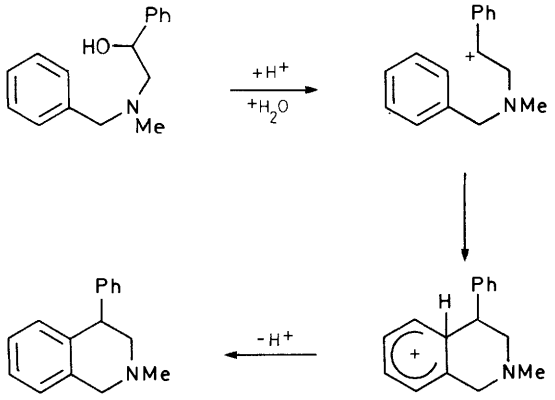
Enantiospecific Synthesis of (+)-(*R*)-6,7-Dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline from (+)-(*S*)-2-Methylamino-1-phenylethanol (Halostachine)

Steven J. Coote,[a] Stephen G. Davies,*[a] David Middlemiss,[b] and Alan Naylor[b]
[a] *The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K.*
[b] *Glaxo Group Research, Ware, Herts, SG12 0DJ, U.K.*

Acid-promoted cyclisation of (+)-(*R*)-*N*-(3,4-dimethoxybenzyl)halostachine tricarbonylchromium at −20 °C is highly stereoselective, proceeding with retention of configuration, to yield, after removal of the tricarbonylchromium unit, homochiral (+)-(*R*)-6,7-dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline. In contrast, cyclisation of (−)-(*R*)-*N*-(3,4-dimethoxybenzyl)halostachine under acidic conditions at −20 °C showed poor stereoselectivity giving predominantly the tetrahydroisoquinoline product corresponding to inversion of configuration, (+)-(*R*)-6,7-dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, with an e.e. of 54%.

The potent pharmacological activity displayed by simple 4-aryl-1,2,3,4-tetrahydroisoquinolines† has stimulated much interest in their synthesis.[1–10] The direct preparation of homochiral 4-aryltetrahydroisoquinolines has not, however, been reported, although a limited number have been resolved by classical procedures.[1–5] In general, the synthesis of 4-aryltetrahydroisoquinolines is accomplished by the biomimetic[11] acid-promoted cyclisation of 2-benzylamino-1-arylethanol (Scheme).[1,3,5–7,10,12–15] If such cyclisations proceed through



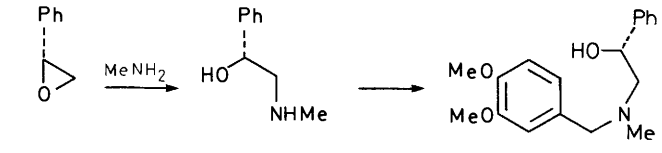
Scheme.

a free carbonium ion then all stereochemical information would be lost: a racemic product would be formed from homochiral starting material. If, however, the benzylamino group acts as a neighbouring group and participates in the ionisation of the benzyl alcohol then stereochemical integrity would be maintained: the cyclisation would be stereospecific with the original chiral centre undergoing inversion of configuration. Thus, starting from a homochiral 2-benzylamino-1-arylethanol, the enantiomeric excess (e.e.) of the product 4-aryltetrahydroisoquinoline will reflect the relative importance of the above two mechanisms for the cyclisation. Furthermore, the complementary stereospecific cyclisation with retention of configuration should be achievable *via* arene tricarbonylchromium methodology.[16] In benzyl alcohol tricarbonylchromium complexes, when the hydroxy group can adopt a conformation close to antiperiplanar to the arene-chromium axis, then retention of configuration has been observed in acid-promoted benzylic substitution reactions.[17] This is consistent with initial inversion to form a configurationally stable carbonium ion and subsequent trapping, again with inversion of configuration, to give overall retention. Furthermore, tricarbonylchromium stabilised benzylic carbonium ions have been trapped intermolecularly with electron-rich arenes.[18]

† The descriptors -1,2,3,4- are omitted henceforth for clarity.

Results

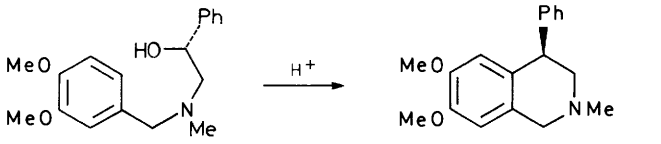
Treatment of homochiral (−)-(*R*)-styrene oxide (−)-(R)-(**1**) with methylamine in ethanol at reflux produced homochiral (−)-(*R*)-halostachine (−)-(*R*)-(**2**) and some 2-methylamino-2-phenylethanol. Similar treatment of racemic styrene oxide (*R,S*)-(**1**) gave racemic halostachine (*R,S*)- (**2**). Treatment of (−)-(*R*)-(**2**) or (*R,S*)-(**2**) with 3,4-dimethoxybenzyl bromide in acetonitrile at reflux in the presence of potassium carbonate yielded pure *N*-3,4-dimethoxybenzylhalostachine (−)-(*R*)-(**3**) and (*R,S*)-(**3**) respectively. The two enantiomers of (*R,S*)-(**3**) were distinguishable by ^{1}H n.m.r. spectroscopy in the presence of the chiral shift reagent (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol[19] which discriminated the benzylic proton [C*H*(OH)] signals. By this criterion (−)-(*R*)-(**3**) appeared to be homochiral.



