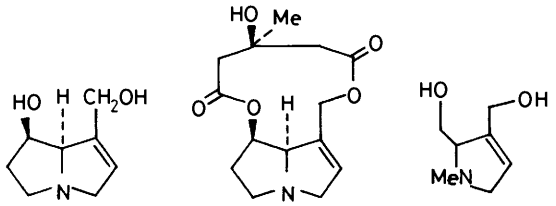
Pyrrolizidine Alkaloid Analogues. Synthesis of Macrocyclic Diesters of (+)-(1*R*,6*R*,8*R*)-6-Hydroxy-1-hydroxymethylpyrrolizidine

Henry A. Kelly and David J. Robins *
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Macrocyclic diesters of (+)-(1*R*,6*R*,8*R*)-6-hydroxy-1-hydroxymethylpyrrolizidine have been synthesized in optically active form. The pyrrolizidinediol (**7**) was prepared from (2*S*,4*R*)-4-hydroxyproline (**4**) and then esterified with different glutaric anhydride derivatives to yield mainly the corresponding 9-mono esters. Lactonisation was achieved under high dilution conditions after formation of the *S*-2-pyridyl thio esters to give a range of 12-membered macrocyclic diesters [(**9**)—(**14**)] of (+)-(1*R*,6*R*,8*R*)-6-hydroxy-1-hydroxymethylpyrrolizidine. Similar treatment of the diol (**7**) with succinic anhydride produced an 11-membered system (**15**).

Pyrrolizidine alkaloids occur in a number of different plant families[1] and show a broad range of biological activities.[2] In particular, macrocyclic diesters containing (+)-retronecine (**1**), such as dicrotaline (**2**), are a hazard to grazing livestock because of their hepatotoxicity.[3] Pyrrolizidine alkaloids are known with ring sizes of 11—14 containing a range of different base portions (necines). However, syntheses of natural macrocyclic pyrrolizidine alkaloids have been confined to a few 11-membered[4–6] or 12-membered[7–9] compounds containing retronecine. In addition, some alkaloid analogues containing (+)-retronecine (**1**) with 10-[10] and 11-membered rings[11] have been prepared, and the one example tested was shown to possess significant hepatotoxicity.[12] The key structural feature required for this hepatotoxic action is believed to be an allylic ester function occurring as part of a 2,5-dihydropyrrole system, as in dicrotaline (**2**). Dehydrogenation of this dihydropyrrole is carried out by liver oxidase enzymes, and the pyrrole diester then acts as a bifunctional alkylating agent.[3]

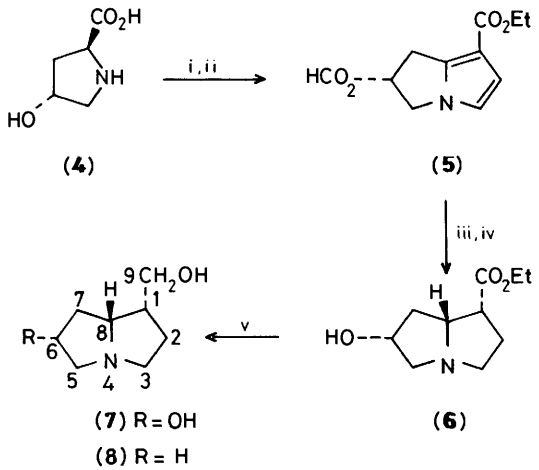


(**1**) (**2**) (**3**)

Pyrrolizidine alkaloids and structural analogues are therefore important synthetic targets for studies of the relationships between their structures and biological activity. For example, a range of macrocyclic diesters incorporating (±)-synthanecine A (**3**)[13] has been prepared and some of these dilactones were shown to produce toxic effects similar to those displayed by natural macrocyclic pyrrolizidine alkaloids.[14] As part of our programme to increase the range of synthetic analogues available for a study of their biological activity, we wished to prepare dilactones incorporating a saturated pyrrolizidinediol. Very few macrocyclic diesters of saturated necine diols occur naturally.[1] The pyrrolizidinediol (**7**) is available in optically active form from (2*S*,4*R*)-4-hydroxyproline (**4**). It was made during the preparation of optically active 1-hydroxymethylpyrrolizidines such as (+)-isoretronecanol (**8**).[15] We therefore sought to prepare a range of macrocyclic diesters incorporating the diol (**7**) in order to provide information about the effect of the double bond in the pyrrolizidine nucleus on the biological activity.

