

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

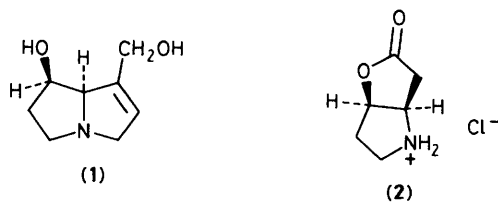
J. Grant Buchanan,* Gurdial Singh, and Richard H. Wightman*

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.

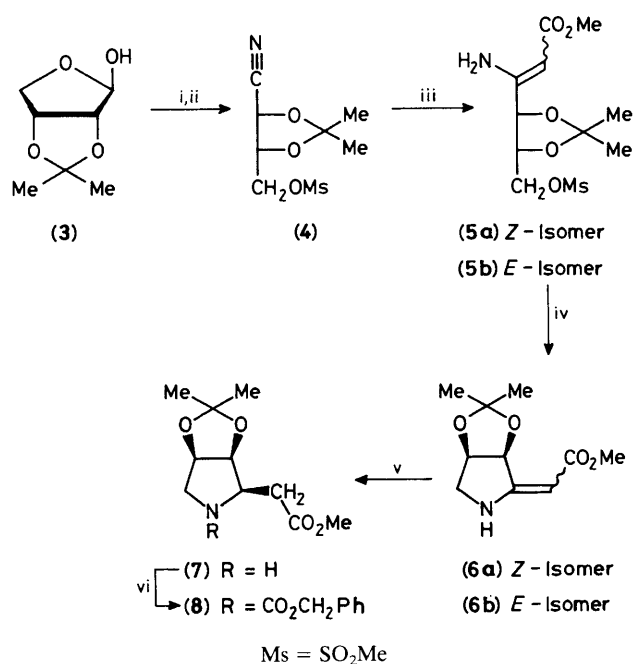
The varied range of biological activities¹ associated with the pyrrolizidine alkaloids² has led to considerable interest in the synthesis of their constituent necine bases, particularly the widely-distributed retronecine,³ derivatives of which have promising anti-tumour activity.⁴ Very recently chiral syntheses of (+)-retronecine (**1**)⁵ and of other pyrrolizidine alkaloids⁶ 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-available⁹ 2,3-*O*-isopropylidene-D-erythrose (**3**) was converted (see Scheme 1) *via* the oxime into the cyanomethanesulphonate (**4**) (95% overall).[†] Treatment of

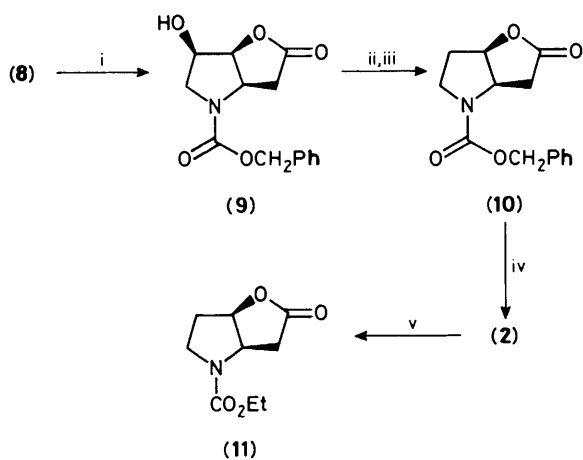


(**4**) with an excess of methyl bromoacetate in the presence of activated zinc dust¹⁰ gave the enamino esters (**5a,b**) [80%; ratio (**5a**):(**5b**) *ca.* 30:1]; the major crystalline isomer (**5a**) is tentatively assigned the *Z*-stereochemistry on n.m.r. spectroscopic evidence.¹¹ Compounds (**5a**) 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, NH₂OH·HCl (10 equiv.), C₅H₅N, room temp.; ii, MeSO₂Cl (12 equiv.), C₅H₅N, -23°C; iii, activated Zn, BrCH₂CO₂Me (5 equiv.), tetrahydrofuran, reflux; iv, DBU (3 equiv.), CH₂Cl₂, room temp., 24 h; v, NaBH₃CN, MeOH, HCl; vi, PhCH₂OCOCl, Et₃N, CH₂Cl₂, 0°C to room temp.



Scheme 2. i, 80% CF₃CO₂H, room temp., 18 h; ii, 1,1'-thiocarbonyldiimidazole, C₅H₅N, tetrahydrofuran, reflux; iii, Bu₃SnH (2.2 equiv.), C₆H₆, reflux; iv, 10% Pd/C, H₂, EtOH, HCl; v, ClCO₂Et, Et₃N, CH₂Cl₂, 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 (ν_{\max} , 1790

cm⁻¹) indicated it was the desired γ -lactone, although recent findings in a related system¹³ necessitated caution. Barton-type deoxygenation¹⁴ gave (10) (90%) (ν_{\max} , 1786 cm⁻¹), which on hydrogenolysis gave (95%) the lactone (2), as its crystalline hydrochloride [m.p. 182–184°C (decomp.), $\alpha_D + 45.6^\circ$ (c 0.83, MeOH); lit.⁵ m.p. 185–186°C, $\alpha_D + 48.5^\circ$ (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 sample⁸ 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 systems⁵ has been accomplished.

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