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

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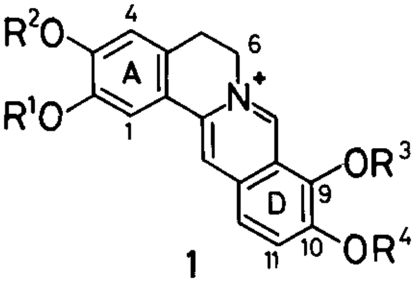
Abstract——— 2,3,10,11-Tetraoxygenated tetrahydroprotoberberine (6) were synthesized from the corresponding 2,3,9,10-tetraoxygenated protoberberine alkaloids (1) through oxidative C_8-C_{8a} bond cleavage, photocyclization, and deoxygenation.

Naturally occurring tetraoxygenated protoberberine alkaloids can be classified into two groups[1] 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 (1a) and the other is 2,3,10,11-tetraoxygenated ones as exemplified by pseudoberberine (2a). Some of the latter type of alkaloids, pseudoberberine (2a),

2,3,9,10-Tetraoxygenated
Protoberberine



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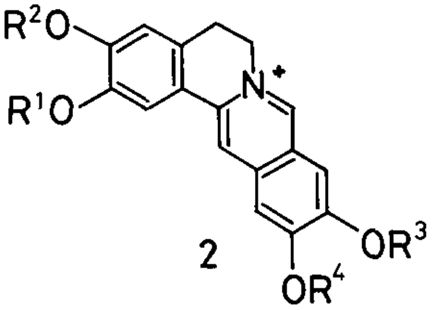
2,3,10,11-Tetraoxygenated
Protoberberine



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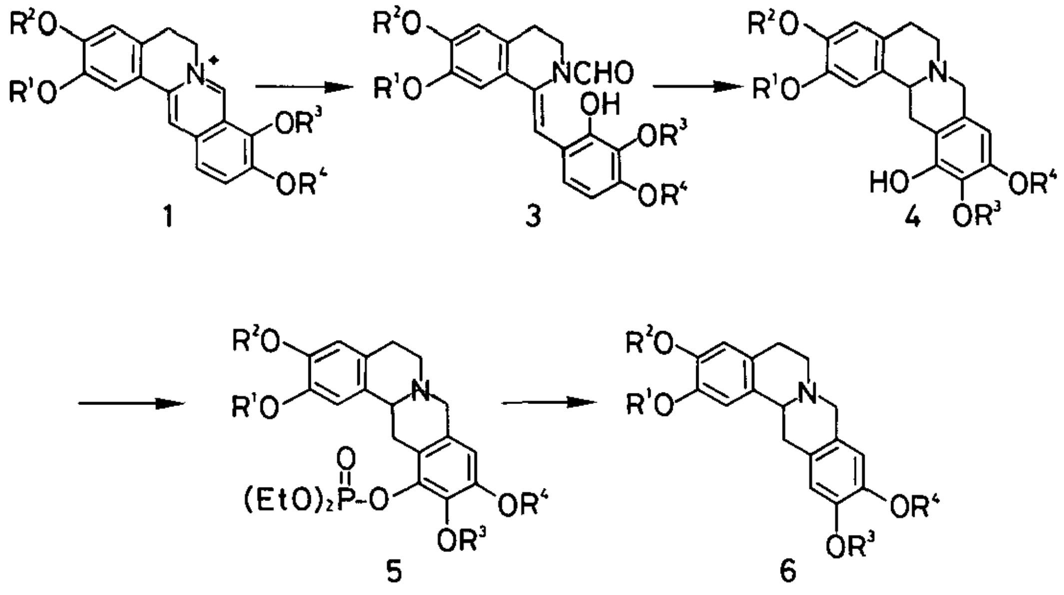
a: $R^1+R^2=CH_2$, $R^3=R^4=Me$ b: $R^1=R^2=R^3=R^4=Me$ c: $R^1+R^2=R^3+R^4=CH_2$

pseudocoptisine (2c), *etc.* have recently isolated.[2]

In the course of our studies on transformation of protoberberine alkaloids to fully aromatized benzo[*c*]phenanthridine alkaloids,[3,4,5] we required pseudoberberine (2a), a 2,3,10,11-tetraoxygenated protoberberine for a synthesis of nitidine,[4] an antileukemic benzo[*c*]phenanthridine alkaloid. Altough pseudoberberine (2a) has so far been synthesized by a conventional method,[6] simple conversion of commercially available berberine (1a) into pseudoberberine (2a) 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 C_8-C_{8a} bond fission of the latter, followed by successive photo-induced cyclization and deoxygenation.

Berberine (1a) was oxidized with 1.3 eq. of *m*-chloroperbenzoic acid[7] in dry tetrahydrofuran in the presence of 2 eq. of sodium hydride in a stream of nitrogen at room temperature to afford polyberbine (3a) [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



a: R^1+R^2=CH_2, R^3=R^4=Me b: R^1=R^2=R^3=R^4=Me c: R^1+R^2=R^3+R^4=CH_2

berberine (1a) 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 3c[11] [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 1a.[13]

Enamide photocyclization[14] of polyberbine (3a) with a high-pressure mercury lamp in ethanol in a stream of nitrogen, followed by sodium borohydride reduction produced 12-hydroxytetrahydropseudoberberine (4a)[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 4a was carried out *via* the phosphate (5a). Treatment of 4a with diethyl chlorophosphate in the presence of sodium hydride afforded the phosphate (5a), *hydrogenolysis of which with sodium in liquid ammonia*[15] at -70°C furnished tetrahydropseudoberberine (6a)[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 treatment[16] as that described for 6a. 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.*

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