Results and Discussion

The synthesis of (+)-(1*R*,6*R*,8*R*)-6-hydroxy-1-hydroxymethylpyrrolizidine (**7**) was carried out as outlined in the Scheme.[15] (2*S*,4*R*)-4-Hydroxyproline (**4**) was converted into its *N*,*O*-diformyl derivative. This underwent 1,3-dipolar cycloaddition with ethyl propiolate to give the dihydropyrrolizine ester (**5**) after elimination of carbon dioxide. Removal of the formyl protecting group was followed by stereospecific addition of hydrogen to the less hindered β-face of the pyrrole to afford the saturated ester (**6**). It was found that use of Pd/C[15] gave low yields of the ester (**6**) accompanied by decomposition of the starting material. Improved yields were obtained using a Rh/C catalyst, and unchanged starting material (**5**) could be recovered and recycled. Reduction of the saturated ester (**6**) gave the optically active pyrrolizidinediol (**7**).



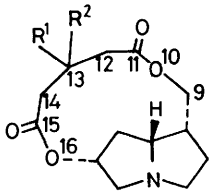
Scheme. *Reagents:* i, Ac_2O, HCO_2H; ii, Ac_2O, $HC{\equiv}CCO_2Et$; iii, NH_3; iv, H_2, Pd/C or Rd/C; v, $LiAlH_4$

Treatment of the pyrrolizidinediol (**7**) with glutaric anhydride in dry 1,2-dimethoxyethane (DME) gave a quantitative yield of the monoester which precipitated from solution. Regioselective esterification at the 9-position of the diol (**7**) was indicated by a downfield shift in the ^1H n.m.r. spectrum of *ca.* 0.5 p.p.m. for the protons at C-9 of the monoester when compared with the spectrum of the diol (**7**). The *S*-2-pyridyl thio ester of

Table. Yields of dilactones and chemical shift differences for the C-9 protons

Dilactone	Yield (%)	Δδ 9-H (p.p.m.)	$J_{1,9}$ Values (Hz) (upfield proton quoted first)	
(**9**)	26	0.47	4.3	1.2
(**10**)	30	0.45	2.2	4.9
(**11**)	41	0.40	2.4	5.2
(**12**)	37	0.39	2.5	5.1
(**13**)	10	0.74	3.9	1.1
(**14**)	21	—	—	—
(**15**)	20	0.82	1.2	3.9

this monoester was prepared by addition of di-2-pyridyl disulphide and triphenylphosphine[16] to a suspension of the monoester in DME. Vigorous stirring produced a homogeneous solution which indicated that formation of the *S*-thio ester was complete. Lactonisation was effected by heating the diluted mixture at reflux in DME for 4 days. The dilactone (**9**) was isolated and purified by preparative silica t.l.c. in 26% yield. An accurate mass measurement of the compound (**9**) gave the molecular formula $C_{13}H_{19}NO_4$ with the major fragment ion at *m/z* 122 ($C_8H_{12}N$), corresponding to loss of the diacyl portion from the dilactone. The i.r. spectrum of the analogue (**9**) displayed ester carbonyl absorption at 1 740 cm^{-1}. In the ^1H n.m.r. spectrum of the diester (**9**), the protons assigned to C-6 and C-9 had both shifted downfield relative to the signals for these protons in the n.m.r. spectrum of the diol (**7**). Moreover, the key feature in the ^1H n.m.r. spectrum of the dilactone (**9**) is an AB system at δ 4.05 and 4.52 (*J* 12.2 Hz) for the diastereotopic protons at C-9, with additional coupling of both protons to the 1-proton (Table). The chemical shift difference for these C-9 protons is thus 0.47 p.p.m. For comparison, the typical range of chemical shift difference values observed for 11-membered diesters of (+)-retronecine is 0—0.9 p.p.m., whereas 12-membered dilactones incorporating (+)-retronecine have higher values of 1.25—1.55 p.p.m.[1]

