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

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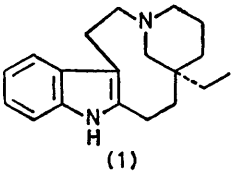
Summary (+)-Quebrachamine (**1**) has been synthesised enantioselectively using L-glutamic acid as a chiral template

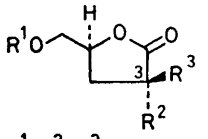
WE report here the first enantioselective synthesis of (+)-quebrachamine (**1**),[1] a parent base of the *Aspidosperma* alkaloids, using L-glutamic acid as a chiral template

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, $[\alpha]_D$ + 21·5° (CH_2Cl_2)} 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

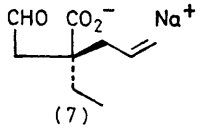
† All new compounds reported in this work gave satisfactory spectral and analytical data (±0·3%) or, except for (**8**), correct high-resolution mass spectral values



(1)



(2) $R^1 = R^2 = R^3 = H$
(3) $R^1 = Ph_3C, R^2 = R^3 = H$
(4) $R^1 = Ph_3C, R^2 = -CH_2CH=CH_2, R^3 = H$
(5) $R^1 = Ph_3C, R^2 = Et, R^3 = -CH_2CH=CH_2$
(6) $R^1 = H, R^2 = Et, R^3 = -CH_2CH=CH_2$



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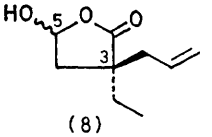
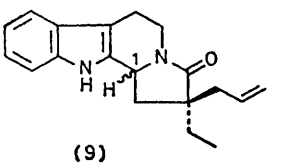


(8)

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 (3N 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. (±) 169—170 °C[3] and 169—171 °C[4]], $[\alpha]_D$ + 61·1° (MeOH)} and the α-1-H-amino-alcohol (**13**) {m.p. 165—166 °C [lit. (±) 166—167 °C[3] and 166—168 °C,[4] $[\alpha]_D$ −56·9° (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,



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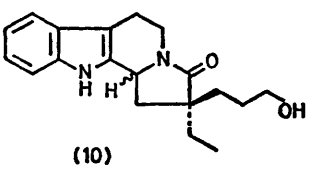

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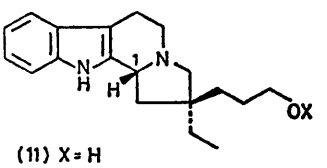
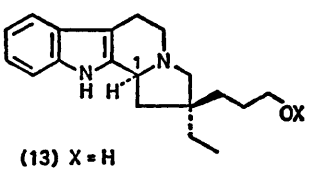
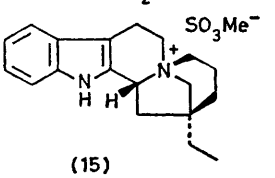


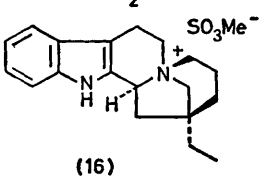
(11) X = H
(12) X = $-SO_2Me$



(13) X = H
(14) X = $-SO_2Me$



(15)



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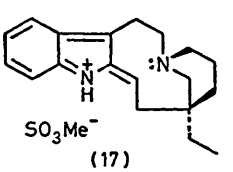

(17)

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° (acetone) [lit.[7] $[\alpha]_D$ + 111° (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 (±)-forms, have been used as key intermediates in syntheses of these alkaloids.

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