Synthesis of a Potential Synthon for the Chiral Synthesis of the Corynanthe-type Indole Alkaloids: Enantioselective Total Synthesis of (–)-Antirhine

By SEIICHI TAKANO,* NOBUHIKO TAMURA, and KUNIO OGASAWARA

(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai* 980, *Japan*)

Summary The chiral formylmethyl(vinyl)tetrahydropyranone (**16**), a potential versatile synthon for the chiral synthesis of the Corynanthe-type indole alkaloids, has been synthesised and converted into (–)-antirhine, the major alkaloid of *Antirhea putaminosa* (F. Muell.) Bail.

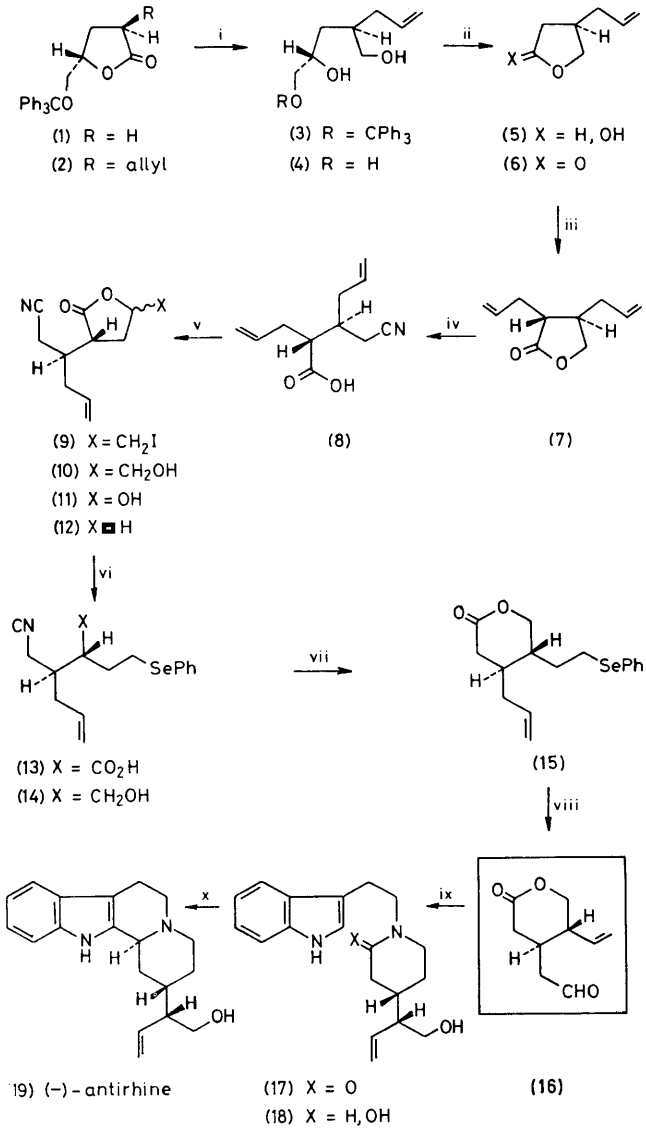
RECENTLY we established an efficient enantioselective route to the Aspidosperma-[1,2] and Iboga-type[3] indole alkaloids using a chiral lactone[4] (**1**) obtained from L-glutamic acid[5] or D-mannitol.[6] We report here the enantioselective synthesis of the formylmethyl(vinyl)tetrahydropyranone (**16**), a potential versatile synthon for the chiral synthesis of the Corynanthe-type indole alkaloids, starting from the same chiral lactone (**1**), along with the first enantioselective synthesis of an unique Corynanthe variant, (–)-antirhine[7,8] (**19**), using the synthon (**16**) thus obtained.

Cautious alkylation of (**1**)[4] with allyl bromide (1·2 mol. equiv.) in the presence of lithium di-isopropylamide (1·2 mol. equiv.) in tetrahydrofuran (THF) at –78 °C afforded the (2*S*)-lactone (**2**)†, m.p. 89—90 °C, $[\alpha]_D$ +24·8° (*c* 1·96, $CHCl_3$) in good yield. Reduction of (**2**) with $LiAlH_4$, followed by acid-catalysed detritylation in methanol gave the triol (**4**)†, b.p. 180—190 °C (0·35 Torr, Kugelrohr), $[\alpha]_D$ –2·5° (*c* 1·95, $CHCl_3$), *via* (**3**). Periodate cleavage of (**4**) yielded the epimeric lactol (**5**)‡ which on Jones' oxidation gave the lactone (**6**)†, b.p. 64—65 °C (0·5 Torr), $[\alpha]_D$ +15·0° (*c* 2·65, $CHCl_3$), in 50·5% overall yield from (**1**). Alkylation of (**6**) with allyl bromide occurred stereoselectively to give the *trans*-diallyl-lactone (**7**),† b.p. 72—73 °C (0·2 Torr), $[\alpha]_D$ +19·5° (*c* 3·00, $CHCl_3$), in 70% yield. Treatment of (**7**) with NaCN (1·3 mol. equiv.) in refluxing dimethylformamide (DMF)[9] furnished the cyano-acid (**8**)‡ in excellent yield and practically pure.

Exposure of (**8**) to iodine (2 mol. equiv.) and potassium iodide (6 mol. equiv.) in aqueous $NaHCO_3$ solution[10] allowed a selective lactonization at the γ-position to give the iodo-lactone (**9**)‡ nearly quantitatively. This was then

† Satisfactory analytical and spectral (i.r., ^{1}H-n.m.r., and m.s.) data were obtained for this compound.

