Enantiospecific Synthesis of (+)-Retronecine, (+)-Crotonecine, and Related Alkaloids

J. Grant Buchanan,* Veerappa B. Jigajinni, Gurdial Singh, and Richard H. Wightman*
Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS

Reaction of 2,3-*O*-isopropylidene-D-ribose (**8**) with diallylzinc gave a triol, which on treatment with periodate was converted into 5,6,7-trideoxy-2,3-*O*-isopropylidene-L-*ribo*-hept-6-enofuranose (**10**) (86%). Reaction with hydroxylamine hydrochloride in pyridine gave an oxime (**11**), which was treated with methanesulphonyl chloride in pyridine to yield 5,6,7-trideoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-L-*ribo*-hept-6-enononitrile (**12**) (87% overall). Reduction with lithium aluminium hydride and cyclisation followed by treatment with benzyl chloroformate gave (2*R*,3*S*,4*R*)-2-allyl-1-benzyloxycarbonyl-3,4-isopropylidenedioxypyrrolidine (**14**), which on oxidation and subsequent reaction with diazomethane yielded (2*R*,3*S*,4*R*)-methyl (1-benzyloxycarbonyl-3,4-isopropylidenedioxypyrrolidin-2-yl)acetate (**15b**) (35%).

A higher-yielding route to diester (**15b**) proceeded from 2,3-*O*-isopropylidene-D-erythrose (**17**), which was converted *via* its oxime into 2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-D-erythrononitrile (**19**) (91%). Reaction with methyl bromoacetate and activated zinc, followed by base-catalysed cyclisation, gave (3*S*,4*R*)-methyl (3,4-isopropylidenedioxypyrrolidin-2-ylidene)acetate (**21**) (78%), which with cyanoborohydride followed by *N*-acylation produced compound (**15b**) (87%).

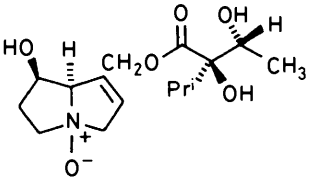
Treatment of diester (**15b**) with acid produced a γ-lactone (**23**), which was deoxygenated *via* its *O*-thiocarbonylimidazolide (**24**). Hydrogenolysis yielded (1*R*,5*R*)-2-oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride (**6**) (69% overall), which can be converted by known methods into (+)-retronecine (**5**) and other pyrrolizidine alkaloids.

(1*S*,5*R*,8*R*)-Ethyl 8-hydroxy-3-oxo-2-oxa-6-azabicyclo[3.3.0]octane-6-carboxylate (**28**) was converted into its silyl ether (**29**), which underwent Dieckmann cyclisation to the pyrrolizidine (**31**), which is convertible by known methods into (+)-crotanecine (**7**).

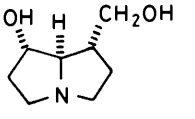
The pyrrolizidine alkaloids[1] continue to attract considerable synthetic attention as a result of both the inherent synthetic challenge of these compounds and their potent biological effects. Ingestion of these alkaloids has resulted in heavy loss of livestock as a result of their hepatotoxic properties, and they can constitute a hazard to humans.[2] On the other hand it has been recognised for some years that certain compounds of this class possess antitumour activity, and in particular indicine *N*-oxide (**1**) is currently undergoing clinical trials as an antitumour agent.[3]

Recent years have seen elegant synthetic routes to pyrrolizidine bases in racemic form,[4] but, increasingly, attention has been directed towards enantiospecific routes to these compounds. After initial work on simple pyrrolidizidine alcohols,[5] chiral syntheses have been reported for the pyrrolizidine diols (+)-hastanecine (**2**) and its enantiomer,[6,7] and (−)-heliotridine (**3**),[7] whilst (+)-hastanecine (**2**), (+)-heliotridine, and a number of other pyrrolizidine diols have been prepared from a common intermediate.[8] The triol (−)-rosmarinecine (**4**) has been prepared enantiospecifically.[9] As regards (+)-retronecine (**5**), the most widely distributed necine base and the heterocyclic component of indicine *N*-oxide (**1**), enantiospecific syntheses have been reported starting from 4-hydroxy-L-proline,[10] and, since our preliminary report,[11] from D-glucose,[12] from L-tartaric acid,[13] and from both (*S*)-(−)-[8] and (*R*)-(+)-malic acid.[14]

We now describe two routes for the synthesis of retronecine (**5**) from carbohydrate precursors, both of which converge on the key intermediate (1*R*,5*R*)-2-oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride (**6**; the 'Geissman–Waiss lactone'). This lactone was first prepared in racemic form during the original total synthesis of retronecine,[15] and it can be converted efficiently[10,15,16] into (+)-retronecine (**5**). Lactone (**6**) can also be used for the synthesis of the pyrrolizidines (−)-platynecine and (+)-croalbinecine,[10] and (+)-retronecine (**5**) can be converted into (+)-heliotridine [enantiomer of (**3**)] by inversion of configuration at C-7.[17] It may be noted that most of the biologically active pyrrolizidine alkaloids are esters of either retronecine or heliotridine, and the $\Delta^{1,2}$ unsaturation seems to be essential for bioactivity.[3] We also report our work on the



(**1**)



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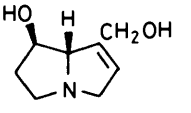
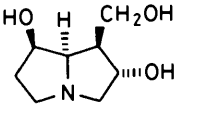
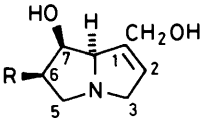


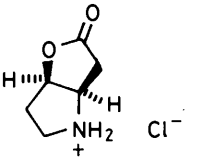
(**3**)



(**4**)



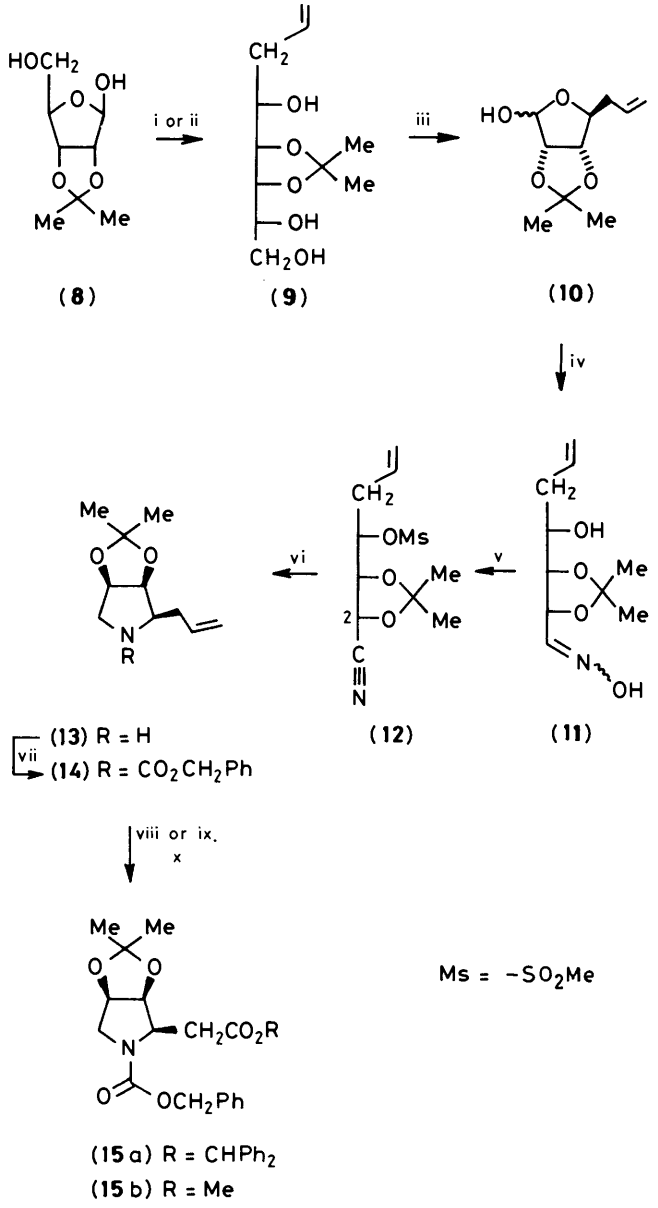
(**5**) R = H
(**7**) R = OH



(**6**)

