Stereoselective and Regioselective Functionalisation of Protopine Alkaloids: The Synthesis of 1-Substituted O-Methyldihydrocryptopines

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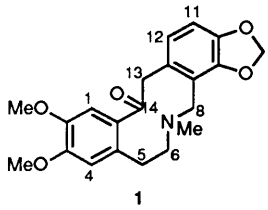
Regio- and diastereo-selective complexation of dihydrocryptopine to the tricarbonylchromium(0) unit proceeds in good yield to give a single diastereoisomer with the chromium attached to the dimethoxyarene ring. An X-ray crystal structure analysis on the product revealed an *exo* disposition of the metal unit relative to the 14-hydroxy group, *O*-Methylation gave *exo*-tricarbonyl(η^6-*O*-methyldihydrocryptopine)chromium(0) which was also the exclusive product of the direct complexation of *O*-methyldihydrocryptopine. Subsequent deprotonation, alkylation (MeI, $CH_2N^+Me_2I^-$) and decomplexation gave the corresponding 1-substituted *O*-methyldihydrocryptopines.

A wide range of naturally occurring protopine alkaloids have been isolated from a variety of sources. These compounds differ primarily in the nature of the substituents on the aromatic rings. A typical example is cryptopine **1** which is present in opium.[1] Many protopine alkaloids have important pharmacological effects.[2] For example, compound **2** has non-narcotic analgesic properties.[3]



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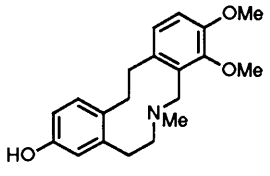

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Many protopine alkaloids possessing a 14-oxo substituent, for example cryptopine **1**, have strong N–C=O transannular interactions, their IR spectra typically showing displacement of the carbonyl absorption bands to lower wavenumber.[1,4] These alkaloids can often be readily converted into protoberberines,[5] and thus there is interest in the synthesis of a wide range of derivatives as possible precursors for biologically active protoberberines. We were interested in the application of tricarbonylchromium(0) methodology to novel derivatives of cryptopine and report here the selective functionalisation of the C-1 position of a derivative in the series.

Results and Discussion

Complexation of cryptopine **1** under standard conditions gave, on work-up, a yellow powder consisting of three compounds. Column chromatography gave two fractions, the major one of which contained two products identified by ^{1}H NMR spectroscopic chemical shifts of the aromatic protons, as the two tricarbonylchromium(0) regioisomers **3** and **4**. Recrystallisation of the mixture from CH_2Cl_2–light petroleum gave exclusively complex **3**, with the metal unit coordinated to the dimethoxy ring. The other chromatographic fraction was identified as a single unassigned diastereoisomer of the bis[tricarbonylchromium(0)] complex **5** also on the basis of its ^{1}H NMR spectrum (Scheme 1). The attachment of the tricarbonylchromium(0) group to either of the two rings of cryptopine **1** in complexes **3**–**5** was confirmed by an upfield shift of the aromatic protons of that ring by 1.2–1.7 ppm in the ^{1}H NMR spectrum (Table 1).

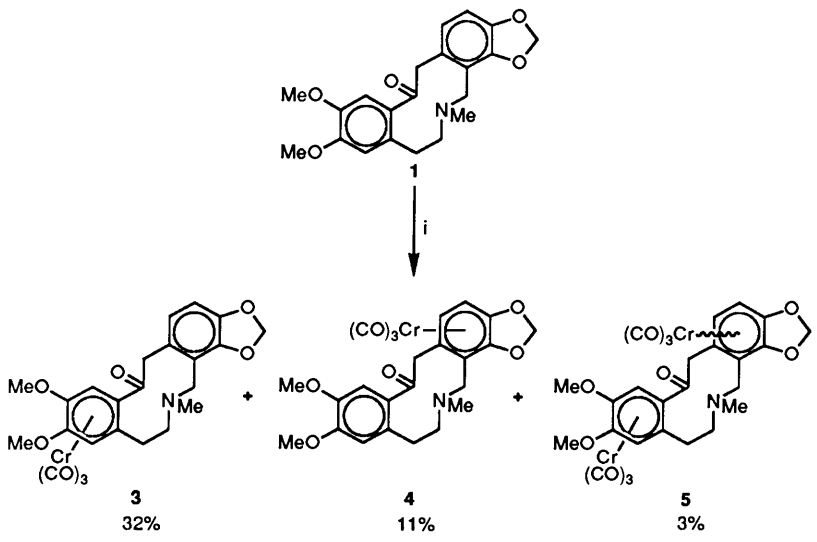
Table 1 ^{1}H NMR chemical shifts ($CDCl_3$) of the aromatic protons of complexes **1** and **3**–**5**

Complex	1-H	4-H	11-H and 12-H
Cryptopine **1**	δ7.01	δ6.69	δ6.72, 6.69 J_{AB} 7.9 Hz
Complex **3**	δ5.73	δ4.97	δ6.75, 6.72 J_{AB} 7.8 Hz
Complex **4**	δ7.03	δ6.69	δ5.52, 4.98 J_{AB} 6.4 Hz
Complex **5**	δ5.67	δ4.94	δ5.52, 4.99 J_{AB} 6.5 Hz

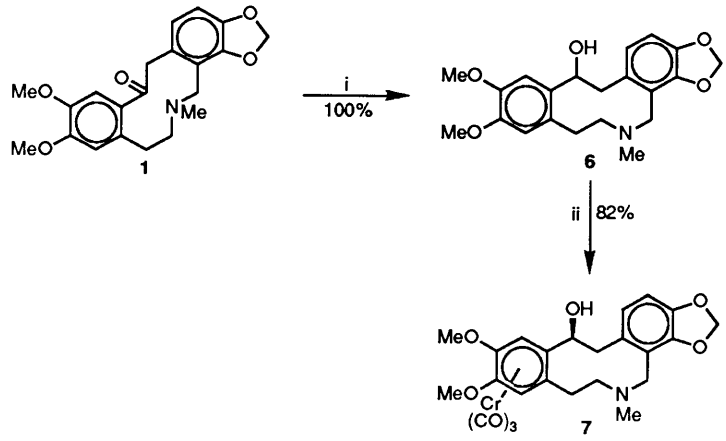
The poor regioselectivity encountered in this reaction demonstrates the similarity in electron density in both arene rings of cryptopine **1**. The 14-oxo group, although somewhat reduced in its electron-withdrawing nature owing to the transannular N–C=O interaction, essentially counteracts the extra electron density[6] provided by the two methoxy functions in the dimethoxy ring.

