HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 765 - 777. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 20th June, 2013, Accepted, 29th July, 2013, Published online, 31st July, 2013
DOI: 10.3987/COM-13-S(S)39

REGIO- AND STEREOSELECTIVE DERIVATISATION OF AN APORPHINE SCAFFOLD†

Jonathan D. M. Atkinson, Stephen G. Davies,* and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford,
Mansfield Road, Oxford, OX1 3TA, U.K.

Abstract – Treatment of 10,11-dimethoxyaporphine with chromium hexacarbonyl was found to give two diastereoisomeric products on regioselective co-ordination of the chromium tricarbonyl fragment to the A ring. For one of the diastereoisomeric complexes, alkylation was found to proceed with high regio- and diastereoselectivity at C(4), whereas regio- and diastereoselective alkylation was observed at C(6a) for the other diastereoisomer. In the case of the C(4)- and C(6a)-methylated products, these substrates were decomplexed in high yield to give the corresponding enantiopure, C(4)- and C(6a)-methyl substituted aporphines.

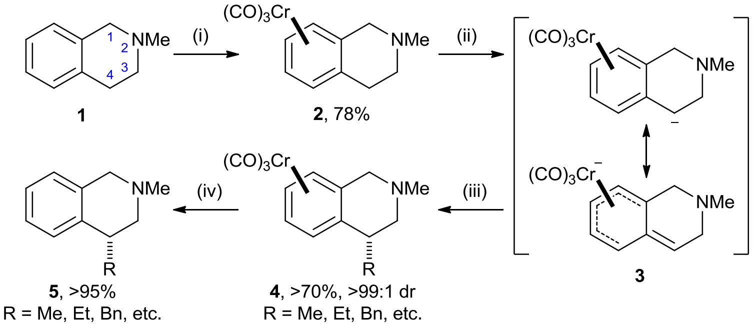
Interest in apomorphine is associated with its activity as a dopaminergic agonist and its consequential anti-Parkinsonian activity.[1] Clinical utility has been demonstrated for apomorphine alone, and in combination with other agents such as levodopa.[2] Additionally, potential uses of apomorphine in ameliorating the symptoms of Huntingdon's chorea, tardive dyskinesia Gilles de la Tourette's syndrome and schizophrenia have been indicated.[3] (–)-(*R*)-Apomorphine, which is synthesised commercially by the acid catalysed rearrangement of (–)-morphine, has been shown to display dopamine agonist activity,[4] whilst its antipode (+)-(*S*)-apomorphine, which is a known dopamine antagonist, is accessible via resolution of the racemate.[5] Molecular modelling studies have shown that the apomorphine-like spatial arrangement of the catechol ring, the nitrogen atom and the nitrogen lone pair (or N–*H* atom in the case of the corresponding ammonium ions) is required for dopamine agonist activity;[6] these findings were consistent with observed biological activities,[7] and this has made the apomorphine ring system an attractive scaffold for studying the effect of structure on dopamine receptor activity. Previous work concerning the modification of this ring

---

* Corresponding Author. E-mail: steve.davies@chem.ox.ac.uk
† Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

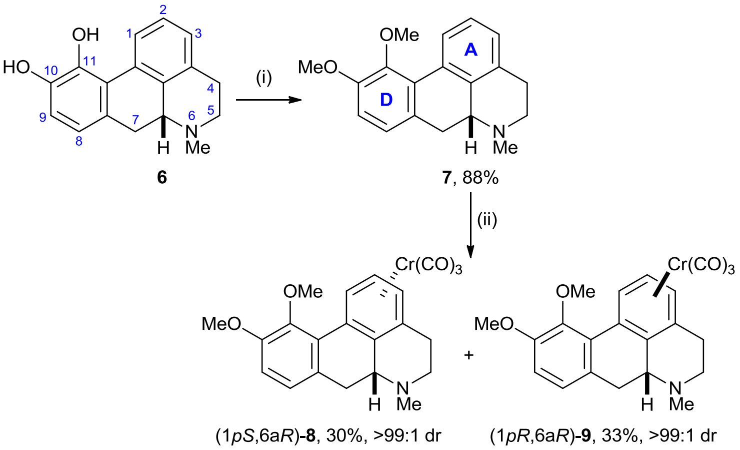
system has largely focused on manipulation of either the aromatic rings or nitrogen functionality.[8] A unique procedure for the regio- and stereoselective functionalisation of this scaffold at either the C(4)- or C(6a)-benzylic positions by manipulation of the corresponding arene chromium tricarbonyl complexes is reported herein.

As part of our extensive research programme concerning the utility of arene chromium tricarbonyl complexes in stereoselective synthesis,[9] we have previously investigated the regio- and stereoselective functionalisation of *N*(2)-methyltetrahydroisoquinolines.[10] For example, thermolysis of $Cr(CO)_6$ with **1** generated the corresponding arene chromium tricarbonyl complex **2** in 78% yield. Regioselective deprotonation of **2** at the C(4) position with BuLi, followed by treatment of the resultant chromium stabilised benzylic anion **3** (deep red colour) with a range of electrophiles (e.g., MeI, EtI, BnBr, etc.) proceeded with high diastereoselectivity, with reaction occurring on the uncomplexed face in all cases. Oxidative decomplexation upon standing solutions of the substituted complexes **4** in Et_2O and exposing them to air and sunlight generated the corresponding 4-substituted-*N*(2)-methyltetrahydroisoquinolines **5** in high yield (Scheme 1).



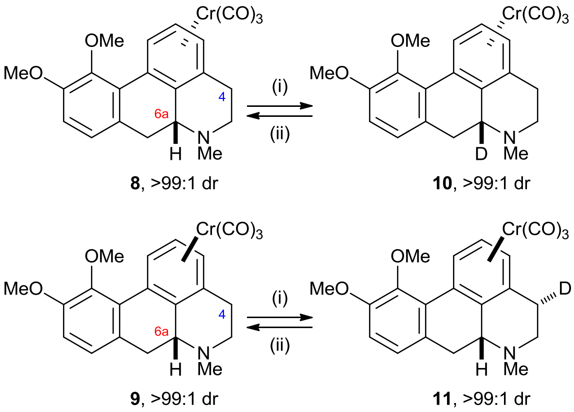
Scheme 1. *Reagents and conditions:* (i) $Cr(CO)_6$, Bu_2O/THF (10:1), reflux, 29 h; (ii) BuLi, THF, –78 °C, 2 h; (iii) RX, THF, –78 °C, 2 h; (iv) O_2, *hν*, Et_2O.

