SYNTHESIS OF THE CHIRAL SYNTHON FOR THE ENANTIOSELECTIVE SYNTHESES OF THE EBURNAMINE TYPE ALKALOIDS

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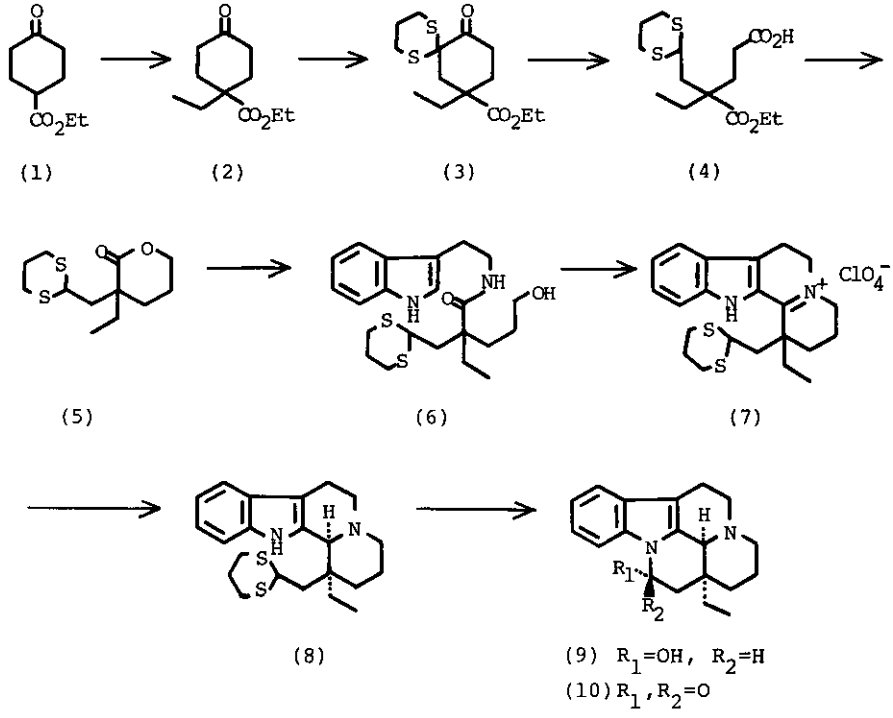
Abstract-----A chiral synthon(5) for the syntheses of the medicinally important indole alkaloid (-)-eburnamonine(10) and the related eburnamine type alkaloids has been prepared in a good yield from the known compound(12) originated from L-glutamic acid or D-mannitol.

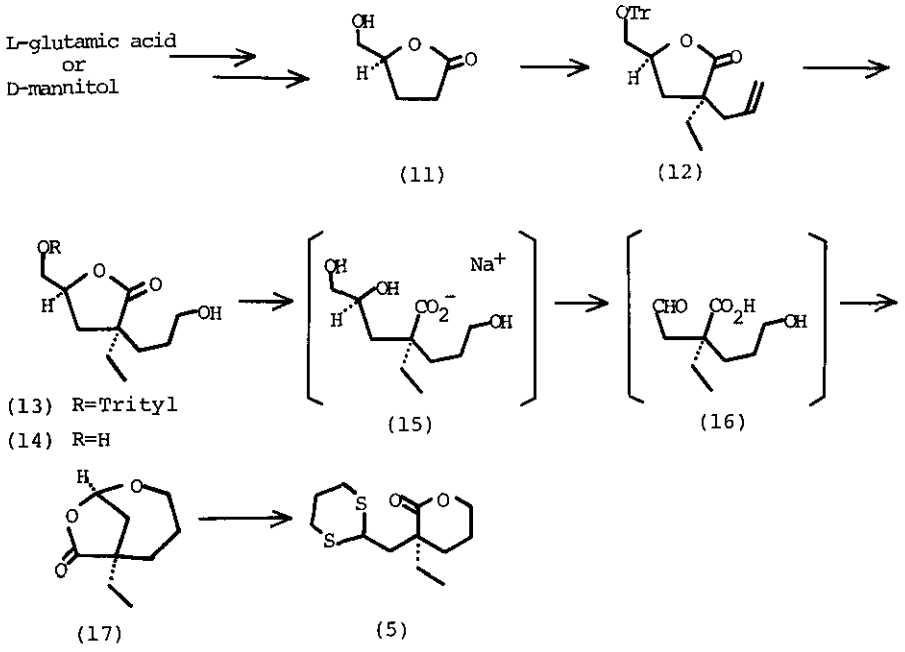
(-)-Eburnamonine(10), first isolated from Vinca minor,[1] has been used as a cerebral vasodilator.[2] Because of its medicinal importance considerable efforts have been devoted to the development of efficient syntheses of this alkaloid and the related eburnamine alkaloids.[3] Among these there were a number of