Reduction of cryptopine **1** to dihydrocryptopine **6** was envisaged as a means of activating the dimethoxy ring to complexation, by removing the electron-withdrawing effect of the carbonyl group. Also benzylic hydroxy groups are known to direct the tricarbonylchromium(0) group to the proximal face in complexations.[7] Furthermore, the presence of a chiral centre at the 14-benzylic position would render the faces of both aromatic rings diastereotopic and, consequently, four possible mono[tricarbonylchromium(0)] complexed products could result. However, whilst overall regioselective complexation to the dimethoxy ring is predicted, the face selectivity will presumably be influenced by the benzylic oxygen substituent, such that the major product diastereoisomer would result from coordination of the metal unit to the arene face proximate to the 14-hydroxy substituent.[7] Treatment of cryptopine **1** with $LiAlH_4$ in THF gave a quantitative yield of dihydrocryptopine **6**. Complexation of compound **6** under standard conditions gave a single product **7** and, therefore, the reaction is both regio-and diastereo-selective as predicted (Scheme 2).

The arene proton peaks in the ^{1}H NMR spectrum of complex **7** consisted of a 2H AB system (δ 6.68, 6.65, J_{AB} 7.9 Hz) and two upfield one proton singlets (δ 5.76, 5.10). The upfield shift of the two singlet peaks is consistent with the metal unit co-ordinated exclusively to the dimethoxy ring of dihydrocryptopine **6**. The identity of complex **7** was confirmed by the presence of a molecular ion *m/z* 507 (M^+) in the mass spectrum and an elemental microanalysis. The regioselectivity of complexation is the same as that observed in the complexation of canadine,



Scheme 1 *Reagents*: i, $Cr(CO)_6$, Bu_2O, THF, heat



Scheme 2 *Reagents*: i, $LiAlH_4$, THF, heat; ii, $Cr(CO)_6$, Bu_2O, THF, heat

where the metal unit also preferentially complexes to the dimethoxy ring due to the greater electron density in this ring.[6] However, the observed regioselectivity may also be due to the benzylic oxygen function directing complexation to the proximate ring.

The regioselectivity of complexation was confirmed by an X-ray crystal structure analysis which also established the relative configurations of the 14-hydroxy and metal moiety. The *exo* disposition of the hydroxy group relative to the chromium within complex **7** is clearly shown in Figure 1. Final atomic co-ordinates and selected torsional angles are presented in Tables 2 and 3.*

The diastereoselective complexation of tricarbonylchromium(0) to dihydrocryptopine **6** to give exclusively the *exo* complex **7**, can be rationalised on the basis of the benzylic oxygen directing effect.[7] Presumably due to the inherent flexibility within the central 10-membered ring, the benzylic hydroxy function can achieve preferred conformations which place it proximate to the *exo* face of the dimethoxy substituted aromatic ring giving, on complexation, the *exo* isomer **7**.

An attempt was made to reduce the ketone function of complex **3**, the major isomer isolated from the complexation of cryptopine **1**, to provide a further route to *exo*-tricarbonyl(η^6-dihydrocryptopine)chromium(0) **7** or its *endo* epimer. Treatment of compound **3** in THF solution with $NaBH_4$ or $LiEt_3BH$ gave no reaction. $LiAlH_4$ reacted with complex **3** to give a low yield of an uncharacterisable mixture of both complexed and decomplexed products. Treatment of complex **3** with Red-Al in THF gave an inseparable mixture of several products containing some *exo*-tricarbonyl(η^6-dihydrocryptopine)-chromium(0) **7** identified by ^1H NMR spectroscopy. The decreased reactivity of the ketone **3** towards hydride donors and lack of diastereoselectivity can be attributed to the presence of a strong transannular N–C=O interaction which drastically reduces the double bond character of the 14-oxo group. Assuming that the conformations of the central 10-membered ring of non-complexed and complexed cryptopine **1** and **3** are similar, the benzylic carbonyl group also lies well out-of-the-plane with the aromatic ring. These two features are responsible for the colour of complex **3**, which is yellow, tricarbonylchromium(0) complexes of arenes possessing a benzylic oxo group are generally orange to red due to the conjugation of the carbonyl with the tricarbonyl(η^6-arene)chromium(0) group.

It is known that treatment of tricarbonyl(η^6-arene)-chromium(0) complexes possessing a benzylic heteroatom substituent undergo rapid S_{N^1} solvolysis upon treatment with acid.[8] Treatment of **7** with both trifluoroacetic acid or HBF_4·OMe_2 in the presence of either water or MeOH gave only starting materials, the resistance of the C(14)–O bond to ionisation presumably demonstrating the inability of the

* Thermal parameters and bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre, See Instructions for Authors (1991), *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

