Tetrahydroisoquinolines. Part 4.[1] Enantioselective Conversion of (+)-Amphetamine into (+)-(1*R*,3*S*,4*S*)- and (−)-(1*S*,3*S*,4*R*)-1,2,3,4-Tetramethyl-1,2,3,4-tetrahydroisoquinoline *via* Tricarbonyl(arene)chromium Methodology

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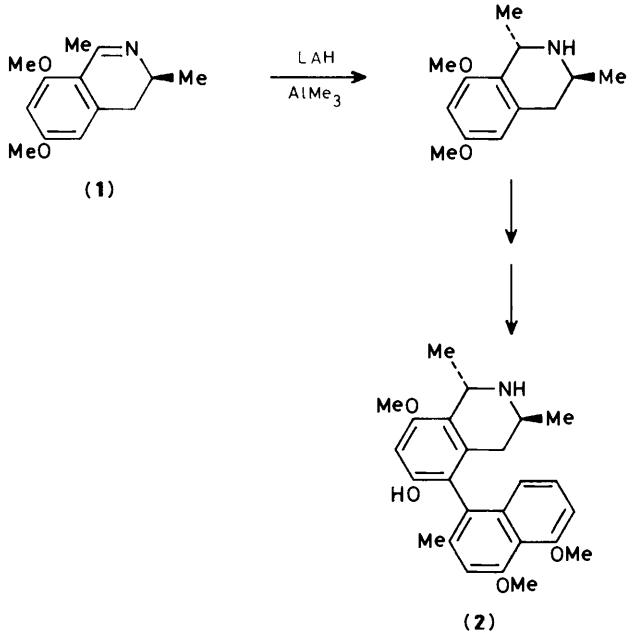
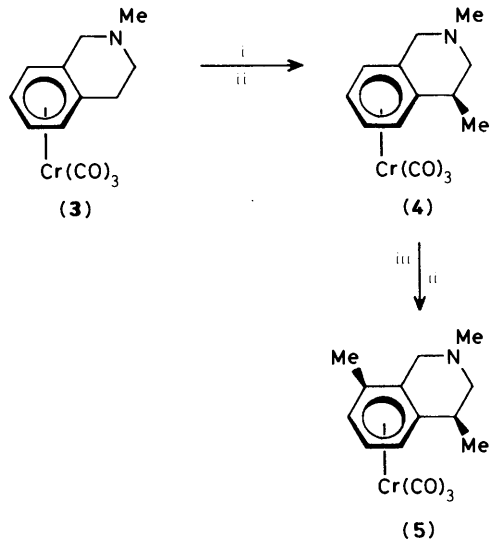
Co-ordination of the tricarbonylchromium moiety to the diastereotopic faces of (+)-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**9**) occurs preferentially to the least hindered face. The mixture of tricarbonyl [*exo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium (**11**) and tricarbonyl-[*endo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium (**12**) thus generated may undergo regio- and stereo-selective *exo*-1,4-dimethylation by sequential treatment with BuLi–MeI and Bu^{t}Li–MeI to give (+)-[tricarbonyl-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium (**15**) and (+)-[tricarbonyl-(1*S*,3*S*,4*S*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium (**16**). The relative and absolute stereochemistry of (**15**) is assigned on the basis of differential n.O.e. experiments and confirmed by single crystal *X*-ray structure determination. Oxidative decomplexation gives (1*R*,3*S*,4*S*)-and (1*S*,3*S*,4*R*)-(−)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinolines (**17**) and (**18**).

The diverse range of physiological and pharmacological effects of tetrahydroisoquinoline† derivatives and their widespread occurrence in Nature has led to the development of a variety of synthetic methods enabling elaboration of the tetrahydroisoquinoline ring system.[2] Few of these methods are, however, stereoselective. Recently Bringmann has reported the diastereoselective reduction of the (3*S*)-3,4-dihydroisoquinoline (**1**) in the first total synthesis of (−)-ancistrocladine[3] (**2**), the *trans* arrangement of the two methyl substituents being common to the *Ancistrocladus* alkaloids (Scheme 1).[4]



Scheme 1.

It has been established that for tricarbonyl(arene)chromium complexes the tricarbonylchromium moiety provides an effective steric block to the co-ordinated face, all reactions occurring from the uncomplexed side.[5] Furthermore, benzylic carbanions co-ordinated to tricarbonylchromium are stabilised.[6] Thus, tricarbonyl(η^6-2-methyltetrahydroisoqinoline)chromium(0) (**3**) undergoes regio- and stereo-selective substitution of the 4-*exo*-hydrogen by methyl with retention of configuration on treatment sequentially with butyl-lithium and methyl iodide to give complex (**4**).[1] The only remaining *exo* benzylic hydrogen in the complex (**4**) may also be replaced stereoselectively with retention of configuration by sequential treatment with t-butyl-lithium and methyl iodide to give the *cis*-1,2,4-trimethyltetrahydroisoquinoline complex (**5**) (Scheme 2).[1]



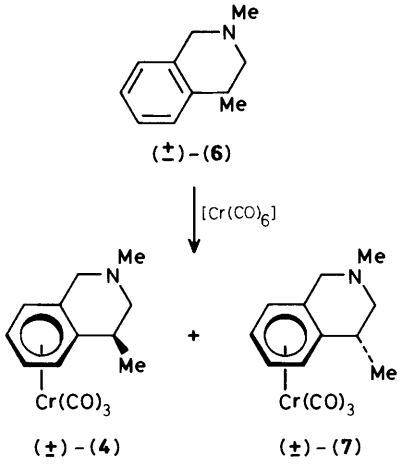
Scheme 2. *Reagents:* i, BuLi; ii, MeI; iii, Bu^{t}Li

We describe herein the extension of this methodology to the enantioselective conversion of (+)-amphetamine into (1*R*,3*S*,4*S*)- and (1*S*,3*S*,4*R*)-1,2,3,4-tetramethyltetrahydroisoquinolines.

