De novo Synthesis of Carbohydrates. Part 14.[1] Preparation of 4-Aminolyxose Derivatives. *X*-Ray Molecular Structure of Ethyl 6-Ethoxycarbonylamino-8-hydroxymethyl-3,3-dimethyl-2,4-dioxa-7-azabicyclo[3.3.0]octane-7-carboxylate

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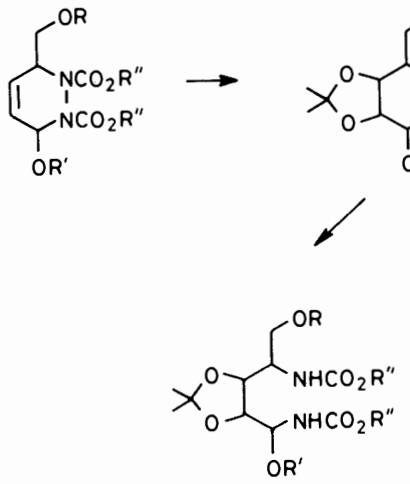
The synthesis of racemic 4-aminolyxose derivatives was carried out *via* the Diels–Alder adduct of diethyl azodicarboxylate and 5-methoxypenta-1,4-dien-1-ol. The N–N bond in the highly functionalised hexahydropyridazine intermediate (**10**) was successfully cleaved using sodium in liquid ammonia. The relative stereochemistry of the product 4-aminopentose derivative was determined by *X*-ray methods.

As an extension to previous work undertaken in these laboratories directed towards the total synthesis of carbohydrates and related natural products using hetero-Diels–Alder reactions,[2] the route to 4-aminopentose derivatives outlined in the Scheme was examined.



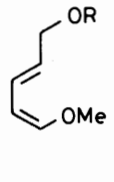
Scheme.

A convenient synthesis of systems with the *ribo* relative stereochemistry could provide a route to the synthesis of 4-amino-4-deoxyribonucleosides, potential anti-tumour or anti-viral agents, and (*via* Wittig reaction) to sphingosine derivatives.[3]

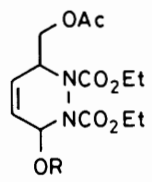
The method of Iwai and Tomita[4] was used to prepare diene (**1**), which reacted with diethyl azodicarboxylate (DEAD) to give the tetrahydropyridazine (**2**) in high yield. As expected the ^{1}H n.m.r. spectrum was poorly resolved at normal temperatures; many studies[5] have shown that at room temperature two processes, assigned as amide bond rotation and ring inversion, are slow on the n.m.r. time-scale. An attempt to obtain a ^{1}H n.m.r. spectrum of (**2**) at 140 °C in $(CD_3)_2SO$ was foiled by sample decomposition. Hydroxylation using OsO_4–H_2O_2 was unsatisfactory and while potassium permanganate in methanol at 0 °C yielded a single crystalline diol (**14**) only a low yield (24%) could be obtained. Use of OsO_4–*N*-methylmorpholine *N*-oxide (NMO),[6] however, gave the same single product in 83% yield.

Measurement of the ^{1}H n.m.r. spectrum at 140 °C in $(CD_3)_2SO$ enabled all chemical shifts and coupling constants to be assigned. In particular the coupling constants of the ring protons were found to be $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 2.75 Hz, $J_{5,6}$ = 5.8 Hz, which seemed to suggest that the configuration was *ribo*.

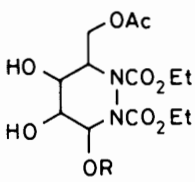
It also proved possible to carry out glycosidation reactions with (**2**); for example, reaction with benzyl alcohol in the presence of 4 Å molecular sieve and a catalytic amount of BF_3·OEt_2 gave a 50% yield of the 6-benzyloxy derivative (**5**). The high-temperature ^{1}H n.m.r. spectrum of the derived diol



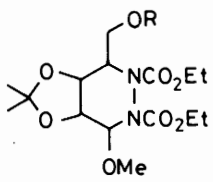
(**1**) R = Ac
(**4**) R = H



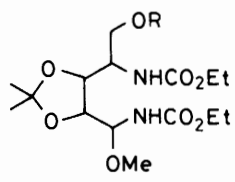
(**2**) R = Me
(**5**) R = CH_2Ph



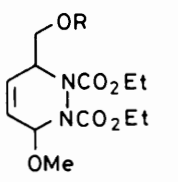
(**3**) R = Me
(**6**) R = CH_2Ph



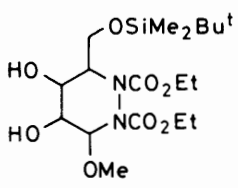
(**7**) R = Ac
(**8**) R = H
(**9**) R = $SiMe_2Bu^t$



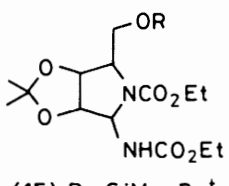
(**10**) R = $SiMe_2Bu^t$
(**11**) R = H



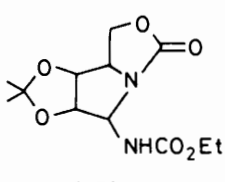
(**12**) R = H
(**13**) R = $SiMe_2Bu^t$



(**14**)



(**15**) R = $SiMe_2Bu^t$
(**16**) R = H



(**17**)

(**6**), prepared using OsO_4–NMO in 80% yield, indicated that the stereochemistries of (**3**) and (**6**) were identical.

The diol function of (**3**) was protected by the isopropylidene group to give (**7**) in 90% yield. It was hoped it would be possible to cleave the N–N bond of (**7**) using a metal in liquid ammonia reduction, a reaction which has some literature precedent.[7] However, reaction of (**7**) with sodium in liquid ammonia at reflux gave a complex mixture which was not investigated further. The acetoxy group of (**7**) would, however, be rapidly cleaved under these conditions and it was decided to replace it with the more stable t-butyldimethylsilyl group. The conversion of (**7**) into the silyl ether (**9**) *via* alcohol (**8**) was achieved in 87% yield from (**7**).

The signals of the isopropylidene methyl groups of (**7**) and (**8**) each appeared in the ^1H n.m.r. spectrum as four lines. While this could be caused by anomerisation, the OMe resonances of (**7**) and (**8**) are both sharp singlets. Moreover, homogeneous compounds can be prepared in high yields (*vide infra*) from (**7**) and (**8**) using reactions which preserve the stereochemistry at the anomeric centre. Thus it is more likely that even at 140 °C the ring inversion is still slow on the n.m.r. time-scale, and that the line shapes have therefore not completely reached their high-temperature forms.

