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Tricarbonylchromium(0) Promoted Stereoselective Cyclisations of the *N*-3,4-Dimethoxyphenethyl Derivatives of the 1-Phenyl Ethanolamines Halostachine, Ephedrine and Pseudoephedrine to 1-Phenyl-*N*-Methyl-7,8-Dimethoxy-1,2,4,5-Tetrahydrobenzazepines

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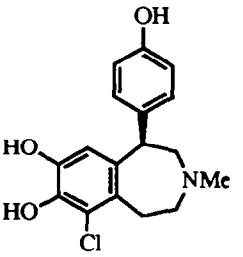
Abstract: Acid promoted cyclisation of homochiral (*R*)-*N*-(3,4-dimethoxyphenethyl)-halostachine proceeds with almost total racemisation to yield 1-phenyl-*N*-methyl-1,2,4,5-tetrahydrobenz[d]azepine (e.e. 6%). Coordination of the cyclisation precursor to the tricarbonylchromium(0) moiety renders the cyclisation completely stereospecific to afford, after decomplexation, homochiral (+)-(*R*)-1-phenyl-*N*-methyl-1,2,4,5-tetrahydrobenz[d]azepine. (-)-(1*R*,2*S*)-*N*-(3,4-Dimethoxyphenethyl)ephedrine undergoes acid mediated cyclisation to furnish *trans*-(-)-(1*R*,2*S*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine as a single diastereoisomer. In contrast, the epimeric cyclisation precursor (-)-(1*R*,2*R*)-*N*-(3,4-dimethoxyphenethyl)pseudoephedrine cyclises to give a mixture (ratio 91:9) of *trans*- and *cis*-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine. However, cyclisation of the tricarbonylchromium(0) complex of (-)-(1*R*,2*R*)-*N*-(3,4-dimethoxyphenethyl)pseudo-ephedrine is completely stereoselective to yield *trans*-(+)-(1*S*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine after decomplexation.

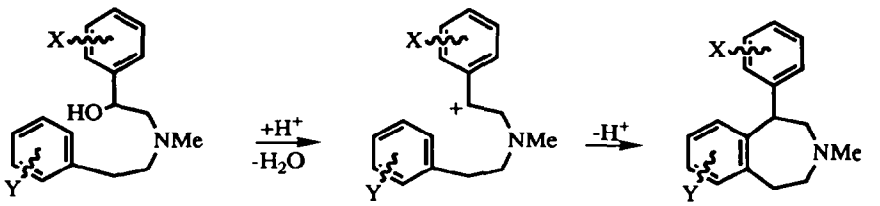
Introduction

The naturally occurring heterocycles possessing the 1,2,4,5-tetrahydro-3H-benz[**d**]azepine† skeleton are commonly referred to as the 'benzazepine alkaloids'.[1] 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.[2,3] 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 (**1**)[4,5] is a D1 agonist that exhibits pharmacological enantioselectivity; the dopaminergic activity residing almost exclusively in the *R* enantiomer.[6,7] 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 1.[1] This cyclisation reaction has been widely used in the search for pharmacologically active benzazepines, the reaction being facilitated by electron releasing aryl substituents and retarded for electron withdrawing groups.

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

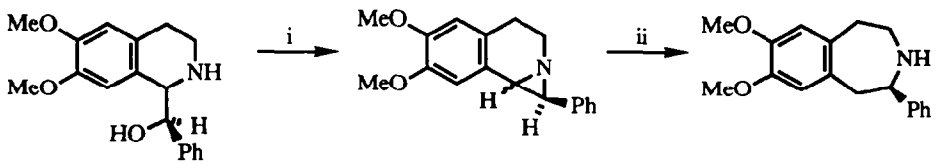


(*R*)-(**1**)



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

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 (**2**) *via* the intermediate aziridine (**3**).[8]

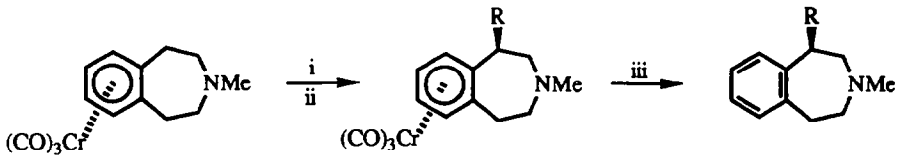


(*S*)-(**2**) (*R*)-(**3**) (-)-(*R*)-(**4**)

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

(Arene)tricarbonylchromium(0) methodology has been exploited in the *exo*-benzylic alkylation of benzazepine complex (**5**), whereby sequential treatment with butyllithium and an electrophile, regio- and stereoselectively generates the corresponding 1-*exo*-substituted complexes [(**6**)-(**9**)] which may be oxidatively decomplexed to liberate the 1-alkylated tetrahydrobenzazepines [(**10**)-(**13**)].[9]

Although there are many reported methods enabling the construction of 1-aryl tetrahydrobenzazepines,[1] 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)tricarbonylchromium(0)



(5)

R=Me (6)
Et (7)
$PhCH_2$ (8)
MeS (9)

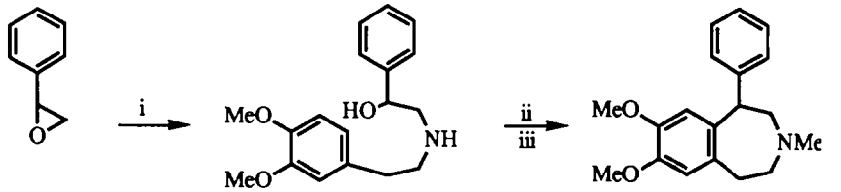
R=Me (10)
Et (11)
$PhCH_2$ (12)
MeS (13)

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

chemistry for the direct synthesis of homochiral 1-phenyl tetrahydrobenzazepines. An account of some of our work in this area has been the subject of a preliminary communication.[10]

Results and Discussion

A dichloromethane solution of racemic amino alcohol (**14**) [readily synthesised according to literature procedure from styrene oxide (**15**) and homoveratrylamine (**16**)][11] 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 (**17**) as a white powder. ^1H n.m.r. analysis of (**17**) in the presence of the chiral shift reagent 2,2,2-trifluoro-(9-anthryl)ethanol [(-)-(*R*)-(**18**)][12] clearly distinguished the two methoxyl singlets, the *N*-methyl singlet, the two aromatic singlets and the C1 proton corresponding to the two enantiomers.



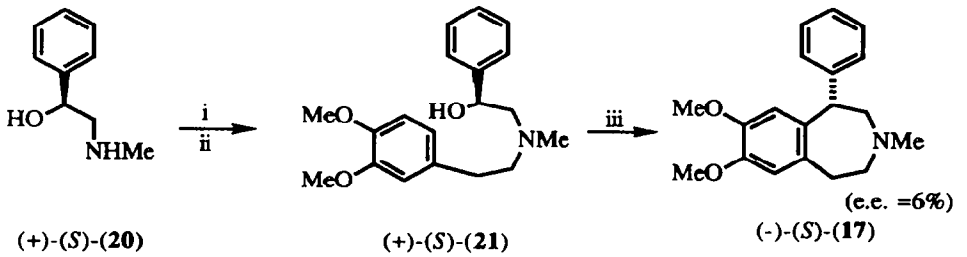
(15) (14) (17)

Reagents: i) 3,4-$(MeO)_2C_6H_3CH_2CH_2NH_2$(**16**), 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 (**19**)[13] with racemic halostachine (**20**) yielded a mixture of diastereoisomeric oxazolidines which were reduced with sodium borohydride in methanol affording amino alcohol (**21**). In a similar fashion, homochiral amino alcohol (+)-(*S*)-(**21**) was synthesised from (+)-(*S*)-halostachine (**20**) and fully characterised. ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(*R*)-(**18**) gave partial separation of the benzylic proton of (*R*,*S*)-(**21**) and indicated that (+)-(*S*)-(**21**) was homochiral, its C1-benzylic proton signal appearing at lower field than that for (-)-(*R*)-(**21**).