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

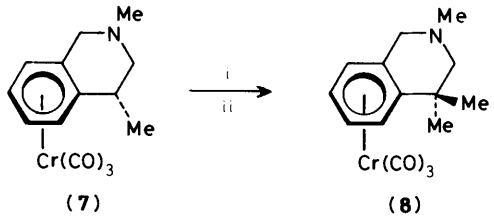
Results and Discussion

Thermolysis of hexacarbonylchromium with (±)-2,4-dimethyltetrahydroisoquinoline (**6**) gave a 2:1 mixture of the *exo*- and *endo*-diastereoisomers (**4**) and (**7**). After separation, the major diastereoisomer (**4**) proved identical in all respects with an authentic sample.[1] The modest selectivity observed in this complexation can be rationalised in terms of the tricarbonylchromium moiety preferentially complexing to the least hindered face of compound (**6**) (Scheme 3).



Scheme 3.

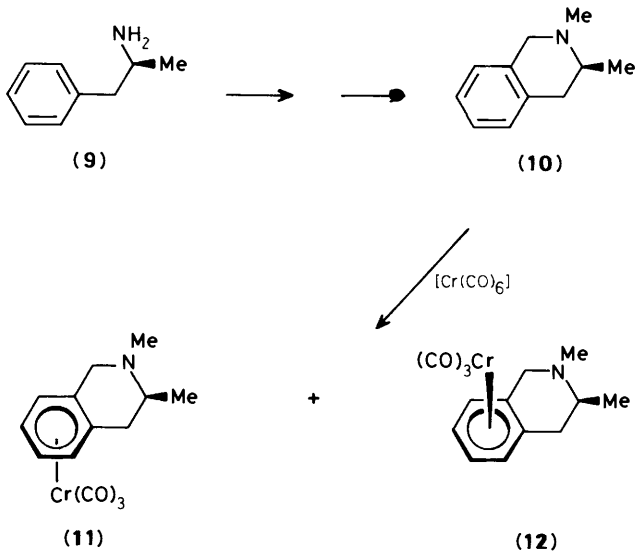
The ^{1}H n.m.r. spectrum of the *endo*-diastereoisomer (**7**) contained a 3 H doublet at δ 1.31 and a multiplet at δ 3.00 assignable to 4-H. Treatment of the *endo*-compound (**7**) with butyl-lithium and subsequent trapping of the resultant anion gave the 4,4-gem-dimethyl complex (**8**) (Scheme 4). The



Scheme 4. *Reagents:* i, BuLi; ii, MeI

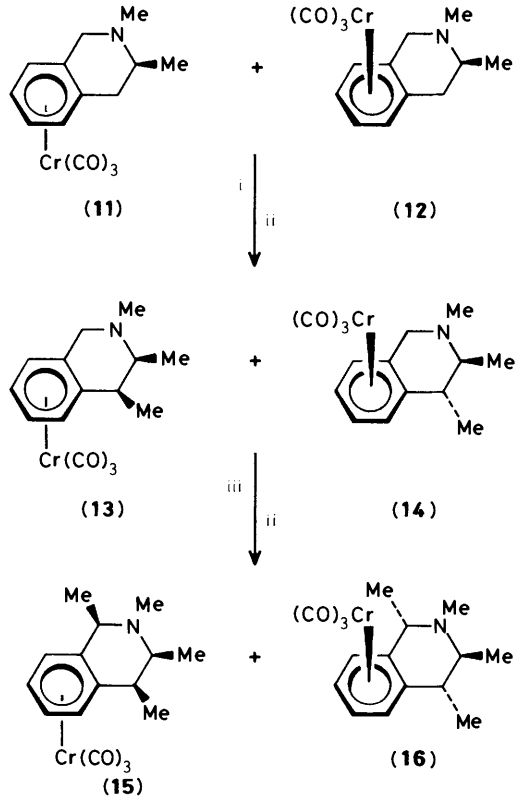
structure of the complex (**8**) was assigned on the basis of its ^{1}H n.m.r. spectrum which comprised of three methyl singlets, two AB systems, and four aromatic protons. The conversions of the *endo*-diastereoisomer (**7**) and the *exo*-diastereoisomer (**4**) into the complexes (**8**) and (**5**), respectively,[1] clearly demonstrate that only benzylic protons *exo* to the tricarbonylchromium unit are susceptible to abstraction by base and that 4-*exo* deprotonation is favoured to the exclusion of 1-*exo* deprotonation. We have previously rationalised the latter regioselectivity in terms of prior co-ordination of the butyl-lithium to the nitrogen lone pair.[1]

A Bischler–Napieralski ring closure of (+)-amphetamine (**9**) according to the literature procedure[7] gave (3*S*)-2,3-dimethyltetrahydroisoquinoline (**10**). Thermolysis of hexacarbonylchromium with compound (**10**) gave both diastereoisomers (**11**) and (**12**) in the ratio 3:2 as determined by ^{1}H n.m.r. and h.p.l.c. analysis (Scheme 5). The major diastereoisomer was assigned as the 3-*exo*-methyl complex (**11**) on the basis of preferential complexation to the least hindered face of compound (**10**). This assignment was confirmed subsequently as described below.



Scheme 5.

