ARENE CHROMIUM TRICARBONYL

COMPLEXES IN SYNTHESIS

A thesis submitted in partial fulfilment

of the requirements of the degree of

Doctor of Philosophy

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July 1989

Abstract

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July 1989

Arene Chromium Tricarbonyl Complexes in Synthesis

The work described in this thesis concerns the application of arene chromium tricarbonyl methodology to the stereoselective elaboration of aromatic systems and in particular to the synthesis of homochiral N-methyl-1,2,3,4-tetrahydroisoquinolines. The first chapter deals with the benzylic alkylation of substituted 1,3-dihydroisobenzofurans. Coordination of the precursors to the chromium tricarbonyl unit renders these alkylations stereoselective, thereby permitting a diastereoselective synthesis of *cis*-1,3-disubstituted-1,3-dihydroisobenzofurans after decomplexation.

In the second chapter, the benzylic carbanion stabilising ability of the chromium tricarbonyl fragment is exploited in the enantioselective conversion of (+)-(S)-amphetamine to (+)-(1R,3S,4S)- and (-)-(1S,3S,4R)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline.

The modified reactivity of some of the protected derivatives of ephedrine and pseudoephedrine upon coordination to the chromium tricarbonyl moiety is discussed in chapter 3 as a method for the functionalisation of these alkaloids.

The fourth chapter assesses the stereoselectivity observed in the acid-mediated cyclisation of homochiral N-(3,4-dimethoxybenzyl)halostachine to N-methyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Complexation of the precursor to the chromium tricarbonyl group renders the cyclisation highly stereoselective. The diastereoselectivity observed in the acid-mediated cyclisation of homochiral N-(substituted-benzyl) phenylpropanolamines to the corresponding 3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines is investigated and the mechanism by which these cyclisations occur is discussed. Coordination of the cyclisation precursors to the chromium tricarbonyl moiety renders the cyclisations completely stereoselective thereby permitting the synthesis of homochiral 4-aryl-1,2,3,4-tetrahydroisoquinolines.

The last chapter describes an extension of this cyclisation reaction enabling the synthesis of homochiral 1-aryl-1,2,4,5-tetrahydrobenzazepines. The stereoselectivity observed in the acid-mediated cyclisation of homochiral N-(3,4-dimethoxyphenethyl)halostachine to N-methyl-1-phenyl-1,2,4,5-tetrahydrobenzazepine is assessed. The chromium tricarbonyl complex of this cyclisation precursor undergoes a stereoselective cyclisation to furnish the homochiral 1-aryl benzazepine after decomplexation. The diastereoselectivity observed in the acid-mediated cyclisation of homochiral N-3,4-dimethoxyphenethyl phenylpropanolamines is also investigated and the mechanism by which they occur is discussed. Coordination of one of these precursors to the chromium tricarbonyl unit renders the cyclisation stereoselective to give homochiral N-methyl-1-phenyl-2-methyl-7,8-dimethoxy-1,2,4,5-tetrahydrobenzazepine after decomplexation.

One thing that I have learned in a long life: that all of our science, measured against reality, is primitive and childlike - and yet it is the most precious thing that we have.

Albert Einstein

Acknowledgements

The work described in this thesis is the culmination of three years 'hard-labour' in the Dyson Perrins Organic Chemistry Department. Having served my 'sentence' I should like to recognise the following people:-

Firstly, I should like to thank my supervisor, Dr S.G. Davies, for his guidance and tireless, sometimes daunting, enthusiasm over the past three years. Under his supervision I have been given a precious opportunity to broaden my outlook of organic chemistry for which I am very grateful. I am endebted to all of the Dyson Perrins' technical staff and in particular I extend my personal thanks to both Mrs Valerie Lamburn for her efforts in obtaining the micro analyses contained in this thesis and to Mrs Shah for tirelessly measuring numerous optical rotations.

I am particularly grateful to Dr David Watkin of the Chemical Crystallography Department for his considerable efforts in helping me with many crystallographic problems and for allowing me access to the facilities in his department. My heartfelt thanks go to all of my lab 61 colleagues (both past and present) for providing such a pleasant working atmosphere. I appreciate the time and effort spent by Steve Case-Green, Dr Henry Kruk, Andy Mortlock and Mark Shipton in proof reading this thesis and to both Jon Williams and Dr John McNally for many fruitful discussions.

Finally, I gratefully acknowledge the support of Glaxo Group Research for their studentship and would like to thank my industrial supervisor, Dr David Middlemiss, for his valuable help and advice.

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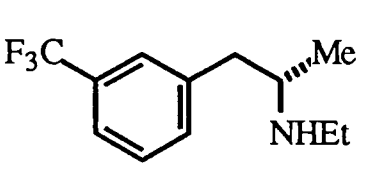
i-Pr	$(CH_3)_2CH$
t-Bu	$(CH_3)_3C$
n-Bu	$CH_3CH_2CH_2CH_2$
Me	CH_3
Et	CH_3CH_2
Ph	C_6H_5
Ac	CH_3CO
n.m.r.	nuclear magnetic resonance
s	singlet
br s	broad singlet
d	doublet
t	triplet
q	quartet
qu	quintet
m	multiplet
br	broad
Tf	triflate
dmso	dimethylsulphoxide

e.e.	enantiomeric excess
d.e.	diastereoisomeric excess
THF	tetrahydrofuran
DIPT	di-isopropyl tartrate
LDA	lithium di-isopropylamide
TMEDA	tetramethylethylenediamine
DMF	dimethylformamide
DMAP	dimethylaminopyridine
TFA	trifluoroacetic acid
CDI	carbonyldi-imidazole
BOC	*t*-butoxycarbonyl
DEAD	diethylazodicarboxylate
*p*TsOH	*para*-toluene sulphonic acid
L	two electron ligand
R	alkyl group
Ar	aryl
NBS	N-bromosuccinimide
h.p.l.c.	high performance liquid chromatography

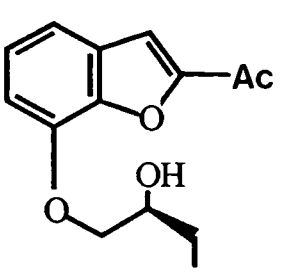
INTRODUCTION

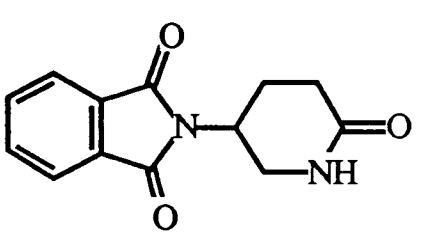
INTRODUCTION

A great deal of time and effort has been spent in recent years in the search for efficient synthetic routes to enantiomerically pure (homochiral) organic molecules. The need to develop such methodologies is of paramount importance to the pharmaceutical industry, a fact that has been repeatedly demonstrated for a number of molecules which possess different pharmacological profiles depending upon which optical antipode is administered. For example, the appetite suppressing activity of Fenfluramine (**1**) resides almost exclusively in the (+)-(S) enantiomer[1] whilst the (-)-(S) optical antipode of the β-adrenergic blocker Befunolol (**2**) is approximately three hundred times more active than its enantiomer.[2] A more notorious example is that of the Thalidomide tragedy of the 1960s which was a direct consequence of marketing Thalidomide (**3**) in racemic form.[3] It is therefore essential to have access to a variety of techniques that can be efficiently utilised to enable the synthesis of homochiral molecules.



(+)-(S)-**1**





3



(-)-(S)-**2**

To date there are four general approaches at the organic chemist's disposal:-

A) *Resolution*

The classical approach enabling separation of a racemic mixture requires derivatisation with a suitable homochiral reagent to afford a mixture of enantiomerically pure diastereoisomers which may then be separated by conventional techniques prior to the release of each enantiomer. This approach, although widely used, is often unpredictable and may be economically unviable if the resolution is performed in the latter stages of a synthetic scheme.

A further advance is that of kinetic resolution which relies upon the different rates at which a homochiral reagent interacts with each of a pair of enantiomers. Diagram 1 shows the dependence of the enantiomeric excess of unreacted starting material upon the relative rate and the progress of the reaction. It can be seen that a relative rate of just 25 gives essentially homochiral unreacted starting material at 60% conversion.

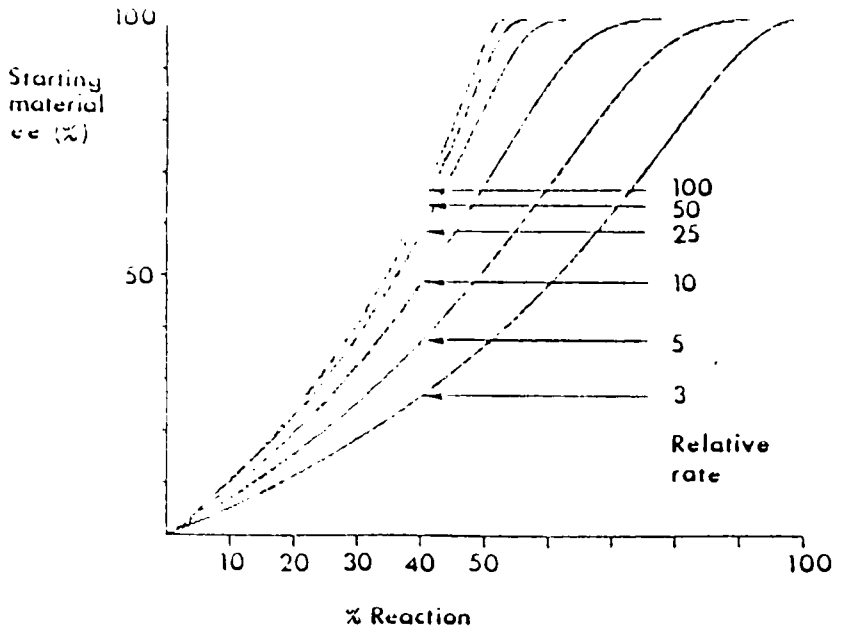
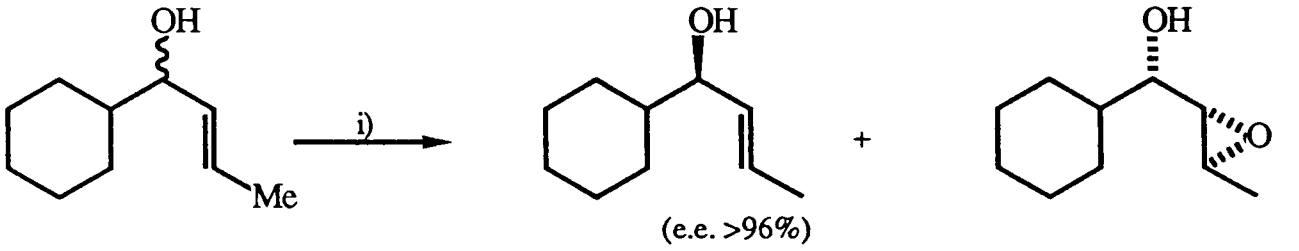


Diagram 1 : E.e. of unreacted starting material as a function of conversion and relative rate for a simple kinetic resolution.

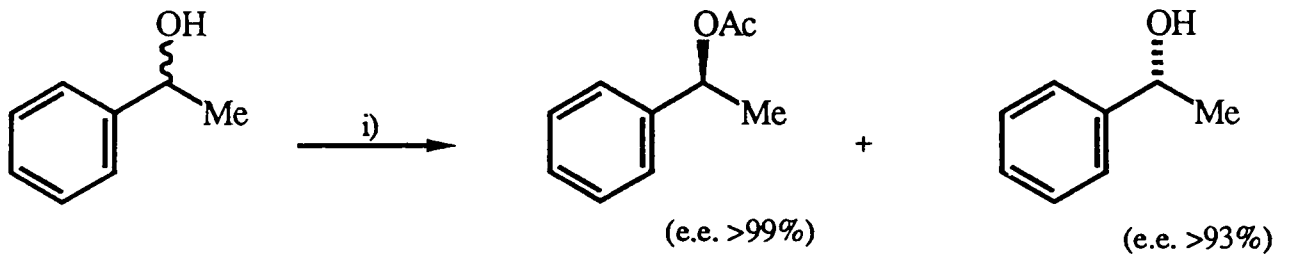
In the case of alkene **4**, the rates at which each of the enantiomers undergoes the Sharpless epoxidation are observed to be in the ratio 104:1. Asymmetric epoxidation thus affords an efficient kinetic resolution of racemic **4** to give epoxide (S)-**5** leaving unreacted alcohol (R)-**4** with an enantiomeric excess of greater than 96% (49% conversion).[4]



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

i) (+)-(L)-DIPT, $Ti(OiPr)_4$, *t*-BuOOH, CH_2Cl_2, 49%.

Enzymes are macromolecular homochiral molecules that may serve as very efficient reagents for kinetic resolutions and are finding increasingly widespread use in organic synthesis. In a recent example, treatment of racemic benzyl alcohol **6** with vinyl acetate in the presence of a suitable esterase gave the enantiomerically pure ester (+)-(S)-**7** (e.e. >99%) in an isolated yield of 45%, allowing recovery of the alcohol (-)-(S)-**6** of good optical purity (e.e. >93%, 41% yield).[5]



6 (+)-(S)-**7** (-)-(S)-**6**

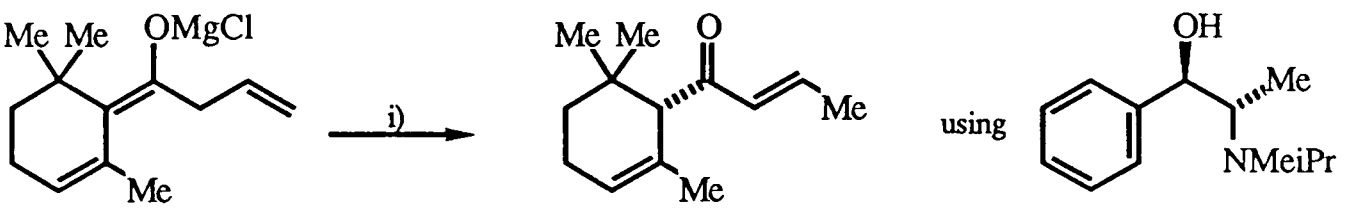
i) CH_2CHOAc, esterase, 86%.

B) ***'Chiron' Approach***

A large number of naturally occurring compounds exist in nature as single enantiomers, often possessing several chiral centres (*e.g.* carbohydrates). They may therefore find use as homochiral 'building blocks' which may be coupled or transformed to give optically pure target molecules.[6] The main advantage of this approach stems from their cheap and plentiful supply and the ability to be able to install several chiral centres in one step. One drawback of this method is that unwanted chirality and functionality may have to be removed which could entail a large number of synthetic transformations thereby reducing the overall yield of the target material.

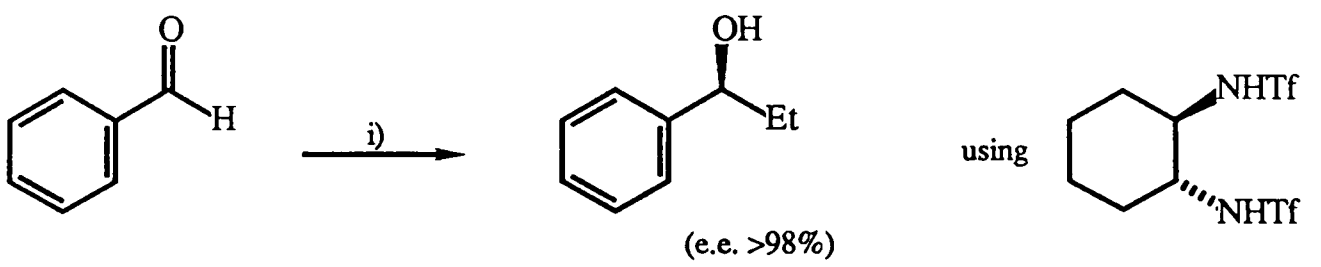
C) ***Enantioselective Synthesis***

This method utilises a reaction between a prochiral substrate and a homochiral reagent to give an optically pure product. There are many examples of reactions that fall into this category including both enantioselective hydrogenation[7] and hydroxylation.[8] An interesting example involves the use of an optically pure proton source in the protonation of enolate **8**. Subsequent isomerisation of the double bond generates the ketone (-)-(S)-**9** with an enantiomeric excess of 84%.[9] The addition of diethylzinc to benzaldehyde (**10**) occurs with very high stereocontrol in the presence of a titanium-based, homochiral catalyst to give (-)-(S)-phenylpropanol (**11**) in excellent yield.[10]



8 (-)-(S)-**9**

i) THF, -50 to -10°C, 1h, 73%.

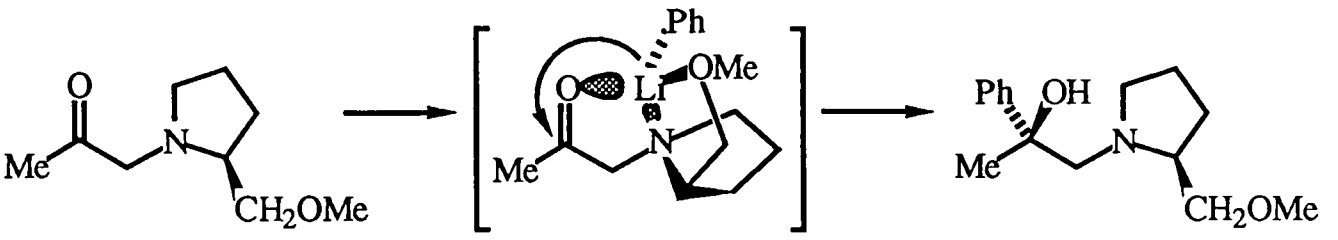


10 (-)-(S)-**11**

i) Et_2Zn, $Ti(OiPr)_4$, toluene, -78 to -20°C, 2h, 96%.

D) *Multiplication of Chirality*

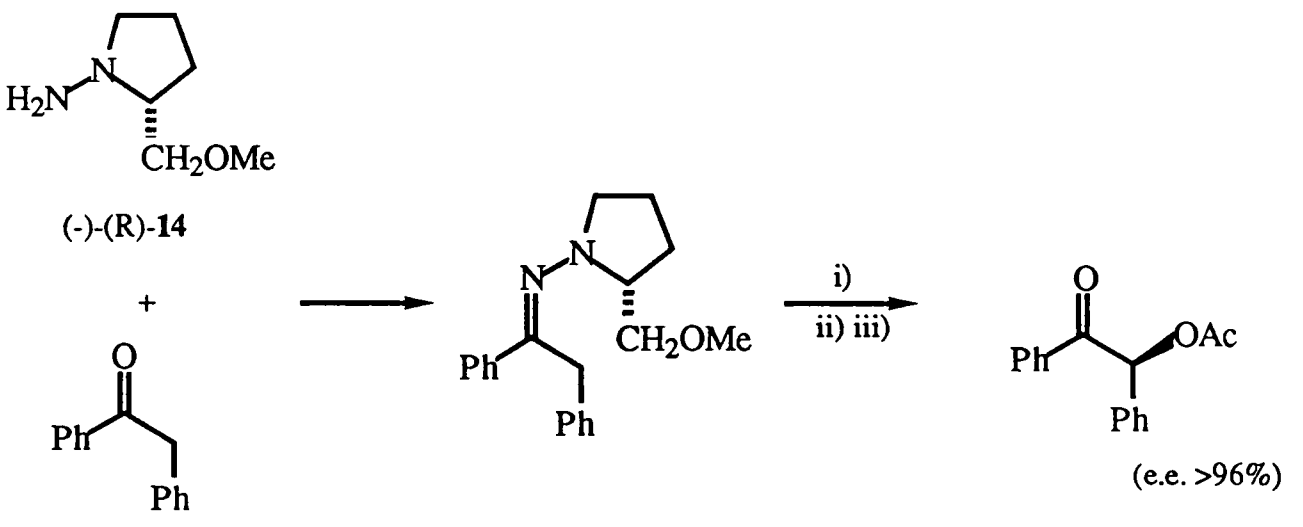
The last general approach enabling the synthesis of optically pure molecules utilises a homochiral substrate that is diastereoselectively elaborated to generate one or more new chiral centres, the chirality present in the substrate being used to control the creation of the new asymmetric centres. For example, the prolinol derivative (S)-**12** undergoes nucleophilic addition of an alkyllithium stereoselectively to its Si face directed by the chelate influence of the methoxyl substituent, to afford the amino alcohol (-)-**13**.[11]



(S)-12 (-)-(S,S)-13

i) PhMgCl, Et_2O, -78°C, 64%.

If the stereodirecting substrate is removed after its elaboration it is said to serve as a *chiral auxiliary*. This approach enabling the synthesis of optically pure targets is very attractive in that the auxiliary may be recycled and only a single enantiomer of product is formed thereby avoiding a wasteful resolution procedure. Many such chiral auxiliaries have been developed in recent years,[12] those of Evans[13] and Williams[14] (amongst others) now being commercially available. Enders has described the powerful utility of prolinol-derived hydrazines in the field of asymmetric synthesis. For example, condensation of (-)-(R)-**14** with ketone **15** gives the hydrazone (-)-(R)-**16**. Subsequent deprotonation and trapping with a suitable electrophile followed by removal of the chiral auxiliary liberates the α-hydroxyketone (+)-(S)-**17** of good enantiomeric purity (e.e. >96%).[15]



(-)-(R)-14 15 (-)-(R)-16 (+)-(S)-17

i) LDA, THF, 2-(phenylsulphonyl)-3-phenyloxaziridine, -85 to -50°C, 1.5h.
ii) O_3, CH_2Cl_2, -78°C. iii) Ac_2O, DMAP, CH_2Cl_2, 3 steps 74%.

It has been recognised for some time that the physical and chemical properties of an organic molecule may be significantly altered upon coordination to a transition metal.[16] The chemistry of such complexes has wide ranging synthetic potential and is currently the subject of a considerable amount of research effort. The work presented in this thesis concerns the application of arene chromium tricarbonyl methodology to the stereoselective elaboration of aromatic systems and in particular to the synthesis of homochiral N-methyl-1,2,3,4-tetrahydroisoquinolines.†

† For clarity the descriptors -1,2,3,4- are henceforth omitted.

ARENE CHROMIUM TRICARBONYL CHEMISTRY

ARENE CHROMIUM TRICARBONYL CHEMISTRY

A) Introduction

The modified reactivity of arenes coordinated to the $Cr(CO)_3$ moiety, and the ease with which the transition metal group may be added and removed has wide-ranging synthetic potential for the construction of polyfunctionalised aromatic systems.[16,17]

(Arene)$Cr(CO)_3$ complexes are generally isolated as yellow to red crystalline solids that are moderately air stable. X-ray crystallographic studies for a number of these complexes reveals that they all possess a pseudo-octahedral geometry with the aromatic ring occupying three of the coordination sites.[18] The three carbon monoxide ligands are disposed at approximately 90^o to each other and occupy the remaining three sites. The aromatic C-C bond lengths are not significantly altered from those of the free arene and the aromatic ring remains essentially planar although some perturbation from planarity occurs when substituents possess lone pairs or are particularly bulky.[19]

The presence of the powerfully electron withdrawing $Cr(CO)_3$ group serves to reduce the net electron density in the aromatic ring. According to the Chatt-Dewar-Duncanson synergic bonding model[20] this indicates that electron donation to the $Cr(CO)_3$ unit from filled arene σ and π orbitals outweighs any back donation from the chromium to the arene. This reduction in electron density has a profound effect upon both the physical and chemical properties of coordinated arenes. Thus, the acidity of the phenol and carboxylic acids shown in Table 1 all increase upon complexation due to the inductive stabilisation of their conjugate bases by the $Cr(CO)_3$ moiety.[16]

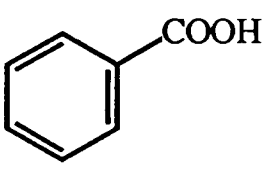
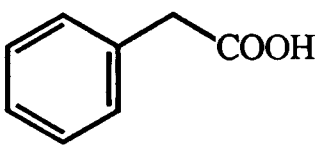
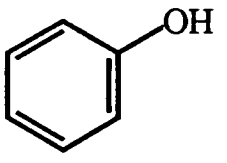
	pKa	pKa $Cr(CO)_3$ complex
	5.68	4.77
	5.64	5.02
	11.02	7.09

Table 1 : Comparative acidities upon coordination to the $Cr(CO)_3$ unit.

The preferred conformation adopted by the carbon monoxide ligands is observed to be influenced by the nature of any ring substituents. Electron withdrawing groups tend to stagger the ligands whilst electron releasing substituents prefer to adopt an eclipsed conformation.[21] Thus, an X-ray crystallographic analysis of (methylbenzoate)$Cr(CO)_3$ (**18**)[22] reveals the staggered conformation shown below, whilst (anisole)$Cr(CO)_3$ (**19**)[23] adopts an eclipsed conformation in the solid state (Figure 1). In solution, there is free rotation of the $Cr(CO)_3$ moiety about the arene centroid. The size of the tripod effectively shields the entire coordinated face of the arene thus restricting approach of all reagents to the unhindered *exo* face. This steric effect in addition to any conformational restrictions imposed on, or by, the $Cr(CO)_3$ moiety has ramifications for the regio- and stereoselective elaboration of coordinated arenes.[24]

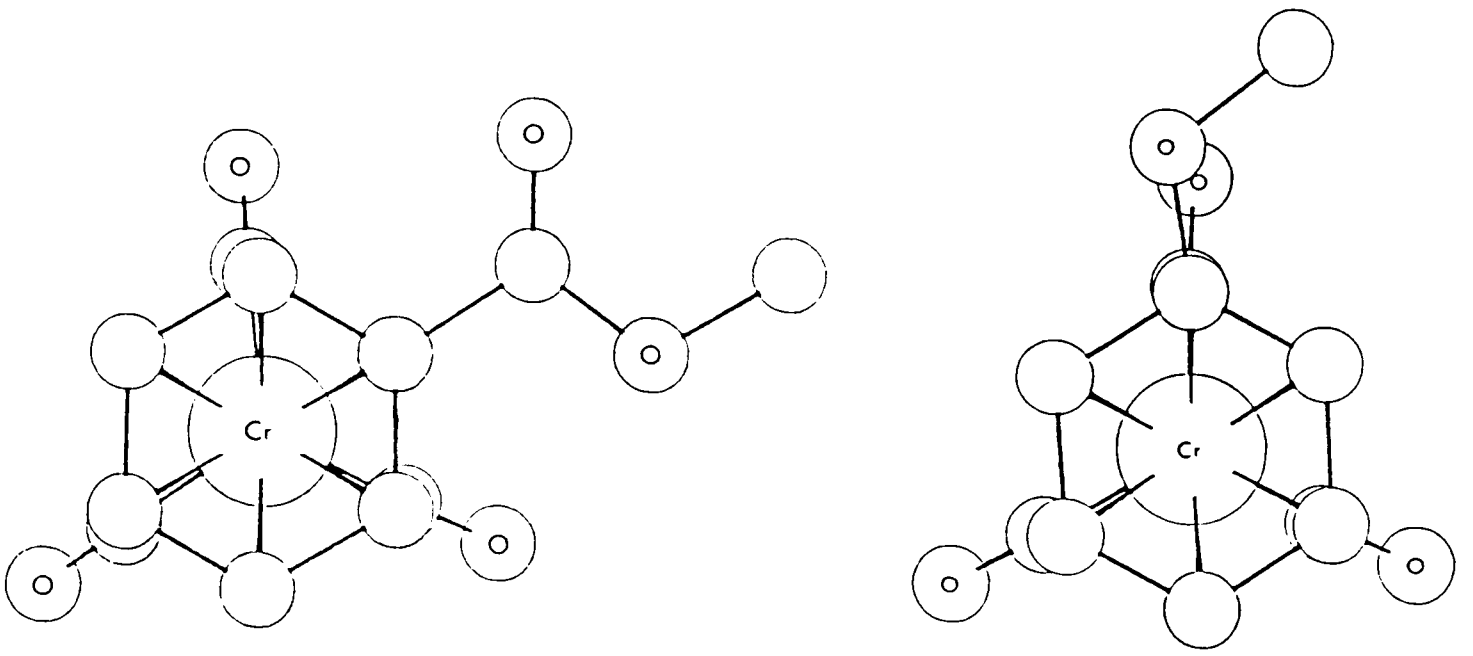
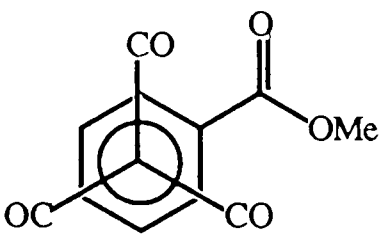
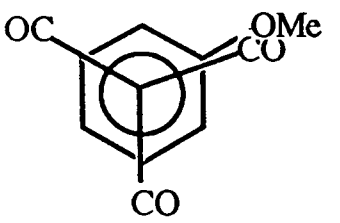


Figure 1 : X-ray crystal structures of complexes **18** and **19**.



18



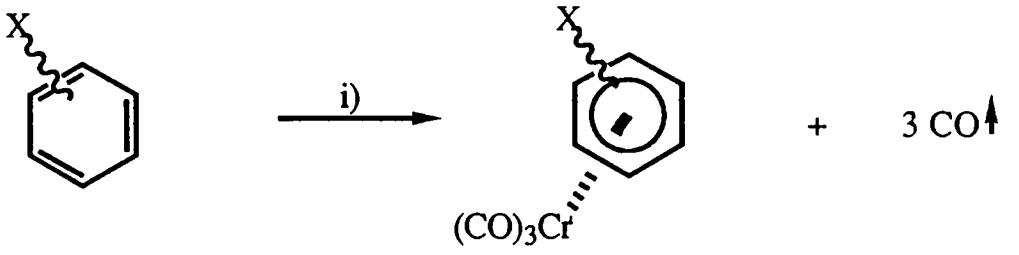
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B) Synthetic Utility

i) *Complexation*

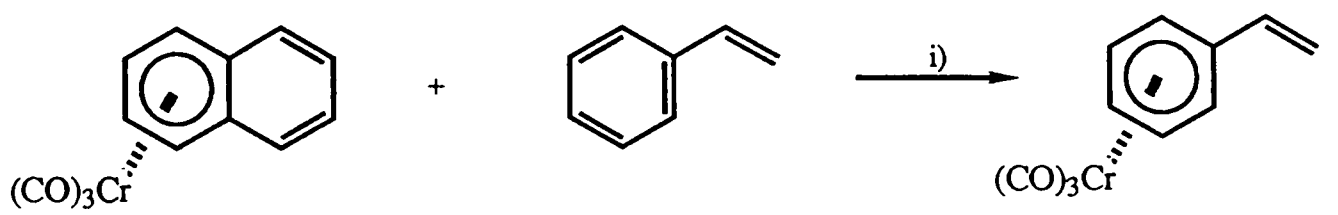
In principle any arene may be coordinated to the $Cr(CO)_3$ unit although in practice certain functional groups are incompatible (*e.g.* CN and NO_2) with the reaction conditions.[25] In general, electron releasing substituents are observed to facilitate complexation whilst electron withdrawing groups retard it. The standard approach requires thermolysis of chromium

hexacarbonyl with the relevant arene, the reaction proceeding *via* direct ligand displacement. A variety of solvent systems have been employed but the use of a 10:1 mixture of dibutylether and tetrahydrofuran has been widely used with good results.[26] Under these conditions the reaction is conveniently monitored by the evolution of carbon monoxide and the colour change to intense yellow upon coordination.



i) $Cr(CO)_6$, Bu_2O/THF (10:1), 120-40°C, 20-30h.

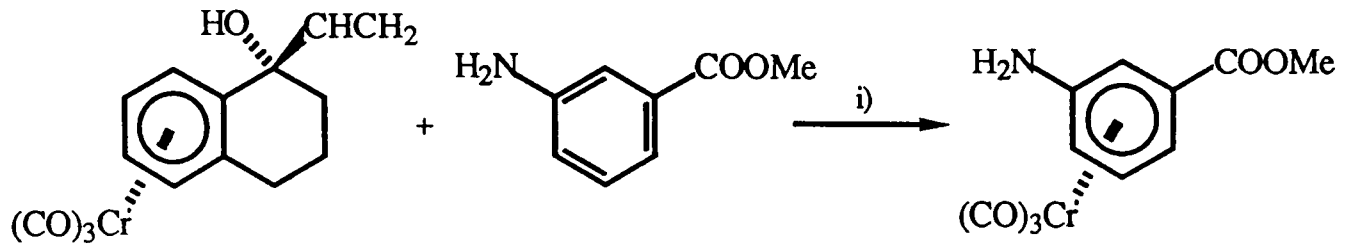
Milder methods for coordination to the $Cr(CO)_3$ unit utilise complexes of general formula $Cr(CO)_3L_3$ which rely upon the increased lability of the ligands (L) bound to the $Cr(CO)_3$ fragment. Use of ligands including NH_3,[27] MeCN,[28] EtCN[29] and pyridine[30] have all been documented and good yields are achievable, although in some cases (L=pyridine) a Lewis acid is necessary to promote coordination. More recently, arene exchange using (naphthalene)$Cr(CO)_3$ (**20**) has been reported as a very mild and convenient method enabling the synthesis of (arene)$Cr(CO)_3$ complexes. For example, (styrene)$Cr(CO)_3$ (**21**) is obtained in 90% yield upon refluxing a diethylether/tetrahydrofuran solution of styrene with (naphthalene)$Cr(CO)_3$ (**20**).[31]



20 **21**

i) Et_2O/THF, 19h, 90%.

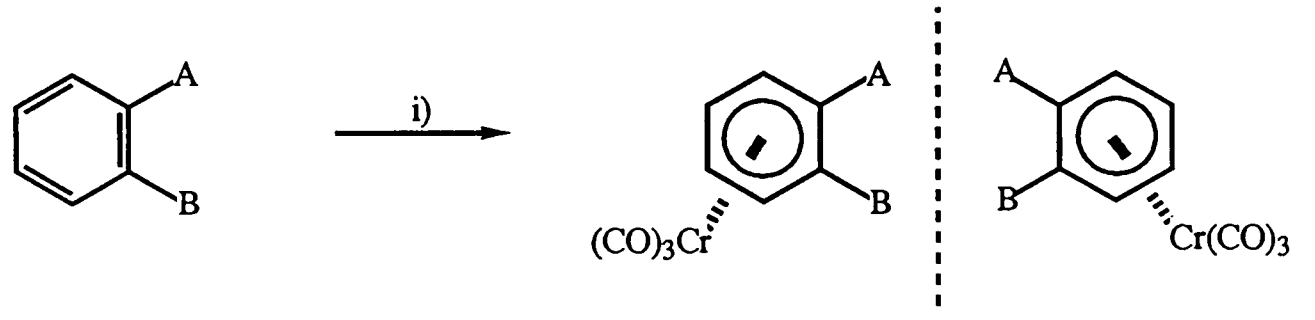
Alternatively, tertiary (benzyl alcohol)$Cr(CO)_3$ complexes may undergo ionisation under acidic conditions to give a $Cr(CO)_3$ stabilised benzylic carbocation, thus weakening the arene-chromium bonds. If another arene is present the $Cr(CO)_3$ unit may be transferred as in the case of *exo* tetralol complex **22** which has been used for the synthesis of complex **23**.[32] Other reported methods include the use of hexadienes with chromium hexacarbonyl[33] and reaction of $Cr(CO)_5$ carbene complexes with alkyne substrates.[34]



22 23

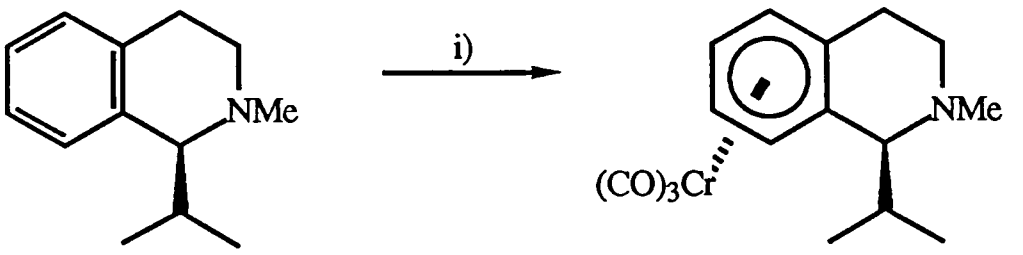
i) 2-Methyl-1,3-cyclopentadione, *t*-BuOH, 95°C, 24h, 80%.

The two faces of an usymmetrically *ortho*-substituted arene are enantiotopic but are rendered diastereotopic if one or more chiral centres are present in a side chain. Upon coordination to the $Cr(CO)_3$ fragment a racemate results in the former case, whilst in the latter a mixture of diastereoisomers is expected. The presence of steric and/or chelate directing effects of ring substituents may result in a marked preference for coordination to one of the two faces.

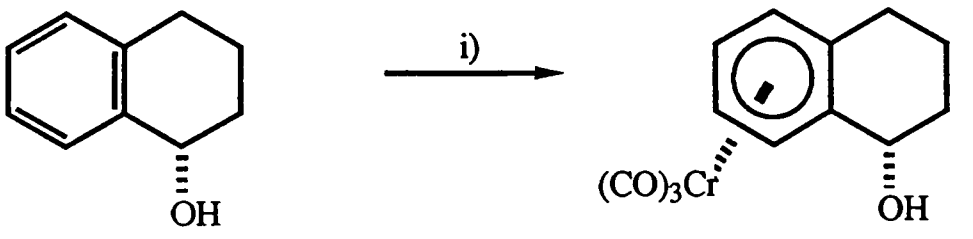


i) $Cr(CO)_6$, heat.

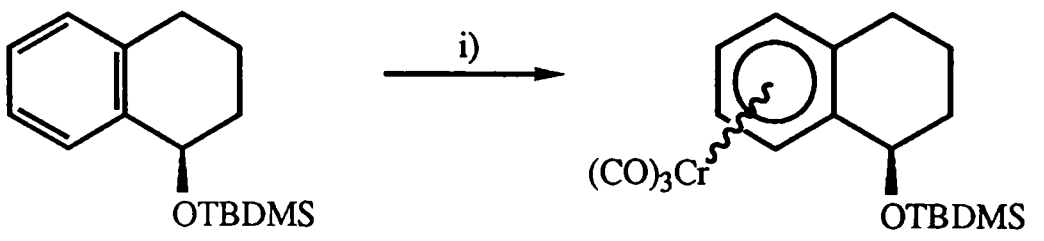
Such a steric directing effect is clearly illustrated in the reported complexation of 1-isopropyl-N-methyl tetrahydroisoquinoline (**24**) which gives only the *exo*-1-isopropyl complex **25** upon complexation using chromium hexacarbonyl.[35] In contrast, 1-tetralol (**26**) gives exclusive formation of *endo*-1-tetralol complex **27** upon complexation due to the oxygen lone pair directing the incoming metal unit to the face proximal to the heteroatom. Evidence for this directing ability is supported by the complexation of silylated tetralol **28** which gives a mixture of diastereoisomers **29** upon complexation.[36]



24 25



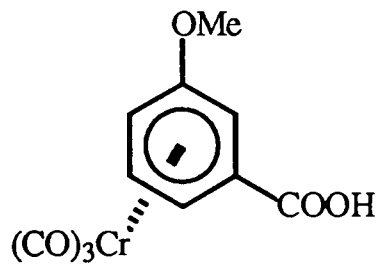
26 27



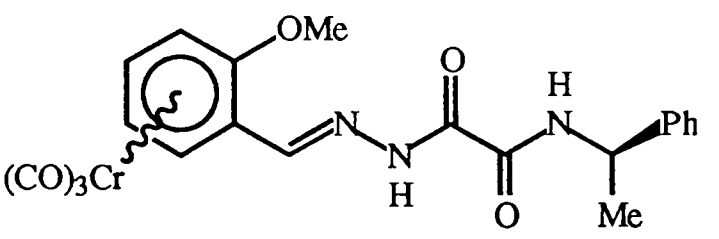
28 **29**

i) $Cr(CO)_6$, Bu_2O/THF (10:1), 140°C.

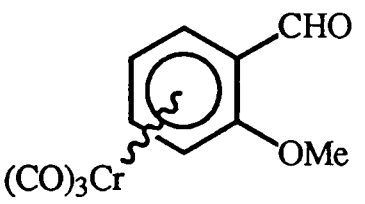
Resolution of racemic $Cr(CO)_3$ complexes has been achieved by a variety of methods. The classical approach is one of derivatisation with a homochiral reagent and separation of the resultant diastereoisomeric mixture by crystallisation. For example, racemic *meta*-(methoxybenzoic acid)$Cr(CO)_3$ (**30**) is efficiently resolved upon treatment with brucine and fractional crystallisation,[37] whilst the diastereoisomeric semioxamazone complexes **31** may be separated by column chromatography to yield upon hydrolysis, both enantiomers of *ortho*-(methoxybenzaldehyde)$Cr(CO)_3$ (**32**).[38] A more convenient resolution procedure for complex **32** relies upon reaction with a homochiral amino alcohol and the differential rate at which each of the diastereoisomeric products is hydrolysed. Thus, chromatography of racemic **32** on alumina impregnated with (L)-valinol gives two well separated fractions upon elution with diethylether, each of which is homochiral.[39]



(-)-**30**



31



32

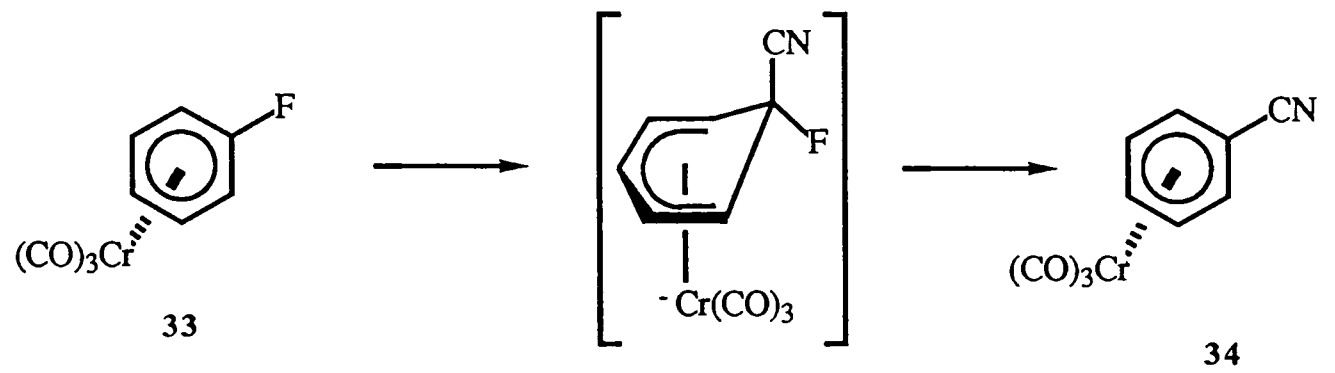
ii) *Decomplexation*

The $Cr(CO)_3$ unit may be removed in a variety of ways, the majority of which rely upon the facile oxidation of Cr^0 to higher oxidation states . Oxidants such as iodine,[40] periodate[41] and electrolysis[42] have all been reported but the most convenient procedure is exposure of a diethylether solution of the complex to air and sunlight (typically 24-48 hours). The precipitated chromium salts may then be removed by filtration and the filtrate evaporated to afford the analytically pure arene in almost quantitative yield.[43] Of course, these oxidative

techniques are destructive in that the chromium salts isolated after decomplexation may not be employed for further complexation reactions. However, the $Cr(CO)_3$ fragment may alternatively be removed as Cr^0 by the use of suitable donor ligands including triphenylphosphine,[25] pyridine[44] and carbon monoxide.[45] In the latter case, chromium hexacarbonyl may be isolated and subsequently recycled for further complexation reactions.

iii) *Nucleophilic Substitution*

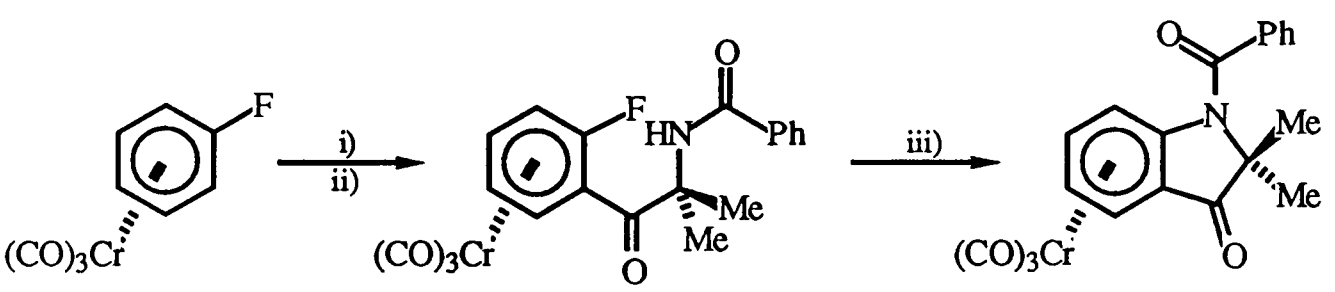
The reduced electron density of aromatic rings coordinated to the $Cr(CO)_3$ unit renders them more susceptible to nucleophilic attack than the corresponding uncomplexed arenes. The electron withdrawing effect of the $Cr(CO)_3$ moiety has been likened to that of an aromatic nitro substituent in that they both undergo analogous nucleophilic substitution reactions.[16,25] Thus, treatment of (fluorobenzene)$Cr(CO)_3$ (**33**) with cyanide gives benzonitrile complex **34** in good yield *via* an addition-elimination mechanism.[46]



33 **34**

i) CN^-, 25°C, 94%.

This type of reactivity may occur in an intramolecular sense and has been utilised in the synthesis of heterocyclic systems. For example, *ortho* deprotonation of complex **33** with *t*-butyllithium followed by reaction with 4,4-dimethyl-2-phenyloxazolin-5-one gives intermediate complex **35**. Subsequent intramolecular nucleophilic substitution furnishes the bicyclic complex **36** upon treatment with LDA.[47]

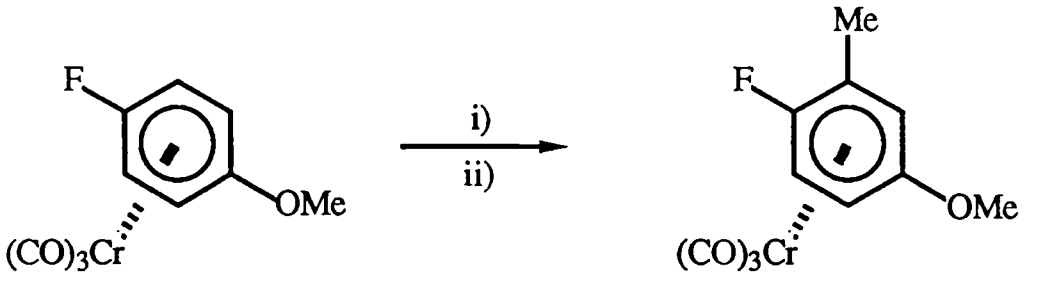


33 **35** **36**

i) *t*-BuLi, THF, TMEDA, -78°C, 0.5h. ii) 4,4-dimethyl-2-phenyloxazolin-5-one, 75%.
iii) LDA, THF, -78°C, 4h, 96%.

iv) *Aryl Anions*

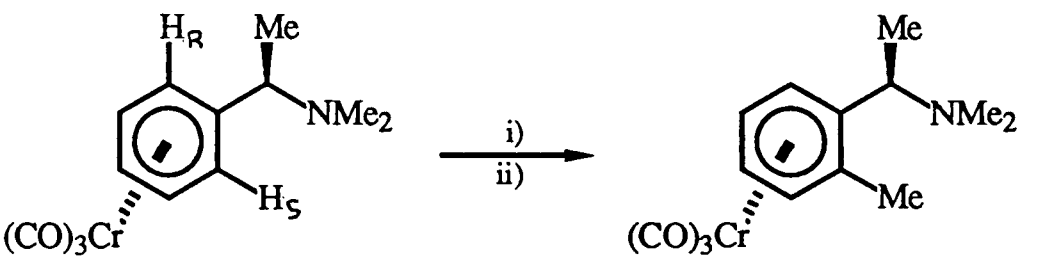
The powerful electron withdrawing nature of the $Cr(CO)_3$ group increases the acidity of complexed arene ring protons by *ca.* 5-6 pKa units owing to the inductive stabilisation of the resultant ring anion. This effect, coupled with steric and chelate directing effects of ring substituents offers a versatile method permitting arene functionalisation. Inductively electron withdrawing substituents direct lithiation to the *ortho* position. If two or more such substituents are present their relative directing abilities follow the order $F>OMe>NR_2>SR>CR_3$.[48] Thus, sequential treatment of *para*-(fluoroanisole)$Cr(CO)_3$ (**37**) with *n*-butyllithium and an electrophile gives regioselective alkylation *ortho* to the fluorine substituent,[49,50] in marked contrast to the behaviour of the free arene.[51]



37 **38**

i) *n*-BuLi, THF, -78°C, 2h. ii) MeI, 72%.

If a ring substituent bears a chiral centre then the sites *ortho* to that substituent are rendered diastereotopic as in the case of (+)-(N,N-dimethyl-α-methylbenzylamine)$Cr(CO)_3$ (**39**). Sequential treatment of complex (+)-**39** with *t*-butyllithium and methyl iodide results in exclusive formation of the *ortho*-methylated complex (+)-**40** as a single diastereoisomer. This is consistent with initial coordination of the base to the nitrogen lone pair and subsequent removal of the *pro*-S-*ortho* proton *via* the transition state that places the α-proton *syn* to the $Cr(CO)_3$ moiety (Diagram 2).[52]



(+)-(*R*)-**39** (+)-(*R*)-**40**

i) *t*-BuLi, THF, -78°C, 2h. ii) MeI, 77%.

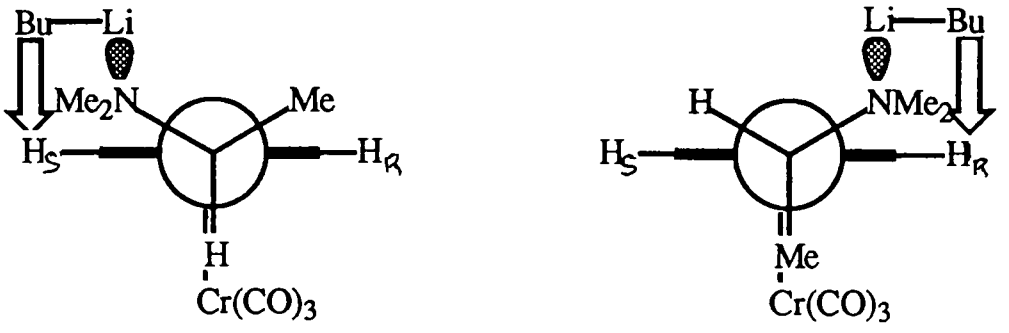
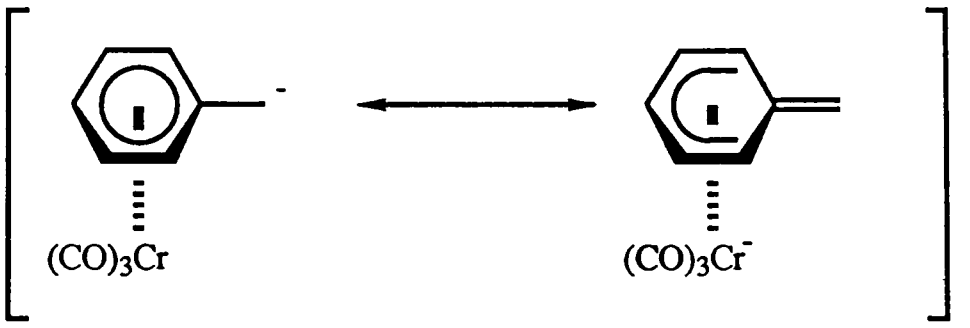


Diagram 2 : Possible transition states permitting chelation controlled *ortho* deprotonation of complex (+)-**39**.

v) *Benzylic Carbanions*

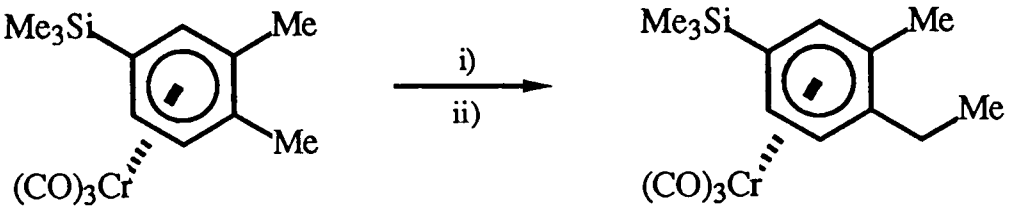
A further consequence of the electron withdrawing nature of the $Cr(CO)_3$ moiety manifests itself in the increased acidity of benzylic protons. In this case there is not only an inductive stabilisation of the resultant benzylic carbanion but also a mesomeric contribution whereby the negative charge is delocalised onto the metal (Scheme 1). The exocyclic double bond character of the anionic intermediate is supported by n.m.r. spectroscopic analysis of the carbanion that reveals that both of the *ortho* hydrogen and carbon atoms are magnetically inequivalent, consistent with hindered rotation about the benzylic carbon-ring carbon bond.[17,53] Formation of a $Cr(CO)_3$ stabilised benzylic carbanion is accompanied by a characteristic colour change from yellow to deep red which is reversed upon treatment with an electrophile. Although there is a possibility of competition between ring and benzylic proton abstraction, generally speaking the benzylic anion may be generated under equilibrating conditions or by the use of non-nucleophilic thermodynamic bases such as butoxide or hexamethyldisilazide.[17]



Scheme 1 : Resonance stabilisation of $Cr(CO)_3$ bound benzylic carbanion.

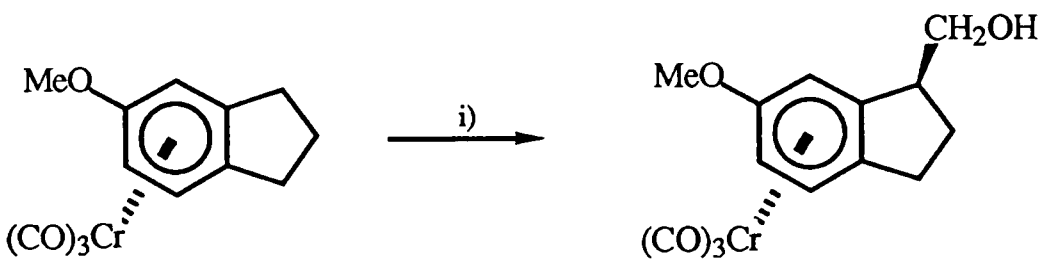
When two or more benzylic protons are available, the site of deprotonation is governed by a number of factors. Firstly, the electronic effect of any other ring substituent may orientate the deprotonation as in the case of (4-trimethylsilyl-*ortho*-xylene)$Cr(CO)_3$ (**41**) which gives

exclusive formation of methylated complex **42** upon sequential treatment with *n*-butyllithium and methyl iodide.[54] In contrast, the electron releasing 5-methoxyl substituent of indane complex **43** gives regioselective deprotonation at C3 upon treatment with base since an anion at C1 would be less stable on electronic grounds. Moreover, in the latter case, subsequent trapping of the C3 anion with formaldehyde is completely stereoselective, approach of the electrophile being restricted to the unhindered *exo* face due to the steric bulk of the $Cr(CO)_3$ unit.[55]



41 **42**

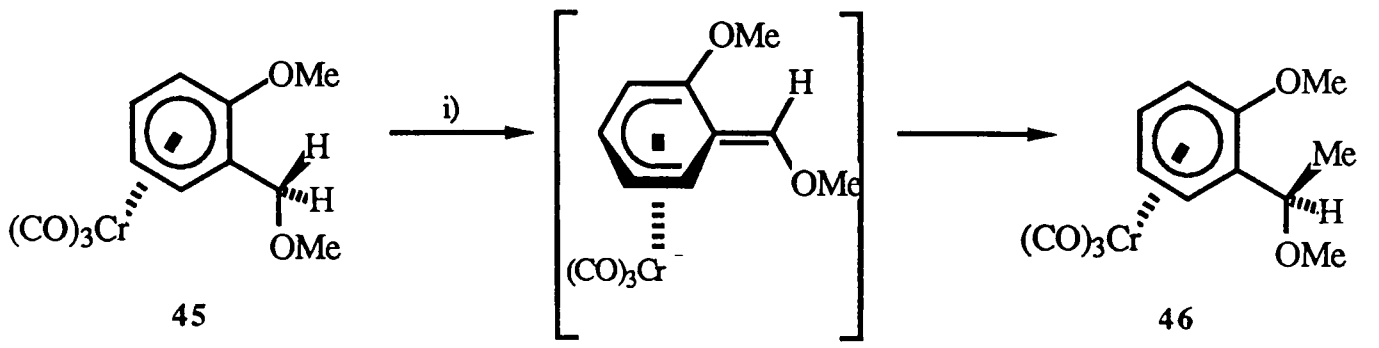
i) *n*-BuLi, THF, -78°C, 2h. ii) MeI, 99%.



43 **44**

i) *t*-BuOK, CH_2O, DMF, 20°C, 95%.

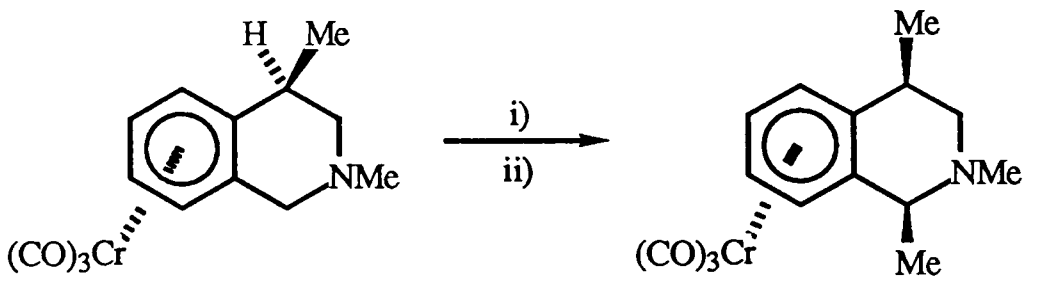
The steric effect of an *ortho* substituent may also dictate which benzylic proton is preferentially removed. For example, (*ortho*-methoxy-α-methyl benzylmethylether)$Cr(CO)_3$ (**45**) possesses diastereotopic benzylic protons. Sequential treatment with *t*-butyllithium and methyl iodide generates a single diastereoisomer of complex **46**, the relative stereochemistry being unambiguously proven by a single crystal X-ray structure determination.[17] In this case the lack of any ring deprotonation is a consequence of the stablilising influence of the inductively electron withdrawing methoxyl substituent upon the benzylic carbanion generated upon treatment with base. The observed stereoselectivity is consistent with *exo* deprotonation of **45** in the sterically least demanding conformation that places the benzylic methoxyl substituent *anti* to the arene methoxyl group. Subsequent *exo* methylation of the resultant anion generates complex **46** with complete suppression of the Wittig rearrangement.[56]



45 46

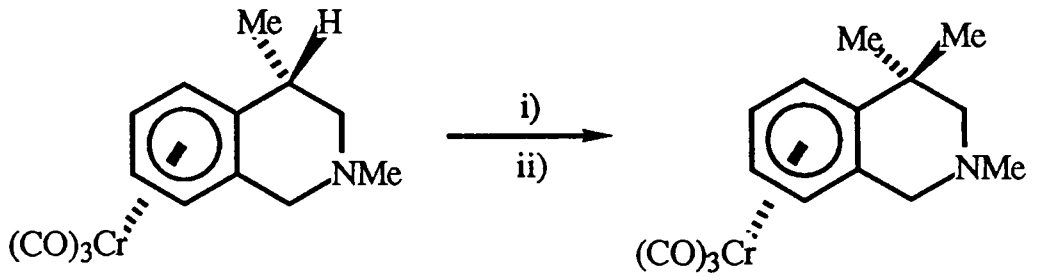
i) *t*-BuLi, THF, -78°C, 2h, then MeI, 99%.

Chelate directing effects may also determine the site of benzylic deprotonation. Treatment of *exo*-4-methyl tetrahydroisoquinoline complex **47** with *t*-butyllithium and methyl iodide gives exclusive *exo*-C1-methylation affording complex **48** as a single diastereoisomer.[57] In marked contrast, similar treatment of *endo*-4-methyl tetrahydroisoquinoline complex **49** yields the C4 *gem* dimethyl complex **50** as the sole product.[58] In the former case the only benzylic proton available for abstraction is the *exo*-C1 proton since both *endo*-C1 and *endo*-C4 protons are inacccessible to the base as a consequence of the bulky $Cr(CO)_3$ tripod. In the latter case, the pseudo-axial nitrogen lone pair may coordinate to the base offering regioselective *exo*-C4 proton removal *via* a cyclic six-membered transition state.



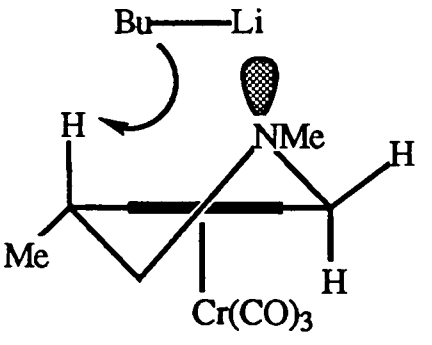
47 48

i) *t*-BuLi, THF, -78°C, 2h. ii) MeI, 77%.

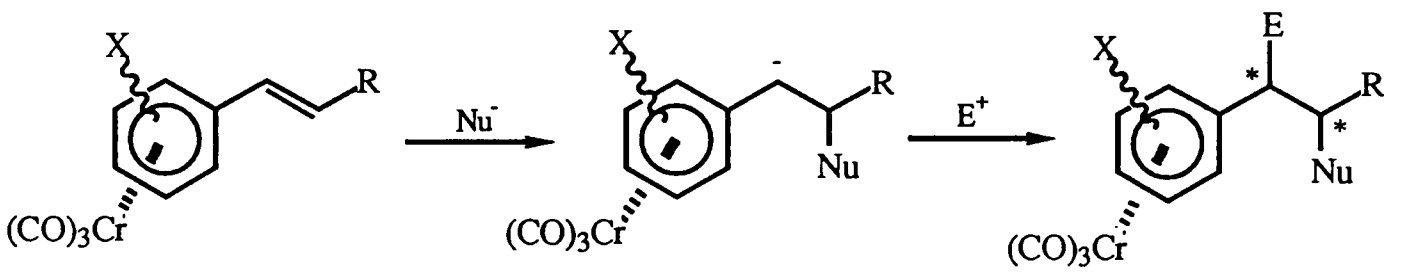


49 50

i) *n*-BuLi, THF, -78°C, 2h. ii) MeI, 87%.



A relatively unexplored area of arene $Cr(CO)_3$ chemistry involves the generation of $Cr(CO)_3$-bound benzylic carbanions *via* nucleophilic addition to substituted (styrene)$Cr(CO)_3$ complexes as outlined in Scheme 2.[59] Uemura has employed this type of reactivity as the key step in a total synthesis of 11-deoxyanthracyclinone.[60]

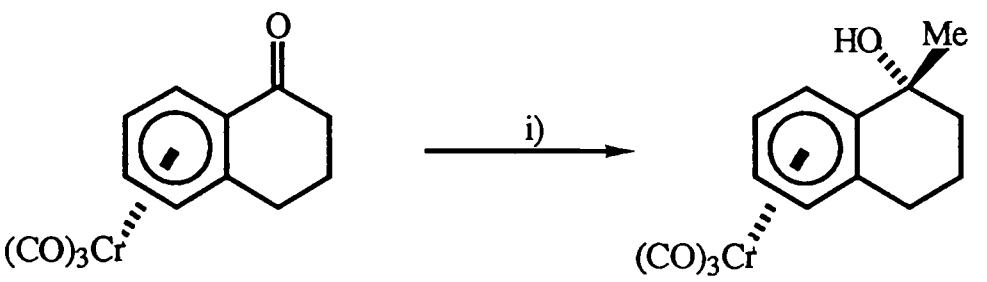


Scheme 2 : Elaboration of substituted (styrene)$Cr(CO)_3$ complexes.

vi) *Nucleophilic Addition to Carbonyls*

The prochiral faces of the carbonyl group of an *ortho*-or *meta*-substituted (benzaldehyde)- or (phenyl ketone)$Cr(CO)_3$ complex are diastereotopic. If the conformation of the carbonyl functionality is restricted, the steric bulk of the $Cr(CO)_3$ unit will direct the approach of nucleophilic reagents to the unhindered face thereby giving rise to the generation of a new asymmetric centre with a high degree of stereocontrol.

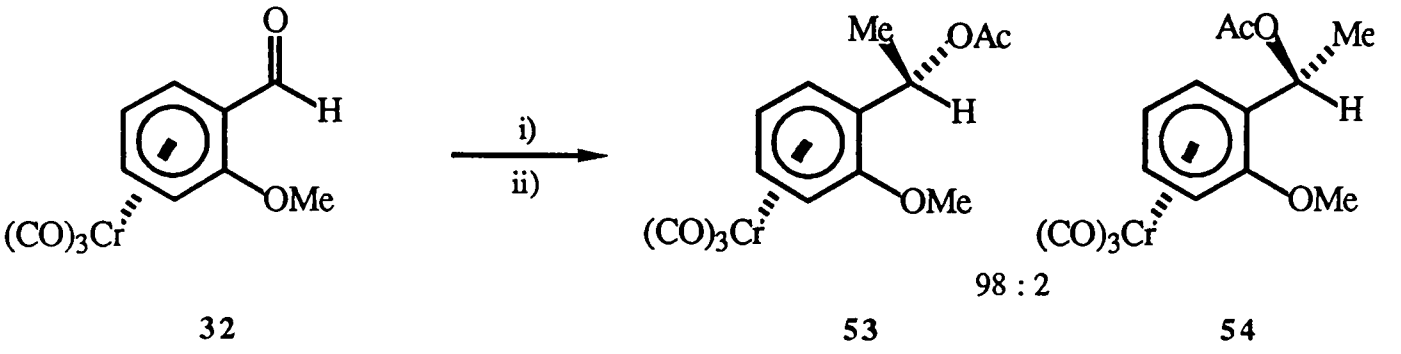
The orientation of the ketonic functionality in tetralone complex **51** is fixed owing to the conformational restriction imposed by the six-membered ring. Treatment of complex **51** with methyllithium stereoselectively generates the corresponding *exo*-1-methyl tetralol complex **52** as a single diastereoisomer, the approach of the nucleophile being prevented from the coordinated *endo* face.[56,61]



51 **52**

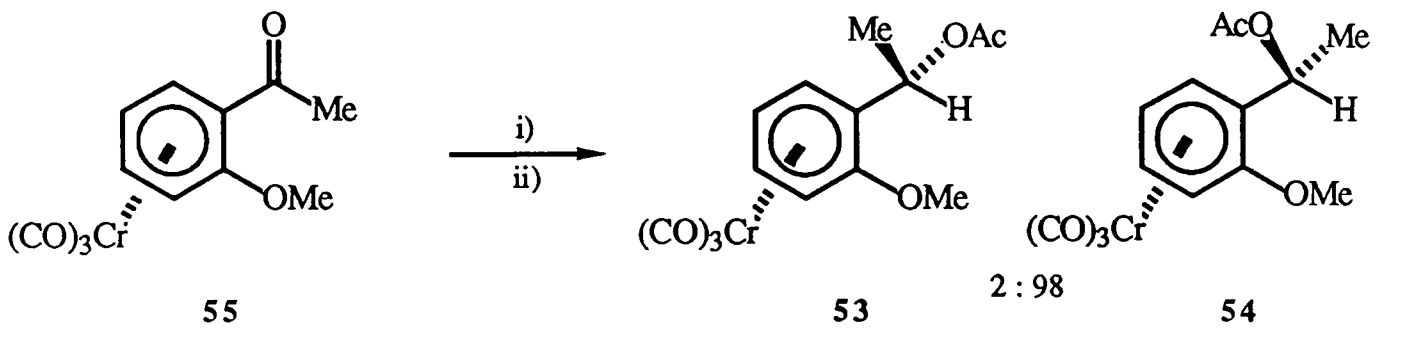
i) MeMgI, Et_2O, -20°C, 1h, 68%.

For *ortho*-methoxybenzaldehyde complex **32** the preferred conformation places the carbonyl group coplanar with the aromatic ring and with the aldehyde proton *syn* to the ring methoxyl substituent. Addition of methyllithium and subsequent acylation gives complex **53** essentially as one diastereoisomer, whilst the other diastereoisomer (**54**) is readily synthesised upon reduction and subsequent acylation of methyl ketone complex **55**. In the latter case the preferred conformation presumably places the carbonyl functionality coplanar with the aromatic ring with the oxygen atom *anti* to the ring methoxyl substituent.[62]



32 **53** **54**

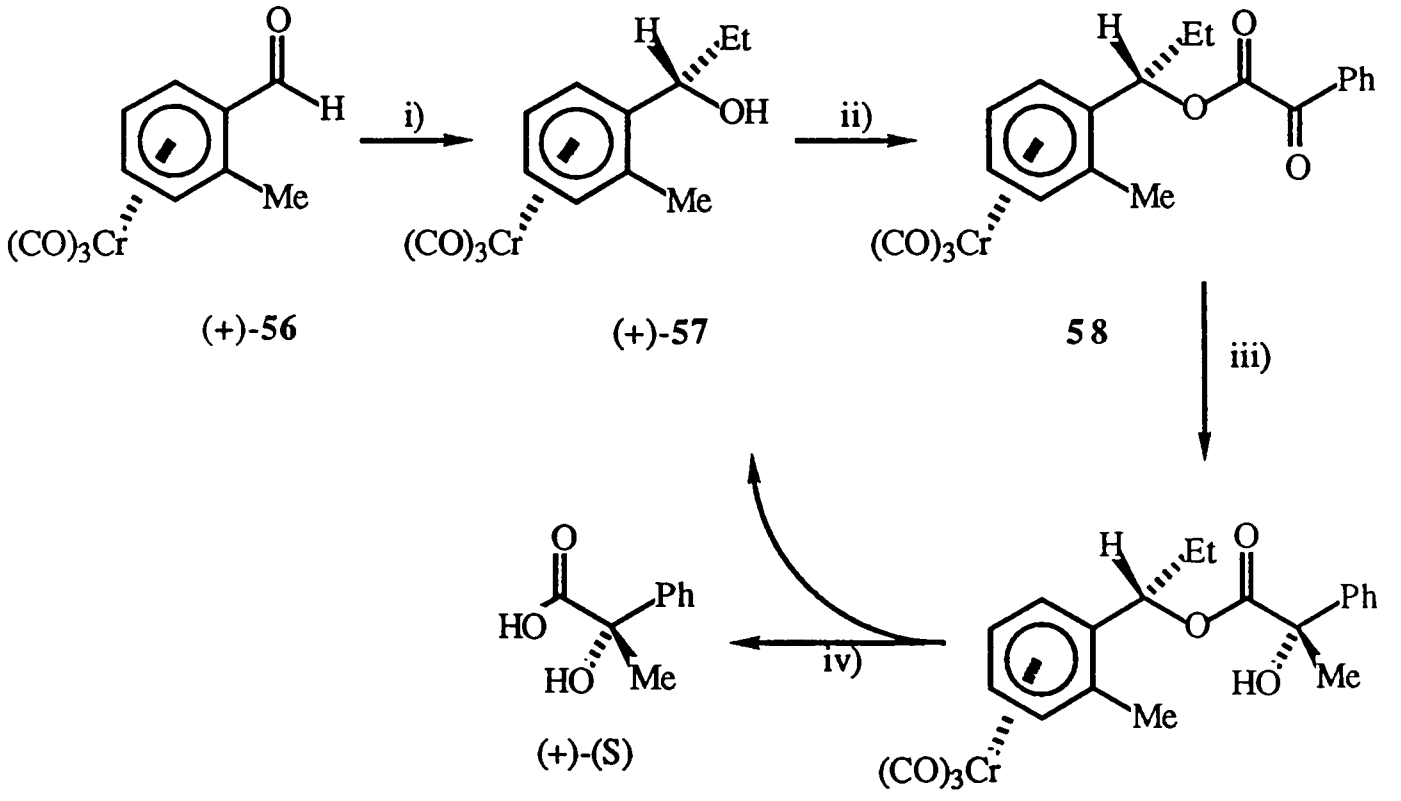
i) MeLi, Et_2O, -78-0°C, 2h. ii) Ac_2O, DMAP, C_6H_5N, 0°C, 4h, 2 steps 66%.



55 **53** **54**

i) $LiAlH_4$, Et_2O, 0°C, 0.5h. ii) Ac_2O, DMAP, C_6H_5N, 0°C, 4h, 2 steps 74%.

In a similar fashion, treatment of (+)-*ortho*-(methylbenzaldehyde)$Cr(CO)_3$ (**56**) with ethyllithium gives the secondary alcohol (+)-**57** as a single diastereoisomer. This has been employed as a chiral auxiliary as in the esterification with the acid chloride of phenyl glyoxylic acid gives complex **58** which reacts with Grignard reagents in a highly stereoselective manner. Subsequent basic hydrolysis regenerates the chiral auxiliary (+)-**56** and liberates the corresponding α-substituted mandelic acid derivative of good optical purity (e.e. >82%).[63]

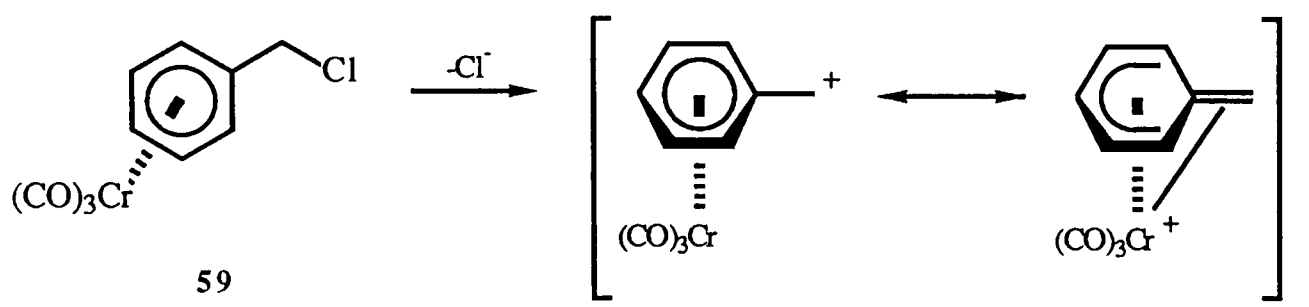


(+)-**56** (+)-**57** **58** (+)-(S)

i) EtLi, Et_2O, -40°C, 87%. ii) ClCOCOPh. iii) MeMgI, Et_2O, -100°C, 99%.
iv) KOH, EtOH, 99% [95% recovery of (+)-**56**].

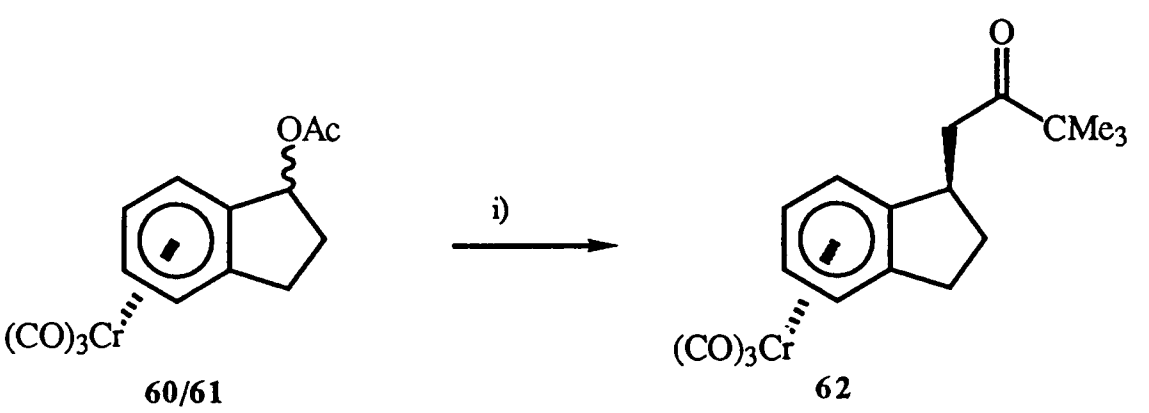
vii) *Benzylic Carbocations*

In 1965 it was reported that S_N1 solvolysis of (benzylchloride)$Cr(CO)_3$ (**59**) occurred at a rate five orders of magnitude faster than the corresponding rate of hydrolysis for the uncomplexed arene.[64] This kinetic phenomenon has been attributed to the anchimeric assistance offered by the $Cr(CO)_3$ unit in the rate-determining ionisation process which may only operate when the leaving group lies antiperiplanar to the arene-$Cr(CO)_3$ axis. The resultant carbocation is stabilised by back donation by filled d orbitals on the metal, thereby delocalising the positive charge onto chromium (Scheme 3).[65]



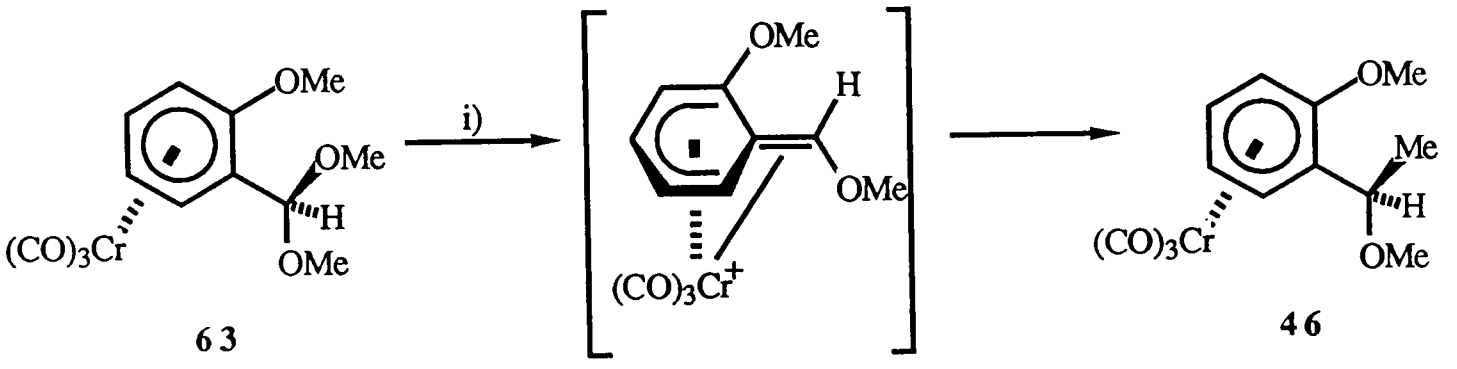
Scheme 3 : Resonance stabilisation of $Cr(CO)_3$ bound benzylic carbocation.

This property of benzylically substituted (arene)$Cr(CO)_3$ complexes has found wide-ranging synthetic application in recent years. Moreover, the configurational stability of the intermediate carbocations has lent itself to a high degree of stereocontrol in related benzylic substitution reactions. A variety of heteroatomic nucleophiles and reducing agents have been used to trap the cationic intermediate but, more recently, carbon nucleophiles have been used to effect C-C bond formation. For example, Reetz has described the stereoconvergent reaction of a diastereoisomeric mixture of *endo* and *exo* indanol derivatives **60** and **61** with silyl enol ethers under Lewis acid catalysis which generates only the *exo*-alkylated complex **62**.[66] The conformational restriction imposed by the five-membered ring requires that the carbocation generated upon ionisation of either complex **60** or **61** may only be trapped from the unhindered *exo* face, thereby accounting for the observed selectivity.



i) $Me_3CC(OSiMe_3)CH_2$, $ZnCl_2$, CH_2Cl_2, 22°C, 91%.

It is apparent that the stereochemical requirement for enhanced ionisation is for the αC-O bond to adopt a conformation antiperiplanar to the arene-$Cr(CO)_3$ axis. This has recently been demonstrated in the stereoselective conversion of dimethoxyacetal complex **63** to methylated complex **46** upon treatment with titanium tetrachloride and trimethylaluminium. In this case the selectivity arises from reaction *via* a transition state that permits *exo* loss of a methoxyl group in the conformation that places the benzylic proton *syn* to the *ortho* methoxyl substituent.[67]



63 **46**

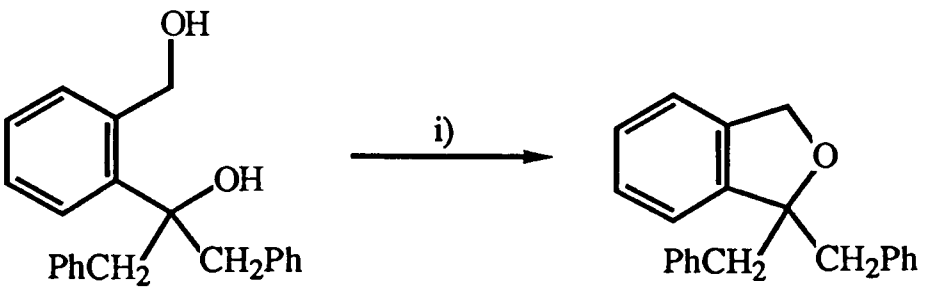
i) $TiCl_4$, Me_3Al, CH_2Cl_2, -78°C, 5min, 80%.

CHAPTER 1

1,3-Dihydroisobenzofurans

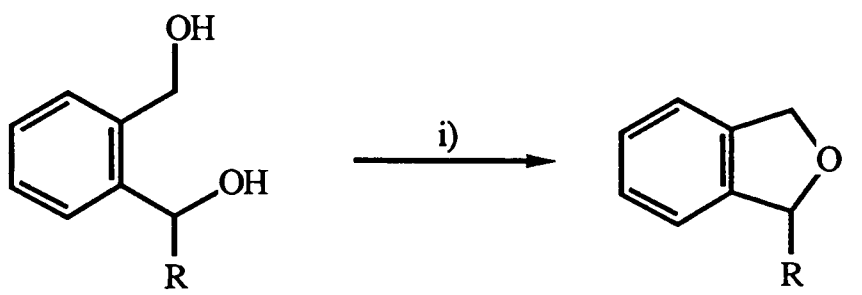
1,3-DIHYDROISOBENZOFURANS

The synthesis of functionalised dihydoisobenzofurans (phthalans) has proved to be of interest owing to both their spectroscopic properties and their pharmacological profiles.[68-70] Many methods have been reported enabling the construction of substituted phthalans, nearly all of them relying upon an acid-mediated cyclisation reaction.[71] For example, acidic treatment of phthalide-derived diol **64** readily affords 1,1-dibenzyl phthalan (**65**),[72] whilst the mono-alkylated diols **66-68** give the corresponding 1-alkyl phthalans **69-71** upon treatment with orthophosphoric acid.



64 **65**

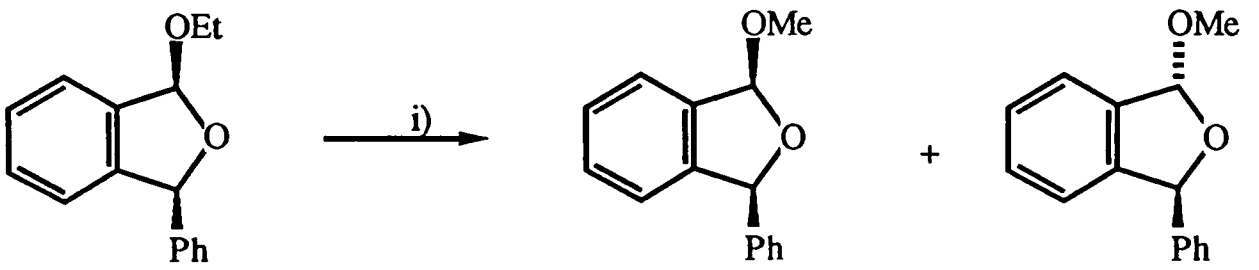
i) *p*TsOH, benzene, 10h, 74%.



R = *t*-Bu **66** R = *t*-Bu **69**
Me **67** Me **70**
Ph **68** Ph **71**

i) Orthophosphoric acid, 2h.

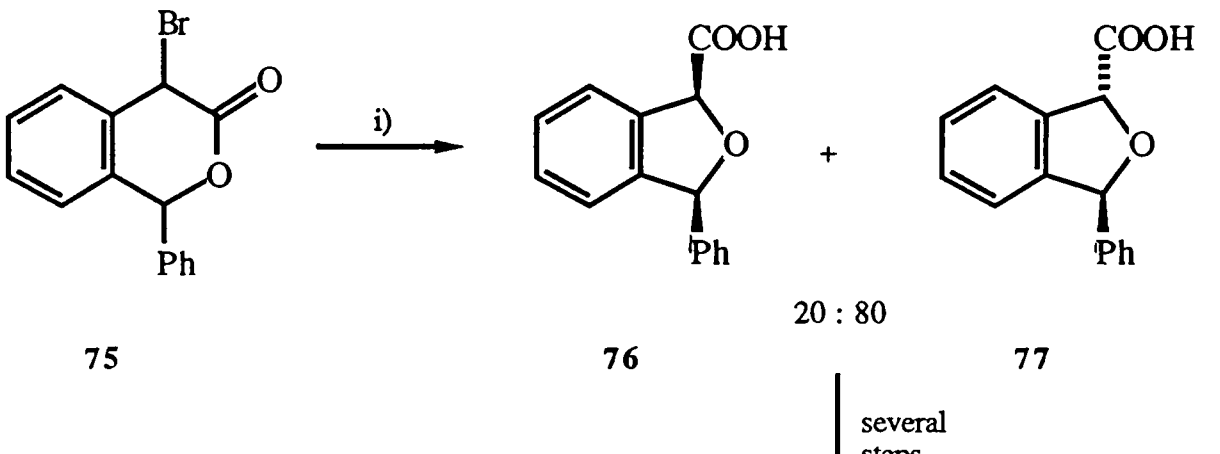
A similar approach for the syntheses of 1,3-disubstituted phthalans normally results in the formation of a mixture of both *cis* and *trans* diastereoisomers, the latter usually predominating on steric grounds. Thus, acid-induced transacetalisation of predominantly *cis*-1-ethoxy-3-methyl phthalan (**72**) (ratio 85:15) in methanol gives an equilibrium mixture of both *cis*- and *trans*-1-ethoxy-3-methyl phthalan (**73** and **74**) in the ratio 44:56.[73] Similarly, alkaline hydrolysis of isochromone **75** gives a 20:80 mixture of both *cis*- and *trans*-1,3-disubstituted phthalans (**76** and **77**) which may be readily converted to both diastereoisomers of 1-N,N-dimethylaminomethyl-3-phenyl phthalan (**78** and **79**) without any epimerisation. These compounds have been shown to possess equipotent antihistaminic activity.[70]



44 : 56

72 **73** **74**

i) TFA, MeOH, 1h, 96%.

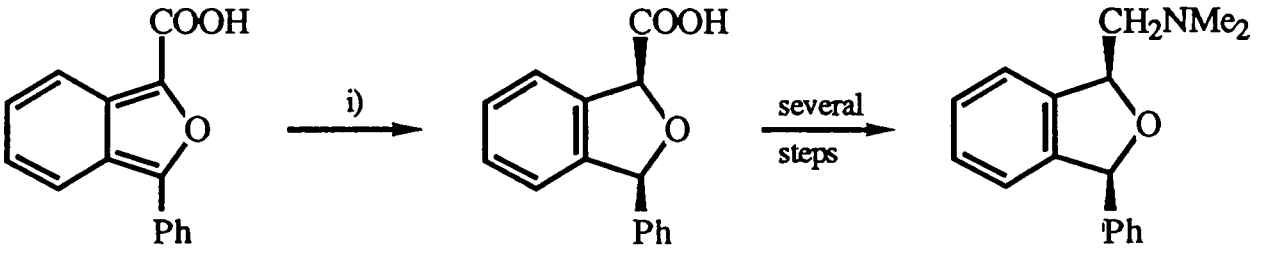


75 **76** **77**

78 **79**

i) NaOH, 8h, 84%.

Although the individual diastereoisomers **78** and **79** may be obtained by fractional crystallisation and subsequent elaboration of their nitro precursors, a stereoselective synthesis of **78** *via* synthesis of *cis*-phthalan **76** has been reported and involves the catalytic hydrogenation of 1-carboxy-3-phenylisobenzofuran (**80**) which yields **76** diastereoisomerically pure.[74]

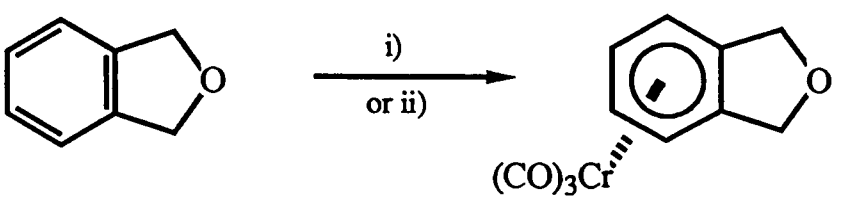


80 **76** **78**

i) H_2, MeOH, PtO_2, 50%.

Results and discussion

(Phthalan)$Cr(CO)_3$ (**81**) was prepared as a crystalline yellow solid by thermolysis of chromium hexacarbonyl with phthalan (**82**) in a 10:1 mixture of dibutyl ether and THF under a nitrogen atmosphere†.[26] Alternatively treatment of phthalan (**82**) with (naphthalene)$Cr(CO)_3$ (**20**)[31] in a refluxing mixture of diethylether and tetrahydrofuran afforded complex **81** in better yield.

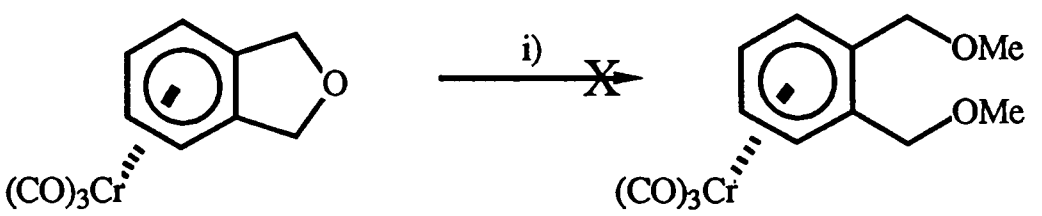


82 **81**

i) $Cr(CO)_6$, Bu_2O/THF (10:1), 22h, 20%.
ii) $C_{10}H_8Cr(CO)_3$ (**20**), Et_2O, THF, 25h, 34%.

A THF solution of complex **81** was treated with concentrated hydrochloric acid in the presence of methanol and water for twelve hours. Subsequent workup afforded only starting material in near-quantitative recovery with no observable ring-opened complexes. An authentic sample of *bis*-methylether complex **83** was synthesised according to the literature procedure.[56]

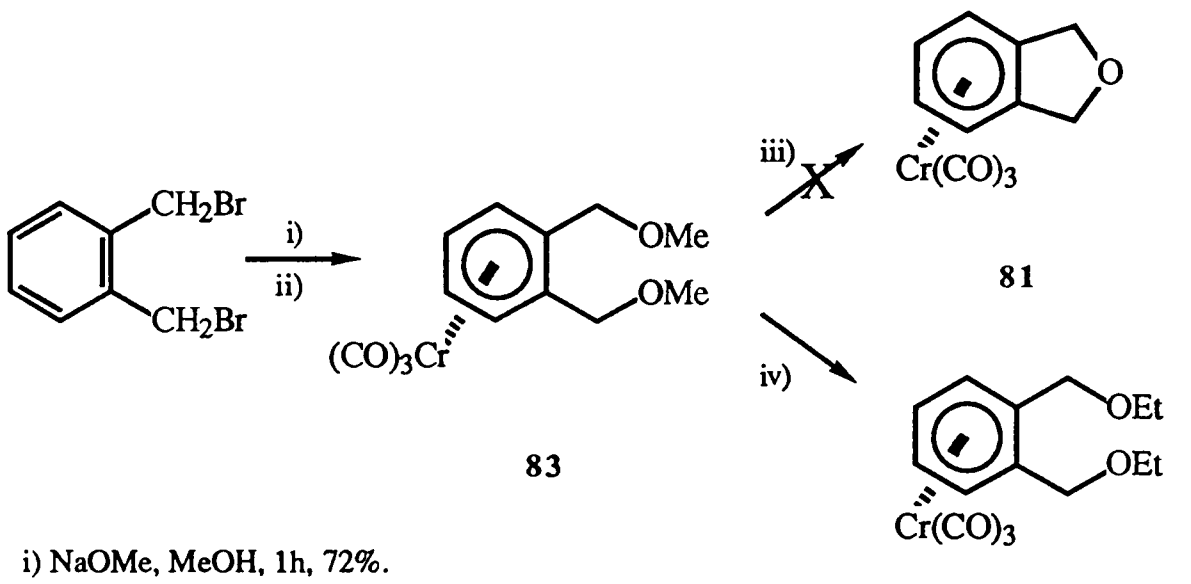
A dichloromethane solution of complex **83** at -40°C was treated with ethanol and tetrafluoroboric acid giving a purple colouration that reverted to yellow after a short time. Basification and workup gave a yellow solution that contained the *bis*-ethylether complex **84** as evidenced by a highfield triplet in its ^1H n.m.r. spectrum and a molecular ion m/z=330. Complex **83** was similarly stirred with a variety of acids (tetrafluoroboric, trifluoroacetic, and orthophosphoric) in several different solvent systems but (phthalan)$Cr(CO)_3$ (**81**) was never observed.