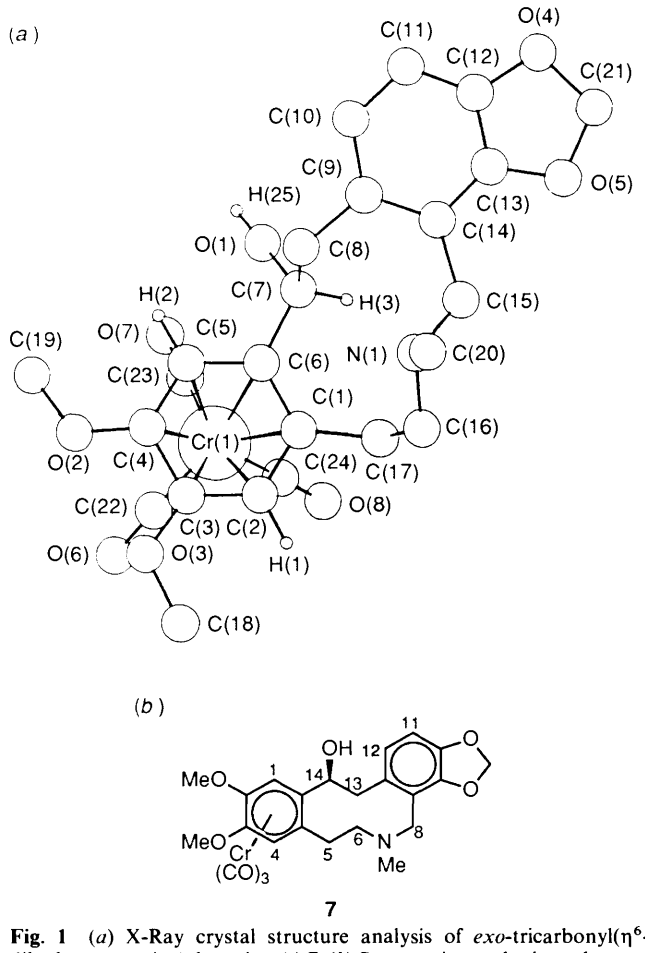


Fig. 1 (*a*) X-Ray crystal structure analysis of *exo*-tricarbonyl(η^6-dihydrocryptopine)chromium(0) **7**. (*b*) Systematic numbering scheme.

complex **7** to achieve a conformation with the hydroxy group *antiperiplanar* to the tricarbonylchromium(0) unit.

exo-Tricarbonyl(η^6-dihydrocryptopine)chromium(0) **7** proved to be unreactive to methylation with MeI in the presence of an excess of BuLi or Bu^{t}Li. Although presumably 14-hydroxy deprotonation was occurring O–Li salts do not readily undergo alkylation when treated with alkyl halides and evidently no dianion was being produced. The 14-hydroxy group was protected by *O*-methylation, performed by sequential treatment of KH and MeI on the *exo* complex **7**, to give the *exo* complex **8**. The ^{1}H NMR spectrum of complex **8** was similar to that of **7** but with the incorporation of a 3 H singlet (δ 3.41) characteristic of a methoxy group. The two aromatic proton signals for the complexed ring (δ 5.73, 4.98) were notably different with one peak being deshielded by about 0.8 ppm. Inspection of the X-ray crystal structure of complex **7** shows the C(1)–H bond *syn* to the C(14)–O bond. Assuming that complex **8** adopts a similar conformation in the solution phase there will be a van der Waals effect due to the steric interaction between the methoxy and C-1 aromatic proton.[9] Consequently, the proton attached to C-1 will be deshielded, by typically 1 ppm. The identity of complex **8** was confirmed by the presence of a molecular ion peak *m*/*z* 522 ($M^+ + 1$) in the mass spectrum and an elemental microanalysis.

A second route to compound **8** was also envisaged involving the *O*-methylation of dihydrocryptopine **6** followed by a chelation controlled regio- and diastereo-selective complexation. Dihydrocryptopine **6** was treated with KH in boiling THF followed by MeI. Work-up gave an excellent yield of *O*-methyldihydrocryptopine **9** characterised by the presence of a new 3 H singlet (δ 3.10) in the ^{1}H NMR spectrum, a molecular ion *m*/*z* 386 ($M^+ + 1$) in the mass spectrum and an elemental microanalysis. Complexation of **9** under standard conditions gave, after work-up, completely regio- and diastereo-selectively a single yellow compound spectroscopically identical with complex **8** (Scheme 3). As for the complexation of dihydrocryptopine **6**, the regioselectivity can be attributed to co-ordination of the metal unit to the most electron-rich ring, whilst the diastereoselectivity may result from *O*-chelate directing effects.

Treatment of *O*-methyldihydrocryptopine **9** with BuLi or Bu^{t}Li under a variety of conditions, followed by MeI quench gave only recovered starting material. In contrast the electron-withdrawing effect of the tricarbonylchromium(0) unit allowed complex **8** to be efficiently metallated at C-1 by BuLi in THF at −40 °C. The metallated species was quenched with MeI or Eschenmoser's salt ($CH_2N^+Me_2I^-$) to give the corresponding novel 1-substituted derivatives **10** and **11** (Scheme 4).

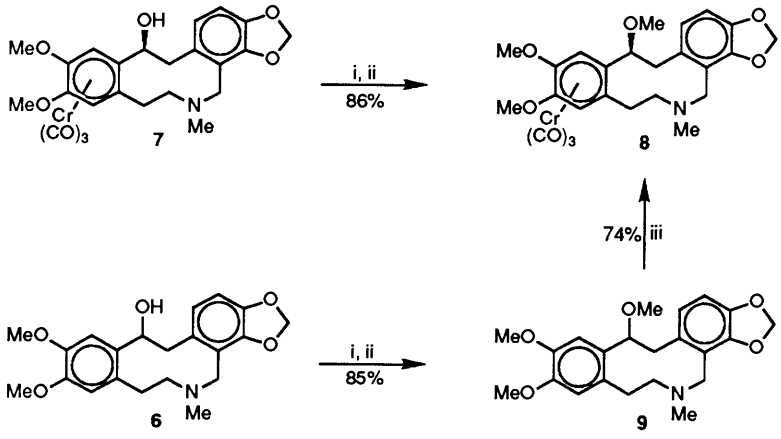
Deprotonation at the C-4 position would be enhanced by the presence of the inductively electron-withdrawing, and possibly chelate-directing, 3-methoxy group, whilst deprotonation at C-1 would be similarly influenced by the 2-methoxy substituent and also favoured by the chelate directing effect of the benzylic 14-methoxy substituent.[10] Consequently, C-1 alkylation would be expected to be favoured over that at C-4.