(−)-(*R*)-(**1**) (−)-(*R*)-(**2**) (−)-(*R*)-(**3**)

Cyclisation of (*R,S*)-(**3**) to (*R,S*)-6,7-dimethoxy-4-phenyl-tetrahydroisoquinoline (*R,S*)-(**4**) was achieved with a mixture of trifluoroacetic acid and concentrated sulphuric acid in dichloromethane at reflux.[20] The ^{1}H n.m.r. spectrum of (*R,S*)-(**4**) exhibited two well separated aromatic singlets corresponding to 5-H and 8-H (indicative of the 6,7-dimethoxy regioisomer), three 3 proton singlets, an ABX and an AB system in addition to a five proton aromatic multiplet. The ^{1}H n.m.r. chiral shift reagent (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol readily distinguished the two enantiomers of (*R,S*)-(**4**), showing well separated signals for both aromatic singlets, for the two methoxys and for the *N*-methyl singlets. Cyclisation of homochiral (*R*)-(**3**) under the same conditions gave (**4**) with an enantiomeric excess of 14%. Cyclisation of homochiral (*R*)-(**3**) under similar conditions but at −20 °C yielded (**4**) with an

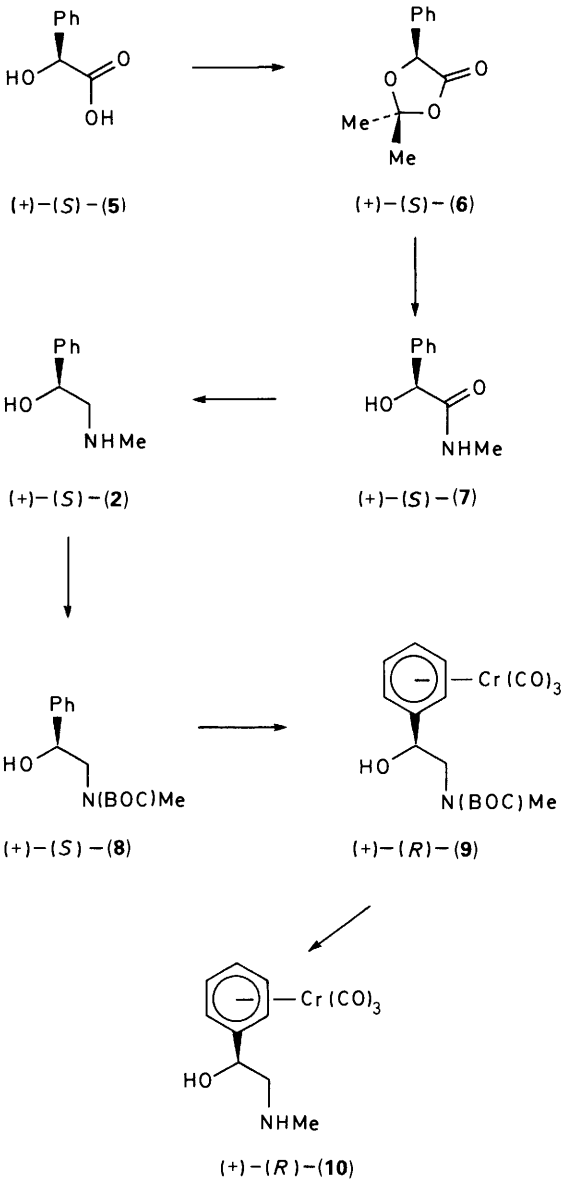
enantiomeric excess of 54%. The enantiomeric excesses of (**4**) were determined by ^{1}H n.m.r. spectroscopy in the presence of (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol, with the *N*-methyl singlets appearing at higher field for the major enantiomer.



(−)-(*R*)-(**3**) (−)-(*R*)-(**4**) −20 °C 54% e.e.
40 °C 14% e.e.

Treatment of (+)-(*S*)-mandelic acid (**5**) with acetone under acid catalysis generated the (+)-(*S*)-dioxolanone derivative (+)-(*S*)-(**6**) which, with methylamine in ethanol, gave *N*-methylmandelamide (+)-(*S*)-(**7**). Reduction of the amide (**7**) with lithium aluminium hydride produced (+)-(*S*)-halostachine (+)-(*S*)-(**2**). Protection of the secondary amine function of halostachine as the t-butoxycarbonyl derivative (+)-(*S*)-(**8**), followed by complexation to tricarbonylchromium under standard conditions,[21] gave complex (+)-(*R*)-(**9**).* *N*-Deprotection of (+)-(*R*)-(**9**) with neat formic acid yielded (+)-(*R*)-halostachine(tricarbonyl)chromium (+)-(*R*)-(**10**).

