Synthesis of Optically Active Pyrrolizidine Bases [1]

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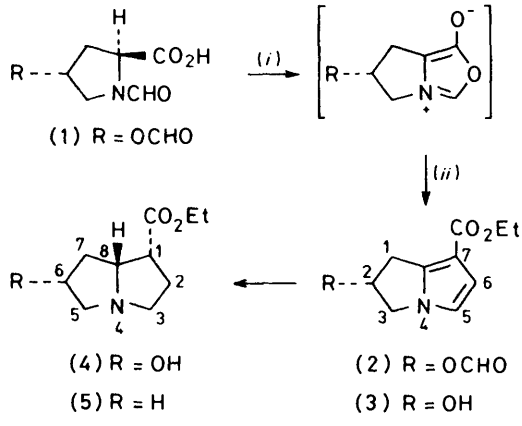
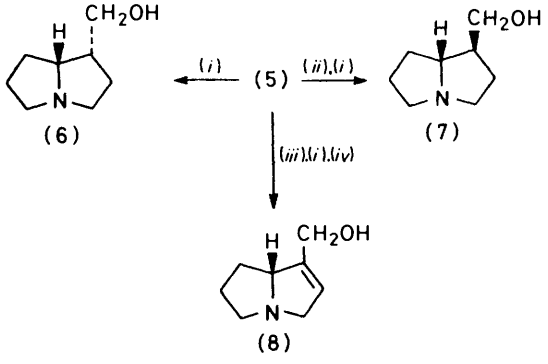
Regiospecific 1,3-dipolar cycloaddition of ethyl propiolate to the *NO*-diformyl derivative (1) of natural (−)-4-hydroxy-L-proline followed by stereospecific hydrogenation gave ethyl (+)-6α-hydroxy-β-pyrrolizidine-1α-carboxylate (4). Confirmation of the absolute configuration of this ester was obtained by its conversion into the naturally occurring 8β-pyrrolizidine bases (+)-isoretronecanol (6), (+)-laburnine (7), and (+)-supinidine (8). The synthesis of the corresponding 8α-bases (−)-isoretronecanol (12), (−)-trachelanthamidine (13), and (−)-supinidine (14) was achieved after epimerisation of ethyl (+)-(2*R*)-2-hydroxy-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (3). The optical purity of all six naturally occurring bases which were synthesized was >80%. Two new optically active pyrrolizidine bases (+)-6α-hydroxy-1α-hydroxymethyl-8β-pyrrolizidine (15) and (−)-6α-acetoxy-1-acetoxymethyl-5,6,7,8-tetrahydro-3*H*-pyrrolizine (16) were also prepared.

PYRROLIZIDINE derivatives with 1-substituents are widely distributed in a number of plant families. Ester derivatives of all six stereoisomeric forms of 1-hydroxy-



SCHEME 1 (*i*) Ac_2O; (*ii*) $HC{\equiv}CCO_2Et$

methylpyrrolizidine and its 1,2-didehydro-analogue have been isolated.[2] Much attention has been directed towards the synthesis of these 1-hydroxymethylpyrrolizidines.[3] Since all the reported syntheses have yielded racemic material, we desired a general route to



SCHEME 2 (*i*) $LiAlH_4$; (*ii*) NaOEt–EtOH; (*iii*) $Pr^i{}_2NH$–Bu^nLi, PhSeCl; (*iv*) H_2O_2

optically active forms of these six stereoisomers without recourse to a resolution step, thus facilitating syntheses of some of the natural ester derivatives.

One of the best methods for construction of the pyrrolizidine nucleus involves the 1,3-dipolar cycloaddition of an alkyne to the mesoionic oxazolone derived from L-proline to produce a dihydropyrrolizine.[4] Pizzorno and Albonico recognised the potential of this reaction for pyrrolizidine alkaloid synthesis, and devised an efficient two-step route to the racemic ester (5) (Scheme 1, R = H).[5] This ester can be converted into (±)-isoretronecanol (6) and (12),[6] (±)-trachelanthamidine (7) and (13),[7] and (±)-supinidine (8) and (14) [8] as shown in Scheme 2.

We decided to investigate the use of natural (—)-4-hydroxy-L-proline in place of L-proline in the reaction sequence shown in Scheme 1, believing that the formation of the two new chiral centres at C-1 and C-8 in (5) would be controlled by the stereochemistry of the hydroxy-group on the proline moiety. Having performed its function of chiral control, the hydroxy-group would be removed,[9] making possible the synthesis of the optically active 8β-forms of the 1-hydroxymethylpyrrolizidines (Scheme 2).

