A highly enantioselective total synthesis of (+)-goniodiol

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A high-yielding enantioselective total synthesis of the bioactive styryllactone (+)-goniodiol has been realised, starting from readily available (*S*)-glycidol. A key step is an oxygen-to-carbon rearrangement of a silyl enol ether linked *via* an anomeric centre, facilitating the rapid and diastereoselective construction of this functionalised system.

Introduction

Studies on natural products isolated from Asian trees of the genus *Goniothalamus* have led to the discovery of several classes of compounds with interesting biological properties, including acetogenins,[1–3] alkaloids[4] and styryllactones.[5,6] (+)-Goniodiol **1**, a styryllactone, (Fig. 1) was isolated in 1985 from petroleum ether extracts of the leaves and twigs of *Goniothalamus sesquipedalis*.[7] More recently, it has been shown by McLaughlin *et al.* to have potent and selective cytotoxic activity against A-549 human lung carcinoma,[8] and closely related bioactive derivatives have been found in a number of other *Goniothalamus* species.[9–11] For example, goniodiol 7-monoacetate isolated from *G. amuyon* in 1991 by Wu *et al.* has potent activity against leukaemia, human melanoma, and CNS carcinoma, though interestingly not against lung carcinoma.[12] The biosynthesis of the styryllactones has been proposed to incorporate a phenylpropanyl moiety in the processive polyketide assembly sequence.[13]

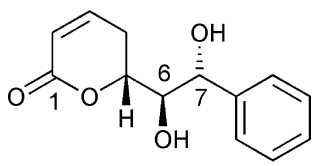

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Fig. 1 (+)-Goniodiol, showing the conventional numbering of the carbon skeleton.

(+)-Goniodiol and its congeners have excited considerable interest amongst synthetic organic chemists—they are relatively small and densely functionalised molecules, making them ideal targets for testing new synthetic methodology. Furthermore, their interesting and varied bioactivity makes them potential drug leads and chemical genetic research tools.[14] The six major routes reported to date towards (+)-goniodiol and its congeners have exemplified the use of the following key synthetic methodologies: generation of oxygenated lactones *via* furan oxidation;[15] glycoside-templated synthesis;[16–19] chiral induction *via* enantiopure chromium aryl complexes;[20,21] anomeric oxygen-to-carbon rearrangements;[22] enantioselective enzymatic oxidation of naphthalene derivatives;[23,24] and ring-closing metathesis.[25–27]

We have developed a general method for the introduction of carbon linked substituents adjacent to the heteroatom in pyranyl and furanyl ring systems *via* Lewis acid mediated oxygen-to-carbon rearrangements of a variety of different anomerically linked carbon centred nucleophiles.[28–35] Anomeric oxygen-to-carbon rearrangement has proved a useful methodology in our recent total syntheses of members of several natural product classes, including the annonaceous acetogenins.[36–38] (+)-Goniodiol represents an excellent target to further test the scope of the method, and we have previously communicated our preliminary results from this total synthesis.[39] Here we report in full our enantioselective total synthesis of compound **1**.

The approach utilises as a key step the rearrangement of an anomerically linked silyl enol ether nucleophile to introduce the 5,6,7-oxygenation pattern and the phenyl ring present in (+)-goniodiol. This strategy represents a significant departure from previously reported routes, each of which focus on ring closure and homologation methodology rather than exploiting the chemistry of an anomeric centre. Key stages in our retrosynthetic analysis of (+)-goniodiol are shown in Scheme 1. The overall strategy is convergent, with a fragment containing what will become the right-hand portion of (+)-goniodiol introduced directly onto a ring system with sufficient functionality to allow subsequent conversion to the oxygenated lactone. This concise route requires control of the *cis*/*trans* selectivity about a THP ring system bearing a stereochemical handle that acts as a latent lactone functionality at C-1. A protected oxymethyl functionality is ideal for this purpose—the bulk of the protecting group provides *trans*-stereocontrol in the rearrangement, and its oxidative degradation can provide a lactol or lactone suitable for elaboration to the natural product. Other noteworthy features include generation of the rearrangement substrate from a readily available starting material, and selective reduction of a hydroxyketone to the C-6, C-7 diol.

Results and discussion

The synthesis commences from commercially available *S*-(−)-glycidol (Scheme 2). Treatment with *tert*-butyldiphenylsilyl-chloride, triethylamine and DMAP gave the protected alcohol

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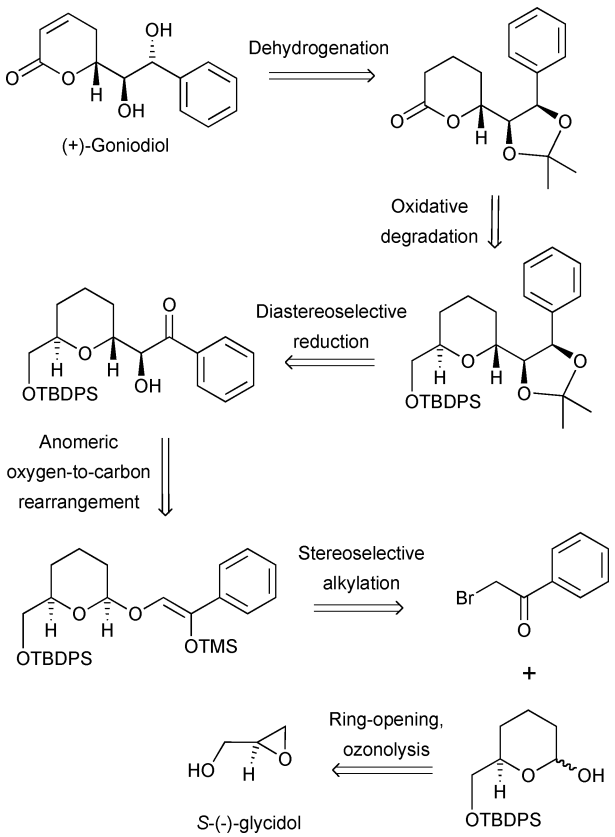
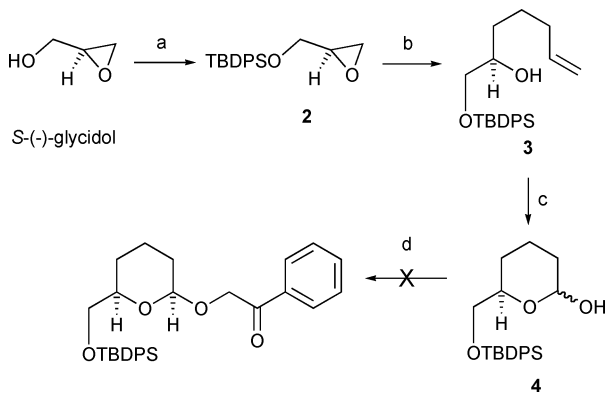


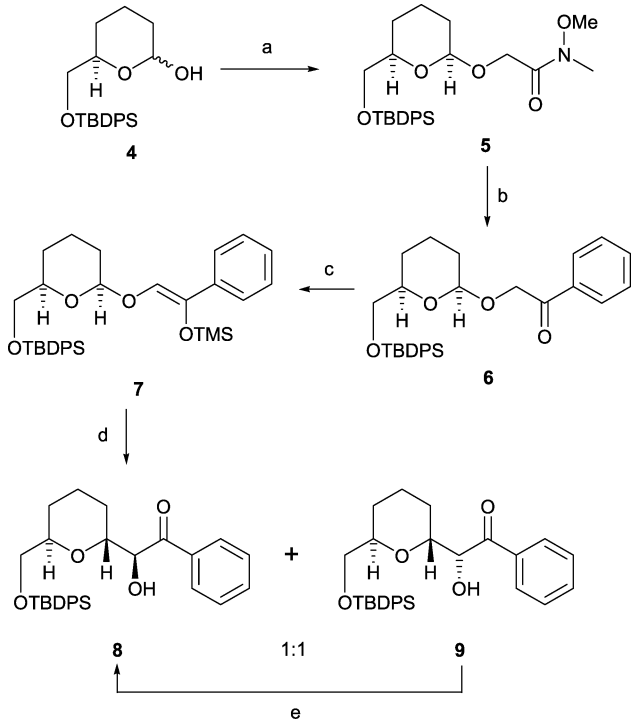
Scheme 1 Key stages in the retrosynthetic analysis of (+)-goniodiol.