Scheme 1

highly efficient approaches, however none of the enantioselective methods have been reported so far. We report here a synthesis of the chiral intermediate(5) which may be useful for the enantioselective syntheses of (-)-eburnamonine(10) and the related alkaloids. As we have already developed a diastereoselective route to (±)-eburnamine(9),[3e] a synthetic progenitor of (±)-eburnamonine(10),[3a] from ethyl 4-cyclohexanone-carboxylate(1) via the intermediate(5), enantioselective preparation of the key compound(5) would promise the entree to (-)-eburnamonine(10).

The 2,2-dialkyllactone(12),[4] $[\alpha]_D$ +24.8°($CHCl_3$), prepared from the chiral lactone(11),[5] was treated with dicyclohexylborane,[6,7] prepared *in situ* from borane-dimethyl sulfide complex(1.5 mol equiv) and cyclohexene(3.0 mol equiv) in tetrahydrofuran, followed by alkaline oxidation(3N NaOH and 30% H_2O_2) to yield the primary alcohol(13) as an oil which on stirring with methanol in the presence of a catalytic amount of conc. hydrochloric acid(15:1) at room temperature for 4h induced smooth detritylation to yield the diol(14)[8] in 77.5% overall yield from (12) as colorless prisms, mp 36-38°C, $[\alpha]_D$ +26.8°(MeOH, c=1.195). Hydrolysis of the diol(14) with sodium hydroxide(3 mol equiv) in aqueous methanol(20%) at reflux temperature formed the carboxylate(15) which, after bubbling CO_2 gas into the reaction mixture to bring its pH about 9, on reaction with aqueous sodium periodate initiated spontaneous glycol cleavage and acetalization to give the bicyclic lactone(17) in 97.8% yield as colorless prisms, mp 82-85°C, $[\alpha]_D$ +6.7°(CH_2Cl_2, c=0.42). The bicyclic lactone(17) was then treated with propane-1,3-dithiol(3 mol equiv) in toluene at reflux temperature in the presence of a catalytic amount of p-toluenesulfonic acid to give the dithian(5) in 61.1% yield as



Scheme 2

colorless prisms, mp 32-33°C,[9] $[\alpha]_D$ +37.6°(CH_2Cl_2, c=1.528), whose spectra(IR, NMR, MS) and tlc behavior were completely in accord with those of the racemic material.

Conversion of the chiral lactone(5) into (-)-eburnamonine(10) and its congeners is now in progress.

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7. Use of diborane itself resulted in a concomitant reduction of the lactone carbonyl group.
8. Satisfactory spectral(IR, ^{1}H-NMR, MS) and analytical data(combustion) were obtained for new compounds: (14) ν_{max}(Nujol) 3350(br), 1740cm^{-1}; $CDCl_3$(δ) 0.98(t, 3H, J=7 Hz), 1.5-1.9(m, 6H), 2.0-2.3(m, 2H), 2.85(br.s, 2H, exchangeable), 3.5-4.0(m, 4H), 4.3-4.75(m, 1H) ppm; m/e 203(M^++1) 171, 156, 144, 99(100%). (17) ν_{max}(Nujol) 1750cm^{-1}; $CDCl_3$(δ) 0.93(t, 3H, J=7 Hz), 1.5-2.0(m, 6H), 2.2-2.5(m, 2H), 3.85-4.0(m, 2H), 5.80(dd, 1H, J=5 and 2 Hz) ppm; m/e 171(M^++1), 97(100%). (5) ν_{max}(Nujol) 1710cm^{-1}; $CDCl_3$(δ) 0.93(t, 3H, J=7 Hz), 1.5-3.05(m, 14H), 3.90(dd, 1H, J=7 and 6 Hz), 4.29(m, 2H) ppm; m/e 260(M^+), 133(100%), 128, 119, 113.
9. The racemic compound was obtained as a viscous oil: see Ref. 3e.

Received, 18th March, 1982