Communications to the Editor

Chem. Pharm. Bull. 30(9)3446—3449(1982)

TRANSFORMATION OF PROTOBERBERINES INTO SPIROBENZYLISOQUINOLINES. STEREOSELECTIVE CONVERSION OF COPTISINE INTO (±)-OCHROBIRINE

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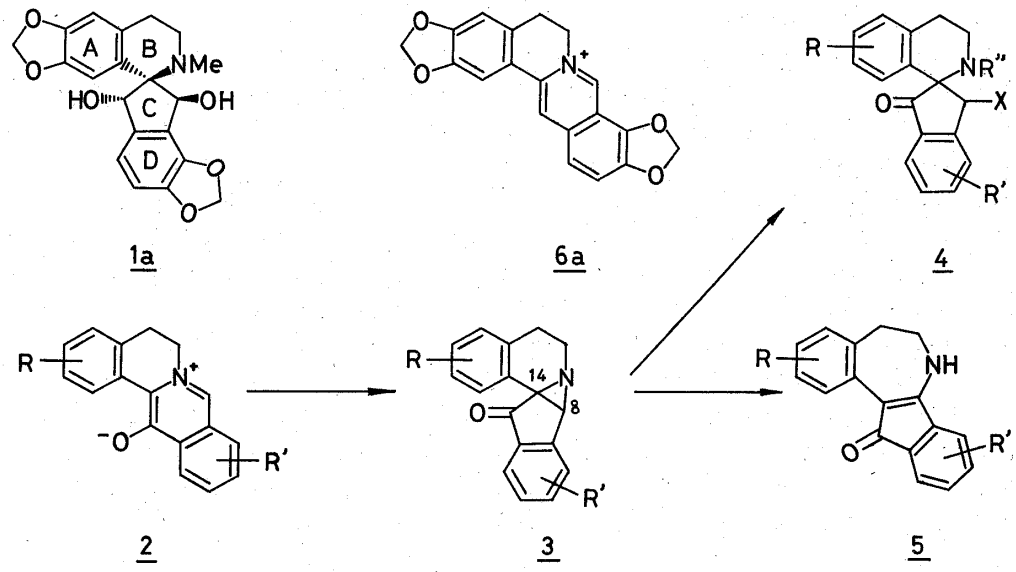
Reduction of the 8,14-cycloberbin-13-one (7a), derived from coptisine (6a), with $LiAlH(OBu^t)_3$ gave stereoselectively the alcohol (8a) which was subsequently treated with ethyl chloroformate to afford the oxazolidinone (10a). Hydrolysis of 10a followed by methylation with methyl iodide provided (±)-ochrobirine (1a).

KEYWORDS—— ochrobirine; spirobenzylisoquinoline alkaloid; coptisine; berberine; protoberberine alkaloid; stereoselective reduction; ethyl chloroformate; regioselective C_8-N bond cleavage; stereoselective transformation

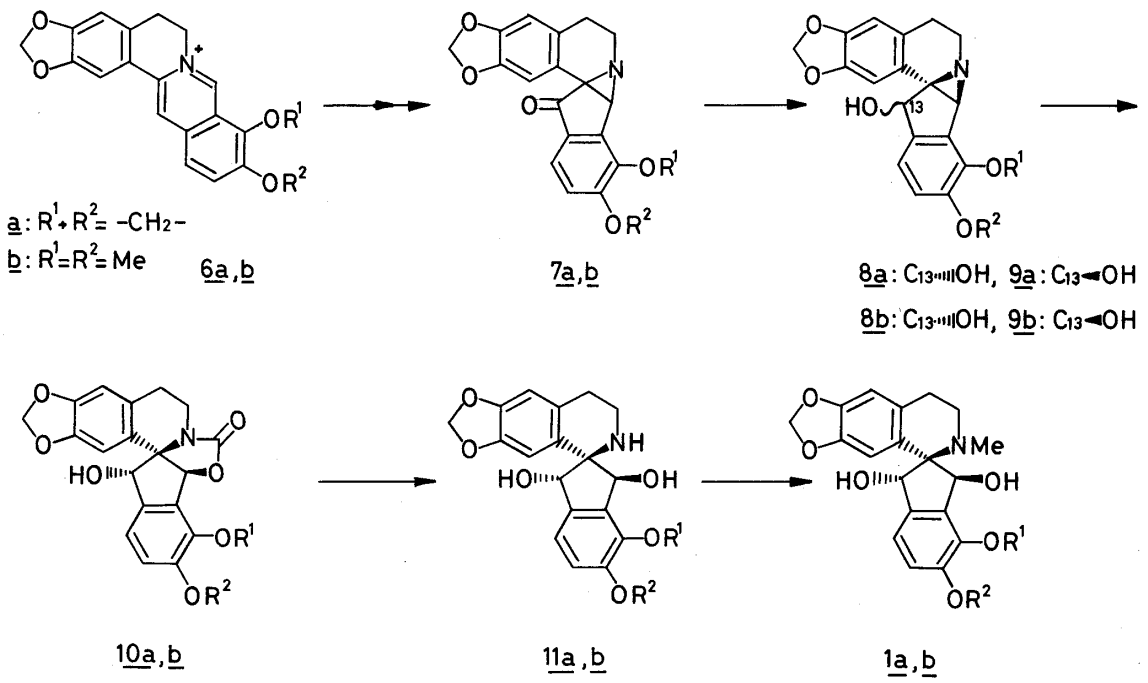
While ochrobirine (1a),[1] a representative spirobenzylisoquinoline alkaloid possessing two hydroxy groups on the five-membered C ring, has been synthesized by four groups,[2-6] no report has so far been made on the synthesis of 1a from its biogenetic precursor,[7] a protoberberine alkaloid.