Scheme 2 *Reagents and conditions*: (a) TBDPSCl, DMAP, triethylamine, CH_2Cl_2, r.t., 3d (86%); (b) 1.2 eq. $CH_2{=}CH(CH_2)_2MgBr$, 0.1 eq. Li_2CuCl_4, THF, −30 °C (100%); (c) O_3, CH_2Cl_2, −78 °C, then PPh_3, r.t. (100%); (d) base, bromoacetophenone.

2 in 86% yield, to which the subsequent addition of but-3-enylmagnesium bromide in the presence of catalytic dilithium copper(II) chloride[40] proceeded with exclusive attack at the less substituted end of the epoxide, to afford the corresponding alkenol **3** in quantitative yield. Ozonolysis of this material followed by reductive work-up afforded lactol **4** in 100% yield. Unfortunately however, all attempts to alkylate the anion of **4** with bromoacetophenone in order to furnish the requisite anomerically linked ketone resulted in degradation; evidently the acidity of the α-protons in bromoacetophenone is such that they are deprotonated by the lactol alkoxide.

We therefore adopted a two step solution to the problem: alkylation with α-bromo *N*,*N*-methylmethoxy acetamide in the presence of KHMDS afforded 81% yield of the exclusively *cis* anomerically-linked Weinreb amide **5** (Scheme 3). This interesting and remarkable stereoselectivity has been further developed for the generation of chiral water equivalents.[41–43] Subsequent treatment with phenylmagnesium bromide in THF at −30 °C then led to the phenyl ketone **6** in 97% yield,[44] which was converted into a single trimethylsilyl (TMS) enol ether **7** on exposure to TMSOTf (1.2 eq.) and triethylamine (1.4 eq.) at −30 °C. TMS enol ether **7** was assigned *cis*/*Z* stereochemistry by analogy to our previous work on anomerically linked silyl enol ethers.[45]



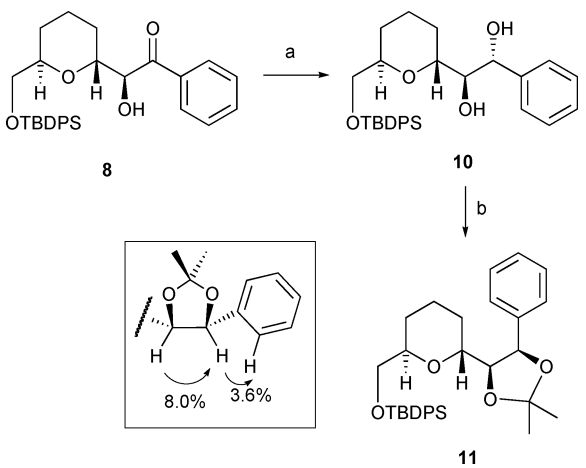
Scheme 3 *Reagents and conditions*: (a) KHMDS, THF, −78 °C then 2-bromo-*N*-methoxy-*N*-methylacetamide (81% + 16% unreacted **4**); (b) PhMgBr, THF, −30 °C (97%); (c) 1.2 eq. TMSOTf, 1.4 eq. Et_3N, CH_2Cl_2, −78 °C to −30 °C; (d) 0.1 eq. TMSOTf, CH_2Cl_2, −30 °C (85% over two steps); (e) (i) THF, PPh_3, DEAD, AcOH, 0 °C; (ii) NaOMe, MeOH (69% over two steps).

On exposure to catalytic TMSOTf at −30 °C **7** was smoothly converted to a separable mixture of the exclusively *trans* α-hydroxy ketones **8** and **9** (**8** : **9** = 1 : 1) in 85% overall combined yield from **6**.† The relative conformation of **8** and **9** was assigned by analogy to the NMR spectra of related isomers from our previous study where the configuration was unambiguously demonstrated by X-ray crystallography methods; this preliminary assignment was later proven correct upon completion of the total synthesis. In light of our previous work where we had observed C-6 diastereomeric ratios of up to 3 : 1 in favour of the desired *erythro*-isomer, it was both surprising and disappointing to find that in the present case no control was observed at the C-6 alcohol.[45]

† Attempts to perform this reaction with a *tert*-butyldimethylsilyl (TBS) group on the oxymethyl substituent met with concurrent deprotection.

Attempts to improve the selectivity at this position by changing the silicon protecting group on the pendent hydroxylmethyl group and enol ether substituent (TES, TBS) or by varying the Lewis acid (TBSOTf, TESOTf, $SnCl_4$, $BF_3.Et_2O$) were unsuccessful, whilst experiments aimed at improving kinetic control by performing the rearrangement reaction at a lower temperature resulted in decomposition. Given that the equatorially positioned $TBDPSOCH_2$ group is presumably too remote from the α-hydroxy position to affect the stereochemistry directly, it remains unclear why the change from the alkyl chain used in previous studies to the more bulky TBDPS protected oxymethyl group results in a decrease in selectivity at the hydroxy position α to the ketone. Fortunately, we found that the undesired diastereoisomer **9** could be inverted by acetic acid under Mitsunobu conditions[46] to provide **8** in 69% yield after basic hydrolysis of the intermediate acetate (Scheme 3). The overall yield for **8** including this recovered material was high (77%), and permitted the rapid generation of large quantities of **8** for use in subsequent steps.

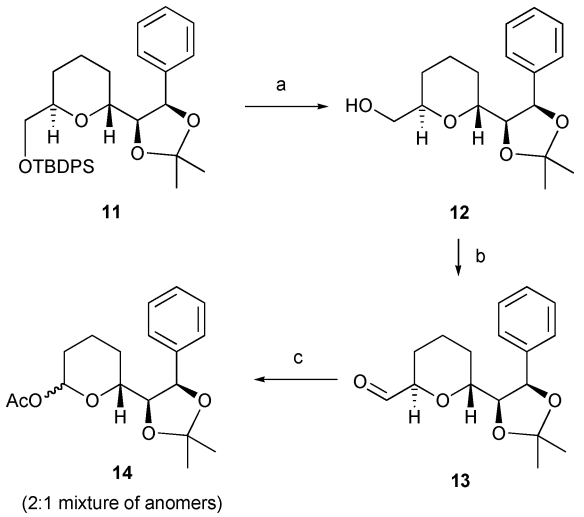
The stereochemistry present at C-7 of (+)-goniodiol was introduced *via* a highly diastereoselective reduction of the ketone moiety of **8** (>95% d.e.) using two equivalents of $NaBH_4$ in MeOH at 0 °C to give diol **10** in quantitative yield (Scheme 4).[47] Subsequent reaction with 2,2-dimethoxypropane in acetone with catalytic camphorsulfonic acid gave the protected diol **11** in 99% yield, and NOE studies on **11** permitted confident assignment of the desired diol stereochemistry.



Scheme 4 *Reagents and conditions*: (a) 2 eq. $NaBH_4$, MeOH, 0 °C (100%); (b) 2,2-dimethoxypropane, acetone, cat. camphorsulfonic acid (99%). The inset figure shows key observed NOE signals used to assign diol stereochemistry.

The sequence to convert the *tert*-butyldiphenylsilyl protected alcohol of **11** into the α,β-unsaturated lactone of the natural product was initiated by treatment with TBAF to release the free alcohol **12** in 99% yield (Scheme 5). We considered two potential strategies for converting **12** to a δ-lactone: oxidation to the acid followed by a radical degradation with concurrent anomeric oxidation or an ionic strategy *via* activation and elimination of the alcohol to form an exo–enol ether, which could be ozonolysed directly to the lactone.