Acid-promoted cyclisation of (+)-(*S*)-(**21**) below -20°C occurred smoothly to give the expected benzazepine (**17**). 300MHz ^1H n.m.r. analysis of the product in the presence of shift reagent (-)-(*R*)-(**18**) revealed an enantiomeric excess of 6%. If a free benzylic carbocation were to be formed as an intermediate,

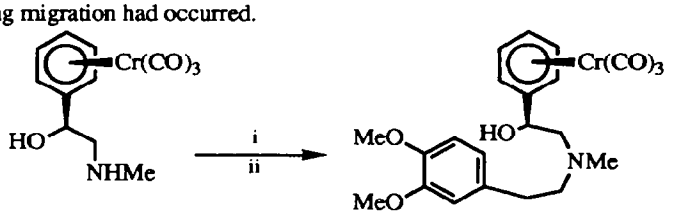
then complete racemisation would be expected. The small enantiomeric excess observed presumably reflects a small degree of cyclisation *via* neighbouring group participation by the dimethoxyphenethyl group in the ionisation of the protonated alcohol functionality with concommittant inversion of configuration. The major enantiomer observed in the cyclisation of (+)-(*S*)-(**21**) is thus assigned as (*S*)-(**17**), consistent with literature precedent[14,15] *i.e.* preferential inversion of configuration during the cyclisation.



(+)-(*S*)-(**20**) (+)-(*S*)-(**21**) (-)-(*S*)-(**17**)

Reagents: i) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**19**), 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 could be rendered highly stereoselective if the cyclisation of complex (*R*)-(**22**) [the tricarbonylchromium(0) complex of (+)-(S)-(**21**)] were to proceed under the stereocontrolling influence of the tricarbonylchromium(0) unit.[10,15] Condensation of (+)-(*R*)-(halostachine)tricarbonylchromium(0) (**23**)[10,14] with homoveratraldehyde (**19**) and subsequent sodium borohydride reduction of the resultant mixture of diastereoisomeric oxazolidine complexes, afforded (*R*)-[*N*-(3,4-dimethoxyphenethyl)halostachine] tricarbonylchromium(0) (**22**) as a yellow oil. The ^1H n.m.r. spectrum of the product (**22**) exhibited a five proton aromatic multiplet at *ca.* δ5 and a three proton aromatic multiplet at lower field indicating that the tricarbonylchromium(0) moiety was coordinated to the unsubstituted phenyl ring and that no ring to ring migration had occurred.

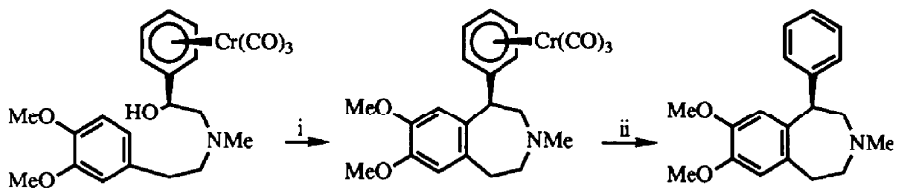


(+)-(*R*)-(**23**) (*R*)-(**22**)

Reagents: i) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**19**), CH_2Cl_2, *p*TsOH, sieves, 86%. ii) $NaBH_4$, MeOH, 62%

Treatment of a dichloromethane solution of (*R*)-(**22**) with tetrafluoroboric acid below -20°C over 40 h 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-

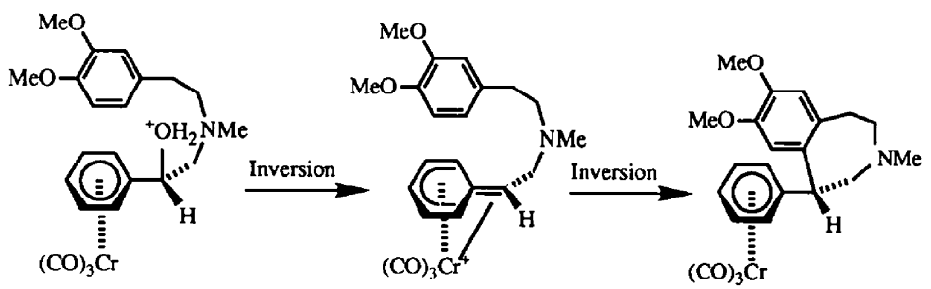
(phenyl)tricarbonylchromium(0)-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**24**), assigned initially as *R* upon the basis of expected retention of configuration during the cyclisation of (*R*)-(**22**).[10,14,15] Oxidative decomplexation, upon exposure to air and sunlight, liberated (+)-(*R*)-1-phenyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**17**) {$[\alpha]_D^{20}$+45.4° (*c* 0.27 in $CHCl_3$)} as a white powder that appeared to be homochiral according to ^1H n.m.r. spectroscopy in the presence of shift reagent (-)-(*R*)-(**18**). 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 in MeOH), lit.[6] $[\alpha]_D^{25}$ +31.8° (*c* 1.0 in MeOH)}, thus supporting the above assignment.



(*R*)-(**22**) (-)-(*R*)-(**24**) (+)-(*R*)-(**17**)

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

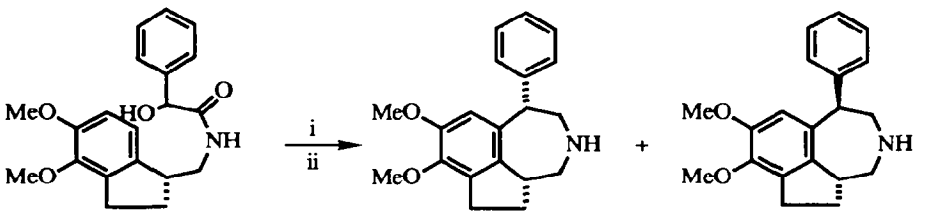
That both uncomplexed and complexed cyclisation precursors are derived from (+)-(*S*)-halostachine (**20**) and preferentially give opposite enantiomers of product requires that the stereochemical courses of the two reactions be complementary; a slight preference for inversion of configuration in the case of (+)-(*S*)-(**21**) but complete retention of configuration for complex (-)-(*R*)-(**22**). This is consistent with participation by the tricarbonylchromium(0) moiety in the ionisation of the benzylic hydroxyl group with inversion of configuration to generate the cationic intermedate (**25**). Intramolecular trapping may subsequently occur only from the unhindered *exo* face, again with inversion, to give complex (-)-(*R*)-(**24**), making the overall process stereospecific with retention of configuration.



