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Template-directed Intramolecular *C*-Glycosidation. Formation of Tetrahydrofurans and Application to the Synthesis of a Higher-order Sugar

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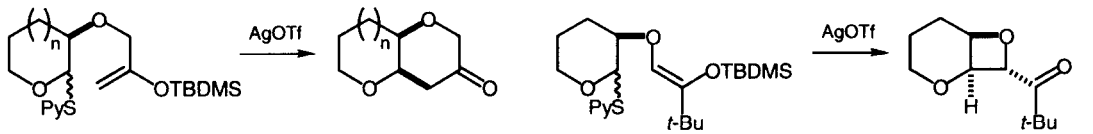
Abstract

Cation-mediated cyclisation reactions of silyl enol ether-containing thioglycosides give bicyclic ketotetrahydrofurans. Cyclisation of an analogous 3-phenyl-2-propenyl ether-containing substrate gives an intermediate in the total synthesis of the higher-order sugar 2,3-dideoxy-D-*manno*-2-octulopyranosonic acid.

Keywords: synthesis, higher-order sugar, cyclisation, *C*-glycoside

1. INTRODUCTION

The term *C*-glycoside is used to describe a wide variety of molecular types in which a common structural motif is the presence of carbon functionality at what would otherwise be the anomeric position of a sugar or derivative.[1] When the functional group contains hydroxyl groups the resulting compound is related to a higher-order or higher-carbon sugar,[2] and compounds containing such residues display significant biological activities.[3] As part of a broad and ongoing programme addressing the utility of cation-mediated cyclisation reactions for the synthesis of *C*-glycosides[4,5] (Scheme 1) we looked at formation of tetrahydrofurans from thioglycosidic substrates possessing appended nucleophilic functional groups, and we developed this work for the assembly of an unnatural analogue of a biologically active natural higher-order sugar. This paper reports our results in full.[6]



1 (n= 0, 1) **2** (n= 0, 1) **3** **4**

Scheme 1

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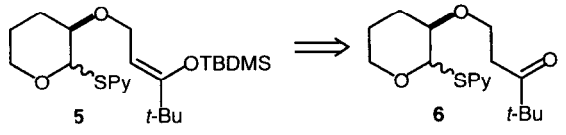
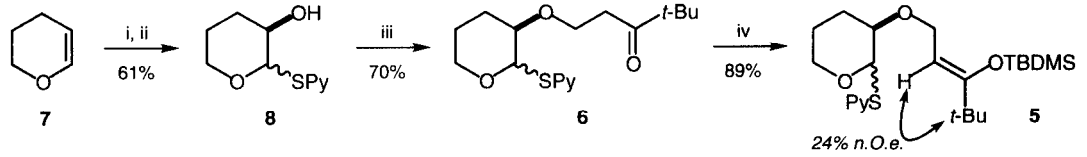
2. RESULTS AND DISCUSSION

At the start of our study we had already demonstrated that thioglycosidic[7(i)] silyl enol ethers **1** and **3** underwent stereoselective cation-mediated cyclisation[7(ii)] to give respectively bicyclic oxotetrahydropyrans **2**[4(i)] and bicyclic oxetane **4**[5(i)] (Scheme 1). The latter result was surprising in view of the strain present in the 4-membered product of what appeared to be an initially reversible C–C bond-forming process, but we showed subsequently that this unusual reaction could be extended to include anomeric sulfones derived from highly oxygenated, sugar-derived precursors.[5(ii)] We were keen to assess whether transformations similar to those depicted in Scheme 1 might give bicyclic *C*-glycosides possessing *five*-membered rings, and by direct analogy with the oxetane-forming reactions we sought the ketonic precursor of a cyclisation substrate in which the regiochemistry of silyl enol etherification would be unambiguous. Therefore, thiopyridyl glycopyranoside **5** was selected for initial study, with thioglycosidic *tert*-butyl ketone **6** as the preliminary synthetic target.



Synthesis of 5

As a general principle we sought synthetic routes to cyclisation substrates in which the nucleophilic side-chain functionality was introduced at a relatively late stage in the sequence, after the incorporation of the sulfur-containing anomeric leaving group. To this end, reaction of the diol[8] derived from dihydropyran **7** under the standard thioglycosidation conditions[7(i)] gave hydroxysulfide **8** as a 9:1 mixture of *anti*- and *syn*- anomers. The intuitive disconnection of **6** indicated the conjugate addition of **8** to 2,2-dimethylpent-4-en-3-one **9**, which was simply prepared by addition of vinylmagnesium bromide to 2,2-dimethylpropanal followed by Swern oxidation of the product secondary alcohol; the volatility of **9** obviated the realisation of high yields in the second step of this sequence.[9] We were mindful of potential problems arising from the reversibility of the base-catalysed addition reaction of **8** with **9**, and reaction of the sodium salt of **8** with the enone indeed resulted in poor yields of **6** together with extensive decomposition of both reactants. After extensive experimentation, phase-transfer catalysed[10] reaction using an excess (1.5 equiv) of **9** allowed the isolation of **6** in acceptable yields. Conversion of **6** into **5** posed the additional problem of enolate instability during silyl enol etherification, but this was overcome by the simple expedient[11] of addition of base to *pre-mixed tert*-butyldimethylsilyl triflate and **6**. Compound **5** was formed as a separable mixture of anomers possessing only *Z*- geometry as evidenced by large n.O.e. effects between the alkene and *t*-butyl hydrogen protons.[12] The synthesis of **5** is summarised in Scheme 2.

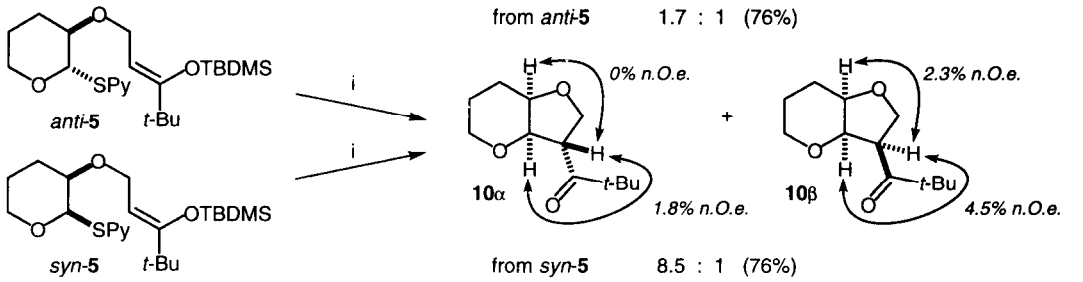


Reagents and conditions: (i) *m*-CPBA, Et_2O–H_2O, 0°C→rt, 12 h; (ii) PySSPy, Bu_3P, CH_2Cl_2, 0°C, 10 min, then rt, 3 h; (iii) 1:1 50% aqueous NaOH–CH_2Cl_2, Aliquat® 336, 2,2-dimethyl-4-penten-3-one (**9**), 20°C, 2 min; chromatography to recover excess **8**; (iv) $TBDMSOSO_2CF_3$, THF, -78°C, then add $KN(SiMe_3)_2$, -78°C, 10 min.

Scheme 2

Cyclisation reactions of 5

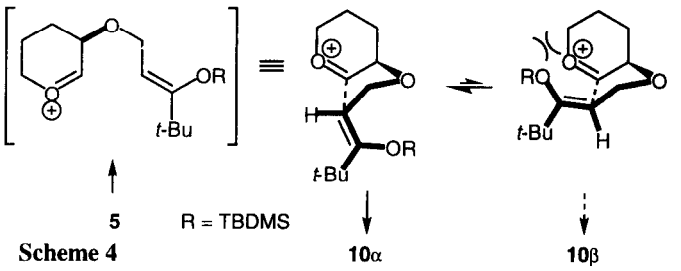
In common with the reactions of **1** and **3**, cyclisation of **5** was carried out by addition of dichloromethane solutions of the substrate to silver(I) triflate in dichloromethane containing molecular sieves; inclusion of the drying agent helped to suppress competing hydrolysis of the thioglycoside function. As with our previous work, off-white precipitates were observed immediately upon addition of **5** to the AgOTf-containing mixture, and reactions were monitored until tlc indicated complete consumption of starting



Reagents and conditions: (i) $AgOSO_2CF_3$, 4Å molecular sieves, CH_2Cl_2, rt.

Scheme 3

material. Initial studies of the mixture of isomeric substrates showed that the cyclisation reaction was poorly selective, giving two readily separable bicyclic ketonic products **10** in a *ca.* 2:1 ratio. The low selectivity observed was in marked contrast to our earlier studies of oxetane-forming reactions,[5(i)] and prompted us to look at the cyclisation reactions of the individual thioglycoside anomers. The major component, *anti*-**5** underwent cyclisation with decreased selectivity compared with the mixture, whilst *syn*-**5** gave an identical yield of the bicyclic *C*-glycoside but with greatly enhanced selectivity. The structures of the major and minor products were assigned as respectively **10**α and **10**β by ^{1}H nmr n.O.e. experiments[12] (Scheme 3). In the cyclisation reactions of **5** both the low selectivity of cyclisation of the *anti*- isomer and the dependence of cyclisation selectivity on the stereochemical relationship between the nucleophilic side-chain and the anomeric leaving group were unexpected. We had anticipated at the outset that the reactions would give predominantly **10**α, since such selectivity would mirror that observed in the formation of **4** from **3**. Also, the reactive conformation leading to **10**α appeared to be more favourable than that corresponding to **10**β from consideration of simple pictorial models of the cyclisations; these indicated less steric crowding in the *exo*-orientation leading to the former (Scheme 4). Brief exposure of either isomer of **10** to a sub-stoichiometric amount of *t*-BuOK in THF containing *t*-BuOH resulted in the clean formation of the same 5.5:1 **10**α:**10**β mixture, indicating the thermodynamic preference for **10**α and the kinetically-controlled nature of the cyclisations. These results demonstrated that the reactions were not purely dissociative; if this had been the case both isomers of **5** would have reacted *via* the same oxocarbenium ion (Scheme 4) and would have given the same product distribution. The *trans*- relationship of nucleophilic side-chain and anomeric leaving group in *anti*-**5** is such that it may react in an S_N1-like *and* an S_N2-like fashion; *syn*-**5** may react only *via* the former pathway. Given that for the former mechanism the stereochemistry is set during the second, more exothermic step of the two-stage reaction, and that according to the Hammond postulate[13] such a process is expected to be more reactant-like (*i.e.* cation-like) it is noteworthy that much greater selectivity is observed in this case. In all of the other intramolecular *C*-glycosidation reactions we have studied product distribution is independent of substrate anomeric stereochemistry.

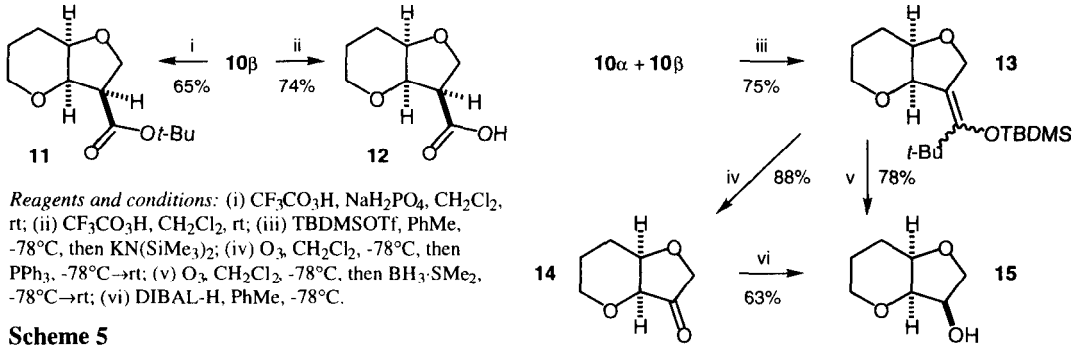


Scheme 4

Derivatisation reactions of ***10***

The next phase of our programme focused on the development of derivatisation reactions of *C*-glycosides **10** which would give products functionalised with groups other than the *tert*-butyl ketone. Baeyer–Villiger reaction of **10**β with trifluoroperacetic acid[14] gave directly the crystalline carboxylic acid **12**;

addition of a buffer (Na_2HPO_4) to the oxidising medium allowed isolation of the intermediate *tert*-butyl ester **11**. Isomer **10α** was completely inert towards Baeyer–Villiger reaction under a range of conditions.[15] Compounds **10** could be converted into the corresponding silyl enol ethers **13** as mixtures of geometric isomers, again by adding base to pre-mixed substrate and silylating agent. The electron-rich double bond in **13** could be cleaved ozonolytically to give ketone **14** on work-up with triphenylphosphine. Ketone **14** showed a distinctively high carbonyl stretching frequency in the infrared spectrum, presumably because of the combined electron-withdrawing effects of two flanking ether linkages.[16] Reduction of **14** using DIBAL-H gave a single carbinol isomer **15**. It was found subsequently that ozonolysis of **13** with reductive work-up using $BH_3{\cdot}SMe_2$ provided **15** in higher yield than for the two-step sequence **13**→**14**→**15** (Scheme 5).