In the event, the former route was selected as there is some literature precedent for such an anomeric oxidative degradation process.[48] Furthermore, it was considered that the enol ether



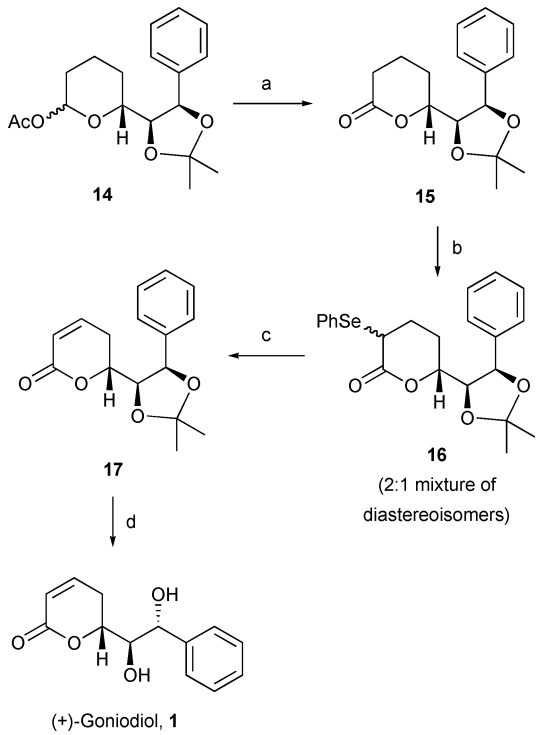
Scheme 5 *Reagents and conditions*: (a) 10% TBAF, THF (99%); (b) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, −78 °C (93%); (c) (i) NaO_2Cl, $KHPO_4$, 2-methyl-2-butene, H_2O/^{t}BuOH (1 : 2); (ii) 2 eq. $Pb(OAc)_4$, 2 eq. pyridine, THF, r.t. (68% over two steps).

formed in the latter route could be unstable, leading to potential problems during ozonolysis. Thus, oxidation of **12** to aldehyde **13** using the Swern protocol[49] in 93% yield, was followed by exposure to NaO_2Cl, $KHPO_4$ and 2-methyl-2-butene in 1 : 2 water/^{t}BuOH[50] to give the corresponding acid, which was used in the following step without further purification (Scheme 5). Exposure to lead tetraacetate[51] in the presence of pyridine in tetrahydrofuran at room temperature afforded the anomeric acetate **14** as a 2 : 1 mixture of anomers. Considering the diverse range of potential fragmentations and alternative couplings available to the radical and ionic intermediates in this reaction, we were pleased to observe the formation of **14** in excellent overall yield from **13**.

Deacetylation of **14** with 0.5 eq. of NaOMe in MeOH was followed by oxidation with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[52] in the presence of *N*-methyl-morpholine *N*-oxide (NMO) to give the lactone **15** in 97% overall yield (Scheme 6). Attempts to introduce the α,β-unsaturation into the lactone system in one step by heating with benzeneselenic anhydride[53] were unsuccessful. However, we found that this transformation could be achieved efficiently in two steps *via* sequential treatment with lithium diisopropylamide and PhSeBr to give an epimeric mixture of selenides **16**, followed by oxidative elimination with H_2O_2 resulting in oxygenated lactone **17** in 82% yield over the two steps.[54] Final deprotection of the C-6, C-7 diol with 50% aqueous acetic acid at 80 °C for 30 minutes gave the natural product (+)-goniodiol **1** in 97% yield. All physical data for the synthetic sample of **1** were in excellent agreement with those reported for the natural product.[7]

Conclusions

The route to (+)-goniodiol described here once again illustrates the utility of anomeric oxygen-to-carbon rearrangements in natural product total synthesis. It provides rapid access to a densely functionalised molecule, starting from a commercially available starting material, which was subsequently converted to the desired product in 21% overall yield. The synthesis described above is likely



Scheme 6 *Reagents and conditions*: (a) (i) 0.5 eq. NaOMe, MeOH; (ii) 5 mol% TPAP, 1.5 eq. NMO, CH_2Cl_2, r.t. (97% over two steps); (b) LDA, THF, −78 °C then 2 eq. PhSeBr; (c) CH_2Cl_2/30% $H_2O_{2(aq)}$ (2 : 1), 0 °C, 10 min (82% over two steps); (d) 50% $AcOH_{(aq)}$, 80 °C, 30 min (97%).

to prove a versatile strategy for the construction of analogues of (+)-goniodiol *via* straightforward variation of the substituent on the ketone used in the rearrangement reaction, and will also allow the synthesis of related families of styryllactones to be approached.

Experimental

General methods

All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven-dried glassware, cooled under vacuum. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone; dichloromethane, methanol and toluene were distilled over calcium hydride. All other solvents and reagents were used as supplied, unless otherwise stated. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh). Analytical thin layer chromatography was performed on glass plates precoated with Merck Kieselgel 60 F254, and visualised under ultraviolet irradiation, or by staining with aqueous acidic ammonium molybdate(IV) or acidic potassium manganate(VII). Melting points were recorded using a Reichert hot stage apparatus, and are uncorrected. Boiling points were obtained during distillation, unless otherwise noted. Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, Lensfield Road, Cambridge. Optical rotations were measured at 29 °C on an Optical Activity AA-1000 polarimeter, and are given in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g per 100 mL. Infrared spectra were obtained on Perkin-Elmer 983G or FTIR 1620 spectrometers, from a thin film deposited onto a sodium chloride plate from dichloromethane. Proton NMR spectra were recorded in $CDCl_3$, on Bruker AC-200, Bruker DPX-200, Bruker AM-400, Bruker DPX-400 or Bruker DPX-600 spectrometers, at 200, 400 or 600 MHz, with residual chloroform as the internal reference (δ_H = 7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on the same spectrometers at 50, 100 or 150 MHz, with the central peak of chloroform as the internal reference (δ_C = 77.0 ppm). Mass spectra and accurate mass data were obtained on a Micromass Platform LC-MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometer, and at the EPSRC Mass Spectrometry Service, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. GC analysis was performed on a Hewlett Packard 5890 Series II Gas Chromatograph [80 °C (10 min) then to 180 °C (at 5 °C min^{-1}), then 10 min at 180 °C]. DEPT135 and two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signals in the proton and ^{13}C NMR spectra.

Syntheses

(*R*)-*tert*-Butyloxiranylmethoxydiphenylsilane (2)[55]. To a stirred solution of *S*-(−)-glycidol (5.0 g, 68.0 mmol) in dichloromethane (150 mL) was added triethylamine (15.1 mL, 109.0 mmol), *tert*-butyldiphenylsilyl chloride (19 mL, 75.0 mmol) and dimethylaminopyridine (2.5 g, 20.4 mmol), and the reaction mixture stirred for 3 days. 1.5 N HCl (100 mL) was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (2 × 100 mL). The combined organics were washed with saturated aqueous bicarbonate solution (150 mL) followed by brine (100 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a slightly yellow oil. Purification by flash column chromatography, eluting with 5% to 10% diethyl ether–petroleum ether (bp 40–60 °C), gave **2** (18.4 g, 86%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, c 2.1) = +2.5; ν_{max} (thin film)/cm^{-1} 3070, 2858, 1589, 1472, 1428, 1390, 1361, 1254; δ_H (400 MHz; $CDCl_3$): 7.75–7.73 (4H, m, Ph), 7.49–7.41 (6H, m, Ph), 3.90 (1H, dd, J 11.8 and 3.1, C*H*HCHCH$_2$OSi), 3.76 (1H, dd, J 11.8 and 4.7, CH*H*CHCH$_2$OSi), 3.18–3.14 (1H, m, C*H*CH$_2$OSi), 2.77 (1H, t, J 4.3, C*H*HOSi), 2.66–2.63 (1H, m, CH*H*OSi), 1.12 (9H, C(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 135.7 (Ph), 135.6 (Ph), 133.3 (Ph, quat.), 129.8 (Ph), 127.8 (Ph), 127.7 (Ph), 64.4 (*C*H$_2$CHCH$_2$OSi), 52.3 (*C*HCH$_2$OSi), 44.4 (*C*H$_2$OSi), 27.0 (C(*C*H$_3$)$_3$), 19.3 (*C*(CH$_3$)$_3$).