(*R*)-(**22**) (**25**) (-)-(*R*)-(**24**)

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. However, a recent report indicated that acidic treatment of (aminomethyl)indane derivative (**26**), followed by lithium

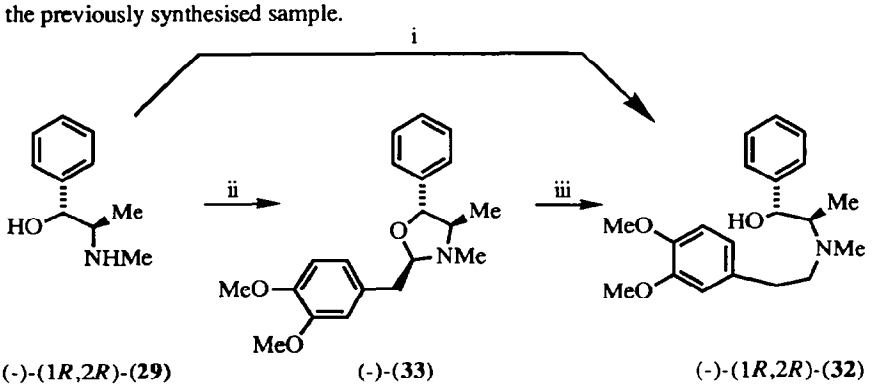
aluminium hydride reduction gave a mixture of *cis*- and *trans*-ethano-bridged tetrahydrobenzazepines (**27**) and (**28**) in the isolated ratio 59:41.[7]



(**26**) (**27**) (**28**)

Reagents: i) Polyphosphoric acid, 100°C, 0.5h, 32%. ii) $LiAlH_4$, Et_2O THF 92%

An ethanol solution of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) and 3,4-dimethoxyphenethyl bromide (**30**)[16] 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 (**31**), whilst the major product was the expected (-)-(1*R*,2*R*)-*N*-(3,4-dimethoxyphenethyl)pseudoephedrine (**32**). A molecular ion *m*/z=330 (M^++1) and an elemental analysis confirmed its identity. Alternatively, condensation of homoveratraldehyde (**19**) with (-)-(1*R*,2*R*)-pseudoephedrine (**29**) gave the corresponding oxazolidine (-)-(**33**) preferentially as one diastereoisomer (ratio 94:6).[17] This was subsequently reduced with sodium borohydride in methanol to give (-)-(1*R*,2*R*)-(**32**) identical to the previously synthesised sample.

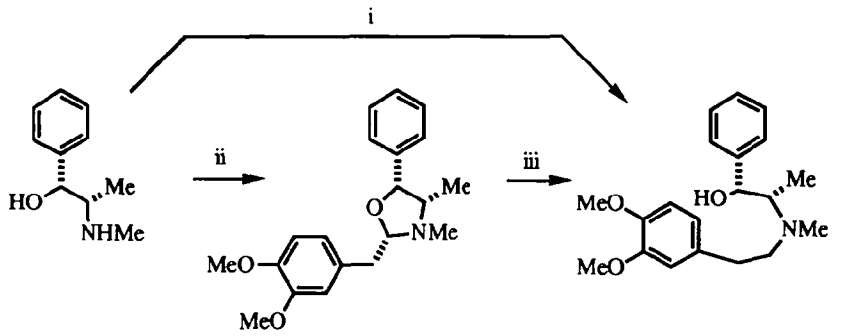


(-)-(1*R*,2*R*)-(**29**) (-)-(**33**) (-)-(1*R*,2*R*)-(**32**)

Reagents: i) 3,4-$(MeO)_2C_6H_3CH_2CH_2Br$ (**30**), $NaHCO_3$, NaI, EtOH, 60h, 29%. ii) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**19**), C_6H_6, *p*TsOH, 21h, quantitative. iii) $NaBH_4$, MeOH, 20°C, 23h, 61%

Similarly, an acetonitrile solution of 3,4-dimethoxyphenethyl bromide and (-)-(1*R*,2*S*)-ephedrine (**34**). 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 (**31**), whilst the major product was

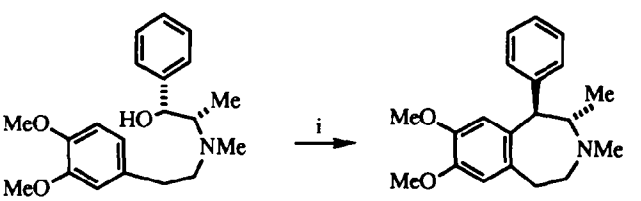
identified as (-)-(1*R*,2*S*)-*N*-(3,4-dimethoxyphenethyl)ephedrine (**35**). Recrystallisation from diethylether/hexane afforded an analytically pure sample that was fully characterised. Alternatively, (-)-(1*R*,2*S*)-(**35**) was readily obtained *via* sodium borohydride reduction of the oxazolidine (-)-(**36**) derived by condensation of homoveratraldehyde (**19**) with (-)-(1*R*,2*S*)-ephedrine (**34**).



(-)-(1*R*,2*S*)-(**34**) (-)-(**36**) (-)-(1*R*,2*S*)-(**35**)

Reagents: i) 3,4-$(MeO)_2C_6H_3CH_2CH_2Br$ (**30**), K_2CO_3, MeCN, 48h, 34%. ii) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**19**), C_6H_6, *p*TsOH, 21h, quantitative. iii) $NaBH_4$, MeOH, 20°C, 23h, 56%

A dichloromethane solution of (-)-(1*R*,2*S*)-(**35**) 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 a single product, two lowfield aromatic singlets being consistent with cyclisation to give a 7,8-disubstituted benzazepine. Recrystallisation of the crude product gave an analytically pure sample of *trans*-(-)-(1*R*,2*S*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**) {$[\alpha]_D^{20}$ -2.4° (*c* 0.84 in $CHCl_3$)}as white blocks.

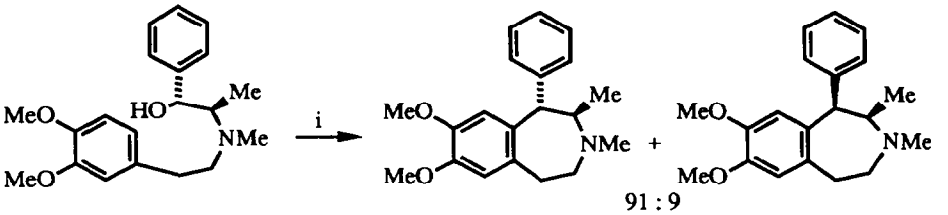


(-)-(1*R*,2*S*)-(**35**) (-)-(1*R*,2*S*)-(**37**)

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

In a similar fashion, pseudoephedrine-derived (-)-(1*R*,2*R*)-(**32**) was cyclised upon exposure to acid affording a mixture of products in the ratio 91:9 according to ^1H n.m.r. spectroscopy of the crude reaction mixture. Crystallisation from dichloromethane/hexane enabled the isolation of the major product which proved

to be identical to (**37**) previously synthesised except for the direction in which it rotated plane polarised light. The major component was therefore assigned as *trans*-(+)-(1*S*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**) {$[\alpha]_D^{20}$ +2.9° (*c* 0.38 in $CHCl_3$)}. An elemental analysis and a molecular ion *m/z*=311 were consistent with this assignment whilst the minor component was assigned as *cis*-(1*R*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**38**).



