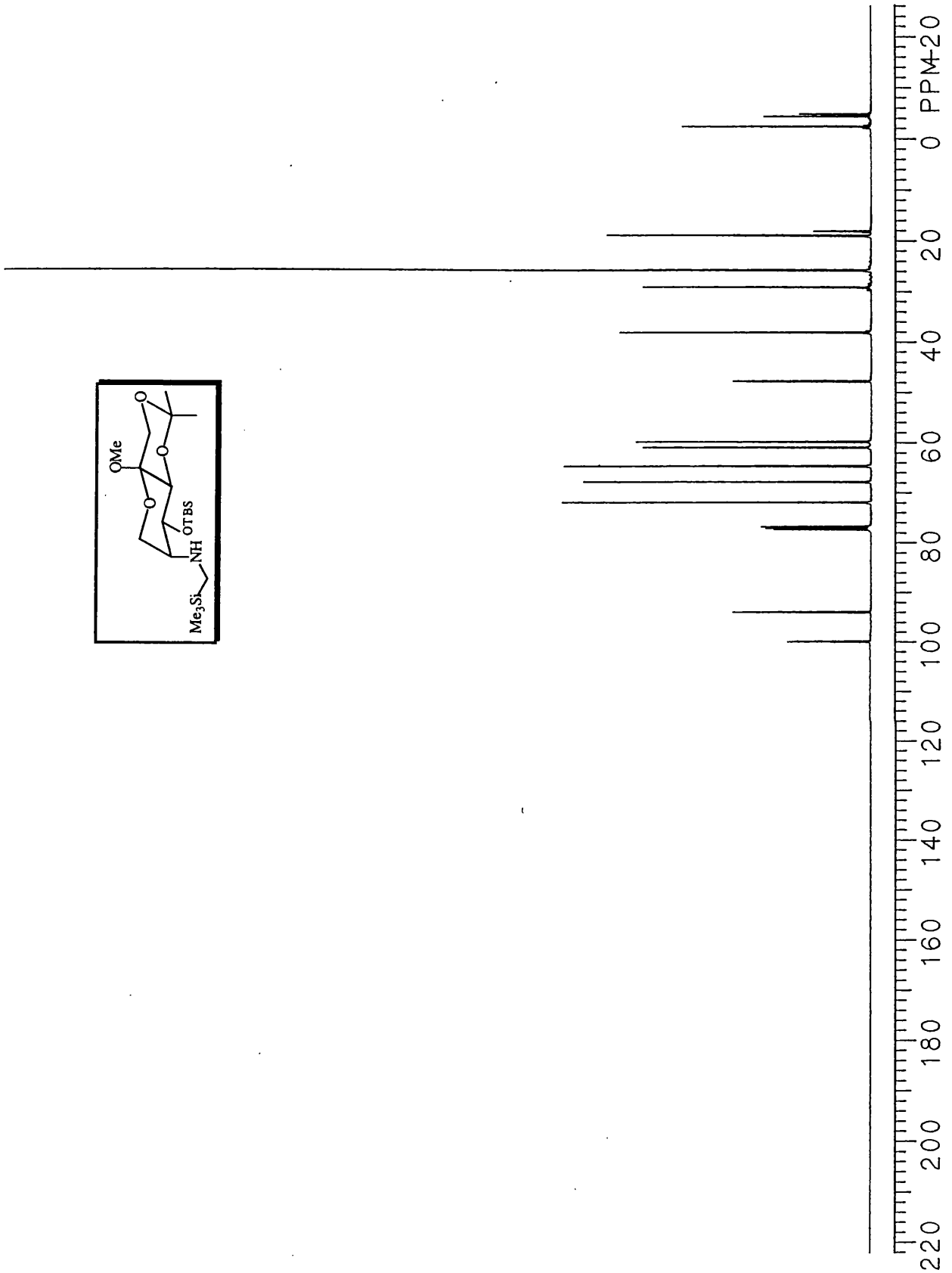


Figure 71 ^{13}C n.m.r. spectrum of methyl 5-(*N*-trimethylsilylmethyl)amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **149**

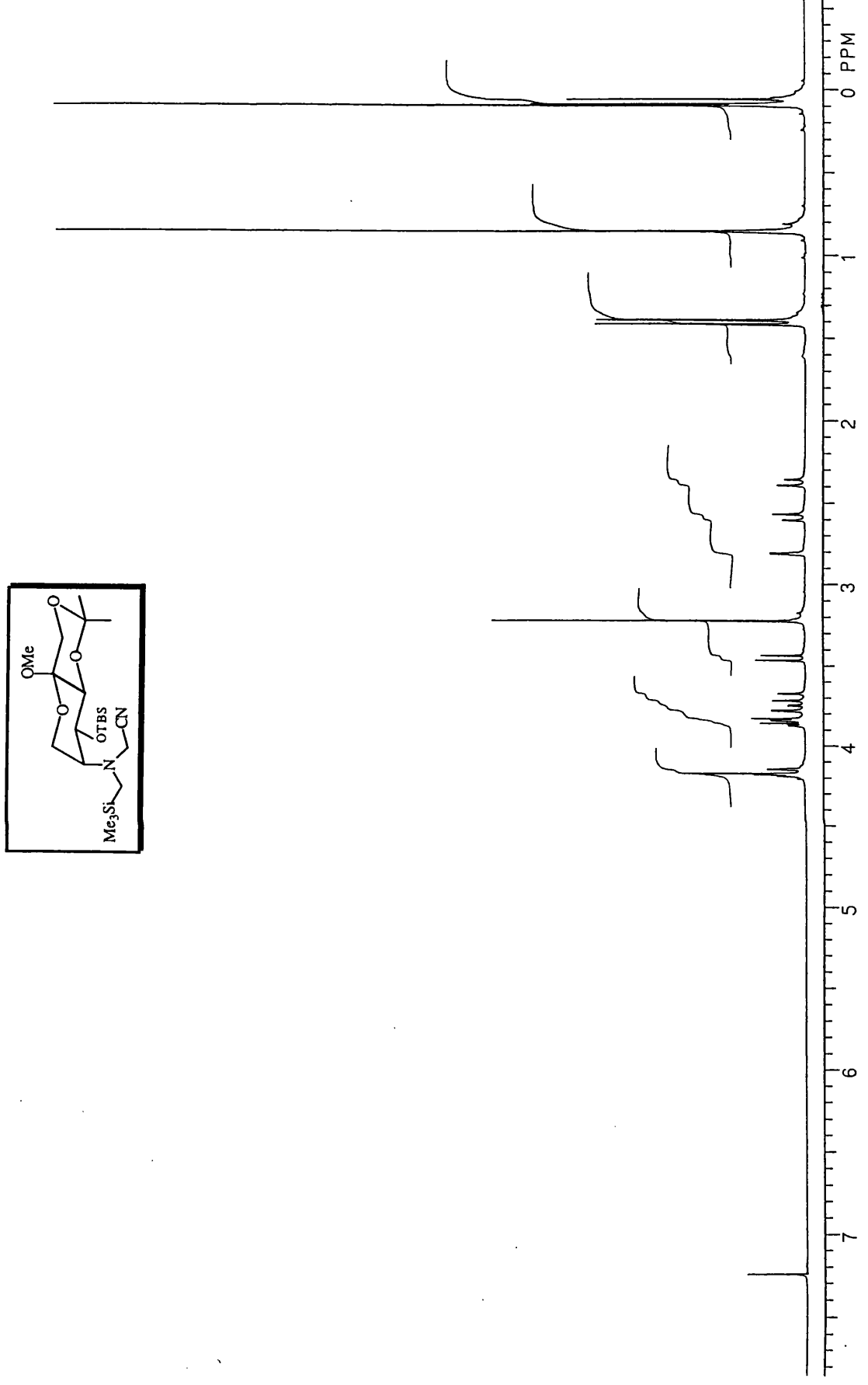


Figure 72 ^{1}H n.m.r. spectrum of methyl 5-(*N*-cyanomethyl-*N*-trimethylsilyl-methyl)-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150**

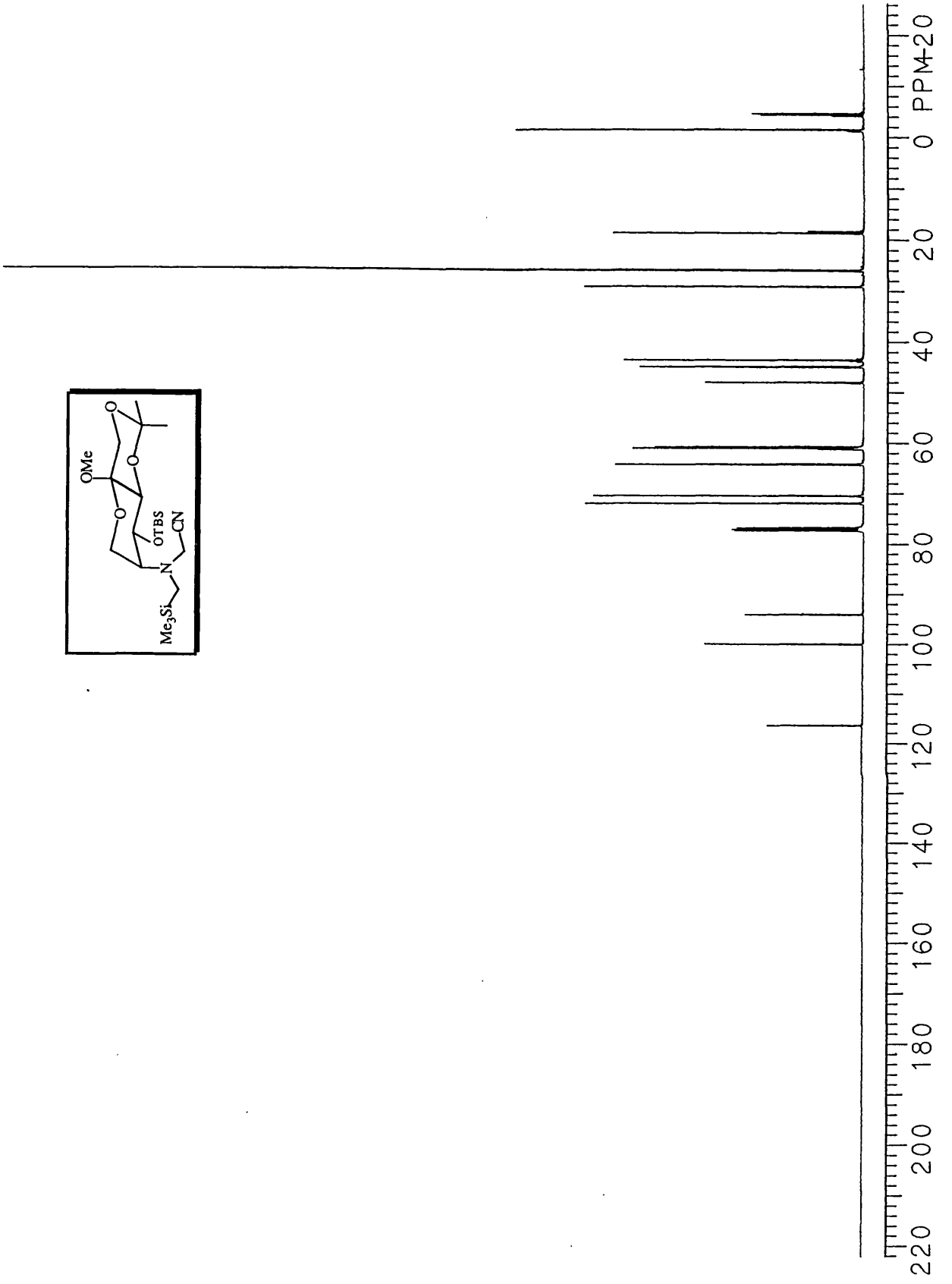


Figure 73 ^{13}C n.m.r. spectrum of methyl 5-(*N*-cyanomethyl-*N*-trimethylsilylmethyl)-amino-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-β-D-fructopyranoside **150**

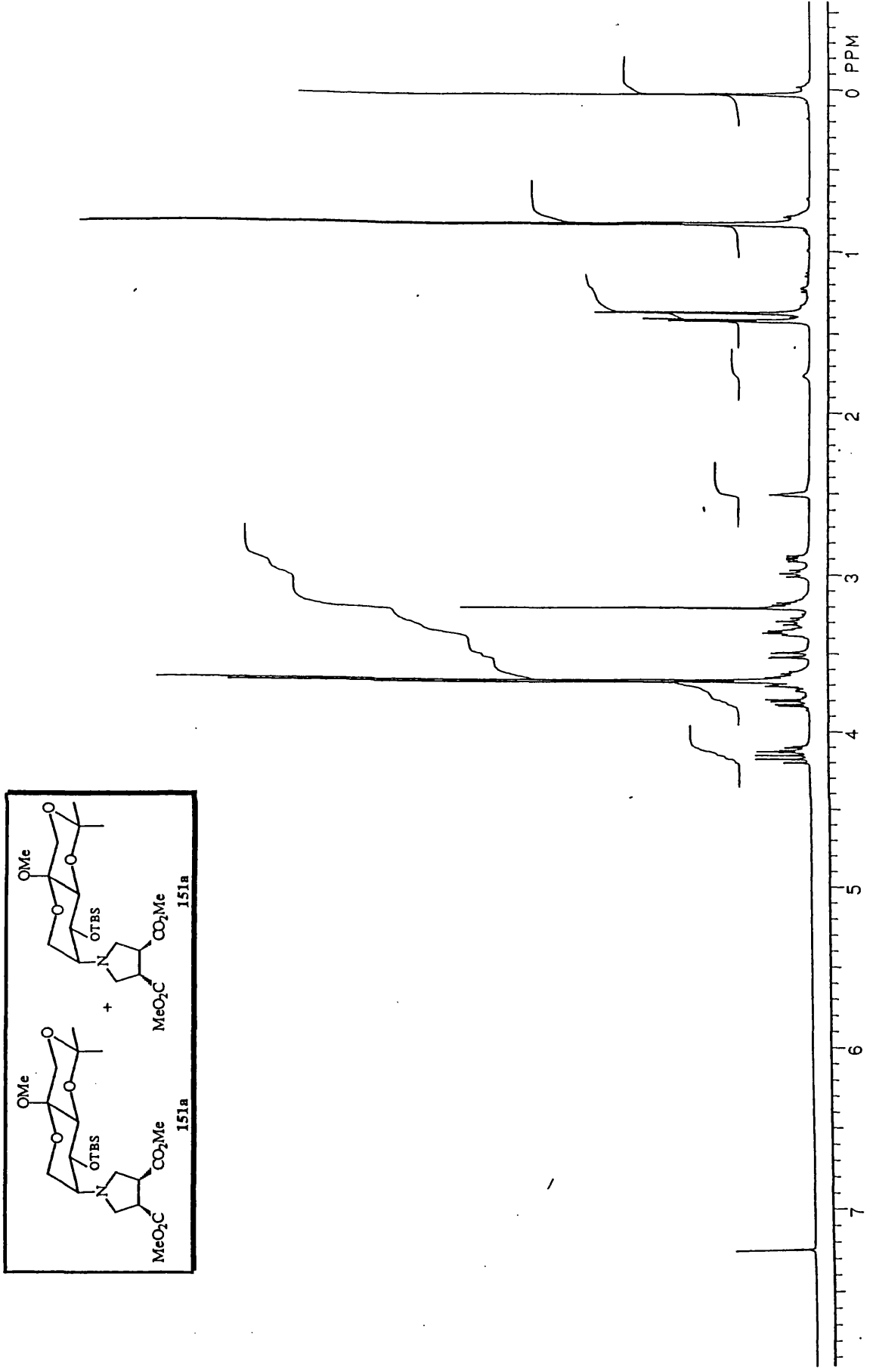


Figure 74 ^{1}H n.m.r. spectrum of methyl 5-*N*-(*trans*-3,4-dicarbomethoxypyrrolidine)-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-*β*-D-fructopyranoside **151ab**

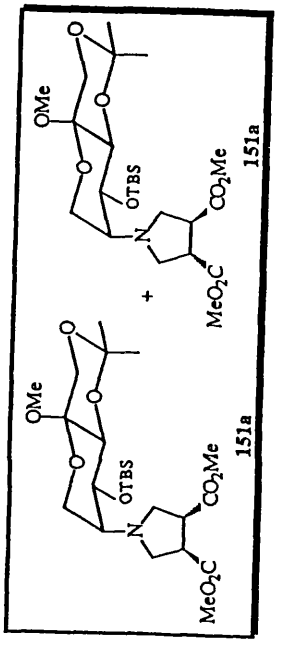


Figure 75 ^{13}C n.m.r. spectrum of methyl 5-*N*-(*trans*-3,4-dicarbomethoxypyrrolidine)-5-deoxy-4-*O*-*tert*-butyldimethylsilyl-1,3-*O*-isopropylidene-*β*-D-fructopyranoside **151ab**

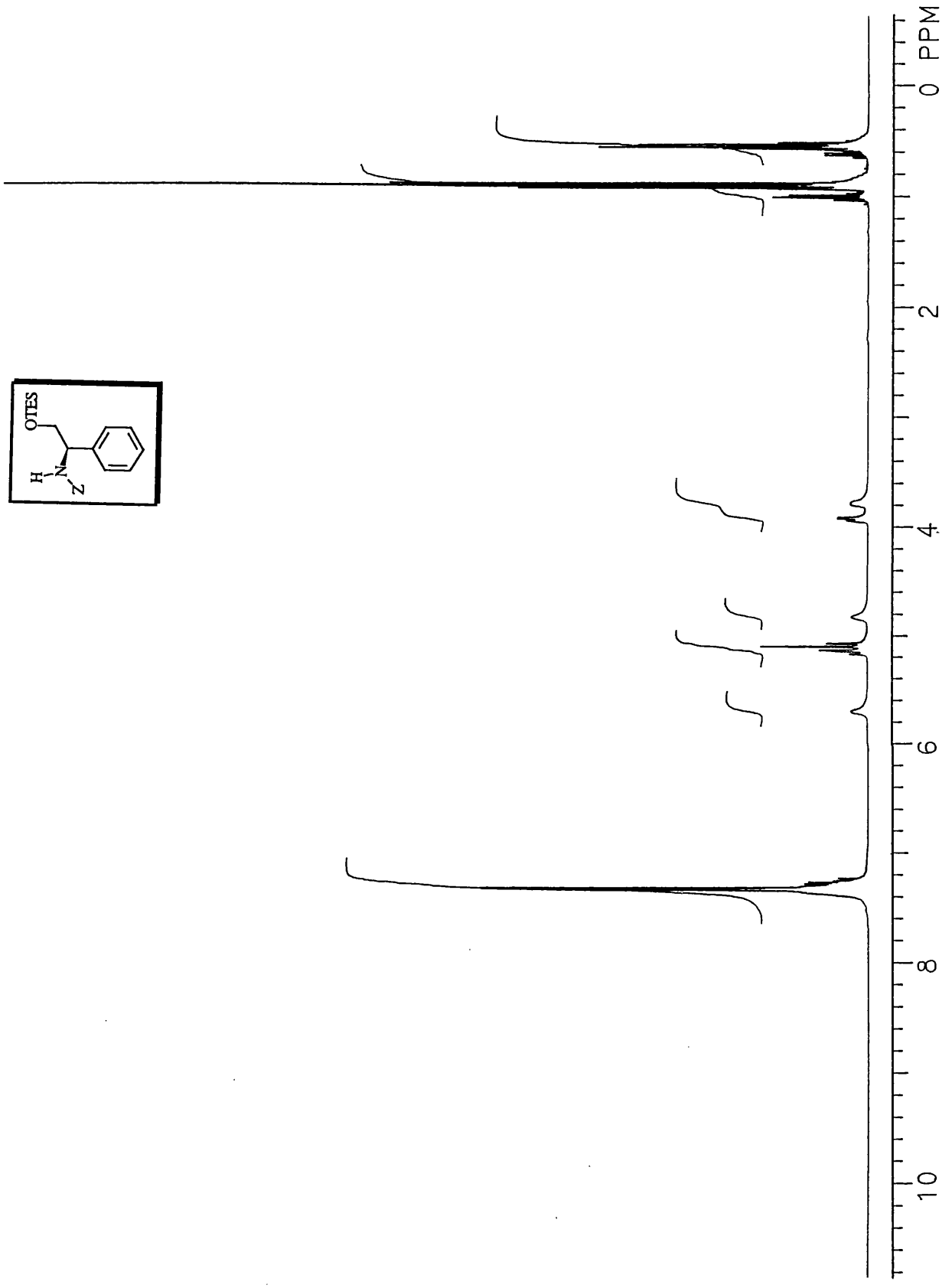


Figure 76 ^{1}H n.m.r. spectrum of *N*-(benzyloxy)carbonyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **166**

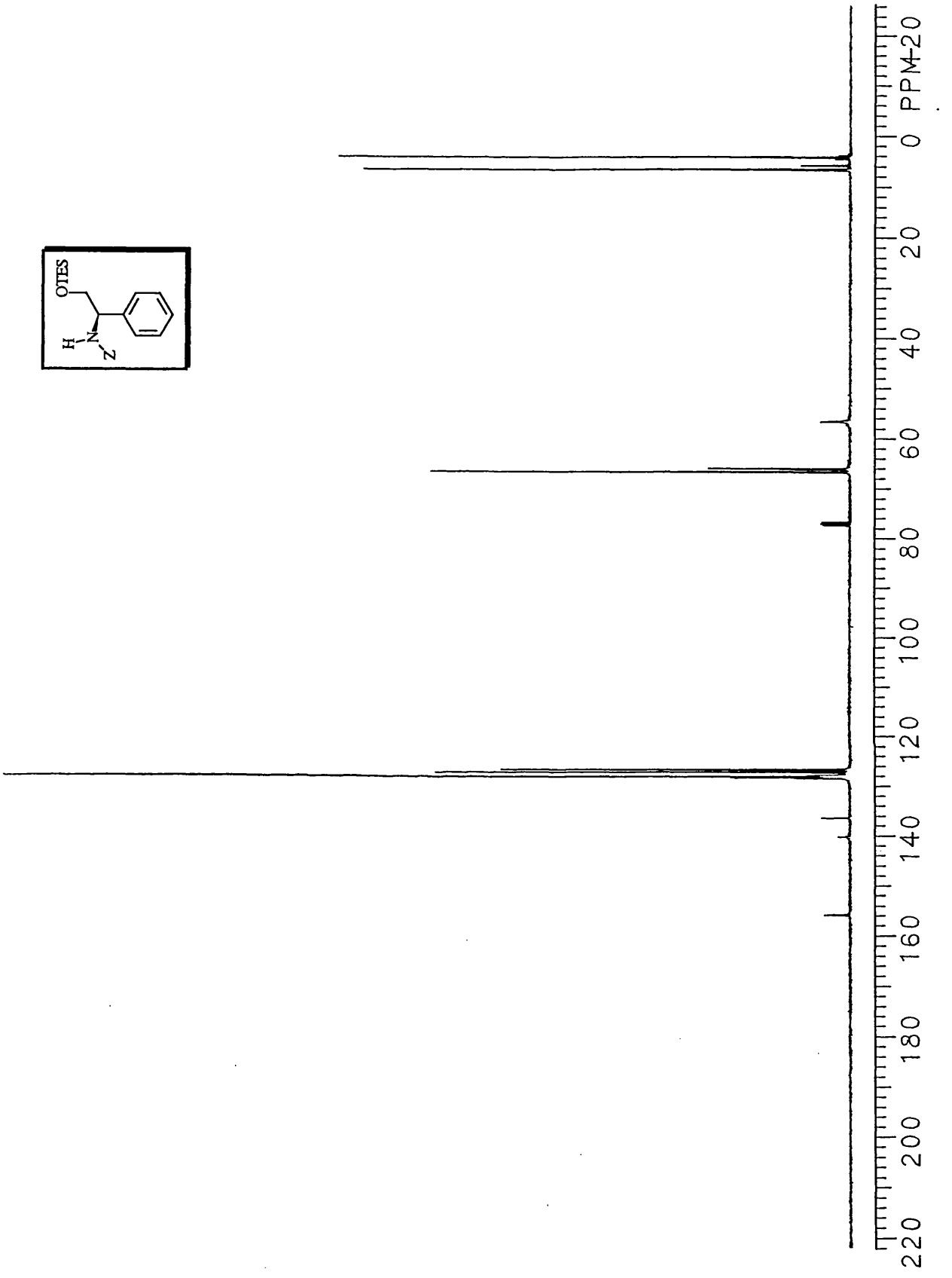


Figure 77 ^{13}C n.m.r. spectrum of *N*-(benzyloxy)carbonyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **166**