(*R*)-1-(*tert*-Butyldiphenylsilanyloxy)-hept-6-en-2-ol (3)[56]. To a stirred solution of **2** (2.0 g, 6.41 mmol) in tetrahydrofuran (10 mL) at −30 °C was added a solution of dilithium tetrachlorocuprate in tetrahydrofuran (0.1 M, 6.41 mL) followed by a solution of butenylmagnesium bromide in tetrahydrofuran (0.5 M, 15.4 mL). After 15 min the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL), distilled water added (10 mL), and the mixture extracted with diethyl ether (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 12% diethyl ether–petroleum ether (bp 40–60 °C) gave the title compound (2.4 g, 100%) as a colourless oil. Found: C, 75.14; H, 8.71%. $C_{23}H_{32}O_2Si$ requires: C, 74.95; H, 8.75%. $[\alpha]_D^{29}$ ($CHCl_3$, c 3.0) = +10.0; ν_{max} (thin film)/cm^{-1} 3565 (br), 3071, 3051, 2931, 2858, 1640, 1589, 1472, 1428, 1261, 1113; δ_H (400 MHz; $CDCl_3$): 7.71–7.69 (4H, m, Ph), 7.48–7.39 (6H, m, Ph), 5.85–5.75 (1H, m,

C*H*CH_2), 5.03–4.94 (2H, m, CHC*H*$_2$), 3.76–3.67 (2H, m, C*H*OH and C*H*HOSi), 3.52 (1H, dd, *J* 10.0 and 7.5, CH*H*OSi), 2.54 (1H, d, *J* 3.3, O*H*), 2.09–2.05 (2H, m, C*H*$_2$), 1.58–1.38 (4H, m, 2 × C*H*$_2$), 1.11 (9H, C(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 138.6 (Ph), 135.6 (Ph), 133.3 (Ph, quat.), 133.2 (Ph, quat.), 129.8 (*C*HCH$_2$), 114.7 (CH*C*H$_2$), 71.8 (*C*HOH), 68.1 (*C*H$_2$O), 33.7 (*C*H$_2$), 32.3 (*C*H$_2$), 26.9 and 26.8 (C(*C*H$_3$)$_3$), 24.8 (*C*H$_2$), 19.3 (*C*(CH$_3$)$_3$); *m*/*z* (EI) 311 (62%, M − C_4H_9), 199 (100%); Found (EI): M − C_4H_9 311.1466. $C_{19}H_{23}O_2Si$ requires 311.1467.

(*R*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-tetrahydropyran-2-ol (4). To a stirred solution of **3** (1.9 g, 5.16 mmol) in dichloromethane (150 mL) at −78 °C was added sodium bicarbonate (0.3 g), and O_3 (1.5 L s^{-1}) bubbled through until the reaction mixture became light blue (about 30 min). Triphenylphosphine (1.65 g, 6.2 mmol) was added to the reaction mixture, which was allowed to warm to ambient temperature and stirred for 16 h. The solvent was removed *in vacuo* to leave a slightly creamy oil which was purified by flash column chromatography, eluting with 10% to 40% diethyl ether–petroleum ether (bp 40–60 °C), to give **4** (1.9 g, 100%), as a 3 : 2 mixture of anomers, as a colourless oil. Found: C, 71.03; H, 8.20%. $C_{22}H_{30}O_3Si$ requires: C, 71.31; H, 8.16%. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 3.0) = −1.5; ν_{max} (thin film)/cm^{-1} 3400 (br), 2930, 2857, 1726, 1461, 1428, 1274, 1113; δ_H (400 MHz; $CDCl_3$): 9.75 (1H of trace tautomeric aldehyde, br s, CH_2CHO), 7.69–7.59 (4H major and minor, m, Ph), 7.44–7.31 (6H major and minor, m, Ph), 5.27 (1H minor, br s, OC*H*O), 4.69–4.64 (1H major, m, OC*H*O), 4.10–4.03 (1H minor, m, C*H*OCHO), 3.80–3.46 (3H major and 2H minor, m, C*H*$_2$OSi major and minor and C*H*OCHO major), 2.88 (1H major, d, *J* 6.0, O*H*), 2.42 (1H minor, d, *J* 1.8, O*H*), 1.89–1.11 (6H major and 6H minor, m, 3 × C*H*$_2$), 1.07 (9H, C(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 135.7 (Ph), 135.6 (Ph), 129.6 (quat. Ph, major and minor), 127.7 (Ph), 127.6 (Ph), 96.3 and 91.8 (*C*HOH, major and minor), 76.8 and 69.4 (*C*HOCHO, major and minor), 67.5 and 67.0 (*C*H$_2$OSi, major and minor), 32.6 and 30.0 (*C*H$_2$ major and minor), 29.1 and 27.9 (*C*H$_2$ major and minor), 27.7 and 27.3 (*C*H$_2$ major and minor), 26.9 (C(*C*H$_3$)$_3$), 22.7 and 19.3 (*C*(CH$_3$)$_3$); *m*/*z* (EI) 313 (7%, M − C_4H_9), 91 (100%). Found (EI) M − C_4H_9 313.1258. $C_{18}H_{21}O_3Si$ requires 313.1260.

(*R*,*R*)-*N*-Methoxy-*N*-methyl-2-(6′-*tert*-butyldiphenylsilanyloxymethylpyranyloxy)-acetamide (5). To a stirred solution of **4** (1.1 g, 3.0 mmol) in tetrahydrofuran (7.0 mL) at −78 °C was added dropwise a solution of potassium hexamethyldisilylamide in toluene (0.5 M, 6.3 mL), and the reaction mixture sucessively warmed to 0 °C and cooled to −78 °C. After the dropwise addition of a solution of freshly distilled 2-bromo-*N*-methoxy-*N*-methylacetamide (0.8 g, 4.5 mmol) in tetrahydrofuran (3.0 mL) the mixture was stirred at −78 °C for 2 h and quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL). Water was added (10 mL), the mixture extracted with diethyl ether (2 × 20 mL), the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a yellow oil. Purification of this oil by flash column chromatography, eluting with 50% to 100% ether–petroleum ether (bp 40–60 °C) isolated unreacted **4** (0.18 g, 16%) and **5** contaminated with unreacted 2-bromo-*N*-methoxy-*N*-methylacetamide. The mixture of **5** and 2-bromo-*N*-methoxy-*N*-methylacetamide was dissolved in dimethyl sulfoxide (7 mL) and treated with NaOAc (1.0 g, 8.0 mmol) at 25 °C for 1 h. The mixture was diluted with diethyl ether (10 mL), washed with water (3 × 10 mL), and the organic layer dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave pure **5** (1.15 g, 81%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 1.6) = +43.8; ν_{max} (thin film)/cm^{-1} 3071, 2940, 1677, 1427, 1390, 1112, 1040; δ_H (400 MHz; $CDCl_3$): 7.70–7.68 (4H, m, Ph), 7.43–7.35 (6H, m, Ph), 4.59–4.47 (3H, m, OC*H*O and OC*H*$_2$CON), 3.78 (1H, dd, *J* 10.0 and 5.7, C*H*HOSi), 3.65–3.58 (5H, m, CH*H*OSi, C*H*OCHO and NC*H*$_3$), 3.16 (3H, s, OC*H*$_3$), 2.02–1.85 (2H, m, C*H*$_2$), 1.62–1.42 (3H, m, C*H*H and C*H*$_2$), 1.24–1.11 (1H, m, CH*H*), 1.06 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 170.7 (*C*ON), 135.5 (Ph), 133.6 (Ph, quat.), 129.6 (Ph), 127.6 (Ph), 101.5 (O*C*HO), 76.8 (*C*HOCHO), 66.9, 65.6, 61.2 (O*C*H$_3$), 32.2 (N*C*H$_3$), 30.9 (*C*H$_2$), 27.1 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 21.5 (*C*H$_2$), 19.2 (*C*(CH$_3$)$_3$). *m*/*z* (FAB) 494 (100%, MNa^+); Found (FAB): 494.2350 (MNa^+). $C_{26}H_{37}O_5SiNNa$: 494.2339.

