Syntheses of 6β-hydroxyshikimic acid and its derivatives

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The conversion of (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol, (5*S*,6*S*)-5,6-dihydroxycyclohexa-1,3-diene-1-carbonitrile and methyl (5*S*,6*S*)-5,6-dihydroxycyclohexa-1,3-diene-1-carboxylate into 6β-hydroxyshikimic acid and protected derivatives is described.

Introduction

The 6α- and 6β-fluoroshikimic[1] acids **1** and **2** are of interest in exploring the enzymology[2] of the shikimic acid pathway which leads to the biosynthesis of the aromatic amino acids. We have previously described two synthetic routes to the fluorinated compounds from quinic acid.[1,3] In the latter route we demonstrated that suitably protected 6-hydroxyshikimic acids could be converted efficiently into the fluoro compounds with Et_2NSF_3. The main problem with the routes from quinic acid lies in the dehydration of quinic to shikimic derivatives which could only be accomplished satisfactorily with a sulfurane. In an effort to develop more efficient routes we have examined the *cis*-1,2-diols, formed by oxidation of mono-substituted benzenes with the bacterium *Pseudomonas putida*,[4] as starting materials.†

Results and discussion

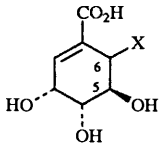
Bromobenzene is oxidised by the bacterium to (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol **3**. The diene has been protected as the acetal **4** and dihydroxylated to give[5] the diol **7** which we have converted into the bis-acetal **8** (90%). Reaction[6] of **8** with Bu^{t}Li–Et_2O at −109 °C and then CO_2 gave an acid (67%) which was converted into the ester **17**† (80%) by reaction with MeI–CsF.[7] The protecting groups were removed (CF_3CO_2H–H_2O) to give methyl 6β-hydroxyshikimate **18** identical with the material prepared[3] previously. Suitable precursors for the fluoro compounds require differentiation of the diol systems and of the 5- and 6-hydroxy groups. To this end the diol **7** was converted into the bis-Bu^{t}Me$_2$Si (TBDMS) ether **9** (72%) and carboxylated (70%) as before to form the acid **19**. Attempts to combine esterification and removal of the isopropylidene group under a variety of conditions led to complete deprotection or unchanged acid **19**. Reaction with CH_2N_2 converted **19** into the ester **20** (99%), but a series of attempts to remove the isopropylidene group selectively failed.

A switch of protecting groups should allow deprotection of the 3,4-diol system under neutral conditions, so the bis-TBDMS ether **5** was prepared (90%) and hydroxylated with OsO_4–*N*-methylmorpholine *N*-oxide (NMMNO)–water[8] to give the diol **10** (66%). The regio- and stereo-chemistry of reaction was established by ^{1}H NMR spectroscopy; in particular the ^3J of 9.5 Hz between 2-H and 3-H established the *cis*-diol systems to be *anti* to each other. The diol **10** was converted into the acetal **11**, but attempts to effect Br–Li exchange at a variety of temperatures failed; presumably the bulk of the TBDMS group at the 4-position sterically hinders the exchange. We then investigated Pd and Ni catalysed carbonylations which can be carried out with an unprotected hydroxy group at C-6. Since the conditions for these reactions are severe, the isopropylidene protection was replaced by the more robust cyclohexylidene; the diol **10** was converted into the acetal **12** (90%) and the silyl protecting groups removed to give the diol **13** (75%). Attempts to effect Pd-catalysed methoxycarbonylation led only to traces of the ester **22**; however reaction[9] of the bromide **13** with $[Ni(CO)_2(PPh_3)_2]$–Et_3N–MeOH gave the ester **22** (70%) contaminated with an unknown impurity which could only be removed by reversed phase HPLC.

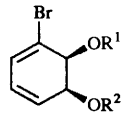
The $Me_3Si(CH_2)_2OCH_2$ (SEM) group[10] can be removed under neutral conditions and should cause less hindrance in the vicinity of the CBr bond so the bis-ether **6** was prepared (97%) and dihydroxylated under standard conditions. In this case two isomers were obtained (72%) in a ratio of 17:1, the major component being the diol **14**; its structure was established by ^{1}H NMR spectroscopy and further transformations. The minor product is likely to be the diol obtained by reaction at the opposite face of the molecule. The cyclohexylidene acetal **15** was prepared (72%) from the diol **14**. Carboxylation using the previous conditions gave the acid in low yield which was improved to 79% by change of solvent to hexane and raising the temp. to −78 °C; debrominated alkene (10%) was also isolated. The ester **21** (72%) was prepared (MeI–CsF) from the acid and reaction[11] with $MgBr_2$–BuSH (1 equiv.) gave (68%) a 7.5:1 mixture of the mono-SEM ethers **23** and **24**. The structures were established by conversion of the compounds into the acetates and comparison of ^{1}H NMR spectra; most notably a doublet at δ 4.83 (*J* 3.4) in the spectrum of **24** shifted to δ 6.13 in the spectrum of its acetate. Reaction of the ester **21** with an excess of $MgBr_2$–BuSH gave the diol **22** (75%) identical with the material prepared previously. Reaction of **22** with an excess of TBDMSCl–Et_3N gave the mono-silyl ether **25** (50%) which can be converted efficiently into the 6α-fluoro compound.

When this work was completed (5*S*,6*S*)-5,6-dihydroxycyclohexa-1,3-diene-1-carbonitrile **35**, prepared by the oxidation of PhCN with *Pseudomonas putida* UV4[15], became avaliable[12] and it was converted into the isopropylidene acetal **36** (93%). Hydroxylation with OsO_4–NMMNO–water gave the diol **39** (53%, together with 36% of recovered starting material); negative evidence supported the assigned stereochemistry in that the diacetate of **39** exhibited only vicinal NOEs and no transannular enhancements. All attempts to hydrolyse the diol **39** and the derived bis-acetonide **40** to the corresponding acids under basic conditions led to decomposition. Reaction of the nitrile **40** with NaOH–H_2O_2 formed the amide **38** and attempts to hydrolyse the nitrile with nitrilase enzymes were unsuccessful. We then attempted to prepare a

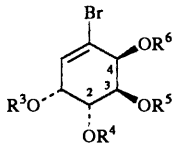
† **Note** For convenience, in the Discussion, the numbering for compounds is that shown in the displayed formulae for **1**, **2** and **7**–**15**. In the Experimental section compounds have been named and numbered according to the IUPAC rules of nomenclature.



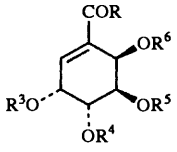
1 X=—F
2 X=⋯F



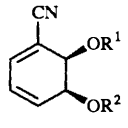
3 $R^1 = R^2 = H$
4 $R^1R^2 = CMe_2$
5 $R^1 = R^2 = TBDMS$
6 $R^1 = R^2 = SEM$



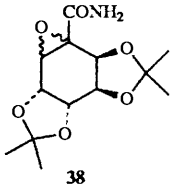
7 $R^3 = R^4 = H$, $R^5R^6 = CMe_2$
8 $R^3R^4 = R^5R^6 = CMe_2$
9 $R^3 = R^4 = TBDMS$, $R^5R^6 = CMe_2$
10 $R^3 = R^4 = H$, $R^5 = R^6 = TBDMS$
11 $R^3R^4 = CMe_2$, $R^5 = R^6 = TBDMS$
12 $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = TBDMS$
13 $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = H$
14 $R^3 = R^4 = H$, $R^5 = R^6 = SEM$
15 $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = SEM$



16 R = OMe, $R^3 = R^4 = H$, $R^5R^6 = CMe_2$
17 R = OMe, $R^3R^4 = R^5R^6 = GMe_2$
18 R = OMe, $R^3 = R^4 = R^5 = R^6 = H$
19 R = OH, $R^3 = R^4 = TBDMS$, $R^5R^6 = CMe_2$
20 R = OMe, $R^3 = R^4 = TBDMS$, $R^5R^6 = CMe_2$
21 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = SEM$
22 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = H$
23 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = H$, $R^6 = SEM$
24 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = SEM$, $R^6 = H$
25 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = TBDMS$, $R^6 = H$
27 R = H, $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = TBDMS$
28 R = OH, $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = TBDMS$
29 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = TBDMS$
30 R = OMe, $R^3 = R^4 = H$, $R^5 = R^6 = TBDMS$
31 R = OMe, $R^3 = R^4 = H$, $R^5R^6 = CMe_2$
32 R = OMe, $R^3 = H$, $R^4 = OAc$, $R^5 = R^6 = TBDMS$
33 R = OMe, $R^3R^4 = C(CH_2)_5$, $R^5 = H$, $R^6 = TBDMS$
34 R = OMe, $R^3 = OAc$, $R^4 = H$, $R^5 = R^6 = TBDMS$



35 $R^1 = R^2 = H$
36 $R^1R^2 = CMe_2$
37 $R^1 = R^2 = TBDMS$



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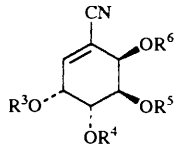
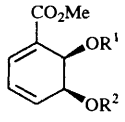
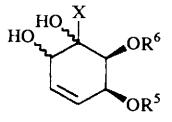
protected 6-fluoro nitrile which there was good reason to believe could be hydrolysed under acidic conditions to the fluoroshikimic acid. Dihydroxylation of the bis-ether **37** gave the diol **41** (84%) accompanied by traces of the enone **53** and the diol **50**. The cyclohexylidene acetal **42** was prepared by a standard method from the diol **41** (90%) and desilylated using Bu_4NF to form the diol **43** (86%). At this stage we attempted to differentiate between the C-5 and C-6 hydroxy groups of **43**. Selective silylation ($TBDMSOSO_2Me$) gave mixtures so the diol



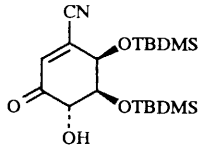
39 $R^3 = R^4 = H$, $R^5R^6 = CMe_2$
40 $R^3R^4 = R^5R^6 = CMe_2$
41 $R^3 = R^4 = H$, $R^5 = R^6 = TBDMS$
42 $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = TBDMS$
43 $R^3R^4 = C(CH_2)_5$, $R^5 = R^6 = H$
44 $R^3R^4 = C(CH_2)_5$, $R^5R^6 = SnBu_2$
45 $R^3R^4 = C(CH_2)_5$, $R^5 = H$, $R^6 = TBDMS$
46 $R^3R^4 = C(CH_2)_5$, $R^5 = H$, $R^6 = CH_2Ph$



47 $R^1 = R^2 = H$
48 $R^1R^2 = CMe_2$
49 $R^1 = R^2 = TBDMS$



50 X = CN, $R^5 = R^6 = TBDMS$
51 X = CO_2Me, $R^5 = R^6 = TBDMS$
52 X = CO_2Me, $R^5R^6 = CMe_2$



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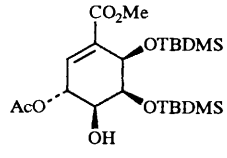

