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A FACILE ROUTE TO (±)-QUEBRACHAMINE

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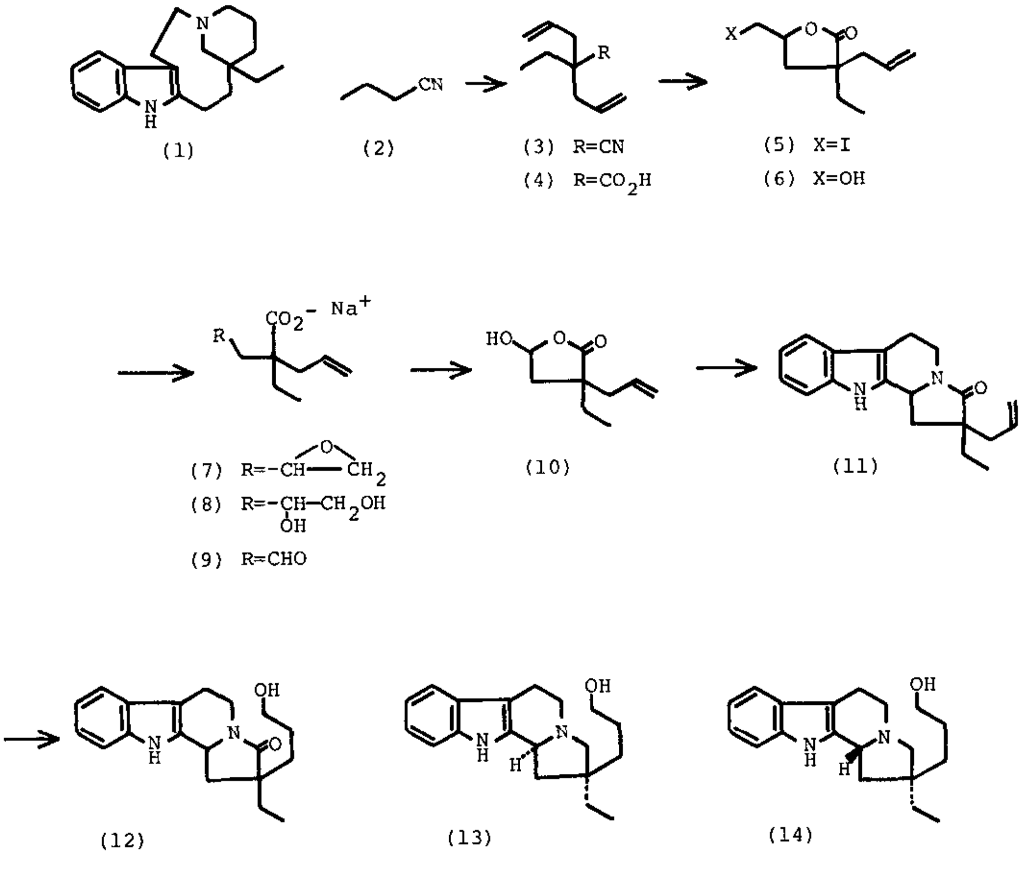
Abstract-----A facile route to (±)-quebrachamine(1), the parent base of the aspidosperma indole alkaloids, has been developed through halolactonization reaction.

As quebrachamine[1](1) is considered to be the parent base of a large group of the aspidosperma type indole alkaloids, there have been developed several synthetic approaches so far.[2] We report here a facile and efficient route to (±)-quebrachamine(1) by employing halolactonization reaction as a key step.

Alkylation of n-butyronitrile(2) with allyl bromide(3 mol equiv) in the presence of lithium diisopropylamide in THF(-78 C°) gave 2,2-diallylbutyronitrile[3](3), bp 100 C°(14 mmHg)(Kugel rohr), in 81 % yield, which gave 2,2-diallylbutylic acid(4), bp 100 °C(0.5 mmHg)(Kugel rohr), in 74 % yield on hydrolysis with 40 % aqueous potassium hydroxide in boiling diethylene glycol(4:3). With iodine and potassium iodide in aqueous sodium bicarbonate solution[4],(4) yielded the iodo-lactone(5), amorphous, quantitatively, as an inseparable mixture of epimers. Treatment of (5) with aqueous potassium hydroxide at room temperature and following acid work-up afforded the primary alcohol(6), oil, in 94 % yield as an inseparable mixture of epimers presumably through the epoxide(7). Hydrolysis of (6) with potassium hydroxide in aqueous methanol, followed by oxidation of the resulting glycol(8) with sodium metaperiodate in the same flask at pH 9[5] gave the hydroxy-lactone(10), oil, in 96 % yield via the aldehyde(9) after acid work-up. Condensation of (10) with tryptamine in boiling acetic acid gave the lactam(11), mp 122∿130 °C, in 74.3 % yield as an inseparable mixture of epimers. Treatment of (11) with diborane-dimethyl sulfide complex in *THF, followed by oxidation with alkaline hydrogen peroxide yielded the crude lactam-*alcohol(12), which on reduction with lithium aluminum hydride in THF at room temperature furnished 60.5 % overall yield of an epimeric mixture(3:1) of the amino alcohols, (13) and (14), which were separated by a silica gel column chromatography to give the 3Hα-amino-alcohol[6] (13), mp 168∿170 °C(lit. mp 166∿167 °C[3c,3d]; 166∿168 °C[3e]), and the 3Hβ-amino-alcohol[6] (14), mp 172∿173 °C(lit. mp 169∿170 °C[3b,3c]; 169∿171 °C[3e]). Since each amino-alcohol has been converted into (±)-quebrachamine(1) in a good yield,[3c,d,e] the present synthesis consists a simple and efficient total synthesis of (1) in formal sense.



References and Notes

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3. All new compounds reported in this work gave satisfactory spectral(IR, NMR, MS) and analytical data.
4. Cf. M.D. Dowle and D.I. Davies, Chem. Soc. Reviews, 8, 171 (1979).
5. pH was adjusted by bubbling CO_2 gas into the reaction mixture.
6. Identical in all respects(IR, NMR, MS, and mixed mp) with a an authentic material obtained by a different route.[3e] For preparative purpose separation of (13) and (14) is not neccessary.

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