Treatment of (**9**) with sodium in liquid ammonia at −45 °C gave a clean reaction, the N–N-cleaved product (**10**) being obtained in 79% yield. Lithium in liquid ammonia gave inferior results; only moderate yields of (**10**) (allowing for incomplete reaction) were obtained. No reaction was observed with calcium in liquid ammonia, even after the addition of hexamethylphosphoric triamide.[8]

The high yield of the pentose derivative (**10**) is particularly gratifying in view of the rarity of reported N–N cleavage reactions in highly functionalised molecules. Grieco used an *N*-dimethylamino protecting group, which was cleaved in the last stage of his synthesis of calcimycin,[9] but otherwise N–N bonds in only relatively simple compounds have been cleaved, either by use of borane–THF (tetrahydrofuran),[10] by sodium in liquid ammonia,[7] or by catalytic hydrogenation.[11] However, catalytic hydrogenation is somewhat sensitive to steric hindrance.[12]

The required substrate (**9**) for the N–N cleavage reaction was prepared in fewer steps from diene (**4**). Attempted purification of (**4**) by distillation resulted in partial conversion into penta-2,4-dienal even in the presence of potassium carbonate,* and thus the diene was used crude. The Diels–Alder adduct (**12**) was silylated to give (**13**) in 74% yield; this was hydroxylated to give (**14**) (87% yield) which was then isopropylidenated to give (**9**) in 71% yield, identical with that produced previously.

Although (**10**) could be purified by column chromatography on silica gel, it was acid sensitive, undergoing cyclisation with elimination of methanol. The ^1H n.m.r. spectrum of the cyclisation product was consistent with structure (**15**), but was broadened at normal temperatures, probably due to slow rotation about an N–CO urethane bond.[13] Measurement of the ^1H n.m.r. spectrum at 60 °C resulted in sharper resonances but the spectrum was still difficult to interpret because of the proximity of the resonances of 1-H, 5-H, and 8-H to one another.

Desilylation of (**10**) gave the crystalline (**11**), which again cyclised with loss of methanol on treatment with acid in THF or toluene to give a solid (**16**) in >80% yield. Obviously, (**11**) could cyclise *via* nitrogen to give a five-membered system or *via* oxygen to give a pyranose system but the ^1H n.m.r. spectrum of the cyclisation product did not show conclusively which had occurred. Desilylation of (**15**) using acid conditions cleanly gave (**16**), while treatment of (**16**) with t-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF) gave (**15**); thus (**11**) undergoes acid-catalysed cyclisation preferentially *via* the amide nitrogen to give (**16**) even though the 5-OH group is available.

Desilylation of (**15**) using tetra-n-butylammonium fluoride in acetonitrile yielded a different product, which had lost an ethoxy group in addition to the silyl group, and which was assigned structure (**17**). Paulsen has prepared a similar system.[14]

On the basis of the ring proton coupling constants the diol (**3**), and thus compounds derived from it, were tentatively assigned as having the *ribo* configuration. However, the conformational effect of the two urethane moieties in (**3**) is uncertain, and no high-quality ^1H n.m.r. data for comparable hexahydropyridazines of known configuration have been published. An unequivocal structure determination was therefore required. The alcohol (**16**) readily yielded well formed single crystals which were used for *X*-ray analysis.

Atomic co-ordinates, and selected bond lengths, bond angles, and torsion angles, are listed in Tables 1 and 2 respectively. The molecular structure including the numbering scheme used is shown in Figure 1, and a stereoview of the molecular structure is shown in Figure 2. The *X*-ray investigation confirmed the bulk structure for (**16**), but indicated an α-D-*lyxo* configuration. The conformation of the five-membered pyrrolidine ring [N(1)–C(7)–C(4)–C(5)–C(6)– in Figure 1] is a distorted

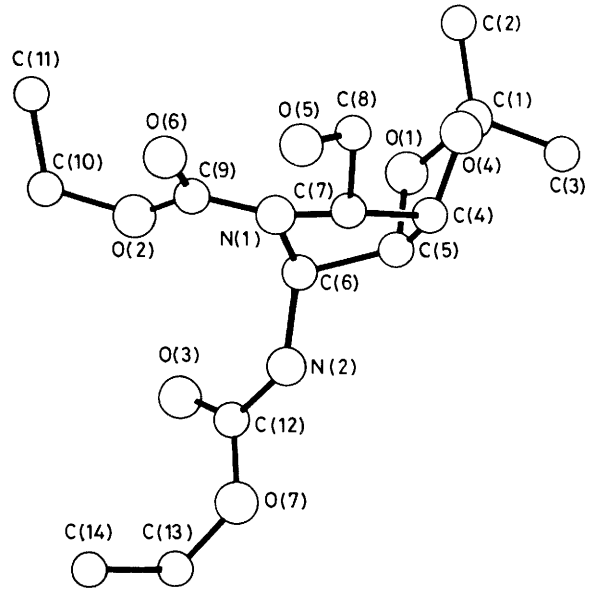


Figure 1. Molecular structure of compound (**16**), with crystallographic numbering scheme

envelope with the pucker at the ring nitrogen. While the urethane substituent at the anomeric centre occupies a pseudoaxial position, the relative lengths of the endo- and exocyclic C–N bonds [C(6)–N(1) = 1.471(6) Å and C(6)–N(2) = 1.446(7) Å] do not indicate any distinct anomeric effect contribution. The hydrogen bond between the alcohol and the N(1) amide carbonyl oxygen [distance H(Y)–O(6) = 1.65 Å, Figure 2] and crystal-packing forces probably account for the observed conformation.

The precursor (**3**) will also have *lyxo* stereochemistry, but the *X*-ray structure determination of (**16**) cannot give any information about the configuration at the anomeric (C-6)

* This conversion is reported to be acid catalysed; see E. L. Pippin and M. Monaka, *J. Org. Chem.*, 1958, **23**, 1580.

