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THE STEREOSPECIFIC SYNTHESIS OF (-)-(8R) AND (-)-(8S)-METHYLCANADINE

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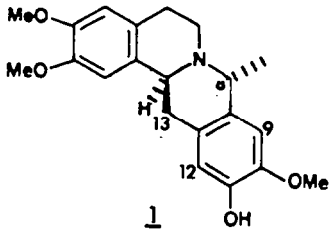
Summary: Regioselective complexation of the dimethoxy arene ring of canadine to the Cr(CO)$_3$ moiety gives two diastereoisomers which are separated by flash chromatography. Deprotonation of either diastereoisomer with n-butyllithium followed by addition of methyl iodide or trimethylsilyl chloride gives C11-methyl- or -trimethylsilylcanadine after decomplexation. Each diastereoisomer of the C11-trimethylsilylcanadine complex may be treated with base and methyl iodide to give, after desilylation and decomplexation, the enantiomerically pure (-)-(8R) and (-)-(8S) methyl canadines; racemic samples of C8-methylcanadines are prepared via an independent route.

INTRODUCTION

The protoberberines are a widespread class of natural products which incorporate the tetrahydroisoquinoline skeleton.[1] Many of these compounds differ only in the nature and position of the oxygen substituents in rings A and D of the tetracyclic ring system. However, a number of C8- and C13-benzylically substituted protoberberines are also known. Corytenchirine (1) has been isolated from Corydalis ochotensis[2] whilst thalictricavine (2) has been isolated from Corydalis tuberosa.[3] Ophiocarpine (3) has a C13-hydroxyl substituent and has been extracted from Corydalis ophiocarpa.[4]



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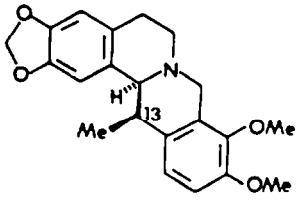

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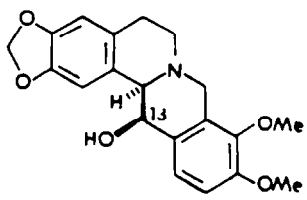

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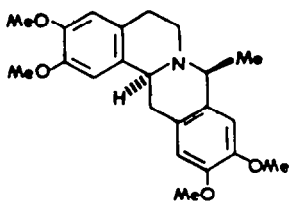
No asymmetric syntheses of C13- or C8-substituted protoberberines have been reported although optically active coralydine (4) and O-methylcorytenchirine (5) have been prepared by cyclisation of (±)-tetrahydropapaverine with acetaldehyde, separation of the resulting diastereoisomeric products and resolution; or by independant cyclisation of either (R)-(+)- or (S)-(-)- tetrahydropapaverine with acetaldehyde and separation of the diastereoisomeric products.[5] The synthesis of racemic mesothalictricavine (6) has also been reported.[6]



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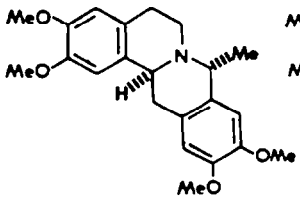

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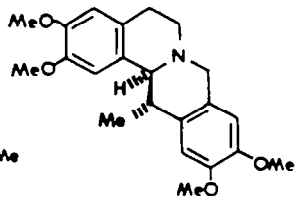


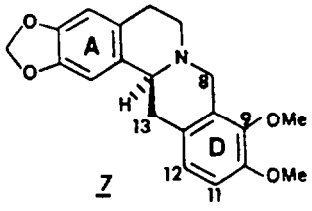
(±)6

We have previously reported the highly stereoselective benzylic functionalisation of tetrahydroisoquinoline systems via complexation to the chromium tricarbonyl moiety[7] and report here the extension of this methodology to the preparation of C11- and C8-substituted protoberberines. The synthesis of (-)-(8R)- and (-)-(8S)-canadine is described. Part of this work has been the subject of a preliminary communication.[8]

(-)-Canadine (7) can be isolated from Hydrastis Canadensis[9] whilst (+)-canadine has been isolated from Corydalis tuberosa.[10] (±)-Canadine is readily obtained by reduction of berberine and, in addition, several total syntheses have been reported.[11] The resolution of (±)-canadine has also been described.[10,12]

Results and Discussion

The complexation of arene systems to the chromium tricarbonyl moiety is facilitated by electron donating arene substituents[13] yet the selective complexation of the chromium tricarbonyl moiety to the more electron rich ring of a molecule containing two isolated, inequivalent aromatic systems has not yet been reported. The two arene rings of (-)-canadine (7) differ only in the nature of the oxygen substituents; ring A bears a methylenedioxy bridge whilst ring D possesses two methoxy substituents.



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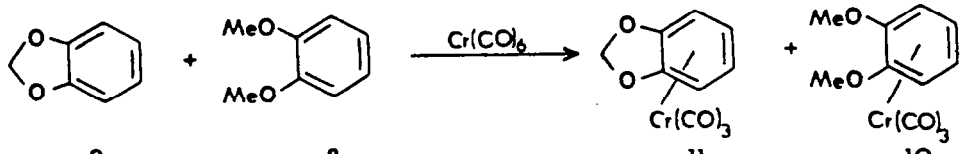
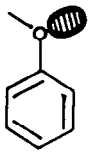
A competition experiment involving the thermolysis of hexacarbonyl chromium in di-n-butyl ether and THF containing 1,2-dimethoxybenzene (8) (1 equivalent) and 1,3-benzodioxole (9) (1 equivalent) gave a 10:1 mixture of complexes (10) and (11) respectively.



9 8 11 10

Preferential complexation to 1,2-dimethoxybenzene (8) implies a greater electron density in this π-arene ligand with respect to 1,3-benzodioxole (9). This may be a result of the greater mesomeric electron donating capacity of the methoxy substituents in (8) with respect to the methylene dioxy bridge in (9), an effect which has been implicated in the enhanced rate of alkaline hydrolysis of ethyl-3,4-methylenedioxybenzoate with respect to ethyl-3,4-dimethoxybenzoate.[14] Calculations have shown that the π-electron density at the ortho-position in anisole (12) which is s-cis to the methoxy group is higher than at the s-trans-position.[15] This has been attributed to mesomeric electron donation by the trans-antiperiplanar lone pair of electrons on the oxygen atom.[16] In 1,2-dimethoxybenzene (8), two such stereoelectronic effects are possible whilst in (9) the constraint of the five membered ring may prevent electron donation by both antiperiplanar lone pairs. Enhanced inductive electron withdrawal by the methylenedioxy bridge with respect to the methoxy substituents may also account for the observed regioselectivity although the pKa's of 3,4-dimethoxybenzoic acid (4.5) and 3,4-methylenedioxybenzoic acid (4.43) are not appreciably different.[14]



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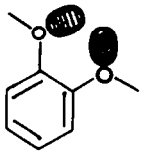

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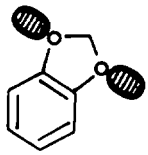

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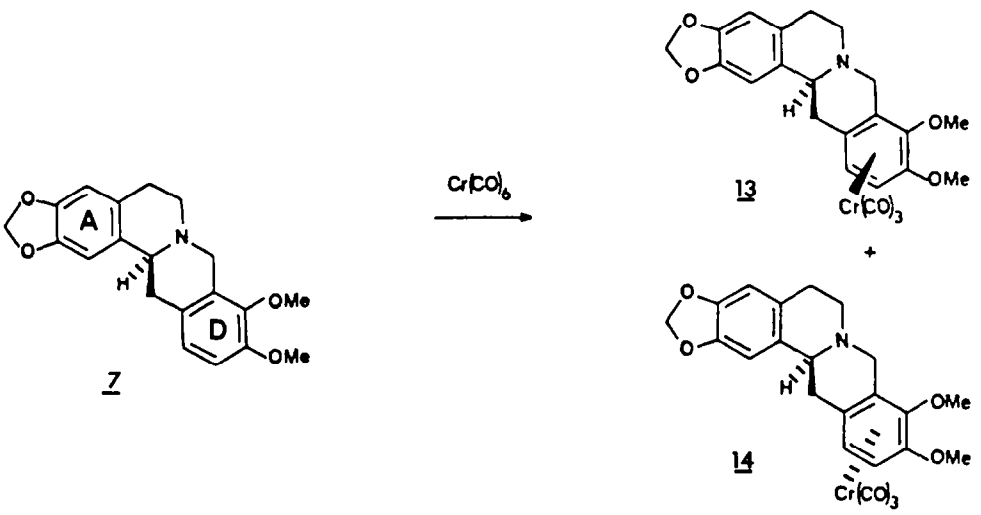
Following the success of the model study, regioselective monocomplexation of (-)-canadine (7) was attempted. (-)-Canadine (7), obtained from its HCl salt, exhibited a melting point (134°) and optical rotation {$[\alpha]_D^{\circ}$ -291° (c, 0.93 in $CHCl_3$)} in agreement with literature values.[17] The ^1H n.m.r. spectrum exhibited an AB quartet δ6.87, 6.80 (J_{AB} = 8.5 Hz, 2H, C11- and C12-protons), singlets δ6.74(1H), 6.60(1H) and 5.93(2H, br) (C1, C4 and OCH_2O protons) and a singlet δ3.86(OMe). The presence of Bohlmann bands in the solution infrared spectrum indicated the presence of a trans-B/C ring junction.[18]

Thermolysis of hexacarbonyl chromium in di-n-butyl ether and THF containing (-)-canadine (7) gave a yellow gum which was shown to consist of (7) and a 3:2 mixture of two of the four possible isomers of (canadine)$Cr(CO)_3$ (13). Flash chromatography enabled the two diastereoisomers to be separated on a large scale. The less polar, major fraction gave a yellow foam which could not be crystallised. The ^1H n.m.r. spectrum showed noticeable differences from that of canadine (7). The AB quartet characteristic of the C11- and C12-protons had shifted upfield, δ5.35, 5.14 (J_{AB} = 6.8 Hz) indicative of complexation of ring D of canadine (7) to the $Cr(CO)_3$ moiety. The C9- and C10-methoxy substituents gave rise to two singlets δ3.93 and δ3.83. Two singlets δ6.59 and δ6.55 were assigned to the C1- and C4-protons of the free arene ring whilst an AB quartet δ4.08, 3.63 (J_{AB} = 16 Hz) was assigned to the diastereotopic C8-protons. A multiplet δ3.51-3.41 (1H) was tentatively assigned to the C14-proton. The presence of Bohlmann bands in the solution infrared spectrum indicated a trans-B/C fused ring system[18].

