

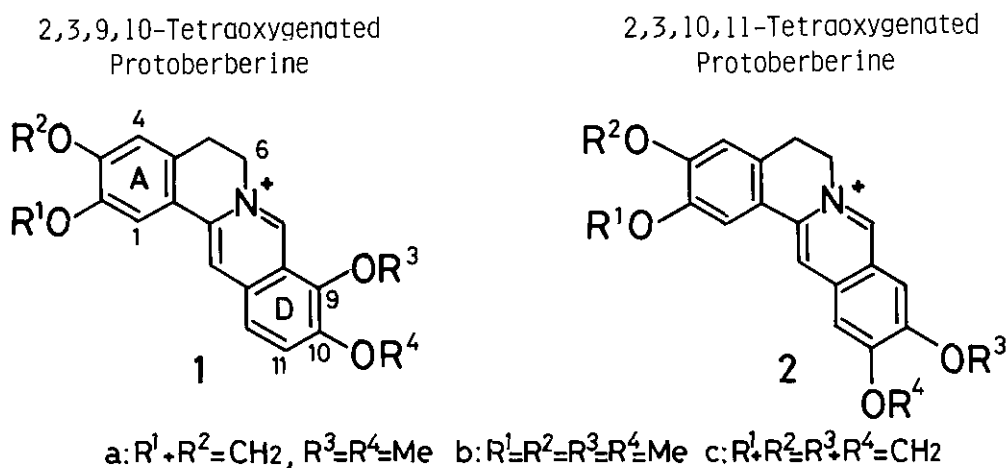
TRANSFORMATION OF 2,3,9,10-TETRAOXYGENATED PROTOBERBERINE
ALKALOIDS INTO 2,3,10,11-TETRAOXYGENATED PROTOBERBERINE
ALKALOIDS

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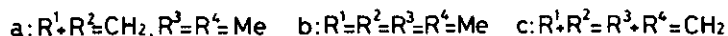
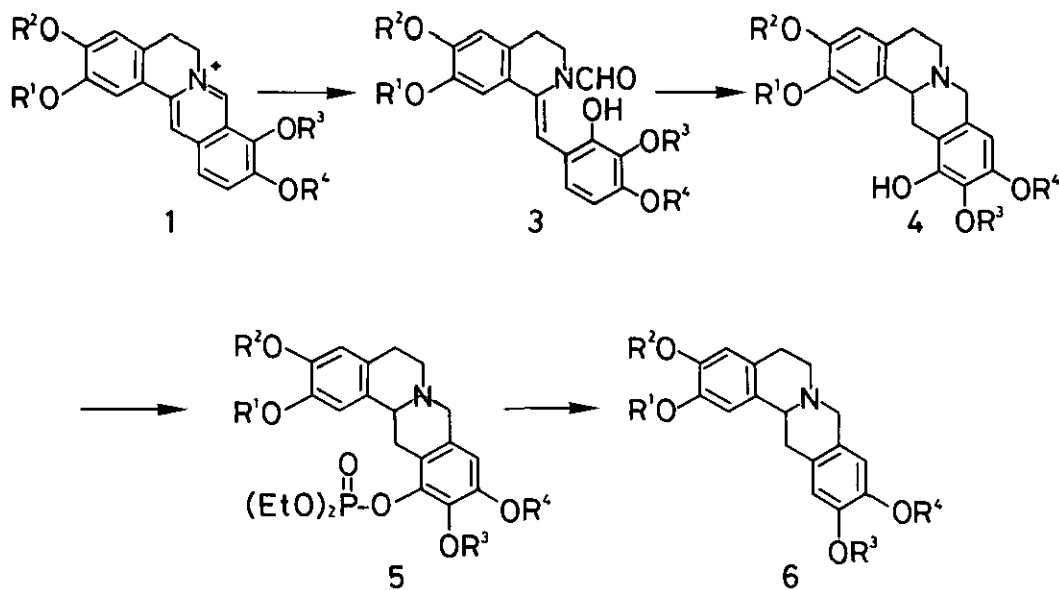
Abstract— 2,3,10,11-Tetraoxygenated tetrahydroprotoberberine (6) were synthesized from the corresponding 2,3,9,10-tetraoxygenated protoberberine alkaloids (1) through oxidative C₈-C_{8a} bond cleavage, photocyclization, and deoxygenation.

Naturally occurring tetraoxygenated protoberberine alkaloids can be classified into two groups¹ according to substitution patterns of oxygen functions in ring A and D. One is naturally abundant 2,3,9,10-tetraoxygenated protoberberines such as berberine (1g) and the other is 2,3,10,11-tetraoxygenated ones as exemplified by pseudoberberine (2g). Some of the latter type of alkaloids, pseudoberberine (2g),



pseudocoptisine (2c), etc. have recently isolated.²

In the course of our studies on transformation of protoberberine alkaloids to fully aromatized benzo[e]phenanthridine alkaloids,^{3,4,5} we required pseudoberberine (2q), a 2,3,10,11-tetraoxygenated protoberberine for a synthesis of nitidine,⁴ an antileukemic benzo[e]phenanthridine alkaloid. Although pseudoberberine (2q) has so far been synthesized by a conventional method,⁶ simple conversion of commercially available berberine (1q) into pseudoberberine (2q) would provide an alternative synthesis because of easy access of the starting material. We report here a novel and convenient method for a synthesis of 2,3,10,11-tetraoxygenated protoberberine alkaloids from 2,3,9,10-tetraoxygenated protoberberine alkaloids through oxidative C₈-C_{8a} bond fission of the latter, followed by successive photo-induced cyclization and deoxygenation. Berberine (1q) was oxidized with 1.3 eq. of *m*-chloroperbenzoic acid⁷ in dry tetrahydrofuran in the presence of 2 eq. of sodium hydride in a stream of nitrogen at room temperature to afford polyberbine (3q) [76%; mp 165-166°C; *m/z* 369 (M⁺); ν 3500, 1660; δ 8.10, 7.27 (each 1H, each s)]. Polyberbine, recently isolated from *Berberis valdiviana* Phil.,⁸ has already been synthesized from