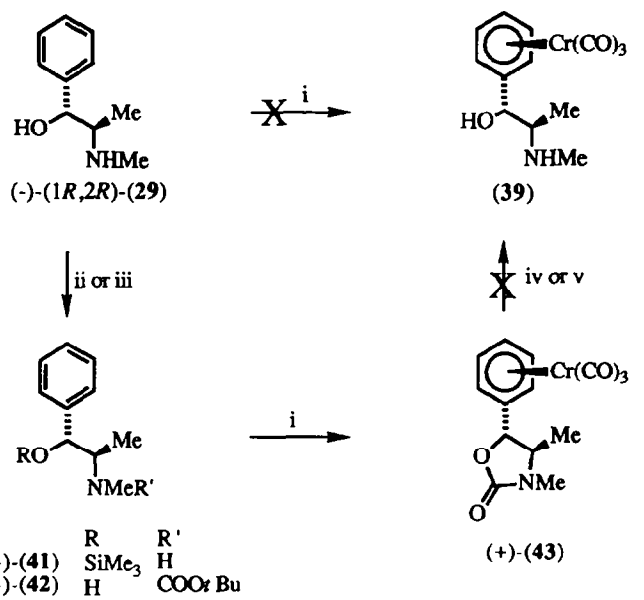
(-)-(1*R*,2*R*)-(**32**) (+)-(1*S*,2*R*)-(**37**) (1*R*,2*R*)-(**38**)

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

The stereoselective cyclisation of (-)-(1*R*,2*S*)-(**35**) to (-)-(1*R*,2*S*)-(**37**) may be rationalised by consideration of two mechanistic pathways. Ionisation of the protonated hydroxyl group of (-)-(1*R*,2*S*)-(**35**) 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 (-)-(**37**) since the transition state leading to its formation will presumably be of considerably lower energy than that which leads to the *cis*-diastereoisomer (**38**) owing to developing steric interactions between the C1-phenyl and the C2-methyl substituents in the latter case. 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 (-)-(**37**). Since the same product is obtained *via* either mechanism, the relative importance of either pathway cannot be deduced. Cyclisation appears, however, to be unlikely to proceed exclusively through the S_N2 mechanism because cyclisation of (+)-(*S*)-(**21**) to (*S*)-(**17**) is observed to occur predominantly *via* an S_N1 pathway leading to a large degree of racemisation. Therefore the S_N1 component must stereospecifically yield the *trans* product. In the case of cyclisation of (-)-(1*R*,2*R*)-(**32**) two different products will result, depending upon which cyclisation mechanism operates. The observed diastereoisomeric excess of 82% in favour of the *trans*-benzazepine (+)-(**37**) is consistent with 9% cyclisation *via* the neighbouring group participation mechanism to give the minor product (**38**) along with 91% cyclisation *via* an S_N1 mechanism which accounts for the formation of *trans*-(+)-(**37**) as the major product.

A potentially versatile route enabling the synthesis of the tricarbonylchromium(0) complexes of the cyclisation precursors (-)-(1*R*,2*R*)-(**32**) and (-)-(1*R*,2*S*)-(**35**) was to use (pseudoephedrine)-tricarbonylchromium(0) (**39**) and (-)-(ephedrine)tricarbonylchromium(0) (**40**) respectively. (-)-(1*R*,2*R*)-Pseudoephedrine (**29**) itself failed to undergo direct coordination to the tricarbonylchromium(0) unit and thus removal of the donor effect of either, or both, oxygen and nitrogen atoms was necessary. Protection as the trimethylsilyl derivative (-)-(**41**) proved fruitless as all complexation attempts gave only very low yields of the corresponding tricarbonylchromium(0) complexes, whilst prolonged thermolysis of hexacarbonylchromium(0)

with *N*-BOC derivative (-)-(**42**) gave only the oxazolidinone complex (+)-(**43**) which failed to hydrolyse under acidic conditions.

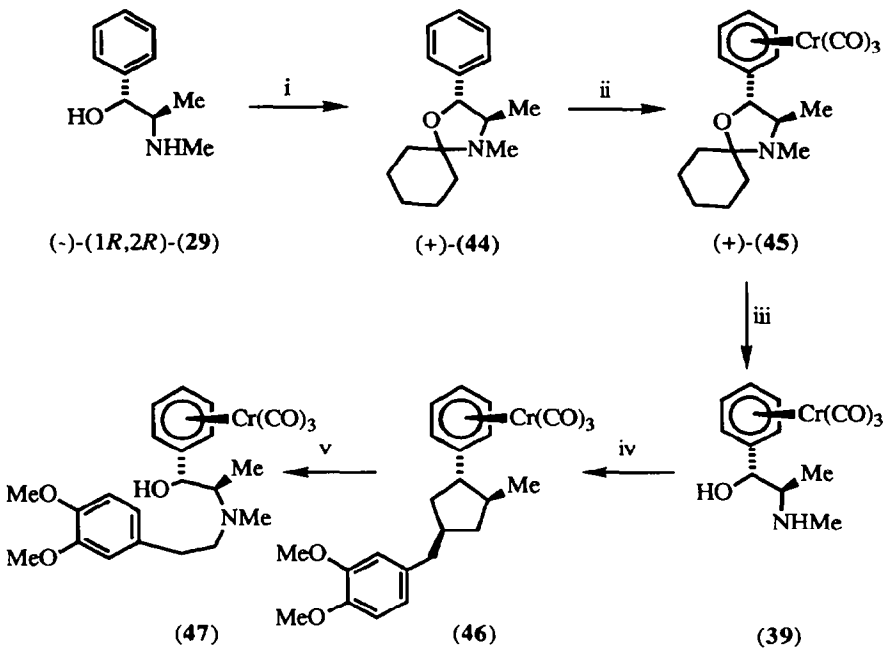


Reagents: i) $Cr(CO)_6$, Bu_2O/THF (10:1). ii) $(Me_3Si)_2NH$, NEt_3, $(CH_2Cl)_2$, 40°C, 2h, quantitative. iii) $(BOC)_2O$, NEt_3, CH_2Cl_2, 21h, 97%. iv) $HBF_4.OMe_2$, THF, 20°C, 24h. v) TFA, CH_2Cl_2, $NaBH_3CN$, 20°C, 14h

Condensation of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) with cyclohexanone furnished the corresponding oxazolidine (+)-(**44**)[19] which underwent ready coordination to the tricarbonylchromium(0) unit under standard conditions[20] to give complex (+)-(**45**) as a yellow solid. Hydrolysis of (+)-(**45**) 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)tricarbonylchromium(0) (**39**) which, without isolation, was treated with homoveratraldehyde (**19**) to afford oxazolidine complex (+)-(**46**). Subsequent reduction with sodium cyanoborohydride furnished complex (**47**), the tricarbonyl chromium(0) complex of pseudoephedrine derivative (-)-(1*R*,2*R*)-(**32**). The ^1H n.m.r. spectrum of the product revealed a three proton aromatic multiplet at δ6.84-6.73 and a five proton aromatic multiplet shifted upfield by approximately 2ppm clearly indicating that the tricarbonylchromium(0) unit was coordinated to the non-substituted phenyl ring and that no migration of it to the more electron rich ring had occurred.

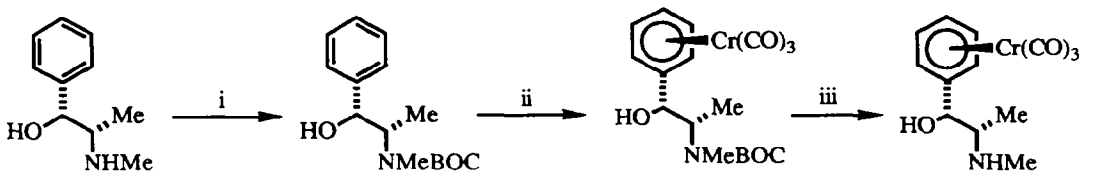
(-)-(1*R*,2*S*)-Ephedrine (**34**), as expected, failed to undergo coordination to the tricarbonylchromium(0) moiety under standard conditions. Complexation of (-)-(1*R*,2*S*)-*N*-BOC-ephedrine (**48**) under standard conditions afforded the corresponding tricarbonylchromium(0) complex (-)-(**49**) as 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)tricarbonylchromium(0) (**40**). A molecular ion *m/z*=302 (M^++1) and an elemental analysis confirmed the identity of this new compound.



