Enantiospecific synthesis of (−)-5-*epi*-shikimic acid and (−)-shikimic acid

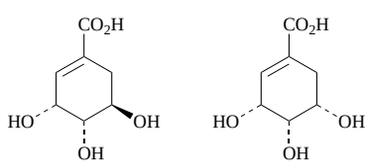
Shende Jiang,[a] Kevin J. McCullough,[b] Boualem Mekki,[a] Gurdial Singh[a] and Richard H. Wightman[b]

[a] *Department of Chemistry, University of Sunderland, Sunderland, UK SR1 3SD*
[b] *Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, UK EH14 4AS*

Diastereoselective reaction of 2,3-*O*-isopropylidene-D-ribose with allylmagnesium chloride gave a 5:1 mixture of triols 4 and 5, which were then converted to nitrones 8 and 9. Intramolecular nitrone cycloaddition gave the isoxazolidines 10 and 11, which on acetylation gave the corresponding acetates 12 and 13 which were separated by repeated crystallisation. The major adduct 12 was converted to (−)-5-*epi*-shikimic acid 2. Reaction of the ribonolactone derivative 20 with allylmagnesium chloride gave the hemiacetal 21. Reduction of compound 21 with DIBAL afforded exclusively the diol 22, which was desilylated to give the triol 5. Similar chemistry to that employed for the synthesis of (−)-5-*epi*-shikimic acid 2 with the diol 5 resulted in the synthesis of (−)-shikimic acid 1.

Introduction

(−)-Shikimic acid **1** is a key biosynthetic intermediate that is produced from D-glucose and gives its name to the pathway by which the aromatic amino acids and a wide range of secondary metabolites are formed in microorganisms and also in the leaves and fruits of many plants.[1] The important role that (−)-shikimic acid **1** has in living systems was established by the pioneering work of Davis,[2] Sprinson[3] and Gibson.[4] However the shikimate pathway is not operative in mammals and thus they have to obtain the three aromatic amino acids (L-Phe, L-Tyr and L-Trp) through dietary means. The biochemical significance of this has led to much interest in the chemistry of acid **1**, and following the early synthesis of natural shikimic acid (−)-**1** from D-arabinose[5a] a number of other reports have appeared on the conversion of sugars to compound (−)-**1**.[5b–g] Here we report new direct routes to both compound (−)-**1** and the previously



1 **2**

unreported (−)-5-*epi*-shikimic acid **2** from D-ribose.[6] Central to our strategy was the intramolecular nitrone cycloaddition reaction which established the carbocyclic ring.

Results and discussion

We have previously shown that the reaction of 2,3-*O*-isopropylidene-D-ribose **3** with diallylzinc gives the D-*allo*-triol **4** (Scheme 1) with high diastereoselectivity,[7] a result that can be rationalised by reaction either *via* a Felkin–Anh transition state (Fig. 1) or a cyclic chelate (Fig. 2).[8] Alternatively treatment of compound **3** with an excess of allylmagnesium chloride results in the formation of a mixture of diastereoisomers **4** and **5** in the ratio 5:1, that proved difficult to separate. Cleavage of this mixture of triols **4** and **5** with sodium periodate gave the lactols **6** and **7** in quantitative yield with each compound being present as an anomeric mixture. The ^{13}C chemical shifts of these anomers were correlated to the configuration of the anomeric carbon[9] as the chemical shift of C-1 in the 1,2-*trans*-anomers

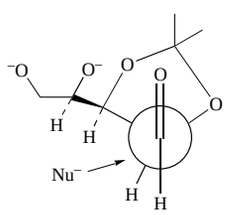


Fig. 1 Felkin–Anh transition state

6β and **7α**† was observed at 102.72 and 100.66 ppm, respectively, whilst the *cis*-anomers **6α** and **7β** gave resonances for C-1 at 95.65 and 96.51 ppm. The mixture of products **6** and **7** was treated with an excess of *N*-methylhydroxylamine hydrochloride (10 mol equiv.) in pyridine to give a mixture of nitrones **8** and **9**. We have found that the use of an excess of *N*-methylhydroxylamine hydrochloride was necessary for the formation of nitrone to proceed to completion. Under other conditions (MeNHOH·HCl 1.5 mol equiv., NEt_3 2.4 mol equiv., 3 Å molecular sieves, in CH_2Cl_2 at room temperature) there was still a large amount of starting material remaining even after 4 days. Cyclisation of the nitrones proceeded smoothly in boiling toluene and afforded the isoxazolidines **10** and **11** in 91% yield for the two steps. Alternatively, the isoxazolidine **10** could be prepared selectively from the triol **4** that was obtained from the organozinc route.[7] The minor adduct **11** would thus provide access to (−)-shikimic acid **1**. Attempts to employ a one-pot procedure to form the isoxazolidines directly from the hemiacetals **6** and **7** (MeNHOH·HCl 3 mol equiv., K_2CO_3 3 mol equiv., 3 Å molecular sieves, in toluene at 125 °C) gave unsatisfactory results (only ~30% yield). Acetylation of the hydroxy function of compounds **10** and **11** was readily accomplished and resulted in the crystalline acetate **12**, mp 103.5–104.5 °C; $[\alpha]_D$ −144.6 (*c* 1.30, $CHCl_3$) and epimer **13**.

The structures and stereochemistry of compounds **10** and **12** were initially assigned on the evidence of ^1H NMR coupling-constant data and nuclear Overhauser effect (NOE) experiments. In the ^1H NMR spectrum of the isoxazolidine **10**, a large coupling constant $J_{3a,7a}$ 9.0 Hz was observed, indicating an

† The α,β-nomenclature used here is that appropriate to carbohydrate derivatives; compound **6** is an L-sugar derivative, whilst epimer **7** is of the D-series.

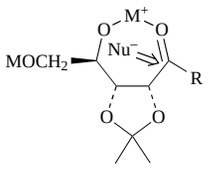


Fig. 2 Cyclic chelate model

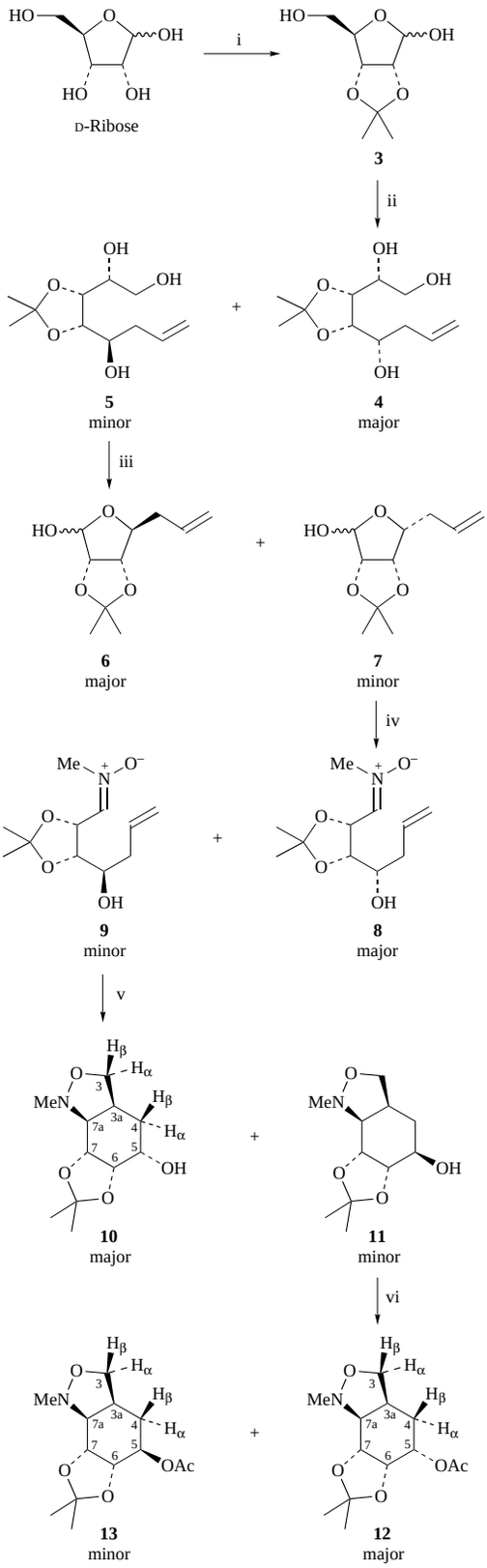
almost eclipsed conformational arrangement between 7a-H and 3a-H, which was also true in the case of 3-H_α and 3a-H ($J_{3\alpha,3a}$ 8.3 Hz). Another large coupling constant, $J_{4\alpha,5}$ 9.5 Hz, between 4-H_α and 5-H suggested a diaxial coupling. Acetylation of isoxazolidine **10** to give **12** caused a down-field shift of the 5-H and 6-H signals; in particular, 5-H was shifted by ~1 ppm. In this case large coupling constants were observed, $J_{3a,7a}$ 8.9 Hz, $J_{3\alpha,3a}$ 8.4 Hz and $J_{4\alpha,5}$ 11.5 Hz. Additionally, a four-bond W coupling, $J_{6,4\beta}$ 1.1 Hz, was detected between 6-H and 4-H_β. These observations led us to assign isoxazolidines **10** and **12** as having boat conformations with the CHOH or CHOAc groups bending up towards the five-membered isoxazolidine ring. Further support for this conformation came from the NOE experiments performed on compound **12**, in particular the observed NOE (5% enhancement) between 5-H and 3-H_β.

In its 400 MHz ^{1}H NMR spectrum the isoxazolidine **13** showed two large coupling constants, $J_{4\beta,3a}$ 12.6 Hz and $J_{4\beta,5}$ 12.6 Hz, assuming near axial–axial couplings between 3a-H and 4-H_β and also between 4-H_β and 5-H in a boat conformation for the cyclohexane ring (Fig. 3). This assignment was supported by NOE experiments. Observed NOEs between 3-H_β and 4-H_β, between 3-H_β and 4-H_α, between 4-H_β and 7-H, and also between 4-H_β and 6-H were strongly indicative of a boat conformation in which the C-4 group and C-7 group are bending up towards each other (Fig. 3), which also resulted in the observed NOEs between 5-H and 3a-H and between 5-H and 7a-H.

The structure of the isoxazolidine **12** was confirmed by single-crystal X-ray crystallographic analysis. In the crystal, there were two crystallographically independent molecules of compound **12** per asymmetric unit, but only one molecule of compound **12** is depicted in Fig. 4 along with the numbering system adopted for the structural study. The two molecules of compound **12** exhibit only minor structural differences apart from the orientation of the acetoxy side chain [*cf.* torsion angles C(8)–O(2)–C(6)–C(7) 82.5(3)° and C(8′)–O(2′)–C(6′)–C(7′) 147.1(2)°]. Since Mo-Kα X-radiation was used, the absolute configuration of compound **12** could not be determined unambiguously from the X-ray analysis and was assigned, therefore, with reference to the starting material, D-ribose. The results of this study clearly show the tricyclic nature of the isoxazolidine **12** which has been formed by the least sterically hindered intramolecular [3 + 2] cycloaddition process, resulting in the two five-membered rings being *anti* with respect to each other. Consistent with ^{1}H NMR data above, the central six-membered ring adopts a flattened boat conformation with atoms C(3) and C(6) being displaced out of the plane defined by atoms C(2), C(4), C(5) and C(7) (+0.34 and +0.67 Å respectively).