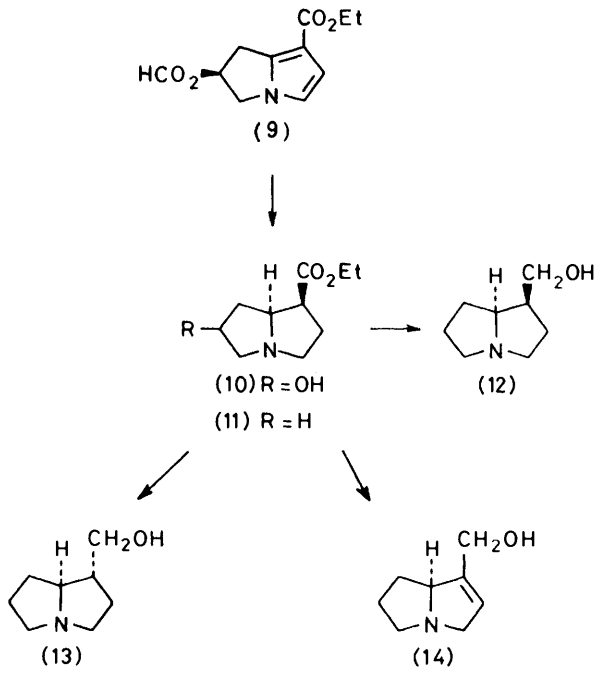
RESULTS AND DISCUSSION

The optically active dihydropyrrolizine ester (2) was prepared in 80% yield by regiospecific 1,3-dipolar cycloaddition of ethyl propiolate to the *NO*-diformyl derivative (1) of natural (—)-4-hydroxy-L-proline. It is formulated as the 7-ester (2) † because of a typical AB quartet in its n.m.r. spectrum due to the adjacent pyrrolic protons. Deformylation of the ester (2) was achieved with ethanolic ammonia in quantitative yield. Catalytic hydrogenation of the hydroxy-ester (3) gave one major optically active crystalline product in 80% yield. The absolute stereochemistry of this pyrrolizidine ester is formulated as in (4), resulting from the stereospecific *cis*-addition of hydrogen to the less sterically hindered β-face of the dihydropyrrolizine ester (3). This stereochemical assignment was proved by conversion of the ester (4) into optically active forms of the three known 8β-pyrrolizidine bases, (+)-isoretronecanol (6),

† Unsaturated pyrrolizidines are numbered as derivatives of 1*H*- or 3*H*-pyrrolizine, whereas saturated pyrrolizidines are numbered as in (4).

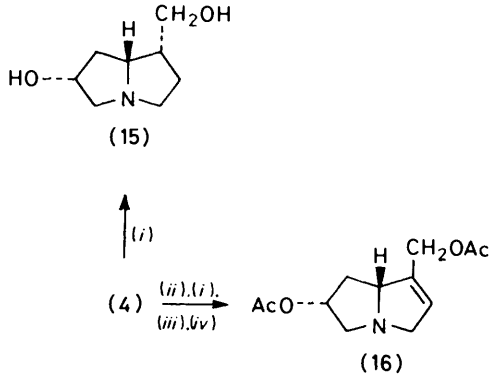
(+)-laburnine (7), and (+)-supinidine (8). Thus, the 6α-hydroxy-group was removed by displacement with chlorine,[9] followed by catalytic hydrogenation to give the optically active pyrrolizidine ester (5) in 82% yield. Reduction [6] of this ester gave (+)-isoretronecanol (6) in 94% yield, and with an optical purity * estimated to be *ca.* 89%. The overall yield of this optically active base was 45% from (−)-4-hydroxy-L-proline. The thermodynamically less stable *endo*-ester (5) was epimerised at C-1,[7] and the product was reduced to give (+)-laburnine (7) in 31% overall yield from (−)-4-hydroxy-L-proline, and with an optical purity of *ca.* 95%. The (+)-ester (5) was also converted in 21% yield into (+)-supinidine (8) of *ca.* 83% optical purity by the method reported for the racemic ester (5).[8] The oily bases (6), (7), and (8), were characterised as their picrates. The picrates of (6) and (8) were identical (spectroscopically and undepressed mixed m.p.) with authentic samples of the picrates of (+)-isoretronecanol and (+)-supinidine, respectively.

