Tetrahydroisoquinolines. Part 3.[1] Stereoselective Synthesis of *cis*- and *trans*-1,4-Disubstituted *N*-Methyl-1,2,3,4-tetrahydroisoquinolines as their Tricarbonylchromium Complexes

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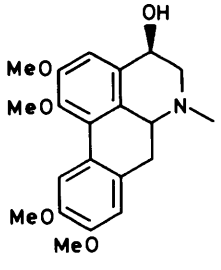
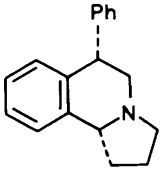
The 1-*exo* proton of tricarbonyl-4-*exo*-methyl- or tricarbonyl-4-*exo*-ethyl-2-methyl-1,2,3,4-tetrahydroisoquinolinechromium (**6**) and (**7**)[1] can be regio- and stereo-selectively removed by t-butyl-lithium and replaced with a variety of electrophiles to give *cis*-1,4-disubstituted 2-methyl-1,2,3,4-tetrahydroisoquinoline complexes. Oxidative decomplexation generates the corresponding *cis*-1,4-disubstituted tetrahydroisoquinolines. Similar methodology applied to tricarbonyl (4-*exo*-trimethylsilyl-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium (**15**) gives, after desilylation, 1-*exo*-substituted tetrahydroisoquinoline complexes.

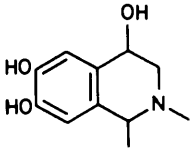
Among the tetrahydroisoquinoline alkaloids* a number have been isolated which contain substituents in the 1- and 4-positions. These include the 4-hydroxyaporphines, *e.g.* cataline (**1**),[2] the pyrroloisoquinolines, *e.g.* (**2**),[3] which exhibit potent antidepressant activity and the 4-hydroxy-1-methyltetrahydroisoquinolines (**3**) which are believed to be involved in alcohol addiction.[4]



(**1**)



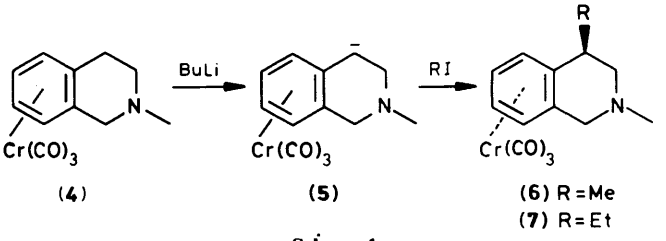
(**2**)



(**3**)

Although syntheses of simple polysubstituted tetrahydroisoquinolines, including the elaboration of 4-oxotetrahydroisoquinolines[5] and the cyclisation of aldehydes with 1-hydroxy-2-phenylethylamines,[6] are available, the stereoselective introduction of substituents into the 1- and 4- positions is generally difficult. Recently a general synthetic route to optically active 1-substituted tetrahydroisoquinolines has been developed by Meyers *et al.*,[7] and we have previously described the application of arene tricarbonylchromium methodology to the introduction of substituents into the 4-position.[1,8]

It has been established that benzylic carbanions co-ordinated to tricarbonylchromium are stabilised.[9] Thus, 2-methyl-tetrahydroisoquinoline (**4**) undergoes regio- and stereo-selective 4-*exo*-deprotonation to generate the anion (**5**) (Scheme 1). Subsequent addition of alkyl halides to (**5**) generates the 4-*exo*-derivatives (**6**) and (**7**) which, after decomplexation, yield the corresponding 4-alkyl-2-methyltetrahydroisoquinolines.[1,8] Exclusive removal of the 4-*exo*-proton of complex (**4**) presumably occurs because co-ordination of the butyl-lithium to the nitrogen directs the base to the 4-position whilst the bulk of the tricarbonylchromium moiety prevents approach to the 4-*endo*-proton.[1,8]



Scheme 1.

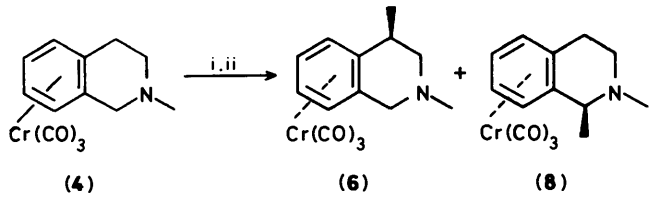
We describe here the extension of this methodology to the stereoselective synthesis of 1,4-disubstituted-2-methyltetrahydroisoquinolines.

Results and Discussion

Treatment of complex (**4**) with t-butyl-lithium at −78 °C followed by the addition of methyl iodide gave, after work-up, a 2:1 mixture of complexes (**6**) and (**8**) which were readily separable by column chromatography. Complex (**6**) was identical with an authentic sample of tricarbonyl-2,4,-*exo*-dimethyltetrahydroisoquinoline)chromium.[1] The structure of complex (**8**) followed from its ^{1}H n.m.r. spectrum; the AB system, δ 3.50, 3.27 (J_{AB} 15 Hz, 1-H) (**4**) being replaced by a 1 H quartet at δ 3.36 (*J* 6.5 Hz) and a doublet appearing at δ 1.40 (*J* 6.5 Hz, 1-Me). *exo*-Stereochemistry was assigned by analogy with all other benzylic substitutions carried out on complexed arene systems where the methyl iodide approached the intermediate 1-lithio derivative from the unhindered *exo*-face.[1,8,10] No isomers other than (**6**) or (**8**) could be detected by 300 MHz ^{1}H n.m.r. spectroscopy indicating that both C-1 and C-4 substitutions were occurring completely stereoselectively.