The N–O bond cleavage of compound **12** proved to be somewhat difficult in that attempted reduction under various conditions (PtO_2/H_2, $Pd/C/H_2$, Zn/AcOH, $TiCl_3$, H_2/Raney nickel) failed to effect this cleavage. Cleavage of the isoxazolidine ring was finally accomplished by hydrogenation over Pearlman's catalyst[10] (20% palladium hydroxide on carbon) to afford the amino alcohol **14** in almost quantitative yield (Scheme 2).

With the amino alcohol **14** in hand we studied its oxidation. Oxidation with pyridinium chlorochromate (PCC) afforded the α,β-unsaturated aldehyde **16**, mp 57–58 °C, $[\alpha]_D$ +34.9 (c 0.93 in $CHCl_3$), but the yield was very low (~15%). Attempts to oxidise **14** with pyridinium dichromate (PDC) under a range of conditions only led to the recovery of starting material. Considering the nature of the β-elimination involved in this reac-



Scheme 1 *Reagents and conditions* (*yields in parentheses*): i, acetone, H_2SO_4 (cat.), room temp., 4 h (73%); ii, allylmagnesium chloride, THF, 0 °C to room temp., 14 h (mixture of diastereoisomers, **4**:**5** = 5:1); iii, aq. $NaIO_4$, room temp., 2 h (94% total for two steps, mixture of anomers); iv, MeNHOH·HCl, pyridine, room temp., 17 h; v, PhMe, reflux, 16 h (91% total, two steps); vi, Ac_2O, pyridine, DMAP, room temp., 9 h (67% for **12** and 11% for **13**)

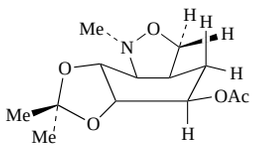
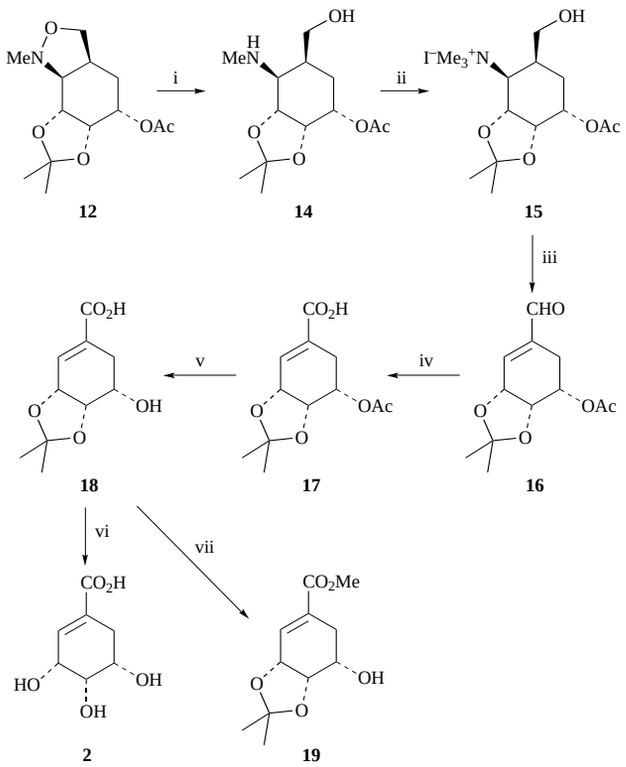


Fig. 3 Boat conformation for cyclohexane moiety



Scheme 2 *Reagents and conditions* (*yields in parentheses*): i, $Pd(OH)_2$–C (20%), H_2 (2 atm), MeOH, 30 h (100%) ii, MeI, K_2CO_3, THF, room temp., 30 h (87%); iii, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 50 min; then Et_3N, −78 °C to room temp. (79%); iv, $NaClO_2$, NaH_2PO_4, H_2O_2, aq. MeCN, room temp., 1 h (67%); v, K_2CO_3, aq. MeOH, room temp., 12 h; vi, aq. TFA (50%), room temp., 10 h (80% two steps); vii, CH_2N_2, Et_2O, 0 °C (62% over two steps from **17**)

tion, we prepared the quaternary ammonium salt **15** in 87% yield by treatment of amine **14** with iodomethane and potassium carbonate in tetrahydrofuran (THF). When salt **15** was subjected to oxidation with PCC in dichloromethane in the presence of 3 Å molecular sieves the aldehyde **16** was isolated in 22% yield due to incomplete reaction. However, we were pleased to find that treatment of salt **15** under Swern conditions[11] afforded α,β-unsaturated aldehyde **16** in good yield (79%). Further oxidation of aldehyde **16** to the carboxylic acid **17** was accomplished with sodium chlorite and hydrogen peroxide.[12] The acid **17** was deacetylated with potassium carbonate in aq. methanol to give the crystalline acid **18**, which was further deprotected by acidic hydrolysis in 50% aqueous trifluoroacetic acid (TFA) to afford 5-*epi*-shikimic acid **2** as crystals, mp 155–156.5 °C; $[a]_D$ −57.6 (*c* 0.83, MeOH), in an overall yield of 80% from compound **17**.

In order to correlate (−)-5-*epi*-shikimic acid **2** stereochemically to known compounds in the literature, we chose to prepare the methyl ester **19**, whose enantiomer as well as the racemate had been reported. Esterification of **18** with diazomethane afforded the methyl ester **19** as an oil, $[a]_D$ +26.8 (*c* 0.67, $CHCl_3$) {lit.,[13] $[a]_D$ −33.0 (c 0.667, $CHCl_3$); lit.,[14] $[a]_D$ −33.5; lit.,[15] $[a]_D$ −23.94 (*c* 1.17, CH_2Cl_2), all for the enantiomer}. The ester **19** exhibited identical IR, ^1H and ^{13}C spectra with those reported.

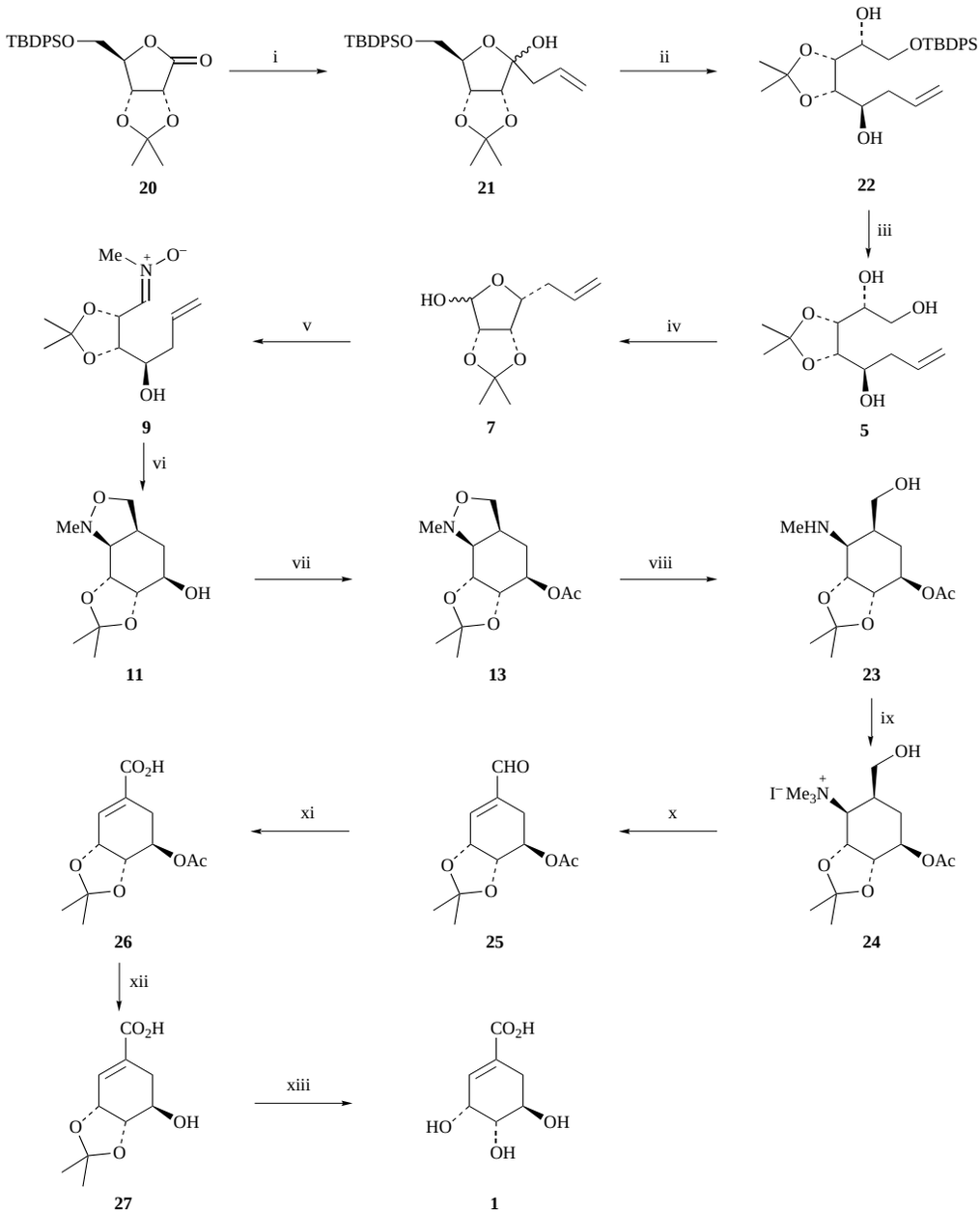
Attempts to carry out an inversion of stereochemistry at C-5 of the isoxazolidine **10**, in order to prepare shikimic acid **1**, were unsuccessful under a variety of conditions, whilst the above Grignard route only provided limited access to **11**. Other workers have reported that racemic methyl ester **19** can be converted to its C-5 epimer, but the procedure was indirect and low yielding.[16] We thus investigated an alternative approach to the synthesis of (−)-shikimic acid **1** (Scheme 3), in which the desired stereochemistry at C-5 was established at an early stage.