In order to synthesize the 8α-pyrrolizidine bases, (−)-isoretronecanol (12), (−)-trachelanthamidine (13), and (−)-supinidine (14), it would be necessary to repeat the above sequence with 4-hydroxyproline with the opposite configuration of the 4-hydroxy-group. A procedure exists for the conversion of (−)-4-hydroxy-L-proline into its enantiomer by epimerisation at both



SCHEME 3

chiral centres.[10] However, this double epimerisation procedure is lengthy, and so an alternative approach was sought, in which the sole chiral centre of the dihydropyrrolizine ester (3) was epimerised. The enantiomer (9) of (2) was prepared by S_N2 displacement of the tosylate derivative of (3) by the formate anion in 78% yield. Deformylation, catalytic hydrogenation, and removal of the 6β-hydroxy-group of (10) gave the (−)-ester (11), which was converted, as outlined above for the (+)-ester into the 8α-pyrrolizidine bases (−)-isoretronecanol (12), (−)-trachelanthamidine (13), and (−)-supinidine (14) (Scheme 3), with optical purities estimated to be 90%, 98%, and 81%, respectively. Characterisation of these bases was again performed *via* the picrates, and the



SCHEME 4 (*i*)$LiAlH_4$; (*ii*) Pr^i_2NH–Bu^nLi, PhSeCl; (*iii*) Ac_2O–pyridine; (*iv*) H_2O_2

picrate of (14) was identical (spectroscopically and undepressed mixed m.p.) with an authentic sample of (−)-supinidine picrate.

Finally, the optically active ester (4) was converted into two new optically active pyrrolizidine bases retaining the 6α-hydroxy-function. Reduction of the hydroxy-ester (4) gave the pyrrolizidine diol (15) in 89% yield. Conversion of the ester (4) into its 1,2-didehydro-derivative was also carried out, but because of its high polarity and water solubility it was found necessary to isolate the diol as its diacetate derivative (16) in 22% overall yield from the ester (4).

All six naturally occurring 1-hydroxymethylpyrrolizidines have been synthesized from natural (−)-4-hydroxy-L-proline with optical purities estimated to be better then 80% in every case. (The range in optical purities reported in the literature is probably partly due to the difficulty in accurately weighing small quantities of these bases.) Syntheses in optically active form of some of the 30 pyrrolizidine alkaloids which are ester derivatives of these six bases can now be contemplated.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Organic solutions were dried with anhydrous $MgSO_4$, and solvents were evaporated off *in vacuo* below 40 °C. N.m.r. spectra were run for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS12 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 Polarimeter. T.l.c. of the bases was carried out on Kieselgel G with chloroform–methanol–ammonia 85 : 14 : 1, and the bases were located with the modified Dragendorff reagent.[11]

(−)-(2S,4R)-N-*Formyl*-4-*formyloxyproline* (1).—Formic

* Optical purity (%) is defined as $\frac{[\alpha]_{obs.}}{[\alpha]_{max.\ reported}} \times 100$.

acid (69 g, 1.5 mol) and acetic anhydride (76 g, 0.75 mol) were stirred at room temperature for 1 h. (−)-(2*S*,4*R*)-4-Hydroxyproline (10 g, 0.076 mol) in formic acid (20 ml) was added, and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed and the residue crystallised from methanol to give (−)-(2S,4R)-N-*formyl*-4-*formyloxyproline* (1) (12.9 g, 91%); m.p. 171—173 °C; $[\alpha]_D^{18}$ −74.0° (*c* 5 in MeOH); $\nu_{max.}$ (KBr) 3 000, 1 765, 1 718, and 1 620 cm^{-1}; δ (CD_3OD) 8.35 (1 H, s, CHO), 8.15 (1 H, s, CHO), 5.50 (1 H, m, H-4), 4.60 (1 H, m, H-1), 3.70 (2 H, m, H-3), and 2.50 (2 H, m, H-5); *m/e* 187 (M^+, 5), 143 (22), 97 (25), 96 (75), and 68 (100%) (Found: C, 44.8; H, 4.7; N, 7.3. $C_7H_9NO_5$ requires C, 44.9; H, 4.9; N, 7.5%).