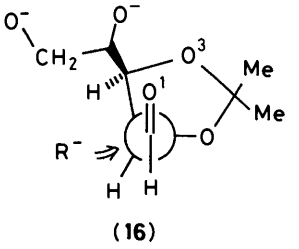
synthesis of the pyrrolizidine triol (+)-crotanecine (**7**);[18] during our studies, Benn and co-workers reported an enantiospecific synthesis of (+)-(**7**) from 4-hydroxyproline, which served to confirm both the structure and the previously unknown absolute configuration of crotanecine.[19]

Our first route to retronecine (**5**) used D-ribose as starting material. The 2,3-*O*-isopropylidene derivative of ribose, compound (**8**),[20] was treated with excess of allylmagnesium bromide to give the triol (**9**) in quantitative yield (Scheme 1).



Scheme 1. *Reagents and conditions:* i, CH_2CHCH_2MgBr (10 mol equiv.), THF, 0 °C then room temp.; ii, $(CH_2CHCH_2)_2Zn$ (12 mol equiv.), ether, 0 °C then room temp.; iii, $NaIO_4$; iv, $NH_2OH{\cdot}HCl$ (10 mol equiv.), C_5H_5N; v, excess of $MeSO_2Cl$, C_5H_5N, −23 °C to room temp.; vi, $LiAlH_4$, THF; vii, $PhCH_2OCOCl$, NEt_3, THF; viii, $NaIO_4$, $KMnO_4$, Bu^{t}OH–water; ix, RuO_2, $NaIO_4$, acetone–water; x, Ph_2CN_2 or CH_2N_2

Based on our previous experience of Grignard reactions of (**8**),[21] it was expected that the reaction would proceed with high stereoselectivity in favour of the D-*allo*-triol (**9**). The material produced appeared homogeneous on chromatography. It was treated with periodate to give the heptanose (**10**), which was converted into the oxime (**11**), a mixture of *E*- and *Z*-isomers. On treatment with methanesulphonyl chloride in pyridine, the oxime underwent dehydration, as well as formation of the *O*-mesyl derivative of the secondary alcohol, to give the nitrile methanesulphonate (**12**); all these reactions proceeded in high yield. However, when compound (**12**) was examined by high-field ^1H n.m.r. spectroscopy, it was clear that a mixture of stereoisomers was present in the ratio *ca.* 3:1, as evidenced most clearly by the appearance of two doublets at δ 4.95 (major) and 4.75 (minor) due to the protons at C-2 in the two isomers. It thus appeared that the Grignard reaction had been less stereoselective than expected from precedents.[21] The stereoselectivity could be much increased by the use of diallylzinc, which has been shown to add to similar systems with high diastereoselectivity;[22] when this reagent was used, and the triol (**9**) formed was processed as described above, the nitrile (**12**) produced was almost entirely ≤25:1) one isomer. The assignment of *S*-chirality at the newly formed chiral centre was not rigorously proved at this point but follows from subsequent correlations described below. The stereoselectivity in the formation of diol (**9**) can be rationalised in terms of reaction proceeding predominantly *via* the Felkin–Anh model[23] for the transition state, as indicated in structure (**16**); the increased selectivity found for the zinc reagent may reflect a greater tendency for zinc to form a β-chelate between O^1 and O^3, leading to a synergistic effect.

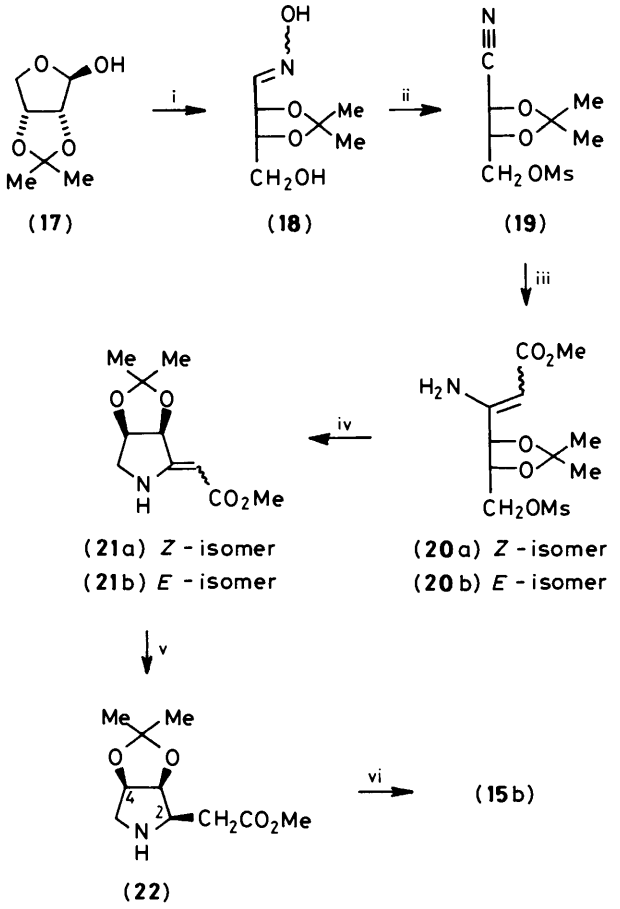


(**16**)

When the nitrile mesylester (**12**) was reduced with lithium aluminium hydride, the somewhat unstable pyrrolidine (**13**) was obtained in 70% yield, and was converted into its benzyloxycarbonyl derivative (**14**). This material had spectroscopic properties in agreement with the proposed structure, but the ^1H n.m.r. spectrum clearly indicated the presence of two rotamers about the amide bond. Compounds (**13**) and (**14**) should have an all-*cis* arrangement of substituents around the pyrrolidine ring if intramolecular displacement of the mesyloxy group occurs with inversion of configuration. At this point we wished to cleave the alkene double bond oxidatively to generate a carboxymethyl side chain. This could be accomplished with either permanganate–periodate[24] or ruthenium salts[25] followed by esterification with diazomethane or diazodiphenylmethane, but the yields of esters (**15a,b**) were invariably low (~30%). Ozonolysis was equally unpromising, and work on this route was discontinued in favour of a more high-yielding sequence which had been developed in parallel.

This alternative route (Scheme 2) used 2,3-*O*-isopropylidene-D-erythrose (**17**) as a chiral starting material. This compound can be prepared from a number of readily available carbohydrates, and a particularly efficient route from D-araboascorbic acid (isoascorbic acid) has been described recently.[26] Although we have employed this method successfully, we found that on the laboratory scale compound (**17**) was conveniently prepared from D-arabinose by kinetic isopropylidenation to give the 3,4-*O*-isopropylidene derivative, as described by Kiso and Hasegawa,[27] followed by periodate cleavage under weakly alkaline conditions.[28]

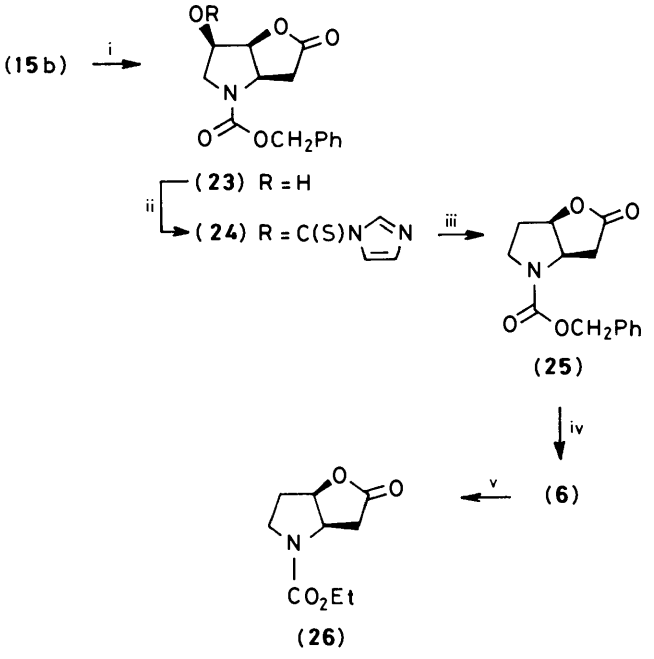
Compound (**17**) was converted into its oxime (**18**), and thence, on treatment with excess of methanesulphonyl chloride in pyridine, into the nitrilemesylester (**19**) in 95% overall yield.