Attempted thermolysis of $Cr(CO)_6$ with apomorphine **6** in a 10:1 mixture of Bu_2O and THF resulted in degradation of the chromium reagent and no complexation to **6** was observed. The catechol functionality within **6** was therefore masked by conversion to 10,11-dimethoxyaporphine **7** upon treatment with freshly prepared diazomethane[5a,b] which gave **7** in 88% isolated yield. Thermolysis of $Cr(CO)_6$ with **7**, under our standard complexation conditions, afforded only two of the possible four products which were both attributable to binding of the chromium to the A ring within **7**. After chromatographic purification both **8** and **9** were isolated as single diastereoisomers (>99:1 dr) in 30 and 33% yield, respectively (Scheme 2). The regioselectivity of this reaction was initially assigned by ^1H NMR spectroscopic analysis: in both cases the ^1H NMR spectra of **8** and **9** contained three aromatic resonances which had all been shifted upfield by ~2 ppm, indicating that **8** and **9** were related as diastereoisomers. The relative configurations within (1*pS*,6a*R*)-**8** and (1*pR*,6a*R*)-**9** were determined by a series of derivatisation experiments and these assignments were subsequently confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative of (1*pS*,6a*R*)-**8**.



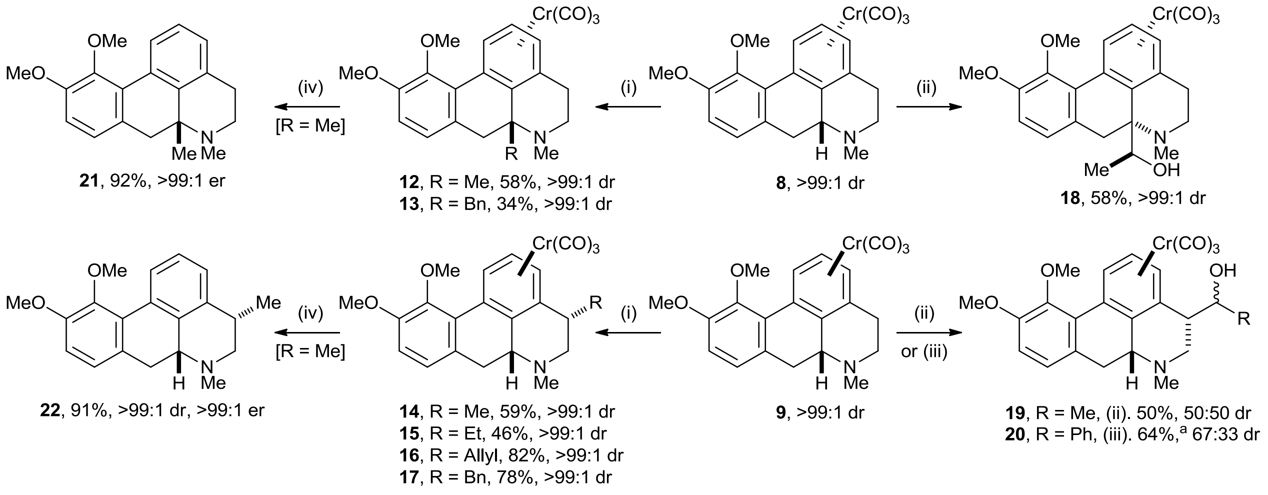
Scheme 2. *Reagents and conditions:* (i) CH_2N_2 (in Et_2O), MeOH, rt, 26 h; (ii) $Cr(CO)_6$, Bu_2O/THF (10:1), reflux, 15 h.

It was predicted that deprotonation of either **8** or **9** (both >99:1 dr) with BuLi would proceed to give the corresponding chromium stabilised benzylic anions, resulting from deprotonation of either the C(4)*H* or C(6a)*H* protons. Indeed, treatment of **8** and **9** with BuLi, followed by treatment of the deep red solutions of the corresponding anionic species with MeOH-d_4 generated the C(6a)- and C(4)-deuterio substituted complexes **10** and **11**, respectively, with high regio- and diastereoselectivity. Subsequent metalation of either deuterated complex **10** or **11** with BuLi, followed by treatment with MeOH, liberated the parent complexes **8** and **9**, respectively, in quantitative yield (Scheme 3).



Scheme 3. *Reagents and conditions:* (i) BuLi, THF, –78 °C, 1 h then MeOH-d_4; (ii) BuLi, THF, –78 °C, 1 h then MeOH.

The regio- and diastereoselective alkylation of these complexes was investigated next. In the case of **8**, deprotonation with BuLi at –78 °C, followed by treatment with MeI produced C(6a)-methyl substituted complex **12** in 58% yield and >99:1 dr. Analogous treatment of **9** produced C(4)-methyl substituted complex **14** in 59% yield and >99:1 dr. A series of other regio- and diastereoselective alkylations also gave **13** and **15**–**17** as single diastereoisomers (>99:1 dr). The carbanions generated upon deprotonation of **8** and **9** with BuLi were next treated with aldehydes. In the case of the carbanion derived from **9** being reacted with acetaldehyde, substitution occurred as expected at the C(4) position to give a 50:50 mixture of two inseparable diastereoisomeric alcohols **19** which were isolated in 50% combined yield. Analogous reaction of the anion derived from **9** with benzaldehyde produced a 67:33 mixture of epimeric alcohols **20** which were isolated in 42 and 22% yield, respectively. However, reaction of the anion derived from **8** with acetaldehyde produced a single diastereoisomeric product **18** which was isolated in 58% yield and >99:1 dr (Scheme 4). The relative configuration within **18** was unambiguously established by single crystal X-ray diffraction analysis (Figure 1);[11] furthermore, the determination of a Flack *x* parameter[12] of 0.004(6) for the crystal structure of **18** confirmed the absolute (1*pS*,6a*R*,1'*S*)-configuration within **18**. This analysis therefore also confirmed the assigned configurations within complexes **8** and **9**. Representative decomplexation reactions were carried out on the C(4)- and C(6a)-methyl substituted complexes **12** and **14**: in both cases, exposing solutions of these complexes in Et_2O to air and sunlight gave the corresponding enantiopure, C(4)- and C(6a)-methyl substituted aporphines **21** and **22** in ≥91% yield (Scheme 4).