berberine (10) by a similar oxidation using sodium bicarbonate instead of sodium hydride though in 20% yield.⁹ Similar treatment of palmatine (1b) and coptisine (1c) gave polycarpine (3b)¹⁰ [44%; mp 176-177°C (lit.⁹ mp 179-180°C); m/z 385 (M^+); ν 3500, 1660; δ 8.13, 7.26 (each 1H, each s)] and 3c¹¹ [39%; m/z 354 (M^++1);¹² ν 3200, 1660; δ 8.03, 7.24 (each 1H, each s)], respectively, the yields are, however, lower in comparison with that of 10.¹³

Enamide photocyclization¹⁴ of polyberberine (30) with a high-pressure mercury lamp in ethanol in a stream of nitrogen, followed by sodium borohydride reduction produced 12-hydroxytetrahydropseudoberberine (40) [79%; mp 219-220°C; m/z 355 (M^+), 176 (base peak); ν 3550; δ 6.81, 6.57, 6.20 (each 1H, each s)]. Reductive removal of the hydroxy group in 40 was carried out *via* the phosphate (50). Treatment of 40 with diethyl chlorophosphate in the presence of sodium hydride afforded the phosphate (50), hydrogenolysis of which with sodium in liquid ammonia¹⁵ at -70°C furnished tetrahydropseudoberberine (60) [53%; mp 177-178.5°C; δ 6.73, 6.64, 6.59, 6.57 (each 1H, each s)]. The product was identified with the authentic specimen⁶ by comparison of their spectra and thin-layer chromatographic behavior. Polycarpine (3b) and 3c also underwent a photo-induced cyclization to provide the 12-hydroxytetrahydroprotoberberine (4b) [70%; m/z 371 (M^+), 192 (base peak); ν 3520; δ 6.78, 6.62, 6.50 (each 1H, each s)] and (4c) [65%; mp 232-233°C; m/z 339 (M^+), 176 (base peak); ν 3400; δ 6.88, 6.65, 6.22 (each 1H, each s)], both of which were subsequently converted into (+)-xylopinine (6b) [62%; mp 157-159°C; δ 6.74, 6.67, 6.62, 6.58 (each 1H, each s)] and tetrahydropseudocoptisine (6c) [44%; mp 213-214°C; δ 6.71, 6.60, 6.58, 6.53 (each 1H, each s)] *via* the phosphate (5b) and (5c), respectively, by the same treatment¹⁶ as that described for 60. The synthetic (+)-xylopinine and tetrahydropseudocoptisine were proved to be identical with the authentic specimens.^{17,18}

Thus, we have developed a novel and convenient method for a synthesis of 2,3,10, 11-tetraoxygenated protoberberines from naturally abundant 2,3,9,10-tetraoxygenated protoberberines.

REFERENCES AND NOTES

- 1) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," vol.2, Kinkodo Publishing Company, Sendai, Japan, 1974, pp. 189-209: a 1,2,10,11-tetraoxy-generated protoberberine, caseadine is also known.
- 2) C. Moulis, J. Gleye, and E. Stanislas, *Phytochemistry*, 1977, 16, 1283.
- 3) M. Hanaoka, T. Motonishi, and C. Mukai, *Chem. Commun.*, 1984, 718.
- 4) M. Hanaoka, H. Yamagishi, M. Mari, and C. Mukai, *Tetrahedron Letters*, 1984, 25, 5169.
- 5) M. Hanaoka, H. Yamagishi, C. Mukai, *Chem. Pharm. Bull.*, 1985, 33, 1763.
- 6) R.D. Haworth, W.H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, 1924, 125, 1686.
- 7) H. Ishii and T. Ishikawa, *J. Chem. Soc. Perkin Trans. 1*, 1984, 1769.
- 8) S. Firdous, A.J. Freyer, M. Shamma, and A. Urzúa, *J. Am. Chem. Soc.*, 1984, 106, 6099.
- 9) N. Murugesan and M. Shamma, *Tetrahedron Letters*, 1979, 4521.
- 10) Polycarpine was isolated from *Enantia polycarpa* Engl. et Diels: A. Jossang, M. Leboeuf, A. Cavé, M. Damak, and C. Riche, *C.R. Acad. Sci., Ser. C*, 1977, 284, 467.
- 11) N. Murugesan and M. Shamma, *Heterocycles*, 1980, 14, 585.
- 12) Measured by Chemical Ionization Method.
- 13) M. Shamma obtained 3D and 3C in 40%⁹ and 40-50%¹¹ yield, respectively.
- 14) G.R. Lenz, *J. Org. Chem.*, 1977, 42, 1117.
- 15) R.A. Rossi and J.K. Bunnett, *J. Org. Chem.*, 1973, 38, 2314.
- 16) n-Butyllithium was used instead of sodium hydride in the case of 4C.
- 17) T. Kametani, M. Takeshita, F. Satoh, and K. Nyu, *Yakugaku Zasshi*, 1974, 94, 478.
- 18) R.M. Sotelo and D. Giacobello, *Aus. J. Chem.*, 1972, 25, 385.

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