(*R*,*R*)-2-(6′-*tert*-Butyldiphenylsilanyloxymethylpyranyloxy)-1-phenylethanone (6). To a stirred solution of **5** (1.0 g, 2.12 mmol) in tetrahydrofuran (10 mL) at −30 °C was added dropwise a solution of phenylmagnesium bromide in diethyl ether (3.0 M, 1.41 mL). After 30 min the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (3 mL), extracted with diethyl ether (2 × 10 mL), the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a yellow oil. Purification of this oil by flash column chromatography, eluting with 15% ether–petroleum ether (bp 40–60 °C) isolated **6** (1.0 g, 97%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 2.0) = +39.8; ν_{max} (thin film)/cm^{-1}: 3070, 2931, 2856, 1703, 1428, 1155, 1112, 1038; δ_H (400 MHz; $CDCl_3$): 7.93–7.87 (2H, m, Ph), 7.73–7.67 (3H, m, Ph), 7.58–7.31 (10H, m, Ph), 5.07 (1H, d, *J* 7.0, C*H*HCOPh), 4.94 (1H, d, *J* 7.0, CH*H*COPh), 4.61–4.59 (1H, m, OC*H*O), 3.82 (1H, dd, *J* 10.2 and 5.9, C*H*HOSi), 3.69–3.57 (2H, m, C*H*OCHO and CH*H*OSi), 2.01–1.16 (6H, m, 3 × C*H*$_2$), 1.08 (9H, SiC(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 195.9 (*C*OPh), 135.9 (Ph), 135.6 (Ph, quat.), 135.1 (Ph, quat.), 134.8 (Ph), 128.7 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 101.7 (O*C*HO), 76.9 (*C*HOCHO), 69.9 (O*C*H$_2$COPh), 66.9 (*C*H$_2$OSi), 31.0 (*C*H$_2$), 27.2 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 21.6 (*C*H$_2$), 19.3 (*C*(CH$_3$)$_3$). *m*/*z* (FAB) 511 (100%, MNa^+); Found (FAB): 511.2317 (MNa^+).$C_{30}H_{36}O_4SiNa$: 511.2281.

***Z*-(2*R*, 2′*R*)-Trimethyl-[1-phenyl-2-(6′-*tert*-butyldiphenylsilanyloxymethylpyran-2′-yloxy)-vinyloxy]-silane (7).** To a stirred solution of **6** (2.70 g, 5.57 mmol) in dichloromethane (10 mL) at −78 °C was added Et_3N (1.10 mL, 7.80 mmol) followed by dropwise addition of TMSOTf (1.21 mL, 6.70 mmol), and the mixture allowed to warm to −30 °C. The reaction mixture was quenched by the rapid addition of saturated aqueous $NaHCO_3$ (5 mL), extracted with dichloromethane (2 × 10 mL), the organic extracts washed with brine (10 mL), dried (Na_2SO_4), filtered and the volatile organics removed *in vacuo* to give crude **7** as a yellow oil. δ_H (400 MHz; $CDCl_3$): 7.76–7.60 (2H, m, Ph), 7.47–7.12 (3H, m, Ph), 7.58–7.31 (10H, m, Ph), 6.78 (1H, s, OC*H*CPh), 4.78–4.72 (1H, m, OC*H*O), 3.83–3.77 (1H, m, C*H*HOSi), 3.73–3.67 (2H, m, C*H*OCHO and CH*H*OSi), 2.00–1.52 (6H, m, 3 × C*H*$_2$), 1.01 (9H, C(C*H*$_3$)$_3$), 0.29 (9H, s, Si(C*H*$_3$)$_3$); δ_C (100 MHz; $CDCl_3$): 137.0 (quat.), 135.7 (Ph), 135.6 (Ph), 134.1 (quat.), 133.0 (quat.), 129.7 (Ph), 123.7 (Ph), 123.6 (Ph), 101.8 (O*C*HO), 77.2 (*C*HOCHO),

66.7 (CH_2OSi), 30.7 (CH_2), 27.0 (CH_2), 26.8 ($C(CH_3)_3$), 21.4 (CH_2), 19.3 ($C(CH_3)_3$), 0.70 ($Si(CH_3)_3$).

(2*S*, 2′*R*, 6′*R*)-2-Hydroxy-2-(6′-*tert*-butyldiphenylsilanyloxymethylpyranyl)-1-phenylethanone (8) and (2*R*, 2′*R*, 6′*R*)-2-hydroxy-2-(6′-*tert*-butyldiphenylsilanyloxymethylpyranyl)-1-phenylethanone (9). The crude oil (**7**) was dissolved in dichloromethane (5 mL), cooled to −30 °C, and TMSOTf (0.10 mL, 0.56 mmol) added dropwise. After 10 min the reaction mixture was quenched with aqueous NaOH (10%, 10 mL), extracted with dichloromethane (2 × 10 mL), the organic extracts washed with brine (10 mL), dried ($MgSO_4$), filtered, and the solvent evaporated *in vacuo* to give a yellow oil; proton NMR spectroscopy showed an **8** : **9** ratio of 1 : 1 (by integration of the signals in the 400 MHz proton NMR spectrum at δ_H = 4.90 (**8**) and 5.17 (**9**)). Purification of this oil by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) isolated **8** and **9** (2.30 g, 85%) as a colourless oil. Repeated medium pressure flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) isolated first **9** (1.14 g, 42%), and then **8** (1.13 g, 42%) as colourless oils. Data for **8**: $[\alpha]_D^{29}$ ($CHCl_3$, *c* 1.6) = −6.75; ν_{max} (thin film)/cm^{-1} 3471 (br), 3070, 2929, 1738, 1693, 1598, 1471, 1266, 1110; δ_H (600 MHz; $CDCl_3$): 7.88–7.33 (15H, m, Ph), 5.17 (1H, dd, *J* 7.1 and 4.2, C*H*OH), 4.04–4.01 (1H, m, OCH_2CH), 3.89 (1H, dt, *J* 8.6 and 4.2, C*H*CHOH), 3.68 (1H, dd, *J* 10.4 and 6.2, OCH*H*), 3.63 (1H, d, *J* 7.1, O*H*), 3.57 (1H, dd, *J* 10.4 and 6.7, OC*H*H), 1.75–1.32 (6H, m, $CH_2CH_2CH_2$), 1.02 (9H, s, $(CH_3)_3Si$); δ_C (150 MHz; $CDCl_3$): 200.2 (*C*OPh), 135.5 (Ph, quat.), 134.9 (Ph), 133.5 (Ph, quat.), 133.4 (Ph, quat.), 133.3 (Ph), 129.6 (Ph), 128.5 (Ph), 128.3 (Ph), 127.7 (Ph), 127.6 (Ph), 76.1 (*C*HOH), 73.3 (*C*HOCHCH), 72.8 (*C*HCHOH), 63.3 (CH_2OSi), 26.8 ($C(CH_3)_3$), 26.4 (CH_2), 24.8 (CH_2), 19.1 ($C(CH_3)_3$), 18.4 (CH_2); *m*/*z* (FAB) 511 (63%, MNa^+), 354 (62%), 197 (100%); Found (FAB): MNa^+ 511.2265. $C_{30}H_{36}O_4SiNa$: 511.2281. Data for **9**: $[\alpha]_D^{29}$ ($CHCl_3$, *c* 1.1) = −23.3°; ν_{max} (thin film)/cm^{-1} 3467 (br), 3068, 2937, 1680, 1598, 1471, 1265, 1111; δ_H (600 MHz; $CDCl_3$): 7.80–7.33 (15H, m, Ph), 4.90 (1H, dd, *J* 6.2 and 3.3, C*H*OH), 3.93–3.90 (1H, m, C*H*CHOH), 3.86 (1H, m, OCH_2CH), 3.73 (1H, d, *J* 6.2, O*H*), 3.46 (1H, dd, *J* 10.1 and 7.5, OC*H*H), 3.26 (1H, dd, J 10.1 and 5.3, OCH*H*), 1.79–1.51 (6H, m, 3 × CH_2), 0.97 (9H, s, $(CH_3)_3Si$). δ_C (150 MHz; $CDCl_3$): 200.3 (*C*OPh), 135.6 (Ph), 135.5 (Ph), 134.6 (Ph, quat.), 133.8 (Ph), 133.7 (Ph, quat.), 133.5 (Ph, quat.), 129.7 (Ph), 128.7 (Ph), 127.7 (Ph), 76.0 (*C*HOH), 73.4 (*C*HOCHCH), 73.3 (*C*HCHOH), 64.1 (CH_2OSi), 26.8 ($C(CH_3)_3$), 25.5 (CH_2), 24.5 (CH_2), 19.2 ($C(CH_3)_3$), 18.4 (CH_2); *m*/*z* (FAB) 511 (70%, MNa^+), 354 (54%), 197 (100%); Found (FAB) MNa^+ 511.2317. $C_{30}H_{36}O_4SiNa$ requires 511.2281.