Scheme 4. *Reagents and conditions:* (i) BuLi, THF, –78 °C, 1 h then RX, –78 °C to rt, 2 h; (ii) BuLi, THF, –78 °C, 1 h then MeCHO, –78 °C, 1 h; (iii) BuLi, THF, –78 °C, 1 h then PhCHO, –78 °C, 1 h;
(iv) O_2, *h*ν, Et_2O. [a combined isolated yield].

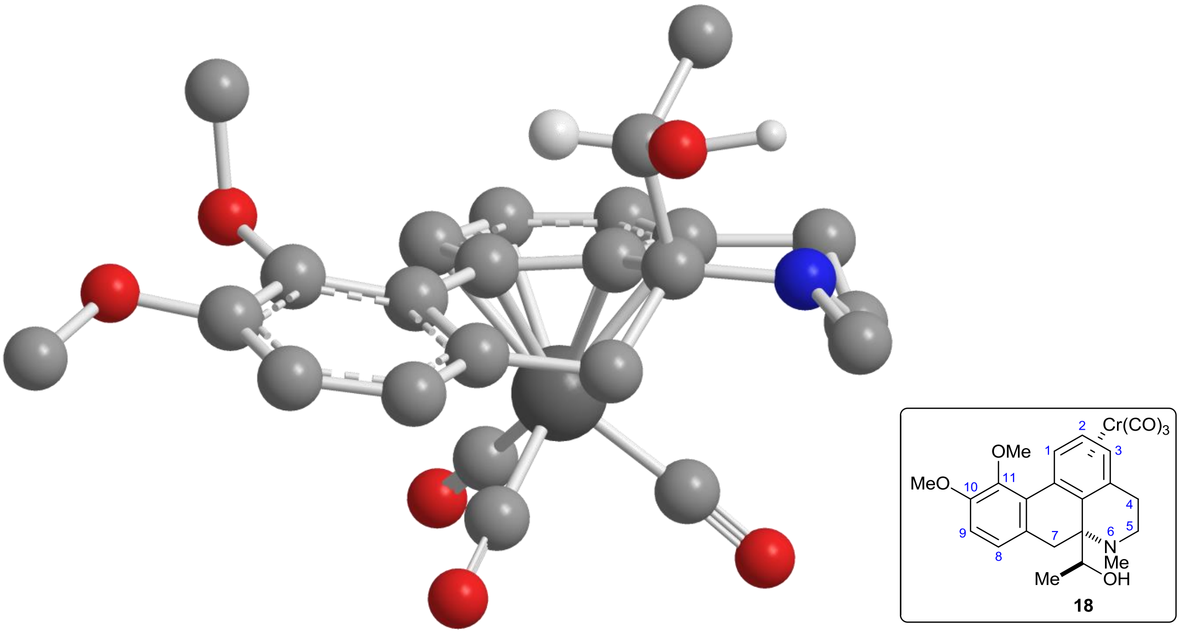


Figure 1. X-Ray crystal structure of (1*pS*,6a*R*,1'*S*)-**18** (selected H atoms are omitted for clarity). X-Ray crystal structure data for **18** [$C_{24}H_{25}CrNO_6$]: M = 475.46, orthorhombic, $P2_12_12_1$, a = 8.942(1) Å, b = 12.108(1) Å, c = 20.545(4) Å, V = 2224 Å^3, Z = 4, μ = 46.29 mm^{-1}, colourless block, crystal dimensions = 0.4 × 0.4 × 0.8 mm^3. A total of 1804 unique reflections were measured for $1 < \theta < 24$ and 1645 reflections were used in the refinement. The final parameters were wR_2 = 0.044 and R_1 = 0.035 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.004(6).[12] CCDC 945389.

The formation of **8** and **9** as the only complexes observed upon thermolysis of $Cr(CO)_6$ with **7** was initially unexpected. Within **7** there are four possible sites for complexation: the A ring and the D ring are each able to present two diastereotopic faces for complexation, giving rise to four possible products in which one chromium tricarbonyl unit is bound to an arene. Despite the prediction that the rate of complexation to the more electron rich D ring within **7** would be faster,[13,14] the regioselectivity observed upon thermolysis of $Cr(CO)_6$ with **7**, where both products **8** and **9** are attributable to binding of the chromium to the electron poor A ring, can be rationalised by inspection of crystallographic data for **18** and similar structures[15] (all containing a 3,4-dimethoxy-9,10-dihydrophenanthrene **23** sub unit). These data reveal that a dihedral angle of ~25° for C(4)–C(4a)–C(4b)–C(5) (i.e., the angle of tilt about the biphenyl bond) is typically observed, and that the C(4)-methoxy group is oriented out of the plane of the aromatic ring [the dihedral angle of the C(4a)–C(4)–O–*C*H_3 bond is normally between 80° and 100°]. In this sort of conformation the C(11)-methoxy group within **7** cannot mesomerically donate electrons into the aromatic ring and exerts a purely inductive electron withdrawing effect; the rate of complexation to the D ring is therefore slower than might initially be expected (Figure 2). The relative configurations within the C(4)- and C(6a)-substituted complexes **10**–**20** were initially assigned following the regioselective deprotonation of complexes **8** and **9**: for both **8** and **9**, the increased acidity of the benzylic protons may be rationalised by considering the configurations of these complexes, with deprotonation occurring from the uncomplexed face in each case.