Recently, we have demonstrated the potential conversion of the intermediate 8,14-cycloberbine (3),[8] derived from the corresponding berberinephenolbetaine (2)



by photo-induced valence tautomerization, into the spirobenzylisoquinoline (4)[8,9] and a rhoeadine alkaloid *via* the benzindenoazepine (5)[10,11] through regioselective C_8-N and C_{14}-N bond fission, respectively. This communication describes the first biomimetic and stereoselective conversion of coptisine (6a) into ochrobirine (1a) by stereoselective reduction of 8,14-cycloberbine as a crucial step.

As a preliminary study, we first investigated a conversion of easily available berberine (6b) into the ochrobirine analogue 1b. Reduction of 7b,[8] obtained from 6b, with $LiAlH(OBu^t)_3$ in dry THF/benzene (1/10) under reflux afforded stereoselectively the alcohol (8b) [67%; mp 198-200°C; ν 3250; δ 7.41, 6.64 (1H x 2, s), 7.10, 6.81 (2H, AB-q, *J*=8.5), 5.90 (2H, s), 4.84 (1H, s), 3.92, 3.84 (3H x 2, s), 3.37 (1H, s); *m/e* 353 (M^+)] along with the diastereoisomeric alcohol (9b)[12,13] [14%; δ 5.63 (1H)], the stereochemistry of which has already been established.[9,12] Upon treatment with refluxing ethyl chloroformate, the alcohol (8b) underwent regioselective C_8-N bond cleavage and simultaneous oxy-functionalization at C_8 with correct stereochemistry to produce the oxazolidinone (10b) [75%; mp 273-274°C; ν 3400, 1720; δ 7.18, 7.15 (2H, AB-q, *J*=9), 6.72 (2H, s), 5.95 (2H, s), 5.92 (1H, s), 5.48 (1H, d, *J*=7), 4.99 (1H, d, *J*=7), 3.83 (6H, s); *m/e* 397 (M^+)] as a sole product. Basic hydrolysis of 10b with 30% aqueous potassium hydroxide solution in ethanol gave the amino-diol (11b) [73%; mp 196-197°C; ν 3500, 3350; δ 7.08, 6.98 (2H, AB-q, *J*=8), 6.61, 6.02 (1H x 2, s), 5.83 (2H, s), 5.03 (2H, s), 3.99, 3.90 (3H x 2, s); *m/e* 371 (M^+)]. The amine (11b) was subsequently methylated with methyl iodide in THF at room temperature to afford the *N*-methyl derivative (1b) [93%; mp 202-203°C; ν 3500; δ 7.07, 6.97 (2H, AB-q, *J*=8.5), 6.62, 5.94 (1H x 2, s), 5.81 (2H, s), 5.49, 5.00 (1H x 2, s), 3.97, 3.89 (3H x 2, s), 2.66 (3H, s); *m/e* 386 (M^++1)[14]] possessing the same stereochemistry as that of ochrobirine (1a).