The D-ribonolactone derivative **20**,[17] prepared either from compound **3** by sequential silylation and oxidation, or from D-ribonolactone,[18] was treated with allylmagnesium chloride at −78 °C to afford the lactol **21** as an anomeric mixture in 87% yield. Reduction of lactol **21** with diisobutylaluminium hydride (DIBAL) gave a single diol **22** in 88% yield together with some recovered starting material. The stereoselectivity can be rationalised by either a Felkin–Anh model, or a chelated transition state, similar to Figs. 1 and 2, respectively. Desilylation of compound **22** gave the triol **5**, which upon cleavage with sodium periodate gave the hemiacetal **7** in 92% yield. Treatment of compound **7** with *N*-methylhydroxylamine hydrochloride in pyridine followed by heating of the crude nitrone in toluene, led to a single isoxazolidine **11** in 95% yield for the two steps. Acetylation with acetic anhydride in pyridine afforded acetate **13**, identical with the minor isomer produced using the chemistry of Scheme 1. Cleavage of the isoxazolidine ring proceeded smoothly with Pearlman's catalyst and provided the amino alcohol **23** in almost quantitative yield. Methylation of free amine **23** with iodomethane gave the quaternary ammonium salt **24** as crystals in 80% yield. Oxidation of compound **24** under Swern conditions afforded the α,β-unsaturated aldehyde **25**. Further oxidation of aldehyde **25** with sodium chlorite and hydrogen peroxide gave the carboxylic acid **26** in 91% yield, and subsequent removal of the acetate and isopropylidene groups led to (−)-shikimic acid **1**, $[a]_D$ −175.4 (*c* 0.59, water) [lit.,[5a] −179.6 (*c* 4, water)], *via* the partially deprotected acid **27**.

Experimental

Mps were determined on either an Electrothermal capillary melting point apparatus or a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR instrument. ^1H NMR spectra were obtained on either a JEOL EX 90 (90 MHz), JEOL FX 270 (270 MHz), Bruker WP 200 (200 MHz) or Bruker WH 400 (400 MHz) instrument. Chemical shifts were measured relative to tetramethylsilane (δ TMS = 0), using either tetramethylsilane or the solvent as internal reference. All coupling constants, *J*, are given in Hertz. ^{13}C NMR spectra were obtained on the same instruments (22.5 MHz, 67.8 MHz, 50 MHz or 100 MHz) with proton decoupling. Chemical shifts were measured relative to δ TMS = 0, using either tetramethylsilane or the solvent as internal reference. Unless otherwise stated, solutions in deuteriochloroform were used for the determination of NMR spectra. Mass spectra were recorded on either an AEI MS 902 or a VG ZAB-E instrument. High-resolution mass spectra were recorded on the VG ZAB-E instrument. Microanalyses were performed by MEDAC Ltd. Optical rotations were measured at room temperature using a Bellingham and Stanley P20 polarimeter, and $[a]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was performed on Fluka silica gel 60 (220–440 mesh), and the solvent light petroleum, which refers to the fraction boiling in the range 40–60 °C, was distilled prior to use. TLC was carried out using pre-coated aluminium plates (Merck Kieselgel 60 F_{254}) which were visualised with UV light and then with either basic aq. potassium permanganate or acidic ammonium molybdate as appropriate.

Dry THF was distilled from sodium–benzophenone ketyl. Dichloromethane, pyridine and dimethyl sulfoxide (DMSO) were distilled from calcium hydride and stored over 3 Å molecular sieves. Toluene was distilled from calcium hydride and



Scheme 3 *Reagents and conditions* (*yields in parentheses*): i, allylmagnesium chloride, THF, −78 °C, 3 h; ii, DIBAL, PhMe, −78 °C, 3 h (88%); iii, Bu_4NF, THF, room temp., 10 h (72%); iv, aq. $NaIO_4$, room temp., 2 h (92%, mixture of anomers); v, MeNHOH·HCl, pyridine, room temp., 20 h (100%); vi, PhMe, reflux, 18 h (95%); vii, Ac_2O, pyridine, DMAP, room temp., 10 h (93%); viii, $Pd(OH)_2$–C (20%), H_2 (2 atm), MeOH, 2 days (100%); ix, MeI, K_2CO_3, THF, room temp., 30 h (80%); x, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 55 min; then Et_3N, −78 °C to room temp. (71%); xi, $NaClO_2$, NaH_2PO_4, H_2O_2, aq. MeCN, room temp., 2 h (91%); xii, K_2CO_3, aq. MeOH, room temp., 12 h; xii, aq. TFA (50%), room temp., 10 h (79% over two steps)

stored over 4 Å molecular sieves. Methanol and ethanol were distilled from Mg/I_2 and stored over 3 Å molecular sieves. Other organic solvents and reagents were purified by standard procedures as necessary. Reactions requiring anhydrous conditions were performed in flame- or oven-dried apparatus under argon or nitrogen.

1,2,3-Trideoxy-5,6-*O*-isopropylidene-D-*allo*-oct-1-enitol 4 and 1,2,3-trideoxy-5,6-*O*-isopropylidene-D-*altro*-oct-1-enitol 5

A THF solution of allylmagnesium chloride (170 ml, 394 mmol) was added dropwise *via* a double-tipped needle to a stirred solution of the hemiacetal **3** (12.25 g, 64.4 mmol) in THF (200 cm^3) at 0 °C. After the addition and stirring of the mixture at 0 °C for 4 h, the mixture was allowed to warm to room temperature at which point it was stirred for 10 h. The reaction was quenched with saturated aq. ammonium chloride (250 cm^3), and the mixture was extracted with ethyl acetate (3 × 250 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a crude mixture of compounds **4** and **5** (12.7 g), which was used directly in the next reaction without further purification. A sample was purified for analysis on silica gel with 14% light petroleum in diethyl ether as eluent to afford a 5:1 mixture of diastereoisomers **4** and **5** as an oil, $[\alpha]_D$ +12.3 (*c* 1.47, $CHCl_3$); ν_{max}(film)/cm^{-1} 3354 (OH), 3077 (C=CH_2), 2987, 2935, 1642 (C=C), 1435, 1382, 1371, 1220, 1169 and 1066; δ_H(400 MHz) (mixture of diastereoisomers, major **4**:minor **5** = 5:1) 1.32 (2.49 H, s, **4** Me), 1.33 (0.51 H, s, **5** Me), 1.37 (2.49 H, s, **4** Me), 1.45 (0.51 H, s, **5** Me), 2.21 (0.83 H, dt, *J* 14.3 and 8.4, **4** C*H*HCH=), 2.39–2.45 (0.51 H, m, **5** CH_2CH=, OH), 2.49 (0.83 H, t, *J* 5.9, **4** OH), 2.62 (0.17 H, d, *J* 8.0, **5** OH), 2.60–2.66 (0.83 H, m, **4** CH*H*CH=), 3.31 (0.83 H, d, *J* 3.1, **4** OH), 3.60–3.72 (1.17 H, m, **4** C*H*HOH; **5** CH_2OH), 3.81–3.90 (2.66 H, m, **4** 2 × C*H*OH, CH*H*OH; **5** OH), 3.94–3.98 (0.34 H, m, **5** C*H*OH, C*H*OR), 4.00 (0.83 H, dd, *J* 9.4 and 5.4, **4** C*H*OR), 4.06–4.12 (0.34 H, m, **5** C*H*OH, C*H*OR), 4.11 (0.83 H, dd, *J* 9.4 and 5.4, **4** C*H*OR), 4.16 (0.83 H, d, *J* 3.2, **4** OH), 5.10–5.22 (2 H, m, CH=CH_2) and 5.79–5.93 (1 H, m, C*H*=CH_2); δ_C(100 MHz) (major **4**) 25.29 (Me), 27.85 (Me), 38.41 (*C*H_2CH=), 64.31

(CH_2OH), 68.33, 69.24, 77.60, 79.45 (4 C, 2 × *C*HOR, 2 × CHOH), 108.66 (CMe_2), 118.97 (CH=CH_2) and 133.79 (*C*H=CH_2); (minor **5**) 25.12 (Me), 27.41 (Me), 39.79 (CH_2CH=), 64.37 (CH_2OH), 68.10, 69.40, 77.02, 78.04 (4 C, 2 × *C*HOR, 2 × CHOH), 108.13 (CMe_2), 117.98 (CH=CH_2) and 134.30 (*C*H=CH_2).

5,6,7-Trideoxy-2,3-*O*-isopropylidene-α,β-L-*ribo*-hept-6-enofuranose 6 and 5,6,7-trideoxy-2,3-*O*-isopropylidene-α,β-D-*lyxo*-hept-6-enofuranose 7

The crude mixture of triols **4** and **5** (12.7 g) was dissolved in water (130 cm^3) and sodium periodate (16.5 g, 77.3 mmol) was added. After being stirred for 2 h at room temperature the mixture was extracted with ethyl acetate (3 × 130 cm^3), the extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography with light petroleum–diethyl ether (3:1) as eluent to yield an inseparable mixture of *lactols* **6** and **7** (12.14 g, 94% overall yield for two steps) as an oil, $[\alpha]_D$ +7.5 (*c* 1.94, $CHCl_3$); ν_{max}(film)/cm^{-1} 3423 (OH), 3077 (C=CH_2), 2983, 2940, 1642 (C=C), 1437, 1374, 1211, 1161 and 1073; δ_H(400 MHz) (mixture of diastereoisomers, major **6**:minor **7** = 83:17, **6α**:**6β**:**7α**:**7β** as 24:59:16:1) 1.29 (2.25 H, s, **6β** Me, **7α** Me), 1.34 (0.03 H, s, **7β** Me), 1.35 (0.72 H, **6α** Me), 1.44 (0.48 H, s, **7α** Me), 1.45 (1.77 H, s, **6β** Me), 1.51 (0.03 H, s, 7**β** Me), 1.54 (0.72 H, s, **6α** Me), 2.20–2.50 (2 H, m, CH_2CH=), 3.22 (0.16 H, d, *J* 2.5, **7α** OH), 3.38 (0.59 H, d, *J* 2.8, **6β** OH), 3.49 (0.01 H, dt, *J* 3.2 and 7.0, **7β** OC*H*CH_2), 3.91 (0.01 H, d, *J* 12.2, **7β** OH), 3.93 (0.24 H, d, *J* 9.2, **6α** OH), 4.12 (0.24 H, dt, *J* 2.8 and 6.8, **6α** OC*H*CH_2), 4.16 (0.16 H, dt, *J* 3.6 and 7.0, **7α** OC*H*CH_2), 4.22 (0.59 H, dt, *J* 1.0 and 7.7, **6β** OC*H*CH_2), 4.46 (0.24 H, dd, *J* 6.8 and 2.8, **6α** C*H*OR), 4.47 (0.01 H, dd, *J* 6.1 and 3.5, **7β** C*H*OR), 4.56 (0.01 H, dd, *J* 6.1 and 3.2, **7β** C*H*OR), 4.57 (0.16 H, d, *J* 5.9, **7α** C*H*OR), 4.58–4.62 (1.42 H, m, **6β** 2 × CHOR, **6α** CHOR), 4.65 (0.16 H, dd, *J* 5.9 and 3.6, **7α** C*H*OR), 4.93 (0.01 H, dd, *J* 12.2 and 3.5, **7β** C*H*OH), 5.04–5.20 (2 H, m, CH=CH_2), 5.26 (0.24 H, dd, *J* 9.2 and 4.1, **6α** C*H*OH), 5.33 (0.16 H, d, *J* 2.5, **6α** C*H*OH), 5.41 (0.59 H, d, *J* 2.8, **6β** C*H*OH) and 5.71–5.89 (1 H, m, C*H*=CH_2); δ_C(22.5 MHz) (**6β**) 24.73 (Me), 26.22 (Me), 39.62 (CH_2C=), 83.44, 85.83, 85.98 (3 C, 3 × *C*HOR), 102.72 (OCHOH), 112.12 (CMe_2), 117.37 (CH=CH_2) and 133.96 (*C*H=CH_2); (**6α**) 24.73 (Me), 25.92 (Me), 36.81 (CH_2C=), 79.30, 79.66, 82.82 (3 C, 3 × *C*HOR), 95.65 (OCHOH), 114.47 (CMe_2), 117.90 (CH=CH_2) and 132.94 (*C*H=CH_2); (**7α**) 24.73 (Me), 25.80 (Me), 32.70 (CH_2C=), 79.30, 79.98, 85.44 (3 C, 3 × *C*HOR), 100.45 (OCHOH), 112.12 (CMe_2), 116.89 (CH=CH_2) and 134.13 (*C*H=CH_2) (Found: C, 59.78; H, 8.01. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%).