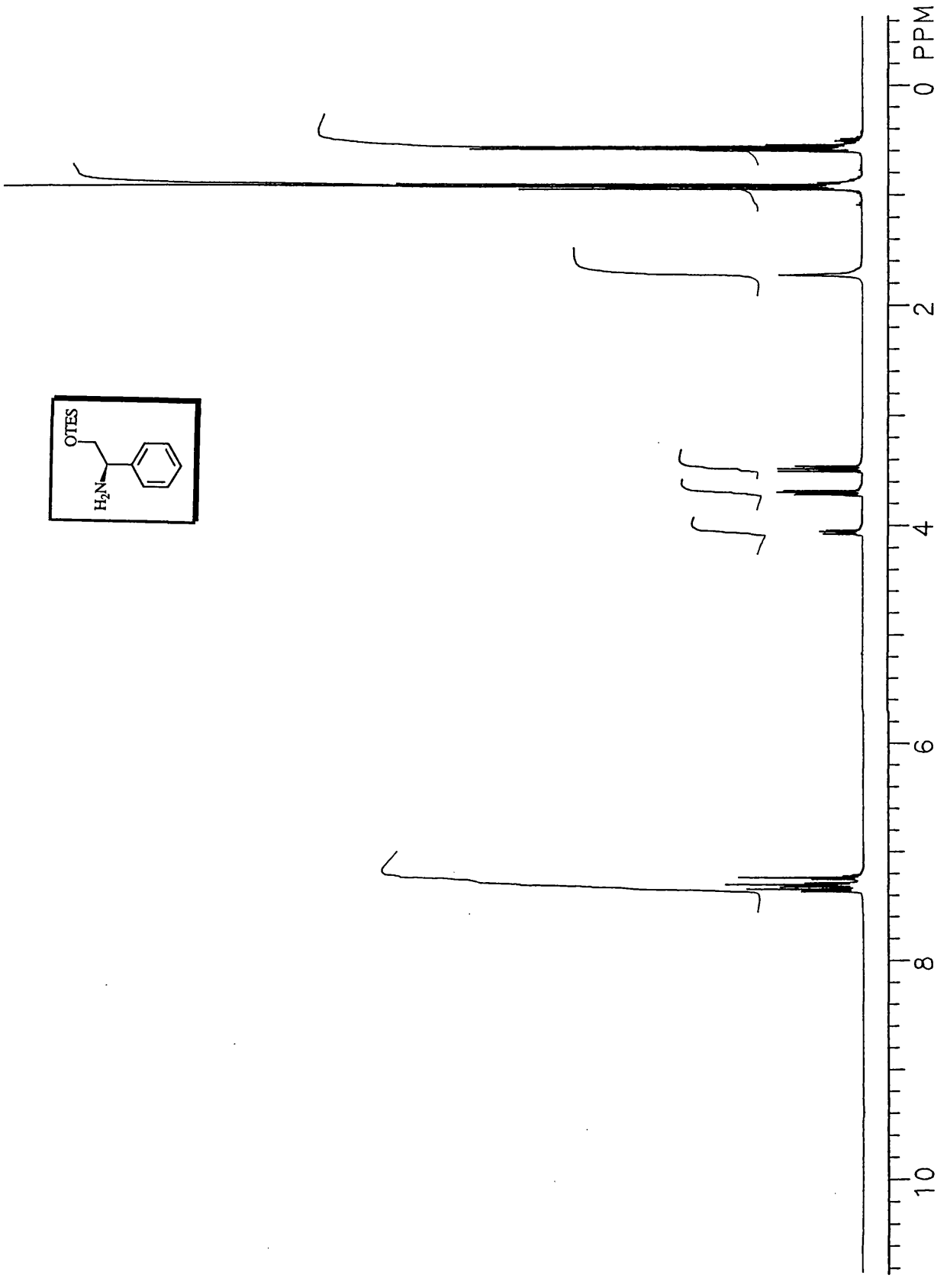


Figure 78 ^{1}H n.m.r. spectrum of *O*-triethylsilyl-D-(-)-α-phenylglycinol **172**

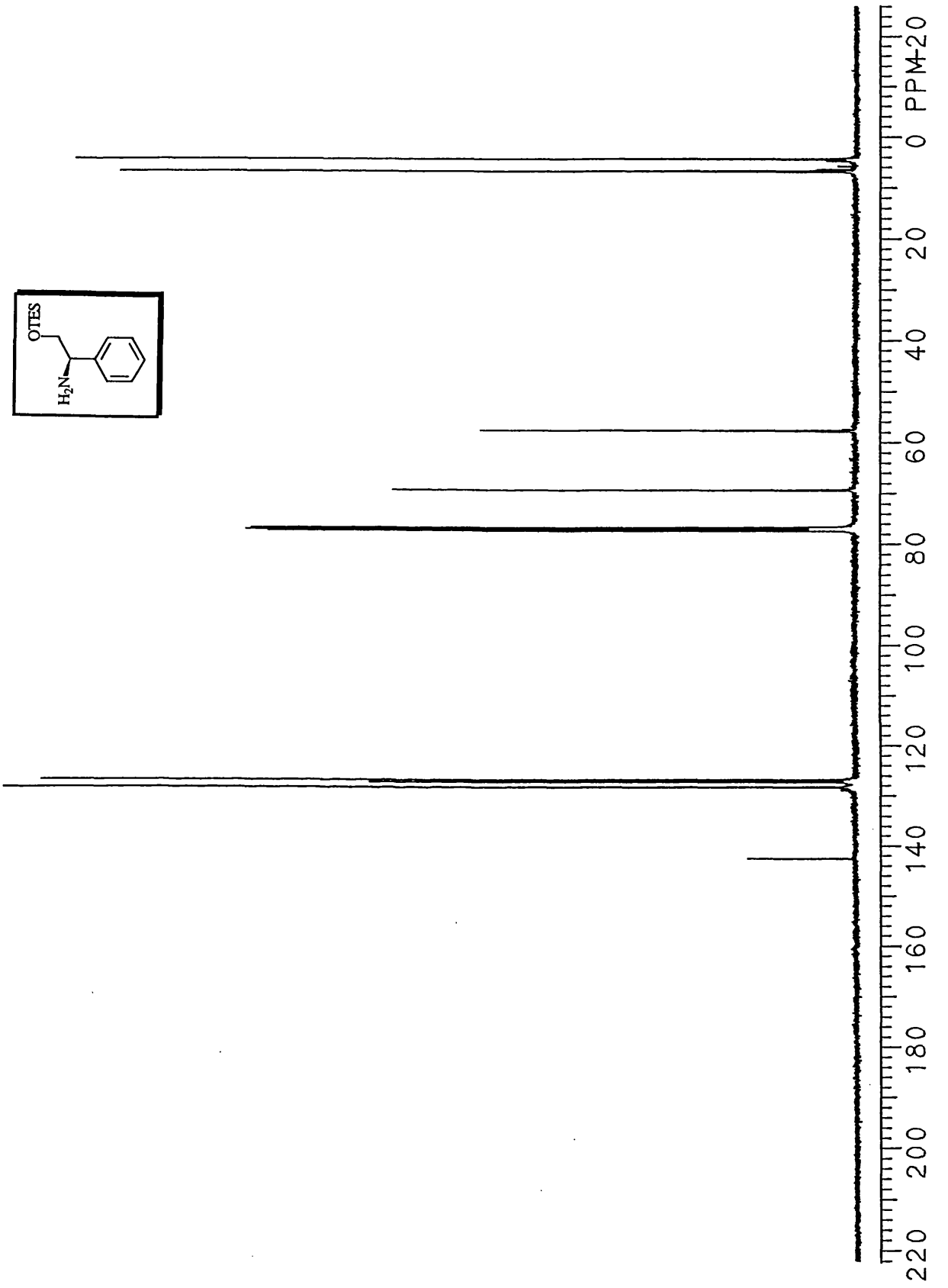


Figure 79 ^{13}C n.m.r. spectrum of *O*-triethylsilyl-D-(-)-α-phenylglycinol **172**

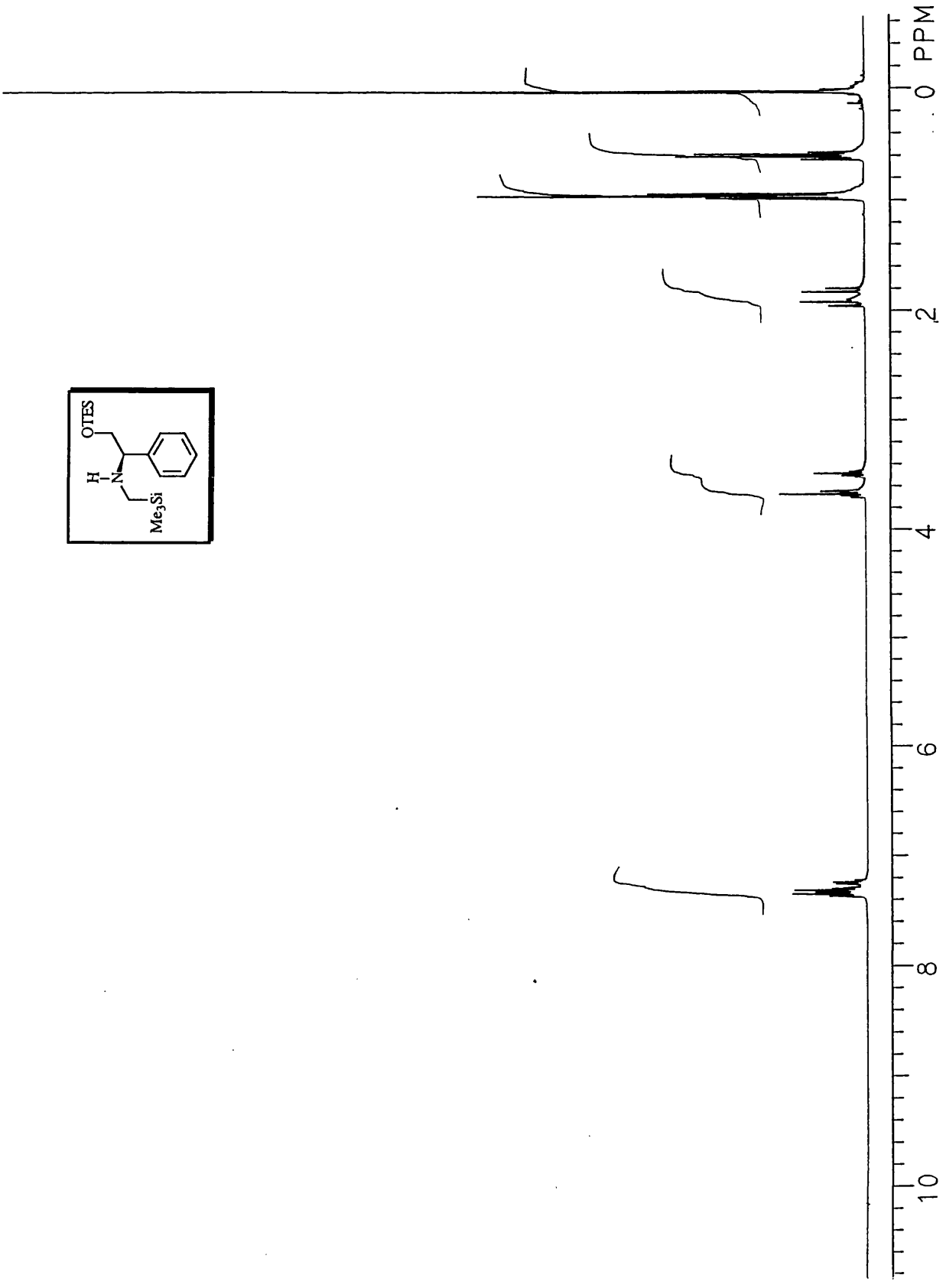


Figure 80 ^{1}H n.m.r. spectrum of *N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **173**

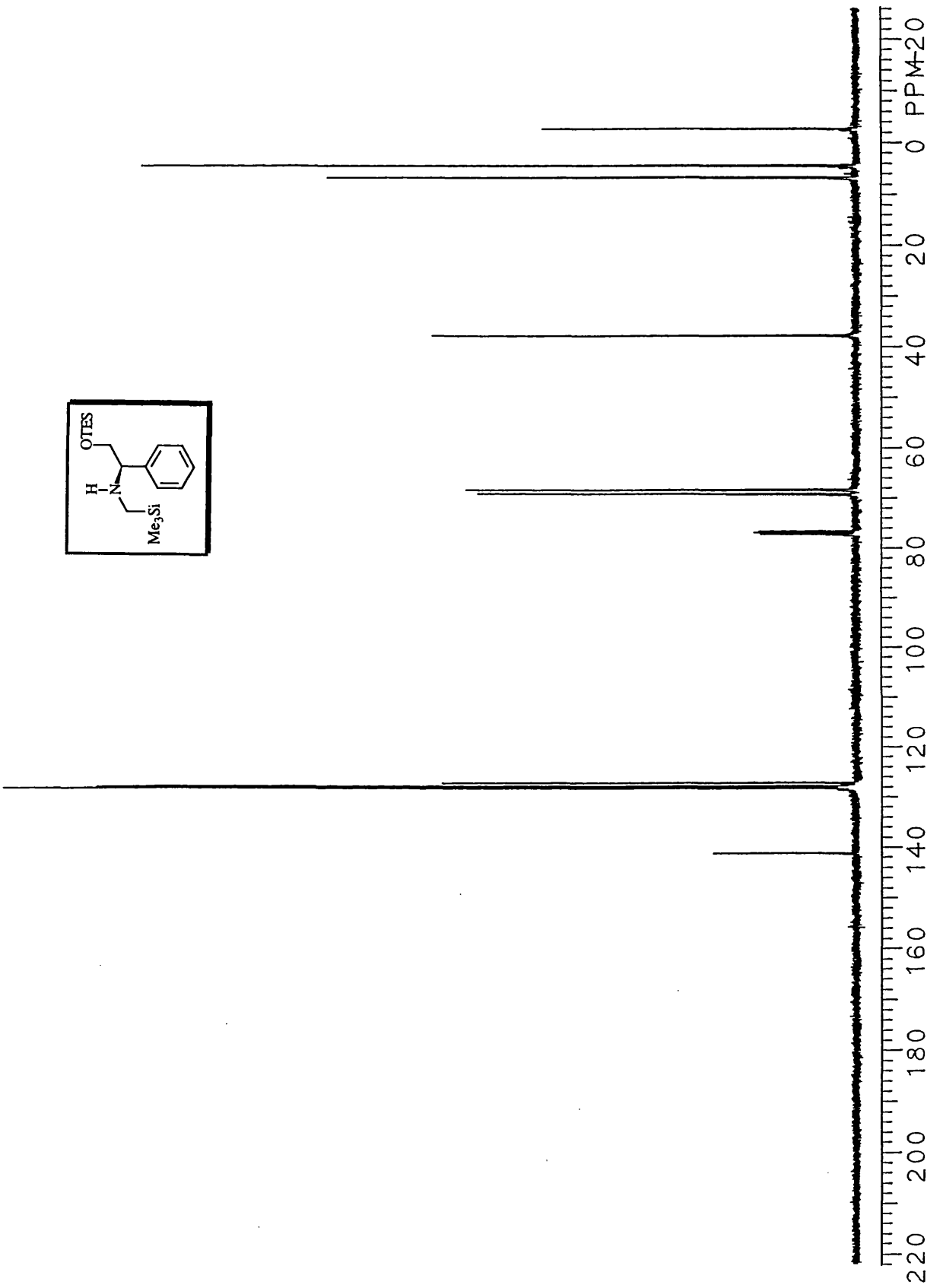


Figure 81 ^{13}C n.m.r. spectrum of *N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **173**

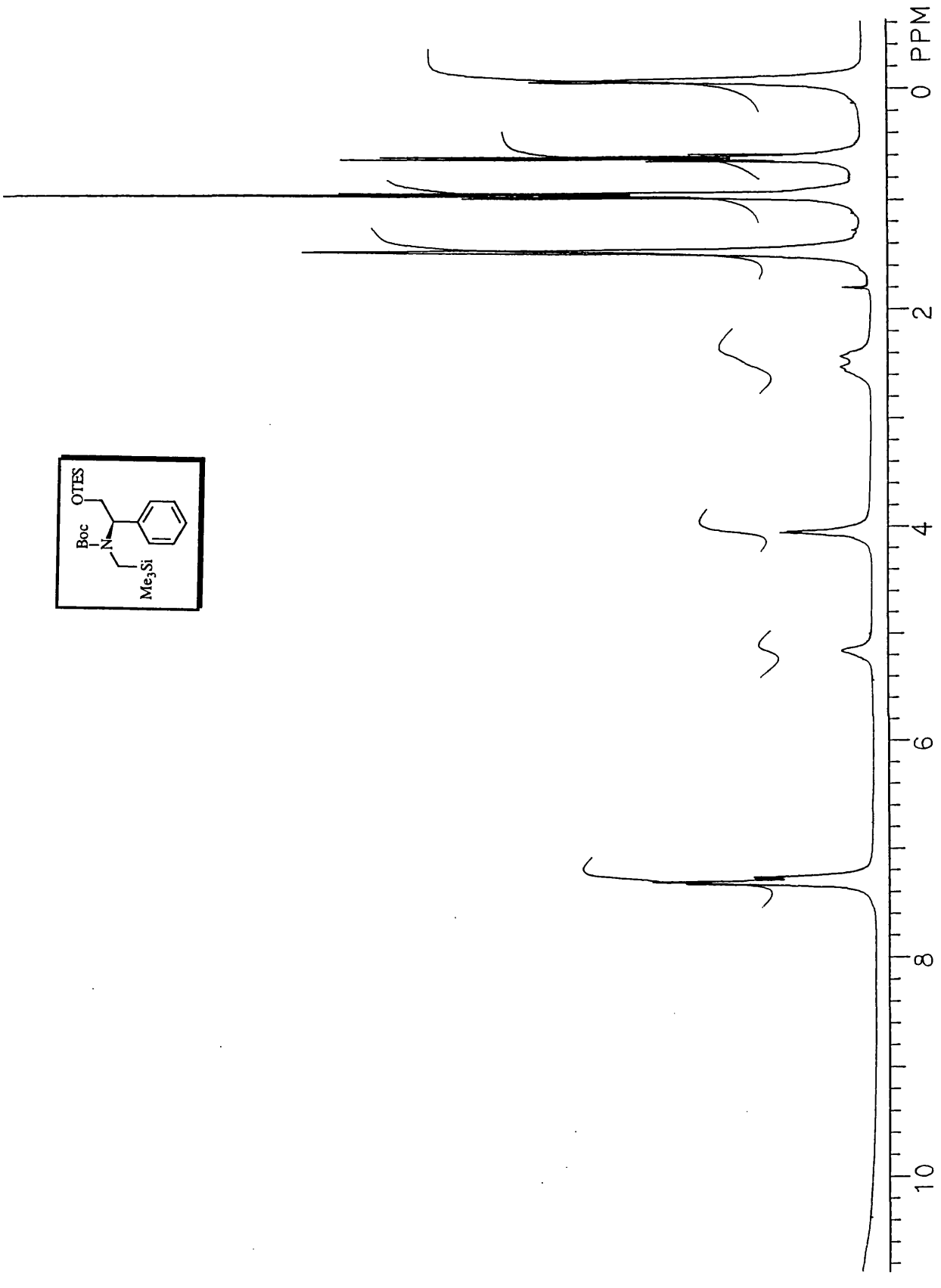


Figure 82 ^{1}H n.m.r. spectrum of *N-tert*-butoxycarbonyl-*N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **174**