For **8**, the *exo*-C(6a)–H bond lies antiperiplanar to the chromium arene-centroid axis giving rise to the chromium stabilised conjugate base, whereas for **9** it is the *exo*-C(4)–H bond that lies antiperiplanar to the chromium arene-centroid axis (Figure 2); these findings are consistent with the well known requirement for *exo*-benzylic C–H bonds to be antiperiplanar to the chromium arene-centroid axis to achieve regio- and diastereoselective deprotonation.[16] These structural analyses are also consistent with the solid state conformation of **18** and the experimentally determined outcomes observed upon deuteration of **8** and **9**, and dedeuteration of **10** and **11**, in which regioselective (and, in the case of **9** and **11**, diastereoselective) deprotonation occurs to give the corresponding chromium stabilised benzylic anions. In all cases, retention of configuration was observed upon reaction of the chromium stabilised benzylic anions with the requisite electrophiles.

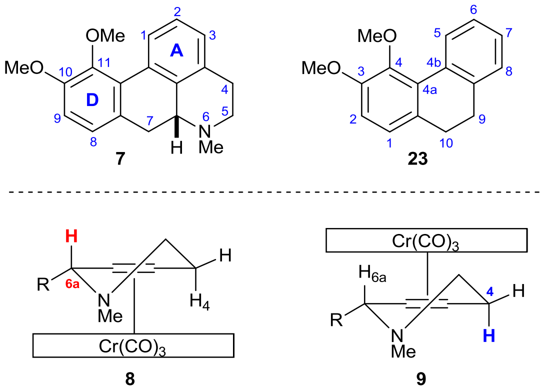


Figure 2. Conformational analyses of 10,11-dimethoxyaporphine **7** and arene chromium tricarbonyl complexes **8** and **9**.

In conclusion, the complexation of 10,11-dimethoxyaporphine with $Cr(CO)_3$ enabled a series of diastereoisoselective transformations to be carried out at either the C(4)- or C(6a)-positions with high levels of regio- and diastereoselectivity, with alkylation occurring on the uncomplexed face in each case. Following the decomplexation of two representative methyl substituted complexes, (*R*)-6a-methyl-10,11-dimethoxyaporphine and (4*S*,6a*R*)-4-methyl-10,11-dimethoxyaporphine were isolated in high yield as single stereoisomers.

EXPERIMENTAL

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi (as a solution in hexanes) was titrated against diphenylacetic acid before use. Solvents were rigorously deoxydenated before use. THF was dried over sodium benzophenone ketyl and freshly distilled before use. Bu_2O and CH_2Cl_2 were dried over CaH_2 and freshly distilled before use.

$Cr(CO)_6$ was steam distilled and sublimed under reduced pressure before use. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Perkin-Elmer 781 spectrometer as solutions in CH_2Cl_2 using 1.0 mm cells. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. Mass spectra were recorded on a VG MicromassMM30F spectrometer.

(*R*)-10,11-Dimethoxyaporphine 7: A freshly prepared solution of (*R*)-apomorphine **6** (1.01 g, 3.78 mmol) in deoxygenated MeOH (40 mL) was treated with a solution of diazomethane in Et_2O, generated from *N*-methyl-*N*-(*p*-tolylsulfonyl)nitrosamide (5.66 g, 26.4 mmol) and KOH (1.35 g, 24.1 mmol). The reaction mixture was allowed to stand until all the unconsumed diazomethane had evapourated (~14 h), and the reaction mixture was then concentrated *in vacuo*. The residue was dissolved in Et_2O (50 mL) and the resultant solution was washed sequentially with 5.0 M aq KOH (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was then dried and concentrated *in vacuo* to give **7** as an orange oil (990 mg, 88%);[5a,b] δ_H (400 MHz, $CDCl_3$) 2.59 (3H, s, N*Me*), 2.53–2.63 (2H, m, C(5)H_A, C(7)H_A), 2.78 (1H, dd, *J* 16.5, 3.6, C(4)H_A), 3.06–3.27 (4H, m, C(4)H_B, C(5)H_B, C(6a)*H*, C(7)H_B), 3.71 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 6.83 (1H, d, *J* 8.2, C(9)*H*), 7.00 (1H, d, *J* 8.2, C(8)*H*), 7.10 (1H, d, *J* 7.6, C(3)*H*), 7.26 (1H, dd, *J* 7.9, 7.6, C(2)*H*), 8.24 (1H, d, *J* 7.9, C(1)*H*).

(1*pS*,6a*R*)- and (1*pR*,6a*R*)-10,11-Dimethoxyaporphine[tricarbonylchromium(0)] 8 and 9: A solution of **7** (845 mg, 2.86 mmol) and $Cr(CO)_6$ (757 mg, 3.44 mmol) in a mixture of Bu_2O/THF (10:1, 50 mL) was heated at reflux for 15 h in the dark. The reaction mixture was then allowed to cool to rt, filtered through a pad of celite (eluent Et_2O), and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/Et_2O, 1:1) and subsequent recrystallisation (hexane/Et_2O) gave (1*pS*,6a*R*)-**8** as a yellow crystalline solid (371 mg, 30%, >99:1 dr); $[\alpha]_D^{25}$ −245.7 (*c* 1.3 in CH_2Cl_2); ν_{max} 1959, 1882 (CO); δ_H (400 MHz, $CDCl_3$) 2.43 (1H, app dt, *J* 12.1, 4.0, C(5)H_A), 2.53 (3H, s, N*Me*), 2.54 (1H, ddd, *J* 12.1, 5.7, 2.9, C(5)H_B), 2.82–2.89 (2H, m, C(6a)*H*, C(7)H_A), 3.02 (1H, ddd, *J* 11.9, 5.7, 1.2, C(4)H_A), 3.12–3.21 (2H, m, C(4)H_B, C(7)H_B), 3.79 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 5.12 (1H, d, *J* 6.1, C(3)*H*), 5.61 (1H, dd, *J* 6.9, 6.1, C(2)*H*), 6.40 (1H, d, *J* 6.9, C(1)*H*), 6.88 (1H, d, *J* 8.2, C(9)*H*), 6.96 (1H, d, *J* 8.2, C(8)*H*); *m/z* (CI^+) 431 ($[M]^+$, 100%); HRMS (CI^+) $C_{22}H_{21}CrNO_5^+$ ($[M]^+$) requires 431.0819; found 431.0820. Further elution (eluent Et_2O/MeOH, 19:1) and subsequent recrystallisation (hexane/Et_2O) gave (1*pR*,6a*R*)-**9** as a yellow crystalline solid (408 mg, 33%, >99:1 dr); $[\alpha]_D^{25}$ +260.0 (*c* 0.6 in CH_2Cl_2); ν_{max} 1958, 1881 (CO); δ_H (400 MHz, $CDCl_3$) 2.53 (3H, s, N*Me*), 2.53–2.62 (3H, m, C(7)H_A, C(5)H_2), 3.07–3.14 (2H, m, C(4)H_A, C(6a)*H*), 2.96 (1H, ddd, *J* 11.6, 6.0, 2.2, C(4)H_B), 3.22 (1H, dd, *J* 13.2, 4.0, C(7)H_B), 3.90 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 5.33 (1H, d, *J* 6.6, C(3)*H*), 5.41 (1H, dd, *J* 6.7, 6.6, C(2)*H*), 6.62 (1H, d, *J* 6.7, C(1)*H*), 6.87 (1H, d, *J* 8.3, C(9)*H*), 6.93 (1H, d, *J* 8.3, C(8)*H*); *m/z* (CI$^+$) 431 ([M]$^+$, 100%); HRMS (CI$^+$) $C_{22}H_{21}CrNO_5^+$ ([M]$^+$) requires 431.0819; found 431.0820.