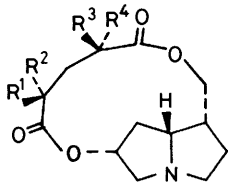


(**9**) $R^1 = R^2 = H$
(**10**) $R^1 = R^2 = Me$
(**11**) R^1, $R^2 = (CH_2)_4$
(**12**) R^1, $R^2 = (CH_2)_5$

Although use of bis(4-t-butyl-1-isopropylimidazol-2-yl) disulphide[17] in place of di-2-pyridyl disulphide failed to improve the yield of dilactone (**9**) substantially, lactonisation was complete more quickly (1 day instead of 4). However, since purification of the lactonised product was more difficult because of the different by-products, this reagent was not used for further lactonisations.

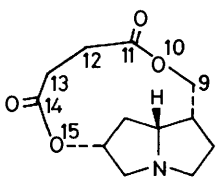
When the (+)-diol (**7**) was treated with 3,3-dimethylglutaric anhydride, 3,3-tetramethyleneglutaric anhydride, and 3,3-pentamethyleneglutaric anhydride, three more macrocyclic diesters (**10**)—(**12**) were produced in moderate yields (Table) as solids which were difficult to crystallise. Lactonisation was effected *via* the *S*-2-pyridyl thio esters and was complete in 2 days. Substituents at the 3-positions of the glutarate moiety are believed to restrict the number of rotational degrees of freedom of the thio ester chains and promote more rapid lactonisation.[18] The three new dilactones (**10**)—(**12**) all gave mass spectra with the major peak at *m/z* 122, and with similar fragmentation patterns to compound (**9**). The chemical shift differences for the C-9 protons for the three cyclic diesters (**10**)—(**12**) and the coupling constants between the 1- and 9-protons are similar (Table). However, these values differ from those for the glutarate diester (**9**), indicating that it may have a different conformation in the macrocyclic portion.

It was considered important to prepare macrocyclic diesters with substituents at the α-positions of the diacid moiety to increase the steric hindrance around the ester groups. With macrocyclic pyrrolizidine alkaloids and analogues, this α-substitution has been shown to enhance the toxicity of the compounds by reducing the extent to which they are detoxified by acidic or enzymic hydrolysis.[12,14] Treatment of the (+)-diol (**7**) with 2,2-dimethylglutaric anhydride produced a single lactonised product (**13a**) or (**13b**), judged by ^{13}C n.m.r. spectroscopic data, as an oil in low yield (Table). The formation of a single product may be due to selective anhydride cleavage (this could occur at the more highly substituted carbonyl group because of the approach trajectory of the nucleophile[19]), or it may be due to preferential lactonisation of the less hindered *S*-2-pyridyl thio ester, both making the dilactone (**13a**) the more likely product. Lactonisation of *meso*-2,4-dimethylglutaric anhydride with the (+)-diol (**7**) *via* the *S*-2-pyridyl thio esters gave a mixture of two diastereoisomers (**14**) in a 1:1 ratio as judged from their ^{13}C n.m.r. spectra. These diastereoisomers could not be separated by chromatography; characterisation data were therefore obtained for the mixture (**14**).



(**13**) **a**; $R^1 = R^2 = H$, $R^3 = R^4 = Me$
b; $R^1 = R^2 = Me$, $R^3 = R^4 = H$
(**14**) **a**; $R^1 = R^3 = H$, $R^2 = R^4 = Me$
and $R^1 = R^3 = Me$, $R^2 = R^4 = H$

Finally, a macrocyclic diester of the (+)-diol (**7**) containing an 11-membered ring was prepared. Treatment of the (+)-diol (**7**) with succinic anhydride produced mainly the 9-mono ester. Lactonisation as before yielded the succinate diester (**15**) as an oil. The i.r. and mass spectral data for this compound were similar to the rest of the dilactones (**9**)—(**14**) prepared. In the ^1H n.m.r. spectrum of the 10-membered analogue (**15**), the largest



(**15**)

chemical shift difference for the C-9 protons of all the lactones prepared in this work was observed (Table).