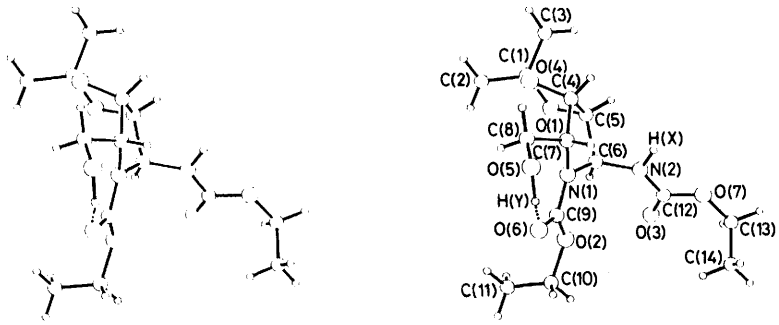


Figure 2. Stereoview of molecular structure of compound (**16**)

Table 1. Atomic co-ordinates for (**16**) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	0.337 1(5)	0.595 4(1)	0.312 9(4)
O(2)	−0.098 3(5)	0.712 6(2)	0.326 6(4)
O(3)	0.286 0(5)	0.818 4(1)	0.116 2(4)
O(4)	0.200 2(5)	0.545 8(1)	0.121 4(4)
O(5)	−0.282 5(5)	0.603 4(2)	−0.084 3(5)
O(6)	−0.283 5(5)	0.667 3(2)	0.151 7(4)
O(7)	0.258 9(5)	0.790 9(2)	0.343 9(4)
N(1)	0.015 2(5)	0.658 0(2)	0.173 6(5)
N(2)	0.223 9(6)	0.731 2(2)	0.150 4(4)
C(1)	0.332 1(7)	0.541 5(2)	0.250 7(6)
C(2)	0.267 7(8)	0.500 8(3)	0.351 8(7)
C(3)	0.508 9(8)	0.525 9(3)	0.210 4(7)
C(4)	0.205 6(7)	0.600 7(2)	0.067 3(6)
C(5)	0.312 4(7)	0.633 9(2)	0.195 3(6)
C(6)	0.191 8(7)	0.681 1(2)	0.227 8(6)
C(7)	0.018 9(7)	0.626 0(2)	0.039 7(6)
C(8)	−0.122 4(8)	0.582 1(3)	−0.000 2(6)
C(9)	−0.131 9(8)	0.678 7(2)	0.213 2(6)
C(10)	−0.249 9(9)	0.733 3(3)	0.385 4(7)
C(11)	−0.302 1(1)	0.694 0(3)	0.493 8(9)
C(12)	0.255 5(7)	0.780 8(2)	0.215 7(6)
C(13)	0.310 7(7)	0.875 6(2)	0.164 1(6)
C(14)	0.136 1(9)	0.904 7(3)	0.150 9(7)

Table 2. Selected (a) bond lengths (Å), (b) bond angles (°), and (c) torsion angles (°) for (**16**) with e.s.d.s in parentheses

(a)

C(4)–C(5)	1.547(7)	C(6)–N(1)	1.471(6)
C(4)–C(7)	1.538(7)	C(6)–N(2)	1.446(7)
C(4)–O(4)	1.416(6)	C(7)–N(1)	1.468(7)
C(5)–C(6)	1.527(7)	C(7)–C(8)	1.513(8)
C(5)–O(1)	1.419(6)	C(9)–N(1)	1.341(7)

(b)

C(7)–N(1)–C(6)	109.7(4)	O(1)–C(5)–C(4)	103.4(4)
C(7)–N(1)–C(9)	124.5(4)	O(1)–C(5)–C(6)	109.8(4)
C(6)–N(1)–C(9)	122.4(4)	C(4)–C(5)–C(6)	106.1(4)
O(4)–C(4)–C(5)	104.6(4)	C(5)–C(6)–N(1)	101.9(4)
O(4)–C(4)–C(7)	110.2(4)	C(4)–C(7)–N(1)	102.7(4)
C(5)–C(4)–C(7)	106.2(4)		

(c)

C(7)–N(1)–C(9)–O(2)	−170.8(4)
C(6)–N(1)–C(9)–O(6)	166.8(5)
C(5)–C(4)–C(7)–N(1)	−16.1(5)
C(4)–C(5)–C(6)–N(1)	25.2(5)
O(1)–C(5)–C(6)–N(1)	−86.4(4)
O(4)–C(4)–C(7)–N(1)	96.7(4)
C(1)–O(4)–C(4)–C(7)	−129.3(4)
C(1)–O(1)–C(5)–C(6)	139.7(4)
C(1)–O(4)–C(4)–C(5)	−15.5(5)
C(1)–O(1)–C(5)–C(4)	26.7(5)
C(9)–N(1)–C(7)–C(8)	−43.2(7)
C(9)–N(1)–C(6)–N(2)	−79.1(6)
C(6)–C(5)–C(4)–C(7)	−5.8(5)
C(4)–C(7)–N(1)–C(6)	34.2(5)
C(7)–N(1)–C(6)–C(5)	−37.8(5)
O(4)–C(4)–C(5)–O(1)	−6.7(5)
C(5)–O(1)–C(1)–O(4)	−36.8(5)
O(1)–C(1)–O(4)–C(4)	32.2(5)

centre of (**3**). However, a 3,6-*trans* arrangement in (**2**) and (**3**) was assigned for two reasons: (a) concerted 4 + 2 addition of DEAD to diene (**1**) will lead to cycloadduct (**2**) with a 3,6-*trans* arrangement, and (b) it is very difficult to imagine that OsO_4 would attack *cis*-(**2**) exclusively from the more hindered side. The ^1H n.m.r. spectrum of (**3**) [and (**6**)] is, however, somewhat puzzling. An equilibrium between two chair forms (Figure 3) would not be expected to result in the observed coupling constants, and thus it may be that twist or boat conformations are present to a significant extent.

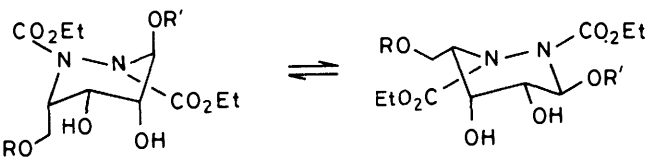


Figure 3. Chair-form equilibrium for the hexahydropyridazines (**3**) and (**6**). Only one enantiomer depicted

Experimental

For general conditions see ref. 2.

(E,Z)-5-*Methoxypenta*-2,4-*dienyl Acetate* (**1**) *and* (E,Z)-5-*Methoxypenta*-2,4-*dien*-1-*ol* (**4**).—To a suspension of ethylmagnesium iodide in THF [prepared from ethyl iodide (124.8 g) and magnesium (19.5 g)] in THF (400 ml) cooled to 0 °C was added 1-methoxybut-1-en-3-yne (61.5 g) in dry THF (200 ml). After being stirred for 2 h at room temperature, the mixture was cooled to 0 °C and gaseous formaldehyde, generated from paraformaldehyde (39 g) was passed through. After being stirred for a further 3 h at room temperature, the mixture was again cooled and dry methanol (21 ml) added dropwise. After the mixture had been stirred for another hour at 0 °C, lithium aluminium hydride (40 g) was added carefully, in portions, during 1.5 h. The mixture was allowed to warm to room temperature overnight. Water (30 ml) in THF (50 ml) was added dropwise to the cooled reaction mixture, which was then filtered. The grey solid was washed successively with water (500 ml) and ethyl acetate (500 ml). The initial filtrate was