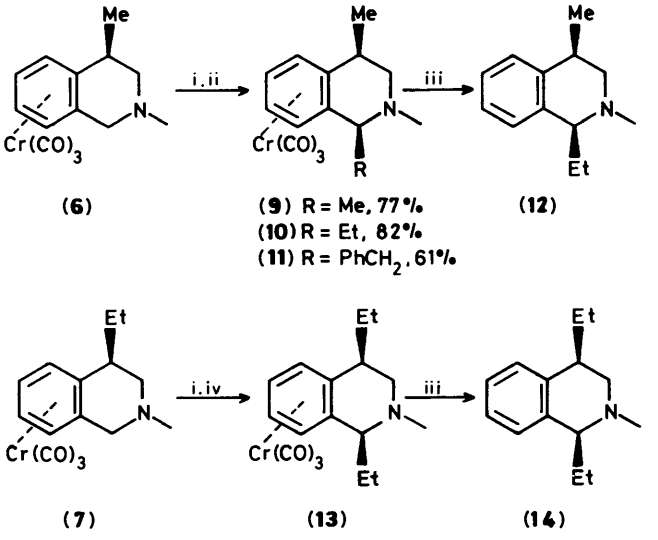
Treatment of complex (**6**) with t-butyl-lithium followed by the addition of methyl iodide gave complex (**9**), the ^{1}H n.m.r. spectrum of which contained a quartet, δ 3.31 (1-H) and two overlapping methyl doublets. No other products could be

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



Scheme 2. *Reagents:* i, Base, −78 °C; ii, MeI, −78 °C

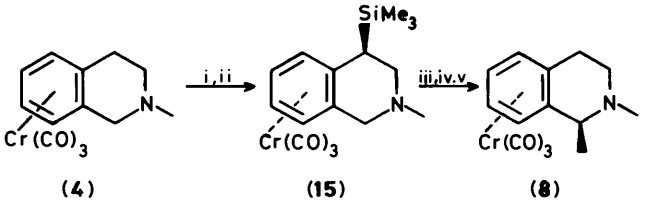
detected by 300 MHz ^{1}H n.m.r. spectroscopy suggesting that (**9**) was being produced with complete control over both the regio- and stereo-chemistry. Treatment of complex (**6**) with butyl-lithium, followed by methyl iodide, however, gave a 2:1 mixture of (**6**) and (**9**) indicating incomplete C-1 deprotonation with the weaker base. Deprotonation of (**6**) with t-butyl-lithium gave, on addition of ethyl iodide or benzyl bromide, the complexes (**10**) and (**11**) respectively. Again only a single diastereoisomer could be detected by 300 MHz ^{1}H n.m.r. spectroscopy in each case. Similar ethylation of complex (**7**) gave the *cis*-1,4-diethyl-2-methyltetrahydroisoquinoline complex (**13**) as a single isomer. Oxidative decomplexation of (**10**) and (**13**) quantitatively liberated the corresponding *cis*-1,4-disubstituted 2-methyl-tetrahydroisoquinolines (**12**) and (**14**) respectively (Scheme 3).



Scheme 3. *Reagents:* i, Bu^{t}Li; ii, MeI, EtI, or $PhCH_2Br$; iii, O_2; iv, EtI

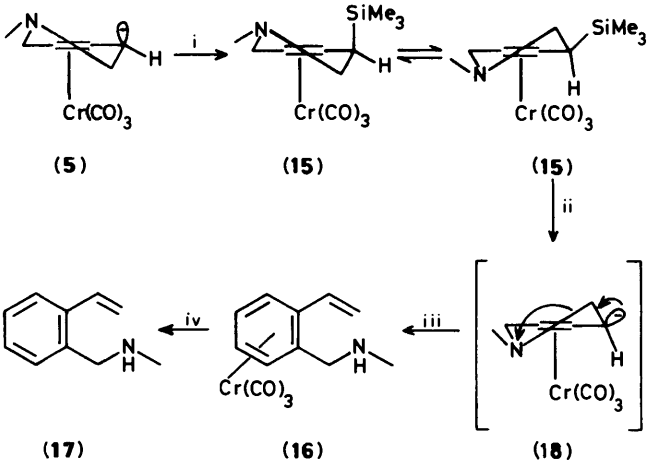
The production of single diastereoisomers in the above reactions is consistent with bases only being able to approach the complexes from the unhindered *exo*-face. For the unsubstituted parent complex (**4**), *exo*-benzylic protons are available at both C-1 and C-4 positions and t-butyl-lithium shows little preference. For the complexes (**6**) and (**7**), however, an *exo*-benzylic proton is available only at C-1 and deprotonation is consequently regioselective.

Complex (**4**) could be efficiently converted into the *exo*-1 methyl derivative (**8**) by protection of the C-4 postion with a trimethylsilyl group. Thus, regioselective deprotonation of (**4**) with butyl-lithium[1,8] followed by trapping of the C-4 anion with trimethylsilyl chloride gave complex (**15**) as a single diastereoisomer. Regio- and stereo-selective methylation of (**15**) was effected as above and work up with wet tetrabutyl-ammonium fluoride removed the trimethylsilyl group to give the 1-*exo*-methyl complex (**8**) isomerically pure (Scheme 4).



Scheme 4. *Reagents:* i, BuLi; ii, Me_3SiCl; iii, Bu^{t}Li; iv, MeI; v, $Bu_4NF{\cdot}3H_2O$

A common side product formed in the preparation and reactions of complex (**15**) was identified as the ring-opened complex (**16**) which could be oxidatively decomplexed to the styrene (**17**) (Scheme 5). The complex presumably arises *via* alkoxide or halide catalysed desilylation to generate the unstable equatorial C-4 anion (**18**) which can undergo concerted ring opening *via* cleavage of the antiperiplanar C–N bond. This behaviour contrasts with the stability of the axial C-4 anion (**5**) which is stabilised by delocalisation of the negative charge into the arene tricarbonylchromium moiety.



