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A silicon-tethered tandem radical cyclisation–trapping strategy to the fully substituted cyclopentene ring in viridenomycin

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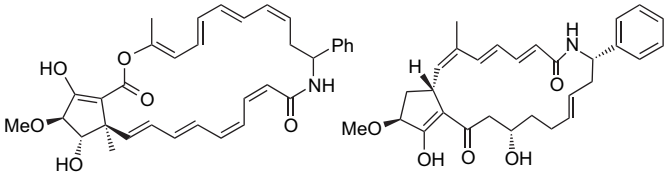
ABSTRACT

Treatment of α-bromosilyl ether **27** derived from the substituted cyclopentenol **26** and (bromomethyl)chlorodimethylsilane, with 1,1′-azobis(cyclohexanecarbonitrile) in *n*-heptane at 100 °C, in the presence of allyltri-*n*-butylstannane leads to the silicon heterocycle **28** by way of a stereocontrolled tandem radical cyclisation (to **11**)–trapping process. Oxidative cleavage of the carbon–silicon bond in **28**, using H_2O_2–KF in THF–MeOH, next led to the corresponding cyclopentane diol **29a**, which was then elaborated to the β-hydroxy ester **30b** using five steps. Oxidation of **30b** using Moffatt conditions, followed by methylation of the resulting enol ester **32a** gave the fully functionalised cyclopentene ring in the antitumoural antibiotic substance viridenomycin **1** isolated from *Streptomyces viridochromogenes* and *Streptomyces gannmycicus*.

1. Introduction

Viridenomycin **1** is an unusual macrocyclic antitumoural antibiotic compound, isolated from *Streptomyces viridochromogenes* and *Streptomyces gannmycicus*.[1,2] It is cytotoxic against Gram-positive bacteria and the parasitic protozoa *Trichomonas vaginalis*, which is responsible for the sexually transmitted disease TV. Viridenomycin is also capable of prolonging the life span of various transgenic mice expressing P388 leukaemia and B16 melanoma. The compound has a structure based on a polyene macrolactam core linked via an enolised β-keto ester unit and a quaternary centre to an oxygenated cyclopentane. Viridenomycin is related structurally to the polyene macrolactam hitachimycin **2**,[3] and to the less-adorned oxygenated cyclopentenones terrein **3**,[4] pentenomycin **4**,[5] and xanthocidin **5**.[6]

It is likely that viridenomycin and the aforementioned relatives share a related biosynthetic origin involving cyclisations of modified poly-β-ketide precursors,[7] in some instances with ring contraction of 6-ring aromatic/quinonoid intermediates.[8] These biosynthetic interrelationships, in combination with the striking structural features and interesting biological properties of viridenomycin, have combined to make the metabolite a challenging target for synthesis. In this paper we present a synthetic route to the fully substituted cyclopentene ring in viridenomycin based on a concise tandem radical cyclisation–trapping strategy.[9,10]



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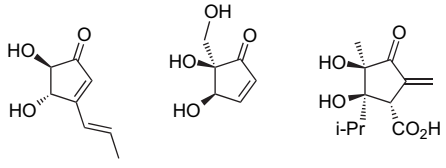

3 **4** **5**

Neither the absolute stereochemistry nor the stereochemistry at the benzylic centre in viridenomycin **1** is known, and no total synthesis of the natural product has been forthcoming. Meyers et al.[11] were the first to describe a synthesis of the substituted cyclopentene **6** with the correct structural and stereochemical features in viridenomycin, which was closely followed by a synthesis of the related substituted cyclopentene **7** by Tadano et al.[12] During our own studies Trost and Jiang[13] presented a synthesis of substituted cyclopentene **8**.

Our own synthetic approach to the cyclopentene ring system **9** (cf. **6**) in viridenomycin uses an intramolecular radical cyclisation from a silicon-tethered 2-cyclopentenol, i.e., **12**, in tandem with in situ trapping of the product radical **11** with allyltri-*n*-butylstannane, leading to **10** as the key stratagem (Scheme 1). The

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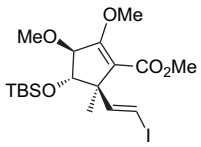

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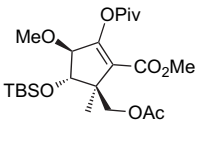

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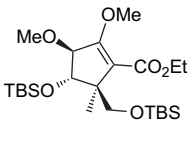

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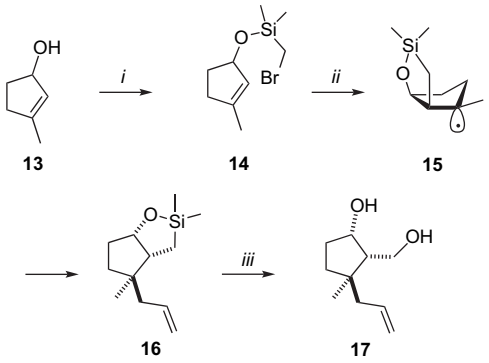
general scope for tandem silicon-tethered radical cyclisation–trapping sequences in the synthesis of substituted cyclopentanes was first highlighted by Stork et al.[14] in their beautiful studies of prostaglandin synthesis.[15] Keck et al.[16] later extolled the use of β-stannyl substituted enones as versatile radical trapping agents in similar tandem processes, and other researchers have since used alternative radical trapping agents,[17] including allyltri-*n*-butylstannane.[18]

