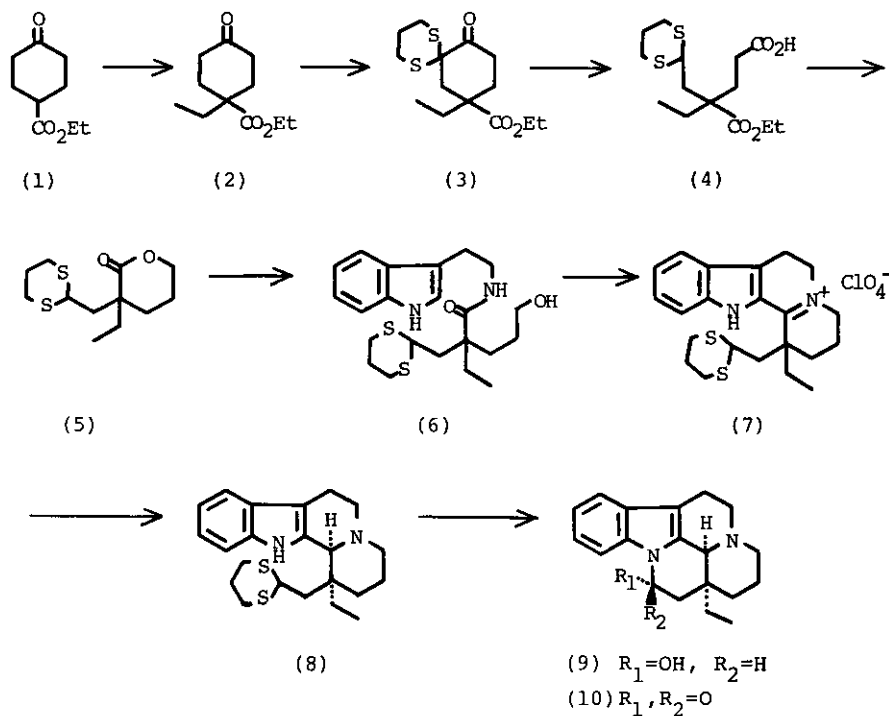


SYNTHESIS OF THE CHIRAL SYNTHON FOR THE ENANTIOSELECTIVE SYNTHESSES OF
THE EBURNAMINE TYPE ALKALOIDS

Seiichi Takano*, Masahiro Yonaga, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,
Japan

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.

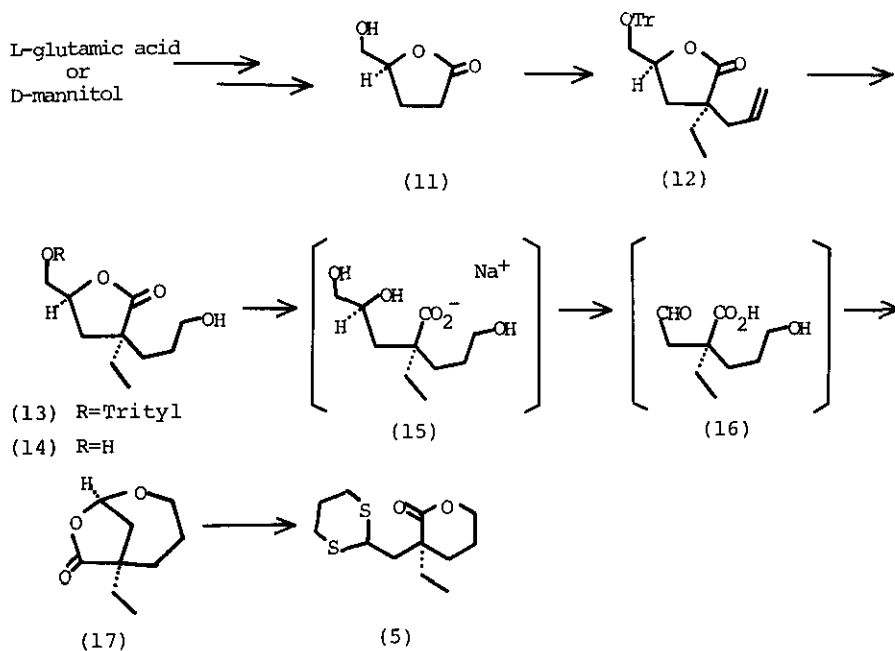
(-)-Eburnamonine(10), first isolated from *Vinca minor*,¹ has been used as a cerebral vasodilator.² Because of its medicinal importance considerable efforts have been devoted to the development of efficient syntheses of this alkaloid and the related eburnamine alkaloids.³ Among these there were a number 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-dialkyl lactone(12),⁴ $[\alpha]_D^{25} +24.8^\circ(\text{CHCl}_3)$, 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% H₂O₂) 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, $[\alpha]_D^{25} +26.8^\circ(\text{MeOH}, c=1.195)$. 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 CO₂ 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, $[\alpha]_D^{25} +6.7^\circ(\text{CH}_2\text{Cl}_2, c=0.42)$. 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, $[\alpha]_D^{20} +37.6^{\circ}(\text{CH}_2\text{Cl}_2, c=1.528)$, 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.