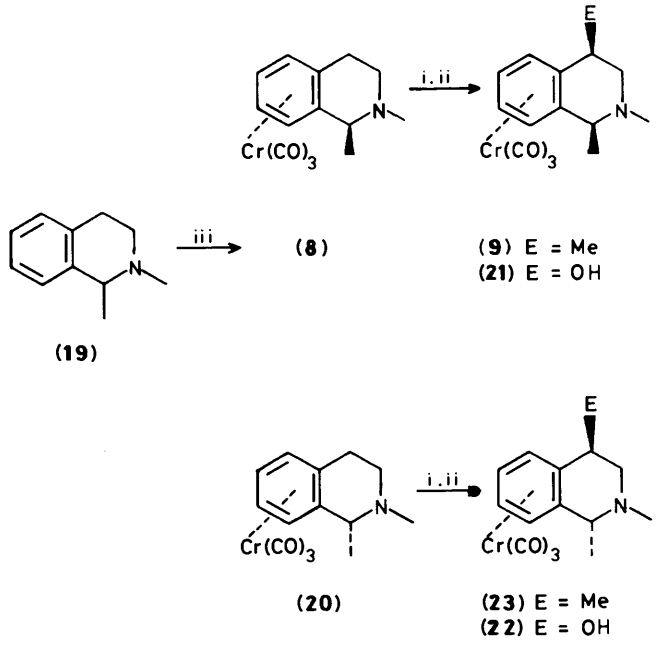
Scheme 5. *Reagents:* i, Me_3SiCl; ii, F^-/MeO^-; iii, H^+; iv, O_2

Thermolysis of 1,2-dimethyltetrahydroisoquinoline (**19**)[11] with hexacarbonylchromium gave a 3:1 mixture of the *exo*-1-methyl (**8**) and *endo*-1-methyl (**20**) complexes. The predominance of (**8**) is consistent with the tricarbonylchromium moiety complexing preferentially to the least hindered face of (**19**).[12] Stereoselective 4-*exo*-hydroxylation of (**8**) and (**20**) was demonstrated by treating a mixture of the two complexes with butyl-lithium followed by the addition of MoOPH * which gave a 3:1 mixture of (**21**) and (**22**). No other isomers could be detected by 300 MHz ^{1}H n.m.r. spectroscopy.

Complexes (**8**) and (**20**) could be separated by careful column chromatography. Stereoselective 4-*exo*-methylation (butyl-lithium, MeI) of both (**8**) and (**20**) gave the *cis*- and *trans*-1,2,4-trimethyltetrahydroisoquinoline complexes (**9**) and (**23**) respectively as single isomers (Scheme 6). Complexes (**8**) and (**9**) prepared *via* this route were identical in all respects with samples prepared using the alternative methodology above.

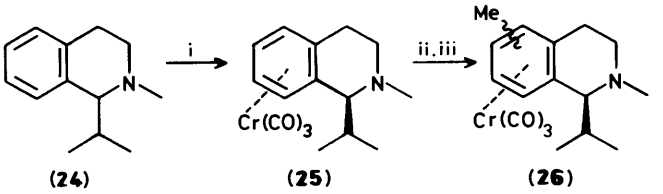
The complexation of 1-isopropyl-2-methyltetrahydroiso-quinoline (**24**) to tricarbonylchromium was completely stereoselective. The stereochemistry of the single product (**25**) was assigned as *exo* by analogy with the complexation of (**19**)

* MoOPH is (Hexamethylphosphoric triamide)oxodi(peroxo)pyridinemolybdenum.[13]



Scheme 6. *Reagents:* i, BuLi; ii, E^+; iii, $Cr(CO)_6$

which occurred preferentially to the least hindered face of the arene ring.[12] Treatment of (**25**) with butyl-lithium followed by methyl iodide resulted in a mixture of three arene methylated products (**26**). The expected nitrogen directed 4-*exo*-deprotonation is presumably precluded in this case because the proximate isopropyl moiety prevents co-ordination of the base to the nitrogen atom.



The results presented above demonstrate that complexation of 2-methyl-tetrahydroisoquinoline to tricarbonylchromium allows the efficient stereoselective introduction of substituents into either, or both, of the 1- and 4-*exo*-positions.

Experimental

All reactions involving the preparation of utilisation of tricarbonyl(arene)chromium(0) complexes were performed under an atmosphere of nitrogen. All commercial reagents were purified according to standard techniques.[14] 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). Di-butyl ether was dried over sodium and distilled under nitrogen prior to use. Hexacarbonylchromium was steam distilled prior to use. Butyl-lithium was used as a 1.6M solution in hexane and t-butyl-lithium as a 2M solution in pentane. Tricarbonyl(η^6-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**4**), tricarbonyl(η^6-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**6**), and tricarbonyl(η^6-4-ethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**7**) were prepared as previously described.[1,8]

Flash chromatography was performed on SiO_2 (Merck, 40—60 μm). I.r. spectra were obtained as solutions in chloroform unless otherwise stated 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.

