Tetrahedron Letters,Vol.26,No.42,pp 5163-5166,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain ©1985 Pergamon Press Ltd.

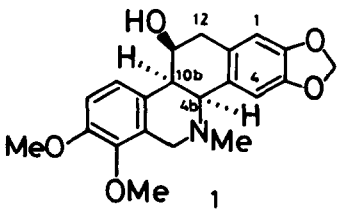
A STEREOSELECTIVE SYNTHESIS OF (±)-HOMOCHELIDONINE

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

Summary: (±)-Homochelidonine (1) was stereoselectively synthesized from berberine (3) through C_6-N bond cleavage, followed by recyclization between C-6 and C-13 position of the latter according to a biogenetic route.

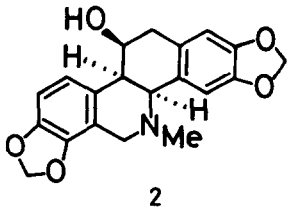
Homochelidonine (1) from *Chelidonium majus* L.[1] and *Bocconia frutescens* L.[2] is a representative B/C *cis*-fused hexahydrobenzo[*c*]phenanthridine alkaloid possessing a hydroxy group at C-11 position. This alkaloid has been synthesized through enamide photocyclization,[3] though yields are not satisfactory. A synthesis of a related alkaloid, chelidonine (2), has also been achieved by two groups.[4,5]

Benzo[*c*]phenanthridine alkaloids have been shown to be biosynthesized[6] from the corresponding protoberberine alkaloids through oxidative C_6-N bond fission followed by recyclization between C-6 and C-13 position. According to this biogenetic process, we have recently developed a novel and efficient method for a synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids.[7,8,9] Next we focused our efforts on a first and convenient conversion of protoberberine alkaloids into hexahydrobenzo[*c*]phenanthridine alkaloids *via* a biogenetic route. This communication deals with a novel and stereoselective synthesis of (±)-homochelidonine (1) from berberine (3), a protoberberine alkaloid.