Treatment of the complex (+)-(*R*)-(**10**) with 3,4-dimethoxybenzyl bromide in dichloromethane gave complex (*R*)-(**11**) as an oil. Cyclisation of complex (*R*)-(**11**) to (*R*)-(**12**) was achieved with tetrafluoroboric acid in dichloromethane at −20 °C for 3 days. The complex (*R*)-(**12**) was fully characterised before oxidative decomplexation afforded (+)-(*R*)-6,7-dimethoxy-4-phenyltetrahydroisoquinoline (+)-(*R*)-(**4**) (e.e. >96%). Recrystallised (+)-(*R*)-(**4**) produced in this way was homochiral according to ^{1}H n.m.r. spectroscopy in the presence of the chiral shift reagent (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Furthermore, use of the chiral shift reagent established that the single enantiomer produced from the complex (+)-(*R*)-(**10**), was the same as the major enantiomer produced in the cyclisation of (−)-(*R*)-(**3**).

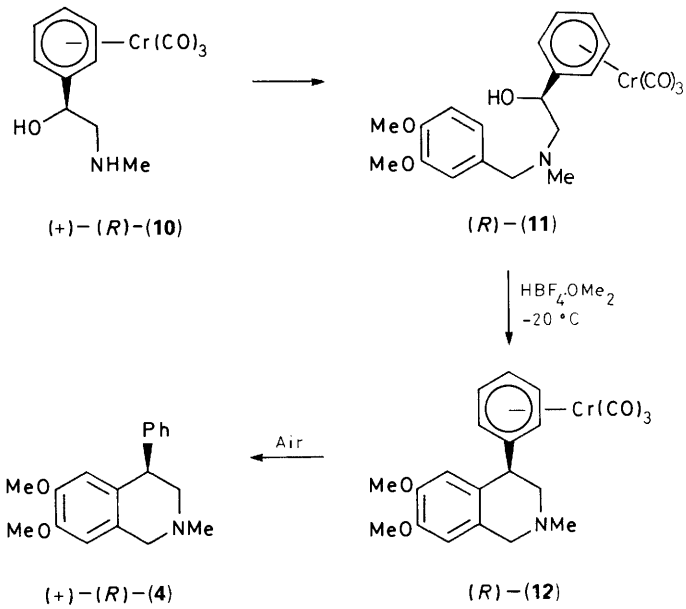


(+)-(*S*)-(**5**) (+)-(*S*)-(**6**)

(+)-(*S*)-(**2**) (+)-(*S*)-(**7**)

(+)-(*S*)-(**8**) (+)-(*R*)-(**9**)

(+)-(*R*)-(**10**)



(+)-(*R*)-(**10**) (*R*)-(**11**)

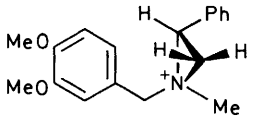
(+)-(*R*)-(**4**) (*R*)-(**12**)

Discussion

The cyclisation of (−)-(*R*)-(**3**), which was derived from (−)-(*R*)-(**2**), at 40 °C proceeds mainly (86%) through an S_N1 mechanism involving an essentially free benzylic carbonium ion, which may be trapped equally well from both sides. A small component (14%) does, however, proceed *via* neighbouring group participation by the dimethoxybenzyl group, which would result in inversion of configuration: the absolute configuration of (*R*)-(**4**) is assigned on this basis. As would be expected, at a lower temperature (−20 °C) the neighbouring group participation mechanism becomes more prominent. Although we have not established details of the mechanism, the probable course of the cyclisation is as follows. Initial protonation of the amine function in the strong acid would prevent participation by the nitrogen lone pair and formation of the aziridinium intermediate (**13**). Moreover, were intermediate (**13**) to be formed it could not be a precursor for (*R*)-(**4**) for stereoelectronic reasons. The cyclisation process itself could proceed, under the influence of the 4-methoxy group, *via* the spiro intermediate (**14**) followed by rearrangement to (**15**).

* The *S*-absolute configuration of compound (**8**) becomes *R* upon coordination to the $Cr(CO)_3$ moiety [compound (**9**)] by definition.

Alternatively, direct cyclisation, under the influence of the 3-methoxy group, is also possible. Literature precedents for both processes are available,[22] and the stereochemical consequences, inversion for the neighbouring group participation manifold, are the same.



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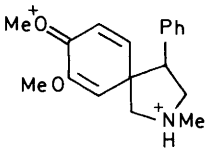

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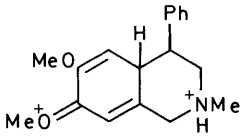

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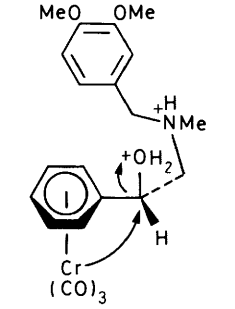
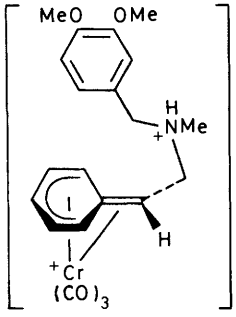


(*R*)-(11)

Inversion



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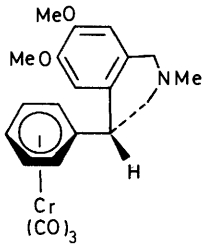
Inversion



(*R*)-(12)

Cyclisation of complex (*R*)-(**11**) derived from (+)-(*S*)-(**2**) was highly stereoselective generating (+)-(*R*)-(**4**). It should be noted that, since the uncomplexed and complexed cyclisation precursors are derived from opposite enantiomers of halostachine and produce predominantly the same enantiomer of product (**4**), then the stereochemical courses of the two processes must be complementary, *i.e.* inversion for the former and retention for the latter. This conclusion, and the assignment of the (*R*)-configuration to (+)-(**4**), is consistent with the expected participation by the chromium in the initial ionisation: the configurationally stable intermediate (**16**) would be formed with inversion with subsequent cyclisation occurring again with inversion to give, overall, retention of configuration.