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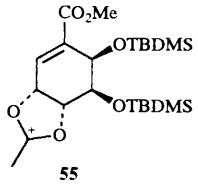
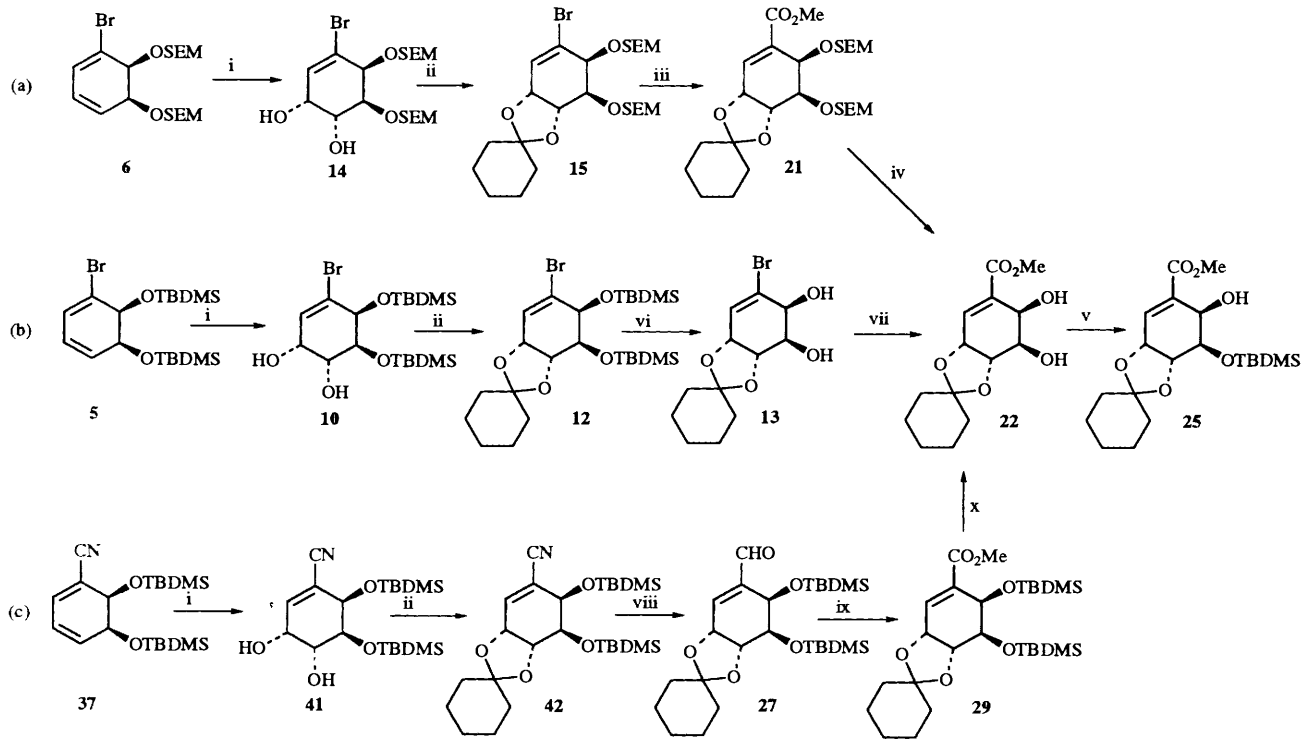


55

was converted[13] into the tin ether **44** (Bu_2SnO) which was treated with TBDMSCl–CsF to form the alcohol **45** (30%) as the sole silylated product; its structure was established by conversion of the compound into its acetate which in the ^1H NMR spectrum showed a downfield shifted signal at δ 5.45 (J 6.7 and 3.7) and the appropriate proton connectivities in a 2D-COSY experiment. Reaction of **44** with $PhCH_2Br$ gave the ether **46** (38%). These failures to protect selectively the 5-OH group of the nitrile **43** contrasts with the successful protection of the ester **22**; the greater steric size of the ester function and its hydrogen bonding to the 6-hydroxy group could contribute to the different reactivities. With the failure of hydrolytic methods for the conversion of the nitrile **42** into an acid function it was reduced with Bu^i_2AlH(DIBAL) to the aldehyde **27** (70%), oxidised with $NaClO_2$[14] to the acid **28** and esterified with MeI–K_2CO_3 to form the ester **29** (80% overall). Desilylation with pyridinium $(HF)_n$ gave the diol **22** (90%) identical with that prepared previously.

The requirement for the ester function in distinguishing between the 5- and 6-hydroxy groups and the difficulties in converting the nitrile into an ester suggested the diene **47** as an attractive starting material. $PhCO_2Me$ was oxidised with an



Scheme 1 *Reagents:* i, OsO_4–NMMNO–water; ii, 1,1-dimethoxycyclohexane-H^+; iii, Bu'Li, then CO_2, then MeI–CsF; iv, $MgBr_2$–BuSH; v, TBDMSCl–Et_3N; vi, Bu_4NF; vii, $[Ni(CO)_2(PPh_3)_2]$–Et_3N; viii, DIBAL; ix, $NaClO_2$ then MeI–K_2CO_3; x, pyridinium $(HF)_n$

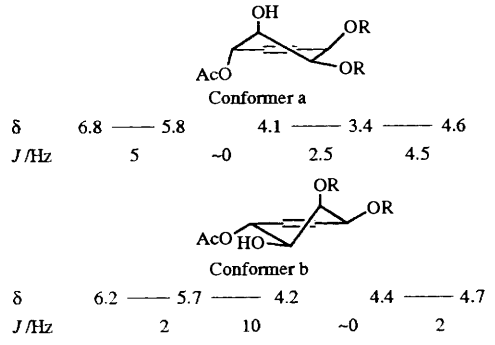


Fig. 1 Connectivities and *J* values for conformers of **54**

aqueous culture of *Pseudomonas putida* UV4[15] to the ester **47** (53%); the structure followed from spectroscopic data and relative and absolute stereochemistry were established by conversion of the compound into methyl 6β-hydroxyshikimate **18**. The silyl ether **49** was prepared and dihydroxylated under standard catalytic conditions to give an inseparable 10:1 mixture (46%) of the diols **51** and **30**. With the isopropylidene acetal **48** dihydroxylation yielded the diols **31** (27%) and **52** (18%); acid hydrolysis converted **31** into the ester **18** and 5β-hydroxyshikimic acid proving the absolute and relative stereochemistry of the diene **47**. The extent of reaction at the 1,2-position in these compounds was both disappointing and puzzling in light of our previous results and the report[16] that methyl 5-*tert*-butyldimethylsiloxycyclohexa-1,3-diene-1-carboxylate is hydroxylated in high yield at the 3,4-position. It is unlikely that the direct steric effect of a 6-substituent would favour 1,2-reaction over 3,4, but indirectly the substituent could cause the carboxymethyl group to rotate out of conjugation with the double bond and thus changing the electron distribution in the diene; MM2 calculations support this view. We also examined the Prevost reaction (AgOAc–AcOH–I_2 and then water) with compound **49**; chromatographic separation of the product gave two fractions. The minor fraction (17%) gave a ^1H NMR spectrum consistent with a 7:1 mixture of the 4- and 3-monoacetates of **30**; in $CDCl_3$ solution the major acetate was converted partially and slowly into the minor. The structure of the second product was more difficult to determine. Its ^1H NMR spectrum at ambient temperature showed broadened signals and cooling to −60 °C resolved the spectrum into that of two conformers which, together with a 2D-COSY experiment, provided the data in Fig. 1 which is best accommodated by the two half-chair conformers of the acetate **54**. Attack of H_2O on the acetoxonium **55** at C-4 would form **54**, while attack at the acetoxonium centre could give rise to the monoacetates of **30**.

The three routes to the protected 6β-hydroxyshikimic acid are summarised in Scheme 1; the overall yields from the diols are (a) 10.7%, (b) 14% and (c) 16.2%.

Experimental

NMR spectra were recorded on a Varian XL300 or a Bruker AC300 spectrometer 300 MHz for ^1H and 75 MHz for ^{13}C. Spectra were measured in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on a Kratos Concept instrument coupled to a DS90/MACH 3 data system and accurate mass measurements (±4 ppm) using a Kratos MS25 instrument with a DS55 data system. Chemical ionisation determinations used NH_3 as the carrier gas. IR spectra were recorded on a Perkin-Elmer 1710 FT spectrometer as thin films. $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1}. The term 'work-up' implies washing the organic extract with brine, drying the solution with $MgSO_4$, filtration and concentration of the extract under reduced pressure. Light petroleum refers to the fraction with distillation range 40–60 °C.

(1*S*,2*S*)-3-Bromocyclohexa-3,5-diene-1,2-diol 3
A 10% solution of compound **3** in EtOAc (10% solution; 15 cm^3) was added to vigorously stirred light petroleum (180 cm^3) cooled to 0 °C. A solid separated and filtration and drying under reduced pressure gave the diene **3** (1.4 g) which was used without further purification or characterisation. This material was stable for a few days if kept in a freezer, but best results were obtained using freshly isolated material.

(3a*R*,5a*S*,8a*S*,8b*R*)-4-Bromo-2,2,7,7-tetramethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*; 3,4-*d'*]bis[1,3]dioxole 8
A solution of the diol **7** (0.95 g), 2,2-dimethoxypropane (0.7 cm^3) and a catalytic amount of toluene-*p*-sulfonic acid (PTSA) in CH_2Cl_2 (10 cm^3) under Ar was stirred for 1 h. The reaction mixture was filtered through a pad of Merck 9385 Silica Gel. The pad was washed with CH_2Cl_2 (3 × 10 cm^3) and the filtrate concentrated under reduced pressure to furnish the crude product as an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; 5:95) to give the *ketal* **8** as an oil (1.06 g, 95%), $[\alpha]_D$ +84.7 (*c* 1.1 in CH_2Cl_2); δ_H 1.38 (6 H, s), 1.41 (6 H, s), 4.64 (1 H, dd, *J* 5 and 2.4) and 6.08 (1 H, m); ν_{max}/cm^{-1} 2990 and 1650; *m/z* (EI) 307 and 305; (CI) 307 and 305 (Found: M^+, 305.0386. $C_{12}H_{17}{}^{79}BrO_4$ requires *M*, 305.0389).