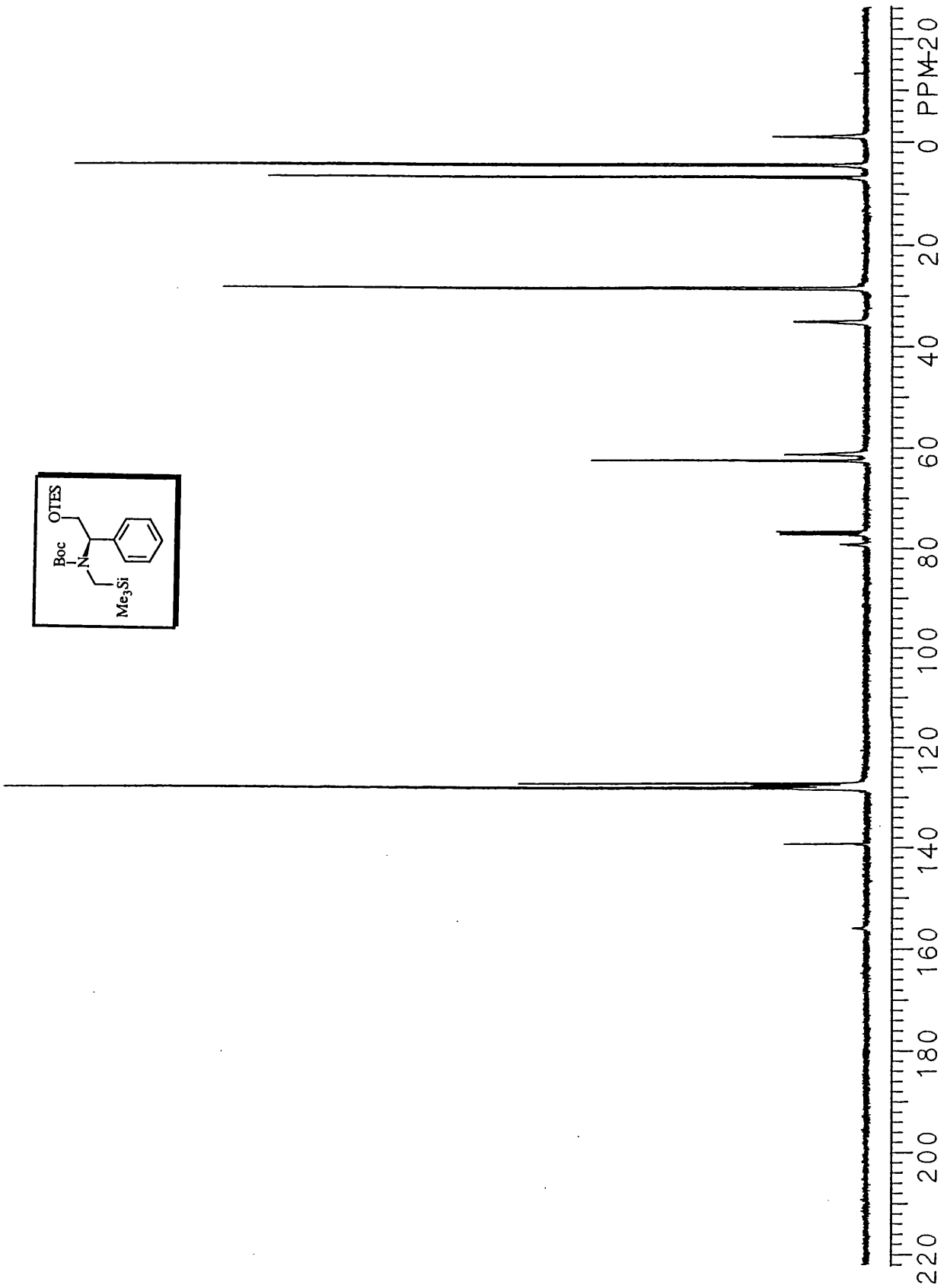


Figure 83 ^{13}C n.m.r. spectrum of *N-tert*-butoxycarbonyl-*N*-trimethylsilylmethyl-*O*-triethylsilyl-D-(-)-α-phenylglycinol **174**

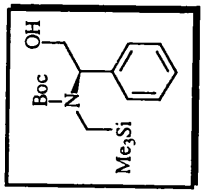


Figure 84 ^{1}H n.m.r. spectrum of *N-tert*-butoxycarbonyl-*N*-trimethylsilylmethyl-D-(-)-α-phenylglycinol **175**

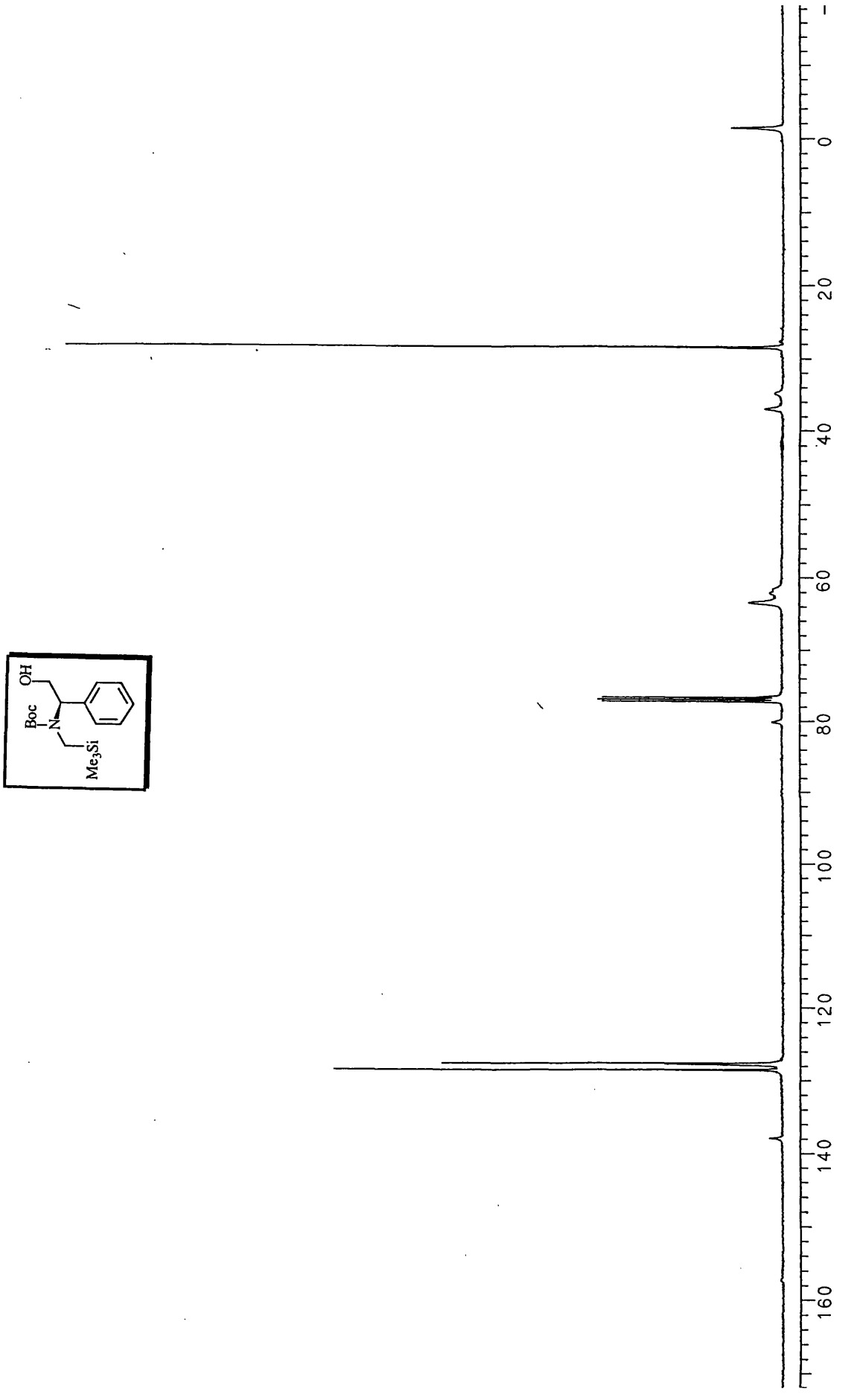


Figure 85 ^{13}C n.m.r. spectrum of *N-tert*-butoxycarbonyl-*N*-trimethylsilylmethyl-D-(-)-α-phenylglycinol **175**

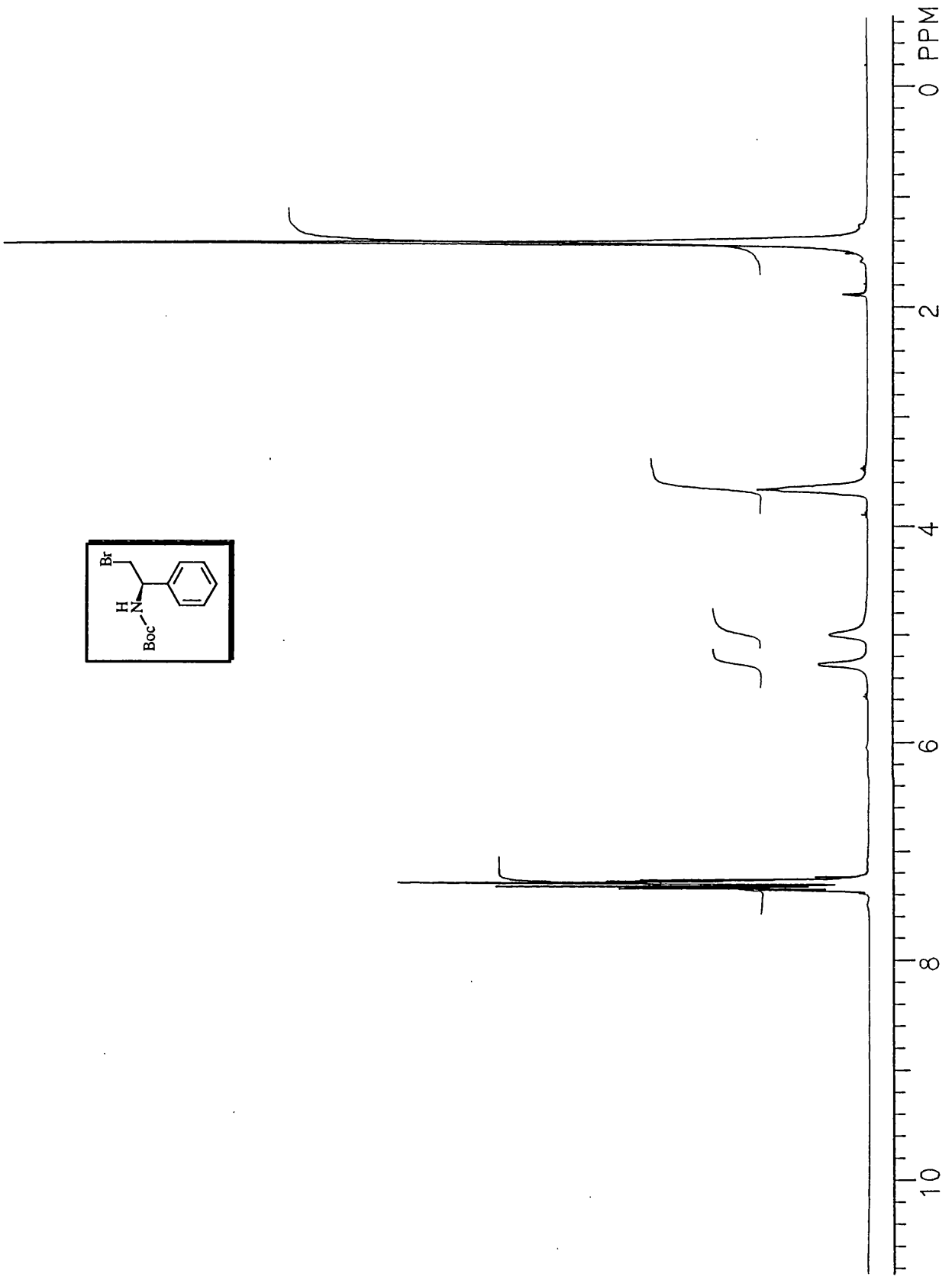


Figure 86 ^{1}H n.m.r. spectrum of D-(-)-α-(1-bromoethyl)-*N*-(*tert*-butoxycarbonyl)-benzylamine **184**

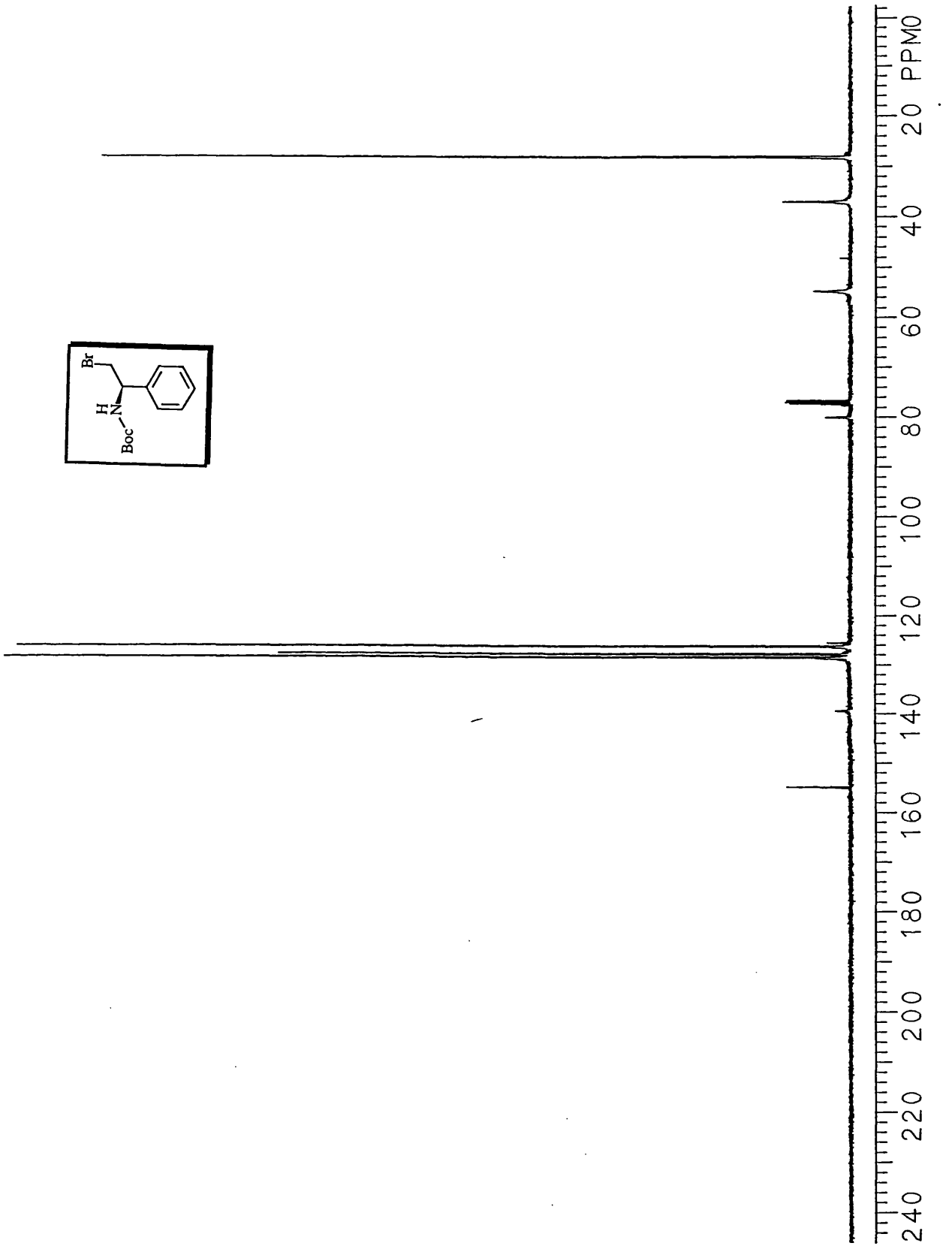


Figure 87 ^{13}C n.m.r. spectrum of D-(-)-α-(1-bromoethyl)-*N*-(*tert*-butoxycarbonyl)-benzylamine **184**

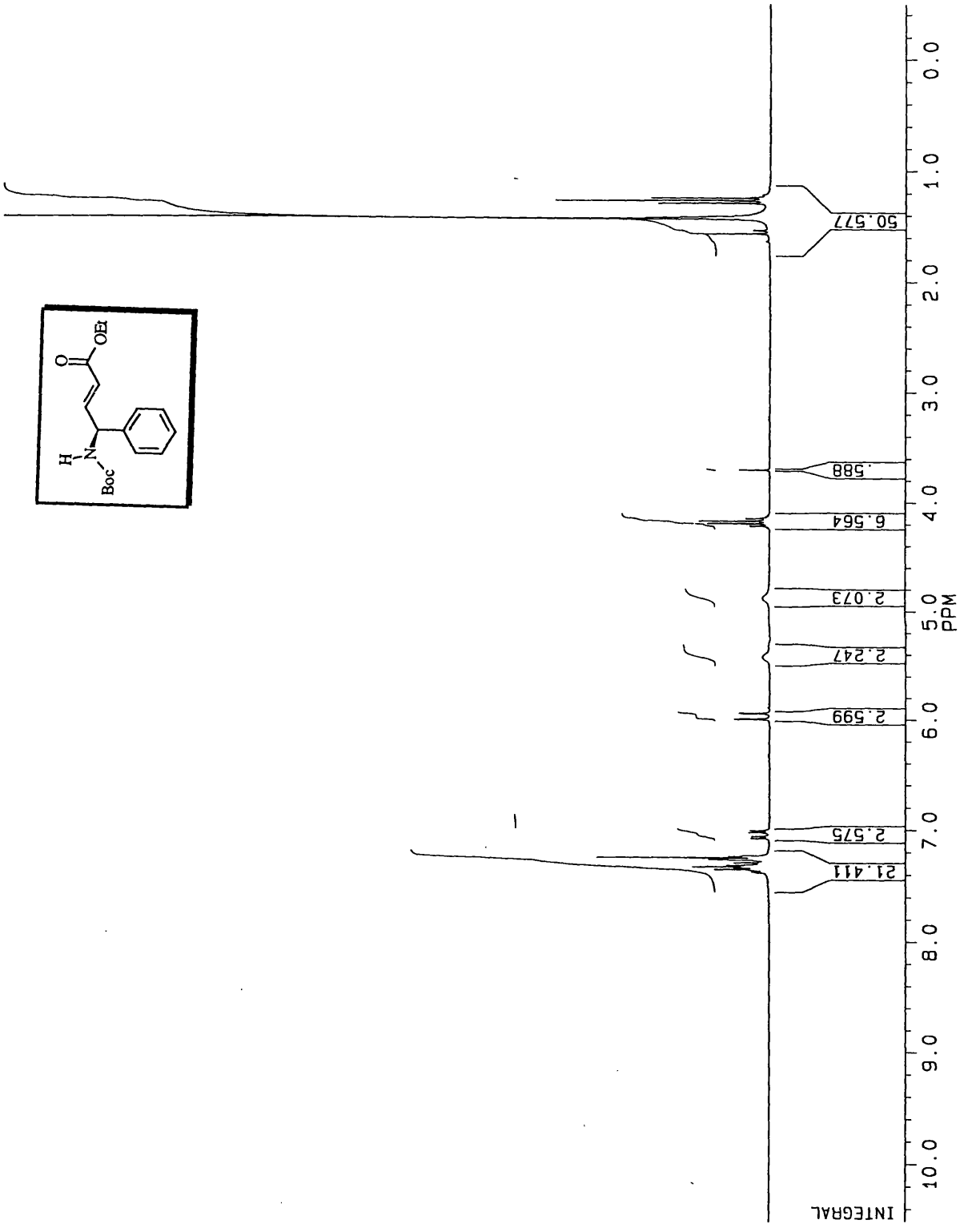


Figure 88 ^{1}H n.m.r. spectrum of (*R*)-(-)-α-4-*tert*-butoxycarbonylamino-4-phenyl-(*E*)-but-2-enoic acid ethyl ester **190**

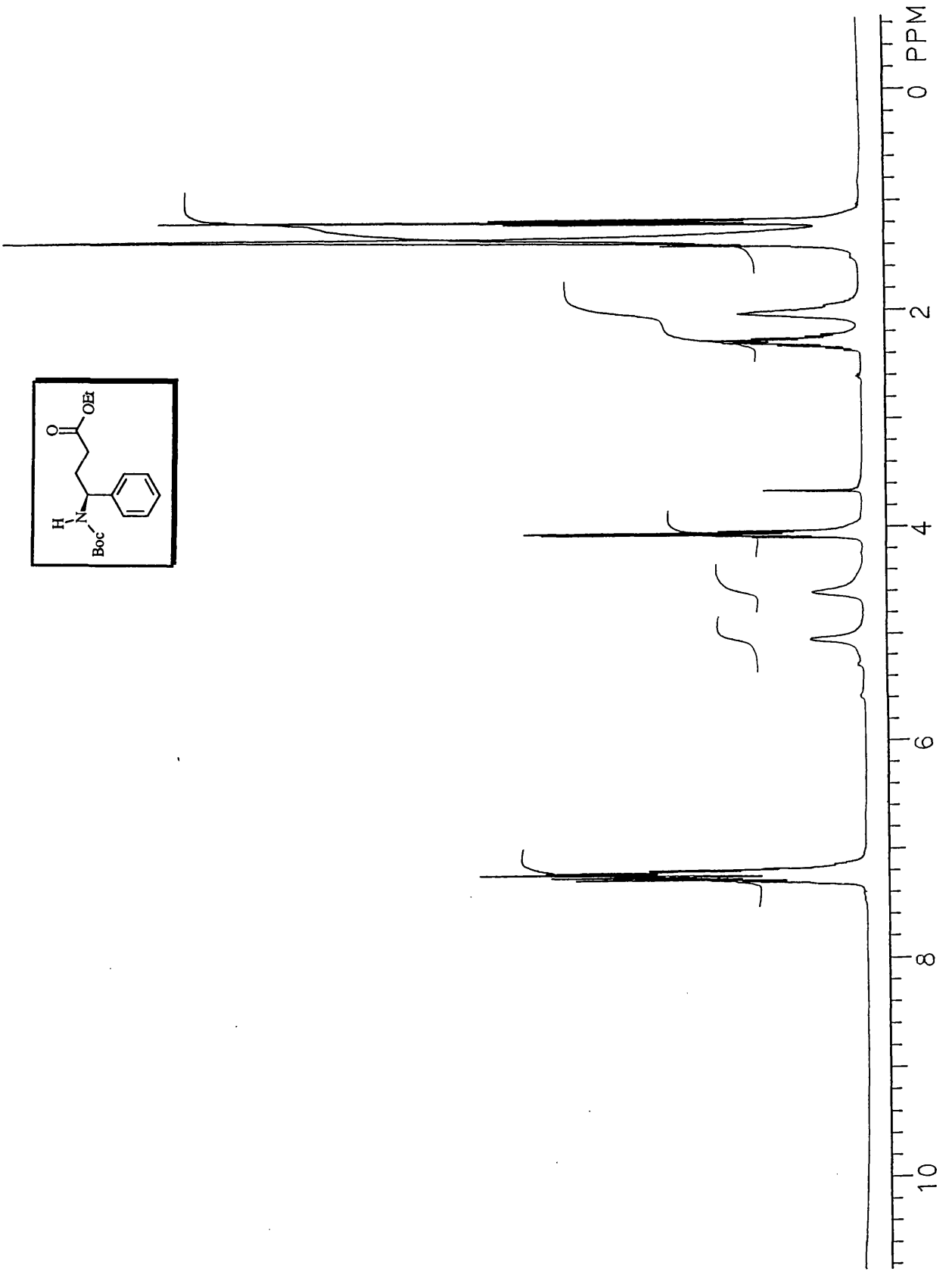


Figure 89 ^{1}H n.m.r. spectrum of (*R*)-(-)-α-4-*tert*-butoxycarbonylamino-4-phenyl-butanoic acid ethyl ester **191**