The different chemical shift differences observed for the C-9 protons of the new pyrrolizidine alkaloid analogues (**9**)—(**15**)

probably reflect the different conformations of the diacid portions in these macrocyclic systems. It is known from *X*-ray crystallographic data that 11-membered macrocyclic diesters of (+)-retronecine (**1**) generally have ester carbonyl groups that are *syn*-parallel, whereas 10- and 12-membered diesters of retronecine have ester carbonyl groups that are *anti*-parallel.[1,2] Attempts will be made to establish the conformations of some of these new analogues by *X*-ray crystallography. These conformations may have an important bearing on the biological activity of the dilactones.

Experimental

M.p.s were measured with a Kofler hot-stage apparatus and are uncorrected. Organic solutions were dried with anhydrous $MgSO_4$ and evaporated under reduced pressure <40 °C. N.m.r. spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as the internal standard on a Bruker WP-200SY spectrometer operating at 200 MHz unless otherwise stated. Mass spectra were obtained with A.E.I. MS 12 or 902 spectrometers. Optical rotations were measured with an Optical Activity Ltd. AA-10 Polarimeter. T.l.c. of the bases was carried out on Kieselgel G plates of 0.25 mm thickness developed with chloroform–methanol–conc. ammonia (85:14:1). The location of the bases was determined by oxidation with *o*-chloranil, followed by treatment with Ehrlich's reagent.[20] 1,2-Dimethoxyethane (DME) was dried by distillation from potassium hydroxide and then from sodium and benzophenone under argon immediately prior to use.

Ethyl (+)-(1R,6R,8R)-6-*Hydroxypyrrolizidine*-1-*carboxylate* (**6**).—A solution of ethyl (+)-(2*R*)-2-hydroxy-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate[15] (5 g, 25 mmol) in acetic acid (75 ml) was hydrogenated at 7 atm for 24 h at 60 °C using 10% Rh–C (1 g) as catalyst. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to give an oil. The oil was taken up in 1M HCl (16 ml) and washed with chloroform (2 × 25 ml). The aqueous solution was basified with conc. ammonia solution and extracted with chloroform (3 × 30 ml). The chloroform extracts were dried, filtered, and concentrated. The product was obtained as white crystals from ethyl acetate, (2.1 g, 47%), m.p. 109 °C (lit.,[15] m.p. 109—110 °C). The chloroform washings were dried, filtered, and concentrated to yield unchanged starting material (1.9 g, 38%).

(+)-(1R,6R,8R)-6-*Hydroxy*-1-*hydroxymethylpyrrolizidine* (**7**).—This compound was prepared as before[15] and had δ_C(25 MHz; CD_3OD) 27.6 (C-2), 33.7 (C-7), 45.6 (C-1), 55.2 (C-3), 62.9 and 63.4 (C-5 and -9), 65.8 (C-8), and 73.1 p.p.m. (C-6). The *picrolonate* had m.p. 171—172 °C (decomp.) (Found: C, 51.2; H, 5.55; N, 16.35. $C_{18}H_{23}N_5O_7$ requires C, 51.3; H, 5.50; N, 16.61%).