Table 2 Atomic co-ordinates (x10^4) for complex 7 with estimated standard deviations in parentheses

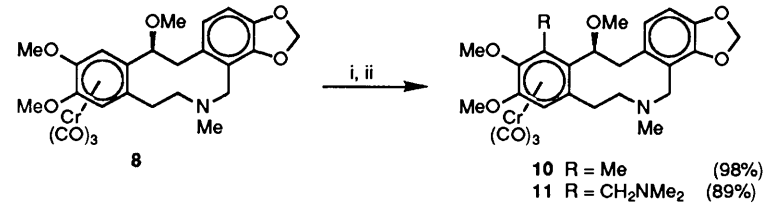
Atom	*x*/*a*	*y*/*b*	*z*/*c*
Cr(1)	8 611(1)	3 287.2(2)	724(1)
N(1)	6 789(5)	4 163.3(9)	−4 228(6)
O(1)	11 636(5)	3 949.2(9)	1 522(6)
O(2)	11 067(6)	2 910.9(9)	−1 575(7)
O(3)	7 534(6)	2 816.9(9)	−3 194(6)
O(4)	10 532(7)	5 303.9(9)	−2 375(7)
O(5)	7 693(5)	5 058.6(8)	−3 140(6)
O(6)	8 169(10)	2 687(1)	2 114(9)
O(7)	11 625(7)	3 393(1)	4 749(7)
O(8)	5 728(7)	3 454(1)	2 532(8)
C(1)	7 347(6)	3 595(1)	−1 812(7)
C(2)	6 748(7)	3 312(1)	−2 553(7)
C(3)	7 983(8)	3 086(1)	−2 492(8)
C(4)	9 963(8)	3 142(1)	−1 595(9)
C(5)	10 570(7)	3 422(1)	−845(8)
C(6)	9 288(6)	3 651(1)	−1 000(7)
C(7)	10 085(7)	3 952(1)	−369(8)
C(8)	10 787(7)	4 081(1)	−1 997(8)
C(9)	10 725(7)	4 409(1)	−2 095(8)
C(10)	12 414(7)	4 564(1)	−1 672(8)
C(11)	12 500(8)	4 865(1)	−1 761(9)
C(12)	10 828(9)	5 009(1)	−2 255(8)
C(13)	9 156(7)	4 863(1)	−2 676(7)
C(14)	9 011(7)	4 566(1)	−2 647(7)
C(15)	7 069(7)	4 432(1)	−3 086(8)
C(16)	5 248(6)	3 985(1)	−4 036(8)
C(17)	5 827(6)	3 821(1)	−2 022(8)
C(18)	5 598(10)	2 747(1)	−4 118(11)
C(19)	12 921(9)	2 922(2)	−346(13)
C(20)	6 546(9)	4 219(2)	−6 341(9)
C(21)	8 529(10)	5 337(1)	−3 002(10)
C(22)	8 374(10)	2 923(1)	1 573(10)
C(23)	10 433(9)	3 353(2)	3 166(10)
C(24)	6 865(8)	3 391(1)	1 829(9)

Table 3 Selected torsional angles for complex 7 (°)

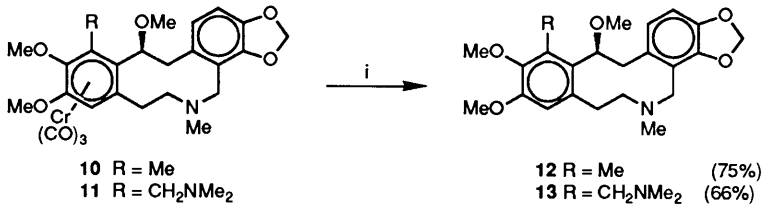
O(1)–C(7)–C(6)–C(5)	−45.47
H(2)–C(5)–C(6)–C(7)	7.53
C(19)–O(2)–C(4)–C(5)	15.20
C(18)–O(3)–C(3)–C(2)	0.24
H(1)–C(2)–C(3)–C(4)	−178.18
C(8)–C(7)–C(6)–C(5)	74.63
C(16)–C(17)–C(1)–C(6)	88.85



Scheme 3 *Reagents:* i, KH, THF; ii, MeI, THF; iii, $Cr(CO)_6$, Bu_2O, THF, heat



Scheme 4 *Reagents:* i, BuLi, THF, −78 °C; ii, MeI or $CH_2N^+Me_2I^-$, THF



Scheme 5 *Reagents:* i, *hv*, O_2

The position of metallation and subsequent alkylation followed from analysis of the ^1H NMR spectrum. The spectrum of complex **8** contained two aryl proton singlets for the complexed ring (δ 5.73, 1-H, δ 4.98, 4-H), assigned on the basis of the extra deshielding of 1-H due to the van der Waals interaction with the C-14 substituent (*vide supra*). The ^1H NMR spectra of the alkylated complexes **10** and **11** both demonstrated loss of the lower field aromatic proton singlet (δ 5.73) with retention of the upfield singlet **10**, δ 4.73; **11**, δ 4.84). This is consistent with exclusive removal of the C-1 aryl proton *via* chelation of BuLi to the benzylic methoxy group, followed by alkylation.[10] Both complexes **10** and **11** were further characterised by elemental microanalyses.

Complexes **10** and **11** were decomplexed by exposing CH_2Cl_2–Et_2O solutions to air and sunlight for several days, giving the free arenes **12** and **13** (Scheme 5).