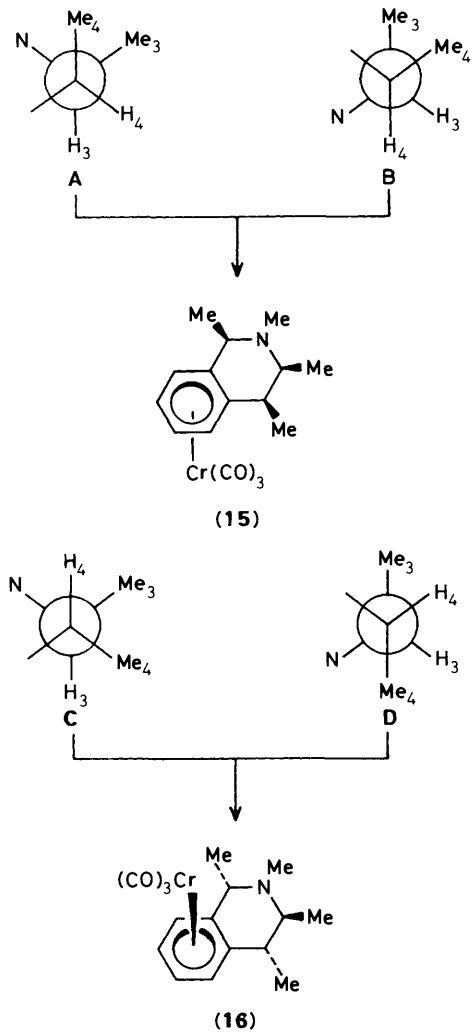
Treatment of this 3:2 mixture of the diastereoisomers (**11**) and (**12**) with butyl-lithium followed by methyl iodide gave a 3:2 mixture of the complexes (**13**) and (**14**) as determined by h.p.l.c. analysis. The expected regioselective C-4 methylation followed from the ^{1}H n.m.r. spectrum which exhibited two sets of methyl doublets and two C-1 AB systems each in the ratio 3:2. Treatment of the 3:2 mixture of the complexes (**13**) and (**14**) with t-butyl-lithium followed by methyl iodide effected *exo*-C-1 methylation to give a 3:2 mixture of the complexes (**15**) and (**16**) which was separated by chromatography (Scheme 6).



Scheme 6. *Reagents:* i, BuLi; ii, MeI, iii, Bu^{t}Li

Regioselective C-1 methylation of compounds (**13**) and (**14**) to give compounds (**15**) and (**16**), respectively, followed from their ^{1}H n.m.r. spectra. The AB system (δ 3.70, 3.38) of the complex (**13**) had been replaced by a quartet at δ 3.32 in the major product (**15**), whilst that of the complex (**14**) had been replaced by a quartet at δ 3.56 in the minor product (**16**). The ^{1}H n.m.r. spectrum of the crude material also revealed a small amount of ring methylation.

The stereochemistry of the major, all-*cis* diastereoisomer (**15**) {$[\alpha]_{546}^{20}$ +160.6° (*c* 1.06 in $CHCl_3$)} was initially assigned by n.O.e. difference experiments. Irradiation of the C-4 methyl resonance of compound (**15**) gave only a single enhancement of the *endo*-C-4 proton (15%) whilst separate irradiation of the C-3 methyl resonance gave enhancements to both 4-H (9%) and 3-H(13%). For the minor diastereoisomer (**16**) {$[\alpha]_D^{23}$ +17.7° (*c* 0.18 in $CHCl_3$)} C-4 methyl resonance irradiation gave enhancements to both 4-H (20%) and 3-H(20%) as was so for separate irradiation of the 3-methyl resonance [3-H(15%), 4-H(15%)]. Assuming that both complexes (**15**) and (**16**) adopt half-chair geometries, both may exist as one of two conformers. The expected n.O.e. responses for these four conformations (**A**, **B**, **C**, and **D**: Scheme 7) are derived by consideration of their



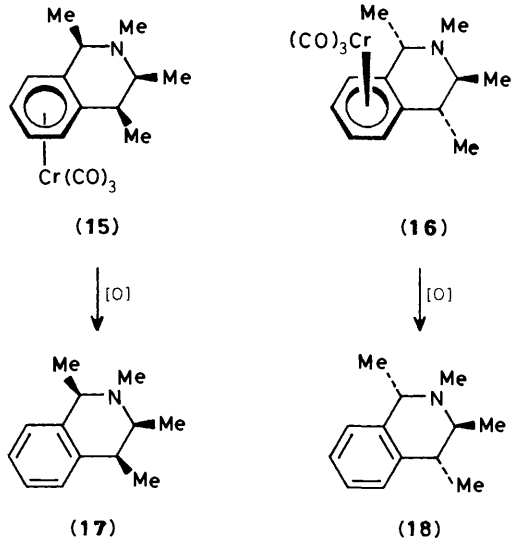
Scheme 7.

proximity to the methyl resonance under irradiation and are summarised in Table 1. The observed enhancements infer that the 3- and 4-methyl groups of the major product (**15**) bear a *cis* relationship indicating that all 3 methyl groups are *trans* to the tricarbonylchromium moiety. Further, the results predict the 3-H and the 4-methyl group to adopt an *anti*-periplanar geometry in compound (**15**), *i.e.* conformation **A** is preferred.

To confirm the above assignments, a single crystal of compound (**15**) suitable for *X*-ray analysis was grown from hot pentane. The solution was found to contain two chemically identical but crystallographically independent molecules in the asymmetric unit (see Figure 1), the two conformations differing only by a small change in the pucker of the nitrogen-containing ring (for fractional atomic co-ordinates and selected bond distances and angles, see Tables 2 and 3). The relative and absolute stereochemistry of compound (**15**), and hence of compound (**16**), was thus confirmed as (+)-tricarbonyl[η^6-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyltetrahydroisoquinoline]-chromium(0), thus proving that both C-1 and C-4 benzylic methylations occur *anti* to the tricarbonylchromium tripod.

The synthesis of the complex (**15**) illustrates that our previously described methodology permitting stereoselective introduction of *cis*-1,4-substituents into the tetrahydroisoquinoline ring[1] is equally applicable to optically active tetrahydroisoquinolines.

Both complexes (**15**) and (**16**) were readily decomplexed in quantitative yield on exposing their ether solutions to air and sunlight. Thus compound (**15**) gave (1*R*,3*S*,4*S*)-(+)-1,2,3,4-tetramethyltetrahydroisoquinoline (**17**) {$[\alpha]_D^{20}$ +99.4° (*c* 0.51 in $CHCl_3$)} whilst compound (**16**) gave (−)-(1*S*,3*S*,4*R*)-1,2,3,4-tetramethyltetrahydroisoquinoline (**18**) {$[\alpha]_D^{20}$ −9.2° (*c* 0.26 in $CHCl_3$)} (Scheme 8).



Scheme 8.