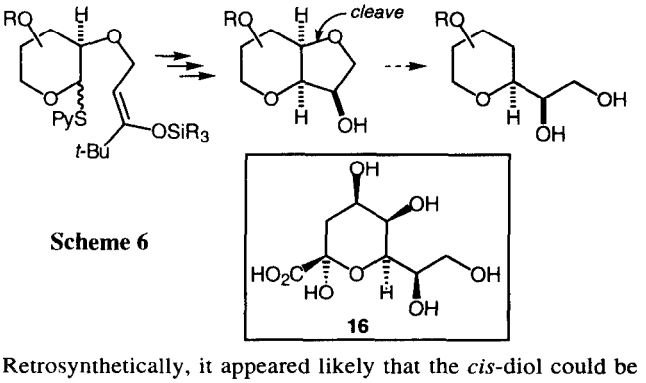


Reagents and conditions: (i) CF_3CO_3H, NaH_2PO_4, CH_2Cl_2, rt; (ii) CF_3CO_3H, CH_2Cl_2, rt; (iii) TBDMSOTf, PhMe, -78°C, then $KN(SiMe_3)_2$; (iv) O_3, CH_2Cl_2, -78°C, then PPh_3, -78°C→rt; (v) O_3, CH_2Cl_2, -78°C, then $BH_3{\cdot}SMe_2$, -78°C→rt; (vi) DIBAL-H, PhMe, -78°C.

Scheme 5

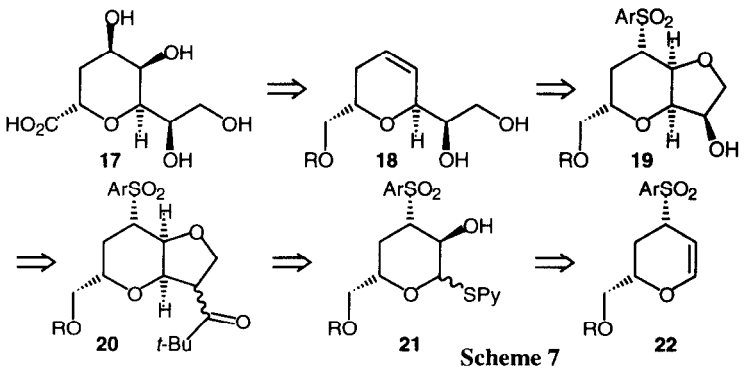
*Application to target-oriented synthesis: synthesis of 2,3-dideoxy-D-*manno*-2-octulopyranosonic acid*

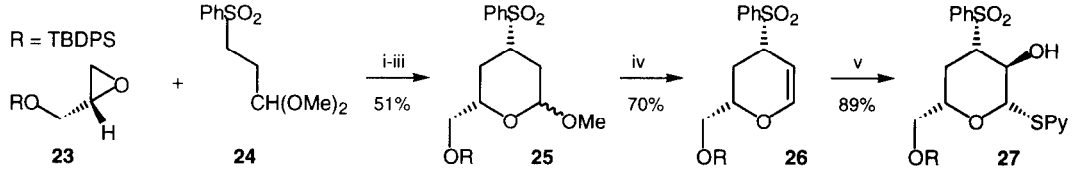
We became interested in applying the cyclisation and subsequent derivatisation reactions described above in synthesis. In particular, we were keen to explore in a target-oriented context the type of sequence exemplified by **5**→**10**→**15**, since overall this had the potential to deliver carbinol functionality to the anomeric position. Cleavage post-cyclisation of the ether linkage which effected delivery of the two-carbon fragment would enable homologation of glycosidic substrates to provide higher-order sugars (Scheme 6). The higher-order sugar 3-deoxy-D-*manno*-2-octulosonic acid (KDO)[17] **16** is a key structural element in the cell walls of gram-negative bacteria, and inhibitors of its biosynthesis, or of its incorporation into the cell wall are being sought as potential anti-bacterial therapies.[18] 2,3-Dideoxy-D-*manno*-2-octulopyranosonic acid **17** is one of the most potent CMP-KDO synthetase inhibitors reported to date,[19] and the presence of the pendant ethane-1,2-diol function made it an attractive target on which to exemplify our new methodology.[20] Retrosynthetically, it appeared likely that the *cis*-diol could be installed by dihydroxylation of a cyclic alkene **18**, and in order to realise this plan we required a modified cyclisation precursor possessing suitable latent functionality to reveal the alkene after cyclisation and subsequent manipulations. In light of our ongoing interest in sulfone chemistry we selected the arylsulfonyl moiety as a reductively labile group which would additionally facilitate substrate assembly and influence stereochemistry of key reactions by virtue of its steric bulk. Our idea was to assemble the arylsulfonyl-substituted glycal **22** and to subject it to an oxidation–thioglycosidation sequence as for dihydropyran **7**, giving **21**; the β-hydroxy stereochemistry would arise from the α-orientation of the bulky sulfone group at C-4. Attachment of the silyl enol ether-containing side-chain and cyclisation as described above would provide **20**,



Scheme 6

which on subsequent manipulation would give sulfone **19** in readiness for reductive cleavage to **18** (Scheme 7). The requisite (arylsulfonyl)glycal was readily prepared starting with the reaction of the TBDPS ether **23** of *R*-glycidol[21] with a two-fold excess of lithiated sulfonylacetal **24**.[22] Treatment of the diastereomeric mixture of adducts with TFA gave a mixture of four diastereomeric methyl glycosides. Since α-phenylsulfonyl glycals were required exclusively, the four-component mixture was subjected to base-mediated epimerisation, giving only the two diastereomers **25**. Treatment of this mixture with TMSI–MeCN followed by hexamethyldisilazane[23] yielded (phenylsulfonyl)glycal **26** as a single diastereomer; interestingly, subjection of **26** to the basic conditions used earlier in the sequence gave an equilibrium mixture enriched in the C-4 epimer.[24] Oxidation of the double bond using the same conditions as before gave a mixture of two anomeric diols, after mildly basic methanolysis during work-up had enabled recovery of small amounts of *m*-chlorobenzoates formed generated in the reaction. Finally, thioglycosidation under the standard conditions yielded **27** as a single diastereomer in readiness for side-chain attachment and activation followed by cyclisation (Scheme 8).

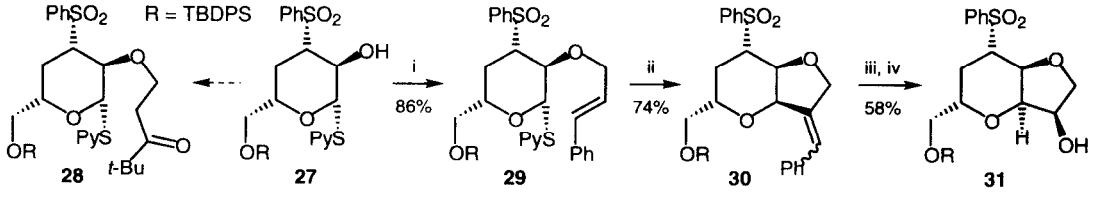




Reagents and conditions: (i) Add *n*-BuLi to **24**, THF, TMEDA, -78°C; add **7**, -78°C→rt, then H^+; (ii) TFA, CH_2Cl_2, rt; (iii) *t*-BuOK, *t*-BuOH, THF, rt; (iv) TMSCl, NaI, MeCN, rt, then add $HN(SiMe_3)_2$; (v) *m*-CPBA, wet ether, rt, then Et_3N, MeOH, rt; (vi) PySSPy, *n*-Bu_3P, CH_2Cl_2, -78°C→rt.

Scheme 8

Attempts to incorporate the ketonic side-chain in readiness for silyl enol ether formation and cyclisation involved the use of phase-transfer-catalysed addition of thioglycoside **27** to enone **9** as in the synthesis of the simple analogue **6**. However, despite extensive experimentation involving the use of excess **9** the required ketone **28** could not be obtained in more than 5% yield. We had observed in the formation of **6** that addition of **8** to **9** was reversible, and inferred that the failure of the analogous reaction of **27** was due to an unfavourable equilibrium, perhaps on account of the increased steric bulk of **27** relative to **8**. With this in mind, *irreversible* alkylation reactions of **27** were sought. The key criteria of any new transformation would be that it would



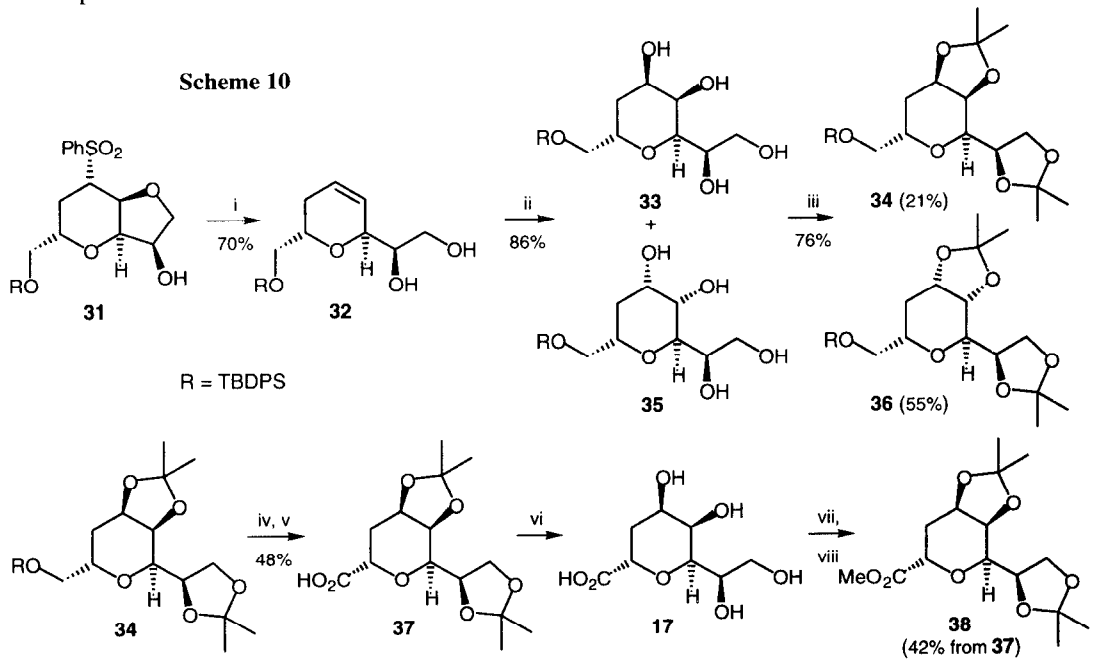
Reagents and conditions: (i) Aliquat® 336, $PhCH{=}CHCH_2Br$, CH_2Cl_2, 50% aq NaOH, rt; (ii) add **29** to $AgOSO_2CF_3$, 4Å ms, CH_2Cl_2, rt, then add DBU; (iii) O_3, CH_2Cl_2, -78°C, then PPh_3, -78°C→rt, then rt; (iv) $NaBH_4$, MeOH, 0°C.

Scheme 9

incorporate a side-chain group sufficiently nucleophilic to trap the intermediate anomeric cation, and give rise to new functionality post-cyclisation amenable to elaboration to give the required carbinol, as in **19** (Scheme 7). In the event, choosing β-styrylmethyl as the appended nucleophilic group solved the alkylation problem *and* shortened the sequence by two steps: treatment of **29**, available in one step from **27** with AgOTf followed by addition of DBU gave directly the benzylidene-substituted bicyclic tetrahydrofuran **30** possessing the double bond required for introduction of the carbinol. Ozonolysis of **30** followed by reduction of the isolated ketone gave **31** as a single diastereomer (Scheme 9).

The final phase of the synthesis of **17** addressed the issue of cleavage of the ether tether in order to reveal the 1,2-diol function, *syn*-dihydroxylation of the resulting alkene and oxidation level/protecting group adjustments. Portionwise treatment of **31** with sodium amalgam in buffered methanol effected ring-opening to give dihydropyran **32**, which was exposed to OsO_4–NMO[25] in aqueous acetone to give a 1:2.5 mixture of tetraols **33** and **35**; these were most conveniently separated after formation of the corresponding bisacetonides **34** and **36**. Desilylation of **34** and oxidation of the product primary alcohol using RuO_4[26] provided the acid **37**, which gave the target 2,3-dideoxy-D-*manno*-2-octulopyranosonic acid **17** upon removal of the diol protecting groups. The ^1H nmr spectrum of synthetic **17** was similar, but not identical to that reported for the derived ammonium salt.[18] Therefore, in order to confirm unequivocally the identity of the synthetic material it was subjected to methyl esterification with diazomethane and reprotection of the two diol functions to provide **38**, whose ^1H and ^{13}C nmr characteristics were identical with those reported.[27] The conclusion of our synthesis of **17** is depicted in Scheme 10.

Scheme 10



Reagents and conditions: (i) 6% Na(Hg), Na_2HPO_4, MeOH, 0°C; (ii) OsO_4, NMO, 9:1 acetone–H_2O, rt; (iii) $CuSO_4$, H_2SO_4, acetone, rt; (iv) *n*-Bu_4NF, THF, rt; (v) $NaIO_4$, $RuO_2{\cdot}H_2O$, H_2O–MeCN–CCl_4, rt; (vi) 9:1 TFA–H_2O, rt; (vii) CH_2N_2, 2-(2-ethoxyethoxy)ethanol, Et_2O; then H_2SO_4, $CuSO_4$, acetone.