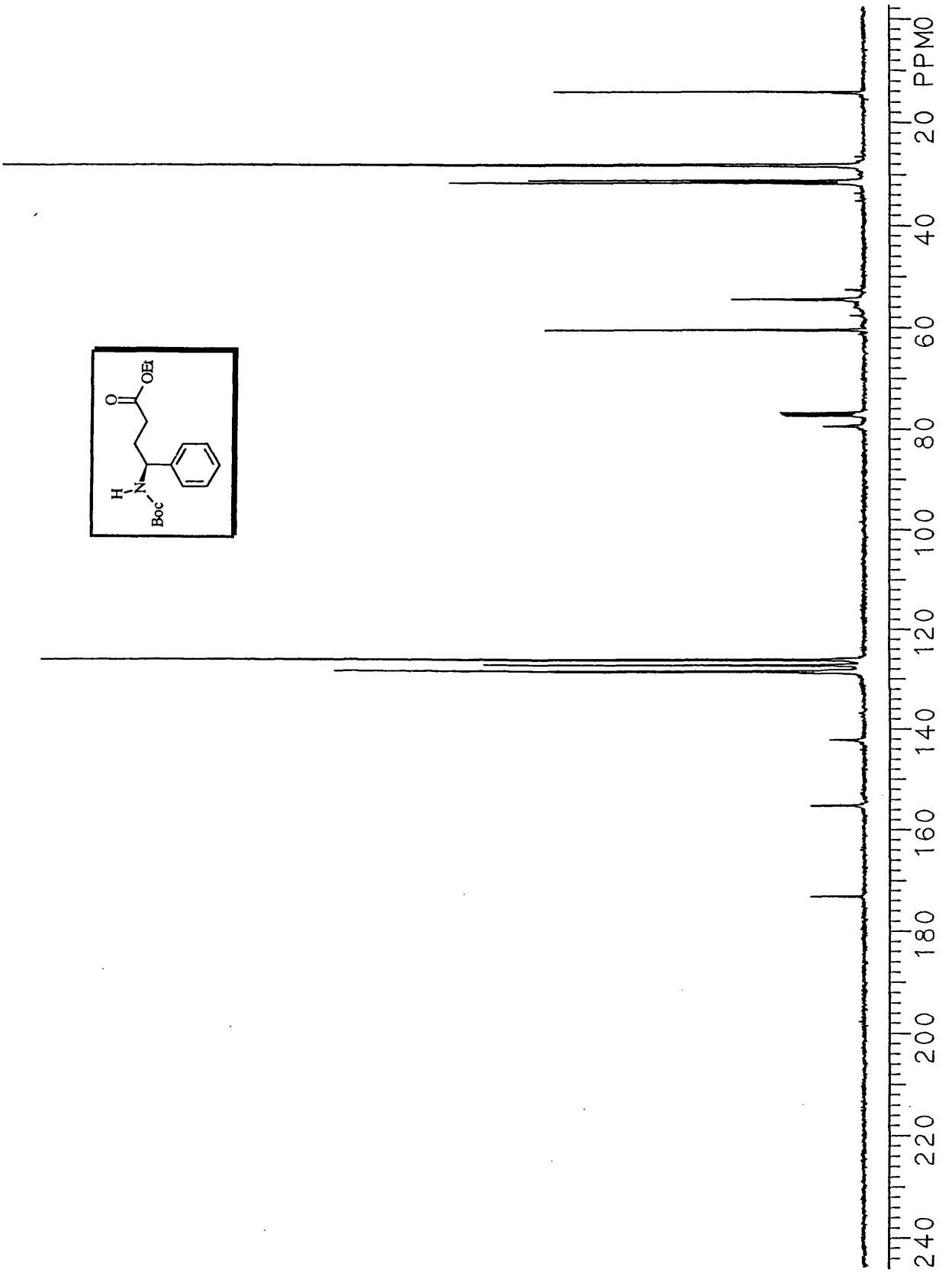


Figure 90 ^{13}C n.m.r. spectrum of (*R*)-(-)-α-4-*tert*-butoxycarbonylamino-4-phenyl-butanoic acid ethyl ester **191**

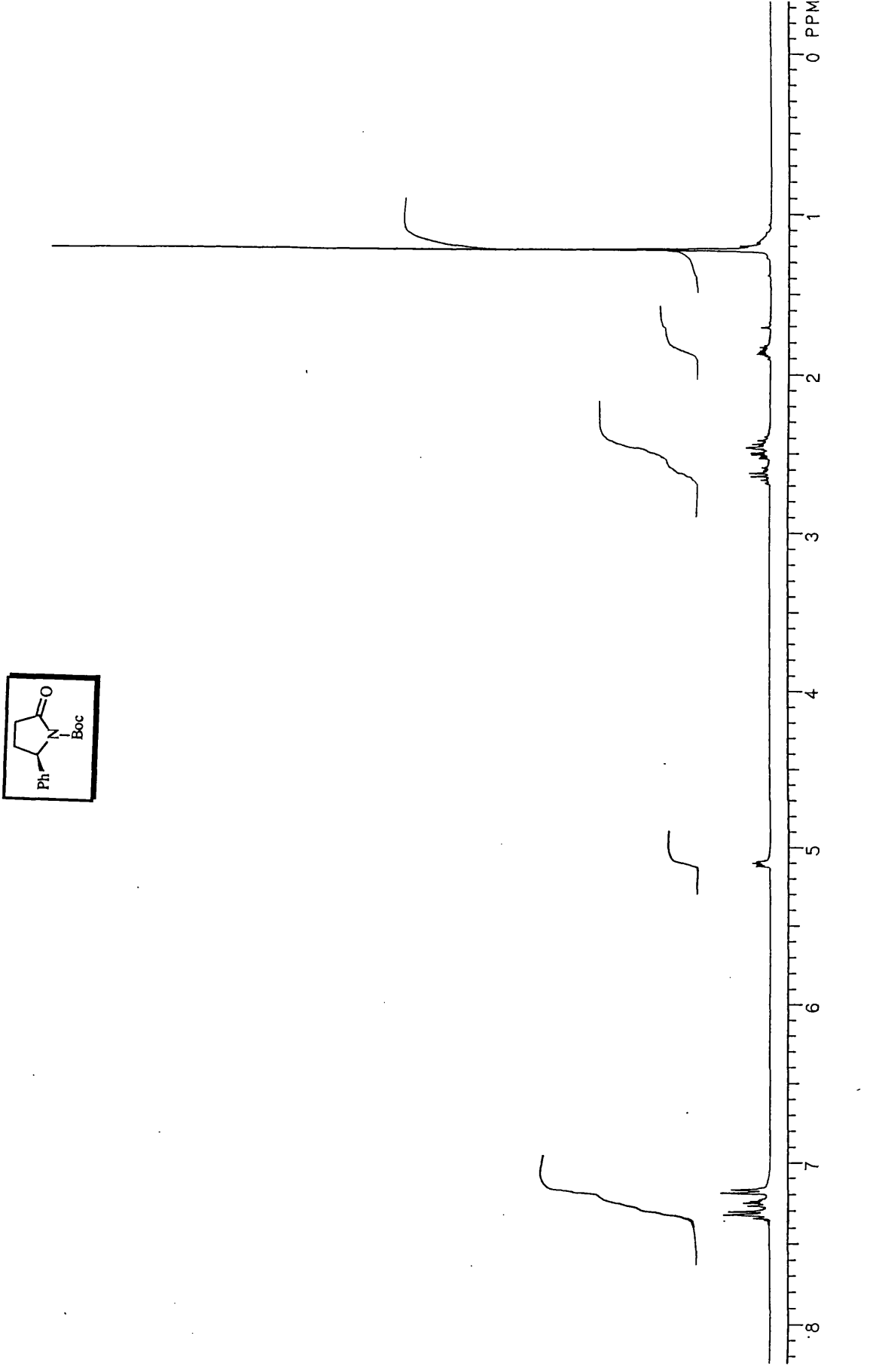


Figure 91 ^{1}H n.m.r. spectrum of (*R*)-(-)-α-*N*-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolidinone **186**

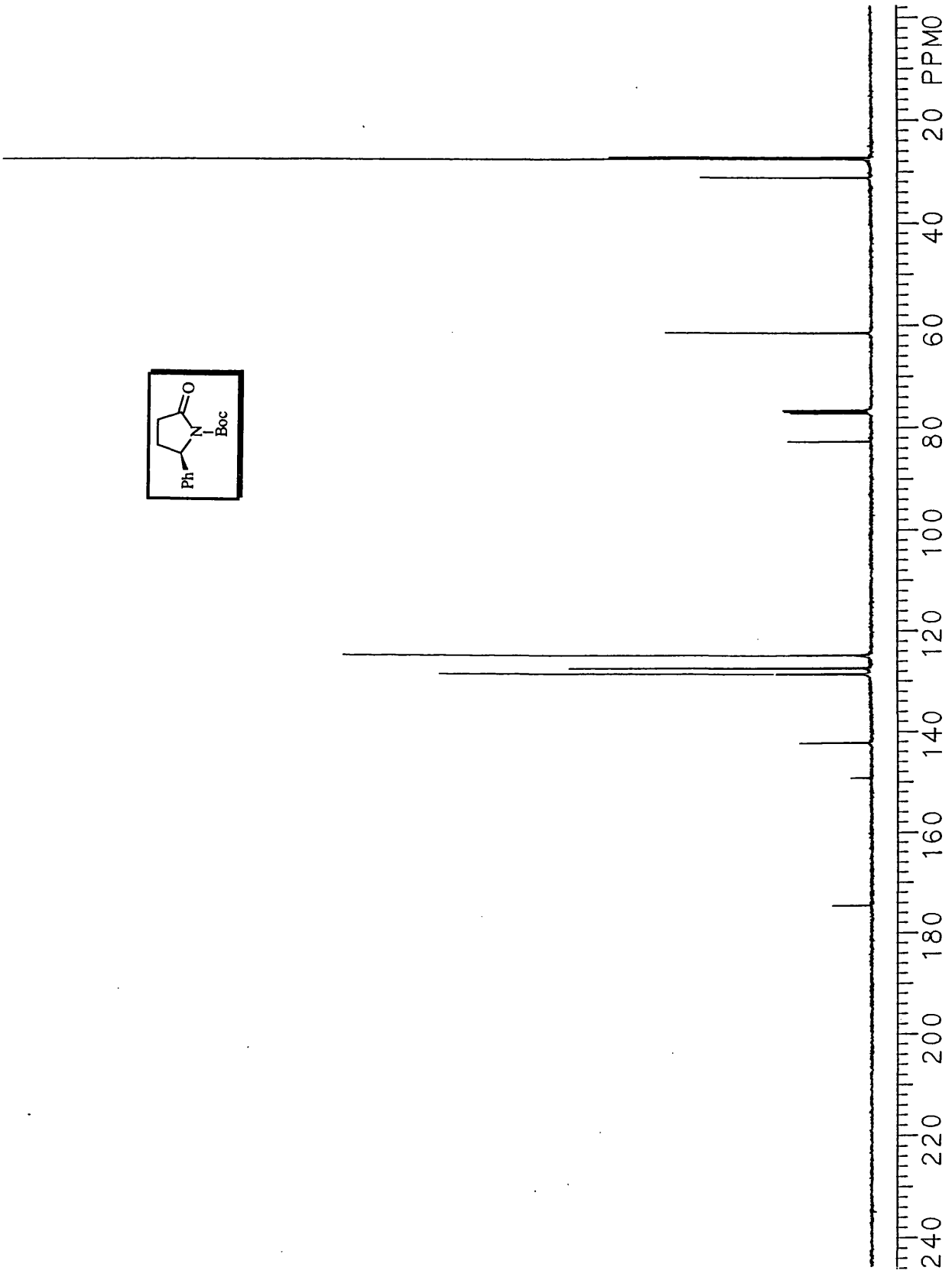


Figure 92 ^{13}C n.m.r. spectrum of (*R*)-(-)-α-*N*-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolidinone **186**

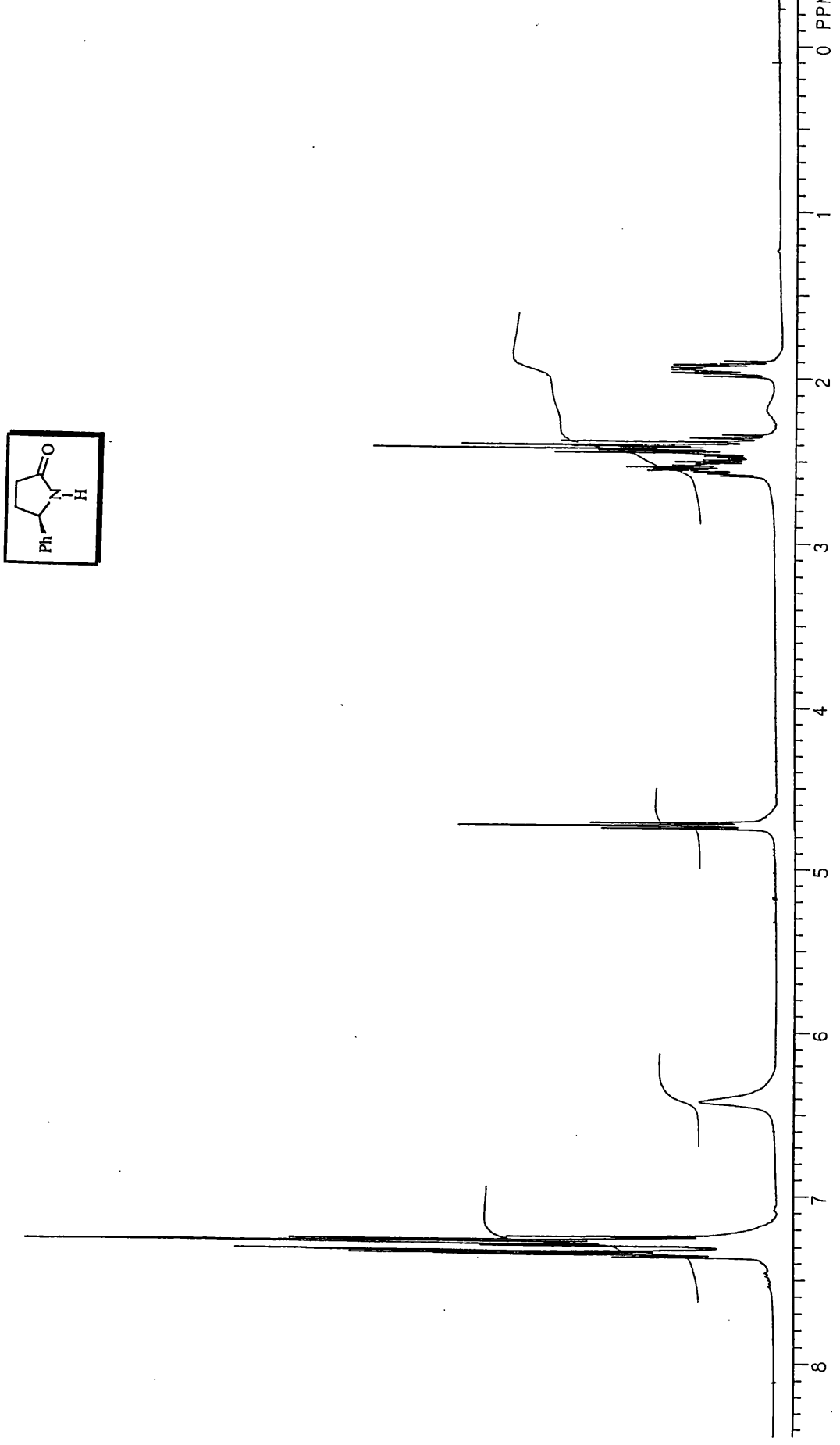


Figure 93 ^{1}H n.m.r. spectrum of (*R*)-α-5-phenyl-2-pyrrolidinone **156**

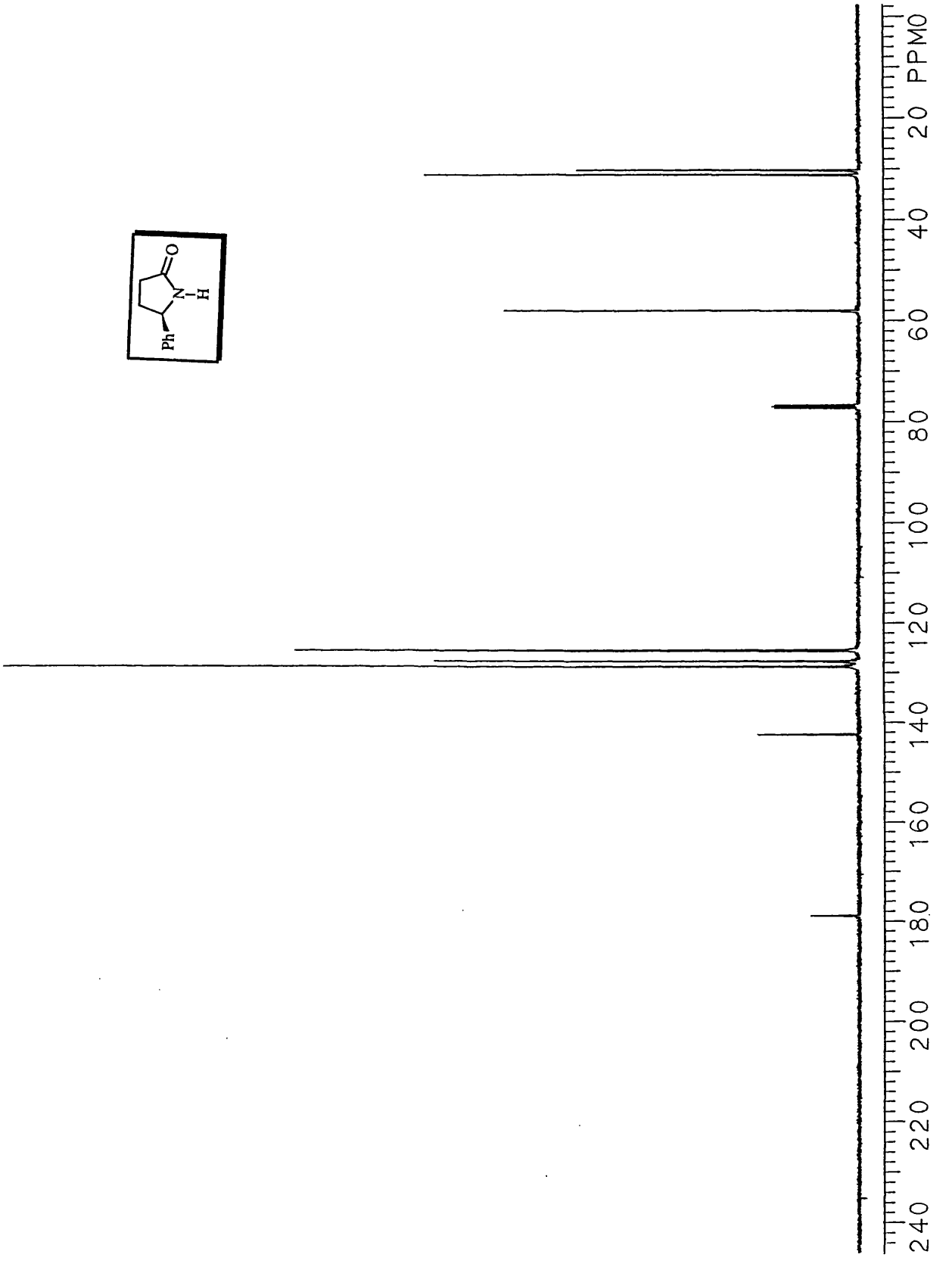


Figure 94 ^{13}C n.m.r. spectrum of (*R*)-α-5-phenyl-2-pyrrolidinone **156**

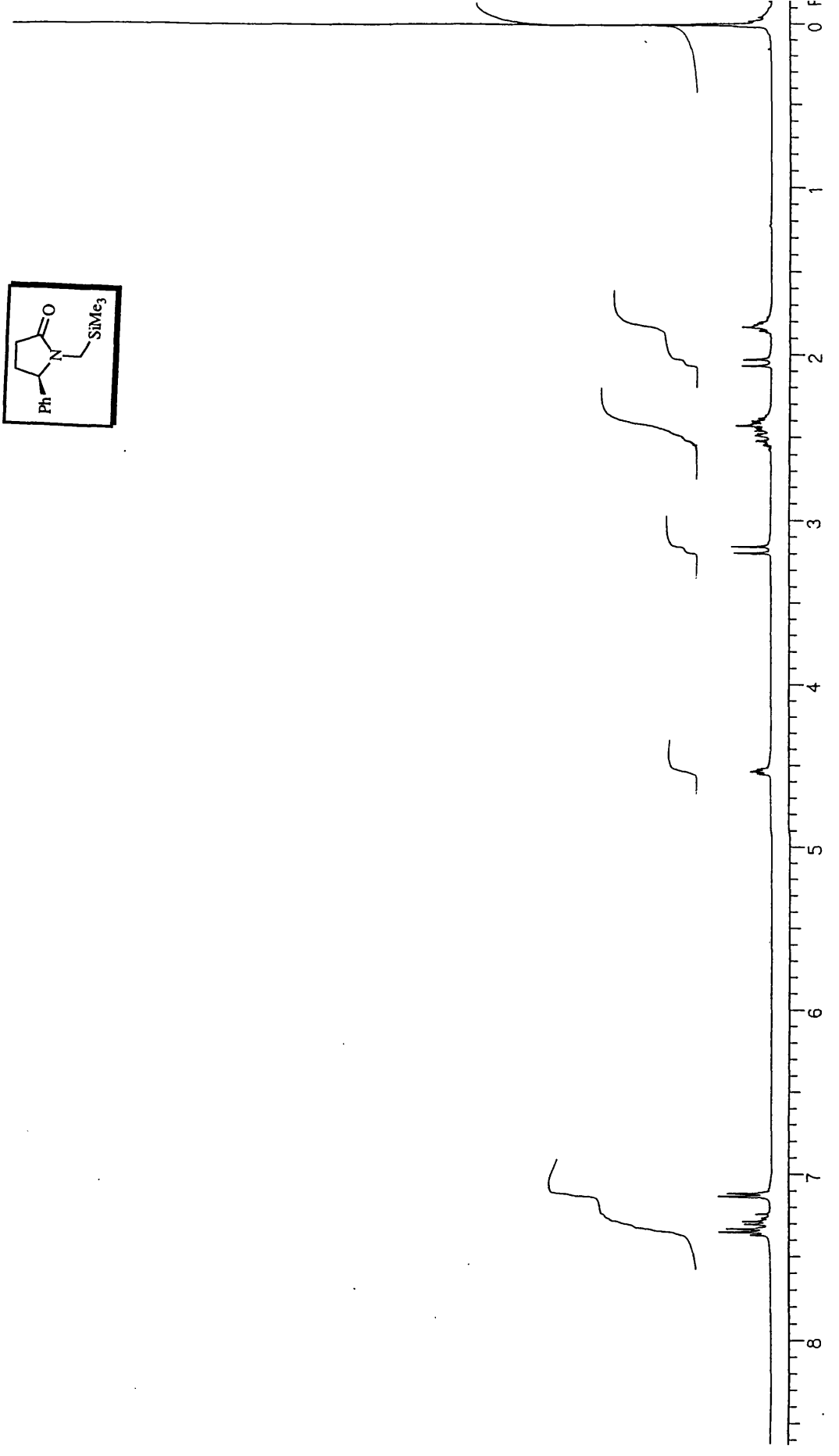


Figure 95 ^{1}H n.m.r. spectrum of (*R*)-α-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**

