The Stereoselective Synthesis of (−)-(8*R*)-Methylcanadine *via* Selective Monocomplexation of Canadine to Chromium Tricarbonyl

Julian Blagg and Stephen G. Davies*

The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K.

Regiospecific complexation of the dimethoxy arene ring of (−)-canadine to chromium tricarbonyl, protection of the C-11 position, followed by stereoselective substitution at C-8 effects, after deprotection and decomplexation, a stereoselective synthesis of (−)-(8*R*)-methylcanadine; a comparison is made with a racemic sample synthesised by an alternative route.

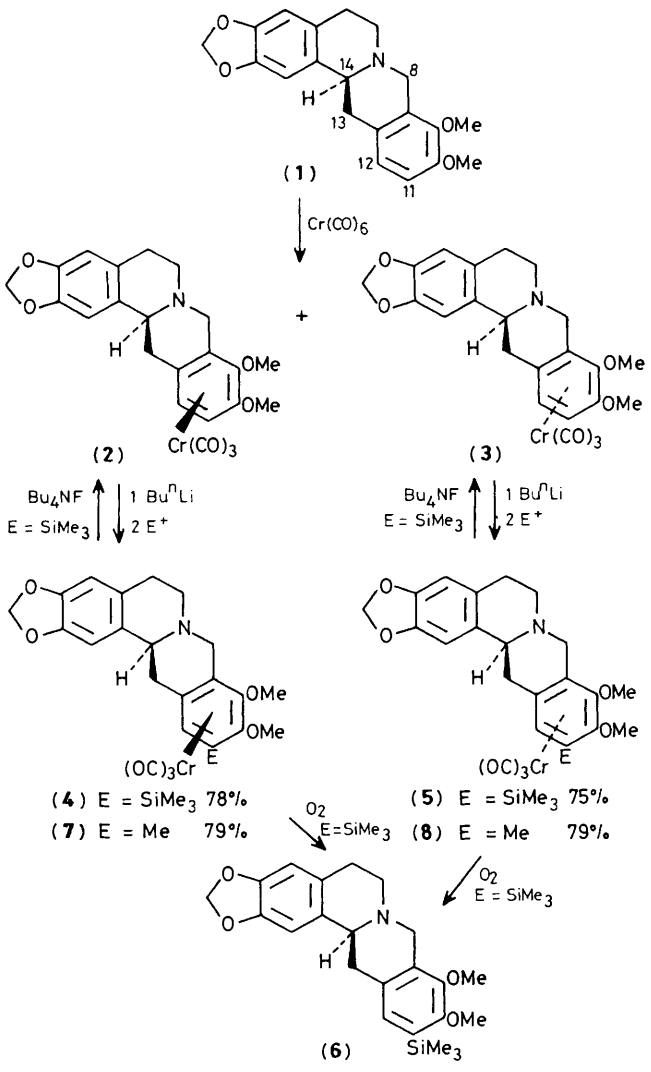
A number of C-8 substituted tetrahydroberberines have been isolated and characterised.[1] However, no asymmetric syntheses of such compounds have been reported.[2] We describe here methodology for the introduction of C-11 and C-8 substituents into the alkaloid (−)-canadine (**1**) *via* regiospecific monocomplexation to chromium tricarbonyl and its application to the synthesis of (−)-(8*R*)-methylcanadine.