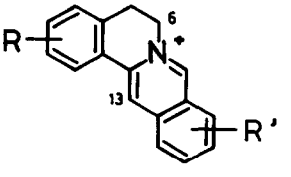
1

homochelidonine



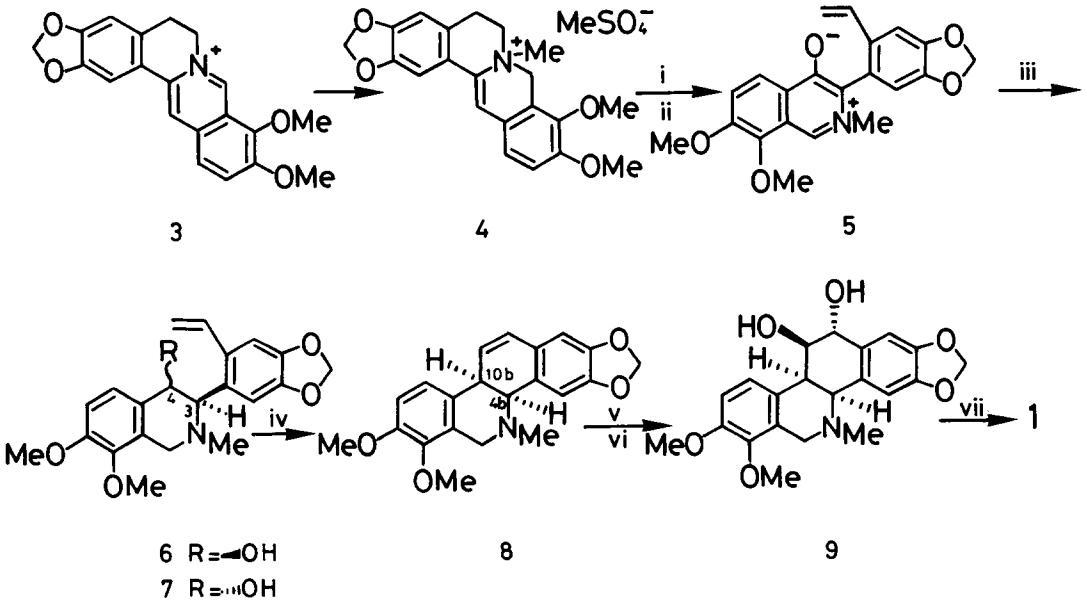
2

chelidonine



protoberberine

The methosulfate (4),[10] easily accessible from berberine (3) by two steps, was treated with 25% methanolic potassium hydroxide under reflux, followed by oxidation with *m*-chloroperbenzoic acid in a stream of nitrogen in methylene chloride at -30° to afford the betaine (5)[92%; *m/z* 365 (M^+); δ 8.34, 7.43 (2H, AB-q, *J*=9), 7.95, 7.14, 6.76 (each 1H, each s), 6.32 (1H, dd, *J*=17 and 11), 5.54 (1H, d, *J*=17), 5.07 (1H, d, *J*=11), 3.77 (3H, s)]. Sodium borohydride reduction of the betaine (5) in ethanol at refluxing temperature yielded predominantly the *cis* alcohol (6)[71%; mp 178-179°; *m/z* 369 (M^+); ν 3550; δ 4.38 (1H, br-s), 4.29, 3.39 (2H, AB-q, *J*=16)] along with a small amount of the *trans* alcohol (7)[10%; mp 150-151°; *m/z* 369 (M^+); ν 3600; δ 4.80 (1H, d, *J*=8), 4.15, 3.48 (2H, AB-q, *J*=16), 3.58 (1H, d, *J*=8)]. The stereochemical relationship between the 3-aryl group and the 4-hydroxy group in both alcohols (6 and 7) was ascertained by their ^{1}H-NMR spectra. The H-4 signal of the *cis* alcohol (6) appeared at 4.38 ppm as a broad singlet, whereas that of the *trans* alcohol (7) resonated at 4.80 ppm as a doublet with a large coupling constant (*J*=8 Hz). Upon treatment with concentrated sulfuric



i:25%KOH/MeOH ii:m-CPBA/CH_2Cl_2 iii:$NaBH_4$/EtOH iv:c.H_2SO_4/AcOH
v:HCO_3H/HCO_2H vi:20%aq.KOH/EtOH vii:Et_3SiH, $BF_3 \cdot OEt_2$/$CHCl_3$

acid in acetic acid at room temperature, the *cis* alcohol (6) underwent cationic cyclization to give stereoselectively the B/c *cis* benzo[*c*]phenanthridine (8) [82%; mp 158-159°; *m/z* 351 (M^+); δ 6.98, 6.86 (2H, AB-q, *J*=8.5), 6.80, 6.63 (each 1H, each s), 6.37 (1H, dd, *J*=9.5 and 3), 5.95 (2H, s), 5.78 (1H, br-d, *J*=9.5), 4.17, 3.42 (2H, AB-q, *J*=16), 3.86, 3.83 (each 3H, each s), 3.72 (1H, m), 3.33 (1H, br-d, *J*=4.3), 2.18 (3H, s)], the stereochemistry of which was elucidated from the coupling constant between the H-4b and the H-10b (*J*=4.3 Hz)[11] in its ^{1}H-NMR spectrum. The *trans* alcohol (7) also gave exclusively the B/C *cis* benzo[*c*]phenanthridine (8), as anticipated, in 84% yield with the same treatment as that for 6.

Introduction of the oxygen functions at C-11 and C-12 position in the benzo[*c*]phenanthridine (8) was realized by oxidation with performic acid in formic acid,[12,13,14] followed by alkaline hydrolysis to furnish 12-hydroxy-homochelidonine (9)[15] [88%; mp 242-244°; *m/z* 385 (M^+); ν 3325; δ 7.03, 6.89 (2H, AB-q, *J*=8.5), 6.94, 6.71 (each 1H, each s), 5.99, 5.96 (2H, AB-q, *J*= 1.2), 4.80 (1H, d, *J*=2.2), 4.23, 3.52 (2H, AB-q, *J*=16), 4.10 (1H, m), 3.56 (1H, m), 3.28 (1H, t, *J*=2.2), 2.32 (3H, s)]. The spectral data and mechanistic consideration[12] are compatible with the stereochemistry depicted for 12-hydroxyhomochelidonine (9). Finally, the 12-hydroxy group in 9 was reductively removed with triethylsilane[16] in the presence of boron trifluoride etherate in chloroform at room temperature to produce (±)-homochelidonine (1) [92%; mp 170-171° (lit.[3] mp 192-193.5°); *m/z* 369 (M^+); δ 6.98, 6.88 (2H, AB-q, *J*=8.5), 6.66 (2H, br-s), 5.96, 5.94 (2H, AB-q, *J*=1.2), 4.26 (1H, m), 4.21, 3.46 (2H, AB-q, *J*=16), 3.88, 3.86 (each 3H, each s), 3.59 (1H, m), 3.24-3.09 (2H, m), 2.97 (1H, t, *J*=2.7), 2.31 (3H, s)]. The synthetic homochelidonine was proved to be identical with natural homochelidonine by comparison with ^{1}H-NMR and IR spectra, and thin-layer chromatographic behavior.