The more polar, minor fraction from the chromatographic separation gave a yellow foam which could be crystallised to yellow blocks. The ^1H n.m.r. spectrum again exhibited an AB quartet δ5.33, 5.12 (J_{AB} = 6.9 Hz) characteristic of the C11- and C12-protons where the $Cr(CO)_3$ ring is attached to ring D. Two singlets δ6.65 and δ6.57 were characteristic of the C1- and C4-protons of the free A ring. The diastereotopic C8-protons appeared as an AB quartet δ4.17, 3.68 (J_{AB} = 16 Hz) whilst the methoxy groups appeared as two singlets δ3.93 and δ3.84. A multiplet δ3.65-3.61 (1H) was tentatively assigned to the C14-proton. The presence of Bohlmann bands in the solution infrared spectrum indicated a trans-B/C fused ring system.[18]

It was evident from the data outlined above that the two diastereoisomers obtained on complexation of (-)-canadine (7) to the $Cr(CO)_3$ moiety both contained a single metal unit attached to the dimethoxy arene ring. That no products corresponding to complexation of the 1,3-benzodioxole moiety could be detected is consistent with the model study outlined above. Since complexation can occur to either face of the dimethoxy arene ring, the two diastereoisomeric products (13) and (14) differ in the relationship of the $Cr(CO)_3$ unit to the C14-hydrogen. An X-ray crystal structure analysis (Figure 1) was performed on a single crystal of the more polar, minor diastereoisomer grown from a saturated dichloromethane/hexane solution. This established the endo-relationship of the C14-hydrogen to the $Cr(CO)_3$ moiety in the minor diastereoisomer (14) and hence the exo-relationship of the C14-hydrogen to the metal moiety in the major diastereoisomer (13).



Selected bond lengths, angles and final atomic coordinates are given in Tables 1 and 2. Features arising from the X-ray crystal structure (Figure 1) include the trans-B/C fused ring junction, consistent with the appearance of Bohlmann bands in the solution infrared spectrum, and the almost planar nature of the organic ligand. The C11-methoxy group is forced exo out of the plane of the arene ring by the two proximate ortho-substituents and the bulky $Cr(CO)_3$ moiety.

Table 1

Atomic Positional Coordinates and Isotropic or Equivalent Isotropic Temperature Factors with Estimated Standard Deviations in Parentheses for endo-(canadine)Cr(10)$_3$ (14).

Atom	x/a	y/b	z/c	U(iso)
CR(1)	-0.8190(1)	0.04582(6)	0.52406(5)	0.0392
O(1)	-0.7459(5)	-0.0895(3)	0.6676(2)	0.0482
O(2)	-0.9745(6)	-0.1555(3)	0.5720(3)	0.0561
O(3)	-0.8507(7)	0.5825(3)	0.6054(2)	0.0634
O(4)	-0.7795(7)	0.6292(3)	0.7275(2)	0.0646
O(5)	-0.8215(9)	0.2005(4)	0.4162(4)	0.0905
O(6)	-0.748(1)	-0.0816(6)	0.3991(4)	0.0987
O(7)	-0.4530(7)	0.0629(7)	0.5461(3)	0.0896
C(1)	-0.8525(6)	-0.0299(3)	0.6318(3)	0.0368
C(2)	-0.9708(7)	-0.0632(3)	0.5814(3)	0.0439
C(3)	-1.0785(8)	-0.0017(4)	0.5447(3)	0.0439
C(4)	-1.0650(8)	0.0917(4)	0.5610(3)	0.0442
C(5)	-0.9494(7)	0.1265(4)	0.6120(3)	0.0395
C(6)	-0.9366(8)	0.2276(4)	0.6277(3)	0.0452
C(7)	-0.7686(7)	0.2527(4)	0.6615(3)	0.0419
C(8)	-0.7650(7)	0.3530(4)	0.6829(3)	0.0431
C(9)	-0.8114(9)	0.4174(4)	0.6296(3)	0.0502
C(10)	-0.814(1)	0.5081(4)	0.6503(3)	0.0499
C(11)	-0.7712(8)	0.5351(4)	0.7205(3)	0.0518
C(12)	-0.7178(8)	0.4745(4)	0.7732(3)	0.0501
C(13)	-0.7132(8)	0.3816(4)	0.7532(3)	0.0470
C(14)	-0.6542(9)	0.3125(4)	0.8089(3)	0.0520
C(15)	-0.6054(8)	0.2248(4)	0.7717(3)	0.0508
N(16)	-0.7434(6)	0.1951(3)	0.7255(2)	0.0398
C(17)	-0.7146(8)	0.0994(4)	0.7024(3)	0.0433
C(18)	-0.8410(7)	0.0658(3)	0.6472(3)	0.0397
C(19)	-0.817(1)	-0.1241(4)	0.7359(3)	0.0590
C(20)	-1.070(1)	-0.1914(4)	0.5122(4)	0.0678
C(21)	-0.863(1)	0.6552(3)	0.6594(3)	0.0664
C(22)	-0.819(1)	0.1400(5)	0.4579(4)	0.0601
C(23)	-0.777(1)	-0.0322(6)	0.4488(4)	0.0652
C(24)	-0.5980(9)	0.0577(6)	0.5359(3)	0.0582
H(1)	-1.1625(8)	-0.0241(4)	0.5081(3)	0.0500
H(2)	-1.1412(8)	0.1355(4)	0.5355(3)	0.0500
H(3)	-1.0267(8)	0.2453(4)	0.6631(3)	0.0500
H(4)	-0.9510(8)	0.2617(4)	0.5800(3)	0.0500
H(5)	-0.6770(7)	0.2383(4)	0.6260(3)	0.0500
H(6)	-0.8436(9)	0.3983(4)	0.5783(3)	0.0500
H(7)	-0.6831(8)	0.4953(4)	0.8237(3)	0.0500
H(8)	-0.7459(9)	0.3002(4)	0.8450(3)	0.0500
H(9)	-0.5562(9)	0.3377(4)	0.8361(3)	0.0500
H(10)	-0.5802(8)	0.1777(4)	0.8103(3)	0.0500
H(11)	-0.5052(8)	0.2347(4)	0.7399(3)	0.0500
H(12)	-0.7200(8)	0.0597(4)	0.7475(3)	0.0500
H(13)	-0.6017(8)	0.0948(4)	0.6797(3)	0.0500
H(14)	-0.737(1)	-0.1669(4)	0.7595(3)	0.0500
H(15)	-0.840(1)	-0.0720(4)	0.7696(3)	0.0500
H(16)	-0.922(1)	-0.1571(4)	0.7240(3)	0.0500
H(17)	-1.063(1)	-0.2596(4)	0.5116(4)	0.0500
H(18)	-1.189(1)	-0.1723(4)	0.5178(4)	0.0500
H(19)	-1.025(1)	-0.1667(4)	0.4645(4)	0.0500
H(20)	-0.983(1)	0.6674(3)	0.6699(3)	0.0500
H(21)	-0.810(1)	0.7115(3)	0.6590(3)	0.0500

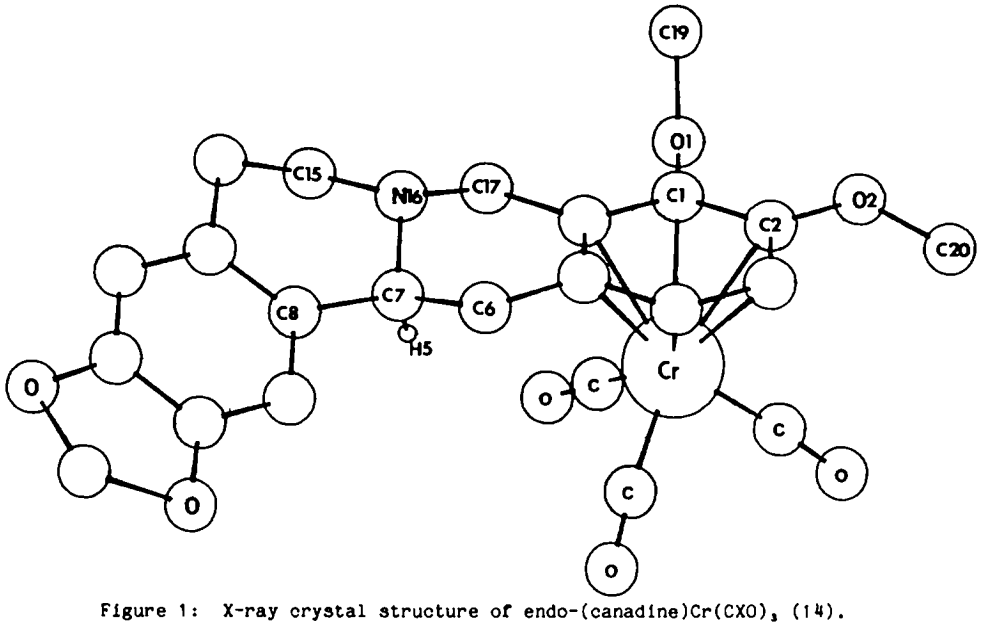


Figure 1: X-ray crystal structure of endo-(canadine)Cr(CXO)$_3$ (14).