Conclusion.—Regioselective complexation of the dimethoxy ring of dihydrocryptopine **6** to tricarbonylchromium(0) has been achieved. The reaction also proved to be face-selective, the metal unit complexing to the arene face *exo* to the benzylic hydroxy group. A similar diastereoselective complexation reaction was observed for the *O*-methyl derivative **9**. Regioselective metallation at C-1 of complex **8** was achieved *via* a chelation-controlled deprotonation, under conditions where the corresponding non-complexed analogue is inert. Oxidative decomplexation of the C-1 functionalised derivatives released the free arenes **12** and **13**.

Experimental

All reactions involving the preparation or utilisation of tricarbonyl(η^6-arene) chromium(0) complexes were performed under an atmosphere of nitrogen.[11] All commercial reagents were purified according to standard techniques.[12] THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. Diethyl ether was peroxide free and dibutyl ether was dried over sodium and distilled under an atmosphere of nitrogen prior to use.

Hexacarbonylchromium(0) was steam distilled prior to use. Butyllithium was used as a 1.6 mol dm^{-3} solution in hexanes, potassium hydride was obtained as a 35% dispersion in oil, from which the oil was removed by repeated washings with light petroleum followed by drying *in vacuo*, and methyl iodide was dried over 4 Å molecular sieves. Eschenmoser's salt ($CH_2N^+Me_2I^-$) was recrystallised from dichloromethane–light petroleum and dried *in vacuo*. Column chromatography was performed on alumina (Grade V: Grade I 10% v/v deactivated with water) unless otherwise stated. M.p.s were obtained on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained as solutions in dichloromethane. ^1H NMR spectra were obtained at 300 MHz unless otherwise stated. Mass spectra were obtained using In Beam Electron Impact or Chemical Ionisation techniques.

General Procedure for Preparation of Tricarbonyl(η^6-arene)-chromium(0) Complexes.—A deoxygenated mixture of Bu_2O–THF (10:1), arene and hexacarbonylchromium(0) was heated

at reflux until the formation of the first trace of green precipitate was observed (24–72 h). The cooled solution was filtered through Celite and the solvent evaporated to give the crude complex.

Complexation of Cryptopine **1**.—Thermolysis of hexacarbonylchromium(0) (1.43 g, 6.50 mmol) with cryptopine **1** (2.00 g, 5.42 mmol) under standard conditions (44 ml solvent, 34 h) followed by work-up gave a yellow solid. Column chromatography (Al_2O_3, Grade II) gave two yellow fractions. Fraction one (CH_2Cl_2) was evaporated to give, after recrystallisation from CH_2Cl_2–light petroleum, (η^6,η^6-cryptopine)bis[tricarbonylchromium(0)] **5** as a yellow powder (104 mg, 3%), m.p. decomposes > 183 °C (Found: C, 49.9; H, 3.5; N, 2.0. $C_{27}H_{23}Cr_2NO_{11}$ requires C, 50.6; H, 3.6; N, 2.2%); ν_{max}/cm^{-1} 1965, 1882 br (CO), and 1666 (C=O); δ_H($CDCl_3$) 6.01, 5.85 (2 H, 2 s, OCH_2O), 5.67, 4.94 (2 H, 2 s, 1-H, 4-H), 5.52, 4.99 (2 H, AB system, J_{AB} 6.4, 11-H, 12-H), 3.90, 3.34 (2 H, AB system, J_{AB} 13.6, 8-H or 13-H), 3.84, 2.98 (2 H, AB system, J_{AB} 16.4, 8-H or 13-H), 3.88, 3.81 (6 H, 2 s, ArOCH_3), 3.32–3.24, 3.06–3.00, 2.53–2.47, 2.37–2.29 (4 H, 4 m, 5-H, 6-H), and 1.95 (3 H, s, RR^{1}NCH_3); *m*/*z* 642 (M^+ + 1). Fraction two (MeOH–CH_2Cl_2, 1:1) was evaporated to give tricarbonyl(η^6-cryptopine)chromium(0) as a mixture of regioisomers **3** and **4** (74:26; 1.18 g, 43%). Recrystallisation from CH_2Cl_2–light petroleum gave complex **3** as a yellow powder, ν_{max}/cm^{-1} 1959, 1879 br (CO), and 1660 (C=O); δ_H($CDCl_3$) 6.75, 6.72 (2 H, AB system, J_{AB} 7.8, 11-H, 12-H), 5.96, 5.94 (2 H, AB system, J_{AB} 1.4 OCH_2O), 5.73, 4.97 (2 H, 2 s, 1-H, 4-H), 3.98–3.89, 3.71–3.65, 3.48–3.38, 3.01–2.96, 2.40–2.35 (6 H, 5 m, 5-H, 6-H, 8-H), 3.87 (3 H, s, ArOCH_3), 3.79 (3 H, s, ArOCH_3), 2.99, 2.47 (2 H, AB system, J_{AB} 14.0, 13-H), 1.83 (3 H, s, RR^{1}NCH_3); *m*/*z* 506 (M^+ + 1).

Dihydrocryptopine **6**.—To a THF (100 ml) suspension of cryptopine **1** (5.00 g, 13.6 mmol) was added $LiAlH_4$ (1.03 g, 27.1 mmol) suspended in THF (100 ml). The mixture was stirred (45 h), cooled (0 °C) and MeOH (10 ml) added slowly. Filtration through Celite and evaporation of the solvent gave a viscous gum. Water (150 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 75 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give dihydrocryptopine **6** as a white powder (5.02 g, 100%), m.p. 192–193 °C (Found: C, 68.0; H, 6.9; N, 3.7. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%); ν_{max}/cm^{-1} 3588sh (OH), 2828 (OCH_3), 2780 (NCH_3) and 1602 (arene ring); δ_H($CDCl_3$) 7.12, 6.64 (2 H, 2s, 1-H, 4-H), 6.73, 6.66 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 5.94, 5.92 (2 H, AB system, J_{AB} 1.4, OCH_2O), 5.32 (1 H, d, *J* 7.5, 14-H), 4.02, 3.46 (2 H, AB system, J_{AB} 14.9, 8-H), 3.94, 3.89 (6 H, 2s, ArOCH_3), 3.07–2.99, 2.89–2.86, 2.84–2.50 (6 H, 3m, 5-H, 6-H, 13-H) and 2.14 (3 H, s, RR^{1}NCH_3); δ_C($CDCl_3$) 147.81, 147.53, 146.56, 145.46, 137.88, 133.45, 130.38, 119.29 (8s, Ar*C*), 123.57, 113.79, 109.91, 108.51 (4d, Ar*C*), 100.54 (t, OCH_2O), 71.17 (d, C-14), 59.69, 52.33, 46.63, 32.93 (4t, CH_2), 55.91 (q, ArOCH_3) and 42.40 (q, RR^1 NCH_3); *m*/*z* 372 (M^+ + 1).