3. CONCLUSIONS

The work described above demonstrates that template-directed intramolecular *C*-glycosidation is an effective and stereoselective strategy for the introduction of hydroxylated carbon-containing fragments at the anomeric positions of sugars and related oxygen heterocycles. We have demonstrated the applicability of this approach to the synthesis of a biologically active higher-order sugar, although the adverse selectivity observed in the dihydroxylation of **32** merits further investigation. We have been exploring also the utility of (arylsulfonyl)glycals such as **22** as substrates for cation-mediated intermolecular C–C bond-forming reactions, and we recently reported our first results in this area.[28] Current studies seek to extend these cyclisation reactions to substrates with nitrogen-containing templates, and will be the subject of further reports from this laboratory.

4. EXPERIMENTAL

General Procedures

^{1}H Nmr and ^{13}C nmr spectra were recorded in $CDCl_3$ on either Jeol GX-270a or Bruker AM-500 spectrometers, using residual isotopic solvent ($CHCl_3$, δ_H = 7.26 ppm; $CDCl_3$, δ_C = 77.0 ppm) as an internal reference. Infra-red spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded using VG-7070B or Jeol SX-102 instruments. Elemental combustion analyses were performed in the microanalytical laboratories of Imperial College and Zeneca Pharmaceuticals,Alderley Park. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-100 polarimeter. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) or Matrex Silica 60 (35-70 micron) under pressure. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light and iodine, acidic ammonium molybdate (IV), vanillin or potassium permanganate solutions as appropriate. Standard solvents were distilled under dried nitrogen; diethyl ether and tetrahydrofuran from sodium-benzophenone ketyl, CH_2Cl_2 from phosphorus pentoxide, acetonitrile from calcium hydride and toluene from sodium. Petrol refers to petroleum ether bp 40-60°C which was distilled prior to use. Solutions were concentrated under vacuum on a rotary evaporator at 25°C, except where otherwise stated. Azeotropically dried compounds were dissolved in dry toluene and concentrated at least three times. Molecular sieves were activated by heating over a flame under vacuum. Other solvents and reagents were purified before use according to standard procedures.[29]

Preparation of [2*R**,3*R**]- and [2*R**,3*S**]-2-(2-pyridylthio)tetrahydro-2*H*-pyran-3-ol (8).

To a stirred solution of *m*-CPBA (30.0 g of a 50-60% suspension in water, *ca.* 87.0 mmol, 1.2 equiv) in water-saturated ether at 0°C was added 3,4-dihydro-2*H*-pyran **7** (6.6 ml, 6.10 g, 72.5 mmol, 1.0 equiv) dropwise with stirring such that the internal temperature did not exceed 10°C. When addition was complete, the reaction mixture was stirred for a further 1 h at 0°C and then allowed to warm to rt. After a further 16 h at rt, most of the solvent was removed by distillation under reduced pressure, leaving a solution of approximately 80 ml. The ethereal solution was extracted with water (4 x 100 ml), the combined aqueous layers washed with ether (2 x 100 ml) and the water removed by distillation under reduced pressure. The resulting crude oil was dissolved in 10% ether–methanol and filtered through a short pad of silica gel, washing through with further portions of 10% ether–methanol. Removal of the solvents by distillation under reduced pressure afforded the expected diols (6.44 g, 75%) as a colourless oil. To a stirred solution of a portion of the diols so formed (3.59 g, 30.4 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (45 ml) at 0°C under nitrogen was added a solution of Aldrithiol-2® (8.03 g, 36.5 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (50 ml). The resulting pale solution was stirred at 0°C for 5 min when tri-*n*-butylphosphine (7.38 g, 9.00 ml, 36.5 mmol, 1.2 equiv) was added dropwise over 10 min, the solution immediately turning bright yellow. When the addition was complete, the

solution was stirred for a further 30 min at 0°C and then 3 h at rt, after which time the reaction was complete (tlc). The solution was washed with 2M aqueous NaOH (3 x 100 ml) and water (100 ml). After drying ($MgSO_4$) the solvent was removed by distillation under reduced pressure. Chromatography (25% ether–petrol→ether) afforded a mixture of *anti*- and *syn*-**8** as a yellow waxy solid (9:1 by ^1H nmr; 3.85 g, 60%); R_f 0.27 (ether); ν_{max} (film) 3371, 2944, 2861, 1578, 1560, 1453, 1418, 1119, 1098, 1072, 1049, 985, 969, 763, 724 cm^{-1}; δ_H (270 MHz) 8.45 (1H, m, H-6 of Py), 7.55 (1H, m, H-4 of Py), 7.36 (1H, m, H-3 of Py), 7.09 (1H, m, H-5 of Py), 6.10 (1H, d, J 4 Hz, H-2 *syn*-), 5.37 (1H, d, J 7 Hz, H-2 *anti*-), 4.06 (1H, dt, J 11, 3.5 Hz, H-6 equatorial), 3.73 (1H, m, H-3), 3.59 (1H, ddd, J 11, 9, 3 Hz, H-6 axial), 2.24-2.14 and 2.05-1.60 (both 2H, m, H-4 + H-5); *m/z* (CI) 212 $[M+H]^+$, 140, 112, 100, 67 (Found: $[M+H]^+$, 212.0737. $C_{10}H_{13}NO_2S$ requires $[M+H]^+$, 212.0745).

Preparation of 2,2-dimethyl-4-penten-3-one (*9*).

To a solution of vinyl magnesium bromide (9.17 g, 70 mmol, 1.17 equiv) in dry THF (70 ml) under argon at 0°C was added, dropwise with stirring trimethylacetaldehyde (5.2 g, 6.5 ml, 60 mmol, 1 equiv) in dry THF (10 ml). After 3 h at rt reaction was quenched with saturated aqueous NH_4Cl (50 ml). The aqueous layer was extracted with ether (3 x 100 ml); the combined organic phases were washed with brine (100 ml) and dried ($MgSO_4$). Concentration and chromatography (10% ether–petrol) yielded 4,4-dimethyl-1-penten-3-ol (5.81 g, 85%) as a colourless oil; R_f 0.3 (10% ether–petrol); ν_{max} (film) 3404, 2956, 1365, 1073 cm^{-1}; δ_H (270 MHz) 5.91 (1H, ddd, J 16.5, 9.5, 6.5 Hz, H-2), 5.18 (1H, dd, J 16.5, 1.5 Hz, H-1 *Z*), 5.12 (1H, dd, J 9.5, 1.5 Hz, H-1 *E*), 3.78-3.63 (1H, m, H-3), 0.91 (9H, s, CMe_3); m/z (EI) 114 $[M]^+$, 97 $[M\text{-}OH]^+$, 87 $[M\text{-}CH_2{=}CH]^+$, 57 $[CMe_3]^+$. A solution of oxalyl chloride (4.86 ml, 56.4 mmol, 1.5 eq) in dry CH_2Cl_2 (50 ml) under an atmosphere of argon was stirred at -78°C. A solution of DMSO (7.91 ml, 112.8 mmol, 3 equiv) in dry CH_2Cl_2 (75 ml) was slowly added to the oxalyl chloride solution, causing effervescence. 4,4-Dimethyl-1-penten-3-ol (4.3 g, 37.6 mmol) was added slowly in dry CH_2Cl_2 (180 ml). After stirring for 15 min Et_3N (15.56 ml, 112.8 mmol, 3 equiv) was added, and the flask warmed to rt. The cloudy white solution was quenched with water (300 ml) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with aqueous NH_4Cl (2 x 75 ml) and brine (2 x 75 ml), and dried ($MgSO_4$). The solution was concentrated to *ca.* 25 ml at 0°C. Kugelrohr distillation under reduced pressure provided the enone **9** (2.10 g, 50%) as a colourless oil, bp_{20} 45°C; ν_{max} (film) 2960, 2871, 1695, 1479, 1366, 1226, 1073, 1048, 988, cm^{-1}; δ_H (270 MHz) 6.82 (1H, dd, J 17.5, 10 Hz, H-2), 6.34 (1H, dd, J 17.5, 2.5 Hz, H-1 *Z*), 5.65 (1H, dd, J 10, 2.5 Hz, H-1 *E*), 1.17 (9H, s, CMe_3); *m/z* (EI) 112 $[M]^+$, 97 $[M\text{-}CH_3]^+$, 57$[CMe_3]^+$, 55 $[M\text{-}CMe_3]^+$.

Preparation of [2*R,3*S**] and [2*R**,3*R**]-3-(4,4-dimethyl-3-oxopentoxy)-2-(2-thiopyridyl)tetrahydro-*2H*-pyran (6).**

To a rapidly-stirred solution of **8** (211 mg, 1 mmol), **9** (178 mg, 1.5 mmol, 1.5 equiv) and Aliquat® 336 (4 mg, 1 mol %) in CH_2Cl_2 (3 ml) was added aqueous NaOH (50% w/w) (2 ml). After 2 min the CH_2Cl_2 layer was diluted with further CH_2Cl_2 and the layers separated. Concentration of the organic layers under reduced pressure followed by chromatography (25% EtOAc–petrol) yielded a mixture of the *syn*- and *anti*- ketones **6** (1:9 by ^1H nmr; 225 mg, 70%) as a yellow oil; R_f 0.2 (50% ether–petrol); ν_{max} (film) 2925, 1705, 1577, 1452, 1417, 1366, 1073, 763, 719 cm^{-1}; δ_H (500 MHz) [8.42 (1H, d, J 4 Hz), 7.49 (1H, td, J 8, 2 Hz), 7.27 (1H, d, J 7 Hz), 7.04-6.99 (1H, m) aromatics], 6.31 (0.1H, d, J 4 Hz, H-2 *syn*-), 6.00 (0.9H, d, J 3 Hz, H-2 *anti*-), 4.05 (1H, td, J 10, 3 Hz, H-6 axial), 3.80 (2H, t, J 6.5 Hz, $COCH_2CH_2$), 3.78-3.72 (0.1H, m, H-3 *syn*-), 3.65 (1H, dt, J 11.5, 3 Hz, H-6 equatorial), 3.56-3.53 (0.9H, m, H-3 *anti*-), [2.84 (1H, dt, J 17, 7 Hz), 2.72 (1H, dt J 17, 6 Hz, $COCH_2CH_2$], 1.97-1.42 (4H, m, H-4, H-5), 1.12 (9H, s, CMe_3); *m/z* (EI) 212 $[M\text{-}PySH]^+$, 113 $[CH_2CH_2COCMe_3]^+$, 111 $[PySH]^+$, 100 $[CH_3COCMe_3]^+$, 57 $[CMe_3]^+$ (Found: C, 63.12; H, 7.89; N, 4.15. $C_{17}H_{25}NO_3S$ requires C, 63.13; H, 7.79; N, 4.33%).

Preparation of [2*R* *, 3*S]-(*Z*)-3-[3-*tert*-butyldimethylsilyloxy-4,4-dimethyl-2-pentenyloxy]-2-(2-thiopyridyl)tetrahydro-2*H*-pyran (*syn*-5) and [2*R* *,3*R**]-(*Z*)-3-(3-*tert*-butyldimethylsilyl-oxy-4,4-dimethyl-2-pentenyloxy)-2-(2-thiopyridyl)tetrahydro-2*H*-pyran (*anti*-5).**

To a solution of ketones **6** (605 mg, 1.87 mmol) in dry THF (100 ml) under an atmosphere of argon at -78°C was added, with stirring TBDMSOTf (1.02 ml, 2.81 mmol, 1.5 equiv), followed by potassium hexamethyldisilazide 9.4 ml of a 0.5M solution in PhMe, 4.7 mmol, 2.5 equiv). After 10 min the reaction was warmed to rt. Water (50 ml) was added and the aqueous phase extracted with EtOAc (3 x 100 ml). The combined organic phases were washed with brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give *syn*-**5** and *anti*-**5** (1:9 by ^1H nmr; 727 mg, 89%) as a yellow oil. Chromatography (20% ether–petrol) enabled partial separation of the diastereomers; *anti*-**5**: R_f 0.25 (20% ether–petrol); ν_{max} (film) 2957, 2860, 1576, 1455, 1414, 1256, 1159, 1070, 925, 832, 778 cm^{-1}; δ_H (500 MHz) [8.44 (1H, ddd, J 5, 2, 1 Hz), 7.51 (1H, td J 7.5, 2 Hz), 7.30 (1H, dt, J 8, 1 Hz), 7.01 (1H, ddd, J 7.5, 5, 1 Hz) aromatics], 6.04 (1H, d, J 3 Hz, H-2), 4.78 (1H, t, J 6.5 Hz, vinyl), [4.20 (1H, dd, J 11.5, 6.5 Hz), 4.06 (1H, dd, J 11.5, 6.5 Hz, OCH_2), 4.03 (1H, ddd, J 13, 10, 3 Hz, H-6 axial), 3.70 (1H, ddd, J 9.5, 4.5, 3.5 Hz, H-6 equatorial), 3.59-3.55 (1H, m, H-3), [2.06-1.98 (1H, m), 1.96-1.91 (1H, m), 1.88-1.82 (1H, m), 1.49-1.43 (1H, m) H-4, H-5], 1.06 (9H, s, $=CCMe_3$), 0.96 (9H, s, $SiCMe_3$), [0.18 (3H, s), 0.17 (3H, s) $SiMe_2$]; *m/z* (EI) 437 $[M]^+$, 320 $[M-MeSiOHCMe_3]^+$, 243 $[OCH_2CH{=}CCMe_3OSiMe_2CMe_3]^+$, 227 $[CH_2CH{=}CCMe_3OSiMe_2CMe_3]^+$, 111 $[PySH]^+$, 57 $[CMe_3]^+$; *syn*-**5**: R_f 0.22 (20% ether–petrol); ν_{max} (film) 2956, 2860, 1658, 1577, 1454, 1416, 1256, 1157, 1074, 925, 831, 777 cm^{-1}; δ_H (500 MHz) [8.45 (1H, br d, J 5 Hz), 7.49 (1H, dt, J 7.5, 2 Hz), 7.28 (1H, d, 8 Hz), 7.00 (1H, ddd, J 8, 6, 1 Hz) aromatics], 6.37 (1H, d, J 4 Hz, H-2), 4.75 (1H, t, J 6.5 Hz, vinyl), 4.12 (2H, qd, J 11.5, 3 Hz, OCH_2), 4.01 (1H, td, J 10, 3 Hz, H-6 axial), 3.77 (1H, dt, J 8, 4 Hz, H-3), 3.66 (1H, dt, J 8, 4 Hz, H-6 equatorial), [1.94-1.89 (1H, m), 1.84-1.75 (2H, m), 1.70-1.64 (1H, m) H-4, H-5], 1.04 (9H, s, $=CCMe_3$), 0.94 (9H, s, $SiCMe_3$), [0.14 (3H, s), 0.13 (3H, s) $SiMe_3$], *m/z* (EI) 437 $[M]^+$, 320 $[M-MeSiOHCMe_3]^+$, 305 $[M-HOSiMe_2CMe_3]^+$, 269 $[M-PySH-CMe_3]^+$, 243 $[OCH_2CH{=}CCMe_3OSiMe_2CMe_3]^+$, 227 $[CH_2CH{=}CCMe_3OSiMe_2CMe_3]^+$, 111 $[PySH]^+$, 57 $[CMe_3]^+$.