Scheme 2. *Reagents and conditions:* i, NH_2OH·HCl (10 mol quiv.), C_5H_5N, room temp.; ii, $MeSO_2Cl$ (12 mol equiv.), C_5H_5N, −23 °C; iii, activated Zn, $BrCH_2CO_2Me$ (5 mol equiv.), THF, reflux; iv, DBU (3 mol 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.

When nitrile (**19**) was subjected to the recently reported improved procedure[29] for the Blaise reaction, two enamino esters (**20a,b**) were produced in 80% yield. The ratio of the major crystalline isomer to the minor oily product was *ca.* 30:1; the major isomer is tentatively assigned the *Z* stereochemistry (**20a**) based on precedent and n.m.r. evidence.[29,30] Both isomers (**20a**) and (**20b**) could be separately cyclised in high yield the pyrrolidines (**21a**) and (**21b**) respectively, on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and both products (**21a**) and (**21b**) gave the same saturated pyrrolidine (**22**) in 80% yield on treatment with sodium cyanoborohydride in acidified methanol. If one makes the reasonable assumption that reagent approach in this reduction is from the convex side of the substrate, then compound (**22**) should have the substituents on the pyrrolidine ring in an all-*cis* arrangement. Indeed, when the pyrrolidine (**22**) was converted into its *N*-benzyloxycarbonyl derivative, the product was (**15b**), identical in all respects with material prepared as in Scheme 1. This correlation confirms that, in Scheme 1, the addition of the allyl organometallics to 2,3-*O*-isopropylidene-D-ribose (**8**) had occurred with the expected stereoselectivity. Additionally, the ^1H n.m.r. spectrum of compound (**22**) was very similar to that of the corresponding ethyl ester prepared by a different route,[31] but very different from that of the ethyl ester epimeric at C-2.[31]

The stereochemistry of diester (**15b**) was further confirmed when, on treatment with aqueous trifluoroacetic acid, a lactone was produced. I.r. evidence ($\nu_{max.}$ 1 790 cm^{-1}) indicated that the product was the γ-lactone (**23**) (see Scheme 3), although some

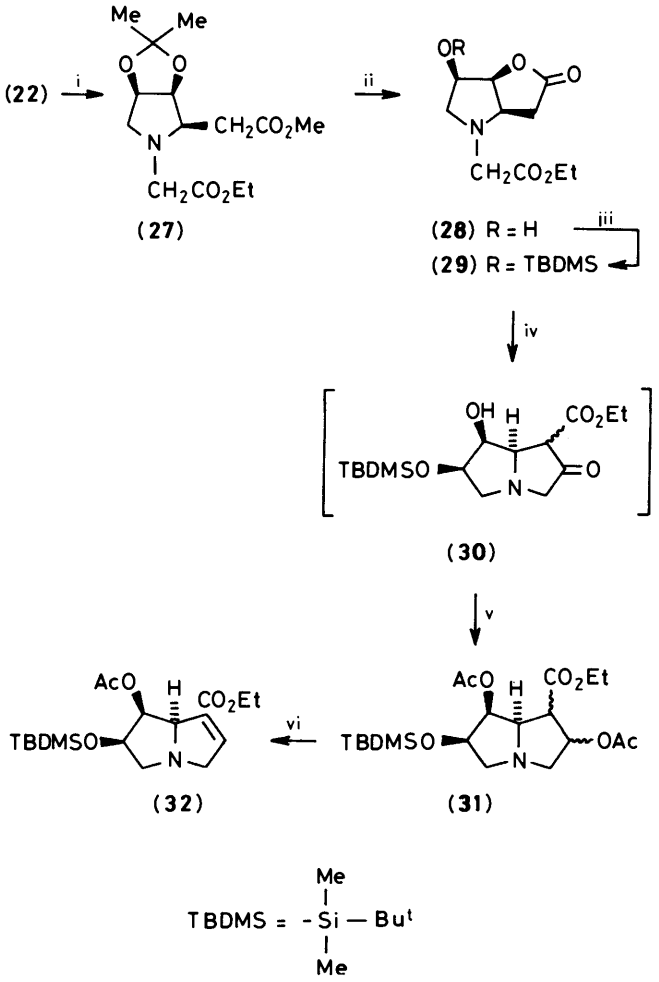


Scheme 3. *Reagents and conditions:* i, 80% CF_3CO_2H, room temp., 18 h; ii, 1,1′-thiocarbonyldi-imidazole, C_5H_5N, THF, reflux; iii, Bu_3SnH (2.2 mol equiv.), C_6H_6, reflux; iv, 10% Pd/C, H_2, EtOH, HCl; v, $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C to room temp.

caution was necessary in view of recent findings in a related system.[32] Alcohol (**23**) was subjected to deoxygenation by formation of the thiocarbonylimidazolide (**24**) and reduction with tri-n-butylstannane[33] to give the lactone (**25**) in 90% overall yield. Hydrogenolysis of compound (**25**) in acidic ethanol gave in 95% yield the Geissman–Waiss lactone as its crystalline hydrochloride (**6**), with physical properties in excellent agreement with those reported,[10] and with spectra in very good agreement with data provided by Professor M. H. Benn. Treatment of our synthetic product (**6**) with ethyl chloroformate and triethylamine gave the urethane (**26**), identical spectroscopically and by t.l.c. with a sample[16] provided by Professor K. Narasaka.

Since lactone (**6**) can be converted *via* Dieckmann cyclisation into (+)-retronecine (**5**)[10,15,16] and other pyrrolizidine alkaloids,[10,17] our work constitutes an enantiospecific route to these compounds.

The routes described above were seen as also giving access to the pyrrolizidine triol (+)-crotanecine (**7**),[18] by annulation of the second ring onto a compound such as (**22**) with retention of the oxygen at C-4. We investigated the feasibility of this using the Dieckmann condensation to form the pyrrolizidine system, as successfully employed[10,15,16] in the conversion of lactone (**6**) into retronecine (**4**). Alkylation of (**22**) with ethyl bromoacetate in the presence of triethylamine gave diester (**27**) in high yield (Scheme 4), but attempts to effect base-catalysed cyclisation of this were unsuccessful under a variety of conditions possibly as a consequence of the steric bulk of the isopropylidene group on the concave side of the molecule. However, when diester (**27**) was converted by acidic hydrolysis into lactone (**28**), and the hydroxy group was subsequently silylated, the silyl ether (**29**) proved more amenable as a substrate for Dieckmann cyclisation. When compound (**29**) was treated with potassium ethoxide in toluene at room temperature, cyclisation occurred; the intermediate keto ester (**30**) was directly reduced with borohydride and the product then acetylated to give a diastereoisomeric mixture of diacetates (**31**) in 40% overall yield. Elimination of acetic acid from compounds (**31**) occurred



Scheme 4. *Reagents and conditions:* i, $BrCH_2CO_2Et$–NEt_3–THF; ii, 80% aqueous TFA, room temp.; iii, Bu^tMe_2SiCl–imidazole–DMF; iv, KOEt–PhMe, room temp., then HOAc; v, $NaBH_4$–EtOH, then Ac_2O–pyridine; vi, DBU–CH_2Cl_2, room temp.