(3a*S*,5*S*,6*S*,7*R*,7a*S*)-Octahydro-5-hydroxy-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 10 and (3a*S*,5*R*,6*S*,7*R*,7a*S*)-octahydro-5-hydroxy-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 11

The hemiacetals **6** and **7** (12.0 g, 59.93 mmol) were dissolved in pyridine (180 cm^3) with *N*-methylhydroxylamine hydrochloride (50.0 g, 598.7 mmol). After stirring of the mixture at room temperature for 17 h the pyridine was removed under reduced pressure and the residue was co-evaporated with toluene. The residue was partitioned between water (200 cm^3) and ethyl acetate (3 × 250 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was passed through a short column of silica gel with light petroleum–diethyl ether (1:2) as eluent to give a mixture of the *nitrones* **8** and **9** (13.74 g, 100%) as an oil which solidified on storage at −20 °C; δ_H(90 MHz), 1.34 (3 H, s, Me), 1.51 (3 H, s, Me), 2.35–2.60 (2 H, m, CH_2CH=), 2.68 (3 H, s, NMe), 3.74 (1 H, br s, OH), 4.02–4.94 (3 H, m, C*H*OH, 2 × CHOR), 5.04–5.31 (2 H, m, CH=CH_2), 5.64–6.02 (1 H, m, C*H*=CH_2) and 6.84 (1 H, d, CH=N).

This mixture of nitrones was then dissolved in dry toluene (400 cm^3) and the solution was heated at reflux for 16 h. The solvent was evaporated off under reduced pressure, and the residue was purified by flash chromatography on silica gel with 5% light petroleum in diethyl ether as eluent to give an inseparable mixture of the *isoxazolidines* **10** and **11** (12.52 g, 91%) as an oil, $[\alpha]_D$ −97.5 (*c* 1.35, $CHCl_3$); ν_{max}(film)/cm^{-1} 3475 (OH), 2870, 2936, 2984, 1456, 1380, 1261, 1210, 1167 and 1053; δ_H(400 MHz) (major **10** and minor **11** in the ratio 6:1) 1.30 (0.84 H, ddd, *J* 13.6, 4.9 and 2.6, major C*H*HCHOH), 1.33 (0.48 H, s, minor Me), 1.35 (2.52 H, s, major Me), 1.45 (0.48 H, s, minor Me), 1.49 (2.52 H, s, major Me), 1.59 (0.16 H, ddd, *J* 14.2, 6.5 and 3.6, minor C*H*HCHOH), 2.00 (0.16 H, ddd, *J* 14.2, 7.7 and 2.9, minor CH*H*CHOH), 2.05 (0.84 H, ddd, *J* 13.6, 9.5 and 7.2, major CH*H*CHOH), 2.29 (0.84 H, d, *J* 6.3, major OH), 2.69 (2.52 H, s, major NMe), 2.73 (0.48 H, s, minor NMe), 2.87–3.05 (1.16 H, m, major C*H*CH_2ON; minor NCH, C*H*CH_2ON), 2.93 (0.84 H, dd, *J* 9.0 and 3.2, major NCH), 3.52 (0.84 H, dd, *J* 8.3 and 6.2, major C*H*HON), 3.74 (0.32 H, dd, *J* 8.1 and 4.2, minor CH_2ON), 4.10 (0.84 H, dq, *J* 3.2 and 6.3, major C*H*OH), 4.18 (0.84 H, t, *J* 8.3, major CH*H*ON), 4.18–4.23 (0.32 H, m, minor C*H*OH, C*H*OR), 4.23 (0.84 H, dd, *J* 7.8 and 3.2, major C*H*OR), 4.25 (0.84 H, d, *J* 7.8 and 3.2, major C*H*OR), 4.29 (0.16 H, dd, *J* 7.2 and 2.3, minor C*H*OR) and 4.33 (0.16 H, br s, minor OH); δ_C(22.5 MHz) (major **10**) 23.80 (Me), 25.98 (Me), 28.16 (CH_2CHOH), 37.62 (*C*HCH_2), 44.06 (NMe), 64.14, 67.81, 71.54, 74.35 (2C) (5 C, CHN, 2 × CHOR, CHOH, CH_2ON) and 108.12 (CMe_2); (minor **11**) 24.13 (Me), 26.76 (Me), 29.20 (CH_2CHOH), 37.62 (*C*HCH_2), 43.70 (NMe), 67.81, 68.65, 72.67 (2C), 77.54 (5 C, CHN, 2 × *C*HOR, CHOH, CH_2ON) and 108.12 (CMe_2) (Found: C, 57.43; H, 8.41; N, 6.05. $C_{11}H_{19}NO_4$ requires C, 57.63; H, 8.35; N, 6.11%).

(3a*S*,5*S*,6*S*,7*R*,7a*S*)-5-Acetoxyoctahydro-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 12 and (3a*S*,5*R*,6*S*,7*R*,7a*S*)-5-acetoxyoctahydro-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 13

The isoxazolidines **10** and **11** (3.39 g, 14.8 mmol) were dissolved in pyridine (70 cm^3) with 4-(dimethylamino)pyridine (DMAP) (361 mg, 3.0 mmol), and acetic anhydride (5.58 ml, 59.15 mmol) was added. The solution was stirred at room temperature for 9 h, the pyridine was then removed under reduced pressure, and further by co-evaporation of the residue with toluene. The residue was partitioned between water (150 cm^3) and ethyl acetate (3 × 160 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated. Column chromatography of the residue on silica gel with light petroleum–diethyl ether (1:2) as eluent gave a mixture, which was then subjected to repeated crystallisation from light petroleum–ethyl acetate to afford the *major compound* **12** (2.67 g, 67%) as crystals and the remaining oil, which was further purified by flash chromatography on silica gel with light petroleum–diethyl ether (1:2) as eluent to give the *minor compound* **13** (0.44 g, 11%) as an oil.

The *major compound* (less polar) **12**, mp 103.5–104.5 °C; $[\alpha]_D$ −144.6 (*c* 1.30, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2987, 2943, 2918, 2877, 1734 (C=O), 1457, 1372, 1248, 1211 and 1053; δ_H(400 MHz) 1.356 (3 H, s, Me), 1.36 (1 H, ddt, *J* 13.2, 1.3 and 2.9, C*H*HCHOAc), 1.52 (3 H, s, Me), 2.09 (3 H, s, COMe), 2.12 (1 H, ddd, *J* 13.2, 11.5 and 7.1, CH*H*CHOAc), 2.70 (3 H, s, NMe), 2.80 (1 H, dd, *J* 8.9 and 2.5, NCH), 2.95–3.03 (1 H, m, C*H*CH_2ON), 3.65 (1 H, dd, *J* 8.4 and 6.5, C*H*HON), 4.17 (1 H, t, *J* 8.4, CH*H*ON), 4.29 (1 H, dd, *J* 7.7 and 2.6, C*H*ORCHN), 4.44 (1 H, ddd, *J* 7.7, 3.6 and 1.1, C*H*ORCHOAc) and 5.30 (1 H, dt, *J* 11.5 and 3.3, C*H*OAc); δ_C(22.5 MHz) 21.27 (CO*Me*), 23.72, 24.52, 26.01 (3 C, C*Me*$_2$, *C*H_2CHOAc), 38.63, 44.15 (2 C, *C*HCH_2ON, NMe), 67.39, 67.78, 71.69, 72.61, 74.14 (5 C, CHN, CH_2ON, *C*HOAc, 2 × *C*HOR), 108.66 (CMe_2) and 170.47 (C=O) (Found; C, 57.62; H, 7.86; N, 5.12. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%).

Crystal structure determination of compound 12. The crystal of compound **12** used for X-ray data collection (approx. dimen-

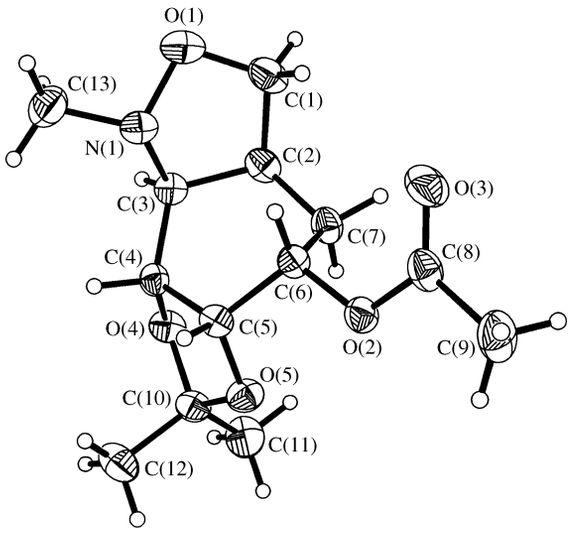


Fig. 4 The molecular structure of one molecule of tricyclic compound **12**. The non-hydrogen atoms are represented by 30% probability ellipsoids, and hydrogen atoms by spheres of arbitrary radius.[21]

sions 0.3 × 0.3 × 0.25 mm) was grown by slow evaporation from ethyl acetate–hexane (1:1) solution and mounted in a sealed Lindemann capillary tube.

Crystal data.—$C_{13}H_{21}NO_5$, M = 271.3, needles, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.804(2), b = 10.032(2), c = 28.607(6) Å, V = 2813.6(10) Å^3, Z = 8, D_c = 1.281 g cm^{-3}, $F(000)$ = 1168, μ(Mo-Kα) = 0.098 mm^{-1}.

Data collection.—The intensity data were collected on an Enraf-Nonius diffractometer fitted with a FAST area detector over the hemisphere [temperature 293(2) K; θ-range: 2.52 to 29.56° $-11 \leqslant h \leqslant 13$, $-13 \leqslant k \leqslant 13$, $-22 \leqslant 1 \leqslant 37$] using graphite-monochromated Mo-Kα X-radiation (λ 0.710 73 Å) and ω-scanning.[19] Of the 7014 unique data [R(int) = 0.081] measured, 4321 had $F_o > 4\sigma(F_o)$. The data were corrected for Lorentz and polarisation effects, but not for absorption.