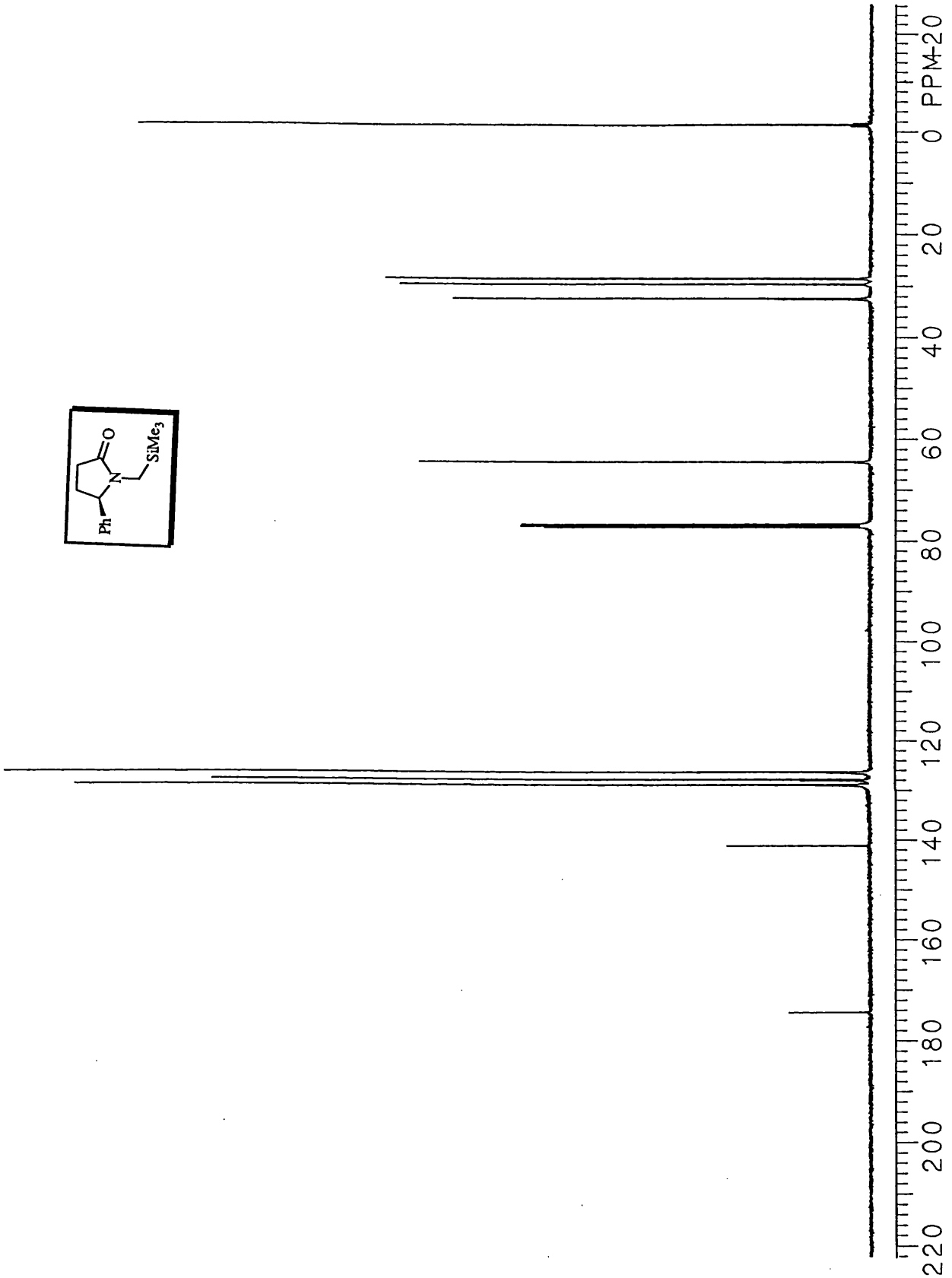


Figure 96 ^{13}C n.m.r. spectrum of (*R*)-α-*N*-(trimethylsilylmethyl)-5-phenyl-2-pyrrolidinone **157**