Experimental

All reactions involving tricarbonyl(η^6-arene)chromium(0) complexes, their preparation and purification were performed under a nitrogen atmosphere using standard vacuum line techniques and deoxygenated solvents. THF was distilled from sodium benzophenone ketyl under nitrogen. Dibutyl ether was dried over sodium and distilled from calcium hydride prior to use. Removal of all solvents was performed under reduced pressure. I.r. spectra were obtained as chloroform solutions on a Perkin-Elmer 781 Infrared Spectrophotometer. Optical rotations were obtained using a Perkin-Elmer 241 Polarimeter. Both ^{1}H n.m.r. and ^{13}C n.m.r. spectra were obtained as [^{2}H]chloroform solutions (unless otherwise stated) at 300 and 62.9 MHz respectively, using Bruker WH300 and Bruker AM250 instruments. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected.

Hexacarbonylchromium, purchased from Strem chemicals, was steam distilled and thoroughly dried prior to use. 3,4-Dimethoxybenzyl bromide was freshly prepared each time by saturation of a benzene solution of 3,4-dimethoxybenzyl alcohol with HBr gas. The resultant solution was stirred (20 °C, 15 min) and calcium carbonate added. The mixture was filtered and evaporated to afford a pale orange oil that solidified with time.

(R,S)-2-*Methylamino*-1-*phenylethanol* (*R,S*)-(**2**).—A stirred solution of styrene oxide (30 ml, 263 mmol) and methylamine (33% solution in ethanol; 50 ml) in ethanol (180 ml) was heated at reflux (6 h) and then concentrated. The residue was distilled under reduced pressure and the lower boiling fraction collected as a colourless oil (<120 °C, 0.1 mmHg), that solidified with time. ^{1}H N.m.r. spectroscopy revealed the presence of both 2-methylamino-1-phenylethanol (*R,S*)-(**2**) and 2-methylamino-2-phenylethanol in the approximate ratio 64:36.[23] Recrystallisation from CH_2Cl_2–hexane at −20 °C afforded the *title compound* as a fluffy white powder (6.57 g, 17%), m.p. 72—73 °C, (lit.,[24] 75—76 °C); δ_H 7.38—7.28 (5 H, m, Ph), 4.76 [1 H, dd, *J* 8.8 and 3.9 Hz, PhC*H*(OH)CH_2], 2.83, 2.74 [2 H, ABX system, J_{AB} 12.1 Hz, J_{AX} 3.9 Hz, J_{BX} 8.8 Hz, PhCH(OH)CH_2], 2.48 (3 H, s, NCH_3), 2.35 (2 H, br s, OH and NH); *m/z* 152 (M^+ + 1).

(R,S)-2-[3,4-*Dimethoxybenzyl*(*methyl*)*amino*]-1-*phenylethanol* (*R,S*)-(**3**).—(*R,S*)-2-Methylamino-1-phenylethanol (*R,S*)-(**2**) (1.00 g. 6.61 mmol) and freshly prepared 3,4-dimethoxybenzyl bromide (1.53 g, 6.62 mmol) in acetonitrile (40 ml) were treated with potassium carbonate (1.83 g, 13.2 mmol) and the mixture was heated at reflux (3 h). The cooled reaction mixture was concentrated, diluted with water (50 ml) and ether (30 ml) and the organic layer separated. The aqueous layer was extracted (Et_2O, 2 × 30 ml) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to give the *title compound* as a colourless oil (1.60 g, 80%); $\nu_{max.}$ 3 420 (OH),

2 840 (OCH_3), and 760 cm^{-1} (mono substituted aromatic); δ_H 7.38—7.34 (5 H, m, Ph), 6.87—6.84 [3 H, m, $(MeO)_2C_6H_3CH_2$], 4.76 [1 H, dd, *J* 10.3 and 3.6 Hz, PhC*H*(OH)CH_2], 3.90 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.70, 3.48 [2 H, AB system, J_{AB} 12.9 Hz, $(MeO)_2C_6H_3CH_2$], 2.61, 2.51 [2 H, ABX system, J_{AB} 12.9 Hz, J_{AX} 10.4 Hz, J_{BX} 3.7 Hz, PhCH(OH)CH_2], 2.34 (3 H, 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, and 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 distinguished between the benzylic proton [C*H*(OH)] of (+)-(*S*)-(**3**) and that of (−)-(*R*)-(**3**).