concentrated (to remove the majority of the THF) and then the filtrates were combined. The organic phase was washed with water (100 ml) and the combined aqueous phases extracted with ethyl acetate (2 × 50 ml). The combined organic phases were dried (Na_2SO_4) and concentrated to yield crude (**10**) as a red liquid (35.9 g). Pyridine (45 ml) and acetic anhydride (45 ml) were added and the solution was heated to 100 °C for 1 h. After having cooled it was poured into ice–water (600 g) containing concentrated HCl (20 ml). The phases were separated, and the aqueous layer extracted with ether (2 × 100 ml). The combined organic phases were washed successively with water (100 ml) and 5% sodium hydrogen carbonate (2 × 100 ml). After the organic phase was dried (Na_2SO_4) and the solvent removed, the dark residual oil was distilled to yield the *diene* (**1**) (15.7 g, 13.5%) as a pale yellow oil, b.p. 51 °C at 0.5 mmHg (Found: C, 61.7; H, 7.8. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%); $\nu_{max.}$(thin film) 1 740 (C=O), 1 660, and 1 620 cm^{-1} (C=C); δ_H (80 MHz; $CDCl_3$) 6.7 (1 H, dd, *J* 16 and 11 Hz, 3-H), 6.02 (1 H, d, *J* 6.5 Hz, 5-H), 5.7 (1 H, dt, *J* 16 and 7 Hz, 2-H), 5.1 (1 H, dd, *J* 11 and 6.5 Hz, 4-H), 4.72 (2 H, d, *J* 7 Hz, 1-H_2), 3.7 (3 H, s, OMe), and 2.02 (3 H, s, MeCO); *m/z* 156 (M^+, 42.4%), 113 (100), and 97 (78.3).

Diethyl (3RS,6SR)-3-*Acetoxymethyl*-6-*methoxy*-1,2,3,6-*tetrahydropyridazine*-1,2-*dicarboxylate* (**2**).—A solution of DEAD (5.3 g, 30.5 mmol) and diene (**1**) (4.7 g, 30.1 mmol) in toluene (30 ml) was heated to 80 °C for 100 min. The toluene was then removed by evaporation under reduced pressure, and the residue purified by chromatography [SiO_2; acetone–toluene (1:9)] to give the Diels–Alder *adduct* (**2**) (8.91 g, 89%), m.p. 33—37 °C [from ether–light petroleum (b.p. 50—70 °C)] (Found: C, 51.1; H, 6.7; N, 8.5. $C_{14}H_{22}N_2O_7$ requires C, 50.9; H, 6.65; N, 8.5%); $\nu_{max.}$ (KBr disc) 1 760—1 660 cm^{-1} (C=O and C=C); δ_H (80 MHz; $CDCl_3$) 6.0 (2 H, br, s 4- and 5-H), 5.5 (1 H, br, s, 6-H), 4.9 (1 H, m, 3-H), 4.2 (4 H, m, OCH_2CH$_3$), 4.05 (2 H, d, *J* 6 Hz, CH_2OAc), 3.4 (3 H, 2 × s, OMe), 1.95 (3 H, s, MeCO), and 1.25 (6 H, m, OCH$_2$CH_3); *m/z* 330 (M^+, 1.0%), 299 (3.5), 270 (18.9), 257 (97.0), and 185 (100).

Diethyl(3RS,4SR,5SR,6RS)-3-*Acetoxymethyl*-4,5-*dihydroxy*-6-*methoxyhexahydropyridazine*-1,2-*dicarboxylate* (**3**).—To a mixture of the Diels–Alder adduct (**2**) (3.3 g), acetone (4 ml), *N*-methylmorpholine *N*-oxide monohydrate (1.46 g), and water (4 ml) was added a catalytic amount of osmium tetraoxide [40 mg dissolved in t-butyl alcohol (4 ml)]. After being stirred for 5 d, the reaction mixture was poured into water (75 ml) containing sodium hydrogen sulphite (2 g). The mixture was extracted with ethyl acetate (6 × 50 ml) and the combined extracts were dried (Na_2SO_4) and concentrated to yield a yellow oil (3.66 g). Crystallisation from ether yielded the *diol* (**3**) as a solid (2.1 g). The mother liquors were purified by chromatography to yield starting material (0.53 g recovery) and a further crop of product (0.47 g). Yield based on consumed starting material, 83%, m.p. 108—109 °C (Found: C, 46.4; H, 6.65; N, 7.8. $C_{14}H_{24}N_2O_9$ requires C, 46.15; H, 6.6; N, 7.8%); $\nu_{max.}$ (KBr disc) 3 440 (OH) and 1 740—1 650 cm^{-1} (MeCO and NCO_2Et); δ_H [250 MHz; $(CD_3)_2SO$; 140 °C] 5.18 (1 H, d, *J* 3.3 Hz, 6-H), 4.7 (2 H, 2 × br s, OH), 4.43 (1 H, ddd, *J* 8.4, 5.8, and 4.3 Hz, 3-H), 4.34 (1 H, dd, *J* 11.6 and 4.3 Hz, C*H*HOAc) 4.28 (1 H, dd, *J* 11.6 and 8.4, CH*H*OAc), 4.130 and 4.133 (both 2 H, q, *J* 7.0 Hz, OCH_2CH$_3$), 3.88 (1 H, dd, *J* 5.8 and 2.7 Hz, 4-H), 3.62 (1 H, dd, *J* 3.3 and 2.7 Hz, 5-H), 3.37 (3 H, s, OMe), 1.97 (3 H, s, MeCO), and 1.226 and 1.220 (both 3 H, t, *J* 7.0 Hz, OCH$_2$CH_3); *m/z* 364 (M^+, 24%), 333 (3.5), 304 (17.4), 291 (17.9), 260 (10.8) 232 (47.7), 219 (47.7), and 187 (100).

Diethyl (3RS,6SR)-3-*Acetoxymethyl*-6-*benzyloxy*-1,2,3,6-*tetrahydropyridazine*-1,2-*dicarboxylate* (**5**).—To a solution of the Diels–Alder adduct (**3**) (1.0 g, 3.03 mmol) in dry methylene dichloride (5 ml) was added benzyl alcohol (0.4 g, 3.7 mmol), 4 Å molecular sieves (1 g), and boron trifluoride•ether complex (0.05 g, 0.36 mmol). After the mixture had been stirred for 6 h, aqueous sodium hydrogen carbonate was added and the mixture was filtered. The molecular sieves and the aqueous layers were both extracted with methylene dichloride, and the combined organic layers were dried, concentrated, and purified by chromatography [SiO_2; gradient elution with ethyl acetate–light petroleum (1:5→2:5)] to give recovered starting material (**3**) (0.075, 7.5% recovery) and the *benzyl ether* (**5**) (0.61 g, 50%) (Found: C, 59.05; H, 6.3; N, 7.0. $C_{20}H_{26}N_2O_7$ requires C, 59.1; H, 6.4; N, 6.9%); $\nu_{max.}$ (NaCl disc) 1 740 and 1 700 (CO); δ_H (250 MHz; $CDCl_3$) 7.3 (5 H, m, Ph), 5.94 (2 H, br s, 4- and 5-H), 5.74 and 5.61 (1 H, 2 × br s, 6-H), 4.98 (1 H, d, *J* 7 Hz, 3-H), 4.4—4.0 (6 H, m, OCH_2CH$_3$ and CH_2OAc), 2.06 and 2.04 (3 H, 2 × s, OAc), and 1.30, 1.29, and 1.19 (6 H, 3 × t, *J* 7 Hz, OCH$_2$CH_3); *m/z* 333 (1.5%), 299 (0.5), 261 (4.9), 227 (20.9), and 91 (100).