Cyclisation of the silyl enol ethers *anti*-5 and *syn*-5.

To a mixture of powdered activated 4Å sieves and AgOTf (dried in a desiccator for 48 h; 810 mg, 3.15 mmol, 2 equiv) in dry CH_2Cl_2 (52 ml) under an atmosphere of argon at rt with stirring was added a solution of the silyl enol ethers (609 mg, 1.57 mmol) *anti*-**5** and *syn*-**5** in dry CH_2Cl_2 (3 ml), forming an off-white precipitate. After 20 min the reaction was filtered through silica gel, rinsing with ether and the filtrate was concentrated under reduced pressure. Chromatography (30→50% ether–petrol) gave, in order of elution the bicyclic *C*-glycosides **10**α (171 mg, 58%) as a colourless oil and **10**β (91 mg, 31%) as a clear waxy solid; [1*R**,6*R**,9*S**]-9-(2,2-dimethyl-1-oxopropyl)-2,7-dioxabicyclo[4.3.0]nonane **10**α: R_f 0.5 (50% ether–petrol); ν_{max} (film) 2956, 1702, 1479, 1367, 1341, 1111, 1041, 954, 902 cm^{-1}; δ_H (500 MHz) 4.25 (1H, t, J 8.5 Hz, H-8), 3.89-3.87 (1H, m, H-3 equatorial), 3.85 (1H, d, J 2.5 Hz, H-1), 3.80 (1H, dd, J 5.5, 2.5 Hz, H-6), 3.66 (1H, dd, J 8, 6 Hz, H-8), 3.61 (1H, dd, J 8.5, 6 Hz, H-9), 3.36 (1H, td, J 8, 2 Hz, H-3 axial), 2.11 (1H, br d, J 10.5 Hz, H-5 equatorial), [1.85 (1H, qt, 13, 4 Hz), 1.76 (1H, tq, 14, 6.5 Hz) H-4 axial, H-5 axial], 1.35 (1H, br d, J 10 Hz, H-4 equatorial), 1.14 (9H, s, CMe_3); *m/z* (EI) 212 $[M]^+$, 155 $[M-CMe_3]^+$, 127 $[M-COCMe_3]^+$, 57 $[CMe_3]^+$; [1*R**,6*R**,9*R**]-9-(2,2-dimethyl-1-oxopropyl)-2,7-dioxabicyclo[4.3.0]nonane **10**β: R_f 0.3 (50% ether–petrol); mp 64-69°C; ν_{max} (film) 2956, 1705, 1478, 1365, 1334, 1116, 1061, 1041, 959, 898 cm^{-1}; δ_H (500 MHz) 4.57 (1H, t, J 8 Hz, H-8), 4.20 (1H, dd, J5, 2 Hz, H-1), 3.89 (1H, br d, J 13.5 Hz, H-3 equatorial), 3.83 (1H, t, J 8.5 Hz, H-8), 3.82-3.79 (1H, m, H-6), 3.65 (1H, dt, J 9.5, 5 Hz, H-9), 3.28 (1H, td, J 12, 2 Hz, H-3 axial), 2.08 (1H, br d, J 14.5 Hz, H-5 equatorial), [1.89 (1H, qt, J 14.5, 4 Hz) 1.71 (1H, tt, J 13.5, 5 Hz) H-4 axial, H-5 axial], 1.30 (1H, br d, J 13.5 Hz, H-3 equatorial), 1.18 (9H, s, CMe_3); *m/z* (EI) 212 $[M]^+$, 155 $[M-CMe_3]^+$, 127 $[M-COCMe_3]^+$, 57 $[CMe_3]^+$ (Found: C, 68.03; H, 9.75. $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%).

Preparation of *t*-butyl [1*R,6*R**,9*R**]-2,7-dioxabicyclo[4.3.0]nonane-9-carboxylate (11).**

Trifluoroperacetic acid was generated by the slow addition of trifluoroacetic anhydride (7 ml, 50 mmol, 1.25 eq) to a solution of H_2O_2 (90%) (1 ml, 40 mmol, 1 equiv) in dry CH_2Cl_2 (5 ml) at 0°C. After stirring for 2 h the solution was used without purification (stable at -18°C for 1 month).[14]

To a stirred solution of the *C*-glycoside **10**β (36 mg, 0.17 mmol) and disodium hydrogen phosphate (100 mg, 0.85 mmol, 5 equiv) in CH_2Cl_2 (0.5 ml) at 0°C, was added the crude trifluoroperacetic acid solution (0.15 ml, 0.47 mmol, 2.75 equiv). The reaction was warmed to rt and stirred for 16 h after which a further 40 mg of disodium hydrogenphosphate (0.34 mmol, 2 equiv) and further trifluoroperacetic acid solution (0.15 ml, 0.47 mmol, 2.77 equiv) were added. After a further 5 h a third portion of trifluoroperacetic acid solution (0.2 ml, 0.63 mmol, 3.67 equiv) was added. The reaction was stirred for 3 h and then quenched with aqueous $NaHCO_3$ (3 ml) and the aqueous phase extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (30→50% ether–petrol) yielded, in order of elution, the ester **11** (25 mg, 65%; 84% based on recovered **10**β) as a colourless oil; R_f 0.45 (50% ether–petrol); ν_{max} (film) 2957, 1736, 1703, 1479, 1368, 1343, 1225, 1164, 1133, 1113, 1041 cm^{-1}; δ_H (500 MHz) 4.37 (1H, dd, J 9.5, 8.5 Hz, H-8 *endo*), 4.11 (1H, dd, J 4, 2 Hz, H-1), 4.01 (1H, t, J 8.5 Hz, H-8 *exo*), 3.94-3.85 (2H, m, H-6, H-3 equatorial), 3.34 (1H, td, J 11.5, 2 Hz, H-3 axial), 3.20 (1H, td, J 9.5, 4 Hz, H-9), 2.10-2.02 (1H, m, H-5 equatorial), 1.86 (1H, qt, J 13, 4 Hz, H-5 axial), 1.75-1.67 (1H, m, H-4 axial), 1.37-1.29 (1H, m, H-4 equatorial), 1.14 (9H, s, CMe_3); *m/z* (EI) 172 $[M-CH_2{=}CMe_2]^+$, 155 $[M-OCMe_3]^+$, 57 $[CMe_3]^+$ (Found: $[M-OCMe_3]^+$, 155.0708. $C_{12}H_{20}O_4$ requires $[M-OCMe_3]^+$, 155.0708); this was followed by recovered **10**β (8.1 mg, 23%) identical in all respects to the previously prepared sample.

Preparation of [1*R,6*R**,9*R**]-2,7-dioxabicyclo[4.3.0]nonane-9-carboxylic acid (12).**

To a stirred solution of the *C*-glycoside **10**β (21.7 mg, 0.10 mmol) in CH_2Cl_2 (0.3 ml) at 0°C was added crude trifluoroperacetic acid solution (85 μl, 0.28 mmol, 2.75 equiv). The reaction was warmed to rt and stirred for 20 h and then quenched with brine (3 ml) and the aqueous phase extracted with EtOAc (3 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50%→100% ether–petrol) yielded the acid **12** (13 mg, 74%) as a colourless solid; mp 140-141°C; R_f 0.05-0.25 (ether); ν_{max} (film) 2924, 1734, 1436, 1332, 1216, 1112, 1039, 945, 893, 818, 768, 694 cm^{-1}; δ_H (500 MHz) 9.3 (1H, br s, OH), 4.31 (1H, dd, J 10.5, 9.5 Hz, H-8), 4.20 (1H, dd, J 4, 2 Hz, H-1), 4.14 (1H, t, J 9.5 Hz, H-8), 4.05-3.99 (1H, m, H-3 equatorial), 3.88 (1H, br s, H-6), 3.44 (1H, td, J 13.5, 2 Hz, H-3 axial), 3.31 (1H, td, J 9.5, 4 Hz, H-9), 2.14-2.07 (1H, m, H-5 equatorial), 1.93 (1H, qt, J 13, 4 Hz, H-4 axial), 1.77-1.69 (1H, m, H-5 axial), 1.39 (1H, ddd, J 13.5, 4.5, 2.5 Hz, H-4 equatorial); *m/z* (EI) 172 $[M]^+$, 155 $[M-OH]^+$, 142 $[M-H_2CO]^+$ (Found: $[M]^+$, 172.0736. $C_8H_{12}O_4$ requires $[M]^+$, 172.0736).

Preparation of [1*R,6*R**]-9-oxo-2,7-dioxabicyclo[4.3.0]nonane (13).**

To a solution of a mixture of *C*-glycosides **10**α and **10**β (308 mg, 1.45 mmol) in dry toluene (7.5 ml) under argon with stirring at -78°C was added TBDMSOTf (0.5 ml, 2.18 mmol, 1.5 equiv), followed by potassium hexamethyldisilazide (7.2 ml of a 0.5M solution in PhMe, 3.6 mmol, 2.5 equiv). After 10 min the reaction was warmed to rt and water (15 ml) added. The aqueous layer was extracted with EtOAc (3 x 25 ml) and the combined organic phases were washed with brine (2 x 25 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (10% EtOAc–petrol) yielded the silyl enol ethers **13** as a mixture of *Z*- and *E*- geometric isomers (87:13 by ^1H nmr; 354 mg, 75%) as a colourless oil; R_f 0.35 (10% EtOAc–petrol); ν_{max} (film) 2954, 2857, 1707, 1660, 1465, 1257, 1144, 1101, 1054, 874, 834, 778 cm^{-1}; δ_H (500 MHz) 4.60 (1H, d, J 12.5 Hz, H-8), 4.47 (1H, d, J 2 Hz, H-1), 4.32 (1H, J 12.4 Hz, H-8), 3.91-3.83 (1H, m, H-3 equatorial), 3.65-3.62 (1H, m, H-6), 3.35 (1H, td, J 11.9, 2 Hz, H-3 axial), 2.14-2.05 (1H, m, H-4 equatorial), 1.88 (1H, qt, J 12.5, 4 Hz, H-4 axial), 1.78-1.68 (1H, m, H-5 axial), 1.37-1.32 (1H, m, H-5 equatorial), [1.21 (7.83H, s), 1.18 (1.17H, s, $=CCMe_3$], [0.95 (7.83H, s), 0.91 (1.17H, s) $SiCMe_3$], [0.20 (3H, s), 0.19 (3H, s) $SiMe_2$]; *m/z* (EI) 326 $[M]^+$, 269 $[M-CMe_3]^+$, 211 $[M-SiMe_2CMe_3]^+$, 57 $[CMe_3]^+$.

Preparation of [1*R,6*R**]-9-(1-*tert*-butyldimethylsilyloxy-2,2-dimethylpropylidene)-2,7-dioxabicyclo[4.3.0]nonane (14).**

Through a solution of the silyl enol ethers **13** (49.3 mg, 0.15 mmol) in CH_2Cl_2 (3 ml) at -78°C was passed ozone (200V, 35 l h^{-1}). After 10 min oxygen was bubbled into the solution during warming to rt. Triphenylphosphine (40 mg, 0.16 mmol, 1.05 equiv) was added and the solution stirred at rt for 16 h. Concentration under reduced pressure and chromatography (50% ether–petrol) yielded the ketone **14** (19 mg, 88%) as a colourless oil; R_f 0.35 (50% ether–petrol); ν_{max} (film) 3516, 2958, 1773, 1436, 1372, 1215, 1170, 1119, 1094, 1050, 884, 810, 745 cm^{-1}; δ_H (500 MHz) 4.23 (1H, d, J 17 Hz, H-8), 4.14-4.10 (1H, m, H-6), 3.92 (1H, d, J 17 Hz, H-8), 3.92 (1H, d, J 4 Hz, H-1), 3.86-3.79 (1H, m, H-3 equatorial), 3.54-3.47 (1H, m, H-3 axial), [2.01-1.89 (3H, m), 1.58-1.39 (1H, m) H-4, H-5]; *m/z* (EI) 142 $[M]^+$, 84 $[C_5H_8O]^+$ (Found: $[M]^+$, 142.0630. $C_7H_{10}O_3$ requires $[M]^+$, 142.0630).