smoothly on treatment with DBU to give unsaturated ester (**32**) in 70% yield. Conversion of compound (**32**) into (+)-crotanecine (**7**) requires reduction of the ester function and deprotection; we have carried out these operations using di-isobutylaluminium hydride as reductant and fluoride ion to desilylate, but the isolation of crotanecine (**7**) in good yield proved problematical. At this stage in our work Benn and co-workers reported a synthesis of (+)-crotanecine (**7**) from (2*S*,4*R*)-4-hydroxyproline;[19] the later stages of this synthesis involved chemistry very similar to our approach, and indeed compounds (**29**), (**30**), and (**31**) were all used as intermediates. Our work, together with that of Benn,[19] thus provides an alternative route to (+)-crotanecine from carbohydrate precusors.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 257 instrument; u.v. spectra were obtained on a Perkin-Elmer 550 spectrometer. Mass spectrometry was performed using an A.E.I. MS 902 instrument. N.m.r. spectra were recorded on Perkin-Elmer R12B, JEOL MH 100, and Bruker WP 200 SY and WH 360 spectrometers with deuteriochloroform as solvent unless otherwise stated. Specific rotations were measured at room temp. on a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.p.s were determined in capillaries and are uncorrected. Adsorption chromatography was carried out using Kieselgel H type 60 (Merck); an external pressure was applied to the top of columns. For t.l.c., precoated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Light petroleum refers to material of b.p. range 40—60 °C. Anhydrous sodium sulphate was used to dry organic extracts. Ether refers to diethyl ether, and hexane refers to a hexane fraction from petroleum, b.p. 67—70 °C.

5,6,7-*Trideoxy*-2,3-O-*isopropylidene*-L-ribo-*hept*-6-*enofuranose* (**10**).—(*a*) To a stirred solution of diallylzinc[34] (150 mmol) in ether (400 ml) at 0 °C was added dropwise during 1 h a solution of 2,3-*O*-isopropylidene-D-ribose (**8**)[20] (2.85 g, 15 mmol) in ether (50 ml). The mixture was stirred at 0 °C for 5 h, and at room temperature for 18 h, and poured into a rapidly stirred mixture of saturated aqueous ammonium chloride (50 ml) and ether (50 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 75 ml). The washed (water), dried organic layers were evaporated to give an oil, which was chromatographed on silica with ether–hexane (3:1) as eluant to give the triol (**9**) (3.10 g, 89%) as an oil; δ_H (100 MHz, after D_2O shake) 1.34, 1.40 (6 H, 2 s, CMe_2), 2.0—2.6 (2 H, m, CH_2), 3.4—4.2 (6 H, m), 5.1—5.3 (2 H, m, $=CH_2$), and 5.9 (1 H, m, $CH=CH_2$).

This material (3.0 g) was dissolved in water (50 ml) and the stirred solution was treated with sodium metaperiodate (3 g). After 0.5 h, the mixture was filtered, and extracted with ethyl acetate (2 × 50 ml). The dried extracts were evaporated to give the *hemiacetal* (**10**) (2.5 g, 86% overall) as an oil; $\nu_{max.}$ 3 480 cm^{-1} (OH); δ_H (60 MHz) 1.35, 1.50 (6 H, 2 s, CMe_2), 2.2—2.6 (2 H, m, 5-H_2), 3.80 (1 H, d, OH), 4.30 (1 H, t, *J* 6 Hz, 4-H), 4.65 (2 H, s, 2- and 3-H), 5.0—5.3 (2 H, m, 7-H_2), 5.50 (1 H, d, $J_{1,OH}$ 2 Hz, 1-H), and 5.6—5.8 (1 H, m, 6-H); *m/z* 200 (M^+) (Found: C, 60.2; H, 8.15. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%).

(*b*) To a stirred solution of allylmagnesium chloride [0.32 mol, from magnesium (7.5 g) and allyl chloride (24.5 g)] in tetrahydrofuran (THF) (100 ml) at 0 °C was added dropwise during 1.5 h a solution of 2,3-*O*-isopropylidene-D-ribose (**8**)[20] (6.09 g, 32 mmol) in THF (50 ml). After 4 h, ethyl acetate (400 ml) and saturated ammonium chloride (200 ml) were added. The resultant two-phase system was stirred for 1 h, the layers were separated, and the dried organic phase was evaporated to give an oil (7.4 g). This was chromatographed and then treated with periodate as described in (*a*) to give the hemiacetal (**10**) in 95% yield.

5,6,7-*Trideoxy*-2,3,-O-*isopropylidene*-L-ribo-*hept*-6-*enose Oxime* (**11**).—A solution of compound (**10**) (5.21 g) and hydroxylamine hydrochloride (6.28 g) in pyridine (50 ml) was stirred at room temperature for 18 h. The residue obtained after evaporation was partitioned between ethyl acetate (200 ml) and 5% aqueous citric acid (200 ml). The dried organic layer was evaporated, and the residue was chromatographed on silica, with ether as eluant, to give the *oxime* (**11**) (5.0 g, 90%) as a *ca.* 2:1 mixture of *E*- and *Z*-isomers, m.p. 112—114 °C; $\nu_{max.}$ (CH_2Cl_2) 3 560, 3 350br (OH), and 1 640 cm^{-1} (C=N); δ_H (60 MHz) 1.38, 1.50 (6 H, 2 s, CMe_2), 2.4 (2 H, m, 5-H_2), 3.5—6.0 (6 H, m), 6.9 [0.3 H, d, *J* 6 Hz, 1-H (*Z*-isomer)], and 7.5 [0.7 H, d, *J* 8 Hz, 1-H (*E*-isomer)] (Found: M^+, 215.115. $C_{10}H_{17}NO_4$ requires *M*, 215.116).

5,6,7-*Trideoxy*-2,3-O-*isopropylidene*-4-O-*methylsulphonyl*-L-ribo-*hept*-6-*enononitrile* (**12**).—A solution of oxime (**11**) (2.79 g) in pyridine (30 ml) was added dropwise during 4 h to a stirred solution of methanesulphonyl chloride (15.1 g) in pyridine (50 ml) at −23 °C. The mixture was allowed to warm to room temperature during 6 h, and was then stirred for a further 12 h. The solvent was evaporated off and the residue taken up in a mixture of aqueous citric acid (5%; 70 ml) and ether (100 ml).

The layers were separated and the aqueous phase was extracted with more ether (3 × 100 ml). The dried organic layers were evaporated to give an oil, which was chromatographed on silica with ether as eluant to give the *nitrile* (**12**) (3.4 g, 97%) as a pale yellow oil; $\nu_{max.}(CH_2Cl_2)$ 1 340 and 1 170 cm^{-1} (OSO_2Me); δ_H (360 MHz) 1.39, 1.58 (6 H, 2 s, CMe_2), 2.62 (1 H, m, 5-H_a), 2.84 (1 H, m, 5-H_b), 3.11 (3 H, s, SO_2Me), 4.30 (1 H, dd, $J_{3,2}$ 5.2, $J_{3,4}$ 7.4 Hz, 3-H), 4.95 (1 H, d, $J_{2,3}$ 5.2 Hz, 2-H), 5.00 (1 H, ddd, $J_{4,5}$ 4.2, 5.7 Hz, 4-H), 5.2—5.3 (2 H, m, 7-H_2), and 5.9 (1 H, m, 6-H); *m/z* 275 (M^+) and 260 ($M^+ - CH_3$) (Found: $[M - CH_3]^+$, 260.058. $C_{10}H_{14}NO_5S$ requires *m/z*, 260.059).