Synthesis of 12-*Membered Macrocyclic Diesters of* (+)-(1R,6R,8R)-6-*Hydroxy*-1-*hydroxymethylpyrrolizidine* (**7**): *General Procedure*.—Glutaric anhydride or a derivative (1.1 mmol) was added to a solution of the optically active diol (**7**) (1 mmol) in dry DME (30 ml) under argon and the reaction mixture was stirred at 40 °C for 1 h; the homogeneous solution was then stirred for 18 h at room temperature to ensure that all the base had reacted to form a zwitterionic monoester (t.l.c., R_F 0.05—0.10). Di-2-pyridyl disulphide (1.5 mmol) and triphenylphosphine (1.5 mmol) were added to the mixture which was then stirred vigorously until thio ester formation was complete (t.l.c., R_F *ca.* 0.65, 24 h). The resultant clear yellow solution was diluted with DME (120 ml) and heated at reflux under argon until lactonisation was complete (t.l.c., R_F 0.35, 1—4 d). The reaction mixture was cooled and then evaporated under reduced pressure to afford a yellow oil. This oil was dissolved in chloroform (10 ml) and extracted with 1M citric acid (4 × 4 ml). The acidic extracts were combined and washed with chloroform (6 × 20 ml) and then basified with concentrated ammonia solution and extracted with chloroform (4 × 25 ml). The chloroform extracts were dried, filtered, and concentrated to give crude cyclised products as yellow oils. Purification was achieved by preparative t.l.c., eluting with chloroform–methanol–conc. ammonia (85:14:1).

(−)-(1R,6R,8R)-6,9-O,O-(*Glutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**9**).—Using glutaric anhydride, the glutarate dilactone (**9**) was obtained as a powder (26% yield), m.p. 79—80 °C (from benzene–hexane); R_F 0.35; $[\alpha]_D^{21}$ −4.1° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 960, 2 930, 2 860, 1 740, 1 330, 1 245, 1 150, and 1 010 cm^{-1}; δ_H(200 MHz) 1.70 (2 H, m, 2-H_2), 2.00 (2 H, m, 13-H_2), 2.12 (2 H, m, 7-H_2), 2.40 (1 H, m, 1-H), 2.45 (4 H, m, 12- and 14-H_2), 3.00—3.40 (4 H, m, 3- and 5-H_2), 3.75 (1 H, m, 8-Hβ), 4.05 (1 H, dd, *J* 12.2 Hz and 4.3 Hz, 9-H), 4.52 (1 H, dd, *J* 12.2 Hz and 1.2 Hz, 9-H), and 5.11 (1 H, m, 6-Hβ); δ_C(50 MHz) 20.0 (C-13), 28.9 (C-2), 33.1 (C-7), 34.5 and 35.1 (C-12 and -14), 40.1 (C-1), 54.3 (C-3), 58.6 and 61.1 (C-5 and -9), 65.0 (C-8), 76.4 (C-6), and 172.2 and 172.5 p.p.m. (C-11 and -15); *m/z* (M^+, 19%), 140, 138, 122 (100%), 121, 120, 110, 109, 108, 82, 81, 80, 69, and 55 (Found: M^+, 253.1315; C, 61.45; H, 7.55; N, 5.35. $C_{13}H_{19}NO_4$ requires *M*, 253.1314; C, 61.64; H, 7.56; N, 5.53%).

(−)-(1R,6R,8R)-6,9-O,O-(3,3-*Dimethylglutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**10**).—The above procedure was repeated using 3,3-dimethylglutaric anhydride to give the title compound (**10**) (30% yield) as a non-crystalline solid, m.p. 84 °C (from benzene–hexane); R_F 0.35; $[\alpha]_D^{15}$ −11° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 955, 2 920, 2 870, 2 850, 1 735, 1 325, 1 170, and 1 145 cm^{-1}; δ_H(200 MHz) 1.27 (6 H, s, 17- and 18-H_3), 1.72 (2 H, m, 2-H_2), 1.98 (2 H, m, 7-H_2), 2.13 and 2.61 (2 H, AB, *J* 13.6 Hz, 12-H_2 or 14-H_2), 2.24 and 2.27 (2 H, AB, *J* 15.3 Hz, 12-H_2 or 14-H_2), 2.42 (1 H, m, 1-H), 2.90 (2 H, complex, 3- and 5-H), 3.15 (1 H, m, 3-H), 3.35 (1 H, dd, *J* 13.5 Hz and 4.5 Hz, 5-Hβ), 3.73 (1 H, m, 8-Hβ), 4.03 (1 H, dd, *J* 12.1 Hz and 2.2 Hz, 9-H), 4.48 (1 H, dd, *J* 12.1 Hz and 4.9 Hz, 9-H), and 4.98 (1 H, t, *J* 4.8 Hz, 6-Hβ); δ_C(50 MHz) 28.3 (C-2), 29.4 and 30.5 (C-17 and -18), 33.3 (C-13), 33.7 (C-7), 41.6 (C-1), 44.7 and 44.8 (C-12 and -14), 56.2 (C-3), 62.2 and 62.8 (C-5 and -9), 65.4 (C-8), 75.8 (C-6), and 171.3 and 171.8 p.p.m. (C-11 and -15); *m/z* 281 (M^+, 20%), 140, 138, 122 (100%), 121, 120, 82, 81, 80, and 55 (Found: M^+, 281.1634; C, 64.00; H, 8.31; N, 4.73. $C_{15}H_{23}NO_4$ requires *M*, 281.1627; C, 64.03; H, 8.24; N, 4.98%).