Treatment of Tricarbonyl(η^6-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**4**)[1,8] *with t-Butyl-lithium and Methyl Iodide.*—t-Butyl-lithium (0.97 ml, 1.94 mmol) was added to a stirred solution of tricarbonyl(η^6-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**4**)[1,8] (500 mg, 1.76 mmol) in THF (40 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.44 ml, 7.06 mmol) was added and stirring continued (−78 °C, 2 h). After addition of methanol (5 ml), the mixture was warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) gave a yellow oil (430 mg, 83%) a portion of which (150 mg) was subjected to flash chromatography (SiO_2, Et_2O) to give as the major product tricarbonyl (η^6-*exo*-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**6**)[1,8] as yellow needles (80 mg) (SiO_2, Et_2O, R_F = 0.35), m.p. 74—75 °C; $\nu_{max.}$ 1 970, 1 900, and 1 860 cm^{-1} (C≡O); δ_H 5.52—5.34 (4 H, m, ArH), 3.57, 3.25 (2 H, AB system, J_{AB} 15 Hz, 1-H_2), 2.84—2.78 (1 H, m, 4-H), 2.59, 2.45 (2 H, AB system, J_{AB} 12 Hz, 3-H), 2.34 (3 H, s, 2-Me), and 1.36 (3 H, d, *J* 7 Hz 4-Me); *m/z* 297 (M^+) (Found: C, 56.6; H, 5.2; N, 4.8. $C_{14}H_{15}CrNO_3$ requires C, 56.6; H, 5.1; N, 4.7%).

The minor product (SiO_2, Et_2O, R_F = 0.2) was recrystallised from diethyl ether–hexane to give tricarbonyl(η^6-*exo*-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0), (**8**) as yellow plates (46 mg), m.p. 95—96 °C; $\nu_{max.}$ 1 965 and 1 890 cm^{-1} (C≡O); δ_H 5.34—5.25 (4 H, m, ArH), 3.36 (1 H, q, *J* 6.5 Hz, 1-H), 2.97—2.50 (4 H, m, 3-H_2 and 4-H_2), 2.48 (3 H, s, 2-Me), and 1.40 (3 H, d, *J* 6.5 Hz, 1-Me); *m/z* 297 (M^+) (Found: C, 56.9; H, 5.1; N, 4.6. $C_{14}H_{15}CrNO_3$ requires C, 56.6; H, 5.1; N, 4.7%).

Tricarbonyl(η^6-cis-1,2,4-trimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**9**).—t-Butyl-lithium (0.5 ml, 1 mmol) was added to a stirred solution of tricarbonyl(η^6-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**6**)[1,8] (270 mg, 0.90 mmol) in THF (20 ml) at −78 °C. The initial yellow solution rapidly became orange. After the mixture had been stirred at −78 °C for 2 h, methyl iodide (0.3 ml, 4.82 mmol) was added and the stirring continued (−78 °C, 2 h). Methanol (5 ml) was added and the mixture warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) followed by evaporation and crystallisation from diethyl ether–hexane gave the title compound as yellow needles (210 mg, 77%), m.p. 106—107 °C; $\nu_{max.}$ 1 965 and 1 890br cm^{-1} (C≡O); δ_H 5.34—5.23 (4 H, m, ArH), 3.31 (1 H, q, *J* 6.5 Hz, 1-H), 2.80—2.62 (3 H, m, 3-H_2 and 4-H), 2.45 (3 H, s, 2-Me), 1.39 (3 H, d, *J* 6.5 Hz, 1-Me), 1.36 (3 H, d, *J* 7.0 Hz, 4-Me); *m/z* 311(M^+) (Found: C, 58.0; H, 5.5; N, 4.5; $C_{15}H_{17}CrNO_3$ requires C, 57.9; H, 5.5; N, 4.5%).

Tricarbonyl(η^6-cis-1-ethyl-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**10**).—t-Butyl-lithium (1.4 ml, 2.8 mmol) was added to a stirred solution of tricarbonyl(η^6-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**6**)[1,8] (760 mg, 2.56 mmol) in THF (30 ml) at −78 °C. The initial yellow solution rapidly became orange. After the mixture had been stirred at −78 °C for 2 h, ethyl iodide (0.85 ml, 10.6 mmol) was added and stirring was continued (−78 °C, 4 h). Methanol (6 ml) was added, and the mixture warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) gave the title compound as a yellow solid (680 mg, 82%), m.p. 97—98 °C; $\nu_{max.}$ 1 965 and 1 890br cm^{-1} (C≡O); δ_H 5.32—5.26 (4 H, m, ArH), 3.32 (1 H, t, *J* 3.8 Hz, 1-H), 2.83, 2.58

(2 H, ABX system, J_{AB} 12 Hz, 3-H), 2.64—2.58 (1 H, m, 4-H), 2.42 (3 H, s, 2-Me), 2.00 (1 H, ddq, *J* 4.0 Hz, 7.4 Hz, 14.7 Hz, $CHCH_2CH_3$), 1.74 (1 H, ddq, *J* 3.8 Hz, 7.4 Hz, 14.7 Hz, $CHCH_2CH_3$), 1.37 (3 H, d, *J* 6.9 Hz, 4-Me), and 0.78 (3 H, t, *J* 7.4 Hz, CH_2CH_3); *m/z* 325 (M^+) (Found: C, 58.7; H, 5.9; N, 4.1; $C_{16}H_{19}CrNO_3$ requires C, 59.1; H, 5.9; N, 4.3%).

