A New Route to Chiral Hydroxypyrrolidines[1] from D-Erythrose *via* Intramolecular 1,3-Cycloaddition

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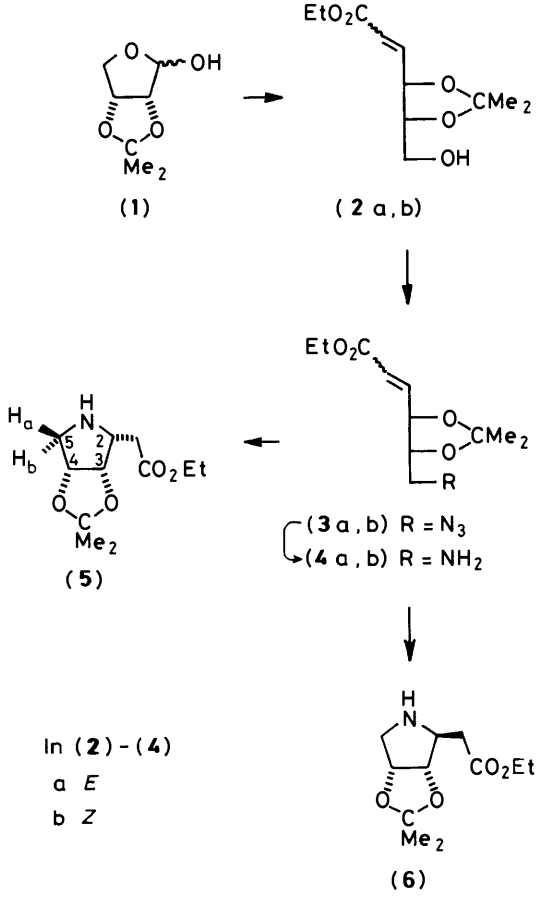
2,3-*O*-Isopropylidene-D-erythrose (**1**) reacted with ethoxycarbonylmethylene(triphenyl)phosphorane in refluxing benzene to give the *E* and *Z* alkene esters (**2a**) and (**2b**). The ester (**2a**) was converted, *via* the 6-triflate (**7a**) and 6-azide (**3a**), into the dihydrotriazole (**8**) by 1,3-cycloaddition. Ring opening of compound (**8**) with sodium ethoxide gave the pyrrolidine diazo ester (**9**) which on hydrogenolysis gave (2*R*,3*S*,4*R*)-ethyl (3,4-isopropylidenedioxypyrrolidin-2-yl)acetate (**5**). A similar series of reactions from the *Z*-ester (**2b**) gave the pyrrolidine ester (**6**), the 2*S*-isomer of (**5**). Thermolysis of the diazo ester (**10**), the 2*S*-isomer of (**9**), gave (*Z*)-(3*S*,4*R*)-ethyl (3,4-isopropylidenedioxypyrrolidin-2-ylidene)acetate (**12**) which was reduced with sodium cyanoborohydride to give the ester (**5**). The esters (**2a**) and (**2b**) undergo rapid and quantitative cyclisation in the presence of ethoxide ion. Kinetically the β-isomer (**18**) is preferred [100% from (**2b**), 86% from (**2a**)]; at equilibrium the α-isomer (**19**) is favoured (82%).

The reaction of sugar lactols with stabilised Wittig reagents was first studied by Zhdanov,[2] Kochetkov,[3] and their co-workers. It has attracted much attention as a means of synthesizing *C*-glycosyl compounds,[4–20] particularly since the thorough examination of the reaction by Moffatt and his colleagues[4] in 1975. As an extension of our interest in chiral pyrrolidines[21] we envisaged the sequence of reactions (**1**) ⟶ (**5**) or (**6**) from 2,3-*O*-isopropylidene-D-erythrose (**1**) shown in Scheme 1. The amines (**4**), derived from the azides (**3**), were expected to undergo conjugate addition to the double bond in the unsaturated ester to give a pyrrolidine ring.

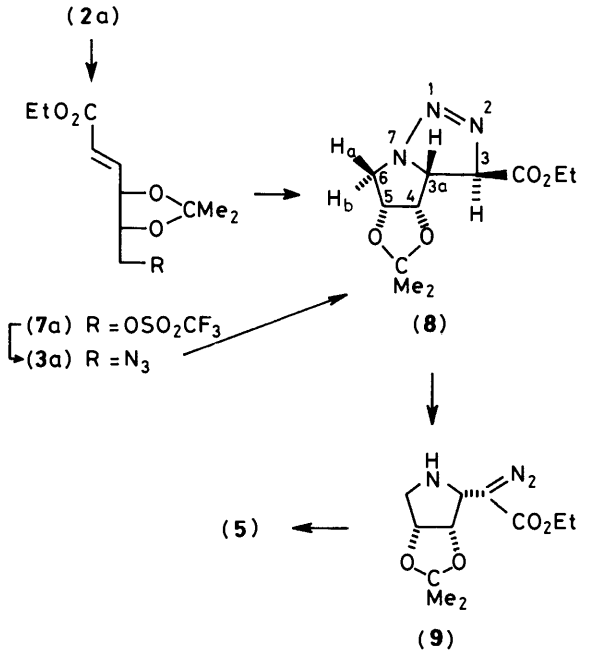


Scheme 1.

