Tetrahedron Letters,Vol.26,No.7,pp 917-920,1985
Printed in Great Britain

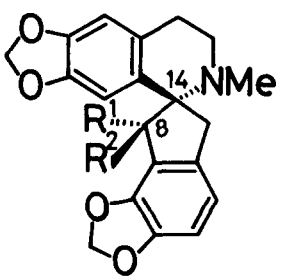
0040-4039/85 $3.00 + .00

A HIGHLY STEREOSELECTIVE SYNTHESIS OF (±)-DIHYDROFUMARILINE-1

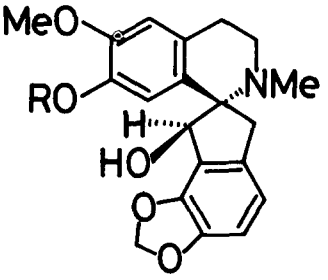
Miyoji Hanaoka,* Masashi Iwasaki, and Chisato Mukai
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

Summary: Stereoselective sodium borohydride reduction of the 8,14-cycloberbine (9) derived from the protoberberine (7), followed by reductive cleavage of C_8-N bond of the resulting 13-hydroxy-8,14-cycloberbine (10) with sodium cyanoborohydride afforded the spirobenzylisoquinoline (12), N-methylation of which *via* the oxazolidine (13) provided (±)-dihydrofumariline-1 (1).

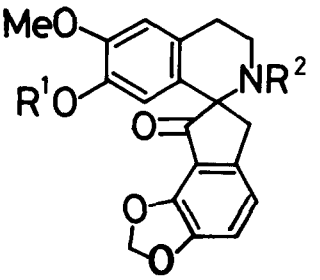
Dihydrofumariline-1 (1),[1,2] isolated from *Fumaria officinalis*,has been shown to be a unique spirobenzylisoquinoline alkaloid having the hydroxy group at C-8 *cis* to the N-methyl group in the five-membered ring. Interestingly, this stereochemistry is contrary to those of the hitherto-known alkaloids, fumaricine (2) and fumaritine (3), possessing the *trans* alcohol, syntheses of which have been accomplished *via* the corresponding ketones (6).[4,5,6] Reduction of such ketones has been found to give predominantly *trans* alcohols[5,6,7] or to proceed with non-stereoselectivity.[4,5] In fact, sodium borohydride reduction of fumariline (5) afforded the *trans*