(η⁶-cis-1-Benzyl-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)-tricarbonylchromium(0) (**11**).—t-Butyl-lithium (0.7 ml, 1.40 mmol) was added to a stirred solution of tricarbonyl(η⁶-2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**6**)[1,8] (400 mg, 1.34 mmol) in THF (20 ml) at −78 °C. The initial yellow solution rapidly became orange. The mixture was stirred at −78 °C for 2 h, after which benzyl bromide (0.64 ml, 5.38 mmol) was added and stirring continued (−78 °C, 2 h). Methanol (5 ml) was added, and the mixture was warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, petroleum then 1:1 petroleum–Et_2O) followed by evaporation and crystallisation from diethyl ether–hexane gave the title compound as yellow needles (320 mg, 61%), m.p. 123—124 °C; $\nu_{max.}$ 1 965 and 1 890br cm^{-1} (C≡O); δ_H 7.20—7.00 (5 H, m, benzyl ArH), 5.28—5.06 (4 H, m, complexed arene protons) 3.60 (1 H, t, *J* 5.0 Hz, 1-H), 3.09 (2 H, d, *J* 5.0 Hz, $CHCH_2Ph$), 2.81, 2.64 (2 H, ABX system, J_{AB} 11.7 Hz, 3-H), 2.57 (3 H, s, 2-Me), 2.54 1 H, m, 4-H), 0.95 (3 H, d, *J* 7.0 Hz, 4-Me); *m/z* (CI–NH_3) 388 (MH^+) (Found: C, 65.1; H, 5.4; N, 3.5; $C_{21}H_{21}CrNO_3$ requires C, 65.1; H, 5.5; N, 3.6%).

Tricarbonyl(η⁶-cis-1,4-diethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**13**).—t-Butyl-lithium (3.9 ml, 7.8 mmol) was added to a stirred solution of tricarbonyl(η⁶-4-ethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**7**)[1,8] (2.17 g, 6.96 mmol) in THF (60 ml) at −78 °C. The mixture was stirred at −78 °C, for 2 h, after which ethyl iodide (2.2 ml, 27.5 mmol) was added and stirring continued (−78 °C, 3 h). Methanol (12 ml) was added, and the mixture was warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2), followed by evaporation gave a yellow oil (2.05 g) a portion of which (1.25 g) was purified by flash chromatography (SiO_2, Et_2O). The first fraction (SiO_2, Et_2O, R_F = 0.72) was recrystallised from diethyl ether–hexane to give the title compound as yellow needles (680 mg, 47%), m.p. 113—115 °C; $\nu_{max.}$ 2 795 (N–Me), 1 965, and 1 890 cm^{-1} (C≡O); δ_H 5.33—5.25 (4 H, m, ArH), 3.33 (1 H, t, *J* 3.6 Hz, 1-H), 2.80, 2.68 (2 H, ABX system, J_{AB} 12 Hz, 3-H), 2.40 (3 H, s, 2-Me), 2.27—2.24 (1 H, m, 4-H), 2.02—1.64 (4 H, m, CH_2CH_3), 1.03 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 0.75 (3 H, t, *J* 7.4 Hz, CH_2CH_3); *m/z* 339 (M^+) (Found: C, 60.1; H, 6.5; N, 4.1. $C_{17}H_{21}CrNO_3$ requires C, 60.2; H, 6.2; N, 4.1%).

General Procedure for the Decomplexation of Complexes (**10**) *and* (**13**).—A solution of the complex (**10**) or (**13**) in diethyl ether (20 mg/ml) was exposed to air and sunlight until the yellow solution became colourless. Chromium(III) residues were removed by filtration (Celite) and the ether evaporated to leave a clear oil. Where necessary, further purification was achieved by flash chromatography (SiO_2; toluene–ethanol–ammonia, 78:20:2). Yields in each case were essentially quantitative.

cis-1-*Ethyl*-2,4-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**12**): $\nu_{max.}$ (thin film) 2 790 (NCH_3) and 740 (1,2-disubstituted arene) cm^{-1}; δ_H 7.22—7.12 (4 H, m, ArH), 3.39 (1 H, t, *J* 5.2 Hz, 1-H), 2.94 (1 H, m, 4-H), 2.85—2.75 (2 H, m, 3-H), 2.47 (3 H, s, 2-Me), 1.88 (2 H, dq, *J* 7.3 Hz, 5.2 Hz, $CHCH_2CH_3$), 1.35 (3 H, d, *J* 6.9 Hz, 4-Me), and 0.89 (3 H, t, *J* 7.3 Hz, CH_2CH_3); ^{13}C-{^1H} n.m.r. δ 140.3, 137.7, 127.8, 126.9, 125.8, 125.5, 65.1, 56.0, 43.4, 30.4, 26.7, 21.1, and 9.5; *m/z* 188 (M^+ − 1) (Found: C, 82.3; H, 10.2; $C_{13}H_{19}N$ requires C, 82.5; H, 10.1%).

cis-1,4-*Diethyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**14**): $\nu_{max.}$ (thin film) 2 795 (NCH_3), 740 (1,2-disubstituted arene) cm^{-1}; δ_H 7.16—7.12 (4 H, m, ArH), 3.36 (1 H, t, *J* 4.6 Hz, 1 H, 1-C), 2.92—2.64 (3 H, m, 3-H_2 and 4-H), 2.43 (3 H, s, 2-Me), 1.93—1.85 (2 H, m, CH_2CH_3), 1.84—1.74 (2 H, m, CH_2CH_3), 1.00 (3 H, t, *J* 7.4 Hz, CH_2CH_3), and 0.80 (3 H, t, *J* 7.3 Hz, CH_2CH_3); ^{13}C-{^1H} n.m.r. δ 139.7, 137.9, 128.4, 126.7, 125.5 (2 C), 65.1, 53.7, 43.7, 38.5, 28.4, 26.2, 12.0, 9.0; *m/z* 202 (M^+ − 1) (Found: C, 82.9; H, 10.5; $C_{14}H_{21}N$ requires C, 82.7; H, 10.4%).