The acetonide (**1**), first described by Ballou[22] and Schaffer,[23] is easily prepared by periodate oxidation of 3,4-*O*-isopropylidene-D-arabinose,[22,24,25] or from D-glucose *via* 2,4-*O*-ethylidene-D-erythrose.[26] It reacted with ethoxycarbonylmethylene(triphenyl)phosphorane in boiling benzene[10] to give a mixture of *E* and *Z* alkenes which were separated by chromatography. The *E* geometry of the major product (**2a**) (56%) was assigned by ^{1}H n.m.r. spectroscopy. The signals due to 2-H and 3-H showed $J_{2,3}$ 15.6 Hz. The corresponding signals in the *Z*-isomer (**2b**) (21%) showed $J_{2,3}$ 12 Hz. In addition, the 4-H signal (δ 5.65) in (**2b**) appeared at considerably lower field compared with the corresponding 4-H signal in (**2a**) (δ 4.78) due to deshielding by the ester carbonyl group.[19]

Structures of type (**2**) readily undergo cyclisation, by an internal Michael addition, to give tetrahydrofurans.[4] This process occurs particularly easily in the case of α,β-unsaturated esters derived from 2,3-acetonides of sugars and can only be avoided by the use of non-basic solvents for the Wittig reaction.[10,14,17–19] The formation of tetrahydrofurans from the alkenes (**2a**) and (**2b**) is discussed later in the paper.

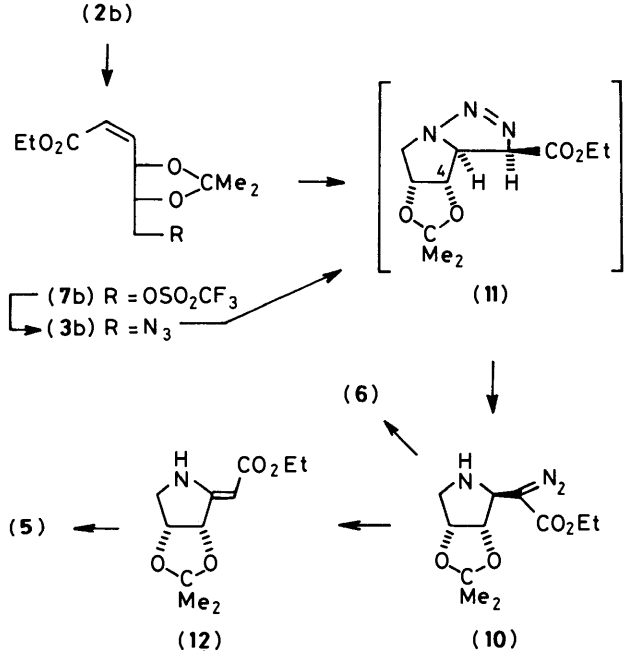
Since sulphonate esters vicinal to an isopropylidenedioxy group are relatively stable to nucleophilic attack[21] we chose the trifluoromethanesulphonate (triflate) ester (**7a**) as an entry to the azide (**3a**) (Scheme 2). The *E*-alkene (**2a**) was treated with trifluoromethanesulphonic (triflic) anhydride and pyridine in dichloromethane. Examination of the crude product by ^{1}H n.m.r. spectroscopy showed that the signals due to 6-H_2 were at lower field, overlapping the methylene quartet of the ethoxy group; otherwise the spectrum was very similar to that of the parent alcohol (**2a**). Reaction of the impure triflate (**7a**) with potassium azide and 1,4,7,10,13,16-hexaoxacyclo-octadecane (18-crown-6) in dichloromethane at room temperature gave not the azide (**3a**) but the crystalline 4,5-dihydrotriazole (**8**), the product of 1,3-cycloaddition of the azido group to the α,β-unsaturated ester; the overall yield from (**2a**) was 68%. The structure (**8**) is based on elemental analysis and spectroscopic data. The i.r. spectrum shows a carbonyl absorption at 1 735 cm^{-1} [*cf.* 1 720 cm^{-1} for (**2a**)] and no strong absorption at 2 100 cm^{-1} expected for an azido group. In the ^{1}H n.m.r. spectrum there were no signals corresponding to vinyl protons; that for 3-H appears as a doublet at δ 5.58, $J_{3,3a}$ 3 Hz, and the remainder



Scheme 2.

of the spectrum is consistent with the dihydrotriazole (**8**). The stereochemistry at C-3a was established fully by further transformations and comparisons. Treatment of compound (**8**) with sodium ethoxide in ethanol gave, in 86% yield, the diazo ester[27,28] (**9**) whose i.r. spectrum showed the presence of an NH group (3 340 cm^{-1}) and a diazo group (2 100 cm^{-1}); the ester carbonyl absorption now appeared at 1 690 cm^{-1}. In the ^1H n.m.r. spectrum of (**9**) the 2-H signal was a doublet, $J_{2,3}$ 4 Hz, indicating a *cis*-relationship of 2-H and 3-H[21] and that (**9**) belonged to the α-series. Catalytic hydrogenolysis[29] of the diazo group in (**9**) (palladium–charcoal) readily gave the acetic ester (**5**), one of our original targets, in 89% yield.

When a similar series of reactions was carried out on *Z*-alkene (**2b**) (Scheme 3) the intermediate triflate (**7b**) was



Scheme 3.