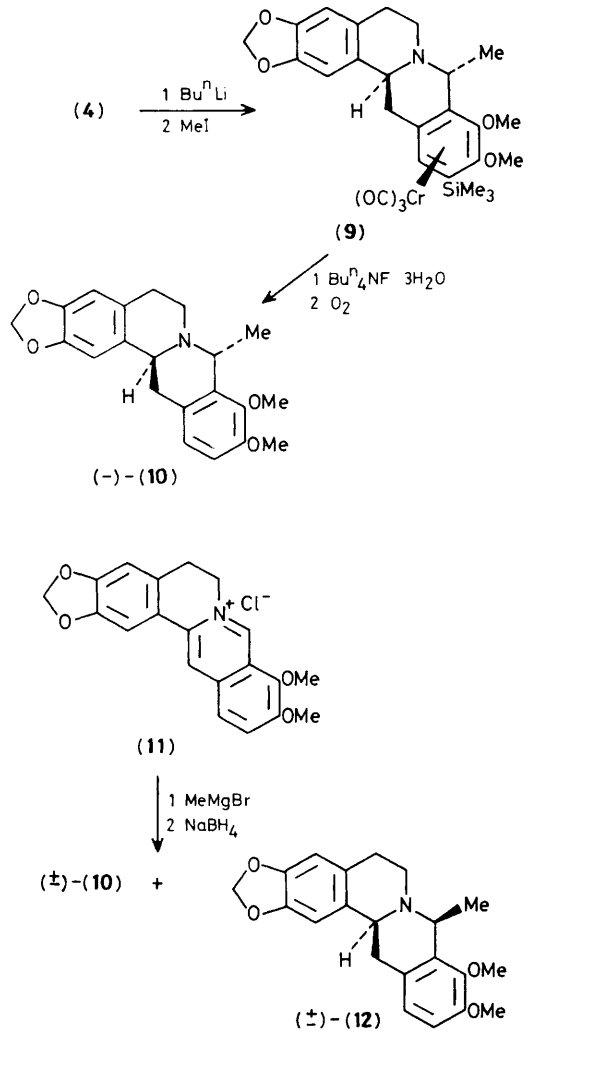
Thermolysis of chromium hexacarbonyl (1.1 equiv.) with (−)-canadine[3] (m.p. 225 °C; $[\alpha]_D^{20}$ −291°, *c* 0.93, $CHCl_3$) in a 10 : 1 mixture of di-n-butyl ether and tetrahydrofuran gave a mixture of two diastereoisomers (**2**) and (**3**). Each diastereoisomer contained a single chromium tricarbonyl unit complexed to the dimethoxy substituted arene ring. No diastereoisomers corresponding to complexation to the 1,3-benzodioxole moiety could be detected. This novel selective complexation can be attributed to differences in the electronic character of the two arene rings in (−) canadine (**1**). Thermolysis of equimolar quantities of 1,2-dimethoxybenzene, 1,3-benzodioxole, and chromium hexacarbonyl under identical conditions resulted in selective (10 : 1) complexation of the former.

Flash chromatography (SiO_2, eluant: diethyl ether) separated complexes (**2**) (20%; $[\alpha]_D^{20}$ −47°, *c* 0.7, $CHCl_3$) and (**3**) (15%; $[\alpha]_D^{20}$ −218°, *c* 0.68, $CHCl_3$).† An *X*-ray crystal structure of the more polar, minor diastereoisomer (**3**) established the *cis*-relationship of the chromium tricarbonyl moiety to the C-14 hydrogen.[4]

Treatment of either (**2**) or (**3**) with n-butyl-lithium in tetrahydrofuran at −78 °C led to deprotonation at C-11 as evidenced by the isolation, after trimethylsilyl chloride addition, of the 11-trimethylsilyl derivatives (**4**) and (**5**) respectively. Treatment of tetrahydrofuran solutions of either (**4**) or (**5**) with tetra-n-butylammonium fluoride trihydrate quantitatively regenerated (**2**) and (**3**) respectively. Exposure of diethyl ether solutions of (**4**) or (**5**) to air and sunlight allowed the isolation in both cases of 11-trimethylsilylcanadine (**6**). A nuclear Overhauser enhancement (n.O.e.) experiment involving irradiation of the C-12 proton

† All new compounds gave satisfactory analytical and spectroscopic data.





of (**6**) gave an enhancement of the C-13 benzylic (3.66%) and C-11 trimethylsilyl (1.3%) resonances with no enhancement of the C-10 methoxy resonance thereby confirming the position of the trimethylsilyl group. The corresponding 11-methyl compounds (**7**) and (**8**) were prepared in a similar manner.

Treatment of (−)-canadine (**1**) with n-butyl-lithium under similar conditions, or using n-butyl-lithium in diethyl ether at 20 °C, followed by addition of an electrophile (*e.g.* methyl iodide) resulted only in recovery of starting material.

Treatment of complex (**4**) with n-butyl-lithium followed by methyl iodide gave a single C-8 methylated diastereoisomer (**9**). The stereoselective formation of (**9**) is consistent with the expected alkylation occurring exclusively from the *exo*-face away from the bulky chromium tricarbonyl moiety.[5] That deprotonation does not occur at the alternative C-13 benzylic position[6] can be attributed to chelation by the C-9 methoxy group directing metallation to C-8. Desilylation and decomplexation of (**9**) as above gave (−)-(8*R*)-methylcanadine (**10**) (64%; $[\alpha]_D^{20}$ −170°, *c* 1.1, $CHCl_3$).

Treatment of berberine chloride (**11**) with methylmagnesium iodide followed by reduction of the resulting enamine with sodium borohydride[7] gave a mixture of (±)-(**12**) and (±)-(**10**) in the ratio 5.5:1. The predominance of (**12**) is consistent with borohydride approaching from the less hindered face opposite to the C-8 methyl group. Flash chromatography (SiO_2, eluant: hexane and diethyl ether, ratio 2:1) gave pure (±)-(**12**) and pure (±)-(**10**), the latter being identical spectroscopically (^{13}C and ^1H n.m.r.) to (−)-(**10**) prepared above.

We thank the S.E.R.C. and Glaxo Group Research Ltd. (Ware) for a C.A.S.E. award (to J. B.).

Received, 16th December 1985; Com. 1773

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