(-)-(1*R*,2*R*)-(**29**) (+)-(**44**) (+)-(**45**) (**39**) (**46**) (**47**)

Reagents: i) $C_6H_{10}O$, C_6H_6, 45h, 96%. ii) $Cr(CO)_6$, Bu_2O/THF (10:1), 21h, 76%. iii) *p*TsOH, HCl, THF/H_2O (2:1), 15h. iv) 3,4-$(MeO)_2C_6H_3CH_2CHO$ (**19**), CH_2Cl_2, *p*TsOH, sieves, 22h. v) $NaBH_3CN$, HCl, MeOH, 20°C, 6h, 2 steps 24%

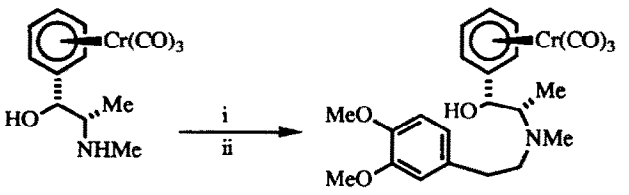


(-)-(1*R*,2*S*)-(**34**) (-)-(1*R*,2*S*)-(**48**) (-)-(**49**) (-)-(**40**)

Reagents: i) $(BOC)_2O$, NEt_3, CH_2Cl_2, 60h, 85%. ii) hexacarbonylchromium(0), Bu_2O/THF (10:1), 48h, 54%. iii) HCOOH, 20°C, 4.5h, quantitative

Treatment of a dichloromethane solution of (-)-(ephedrine)tricarbonylchromium(0) (**40**) with homoveratraldehyde (**19**) in the presence of molecular sieves and *para*-toluenesulphonic acid gave the corresponding oxazolidine complex. Without isolation, this material was reduced with sodium

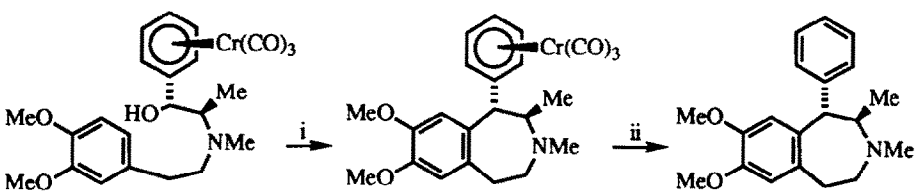
cyanoborohydride to give, after crystallisation, [*N*-(3,4-dimethoxyphenethyl)ephedrine] tricarbonylchromium(0) (**50**).



(-)-(**40**) (**50**)

Reagents: i) 3,4-(MeO)$_2$C$_6$H$_3$CH$_2$CHO (**19**), CH_2Cl_2, *p*TsOH, sieves, 13h, 82%.
ii) $NaBH_3CN$, HCl, MeOH, 20°C, 20h, 91%

A dichloromethane solution of complex (**47**) 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 ^{1}H n.m.r. spectroscopy of the reaction mixture) identified as *trans*-tetrahydrobenzazepine complex (**51**). This assignment was confirmed by subsequent oxidative decomplexation which yielded *trans*-(+)-(1*S*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**) {$[\alpha]_D^{21}$ +5.4° (*c* 1.49 in $CHCl_3$)}. 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 (**50**) under similar conditions failed to give any isolable benzazepine after decomplexation. The lack of cyclisation in this latter case may be a consequence of the developing steric interactions between the *cis*-orientated C1-phenyl and the C2-methyl groups giving rise to a sufficiently high cyclisation transition state energy to permit competing side reactions to predominate.



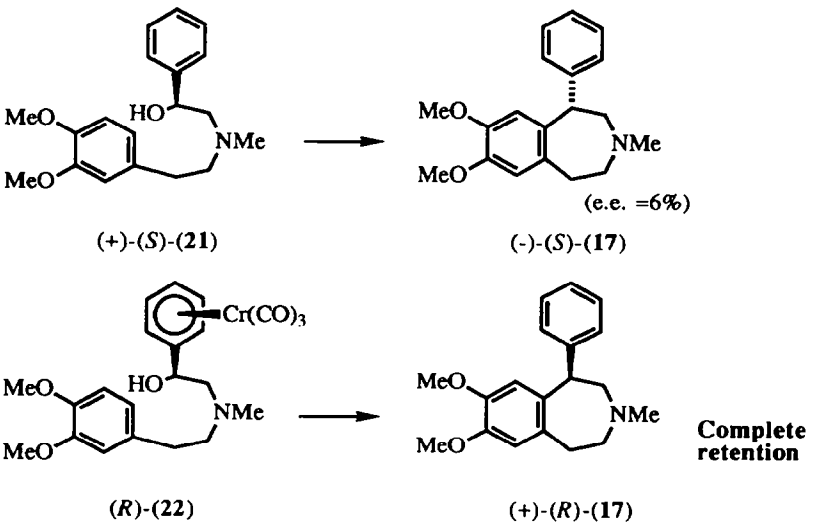
(+)-(**47**) (**51**) (+)-(1*S*,2*R*)-(**37**)

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

The stereoselective cyclisation of complex (+)-(**47**) to (**51**) 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 (**51**).

Summary

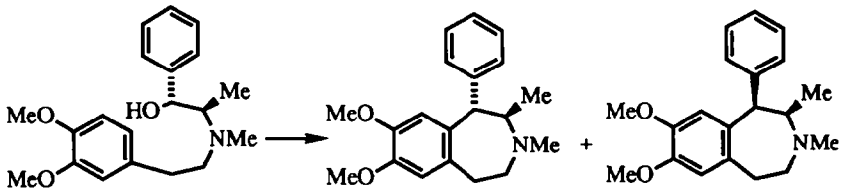
The cyclisation of (+)-(*S*)-*N*-(3,4-dimethoxyphenethyl)halostachine (**21**) occurs *via* two mechanistic pathways, the more important of which involves the formation of a planar benzylic carbocation upon ionisation of the protonated hydroxyl group. This carbocation is trapped from either face with equal preference to give a racemic mixture of 1-phenyl-N-methyl-7,8-dimethoxy benzazepine (**17**). 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 (**21**) to the tricarbonylchromium(0) unit to afford, upon decomplexation, homochiral 1-phenyl benzazepine (+)-(*R*)-(**17**) in the cyclisation of complex (*R*)-(**22**).



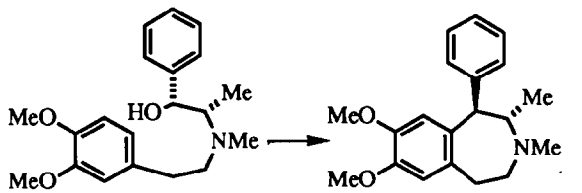
(+)-(*S*)-(**21**) (-)-(*S*)-(**17**)

(*R*)-(**22**) (+)-(*R*)-(**17**)

Cyclisation of both (-)-(1*R*,2*R*)-(**32**) and (-)-(1*R*,2*S*)-(**35**) 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 (**37**) 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 (-)-(**37**) arising from the cyclisation of (-)-(1*R*,2*S*)-(**35**) allows no prediction as to the relative importance of the two mechanisms, whereas in the case of (-)-(1*R*,2*R*)-(**32**) the opposing mechanisms give diastereoisomeric products. The diastereoisomeric excess of 82% observed in the cyclisation of (-)-(**32**) therefore reflects a small degree of cyclisation (9%) *via* the neighbouring group participation mechanism to give *cis*-benzazepine (**38**) as the minor product. Cyclisation of (**47**) [the tricarbonylchromium(0) complex of (-)-(1*R*,2*R*)-(**32**)] is completely stereoselective, occurring with retention of configuration to furnish (+)-(1*S*,2*R*)-(**37**) after decomplexation.