exo-*Tricarbonyl*(η^6-*dihydrocryptopine*)*chromium*(0) **7**.—Thermolysis of hexacarbonylchromium(0) (1.42 g, 6.45 mmol) with dihydrocryptopine **6** (2.00 g, 5.39 mmol) under standard conditions (110 ml solvent, 39 h) followed by work-up gave a yellow powder. Column chromatography (Al_2O_3, CH_2Cl_2) gave *exo*-tricarbonyl(η^6-dihydrocryptopine)chromium(0) **7** as a yellow powder (2.24 g, 82%), m.p. decomposes >175 °C (Found: C, 56.7; H, 4.9; N, 2.6. $C_{24}H_{25}CrNO_8$ requires C, 56.8; H, 5.0; N, 2.8%); ν_{max}/cm^{-1} 3590sh (OH), 2836 (OCH_3), 2784 (NCH_3), and 1954 and 1870br (CO); δ_H($CDCl_3$, 500 MHz) 6.68, 6.65 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 5.93, 5.92 (2 H, AB system, J_{AB} 1.0, OCH_2O), 5.76 (1 H, s, 1-H), 5.10 (1 H, s, 4-H), 4.88 (1 H, d, *J* 6.5, 14-H), 3.91, 3.47 (2 H, AB system, J_{AB} 14.9, 8-H), 3.86, 3.86 (6 H, 2 s, ArOCH_3), 3.58–3.56, 2.90–2.81, 2.77–2.72, 2.62–2.57, 2.28–2.25 (6 H, 5m, 5-H, 6-H, 13-H), 2.16 (3 H, s, RR^{1}NCH_3), 1.61 (1 H, s, br, ROH); *m*/*z* 507 (M^+). Recrystallisation from CH_2Cl_2–light petroleum gave small yellow blocks.

X-Ray Crystal Structure Analysis of exo-*Tricarbonyl*(η-*dihydrocryptopine*)*chromium*(0) **7**.—Cell parameters and reflection intensities were measured using graphite monochromated Cu-Kα radiation on an Enraf–Nonius CAD4-F 4-circle diffractometer operating in the $\omega/2\theta$ scan mode. The scan range (ω) was calculated from [1.00 + 0.14 tanθ]°, and the scan speed varied from 1.7 to 6.7° min^{-1} depending upon the intensity. Reflections were measured in the range $0 < \theta < 65°$. Three standard reflections measured every hour were used to scale the data and correct for crystal decomposition. The data were corrected for Lorentz-polarisation and absorption effects [13] and equivalent reflections were merged to give 3667 unique reflections of which 1999 were considered to be observed [$I > 3\sigma(I)$] and used in the structure analysis. Scattering factors were taken from International Tables.[14]

Crystal data. $C_{16}H_{19}CrNO_5$, M = 507.46 monoclinic, space group $P2_1/a$ (established from systematic absences), crystal dimensions 0.4 × 0.5 × 0.7 mm, a = 7.576(2), b = 46.059(7), c = 7.017(3) Å, β = 110.39°, U = 2294.7 Å^3, Z = 4, D_c = 1.47 Mg m^{-3}, μ(Cu-Kα) = 45.90 cm^{-1}. The structure was solved by direct methods and electron density Fourier synthesis. Final full-matrix least-squares refinement included parameters for positional coordinates, anisotropic temperature factors (non-hydrogen atoms), an overall scale factor and an extinction parameter.[15] Hydrogen atoms were included in calculated positions and were allowed to ride on their respective carbon atoms. The refinement was terminated when all shifts were less than 0.001σ with R 0.046, (R_w 0.059). The weight for each reflection was calculated from the Chebyshev series $w = [11.353t_0(X) - 3.746t_1(X) + 7.752t_2(X)]$ where $X = F_0/F_{max}$.[16] Final difference electron-density Fourier synthesis revealed no significant features and a detailed analysis failed to reveal any systematic errors. All calculations were performed using the CRYSTALS package[17] on the Chemical Crystallography Laboratory VAX 11/750 computer.

O-*Methyldihydrocryptopine* **9**.—A solution of dihydrocryptopine **6** (9.60 g, 25.9 mmol) in THF (200 ml) was added dropwise to a stirred suspension of KH (2.41 g, 60.3 mmol) in THF (200 ml). The solution was stirred and heated at reflux (20 h). After cooling (0 °C), MeI (4.78 g, 33.7 mmol) was added and the solution stirred (20 °C, 1.5 h). MeOH (5 ml) was added cautiously and the solution filtered through Celite and evaporated to a pale brown oil. Water (120 ml) was added and the aqueous mixture extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a white powder. Recrystallisation from CH_2Cl_2–light petroleum gave *O*-methyldihydrocryptopine **9** as a white powder (8.46 g, 85%), m.p. 158–160 °C (Found: C, 68.4; H, 7.3; N, 3.5. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.1; N, 3.6%); ν_{max}/cm^{-1} 2828, 2818 (OCH_3), 2781 (NCH_3), 1601 (arene ring), 1091 (C–O–C); δ_H($CDCl_3$) 7.01, 6.65 (2 H, 2 s, 1-H, 4-H), 6.70, 6.63 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 5.94, 5.91 (2 H, AB system, J_{AB} 1.4, OCH_2O), 4.82 (1 H, d, *J* 7.1, 14-H), 4.07, 3.45 (2 H, AB system, J_{AB} 14.9, 8-H), 3.92, 3.89 (6 H, 2s, ArOCH_3), 3.45–3.41, 2.83–2.80, 2.79–2.74, 2.61–2.44 (6 H, 4 m, 5-H, 6-H, 13-H), 3.10 (3 H, s, ROCH_3) and 2.10 (3 H, s, RR^1 NCH_3); δ_C($CDCl_3$) 148.01, 147.57, 146.50, 145.26, 135.59, 133.59, 131.90, 119.10 (8s, Ar*C*), 124.02, 113.38, 108.14, 106.19 (4d, Ar*C*), 100.48 (t, OCH_2O), 80.12 (d, 14-C), 59.67, 52.11,