81 **83**

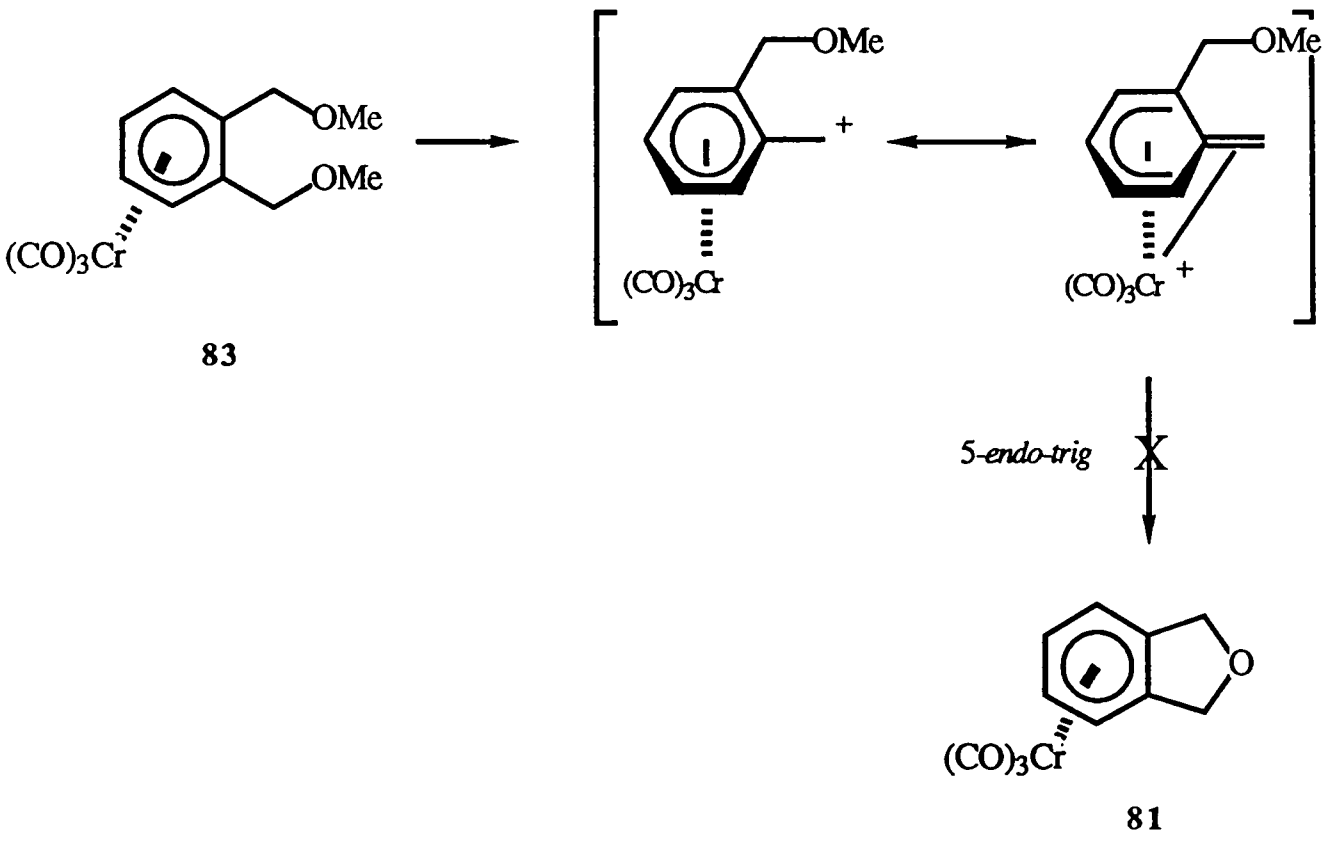
i) HCl, MeOH, H_2O, 12h.

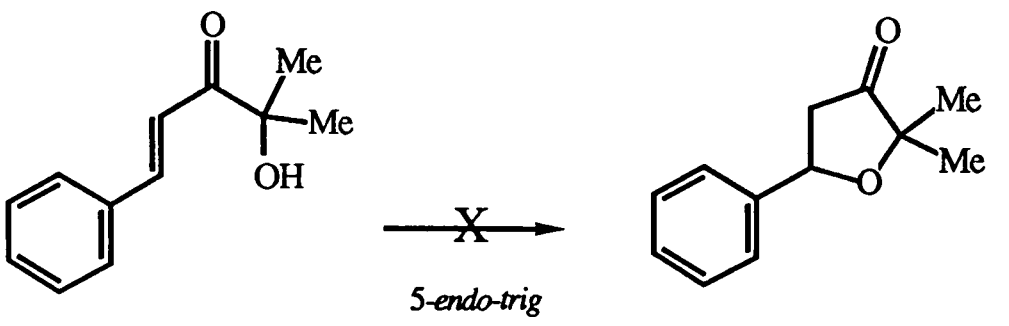
† Henceforth referred to as standard conditions for complexation.



i) NaOMe, MeOH, 1h, 72%.
ii) $Cr(CO)_6$, Bu_2O/THF (10:1), 40h, 78%.
iii) H^+
iv) $HBF_4.OMe_2$, CH_2Cl_2, -40°C, EtOH, 10min.

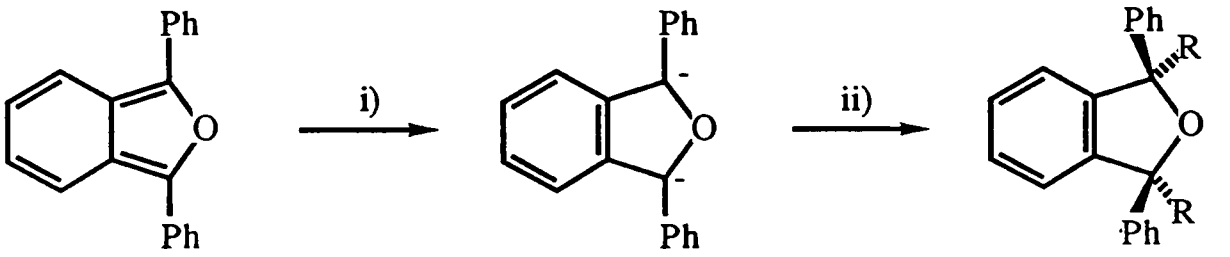
The failure of complexes **81** and **83** to interconvert is a consequence of a kinetic rather than a thermodynamic barrier and may be rationalised in stereoelectronic terms. Due to the constraints imposed by the five-membered ring, the carbon oxygen bonds of complex **81** are unable to attain a conformation that places either of them antiperiplanar to the arene-chromium axis (required for promoted ionisation) which thus prevents ring opening. That *bis*-methylether complex **83** readily forms a benzylic carbocation was evidenced both by the colour change from yellow to purple upon addition of acid (indicative of a $Cr(CO)_3$ stabilised benzylic carbocation)[65] and the ready transetherification to *bis*-ethylether complex **84**. The cationic complex thus generated may be envisaged as intermediate between the two extreme canonical forms shown below, the major emphasis being on the canonical form that delocalises the positive charge onto chromium. Cyclisation of this intermediate benzylic carbocation would necessitate an unfavourable 5-*endo-trig* process.[75] Alcohol **85** fails an analogous cyclisation under basic conditions for the same reason.[76]





85

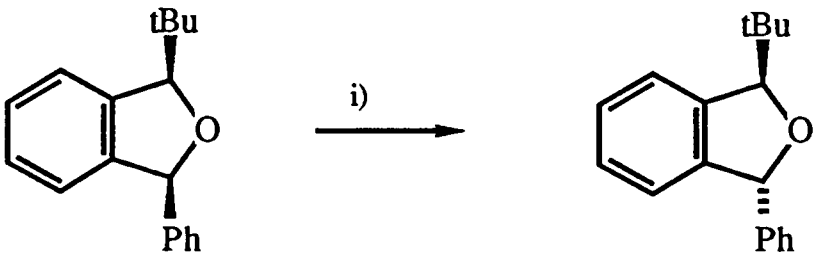
Benzylic substitution of 1,3-diphenyl phthalan has been reported and involves a two electron reduction of 1,3-diphenyl isobenzofuran (**86**) to generate the intermediate dianion **87**. Subsequent quenching with an electrophile generates the benzylically disubstituted products as a mixture of diastereoisomers; *cis* stereochemistry predominating presumably because the two phenyl groups in the intermediate dianion **87** prefer to adopt a pseudo-equatorial geometry.[77] The thermodynamic preference for *trans* stereochemistry has been shown by *t*-butoxide-mediated isomerisation of *cis*-1-phenyl-3-*t*-butyl phthalan (**88**) which gives the corresponding *trans*-isomer **89**.[78]



86 **87**

	cis : *trans*
R = Me	9 : 1
COOH	11: 1
H	4 : 1

i) Na, THF, 8h. ii) R^+, THF, -70-20°C, 14h.

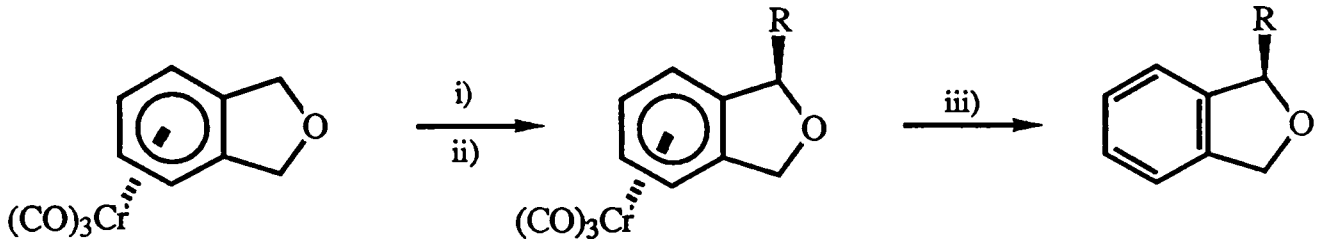


88 **89**

i) *t*-BuOK, *t*-BuOH.

The ability of the $Cr(CO)_3$ moiety to promote stereoselective benzylic alkylations is well documented.[35,56-58] It was envisaged that (phthalan)$Cr(CO)_3$ (**81**) could be regio- and stereoselectively dialkylated to give, after decomplexation, the corresponding *cis*-1,3-disubstituted phthalans. Treatment of a tetrahydrofuran solution of complex (**81**) with *t*-butyllithium at -78°C gave an immediate colour change from yellow to deep red, indicative of benzylic deprotonation. Subsequent addition of methyl iodide gave *exo*-(1-methyl phthalan)$Cr(CO)_3$ (**90**) as a single diastereoisomer in 88% isolated yield. *Exo* stereochemistry

was assigned by analogy with similar benzylic alkylations reported in the literature and is consistent with approach of the electrophile from the less hindered *exo* face, away from the steric bulk of the $Cr(CO)_3$ group. That benzylic methylation had occurred was evident from the ^1H n.m.r. spectrum of the product which exhibited a high field three proton doublet, a doublet of quartets and a two proton ABX system (substantial 3-bond coupling is documented in the literature for similar compounds).[69,71,79] An elemental analysis and a molecular ion *m/z*=270 were consistent with the structure of complex **90**. Treatment of the anion derived from complex **81** with other electrophiles (ethyl iodide, benzyl bromide and deuteriomethanol) similarly gave the corresponding *exo*-1-substituted phthalan complexes **91-93** completely stereoselectively and were fully characterised. Exposure of diethyl ether solutions of complexes **90-92** to air and sunlight† liberated the correponding 1-alkyl phthalans **70**,[68,80,81] **94** and **95** which were isolated as colourless oils. Despite the ready autoxidation of 1,3-disubstituted phthalans,[80] satisfactory elemental analyses were obtained for the previously unreported phthalans **94** and **95**.



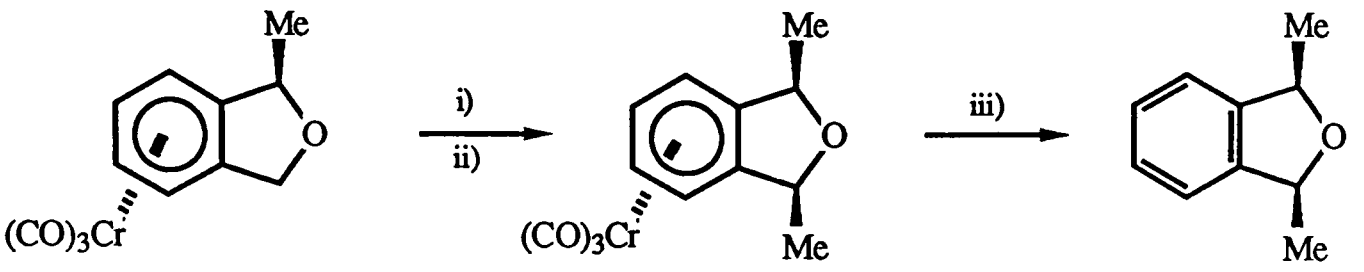
81

R =	Me	**90**	(88%)	R =	Me	**70**	(80%)
	Et	**91**	(72%)		Et	**94**	(75%)
	$PhCH_2$	**92**	(82%)		$PhCH_2$	**95**	(81%)
	D	**93**	(92%)				

i) *t*-BuLi, THF, -78°C, 2h. ii) RX.
iii) Et_2O, air, sunlight.

A tetrahydrofuran solution of complex **90** was treated with *t*-butyllithium at -78°C giving a deep red colouration. Addition of methyl iodide and subsequent workup gave a single diastereoisomer of *exo-cis*-(1,3-dimethyl phthalan)$Cr(CO)_3$ (**96**) as a yellow solid in 91% isolated yield. The structure of complex **96** followed from its ^1H n.m.r. spectrum which comprised a single high field doublet and a single quartet indicating the equivalence of the methyl and the benzylic protons, consistent with the expected *cis* stereochemistry. A *trans* relationship would be expected to give rise to two three proton doublets at markedly different chemical shifts. A molecular ion *m/z*=284 and a satisfactory elemental analysis were consistent with the structure of complex **96**. Oxidative decomplexation liberated the known *cis*-1,3-dimethyl phthalan (**97**) as an unstable oil.[81,82]

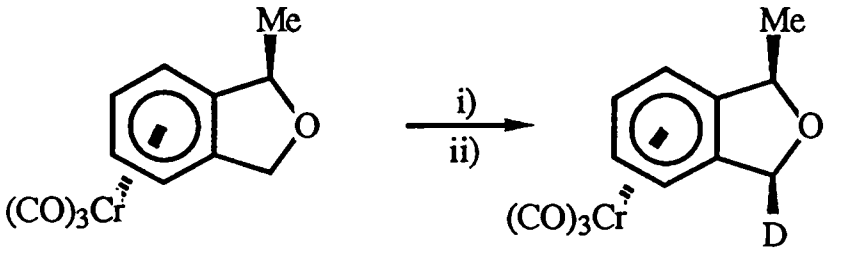
† Henceforth referred to as oxidative decomplexation.



90 **96** **97**

i) *t*-BuLi, THF, -78°C, 1h. ii) MeI, 91%. iii) Et_2O, air, sunlight.

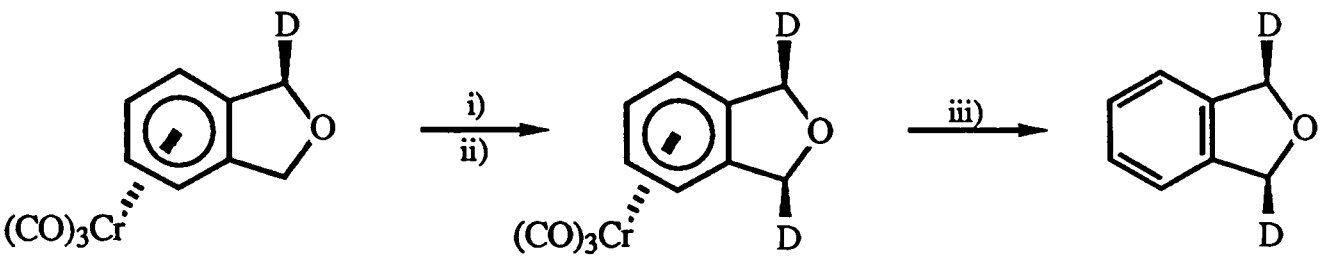
In a similar fashion, deuteriation of complex **90** was effected upon sequential treatment with *t*-butyllithium and deuteriomethanol to give *cis*-(1-methyl-3-deuterio phthalan)$Cr(CO)_3$ (**98**). ^2H n.m.r. spectroscopy and a mass spectrum comparison with that of complex **90** indicated that the product contained >90% deuterium in the *exo*-3 position and none in the *endo*-3 position.



90 **98**

i) *t*-BuLi, THF, -78°C, 1h. ii) CD_3OD, 93%.

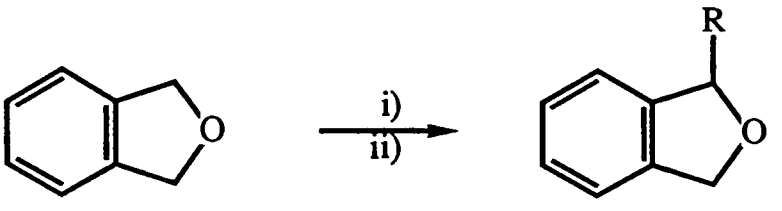
Deuteriation of *exo*-(1-deuterio phthalan)$Cr(CO)_3$ (**93**) upon sequential treatment with *t*-butyllithium and deuteriomethanol stereoselectively gave *cis*-(1,3-dideuterio phthalan)$Cr(CO)_3$ (**99**) as a yellow oil, the ^2H n.m.r. spectrum of which revealed the absence of any deuterium in the *endo*-3 position. ^1H n.m.r. spectroscopy indicated that the product of the reaction comprised a mixture of complexes **93** and **99** that corresponded to approximately 82% deuterium incorporation. This ratio is consistent with a kinetic isotope effect of at least 1.8 for the preferential removal of the *exo*-3 proton over the *exo*-1 deuteron of complex **93**. Decomplexation of the product under standard condition furnished *cis*-1,3-dideuterio phthalan (**100**).



93 **99** **100**

i) *t*-BuLi, THF, -78°C, 1h. ii) CD_3OD, 92%. iii) Et_2O, air, sunlight.

Direct alkylation of phthalan (**82**) was also achieved but deprotonation proved to be considerably slower than for the corresponding $Cr(CO)_3$ complex **81**. A THF solution of phthalan (**82**) at -78°C was treated with *t*-butyllithium giving a slow colour change from colourless to deep red. Addition of methyl iodide after one hour and subsequent work-up gave a 55:45 mixture of the benzylically alkylated 1-methyl phthalan (**70**) and phthalan (**82**) with no observable ring methylation. That the benzylic methylation of (phthalan)$Cr(CO)_3$ (**81**) is complete under identical conditions clearly demonstrates the benzylic carbanion stabilising ability of the $Cr(CO)_3$ unit. Prolonging the deprotonation reaction time to six hours at -78°C and subsequent addition of methyl iodide gave complete methylation affording 1-methyl phthalan (**70**) in 64% isolated yield. Similarly, ethylation with ethyl iodide and benzylation employing benzyl bromide gave 1-ethyl- and 1-benzyl phthalan (**94** and **95**) repectively.

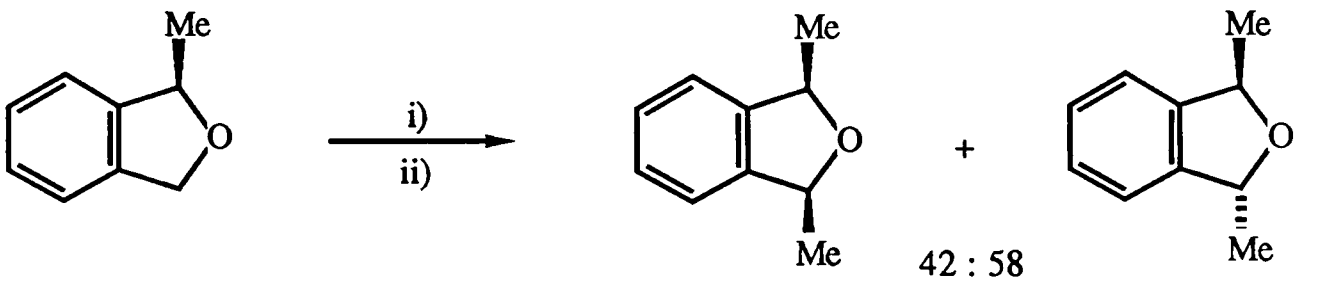


82

R =
70 Me (64%)
94 Et (76%)
95 $PhCH_2$ (57%)

i) *t*-BuLi, THF, -78°C, 6h. ii) RX.

Lithiation of 1-methyl phthalan (**70**) using *t*-butyllithium at -78°C over four hours and addition of methyl iodide gave a mixture of both *cis*- and *trans*-1,3-dimethyl phthalan (**97** and **101**) in the ratio 42:58, the thermodynamically more stable *trans* diastereoisomer predominating.[78]



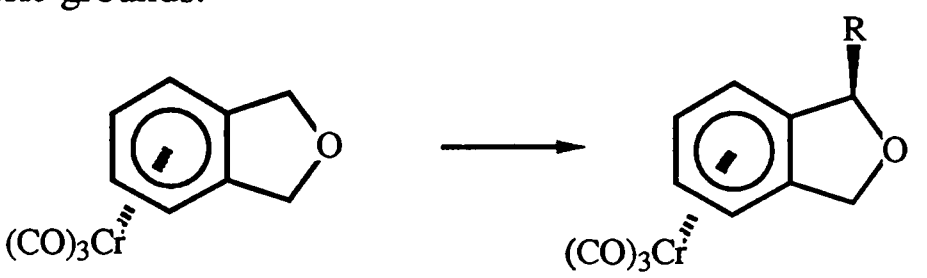
70 **97** **101**

i) *t*-BuLi, THF, -78°C, 4h. ii) MeI, 74%.

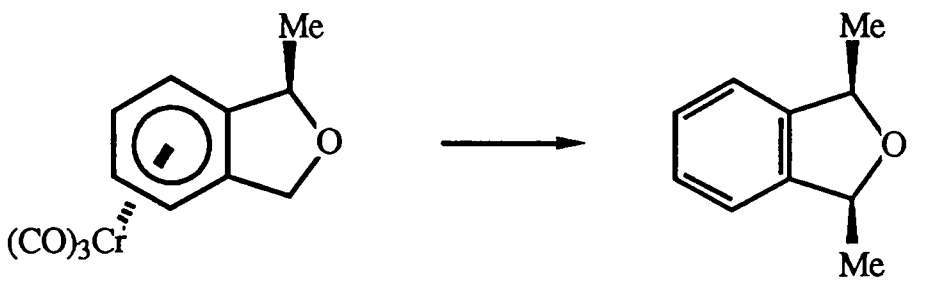
Summary

(Phthalan)$Cr(CO)_3$ (**81**) undergoes regio- and stereoselective *exo*-C1 alkylation upon sequential treatment with *t*-butyllithium and an electrophile. Subsequent decomplexation affords the corresponding 1-alkyl phthalans. Methylation of *exo*-(1-methyl phthalan)$Cr(CO)_3$

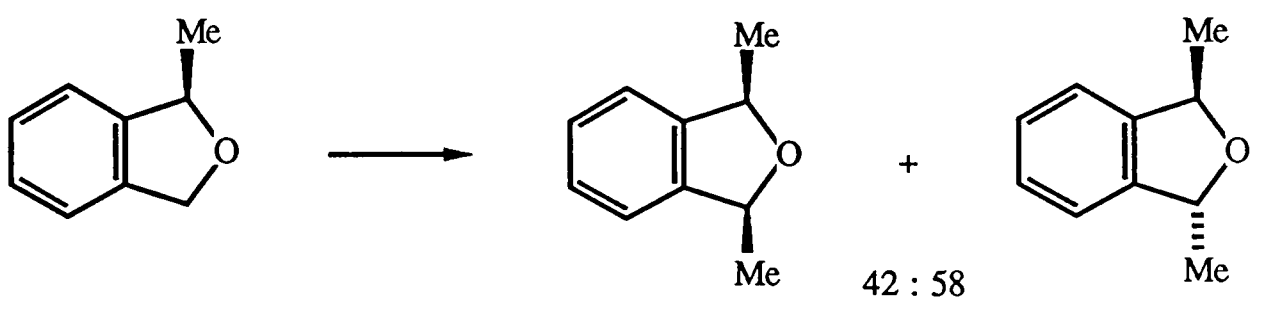
(**90**) with *t*-butyllithium and methyl iodide is completely stereoselective affording *cis*-1,3-dimethyl phthalan (**97**) after decomplexation. Analogous methylation of 1-methyl phthalan (**70**) affords a 58:42 mixture of *trans*- and *cis*-1,3-dimethyl phthalan (**101** and **97**), the former predominating on steric grounds.



81



90 **97**



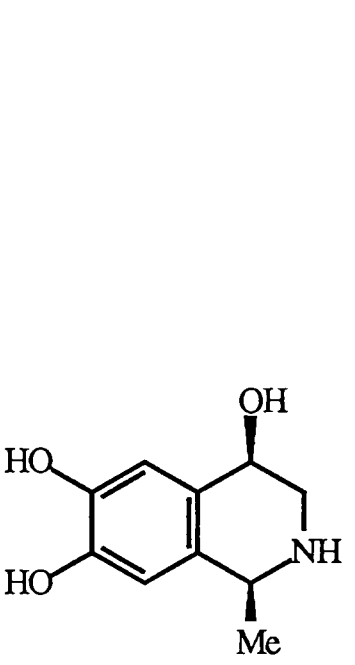
70 **97** **101**

CHAPTER 2

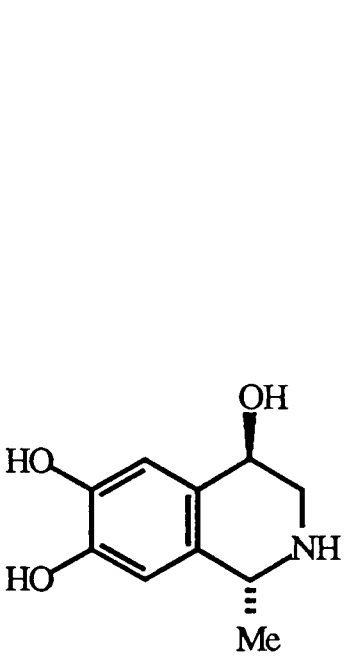
Synthesis of (+)-(1R,3S,4S)- and (-)-(1S,3S,4R)-1,2,3,4-tetramethyl tetrahydroisoquinoline

SYNTHESIS OF (+)-(1R,3S,4S)- AND (-)-(1S,3S,4R)-1,2,3,4-TETRAMETHYL TETRAHYDROISOQUINOLINE

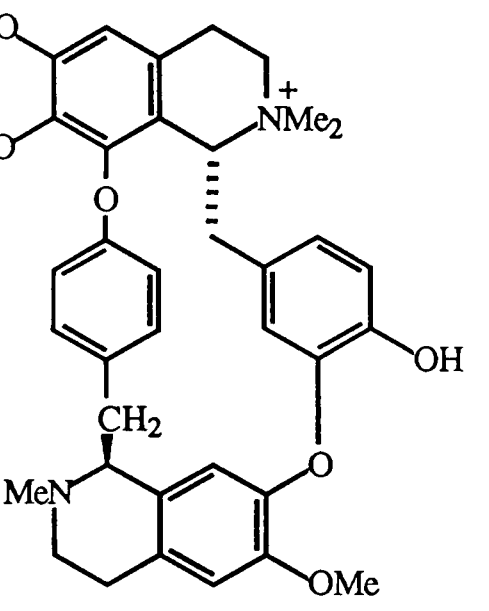
The diverse range of pharmacological effects and widespread natural occurrence of substituted tetrahydroisoquinolines has led to much interest in their synthesis.[83] For example, the diastereoisomeric amino alcohols **102** and **103** are readily derived upon condensation of noradrenaline with acetaldehyde (the primary metab olite of ethanol) and as a consequence are believed to be linked with the physiological effects associated with alcohol addiction.[84] By way of contrast, the naturally occurring curare alkaloid (+)-Tubocurarine (**104**) is the active constituent of the poison tip of blowpipe darts still used by South American Indians. The potent neuromuscular blocking activity of (+)-**104** has led to its widespread clinical use as a muscle relaxant, a dose of 20-30mg being sufficient to cause paralysis in man for upto thirty minutes.[85]



102

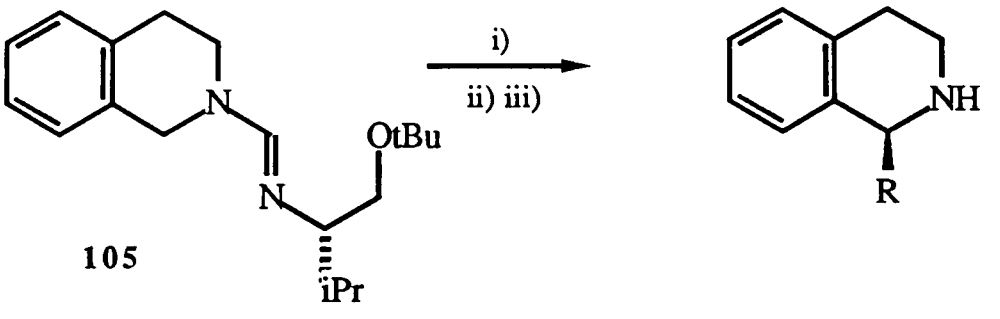


103



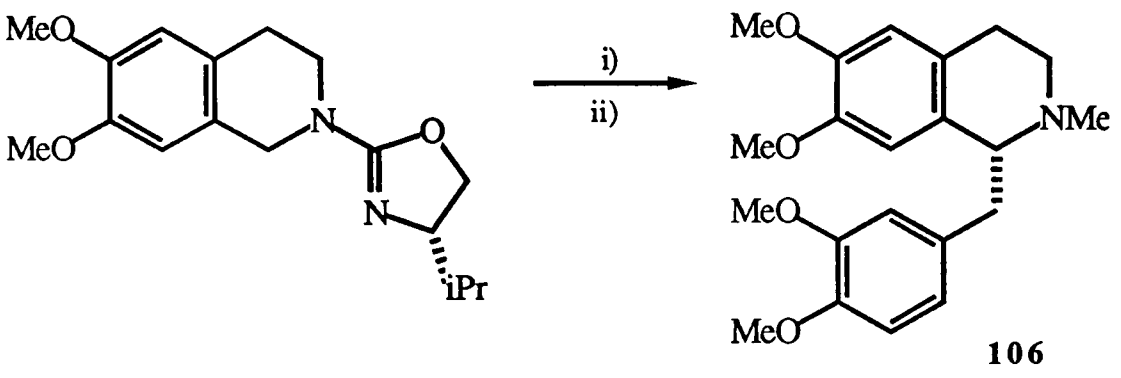
(+)-104

Of the many methods developed for the elaboration of the tetrahydroisoquinoline nucleus relatively few permit the creation of new asymmetric centres with a high degree of stereocontrol. Meyers has successfully employed a nitrogen-bound chiral auxiliary in the guise of formamidine **105** which enables the synthesis of 1-substituted tetrahydroisoquinolines of excellent optical purity,[86] whilst Gawley has used a similar approach in a recently reported synthesis of (R)-Laudanosine (**106**).[87] Yamato has shown that reaction of homochiral oxazolidine **107** with methyl magnesium iodide occurs with inversion of configuration to afford, upon hydrogenation, (-)-(S)-Salsolidine (**108**), identical in all respects to the naturally occurring alkaloid.[88]



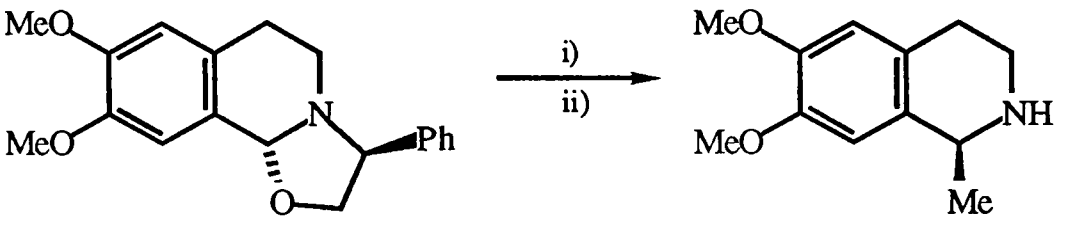
105

i) *t*-BuLi, THF, -100°C. ii) RX. iii) N_2H_4.



106

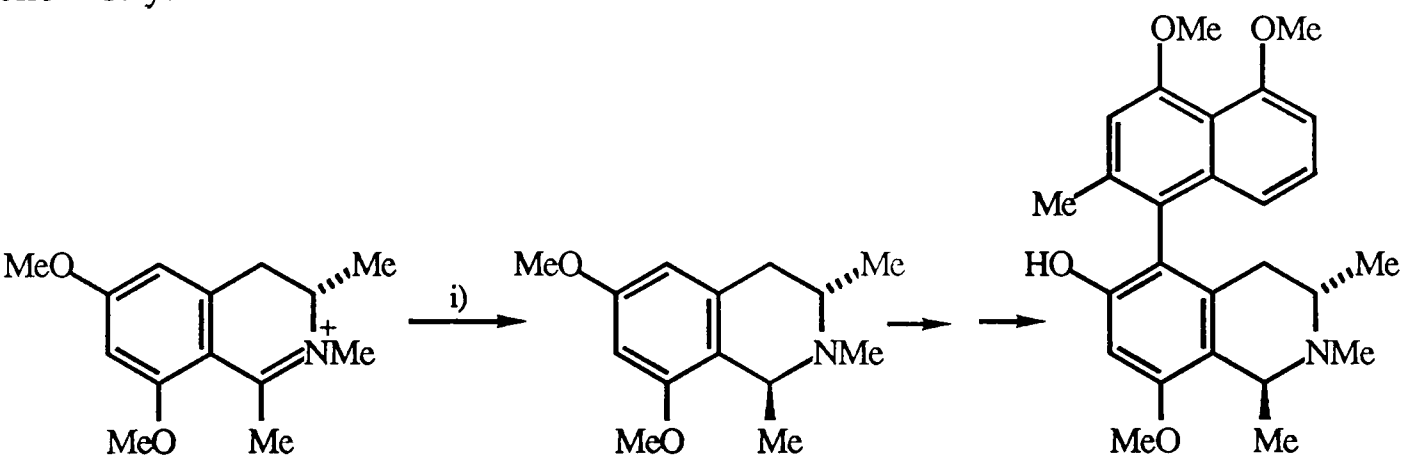
i) *t*-BuLi, THF, -100°C, 3,4-$(MeO)_2C_6H_3CH_2Br$, 87%.
ii) Acetic formic anhydride, $LiAlH_4$, 80%.



107 **108**

i) MeMgI, THF, Et_2O, -78°C, 1h. ii) H_2, Pd/C, EtOH, 2 steps 92%.

The two methyl groups of (-)-Ancistrocladine (**109**) bear a *trans* orientation, a structural feature common to the Ancistrocladus alkaloids.[89] The first total synthesis of (-)-**109** was reported in 1986 by Bringmann who employed a diastereoselective reduction of 3,4-dihydroisoquinoline **110** as the key synthetic step for the incorporation of the required relative stereochemistry.[90]



110 (-)-**109**

i) $LiAlH_4$, $AlMe_3$, THF, -78-0°C, 3h, 85%.

The ability of the $Cr(CO)_3$ moiety to stabilise benzylic carbanions and to permit a high degree of stereocontrol in the construction of asymmetric benzylic centres is well documented.[17] We have previously shown that a diastereoisomeric mixture of *exo*- and *endo*-tetrahydroisoquinoline complexes **111** and **112** undergoes stereo- and regioselective *exo*-C4 methylation upon treatment with *n*-butyllithium and methyl iodide to give complexes **113** and **114**, the complete stereocontrol arising as a consequence of the steric blocking effect of the

$Cr(CO)_3$ unit upon the coordinated face. Subsequent stereoselective *exo* C1 methylation of complexes **113** and **114** is achieved upon treatment with *t*-butyllithium and methyl iodide to yield tetramethyl complexes **115** and **116**. From this mixture it has proved possible to isolate the all *cis*, all *exo* complex **115** for which a single crystal X-ray structure determination unambiguously proved both its relative and its absolute stereochemistry (Figure 2).[58] It was of interest to optimise this sequence of reactions and to characterise the separate diastereoisomers of decomplexed tetrahydroisoquinolines **117** and **118**.

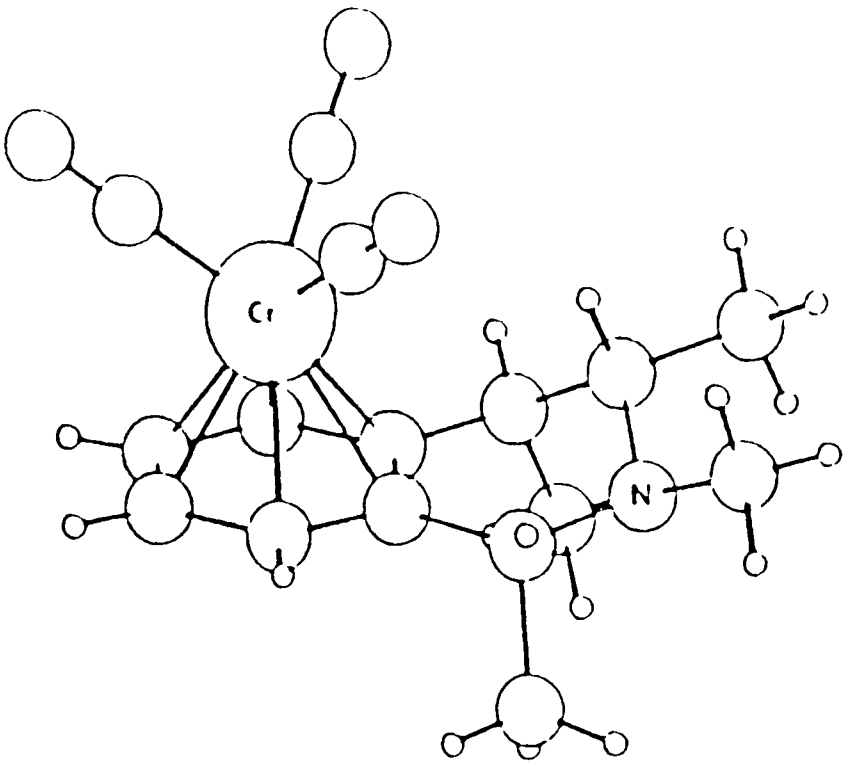
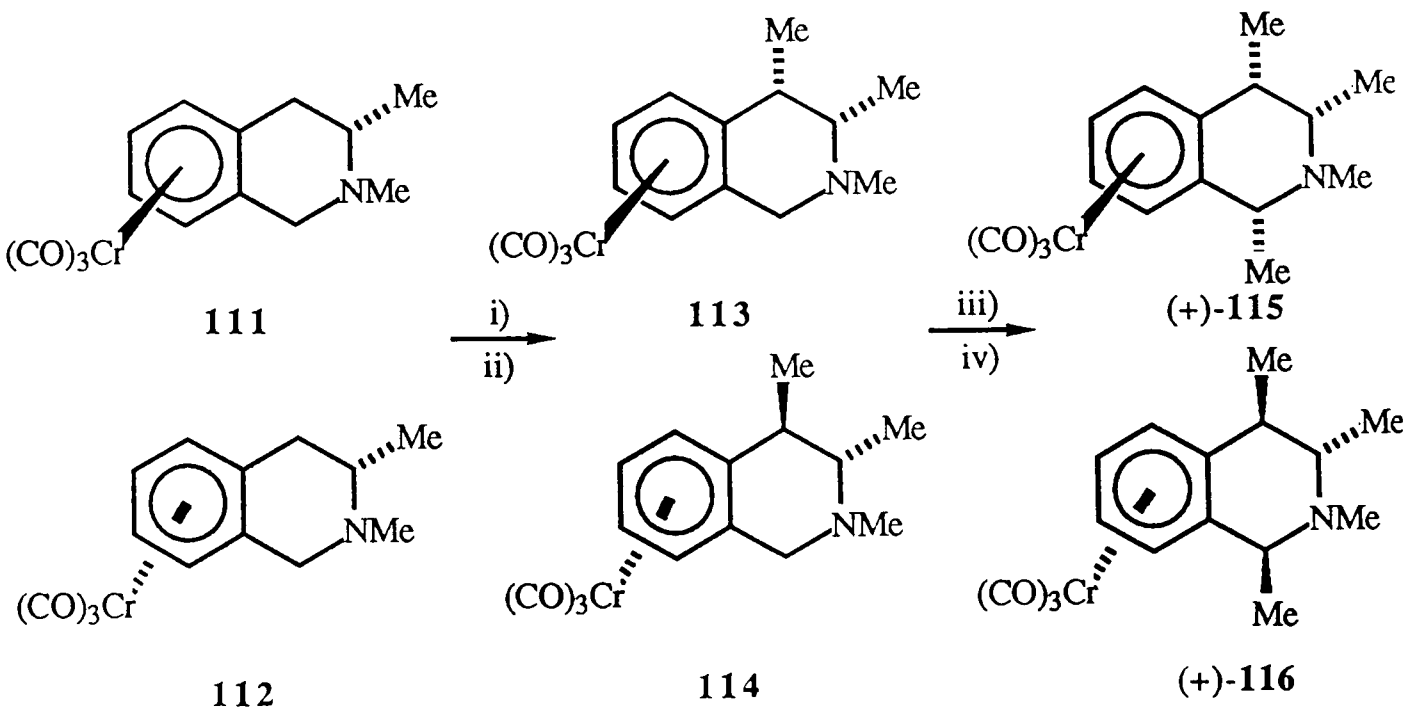
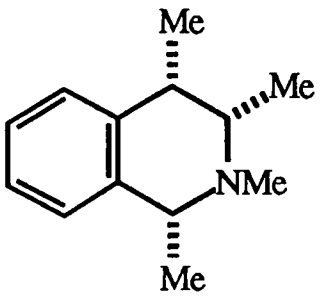


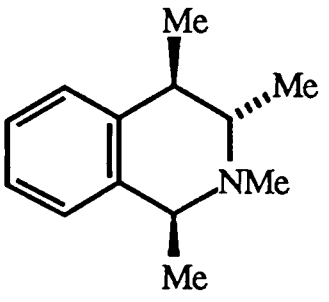
Figure 2: X-ray crystal structure of complex (+)-**115**.



i) *n*-BuLi, THF, -78°C, 2h. ii) MeI. iii) *t*-BuLi, THF, -78°C, 2h. iv) MeI.



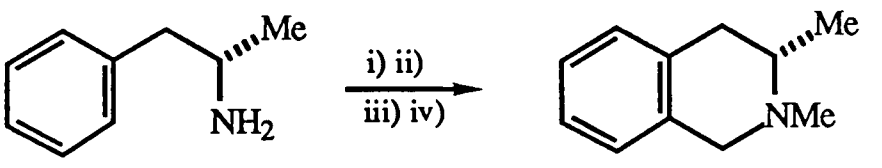
117



118

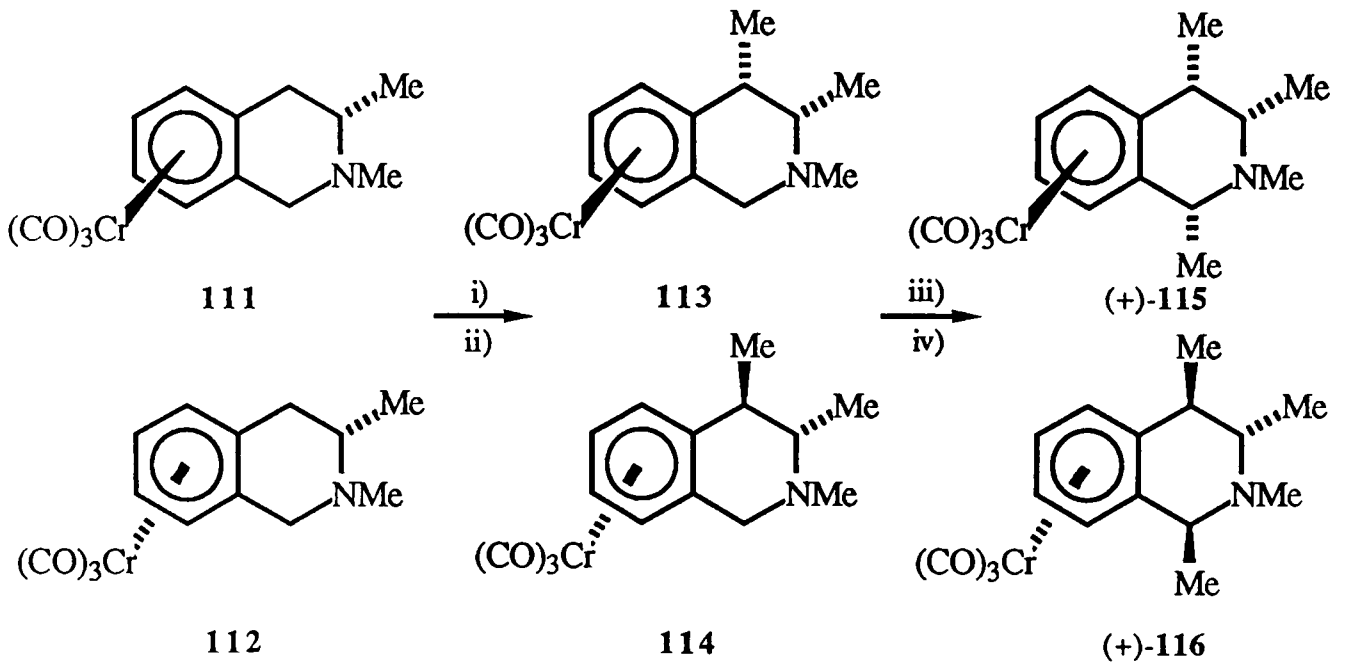
Results and discussion

(+)-(S)-2,3-Dimethyl tetrahydroisoquinoline (**119**) was synthesised from (+)-(S)-amphetamine (**120**) according to the literature procedure.[91] Thermolysis of chromium hexacarbonyl with **119** for twenty three hours gave a yellow solid after column chromatography in an improved 87% isolated yield. ^{1}H n.m.r. analysis of the product revealed a mixture of *exo* and *endo* complexes **111** and **112** in the ratio 60:40 which could only be partially separated by flash chromatography. A solution of the diastereoisomeric mixture (ratio 60:40) in tetrahydrofuran was cooled to -78°C and treated with *n*-butyllithium giving a deep red colouration indicative of benzylic carbanion formation. The colour was discharged upon treatment with methyl iodide to afford a mixture of *exo*-C4-methylated complexes **113** and **114** in the ratio 60:40. Sequential treatment of this mixture with *t*-butyllithium and methyl iodide gave stereoselective *exo*-C1-methylation generating a 60:40 mixture of the tetramethyl diastereoisomers **115** and **116**. Both complexation and benzylic methylation steps gave improved yields over those previously reported by careful monitoring of the complexation reaction and rigorous drying of the methyl iodide used to trap the benzylic carbanions. Both methylations occurred as previously reported, consistent with the steric bulk of the $Cr(CO)_3$ fragment restricting approach of both the base and the electrophile to the unhindered, uncomplexed face. The preponderance of *exo* complex **111** in the complexation of (+)-(S)-**119** may be rationalised in terms of preferential coordination to its least hindered face.[35,92]



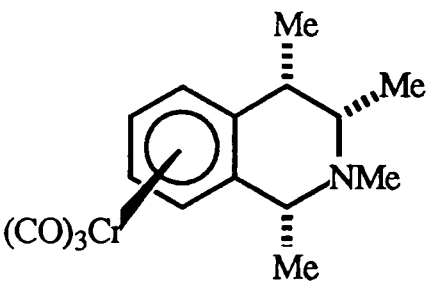
(+)-(S)-**120** (+)-(S)-**119**

i) HCOOH. ii) H_3PO_4, P_2O_5, 200°C, 3h.
iii) MeI, Me_2CO. iv) $NaBH_4$, EtOH, 4 steps 50%.

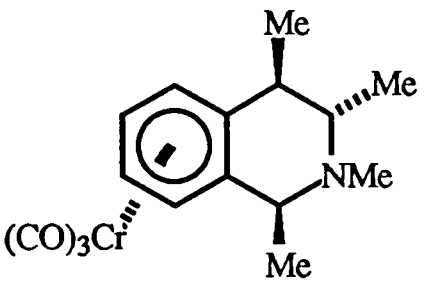


i) *n*-BuLi, THF, -78°C, 2h. ii) MeI, 87%. iii) *t*-BuLi, THF, -78°C, 2h. iv) MeI, 88%.

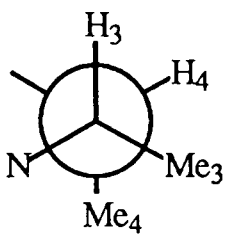
Flash chromatography of the 60:40 mixture of complexes **115** and **116** enabled their separation. The less polar, major component proved to be identical in all respects to complex (+)-**115** previously reported for which an X-ray crystal structure has been obtained (Figure 2).[58] The minor component (+)-**116** exhibited the same coupling patterns in its ^{1}H n.m.r. spectrum as those for complex (+)-**115** but at different chemical shifts. Crystallisation gave an analytically pure sample of (+)-**116** which was fully characterised. Separate nOe difference experiments performed upon deuteriobenzene solutions of each of the diastereoisomers **115** and **116** at 500MHz were consistent with the assigned stereochemistry for both complexes. Thus, irradiation of the C4-methyl resonance of complex (+)-**116** gave enhancements to both H3 (20%) and H4 (20%) as did C3-methyl irradiation [H3 (15%) and H4 (15%)]. For the major product (+)-**115**, irradiation of the C4-methyl resonance gave only enhancement to the H4-proton (15%) whilst separate irradiation of the C3-methyl resonance gave enhancements to both H4 (9%) and H3 (13%). These results are summarised in Table 2 along with the expected proton responses derived by consideration of their proximity to the methyl group under irradiation assuming half-chair geometries for both complexes (conformations **A-D**).



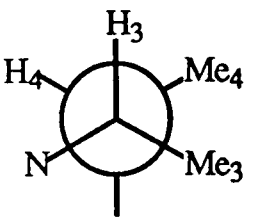
(+)-**115**



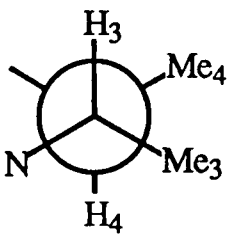
(+)-**116**



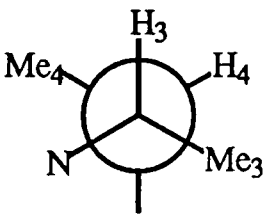
A



B



C

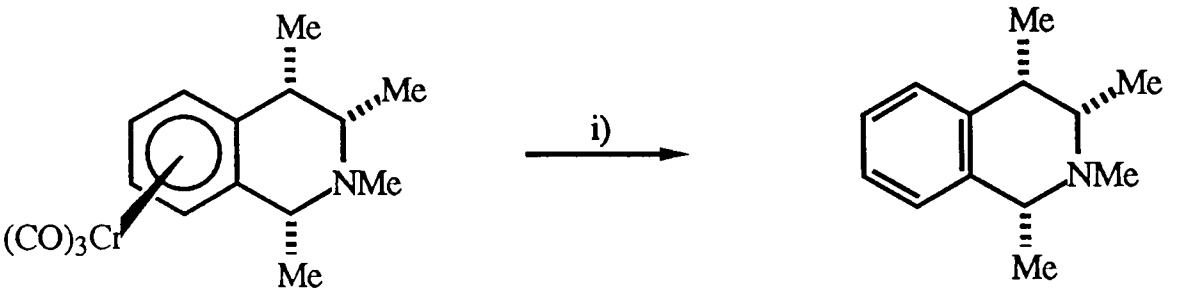


D

Irradiated methyl doublet	Expected proton response A		B		C		D		Found (%) (+)-115		(+)-116	
	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4
4-Me	X	✓	✓	✓	✓	✓	✓	✓	0	15	20	20
3-Me	✓	✓	✓	X	✓	✓	✓	✓	13	9	15	15

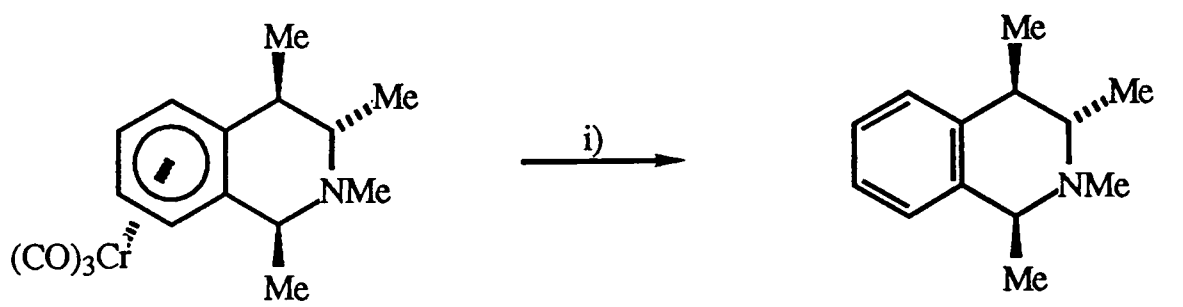
Table 2: Expected and observed nOe responses of complexes (+)-**115** and (+)-**116**.

A diethylether solution of complex **115** was decomplexed according to the standard procedure to afford (+)-(1R,3S,4S)-1,2,3,4-tetramethyl tetrahydroisoquinoline (**117**) {$[\alpha]_D^{20}$ +99.4 (*c* 0.51 $CHCl_3$)} as a colourless oil that was fully characterised. Similar decomplexation of (+)-**116** liberated (-)-(1S,3S,4R)-1,2,3,4-tetramethyl tetrahydroisoquinoline (**118**) as a colourless oil {$[\alpha]_D^{20}$ -9.2 (*c* 0.26 $CHCl_3$)}.



(+)-**115** (+)-**117**

i) Air, sunlight, 96 %.

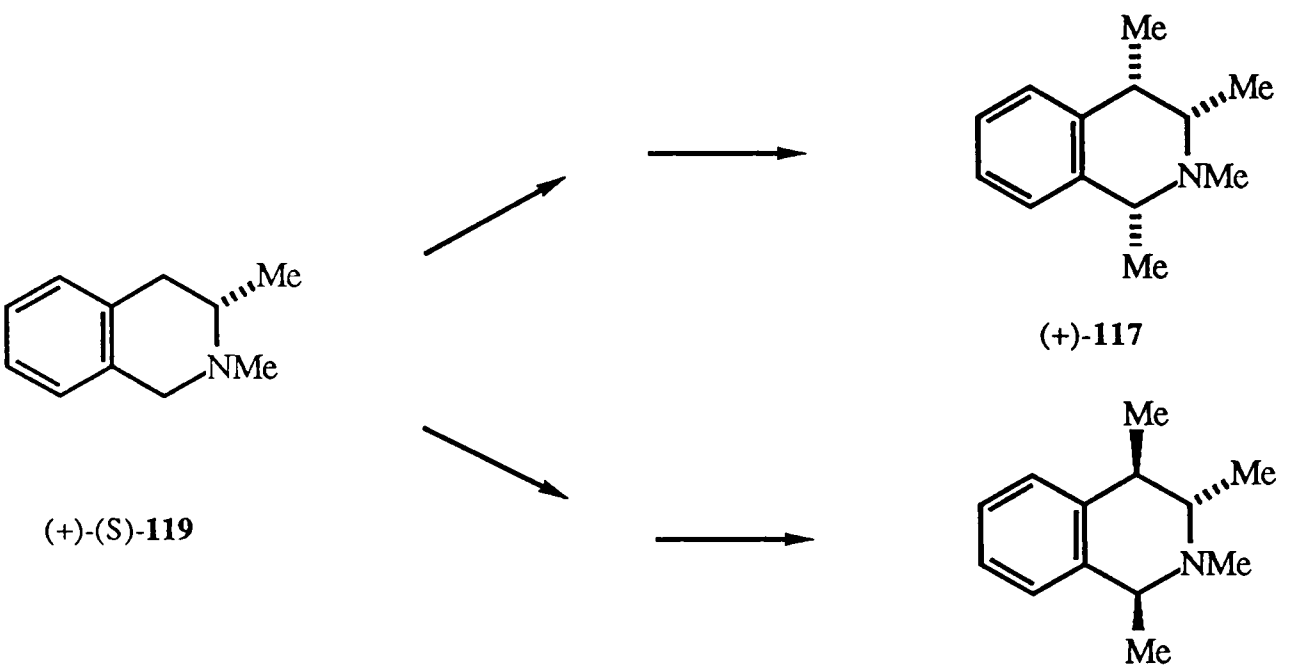


(+)-**116** (-)-**118**

i) Air, sunlight, 87%.

Summary

Coordination of (+)-(S)-2,3-dimethyl tetrahydroisoquinoline (**119**) to the $Cr(CO)_3$ unit occurs preferentially to the less hindered face giving a mixture of *exo* and *endo* complexes **111** and **112** (ratio 60:40). Sequential treatment of this mixture with *n*-butyllithium and methyl iodide stereoselectively generates a 60:40 mixture of the corresponding *exo*-C4-methylated complexes **113** and **114**. Subsequent deprotonation with *t*-butyllithium and trapping with methyl iodide furnishes a 60:40 mixture of the corresponding tetramethyl complexes (+)-**115** and (+)-**116** which were separated by flash chromatography. Oxidative decomplexation of (+)-**115** liberated (+)-(1R,3S,4S)-tetramethyl tetrahydroisoquinoline (**117**) whilst similar decomplexation of (+)-**116** gave the diastereoisomeric (-)-(1S,3S,4R)-tetramethyl tetrahydroisoquinoline (**118**).



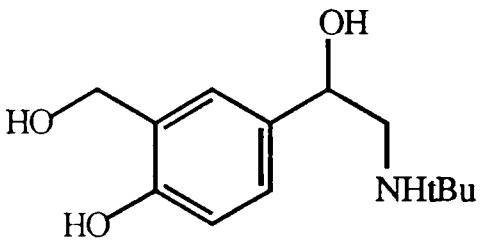
CHAPTER 3

Elaboration of ephedrine and pseudoephedrine

ELABORATION OF EPHEDRINE AND PSEUDOEPHEDRINE

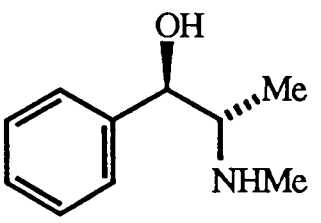
Introduction

The synthesis of substituted β-amino alcohols has proved to be of considerable interest owing to both their pharmacological profiles and their potential use in asymmetric synthesis. A large number of substituted phenethanolamines have been synthesised in the search for selective α and β receptor agonists, their specificity relying upon the exact nature of the substitution pattern.[93] The bronchiodilator Salbutamol (**121**) is currently the world's twelfth best selling prescription medicine and exhibits selective β_2 agonist activity useful in the treatment of bronchial asthma.[94]

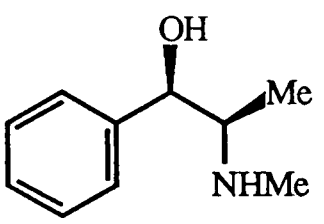


121

The alkaloids ephedrine (**122**) and ps-.eudoephedrine (**123**) are commercially available as either optical antipode and their derivatives have found extensive use in the field of asymmetric synthesis.[95] Their ability to serve as catalysts in the asymmetric addition of nucleophiles to aldehydes and αβ-unsaturated ketones has been documented with good enantiomeric excesses being obtained in certain cases.[96]

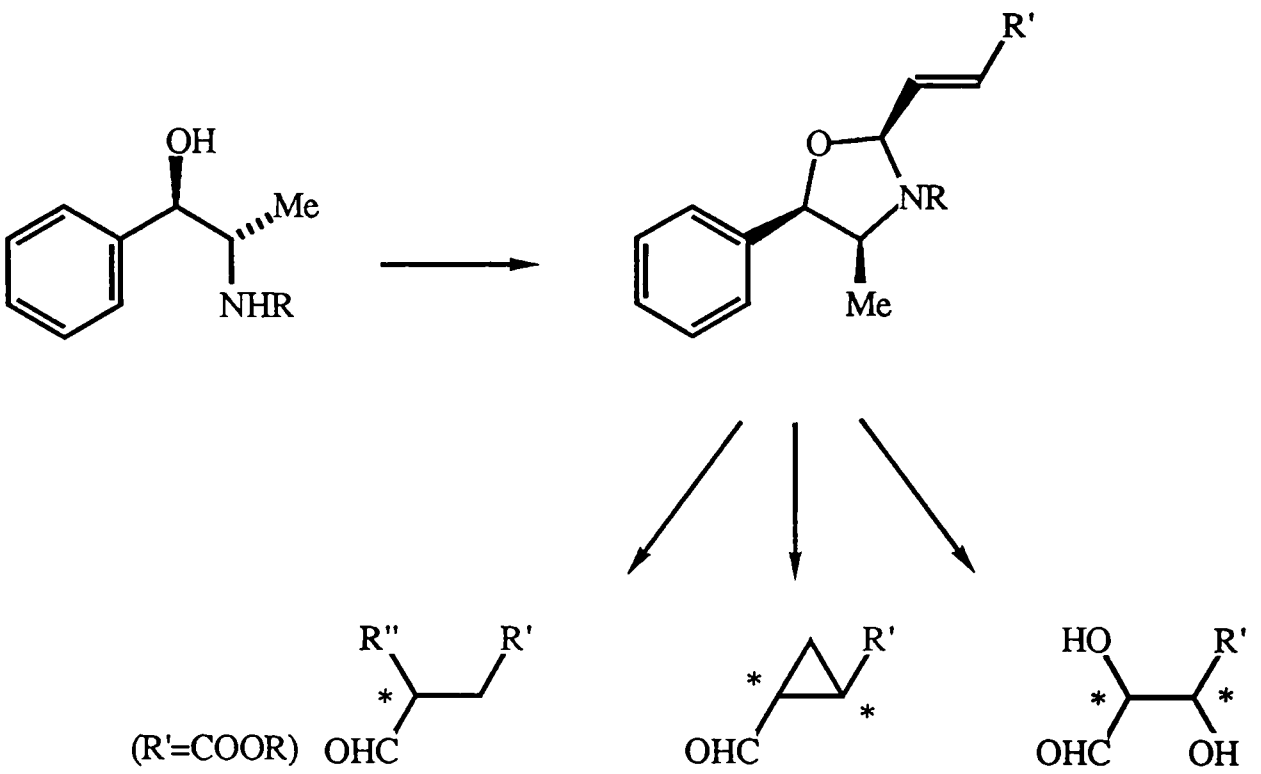


(-)-(1R,2S)-**122**



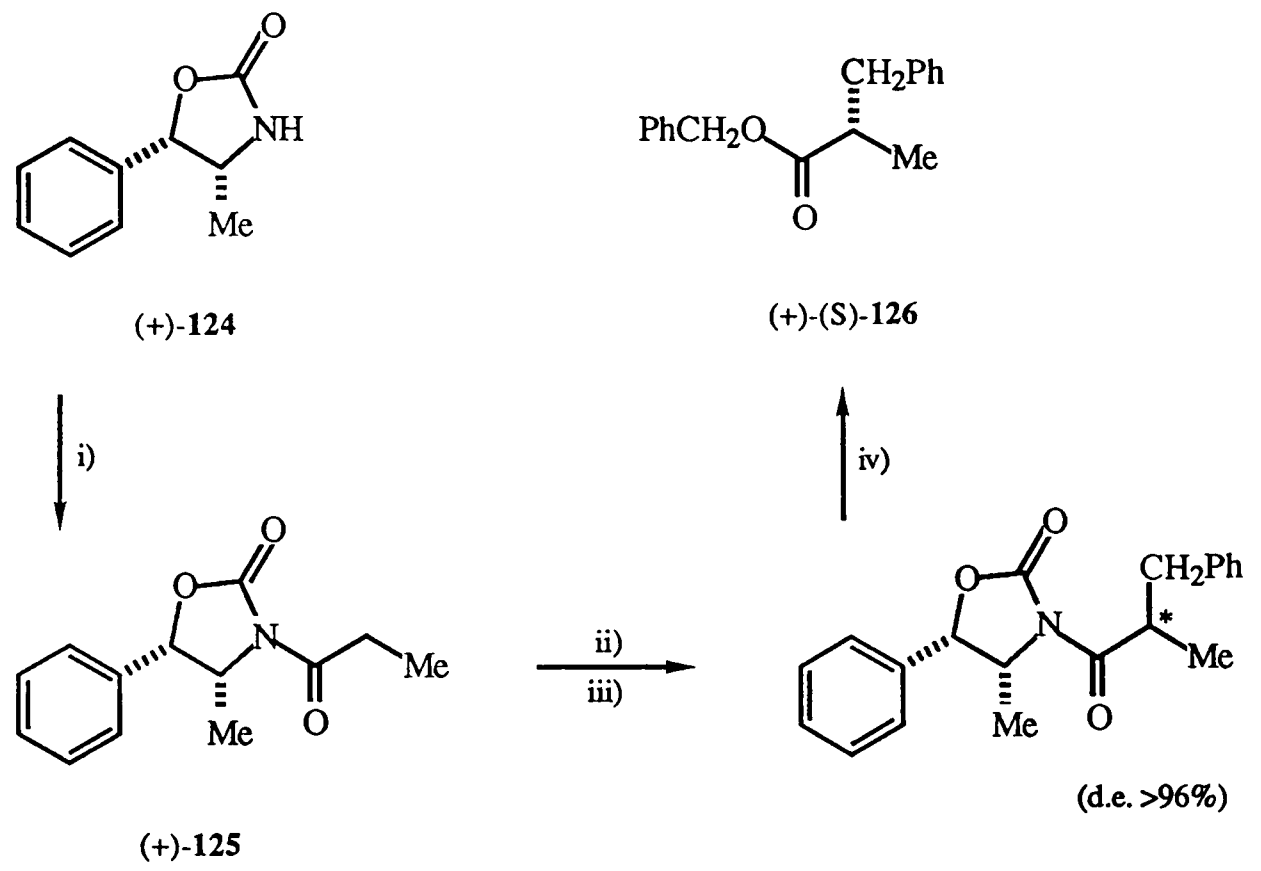
(-)-(1R,2R)-**123**

Oxazolidines derived from phenethanolamines have also proved to be powerful tools in asymmetric synthesis, serving as chiral auxiliaries. Condensation of appropriately substituted aldehydes with derivatives of ephedrine (**122**) give diastereoisomerically pure oxazolidines, after crystallisation, which may be further elaborated; the new chiral centres being formed with a high degree of stereocontrol. Subsequent hydrolysis readily liberates the enantiomerically enriched aldehyde and returns the homochiral amino alcohol as outlined in Scheme 4.[97]



Scheme 4 : Asymmetric synthesis employing ephedrine-derived oxazolidines.

Evans has developed an alternative strategy employing phenethanolamine-derived oxazolidines that have been widely used for the highly stereoselective formation of carbon-carbon bonds in aldol-type condensation reactions. For example, acylation of oxazolidine (+)-**124** generates (+)-**125** which is readily alkylated upon treatment with a chelating base and an electrophile with a high degree of stereocontrol. Subsequent treatment with the lithium salt of benzyl alcohol regenerates the chiral auxiliary (+)-**124** and liberates the enantiomerically enriched benzyl ester (+)-(S)-**126**.[98]

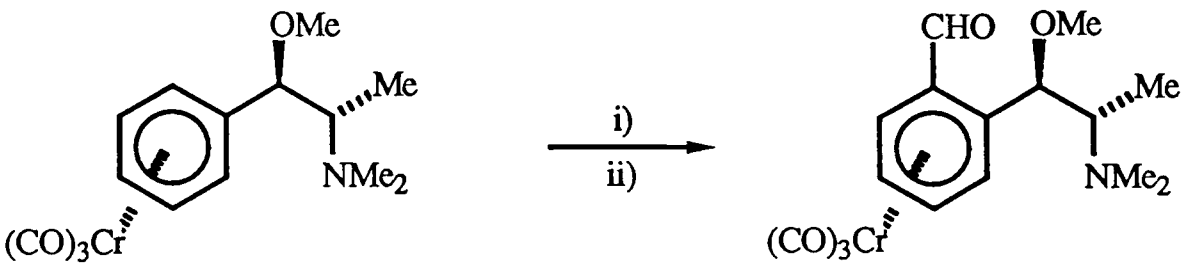


i) *n*-BuLi, THF, EtCOCl, -78°C, 80%. ii) LDA, -78°C, THF.
iii) $PhCH_2Br$, 78%. iv) $PhCH_2OLi$, $PhCH_2OH$, THF, 0°C, 1h, 93%.

It was of interest to try and develop new synthetic strategies for the fuctionalisation of both (-)-ephedrine (**122**) and (-)-pseudoephedrine (**123**) by exploiting the modified chemistry of these compounds when coordinated to the $Cr(CO)_3$ moiety.

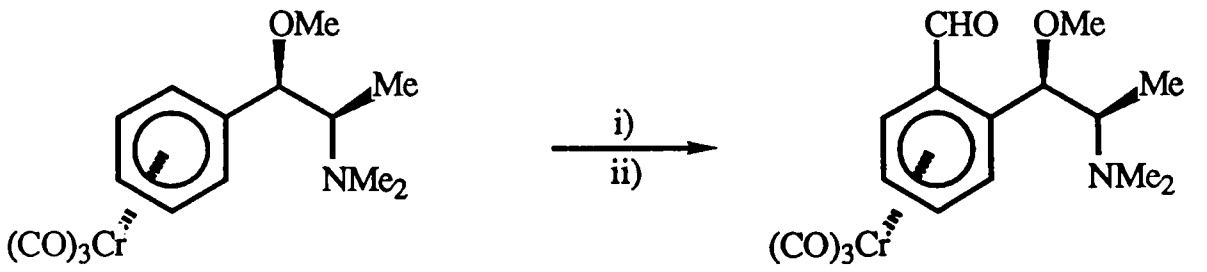
Results and discussion

(-)-[(N-Methyl-O-methyl)ephedrine]$Cr(CO)_3$ (**127**) was obtained as a highly crystalline yellow solid from (-)-(1R,2S)-ephedrine (**122**) according to the literature procedure.[99] In a similar fashion the diastereoisomeric complex (-)-**128** was prepared from (-)-(1R,2R)-pseudoephedrine (**123**). A solution of complex (-)-**127** was cooled to -78°C and treated with *t*-butyllithium producing a slight darkening in colour. Addition of ethyl formate and subsequent workup gave a red solid, the ^1H n.m.r. spectrum of which revealed some starting material along with one other set of peaks that included a one proton singlet at δ10.11 indicative of the proton of a formyl group. Chromatography and crystallisation enabled their separation affording (+)-**129** as a single diastereoisomer, an infrared stretch of 1675cm^{-1}, a molecular ion *m/z*=358 (M^++1) and an elemental analysis confirming its identity. In a similar fashion, formylation of (-)-**128** proved to be completely stereoselective affording (+)-**130** after recovery of the unreacted starting material. In both cases, use of *n*-butyllithium as the base or dimethylformamide as the electrophile offered no difference in the observed stereoselectivity of the two reactions.



(-)-**127** (+)-**129**

i) *t*-BuLi, THF, -78°C, 2h. ii) HCOOEt, 96%.

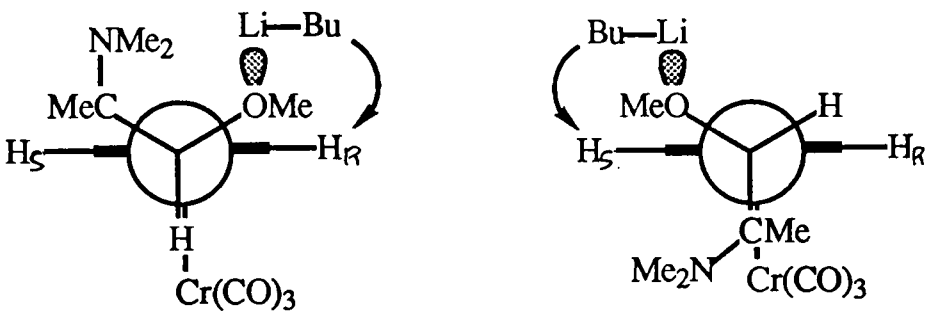


(-)-**128** (+)-**130**

i) *t*-BuLi, THF, -78°C, 2h. ii) HCOOEt, 84%.

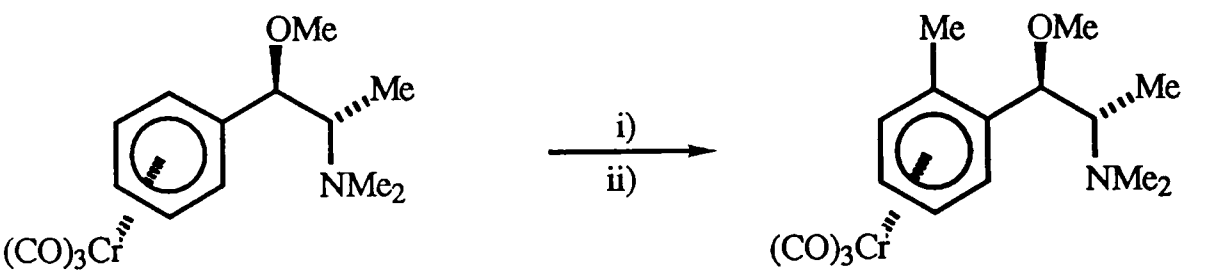
The diastereoselective functionalisation of both (-)-**127** and (-)-**128** may be rationalised by consideration of the chelate directing effect of the benzylic methoxyl substituent. In both

cases, coordination of the alkyllithium base to the nitrogen lone pair may be followed by abstraction of either of the diastereotopic *ortho* protons. The transition state that removes the *pro*-R-*ortho* proton, as observed, places the benzylic proton *syn* to the bulky $Cr(CO)_3$ unit and may be expected to be of a lower energy than that which leads to removal of the *pro*-S-*ortho* proton [which would necessitate the bulky methylamino group being placed proximal to the $Cr(CO)_3$ moiety]. Since both complexes (-)-**127** and (-)-**128** bear the same absolute stereochemistry at their benzylic centres, the *pro*-R-*ortho* proton is the one removed in both cases. Subsequent addition of ethyl formate or dimethylformamide quenches the ring anion to afford, upon workup, the observed formylated complexes as single diastereoisomers.



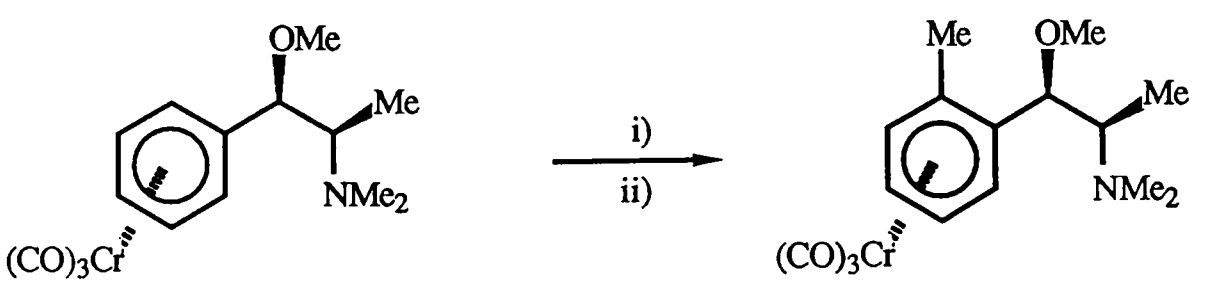
Favoured Disfavoured

The observed diastereoselectivity is consistent with that previously reported for the methylation of (-)-**127** and (-)-**128** which generates complexes (-)-**131** and (-)-**132** as single diastereoisomers respectively upon sequential treatment with base and methyl iodide. Single crystal X-ray structure determinations of both (-)-**131** and (-)-**132** have unambiguously proved that it is the *pro*-R-*ortho* proton that is substituted for the methyl group in both cases (Figure 3).[99,100]



(-)-**127** (-)-**131**

i) *n*-BuLi, THF, -78°C, 2h. ii) MeI, 70%.



(-)-**128** (-)-**132**

i) *t*-BuLi, THF, -78°C, 2h. ii) MeI, 76%.

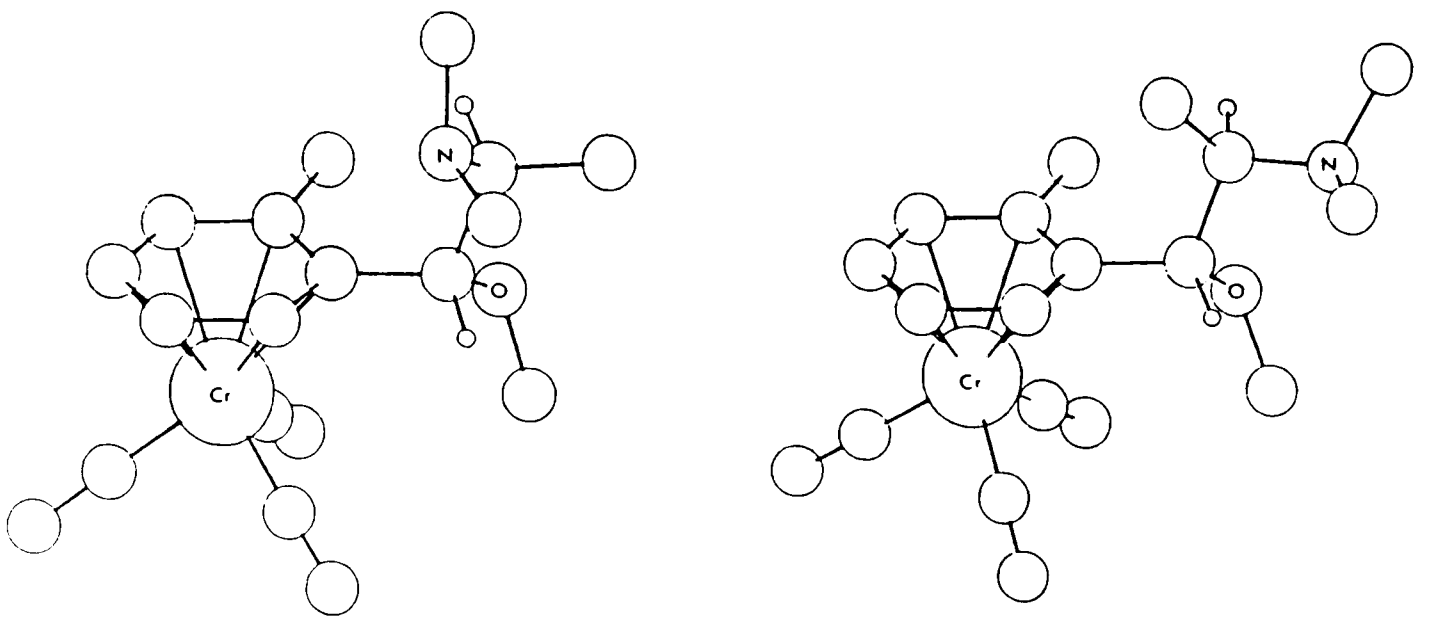
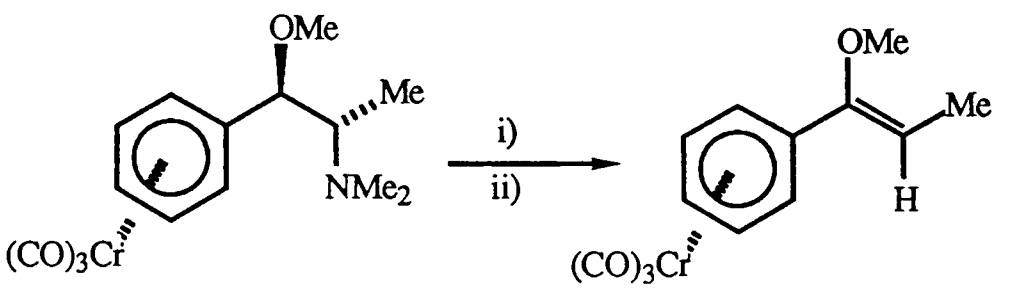


Figure 3 : X-Ray crystal structures of complexes (-)-**131** and (-)-**132**.

Attempts at trapping the ring anion derived from (-)-**127** with ethylene oxide gave only recovery of starting material. Addition of boron trifluoride etherate to the reaction mixture to try to enhance the electrophilicity of the epoxide led to the isolation, after chromatography, of a red oil which was crystallised from pentane at low temperature. The ^{1}H n.m.r. spectrum of the product exhibited a highfield three proton doublet, a three proton singlet at δ3.75 and a six proton multiplet at δ5-6 consistent with the enol ether complex **133**. NOe difference spectroscopic analysis indicated that the probable geometry about the double bond was Z since irradiation of the methoxyl singlet gave enhancements to both the methyl doublet and aromatic protons, whilst separate irradiation of the methyl doublet resonance enhanced only the methoxyl singlet (3.7%) with no apparent enhancement of any aromatic protons. A molecular ion *m/z*=284 and a high resolution mass spectrum confirmed the assignment of complex **133**. The formation of **133** may result from a *syn* elimination of the amine function promoted by coordination of the Lewis acid to the nitrogen lone pair.

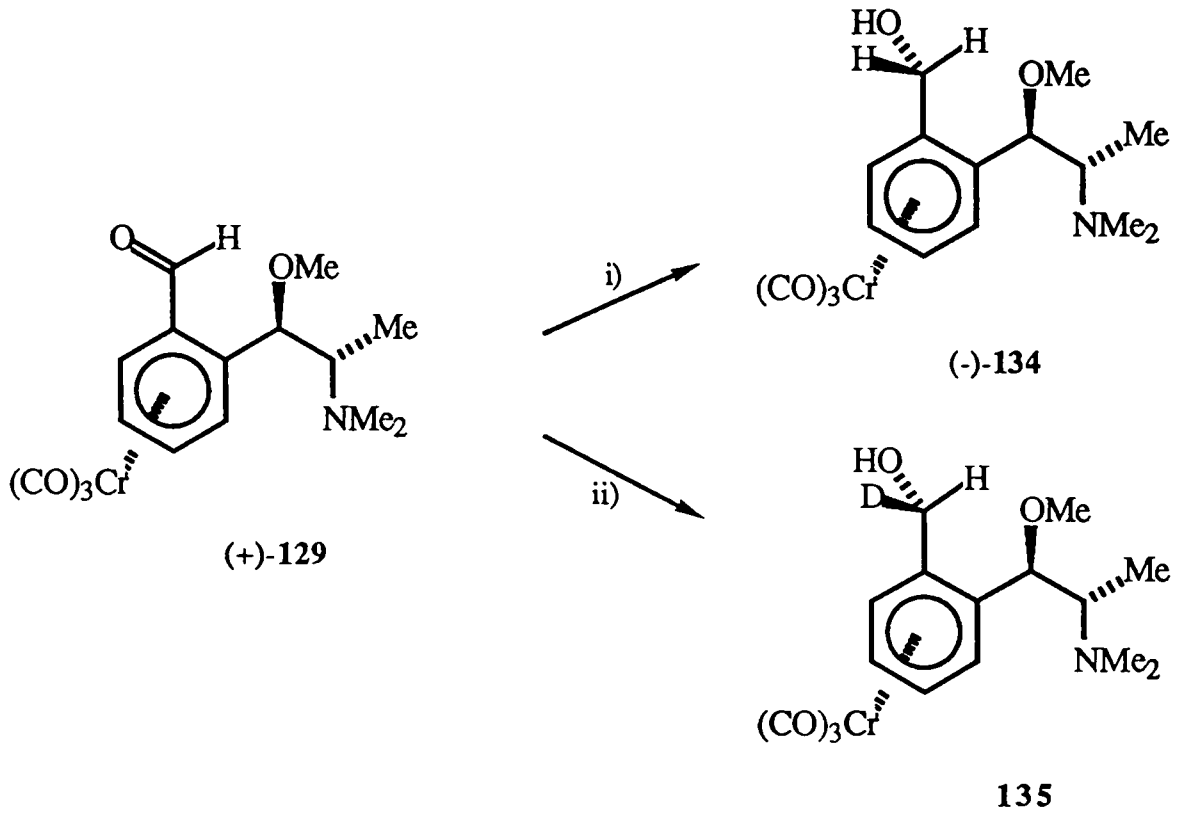


(-)-**127** **133**

i) *t*-BuLi, THF, -78°C, 2h. ii) Ethylene oxide, $BF_3.OMe_2$.

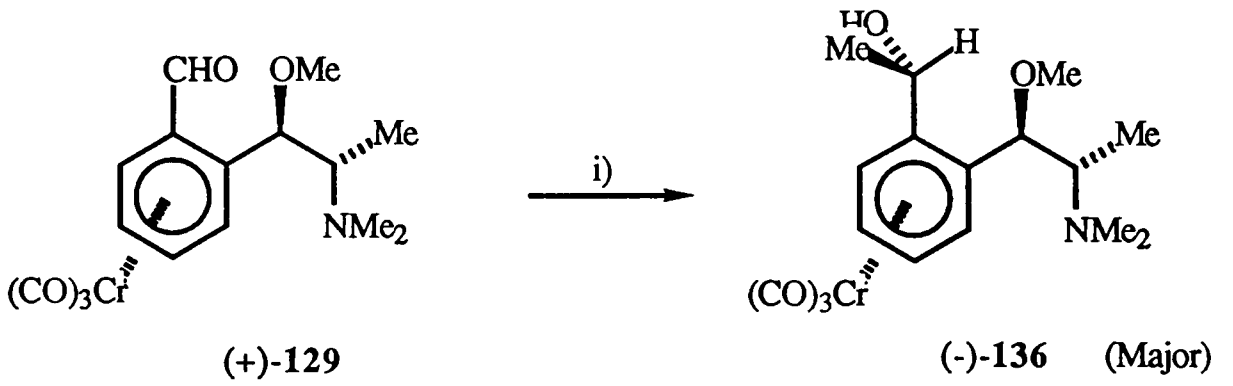
A solution of complex (+)-**129** was treated with sodium borohydride to afford the corresponding alcohol complex (-)-**134** as a yellow solid. The structure of the product followed from comparison of its ^{1}H n.m.r. spectrum with that of (+)-**129** which exhibited a new AB system and the disappearance of the lowfield formyl proton resonance. A molecular

ion *m/z*=360 (M^++1) and an elemental analysis confimed the identity of this new compound. In a similar manner sodium borodeuteride reduction of (+)-**129** gave complex **135** that showed good deuterium incorporation according to its mass spectrum in comparison to that of complex (-)-**134**. Owing to the similarity in the ^1H n.m.r. spectra of (-)-**134** and **135** the diastereoselectivity of this reduction was not assessed.



i) $NaBH_4$, THF, 20°C, 3h, 66%. ii) $NaBD_4$, THF, 20°C, 3h, 64%.

To investigate the stereoselectivity of these addition reactions a tetrahydrofuran solution of complex (+)-**129** at -78°C was treated with excess methyllithium giving an immediate red to yellow colour change indicative of addition to the aldehyde. ^1H n.m.r. analysis of the crude product revealed the presence of two sets of peaks in the approximate ratio 86:14, each of which included two methyl doublets. Two recrystallisations from diethylether/hexane yielded the major component as a single diastereoisomer identified as the addition complex (-)-**136** after full characterisation. A single crystal X-ray structure determination of this material unambiguously proved the relative stereochemistry of complex (-)-**136** (Figure 4). Furthermore, a Flack enantiopole refinement indicated that the absolute stereochemistry of (-)-**136** was that shown, consistent with the known absolute stereochemistry of the starting material.



i) MeLi or MeMgI, THF, -78°C, 2-6h.

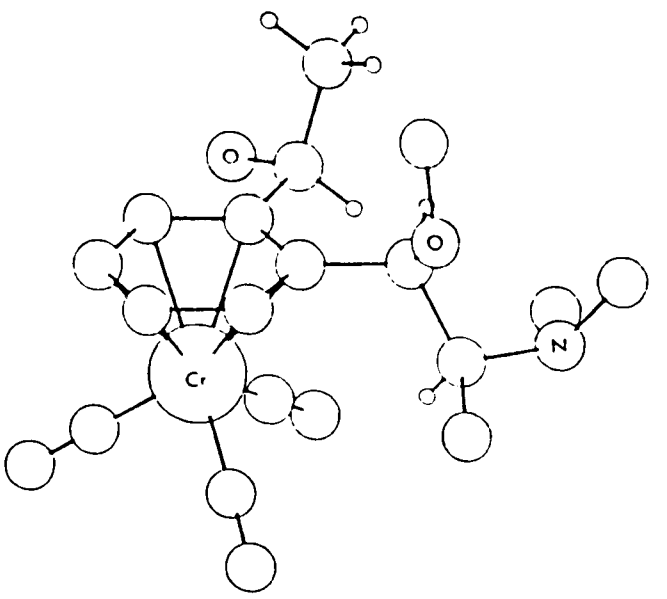
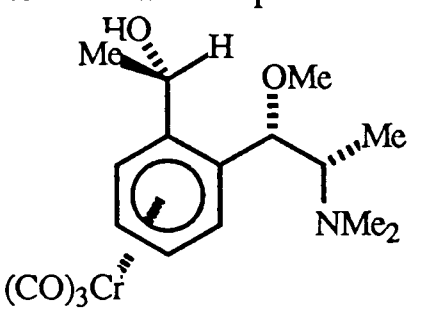
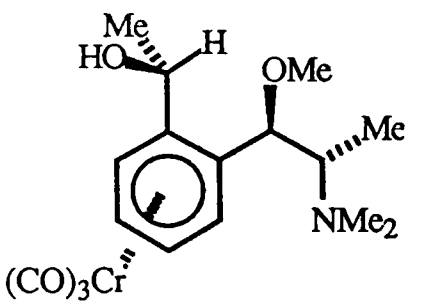


Figure 4 : X-Ray crystal structure of complex (-)-**136.**

Although the structure of the minor product was not determined, it is likely to be that of either complex **137** or **138**, the former resulting from epimerisation of the benzylic methoxyl substituent derived upon removal of the acidic benzylic proton of (+)-**129** and subsequent reprotonation from the opposite face followed by nucleophilic addition to the aldehyde. The presence of the formyl group in complex (+)-**129** enhances the acidity of the benzylic proton since it is equivalent to a vinylogous aldehyde, a feature that has been previously reported for similar *ortho*-substituted benzaldehyde complexes.[101] The formation of complex (-)-**136** as the major product is consistent with the formyl group of complex (+)-**129** adopting a conformation coplanar with the aromatic ring with the carbonyl oxygen being placed *anti* to the bulky *ortho* substituent on steric and, possibly dipole grounds. Addition of methyllithium may only occur from the unhindered *exo* face generating the new chiral centre with good stereocontrol. That chelation control was not operating was concluded as a result of an identical reaction performed in the presence of the chelating base TMEDA which did not significantly alter the ratio of products.



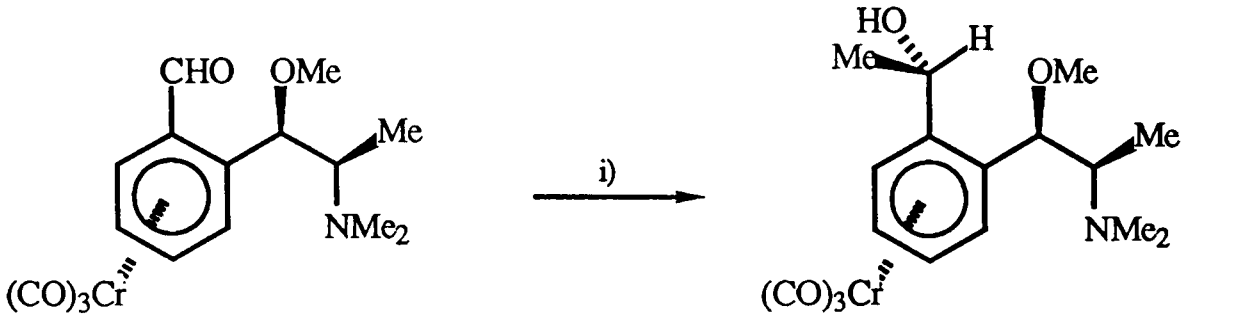
137



138

The use of methyl magnesium iodide in the addition to complex (+)-**129** gave an 88:12 mixture of addition products along with recovery of a considerable amount of starting material. Presumably the Grignard reagent is a better Lewis acid than methyllithium and can attach itself to the benzylic heteroatom thereby incereasing the acidity of the benzylic proton. The Grignard reagent may then serve as a base rather than as a nucleophile to afford the resonance stabilised benzylic carbanion which, upon reprotonation during workup regenerates the starting material. Addition of methyllithium to complex (+)-**130** again gave two products in the approximate

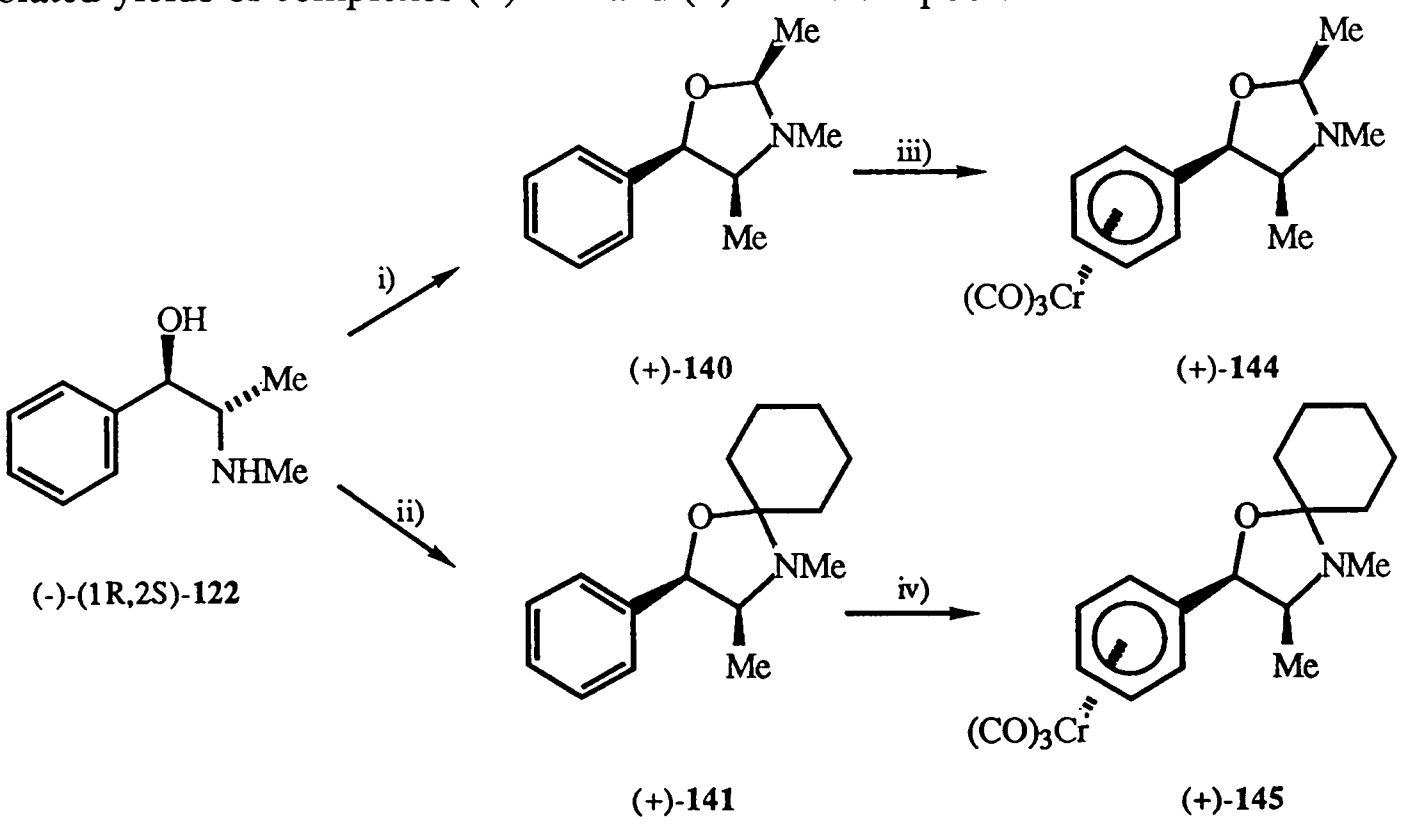
ratio 86:14 which could not be separated. The major component was assigned as complex **139** by analogy with the previously described reaction of (+)-**129**. Use of methyl magnesium iodide in the addition resulted in recovery of a large amount of starting material.