Ethyl (+)-(2R)-2-*Formyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (2).—A solution of the *NO*-diformyl derivative (1) (1.87 g, 10 mmol) and ethyl propiolate (4.9 g, 50 mmol) in acetic anhydride (10 ml) was heated at 140 °C for 10 h under nitrogen. The excess of reagents was evaporated leaving a red-brown oil which was distilled through a short-path apparatus, b.p. 139—140 °C (0.8 mmHg) to give an oil, which afforded colourless needles of *ethyl* (+)-(2R)-2-*formyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (2) from ether (1.79 g, 80%), m.p. 62.5—63.5 °C; $[\alpha]_D^{18}$ +35.3° (*c* 4 in $CHCl_3$); $\nu_{max.}$ (CCl_4) 1 730, 1 715, 1 580, and 1 170 cm^{-1}; $\lambda_{max.}$ (EtOH) 261 nm (ε 10 250); δ 8.10 (1 H, s, CHO), 6.60, 6.65 (2 H, AB q, *J* 3 Hz, H-5,6), 5.90 (1 H, m, H-2), 4.30 (4 H, m, H-3 and CH_2Me), 3.40 (2 H, m, H-1), and 1.35 (3 H, t, *J* 7 Hz, Me); *m/e* 223 (M^+, 9), 177 (16), 123 (84), and 93 (100%) (Found: C, 59.3; H, 5.7; N, 6.0. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.8; N, 6.3%).

Ethyl (+)-(2R)-2-*Hydroxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (3).—A solution of the ethyl ester (2) (1.784 g, 8 mmol) in ethanol (100 ml) and concentrated ammonia solution (10 ml) was stirred at room temperature for 16 h. The solvent was removed, and the residue, in chloroform (50 ml), was washed with water (2 × 30 ml), dried, filtered, and concentrated to give *ethyl* (+)-(2R)-2-*hydroxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (3) as a pale yellow oil (1.56 g, 100%); $[\alpha]_D^{18}$ +34.6° (*c* 4 in $CHCl_3$); $\nu_{max.}$ (liquid film) 3 350, 1 680, and 1 560 cm^{-1}; $\lambda_{max.}$ (EtOH) 252 nm (ε 11 370); δ 6.60, 6.50 (2 H, AB q, *J* 3 Hz, H-5, 6), 5.00 (1 H, m, H-2), 4.20 (4 H, m, H-3 and CH_2Me), 3.20 (2 H, m, H-1), and 1.30 (3 H, t, *J* 7 Hz, Me); *m/e* 195 (M^+, 95) 177 (15), 150 (100), 132 (50), 122 (40), and 94 (40%) (Found: M^+ 195.089 68. $C_{10}H_{13}NO_3$ requires *M*, 195.089 53).

Ethyl (+)-6α-*Hydroxy*-8β-*pyrrolizidine*-1α-*carboxylate* (4).—A solution of the ethyl ester (3) (1.95 g, 10 mmol) in acetic acid (30 ml) was hydrogenated at 21 atm for two days at room temperature using 10% Pd–C (2 g) as catalyst. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to give an oil, which yielded *ethyl* (+)-6α-*hydroxy*-8β-*pyrrolizidine*-1α-*carboxylate* (4) as needles from ethyl acetate (1.60 g, 80%), m.p. 109—110 °C; $[\alpha]_D^{18}$ +73.4° (*c* 4 in $CHCl_3$); $\nu_{max.}$ (KBr) 3 100 (br) and 1 720 cm^{-1}; δ 4.38 (1 H, m, H-6), 4.15 (2 H, q, *J* 7 Hz, CH_2Me), 3.75 (1 H, q, *J* 7 Hz, H-8), 3.25—2.00 (10 H, complex), and 1.25 (3 H, t, *J* 7 Hz, Me); *m/e* 199 (M^+, 12), 155 (16), 154 (19), 106 (28), 99 (47), and 82 (100%) (Found: C, 60.4; H, 8.4; N, 7.1. $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.5; N, 7.0%).

Ethyl 6-*Chloro*-8β-*pyrrolizidine*-1α-*carboxylate Hydrochloride*.—The ethyl ester (4) (995 mg, 5 mmol) was treated with thionyl chloride (40 ml) at 5 °C and then was heated at reflux for 5 h. Excess of reagent was removed to give *ethyl* 6-*chloro*-8β-*pyrrolizidine*-1α-*carboxylate hydrochloride*, which crystallised from acetone (1.144 g, 90%), m.p. 172—174 °C; $\nu_{max.}$ (KBr) 2 515, 2 300, and 1 740 cm^{-1}; δ 4.90 (1 H, m, H-6), 4.20 (2 H, q, *J* 7 Hz, CH_2Me), 4.00—3.40 (6 H, complex), 2.40 (4 H, complex), and 1.22 (3 H, t, *J* 7 Hz, Me); *m/e* 217 (M^+ −HCl, 10), 182 (65), 172 (24), 136 (24), 115 (29), 117 (88), 108 (33), 106 (33), and 82 (100%) [Found: $(M - HCl)^+$, 217.086 93. $C_{10}H_{16}NO_2Cl$ requires *M*, 217.086 93].