(3a*R*,5a*R*,8a*S*,8b*R*)-2,2,7,7-Tetramethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*; 3,4-*d'*]bis[1,3]dioxole-4-carboxylic acid
Bu^{t}Li (1.7 mol dm^{-3} in pentane; 1 cm^3) was added dropwise to a stirred solution of the acetonide **8** (0.5 g) in dry Et_2O (10 cm^3) at −109 °C under N_2. After 15 min at −109 °C dry CO_2 was bubbled into the reaction mixture. The cooling bath was then removed and the reaction mixture was allowed to warm to room temp. A white precipitate was formed. Saturated aq. $NaHCO_3$ (10 cm^3) was added to the mixture which was then extracted with CH_2Cl_2 (3 × 10 cm^3). The aqueous phase was acidified with 10 mol dm^{-3} HCl to pH 1 and then extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield the *acid* as an oil (0.29 g, 67%); δ_H 1.31 (3 H, s), 1.33 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 4.60 (1 H, m), 4.69 (2 H, m), 4.94 (1 H, d, *J* 5.7) and 6.83 (1 H, s); ν_{max}/cm^{-1} 2990 and 1705; *m/z* (EI) 271, (CI) 288 (Found: M^+, 271.1178. $C_{13}H_{18}O_6$ requires *M* + H, 271.1182).

(3a*R*,5a*R*,8a*R*,8b*R*)-Methyl 2,2,7,7-tetramethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*; 3,4-*d'*]bis[1,3]dioxole-4-carboxylate 17
CsF (0.42 g) and MeI (0.17 cm^3) were added to a stirred solution of the above acid (0.5 g) in Me_2NCHO (8 cm^3) under Ar. The reaction mixture was stirred for 16 h and then poured into a mixture of saturated aq. $NaHCO_3$ (40 cm^3) and water (40 cm^3). The mixture was extracted with Et_2O (3 × 30 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:9) to furnish the *ester* **17** as an oil (0.43 g, 80%), δ_H 1.31 (3 H, s), 1.33 (3 H, s), 1.38 (3 H, s), 1.41 (3 H, s), 3.82 (3 H, s), 4.59 (1 H, m), 4.68 (2 H, m), 4.97 (1 H, d, *J* 5.7) and 6.72 (1 H, m); ν_{max}/cm^{-1} 1730; *m/z* (EI) 285; (CI) 302 (Found: M^+, 285.1331. $C_{14}H_{20}O_6$ requires *M* + H, 285.1338).

(3*R*,4*R*,5*R*,6*R*)-Methyl 3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate 18
Water (1 cm^3) and CF_3CO_2H (0.5 cm^3) were added to the ester **17** (0.157 g) in tetrahydrofuran (THF) (2 cm^3). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was azeotroped with PhMe to give an oil which was purified by dry column chromatography on silica gel 60H (Pr^{i}OH–$CHCl_3$, 2:8) to give the ester **18** as a colourless oil (0.114 g, 90%) identical with a sample prepared previously, δ_H 3.73 (3 H, s), 3.8 (1 H, dd, *J* 10 and 3.5), 3.87 (1 H, dd, *J* 10 and 4), 4.48 (1 H, dd, *J* 5 and 4), 4.6 (1 H, d, *J* 3.5) and 6.88 (1 H, d, *J* 5); *m/z* (EI) 205 and (CI) 222 (Found: M^+, 205.0719. $C_8H_{12}O_6$ requires *M* + H, 205.0712).

(3a*S*,6*R*,7*R*,7a*S*)-4-Bromo-6,7-di-*tert*-butyldimethylsiloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole 9
TBDMSOSO$_2$CF$_3$ (1.56 cm^3) was added dropwise to a stirred solution of the diol **7** (0.6 g) and imidazole (0.6 g) in Me_2NCHO (6 cm^3) under Ar. After 1.5 h the reaction mixture was poured into water (30 cm^3) and extracted with Et_2O (3 × 15 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 2:98) to give the *ether* **9** as a solid (0.79 g, 71%), $[\alpha]_D$ −69.1 (*c* 1.0 in CH_2Cl_2); δ_H 0.09 (3 H, s), 0.095 (3 H, s), 0.10 (6 H, s), 0.88 (9 H, s), 0.92 (9 H, s), 1.4 (3 H, s), 1.42 (3 H, s), 4.13 (1 H, m), 4.28 (1 H, t, *J* 5.2), 4.37 (1 H, m), 4.6 (1 H, dd, *J* 5.5 and 1.2) and 5.98 (1 H, m); δ_C −4.835, −4.735, −4.495, −4.353, 18.13, 18.34, 25.77, 26.03, 26.22, 27.53, 69.12, 72.08, 77.24, 110.09, 121.51 and 132.91; ν_{max}/cm^{-1} 1640; *m/z* (EI) 495 and 493; (CI) 512 and 510 (Found: C, 51.1; H, 8.4; M^+, 510.2076. $C_{21}H_{41}BrO_4Si_2$ requires C, 51.1; H, 8.4%; *M*, 510.2071).

(3a*R*,6*R*,7*R*,7a*R*)-6,7-Di-*tert*-butyldimethylsiloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylic acid 19
Bu^{t}Li (1.7 mol dm^{-3} in pentane; 0.65 cm^3) was added to a stirred solution of the ether **9** (0.5 g) in Et_2O (5 cm^3) cooled to −109 °C under Ar. After 30 min, dry CO_2 was bubbled into the reaction mixture which was then allowed to warm to room temp. The solution became very viscous and was diluted with EtOAc–light petroleum (2:8; 20 cm^3) and then loaded directly onto a dry silica gel 60H column, eluted first with EtOAc–light petroleum (1:9; 3 × 20 cm^3) and then with AcOH–EtOAc (0.1:99.9; 3 × 20 cm^3). The latter fractions furnished the *acid* **19** (0.37 g, 79%), mp 135–136 °C (from EtOAc–light petroleum), δ_H 0.07 (3 H, s), 0.09 (3 H, s), 0.127 (3 H, s), 0.131 (3 H, s), 0.83 (9 H, s), 0.94 (9 H, s), 1.35 (3 H, s), 1.4 (3 H, s), 4.2 (1 H, m), 4.32 (1 H, dd, *J* 5.9 and 3.9), 4.6 (1 H, s), 5.0 (1 H, dd, *J* 5.9 and 1) and 6.91 (1 H, t, *J* 1.7); ν_{max}/cm^{-1} 2930, 1700 and 1650; *m/z* (CI) 459 and 476 (Found: M^+, 459.2594. $C_{22}H_{42}Si_2O_6$ requires *M* + H, 459.2598).

(3a*R*,6*R*,7*R*,7a*R*)-Methyl 6,7-di-*tert*-butyldimethylsiloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate 20
CH_2N_2 in Et_2O was added dropwise to a solution of the acid **19** (0.59 g) in CH_2Cl_2 (5 cm^3) until a permanent yellow colour was obtained. The excess of CH_2N_2 was destroyed by adding AcOH to the solution which was then filtered through a pad of Merck 9385 Silica Gel with EtOAc as eluent. The filtrate was concentrated under reduced pressure to furnish the *ester* **20** as an oil (0.61 g, 99%), δ_H 0.07 (3 H, s), 0.09 (3 H, s), 0.13 (6 H, s), 0.83 (9 H, s), 0.94 (9 H, s), 1.34 (3 H, s), 1.4 (3 H, s), 3.8 (3 H, s), 4.18 (1 H, m), 4.3 (1 H, dd, *J* 6 and 4), 4.56 (1 H, s), 5.02 (1 H, dd, *J* 6 and 1) and 6.77 (1 H, t, *J* 1.6); ν_{max}/cm^{-1} 2930, 1730 and 1655; *m/z* (EI) 472; (CI) 490 (Found: M^+, 472.2662. $C_{23}H_{44}O_6Si_2$ requires *M*, 472.2676).

(1*S*,2*S*)-1,2-Di-*tert*-butyldimethylsiloxy-3-bromocyclohexa-3,5-diene 5
TBDMSOSO$_2$CF$_3$ (7.9 cm^3) was added dropwise to a stirred solution of the diene **3** (3.0 g) and imidazole (6.4 g) in Me_2NCHO (30 cm^3) under Ar. After 2 h the reaction mixture was poured into water (150 cm^3) and extracted with Et_2O (3 × 75 cm^3). Work-up gave an oil (8.26 g) purified by dry column chromatography on silica gel 60H (EtOAc–light petroleum; gradient elution 0:1 to 2:8) to give the *ether* **5** as an oil (6.0 g, 90%); δ_H 0.24 (3 H, s), 0.25 (3 H, s), 0.26 (3 H, s), 0.27 (3 H, s), 1.00 (9 H, s), 1.05 (9 H, s), 4.2 (1 H, d, *J* 5), 4.68 (1 H, m), 5.93 (1 H, ddd, *J* 9.6, 5.2 and 2.3), 6.02 (1 H, dm, *J* 9.6) and

6.49 (1 H, d, *J* 5.2); *m/z* (EI) 420 and 418; (CI) 438 and 436 (Found: M^+, 418.1368. $C_{18}H_{35}{}^{79}BrO_2Si_2$ requires *M*, 418.1359).

(1*R*,2*R*,5*S*,6*S*)-4-Bromo-5,6-di-*tert*-butyldimethylsiloxycyclohex-3-ene-1,2-diol 10

The ether **5** (6 g) was dissolved in Bu^{t}OH (60 cm^3) containing *N*-methylmorpholine *N*-oxide (NMMNO) (1.7 g), water (0.6 cm^3) and a catalytic amount of OsO_4 under Ar. The reaction mixture was stirred for 18 h during which time it turned black. $Na_2S_2O_5$ (15 g) and EtOAc (60 cm^3) were added to the reaction mixture which was then stirred for a further 1 h. The reaction mixture was filtered through a pad of Merck 9385 Silica Gel, pre-eluted with EtOAc, and the pad was washed with several portions of EtOAc. The filtrate was concentrated under reduced pressure to furnish the crude product as an oil, purification of which by chromatography on silica gel 60 (EtOAc–light petroleum; 2:8) gave the *diol* **10** as an oil (2.2 g, 66%), $[\alpha]_D$ −7.5 (*c* 2.2 in CH_2Cl_2); δ_H 0.13 (3 H, s), 0.14 (3 H, s), 0.15 (3 H, s), 0.20 (3 H, s), 0.91 (9 H, s), 0.94 (9 H, s), 2.42 (1 H, s), 2.72 (1 H, s), 4.04 (1 H, dd, *J* 9.5 and 2.7), 4.1 (1 H, dd, *J* 9.5 and 3.9), 4.28 (1 H, d, *J* 2.7), 4.37 (1 H, t, *J* 4.4) and 6.15 (1 H, d, *J* 4.9); ν_{max}/cm^{-1} 3410, 2955 and 1640; *m/z* (EI) 454 and 452; (CI) 472 and 470 (Found: M^+, 472.1725. $C_{18}H_{41}{}^{81}BrNO_4$ requires *M*, 472.1738).