(1*pS*,6a*R*)-6a-Deuterio-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 10: BuLi (1.64 M, 0.75 mL, 1.23 mmol) was added to a solution of **8** (110 mg, 0.26 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH-d_4 (2 mL) was then added, the reaction mixture was stirred at –78 °C for 1 h, and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **10** as a yellow solid (106 mg, 96%, >99:1 dr); Anal. Calcd for $C_{22}H_{20}DCrNO_5$: C, 61.1; H, 5.1; N, 3.2%. Found C, 61.1; H, 4.8; N, 3.05%; ν_{max} 1959, 1882 (CO); δ_H (400 MHz, $CDCl_3$) 2.44 (1H, app td, *J* 12.1, 3.9, C(5)H_A), 2.52 (3H, s, N*Me*), 2.56 (1H, ddd, *J* 7.4, 3.9, 1.4, C(5)H_B), 2.85 (1H, d, *J* 14.2, C(7)H_A), 3.02 (1H, ddd, *J* 12.0, 6.2, 1.4, C(4)H_A), 3.16 (1H, d, *J* 14.2, C(7)H_B), 3.17 (1H, ddd, *J* 12.0, 7.4, 6.2, C(4)H_B), 3.79 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 5.13 (1H, d, *J* 5.6, C(3)*H*), 5.62 (1H, dd, *J* 6.9, 5.6, C(2)*H*), 6.40 (1H, d, *J* 6.9, C(1)*H*), 6.88 (1H, d, *J* 8.3, C(9)*H*), 6.96 (1H, d, *J* 8.3, C(8)*H*); *m/z* (CI$^+$) 433 ([M+H]$^+$, 100%).

(1*pR*,4*S*,6a*R*)-4-Deuterio-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 11: BuLi (1.64 M, 1.1 mL, 1.80 mmol) was added to a solution of **9** (151 mg, 0.35 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH-d_4 (2 mL) was then added, the reaction mixture was stirred at –78 °C for 1 h, and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **11** as a yellow solid (148 mg, 98%, >99:1 dr); Anal. Calcd for $C_{22}H_{20}DCrNO_5$: C, 61.1; H, 5.1; N, 3.2%. Found C, 61.4; H, 5.1; N, 3.4%; ν_{max} 1958, 1881 (CO); δ_H (400 MHz, $CDCl_3$) 2.53 (3H, s, N*Me*), 2.55–2.62 (3H, m, C(5)H_2, C(7)H_A), 2.96 (1H, dd, *J* 10.4, 5.3, C(4)*H*), 3.11 (1H, dd, *J* 14.3, 4.0, C(6a)*H*), 3.22 (1H, dd, *J* 13.2, 4.0, C(7)H_B), 3.90 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 5.33 (1H, d, *J* 6.5, C(3)*H*), 5.42 (1H, dd, *J* 6.6, 6.5, C(2)*H*), 6.61 (1H, d, *J* 6.6, C(1)*H*), 6.87 (1H, d, *J* 8.3, C(9)*H*), 6.93 (1H, d, *J* 8.3, C(8)*H*); *m/z* (CI$^+$) 433 ([M+H]$^+$, 100%).

(1*pS*,6a*R*)-6a-Methyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 12: BuLi (1.4 M in hexanes, 1.3 mL, 1.82 mmol) was added to a solution of **8** (95 mg, 0.22 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeI (1.0 mL, 16.1 mmol) was then added, the reaction mixture was stirred at –78 °C for 2 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **12** as a yellow solid (58 mg, 58%, >99:1 dr); Anal. Calcd for $C_{23}H_{23}CrNO_5$: C, 62.0; H, 5.2; N, 3.1%. Found C, 62.0; H, 5.6; N, 2.95%; $[\alpha]_D^{25}$ −292.4 (*c* 0.7 in CH_2Cl_2); ν_{max} 1957, 1880 (CO); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, s, C(6a)*Me*), 2.52 (3H, s, N*Me*), 2.40–3.20 (6H, m, C(4)H_2, C(5)H_2, C(7)H_2), 3.78 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 5.15 (1H, d, *J* 6.0, C(3)*H*), 5.62 (1H, dd, *J* 6.0, 5.8, C(2)*H*), 6.47 (1H, d, *J* 5.8, C(1)*H*), 6.86 (1H, d, *J* 8.4, C(9)*H*), 6.93 (1H, d, *J* 8.4, C(8)*H*); *m/z* (CI^+) 446 ($[M+H]^+$, 100%), 445 ($[M]^+$, 80%).