Preparation of [1*R,6*R**,9*R**]-2,7-dioxabicyclo[4.3.0]nonan-9-ol (15).**

To a solution of ketones **14** (24.3 mg, 0.17 mmol) in dry toluene (1 ml) under argon at -78°C was added DIBAL-H (0.17 ml of a 1.5M solution in toluene, 0.26 mmol, 1.5 equiv) with stirring. After 5 min the reaction was quenched with water (0.5 ml), the mixture warmed to rt, diluted with a 1:1 mixture of EtOAc–saturated aqueous $NaHCO_3$ (5 ml), and stirred for 15 min. The aqueous phase was saturated with NaCl and extracted with EtOAc (3 x 15 ml), and the combined organic phases dried ($MgSO_4$). Concentration under reduced pressure and chromatography (ether) yielded the alcohol **15** (15.5 mg, 63%) as a colourless oil; R_f 0.25 (ether); ν_{max} (film) 3422, 2942, 1435, 1219, 1124, 1090, 1040, 952, 890, 811, 757, 663 cm^{-1}; δ_H (500 MHz) 4.42 (1H, br s, H-9), 4.04 (1H, t, J 8.5 Hz, H-8), 4.04-3.99 (1H, m, H-3 equatorial), 3.82 (1H, dd, J 5.5, 2.5 Hz, H-6), 3.78 (1H, dd, J 4.5, 2 Hz, H-1), 3.71 (1H, dd, J 8.5, 7.5 Hz, H-8), 3.45 (1H, td, J 11.5, 2 Hz, H-3 axial), 2.67 (1H, br d, J 10 Hz, OH), [2.04-1.99 (1H, m), 1.89 (1H, qt, J 12.5, 8 Hz), 1.74-1.66 (1H, m), 1.43-1.37 (1H, m) H-4, H-5]; *m/z* (EI) 144 $[M]^+$, 126 $[M-H_2O]^+$, 101 $[C_5H_9O_2]^+$, 84 $[C_5H_8O]^+$.

One-step ozonolysis–reduction of silyl enol ether (13).

Through a solution of the silyl enol ethers **13** (35.8 mg, 0.11 mmol) in CH_2Cl_2 (5 ml) at -78°C was passed ozone (200V, 35 l h^{-1}). After 10 min argon was bubbled into the solution during warming to rt. $BH_3{\cdot}SMe_2$ (40 µl, 0.42 mmol, 4 equiv) was added and the solution stirred at rt for 16 h. Aqueous HCl (5%) (0.25 ml) was added, and after stirring for 10 min the solution was neutralised with $NaHCO_3$. The solution was diluted with CH_2Cl_2 (100 ml) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (ether) yielded the alcohol **15** (12.3 mg, 78%) identical in all respects to the previously prepared sample.

[2*R,4*S*,6*S*]-6-(*tert*-Butyldiphenylsilyloxymethyl)-2-methoxy-4-(phenylsulfonyl)tetrahydro-2*H*-pyran (25).**

To a solution of sulfone **24** (10.71 g, 43.8 mmol, 2 equiv) in dry THF–TMEDA (1:1; 150 ml) at -78°C with stirring was added *n*-BuLi (18.4 ml of a 2.5M solution in pentanes, 46 mmol, 2.1 equiv), causing the solution to become yellow. After 10 min a solution of the epoxide **23** (6.85 g, 21.9 mmol, 1 equiv) in dry THF (30 ml) was added dropwise. The reaction was warmed to rt and quenched with AcOH (46 ml of a 1M solution in THF). Water (200 ml) was added and the aqueous phase extracted with ether (3 x 200 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (150 ml) and brine (150 ml). Drying ($MgSO_4$), concentration under reduced pressure and chromatography (20→80% ether–petrol) yielded, in order of elution, the epoxide **23** (753 mg, 11%) followed by a mixture of the desired alcohols and **23**. This mixture was dissolved in dry CH_2Cl_2 (250 ml) and TFA (3.2 ml, 41.5 mmol, 1 equiv) added with stirring at rt.. After 4 h the reaction mixture was cooled to 0°C and quenched with saturated aqueous $NaHCO_3$ (150 ml). The aqueous phase was extracted with ether (3 x 200 ml) and the combined organic phases were washed with aqueous $NaHCO_3$ (150 ml) and brine (150 ml). Drying ($MgSO_4$), concentration and chromatography (50→70% ether–petrol) yielded a mixture of four diastereomeric pyranosides (7.67 g, 94%). To a stirred

solution of this material in dry THF (170 ml) at rt was added dry *t*-BuOH (18.9 ml, 1.78 mol, 20 equiv), followed by *t*-BuOK (7.3 ml of a 1M solution in THF, 7.3 mmol, 0.5 equiv). After 1 h the reaction was quenched with water (150 ml). The aqueous phase was extracted with ether (3 x 200 ml), and the combined organic phases were washed with brine (200 ml). Drying ($MgSO_4$), concentration and chromatography (50% ether–petrol) yielded a mixture of the [2*S*,4*S*,6*S*]- and [2*R*,4*S*,6*S*]-pyranosides **25** (3:2 by ^{1}H nmr; 6.96 g, 91%) as a colourless oil. Further chromatography (30→50% ether–petrol) provided a sample of each epimer; [2*S*,4*S*,6*S*]-6-(*tert*-butyldiphenylsilyloxy-methyl)-2-methoxy-4-(phenylsulfonyl)tetrahydro-2*H*-pyran, [2*S*,4*S*,6*S*]-(**25**): R_f 0.75 (70% ether–petrol); $[\alpha]_D^{25}$ +38 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2956, 2931, 2857, 1447, 1306, 1149, 1114, 1087, 1047, 824, 703 cm^{-1}; δ_H (500 MHz) 7.87 (2H, d, J 8.5 Hz, *o*-$PhSO_2$), 7.68 (1H, t, J 6 Hz, *p*-$PhSO_2$), 7.62 (4H, d, J 8.5 Hz, *o*-Ph), 7.56 (2H, t, J 8 Hz, *m*-$PhSO_2$), 7.44-7.39 (2H, m, *p*-Ph), 7.38-7.34 (4H, m, *m*-Ph), 4.84 (1H, d, J 2.5 Hz, H-2), 3.79-3.72 (1H, m, H-6), [3.68 (1H, dd, J 10, 4.5 Hz), 3.57 (1H, dd, J 10.5, 5 Hz) CH_2OSi], 3.51 (1H, tt, J 12.5, 3.7 Hz, H-4), 3.27 (3H, s, Me), 2.06-1.94 (1H, m, H-3 equatorial), 1.77 (1H, td, J 13, 3.5 Hz, H-5 equatorial), 1.58-1.48 (1H, m, H-5 axial), 1.22-1.07 (1H, m, H-3 axial), 1.01 (9H, s, CMe_3); δ_C (62.9 MHz) 136.8 (*i*-$PhSO_2$), 135.6 (*o*-Ph), 133.8 (*p*-$PhSO_2$), [133.4, 133.3 (*i*-Ph)], 129.7 (*p*-Ph), [129.2, 129.1 (*o*-$PhSO_2$, *m*-$PhSO_2$), 127.7 (*m*-Ph), 97.1 (C-2), 67.8 (C-6), 66.6 (CH_2OSi), 56.3 (C-4), 54.44 (Me), 29.0 (C-3), 26.8 (C-5, CMe_3), 19.2 (CMe_3); *m/z* (CI) 542 $[M+NH_4]^+$, 510 $[M\text{-}MeOH+NH_4]^+$, 493 $[M\text{-}MeO]^+$, 368 $[M\text{-}MeOH\text{-}PhSO_2H+NH_4]^+$, 351 $[M\text{-}MeOH\text{-}PhSO_2]^+$ (Found: $[M+NH_4]^+$, 542.2382. $C_{29}H_{36}O_5SSi$ requires $[M+NH_4]^+$, 542.2396); [2*R*,4*S*,6*S*]-6-(*tert*-butyldiphenyl-silyloxymethyl)-2-methoxy-4-(phenylsulfonyl)tetrahydro-2*H*-pyran, [2*R*,4*S*,6*S*]-(**25**): R_f 0.70 (70% ether–petrol); $[\alpha]_D^{25}$ -12.4 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2958, 2930, 2857, 1447, 1306, 1149, 1114, 1086, 1070, 704 cm^{-1}; δ_H (500 MHz) 7.85 (2H, d, J 8.5 Hz, *o*-$PhSO_2$), 7.67 (1H, t, J 7 Hz, *p*-$PhSO_2$), 7.62 (4H, d, J 7.5 Hz, *o*-Ph), 7.55 (2H, t, J 8.5 Hz, *m*-$PhSO_2$), 7.46-7.42 (2H, m, *p*-Ph), 7.38 (4H, t, J 8 Hz, *m*-Ph), 4.28 (1H, dd, J 9, 1.5 Hz, H-2), [3.77 (1H, dd, J 10.5, 5.5 Hz), 3.62 (1H, dd, J 10.5, 5.5 Hz) CH_2OSi], 3.53-3.47 (1H, m, H-6), 3.44 (3H, s, Me), 3.19 (1H, tt, J 12.5, 3.5 Hz, H-4), 2.18-2.12 (1H, m, H-3 equatorial), 2.11-2.06 (1H, m, H-5 equatorial), 1.52-1.45 (1H, m, H-3 axial), 1.38 (1H, q, J 11.5 Hz, H-5 axial), 1.01 (9H, s, CMe_3); δ_C (62.9 MHz) 136.6 (*i*-$PhSO_2$), [135.6, 135.5 (*o*-Ph)], 134.0 (*p*-$PhSO_2$), [133.4, 133.2 (*i*-Ph)], [129.8, 129.7 (*p*-Ph)], [129.3, 129.2 (*o*-$PhSO_2$, *m*-$PhSO_2$)], 127.7 (*m*-Ph), 101.3 (C-2), 74.3 (C-6), 66.2 (CH_2OSi), 59.9 (C-4), 56.2 (Me), 30.8 (C-3), 27.1 (C-5), 26.8 (CMe_3), 19.2 (CMe_3); *m/z* (CI) 542 $[M+NH_4]^+$, 510 $[M\text{-}MeOH+NH_4]^+$, 493 $[M\text{-}MeO]^+$, 368 $[M\text{-}MeOH\text{-}PhSO_2H+NH_4]^+$, 351 $[M\text{-}MeOH\text{-}PhSO_2]^+$ (Found: $[M+NH_4]^+$, 542.2471. $C_{29}H_{36}O_5SSi$ requires $[M+NH_4]^+$, 542.2396).

Preparation of [2*S*,4*S*]-2-(*tert*-butyldiphenylsilyloxymethyl)-4-phenylsulfonyl-3,4-dihydro-2*H*-pyran (26).

To a solution of epimeric pyranosides **25** (5.89 g, 11.2 mmol) in acetonitrile (115 ml) under an atmosphere of argon at rt with stirring was added sodium iodide (9.9 g, 66 mmol, 6 equiv). Chlorotrimethylsilane (8.1 ml, 66 mmol, 6 equiv) was added, causing the solution to become pale yellow. After 40 min HMDS (24.8 ml, 0.11 mol, 10 equiv) was added. The reaction was quenched with aqueous $NaHCO_3$ (150 ml). The aqueous phase was extracted with ether (3 x 150 ml) and the combined organic phases washed with aqueous $NaHCO_3$ (200 ml) and brine (150 ml). Drying ($MgSO_4$), concentration under reduced pressure and chromatography (40% ether–petrol) yielded the glycal **26** (3.86 g, 70%) as a colourless oil; R_f 0.55 (50% ether–petrol); $[\alpha]_D^{25}$ -12.5 (*c* 1, $CHCl_3$); ν_{max} (film) 2956, 2931, 1642, 1472, 1428, 1306, 1245, 1132, 1114, 1056, 824, 738, 704 cm^{-1}; δ_H (500 MHz) 7.88 (2H, d, J 8 Hz, *o*-$PhSO_2$), 7.66 (1H, t, 7.5 Hz, *p*-$PhSO_2$), 7.63-7.59 (4H, m, *o*-Ph), 7.55 (2H, t, J 8 Hz, *m*-$PhSO_2$), 7.46-7.41 (2H, m, *p*-Ph), 7.40-7.34 (4H, m, *m*-Ph), 6.53 (1H, dd, J 6, 2 Hz, H-6), 4.90 (1H, dt, J 6, 1.5 Hz, H-5), 3.99-3.92 (1H, m, H-4), 3.90-3.84 (1H, m, H-2), 3.71 (2H, m, CH_2OSi), 2.21 (1H, dd, J 13.5, 6.5 Hz, H-3 equatorial), 1.89 (1H, q, J 12 Hz, H-3 axial), 1.00 (9H, s, CMe_3); δ_C (62.9 MHz) 148.9 (C-2), 136.1 (*i*-$PhSO_2$), [135.6, 135.5 (*o*-Ph)], 133.8 (*p*-$PhSO_2$), [133.2, 133.0 (*i*-Ph)], 129.8 (*p*-Ph), [129.4, 129.0 (*o*-$PhSO_2$, *m*-$PhSO_2$)], [127.7, 127.7 (*m*-Ph)], 93.4 (C-3), 74.7 (C-4), 65.6 (C-6), 58.4 (CH_2OSi), 26.8 (CMe_3), 25.8 (C-5), 19.2 (CMe_3); *m/z* (CI) 510 $[M+NH_4]^+$, 435 $[M\text{-}CMe_3]^+$, 368 $[M\text{-}PhSO_2H+NH_4]^+$, 351 $[M\text{-}PhSO_2]^+$, 293 $[M\text{-}PhSO_2H\text{-}CMe_3]^+$, 78 $[PhH]^+$ (Found: $[M+NH_4]^+$, 510.2122. $C_{28}H_{32}O_4SSi$ requires $[M+NH_4]^+$, 510.2134).

