Journal of

The Chemical Society,

Chemical Communications

NUMBER 22/1981

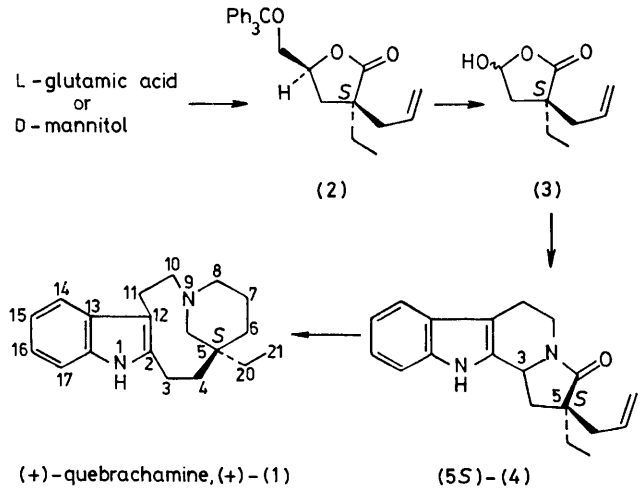
Enantioselective Route to Both (+)- and (−)-Enantiomers of Quebrachamine using a Single Chiral Synthon

By Seiichi Takano,* Masahiro Yonaga, and Kunio Ogasawara

(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai* 980, *Japan*)

Summary An enantioselective route to both the (+)- and (−)-enantiomers of the Aspidosperma-type indole alkaloid, quebrachamine, has been established using a single chiral lactone obtained from L-glutamic acid or D-mannitol.

Recently we reported an efficient enantioselective synthesis of (+)-quebrachamine, (+)-(**1**), using a chiral synthon[1] (**2**) obtained from L-glutamic acid[2] or D-mannitol,[3] Scheme 1.