(1*pS*,6a*R*)-6a-Benzyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 13: BuLi (1.6 M in hexanes, 0.90 mL, 1.44 mmol) was added to a solution of **8** (93 mg, 0.22 mmol, >99:1 dr) in THF (30 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. BnBr (1.0 mL, 8.41 mmol) was then added, the reaction mixture was stirred at −78 °C for 1 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/Et_2O, 1:1) gave **13** as a yellow solid (38 mg, 34%, >99:1 dr); $[\alpha]_D^{20}$ −143.4 (*c* 0.4 in $CHCl_3$); ν_{max} 1957, 1882 (CO); δ_H (400 MHz, $CDCl_3$) 2.00–2.34 (2H, m, C(5)H_2), 2.63 (3H, s, N*Me*), 2.72 (2H, s, CH_2Ph), 2.94–3.06 (3H, m, C(4)H_2, C(7)H_A), 3.38 (1H, d, *J* 14.9, C(7)H_B), 3.87 (3H, s, O*Me*), 3.93 (3H, s, O*Me*), 5.00 (1H, d, *J* 6.6, C(3)*H*), 5.56 (1H, dd, *J* 6.7, 6.6, C(2)*H*), 6.70–6.75 (2H, m, *Ph*), 6.80 (1H, d, *J* 6.7, C(1)*H*), 6.90 (1H, d, *J* 7.9, C(9)*H*), 6.99 (1H, d, *J* 7.9, C(8)*H*), 7.08–7.15 (3H, m, *Ph*); *m/z* (CI^+) 552 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{29}H_{27}CrNO_5^+$ ($[M]^+$) requires 521.1289; found 521.1294.

(1*pR*,4*S*,6a*R*)-4-Methyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 14: BuLi (1.4 M in hexanes, 0.30 mL, 0.42 mmol) was added to a solution of **9** (89 mg, 0.21 mmol, >99:1 dr) in THF (30 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. MeI (1.0 mL, 16.1 mmol) was then added, the reaction mixture was stirred at −78 °C for 2 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **14** as a yellow solid (54 mg, 59%, >99:1 dr); Anal. Calcd for $C_{23}H_{23}CrNO_5$: C, 62.0; H, 5.2; N, 3.1%. Found C, 61.7; H, 5.4; N, 3.2%; $[\alpha]_D^{25}$ +211.2 (*c* 0.4 in CH_2Cl_2); ν_{max} 1958, 1880 (CO); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 7.0, C(4)*Me*), 2.48 (3H, s, N*Me*), 2.56 (1H, app t, *J* 4.1, C(6a)*H*), 2.68 (2H, app s, C(5)H_2), 2.75 (1H, app q, *J* 7.0, C(4)*H*), 3.09 (1H, dd, *J* 13.0, 4.1, C(7)H_A), 3.17 (1H, dd, *J* 13.0, 4.1, C(7)H_B), 3.90 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 5.33 (1H, d, *J* 6.5, C(3)*H*), 5.42 (1H, dd, *J* 6.6, 6.5, C(2)*H*), 6.61 (1H, d, *J* 6.6, C(1)*H*), 6.86 (1H, d, *J* 8.3, C(9)*H*), 6.92 (1H, d, *J* 8.3, C(8)*H*); *m/z* (CI^+) 446 ($[M+H]^+$, 100%).

(1*pR*,4*S*,6a*R*)-4-Ethyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 15: BuLi (1.6 M in hexanes, 0.50 mL, 0.80 mmol) was added to a solution of **9** (80 mg, 0.19 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. EtI (0.15 mL, 1.88 mmol) was then added, the reaction mixture was stirred at –78 °C for 1 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/Et_2O, 1:1) gave **15** as a yellow solid (39 mg, 46%, >99:1 dr); Anal. Calcd for $C_{24}H_{25}CrNO_5$: C, 62.7; H, 5.5; N, 3.05%. Found C, 63.0; H, 5.7; N, 3.0%; $[\alpha]_D^{20}$ +191.3 (*c* 0.5 in CH_2Cl_2); ν_{max} 1957, 1879 (CO); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.4, C(2')*H*$_3$), 1.67–2.02 (2H, qd, *J* 7.4, 6.2, C(1')*H*$_2$), 2.49 (3H, s, N*Me*), 2.40–2.61 (2H, m), 2.90–3.23 (4H, m), 3.91 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 5.36 (1H, d, *J* 6.6, C(3)*H*), 5.44 (1H, dd, *J* 6.6, 6.2, C(2)*H*), 6.64 (1H, d, *J* 6.2, C(1)*H*), 6.86 (1H, d, *J* 8.2, C(9)*H*), 6.94 (1H, d, *J* 8.2, C(8)*H*); *m/z* (CI^+) 460 ($[M+H]^+$, 100%).

(1*pR*,4*S*,6a*R*)-4-Allyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 16: BuLi (1.4 M in hexanes, 0.50 mL, 0.70 mmol) was added to a solution of **9** (70 mg, 0.16 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. Allyl iodide (0.6 mL, 6.54 mmol) was then added, the reaction mixture was stirred at –78 °C for 1 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/Et_2O, 1:9) gave **16** as a yellow solid (63 mg, 82%, >99:1 dr); Anal. Calcd for $C_{25}H_{25}CrNO_5$: C, 63.7; H, 5.3; N, 3.0%. Found C, 63.4; H, 5.45; N, 2.8%; ν_{max} 1958, 1880 (CO); δ_H (400 MHz, $CDCl_3$) 0.88 (2H, dd, *J* 10.5, 4.8, C(1')*H*$_2$), 2.47 (3H, s, N*Me*), 2.56–2.87 (4H, m), 3.06–3.25 (2H, m), 3.91 (3H, s, O*Me*), 4.00 (3H, s, O*Me*), 5.10–5.17 (2H, m, C(3')*H*$_2$), 5.36–5.39 (2H, m, C(2)*H*, C(3)*H*), 5.92–5.95 (1H, m, C(2')*H*), 6.64 (1H, d, *J* 5.2, C(1)*H*), 6.87 (1H, d, *J* 8.2, C(9)*H*), 6.94 (1H, d, *J* 8.2, C(8)*H*); *m/z* (CI^+) 471 ($[M]^+$, 100%).