Diethyl (3RS,4SR,5SR,6RS)-3-*Acetoxymethyl*-6-*benzyloxy*-4,5-*dihydroxyhexahydropyridazine*-1,2-*dicarboxylate* (**6**).—To a solution of the benzyl ether (**5**) (7.6 g, 18.7 mmol) in acetone (20 ml) was added NMO (4.0 g, 29.6 mmol) and water (12 ml). To this mixture was added t-butyl alcohol (10 ml) containing osmium tetraoxide (0.1 g). After reaction for 8 d at room temperature the black solution was poured into water (20 ml) containing sodium hydrogen sulphite (1.5 g). Extraction with methylene dichloride and purification of the organic-soluble material by chromatography [SiO_2; ether–methylene dichloride (1:1)] and crystallisation (from toluene–light petroleum) gave the *diol* (**6**) as a solid (6.6 g, 80%), m.p. 132—133 °C (from toluene–light petroleum) (Found: C, 54.1; H, 6.35; N, 6.1. $C_{20}H_{28}N_2O_9$ requires C, 54.55; H, 6.4; N, 6.35%); $\nu_{max.}$ (KBr disc) 3 385 (OH), 1 740, 1 720, and 1 700 cm^{-1} (CO); δ_H [250 MHz; $(CO_3)_2SO$; 140 °C] 7.32 (5 H, br s, Ph), 5.39 (1 H, d, *J* 3.4 Hz, 6-H), 2.75 and 2.55 (2 H, ABq, *J* 12.2 Hz, OCH_2Ph), 5.50 (1 H, ddd, *J* 4.6, 5.8, and 8.2 Hz, 3-H), 4.46 (1 H, dd, *J* 4.6 and 11.6, C*H*HOAc), 4.40 (1 H, dd, *J* 8.2 and 11.6 Hz, CH*H*OAc), 4.10 (4 H, m, OCH_2CH$_3$), 3.96 (1 H, dd, *J* 2.7 and 5.8 Hz, 4-H), 3.69 (1 H, dd, *J* 2.7 and 3.4 Hz, 5-H), 2.7 (2 H, br s, OH), 1.98 (3 H, s, OAc), and 1.22 and 1.17 (6 H, 2 × t, *J* 7 Hz, OCH$_3$CH_3); *m/z* 440 (M^+, 0.08%), 397 (0.34), 333 (19.2), 316 (13.2), 289 (24.7), 261 (56.9), 201 (100), and 91 (100).

Diethyl (1SR,2RS,5RS,6SR)-2-*Acetoxymethyl*-5-*methoxy*-8,8-*dimethyl*-7,9-*dioxa*-3,4-*diazabicyclo*[4.3.0]*nonane*-3,4-*dicarboxylate* (**7**).—The diol (**3**) (3.6 g) was dissolved in a mixture of dry acetone (40 ml) and 2,2-dimethoxypropane (12 ml) and bis-*p*-nitrophenylphosphoric acid (0.3 g) added. After the mixture had been kept at room temperature for 24 h, sodium hydrogen carbonate (0.2 g) was added, and the mixture was stirred for 0.5 h. The solvent was removed under reduced pressure, and the residue purified by column chromatography to yield the required *isopropylidene derivative* (**7**) as an oil (6.01 g, 90%) (Found: C, 50.5; H, 6.95; N, 7.2. $C_{17}H_{28}N_2O_9$ requires C, 50.5; H, 6.95; N, 6.95%); $\nu_{max.}$ (NaCl disc) 1 740, 1 720, and 1 710 cm^{-1} (CO); δ_H [250 MHz; $(CD_3)_2SO$; 140 °C] 5.19 (1 H, d, *J* 0.75 Hz, 5-H), 4.57 (1 H, dd, *J* 5.8 and 6.4 Hz, 1-H), 4.51 (1 H, ddd, *J* 6.4, 6.3, and 7.0 Hz, 2-H), 4.32 (1 H, dd, *J* 6.3 and 10.9 Hz, C*H*HOAc), 4.25 (1 H, dd, *J* 7 and 10.9 Hz, CH*H*OAc), 4.16 (4 H, m, OCH_2CH$_3$), 4.07 (1 H, br, d, *J* 5.8 Hz, 6-H), 3.39 (3 H, s, OMe), 2.0 (3 H, s, COMe), 1.370, 1.368, 1.312, and 1.309 (6 H, 4 × s, CMe_2), and 1.245 and 1.240 (2 × 3 H, 2 × t, *J* 7.1 Hz, OCH$_2$CH_3); *m/z* 404 (M^+, 2.6%), 389 (7.6), 344 (6.1), 332 (15.9), 287 (14.5), 272 (30.4), 259 (7.2), and 29 (100).

Diethyl (1SR,2RS,5RS,6SR)-2-*Hydroxymethyl*-5-*methoxy*-8,8-*dimethyl*-7,9-*dioxa*-3,4-*diazabicyclo*[4.3.0]*nonane*-3,4-*dicarboxylate* (**8**) *and Diethyl* (1SR,2RS,5RS,6SR)-2-*t-Butyl*-

