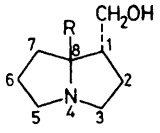
Synthesis of the 8β-Pyrrolizidine Bases (+)-Isoretronecanol, (+)-Laburnine, and (+)-Supinidine

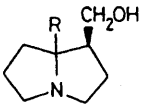
By DAVID J. ROBINS* and SANTI SAKDARAT
(*Department of Chemistry, University of Glasgow, Glasgow* G12 8QQ)

Summary The synthesis of the three title compounds in optically active form from natural 4-hydroxy-L-proline is described.

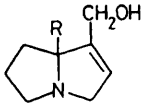
OVER 30 pyrrolizidine alkaloids have been characterised as ester derivatives of the six bases (**1**)—(**6**).[1] We report a general route to the synthesis of all six bases in optically active form, and exemplify our approach with the synthesis of (+)-isoretronecanol (**1**), (+)-laburnine (**3**), and (+)-supinidine (**5**).



(1) R = β-H
(2) R = α-H

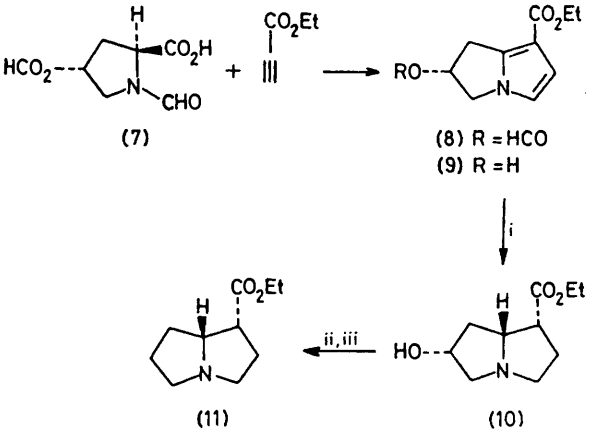


(3) R = β-H
(4) R = α-H



(5) R = β-H
(6) R = α-H

Regiospecific 1,3-dipolar cycloaddition of ethyl propiolate to the postulated azomethine ylide[2] formed by heating the *NO*-diformyl derivative (**7**)† of natural (−)-4-hydroxy-L-proline with acetic anhydride at 140 °C for 10 h gave the dihydropyrrolizine ester (**8**) {$[\alpha]_D^{18}$ + 35·3° ($CHCl_3$)} in 80% yield (Scheme). Removal of the formyl group with ethanolic ammonia afforded the alcohol (**9**). Catalytic hydrogenation of (**9**) gave (80%) the crystalline ester (**10**) {$[\alpha]_D^{18}$ + 73·4° ($CHCl_3$)}, formed by stereospecific *cis*-addition of hydrogen to the less sterically hindered β-face of the ester (**9**). Proof of the stereochemistry of the ester (**10**) was obtained as follows. Replacement[3] of the 6α-hydroxy-group of (**10**) by chlorine followed by catalytic hydrogenation yielded (82%) the pyrrolizidine ester (**11**) {$[\alpha]_D^{18}$ + 61·2° (EtOH)}. Lithium aluminium hydride reduction of the ester (**11**) gave (94%) (+)-isoretronecanol (**1**) {$[\alpha]_D^{20}$ + 70·2° (EtOH); lit.[4] $[\alpha]_D^{20}$ + 71·7° (EtOH)}. The overall yield of optically active product was 45% from the readily available (−)-4-hydroxy-L-proline.



(7) (8) R = HCO (9) R = H (10) (11)

SCHEME. Reagents; i, H_2, 10% Pd–C, AcOH; ii, $SOCl_2$; iii, H_2, Raney Ni.

Epimerisation at C-1 of the thermodynamically less stable ester (**11**) was achieved with sodium ethoxide in ethanol,[5] and the product was reduced with lithium aluminium hydride to give (+)-laburnine (**3**) [64% yield from (**11**)] {$[\alpha]_D^{22}$ + 14·6° (EtOH); lit.[6] $[\alpha]_D$ + 15·4° (EtOH)}. The ester (**11**) was also converted (21% overall yield) into (+)-supinidine (**5**) {$[\alpha]_D^{18}$ + 7·6° (EtOH); lit.[4] $[\alpha]_D^{20}$ + 9·2° (EtOH)} by the steps reported[7] for the racemic compound. (A higher overall yield was obtained when rigorous purification of the intermediate selenides was omitted.)

Compounds (**1**), (**3**), and (**5**) were characterised as their picrates. The picrates of (**1**) and (**5**) were identical (i.r., ^1H n.m.r., and mass spectra, mixed m.p.) with samples of natural (+)-isoretronecanol picrate and (+)-supinidine picrate, respectively.

Since natural (−)-4-hydroxy-L-proline can be converted into its enantiomer by epimerisation of both chiral centres,[8] the foregoing route can be used in principle to synthesize the 8α-pyrrolizidine bases (**2**), (**4**), and (**6**). However, a better procedure was devised using the intermediate (**9**), which has only one chiral centre. Accordingly, the

† All new compounds gave satisfactory analytical and spectroscopic data.

hydroxy-ester (**9**) was converted into its tosylate derivative (91% yield). Inversion of stereochemistry was then achieved by S_N2 displacement with formate anion (tetraethylammonium formate in dry acetone) to give (84%) the enantiomer of (**8**) {$[\alpha]_D^{23}$ $-34{\cdot}2°$ ($CHCl_3$)} required for conversion, as outlined above, into the 8α-pyrrolizidine bases (−)-isoretronecanol (**4**), (−)-trachelanthamidine (**2**), and (−)-supinidine (**6**).

This strategy makes possible the synthesis of all six 1-hydroxymethylpyrrolizidines in good yield in optically active form. Total syntheses of optically active ester alkaloids derived from these bases can now be envisaged.

We thank Dr. C. C. J. Culvenor, C.S.I.R.O., Parkville, Victoria, Australia, for samples of (+)-isoretronecanol picrate and (+)-supinidine picrate. One of us (S.S.) thanks the University of Glasgow for a studentship.

(*Received*, 17*th September* 1979; *Com.* 999.)

[1] L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids,' North-Holland, Amsterdam, 1968; 'The Alkaloids' Specialist Periodical Reports, The Chemical Society, London, 1971—9, vols. 1—9; D. J. Robins, *Adv. Heterocyclic Chem.*, 1979, **24**, 247; N. K. Kochetkov and A. M. Likhosherstov, *ibid.*, 1965, **5**, 315.
[2] M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, 1974, **39**, 731.
[3] R. S. Sawhney, C. K. Atal, C. C. J. Culvenor, and L. W. Smith, *Austral. J. Chem.*, 1974, **27**, 1805.
[4] C. C. J. Culvenor and L. W. Smith, *Austral. J. Chem.*, 1967, **20**, 2499.
[5] S. Brandange and C. Lundin, *Acta Chem. Scand.*, 1971, **25**, 2447.
[6] N. K. Hart and J. A. Lamberton, *Austral. J. Chem.*, 1966, **19**, 1259.
[7] D. J. Robins and S. Sakdarat, *J.C.S. Perkin I*, 1979, 1734.
[8] D. S. Robinson and J. P. Greenstein, *J. Biol. Chem.*, 1952, **195**, 383.