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

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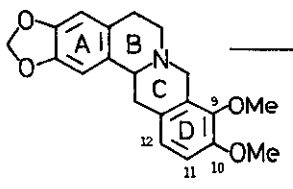
Abstract—— Three methods were developed for the transformation of a naturally occurring 9,10-oxygenated protoberberine, berberine into a non-naturally occurring 11,12-oxygenated protoberberine through ring D inversion *via* a corresponding spirobenzylisoquinoline.

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



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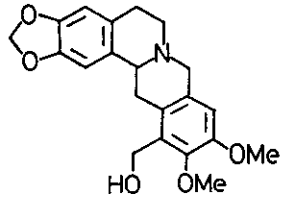

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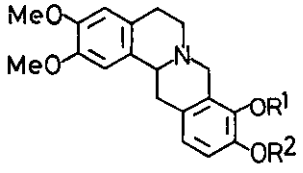
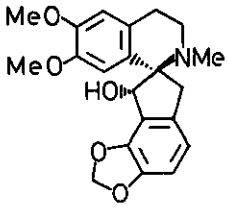


Sinactine: $R^1+R^2=CH_2$

Tetrahydropalmatine: $R^1=R^2=Me$



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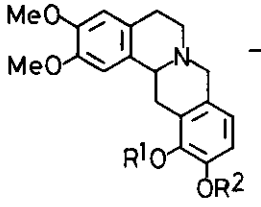
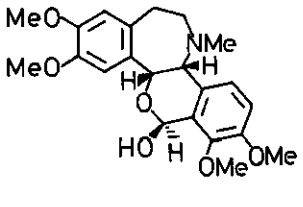


4: $R^1+R^2=CH_2$

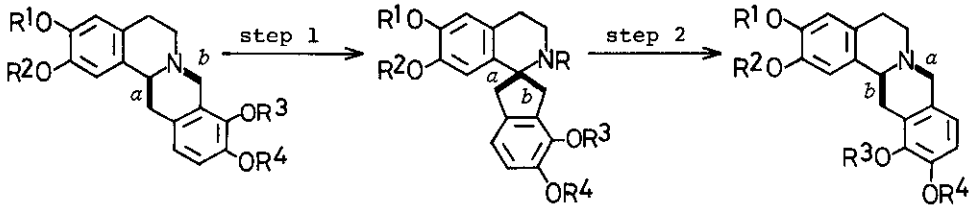
5: $R^1=R^2=Me$



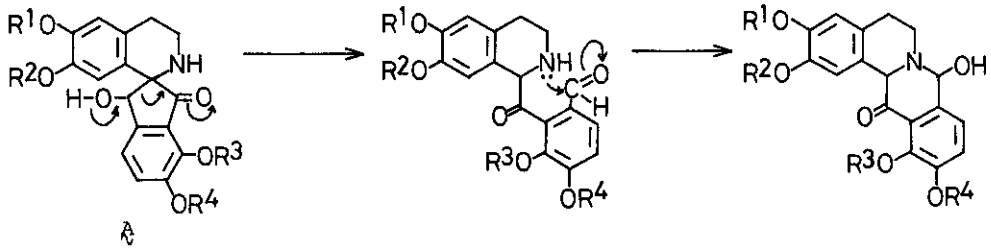
6

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).[4]

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.