Tricarbonyl(η⁶-2-methyl-4-trimethylsilyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**15**).—Butyl-lithium (7.3 ml, 11.7 mmol) was added to a stirred solution of tricarbonyl(η⁶-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**4**)[1,8] (3.00 g, 10.6 mmol) in THF (100 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which trimethylsilyl chloride (4 ml, 31.5 mmol) was added and stirring continued (2 h, −78 °C). t-Butyl chloride was added, and the solution warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, Et_2O–petroleum) gave two fractions. The first fraction, recrystallised from diethyl ether–petroleum, gave the title compound as yellow needles (1.57 g, 42%), m.p. 108—109 °C; $\nu_{max.}$ 2 790 (N–CH_3), 1 960, and 1 880 cm^{-1} (C≡O); δ_H 5.26—5.11 (4 H, m, ArH), 3.61, 3.26 (2 H, AB system, J_{AB} 15.2 Hz, 1-H), 2.86, 2.63 (2 H, ABX system, J_{AB} 11.3 Hz, 3-H), 2.33 (3 H, s, 2-Me), 1.97 (1 H, s, br, 4-H), and 0.05 (9 H, s, $SiMe_3$); *m/z* 355 (M^+) (Found: C, 54.2; H, 6.1; N, 3.9. $C_{16}H_{21}CrNO_3$ requires C, 54.1; H, 6.0; N, 3.9%). The second fraction gave tricarbonyl(η⁶-*N*-methyl-*o*-vinylbenzylamine)chromium(0) (**16**) as a yellow oil (1.42 g, 47%); $\nu_{max.}$ 3 320 (NH), 2 795 (*N*Me), 1 960, and 1 880 cm^{-1} (C≡O); δ_H 6.66 (1 H, dd, J_{trans} 17.3 Hz, J_{cis} 10.9 Hz, $ArCH{=}CH_2$), 5.67 (1 H, d, J_{trans} 17.1 Hz, $ArCH{=}CH_2$), 5.40 (1 H, d, J_{cis} 10.6 Hz, $ArCH{=}CH_2$), 5.60—5.34 (4 H, m, ArH), 3.74, 3.42 (2 H, AB system, J_{AB} 13.7 Hz, $ArCH_2N$), 2.50 (3 H, s, NMe); *m/z* 283 (M^+) (Found: M^+, 283.0301. $C_{13}H_{13}CrNO_3$ requires *M*, 283.0300).

N-*Methyl*-o-*vinylbenzylamine* (**17**).—This was prepared by decomplexation of tricarbonyl(η⁶-*N*-methyl-*o*-vinylbenzylamine)chromium(0) (**16**) according to the general method outlined above; $\nu_{max.}$ 3 320 (NH) and 2 795 (NMe) cm^{-1}, δ_H 7.55—7.13 (4 H, m, ArH), 7.07 (1 H, dd, J_{trans} 17.4 Hz, J_{cis} 10.9 Hz, $ArCH{=}CH_2$), 5.70 (1 H, d, J_{trans} 17.3 Hz, $ArCH{=}CH_2$), 5.34 (1 H, d, J_{cis} 10.8 Hz, $ArCH{=}CH_2$), 3.80 (2 H, s, $ArCH_2N$), and 2.48 (3 H, s, 2-Me); ^{13}C {^1H} n.m.r. δ 137.2, 136.8, 134.2, 129.3, 127.7, 127.4, 125.8, 115.9, 53.7, and 36.3; *m/z* 147 (M^+).

Tricarbonyl(η⁶-exo-1,2-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline)chromium*(0) (**8**) *prepared from Tricarbonyl*(η⁶-2-*methyl*-4-*trimethylsilyl*-1,2,3,4-*tetrahydroisoquinoline)-chromium*(0) (**15**).—t-Butyl-lithium (0.075 ml, 0.15 mmol) was added to a stirred solution of complex (**15**) (50 mg, 0.14 mmol) in THF (10 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.05 ml, 0.8 mmol) was added and stirring continued (2 h, −78 °C). Work-up with an excess of $Bu_4NF.3H_2O$ and stirring (12 h, 20 °C) gave a yellow oil. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) gave the title compound (25 mg, 60%) identical in all respects with a sample prepared by an alternative route.

1,2-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**19**).[11]—2-Phenylethylamine (9.5 ml, 75.6 mmol) was heated with formic acid (4.5 ml, 119 mmol) at 180 °C (3 h). The resulting oil was dissolved in orthophosphoric acid (45 ml, 77.4 mmol), treated with phosphorus pentaoxide (75 g, 528 mmol) and heated (3 h, 200 °C). After being cooled the mixture was poured onto crushed ice (700 ml), washed with benzene (3 × 100 ml), and neutralised (pH 7) with $NaHCO_3$. Benzene extraction (3 × 100 ml), drying (Na_2SO_4), and evaporation gave a yellow oil.

Treatment with acetone (45 ml) and methyl iodide (7.5 ml, 120 mmol) gave 2-methyl-1,2-dihydroisoquinolinium iodide as yellow needles (9.2 g, 45%). A portion of this material (5 g, 0.02 mol) was treated with sodium-dried diethyl ether (75 ml) and methyl magnesium iodide (2.05M solution in diethyl ether; 16 ml, 0.03 mol). The mixture was heated under reflux (1 h) and then stirred (20 °C, 14 h). Saturated aqueous ammonium chloride (30 ml) was added, and the ether layer decanted and dried ($MgSO_4$). Evaporation followed by distillation (64 °C, 0.1 mmHg) (lit.,[11] 110 °C, 9 mmHg) gave the title compound as a clear oil (2.5 g, 85%); δ (60 MHz, $CDCl_3$), 7.0 (4 H, s, ArH), 3.35 (1 H, q, *J* 7 Hz, 1-H), 2.9—2.4 (4 H, m, 3-H_2 and 4-H_2), 2.3 (3 H, s, NMe), and 1.15 (3 H, d, *J* 7 Hz, 1-Me); *m/z* 161 (M^+).