dimethylsilyloxymethyl-5-methoxy-8,8-dimethyl-7,9-dioxa-3,4-diazabicyclo[4.3.0]nonane-3,4-dicarboxylate (**9**).—The acetate (**7**) (1.0 g, 2.48 mmol) was dissolved in dry methanol (20 ml) and dry potassium carbonate (2 g) was added. The mixture was stirred at room temperature for 0.5 h before being filtered into ice-cold water (30 ml). The potassium carbonate was washed with methylene dichloride, and the aqueous methanol solution of the product was extracted with methylene dichloride (6 × 30 ml). The combined extracts were dried (Na_2SO_4) and concentrated to yield a nearly colourless oil (0.84 g), pure enough for the following reaction. A sample, prepared as above, was purified by chromatography [SiO_2; ether–light petroleum (1:1)] to yield an analytical sample of *alcohol* (**8**) as an oil (Found: C, 49.3; H, 7.2; N, 7.65. $C_{15}H_{26}N_2O_8$ requires C, 49.7; H, 7.2; N, 7.75%); $\nu_{max.}$ (NaCl disc) 3 500 (OH) and 1 710 cm^{-1} (CO); δ_H [250 MHz; $(CD_3)_2SO$; 140 °C] 5.16 (1 H, d, *J* 0.8 Hz, 5-H), 4.60 (1 H, dd, *J* 6.0 and 5.8 Hz, 1-H), 4.2 (5 H, m, OCH_2CH_3 and 2-H), 4.03 (1 H, br d, *J* 5.8 Hz, 6-H), 3.74 (2 H, br d, *J* 7.3 Hz, CH_2OH), 3.38 (3 H, s, OMe), 2.75 (3 H, br, s, OH + H_2O), and 1.363, 1.361, 1.311, and 1.309 (6 H, 4 × s, CMe_2); *m/z* 362 (M^+, 1.2%), 290 (2.4), 287 (7.6), 259 (6.4), and 132 (100).

To the crude alcohol (**8**) (0.84 g, 2.22 mol) was added t-butyldimethylsilyl chloride (0.61 g, 4.07 mmol), imidazole (0.35 g, 5.1 mmol), and dry DMF (3 ml). The mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation under reduced pressure and then under high vacuum, and the residue was dissolved in methylene dichloride (50 ml) and the solution was washed with water (2 × 20 ml). The dried (Na_2SO_4) organic layer was concentrated and purified by chromatography [SiO_2; ether–light petroleum (2:3)] to give the *protected product* (**9**) as an oil [1.03 g, 87% based on (**7**)] (Found: C, 52.8; H, 8.3; N, 6.05. $C_{21}H_{40}N_2O_8Si$ requires C, 52.95; H, 8.4; N, 5.9%); $\nu_{max.}$ (NaCl disc) 1 710 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$; 60 °C) 5.22 and 5.06 (1 H, 2 × s, 5-H), 4.55 (1 H, br t, *J* 4.4 Hz, 1-H), 4.2 (5 H, m, OCH_2CH_3 and 2- or 6-H), 3.95 (3 H, m, CH_2OSi and 6- or 2-H), 3.39 (3 H, s, OMe), 1.38, 1.36, 1.29, and 1.28 (6 H, 4 × s, CMe_2), 1.25 (6 H, t, *J* 7 Hz, OCH_2CH_3), 0.88 (9 H, s, $SiBu^t$), and 0.07 and 0.05 (6 H, 2 × s, $SiMe_2$); *m/z* 461 (M^+ − Me, 3.9%), 419 (81.4), and 73 (100).

(±)-5-*t-Butyldimethylsilyl-4-deoxy-1,4-bis(ethoxycarbonylamino)-2,3-O-isopropylidene-1-o-methyl-lyxitol* [1-O-*t-Butyldimethylsilyl-2-deoxy-2,5-bis(ethoxycarbonylamino)-3,4-O-isopropylidene-5-O-methylarabinitol*] (**10**).—To sodium (0.14 g, 6.1 mg-atom) in liquid ammonia (40 ml) cooled to −45 °C under dry nitrogen was added dropwise a solution of (**9**) (1.12 g, 2.3 mmol) in THF (10 ml). After reaction for 40 min, ammonium chloride (0.16 g, 3 mmol) was added and the solvents were removed under reduced pressure. To the residue was added ether, and the mixture was filtered through Kieselguhr and concentrated to yield a yellow gum (1.1 g). After chromatographic purification [SiO_2; ether–light petroleum (1:1)] the *product* (**10**) was obtained as a *gum* (0.89 g, 79%) (Found: C, 52.55; H, 8.85; N, 5.75. $C_{21}H_{42}N_2O_8Si$ requires C, 52.7; H, 8.8; N, 5.85%); $\nu_{max.}$ (NaCl disc) 3 455 and 3 330 (N–H), and 1 730 cm^{-1} (CO); δ_H* (250 MHz; CD_3CN) 6.1 (1 H, br, d, *J* 6 Hz, NH), 5.25 (1 H, br d, *J* 6 Hz, NH), 4.90 (1 H, dd, *J* 6.4 and 10.1 Hz, 1-H), 4.35 (1 H, dd, *J* 4.0 and 6.7 Hz, 3-H), 4.21 (1 H, dd, *J* 6.4 and 6.7 Hz, 2-H), 4.1 (4 H, m, OCH_2CH_3), 3.8 (1 H, br, m, 4-H), 3.62 (1 H, dd, *J* 5.1 and 10.1 Hz, 5-H), 3.45 (1 H, dd, *J* 8.1 and 10.1 Hz, 5′-H), 3.29 (3 H, s, OMe), 1.43 and 1.32 (6 H, 2 × s, CMe_2), 0.90 (9 H, s, $SiBu^t$), and 0.07 (6 H, s, $SiMe_2$); *m/z* 463 (M^+ − Me, 3.6%), 421 (29.0), 332 (8.4), 301 (14.2), 244 (33.2), 144 (63.1), and 73 (100).

* Lyxitol numbering.

(3RS,6SR)-3-*Hydroxymethyl-6-methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate* (**12**).—To the crude dienol (**4**) [10 g, prepared from methoxybutenyne (17.8 g, 217 mmol) in toluene (40 ml)] was added DEAD (8 g), in toluene (40 ml). The mixture was kept at room temperature for 1 h before the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO_2; ether) to give the *cyclised product* (**12**) (7.4 g, 12.5% yield from methoxybutenyne) as an oil (Found: C, 49.95; H, 7.1; N, 9.5. $C_{12}H_{20}N_2O_6$ requires C, 50.0; H, 7.0; N, 9.7%); $\nu_{max.}$ (NaCl disc) 3 500 (OH) and 1 710 cm^{-1} (CO); δ_H (80 MHz; $CDCl_3$) 5.75 (2 H, m, 4- and 5-H), 5.5 and 5.4 (1 H, 2 × s, 6-H), 4.85 (1 H, m, 3-H), 4.3 (4 H, m, OCH_2CH_3), 3.5 (2 H, m, CH_2OH), 3.5 (3 H, br s, OMe), and 1.2 and 1.15 (6 H, 2 × t, *J* 7 Hz, OCH_2CH_3); *m/z* 257 (24.6%), 226 (86.3), 213 (10.0), 185 (61.5), 153 (92.1), and 81 (100).