Conclusion

We have described the exploitation of tricarbonyl(arene)-chromium methodology for the enantioselective conversion of (+)-amphetamine into (+)-(1*R*,3*S*,4*S*)-and (−)-(1*S*,3*S*,4*R*)-1,2,3,4-tetramethyltetrahydroisoquinolines (**17**) and (**18**). Co-ordination of the tricarbonylchromium tripod to both diastereotopic faces of (+)(3*S*)-2,3-dimethyltetrahydroisoquinoline (**10**) is shown to occur preferentially to the least hindered face yielding a mixture of the diastereomeric *exo* and *endo* complexes (**11**) and (**12**). Sequential 1,4-benzylic dimethylation of this mixture occurs with retention of configuration at C-3 to give the tetramethyl complexes (**15**) and (**16**), the stereochemistry of the

Table 1. Expected n.O.e. enhancements of 3-H and 4-H

	Conformation and expected proton response								Found (%)			
	A		B		C		D		(15)		(16)	
Irradiated methyl doublet	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4	H_3	H_4
4-Me	×	√	√	√	√	√	√	√	0	15	20	20
3-Me	√	√	√	×	√	√	√	√	13	9	15	15

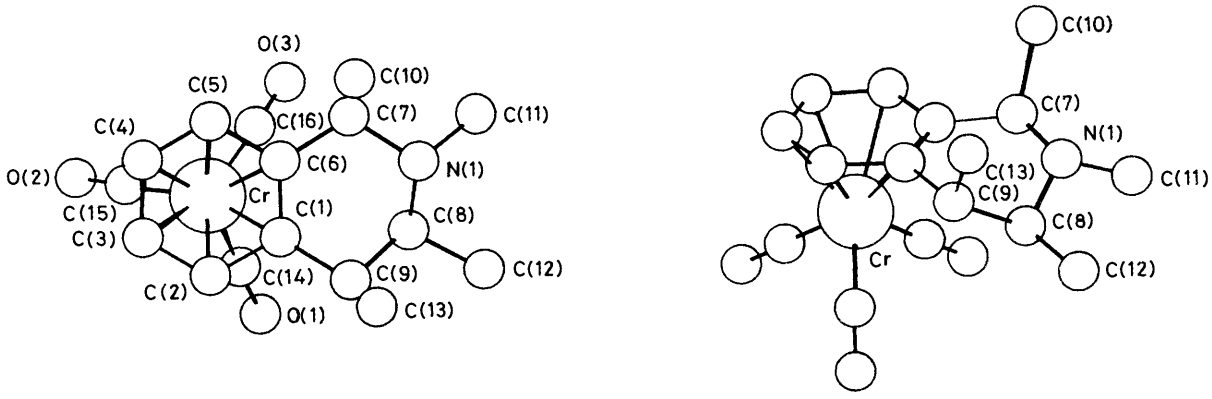


Figure 1. *X*-Ray crystal structure of complex (**15**) (conformation 1); non-systematic numbering corresponding to crystal data in Table 2

major product (**15**) being assigned by differential n.O.e. experiments. Oxidative decomplexation of compounds (**15**) and (**16**) liberates the diastereoisomeric tetramethyltetrahydroisoquinolines (**17**) and (**18**). Single crystal *X*-ray structure determination confirmed the relative and absolute stereochemistry of compound (**15**) as (+)-[tricarbonyl-η^6-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyltetrahydroisoquinoline]chromium(0); the *exo* stereochemistry at C-1 and C-4 providing conclusive evidence that benzylic alkylations in these and related systems occur *anti* to the tricarbonylchromium moiety.

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. THF was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Diethyl ether was peroxide-free and hexane refers to light petroleum (b.p. 67—70 °C). Dibutyl ether was dried over sodium and distilled under nitrogen prior to use. Removal and evaporation of all solvents was carried out under reduced pressure. All commercial reagents were purified according to standard techniques.[8] Hexacarbonylchromium was steam-distilled prior to use. Butyl-lithium was used as a 1.65M solution in hexane and t-butyl-lithium as a 2.62M solution in pentane.

Flash chromatography was performed on SiO_2 (Merck, 40—60 μm). I.r. spectra were obtained as chloroform solutions and ^1H n.m.r. spectra were obtained in [^2H]chloroform at 300 MHz unless otherwise stated. ^{13}C N.m.r. spectra were obtained in [^2H]chloroform at 62.90 MHz. M.p.s were obtained on a Kofler hot-stage apparatus and are uncorrected.

(±)-2,4-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**6**).—A stirred solution of *N*-methyl-*N*-prop-2-ynylbenzylamine (1.98 g, 12.4 mmol) was heated with polyphosphoric acid (30 g) under nitrogen (160 °C, 6 h). After cooling, the brown oil was poured onto crushed ice and neutralised with aqueous NH_4OH. The mixture was extracted with Et_2O and the combined extracts were dried (Na_2SO_4) and evaporated. The oil obtained was dissolved in MeOH (100 ml) and treated with $NaBH_4$ (2 g, 52.9 mmol). The mixture was stirred (12 h), diluted with water (50 ml), and treated with saturated aqueous NH_4Cl. It was then extracted with Et_2O and the extract dried ($MgSO_4$), evaporated, and distilled to give the title compound as a colourless oil (0.92 g, 46%); δ_H 7.37—7.01 (4 H, m, ArH), 3.11 and 3.06 (2 H, AB system J_{AB} 15.3 Hz, 1-H), 3.14—3.03 (1 H, m, 4-H), 2.83—2.77 (1 H, m, 3-H), 2.44 (3 H, s, 2-Me), 2.36—2.29 (1 H, m, 3-H), and 1.33 (3 H, d, *J* 6.9 Hz, 4-Me).