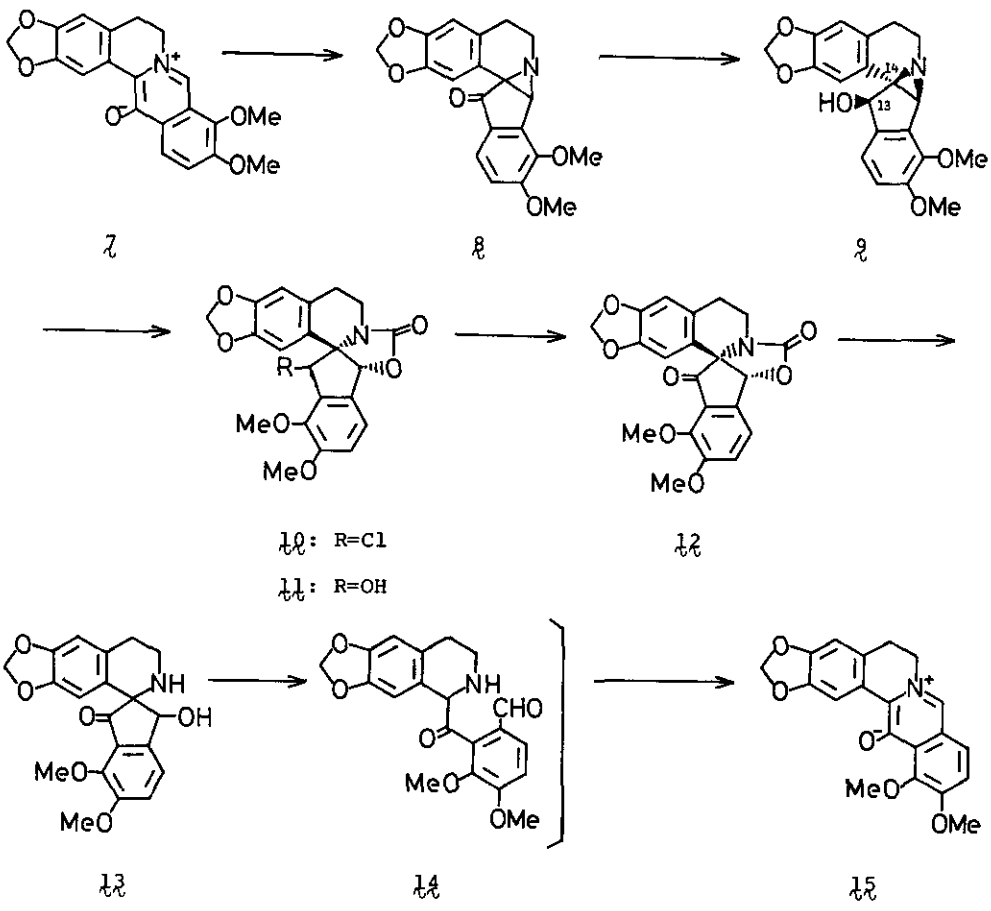


In a previous paper,[5] we developed a novel and versatile synthetic method for spirobenzylisoquinolines from protoberberines *via* 8,14-cycloberbines, which were easily obtained by photochemical valence tautomerization of berberinephenolbetaines. This method could be applied to the step 1 in the above 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 retro-aldol reaction and subsequent cyclization to revert to a protoberberine with ring D inversion.



A

The 8,14-cycloberbine (8)[5] derived from berberinephenolbetaine (7)[6] was reduced with sodium borohydride in methanol-chloroform to give the alcohol (9) [95%, mp 168.5-169.5°, *m/e* 353 (M^+), ν 3350, δ 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)],