Table 2

Selected Bond Lengths and Torsional Angles for endo-(canadine)Cr(CO)$_3$ (14).

Mean CR(1) - Arene C	**2.24**
Mean Arene C - Arene C	**1.41**

C(3)-C(2)-O(2)-C(20)	**+13**
C(2)-C(1)-O(1)-C(19)	**-92**
C(8)-C(7)-N(16)-C(17)	**-165**
C(15)-N(16)-C(7)-C(6)	**-169**
H(5)-C(7)-N(16)-C(17)	**-45**
H(5)-C(7)-N(16)-C(15)	**+75**

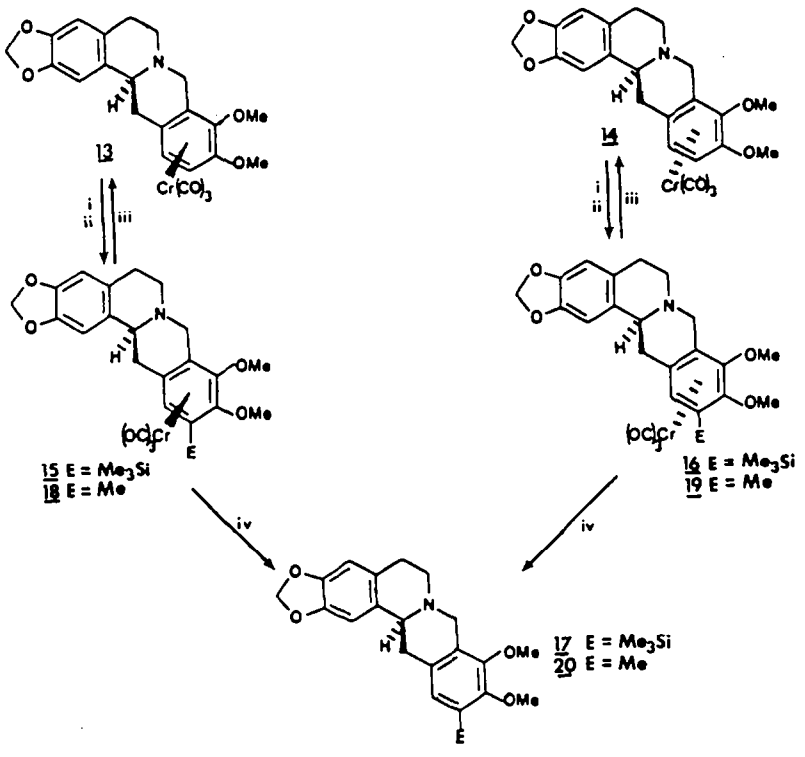
Treatment of either (13) or (14) with n-butyllithium at -78°C followed by trimethylsilyl chloride gave in each case a single diastereoisomer of substituted product (Scheme 1). In both cases the AB quartet attributable to the C11- and C12-protons in the ^{1}H n.m.r. spectra of (13) and (14) had collapsed to a singlet (1H), whilst a high field nine proton singlet had appeared indicative of C11 or C12 functionalisation. Decomplexation of either product (15) or (16) according to the standard procedure gave the same compound (17). The ^{1}H n.m.r. spectrum of compound (17) exhibited three downfield singlets, δ6.92 (1H, C11 or C12 proton) and δ6.74 (1H), 6.60 (1H) (C1 and C4 protons). Other characteristic resonances included a multiplet δ5.93-5.92 (2H, OCH_2O), singlets δ3.85 (6H, C9 and C10 OCH_3) and δ0.29 (9H, $SiMe_3$) and an AB quartet δ4.28, 3.57 (J_{AB} = 16 Hz) indicative of the diastereotopic C8-protons. A nuclear Overhauser enhancement (n.O.e.) experiment involving irradiation of the downfield singlet δ6.92 gave an enhancement to the C13-benzylic (3.71%) and trimethylsilyl (1.3%) resonances with no enhancement to the C10-methoxy resonance. This established that the trimethylsilyl group had been introduced at C11 and the singlet δ6.92 (1H) corresponded to the remaining C12-proton. The formation of complexes (15) and (16) is consistent with n-butyllithium mediated arene deprotonation directed by the C10-methoxy group. The ortho-directing effect of the methoxy substituent in lithiations of anisole and (anisole)Cr(CO)$_3$ is well known.[19]

Treatment of THF solutions of complexes (15) or (16) with tetra-n-butylammonium fluoride trihydrate regenerated complexes (13) and (14) respectively. The optical rotations of complexes (13) and (14) were identical with those of authentic samples. The facile removal of the trimethylsilyl group can be attributed to stabilisation of the resulting anion by the chromium tricarbonyl moiety.[20] Phenyltrimethylsilane does not undergo fluoride catalysed desilylation. This

methodology allows the trimethylsilyl group to be used as protection for the C11 proton of (canadine)$Cr(CO)_3$.

In a control experiment treatment of (-)-canadine (13) with n-butyllithium under similar conditions to those used above followed by the addition of an electrophile (e.g. methyl iodide) resulted only in recovery of starting material.

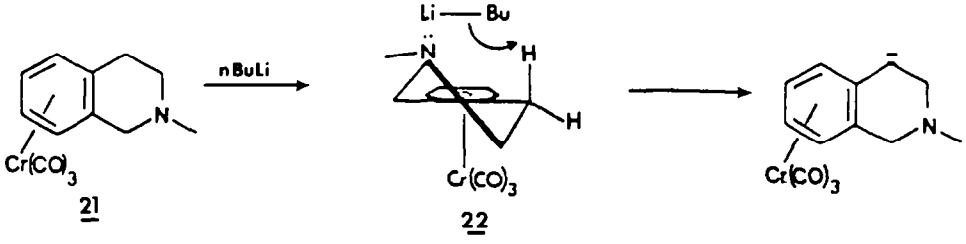
Treatment of either (13) or (14) with n-butyllithium followed by methyl iodide gave the C11-methylated complexes (18) and (19) respectively which were assigned by analogy with the trimethylsilyl substituted complexes (15) and (16). Decomplexation of either (18) or (19) gave 11-methylcanadine (20) as a white solid.



(i) nBuLi, (ii) E^+(MeI, Me_3SiCl), (iii) nBu_4NF(E=Me_3Si), (iv) O_2.

Scheme 1

It was predicted that treatment of the 11-trimethylsilylcanadine complexes (15) and (16) with base would generate either a C8- or C13-benzylic carbanion since the remaining activated arene proton (C12-H) is effectively protected by the bulky C11-trimethylsilyl group. We have previously shown that the exo-C4-proton of (N-methyl-tetrahydroisoquinoline) $Cr(CO)_3$ (21) may be removed by treatment with n-butyllithium.[7] The regio- and stereoselectivity of this deprotonation can be understood in terms of initial coordination of the lithium of n-butyllithium to the axial nitrogen lone pair of the heterocycle followed by stereoselective removal of the exo-C4-proton via a six-membered cyclic transition state (22).[7]



Treatment of complex (21) with t-butyllithium, however, gives rise to both exo-C4 deprotonation via the mechanism shown above and exo-C1-deprotonation without chelation of the base to the nitrogen lone pair.[7]

In complex (15) the nitrogen lone pair is forced endo with respect to the $Cr(CO)_3$ moiety by the trans-B/C ring junction (Figure 2). Chelation controlled, n-butyllithium mediated deprotonation via coordination of the base to the nitrogen lone pair is therefore unlikely. Any coordination of the base to the nitrogen lone pair would require a ring 'flip' to give the cis-B/C fused system; this would place the A and B rings proximate to the bulky $Cr(CO)_3$ moiety.

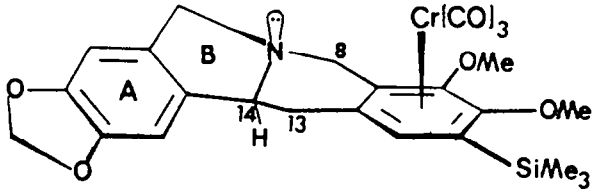


Figure 2. exo-(11-Trimethylsilylcanadine)$Cr(CO)_3$ (15)

The stabilising effect of a para-trimethylsilyl group towards benzylic carbanion formation demonstrated by Jaouen[21] along with the possible chelating ability of the C9-methoxy group suggested that deprotonation of (15) would occur at the C8-position.