(+)-**130** **139** (Major)

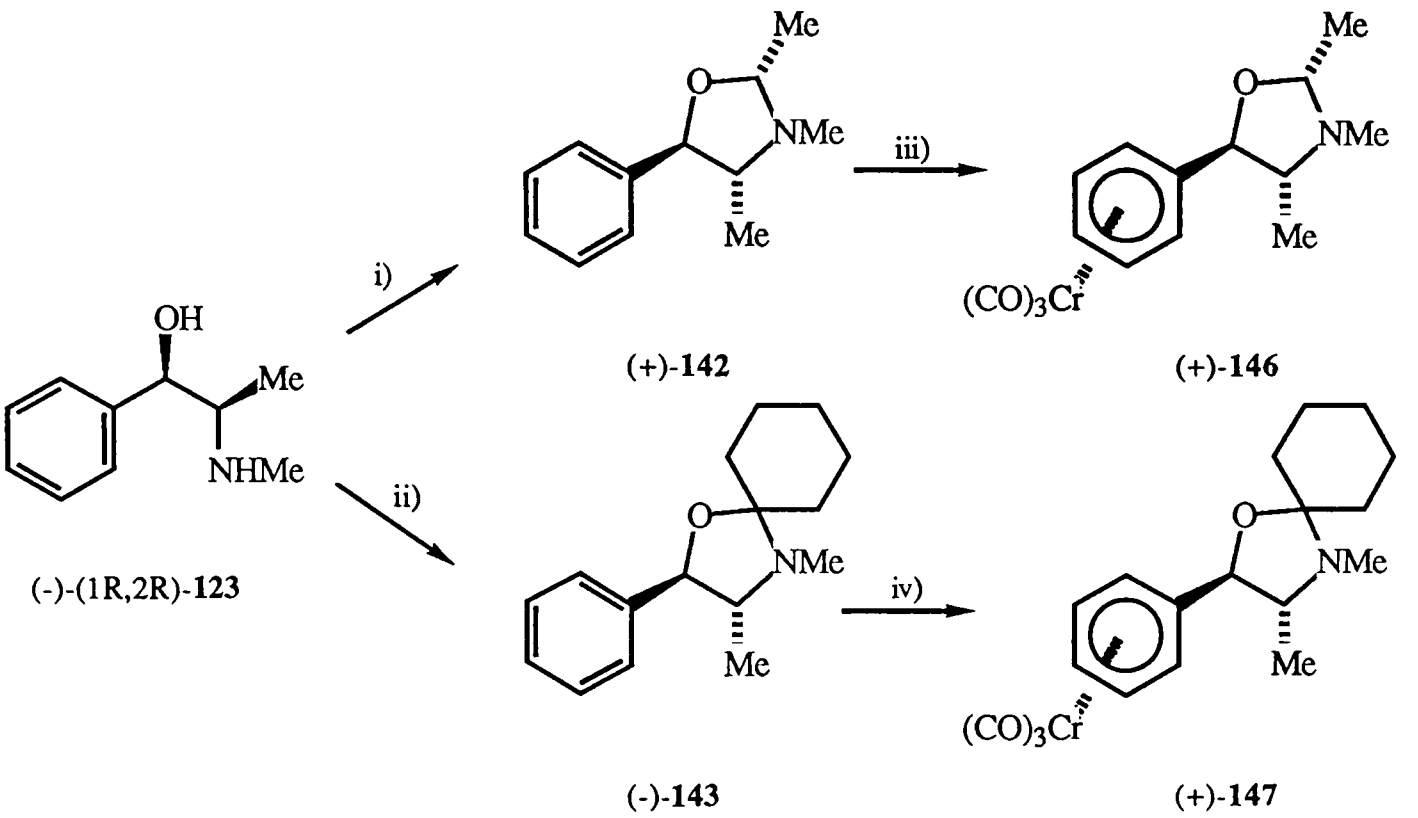
i) MeLi, THF, -78°C, 2-6h.

The enhanced acidity of the benzylic proton of derivatives of (-)-**122** and (-)-**123** upon coordination to the $Cr(CO)_3$ tripod due to the benzylic carbanion stabilising influence of the transition metal unit offered potential for their stereoselective removal and subsequent substitution for electrophiles.[17] Condensation of (-)-(1R,2S)-ephedrine (**122**) with acetaldehyde or cyclohexanone gave the known oxazolidines (+)-**140**[102] and (+)-**141**[103] respectively, the former being obtained as essentially one diastereoisomer. The highly stereoselective formation of oxazolidine (+)-**140** has been documented. The newly generated chiral centre is that shown as a consequence of minimising 1,3 interactions in the five-membered ring.[104] Similar reactions using (-)-(1R,2R)-pseudoephedrine (**123**) afforded the corresponding oxazolidines (+)-**142**[102] and (-)-**143**.[103] Thermolysis of chromium hexacarbonyl with each of these products under standard complexation conditions yielded the corresponding $Cr(CO)_3$ complexes (+)-**144-147** as highly crystalline yellow solids although the isolated yields of complexes (+)-**144** and (+)-**146** were poor.



(-)-(1R,2S)-**122** (+)-**140** (+)-**144** (+)-**141** (+)-**145**

i) MeCHO, CH_2Cl_2, sieves, 0.5h, 99%. ii) $C_6H_{10}O$, C_6H_6, 22h, 91%.
iii) $Cr(CO)_6$, Bu_2O/THF (8:1), 14.5h, 3%. iv) $Cr(CO)_6$, Bu_2O/THF (12:1), 16.5h, 42%.



(-)-(1R,2R)-**123**

(+)-**142**

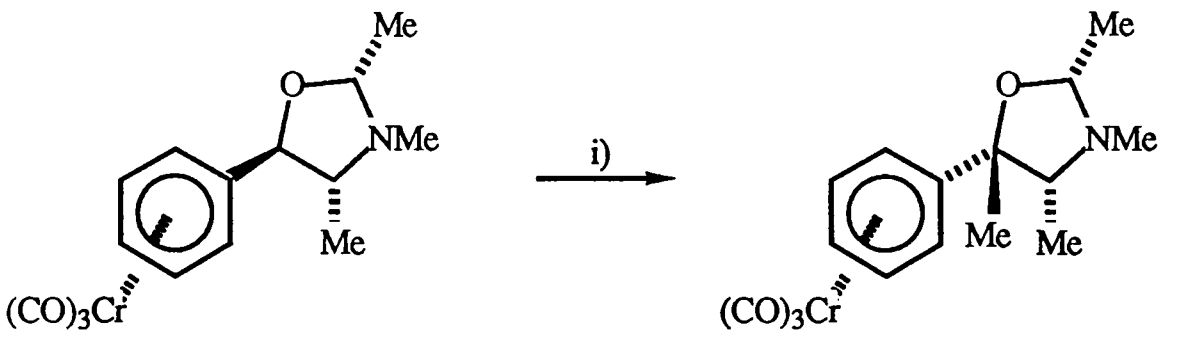
(+)-**146**

(-)-**143**

(+)-**147**

i) MeCHO, CH_2Cl_2, sieves, 0.5h, quantitative. ii) $C_6H_{10}O$, C_6H_6, 45h, 96%.
iii) $Cr(CO)_6$, Bu_2O/THF (8:1), 25h, 13%. iv) $Cr(CO)_6$, Bu_2O/THF (8:1), 21h, 76%.

Tetrahydrofuran solutions of each of the complexes (+)-**144-147** were separately treated with one equivalent of *t*-butyllithium and subsequently quenched with methyl iodide. For each of the complexes only starting material was isolated upon workup with the exception of complex (+)-**146**. In this case ^1H n.m.r. spectroscopy of the crude product revealed the formation of a single diastereoisomer that exhibited all of the features of the starting material (+)-**146** but differed in that the benzylic proton doublet at δ4.20 had disappeared and a new three proton singlet had appeared at δ1.41. The product was therefore assigned as the benzylically methylated complex (+)-**148** which was fully characterised. Although the stereochemistry at the benzylic centre was not determined it is likely to be that shown since the benzylic carbanion generated upon deprotonation of (+)-**146** would be expected to be quenched from the sterically more accessible face.



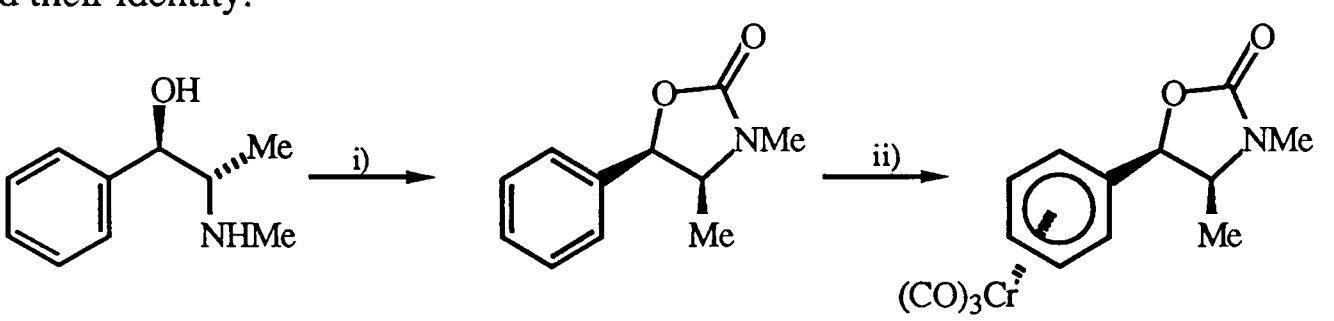
(+)-**146**

(+)-**148**

i) *t*-BuLi, THF, -78°C, 2h. ii) MeI, 94%.

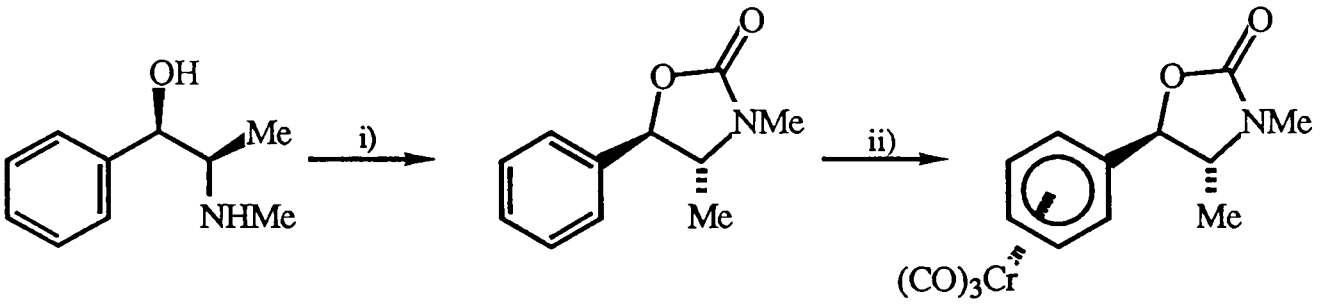
The non-lithiation of complexes (+)-**144**, (+)-**145** and (+)-**147** may reflect the relatively high activation energy of the transition states that permit *exo* loss of their benzylic protons. The stereoelectronic requirement governing the deprotonation of complex (+)-**146** requires that the benzylic proton adopts a conformation that places it antiperiplanar to the arene-$Cr(CO)_3$ axis. That methylation of complex (+)-**146** readily occurs indicates that this requirement is met without sterically encumbering the transition state.

The diastereoisomeric oxazolidinones (-)-**149** and (-)-**150**, derived upon condensation of carbonyldi-imidazole with (-)-**122** and (-)-**123** respectively, underwent ready complexation under standard conditions to furnish the corresponding $Cr(CO)_3$ complexes (-)-**151** and (+)-**152**. For both compounds, a molecular ion *m/z*=328 (M^++1) and an elemental analysis confirmed their identity.



(-)-(1R,2S)-**122** (-)-**149** (-)-**151**

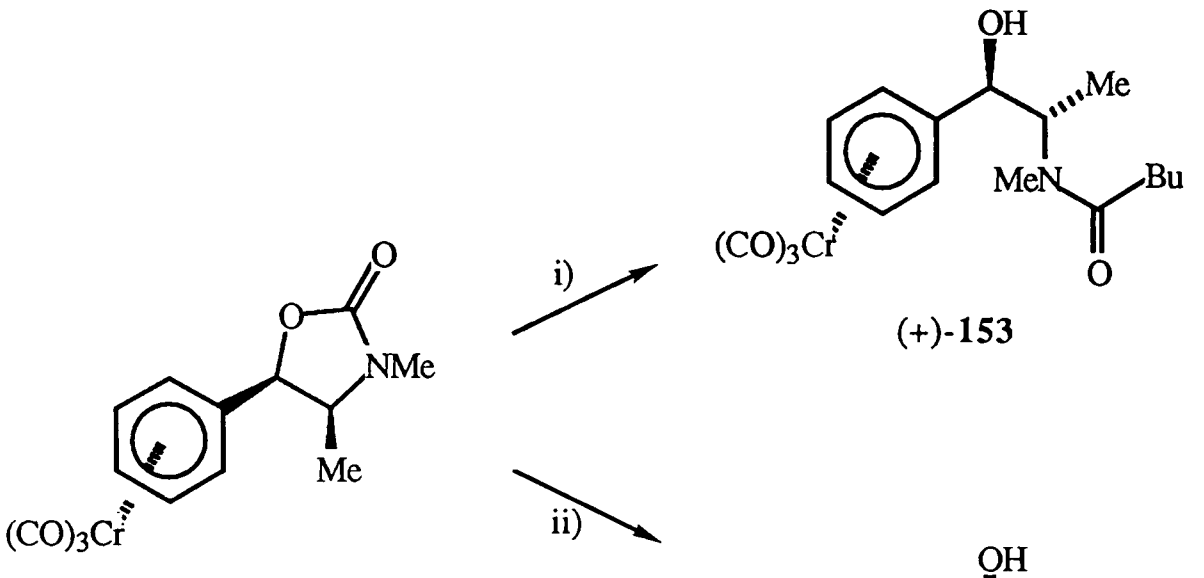
i) CDI, THF, 3h, 74%. ii) $Cr(CO)_6$, Bu_2O/THF (10:1), 24h, 34%.



(-)-(1R,2R)-**123** (-)-**150** (+)-**152**

i) CDI, THF, 3h, 80%. ii) $Cr(CO)_6$, Bu_2O/THF (7:1), 21h, 76%.

A solution of (-)-**151** at -78°C was treated with *n*-butyllithium giving no apparent colour change. Addition of dimethylformamide followed by chromatrography led to the isolation of a yellow crystalline solid that exhibited a carbonyl stretch of 1615cm^{-1} in its infrared spectrum and a molecular ion *m/z*=386 (M^++1). The ^1H n.m.r. spectrum of the product included a high field triplet which led to its assignment as the amide complex (+)-**153**, an elemental analysis being consistent with this assignment. In a similar fashion the N-acylated complexes (-)-**154** and (+)-**155** were prepared upon treatment of (-)-**151** and (+)-**152** with methyllithium respectively and were both fully characterised. Analogous treatment of oxazolidinones (-)-**149** and (-)-**150** yielded (-)-(N-acetyl)ephedrine (**156**) and (-)-(N-acetyl)pseudephedrine (**157**) respectively as a consequence of nucleophilic attack at the carbamate carbon. This reaction sequence offers an alternative method for the selective N-acylation of β-amino alcohols.

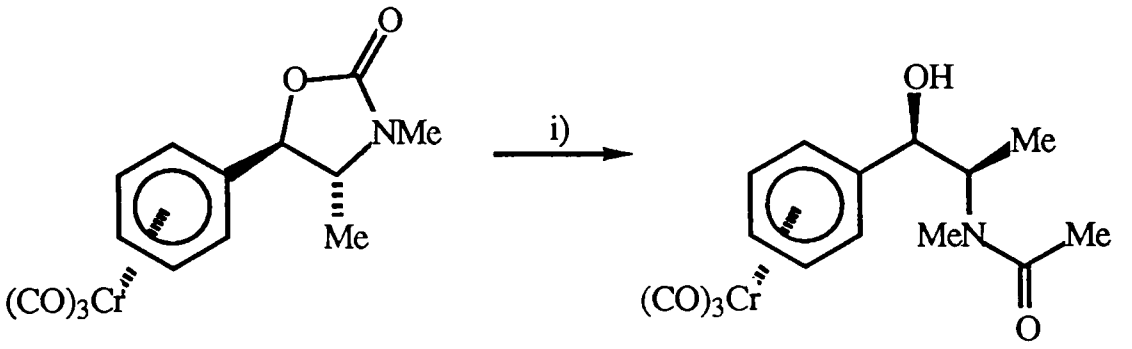


(-)-**151**

(+)-**153**

(-)-**154**

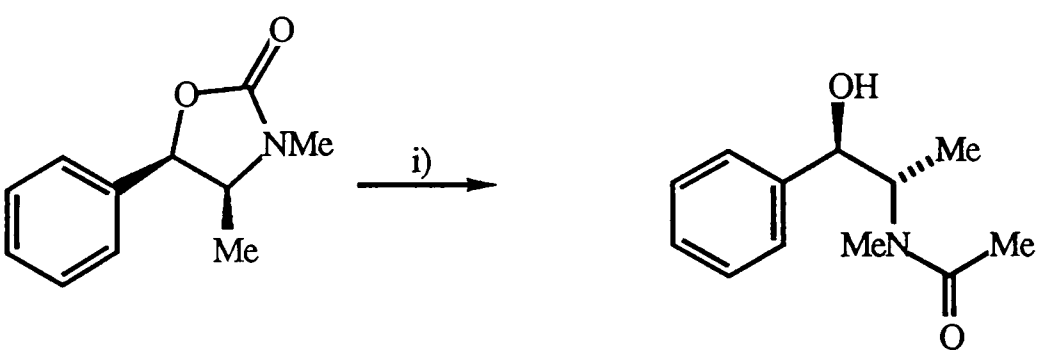
i) *n*-BuLi, THF, -86°C, 2h, 61%. ii) MeLi, THF, -78°C, 2.5h, 80%.



(+)-**152**

(+)-**155**

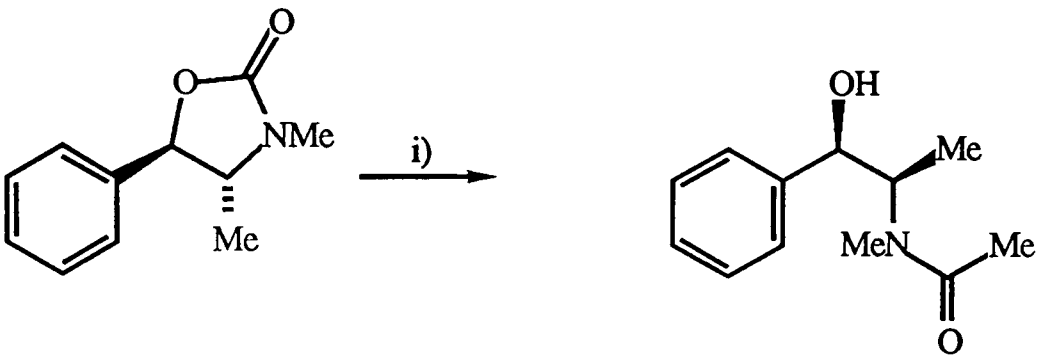
i) MeLi, THF, -78°C, 2h, 69%.



(-)-**149**

(-)-**156**

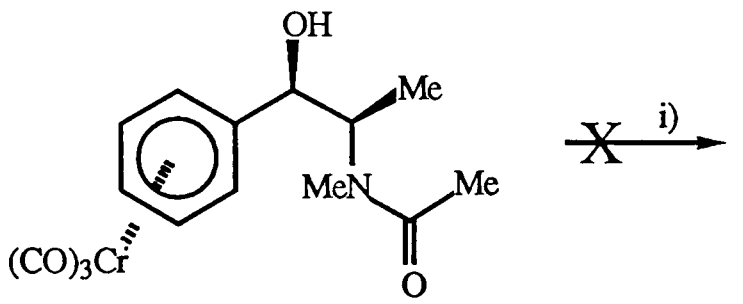
i) MeLi, THF, -78°C, 2h, 85%.



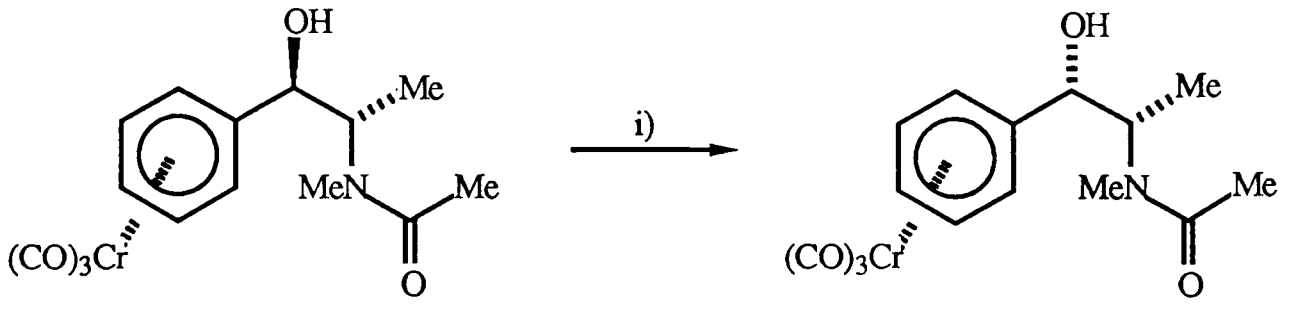
(-)-**150** (-)-**157**

i) MeLi, THF, -78°C, 2.5h, 80%.

A methanol solution of (+)-[(N-acetyl)pseudoephedrine]$Cr(CO)_3$ (**155**) was treated with tetrafluoroboric acid giving no apparent colour change. The solution was stirred overnight and worked up with base to afford only starting material. Identical treatment of (-)-[(N-acetyl)ephedrine]$Cr(CO)_3$ (**154**) again gave no apparent colour change but yielded the epimeric complex (-)-**155** as the major product as evidenced by the ^1H n.m.r. spectrum of the product which was superimposable with that of (+)-**155**.



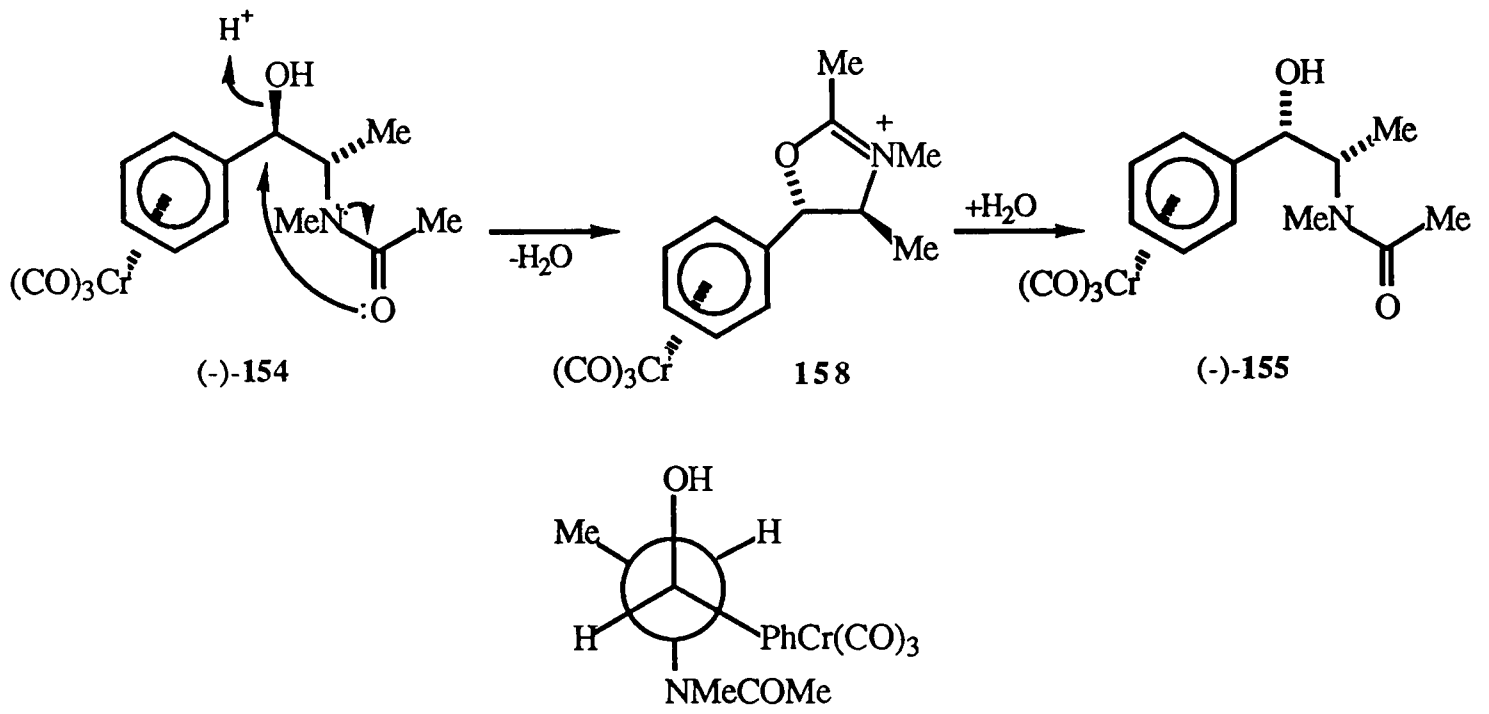
(+)-**155**



(-)-**154** (-)-**155**

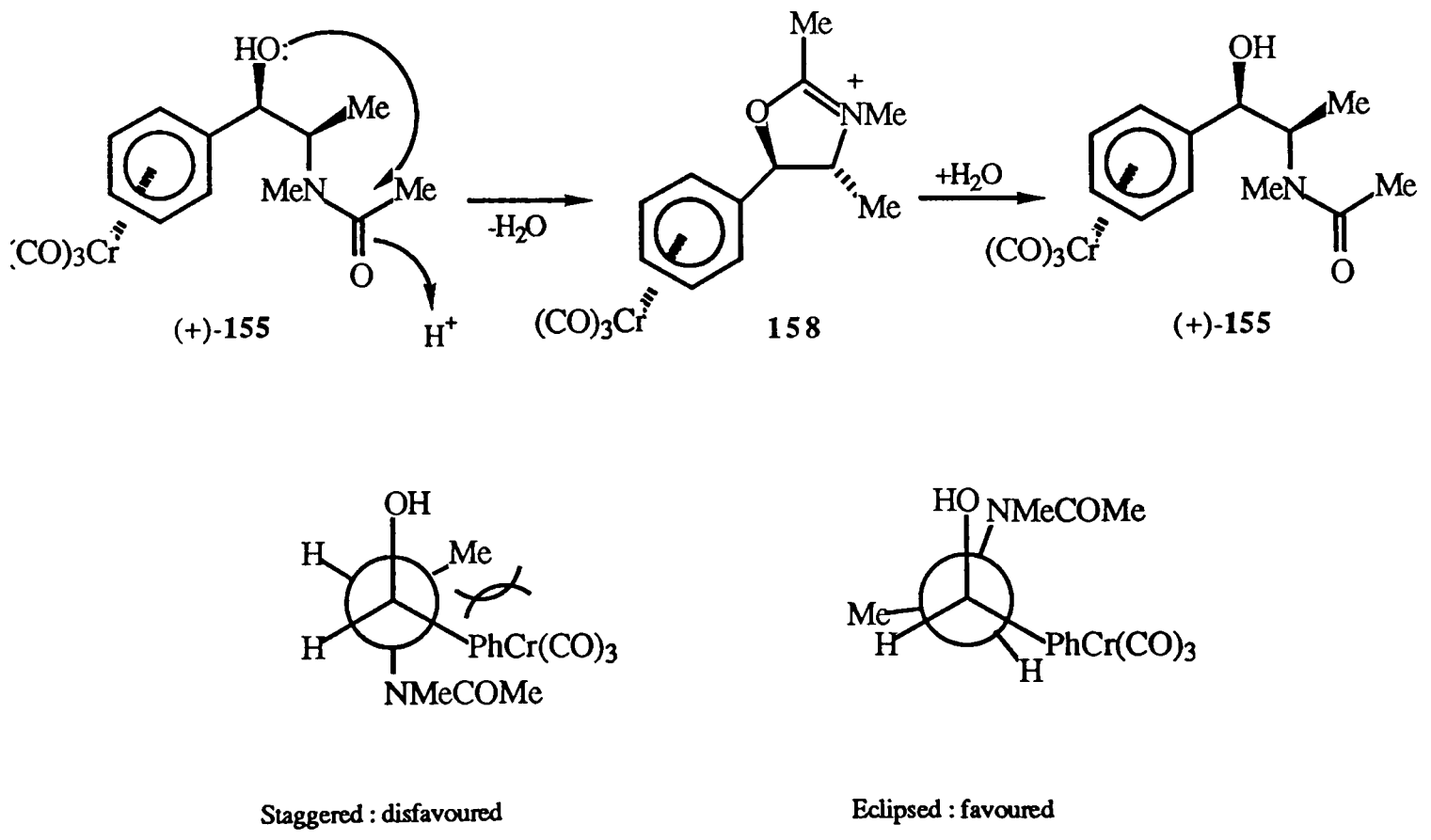
i) $HBF_4.OMe_2$, MeOH, THF.

The epimerisation of (-)-**154** to (-)-**155** may be rationalised by considering the neighbouring group participation offered by the amide oxygen atom as outlined in Scheme 5. The Newman projection along the C1-C2 bond shown reveals that the C1-phenyl and the C2-methyl substituents are *trans* orientated in the conformation that permits backside displacement of the protonated hydroxyl functionality. Subsequent hydrolysis of the cyclic intermediate **158** upon workup accounts for the observed inversion of configuration at the benzylic centre.



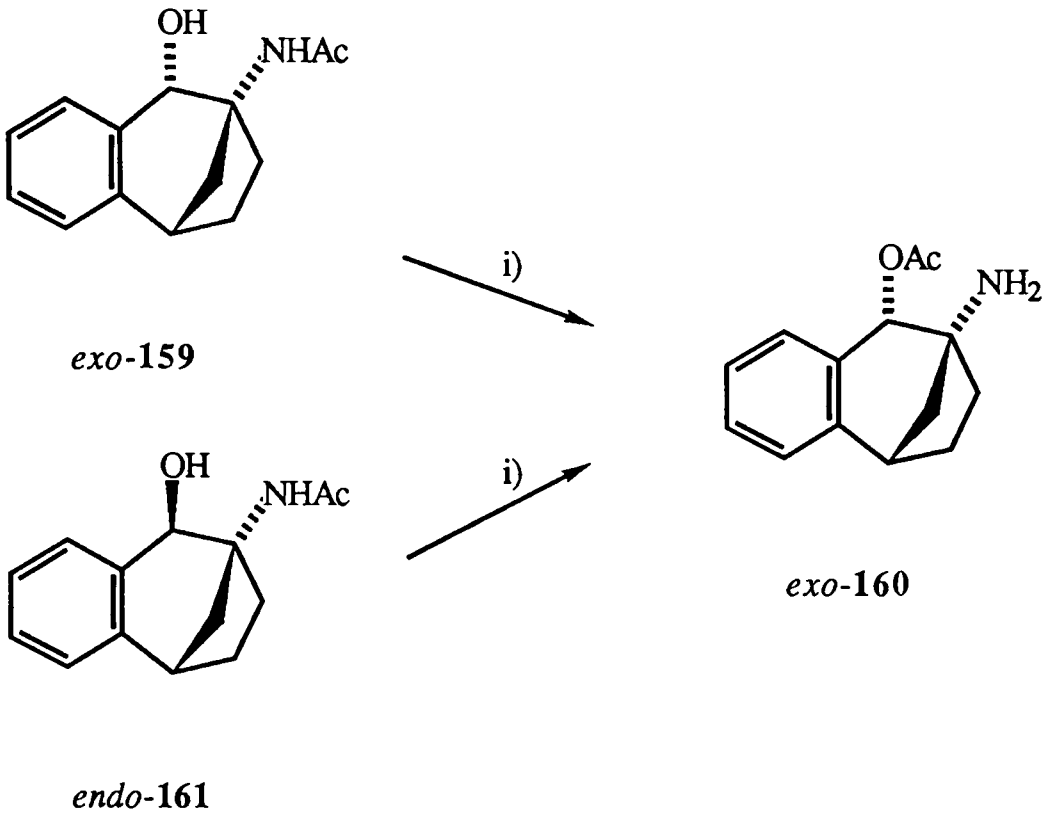
Scheme 5 : Epimerisation of complex (-)-**154** *via* a neighbouring group participation mechanism.

In the case of (+)-**155**, similar neighbouring group participation by the amide functionality will be disfavoured since the transition state that would allow backside displacement of the protonated hydroxyl group would necessitate steric compression between the C1-phenyl and the C2-methyl groups. This unfavourable interaction is relieved in the eclipsed conformation shown below and permits the formation of intermediate **158** by the anchimeric assistance of the alcohol functionality. Hydrolysis of **158** produced in this way would return the unepimerised complex (+)-**155** (Scheme 6).



Scheme 6 : Neighbouring group participation in the acidic treatment of complex (+)-**155**.

Neighbouring group participation mechanisms of this type are well documented in the chemistry of β-amino alcohols.[105] The conversion of norephedrine to norpseudoephedrine has been reported[106] whilst, in a recent example it was shown that *exo* amide **159** underwent a nitrogen to oxygen acyl migration with retention of configuration upon treatment with acid to give the *exo* amine **160**. In contrast, a similar migration in the reaction of *endo* amide **161** occurred with inversion of configuration to afford the *exo* amine **160**.[105]



exo-**159**

exo-**160**

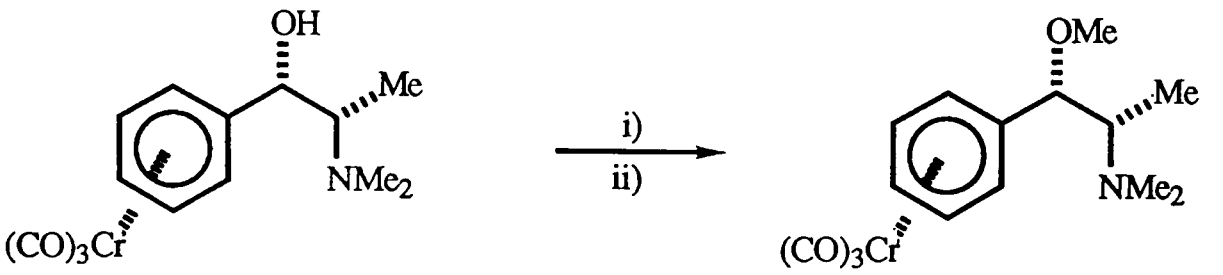
endo-**161**

i) HCl (0.3M), 100°C, 18h, 82%.

The alkylation of the alcohol functionality of (-)-**122** and (-)-**123** in the synthesis of complexes (-)-**127** and (-)-**128** necessitated the use of potassium hydride at reflux overnight and subsequent methylation with one equivalent of methyl iodide to avoid any Hofmann elimination. Although the yields obtained were reasonable it was considered that the known benzylic carbocation stabilising ability of the $Cr(CO)_3$ unit should lend itself to the substitution of the hydroxyl group for a variety of nucleophiles.

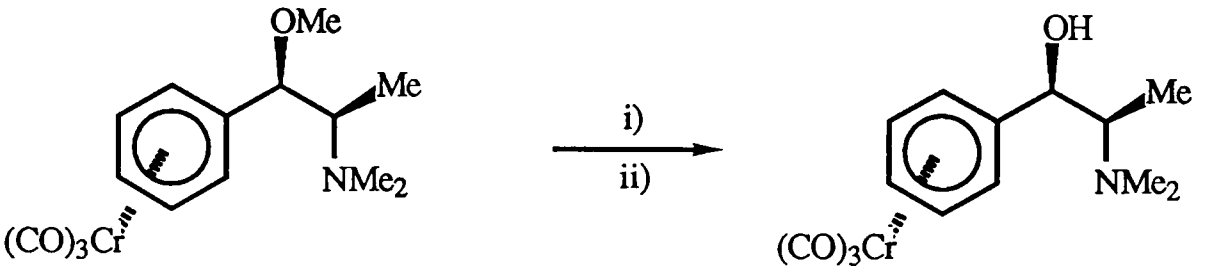
(-)-[N-Methyl(pseudoephedrine)]$Cr(CO)_3$ (**162**)[107] was treated with tetrafluoroboric acid in the presence of dimethoxybenzene giving an intense purple colouration indicative of benzylic carbocation formation. Addition of methanol followed by basic workup afforded the methylether complex (+)-**128** as the major product along with recovery of some starting material. The nucleophilic substitution of the hydroxyl group with retention of configuration is consistent with a mechanism involving neighbouring group participation by the chromium atom. The protonated hydroxyl functionality may be displaced with inversion of configuration when it lies antiperiplanar to the arene-chromium axis to give a configurationally stable carbocation. Subsequent nucleophilic attack by methanol may only occur with inversion from the *exo* face owing to the steric bulk of the $Cr(CO)_3$ tripod giving overall retention of configuration by double inversion. The non-incorporation of the dimethoxybenzene group

indicates that methanol is a better nucleophile in the intermolecular trapping of the cationic intermediate. In a similar fashion, methylether complex (-)-**128** was readily converted to alcohol (+)-**162** as the major product upon treatment with acid and water along with recovery of some starting material.



(-)-**162** (+)-**128**

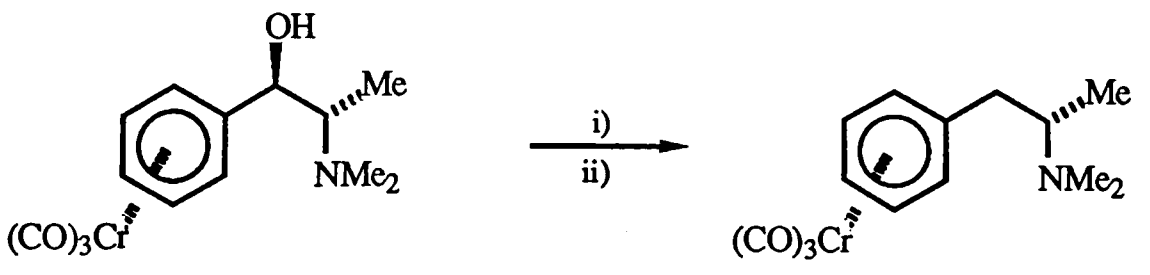
i) $HBF_4.OMe_2$, CH_2Cl_2, $(MeO)_2C_6H_4$, 10min. ii) MeOH, 72%.



(-)-**128** (+)-**162**

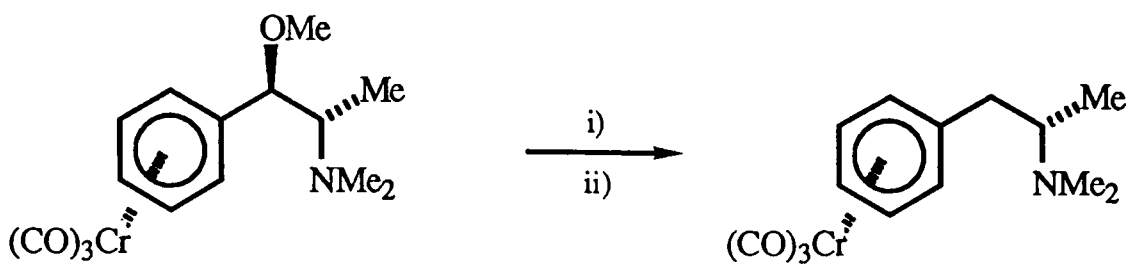
i) $HBF_4.OMe_2$, CH_2Cl_2, 10 min. ii) H_2O, 44%.

Analogous treatment of ephedrine-derived complex (-)-**163**[107] with tetrafluoroboric acid again gave an intense purple colouration indicative of benzylic carbocation formation. Addition of methanol led to the isolation of a single complex after chromatography. The ^1H n.m.r. spectrum of the product revealed the presence of an ABX system which had replaced the benzylic proton doublet of starting material (-)-**163** suggesting reduction to dimethylamphetamine complex (-)-**164**. This assignment was confirmed upon comparison with an authentic sample,[107] its specific rotation indicating that the reduction had occurred without racemisation at the β-centre. Similar treatment of methyl ether complex (-)-**127** with acid gave a purple colouration that was discharged upon addition of water to furnish (-)-**164** as the major product after workup.



(-)-**163** (-)-**164**

i) $HBF_4.OMe_2$, CH_2Cl_2, 10min. ii) MeOH, 44%.

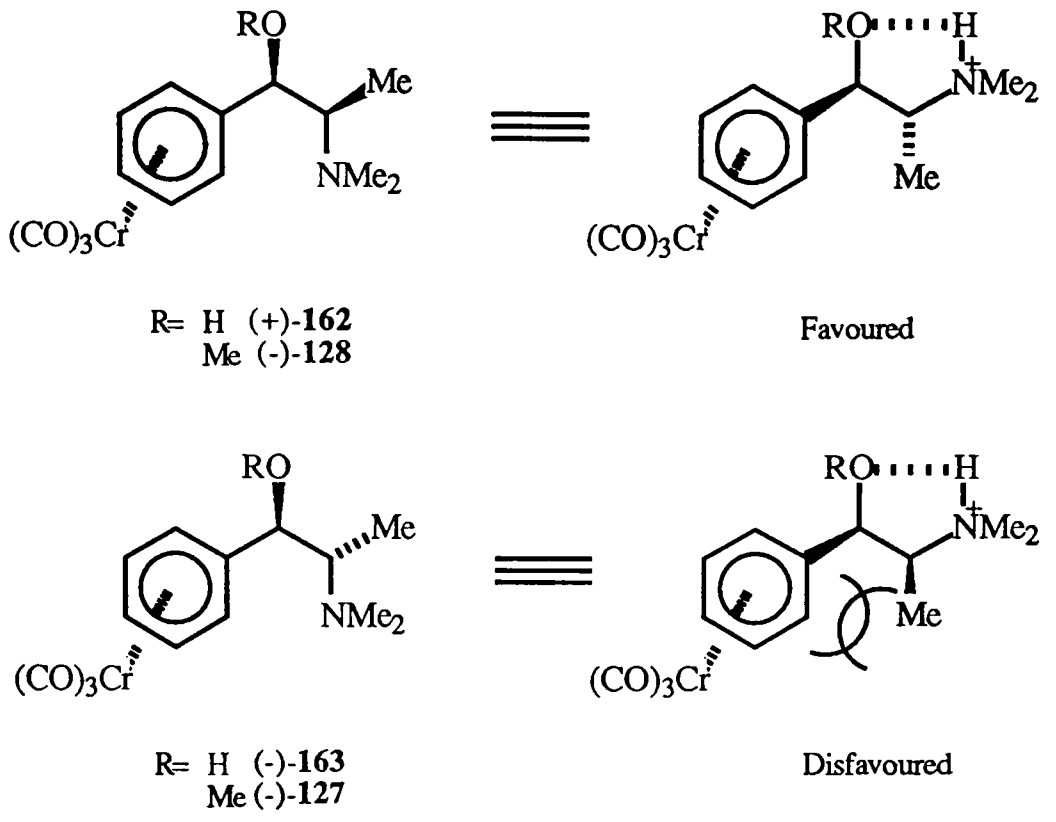


(-)-**127** (-)-**164**

i) $HBF_4.OMe_2$, CH_2Cl_2, 0.5h. ii) H_2O, 38%.

The apparent disparity revealed in the substitution reactions of pseudoephedrine-derived complexes (-)-**162** and (-)-**128** and the reductions of ephedrine-derived complexes (-)-**163** and (-)-**127** is presumably a consequence of the relative configuration between the two asymmetric centres. The observed formation of complex (-)-**164** in the latter case probably arises by a hydride reduction although a radical pathway has not been dismissed. Deuteriomethanol quench in the reaction of (-)-**163** gave no apparent deuterium incorporation in the product (-)-**164** indicating that it does not serve as the deuteride source in this case. It is unlikely that the dichloromethane solvent performs the reduction suggesting that the reducing agent is the tetrafluoroboric acid dimethyl ether complex used to promote reaction. The different reactivity of complexes (-)-**162** and (-)-**128** in comparison to that of complexes (-)-**163** and (-)-**127** may be a consequence of an internal hydrogen bond in the former cases. Under the strongly acidic conditions employed, the tertiary amine functionality of complexes (-)-**162** and (-)-**128** will be protonated and the nitrogen-bound proton may form an intramolecular hydrogen bond to the benzylic oxygen atom. The five-membered ring thereby generated will orientate the methyl and (Ph)$Cr(CO)_3$ groups *trans* to each other thereby offering no steric hinderance to the formation of the hydrogen bond. In this situation, the methoxyl group of complex (-)-**128** and the hydroxyl group of complex (-)-**162** are rendered poorer leaving groups than methanol and water respectively and thus ionisation to the corresponding benzylic carbocation is disfavoured. Addition of methanol in the case of (-)-**162** [water in the case of (-)-**128**] immediately increases the polarity of the reaction mixture thereby allowing ionisation to give a stabilised benzylic carbocation. Subsequent trapping from the unhindered *exo* face therefore accounts for the observed substitution reactions (Scheme 7).

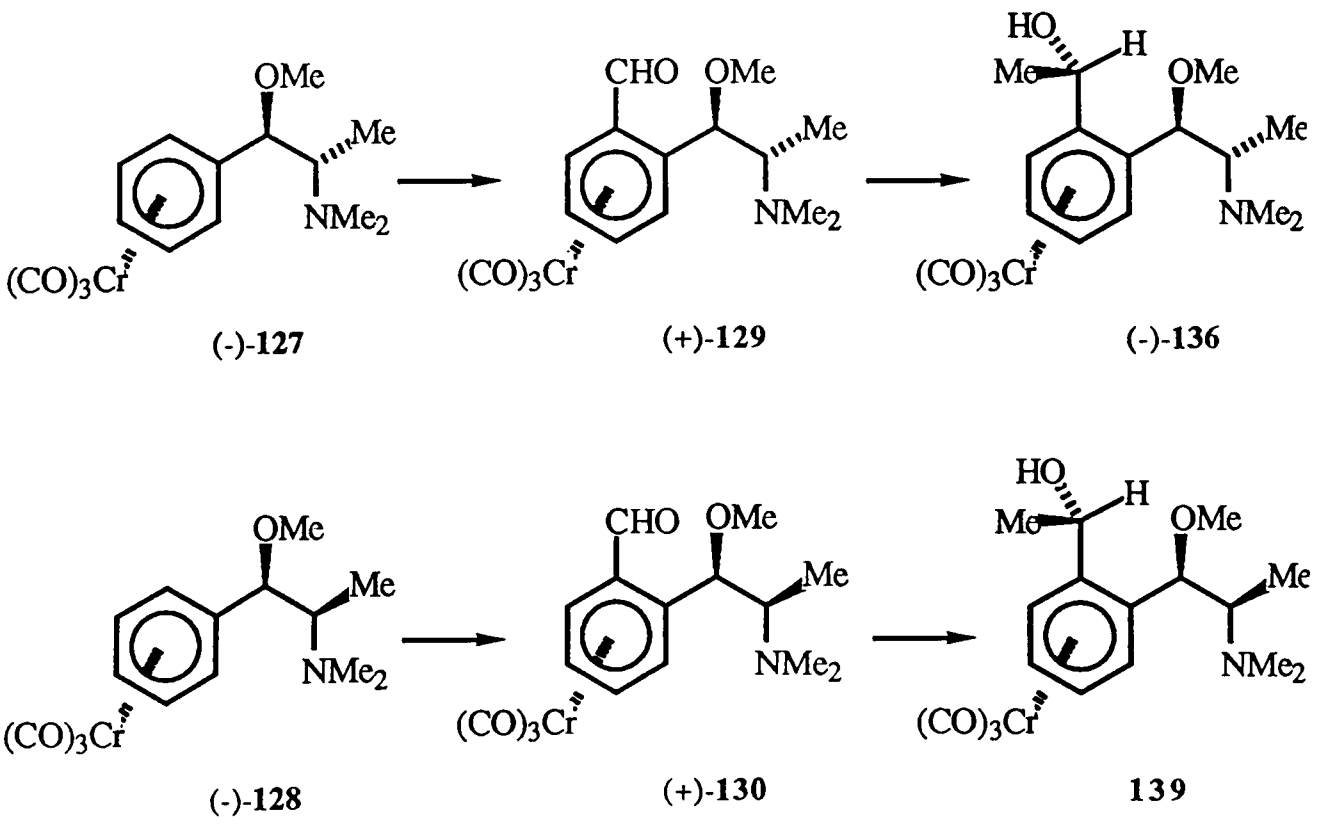
In the case of both (-)-**163** and (-)-**127** a similar hydrogen bond would be disfavoured since it would cause adverse steric compression between the *cis* orientated methyl and (Ph)$Cr(CO)_3$ groups. Direct protonation of the benzylic oxygen atom of either complex permits the elimination of water or methanol respectively. The observed formation of (dimethylamphetamine)$Cr(CO)_3$ (**164**) in less than 50% yield in both cases is consistent with a disproportionation reaction. Such a reaction pathway would generate the corresponding phenyl ketone complex which would presumably polymerise under the acidic reaction conditions (Scheme 7).



Scheme 7 : Intramolecular hydrogen bonding for complexes (-)-**127**, (-)-**128**, (-)-**162** and (-)-**163**.

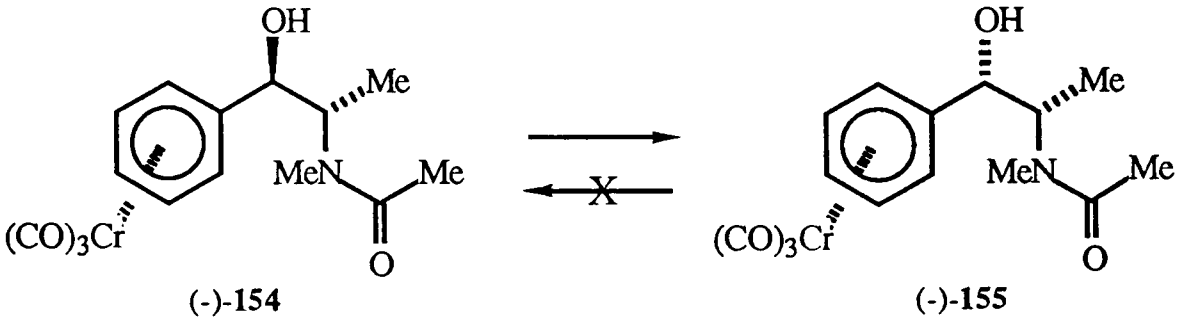
Summary

Complexes (-)-**127** and (-)-**128** both undergo stereoselective *ortho* formylation upon sequential treatment with *t*-butyllithium and ethyl formate to give complexes (+)-**129** and (+)-**130** respectively. The stereoselectivity is believed to arise as a consequence of the benzylic methoxyl substituent which permits a chelation controlled *ortho* lithiation *via* the transition state that minimises steric interactions. Addition of methyllithium to either (+)-**129** or (+)-**130** occurs with relati vely low selectivity to furnish the corresponding secondary alcohols as a mixture of diastereoisomers (ratio 86:14).



In the case of complex (+)-**129**, the relative stereochemistry of the major addition product [(-)-**136**] has been unambiguously determined by a single crystal X-ray structure determination.

Reaction of (-)-[(N-acetyl)ephedrine]$Cr(CO)_3$ (**154**) with acid causes epimerisation at the α centre to furnish (-)-[(N-acetyl)pseudoephedrine]$Cr(CO)_3$ (**155**) as the major product whilst complex (+)-**155** is observed to be configurationally stable under identical acidic conditions. This behaviour may be attributed to neighbouring group participation by the amide oxygen in the case of complex (-)-**154** with concomitant inversion of configuration at the benzylic centre. Hydrolysis of the cyclic intermediate thereby generated accounts for the observed epimerisation to yield complex (-)-**155**. In the case of complex (+)-**155**, an analogous mechanism would be disfavoured owing to steric encumberance due to the *cis* orientated methyl and (Ph)$Cr(CO)_3$ groups thereby preventing epimerisation by this mechanism.



(-)-154 (-)-155

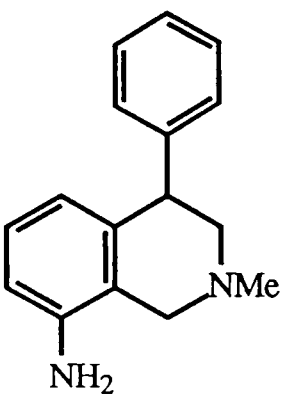
CHAPTER 4

4-Aryl tetrahydroisoquinolines

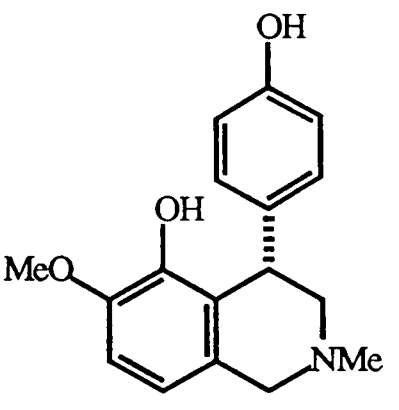
4-ARYL TETRAHYDROISOQUINOLINES

A) Stereoselectivity in the cyclisation of N-(3,4-dimethoxybenzyl)halostachine

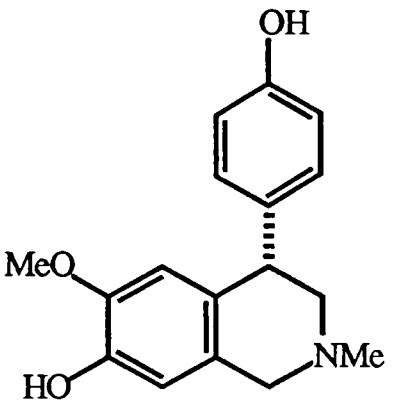
The widespread natural occurrence and potent pharmacological activity displayed by simple 4-aryl tetrahydroisoquinolines has stimulated much interest in their synthesis.[108-117] Nomifensine (**165**) is a powerful inhibitor of the uptake of monoamine neurotransmitters and has been marketed under the trade names Alivar and Meritil[118] for the treatment of depression. More importantly, this compound displays enantioselective pharmacological activity: all of the desired activity residing exclusively in the (+)-(S) enantiomer.[108,109] In general the construction of 4-aryl tetrahydroisoquinolines is readily achieved by the biomimetic[119] cyclisation of an appropriately substituted N-benzyl-1-aryl ethanolamine.[120,121] For example, the alkaloids (+)-(S)-Latifine (**166**)[122] and (+)-(S)-Cherylline (**167**)[123] are believed to be biogenetically derived from the same precursor **168**, whilst acid-promoted cyclisation of N-benzyl-1-phenyl ethanolamine (**169**) gives 4-phenyl tetrahydroisoquinoline (**170**) in good yield.[124]



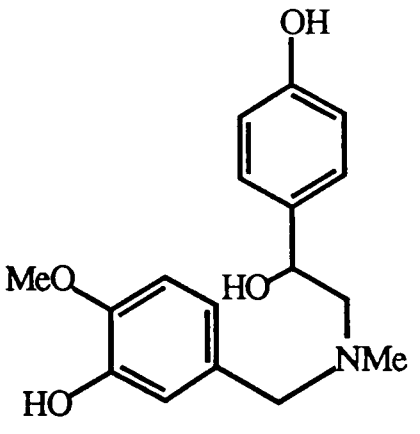
165



(+)-(S)-**166**

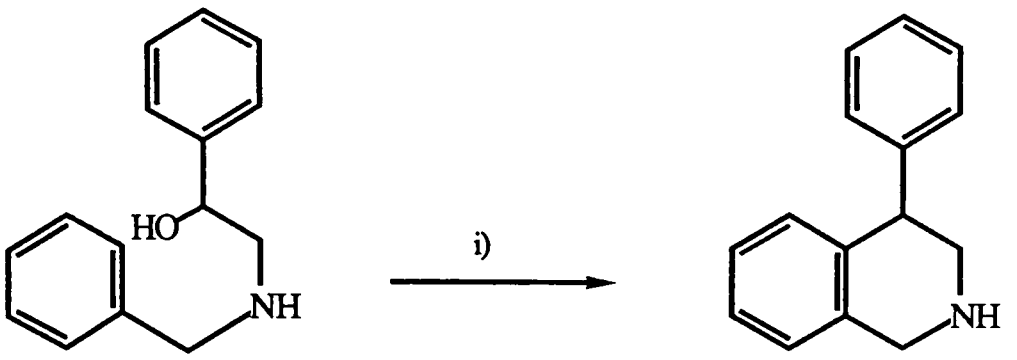


(+)-(S)-**167**



168

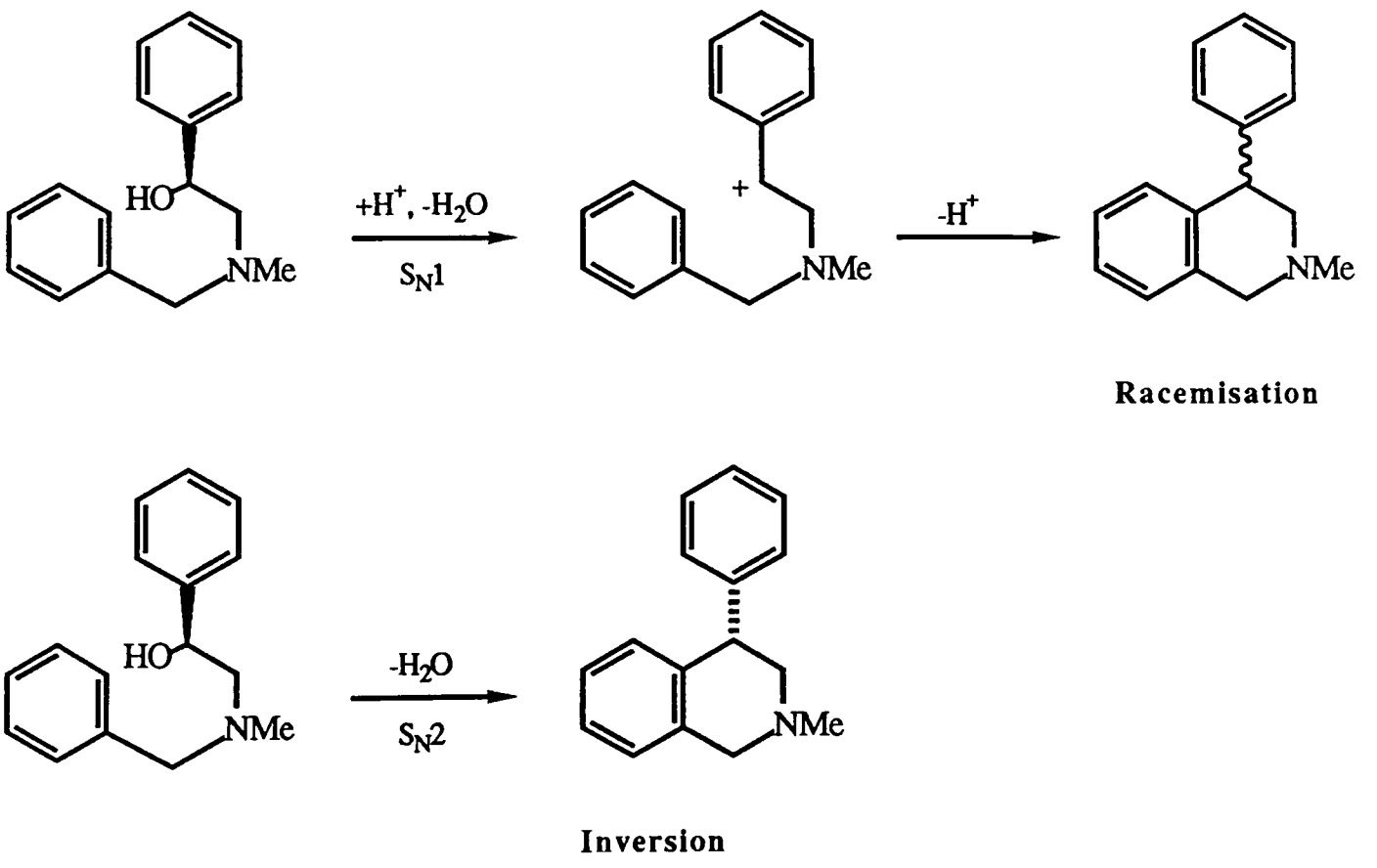
This synthetic strategy has been widely employed for the preparation of 4-aryl tetrahydroisoquinolines functionalised in both aromatic rings; the ring closure being facilitated by the presence of electron releasing substituents on the N-benzyl group and retarded for electron withdrawing substituents. However, the direct asymmetric synthesis of homochiral 4-aryl tetrahydroisoquinolines has not been reported, although a limited number have been prepared by classical resolution procedures.[108-112]



169 **170**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 0.5h, 78%.

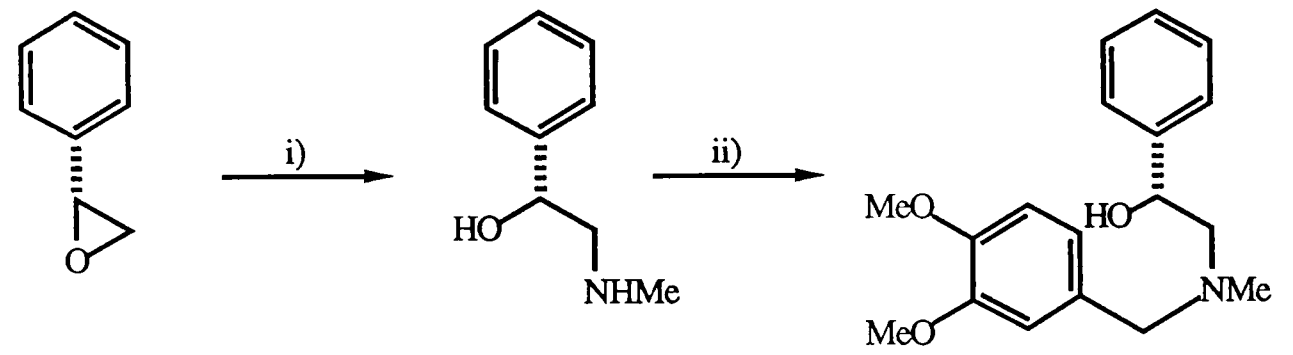
Despite the ready availability of homochiral phenethanolamines there are no reports concerning the stereoselectivity of their acid-catalysed cyclisation to 4-aryl tetrahydroisoquinolines. If the mechanism were to proceed *via* a free benzylic carbocation then all stereochemical information would be lost giving rise to a racemic product. If, however, the N-benzyl substituent participates in the ionisation of the alcohol functionality and thereby serves as a neighbouring group, stereochemical integrity would be maintained, rendering the cyclisation stereospecific with the original chiral centre undergoing complete inversion of configuration (Scheme 8). The enantiomeric excess of the 4-aryl tetrahydroisoquinoline produced as a consequence of the acid promoted cyclisation of a homochiral N-benzyl-1-aryl ethanolamine will reflect the relative importance of these two competing mechanistic pathways, any enantiomeric excess arising as a consequence of the latter mechanism. It was thus of interest to investigate the stereoselectivity of the cyclisation of homochiral N-benzyl-1-aryl ethanolamines.



Scheme 8 : Stereochemical consequences of cyclisation *via* S_N1 or S_N2 mechanisms.

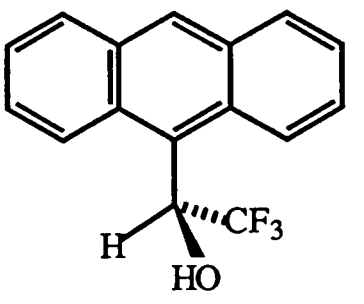
Results and Discussion

Reaction of an ethanol solution of racemic styrene oxide (**171**) with excess methylamine at reflux gave a mixture of N-methyl-1-phenyl ethanolamine (halostachine) (**172**) and its regioisomer N-methyl-2-phenyl ethanolamine in the ratio 64:36. Crystallisation of the product from dichloromethane/hexane at -20°C afforded pure halostachine (**172**) as slender needles. A solution of halostachine (**172**) in acetonitrile was heated at reflux in the presence of one equivalent of 3,4-dimethoxybenzyl bromide and potassium carbonate to yield previously unreported N-(3,4-dimethoxybenzyl)halostachine (**173**) as a colourless oil in 80% isolated yield. ^{1}H n.m.r. spectroscopy of the product in the presence of approximately one molar equivalent of the chiral shift reagent (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) distinguished between the C1 benzylic proton of the two enantiomers of (R,S)-**173**. In a similar fashion, (-)-(R)-N-(3,4-dimethoxybenzyl)halostachine (**173**) was synthesised from a single enantiomer of styrene oxide [(-)-(R)-**171**]. This new compound was fully characterised and ^{1}H n.m.r. spectroscopy in the presence of the shift reagent (-)-(R)-**174**[125] was consistent with it being homochiral with the C1 benzylic proton resonance appearing at lower field for (-)-(R)-**173**.



(-)-(R)-**171** (-)-(R)-**172** (-)-(R)-**173**

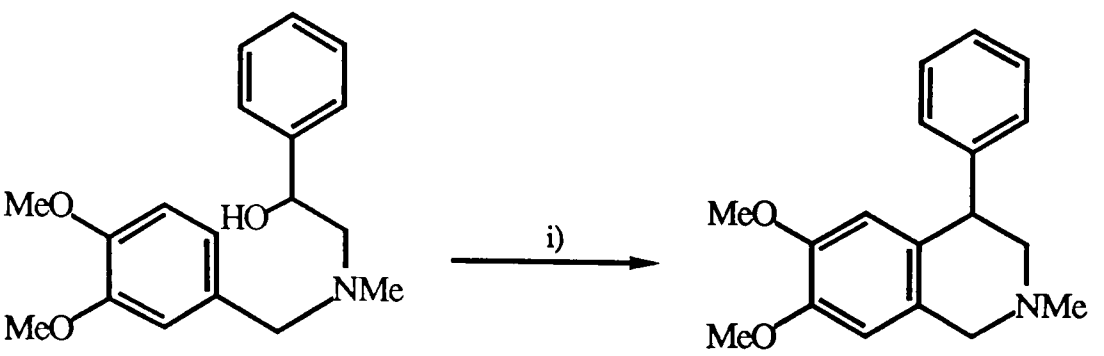
i) $MeNH_2$, EtOH, 12h, 17%. ii) 3,4-$(MeO)_2C_6H_3CH_2Br$, K_2CO_3, MeCN, 3h, 80%.



(-)-(R)-**174**

Cyclisation of (R,S)-**173** to N-methyl-4-phenyl-6,7-dimethoxytetrahydroisoquinoline (**175**) was achieved with a mixture of trifluoroacetic acid and concentrated sulphuric acid in dichloromethane at reflux for thirty minutes according to a reported method for the cyclisation of a similar compound.[124] The ^{1}H n.m.r. spectrum of (R,S)-**175** exhibited two well separated aromatic singlets corresponding to the aromatic protons at C5 and C8 (indicative of the 6,7-dimethoxy regioisomer), three three-proton singlets, an ABX and an AB system in addition to a five proton multiplet. The shift reagent (-)-(R)-**174** readily distinguished the two enantiomers

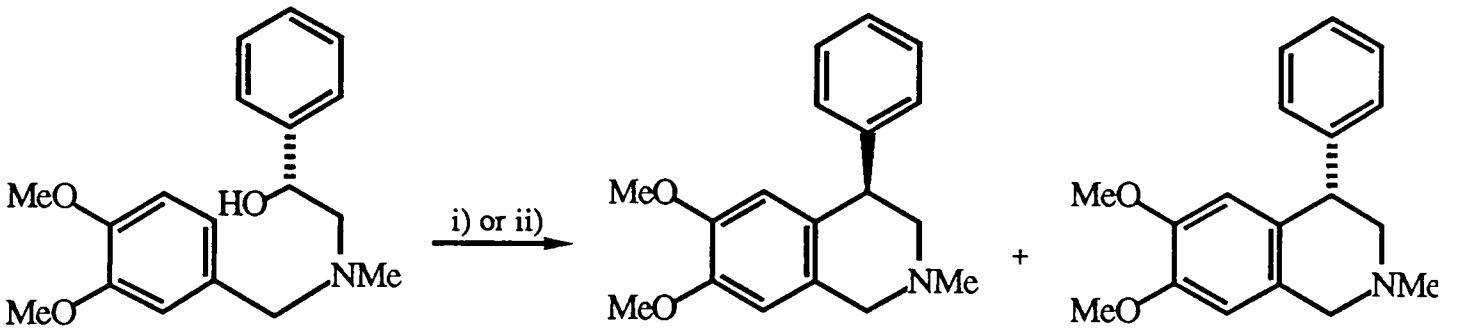
of (R,S)-**175** showing well separated signals for both aromatic singlets, the two methoxyls and the N-methyl singlets. An elemental analysis and a molecular ion *m/z*=283 confirmed the identity of (R,S)-**175**.



(R,S)-**173** (R,S)-**175**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 0.5h, 92%.

Cyclisation of (-)-(R)-**173** under identical conditions afforded a mixture of both enantiomers of tetrahydroisoquinoline **175** in the ratio 57:43 (e.e. =14%). Similar cyclisation of (-)-(R)-**173**, but at a lower temperature (<-20°C), gave a 50% conversion after three days to **175** with an improved enantiomeric excess of 54% (ratio 77:23). The enantiomeric excesses were readily determined by ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(R)-**174** with the N-methyl singlets appearing at higher field for the major enantiomer.



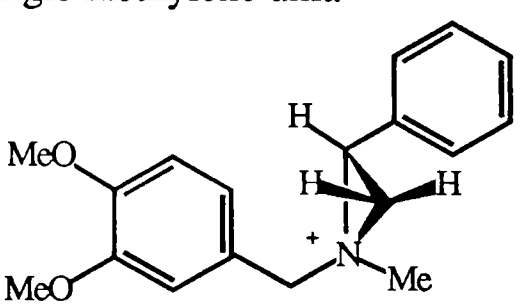
(-)-(R)-**173** (+)-(R)-**175** (-)-(S)-**175**

Conditions	Ratio
i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 0.5h, 97%.	57 : 43
ii) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 69h, 50%.	77 : 23

The enantiomeric excess for the cyclisation of homochiral (-)-(R)-**173** reflects the relative importance of two competing mechanistic pathways. The planar benzylic carbocation generated upon ionisation of the alcohol functionality possesses enantiotopic faces that are indistinguishable to the intramolecular nucleophile; an S_N1 reaction pathway would give a racemic product. If, however, the N-(3,4-dimethoxybenzyl) substituent acts as a neighbouring group and assists in the ionisation of the alcohol functionality, then total inversion of configuration would result during the cyclisation. That a modest enantiomeric excess of 14% was obtained at 40°C demonstrates that *both* mechanistic pathways are operative, with cyclisation occurring predominantly *via* the S_N1 mechanism. At lower temperature (<-20°C)

the improved enantiomeric excess of 54% indicates that the neighbouring group participation mechanism becomes more prominent. On this basis, the major enantiomer produced in both cases is assigned as (R)-**175** as a consequence of preferential inversion of configuration at the benzylic centre.

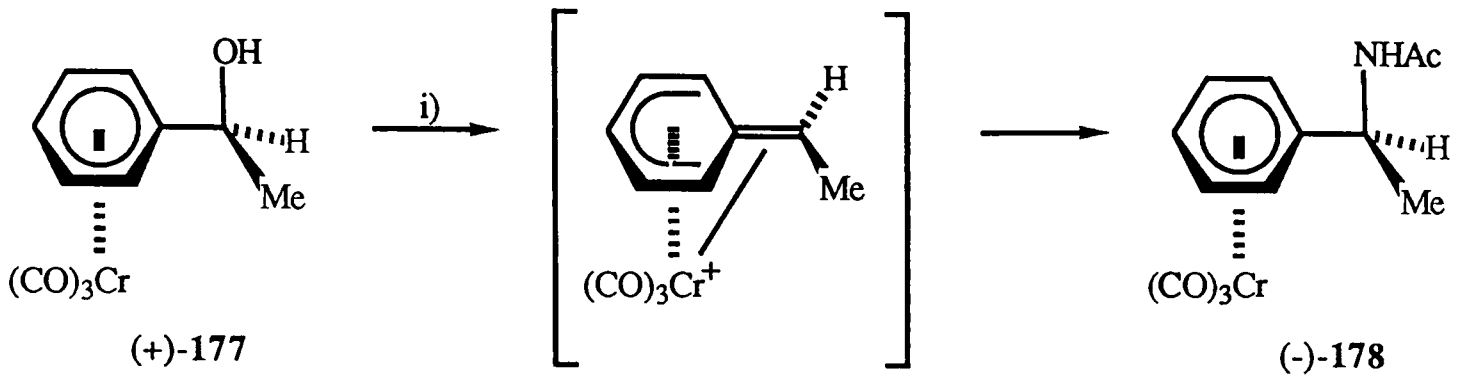
It is unlikely that the nitrogen lone pair of (-)-(R)-**173** participates in the cyclisation as the strongly acidic conditions employed would protonate the amine functionality thus preventing formation of the aziridinium intermediate **176**. Moreover, were intermediate **176** to be formed it could not be a precursor of (+)-(R)-**175** because the internal nucleophile is unable to attain an S_N2 transition state of low enough energy to react because it is attached to the quaternary nitrogen atom by a single methylene unit.



176

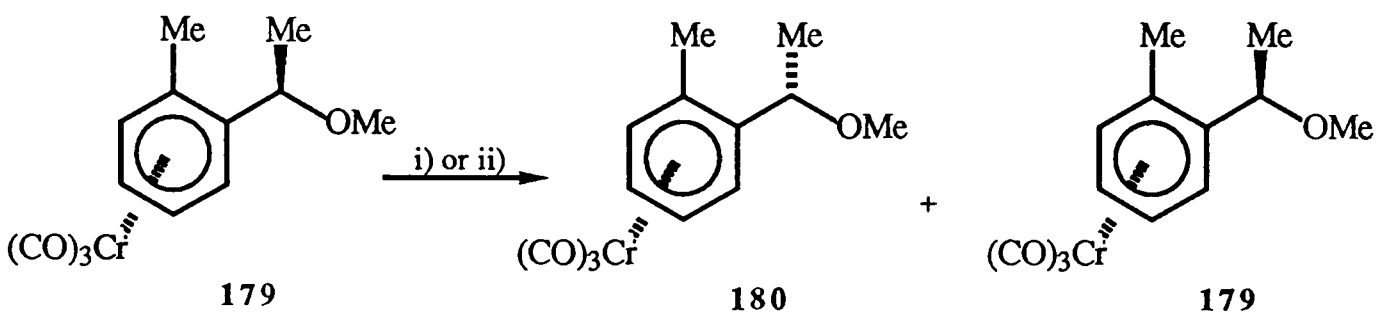
Substituted (benzyl alcohol)$Cr(CO)_3$ complexes have been observed to undergo solvolysis reactions at a rate much faster than those for their uncomplexed analogues.[64] Moreover, where such substitution reactions occur at an asymmetric centre a high degree of stereocontrol has been reported. Thus, treatment of (+)-(α-methyl benzyl alcohol)$Cr(CO)_3$ (**177**) under Ritter reaction conditions gives amide complex (-)-**178** with complete retention of configuration.[126] The reason for this property of (arene)$Cr(CO)_3$ complexes has been ascribed to anchimeric assistance by chromium to promote the ionisation of the alcohol functionality when it lies antiperiplanar to the arene-chromium axis, with concomitant inversion of configuration. The intermediate benzylic carbocation has been described as configurationally stable as there is some degree of double bond character between the ring and the benzylic carbon atoms. Owing to the steric bulk of the $Cr(CO)_3$ unit, subsequent trapping with a nucleophile may only occur from the unhindered, *exo* face with inversion giving rise to overall retention of configuration. Recent work has suggested that complete stereocontrol is only achievable when the intermediate carbocation is generated in the presence of the nucleophile. For example, exposure of a dichloromethane solution of the *ortho*-methoxy α-methyl benzyl alcohol methylether complex **179** to tetrafluoroboric acid for thirty seconds followed by addition of methanol gives a 98:2 mixture of diastereoisomers with the epimeric complex **180** predominating, suggesting that the intermediate benzylic carbocation has time to equilibrate. In stark contrast, exposure of a methanol solution of complex **179** to acid gives virtually no epimerisation to its diastereoisomer complex **180** even after four hours at room temperature.[67] Since there is an excess of the nucleophile any carbocation formation may be immediately trapped from the unhindered *exo* face and therefore the cation has insufficient lifetime to undergo equilibration. That no epimerisation of either diastereoisomer of the corresponding

meta-substituted complexes is observed indicates that the *ortho* substituent of complexes **179** or **180** possesses a stereocontrolling influence upon the preferred conformation of the intermediate benzylic carbocation.



(+)-**177** (-)-**178**

i) MeCN, H_2SO_4, 86%.



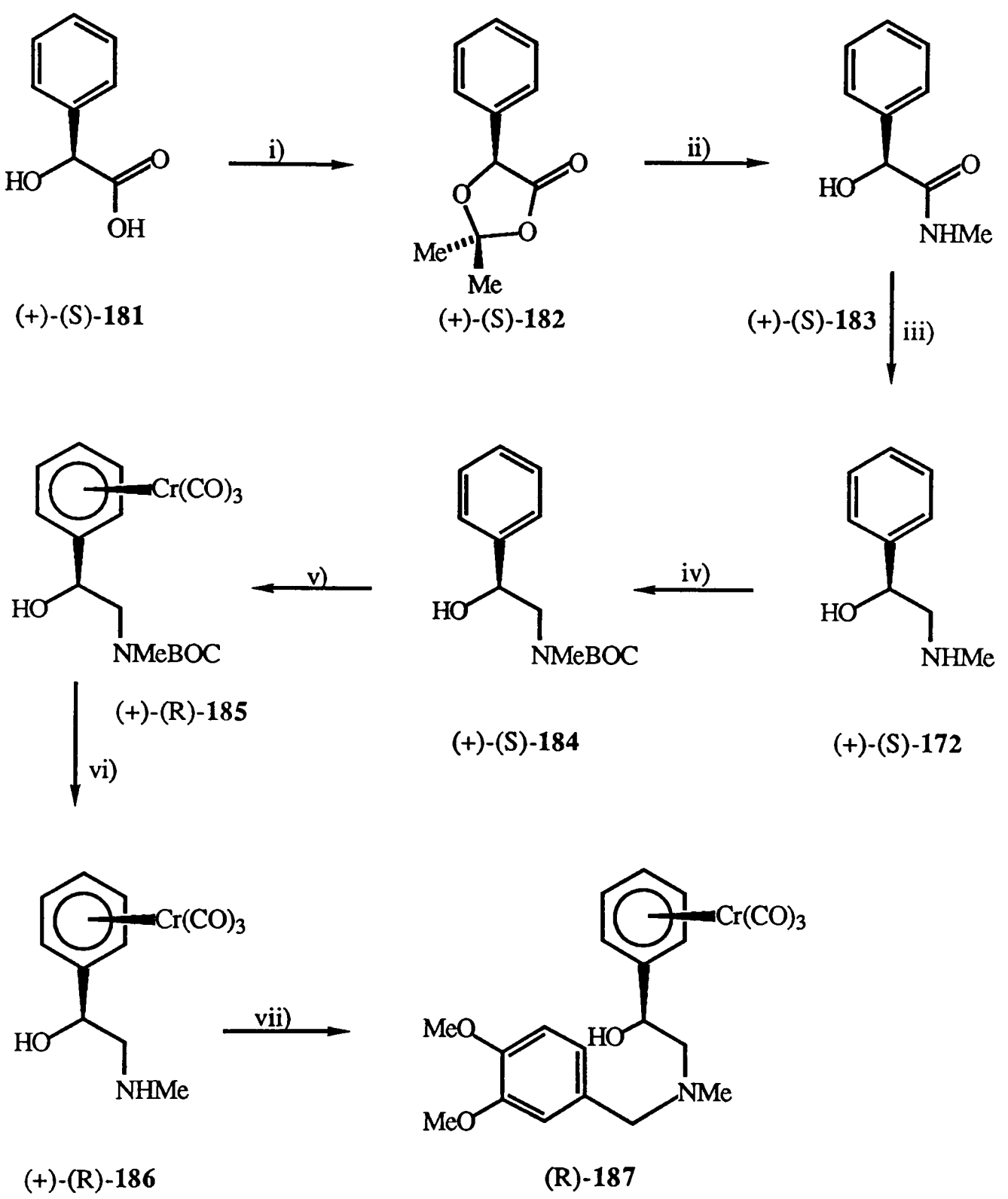
179 **180** **179**

Conditions	Ratio
i) $HBF_4.OMe_2$, CH_2Cl_2, 0°C, 0.5min, then MeOH.	98 : 2
ii) MeOH, H_2SO_4, 4h, 20°C.	4 : 96

Since $Cr(CO)_3$ stabilised benzylic carbocations have been trapped intermolecularly with electron rich arenes,[127] it was envisaged that an acid-mediated cyclisation of a homochiral (N-benzyl-1-aryl ethanolamine)$Cr(CO)_3$ complex would occur with complete retention of configuration to give, after decomplexation, a single enantiomer of a substituted 4-aryl tetrahydroisoquinoline.[128]

(+)-(S)-Mandelic acid (**181**) was condensed with acetone according to the literature procedure to give the dioxolanone derivative (+)-(S)-**182** which, upon reaction with methylamine in ethanol, gave (+)-(S)-N-methyl mandelamide (**183**). Subsequent lithium aluminium hydride reduction of amide **183** furnished (+)-(S)-halostachine (**172**) as a white solid. Separate ^1H n.m.r. spectroscopy of both (R,S)-**172** and (+)-(S)-**172** in the presence of the shift reagent (-)-(R)-**174** indicated that the reduction of (+)-(S)-**183** had occurred with no apparent racemisation, the N-methyl singlet appearing at higher field for (+)-(S)-**172**. Unfortunately this compound failed to undergo coordination to the $Cr(CO)_3$ unit under standard complexation conditions,[26] probably because the nitrogen and oxygen lone pairs of amino alcohol (+)-(S)-**172** render it a bidentate ligand towards chromium. Removal of the donor effect of the nitrogen atom of (+)-(S)-halostachine (**172**) was readily achieved by protecting the secondary amine function as the *t*-butoxycarbonyl (BOC) derivative (+)-(S)-**184**. This new

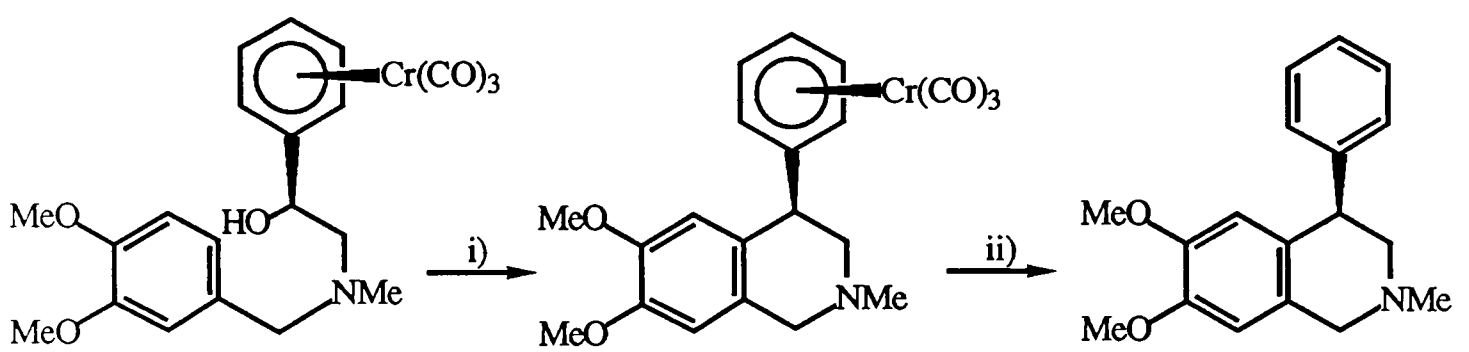
compound readily underwent coordination to the $Cr(CO)_3$ unit under standard complexation conditions to give the corresponding $Cr(CO)_3$ complex (+)-(R)-**185**† which was fully characterised. N-Deprotection of complex (+)-(R)-**185** upon exposure to neat formic acid liberated (+)-(R)-(halostachine)$Cr(CO)_3$ (**186**) as fine yellow needles. A molecular ion *m/z*=288 (M^++1) and an elemental analysis confirmed the identity of this new compound. Treatment of complex (+)-(R)-**186** with 3,4-dimethoxybenzyl bromide in dichloromethane gave the N-benzylated complex (R)-**187** as a yellow oil.



i) $(CH_3)_2CO$, H_2SO_4, <-10°C, 80%. ii) $MeNH_2$, EtOH, 2h, 97%. iii) $LiAlH_4$, THF, 92%.
iv) $(BOC)_2O$, NEt_3, CH_2Cl_2, 15.5h, 89%. v) $Cr(CO)_6$, Bu_2O/THF (10:1), 22h, 63%.
vi) HCOOH, 5h, 95%. vii) 3,4-$(MeO)_2C_6H_3CH_2Br$, CH_2Cl_2, 38.5h, 36%.

† The (S) absolute configuration of compound **184** becomes (R) upon coordination to the $Cr(CO)_3$ moiety (complex **185**) by definition.

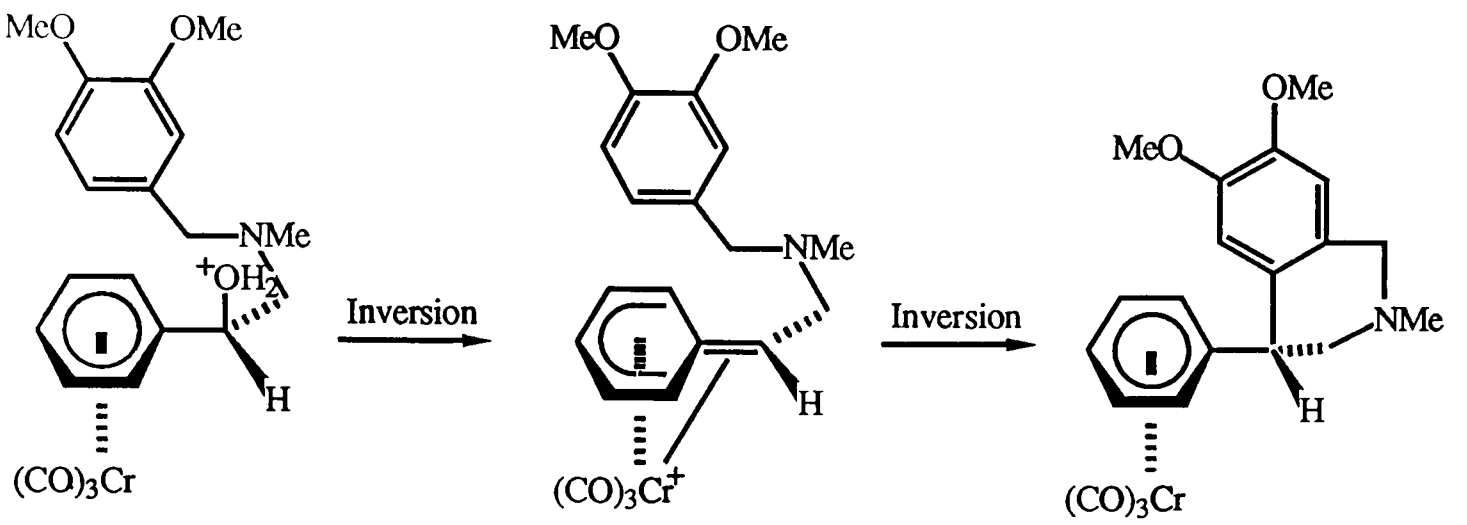
Treatment of a dichloromethane solution of complex (R)-**187** with tetrafluoroboric acid at -20°C for three days gave the tetrahydroisoquinoline complex **188** as the exclusive product which was initially assigned as (R) on the assumption of expected retention of configuration during the cyclisation. This assignment was subsequently confirmed upon decomplexation (*vide infra*). Complex **188** was fully characterised before oxidative decomplexation furnished N-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**175**) as a white powder. ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(R)-**174** established that the product was the same as the major enantiomer derived from the cyclisation of (-)-(R)-**173** and was therefore assigned as (+)-(R)-**175** (e.e. >96%), consistent with preferential retention of configuration during the cyclisation of complex (R)-**187**. Recrystallisation from hot diethylether/hexane afforded an analytically pure sample of (+)-(R)-**175** {$[\alpha]_D^{20}$ +16.9 (*c* 0.12 $CHCl_3$)} that appeared to be homochiral according to 300MHz ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(R)-**174**.



(R)-**187** (R)-**188** (+)-(R)-**175**

i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 72h, 67%. ii) Air, sunlight, 98%.

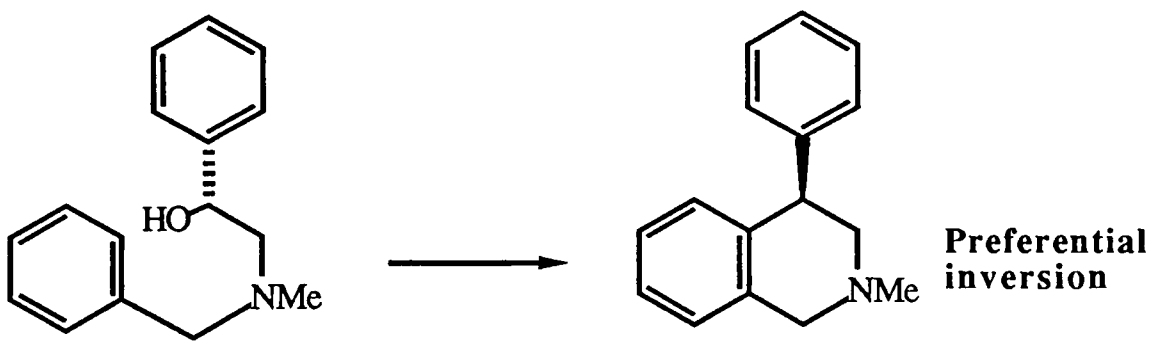
Because the uncomplexed and complexed cyclisation precursors are derived from opposite enantiomers of halostachine (**172**) and give predominantly the same enantiomer of product, (+)-(R)-**175**, then the stereochemical courses of the two reactions must be complementary, *i.e.* predominant inversion of configuration in the case of (-)-(R)-**173** but retention of configuration for complex (R)-**187**. That the cyclisation of complex (R)-**187** occurred with a high degree of stereocontrol (e.e. >96%) is consistent with the expected participation by chromium in the ionisation of the benzyl alcohol to give the cationic intermediate **189**. This intermediate is trapped intramolecularly by the internal nucleophile from the unhindered *exo* face to give (R)-**188** with overall retention of configuration.



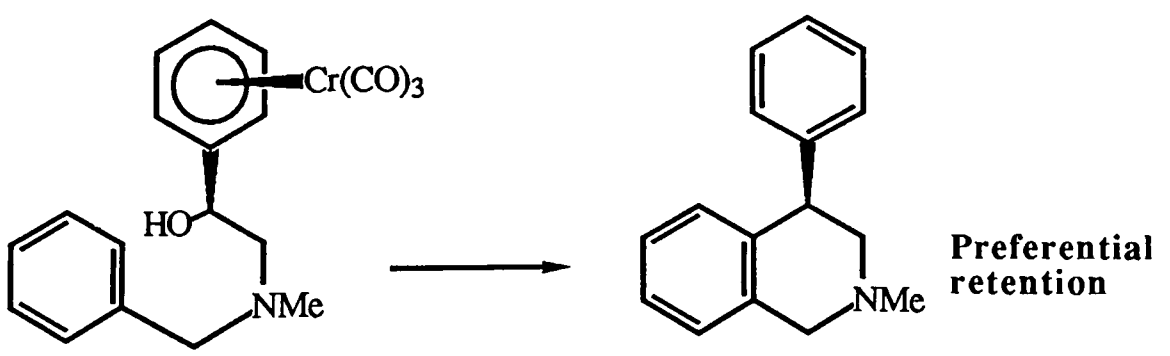
(R)-187 **189** (R)-188

Summary

The acid promoted cyclisation of (-)-(R)-N-(3,4-dimethoxybenzyl)halostachine (**173**) to tetrahydroisoquinoline **175** is observed to proceed *via* two competing mechanistic pathways. Ionisation of the protonated alcohol functionality of (-)-(R)-**173** leads to the formation of a planar benzylic carbocation which may be trapped with equal preference from either face leading to a racemate. Alternatively, the dimethoxybenzyl moiety may serve as a neighbouring group in the ionisation of the protonated hydroxyl group with concomitant inversion of configuration. The enantiomeric excess of 54% observed in the cyclisation of (-)-(R)-**173** is consistent with preferential cyclisation *via* the neighbouring group participation mechanism. Cyclisation of the (R)-**187** [the $Cr(CO)_3$ complex of (+)-(S)-**173**] is highly stereoselective, proceeding with retention of configuration under the stereocontrolling influence exerted by the $Cr(CO)_3$ unit to give (+)-(R)-**175** after decomplexation.