Ethyl (+)-8β-*Pyrrolizidine*-1α-*carboxylate* (5).—The hydrochloride salt of ethyl 6-chloro-8β-pyrrolizidine-1α-carboxylate (635 mg, 2.5 mmol) was hydrogenated at 15 atm in ethanol at room temperature, using Raney nickel as catalyst. When the uptake of hydrogen had ceased, the catalyst was removed by filtration through Celite, and the filtrate was concentrated to give an oil. Saturated Na_2CO_3 solution was added to this oil, and the aqueous layer was extracted with chloroform (3 × 50 ml). The chloroform extracts were dried, filtered, and concentrated to yield *ethyl* (+)-8β-*pyrrolizidine*-1α-*carboxylate* (5) as an oil (413 mg, 90%); R_F 0.48, $[\alpha]_D^{18}$ +61.2° (*c* 5 in EtOH); the spectral data were the same as for a sample of the racemic compound, prepared earlier.[8] The picrate had m.p. 111—112 °C (EtOH) (Found: C, 46.4; H, 4.7; N, 13.3. $C_{16}H_{20}N_4O_9$ requires C, 46.6; H, 4.8; N, 13.6%).

(+)-1α-*Hydroxymethyl*-8β-*pyrrolizidine* [(+)-*Isoretronecanol*] (6).[6]—A solution of the ethyl ester (5) (183 mg, 1 mmol), in dry ether (10 ml) was added to a suspension of lithium aluminium hydride (76 mg, 2 mmol) in dry ether (10 ml) under nitrogen. The reaction mixture was stirred at room temperature for 2 h, and then wet ether (10 ml) and 1M-sodium hydroxide (0.3 ml) were added slowly. The resulting suspension was filtered through Celite, and the filtrate was dried, filtered, and concentrated to give (+)-isoretronecanol (6) as an oil (132 mg, 94%), $[\alpha]_D^{25}$ +70.2° (*c* 5 in EtOH) {lit.,[12] $[\alpha]_D^{20}$ +71.7° (*c* 1.04 in EtOH); lit.,[13] $[\alpha]_D$ +79.1°}; $\nu_{max.}$ ($CHCl_3$) 3 350 cm^{-1}; δ 4.32 (1 H, br s, OH), 3.62 (2 H, d, *J* 7 Hz, H-9), and 3.20—1.50 (12 H, complex); *m/e* 141 (M^+, 35), 140 (20), 124 (30), 110 (30), 108 (22), 85 (35), 83 (100), and 82 (76%). The picrate had m.p. 193—194 °C (EtOH) (lit.,[13] 193—194 °C) (Found: C, 45.3; H, 4.8; N, 14.9. Calc. for $C_{14}H_{18}N_4O_8$ C, 45.4; H, 4.9; N, 15.1%). The mixed m.p. with an authentic sample of (+)-isoretronecanol picrate was undepressed. The i.r., n.m.r., and mass spectra of these two samples were identical.

Ethyl (+)-8β-*Pyrrolizidine*-1β-*carboxylate*.—The epimerisation at C-1 of the ester (5) was carried out by the procedure of Brandange and Lundin [7] for the methyl ester, except that ethanol was used as solvent. *Ethyl* (+)-8β-*pyrrolizidine*-1β-*carboxylate* was obtained as an oil (68%), $[\alpha]_D^{23}$ +39.1° (*c* 3 in $CHCl_3$); $\nu_{max.}$ 1 735 and 1 180 cm^{-1}; δ 4.20 (2 H, q, *J* 7 Hz, H-9), 3.70 (1 H, m, H-8), 3.20—1.80 (11 H, complex), and 1.25 (3 H, t, *J* 7 Hz, Me); *m/e* 183 (M^+, 22) 154 (20), 138 (20), 136 (20), 106 (46), 83 (100), and 82 (60%). The *picrate* had m.p. 179—181 °C (EtOH) (Found: C, 46.5; H, 4.9; N, 13.5. $C_{16}H_{20}N_4O_9$ requires C, 46.6; H, 4.9; N, 13.6%).