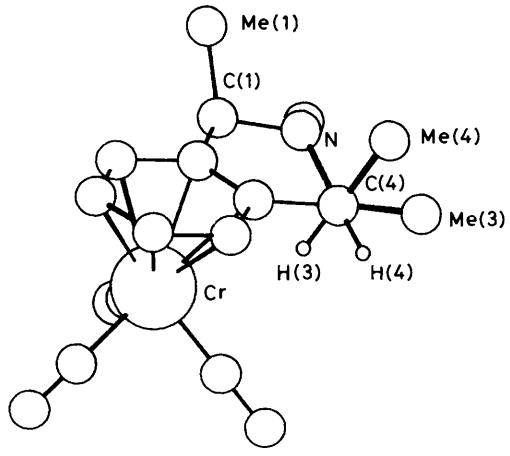


Figure 2. Newman projection along C(4)–O(3) bond of complex (**15**) with systematic numbering (*cf.* Scheme 7). [Me(3)–C(4)–C(3)–H(3) torsional angle = 180°]

Table 2. Fractional atomic co-ordinates with e.s.d.s in parentheses for compound (**15**)

Conformation 1:

Atom	*x/a*	*y/b*	*z/c*
Cr(1)	0.0004(2)	0.0008(1)	−0.000 12(8)
N(1)	0.3560(9)	0.1740(7)	−0.2423(4)
O(1)	0.1407(9)	−0.2350(6)	−0.0963(5)
O(2)	−0.216(1)	−0.219(1)	0.1445(7)
O(3)	0.391(1)	0.1672(8)	0.1611(5)
C(1)	0.119(1)	0.2151(6)	−0.0739(4)
C(2)	0.004(1)	0.2359(8)	0.0110(5)
C(3)	−0.204(1)	0.117(1)	0.0154(5)
C(4)	−0.304(1)	−0.028(1)	−0.0631(6)
C(5)	−0.196(1)	−0.0496(8)	−0.1480(5)
C(6)	0.0153(9)	0.0747(7)	−0.1544(4)
C(7)	0.124(1)	0.0476(7)	−0.2488(5)
C(8)	0.4666(9)	0.2575(8)	−0.1353(5)
C(9)	0.347(1)	0.3431(7)	−0.0758(5)
C(10)	0.000(1)	0.052(1)	−0.3467(5)
C(11)	0.463(1)	0.101(1)	−0.3065(6)
C(12)	0.707(1)	0.377(1)	−0.1379(6)
C(13)	0.363(1)	0.4794(9)	−0.1203(7)
C(14)	0.087(1)	−0.1445(8)	−0.0579(5)
C(15)	−0.134(1)	−0.1334(9)	0.0902(6)
C(16)	0.236(1)	0.0997(8)	0.0983(5)

Conformation 2:

Atom	*x/a*	*y/b*	*z/c*
Cr(101)	0.1950(2)	0.6468(1)	0.297 84(8)
N(101)	−0.2498(9)	0.3408(7)	0.4698(4)
O(101)	0.400(1)	0.837(1)	0.1381(6)
O(102)	−0.208(1)	0.4692(8)	0.1485(5)
O(103)	0.0562(8)	0.8888(6)	0.3836(5)
C(101)	0.1733(9)	0.5886(6)	0.4549(4)
C(102)	0.386(1)	0.7089(9)	0.4485(6)
C(103)	0.508(1)	0.687(1)	0.3684(6)
C(104)	0.410(1)	0.5398(9)	0.2902(6)
C(105)	0.195(1)	0.4202(8)	0.2956(4)
C(106)	0.0792(9)	0.4426(7)	0.3789(4)
C(107)	−0.141(1)	0.3052(7)	0.3831(5)
C(108)	−0.188(1)	0.5114(8)	0.5021(5)
C(109)	0.052(1)	0.6096(8)	0.5420(4)
C(110)	−0.122(1)	0.1542(8)	0.3959(7)
C(111)	−0.480(1)	0.234(1)	0.4404(6)
C(112)	−0.320(1)	0.538(1)	0.5881(6)
C(113)	0.121(1)	0.576(1)	0.6404(5)
C(114)	0.325(1)	0.762(1)	0.1988(7)
C(115)	−0.058(1)	0.5342(8)	0.2060(5)
C(116)	0.111(1)	0.7937(7)	0.3492(6)

Thermolysis of 2,4-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**6**) *with Hexacarbonylchromium.*—A deoxygenated mixture of dibutyl ether (50 ml), THF (6 ml), 2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (**6**) (0.92 g, 5.71 mmol), and hexacarbonylchromium (1.4 g, 6.36 mmol) was heated at reflux under nitrogen (23 h). The cooled solution was filtered and evaporated. Column chromatography of the residue (Al_2O_3 Grade V, gradient eluant light petroleum–Et_2O) gave tricarbonyl(η^6-*exo*-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**4**) (0.38 g, 22%) identified by comparison with an authentic sample and tricarbonyl(η^6-*endo*-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**7**) (0.17 g, 10%), m.p. 107 °C; $\nu_{max.}$ 2 800 (NMe), 1 965, and 1 890 cm^{-1} (C≡O); δ_H 5.53—5.04 (4 H, m, ArH), 3.55 and 3.37 (2 H, AB system, J_{AB} 15 Hz, 1-H), 3.01—2.98 (1 H, m, 4-H), 2.83—2.77 (1 H, m, 3-H), 2.40 (3 H, s, 2-Me), 2.26—2.19 (1 H, m, 3-H), and 1.31 (3 H, d, *J* 6.7 Hz, 4-Me); *m/z* 197 (M^+) (Found: C, 56.9; H, 5.1; N, 4.7. $C_{14}H_{15}CrNO_3$ requires C, 56.6; H, 5.1; N, 4.7%).

Tricarbonyl(η^6-2,4,4-*trimethyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**8**).—Butyl-lithium (0.1 ml, 0.17 mmol) was added to a stirred solution of tricarbonyl(η^6-*endo*-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**7**) (0.034 g, 0.11 mmol) in THF (10 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.1 ml, 1.61 mmol) was added and stirring continued (2 h, −78 °C). Methanol (2 ml) was added and the mixture warmed to 20 °C and evaporated. Column chromatography of the residue (Al_2O_3 Grade V, CH_2Cl_2) gave a single fraction as a yellow solid. Recrystallisation from Et_2O–hexane gave the *title compound* as bright yellow plates (0.031 g, 87%), m.p. 102 °C; $\nu_{max.}$ 1 965 and 1 880 cm^{-1} (C≡O); δ_H 5.59—5.01 (4 H, m, ArH), 3.51 and 3.35 (2 H, AB system, J_{AB} 14.9 Hz, 1-H), 2.39 (5 H, brs, 2-Me and 3-H), 1.35 (3 H, s, 4-Me), and 1.34 (3 H, s, 4-Me); *m/z* 311 (M^+) (Found: C, 57.65; H, 5.5; N, 4.3. $C_{15}H_{17}CrNO_3$ requires C, 57.9; H, 5.5; N, 4.5%).

