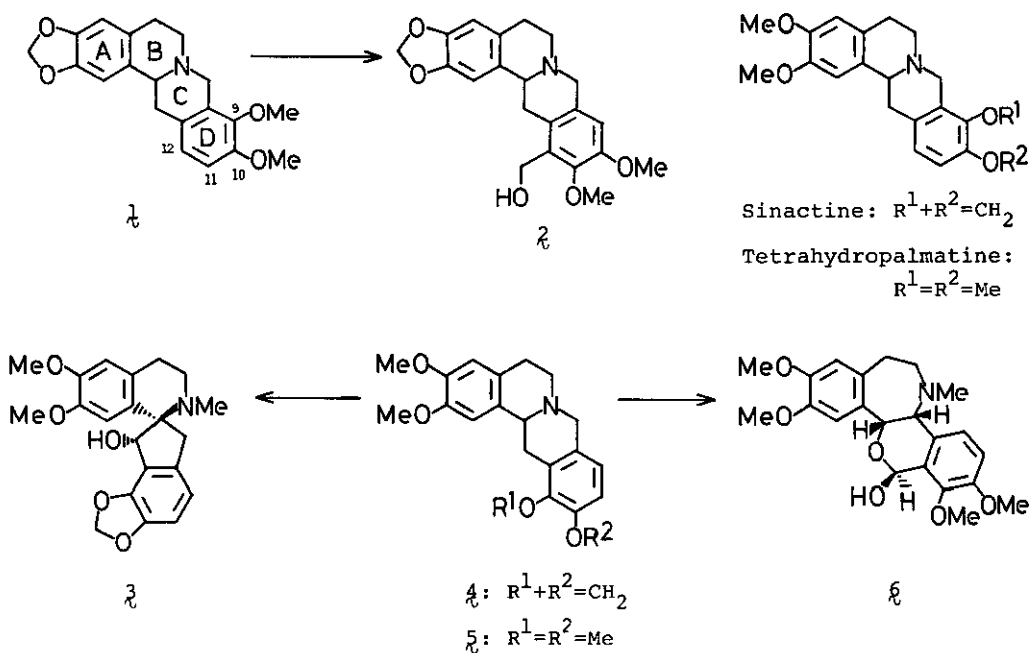


RING D INVERSION OF PROTOBERBERINE ALKALOIDS. CONVERSION OF  
BERBERINE INTO NON-NATURALLY OCCURRING 11,12-OXYGENATED  
PROTOBERBERINES

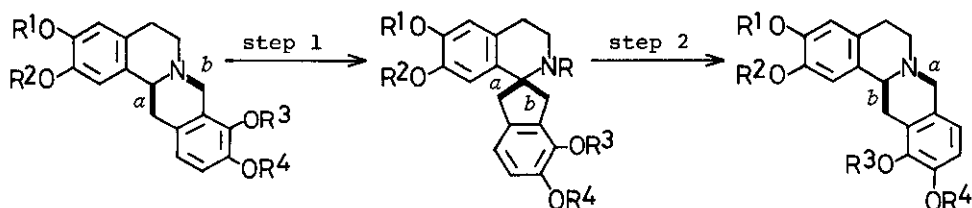
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*Abstract*— Three methods were developed for the transformation of a naturally occurring 9,10-oxygenated protoberberine, berberine into a non-naturally occurring 11,12-oxygenated protoberberine through ring D inversion *via* a corresponding spirobenzylisoquinoline.