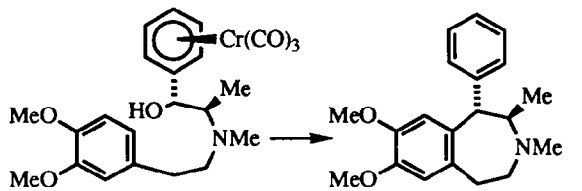


(-)-(1*R*,2*R*)-(**32**) (+)-(1*S*,2*R*)-(**37**) (1*R*,2*R*)-(**38**)



Complete inversion

(-)-(1*R*,2*S*)-(**35**) (-)-(1*R*,2*S*)-(**37**)



Complete retention

Experimental

General experimental procedures - All reactions involving (arene)tricarbonylchromium(0) complexes, their preparation and purification were carried out under a nitrogen atmosphere using standard vacuum line techniques[21] and all solvents were deoxygenated prior to use. 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.[22] Hexacarbonylchromium(0) was purchased from Strem Chemicals and was steam distilled before use. Flash chromatography[23] was performed on SiO_2 (Merck, 40-60μm) and grade V Al_2O_3 refers to alumina (Grade I) 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 using a Bruker AM250 instrument. I.r. spectra were obtained as $CHCl_3$ solutions using a Perkin-Elmer 781 Infrared Spectrophotometer and were calibrated against polystyrene (1601cm^{-1}). A Perkin-Elmer 241 Polarimeter was used to measure optical rotations. 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 hexacarbonylchromium(0) in Bu_2O and THF (ratio 10:1) was heated at reflux under a nitrogen atmosphere until the onset of

decomplexation (10-30h).[20] The cooled solution was filtered and evaporated and the residue subjected to column chromatography. The corresponding tricarbonylchromium(0) 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 or chromatography.

Homoveratraldehyde (19).[13] 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. 62-64°C (lit.[13] 65-66°C); δ_H 6.92-6.74 [3H, m, $(MeO)_2C_6H_3$], 4.06 [1H, d, J 1.7Hz, $(MeO)_2C_6H_3CH$], 3.88 (3H, s, OCH_3), (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.51 (1H, d, J 1.8Hz, CHCOOMe). 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, CHO), 6.89-6.71 [3H, m, $(MeO)_2C_6H_3$], 3.88 (6H, s, $2OCH_3$), 3.63 (2H, d, J 2.5Hz, CH_2CHO); *m/z* 180 (M^+).

3,4-Dimethoxyphenethyl bromide (30).[16] 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 (14).[11] A solution of 3,4-dimethoxyphenethylamine (15.9g, 87.7mmol) and styrene oxide (**15**) (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, PhC**H**(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).

General procedure for the cyclisation of N-(3,4-dimethoxyphenethyl)amino alcohols.

Procedure A. 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 evaporated to furnish the crude cyclised product. Further purification was achieved where necessary in the specified manner.

Procedure B. 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 A. In the case of cyclisations employing precursors coordinated to the tricarbonylchromium(0) 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.

1-Phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (17).[6,11] A solution of 1-phenyl-*N*-(3,4-dimethoxyphenethyl)ethanolamine (**14**) (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[11] 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. 70-72°C (lit.[11] 82-84°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, $(MeO)_2C_6H_3$ $CH_2CH_2N(Me)CH_2$], 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 (**18**) (approximately 1 molar equivalent) gave baseline separation of both methoxyl singlets and the C1 benzylic proton doublet.

N-(3,4-Dimethoxyphenethyl)halostachine (21). A solution of halostachine (**20**)[10,14] (0.101g, 0.67mmol) in CH_2Cl_2 (10ml) was treated with homoveratraldehyde (**19**) (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 $(MeO)_2C_6\mathbf{H}_3$], 4.69 [1H, t, J 7.0Hz, ArC**H**(OH)], 3.90 (3H, s, OC**H**$_3$), 3.87 (3H, s, OC**H**$_3$), 2.87-2.54 [6H, m, $(MeO)_2C_6H_3\mathbf{CH_2CH_2}N(Me)\mathbf{CH_2}$], 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 (**18**) gave partial separation of the C1 benzylic proton of (*R*,*S*)-(**21**).

(+)-(S)-N-(3,4-Dimethoxyphenethyl)halostachine (21). A solution of (+)-(*S*)-halostachine (**20**)[10,14] (0.45g, 2.98mmol) in CH_2Cl_2 (15ml) was treated with homoveratraldehyde (**19**) (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 (2*R*,5*S*)- and (2*S*,5*S*)-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, m.p. 68-69°C; $[\alpha]_D^{20}$ +67.1° (*c* 0.89 in $CHCl_3$); (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%); ν_{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**H**$_3$), 3.87 (3H, s, OC**H**$_3$), 2.87-2.54 [6H, m, $(MeO)_2C_6H_3\mathbf{CH_2CH_2}N(Me)\mathbf{CH_2}$], 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). ^{1}H n.m.r. spectroscopy of the product in the presence of (-)-(*R*)-2,2,2-trifluoro-(9-anthryl)ethanol (**18**) indicated that the product was enantiomerically pure with the C1 benzylic proton resonance appearing at lower field than that for (-)-(*R*)-(**21**).

Cyclisation of (+)-(S)-N-(3,4-Dimethoxyphenethyl)halostachine (21). A solution of (+)-(*S*)-*N*-(3,4-dimethoxyphenethyl)halostachine (**21**) (0.088g, 0.28mmol) in CH_2Cl_2 (10ml) was cyclised according to standard procedure **B** (<-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 (**18**) that indicated that the product [1-phenyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**17**)] possessed an enantiomeric excess of 6% with no unreacted starting material.

(R)-[N-(3,4-Dimethoxyphenethyl)halostachine]tricarbonylchromium(0) (22). A solution of (+)-(*R*)-(halostachine)tricarbonylchromium(0) (**23**) (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, $(MeO)_2C_6H_3$], 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)tricarbonylchromium(0)-N-methyl-7,8-dimethoxy tetrahydrobenzazepine) (24). A solution of (*R*)-[*N*-3,4-dimethoxyphenethyl(halostachine)]tricarbonylchromium(0) (**22**) (0.318g, 0.70mmol) in CH_2Cl_2 (15ml) was cyclised according to standard procedure **B** (<-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, m.p. 151-152°C (decomp.); $[\alpha]_D^{20}$ -148.7° (*c* 0.40 in $CHCl_3$); (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%); $\nu_{max.}$ 1970 and 1895 (C≡O), 1518 (Ar) cm^{-1}; δ_H 6.72 and 6.64 (2H, s, **6H** and **9H**), 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).

(+)-(R)-1-Phenyl-N-methyl-7,8-dimethoxy tetrahydrobenzazepine (17).[6] A solution of (-)-(*R*)-1-(phenyl)tricarbonylchromium(0)-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**24**) (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 (**18**) indicated that it was enantiomerically pure with the *N*-methyl resonance appearing at lower field than that of (-)-(S)-(**17**). A portion of this material was recrystallised from Et_2O/hexane to give a pure sample for characterisation, m.p. 103-104°C; $[\alpha]_D^{20}$ +45.4° (*c* 0.27 in $CHCl_3$), $[\alpha]_D^{18}$ +31.2° (*c* 0.99 in MeOH) [lit.[6] $[\alpha]_D^{25}$ +31.8° (*c* 1.00 in MeOH)]; (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%); $\nu_{max.}$ 1515 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-7.18 (5H, m, Ph), 6.68 and 6.24 (2H, s, **6H** and **9H**), 4.28 (1H, d, J 8.4Hz, PhCH), 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).