(2R,3S,4R)-2-*Allyl*-1-*benzyloxycarbonyl*-3,4-*isopropylidenedioxypyrrolidine* (**14**).—A solution of nitrile (**12**) (3.0 g) in THF (15 ml) was added dropwise during 10 min to a stirred suspension of lithium aluminium hydride (1.62 g) in THF (10 ml). After 18 h, the mixture was poured into a vigorously stirred mixture of ethyl acetate (100 ml) and saturated aqueous ammonium chloride (40 ml). After 1 h, the phases were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 ml). The dried organic layers were evaporated to give a yellow oil, which was chromatographed on silica doped with triethylamine, and eluted with chloroform–methanol (99.5:0.5) to give the pyrrolidine (**13**) (1.37 g); δ_H (100 MHz) 1.32, 1.48 (6 H, 2 s, CMe_2), 2.0—3.3 (5 H, m, 2-H, 5-H_2, and $CH_2CH{=}CH_2$), 4.4—4.8 (2 H, m, 3- and 4-H), 5.0—5.2 (2 H, m, $=CH_2$), and 5.9 (1 H, m, $CH{=}CH_2$).

Triethylamine (2.15 g) and benzyl chloroformate were added to a stirred solution of compound (**13**) (1.95 g) in dry ether (30 ml) at 0 °C. The mixture was allowed to warm to room temperature and, after 12 h, it was mixed with ether (50 ml)–water (20 ml). The dried organic layer was evaporated and the residue was chromatographed on silica, with ethyl acetate–hexane (1:1) as eluant, to give the *benzyl ester* (**14**) (2.52 g, 53% overall) as an oil; $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ_H (100 MHz) 1.28, 1.32, 1.40, and 1.52 (6 H, 4 s, CMe_2), 2.1—2.6 (2 H, m, $CH_2CH{=}CH_2$), 3.4 (1 H, m, 5-H_a), 3.8—4.0 (2 H, m, 2-H and 5-H_b), 4.7 (2 H, m, 3- and 4-H), 4.9—5.2 (4 H, m, $=CH_2$ and OCH_2Ph), 5.8 (1 H, m, $CH{=}CH_2$), and 7.4 (5 H, br s, Ph); *m/z* 317 (M^+) and 302 ($M^+ - 15$) (Found: $[M - CH_3]^+$, 302.135. $C_{17}H_{20}NO_4$ requires *m/z*, 302.138).

(2R,3S,4R)-*Diphenylmethyl* (1-*Benzyloxycarbonyl*-3,4-*isopropylidenedioxypyrrolidin*-2-*yl*)*acetate* (**15a**).—A solution of ester (**14**) (0.5 g) in t-butyl alcohol was treated with a solution of sodium periodate (1.522 g, 5 mol equiv.) and potassium permanganate (0.372 g, 1.5 mol equiv.) in water (40 ml). The pH of the mixture was adjusted to 8 (5% aqueous K_2CO_3), and it was stirred at room temperature for 18 h, acidified (dilute H_2SO_4) to pH 2.5, and extracted with ether (3 × 60 ml). The washed (water), dried extracts were evaporated and the residue was taken up in dichloromethane (20 ml). Diazodiphenylmethane (0.4 g) was added and after 4 h excess of reagent was destroyed with acetic acid. The solution was washed with aqueous $NaHCO_3$, dried, and evaporated to give a yellow oil, which was chromatographed on silica, with ether–hexane (1:1) as eluant, to give the *diphenylmethyl ester* (**15a**) (0.24 g, 30%) as an oil; $\nu_{max.}(CH_2Cl_2)$ 1 730 (ester) and 1 695 cm^{-1} (N–CO_2); δ_H (100 MHz) 1.24, 1.39 (6 H, 2 s, CMe_2), 2.78 (1 H, dd, *J* 16, 9 Hz, 5-H_a), 3.0—4.0 (3 H, m, 5-H_b and CH_2CO_2R), 4.2—4.9 (3 H, m, 2-, 3-, and 4-H), 5.10 (2 H, br s, $PhCH_2$), 6.92 (1 H, s, $CHPh_2$), and 7.4 (15 H, m, 3 Ph); *m/z* 501 (M^+) and 334 ($M^+ - CHPh_2$) (Found: $[M - CHPh_2]^+$, 334.128. $C_{17}H_{20}NO_6$ requires *m/z*, 334.129).

2,3-O-*Isopropylidene*-D-*erythrose Oxime* (**18**).—A solution of hydroxylamine hydrochloride (21.7 g) and 2,3-*O*-isopropylidene-D-erythrose (**17**)[27,28] (5.2 g) in pyridine (100 ml) was stirred at room temperature for 18 h. The residue obtained after evaporation was partitioned between ethyl acetate (100 ml) and 5% aqueous citric acid (100 ml), and the aqueous layer was extracted with additional ethyl acetate (5 × 50 ml). The dried organic layers were evaporated to give the *oxime* (**18**) (5.44 g, 96%), m.p. 80—82 °C; δ_H (100 MHz) 1.40, 1.54 (6 H, 2 s, CMe_2), 3.6 (2 H, m, 4-H_2), 4.5 (1 H, m, 3-H), 4.76 [0.5 H, t, *J* 8 Hz, 2-H (*E*-isomer)], 5.26 [0.5 H, dd, *J* 7.5, 5 Hz, 2-H (*Z*-isomer)], 6.95 [0.5 H, d, *J* 5 Hz, 1-H (*Z*-isomer)], and 7.44 [0.5 H, d, *J* 8 Hz, 1-H (*E*-isomer)] (Found: C, 47.7; H, 7.5; N, 7.7. $C_7H_{13}NO_4$ requires C, 48.0; H, 7.4; N, 8.0%).

2,3-O-*Isopropylidene*-4-O-*methylsulphonyl*-D-*erythrononitrile* (**19**).—A solution of the oxime (**18**) (5.44 g) in pyridine (70 ml) was added dropwise during 3 h to a stirred solution of methanesulphonyl chloride (27 ml) in pyridine (70 ml) maintained at −23 °C. The mixture was allowed to warm to room temperature, then was stirred for 15 h, and evaporated to dryness (bath temperature < 50 °C). The residue was partitioned between ether (100 ml) and 5% aqueous citric acid (100 ml), and the aqueous phase was extracted with more ether (9 × 75 ml). The washed (brine), dried organic layers were evaporated and the residue was chromatographed on silica with ether–hexane (1:1) as eluant to give *nitrile* (**19**) (7.3 g, 95%) as an oil, $[\alpha]_D$ −50.4° (*c* 1.07 in $CHCl_3$); $\nu_{max.}$ 1 360 and 1 175 cm^{-1} (OSO_2Me); δ_H (100 MHz) 1.40, 1.57 (6 H, 2 s, CMe_2), 3.12 (3 H, s, SO_2Me), 4.5 (3 H, m, 3-H and 4-H_2), and 5.00 (1 H, d, *J* 5 Hz, 2-H); *m/z* 235 (M^+) and 220 ($M^+ - CH_3$) (Found: C, 40.6; H, 5.5; N, 5.8; S, 13.7. $C_8H_{13}NO_5S$ requires C, 40.85; H, 5.5; N, 5.95; S, 13.6%).

Methyl 3-*Amino*-2,3-*dideoxy*-4,5-O-*isopropylidene*-6-O-*methylsulphonyl*-D-erythro-*hex*-2-*enonate* (**20a,b**).—To a suspension of activated zinc[29] (6.24 g, 5 mol equiv.) in THF (58 ml) at reflux were added several portions (0.1 ml each) of methyl bromoacetate, until reaction was initiated. When a green colour persisted, a solution of nitrile (**18**) (4.5 g) in THF (19 ml) was added during 5 min. Methyl bromoacetate (7.36 ml, 4 mol equiv.) was added dropwise during 45 min. The mixture was heated under reflux for a further 10 min, cooled to room temperature, diluted with THF (167.6 ml), and quenched with 50% aqueous potassium carbonate (27.8 ml).[29] After being rapidly stirred for 45 min, the mixture separated into two layers. The upper organic layer was separated, and the aqueous phase was washed with THF (4 × 50 ml). The dried organic layers were evaporated, and the yellow residue was chromatographed on Florisil and then on silica with ether as eluant to give firstly the E-*isomer* (**20b**) (0.135 g, 2.2%) as an oil; $\nu_{max.}(CH_2Cl_2)$ 3 460 and 3 350 (NH), 1 670 (C=O), 1 620 (C=C), 1 360, and 1 180 cm^{-1} (OSO_2Me); δ_H (100 MHz) 1.40, 1.56 (6 H, 2 s, CMe_2), 3.02 (3 H, s, SO_2Me), 3.64 (3 H, s, CO_2Me), 3.75 (2 H, m, 6-H_2), and 4.2—4.8 (3 H, m, 2-, 4-, and 5-H) (Found: M^+, 309.089. $C_{11}H_{19}NO_7S$ requires *M*, 309.088).