In complex (16) the nitrogen lone pair is now exo with respect to the metal moiety and therefore available for coordination to an incoming base (Figure 3). Deprotonation by n-butyllithium would therefore be expected to occur at C13 via a six-membered cyclic transition state. However the presence of a silyl group para to the C8-position would be expected to enhance the acidity of the exo-C8-proton and favour t-butyllithium mediated C8-deprotonation without prior coordination of the base to the nitrogen lone pair.

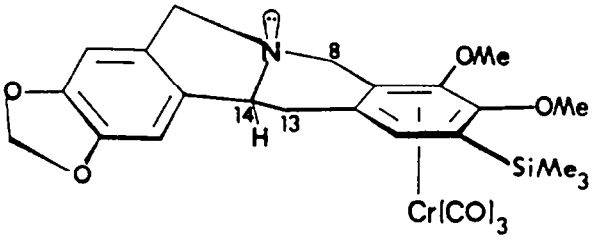
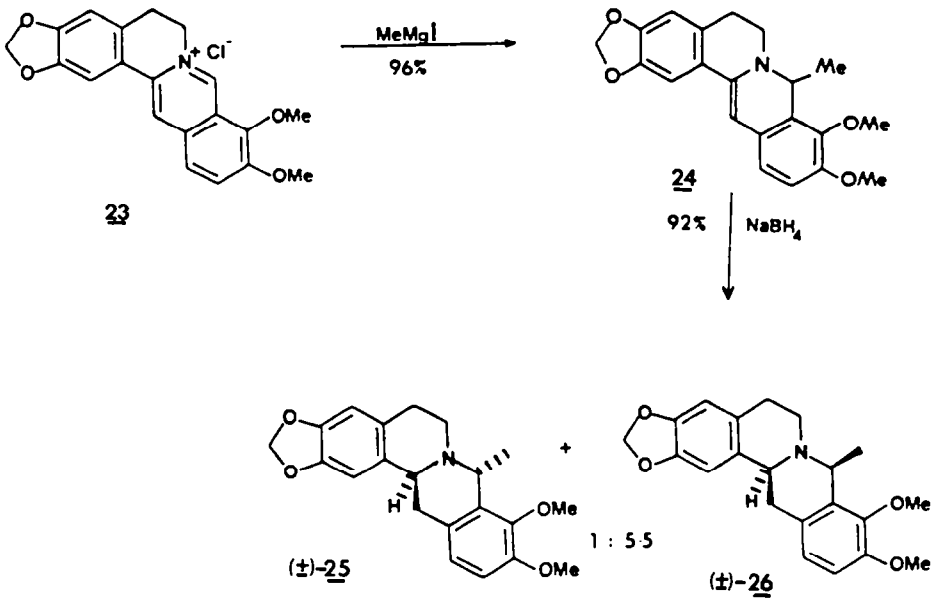


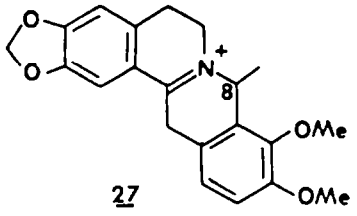
Figure 3. (11-Trimethylsilylcanadine)$Cr(CO)_3$ (16)

Methylation of the carbanions generated from complexes (15) and (16) followed by desilylation (vide supra) and decomplexation would give the C8- and/or C13-methylcanadines. Both diastereoisomers of 13-methylcanadine have been reported (vide supra).[22]

The C8-methylcanadines have not been isolated from natural sources and their synthesis has not been reported. Gear and Spenser have prepared the analogous C8-benzyl compound however,[23] and modification of their procedure gave the required authentic samples of C8-methylcanadine with the C8-methyl group cis- or trans- to the C14-hydrogen. Treatment of achiral berberine chloride (23) with methylmagnesium iodide gave the enamine (24) as a yellow crystalline solid. Reduction of (24) with sodium borohydride gave a mixture of (±)-(25) and (±)-(26) (in the ratio 1:5.5) which were separated by flash chromatography.



The predominance of (26) bearing the C8-methyl group trans with respect to the C14-hydrogen is consistent with approach of borohydride from less hindered face away from the C8-methyl group in the reduction of the intermediate imine (27).



Essential features of the ^{1}H n.m.r. spectra of compounds (25) and (26) are given in Table 3. The major differences between the chemical shifts of the C8-methyl group, C8-proton and C14-proton along with the presence of strong and weak Bohlmann bands for (25) and (26) respectively are consistent with compound (26) adopting a conformation in which the B/C ring junction is cis-fused and compound (25) adopting a trans-B/C fused-ring junction.[1,2,18,28]

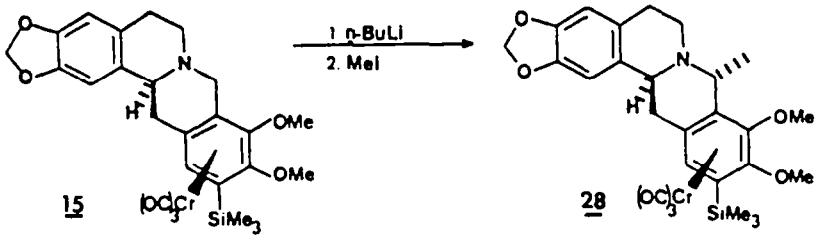
Table 3. Selected ^{1}H n.m.r. data for the C8-methylcanadines (25) and (26)

Compound	δ_H p.p.m. C11, C13-H	C1, C4-H	C8-H	C14-H	C9, C10-OMe	C8-Me
(25)	6.82, 6.79 (AB system) (J_{AB}=8.5Hz)	6.59(s) 6.69(s)	4.33(q) (J=6.7Hz)	4.24-4.18 (m)	3.90(s) 3.86(s)	1.39(d) (J=6.7Hz)
(26)	6.89, 6.81 (AB system) (J_{AB}=8.5Hz)	6.77(s) 6.60(s)	3.83(q) (J=6.1Hz)	3.55(d,br) (J=10.9Hz)	3.88(s) 3.87(s)	1.52(d) (J=6.1Hz)

The above method therefore gives the 8-methylcanadines (25) and (26) but the reaction is neither enantio- nor highly diastereoselective.

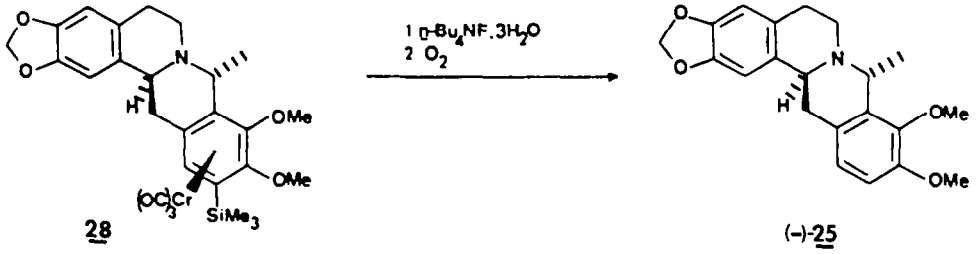
The trimethylsilyl substituted complex (15) with the C14-hydrogen exo- and the nitrogen lone pair endo- with respect to the Cr(CO)$_3$ moiety was treated with n-butyllithium followed by methyl iodide to give a yellow foam. The ^{1}H n.m.r. spectrum of this crude product exhibited a new

doublet δ1.47 (J = 6.7 Hz) and a quartet δ4.25 (J = 6.7 Hz) characteristic of a methyl substituent at the C8-position. The AB quartet characteristic of the C8-protons present in the ^{1}H n.m.r. spectrum of complex (15) was no longer evident. Only a single diastereoisomer could be detected and this was assigned as the (8R, 14S)-exo-methylcanadine complex (28) by analogy with other benzylic substitutions of (arene)Cr(CO)$_3$ complexes where the alkylating agent approaches from the exo-face away from the Cr(CO)$_3$ moiety.[24]



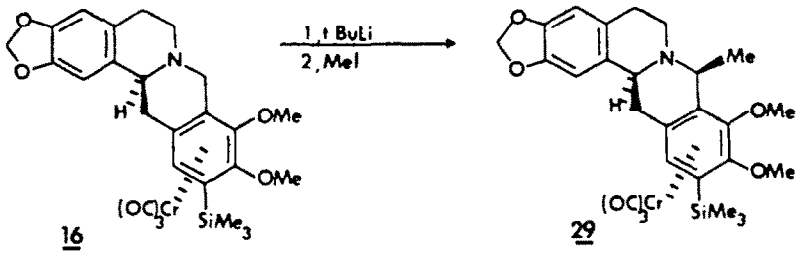
Treatment of complex (15) with n-butyllithium and methanol regenerated complex (15) which exhibited an optical rotation identical with that of an authentic sample. The chiral centre at C14 is, therefore, configurationally stable under the conditions used for C8-functionalisation.

Treatment of complex (28) with tetra-n-butylammonium fluoride trihydrate followed by decomplexation gave (-)-8R-methylcanadine (25), {[α]$_D^0$ -170° (c, 1.1 in $CHCl_3$)}. This compound was identical with the racemic sample prepared above and confirms the initial assignment of compounds (25) and (26) where borohydride attack on the iminium ion (27) was assumed to occur predominantly from the least hindered face to give mainly (26).