(−)-(R)-2-[3,4-*Dimethoxybenzyl*(*methyl*)*amino*]-1-*phenylethanol* (−)-(*R*)-(**3**).—A stirred solution of (−)-(*R*)-styrene oxide (−)-(*R*)-(**1**) (7.97 g, 66.3 mmol), methylamine (33% solution in ethanol; 50 ml), and potassium carbonate (3.00 g, 21.7 mmol) in ethanol (80 ml) was heated at reflux (6.5 h) and then concentrated. The residue was distilled under reduced pressure and the lower boiling fraction collected as a viscous, colourless oil (< 110 °C, 0.1 mmHg) (3.87 g, 39%). ^1H N.m.r. spectroscopy revealed the presence of both (−)-(*R*)-2-methylamino-1-phenylethanol (−)-(*R*)-(**2**) and 2-methylamino-2-phenylethanol but all attempts to isolate pure (−)-(*R*)-(**2**) failed.

A solution of this mixture (2.07 g, 13.7 mmol), freshly prepared 3,4-dimethoxybenzyl bromide (1.59 g, 6.88 mmol), and potassium carbonate (1.90 g, 13.7 mmol) in acetonitrile (50 ml) was heated at reflux (3 h). After removal of the solvent, water (100 ml) and CH_2Cl_2 (50 ml) were added and the organic layer separated. The aqueous layer was extracted (CH_2Cl_2, 2 × 50 ml) and the combined extracts were dried ($MgSO_4$). Filtration and evaporation gave an oil that was purified by flash chromatography (SiO_2, Et_2O) to afford the *title compound* as a colourless oil (1.00 g, 48%); $[\alpha]_D^{20}$ −104.07° (*c* 2.17 in $CHCl_3$); $\nu_{max.}$ 3 440 (OH), 3 010 (ArH), 2 840 (OCH_3), 2 800 (NCH_3), and 1 595 and 1 515 cm^{-1} (Ar); δ_H 7.38—7.34 (5 H, m, Ph), 6.87—6.84 [3 H, m, $(MeO)_2C_6H_3CH_2$], 4.76 [1 H, dd, *J* 10.3 and 3.6 Hz, PhC*H*(OH)CH_2], 3.90 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.70, 3.48 [2 H, AB system, J_{AB} 12.9 Hz, $(MeO)_2C_6H_3CH_2$], 2.61, 2.51 [2 H, ABX system, J_{AB} 12.9 Hz, J_{AX} 10.4 Hz, J_{BX} 3.7 Hz, PhCH(OH)CH_2], and 2.34 (3 H, 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, and 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 revealed the presence of a single enantiomer of (−)-(*R*)-(**3**).

(R,S)-6,7-*Dimethoxy*-2-*methyl*-4-*phenyl*-1,2,3,4-*tetrahydroisoquinoline* (*R,S*)-(**4**).—To a stirred solution of (*R,S*)-2-[3,4-dimethoxybenzyl(methyl)amino]-1-phenylethanol (*R,S*)-(**3**) (1.30 g, 4.31 mmol) in CH_2Cl_2 (35 ml) was added concentrated sulphuric acid (0.5 ml) and trifluoroacetic acid (0.5 ml) to give a red colouration. The mixture was heated at reflux (0.5 h) during which time the colour changed from red to blue. Saturated aqueous potassium carbonate was cautiously added to neutralise the acidic reaction mixture and the organic layer separated. The aqueous layer was extracted (CH_2Cl_2; 3 × 50 ml) and the combined extracts were washed (water, 2 × 100 ml), dried ($MgSO_4$), filtered, and evaporated to afford the *title compound* as a pale yellow oil that solidified with time (1.13 g, 92%), m.p. 89—91 °C;[25] $\nu_{max.}$ 3 010 (ArH), 2 940 ($ArCH_2$), 2 840 (OCH_3), 2 790 (NCH_3), 1 600 and 1 510 (Ar), and 700 cm^{-1} (mono substituted arene); δ_H 7.32—7.18 (5 H, m, Ph), 6.57 and 6.34 [2 H, s, $(MeO)_2C_6H_2$], 4.21 [1 H, br t, ArC*H*(Ph)CH_2], 3.86 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 3.66 (2 H, AB system, J_{AB} 14.4 Hz, $ArCH_2$), 3.00, 2.53 [2 H, ABX system, J_{AB} 11.5 Hz, J_{AX} 5.6 Hz, J_{BX} 8.4 Hz, ArCH(Ph)CH_2], 2.42 (3 H, 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, and 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 (*ca.* 1 mol equiv.) gave baseline separation of all three methyl singlets, the two aromatic singlets corresponding to 5-H and 8-H and the benzylic proton multiplet.

An analogous reaction employing homochiral (−)-(*R*)-2-[3,4-dimethoxybenzyl(methyl)amino]-1-phenylethanol (−)-(*R*)-(**3**) gave the *title compound* as a mixture of both (+)-(*R*)-(**4**) and (−)-(*S*)-(**4**). The ^1H n.m.r. spectrum of the crude product in the presence of (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol revealed an enantiomeric excess of 14% in favour of (+)-(*R*)-(**4**).

Treatment of a CH_2Cl_2 (25 ml) solution of (−)-(*R*)-2-[3,4-dimethoxybenzyl(methyl)amino]-1-phenylethanol (−)-(*R*)-(**3**) (0.215 g, 0.713 mmol) with HBF_4•OMe_2 (0.5 ml) at low temperature (< −20 °C) for 69 h, and subsequent work-up, similarly gave the *title compound* as a mixture of both (+)-(*R*)-(**4**) and (−)-(*S*)-(**4**) (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 revealed an enantiomeric excess of 54% in favour of (+)-(*R*)-(**4**).