Preparation of [2*S*,3*R*,4*S*,6*S*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3-hydroxy-4-phenylsulfonyl-2-(2-thiopyridyl)tetrahydro-2*H*-pyran (27).

To a solution of the glycal **26** (4.26 g, 8.6 mmol) in ether saturated with water (43 ml) at rt, was added *m*-CPBA (4.61 g of 55% suspension in water, 14.6 mmol, 1.7 equiv). After stirring for 16 h the reaction was quenched with saturated aqueous $NaHCO_3$ (100 ml). The aqueous phase was extracted with ether (3 x 200 ml), and the combined organic layers were washed with brine (100 ml). Drying ($MgSO_4$) and concentration yielded a waxy yellow foam which was redissolved in methanol (150 ml). Triethylamine (2.1 ml, 15 mmol, 2 equiv) was added and the reaction stirred at rt for 15 min. Concentration under reduced pressure and chromatography (50-90% ether–petrol) yielded a mixture of epimeric diols (1:1 by ^1H nmr; 3.19 g, 70%) as a foam. The diols (448 mg, 0.85 mmol) were azeotropically dried and dissolved in dry CH_2Cl_2 (8.5 ml) under an atmosphere of argon. 2-Aldrithiol® (225 mg, 1 mmol, 1.2 equiv) was added and the solution stirred at -78°C. Tri-*n*-butylphosphine (0.21 ml, 0.92 mmol, 1.1 equiv) was added whereupon the solution immediately turned yellow. The reaction was warmed to rt and stirred for 30 min. The solution was filtered through silica gel, rinsing with ether. Concentration under reduced pressure and chromatography (80% ether–petrol) yielded a single thioglycoside **27** (471 mg, 89% from the diols) as waxy yellow solid; R_f 0.45 (ether); $[\alpha]_D^{25}$ +26 (*c* 1, $CHCl_3$); ν_{max} (film) 3487, 2957, 2930, 2857, 1449, 1305, 1145, 1112, 1082, 824, 741 cm^{-1}; δ_H (500 MHz) 8.39 (1H, dd, J 7, 1 Hz, SPy), 7.97 (2H, d, J 9 Hz, *o*-$PhSO_2$), 7.70 (1H, t, J 8 Hz, *p*-$PhSO_2$), 7.65-7.56 (7H, m, SPy, *m*-$PhSO_2$, *o*-Ph), 7.52 (1H, td, J 8, 2 Hz, SPy), 7.44-7.38 (2H, m, *p*-Ph), 7.38-7.31 (4H, m, *m*-Ph), 7.08-7.03 (1H, m, SPy), 5.24 (1H, d, J 9.5 Hz, H-2), 3.91 (1H, t, J 9.5, Hz, H-3), 3.73 (1H, dd, J 10, 4.5 Hz, CHOSi), 3.75-3.68 (1H, m, H-6), 3.57 (1H, dd, J 9.5, 4.5 Hz, CHOSi), 3.45-3.39 (1H, m, H-4), 2.21 (1H, ddd, J 13, 4, 1.5 Hz, H-5 equatorial), 1.72-1.64 (1H, m, H-5 axial), 1.6 (1H, br s, OH), 0.99 (9H, s, CMe_3); δ_C (62.9 MHz) 156.1 (C-1 SPy), 149.4 (C-5 SPy), 137.6 (*i*-$PhSO_2$), 136.1 (*p*-$PhSO_2$), [135.6, 135.5 (*o*-Ph)], 134.0 (C-3 SPy), [133.2, 133.1 (*i*-Ph)], 129.7 (*o*-$PhSO_2$), 129.2 (*p*-Ph), 129.2 (*m*-$PhSO_2$), 127.7 (*m*-Ph), 124.2 (C-4 SPy), 120.9 (C-2 SPy), 85.8 (C-2), 77.6 (C-3), [68.8, 67.0 (C-6, C-4)], 65.8 (CH_2OSi), 27.7 (C-5), 26.8 (CMe_3), 19.2 (CMe_3); *m/z* (CI) 620 $[M+H]^+$, 490 $[M-PhSO_2H+NH_4]^+$, 431 $[M-PySH-Ph]^+$, 199 $[Ph_2SiOH]^+$, 112 $[PySH+H]^+$, 78 $[PhH]^+$ (Found: C, 63.65; H, 6.03; N, 2.07. $C_{33}H_{37}NO_5S_2Si$ requires C, 63.94; H, 6.02; N, 2.26%).

Preparation of [2*S*,3*R*,4*S*,6*S*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3-(3-phenyl-2-propenyloxy)-4-phenylsulfonyl-2-(2-thiopyridyl)tetrahydro-2*H*-pyran (29).

To a solution of thioglycoside **27** (160 mg, 0.26 mmol) in CH_2Cl_2 (0.5 ml) containing Aliquat® 336 (5 mg, 5 mol %) was added *trans*-1-bromo-3-phenyl-2-propene (102 mg, 0.52 mmol, 2 equiv). The reaction was rapidly stirred at rt and 50% aqueous NaOH (1 ml) was added. After 15 min the reaction was diluted with CH_2Cl_2 (10 ml). Concentration of the organic layer under reduced pressure and chromatography (50% ether–petrol) yielded the ether **29** (163 mg, 86%) as a colourless oil; R_f 0.6 (70% ether–petrol); $[\alpha]_D^{25}$ +6.8 (*c* 0.1, $CHCl_3$); ν_{max} (film) 2956, 2930, 2857, 1577, 1448, 1307, 1148, 1112, 1086, 736, 703 cm^{-1}; δ_H (500 MHz) 8.41 (1H, dt, J 5, 1 Hz, SPy), 7.95 (2H, d, J 8 Hz, *o*-$PhSO_2$), 7.64-7.59 (4H, m, SPy, *o*-CH=CH*Ph*, *p*-CH=CH*Ph*), 7.58 (1H, t, J 7.5 Hz, *p*-$PhSO_2$), 7.51 (2H, t, J 8 Hz, *m*-$PhSO_2$), 7.46-7.39 (3H, m, SPy, *p*-Ph), 7.38-7.33 (4H, m, *o*-Ph), 7.29-7.19 (6H, m, *m*-Ph, *m*-CH=CH*Ph*), 6.99 (1H, dd, J 7.5, 5 Hz, SPy), 6.34 (1H, d, J 16 Hz Ph*CH*=), 5.94 (1H, dt, J 16, 6 Hz, PhCH=*CH*), 5.45 (1H, d, J 9.5 Hz, H-2), [4.55 (1H, dd, J 11.5, 6 Hz), 4.34 (1H, dd, J 11.5, 6 Hz) OCH_2], 4.00 (1H, t, J 9.5 Hz, H-3), 3.76 (1H, dd, J 10, 5.5 Hz, CHOSi), 3.75-3.69 (1H, m, H-6), 3.68-3.55 (1H, m, H-4), 3.60 (1H, dd, J 10, 5 Hz, CHOSi), 2.22 (1H, ddd, J 13.5, 4, 3 Hz, H-5 equatorial), 1.81 (1H, q, J 11.5 Hz, H-5 axial), 0.99 (9H, s, CMe_3); δ_C (62.9 MHz) 156.7 (C-1 SPy), 149.5 (C-5 SPy), 139.9 (*i*-$PhSO_2$), 136.7 (*i*-*Ph*CH=CH), 136.5 (*p*-$PhSO_2$), [135.6, 135.5 (*o*-Ph)], 133.4 (Ph*C*H_2=), [133.1, 133.1 (*i*-Ph)], 132.4 (C-3 SPy), [129.7, 129.7 (*o*-$PhSO_2$, *p*-*Ph*CH=CH)], 129.1 (*p*-Ph), 128.4 (*o*-*Ph*CH=CH), 128.0 (*m*-$PhSO_2$), [127.7, 127.6 (*m*-Ph)], 126.4 (*m*-*Ph*CH=CH), 125.1 (C-4 SPy), 123.2 (C-2 SPy), 120.5 (PhCH=*CH*), 84.9 (C-2), 77.3 (C-4), 75.2 (OCH_2), 72.9 (C-3), [65.9, 65.9 (C-6, CH_2OSi)], 27.8 (C-5), 26.8 (CMe_3), 19.1 (CMe_3); *m/z* (CI) 642 $[M-SPy+NH_4]^+$, 199 $[Ph_2SiOH]^+$, 112 $[PySH+H]^+$, 78 $[PhH]^+$ (Found: $[M-SPy+NH_4]^+$, 642.2709. $C_{42}H_{45}NO_5S_2Si$ requires $[M-HSPy+NH_4]^+$, 642.2710).

Preparation of (*E*)- and (*Z*)-[1*R*,3*S*,5*S*,6*S*]-3-(*tert*-butyldiphenylsilyloxymethyl)-9-benzylidene-5-phenylsulfonyl-2,7-dioxabicyclo[4.3.0]nonane (30).

The ether **29** (890 mg, 1.21 mmol) was added to a mixture of AgOTf (0.83 g, 3.6 mmol, 3 equiv) and activated 4Å molecular sieves in dry CH_2Cl_2 (35 ml) under argon. Whilst stirring at rt an off-white precipitate formed, and after 20 min DBU (0.9 ml, 6 mmol, 5 equiv) was added, turning the solution clear. The reaction was filtered through silica gel, rinsing with ether. Concentration under reduced pressure and chromatography (50% ether–petrol) yielded a mixture of *E*- and *Z*-bicyclic tetrahydrofurans **30** (4:1 by ^{1}H nmr; 543 mg, 74%) as a colourless waxy solid; R_f 0.4 (50% ether–petrol); ν_{max} (film) 2956, 2930, 2857, 1588, 1447, 1307, 1148, 1112, 1087, 911, 730, 703 cm^{-1}; δ_H (500 MHz) 7.94 (1.6H, d, J 7.5 Hz, *o*-PhSO$_2$ *E*), 7.88 (0.4H, d, J 7 Hz, *o*-PhSO$_2$ *Z*), 7.69-7.64 (4H, m, *o*-Ph), 7.57 (0.8H, t, J 8 Hz, *p*- PhSO$_2$ *E*), 7.52 (0.2H, t, J 8 Hz, *p*- PhSO$_2$ *Z*), 7.46-7.34 (8H, *m*-*Ph*CH=, *m*-PhSO$_2$, *m*-Ph), 7.36 (2H, t, J 7.5 Hz, *p*-Ph), 7.27 (0.8H, t, J 7.5 Hz, *p*-*Ph*CH= *E*), 7.24-7.21 (0.2H, m, *p*-*Ph*CH= *Z*), 7.16 (0.4H, d, J 7.5 Hz, *o*-*Ph*CH= *Z*), 7.08 (1.6H, d, J 8 Hz, *o*-*Ph*CH= *E*), 6.49-6.46 (1H, m, Ph*CH*=), 5.04-4.99 (0.8H, m, H-1 *E*), 4.73-4.70 (0.2H, m, H-1 *Z*), 4.58 (1H, br d, J 15 Hz, H-8), 4.46 (1H, d, J 2 Hz, H-6), 4.44 (1H, dd, J 5.5, 2 Hz, H-8), 3.86-3.8 (1H, m, H-3), [3.78 (1H, dd, J 11.5, 5 Hz), 3.69 (1H, dd, J 10, 5 Hz) CH_2OSi], 3.18 (1H, ddd, J 13.5, 9.5, 3.5 Hz, H-5), 2.17-2.11 (1H, m, H-4 equatorial), 1.65 (1H, q, J 10 Hz, H-4 axial), 1.08 (9H, s, CMe_3); *m/z* (CI) 642 $[M+NH_4]^+$, 483 $[M-PhSO_2]^+$, 199 $[Ph_2SiOH]^+$, 78 $[PhH]^+$ (Found: $[M+NH_4]^+$, 642.2741. $C_{37}H_{40}O_5SSi$ requires $[M+NH_4]^+$, 642.2709).

Preparation of [1*S*,3*S*,5*S*,6*S*]-3-(*tert*-butyldiphenylsilyloxymethyl)-9-oxo-5-phenylsulfonyl-2,7-dioxabicyclo[4.3.0]nonane (31).