(3a*R*,6*S*,7*S*,7a*R*)-5-Bromo-6,7-di-*tert*-butyldimethylsiloxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole 11

The diol **10** (0.87 g), 2,2-dimethoxypropane (0.28 cm^3) and a catalytic amount of PTSA in CH_2Cl_2 (10 cm^3) were stirred for 30 min under Ar. The reaction mixture was loaded directly onto a dry column of silica gel 60H which was then eluted with CH_2Cl_2 to furnish the *acetal* **11** as an oil (0.75 g, 80%); δ_H 0.11 (3 H, s), 0.12 (3 H, s), 0.14 (3 H, s), 0.17 (3 H, s), 0.91 (18 H, s), 1.36 (3 H, s), 1.45 (3 H, s), 3.88 (1 H, m), 4.18 (1 H, s), 4.32 (1 H, t, *J* 7.2), 4.71 (1 H, dd, *J* 6.8 and 3.5) and 6.15 (1 H, d, *J* 3.5); ν_{max}/cm^{-1} 1640; *m/z* (CI) 512 and 510 (Found: M^+, 510.2065. $C_{21}H_{45}{}^{79}BrO_4Si_2$ requires *M*, 510.2071).

(3a*R*,4*S*,5*S*,7a*R*)-6-Bromospiro[3a,4,5,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-4,5-diol 13

A solution of the ether **9** (2.3 g) in CH_2Cl_2 (14 cm^3) and Bu_4NF (1 mol dm^{-3} in THF; 16.6 cm^3) was stirred for 3.5 h after which it was diluted with CH_2Cl_2 (30 cm^3), water (10 cm^3) and brine (10 cm^3). Work-up gave an oil which was purified by chromatography on silica gel 60H (EtOAc–light petroleum; gradient elution, 1:4 to 4:1) to give the *diol* **13** as a white solid (1.03 g, 75%), mp 124–126 °C (from EtOAc–light petroleum); $[\alpha]_D$ −18.7 (*c* 2.1 in CH_2Cl_2); δ_H 1.39 (2 H, s), 1.59 (18 H, s), 2.69 (1 H, s), 2.74 (1 H, s), 4.23 (1 H, m), 4.37 (2 H, m), 4.64 (1 H, m) and 6.24 (1 H, d, *J* 3.8); ν_{max}/cm^{-1} 3420, 2930 and 1640; *m/z* (EI) 306 and 304; (CI) 324 and 322 (Found: C, 47.0; H, 5.6; M^+, 304.0311. $C_{12}H_{17}{}^{79}BrO_4$ requires C, 47.2; H, 5.61%; *M*, 304.0311).

(3a*R*,6*S*,7*S*,7a*R*)-5-Bromo-6,7-di-*tert*-butyldimethylsiloxyspiro-[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane] 12

A solution of 1,1-diethoxycyclohexane (1.0 g), the diol **10** (2.2 g), and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (20 cm^3) was stirred for 3 h under Ar after which it was treated with saturated aq. $NaHCO_3$ (5 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). Work-up gave an oil purified by chromatography on silica gel 60H (EtOAc–light petroleum; 1:99) to give the *acetal* **12** as an oil (2.3 g, 90%); δ_H 0.01 (3 H, s), 0.13 (3 H, s), 0.14 (3 H, s), 0.16 (3 H, s), 0.90 (18 H, s), 1.4 (2 H, m), 1.56 (8 H, m), 3.85 (1 H, m), 4.15 (1 H, s), 4.3 (1 H, t, *J* 7), 4.72 (1 H, dd, *J* 7 and 3.3) and 6.17 (1 H, d, *J* 3.3); ν_{max}/cm^{-1} 2930 and 1644; *m/z* (EI) 533 and 531 (Found: M^+, 531.1964. $C_{24}H_{43}{}^{79}BrO_4Si_2$ requires *M* + H, 531.1961).

(3a*R*,6*R*,7*R*,7a*S*)-Methyl 6,7-dihydroxyspiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylate 22

(*a*) A solution of the diol **13** (0.2 g), Et_3N (1.2 cm^3), $[Ni(CO)_2(Ph_3P)_2]$ (0.63 g) and MeOH (1 cm^3) in THF (6 cm^3) was stirred for 24 h in a heavy-wall sealed tube at 60 °C under Ar. After being cooled in ice the tube was opened and the reaction mixture diluted with EtOAc–light petroleum (1:1) and applied to a column of silica gel 60H. Elution with the same solvent mixture gave the ester **22** (0.125 g) contaminated with an unknown compound. A pure sample of **22** was obtained by HPLC on a Dynamax 60 Å column using CH_3CN–water (1:1) as eluent; $[\alpha]_D$ −24.0 (*c* 1.0 in CH_2Cl_2); δ_H 3.85 (3 H, s), 4.13 (1 H, dd, *J* 6.0 and 3.6), 4.47 (1 H, t, *J* 6.0), 4.70 (1 H, d, *J* 3.6), 4.81 (1 H, dd, *J* 6.0 and 3.6) and 6.96 (1 H, d, *J* 3.6); δ_C 23.729, 24.020, 24.975, 35.175, 37.661, 52.325, 65.254, 70.287, 71.383, 74.732, 110.622, 130.377, 137.392 and 162.017; ν_{max}/cm^{-1} 3385 and 1720; *m/z* (EI) 284; (CI) 285 and 302 (Found: M^+, 284.1259. $C_{14}H_{20}O_6$ requires *M*, 284.1260).

(*b*) $MgBr_2$ (1 mol dm^{-3} in Et_2O; 2.5 cm^3) and BuSH (0.18 cm^3) were added to a stirred solution of the methyl ester **32** (0.3 g) in Et_2O (3 cm^3), under Ar. The reaction mixture was stirred for 1.5 h and then treated with 1 mol dm^{-3} HCl (30 cm^3). The crude product was extracted with EtOAc (3 × 30 cm^3) and worked up to give an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:3) to give the diol **22** (0.117 g, 75%).

(*c*) Pyridinium $(HF)_n$ (1.0 cm^3) was added to a solution of the ester **28** (1.0 g) in THF (2.5 cm^3) in a polyethylene reaction vessel; an exotherm was observed. After 16 h Et_3N (3.75 cm^3), CH_2Cl_2 (5 cm^3) and Merck 9385 Silica were added to the reaction mixture which was then concentrated under reduced pressure and purified as above to give the ester **22** (0.5 g, 90%).

(5*S*,6*S*)-1-Bromo-5,6-bis(2′-trimethylsilylethoxymethoxy)-cyclohexa-1,3-diene 6

2-(Trimethylsilyl)ethoxymethyl (SEM) chloride (3.66 cm^3) was added dropwise to a stirred solution of the diene **8** (1.31 g) in CH_2Cl_2 (7.5 cm^3) at 0 °C containing Pr$^i_2$NEt (6 cm^3) and a catalytic amount of 4-(dimethylamino)pyridine under Ar. The reaction mixture was stirred at room temp. for 1.5 h after which a further portion of SEM chloride (1 cm^3) was added to it. After a further 1 h the reaction mixture was poured into CH_2Cl_2 (50 cm^3) and 2 mol dm^{-3} HCl (20 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 5:95) to furnish diene **6** as an oil (3.0 g, 97%); δ_H 0.05 (9 H, s), 0.06 (9 H, s), 1.0 (4 H, m), 3.65 (4 H, m), 4.36 (1 H, d, *J* 8 and 5), 4.63 (1 H, m), 4.83 (2 H, s), 4.9 (2 H, s), 5.9 (1 H, ddd, *J* 9.6, 5.6 and 2.3), 6.01 (1 H, dd, *J* 9.6 and 2.3) and 6.48 (1 H, d, *J* 5.6); *m/z* (CI) 470 and 468.

(1*R*,2*R*,5*S*,6*S*)-4-Bromo-5,6-bis(2′-trimethylsilylethoxymethoxy)cyclohex-3-ene-1,2-diol 14

The ether **6** (1.26 g) was dissolved in Bu^{t}OH (60 cm^3) containing NMMNO (0.86 g), water (2 cm^3) and a catalytic amount of OsO_4 under Ar. After the reaction mixture had been stirred for 19 h, during which time it turned black, it was treated with $Na_2S_2O_5$ (15 g) and EtOAc (60 cm^3) and stirred for a further 1 h. The reaction mixture was then filtered through a pad of Merck 9385 Silica Gel pre-eluted with EtOAc and the pad was washed with several portions of EtOAc. The filtrate was concentrated under reduced pressure to give an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 3:7) to give (1S,2S,5S,6S)-4-*bromo*-5,6-*bis*(2′-*trimethylsilylethoxymethoxy*)*cyclohex*-3-*ene*-1,2-*diol* (0.063 g, 5%). $[\alpha]_D$ −15.8 (*c* 1.0 in CH_2Cl_2); δ_H 0.06 (18 H, s), 1.0 (4 H, m), 3.72 (4 H, m), 3.91 (1 H, m), 4.05 (3 H, m), 4.44 (1 H, d, *J* 3.6), 4.81 (1 H, d, *J* 7), 4.88 (1 H, d, *J* 7), 4.91 (1 H, d, *J* 7), 5.00 (1 H, d, *J* 7) and 6.32 (1 H, d, *J* 3.5); ν_{max}/cm^{-1} 3480; *m/z* (CI) 504 and

502 (Found: M^+, 502.1657. $C_{18}H_{41}{}^{79}BrNO_6Si_2$ requires M, 502.1656) and the *diol* **14** (1.26 g, 67%); δ_H 0.06 (9 H, s), 0.07 (9 H, s), 1.01 (4 H, m), 3.6 (2 H, m), 3.9 (2 H, m), 4.01 (1 H, dd, J 10 and 3.6), 4.1 (1 H, dd, J 10 and 4.2), 4.38 (1 H, t, J 4.2), 4.50 (1 H, d, J 3.6), 4.76 (1 H, d, J 7), 4.87 (1 H, d, J 7), 4.90 (1 H, d, J 7), 4.98 (1 H, d, J 7) and 6.34 (1 H, d, J 5.3); ν_{max}/cm^{-1} 3400 and 2953; *m/z* (CI) 504 and 502 (Found: M^+, 502.1657. $C_{18}H_{41}{}^{79}BrNO_6Si_2$ requires M, 502.1656).

(3a*R*,6*S*,7*S*,7a*R*)-5-Bromo-6,7-bis(2′-trimethylsilylethoxymethoxy)spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane] 15

A solution of 1,1-diethoxycyclohexane (0.29 g), the diol **14** (0.75 g), and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (7.5 cm^3) was stirred under Ar for 10 min after which it was treated with saturated aq. $NaHCO_3$ (30 cm^3) and extracted with CH_2Cl_2 (30 cm^3). Work-up gave an oil purified by chromatography on silica gel 60H (EtOAc–light petroleum; 6:94) to furnish the *ether* **15** (0.63 g, 72%); δ_H 0.06 (9 H, s), 0.065 (9 H, s), 1.02 (4 H, m), 1.43 (2 H, s), 3.75 (4 H, m), 4.07 (1 H, dd, J 8 and 3.2), 4.43 (1 H, d, J 3.2), 4.48 (1 H, dd, J 8 and 6.2), 4.69 (1 H, dd, J 6.2 and 3.8), 4.87 (2 H, s), 4.88 (1 H, d, J 7), 4.92 (1 H, d, J 7) and 6.33 (1 H, d, J 3.8); ν_{max}/cm^{-1} 2950 and 1640; *m/z* (CI) 584 and 582 (Found: M^+, 582.2287. $C_{24}H_{49}{}^{79}BrNO_6Si_2$ requires M, 582.2282).

