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-C₈a 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),

2,3,9,10-Tetraoxygenated Protoberberine

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\begin{align*}
\text{A} & \quad \text{D} \\
R^1O & \quad R^3O \\
R^2O & \quad \text{Me} \\
\end{align*}
\]

\[ \text{a: } R^1=R^2=CH_2, \quad R^3=R^4=\text{Me} \]

2,3,10,11-Tetraoxygenated Protoberberine

\[
\begin{align*}
\text{A} & \quad \text{D} \\
R^1O & \quad \text{Me} \\
R^2O & \quad \text{Me} \\
\end{align*}
\]

\[ \text{b: } R^1=R^2=R^3=\text{Me} \]

\[ \text{c: } R^1=R^2=R^3=R^4=\text{CH}_2 \]
pseudocoptisine (2c), etc. have recently isolated.\textsuperscript{2}

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

Berberine (1g) was oxidized with 1.3 eq. of m-chloroperbenzoic acid\textsuperscript{7} in dry tetrahydrofuran in the presence of 2 eq. of sodium hydride in a stream of nitrogen at room temperature to afford polyberbine (3g) [76%; mp 165-166°C; m/z 369 (M\textsuperscript{+}); v 3500, 1660; δ 8.10, 7.27 (each 1H, each s)]. Polyberbine, recently isolated from \textit{Berberis valdiviana} Phil.,\textsuperscript{8} has already been synthesized from
berberine (10) by a similar oxidation using sodium bicarbonate instead of sodium hydride though in 20% yield. Similar treatment of palmatine (1b) and coptisine (1c) gave polycarpine (3b) [44%; mp 176-177°C (lit. mp 179-180°C); m/z 385 (M⁺); ν 3500, 1660; δ 8.13, 7.26 (each 1H, each s)] and 3c [39%; m/z 354 (M⁺+1); 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 polyberbine (3g) with a high-pressure mercury lamp in ethanol in a stream of nitrogen, followed by sodium borohydride reduction produced 12-hydroxytetrahydropseudoberberine (4g) [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 4g was carried out via the phosphate (5g). Treatment of 4g with diethyl chlorophosphate in the presence of sodium hydride afforded the phosphate (5g), hydrogenolysis of which with sodium in liquid ammonia15 at -70°C furnished tetrahydropseudoberberine (6g) [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 (4g) [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 (±)-xylopine (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 6g. The synthetic (±)-xylopine 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


12) Measured by Chemical Ionization Method.

13) M. Shamma obtained 3b and 3c in 40\% and 40-50\% yield, respectively.


16) n-Butyllithium was used instead of sodium hydride in the case of 4c.


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