REFERENCES AND NOTES

1. W. Doepke and H. Meisel, *Pharmazie*, **21**, 444(1966).
2. E.A. Trutneva and V.V. Berezinskaya, *Farmakol. Toskikol.*, **29**, 171(1966).
3. (a) M.F. Bartlett and W.I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941(1960). (b) E. Wenkert and B. Wickberg, *ibid.*, **87**, 1580(1965). (c) D. Cartier, J. Levy, and J. LeMen, *Bull. Soc. Chim. Fr.*, 1961(1976). (d) J.L. Herrmann, G.R. Kieczkowski, S.E. Normandin, and R.H. Schlessinger, *Tetrahedron Lett.*, 801(1976). (e) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Comm.*, 68(1977); *idem.*, *J. Chem. Soc., Perkin Trans. I*, 457(1980). (f) G. Costerousse, J. Buendia, E. Toromanoff, and J. Martel, *Bull. Soc. Chim. Fr.*, II-355(1978). (g) J.L. Herrmann, R.J. Cregge, J.E. Richman, G.R. Kieczkowski, S.N. Normandin, M.L. Quesada, C.L. Semmelhack, A.J. Poss, and R.H. Schlessinger, *J. Am. Chem. Soc.*, **101**, 1540(1979). (h) E. Bolsing, F. Klatte, U. Rosentreter, and E. Winterfeldt, *Chem. Ber.*, **112**, 1902(1979). (i) K. Irie, M. Okita, T. Wakamatsu, and Y. Ban, *Nouv. J. Chem.*, **4**, 275(1980). (j) K. Irie and Y. Ban, *Heterocycles*, **15**, 201(1981). (k) C. Szantay, L. Szabo, G. Kalas, P. Gyory, J. Sapi, and K. Nogradi, "Organic Synthesis Today and Tomorrow", B.M. Trost and C.R. Hutchinson, Edn., Pergamon, Oxford, 1981, pp.285-298. (l) E. Wenkert, T.D.J. Halls, L.D. Kwart, G. Magnusson, and H.D.H. Showalter, *Tetrahedron*, **37**, 4017(1981).
4. S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Comm.*, 616(1980).
5. (a) M. Taniguchi, K. Koga, and S. Yamada, *Tetrahedron*, **30**, 3547(1974). (b) S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Heterocycles*, **16**, 951(1981).
6. H.C. Brown, "Organic Syntheses via Boranes", Wiley, New York, 1975, pp.28-29.
7. Use of diborane itself resulted in a concomitant reduction of the lactone carbonyl group.
8. Satisfactory spectral(IR, $^1\text{H-NMR}$, MS) and analytical data(combustion) were obtained for new compounds: (14) $\nu_{\text{max}}(\text{Nujol})$ 3350(br), 1740 cm^{-1} ; $\text{CDCl}_3(\delta)$ 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) $\nu_{\text{max}}(\text{Nujol})$ 1750 cm^{-1} ; $\text{CDCl}_3(\delta)$ 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) $\nu_{\text{max}}(\text{Nujol})$ 1710 cm^{-1} ; $\text{CDCl}_3(\delta)$ 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