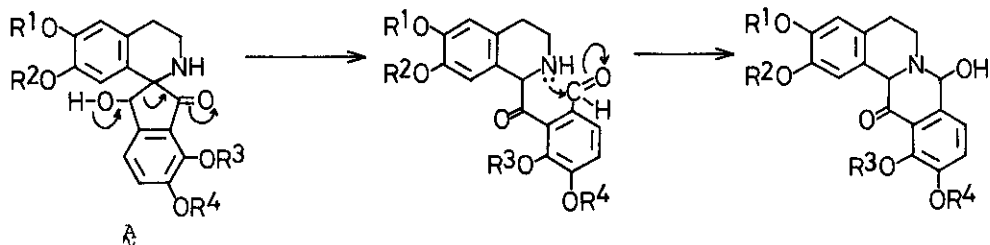
Ring D inversion would be one of the key-steps in the bio-transformation<sup>1</sup> of protoberberine alkaloids to related alkaloids such as retroprotoberberines, some spirobenzylisoquinolines, and rhoeadines. On this assumption we synthesized the retroprotoberberine (2)<sup>2</sup> from tetrahydroberberine (1), and (±)-fumaricine (3)<sup>3</sup> from



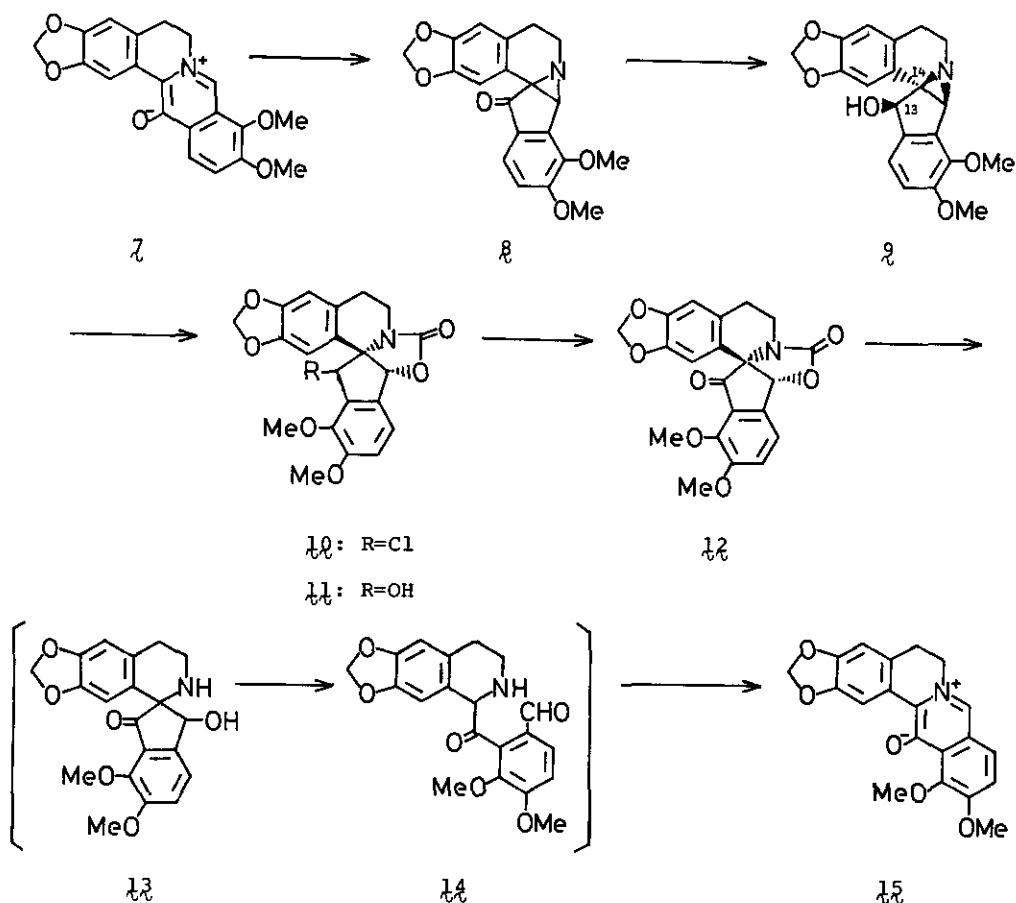
the non-natural 11,12-oxygenated protoberberine (4), which could be regarded as the ring D inverted product of the natural 9,10-oxygenated protoberberine, (+)-sinactine. And the non-natural protoberberine (5), the ring D inverted product of (+)-tetrahydropalmatine was converted into (+)-*cis*-alpinigenine (6).<sup>4</sup> This communication deals with the efficient methods for ring D inversion of protoberberine alkaloids, namely the transformation of a naturally occurring 9,10-oxygenated protoberberine, berberine to a non-naturally occurring 11,12-oxygenated protoberberine *via* a spirobenzylisoquinoline. The strategy for this transformation consisted of the transposition of *a*- and *b*-bond in a protoberberine with each other as shown below.