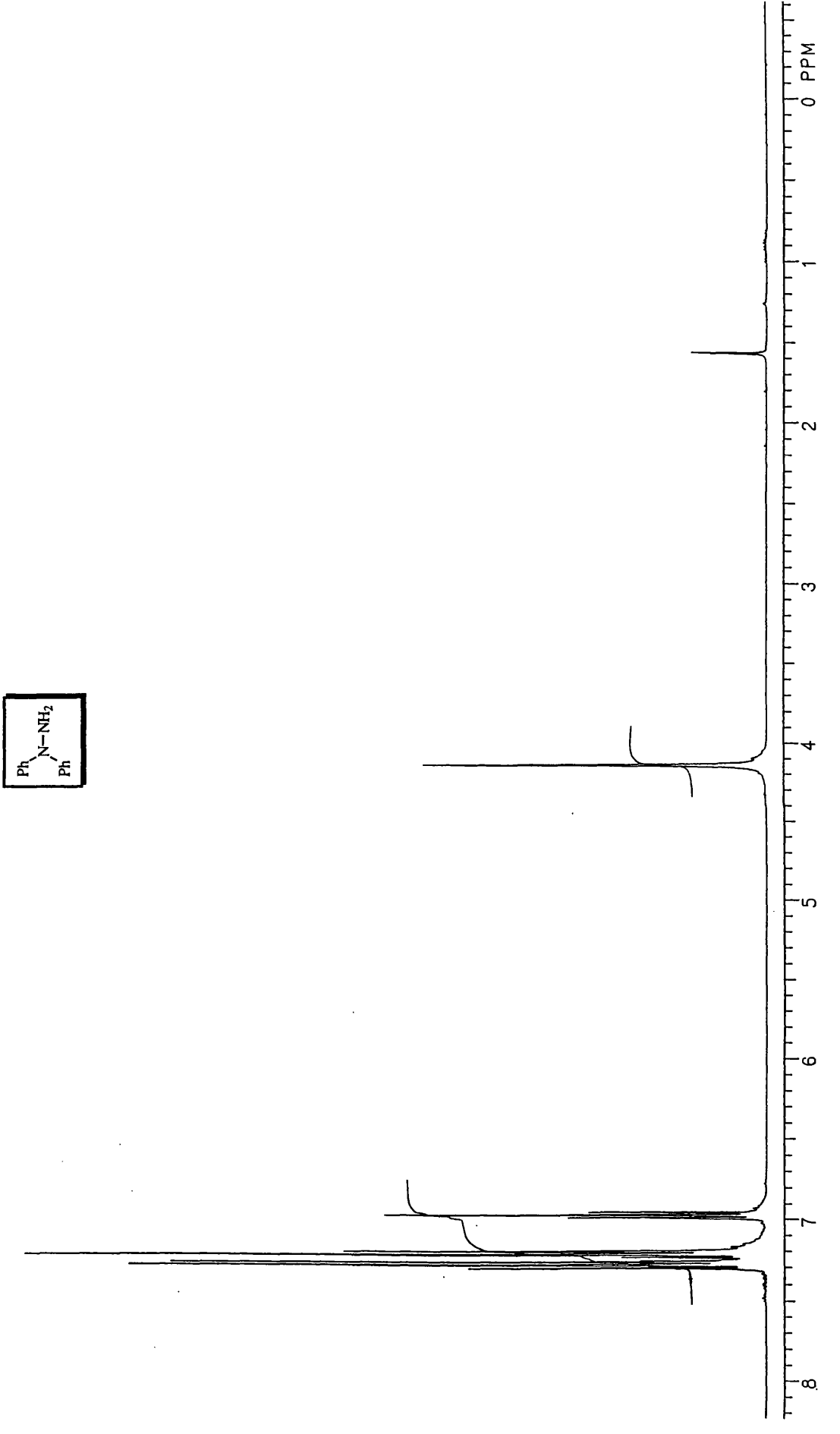


Figure 97 ^{1}H n.m.r. spectrum of *N*-amino-diphenylamine **200**

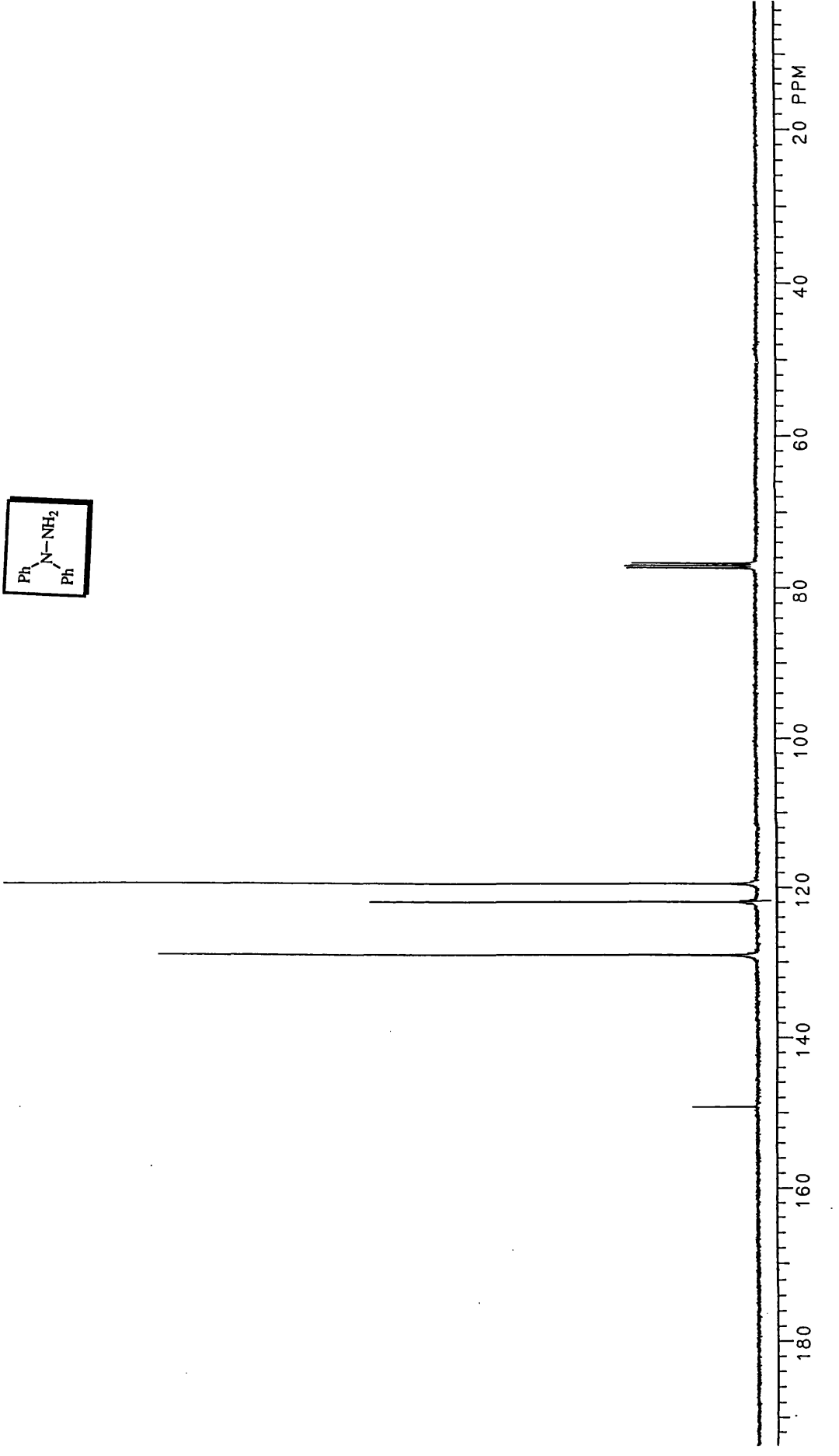


Figure 98 ^{13}C n.m.r. spectrum of *N*-amino-diphenylamine **200**

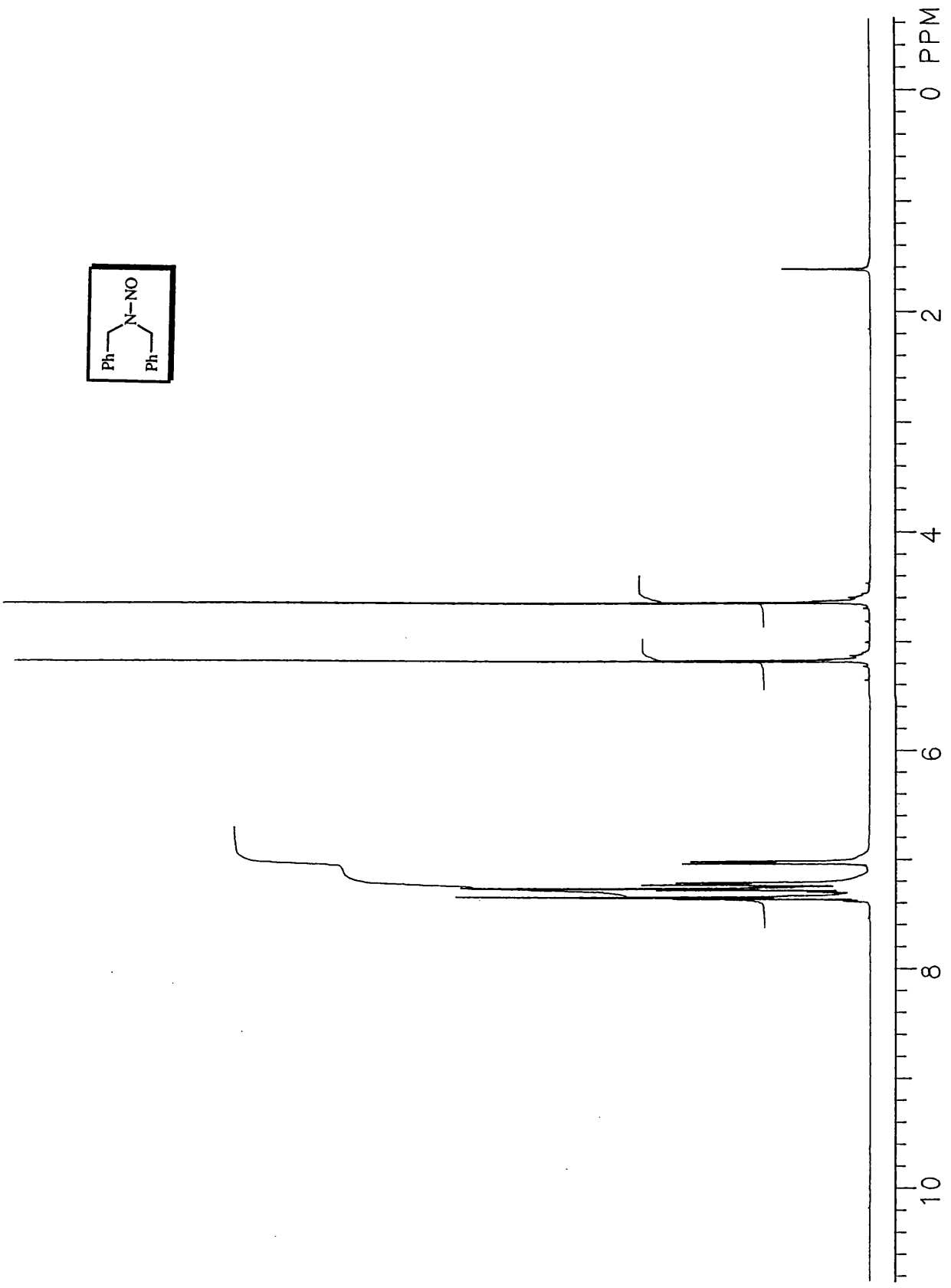


Figure 99 ^{1}H n.m.r. spectrum of *N*-nitroso-dibenzylamine **201**

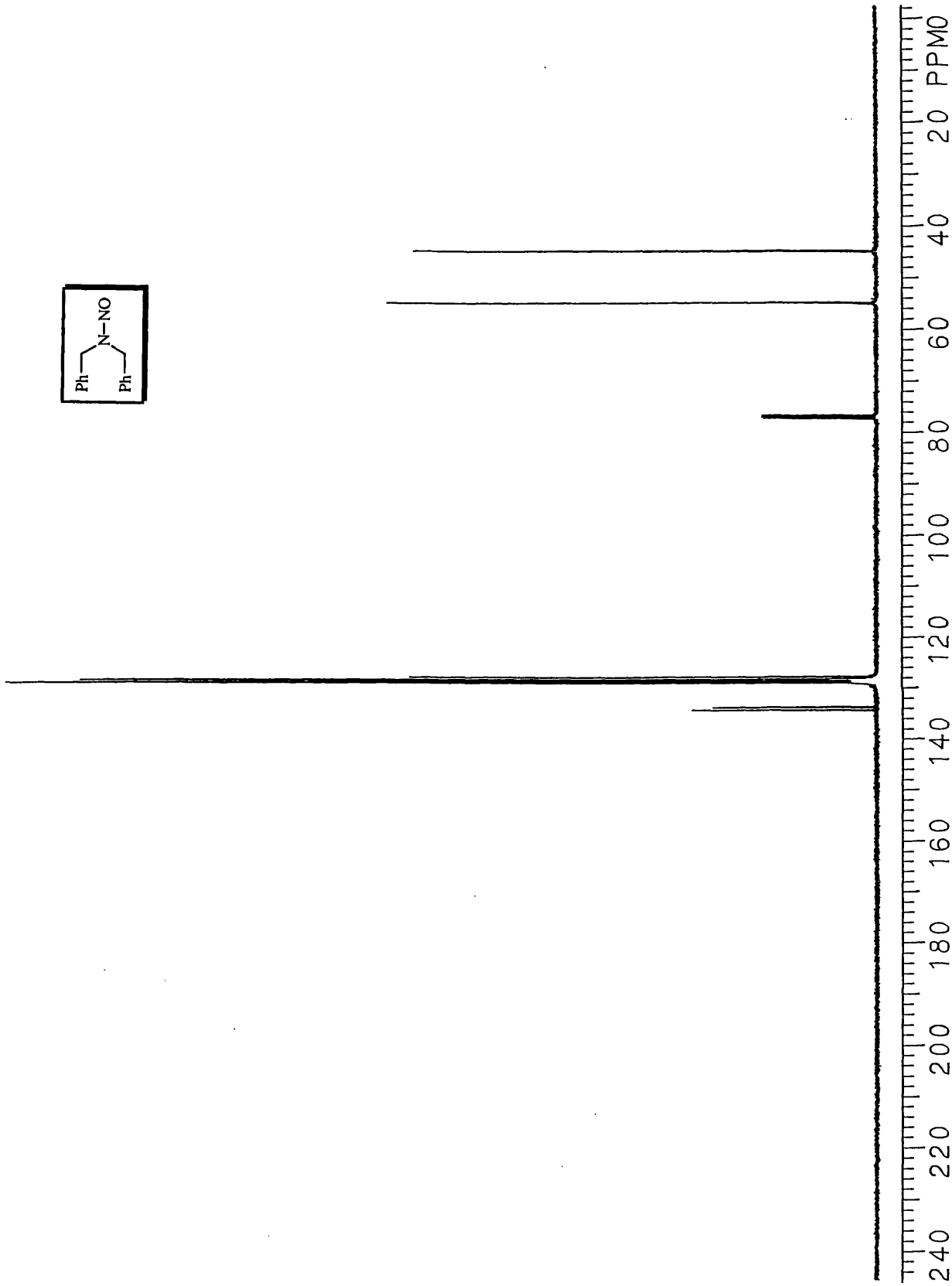


Figure 100 ^{13}C n.m.r. spectrum of *N*-nitroso-dibenzylamine **201**

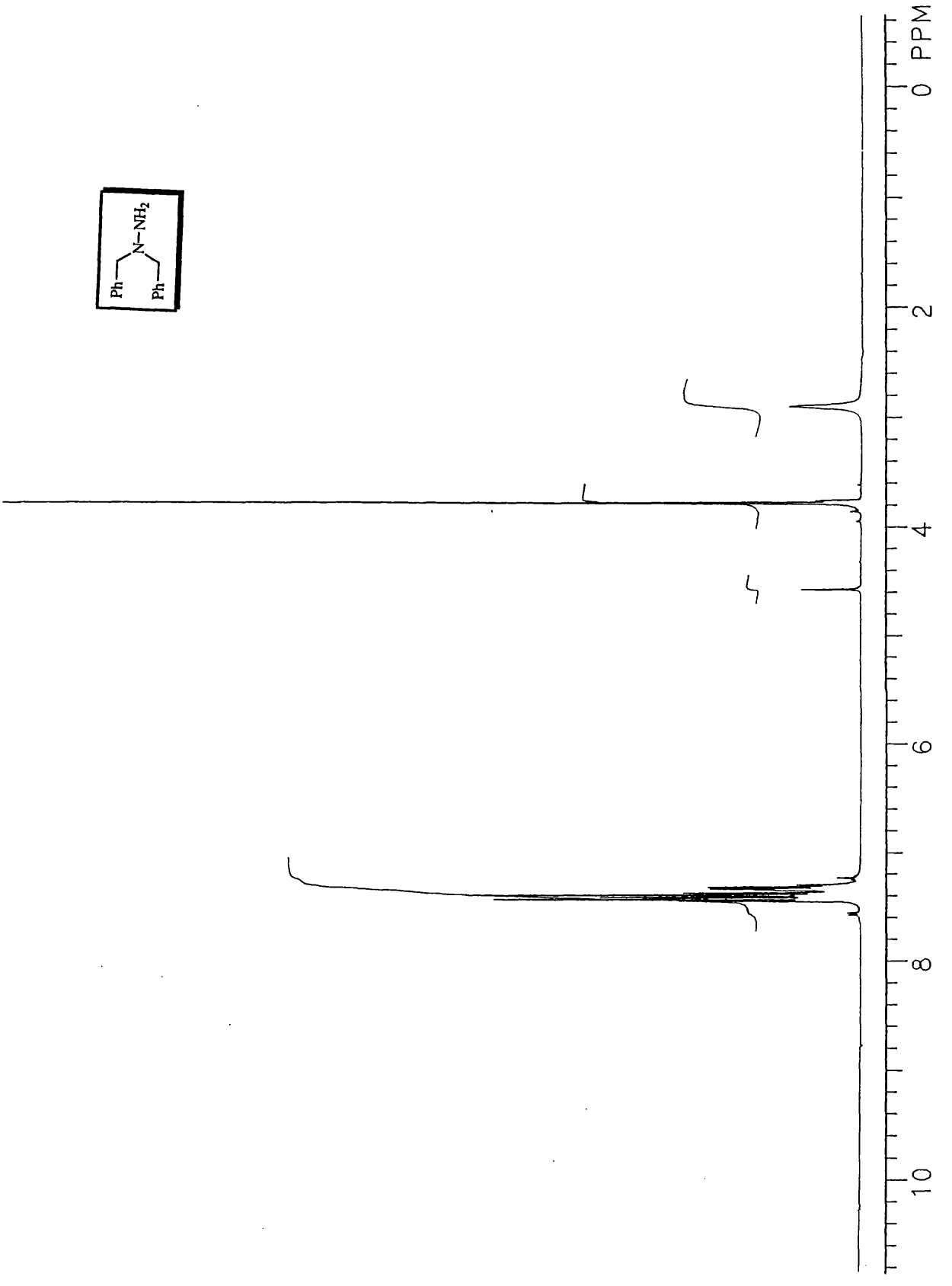


Figure 101 ^{1}H n.m.r. spectrum of *N*-amino-dibenzylamine **202**

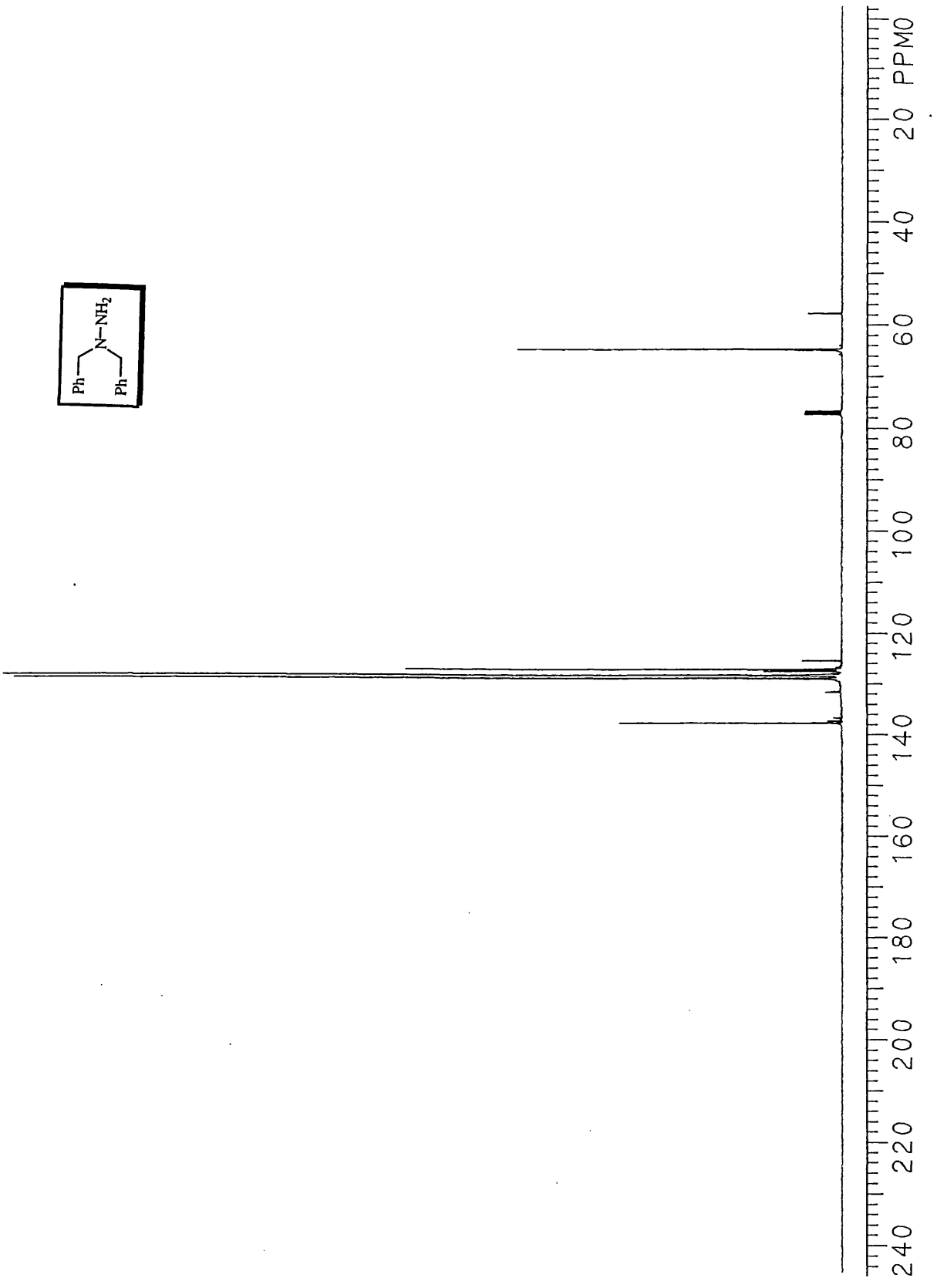


Figure 102 ^{13}C n.m.r. spectrum of *N*-amino-dibenzylamine **202**

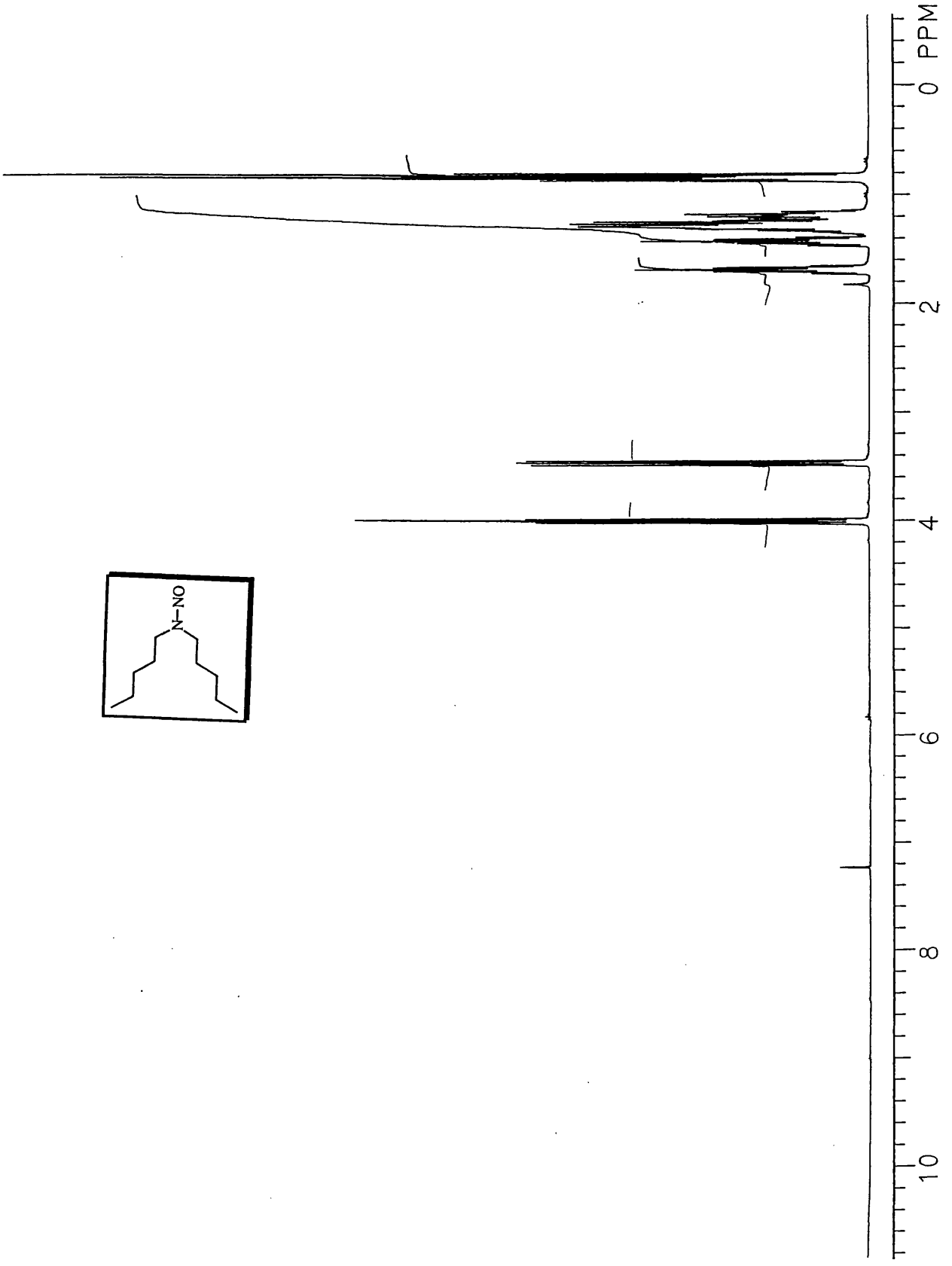


Figure 103 ^{1}H n.m.r. spectrum of *N*-nitroso-dipentylamine **203**

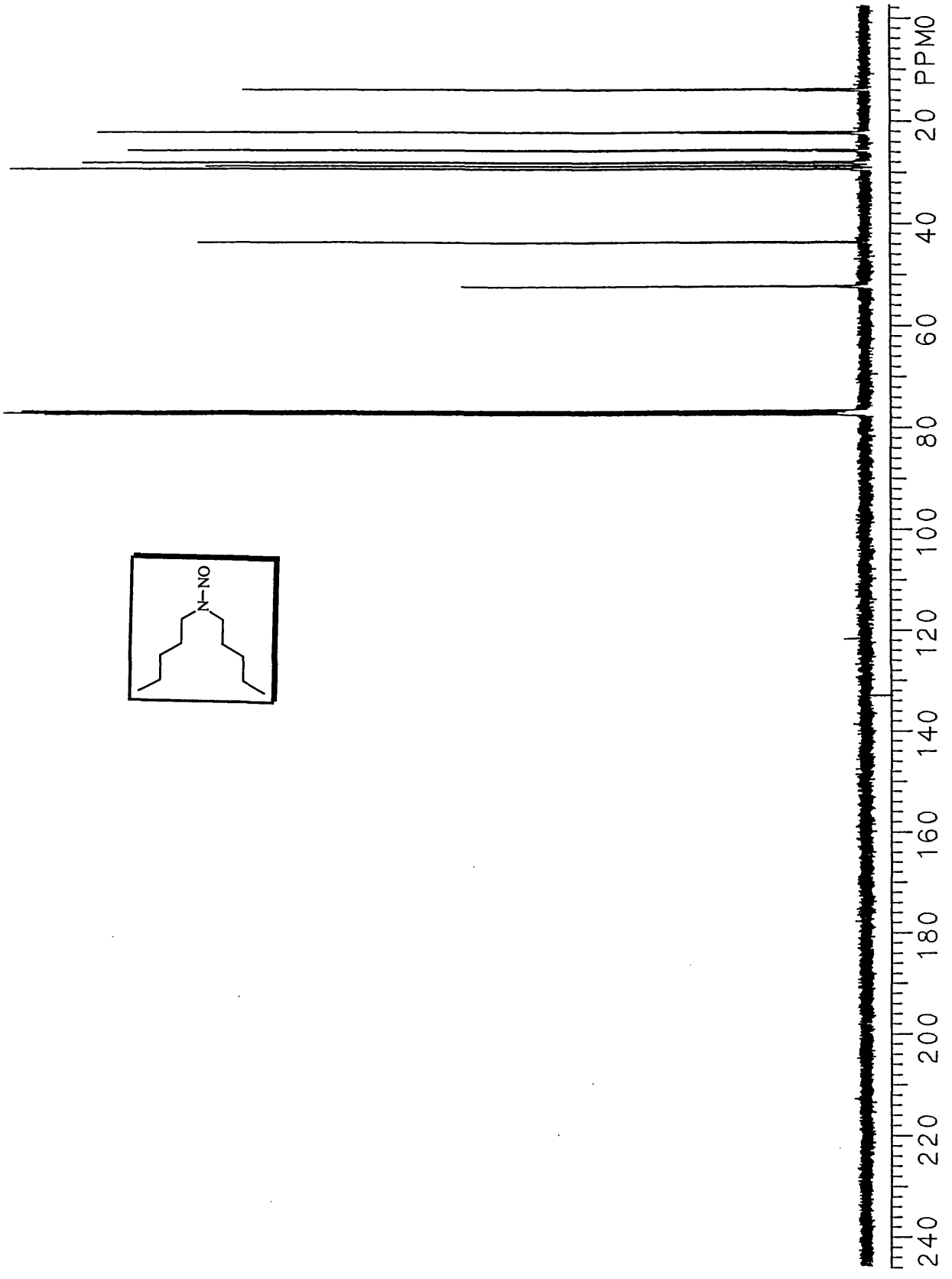


Figure 104 ^{13}C n.m.r. spectrum of *N*-nitroso-dipentylamine **203**

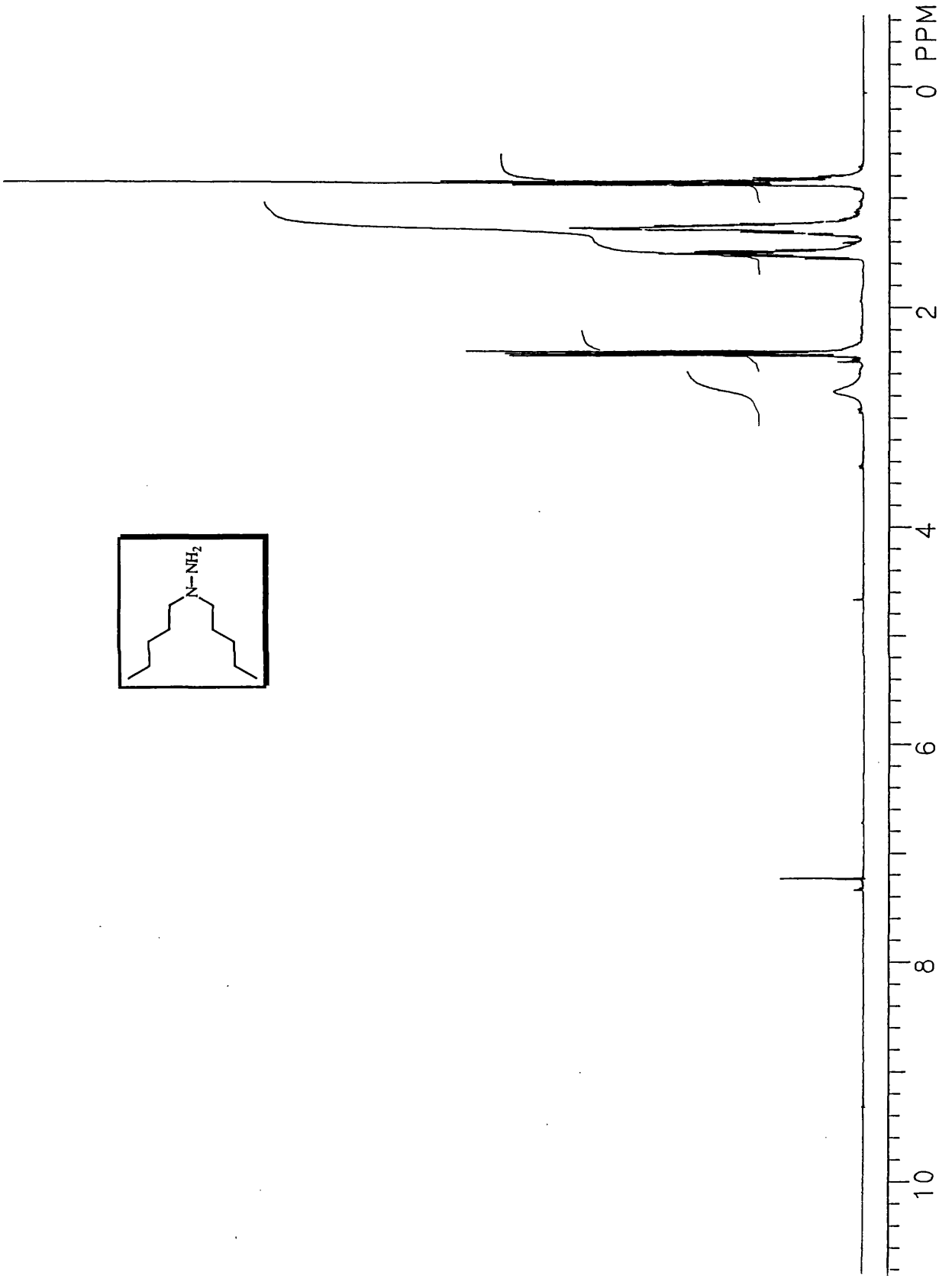


Figure 105 ^{1}H n.m.r. spectrum of *N*-amino-dipentylamine **204**

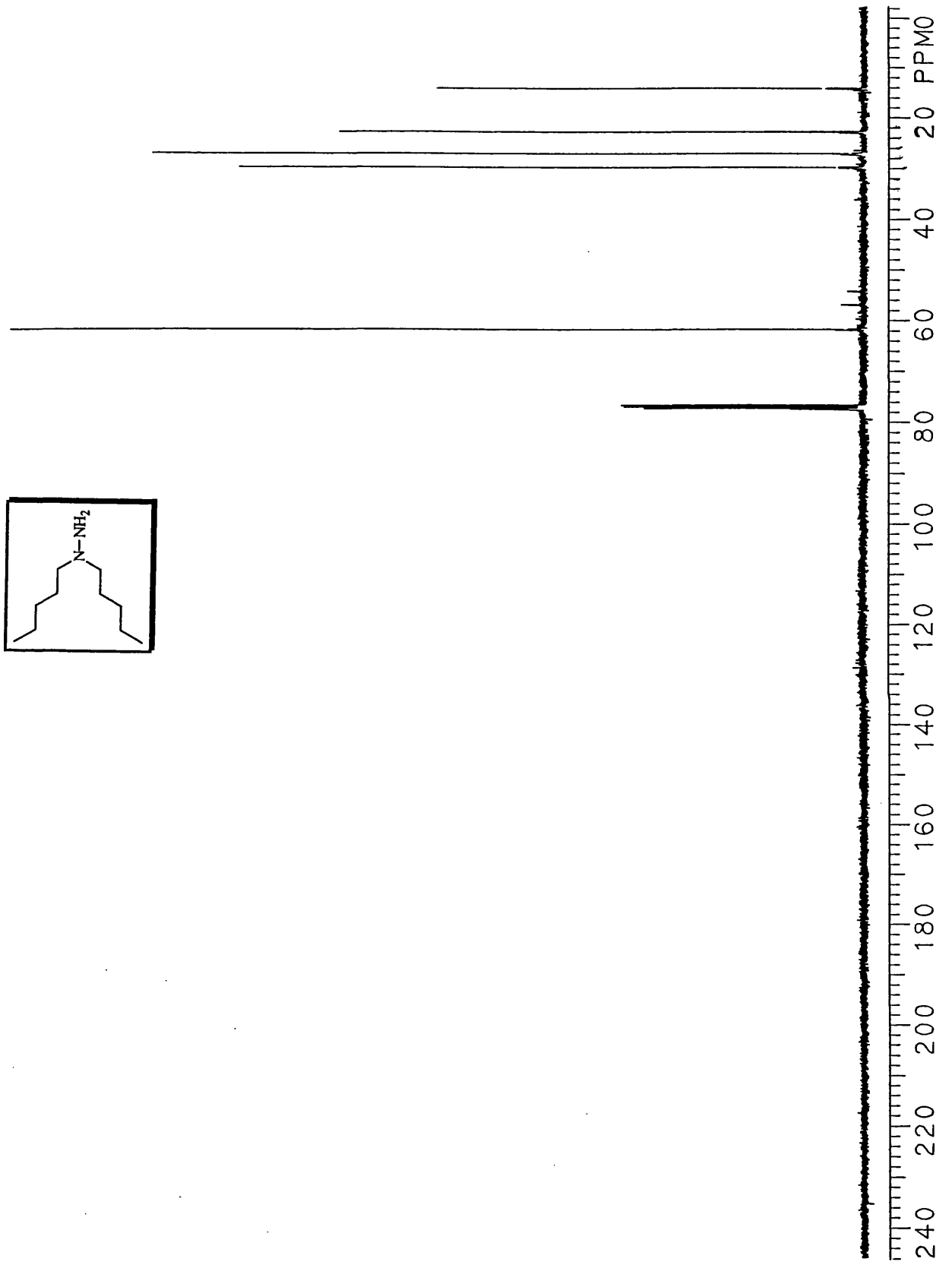


Figure 106 ^{13}C n.m.r. spectrum of *N*-amino-dipentylamine **204**

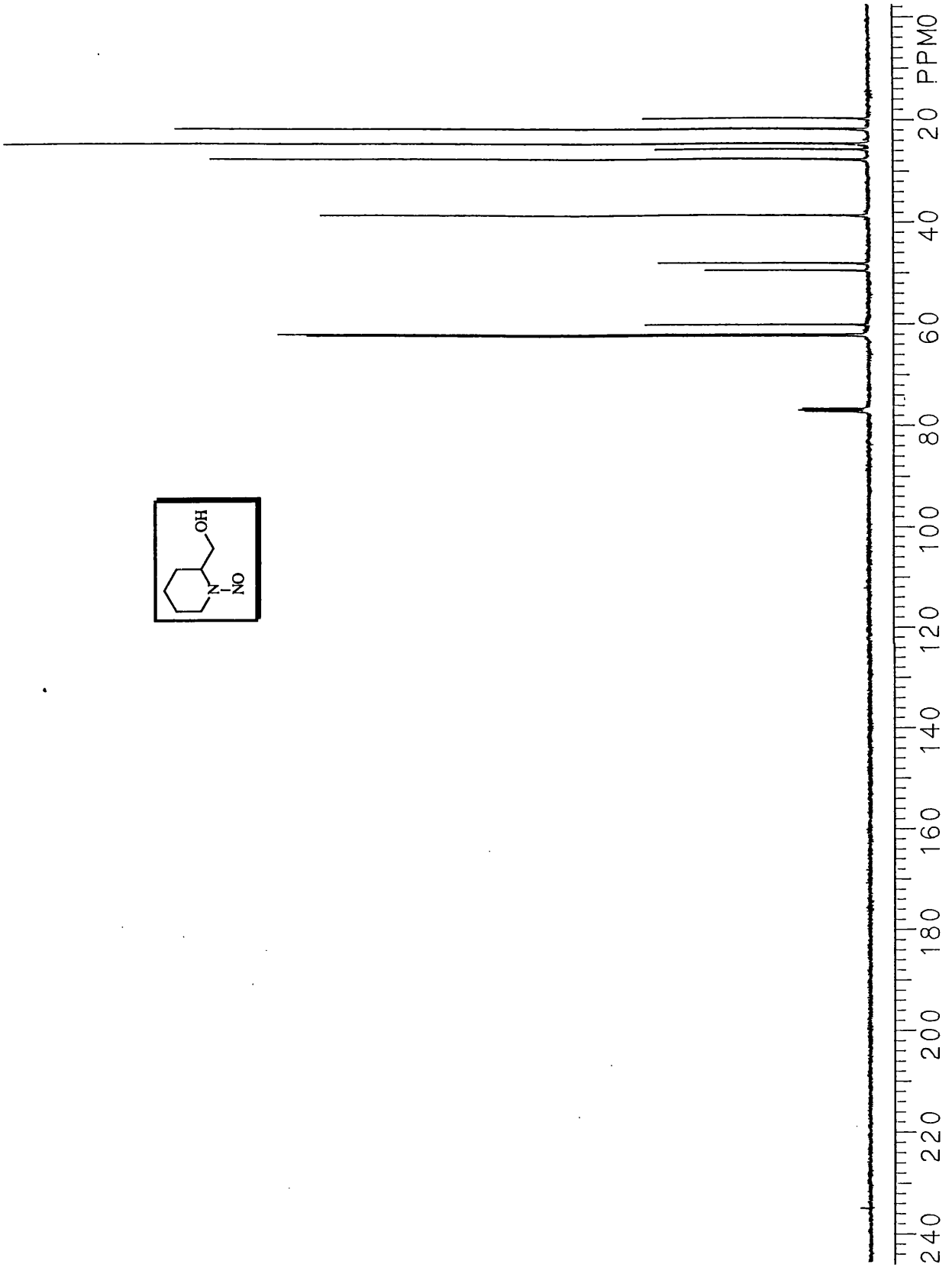


Figure 107 ^{13}C n.m.r. spectrum of (±)-*N*-nitroso-2-piperidinemethanol **209**