(-)-(R)-**173** (+)-(R)-**175**

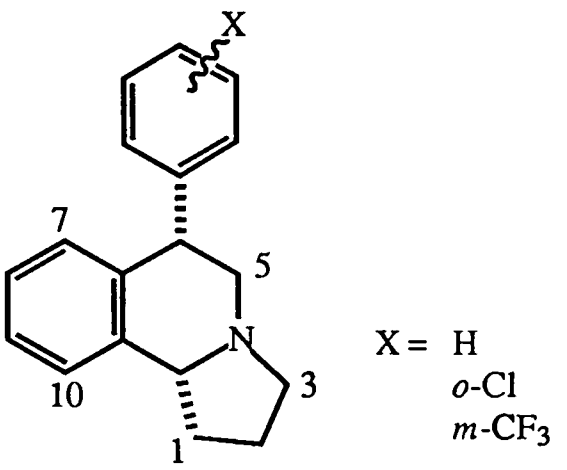


(R)-**187** (+)-(R)-**175**

B) Diastereoselectivity in the cyclisation of substituted N-benzyl phenylpropanolamines

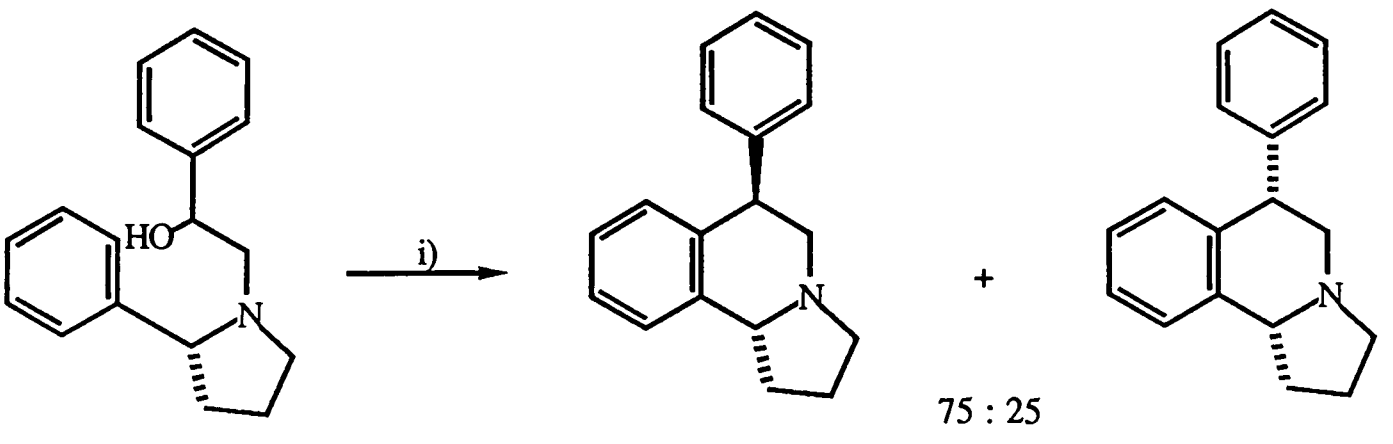
i) ***N-3,4-Dimethoxybenzyl substituents***

The biological acitivity of 6-aryl hexahydropyrrolo[2,1-*a*]isoquinolines has been shown to reside almost exclusively in the *cis* diastereoisomers (**190**). Furthermore, the (+)-(6S) enantiomers are up to three orders of magnitude more active than their corresponding (-)-(6R) optical antipodes.[110,112] Thus, asymmetric syntheses of the *cis* isomers are desirable.



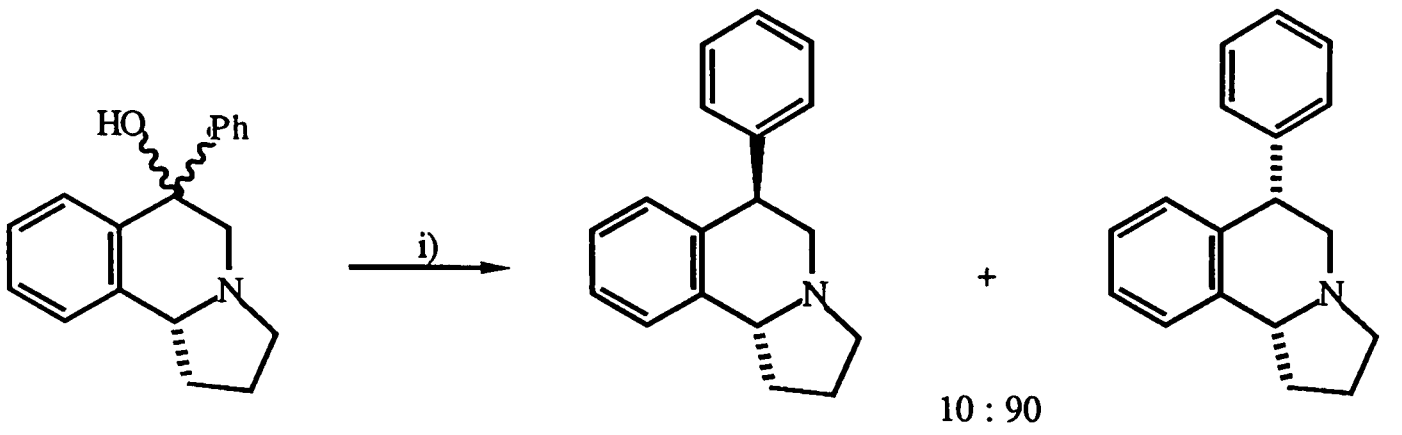
(+)-(6S)-**190**

Acid-catalysed cyclisation of the 2-arylpyrrolidine-derived amino alcohol **191** gives a diastereoisomeric mixture of products in which the *trans* isomer **192** predominates in a 75:25 ratio.[110,112] Base-induced equilibration improves the percentage of the *cis* isomer **193** but preparative h.p.l.c. is required to separate the diastereoisomers.[112] Recently, a highly stereoconvergent synthesis of **192** has been reported whereby either diastereoisomer of the 6-hydroxy derivatives **194** may be deoxygenated with a mixture of borane and trifluoroacetic acid to give mainly the *cis* isomer **193**.[116] It has also been reported that catalytic hydrogenation of the 3,4-dihydoisoquinoline **195** gives a marked preference for the formation of the *cis*-4-aryl tetrahydroisoquinoline **196**.[111]



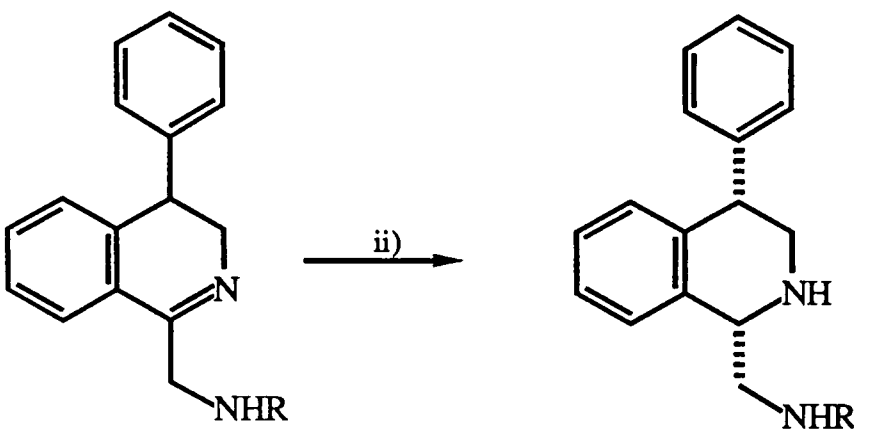
191 **192** **193**

i) Polyphosphoric acid, 4h.



194 **192** **193**

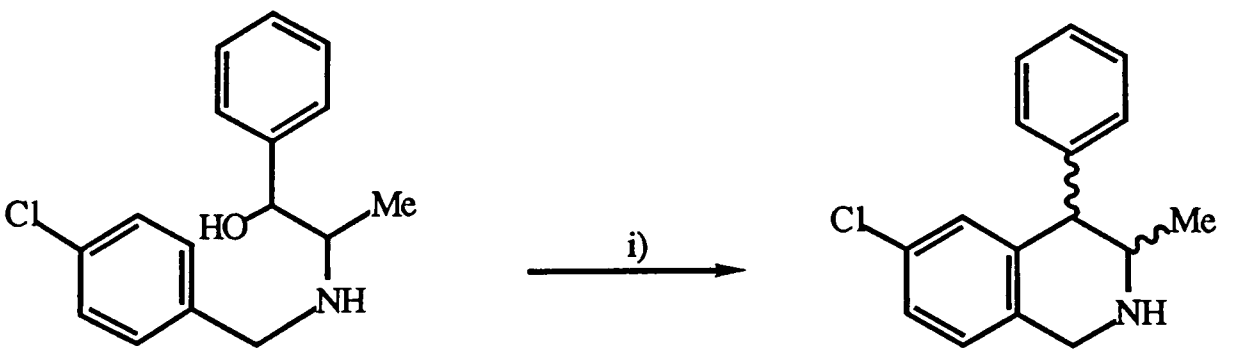
i) BH_3.THF, TFA, 5°C.



195 **196**

i) H_2 (40 psi), 10% Pd/C, MeOH, 1h.

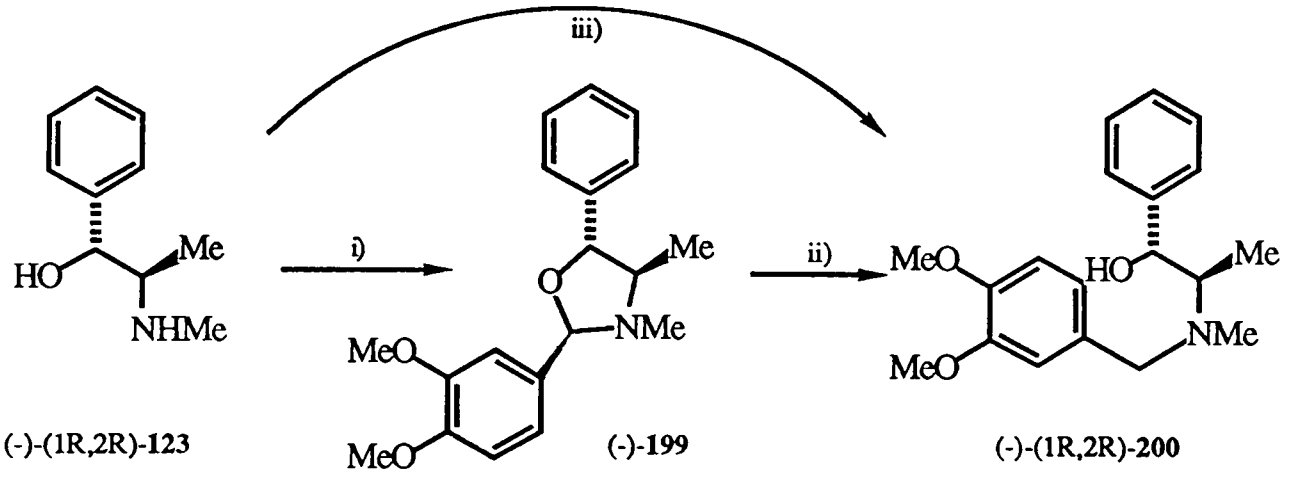
To date, there appears to be no report in the literature assessing the diastereoselectivity of the synthesis of 3-substituted-4-aryl tetrahydroisoquinolines derived from an acid-mediated cyclisation reaction.[129] A single account of work in this area concluded that insufficient resolution by ^1H n.m.r. spectroscopy did not permit an assessment of the ratio of the diastereoisomeric products **197** resulting from the cyclisation of amino alcohol **198** under acidic conditions.[117] It was thus of interest to investigate the diastereoselectivity of this cyclisation reaction and also to exploit arene chromium tricarbonyl chemistry for the control of absolute stereochemistry in the constuction of the new asymmetric centre at C4 during the cyclisation of an analogous precursor coordinated to the $Cr(CO)_3$ unit.



198 **197**

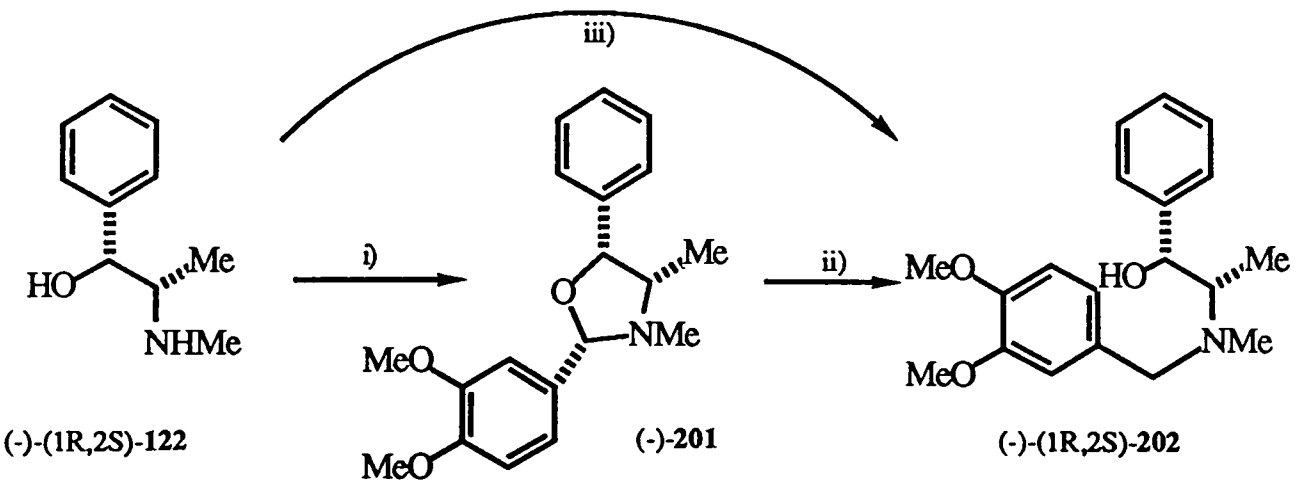
i) 48% HBr, 18h, 66%.

In order to assess the diastereoselectivity in the synthesis of 3-substituted 4-aryl tetrahydroisoquinolines it was necessary to synthesise the diastereoisomeric amino alcohols **200** and **202**. Commercially available (-)-(1R,2R)-pseudoephedrine (**123**) was condensed with 3,4-dimethoxybenzaldehyde in a Dean-Stark trap to afford the corresponding oxazolidine derivative (-)-**199** as a single enantiomer, the newly generated chiral centre being that shown as a consequence of minimising 1,3 interactions in the five-membered ring. Sodium borohydride reduction of a methanol solution of the product yielded (-)-(1R,2R)-N-(3,4-dimethoxybenzyl)pseudoephedrine (**200**) as a colourless oil in near-quantitative yield; a molecular ion m/z=316 (M^++1) and an elemental analysis confirming its identity. Alternatively, reaction of an acetonitrile solution of 3,4-dimethoxybenzyl bromide with (-)-(1R,2R)-pseudoephedrine (**123**) in the presence of potassium carbonate afforded (-)-(1R,2R)-**200** again, in excellent yield. In a similar fashion the diastereoisomer (-)-(1R,2S)-**202** was readily obtained from (-)-(1R,2S)-ephedrine (**122**) by condensation with 3,4-dimethoxybenzaldehyde to give oxazolidine (-)-**201**. Subsequent lithium aluminium hydride reduction afforded (-)-(1R,2S)-N-(3,4-dimethoxybenzyl)ephedrine (**202**) as a colourless oil that was fully characterised. Alternatively, (-)-(1R,2S)-**202** was easily synthesised from (-)-(1R,2S)-ephedrine (**122**) and 3,4-dimethoxybenzyl bromide.



(-)-(1R,2R)-**123** (-)-**199** (-)-(1R,2R)-**200**

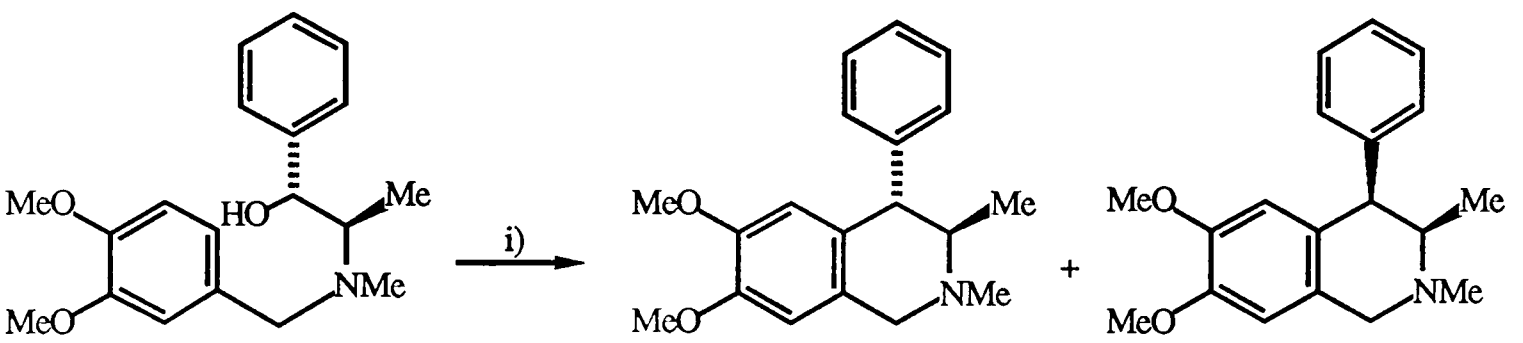
i) 3,4-$(MeO)_2C_6H_3CHO$, *p*TsOH, benzene, quantitative. ii) $NaBH_4$, MeOH, 99%.
iii) 3,4-$(MeO)_2C_6H_3CH_2Br$, K_2CO_3, MeCN, 3h, 99%.



(-)-(1R,2S)-**122** (-)-**201** (-)-(1R,2S)-**202**

i) 3,4-$(MeO)_2C_6H_3CHO$, *p*TsOH, benzene, 79%. ii) $LiAlH_4$, THF, quantitative.
iii) 3,4-$(MeO)_2C_6H_3CH_2Br$, K_2CO_3, MeCN, 3h, 89%.

Cyclisation of (-)-(1R,2R)-N-(3,4-dimethoxybenzyl)pseudoephedrine (**200**) was achieved upon exposure of a dichloromethane solution to a mixture of trifluoroacetic acid and sulphuric acid (1:1) at reflux. 300MHz ^{1}H n.m.r. spectroscopy of the crude product revealed the presence of two compounds in the ratio 88:12. The major product was assigned as *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**203**) based upon the observed H3-H4 coupling constant of 8.0Hz in comparison to those reported for several *trans*-3,4-disubstituted tetrahydroisoquinolines.[58,129] The minor component was therefore assigned as the corresponding *cis* diastereoisomer (-)-(3R,4R)-**204**. Identical treatment of (-)-(1R,2S)-N-(3,4-dimethoxybenzyl)ephedrine (**202**) gave an exclusive product that was identified as (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**203**) {$[\alpha]_D^{20}$ -13.7 (*c* 1.25 $CHCl_3$)}. A high resolution mass spectrum on the molecular ion (*m/z*=297) confirmed the identity of (-)-(3S,4R)-**203**.



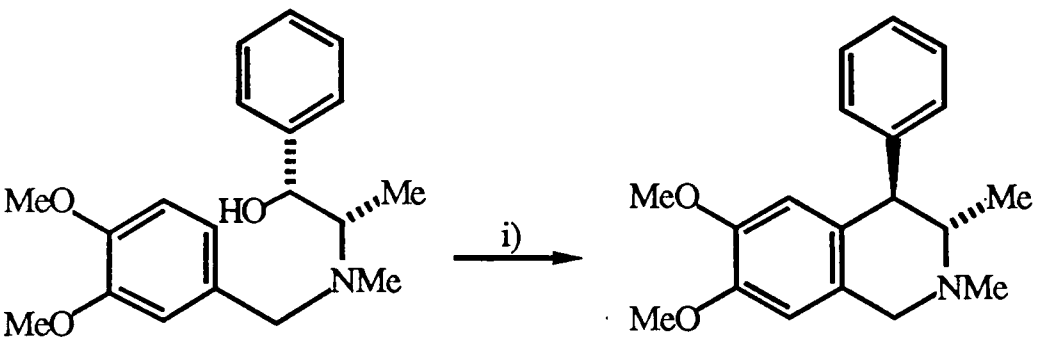
(-)-(1R,2R)-**200**

88 : 12

(+)-(3R,4S)-**203**

(-)-(3R,4R)-**204**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 0.5h, 79%.



(-)-(1R,2S)-**202**

(-)-(3S,4R)-**203**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 0.5h, 74%.

The stereoselective cyclisation of (-)-(1R,2S)-**202** to (-)-(3S,4R)-**203** with complete inversion of configuration may be rationalised by invoking the formation of a benzylic carbocation upon ionisation of the protonated benzylic hydroxyl group. The faces of the planar cationic intermediate thereby generated are rendered diastereotopic by virtue of the adjacent asymmetric centre and the internal nucleophile may discriminate between them exclusively in

favour of the *trans* diastereoisomer [(-)-(3S,4R)-**203**]. This is to be expected since the transition state leading to **203** will be of a considerably lower energy than that leading to its diastereoisomer (+)-(3S,4S)-**204** owing to the developing steric interactions between the phenyl and C3 methyl groups in the latter case. Alternatively, neighbouring group participation by the dimethoxybenzyl moiety in the ionisation of the protonated benzylic hydroxyl group would also lead to inversion of configuration. As the *trans*-tetrahydroisoquinoline (-)-**203** is formed in either case, this allows for no prediction as to the relative importance of the two mechanistic pathways. However, in the case of the cyclisation of (-)-(1R,2R)-**200** the two competing mechanisms will generate diastereoisomeric products since the neighbouring group participation mechanism would lead to *cis*-(-)-**204** by inversion of configuration at the benzylic centre, whilst the S_N1 mechanism would be expected to give the *trans* product (+)-**203**. The observed diastereoisomeric excess of 76% in favour of (+)-**203** is consistent with 88% cyclisation *via* the S_N1 mechanism along with a small amount (12%) of cyclisation *via* the neighbouring group participation mechanism.

A potentially versatile route enabling the synthesis of the $Cr(CO)_3$ complexes **207** and **208** [corresponding to the cyclisation precursors (-)-(1R,2R)-**200** and (-)-(1R,2S)-**202** respectively] along with other related complexes was to use (pseudoephedrine)$Cr(CO)_3$ (**205**) and (-)-(ephedrine)$Cr(CO)_3$ (**206**) respectively.



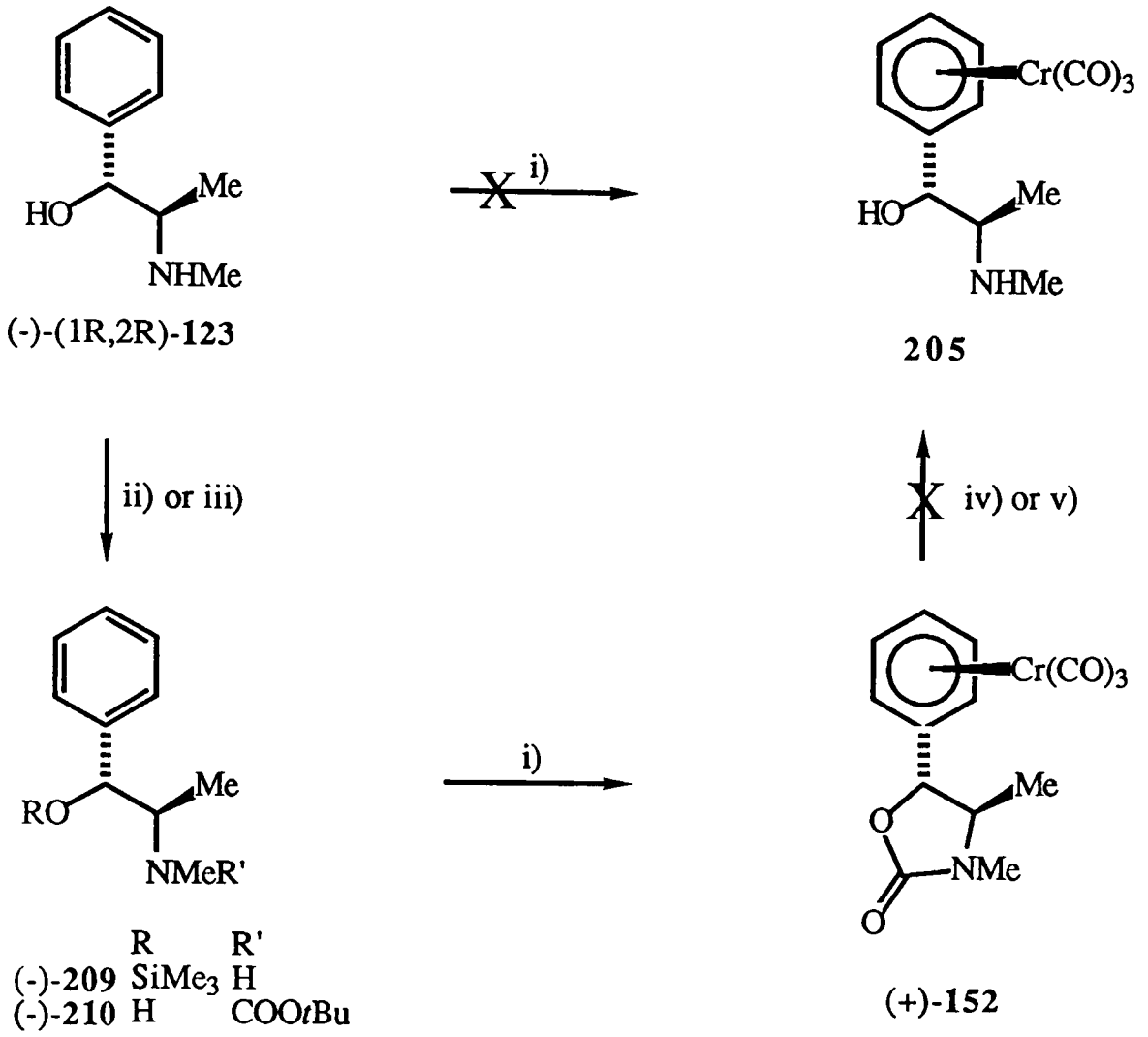
205 **207**



(-)-**206** **208**

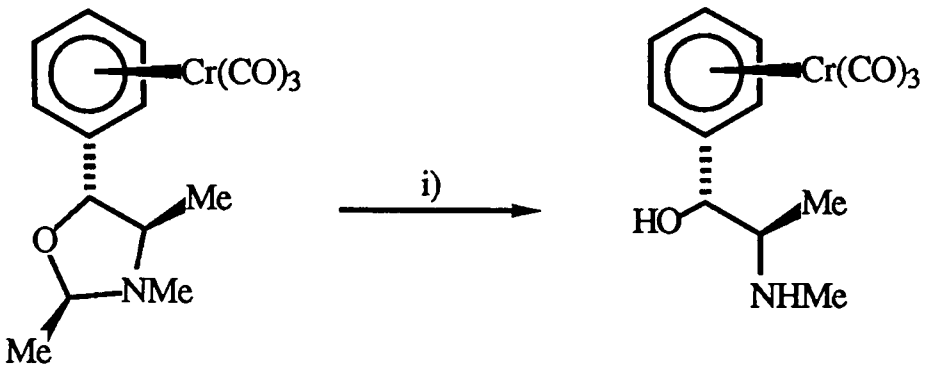
As expected, (-)-(1R,2S)-pseudoephedrine (**123**) itself failed to undergo direct coordination to the $Cr(CO)_3$ unit, presumably for the same reason as that for (+)-(S)-halostachine (**172**) (*vide supra*) and thus removal of the donor effect of either, or both, oxygen or nitrogen atoms was necessary. Protection as the trimethylsilyl derivative (-)-**209** or the oxazolidine (-)-**199** proved fruitless as all complexation attempts gave only very low yields of

the corresponding $Cr(CO)_3$ complexes, whilst prolonged thermolysis of $Cr(CO)_6$ with N-BOC derivative (-)-**210** gave only the oxazolidinone complex (+)-**152** which failed to hydrolyse under acidic conditions.



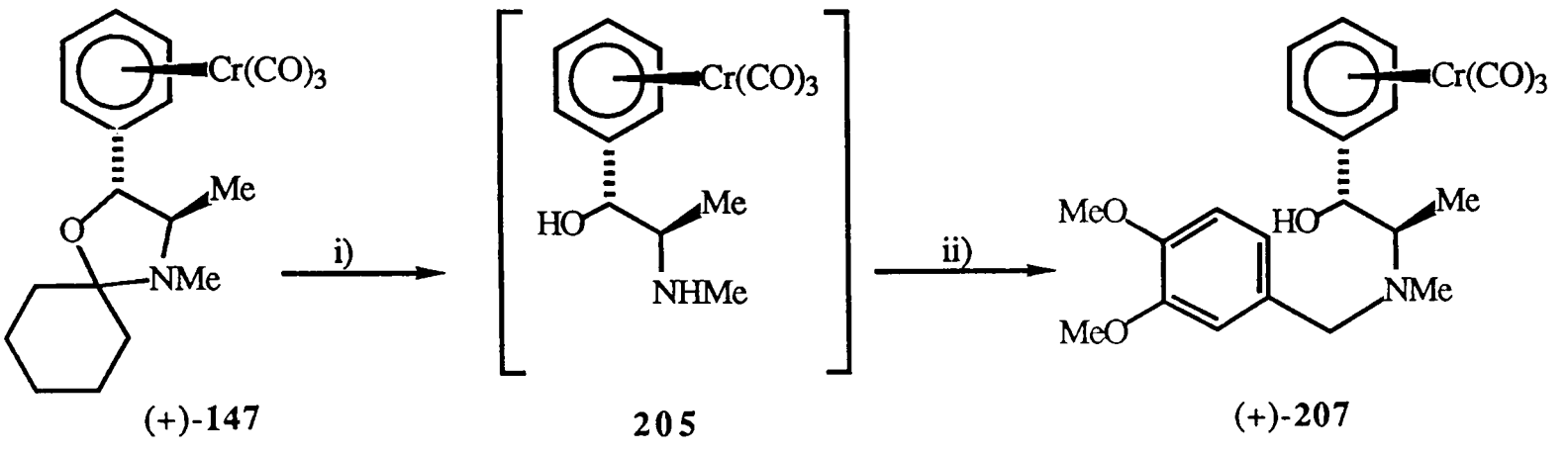
i) $Cr(CO)_6$, Bu_2O/THF (10:1). ii) $(Me_3Si)_2NH$, NEt_3, $(CH_2Cl)_2$, 40°C, 2h, quantitative.
iii) $(BOC)_2O$, NEt_3, CH_2Cl_2, 21h, 97%. iv) $HBF_4.OMe_2$, MeOH, THF, 20°C, 24h.
v) TFA, CH_2Cl_2, $NaBH_3CN$, 20°C, 14h.

Hydrolysis of the oxazolidine complex (+)-**146**, although readily achieved upon exposure of a THF/water solution to acid, was not a satisfactory route to complex **205** because complexation of the corresponding oxazolidine (+)-**142** was low yielding and not reproducible (see chapter 3). Hydrolysis of complex (+)-**147** was particularly slow at room temperature, but achieved as a THF/water solution (2:1) in the presence of *para*-toluenesulphonic acid (*ca.* one equivalent) and concentrated hydrochloric acid at reflux for fifteen hours. Under these conditions subsequent basic workup furnished a mixture of cyclohexanone and (pseudoephedrine)$Cr(CO)_3$ (**205**) which, without isolation, was alkylated with 3,4-dimethoxybenzyl bromide to afford complex (+)-**207**, the $Cr(CO)_3$ complex of pseudoephedrine derivative (-)-(1R,2R)-**200**. The ^1H n.m.r. spectrum of the product revealed a three proton aromatic multiplet at δ6.84-6.82 and a five proton aromatic multiplet shifted upfield by approximately 2ppm clearly indicating that the $Cr(CO)_3$ unit was coordinated to the non-substituted phenyl ring and that no migration of it to the more electron rich ring had occurred. A molecular ion *m/z*=452 (M^++1) and an elemental analysis confirmed the identity of (+)-**207**.



(+)-146 **205**

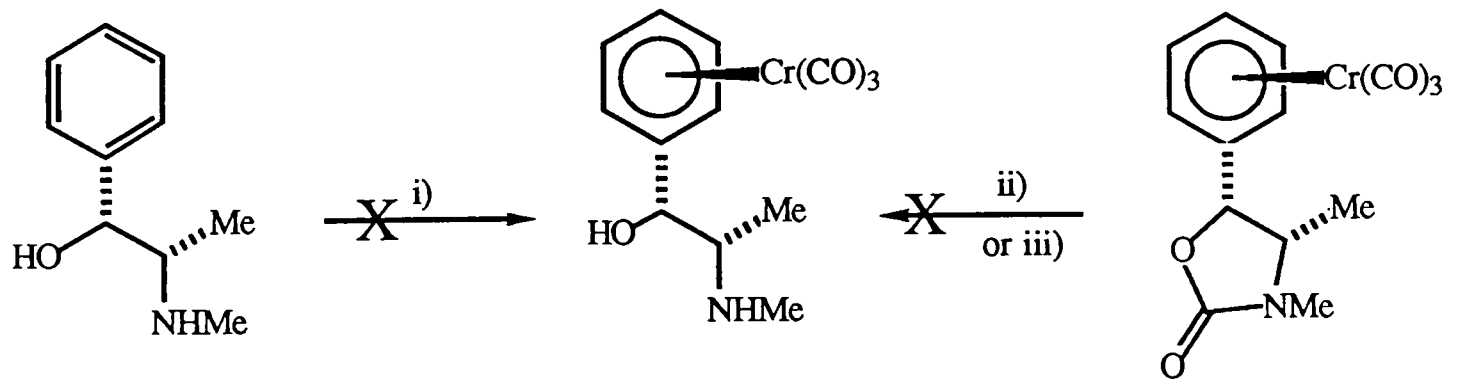
i) *p*TsOH, HCl, THF/H_2O (4:1), 20°C, 27h.



(+)-147 **205** **(+)-207**

i) *p*TsOH, HCl, THF/H_2O (2:1), 15h. ii) 3,4-$(MeO)_2C_6H_3CH_2Br$, K_2CO_3, MeCN, 3h, 61%.

(-)-(1R,2S)-Ephedrine (**122**), as expected, failed to undergo coordination to the $Cr(CO)_3$ moiety under standard conditions whilst hydrolysis of the corresponding oxazolidinone complex (-)-**151** to give (-)-(ephedrine)$Cr(CO)_3$ **206** also failed.

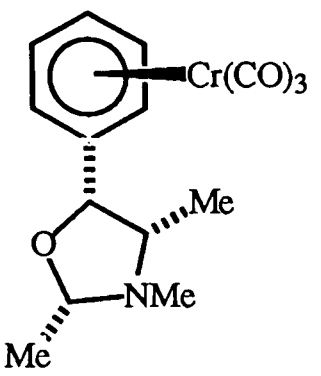


(-)-(1R,2S)-**122** (-)-**206** (-)-**151**

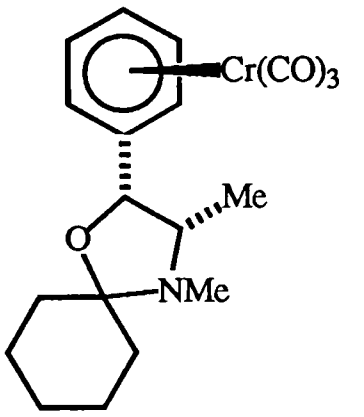
i) $Cr(CO)_6$, Bu_2O/THF (10:1). ii) $HBF_4.OMe_2$, MeOH, THF, 12h, 20°C.
iii) NaOH (5M), THF, 100°C, 19h.

Although oxazolidine complexes (+)-**144** and (+)-**145** could be hydrolysed under acidic conditions, a better route to (-)-(ephedrine)$Cr(CO)_3$ (**206**) employed the N-BOC protected amine (-)-**211**. Thus, complexation of (-)-N-BOC-ephedrine (**211**) under standard conditions afforded the corresponding $Cr(CO)_3$ complex (-)-**212** as a fluffy yellow solid which

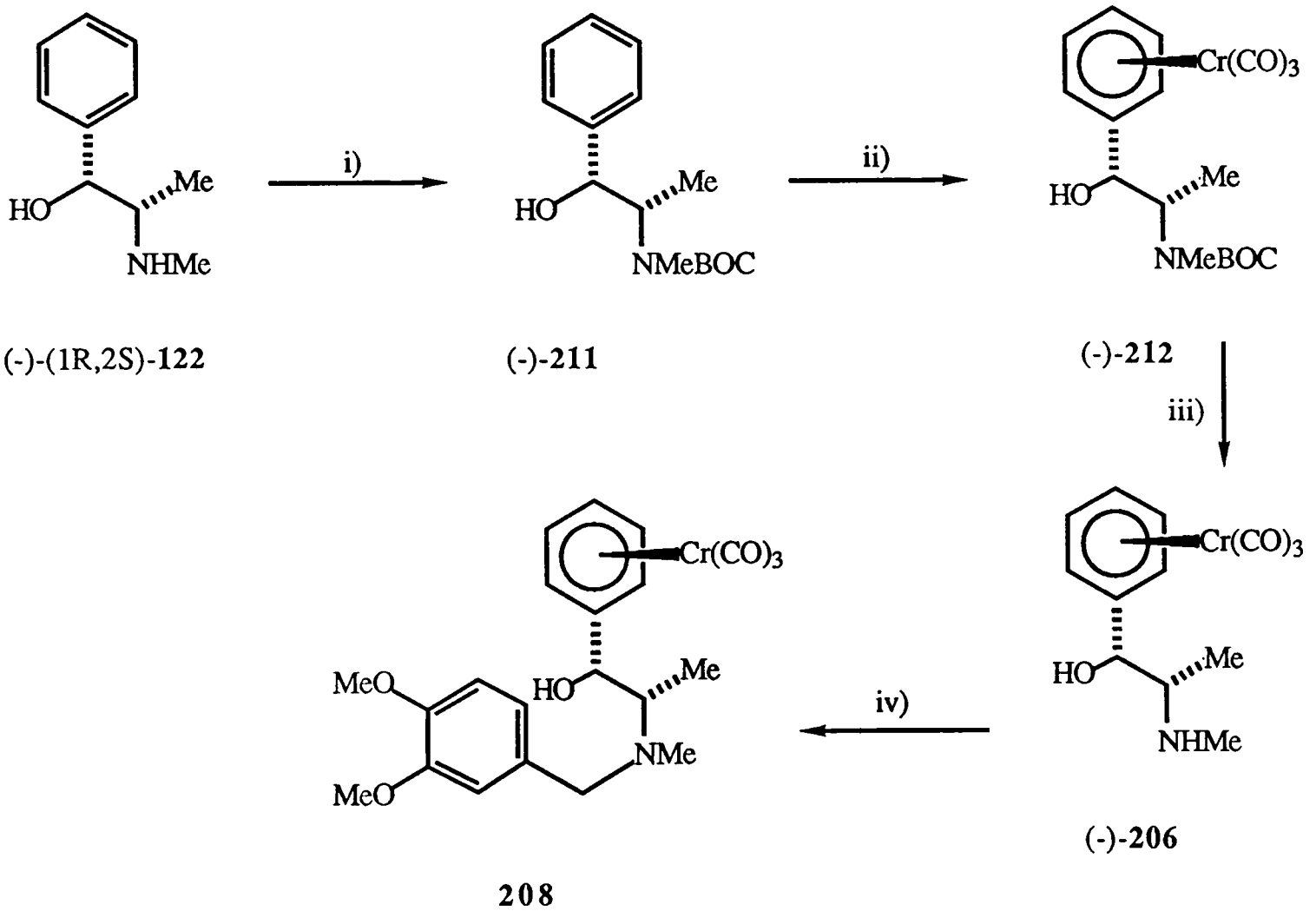
was fully characterised. Subsequent deprotection was accomplished upon exposure to neat formic acid, basic workup and recrystallisation from diethylether/hexane giving slender yellow needles of (-)-(ephedrine)$Cr(CO)_3$ (**206**). A molecular ion *m/z*=302 (M^++1) and an elemental analysis confirmed the identity of this new compound. [N-(3,4-Dimethoxybenzyl)ephedrine]$Cr(CO)_3$ (**208**), the $Cr(CO)_3$ complex of ephedrine derivative (-)-(1R,2S)-**202**, was readily obtained as a yellow oil upon alkylation of (-)-**206** with 3,4-dimethoxybenzyl bromide. The ^1H n.m.r. spectrum of the product again indicated that the $Cr(CO)_3$ unit had not undergone ring migration to the more electron rich ring.



(+)-**144**



(+)-**145**

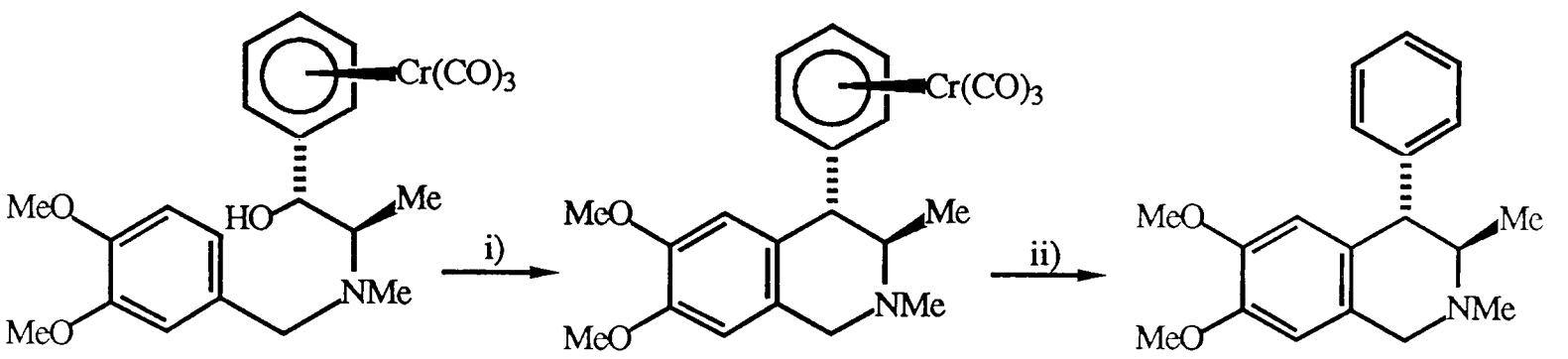


(-)-(1R,2S)-**122** (-)-**211** (-)-**212** (-)-**206** **208**

i) $(BOC)_2O$, NEt_3, CH_2Cl_2, 20°C, 60h, 85%. ii) $Cr(CO)_6$, Bu_2O/THF (10:1), 48h, 54%.
iii) HCOOH, 20°C, 4.5h, quantitative. iv) 3,4-$(MeO)_2C_6H_3CH_2Br$, K_2CO_3,MeCN, 3h, 49%.

A dichloromethane solution of (+)-[N-(3,4-dimethoxybenzyl)pseudoephedrine] $Cr(CO)_3$ (**207**) at 0°C was treated with one equivalent of tetrafluoroboric acid, but gave only

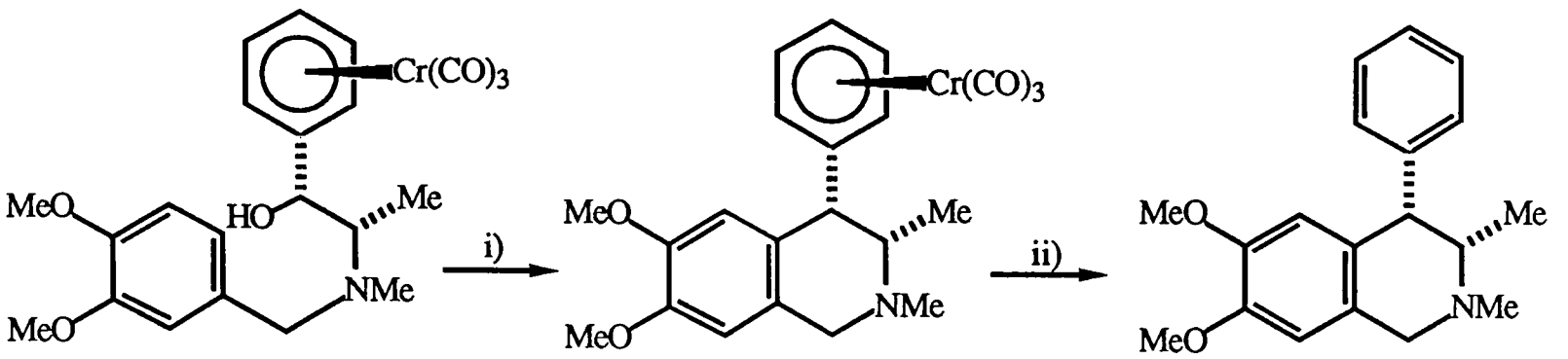
starting material upon workup. Use of excess acid gave rise to an exclusive product according to 300MHz ^{1}H n.m.r. spectroscopy of the crude material, the two low field aromatic singlets at δ6.91 and 6.56 indicating that cyclisation to a 6,7-dimethoxy tetrahydroisoquinoline complex had occurred. Furthermore, the fact that the benzylic proton signal at δ3.44 was a singlet indicated that there was no coupling between the H3 and H4 protons suggesting a torsional angle of approximately 90°.[130] Since adjacent protons in a cyclohexene ring that are *cis* orientated cannot adopt a torsional angle of more than 60° implies that the methyl and the phenyl groups of the product were *trans* orientated and thus the product was tentatively assigned as *trans*-(N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline) $Cr(CO)_3$ (**213**). Oxidative decomplexation liberated the corresponding arene, the ^{1}H n.m.r. spectrum of which was identical to that of *trans*-(3S,4R)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline [(-)-**203**]. That the optical rotation of the product {$[\alpha]_D^{20}$ +13.8 (*c* 0.24 $CHCl_3$)} was both equal and opposite to that of *trans*-(-)-**203** previously prepared [*via* the cyclisation of (-)-(1R,2S)-**202**] confirmed the assignment of *trans* stereochemistry of complex **213** and implied that the cyclisation of complex (+)-**207** had occurred stereoselectively with complete retention of configuration at the benzylic centre.



(+)-**207** **213** (+)-(3R,4S)-**203**

i) $HBF_4.OMe_2$, CH_2Cl_2, 0°C, 2h. ii) Air, sunlight, 95% for 2 steps.

Similar treatment of [N-(3,4-dimethoxybenzyl)ephedrine]$Cr(CO)_3$ (**208**) over three days below -20°C again gave a single product as a yellow solid. The ^{1}H n.m.r. spectrum of the crude product revealed two low field aromatic singlets indicative of a 6,7-dimethoxy tetrahydroisoquinoline complex and was not superimposable with that of *trans* complex **213**. A coupling constant of 3.2Hz between the H3 and H4 protons, a molecular ion *m/z*=434 (M^++1) and an elemental analysis after crystallisation from dichloromethane/hexane led to its assignment as *cis*-(+)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**214**). Decomplexation according to the standard procedure liberated the corresponding *cis*-tetrahydroisoquinoline (+)-(3S,4S)-**204** {$[\alpha]_D^{20}$ +108.1 (*c* 0.11 $CHCl_3$)}, the ^{1}H n.m.r. spectrum of which proved to be identical to that of (-)-(3R,4R)-**204** derived as the minor product from the cyclisation of (-)-(1R,2R)-**200**.



208 (+)-**214** (+)-(3S,4S)-**204**

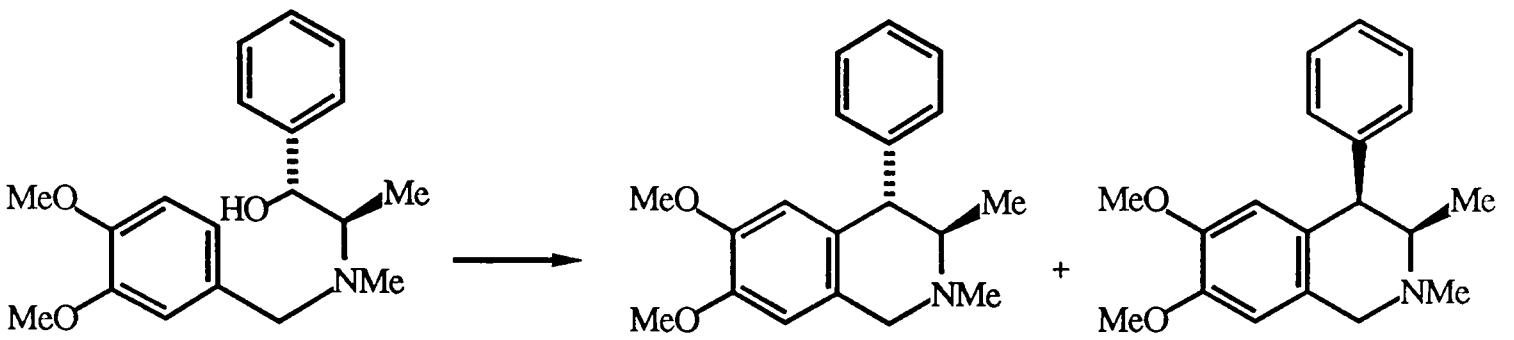
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 43h. ii) Air, sunlight, 75% for 2 steps.

The stereoselective cyclisations of complexes (+)-**207** and **208** to **213** and (+)-**214** respectively are occurring as expected, with retention of configuration at their benzylic centres. This is consistent with neighbouring group participation by the chromium in the ionisation of the protonated hydroxyl group with initial inversion of configuration. Subsequent intramolecular trapping of the resultant cation must occur from the unhindered *exo* face, again with inversion, to account for the overall retention of configuration observed during the cyclisations. That the cyclisation of (+)-**207** requires more than one equivalent of acid implies that the first equivalent of acid merely protonates the tertiary amine and that excess acid is then required to effect the cyclisation.

The cyclisations of ephedrine-derived (-)-(1R,2S)-**202** and its $Cr(CO)_3$ complex **208** are complementary; the former giving *trans*-(-)-(3S,4R)-**203** upon exposure to acid, the latter affording *cis*-(+)-(3S,4S)-**204** after decomplexation. This clearly demonstrates that the stereocontrol exerted by the $Cr(CO)_3$ moiety overrides the steric directing influence of the β-methyl substituent during the cyclisation reactions.

Summary

The cyclisations of phenylpropanolamines (-)-(1R,2R)-**200** and (-)-(1R,2S)-**202** are observed to occur by two competing mechanistic pathways. The benzylic carbocation generated upon ionisation of the protonated hydroxyl group is believed to be exclusively trapped from the face that leads to the *trans*-tetrahydroisoquinoline **203**. The neighbouring group participation mechanism is, by definition, associated with inversion of configuration and thus (-)-**202** would give *trans*-(-)-**203** whilst the diastereoisomeric precursor (-)-**200** would generate *cis*-(-)-**204**. The stereoselective cyclisation of (-)-**202** to (-)-**203** therefore allows no prediction as to the relative importance of the two pathways. However, in the case of (-)-**200**, the observed diastereoisomeric excess of 76% is consistent with cyclisation predominantly *via* the S_N1 mechanism alongside a small amount (12%) of the neighbouring group participation mechanism. Both cyclisations are rendered completely stereoselective upon coordination of the precursors to the $Cr(CO)_3$ unit since the stereocontrolling influence of the transition metal fragment overrides the inherent steric directing influence of the β-methyl substituent during the cyclisations of complexes **207** and **208**.

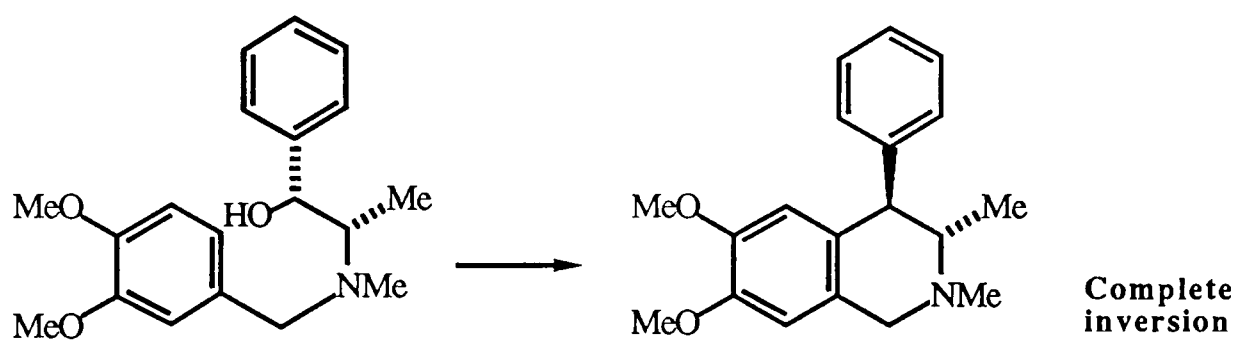


(-)-(1R,2R)-**200**

88 : 12

(+)-(3R,4S)-**203**

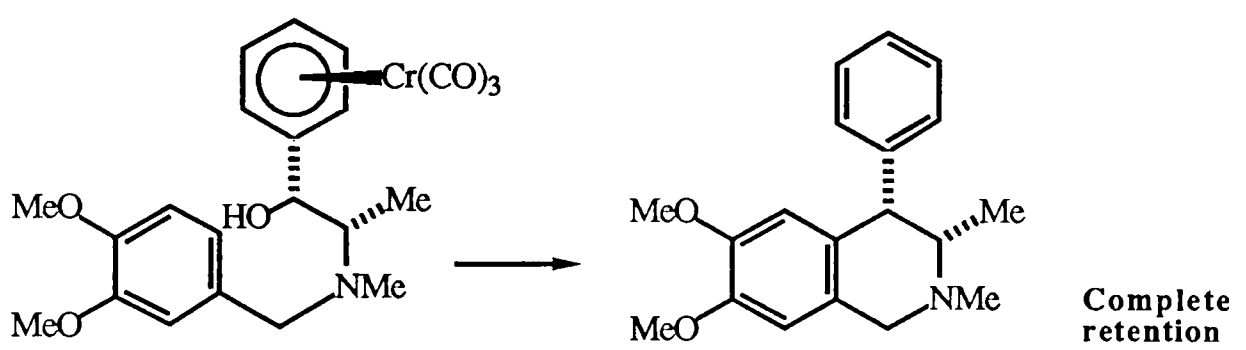
(-)-(3R,4R)-**204**



(-)-(1R,2S)-**202**

(-)-(3S,4R)-**203**

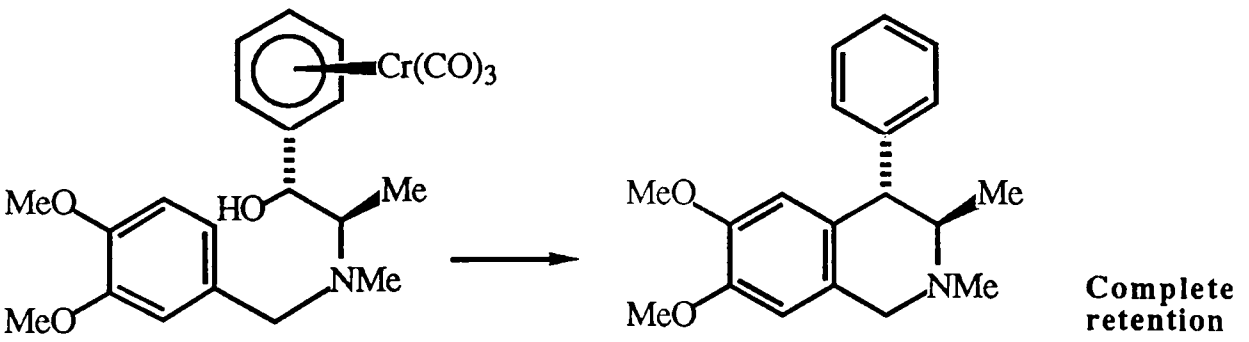
Complete inversion



208

(+)-(3S,4S)-**204**

Complete retention



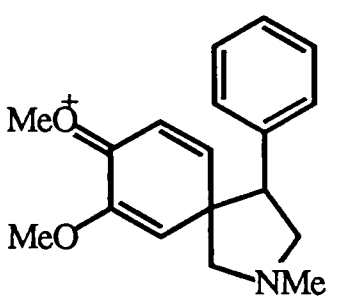
(+)-**207**

(+)-(3R,4S)-**203**

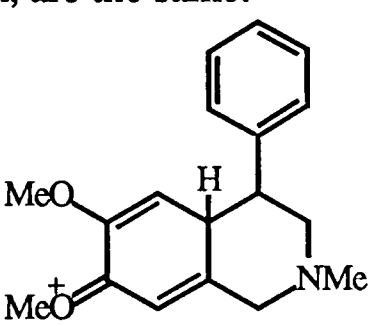
Complete retention

ii) ***N-Mono-Methoxybenzyl substituents***

It was apparent that the mesomerically electron releasing methoxyl substituents of the tetrahydroisoquinoline precursors may facilitate all of the previously described cyclisation reactions. Under the influence of the 4-methoxyl group the cyclisation may proceed *via* the spiro intermediate **215** followed by rearrangement to **216**, whilst the influence of the 3-methoxyl group may effect a direct cyclisation to **216**. Subsequent loss of a proton in either case would give rise to the observed 4-aryl tetrahydroisoquinoline. Literature precedents are available for both processes and the stereochemical consequences, inversion of configuration for the neighbouring group participation mechanism, are the same.[131]

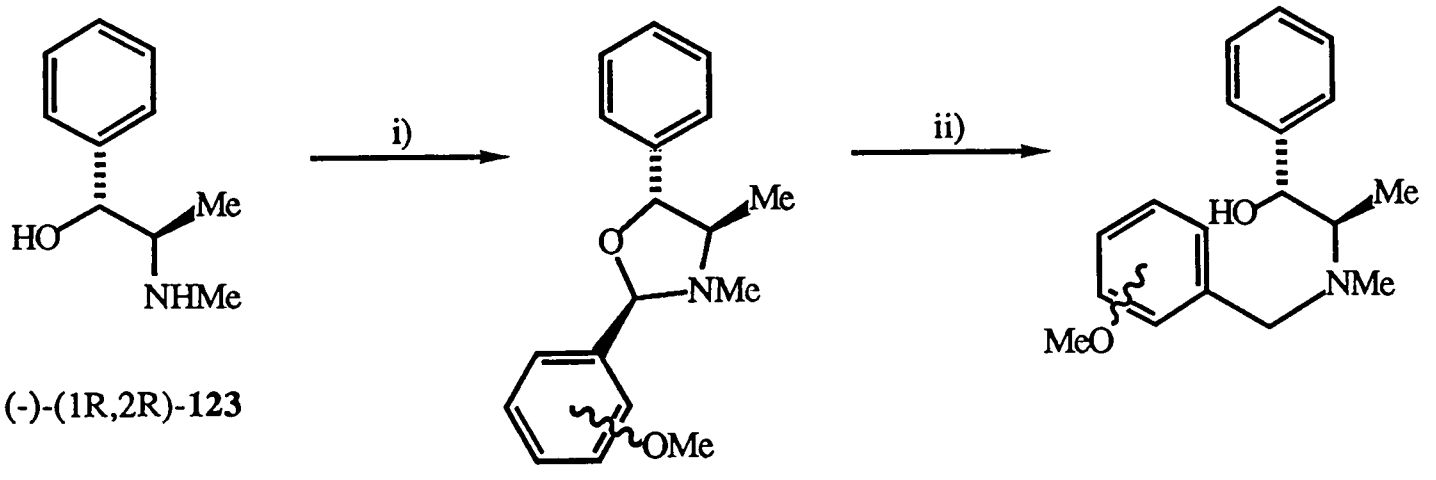


215



216

In order to elucidate the mechanistic influence of the methoxyl substituents and to explore the scope of the cyclisation reaction it was necessary to synthesise each regioisomer of (-)-(1R,2R)-N-(monomethoxybenzyl)pseudoephedrine (**217**, **218** and **219**) and their corresponding diastereoisomers **220**, **221** and **222**. Condensation of the relevant regioisomer of methoxybenzaldehyde with either (-)-(1R,2R)-pseudoephedrine (**123**) or (-)-(1R,2S)-ephedrine (**122**) gave the corresponding oxazolidines **223-228** as predominantly single diastereoisomers. In each case the product was fully characterised after any necessary purification prior to lithium aluminium hydride reduction. The amino alcohols thus produced were purified where necessary by crystallisation, distillation or column chromatography to afford the N-monomethoxybenzyl derivatives **217-222** for which satisfactory elemental analyses were obtained.

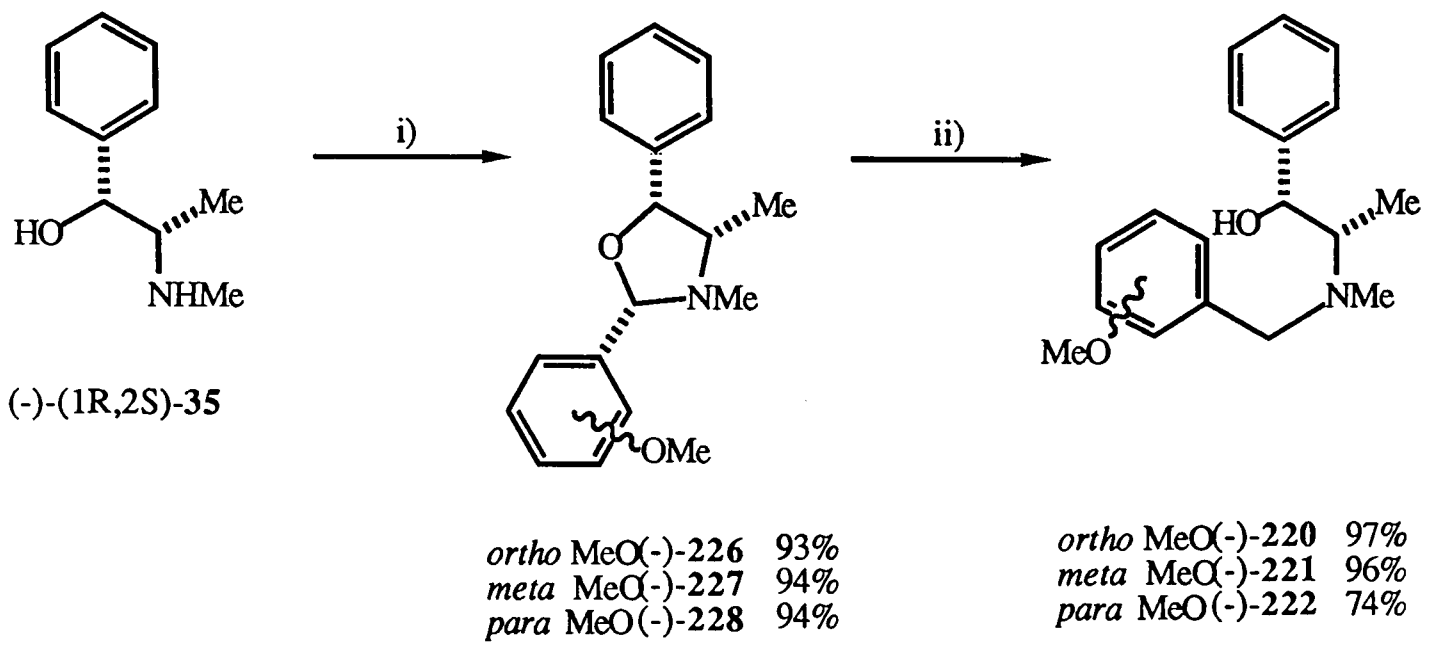


(-)-(1R,2R)-**123**

ortho MeO(-)-**223** 91%
meta MeO(-)-**224** 95%
para MeO(-)-**225** 85%

ortho MeO(-)-**217** 91%
meta MeO(-)-**218** 94%
para MeO(-)-**219** 94%

i) 2-,3- or 4-$MeOC_6H_4CHO$, *p*TsOH, benzene. ii) $LiAlH_4$, THF.



(-)-(1R,2S)-**35**

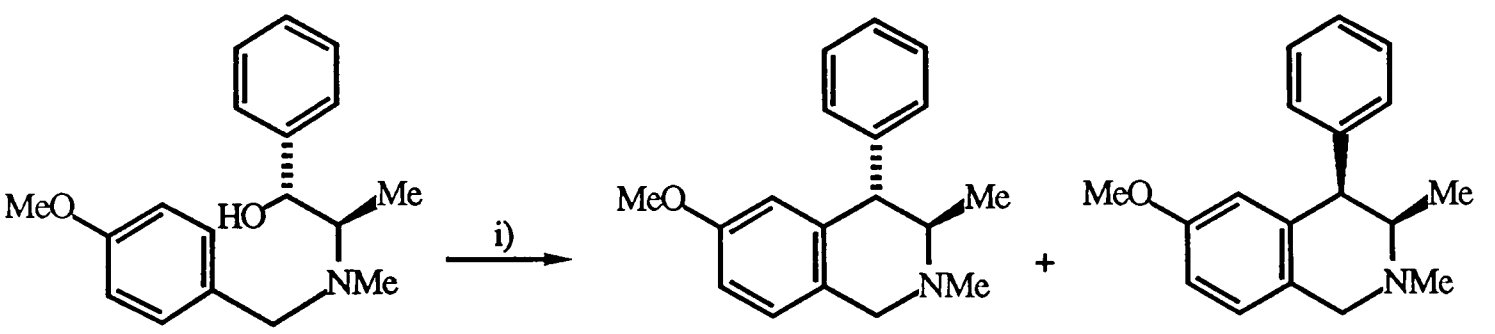
ortho MeO(-)-**226** 93%
meta MeO(-)-**227** 94%
para MeO(-)-**228** 94%

ortho MeO(-)-**220** 97%
meta MeO(-)-**221** 96%
para MeO(-)-**222** 74%

i) 2-,3- or 4-$MeOC_6H_4CHO$, *p*TsOH, benzene. ii) $LiAlH_4$, THF.

Of diagnostic relevance, it is worthy of note that the ^1H n.m.r. spectra of all of the ephedrine derivatives (**220-222** and all of those previously synthesised) contain a benzylic proton doublet with a coupling constant smaller than that exhibited for the equivalent proton in the corresponding pseudoephedrine analogues (**217-219** and others).

Treatment of a dichloromethane solution of (-)-(1R,2R)-**219** with a mixture of trifluoroacetic acid and sulphuric acid (1:1) and subsequent basic work up afforded a 93:7 mixture of the corresponding *trans*- and *cis*-tetrahydroisoquinolines (**229** and **230**) assigned on the basis of a H3-H4 coupling constant of 8.4Hz for the major product. Flash chromatography followed by crystallisation from diethylether/hexane enabled the isolation of diastereoisomerically pure *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) $\{[\alpha]_D^{20}$ +4.3 (*c* 0.52 $CHCl_3)\}$, a molecular ion *m/z*=268 (M^++1) and an elemental analysis confirming the assignment.



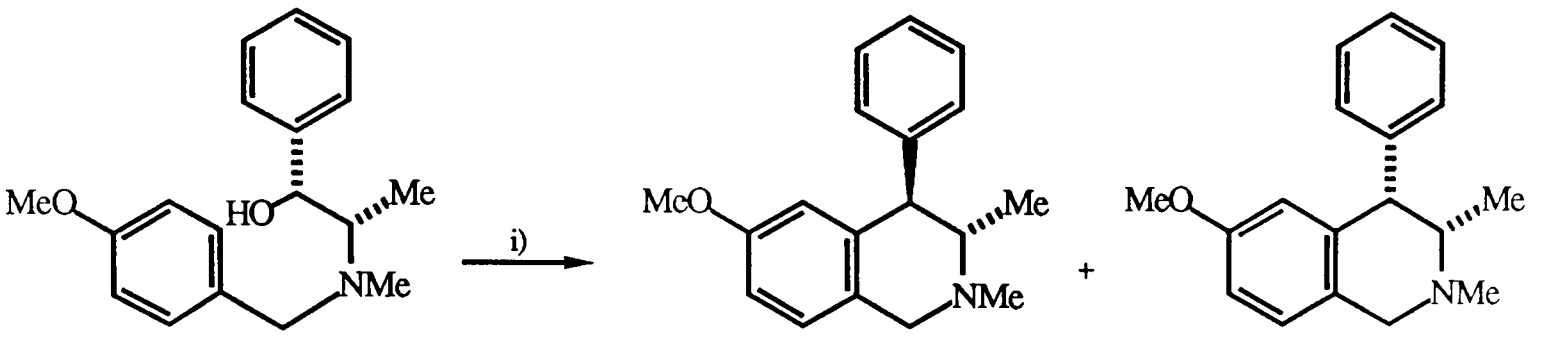
(-)-(1R,2R)-**219**

93 : 7

(+)-(3R,4S)-**229** (3R,4R)-**230**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1h, 99%.

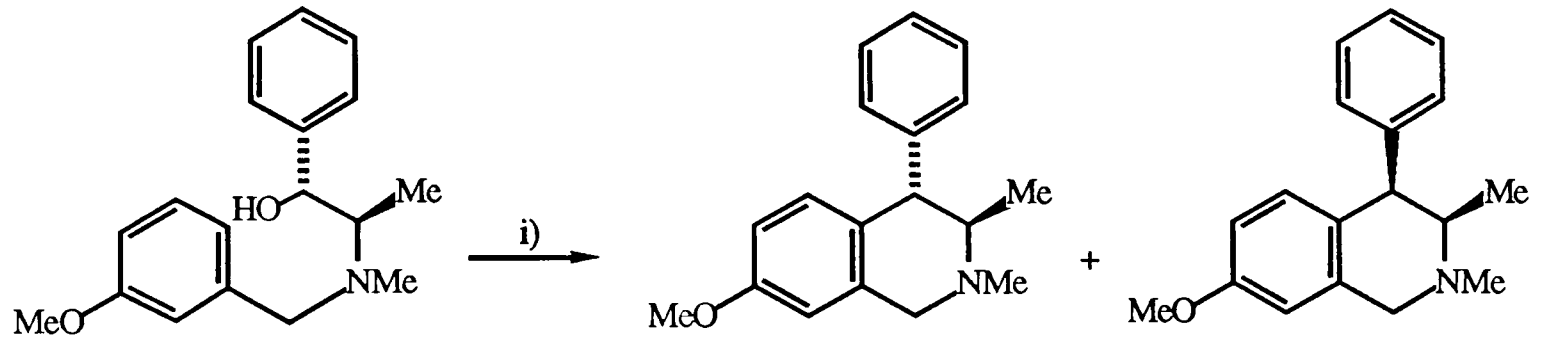
Analogous cyclisation of (-)-(1R,2S)-**222** gave a 97:3 mixture of *trans* and *cis* diastereoisomers **229** and **230**. Recrystallisation of the crude product afforded diastereoisomerically pure *trans*-(-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) $\{[\alpha]_D^{20}$ -3.8 (*c* 0.81 $CHCl_3)\}$ that was identical in all respects to (+)-**229** except in the direction of rotation of plane polarised light.



(-)-(1R,2S)-**222** 97 : 3 (-)-(3S,4R)-**229** (3S,4S)-**230**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1h, 95%.

In a similar fashion, acid-catalysed cyclisation of (-)-(1R,2R)-**218** gave a 87:13 mixture of the corresponding *trans*- and *cis*-tetrahydroisoquinolines (**231** and **232**) as a red oil which were separable by flash chromatography. Recrystallisation of the less polar, minor component yielded diastereoisomerically pure *cis*-(-)-(3R,4R)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydro-isoquinoline (**232**) {$[\alpha]_D^{20}$ -145.0 (*c* 0.06 $CHCl_3$)} as a white solid that was fully characterised. The major product was isolated as a low melting solid that was assigned as *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**231**) {$[\alpha]_D^{20}$ +44.9 (*c* 0.94 $CHCl_3$)} after full characterisation.

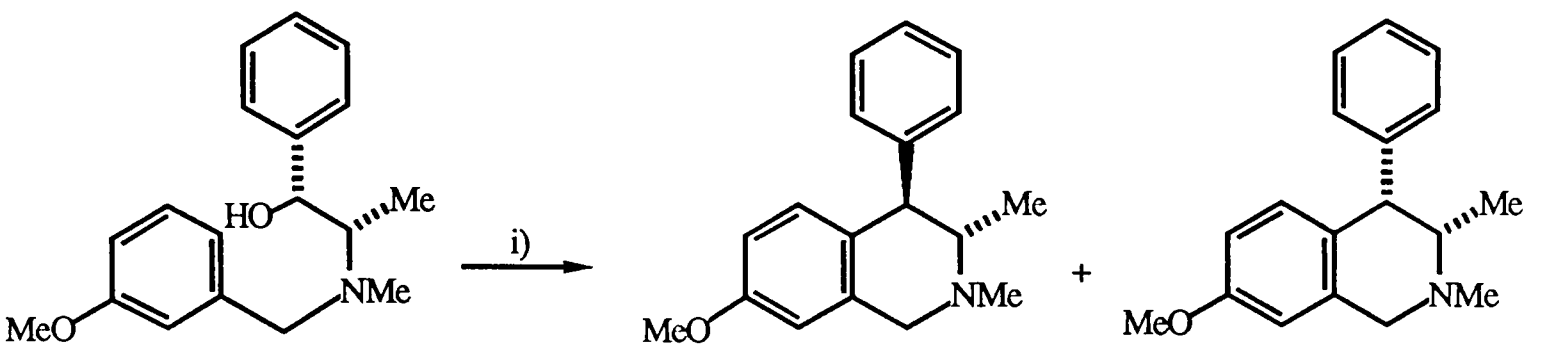


(-)-(1R,2R)-**218** 87 : 13 (+)-(3R,4S)-**231** (-)-(3R,4R)-**232**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1.75h, 45%.

Cyclisation of (-)-(1R,2S)-**221** occurred, as expected, to yield a diastereoisomeric mixture of *trans*-and *cis*-tetrahydroisoquinolines (**231** and **232**) in the ratio 93:7. Flash chromatography enabled their separation to yield *cis*-(+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**232**) {$[\alpha]_D^{20}$ +132.6 (*c* 0.05 $CHCl_3$)}as the minor component, that proved identical in all respects to (-)-**232** except in the direction of rotation of plane polarised light. The major product was isolated as a colourless oil that solidified upon standing and proved to be identical to (+)-**231** in all respects other than the sign of optical rotation and was therefore assigned as *trans*-(-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**231**) {$[\alpha]_D^{20}$ -45.4 (*c* 0.70 $CHCl_3$)}. Assignment of *cis* and *trans* stereochemistry to the diastereoisomers **232** and **231** was based initially upon analogy with the previous cyclisations and by the observed ^1H n.m.r. 3H-4H coupling constants of 4.6Hz and 8.4Hz respectively. A subsequent nOe difference spectroscopic

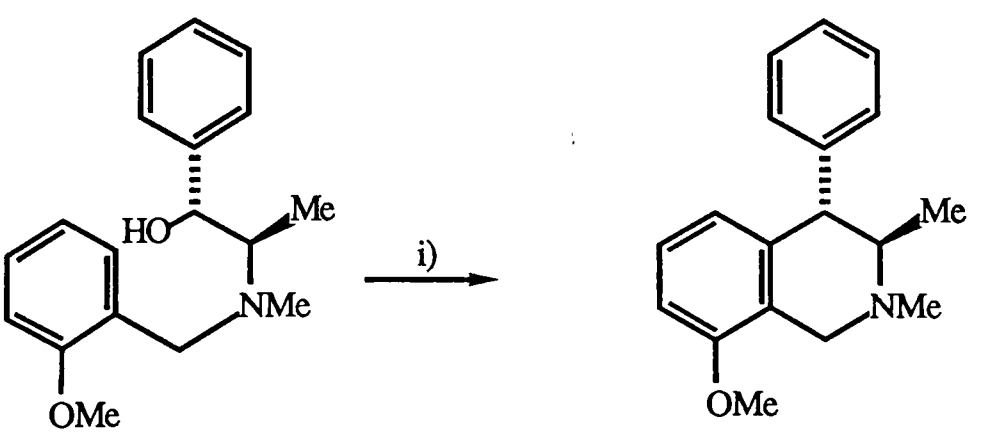
analysis performed on both diastereoisomers **231** and **232** conducted as benzene solutions at 500MHz was in agreement with this assignment. Thus, irradiation of the benzylic proton doublet at δ3.75 of *trans*-**231** gave a small enhancement of the adjacent H3 proton of just 4% whilst separate irradiation of the H4 proton of *cis*-**232** gave a much larger enhancement of 8.5% to the adjacent H3 proton.



(-)-(1R,2S)-**221** 93 : 7 (-)-(3S,4R)-**231** (+)-(3S,4S)-**232**

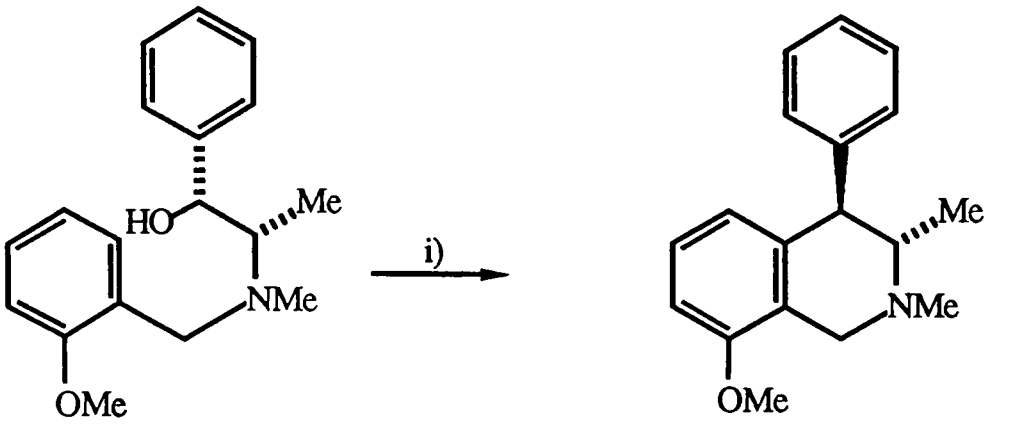
i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1.5h, 58%.

Treatment of the pseudoephedrine-derived (-)-(1R,2R)-**217** with acid gave predominantly one diastereoisomer of the corresponding *trans*-tetrahydroisoquinoline **233** (ratio 99:1) as a pale yellow solid. Recrystallisation from diethylether/hexane afforded colourless blocks of analytically pure *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) {$[\alpha]_D^{20}$ +65.5 (*c*1.10 $CHCl_3$)}. The observed H3-H4 coupling constant of 8.0Hz was consistent with *trans* stereochemistry and was subsequently confirmed by single crystal X-ray structure determination (*vide infra*). Similar cyclisation of ephedrine derivative (-)-(1R,2S)-**220** occurred stereoselectively yielding a single diastereoisomer of optically pure *trans*-tetrahydroisoquinoline **233**. Crystallisation from diethylether/hexane gave a pure sample of *trans*-(-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) {$[\alpha]_D^{20}$ -64.5 (*c* 0.51 $CHCl_3$)} for characterisation that proved to identical in all respects to previously synthesised (+)-**233** except for the direction in which it rotated plane polarised light.



(-)-(1R,2R)-**217** (+)-(3R,4S)-**233**

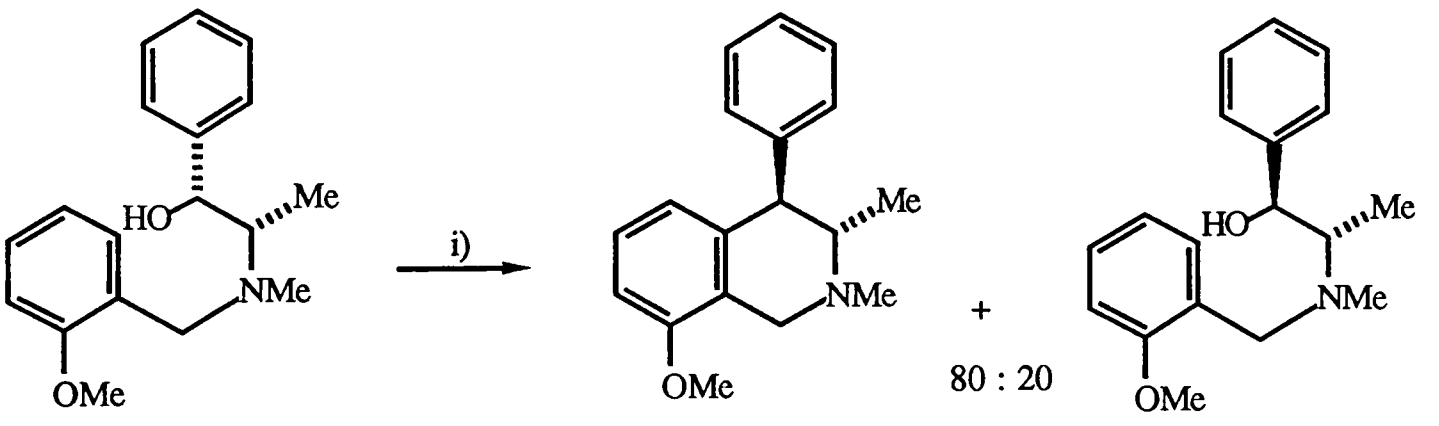
i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 5h, 91%.



(-)-(1R,2S)-**220** (-)-(3S,4R)-**233**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 2.5h, 57%.

Interestingly, in a repeat attempt to cyclise (-)-(1R,2S)-**220**, two products were isolated (ratio 4:1), the major component proving identical in all respects to *trans*-(-)-**233**. The minor component was insoluble in diethylether and was recrystallised from dichloromethane/hexane affording a white powder. An elemental analysis was consistent with an acid salt of the amine precursor and was therefore subjected to prolonged exposure to caustic soda. The ^1H n.m.r. spectrum of the amine thus liberated proved identical to that of pseudoephedrine derivative **217** but the optical rotation of the crude material was of opposite sign indicating the formation of (+)-(1S,2S)-**217** as the minor product. A single crystal X-ray structure determination of (-)-(3S,4R)-**233** conclusively proved that not only was the methoxyl substituent in the 8-position but also that the C3-methyl substituent and the C4-phenyl group were *trans* orientated in agreement with the previous assignments (Figure 5).[129]



(-)-(1R,2S)-**220** (-)-(3S,4R)-**233** (+)-(1S,2S)-**217**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 2.5h.

In every case, each isomer of the precursor **217-222** undergoes preferential cyclisation to the *trans*-tetrahydroisoquinolines (**229**, **231** and **233**) with better diastereoisomeric excesses being obtained for the ephedrine-derived precursors (**220-222**). The lack of complete selectivity in the cyclisations of the ephedrine derivatives (**220-222**) appears initially to be at discord with the stereospecific cyclisation of (N-3,4-dimethoxybenzyl)ephedrine (**202**) which was observed to give exclusive formation of the *trans*-tetrahydroisoquinoline (-)-**203**. This apparent anomaly may be rationalised by consideration of the relative nucleophilicities of

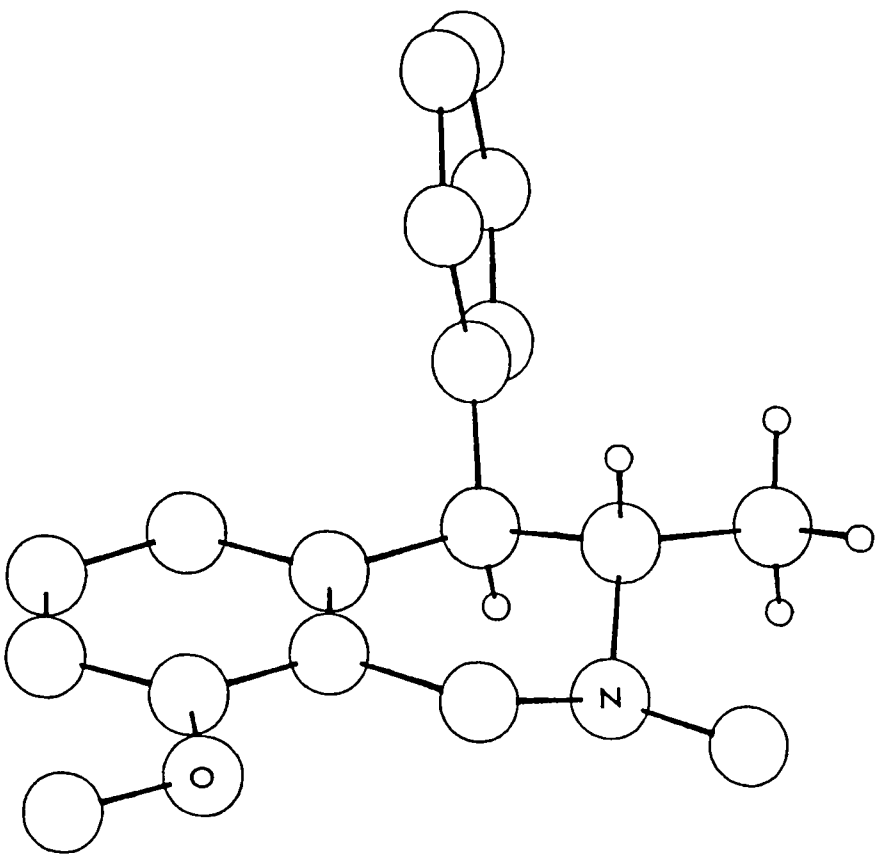
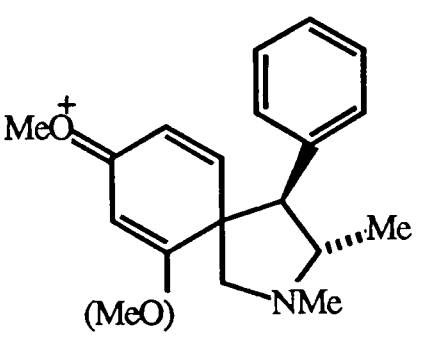


Figure 5 : X-Ray crystal structure of (-)-**233**.

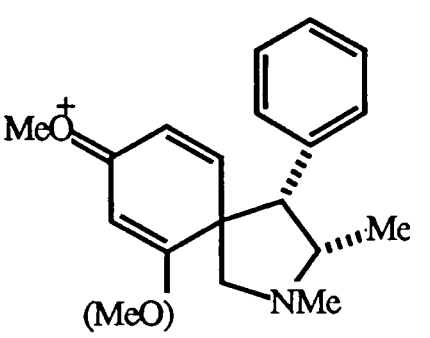
the mono-methoxybenzyl substituents of the precursors when compared to that of the dimethoxybenzyl substituent of (-)-**202**. It would be expected that in the latter case the dimethoxybenzyl group would be of decreased relative nucleophilicity owing to the presence of the second methoxyl substituent which would exert a destabilising inductive effect upon any positive charge delocalised in the aromatic ring (formed as an intermediate as a consequence of ring closure *meta* to it). The increased relative nucleophilicity of the mono-methoxybenzyl substituents of **220**-**222** renders them more reactive in the intramolecular trapping of the benzylic carbocation generated upon ionisation of the protonated hydroxyl group. This increased relative reactivity over that of the dimethoxybenzyl substituent of (-)-**202** may be expected to manifest itself in the decreased selectivity in the intramolecular ring closure thus affording both *cis*- and *trans*-tetrahydroisoquinoline products. The carbocation generated upon ionisation of the benzylic alcohol functionality possesses diastereotopic faces by virtue of the chiral centre at C3 and thus would be expected to be trapped preferentially from the least sterically hindered side leading to preferential, but not exclusive, formation of the *trans*-tetrahydroisoquinoline. However, this trapping should proceed under the influence of the methoxyl substituent since it can effectively delocalise the positive charge.

In the case of both **220** and **222** the influence of the methoxyl group would give rise to intramolecular trapping of the benzylic carbocation leading to the formation of the spiro intermediate (**234** or **235**) bearing a five-membered ring, whilst cyclisation of the cation derived from **221** would close directly to a six-membered ring (**236** or **237**) under the influence of the *meta* methoxyl substituent. In both situations, the intramolecular trapping could occur from either face of the planar carbocation to give the cyclised intermediates as a

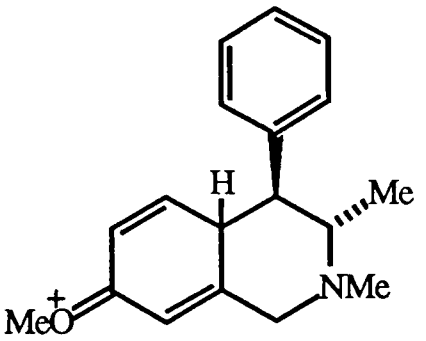
mixture of diastereoisomers. If it is assumed that the ring closure is irreversible, that the lowest diastereoisomeric excess was observed upon cyclisation of **221** (product ratio 93:7) indicates that there is a larger energy barrier to the formation of the spiro intermediate **235** (relative to the formation of **234**) than that leading to the formation of the intermediate **237** (relative to the formation of **236**). This may be interpreted as a consequence of greater steric compression of adjacent *cis* groups in a five-membered ring than that for adjacent *cis* groups in a six-membered ring. A similar argument may be used to explain the diastereoselectivities observed in the cyclisations of pseudoephedrine derivatives (**217-219**). However, in these cases consistently lower selectivities are obtained as a consequence of some degree of cyclisation *via* the neighbouring group participation mechanism which gives rise to the *cis*-tetrahydroisoquinoline products (*vide supra*).



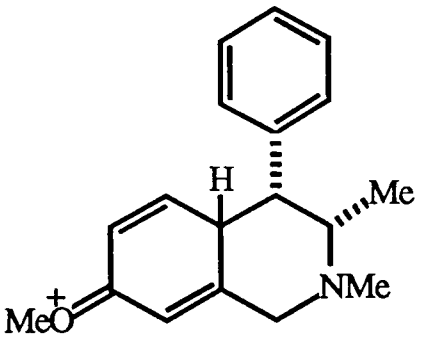
234 *trans*



235 *cis*



236 *trans*



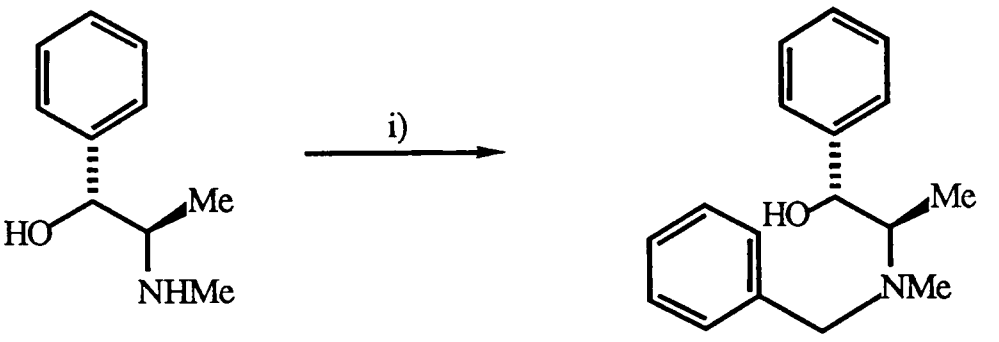
237 *cis*

For spiro intermediates **234** and **235** there is a possibility of migration of either alkyl group leading to the formation of regioisomeric products. That all of the cyclisation reactions previously described give exclusive formation of a single regioisomer of the corresponding 4-phenyl tetrahydroisoquinoline may have two mechanistic interpretations. Firstly, it is possible that the cyclisations do not proceed under the influence of the methoxyl groups at all and that direct closure to the six-membered ring occurs to give the least sterically hindered regioisomer. Alternatively, if the spiro intermediate (**234** or **235**) is invoked then the observed regiospecificity is evidence for the greater migratory aptitude of the group bearing the phenyl substituent. This fact seems reasonable as the migrating group must be able to stabilise a developing positive charge; a role which the methylamino group is unable to perform since the nitrogen atom is presumably protonated under the conditions of the reaction. The assumption

that the ring closure to intermediates **234-237** is irreversible is supported by the different diastereoisomeric excesses observed in the cyclisations of the regioisomers of **217-219** relative to the corresponding regioisomers **220-222**. In addition, that the diastereoisomeric excess observed in the cyclisation of (-)-(1R,2R)-**218** (product ratio 87:13) was almost identical to that observed for the cyclisation of (-)-(1R,2R)-**200** (product ratio 88:12) suggests that cyclisation of the latter proceeds under the influence of the *meta*-methoxyl substituent and presumably, therefore, shuts directly to a six-membered ring.

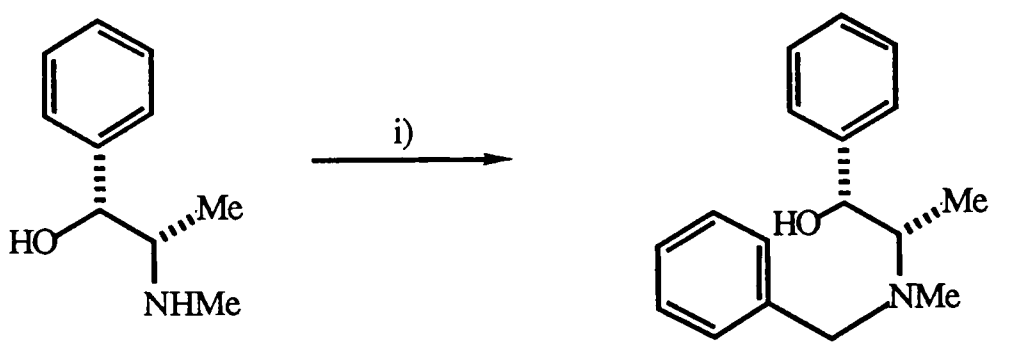
iii) *N-Benzyl substituents*

In order to elucidate the mechanism further, the precursors **238** and **239** were synthesised from (-)-(1R,2R)-pseudoephedrine (**123**) and (-)-(1R,2S)-ephedrine (**122**) respectively upon treatment with benzyl bromide.



(-)-(1R,2R)-**123** (-)-(1R,2R)-**238**

i) $PhCH_2Br$, K_2CO_3, MeCN, 3.5h, 77%.

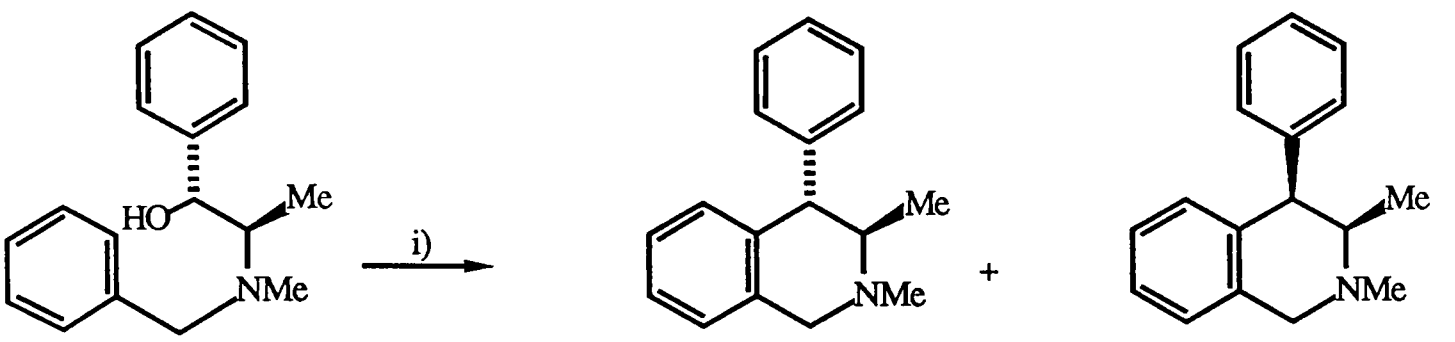


(-)-(1R,2S)-**122** (-)-(1R,2S)-**239**

i) $PhCH_2Br$, K_2CO_3, MeCN, 6h, 62%.