Thermolysis of 1,2-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**19**) *with Hexacarbonylchromium*.—A deoxygenated mixture of dibutyl ether (60 ml), THF (7 ml), 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**19**) (2.0 g, 12.4 mmol), and hexacarbonylchromium (3.41 g, 16 mmol) was heated under reflux under nitrogen (30 h). The cooled solution was filtered and the solvents removed. Column chromatography (Al_2O_3 Grade V, Et_2O–petroleum, 1:1, then Et_2O) gave after evaporation a yellow solid (3.42 g, 93%). H.p.l.c. analysis (Hypersil 5μ, hexane–ethanol, 4:1) on this crude product gave two peaks (R_t 4.6 min, 75.55% and R_t 10.5 min, 24.45%). Flash chromatography (SiO_2, hexane–ethanol, 1:1) on a portion of the crude material (1.2 g) gave tricarbonyl(η⁶-*exo*-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**8**) [R_F 0.38 (SiO_2; hexane–ethanol, 1:1)] (850 mg) identified by comparison with an authentic sample and tricarbonyl(η⁶-*endo*-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**20**) [R_F 0.21 (SiO_2; hexane–ethanol, 1:1)] (220 mg); $\nu_{max.}$ 2 795 (NMe), 1 970, and 1 890br cm^{-1} (C≡O); δ_H 5.50—5.41 (2 H, m, ArH), 5.10—4.98 (2 H, m, ArH), 3.58 (q, *J* 6.5 Hz, 1-H), 3.05—2.60 (4 H, m, 3-H_2 and 4-H_2), 2.45 (3 H, s, N-Me), and 1.41 (3 H, d, *J* 6.5 Hz, 1-Me); *m/z* 297 (M^+) (Found: C, 56.9; H, 5.1; N, 4.6. $C_{14}H_{15}CrNO_3$ requires C, 56.6; H, 5.1; N, 4.7%).

Tricarbonyl(η⁶-4-*hydroxy*-1,2-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0): 3:1 *Mixture of* cis *and* trans *Isomers*. (**21**) *and* (**22**).—Butyl-lithium (0.85 ml, 1.36 mmol) was added to a stirred solution of tricarbonyl(η⁶-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (as a 3:1 mixture of 1-*exo*(**8**) and 1-*endo* (**20**) isomers, 325 mg, 1.1 mmol) in THF (40 ml) at −78 °C. After being stirred at −78 °C for 2 h the solution was warmed to 40 °C and (hexamethylphosphoric triamide)oxodi(peroxo)pyridinemolybdenum [MoOPH][13] (720 mg, 1.66 mmol) added. Stirring was continued (−40 °C) until the reagent had dissolved (20 min). Saturated aqueous Na_2SO_3 (10 ml) was added, and the mixture warmed to 20 °C, and treated with water (30 ml). The organic material was extracted with diethyl ether and the combined extracts were concentrated and chromatographed (Al_2O_3 Grade V, 1:1 Et_2O–CH_2Cl_2) to give a yellow oil. Crystallisation from dichloromethane–hexane gave the title compound as a yellow solid (90 mg, 26%); $\nu_{max.}$ 3 100br (OH), 2 795 (NMe), 1 950, and 1 890br cm^{-1} (C≡O); δ_H 5.52—5.13 (4 H, m, ArH), 4.25 (1 H, s, br, 4-H), 3.76 [1 H, q, *J* 6.5 Hz, 1-H, (**22**)], 3.33 [1 H, q, *J* 6.5 Hz, 1-H, (**21**)], 3.15, 2.61 [AB system, J_{AB} 12 Hz, 3-H, (**22**)], 2.90 [d, *J* 2.5 Hz, 3-H, (**21**)], 2.48 [3 H, s, 2-Me, (**21**)], 2.45 [3 H, s, NMe, (**22**)], 1.43 [3 H, d, *J* 6.4 Hz, 1-Me (**21**)], 1.29 [3 H, d, *J* 6.5 Hz, 1-Me, (**22**)]; *m/z* 313 (M^+) (Found: C, 53.5; H, 4.7; N, 4.3. $C_{14}H_{15}CrNO_4$ requires C, 53.7; H, 4.8; N, 4.5%).

Tricarbonyl(η⁶-cis-1,2,4-*trimethyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**9**) *from Tricarbonyl*(η⁶-exo-1,2-*dimethyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**8**).—Butyl-lithium (0.5 ml, 0.8 mmol) was added to a stirred solution of complex (**8**) (200 mg, 0.67 mmol) in THF (20 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.2 ml, 3.21 mmol) was added and stirring continued (2 h, −78 °C). Methanol (5 ml) was added, the mixture warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) followed by evaporation and crystallisation from diethyl ether–hexane gave the title compound as yellow needles (140 mg, 67%). This compound was identical with a sample prepared *via* an alternative route.