Complex (16) with the C14 hydrogen endo- and the nitrogen lone pair exo- with respect to the metal moiety was treated with n-butyllithium. Subsequent addition of methyl iodide and work-up gave a very air sensitive red gum. The ^{1}H n.m.r. spectrum of this material was not well resolved and indicated that a complex mixture of products had been formed. This unusually unstable red gum may be the result of prior coordination of the n-butyllithium to the available nitrogen lone pair of complex (16). An alternative to chelation controlled C13-deprotonation via a six-membered cyclic transition state is n-butyl addition para to the trimethylsilyl group by analogy with similar reactions which have been carried out on silyl substituted (arene)Cr(CO)$_3$ complexes.[25] This nucleophilic addition may account for the observed complex mixture of products.

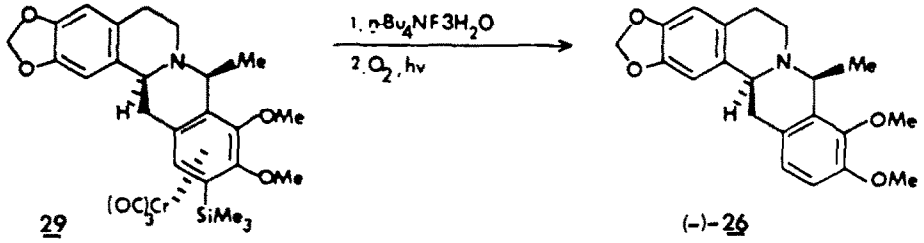
Treatment of complex (16) with t-butyllithium (1 equivalent) at -78°C followed by methyl iodide gave a yellow gum. Column chromatograpy gave two fractions. The less polar, minor fraction exhibited a doublet δ1.54 (J = 6.1 Hz) in the crude ^{1}H n.m.r. spectrum indicative of benzylic methylation. The AB quartet attributed to the diastereotopic C8-protons of complex (16) had been replaced by a quartet δ3.91 (J = 6.1 Hz, 1H). This complex was assigned as (8S, 14S)-endo(8-methyl-11-trimethylsilyl canadine)Cr(CO)$_3$ (29) by analogy with other benzylic functionalisations of arene chromium tricarbonyl complexes where the alkylating agent approaches from the exo-face away from the bulky Cr(CO)$_3$ moiety.[24] The more polar, major fraction was identical in all respects with the starting complex (16).



16 29

Treatment of complex (16) with t-butyllithium and methanol regenerated complex (16) which exhibited an optical rotation identical with that of an authentic sample. The chiral centre at C14 is therefore configurationally stable under the conditions used for C8-functionalisation.

Treatment of complex (29) with tetra-n-butylammonium fluoride trihydrate followed by decomplexation gave (-)-8S-methylcanadine (26), {[α]$_D^{\beta}$ -150.6° (c, 0.25 in $CHCl_3$)}. This compound was identical with the racemate prepared above and confirms the initial assignment of compounds (25) and (26) where borohydride attack on the iminium ion (27) was assumed to occur predominantly from the least hindered face, to give mainly (26).



29 (-)-26

Conclusions

The novel regioselective complexation of the more electron rich dimethoxy-arene ring of (-)-canadine (7) to the Cr(CO)$_3$ moiety has been achieved and this has been shown to be consistent with a model study. The resulting diastereoisomeric complexes (13) and (14) have been separated. Independent deprotonation of either (13) or (14) with n-butyllithium occurs in each case at the C11-position via chelation of the base to the C10-methoxy group. Treatment of the resulting anions with trimethylsilyl chloride gives the 11-protected complexes (15) and (16). Complex (15) with the nitrogen lone pair endo with respect to the metal moiety undergoes stereoselective exo-8-methylation via n-butyllithium mediated carbanion formation, whilst complex (16) with the nitrogen lone pair exo with respect to the metal moiety undergoes stereoselective exo-8-methylation via t-butyllithium mediated carbanion formation. These reactions effect the first asymmetric synthesis of (-)-(8R) and (-)-(8S)-methylcanadine and illustrate the use of the trimethylsilyl group to protect an arene position.

EXPERIMENTAL

All reactions involving the preparation and utilisation of (arene)Cr(CO)$_3$ complexes were performed under an atmosphere of nitrogen using standard vacuum line and Schlenk techniques,[26] unless otherwise stated. Removal of all solvents was performed under reduced pressure.

All commerical reagents were purified according to standard procedures.[27] THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Diethyl ether was peroxide free and di-n-butyl ether was dried over sodium wire and distilled under nitrogen before use. Petroleum ether refers to that fraction boiling between 40 and 60°C and hexane refers to that fraction of petroleum ether boiling between 67 and 70°C.

n-Butyllithium was used as a 1.6M solution in hexane and t-butyllithium as a 2.36 M solution in pentane. Hexacarbonyl chromium was steam distilled prior to use and stored under nitrogen.

Flash chromatography was performed on SiO_2 (Merck, 40-60 μm) under a positive nitrogen pressure. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a V.G. Micromass ZAB 1F or MM 30F instrument using In beam Electron Impact Techniques unless otherwise stated. Infrared spectra were obtained as chloroform solutions using 0.1 or 1.0 mm cells. ^1H n.m.r. spectra were obtained in d^1-chloroform at 300 MHz unless otherwise stated. ^{13}C n.m.r. spectra were obtained in d^1-chloroform at 62.90 MHz.

Competitive complexation of 1,3-benzodioxole (9) and 1,2-dimethoxybenzene (8)

A deoxygenated mixture of di-n-butyl ether (50 ml), THF (5 ml), 1,3-benzodioxole (9) (830 mg, 6.80 mmol), 1,2-dimethoxybenzene (8) (940 mg, 6.81 mmol) and hexacarbonylchromium (1.50 g, 6.82 mmol) was heated at reflux (27 h). The cooled solution was filtered and the solvents removed to give a yellow solid. Filtration (Al_2O_3 Grade V, CH_2Cl_2) gave a yellow solid (825 mg) which was shown to contain a 10:1 mixture of (η^6-1,2-dimethoxybenzene)tricarbonylchromium(0) (10) and (η^6-1,3-benzodioxole)tricarbonylchromium(0) (11) by ^1H n.m.r. spectroscopy: Complex (10) δ_H 5.33-5.30 (m, 2H, ArH), 5.10-5.07 (m, 2H, ArH), 3.81 (s, 6H, OCH_3); Complex (11) δ_H 5.96 and 5.75 (2s, 1H, OCH_2O), 5.54-5.51 (m, 2H, ArH), 4.99-4.97 (m, 2H, ArH).

(−)-Canadine (7)

(−)-Canadine HCl (4.50 g, 11.98 mmol) was treated with 2M NaOH solution and the organics extracted with chloroform (3 x 100 ml). Drying ($MgSO_4$) and evaporation gave a pale yellow solid. Filtration (SiO_2, Et_2O) gave the title compound as a white solid (4.0 g, 98.5%); m.p. 134°C; ν_{max} 2800-2700 (trans-quinolizidine), 940 (OCH_2O) cm^{-1}; δ_H 6.87, 6.80 (AB system, J_{AB} = 8.5 Hz, 2H, C11 and C12 protons), 6.74 and 6.60 (2s, 1H, C1 and C4 protons), 5.93 (s, br, 2H, OCH_2O), 4.24, 3.54 (AB system, J_{AB} = 15.5 Hz, 2H, C8 protons), 3.86 (s, 6H, OCH_3), 3.57-2.60 (m, 7H); m/z (DCI/NH_3) = 340 (M^+ + 1); $[\alpha]_D^{\circ}$ -291° (c, 0.93 in $CHCl_3$); [Lit[17,11] m.p. 134°C; δ_H (60 MHz, $CHCl_3$) 6.79br (2H, s, C11 and C12 protons), 6.69 (1H, s, C1 proton), 6.55 (1H, s, C4 proton), 5.89 (2H, s, OCH_2O), 3.83 (6H, s, OCH_3); $[\alpha]_D^{25}$ -299° (c, 0.93 in $CHCl_3$)].

exo and endo-(η^6-Canadine)tricarbonylchromium(0) (13) and (14)†

A deoxygenated mixture of di-n-butyl ether (100 ml), THF (10 ml), (-)-canadine (7) (3.90 g, 11.50 mmol) and hexacarbonyl chromium (2.78 g, 12.64 mmol) was heated at reflux (30 h). The cooled solution was filtered and the solvents removed to give a yellow foam. Cold (0°C) diethyl ether was added and the resulting yellow solution filtered clear of a white precipitate. The precipitate (2.05 g) was identical in all respects to an authentic sample of (-)-canadine (173). The yellow solution was concentrated to a yellow foam. Flash chromatography (SiO_2, Et_2O) gave two fractions. Fraction one gave exo-(η^6-canadine)tricarbonylchromium(0) (13) as a yellow foam (1.20 g, 22%); ν_{max} 2800-2750 (trans-quinolizidine), 1965, 1880br (C≡O) cm^{-1}; δ_H 6.59 and 6.55 (2s, 1H, C1 and C4 protons), 5.91 (s, 2H, OCH_2O), 5.35, 5.14 (AB system, J_{AB} = 6.8 Hz, C11 and C12 protons), 4.08, 3.63 (AB system, J_{AB} = 16 Hz, 2H, C8 protons), 3.93 and 3.83 (2s, 3H, OCH_3), 3.51-3.41 (m, 1H, C14 proton), 3.24-2.62 (m, 6H); m/z = 475 (M^+); $[\alpha]_D^{\circ}$ -47.0° (c, 0.7 in $CHCl_3$); (Found C, 58.4; H, 4.6; N, 2.9; $C_{23}H_{21}CrNO_7$ requires C, 58.1; H, 4.5; N, 2.9%). Fraction two was crystallised (CH_2Cl_2/hexane) to yellow needles (950 mg, 17%) of endo-(η^6-canadine)tricarbonylchromium(0) (14); ν_{max} 2850-2750 (trans-quinolizidine), 1965, 1875br (C≡O) cm^{-1}; δ_H 6.65 and 6.57 (2s, 1H, C1 and C4 protons), 5.91 (s, 2H, OCH_2O), 5.33, 5.12 (AB system, J_{AB} = 6.9 Hz, 2H, C11 and C12 protons), 4.17, 3.68 (AB system, J_{AB} = 16 Hz, 2H, C8 protons), 3.93 and 3.84 (2s, 3H, OCH_3), 3.65-3.61 (m, 1H, C14 proton), 3.12-2.61 (m, 6H); ^{13}C-{^1H} n.m.r. δ_C 234.2 (CO), 146.7, 146.4, 134.6, 129.2, 127.5, 127.1, 108.4, 105.6, 100.9, 100.5, 107.1, 90.2, 75.2, 64.95, 58.1, 56.45, 52.7, 50.6, 36.3, 29.5; m/z (DCI/NH_3) =476 (M^+ + 1); $[\alpha]_D^{\circ}$ -217.7° (c, 0.65 in $CHCl_3$); (Found; C, 58.1; H, 4.6; N, 2.8; $C_{23}H_{21}CrNO_7$ requires C, 58.1; H, 4.5; N, 2.9%). For X-ray crystal structure date see Tables 1 and 2.