(+)-(S)-2,2-*Dimethyl*-5-*phenyl*-1,3-*dioxolan*-4-*one* (+)-(*S*)-(**6**).—A stirred solution of (+)-(*S*)-1-hydroxyphenylacetic acid (+)-(*S*)-(**5**) (14.6 g, 96.0 mmol) in acetone (44 ml, 599 mmol) was externally cooled (< −10 °C) and treated dropwise with concentrated sulphuric acid (5.3 ml) at a rate sufficient to maintain a reaction temperature of below −10 to −5 °C, resulting in the formation of a white precipitate. The mixture was poured into ice-cold aqueous sodium carbonate (20 g in 180 ml) and the resultant precipitate collected by filtration. The white solid thus obtained was washed with ice-cold water (150 ml) and dried under reduced pressure to give the crude dioxolanone as a fluffy white powder. Recrystallisation from hot ethanol gave the *title compound* as long, slender needles (14.77 g, 80%), $[\alpha]_D^{20}$ +55.43° (*c* 2.63 in CCl_4) {lit.,[26] $[\alpha]_D^{20}$ +52.7° (*c* 2.0 in CCl_4)}; m.p. 71—72 °C (lit.,[26] 71 °C); $\nu_{max.}$ 3 010 (ArH), 1 788 (C=O), 1 384 and 1 377 (CH_3), 1 125 (C–O), and 690 cm^{-1} (mono substituted arene); δ_H 7.50—7.36 (5 H, m, Ph), 5.41 (1 H, s, PhCH), 1.74 (3 H, s, CH_3), 1.69 (3 H, s, CH_3); δ_C 172.11, 134.23, 128.91, 128.62, 126.10, 111.29, 72.20, and 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* (+)-(*S*)-(**7**).—A solution of (+)-(*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-one (+)-(*S*)-(**6**) (14.77 g, 76.8 mmol) in ethanol (45 ml) was treated with methylamine (33% in ethanol; 45 ml) and the mixture stirred (20 °C, 2 h). The reaction mixture was filtered and evaporated to afford the *title compound* as a white solid (12.33 g, 97%). Recrystallisation from hot benzene gave a pure sample for characterisation; $[\alpha]_D^{20}$ +55.51° (*c* 1.34 in Me_2CO), m.p. 96—99 °C (lit.,[27,28] 94—95 °C); $\nu_{max.}$ 3 440 (NH), 3 380 (OH), 3 010 (ArH), 1 673 and 1 540 (C=O), and 700 cm^{-1} (mono substituted arene); δ_H 7.35—7.25 (5 H, m, Ph), 6.83 (1 H, br s, OH), 5.04 (1 H, br s, NH), 4.85 [1 H, s, PhC*H*(OH)], and 2.62 and 2.61 [3 H, s, C(O)NHC*H*$_3$, two amide conformers]; δ_C 173.84, 139.88, 128.63, 128.36, 127.54, 127.07, 126.85, 73.93, and 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)-2-*Methylamino*-1-*phenylethanol* (+)-(*S*)-(**2**).—A stirred suspension of lithium aluminium hydride (12.5 g, 329 mmol) in THF (150 ml) under a nitrogen atmosphere was treated dropwise with a THF solution (100 ml) of (+)-(*S*)-*N*-

methyl-1-hydroxyphenylacetamide (+)-(*S*)-(**7**) (12.33 g, 74.6 mmol) and the mixture stirred (20 °C, 1 h). The reaction mixture was heated at reflux (17.5 h) and the cooled solution cautiously treated with water (12.5 ml) and sodium hydroxide (15% w/w in water; 12.5 ml). Water (37.5 ml) 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 with time (11.44 g, 92%). Distillation under reduced pressure (99—102 °C, 0.1 mmHg) afforded an analytically pure sample; $[\alpha]_D^{20}$ +40.41° (*c* 1.89 in EtOH) {lit.,[28] $[\alpha]_D^{25}$ +37.43° (*c* 2.37 in EtOH)}; m.p. 39—40 °C (lit.,[24,28] 43—45 °C); $\nu_{max.}$ 3 380 and 3 330 (OH and NH), and 700 cm^{-1} (mono substituted arene); δ_H 7.38—7.28 (5 H, m, Ph), 4.76 [1 H, dd, *J* 8.8 and 3.9 Hz, PhC*H*(OH)CH_2], 2.83, 2.74 [2 H, ABX system, J_{AB} 12.1 Hz, J_{AX} 3.9 Hz, J_{BX} 8.8 Hz, PhCH(OH)CH_2], 2.48 (3 H, s, NCH_3), and 2.35 (2 H, br s, OH and NH); δ_C 143.64, 128.45, 127.50, 127.07, 125.94, 71.63, 59.25, and 35.70; *m*/*z* 152 ($M^+ + 1$).