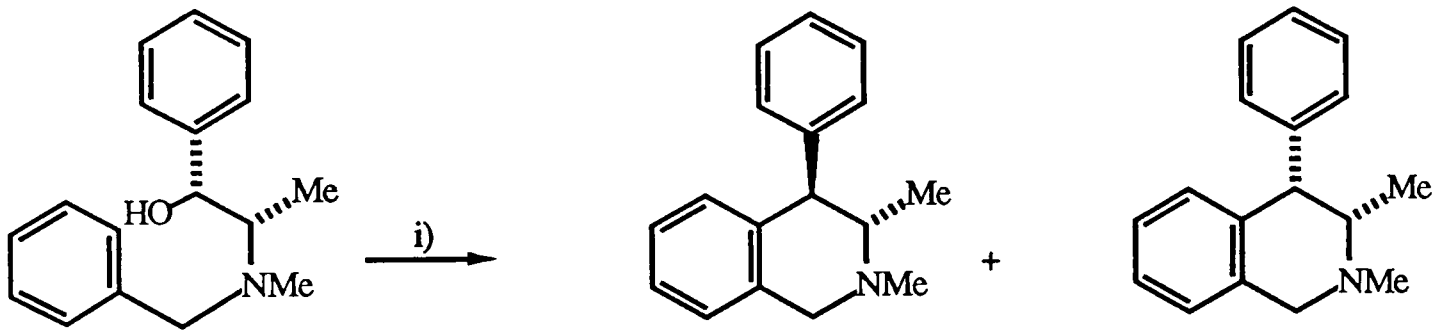
Acid-mediated cyclisation of pseudoephedrine derivative (-)-(1R,2R)-**238** occurred as before to give a mixture of the corresponding *trans*- and *cis*-tetrahydroisoquinolines (ratio 94:6) assigned on the basis of their H3-H4 coupling constants of 8.6Hz and 4.5Hz respectively. Flash chromatography enabled the isolation of *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**240**) {$[\alpha]_D^{20}$ +52.2 (*c* 0.36 $CHCl_3$)} as a colourless oil and was fully characterised. Analogous cyclisation of (-)-(1R,2S)-**239** again gave a diastereoisomeric

mixture of *trans*-and *cis*-tetrahydroisoquinolines but in the improved ratio of 97:3. The product was subjected to flash chromatography enabling the separation of the diastereoisomeric products. The less polar, minor component was assigned as *cis*-(+)-(3S,4S)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**241**) {$[\alpha]_D^{20}$ +159.5 (*c* 0.18 $CHCl_3$)} and was fully characterised after crystallisation from diethylether/hexane. The major product, isolated as a colourless oil, proved identical in all respects to (+)-**240** except for the direction in which it rotated plane polarised light and was therefore identified as *trans*-(-)-(3S,4R)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**240**) {$[\alpha]_D^{20}$ -51.0 (*c* 0.90 $CHCl_3$)}.



(-)-(1R,2R)-**238** 94 : 6 (+)-(3R,4S)-**240** (-)-(3R,4R)-**241**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 3.25h, quantitative.



(-)-(1R,2S)-**239** 97 : 3 (-)-(3S,4R)-**240** (+)-(3S,4S)-**241**

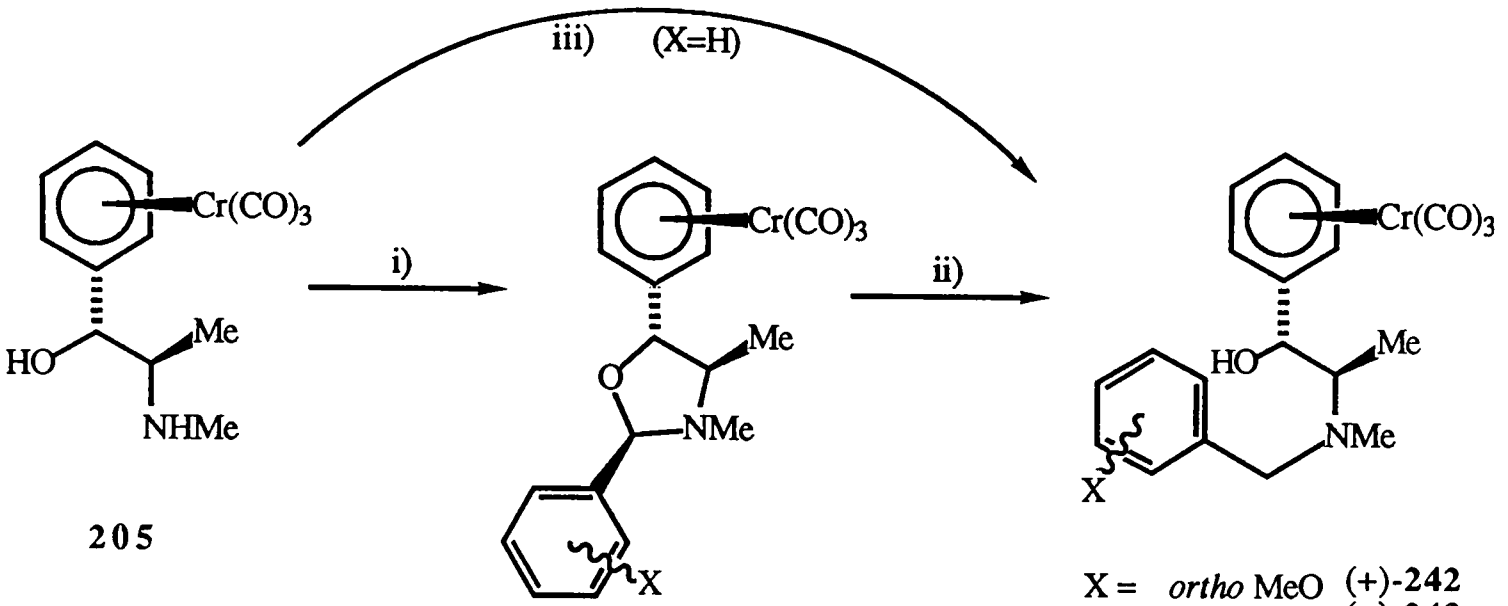
i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 5h, 97%.

The highly stereoselective conversion of (-)-(1R,2S)-**239** to (-)-(3S,4R)-**240** (ratio 97:3) is again consistent with cyclisation occurring *via* two competing mechanistic pathways. An S_N1 type process would generate a planar benzylic carbocation which would be expected to be trapped preferentially, but not exclusively, from the face that gives the *trans*-tetrahydroisoquinoline (-)-**240**. Alternatively, an S_N2 process that requires neighbouring group participation by the N-benzyl substituent would proceed with inversion of configuration to also give (-)-**240**. That both cyclisations were high yielding clearly implies that the presence of methoxyl substituents is not a prerequisite. Further, the diastereoisomeric excess observed in the cyclisation of (-)-(1R,2R)-**238** (ratio 94:6) when compared to that of (-)-(1R,2R)-**218** (ratio 87:13) reveals that the presence of a *meta*-methoxyl substituent impairs the stereoselectivity of the cyclisation reaction. Given that the influence of a *para*- or an *ortho*-

methoxyl substituent gives comparable (or better) stereocontrol [93:7 in the case of (-)-(1R,2R)-**219** and 99:1 in the case of (-)-(1R,2R)-**217**] and that the higher stereocontrol may be accounted for by invoking a spiro intermediate (*vide supra*), then it may be surmised that the cyclisation of (-)-(1R,2R)-**238** could proceed *via* a spiro intermediate thus accounting for the observed stereoselectivity (product ratio 94:6). A likely general reaction mechanism, therefore, may be as follows: initial protonation of the tertiary amine gives the corresponding quaternary ammonium salt thus preventing aziridinium ion formation. Subsequent protonation of the hydroxyl functionality renders it a good leaving group and can thus be directly displaced with inversion of configuration by the neighbouring group participation mechanism. Alternatively, subsequent ionisation generates a benzylic carbocation, the faces of which are diastereotopic. Intramolecular trapping of this cation proceeds irreversibly under the influence of any methoxyl substituents present to generate a mixture of diastereoisomeric intermediates depending upon the substitution pattern. In the absence of electron releasing groups ring closure may occur *via* a spiro intermediate (thereby associated with a higher degree of stereoselectivity) which rearranges and loses a proton to afford the observed 4-aryl tetrahydroisoquinoline product.

To assess which of these steps might be rate determining, some relative rate experiments were carried out on the ephedrine derivatives **220**-**222** and **239**. In separate experiments, an equimolar solution of **239** and either **220**, **221** or **222** in dichloromethane was treated with excess acid, aliquots of the reaction mixture removed at regular time intervals and immediately quenched with caustic soda. ^{1}H n.m.r. spectroscopy of each aliquot revealed that, in each case, the reaction was essentially complete after five minutes at room temperature indicating a very facile reaction. More importantly, the rate at which each of the precursors were consumed was identical in all cases, indicating that the presence and position of the methoxyl substituent does not control the rate of reaction. This implies that the rate determining step is either the protonation of the benzylic hydroxyl group or its subsequent ionisation.

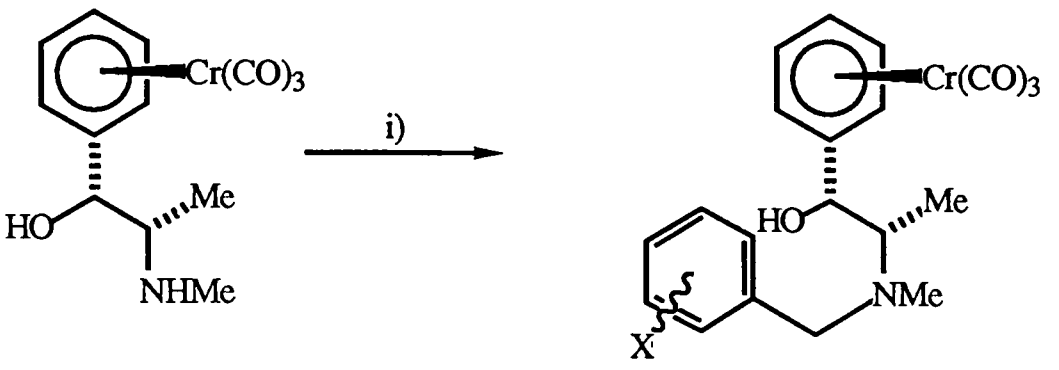
The $Cr(CO)_3$ complexes of pseudoephedrine derivatives **217**, **218** and **219** were readily obtained from (pseudoephedrine)$Cr(CO)_3$ (**205**) by condensation with the relevant isomer of methoxybenzaldehyde and subsequent reduction of the resultant oxazolidine complexes with methanolic sodium borohydride. In the case of the $Cr(CO)_3$ complex of **238** optimum reaction conditions required benzylation of an ethanol solution of complex **205** using benzyl bromide in the presence of a catalytic quantity of sodium iodide. In this manner all four pseudoephedrine-derived complexes (+)-**242**-**245** were isolated as high melting solids and fully characterised. In a similar fashion the corresponding ephedrine-derived complexes **246**-**249** were prepared from (-)-(ephedrine)$Cr(CO)_3$ (**206**) upon alkylation with the appropriately substituted benzyl bromide.



205

X = *ortho* MeO (+)-242
meta MeO (+)-243
para MeO (+)-244
H (+)-245

i) 2-,3- or 4-$MeOC_6H_4CHO$, *p*TsOH, CH_2Cl_2, sieves. ii) $NaBH_4$ or $NaBH_3CN$, MeOH.
iii) $C_6H_5CH_2Br$, $NaHCO_3$, NaI, EtOH.



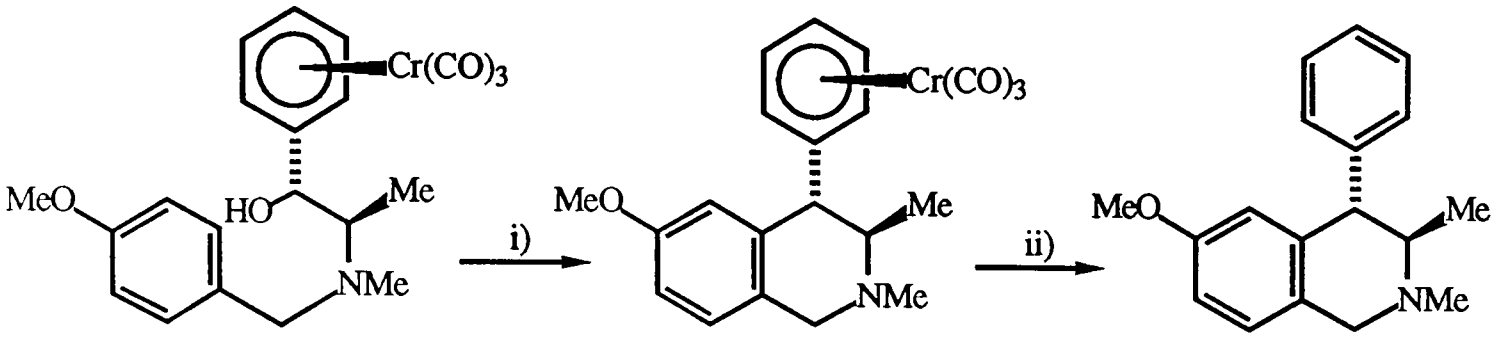
(-)-206

X = *ortho* MeO (+)-246
meta MeO 247
para MeO 248
H 249

i) 2-,3- or 4-$MeOC_6H_4CH_2Br$ or $C_6H_5CH_2Br$, $NaHCO_3$, NaI, EtOH.

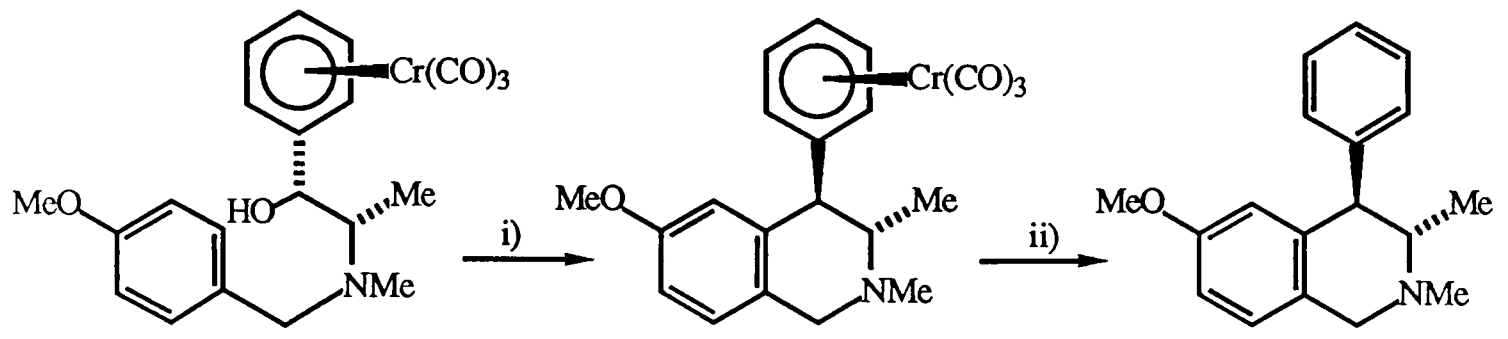
Treatment of a dichloromethane solution of (+)-**244** with excess tetrafluoroboric acid at -78°C gave no apparent colour change even after thirty minutes at this temperature. Upon warming to -20°C the solution turned deep purple in colour indicative of benzylic carbocation formation. Within twenty four hours the colour of the solution had reverted to yellow. After basic workup, ^1H n.m.r. spectroscopy of the crude product indicated the formation of a single diastereoisomer of a tetrahydroisoquinoline complex. A low field singlet with a small *meta* coupling was indicative of 6- or 7-methoxy substitution, whilst the lack of any H3-H4 coupling (evidenced by a benzylic proton singlet at δ3.45) suggested that the product was *trans*-tetrahydroisoquinoline complex **250**. Oxidative decomplexation afforded a white powder that was identical to *trans*-(+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) in all respects including mixed melting point and optical rotation {$[\alpha]_D^{20}$ +4.1 (*c* 0.41 $CHCl_3$)}. Similar acid-mediated cyclisation of complex **248** underwent the same colour changes and again gave an exclusive product, the ^1H n.m.r. spectrum of which was identical to that of complex **250**. Oxidative decomplexation gave a white powder that was identical in all respects to *trans*-(-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6-methoxy

tetrahydro-isoquinoline (**229**) including mixed melting point and optical rotation {$[\alpha]_D^{20}$ -3.9 (*c* 0.46 $CHCl_3$)}.



(+)-**244** **250** (+)-(3R,4S)-**229**

i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 24h, 95%. ii) Air, sunlight, 94%.

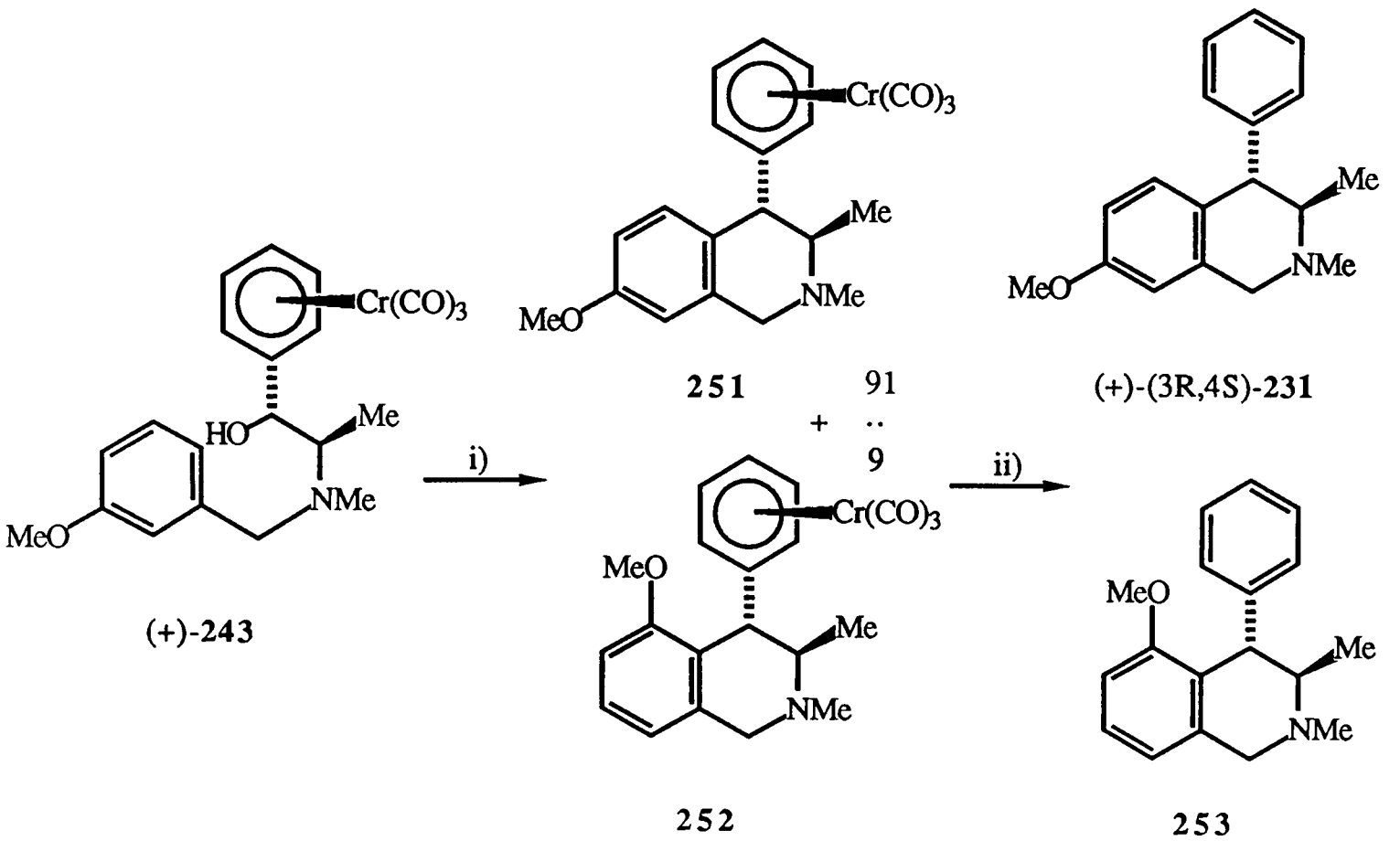


248 **250** (-)-(3S,4R)-**229**

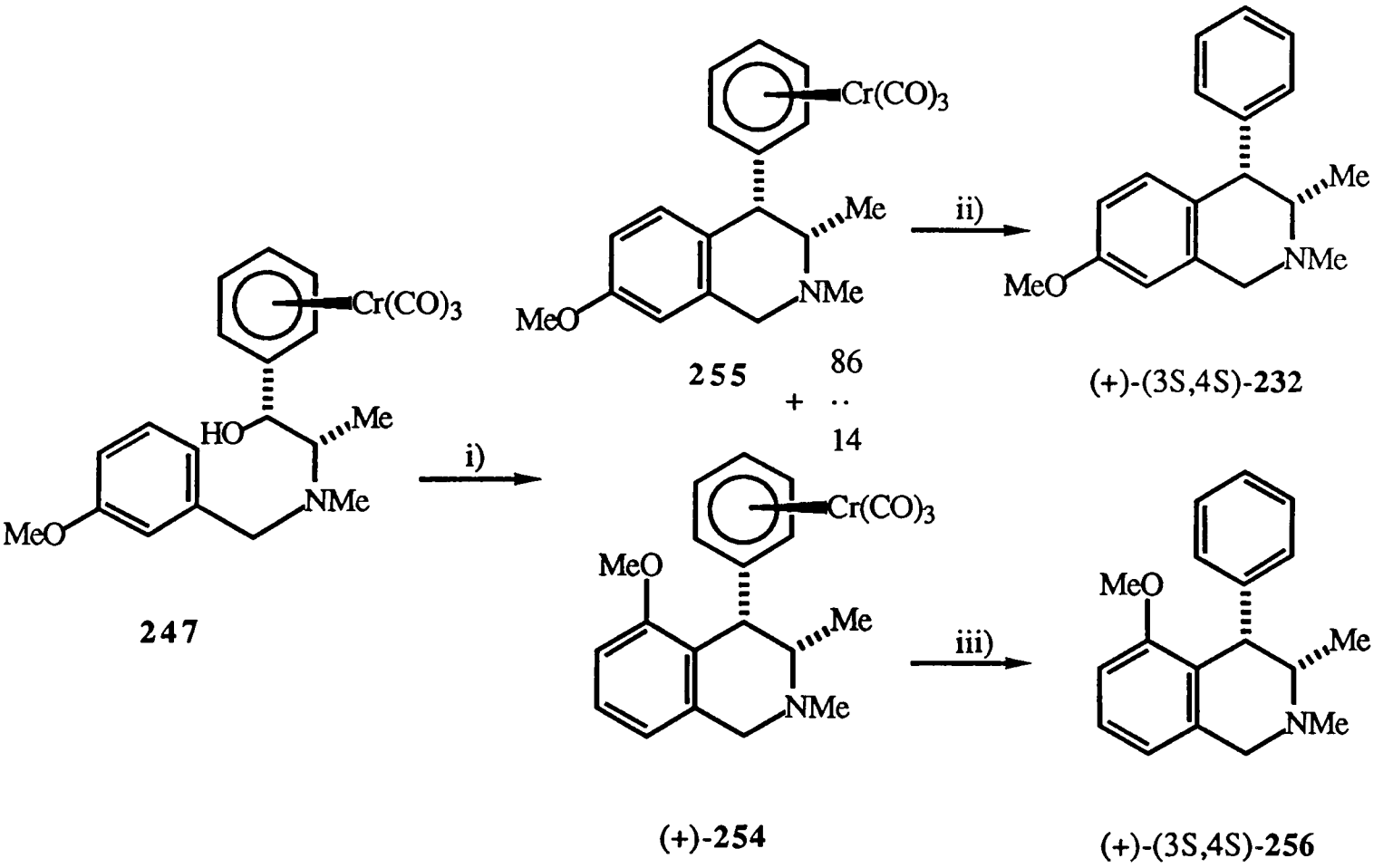
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 46h, 93%. ii) Air, sunlight, 84%.

Analogous cyclisation of (+)-**243** and subsequent decomplexation afforded a mixture of products in the ratio 91:9. The major component was identical to (+)-(3R,4S)-**231** according to ^1H n.m.r. spectroscopy, whilst the minor component was tentatively assigned by ^1H n.m.r. spectroscopy as the corresponding *trans*-5-methoxy regioisomer **253**. Similar cyclisation of ephedrine-derived complex **247** again gave two tetrahydroisoquinoline complexes but in the ratio 86:14 that were easily separable by column chromatography. The minor, less polar component was isolated as a yellow powder and exhibited a H3-H4 coupling constant of 2.6Hz in its ^1H n.m.r. spectrum which led to its assignment as *cis*-(+)-(N-methyl-3-methyl-4-phenyl-5-methoxy tetrahydroisoquinoline)$Cr(CO)_3$ (**254**). A satisfactory elemental analysis and a molecular ion *m/z*=403 supported this assignment. The major product was isolated as a yellow oil and identified as the regioisomeric *cis*-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline complex **255**. Subsequent oxidative decomplexation confirmed this assignment in that the liberated arene was identical in all respects to (+)-(3S,4S)-**232** previously synthesised including melting point and optical rotation {$[\alpha]_D^{20}$ +143.6 (*c* 0.11 $CHCl_3$)}. Decomplexation of complex (+)-**254** afforded previously unreported *cis*-(+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-5-methoxy tetrahydroisoquinoline (**256**) {$[\alpha]_D^{20}$ +231.9 (*c* 0.11 $CHCl_3$)} as white needles after

recrystallisation from diethylether/hexane. A satisfactory elemental analysis and a molecular ion *m/z*=267 were both consistent with this assignment.



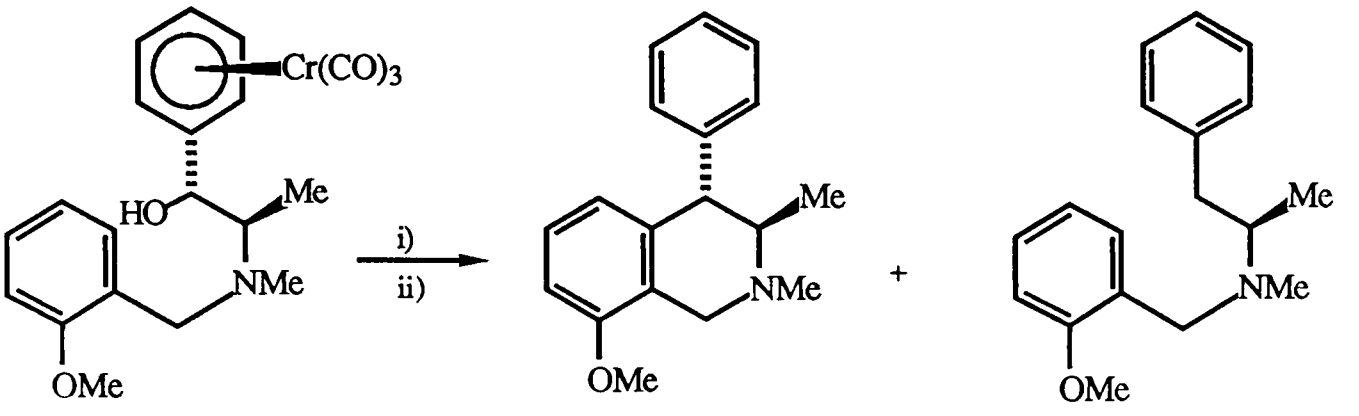
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 42h, 74%. ii) Air, sunlight, 88%.



i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 142h, 58%. ii) Air, sunlight, 82%. iii) Air, sunlight, quantitative.

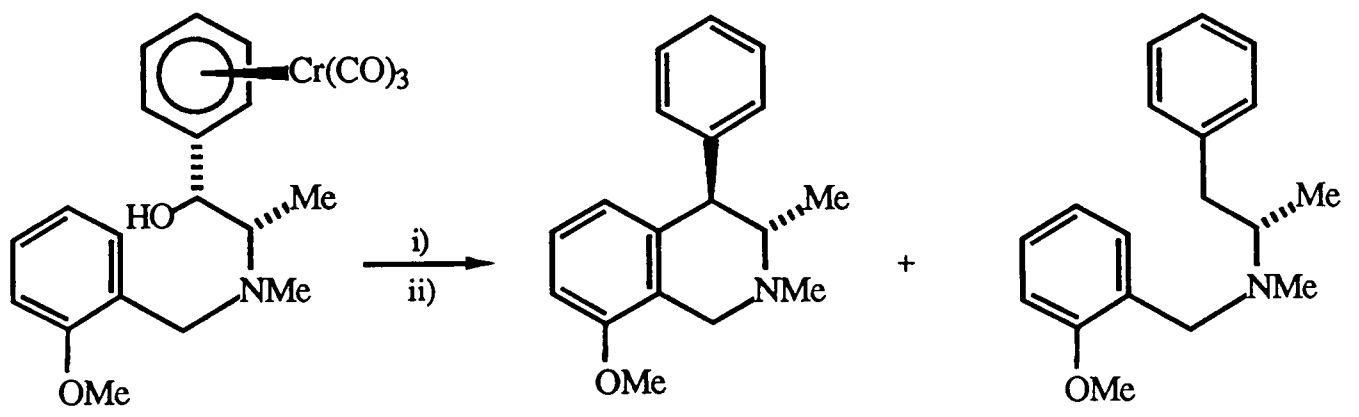
Cyclisation of (+)-**242** and subsequent decomplexation afforded an equimolar mixture of (+)-(3R,4S)-**233** and the reduced compound **257** contaminated with small quantities of

unidentified compounds. Crystallisation from diethylether/hexane afforded pure (+)-(3R,4S)-**233** that proved identical in all respects to that of the previously synthesised material {$[\alpha]_D^{21}$ +65.2 (*c* 0.02 $CHCl_3$)} including both optical rotation and melting point. Similar cyclisation of (+)-**246** and decomplexation gave a mixture of (-)-(3S,4R)-**233** and the fully reduced compound **257**. Crystallisation enabled the isolation of pure (-)-(3S,4R)-**233** as white blocks that were identical in all respects to the sample previously prepared {$[\alpha]_D^{20}$ -66.4 (*c* 0.11 $CHCl_3$)}. An authentic sample of (+)-**257**, synthesised from N-(methyl)amphetamine and 2-methoxybenzyl bromide, proved identical to compound **257** produced during the cyclisations of **242** and **246**.



(+)-**242** (+)-(3R,4S)-**233** (-)-**257**

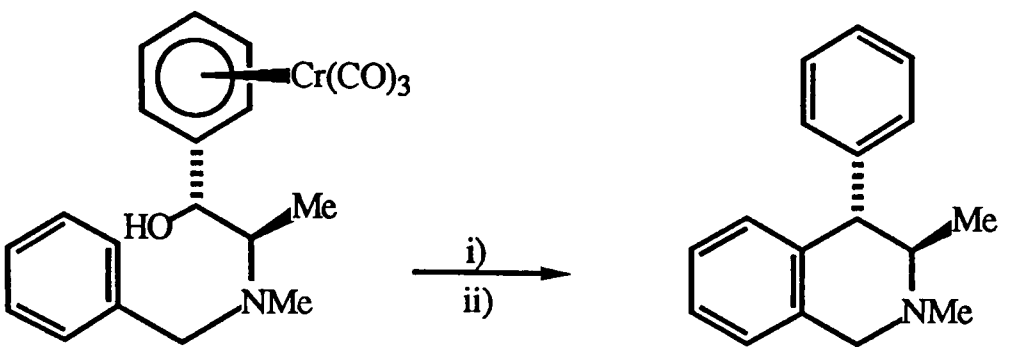
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 28h. ii) Air, sunlight, two steps 46%.



(+)-**246** (-)-(3S,4R)-**233** (+)-**257**

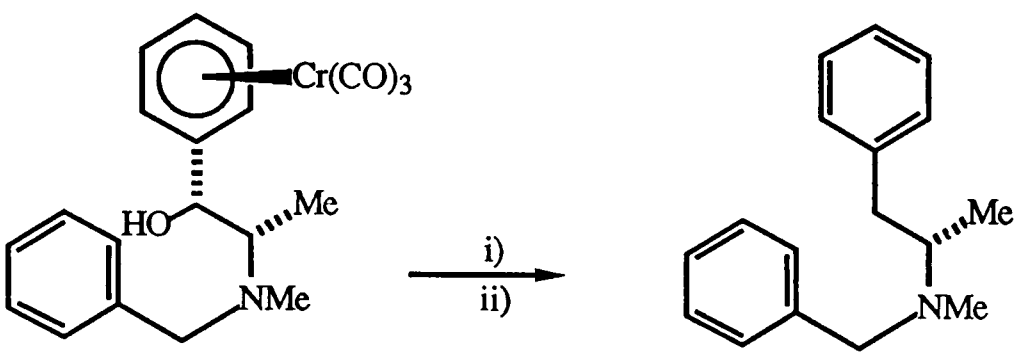
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 36h. ii) Air, sunlight, two steps 90%.

Similarly, cyclisation of (+)-**245** and decomplexation afforded *trans*-(+)-(3R,4S)-**240** along with recovery of a small quantity of uncomplexed starting material (-)-(1R,2R)-**238**. Flash chromatography enabled the isolation of pure (+)-(3R,4S)-**240** that proved to be identical to that previously synthesised {$[\alpha]_D^{20}$ +47.0 (*c* 0.09 $CHCl_3$)}. All attempts to cyclise the diastereoisomeric complex **249** led to isolation of the reduced compound **258** after decomplexation of the reaction mixture.



(+)-**245** (+)-(3R,4S)-**240**

i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 24.5h. ii) Air, sunlight, two steps 89%.

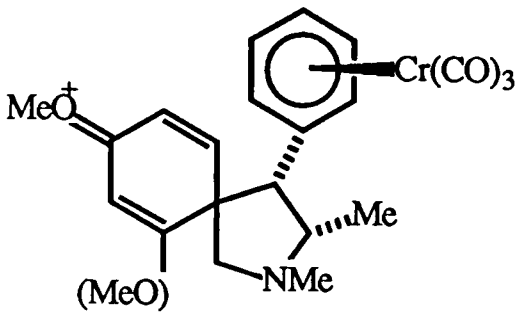


249 **258**

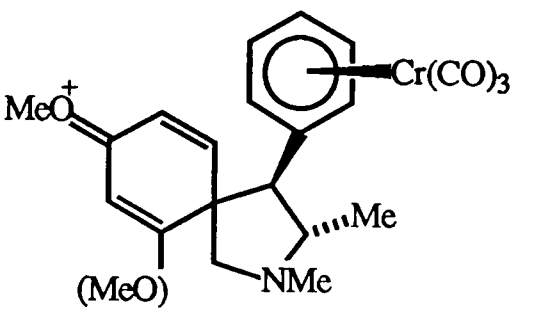
i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 48h. ii) Air, sunlight, two steps 40%.

In the cases of the pseudoephedrine-derived complexes (**242-245**) the cyclisations are proceding as expected under the stereocontrol of the $Cr(CO)_3$ unit to give exclusive formation of the corresponding *trans*-tetrahydroisoquinolines. This may be rationalised as overall retention of configuration by double inversion as previously explained. For the ephedrine-derived complexes (**246-248**) the stereochemical outcome of the cyclisation is dependent upon the position of the methoxyl substituent; *ortho*- and *para*-substituted precursor complexes (**246** and **248**) cyclise with complete inversion of configuration whereas the *meta*-substituted complex **247** gives arise to complete retention. This observation implies that the cyclisations of **246** and **248** must proceed under the influence of the methoxyl groups and therefore *via* a spiro intermediate, whilst ring closure of **247** can occur directly to a six-membered ring under the influence of the *meta*-methoxyl group. The $Cr(CO)_3$ stabilised benzylic carbocations generated upon ionisation of complexes **246**, **247** and **248** (after *exo* loss of water) can only be trapped from the unhindered *exo* face. In the case of **246** and **248** such a closure would orientate the methyl and $(Ph)Cr(CO)_3$ groups *cis* in the five-membered ring of spiro intermediate **259** whilst analogous closure of the carbocation similarly derived from **247** places these groups *cis* in a six-membered ring **261**. The greater steric compression associated with intermediate **259** (relative to **261**) may manifest itself as a sufficiently high transition state energy to prevent its formation and thereby prolong the lifetime of the benzylic carbocation. A lower energy reaction pathway would result from intramolecular trapping of the epimerised benzylic carbocation from the unhindered *exo* face to give the spiro intermediate **260**,

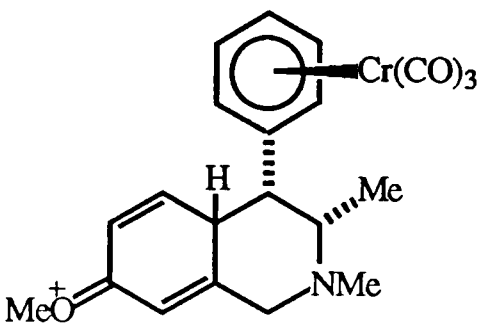
subsequent rearrangement and proton loss accounting for the observed *trans* products. That the cyclisation of **247** gives the corresponding *cis*-tetrahydroisoquinoline implies that intermediate **261** has a sufficiently low activation energy to permit its formation which may be attributed to less steric compression relative to **259**.



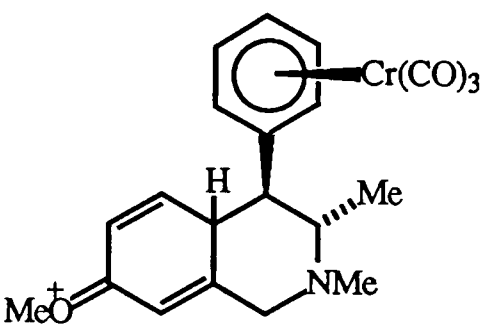
259



260



261

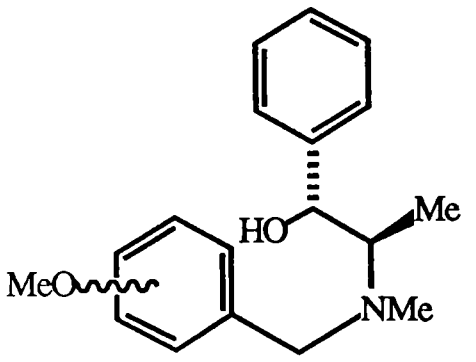


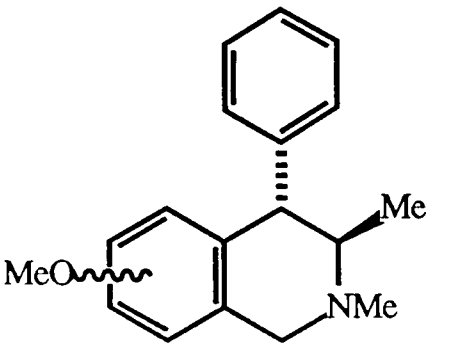
262

The isolation of the fully reduced compounds **257** and **258** from the attempted cyclisations of (+)-**246** and **249** respectively, requires the presence of a hydride source. Given that the observed yields of **257** and **258** are less than 50% it is possible that the reduction is a consequence of a disproportionation reaction, where the secondary alcohol itself serves as the reducing agent.[132] In this case a phenyl ketone complex would be generated but this would presumably polymerise under the strongly acidic reaction conditions.

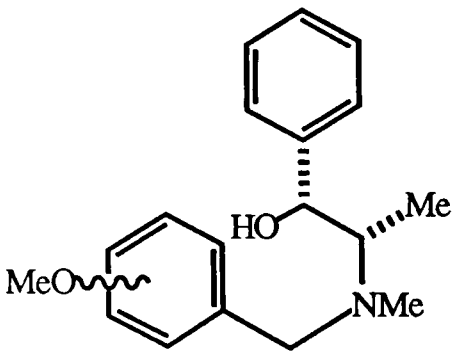
Summary

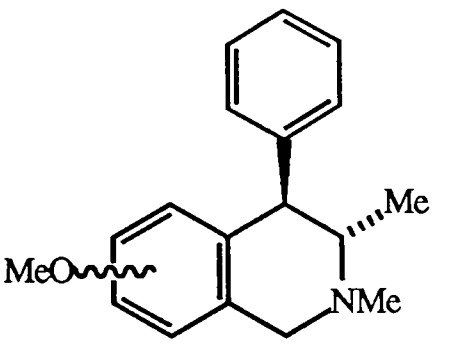
The cyclisations of N-mono-methoxybenzyl phenylpropanolamines are observed to proceed by two competing mechanistic pathways leading to preferential formation of the *trans*-tetrahydroisoquinoline products. The stereoselectivities observed during these cyclisations may be accounted for by consideration of the position of the methoxyl substituent present and its influence upon the cyclisation mechanism, higher selectivities being obtained from the *ortho*- and *para*-substituted isomers. These cyclisations are rendered completely stereoselective upon coordination of the precursors to the $Cr(CO)_3$ unit, proceeding with retention of configuration in all cases except for those of **246** and **248** which proceed with complete inversion.



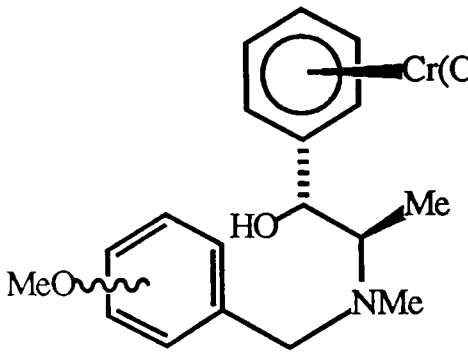


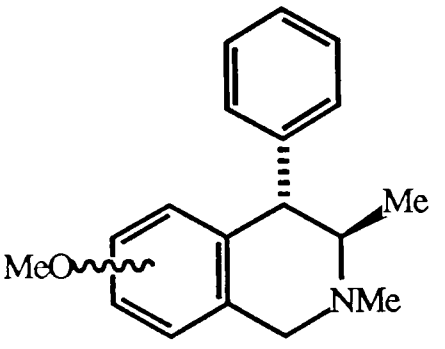
Preferential retention



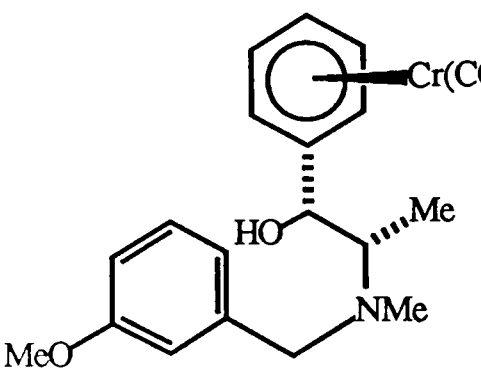


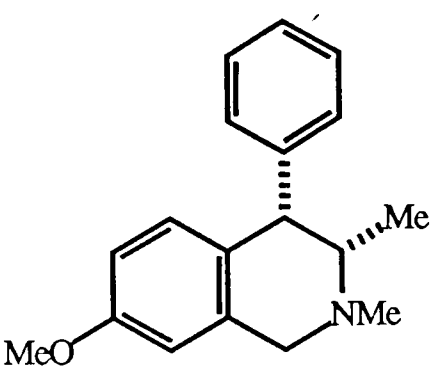
Preferential inversion



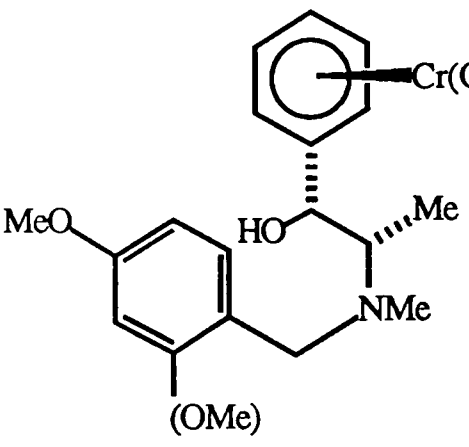


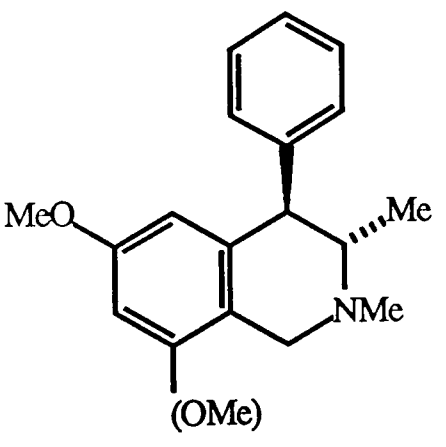
Complete retention





Complete retention





Complete inversion

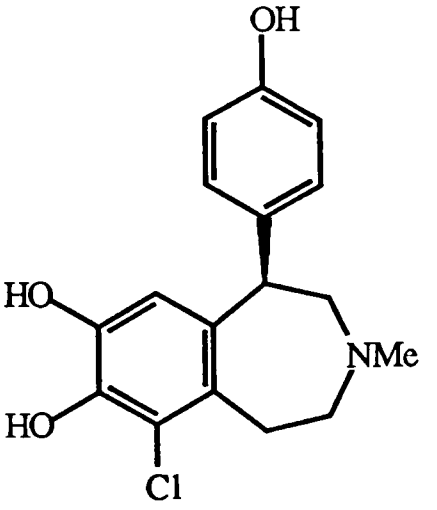
CHAPTER 5

1-Aryl-7,8-dimethoxy tetrahydrobenzazepines

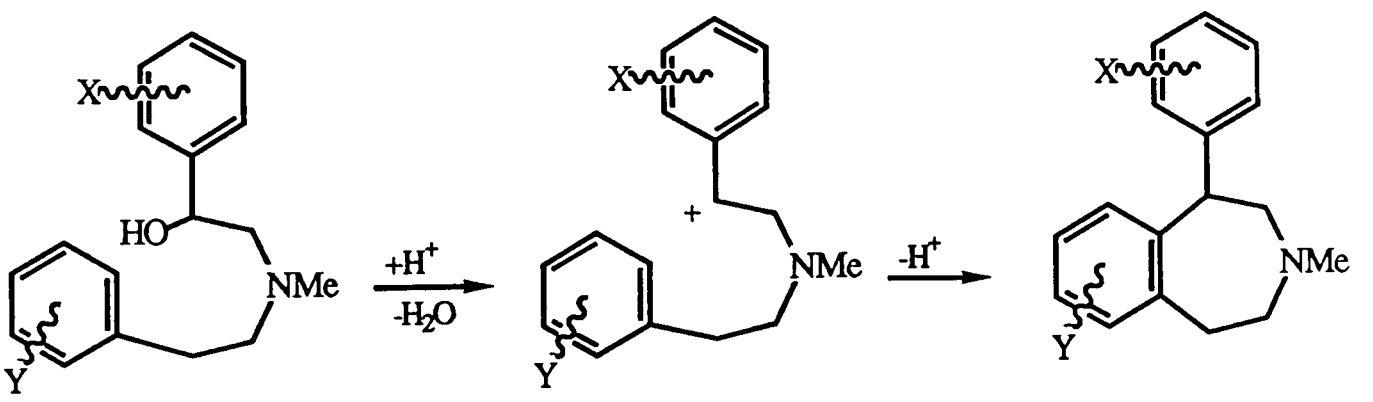
1-ARYL-7,8-DIMETHOXY-1,2,4,5-TETRAHYDROBENZAZEPINES

A) Stereoselectivity in the cyclisation of N-(3,4-dimethoxyphenethyl)halostachine

The naturally occurring heterocycles possessing the 1,2,4,5-tetrahydro-3H-benz[**d**]azepine† skeleton are commonly referred to as the 'benzazepine alkaloids'.[133] In particular, the presence of both a 1-aryl substituent and a 7,8-dioxygenation pattern gives rise to benzazepines that produce many dopaminergic effects in both the central and peripheral nervous systems, pharmacological effects that are believed to arise as a consequence of dopamine D1 receptor activation.[134,135] Considerable time and effort has been spent in the search for selective D1 receptor agonists and antagonists in order that ailments including Parkinsons disease, schizophrenia, renal disorder, hypertension and congestive heart failure may be successfully treated. The renal vasodilator Fenoldopam (**263**)[136,137] is a D1 agonist that exhibits pharmacological enantioselectivity; the dopaminergic activity residing almost exclusively in the R enantiomer.[138,139] The standard approach for the synthesis of 1-aryl tetrahydrobenzazepines is *via* an acid-promoted dehydration of an appropriately substituted phenethyl phenethanolamine as outlined in Scheme 9.[133] This cyclisation reaction has been widely used in the search for pharmacologically active benzazepines, the reaction being facilitated be electron releasing aryl substituents and retarded for electron withdrawing groups.



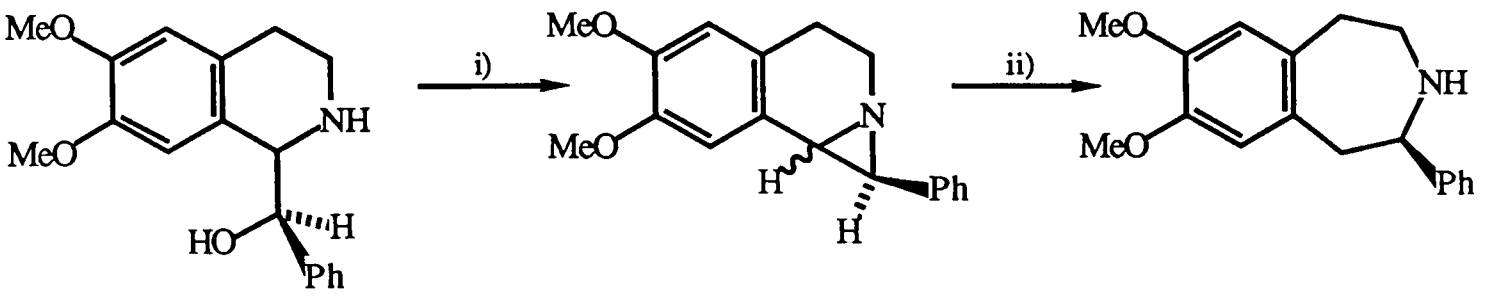
(R)-**263**



Scheme 9: Synthetic strategy for the synthesis of 1-aryl tetrahydrobenzazepines.

†The descriptors -1,2,4,5,and [**d**] are henceforth omitted for clarity.

Owing to the enantioselective pharmacological activity of these compounds their synthesis in homochiral form is highly desirable. One enantioselective route to 2-aryl tetrahydrobenzazepines that has been reported involves a ring expansion of the 1-substituted tetrahydroisoquinoline **264** *via* the intermediate aziridine **265**.[140]



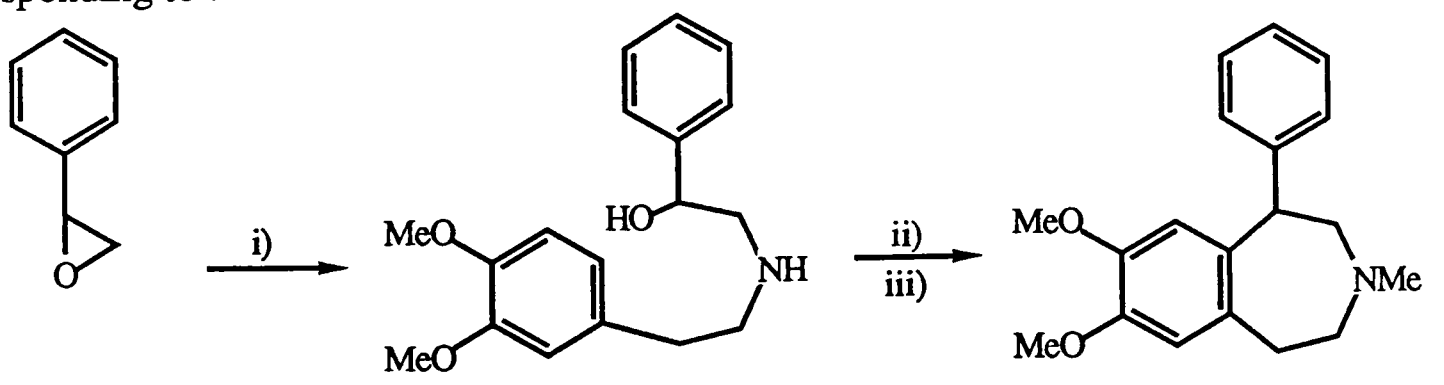
(S)-**264** (R)-**265** (-)-(R)-**266**

i) PPh_3, DEAD, 72%. ii) H_2, Raney Nickel, MeOH, 82%.

Although there are many reported methods enabling the construction of 1-aryl tetrahydrobenzazepines,[133] none of them permit a direct synthesis of homochiral material; a classical resolution procedure being required for the separation of the optical antipodes. It was thus of interest to assess the stereoselectivity in the cyclisation of homochiral N-phenethyl phenethanolamines and to exploit (arene)$Cr(CO)_3$ chemistry for the direct synthesis of homochiral 1-aryl tetrahydrobenzazepines.[141]

Results and Discussion

A dichloromethane solution of racemic amino alcohol **267** (readily synthesised according to literature procedure from styrene oxide (**171**) and homoveratrylamine)[142] was treated with a mixture of trifluoroacetic acid and sulphuric acid (1:1) at reflux to afford the corresponding benzazepine as evidenced by the appearance of two lowfield aromatic singlets in its ^1H n.m.r. spectrum. N-Methylation upon exposure to formic acid and formaldehyde gave racemic 1-phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**268**) as a white powder. ^1H n.m.r. analysis of **268** in the presence of shift reagent (-)-(R)-**174** clearly distiguished the two methoxyl singlets, the N-methyl singlet, the two aromatic singlets and the C1 proton corresponding to the two enantiomers.

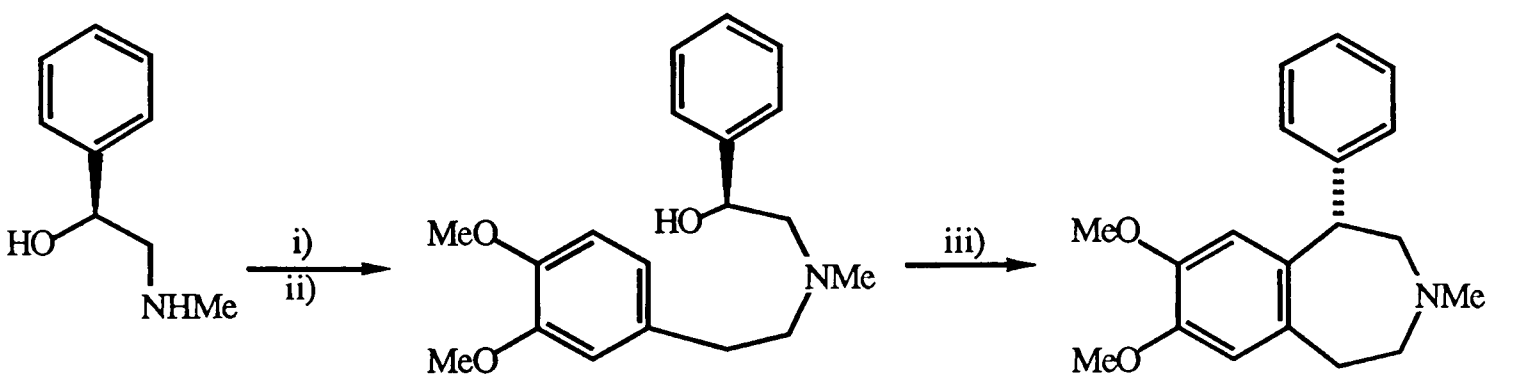


171 **267** **268**

i) 3,4-$(MeO)_2C_6H_3CH_2CH_2NH_2$, K_2CO_3, MeCN, 19h, 79%.
ii) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1h, 51%. iii) HCOOH, CH_2O, 7.5h, 85%.

Condensation of homoveratraldehyde[143] with racemic halostachine (**172**) yielded a mixture of diastereoisomeric oxazolidines which were reduced with sodium borohydride in methanol affording amino alcohol **269**. In a similar fashion, homochiral amino alcohol (+)-(S)-**269** was synthesised from (+)-(S)-halostachine (**172**) and fully characterised. ^{1}H n.m.r. spectroscopy in the presence of shift reagent (-)-(R)-**174** gave partial separtion of the benzylic proton of (R,S)-**269** and indicated that (+)-(S)-**269** was enantiomerically pure, its C1-benzylic proton signal appearing at lower field than that for (-)-(R)-**269**.

Acid-promoted cyclisation of (+)-(S)-**269** below -20°C occurred smoothly to give the expected benzazepine **268**. 300MHz ^{1}H n.m.r. analysis of the product in the presence of shift reagent (-)-(R)-**174** revealed an enantiomeric excess of 6%. If a free benzylic carbocation were to be formed as an intermediate, then complete racemisation would be expected. The small enantiomeric excess observed reflects a small degree of cyclisation *via* neighbouring group participation by the dimethoxybenzyl group in the ionisation of the protonated alcohol functionality with concommittant inversion of configuration. The major enantiomer observed in the cyclisation of (+)-(S)-**269** is thus assigned as (S)-**268**, consistent with preferential inversion of configuration during the cyclisation. The lower stereoselectivity observed for the cyclisation of (+)-(S)-**269** (e.e. 6%), in comparison to that observed in the cyclisation of the tetrahydroisoquinoline precursor (-)-(R)-**173** (e.e. 54%), reflects a greater propensity for neighbouring group participation in the cyclisation to a six-membered ring than in that to a seven-membered ring.



(+)-(S)-**172**

(+)-(S)-**269**

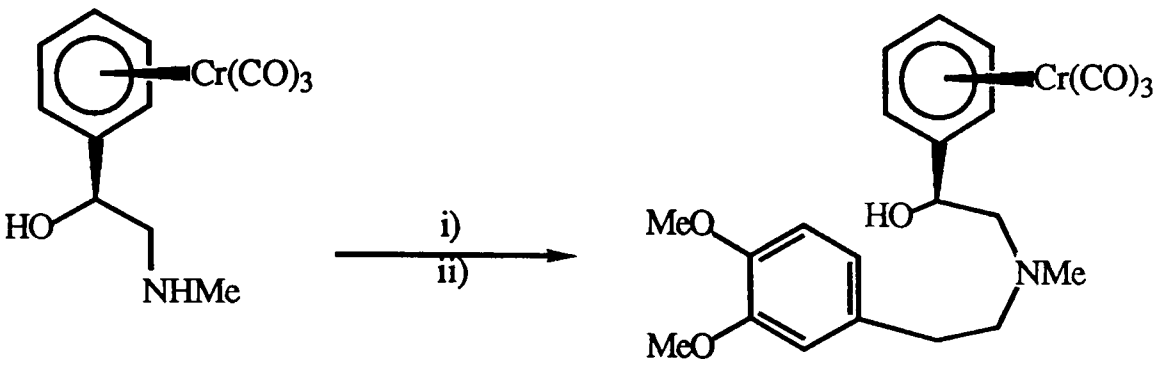
(-)-(S)-**268**

(e.e. =6%)

i) 3,4-$(MeO)_2C_6H_3CH_2CHO$, CH_2Cl_2, *p*TsOH, sieves, 91%. ii) $NaBH_4$, MeOH, 92%.
iii) $HBF_4.OMe_2$, CH_2Cl_2, -20°C, 69h.

It appeared likely that this cyclisation should be rendered highly stereoselective if the cyclisation of complex (R)-**270** [the $Cr(CO)_3$ complex of (+)-(S)-**269**] were to proceed under the stereocontrolling influence of the $Cr(CO)_3$ unit. Condensation of (+)-(R)-(halostachine)$Cr(CO)_3$ (**186**) with homoveratraldehyde and subsequent sodium borohydride reduction of the resultant mixture of diastereoisomeric oxazolidine complexes, afforded (R)-[N-(3,4-dimethoxy phenethyl)halostachine]$Cr(CO)_3$ (**270**) as a yellow oil. The ^{1}H n.m.r. spectrum of the product **270** exhibited a five proton aromatic multiplet at *ca.* δ5 and a three

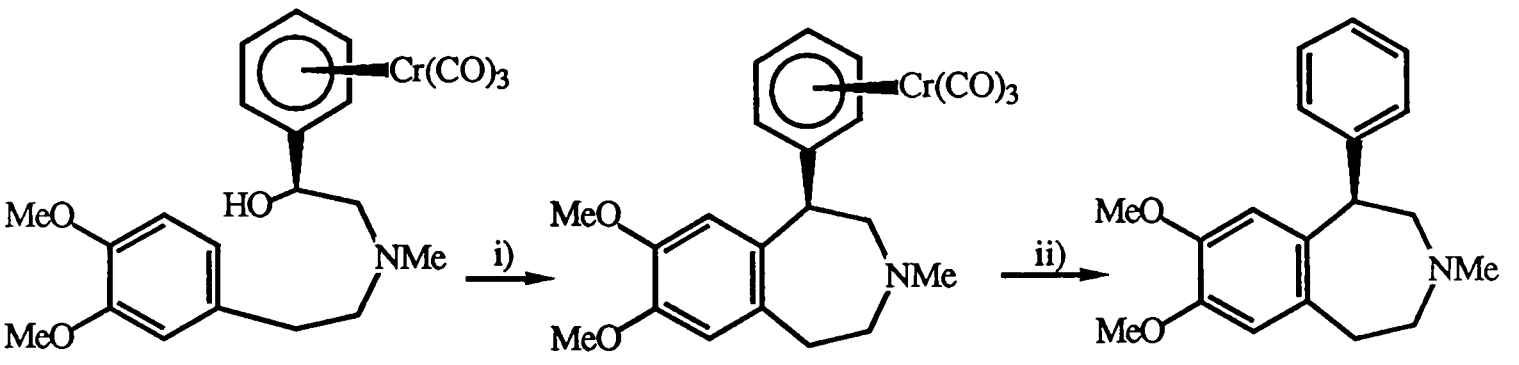
proton aromatic multiplet at lower field indicating that the $Cr(CO)_3$ moiety was coordinated to the unsubstituted phenyl ring and that no ring migration had occurred.



(+)-(R)-**186** (R)-**270**

i) 3,4-$(MeO)_2C_6H_3CH_2CHO$, CH_2Cl_2, *p*TsOH, sieves, 86%. ii) $NaBH_4$, MeOH, 62%.

Treatment of a dichloromethane solution of (R)-**270** with tetrafluoroboric acid below -20°C over forty hours gave an initial colour change from yellow to deep purple slowly reverting to yellow with time. Basic workup afforded a single product as a yellow oil that solidified on standing. Two, one proton aromatic singlets at δ6.72 and 6.64, an upfield five proton aromatic multiplet in the ^1H n.m.r. spectrum of the product, a molecular ion *m/z*=434 (M^++1) and an elemental analysis confirmed its identity as (-)-(1-phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine)$Cr(CO)_3$ (**271**), assigned initially as R upon the basis of expected retention of configuration during the cyclisation of (R)-**270**.[126,128] Oxidative decomplexation according to the standard procedure liberated (+)-(R)-1-phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**268**) {$[\alpha]_D^{20}$ +45.4 (*c* 0.27 $CHCl_3$)} as a white powder that appeared to be homochiral according to ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(R)-**174**. This product was fully characterised as the free base and possessed an optical rotation similar to that reported in the literature {$[\alpha]_D^{18}$ +31.2 (*c* 0.99 MeOH), lit.[138] $[\alpha]_D^{25}$ +31.8 (*c* 1.0 MeOH)}, thus supporting the above assignment.

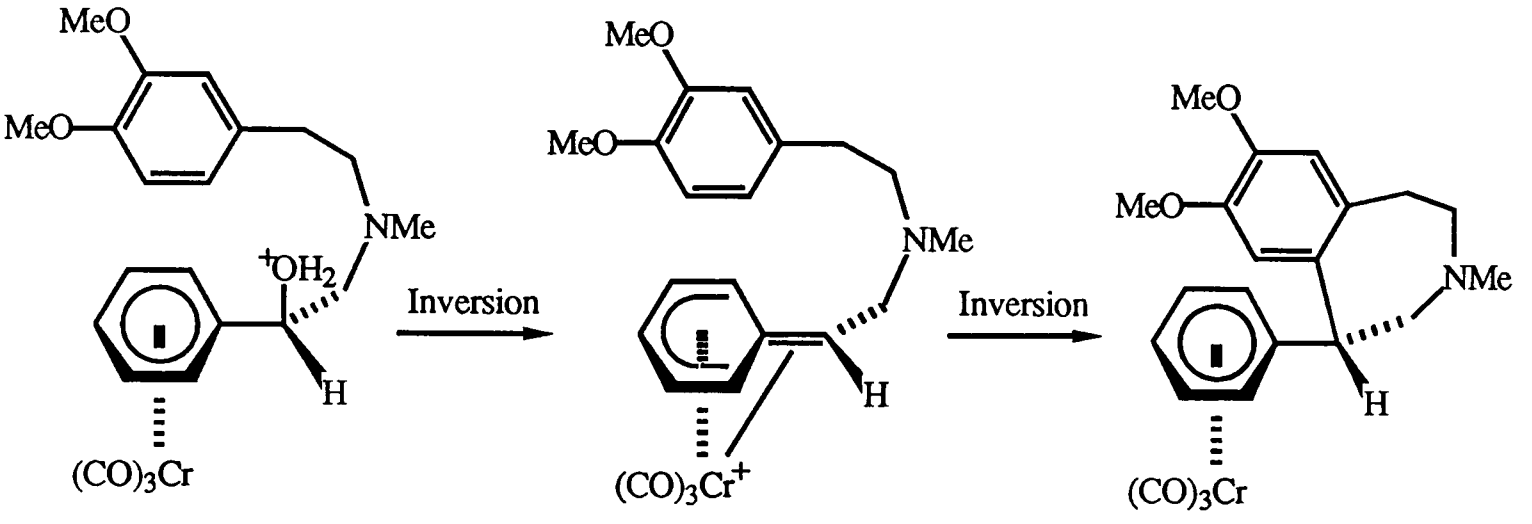


(R)-**270** (-)-(R)-**271** (+)-(R)-**268**

i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 40h, 76%. ii) Air, sunlight, 99%.

That both uncomplexed and complexed cyclisation precursors are derived from (+)-(S) halostachine (**172**) and preferentially give opposite enantiomers of product requires that the stereochemical courses of the two reactions be complementary; a slight preference for inversion

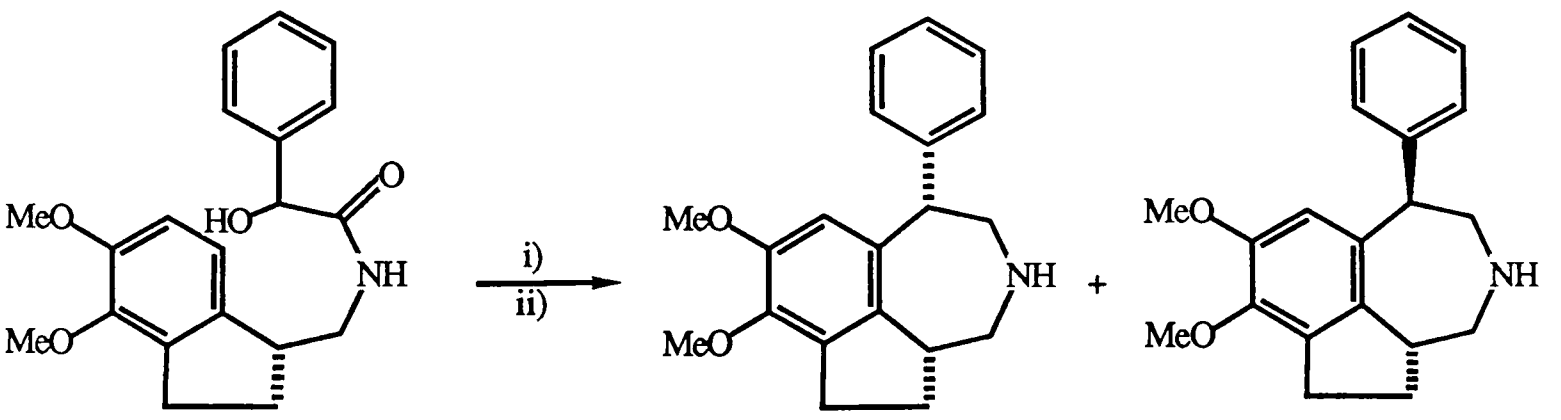
of configuration in the case of (+)-(S)-**269** but complete retention of configuration for complex (-)-(R)-**270**. Again, this is consistent with participation by the $Cr(CO)_3$ moiety in the ionisation of the benzylic hydroxyl group with inversion of configuration to generate the cationic intermedate **272**. Intramolecular trapping may subsequently occur only from the unhindered *exo* face, again with inversion, to give complex (-)-(R)-**271**, making the overall process stereospecific with retention of configuration.



(R)-270 **272** (-)-(R)-271

B) Diastereoselectivity in the cyclisation of substituted N-3,4-dimethoxyphenethyl phenylpropanolamines

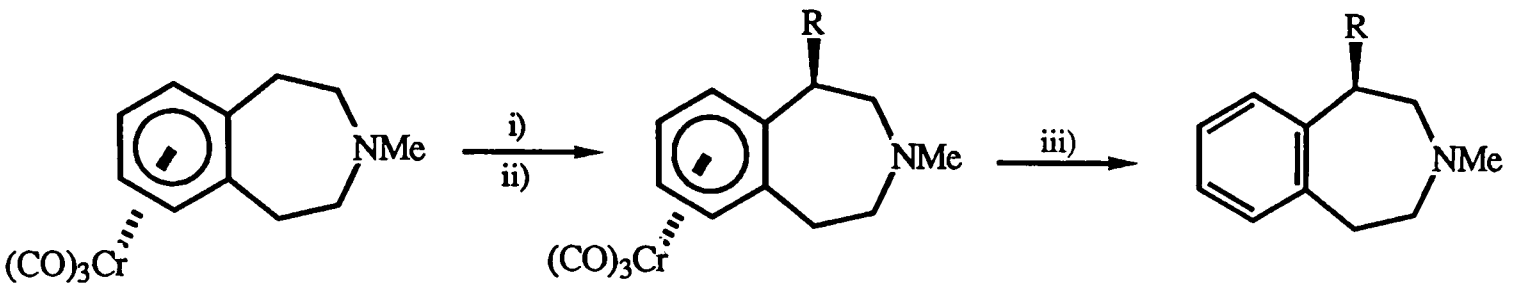
There appears to be no account in the literature assessing the diastereoselectivity of the synthesis of 2-substituted 1-aryl tetrahydrobenzazepines derived from an acid-mediated cyclisation reaction. A recent report indicated that acidic treatment of (aminomethyl)indane derivative **273**, followed by lithium aluminium hydride reduction gave a mixture of *cis* and *trans* ethano-bridged tetrahydrobenzazepines **274** and **275** in the isolated ratio 59:41.[139] (Arene)$Cr(CO)_3$ methodology has been exploited in the *exo* benzylic alkylation of benzazepine complex **276**, whereby sequential treatment with *n*-butyllithium and an electrophile, regio- and stereoselectively generates the corresponding 1-*exo*-substituted complexes (**277-280**) which may be oxidatively decomplexed to liberate the 1-alkylated tetrahydrobenzazepines (**281-284**).[144]



59 : 41

273 **274** **275**

i) Polyphosphoric acid, 100°C, 0.5h, 32%. ii) $LiAlH_4$, EtOH, THF 92%.



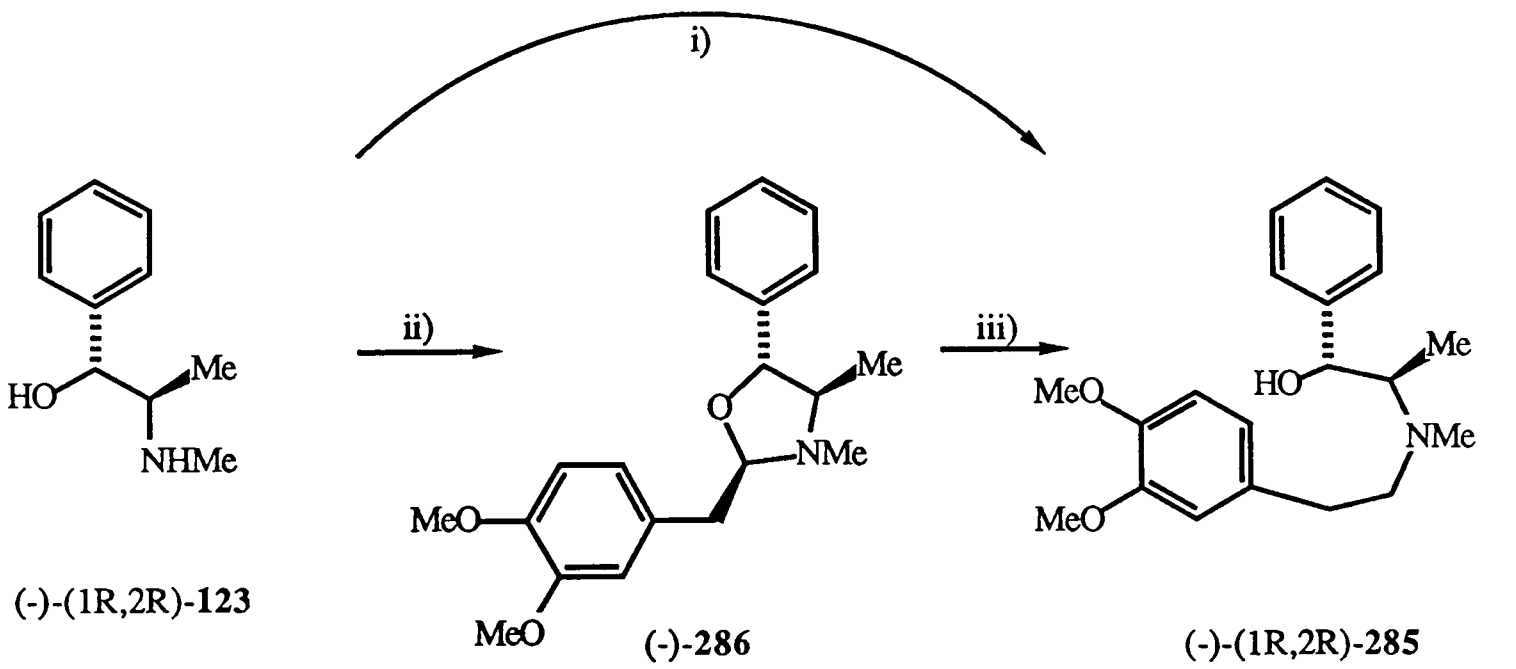
276

R= Me **277**
Et **278**
$PhCH_2$ **279**
MeS **280**

R= Me **281**
Et **282**
$PhCH_2$ **283**
MeS **284**

i) *n*-BuLi, THF, -78°C, 2h. ii) RX. iii) Air, sunlight.

An ethanol solution of (-)-(1R,2R)-pseudoephedrine (**123**) and 3,4-dimethoxyphenethyl bromide[145] was heated at reflux in the presence of sodium bicarbonate and a catalytic quantity of sodium iodide. From the reaction mixture two products were isolated after flash chromatography. The less polar component was identified as 3,4-dimethoxystyrene by comparison with an authentic sample,[146] whilst the major product was the required (-)-(1R,2R)-N-(3,4-dimethoxyphenethyl)pseudoephedrine (**285**). A molecular ion *m/z*=330 (M^++1) and an elemental analysis confirmed its identity. Alternatively, condensation of homoveratraldehyde with (-)-(1R,2R)-pseudoephedrine (**123**) gave a quantitative yield of the corresponding oxazolidine (-)-**286** preferentially as one diastereoisomer (ratio 94:6). This was subsequently reduced with sodium borohydride in methanol to give (-)-(1R,2R)-**285** identical to the previously synthesised sample.



(-)-(1R,2R)-**123**

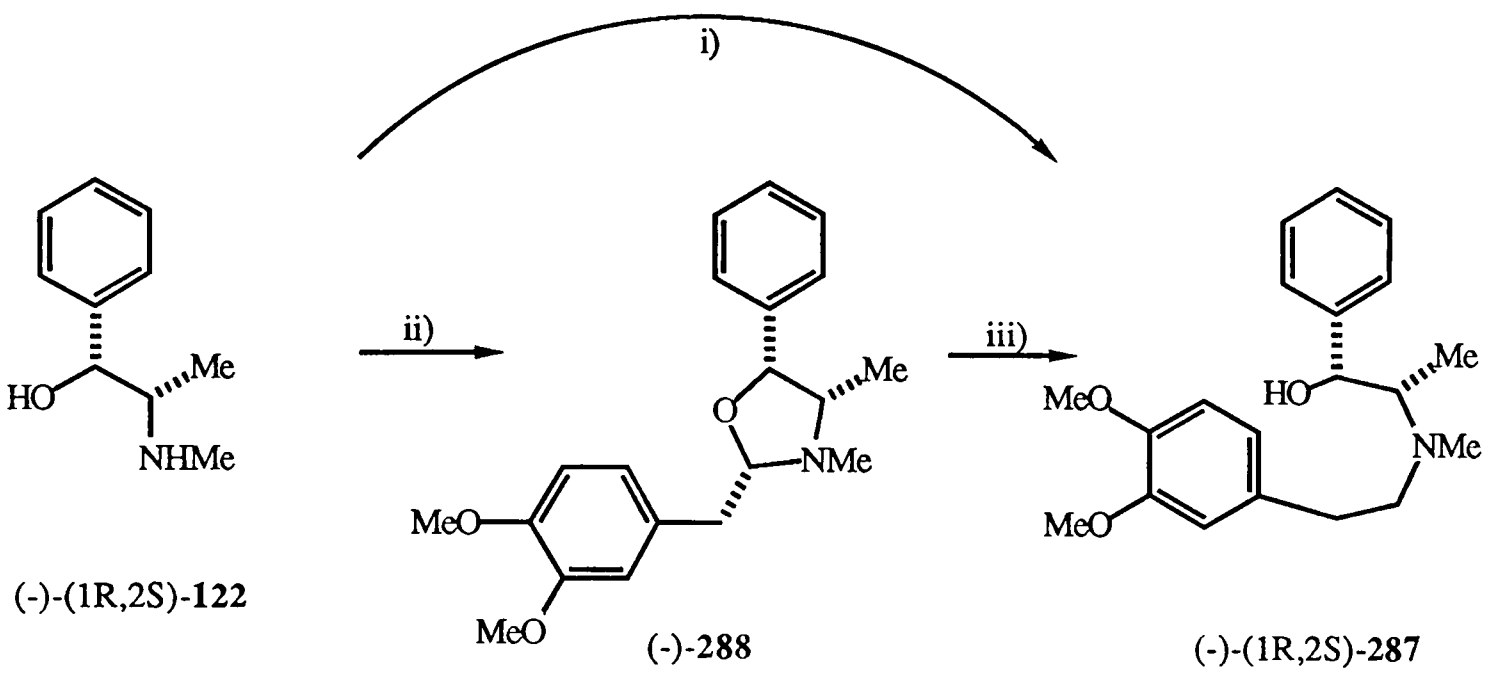
(-)-**286**

(-)-(1R,2R)-**285**

i) 3,4-$(MeO)_2C_6H_3CH_2CH_2Br$, $NaHCO_3$, NaI, EtOH, 60h, 29%.
ii) 3,4-$(MeO)_2C_6H_3CH_2CHO$, *p*TsOH, C_6H_6, 21h, quantitative. iii) $NaBH_4$, MeOH, 20°C, 23h, 61%.

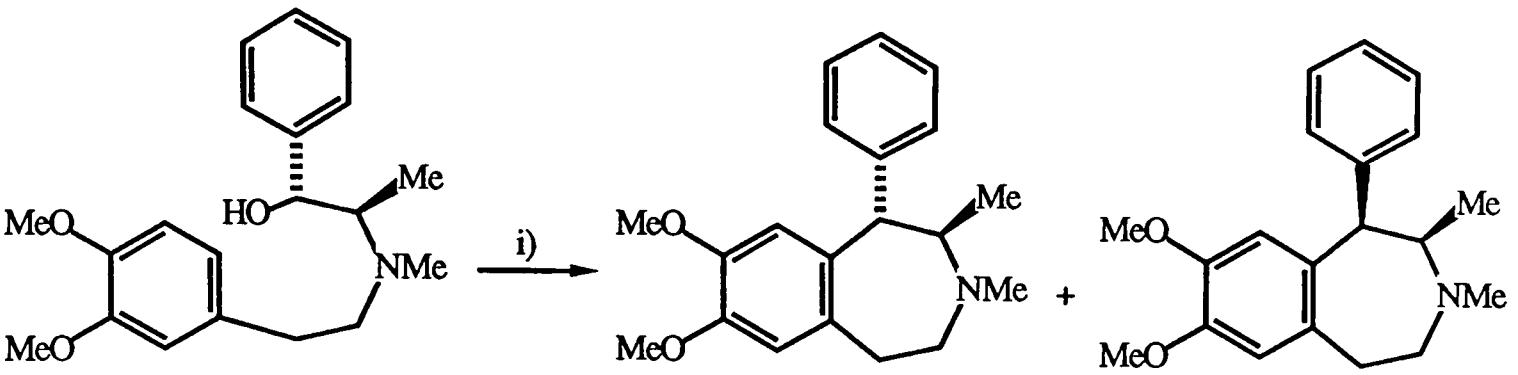
Similarly, an acetonitrile solution of 3,4-dimethoxyphenethyl bromide and (-)-(1R,2S)-ephedrine (**122**) was heated at reflux in the presence of potassium carbonate to afford a mixture

of products. The minor component was identical to an authentic sample of 3,4-dimethoxystyrene, whilst the major product was identified as (-)-(1R,2S)-N-(3,4-dimethoxyphenethyl)ephedrine (**287**). Recrystallisation from diethylether/hexane afforded an analytically pure sample that was fully characterised. Alternatively, (-)-(1R,2S)-**287** was readily obtained *via* sodium borohydride reduction of the oxazolidine (-)-**288** derived by condensation of homoveratraldehyde with (-)-(1R,2S)-ephedrine (**122**).



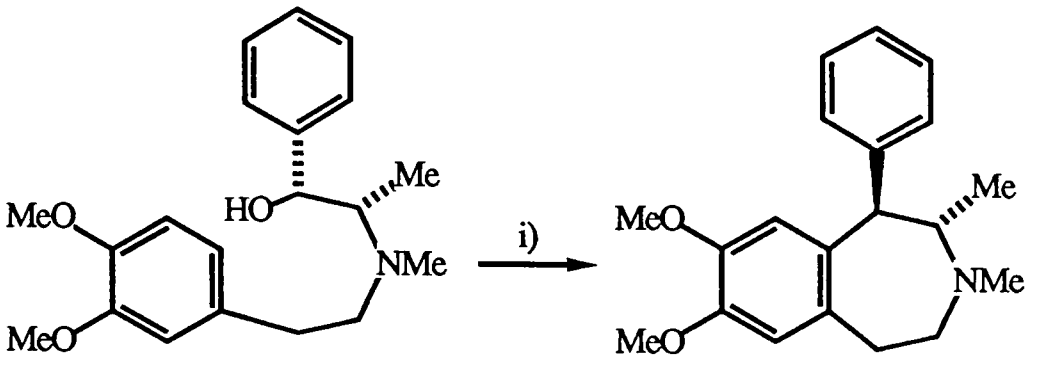
i) 3,4-$(MeO)_2C_6H_3CH_2CH_2Br$, K_2CO_3, MeCN, 48h, 34%.
ii) 3,4-$(MeO)_2C_6H_3CH_2CHO$, *p*TsOH, C_6H_6, 21h, quantitative. iii) $NaBH_4$, MeOH, 20°C, 23h, 56%.

A dichloromethane solution of (-)-(1R,2R)-**285** was treated with a mixture of trifluoracetic acid and sulphuric acid at reflux to effect cyclisation to the corresponding 1-phenyl benzazepine. ^1H n.m.r. analysis of the crude reaction mixture revealed the presence of two products in the ratio 91:9, each component exhibiting two lowfield aromatic singlets indicative of a 7,8-dimethoxy ring substitution pattern. Crystallisation from dichloromethane/hexane enabled the isolation of the major product which was identified as *trans*-(+)-(1S,2R)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**) {$[\alpha]_D^{20}$ +2.9 (*c* 0.38 $CHCl_3$)}. An elemental analysis and a molecular ion *m/z*=311 were consistent with this assignment whilst the minor component was assigned as *cis*-(1R,2R)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**290**). In a similar fashion, ephedrine-derived (-)-(1R,2S)-**287** was cyclised upon exposure to acid affording a single product that was identical to **289** according to ^1H n.m.r. spectroscopy of the crude reaction mixture. Recrystallisation gave an analytically pure sample of *trans*-(-)-(1R,2S)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**) {$[\alpha]_D^{20}$ -2.4 (*c* 0.84 $CHCl_3$)}as white blocks.



(-)-(1R,2R)-**285** (+)-(1S,2R)-**289** (1R,2R)-**290**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 2h, 58%.



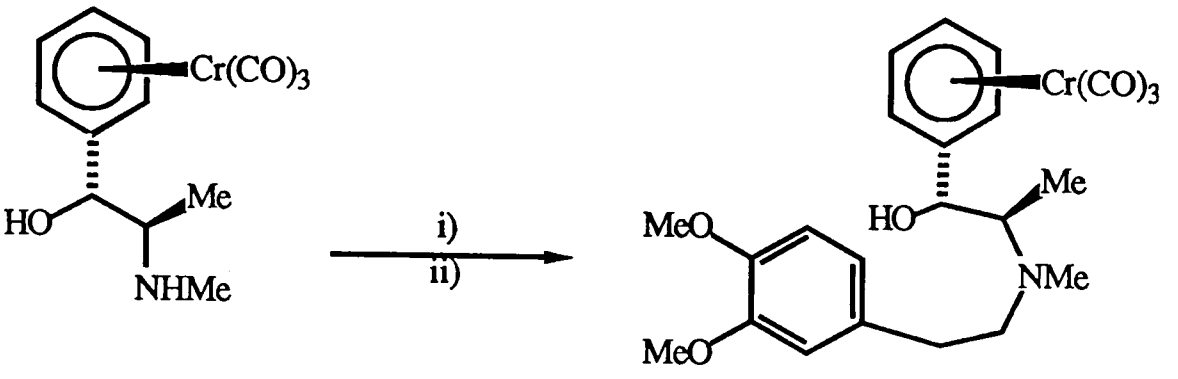
(-)-(1R,2S)-**287** (-)-(1R,2S)-**289**

i) TFA/H_2SO_4 (1:1), CH_2Cl_2, 40°C, 1.5h, 85%.

The stereoselective cyclisation of (-)-(1R,2S)-**287** to (-)-(1R,2S)-**289** may be rationalised by consideration of two mechanistic pathways. Ionisation of the protonated hydroxyl group generates a planar benzylic carbocation, the faces of which are rendered diastereotopic by virtue of the adjacent chiral centre. Exclusive trapping of this cation may occur from the face that leads to the *trans*-benzazepine (-)-**289** since the transition state leading to its formation will be of considerably lower energy than that which leads to the *cis* diastereoisomer **290** on steric grounds. Alternatively, neighbouring group participation by the dimethoxyphenethyl substituent in the ionisation of the benzylic hydroxyl group may occur to give inversion of configuration to again generate the *trans*-benzazepine (-)-**289**. Since the same product is obtained *via* either mechanism, the relative importance of either pathway cannot be deduced. However, the cyclisation of (-)-(1R,2R)-**285** will give two different products depending upon which cyclisation mechanism operates. The observed diastereoisomeric excess of 82% in favour of the *trans*-benzazepine (+)-**289** is consistent with 9% cyclisation *via* the neighbouring group participation mechanism to give the minor product (**290**) along with 91% cyclisation *via* an S_N1 mechanism which accounts for the formation of *trans*-(+)-**289** as the major product.

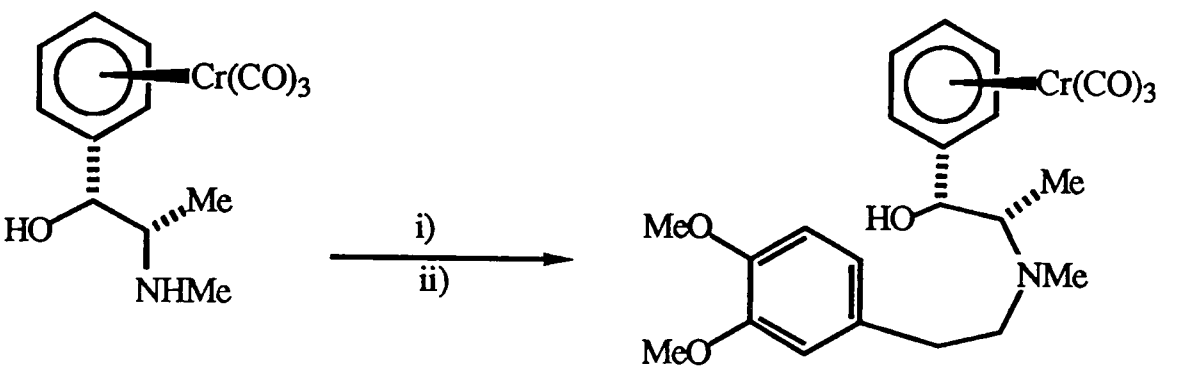
The $Cr(CO)_3$ complexes of (-)-(1R,2R)-**285** and (-)-(1R,2S)-**287** were prepared in a similar manner to complex (R)-**270**. Thus, treatment of a dichloromethane solution of (pseudoephedrine)$Cr(CO)_3$ (**205**) with homoveratraldehyde in the presence of molecular sieves and *para*-toluenesulphonic acid gave the corresponding oxazolidine complex. Without

isolation, this material was reduced with sodium cyanoborohydride to give, after crystallisation, (+)-[N-(3,4-dimethoxyphenethyl)pseudoephedrine]$Cr(CO)_3$ (**291**) as a yellow solid which was fully characterised. In an analogous manner, [N-(3,4-dimethoxyphenethyl)ephedrine]$Cr(CO)_3$ (**292**) was prepared from (-)-(ephedrine)$Cr(CO)_3$ (**206**) as a yellow oil.



205 (+)-**291**

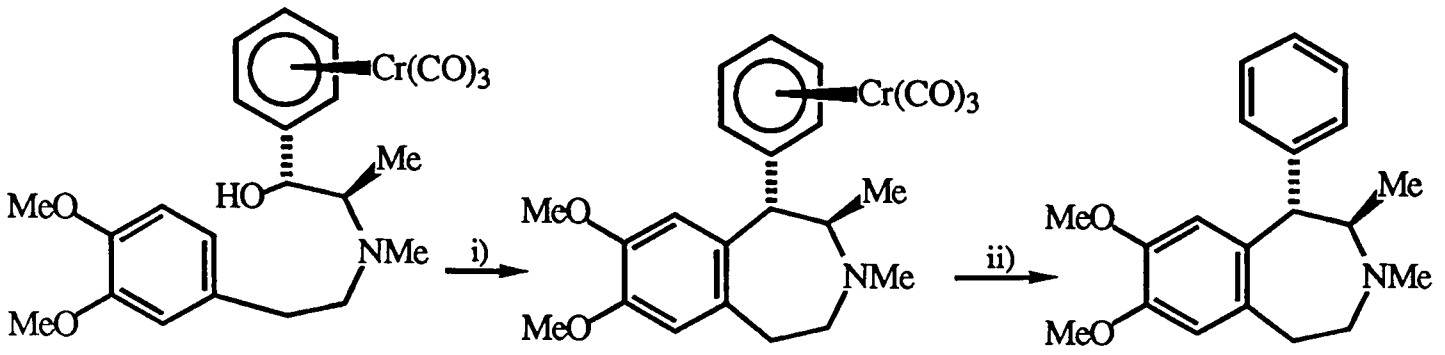
i) 3,4-$(MeO)_2C_6H_3CH_2CHO$, *p*TsOH, sieves, CH_2Cl_2, 20°C, 22h.
ii) $NaBH_3CN$, HCl, MeOH, 20°C, 6h, 2 steps 24%.



(-)-**206** **292**

i) 3,4-$(MeO)_2C_6H_3CH_2CHO$, *p*TsOH, sieves, CH_2Cl_2, 20°C, 13h, 82%.
ii) $NaBH_3CN$, HCl, MeOH, 20°C, 20h, 91%.

A dichloromethane solution of complex (+)-**291** was cooled to -78°C and treated with tetrafluoroboric acid giving no apparent colour change. On warming to -20°C, the solution rapidly turned deep blue, reverting to yellow within twenty four hours. Basic workup afforded a single product (as evidenced by ^1H n.m.r. spectroscopy of the reaction mixture) identified as *trans*-tetrahydrobenzazepine complex **293**. This assignment was confirmed by subsequent oxidative decomplexation which yielded *trans*-(+)-(1S,2R)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**) {$[\alpha]_D^{21}$ +5.4 (*c* 1.49 $CHCl_3$)}. This product was identical in all respects to the previously synthesised sample including no depression of the mixed melting point. All attempts to cyclise complex **292** under similar conditions failed to give any isolable benzazepine after decomplexation.



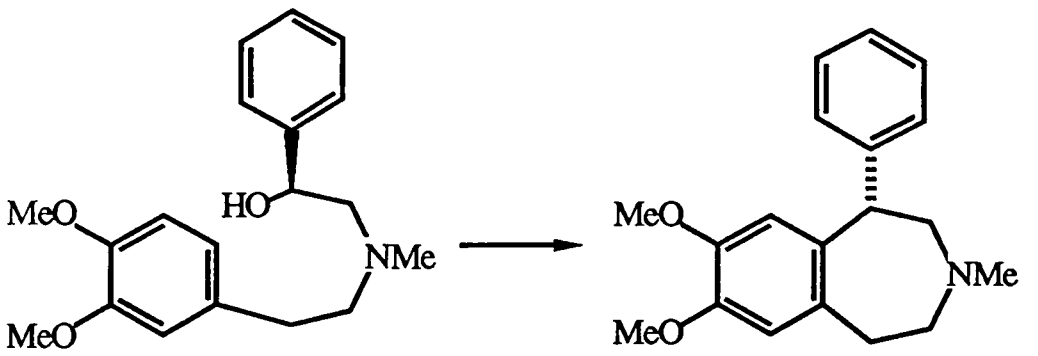
(+)-**291** **293** (+)-(1S,2R)-**289**

i) $HBF_4.OMe_2$, CH_2Cl_2, <-20°C, 23h, 64%. ii) Air, sunlight, 95%.

The stereoselective cyclisation of complex (+)-**291** to **293** is occurring as expected, with retention of configuration at the benzylic centre. This is consistent with neighbouring group participation by chromium with inversion followed by intramolecular trapping, again with inversion, by the dimethoxyphenethyl group thus accounting for the observed formation of *trans* complex **293**.

