

Enantioselective Synthesis of (+)-Quebrachamine using L-Glutamic Acid as a Chiral Template

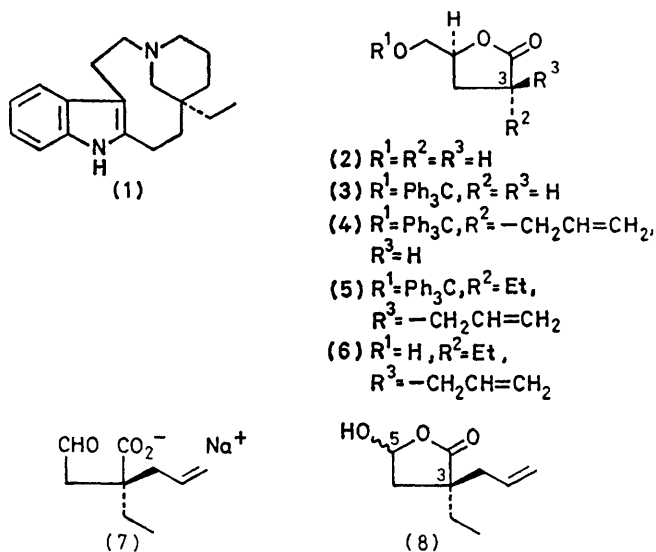
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Summary (+)-Quebrachamine (**1**) has been synthesised enantioselectively using L-glutamic acid as a chiral template

WE report here the first enantioselective synthesis of (+)-quebrachamine (**1**),¹ a parent base of the *Aspidosperma* alkaloids, using L-glutamic acid as a chiral template

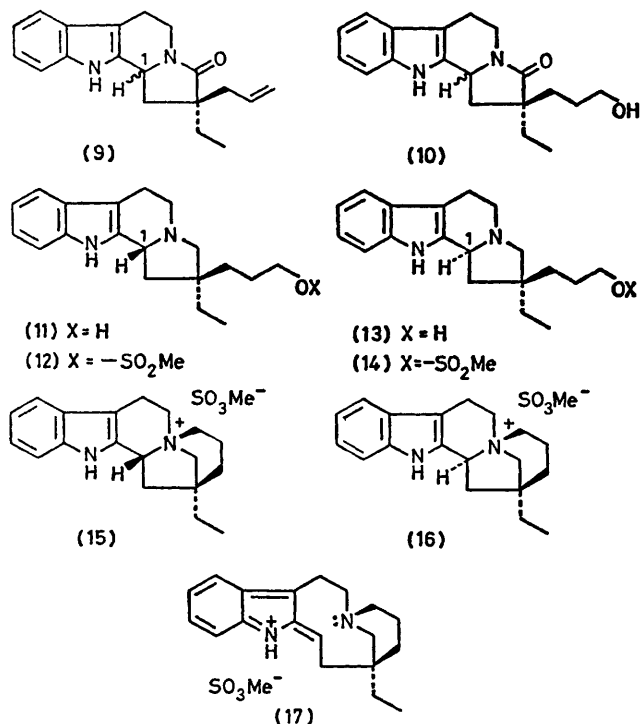
Tritylation of the lactone-alcohol (**2**), obtained from L-glutamic acid by the method of Yamada and co-workers,² with trityl chloride in pyridine (room temperature, 20 h) afforded the lactone-ether (**3**),[†] {m p 153—154 °C, $[\alpha]_D^{20} + 21.5^\circ$ (CH₂Cl₂)} in 64% yield. Treatment of (**3**) with allyl bromide in tetrahydrofuran (THF) in the presence of lithium di-isopropylamide (LDA) (−78 to −30 °C, 4 h) led