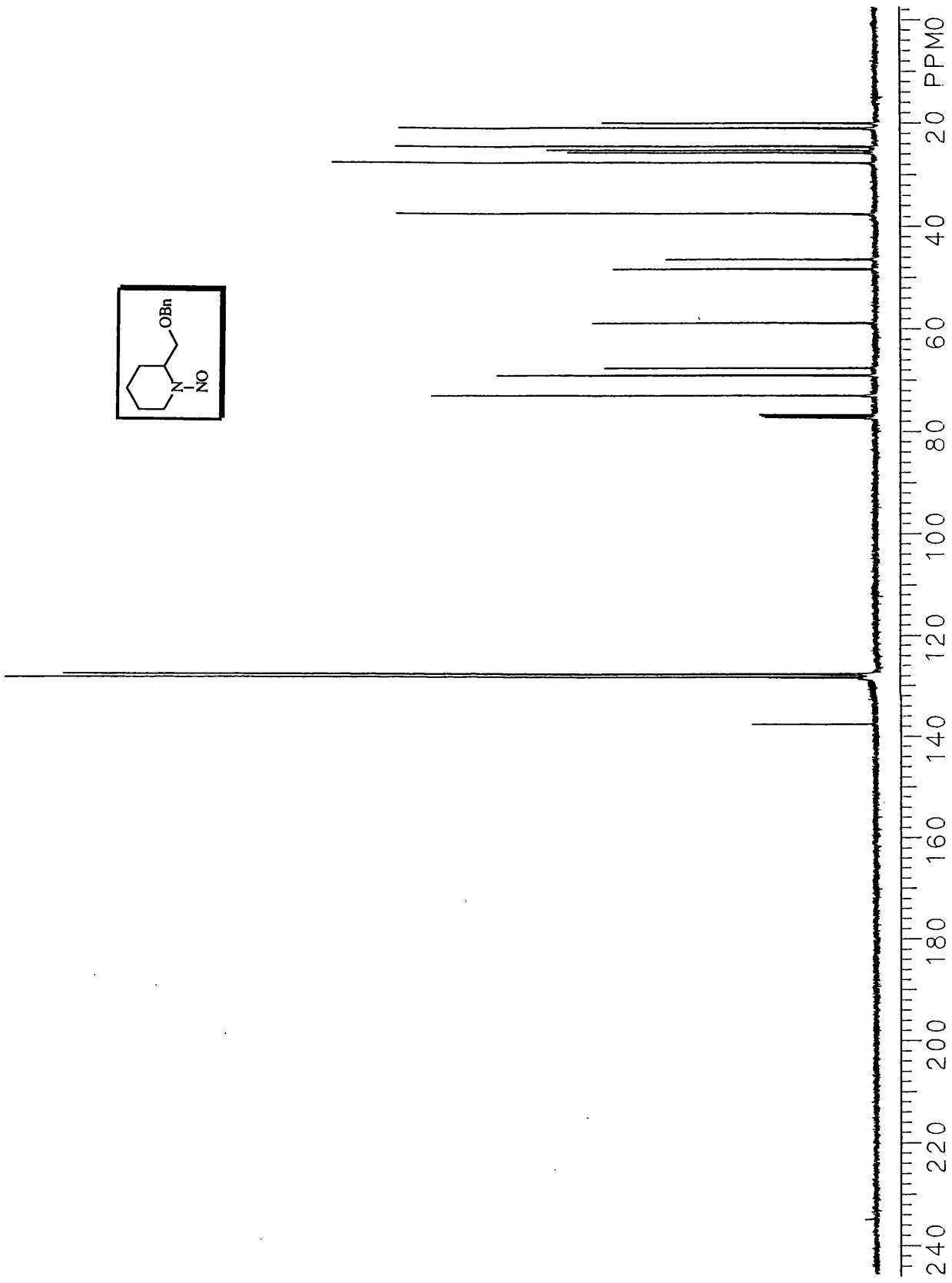


Figure 108 ^{13}C n.m.r. spectrum of (±)-*O*-benzyl-*N*-nitroso-2-piperidinemethanol **210**

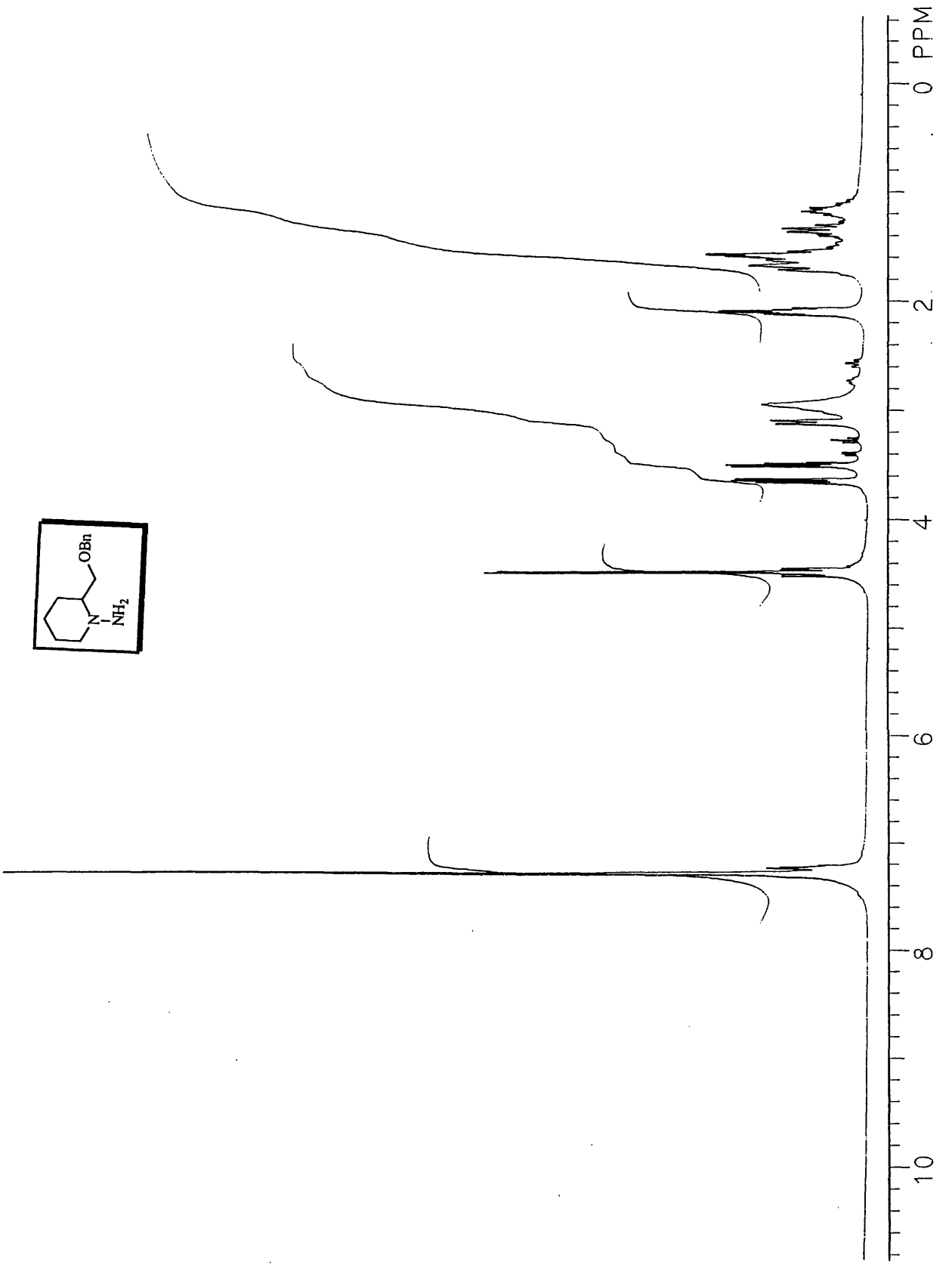


Figure 109 ^{1}H n.m.r. spectrum of (±)-*N*-amino-*O*-benzyl-2-hydroxymethyl piperidine **211**

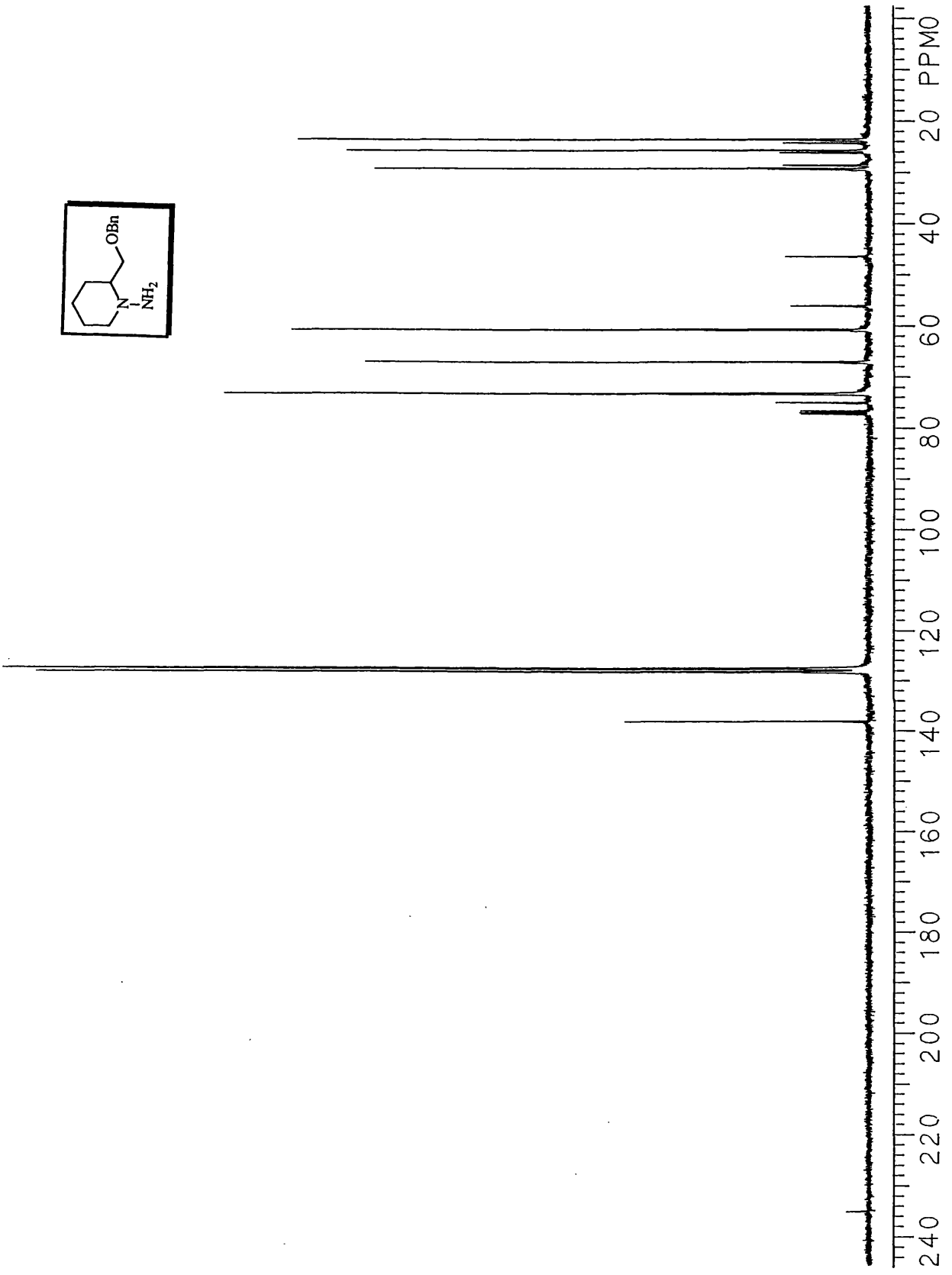


Figure 110 ^{13}C n.m.r. spectrum of (±)-*N*-amino-*O*-benzyl-2-hydroxymethyl piperidine **211**