Thus, we have efficiently accomplished a highly stereoselective synthesis of (±)-homochelidonine (1) from berberine (3), a protoberberine alkaloid according to a biogenetic process. This transformation provides a general and convenient method for a synthesis of B/C *cis*-fused hexahydrobenzo[*c*]-phenanthridine alkaloids.

ACKNOWLEDGEMENT: We are very grateful to Professor J. Slavík, J.E. Purkyně University, Czechoslovakia, for a generous supply of natural homochelidonine.

REFERENCES AND NOTES

1) a) R.H.F. Manske, *Can. J. Res.*, 21B, 140 (1943); b) J. Slavík, L. Slavíková, and J. Brabenec, *Coll. Czech. Chem. Commun.*, 30, 3697 (1965); c) N. Takao, M. Kamigauchi, K. Iwasa, and N. Morita, *Arch. Pharm.*, 317, 223 (1984); and references cited therein.

2) E.R. Miller, *J. Am. Pharm. Assoc.*, 18, 12 (1929).
3) I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 7, 137 (1977); *idem*, *J. Chem. Soc. Perkin Trans.* 1, 1983, 2171.
4) W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, 93, 3836 (1971); W. Oppolzer, *Heterocycles*, 14, 1615 (1980); W. Oppolzer and C. Robbiani, *Helv. Chim. Acta*, 66, 1119 (1983).
5) M. Cushman, T.-C. Choong, J.T. Valko, and M.P. Koleck, *Tetrahedron Letters*, 21, 3845 (1980); *idem. J. Org. Chem.*, 45, 5067 (1980).
6) A. Yagi, G. Nonaka, S. Nakayama, and I. Nishioka, *Phytochemistry*, 16, 1197 (1977); E. Leete and S.J.B. Murrill, *ibid.*, 6, 231 (1967); A.R. Battersby, J. Staunton, H.C. Summers, and R. Southgate, *J. Chem. Soc. Perkin Trans.* 1, 1979, 45; N. Takao, H. Kamigauchi, and M. Okada, *Helv. Chim. Acta*, 66, 473 (1983); and references cited therein.
7) M. Hanaoka, T. Motonishi, and C. Mukai, *J. Chem. Soc. Chem. Commun.*, 1984, 718.
8) M. Hanaoka, H. Yamagishi, M. Marutani, and C. Mukai, *Tetrahedron Letters*, 25, 5169 (1984).
9) M. Hanaoka, H. Yamagishi, and C. Mukai, *Chem. Pharm. Bull.*, 33, 1763 (1985).
10) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.*, 19, 31 (1971).
11) I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J. Chem. Soc. Perkin Trans.* 1, 1973, 1696.
12) I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc. Perkin Trans.* 1, 1980, 212; *idem*, *ibid.*, 1983, 2165.
13) M. Onda, H. Yamaguchi, and Y. Harigaya, *Chem. Pharm. Bull.*, 28, 866 (1980).
14) G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.*, 23, 521 (1975).
15) Salvík *et al.* have isolated a benzo[*c*]phenanthridine alkaloid, chelamidine from *C. majus* and established its structure as 12-hydroxyhomochelidonine without assignment of its stereochemistry.[1b] It is very possible that the configuration of chelamidine corresponds to the formula 9 as depicted from the consideration of the stereochemical relationship between corynoline and 12-hydroxycorynoline.[14] Identification of 12-hydroxyhomochelidonine (9) with chelamidine could not be realized because of the lack of natural chelamidine.
16) D.N. Kursanov, Z.N. Parnes, and N.M. Loim, *Synthesis*, 1974, 633.
(Received in Japan 13 July 1985)