Tricarbonyl(η⁶-trans-1,2,4-*trimethyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**23**).—Butyl-lithium (0.25 ml, 0.4 mmol) was added to a stirred solution of tricarbonyl(η⁶-*endo*-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**20**) (90 mg, 0.3 mmol) in THF at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.2 ml, 3.21 mmol) was added and stirring continued (2 h, −78 °C). Methanol (1 ml) was added, the mixture warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, Et_2O) followed by removal of the solvent gave a bright yellow solid (65 mg, 69%); $\nu_{max.}$ 1 960 and 1 890br cm^{-1} (C≡O); δ_H 5.53—5.0 4 H, m, ArH), 3.53 (1 H, q, *J* 6.4 Hz, 1-H), 2.98, 2.22 (2 H, ABX system, J_{AB} 12 Hz, 3-H_2), 2.87—2.80 (1 H, m, 4-H), 2.41 (3 H, s, 2-Me), 1.37 (3 H, d, *J* 6.4 Hz, 1-Me), and 1.29 (3 H, d, *J* 7.0 Hz, 4-Me); *m/z* 311 (M^+) (Found: C, 58.2; H, 5.5; N, 4.4. $C_{15}H_{17}CrNO_3$ requires C, 57.9; H, 5.5; N, 4.5%).

1-*Isopropyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**24**).—2-Phenylethylamine (6.3 ml, 50 mmol) was heated with isobutyric acid (7.5 ml, 81 mmol) at 180 °C (3 h). The resulting oil was dissolved in orthophosphoric acid (30 ml, 51.6 mmol), treated with phosphorus pentaoxide (50 g, 352 mmol) and heated (3 h, 200 °C). After being cooled, the mixture was poured onto crushed ice (500 ml), washed with benzene (3 × 100 ml), and neutralised to pH 7 ($NaHCO_3$). The mixture was extracted with benzene and the extract dried (Na_2SO_4) and evaporated to give a yellow oil. Treatment of the latter with ethanol (150 ml) and methyl iodide (7 ml, 112 mmol) followed by heating under reflux (3 h) gave, on cooling, 1-isopropyl-2-methyl-1,2-dihydroisoquinolinium iodide (5.9 g, 37%). A portion of this material (4.0 g, 12.7 mmol) was treated with ethanol (50 ml) and $NaBH_4$ (2.0 g, 53 mmol) with stirring at 20 °C for 6 h, after which the mixture was diluted with water and the product extracted with diethyl ether. Evaporation of the extract gave the title compound as a clear oil (1.11 g, 46%); $\nu_{max.}$ 2 795 (NMe) and 740 (1,2 disubstituted arene) cm^{-1}; δ_H 7.14—7.02 (4 H, m, ArH), 3.22—3.16 (2 H, m), 2.79—2.73 (2 H, m), 2.68—2.62 (1 H, m), 2.46 (3 H, s, 2-Me), 1.96—1.90 (1 H, m), 1.0 [d, *J* 7 Hz, $CH(CH_3)_2$], and 0.85 [d, *J* 7 Hz, $CH(CH_3)_2$]; *m/z* 189 (M^+).

Tricarbonyl(η⁶-1-*isopropyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**25**).—A deoxygenated mixture of dibutyl ether (40 ml), THF (4 ml), 1-isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**24**) (1.0 g, 5.3 mmol), and hexacarbonylchromium (1.4 g, 6.36 mmol) was heated under reflux under nitrogen (27 h). The cooled solution was filtered free from excess of hexacarbonylchromium and the solvents removed. Column chromatography (Al_2O_3 Grade V, Et_2O) followed by evaporation and crystallisation from dichloromethane–hexane gave the title compound as yellow needles (850 mg, 49%), m.p. 84—85 °C; $\nu_{max.}$ 1 970 and 1 890 cm^{-1} (C≡O); δ_H 5.38—5.09 (4 H, m, ArH), 3.23 (1 H, d, *J* 3 Hz, 1-H), 3.06—3.01 (1 H, m, 2.78—2.65 (2 H, m), 2.54 (3 H, s, 2-Me), 2.33—2.28 (1 H, m), 2.00—1.94 [1 H, m, $CH(CH_3)_2$], 0.96—0.90 [6 H, dd, *J* 7 Hz, $CH(CH_3)_2$]; *m/z* 325 (M^+) (Found: C, 59.0; H, 6.1; N, 4.3. $C_{16}H_{19}CrNO_3$ requires C, 59.1; H, 5.9; N, 4.3%).

Methylation of Tricarbonyl(η^6-1-*isopropyl*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline*)*chromium*(0) (**25**) *to give* (**26**).—Butyllithium (1.35 ml, 2.16 mmol) was added to a stirred solution of tricarbonyl(η^6-1-isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinoline)chromium(0) (**25**) (460 mg, 1.42 mmol) in THF (30 ml) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which methyl iodide (0.4 ml, 6.4 mmol) was added and stirring continued (−78 °C, 2 h). Methanol (1 ml) was added and the mixture warmed to 20 °C and concentrated. Column chromatography (Al_2O_3 Grade V, Et_2O–petroleum, 1:1) followed by evaporation gave a yellow oil (340 mg, 55%) which was shown by ^1H n.m.r. spectroscopy to contain three of the four possible arene methylated products in the ratio 1:3:3.3. Important features of the ^1H n.m.r. spectrum for the two major isomers are given: δ_H 5.43—4.97 (m, ArH), 3.27 (d, *J* 3 Hz, 1-H), 3.15 (d, *J* 3 Hz, 1-H other isomer), 2.54 (s, 2-Me), 2.51 (s, 2-Me, other isomer), 2.17 (s, aryl methyl H), 2.15 (s, aryl methyl H other isomer), and 0.96—0.88 (m, $CHMe_2$); $\nu_{max.}$ 1 965, 1 890br cm^{-1} (C≡O); *m/z* 339 (M^+) (Found: C, 59.8; H, 6.3; N, 4.2. $C_{19}H_{21}CrNO_3$ requires C, 60.2; H, 6.3; N, 4.1%).

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