(+)-1β-*Hydroxymethyl*-8β-*pyrrolizidine* [(+)-*Laburnine*] (7).—Reduction of ethyl (+)-8β-pyrrolizidine-1β-carboxylate (91.5 mg, 0.5 mmol) was carried out as described for the epimeric compound (5) to yield an oil (65 mg, 92%), $[\alpha]_D^{22}$ +14.6° (*c* 3.25 in EtOH) {lit.,[14] $[\alpha]_D$ +15.4° (*c* 1.44 in EtOH)}; $\nu_{max.}$ ($CHCl_3$) 3 350 cm^{-1}; δ 3.90 (1 H, br s, OH), 3.65 (2 H, d, *J* 7 Hz, H-9), and 3.20—1.60 (12 H, complex); *m/e* 141 (M^+, 28), 140 (28), 124 (40), 110 (28), 83 (100), and 82 (80%).

The picrate had m.p. 174—175 °C (lit.,[14] m.p. 174—175 °C) (Found: C, 45.7; H, 4.7; N, 14.8. Calc. for $C_{14}H_{18}N_4O_8$ C, 45.4; H, 4.9; N, 15.1%).

Phenylselenenylation of the (+)-*Ester* (5).—This was carried out as described for the racemic ester [8] to give *ethyl* (+)-1-*phenylseleno*-8β-*pyrrolizidine*-1-*carboxylate* as a pale yellow oil (62%), $[\alpha]_D^{18}$ +42.1° (*c* 5 in $CHCl_3$) (Found: M^+, 339.073 22. $C_{16}H_{21}NO_2Se$ requires *M*, 339.073 71).

(−)-1-*Hydroxymethyl*-1-*phenylseleno*-8β-*pyrrolizidine*.—Reduction of ethyl (+)-1-phenylseleno-8β-pyrrolizidine-1-carboxylate was carried out as described for racemic material [8] to give crystalline (−)-1-*hydroxymethyl*-1-*phenylseleno*-8β-*pyrrolizidine* (61%), m.p. 142—144 °C, $[\alpha]_D^{18}$ −22.9° (*c* 3 in $CHCl_3$) (Found: C, 56.8; H, 6.5; N, 5.0. $C_{14}H_{19}NOSe$ requires C, 56.8; H, 6.4; N, 4.7%).

(+)-*Supinidine* (8).—Oxidation of (−)-1-hydroxymethyl-1-phenylseleno-8β-pyrrolizidine was performed as stated for racemic material [8] to yield (+)-supinidine (8) as an oil (55%); $[\alpha]_D^{18}$ +7.60° (*c* 3 in EtOH), {lit.,[12] $[\alpha]_D^{20}$ +9.2° (*c* 2.07 in EtOH)}. The i.r., n.m.r., and mass spectra were in accord with reported values for (±)-supinidine.[8] The picrate had m.p. 144—145 °C (EtOH) (lit.,[12] 144—145 °C) (Found: C 45.8; H, 4.4; N, 15.2. Calc. for $C_{14}H_{16}N_4O_8$ C, 45.7; H, 4.4; N, 15.2%). The mixed m.p. with an authentic sample of (+)-supinidine picrate was undepressed. The i.r., n.m.r., and mass spectra of the two samples were identical.

Ethyl (+)-(2R)-2-*Tosyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate*.—Ethyl (+)-(2*R*)-2-hydroxy-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (3) (195 mg, 1 mmol) in dry pyridine (5 ml) was treated with a solution of toluene-*p*-sulphonyl chloride (572 mg, 3 mmol) in pyridine (2 ml), and the mixture was stirred at room temperature for 18 h. The mixture was acidified and extracted with chloroform (3 × 50 ml). The chloroform extracts were washed with 1M-HCl, brine, and then dried. Filtration and concentration gave *ethyl* (+)-(2R)-2-*tosyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (318 mg, 91%), m.p. 123—125 °C (ether–light petroleum), $[\alpha]_D^{25}$ +25.8° (*c* 5 in CHCl); $\nu_{max.}$ (KBr) 1 705, 1 695, 1 600, 1 570, and 1 255 cm^{-1}; $\lambda_{max.}$ (EtOH) 252 nm (ε 15 350); δ 7.77, 7.36 (4 H, A_2B_2, *J* 9 Hz), 6.60, 6.50 (2 H, AB q, H-5, 6), 5.55 (1 H, m, H-2), 4.20 (4 H, m, H-3 and CH_2Me), 3.25 (2 H, m, H-1), 2.45 (3 H, s, Ar-Me), and 1.25 (3 H, t, *J* 7 Hz, Me); *m/e* 349 (M^+, 8), 304 (10), 191 (12), 177 (100), 149 (30), 132 (32), 104 (70), and 91 (35%) (Found: C, 58.6; H, 5.3; N, 4.0; S, 9.4. $C_{17}H_{19}NO_5S$ requires C, 58.5; H, 5.4; N, 4.0; S, 9.2%).