(−)-(1R,6R,8R)-6,9-O,O-(3,3-*Tetramethyleneglutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**11**).—The title compound (**11**) was prepared (41% yield) as a powdered solid when 3,3-tetramethyleneglutaric anhydride and the pyrrolizidinediol (**7**) were treated as described in the general procedure; m.p. 90—91 °C (from benzene–hexane); R_F 0.35; $[\alpha]_D^{21}$ −26° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 960, 2 920, 2 870, 2 850, 1 730, 1 155, 1 135, and 1 120 cm^{-1}; δ_H(200 MHz) 1.66 (8 H, m, 17-, 18-, 19-, and 20-H_2), 1.72 (2 H, m, 2-H_2), 2.00 (2 H, m, 7-H_2), 2.22 and 2.59 (2 H, AB, *J* 13.6 Hz, 12-H_2 or 14-H_2), 2.29 and 2.35 (2 H, AB, *J* 15.2 Hz, 12-H_2 or 14-H_2), 2.42 (1 H, m, 1-H), 2.91 (2 H, complex, 3- and 5-H), 3.15 (1 H, m, 3-H), 3.35 (1 H, dd, *J* 13.5 Hz and 4.8 Hz, 5-Hβ), 3.73 (1 H, m, 8-Hβ), 4.05 (1 H, dd, *J* 12.1 Hz and 2.4 Hz, 9-H), 4.45 (1 H, dd, *J* 12.1 Hz and 5.2 Hz, 9-H), and 5.10 (1 H, t, *J* 5 Hz, 6-Hβ); δ_C(50 MHz) 23.2 and 24.0 (C-18 and -19), 28.6 (C-2), 33.6 (C-7), 38.9 and 39.4 (C-17 and -20), 41.7 (C-1), 42.8 and 43.2 (C-12 and -14), 44.1 (C-13), 56.1 (C-3), 62.1 and 62.8 (C-5 and -9), 65.8 (C-8), 76.0 (C-6), and 171.6 and 172.1 p.p.m. (C-11 and -15); *m/z* 307 (M^+, 8%), 122 (100%), 121, 120, 108, 82, 81, 80, and 55 (Found: M^+, 307.1787; C, 66.6; H, 8.27; N, 4.40. $C_{17}H_{25}NO_4$ requires *M*, 307.1783; C, 66.4; H, 8.20; N, 4.56%).