7 8 9

10: R=Cl

11: R=OH

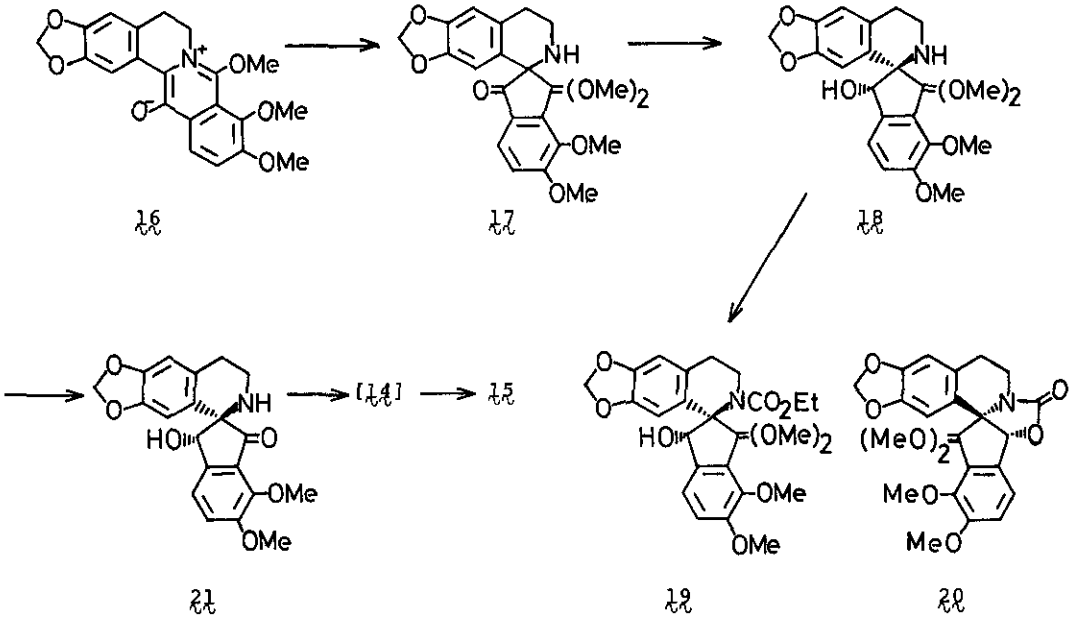
12

13 14 15

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^+), ν 1750, δ 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_{13}-OH and C_{14}-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^+), ν 3450, 1735, δ 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[7] in dimethylformamide at room temperature for 3 hr resulted in the keto-oxazolidinone (12) [85%, mp 274-275°, *m/e* 395 (M^+), ν 1750, 1715, δ 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^+), λ 222, 246, 289, 384, 430, δ 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),[5,8] obtained from 8-methoxyberberinephenolbetaine (16)[9] in 73% yield.[10] 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), ν 3350, δ 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^+), ν 3350, 1715, δ 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

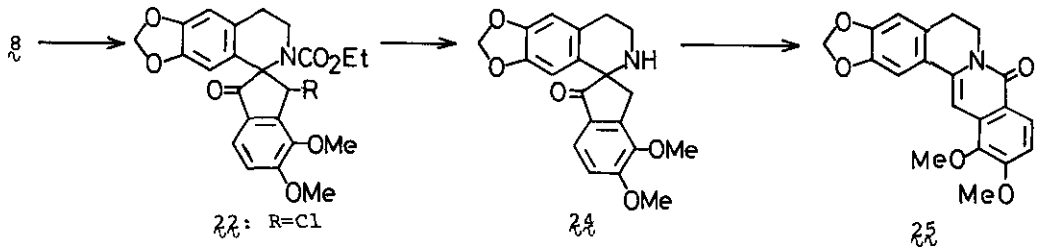


16 17 18

21 19 20

(1H, s), 4.03 (3H, s), 3.94 (3H, s)], which has exactly the same functionality with the key compound (A) 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.[11] Hydrogenolysis of the spirobenzylisoquinoline (22),[5] derived from 8, over 10% palladium-charcoal in ethanol afforded the dehalogenated ketone (23) [88%, *m/e* 425 (M^+), ν 1717, 1680, δ 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^+), ν 1700, δ 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^+), ν 1640, 1615, δ 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_9-H at very low field in its PMR spectrum.[12]



22: R=Cl

23: R=H

24

25

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.

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REFERENCES AND FOOTNOTES

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10. The yield (65%) reported earlier[5] has been improved.
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12. The PMR spectrum of the corresponding 9,10-oxygenated protoberberine, oxyberberine revealed the signals due to C_{11}-H and C_{12}-H at 7.30 and 7.27 ppm.

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