Ethyl (−)-(2S)-2-*Formyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (9).—Tetraethylammonium formate (523 mg, 3.0 mmol) was added to a solution of ethyl (+)-(2*R*)-2-tosyloxy-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (174.5 mg, 0.5 mmol) in dry acetone (10 ml), and the mixture was stirred at room temperature for 24 h. The solvent was removed, and water was added to the residue. This mixture was extracted with chloroform (2 × 20 ml). The chloroform extracts were washed with water (2 × 20 ml) and saturated $NaHCO_3$ (20 ml), dried, filtered, and concentrated to give a brown oil containing one major component, R_F 0.33 ($CHCl_3$–Et_2O; 1 : 1). Preparative t.l.c. afforded *ethyl* (−)-(2S)-2-*formyloxy*-2,3-*dihydro*-1H-*pyrrolizine*-7-*carboxylate* (9) (94 mg, 84%) as needles, m.p. 62—63 °C (Et_2O), $[\alpha]_D^{23}$ −34.2° (*c* 4 in $CHCl_3$) (Found: C, 59.3; H, 6.1; N, 6.2. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.8; N, 6.3%). The i.r., u.v., n.m.r., and mass spectra were identical to those of the enantiomer (2).

Ethyl (−)-6β-*Hydroxy*-8α-*pyrrolizidine*-1β-*carboxylate* (10).—This was prepared from ethyl (−)-(2S)-formyloxy-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (9) as described for the preparation of the corresponding (+)-enantiomer (4) from (2). *Ethyl* (−)-6β-*hydroxy*-8α-*pyrrolizidine*-1β-*carboxylate* (10) was obtained as needles, m.p. 109.5—110 °C, $[\alpha]_D^{18}$ −72.1° (*c* 4 in $CHCl_3$) (Found: C, 60.5; H, 8.4; N, 6.9. $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.5; N, 7.0%). The i.r., n.m.r., and mass spectra were identical to those of the enantiomer (4).

(−)-*Isoretronecanol* (12), (−)-*Trachelanthamidine* (13), *and* (−)-*Supinidine* (14).—These bases were synthesized from (10) by exactly the same procedure as described for the corresponding (+)-stereoisomers from (4). (−)-Isoretronecanol had $[\alpha]_D^{18}$ −70.9° (*c* 2 in EtOH) {lit.,[15] $[\alpha]_D^{27}$ −78.2° (*c* 2.8 in EtOH)}. The picrate had m.p. 193—194 °C (EtOH) (lit.,[15] m.p. 194—195 °C) (Found: C, 45.5; H, 5.0; N, 15.0. Calc. for $C_{14}H_{18}N_4O_8$: C, 45.4; H, 4.9; N, 15.1%).

(−)-Trachelanthamidine (13) had $[\alpha]_D^{18}$ −13.5° (*c* 2 in EtOH) {lit.,[16] $[\alpha]_D$ −13.8° (*c* 1.28 in EtOH)}. The picrate had m.p. 175—176 °C (lit.,[16] m.p. 178—179 °C) (Found: C, 45.6; H, 4.7; N, 14.8. Calc. for $C_{14}H_{18}N_4O_8$: C, 45.4; H, 4.9; N, 15.1%).

(−)-Supinidine (14) had $[\alpha]_D^{18}$ −8.3° (*c* 2 in EtOH) {lit.,[17] $[\alpha]_D^{18}$ −10.3° (*c* 1.65 in EtOH)}. The picrate had m.p. 143—144 °C (lit.,[17] m.p. 144 °C) (Found: C, 45.5; H, 4.5; N, 15.1. Calc. for $C_{14}H_{16}N_4O_8$: C, 45.7; H, 4.4; N, 15.2%).

The mixed m.p. with an authentic sample of (−)-supinidine picrate was undepressed.