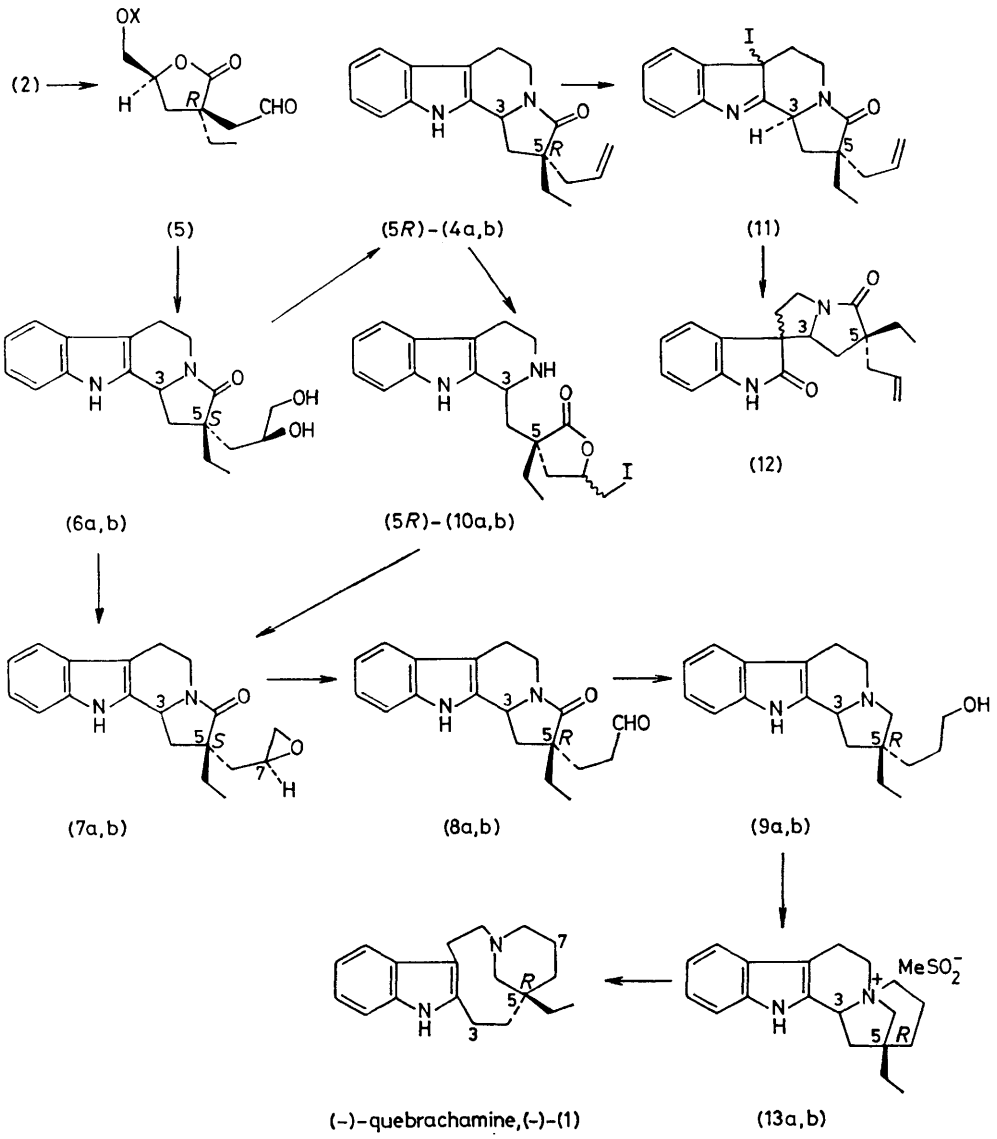


Scheme 1

We have now developed a method for the conversion of the same chiral synthon (**2**) into (−)-quebrachamine, (−)-(**1**) which is here described along with an alternative synthesis of (+)-(**1**). Since the occurrence of both enantiomers is known for various indole alkaloids,[4] the present method provides a promising prospect for the stereospecific synthesis of Aspidosperma and the Vincamine–Eburnamine indole alkaloids.

Detritylation of the chiral lactone[1] (**2**) with methanol containing a trace of hydrochloric acid, followed by ozonolysis in the presence of triethylamine,[5] gave the aldehyde (**5**; X = H) which, without purification, was refluxed with tryptamine in 70% acetic acid to give two diastereomeric lactams, (**6a**),† amorphous, $[\alpha]_D$ − 158·0° (*c* 0·514, MeOH), and (**6b**),† m.p. 219—223 °C, $[\alpha]_D$ + 155·7° (*c* 1·031, MeOH), as a chromatographically separable mixture (1 : 1) in 47% overall yield from (**2**), Scheme 2. Upon treatment with diethyl azodicarboxylate and triphenylphosphine in refluxing benzene,[6,7] the former (**6a**) gave the amorphous epoxide† (**7a**) and the latter (**6b**) gave the crystalline epoxide† (**7b**), m.p. 180—181 °C, $[\alpha]_D$ + 165·0° (*c* 0·794, $CHCl_3$). Treatment of both epoxides [(**7a**) and (**7b**)] with a mixture (10 : 1) of ground molecular sieves (5A) and silica-gel in refluxing benzene[8] induced rearrangements to yield the corresponding aldehydes, (**8a**)† and (**8b**)†, both as amorphous forms. Upon reduction using lithium aluminium hydride in refluxing tetrahydrofuran, the former (**8a**) afforded the amino-alcohol† (**9a**), m.p. 191—193 °C, $[\alpha]_D$ − 68·0° (*c* 1·414, MeOH), in 11% overall yield from (**6a**), and the latter (**8b**) afforded the isomeric amino-alcohol† (**9b**),

† Satisfactory spectral (i.r., ^{1}H-n.m.r., m.s.) and analytical (combustion and/or high resolution m.s.) data were obtained for this compound.



SCHEME 2. **a**; 3-α-H
b; 3-β-H

m.p. 160—161 °C, $[\alpha]_D$ + 78·5° (*c* 0·762, MeOH), in 30% overall yield from (**6b**).

The same amino-alcohols could be obtained from the same precursors, (**6a**) and (**6b**), through a different route. Thus, treatment of each precursor with dimethylformamide dimethylacetal, followed by acetic anhydride,[9] gave the corresponding vinyl lactams, (5*R*)-(**4a**),† m.p. 182—184 °C, $[\alpha]_D$ −161·7° (*c* 1·066, $CHCl_3$), and (5*R*)-(**4b**),† m.p. 113—116 °C, $[\alpha]_D$ +126·6° (*c* 1·160, $CHCl_3$), respectively, in yields of 56 and 70%. On exposure to iodine in aqueous tetrahydrofuran, followed by alkaline work-up[10] (KOH, aq. MeOH), the former gave the epoxide (**7a**)‡ and the oxindole (**12**)†§, m.p. 177—179 °C, $[\alpha]_D$ −20·14° (*c* 0·576, $CHCl_3$), in yields of 34 and 41%, while the latter furnished only the epoxide (**7a**)‡ exclusively in 86·5% yield. Apparently, both epoxides were formed *via* the corresponding iodo-lactone intermediates (**10a** and **b**). The concomitant formation of the undesired by-product (**12**) from the former may be due either to the 1,3-interaction between the C-3 proton¶ and the allylic group which prevents the conformation (quasi-axial allyl) required for iodo-lactonization, or to competitive electrophilic attack of iodine at the β-position of the indole ring from the less hindered side to give (**12**) *via* the intermediate (**11**). Both epoxides, upon the same sequential rearrangements [molecular sieves (5A)–SiO_2] and reduction ($LiAlH_4$) as above, furnished the corre-

‡ This compound was obtained as an epimeric (C-7) mixture.