Further elution of the column gave the Z-*isomer* (**20a**) (4.61 g, 78%), m.p. 97—98 °C; $[\alpha]_D$ −156.1° (*c* 1.66 chloroform); $\lambda_{max.}$(EtOH) 272 nm; $\nu_{max.}(CH_2Cl_2)$ 3 480 and 3 340 (NH), 1 670 (C=O), 1 620 (C=C), 1 360, and 1 170 cm^{-1} (OSO_2Me); δ_H (360 MHz) 1.41, 1.59 (6 H, 2 s, CMe_2), 3.01 (3 H, s, SO_2Me), 3.66 (3 H, s, CO_2Me), 4.19 (1 H, dd, $J_{6a,6b}$ 11.1, $J_{6a,5}$ 7.8 Hz, 5-H_a), 4.28 (1 H, dd, $J_{6b,5}$ 3.4 Hz, 6-H_b), 4.55 (1 H, dt, 5-H), 4.57 (1 H, d, $J_{2,4}$ 0.5 Hz, 2-H), and 4.67 (1 H, dd, $J_{4,5}$ 7.5 Hz, 4-H) (Found: C, 42.7; H, 6.2; N, 4.4. $C_{11}H_{19}NO_7S$ requires C, 42.7; H, 6.1; N, 4.5%).

(3S,4R)-*Methyl* (3,4-*Isopropylidenedioxypyrrolidin*-2-*ylidene*)*acetate* (**21a,b**).—A solution of compound (**20a**) (1.0 g) in dichloromethane (6 ml) was treated with DBU (1.47 g). The mixture was stirred for 48 h at room temperature, after which dichloromethane (20 ml) and water (10 ml) were added. The

dried organic layer was evaporated and the residue was chromatographed on silica with ether as eluant to give Z-*isomer* (**21a**) (0.68 g, 98%), m.p. 136—137 °C; $[\alpha]_D$ −144.1° (*c* 1.65 in $CHCl_3$); $\nu_{max.}$(KBr) 3 360 and 3 330 (NH), 1 665 (C=O), 1 615 (C=C), and 1 580 cm^{-1}; δ_H (200 MHz) 1.38, 1.42 (6 H, 2 s, CMe_2), 3.65 (3 H, s, CO_2Me), 3.7 (2 H, m, 5-H_2), 4.75 (1 H, m, 4-H), 4.77 (1 H, s, alkene), 5.01 (1 H, d, *J* 5.9 Hz, 3-H), and 7.6 (1 H, br s, exchangeable, NH); δ_C (50 MHz) 26.0, 27.3 (CMe_2), 50.3, 51.7, 76.1, 79.1, 81.6, 112.9 (CMe_2), 163.2 (C-2), and 171.2 (C=O); *m/z* 213 (M^+) (Found: C, 56.4; H, 7.1; N, 6.5. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.0; N, 6.6%).

A similar reaction carried out on compound (**20b**) (0.1 g) gave the E-*isomer* (**21b**) (55 mg, 80%) as an oil; $\nu_{max.}$(CH_2Cl_2) 3 480 and 3 360 (NH), 1 670 (C=O), and 1 625 cm^{-1} (C=C); δ_H (100 MHz) 1.40, 1.48 (6 H, 2 s, CMe_2), 3.72 (3 H, s, OMe), 4.3—4.9 (3 H, m, 4-H and 5-H_2), and 5.2 (1 H, s + m, 3-H and alkene) (Found: M^+ 213.100. $C_{10}H_{15}NO_4$ requires *M*, 213.100).

(2R,3S,4R)-*Methyl* (3,4-*Isopropylidenedioxypyrrolidin*-2-*yl*)*acetate* (**22**).—To a solution of compound (**21a**) (0.465 g) and a trace of Bromocresol Green [35] in methanol (16 ml) was added sodium cyanoborohydride (0.137 g). The pH of the solution was adjusted with dilute methanolic HCl until a yellow colour was maintained. The mixture was stirred for 2 h, poured into 0.1M-NaOH (20 ml), and extracted with dichloromethane (3 × 30 ml). The dried organic extracts were evaporated, and the residue, dissolved in ether, was passed quickly through a silica plug to give, after evaporation, the *amine* (**22**) (0.414 g, 90%) as an oil, $[\alpha]_D$ −52.9° (*c* 2.00 in $CHCl_3$); $\nu_{max.}$(CH_2Cl_2) 3 380 (NH) and 1 730 cm^{-1} (C=O); δ_H (200 MHz) 1.30, 1.43 (6 H, 2 s, CMe_2), 2.18 (1 H, br s, NH), 2.7 (3 H, m, 5-H_a and CH_2CO_2R), 3.05 (1 H, m, 2-H), 3.08 (1 H, d, $J_{5b,5a}$ 13.1, $J_{5b,4}$ 0 Hz, 5-H_b), 3.71 (3 H, s, OMe), 4.62 (1 H, t, *J* 5 Hz, 3- or 4-H), and 4.70 (1 H, dd, *J* 5.5, 3.7 Hz, 4- or 3-H); *m/z* 216 $(M + H)^+$ and 200 $(M - CH_3)$ (Found: $[M - CH_3]^+$ 200.089. $C_9H_{14}NO_4$ requires *m/z* 200.092).

(2*R*,3*S*,4*R*)-*Methyl* (1-*Benzyloxycarbonyl*-3,4-*isopropylidene dioxypyrrolidin*-2-*yl*)*acetate* (**15b**).—(*a*) Treatment of ester (**14**) (0.137 g) as described above for the preparation of (**15a**), except that an ethereal solution of excess of diazomethane was used in place of diazodiphenylmethane, gave the methyl ester (**15b**) (0.122 g, 35%) as an oil; $\nu_{max.}$ 1 735 (ester) and 1 700 cm^{-1} (NCO_2); δ_H (200 MHz) 1.32, 1.49 (6 H, 2 s, CMe_2), 2.62 (1 H, dd, *J* 16.4, 9.9 Hz, CH_aHCO_2Me), 3.05 (1 H, br s, CHH_bCO_2Me), 3.66 (3 H, s, OMe), 3.7 (2 H, m, 5-H_2), 4.35 (1 H, m, 2-H), 4.8 (2 H, m, 3- and 4-H), 5.11 (1 H, s, $PhCH_2$), and 7.35 (5 H, s, Ph) (Found: M^+, 349.155. $C_{18}H_{23}NO_6$ requires *M*, 349.153).

(*b*) A solution of compound (**22**) (0.17 g) and triethylamine (0.12 ml) in dichloromethane (7 ml) was cooled in ice, and benzyl chloroformate (0.15 g) was added dropwise. The mixture was stirred at 0 °C for 3 h, diluted with dichloromethane (20 ml), and washed with water (5 ml). The dried organic layer was evaporated and the residue was chromatographed on silica, with ether as eluant, to give diester (**15b**) (0.27 g, 97%), with spectroscopic and t.l.c. properties as for the material prepared in (*a*) above.