(+)-6α-*Hydroxy*-1α-*hydroxymethyl*-8β-*pyrrolizidine* (15).—Ethyl (+)-6α-hydroxy-8β-pyrrolizidine-1α-carboxylate (4) was reduced in analogous fashion to that described for reduction of (5) ⟶ (6) to give (+)-6α-hydroxy-1α-hydroxymethyl-8β-pyrrolizidine (15) in 89% yield as an oil, R_F 0.04, $[\alpha]_D^{18}$ +68.2° (*c* 4 in MeOH); $\nu_{max.}$ (film) 3 350 cm^{-1}; δ (CD_3OD) 4.80 (2 H, br s, OH), 4.30 (1 H, m, H-6), 3.62 (2 H, d, *J* 7 Hz, H-9), and 3.50—1.20 (10 H, complex); *m/e* 157 (M^+, 30), 156 (25), 140 (20), 113 (40), 106 (40), 99 (55), and 82 (100%). The *picrate* had m.p. 151—152 °C (EtOH) (Found: C, 43.2; H, 4.6; N, 14.3. $C_{14}H_{18}N_4O_9$ requires C, 43.5; H, 4.9; N, 14.5%).

Ethyl (+)-6α-*Hydroxy*-1-*phenylseleno*-8β-*pyrrolizidine*-1-*carboxylate*.—This was prepared from the ethyl ester (4) as described for the corresponding 6-deoxy-compound (5) to give *ethyl* (+)-6α-*hydroxy*-1-*phenylseleno*-8β-*pyrrolizidine*-1-*carboxylate* as a pale yellow oil (60%), R_F 0.45, $[\alpha]_D^{18}$ +36.9° (*c* 4 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 720, and 1 580 cm^{-1}; δ 7.50 (5 H, m, Ph), 4.40 (1 H, m, H-6), 4.10 (2 H, m, CH_2Me), 3.80—1.80 (10 H, complex), and 1.20 (3 H, m, Me); *m/e* 355 (M^+, 24), 198 (40), 197 (24), 158 (28), 154 (33), 152 (30), 106 (40), and 99 (100%) (Found: M^+, 355.073 02. $C_{16}H_{21}NO_3Se$ requires *M*, 355.073 10).

(−)-6α-*Hydroxy*-1-*hydroxymethyl*-1-*phenylseleno*-8β-*pyrrolizidine*.—Reduction of the phenylseleno ester was performed as stated for the corresponding 6-deoxy-compound to give (−)-6α-*hydroxy*-1-*hydroxymethyl*-1-*phenylseleno*-8β-*pyrrolizidine* (58%), R_F 0.17, m.p. 148—150 °C ($CHCl_3$); $[\alpha]_D^{18}$ −32.1° (*c* 5 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 400 and 1 580 cm^{-1}; δ 7.50 (5 H, m, Ph), 4.50 (1 H, m, H-6), 4.15 (2 H, s, H-9), and 3.75—1.20 (11 H, complex); *m/e* 313 (M^+, 10), 155 (50), 139 (20), 112 (30), and 99 (100%) (Found: C, 53.7; H, 6.1; N, 4.3. $C_{14}H_{19}NO_2Se$ requires C, 53.9; H, 6.1; N, 4.5%).

(−)-6α-*Acetoxy*-1-*acetoxymethyl*-5,6,7,8-*tetrahydro*-3H-*pyrrolizine* (16).—Ethyl (−)-6α-hydroxy-1-hydroxymethyl-

1-phenylseleno-8β-pyrrolizidine was acetylated with acetic anhydride in pyridine at room temperature for 16 h. The crude diacetate was obtained by removal of excess reagents, and was then oxidised as described for the corresponding unacetylated 6-deoxy-compound. Preparative t.l.c. of the yellow oil gave the major component as a pale yellow oil (63%), R_F 0.32, $[\alpha]_D^{18}$ −45.0° (*c* 5 in $CHCl_3$); $\nu_{max.}$ (CCl_4) 1 750 and 1 230 cm^{-1}; δ 5.75 (1 H, m, H-2), 5.50 (1 H, m, H-6), 4.65 (2 H, s, H-9), 4.60—4.20 (5 H, complex), 3.90—2.90 (2 H, m, H-7), 2.08 (3 H, s, Me), and 2.00 (3 H, s, Me); *m/e* 239 (M^+, 3), 155 (25), 112 (25), 111 (75), 94 (30), 93 (25), and 80 (100%). The *picrate* had m.p. 115—117 °C (EtOH) (Found: C 46.1; H 4.2; N, 12.0. $C_{18}H_{20}N_4O_{11}$ requires C, 46.2; H, 4.3; N, 12.0%).

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