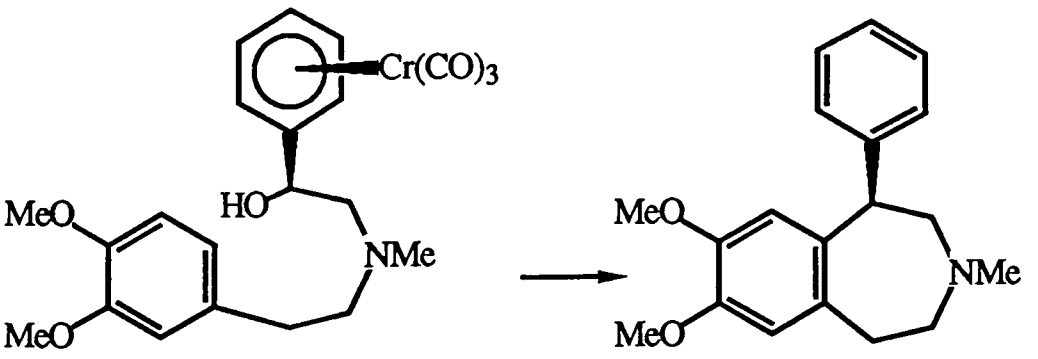
Summary

The cyclisation of (+)-(S)-N-(3,4-dimethoxyphenethyl)halostachine (**269**) occurs *via* two mechanistic pathways, the more important of which involves the formation of a planar benzylic carbocation upon ionisation of the protonated hydroxyl group. This carbocation is trapped from either face with equal preference to give a racemic mixture. A small amount (6%) of cyclisation occurs *via* a competing neighbouring group participation mechanism necessitating inversion of configuration. This cyclisation is rendered completely stereoselective upon coordination of the precursor to the $Cr(CO)_3$ unit to afford, upon decomplexation, homochiral 1-phenyl benzazepine (+)-(R)-**268** in the cyclisation of complex (R)-**270**.



(e.e. =6%)

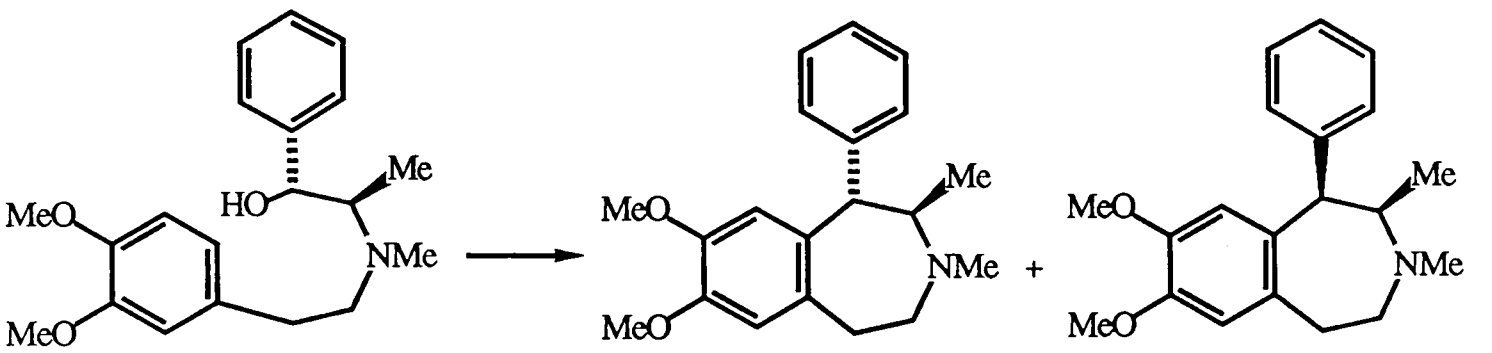
(+)-(S)-**269** (-)-(S)-**268**



Complete retention

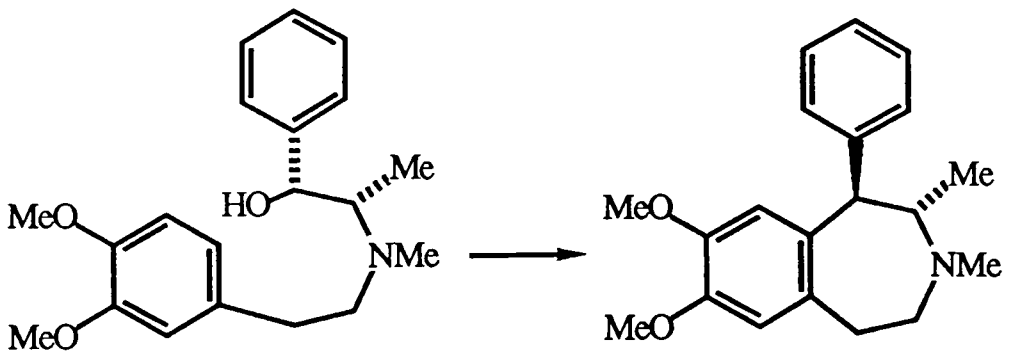
(R)-**270** (+)-(R)-**268**

Cyclisation of both (-)-(1R,2R)-**285** and (-)-(1R,2S)-**287** may also occur by two competing mechanistic pathways. In both cases an S_N1 mechanism generates a planar benzylic carbocation, the faces of which are diastereotopic. Intramolecular trapping occurs exclusively from the face that gives the *trans*-benzazepine **289** on steric grounds. Alternatively, neighbouring group participation by the dimethoxybenzyl moiety may promote the ionisation of the protonated hydroxyl group with concommittant inversion of configuration. The exclusive formation of (-)-**289** arising from the cyclisation of (-)-(1R,2S)-**287** allows no prediction as to the relative importance of the two mechanisms, whereas in the case of (-)-(1R,2R)-**285** the opposing mechanisms give diastereoisomeric products. The diastereoisomeric excess of 82% observed in the cyclisation of (-)-**285** therefore reflects a small degree of cyclisation (9%) *via* the neighbouring group participation mechanism to give *cis*-benzazepine **290** as the minor product. Cyclisation of (+)-**291** [the $Cr(CO)_3$ complex of (-)-(1R,2R)-**285**] is completely stereoselective, occurring with retention of configuration to furnish (+)-(1S,2R)-**289** after decomplexation.



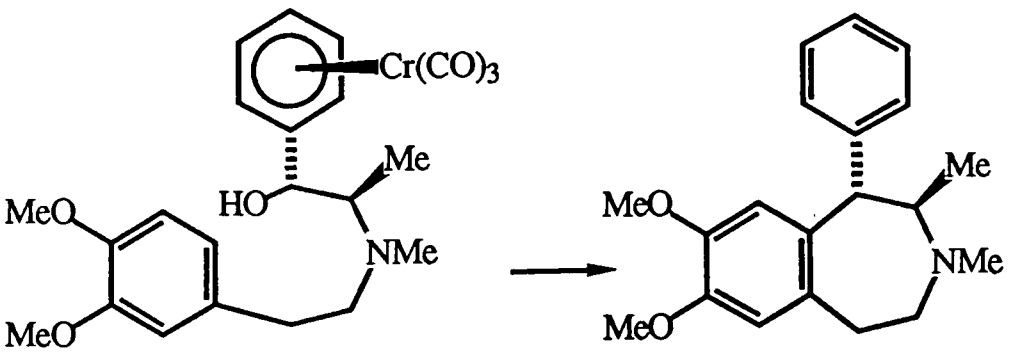
91 : 9

(-)-(1R,2R)-**285** (+)-(1S,2R)-**289** (1R,2R)-**290**



(-)-(1R,2S)-**287** (-)-(1R,2S)-**289**

Complete inversion



(+)-**291** (+)-(1S,2R)-**289**

Complete retention

EXPERIMENTAL

General experimental procedures. All reactions involving (arene)$Cr(CO)_3$ complexes, their preparation and purification were carried out under a nitrogen atmosphere using standard vacuum line techniques[147] and all solvents were deoxygenated prior to use. Benzene was dried with sodium wire and THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Bu_2O was sodium dried and distilled from CaH_2 under nitrogen. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen prior to use. Petroleum ether refers to that fraction which boils in the range 40-60°C and was redistilled prior to use. Removal of all solvents was carried out under reduced pressure and all commercial reagents were purified (where necessary) according to standard techniques.[148] $Cr(CO)_6$ was purchased from Strem Chemicals and was steam distilled before use. Molecular sieves (4A) were activated prior to use by heating under reduced pressure (100°C, 12h). *n*-Butyllithium was used as a 1.65M solution in hexane, *t*-butyllithium was used as a 2.62M solution in pentane and methyllithium was used as a 1.0 or a 1.4M solution in Et_2O. MeMgI was prepared according to the standard procedure and was used as a 4.4M solution in Et_2O. Flash chromatography[149] was performed on SiO_2 (Merck, 40-60μm) and grade V Al_2O_3 refers to alumina that has been deactivated by the addition of water (10%, v/v). ^1H n.m.r. spectra were obtained as $CDCl_3$ solutions at 300MHz (unless otherwise stated) using a Bruker WH300 instrument. ^{13}C n.m.r. spectra were obtained as $CDCl_3$ solutions at 62.9MHz (unless otherwise stated) using a Bruker AM250 instrument. ^2H n.m.r. spectra were obtained as $CHCl_3$ solutions using the same instrument. I.r. spectra were obtained as $CHCl_3$ solutions (unless otherwise stated) using a Perkin-Elmer 781 Infrared Spectrophotometer and were callibrated against polystyrene (1601cm^{-1}). A Perkin-Elmer 241 Polarimeter was used to measure optical rotations and were obtained as solutions in the specified solvent at the specified concentration. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained on a V.G. Micromass ZAB 1F instrument using electron impact or chemical ionisation techniques.

General complexation procedure. A deoxygenated mixture of the relevant arene and $Cr(C0)_6$ in Bu_2O and THF (ratio 10:1) was heated at reflux under a nitrogen atmosphere (10-30h).[26] The cooled solution was filtered and evaporated and the residue subjected to column chromatography. The corresponding $Cr(CO)_3$ complex was invariably isolated as a yellow solid and further purified where necessary by recrystallisation.

General decomplexation procedure. A solution of the relevant complex in Et_2O (10mg ml^{-1}) was allowed to stand in air and sunlight until the yellow solution became colourless (24-48h). The precipitated chromium residues were removed by filtration (celite) and the filtrate evaporated to furnish the free arene. Further purification (where necessary) was achieved by crystallisation, chromatography or by cup distillation under reduced pressure.

(Naphthalene)$Cr(CO)_3$ (20). A mixture of naphthalene (5.30g, 41.4mmol) and $Cr(CO)_6$ (4.40g, 20.0mmol) in Bu_2O (100ml) and THF (1ml) was reacted according to the standard complexation procedure to give a red solid. This material was recrystallised from toluene/hexane at -78°C to furnish the *title compound* as red crystals (1.40g, 26%). Alternatively, purification was achieved by column chromatography [Al_2O_3 grade V, petroleum ether/Et_2O (1:1)], δ_H 7.58-7.26 [4H, m, 2$(CO)_3CrC_6H_4CHCH$], 6.14-5.51 [4H, m, $(CO)_3CrC_6H_4$].

(Phthalan)Cr(CO)$_3$ (81). Phthalan (**82**) (2.31g, 19.2mmol) and $Cr(CO)_6$ (4.66g, 21.2mmol) in Bu_2O (50ml) and THF (6ml) were reacted according to the standard complexation procedure (22h). Recrystallisation from Et_2O/hexane gave the *title compound* as yellow needles (0.99g, 20%), $\nu_{max.}$ 1970 and 1890 (C≡O) cm^{-1}; δ_H 5.53-5.25 [4H, m, $C_6\mathbf{H}_4Cr(CO)_3$], 4.93, 4.88 (4H, AB system J_{AB} 10.8Hz, $ArCH_2$); *m/z* 256 (M^+) (Found: C, 51.4; H, 3.2. $C_{11}H_8CrO_4$ requires C, 51.6; H, 3.15%).

Alternative procedure: A deoxygenated solution of phthalan (**82**) (0.55g, 4.58mmol) and (naphthalene)Cr(CO)$_3$ (**20**) (0.21g, 0.79mmol) in Et_2O (25ml) and THF (2.5ml) was heated at reflux (25h). The solvent was evaporated and the residue purified by column chromatography (Al_2O_3 grade V, Et_2O). The less polar fraction was evaporated to leave (naphthalene)Cr(CO)$_3$ (**20**) as a red solid (0.070g). The second fraction was evaporated to leave the title compound as a yellow solid (0.046g, 23%, 34% yield based upon recovered starting material).

Treatment of (phthalan)Cr(CO)$_3$ (81) with acid. A solution of (phthalan)Cr(CO)$_3$ (**81**) (0.150g, 0.59mmol) in THF (3ml), MeOH (3ml) and water (3ml) was treated with HCl (conc., 1ml) and the yellow solution stirred (20°C, 12h). The mixture was basified ($NaHCO_3$) and the aqueous phase extracted (CH_2Cl_2). The combined extracts were evaporated to leave a yellow solid. Column chromatography (Al_2O_3 grade V, Et_2O) gave a single fraction as a yellow solid identified as starting material (0.121g, 81%).

Treatment of [*ortho*-xylene-α,α'-diyl bis(methylether)]Cr(CO)$_3$ (83) with acid. A solution of [*ortho*-xylene-α,α'-diyl bis(methylether)]Cr(CO)$_3$ (**83**)[56] (0.122g, 0.409mmol) in CH_2Cl_2 (2.5ml) and EtOH (0.3ml) was cooled to -40°C and treated with $HBF_4.OMe_2$ (0.13ml, excess) producing a dark red/purple colouration that reverted to yellow after *ca.* 20 seconds. The solution was stirred (-40°C, 10min), water (0.2ml) added and the solvents evaporated. Basification and column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a yellow solid (0.105g). ^1H n.m.r. spectroscopy of the product revealed the presence of several components but the absence of (phthalan)Cr(CO)$_3$ (**81**). A highfield triplet (*ca.* δ1.25) and a molecular ion *m/z* 330 (M^+) was consistent with the presence of [*ortho*-xylene-α,α'-diyl bis(ethylether)]Cr(CO)$_3$ (**84**). Analogous efforts to cyclise complex **83** using HBF_4 (aq.) in THF, $HBF_4.OMe_2$ in CH_2Cl_2, CF_3COOH in CH_2Cl_2 or orthophosphoric acid in THF all failed to give (phthalan)Cr(CO)$_3$ (**81**).

***Exo*-(1-Methyl phthalan)Cr(CO)$_3$ (90).** To a stirred solution of (phthalan)Cr(CO)$_3$ (**81**) (0.163g, 0.64mmol) in THF (20ml) at -78°C was added *t*-butyllithium (0.25ml, 0.66mmol) and the resultant red solution stirred (-78°C, 1.75h). MeI (1ml, 16.1mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (1ml) the reaction mixture was warmed and evaporated. Column chromatography (Al_2O_3 grade V, Et_2O) gave a single fraction as a yellow oil (0.151g, 88%). Crystallisation from *n*-pentane (-20°C) gave the *title compound* as fine yellow needles, $\nu_{max.}$ 1970 and 1880 (C≡O), 1250 (C-O) cm^{-1}; δ_H 5.52-5.23 [4H, m, $C_6\mathbf{H}_4Cr(CO)_3$], 5.16 (1H, dq, J 1.7 and 6.5Hz, $ArC\mathbf{H}CH_3$), 4.98, 4.87 (2H, ABX system, J_{AB} 12.3Hz, J_{AX} 1.7Hz, $ArC\mathbf{H}_2O$), 1.44 (3H, d, J 6.6Hz, $CHC\mathbf{H}_3$); *m/z* 270 (M^+) (Found: C, 53.0; H, 3.7. $C_{12}H_{10}CrO_4$ requires C, 53.3; H, 3.7%).

***Exo*-(1-Ethyl phthalan)Cr(CO)$_3$ (91).** To a stirred solution of (phthalan)Cr(CO)$_3$ (**81**) (0.727g, 2.84mmol) in THF (30ml) at -78°C was added *t*-butyllithium (1.2ml, 3.14mmol) and the resultant red solution

stirred (-78°C, 2h). EtI (0.7ml, 8.75mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (5ml) the reaction mixture was warmed and evaporated. Column chromatography (Al_2O_3 grade V, gradient elute light petroleum/Et_2O) gave the *title compound* as a yellow oil (0.580g, 72%), $\nu_{max.}$ 1960 and 1890 (C≡O) cm^{-1}; δ_H 5.51-5.22 [4H, m, $C_6\mathbf{H}_4Cr(CO)_3$], 4.99 (1H, m, ArC**H**Et), 4.97, 4.87 (2H, AB system, J_{AB} 11.4Hz, Ar$\mathbf{CH}_2$O), 1.74 (2H, m, $CH_3\mathbf{CH}_2$), 1.00 (3H, t, J 7.4Hz, $CH_2\mathbf{CH}_3$); *m/z* 284 (M^+) (Found: M^+, 284.0143. $C_{13}H_{12}CrO_4$ requires M, 284.0141).

***Exo*-(1-Benzyl phthalan)Cr(CO)$_3$ (92).** To a stirred solution of (phthalan)Cr(CO)$_3$ (**81**) (0.632g, 2.47mmol) in THF (30ml) at -78°C was added *t*-butyllithium (1.02ml, 2.67mmol) and the resultant red solution stirred (-78°C, 2h). Benzyl bromide (0.9ml, 7.57mmol) was added and stirring continued (-78°C, 3h). After addition of MeOH (2ml) the reaction mixture was warmed and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave the *title compound* as a yellow oil (0.699g, 82%), $\nu_{max.}$ 1970 and 1880 (C≡O) cm^{-1}; δ_H 7.38-7.15 (5H, m, Ph), 5.42-5.07 [4H, m, $C_6\mathbf{H}_4Cr(CO)_3$], 4.80 (2H, br s, Ar$\mathbf{CH}_2$O), 3.49, 3.11 (2H, ABX system, J_{AB} 14.0Hz, J_{AX} 7.0Hz, J_{BX} 5.9Hz, PhC$\mathbf{H}_2$CH); *m/z* 346 (M^+) (Found: M^+, 346.0293. $C_{18}H_{14}CrO_4$ requires M, 346.0297).

***Exo*-(1-Deuterio phthalan)Cr(CO)$_3$ (93).** To a stirred solution of (phthalan)Cr(CO)$_3$ (**81**) (0.030g, 0.12mmol) in THF (15ml) at -78°C was added *t*-butyllithium (0.05ml, 0.13mmol) and the resultant red solution stirred (-78°C, 1h). CD_3OD (0.5ml) was added and stirring continued (-78°C, 30min). The reaction mixture was warmed, evaporated and subjected to column chromatography (Al_2O_3 Grade V, Et_2O). Evaporation gave the *title compound* as a yellow oil (0.028g, 92%), δ_H 5.53-5.24 [4H, m, $C_6\mathbf{H}_4Cr(CO)_3$], 5.95-5.85 (3H, m, Ar$\mathbf{CH}_2$OC**H**D); δ_D 4.93 (1D, br s, ArC**H**D); *m/z* 257 (M^+).

1-Methyl phthalan (70).[68,80,81] *Exo*- (1-Methyl phthalan)Cr(CO)$_3$ (**90**) was decomplexed according to the standard procedure to afford the *title compound* as a colourless oil (80%), δ_H 7.32-7.16 (4H, Ar), 5.34 (1H, dq, J 6.4 and 1.8Hz, ArC**H**CH_3), 5.15, 5.06 (2H, ABX system, J_{AB} 12.2Hz, J_{AX} 2.2Hz, J_{BX} 1.7Hz, Ar$\mathbf{CH}_2$O), 1.52 (3H, d, J 6.1Hz, ArCHC$\mathbf{H}_3$); *m/z* 133 (M^+-1).

1-Ethyl phthalan (94). *Exo*- (1-Ethyl phthalan)Cr(CO)$_3$ (**91**) was decomplexed according to the standard procedure to afford the *title compound* as a colourless oil (75%), $\nu_{max.}$ 1260 (C-O) cm^{-1}; δ_H 7.29-7.16 (4H, m, Ar), 5.22 (1H, br s, ArC*H*Et), 5.14, 5.08 (2H, ABX system, J_{AB} 12.1Hz, J_{AX} 2.5Hz, J_{BX} 1.3Hz, Ar$\mathbf{CH}_2$O), 1.99-1.71 (2H, m, $\mathbf{CH}_2CH_3$), 0.99 (3H, t, J 7.4Hz, $CH_2\mathbf{CH}_3$); δ_C 141.97, 139.65, 127.29, 127.14, 121.14, 120.90, 85.02, 72.59, 29.01, 9.16; *m/z* 147 (M^+-1) (Found: C, 80.95; H, 8.6. $C_{10}H_{12}O$ requires C, 81.0; H, 8.2%).

1-Benzyl phthalan (95). *Exo*- (1-Benzyl phthalan)Cr(CO)$_3$ (**92**) was decomplexed according to the standard procedure to afford the *title compound* as a colourless oil (81%), $\nu_{max.}$ 1255 (C-O) cm^{-1}; δ_H 7.43-7.05 (9H, m, Ar), 5.55 (1H, br s, ArC**H**$\mathbf{CH}_2$Ph), 5.09 (2H, br s, Ar$\mathbf{CH}_2$O), 5.14 (2H, m, PhC$\mathbf{H}_2$CH); δ_C 141.47, 139.43, 137.72, 129.52, 128.31, 128.17, 128.05, 127.34, 126.87, 126.17, 121.40, 120.76, 84.32, 72.34, 42.68; *m/z* 209 (M^+-1) (Found: C, 85.8; H, 7.1. $C_{15}H_{14}O$ requires C, 85.7; H, 6.7%).

***Exo-Cis*-(1-3-Dimethyl phthalan)Cr(CO)$_3$ (96).** To a stirred solution of *exo*-(1-methyl phthalan)Cr(CO)$_3$ (**90**) (0.124g, 0.46mmol) in THF (20ml) at -78°C was added *t*-butyllithium (0.2ml, 0.52mmol) and the resultant red solution stirred (-78°C, 1h). MeI (1ml, 16.1mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (2ml) the reaction mixture was warmed and evaporated. Column chromatography (Al_2O_3 grade V, Et_2O) gave a single fraction as a yellow oil that solidified on standing (0.118g, 91%). Recystallisation from Et_2O/pentane afforded the *title compound* as yellow plates, $\nu_{max.}$ 1970 and 1880 (C≡O) cm^{-1}; δ_H 5.46-5.25 [4H, m, $C_6H_4Cr(CO)_3$], 5.13 (2H, q, J 6.5Hz, ArC**H**CH$_3$), 1.49 (6H, d, J 6.5Hz, ArCHC**H**$_3$); *m/z* 284 (M^+) (Found: C, 55.0; H, 4.1. $C_{13}H_{12}CrO_4$ requires C, 54.9; H, 4.3%).

***Cis*-1-3-Dimethyl phthalan (97).**[81,82] *Exo-Cis*-(1-3-Dimethyl phthalan)Cr(CO)$_3$ (**96**) was decomplexed according to the standard procedure to afford the *title compound* as a colourless oil, δ_H 7.30-7.13 (4H, m, Ar), 5.23 (2H, q, J 6.2Hz, ArC**H**CH$_3$), 1.54 (6H, d, J 6.3Hz, ArCHC**H**$_3$); *m/z* 147 (M^+-1).

***Exo-Cis*-(1-Methyl-3-deuterio phthalan)Cr(CO)$_3$ (98).** To a stirred solution of *exo*-(1-methyl phthalan)Cr(CO)$_3$ (**90**) (0.306g, 1.13mmol) in THF (30ml) at -78°C was added *t*-butyllithium (0.45ml, 1.18mmol) and the resultant red solution stirred (-78°C, 1h). CD_3OD (1ml) was added and stirring continued (-78°C, 30min). The reaction mixture was warmed, evaporated and subjected to column chromatography (Al_2O_3 grade V, Et_2O) to give the *title compound* as a yellow oil (0.118g, 93%), δ_H 5.53-5.23 [4H, m, $C_6H_4Cr(CO)_3$], 5.14 (1H, q, J 6.5Hz, ArC**H**CH$_3$), 4.82 (1h, br s, ArC**H**D), 1.43 (3H, d, J 6.5Hz, ArCHC**H**$_3$); δ_D 5.53 (1D, br s, ArC**H**D); *m/z* 271 (M^+). Integration of the molecular ion peak (M^+ 271) with respect to that of complex **90** revealed *ca.* 95% deuterium incorporation.

***Exo-Cis*-(1-3-Dideuterio phthalan)Cr(CO)$_3$ (99).** To a stirred solution of *exo*-(1-deuterio phthalan)Cr(CO)$_3$ (**93**) (0.028g, 0.11mmol) in THF (15ml) at -78°C was added *t*-butyllithium (0.07ml, 0.18mmol) and the resultant red solution stirred (-78°C, 1h). CD_3OD (0.5ml) was added and stirring continued (-78°C, 30min). The reaction mixture was warmed, evaporated and subjected to column chromatography (Al_2O_3 grade V, Et_2O) to give the *title compound* as a yellow solid (0.026g, 92%), δ_H 5.53-5.25 [4H, m, $C_6H_4Cr(CO)_3$], 4.86 (2H, br s, ArC**H**D); δ_D 4.93 (2D, br s, ArC**H**D); *m/z* 258 (M^+). Integration of the ^1H n.m.r. signals of the *endo* benzylic protons with respect to those for the *exo* benzylic protons of complex **93** revealed *ca.* 82% deuterium incorporation consistent with a kinetic isotope effect of *ca.* 2 for the preferential removal of the 3-*exo* proton over the 1-*exo*-deuteron in complex **93**.

***Cis*-1,3-Dideuterio phthalan (100).** *Exo-cis*-(1-3-dideuterio phthalan)Cr(CO)$_3$ (**99**) was decomplexed according to the standard procedure to afford the *title compound* as a colourless oil, δ_H 7.32-7.30 (4H, br s, Ar), 5.16 (2H, br s, ArC**H**D).

General procedure for the alkylation of phthalan (82). A stirred solution of phthalan (**82**) (1.44g, 11.9mmol) in THF (30ml) at -78°C was treated with *t*-butyllithium (4.8ml, 12.6mmol) giving a red colouration that darkened with time. The mixture was stirred (-78°C, 6h) and treated with MeI (2ml,

32.1mmol) discharging the colouration immediately. Stirring was continued (-78°C, 1.6h), MeOH (10ml) added and the solution stirred (20°C, 12h). The solvent was removed, water (40ml) added and the aqueous layer extracted (Et_2O, 3x40ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated affording 1-methyl phthalan (**70**) as a pale brown oil that darkened upon prolonged exposure to air (1.02g, 64%). The use of EtI as the electrophile yielded 1-ethyl phthalan (**94**) as a colourless oil (76%) whilst benzyl bromide afforded 1-benzyl phthalan (**95**) (57%).

Methylation of 1-methyl phthalan (70). A stirred solution of 1-methyl phthalan (**70**) (0.129g, 0.96mmol) in THF (10ml) at -78°C was treated with *t*-butyllithium (0.4ml, 1.05mmol). The mixture was stirred (-78°C, 4.3h) and treated with MeI (0.5ml, 8.05mmol) discharging the colouration. Stirring was continued (-78°C, 1h) and the reaction quenched by the addition of MeOH (5ml). The solution was stirred (20°C, 12h), concentrated and water (15ml) added. The aqueous layer was extracted (Et_2O, 3x10ml) and the combined extracts dried ($MgSO_4$). Filtration and evaporation gave a pale yellow oil (0.105g, 74%). ^1H n.m.r. of the product revealed the presence of both *cis*- and *trans*-1,3-dimethyl phthalan (**97** and **101** respectively)[81,82] in the ratio 42:58. δ_H (**101**) 7.30-7.14 (4H, m, Ar), 5.41 (2H, q, J 5.7Hz, ArC**H**CH$_3$), 1.48 (3H, d, J 6.2Hz, ArCHC**H**$_3$); *m/z* 166 (M^++18).

(+)-(S)-2,3-Dimethyl tetrahydroisoquinoline (119).[91] (D)-Amphetamine sulphate (17.9g, 48.6mmol) was treated with NaOH (1M, 200ml) and the solution extracted with benzene (3x100ml). The combined extracts were dried ($MgSO_4$) and evaporated to furnish (+)-(S)-amphetamine (**120**) (13.0g, 99%). This material was heated with HCOOH (11.1g, 241mmol) (180°C, 4h), the oil obtained dissolved in orthophosphoric acid (60ml, 876mmol) and treated with P_2O_5 (100g, 705mmol). The mixture was heated (200°C, 3h) and the cooled solution poured onto crushed ice (800ml). The solution was washed with benzene (3x100ml), neutralised with $NaHCO_3$ and mixture extracted with benzene (5x100ml). The combined extracts were dried (Na_2SO_4), evaporated and the yellow oil obtained dissolved in $(CH_3)_2CO$ (60ml). Addition of MeI (10.0ml, 161mmol) resulted in the formation of yellow needles which were collected by filtration, dissolved in EtOH (87ml) and treated with $NaBH_4$ (6.92g, 183mmol). The solution was stirred (20°C, 12h), water added and the mixture extracted (Et_2O, 3x100ml). The combined extracts were evaporated to afford the *title compound* as a colourless oil (7.85g, 50%); $\nu_{max.}$ 2780 (NMe) cm^{-1}; δ_H 7.15-7.03 (4H, m, C_6H_4), 3.84, 3.58 (2H, AB system, J_{AB} 15.4Hz, $C_6H_4CH_2N$), 2.89-2.65 (3H, m, $C_6H_4CH_2CHMe$), 2.43 (3H, s, NC**H**$_3$), 1.19 (3H, d, J 6.2Hz, CHC**H**$_3$).

Thermolysis of $Cr(CO)_6$ with (+)-(S)-2,3-dimethyl tetrahydroisoquinoline (119).[58] A mixture of (+)-(S)-2,3-dimethyl tetrahydroisoquinoline (**119**) (1.77g, 11.0mmol) and $Cr(CO)_6$ (2.66g, 12.1mmol) in Bu_2O (140ml) and THF (17ml) was reacted according to the standard complexation procedure (23h) to give a mixture of *exo*-(2,3-dimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**111**) and *endo*-(2,3-dimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**112**) (ratio 59:41) as a yellow solid (2.82g, 87%). H.p.l.c. analysis [Hypersil 5μ, hexane/EtOH (6:1) + 0.2% H_2O (v/v) gave two peaks (R_f 8.05min, 59.2% and R_f 9.40min, 40.8%)], $\nu_{max.}$ (Nujol) 1960 and 1890 (C≡O) cm^{-1}; δ_H 5.30-5.21 [4H, m, $(CO)_3CrC_6H_4$], 3.68, 3.47 [2H, AB system, J_{AB} 15.5Hz, $(CO)_3CrC_6H_4CH_2N$ for **111**], 3.59, 3.47 [2H, AB system, J_{AB} 15.6Hz, $(CO)_3CrC_6H_4CH_2N$ for

112], 2.66-2.59 [3H, m, $(CO)_3CrC_6H_4CH_2CHMe$], 2.40 (3H, s, NCH_3 for **112**), 2.37 (3H, s, NCH_3 for **111**), 1.19 (3H, d, J 5.7Hz, $CHCH_3$); *m/z* 297 (M^+).

Treatment of *exo*- and *endo*-(2,3-dimethyl tetrahydroisoquinoline)Cr(CO)$_3$ (111 and 112) with *n*-butyllithium and MeI. A stirred solution of *exo*-(2,3-dimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**111**) and *endo*-(2,3-dimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**112**) (ratio 60:40) (2.74g, 9.22mmol) in THF (60ml) at -68°C was treated with *n*-butyllithium (6.15ml, 10.1mmol) and the resultant red solution stirred (-68°C, 2h). MeI (1.70ml, 27.3mmol) was added and stirring continued (-68°C, 2h). The reaction was quenched with MeOH (3ml), the solution warmed and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a mixture of *cis*-(2,3,4-trimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**113**) and *trans*-(2,3,4-trimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**114**) as a yellow solid (ratio 60:40) as a yellow solid (2.53g, 88%). H.p.l.c. analysis [Hypersil 5μ, hexane/EtOH (9:1) gave two peaks (R_f 2.75min, 60% and R_f 3.13min, 40%)], $\nu_{max.}$ 1965 and 1880 (C≡O) cm^{-1}; δ_H 5.34-5.21 [4H, m, $(CO)_3CrC_6H_4$], 3.70, 3.38 [2H, AB system, J_{AB} 15.6Hz, $(CO)_3CrC_6H_4CH_2N$ for **113**], 3.45, 3.42 [2H, AB system, J_{AB} 14.8Hz, $(CO)_3CrC_6H_4CH_2N$ for **114**], 2.69-2.45 [2H, m, $(CO)_3CrC_6H_4CHMeCHMe$], 2.40 (3H, s, NCH_3 for **114**), 2.33 (3H, s, NCH_3 for **113**), 1.33 [3H, d, J 6.9Hz, $(CO)_3CrC_6H_4CHCH_3$ for **114**], 1.24 [3H, d, J 7.1Hz, $(CO)_3CrC_6H_4CHCH_3$ for **113**], 1.21 (3H, d, J 6.5Hz, $CHCH_3$ for **114**), 1.11 (3H, d, J 5.7Hz, $CHCH_3$ for **113**); *m/z* 311 (M^+).

Treatment of *cis*- and *trans*-(2,3,4-trimethyl tetrahydroisoquinoline)Cr(CO)$_3$ (113 and 114) with *t*-butyllithium and MeI. A stirred solution of *cis*-(2,3,4-trimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**113**) and *trans*-(2,3,4-trimethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**114**) (ratio 60:40) (2.57g, 8.13mmol) in THF (60ml) at -70°C was treated with *t*-butyllitium (3.25ml, 8.52mmol) and the resultant red solution stirred (-70°C, 2h). MeI (1.60ml, 25.7mmol) was added and stirring continued (-70°C, 2h). The reaction was quenched with MeOH (3ml), the solution warmed and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a yellow oil that comprised two components in the ratio 60:40 according to ^1H n.m.r. spectroscopy. A portion of this material was subjected to flash chromatography (SiO_2, Et_2O) to give two fractions, the first of which was identified as (+)-(1R,3S,4R)-(1,2,3,4-tetramethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**115**), $[\alpha]_{546}^{20}$ +160.60 (*c* 1.06 $CHCl_3$); δ_H 5.38-5.17 [4H, m, $(CO)_3CrC_6H_4$], 3.32 [1H, q, J 6.5Hz, $(CO)_3CrC_6H_4CHMeN$], 2.83 (1H, dq, J 2.6 and 5.7Hz, $CHCH_3$), 2.35 (3H, s, NCH_3), 2.30 [1H, dq, J 2.6 and 7.0Hz, $(CO)_3CrC_6H_4CHMe$], 1.41 [3H, d, J 6.5Hz, $(CO)_3CrC_6H_4CHCH_3N$], 1.22 [3H, d, J 5.7Hz, $(CO)_3CrC_6H_4CHCH_3$], 1.16 (3H, d, J 6.5Hz, $CHCH_3$); *m/z* 325 (M^+). The second fraction was subjected to further purification [SiO_2, petroleum ether/Et_2O (4:1)] to furnish (+)-(1S,3S,4S)-(1,2,3,4-tetramethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**116**) as a yellow powder, $[\alpha]_D^{23}$ +17.70 (*c* 0.35 $CHCl_3$); $\nu_{max.}$ 2795 (NMe), 1970 and 1880 (C≡O) cm^{-1}; δ_H 5.35-5.24 [4H, m, $(CO)_3CrC_6H_4$], 3.56 [1H, q, J 5.7Hz, $(CO)_3CrC_6H_4CHMeN$], 2.71 (1H, qu, J 6.5Hz, $CHCH_3$), 2.52 [1H, qu, J 6.9Hz, $(CO)_3CrC_6H_4CHMe$], 2.47 (3H, s, NCH_3), 1.37 [3H, d, J 6.8Hz, $(CO)_3CrC_6H_4CHCH_3N$], 1.30 [3H, d, J 7.0Hz, $(CO)_3CrC_6H_4CHCH_3$], 1.24 (3H, d, J 6.6Hz, $CHCH_3$); *m/z* 325 (M^+) (Found: C, 59.2; H, 6.1; N, 4.05. $C_{16}H_{19}CrNO_3$ requires C, 59.1; H, 5.9; N, 4.3%). Differential nOe experiments were performed separately on both (+)-**115** and (+)-**116** as [d]$_6$-benzene solutions at 500MHz. For complex (+)-**115**, irradiation of the C3-methyl doublet gave enhancements to both H3 (13%) and H4 (9%) whilst irradiation of the

C4-methyl doublet gave a single enhancement to H4 (15%). For complex (+)-**116**, irradiation of the C3-methyl doublet gave enhancements of H3 (15%) and H4 (15%) whilst separate irradiation of the C4-methyl doublet gave enhancements to both H3 (20%) and H4 (20%).

(+)-(1R,3S,4S)-1,2,3,4-Tetramethyl tetrahydroisoquinoline (117). A solution of (+)-(1R,3S,4R)-(1,2,3,4-tetramethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**115**) (0.224g, 0.69mmol) was decomplexed according to the standard procedure to furnish the *title compound* as a colourless oil (0.125g, 96%), $[\alpha]_D^{20}$ +99.40 (*c* 0.51 $CHCl_3$); $\nu_{max.}$ 2787 (NMe) cm^{-1}; δ_H 7.18-7.06 (4H, m, $C_6\mathbf{H}_4$), 3.44 (1H, q, J 6.4Hz, $C_6H_4C\mathbf{H}MeN$), 2.64 (2H, m, $C_6H_4C\mathbf{H}MeC\mathbf{H}Me$), 2.40 (3H, s, $NC\mathbf{H}_3$), 1.48 (3H, d, J 6.4Hz, $C_6H_4CHC\mathbf{H}_3N$), 1.23 (3H, d, J 6.8Hz, $C_6H_4CHC\mathbf{H}_3$), 1.19 (3H, d, J 6.3Hz, $CHC\mathbf{H}_3$); δ_C 141.8, 139.3, 127.5, 126.6, 125.7, 125.5, 61.2, 57.4, 40.3 (2C), 23.5, 18.9, 17.0; *m/z* 188 (M^+-1) (Found: M^+-1, 188.1439. $C_{13}H_{19}N$ requires M^+-1 188.1439).

(-)-(1S,3S,4R)-1,2,3,4-Tetramethyl tetrahydroisoquinoline (118). A solution of (+)-(1S,3S,4S)-(1,2,3,4-tetramethyl tetrahydroisoquinoline)$Cr(CO)_3$ (**116**) (0.221g, 0.68mmol) was decomplexed according to the standard procedure to furnish the *title compound* as a colourless oil (0.112g, 87%), $[\alpha]_D^{19}$ -9.20 (*c* 0.26 $CHCl_3$); $\nu_{max.}$ 2790 (NMe) cm^{-1}; δ_H 7.80-7.07 (4H, m, $C_6\mathbf{H}_4$), 3.66 (1H, q, J 6.6Hz, $C_6H_4C\mathbf{H}MeN$), 2.91 (1H, qu, J 6.3Hz, $C\mathbf{H}Me$), 2.62 (1H, qu, J 6.6Hz, $C_6H_4C\mathbf{H}Me$), 2.43 (3H, s, $NC\mathbf{H}_3$), 1.41 (3H, d, J 6.6Hz, $C_6H_4CHC\mathbf{H}_3N$), 1.36 (3H, d, J 6.9Hz, $C_6H_4CHC\mathbf{H}_3$), 1.06 (3H, d, J 6.5Hz, $CHC\mathbf{H}_3$); δ_C 139.1, 138.7, 128.4, 126.6, 125.9, 125.4, 57.4, 57.0, 39.2, 38.4, 21.8, 20.8, 14.5; *m/z* 188 (M^+-1) (Found: M^+-1, 188.1439. $C_{13}H_{19}N$ requires M^+-1 188.1439).

(-)-[(N-Methyl-O-methyl)ephedrine]$Cr(CO)_3$ (127).[99] A mixture of (-)-(1R,2S)-ephedrine (**122**) (80.0g, 484mmol) and HCOOH (98-100%, 500ml) was treated with formaldehyde (37% aqueous solution, 500ml) and the mixture heated at reflux (3h). The acid was removed under reduced pressure, the solution basified (NaOH) and the aqueous phase extracted (Et_2O). The combined extracts were evaporated and the solid obtained recrystallised from MeOH to give (-)-(1R,2S)-N-(methyl)ephedrine as colourless needles (74.15g, 85%), $[\alpha]_D^{20}$ -30.30 (MeOH) {lit.[150] $[\alpha]_D^{20}$ -29.2 (MeOH)}; m.p. 85-6°C (lit.[150] 87-8°C). A portion of this material (65.44g, 365 mmol) in THF (200ml) was added in a dropwise manner to a stirred suspension of KH (43.8g, 1.09mol) in THF (200ml). The mixture was heated at reflux (20h) and the externally cooled solution (<0°C) treated with MeI (25ml, 402mmol). The mixture was stirred (20°C, 1h) and MeOH (40ml) cautiously added. The product was filtered (celite) and evaporated to leave a pale yellow oil. Distillation under reduced pressure gave (-)-(1R,2S)-(N-methyl-O-methyl)ephedrine[99] as a colourless oil (87°C, 0.06mm Hg) (44.0g, 62%), $[\alpha]_D^{20}$ -30.30 (*c* 1.32 MeOH); δ_H 7.48-7.22 (5H, m, Ph), 4.36 (1H, d, J 4.3Hz, PhC**H**), 3.28 (3H, s, $OC\mathbf{H}_3$), 2.62 (1H, m, CHMe), 2.38 [6H, s, $N(C\mathbf{H}_3)_2$], 0.99 (3H, d, J 6.6Hz, $CHC\mathbf{H}_3$); δ_C 129.01-125.73 (6C), 84.52, 65.09, 56.58, 41.68 (2C), 7.97; *m/z* 194 (M^++1) (Found: C, 74.8; H, 10.0; N, 7.3. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.9; N, 7.25%). A portion of this material (1.26g, 6.54mmol) and $Cr(CO)_6$ (1.55g, 7.05mmol) in dioxan (50ml) were reacted according to the standard complexation procedure to give a yellow solid. Recrystallisation from CH_2Cl_2/hexane gave the *title compound* as yellow plates (0.615g, 29%), m.p. 81-2°C;

δ_H 5.66-5.26 [5H, m, $(CO)_3CrPh$]; 4.00 [1H, d, J 4.4Hz, $(CO)_3CrPhCH(OH)$], 3.58 (3H, s, OCH_3), 2.55 (1H, dq, J 4.4 and 6.8Hz, CHMe), 2.31 [6H, s, $N(CH_3)_2$], 0.97 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 330 (M^+).

(-)-[(N-Methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (128).[99] (-)-(1R,2R)-(N-Methyl-O-methyl)pseudoephedrine [prepared from (-)-(1R,2R)-pseudoephedrine (**123**) in a manner analogous to that for (-)-(1R,2S)-(N-methyl-O-methyl)ephedrine] (2.09g, 10.8mmol) and $Cr(CO)_6$ in Bu_2O (50ml) and THF (8ml) were reacted according to the standard complexation procedure to give a yellow solid. Recrystallisation from CH_2Cl_2/hexane afforded the *title compound* as yellow blocks (1.59g, 44%), m.p. 59-61°C; δ_H 5.65-5.23 [5H, m, $(CO)_3CrPh$]; 3.91 [1H, d, J 4.7Hz, $(CO)_3CrPhCH(OH)$], 3.58 (3H, s, OCH_3), 2.64 (1H, dq, J 4.7 and 6.8Hz, CHMe), 2.26 [6H, s, $N(CH_3)_2$], 0.90 (3H, d, J 6.8Hz, $CHCH_3$).

(+)-[*Ortho*-Formyl-(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (129). To a stirred solution of (-)-[(N-methyl-O-methyl)ephedrine]$Cr(CO)_3$ (**127**) (0.549g, 1.67mmol) in THF (40ml) at -78°C was added *t*-butyllithium (0.65ml, 1.70mmol) and the solution stirred (-78°C, 2h). Ethyl formate (1.5ml, 18.6mmol) was added and stirring continued (-78°C, 6.75h). After addition of MeOH (1ml) the red solution was warmed and evaporated. Column chromatography [Al_2O_3 grade V, CH_2Cl_2/MeOH (10:1)] gave a red fraction as an oil that solidified on standing. ^1H n.m.r. spectroscopy of the crude material revealed the presence of the *title compound* and the starting material in the ratio 75:25 [0.425g, 71% (96% based on recovered starting material)]. Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ +392.8 (*c* 0.14 $CHCl_3$); m.p. 113-5°C; $\nu_{max.}$ 1970 and 1890 (C≡O), 1675 (C=O) cm^{-1}; δ_H 10.11 (1H, s, CHO), 5.90-5.18 [4H, m, $(CO)_3CrC_6H_4$], 3.85 [1H, d, J 4.4Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.57 (3H, s, OCH_3), 3.00 (1H, dq, J 4.3 and 7.0Hz, CHMe), 2.13 [6H, s, $N(CH_3)_2$], 1.01 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 358 (M^++1) (Found: C, 53.5; H, 5.5; N, 3.6. $C_{16}H_{19}CrNO_5$ requires C, 53.8; H, 5.4; N, 3.9%). The use of *n*-butyllithium as the base or DMF as the electrophile also furnished the *title compound* along with recovery of some starting material.

(+)-[*Ortho*-Formyl-(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (130). To a stirred solution of (-)-[(N-methyl-O-methyl)pseudoephedrine]$Cr(CO)_3$ (**128**) (0.513g, 1.56mmol) in THF (40ml) at -78°C was added *t*-butyllithium (0.60ml, 1.57mmol) and the solution stirred (-78°C, 2h). Ethyl formate (1.5ml, 18.6mmol) was added and stirring continued (-78°C, 6.75h). After addition of MeOH (1ml) the red solution was warmed and evaporated. Column chromatography [Al_2O_3 grade V, CH_2Cl_2/MeOH (10:1)] gave a red oil that, according to ^1H n.m.r. spectroscopy of the crude material comprised the *title compound* and the starting material in the ratio 26:74 [0.50g, 24% (84% based on unreacted starting material)]. Crystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ +220.0 (*c* 0.13 $CHCl_3$); m.p. 98-100°C; $\nu_{max.}$ 1975 and 1905 (C≡O), 1675 (C=O) cm^{-1}; δ_H 9.88 (1H, s, CHO), 5.85-5.26 [4H, m, $(CO)_3CrC_6H_4$], 3.76 [1H, d, J 2.6Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.64 (3H, s, OCH_3), 2.50 (1H, dq, J 2.6 and 7.0Hz, CHMe), 2.12 [6H, s, $N(CH_3)_2$], 1.20 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 358 (M^++1) (Found: C, 53.9; H, 5.1; N, 3.9. $C_{16}H_{19}CrNO_5$ requires C, 53.8; H, 5.4; N, 3.9%). The use of *n*-butyllithium as the base or DMF as the electrophile also furnished the *title compound* along with recovery of some starting material.

[(α-Methoxy-β-methyl)styrene]Cr(CO)$_3$ (133). A stirred solution of (-)-[(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (**127**) (0.606g, 1.84mmol) in THF (30ml) at -78°C was treated *t*-butyllithium (0.77ml, 2.02mmol) and the solution stirred (-78°C, 2h). Ethylene oxide (excess) and $BF_3.OMe_2$ (0.23ml, 1.84mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (4ml) the mixture was evaporated and the residue purified by column chromatography (Al_2O_3 grade V, Et_2O) to furnish the *title compound* as a red oil. Crystallisation from *n*-pentane gave a pure sample as slender needles, $\nu_{max.}$ 1960 and 1895 (C≡O) cm^{-1}; δ_H 5.65-5.34 [6H, m, $(CO)_3CrPh$ and **CH**Me], 3.75 (3H, s, OCH_3), 1.83 (3H, d, J 7.0Hz, $CHCH_3$); *m/z* 284 (M^+) (Found: M^+, 284.0140. $C_{13}H_{12}CrO_4$ requires M 284.0141). Differential nOe experiments were performed on complex **133** as $CDCl_3$ solutions at 300MHz. Irradiation of the methyl doublet gave an enhancement to the methoxyl singlet (3.7%) whilst separate irradiation of the methoxyl singlet gave enhancements to both the methyl doublet (5%) and to the aromatic protons (11.2%). These results are consistent with Z geometry about the double bond.

(-)-[*Ortho*-(2-Hydroxymethyl)-(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (134). A stirred solution of (+)-[*ortho*-formyl-(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (**129**) (0.091g, 0.25mmol) in THF (15ml) was treated with $NaBH_4$ (0.024g, 0.64mmol) producing a colour change from red to yellow. The solution was stirred (20°C, 3h), MeOH (5ml) added followed by addition of aqueous NH_4Cl (10ml). The solvent was evaporated, water (5ml) added and the aqueous phase extracted (Et_2O, 3x25ml). The combined extracts were purified by column chromatography [Al_2O_3 grade V, Et_2O/petroleum ether (1:1)] to furnish the *title compound* as a yellow oil (0.060g, 66%). Crystallisation from Et_2O/petroleum ether gave a pure sample for characterisation, $[\alpha]_D^{23}$ -66.17 (*c* 0.11 $CHCl_3$); m.p. 115-8°C; $\nu_{max.}$ 1970 and 1890 (C≡O) cm^{-1}; δ_H 5.53-5.15 [4H, m, $(CO)_3CrC_6H_4$], 4.83, 4.16 [2H, AB system, J_{AB} 12.3Hz, $(CO)_3CrC_6H_4CH_2OH$], 3.47 (3H, s, OCH_3), 3.05 (1H, dq, J 5.0 and 7.0Hz, **CH**Me), 2.18 [6H, s, $N(CH_3)_2$], 1.10 (3H, d, J 7.0Hz, $CHCH_3$); *m/z* 360 (M^++1) (Found: C, 53.1; H, 6.0; N, 4.2. $C_{16}H_{21}CrNO_5$ requires C, 53.5; H, 5.9; N, 3.9%). In a repeat experiment, $NaBD_4$ was used as the reducing agent to afford complex **135** as a yellow solid (64%). The ^1H n.m.r. spectrum of the product exhibited the same features as that of complex (-)-**134** except that the AB system at δ4.83, 4.16 had been replaced by a 1 proton broad singlet at δ4.16; *m/z* 361 (M^++1).

(-)-[*Ortho*-(2-Hydroxyethyl)-(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (136). To a stirred solution of (+)-[*ortho*-formyl-(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (**129**) (0.037g, 0.10mmol) in THF (15ml) at -78°C was added methyllithium (1.0ml, 1.1mmol) and the solution stirred (-78°C, 6h). MeOH (2ml) was added, the solution warmed and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a yellow oil that comprised three components according to ^1H n.m.r. spectroscopy. The minor component was identified as starting material whilst the other two components (ratio 86:14) were assigned as the *title compound* (major) and either complex **137** or **138** (minor). Two crystallisations from Et_2O/hexane furnished a pure sample of the *title compound* as slender yellow needles, $[\alpha]_D^{20}$ -32.71 (*c* 0.17 $CHCl_3$); m.p. 99-100°C; $\nu_{max.}$ 1965 and 1880 (C≡O) cm^{-1}; δ_H 5.69-5.13 [4H, m, $(CO)_3CrC_6H_4$], 5.01 [1H, q, J 6.3Hz, $(CO)_3CrC_6H_4CHMe$], 3.85 [1H, d, J 6.3Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.29 (3H, s, OCH_3), 3.10 (1H, br s, **OH**), 2.91 (1H, qu, J 6.5Hz, **CH**Me), 2.28 [6H, s, $N(CH_3)_2$], 1.51 (3H, d, J 6.3Hz, $CHCH_3$), 1.11 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 374 (M^++1) (Found: C, 54.9; H, 6.3; N, 3.6. $C_{17}H_{23}CrNO_5$ requires C, 54.7; H, 6.2;

N, 3.75%). A repeat experiment in the presence of TMEDA (16 equivalents) again gave an 86:14 mixture of addition products. A repeat experiment using MeMgI (2 equivalents) over 2 hours gave less than 30% conversion to the addition products. A longer reaction time (6.5h) in the presence of 10 equivalents of the Grignard reagent gave near complete conversion to give the two addition products in the ratio 88:12. A single crystal X-ray structure determination of (+)-**136** confirmed both the relative and absolute stereochemistry of this complex (see appendix).

[*Ortho*-(2-Hydroxyethyl)-(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (139). To a stirred solution of (+)-[*ortho*-formyl-(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (**130**) (0.030g, 0.08mmol) in THF (15ml) at -78°C was added methyllithium (0.15ml, 0.23mmol) and the solution stirred (-78°C, 2h). MeOH (0.5ml) was added, the solution warmed and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a single fraction as a yellow oil (0.016g, 52%) that comprised two components in the ratio 86:14 according to ^{1}H n.m.r. spectroscopy of the crude material. The major product was assigned as the *title compound* by analogy with the previous reaction but all attempts at its isolation failed, δ_H 5.85-5.15 [5H, m, (CO)$_3$CrC$_6$H$_4$ and (CO)$_3$CrC$_6$H$_4$CHMe], 3.76 [1H, br s, (CO)$_3$CrC$_6$H$_4$CH(OMe)], 3.51 (3H, s, OCH$_3$), 2.91 (1H, qu, J 7.1Hz, CHMe), 2.34 [6H, s, N(CH$_3$)$_2$], 1.47 (3H, d, J 6.3Hz, CHCH$_3$), 0.93 (3H, d, J 6.9Hz, CHCH$_3$).

(+)-(2-Methyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (144). A mixture of (-)-(1R,2S)-ephedrine (**122**) (4.00g, 24.2mmol) and acetaldehyde (3.0ml, 53.1mmol) in CH_2Cl_2 (50ml) was treated with molecular sieves and the solution stirred (20°C, 0.5h). The mixture was filtered and evaporated to leave (+)-(2S,4S,5R)-2-methyl-N-methyl-4-methyl-5-phenyloxazolidine (**140**)[102] as a colourless oil that was essentially a single diastereoisomer (4.58g, 99%), δ_H 7.32-7.25 (5H, m, Ph), 5.00 (1H, d, J 8.0Hz, PhCH), 3.95 (1H, q, J 5.2Hz, OCHMe), 2.77 (1H, dq, J 6.5 and 8.0Hz, CHMe), 2.25 (3H, s, NCH$_3$), 1.48 (3H, d, J 5.1Hz, OCHCH$_3$), 0.68 (3H, d, J 6.5Hz, CHCH$_3$); *m/z* 192 (M^++1). This material was distilled under reduced pressure (78-80°C, 0.06mm Hg) and a portion of the colourless oil obtained (4.33g, 22.6mmol) was reacted with Cr(CO)$_6$ (5.00g, 22.7mmol) in Bu_2O (100ml) and THF (12ml) according to the standard complexation procedure (14.5h). The *title compound* was isolated as a yellow solid after recrystallisation from Et_2O/hexane {0.129g, 2% [3% based on recovered Cr(CO)$_6$]}, $[\alpha]_D^{20}$ +160.70 (*c* 0.12 $CHCl_3$); $\nu_{max.}$ 1975 and 1895 (C≡O) cm^{-1}; δ_H 5.55-5.14 [5H, m, (CO)$_3$CrPh], 4.56 [1H, d, J 7.7Hz, (CO)$_3$CrPhCH], 3.92 (1H, q, J 5.2Hz, OCHMe), 2.74 (1H, qu, J 7.0Hz, CHMe), 2.21 (3H, s, NCH$_3$), 1.43 (3H, d, J 5.2Hz, OCHCH$_3$), 0.88 (3H, d, J 6.4Hz, CHCH$_3$); *m/z* 327 (M^+) (Found: C, 55.8; H, 5.5; N, 4.1. $C_{15}H_{17}CrNO_4$ requires C, 55.05; H, 5.2; N, 4.3%).

(+)-(2-Cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (145). A mixture of (-)-(1R,2S)-ephedrine (**122**) (10.0g, 60.5mmol) and cyclohexanone (10.0ml, 96.5mmol) in benzene (100ml) was heated at reflux in a Dean-Stark water separator (22h). The solvent was evaporated and the residue subjected to distillation under reduced pressure to afford (+)-(4S,5R)-2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine (**141**)[103] as a colourless oil that that solidified on standing (166°C, 0.06mm Hg) (13.56g, 91%), $[\alpha]_D^{20}$ +9.53 (*c* 1.18 $CHCl_3$) {lit.[103] $[\alpha]_D^{20}$ +8.0 ($CHCl_3$)}; m.p. 72-3°C (lit.[103] 77-7.5°C); $\nu_{max.}$ 3010 (aryl-H), 700

(mono-substituted arene) cm^{-1}; δ_H 7.34-7.22 (5H, m, Ph), 5.07 (1H, d, J 8.0Hz, PhC**H**), 3.25 (1H, dq, J 6.5 and 7.9Hz, C**H**Me), 2.30 (3H, s, NC**H**$_3$), 1.75-1.13 [10H, m, (C**H**$_2$)$_5$], 0.63 (3H, d, J 6.4Hz, CHC**H**$_3$); δ_C 140.55, 127.68 (2C), 127.52 (2C), 127.20, 95.41, 80.38, 60.21, 35.68, 33.33, 27.30, 25.80, 23.63, 22.78, 15.60; *m/z* 245 (M^+). A portion of this material (3.00g, 12.2mmol) and $Cr(CO)_6$ (3.00g, 13.6mmol) in Bu_2O (50ml) and THF (4ml) were reacted according to the standard complexation procedure (16.5h) to furnish the *title compound* as a yellow solid (1.98g, 42%), $[\alpha]_D^{20}$ +155.94 (*c* 0.32 $CHCl_3$); m.p. 107°C; $\nu_{max.}$ 1973 and 1890 (C≡O) cm^{-1}; δ_H 5.57-5.13 [5H, m, (CO)$_3$CrPh], 4.57 [1H, d, J 8.0Hz, (CO)$_3$CrPhC**H**], 3.20 (1H, dq, J 6.5 and J 7.7Hz, C**H**Me), 2.26 (3H, s, NC**H**$_3$), 1.89-1.09 [10H, m, (C**H**$_2$)$_5$], 0.83 (3H, d, J 6.4Hz, CHC**H**$_3$); *m/z* 381 (M^+) (Found: C, 59.55; H, 6.2; N, 3.8. $C_{19}H_{23}CrNO_4$ requires C, 59.8; H, 6.1; N, 3.7%).

(+)-(2-Methyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (146). A mixture (-)-(1R,2R)-pseudoephedrine (**123**) (3.30g, 20.0mmol) and acetaldehyde (3.50ml, 62.6mmol) in CH_2Cl_2 (40ml) was treated with molecular sieves and the solution stirred (20°C, 0.5h). The mixture was filtered and evaporated to leave (+)-(2R,4R,5R)-2-methyl-N-methyl-4-methyl-5-phenyloxazolidine (**142**)[102] as a colourless oil that was essentially a single diastereoisomer (3.83g, quantitative), δ_H 7.36-7.26 (5H, m, Ph), 4.54 (1H, d, J 8.8Hz, PhC**H**), 4.24 (1H, q, J 5.2Hz, OC**H**Me), 2.36 (1H, m, C**H**Me), 2.28 (3H, s, NC**H**$_3$), 1.40 (3H, d, J 5.2Hz, OCHC**H**$_3$), 1.15 (3H, d, J 6.1Hz, CHC**H**$_3$); *m/z* 192 (M^++1). This material was distilled under reduced pressure (67°C, 0.06mm Hg) and a portion of the colourless oil obtained (1.32g, 6.90mmol) was reacted with $Cr(CO)_6$ (1.30g, 5.91mmol) in Bu_2O (50ml) and THF (6ml) according to the standard complexation procedure (25h) to afford the *title compound* as a yellow solid (0.30g, 13%), $[\alpha]_D^{20}$ +93.20 (*c* 0.09 $CHCl_3$); $\nu_{max.}$ 1970 and 1890 (C≡O) cm^{-1}; δ_H 5.48-5.28 [5H, m, (CO)$_3$CrPh], 4.20 [1H, d, J 8.5Hz, (CO)$_3$CrPhC**H**], 4.11 (1H, q, J 5.2Hz, OC**H**Me), 2.36 (1H, m, C**H**Me), 2.26 (3H, s, NC**H**$_3$), 1.37 (3H, d, J 5.2Hz, OCHC**H**$_3$), 1.27 (3H, d, J 6.1Hz, CHC**H**$_3$); *m/z* 328 (M^++1) (Found: C, 55.2; H, 5.3; N, 4.1. $C_{15}H_{17}CrNO_4$ requires C, 55.05; H, 5.2; N, 4.3%).

(+)-(2-Cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (147). A mixture of (-)-(1R,2R)-pseudoephedrine (**123**) (10.0g, 60.5mmol) and cyclohexanone (10.0ml, 96.5mmol) in benzene (100ml) was heated at reflux in a Dean-Stark water separator (45h). The solvent was evaporated and the residue subjected to distillation under reduced pressure to afford (+)-(4R,5R)-2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine (**143**)[103] as an oil that that solidified on standing (136°C, 0.06mm Hg) (14.22g, 96%). Recrystallisation from hexane at -78°C gave a pure sample for characterisation, $[\alpha]_D^{20}$ -41.68 (*c* 1.21 $CHCl_3$) {lit.[103] $[\alpha]_D^{20}$ +41.3 for opposite enantiomer ($CHCl_3$)}; m.p. 69-70°C (lit.[103] 72-2.5°C); $\nu_{max.}$ 700 (mono-substituted arene) cm^{-1}; δ_H 7.39-7.26 (5H, m, Ph), 4.46 (1H, d, J 8.8Hz, PhC**H**), 2.62 (1H, dq, J 6.0 and 8.7Hz, C**H**Me), 2.33 (3H, s, NC**H**$_3$), 1.81-1.14 [10H, m, (C**H**$_2$)$_5$], 1.10 (3H, d, J 6.0Hz, CHC**H**$_3$); δ_C 140.46, 128.20 (2C), 127.61, 126.61 (2C), 95.53, 84.91, 65.06, 36.33, 32.80, 31.22, 25.69, 23.65, 22.69, 14.66; *m/z* 245 (M^+) (Found: C, 78.1; H, 10.0; N, 5.5. $C_{16}H_{23}NO$ requires C, 78.3; H, 9.45; N, 5.7%). A portion of this material (2.00g, 8.15mmol) and $Cr(CO)_6$ (5.00g, 22.7mmol) in Bu_2O (100ml) and THF (12ml) were reacted according to the standard complexation procedure (21h) to furnish the *title compound* as a yellow solid (2.36g, 76%), $[\alpha]_D^{20}$ +156.78 (*c* 0.44 $CHCl_3$); m.p. 114-5°C; $\nu_{max.}$ 1977 and 1890 (C≡O) cm^{-1}; δ_H 5.53-5.26 [5H, m, (CO)$_3$CrPh], 3.99 [1H, d, J 8.7Hz, (CO)$_3$CrPhC**H**], 2.62 (1H, dq, J 6.0 and J 8.7Hz,

CHMe), 2.30 (3H, s, NCH_3), 1.80-1.40 [10H, m, $(CH_2)_5$], 1.15 (3H, d, J 6.0Hz, $CHCH_3$); *m/z* 382 (M^++1) (Found: C, 59.95; H, 6.1; N, 3.7. $C_{19}H_{23}CrNO_4$ requires C, 59.8; H, 6.1; N, 3.7%).

Methylation of (+)-(2-Methyl-N-methyl-4-methyl-5-phenyloxazolidine) $Cr(CO)_3$ (146). A stirred solution of (+)-(2-methyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**146**) (0.057g, 0.17mmol) was treated with *t*-butyllithium (0.07ml, 0.18mmol) producing no apparent colour change. The solution was stirred (-78°C, 2h), MeI (0.5ml, 8.05mmol) added and stirring continued (-78°C, 2h). MeOH (1ml) was added, the solution warmed and evaporated. The residue was purified by column chromatography (Al_2O_3 grade V, CH_2Cl_2) to give the *title compound* as a yellow solid (0.056g, 94%). Recrystallisation from CH_2Cl_2./hexane furnished a pure sample for characterisation, $[\alpha]_D^{20}$ +65.98 (*c* 0.21 $CHCl_3$); $\nu_{max.}$ 1970 and 1885 (C≡O) cm^{-1}; δ_H 5.59-5.17 [5H, m, $(CO)_3CrPh$], 4.05 (1H, q, J 5.2Hz, OC**H**Me), 2.47 (1H, q, J 6.2Hz, C**H**Me), 2.24 (3H, s, NCH_3), 1.41 [3H, s, $(CO)_3CrPhCCH_3$], 1.36 (3H, d, J 5.1Hz, $CHCH_3$), 1.18 (3H, d, J 6.4Hz, $CHCH_3$); *m/z* 341 (M^+) (Found: M^+, 341.0720. $C_{16}H_{19}CrNO_4$ requires M, 341.0719). Similar experiments performed separately on complexes (+)-**144**, (+)-**145** and (+)-**147** all resulted in the recovery of unreacted starting material as the major product.

(-)-(4S,5R)-(N-Methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (151). A solution of (-)-(1R,2S)-ephedrine (**122**) (20.0g, 121mmol) in THF (200ml) was treated with N,N-carbonyldi-imidazole (20.0g, 123mmol) and the mixture heated at reflux (3h). The cooled solution was acidified with HCl (2M, 200ml) and the mixture extracted (Et_2O, 3x100ml). The combined extracts were washed (brine, 3x100ml), dried ($MgSO_4$) and evaporated to leave (-)-(4S,5R)-N-methyl-4-methyl-5-phenyloxazolidin-2-one (**149**)[103] as a colourless oil that solidified on standing (17.07g, 74%), $[\alpha]_D^{20}$ -115.90 (*c* 1.00 $CHCl_3$) {lit.[103] $[\alpha]_D^{20}$ -110.6 ($CHCl_3$)}; m.p. 89-90°C (lit.[103] 91-2°C); $\nu_{max.}$ 3019 (aryl-H), 1752 (C=O), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-7.22 (5H, m, Ph), 5.55 (1H, d, J 8.2Hz, Ph**CH**), 4.00 (1H, dq, J 6.6 and 8.1Hz, CHMe), 2.84 (3H, s, NCH_3), 0.74 (3H, d, J 6.6Hz, $CHCH_3$); δ_C 157.70, 135.02, 128.16 (2C), 128.10 (2C), 125.84, 78.00, 56.66, 28.60, 13.90; *m/z* 191 (M^+) (Found: C, 69.4; H, 6.9; N, 7.2. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%). A portion of this material (3.50g, 18.3mmol) and $Cr(CO)_6$ (4.43g, 20.1mmol) in Bu_2O (140ml) and THF (14ml) were reacted according to the standard complexation procedure (24h) to furnish the *title compound* as a yellow solid (2.05g, 34%), $[\alpha]_D^{20}$ +56.00 (*c* 0.33 MeOH); m.p. 185-7°C; $\nu_{max.}$ 1970 and 1900 (C≡O), 1755 (C=O) cm^{-1}; δ_H 5.40-5.07 [5H, m, $(CO)_3CrPh$], 5.22 [1H, d, J 8.2Hz, $(CO)_3CrPhCH$], 4.00 (1H, dq, J 6.6 and J 8.1Hz, C**H**Me), 2.87 (3H, s, NCH_3), 1.02 (3H, d, J 6.6Hz, $CHCH_3$); *m/z* 328 (M^++1) (Found: C, 51.4; H, 3.9; N, 4.2. $C_{14}H_{13}CrNO_5$ requires C, 51.4; H, 4.0; N, 4.2%).

(+)-(N-Methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (152). A solution of (-)-(1R,2R)-pseudoephedrine (**123**) (6.65g, 40.3mmol) in THF (60ml) was treated with N,N-carbonyldi-imidazole (6.53g, 40.3mmol) and the mixture heated at reflux (3h). The cooled solution was acidified with HCl (2M, 75ml) and the mixture extracted (Et_2O, 3x50ml). The combined extracts were dried ($MgSO_4$) and evaporated to leave (-)-(4R,5R)-N-methyl-4-methyl-5-phenyloxazolidin-2-one (**150**)[103] as a colourless oil that solidified on standing (6.17g, 80%), $[\alpha]_D^{20}$ -32.94 (*c* 0.93 $CHCl_3$) {lit.[103] $[\alpha]_D^{20}$ +29.9 for the opposite enantiomer ($CHCl_3$)}; m.p. 46.5-7°C (lit.[103] 50-1°C); $\nu_{max.}$ 3018 (aryl-H), 1752 (C=O), 700 (mono-substituted arene) cm^{-1}; δ_H 7.40-7.32

(5H, m, Ph), 4.87 (1H, d, J 7.8Hz, PhC**H**), 3.52 (1H, dq, J 7.8 and 6.2Hz, C**H**Me), 2.84 (3H, s, NC**H**$_3$), 1.34 (3H, d, J 6.2Hz, CHC**H**$_3$); δ_C 157.52, 137.50, 128.63 (2C), 128.59 (2C), 125.69, 82.18, 61.01, 28.51, 17.08; *m/z* 191 (M^+) (Found: C, 69.2; H, 7.0; N, 7.0. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%). A portion of this material (1.79g, 9.36mmol) and $Cr(CO)_6$ (2.27g, 10.3mmol) in Bu_2O (50ml) and THF (7ml) were reacted according to the standard complexation procedure (21h) to furnish the *title compound* as a yellow solid (2.33g, 76%). Recrystallisation from Et_2O/hexane furnished a pure sample for characterisation, $[\alpha]_D^{24}$ +36.52 (*c* 0.41 $CHCl_3$); m.p. 121-2°C; $\nu_{max.}$ 1970 and 1900 (C≡O), 1750 (C=O) cm^{-1}; δ_H 5.41-5.32 [5H, m, $(CO)_3$CrPh], 4.64 [1H, d, J 6.4Hz, $(CO)_3$CrPhC**H**], 3.66 (1H, qu, J 6.2Hz, C**H**Me), 2.89 (3H, s, NC**H**$_3$), 1.45 (3H, d, J 6.2Hz, CHC**H**$_3$); *m/z* 328 (M^++1) (Found: C, 51.5; H, 3.9; N, 4.2. $C_{14}H_{13}CrNO_5$ requires C, 51.4; H, 4.0; N, 4.2%).

Treatment of (-)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)Cr(CO)$_3$ (151) with *n*-butyllithium. A stirred solution of (-)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**151**) (0.140g, 0.43mmol) in THF (20ml) at -86°C was treated with *n*-butyllithium (0.50ml, 0.51mmol) and the solution stirred (-86°C, 2h). The solution was treated with DMF (0.17ml, 2.10mmol) and the mixture warmed and stirring continued (0°C, 2h). Water (10ml) was added, the solvent evaporated and the aqueous phase extracted (CH_2Cl_2). The combined extracts were subjected to column chromatography (Al_2O_3 grade V, Et_2O) to give complex (+)-**153** as a yellow oil (0.10g, 61%). Crystallisation from Et_2O/petroleum ether gave a pure sample as yellow needles for characterisation, $[\alpha]_D^{20}$ +69.63 (*c* 0.14 $CHCl_3$); m.p. 102-3°C; $\nu_{max.}$ 1968 and 1895 (C≡O), 1615 (C=O) cm^{-1}; δ_H 5.60-5.31 [6H, m, $(CO)_3$CrPhCH(OH)], 4.50-4.40 [2H, m, $(CO)_3$CrPhCH(O**H**)C**H**Me], 2.98 (3H, s, NC**H**$_3$), 2.31 (2H, t, J 7.6Hz, COC**H**$_2$), 1.60 (2H, m, $COCH_2CH_2$), 1.35 (2H, m, C**H**$_2$Me), 1.22 (3H, d, J 7.4Hz, CHC**H**$_3$), 0.94 and 0.89 (3H, t, J 7.2Hz, CH_2CH_3 for two amide conformers); *m/z* 386 (M^++1) (Found: C, 56.3; H, 6.05; N, 3.6. $C_{18}H_{23}CrNO_5$ requires C, 56.1; H, 6.0; N, 3.6%).

(-)-[(N-Acetyl)ephedrine]Cr(CO)$_3$ (154). A stirred solution of (-)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**151**) (0.562g, 1.72mmol) in THF (30ml) at -78°C was treated with methyllithium (1.70ml, 2.55mmol) and the solution stirred (-78°C, 2.5h). The solution was quenched with MeOH (2ml) and evaporated. The residue was subjected to column chromatography (Al_2O_3 grade V, CH_2Cl_2) to furnish the *title compound* as a yellow solid (0.474g, 80%). Recrystallisation from Et_2O/petroleum ether gave a pure sample for characterisation, $[\alpha]_D^{20}$ -58.09 (*c* 0.38 $CHCl_3$); $\nu_{max.}$ 1975 and 1898 (C≡O), 1620 (C=O) cm^{-1}; δ_H 5.58-5.31 [5H, m, $(CO)_3$CrPh], 4.54 [1H, br s, $(CO)_3$CrPhCH(O**H**)], 4.47 (1H, m, C**H**Me), 3.12 (1H, br s, O**H**), 3.00 (3H, s, NC**H**$_3$), 2.11 (3H, s, COC**H**$_3$), 1.22 (3H, d, J 7.0Hz, CHC**H**$_3$); *m/z* 344 (M^++1) (Found: C, 52.8; H, 5.0; N, 4.0. $C_{15}H_{17}CrNO_5$ requires C, 52.5; H, 5.0; N, 4.1%).

(+)-[(N-Acetyl)pseudoephedrine]Cr(CO)$_3$ (155). A stirred solution of (+)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**152**) (0.243g, 0.74mmol) in THF (20ml) at -78°C was treated with methyllithium (0.80ml, 1.12mmol) and the solution stirred (-78°C, 2h). The reaction mixture was quenched with MeOH (2ml) and evaporated. The residue was subjected to column chromatography (Al_2O_3 grade V, CH_2Cl_2) and recrystallised from Et_2O/petroleum ether to furnish the *title compound* as a yellow solid (0.176g,

69%), $[\alpha]_D^{24}$ +88.98 (*c* 0.56 $CHCl_3$); $\nu_{max.}$ 3290br (OH), 1970 and 1890 (C≡O), 1620 (C=O) cm^{-1}; δ_H 5.57-5.23 [5H, m, $(CO)_3CrPh$], 4.47 [1H, br s, OH], 4.36 [1H, br s, $(CO)_3CrPhCH(OH)$], 3.79 (1H, m, CHMe), 2.94 (3H, s, NCH_3), 2.03 (3H, s, $COCH_3$), 1.31 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 344 (M^++1) (Found: C, 52.6; H, 5.0; N, 4.15. $C_{15}H_{17}CrNO_5$ requires C, 52.5; H, 5.0; N, 4.1%).

(-)-(1R,2S)-(N-Acetyl)ephedrine (156).[150] A solution of (-)-(4S,5R)-N-methyl-4-methyl-5-phenyloxazolidin-2-one (**149**) (1.00g, 5.23mmol) in THF (20ml) at -78°C was treated with methyllithium (7.5ml, 10.5mmol) and the solution stirred (-78°C, 2h). The reaction mixture was quenched with MeOH (5ml), warmed and evaporated. Water (40ml) was added and the aqueous phase extracted (Et_2O, 3x25ml). The combined extracts were dried ($MgSO_4$) and evaporated to furnish the *title compound* as a colourless oil (0.920g, 85%). Crystallisation from CH_2Cl_2/petroleum ether gave a pure sample for characterisation, $[\alpha]_D^{20}$ +87.27 (*c* 1.23 $CHCl_3$); m.p. 85-6°C (lit.[150] 85-6°C); $\nu_{max.}$ 3370br (OH), 1625 (C=O), 703 (mono-substituted arene) cm^{-1}; δ_H (two amide conformers) 7.39-7.24 (5H, m, Ph), 4.87 [1H, t, J 3.3Hz, PhC**H**(OH)], 4.66 [1H, dd, J 3.1 and 7.6Hz, PhC**H**(OH)], 4.45 (1H, m, C**H**Me), 4.24 (1H, d, J 3.2Hz, O**H**), 3.94 (1H, m, C**H**Me), 2.82 (3H, s, NCH_3), 2.72 (3H, s, NCH_3), 2.57 (1H, d, J 3.2Hz, O**H**), 2.06 (3H, s, $COCH_3$), 1.73 (3H, s, $COCH_3$), 1.38 (3H, d, J 6.7Hz, $CHCH_3$), 1.21 (3H, d, J 7.2Hz, $CHCH_3$); δ_C (two amide conformers) 172.24, 170.51, 142.11, 141.84, 128.40, 128.04, 127.37, 126.16, 125.89, 76.94, 75.81, 59.19, 57.90, 33.86, 27.95, 22.40, 21.12, 14.60, 11.82; *m/z* 208 (M^++1) (Found: C, 69.7; H, 8.2; N, 6.5. $C_{12}H_{17}NO_2$ requires C, 69.5; H, 8.3; N, 6.8%).

(-)-(1R,2R)-(N-Acetyl)pseudoephedrine (157). A solution of (-)-(4R,5R)-N-methyl-4-methyl-5-phenyloxazolidin-2-one (**150**) (1.21g, 6.34mmol) in THF (20ml) at -78°C was treated with methyllithium (9.0ml, 12.6mmol) and the solution stirred (-78°C, 2.5h). The reaction mixture was quenched with MeOH (5ml), warmed and evaporated. Water (50ml) was added and the aqueous phase extracted (Et_2O, 3x30ml). The combined extracts were dried ($MgSO_4$) and evaporated to furnish the *title compound* as a white solid (1.05g, 80%). Recrystallisation from CH_2Cl_2/petroleum ether gave a pure sample for characterisation, $[\alpha]_D^{20}$ -129.15 (*c* 0.96 $CHCl_3$); m.p. 97-9°C; $\nu_{max.}$ 3392br (OH), 1621 (C=O), 702 (mono-substituted arene) cm^{-1}; δ_H (two amide conformers) 7.41-7.23 (5H, m, Ph), 4.58-4.53 (1H, br s, PhC**H**), 4.49 [1H, m, PhC**H**Me), 4.37 (1H, br s, O**H**), 3.93 (1H, dq, J 1.5 and 8.5Hz, C**H**Me), 3.65 (1H, br s, O**H**), 2.89 (3H, s, NCH_3), 2.81 (3H, s, NCH_3), 2.15 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 1.06 (3H, d, J 6.7Hz, $CHCH_3$), 0.96 (3H, d, J 6.8Hz, $CHCH_3$); δ_C (two amide conformers) 172.69, 171.74, 142.28, 141.58, 128.46, 128.22, 128.02, 127.52, 126.79, 126.42, 76.21, 75.30, 59.38, 57.58, 32.95, 26.60, 22.36, 21.78, 15.23, 14.25; *m/z* 208 (M^++1) (Found: C, 69.5; H, 8.6; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.5; H, 8.3; N, 6.8%).

Treatment of (+)-[(N-acetyl)pseudoephedrine]$Cr(CO)_3$ (155) with acid. A solution of (+)-[(N-acetyl)pseudoephedrine]$Cr(CO)_3$ (**155**) (0.176g, 0.51mmol) in MeOH (25ml) and THF (10ml) was treated with $HBF_4.OMe_2$ (1ml, excess). The mixture was stirred (20°C, 19h) and the solution quenched with $NaHCO_3$. The mixture was extracted (CH_2Cl_2) and the combined extracts purified by column chromatography [Al_2O_3 grade V, Et_2O/MeOH (3:1)] to afford a yellow oil. ^1H n.m.r. spectroscopy of the crude product revealed only starting material as the major component.

Treatment of (-)-[(N-acetyl)ephedrine]Cr(CO)$_3$ (154) with acid. A solution of (-)-[(N-acetyl)ephedrine]Cr(CO)$_3$ (**154**) (0.123g, 0.36mmol) in MeOH (25ml) and THF (10ml) was treated with $HBF_4.OMe_2$ (1ml, excess). The mixture was stirred (20°C, 15h) and the solution quenched with $NaHCO_3$. The mixture was extracted (CH_2Cl_2) and the combined extracts purified by column chromatography [Al_2O_3 grade V, Et_2O/MeOH (10:1)] to afford a yellow oil. ^{1}H n.m.r. spectroscopy of the crude product revealed the presence of (-)-[(N-acetyl)pseudoephedrine]Cr(CO)$_3$ (**155**) as the major product.

Treatment of (-)-[(N-methyl)pseudoephedrine]Cr(CO)$_3$ (162) with acid. A solution of (-)-[(N-methyl)pseudoephedrine]Cr(CO)$_3$ (**162**) (0.042g, 0.13mmol) and 1,2-dimethoxybenzene (0.10ml, 0.78mmol) in CH_2Cl_2 (10ml) was treated with $HBF_4.OMe_2$ (0.3ml, excess) resulting in an instant colour change from yellow to purple. The mixture was stirred (20°C, 10min) and MeOH (0.5ml) added which immediately returned the colour of the solution to yellow. The solution was basified with $NaHCO_3$, the organic phase separated and the aqueous phase extracted (CH_2Cl_2). The combined organic phases were purified by column chromatography [Al_2O_3 grade V, Et_2O/petroleum ether (1:1)] to give a yellow oil that was identified as (+)-[(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (**128**) by ^{1}H n.m.r. spectroscopy (0.032g, 72%).

Treatment of (-)-[(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (128) with acid. A solution of (-)-[(N-methyl-O-methyl)pseudoephedrine]Cr(CO)$_3$ (**128**) (0.019g, 0.06mmol) in CH_2Cl_2 (4ml) was treated with $HBF_4.OMe_2$ (0.4ml, excess) resulting in an instant colour change from yellow to purple. The mixture was stirred (20°C, 10min) and water (2ml) added which immediately returned the colour of the solution to yellow. The solution was basified ($NaHCO_3$), the organic phase separated and the aqueous phase extracted (CH_2Cl_2). The combined organic phases were filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2) and evaporated to give a yellow oil. ^{1}H n.m.r. spectroscopy of the crude product revealed the presence of (+)-[(N-methyl)pseudoephedrine]Cr(CO)$_3$ (**162**) (0.08g, 44%) as the major component along with equal amounts of the starting material [(-)-**128**] and [N,N-(dimethyl)amphetamine]Cr(CO)$_3$ (**164**).[107]

Treatment of (-)-[(N-methyl)ephedrine]Cr(CO)$_3$ (163) with acid. A solution of (-)-[(N-methyl)ephedrine]Cr(CO)$_3$ (**163**) (0.149g, 0.47mmol) in CH_2Cl_2 (25ml) was treated with $HBF_4.OMe_2$ (0.9ml, excess) resulting in an instant colour change from yellow to purple. The mixture was stirred (20°C, 10min) and MeOH (1.5ml) added which immediately returned the colour of the solution to yellow. The solution was basified ($NaHCO_3$), the organic phase separated and the aqueous phase extracted (CH_2Cl_2). The combined organic phases were purified by column chromatography (Al_2O_3 grade V, CH_2Cl_2) to give a yellow solid (0.062g, 44%). ^{1}H n.m.r. spectroscopy of the crude product revealed the identity of the product as (-)-[N,N-(dimethyl)amphetamine]Cr(CO)$_3$ (**164**), identified by comparison with an authentic sample.[107] Recrystallisation from CH_2Cl_2/hexane afforded a pure sample, $[\alpha]_D^{20}$ -38.32 (*c* 0.11 $CHCl_3$) {lit.[107] $[\alpha]_D^{20}$ -26.5 (*c* 0.1 $CHCl_3$)}. In an identical experiment, the reaction was quenched with CD_3OD but revealed no incorporation of deuterium in the product [(-)-**164**] according to ^{1}H n.m.r. spectroscopy.

Treatment of (-)-[(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (127) with acid. A mixture of (-)-[(N-methyl-O-methyl)ephedrine]Cr(CO)$_3$ (**127**) (0.156g, 0.47mmol) in CH_2Cl_2 (10ml) was treated with

$HBF_4.OMe_2$ (0.8ml, excess) resulting in an instant colour change from yellow to purple. The mixture was stirred (20°C, 0.5h) and water (1ml) added which immediately returned the colour of the solution to yellow. The solution was basified ($NaHCO_3$), the organic phase separated and the aqueous phase extracted (CH_2Cl_2). The combined organic phases were purified by column chromatography (Al_2O_3 grade V, CH_2Cl_2) to give a yellow oil (0.074g, 47%). ^1H n.m.r. spectroscopy of the crude product revealed the presence of starting material (9%) and (-)-[N,N-(dimethyl)amphetamine]$Cr(CO)_3$ (**164**) (38%) in the approximate ratio 20:80, identified by comparison with authentic samples.[107]

General procedure for the synthesis of (substituted-benzyl)bromides. HBr gas was bubbled through an efficiently stirred solution of the appropriately substituted benzyl alcohol in benzene (50mg ml^{-1}). The orange solution was stirred (20°C, 1h), basified with excess $CaCO_3$ and the mixture filtered. The filtrate was evaporated to furnish the corresponding benzyl bromide as a pale brown oil (90-95% yield). The products could not be stored for any length of time and were freshly prepared on each occasion prior to use. 3-Methoxybenzyl bromide was prepared from 3-methylanisole (4.12g, 33.7mmol) upon treatment with NBS (6.00g, 33.7mmol) in CCl_4 (50ml). A catalytic quantity of dibenzoylperoxide was added and the mixture heated at reflux (4h). The precipitated succinimide was removed by filtration and the filtrate evaporated to leave 3-methoxybenzyl bromide as a mobile oil (6.48g, 96%).[151]

General procedure for the synthesis of N-(substituted benzyl) amino alcohols.

Procedure A. A solution of the amino alcohol and one equivalent of the appropriately substituted benzyl bromide in the specified solvent was heated at reflux in the presence of K_2CO_3 (2-3 equivalents) for 3 hours. The solution was evaporated, water added and the product extracted (CH_2Cl_2 or Et_2O). The combined extracts were dried ($MgSO_4$) and evaporated to afford the crude product. Further purification was achieved, where necessary, in the specified manner. In the case of amino alcohols coordinated to the $Cr(CO)_3$ unit, the crude reaction mixture was treated with water and the organic phase separated. The aqueous layer was extracted (CH_2Cl_2) and the combined organic phases filtered through a plug of Al_2O_3 (grade V, CH_2Cl_2). Evaporation afforded the crude product which was further purified, where necessary, in the specified manner.

Procedure B. A CH_2Cl_2 solution of the amino alcohol was treated with the appropriately substituted benzaldehyde and a catalytic quantity of *p*TsOH added. The solution was stirred in the presence of molecular sieves (20°C, 10-20h), filtered and basified ($NaHCO_3$). The organic phase was filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2) and evaporated to afford the corresponding oxazolidine. A portion of this material was dissolved in MeOH, treated with $NaBH_4$ [or $NaBH_3CN$ in the presence of HCl (5M)] and the solution stirred (20°C, 10-20h). HCl (5M) was added, stirring continued (20°C, 1h) and the reaction mixture basified (NaOH, 2M). The organic phase was separated and the aqueous layer repeatedly extracted (CH_2Cl_2). The combined organic phases were filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2) and evaporated to leave the crude product as a yellow oil. Further purification was achieved where necessary in the specified manner.

Procedure C. A solution of the amino alcohol and one equivalent of the appropriately substituted benzaldehyde in benzene was treated with a catalytic quantity of *p*TsOH and the mixture heated at reflux in a Dean-Stark water separator (10-20h). The solvent was evaporated, water added and the aqueous phase extracted (Et_2O or CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to leave the corresponding

oxazolidine as a mixture of diasteroisomers. The crude product was purified where necessary in the specified manner, furnishing the pure oxazolidine for characterisation. A portion of this material was dissolved in THF, cautiously treated with $LiAlH_4$ (*ca.* 1.2 equivalents) and the mixture heated at reflux (20-30h). The externally cooled solution was quenched with water and NaOH (15% w/v, aqueous) and vigorously stirred. The precipitated aluminium salts were removed by filtration and the mother liquor evaporated to furnish the crude product. Further purification was achieved where necessary in the specified manner.

Halostachine (172). A stirred solution of styrene oxide (**171**) (30 ml, 263 mmol) and $MeNH_2$ (33% solution in EtOH, 50 ml) in EtOH (180 ml) was heated at reflux (6h) and the mixture concentrated. The residue was distilled under reduced pressure and the lower boiling fraction collected as a colourless oil (<120°C, 0.06mm Hg) that solidified on standing. ^1H n.m.r. spectroscopy revealed the presence of both halostachine (**11**) and N-methyl-2-phenyl ethanolamine in the approximate ratio 64:36.[152] Recrystallisation from CH_2Cl_2/hexane at -20°C afforded the *title compound* as a fluffy white powder (6.57g, 17%), m.p. 72-3°C, (lit.[153] 75-76°C); δ_H 7.38-7.28 (5H, m, Ph), 4.76 [1H, dd, J 8.8 and 3.9Hz, PhC**H**(OH)], 2.83, 2.74 [2H, ABX system, J_{AB} 12.1Hz, J_{AX} 3.9Hz, J_{BX} 8.8Hz, PhCH(OH)C**H**$_2$], 2.48 (3H, s, NC**H**$_3$), 2.35 (2H, br s, OH and NH); *m/z* 152 (M^++1). ^1H n.m.r. spectroscopy (C_6D_6 solution) in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) distinguished between the N-methyl singlet of (+)-(S)-**172** and that of (-)-(R)-**172**.

N-(3,4-Dimethoxybenzyl)halostachine (173). Halostachine (**172**) (1.00g, 6.61mmol) was treated with freshly prepared 3,4-dimethoxybenzyl bromide (1.53g, 6.62mmol) in MeCN (40ml) according to standard procedure **A**. The *title compound* was isolated as a colourless oil (1.60g, 80%), $\nu_{max.}$ 3420 (OH), 2840 (OCH_3), 760 (mono-substituted arene) cm^{-1}; δ_H 7.38-7.34 (5H, m, Ph), 6.87-6.84 [3H, m, $(MeO)_2C_6H_3$], 4.76 [1H, dd, J 10.3 and 3.6Hz, PhC**H**(OH)], 3.90 (3H, s, OC**H**$_3$), 3.89 (3H, s, OC**H**$_3$), 3.70, 3.48 [2H, AB system, J_{AB} 12.9Hz, $(MeO)_2C_6H_3CH_2$], 2.61, 2.51 [2H, ABX system, J_{AB} 12.9Hz, J_{AX} 10.4Hz, J_{BX} 3.7Hz, PhCH(OH)C**H**$_2$], 2.34 (3H, s, NC**H**$_3$); δ_C 149.15, 148.43, 142.54, 131.04, 128.51, 127.64, 126.09, 121.43, 112.14, 111.03, 69.49, 65.22, 62.13, 55.84, 41.79; *m/z* 302 (M^++1) (Found: C, 71.4; H, 8.1; N, 4.6. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7; N, 4.65%). ^1H n.m.r. spectroscopy in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) distinguished between the C1 benzylic proton [CH(OH)] of (+)-(S)-**173** and that of (-)-(R)-**173**.

(-)-(R)-N-(3,4-Dimethoxybenzyl)halostachine (173). A stirred solution of (-)-(R)-styrene oxide (**171**) (7.97g, 66.3mmol), $MeNH_2$ (33% solution in EtOH, 50ml) and K_2CO_3 (3.00g, 21.7mmol) in EtOH (80 ml) was heated at reflux (6.5h) and the mixture concentrated. The residue was distilled under reduced pressure and the lower boiling fraction collected as a viscous, colourless oil (<110°C, 0.06mm Hg) (3.87g, 39%). ^1H n.m.r. spectroscopy revealed the presence of both (-)-(R) halostachine (**172**) and N-methyl-2-phenyl ethanolamine but all attempts to isolate pure (-)-(R)-**172** failed. A solution of this mixture (2.07g, 13.7mmol) was treated with freshly prepared 3,4-dimethoxybenzyl bromide (1.59g, 6.88mmol) in MeCN (50ml) according to standard procedure **A**. The *title compound* was isolated as a colourless oil after flash chromatography (SiO_2, Et_2O) (1.00g, 48%). $[\alpha]_D^{20}$ -104.07 (*c* 2.17 $CHCl_3$); $\nu_{max.}$ 3440 (OH), 3010 (aryl-H), 2840 (OCH_3), 2800

(NCH_3), 1595 and 1515 (Ar) cm^{-1}; δ_H 7.38-7.34 (5H, m, Ph), 6.87-6.84 [3H, m, $(MeO)_2C_6H_3$], 4.76 [1H, dd, J 10.3 and 3.6Hz, PhCH(OH)], 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.70, 3.48 [2H, AB system, J_{AB} 12.9Hz, $(MeO)_2C_6H_3CH_2$], 2.61, 2.51 [2H, ABX system, J_{AB} 12.9Hz, J_{AX} 10.4Hz, J_{BX} 3.7Hz, $PhCH(OH)CH_2$], 2.34 (3H, s, NCH_3); δ_C 149.15, 148.43, 142.54, 131.04, 128.51, 127.64, 126.09, 121.43, 112.14, 111.03, 69.49, 65.22, 62.13, 55.84, 41.79; *m/z* 302 (M^++1) (Found: C, 71.5; H, 7.9; N, 4.35. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7; N, 4.65%). ^1H n.m.r. spectroscopy in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) revealed the presence of a single enantiomer of (-)-(R)-**173**, the C1 benzylic proton [CH(OH)] resonance appearing at lower field than that for (+)-(S)-**173**.

General procedure for the cyclisation of N-(substituted-benzyl)- or (substituted-phenethyl)amino alcohols.

Procedure D. A stirred solution of the relevant amino alcohol in CH_2Cl_2 was treated with H_2SO_4 and CF_3COOH (1:1, excess) producing a red/purple colouration. The mixture was heated at reflux for the specified period of time and quenched with aqueous base (NaOH or K_2CO_3). The organic layer was separated and the aqueous phase extracted (CH_2Cl_2). The combined organic phases were washed (H_2O), dried ($MgSO_4$) and evaportated to furnish the crude cyclised product. Further purification was achieved where necessary in the specified manner.

Procedure E. A stirred solution of the relevant amino alcohol in CH_2Cl_2 at -78°C was treated with $HBF_4.OMe_2$ (excess) and the solution stirred (-78°C, 1h). The reaction vessel was transferred to a freezer where a temperature of <-20°C was maintained for the specified period of time. The mixture was quenched at low temperature in a manner identical to that for procedure **D**. In the case of cyclisations employing precursors coordinated to the $Cr(CO)_3$ unit, the reaction mixture was quenched at low temperature and the organic phase separated. The aqueous phase was extracted (CH_2Cl_2) and the combined organic phases filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2). Evaporation afforded the crude cyclised product which was further purified where neccessary in the specified manner.

N-Methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (175).[154] A solution of N-(3,4-dimethoxybenzyl)halostachine (**173**) (1.30g, 4.31mmol) in CH_2Cl_2 (35ml) was cyclised according to standard procedure D (40°C, 0.5h) to afford the *title compound* as a pale yellow oil that solidified upon standing (1.13g, 92%), m.p. 89-91°C; $\nu_{max.}$ 3010 (aryl-H), 2940 ($ArCH_2$), 2840 (OCH_3), 2790 (NCH_3), 1600 and 1510 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.32-7.18 (5H, m, Ph), 6.57 and 6.34 [2H, s, 5H and 8H], 4.21 (1H, br t, PhCH), 3.86 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.66 [2H, AB system, J_{AB} 14.4Hz, $(MeO)_2C_6H_2CH_2$], 3.00, 2.53 (2H, ABX system, J_{AB} 11.5Hz, J_{AX} 5.6Hz, J_{BX} 8.4Hz, $PhCHCH_2$), 2.42 (3H, s, NCH_3); δ_C 147.70, 147.63, 144.97, 129.11, 128.96, 128.45, 127.58, 126.58, 112.00, 108.79, 61.99, 58.09, 55.76, 45.86, 45.46; *m/z* 283 (M^+) (Found: C, 76.0; H, 7.6; N, 5.0. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). ^1H n.m.r. spectroscopy in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) (approximately 1 molar equivalent) gave baseline separation of all three methyl singlets, the two aromatic singlets corresponding to 5H and 8H and the C1 benzylic proton multiplet.