X-ray crystal structure analysis of (14):

Cell parameters and reflection intensities were measured using graphite-monochromated Cu-Kα radiation on an Enraf-Nonius CAD-4 diffractometer operating in the w/2θ scan mode for a crystal having approximate dimensions 0.20 x 0.20 x 0.58 mm. The omega scan angle was calculated from [0.90 + 0.14 tan θ]° and increased by 25% on each side for background determination. The scan speed was varied from 0.8 to 5.5°min^{-1} depending upon the intensity. Reflections were scanned in the range $1 \leq \theta \leq 75°$. Four standard reflections measured every hour showed no appreciable variation with time. The data were corrected for Lorentz, polarisation and absorption effects[28] (relative transmission factors 1.00-1.15) and equivalent reflections merged to give 2492 unique reflections (R_m = 0.067), of which 1681 were considered to be observed [$I > 3\sigma(I)$] and used in the structure analysis.

Crystal Data, $C_{23}H_{21}O_7CrN$, M=475.4, orthorhombic, a = 8.061(2), b = 14.658(1), c = 18.001(1) A, U = 2127.1 A^3, Z = 4, D_c = 1.48 Mgm^{-3}, μ(Cu-Kα) = 48.8 cm^{-1}, space group $P2_12_12_1$ (established from systematic absences).

The structure was solved using MULTAN[29] and Fourier electron density synthesis. Final full-matrix least squares refinement included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms) and an overall scale factor. All hydrogen atoms were

† exo- and endo- refer to the relationship between the C14 proton and the $Cr(CO)_3$ moiety.

included in calculated positions and were allowed to "ride" on their respective carbon atoms after being given chemically sensible isotropic temperature factors. The refinement was terminated when the r.m.s. (shift/e.s.d.) was less than 0.1 with R = 0.045 (R_w = 0.052, GOF = 1.02). The weight for each reflection was calculated from the Chebyshev series w = [3.03 t_0 (X) + 1.66 t_1 (X) + 1.82 t_2(X)] where X = F_o/F_{max}[30]. Final difference Fourier synthesis showed no significant residual electron density and a detailed analysis failed to reveal any systematic errors. All calculations were performed using the CRYSTALS package[31] on the Chemical Crystallography Laboratory VAX 11/750 computer. Final atomic positional coordinates with e.s.d.'s in parentheses are listed in Table 1. Selected bond lengths, angles and torsional angles are listed in Table 2.

General procedure for the generation of exo- or endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15) and (16)

n-Butyllithium (0.8 ml, 1.28 mmol) was added to a stirred solution of exo- or endo-(η^6-canadine)tricarbonylchromium(0) (13) or (14) (420 mg, 0.88 mmol) in THF (20 ml) at -78°C. After stirring (2 h, -78°C), trimethylsilyl chloride (0.3 ml, 2.36 mmol) was added and stirring continued (2h, -78°C). Methanol was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the title compound as a yellow foam.

exo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15)

(280 mg, 58%); ν_{max} 2840-2750 (trans-quinolizidine), 1970, 1960, 1885br (C≡O), 1600 (aromatic ring) cm^{-1}; δ_H 6.59 and 6.55 (2s, 1H, C1 and C4 protons), 5.91 (s, br, 2H, OCH_2O), 5.25 (s, 1H, C12 proton), 4.12, 3.65 (AB system, J_{AB} = 16 Hz, 2H, C8 protons), 3.86 and 3.83 (2s, 3H, OCH_3), 3.50-3.47 (m, 1H, C14 proton), 3.25-2.59 (m, 6H), 0.37 (s, 9H, $(CH_3)_3Si$); m/z (DCI/NH_3) = 548 (M^+ + 1); $[\alpha]_D^{\circ}$ -215.3° (c, 0.61 in $CHCl_3$).

endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16)

(425 mg, 88%); ν_{max} 2850-2750w (trans-quinolizidine), 1965, 1885 (C≡O) cm^{-1}; δ_H 6.66, 6.57 (2s, 1H, C1 and C4 protons), 5.93 (s, 2H, OCH_2O), 5.24 (s, 1H, C12 proton), 4.15, 3.73 (AB system, J_{AB} = 15 Hz, 2H, C8 protons), 3.88, 3.85 (2s, 3H, OCH_3), 3.63-3.59 (m, 1H, C14 proton), 3.14-2.59 (m, 6H), 0.36 (s, 9H, $(CH_3)_3Si$); m/z (DCI/NH_3) = 548 (M^+ + 1); $[\alpha]_D^{\circ}$ -59.64° (c, 0.55 in $CHCl_3$).

exo- or endo- (η^6-Canadine)tricarbonylchromium(0) (13) or (14)

A solution of exo- or endo- (η^6-11-trimethylsilylcanadine)- tricarbonylchromium(0) (15) or (16) (30 mg, 0.06 mmol) in THF (2 ml) at 20°C was treated with a solution of n-$Bu_4NF.3H_2O$ (43 mg, 0.14 mmol) in THF (1 ml). After stirring (6 h, 20°C), water (3 drops) was added and the solution evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the title compounds (13) or (14) as yellow foams (22 mg, 84%) identical in all respects with authentic samples.

11-Trimethylsilylcanadine (17)

A solution of exo- or endo-(η^6-11-trimethylsilylcanadine)carbonylchromium(0) (15) or (16) (150 mg, 0.27 mmol) in diethyl ether (20 ml) was allowed to stand in air and sunlight until colourless. Filtration through celite and evaporation gave a white foam. Flash chromatography (SiO_2 1:1 Et_2O/petroleum ether) gave the title compound as a white solid (105 mg, 93%); ν_{max} 2840-2750 (trans-quinolizidine), 1600 (aromatic ring) cm^{-1}; δ_H 6.92 (s, 1H, C12 proton), 6.74 and 6.60 (2s, 1H, C1 and C4 protons), 5.93-5.92 (m, 2H, OCH_2O), 4.28, 3.57 (AB system, J_{AB} = 16 Hz, 2H, C8 protons), 3.85 (s, 6H, C9 and C10 OCH_3), 3.32-2.62 (m, 7H), 0.29 (s, 9H, $(CH_3)_3Si$); irradiation of the C12 proton singlets δ6.92 gave n.O.e's to a C13 benzylic proton δ3.32-3.23 (3.66%) and the trimethylsilyl group 0.29 (1.3%); m/z (DCI/NH_3) = 412 (M^+ + 1); $[\alpha]_D^{\circ}$ -197.0° (c, 0.18 in $CHCl_3$); (Found; C, 67.3; H, 7.3; N, 3.0; $C_{23}H_{29}NO_4Si$ requires C, 67.1; H, 7.1; N, 3.4%).

General Procedure for the generation of exo- or endo- η^6-11-methylcanadine)tricarbonylchromium(0) (18) or (19)

n-Butyllithium (0.15 ml, 0.24 mmol) was added to a stirred solution of exo- or endo-(η^6-canadine)tricarbonylchromium(0) (13) and (14) (100 mg, 0.21 mmol) in THF (20 ml) at -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2 h, -78°C). Methanol was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the title compound as a yellow foam.

exo-(η^6-11-methylcanadine)tricarbonylchromium(0) (18)

(95 mg, 92%); ν_{max} 2850-2750 (trans-quinolizidine), 1975, 1885 (C≡O), 1600 (aromatic ring) cm^{-1}; δ_H 6.59 and 6.55 (2s, 1H, C1 and C4 protons), 5.92 (s, 2H, OCH_2O), 4.93 (s, 1H, C12 proton), 4.00, 3.57 (AB system, J_{AB} = 15 Hz, 2H, C8 protons), 3.92 and 3.83 (2s, 3H, C9 and C10 OCH_3), 3.56-3.47 (m, 1H, C14 proton), 3.22-2.58 (m, 6H), 2.22 (s, 3H, $ArCH_3$); m/z = 489 M^+); $[\alpha]_D^{\circ}$ -231° (c, 0.25 in $CHCl_3$).

endo-(η^6-11-methylcanadine)tricarbonylchromium(0) (19)

(100 mg 97%); ν_{max} 2840-2750 (trans-quinolizidine), 1970, 1880br (C≡O), 1600 (aromatic ring) cm^{-1}; δ_H 6.71 and 6.59 (2s, 1H, C1 and C4 protons), 5.92 (s, 2H, OCH_2O), 4.93 (s, 1H, C12 proton), 4.00, 3.56 (AB system, J_{AB} = 15Hz, 2H, C8 protons), 3.95 and 3.86 (2s, 3H, C9 and C10 OCH_3), 3.70-3.62 (m, 1H, C14 proton), 3.11-2.97 (m, 3H), 2.76-2.61 (m, 3H), 2.19 (s, 3H, $ArCH_3$); m/z = 489 (M^+); $[a]_D^{\circ}$ -58° (c, 0.27 in $CHCl_3$).