Structure solution.—The approximate positions of the non-hydrogen atoms were determined by direct methods (SHELXS-86[20]). The structure was refined by full-matrix least-squares methods on F^2 (SHELXTL/PC[21]) using all F_o^2 data and anisotropic temperature factors for all the non-hydrogen atoms. All the hydrogen atoms were located on difference Fourier maps and included in the refinement process at idealised positions with isotropic temperature factors (1.5 times U_{iso} of the bonded heavy atom). At convergence, the discrepancy factors[21] R_1 [$F_o > 4\sigma(F_o)$] and wR_2 were 0.057 and 0.122 respectively. The weighting scheme, $w = 1/[\sigma^2(F_o^2) + (0.0724P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$, was found to give satisfactory analysis variance. The final difference Fourier map was essentially featureless (general noise level less than ±0.10 e Å^{-3} with the largest difference peak and hole being 0.27 and −0.19 e Å^{-3}, respectively.‡ A molecular structure is presented in Fig. 4.

The *minor compound* (more polar) **13**, $[a]_D$ −109.6 (*c* 1.15, $CHCl_3$); ν_{max}(film)/cm^{-1} 2985, 2938, 2873, 1738 (C=O), 1456, 1436, 1372, 1240, 1169, 1065 and 864; δ_H(400 MHz) 1.35 (3 H, s, Me), 1.48 (3 H, s, Me), 1.48 (1 H, ~q, *J* 12.6, C*H*HCHOAc), 1.95 (1 H, ddd, *J* 12.6, 6.0 and 3.6, CH*H*CHOAc), 2.08 (3 H, s, COMe), 2.74 (3 H, s, NMe), 2.87–3.01 (2 H, m, NCH, C*H*CH$_2$ON), 3.56 (1 H, dd, *J* 8.2 and 3.1, C*H*HON), 4.14–4.23 (3 H, m, 2 × CHOR, CH*H*ON) and 4.83 (1 H, ddd, *J* 12.6, 7.5 and 3.6, C*H*OAc); δ_C(22.5 MHz) 21.18 (CO*Me*), 25.48 (Me), 27.68 (Me), 29.56 (*C*H$_2$CHOAc), 40.01 (*C*HCH$_2$ON), 44.54 (NMe), 69.06, 70.94, 72.91, 75.18, 76.61 (5 C, CHN, CH$_2$ON, *C*HOAc, 2 × *C*HOR), 108.89 (*C*Me$_2$) and 170.53 (C=O); *m/z* (EI) 272 (M^+ + H), 271 (M^+), 256 (M^+ − Me), 214, 154, 124, 98, 85 and 70; *m/z* (CI, NH_3) 272 (M^+ + H) (Found: M^+, 271.1420. $C_{13}H_{21}NO_5$ requires *m/z* 271.1420).

‡ Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and reference number 207/112.

(1*S*,2*S*,3*R*,4*S*,5*S*)-5-Acetoxy-3,4-isopropylidenedioxy-2-(methylamino)cyclohexane-1-methanol 14

The isoxazolidine **12** (1.13 g, 4.17 mmol) was shaken in dry methanol (100 cm^3) with Pearlman's catalyst [20% Pd(OH)$_2$–C] under hydrogen (2 atm) for 30 h. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to afford the *amino alcohol* **14** (1.14 g, 100%) as an oil, R_f 0.20 (ethyl acetate–methanol 1:1); $[a]_D$ −29.8 (*c* 1.24, $CHCl_3$); ν_{max}(film)/cm^{-1} 3346 (NH, OH), 2988, 2937, 2801, 1732 (C=O), 1452, 1374, 1244, 1048 and 756; δ_H(400 MHz) 1.35 (3 H, s, Me), 1.52 (3 H, s, Me), 1.72 (1 H, dt, *J* 13.5 and 5.0, C*H*HCHOAc), 1.88 (1 H, ddd, *J* 13.5, 11.0 and 5.8, CH*H*CHOAc), 2.10 (3 H, s, COMe), 2.41–2.47 (1 H, m, C*H*CH$_2$OH), 2.49 (3 H, s, NMe), 2.82 (1 H, ddd, *J* 8.0, 4.4 and 1.0, C*H*NMe), 3.00–3.60 (2 H, br s, NH, OH), 3.61 (1 H, ddd, *J* 11.1, 4.1 and 1.0, C*H*HH), 3.81 (1 H, dd, *J* 11.1 and 10.0, CH*H*OH), 4.20 (1 H, dd, *J* 8.0 and 5.4, C*H*ORCHN), 4.39 (1 H, dd, *J* 5.4 and 4.0, C*H*ORCHOAc) and 5.16 (1 H, ddd, *J* 11.0, 5.8 and 4.0, C*H*OAc); δ_C(22.5 MHz) 21.06 (CO*Me*), 25.65, 26.49, 27.77 (3 C, 2 × Me, *C*H$_2$CHOAc), 33.23, 34.93 (2 C, NMe, *C*HCH$_2$OH), 63.04, 64.17, 67.54, 73.63, 76.55 (5 C, *C*HOAc, *C*HNMe, CH$_2$OH, 2 × *C*HOR), 109.34 (*C*Me$_2$) and 170.29 (CO); *m/z* (EI) 274 (M^+ + H) and 232; *m/z* (CI, NH_3) 274 (M^+ + H) and 232 [Found (CI, NH_3): MH^+, 274.1654. $C_{13}H_{24}NO_5$ requires *m/z* 274.1653].

[(1*S*,2*R*,3*S*,4*S*,6*S*)-4-Acetoxy-6-hydroxymethyl-2,3-(isopropylidenedioxy)cyclohexyl]trimethylammonium iodide 15

Potassium carbonate (142 mg, 1.02 mmol) and iodomethane (2 cm^3, 32 mmol) were added to a solution of the amino alcohol **14** (140 mg, 0.51 mmol) in dry THF (30 cm^3); the reaction mixture was stirred at room temperature for 30 h, and then evaporated. The residue was taken up in chloroform (50 cm^3), filtered through Celite, and washed with chloroform (20 cm^3). The filtrate was evaporated under reduced pressure to leave a residue, which was partitioned between water (50 cm^3) and diethyl ether (3 × 50 cm^3). The aqueous solution was freeze-dried to furnish the *title compound* **15** (190 mg, 87%) as fine crystals, mp 102–107 °C; $[a]_D$ +3.8 (*c* 1.04, water); ν_{max}(KBr)/cm^{-1} 3344 (OH), 3055, 2985, 2941, 1732 (C=O), 1376, 1245 and 1051; δ_H(400 MHz) 1.37 (3 H, s, Me), 1.63 (3 H, s, Me), 1.96 (1 H, dt, *J* 13.8 and 4.2, C*H*HCHOAc), 2.10 (3 H, s, COMe), 2.29 (1 H, ddd, *J* 13.8, 10.6 and 4.6, CH*H*CHOAc), 2.94–3.01 (1 H, m, C*H*CH$_2$OH), 3.59 (9 H, s, NMe$_3$), 3.83 (1 H, ddd, *J* 11.7, 6.7 and 4.9, C*H*HOH), 3.89 (1 H, dt, *J* 11.7 and 3.8, CH*H*OH), 4.07 (1 H, dd, *J* 9.8 and 3.9, C*H*NMe$_3$), 4.13 (1 H, t, *J* 4.2, OH), 4.57 (1 H, t, *J* 4.9, C*H*ORCHOAc), 4.97 (1 H, dd, *J* 9.8 and 5.6, C*H*ORCHN) and 5.22 (1 H, dt, *J* 10.6 and 4.9, C*H*OAc); δ_C(100 MHz) 20.98 (CO*Me*), 25.53, 27.63, 30.64, 35.81 (4 C, *C*HCH$_2$OH, *C*H$_2$CHOAc, 2 × Me), 54.94 (3 C, NMe$_3$), 60.11, 65.96, 72.67, 74.38, 75.76 (5 C, CH$_2$OH, CHN, *C*HOAc, 2 × *C*HOR), 110.51 (*C*Me$_2$) and 170.01 (CO); *m/z* (FAB) 302 (M^+ − I), 270, 258, 242, 143 and 125 [Found (FAB): M^+ − I, 302.1970. $C_{15}H_{28}NO_5$ requires *m/z* 302.1967].

(3*R*,4*S*,5*S*)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarbaldehyde 16

DMSO (0.16 ml, 2.29 mmol) was added to a solution of oxalyl dichloride (0.1 ml, 1.15 mmol) in dry dichloromethane (10 cm^3) at −78 °C. After stirring the mixture for 20 min, the quaternary ammonium iodide **15** (122.2 mg, 0.28 mmol) in dichloromethane (2 cm^3) was added. The solution was stirred for 50 min at −78 °C, after which triethylamine (0.81 ml, 5.75 mmol) was added and the reaction mixture was allowed to warm to

room temperature. After 40 min the mixture was diluted with dichloromethane (100 cm^3) and washed with water (120 cm^3). The aqueous layer was then extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were washed with saturated aq. sodium chloride (300 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on silica gel with light petroleum–diethyl ether (1:1) as eluent to give the α,β-*unsaturated aldehyde* **16** (53 mg, 79%) as an oil which solidified on storage at −20 °C, and which was recrystallised from light petroleum–ethyl acetate to yield a solid, mp 57–58 °C; $[\alpha]_D$ +34.9 (*c* 0.92, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2988, 2935, 2829, 1737 (ester C=O), 1689 (CH=O), 1647 (C=C), 1373, 1236 and 1032; δ_H(400 MHz) 1.35 (3 H, s, Me), 1.40 (3 H, s, Me), 2.13 (3 H, s, COMe), 2.39 (1 H, ddt, *J* 16.5, 10.5 and 2.5, C*H*HC=), 2.69 (1 H, dd, *J* 16.5 and 5.5, CH*H*C=), 4.49–4.51 (1 H, m, C*H*OR), 4.87 (1 H, dt, *J* 5.1 and 2.3, C*H*OR), 5.08 (1 H, ddd, *J* 10.5, 5.5 and 2.2, C*H*OAc), 6.53 (1 H, ~ t, *J* 2.9, CH=C) and 9.52 (1 H, s, CHO); δ_C(22.5 MHz) 21.03, 21.33, 26.34, 27.59 (4 C, CO*Me*, 2 × Me, CH_2C=), 68.73, 73.30, 74.20 (3 C, *C*HOAc, 2 × *C*HOR), 110.86 (*C*Me_2), 138.28 (=*C*CHO), 144.10 (*C*H=C), 170.29 (*C*OMe) and 192.52 (CHO); *m/z* (EI) 225 (M^+ − Me), 123 and 95; *m/z* (CI, NH_3) 258 ($M^+ + NH_4$), 241 (M^+ + H), 183 and 109 [Found (CI, NH_3): MH^+, 241.1076. $C_{12}H_{17}O_5$ requires *m/z* 241.1076] (Found: C, 59.76; H, 6.79. $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71%).