‡ Satisfactory spectral (i.r., ^{1}H-n.m.r., and m.s.) data were obtained for this compound.



i, $LiAlH_4$, THF, reflux, then conc. HCl (cat.)–MeOH, room temp.; ii, $NaIO_4$, then Jones' reagent; iii, allyl bromide, lithium di-isopropylamide, THF, −78 °C; iv, NaCN, DMF, reflux; v, (a) I_2–KI, aq. $NaHCO_3$, room temp., (b) aq. KOH, then dil. HCl, (c) aq. KOH, then aq. $NaIO_4$, (d) $NaBH_4$, then acid work-up; vi, PhSeNa, THF, reflux, then $ClCO_2Et$, Et_3N, then $NaBH_4$; vii, KOH–EtOH, then acid work-up; viii, O_3, CH_2Cl_2, −78 °C to room temp.; ix, tryptamine, $NaBH_3CN$, aq. MeOH, pH 6, then $(Me_2CHCH_2)_2AlH$, THF, −78 °C; x, dil. HCl, room temp.

SCHEME

converted into the cyano-lactone (**12**)†, b.p. 145—150 °C (0·2 Torr, Kugelrohr), $[\alpha]_D$ +2·2° (*c* 2·95, $CHCl_3$), in 79% overall yield from (**7**) *via* (**9**),‡ (**10**),‡ and (**11**).‡ Reaction of (**12**) with sodium phenyl selenide,[11] prepared *in situ* from diphenyl diselenide and sodium metal, in refluxing THF yielded the acid (**13**)‡ whose carboxy-group was selectively reduced *via* the mixed anhydride method[12] to give the primary alcohol (**14**)‡. This could be used without further purification and was hydrolysed and worked up with acid to give the δ-lactone (**15**), b.p. 195—200 °C (0·2 Torr, Kugelrohr), $[\alpha]_D$ −19·5° (*c* 3·65, $CHCl_3$), in 79% overall yield from (**12**). Ozonolysis of (**15**) in methylene chloride (−78 °C), followed by treatment of the reaction mixture with Et_3N[13] (−78 °C to room temperature), furnished the formylmethyl derivative (**16**), $[\alpha]_D$ +1·1° (*c* 1·68, $CHCl_3$) in 61·5% yield by simultaneous double bond fission and double bond formation. The overall yield of (**16**) from the chiral lactone (**1**) was 14%.

The potential of (**16**) as a synthon for the chiral synthesis of the Corynanthe-type indole alkaloids was demonstrated by its conversion into an unique Corynanthe variant, (−)-antirhine (**1**), previously isolated from *Antirhea putaminosa* (F. Muell) Bail. by Johns *et al.*[7] Reductive condensation of (**16**) with tryptamine using sodium cyanoborohydride at pH 6 in aqueous methanol yielded the lactam (**17**)‡ *via* spontaneous cyclization. Partial reduction of (**17**) with di-isobutylaluminium hydride at −78 °C gave the hemiacetal (**18**)‡ which, without purification, was treated with dil. HCl at room temperature overnight to furnish (−)-antirhine§ (**19**), (c.d. $\Delta\epsilon_{256}$ +0·77, $\Delta\epsilon_{293}$ +0·36, $CHCl_3$; natural antirhine, $\Delta\epsilon_{265}$ +1·44, $\Delta\epsilon_{293}$ +0·96, $CHCl_3$).

Although the present report is limited to the synthesis of (−)-antirhine, the formylmethyl(vinyl)tetrahydropyranone (**16**) will undoubtedly serve as the chiral synthon for a large number of Corynanthe-type indole alkaloids.

(*Received, 7th August* 1981; *Com.* 960.)

§ The synthetic material had R_f values and i.r., ^{1}H-n.m.r., and m.s. data identical to those of the natural product. We are greatly indebted to Professors J. Ficini (Université Pierre et Marie Curie, Paris), H.-P. Husson and P. Potier (Institute de Chimie des Substances Naturelles, Gif-sur-Yvette), and J. A. Lamberton (CSIRO Chemical Research Laboratories, Melbourne) for generous gifts of natural (−)-antirhine.

[1] S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1980, 616.
[2] S. Takano, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, preceding communication.
[3] S. Takano, M. Yonaga, K. Chiba, and K. Ogasawara, *Tetrahedron Lett.*, 1980, **21**, 3697.
[4] S. Takano, M. Yonaga, and K. Ogasawara, *Synthesis*, 1981, 265.
[5] M. Taniguchi, K. Koga, and S. Yamada, *Tetrahedron*, 1974, **30**, 3547.
[6] S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Heterocycles*, 1981, **16**, 381, 951.
[7] S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.*, 1967, **20**, 1463.
[8] For a synthesis of racemic antirhine by a fundamentally different approach see S. Takano, M. Takahashi, and K. Ogasawara, *J. Am. Chem. Soc.*, 1980, **102**, 4282.
[9] B. Belleau and J. Puranen, *Can. J. Chem.*, 1965, **43**, 2551.
[10] *Cf.* M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, 1979, **8**, 171.
[11] D. Liotta, W. Markiewicz, and H. Santiesteban, *Tetrahedron Lett.*, 1977, 4365.
[12] K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492.
[13] H. Iio, M. Isobe, T. Kawai, and T. Goto, *Tetrahedron*, 1979, **35**, 941.