1: R^1=OH, R^2=H
4: R^1=H, R^2=OH
5: R^1+R^2=O



2: R=Me
3: R=H

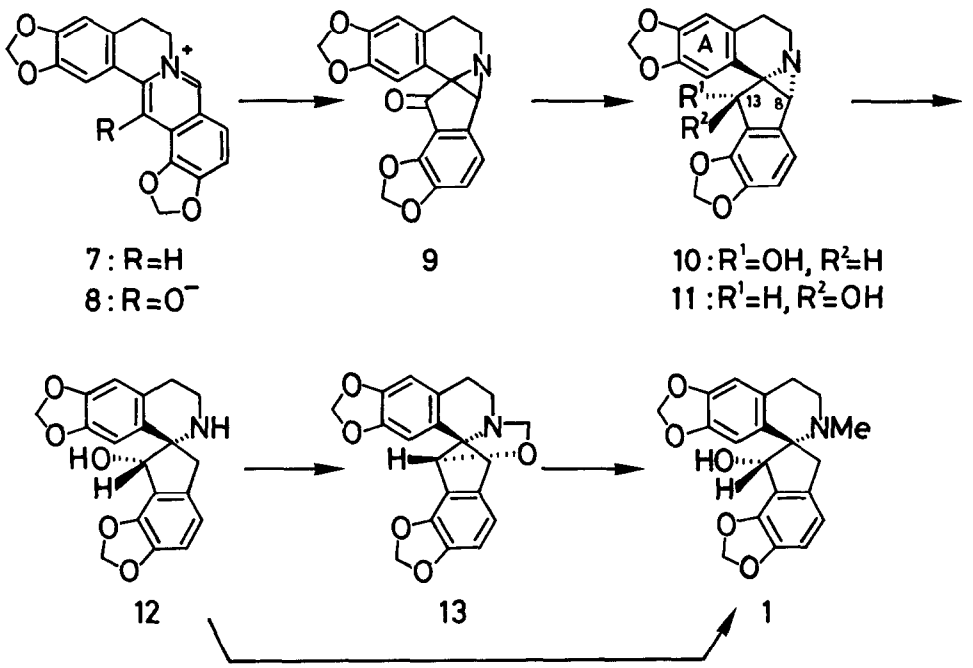


6

alcohol, dihydrofumariline-2 (4) along with dihydrofumariline-1 (1) as a minor product.[1,8)]

No general and simple method has so far been developed for a stereoselective synthesis of a spirobenzylisoquinoline possessing a *cis* alcohol. This communication deals with a highly stereoselective total synthesis of (±)-dihydrofumariline-1 (1) from the corresponding protoberberine (7) *via* the 8,14-cycloberbine (9) by a stereoselective reduction and a reductive C_8-N bond fission as crucial steps.

The protoberberine (7)[9)] was reduced with lithium aluminum hydride in dry tetrahydrofuran (THF) and followed by oxidation with *m*-chloroperbenzoic acid in methylene chloride to give the phenolbetaine (8) [81%; mp 252-253° (dec.); *m/z* 335 (M^+); δ 9.06, 7.46, 6.64 (each 1H, each s), 7.26, 7.19 (2H, AB-q, *J*=8.5), 4.40 (2H, t, *J*=6), 3.04 (2H, t, *J*=6)]. The phenolbetaine (8) was irradiated[10)] in methanol with a high-pressure mercury lamp through a Pyrex filter to afford the 8,14-cycloberbine (9) [64%; mp 246-248° (dec.); *m/z* 335 (M^+); ν 1715; δ 7.30, 6.64 (each 1H, each s), 6.92 (2H, s), 3.82 (1H, s)]. Sodium borohydride reduction of the 8,14-cycloberbine (9) in methanol at room temperature afforded exclusively the alcohol (10) [99%; mp 192-193.5°(dec.); *m/z* 337 (M^+); ν 3530; δ 7.13, 6.63 (each 1H, each s), 6.77,



6.70 (2H, AB-q, J=7.5), 5.79 (1H, d, J=12), 3.48 (1H, s)], whereas the diastereoisomeric alcohol (11)[54%; mp 192-194°; m/z 337 (M^+); ν 3600; δ 7.38, 6.66 (each 1H, each s), 6.89, 6.72 (2H, AB-q, J=8), 5.08 (1H, d, J=3), 3.11 (1H, d, J=1.5)] was predominantly obtained along with the alcohol (10)(19%) when the reduction was carried out with $LiAlH(OBu^t)_3$[11,12] instead of sodium borohydride in a dry benzene/THF (10/1) solution under reflux. The stereochemistry of both alcohols (10 and 11) was elucidated by ^{1}H-NMR spectral consideration. The C_{13}-H signal of 10 (5.79 ppm) appeared at lower field than that of 11 (5.08 ppm). This down field shift of the former could be well explained by the inspection of the molecular model, from which the C_{13}-H of 10 is indicated to lie on nearly the same plane with the benzene ring A.[11,12]