(3a*R*,6*R*,7*R*,7a*R*)-6,7-Bis(2′-trimethylsilylethoxymethoxy)-spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylic acid

Bu^{t}Li (1.7 mol dm^{-3} in pentane; 1.56 cm^3) was added to a stirred solution of the ketal **15** (0.6 g) in hexane (6 cm^3) cooled −78 °C under Ar. After 25 min dry CO_2 was bubbled into the reaction mixture which was then allowed to warm to room temp. with continued passage of CO_2. This resulted in the loss of most of the solvent. The residue was diluted with CH_2Cl_2 (50 cm^3) and treated with 2 mol dm^{-3} HCl (50 cm^3) after which work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:4) to afford (3aS,6R,7R,7aS)-*bis*(2′-*trimethylsilylethoxymethoxy*)*spiro*[3a,6,7,7a-*tetrahydro*-1,3-*benzodioxole*-2,1′-*cyclohexane*] (0.05 g, 10%), $[\alpha]_D$ −66.8 (*c* 1.0 in CH_2Cl_2); δ_H 0.06 (18 H, s), 0.97 (4 H, m), 1.43 (2 H, br s), 1.65 (8 H, s), 3.7 (4 H, m), 4.03 (1 H, dd, J 7.2 and 3.4), 4.32 (1 H, t, J 3.4), 4.5 (1 H, t, J 6.3), 4.71 (1 H, m), 4.81 (2 H, s), 4.87 (1 H, d, J 7), 4.90 (1 H, d, J 7) and 5.98 (2 H, m); *m/z* (CI) 486 (Found: M^+, 486.2816. $C_{24}H_{46}O_6Si_2$ requires M, 486.2833) and the title *acid* (0.44 g, 79%), $[\alpha]_D$ −76.3 (*c* 1.0 in CH_2Cl_2); δ_H 0.03 (9 H, s), 0.05 (9 H, s), 0.95 (4 H, m), 1.42 (2 H, s), 1.64 (8 H, s), 3.7 (7 H, m), 4.61 (1 H, t, J 7.5), 4.76 (1 H, d, J 3), 4.82 (2 H, s), 4.85 (3 H, m) and 7.12 (1 H, d, J 3); in C_6D_6 0.10 (18 H, br s), 1.12 (4 H, t, J 8), 1.33 (2 H, br s), 1.6 (4 H, br s), 1.71 (2 H, m), 1.84 (2 H, m), 3.78 (2 H, m), 3.93 (2 H, m), 4.03 (1 H, dd, J 8 and 3), 4.86 (2 H, m), 5.05 (4 H, m), 5.16 (1 H, d, J 3) and 7.29 (1 H, d, J 3); ν_{max}/cm^{-1} 1700; *m/z* (CI) 530 (Found: M^+, 530.2738. $C_{25}H_{46}O_8Si_2$ requires M, 530.2731).

(3a*R*,6*R*,7*R*,7a*S*)-Methyl 6,7-bis(2′-trimethylsilylethoxymethoxy)spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylate 21

MeI (0.24 cm^3) was added to a solution of CsF (0.34 g) and the above acid (0.4 g) in Me_2NCHO (4 cm^3) under Ar and the mixture was stirred for 2.5 h. After this, further CsF (0.2 g) and MeI (0.09 cm^3) were added to it. After 1.5 h the mixture was diluted with water (20 cm^3) and extracted with Et_2O (3 × 20 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:9) to give the *ester* **21** as an oil (0.32 g, 78%), $[\alpha]_D$ −60.9 (*c* 0.65 in CH_2Cl_2); δ_H 0.04 (9 H, s), 0.06 (9 H, s), 0.9 (2 H, s), 0.97 (2 H, m), 1.44 (2 H, br s), 3.50 (2 H, m), 3.72 (3 H, m), 3.82 (3 H, s), 4.6 (1 H, dd, J 7.5 and 1), 4.78 (1 H, d, J 2.8), 4.81 (2 H, s), 4.93 (3 H, m) and 7.03 (1 H, d, J 2.8); in C_6D_6 0.09 (9 H, s), 0.1 (9 H, s), 1.10 (4 H, m), 1.32 (2 H, m), 1.6 (4 H, br s), 3.46 (3 H, s), 3.77 (2 H, m), 3.9 (2 H, m), 4.04 (1 H, dd, J 8 and 2.8), 4.85 (1 H, dd, J 8 and 2.8), 4.92 (1 H, dd, J 15 and 8), 5.03 (2 H, t, J 8), 5.12 (2 H, m), 5.17 (1 H, d, J 2.7) and 7.14 (1 H, d, J 2.7); ν_{max}/cm^{-1} 1725; *m/z* (EI) 544; (CI) 562 (Found: M^+, 544.2892. $C_{26}H_{48}O_8Si_2$ requires M, 544.2888).

(3a*R*,6*R*,7*R*,7a*S*)-Methyl 7(6)-hydroxy-6(7)-(2′-trimethylsilylethoxymethoxy)spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylate 23 and 24

$MgBr_2$ (1 mol dm^{-3} in Et_2O; 0.46 cm^3) and BuSH (0.03 cm^3) were added to a stirred solution of the ester **21** (0.05 g) in Et_2O (0.5 cm^3), under Ar. After the reaction mixture had been stirred for 10 min it was treated with 10% aq. NaOH (2 cm^3) and extracted with EtOAc (3 × 5 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:3) to give the *ether* **23** as an oil (0.023 g, 60%), δ_H 0.05 (9 H, s), 1.0 (2 H, t, J 8), 1.45 (2 H, m), 3.58 (1 H, m), 3.73 (2 H, m), 3.83 (3 H, s), 4.37 (1 H, dd, J 8.5 and 7), 4.6 (1 H, d, J 3), 4.83 (2 H, s), 4.9 (1 H, dd, J 7 and 3.3) and 7.03 (1 H, d, J 3.3); ν_{max}/cm^{-1} 3450 and 1724; *m/z* (EI) 414; (CI) 414 (Found: M^+, 414.2082. $C_{20}H_{34}O_7Si$ requires M, 414.2074); and the *ether* **24** as an oil (0.008 g, 8%), δ_H 0.07 (9 H, s), 1.0 (2 H, t, J 8), 1.4 (2 H, m), 1.67 (8 H, m), 3.75 (2 H, t, J 8), 3.84 (4 H, m), 4.53 (1 H, dd, J 8 and 6.7), 4.83 (1 H, d, J 3.4), 4.87 (1 H, dd, J 7 and 3.4), 4.94 (2 H, s) and 7.08 (1 H, d, J 3.4); ν_{max}/cm^{-1} 1725; *m/z* (EI) 414; (CI) 414 (Found: M^+, 414.2063. $C_{20}H_{34}O_7Si$ requires M, 414.2074).

The acetate of compound **23**, δ_H 0.03 (9 H, s), 0.92 (2 H, m), 2.18 (3 H, s), 3.56 (2 H, m), 3.81 (3 H, s), 4.65 (1 H, dd, J 9 and 7), 4.77 (3 H, m), 4.92 (1 H, t, J 2), 4.95 (1 H, d, J 3) and 7.07 (1 H, d, J 3.2); ν_{max}/cm^{-1} 1750 and 1725; and of compound **24**, δ_H 0.05 (9 H, s), 2.08 (3 H, s), 3.6 (2 H, m), 3.82 (3 H, s), 3.9 (1 H, m), 4.45 (1 H, dd, J 8.5 and 6.5), 4.76 (1 H, d, J 7), 4.92 (2 H, m), 6.13 (1 H, d, J 3.4) and 7.15 (1 H, d, J 3.5); ν_{max}/cm^{-1} 1750 and 1730, were prepared.

(3a*R*,6*R*,7*R*,7a*S*)-Methyl 7-*tert*-butyldimethylsiloxy-6-hydroxyspiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylate 25

A solution of the diol **22** (0.1 g), Et_3N (0.16 cm^3), TBDMSCl (0.06 g) and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 (1 cm^3) were set aside for 24 h after which TBDMSCl (0.03 g) and 4-(dimethylamino)pyridine were added to it. After a further 2.5 h the mixture was diluted with water (5 cm^3) and CH_2Cl_2 (5 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 15:85) to give the *ether* **25** (0.068 g, 50%), $[\alpha]_D$ −56.2 (*c* 1.0 in CH_2Cl_2); δ_H 0.15 (3 H, s), 0.2 (3 H, s), 0.98 (3 H, s), 1.45 (2 H, br s), 1.65 (8 H, m), 3.78 (1 H, dd, J 7.5 and 3.5), 3.84 (3 H, s), 4.35 (1 H, t, J 7.5), 4.57 (1 H, d, J 3.3), 4.98 (1 H, dd, J 7 and 3.2) and 7.10 (1 H, d, J 3.2); δ_C −4.869, −4.396, 18.118, 23.699, 24.054, 25.137, 25.834, 29.700, 34.559, 37.488, 52.249, 66.480, 72.190, 73.523, 75.587, 110.283, 131.873, 137.929 and 166.006; ν_{max}/cm^{-1} 1730; *m/z* (EI) 398; (CI) 399 (Found: M^+, 399.2199. $C_{20}H_{34}O_6Si$ requires M + H, 399.2203).

(5*S*,6*S*)-5,6-Dihydroxycyclohexa-1,3-diene-1-carbonitrile 35

An aq. culture (≈ 5 dm^3) of *Pseudomonas putida* UV4, buffered with KH_2PO_4 and maintained at a pH ≈ 7.5 with 20% aq. KOH was aerated and vigorously stirred at 28 °C. EtOH (20 cm^3) was added to the culture followed by PhCN (24 g) at a feed rate of 4 cm^3 h^{-1}. During the oxidation a bright pink colour was observed. The appearance of the diene was monitored by UV spectroscopy (λ_{max} 280 nm). The reaction mixture was centrifuged, decanted from the cells and concentrated under

reduced pressure to 400 cm^3. $MgSO_4 \cdot 7H_2O$ (400 g) was added to the concentrate which was then filtered through Celite. The filtrate was extracted with EtOAc (4 × 200 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure at room temp. to furnish the *diene* **35** (contaminated with a small amount of an unknown impurity) as a solid (19.7 g): λ_{max}/nm 280; δ_H 4.10 (2 H, br s), 4.45 (2 H, br s), 6.25 (2 H, m) and 7.80 (1 H, d) (Found: C, 60.4; H, 5.5; N, 10.0. $C_7H_7NO_2$ requires C, 61.3; H, 5.1; N, 10.2%). The diene was stored as a 10% solution in EtOAc containing 1% Et_3N and precipated from solution with light petroleum cooled to 0 °C as required.