(1S,5R,8R)-*Benzyl* 8-*Hydroxy*-3-*oxo*-2-*oxa*-6-*azabicyclo*-[3.3.0]*octane*-6-*carboxylate* (**23**).—A solution of diester (**15b**) (0.12 g) in a mixture of trifluoroacetic acid (4 ml) and water (1 ml) was kept for 18 h. The solvent was evaporated off, benzene (5 ml) was added, and the mixture was again evaporated. Chromatography on silica, with ethyl acetate as eluant, gave a solid, which was crystallised from ethyl acetate–hexane to give the *lactone* (**23**) (84 mg, 82%), m.p. 74—76 °C; $[\alpha]_D$ −59.4° (*c* 0.32 in $CHCl_3$); $\nu_{max.}$(CH_2Cl_2) 3 300 (OH), 1 790 (γ-lactone), and 1 700 cm^{-1} (NCO_2); δ_H (200 MHz) 2.8 (2 H, m, 4-H_2), 3.35 (1 H, m, 7-H_a), 3.87 (1 H, dd, *J* 11.2, 6.7 Hz, 7-H_b), 4.35 (1 H, m, 8-H), 4.5 (1 H, m, 5-H), 4.92 (1 H, dd, *J* 5.5, 4.5 Hz, 1-H), 5.11 (2 H, AB system, $PhCH_2$), and 7.35 (5 H, s, Ph); δ_C (50 MHz) 35.8 and 36.4, 49.9 and 50.4, 55.7 and 56.3, 67.5, 69.9 and 70.6, 81.5 and 82.1, 128.1, 128.3, 128.6, 135.9, 153.9 and 154.4 (NCO_2), and 174.7 and 174.9 (lactone) (Found: M^+, 277.096. $C_{14}H_{15}NO_5$ requires *M*, 277.095).

(1R,5R)-*Benzyl* 3-*Oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**25**).—To a solution of lactone (**23**) (9.27 g) in THF (10 ml) were added 1,1′-thiocarbonyldi-imidazole (0.27 g) and pyridine (1 ml). The resultant solution was heated under reflux for 18 h, then evaporated to dryness, and the residue was chromatographed on silica, with ethyl acetate–hexane (4:1) as eluant, to give the imidazolylthiocarbonyl derivative (**24**) (0.34 g); δ_H (200 MHz) 2.9 (2 H, m, 4-H_2), 3.65 (1 H, m, 7-H_a), 4.3 (1 H, m, 7-H_b), 4.7 (1 H, m, 5-H), 5.17 (2 H, s, CH_2Ph), 5.33 (1 H, t, *J* *ca.* 4.8 Hz, 1-H), 5.85 (1 H, td, $J_{8,1}$ 4.4, $J_{8,7a} \simeq J_{8,7b}$ 8 Hz, 8-H), 7.05 (1 H, br s, 5′-H), 7.37 (5 H, br s, Ph), 7.59 (1 H, br s, 4′-H), and 8.34 (1 H, s, 2′-H).

A solution of the thiocarbonyl derivative (**24**) (132 mg) in degassed benzene (20 ml) was added dropwise to a solution of tri-n-butylstannane (218 mg) in benzene (200 ml) at reflux. After 1 h of further reflux, the cooled solution was evaporated and the residue was partitioned between acetonitrile (30 ml) and hexane (15 ml). Evaporation of the acetonitrile layer and chromatography of the residue on silica, with ethyl acetate as eluant, afforded compound (**25**) (88 mg, 89%) as an oil, $[\alpha]_D$ −73.3° (*c* 0.45 in $CHCl_3$); $\nu_{max.}$(CH_2Cl_2) 1 780 (γ-lactone) and 1 700 cm^{-1} (NCO_2); δ_H (200 MHz) 2.05 (1 H, m, 8-H_{exo}), 2.34 (1 H, dd, J_{gem} 14.1, $J_{8endo,7endo}$ 6.1 Hz, 8-H_{endo}), 2.85 (2 H, m, 4-H_2), 3.43 (1 H, dt, *J* 11.2, $J_{7endo,8exo}$ 6.2 Hz, 7-H_{endo}), 3.85 (1 H, m, 7-H_{exo}), 4.5 (1 H, m, 5-H), 5.1 (3 H, m, $PhCH_2$ and 1-H), and 7.35 (5 H, s, Ph) (Found: M^+ 261.009. $C_{14}H_{15}NO_4$ requires *M*, 261.100).

(1R,5R)-2-*Oxa*-6-*azabicylo*[3.3.0]*octan*-3-*one Hydrochloride* (**6**).—A solution of ester (**25**) (75 mg) in ethanol saturated with HCl (g) (5 ml) was hydrogenated for 24 h at 1 atm using palladium–charcoal (10%; 5 mg) as catalyst. The suspension was filtered through Celite, which was then washed with ethanol (50 ml). Evaporation of the combined filtrate and washings gave a yellow gum, which on crystallisation from ethanol–ether gave the lactone (**6**) (50 mg, 95%), m.p. 182—184 °C (decomp.); $[\alpha]_D$ +45.6° (*c* 0.3 in methanol) {lit.,[10] m.p. 185—186 °C; $[\alpha]_D$ +48.5° (*c* 1.5 in methanol)}; $\nu_{max.}$(KBr) 3 000br (NH_2^+) and 1 773 cm^{-1} (γ-lactone); δ_H (360 MHz; D_2O) 2.35 (1 H, m, 8-H_a), 2.45 (1 H, br d, *J* 14.8 Hz, 8-H_b), 2.99 (1 H, dd, J_{gem} 19.7, $J_{4endo,5}$ 1.4 Hz, 4-H_{endo}), 3.30 (1 H, dd, $J_{4exo,5}$ 8.9 Hz, 4-H_{exo}), 3.45 (1 H, td, *J* *ca.* 11.5, 6.4 Hz, 7-H_a), 3.55 (1 H, ddd, *J* 12.0, 7.7, and 3.4 Hz, 7-H_b), 4.75 (1 H, m, 5-H), and 5.42 (1 H, td, *J* 5.5, 1.0 Hz, 1-H).

(1R,5R)-*Ethyl* 3-*Oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**26**).—A suspension of compound (**6**) (15 mg) in dichloromethane (5 ml) was stirred at 0 °C and treated with a mixture of triethylamine (0.5 ml) and ethyl chloroformate (0.1 ml). The mixture was warmed to room temperature, and stirred for 1 h, and then diluted with dichloromethane (30 ml). The washed (brine), dried organic layer was evaporated, and the residue was chromatographed on silica, with ether as eluant, to give the urethane (**26**) (18 mg, 91%) as an oil, identical (t.l.c., i.r., ^1H n.m.r.) with a sample of the racemate provided by Professor K. Narasaka; $\nu_{max.}$(CH_2Cl_2) 1 785 (γ-lactone) and 1 700 cm^{-1} (urethane); δ_H (200 MHz) 1.25 (3 H, t, CH_2Me), 2.05 (1 H, m, 8-H_{exo}), 2.30 (1 H, dd, *J* 14.2, 6.1 Hz, 8-H_{endo}), 2.8 (2 H, m, 4-H_2), 3.40 (1 H, m, 7-H_a), 3.78 (1 H, m, 7-H_b), 4.13 (2 H, q, CH_2Me), 4.46 (1 H, m, 5-H), and 5.07 (1 H, m, 1-H).