(+)-(S)-2-[*t-Butoxycarbonyl(methyl)amino*]-1-*phenylethanol* (+)-(*S*)-(**8**).—An externally cooled (< 0 °C) solution of (+)-(*S*)-2-methylamino-1-phenylethanol (+)-(*S*)-(**2**) (8.85 g, 58.5 mmol) in CH_2Cl_2 (70 ml) was treated with di-t-butyl dicarbonate (15 ml, 65.3 mmol) and triethylamine (8.2 ml, 58.8 mmol) and the solution set aside (20 °C, 15.5 h). The solution was acidified with saturated aqueous citric acid, and the organic layer separated, washed sequentially with aqueous sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), filtered, and evaporated to give a colourless oil. This was distilled under reduced pressure (130—132 °C, 0.1 mmHg) to give the *title compound* as a viscous oil that solidified with time (13.07 g, 89%); $[\alpha]_D^{20}$ +50.18° (*c* 1.28 in $CHCl_3$), m.p. 59—60 °C; $\nu_{max.}$ 3 400 (OH), 3 005 (ArH), 1 680 (C=O), and 700 cm^{-1} (mono substituted arene); δ_H {[^{2}H]$_6$-DMSO (360 K)} 7.35—7.21 (5 H, m, Ph), 5.15 [1 H, d, *J* 4.6 Hz, PhCH(O*H*)], 4.76 [1 H, m, PhC*H*(OH)CH_2], 3.38, 3.28 [2 H, ABX system, J_{AB} 13.9 Hz, J_{AX} 5.3 Hz, J_{BX} 7.4 Hz, PhCH(OH)CH_2], 2.79 (3 H, s, NCH_3), and 1.37 [9 H, s, C$(CH_3)_3$]; δ_C 142.54, 128.49, 127.65, 125.97, 80.26, 73.56, 57.40, 36.26, and 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)-*Tricarbonyl*{η^6-2-[*t-butoxycarbonyl(methyl)amino*]-1-*phenylethanol*}*chromium*(0) (+)-(*R*)-(**9**).—A deoxygenated mixture of (+)-(*S*)-2-[t-butoxycarbonyl(methyl)amino]-1-phenylethanol (+)-(*S*)-(**8**) (0.50 g, 1.99 mmol) and hexacarbonylchromium (0.50 g, 2.27 mmol) in dibutyl ether (40 ml) and THF (6 ml) was heated at reflux under a nitrogen atmosphere (22 h). The solution was cooled, filtered through a plug of Al_2O_3 (Grade V, CH_2Cl_2), and evaporated to leave a yellow oil. Crystallisation of this from CH_2Cl_2–hexane gave the *title compound* as a yellow powder (0.488 g, 63%), $[\alpha]_D^{23}$ +8.97° (*c* 0.2 in $CHCl_3$); m.p. 105—106 °C; $\nu_{max.}$ 3 370 (OH), 1 975 and 1 890 (C≡O), 1 680 (C=O), and 708 cm^{-1} (mono substituted arene); δ_H {[$^2H_6$]-DMSO (360 K)} 5.76—5.60 [5 H, m, PhCr(CO)$_3$], 5.50 [1 H, d, *J* 5.7 Hz, PhCr(CO)$_3$CH(O*H*)], 4.44 [1 H, m, PhCr(CO)$_3$C*H*(OH)CH_2], 3.42, 3.29 [2 H, ABX system, J_{AB} 14.0, J_{AX} 5.0, J_{BX} 7.1 Hz, PhCr(CO)$_3$CH(OH)CH_2], 2.86 (3 H, s, NCH_3), and 1.37 [9 H, 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)-*Tricarbonyl*(η^6-2-*methylamino*-1-*phenylethanol*)-*chromium*(0) (+)-(*R*)-(**10**).—(+)-(*R*)-Tricarbonyl{η^6-2-[t-butoxycarbonyl(methyl)amino]-1-phenylethanol}chromium(0) (+)-(*R*)-(**9**) (0.498 g 1.29 mmol) dissolved in formic acid (98—100%; 15 ml) was thoroughly degassed and the solution stirred under a nitrogen atmosphere (20 °C, 5 h). The mixture was concentrated, treated with sodium hydroxide (2M; 50 ml) and CH_2Cl_2 (30 ml) was added. The organic layer was separated and the aqueous layer extracted (CH_2Cl_2; 2 × 30 ml). The combined extracts were evaporated to afford the *title compound* as a yellow solid (0.352 g, 95%). Recrystallisation from Et_2O–hexane gave an analytically pure sample, $[\alpha]_D^{20}$ +40.19° (*c* 0.264 in $CHCl_3$); m.p. 94—98 °C (decomp.); $\nu_{max.}$ 1 975 and 1 890 cm^{-1} (C≡O); δ_H 5.60—5.31 [5 H, m, PhCr(CO)$_3$], 4.40 [1 H, dd, *J* 3.5 and 8.9 Hz, PhCr(CO)$_3$C*H*(OH)CH_2], 2.85, 2.70 [2 H, ABX system, J_{AB} 12.2 Hz, J_{AX} 3.4 Hz, J_{BX} 8.8 Hz, PhCr(CO)$_3$CH(OH)CH_2], 2.48 (3 H, s, NCH_3), and 1.60 (2 H, 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)-*Tricarbonyl*{η^6-2-[3,4-*dimethoxybenzyl*(*methyl*)*amino*]-1-*phenylethanol*}*chromium*(0) (*R*)-(**11**).—(+)-(*R*)-Tricarbonyl-(η^6-2-methylamino-1-phenylethanol)chromium(0) (+)-(*R*)-(**10**) (0.281 g, 0.978 mmol) was added to a solution of freshly prepared 3,4-dimethoxybenzyl bromide (0.226 g, 0.978 mmol) in CH_2Cl_2 (30 ml) and the yellow solution stirred under a nitrogen atmosphere (20 °C, 38.5 h). The mixture was neutralised with aqueous potassium carbonate and the organic layer separated. The aqueous layer was extracted (CH_2Cl_2, 2 × 30 ml) and the combined extracts were evaporated to leave a yellow gum. This on column chromatography [Al_2O_3 Grade V, Et_2O–petroleum (1:1)] gave the *title compound* as a yellow oil (0.155 g, 36%). All attempts to crystallise the product failed; δ_H 6.82 [3 H, br s, $(MeO)_2C_6H_3$], 5.54—5.27 [5 H, m, PhCr(CO)$_3$], 4.37 [1 H, dd, *J* 4.1 and 10.0 Hz, PhCr(CO)$_3$C*H*(OH)CH_2], 3.89 [6 H, s, $(CH_3O)_2C_6H_3$], 3.68, 3.48 [2 H, AB system, J_{AB} 12.9 Hz, $(MeO)_2C_6H_3CH_2$], 2.58, 2.53 [2 H, ABX system, J_{AB} 12.9 Hz, J_{AX} 10.2 Hz, J_{BX} 4.1 Hz, PhCr(CO)$_3$CH(OH)CH_2], 2.34 (3 H, s, NCH_3), and 1.62 (1 H, br s, OH); *m*/*z* 438 ($M^+ + 1$).