(3a*S*,7a*S*)-2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxole-4-carbonitrile 36

A solution of the nitrile **35** (1.17 g), 2,2-dimethoxypropane (2.1 cm^3) and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (12 cm^3) was stirred for 3 h under Ar after which it was treated with 1 mol dm^{-3} aq. NaOH (25 cm^3) and extracted with CH_2Cl_2 (4 × 25 cm^3). Work-up gave the *acetonide* **36** (1.4 g, 93%) as a white solid, δ_H 1.41 (6 H, s), 4.7 (2 H, m), 6.12 (1 H, dd, *J* 9.7 and 5.6), 6.23 (1 H, dd, *J* 9.7 and 2.7) and 6.7 (1 H, d, *J* 5.6); ν_{max}/cm^{-1} 2210; *m*/*z* (CI) 195 (Found: M^+, 195.1137. $C_{10}H_{10}NO_2 + NH_4$ requires *M*, 195.1133).

(3a*R*,6*R*,7*S*,7a*R*)-6,7-Dihydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carbonitrile 39

The diene **36** (1.4 g) was dissolved in Bu^{t}OH (25 cm^3) containing NMMNO (1.0 g), water (1 cm^3) and a catalytic amount of OsO_4 under dry Ar. The reaction mixture was stirred for 18 h during which time it turned black. $Na_2S_2O_5$ (8 g) and EtOAc (25 cm^3) were added to the reaction mixture and stirring continued for a further 1 h. The reaction mixture was then filtered through a pad of Merck 9385 Silica Gel pre-eluted with EtOAc and the pad was washed with several portions of EtOAc. The filtrate was concentrated under reduced pressure to furnish the crude product as an oil. Purification of the oil by chromatography on silica gel 60 (EtOAc–light petroleum; 2:3) furnished starting material (0.5 g) and the *diol* **39** as a white solid (0.88 g, 53%), mp 114–115 °C (from EtOAc–light petroleum), $[\alpha]_D$ −35.4 (*c* 1.0 in CH_2Cl_2); δ_H 1.44 (6 H, s), 4.38 (1 H, m), 4.54 (2 H, m), 4.70 (1 H, dd, *J* 5.2 and 1.4) and 6.55 (1 H, t, *J* 1.7); ν_{max}/cm^{-1} 3405 and 2230; *m*/*z* (CI) 229 (Found: C, 56.9; H, 6.4; N, 6.5; M^+, 229.1188. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%; *M* + NH_4, 229.1188).

Acetylation of the product gave a diacetate, $[\alpha]_D$ −93 (*c* 0.5 in CH_2Cl_2); δ_H 1.38 (3 H, s), 1.42 (3 H, s), 2.06 (3 H, s), 2.07 (3 H, s), 4.41 (1 H, t, *J* 5.1), 4.67 (1 H, dd, *J* 5.1 and ~ 1), 5.58 (1 H, m), 5.66 (1 H, m) and 6.47 (1 H, m); ν_{max}/cm^{-1} 2230 and 1755; *m*/*z* (CI) 313 (Found: M^+, 313.1399. $C_{14}H_{17}NO_6$ requires *M* + NH_4, 313.1400).

(3a*R*,5a*R*,8a*S*,8b*R*)-2,2,7,7-Tetramethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*; 3,4-*d*′]bis[1,3]dioxole-4-carbonitrile 40

A solution of the diol **39** (0.4 g), 2,2-dimethoxypropane (0.7 cm^3) and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (5 cm^3) was stirred under Ar for 1 h after which it was diluted with EtOAc–light petroleum (1:9; 5 cm^3) and loaded onto a silica gel 60H column. Elution with the same solvents gave the *acetonide* **40** as a white solid (0.4 g, 84%), mp 91–92 °C (from EtOAc–light petroleum), $[\alpha]_D$ +52 (*c* 1.0 in CH_2Cl_2); δ_H 1.37 (3 H, s), 1.41 (3 H, s), 1.44 (6 H, s), 4.63 (3 H, m), 4.70 (1 H, m) and 6.48 (1 H, m); in C_6D_6 1.18 (6 H, s), 1.20 (3 H, s), 1.29 (3 H, s), 4.09 (1 H, m), 4.21 (1 H, br d, *J* 5), 4.3 (2 H, m), 5.90 (1 H, m), 6.35 (1 H, s) and 6.5 (1 H, s); δ_C 26.14, 27.61, 27.78, 69.43, 69.55, 72.17, 72.63, 110.20, 110.71, 114.08, 116.63 and 141.20; ν_{max}/cm^{-1} 2990 and 2230; *m*/*z* (CI) 252 and 269 (Found: C, 62.1; H, 6.8; N, 5.6; M^+, 269.1492. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%; *M* + NH_4, 269.1501).

(3a*R*,5a*R*,8a*S*,8b*R*)-4,5-Epoxy-2,2,7,7-tetramethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*; 3,4-*d*′]bis[1,3]dioxole-4-carboxamide 38

30% w/v aq. H_2O_2 (0.25 cm^3), $(Bu_4N)_2SO_4$ (20 mg) and 20% aq. NaOH (0.2 cm^3) were added to a solution of the bis(acetonide) **40** (0.1 g) in CH_2Cl_2 (0.5 cm^3) and stirred at 0 °C. After 2.75 h the mixture was extracted with CH_2Cl_2 (2 × 5 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield *amide* **38** as an oil (0.07 g, 67%); δ_H 1.37 (6 H, s), 1.40 (3 H, s), 1.50 (3 H, s), 3.4 (1 H, br s), 4.56 (3 H, m) and 5.34 (1 H, d, *J* 6.2); δ_C 25.19, 25.61, 26.42, 27.41, 59.40, 61.97, 69.39, 71.50, 73.96, 109.44, 109.74 and 170.99; ν_{max}/cm^{-1} 3425 and 1680; *m*/*z* (CI) 303 and 286 (Found: M^+, 286.1293. $C_{13}H_{19}NO_6$ + H requires *M*, 286.1291).

(3a*R*,6*R*,7*R*,7a*S*)-6,7-Dihydroxyspiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carbonitrile 43

Bu_4NF (1 mol dm^{-3} in THF; 13.4 cm^3) was added to the bis-TBDMS ether **42** (2.1 g) in CH_2Cl_2 (20 cm^3). After 3 h the mixture was concentrated under reduced pressure and the residue dissolved in Et_2O (100 cm^3). Work-up and purification by chromatography on silica gel 60H (EtOAc–light petroleum; gradient elution, 1:4 to 4:1) gave the *diol* **43** as a white solid (0.95 g, 86%), mp 113–114 °C (from EtOAc–light petroleum), $[\alpha]_D$ −22 (*c* 1.0 in CH_2Cl_2); δ_H 1.40 (2 H, br s), 1.60 (8 H, m), 3.90 (2 H, br s), 4.32 (1 H, m), 4.45 (2 H, m), 4.71 (1 H, t, *J* 4) and 6.61 (1 H, br d, *J* 1.7); ν_{max}/cm^{-1} 3425 and 2225; *m*/*z* (EI) 251; (CI) 269 (Found: C, 62.0; H, 6.8; N, 5.6: M^+. 251.1154. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%; *M*, 251.1157).

(5*S*,6*S*)-5,6-Di-*tert*-butyldimethylsiloxycyclohexa-1,3-diene-1-carbonitrile 37

$TBDMSOSO_2CF_3$ (10.7 cm^3) was added dropwise to a stirred solution of the diene **35** (2.5 g) and imidazole (5 g) in Me_2NCHO (25 cm^3) under Ar. After 3 h the reaction mixture was poured into water (120 cm^3) and extracted with Et_2O (3 × 100 cm^3). Work-up and purification by dry column chromatography on silica gel 60H (EtOAc–light petroleum; gradient elution, 0:1 to 8:92) gave the *ether* **37** as a white solid (5.6 g, 85%), λ_{max} 286 nm; δ_H 0.13 (3 H, s), 0.15 (3 H, s), 0.16 (3 H, s), 0.21 (3 H, s), 0.95 (18 H, s), 4.16 (1 H, d, *J* 5), 4.31 (1 H, m), 6.07 (1 H, ddd, *J* 9.5, 5.3 and 1.8), 6.25 (1 H, dd, *J* 9.5 and 3.2) and 6.73 (1 H, d, *J* 5.3); ν_{max}/cm^{-1} 2215; *m*/*z* (EI) 365; (CI) 366 and 383 (Found: M^+, 365.2204. $C_{19}H_{35}NO_2Si_2$ requires *M*, 365.2206).

(3*R*,4*S*,5*R*,6*R*)-5,6-Di-*tert*-butyldimethylsiloxy-3,4-dihydroxycyclohex-1-ene-1-carbonitrile 41

OsO_4 (4% aq. solution; 4 drops) was added to the diene **37** (4.4 g) dissolved in Bu^{t}OH (60 cm^3) containing NMMNO (1.52 g) and water (2 cm^3) under Ar. The reaction mixture was stirred for 18 h after which it was treated with $Na_2S_2O_5$ (15 g) and EtOAc (60 cm^3) and stirred for a further 1 h. The reaction mixture was then filtered through a pad of Merck 9385 Silica Gel pre-eluted with EtOAc and the pad was washed with several portions of EtOAc. The filtrate was concentrated under reduced pressure to furnish the crude product as an oil, purification of which by chromatography on silica gel 60 (EtOAc–light petroleum; 1:4) gave the *diol* **41** (4.1 g, 85%), mp 165–166 °C (from EtOAc–light petroleum), $[\alpha]_D$ −108.4 (*c* 1.0 in CH_2Cl_2); δ_H 0.14 (3 H, s), 0.16 (3 H, s), 0.18 (3 H, s), 0.25 (3 H, s), 0.92 (9 H, s), 0.98 (9 H, s), 1.75 (2 H, br s), 4.13 (2 H, m), 4.52 (2 H, br s) and 6.5 (1 H, br d, *J* 1.8); ν_{max}/cm^{-1} 3430 and 2240; *m*/*z* (EI) 399; (CI) 400 and 417 (Found: C, 57.0; H, 9.5; N, 3.6; M^+, 400.2338. $C_{19}H_{37}NO_4Si_2$ requires C, 57.1; H, 9.3; N, 3.5%; *M* + H, 400.2339) and the *enone* **53** (0.12 g, 3%); δ_H 0.16 (3 H, s), 0.17 (3 H, s), 0.25 (3 H, s), 0.27 (3 H, s), 0.95 (18 H, s),

3.19 (1 H, br s), 3.9 (1 H, d, *J* 8), 4.53 (1 H, s), 4.58 (1 H, d, *J* 8) and 6.6 (1 H, s); ν_{max}/cm^{-1} 2895 and 1695; *m/z* (EI) 398; (CI) 398 (Found: M^+, 397.1404. $C_{19}H_{35}NO_4Si_2$ requires *M*, 397.1400); and the *diol* **50** (0.07 g, 2%); δ_H 0.16 (3 H, s), 0.17 (3 H, s), 0.18 (3 H, s), 0.24 (3 H, s), 0.94 (9 H, s), 0.97 (9 H, s), 2.5 (1 H, br s), 3.74 (1 H, s), 4.36 (1 H, m), 4.61 (1 H, m), 4.70 (1 H, m), 5.54 (1 H, dt, *J* 10.5 and 2.4) and 5.68 (1 H, br d, *J* 10.5); ν_{max}/cm^{-1} 3380 and 2260; *m/z* (EI) 399; (CI) 400 (Found: M^+, 400.2332. $C_{19}H_{37}NO_4Si_2$ requires *M* + H, 400.2339).