In a previous paper,<sup>5</sup> we developed a novel and versatile synthetic method for spirobenzylisoquinolines from protoberberines *via* 8,14-cycloberbines, which were easily obtained by photochemical valence tautomerization of berberinephenolbetaines. This method could be applied to the step 1 in the above strategy for ring D inversion. In order to complete the step 2, an intermediate spirobenzylisoquinoline should be modified with appropriate functionality. The most promising one would be the amino-hydroxy-ketone (A), treatment of which with alkali would effect retroaldol reaction and subsequent cyclization to revert to a protoberberine with ring D inversion.



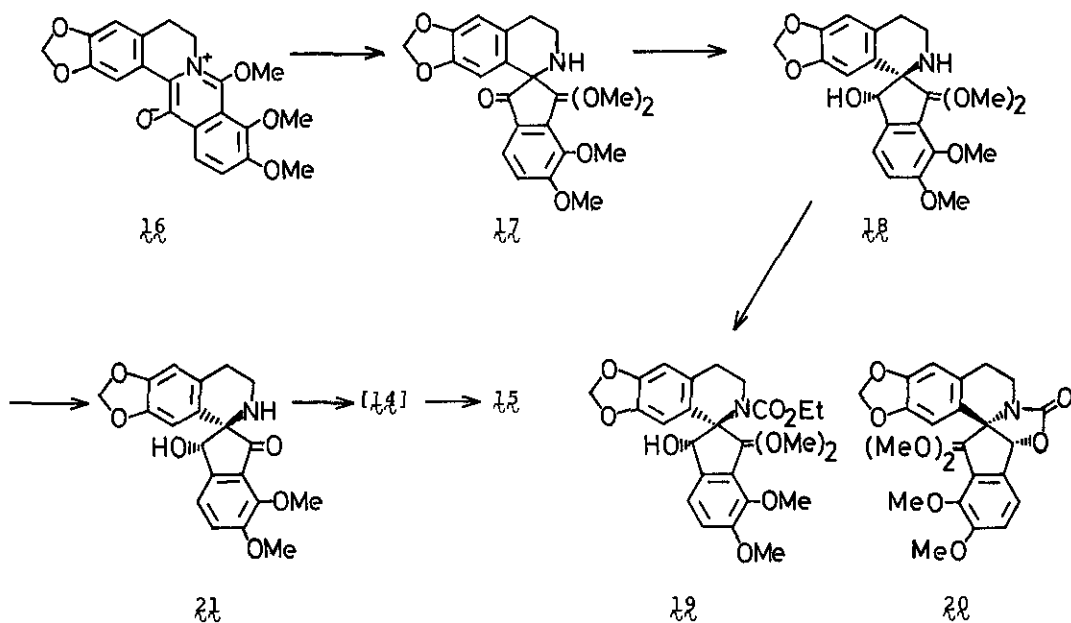
The 8,14-cycloberbine (8)<sup>5</sup> derived from berberinephenolbetaine (7)<sup>6</sup> was reduced with sodium borohydride in methanol-chloroform to give the alcohol (9) [95%, mp 168.5–169.5°, *m/e* 353 ( $M^+$ ),  $\nu$  3350,  $\delta$  7.03 (1H, s), 6.99, 6.70 (2H, AB-q,  $J=8.5$ ), 6.53 (1H, s), 5.77 (2H, s), 5.53 (1H, s), 3.88 (3H, s), 3.78 (3H, s), 3.64 (1H, s)],