Through a solution of the *C*-glycoside **30** (22.7 mg, 36 μmol) in CH_2Cl_2 (1 ml) at -78°C was passed ozone (200V, 15 l h^{-1}). After 10 min, oxygen was bubbled through the solution during warming to rt. Triphenylphosphine (9.5 mg, 36 μmol, 1 equiv) was added and the solution stirred at rt for 16 h. Concentration under reduced pressure and chromatography (50-80% ether–petrol) yielded the intermediate ketone (15.8 mg, 79%) as a colourless waxy solid; R_f 0.7 (80% ether–petrol); ν_{max} (film) 2956, 2930, 2857, 1773, 1447, 1428, 1307, 1192, 1112, 1000, 738 cm^{-1}; δ_H (500 MHz) 7.94 (2H, dd, J 8, 1 Hz *o*-PhSO$_2$), 7.69 (1H, t, J 6.5 Hz, *p*-PhSO$_2$), 7.73-7.68 (6H, m, *o*-phen, *p*-Ph), 7.46-7.42 (2H, m, *m*-PhSO$_2$), 7.40-7.36 (4H, m, *m*-Ph), 4.79 (1H, dd, J 9.5, 8.5 Hz, H-6), 4.59 (1H, d, J 8 Hz, H-1), 3.95 (1H, dd, J 18, 1 Hz, H-8), 3.75 (1H, dd, J 10.5, 4 Hz, CHOSi), 3.65 (1H, d, J 18 Hz, H-8), 3.62 (1H, dd, J 10.5, 5.5 Hz, CHOSi), 3.57-3.51 (1H, m, H-3), 3.20 (1H, ddd, J 13.5, 9.5, 4 Hz, H-5), 2.24 (1H, ddd, J 13.5, 4, 2 Hz, H-4 equatorial), 1.66 (1H, dt, J 13.5, 11.5 Hz, H-4 axial), 1.03 (9H, s, CMe_3); *m/z* (CI) 584 $[M+H_2O+NH_4]^+$, 568 $[M+NH_4]^+$, 493 $[M-CMe_3]^+$, 473 $[M-Ph]^+$, 199 $[PhSiOH]^+$ (Found: $[M+NH_4]^+$, 568.2192. $C_{30}H_{34}O_6SSi$ requires $[M+NH_4]^+$, 568.2189). To a solution of the ketone (15.3 mg, 28 μmol) in dry methanol (0.5 ml) under an atmosphere of argon with stirring at 0°C was added $NaBH_4$ (3.8 mg, 84 μmol, 3 equiv) causing effervescence. After 1 h the reaction was diluted in a 1:1 mixture of ether–saturated aqueous NH_4Cl (3 ml). The aqueous phase was extracted with ether (3 x 10 ml), and the combined organic phases washed with brine (10 ml). Drying ($MgSO_4$), concentration under reduced pressure and chromatography (80% ether–petrol) yielded the alcohol **31** (11.3 mg, 74%) as a colourless waxy solid; R_f 0.5 (80% ether–petrol); $[\alpha]_D^{25}$ -33.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3462, 2955, 2925, 2854, 1447, 1306, 1148, 1086, 825 cm^{-1}; δ_H (500 MHz) 7.92 (2H, d, J 8.5 Hz, *o*-PhSO$_2$), 7.68-7.60 (5H, m, *p*-PhSO$_2$, *o*-Ph), 7.56 (2H, t, J 8 Hz, *m*-PhSO$_2$), 7.46-7.42 (2H, m, *p*-Ph), 7.42-7.38 (4H, m, *m*-Ph), 4.30 (1H, dd, J 7.5, 4.5 Hz, H-6), 4.26-4.2 (1H, m, H-9), 4.21-4.17 (1H, m, H-1), 4.12-4.06 (1H, m, H-3), 3.75-3.68 (2H, m, H-8, CHOSi), 3.65 (1H, dd, J 11, 5 Hz, CHOSi), 3.56 (1H, dd, J 9.5, 6 Hz, H-8), 3.32 (1H, ddd, J 13.5, 7.5, 3.5 Hz, H-5), 2.55 (1H, br d, J 5.5 Hz, OH), 2.14 (1H, ddd, J 13.5, 5.5, 3.5 Hz, H-4 equatorial), 1.77 (1H, td, J 13.5, 11.5 Hz, H-4 axial), 1.03 (9H, s, CMe_3); δ_C (62.9 MHz) 138.0 (*i*-PhSO$_2$), [135.6, 135.6 (*o*-Ph)], 133.9 (*p*-PhSO$_2$), (132.9, *i*-Ph), 129.9 (*p*-Ph), [129.1, 128.9 (*o*, *m*-PhSO$_2$)], 127.8 (*m*-Ph), 76.1 (C-5), 73.4 (C-6), 72.6 (C-1), 72.3 (C-8), 71.6 (C-9), 65.7 (C-3), 62.8 (CH_2OSi), 30.3 (C-4), 26.8 (CMe_3), 19.2 (CMe_3); *m/z* (CI) 570 $[M+NH_4]^+$, 493 $[M-Ph+NH_4]^+$, 475 $[M-Ph]^+$, 160 $[PhSO_2H+NH_4]^+$, 94 $[Ph+NH_4]^+$ (Found: $[M+NH_4]^+$, 570.2355. $C_{30}H_{36}O_6SSi$ requires $[M+NH_4]^+$, 570.2345).

Preparation of [4*S*,6*S*,1'*R*]-2-(*tert*-butyldiphenylsilyloxymethyl)-6-(1,2-dihydroxyethyl)-3,6-dihydro-2*H*-pyran (32).

To a solution of the alcohol **31** (406 mg, 0.74 mmol) and Na_2HPO_4 (170 mg, 0.93 mmol, 1.25 equiv) in methanol (3 ml) under an atmosphere of argon at 0°C with stirring was added 6% Na(Hg) (70 mg, 3 mmol, 4 equiv). After 0.5 h a further portion of 6% Na(Hg) (140 mg, 6 mmol, 8 equiv) was added. After a further 15 min a further portion of 6% Na(Hg) (8 equiv) was added, and after a further 15 min the reaction was quenched with brine (5 ml). The reaction mixture was decanted from the mercury layer and the aqueous phase extracted with ether (3 x 10 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80→100% ether–petrol) yielded the alkene **32** (211 mg, 70%) as a colourless oil; R_f 0.45 (ether); $[\alpha]_D^{25}$ -9.1 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3405 2929, 2857, 1428, 1188, 1112, 1042, 824, 741, 703 cm^{-1}; δ_H (500 MHz) 7.68-7.64 (4H, m, *m*-Ph), 7.46-7.37 (6H, m, *o*-phen, *p*-Ph), 5.93 (1H, ddt, J 10.5, 4.5, 2.5 Hz, H-5), 5.87 (1H, dt, J 12, 2.5 Hz, H-4), 4.17-4.12 (1H, m, H-2), 3.89 (1H, ddd, J 12, 7.5, 4.5 Hz, H-6), 3.81-3.7 (3H, H-1', H-2'), 3.71 (1H, dd, J 10.5, 7 Hz, CHOSi), 3.59 (1H, dd, J 10.5, 5 Hz, CHOSi), 2.30 (1H, br s, OH-2'), 2.22 (1H, br d, J 5 Hz, OH-1'), 2.19-2.13 (1H, m, H-3 equatorial), 1.97-1.89 (1H, m, H-3 axial), 1.06 (9H, s, CMe_3); δ_C (62.9 MHz) 135.6 (*m*-Ph), 133.3 (*i*-Ph), 129.7 (*p*-Ph), 127.7 (*o*-Ph), [126.2, 125.1 (C-5, C-4)], [73.4, 73.3, 70.8 (C-6, CHOH, CH_2OH)], [66.0, 64.6 (C-2, CH_2OSi)], 26.8 (CMe_3), 26.3 (C-3), 19.2 (CMe_3); *m/z* (EI) 430 $[M+NH_4]^+$, 352 $[M-PhH+NH_4]^+$, 335 $[M-Ph]^+$, 317 $[M-PhH-OH]^+$, 257 $[Ph_2CMe_3SiOH_2]^+$ (Found: $[M+NH_4]^+$, 430.2447. $C_{24}H_{32}O_4Si$ requires $[M+NH_4]^+$, 430.2414).

Preparation of [2*R*,3*R*,4*R*,6*S*,1'*R*] and [2*R*,3*S*,4*S*,6*S*,1'*R*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydroxy-2-(1,2-dihydroxyethyl)tetrahydro-2*H*-pyran (33) and (35).

To a stirred solution of the alkene **32** (210 mg, 0.51 mmol) in acetone–water (9:1; 2.5 ml) under an atmosphere of argon was added *N*-methylmorpholine-*N*-oxide (90 mg, 0.76 mmol, 1.5 equiv) and OsO_4 (2.6 mg, 10 μmol, 2 mol %). After 30 h the solution was concentrated under reduced pressure. Chromatography of the residue (10% ethanol–ether) yielded a mixture of tetraols **35** and **33** (5:2 by ^1H nmr; 196 mg, 86%) as a colourless solid. Further chromatography (5→10% ethanol–ether) allowed separation of a small sample of each tetraol; [2*R*,3*S*,4*S*,6*S*,1'*R*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydroxy-2-(1,2-dihydroxyethyl)-tetrahydro-2*H*-pyran **35**; R_f 0.15 (6% methanol–ether); mp 107°C dec.; $[\alpha]_D^{25}$ -8.1 (*c* 1.7, $CHCl_3$); ν_{max} (film) 3383, 2927, 2856, 1463, 1428, 1378, 1112, 1083, 1039, 739 cm^{-1}; δ_H (500 MHz) 7.68-7.64 (4H, m, *m*-Ph), 7.46-7.37 (6H, m, *o*-phen, *p*-Ph), 4.37 (1H, br s, OH), 4.14 (1H, br s, OH), 3.98-3.84 (2H, m, H-2, H-4), 3.78 (2H, br s, H-2'), 3.73-3.62 (4H, m, H-6, H-1', CH_2OSi), 3.54 (1H, dd, J 6, 2 Hz, H-3), 1.78-1.72 (1H, m, H-5), 1.69-1.51 (1H, m, H-5), 1.05 (9H, s, CMe_3); δ_C (62.9 MHz) 135.6 (*m*-Ph), [133.2, 133.2 (*i*-Ph)], 129.8 (*p*-Ph), 127.8 (*o*-Ph), [73.9, 72.4, 70.9, 68.5, 66.0, 65.9, 63.7, (C-2, C-4, C-5, C-6, CH_2OSi, C-1', C-2')], 39.7 (C-3), 26.8 (CMe_3), 19.1 (CMe_3); *m/z* (EI) 464 $[M+NH_4]^+$, 256 $[Ph_2CMe_3SiOH]^+$, 94 $[PhH+NH_4]^+$ (Found: $[M+NH_4]^+$, 464.2521. $C_{24}H_{34}O_6Si$ requires $[M+NH_4]^+$, 464.2468); [2*R*,3*R*,4*R*,6*S*,1'*R*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydroxy-2-(1,2-dihydroxyethyl)tetrahydro-2*H*-pyran **33**; R_f 0.12 (6% methanol–ether); mp 88-92°C; $[\alpha]_D^{25}$ -16.1 (*c* 0.61, $CHCl_3$); ν_{max} (film) 3396, 2927, 2856, 1463, 1428, 1112, 1039, 824, 739, 703 cm^{-1}; δ_H (500 MHz) 7.68-7.64 (4H, m, *m*-Ph), 7.46-7.37 (6H, m, *o*-phen, *p*-Ph), 4.09-3.98 (1H, m, H-6), 3.99 (1H, s, H-3), 3.96-3.88 (3H, m, H-2, CH_2OSi), 3.71 (1H, m, H-4, H-1'), 3.59-3.54 (2H, m, H-2'), 1.93-1.86 (1H, m, H-3), 1.69-1.62 (1H, m, H-3), 1.05 (9H, s, CMe_3); δ_C (62.9 MHz) [135.6, 135.6 (*m*-Ph)], 133.0 (*i*-Ph), 129.9 (*p*-Ph), 127.8 (*o*-Ph), [70.6, 67.8, 66.9, 66.2, 64.6, 63.7, (C-2, C-4, C-5, C-6, C-1', C-2')], 55.4 (CH_2OSi), 29.3 (C-3), 26.8 (CMe_3), 19.1 (CMe_3); *m/z* (EI) 464 $[M+NH_4]^+$, 256 $[Ph_2CMe_3SiOH]^+$, 94 $[PhH+NH_4]^+$ (Found: $[M+NH_4]^+$, 464.2505. $C_{24}H_{34}O_6Si$ requires $[M+NH_4]^+$, 464.2468).

Preparation of [2*R*,3*S*,4*R*,6*S*,1'*R*] and [2*R*,3*R*,4*S*,6*S*,1'*R*]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-isopropylidenedioxy-2-[(1,2-isopropylidenedioxy)ethyl]tetrahydro-2*H*-pyran (34) and (36).

To a mixture of tetraols **33** and **35** (57 mg, 0.13 mmol) in dry acetone (2 ml) containing half a drop (*ca.* 2 μmol) of concentrated sulfuric acid was added anhydrous $CuSO_4$ (48 mg, 0.13 mmol, 1 equiv) with stirring.