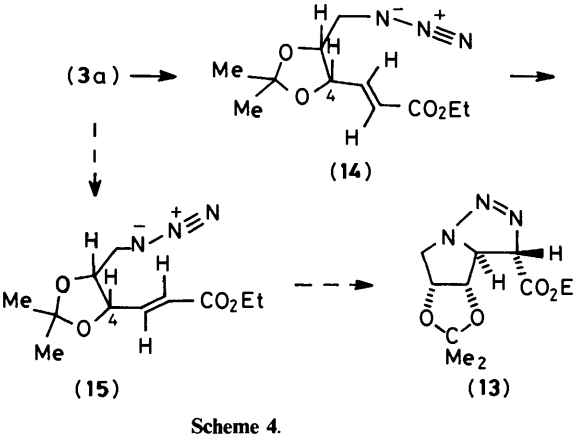
Table. ^{13}C N.m.r. data for pyrrolidines (**5**) and (**6**) and tetrahydrofurans (**18**) and (**19**) (δ-values in $CDCl_3$; 50 MHz)

		Isopropylidene	
Compound	CH_2CO	Acetal	Me_2
(**5**) (α)	33.55	110.63	23.94, 25.73
(**6**) (β)	34.76	112.44	24.21, 26.34
(**18**) (β)	36.53	113.07	25.08, 26.65
(**19**) (α)	33.63	111.97	24.73, 25.84

detected by n.m.r. spectroscopy. Subsequent reaction with potassium azide led to the isolation of the diazo ester (**10**) directly (65%) and neither the azide (**3b**) nor the dihydrotriazole (**11**) was observed as a stable intermediate. The i.r. spectrum of compound (**10**) was similar to that of the diazo ester (**9**); the ^1H n.m.r. spectrum showed the signal for 2-H as a singlet, δ 4.08, indicating a *trans* relationship with 3-H[21] and that compound (**10**) belonged to the β-series. Hydrogenolysis as before afforded the acetic ester (**6**) in 91% yield. The Table shows the ^{13}C n.m.r. data for the esters (**5**) and (**6**), which confirm the stereochemical assignments. In the all-*cis* isomer (**5**) the chemical shifts of the carbon atoms of the isopropylidene group and the acetate methylene group are shielded relative to those in (**6**).[4] The ^1H n.m.r. spectra of esters (**5**) and (**6**) are consistent with this assignment.[4,20,21]

There is a further entry into the all-*cis* pyrrolidine (**5**) from the β-series. When the diazo ester (**10**) was heated in boiling toluene[30] the vinylogous urethane (**12**) was isolated in 85% yield. We assign *Z*-stereochemistry to (**12**) by analogy and by comparison of ^1H n.m.r. data with known examples.[30–32] Reduction of the ester (**12**), at the β-face, was achieved using sodium cyanoborohydride to give the α-acetic ester (**5**) (69%). The ^1H n.m.r. spectra and other data for the ethyl esters (**5**) and (**12**) closely resemble those for the corresponding methyl esters which have been prepared by an alternative route[33] and used in a synthesis of the pyrrolizidine necine base retronecine.

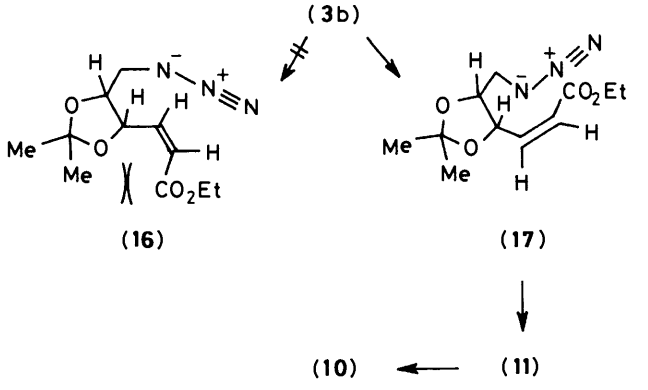
The formation of a 4,5-dihydrotriazole by 1,3-cycloaddition of an azide and an alkene[28] is concerted and stereospecific, and proceeds in a *cis*-manner.[34,35] For alkenes containing an electron-withdrawing substituent high regioselectivity is shown, leading to a 1,4-disubstituted 4,5-dihydrotriazole.[27,28] When the cycloaddition is intramolecular[36] a bicyclic system results.[28,36–39] In the case of our own azides (**3a**) and (**3b**) the dihydrotriazoles (**8**) and (**11**) show the expected regioselectivity. The high stereoselectivity calls for comment, particularly in the light of recent interest in the stereoselectivity of 3 + 2 dipolar cycloadditions.[40] Considering first the *E*-azide (**3a**), there was no evidence for the formation of the alternative dihydrotriazole (**13**) in which 3-H and 3a-H bear a *trans* relationship (Scheme 4).



Scheme 4.

From the examination of models there appears to be no steric preference for either of the transition states derived from the conformations (**14**) and (**15**) and leading to (**8**) and (**13**), respectively. It is apparent, however, that 4-O in (**14**) corresponds to an 'inside alkoxy' conformation similar to that described for nitrile oxide cycloadditions by Houk *et al.*[40] The transition state derived from (**15**) would be less stable, having 4-O 'outside.' This model is consistent with our finding that the dihydrotriazole (**8**) is formed exclusively from the *E*-azide (**3a**).