(3*R*,4*S*,5*S*)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarboxylic acid 17

To a solution of aldehyde **16** (153.6 mg, 0.64 mmol) in acetonitrile (6 cm^3) was added aq. monobasic sodium phosphate monohydrate (27.5 mg, 0.2 mmol in 0.6 cm^3) and hydrogen peroxide (30% aq. solution, ~ 9.8 M; 0.66 cm^3, 6.6 mmol), followed by dropwise addition of a solution of sodium chlorite (from Aldrich; 80% purity; 108.4 mg, 0.96 mmol) in water (1.5 cm^3). The reaction mixture was stirred at room temperature for 1 h, diluted with saturated aq. sodium chloride (60 cm^3), and extracted with diethyl ether (3 × 60 cm^3). The ethereal solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with 0.3% acetic acid in light petroleum–diethyl ether (1:5) as eluent to give the *acid* **17** (109.6 mg, 67%) as a solid, which was recrystallised from light petroleum–ethyl acetate as fine needles, mp 142–143 °C; $[\alpha]_D$ +36.5 (*c* 1.10, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3444 (OH), 2990, 2933, 1730 (ester C=O), 1685 (acid C=O), 1649 (C=C), 1438, 1378, 1244, 1072 and 1037; δ_H(400 MHz) 1.37 (3 H, s, Me), 1.40 (3 H, s, Me), 2.14 (3 H, s, COMe), 2.52 (1 H, ddt, *J* 16.5, 10.4 and 2.7, C*H*HC=), 2.71 (1 H, dd, *J* 16.5 and 5.1, CH*H*C=), 4.45 (1 H, dd, *J* 5.0 and 1.8, C*H*OR), 4.79 (1 H, dt, *J* 5.0 and 2.5, C*H*OR), 5.10 (1 H, ddd, *J* 10.4, 5.5 and 2.2, C*H*OAc), 6.85 (1 H, t, *J* 3.0, CH=C) and 9.00 (1 H, br s, CO_2H); δ_C(22.5 MHz) 21.18 (CO*Me*), 23.87, 26.55, 27.75 (3 C, 2 × Me, CH_2C=), 68.95, 73.51, 73.51 (3 C, *C*HOAc, 2 × *C*HOR), 110.90 (*C*Me_2), 128.23 (=*C*CO_2H), 137.45 (*C*H=C), 170.57 (*C*OMe) and 171.01 (CO_2H); *m/z* (EI) 241 (M^+ − Me), 139 and 95; *m/z* (CI, NH_3) 274 ($M^+ + NH_4$), 257 (M^+ + H), 216 and 199 [Found (CI, NH_3): MH^+, 257.1025. $C_{12}H_{17}O_6$ requires *m/z*, 257.1025] (Found: C, 56.37; H, 6.41. $C_{12}H_{16}O_6$ requires C, 56.25; H, 6.29%).

(3*R*,4*S*,5*S*)-3,4,5-Trihydroxycyclohex-1-enecarboxylic acid (5-*epi*-shikimic acid) 2

The acid **17** (46.2 mg, 0.18 mmol) was dissolved in 5% aq. methanol (10 cm^3) with potassium carbonate (249 mg, 1.8 mmol) and the reaction mixture was stirred at room temperature for 12 h. The solution was acidified with aq. hydrochloric acid (2 M), and extracted with diethyl ether (3 × 50 cm^3). The ethereal solution was dried (Na_2SO_4) and concentrated to give (3*R*,4*S*,5*S*)-5-hydroxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarboxylic acid **18** as a crystalline solid, which was then dissolved in 50% aq. TFA (2 cm^3), and stirred at room temperature for 10 h. Evaporation of the reaction mixture and further co-evaporation with dry ethanol afforded 5-epi-*shikimic acid* **2** (25 mg, 80%) as a crystalline solid, mp 155–156.5 °C; $[\alpha]_D$ −57.6 (*c* 0.83, CH_3OH); ν_{max}(KBr)/cm^{-1} 3447 (OH), 2927, 1693 (C=O) and 1649 (C=C); δ_H(270 MHz; CD_3OD) 2.36 (1 H, dddd, *J* 17.2, 9.6, 3.3 and 2.6, C*H*HC=CH), 2.52 (1 H, dddd, *J* 17.2, 5.9, 1.7 and 1.3, CH*H*C=CH), 3.82 (1 H, dd, *J* 9.2 and 5.9, C*H*OH), 3.83 (1 H, dd, *J* 9.6 and 5.9, C*H*OH), 3.90–3.95 (1 H, m, C*H*OH) and 6.67 (1 H, ~ septet, *J* 1.3, CH=C); δ_C(22.5 MHz; CD_3OD) 29.79 (CH_2CHOH), 69.56, 69.68, 72.30 (3 C, 3 × CHOH), 130.30 (=*C*CO_2H), 139.97 (*C*H=C) and 169.89 (CO_2H); *m/z* (EI) 156 ($M^+ - H_2O$), 138 ($M^+ - 2H_2O$), 115, 97, 81, 69 and 60; *m/z* (CI, NH_3) 192 ($M^+ + NH_4$) [Found (CI, NH_3): MNH_4^+, 192.0870. $C_7H_{14}NO_5$ requires *m/z* 192.0872] (Found: C, 48.46; H, 6.16. $C_7H_{10}O_5$ requires C, 48.28; H, 5.79%).

Methyl (3*R*,4*S*,5*S*)-5-hydroxy-3,4-(isopropylidenedioxy)-cyclohex-1-enecarboxylate 19

The acid **18** (36.6 mg, 0.143 mmol) and potassium carbonate (197.4 mg, 1.43 mmol) were dissolved in 5% aq. methanol (9.5 cm^3), and the reaction mixture was stirred at room temperature for 12 h. The solution was then acidified with aq. hydrochloric acid (2 M), and extracted with diethyl ether (3 × 20 cm^3). The combined extracts were washed with saturated aq. sodium chloride (60 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to leave (3*R*,4*S*,5*S*)-5-hydroxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarboxylic acid **18** as a crystalline solid. The solid was then dissolved in diethyl ether (5 cm^3), the solution was cooled to 0 °C, and a dilute ethereal solution of diazomethane was added. After stirring the mixture at 0 °C for 15 min, the excess of diazomethane was destroyed by careful addition of glacial acetic acid, then the solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with light petroleum–diethyl ether (1:3) as eluent to afford the *methyl ester* **19** (20.2 mg, 62%) as an oil, $[\alpha]_D$ +26.8 (*c* 0.67, $CHCl_3$) {lit.,[13] −33.0 (*c* 0.667, $CHCl_3$) for the enantiomer; lit.,[14] $[\alpha]_D$ −33.5 for the enantiomer; lit.,[15] $[\alpha]_D$ −23.93 (*c* 1.17 in CH_2Cl_2) for the enantiomer}; ν_{max}(film)/cm^{-1} 3472 (OH), 2991, 2933, 2953, 1714 (C=O), 1652 (C=C), 1438, 1379, 1060 and 1033; δ_H(400 MHz) 1.37 (3 H, s, Me), 1.40 (3 H, s, Me), 2.17 (1 H, d, *J* 8.1, OH), 2.48 (1 H, ddt, *J* 16.7, 9.0 and 2.3, C*H*HC=), 2.63 (1 H, dd, *J* 16.7 and 4.3, CH*H*C=), 3.76 (3 H, s, COMe), 3.91–3.97 (1 H, m, C*H*OH), 4.40 (1 H, dd, *J* 5.8 and 2.7, C*H*OR), 4.70–4.3 (1 H, m, C*H*OR) and 6.77 (1 H, ~ t, *J* 2.7, CH=); δ_C(22.5 MHz) 25.95 (Me), 27.36, 27.77 (2 C, Me, CH_2C=), 52.06 (OMe), 66.92, 72.91, 75.45 (3 C, CHOH, 2 × *C*HOR), 110.03 (*C*Me_2), 129.21 (=*C*CO_2Me), 134.79 (*C*H=C) and 166.74 (CO); *m/z* (EI) 213 (M^+ − Me), 153, 139, 121, 109, 81 and 59.

8-*O*-(*tert*-Butyldiphenylsilyl)-1,2,3-trideoxy-5,6-*O*-isopropylidene-α,β-D-*ribo*-oct-1-en-4-ulofuranose 21

The lactone **20** (1.61 g, 3.77 mmol) was dissolved in dry THF (100 cm^3), the solution was cooled to −78 °C and allylmagnesium chloride (2.0 M in THF; 1.98 cm^3, 3.96 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, quenched with saturated aq. ammonium chloride (150 cm^3), and extracted with ethyl acetate (3 × 150 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a residue, which was purified by flash column chromatography on silica gel with 11% diethyl ether in light petroleum as eluent to give the starting material (0.13 g, 8% recovery) and the *lactol* **21** (1.42 g, 87% based on consumed starting material) as an oil, $[\alpha]_D$ −7.8 (*c* 1.22, $CHCl_3$); ν_{max}(film)/cm^{-1} 3404 (OH), 3073 (C=CH_2), 2934, 2859, 1643 (C=C), 1590, 1472, 1428, 1382, 1211, 1113 and 1073; δ_H(400 MHz) (2:5 mixture of α and β anomers) 1.06 (2.61 H, s, minor CMe_3), 1.08 (6.39 H, s, major CMe_3), 1.32 (2.13 H, s, major Me), 1.40 (0.87 H, s, minor Me), 1.49 (2.13 H, s, major Me), 1.59 (0.87 H, s, minor Me), 2.46–2.67 (2 H, m, CH_2CH=), 3.65 (0.71 H, dd, *J*

11.1 and 3.5, major C*H*HOSi), 3.78 (0.29 H, dd, *J* 11.3 and 3.3, minor C*H*HOSi), 3.82 (0.71 H, dd, *J* 11.1 and 3.9, major CH*H*OSi), 3.83 (0.29 H, dd, *J* 11.3 and 3.4, minor CH*H*OSi), 3.98 (0.29 H, s, minor OH), 4.16 (0.29 H, q, *J* 3.7, minor OC*H*-CH_2OSi), 4.18 (0.71 H, s, major OH), 4.21 (0.71 H, dt, *J* 1.5 and 3.6, major OC*H*CH_2OSi), 4.48 (0.29 H, d, *J* 7.2, minor C*H*ORCO), 4.51 (0.71 H, d, *J* 5.8, major C*H*ORCO), 4.80 (0.71 H, dd, *J* 5.8 and 1.5, major C*H*ORCHORCH_2OSi), 4.83 (0.29 H, dd, *J* 7.2 and 4.1, minor C*H*ORCHORCH_2OSi), 5.12–5.23 (2 H, m, CH=CH_2), 5.83–5.93 (0.29 H, m, minor C*H*=CH_2), 6.01 (0.71 H, ddt, *J* 17.2, 10.2 and 7.1, major C*H*=CH_2), 7.35–7.47 (6 H, m, *m*- and *p*-H Ph) and 7.63–7.90 (4 H, m, *o*-H Ph); δ_C(22.5 MHz) (major, β anomer) 19.15 (*C*Me_3), 25.24 (Me), 26.91 (4 C, Me, C*Me*$_3$), 39.83 (*C*H_2C=), 65.52 (CH_2OSi), 82.02, 86.13, 86.94 (3 C, 3 × *C*HOR), 106.93 (anomeric C), 112.51 (*C*Me_2), 118.48 (CH=*C*H_2), 127.96 (4 C, Ph), 130.05 (C, Ph), 130.20 (C, Ph), 132.14 (C, Ph), 132.20 (C, Ph), 132.92 (*C*H=CH_2) and 135.63 (4 C, Ph); (minor, α anomer) 19.27 (*C*Me_3), 25.00 (Me), 26.64 (4 C, Me, C*Me*$_3$), 43.65 (*C*H_2C=), 63.52 (CH_2OSi), 81.00, 81.87, 82.37 (3 C, 3 × *C*HOR), 102.57 (anomeric C), 115.49 (*C*Me_2), 118.74 (CH=*C*H_2), 127.75 (4 C, Ph), 129.82 (2 C, Ph), 132.74 (*C*H=CH_2), 133.12 (C, Ph), 133.27 (C, Ph) and 135.75 (4 C, Ph) (Found: C, 69.13; H, 7.80. $C_{27}H_{36}O_5Si$ requires C, 69.20; H, 7.74%).