(1*pR*,4*S*,6a*R*)-4-Benzyl-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 17: BuLi (1.4 M in hexanes, 0.60 mL, 0.84 mmol) was added to a solution of **9** (98 mg, 0.23 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. BnBr (1.0 mL, 16.1 mmol) was then added, the reaction mixture was stirred at –78 °C for 1 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **17** as a yellow solid (92 mg, 78%, >99:1 dr); Anal. Calcd for $C_{29}H_{27}CrNO_5$: C, 66.8; H, 5.2; N, 2.7%. Found C, 67.1; H, 5.3; N, 2.6%; ν_{max} 1960, 1886 (CO); δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, N*Me*), 2.54–2.81 (5H, m), 2.95–2.31 (3H, m), 3.92 (3H, s, O*Me*), 4.01 (3H, s, O*Me*), 5.15 (1H, d, *J* 6.6, C(3)*H*), 5.36 (1H, app t, *J* 6.6, C(2)*H*), 6.64 (1H, d, *J* 6.6, C(1)*H*), 6.89 (1H, d, *J* 8.3, C(9)*H*), 6.97 (1H, d, *J* 8.3, C(8)*H*), 7.20–7.40 (5H, m, *Ph*); *m/z* (CI^+) 521 ($[M]^+$, 100%).

(1*pS*,6a*R*,1'*S*)-6a-(1'-Hydroxyethyl)-10,11-dimethoxyaporphine[tricarbonylchromium(0)] 18: BuLi (1.6 M in hexanes, 0.50 mL, 0.80 mmol) was added to a solution of **8** (162 mg, 0.38 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeCHO (0.40 mL, 7.16 mmol) was then added, the reaction mixture was stirred at –78 °C for 1 h, then MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt. The reaction mixture was then filtered through a pad of celite (eluent Et_2O) and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/Et_2O, 1:1) gave **18** as a yellow solid (103 mg, 58%, >99:1 dr); $[\alpha]_D^{25}$ –157.0 (*c* 1.0 in CH_2Cl_2); ν_{max} 3500–2800 (O–H), 1957, 1880 (CO); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.3, C(2')H_3), 2.50 (1H, dt, *J* 15.6, 3.4, C(5)H_A), 2.73 (3H, s, N*Me*), 2.86–3.15 (3H, m, C(4)H_2, C(5)H_B), 3.20 (1H, d, *J* 15.2, C(7)H_A), 3.44 (1H, d, *J* 15.2, C(7)H_B), 3.68 (1H, q, *J* 6.3, C(1')*H*), 3.79 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 5.24 (1H, d, *J* 6.2, C(3)*H*), 5.58 (1H, app t, *J* 6.5, C(2)*H*), 6.85 (1H, d, *J* 8.3, C(9)*H*), 6.86 (1H, d, *J* 6.8, C(1)*H*), 6.98 (1H, d, *J* 8.3, C(8)*H*); *m/z* (CI^+) 476 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{24}H_{25}CrNO_6^+$ ($[M]^+$) requires 475.1082; found 475.1087.

(*R*)-6a-Methyl-10,11-dimethoxyaporphine 21: A solution of **12** (58 mg, 0.13 mmol, >99:1 dr) in Et_2O (10 mL) was exposed to air and sunlight until a colourless solution containing a green precipitate was evident. The reaction mixture was then filtered through celite (eluent Et_2O) and concentrated *in vacuo* to give **21** as a pale orange oil (37 mg, 92%, >99:1 er); $[\alpha]_D^{25}$ –135.9 (*c* 0.3 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, C(6a)*Me*), 2.51 (3H, s, N*Me*), 2.53–3.25 (6H, m, C(4)H_2, C(5)H_2, C(7)H_2), 3.70 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 6.82 (1H, d, *J* 8.2, C(9)*H*), 6.95 (1H, d, *J* 8.2, C(8)*H*), 7.07 (1H, d, *J* 7.6, C(3)*H*), 7.23 (1H, dd, *J* 7.8, 7.6, C(2)*H*), 8.27 (1H, d, *J* 7.8, C(1)*H*); *m/z* (CI^+) 309 ($[M]^+$, 100%); HRMS (CI^+) $C_{20}H_{23}NO_2^+$ ($[M]^+$) requires 309.1723; found 309.1726.

(4*S*,6a*R*)-4-Methyl-10,11-dimethoxyaporphine 22: A solution of **14** (57 mg, 0.13 mmol, >99:1 dr) in Et_2O (10 mL) was exposed to air and sunlight until a colourless solution containing a green precipitate was evident. The reaction mixture was then filtered through celite (eluent Et_2O) and concentrated *in vacuo* to give **22** as a pale orange oil (36 mg, 91%, >99:1 dr, >99:1 er); $[\alpha]_D^{25}$ –123.2 (*c* 1.9 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.1, C(4)*Me*), 3.32–2.58 (4H, m, C(4)*H*, N*Me*), 2.69 (1H, dd, *J* 11.3, 3.6, C(5)H_A), 2.79 (1H, d, *J* 11.3, C(5)H_B), 2.92–2.98 (1H, m, C(7)H_A), 3.04–3.13 (3H, m, C(6a)*H*, C(7)H_B), 3.72 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 6.83 (1H, d, *J* 8.2, C(9)*H*), 6.99 (1H, d, *J* 8.2, C(8)*H*), 7.14 (1H, d, *J* 7.5, C(3)*H*), 7.28 (1H, dd, *J* 7.8, 7.5, C(2)*H*), 8.25 (1H, d, *J* 7.8, C(1)*H*); *m/z* (CI^+) 309 ($[M]^+$, 100%); HRMS (CI^+) $C_{20}H_{23}NO_2^+$ ($[M]^+$) requires 309.1723; found 309.1726.

ACKNOWLEDGEMENTS

The authors would like to thank David Watkin and Alison Edwards for assistance with X-ray crystal structure determination.