(−)-(1R,6R,8R)-6,9-O,O-(3,3-*Pentamethyleneglutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**12**).—When the base (**7**) was treated with 3,3-pentamethyleneglutaric anhydride by the standard procedure, the title compound (**12**) was obtained (37% yield); m.p. 97—98 °C (from benzene–hexane); R_F 0.35; $[\alpha]_D^{18}$ −15° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 930, 2 855, 1 730, 1 450, 1 330, and 1 165 cm^{-1}; δ_H(200 MHz), 1.44 (10 H, m, 17-, 18, 19-, 20-, and 21-H_2), 1.73 (2 H, m, 2-H_2), 2.00 (2 H, m, 7-H_2), 2.12 and 2.44 (2 H, AB, *J* 15.3 Hz, 12-H_2 or 14-H_2), 2.30 and 2.50 (2 H, AB, *J* 13.6 Hz, 12-H_2 or 14-H_2), 2.45 (1 H, m, 1-H), 2.87 (1 H, m, 5-H), 2.89 (1 H, m, 3-H), 3.12 (1 H, m, 3-H), 3.35 (1 H, dd, *J* 13.4 Hz and 4.5 Hz, 5-Hβ), 3.70 (1 H, m, 8-Hβ), 4.05 (1 H, dd, *J* 12.1 Hz and 2.5 Hz, 9-H), 4.44 (1 H, dd, *J* 12.1 Hz and 5.1 Hz, 9-H), and 4.98 (1 H, t, *J* 4.8 Hz, 6-Hβ); δ_C(50 MHz) 21.3 and 21.4 (C-18 and -20), 25.7 (C-19), 28.4 (C-2), 33.7 (C-7), 36.0 (C-13), 36.6 and 38.0 (C-17 and -21), 41.8 (C-1), 42.1 and 42.5 (C-12 and -14), 56.2 (C-3), 62.3 and 62.8 (C-5 and -9), 65.5 (C-8), 75.7 (C-6), and 171.5 and 171.9 p.p.m. (C-11 and -15); *m/z* 321 (M^+ 19%), 122 (100%), 121, 120, 95, 82, 81, 80, 68, 67, and 55 (Found: M^+, 321.1925; C, 67.3; H, 8.4; N, 4.2. $C_{18}H_{27}NO_4$ requires *M*, 321.1935; C, 67.26; H, 8.47; N, 4.36%).

(−)-(1R,6R,8R)-6,9-O,O-(2,2-*Dimethylglutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**13a**) *or* (**13b**).—Treatment of 2,2-dimethylglutaric anhydride as described in the general procedure afforded the title compound (**13a**) or (**13b**) (10% yield), as an oil, R_F 0.35; $[\alpha]_D^{20}$ −19° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 960, 2 920, 2 890, 2 870, 1 735, 1 295, 1 270, 1 140, and 1 120 cm^{-1}; δ_H(200 MHz) 1.24 and 1.27 (3 H, s, 17-H_3 or 18-H_3), 1.78 (2 H, m, 2-H_2), 1.90—2.45 (6 H, m, 7-, 13- and 14-H_2), 2.57 (1 H, m, 1-H), 2.95—3.13 (3 H, m, 3-H_2 and 5-H), 3.20 (1 H, dd, *J* 13.4 Hz and 4.8 Hz, 5-Hβ), 3.77 (1 H, m, 8-Hβ), 3.87 (1 H, dd, *J* 12.1 Hz and 3.9 Hz, 9-H), 4.61 (1 H, dd, *J* 12.1 Hz and 1.1 Hz, 9-H), and 5.05 (1 H, m, 6-H); δ_C(50 MHz) 24.4 and 27.1 (C-17 and -18), 28.6 (C-2), 30.8 (C-13), 33.2 (C-12 or -14), 34.9 (C-7), 40.1 (C-1), 41.6 (C-12 or -14), 53.8 (C-3), 58.3 and 63.5 (C-5 and -9), 64.7 (C-8), 78.1 (C-6), and 172.7 and 176.5 p.p.m. (C-11 and -15); *m/z* 281 (M^+, 11%), 122 (100%), 121, 120, 108, 82, 81, 80, 69, 68, and 55 (Found: M^+, 281.1632. $C_{15}H_{23}NO_4$ requires *M*, 281.1627).