8-*O*-(*tert*-Butyldiphenylsilyl)-1,2,3-trideoxy-5,6-*O*-isopropylidene-D-*altro*-oct-1-enitol 22

The lactol **21** (2.88 g, 6.15 mmol) was dissolved in dry toluene (100 cm^3), and the solution was cooled to −78 °C. DIBAL (1.5 M in toluene; 41 cm^3, 61.5 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h. The reaction was quenched by careful addition of aq. hydrochloric acid (2 M; 150 cm^3), and extracted with ethyl acetate (3 × 200 cm^3). The extracts were dried (Na_2SO_4), and evaporated under reduced pressure to leave a residue, which was purified on silica gel with 25% diethyl ether in light petroleum as eluent to give the recovered starting material (0.76 g, 26% recovery) and the *diol* **22** (1.87 g, 88% based on consumed starting material) as an oil, $[\alpha]_D$ −4.6 (*c* 1.41, $CHCl_3$); ν_{max}(film)/cm^{-1} 3441 (OH), 3072 (C=CH_2), 3050, 2983, 2932, 2858, 1642 (C=C), 1590, 1472, 1428, 1381, 1215, 1113 and 1062; δ_H(400 MHz) 1.07 (9 H, s, CMe_3), 1.32 (3 H, s, Me), 1.37 (3 H, s, Me), 2.36–2.41 (2 H, m, CH_2CH=), 2.48 (1 H, d, *J* 6.7, OH), 2.89 (1 H, d, *J* 4.5, OH), 3.77 (1 H, dd, *J* 10.3 and 5.2, C*H*HOSi), 3.88 (1 H, dd, *J* 10.3 and 2.4, CH*H*OSi), 4.06–4.13 (4 H, m, 2 × CHOR, 2 × C*H*OH), 5.09–5.17 (2 H, m, CH=CH_2), 5.89 (1 H, ddt, *J* 17.2, 10.1 and 7.1, C*H*=CH_2), 7.36–7.46 (6 H, m, *m*- and *p*-H Ph) and 7.65–7.69 (4 H, m, *o*-H Ph); δ_C(22.5 MHz) 19.21 (*C*Me_3), 24.88 (Me), 26.82 (3 C, C*Me*$_3$), 27.09 (Me), 39.44 (*C*H_2C=), 65.43 (CH_2OSi), 68.20, 69.46, 76.41, 78.71 (4 C, 2 × *C*HOR, 2 × CHOH), 108.06 (*C*Me_2), 117.31 (CH=*C*H_2), 127.72 (4 C, Ph), 129.78 (2 C, Ph), 132.92 (C, Ph), 132.98 (C, Ph), 134.94 (*C*H=CH_2) and 135.51 (4 C, Ph) (Found: C, 68.64; H, 8.30. $C_{27}H_{38}O_5Si$ requires C, 68.90; H, 8.14%).

1,2,3-Trideoxy-5,6-*O*-isopropylidene-D-*altro*-oct-1-enitol 5

The diol **22** (608.8 mg, 1.29 mmol) was dissolved in dry THF (50 cm^3) and tetrabutylammonium fluoride (TBAF) (1.0 M in THF; 3.23 cm^3, 3.23 mmol) was added. The solution was stirred at room temperature for 10 h, and then was evaporated under reduced pressure to leave a residue, which was partitioned between water (100 cm^3) and ethyl acetate (3 × 100 cm^3). The organic layers were combined, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue on silica gel with diethyl ether as eluent afforded the *title compound* **5** (214.4 mg, 72%) as an oil, $[\alpha]_D$ +9.6 (*c* 1.66, $CHCl_3$); ν_{max}(film)/cm^{-1} 3384 (OH), 3077 (C=CH_2), 2984, 2936, 1642 (C=C), 1434, 1382, 1244, 1217, 1166 and 1062; δ_H(400 MHz) 1.33 (3 H, s, Me), 1.45 (3 H, s, Me), 2.36–2.48 (3 H, m, CH_2CH=, OH), 2.60 (1 H, d, *J* 8.1, OH), 3.60–3.70 (2 H, m, CH_2OH), 3.84 (1 H, d, *J* 11.0, OH), 3.95–4.00 (1 H, m, C*H*OH), 3.97 (1 H, d, *J* 2.0, CHOR), 4.04–4.10 (1 H, m, C*H*OH), 4.11 (1 H, dd, *J* 5.5 and 2.0, CHOR), 5.10–5.18 (2 H, m, CH=CH_2) and 5.84 (1 H, ddt, *J* 17.2, 10.1 and 7.1, C*H*=CH_2); δ_C(22.5 MHz) 25.12 (Me), 27.38 (Me), 39.74 (*C*H_2CH=), 64.44 (CH_2OH), 68.17, 69.63, 77.00, 78.22 (4 C, 2 × CHOH, 2 × *C*HOR), 108.18 (*C*Me_2), 117.84 (CH=CH_2) and 134.58 (*C*H=CH_2) (Found: C, 56.56; H, 8.69. $C_{11}H_{20}O_5$ requires C, 56.88; H, 8.68%).

5,6,7-Trideoxy-2,3-*O*-isopropylidene-α,β-D-*lyxo*-6-enofuranose 7

The triol **5** (1.00 g, 4.31 mmol) was dissolved in water (25 cm^3) and sodium periodate (1.20 g, 5.6 mmol) was added. The solution was stirred at room temperature for 2 h, and extracted with ethyl acetate (3 × 80 cm^3). The combined organic extracts were dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with 25% diethyl ether in light petroleum as eluent to give the *hemiacetal* **7** (794.5 mg, 92%) as an oil, $[\alpha]_D$ +15.9 (*c* 1.48, $CHCl_3$); ν_{max}(film)/cm^{-1} 3420 (OH), 3079 (C=CH_2), 2983, 2940, 1643 (C=C), 1434, 1375, 1210, 1164, 1063 and 1013; δ_H(400 MHz) (mixture of anomers, α:β = 7.5:1) 1.31 (2.64 H, s, major Me), 1.36 (0.36 H, s, minor Me), 1.46 (2.64 H, s, major Me), 1.53 (0.36 H, s, minor Me), 2.45–2.49 (2 H, m, CH_2CH=), 2.58 (0.88 H, d, *J* 2.4, major OH), 3.51 (0.12 H, dt, *J* 3.2 and 7.0, minor OC*H*CH_2), 3.86 (0.12 H, d, *J* 12.2, minor OH), 4.18 (0.88 H, dt, *J* 3.6 and 7.0, major OC*H*CH_2), 4.48 (0.12 H, dd, *J* 6.0 and 3.5, minor C*H*ORCHOH), 4.589 (0.12 H, dd, *J* 6.0 and 3.2, minor C*H*ORHCH_2), 4.593 (0.88 H, d, *J* 5.9, major C*H*ORCHOH), 4.67 (0.88 H, dd, *J* 5.9 and 3.6, major C*H*ORCHCH_2), 4.94 (0.12 H, dd, *J* 12.2 and 3.5, minor OC*H*OH), 5.06–5.20 (2 H, m, CH=CH_2), 5.35 (0.88 H, d, *J* 2.4, major OC*H*OH), 5.80–5.89 (0.12 H, m, minor C*H*=CH_2) and 5.87 (0.88 H, ddt, *J* 17.1, 10.2 and 6.9, major C*H*=CH_2); δ_C(22.5 MHz) (major, α anomer) 24.79 (Me), 25.92 (Me), 32.79 (*C*H_2C=), 79.48, 80.10, 85.53 (3 C, 3 × *C*HOR), 100.66 (OCHOH), 112.27 (*C*Me_2), 117.04 (CH=*C*H_2) and 134.19 (*C*H=CH_2); (minor, β anomer) 24.79 (Me), 25.65 (Me), 32.49 (*C*H_2C=), 75.39, 78.61, 79.89 (3 C, 3 × *C*HOR), 96.51 (OCHOH), 112.89 (*C*Me_2), 117.31 (CH=*C*H_2) and 133.81 (*C*H=CH_2) (Found: C, 59.63; H, 8.13. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%).

(3a*S*,5*R*,6*S*,7*R*,7a*S*)-Octahydro-5-hydroxy-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 11

The hemiacetal **7** (591.3 mg, 2.95 mmol) and *N*-methylhydroxylamine hydrochloride (2.47 g, 29.5 mmol) were dissolved in dry pyridine (25 cm^3), and the solution was stirred at room temperature for 20 h, after which the pyridine was evaporated off and the residue was co-evaporated with toluene under reduced pressure. The residue was partitioned between water (100 cm^3) and ethyl acetate (3 × 120 cm^3). The combined organic extracts were dried (Na_2SO_4), and evaporated under reduced pressure. The residue was passed through a short column of silica gel with light petroleum–diethyl ether (1:2) as eluent to give the *nitrone* **9** (676.3 mg, 100%) as a crystalline solid, which was then dissolved in dry toluene (100 cm^3) and the solution was refluxed for 18 h. The toluene was removed under reduced pressure and the residue was purified by flash chromatography on silica gel with diethyl ether as eluent to afford the *isoxazolidine* **11** (640.3 mg, 95%) as an oil, $[\alpha]_D$ −115.6 (*c* 1.45, $CHCl_3$); ν_{max}(film)/cm^{-1} 3419 (OH), 2987, 2936, 2879, 1457, 1380, 1244, 1214, 1164, 1058 and 1012; δ_H(400 MHz) 1.33 (3 H, s, Me), 1.45 (3 H, s, Me), 1.58 (1 H, ddd, *J* 14.2, 6.5 and 3.6, C*H*HCHOH), 2.00 (1 H, ddd, *J* 14.2, 7.7 and 2.9, CH*H*-CHOH), 2.73 (3 H, s, NMe), 2.87–2.94 (2 H, m, NCH, C*H*CH_2ON), 3.73 (2 H, dd, *J* 8.1 and 4.2, CH_2ON), 4.17–4.23 (2 H, m, C*H*OH, C*H*OR), 4.29 (1 H, dd, *J* 7.2 and 2.3, CHOR) and 4.34 (1 H, br s, OH); δ_C(22.5 MHz) 24.10 (Me), 26.73 (Me), 29.47 (*C*H_2CHOH), 37.71 (*C*HCH_2), 43.65 (NMe), 67.90,

68.68, 72.35, 72.88, 77.75 (5 C, CHN, CHOH, CH_2ON, 2 × *C*HOR) and 107.94 (*C*Me_2); *m/z* (EI) 229 (M^+), 214 ($M^+ - Me$), 128, 98, 84 and 70; *m/z* (CI, NH_3) 230 ($M^+ + H$) (Found: M^+, 229.1314; C, 57.34; H, 8.30; N, 6.01%. $C_{11}H_{19}NO_4$ requires *m/z* 229.1314; C, 57.63; H, 8.35; N, 6.11%).