45.29, 32.51 (4t, CH_2), 56.74, 55.94, 55.86 (3q, ROCH_3) and 42.54 (q, RR^1 NCH_3); *m/z* 386 (M^+ + 1).

exo-*Tricarbonyl*(η^6-O-*methyldihydrocryptopine*)-*chromium*(0) **8**.—*Method 1*. A solution of *exo*-tricarbonyl(η^6-dihydrocryptopine)chromium(0) **7** (500 mg, 0.99 mmol) in THF (15 ml) was added dropwise to a stirred suspension of KH (103 mg, 2.58 mmol) in THF (15 ml) to give an orange solution. Stirring was continued (2 h) followed by addition of MeI (356 mg, 2.51 mmol). After further stirring (3.5 h), MeOH (2 ml) was added and the solution filtered through Celite. Evaporation of the solvent, column chromatography (Al_2O_3, CH_2Cl_2) and recrystallisation of the product from CH_2Cl_2–light petroleum gave *exo*-tricarbonyl(η^6-*O*-methyldihydrocryptopine)-chromium(0) **8** as a yellow powder (445 mg, 86%), m.p. decomposes >194 °C (Found: C, 57.35; H, 5.0; N, 2.7. $C_{25}H_{27}CrNO_8$ requires C, 57.6; H, 5.2; N, 2.7%); ν_{max}/cm^{-1} 2837 (OCH_3), 2785 (NCH_3), 1958 and 1870br (CO); δ_H($CDCl_3$; 500 MHz) 6.67, 6.63 (2 H, AB system, J_{AB} 7.5, 11-H, 12-H), 5.94, 5.91 (2 H, 2 s, OCH_2O), 5.73 (1 H, s, 1-H), 4.98 (1 H, s, 4-H), 4.31 (1 H, d, *J* 5.7, 14-H), 3.91, 3.46 (2 H, AB system, J_{AB} 14.8, 8-H), 3.86, 3.84 (6 H, 2s, ArOCH_3), 3.41 (3 H, s, ROCH_3), 3.46–3.38, 2.90–2.83, 2.79–2.75, 2.62–2.57, 2.27–2.24 (6 H, m, 5-H, 6-H, 13-H) and 2.15 (3 H, s, RR^1NCH_3); *m/z* 522 (M^+ + 1).

Method 2. Thermolysis of hexacarbonylchromium(0) (1.00 g, 4.55 mmol) with *O*-methyldihydrocryptopine **9** (1.00 g, 2.60 mmol) under standard conditions (55 ml solvent, 23 h) gave after work-up and column chromatography (SiO_2, CH_2Cl_2) *exo*-(η^6-*O*-methyldihydrocryptoptine)chromium(0) **8** as a yellow powder (1.00 g, 74%), identified by comparison with an authentic sample.

exo-*Tricarbonyl*(η^6-1,O-*dimethyldihydrocryptopine*)-*chromium*(0) **10**.—BuLi (1.6 mol dm^{-3}; 0.53 ml, 0.85 mmol) was added to a cooled (−78 °C) THF (10 ml) solution of *exo*-tricarbonyl(η^6-*O*-methyldihydrocryptopine)chromium(0) **8** (400 mg, 0.77 mmol) and the mixture stirred (10 min). After warming (−40 °C) and further stirring (2 h), MeI (584 mg, 4.11 mmol) was added and stirring continued (−40 °C, 2 h). The solution was allowed to warm slowly (20 °C) and MeOH (1 ml) added. Evaporation and column chromatography (Al_2O_3, CH_2Cl_2) gave *exo*-tricarbonyl(η^6-1,*O*-dimethyldihydrocryptoptine)chromium(0) **10** as a yellow powder (402 mg, 98%), m.p. decomposes >210 °C (Found: C, 58.4; H, 5.45; N, 2.1. $C_{26}H_{29}CrNO_8$ requires C, 58.3; H, 5.5; N, 2.6%); ν_{max}/cm^{-1} 2839 (OCH_3), 2792 (NCH_3), 1950 and 1870br (CO); δ_H($CDCl_3$) 6.65, 6.63 (2 H, AB system, J_{AB} 8.7, 11-H, 12.-H), 5.95, 5.92 (2 H, AB system, J_{AB} 1.2, OCH_2O), 4.73 (s, 1 H, 4-H), 4.49 (1 H, m, br, 14-H), 3.98, 3.52 (2 H, AB system, J_{AB} 15.2 Hz, 8-H), 3.85, 3.44 (6 H, 2s, ArOCH_3), 3.43–3.37, 2.64–2.56, 2.28–2.23 (3 H, 3m, 5-H, 6-H, 13-H), 3.37 (3 H, s, ROCH_3), 3.16–2.87 (3 H, m, 5-H, 6-H, 13-H), 2.57 (3 H, s, ArCH_3), 2.15 (s, 3 H, RR′NCH_3); *m/z* 535 (M^+). Recrystallisation from CH_2Cl_2–light petroleum gave tin yellow crystals.