11-Methylcanadine (20)

A solution of exo- or endo- (η^6-methylcanadine)tricarbonylchromium(0) (18) or (19) (90 mg, 0.18 mmol) (90 mg, 0.18 mmol) in diethyl ether (20 ml) was allowed to stand in air and sunlight until colourless. Filtration through celite and evaporation gave a white foam. Flash chromatography (SiO_2, Et_2O) gave the title compound as a white solid (63 mg, 97%); ν_{max} 2840-2750 (trans-quinolizidine), 1600 (aromatic ring) cm^{-1}; δ_H 6.72 (s, 2H, C12 and C1 or C4 proton), 6.60 (s, 1H, C1 or C4 proton), 5.92 (s 2H, OCH_2O), 4.17, 3.50 (AB system, J_{AB} = 15.6 Hz, 2H, C8 protons), 3.88 and 3.81 (2s, 3H, C9 and C10 OCH_3), 3.55-3.45 (m, 1H, C14 proton), 3.22-3.12 (m, 3H), 2.84-2.75 (m, 1H), 2.68-2.59 (m, 2H), 2.24 (s, 3H, $ArCH_3$); m/z (DCI/NH_3) = 354 (M^+ + 1): $[\alpha]_D^{20}$ -229.0° (c, 0.08 in $CHCl_3$); (Found; C, 71.5; H, 6.7; N, 3.8; $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0%).

Treatment of canadine (7) with n-butyllithium

n-Butyllithium (1.3 ml, 2.08 mmol) was added to a solution of canadine (7) (600 mg, 1.77 mmol) in THF (30 ml) at -78°C. After stirring (2 h, -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2 h, -78°C). Methanol was added, the solution warmed to 20°C and evaporated. Filtration (SiO_2, Et_2O) gave a white solid (510 mg) identical in all respects with an authentic sample of canadine (7).

8-Methyldihydroberberine (24)

A suspension of dried berberine chloride (23) (2.00 g, 4.90 mmol) in sodium dried diethyl ether (50 ml) at 0°C was treated with methylmagnesium iodide (5 ml, 2M solution in Et_2O, 10 mmol). After the initial reaction ceased the solution was heated at reflux (15 min). On cooling, saturated aqueous ammonium chloride was added and the diethyl ether layer decanted away from the aqueous layer. The aqueous layer was basified (dil. NH_4OH) and the organics extracted with diethyl ether (3 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the title compound as a yellow solid (1.65 g, 96%); δ_H 7.17 (s, 1H, ArH), 6.75 (s, 2H, ArH), 6.60 (s, 1H, ArH), 5.96-5.94 (m, 2H, OCH_2O), 5.87 (s, 1H, C13 proton), 4.86 (q, J = 6.3 Hz, 1H, C8 proton), 3.91 and 3.85 (2s, 3H, C9 and C10 OCH_3), 3.50 - 2.76 (m, 4H), 1.19 (d, J = 6.3 Hz, 3H, C8 methyl protons); m/z (CI/NH_3) = 352 (M^++1).

(SR,RS) and (SS,RR)-8-Methylcanadine (25) and (26)

A cooled (0°C) solution of 8-methyldihydroberberine (24) (810 mg, 2.31 mmol) in methanol (50 ml) was treated with sodium borohydride (2.00 g, 52.87 mmol) and allowed to stir (1 h, 20°C). The mixture was cooled (0°C) and treated with water (50 ml). Evaporation of the methanol followed by diethyl ether extraction (3 x 40 ml), drying ($MgSO_4$) and evaporation gave a white solid. Flash chromatography (SiO_2, 1:2 Et_2O/petroleum ether) gave two fractions. Fraction one Rf (SiO_2, 1:2 Et_2O/petroleum ether) = 0.20, gave the title compound (26) as a white solid (635.0 mg, 78%); ν_{max} 2840-2720 (trans-quinolizidine), 1600 (aromatic ring) cm^{-1}; δ_H 6.81 (AB system, J_{AB} = 8.3 Hz, 2H, C11 and C12 protons), 6.77 and 6.60 (2s, 1H, C1 and C4 protons), 5.92, 5.91 (AB system, J_{AB} = 1.5 Hz, 2H, OCH_2O), 3.88, 3.87 (2s, 3H, C9 and C10 OCH_3), 3.83 (q, J = 6.1 Hz, 1H, C8 proton), 3.55 (d, br, J = 10.9 Hz, 1H, C14 proton), 3.38, 2.83 (AB part of ABX system, J_{AB} = 11 Hz, 2H, C13 protons), 3.35-3.06 (m, 2H), 2.70-2.49 (m, 2H), 1.52 (d, J = 6.1 Hz, 3H, C8 methyl protons); ^{13}C-{^1H}n.m.r: δ_C 150.9, 146.0 (2C), 145.8, 133.8, 131.4, 129.0, 128.3, 123.4, 110.6, 108,3, 105.6, 100.6, 60.2, 58.9, 57.1, 55.8, 49.1, 37.6,. 30.6, 22.75; m/z (CI/NH_3) = 354 (M^++1); (Found; C, 71.1; H, 6.5; N, 3.9; $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0%). Fraction two Rf (SiO., 1:2 Et_2O/petroleum ether) = 0.11 gave the title compound (25) as a white solid (115.0 mg, 14%); δ_{max} 2840-2750w (trans-quinolizidine), 1600 (aromatic ring) cm^{-1}; δ_H 6.82, 6.79 (AB system, J_{AB} = 8.5 Hz, 2H, C11 and C12 protons), 6.69 and 6.59 (2s, 1H, C1 and C4 protons), 5.92 (s, 2H, OCH_2O), 4.33 (q, J = 6.7 Hz, 1H, C8 proton), 4.24-4.18 (m, 1H, C14 proton), 3.90 and 3.86 (2s, 3H, C9 and C10 OCH_3), 3.11-2.70 (m, 6H), 1.39 (d, J = 6.7 Hz, 3H, C8 methyl protons); ^{13}C-{^1H}n.m.r: δ_C 150.3, 145.9, 145.8, 145.3, 133.8, 132.3, 127.6, 126.6, 123.9, 111.1, 108.6, 106.2, 100.7, 60.4, 55.8, 55.4, 50.5, 47.1, 35.1, 30.0, 15.8; m/z (DCI/NH_3) = 354(M^++1); (Found; C, 71.7; H, 6.5; N, 4.0; $C_{21}H_{23}NO_4$ requires C, 71.4; H, 5.5; N, 4.0%).

(8R,14S)-exo-(η^6-8-Methyl-11-trimethylsilylcanadine)tricarbonylchromium(0) (28)

n-Butyllithium (0.4 ml, 0.64 mmol) was added to a stirred solution of exo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15) (220 mg, 0.40 mmol) in THF (20 ml) at -78°C. After stirring (2 h, -78°C) methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2h, -78°C). Methanol was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the title compound as a yellow foam (180 mg, 80%); δ_{max} 2840-2750w (trans-quinolizidine), 1965, 1890 (C≡O) cm^{-1}; δ_H 6.58 and 6.50 (2s, 1H, C1 and C4 protons), 5.90-5.89 (m, 2H, OCH_2O), 5.30 (s, 1H, C12 proton), 4.25 (q, J = 6.7 Hz, 1H, C8 proton), 4.14-4.06 (m, 1H, C14 proton), 3.91 and 3.77 (2s, 3H, C9 and C10 OCH_3), 3.18-2.53 (m, 6H), 1.47 (d, J = 6.7 Hz, 3H, C8 methyl protons), 0.36 (s, 9H, $(CH_3)_3Si$); m/z (DCI/NH_3) = 562 (M^++1).

Treatment of exo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15) with n-butyllithium and methanol

n-Butyllithium (0.15 ml, 0.24 mmol) was added to a stirred solution of exo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15) (100 mg, 0.18 mmol) in THF at -78C. After stirring (2 h, -78°C), methanol (1 ml) was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3, Grade V, Et_2O) gave a yellow foam (91 mg, 91%) identical in all respects with an authentic sample of exo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (15).

(8R,14S)-8-Methylcanadine (25)

A solution of (8R,14S)-exo-(η^6-8-methyl-11-trimethylsilylcanadine)-tricarbonylchromium(0) (28) (100 mg, 0.18 mmol) in THF (20 ml) at 20°C was treated with a solution of n-$Bu_4NF.3H_2O$ (200 mg, 0.63 mmol) in THF (5 ml). After stirring (12 h, 20°C), water (3 drops) was added and the solution evaporated. Column chromatography (Al_2O_3, Grade V, Et_2O) gave a yellow foam which was dissolved in diethyl ether (40 ml) and allowed to stand in air and sunlight until colourless. Filtration (celite) followed by flash chromatography (SiO_2, 1:2 Et_2O/petroleum ether) gave the title compound as a white foam (42 mg, 67%). This compound was identical, in all respects to an authentic sample except that it exhibited an optical rotation: $[\alpha]_D^{\circ}$ - 170° (c, 1.1 in $CHCl_3$).