(R)-*Tricarbonyl*(η^6-6,7-*dimethoxy*-2-*methyl*-4-*phenyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (*R*)-(**12**).—To an externally cooled (< −20 °C) solution of (*R*)-tricarbonyl{η^6-2-(3,4-dimethoxybenzyl)methylamino]-1-phenylethanol}chromium(0) (R)-(**11**) (0.136 g, 0.311 mmol) under a nitrogen atmosphere in CH_2Cl_2 (10 ml) was added HBF_4·OMe_2 (0.5 ml) and the solution set aside (< −20 °C, 72 h). The yellow solution was basified with saturated aqueous sodium hydrogen carbonate, and the organic layer separated and filtered through a short plug of Al_2O_3 (Grade V, CH_2Cl_2). Evaporation afforded the *title compound* as a yellow oil (0.088 g, 67%) that could not be crystallised; δ_H 6.91 and 6.56 [2 H, s, $(MeO)_2C_6H_2$], 5.68—4.95 [5 H, m, PhCr(CO)$_3$], 3.89 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.79, 3.26 [2 H, AB system, J_{AB} 14.6 Hz, $(MeO)_2C_6H_2CH_2$], 3.72 [1 H, br s, $(MeO)_2C_6H_2CH$], 2.92, 2.76 [2 H, ABX system, J_{AB} 11.9 Hz, J_{AX} 2.2 Hz, J_{BX} 4.2 Hz, $(MeO)_2C_6H_2CHCH_2$], and 2.36 (3 H, s, NCH_3); *m*/*z* 419 (M^+) (Found: M^+, 419.0820. $C_{21}H_{12}CrNO_5$ requires M^+, 419.0825).

(+)-(R)-6,7-*Dimethoxy*-2-*methyl*-4-*phenyl*-1,2,3,4-*tetrahydroisoquinoline* (+)-(*R*)-(**4**).—A yellow solution of (*R*)-tricarbonyl(η^6-6,7-dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (*R*)-(**12**) (0.088 g, 0.210 mmol) in Et_2O (15 ml) was exposed to air and sunlight (48 h) to give a deep red colouration that reverted to yellow out of sunlight. When the solution had become colourless, the precipitated chromium salts were removed by filtration (Celite) and the filtrate evaporated to leave the *title compound* as a white powder (0.058 g, 98%). Recrystallisation from Et_2O–hexane gave an analytically pure sample as colourless needles,[25] $[\alpha]_D^{20}$ +16.93 (*c* 0.116 in $CHCl_3$); m.p. 109—110 °C; $\nu_{max.}$ 3 019 (ArH), 1 514 (Ar), and 702 cm^{-1} (mono substituted arene); δ_H 7.32—7.18

(5 H, m, Ph), 6.57 and 6.34 [2 H, s, $(MeO)_2C_6H_2$], 4.21 [1 H, br t, $ArCH(Ph)CH_2$], 3.86 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 3.66 (2 H, AB system, J_{AB} 14.4 Hz, $ArCH_2$), 3.00, 2.53 [2 H, ABX system, J_{AB} 11.5 Hz, J_{AX} 5.6 Hz, J_{BX} 8.4 Hz, $ArCH(Ph)CH_2$], and 2.42 (3 H, 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, and 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 revealed the enantiomeric excess of (+)-(*R*)-(**4**) to be greater than 96%, whilst that of the recrystallised material appeared to be homochiral by this criterion.

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