Conversion of (9) to (8). To a stirred solution of **9** (0.71 g, 1.45 mmol), acetic acid (0.11 mL, 1.89 mmol) and triphenylphosphine (0.50 g, 1.89 mmol) in tetrahydrofuran (10 mL) at 0 °C was added diethyl azodicarboxylate (0.3 mL, 1.89 mmol) dropwise *via* syringe. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h, diluted with diethyl ether (10 mL), washed with distilled water (3 × 20 mL), and the volatile components removed *in vacuo* to leave a yellow oil which was dissolved in methanol (5 mL) and stirred at ambient temperature. A solution of sodium methoxide (2.0 M, 0.010 mL) was added, and the reaction mixture stirred for 30 min and the solvent removed *in vacuo* to leave a yellow oil which was purified by flash column chromatography, eluting with 5%–50% diethyl ether–petroleum ether (bp 40–60 °C), to give **8** (0.49 g, 69%) as a colourless oil. Spectroscopic data for **8** were identical to those reported above.

(4*R*, 5*R*, 2′*R*, 6′*R*)-2-(6′-*tert*-Butyldiphenylsilanyloxymethylpyranyl)-1-phenylethane-1,2-diol (10). To a stirred solution of **8** (0.45 g, 0.92 mmol) in methanol (5 mL) at 0 °C was added sodium borohydride (0.07 g, 1.84 mmol). After 1 min the reaction was quenched by the addtion of distilled water (1 mL), and the reaction mixture extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave **10** (0.45 g, 100%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 0.37) = −4.3; ν_{max} (thin film)/cm^{-1} 3452 (br), 3070, 2934, 2857, 1428, 1261, 1112; δ_H (600 MHz; $CDCl_3$): 7.71–7.68 (6H, m, Ph), 7.67–7.21 (9H, m, Ph), 4.93–4.92 (1H, OCHC*H*OH), 4.02–3.98 (1H, m, C*H*CH_2OSi), 3.89–3.83 (2H, m, C*H*HOSi and OCHCHO*H*), 3.72–3.64 (2H, m, OC*H*CHOH and C*H*OHPh), 3.54 (1H, dd, *J* 10.7 and 5.8, CH*H*OSi), 2.80 (1H, d, *J* 6.1, CHO*H*Ph), 1.68–1.12 (6H, 3 × CH_2), 1.09 (9H, s, $C(CH_3)_3$); δ_C (150 MHz; $CDCl_3$): 141.4 (Ph, quat.), 135.6, 135.5, 133.4 (Ph, quat.), 133.3 (Ph, quat.), 129.8 (Ph), 128.3 (Ph), 127.8 (Ph), 127.7 (Ph), 127.3 (Ph), 126.0 (Ph), 76.4 (*C*HOHCHOHPh), 75.6 (*C*OHPh), 73.8 (*C*HCH_2OSi), 70.0 (*C*HCHOHCHOH), 63.1 (CH_2OSi), 26.8 (CH_2), 26.7 ($C(CH_3)_3$), 25.0 (CH_2), 19.1 ($C(CH_3)_3$), 18.2 (CH_2); *m*/*z* (FAB) 513 (3%, MNa^+), 147 (100%). Found (FAB): MNa^+ 513.2448. $C_{30}H_{38}O_4SiNa$ requires 513.2437.

(4*R*, 5*S*, 2′*R*, 6′*R*)-2,2-Dimethyl-5-(6′-*tert*-butyldiphenylsilanyloxymethylpyranyl)-4-phenyl-[1,3]dioxolane (11). To a stirred solution of **10** (0.45 g, 0.92 mmol) in acetone (6 mL) was added 2,2-dimethoxypropane (1 mL, 8.2 mmol) and (±)-camphorsulfonic acid (0.02 g). After 30 min the reaction was quenched by the addition of triethylamine (0.2 mL), and the volatile components removed *in vacuo* to leave a slightly yellow oil. Purification of this oil by flash column chromatography, eluting with 12% diethyl ether–petroleum ether (bp 40–60 °C) isolated **11** (0.47 g, 99%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 0.83) = −15.0; ν_{max} (thin film)/cm^{-1} 2934, 2856, 1589, 1460, 1378, 1218, 1111, 1052; δ_H (600 MHz; $CDCl_3$): 7.64–7.62 (4H, m, Ph), 7.43–7.35 (6H, m, Ph), 7.30–7.26 (2H, m, Ph), 7.20–7.16 (3H, m, Ph), 5.06 (1H, d, *J* 6.9, C*H*Ph), 4.37 (1H, t, *J* 6.9, C*H*CHPh), 3.93–3.90 (1H, m, C*H*CH_2OSi), 3.53–3.51 (2H, m, CH_2OSi), 3.34–3.31 (1H, br q, *J* 5.9, C*H*CHCHPh), 1.63 (3H, s, CH_3), 1.61–1.52 (2H, m, $SiOCH_2CHCH_2$), 1.47 (3H, s, CH_3), 1.45–1.21 (2H, m, $CH_2CH_2CH_2$), 1.10–1.07 (2H, m, CH_2CHCH), 1.03 (9H, s, $C(CH_3)_3$); δ_C (150 MHz; $CDCl_3$): 135.6 (Ph), 133.7 (Ph, quat.), 129.6 (Ph, quat.), 129.5 (Ph, quat.), 128.0 (Ph), 127.9 (Ph), 127.6 (Ph), 127.5 (Ph), 108.9 (CCH_3), 79.6 (*C*HCHPh), 79.4 (*C*HPh), 71.9 ($SiOCH_2CH$), 70.1 (*C*HCHCHPh), 63.7 ($SiOCH_2$), 26.9 (CH_3), 26.8 ($C(CH_3)_3$), 26.2 (CH_2CHCH), 25.4 (CH_2CHCH_2), 25.1 (CH_3), 19.2 ($C(CH_3)_3$), 17.8 ($CH_2CH_2CH_2$); *m*/*z* (FAB) 530 (34%, MNa^+), 276 (100%). Found (FAB) MNa^+ 530.2873. $C_{33}H_{42}O_4SiNa$ requires 530.2852.