Diethyl (3RS,6SR)-3-*t-Butyldimethylsilyloxymethyl-6-methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate* (**13**).—To the Diels–Alder adduct (**12**) (1.24 g, 4.3 mmol) was added imidazole (0.73 g, 10.7 mmol), t-butyldimethylsilyl chloride (0.973 g, 6.5 mmol), and dry DMF (4 ml). The mixture was stirred for 3 h at room temperature. The volatiles were removed under reduced pressure and then under high vacuum, the residue was dissolved in methylene dichloride, and the solution was washed with water. After the solution had been dried (Na_2SO_4) and concentrated, the crude product (1.8 g) was purified by chromatography [SiO_2, ether–light petroleum (1:1)] to yield the *protected product* (**13**) as an oil (1.33 g, 74%) (Found: C, 53.25; H, 8.3; N, 6.8. $C_{18}H_{34}N_2O_6Si$ requires C, 53.7; H, 8.5; N, 6.95%); $\nu_{max.}$ (NaCl disc) 1 710 cm^{-1} (CO); δ_H (80 MHz; $CDCl_3$) 6.0 (2 H, m, 4- and 5-H), 6.5 (1 H, m, 6-H), 4.7 (1 H, m, 3-H), 4.2 (4 H, q, *J* 7 Hz, OCH_2CH_3), 4.0—3.5 (2 H, m, CH_2OSi), 3.5 (3 H, s, OMe), 1.3 (6 H, t, *J* 7 Hz, OCH_2CH_3), 1.0 (9 H, s, $SiBu^t$), and 0.2 (6 H, s, SiMe); *m/z* 387 (6.2%), 345 (100), 256 (21.2), 226 (9.4), 185 (61.5), 153 (88.8), and 81 (100).

Diethyl (3RS,4SR,5SR,6RS)-3-*t-Butyldimethylsilyloxymethyl-4,5-dihydroxy-6-methoxyhexahydropyridazine-1,2-dicarboxylate* (**14**).—To the tetrahydropyridazine (**13**) (1.02 g, 2.54 mmol) was added acetone (2 ml), *N*-methylmorpholine *N*-oxide monohydrate (0.5 g, 3.7 mmol), water (1 ml), and a catalytic amount of osmium tetraoxide [0.001 g dissolved in t-butyl alcohol (1 ml)]. After 7 d at room temperature under nitrogen, the reaction mixture was poured into water (20 ml) containing sodium hydrogen sulphite (0.5 g). This mixture was extracted with methylene dichloride (3 × 30 ml), and the combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography [SiO_2, ether–light petroleum (1:1)] to yield starting material (**13**) (0.21 g, recovery) and the *required product* (**14**) (0.76 g, 87% based on consumed starting material) as a solid, m.p. 85 °C (from ether–light petroleum) (Found: C, 49.5; H, 8.4; N, 6.4. $C_{18}H_{36}N_2O_8Si$ requires C, 49.5; H, 8.3; N, 6.4%); $\nu_{max.}$ (KBr disc) 3 480 and 3 380 (OH), 1 720, and 1 690 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 5.2 (1 H, m, 6-H), 4.5—3.8 (9 H, m, 4- and 5-H, CH_2OSi, OCH_2CH_3, and OH), 3.7 (1 H, m, 3-H), 3.3 (3 H, br s, OMe), 3.2 (1 H, br s, OH), 1.25 (6 H, 2 × t, *J* 7 Hz, OCH_2CH_3), 0.9 (9 H, s, $SiBu^t$), and 0.2 (6 H, 2 × s, $SiMe_2$); *m/z* 379 (100%), 275 (17.9), and 75 (43.6).

Acetonide (**9**) *from Diol* (**14**).—The diol (**14**) (0.1 g, 0.23 mmol) was dissolved in acetone (1 ml) and 2,2-dimethoxypropane (0.5 ml). Bis-*p*-nitrophenyl hydrogen phosphate (5 mg, 15 μmol) was added as an acid catalyst and the mixture was left at room temperature for 21 h. Potassium carbonate (5 mg, 36 μmol) was added and the mixture was stirred at room temperature for 0.5 h. After filtration and concentration the product was purified

by chromatography [SiO_2, ether–light petroleum (3:7)] to give (**9**) (0.08 g, 71%).

Ethyl (1SR,5RS,6SR,8RS)-6-*t-Butyldimethylsilyloxymethyl*-8-*ethoxycarbonylamino*-3,3-*dimethyl*-2,4-*dioxa*-7-*azabicyclo*-[3.3.0]*octane*-7-*carboxylate* (**15**).—To a solution of the lyxose derivative (**10**) (0.57 g, 1.19 mmol) in methylene dichloride (10 ml) was added bis-*p*-nitrophenyl phosphate (2 mg, 5.9 μmol). The mixture was left at room temperature for 30 min. The reaction was quenched with pyridine, and the mixture was concentrated and purified by chromatography [SiO_2; ether–light petroleum (1:1)] to give the pyrrolidine (**15**) (0.29 g) and recovered (**10**) (0.182 g). Yield of (**15**) based on consumed starting material 79%, m.p. 106.5—107 °C (from light petroleum) (Found: C, 53.95; H, 8.65; N, 6.4. $C_{20}H_{38}N_2O_7Si$ requires C, 53.8; H, 8.6; N, 6.25%); $\nu_{max.}$ (KBr disc) 3 300 (NH) and 1 700 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$; 60 °C) 5.45 (1 H, br s, NH), 5.0—4.85 (3 H, m, 1-, 5-, and 8-H), 4.40 (1 H, dd, *J* 9 and 4 Hz, C*H*HOSi), 4.2—4.0 (5 H, m, OCH_2CH_3 and 6-H), 3.80 (1 H, t, *J* 9 Hz, CH*H*OSi), 1.45 and 1.30 (6 H, 2 × s, CMe_2), 1.24 and 1.22 (6 H, 2 × q, *J* 7 Hz, OCH_2CH_3) 0.89 (9 H, s, SiBu^t), and 0.05 (6 H, s, $SiMe_2$); *m/z* 431 (14.3), 389 (91.3), 331 (100), and 242 (59.2).