(+)-(3S)-2,3-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**10**).—(D)-Amphetamine sulphate (17.9 g, 48.6 mmol) was treated with NaOH (1M; 200 ml) and extracted with benzene (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give (+)-(*S*)-amphetamine (13 g, 99%). This was heated with formic acid (11.1 g, 241 mmol) (180 °C, 4 h) and the oil so obtained dissolved in orthophosphoric acid (60 ml, 876 mmol) and treated with P_2O_5 (100 g, 705 mmol) for 3 h at 200 °C. After cooling, the mixture was poured onto crushed ice (800 ml), washed with benzene (3 × 100 ml), and neutralised with $NaHCO_3$. The mixture was extracted with benzene (5 × 100

Table 3. Selected bond lengths (Å) and angles (°) for compound (**15**) with e.s.d.s (or range of e.s.d.s for mean bond lengths) in parentheses

Conformation 1		Conformation 2	
Mean Cr(1)–Arene C	2.225(5—7)	Mean Cr(101)–Arene C	2.214(5—7)
Mean Arene C–Arene C	1.406(1—8)	Mean Arene C–Arene C	1.416(1—8)
Mean (C≡O)	1.158(8—9)	Mean (C≡O)	1.148(8—9)
C(6)–C(7)	1.515(8)	C(106)–C(107)	1.502(9)
C(7)–N(1)	1.497(8)	C(107)–N(101)	1.461(9)
N(1)–C(8)	1.468(8)	N(101)–C(108)	1.453(9)
C(8)–C(9)	1.570(1)	C(108)–C(109)	1.522(9)
C(9)–C(1)	1.497(8)	C(109)–C(101)	1.481(7)
C(1)–C(6)–C(7)	121.8(5)	C(101)–C(106)–C(107)	121.9(5)
C(6)–C(7)–N(1)	114.3(5)	C(106)–C(107)–N(101)	114.3(5)
C(7)–N(1)–C(8)	114.9(4)	C(107)–N(101)–C(108)	113.7(5)
N(1)–C(8)–C(9)	109.3(5)	N(101)–C(108)–C(109)	108.9(6)
C(8)–C(9)–C(1)	107.9(5)	C(108)–C(109)–C(101)	108.5(5)
C(9)–C(1)–C(6)	121.1(5)	C(109)–C(101)–C(106)	119.3(5)

ml) and the combined extracts dried (Na_2SO_4), and evaporated to give a yellow oil. This was dissolved in acetone (60 ml) and treated with methyl iodide (10 ml, 161 mmol). The resulting yellow needles were filtered off, dissolved in ethanol (87 ml), and treated with $NaBH_4$ (6.92 g, 183 mmol). After being stirred (12 h), the mixture was diluted with water (40 ml), extracted with Et_2O (3 × 100 ml), and the combined extracts were evaporated to give the title compound as a colourless oil (7.85 g, 50%; lit.,[7] 38%); $\nu_{max.}$ 2 780 cm^{-1} (NMe); δ_H 7.15—7.03 (4 H, m, ArH), 3.84 and 3.58 (2 H, AB system, J_{AB} 15.4 Hz, 1-H), 2.89—2.65 (3 H, m, 3-H and 4-H), 2.43 (3 H, s, 2-Me), and 1.19 (3 H, d, J 6.2 Hz, 3-Me).

Thermolysis of (+)-(3S)-2,3-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**10**) *with Hexacarbonylchromium*.—A deoxygenated mixture of dibutyl ether (140 ml), THF (17 ml), (+)-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**10**) (1.77 g, 11.0 mmol), and hexacarbonylchromium (2.66 g 12.1 mmol) was heated at reflux under nitrogen (23 h). The cooled solution was filtered and evaporated. Column chromatography of the residue (Al_2O_3 Grade V, light petroleum then CH_2Cl_2)and evaporation of the eluant gave a mixture (3:2) of tricarbonyl[η^6-*exo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**11**) and tricarbonyl[η^6-*endo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**12**) as a yellow solid (2.82 g, 87%). H.p.l.c. analysis (Hypersil 5μ, hexane–ethanol, 6:1 +0.2% H_2O v/v) gave two peaks (R_t 8.05 min, 59.2% and R_t 9.4 min, 40.8%), m.p. 82—38 °C; $\nu_{max.}$(Nujol) 1 960, 1 890, and 1 850 cm^{-1} (C≡O); δ_H 5.30—5.21 (4 H, m, ArH), 3.68 and 3.47 [2 H, AB system, J_{AB} 15.5 Hz, 1-H (**11**)], 3.59, 3.47 [2 H, AB system, J_{AB} 15.6 Hz, 1-H (**12**)], 2.66—2.59 (3 H, m, 3-H and 4-H), 2.40 [3 H, s, 2-Me (**12**)] 2.37 [3 H, s, 2-Me (**11**)], and 1.19 (3 H, d, J 5.7 Hz, 3-Me); m/z 297 (M^+) (Found: C, 56.6; H, 5.1; N, 4.7. $C_{14}H_{15}CrNO_3$ requires C, 56.6; H, 5.1; N, 4.7%).