(-)-(1R,2R)-N-(3,4-Dimethoxyphenethyl)pseudoephedrine (32). A solution of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) (0.50g, 3.03mmol) and 3,4-dimethoxyphenethyl bromide (**30**) (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 (**31**) 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%), m.p. 61-63°C; $[\alpha]_D^{20}$ -52.8° (*c* 0.60 in $CHCl_3$); (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%); $\nu_{max.}$ 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, ArC**H**(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, C**H**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).

Alternative synthesis: A solution of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) (1.83g, 11.1mmol) and homoveratraldehyde (**19**) (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 (2*R*,4*R*,5*R*)- and (2*S*,4*R*,5*R*)-2-(3,4-dimethoxybenzyl)-*N*-methyl-4-methyl-5-phenyloxazolidine (**33**) as a colourless oil (3.60g, quantitative) (ratio 94:6), $[\alpha]_D^{20}$ -5.6° (*c* 1.48 in $CHCl_3$); (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%); $\nu_{max.}$ 3010 (aryl-H), 1517 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-6.80 [8H, m, Ph and $(MeO)_2C_6H_3$], 4.47 [1H, d, J 8.8Hz, PhC**H**(OH)], 4.37 [1H, dd, J 3.4 and 6.0Hz, $(MeO)_2C_6H_3CH_2CH$], 3.88 (6H, s, $2OCH_3$), 2.98, 2.92 [2H, ABX system, J_{AB} 14.2Hz, J_{AX} 3.4Hz, J_{BX} 6.0Hz, $(MeO)_2C_6H_3CH_2$], 2.37 (1H, dq, J 6.0 and 8.8Hz, C**H**Me), 2.31 (3H, s, NCH_3), 1.13 (3H, d, J 6.1Hz, $CHCH_3$); 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). 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 (35). A solution of (-)-(1*R*,2*S*)-ephedrine (**34**) (1.50g, 9.08mmol) and 3,4-dimethoxyphenethyl bromide (**30**) (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 (**31**) (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, m.p. 94-95°C; $[\alpha]_D^{20}$ -8.7° (*c* 0.71 in $CHCl_3$); (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%); $\nu_{max.}$ 3400br (OH), 3003 (aryl-H), 1515 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.36-6.68 [8H, m, Ph and $(MeO)_2C_6H_3$],

4.79 [1H, d, J 4.3Hz, ArCH(OH)], 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.75-2.67 [4H, m, $(MeO)_2C_6H_3CH_2CH_2$], 2.89 (1H, dq, J 4.4 and 6.9Hz, CHMe), 2.36 (3H, s, NCH_3), 0.90 (3H, d, J 6.9Hz, $CHCH_3$); 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).

Alternative synthesis: A solution of (-)-(1*R*,2*S*)-ephedrine (**34**) (1.83g, 11.1mmol) and homoveratraldehyde (**19**) (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 (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-2-(3,4-dimethoxybenzyl)-*N*-methyl-4-methyl-5-phenyloxazolidine (**36**) as a colourless oil (3.60g, quantitative) (ratio 93:7), $[\alpha]_D^{20}$ -94.1° (*c* 0.75 in $CHCl_3$); (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%); $\nu_{max.}$ 3008 (aryl-H), 1516 (Ar), 700 (mono-substituted arene) cm^{-1}; δ_H 7.37-6.80 [8H, m, Ph and $(MeO)_2C_6H_3$], 5.00 (1H, d, J 7.9Hz, PhCH), 4.04 [1H, dd, J 3.2 and 6.8Hz, $(MeO)_2C_6H_3CH_2CH$], 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_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). 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 (32). A solution of (-)-(1*R*,2*R*)-*N*-(3,4-dimethoxyphenethyl)pseudoephedrine (**32**) (0.22g, 0.67mmol) in CH_2Cl_2 (50ml) was cyclised according to standard procedure **A** (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 (+)-(1*S*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**), m.p. 116-118°C; $[\alpha]_D^{20}$ +2.9° (*c* 0.38 in $CHCl_3$); (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%); $\nu_{max.}$ 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, 6H and 9H), 3.94 (1H, d, J 5.4Hz, PhCH), 3.89 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.75 (1H, qu, 6.1Hz, CHMe), 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^+).

Cyclisation of (-)-(1R,2S)-N-(3,4-dimethoxyphenethyl)ephedrine (35). A solution of (-)-(1*R*,2*S*)-*N*-(3,4-dimethoxyphenethyl)ephedrine (**35**) (0.409g, 1.24mmol) in CH_2Cl_2 (25ml) was cyclised according to standard procedure **A** (40°C, 1.5h) to furnish (-)-(1*R*,2*S*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**) as a white solid (0.33g, 85%). Recrystallisation from Et_2O/hexane gave a pure

sample for characterisation, m.p. 115-117°C; $[\alpha]_D^{20}$ -2.4° (*c* 0.84 in $CHCl_3$); (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%); *m/z* 311 (M^+).

(-)-(1R,2R)-(O-Trimethylsilyl)pseudoephedrine (41). A solution of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) (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.[18] 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), $[\alpha]_D^{20}$ -81.3° (*c* 1.56 in $CHCl_3$); (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%); $\nu_{max.}$ 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, PhC**H**(OH)], 2.68 (1H, dq, J 6.4 and 7.7Hz, C**H**Me), 2.41 (3H, s, NCH_3), 2.08 (1H, br s, N**H**), 0.77 (3H, d, J 6.4Hz, $CHCH_3$), -0.03 [9H, s, $C(CH_3)_3$]; 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).

(-)-(1R,2R)-(N-t-Butoxycarbonyl)pseudoephedrine (42). An externally cooled (<0°C) solution of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) (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, m.p. 66-67°C; $[\alpha]_D^{20}$ -88.1° (*c* 0.97 in $CHCl_3$); (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%); $\nu_{max.}$ 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, PhC**H**(OH)], 4.18 (1H, qu, J 7.1Hz, C**H**Me), 2.73 (3H, s, NCH_3), 1.36 [9H, s, $C(CH_3)_3$], 0.95 (3H, d, J 7.0Hz, $CHCH_3$); 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).

Thermolysis of hexacarbonylchromium(0) with (-)-(1R,2R)-(N-t-butoxycarbonyl)pseudoephedrine (42). (-)-(1*R*,2*R*)-(*N*-*t*-Butoxycarbonyl)pseudoephedrine (**42**) (1.00g, 3.77mmol) and hexacarbonylchromium(0) (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)tricarbonylchromium(0) (**43**) as a yellow solid (0.204g, 17%), m.p. 121-2°C; $[\alpha]_D^{24}$ +36.5° (*c* 0.41 in $CHCl_3$); (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%); $\nu_{max.}$ 1970 and 1900 (C≡O), 1750 (C=O) cm^{-1}; δ_H 5.60-5.31 [6H, m, $(CO)_3CrPh$], 4.64 [1H, d, J 6.4Hz, $(CO)_3CrPhCH$], 3.66 (1H, q, J 6.2Hz, C**H**Me), 2.89 (3H, s, NCH_3), 1.45 (3H, d, J 6.2Hz, $CHCH_3$); *m/z* 328 (M^++1).

Attempted hydrolysis of (+)-(N-methyl-4-methyl-5-phenyloxazolidin-2-one)tricarbonylchromium(0) (43). A solution of (+)-(*N*-methyl-4-methyl-5-phenyloxazolidin-2-one)tricarbonylchromium(0) (**43**) (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% recovery). 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.