On treatment with sodium cyanoborohydride in THF in the presence of *p*-toluenesulfonic acid at 60-65°, the desired alcohol (10) regioselectively underwent a reductive C_8-N bond fission to produce the spirobenzylisoquinoline (12)[81%; mp 192-193°; m/z 339 (M^+); ν 3300; δ 6.75, 6.66 (2H, AB-q, J=8), 6.57, 6.54 (each 1H, each s), 5.12 (1H, s), 3.15 (2H, s)], which was methylated with methyl iodide in THF to furnish (±)-dihydrofumariline-1 (1)[56%; mp 198-199°; m/z 353 (M^+); ν 3250; δ 6.77, 6.72 (2H, AB-q, J=8), 6.54, 6.26 (each 1H, each s), 5.99, 5.95 (2H, AB-q, J=1.5), 5.83, 5.81 (2H, AB-q, J=1.5), 4.84 (1H, s), 3.43, 2.97 (2H, AB-q, J=15), 2.45 (3H, s)]. Alternatively, the same product was obtained more efficiently. The amino-alcohol (12) was converted into the oxazolidine (13)[mp 155-156.5°; m/z 351 (M^+); δ 6.82, 6.67 (2H, AB-q, J=8), 6.56, 6.30 (each 1H, each s), 5.16 (1H, s), 4.62, 4.55 (2H, AB-q, J=7), 3.28 (2H, s)] in 90% yield by treatment with 37% aqueous formaldehyde in methanol at room temperature. Subsequent exposure of 13 to sodium cyanoborohydride in methanol in the presence of 10% hydrochloric acid effected a reductive cleavage of the oxazolidine ring[13,14] to produce (±)-dihydrofumariline-1 (1) in a quantitative yield. The synthetic dihydrofumariline-1 thus obtained was proved to be identical with natural dihydrofumariline-1 by comparison with IR and ^{1}H-NMR spectra, and thin-layer chromatographic behavior.

The formation of the oxazolidine ring in 13 confirmed unambiguously not only the stereochemistry of the alcohol (10) assigned earlier, but also the *cis* stereochemical relationship between the hydroxy group and the N-methyl group in dihydrofumariline-1. Thus we have accomplished a highly stereoselective synthesis of (±)-dihydrofumariline-1 (1) from the corresponding protoberberine (7) and its stereochemistry has been completely established by the present synthesis.

The present efficient and stereoselective synthesis provides a general method for the synthesis of spirobenzylisoquinoline alkaloids having the *cis* hydroxy group in the five-membered ring.

ACKNOWLEDGEMENT: We are indebted to Professor D.B. MacLean, McMaster University, Canada, and Dr. H.G. Kiryakov, Higher Medical Institute, Bulgaria, for the generous gift of natural dihydrofumariline-1 and fumariline.

REFERENCES AND NOTES

1) Z.H. Hardirossian, H.G. Kiryakov, J.P. Ruder, and D.B. MacLean, *Phytochemistry*, 22, 759 (1983).

2) Popova *et al.* have reported an isolation of dihydrofumariline from *Fumaria schrammii* without statement of its stereochemistry.[3] However, this alkaloid has seemed to be dihydrofumariline-2 (4) from the comparison of their ^{1}H-NMR spectral data.[1]

3) M.E. Popova, A.N. Boeva, L. Dolejš, V. Preininger, V. Šimánek, and F. Šantavý, *Planta Medica*, 40, 156 (1980).

4) T. Kishimoto and S. Uyeo, *J. Chem. Soc.(C)*, 1969, 2600.

5) T. Kishimoto and S. Uyeo, *J. Chem. Soc.(C)*, 1971, 1644.

6) M. Hanaoka, S. Yasuda, Y. Hirai, K. Nagami, and T. Imanishi, *Heterocycles*, 14, 1455 (1980).

7) H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc. Perkin Trans.*1, 1972, 2986.

8) D.B. MacLean, R.A. Bell, J.K. Saunders, C.-Y. Chen, and R.H.F. Manske, *Can. J. Chem.* 47, 3593 (1969).

9) A synthesis of the protoberberine (7) will be reported in a separate paper in detail.

10) M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Letters*, 1979, 3749; M. Hanaoka, C. Mukai, K. Nagami, K. Okajima, and S. Yasuda, *Chem. Pharm. Bull.*, 32, 2230 (1984).

11) M. Hanaoka, S. Sakurai, T. Ohshima, S. Yasuda, and C. Mukai, *Chem. Pharm. Bull.*, 30, 3446 (1982).

12) M. Hanaoka, S. Sakurai, Y. Sato, and C. Mukai, *Heterocycles*, 19, 2263 (1982).

13) S. McLean and D. Dime, *Can. J. Chem.* 55, 924 (1977).

14) D. Dime and S. McLean, *Can. J. Chem.* 57, 1569 (1979).

(Received in Japan 1 December 1984)