which was treated with ethyl chloroformate in benzene at 90°C for 2 hr to afford the oxazolidinone (10) [50%, mp 180–182.5°,  $m/e$  415, 417 ( $M^+$ ),  $\nu$  1750,  $\delta$  7.10, 6.98 (2H, AB-q,  $J=8$ ), 6.65 (1H, s), 6.54 (1H, s), 5.87 (2H, s), 5.78 (1H, s), 5.48 (1H, s), 3.93 (3H, s), 3.85 (3H, s)] with regioselective cleavage of the aziridine ring. The *cis*-relationship between C<sub>13</sub>-OH and C<sub>14</sub>-N in 9 was confirmed by the formation of 10. On treatment with silver nitrate in aqueous tetrahydrofuran at room temperature 10 gave the hydroxy-oxazolidinone (11) [50%, mp 258–260°,  $m/e$  397 ( $M^+$ ),  $\nu$  3450, 1735,  $\delta$  7.23, 7.07 (2H, AB-q,  $J=8.5$ ), 6.61 (1H, s), 6.24 (1H, s), 5.39 (1H, s), 5.36 (1H, d,  $J=7.5$ )]. Although treatment of 11 with Jones reagent or pyridinium chlorochromate afforded only the starting material recovered, oxidation of 11 with pyridinium dichromate<sup>7</sup> in dimethylformamide at room temperature for 3 hr resulted in the keto-oxazolidinone (12) [85%, mp 274–275°,  $m/e$  395 ( $M^+$ ),  $\nu$  1750, 1715,  $\delta$  7.29 (2H, s), 6.56 (1H, s), 6.09 (1H, s), 5.53 (1H, s)], which has sufficient functionality, properly situated, for rearrangement to a protoberberine with ring

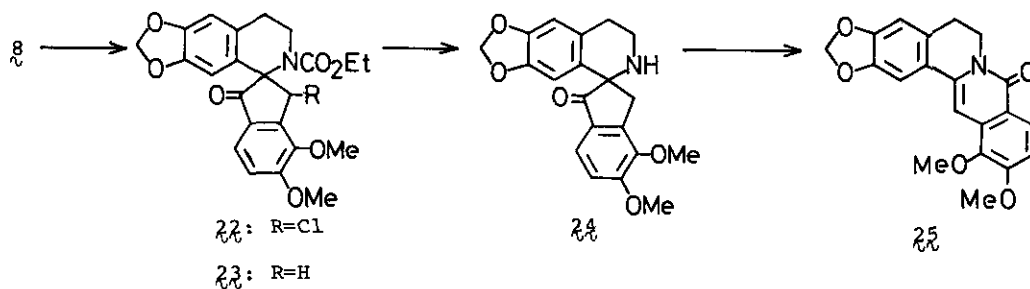
D inversion to be effected. Heating of **12** with 10% aqueous sodium hydroxide in ethanol effected hydrolysis of the oxazolidinone ring, retro-aldol reaction, cyclization, and subsequent dehydration to provide successfully the 11,12-oxygenated phenolbetaine (**15**) [quant., mp 181-182°, *m/e* 351 ( $M^+$ ),  $\lambda$  222, 246, 289, 384, 430,  $\delta$  8.93 (1H, s), 7.40, 7.29 (2H, AB-q,  $J=8$ ), 7.37 (1H, s), 6.62 (1H, s), 5.94 (2H, s), 4.37 (2H, t,  $J=6$ ), 4.03 (3H, s), 3.98 (3H, s), 2.99 (2H, t,  $J=6$ )] *via* **13** and **14**. The 11,12-oxygenated structure of **15** was well established from the fact that the AB-quartet due to two protons at ring D appeared at higher field in comparison with that of **7** (8.18 and 7.24 ppm).