After 15 min the reaction was quenched with aqueous $NaHCO_3$ (5 ml) and the aqueous phase extracted with ether (3 x 5 ml). Concentration under reduced pressure and chromatography (10→20% ether–petrol) yielded, in order of elution **34** (14.4 mg, 21%) and **36** (37.2 mg, 55%) as colourless oils; [2*R*,3*S*,4*R*,6*S*,1'*R*]-3,4:1',2'-diisopropylidene-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydroxy-2-(1,2-dihydroxyethyl)tetrahydro-2*H*-pyran **36**; R_f 0.2 (20% ether–petrol); $[\alpha]_D^{25}$ +23.9 (*c* 1.5, CH_2Cl_2); ν_{max} (film) 2957, 2932, 2860, 1463, 1428, 1368, 1218, 1112, 1065, 824, 740, 704 cm^{-1}; δ_H (500 MHz) [7.67 (2H, dd, J 8, 1.5 Hz), 7.63 (2H, dd, J 8, 1.5 Hz) *m*-phen], 7.44-7.35 (6H, m, *o*-phen, *p*-Ph), 4.62 (1H, dt, J 8, 2.5 Hz, H-4), 4.37 (1H, dd, J 8, 1.5 Hz, H-3), 4.21-4.17 (1H, m, H-1'), 4.09 (1H, dd, J 8.5, 6 Hz, H-2'), 4.1-4.04 (1H, m, H-6), 4.02 (1H, dd, J 8.5, 4.5 Hz, H-2'), 3.77 (1H, dd, J 10.5, 4.5 Hz, CHOSi), 3.59-3.54 (2H, m, CHOSi, H-1), 2.03 (1H, ddd, J 14.5, 12, 2.5 Hz, H-5 axial), 1.89 (1H, ddd, J 15, 4.5, 3 Hz, H-5 equatorial), [1.49 (3H, s), 1.39 (3H, s), 1.39 (3H, s), 1.36 (3H, s) Me], 1.06 (9H, s, CMe_3); δ_C (62.9 MHz) [135.6, 135.6 (*m*-Ph)], [133.4, 133.0 (*i*-Ph)], 129.7 (*p*-Ph), 127.7 (*o*-Ph), [109.2, 108.7 Me_2C], [74.3, 72.3, 72.4, 70.4, 69.0, 67.4, 65.9, (C-2, C-3, C-4, C-6, CH_2OSi, C-1', C-2')], 27.0 (C-5), 26.8 (CMe_3), [26.7, 26.2, 25.3, 24.5 CMe_2], 19.2 (CMe_3); *m/z* (EI) 544 $[M+NH_4]^+$, 469 $[M-CMe_3]^+$, 449 $[M-Ph]^+$ (Found: $[M+NH_4]^+$, 544.3057. $C_{30}H_{42}O_6Si$ requires $[M+NH_4]^+$, 544.3094); [2*R*,3*R*,4*S*,6*S*,1*R*]-3,4:1',2'-diisopropylidene-6-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydroxy-2-(1,2-dihydroxyethyl)tetrahydro-2*H*-pyran **34**; R_f 0.15 (20% ether–petrol); $[\alpha]_D^{25}$ -10.5 (*c* 0.8, $CHCl_3$); ν_{max} (film) 2957, 2932, 2860, 1461, 1428, 1371, 1217, 1112, 1066, 824, 741, 704 cm^{-1}; δ_H (270 MHz) 7.78 (4H, dd, J 9, 1.5 Hz, *m*-Ph), 7.56-7.42 (4H, m, *o*-Ph), 7.37-7.21 (2H, m, *p*-Ph), 4.46-4.40 (1H, m, H-4), 4.40-4.26 (2H, m, H-1', H-6), 4.13-4.02 (2H, m, H-3, H-2'), 3.86-3.72 (4H, m, H-2', H-2, CH_2OSi), 2.11 (1H, ddd, J 12.5, 6, 5 Hz, H-5 equatorial), 1.89 (1H, dt, J 15, 9 Hz, H-5 axial), [1.53 (3H, s), 1.52 (3H, s), 1.45 (3H, s), 1.42 (3H, s) Me], 1.09 (9H, s, CMe_3); δ_C (62.9 MHz) 135.6 (*m*-Ph), 133.4, (*i*-Ph), 129.7 (*p*-Ph), 127.7 (*o*-Ph), [109.8, 108.7 (CMe_2)], [76.6, 72.9, 71.9, 71.4, 66.0, (C-2, C-3, C-4, C-6, CH_2OSi, C-1', C-2')], 29.3 (C-5), 27.8 (CMe_3), [27.9, 26.4, 25.7, 25.5 (CMe_2)], 19.2 (CMe_3); *m/z* (EI) 544 $[M+NH_4]^+$, 469 $[M-CMe_3]^+$, 449 $[M-Ph]^+$ (Found: $[M+NH_4]^+$, 544.3045. $C_{30}H_{42}O_6Si$ requires $[M+NH_4]^+$, 544.3094).

Preparation of [2*R*,3*S*,4*R*,6*S*,1'*R*]-3,4-isopropylidenedioxy-2-[(1,2-isopropylidenedioxy)ethyl]-tetrahydro-2*H*-pyran-6-carboxylic acid (37).

To a stirred solution of the diacetonide **34** (41.3 mg, 78 μmol) in THF (1 ml) at rt, was added TBAF (0.19 ml of a 1M solution in THF, 0.19 mmol, 2.4 equiv) turning the solution yellow. After 30 min the reaction was quenched by the addition of brine (1.5 ml). The aqueous phase was extracted with ether (3 x 5 ml). The combined organic fractions were dried ($MgSO_4$), concentrated under reduced pressure and chromatographically separated (ether) to yield the expected primary alcohol (18.6 mg, 82%) as a colourless waxy solid; R_f 0.2 (ether); $[\alpha]_D^{25}$ +38.3 (*c* 2, $CHCl_3$); ν_{max} (film) 3466, 2986, 2933, 1372, 1212, 1165, 1121, 1070, 998, 847 cm^{-1}; δ_H (270 MHz) 4.57 (1H, dt, J 8, 2.5 Hz, H-4), 4.34 (1H, dd, J 8, 1.5 Hz, H-3), 4.27-4.19 (1H, m, H-1'), 4.18-4.03 (2H, m, H-6, H-2'), 4.00 (1H, dd, J 8.5, 4 Hz, H-2'), 3.62 (1H, dd, J 11.5, 3 Hz, CHOSi), 3.54-3.47 (2H, m, CHOSi, H-2), 2.04 (1H, br s, OH), 1.88-1.74 (2H, m, H-5), [1.49 (3H, s), 1.41 (3H, s), 1.36 (3H, s), 1.35 (3H, s) Me]; δ_C (100.6 MHz) [109.1, 108.8, CMe_2], [74.5, 72.6, 71.4, 70.1, 69.1, 66.8, 65.6, (C-2, C-3, C-4, C-6, CH_2OSi, C-1', C-2')], 28.9 (C-5), [27.8, 26.1, 25.2, 24.4 (CMe_2)]; *m/z* (EI) 306 $[M+NH_4]^+$, 289 $[M+H]^+$, 273 $[M-OH]^+$, 231 $[M-Me_2CO+H]^+$, 173 $[M-2Me_2CO+H]^+$, 101 $[C_5H_9O_2]^+$ (Found: $[M+H]^+$, 289.1637. $C_{14}H_{25}O_6$ requires $[M+H]^+$, 289.1651). The alcohol (11.1 mg, 39 μmol) was dissolved in CCl_4–MeCN–H_2O (2:2:3; 0.7 ml) and stirred rapidly at rt. $NaIO_4$ (19 mg, 0.12 mmol, 3 equiv) and $RuO_2 \cdot H_2O$ (0.9 mg, 7 μmol, 0.2 equiv) were added. After 0.5 h the reaction was quenched by the addition of brine (1 ml). The aqueous layer was acidified with a drop of AcOH and extracted with EtOAc (3 x 10 ml). The combined organic fractions were dried ($MgSO_4$). Concentration under reduced pressure and chromatography (0→10% methanol–EtOAc) yielded the acid **37** (7.9 mg, 68%) as a colourless solid; R_f 0.3 (10% methanol–EtOAc); $[\alpha]_D^{25}$ +38 (*c* 2, CH_2Cl_2); ν_{max} (film) 3463, 2986, 2926, 1372, 2854, 1729, 1378, 1246, 1164, 1067, cm^{-1}; δ_H (270 MHz) 4.62-4.48 (2H, m, H-6, H-1'), 4.29 (1H, d, J 8 Hz, H-4), 4.24-4.18 (2H, m, H-2'), 4.10-4.05 (1H, m, H-3), 3.62-3.59 (1H, m, H-2), 2.41-2.33 (1H, m, H-5), 1.92-1.86 (1H, m, H-5), [1.47 (3H, s), 1.42 (3H, s), 1.36 (3H, s), 1.25 (3H, s) Me]; δ_C (100.6 MHz) [109.3, 108.2 (CMe_2)], [77.2, 74.2, 72.1, 72.0, 69.9, 66.3, (C-2,

C-3, C-4, C-6, C-1', C-2')], 29.7 (C-5), [26.8, 26.1, 25.1, 24.7 (*CMe*$_2$)]; *m/z* (EI) 320 [M+NH$_4$]$^+$, 303 [M+H]$^+$, 287 [M-OH]$^+$, 259 [M-CO$_2$+H]$^+$, 245 [M-Me$_2$CO+H]$^+$, 101 [C$_5$H$_9$O$_2$]$^+$ (Found: [M+NH$_4$]$^+$, 320.1725. C$_{14}$H$_{22}$O$_7$ requires [M+NH$_4$]$^+$, 320.1709).

Preparation of [2*R*,3*S*,4*R*,6*S*,1'*R*]-3,4-isopropylidenedioxy-2-[(1,2-isopropylidenedioxy)ethyl]tetrahydro-2*H*-pyran-6-carboxylic acid (2-deoxy-β-KDO; 17).

The acid **37** (7.9 mg, 26 μmol) was dissolved in TFA–H$_2$O (9:1; 1 ml) and stirred for 1 h. The reaction mixture was neutralised with aqueous NH$_4$OH (5 ml). The water was azeotropically removed yielding the crude acid **17** as a colourless solid; R$_f$ 0.1 (20% methanol–EtOAc); δ_H (270 MHz) 4.32 (1H, d, J 6.5 Hz, H-6), 3.97 (1H, s, H-3), 3.84-3.78 (2H, m, H-1', H-2'), 3.77-3.69 (2H, m, H-4, H-2'), 3.54-3.49 (1H, m, H-2), 2.22-2.16 (1H, m, H-5), 2.04-1.95 (1H, m, H-5); *m/z* (FAB) 245 [M+Na]$^+$.

Preparation of methyl [2*R*, 3*S*,4*R*,6*S*,1'*R*]-3,4-isopropylidenedioxy-2-[(1,2-isopropylidenedioxy)ethyl]tetrahydro-2*H*-pyran-6-carboxylate (38).

To a solution of the crude acid **17** in 2-(2-ethoxyethoxy)ethanol (2 ml) was added, dropwise with stirring a solution of diazomethane in ether until effervescence ceased. The solution was concentrated under reduced pressure and diluted in acetone (dried by passing through a column of K$_2$CO$_3$; 15 ml) containing 5 drops of concentrated sulfuric acid (*ca.* 25 μl). Anhydrous CuSO$_4$ (40 mg, 0.25 mmol) was added and the reaction was stirred under an atmosphere of argon at rt. After 30 min the reaction was quenched with saturated aqueous NaHCO$_3$ (2 ml) and the organic phase was dried (MgSO$_4$). Concentration under reduced pressure and chromatography (25→50% ether–petrol) yielded the ester **38** (3.5 mg, 42% from acid **37**) as a colourless solid; R$_f$ 0.3 (30% ether–petrol); ν_{max} (film) 2986, 2934, 1753, 1380, 1263, 1246, 1164, 1069, 846 cm^{-1}; δ_H (500 MHz) 4.59 (1H, dt, J 8, 3 Hz, H-4), 4.55 (1H, dd, J 11.5, 6 Hz, H-6), 4.34 (1H, dd, J 8, 1.5 Hz, H-3), 4.23-4.20 (2H, m, H-1', H-2'), 4.12-4.09 (1H, m,. H-2'), 3.75 (3H, s, Me), 3.51-3.45 (1H, m, H-2), 2.30 (1H, ddd, J 15, 6, 3.5 Hz, H-5 equatorial), 1.86 (1H, ddd, J 14.5, 11.5, 2.5 Hz, H-5 axial), [1.49 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.36 (3H, s) Me]; δ_C (100.6 MHz) 173.4 (COOH), [109.4, 109.330 (*C*Me$_2$)], 73.7 (C-1'), 72.8 (C-2), 72.2 (C-3), 69.7 (C-4), 68.3 (C-6), 67.2, (C-2'), 52.0 (OMe), 26.7 (C-5), [27.0, 26.2, 25.1, 24.9 (*CMe*$_2$)]; *m/z* (EI) 334 [M+NH$_4$]$^+$, 317 [M+H]$^+$, 101 [C$_5$H$_9$O$_2$]$^+$ (Found: [M+H]$^+$, 317.1583. C$_{15}$H$_{24}$O$_7$ requires [M+H]$^+$, 317.1600).

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