exo-*Tricarbonyl*(η^6-O-*methyl*-1-*dimethylaminomethyldihydrocryptopine*)*chromium*(0) **11**.—BuLi (1.6 mol dm^{-3}; 0.66 ml, 1.06 mmol) was added to a cooled (−78 °C) THF (12 ml) solution of *exo*-tricarbonyl(η^6-*O*-methyldihydrocryptopine)-chromium(0) **8** (500 mg, 0.96 mmol) and the mixture stirred (10 min). After the mixture had been warmed (−40 °C) and further stirred (2 h), $CH_2N^+Me_2I^-$ (Eschenmoser's salt, 303 mg, 1.64 mmol) was added and stirring continued (−40 °C, 2 h). After warming slowly (20 °C), MeOH (1 ml) was added. Evaporation, column chromatography (SiO_2, CH_2Cl_2) and recrystallisation from MeOH–CH_2Cl_2, gave the title compound **11** as yellow plates (495 mg, 89%), m.p. >140 °C (decomp.) (Found: C, 58.0; H, 5.9; N, 4.5. $C_{28}H_{34}CrN_2O_8$ requires C, 58.1; H, 5.9; N, 4.8%); ν_{max}/cm^{-1} 2834, 2817 (OCH_3), 2774, 2760 (NMe), 1951 and 1868br (CO); δ_H($CDCl_3$) 6.69, 6.63 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 5.95, 5.91 (2 H, AB system, J_{AB} 1.3, OCH_2O), 4.84 (1 H, s, 4-H), 4.45 (1 H, d, *J* 8.8, 14-H), 4.38, 3.14 (2 H, AB system, J_{AB} 11.9, ArCH_2NR_2), 4.01, 3.49 (2 H, AB system, J_{AB} 15.2, 8-H), 3.89–3.80, 3.36–3.31, 3.21–3.10, 2.96–2.91, 2.72–2.64, 2.30–2.18 (6 H, 6m, 5-H, 6-H, 13-H), 3.87, 3.83 (6 H, 2s, ArOCH_3), 3.31 (3 H, s, ROCH_3), 2.36 [6 H, s, RN(CH_3)$_2$] and 2.16 (3 H, s, RR^1 NCH_3); *m/z* 579 (M^+ + 1).

1,O-*Dimethyldihydrocryptopine* **12**.—*exo*-Tricarbonyl(η^6-1,*O*-dimethyldihydrocryptopine)chromium(0) **10** (250 mg, 0.47 mmol) was suspended in Et_2O (100 ml) and CH_2Cl_2 added until the solid just dissolved. Decomplexation in air and sunlight (96 h) gave on work-up and recrystallisation from CH_2Cl_2–light petroleum, 1,*O*-dimethyldihydrocryptopine **12** as fine white needles (140 mg, 75%), m.p. 168–170 °C (Found: C, 69.2; H, 7.4; N, 3.3. $C_{23}H_{29}NO_5$ requires C, 69.15; H, 7.3; N, 3.5%); ν_{max}/cm^{-1} 2838 (OMe), 2784 (NMe) and 1268 (C–O–C); δ_H($CDCl_3$) 6.71, 6.62 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 6.55 (s, 1 H, 4-H), 5.05 (1 H, d, *J* 8.0, 14-H), 4.11, 3.48 (2 H, AB system, J_{AB} 15.1, 8-H), 3.86, 3.80 (6 H, 2s, ArOCH_3), 3.53–3.48, 2.84–2.78 (2 H, 2 m, 5-H, 6-H, 13-H), 3.26–3.10, 2.56–2.43 (4 H, 2m, 5-H, 6-H, 13-H), 3.09 (3 H, s, ROCH_3), 2.53 (3 H, s, ArCH_3) and 2.09 (3 H, s, RR^1NCH_3); δ_C($CDCl_3$) 151.13, 146.63, 146.53, 145.31, 136.93, 133.46, 132.67, 131.14, 118.76 (9s, ArC), 124.43, 111.80, 106.23 (3d, ArC), 100.52 (t, OCH_2O), 80.92 (d, 14-C), 59.96, 56.47, 55.54 (3q, ArOCH_3, ROCH_3), 59.96, 52.14, 42.74, 33.78 (4t, CH_2), 43.18 (q, RR^1NCH_3) and 12.31 (q, ArCH_3); *m/z* 399 (M^+).

O-*Methyl*-1-*dimethylaminomethyldihydrocryptopine* **13**.—*exo*-Tricarbonyl(η^6-*O*-methyl-1-dimethylaminomethyldihydrocryptopine)chromium(0) **11** (238 mg, 0.41 mmol) was dissolved in a mixture of Et_2O–CH_2Cl_2 (1:1; 100 ml). Decomplexation in air and sunlight (96 h) gave on work-up and recrystallisation from CH_2Cl_2–light petroleum, the title compound **13** as white blocks (120 mg, 66%), m.p. 100–103 °C; ν_{max}/cm^{-1} 2834, 2810 (OMe), 2781, 2761 (NMe) and 1589 (arene ring); δ_H($CDCl_3$) 6.71, 6.62 (2 H, AB system, J_{AB} 7.9, 11-H, 12-H), 6.65 (1 H, s, 4-H), 5.94, 5.91 (2 H, 2s, OCH_2O), 5.08 (1 H, d, *J* 7.3, 14-H), 4.07–4.02, 3.49–3.43, 2.86–2.82 (3 H, 3m, 5-H, 6-H, 8-H, 13-H or ArCH_2NR_2), 3.87, 3.86 (6 H, 2s, ArOCH_3), 3.65–3.60, 2.65–2.47 (4 H, 2m, 5-H, 6-H, 8-H, 13-H or ArCH_2NR_2), 3.28–3.18 (3 H, m, 5-H, 6-H, 8-H, 13-H or ArCH_2NR_2), 3.09 (3 H, s, ROCH_3), 2.11 [6 H, s, RN(CH_3)$_2$] and 2.02 (3 H, s, RR^1NCH_3); *m/z* 442 (M^+).

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