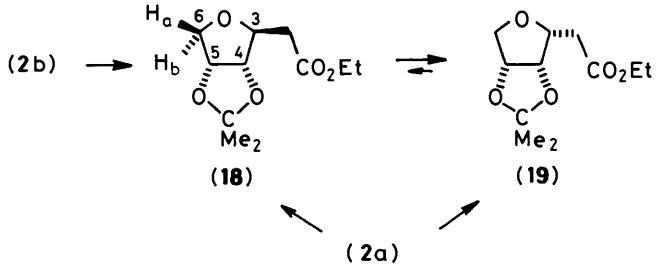
Turning now to the *Z*-azide (**3b**), there is good circumstantial evidence that an unstable 4,5-dihydrotriazole (**11**) is an intermediate in the formation of the β-diazo ester (**10**). The conformations of compound (**3b**) which would lead to cycloaddition are (**16**) and (**17**) (Scheme 5). It is evident that in



Scheme 5.

(**16**), corresponding to the 'inside alkoxy' conformation, there is a severe steric interaction of the ester group and a methyl of the isopropylidene group. The cycloaddition will therefore proceed *via* conformation (**17**), leading to the dihydrotriazole (**11**). It is interesting that in the case of nitrile oxide cycloadditions Houk *et al.*[40] suggest that a conformation similar to (**17**) is responsible for the formation of the minor isomer in their system. The relative instability of the dihydrotriazole (**11**) compared with (**8**) may be due to the eclipsing interaction of the ester group and C-4 together with the greater accessibility of 3-H for deprotonation (*cf.* ref. 38).

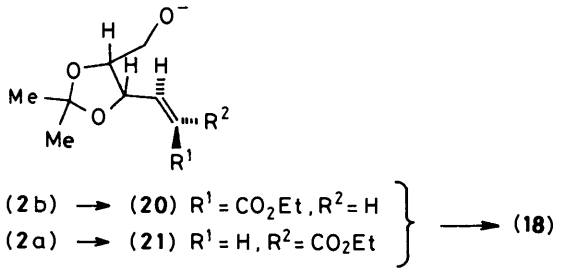
We have studied the behaviour of the unsaturated esters (**2a**) and (**2b**) towards ethanolic sodium ethoxide (Scheme 6). In the



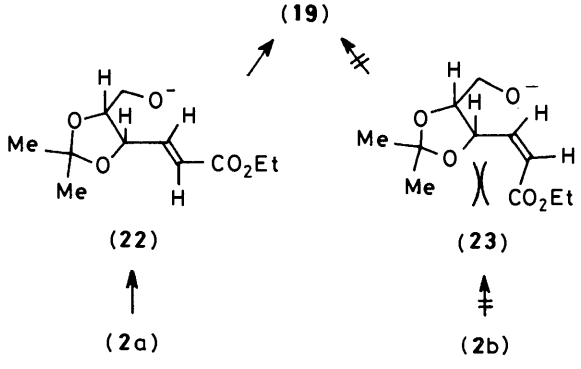
Scheme 6.

presence of a catalytic quantity of ethoxide the ester (**2b**) was converted, within two minutes at room temperature, into the tetrahydrofuran (**18**). The ^{13}C n.m.r. spectrum showed that a single isomer had been formed, and the β-configuration was assigned from the ^{1}H spectrum ($J_{3,4}$ 1.8, $J_{5,6a}$ 4.1, $J_{5,6b}$ 1.6 Hz).[20] When the ester (**2a**) was treated in the same way, a mixture of the tetrahydrofuran (**18**) and its α-epimer (**19**) was formed rapidly. The two compounds could not be separated by chromatography, but in the ^{1}H n.m.r. spectrum of the mixture the doublets due to the C-2 methylene protons were resolved [δ 2.5 for (**18**) and δ 2.8 for (**19**)]. This enabled the two isomers to be identified and the isomer ratio to be determined as 6:1 in favour of the β-epimer (**18**). When the ester (**18**) or its mixture with (**19**) was treated with 0.17M-ethanolic sodium ethoxide at room temperature for 48 h equilibration took place[4] giving a mixture which favoured the α-epimer (**19**) (4.5:1). From the ^{13}C n.m.r. spectrum of the equilibrated mixture the spectrum of the α-epimer (**19**) could easily be obtained. The signals due to C-2 and the isopropylidene carbons of (**19**) were shielded relative to those for (**18**) (Table), thereby confirming both structures.[4]

The stereoselectivity of the ring closures and the factors affecting the isomer ratio at equilibrium are interesting features of these reactions, and we shall discuss them in turn. The ring closure of the esters (**2a**) and (**2b**) is an intramolecular conjugate addition,[41] designated *5-exo-trig* in the Baldwin nomenclature.[41,42] Taking into account steric interactions and the necessity for the correct angle of attack by the 6-oxyanion the likely conformations leading to the β-epimer (**18**) are (**20**) [from the *Z*-alkene (**2b**)] and (**21**) [from (**2a**)] (Scheme 7). It is suggested (Scheme 8) that the α-epimer (**19**) is formed, from the



Scheme 7.

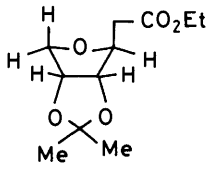


Scheme 8.

