

## A Biomimetic Conversion of Berberine into Chelerythrine and Dihydrochelerythrine

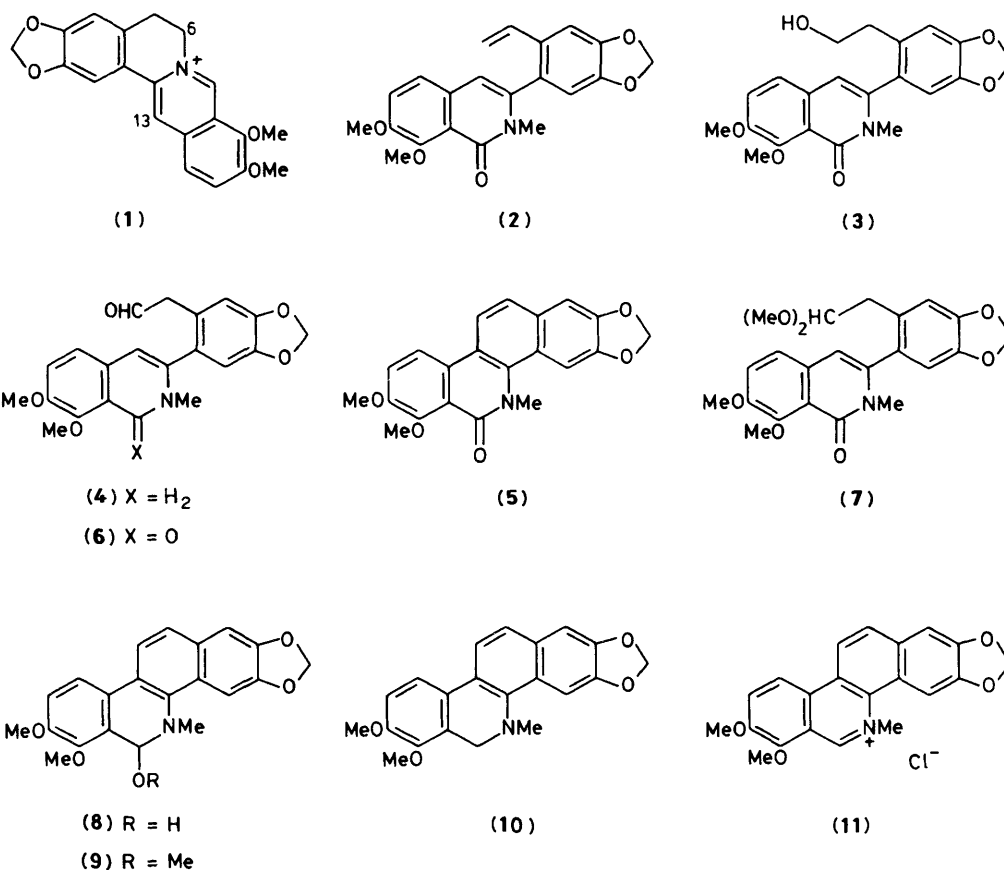
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A novel and efficient synthesis of the benzo[c]phenanthridine alkaloids, chelerythrine and dihydrochelerythrine, from berberine was developed *via* a biogenetic route.

Benzo[c]phenanthridine alkaloids have been shown<sup>1,2</sup> to be biosynthesised from protoberberine alkaloids through oxidative C(6)–N bond fission followed by intramolecular condensation between the C(6) and C(13) position of the latter alkaloids *via* suggested aldehyde intermediates such as (4). However, no report<sup>3</sup> has so far been made on the conversion

of protoberberine alkaloids into benzo[c]phenanthridine alkaloids in accordance with the above biogenetic process despite current interest<sup>4</sup> in the synthesis of benzo[c]phenanthridine alkaloids. We now describe the first biomimetic transformation of a protoberberine alkaloid into benzo[c]phenanthridine alkaloids.



Hydroboration of the enamide (2),<sup>5</sup> easily derived from berberine (1), with diborane in dry tetrahydrofuran (THF) at 0 °C followed by oxidation with hydrogen peroxide gave the alcohol (3) [70%; m.p. 163–163.5 °C;  $\nu_{\max}$  3450, 1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  n.m.r.  $\delta$  3.72 (2H, t,  $J$  7 Hz), 2.62 (2H, t,  $J$  7 Hz);  $m/z$  383 ( $M^+$ )]. The alcohol (3) was subsequently oxidised with pyridinium chlorochromate in methylene dichloride at room temperature to afford directly the benzo[c]phenanthridine, oxychelerythrine (5) [65%; m.p. 197–198 °C (lit.<sup>5</sup> 199.5–201 °C);  $\nu_{\max}$  1645  $\text{cm}^{-1}$ ;  $^1\text{H}$  n.m.r.  $\delta$  7.97, 7.51 (1H each, ABq,  $J$  8 Hz);  $m/z$  363 ( $M^+$ )]. The formation of (5) can be rationalised in terms of the intermediacy of the aldehyde (6), although the latter was not detected in the reaction mixture.

An alternative and more efficient procedure for the synthesis of (5) was developed. Treatment of the enamide (2) with thallium(III) nitrate<sup>6</sup> in methanol at room temperature for 3 min afforded the acetal (7) [97%; m.p. 181–182 °C;  $\nu_{\max}$  1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  n.m.r.  $\delta$  4.39 (1H, dd,  $J$  5 and 6 Hz), 3.25 (3H, s), 3.18 (3H, s), 2.88 (1H, dd,  $J$  6 and 15 Hz), 2.64 (1H, dd,  $J$  5 and 15 Hz);  $m/z$  427 ( $M^+$ )] which was hydrolysed in methanol with a catalytic amount of hydrochloric acid to produce (5) quantitatively.

Reduction of (5) with lithium aluminium hydride in dry THF at 0 °C gave quantitatively the amino-alcohol (8) [ $^1\text{H}$  n.m.r.  $\delta$  5.60 (1H,  $J$  12 Hz)], recrystallisation of which from methanol yielded the methoxy derivative (9) [93%; m.p. 203–204 °C;  $^1\text{H}$  n.m.r.  $\delta$  5.54 (1H, s), 3.46 (3H, s);  $m/z$  379 ( $M^+$ )]. The compound (8) was further reduced with sodium borohydride in methanol to give dihydrochelerythrine (10) [m.p. 164–165 °C (lit.<sup>7</sup> 161–165 °C);  $^1\text{H}$  n.m.r.  $\delta$  4.29 (2H, s);  $m/z$  349 ( $M^+$ )] in 96% overall yield from (5). On the other hand, upon treatment with 10% hydrochloric acid, the compound (8) afforded quantitatively chelerythrine chloride (11) [m.p. 190–191 °C (lit.<sup>3a</sup> 196–197 °C)]. Synthetic (10)

and (11) were identical with the corresponding natural alkaloids.

Thus, we have developed a novel and efficient method for the synthesis of chelerythrine and dihydrochelerythrine, and this method provides the first example of the biomimetic conversion of protoberberine alkaloids into benzo[c]phenanthridine alkaloids.

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