(4*R*, 5*S*, 2′*R*, 6′*R*)-2,2-Dimethyl-5-(6′-hydroxymethylpyranyl)-4-phenyl[1,3]dioxolane (12). **11** (0.42 g, 0.80 mmol) was dissolved in a stirred solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 8 mL). After 2 h the solvent was removed *in vacuo*, and the brown residue purified by flash column chromatography, eluting with 30% to 100% diethyl ether–petroleum ether

(bp 40–60 °C) isolated **12** (0.23 g, 99%) as a colourless oil. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 0.87) = −46.0; ν_{max} (thin film)/cm^{-1} 3451 (br), 2937, 1457, 1372, 1217, 1104, 1046; δ_H (400 MHz; $CDCl_3$): 7.42–7.26 (5H, m, Ph), 5.16 (1H, d, *J* 6.9, C*H*Ph), 4.48 (1H, t, *J* 7.0, C*H*CHPh), 3.90–3.84 (1H, m, C*H*CH_2OSi), 3.58–3.47 (2H, m, and C*H*CHCHPh), 3.33 (1H, dd, *J* 11.3 and 3.7, CH*H*OSi), 1.88 (1H, br s, O*H*), 1.66 (3H, s, CH_3), 1.62–1.51 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.40–1.26 (2H, m, CH_2), 1.18–1.03 (2H, m, CH_2); δ_C (100 MHz; $CDCl_3$): 137.5 (Ph, quat.), 128.3 (Ph), 127.7 (Ph), 127.5 (Ph), 108.9 (*C*CH_3), 79.1 (*C*HPh), 77.4 (*C*HCHPh), 72.0 (OHCH_2*C*H), 69.3 (*C*HCHCHPh), 62.3 (CH_2OH), 27.0 (CH_3), 25.8 (*C*H_2), 25.5 (*C*H_2), 25.1 (CH_3), 18.3 (*C*H_2); *m/z* (FAB) 315 (100%, MNa^+); Found (FAB) MNa^+ 315.1589. $C_{17}H_{24}O_4Na$ requires 315.1573.

(2*R*, 6*R*, 4′*S*, 5′*R*)-6-(2′,2′-Dimethyl-5′-phenyl-[1′,3′]dioxolan-4′-yl)-pyran-2-carbaldehyde (13). To a stirred solution of oxalyl chloride (0.084 mL) in dichloromethane (20 mL) at −78 °C was dropwise added a solution of dimethyl sulfoxide (0.148 mL) in dichloromethane (10 mL). After 30 min a solution of **12** (100 mg, 0.34 mmol) in dichloromethane (5 mL) was added dropwise, and the reaction mixture stirred at −78 °C for 60 min before triethylamine (0.39 mL) was added and the reaction mixture allowed to warm to ambient temperature. The reaction mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a colourless oil. Purification by flash column chromatography, eluting with 30% diethyl ether–petroleum ether (bp 40–60 °C), isolated **13** (0.092 g, 93%) as a white crystalline solid (mp 76–78 °C). $[\alpha]_D^{29}$ ($CHCl_3$, *c* 1.0) = +4.0; ν_{max} (thin film)/cm^{-1} 2938, 1727, 1454, 1378, 1219, 1116, 1052, 1014; δ_H (400 MHz; $CDCl_3$): 9.17 (1H, d, *J* 0.6, C*H*O), 7.39–7.27 (5H, m, Ph), 5.21 (1H, d, *J* 6.9, C*H*Ph), 4.31 (1H, t, *J* 6.3, C*H*CHPh), 4.11 (1H, d, *J* 4.9, C*H*CHO), 3.35–3.30 (1H, m, C*H*CHCHPh), 1.92–1.88 (1H, m, C*H*H), 1.70 (3H, s, CH_3), 1.65–1.52 (1H, m, CH*H*), 1.51 (3H, s, CH_3), 1.49–0.99 (4H, m, 2 × CH_2); δ_C (100 MHz; $CDCl_3$): 206.0 (*C*HO), 137.5 (Ph, quat.), 128.1 (Ph), 128.0 (Ph), 127.5 (Ph), 109.2 (*C*CH_3), 81.0 (*C*HPh), 79.0 (*C*HCHPh), 78.9 (*C*HCHO), 73.2 (*C*HCHCHPh), 26.8 (*C*H_3), 26.5, 25.2 (CH_3), 23.5 (*C*H_2), 19.2; *m/z* (FAB) 290 (55%, M^+); Found (FAB) 290.1527 (M^+). $C_{17}H_{22}O_4$ requires 290.1518.

(6*R*, 4′*S*, 5′*R*) 6-(2′,2′-Dimethyl-5′-ethyl-[1′,3′]dioxolan-4′-yl)-pyranyl acetate (14). To a stirred solution of **13** (0.082 g, 0.282 mmol) in ^{t}BuOH (1.5 mL) was added 1,2-dimethoxyprop-1-ene (0.34 mL, 3.2 mmol) and a solution of sodium perchlorite (0.226 g) in aqueous monobasic potassium phosphate (1.0 M, 1.7 mL). After 10 min the reaction mixture was diluted with ethyl acetate (10 mL), washed with distilled water (5 mL), extracted with ethyl actetate (4 × 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave the acid as a white powder. This white powder was stirred in tetrahydrofuran (5 mL), and pyridine (0.1 mL, 0.846 mmol) added followed by lead tetraacetate (0.37 g, 0.846 mmol). After 30 min the reaction mixture was filtered through Celite, washed with tetrahydrofuran, and the solvent evaporated *in vacuo* to leave an orange oil. Purification by flash column chromatography, eluting with 1% triethylamine–19% ethyl acetate–petroleum ether (bp 40–60 °C), isolated **14** (0.061 g, 68% from **13**) as a colourless oil. Data for **14** (isolated as a 2 : 1 mixture of anomers): $[\alpha]_D^{29}$ ($CHCl_3$, *c* 1.0) = −116.0; ν_{max} (thin film)/cm^{-1} 2982, 2938, 1746, 1456, 1371, 1241, 1166, 1061, 1038, 1008; δ_H (600 MHz; $CDCl_3$): 7.39–7.26 (5H, m, Ph), 6.13 (1H major, br s, C*H*OAc), 5.46 (1H minor, dd, *J* 9.3 and 1.9, C*H*OAc), 5.19 (1H major, d, *J* 6.9, C*H*Ph), 5.13 (1H minor, d, *J* 6.5, C*H*Ph), 4.26 (1H minor, t, *J* 6.4, C*H*CHPh), 4.18 (1H major, dd, *J* 6.8 and 1.8, C*H*CHPh), 3.51–3.46 (1H major, m, C*H*CHCHPh), 3.25–3.20 (1H minor, m, C*H*CHCHPh), 2.09 (3H minor and 3H major, s, COCH_3), 1.85 (3H major and 3H minor, s, COCH_3), 1.69–0.97 (6H major and 6H minor, m, 3 × CH_2); *m/z* (FAB) 344 (88%, MNa^+), 149 (100%); Found (FAB) MNa^+ 342.1535. $C_{18}H_{24}O_5Na$ requires 343.1522.

(6*R*, 4′*S*, 5′*R*)-6-(2′,2′-Dimethyl-5′-phenyl-[1′,3′]dioxolan-4′-yl)-pyran-2-one (15). To a stirred solution of **14** (0.10 g, 0.313 mmol) in methanol (2 mL) was added a solution of sodium methoxide in methanol (0.5 M, 0.02 mL). After 10 min the reaction mixture was diluted with diethyl ether (20 mL) and the solution filtered through a silica plug, eluting with diethyl ether, and the solvent removed *in vacuo* to leave the lactol as a colourless oil which was used without further purification. Following the protocol of Ley *et al.*,[57] this colourless oil was dissolved in dichloromethane (2 mL) and stirred at ambient temperature. 4 Å molecular sieves (0.2 g) were added followed by *N*-methylmorpholine *N*-oxide (0.055 g, 0.47 mmol) and tetra-*n*-propylammonium perruthenate (0.006 g, 0.016 mmol). After 10 min the reaction mixture was filtered through Celite (eluting with diethyl ether) and the solvent was removed *in vacuo* to leave a brown oil. Purification by flash column chromatography, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), isolated **15** (0.084 g, 97% from **14**) as a colourless oil. Found: C, 69.53; H, 7.17%. $C_{16}H_{20}O_4$ requires C, 69.54; H, 7.30%. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 0.54) = −51.9; ν_{max} (thin film)/cm^{-1} 2960, 2940, 1735, 1456, 1380, 1244, 1159, 1055; δ_H (400 MHz; $CDCl_3$): 7.47–7.45 (2H, m, Ph), 7.37–7.34 (2H, m Ph), 7.32–7.29 (1H, m, Ph), 5.32 (1H, d, *J* 7.1, C*H*Ph), 4.28 (1H, dd, *J* 7.1 and 3.4, C*H*CHPh), 3.88 (1H, dt, *J* 10.2, 7.0 and 3.5, C*H*CHCHPh), 2.37–2.30 (2H, m, OOCCH_2), 1.81–1.50 (7H, m, CH_3 and 2 × CH_2), 1.49 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$): 170.7 (*C*OO), 136.1 (Ph, quat.), 128.3 (Ph), 128.2 (Ph), 127.4 (Ph), 80.2 (*C*HCHPh), 79.3 (*C*HPh), 77.4 (*C*HCHCHPh), 34.0 (*C*CH_3), 29.5 (OOC*C*H_2), 26.5 (*C*H_3), 25.2 (*C*H_3), 24.6 (*C*H_2CH), 18.0 (CH_2*C*$H_2$$CH_2$); *m/z* (FAB) 300 (57%, MNa^+), 154 (100%); Found (FAB): MNa^+ 299.12546. $C_{16}H_{20}O_4Na$ requires 299.10162.