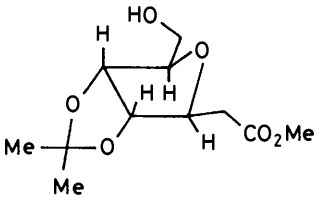
E-alkene (**2a**), *via* the less stable conformation (**22**), which resembles conformation (**14**) for the azide cycloaddition. The complete selectivity in the conversion of the *Z*-alkene (**2b**) into the β-epimer (**18**) is explained by the steric demands of anion (**23**), the conformation necessary to produce the α-epimer (**19**). The difference in stereoselectivity in the formation of 'α'-dihydrotriazole (**8**) from (**3a**) and mainly the 'β'-tetrahydrofuran (**18**) from (**2a**) is accommodated by the 'inside alkoxy' rule[40] for the azide–alkene cycloaddition and the requirement for *exo*-trigonal geometry[41] for tetrahydrofuran formation. Fukomoto and his colleagues[43] have recently described examples of the intramolecular conjugate addition of a deprotonated acetamide group to give chiral pyrrolidines; the stereoselectivity is consistent with our results for the tetrahydrofurans.

The equilibration of the esters (**18**) and (**19**) under basic conditions was to be expected, as was the preference for the

all-*cis* isomer (**19**) at equilibrium.[4] It is interesting that the β-epimer (**18**) appears, from the ^{1}H n.m.r. data, to adopt the E_o conformation (**24**)[20] whereas in the D-*ribo* series the corresponding β-epimer exists in the ^oE conformation (**25**).[4,20] The mechanism of interconversion in base must involve retro-Michael addition,[4] with the *E*-alkene (**2a**) as the crucial intermediate.



(**24**)



(**25**)

Experimental

I.r. spectra were measured for KBr discs or for films, using Perkin-Elmer *157G*, 257, or 5800 spectrophotometers. N.m.r spectra were recorded on the following spectrometers: JEOL MH100 (100 MHz), Bruker WP200SY (200 MHz), and Bruker WH360 (360 MHz) with internal tetramethylsilane as standard. Specific rotations refer to room temperature (20—25 °C) and were measured using a Bendix NPL 143D automatic polarimeter with a path length of 1 cm.

Evaporations were carried out under reduced pressure (rotary evaporator). Column chromatography was carried out using silica gel (Merck 7734 or equivalent). For t.l.c., precoated aluminium plates (Kieselgel $60F_{254}$, Merck 5554) was used, with detection by *p*-anisaldehyde in ethanol,[44] followed by heating on an electric plate. Ether refers to diethyl ether.

(Z)-*Ethyl* 2,3-*Dideoxy*-4,5-O-*isopropylidene*-D-erythro-*hex*-2-*enonate* (**2b**) *and its* E-*isomer* (**2a**).—2,3-*O*-Isopropylidene-D-erythrose (**1**)[22] (4.0 g, 25 mmol) was dissolved in dry benzene (50 ml) containing ethoxycarbonylmethylene(triphenyl)phosphorane (17.4 g, 50 mmol) and the solution was heated at reflux for 6 h. Analysis (t.l.c.) showed complete consumption of the sugar (**1**) and the appearance of two spots of greater polarity which instantly decolorised permanganate. Ether (100 ml) was added to the cool solution and the mixture was kept at 4 °C for 2 h. After filtration, solvents were removed by evaporation and the residue was chromatographed on silica. Hexane–ether (85:15) eluted first the Z-*alkene* (**2b**) as a syrup (1.2 g, 21%); $[\alpha]_D$ +152.3° (*c* 2.4 in $CHCl_3$); $\nu_{max.}$(film) 3 500, 3 000, 2 950, 2 890, and 1 720 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.30 (3 H, t, CH_2Me), 1.40 and 1.56 (2 × 3 H, 2 s, CMe_2), 2.15 (1 H, br s, OH), 3.55 (2 H, m, 6-H_2), 4.20 (2 H, q, CH_2Me), 4.60 (1 H, m, 5-H), 5.65 (1 H, ddd, 4-H), 5.95 (1 H, dd, $J_{2,3}$ 12, $J_{2,4}$ 2 Hz, 2-H), and 6.45 (1 H, dd, $J_{3,2}$ 12, $J_{3,4}$ 8 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 14.16 (CH_2Me), 24.66 and 27.39 (CMe_2), 60.60 and 61.54 (CH_2Me and C-6), 74.35 and 78.35 (C-4 and -5), 108.87 (CMe_2), 121.09 (C-2), 147.11 (C-3), and 165.96 p.p.m. (C-1) (Found: M^+, 230.111. $C_{11}H_{18}O_5$ requires *M*, 230.115).

Eluted second was the E-*alkene* (**2a**) as a syrup (3.2 g, 56%); $[\alpha]_D$ +32.7° (*c* 1.6 in $CHCl_3$); $\nu_{max.}$(film) 3 490, 2 980, and 1 720 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.38 and 1.50 (2 × 3 H, 2 s, CMe_2), 2.22 (1 H, br s, exch. D_2O, OH), 3.55 (2 H, d, 6-H_2), 4.18 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.35 (1 H, m, 5-H), 4.78 (1 H, ddd, $J_{4,3} = J_{4,5} = 5.5$, $J_{4,2}$ 1.6 Hz, 4-H), 6.10 (1 H, dd, $J_{2,3}$ 15.6, $J_{2,4}$ 1.6 Hz, 2-H), and 6.87 (1 H, dd, $J_{3,2}$ 15.6, $J_{3,4}$ 5.5 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 14.25 (CH_2Me), 25.28 and 27.73 (CMe_2), 60.64 and 61.91 (CH_2Me and C-6), 76.11 and 78.43 (C-4 and -5), 109.59 (CMe_2), 123.23 (C-2), 142.18 (C-3), and 165.92 p.p.m. (C-1) (Found: M^+, 230.114. $C_{11}H_{18}O_5$ requires *M*, 230.115).

