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TOTAL SYNTHESIS OF A CYCLOPHANE ALKALOID, (±)-LYTHRANIDINE

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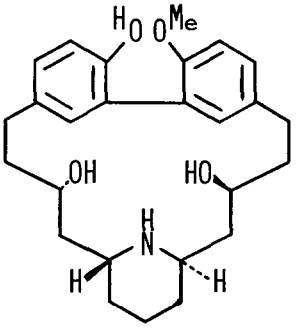
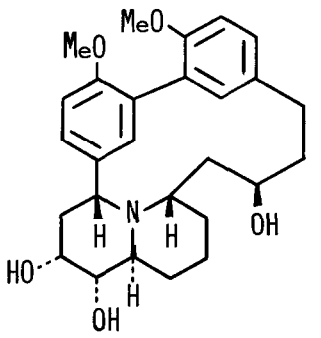
Over 40 alkaloids have been isolated from the Lythraceae family of plants.[1,2] They are classified to five structural types, i.e. type A-E,[3] which are shown in Chart I with representative alkaloids. Though several of the type C-E alkaloids have been synthesized,[4] the synthesis of the type A and B alkaloids has never been achieved.[5] We now wish to report the first total synthesis of the type A alkaloid, lythranidine (1).

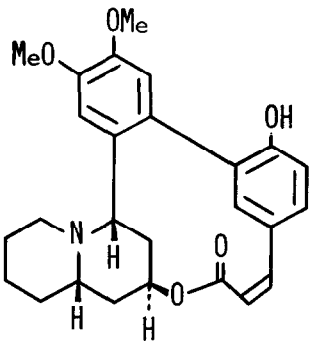
Chart I. Classification of Lythraceous Alkaloids.



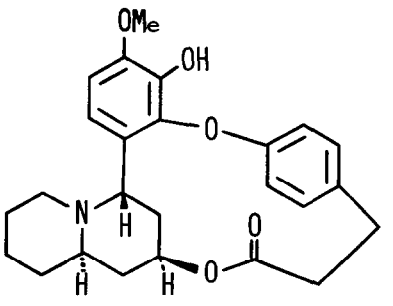
Type A: Lythranidine (1)



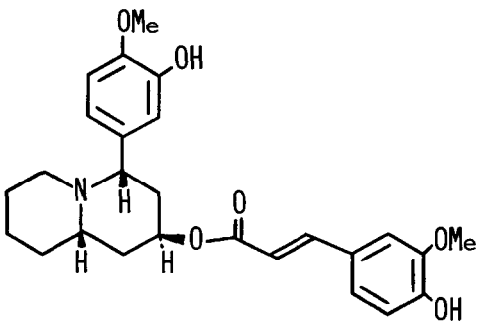
Type B: Lythrancine-I



Type C: Lythrine

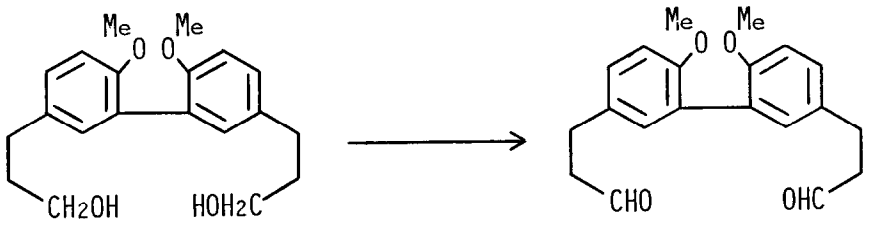


Type D: Lagerine



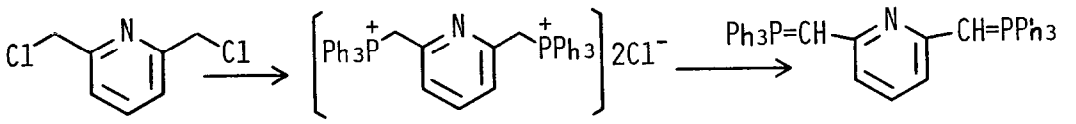
Type E: Abresoline

Oxidation of the diol 2[6] with CrO_3-pyridine afforded a 76% yield of the dialdehyde 3 isolated as a foam: ir ($CHCl_3$) 1724, 1605, 1504 cm^{-1}; nmr ($CDCl_3$) δ 2.84 (m,8H), 3.72 (s,6H), 6.83-7.23 (m,6H), 9.83 (t,2H,J=1.4Hz).



2 3

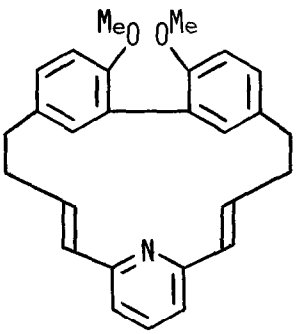
Reaction of 2,6-dichloromethylpyridine (4)[7] with 3 eq. of triphenylphosphine in refluxing DMF gave the diphosphonium salt 5 (mp 280-282 °C) in 88% yield. Compound 5 exhibited the following spectral data: ir ($CHCl_3$) 1589, 1488, 1439 cm^{-1}; nmr ($CDCl_3$) δ 5.45 (d,4H,J=15Hz), 7.29-8.00 (m,33H).