(2R,3S,4R)-*Ethyl* (3,4-*Isopropylidenedioxy*-2-*methoxycarbonylmethylpyrrolidin*-1-*yl*)*acetate* (**27**).—To a stirred

solution of amine (**22**) (1.2 g) in THF (20 ml) at room temperature were added triethylamine (0.58 g) and ethyl bromoacetate 0.94 g). After 16 h, the product was isolated with ether. Evaporation of the organic extracts and chromatography on silica, with ether as eluant, gave the *alkylated pyrrolidine* (**27**) (1.5 g, 89%) as an oil, $[\alpha]_D$ −35.4° (*c* 4.8 in $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 1 735 cm^{-1} (C=O); δ_H (200 MHz) 1.25 (3 H, t, CH_2Me), 1.30, 1.48 (6 H, 2 s, CMe_2), 2.56 (1 H, dd, *J* 16.9, 4.9 Hz, CH_aHCO_2Me), 2.65—2.85 (2 H, m, CH_bCO_2Me and 5-H_a), 3.0—3.3 (3 H, m, 2-H, 5-H_b, and CH_aHCO_2Et), 3.46 (1 H, d, *J* 17.0 Hz, CH_bCO_2Et), 3.68 (1 H, s, OMe), 4.14 (2 H, q, CH_2Me), and 4.7 (2 H, m, 3- and 4-H) (Found: M^+, 301.152. $C_{14}H_{23}NO_6$ requires *M*, 301.152).

(1S,5R,8R)-*Ethyl* 8-*Hydroxy*-3-*oxo*-2-*oxa*-6-*azabicyclo*-[3.3.0]*octane*-6-*carboxylate* (**28**).—Diester (**27**) (602 mg) was kept in trifluoroacetic acid–water (4:1; 10 ml) at room temperature for 18 h. The solvent was evaporated off and the residue was chromatographed on silica, with ethyl acetate as eluant. Crystallisation from ethyl acetate–hexane yielded the γ-*lactone* (**28**) (370 mg, 77%), m.p. 124—126 °C; $[\alpha]_D$ −10.9° (*c* 0.66 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 580 (OH), 1 780 (γ-lactone), and 1 740 cm^{-1} (ester); δ_H (360 MHz) 1.28 (3 H, t, OCH_2Me), 2.62 (1 H, dd, J_{gem} 18.2, $J_{4a,5}$ 4.1 Hz, 4-H_a), 2.67 (1 H, dd, $J_{4b,5}$ 6.4 Hz, 4-H_b), 3.11 (1 H, dd, J_{gem} 10.5, $J_{7a,8}$ 4.8 Hz, 7-H_a), 3.13 (1 H, dd, $J_{7b,8}$ 3.5 Hz, 7-H_b), 3.48 (2 H, dd, J_{gem} 17.5 Hz, CH_2CO_2Et), 3.87 (1 H, td, 5-H), 4.17 (2 H, q, OCH_2Me), 4.46 (1 H, td, 8-H), and 4.94 (1 H, dd, $J_{1,5}$ 6.9 Hz, $J_{1,8}$ 5.3 Hz, 1-H) (Found: M^+, 229.096. $C_{10}H_{15}NO_5$ requires *M*, 229.095).

(1S,5R,8R)-*Ethyl* 8-(*Dimethyl-t-butylsiloxy*)-2-*oxa*-6-*aza*-*bicyclo*[3.3.0]*octane*-6-*carboxylate* (**29**).—A solution of alcohol (**28**) (0.35 g) in dimethylformamide (DMF) (1 ml) was added to a solution of imidazole (0.11 g) and dimethyl-t-butylsilyl chloride (0.243 g) in DMF (2 ml) stirred in an ice-bath. The mixture was stirred at room temperature for 48 h, then evaporated to dryness at <45 °C, and the residue was chromatographed on silica with ethyl acetate as eluant to give the *silyl ether* (**29**) (0.499 g, 95%) as an oil, $[\alpha]_D$ −10.6° (*c* 1.33 in $CHCl_3$); $\nu_{max.}$ 1 780 (γ-lactone) and 1 740 cm^{-1} (ester); δ_H (200 MHz) 0.10 (6 H, s, $SiMe_2$), 0.90 (9 H, s, CMe_3), 1.28 (3 H, t, OCH_2Me), 2.6 (2 H, m, 4-H_2), 3.05 (2 H, m, 7-H_2), 3.47 (2 H, dd, J_{gem} 17.7 Hz, CH_2CO_2Et), 3.85 (1 H, q, *J ca.* 7 Hz, 5-H), 4.16 (2 H, q, OCH_2Me), 4.40 (1 H, m, 8-H), and 4.89 (1 H, dd, *J* 7.8, 4.8 Hz, 1-H); *m/z* 343 (M^+) and 286 ($M^+ - CMe_3$) (Found $[M - CMe_3]^+$, 286.114. $C_{12}H_{20}NO_5Si$ requires *m/z*, 286.111).

(6R,7S,7aR)-*Ethyl* 2,7-*Diacetoxy*-6-(*dimethyl-t-butylsiloxy*)-*pyrrolizidine*-1-*carboxylate* (**31**).—To a stirred solution of lactone (**29**) (0.30 g) in toluene (6 ml) was added freshly prepared solid potassium ethoxide (0.30 g). After 4 h, the pH of the solution was adjusted to *ca.* 3 by addition of acetic acid, and the solvent was evaporated off. To a solution of the residue in ethanol (3 ml) was added sodium borohydride (0.15 g). The mixture was stirred for 4 h and then evaporated to dryness. The residue was kept in a mixture of acetic anhydride (1.5 ml) and pyridine (3 ml) for 18 h. After evaporation, the residue was partitioned between ethyl acetate (20 ml) and water (4 ml). The dried organic layer was evaporated and the residue was chromatographed on silica, with ethyl acetate–hexane (1:1) as eluant, to give the *diacetate* (**31**) (0.145 g, 39%) as a mixture of isomers [R_F 0.8 and 0.75 (ethyl acetate)]; $\nu_{max.}(CH_2Cl_2)$ 1 735 cm^{-1} (C=O); δ_H (200 MHz) 0.1 (6 H, s, $SiMe_2$), 0.9 (9 H, s, CMe_3), 1.25 (3 H, t, OCH_2Me), 2.05 and 2.10 (6 H, 2 s, OAc), 2.6—4.5 (9 H, m), and 5.1—5.6 (2 H, m, 2- and 7-H) (Found: $[M - CH_3]^+$, 414.194. $C_{19}H_{32}NO_7Si$ requires *m/z*, 414.195).

(6R,7S,7aR)-*Ethyl* 7-*Acetoxy*-6-(*dimethyl-t-butyloxy*)-5,6,7,7a-*tetrahydro*-3H-*pyrrolizine*-1-*carboxylate* (**32**).—A solution of the diacetate (**31**) (43 mg) in dichloromethane (5 ml) was treated with DBU (0.2 ml). The mixture was stirred at room temperature overnight, diluted with dichloromethane (15 ml), and washed with water. The dried organic layers were evaporated to give an oil, which was chromatographed on silica with ethyl acetate–hexane (7:3) as eluant to give a solid. This was crystallised from ethyl acetate–light petroleum to give *unsaturated ester* (**32**) (34 mg, 90%), m.p. 76—77 °C; δ_H (360 MHz) 0.05 and 0.07 (2 × 3 H, 2 s, $SiMe_2$), 0.85 (9 H, s, CMe_3), 1.25 (3 H, t, OCH_2Me), 1.96 (3 H, s, OAc), 2.55 (1 H, dd, $J_{5a,6}$ 9.7, $J_{5a,5b}$ 8.6 Hz, 5-H_a), 3.29 (1 H, dd, $J_{5b,6}$ 6.4 Hz, 5-H_b), 3.56 (1 H, ddd, *J* 17.8, 5.8, and 2.2 Hz, 3-H_a), 4.03 (1 H, ddd, *J* 17.7, 3.4, and 2.0 Hz, 3-H_b), 4.17 (2 H, q, OCH_2Me), 4.35 (1 H, ddd, $J_{6,7}$ 4.0 Hz, 6-H), 4.52 (1 H, m, 7a-H), 5.46 (1 H, t, $J_{7,7a}$ *ca.* 4.2 Hz, 7-H), and 6.82 (1 H, q, *J ca.* 2.1 Hz, 2-H) (Found: $[M + H^+]$, 370.207. $C_{18}H_{32}NO_5Si$ requires *m/z*, 370, 205.

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