(3a*R*,6*R*,7*R*,7a*S*)-6,7-Bis(di-*tert*-butyldimethylsiloxy)spiro-[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carbonitrile 42

A solution of 1,1-diethoxycyclohexane (1.25 g), the diol **41** (2 g), and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (20 cm^3) was stirred under Ar for 3 h after which it was treated with saturated aq. $NaHCO_3$ (2 × 20 cm^3) and extracted with CH_2Cl_2 (30 cm^3). Work-up gave an oil purified by chromatography on silica gel 60 (EtOAc–light petroleum; 4:96) to give the *acetal* **42** as a white solid (2.15 g, 90%), mp 83–86 °C (from EtOAc–light petroleum), $[\alpha]_D$ −59 (*c* 1.0 in CH_2Cl_2); δ_H 0.15 (6 H, s), 0.19 (3 H, s), 0.22 (3 H, s), 0.91 (9 H, s), 0.98 (9 H, s), 1.45 (2 H, br s), 1.60 (8 H, m), 4.02 (1 H, br s), 4.32 (1 H, t, *J* 5.9), 4.38 (1 H, br s), 4.76 (1 H, m) and 6.59 (1 H, br d, *J* 3); ν_{max}/cm^{-1} 2935 and 2225; *m/z* (CI) 497 (Found: C, 62.5; H, 9.8; N, 2.9; M^+, 497.3224. $C_{25}H_{45}NO_4Si_2$ requires C, 62.6; H, 9.5; N, 2.9%; *M* + NH_4, 497.3231).

(3a*R*,6*R*,7*R*,7a*S*)-6-*tert*-Butyldimethylsiloxy-7-hydroxyspiro-[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carbonitrile 45

A solution of the diol **43** (0.34 g), Bu_2SnO (0.3 g) and PhMe (10 cm^3) were heated under reflux with azeotropic removal of water for 8 h after which the solvent was removed under reduced pressure. CsF (0.185 g) was added to the residue and the crude product, a solid, was kept under reduced pressure for a further 1 h. The solids were suspended in Me_2NCHO (5 cm^3) and TBDMSCl (0.225 cm^3) was added to the stirred solution blanketed with Ar. After 18 h the mixture was diluted with water (25 cm^3) and extracted with Et_2O (3 × 25 cm^3). Work-up and purification by chromatography on silica gel 60 (EtOAc–light petroleum; 1:9) gave the *ether* **45** as an oil (0.14 g, 28%); δ_H 0.24 (3 H, s), 0.30 (3 H, s), 1.0 (9 H, s), 2.61 (1 H, br s), 4.26 (1 H, t, *J* 4), 4.43 (1 H, m), 4.51 (1 H, t, *J* 4.5), 4.70 (1 H, m) and 6.54 (1 H, m); in C_6D_6 0.05 (3 H, m), 0.26 (3 H, s), 0.96 (9 H, s), 1.25 (2 H, br s), 2.5 (1 H, br s), 4.17 (1 H, t, *J* 3.9), 4.37 (1 H, m), 4.40 (1 H, t, *J* 4.5), 4.49 (1 H, m) and 6.1 (1 H, m); ν_{max}/cm^{-1} 3485 and 2225; *m/z* (EI) 365; (CI) 383 and 366 (Found: M^+, 365.2015. $C_{19}H_{31}NO_4Si$ requires *M*, 365.2022).

Acetylation of the product furnished an acetate, $\delta_H(C_6D_6)$ 0.13 (3 H, s), 0.25 (3 H, s), 1.02 (9 H, s), 1.78 (3 H, s), 4.19 (1 H, dd, *J* 5.5 and 3.7), 4.32 (1 H, t, *J* 6.2), 4.54 (1 H, d, *J* 3.3), 5.45 (1 H, dd, *J* 6.7 and 3.3) and 6.11 (1 H, d, *J* 3.7); ν_{max}/cm^{-1} 2225 and 1750; *m/z* (EI) 407 and 408; (CI) 408 and 425 (Found: M^+, 407.2127. $C_{21}H_{33}NO_5Si$ requires *M*, 407.2128).

(3a*R*,6*R*,7*R*,7a*S*)-6-Benzyloxy-7-hydroxyspiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carbonitrile 46

A solution of the diol **43** (0.1 g) and Bu_2SnO (0.11 g) in PhMe (2 cm^3) was heated under reflux for 1.5 h in the presence of ground 3 Å molecular sieve (0.2 g). After concentration under reduced pressure, the mixture was treated with CsF (0.066 g) and kept under reduced pressure for a further 30 min. It was then suspended in Me_2NCHO (2 cm^3) and treated with $PhCH_2Br$ (0.052 cm^3). After being stirred for 18 h the mixture was diluted with water (10 cm^3) and extracted with Et_2O (3 × 10 cm^3). Work-up and purification by chromatography on silica gel 60 (EtOAc–light petroleum; 15:85) gave the *ether* **46** as an oil (0.052 g, 38%); δ_H 4.25 (1 H, m), 4.38 (1 H, dd, *J* 4.9 and 3.5), 4.5 (1 H, t, *J* 4.9), 4.72 (1 H, m), 4.77 (1 H, d, *J* 11.3), 4.91 (1 H, d, *J* 11.3), 6.6 (1 H, m) and 7.42 (5 H, m); ν_{max}/cm^{-1} 2930 and 2225; *m/z* (EI) 341; (CI) 359 and 342 (Found: M^+, 341.1628. $C_{20}H_{23}NO_4$ requires *M*, 341.1625).

An acetate of the product was prepared; δ_H 1.42 (2 H, br s), 2.11 (3 H, s), 4.33 (1 H, m), 4.50 (1 H, t, *J* 6), 4.75 (3 H, m), 5.51 (1 H, dd, *J* 6.2 and 3.4) and 6.67 (1 H, br d, *J* 3.2); ν_{max}/cm^{-1} 2940, 2225 and 1750; *m/z* (EI) 383; (CI) 384 and 401 (Found: M^+, 383.1742. $C_{22}H_{25}NO_5$ requires *M*, 383.1731).

(3a*R*,6*R*,7*R*,7a*S*)-6,7-Bis(di-*tert*-butyldimethylsiloxy)-spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carbaldehyde 27

DIBAL (1 mol dm^{-3} in hexane, 5.2 cm^3) was added dropwise to a cold (−78 °C) stirred solution of the bis-TBDMS ether **53** (2.0 g) in hexane (40 cm^3) and, after 40 min, the mixture was diluted with EtOAc (20 cm^3) and treated with 60% aq. tartaric acid (10 cm^3). The reaction mixture was warmed to room temp. after which it was treated with a further portion of aq. tartaric acid (25 cm^3) and extracted with EtOAc (50 cm^3). Work-up and purification by chromatography on silica gel 60 (EtOAc–light petroleum; 2:98) gave the *aldehyde* **27** as a white solid (1.4 g, 70%), mp 96–97 °C (from EtOAc–light petroleum); δ_H 0.03 (3 H, s), 0.13 (3 H, s), 0.16 (3 H, s), 0.18 (3 H, s), 0.84 (9 H, s), 0.96 (9 H, s), 3.5 (3 H, dd, *J* 7.4 and 2.3), 4.5 (1 H, t, *J* 7.6), 4.58 (1 H, d, *J* 2.0), 5.13 (1 H, dd, *J* 7.8 and 2.4), 6.76 (1 H, d, *J* 2.0) and 9.55 (1 H, s); ν_{max}/cm^{-1} 2935 and 1695; *m/z* (EI) 482; (CI) 483 (Found: C, 62.2; H, 9.5; M^+, 483.2951. $C_{25}H_{46}O_5Si_2$ requires C, 62.2; H, 9.6%; *M* + H, 483.2962).

(3a*R*,6*R*,7*R*,7a*S*)-Methyl 6,7-bis(di-*tert*-butyldimethylsiloxy)-spiro[3a,6,7,7a-tetrahydro-1,3-benzodioxole-2,1′-cyclohexane]-5-carboxylate 29

2-Methylbut-2-ene (6.5 cm^3) was added to a suspension of the aldehyde **27** (1.3 g) in Bu^tOH (39 cm^3) followed by an aqueous solution (26 cm^3) containing $NaClO_2$ (3.12 g) and NaH_2PO_4 (4.16 g). After 1 h the reaction mixture was concentrated under reduced pressure, treated with 2 mol dm^{-3} HCl (30 cm^3) and extracted with EtOAc (3 × 30 cm^3). Work-up gave compound **28** (1.3 g) which was dissolved in Me_2CO (10 cm^3) and treated with K_2CO_3 (0.86 g) and MeI (3 cm^3) After 2 h the reaction mixture was filtered, concentrated under reduced pressure and purified by chromatography on silica gel 60 (EtOAc–light petroleum; 2:98) to give the *ester* **29** as an oil (1.1 g, 80%), $[\alpha]_D$ −10.5 (*c* 1.0 in CH_2Cl_2); δ_H 0.02 (3 H, s), 0.14 (3 H, s), 0.17 (6 H, s), 0.86 (9 H, s), 0.97 (9 H, s), 3.57 (1 H, dd, *J* 7.6 and 2.4), 3.81 (3 H, s), 4.43 (1 H, t, *J* 7.6), 4.60 (1 H, d, *J* 2.4), 5.00 (1 H, dd, *J* 7.6 and 2.4) and 6.96 (1 H, d, *J* 2.4); ν_{max}/cm^{-1} 1725; *m/z* (CI) 513 (Found: M^+, 513.3076. $C_{20}H_{48}O_6Si_2$ requires *M* + H, 513.3068).