Treatment of Tricarbonyl[η^6-exo-(3S)-2,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline*]*chromium*(0) (**11**) *and Tricarbonyl*[η^6-endo-(3S)-2,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline*]*chromium*(0) (**12**) *with Butyl-lithium and Methyl Iodide*.—Butyllithium (6.15 ml, 10.1 mmol) was added to a stirred solution of a mixture (3:2) of tricarbonyl[η^6-*exo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**11**) and tricarbonyl[η^6-*endo*-(3*S*)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**12**) (2.74 g, 9.22 mmol) in THF (60 ml) at −68 °C. The deep red solution was stirred (−68 °C, 2 h), treated with methyl iodide (1.7 ml, 27.3 mmol), and stirring continued (−68 °C, 2 h). After addition of methanol (3 ml) and subsequent stirring (−68 °C, 1 h), the mixture was warmed to 20 °C and evaporated. Column chromatography of the residue (Al_2O_3 Grade V, light petroleum then CH_2Cl_2) and evaporation of the eluant gave a mixture (3:2) of tricarbonyl[η^6-*cis*-(3*S*,4*R*)-2,3,4-trimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**13**) and tricarbonyl[η^6-*trans*-(3*S*,4*S*)-2,3,4-trimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**14**) as a yellow solid (2.53 g, 88%). H.p.l.c. analysis (Hypersil 5μ, hexane–ethanol, 9:1) gave two peaks (R_t 2.75 min, 60% and R_t 3.13 min, 40%); $\nu_{max.}$ 1 965 and 1 880 cm^{-1} (C≡O); δ_H 5.34—5.21 (4 H, m, ArH), 3.70 and 3.38 [2 H, AB system, J_{AB} 15.6 Hz, 1-H (**13**)], 3.45 and 3.42 [2 H, AB system, J_{AB} 14.8 Hz, 1-H (**14**)], 2.69—2.45 (2 H, m, 3-H and 4-H), 2.40 [3 H, s, 2-Me (**14**)], 2.33 [3 H, s, 2-Me (**13**)], 1.33 [3 H, d, J 6.9 Hz, 4-Me (**14**)], 1.24 [3 H, d, J 7.1 Hz, 4-Me (**13**)], 1.21 [3 H, d, J 6.5 Hz, 3-Me (**14**)], and 1.11 [3 H, d, J 6.6 Hz, 3-Me (**13**)]; m/z 311 (M^+) (Found: M^+, 311.0615. $C_{15}H_{17}CrNO_3$ requires M, 311.0613).

Treatment of Tricarbonyl[η^6-cis-(3S,4R)-2,3,4-*trimethyl*-1,2,3,4-*tetrahydroisoquinoline*]*chromium*(0) (**13**) *and Tricarbonyl*[η^6-trans-(3S,4S)-2,3,4-*trimethyl*-1,2,3,4-*tetrahydroisoquinoline*]*chromium*(0) (**14**) *with t-Butyl-lithium and Methyl Iodide*.—t-Butyl-lithium (3.25 ml, 8.52 mmol) was added to a stirred solution of a mixture (3:2) of tricarbonyl[η^6-*cis*-(3*S*,4*R*)-2,3,4-trimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**13**) and tricarbonyl[η^6-*trans*-(3*S*,4*S*)-2,3,4-trimethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**14**) (2.57 g, 8.13 mmol) in THF (60 ml) at −70 °C. The deep red solution was stirred (−70 °C, 2 h), treated with methyl iodide (1.6 ml, 25.7 mmol), and stirring continued (−70 °C, 2 h). After addition of methanol (3 ml), the mixture was warmed to 20 °C and evaporated. Column chromatography of the residue (Al_2O_3 Grade V, light petroleum then CH_2Cl_2) and evaporation of the eluant gave a yellow oil that later crystallised (2.36 g, 89%). Flash chromatography (SiO_2, Et_2O) on a portion of the crude material gave two fractions. The first fraction was evaporated to give (+)-tricarbonyl[η^6-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**15**) (0.36 g); $[\alpha]_{546}^{20}$ +160.6° (*c* 1.06 in $CHCl_3$), m.p. 135—136 °C; $\nu_{max.}$ 2 790 (NMe), 1 970, and 1 890 cm^{-1} (C≡O); δ_H 5.38—5.17 (4 H, m, ArH), 3.32 (1 H, q, J 6.5 Hz, 1-H), 2.83 (1 H, dq, J 2.6 Hz, 3-H), 2.35 (3 H, s, 2-Me), 2.30 (1 H, dq, J 2.6 and 7.0 Hz, 4-H), 1.41 (3 H, d, J 6.5 Hz, 1-Me), 1.22 (3 H, d, J 5.7 Hz, 4-Me), and 1.16 (3 H, d, J 6.5 Hz, 3-Me); m/z 325 (M^+) (Found: C, 59.5; H, 5.9; N, 4.3. $C_{16}H_{19}CrNO_3$ requires C, 59.1; H, 5.9; N, 4.3%).

The second fraction was subject to further purification (SiO_2, light petroleum–Et_2O, 4:1) to give (+)-tricarbonyl[η^5-(1*S*,3*S*,4*S*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]-chromium(0) (**16**) (0.30 g); $[\alpha]_D^{23}$ +17.7° (*c* 0.35 in $CHCl_3$); $\nu_{max.}$ 2 795 (N Me), 1 970, and 1 880 cm^{-1} (C≡O); δ_H 5.35—5.24 (4 H, m, ArH), 3.56 (1 H, q, J 56.8 Hz, 1-H), 2.71 (1 H, qu, J 6.5 Hz, 3-H), 2.52 (1 H, qu, J 6.9 Hz, 4-H), 2.47 (3 H, s, 2-Me), 1.37 (3 H, d, J 6.8 Hz, 1-Me), 1.30 (3 H, d, J 7.0 Hz, 4-Me), and 1.24 (3 H, d, J 6.6 Hz, 3-Me); m/z 325 (M^+) (Found: C, 59.2; H, 6.1; N, 4.05. $C_{16}H_{19}CrNO_3$ requires C, 59.1; H, 5.9; N, 4.3%).

Differential n.O.e. experiments were performed separately on both (+)-tricarbonyl[η^6-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyl-1,-2,3,4-tetrahydroisoquinoline]chromium(0) (**15**) and (+)-tricarbonyl[η^6-(1*S*,3*S*,4*S*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**16**) as [$^2H_6$]benzene solutions at 500 MHz. For the complex (**15**) irradiation of the 3-methyl doublet gave enhancements of 3-H (13%) and 4-H (9%), whereas irradiation of the 4-methyl doublet gave a single enhancement of 4-H (15%). For the complex (**16**) irradiation of the 3-methyl doublet gave enhancements of 3-H (15%) and 4-H (15%), whereas irradiation of the 4-methyl doublet gave enhancements of 3-H (20%) and 4-H (20%).