(−)-(1R,6R,8R)-6,9-O,O-(meso-2,4-*Dimethylglutaryl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**14**).—A mixture of two diastereoisomers (**14**) (R_F 0.30—0.35) was obtained when the optically active pyrrolizidine diol (**7**) was treated with *meso*-2,4-dimethylglutaric anhydride as described in the standard procedure (21% yield); $\nu_{max.}(CCl_4)$ 2 960, 2 930, 2 870, 1 730, 1 260, and 1 165 cm^{-1}; δ_H(200 MHz) 1.10—1.20 (6 H, 2d, *J* 7.1 Hz, 17- and 18-H_3), 1.31 and 1.38 (2 H, t, *J* 2.7 Hz, 13-H_2), 1.72—2.20 (6 H, complex, 2-H_2, 7-H_2, 12-H and 14-H), 2.45 (1 H, m, 1-H), 2.95—3.30 (4 H, m, 3- and 5-H_2), 3.75 (1 H, m, 8-Hβ), 4.05—4.45 (2 H, m, 9-H_2), and 5.00 (1 H, m, 6-H); δ_C(50 MHz) 17.5, 18.0, 19.5 and 19.7 (C-17 and -18), 28.7 and 29.0 (C-2), 33.6 and 33.8 (C-7), 36.6 and 37.5 (C-12 and -14), 37.9 and 38.0 (C-13), 40.0 and 40.2 (C-1), 55.0 and 55.8 (C-3), 61.4, 63.3, 63.4 and 63.6 (C-5 and -9), 64.7 and 65.7 (C-8), 76.4 and 76.7 (C-6), and 174.9, 175.2, 175.5 and 176.1 p.p.m. (C-11 and -15); *m/z* 281 (M^+, 11%), 122 (100%), 121, 120, 108, 82, 81, 80, 68, and 55 (Found: M^+, 281.1630. $C_{15}H_{23}NO_4$ requires *M*, 281.1627).

(+)-(1R,6R,8R)-6,9-O,O-(*Succinyl*)-6-*hydroxy*-1-*hydroxymethylpyrrolizidine* (**15**).—The title compound (**15**) was prepared (20% yield) as an oil when succinic anhydride was treated with the optically active diol (**7**) as described in the general procedure; R_F 0.30; $[\alpha]_D^{20}$ +8° (*c* 3 in MeOH); $\nu_{max.}(CCl_4)$ 2 965, 2 930, 1 745, 1 440, 1 260, and 1 170 cm^{-1}; δ_H(200 MHz) 1.59 (2 H, m, 2-H_2), 1.92 (2 H, m, 7-H_2), 2.35—2.50 (4 H, m, 12- and 13-H_2), 2.56 (1 H, m, 1-H), 2.75—3.10 (3 H, m, 3-H_2 and 5-Hα), 3.35 (1 H, dd, *J* 13.9 Hz and 4 Hz, 5-Hβ), 3.69 (1 H, m, 8-Hβ), 3.90 (1 H, dd, *J* 12.1 Hz and 1.2 Hz, 9-H), 4.72 (1 H, dd, *J* 12.1 Hz and 3.9 Hz, 9-H), and 4.94 (1 H, t, *J* 4.3 Hz, 6-Hβ); δ_C(50 MHz) 27.1 (C-2), 31.4 and 32.4 (C-12 and -13), 34.5 (C-7), 43.1 (C-1), 56.6 (C-3), 61.8 and 62.3 (C-5 and -9), 64.5 (C-8), 76.7 (C-6), and 171.2 and 173.1 p.p.m. (C-11 and -14); *m/z* 239 (M^+, 25%), 154, 122 (100%), 121, 120, 110, 108, 107, 106, 95, 94, 82, 81, 80, and 55 (Found: M^+, 239.1157. $C_{12}H_{17}NO_4$ requires *M*, 239.1158).

Modification of the General Procedure.—Use of Bis(1-*isopropyl*-4-*t-butylimidazol*-2-*yl Disulphide*).[17] (+)-(1*R*,6*R*,8*R*)-6-Hydroxy-1-hydroxymethylpyrrolizidine (**7**) (100 mg, 6.37 mmol) was treated with glutaric anhydride (80 mg, 7.02 mmol) as described in the general procedure, except that bis(1-isopropyl-4-t-butylimidazol-2-yl disulphide) was added instead of di-2-pyridyl disulphide. The solution of the intermediate thio ester in DME was heated at reflux for 24 h only. The cyclised product obtained after the work-up (45 mg, 28%), was identical in all respects with (−)-(1*R*,6*R*,8*R*)-6,9-*O*,*O*-glutaryl-6-hydroxy-1-hydroxymethylpyrrolizidine (**9**) obtained previously.

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