REFERENCES AND NOTES

1. P. J. Davis, S. Seyhan, W. Soine, and R. V. Smith, *J. Pharm. Sci.*, 1980, **69**, 1056.
2. R. J. Borgman, R. J. Baldessarini, and K. G. Walton, *J. Med. Chem.*, 1976, **19**, 717.
3. C. A. Tamminga, M. H. Schaffer, R. C. Smith, and J. M. Davis, *Science*, 1978, **200**, 567.
4. (a) S. G. Holtzman and G. F. Steinfels, *Pharmacol. Biochem. Behavior*, 1994, **47**, 575; (b) C. K. Mak, M. Avalos, P. K. Randall, S.-W. Kwan, C. W. Abell, J. L. Neumeyer, R. Whisennand, and R. Wilcox, *Neuropharmacol.*, 1996, **35**, 549.
5. (a) J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, 1970, **59**, 1850; (b) J. L. Neumeyer, B. Neustadt, K. Oh, K. Weinhardt, C. Boyce, F. Rosenberg, and D. Teiger, *J. Med. Chem.*, 1973, **16**, 1223; (c) Y. Gao, V. J. Ram, A. Campbell, N. S. Kula, R. J. Baldessarini, and J. L. Neumeyer, *J. Med. Chem.*, 1990, **33**, 39; (d) W. S. Saari, S. W. King, and V. J. Lotti, *J. Med. Chem.*, 1973, **16**, 171.
6. I. Pettersson and T. Liljefors, *Computer Aided Mol. Design*, 1987, **1**, 143.
7. (a) C. Kaiser and T. Jain, *Med. Res.*, 1985, **Q5**, 145; (b) W. S. Saari, S. W. King, V. J. Lotti, and A. Scriabine, *J. Med. Chem.*, 1974, **17**, 1086; (c) M. Froimowitz and R. J. Baldessarini, *J. Pharm. Sci.*, 1987, **76**, 557.
8. (a) J. G. Cannon, P. Mohan, J. Bojarski, J. P. Long, R. K. Bhatnagar, P. A. Leonard, J. R. Flynn, and T. K. Chatterjee, *J. Med. Chem.*, 1988, **31**, 313; (b) R. A. Abramovitch, P. Chinnasamy, K. Evertz, and G. Huttner, *J. Chem. Soc., Chem. Commun.*, 1989, 3; (c) S. Ramsby, J. L. Neumeyer, D. Grigoriadis, and P. Seeman, *J. Med. Chem.*, 1989, **32**, 1198; (d) J. G. Cannon, H. Jackson, J. P. Long, P. Leonard, and R. K. Bhatnagar, *J. Med. Chem.*, 1989, **32**, 1959; (e) V. J. Ram and J. L. Neumeyer, *J. Org. Chem.*, 1982, **47**, 4372. See also: Refs. 5c, 7b.
9. For instance, see: (a) J. Blagg, S. G. Davies, N. J. Holman, C. A. Laughton, and B. E. Mobbs, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1581; (b) S. G. Davies and C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. 1*, 1990, 393; (c) L. A. Bromley, S. G. Davies, and C. L. Goodfellow, *Tetrahedron: Asymmetry*, 1991, **2**, 139; (d) S. G. Davies, T. J. Donohoe, and M. A. Lister, *Tetrahedron: Asymmertry*, 1991, **2**, 1089; (e) S. G. Davies, T. J. Donohoe, and M. A. Lister, *Tetrahedron: Asymmertry*, 1991, **2**, 1085; (f) S. G. Davies, C. L. Goodfellow, and K. H. Sutton, *Tetrahedron: Asymmetry*, 1992, **3**, 1303; (g) S. G. Davies and T. J. Donohoe, *Synlett*, 1993, 323; (h) S. G. Davies and W. E. Hume, *J. Chem. Soc., Chem. Commun.*, 1995, 251; (i) S. G. Davies, O. M. L. R. Furtado, D. Hepworth, and T. Loveridge, *Synlett*, 1995, 69; (j) S. J. Coote, S. G. Davies, A. M. Fletcher, P. M. Roberts, and J. E. Thomson, *Chem. Asian J.*, 2010, **5**, 589;

(k) S. G. Davies, E. W. Hume, P. M. Roberts, and J. E. Thomson, *Tetrahedron*, 2010, **66**, 8076.

10. (a) J. Blagg, S. J. Coote, S. G. Davies, and B. E. Mobbs, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2257; (b) S. G. Davies, *Chem. & Ind.*, 1986, 506.

11. Crystallographic data (excluding structure factors) for the structure of (1*pS*,6a*R*,1'*S*)-**18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 945389.

12. (a) H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876; (b) H. D. Flack and G. Bernardinelli, *Acta Crystallogr., Sect. A*, 1999, **55**, 908; (c) H. D. Flack and G. Bernardinelli, *J. Appl. Crystallogr.*, 2000, **33**, 1143.

13. B. Nicholls and M. C. Whiting, *J. Chem. Soc.*, 1959, 551.

14. (a) S. G. Davies, *J. Organomet. Chem.*, 1990, **400**, 223; (b) S. G. Davies, C. L. Goodfellow, J. M. Peach, and A. Waller, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1019.

15. (a) V. Zabel, W. H. Watson, A. Urzua, and B. K. Cassels, *Acta Crystallogr., Sect. B*, 1979, 35, 3126; (b) L. Castedo, R. Riguera, J. Sardina, S. García-Blanco, and I. Fonseca, *Heterocycles*, 1982, 19, 1591; (c) K. L. Wert, S. Chackalamannil, E. Miller, D. R. Dalton, D. E. Zacharias, and J. P. Glusker, *J. Org. Chem.*, 1982, 47, 5141; (d) M. D. Menachery, P. Carroll, and M. P. Cava, *Tetrahedron Lett.*, 1983, 24, 167; (e) I. Fonseca and S. García-Blanco, *Acta Crystallogr., Sect. C*, 1984, 40, 176; (f) S. Touré, G. Germain, and L. A. Djakoure, *Acta Crystallogr., Sect. C*, 1985, 41, 1827; (g) G. R. Pettit, S. B. Singh, M. L. Niven, and J. M. Schmidt, *Can. J. Chem.*, 1988, 66, 406; (h) B. Ribár, C. Mészáros, P. Engel, O. Gasic, and I. Kanyó, *Acta Crystallogr., Sect. C*, 1991, 47, 2500; (i) B. Ribár, D. Lazar, O. Gasic, I. Kanyó, and P. Engel, *Acta Crystallogr., Sect. C*, 1992, 48, 945; (j) O. Simonsen, S. K. Singh, J. Wengel, and V. S. Parmar, *Acta Crystallogr., Sect. C*, 1996, 52, 3195.

16. S. J. Coote, S. G. Davies, and C. L. Goodfellow 'Advances in Metal-Organic Chemistry', Vol. 2, ed. by L. S. Liebeskind, JAI Press, London, 1991, 2, pp. 1–57.