(+)-(1R,3S,4S)-1,2,3,4-*Tetramethyl*-1,2,3,4-*tetrahydroisoquinoline* (**17**).—(+)-Tricarbonyl[η^6-(1*R*,3*S*,4*R*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**15**) (0.224 g, 0.69 mmol) was dissolved in Et_2O (20 ml) and the yellow solution exposed to air and sunlight (40 h). The colourless solution was filtered free of precipitated chromium(III) residues and evaporated to give the *title compound* (**17**) as an oil (0.125 g, 96%); $[\alpha]_D^{20}$ + 99.4° (*c* 0.51 in $CHCl_3$); $\nu_{max.}$ 2 787 cm^{-1} (NMe); δ_H 7.18—7.06 (4 H, m, ArH), 3.44 (1 H, q, J 6.4 Hz, 1-H), 2.64 (2 H, m, 3-H and 4-H), 2.40 (3 H, s, 2-Me), 1.48 (3 H, d, J 6.4 Hz, 1-Me), 1.23 (3 H, d, J 6.8 Hz, 4-Me), and 1.19 (3 H, d, J 6.3 Hz, 3-Me); ^{13}C-{^1H} δ 141.8, 139.3, 127.5, 126.6, 125.7, 125.5, 61.2, 57.4, 40.3 (2 C), 23.5, 18.9, and 17.0; m/z 188 ($M^+ - 1$) (Found: $M^+ - 1$, 188.1439. $C_{13}H_{19}N$ requires $M - 1$, 188.1439).

(−)-(1S,3S,4R)-1,2,3,4-*Tetramethyl*-1,2,3,4-*tetrahydroisoquinoline* (**18**).—Tricarbonyl[η^6-(1*S*,3*S*,4*S*)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**16**) (0.221 g, 0.68 mmol) was dissolved in Et_2O (20 ml) and the yellow solution exposed to air and sunlight (40 h). The colourless solution was

filtered free of precipitated chromium(III) residues and evaporated to give the *title compound* (**18**) as a clear oil (0.112 g, 87%); $[\alpha]_D^{19}$ −9.2° (*c* 0.26 in $CHCl_3$); $\nu_{max.}$ 2 790 cm^{-1} (NMe); δ_H 7.8—7.07 (4 H, m, ArH), 3.66 (1 H, q, *J* 6.6 Hz, 1-H), 2.91 (1 H, qu, *J* 6.3 Hz, 3-H), 2.62 (1 H, qu, *J* 6.6 Hz, 5-H), 2.43 (3 H, s, 2-Me), 1.41 (3 H, d, *J* 6.6 Hz, 1-Me), 1.36 (3 H, d, *J* 6.9 Hz, 4-Me), and 1.06 (3 H, d, *J* 6.5 Hz, 3-Me); ^{13}C-{^1H} δ 139.1, 138.7, 128.4, 126.6, 125.9, 125.4, 57.4, 57.0, 39.2, 38.4, 21.8, 20.8, and 14.5; *m/z* 188 ($M^+ - 1$) (Found: $M^+ - 1$, 188.1439. $C_{13}H_{19}N$ requires $M - 1$, 188.1439).

Single Crystal X-Ray Analysis of (+)-Tricarbonyl[η⁶-(1R,3S,4R)-1,2,3,4-tetramethyl-1,2,3,4-tetrahydroisoquinoline]chromium(0) (**15**).—Crystals suitable for *X*-ray structure determination were grown from hot pentane as slender yellow needles.

Crystal Data.—$C_{16}H_{19}CrNO_3$, M = 325.3, triclinic, a = 7.142(1), b = 9.668(1), c = 13.093(1) Å, α = 101.19(1)°, β = 90.70(1)°, γ = 118.96(1)°, V = 770.1 $Å^3$ (by least-squares refinement on diffractometer angles for 25 accurately centred reflections, λ = 1.541 89 Å), space group $P\bar{1}$, Z = 2, D_x = 1.40 g cm^{-3}. Crystal dimensions 0.83 × 0.31 × 0.27 mm, μ(Cu-K_α) = 62.8 cm^{-1}.

Data Collection and Processing.—CAD4-F diffractometer, ω/2θ mode with ω scan width = 1.00 + 0.14 tan θ, ω scan speed = 1.0—6.7° min^{-1}, graphite-monochromated Cu-K_α radiation. The data were corrected for Lorentz and polarisation effects and for absorption. 3 289 Reflections measured ($0 < \theta < 70°$), 3 149 unique (merging R = 0.029 after absorption correction), giving 2 554 with $I > 3\sigma(I)$.

Structure Analysis and Refinement.—The structure was solved by Patterson and electron-density Fourier synthesis. The solution contains two chemically identical but crystallographically independent molecules in the asymmetric unit. The structure was refined by large-block least-squares refinement which included parameters for atomic co-ordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor, and an extinction parameter. Reflections were weighted by applying a 4 term Chebyshev series of the form $\omega = [0.605t_0(X) + 14.183t(X) - 1.561t_2(X) + 3.682t_3(X)]$ where $X = F_0/F_{max.}$[10] Final difference Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.[11] Final R and R_w values are 0.051 and 0.062. Final atomic positional parameters are listed in Table 2. Selected bond lengths and angles are tabulated in Table 3. 'CRYSTALS' performed the 'Flack enantiopole refinement' and confirmed the absolute stereochemistry of the complex (**15**) as 1*R*,3*S*,4*R*. Bond lengths, bond angles, fractional atomic co-ordinates, and isotropic and anisotropic thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

Acknowledgements

We thank the S.E.R.C. for financial support (K. H. S.), Dr. K. Prout for access to the Chemical Crystallography facilities and Glaxo Group Research Ltd. (Ware), for a studentship (S. J. C.) and technical assistance.

* For details of the Supplementary publications scheme, see Instructions for Authors (1988), *J. Chem. Soc., Perkin Trans. 1*, 1988, Issue 1.

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Received 19*th June* 1987; *Paper* 7/1098