4 5 6

The Wittig reaction of the dialdehyde 3 with 6, generated from 5 with NaH, under the dilution conditions in dichloromethane under nitrogen afforded a 86% yield of 7 (mp 230-232 °C); ir ($CHCl_3$) 1650, 1614, 1561, 1499 cm^{-1}; nmr (CCl_4) δ 2.30-3.10 (m,8H), 3.71 (s,6H), 6.28 (d,2H,J=15Hz), 6.49-7.50 (m,11H). The cyclophane structure of 7 was unequivocally confirmed by the fact that 7 on hydrogenation over Pd-C gave 8 which was identical with the authentic specimen previously synthesized.[6]

Epoxidation of the compound 7 with m-chloroperbenzoic acid followed by hydrogenolysis over Pd-C and acetylation afforded 9 (70% yield from 7) which was hydrogenated over PtO_2-Raney Ni to give the 2,6-cis-substituted piperidine derivative 10 in 98% yield.[8]



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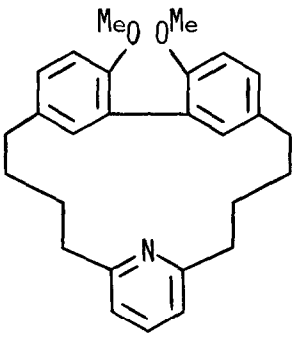

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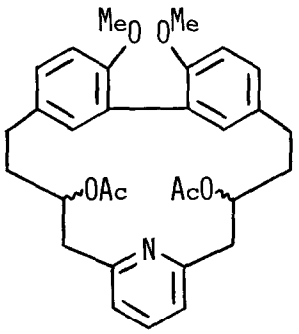
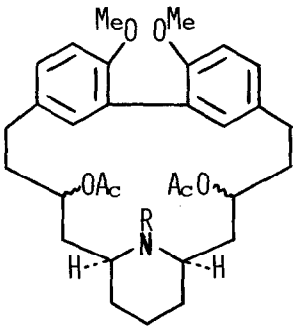
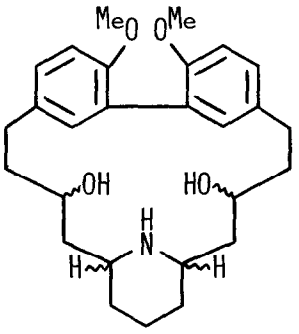


9

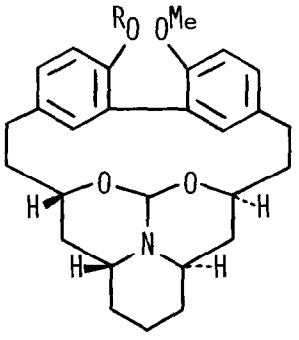


10, R=H

11, R=NO



12



13, R=Me

14, R=H

Equilibrium studies of N-nitroso 2,6-disubstituted piperidine derivatives by Fraser et al. demonstrated that the trans isomers are thermodynamically more stable than the corresponding cis isomers.[9] Thus, the N-nitroso derivative 11 derived from 10 with isoamyl nitrite was subjected to the equilibrium conditions (t-BuOK/DMSO, 90 °C, 60 h under nitrogen) to yield a cis/trans mixture which was denitrosated (Raney Ni/H_2) and hydrolyzed to afford a mixture 12. When refluxed in ethyl orthoformate with p-toluenesulfonic acid for 4 h, 12 gave 13, mp 240-241.5 °C (14% from 11). Amidoacetal 13 exhibited the following spectral data: ir ($CHCl_3$) 1610, 1580, 1500 cm^{-1}; nmr ($CDCl_3$) δ 3.79 (s,3H), 3.83 (s,3H), 4.02 (br,2H), 5.25 (s,1H), 6.70-7.95 (m,6H) which were identical with those of the amidoacetal[10] derived from natural lythranidine

Monodemethylation of 13 was achieved by a new method developed recently.[11] Thus, treatment of 13 with 6 eq. of $AlCl_3$ in EtSH-CH_2Cl_2 (1:5) at -10 °C for 10 min. led to smooth monodemethylation giving 14. The hydrolysis of 14 with 20% HCl afforded (±)-lythranidine 1 crystallized as an acetic acid salt, mp 136-137 °C (45% from 13) [ir ($CHCl_3$) 3350, 1586, 1505 cm^{-1}; nmr ($CDCl_3$) δ 1.41 (s,3H), 3.85 (s,3H), 4.09 (m,2H), 6.63-7.74 (m,6H)] which exhibited spectral and chromatographic properties identical with those of the salt of the natural lythranidine.[12]

References and Notes

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7. We express our gratitude to Dr. Ito, Toagosei Chemical Industry, for a generous gift of this material.
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