Treatment of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) with n-butyllithium

n-Butyllithium (0.6 ml, 0.90 mmol) was added to a stirred solution of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) (1 eq) in THF (20 ml) at -78°C. A deep red solution was formed. After stirring (2 h, -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2 h, -78°C). Methanol was added, the solution warmed to 20°C and evaporated to a very air sensitive orange oil. Column chromatography (Al_2O_3, Grade V, 1:1 Et_2O/petroleum ether) gave a brown foam which could not be characterised.

The use of methanol as the electrophile in the above reaction did not give rise to any recovered starting material; a very sensitive brown foam was obtained which could not be characterised.

(8S,14S)-endo-(η^6-8-Methyl-11-trimethylsilylcanadine)tricarbonylchromium(0) (29)

t-Butyllithium (0.17 ml, 0.40 mmol) was added to a stirred solution of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) (230 mg, 0.42 mmol) in THF (20 ml) at -78°C. After stirring (2 h, -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2 h, -78°C). Methanol was added, the solution warmed to room temperature and evaporated. Flash chromatography (SiO_2 2:3 Et_2O/petroleum ether) gave two fractions. Fraction one gave the title compound as a yellow foam (100 mg, 42%); ν_{max} 2850-2740 (trans-quinolizidine), 1965, 1890br (C≡O)cm^{-1}; δ_H 6.69 and 6.57 (2s, 1H, C1 and C4 protons), 5.91-5.90 (m, 2H, OCH_2O), 5.42 (s, 1H, C12 proton), 3.90 and 3.79 (2s, 3H, C9 and C10 OCH_3), 3.91 (q, J = 6.1 Hz, 1H, C8 proton), 3.25 -2.42 (m, 6H), 1.54 (d, J = 6.1 Hz, 3H, C8 methyl protons), 0.39 (s, 9H, $(CH_3)_3Si$); m/z (DCI/NH_3) = 562(M^++1). Fraction two gave endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) (120 mg, 52%) identical in all respects with an authentic sample.

Treatment of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) with t-butyllithium and methanol

t-Butyllithium (0.08 ml, 0.19 mmol) was added to a stirred solution of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16) (100 mg, 0.18 mmol) in THF at -78°C. After stirring (2 h, -78°C), methanol (1 ml) was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3, Grade V, Et_2O) gave a yellow foam (85 mg, 85%) identical in all respects with an authentic sample of endo-(η^6-11-trimethylsilylcanadine)tricarbonylchromium(0) (16).

(8S,14S)-8-Methylcanadine (26)

A solution of (8S,14S)-endo-(η^6-8-methyl-11-trimethylsilylcanadine)tricarbonylchromium(0) (29) (50 mg, 0.09 mmol) in THF (20 ml) at 20°C was treated with a solution of n-$Bu_4NF.3H_2O$ (100 mg, 0.32 mmol) in THF (5 ml). After stirring (5 h, 20°C), water (3 drops) was added and the solution evaporated. Column chromatography (Al_2O_3, Grade V, Et_2O) gave a yellow foam which was dissolved in diethyl ether (20 ml) and allowed to stand in air and sunlight until colourless. Filtration (celite) followed by flash chromatography (SiO_2, 1:2 Et_2O/petroleum ether) gave the title compound as a white foam (20 mg, 63.6%). This compound was identical in all respects to an authentic sample except that it exhibited an optical rotation: $[\alpha]_D^{\circ}$ - 150.6° (c, 0.25 in $CHCl_3$).

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References

1. P.W. Jeffs in "The Alkaloids", ed. R.H.F. Manske, Academic Press, New York, 1967, 9, 41; T. Honda, M. Ihara and T Kametani, Heterocycles, 1976, 4, 483; K. Nagarajan, S. Natarajan, B. Pai and H. Suguna, ibid, 1977, 6, 1377.

2. K. Fukumoto, M. Ihara, T. Kametani, S-T. Lu, T-L. Su and A. Ujiie, J.Chem.Soc., Perkin Trans. 1, 1976, 63.

3. R.H.F. Manske, J.Amer.Chem.Soc., 1953, 75, 4928.

4. R.H.F. Manske, Can.J.Research, 1939, 17B, 51.

5. A. Brossi, H. Bruderer and J. Metzger, Helv.Chim.Acta, 1975, 58, 1719; A. Brossi, H. Bruderer and J. Daly, ibid, 1976, 59, 2793.

6. C.D. Jones, M. Shamma and J.A. Weis, Tetrahedron, 1969, 25, 4347; H.W. Bersch, Arch.Pharm., 1950, 283, 36.

7. (a) J. Blagg, S.G. Davies and B.E. Mobbs, J.Chem.Soc., Chem.Commun., 1985, 619; (b) J. Blagg, S.J. Coote, S.G. Davies and B.E. Mobbs, J.Chem.Soc., Perkin Trans. 1, 1986, 2257; (c) J. Blagg, S.J. Coote, S.G. Davies, D. Middlemiss and A. Naylor, J.Chem.Soc., Perkin Trans. 1, 1987, 689.

8. J. Blagg and S.G. Davies, J.Chem.Soc., Chem.Commun., 1986, 492.

9. R.H.F. Manske, Can.J.Research, 1942, 20B, 57.

10. E. Späth and P.L. Julian, Chem.Ber., 1931, 64, 1131.

11. T. Kametani, S. Kaneda, I. Noguchi and K. Saito, J.Chem.Soc.(c), 1969, 2036 and references therein.

12. J. Gadamer, Arch.Pharm., 1901, 239, 648.

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

14. M.M. Byrne and N.H.P. Smith, J.Chem.Soc.(B), 1968, 809.

15. G.M. Anderson III, P.A. Kollman, L.N. Domelsmith and K.N. Houk, J.Amer.Chem.Soc., 1979, 101, 2344.

16. J.K. Cha and L.I. Kruse, J.Chem.Soc., Chem.Commun., 1982, 1333.

17. "Dictionary of Organic Compounds", ed. J. Buckingham, Chapman and Hall, New York, 1982.

18. T.A. Crab, D. Jackson and R.F. Newton, Chem.Rev., 1971, 71, 109; K. Iwasa and N. Takao, Chem.Pharm.Bull., 1976, 24, 3185.

19. H.W. Gschwend and H.R. Rodriguez, Org.React.(N.Y.), 26, 1; R.J. Card and W.S. Trahanovsky, J.Org.Chem., 1980, 45, 2560; J. Bisaha, M. Czarny and M.F. Semmelhack, J.Amer.Chem.Soc., 1979, 101, 768.

20. F. Effenberger and K. Schöllkopf, Chem.Ber., 1985, 118, 4356; idem, ibid, 1985, 118, 4377.

21. M.J. McGlinchey, G. Jaouen, B.G. Sayer and S. Top, J.Amer.Chem.Soc., 1983, 105, 6426.

22. For relevant ^{1}H n.m.r. data see R. Charubala, T.R. Govindachari, K. Nagarajan, B.R. Pai and P.S. Subramanian, Ind.J.Chem., 1970, 8, 768.

23. J.R. Gear and J.D. Spenser, Can.J.Chem., 1963, 41, 783.

24. R.J. Card and W.S. Trahanovsky, J.Amer.Chem.Soc., 1972, 94, 2897; H. des Abbayes and M.A. Boudeville, J.Org.Chem., 1977, 42, 4104; J. Brocard, D. Couturier and J. Lebibi, J.Chem. Soc., Chem.Commun., 1981, 1264; H.B. Arzeno, D.H.R. Barton, S.G. Davies, X. Lusinchi, B. Meunier and C. Pascard, Nouv.J.Chim., 1980, 4, 369; J. Brocard, D. Couturier and J. Lebibi, Bull.Soc.Chim.Fr.II, 1982, 357; J-P. Abjean, G. Jaouen, S. Top and A. Vessieres, J.Chem.Soc., Chem.Commun., 1984, 428; J. Brocard, D. Couturier, G. Jouen, A. Laconi and S. Top, J.Amer.Chem.Soc., 1984, 106, 2207.

25. G.R. Clarke, J.L. Garcia, J.J. Harrison, M.F. Semmelhack, Y. Thebtaranonth, W. Wulff and A. Yamashita, Tetrahedron, 1981, 37, 3957.

26. D.F. Shriver, "The Manipultion of Air Sensitive Compounds", McGraw-Hill, New York, 1969.

27. W.L.F. Armarego, D.D. Perrin and D.R. Perrin, "The Purificaion of Laboratory Chemicals", Pergamon Press, Oxford, 1966.

28. A.C.T. North, D.C. Phillips and F.S. Mathews, Acta. Crystallogr., 1968, A24, 351.

29. P. Main, "MULTAN 80: A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Data", Department of Physics, University of York, 1980.

30. J.R. Carruthers and D.J. Watkin, Acta. Crystallogr., 1979, A35, 698.

31. D.J. Watkin, J.R. Carruthers and P.W. Betheridge, "CRYSTALS User Guide", Chemical Crystallography Laboratory, Oxford, 1985.