(3R,3aR,4S,5R)-*Ethyl* 3a,4,5,6-*Tetrahydro*-4,5-*isopropylidenedioxy*-3H-*pyrrolo*[1,2-c][1,2,3]*triazole*-3-*carboxylate* (**8**).—A solution of the alkene (**2a**) (100 mg) in dichloromethane (3 ml) was injected into a cooled (−78 °C) mixture of dichloromethane (5 ml), pyridine (1 ml), and trifluoromethanesulphonic anhydride (0.17 ml, 1.5 mol equiv.) under nitrogen. The reaction mixture was allowed to warm to room temperature and was stirred for a further 15 min. After addition of more dichloromethane (to 30 ml) the solution was extracted with M-HCl and dried ($MgSO_4$). In a parallel experiment the solution was examined by ^{1}H n.m.r. spectroscopy: δ_H (100 MHz; $CDCl_3$) 1.27 (3 H, t, CH_2Me), 1.38 and 1.55 (2 × 3 H, 2 s, CMe_2), 4—4.3 (4 H, m, CH_2Me and 6-H_2), 4.4 (1 H, m, 5-H), 4.8 (1 H, m, 4-H), 6.08 (1 H, d, 2-H), and 6.72 (1 H, dd, 3-H), these data corresponding to those of the triflate (**7a**). To the solution was added potassium azide (36 mg, 1.1 mol equiv.) and 18-crown-6 (121 mg, 1.1 mol equiv.) and the mixture was stirred overnight. The residue left after evaporation was chromatographed on silica. Hexane–ether (8:2) eluted the *dihydrotriazole* (**8**), which crystallised from ether–hexane as needles (76 mg, 68%), m.p. 60—62 °C; $[\alpha]_D$ −493° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$(KBr) 3 300, 2 950, 1 736, 1 190, and 1 090 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.23—1.33 (9 H, m, CMe_2 and CH_2Me), 3.44 (1 H, dd, $J_{6a,6b}$ 14.4, $J_{6a,5}$ 3.9 Hz, 6-H_a) 3.96 (1 H, dd, $J_{3a,4}$ 5.6, $J_{3a,3}$ 3.0 Hz, 3a-H), 4.25 (1 H, dq, CH_2Me), 4.47 (1 H, d, $J_{6b,6a}$ 14.4 Hz, 6-H_b), 4.59 (1 H, app. t, $J_{4,3a} = J_{4,5} \sim 5.7$ Hz, 4-H), 4.74 (1 H, dd, $J_{5,4}$ 5.7, $J_{5,6a}$ 3.9 Hz, 5-H), and 5.58 (1 H, d, $J_{3,3a}$ 3.0 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 14.10 (CH_2Me), 24.05 and 25.85 (CMe_2), 53.98, 62.10, 63.57, 80.29, 80.54, 92.31, 112.38 (CMe_2), and 167.88 p.p.m. (C=O) (Found: C, 51.5; H, 6.65; N, 16.5. $C_{11}H_{17}N_3O_4$ requires C, 51.8; H, 6.7; N, 16.5%).

(2R,3S,4R)-*Ethyl Diazo*(3,4-*isopropylidenedioxypyrrolidin*-2-*yl*)*acetate* (**9**).—The dihydrotriazole (**8**) (200 mg, 0.78 mmol) was dissolved in ethanol (10 ml) and a solution of 0.5M-sodium ethoxide in ethanol (3 ml, 1.5 mmol) was added. The solution became pale yellow almost immediately, due to formation of the diazo ester (**9**). After 30 min at room temperature the mixture was diluted with dichloromethane and extracted with water. The organic layer was dried ($MgSO_4$) and evaporated to give the *diazo ester* (**9**), as a yellow syrup (172 mg, 86%); $[\alpha]_D$ −80.6° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(film) 3 340, 2 980, 2 100 (C=N_2), and 1 690 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.31 and 1.43 (2 × 3 H, 2 s, CMe_2) 2.00 (1 H, br s, NH), 2.73 (1 H, dd, $J_{5a,5b}$ 12.1, $J_{5a,4}$ 3.8 Hz, 5-H_a), 3.16 (1 H, d, $J_{5b,5a}$ 12.1 Hz, 5-H_b), 3.65 (1 H, d, $J_{2,3}$ 4.0 Hz, 2-H), 4.21 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.64 (1 H, dd, $J_{3,2} \sim 4$, $J_{3,4}$ 5.8 Hz, 3-H), and 4.70 (1 H, $J_{4,3}$ 5.8, $J_{4,5a}$ 3.8 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 14.48 (CH_2Me), 24.21 and 25.90 (CMe_2), 51.42, 56.41, 60.80, 80.31, 91.25, 111.25 (CMe_2), and 166.48 p.p.m. (C=O) (no signal due to C=N_2 was detected) (Found: $[M + H]^+$, 256.128. $C_{11}H_{18}N_3O_4$ requires *m/z*, 256.130).