(±)-4-*Deoxy*-1,4-*bis*(*ethoxycarbonylamino*)-2,3-O-*isopropylidene*-1-O-*methyl*-*lyxitol* [2-*Deoxy*-2,5-*bis*(*ethoxycarbonylamino*)-3,4-O-*isopropylidene*-5-O-*methylarabinitol*] (**11**).—To a solution of the initial product from the N–N cleavage reaction [compound (**10**)] (0.19 g, 0.40 mmol) in acetonitrile (1 ml) was added tetra-n-butylammonium fluoride trihydrate (0.15 g, 0.57 mmol). After 5 min the reaction mixture was acidified with acetic acid (0.04 g, 0.66 mmol). The solvent was removed under reduced pressure, and the residue purified by column chromatography [SiO_2; gradient elution with ethyl acetate–light petroleum (1:1→1.0)] and crystallised from ethyl acetate–light petroleum to yield the *alcohol* (**11**) (0.13 g, 89%), m.p. 108—109 °C (Found: C, 49.3; H, 7.95; N, 7.55. $C_{15}H_{28}N_2O_8$ requires C, 49.45; H, 7.75; N, 7.7%); $\nu_{max.}$ (KBr disc) 3 460 (OH), 3 320 (NH), 1 740, and 1 700 cm^{-1} (CO); δ_H* [250 MHz; $(CD_3)_2SO$] 7.50 (1 H, br d, *J* 7 Hz, NH), 6.08 (1 H, br, d, *J* 6 Hz, NH), 4.88 (1 H, br m, 1-H), 4.27 and 4.13 (2 H, 2 × br m, 2- and 3-H), 4.0 (4 H, m, OCH_2CH_3), 3.66 (1 H, br s, OH), 3.2—3.4 (6 H, m, OMe, 4-H, and 5-H_2), 1.41 and 1.25 (6 H, 2 × s, CMe_2), and 1.17 (6 H, m, OCH_2CH_3); *m/z* 349 (0.5%), 317 (0.9), 314 (0.7), 301 (5.7), and 244 (23.7).

Ethyl (1SR,5RS,6SR,8RS)-6-*Ethoxycarbonylamino*-8-*hydroxymethyl*-3,3-*dimethyl*-2,4-*dioxa*-7-*azabicyclo*[3.3.0]*octane*-7-*carboxylate* (**16**).—The previous preparation was repeated using compound (**15**) (0.24 g). To a solution of the crude product in THF (1 ml) was added THF (1 ml) containing 1 drop of concentrated HCl. After 15 min sodium hydrogen carbonate was added and the mixture was stirred for 15 min. After filtration, and concentration of the filtrate, the residue was purified by column chromatography [SiO_2; ether–methylene dichloride (4:1)] to give the alcohol (**16**) (0.139 g, 81%) as an oil. This was crystallised from ether–light petroleum to yield a solid. Similarly, after desilylation of (**15**) (0.12 g), the crude product was treated with bis-*p*-nitrophenyl phosphate (5 mg, 15 μmol) in toluene (2 ml) for 15 min. After the mixture had been quenched with pyridine the same product (**16**) (72 mg, 86%) was isolated, m.p. 89—90 °C (Found: C, 50.55; H, 7.2; N, 8.2. $C_{14}H_{24}N_2O_7$ requires C, 50.6; H, 7.3; N, 8.45%); $\nu_{max.}$ (KBr disc) 3 460 (OH), 3 320 (NH), 1 725, 1 700, and 1 660 cm^{-1} (NCO_2Et); δ_H (250 MHz; $CDCl_3$; 60 °C) 5.47 (1 H, br s, NH), 5.00 (2 H, m, 6-H and 1- or 5-H), 4.91 (1 H, d, *J* 6.1 Hz, 5- or 1-H), 4.3—4.0 (5 H, m, 8-H and OCH_2CH_3), 4.1 (1 H, br s, OH), 3.9 (2 H, br, t, *J* 6 Hz, CH_2OH), 1.45 and 1.31 (6 H, 2 × s, CMe_2), and 1.28 and 1.23 (6 H, 2 × t, *J* 7.3 Hz, OCH_2CH_3); *m/z* 317 (4.7%), 301 (16.3), 257 (6.1), 243 (11.7), and 29 (100).

(1RS,2SR,6RS,7SR)-7-*Ethoxycarbonylamino*-4,4-*dimethyl*-3,5,10-*trioxa*-8-*azatricyclo*[6.4.0.0^{2,6}]*undecan*-9-*one* (**17**).—To a solution of the pyrrolidine (**15**) (0.09 g, 0.20 mmol) in dry acetonitrile (2 ml) was added tetra-n-butylammonium fluoride trihydrate (0.11 g, 0.4 mmol) and the mixture kept at room temperature for 18 h. The solvent was evaporated off and the residue purified by chromatography [SiO_2; ether–methylene dichloride (1:4)] to yield the *tricyclic ketone* (**17**) as a solid (55 mg, 95%), m.p. 175—177 °C (from methylene dichloride–light petroleum) (Found: C, 50.15; H, 6.4; N, 10.0. $C_{12}H_{18}N_2O_6$ requires C, 50.35; H, 6.3; N, 9.8%); $\nu_{max.}$ (KBr disc) 3 360 (NH) and 1 745 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$; 60 °C) 5.34 (1 H, br s, NH), 5.15 (1 H, d, *J* 4 Hz, 7-H), 5.05 (1 H, d, *J* 5 Hz, 2-H), 4.85 (1 H, t, *J* 4 and 5 Hz, 6-H), 4.55 (2 H, m, 11-H_2), 4.41 (1 H, t, *J* 8 Hz, 1-H), 4.12 (2 H, q, *J* 7 Hz, OCH_2CH_3), 1.46 and 1.32 (6 H, 2 × s, CMe_2), and 1.27 (3 H, t, *J* 7 Hz, OCH_2CH_3); *m/z* 271 (5.7%), 228 (10.6), 167 (27.9), 142 (29.3), and 18 (100).

Crystal Data for (**16**).—$C_{14}H_{24}N_2O_7$, *M* = 332.0, monoclinic, *a* = 7.675(2), *b* = 24.063(7), *c* = 9.288(2) Å, β = 99.83(2)°, *V* = 1 969 Å^3, *Z* = 4, D_c = 1.31 g cm^{-3}, *F*(000) = 712, space group $P2_1/c$. *X*-Ray intensity data were collected on a Nicolet P3 diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.710 69 Å) using ω-scan with $2.0 < \dot{\omega} < 29.3°$ min^{-1} and $2.0 < 2\theta < 42°$. Of the 1 816 reflections collected, 1 437 with $I \geqslant 2\sigma(I)$ were considered observed. The structure was solved by direct methods using the SHELXTL program and refined by least squares to R_1 = 0.066 and R_2 = 0.067 {$R_1 = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$; $R_2 = [\Sigma w(|F_o| - |F_c|)^2]^{\frac{1}{2}}/[\Sigma w|F_o|^2]^{\frac{1}{2}}$; total reflections = 1 816, unobserved reflections = 379 with $I \leqslant 2\sigma$; 1 437 unique reflections with $I > 2\sigma$}. Weights based on counting statistics were used throughout. Tables of observed and calculated structure factors and positional and thermal parameters are given in Supplementary Publication No. SUP 23969 (25 pp.).†

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