An analogous reaction employing homochiral (-)-(R)-N-(3,4-dimethoxybenzyl)halostachine (**173**) gave the *title compound* as a mixture of both (+)-(R)-**175** and (-)-(S)-**175** (97%). The ^1H n.m.r. spectrum of the

crude product in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) revealed an enantiomeric excess of 14% in favour of (+)-(R)-**175.**

A solution of (-)-(R)-N-(3,4-dimethoxybenzyl)halostachine (**173**) (0.215g, 0.713mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **E** (<-20°C, 69h) to afford the *title compound* as a mixture of both (+)-(R)-**175** and (-)-(S)-**175** (50% conversion). The ^1H n.m.r. spectrum of the crude product in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) revealed an enantiomeric excess of 54% in favour of (+)-(R)-**175**.

(+)-(S)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-one (182).[155] A stirred solution of (+)-(S)-mandelic acid (**181**) (14.6g, 96.0mmol) in $(CH_3)_2CO$ (44ml, 599mmol) was externally cooled (<-10°C) and treated dropwise with H_2SO_4 (conc., 5.3ml) at a rate sufficient to maintain a reaction temperature between -10°C and -5°C, resulting in the formation of a white precipitate. The mixture was poured into ice-cold Na_2CO_3 solution (20g in 180ml) and the resultant precipitate collected by filtration. The white solid thus obtained was washed with ice-cold water (150ml) and dried under reduced pressure to give the crude dioxolanone as a fluffy white powder. Recrystallisation from hot EtOH gave the *title compound* as long, slender needles (14.77g, 80%), $[\alpha]_D^{20}$ +55.43 (*c* 2.63 CCl_4) {lit.[155] $[\alpha]_D^{20}$ +52.7 (*c* 2.0 CCl_4)}; m.p. 71-2°C (lit.[155] 71°C); $\nu_{max.}$ 3010 (aryl-H), 1788 (C=O), 1384 and 1377 (CH_3), 1125 (C-O), 690 (mono-substituted arene) cm^{-1}; δ_H 7.50-7.36 (5H, m, Ph), 5.41 (1H, s, PhC**H**), 1.74 (3H, s, CH_3), 1.69 (3H, s, CH_3); δ_C 172.11, 134.23, 128.91, 128.62, 126.10, 111.29, 72.20, 26.34; *m/z* 192 (M^++1) (Found: C, 68.6; H, 6.3. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

(+)-(S)-N-Methyl-1-hydroxyphenylacetamide (183).[156,157] A solution of (+)-(S)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-one (**182**) (14.77g, 76.8mmol) in EtOH (45ml) was treated with $MeNH_2$ (33% in EtOH, 45ml) and the mixture stirred (20°C, 2h). The reaction mixture was filtered and evaporated to afford the *title compound* as a white solid (12.33g, 97%). Recrystallisation from hot benzene gave a pure sample for characterisation. $[\alpha]_D^{20}$ +55.51 [*c* 1.34 $(CH_3)_2CO$]; m.p. 96-9°C (lit.[156,157] 94-5°C); $\nu_{max.}$ 3440 (NH), 3380 (OH), 3010 (aryl-H), 1673 and 1540 (C=O), 700 (mono-substituted arene) cm^{-1}; δ_H 7.35-7.25 (5H, m, Ph), 6.83 (1H, br s O**H**), 5.04 (1H, br s, N**H**), 4.85 [1H, s, PhC**H**(OH)], 2.62 and 2.61 [3H, s, $C(O)NHCH_3$, two amide conformers]; δ_C 173.84, 139.88, 128.63, 128.36, 127.54, 127.07, 126.85, 73.93,. 25.77; *m/z* 165 (M^+) (Found: C, 65.5; H, 6.7; N, 8.15. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%).

(+)-(S)-Halostachine (172).[157] A stirred suspension of $LiAlH_4$ (12.5g, 329mmol) in THF (150ml) was treated dropwise with a THF solution (100ml) of (+)-(S)-N-methyl-1-hydroxyphenylacetamide (**183**) (12.33g, 74.6mmol) and the mixture stirred (20°C, 1h). The reaction mixture was heated at reflux (17.5h) and the cooled solution cautiously treated with water (12.5ml) and NaOH (15% w/v, 12.5ml). Water (37.5ml) was added and the mixture efficiently stirred until a manageable white precipitate resulted. The white precipitate was collected by filtration and thoroughly washed (CH_2Cl_2). The combined organic phases were evaporated to leave the *title compound* as a colourless oil that solidified upon standing (11.44g, 92%). Distillation under reduced pressure (99-102 °C, 0.06mm Hg) afforded an analytically pure sample. $[\alpha]_D^{20}$ +40.41 (*c* 1.89 EtOH) {lit.[157] $[\alpha]_D^{25}$ +37.43 (*c* 2.37 EtOH)}; m.p. 39-40°C (lit.[153,157] 43-45°C); $\nu_{max.}$ 3380 and 3330 (OH and NH), 700

(mono-substituted arene) cm^{-1}; δ_H 7.38-7.28 (5H, m, Ph), 4.76 [1H, dd, J 8.8 and 3.9Hz, PhCH(OH)], 2.83, 2.74 [2H, ABX system, J_{AB} 12.1Hz, J_{AX} 3.9Hz, J_{BX} 8.8Hz, PhCH(OH)CH_2], 2.48 (3H, s, NCH_3), 2.35 (2H, br s, OH and NH); δ_C 143.64, 128.45, 127.50, 127.07, 125.94, 71.63, 59.25, 35.70; *m/z* 152 (M^++1). ^1H n.m.r. spectroscopy (C_6D_6 solution) in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) indicated that this material was homochiral, the N-methyl singlet appearing at higher field than that of (+)-(S)-**172**.

(+)-(S)-(N-*t*-Butoxycarbonyl)halostachine (184). An externally cooled (<0°C) solution of (+)-(S)-halostachine (**172**) (8.85g, 58.5mmol) in CH_2Cl_2 (70ml) was treated with di-*t*-butyl dicarbonate (15ml, 65.3mmol) and NEt_3 (8.2ml, 58.8mmol) and the solution left to stand (20°C, 15.5h). The solution was acidified with saturated citric acid solution, the organic layer separated and washed sequentially with $NaHCO_3$ solution, water and brine. Drying ($MgSO_4$), filtration and evaporation gave a colourless oil that was distilled under reduced pressure (130-2°C, 0.06mm Hg) to give the *title compound* as a viscous oil that solidified on standing (13.07g, 89%), $[\alpha]_D^{20}$ +50.18 (*c* 1.28 $CHCl_3$); m.p. 59-60°C; $\nu_{max.}$ 3400 (OH), 3005 (aryl-H), 1680 (C=O), 700 (mono-substituted arene) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 7.35-7.21 (5H, m, Ph), 5.15 (1H, d, J 4.6Hz, OH), 4.76 ([1H, m, PhCH(OH)], 3.38, 3.28 [2H, ABX system, J_{AB} 13.9Hz, J_{AX} 5.3Hz, J_{BX} 7.4Hz, PhCH(OH)CH_2], 2.79 (3H, s, NCH_3), 1.37 [9H, s, $C(CH_3)_3$]; δ_C 142.54, 128.49, 127.65, 125.97, 80.26, 73.56, 57.40, 36.26, 28.21; *m/z* 252 (M^++1) (Found: C, 66.6; H, 8.4; N, 5.5. $C_{14}H_{11}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%).

(+)-(R)-[(N-*t*-Butoxycarbonyl)halostachine]Cr(CO)$_3$ (185). (+)-(S)-(N-*t*-Butoxycarbonyl)halostachine (**184**) (0.50g, 1.99mmol) and $Cr(CO)_6$ (0.50g, 2.27mmol) in Bu_2O (40ml) and THF (6ml) were reacted according to the standard complexation procedure (22h). Crystallisation from CH_2Cl_2/hexane gave the *title compound* as a yellow powder (0.488g, 63%), $[\alpha]_D^{23}$ +8.97 (*c* 0.20 $CHCl_3$); m.p. 105-6°C; $\nu_{max.}$ 3370 (OH), 1975 and 1890 (C≡O), 1680 (C=O), 708 (mono-substituted arene) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 5.76-5.60 [5H, m, PhCr(CO)$_3$], 5.50 (1H, d, J 5.7Hz, OH), 4.44 [1H, m, (CO)$_3$CrPhCH(OH)], 3.42, 3.29 [2H, ABX system, J_{AB} 14.0Hz, J_{AX} 5.0Hz, J_{BX} 7.1Hz, (CO)$_3$CrPhCH(OH)CH_2], 2.86 (3H, s, NCH_3), 1.37 [9H, s, $C(CH_3)_3$]; *m/z* 387 (M^+) (Found: C, 52.5; H, 5.5; N, 3.6%. $C_{17}H_{21}CrNO_6$ requires C, 52.7; H, 5.5; N, 3.6%).

(+)-(R)-(Halostachine)Cr(CO)$_3$ (186). [(N-*t*-Butoxycarbonyl)halostachine]Cr(CO)$_3$ (**185**) (0.498g, 1.29mmol) dissolved in HCOOH (98-100%, 15ml) was thoroughly degassed and the solution stirred (20°C, 5h). The mixture was concentrated, treated with NaOH (2M, 50ml) and CH_2Cl_2 (30ml) added. The organic layer was separated and the aqueous layer extracted (CH_2Cl_2, 2x30ml). The combined organic phases were evaporated affording the *title compound* as a yellow solid (0.352g, 95%). Recrystallisation from Et_2O/hexane gave an analytically pure sample, $[\alpha]_D^{20}$ +40.19 (*c* 0.26 $CHCl_3$); m.p. 94-8°C (decomp.); $\nu_{max.}$ 1975 and 1890 (C≡O) cm^{-1}; δ_H 5.60-5.31 [5H, m, PhCr(CO)$_3$], 4.40 [1H, dd, J 3.5 and 8.9Hz, (CO)$_3$CrPhCH(OH)], 2.85, 2.70 (2H, ABX system, J_{AB} 12.2Hz, J_{AX} 3.4Hz, J_{BX} 8.8Hz, (CO)$_3$CrPhCH(OH)CH_2], 2.48 (3H, s, NCH_3), 1.60 (2H, br s, OH and NH); *m/z* 288 (M^++1) (Found: C, 50.1; H, 4.5; N, 4.8. $C_{12}H_{13}CrNO_4$ requires C, 50.2; H, 4.6; N, 4.9%).

(R)-[N-(3,4-Dimethoxybenzyl)halostachine]Cr(CO)$_3$ (187). (+)-(R)-(Halostachine)Cr(CO)$_3$ (**186**) (0.281g, 0.978mmol) was treated with freshly prepared 3,4-dimethoxybenzyl bromide (0.226g, 0.978mmol) in CH_2Cl_2 (30ml) according to standard procedure **A** (20^oC, 38.5h). The *title compound* was isolated as a yellow oil after column chromatography [Al_2O_3 gradeV, petroleum ether/Et_2O (1:1)] (0.155g, 36%), δ_H 6.82 [3H, br s, $(MeO)_2C_6\mathbf{H}_3$], 5.54-5.27 [5H, m, $PhCr(CO)_3$], 4.37 [1H, dd, J 4.1 and 10.0Hz, $(CO)_3CrPhC\mathbf{H}(OH)$], 3.89 (6H, s, $2OCH_3$), 3.68, 3.48 [2H, AB system, J_{AB} 12.9Hz, $(MeO)_2C_6H_3CH_2$], 2.58, 2.53 [2H, ABX system, J_{AB} 12.9Hz, J_{AX} 10.2Hz, J_{BX} 4.1Hz, $PhCr(CO)_3CH(OH)C\mathbf{H}_2$], 2.34 (3H, s, $NC\mathbf{H}_3$), 1.62 (1H, br s, OH); *m/z* 438 (M^++1).

(R)-(N-Methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline)Cr(CO)$_3$ (188). A solution of (R)-N-[(3,4-dimethoxybenzyl)halostachine]Cr(CO)$_3$ (**187**) (0.136g, 0.311mmol) in CH_2Cl_2 (10ml) was cyclised according to standard procedure **E** (<-20^oC, 80h)to afford the *title compound* as a yellow oil (0.088g, 67%). δ_H 6.91 and 6.56 (2H, s, 5**H** and 8**H**), 5.68-4.95 [5H, m, $PhCr(CO)_3$], 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.79, 3.26 [2H, AB system, J_{AB} 14.6Hz, $(MeO)_2C_6H_2CH_2$], 3.72, [1H, br s, $(CO)_3CrPhCH$], 2.92, 2.76 [2H, ABX system, J_{AB} 11.9Hz, J_{AX} 2.2Hz, J_{BX} 4.2Hz, $(CO)_3CrPhCHCH_2$], 2.36 (3H, s, NCH_3); *m/z* 419 (M^+) (Found: M^+, 419.0820. $C_{21}H_{12}CrNO_5$ requires M^+, 419.0825).

(+)-(R)-N-Methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (175).[154] A solution of (R)-(N-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**188**) (0.088g, 0.210mmol) in Et_2O (15ml) was decomplexed according to the standard procedure to furnish the *title compound* as a white powder (0.058g, 98%). Recrystallisation from Et_2O/hexane gave an analytically pure sample as colourless needles. $[\alpha]_D^{20}$ +16.93 (*c* 0.12 $CHCl_3$); m.p. 109-10^oC; $\nu_{max.}$ 3019 (aryl-H), 1514 (Ar), 702 (mono-substituted arene) cm^{-1}; δ_H 7.32-7.18 (5H, m, Ph), 6.57 and 6.34 (2H, s, 5**H** and 8**H**), 4.21 (1H, br t, PhC**H**), 3.86 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.66 [2H, AB system, J_{AB} 14.4Hz, $(MeO)_2C6H_2CH_2$], 3.00, 2.53 (2H, ABX system, J_{AB} 11.5Hz, J_{AX} 5.6Hz, J_{BX} 8.4Hz, $PhCH_2CH_2$), 2.42 (3H, s, NCH_3); δ_C 147.20, 147.63, 144.97, 129.11, 128.96, 128.45, 127.58, 126.58, 112.00, 108.79, 61.99, 58.09, 55.76, 45.86, 45.46; *m/z* 283 (M^+) (Found: C, 76.6; H, 7.7; N, 4.7. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). ^1H n.m.r. spectroscopy of the crude product in the presence of (-)-(R)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**174**) revealed the enantiomeric excess of (+)-(R)-**175** to be greater than 96%, whilst the recrystallised material appeared to be homochiral by this criterion.

(-)-(1R,2R)-N-(3,4-Dimethoxybenzyl)pseudoephedrine (200). (-)-(1R,2R)-Pseudoephedrine (**123**) (1.37g, 8.29mmol) was reacted with freshly prepared 3,4-dimethoxybenzyl bromide (1.92g, 8.31mmol) in MeCN (100ml) according to standard procedure **A** (5h) to afford the *title compound* as a white solid (2.60g, 99%). Recrystallisation from Et_2O/hexane furnished a pure sample for characterisation, $[\alpha]_D^{20}$ -130.78 (*c* 0.95 $CHCl_3$); m.p. 77-8^oC; $\nu_{max.}$ 3340br (OH), 3010 (aryl-H), 704 (mono-substituted arene) cm^{-1}; δ_H 7.34-6.82 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.33 [1H, d, J 9.7Hz, $PhC\mathbf{H}(OH)$], 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.72, 3.45 [2H, AB system, J_{AB} 12.9Hz, $(MeO)_2C_6H_3CH_2$], 2.76 (1H, dq J 6.6 and 9.7Hz, CHMe), 2.25 (3H, s, NCH_3), 0.81 (3H, d, J 6.6Hz, $CHC\mathbf{H}_3$); δ_C 149.07, 148.25, 141.88, 131.17, 128.11 (2C), 127.61,

127.26 (2C), 121.02, 111.81, 110.95, 74.68, 64.35, 57.83, 55.82 (2C), 35.63, 7.11; *m/z* 316 (M^++1) (Found: C, 72.6; H, 8.2; N, 4.3. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 8.0; N, 4.4%).

Alternative procedure : (-)-(1R,2R)-Pseudoephedrine (**123**) (9.12g, 55.2mmol) and 3,4-dimethoxybenzaldehyde (9.17g, 55.2mmol) in benzene (100ml) were reacted according to standard procedure C (14h) to furnish (-)-(2R,4R,5R)-2-(3,4-dimethoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**199**) as a white solid (17.29g, quantitative) (crude ratio 98:2), $[\alpha]_D^{20}$ -47.14 (*c* 0.96 $CHCl_3$); m.p. 54-6°C; $\nu_{max.}$ 3008 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.45-6.86 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.91 [1H, s, $(MeO)_2C_6H_3\mathbf{CH}$)], 4.76 (1H, d, J 8.7Hz, Ph**CH**), 3.95 (3H, s, OCH_3), 3.90 (3H, s, OCH_3) 2.54 (1H, dq J 6.0 and 8.7Hz, **CH**Me), 2.22 (3H, s, NCH_3), 1.25 (3H, d, J 6.0Hz, $CHCH_3$); δ_C 149.89, 149.37, 140.71, 132.02, 128.52 (2C), 127.07 (2C), 126.79, 120.91, 110.61, 110.40, 99.61, 86.34, 68.76, 55.76 (2C), 35.09, 14.24; *m/z* 314 (M^++1) (Found: C, 72.9; H, 7.6; N, 4.4. $C_{19}H_{23}NO_3$ requires C, 72.8; H, 7.4; N, 4.5%). A portion of this material (3.59g, 11.5mmol) in MeOH (40ml) was reduced with $NaBH_4$ (1.00g, 26.4mmol) according to standard procedure **B** to furnish the *title compound* (3.60g, 99%).

(-)-(1R,2S)-N-(3,4-Dimethoxybenzyl)ephedrine (202). (-)-(1R,2S)-Ephedrine (**122**) (1.01g, 6.11mmol) was reacted with freshly prepared 3,4-dimethoxybenzyl bromide (1.41g, 6.10mmol) in MeCN (100ml) according to standard procedure **A** (4h) to afford the *title compound* as a colourless oil (1.71g, 89%). Cup distillation under reduced pressure gave a pure sample for characterisation, $[\alpha]_D^{20}$ -30.43 (*c* 0.47 $CHCl_3$); $\nu_{max.}$ 3019 (aryl-H), 1515 (Ar), 723 (mono-substituted arene) cm^{-1}; δ_H 7.35-6.74 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.85 [1H, d, J 5.3Hz, Ph**CH**(OH)], 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.55 [2H, d, J 2.4Hz, $(MeO)_2C_6H_3\mathbf{CH}_2$], 2.96 (1H, dq J 6.8 and 5.4Hz, **CH**Me), 2.18 (3H, s, NCH_3), 1.02 (3H, d, J 6.8Hz, $CHCH_3$); δ_C 148.99, 148.04, 142.75, 132.11, 127.96 (2C), 126.94, 126.25 (2C), 120.67, 111.73, 110.89, 74.09, 63.20, 58.86, 55.86, 55.80, 38.21, 9.65; *m/z* 316 (M^++1) (Found: C, 72.0; H, 8.4; N, 4.4. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 8.0; N, 4.4%).

Alternative procedure : (-)-(1R,2S)-Ephedrine (**122**) (5.00g, 30.3mmol) and 3,4-dimethoxybenzaldehyde (5.00g, 30.1mmol) in benzene (80ml) were reacted according to standard procedure C (23h) to furnish (-)-(2S,4S,5R)-2-(3,4-dimethoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**201**)[158] as long needles after recrystallisation from CH_2Cl_2/hexane (7.49g, 79%) (crude ratio 93:7), $[\alpha]_D^{20}$ -48.62 (*c* 1.85 $CHCl_3$); m.p. 93°C; $\nu_{max.}$ 3010 (aryl-H), 1517 (Ar) cm^{-1}; δ_H 7.47-6.90 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 5.13 (1H, d, J 8.2Hz, Ph**CH**), 4.66 [1H, s, $(MeO)_2C_6H_3\mathbf{CH}$)], 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3) 2.97 (1H, dq J 6.5 and 8.1Hz, CHMe), 2.19 (3H, s, NCH_3), 0.81 (3H, d, J 6.4Hz, $CHCH_3$); δ_C 149.92, 149.34, 140.21, 130.89, 128.19 (2C), 127.98 (2C), 127.76 (2C), 121.17, 110.94, 98.75, 82.30, 63.81, 55.76 (2C), 35.56, 14.77; *m/z* 312 (M^+-1) (Found: C, 72.9; H, 7.6; N, 4.4. $C_{19}H_{23}NO_3$ requires C, 72.8; H, 7.4; N, 4.5%). A portion of this material (1.95g, 6.22mmol) was reduced with $LiAlH_4$ (0.354g, 9.33mmol) to furnish the *title compound* (1.96g, quantitative).

Cyclisation of (-)-(1R,2R)-N-(3,4-dimethoxybenzyl)pseudoephedrine (200). A solution of (-)-(1R,2R)-N-(3,4-dimethoxybenzyl)pseudoephedrine (**200**) (0.641g, 2.03mmol) in CH_2Cl_2 (11ml) was cyclised according to standard procedure **D** (40°C, 0.5h) to leave a brown gum. ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 88:12. Flash chromatography (SiO_2, Et_2O) gave a colourless oil

(0.48g, 79%) that constituted an inseparable mixture of (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**203**) and (-)-(3R,4R)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**204**), *m/z* 298 (M^++1).

Cyclisation of (-)-(1R,2S)-N-(3,4-dimethoxybenzyl)ephedrine (202). A solution of (-)-(1R,2S)-N-(3,4-dimethoxybenzyl)ephedrine (**202**) (0.685g, 2.17mmol) in CH_2Cl_2 (12ml) was cyclised according to standard procedure **D** (40°C, 0.5h) to leave a brown oil (0.48g, 74%). ^1H n.m.r. spectroscopy of the crude product revealed a single diastereoisomer identified as (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**203**). Cup distillation under reduced pressure gave a pure sample for characterisation, $[\alpha]_D^{20}$ -13.65 (*c* 1.25 $CHCl_3$); $\nu_{max.}$ 3010 (aryl-H), 1514 (Ar), 705 (mono-substituted arene) cm^{-1}; δ_H 7.32-7.12 (5H, m, Ph), 6.56 and 6.19 [2H, s, 5**H** and 8**H**], 3.86 (3H, s, OC**H**$_3$), 3.81 [2H, br s, $(MeO)_2C_6H_2CH_2$], 3.75 (1H, d, J 8.0Hz, PhC**H**), 3.60 (3H, s, OC**H**$_3$), 2.73 (1H, dq, J 6.4 and 8.1Hz, C**H**Me), 2.44 (3H, s, NC**H**$_3$), 1.09 (3H, d, J 6.4Hz, CHC**H**$_3$); δ_C 147.60, 147.40, 145.09, 129.58, 129.43 (2C), 128.14 (2C), 126.60, 126.24, 112.64, 108.53, 62.39, 57.03, 55.75 (2C), 51.74, 40.74, 15.95; *m/z* 297 (M^+) (Found: M^+ 297.1728. $C_{19}H_{23}NO_3$ requires M, 297.1729).

(-)-(1R,2R)-(O-Trimethylsilyl)pseudoephedrine (209).[86] A solution of (-)-(1R,2R)-pseudoephedrine (**123**) (1.87g, 11.3mmol), $NH(SiMe_3)_2$ (6.0ml, 28.4mmol) and NEt_3 (5.0ml, 35.9mmol) in dichloroethane (10ml) was heated at reflux (2h) producing a white precipitate. The cooled solution was basified ($NaHCO_3$) and the organic phase separated. The aqueous layer was extracted (CH_2Cl_2) and the combined organic phases dried ($MgSO_4$). Filtration and evaporation afforded the *title compound* as a mobile oil (2.68g, quantitative). Bulb to bulb distillation under reduced pressure gave a pure sample for characterisation (*ca.* 110°C, 0.06mm Hg), $[\alpha]_D^{20}$ -81.31 (*c* 1.56 $CHCl_3$); $\nu_{max.}$ 2960 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.32-7.22 (5H, m, Ph), 4.33 [1H, d, J 7.9Hz, PhCH(OH)], 2.68 (1H, dq, J 6.4 and 7.7Hz, C**H**Me), 2.41 (3H, s, NC**H**$_3$), 2.08 (1H, br s, N**H**), 0.77 (3H, d, J 6.4Hz, CHC**H**$_3$), -0.03 [9H, s, C(C**H**$_3$)$_3$]; δ_C 142.68, 128.12 (2C), 127.60, 127.36 (2C), 79.53, 61.25, 33.59, 14.81, -0.11 (3C); *m/z* 238 (M^++1) (Found: C, 65.5; H, 10.0; N, 6.4. $C_{13}H_{23}NOSi$ requires C, 65.8; H, 9.8; N, 5.9%).

(-)-(1R,2R)-(N-*t*-Butoxycarbonyl)pseudoephedrine (210). An externally cooled (<0°C) solution of (-)-(1R,2R)-pseudoephedrine (**123**) (5.00g, 30.3mmol) in CH_2Cl_2 (40ml) was treated with di-*t*-butyl dicarbonate (7.90ml, 34.4mmol) and NEt_3 (4.20ml, 30.3mmol) and the solution stirred (20°C, 21h). The solution was acidified with saturated citric acid solution, the organic phase separated and washed sequentially with $NaHCO_3$ solution, water and brine. Drying ($MgSO_4$), filtration and evaporation afforded the *title compound* as a colourless oil that solidified on standing (7.82g, 97%). Recrystallisation from CH_2Cl_2/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ -88.10 (*c* 0.97 $CHCl_3$); m.p. 66-7°C; $\nu_{max.}$ 3410br (OH), 3008 (aryl-H), 1675 (C=O), 703 (mono-substituted arene) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 7.33-7.23 (5H, m, Ph), 5.02 (1H, d, J 4.5Hz, O**H**), 4.55 [1H, dd, J 4.5 and 7.4Hz, PhCH(OH)], 4.18 (1H, qu, J 7.1Hz, C**H**Me), 2.73 (3H, s, NC**H**$_3$), 1.36 [9H, s, C(C**H**$_3$)$_3$], 0.95 (3H, d, J 7.0Hz, CHC**H**$_3$); δ_C 152.20, 137.98, 128.52 (2C), 127.87, 126.81 (2C), 80.02, 28.27 (3C), 14.46; *m/z* 266 (M^++1) (Found: C, 68.2; H, 9.0; N, 5.2. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%).

Thermolysis of $Cr(CO)_6$ with (-)-(1R,2R)-(N-*t*-butoxycarbonyl)pseudoephedrine (210). (-)-(1R,2R)-(N-*t*-Butoxycarbonyl)pseudoephedrine (**210**) (1.00g, 3.77mmol) and $Cr(CO)_6$ (0.90g, 4.09mmol) in Bu_2O (50ml) and THF (8ml) were reacted according to the standard complexation procedure (17h) to give (+)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**152**) as a yellow solid that proved identical in all respects to the previously synthesised sample (0.204g, 17%).

Attempted hydrolysis of (+)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (152). A solution of (+)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**152**) (0.30g, 0.92mmol) in MeOH (25ml) and THF(5ml) was treated with $HBF_4.OMe_2$ (0.5ml, excess) and the yellow solution stirred (20°C, 24h). The solution was basified ($NaHCO_3$), the organic phase separated and evaporated. Column chromatography (Al_2O_3 grade V, CH_2Cl_2) gave a single fraction as a yellow solid that was identified as starting material (0.259g, 86%). A portion of this material (0.219g, 0.67mmol) in CH_2Cl_2 (15ml) was treated with CF_3COOH (0.60ml, excess). The yellow solution was stirred (20°C, 0.5h), $NaBH_3CN$ (0.285g, 4.54mmol) added and stirring continued (20°C, 0.5h). Similar basic workup and column chromatography again gave only starting material. In an analogous reaction, a longer reaction time again gave starting material.

(Pseudoephedrine)$Cr(CO)_3$ (205). A solution of (+)-(2-methyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**146**) (0.177g, 0.54mmol) in THF (20ml) and water (5ml) was treated with a catalytic quantity of *p*TsOH and HCl (conc., 10 drops). The mixture was stirred (20°C, 27h), basified (K_2CO_3) and the separated organic phase evaporated to leave the *title compound* as a yellow oil. This material could not be stored for any length of time and was freshly prepared on each occasion prior to use. The polarity of this complex prevented further purification by normal phase chromatography and attempts at crystallisation from a variety of solvent systems failed. ^1H n.m.r. spectroscopy of the crude material revealed the following features, δ_H 5.64-5.32 [5H, m, $(CO)_3CrPh$], 3.94 [1H, d, J 6.8Hz, $(CO)_3CrPhCH(OH)$], 2.59-2.47 (1H, m, CHMe), 2.44 (3H, s, NCH_3), 1.12 (3H, d, J 6.3Hz, $CHCH_3$).

Alternative procedure : A solution of (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**147**) (0.302g, 0.79mmol) and *p*TsOH (0.103g, 0.54mmol) in THF (10ml) and water (5ml) was treated with HCl (conc., 1ml) and the mixture heated at reflux (15h). The cooled solution was basified (NaOH, 2M), the solvent evaporated and the aqueous phase extracted (Et_2O). The combined extracts were evaporated to leave the *title compound* which was used straight away for subsequent reactions.

Attempted hydrolysis of (-)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (151). A solution of (-)-(4S,5S)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)$Cr(CO)_3$ (**151**) (0.916g, 2.80mmol) in THF (10ml) was treated with NaOH (5M, 20ml) and the mixture heated at reflux (100°C, 19h). The solvent was evaporated, the aqueous phase extracted (CH_2Cl_2) and the combined extracts evaporated to leave a yellow solid that was identified as starting material (0.420g, 46%).

(-)-(1R,2S)-(N-*t*-Butoxycarbonyl)ephedrine (211). An externally cooled solution (<0°C) of (-)-(1R,2S)-ephedrine (**122**) (20.0g, 121mmol) in CH_2Cl_2 (400ml) was treated with di-*t*-butyl dicarbonate (32ml, 139mmol) and NEt_3 (16.8ml, 121mmol) and the solution left to stand (20°C, 60h). The solution was acidified

with saturated citric acid solution, the organic phase separated and washed sequentially with $NaHCO_3$ solution, water and brine. Drying ($MgSO_4$), filtration and evaporation afforded a colourless oil that was distilled under reduced pressure to furnish the *title compound* as a colourless oil (160°C, 0.06mm Hg) (27.3g, 85%), $[\alpha]_D^{20}$ -26.81 (*c* 1.85 $CHCl_3$); $\nu_{max.}$ 3420br (OH), 3008 (aryl-H), 1675 (C=O), 703 (mono-substituted arene) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 7.34-7.18 (5H, m, Ph), 5.17 (1H, d, J 5.0Hz, O**H**), 4.57 [1H, dd, J 4.9 and 7.1Hz, PhC**H**(OH)], 4.06 (1H, qu, J 6.9Hz, C**H**Me), 2.64 (3H, s, NC**H**$_3$), 1.30 [9H, s, C(C**H**$_3$)$_3$], 1.17 (3H, d, J 6.9Hz, CHC**H**$_3$); δ_C (two amide conformers) 142.37, 142.28, 128.23 (2C), 127.60, 126.44 (2C), 79.68, 76.68, 58.09, 31.82, 28.19 (3C), 12.76; *m/z* 266 (M^++1) (Found: C, 68.2; H, 9.0; N, 5.2. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%).

(-)-[(N-*t*-Butoxycarbonyl)ephedrine]Cr(CO)$_3$ (212). (-)-(1R,2S)-(N-*t*-Butoxycarbonyl)ephedrine (**211**) (20.13g, 75.8mmol) and $Cr(CO)_6$ (16.7g, 75.9mmol) in Bu_2O (400ml) and THF (40ml) were reacted according to the standard complexation procedure (48h) to give a yellow solid. Recrystallisation from CH_2Cl_2/hexane furnished the *title compound* as a fluffy yellow powder (16.48g, 54%), $[\alpha]_D^{20}$ -36.23 (*c* 0.07 $CHCl_3$); m.p. 84°C; $\nu_{max.}$ 1965 and 1885 (C≡O), 1668 (C=O) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 5.77-5.47 [5H, m, (CO)$_3$CrPh], 4.21 [1H, t, J 6.9Hz, (CO)$_3$CrPhC**H**], 3.93 (1H, qu, J 6.9Hz, C**H**Me), 2.72 (3H, s, NC**H**$_3$), 1.34 [9H, s, C(C**H**$_3$)$_3$], 1.17 (3H, d, J 6.9Hz, CHC**H**$_3$); *m/z* 402 (M^++1) (Found: C, 54.2; H, 6.0; N, 3.2. $C_{18}H_{23}CrNO_6$ requires C, 53.9; H, 5.8; N, 3.5%).

(-)-(Ephedrine)Cr(CO)$_3$ (206). Hydrolysis of either (+)-(2-methyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (**144**) or (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (**145**) was achieved under acidic conditions analogous to those employed for the preparation of (pseudoephedrine)Cr(CO)$_3$ (**205**).

Alternative procedure : (-)-[(N-*t*-Butoxycarbonyl)ephedrine]Cr(CO)$_3$ (**212**) (0.439g, 1.09mmol) was dissolved in HCOOH (98-100%, 15ml) and the yellow solution left to stand (20°C, 4.5h). The acid was evaporated, the residue treated with NaOH (2M) and the aqueous layer extracted (Et_2O). The combined extracts were evaporated to leave the *title compound* as a yellow solid (0.330g, quantitative). Recrystallisation from Et_2O/hexane afforded a pure sample for characterisation, $[\alpha]_D^{20}$ -32.98 (*c* 0.21 $CHCl_3$); m.p. 92-7°C (decomp.); $\nu_{max.}$ 1970 and 1885 (C≡O) cm^{-1}; δ_H 5.66-5.16 [5H, m, (CO)$_3$CrPh], 4.46 [1H, d, J 3.4Hz, (CO)$_3$CrPhCH(OH)], 2.72 (1H, dq, 3.4 and 6.5Hz, C**H**Me), 2.48 (3H, s, NC**H**$_3$), 0.93 (3H, d, J 6.5Hz, CHC**H**$_3$); *m/z* 302 (M^++1) (Found: C, 51.9; H, 5.0; N, 4.7. $C_{13}H_{15}CrNO_4$ requires C, 51.8; H, 5.0; N, 4.65%).

(+)-[N-(3,4-Dimethoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (207). A mixture of (pseudoephedrine)Cr(CO)$_3$ (**205**) [freshly prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (**147**) (0.26g, 0.54mmol)] and freshly prepared 3,4-dimethoxybenzyl bromide (0.128g, 0.55mmol) in MeCN (40ml) was reacted according to standard procedure **A** (3h) to give a yellow oil. Column chromatography (Al_2O_3 grade V, Et_2O) furnished the *title compound* as a yellow solid (0.149g, 61%) that was recrystallised from CH_2Cl_2/hexane to provide a pure sample for characterisation, $[\alpha]_D^{20}$ +83.65 (*c* 0.09 $CHCl_3$); m.p. 124-8°C; $\nu_{max.}$ 1975 and 1885 (C≡O) cm^{-1}; δ_H 6.84-6.82 [3H, m, (MeO)$_2$C$_6$**H**$_3$], 5.52-5.22 [5H, m, (CO)$_3$CrPh], 5.14 (1H, br s, O**H**), 3.97 [1H, d, J 8.8Hz, (CO)$_3$CrPhC**H**(OH)], 3.90 (3H, s,

OCH_3), 3.89 (3H, s, OCH_3), 3.67, 3.44 [2H, AB system, J_{AB} 12.8Hz, $(MeO)_2C_6H_3CH_2$], 2.58 (1H, dq J 6.7 and 9.3Hz, CHMe), 2.21 (3H, s, NCH_3), 1.00 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 452 (M^++1) (Found: C, 58.5; H, 5.8; N, 3.0. $C_{22}H_{25}CrNO_6$ requires C, 58.5; H, 5.6; N, 3.1%).

[N-(3,4-Dimethoxybenzyl)ephedrine]Cr(CO)$_3$ (208). A mixture of (ephedrine)$Cr(CO)_3$ (**206**) (0.991g, 3.29mmol) and freshly prepared 3,4-dimethoxybenzyl bromide (0.76g, 3.29mmol) in MeCN (40ml) was reacted according to standard procedure **A** (3h) to give a yellow oil. Flash chromatography (SiO_2, Et_2O) furnished the *title compound* as a yellow oil (0.727g, 49%), δ_H 6.79-6.69 [3H, m, $(MeO)_2C_6H_3$], 5.55-5.21 [5H, m, $(CO)_3CrPh$], 4.38 [1H, d, J 6.0Hz, $(CO)_3CrPhCH(OH)$], 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.51, 3.45 [2H, AB system, J_{AB} 13.2Hz, $(MeO)_2C_6H_3CH_2$], 2.78 (1H, dq J 6.6 and 6.4Hz, CHMe), 2.23 (3H, s, NCH_3), 1.11 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 452 (M^++1).

Cyclisation of (+)-[N-(3,4-dimethoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (207). A solution of (+)-[N-(3,4-dimethoxybenzyl)pseudoephedrine]$Cr(CO)_3$ (**208**) (0.10g, 0.22mmol) in CH_2Cl_2 (15ml) was cyclised according to standard procedure **E** (0°C, 2h) to afford a yellow oil. ^1H n.m.r. spectroscopy of the crude product revealed a single product identified as (+)-*trans*-(N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline) $Cr(CO)_3$ (**213**) after column chromatography (Al_2O_3 grade V, CH_2Cl_2), δ_H 6.91 and 6.56 (2H, s, 5H and 8H), 5.71-4.87 [5H, m, $(CO)_3CrPh$], 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.70, 3.44 [2H, AB system, J_{AB} 15.6Hz, $(MeO)_2C_6H_2CH_2$], 3.44 [1H, s, $(CO)_3CrPhCH$], 3.12 (1H, q, J 6.5Hz, CHMe), 2.34 (3H, s, NCH_3), 1.01 (3H, d, J 6.6Hz, $CHCH_3$); *m/z* 434 (M^++1). This material was decomplexed according to the standard procedure to give (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**203**) as a colourless oil (0.064g, 95% for 2 steps), $[\alpha]_D^{20}$ +13.78 (*c* 0.24 $CHCl_3$); *m/z* 297 (M^+) (Found: M^+, 297.1728. $C_{19}H_{23}NO_2$ requires M, 297.1729). A repeat experiment employing one equivalent of acid during the cyclisation gave only recovery of starting material.

Cyclisation of [N-(3,4-dimethoxybenzyl)ephedrine]Cr(CO)$_3$ (208). A solution of [N-(3,4-dimethoxybenzyl)ephedrine]$Cr(CO)_3$ (**208**) (0.061g, 0.14mmol) in CH_2Cl_2 (5ml) was cyclised according to standard procedure **E** (<-20°C, 43h) to afford a yellow solid. ^1H n.m.r. spectroscopy of the crude product revealed a single product identified as (+)-*cis*-(N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline)$Cr(CO)_3$ (**214**) (0.048g, 82%). Column chromatography (Al_2O_3 grade V, Et_2O) and recrystallisation from CH_2Cl_2/hexane afforded a pure sample for characterisation, $[\alpha]_D^{20}$ +172.94 (*c* 0.22 $CHCl_3$); $\nu_{max.}$ 1965 and 1885 (C≡O) cm^{-1}; δ_H 7.03 and 6.52 (2H, s, 5H and 8H), 5.63-5.06 [5H, m, $(CO)_3CrPh$], 3.94, 3.40 [2H, AB system, J_{AB} 15.2Hz, $(MeO)_2C_6H_2CH_2$], 3.93 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.46 [1H, d, J 3.2Hz, $(CO)_3CrPhCH$], 2.76 (1H, dq J 6.7 and 3.2Hz, CHMe), 2.28 (3H, s, NCH_3), 1.06 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 434 (M^++1) (Found : C, 61.0; H, 5.6; N, 3.5. $C_{22}H_{23}CrNO_5$ requires C, 61.0; H, 5.35; N, 3.2. This material (0.048g, 0.11mmol) was decomplexed according to the standard procedure to give (+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-6,7-dimethoxy tetrahydroisoquinoline (**204**) as a white powder (0.030g, 92%), $[\alpha]_D^{20}$ +108.07 (*c* 0.11 $CHCl_3$); m.p. 92.5-4°C; $\nu_{max.}$ 3010 (aryl-H), 1520 (Ar), 705 (mono-substituted arene) cm^{-1}; δ_H 7.29-7.17 (5H, m, Ph), 6.57 and 6.42 [2H, s, 5H and 8H], 4.02 (1H, d, J 4.4Hz, PhCH), 3.91, 3.48 [2H, AB system, J_{AB} 15.1Hz, $(MeO)_2C_6H_2CH_2$], 3.86 (3H, s, OCH_3),

3.68 (3H, s, OCH_3), 2.85 (1H, dq, J 6.6 and 4.5Hz, CHMe), 2.38 (3H, s, NCH_3), 0.83 (3H, d, J 6.6Hz, $CHCH_3$); δ_C 147.57, 147.52, 142.81, 130.41 (2C), 129.52, 127.61 (2C), 126.90, 126.14, 112.35, 108.59, 59.15, 56.62, 55.86 (2C), 50.83, 42.27, 14.38; *m/z* 297 (M^+) (Found: M^+, 297.1728. $C_{19}H_{23}NO_2$ requires M, 297.1729).

(-)-(1R,2R)-N-(2-Methoxybenzyl)pseudoephedrine (217). A mixture of (-)-(1R,2R)-pseudoephedrine (**123**) (8.00g, 48.4mmol) and 2-methoxybenzaldehyde (6.59g, 48.4mmol) in benzene (100ml) was reacted according to standard procedure C to furnish (-)-(2R,4R,5R)-2-(2-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**223**) as a colourless oil after distillation under reduced pressure (180°C, 0.06mm Hg) (12.52g, 91%) (crude ratio 95:5), $[\alpha]_D^{20}$ -4.84 (*c* 0.95 $CHCl_3$); $\nu_{max.}$ 3010 (aryl-H), 1495 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.76-6.90 [9H, m, Ph and $(MeO)C_6H_4$], 5.58 [1H, s, $(MeO)C_6H_4CH$)], 4.75 (1H, d, J 8.7Hz, PhCH), 3.87 (3H, s, OCH_3), 2.58 (1H, dq J 6.1 and 8.7Hz, CHMe), 2.26 (3H, s, NCH_3), 1.24 (3H, d, J 6.1Hz, $CHCH_3$); δ_C 158.58, 140.90, 129.87, 128.46 (2C), 128.26, 127.80, 127.02, 126.89 (2C), 121.06, 110.76, 92.41, 86.25, 68.98, 55.57, 35.34, 14.20; *m/z* 284 (M^++1) (Found: C, 76.6; H, 7.5; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). A portion of this material (5.03g, 17.7mmol) was reduced with $LiAlH_4$ (0.80g, 21.1mmol) to furnish the *title compound* as a white solid (4.62g, 91%). Recrystallisation from Et_2O/hexane furnished a pure sample for characterisation, $[\alpha]_D^{20}$ -120.08 (*c* 1.32 $CHCl_3$); m.p. 62-5°C; $\nu_{max.}$ 3360br (OH), 3010 (aryl-H), 1496 (Ar), 702 (mono-substituted arene) cm^{-1}; δ_H 7.37-6.90 [9H, m, Ph and $(MeO)C_6H_4$], 5.37 (1H, br s, OH), 4.34 [1H, d, J 9.7Hz, PhCH(OH)], 3.88 (3H, s, OCH_3), 3.81, 3.47 [2H, AB system, J_{AB} 12.7Hz, $(MeO)C_6H_4CH_2$], 2.77 (1H, dq J 6.7 and 9.7Hz, CHMe), 2.23 (3H, s, NCH_3), 0.82 (3H, d, J 6.6Hz, $CHCH_3$); δ_C 158.26, 142.53, 131.04, 128.77, 128.31 (2C), 127.71, 127.56 (2C), 126.98, 120.32, 110.50, 74.99, 65.53, 55.14, 52.82, 36.28, 7.31; *m/z* 286 (M^++1) (Found: C, 76.0; H, 8.4; N, 4.95. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

(-)-(1R,2S)-N-(2-Methoxybenzyl)ephedrine (220). A mixture of (-)-(1R,2S)-ephedrine (**122**) (8.00g, 48.4mmol) and 2-methoxybenzaldehyde (6.59g, 48.4mmol) in benzene (100ml) was reacted according to standard procedure C to furnish (-)-(2S,4S,5R)-2-(2-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**226**) as a white solid (12.74g, 93%) and as a single diastereoisomer. Recrystallisation from Et_2O/hexane furnished a pure sample for characterisation, $[\alpha]_D^{20}$ -75.11 (*c* 1.33 $CHCl_3$); m.p. 100-1°C; $\nu_{max.}$ 3010 (aryl-H), 1496 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.97-6.95 [9H, m, Ph and $(MeO)C_6H_4$], 5.31 [1H, s, $(MeO)C_6H_4CH$)], 5.21 (1H, d, J 8.1Hz, PhCH), 3.90 (3H, s, OCH_3), 3.04 (1H, dq J 6.5 and 7.7Hz, CHMe), 2.26 (3H, s, NCH_3), 0.83(3H, d, J 6.4Hz, $CHCH_3$); δ_C 159.12, 140.32, 130.09, 128.57, 128.16 (2C), 127.94 (2C), 127.61, 126.08, 121.02, 110.91, 91.84, 82.73, 63.81, 55.56, 35.97, 14.79; *m/z* 284 (M^++1) (Found: C, 76.6; H, 7.6; N, 4.75. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). A portion of this material (4.71g, 16.6mmol) was reduced with $LiAlH_4$ (0.80g, 21.1mmol) to furnish the *title compound* as a white powder (4.62g, 97%). Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ -64.81 (*c* 0.92 $CHCl_3$); m.p. 88°C; $\nu_{max.}$ 3420br (OH), 3005 (aryl-H), 1495 (Ar), 704 (mono-substituted arene) cm^{-1}; δ_H 7.39-6.91 [9H, m, Ph and $(MeO)C_6H_4$], 4.97 [1H, d, J 3.9Hz, PhCH(OH)], 4.25 (1H, br s, OH), 3.90 (3H, s, OCH_3), 3.84, 3.59 [2H, AB system, J_{AB} 13.1Hz, $(MeO)C_6H_4CH_2$], 2.95 (1H, dq J 6.9 and 4.2Hz, CHMe), 2.15 (3H, s, NCH_3), 0.97 (3H, d, J 6.9Hz, $CHCH_3$); δ_C 158.08, 142.51,

131.03, 128.52, 128.02, 127.57, 127.07, 126.85, 126.36 (2C), 120.40, 110.56, 73.65, 64.04, 55.22, 54.79, 38.69, 9.94; *m/z* 286 (M^++1) (Found: C, 76.0; H, 8.4; N, 4.6. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

(-)-(1R,2R)-N-(3-Methoxybenzyl)pseudoephedrine (218). A mixture of (-)-(1R,2R)-pseudoephedrine (**123**) (10.0g, 60.5mmol) and 3-methoxybenzaldehyde (8.24g, 60.5mmol) in benzene (100ml) was reacted according to standard procedure C to furnish (-)-(2R,4R,5R)-2-(3-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**224**) as a colourless oil (16.25g, 95%) (crude ratio 93:7). Distillation under reduced pressure gave a pure sample as an oil that solidified on standing (152-60°C, 0.06mm Hg), $[\alpha]_D^{20}$ -44.01 (*c* 0.96 $CHCl_3$); m.p. 58°C; $\nu_{max.}$ 3010 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.46-6.90 [9H, m, Ph and (MeO)C_6H_4], 4.95 [1H, s, (MeO)C_6H_4CH], 4.78 (1H, d, J 8.8Hz, PhC**H**), 3.86 (3H, s, OCH_3), 2.58 (1H, dq J 6.0 and 8.7Hz, C**H**Me), 2.25 (3H, s, NCH_3), 1.25 (3H, d, J 6.1Hz, $CHCH_3$); δ_C 160.00, 141.34, 140.59, 129.51, 128.55 (2C), 127.87, 126.85 (2C), 120.58, 115.05, 113.05, 99.51, 86.59, 68.82, 55.22, 35.16, 14.22; *m/z* 284 (M^++1) (Found: C, 76.1; H, 7.6; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). A portion of this material (5.03g, 17.7mmol) was reduced with $LiAlH_4$ (0.80g, 21.1mmol) to furnish the *title compound* as a colourless oil (4.77g, 94%). Further purification was achieved by flash chromatography (SiO_2, Et_2O) to give a pure sample for characterisation, $[\alpha]_D^{20}$ -121.10 (*c* 1.04 $CHCl_3$); $\nu_{max.}$ 3350br (OH), 3010 (aryl-H), 1496 (Ar), 702 (mono-substituted arene) cm^{-1}; δ_H 7.35-6.82 [9H, m, Ph and (MeO)C_6H_4], 5.17 (1H, br s, O**H**), 4.32 [1H, d, J 9.7Hz, PhC**H**(OH)], 3.83 (3H, s, OCH_3), 3.73, 3.49 [2H, AB system, J_{AB} 13.0Hz, (MeO)$C_6H_4CH_2$], 2.76 (1H, dq J 6.7 and 9.7Hz, C**H**Me), 2.25 (3H, s, NCH_3), 0.81 (3H, d, J 6.7Hz, $CHCH_3$); δ_C 160.01, 142.14, 140.54, 129.61, 128.38 (2C), 127.86, 127.53 (2C), 121.35, 114.44, 112.87, 74.80, 64.85, 58.18, 55.15, 35.67, 7.11; *m/z* 286 (M^++1) (Found: C, 75.6; H, 8.2; N, 4.45. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

(-)-(1R,2S)-N-(3-Methoxybenzyl)ephedrine (221). A mixture of (-)-(1R,2S)-ephedrine (**122**) (10.0g, 60.5mmol) and 3-methoxybenzaldehyde (8.24g, 60.5mmol) in benzene (100ml) was reacted according to standard procedure C to furnish (-)-(2S,4S,5R)-2-(3-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**227**) as a pale yellow oil (16.09g, 94%) (crude ratio 88:12). Distillation under reduced pressure gave a pure sample as a colourless oil for characterisation (160-72°C, 0.06mm Hg), $[\alpha]_D^{20}$ -49.12 (*c* 1.14 $CHCl_3$); $\nu_{max.}$ 3010 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.47-6.89 [9H, m, Ph and (MeO)C_6H_4], 5.15 (1H, d, J 8.2Hz, PhCH), 4.69 [1H, s, (MeO)C_6H_4C**H**)], 3.86 (3H, s, OCH_3), 2.98 (1H, dq J 6.4 and 8.2Hz, C**H**Me), 2.21 (3H, s, NCH_3), 0.80 (3H, d, J 6.4Hz, $CHCH_3$); δ_C 160.04, 140.02, 129.65, 129.47, 128.52, 128.19 (2C), 128.04 (2C), 120.87, 115.02, 113.62, 98.74, 82.54, 63.92, 55.20, 35.65, 14.82; *m/z* 284 (M^++1) (Found: C, 76.5; H, 7.8; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). A portion of this material (5.00g, 17.6mmol) was reduced with $LiAlH_4$ (0.80g, 21.1mmol) to furnish the *title compound* as a colourless oil (4.86g, 96%). Flash chromatography (SiO_2, Et_2O) gave a pure sample for characterisation, $[\alpha]_D^{20}$ -28.39 (*c* 1.02 $CHCl_3$); $\nu_{max.}$ 3420br (OH), 3010 (aryl-H), 703 (mono-substituted arene) cm^{-1}; δ_H 7.36-6.78 [9H, m, Ph and (MeO)C_6H_4], 4.88 [1H, d, J 5.0Hz, PhC**H**(OH)], 3.79 (3H, s, OCH_3), 3.61, 3.59 [2H, AB system, J_{AB} 13.5Hz, (MeO)$C_6H_4CH_2$], 3.32 (1H, br s, O**H**), 2.95 (1H, dq J 6.8 and 5.1Hz, C**H**Me), 2.21 (3H, s, NCH_3), 1.01 (3H, d, J 6.8Hz, $CHCH_3$); δ_C 159.90, 142.77, 141.44, 129.39, 128.16 (2C), 127.07, 126.37

(2C), 121.08, 114.07, 112.58, 73.79, 63.44, 59.04, 55.11, 38.58, 9.72; *m/z* 286 (M^++1) (Found: C, 75.9; H, 8.4; N, 4.9. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

(-)-(1R,2R)-N-(4-Methoxybenzyl)pseudoephedrine (219). A mixture of (-)-(1R,2R)-pseudoephedrine (**123**) (5.00g, 30.3mmol) and 4-methoxybenzaldehyde (4.12g, 30.3mmol) in benzene (150ml) was reacted according to standard procedure C to furnish (-)-(2R,4R,5R)-2-(4-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**225**) as an oil that solidified on standing (7.32g, 85%) (crude ratio 96:4). Recrystallisation from Et_2O/hexane gave a pure sample as large blocks for characterisation, $[\alpha]_D^{20}$ -51.03 (*c* 2.15 $CHCl_3$); m.p. 65°C (lit. 70-1°C); $\nu_{max.}$ 3010 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.53-6.95 [9H, m, Ph and (MeO)C_6H_4], 4.94 [1H, s, (MeO)C_6H_4**CH**], 4.78 (1H, d, J 8.7Hz, Ph**CH**), 3.83 (3H, s, O**CH**$_3$), 2.55 (1H, dq J 6.1 and 8.8Hz, **CH**Me), 2.22 (3H, s, N**CH**$_3$), 1.26 (3H, d, J 6.0Hz, CH**CH**$_3$); δ_C 160.48, 140.77, 131.76, 129.43 (2C), 128.49 (2C), 128.01, 126.81 (2C), 113.85 (2C), 99.40, 86.35, 68.76, 55.25, 35.02, 14.26; *m/z* 284 (M^++1) (Found: C, 76.2; H, 7.8; N, 4.9. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%). A portion of this material (2.50g, 8.80mmol) was reduced with $LiAlH_4$ (0.40g, 10.5mmol) to furnish the *title compound* as a colourless oil (4.77g, 94%), $[\alpha]_D^{20}$ -124.64 (*c* 0.76 $CHCl_3$); $\nu_{max.}$ 3340br (OH), 3010 (aryl-H), 703 (mono-substituted arene) cm^{-1}; δ_H 7.35-6.90 [9H, m, Ph and (MeO)C_6H_4], 4.33 [1H, d, J 9.7Hz, PhCH(OH)], 3.83 (3H, s, O**CH**$_3$), 3.70, 3.46 [2H, AB system, J_{AB} 12.8Hz, (MeO)C_6H_4**CH**$_2$], 2.76 (1H, dq J 6.7 and 9.7Hz, **CH**Me), 2.23 (3H, s, N**CH**$_3$), 0.81 (3H, d, J 6.7Hz, CH**CH**$_3$); δ_C 159.07, 142.21, 130.88, 130.23 (2C), 128.34 (2C), 127.81, 127.51 (2C), 113.93, 74.73, 64.54, 57.59, 55.21, 35.40, 7.06; *m/z* 286 (M^++1) (Found: C, 75.6; H, 8.5; N, 5.0. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

(-)-(1R,2S)-N-(4-Methoxybenzyl)ephedrine (222). A mixture of (-)-(1R,2S)-ephedrine (**122**) (5.00g, 30.3mmol) and 4-methoxybenzaldehyde (4.12g, 30.3mmol) in benzene (150ml) was reacted according to standard procedure C to furnish (-)-(2S,4S,5R)-2-(4-methoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**228**) as a white solid and as a single diastereoisomer (8.09g, 94%). Recrystallisation from Et_2O/hexane gave a pure sample as slender needles for characterisation, m.p. 85-6°C (lit.[104] 86°C); $[\alpha]_D^{20}$ -55.20 (*c* 1.50 $CHCl_3$); $[\alpha]_D^{20}$ -38.93 (*c* 1.93 benzene) {lit.[104] $[\alpha]_D^{20}$ -38.30 (*c* 1.50 benzene)}; $\nu_{max.}$ 3010 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.61-6.96 [9H, m, Ph and (MeO)C_6H_4], 5.14 (1H, d, J 8.3Hz, PhCH), 4.67 [1H, s, (MeO)C_6H_4**CH**)], 3.85 (3H, s, O**CH**$_3$), 2.96 (1H, dq J 6.5 and 8.3Hz, **CH**Me), 2.18 (3H, s, N**CH**$_3$), 0.80 (3H, d, J 6.5Hz, CH**CH**$_3$); δ_C 160.59, 140.17, 130.43, 129.79 (2C), 128.15 (2C), 128.02 (2C), 127.73, 114.00 (2C), 98.62, 82.27, 63.89, 55.26, 35.60, 14.89; *m/z* 284 (M^++1). A portion of this material (2.68g, 9.44mmol) was reduced with $LiAlH_4$ (0.43g, 11.3mmol) to furnish the *title compound* as an oil that solidified on standing (2.00g, 74%). Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ -33.42 (*c* 0.98 $CHCl_3$); m.p. 50-2°C; $\nu_{max.}$ 3400br (OH), 3010 (aryl-H), 1514 (Ar), 702 (mono-substituted arene) cm^{-1}; δ_H 7.41-6.86 [9H, m, Ph and (MeO)C_6H_4], 4.88 [1H, d, J 4.9Hz, PhCH(OH)], 3.82 (3H, s, O**CH**$_3$), 3.59, 3.55 [2H, AB system, J_{AB} 13.2Hz, (MeO)C_6H_4**CH**$_2$], 2.93 (1H, dq J 6.8 and 5.0Hz, **CH**Me), 2.19 (3H, s, N**CH**$_3$), 1.00 (3H, d, J 6.8Hz, CH**CH**$_3$); δ_C 158.88, 142.97, 131.66, 130.01 (2C), 128.15 (2C), 127.07 (2C), 126.41 (2C), 113.79, 73.67, 63.15, 58.47, 55.18, 38.33, 9.69; *m/z* 286 (M^++1) (Found: C, 75.9; H, 8.4; N, 5.0. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%).

Cyclisation of (-)-(1R,2R)-N-(4-methoxybenzyl)pseudoephedrine (219). A solution of (-)-(1R,2R)-N-(4-methoxybenzyl)pseudoephedrine (**219**) (0.81g, 2.84mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 1h) to leave a pale yellow oil (0.75g, 99%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 93:7. Flash chromatography (SiO_2, Et_2O) and recrystallisation from Et_2O/hexane furnished (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) as colourless blocks, $[\alpha]_D^{20}$ +4.25 (*c* 0.52 $CHCl_3$); m.p. 75°C; $\nu_{max.}$ 1505 (Ar), 703 (mono-substituted arene) cm^{-1}; δ_H 7.32-7.13 (5H, m, Ph), 7.00 [1H, d, J 8.4Hz, 8**H**], 6.70 [1H, dd, J 2.7 and 8.4Hz, 7**H**], 6.27 [1H, d, J 2.7Hz, 5**H**], 3.80 [2H, br s, (MeO)$C_6H_3CH_2$], 3.77 (1H, d, J 8.4Hz, PhC**H**), 3.62 (3H, s, OCH_3), 2.73 (1H, dq, J 6.4 and 8.4Hz, C**H**Me), 2.43 (3H, s, NCH_3), 1.08 (3H, d, J 6.4Hz, CHCH_3); δ_C (C_6D_6) 158.65, 145.80, 138.82, 129.60, 127.80 (2C), 127.31 (2C), 126.97, 126.27, 114.64, 112.74, 61.85, 55.58, 54.14, 52.70, 41.05, 14.36; *m/z* 268 (M^++1) (Found: C, 80.8; H, 8.2; N, 5.0. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%).

Cyclisation of (-)-(1R,2S)-N-(4-methoxybenzyl)ephedrine (222). A solution of (-)-(1R,2S)-N-(4-methoxybenzyl)ephedrine (**222**) (1.176g, 4.12mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 1h) to leave a white solid (1.05g, 95%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 97:3. Recrystallisation from Et_2O/hexane furnished (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) as colourless blocks, $[\alpha]_D^{20}$ -3.82 (*c* 0.81 $CHCl_3$); m.p. 75-6°C; *m/z* 267 (M^+) (Found: C, 81.0; H, 8.05; N, 5.2. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%).

Cyclisation of (-)-(1R,2R)-N-(3-methoxybenzyl)pseudoephedrine (218). A solution of (-)-(1R,2R)-N-(3-methoxybenzyl)pseudoephedrine (**218**) (1.69g, 5.92mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 1.75h) to leave a red oil (0.71g, 45%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 87:13.[159] Flash chromatography (SiO_2, Et_2O) gave two well separated fractions. The less polar, minor component was recrystallised from Et_2O/hexane to give (-)-(3R,4R)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**232**) as a white powder, $[\alpha]_D^{20}$ -144.95 (*c* 0.05 $CHCl_3$); m.p. 121-2°C; $\nu_{max.}$ 3018 (aryl-H), 1504 (Ar), 704 (mono-substituted arene) cm^{-1}; δ_H 7.29-6.62 [8H, m, Ph and (MeO)C_6**H**$_3$], 4.05 (1H, d, J 4.6Hz, PhC**H**), 3.95, 3.53 [2H, AB system J_{AB} 15.5Hz, (MeO)C_6H_3C**H**$_2$], 3.78 (3H, s, OCH_3), 2.86 (1H, dq, J 4.5 and 6.6Hz, C**H**Me), 2.39 (3H, s, NCH_3), 0.84 (3H, d, J 6.7Hz, CHC**H**$_3$); δ_C 157.79, 143.30, 136.03, 131.07, 130.89, 130.56 (2C), 130.05, 127.78, 126.23, 112.79, 110.35, 59.23, 57.11, 55.11, 50.37, 42.24, 14.28; *m/z* 267 (M^+) (Found: C, 80.6; H, 8.3; N, 5.0. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%). Evaporation of the second fraction gave (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**231**) as a colourless oil that solidified on standing, $[\alpha]_D^{20}$ +44.90 (*c* 0.94 $CHCl_3$); m.p. 41-2°C; $\nu_{max.}$ 3010 (aryl-H), 1504 (Ar), 702 (mono-substituted arene) cm^{-1}; δ_H 7.32-6.61 [8H, m, Ph and (MeO)C_6**H**$_3$], 3.84 [2H, br s, (MeO)C_6H_3C**H**$_2$], 3.77 (3H, s, O**CH**$_3$), 3.76 (1H, d, J 8.4Hz, PhC**H**), 2.74 (1H, dq, J 6.4 and 8.6Hz, C**H**Me), 2.44 (3H, s, N**CH**$_3$), 1.08 (3H, d, J 6.4Hz, CHC**H**$_3$); δ_C 157.82, 145.56, 135.72, 131.11, 129.73 (2C), 128.45 (2C), 127.07, 126.46, 112.87, 110.42, 62.64, 57.92, 55.07, 51.54, 40.81, 16.27; *m/z* 267 (M^+) (Found: C, 81.2; H, 8.3; N, 5.1. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%). Differential nOe experiments were performed separately

on both (-)-(3R,4R)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**232**) and (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydro isoquinoline (**231**) as $[d]_6$ benzene solutions at 500MHz. For (-)-**232**, irradiation of the methyl doublet gave enhancements to both H3 (21.8%) and H4 (8.0%) whilst irradiation of H4 gave an enhancement to H3 (8.5%). For (-)-**231**, irradiation of the methyl doublet gave enhancements to both H3 (13.2%) and H4 (10.8%) whilst irradiation of H4 gave a smaller enhancement to H3 (4%).

Cyclisation of (-)-(1R,2S)-N-(3-methoxybenzyl)ephedrine (221). A solution of (-)-(1R,2S)-N-(3-methoxybenzyl)ephedrine (**221**) (2.24g, 7.85mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **D** (40°C, 1.5h) to leave a pale brown oil (1.22g, 58%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 93:7.[159] Flash chromatography (SiO_2, Et_2O) gave two well separated fractions. The less polar, minor component was recrystallised from Et_2O/hexane to give (+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**232**) as a fine powder, $[\alpha]_D^{20}$ +132.61 (*c* 0.05 $CHCl_3$); m.p. 121.5°C; *m/z* 267 (M^+) (Found: C, 80.7; H, 8.3; N, 5.1. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%). Evaporation of the second fraction gave (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**231**) as a colourless oil that solidified on standing, $[\alpha]_D^{20}$ -45.40 (*c* 0.70 $CHCl_3$); m.p. 41-2°C; *m/z* 267 (M^+) (Found: C, 81.1; H, 8.3; N, 5.15. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%).

Cyclisation of (-)-(1R,2R)-N-(2-methoxybenzyl)pseudoephedrine (217). A solution of (-)-(1R,2R)-N-(2-methoxybenzyl)pseudoephedrine (**217**) (1.85g, 6.47mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 5h) to leave a pale yellow solid (1.57g, 91%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 99:1. Recrystallisation from Et_2O/hexane furnished (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) as large blocks, $[\alpha]_D^{20}$ +65.49 (*c* 1.10 $CHCl_3$); m.p. 114-6°C; $\nu_{max.}$ 3005 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.31-6.36 [8H, m, Ph and (MeO)$C_6\mathbf{H}_3$], 3.98, 3.63 [2H, AB system, J_{AB} 16.3Hz, (MeO)$C_6H_3CH_2$], 3.85 (3H, s, O$\mathbf{CH}_3$), 3.81 (1H, d, J 8.0Hz, PhC**H**), 2.73 (1H, dq, J 6.4 and 7.9Hz, C**H**Me), 2.47 (3H, s, N$\mathbf{CH}_3$), 1.07 (3H, d, J 6.3Hz, CH$\mathbf{CH}_3$); δ_C 155.65, 145.34, 139.19, 129.68 (2C), 128.34 (2C), 126.63, 126.40, 123.71, 122.18, 106.93, 61.66, 55.18, 52.30, 52.11, 41.28, 15.84; *m/z* 268 (M^++1) (Found: C, 80.6; H, 8.2; N, 5.5. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%).

Cyclisation of (-)-(1R,2S)-N-(2-methoxybenzyl)ephedrine (220). A solution of (-)-(1R,2S)-N-(2-methoxybenzyl)ephedrine (**220**) (0.50g, 1.75mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **D** (40°C, 2.5h) to leave a pale yellow solid (0.269g, 57%). ^1H n.m.r. spectroscopy of the crude product revealed a single diastereoisomer identified as (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) Recrystallisation from Et_2O/hexane furnished a pure sample for characterisation, $[\alpha]_D^{20}$ -64.46 (*c* 0.51 $CHCl_3$); m.p. 114-6°C; *m/z* 268 (M^++1) (Found: C, 81.2; H, 7.75; N, 5.0. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%). A single crystal X-ray structure determination of (-)-233 confirmed the relative stereochemistry of this compound (see appendix). In a repeat experiment, ^1H n.m.r. spectroscopy of the crude product revealed the presence of two components (ratio 80:20), the major proving

identical to (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**). Crystallisation from CH_2Cl_2/hexane gave the minor component as a white powder that was dissolved in THF and treated with NaOH. The mixture was stirred (20°C, 2h) and the solvent evaporated. The aqueous phase was extracted (CH_2Cl_2) and the combined extracts evaporated to leave a colourless oil identified as (+)-(1S,2S)-N-(2-methoxybenzyl)pseudoephedrine (**217**), $[\alpha]_D^{20}$ +98.67 (*c* 0.19 $CHCl_3$).

(-)-(1R,2R)-N-(Benzyl)pseudoephedrine (238).[160] A mixture of (-)-(1R,2R)-pseudoephedrine (**123**) (6.00g, 36.3mmol) and benzyl bromide (4.30ml, 36.2mmol) in MeCN (50ml) was reacted according to standard procedure **A** to furnish the *title compound* as a white solid after recrystallisation from CH_2Cl_2/hexane (7.18g, 77%), $[\alpha]_D^{20}$ -125.07 (*c* 1.53 $CHCl_3$) {lit.[160] $[\alpha]_D^{20}$ +60 (no solvent specified)}; m.p. 57-8°C (lit.[160] 122-4°C for picrate); δ_H 7.38-7.26 (10H, m, 2Ph), 5.24 (1H, br s, **OH**), 4.33 [1H, d, J 9.7Hz, Ph**CH**(OH)], 3.76, 3.52 (2H, AB system, J_{AB} 12.9Hz, Ph**CH**$_2$), 2.76 (1H, dq J 6.6 and 9.7Hz, **CH**Me), 2.24 (3H, s, NC**H**$_3$), 0.82 (3H, d, J 6.6Hz, CHC**H**$_3$); δ_C 142.32, 138.93, 129.16 (2C), 128.70 (2C), 128.42 (2C), 128.13, 127.91, 127.60 (2C), 74.84, 64.92, 58.23, 35.69, 7.21; *m/z* 256 (M^++1).

(-)-(1R,2S)-N-(Benzyl)ephedrine (239).[161] A mixture of (-)-(1R,2S)-ephedrine (**122**) (8.00g, 48.4mmol) and benzyl bromide (5.40ml, 45.4mmol) in MeCN (50ml) was reacted according to standard procedure **A** to furnish the *title compound* as a white solid after recrystallisation from Et_2O/hexane (7.66g, 62%), $[\alpha]_D^{20}$ -29.68 (*c* 1.48 $CHCl_3$) {lit.[161] $[\alpha]_D^{20}$ +93 (H_2O)}; m.p. 45-6°C (lit.[161] 42-5°C) ; δ_H 7.35-7.24 (10H, m, 2Ph), 4.89 [1H, d, J 4.9Hz, Ph**CH**(OH)], 3.64, 3.61 (2H, AB system, J_{AB} 13.5Hz, PhCH_2), 3.46 (1H, br s, **OH**), 2.94 (1H, dq J 6.8 and 4.9Hz, **CH**Me), 2.20 (3H, s, NC**H**$_3$), 1.00 (3H, d, J 6.8Hz, CHC**H**$_3$); δ_C 142.92, 139.73, 129.15, 128.89, 128.49, 128.19, 127.94, 127.75, 127.46, 127.13, 127.05, 126.41, 73.74, 63.45, 59.11, 38.55, 9.73; *m/z* 256 (M^++1).

Cyclisation of (-)-(1R,2R)-N-(benzyl)pseudoephedrine (238). A solution of (-)-(1R,2R)-N-(benzyl)pseudoephedrine (**238**) (2.40g, 9.40mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 3.25h) to leave a colourless oil (2.23g, quantitative). ^{1}H n.m.r. spectroscopy of the crude product revealed two components in the ratio 94:6. Flash chromatography (SiO_2, Et_2O) enabled the isolation of the major component, identified as (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**240**), $[\alpha]_D^{20}$ +57.16 (*c* 0.36 $CHCl_3$); $\nu_{max.}$ 3005 (aryl-H), 1485 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.33-6.73 (9H, m, Ph and C$_6$**H**$_4$), 3.86 (2H, br s, C$_6$H$_4$C**H**$_2$), 3.85 (1H, d, J 8.6Hz, PhC**H**), 2.75 (1H, dq, J 6.4 and 8.3Hz, **CH**Me), 2.45 (3H, s, NC**H**$_3$), 1.09 (3H, d, J 6.3Hz, CHC**H**$_3$); δ_C 145.30, 138.06, 134.61, 130.01, 129.80 (2C), 128.43, 127.07, 126.48 (2C), 126.00, 125.90, 62.57, 57.77, 52.34, 41.05, 16.31; *m/z* 237 (M^+) (Found: C, 85.7; H, 8.2; N, 6.3. $C_{17}H_{19}N$ requires C, 86.0; H, 8.1; N, 5.9%).

Cyclisation of (-)-(1R,2S)-N-(benzyl)ephedrine (239). A solution of (-)-(1R,2S)-N-(benzyl)ephedrine (**239**) (2.00g, 7.83mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 5h) to leave a colourless oil (1.80g, 97%). ^{1}H n.m.r. spectroscopy of the crude product revealed two components in the ratio 97:3. Flash chromatography (SiO_2, Et_2O) gave two well separated fractions. The less polar, minor component was recrystallised from Et_2O/hexane to give (+)-(3S,4S)-N-methyl-3-methyl-4-phenyl

tetrahydroisoquinoline (**241**) as a white solid, $[\alpha]_D^{20}$ +159.54 (*c* 0.18 $CHCl_3$); m.p. 102-3°C; $\nu_{max.}$ 3005 (aryl-H), 700 (mono-substituted arene) cm^{-1}; δ_H 7.28-6.95 (9H, m, Ph and $C_6\mathbf{H}_4$), 4.10 (1H, d, J 4.5Hz, PhC**H**), 3.99, 3.56 (2H, AB system, J_{AB} 15.5Hz, $C_6H_4C\mathbf{H}_2$), 2.88 (1H, dq, J 4.5 and 6.7Hz, C**H**Me), 2.40 (3H, s, NCH_3), 0.86 (3H, d, J 6.6Hz, $CHCH_3$); *m/z* 237 (M^+) (Found: M+, 237.1519. $C_{17}H_{19}N$ requires M, 237.1517). Evaporation of the second fraction gave (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**240**) as a colourless oil, $[\alpha]_D^{20}$ -51.02 (*c* 0.90 $CHCl_3$); *m/z* 237 (M^+) (Found: C, 86.35; H, 8.1; N, 5.9. $C_{17}H_{19}N$ requires C, 86.0; H, 8.1; N, 5.9%).

Relative rate experiments. In separate experiments an equimolar solution of (-)-(1R,2S)-N-(benzyl)ephedrine (**239**) and either (-)-(1R,2S)-N-(2-, 3-, or 4-methoxybenzyl)ephedrine (**220**, **221** or **222**) was cyclised according to standard procedure D (20°C). Aliquots of the reaction mixture were removed at regular time intervals (t=0, 0.5min, 1min, 2min, 5min, 10min, 0.5h, 1h, 4h) and immediately quenched with NaOH (2M). In each case, the organic phase was separated and evaporated and the residue studied by ^1H n.m.r. spectroscopy. In each case all of the starting materials had been consumed within 5 minutes and the rate at which this occurred was the same for all of the cyclisation precursors used in this study.

(+)-[N-(2-Methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (242). A mixture of (pseudoephedrine)$Cr(CO)_3$ (**205**) [freshly prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**147**) (0.146g, 0.38mmol)] and 2-methoxybenzaldehyde (0.06g, 0.44mmol) in CH_2Cl_2 (5ml) was reacted according to standard procedure **B** to furnish the corresponding oxazolidine as a yellow oil. Without further purification, this material was reduced ($NaBH_4$) and the *title compound* isolated as a yellow solid after recrystallisation from CH_2Cl_2/hexane (0.021g, 13%), $[\alpha]_D^{22}$ +68.16 (*c* 0.05 $CHCl_3$); m.p. 124-5°C; $\nu_{max.}$ 3020 (aryl-H), 1970 and 1895 (C≡O) cm^{-1}; δ_H 7.32-6.89 [4H, m, (MeO)$C_6\mathbf{H}_4$], 5.55-5.21 [5H, m, $(CO)_3$CrPh], 3.93 [1H, d, J 9.5Hz, $(CO)_3$CrPhC**H**(OH)], 3.87 (3H, s, OCH_3), 3.75, 3.44 [2H, AB system, J_{AB} 12.6Hz, (MeO)$C_6H_4C\mathbf{H}_2$], 2.58 (1H, dq J 6.7 and 9.4Hz, C**H**Me), 2.19 (3H, s, NCH_3), 1.02 (3H, d, J 6.7Hz, $CHC\mathbf{H}_3$); *m/z* 422 (M^++1) [Found: M^+-2(CO) . $C_{19}H_{23}CrNO_3$ requires M, 365.3961].

(+)-[N-(3-Methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (243). A mixture of (pseudoephedrine)$Cr(CO)_3$ (**205**) [freshly prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**147**) (0.51g, 1.34mmol)] and 3-methoxybenzaldehyde (0.19g, 1.40mmol) in CH_2Cl_2 (25ml) was reacted according to standard procedure **B** to furnish the corresponding oxazolidine as a yellow oil (0.332g, 59%). This material was reduced ($NaBH_3CN$) to furnish the *title compound* as a yellow solid (0.101g, 67%). Recrystallisation from CH_2Cl_2/hexane gave a pure sample as yellow blocks for characterisation, $[\alpha]_D^{22}$ +82.22 (*c* 0.09 $CHCl_3$); m.p. 118-9°C; $\nu_{max.}$ 3020 (aryl-H), 1972 and 1890 (C≡O) cm^{-1}; δ_H 7.29-6.81 [4H, m, (MeO)$C_6\mathbf{H}_4$], 5.54-5.22 [5H, m, $(CO)_3$CrPh], 5.08 (1H, br s, O**H**), 3.92 [1H, d, J 9.6Hz, $(CO)_3$CrPhC**H**(OH)], 3.83 (3H, s, $OC\mathbf{H}_3$), 3.69, 3.48 [2H, AB system, J_{AB} 13.0Hz, (MeO)$C_6H_4C\mathbf{H}_2$], 2.59 (1H, dq J 6.6 and 9.4Hz, C**H**Me), 2.22 (3H, s, NCH_3), 1.01 (3H, d, J 6.6Hz, $CHC\mathbf{H}_3$); *m/z* 422 (M^++1) (Found: C, 59.6; H, 5.6; N, 3.3. $C_{21}H_{23}CrNO_5$ requires C, 59.85; H, 5.5; N, 3.3%).

(+)-[N-(4-Methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (244). A mixture of (pseudoephedrine)Cr(CO)$_3$ (**205**) [freshly prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (**147**) (1.09g, 2.85mmol)] and 4-methoxybenzaldehyde (0.70g, 5.14mmol) in CH_2Cl_2 (20ml) was reacted according to standard procedure **B** to furnish the corresponding oxazolidine as a yellow oil after column chromatography (Al_2O_3 grade V, Et_2O). This material was reduced ($NaBH_4$) and the product recrystallised from CH_2Cl_2/hexane to give the *title compound* as a yellow solid (0.072g, 6%), $[\alpha]_D^{22}$ +91.64 (*c* 0.14 $CHCl_3$); m.p. 154-5°C; $\nu_{max.}$ 3010 (aryl-H), 1975 and 1890 (C≡O) cm^{-1}; δ_H 7.24-6.86 [4H, m, (MeO)C$_6$**H**$_4$], 5.53-5.21 [5H, m, (CO)$_3$CrPh], 5.14 (1H, br s, O**H**), 3.90 [1H, d, J 9.6Hz, (CO)$_3$CrPhC**H**(OH)], 3.82 (3H, s, OC**H**$_3$), 3.65, 3.43 [2H, AB system, J_{AB} 12.8Hz, (MeO)C$_6$H$_4$C**H**$_2$], 2.58 (1H, dq J 6.6 and 9.5Hz, C**H**Me), 2.19 (3H, s, NC**H**$_3$), 0.99 (3H, d, J 6.6Hz, CHC**H**$_3$); *m/z* 422 (M^++1) (Found: C, 60.0; H, 5.8; N, 3.2. $C_{21}H_{23}CrNO_5$ requires C, 59.85; H, 5.5; N, 3.3%).

(+)-[N-(Benzyl)pseudoephedrine]Cr(CO)$_3$ (245). A mixture of (pseudoephedrine)Cr(CO)$_3$ (**205**) [freshly prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)Cr(CO)$_3$ (**147**) (0.146g, 0.38mmol)] and benzyl bromide (0.05ml, 0.42mmol) in EtOH (10ml) was reacted according to standard procedure **A** in the presence of $NaHCO_3$ (0.05g, 0.60mmol) and a catalytic quantity of NaI (20°C, 71h). Recrystallisation of the product from CH_2Cl_2/hexane afforded the *title compound* as a yellow solid (0.04g, 27%), $[\alpha]_D^{22}$ +80.0 (*c* 0.07 $CHCl_3$); m.p. 159°C; $\nu_{max.}$ 3020 (aryl-H), 1972 and 1895 (C≡O) cm^{-1}; δ_H 7.38-7.29 (5H, m, Ph), 5.53-5.22 [5H, m, (CO)$_3$CrPh], 5.12 (1H, br s, O**H**), 3.92 [1H, d, J 9.5Hz, (CO)$_3$CrPhC**H**(OH)], 3.72, 3.50 (2H, AB system, J_{AB} 12.9Hz, PhCH_2), 2.59 (1H, dq J 6.7 and 9.5Hz, C**H**Me), 2.21 (3H, s, NC**H**$_3$), 1.01 (3H, d, J 6.7Hz, CHC**H**$_3$); *m/z* 392 (M^++1) (Found: C, 61.25; H, 5.5. $C_{20}H_{21}CrNO_4$ requires C, 61.4; H, 5.4%).

(+)-[N-(2-Methoxybenzyl)ephedrine]Cr(CO)$_3$ (246). A mixture of (-)-(ephedrine)Cr(CO)$_3$ (**206**) (0.176g, 0.58mmol) and freshly prepared 2-methoxybenzyl bromide (0.127g, 0.63mmol) in EtOH (5ml) was reacted according to standard procedure **A** in the presence of $NaHCO_3$ (0.067g, 0.80mmol) and a catalytic quantity of NaI (20°C, 63h) to furnish the *title compound* as a yellow oil (0.111g, 45%). Crystallisation from Et_2O/hexane gave a pure sample for characterisation , $[\alpha]_D^{22}$ +28.80 (*c* 0.09 $CHCl_3$); $\nu_{max.}$ 1965 and 1885 (C≡O) cm^{-1}; δ_H 7.29-6.88 [4H, m, (MeO)C$_6$**H**$_4$], 5.60-5.18 [5H, m, (CO)$_3$CrPh], 4.49 [1H, br s, (CO)$_3$CrPhC**H**(OH)], 3.87 (3H, s, OC**H**$_3$), 3.69, 3.57 [2H, AB system, J_{AB} 13.2Hz, (MeO)C$_6$H$_4$C**H**$_2$], 3.65 (1H, d, J 3.3Hz, O**H**), 2.83 (1H, dq J 6.7 and 5.4Hz, C**H**Me), 2.19 (3H, s, NC**H**$_3$), 1.07 (3H, d, J 6.9Hz, CHC**H**$_3$); *m/z* 421 (M^+) (Found: C, 59.65; H, 5.6; N, 3.1. $C_{21}H_{23}CrNO_5$ requires C, 59.85; H, 5.5; N, 3.3%).

[N-(3-Methoxybenzyl)ephedrine]Cr(CO)$_3$ (247). A mixture of (-)-(ephedrine)Cr(CO)$_3$ (**206**) (0.62g, 2.06mmol) and freshly prepared 3-methoxybenzyl bromide (0.50g, 2.49mmol) in EtOH (10ml) was reacted according to standard procedure **A** in the presence of $NaHCO_3$ (0.26g, 3.09mmol) and a catalytic quantity of NaI (20°C, 19.5h) to give a yellow oil. Column chromatography (Al_2O_3 grade V, gradient elute petroleum ether/Et_2O) furnished the *title compound* as a yellow oil (0.427g, 49%), δ_H 7.21-6.70 [4H, m, (MeO)C$_6$**H**$_4$], 5.54-5.22 [5H, m, (CO)$_3$CrPh], 4.35 [1H, dd, J 2.8 and 6.4Hz, (CO)$_3$CrPhC**H**(OH)], 3.80 (3H, s, OC**H**$_3$),

3.58, 3.53 [2H, AB system, J_{AB} 13.5Hz, (MeO)$C_6H_4CH_2$], 2.78 (1H, qu J 6.7Hz, CHMe), 2.73 (1H, d, J 3.3Hz, OH), 2.24 (3H, s, NCH_3), 1.12 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 422 (M^++1).

[N-(4-Methoxybenzyl)ephedrine]Cr(CO)$_3$ (248). A mixture of (-)-(ephedrine)Cr(CO)$_3$ (**206**) (0.33g, 1.09mmol) and freshly prepared 4-methoxybenzyl bromide (0.22g, 1.09mmol) in CH_2Cl_2 (30ml) was reacted according to standard procedure **A** (20°C, 28h) to give a yellow oil. Column chromatography [Al_2O_3 grade V, petroleum ether/Et_2O (1:1)] furnished the *title compound* as a yellow oil (0.047g, 10%), δ_H 7.07-6.79 [4H, m, (MeO)C_6H_4], 5.54-5.22 [5H, m, $(CO)_3CrPh$], 4.35 [1H, d, J 6.3Hz, $(CO)_3CrPhCH(OH)$], 3.81 (3H, s, OCH_3), 3.55, 3.50 [2H, AB system, J_{AB} 13.2Hz, (MeO)$C_6H_4CH_2$], 2.78 (1H, dq J 6.6 and 6.4Hz, CHMe), 2.22 (3H, s, NCH_3), 1.10 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 422 (M^++1).

[N-(Benzyl)ephedrine]Cr(CO)$_3$ (249). A mixture of (-)-(ephedrine)Cr(CO)$_3$ (**206**) (0.792g, 2.63mmol) and benzyl bromide (0.35ml, 2.94mmol) in EtOH (10ml) was reacted according to standard procedure **A** in the presence of $NaHCO_3$ (0.331g, 3.94mmol) and a catalytic quantity of NaI (20°C, 68h) to furnish the *title compound* as a yellow oil (0.653g, 63%), δ_H 7.40-7.12 (5H, m, Ph), 5.53-5.22 [5H, m, $(CO)_3CrPh$], 4.36 [1H, d, J 6.4Hz, $(CO)_3CrPhCH(OH)$], 3.61, 3.56 (2H, AB system, J_{AB} 13.5Hz, $PhCH_2$), 2.78 (1H, qu J 6.6 Hz, CHMe), 2.24 (3H, s, NCH_3), 1.12 (3H, d, J 6.7Hz, $CHCH_3$).

Cyclisation of (+)-[N-(4-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (244). A solution of (+)-[N-(4-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (**244**) (0.044g, 0.10mmol) in CH_2Cl_2 (10ml) was cyclised according to standard procedure **E** (<-20°C, 24h) to give a yellow oil. ^1H n.m.r. spectroscopy of the crude product revealed a single diastereoisomer identified as *trans*-(N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**250**) as a yellow oil (0.04g, 95%). This material (0.04g, 0.10mmol) was decomplexed according to the standard procedure to give (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) as a white solid (0.025g, 94%). Recrystallisation from Et_2O/hexane gave large blocks, $[\alpha]_D^{20}$ +4.30 (*c* 0.41 $CHCl_3$); m.p. 75°C (this melting point was not depressed when mixed with the previously synthesised sample).

Cyclisation of [N-(4-methoxybenzyl)ephedrine]Cr(CO)$_3$ (248). A solution of [N-(4-methoxybenzyl)ephedrine]Cr(CO)$_3$ (**248**) (0.047g, 0.11mmol) in CH_2Cl_2 (15ml) was cyclised according to standard procedure **E** (<-20°C, 46h) to give a yellow solid (0.042g, 93%). ^1H n.m.r. spectroscopy of the crude product revealed a single diastereoisomer identified as *trans*-(N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**250**), δ_H 7.00 (1H, d, J 8.5Hz, **8H**), 6.92 (1H, d, J 2.5Hz, **5H**), 6.81 (1H, dd, J 2.6 and 8.5Hz, **7H**), 5.83-4.94 [5H, m, $(CO)_3CrPh$], 3.83 (3H, s, OCH_3), 3.73, 3.46 [2H, AB system, J_{AB} 15.5Hz, (MeO)$C_6H_3CH_2$], 3.45 [1H, s, $(CO)_3CrPhCH$], 3.17 (1H, q J 6.7Hz, CHMe), 2.37 (3H, s, NCH_3), 1.00 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 403 (M^+) (Found: M^+ 403.0880. $C_{21}H_{21}CrNO_4$ requires M, 403.0876). This material (0.042g, 0.10mmol) was decomplexed according to the standard procedure to furnish (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-6-methoxy tetrahydroisoquinoline (**229**) as a white solid (0.023g, 84%). Recrystallisation from Et_2O/hexane gave colourless blocks, $[\alpha]_D^{20}$ -3.92 (*c* 0.46 $CHCl_3$); m.p. 75°C (this melting point was not depressed when mixed with the previously synthesised sample).

Cyclisation of (+)-[N-(3-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (243). A solution of (+)-[N-(3-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (**243**) (0.051g, 0.12mmol) in CH_2Cl_2 (5ml) was cyclised according to standard procedure **E** (<-20^{o}C, 42h) to give a yellow oil (0.04g, 74%). ^{1}H n.m.r. spectroscopy of the crude product revealed two components, the major being identified as *trans*-(N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**251**), δ_H 7.27 (1H, d, J 8.5Hz, 5**H**), 6.82 (1H, dd, J 2.7 and 8.5Hz, 6**H**), 6.61 (1H, d, J 2.7Hz, 8**H**), 5.86-4.95 [5H, m, (CO)$_3$CrPh], 3.80 (3H, s, OC**H**$_3$), 3.74, 3.50 [2H, AB system, J_{AB} 16.2Hz, (MeO)C$_6$H$_3$C**H**$_2$], 3.42 [1H, s, (CO)$_3$CrPhC**H**], 3.21 (1H, q J 6.5Hz, C**H**Me), 2.38 (3H, s, NC**H**$_3$), 1.00 (3H, d, J 6.6Hz, CHC**H**$_3$); *m/z* 404 (M^++1). This material (0.036g, 0.09mmol) was decomplexed according to the standard procedure to give an inseparable mixture of (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**231**) and (3R,4S)-N-methyl-3-methyl-4-phenyl-5-methoxy tetrahydroisoquinoline (**253**) in the ratio 91:9 (0.021g, 88%).

Cyclisation of [N-(3-methoxybenzyl)ephedrine]Cr(CO)$_3$ (247). A solution of [N-(3-methoxybenzyl)ephedrine]Cr(CO)$_3$ (**247**) (0.427g, 1.01mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **E** (<-20^{o}C, 142h) to give a yellow oil. ^{1}H n.m.r. spectroscopy of the crude product revealed two components in the ratio 86:14. Column chromatography [Al_2O_3 grade V, petroleum ether/Et_2O (8:1)] gave two well separated fractions, the less polar of which was identified as (+)-*cis*-(N-methyl-3-methyl-4-phenyl-5-methoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**254**) (0.032g, 8%), $[\alpha]_D^{19}$ +9.41 (*c* 0.10 $CHCl_3$); $\nu_{max.}$ 1966 and 1890 (C≡O) cm^{-1}; δ_H 7.21 (1H, t, J 7.9Hz, 7**H**), 6.77-6.70 (2H, m, 6**H** and 8**H**), 5.73-4.89 [5H, m, (CO)$_3$CrPh], 4.11, 3.43 [2H, AB system, J_{AB} 16.0Hz, (MeO)C$_6$H$_3$C**H**$_2$], 3.89 (3H, s, OC**H**$_3$), 3.67 [1H, d, J 2.6Hz, (CO)$_3$CrPhC**H**], 2.61 (1H, dq J 6.7 and 2.7Hz, C**H**Me), 2.25 (3H, s, NC**H**$_3$), 1.01 (3H, d, J 6.7Hz, CHC**H**$_3$); *m/z* 403 (M^+) (Found: C, 62.6; H, 5.3; N, 3.2. $C_{21}H_{21}CrNO_4$ requires C, 62.5; H, 5.25; N, 3.5). Evaporation of the major component furnished *cis*-(N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline)Cr(CO)$_3$ (**255**) (0.205g, 50%) as a yellow oil, δ_H 7.42 (1H, d, J 8.6Hz, 5**H**), 6.84 (1H, dd, J 8.6 and 2.7Hz, 6**H**), 6.58 (1H, d, J 2.6Hz, 8**H**), 5.63-5.02 [5H, m, (CO)$_3$CrPh], 3.98, 3.44 [2H, AB system, J_{AB} 15.7Hz, (MeO)C$_6$H$_3$C**H**$_2$], 3.80 (3H, s, OC**H**$_3$), 3.50 [1H, d, J 3.3Hz, (CO)$_3$CrPhC**H**], 2.76 (1H, dq J 3.2 and 6.7Hz, C**H**Me), 2.28 (3H, s, NC**H**$_3$), 1.07 (3H, d, J 6.8Hz, CHC**H**$_3$); *m/z* 403 (M^+) (Found: M^+ 403.0880. $C_{21}H_{21}CrNO_4$ requires M, 403.0876). The minor product [(+)-**254**] (0.030g, 0.08mmol) was decomplexed according to the standard procedure to give (+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-5-methoxy tetrahydroisoquinoline (**256**) as a white powder (0.020g, quantitative). Recrystallisation from Et_2O/hexane afforded a pure sample for characterisation as slender needles, $[\alpha]_D^{20}$ +231.86 (*c* 0.11 $CHCl_3$); m.p. 151-2^{o}C; δ_H 7.28-6.57 [8H, m, Ph and (MeO)C$_6$H$_3$], 4.09, 3.45 [2H, AB system, J_{AB} 15.5Hz, (MeO)C$_6$H$_3$C**H**$_2$], 3.98 (1H, d, J 3.7Hz, PhC**H**), 3.55 (3H, s, OC**H**$_3$), 2.62 (1H, dq, J 3.8 and 6.7Hz, C**H**Me), 2.29 (3H, s, NC**H**$_3$), 0.88 (3H, d, J 6.6Hz, CHC**H**$_3$); *m/z* 267 (M^+) (Found: C, 80.8; H, 8.1; N, 5.0. $C_{18}H_{21}NO$ requires C, 80.9; H, 7.9; N, 5.2%). The major product (**255**) (0.205g, 0.51mmol) was decomplexed according to the standard procedure to give (+)-(3S,4S)-N-methyl-3-methyl-4-phenyl-7-methoxy tetrahydroisoquinoline (**232**) as a white powder (0.112g, 82%). Recrystallisation from Et_2O/hexane afforded a pure sample that proved identical in all respects to the previously synthesised sample, $[\alpha]_D^{20}$ +143.64 (*c* 0.11 $CHCl_3$); m.p. 122^{o}C.

Cyclisation of (+)-[N-(2-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (242). A solution of (+)-[N-(2-methoxybenzyl)pseudoephedrine]Cr(CO)$_3$ (**242**) (0.016g, 0.04mmol) in CH_2Cl_2 (5ml) was cyclised according to standard procedure **E** (<-20°C, 28h) and the yellow oil obtained decomplexed according to the standard procedure. ^{1}H n.m.r. spectroscopy of the crude product revealed the presence of both (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) and (-)-(R)-N-(2-methoxybenzyl)-N-(methyl) amphetamine (**257**) in the approximate ratio 50:50, contaminated with minor amounts of unidentified compounds (0.005g, 46% for 2 steps). Crystallisation from Et_2O/hexane furnished a pure sample of (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydro isoquinoline (**233**) as small stars which proved identical in all respects to the previously synthesised sample, $[\alpha]_D^{21}$ +65.22 (*c* 0.02 $CHCl_3$); m.p. 115°C.