(2R,3S,4R)-*Ethyl* (3,4-*Isopropylidenedioxypyrrolidin*-2-*yl*)-*acetate* (**5**).—The diazo ester (**9**) (100 mg) was dissolved in ethanol (25 ml) and hydrogenated over palladium–charcoal (10%; 5 mg) for 4 h. The suspension was filtered through Celite and the filtrate was evaporated. The resulting syrup was dissolved in ether and the solution was filtered through silica gel. Evaporation afforded the *ester* (**5**) as a syrup (80 mg, 89%); $[\alpha]_D$ −55.8° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$(film) 3 300, 2 980, 2 930, and 1 735 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.30 and 1.44 (2 × 3 H, 2 s, CMe_2), 1.96 (1 H, br s, NH), 2.65 (3 H, m, $COCH_2$ and 5-H_a), 3.06 (1 H, m, 2-H), 3.10 (1 H, d, $J_{5b,5a}$ 13.1, $J_{5b,4}$ 0 Hz, 5-H_b), 4.16 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.62 (1 H, app. t, $J \sim 4.5$ Hz, 3- or 4-H), and 4.69 (1 H, app. t, $J \sim 4.5$ Hz, 4- or 3-H); δ_C (50 MHz; $CDCl_3$) 14.18 (CH_2Me), 23.94 and 25.73 (CMe_2), 33.55 ($COCH_2$), 52.39,

59.78, 60.57, 81.37, 81.91, 110.63 (CMe_2), and 171.89 p.p.m. (C=O) (Found: $[M + H]^+$, 230.137. $C_{11}H_{20}NO_4$ requires *m/z* 230.139).

(2S,3S,4R)-*Ethyl Diazo*(3,4-*isopropylidenedioxypyrrolidin*-2-*yl*)*acetate* (**10**).—The alkene (**2b**) (100 mg) dissolved in dichloromethane (3 ml) was subjected to reaction with trifluoromethanesulphonic anhydride as described for the alkene (**2a**). The intermediate triflate (**7b**) was examined by ^1H n.m.r. spectroscopy: δ_H (100 MHz; $CDCl_3$) 1.33 (3 H, t, CH_2Me), 1.43 and 1.56 (2 × 3 H, 2 s, CMe_2), 4.28 (2 H, q, CH_2Me), 4.33 (1 H, dd, 6-H_a), 4.56 (1 H, dd, 6-H_b), 4.80—4.96 (1 H, m, 5-H), 5.6—5.8 (1 H, m, 4-H), 6.09 (1 H, dd, 2-H), and 6.47 (1 H, dd, 3-H). Reaction with potassium azide gave a product which was purified by chromatography on silica. Hexane–ether (1:1) eluted the *diazo ester* (**10**) (72 mg, 65%) as a yellow syrup; $[\alpha]_D$ −53.1° (*c* 7.0 in $CHCl_3$); $\nu_{max.}$(film) 3 340, 2 980, 2 090 (C=N_2), and 1 690 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.31 and 1.47 (2 × 3 H, 2 s, CMe_2), 2.42 (1 H, br s, NH), 2.78 (1 H, dd, $J_{5a,5b}$ 13.6, $J_{5a,4}$ 3.6 Hz, 5-H_a), 3.10 (1 H, d, $J_{5b,5a}$ 13.6 Hz, 5-H_b), 4.08 (**1** H, s, 2-H), 4.22 (2 H, q, *J* 7.1 Hz, CH_2Me), and 4.72—4.81 (2 H, m, 3- and 4-H); δ_C 14.48 (CH_2Me), 24.12 and 26.34 (CMe_2), 53.18, 58.15 (weak), 60.30, 60.77, 81.69, 85.40, 111.47 (CMe_2), and 166.38 p.p.m. (C=O) (Found: $[M + H]^+$, 256.128. $C_{11}H_{18}N_3O_4$ requires *m/z* 256.130).

(2S,3S,4R)-*Ethyl* (3,4-*Isopropylidenedioxypyrrolidin*-2-*yl*)-*acetate* (**6**).—The diazo ester (**10**) (150 mg) was dissolved in ethanol (25 ml) and hydrogenated over palladium–charcoal (10%; 7.5 mg) for 4 h. Isolation of the product as for the ester (**5**) gave the *ester* (**6**) as an oil (122 mg, 91%); $[\alpha]_D$ +36.0° (*c*, 4.2 in $CHCl_3$); $\nu_{max.}$(film) 3 320, 2 980, 1 730, and 1 370 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.28 and 1.45 (2 × 3 H, 2 s, CMe_2), 2.32 (3 H, *J* 7.8 Hz, $COCH_2$ and NH), 2.85 (1 H, dd, $J_{5a,b}$ 13.6, $J_{5a,4}$ 4.0 Hz, 5-H_a), 3.04 (1 H, d, $J_{5b,5a}$ 13.6 Hz, 5-H_b), 3.60 (1 H, t, *J* 7.8 Hz, 2-H), 4.14 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.41 (1 H, d, $J_{3,4}$ 5.6 Hz, 3-H), and 4.68 (1 H, app. t, *J* ~ 5 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 14.11 (CH_2Me), 24.21 and 26.34 (CMe_2), 34.76 ($COCH_2$), 50.89, 61.14, 61.24, 79.78, 84.25, 112.44 (CMe_2), and 170.39 p.p.m. (C=O) (Found: $[M + H]^+$, 230.139. $C_{11}H_{20}NO_4$ requires *m/z* 230.139).