(3a*S*,5*R*,6*S*,7*R*,7a*S*)-5-Acetoxyoctahydro-6,7-isopropylidenedioxy-1-methyl-2,1-benzisoxazole 13

To a solution of the isoxazolidine **11** (144.5 mg, 0.63 mmol) and DMAP (20 mg, 0.16 mmol) in dry pyridine (10 cm^3) was added acetic anhydride (0.24 cm^3, 2.52 mmol). After stirring the mixture for 10 h, the pyridine was evaporated off and the residue was co-evaporated with toluene under reduced pressure to leave a residue, which was purified by flash chromatography on silica gel with light petroleum–diethyl ether (2:5) as eluent to afford the *title compound* **13** (166 mg, 93%) with data as reported above.

[(1*S*,2*R*,3*S*,4*R*,6*S*)-4-Acetoxy-6-hydroxymethyl-2,3-(isopropylidenedioxy)cyclohexyl]trimethylammonium iodide 24

The isoxazolidine **13** (178.7 mg, 0.66 mmol) as a solution in dry methanol (100 cm^3) was hydrogenated (2 atm) over Pearlman's catalyst [20% $Pd(OH)_2$–C] at room temperature for two days. The mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure to leave the crude (1*S*,2*S*,3*R*,4*S*,5*R*)-5-acetoxy-3,4-isopropylidenedioxy-2-(methylamino)cyclohexane-1-methanol **23** (180 mg) as a solid, ν_{max}(KBr)/cm^{-1} 3418 (NH, OH), 2986, 2937, 1735 (C=O), 1460, 1375, 1242 and 1040; δ_H(90 MHz) 1.37 (3 H, s, Me), 1.49 (3 H, s, Me), 1.60–2.00 (2 H, m, C*H*$_2$CHOAc), 2.07 (3 H, s, COMe), 2.00–3.00 (4 H, m, CHNH, C*H*CH_2O*H*), 2.53 (3 H, s, NMe), 3.60–3.95 (2 H, m, C*H*$_2$OH), 4.05–4.60 (2 H, m, 2 × C*H*OR) and 4.80–5.15 (1 H, m, C*H*OAc).

This crude amino alcohol **23** was then dissolved in dry THF (20 cm^3), to which potassium carbonate (274 mg, 1.98 mmol) and iodomethane (2 cm^3, 32 mmol) were added. The reaction mixture was stirred at room temperature for 30 h, after which the solvent was removed by evaporation under reduced pressure, and the residue was taken up in chloroform (50 cm^3) and filtered through Celite. The filtrate was evaporated under reduced pressure to give a residue, which was then partitioned between water (50 cm^3) and diethyl ether (3 × 50 ml). The aqueous layer was freeze-dried to afford the *title compound* **24** (226.7 mg, 80%) as fine crystals, mp 100–110 °C; $[\alpha]_D$ +12.2 (*c* 1.31, water); ν_{max}(KBr)/cm^{-1} 3381 (OH), 3056, 2939, 2985, 1734 (C=O), 1375, 1242 and 1048; δ_H(270 MHz; CD_3OD) 1.41 (3 H, s, Me), 1.57 (3 H, s, Me), 1.83 (1 H, dt, *J* 15.2 and 3.8, C*H*H-CHOAc), 2.07 (3 H, s, COMe), 2.27 (1 H, dt, *J* 15.2 and 5.8, CH*H*CHOAc), 2.80–2.85 (1 H, m, C*H*CH_2OH), 3.41 (9 H, s, NMe_3), 3.68 (1 H, dd, *J* 11.9 and 3.6, C*H*HOH), 3.81–3.95 (2 H, m, CH*H*OH, C*H*NMe_3), 4.39–4.43 (1 H, m, C*H*OR) and 5.05–5.17 (2 H, m, C*H*OR, C*H*OAc); *m/z* (FAB) 302 ($M^+ - I$), 270, 258, 242, 143 and 125 [Found (FAB): $M^+ - I$, 302.1969. $C_{15}H_{28}NO_5$ requires *m/z* 302.1967].

(3*R*,4*S*,5*R*)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarbaldehyde 25

DMSO (0.16 ml, 2.29 mmol) was added to a solution of oxalyl dichloride (0.1 ml, 1.15 mmol) in dry dichloromethane (10 cm^3) at −78 °C. After 15 min, a solution of the quaternary ammonium iodide **24** (168 mg, 0.39 mmol) in dichloromethane (2 cm^3) was added, and the reaction mixture was stirred at −78 °C for 55 min. Triethylamine (0.81 cm^3, 5.75 mmol) was then added; after a further 10 min the mixture was allowed to come to room temperature, diluted with dichloromethane (100 cm^3) and washed with water (100 cm^3). The aqueous layer was extracted with dichloromethane (2 × 100 cm^3), and the combined organic extracts were washed with saturated aq. sodium chloride (200 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure. Flash chromatography of the residue on silica gel with light petroleum–diethyl ether (1:1) as eluent afforded the *α,β-unsaturated aldehyde* **25** (66.5 mg, 71%) as an oil, $[\alpha]_D$ −84.1 (*c* 1.38, $CHCl_3$); ν_{max}(film)/cm^{-1} 2987, 2936, 2828, 1748 (ester C=O), 1691 (CH=O), 1652 (C=C), 1372, 1237, 1160, 1063 and 1041; δ_H(400 MHz) 1.39 (3 H, s, Me), 1.40 (3 H, s, Me), 2.04 (3 H, s, COMe), 2.31 (1 H, ddt, *J* 17.7, 6.0 and 1.4, C*H*HC=), 2.65 (1 H, ddt, *J* 17.7, 4.5 and 1.4, CH*H*C=), 4.30 (1 H, t, *J* 6.0, C*H*ORCHOAc), 4.83 (1 H, dd, *J* 5.8 and 3.4, C*H*ORCH=), 5.20 (1 H, dt, *J* 4.5 and 6.0, C*H*OAc), 6.70 (1 H, dt, *J* 3.4 and 1.4, CH=C) and 9.54 (1 H, s, CHO); δ_C(22.5 MHz) 21.00 (CO*Me*), 23.33 (Me), 25.92 (Me), 27.74 (*C*H_2C=), 69.21, 71.69, 74.38 (3 C, 2 × *C*HOR, *C*HOAc), 110.30 (*C*Me_2), 138.76 (=*C*CHO), 143.32 (*C*H=C), 170.00 (*C*OMe) and 192.76 (CHO); *m/z* (EI) 241 ($M^+ + H$), 225 ($M^+ - Me$), 183, 123 and 95; *m/z* (CI, NH_3) 258 ($M^+ + NH_4$), 241 ($M^+ + H$), 225 ($M^+ - Me$) and 183 [Found (CI, NH_3): MH^+, 241.1076. $C_{12}H_{17}O_5$ requires *m/z* 241.1076].

(3*R*,4*S*,5*R*)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarboxylic acid 26

To a solution of the aldehyde **25** (21.8 mg, 0.091 mmol), monobasic sodium phosphate monohydrate (20 mg, 0.14 mmol) and hydrogen peroxide (30% aq. solution, ~ 0.98 M; 0.05 cm^3, 0.49 mmol) in acetonitrile–water (2:1; 3 cm^3) at room temperature was added sodium chlorite (80% purity from Aldrich; 40 mg, 0.35 mmol). After 2 h the mixture was diluted with saturated aq. sodium chloride (25 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification was effected by flash chromatography on silica gel with 0.1% acetic acid in light petroleum–diethyl ether (1:4) as eluent to yield the *acid* **26** (21.2 mg, 91%) as an oil, $[\alpha]_D$ −76.4 (*c* 0.71, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2990, 2936, 1732 (ester C=O), 1699 (acid C=O), 1653 (C=C), 1374 and 1239; δ_H(90 MHz) 1.39 (6 H, s, 2 × Me), 2.06 (3 H, s, COMe), 2.10–2.90 (2 H, m, CH_2C=), 4.23 (1 H, t, *J* 6.2, C*H*OR), 4.69–4.79 (1 H, m, C*H*OR), 5.09–5.28 (1 H, m, C*H*OAc), 6.98–7.03 (1 H, m, CH=C) and 8.60 (1 H, br s, CO_2H); δ_C(22.5 MHz) 21.06 (CO*Me*), 25.95 (2 C, C*Me*$_2$), 27.74 (*C*H_2C=), 69.69, 71.78, 73.78 (3 C, 2 × *C*HOR, *C*HOAc), 110.15 (*C*Me_2), 128.82 (=*C*CO_2H), 136.58 (*C*H=C), 170.20 (*C*OMe) and 170.89 (CO_2H); *m/z* (EI) 241 ($M^+ - Me$), 205, 139, 95 and 84; *m/z* (CI, NH_3) 274 ($M^+ + NH_4$), 257 ($M^+ + H$), 241 ($M^+ - Me$), 216 and 199 ($M^+ - Me - C_3H_6$) [Found (CI, NH_3): MH^+, 257.1025. $C_{12}H_{17}O_6$ requires *m/z* 257.1025].

(3*R*,4*S*,5*R*)-3,4,5-Trihydroxycyclohex-1-enecarboxylic acid (shikimic acid) 1

A solution of acid **26** (40 mg, 0.16 mmol) and potassium carbonate (251 mg, 1.6 mmol) in 5% aq. methanol (10 cm^3) was stirred at room temperature for 12 h, then was acidified with aq. hydrochloric acid (2 M) and extracted with diethyl ether (3 × 50 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the crude (3*R*,4*S*,5*R*)-5-hydroxy-3,4-(isopropylidenedioxy)cyclohex-1-enecarboxylic acid **27** as an oil, which was then dissolved in 50% aq. TFA (2 cm^3), and the solution was stirred at room temperature for 10 h. Concentration of the reaction mixture and further co-evaporation with dry ethanol under reduced pressure furnished the *shikimic acid* **1** (21.5 mg, 79%) as a crystalline solid, mp 183–185 °C; $[\alpha]_D$ −175.4 (*c* 0.59, water) {lit.,[5a] mp 189 °C; $[\alpha]_D$ −179.7 (*c* 4, water); lit.,[5e] mp 184–186 °C; $[\alpha]_D$ −170 (*c* 0.86, water)}, identical with an authentic sample of shikimic acid.

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