An Enantiospecific Synthesis of (+)-Retronecine and Related Alkaloids

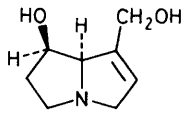
J. Grant Buchanan,* Gurdial Singh, and Richard H. Wightman*

Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, U.K.

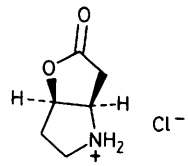
Carbohydrate precursors have been converted enantiospecifically into (1*R*,5*R*)-6-aza-2-oxabicyclo[3.3.0]octan-3-one hydrochloride (**2**), a precursor of (+)-retronecine (**1**) and related pyrrolizidines.

The varied range of biological activities[1] associated with the pyrrolizidine alkaloids[2] has led to considerable interest in the synthesis of their constituent necine bases, particularly the widely-distributed retronecine,[3] derivatives of which have promising anti-tumour activity.[4] Very recently chiral syntheses of (+)-retronecine (**1**)[5] and of other pyrrolizidine alkaloids[6] have been reported, from a variety of optically-active precursors. We now report an enantiospecific synthesis of the hydrochloride of (1*R*,5*R*)-6-aza-2-oxabicyclo-[3.3.0]octan-3-one (**2**) from carbohydrate precursors; this lactone was originally prepared in racemic form during the first total synthesis of retronecine,[7] and can be converted efficiently[5,7,8] into (+)-retronecine, and other pyrrolizidines.[5]

The readily-available[9] 2,3-*O*-isopropylidene-D-erythrose (**3**) was converted (see Scheme 1) *via* the oxime into the cyanomethanesulphonate (**4**) (95% overall).† Treatment of



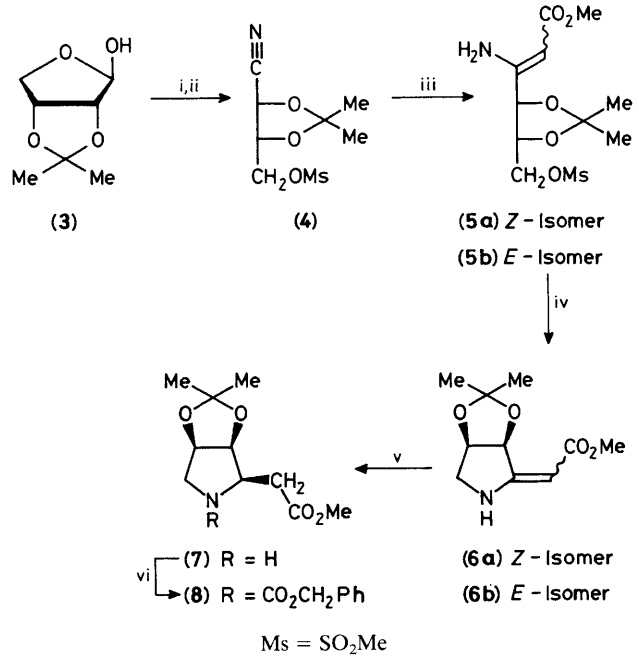
(1)



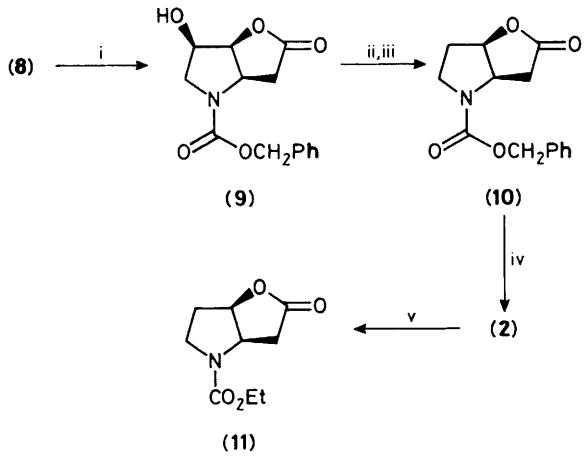
(2)

(**4**) with an excess of methyl bromoacetate in the presence of activated zinc dust[10] gave the enamino esters (**5a,b**) [80%; ratio (**5a**) : (**5b**) *ca.* 30 : 1]; the major crystalline isomer (**5a**) is tentatively assigned the *Z*-stereochemistry on n.m.r. spectroscopic evidence.[11] Compounds (**5a**) and (**5b**) could be separately cyclised in high yield to (**6a**) and (**6b**) respectively on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), both of which gave the same saturated pyrrolidine (**7**) (80%) with sodium cyanoborohydride.[12] Treatment of (**7**) with benzyl chloroformate gave (**8**). This material proved

† All new compounds gave satisfactory analytical and spectroscopic data.



Scheme 1. i, $NH_2OH{\cdot}HCl$ (10 equiv.), C_5H_5N, room temp.; ii, $MeSO_2Cl$ (12 equiv.), C_5H_5N, −23 °C; iii, activated Zn, $BrCH_2CO_2Me$ (5 equiv.), tetrahydrofuran, reflux; iv, DBU (3 equiv.), CH_2Cl_2, room temp., 24 h; v, $NaBH_3CN$, MeOH, HCl; vi, $PhCH_2OCOCl$, Et_3N, CH_2Cl_2, 0 °C to room temp.



Scheme 2. i, 80% CF_3CO_2H, room temp., 18 h; ii, 1,1′-thiocarbonyldiimidazole, C_5H_5N, tetrahydrofuran, reflux; iii, Bu_3SnH (2.2 equiv.), C_6H_6, reflux; iv, 10% Pd/C, H_2, EtOH, HCl; v, $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C to room temp.

identical with that produced by an alternative lower-yielding route, details of which will be given in a full paper.

Hydrolysis of the isopropylidene group gave in 82% yield a lactone (**9**) (Scheme 2) the i.r. spectrum of which ($\nu_{max.}$ 1790 cm^{-1}) indicated it was the desired γ-lactone, although recent findings in a related system[13] necessitated caution. Barton-type deoxygenation[14] gave (**10**) (90%) ($\nu_{max.}$ 1786 cm^{-1}), which on hydrogenolysis gave (95%) the lactone (**2**), as its crystalline hydrochloride [m.p. 182—184 °C(decomp.), α_D + 45.6° (*c* 0.83, MeOH); lit.[5] m.p. 185—186 °C, α_D + 48.5° (*c* 1.5, MeOH)], with spectra in good agreement with data provided by Professor M. H. Benn. Treatment of (**2**) with ethyl chloroformate gave (**11**), identical (spectra, t.l.c.) with a sample[8] kindly provided by Professor K. Narasaka.

Since (**2**) can be readily converted into (+)-retronecine (**1**),[5,7,8] a total enantiospecific synthesis of (**1**) and some related systems[5] has been accomplished.

We thank the S.E.R.C. and Nuffield Foundation (One-Year Science Research Fellowship to R. H. W.) for financial support, Professor K. Narasaka (Tokyo), Professor M. H. Benn, and Dr. V. Yadav (Calgary) for samples and spectroscopic data, and Dr. I. H. Sadler (University of Edinburgh) for n.m.r. spectra obtained on the S.E.R.C. high-field facility.

Received, 30th May 1984; Com. 737

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