(Z)-(3S,4R)-*Ethyl* (3,4-*Isopropylidenedioxypyrrolidin*-2-*yl*-*idene*)*acetate* (**12**).—The diazo ester (**10**) (100 mg) was dissolved in dry, deoxygenated toluene (30 ml) and the solution was heated under reflux for 4 h. Examination by t.l.c. showed that complete conversion of (**10**) into a less polar compound had occurred. Evaporation of the solvent followed by chromatography of the residue on silica [hexane–ether (9:1)] gave the *ester* (**12**), which crystallised from ether–hexane as needles (75 mg, 85%), m.p. 98—99 °C; $\nu_{max.}$(KBr) 3 340, 2 980, 1 660, and 1 150 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.37 and 1.42 (2 × 3 H, 2 s, CMe_2), 3.67 (2 H, m, 5-H_2), 4.10 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.73 (2 H, m, 4-H and =CH), 5.00 (1 H, d, *J* 5.8 Hz, 3-H), and 7.6 (1 H, br s, NH); δ_C (50 MHz; $CDCl_3$), 14.60 (CH_2Me), 26.05 and 27.34 (CMe_2), 51.71, 58.81, 76.15, 79.54, 81.68, 112.85 (CMe_2), 163.09, and 170.91 p.p.m. (Found: C, 57.9; H, 7.5; N, 5.8. $C_{11}H_{17}NO_4$ requires C, 58.15; H, 7.5; N, 6.2%).

Reduction of Ester (**12**) *with Sodium Cyanoborohydride*.—The ester (**12**) (50 mg) was dissolved in ethanol (5 ml) containing sodium cyanoborohydride (50 mg) and Bromocresol Green (~1 mg). 0.5M-Hydrochloric acid was added to the stirred solution until the indicator remained yellow. After a further 1 h the mixture was poured into water (20 ml) rendered alkaline by addition of 0.1M-sodium hydroxide, and extracted (4 times) with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by chromatography on silica with ether as eluant afforded the pyrrolidine ester (**5**) (35 mg, 69%) as an oil, indistinguishable (i.r., ^1H n.m.r., and t.l.c.) from an authentic sample obtained by the earlier method.

Ethyl 3,6-*Anhydro*-2-*deoxy*-4,5-O-*isopropylidene*-D-*ribo*-*hexonate* (**18**).—The alkene (**2b**) (100 mg) was dissolved in absolute ethanol (4 ml) and sodium ethoxide (0.1M; 3 ml) was added. After 2 min the reaction mixture was poured into water and extracted with dichloromethane (3 × 30 ml). The combined extracts were dried ($CaCl_2$) and evaporated to give the *tetrahydrofuran* (**18**) as an oil (95 mg, 95%); $[\alpha]_D$ −47.9° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$(film) 2 980, 2 940, 2 860, and 1 735 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.32 and 1.50 (2 × 3 H, 2 s, CMe_2) 2.47 (2 H, d, $J_{2,3}$ ~7 Hz, 2-H), 3.86 (1 H, dd, $J_{6a,6b}$ 10.6, $J_{6a,5}$ 4.1 Hz, 6-H_a), 3.95 (1 H, dd, $J_{6b,6a}$ 10.6, $J_{6b,5}$ ~1.6 Hz, 6-H_b), 4.16 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.43 (1 H, dt, $J_{3,2}$ ~7, $J_{3,4}$ 1.8 Hz, 3-H), 4.56 (1 H, dd, $J_{4,5}$ 6.2, $J_{4,3}$ 1.8 Hz, 4-H), and 4.81 (1 H, m, 5-H); δ_C (50 MHz; $CDCl_3$) 14.14 (CH_2Me), 25.08 and 26.65 (CMe_2), 36.53 (C-2), 60.77 (CH_2Me), 72.34 (C-6), 81.00, 81.10, and 84.57 (C-3, -4, and -5), 113.07 (CMe_2), and 170.37 p.p.m. (C-1) (Found: C, 57.3; H, 8.0. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.8%).

Reaction of the E-*Alkene* (**2a**) *with Sodium Ethoxide*.—The alkene (**2a**) (100 mg, 0.43 mmol) was treated as for (**2b**) above to give a mixture of tetrahydrofurans (**18**) and (**19**) (94 mg, 94%) which were not separable by t.l.c. The ^1H n.m.r. spectrum of the mixture (60 MHz; $CDCl_3$) showed doublets (due to 2-H_2) at δ 2.5 [β-isomer (**18**)] and δ 2.8 [α-isomer (**19**)] whose integrals were in the ratio 6:1.

Equilibration of the above mixture was effected by dissolving the oil in absolute ethanol containing sodium ethoxide (0.17M; 4.5 ml). After 48 h at room temperature the product was isolated as before to give an oil (90 mg, 96%) whose ^1H n.m.r. spectrum showed the ratio of (**18**) and (**19**) to be 1:4.5, by integration of the C-2 methylene doublets. From this α-enriched mixture the ^{13}C n.m.r. spectrum of methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*arabino*-hexonate (**19**) was determined by subtraction of the spectrum due to the D-*ribo* isomer (**18**); δ_C (50 MHz; $CDCl_3$) 13.95 (CH_2Me), 24.73 and 25.84 (CMe_2), 33.63 (C-2), 60.31 (CH_2Me), 72.47 (C-6), 78.18, 80.67, and 80.97 (C-3, -4, and -5), 111.97 (CMe_2), and 170.85 p.p.m. (C-1).

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