A similar procedure was applied to the stereoselective transformation of coptisine (6a)[15] into ochrobirine (1a). The 8,14-cycloberbine (7a)[16] derived from coptisine (6a) was reduced with $LiAlH(OBu^t)_3$ under the same condition as described for the preparation of 8b to give two diastereomeric alcohols, 8a [64%; mp 194-195°C; ν 3550; δ 7.37, 6.64 (1H x 2, s), 6.92, 6.74 (2H, AB-q, *J*=8), 5.97, 5.92 (2H x 2, s), 4.84 (1H, s), 3.24 (1H, s); *m/e* 337 (M^+)] and 9a [20%; mp 198-199°C; ν 3550; δ 7.13, 6.63 (1H x 2, s), 6.91, 6.75 (2H, AB-q, *J*=8), 5.97, 5.95 (1H x 2, br-s), 5.94 (2H, s), 5.61 (1H, s), 3.61 (1H, s); *m/e* 337 (M^+)]. The stereochemical assignment of 8a and 9a was based on ^{1}H-NMR spectral considerations. The C_{13}-H signal of 9a appeared at a 0.77 ppm lower field than that of 8a.[18] This down field shift of the former could be attributed to the deshielding effect of the benzene ring (ring A), because examination of the molecular model indicates that the C_{13}-H of 9a (stereochemical relationship between the ring A and H-13 is *cis*) lies on nearly the same plane with the ring A. Being refluxed in ethyl chloroformate for 1 h, 8a was converted into the oxazolidinone (10a) [67%; mp >300°C; ν 3350, 1720; δ 7.05, 6.96 (2H, AB-q, *J*=8), 6.79 (1H, s), 6.73 (1H, s), 6.16, 6.10 (1H x 2, br-s), 5.97 (3H, s), 5.54 (1H, d, *J*=7), 4.99 (1H, d, *J*=7); *m/e* 381 (M^+)]. Alkaline hydrolysis of 10a was accomplished with refluxing with 30% aqueous potassium hydroxide solution in dioxane for 48 h to afford the amino-diol (11a) [74%; mp 234-235°C; ν 3400, 3250; δ 6.87 (2H, s), 6.62, 6.28 (1H x 2, s), 6.04, 5.86 (2H x 2, s), 5.03, 4.96 (1H x 2, s); *m/e* 356 (M^++1)[14]]. Treatment of 11a with methyl iodide in THF at room temperature gave the final product (±)-ochrobirine (1a)[19] [73%; mp 233-235°C; ν 3550; δ 6.86 (2H, s), 6.63, 6.06 (1H x 2, s), 6.02, 5.83 (2H x 2, s), 5.44, 4.87 (1H x 2, s), 2.66 (3H, s); *m/e* 369 (M^+)] which was proved to be identical with the natural product[1] by spectral comparison and thin-layer chromatographic behavior.

This simple and stereoselective transformation reaction provides a novel and general method for the preparation of spirobenzylisoquinoline alkaloids having two oxygenated substituents on the five-membered ring.

ACKNOWLEDGEMENT we wish to thank Prof. D.B. MacLean, McMaster University, Canada, for a generous supply of natural ochrobirine and its ^{1}H-NMR and mass spectra.

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13) As reported previously,[9,12] reduction of 7b with $NaBH_4$ in methanol afforded exclusively the alcohol (9b). A similar result was obtained on treatment of 7b with $LiAlH_4$ (THF), L-Selectride (THF), or DIBAL (toluene) as a reducing agent.

14) Measured by Chemical Ionization Method.

15) Coptisine (6a) was obtained from berberine (6b) by the following reaction sequence; i) $NaBH_4$, ii) BBr_3, iii) CH_2Cl_2, NaOH, iv) I_2. The results will be described in a separate paper.

16) Compound 7a was prepared from coptisinephenolbetaine[17] by irradiation[8] with a high-pressure mercury lamp in 63% yield [mp 166-168°C; ν 1710; δ 7.29, 6.71 (2H, AB-q, *J*=8), 7.16, 6.53 (1H x 2, s), 5.99, 5.84 (2H x 2, s), 3.83 (1H, s); *m/e* 335 (M^+)].

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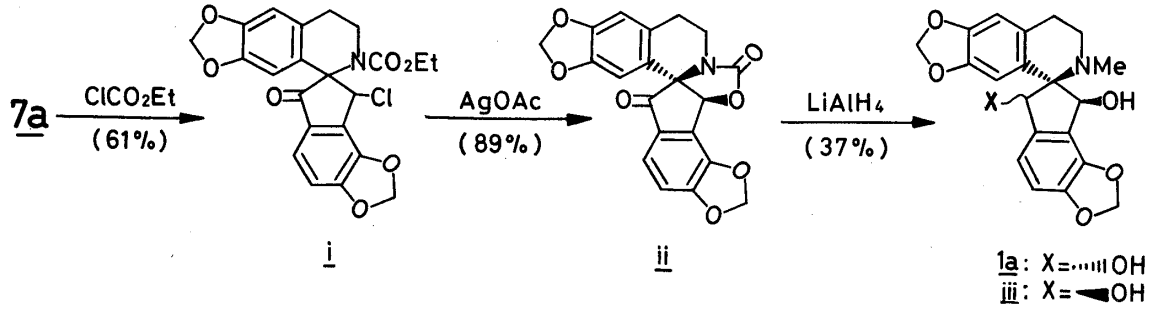
18) This observation is in good agreement with that obtained in the berberine series where the C_{13}-H signal of 9b appeared at 0.79 ppm lower field than that of 8b

19) (±)-Ochrobirine was also synthesized from the 8,14-cycloberbine (7a) *via* a different route, but the last step was found to be non-stereoselective (1a:iii = 2:3).



(Received July 28, 1982)