(5*S*,6*S*)-Methyl 5,6-dihydroxycyclohexa-1,3-diene-1-carboxylate 47

An aq. culture (≈4 dm^3) of *Pseudomonas putida* UV4, buffered with KH_2PO_4 and maintained at pH ≈ 7.5 with 20% aq. KOH was aerated and vigorously stirred at 28 °C whilst EtOH (20 cm^3) was added followed by $PhCO_2Me$ (17 g) at a feed rate of 2 cm^3 h^{-1} for the first h and then at 4 cm^3 h^{-1}. During the oxidation a bright orange colour was observed. The appearance of the diene was monitored by UV spectroscopy (λ_{max} 290 nm). The reaction mixture was centrifuged, decanted from the cells and concentrated under reduced pressure to 400 cm^3. $MgSO_4 \cdot 7H_2O$ (400 g) was added to the reaction mixture which was then filtered through Celite. The filtrate was extracted with EtOAc (4 × 200 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure at room temp. to furnish the *diene* **47** as an oil (9 g), contaminated with a

small amount of an unknown compound; $[\alpha]_D$ +58.7 (*c* 1.0 in CH_2Cl_2); λ_{max}/nm 282 (ε 9300); δ_H 3.0 (2 H, br s), 3.80 (3 H, s), 4.52 (1 H, dt, *J* 6.4 and 2.2), 4.62 (1 H, d, *J* 6.4), 6.13 (1 H, ddd, *J* 9.6, 5.5 and 2.2), 6.25 (1 H, dm, *J* 9.6) and 7.10 (1 H, d, *J* 5.5); δ_C 52.135, 65.009, 69.150, 122.691, 128.382, 134.177, 138.477 and 162.479; ν_{max}/cm^{-1} 3400 and 1703; *m/z* (CI) 170 and 188 (Found: M^+, 188.0917. $C_8H_{10}O_4$ requires $M + NH_4$, 188.0923). The compound was stored as a 10% solution in EtOAc containing 1% Et_3N.

(3*R*,4*S*,5*R*,6*R*)-3,4,5,6-Tetrahydroxycyclohex-1-ene-1-carboxylic acid

A solution of methyl 6β-hydroxyshikimate **18** (0.09 g) in a mixture of water (2 cm^3) and 10 mol dm^{-3} HCl (2 cm^3) was heated at 60 °C for 4 h and then concentrated under high vacuum to give an oil. Purification of this by reverse phase HPLC using a Dynamax 60 Å HPLC column (t_R 4.75 min) with aq. CF_3CO_2H (99.9:0.1) as eluent gave the acid as an oil (0.05 g, 60%). $[\alpha]_D$ −140 (*c* 1.0 in water); $\delta_H(D_2O)$ 3.82 (1 H, dd, *J* 10.5 and 4), 3.89 (1 H, dd, *J* 10.5 and 4), 4.41 (1 H, t, *J* 4.5), 4.60 (1 H, d, *J* 4) and 6.91 (1 H, d, *J* 5); $\delta_C(D_2O)$ 66.458, 66.514, 68.729, 69.228, 133.128, 140.697 and 169.991; *m/z* (CI) 208 and 191.

(5*S*,6*S*)-Methyl 5,6-di-*tert*-butyldimethylsiloxycyclohexa-1,3-diene-1-carboxylate 49

$TBDMSOSO_2CF_3$ (3 cm^3) was added dropwise to a stirred solution of the diene **47** (0.9 g) and imidazole (1.44 g) in Me_2NCHO (5 cm^3) under Ar. After 1.25 h the reaction mixture was poured into water (25 cm^3) and extracted with Et_2O (3 × 25 cm^3). Work-up and purification by dry column chromatography on silica gel 60H (EtOAc–light petroleum; 3:97) gave the oily *ether* **49** (1.3 g, 62%); δ_H 0.06 (3 H, s), 0.13 (3 H, s), 0.16 (3 H, s), 0.15 (3 H, s), 0.98 (9 H, s), 1.03 (9 H, s), 3.82 (3 H, s), 4.45 (2 H, m), 6.07 (1 H, ddd, *J* 9, 5 and 2.5), 6.17 (1 H, dm, *J* 9) and 7.05 (1 H, m); ν_{max}/cm^{-1} 2955 and 1720; *m/z* (EI) 398; (CI) 399 (Found: M^+, 398.2306. $C_{20}H_{38}O_6Si_2$ requires *M*, 398.2308).

(3*R*,4*S*,5*R*,6*R*)-Methyl 5,6-di-*tert*-butyldimethylsiloxy-3,4-dihydroxycyclohex-1-ene-1-carboxylate 51

OsO_4 (4% aq. solution; 2 drops) was added to the diene **49** (0.13 g) dissolved in Bu^{t}OH (3 cm^3) containing NMMNO (0.03 g) and water (4 drops) under Ar. The reaction mixture was stirred for 18 h during which time it turned black. $Na_2S_2O_5$ (0.5 g) and EtOAc (5 cm^3) were added to the reaction mixture which was then stirred for a further 1 h. After this, the reaction mixture was filtered through a pad of Merck 9385 Silica Gel pre-eluted with EtOAc and the pad was washed with several portions of EtOAc. The combined filtrate and washings were concentrated under reduced pressure to furnish the crude product as an oil, purification of which by chromatography on silica gel 60 (EtOAc–light petroleum; 15:85) furnished an inseparable mixture [0.069 g; 10:1; *m/z* (EI) 433; (CI) 433] of the *diols* **51**; δ_H 0.06 (3 H, s), 0.13 (3 H, s), 0.16 (3 H, s), 0.17 (3 H, s), 0.84 (9 H, s), 0.98 (9 H, s), 3.85 (3 H, s), 4.38 (1 H, m), 4.78 (1 H, m), 4.95 (1 H, m) and 5.60 (2 H, m); and **30**, δ_H 0.05 (3 H, s), 0.13 (3 H, s), 0.16 (3 H, s), 0.87 (9 H, s), 0.99 (9 H, s), 3.81 (3 H, s), 3.9 (1 H, m), 4.25 (1 H, dd, *J* 10 and 5), 4.60 (1 H, t, *J* 5), 4.74 (1 H, d, *J* 5) and 6.92 (1 H, d, *J* 4.5).

Methyl (3a*R*,6*R*,7*S*,7a*R*)-6,7-dihydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate 16

A solution of the diol **47** (0.5 g), 2,2-dimethoxypropane (1.1 cm^3) and a catalytic amount of camphorsulfonic acid in CH_2Cl_2 (5 cm^3) was stirred under Ar for 1 h after which the mixture was diluted with CH_2Cl_2 (10 cm^3) and 1 mol dm^{-3} NaOH (10 cm^3). The aq. phase was extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined extracts were dried and concentrated to furnish the *acetonide* **48** as an oil (0.48 g, 78%); δ_H 1.42 (3 H, s), 1.48 (3 H, s), 3.85 (3 H, s), 4.90 (1 H, dd, *J* 8.4 and 1.8), 4.95 (1 H, d, *J* 8.4), 6.15 (2 H, m) and 7.15 (1 H, m); ν_{max}/cm^{-1} 1720; *m/z* (CI) 212. The acetonide **48** (0.45 g) was hydroxylated by the method described previously and the products were separated by chromatography on silica gel 60 (EtOAc–light petroleum; 4:6 then 6:4) to give the *diol* **52** (0.092 g, 18%), mp 98–100 °C (from EtOAc–light petroleum), $[\alpha]_D$ +134 (*c* 1.0 in CH_2Cl_2); δ_H 1.30 (3 H, s), 1.34 (3 H, s), 3.87 (3 H, s), 4.31 (1 H, d, *J* 5), 4.65 (1 H, m), 4.76 (1 H, br s), 5.64 (1 H, br d, *J* 11) and 5.70 (1 H, br d, *J* 11); ν_{max}/cm^{-1} 3430 and 1735; *m/z* (CI) 262 and 245 (Found: C, 54.0; H, 6.7; M^+, 262.1291. $C_{11}H_{19}NO_6$ requires C, 54.1; H, 6.6%; $M + NH_4$, 262.1291) and the *diol* **16** (0.14 g, 27%), mp 143–145 °C (from EtOAc–light petroleum), $[\alpha]_D$ −41.0 (*c* 1.0 in CH_2Cl_2); δ_H 1.39 (3 H, s), 1.44 (3 H, s), 2.9 (2 H, br s), 3.85 (3 H, s), 4.27 (1 H, t, *J* 3.6), 4.53 (1 H, t, *J* 4.8), 4.55 (1 H, br s), 5.07 (1 H, d, *J* 5.7) and 6.9 (1 H, m); δ_C 25.751, 27.556, 52.351, 66.033, 70.086, 70.488, 75.179, 109.571, 130.016, 140.382 and 166.184; ν_{max}/cm^{-1} 3450 and 1705; *m/z* (CI) 262 and 245 (Found: C, 54.0; H, 6.8; M^+, 262.1295. $C_{11}H_{16}O_6$ requires C, 54.1; H, 6.6%; $M + NH_4$, 262.129).

Prévost reaction on (5*S*,6*S*)-methyl 5,6-di-*tert*-butyldimethylsiloxycyclohexa-1,3-diene-1-carboxylate

A mixture of AgOAc (0.125 g) and I_2 (0.1 g) in AcOH (6 cm^3) was stirred at room temp. until all the I_2 had been consumed. The diene **49** (0.15 g) in AcOH (2 cm^3) was added to the reaction mixture after which it was stirred at 70 °C for 2 h and then treated with AcOH (0.5 cm^3) and water (0.0067 cm^3). After the reaction mixture had been heated for a further 9 h, the yellow precipitate was filtered off and washed with $CHCl_3$. The combined filtrate and washings were concentrated under reduced pressure and the product was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 3:97 to 20:80) to give a mixture (0.03 g) (Found: M^+, 475.2547. $C_{22}H_{42}O_7Si_2$ requires M + H, 475.2547) of the acetate **32**, δ_H 0.14 (3 H, s), 0.16 (3 H, s), 0.19 (6 H, s), 0.88 (9 H, s), 0.95 (9 H, s), 2.20 (3 H, s), 3.85 (3 H, s), 4.05 (1 H, dd, *J* 10 and 3), 4.70 (2 H, m), 5.45 (1 H, dd, *J* 10 and 3) and 6.84 (1 H, d, *J* 3); and the acetate **34**, δ_H 0.05 (3 H, s), 0.19 (9 H, s), 0.88 (9 H, s), 1.0 (9 H, s), 2.14 (3 H, s), 3.85 (3 H, s), 3.95 (1 H, dd, *J* 10 and 3), 4.35 (1 H, dd, *J* 10 and 3), 4.70 (1 H, d, *J* 3), 5.70 (1 H, t, *J* 4) and 6.69 (1 H, d, *J* 3); and the acetate **54** (0.06 g), δ_H(−60 °C) (conformer a) 0.1 (9 H, s), 0.15 (3 H, s), 0.75 (9 H, s), 0.90 (9 H, s), 2.05 (3 H, s), 3.40 (1 H, dd, *J* 4.5 and 2.5), 3.75 (3 H, s), 4.10 (1 H, d, *J* 2.5), 4.60 (1 H, d, *J* 4.5), 5.80 (1 H, d, *J* 5) and 6.8 (1 H, d, *J* 5); (conformer b) 0.10 (9 H, s), 0.15 (3 H, s), 0.75 (9 H, s), 0.90 (9 H, s), 2.11 (3 H, s), 3.68 (3 H, s), 4.20 (1 H, d, *J* 10), 4.40 (1 H, d, *J* 2), 4.70 (1 H, d, *J* 2), 5.70 (1 H, d, *J* 10) and 6.2 (1 H, d, *J* 2).

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