[†] All new compounds reported in this work gave satisfactory spectral and analytical data ($\pm 0.3\%$) or, except for (**8**), correct high-resolution mass spectral values



to a stereoselective alkylation to give the allyl lactone (4) (amorphous) in 96% yield. Further alkylation of (4) with ethyl bromide (in THF, LDA, -78 to 20 °C, 20 h) again allowed a stereoselective introduction of the ethyl group giving the lactone (5) with the 3*S* configuration, {m.p. 144 – 145 °C, $[\alpha]_D + 30.75$ (CH_2Cl_2)} in 92.5% yield as a single isomer. The observed stereoselectivity clearly reflected the stereochemistry at the C-5 centre which allowed preferential alkylation from the less hindered side of an enolate intermediate formed. Detritylation of (5) with conc. HCl–MeOH (1:4) (room temperature, 2 h) gave the alcohol (6) (oil) in 92.5% yield. Hydrolysis of (6) (NaOH–aq. MeOH, room temperature, 2 h), followed by oxidation with sodium metaperiodate (0 °C, 3 h), provided the hydroxy-lactone (8) (oil) in 65% overall yield, as a mixture of epimers differing in stereochemistry at the C-5 centre, presumably *via* the aldehyde (7). Condensation of (8) with tryptamine in boiling acetic acid (3 h) formed the lactam (9) (amorphous) in 74% yield as a mixture of epimers (1:1) differing in stereochemistry at C-1. Treatment of (9) with diborane–dimethyl sulphide complex in THF (room temperature, 5 h), followed by oxidation with alkaline hydrogen peroxide (3*N* NaOH–30% H_2O_2 , 0 °C, 3 h) gave the primary alcohol (10) (amorphous) which was reduced with lithium aluminium hydride in boiling THF (12 h) to furnish the β -1-H-amino-alcohol (11) {m.p. 193 – 194 °C [lit. (\pm) 169 – 170 °C³ and 169 – 171 °C⁴], $[\alpha]_D + 61.1^\circ$ (MeOH)} and the α -1-H-amino-alcohol (13) {m.p. 165 – 166 °C [lit. (\pm) 166 – 167 °C³ and 166 – 168 °C⁴], $[\alpha]_D - 56.9^\circ$ (MeOH)} in 23.6 and 22.2% overall yield, respectively, after preparative t.l.c. (silica gel) purification.

According to the established method,^{3,4} each isomer was converted into the corresponding pentacyclic quaternary salts, (15)⁵ and (16),⁵ respectively, *via* the corresponding mesylates, (12) and (14). Interestingly, the quaternary salt (16), which possessed the more unstable configuration,



was cleanly transformed into the more stable (15) upon reflux in chloroform (1 day) presumably through a *c/D* *seco* intermediate,⁶ such as (17). On dissolving-metal reduction (Na, liq. NH_3 –EtOH), both quaternary salts provided (+)-quebrachamine (1) {m.p. 147 – 149 °C [lit.⁷ 147 – 149 °C] $[\alpha]_D + 108.9^\circ$ (acetone) [lit.⁷ $[\alpha]_D + 111^\circ$ (acetone)] in yields of 51.2 [from (11)] and 65.0% [from (13)] after recrystallization from methanol.

The present synthesis may provide a pathway for the formal chiral synthesis of other *Aspidosperma*³ and medicinally important *Vincamine* alkaloids,⁸ since the quaternary salts, (15) and (16), in their (\pm)-forms, have been used as key intermediates in syntheses of these alkaloids.

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¹ Cf. M. Hesse, 'Indolalkaloide in Tabellen,' Springer Verlag, Berlin, 1964 and 1968.

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⁴ S. Takano, M. Hirama, T. Araki, and K. Ogasawara, *J. Am. Chem. Soc.*, 1976, **98**, 7084.

⁵ S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Am. Chem. Soc.*, 1976, **98**, 3022; 1979, **101**, 6414.

⁶ Cf. S. Takano, M. Sato, S. Hatakeyama, M. Hirama, and K. Ogasawara, *Heterocycles*, 1976, **5**, 221.

⁷ F. Walls, O. Collera, and A. Sandval, *Tetrahedron*, 1958, **2**, 173.

⁸ G. Hugel, J. Lévy, and J. LeMen, *C.R. Hebd. Seances Acad. Sci., Ser. C*, 1972, **274**, 1350.