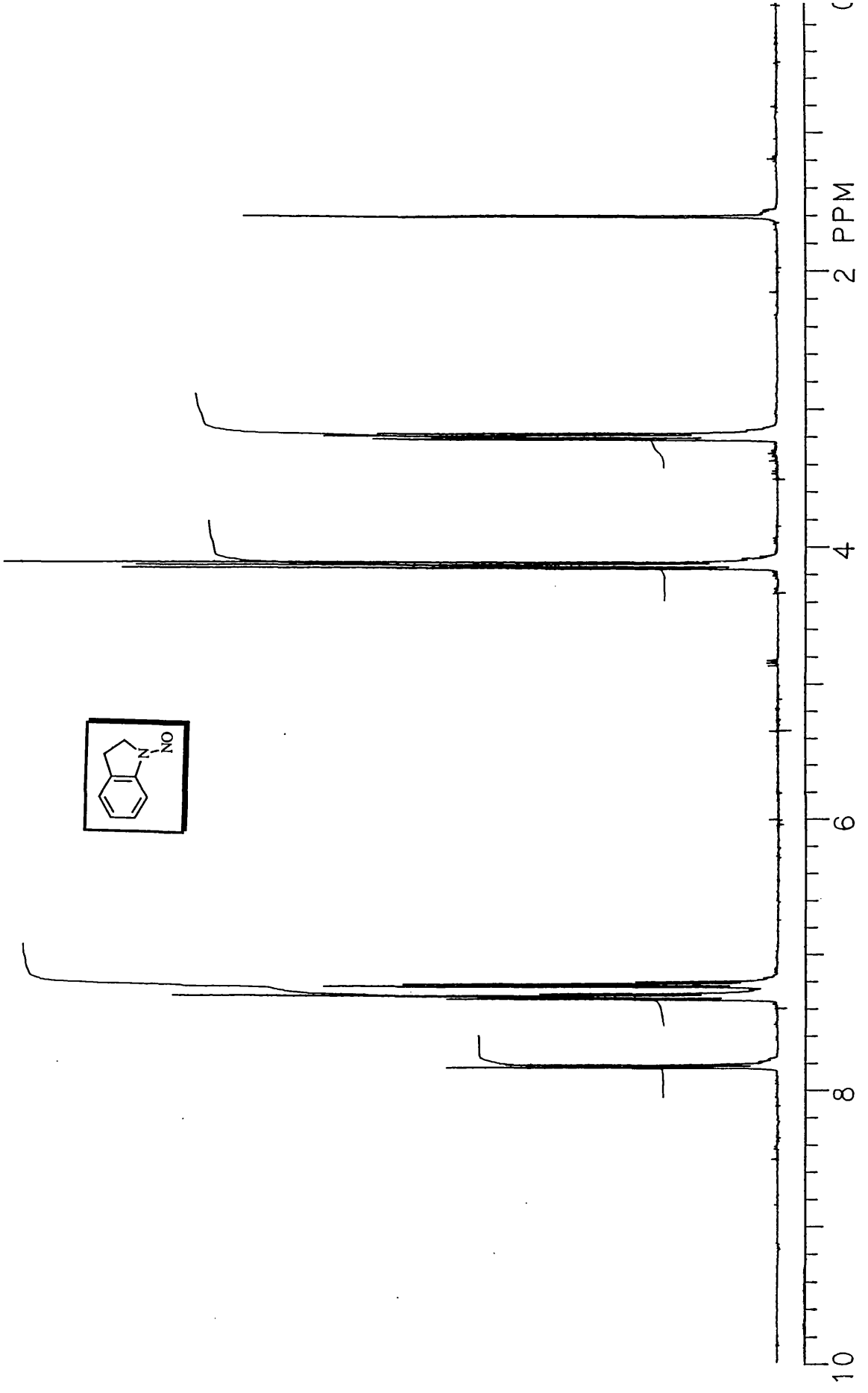


Figure 111 ^{1}H n.m.r. spectrum of *N*-nitroso-indoline **212**

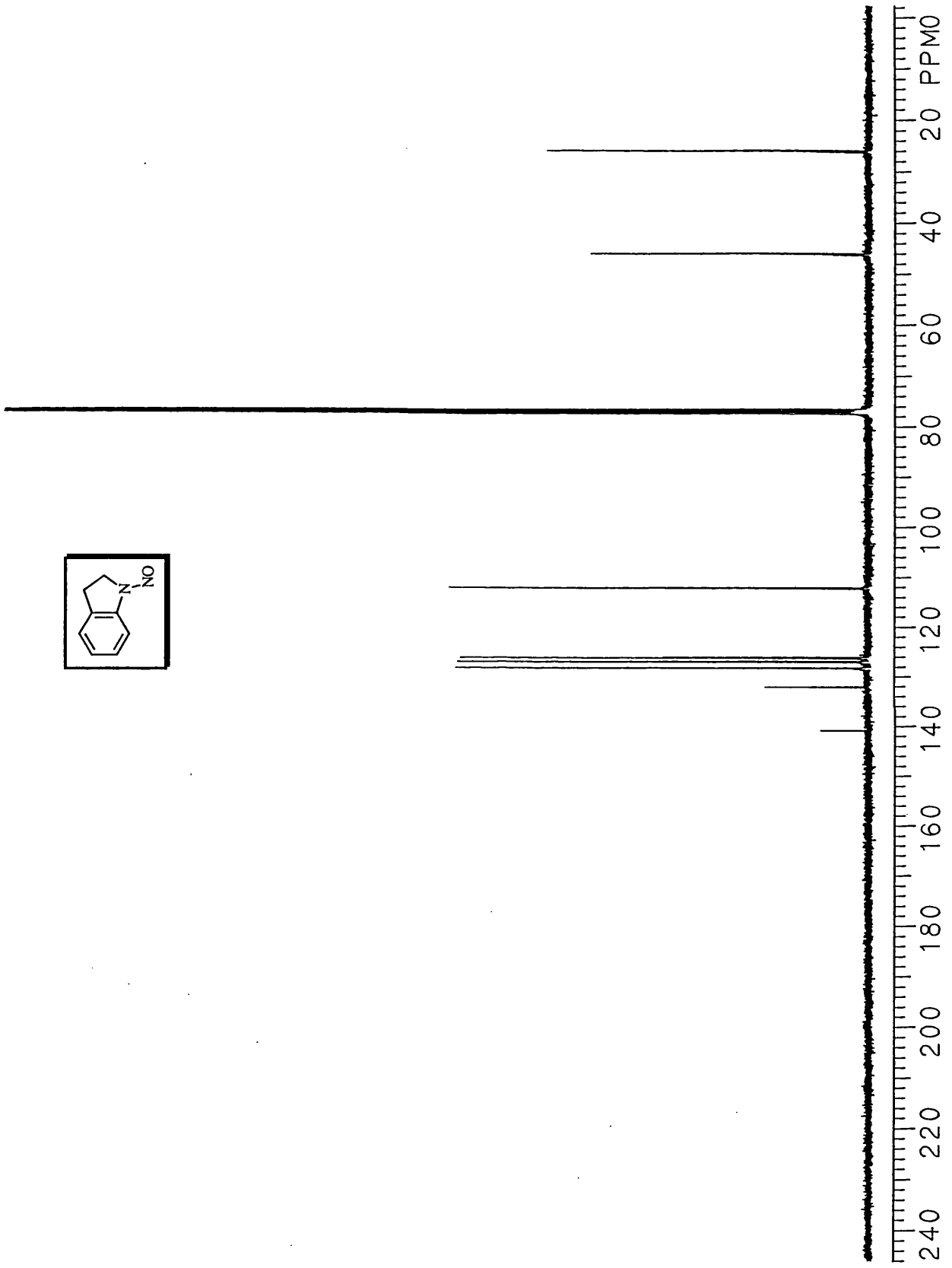


Figure 112 ^{13}C n.m.r. spectrum of *N*-nitroso-indoline **212**

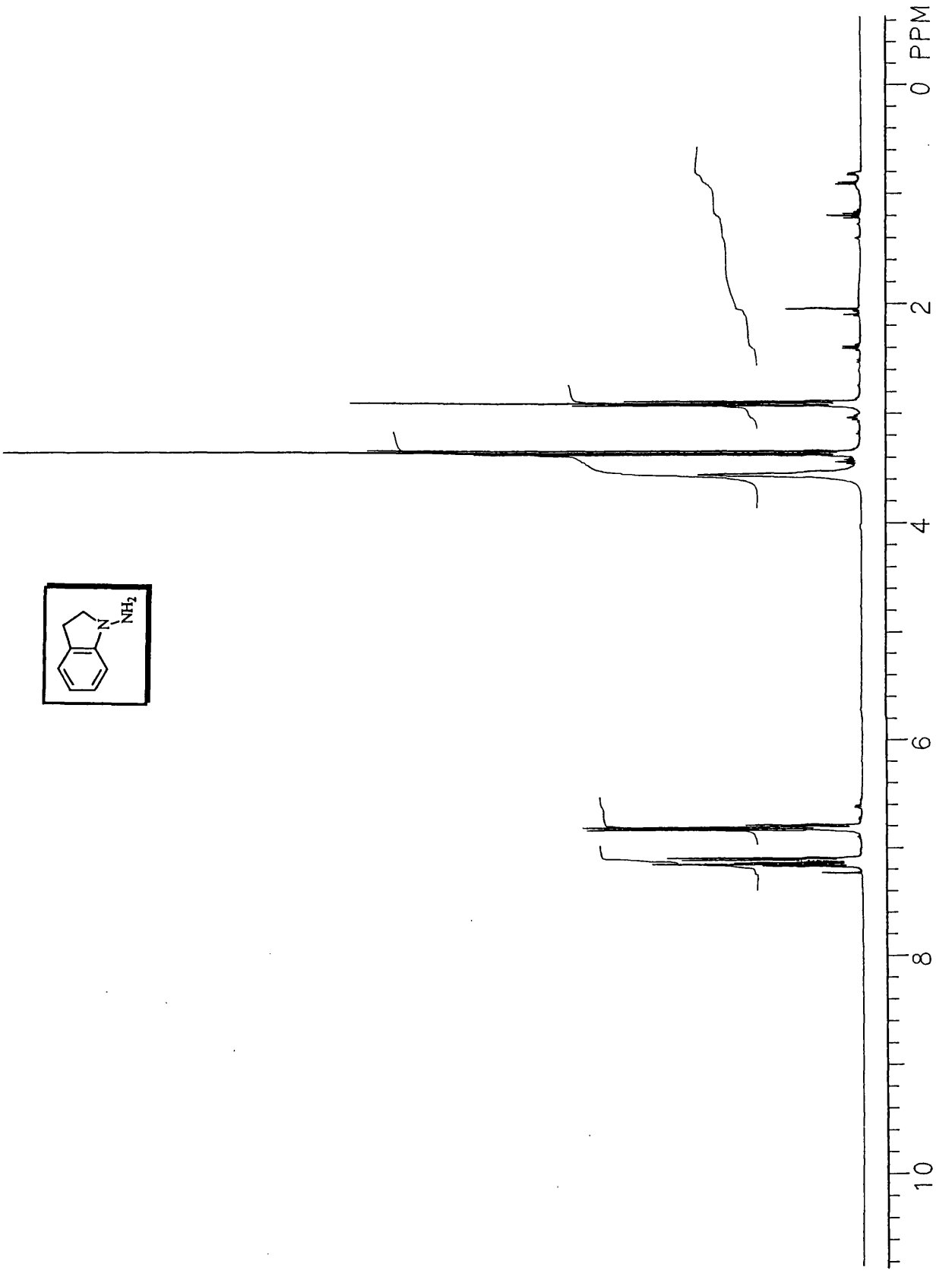


Figure 113 ^{1}H n.m.r. spectrum of *N*-amino-indoline **213**

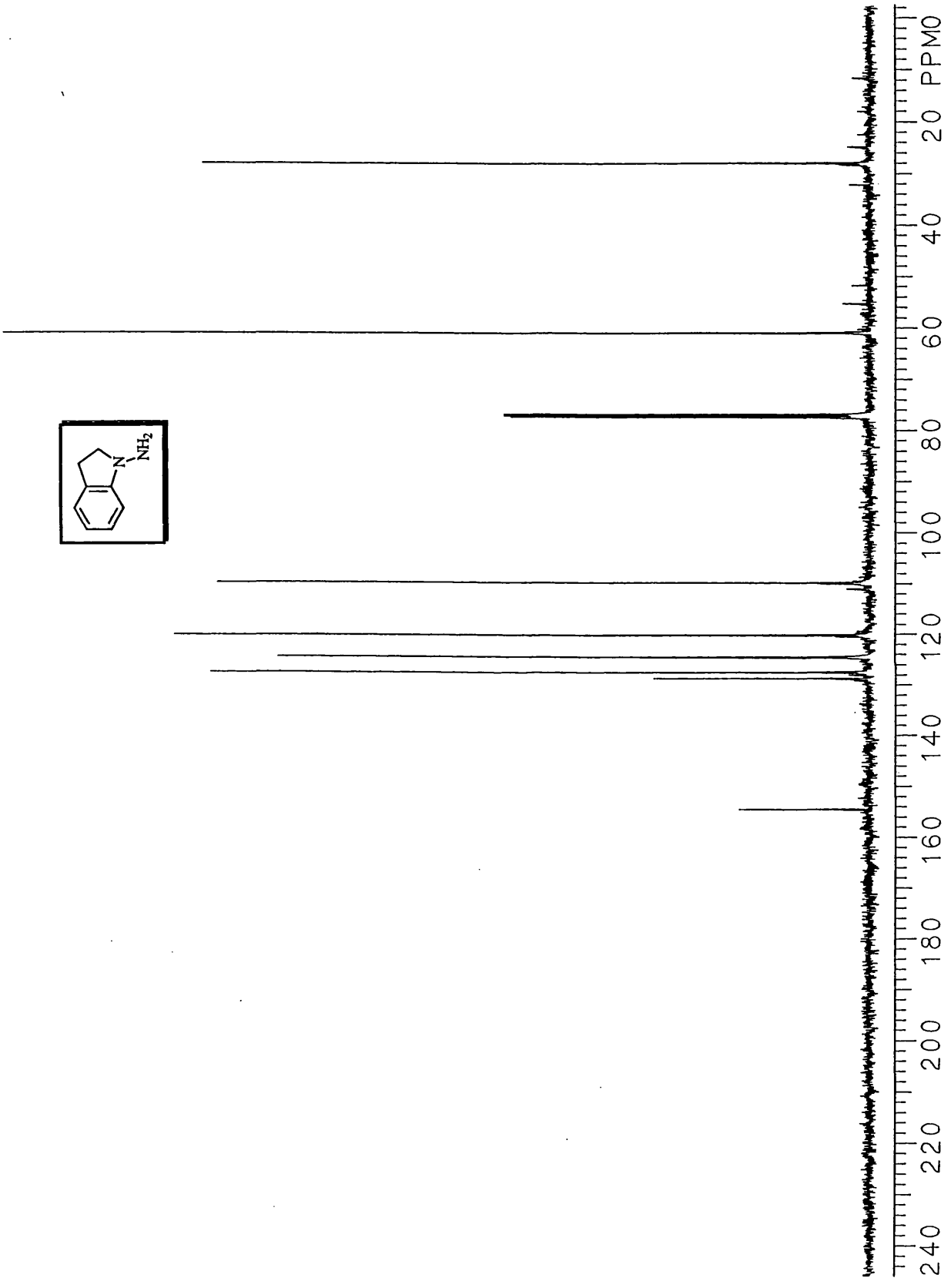


Figure 114 ^{13}C n.m.r. spectrum of *N*-amino-indoline **213**

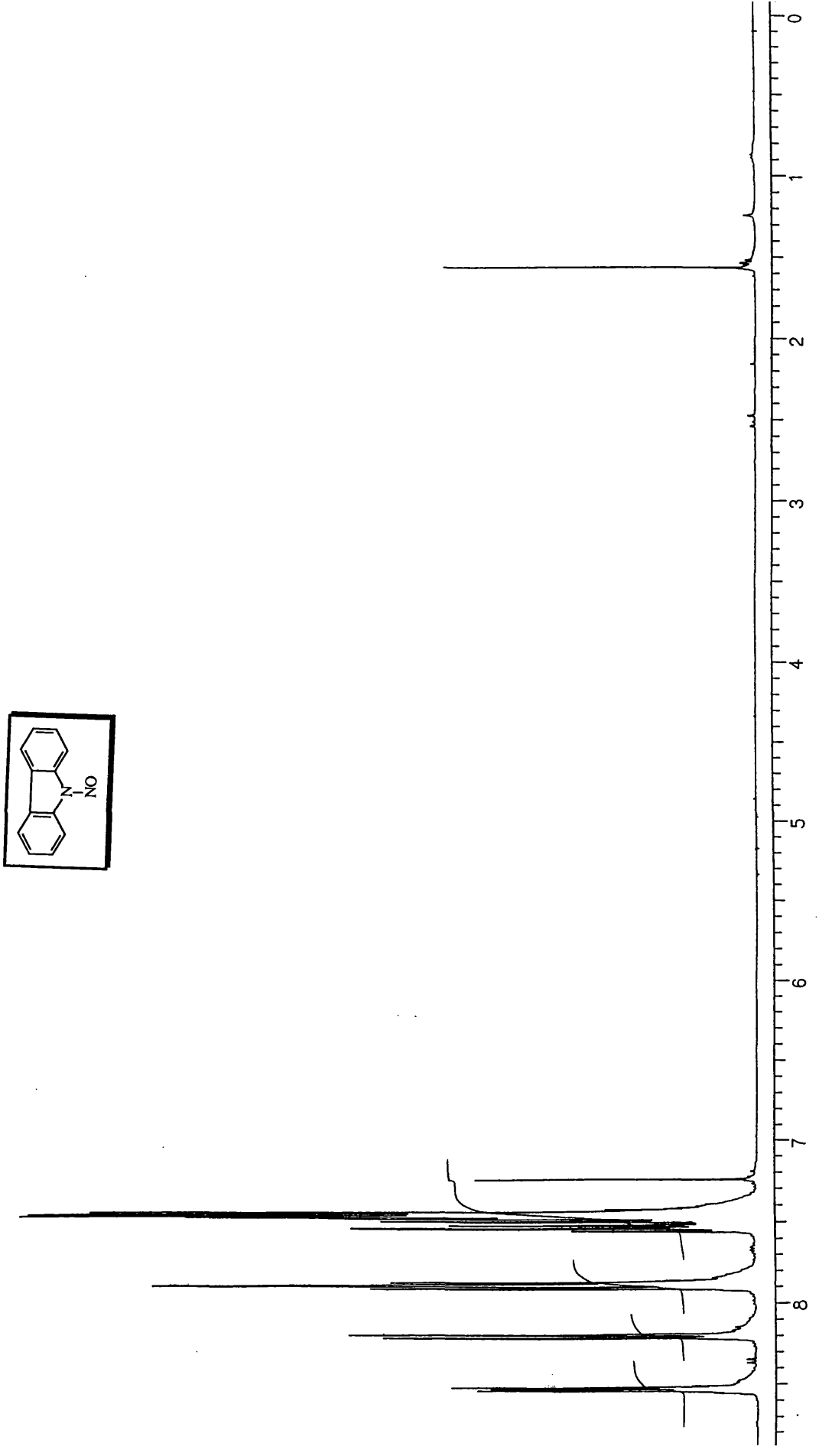


Figure 115 ^{1}H n.m.r. spectrum of *N*-nitroso carbazole **214**

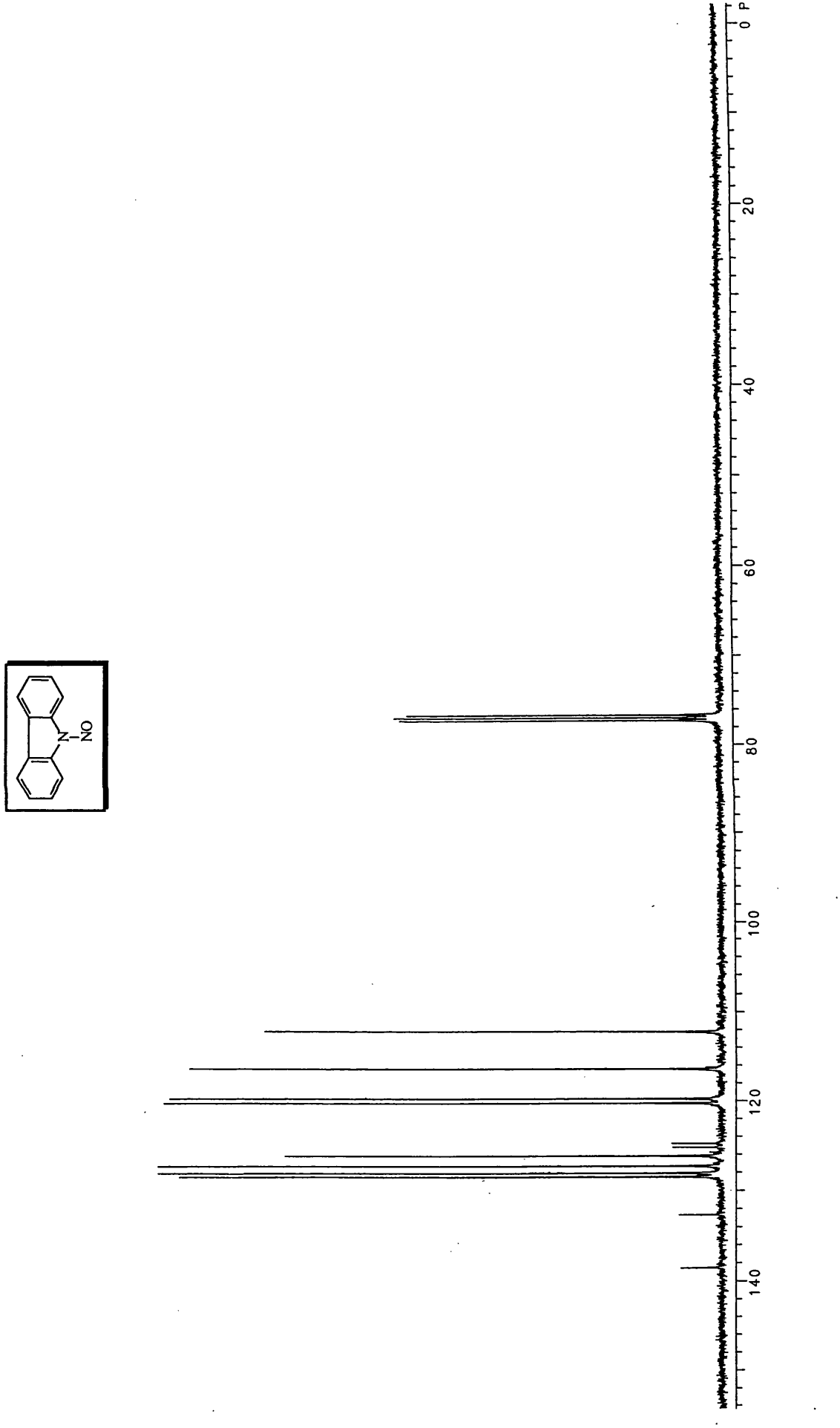


Figure 116 ^{13}C n.m.r. spectrum of *N*-nitroso carbazole **214**

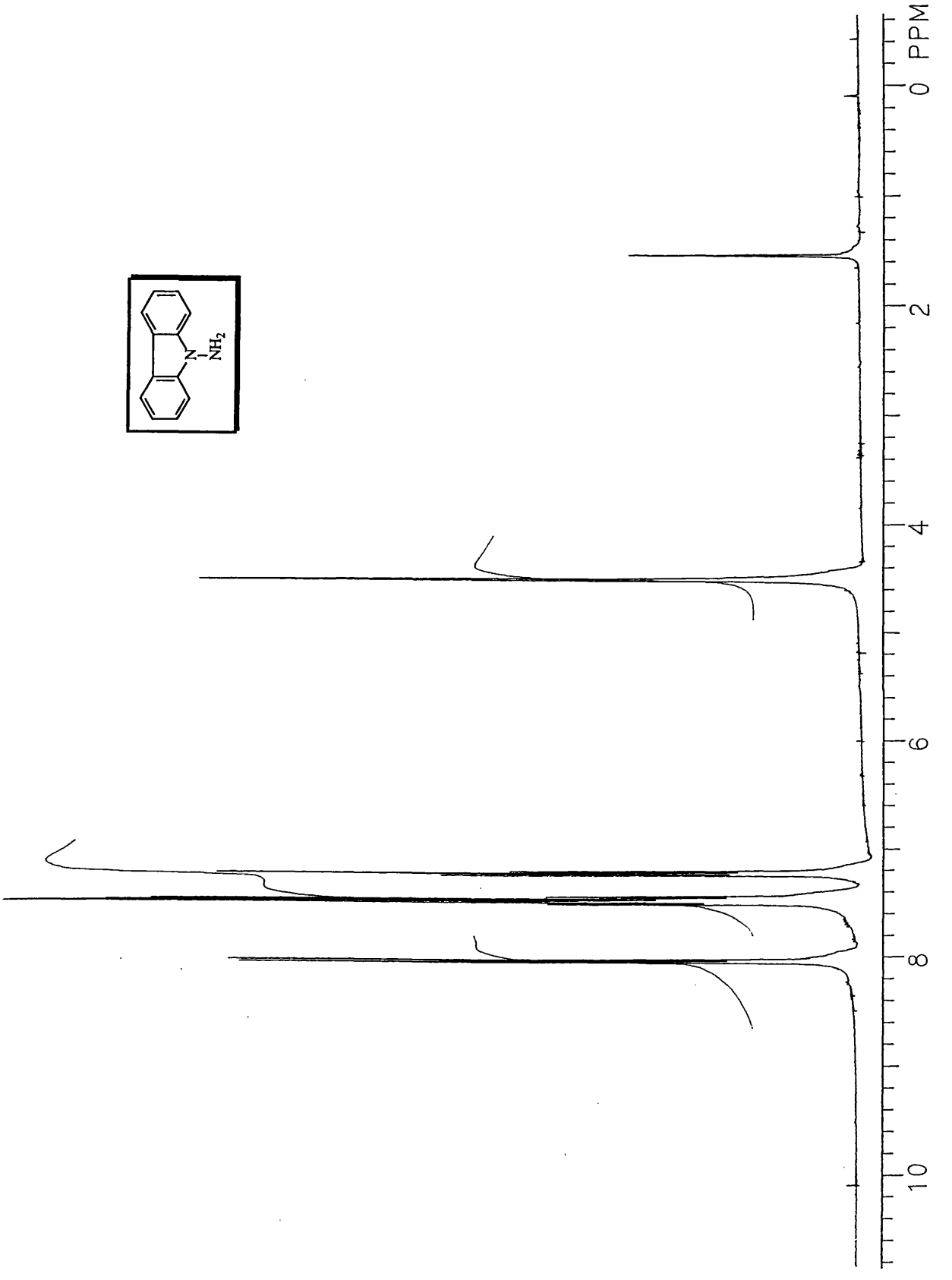


Figure 117 ^{1}H n.m.r. spectrum of *N*-amino carbazole **215**

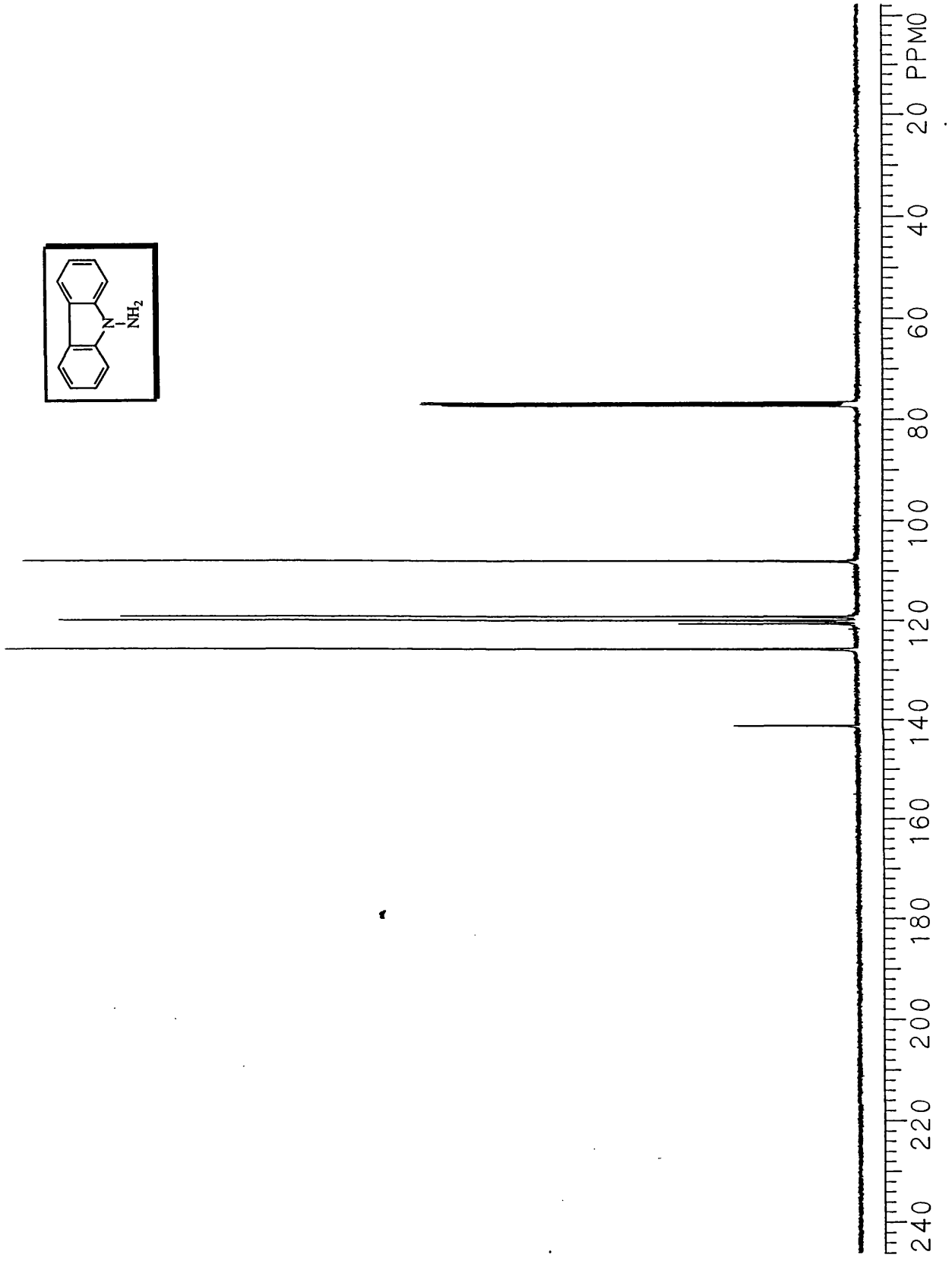


Figure 118 ^{13}C n.m.r. spectrum of *N*-amino carbazole **215**