(-)-(4R,5R)-2-Cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine (44).[19] A mixture of (-)-(1*R*,2*R*)-pseudoephedrine (**29**) (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 the *title compound* 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, m.p. 69-70°C (lit.[19] 72-72.5°C); $[\alpha]_D^{20}$ -41.7° (*c* 1.21 in $CHCl_3$) [lit.19 $[\alpha]_D^{20}$ +41.3° for opposite enantiomer ($CHCl_3$)]; (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%); $\nu_{max.}$ 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^+).

(+)-(2-Cyclohexyl-N-methyl-4-methyl-5-phenyloxazolidine)tricarbonylchromium(0) (45). A mixture of (-)-(4*R*,5*R*)-2-cyclohexyl-*N*-methyl-4-methyl-5-phenyloxazolidine (**44**) (2.00g, 8.15mmol) and hexacarbonylchromium(0) (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%), m.p. 114-5°C; $[\alpha]_D^{20}$ +156.8 (*c* 0.44 $CHCl_3$); (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%); $\nu_{max.}$ 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, C**H**Me), 2.30 (3H, s, NC**H**$_3$), 1.80-1.40 [10H, m, (C**H**$_2$)$_5$], 1.15 (3H, d, J 6.0Hz, CHC**H**$_3$); *m/z* 382 (M^++1).

(Pseudoephedrine)tricarbonylchromium(0) (39). A solution of (+)-(2-cyclohexyl-*N*-methyl-4-methyl-5-phenyloxazolidine)tricarbonylchromium(0) (**45**) (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 immediately for subsequent reactions. 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)$_3$CrPh], 3.94 [1H, d, J 6.8Hz, (CO)$_3$CrPhC**H**(OH)], 2.59-2.47 (1H, m, C**H**Me), 2.44 (3H, s, NC**H**$_3$), 1.12 (3H, d, J 6.3Hz, CHC**H**$_3$).

(+)-[N-(3,4-Dimethoxyphenethyl)pseudoephedrine]tricarbonylchromium(0) (47). A freshly prepared solution of (pseudoephedrine)tricarbonylchromium(0) (**39**) [prepared from (+)-(2-cyclohexyl-*N*-methyl-4-methyl-5-

phenyloxazolidine)tricarbonylchromium(0) (**45**) (0.381g, 1.00mmol)] in CH_2Cl_2 was treated with homoveratraldehyde (**19**) (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, m.p. 115°C; $[\alpha]_D^{18}$ +50.4° (*c* 0.08 in $CHCl_3$); (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%); $\nu_{max.}$ 1973 and 1900 (C≡O) cm^{-1}; δ_H 6.84-6.73 [3H, m, $(MeO)_2C_6H_3$], 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).

(-)-(1R,2S)-(N-t-Butoxycarbonyl)ephedrine (48). An externally cooled solution (<0°C) of (-)-(1*R*,2*S*)-ephedrine (**34**) (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%), $[\alpha]_D^{20}$ -26.8° (*c* 1.85 in $CHCl_3$); (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%); $\nu_{max.}$ 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, **OH**), 4.57 [1H, dd, J 4.9 and 7.1Hz, $PhCH(OH)$], 4.06 (1H, qu, J 6.9Hz, **CH**Me), 2.64 (3H, s, NCH_3), 1.30 [9H, s, $C(CH_3)_3$], 1.17 (3H, d, J 6.9Hz, $CHCH_3$); 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).

(-)-[(N-t-Butoxycarbonyl)ephedrine]tricarbonylchromium(0) (49). (-)-(1*R*,2*S*)-(*N*-*t*-Butoxycarbonyl) ephedrine (**48**) (20.13g, 75.8mmol) and hexacarbonylchromium(0) (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 yellow powder (16.48g, 54%), m.p. 84°C; $[\alpha]_D^{20}$ -36.2° (*c* 0.07 in $CHCl_3$); (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%); $\nu_{max.}$ 1965 and 1885 (C≡O), 1668 (C=O) cm^{-1}; δ_H {[d]$_6$-dmso (360°K)} 5.77-5.47 [5H, m, $(CO)_3CrPh$], 4.21 [1H, t, J 6.9Hz, $(CO)_3CrPhCH$], 3.93 (1H, qu, J 6.9Hz, **CH**Me), 2.72 (3H, s, NCH_3), 1.34 [9H, s, $C(CH_3)_3$], 1.17 (3H, d, J 6.9Hz, $CHCH_3$); *m/z* 402 (M^++1).

(-)-(Ephedrine)tricarbonylchromium(0) (40). (-)-[(*N*-*t*-Butoxycarbonyl)ephedrine]tricarbonylchromium(0) (**49**) (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, m.p. 92-97°C (decomp.); $[\alpha]_D^{20}$ -33.0° (*c* 0.21 in $CHCl_3$); (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%); $\nu_{max.}$ 1970 and 1885 (C≡O) cm^{-1}; δ_H 5.66-5.16 [5H, m, $(CO)_3CrPh$], 4.46 [1H, d, J 3.4Hz, $(CO)_3CrPhCH(OH)$], 2.72 (1H, dq, 3.4 and 6.5Hz, CHMe), 2.48 (3H, s, NCH_3), 0.93 (3H, d, J 6.5Hz, $CHCH_3$); *m/z* 302 (M^++1).

[N-(3,4-Dimethoxyphenethyl)ephedrine]tricarbonylchromium(0) (50). A solution of (-)-(ephedrine)tricarbonylchromium(0) (**40**) (0.545g, 1.81mmol) in CH_2Cl_2 (15ml) was treated with homoveratraldehyde (**19**) (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 (2*S*,4*S*,5*R*)-2-(3,4-dimethoxybenzyl)-*N*-methyl-4-methyl-5-phenyl[tricarbonylchromium(0)]oxazolidine as a yellow solid (0.685g, 82%), δ_H 6.95-6.81 [3H, m, $(MeO)_2C_6H_3$], 5.29-5.11 [5H, m, $PhCr(CO)_3$], 4.54 [1H, d, J 7.8Hz, $(CO)_3CrPhCH$], 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, CHMe), 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, $(MeO)_2C_6H_3$], 5.55-5.07 [5H, m, $PhCr(CO)_3$], 4.30 [1H, d, J 5.4Hz, $(CO)_3CrPhCH(OH)$], 3.87 (6H, s, $2OCH_3$), 3.05 (1H, br s, OH), 2.74 (1H, dq, 5.9 and 6.7Hz, CHMe), 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] tricarbonylchromium(0) (47). A solution of (+)-[*N*-(3,4-dimethoxyphenethyl)pseudoephedrine]tricarbonylchromium(0) (**47**) (0.072g, 0.15mmol) in CH_2Cl_2 (10ml) was cyclised according to the standard procedure **B** (<-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)tricarbonylchromium(0)-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**51**) as a yellow oil (0.044g, 64%), δ_H 6.75 and 6.61 (2H, s, 6H and 9H), 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, $(CO)_3CrPhCH$], 3.53 (1H, dq J 4.8 and 6.5Hz, CHMe), 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 (+)-(1*S*,2*R*)-1-phenyl-2-methyl-*N*-methyl-7,8-dimethoxy tetrahydrobenzazepine (**37**) as a white powder (0.028g, 95%). Recrystallisation from Et_2O/hexane gave white blocks identical to the previously synthesised sample, m.p. 115°C (this melting point was not depressed when mixed with the previously synthesised sample); $[\alpha]_D^{21}$ +5.4° (*c* 1.49 in $CHCl_3$).

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