Alternatively and more conveniently ring D inversion was accomplished starting from the spirobenzylisoquinoline (**17**),<sup>5,8</sup> obtained from 8-methoxyberberinephenolbetaine (**16**)<sup>9</sup> in 73% yield.<sup>10</sup> Reduction of **17** with sodium borohydride in methanol at 0°C yielded stereoselectively the alcohol (**18**) [quant., mp 188-189°, *m/e* 400 ( $M^+-15$ ),  $\nu$  3350,  $\delta$  7.16, 6.94 (2H, AB-q,  $J=8.5$ ), 6.60 (1H, s), 6.16 (1H, s), 5.84, 5.80 (2H, AB-q,  $J=1.5$ ), 4.89 (1H, s), 3.91 (3H, s), 3.86 (3H, s), 3.33 (3H, s), 3.19 (3H, s)]. Stereochemistry of **18** was supported by the formation of the carbamate (**19**) instead of the oxazolidinone (**20**) from the reaction of **18** with ethyl chloroformate. Deketalization of **18** with 10% hydrochloric acid in methanol gave the ketone (**21**) [quant., mp 113-115°, *m/e* 369 ( $M^+$ ),  $\nu$  3350, 1715,  $\delta$  7.38 (1H, d-d,  $J=8.5$ ; 0.5), 7.34 (1H, d,  $J=8.5$ ), 6.64 (1H, s), 5.95 (1H, s), 5.84, 5.83 (2H, AB-q,  $J=1.5$ ), 5.19



(1H, s), 4.03 (3H, s), 3.94 (3H, s)], which has exactly the same functionality with the key compound (8) in our strategy. The compound (21) was treated with 10% aqueous sodium hydroxide in ethanol to provide the expected phenolbetaine (15, 95%) via 14. The product was identical with the authentic specimen obtained above.

The third conversion was achieved by the application of photochemical transformation of a spirobenzylisoquinoline to a protoberberine.<sup>11</sup> Hydrogenolysis of the spirobenzylisoquinoline (22),<sup>5</sup> derived from 8, over 10% palladium-charcoal in ethanol afforded the dehalogenated ketone (23) [88%, *m/e* 425 ( $M^+$ ),  $\nu$  1717, 1680,  $\delta$  7.53, 6.94 (2H, AB-q,  $J=8.5$ ), 6.54 (1H, s), 6.08 (1H, s), 5.78, 5.73 (2H, AB-q,  $J=1.5$ ), 3.95 (3H, s), 3.89 (3H, s), 3.53 (2H, s)], which was hydrolyzed with 10% aqueous potassium hydroxide in ethanol to give the amino-ketone (24) [73%, *m/e* 353 ( $M^+$ ),  $\nu$  1700,  $\delta$  7.47, 6.87 (2H, AB-q,  $J=8.5$ ), 6.43 (1H, s), 5.99 (1H, s), 5.70 (2H, s), 3.89 (3H, s), 3.82 (3H, s), 3.35 (2H, s)]. Irradiation (100W high-pressure Hg lamp, with Pyrex filter) of 24 in tetrahydrofuran in a stream of argon for 2 hr provided the 11,12-oxygenated protoberberine (25) [43%, mp 236-237°, *m/e* 351 ( $M^+$ ),  $\nu$  1640, 1615,  $\delta$  8.10 (1H, d,  $J=8.5$ ), 7.18 (1H, s), 6.97 (1H, s), 6.95 (1H, d,  $J=8.5$ ), 6.57 (1H, s), 5.89 (2H, s), 4.23 (2H, t,  $J=6.5$ ), 3.90 (3H, s), 3.88 (3H, s), 2.83 (2H, t,  $J=6.5$ )]. Its structure was confirmed by appearance of the doublet due to C<sub>9</sub>-H at very low field in its PMR spectrum.<sup>12</sup>



Thus, three methods were developed for the conversion of the naturally occurring 9,10-oxygenated protoberberine to the non-naturally occurring 11,12-oxygenated protoberberine by ring D inversion. These results will provide a new route for biogenetic transformation of protoberberines into related alkaloids and suggest the importance of spirobenzylisoquinolines in the bio-transformation in these alkaloids.

*Acknowledgement:* The authors are grateful for a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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Received, 16th September, 1981