(6*R*, 4′*S*, 5′*R*)-6-(2′,2′-Dimethyl-5′-phenyl-[1′,3′]dioxolan-4′-yl)-3-phenylselanyltetrahydropyran-2-one (16). To a stirred solution of diisopropylamine (0.12 mL, 0.761 mmol) in tetrahydrofuran (1.5 mL) at −78 °C was added a solution of *n*-butyllithium in hexanes (1.6 M, 0.476 mL), and the reaction mixture warmed to 0 °C before cooling to −78 °C. **15** (0.070 g, 0.254 mmol) in tetrahydrofuran (0.5 mL) was added dropwise, and after 30 min phenylselenenyl chloride (0.146 g, 0.761 mmol) was added. After 60 min the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (2 mL), distilled water (5 mL) was added and the mixture extracted with diethyl ether (3 × 10 mL). The combined organic extracts were filtered through a plug of silica (eluting with diethyl ether), and the solvent removed *in vacuo* to leave **16** as a slightly orange oil. **16** was obtained as a 2 : 1 mixture of diastereomers, separable by flash column

chromatography, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), partially characterised by proton NMR. Data for minor (first eluting) isomer: δ_H (400 MHz; $CDCl_3$): 7.63–7.60 (1H, m Ph), 7.44–7.41 (1H, m, Ph), 7.37–7.22 (8H, m, Ph), 5.24 (1H, d, *J* 4.3, C*H*Ph), 4.23 (1H, dd, *J* 4.1 and 1.9, C*H*CHPh), 3.92–3.88 (1H, m, C*H*CHCHPh), 3.84–3.82 (1H, m, SeC*H*), 2.03–1.90 (2H, m, SeCHCH_2), 1.63 (3H, s, CH_3), 1.56–1.20 (5H, m, 2 × CH_2 and CH_3); Data for major (second eluting) isomer: δ_H (400 MHz; $CDCl_3$): 7.47–7.22 (10H, m, Ph), 5.33 (1H, d, *J* 4.7, C*H*Ph), 4.25 (1H, dd, *J* 3.7 and 1.1, C*H*CHPh), 4.07–4.02 (1H, m, C*H*CHCHPh), 3.80 (1H, t, *J* 4.9, SeC*H*), 2.24–2.15 (1H, m, SeCHC*H*H), 1.77–1.43 (9H, m, 2 × CH_3, SeCHCH*H*, and CH_2CH_2CH).

(6*R*, 4′*S*, 5′*R*)-6-(2′,2′-Dimethyl-5′-phenyl-[1′,3′]dioxolan-4′-yl)-5,6-dihydropyran-2-one (17). To a stirred solution of this orange oil (**16**) in dichloromethane (4 mL) at 0 °C was added aqueous hydrogen peroxide (30%, 2 mL), and the reaction mixture stirred for 10 min. The reaction mixture was extracted with dichloromethane (10 mL), and the organic extract dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a colourless oil. Purification by flash column chromatography, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), isolated **17** (0.057 g, 82% from **16**) as a colourless foam. $[\alpha]_D^{29}$ ($CHCl_3$, *c* 0.55) = −34.2; ν_{max} (thin film)/cm^{-1} 2986, 2933, 1720, 1494, 1454, 1380, 1248, 1155, 1115, 1063, 1030; δ_H (600 MHz; $CDCl_3$): 7.51–7.45 (2H, m, Ph), 7.36 (2H, t, *J* 7.0, Ph), 7.31–7.27 (1H, m, Ph), 6.68–6.63 (1H, m, OOCCHC*H*), 5.85 (1H, dd, *J* 9.8 and 2.1, OOCC*H*), 5.33 (1H, d, *J* 6.9, C*H*Ph), 4.33 (1H, dd, *J* 7.0 and 4.0, C*H*CHPh), 4.00 (1H, dt, *J* 12.1 and 3.9, C*H*CHCHPh), 2.43–2.35 (1H, m, C*H*H), 1.88–1.80 (1H, m, CH*H*), 1.69 (3H, s, CH_3), 1.51 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$): 163.1 (*C*OO), 144.3 (OOCCH*C*H), 135.8 (Ph, quat.), 128.4 (Ph), 127.3 (Ph), 121.1 (OOC*C*H), 109.9 (*C*CH_3), 79.5 (*C*HPh), 79.1 (*C*HCHPh), 75.6 (*C*HCHCHPh), 26.7 (*C*H_3), 26.0 (*C*H_2), 25.3 (*C*H_3); *m/z* (FAB) 297 (98%, MNa^+), 149 (100%). Found (FAB): 297.1100 (MNa^+). $C_{16}H_{18}O_4Na$ requires 297.1103.

(+)-Goniodiol (1). **17** (0.018 g, 0.066 mmol) was dissolved in aqueous acetic acid (50%, 3 mL) and stirred at 80 °C for 30 min. The reaction mixture was quenched by the careful addition of saturated aqueous sodium bicarbonate (3 mL), extracted with diethyl ether (3 × 10 mL), and the combined extracts dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a colourless oil. Purification by flash column chromatography, eluting with 0% to 100% ethyl acetate–diethyl ether, isolated **1** (0.015 g, 97%) as a colourless foam. Spectroscopic data for **1** were consistent with those reported in the literature.[7] $[\alpha]_D^{30}$ ($CHCl_3$, *c* 0.74) = +71.4 (lit.: $[\alpha]_D^{30}$ ($CHCl_3$, *c* not reported) = +75.8;[7] $[\alpha]_D^{30}$ ($CDCl_3$, *c* 0.3) = +74.4);[8] ν_{max} (thin film)/cm^{-1} 3390 (br), 1698, 1391, 1259, 1037; δ_H (600 MHz; $CDCl_3$): 7.40–7.31 (5H, m, Ph), 6.93 (1H, ddd, *J* 9.5, 6.3 and 2.0, OOCCHC*H*), 6.01 (1H, dd, *J* 10.8 and 2.4, OOCC*H*), 4.95 (1H, dd, *J* 7.2 and 5.5, C*H*Ph), 4.80 (1H, ddd, *J* 6.0, 3.7 and 2.3, C*H*CHCHPh), 3.73 (1H, td, *J* 8.0 and 2.2, C*H*CHPh), 2.80 (1H, ddt, *J* 17.3, 13.2 and 2.6, C*H*H), 2.53 (1H, d, *J* 5.4, O*H*), 2.25 (1H, d, *J* 8.3, O*H*), 2.18 (1H, ddd, *J* 18.6, 6.0 and 4.2, CH*H*); δ_C (100 MHz; $CDCl_3$): 163.9 (OO*C*), 146.3 (OOCCH=*C*H), 140.8 (quat. Ph), 128.6 (*m*-Ph), 128.1 (*p*-Ph), 126.5 (*o*-Ph), 120.4 (OOC*C*H=CH), 76.8 (*C*HCHOH), 75.0 (Ph*C*HOH), 73.6 (CH*C*HOH), 26.0 (*C*H_2); *m/z* (FAB) 234 (25%, M^+), 85 (100%); Found (FAB) M^+ 234.0885. $C_{13}H_{14}O_4$ requires 234.0892.

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