Cyclisation of (+)-[N-(2-methoxybenzyl)ephedrine]Cr(CO)$_3$ (246). A solution of (+)-[N-(3-methoxybenzyl)ephedrine]Cr(CO)$_3$ (**246**) (0.066g, 0.16mmol) in CH_2Cl_2 (20ml) was cyclised according to standard procedure **E** (<-20°C, 36h) and the yellow oil obtained decomplexed according to the standard procedure. ^{1}H n.m.r. spectroscopy of the crude product revealed the presence of both (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (**233**) and (+)-(S)-N-(2-methoxybenzyl)-N-(methyl)amphetamine (**257**) (0.038g, 90% for 2 steps). Crystallisation from Et_2O/hexane afforded a pure sample of the former compound that proved identical in all respects to the previously synthesised sample, $[\alpha]_D^{20}$ -66.36 (*c* 0.11 $CHCl_3$); m.p. 115°C. The mother liquor was subjected to flash chromatography (SiO_2, Et_2O) to give (+)-(S)-N-(2-methoxybenzyl)-N-(methyl)amphetamine (**257**) that proved identical in all respects to an authentic sample.

(+)-(S)-N-(2-Methoxybenzyl)-N-(methyl)amphetamine (257). The HCl salt of N-(methyl)amphetamine (1.77g, 9.54mmol) was dissolved in excess NaOH (2M) and the free base extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to leave N-(methyl)amphetamine as a mobile oil (1.41g, 99%). A mixture of this material and freshly prepared 2-methoxybenzyl bromide (1.92g, 9.54mmol) in MeCN (50ml) was reacted according to standard procedure **A** to furnish the *title compound* as a pale yellow gum (2.45g, 96%). Bulb to bulb distillation under reduced pressure (*ca.* 180°C, 0.06mm Hg) gave a pure sample for characterisation, $[\alpha]_D^{20}$ +37.09 (*c* 1.32 $CHCl_3$); $\nu_{max.}$ 3010 (aryl-H), 1492 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.34-6.86 [9H, m, Ph and (MeO)C_6H_4], 3.85 (3H, s, OCH_3), 3.67, 3.64 [2H, AB system, J_{AB} 14.1Hz, (MeO)$C_6H_4CH_2$], 3.12-2.50 (3H, m, $PhCH_2CHMe$), 2.32 (3H, s, NCH_3), 1.04 (3H, d, J 6.5Hz, $CHCH_3$); δ_C 157.89, 141.22, 130.28, 129.44, 128.31 (2C), 128.16, 127.80, 127.07, 125.82, 120.43, 110.32, 60.57, 55.26, 50.89, 39.38, 37.45, 13.95; *m/z* 270 (M^++1) (Found: C, 80.2; H, 8.8; N, 5.1. $C_{18}H_{23}NO$ requires C, 80.3; H, 8.6; N, 5.2%).

Cyclisation of (+)-[N-(benzyl)pseudoephedrine]Cr(CO)$_3$ (245). A solution of (+)-[N-(benzyl)pseudoephedrine]Cr(CO)$_3$ (**245**) (0.029g, 0.07mmol) in CH_2Cl_2 (6ml) was cyclised according to standard procedure **E** (<-20°C, 24.5h) and the yellow oil obtained decomplexed according to the standard procedure. ^{1}H n.m.r. spectroscopy of the crude product revealed 3 products in the ratio 84:13:3 corresponding to (+)-(3R,4S)-N-methyl-3-methyl-4-phenyl tetrahydroisoquinoline (**240**), (-)-(1R,2R)-N-(benzyl)pseudoephedrine (**238**) and the reduced compound N-(benzyl)-N-(methyl)amphetamine (**258**) respectively (0.018g, 89% for 2 steps). Flash chromatography (SiO_2, Et_2O) enabled the isolation of pure (+)-(3R,4S)-N-methyl-3-methyl-4-

phenyl tetrahydroisoquinoline (**240**) as a colourless oil that proved identical in all respects to the previously synthesised sample, $[\alpha]_D^{20}$ +46.95 (*c* 0.09 $CHCl_3$).

Attempted cyclisation of [N-(benzyl)ephedrine]Cr(CO)$_3$ (249). A solution of [N-(benzyl)ephedrine]$Cr(CO)_3$ (**249**) (0.319g, 0.82mmol) in CH_2Cl_2 (20ml) was treated according to standard procedure E (<-20°C, 48h) and the yellow oil obtained decomplexed according to the standard procedure to give N-(benzyl)-N-(methyl)amphetamine (**258**) as a colourless oil (0.078g, 40% for 2 steps), δ_H 7.44-7.11 (10H, m, 2Ph), 3.62 (2H, br s, PhC**H**$_2$N), 3.10-2.39 (3H, m, PhC**H**$_2$CHMe), 2.28 (3H, s, NC**H**$_3$), 1.04 (3H, d, J 6.5Hz, CHC**H**$_3$); *m/z* 240 (M^++1).

Homoveratraldehyde.[143] To a freshly prepared solution of NaOMe in MeOH [generated by careful addition of Na (10.37g, 451mmol) to externally cooled MeOH (150ml)] was added finely powdered 3,4-dimethoxybenzaldehyde (50.0g, 301mmol). The resulting suspension was mechanically stirred and treated dropwise with methylchloroacetate (39.6ml, 452mmol) over a period of 3 hours with external cooling (<-10°C). Stirring was continued (-5°C, 2h then 20°C, 3h) and the resultant thick paste poured into ice-cold water (585ml) containing MeCOOH (3.35ml, 58.5mmol). The white precipitate produced was collected by filtration, repeatedly washed (H_2O) and dried to afford the glycidic ester as a pale yellow solid (52.1g, 73%). Recrystallisation from hot MeOH gave a pure sample of the glycidic ester, m.p. 62-4°C (lit.[143] 65-6°C); δ_H 6.92-6.74 [3H, m, $(MeO)_2C_6$**H**$_3$], 4.06 [1H, d, J 1.7Hz, $(MeO)_2C_6$**H**$_3$C**H**], 3.88 (3H, s, OC**H**$_3$), (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 3.51 (1H, d, J 1.8Hz, C**H**COOMe). A portion of this material (24.0g, 101mmol) in benzene (126ml) was cautiously treated with a MeOH solution of NaOMe [generated by careful addition of Na (2.38g, 104mmol) to externally cooled MeOH (34ml)]. Addition of water (2.1ml) resulted in the formation of a white precipitate. The mixture was treated with Et_2O (70ml), the solution stirred and then left to stand (5-10°C, 3h). The white precipitate was collected by filtration to afford the crude sodium salt as a white powder (23.8g, 96%). A suspension of this material (23.8g, 96.8mmol) in benzene (100ml) was treated with MeCOOH (6ml, 10.5mmol) and heated at reflux until no more CO_2 was evolved (3h). Water (50ml) was added, the mixture stirred and the organic phase separated. The aqueous phase was extracted (benzene) and the combined organic phases washed (H_2O). Drying ($MgSO_4$) and evaporation afforded the *title compound* as a pale yellow oil (11.5g, 66%) that was further purified by distillation under reduced pressure (99-106°C, 0.06mm Hg), δ_H 9.73 (1H, t, J 2.4Hz, C**H**O), 6.89-6.71 [3H, m, $(MeO)_2C_6$**H**$_3$], 3.88 (6H, s, 2OC**H**$_3$), 3.63 (2H, d, J 2.5Hz, C**H**$_2$CHO); *m/z* 180 (M^+).

3,4-Dimethoxyphenethyl bromide.[145] An externally cooled solution of 3,4-dimethoxyphenethyl alcohol (5.00g, 27.4mmol) in benzene (50ml) was treated portionwise with PPh_3 (8.00g, 30.5mmol) maintaining a reaction temperature of <10°C. After complete addition, the solution was stirred (20°C, 2h) and quenched with $Na_2S_2O_3$ (10% w/v, 30ml). The separated organic layer was washed twice (NaOH, 1M, 30ml) (H_2O, 30ml) and each aqueous layer extracted (Et_2O, 20ml). The combined organic phases were dried ($MgSO_4$) and evaporated to leave an orange solid. This material was treated with Et_2O (50ml) and the precipitated Ph_3PO removed by filtration. Evaporation of the mother liquor and distillation under reduced pressure (138°C, 0.06mm Hg) gave the *title compound* as a colourless oil (4.66g, 69%) that solidified on standing and darkened upon

exposure to air over a period of time, δ_H 6.84-6.73 [3H, m, $(MeO)_2C_6H_3$], 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.56 (2H, t, J 7.6Hz, CH_2CH_2Br), 3.11 (2H, t, J 7.7Hz, CH_2CH_2Br).

1-Phenyl-N-(3,4-dimethoxyphenethyl)ethanolamine (267).[142] A solution of 3,4-dimethoxyphenethylamine (15.9g, 87.7mmol) and styrene oxide (**171**) (10.0ml, 87.7mmol) in MeCN (100ml) was heated at reflux in the presence of K_2CO_3 (24.3g, 176mmol) for 19 hours. The solvent was evaporated, water (50ml) added and the product extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to afford a pale oil that solidified on standing. Recrystallisation from CH_2Cl_2/hexane afforded the *title compound* as a white solid (20.86g, 79%); δ_H 7.36-6.71 [8H, m, Ph and $(MeO)_2C_6H_3$], 4.69 [1H, dd, J 3.7 and 8.9Hz, PhCH(OH)], 3.85 (6H, s, $2OCH_3$), 2.93-2.42 [6H, m, $(MeO)_2C_6H_3CH_2CH_2N(H)CH_2$]; *m/z* 302 ($M^+$+1).

1-Phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (268).[138,142] A solution of 1-phenyl-N-(3,4-dimethoxyphenethyl)ethanolamine (**267**) (7.2g, 23.9mmol) in CH_2Cl_2 was cyclised according to standard procedure **A** (40°C, 1h) to afford 1-phenyl-7,8-dimethoxy tetrahydrobenzazepine[142] as a white powder (3.43g, 51%); δ_H 7.38-7.13 (5H, m, Ph), 6.68 and 6.32 (2H, s, 6**H** and 9**H**), 4.42 (1H, t, J 4.7Hz, PhC**H**), 3.88 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.61-2.83 (6H, m, $(MeO)_2C_6H_3CH_2CH_2N(H)CH_2$]. A portion of this material (2.00g, 7.06mmol) was heated at reflux with HCOOH (98-100%, 10ml) and formaldehyde (37% aqueous solution, 10ml) for 7.5hours. The acid was evaporated and the resultant orange oil basified with excess NaOH (2M). Extraction (CH_2Cl_2, 3x30ml) and evaporation afforded the *title compound* as a brown oil (1.78g, 85%). This material was further purified by flash chromatography (SiO_2, Et_2O) to leave a colourless solid, m.p. 70-2°C (lit.[142] 82-4°C); δ_H 7.37-7.18 (5H, m, Ph), 6.68 and 6.24 (2H, s, 6**H** and 9**H**), 4.28 (1H, d, J 8.4Hz, PhC**H**), 3.86 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.06-2.78 [6H, m, $(MeO)_2C_6H_3CH_2CH_2N(Me)CH_2$], 2.39 (3H, s, NCH_3); *m/z* 297 (M^+) ^{1}H n.m.r. spectroscopy of the product in the presence of (-)-(R)-2,2,2-trifluoro-(9-anthryl)ethanol (**174**) (approximately 1 molar equivalent) gave baseline separation of both methoxyl singlets and the C1 benzylic proton doublet.

N-(3,4-Dimethoxyphenethyl)halostachine (269). A solution of halostachine (**172**) (0.101g, 0.67mmol) in CH_2Cl_2 (10ml) was treated with homoveratraldehyde (0.12g, 0.67mmol) and a catalytic quantity of *p*TsOH and the solution stirred in the presence of molecular sieves (20°C, 19h). The reaction mixture was filtered, basified ($NaHCO_3$) and the product extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to leave a colourless oil. This material was dissolved in MeOH (25ml), treated with $NaBH_4$ (0.20g, 5.29mmol) and the solution stirred (20°C, 18.5h). HCl (5M, 10ml) was added, stirring continued (20°C, 1h) and the solution basified with excess NaOH (2M). After evaporation of the solvent, the product was extracted (CH_2Cl_2), the combined extracts dried ($MgSO_4$) and evaporated to afford the *title compound* as a colourless oil (0.208g, 99%); δ_H 7.39-6.73 [8H, m, Ph and $(MeO)_2C_6H_3$], 4.69 [1H, t, J 7.0Hz, ArC**H**(OH)], 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.87-2.54 [6H, m, $(MeO)_2C_6H_3CH_2CH_2N(Me)CH_2$], 2.44 (3H, s, NCH_3). ^{1}H n.m.r. spectroscopy of the product in the presence of (-)-(R)-2,2,2-trifluoro-(9-anthryl)ethanol (**174**) gave partial separation of the C1 benzylic proton of (R,S)-**269**.

(+)-(S)-N-(3,4-Dimethoxyphenethyl)halostachine (269). A solution of (+)-(S)-halostachine (**172**) (0.45g, 2.98mmol) in CH_2Cl_2 (15ml) was treated with homoveratraldehyde (0.536g, 2.97mmol) and a catalytic quantity of *p*TsOH and the solution stirred in the presence of molecular sieves (20°C, 18h). The reaction mixture was filtered, basified ($NaHCO_3$) and the product extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to leave (2R,5S)- and (2S,5S)-2-(3,4-dimethoxybenzyl)-N-methyl-5-phenyloxazolidine as a mixture of diastereoisomers (1:1) (0.845g, 91%); *m/z* 314 (M^++1). This material was dissolved in MeOH (30ml), treated with $NaBH_4$ (0.50g, 13.2mmol) and the solution stirred (20°C, 21h). HCl (5M, 10ml) was added, stirring continued (20°C, 1h) and the solution basified with excess NaOH (2M). After evaporation of the solvent, the product was extracted (CH_2Cl_2), the combined extracts dried ($MgSO_4$) and evaporated to afford the *title compound* as a colourless oil (0.786g, 92%). A portion of this material was further purified by flash chromatography (SiO_2, Et_2O) and crystallised from Et_2O/hexane to give a pure sample for characterisation, $[\alpha]_D^{20}$ +67.11 (*c* 0.89 $CHCl_3$); m.p. 68-9°C; $\nu_{max.}$ 3415br (OH), 3010 (aryl-H), 1517 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.39-6.73 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.69 [1H, t, J 7.0Hz, PhC**H**(OH)], 3.90 (3H, s, $OC\mathbf{H}_3$), 3.87 (3H, s, $OC\mathbf{H}_3$), 2.87-2.54 [6H, m, $(MeO)_2C_6H_3C\mathbf{H}_2C\mathbf{H}_2N(Me)C\mathbf{H}_2$], 2.44 (3H, s, NCH_3); δ_C 149.09, 147.59, 142.40, 132.70, 128.45 (2C), 127.58, 125.94 (2C), 120.66, 112.03, 111.35, 69.27, 65.77, 59.57, 55.82 (2C), 41.72, 33.35; *m/z* 316 (M^++1) (Found: C, 72.4; H, 8.1; N, 4.1. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 8.0; N, 4.4%). ^{1}H n.m.r. spectroscopy of the product in the presence of (-)-(R)-2,2,2-trifluoro-(9-anthryl)ethanol (**174**) indicated that the product was enantiomerically pure with the C1 benzylic proton resonance appearing at lower field than that for (-)-(R)-**269**.

Cyclisation of (+)-(S)-N-(3,4-Dimethoxyphenethyl)halostachine (269). A solution of (+)-(S)-N-(3,4-dimethoxyphenethyl)halostachine (**269**) (0.088g, 0.28mmol) in CH_2Cl_2 (10ml) was cyclised according to standard procedure **E** (<-20°C, 69h). After basic workup, the crude reaction mixture was analysed by ^{1}H n.m.r. spectroscopy in the presence of the shift reagent (-)-(R)-2,2,2-trifluoro-(9-anthryl)ethanol (**174**) that indicated that the product [1-phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**268**)] possessed an enantiomeric excess of 6% with no unreacted starting material.

(R)-[N-(3,4-Dimethoxyphenethyl)halostachine]Cr(CO)$_3$ (270). A solution of (+)-(R)-(halostachine)$Cr(CO)_3$ (**186**) (1.08g, 3.48mmol) in CH_2Cl_2 (15ml) was treated with homoveratraldehyde (0.637g, 3.53mmol) and a catalytic quantity of *p*TsOH and the solution stirred in the presence of molecular sieves (20°C, 23h). The reaction mixture was filtered, basified ($NaHCO_3$) and the organic phase separated. The aqueous phase was extracted (CH_2Cl_2), the combined organic phases filtered through a short plug of alumina (grade V, CH_2Cl_2) and evaporated to leave a yellow oil (1.345g, 86%). This material (1.34g, 2.98mmol) was dissolved in MeOH (30ml), treated with $NaBH_4$ (0.50g, 13.2mmol) and the yellow solution stirred (20°C, 23h). The solution was acidified with HCl (5M, 10ml) and stirring continued (20°C, 1h). After basification with excess NaOH (2M) the solvent was evaporated and the aqueous phase extracted (CH_2Cl_2). The combined extracts were evaporated affording the crude product as a yellow oil. Column chromatography (Al_2O_3 grade V, gradient elute petroleum ether/Et_2O) gave a single fraction as a streaking yellow band that was evaporated to leave the *title compound* as a yellow oil (0.834g, 62%), δ_H 6.83-6.72 [3H, m, $(MeO)_2C_6\mathbf{H}_3$], 5.57-5.30 [5H,

m, $PhCr(CO)_3$], 4.30 [1H, dd, J 4.0 and 9.7Hz, $(CO)_3CrPhCH(OH)$], 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 2.83-2.48 [6H, m, $(MeO)_2C_6H_3CH_2CH_2N(Me)CH_2$], 2.40 (3H, s, NCH_3); *m/z* 452 (M^++1).

(-)-(R)-(1-Phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine)Cr(CO)$_3$ (271). A solution of (R)-[N-3,4-dimethoxyphenethyl(halostachine)]$Cr(CO)_3$ (**270**) (0.318g, 0.70mmol) in CH_2Cl_2 (15ml) was cyclised according to standard procedure **E** (<-20°C, 40h) to furnish the *title compound* as a yellow oil that solidified upon standing (0.232g, 76%). A portion of this material was recrystallised from CH_2Cl_2/hexane to give a pure sample for characterisation, $[\alpha]_D^{20}$ -148.67 (*c* 0.40 $CHCl_3$); m.p. 151-2°C (decomp.); $\nu_{max.}$ 1970 and 1895 (C≡O), 1518 (Ar) cm^{-1}; δ_H 6.72 and 6.64 (2H, s, 6**H** and 9**H**), 5.80-4.88 [5H, m, $PhCr(CO)_3$], 4.00 [1H, d, J 4.5Hz, $(CO)_3CrPhCH$], 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.25-2.66 [6H, m, $(MeO)_2C_6H_2CH_2CH_2N(Me)CH_2$], 2.37 (3H, s, NCH_3); *m/z* 434 (M^++1) (Found: C, 61.2; H, 5.3; N, 2.95. $C_{22}H_{23}CrNO_5$ requires C, 61.0; H, 5.35; N, 3.2%).

(+)-(R)-1-Phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (268).[138] A solution of (-)-(R)-(1-phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine)$Cr(CO)_3$ (**271**) (0.10g, 0.23mmol) was decomplexed according to the standard procedure to afford the *title compound* as a white powder (0.068g, 99%). ^1H n.m.r. spectroscopy of the product in the presence of (-)-(R)-2,2,2-trifluoro-(9-anthryl)ethanol (**174**) indicated that it was enantiomerically pure with the N-methyl resonance appearing at lower field than that of (-)-(S)-**268**. A portion of this material was recrystallised from Et_2O/hexane to give a pure sample for characterisation, $[\alpha]_D^{20}$ +45.35 (*c* 0.27 $CHCl_3$), $[\alpha]_D^{18}$ +31.24 (*c* 0.99 MeOH) [lit.[138] $[\alpha]_D^{25}$ +31.8 (*c* 1.00 MeOH)]; m.p. 103-4°C; $\nu_{max.}$ 1515 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-7.18 (5H, m, Ph), 6.68 and 6.24 (2H, s, 6**H** and 9**H**), 4.28 (1H, d, J 8.4Hz, Ph**CH**), 3.86 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.06-2.78 [6H, m, $(MeO)_2C_6H_2CH_2CH_2N(Me)CH_2$], 2.39 (3H, s, NCH_3); δ_C 146.94, 146.83, 143.48, 136.53, 133.65, 128.67 (2C), 128.45 (2C), 126.48, 113.41, 112.87, 62.94, 57.33, 55.90, 55.66, 49.58, 47.76, 35.90; *m/z* 298 (M^++1) (Found: C, 77.0; H, 8.0; N, 4.5. $C_{19}H_{23}NO_2$ requires C, 76.7; H, 7.8; N, 4.7%).

(-)-(1R,2R)-N-(3,4-Dimethoxyphenethyl)pseudoephedrine (285). A solution of (-)-(1R,2R)-pseudoephedrine (**123**) (0.50g, 3.03mmol) and 3,4-dimethoxyphenethyl bromide (0.742g, 3.03mmol) in EtOH (30ml) was treated with $NaHCO_3$ (0.34g, 4.05mmol) and a catalytic quantity of NaI and the mixture heated at reflux (60h). The solvent was evaporated, water (30ml) added and the aqueous phase extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to leave a gum that was subjected to flash chromatography (SiO_2, CH_2Cl_2). Evaporation of the less polar fraction gave a colourless oil identified as 3,4-dimethoxystyrene by comparison with an authentic sample. Et_2O elution gave a second fraction that was evaporated to leave the *title compound* as a white solid (0.29g, 29%), $[\alpha]_D^{20}$ -52.81 (*c* 0.60 $CHCl_3$); m.p. 61-3°C; $\nu_{max.}$ 3340br (OH), 3005 (aryl-H), 1515 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.36-6.77 [8H, m, Ph and $(MeO)_2C_6H_3$], 4.95 (1H, br s, **OH**), 4.21 [1H, d, J 9.7Hz, Ar**CH**(OH)], 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.84-2.35 (4H, m, $(MeO)_2C_6H_3CH_2CH_2$], 2.64 (1H, dq, J 6.3 and 9.2Hz, **CH**Me), 2.35 (3H, s, NCH_3), 0.76 (3H, d, J 6.7Hz, $CHCH_3$); δ_C 149.14, 147.68, 142.21, 132.71, 128.34 (2C), 127.80, 127.47 (2C), 120.73, 112.14, 111.43, 74.69, 65.70, 55.84 (2C), 55.47, 35.99, 34.44, 7.25; *m/z* 330 (M^++1) (Found: C, 73.2; H, 8.5; N, 4.0. $C_{20}H_{27}NO_3$ requires C, 72.9; H, 8.3; N, 4.25%).

Alternative synthesis: A solution of (-)-(1R,2R)-pseudoephedrine (**123**) (1.83g, 11.1mmol) and homoveratraldehyde (2.00g, 11.1mmol) in benzene (60ml) was treated with a catalytic quantity of *p*TsOH and the solution heated at reflux in a Dean-Stark water separator (21h). The solvent was evaporated, basified ($NaHCO_3$) and the product extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to afford (2R,4R,5R)- and (2S,4R,5R)-2-(3,4-dimethoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**286**) as a colourless oil (3.60g, quantitative) (ratio 94:6), $[\alpha]_D^{20}$ -5.62 (*c* 1.48 $CHCl_3$); $\nu_{max.}$ 3010 (aryl-H), 1517 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-6.80 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.47 [1H, d, J 8.8Hz, PhC**H**(OH)], 4.37 [1H, dd, J 3.4 and 6.0Hz, $(MeO)_2C_6H_3CH_2C\mathbf{H}$], 3.88 (6H, s, $2OC\mathbf{H}_3$), 2.98, 2.92 [2H, ABX system, J_{AB} 14.2Hz, J_{AX} 3.4Hz, J_{BX} 6.0Hz, $(MeO)_2C_6H_3C\mathbf{H}_2$], 2.37 (1H, dq, J 6.0 and 8.8Hz, **C**HMe), 2.31 (3H, s, $NC\mathbf{H}_3$), 1.13 (3H, d, J 6.1Hz, $CHC\mathbf{H}_3$); δ_C 148.73, 147.66, 140.59, 130.44, 128.48 (2C), 127.98, 126.70 (2C), 121.82, 113.09, 111.01, 98.92, 85.39, 68.95, 55.76 (2C), 40.45, 36.37, 14.20; *m/z* 328 (M^++1) (Found: C, 73.4; H, 7.8; N, 4.15. $C_{20}H_{25}NO_3$ requires C, 73.4; H, 7.7; N, 4.3%). A portion of this material (2.78g, 8.49mmol) was dissolved in MeOH (50ml), treated with $NaBH_4$ (0.80g, 21.1mmol) and the solution stirred (20°C, 23h). HCl (5M, 10ml) was added, stirring continued (20°C, 1h) and the solution basified with excess NaOH (2M). After evaporation of the solvent, the product was extracted (CH_2Cl_2), the combined extracts dried ($MgSO_4$) and evaporated to leave a colourless oil that solidified on standing. Recrystallisation from Et_2O/hexane furnished the *title compound* as white blocks (1.71g, 61%).

(-)-(1R,2S)-N-(3,4-Dimethoxyphenethyl)ephedrine (287). A solution of (-)-(1R,2S)-ephedrine (**122**) (1.50g, 9.08mmol) and 3,4-dimethoxyphenethyl bromide (2.23g, 9.10mmol) in MeCN (80ml) was heated at reflux (48h). The solvent was evaporated, water (100ml) added and the aqueous phase extracted (CH_2Cl_2, 3x50ml). The combined extracts were dried ($MgSO_4$) and evaporated to leave a pale yellow solid. Flash chromatography (SiO_2, Et_2O) gave two fractions, the first of which was evaporated to afford 3,4-dimethoxystyrene (0.81g, 54%) as a colourless oil identified by comparison with an authentic sample. Evaporation of the second fraction gave the *title compound* as a white solid (1.02g, 34%). Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ -8.72 (*c* 0.71 $CHCl_3$); m.p. 94-5°C; $\nu_{max.}$ 3400br (OH), 3003 (aryl-H), 1515 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.36-6.68 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 4.79 [1H, d, J 4.3Hz, ArC**H**(OH)], 3.88 (3H, s, $OC\mathbf{H}_3$), 3.87 (3H, s, $OC\mathbf{H}_3$), 2.75-2.67 [4H, m, $(MeO)_2C_6H_3C\mathbf{H}_2C\mathbf{H}_2$], 2.89 (1H, dq, J 4.4 and 6.9Hz, C**H**Me), 2.36 (3H, s, $NC\mathbf{H}_3$), 0.90 (3H, d, J 6.9Hz, $CHC\mathbf{H}_3$); δ_C 149.02, 147.53, 142.43, 132.96, 128.04 (2C), 126.97, 126.24 (2C), 120.66, 112.07, 111.34, 72.98, 63.54, 56.72, 55.82 (2C), 39.14, 33.63, 9.95; *m/z* 330 (M^++1) (Found: C, 72.9; H, 8.4; N, 4.1. $C_{20}H_{27}NO_3$ requires C, 72.9; H, 8.3; N, 4.25%).

Alternative synthesis: A solution of (-)-(1R,2S)-ephedrine (**122**) (1.83g, 11.1mmol) and homoveratraldehyde (2.00g, 11.1mmol) in benzene (60ml) was treated with a catalytic quantity of *p*TsOH and the solution and the solution heated at reflux in a Dean-Stark water separator (21h). The solvent was evaporated, basified ($NaHCO_3$) and the product extracted (CH_2Cl_2). The combined extracts were dried ($MgSO_4$) and evaporated to afford (2S,4S,5R)- and (2R,4S,5R)-2-(3,4-dimethoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine (**288**) as a colourless oil (3.60g, quantitative) (ratio 93:7), $[\alpha]_D^{20}$ -94.08 (*c* 0.75 $CHCl_3$); $\nu_{max.}$ 3008 (aryl-H), 1516 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-6.80 [8H, m, Ph and $(MeO)_2C_6\mathbf{H}_3$], 5.00 (1H, d, J 7.9Hz, PhC**H**), 4.04 [1H, dd, J 3.2 and 6.8Hz, $(MeO)_2C_6H_3CH_2C\mathbf{H}$], 3.87 (3H, s, $OC\mathbf{H}_3$), 3.85 (3H, s, $OC\mathbf{H}_3$),

3.08, 3.02 [2H, ABX system, J_{AB} 14.1Hz, J_{AX} 3.2Hz, J_{BX} 6.8Hz, $(MeO)_2C_6H_3CH_2$], 2.81 (1H, dq, J 6.5 and 7.7Hz, CHMe), 2.33 (3H, s, NCH_3), 0.69 (3H, d, J 6.5Hz, $CHCH_3$); δ_C 148.84, 147.81, 140.19, 130.23, 127.95 (2C), 127.83 (2C), 127.59, 121.87, 113.13, 111.16, 98.43, 81.93, 64.10, 55.77 (2C), 39.75, 36.58, 14.68; *m/z* 328 (M^++1) (Found: C, 73.1; H, 8.0; N, 4.0. $C_{20}H_{25}NO_3$ requires C, 73.4; H, 7.7; N, 4.3%). A portion of this material (1.80g, 5.50mmol)was dissolved in MeOH (50ml), treated with $NaBH_4$ (0.80g, 21.1mmol) and the solution stirred (20°C, 23h). HCl (5M, 10ml) was added, stirring continued (20°C, 1h) and the solution basified with excess NaOH (2M). After evaporation of the solvent, the product was extracted (CH_2Cl_2), the combined extracts dried ($MgSO_4$) and evaporated to leave a colourless oil that solidified on standing. Recrystallisation from Et_2O/hexane furnished the *title compound* as white blocks (1.02g, 56%).

Cyclisation of (-)-(1R,2R)-N-(3,4-dimethoxyphenethyl)pseudoephedrine (285). A solution of (-)-(1R,2R)-N-(3,4-dimethoxyphenethyl)pseudoephedrine (**285**) (0.22g, 0.67mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **D** (40°C, 2h) to leave a pale yellow gum (0.12g, 58%). ^1H n.m.r. spectroscopy of the crude product revealed two components in the ratio 91:9. Crystallisation from CH_2Cl_2/hexane gave large blocks of (+)-(1S,2R)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**), $[\alpha]_D^{20}$ +2.89 (*c* 0.38 $CHCl_3$); m.p. 116-8°C; $\nu_{max.}$ 3010 (aryl-H), 1518 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.31-7.16 (5H, m, Ph), 6.66 and 6.60 (2H, s, 6**H** and 9**H**), 3.94 (1H, d, J 5.4Hz, PhC**H**), 3.89 (3H, s, O**CH**$_3$), 3.82 (3H, s, O**CH**$_3$), 3.75 (1H, qu, 6.1Hz, C**H**Me), 2.86-2.42 [4H, m, $(MeO)_2C_6H_2CH_2CH_2$], 2.38 (3H, s, NCH_3); 0.93 (3H, d, J 6.6Hz, $CHCH_3$); δ_C 147.31, 147.02, 142.54, 133.32, 132.23, 128.27 (2C), 128.15 (2C), 125.94, 115.38, 113.57, 58.32, 57.39, 55.80 (2C), 48.61, 45.24, 35.45, 9.88; *m/z* 311 (M^+) (Found: C, 77.0; H, 8.0; N, 4.4. $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%).

Cyclisation of (-)-(1R,2S)-N-(3,4-dimethoxyphenethyl)ephedrine (287). A solution of (-)-(1R,2S)-N-(3,4-dimethoxyphenethyl)ephedrine (**287**) (0.409g, 1.24mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **D** (40°C, 1.5h) to furnish (-)-(1R,2S)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**) as a white solid (0.33g, 85%). Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, $[\alpha]_D^{20}$ -2.39 (*c* 0.84 $CHCl_3$); m.p. 115-7°C; *m/z* 311 (M^+) (Found: C, 76.9; H, 8.5; N, 4.3. $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%).

(+)-(N-(3,4-Dimethoxyphenethyl)pseudoephedrine]Cr(CO)$_3$ (291). A freshly prepared solution of (pseudoephedrine)$Cr(CO)_3$ (**205**) [prepared from (+)-(2-cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)$Cr(CO)_3$ (**147**) (0.381g, 1.00mmol)] in CH_2Cl_2 was treated with homoveratraldehyde (0.191g, 1.06mmol), molecular sieves and a catalytic quantity of *p*TsOH. The mixture was left to stand (20°C, 22h), filtered and basified ($NaHCO_3$). The organic phase was filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2) and evaporated to leave a yellow oil. This material was dissolved in MeOH (20ml) and treated with $NaBH_3CN$ (0.194g, 3.09mmol) followed by addition of HCl (5M, 5ml). The yellow solution was stirred (20°C, 6h), basified (NaOH, 2M) and the solvent evaporated. The aqueous phase was extracted (CH_2Cl_2), the combined organic phases filtered through a short plug of Al_2O_3 (gradeV, CH_2Cl_2) and evaporated to leave a yellow oil. Column chromatography (Al_2O_3 grade V, gradient elute hexane/Et_2O) gave a single fraction of the *title compound* as a yellow solid (0.11g, 24%). A portion of this material was recrystallised from

Et_2O/CH_2Cl_2/hexane to give a pure sample for characterisation, $[\alpha]_D^{18}$ +50.42 (*c* 0.08 $CHCl_3$); m.p. 115°C; $\nu_{max.}$ 1973 and 1900 (C≡O) cm^{-1}; δ_H 6.84-6.73 [3H, m, $(MeO)_2C_6\mathbf{H}_3$], 5.59-5.24 [5H, m, $PhCr(CO)_3$], 4.94 (1H, br s, **OH**), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.82 [1H, d, J 9.6Hz, $(CO)_3CrPhCH(OH)$], 2.79-2.58 [4H, m, $(MeO)_2C_6H_3CH_2CH_2$], 2.50 (1H, m, **CH**Me), 2.31 (3H, s, NCH_3), 0.96 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 466 (M^++1) (Found: C, 59.1; H, 6.0; N, 2.7. $C_{23}H_{27}CrNO_6$ requires C, 59.35; H, 5.85; N, 3.0%).

[N-(3,4-Dimethoxyphenethyl)ephedrine]Cr(CO)$_3$ (292). A solution of (-)-(ephedrine)$Cr(CO)_3$ (**206**) (0.545g, 1.81mmol) in CH_2Cl_2 (15ml) was treated with homoveratraldehyde (0.326g, 1.81mmol), molecular sieves and a catalytic quantity of *p*TsOH. The mixture was left to stand (20°C, 13h), filtered and basified ($NaHCO_3$). The organic phase was filtered through a short plug of Al_2O_3 (grade V, CH_2Cl_2) and evaporated to afford (2S,4S,5R)-[2-(3,4-dimethoxybenzyl)-N-methyl-4-methyl-5-phenyloxazolidine]$Cr(CO)_3$ as a yellow solid (0.685g, 82%), δ_H 6.95-6.81 [3H, m, $(MeO)_2C_6\mathbf{H}_3$], 5.29-5.11 [5H, m, $PhCr(CO)_3$], 4.54 [1H, d, J 7.8Hz, $(CO)_3CrPhC\mathbf{H}$], 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.00, 2.91 [2H, ABX system, J_{AB} 14.2Hz, J_{AX} 2.4Hz, J_{BX} 6.6Hz, $(MeO)_2C_6H_3CH_2$], 2.70 (1H, q, 7.0Hz, **CH**Me), 2.29 (3H, s, NCH_3), 0.84 (3H, d, J 6.4Hz, $CHCH_3$); *m/z* 464 (M^++1). A portion of this material (0.68g, 1.47mmol) was dissolved in a mixture of MeOH (40ml) and THF (5ml) and treated with $NaBH_3CN$ (0.50g, 7.96mmol) followed by addition of HCl (5M, 5ml). The yellow solution was stirred (20°C, 20h), basified (NaOH, 2M) and the solvent evaporated. The aqueous phase was extracted (CH_2Cl_2), the combined organic phases filtered through a short plug of Al_2O_3 (gradeV, CH_2Cl_2) and evaporated to leave a yellow oil. Column chromatography (Al_2O_3 grade V, gradient elute hexane/Et_2O) gave a single fraction of the *title compound* as a yellow oil (0.622g, 91%), δ_H 6.84-6.66 [3H, m, $(MeO)_2C_6\mathbf{H}_3$], 5.55-5.07 [5H, m, $PhCr(CO)_3$], 4.30 [1H, d, J 5.4Hz, $(CO)_3CrPhC\mathbf{H}(OH)$], 3.87 (6H, s, $2OC\mathbf{H}_3$), 3.05 (1H, br s, **OH**), 2.74 (1H, dq, 5.9 and 6.7Hz, **CH**Me), 2.70-2.67 [4H, m, $(MeO)_2C_6H_3CH_2CH_2$], 2.31 (3H, s, NCH_3), 1.02 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 466 (M^++1).

Cyclisation of (+)-[N-(3,4-dimethoxyphenethyl)pseudoephedrine]Cr(CO)$_3$ (291). A solution of (+)-[N-(3,4-dimethoxyphenethyl)pseudoephedrine]$Cr(CO)_3$ (**291**) (0.072g, 0.15mmol) in CH_2Cl_2 (10ml) was cyclised according to the standard procedure **E** (<-20°C, 23h). The reaction mixture was basified ($NaHCO_3$), the organic phase separated and filtered through Al_2O_3 (grade V, CH_2Cl_2). Evaporation gave *trans*-(1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine)$Cr(CO)_3$ (**293**) as a yellow oil (0.044g, 64%), δ_H 6.75 and 6.61 (2H, s, 6**H** and 9**H**), 5.98-4.87 [5H, m, $PhCr(CO)_3$], 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.79 [1H, d, J 4.8Hz, $(CO)_3CrPhC\mathbf{H}$], 3.53 (1H, dq J 4.8 and 6.5Hz, **CH**Me), 2.97-2.43 [4H, m, $(MeO)_2C_6H_3CH_2CH_2$], 2.39 (3H, s, NCH_3), 0.87 (1H, d, J 6.6Hz, $CHCH_3$); *m/z* 448 (M^++1). A portion of this material was decomplexed according to the standard procedure to liberate (+)-(1S,2R)-1-phenyl-2-methyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (**289**) as a white powder (0.028g, 95%). Recrystallisation from Et_2O/hexane gave white blocks identical to the previously synthesised sample, $[\alpha]_D^{21}$ +5.43 (*c* 1.49 $CHCl_3$); m.p. 115°C (this melting point was not depressed when mixed with the previously synthesised sample).

REFERENCES

References

1. G.Coquerel, R.Bouaziz and M.Brienne, *Chem. Lett.*, 1988, 1081.

2. J.Nakano, M.Mimura, M.Hayashida, M.Fujii, K.Kimura and T.Nakanishi, *Chem. Pharm. Bull.*, 1988, **36**, 1399.

3. R.T.Williams, *Arch. Environ. Health*, 1968, **16**, 493.

4. i) For an overview of the Sharpless epoxidation see 'Asymmetric Synthesis', ed. J.D.Morrison, Academic Press, New York, 1983, vol. **5**, chapters 7 and 8. ii) V.S.Martin, S.S.Woodard, T.Katsuki, Y.Yamada, M.Ikeda and K.B.Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.

5. K.Laumen, D.Breitgoff and M.P.Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 1459; D.Bianchi, P.Cesti and E.Battistel, *J. Org. Chem.*, 1988, **53**, 5531. For the use of enzymes as chiral catalysts see reference **4** i), chapter 9.

6. For reviews of this approach see 'Asymmetric Synthesis', ed. J.D.Morrison and J.W.Scott, Academic Press, New York, 1983, vol. **4**; S.Hanessian, "Total Synthesis of Natural Products : the 'Chiron Approach", Pergamon Press, 1983.

7. For reviews in this area see reference **4** i), chapters 2 and 3. For a recent example see H.Takeda, T.Tachinami and M.Aburatani, *Tetrahedron Lett.*, 1989, **30**, 363 and 367.

8. B.B.Lohray, T.H.Kalantar, B.M.Kim, C.Y.Park, T.Shibata, J.S.M.Wai and K.B.Sharpless, *Tetrahedron Lett.*, 1989, **30**, 2041.

9. C.Fehr and J.Galindo, *J. Am. Chem. Soc.*, 1988, **110**, 6909.

10. M.Yoshioka, T.Kawakita and M.Ohno, *Tetrahedron Lett.*, 1989, **30**, 1657. For an alternative approach see K.Soai, M.Nishi and Y.Ito, *Chem. Lett.*, 1987, 2405.

11. T.Fujisawa, M.Funabora, Y.Ukaji and T.Sato, *Chem. Lett.*, 1988, 59.

12. G.M.Coppola and H.F.Schuster, 'Asymmetric Synthesis', Wiley-interscience, 1987; M.Nogradi, 'Stereoselective Syntheses', Weinheim, New York, VCH, 1986.

13. D.A.Evans, J.M.Takacs, L.R.McGee, M.D.Ennis, D.J.Mathre and J.Bartroli, *Pure Appl. Chem.*, 1981, **53**, 1109; D.A.Evans, *Aldrichemica Acta*, 1982, **15**, 23.

14. R.M.Williams, P.J.Sinclair, D.Zhai and D.Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547. For a related example see J.F.Dellaria and B.D.Santarsiero, *Tetrahedron Lett.*, 1988, **29**, 6079.

15. D.Enders and V.Bhushan, *Tetrahedron Lett.*, 1988, **29**, 2437. For a recent review of 'RAMP' and 'SAMP' hydrazones see 'Asymmetric Synthesis', ed. J.D.Morrison, Academic Press, New York, 1984, vol. **3**, 275. For practical details see D.Enders, H.Kipphardt and P.Fey, *Org. Synth.*, 1987, **65**, 173 and 183. For a crystal structure of a lithium enolate see D.Enders and G.Bachstadter, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1522.

16. S.G.Davies, 'Organotransition Metal Chemistry : Applications to Organic Synthesis', Pergamon Press, Oxford, 1982.

17. Synthetic Applications of Chromium Tricarbonyl Stabilised Benzylic Carbanions, S.J.Coote, S.G.Davies and C.L.Goodfellow, 'Advances in Metal-Organic Chemistry', ed. L.S.Liebskind, in press.

18. For crystal structures of (benzene)$Cr(CO)_3$ see B.Rees and P.Coppens, *Acta Crystallogr., Sect. B*, 1973, **B29**, 2516; M.F.Bailey and L.F.Dahl, *Inorg. Chem.*, 1965, **4**, 1314.

19. J.Y.Saillard, D.Grandjean, P.LeMaux and G.Jaouen, *Nouv. J. Chim.*, 1981, **5**, 153; G.A.Sim, *Annu. Rev. Phys. Chem.*, 1967, **18**, 57.

20. J.Chatt and L.A.Duncanson, *J. Chem. Soc.*, 1953, 2939; M.J.S.Dewar, *Bull. Soc. Chim. Fr.*, 1951, C71.

21. For examples see M.Fukui, T.Ikeda and T.Oishi, *Chem. Pharm. Bull.*, 1983, **31**, 466; J.Brocard, A.Laconi and D.Couturier, *Org. Magn. Reson.*, 1984, **22**, 369; W.R.Jackson, W.B.Jennings, S.C.Rennison and R.Spratt, *J. Chem. Soc. (B)*, 1969, 1214.

22. O.L.Carter, A.T.McPhail and G.A.Sim, *J. Chem. Soc. (A)*, 1967, 1619.

23. O.L.Carter, A.T.McPhail and G.A.Sim, *J. Chem. Soc. (A)*, 1966, 822.

24. It has been suggested that the preferred conformation adopted by the $Cr(CO)_3$ unit influences the regioselectivity of metallation, nucleophilic and electrophilic attack of (arene)$Cr(CO)_3$ complexes, W.R.Jackson, I.D.Rae and M.G.Wong, *Aust. J. Chem.*, 1986, **39**, 303.

25. B.Nichols and M.C.Whiting, *J. Chem. Soc.*, 1959, 551.

26. C.A.L.Mahaffy and P.L.Pauson, *Inorg. Synth.*, 1979, **19**, 154.

27. D.Seyferth, J.S.Merola and C.S.Eschbach, *J. Am. Chem. Soc.*, 1978, **100**, 4124.

28. W.S.Trahanovsky and D.K.Wells, *J. Am. Chem. Soc.*, 1969, **91**, 5870.

29. M.Stobbe, O.Reiser, T.Thiemann, R.G.Daniels and A.de Meijere, *Tetrahedron Lett.*, 1986, **27**, 2353.

30. D.E.F.Gracey, W.R.Jackson, W.B.Jennings, and T.R.B.Mitchell, *J. Chem. Soc. (B)*, 1969, 1204.

31. E.P.Kundig, C.Perret, S.Spichiger and G.Bernardinelli, *J. Organomet. Chem.*, 1985, **286**, 183.

32. F.Goasmat, R.Dabard and H.Patin, *Tetrahedron Lett.*, 1975, **16**, 2359.

33. A.J.Birch, P.E.Cross and H.Fitton, *J. Chem. Soc., Chem. Commun.*, 1965, 366; R.B.King, *J. Organomet. Chem.*, 1967, **8**, 139.

34. For example see K.H.Dotz, I.Pruskil and J.Muhlemeier, *Chem. Ber.*, 1982, **115**, 1278; K.H.Dotz, *Pure Appl. Chem.*, 1983, **55**, 1689.

35. J.Blagg, S.J.Coote, S.G.Davies, D.Middlemiss and A.Naylor, *J. Chem. Soc., Perkin Trans. 1*, 1987, 689.

36. S.G.Davies and C.L.Goodfellow, *J. Organometal. Chem.*, 1988, **340**, 195.

37. A.Mandelbaum, Z.Neuwirth and M.Cais, *Inorg. Chem.*, 1963, **2**, 902.

38. A.Solladie-Cavallo, G.Solladie and E.Tsamo, *J. Org. Chem.*, 1979, **44**, 4189.

39. S.G.Davies and C.L.Goodfellow, *J. Chem. Soc., Perkin Trans. 1*, 1989, 192.

40. M.F.Semmelhack, H.T.Hall, M.Yoshifuji and G.Clark, *J. Am. Chem. Soc.*, 1975, **97**, 1247.

41. S.G.Davies, unpublished results.

42. K.M.Doxsee, R.H.Grubbs, and F.C.Anson, *J. Am. Chem. Soc.*, 1984, **106**, 7819; F.Rourke and J.A.Crayston, *J. Chem. Soc., Chem. Commun.*, 1988, 1264.

43. For example see G.Jaouen and A.Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4667.

44. G.Carganico, P.Del Buttero, S.Maiorana and G.Riccardi, *J. Chem. Soc., Chem. Commun.*, 1978, 989 and references therein.

45. E.P.Kundig, V.Desobry, C.Grivet, B.Rudolph and S.Spichiger, *Organometallics*, 1987, 6, 1173.

46. M.F.Semmelhack, *J. Organometal. Chem. Libr.*, 1976, **1**, 361.

47. P.J.Dickens, A.M.Z.Slawin, D.A.Widdowson and D.J.Williams, *Tetrahedron Lett.*, 1988, **29**, 103. Also see M.Ghavshou and D.A.Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 3065; P.J.Beswick and D.A.Widdowson, *Synthesis*, 1985, 492.

48. D.A.Widdowson, *Philos. Trans. R. Soc. London A*, 1988, **326,** 595.

49. J.P.Gilday and D.A.Widdowson, *Tetrahedron Lett.*, 1986, **27**, 5525. Also see *idem, J. Chem. Soc., Chem. Commun.*, 1986, 1235.

50. In some cases the aryl anion generated is of relatively low nucleophilicity in comparison to its basicity. Transmetallation has been utilised to avoid this problem, see P.J.Beswick, S.J.Leach, N.F.Masters and D.A.Widdowson, *J. Chem. Soc., Chem. Commun.*, 1984, 46.

51. For examples of aryl lithiation see H.W.Gschwend and H.Rodriguez, *Org. React.*, **26**, 1; H.P.Plaumann, B.A.Keay and R.Rodrigo, *Tetrahedron Lett.*, 1979, **20**, 4921; A.I.Meyers and E.D.Mihelich, *J. Org. Chem.*, 1975, **40**, 3158; F.E.Ziegler and K.W.Fowler, *ibid*, 1976, **41**, 1564; P.Beak and R.A.Brown, *ibid*, 1977, **42**, 1823.

52. J.Blagg, S.G.Davies, C.L.Goodfellow and K.H.Sutton *J. Chem. Soc., Perkin Trans. 1*, 1987, 1805.

53. A.Ceccon, A.Gambaro and A.Venzo, *J. Organometal. Chem.*, 1984, **275**, 209. Also see M.Acampora, A.Ceccon, M.Dal Farra, G.Giacometti and G.Rigatti, *J. Chem. Soc., Perkin Trans. 2*, 1977, 483.

54. S.J.Coote and S.G.Davies, unpublished results.

55. J.Brocard, L.Pelinski and J.Lebibi, *J. Organometal. Chem.*, 1986, **309**, 299; G.Jaouen, S.Top, A.Laconi, D.Couturier and J.Brocard, *J. Am. Chem. Soc.*, 1984, **106**, 2207.

56. The benzylic functionalisation of (arene)Cr(CO)3 complexes with complete suppression of the Wittig Rearrangement has been documented, J.Blagg, S.G.Davies, N.J.Holman, C.A.Laughton and B.E.Mobbs, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1581. However, for a recent conflicting report see J.Brocard, M.Mahmoudi, L.Pelinski and L.Maciejewski, *Tetrahedron Lett.*, 1989, **30**, 2549.

57. J.Blagg, S.J.Coote, S.G.Davies, and B.E.Mobbs, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2257.

58. S.J.Coote, S.G.Davies and K.H.Sutton, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1481.

59. G.R.Knox, D.G.Leppard, P.L.Pauson and W.E.Watts, *J. Organometal. Chem.*, 1972, **34**, 347; M.F.Semmelhack, W.Seufert and L.Keller, *J. Am. Chem. Soc.*, 1980, **102**, 6584.

60. M.Uemura, T.Minami and Y.Hayashi, *J. Chem. Soc., Chem. Commun.*, 1984, 1193.

61. M.Uemura, K.Isobe and Y.Hayashi, *Tetrahedron Lett.*, 1985, **26**, 767.

62. M.Uemura, T.Kobayashi, K.Isobe, T.Minami and Y.Hayashi, *J. Org. Chem.*, 1986, **51**, 2859.

63. A.Solladie-Cavallo and J.Suffert, *Tetrahedron Lett.*, 1984, **25**, 1897.

64. J.D.Holmes, D.A.K.Jones and R.Pettit, *J. Organometal. Chem.*, 1965, **4**, 324. Also see S.P.Gubin, S.Khandkarova and A.Z.Kreindlen, *ibid*, 1974, **64**, 229.

65. Asymmetric Synthesis *via* Chiral Transition Metal Auxiliaries, S.G.Davies, G.Bashiardes, R.P.Beckett, S.J.Coote, I.M.Dordor-Hedgecock, C.L.Goodfellow, G.L.Gravatt, J.P.McNally and M.Whittaker, *Philos. Trans. R. Soc. London A*, 1988, **326**, 619.

66. M.T.Reetz and M.Sauerwald, *Tetrahedron Lett.*, 1983, **24**, 2837.

67. S.G.Davies and J.M.J.Williams, unpublished results. For related reactions employing cyclic acetal complexes as substrates see S.G.Davies, R.F.Newton and J.M.J.Williams, *Tetrahedron Lett.*, 1989, **30**, 2867.

68. M.Barfield, R.J.Spear and S.Sternhell, *J. Am. Chem. Soc.*, 1975, **97**, 5160.

69. R.R.Fraser and R.N.Renaud, *Can. J. Chem.*, 1971, **49**, 755.

70. S.Ram, A.K.Saxena, P.C.Jain and G.K.Patnaik, *Indian J. Chem., Sect. B*, 1984, **23B**, 1261.

71. For example see H.C.Lacey and K.L.Erickson, *Tetrahedron*, 1973, **29**, 4025. R.L.Vaulx, F.N.Jones and C.R.Hauser, *J. Org. Chem.*, 1964, **29**, 505.

72. J.G.Smith and R.T.Wikman, *Tetrahedron*, 1974, **30**, 2603.

73. D.Tobia and B.Rickborn, *J. Org. Chem.*, 1986, **51**, 3849.

74. F.J.Petracek, N.Sugisaka, M.W.Klohs, R.G.Parker, J.Bordner and J.D.Roberts, *Tetrahedron Lett.*, 1970, **11**, 707.

75. J.E.Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

76. J.E.Baldwin, J.Cutting, W.Dupont, L.Kruse, L.Silberman and R.C.Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736.

77. J.G.Smith and R.B.McCall, *J. Org. Chem.*, 1980, **45**, 3982.

78. J.G.Smith and R.T.Wikman, *J. Chem. Soc., Chem. Commun.*, 1983, 1448.

79. J.T.Gerig, *Tetrahedron Lett.*, 1967, 4625; W.Metlesics, T.Anton and L.H.Sternback, *J. Org. Chem.*, 1967, **32**, 2185.

80. A.Reiche and M.Schultz, *Liebigs Ann. Chem.*, 1962, **653**, 32.

81. E.Berner, *Acta Chem. Scand., Ser. B*, 1982, **36B**, 729.

82. F.Nelken and H.Simonis, *Chem. Ber.*, 1908, **41**, 986.

83. T.Kametani in 'The Total Synthesis of Natural Products', ed. J.Apsimon, Wiley-Interscience, 1977, volume 3.

84. G.Cohen and M.Collins, *Science*, 1970, **167**, 1748; H.A.Bates, *J. Org. Chem.*, 1983, **48**, 1932; H.A. Bates and J.S.Garelick, *ibid*, 1984, **49**, 4552; H.A.Bates, K.Bagheri and P.M.Vertino, *ibid*, 1986, **51**, 3061.

85. W.C.Bowman and M.J.Rand, 'Textbook of Pharmacology', second edition, Blackwell Scientific Publications, Oxford, 1980, chapter 17, 17.33.

86. A.I.Meyers and L.M.Fuentes, *J. Am. Chem. Soc.*, 1983, **105**, 117; A.I.Meyers and D.A.Dickman, *ibid*, 1987, **109**, 1263; A.I.Meyers, L.M.Fuentes and Y.Kubota, *Tetrahedron*, 1984, **40**, 1361; A.I.Meyers, D.A.Dickman and M.Boes, *ibid*, 1987, **43**, 5095; A.I.Meyers, *Aldrichemica Acta*, 1985, **18**, 59.

87. R.E.Gawley, G.Hart, M.Goicoechea-Pappas and A.L.Smith, *J. Org. Chem.*, 1986, **51**, 3076; R.E.Gawley and G.A.Smith, *Tetrahedron Lett.*, 1988, **29**, 301.

88. M.Yamato, K.Hashigaki, S.Ishikawa and N.Qais, *Tetrahedron Lett.*, 1988, **29**, 6949.

89. T.R.Govindachari and P.C.Parthasarathy, *Heterocycles*, 1977, **7**, 661.

90. G.Bringmann, J.R.Jansen and H.Rink, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 913.

91. M.Sainsbury, S.F.Dyke, D.W.Brown and R.G.Kinsman, *Tetrahedron*, 1970, **26**, 5265.

92. For a related example see K.R.Stewart, S.G.Levine and J.Bordner, *J. Org. Chem.*, 1984, **49**, 4082.

93. For an example see G.L.Grunewald, Q.Ye, L.Kieffer and J.A.Monn, *J. Med. Chem.*, 1988, **31**, 169 and references therein.

94. As of March 1988 Salbutamol had become the twelfth best-selling prescription medicine in the world, 'Glaxo Holdings p.l.c. Annual Report and Accounts', 1988, 14. The (-)-(R) enantiomer of Salbutamol is observed to be 80 times more active than its opposite optical antipode, R.Hartley and D.Middlemiss, *J. Med. Chem.*, 1971, **14**, 895.

95. J.M.McIntosh and L.C.Matassa, *J. Org. Chem.*, 1988, **53**, 4452 and references therein.

96. K.Soai, S.Yokoyama, T.Hayasaka and K.Ebihara, *J. Org. Chem.*, 1988, **53**, 4148.

97. For accounts of the examples given in Scheme 4 see A.Bernardi, S.Cardani, T.Pilati, G.Poli, C.Scolastico and R.Villa, *J. Org. Chem.*, 1988, **53**, 1600; A.Alexakis, R.Sedrani,

P.Mangeney and J.F.Normant, *Tetrahedron Lett.*, 1988, **29**, 4411; H.Abdallah, R.Gree and R.Carrie, *ibid*, 1982, **23**, 503; L.Colombo, C.Gennari, C.Poli, C.Scolastico and S.De Munari, *ibid*, 1985, **26**, 5459.

98. D.A.Evans, M.D.Ennis and D.J.Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.

99. C.L.Goodfellow, Part II thesis, Oxford, 1986.

100. S.G.Davies, C.L.Goodfellow and K.H.Sutton, unpublished results.

101. S.G.Davies and I.Rodriguez, unpublished results; M.Brunavs, Part II thesis, Oxford, 1989.

102. R.Contreras, F.Santiesteban and M.A.Paz-Sandoval, *Tetrahedron*, 1984, **40**, 3829; L.Neelakantan, *J. Org. Chem.*, 1971, **36**, 2256.

103. S.A.Soliman, H.Abdine and S.El-Nenaey, *Aust. J. Chem.*, 1975, **28**, 49; J.B.Hyne, *J. Am. Chem. Soc.*, 1959, **81**, 6058.

104. Early reports in the literature assigned the wrong relative configuration to the newly generated chiral centre, see L.Neelakantan and J.A.Molin-Case, *J. Org. Chem.*, 1971, **36**, 2261. It has since been shown that the thermodynamic oxazolidine orientates all three alkyl substituents *cis* in (+)-**140**, see G.Just, P.Potvin and P.Uggowitzer, *ibid*, 1983, **48**, 2923; C.Agami and T.Rizk, *Tetrahedron*, 1985, **41**, 537.

105. G.L.Grunewald and Q.Ye, *J. Org. Chem.*, 1988, **53**, 4021 and references therein; L.Welsh, *ibid*, 1967, **32**, 119.

106. G.L.Grunewald and Q.Ye, *J. Med. Chem.*, 1988, **31**, 1984.

107. I thank Dr. J.Blagg for a generous gift of complex (-)-**162**. For its preparation and data for complex (-)-**164** see J.Blagg and S.G.Davies, *Tetrahedron*, 1987, **43**, 4463.

108. P.A.Dandridge, C.Kaiser, M.Brenner, D.Gaitanopoulos, L.D.Davis, R.L.Webb, J.J.Foley and H.M.Sarau, *J. Med. Chem.*, 1984, **27**, 28.

109. R.Kunstmann, H.Gerhards, H.Kruse, M.Leven, E.F.Paulus, U.Schacht, K.Schmitt and P.U.Witte, *J. Med. Chem.*, 1987, **30**, 798.

110. B.E.Maryanoff, D.F.McComsey, M.J.Costanzo, P.E.Setler, J.F.Gardocki, R.P.Shank and C.R.Schneider, *J. Med. Chem.*, 1984, **27**, 943.

111. R.C.Griffith, R.J.Gentile, R.C.Robichaud and J.Frankenheim, *J. Med. Chem.*, 1984, **27**, 995.

112. B.E.Maryanoff, D.F.McComsey, J.F.Gardocki, R.P.Shank, M.J.Costanzo, S.O.Nortey, C.R.Schneider and P.E.Setler, *J. Med. Chem.*, 1987, **30**, 1433.

113. J.N.Jacob, D.E.Nichols, J.D.Kohli and D.Glock, *J. Med. Chem.*, 1981, **24**, 1013.

114. E.Zara-Kaczian, G.G.Deak, A.Seregi and M.Doda, *J. Med. Chem.*, 1986, **29**, 1189.

115. R.M.Riggs, D.E.Nichols, M.M.Foreman, L.L.Truex, D.Glock and J.D.Kohli, *J. Med. Chem.*, 1987, **30**, 1454.

116. B.E.Maryanoff, D.F.McComsey, M.S.Mutter, K.L.Sorgi and C.A.Maryanoff, *Tetrahedron Lett.*, 1988, **29**, 5073.

117. T.J.Schwan, G.S.Lougheed and S.E.Burrows, *J. Heterocycl. Chem.*, 1974, **11**, 807; G.Bobowski, J.M.Gottlieb and B.West, *ibid*, 1980, **17**, 1563; G.Bobowski and J.M.Gottlieb, *ibid*, 1982, **19**, 21.

118. British National Formulary, Number 4 (1982), British Medical Association, London.

119. C.Fuganti, 'The Alkaloids', ed. R.H.F.Manske, Academic Press, 1975, vol. XV, p. 141.

120. W.L.Mendelson, C.B.Spainhour, S.S.Jones, B.L.Lam and K.L.Wert, *Tetrahedron Lett.*, 1980, **21**, 1393.

121. M.R.Euerby and R.D.Waigh, *J. Chem. Soc., Chem. Commun.*, 1984, 127.

122. S.Kobayashi, T.Tokumoto and Z.Taira, *J. Chem. Soc., Chem. Commun.*, 1984, 1043.

123. M.A.Shwartz and S.W.Scott, *J. Org. Chem.*, 1971, **36**, 1827; D.J.Hart, P.A.Cain and D.A.Evans, *J. Am. Chem. Soc.*, 1978, **100**, 1548.

124. L.N.Pridgen, L.B.Killmer and R.L.Webb, *J. Org. Chem.*, 1982, **47**, 1985.

125. W.H.Pirkle and C.W.Boeder, *J. Org. Chem.*, 1977, **42**, 3697.

126. S.Top and G.Jaouen, *J. Org. Chem.*, 1981, **46**, 78.

127. M.Uemura, T.Minami and Y.Hayashi, *J. Organomet. Chem.*, 1986, **299**, 119.

128. S.J.Coote and S.G.Davies, *J. Chem. Soc., Chem. Commun.*, 1988, 648; S.J.Coote and S.G.Davies, *J. Chem. Soc., Perkin Trans. 1*, in the press.

129. It has been reported that N-3,4-dimethoxybenzyl-N-methyl-1-phenyl-2-phenyl ethanolamine undergoes acid-mediated cyclisation to give *trans* N-methyl-3-phenyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, H.Hara, R.Shirai, O.Hoshino and B.Umezawa, *Heterocycles*, 1983, **20**, 1945.

130. D.H.Williams and I.Fleming, 'Spectroscopic methods in organic chemistry', third edition, McGraw-Hill, London, 1980, 100.

131. L.M.Jackman and V.R.Haddon, *J. Am. Chem. Soc.*, 1974, **96**, 5130; M.Gates, D.L.Frank and W.C. von Felten, *ibid*, 1974, **96**, 5138; T.Ando, J.Yamawaki, Y.Saito, Y.Takai and K.Yamataka, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2348; A.Pelter, R.S.Ward and R.R.Rao, *Tetrahedron*, 1985, **41**, 2933.

132. This type of reactivity is analogous to the role played by isopropyl alcohol in the Meerwein-Ponndorf-Verley reduction. For example see V.J.Shiner and D.Whittaker, *J. Am. Chem. Soc.*, 1963, **85**, 2337; E.W.Warnhoff, P.Reynolds-Warnhoff and M.Y.H.Wong, *ibid*, 1980, **102**, 5956.

133. T.Kametani and K.Fukumoto, *Heterocycles,* 1975, **3**, 931.

134. N.Baindur, J.L.Neumeyer, H.B.Niznik, N.H.Bzowej, K.R.Jarvie, P.Seeman, R.K.Garlick and J.J.Miller, *J. Med. Chem.*, 1988, **31**, 2069.

135. S.T.Ross, R.G.Franz, G.Gallagher, M.Brenner, J.W.Wilson, R.M.DeMarinis, J.P.Hieble and H.M.Sarau, *J. Med. Chem.*, 1987, **30**, 35.

136. D.L.Ladd, J.Weinstock, M.Wise, G.W.Gessner, J.L.Sawyer and K.E.Flaim, *J. Med. Chem.*, 1986, **29**, 1904.

137. J.Weinstock, D.L.Ladd, J.W.Wilson, C.K.Brush, N.C.F.Yim, G.Gallagher, M.E.McCarthy, J.Silvestri, H.M.Sarau, K.E.Flaim, D.M.Ackerman, P.E.Setler, A.J.Tobia and R.A.Hahn, *J. Med. Chem.*, 1986, **29**, 2315.

138. C.Kaiser, P.A.Dandridge, E.Garvey, R.A.Hahn, H.M.Sarau, P.E.Setler, L.S.Bass and J.Clardy, *J. Med. Chem.*, 1982, **25**, 697.

139. J.Weinstock, H.Oh, C.W.DeBrosse, D.S.Eggleston, M.Wise, K.E.Flaim, G.W.Gessner, J.L.Sawyer and C.Kaiser, *J. Med. Chem.*, 1987, **30**, 1303.

140. J.R.Pfister, *Heterocycles*, 1986, **24**, 2099.

141. S.J.Coote and S.G.Davies, *Tetrahedron Lett.*, 1989, **30**, in the press.

142. *Chem. Abstr.*, 1977 **86** 189747p, 1968 **69** 96507u, 1978 **88** 89536s.

143. Prepared according to the precedure of Y.Ban and T.Oishi, *Chem and Pharm Bull.*, 1958, **6**, 574.

144. J.Blagg, PhD thesis, Oxford, 1986.

145. Prepared according to the precedure of R.T.Dean and H.Rapoport, *J. Org. Chem.*, 1978, **43**, 2115. For an alternative method see J.E.Toth, P.R.Hamann and P.L.Fuchs, *ibid*, 1988, **53**, 4694.

146. ^{1}H n.m.r. data for 3,4-dimethoxystyrene is contained in 'The Aldrich Library of n.m.r. spectra', ed. C.J.Pouchert, Aldrich Chemical Company Inc., 1983.

147. D.F.Shriver and M.A.Dreszdon, 'The Manipulation of Air Sensitive Compounds', second edition, John Wiley and Sons, 1986.

148. D.D.Perrin and W.L.F.Armarego, 'Purification of Laboratory Chemicals', third edition, Pergamon Press, Oxford, 1988.

149. W.C.Still, M.Kahn and A.Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

150. 'Dictionary of Organic Compounds', fifth edition, Chapman and Hall, New York, 1982.

151. J.R.Wiseman, J.J.Pendery, C.A.Otto and K.G.Chiong, *J. Org. Chem.*, 1980, **45**, 516.

152. M.Fujiwara, M.Imada, A.Baba and H.Matsuda, *Tetrahedron Lett.*, 1989, **30**, 739.

153. G.P.Men'shikov and G.M.Borodina, *J. Gen. Chem. U. S. S. R.*, 1947, **17**, 1569; *Chem. Abstr.*, 1948, **42**, 2245.

154. V.Toome, J.F.Blount, G.Grethe and M.Uskokovic, *Tetrahedron Lett.*, 1970, **11**, 49; V.Toome, *Spectrosc. Lett.*, 1975, **8**, 1.

155. M.Farines and J.Soulier, *Bull. Soc. Chim. Fr.*, 1970, 332; T.Polonski, *Tetrahedron*, 1983, **39**, 3131; U.Gerlach and S.Hunig, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 1283.

156. C.F.Howell, N.Q.Quinones and R.A.Hardy, *J. Org. Chem.*, 1962, **27**, 1679.

157. G.G.Lyle, *J. Org. Chem.*, 1960, **25**, 1779.

158. C.Fuganti, D.Ghiringhelli and P.Grasselli, *Tetrahedron Lett.*, 1974, **15**, 2261.

159. *Chem. Abstr.*, 1977, **87**, 5827f.

160. *Chem. Abstr.*, 1957, **51**, 4304f.

161. R.J.Vijn, W.N.Speckamp, B.S.de Jong and H.Hiemstra, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 165; *Chem. Abstr.*, 1957, **51**, 16563g.

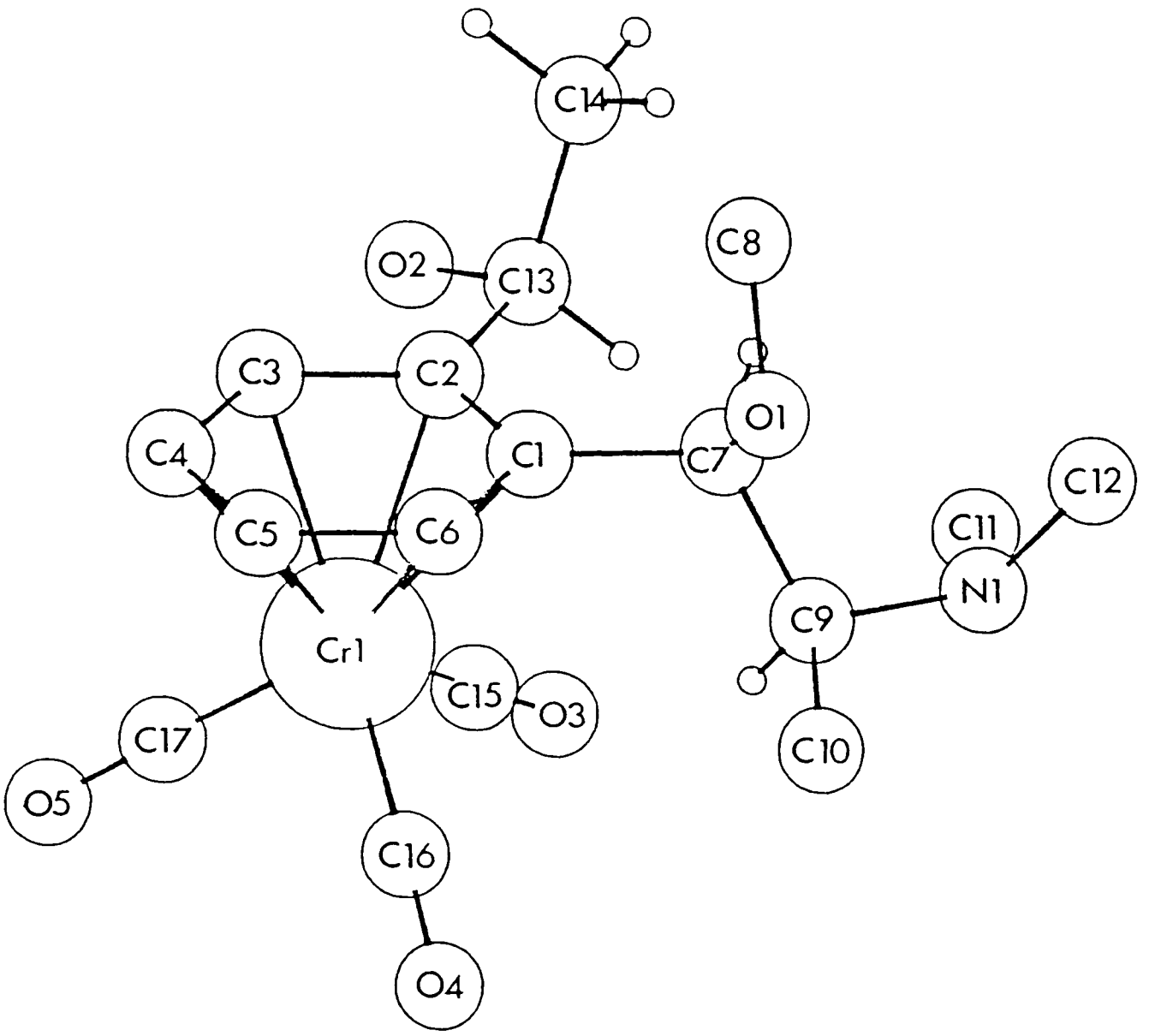
APPENDIX

X-Ray crystal structure determination of (-)-[*ortho*-(2-hydroxyethyl)-(N-methyl-O-methyl)ephedrine]$Cr(CO)_3$ (136).

Crystal data for the x-ray structure analysis of complex (-)-**136** were measured using an Enraf-Nonius CAD4-F 4-circle diffractometer and are presented below. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.5418A] using the $\omega/2\theta$ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis but initially indicated by the optical activity of the sample compound. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.7 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects. An absorption correction was also applied to obtain correct relative intensities.

Crystal data for (-)-**136**; $C_{17}H_{23}CrNO_5$, M 373.368, orthorhombic, space group P 2_1 2_1 2_1, **a** 8.761(4), **b** 13.269(3), **c** 15.744(5) A, α 90, β 90, γ 90, U 1830.2 A^3, D_{calc} 1.36 gcm^{-3}, Z 4, μ(Cu-Kα) 54.3cm^{-1}. The crystal used for data collection was yellow in colour and of approximate dimensions 0.18 by 0.26 by 2.09 mm. Number of independent reflections measured 2149, number with $I>3\sigma(I)$ 1478; R-factor 0.058; weighted R-factor 0.066; absorption corrections, maximium 2.07, minimum 1.91.

The structure was solved by direct methods and electron-density Fourier synthesis. The structure was refined by large-block, least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections were weighted by applying a 3 term Chebychev series of the form $w = [10.45\ t_0(X) - 1.312\ t_1(X) + 6.969\ t_2(X)]$ where $X = F_o/F_{max}$. Final Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors. All calculations were performed on the Chemical Crystallography VAX11/750 computer using the CRYSTALS software package incorporating SHELXS.



X-Ray crystal structure of complex (-)-**136** showing non-systematic numbering.

CR(1)	C(1)	2.238(6)
CR(1)	C(2)	2.224(6)
CR(1)	C(3)	2.211(7)
CR(1)	C(4)	2.196(8)
CR(1)	C(5)	2.231(7)
CR(1)	C(6)	2.220(7)
CR(1)	C(15)	1.831(8)
CR(1)	C(16)	1.840(8)
CR(1)	C(17)	1.834(8)
C(1)	C(2)	1.425(8)
C(1)	C(6)	1.40(1)
C(1)	C(7)	1.546(9)
C(2)	C(3)	1.40(1)
C(2)	C(13)	1.51(1)
C(3)	C(4)	1.39(1)
C(4)	C(5)	1.421(9)
C(5)	C(6)	1.40(1)
C(7)	C(9)	1.56(1)
C(7)	O(1)	1.429(8)
C(8)	O(1)	1.403(9)
C(9)	C(10)	1.524(9)
C(9)	N(1)	1.48(1)
C(11)	N(1)	1.44(1)
C(12)	N(1)	1.46(1)
C(13)	C(14)	1.52(1)
C(13)	O(2)	1.430(8)
C(15)	O(3)	1.157(9)
C(16)	O(4)	1.150(9)
C(17)	O(5)	1.16(1)

Selected bond lengths for complex (-)-**136**.

C(1)	C(2)	CR(1)	71.9(3)
C(3)	C(2)	CR(1)	71.1(4)
C(3)	C(2)	C(1)	119.2(7)
C(13)	C(2)	CR(1)	131.8(5)
C(13)	C(2)	C(1)	122.8(7)
C(13)	C(2)	C(3)	117.9(6)
C(2)	C(3)	CR(1)	72.1(4)
C(4)	C(3)	CR(1)	71.0(4)
C(4)	C(3)	C(2)	120.9(6)
C(3)	C(4)	CR(1)	72.2(4)
C(5)	C(4)	CR(1)	72.6(5)
C(5)	C(4)	C(3)	121.0(8)
C(4)	C(5)	CR(1)	69.9(5)
C(6)	C(5)	CR(1)	71.2(4)
C(6)	C(5)	C(4)	117.7(7)
C(1)	C(6)	CR(1)	72.3(4)
C(5)	C(6)	CR(1)	72.1(4)
C(5)	C(6)	C(1)	122.1(6)
C(9)	C(7)	C(1)	115.5(5)
O(1)	C(7)	C(1)	110.0(6)
O(1)	C(7)	C(9)	107.2(5)
C(10)	C(9)	C(7)	113.5(7)
N(1)	C(9)	C(7)	112.9(5)
N(1)	C(9)	C(10)	109.2(6)
C(14)	C(13)	C(2)	110.4(6)
O(2)	C(13)	C(2)	108.4(6)
O(2)	C(13)	C(14)	108.4(6)
O(3)	C(15)	CR(1)	179.0(8)
O(4)	C(16)	CR(1)	177.8(7)
O(5)	C(17)	CR(1)	179.4(9)
C(8)	O(1)	C(7)	114.5(6)
C(11)	N(1)	C(9)	117.0(7)
C(12)	N(1)	C(9)	110.6(6)
C(12)	N(1)	C(11)	110.5(8)

Selected bond angles for complex (-)-**136**.

C(2)	CR(1)	C(1)	37.3(2)
C(3)	CR(1)	C(1)	66.4(2)
C(3)	CR(1)	C(2)	36.8(3)
C(4)	CR(1)	C(1)	78.7(3)
C(4)	CR(1)	C(2)	66.7(3)
C(4)	CR(1)	C(3)	36.8(3)
C(5)	CR(1)	C(1)	66.7(3)
C(5)	CR(1)	C(2)	79.3(3)
C(5)	CR(1)	C(3)	66.9(3)
C(5)	CR(1)	C(4)	37.4(2)
C(6)	CR(1)	C(1)	36.7(2)
C(6)	CR(1)	C(2)	66.6(2)
C(6)	CR(1)	C(3)	78.0(3)
C(6)	CR(1)	C(4)	66.3(3)
C(6)	CR(1)	C(5)	36.7(3)
C(15)	CR(1)	C(1)	162.7(3)
C(15)	CR(1)	C(2)	126.9(3)
C(15)	CR(1)	C(3)	96.3(3)
C(15)	CR(1)	C(4)	87.6(3)
C(15)	CR(1)	C(5)	108.1(3)
C(15)	CR(1)	C(6)	143.9(3)
C(16)	CR(1)	C(1)	107.3(3)
C(16)	CR(1)	C(2)	143.2(3)
C(16)	CR(1)	C(3)	162.9(3)
C(16)	CR(1)	C(4)	127.9(3)
C(16)	CR(1)	C(5)	96.0(3)
C(16)	CR(1)	C(6)	87.8(3)
C(17)	CR(1)	C(1)	95.7(3)
C(17)	CR(1)	C(2)	85.8(3)
C(17)	CR(1)	C(3)	106.1(3)
C(17)	CR(1)	C(4)	141.7(3)
C(17)	CR(1)	C(5)	162.4(3)
C(17)	CR(1)	C(6)	127.5(3)
C(16)	CR(1)	C(15)	89.4(4)
C(17)	CR(1)	C(15)	88.5(4)
C(17)	CR(1)	C(16)	90.2(3)
C(2)	C(1)	CR(1)	70.8(4)
C(6)	C(1)	CR(1)	71.0(4)
C(6)	C(1)	C(2)	119.1(7)
C(7)	C(1)	CR(1)	132.8(4)
C(7)	C(1)	C(2)	123.9(6)
C(7)	C(1)	C(6)	116.9(5)

Selected bond angles for complex (-)-**136**.

Atom	x/a	y/b	z/c	U(iso)
CR(1)	1278(1)	7293.7(8)	3833.1(7)	391
C(1)	1309(8)	7668(4)	2447(4)	352
C(2)	1251(9)	6601(4)	2547(4)	359
C(3)	80(9)	6176(5)	3033(5)	441
C(4)	-996(9)	6781(6)	3438(5)	487
C(5)	-963(9)	7847(5)	3348(5)	473
C(6)	206(9)	8266(5)	2853(4)	423
C(7)	2479(9)	8219(5)	1877(4)	377
C(8)	859(12)	8640(7)	715(6)	675
C(9)	3841(9)	8721(5)	2353(4)	431
C(10)	3483(10)	9775(5)	2683(5)	553
C(11)	5109(10)	9147(7)	984(6)	614
C(12)	6003(10)	7778(6)	1828(7)	652
C(13)	2350(10)	5896(5)	2107(5)	433
C(14)	1881(11)	5742(6)	1189(6)	608
C(15)	945(9)	6655(6)	4847(5)	499
C(16)	1775(9)	8451(6)	4415(5)	496
C(17)	3273(9)	6879(5)	3886(5)	497
O(1)	1733(6)	8992(3)	1400(3)	453
O(2)	2299(7)	4942(3)	2530(4)	509
O(3)	756(8)	6251(5)	5490(4)	714
O(4)	2040(8)	9187(4)	4772(4)	627
O(5)	4533(8)	6619(4)	3912(5)	700
N(1)	5248(8)	8759(5)	1835(4)	489
H(1)	84(9)	5382(5)	3089(5)	925(69)
H(2)	-1827(9)	6442(6)	3796(5)	925(69)
H(3)	-1810(9)	8322(5)	3623(5)	925(69)
H(4)	262(9)	9039(5)	2785(4)	925(69)
H(5)	2793(9)	7687(5)	1482(4)	925(69)
H(6)	358(12)	9218(7)	371(6)	925(69)
H(7)	1500(12)	8252(7)	271(6)	925(69)
H(8)	8(12)	8178(7)	891(6)	925(69)
H(9)	4149(9)	8313(5)	2879(4)	925(69)
H(10)	4390(10)	10092(5)	3000(5)	925(69)
H(11)	3204(10)	10259(5)	2212(5)	925(69)
H(12)	2599(10)	9776(5)	3105(5)	925(69)
H(13)	6131(10)	9152(7)	667(6)	925(69)
H(14)	4738(10)	9880(7)	980(6)	925(69)
H(15)	4373(10)	8745(7)	634(6)	925(69)
H(16)	6940(10)	7784(6)	1426(7)	925(69)
H(17)	6298(10)	7561(6)	2381(7)	925(69)
H(18)	5287(10)	7236(6)	1554(7)	925(69)
H(19)	3402(10)	6183(5)	2172(5)	925(69)
H(20)	2584(11)	5261(6)	877(6)	925(69)
H(21)	1863(11)	6396(6)	855(6)	925(69)
H(22)	798(11)	5441(6)	1133(6)	925(69)
H(23)	2987(7)	4447(3)	2243(4)	925(69)

Fractional atomic coordinates ($x10^3$) for complex (-)-**136**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
CR(1)	509(6)	295(4)	402(5)	-8(5)	-29(6)	12(5)
C(1)	463(34)	247(23)	389(26)	2(26)	-34(33)	
C(2)	459(39)	251(25)	429(31)	-30(23)	-102(35)	7(31)
C(3)	448(41)	393(35)	516(39)	37(31)	-44(34)	-86(32)
C(4)	477(51)	464(38)	541(40)	4(34)	-83(34)	
C(5)	470(47)	434(38)	550(40)	62(32)	-32(32)	81(32)
C(6)	565(48)	286(30)	484(37)	11(27)	-7(36)	70(30)
C(7)	498(40)	251(29)	431(33)	12(26)	-41(32)	-9(29)
C(8)	865(75)	701(58)	629(52)	127(43)	-289(50)	-136(52)
C(9)	539(43)	358(30)	434(33)	37(27)	-29(36)	-76(33)
C(10)	698(60)	397(35)	634(45)	-80(34)	47(45)	
C(11)	624(55)	723(53)	601(53)	33(42)	77(44)	-235(48)
C(12)	444(52)	550(46)	1141(73)	-20(53)	32(47)	23(41)
C(13)	583(47)	215(28)	654(46)	-26(29)	-14(39)	22(31)
C(14)	881(61)	448(38)	612(47)	-130(41)	18(51)	54(40)
C(15)	537(55)	457(37)	543(42)	57(35)	-99(37)	62(33)
C(16)	518(50)	499(39)	488(41)	-61(34)	16(34)	64(34)
C(17)	659(53)	353(31)	544(41)	-56(34)	-64(41)	-12(33)
O(1)	539(33)	354(24)	532(30)	98(20)	-75(22)	37(21)
O(2)	573(34)	229(20)	1065(44)	96(28)	-82(33)	20(22)
O(3)	871(50)	821(44)	657(38)	345(37)	17(34)	54(38)
O(4)	833(44)	507(30)	694(36)	-226(29)	-16(34)	-67(30)
O(5)	631(41)	617(35)	1104(52)	-116(38)	-229(41)	230(31)
N(1)	524(41)	400(31)	577(38)	-9(28)	66(31)	-60(29)

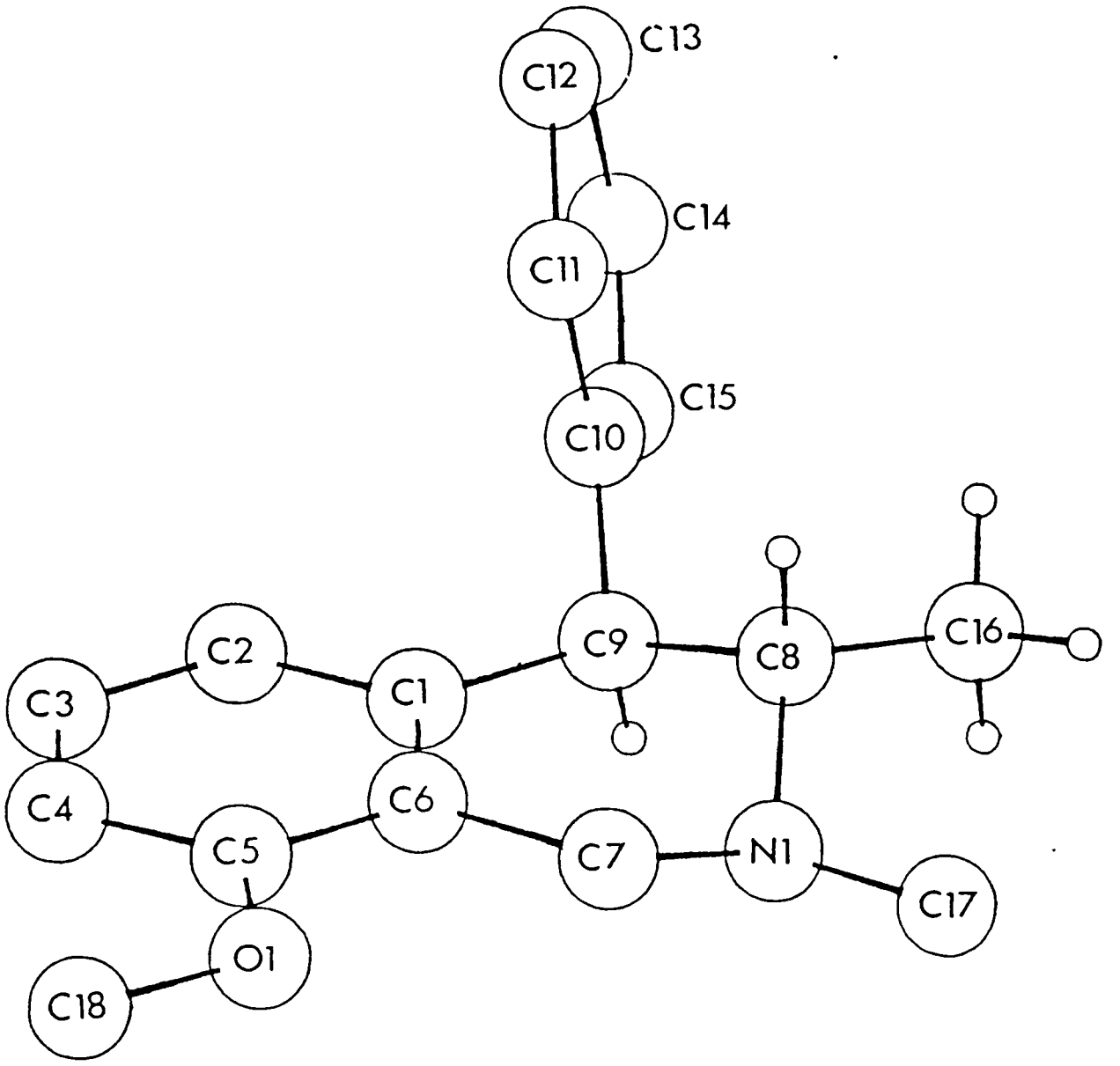
Thermal parameters for complex (-)-**136**.

X-Ray crystal structure determination of (-)-(3S,4R)-N-methyl-3-methyl-4-phenyl-8-methoxy tetrahydroisoquinoline (233).

Crystal data for the x-ray structure analysis of (-)-(3S,4R)-**233** were measured using an Enraf-Nonius CAD4-F 4-circle diffractometer and are presented below. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.5418A] using the ω/2θ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis but initially indicated by the optical activity of the sample compound. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.7 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects. An absorption correction was also applied to obtain correct relative intensities.

Crystal data for (-)-(3S,4R)-**233**; $C_{18}H_{21}NO$, M 267.370, orthorhombic, space group P 2_1 2_1 2_1, **a** 5.978(2), **b** 9.257(1), **c** 26.799(4) A, α 90, β 90, γ 90, U 1482.9 A^3, D_{calc} 1.27 gcm^{-3}, Z 4, μ(Cu-Kα) 6.15cm^{-1}. The crystal used for data collection was of approximate dimensions 0.40 by 0.60 by 0.80 mm. Number of independent reflections measured 1804, number with I>3σ(I) 1645; R-factor 0.075; weighted R-factor 0.091.

The structure was solved by direct methods and electron-density Fourier synthesis. The structure was refined by large-block, least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections were weighted by applying a 3 term Chebychev series of the form $w = [27.686\ t_0(X) + 4.573\ t_1(X) + 22.085\ t_2(X)]$ where $X = F_o/F_{max}$. During refinement, Fourier synthesis revealed the oxygen atom of a water molecule of crystallisation and the structure was further refined to include this molecule. Final Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors. All calculations were performed on the Chemical Crystallography VAX11/750 computer using the CRYSTALS software package incorporating SHELXS.



X-Ray crystal structure of (-)-**233** showing non-systematic numbering.

C(1)	C(2)	1.40
C(1)	C(6)	1.39
C(1)	C(9)	1.52
C(2)	C(3)	1.38
C(3)	C(4)	1.39
C(4)	C(5)	1.39
C(5)	C(6)	1.41
C(5)	O(1)	1.36
C(6)	C(7)	1.51
C(7)	N(1)	1.45
C(8)	C(9)	1.55
C(8)	C(16)	1.52
C(8)	N(1)	1.47
C(9)	C(10)	1.53
C(10)	C(11)	1.39
C(10)	C(15)	1.39
C(11)	C(12)	1.39
C(12)	C(13)	1.38
C(13)	C(14)	1.37
C(14)	C(15)	1.39
C(17)	N(1)	1.46
C(18)	O(1)	1.43

Selected bond lengths for (-)-**233**.

C(6)	C(1)	C(2)	119.16
C(9)	C(1)	C(2)	120.58
C(9)	C(1)	C(6)	120.25
C(3)	C(2)	C(1)	120.21
C(4)	C(3)	C(2)	121.27
C(5)	C(4)	C(3)	118.63
C(6)	C(5)	C(4)	120.54
O(1)	C(5)	C(4)	124.31
O(1)	C(5)	C(6)	115.14
C(5)	C(6)	C(1)	120.18
C(7)	C(6)	C(1)	120.98
C(7)	C(6)	C(5)	118.84
N(1)	C(7)	C(6)	112.64
C(16)	C(8)	C(9)	110.27
N(1)	C(8)	C(9)	107.76
N(1)	C(8)	C(16)	111.33
C(8)	C(9)	C(1)	112.28
C(10)	C(9)	C(1)	112.00
C(10)	C(9)	C(8)	111.05
C(11)	C(10)	C(9)	120.52
C(15)	C(10)	C(9)	120.64
C(15)	C(10)	C(11)	118.84
C(12)	C(11)	C(10)	120.95
C(13)	C(12)	C(11)	119.50
C(14)	C(13)	C(12)	119.91
C(15)	C(14)	C(13)	120.74
C(14)	C(15)	C(10)	120.05
C(18)	O(1)	C(5)	117.98
C(8)	N(1)	C(7)	110.40
C(17)	N(1)	C(7)	108.88
C(17)	N(1)	C(8)	114.33

Selected bond angles for (-)-**233**.

Atom	x/a	y/b	z/c	U(iso)
C(1)	-9081	-1240	-1084	405
C(2)	-8191	-1253	-601	538
C(3)	-6422	-2157	-485	566
C(4)	-5478	-3063	-842	527
C(5)	-6360	-3055	-1322	442
C(6)	-8175	-2149	-1442	399
C(7)	-9116	-2199	-1964	458
C(8)	-11397	-134	-1782	417
C(9)	-11041	-269	-1213	409
C(10)	-10834	1218	-970	431
C(11)	-12459	1706	-638	539
C(12)	-12294	3063	-418	653
C(13)	-10503	3947	-535	597
C(14)	-8891	3474	-862	613
C(15)	-9036	2110	-1078	521
C(16)	-13610	620	-1892	550
C(17)	-12125	-1685	-2511	591
C(18)	-3643	-4746	-1618	611
O(1)	-5602	-3896	-1702	534
N(1)	-11352	-1597	-1995	439
H(1)	-8833	-603	-336	4840
H(2)	-5818	-2151	-137	4840
H(3)	-4210	-3718	-753	4840
H(4)	-3447	-5389	-1841	4840
H(5)	-3933	-5439	-1339	4840
H(6)	-2345	-4114	-1529	4840
H(7)	-9224	-3124	-1992	4840
H(8)	-8111	-1630	-2189	4840
H(9)	-13668	-1275	-2538	4840
H(10)	-12137	-2714	-2624	4840
H(11)	-11081	-1114	-2726	4840
H(12)	-13604	1615	-1746	4840
H(13)	-13823	683	-2261	4840
H(14)	-14860	48	-1742	4840
H(15)	-10188	443	-1946	4840
H(16)	-12397	-747	-1070	4840
H(17)	-13753	1062	-557	4840
H(18)	-13478	3393	-180	4840
H(19)	-10521	4888	-442	4840
H(20)	-7599	4112	-950	4840
H(21)	-7852	1752	-1311	4840
O(2)	-7841	-3199	-2527	5323

Fractional atomic coordinates ($x10^3$) for (-)-**233**.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
C(1)	486	355	391	26	15	-50
C(2)	792	454	436	14	-40	17
C(3)	825	478	501	44	-176	-3
C(4)	641	440	547	43	-125	4
C(5)	465	372	504	17	-26	-28
C(6)	416	365	423	13	11	-38
C(7)	438	522	437	-70	-26	54
C(8)	429	389	433	-6	-1	5
C(9)	435	378	438	-17	90	-44
C(10)	471	401	431	-14	53	-16
C(11)	594	572	481	-67	84	21
C(12)	783	650	602	-116	65	138
C(13)	810	430	658	-105	-112	82
C(14)	698	474	721	-46	-69	-76
C(15)	514	459	628	-45	64	-82
C(16)	517	517	659	-51	-67	103
C(17)	658	646	603	-182	-215	107
C(18)	536	597	755	12	-14	130
O(1)	489	554	600	-84	-37	106
N(1)	421	455	452	-56	-22	10

Thermal parameters for (-)-**233**.