§ This compound was obtained as one epimer but its stereochemistry could not be determined.

¶ The numbering described in this report is based on that of quebrachamine (**1**).

sponding amino-alcohols, (**9a**) and (**9b**), in comparable yields, *via* the corresponding aldehydes, (**8a**) and (**8b**).

Mesylation of the amino-alcohol (**9a**) with methanesulphonyl chloride in pyridine gave the enantiomerically pure pentacyclic salt (**13a**), amorphous, $[\alpha]_D$ −103·47° (*c* 2·13, MeOH), formed by spontaneous quaternization. The isomer (**9b**), on the same treatment, gave a mixture of the quaternary salts, (**13a**) and (**13b**), with concurrent partial epimerization at the C-3 centre.[1] Dissolving metal reduction (Na, in liq. NH_3 and EtOH) of both (**13a**) and a mixture of (**13a**) and (**13b**) furnished (−)-quebrachamine, m.p. 147—148 °C (lit.[11] 147 °C), $[\alpha]_D$ −110·0° (*c* 0·496, acetone) [from (**13a**)]; $[\alpha]_D$ −116·0° (*c* 1·1, acetone) [from the mixture of (**13a**) and (**13b**)] [lit.[11] $[\alpha]_D$ −109·5° (*c* 10, acetone)], in yields of 85% from (**9a**) and 89% from (**9b**).

Application of the newly developed iodo-lactone method to the known lactam[1] (5*S*)-(**4**), obtained from the same chiral lactone (**2**) *via* (**3**) [i, conc. HCl (cat.)–MeOH; ii, aq. NaOH, then aq. $NaIO_4$; iii, tryptamine, 70% AcOH, reflux], gave the enantiomeric amines, (5*S*)-(**9a**), m.p. 190—191 °C (lit.[1] m.p. 193—194 °C), $[\alpha]_D$ +70·56° (*c* 0·53, MeOH) {lit.[1] $[\alpha]_D$ +61·14° (*c* 0·965, MeOH)}, and (5*S*)-(**9b**), m.p. 157—158 °C (lit.[1] m.p. 165—166 °C), $[\alpha]_D$ −62·37° (*c* 0·404, MeOH) {lit.[1] $[\alpha]_D$ −56·86° (*c* 1·996, MeOH)}, which were similarly converted into (+)-quebrachamine, m.p. 147—149 °C (lit.[12] m.p. 147—149 °C), $[\alpha]_D$ +103·5° (*c* 0·398, $CHCl_3$) {lit.[12] $[\alpha]_D$ +111° ($CHCl_3$)}.

(*Received*, 28*th July* 1981; *Com.* 919.)

[1] S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1980, 616.
[2] M. Taniguchi, K. Koga, and S. Yamada, *Tetrahedron*, 1974, **30**, 3547.
[3] S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Heterocycles*, 1981, **16**, 381, 951.
[4] *Cf.* M. Hesse, 'Indolalkaloide in Tabellen,' Springer Verlag, Berlin, 1964 and 1968.
[5] H. Iio, M. Isobe, T. Kawai, and T. Goto, *Tetrahedron*, 1979, **35**, 941.
[6] J. T. Carlock and M. P. Mack, *Tetrahedron Lett.*, 1978, 5153.
[7] O. Mitsunobu, T. Kudo, M. Nishida, and N. Tsuda, *Chem. Lett.*, 1980, 1613.
[8] T. Kutsuma, I. Nagayama, T. Okazaki, K. Matsuoka, S. Takano, and K. Ogasawara, unpublished data.
[9] F. W. Eastwood, L. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, 1970, 5223.
[10] S. Takano, M. Hirama, and K. Ogasawara, *J. Org. Chem.*, 1980, **45**, 3729.
[11] E. Field, *J. Chem. Soc.*, 1924, 1444.
[12] F. Walls, O. Collera, and A. Sandval, *Tetrahedron*, 1958, **2**, 173.