2. Results and discussion

We assessed the viability of the tandem radical cyclisation–trapping strategy shown in Scheme 1 by first conducting a model study with the less sophisticated substrate **14** produced from silylation of the cyclopentenol **13** using (bromomethyl)-chlorodimethylsilane in the presence of DMAP and Et_3N. To our satisfaction when a solution of the bromide **14** and allyltri-*n*-butylstannane in benzene was irradiated with UV light,[19] followed by in situ oxidative cleavage of the silacycle intermediate **16**[20] using H_2O_2, KF, $KHCO_3$,[21] the required 1,3-diol **17** was isolated in an unoptimised 45% yield over the two steps. The relative stereochemistry of the substituents about the cyclopentane ring in the product **17** followed from NOE experiments in the ^1H NMR spectrum.[22] These data confirmed that, as anticipated, the allylstannane reagent was trapped from the least hindered (convex) face of the bicyclic radical intermediate **15** in the overall sequence (Scheme 2).

We next examined a synthesis of the more elaborately substituted cyclopentenol **26**, corresponding to **13** in order to pursue our proposed synthesis of the fully substituted cyclopentene ring **9** in viridenomycin (Scheme 1). The high density of stereo-defined hydroxyl group functionality in **26** suggested that a sugar derivative, i.e., the commercially available glucofuranose **18**, would be an ideal starting material. Our plan then was to elaborate the glucofuranose **18** to the 1,6-diene **24** via the known tetrahydrofuran **19**,[23] and then to convert **24** into the cyclopentene **25** using ring closure metathesis.

Thus, the substituted tetrahydrofuran **19** was first produced from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose **18**, using the procedures described by Josan and Eastwood.[23] Deprotection of the

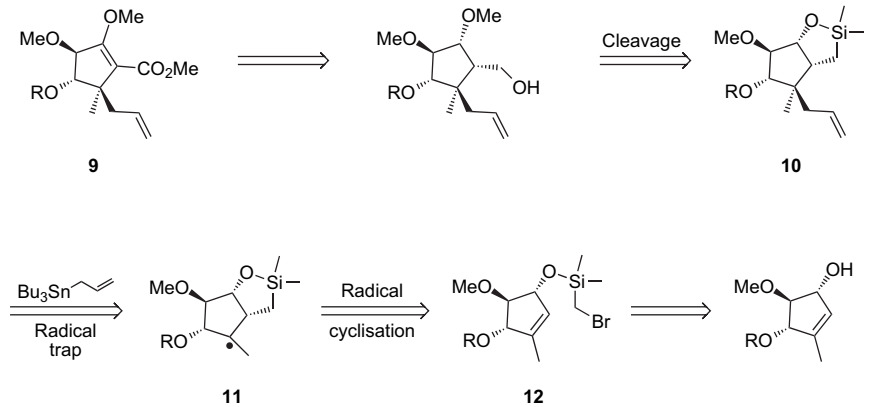


Scheme 2. Reagents and conditions: (i) $(BrCH_2)SiMe_2Cl$, Et_3N, DMAP, 0 °C (96%); (ii) $(Bu_3Sn)_2$, PhH, allyltri-*n*-butylstannane, hν; (iii) H_2O_2, KF, $KHCO_3$, reflux (45% over two steps).

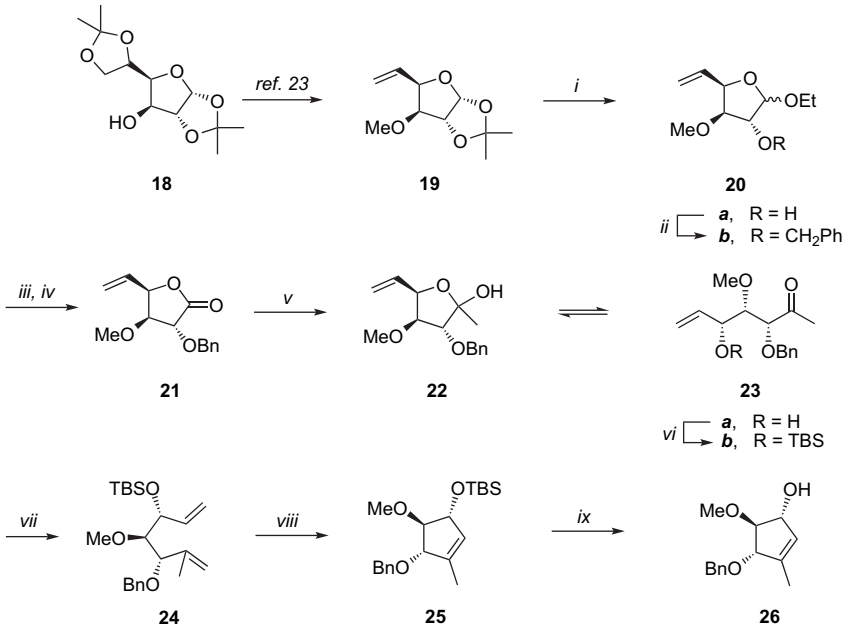
acetonide group in **19**, using EtOH–HCl, next gave the cyclic acetal **20a** as a mixture of anomers, which was then converted into the corresponding benzyl ether **20b** (Scheme 3). Hydrolysis of the acetal **20b** in the presence of 75% acetic acid, followed by oxidation of the intermediate cyclic hemiacetal, using DMSO–Ac_2O, now gave the lactone **21** in an excellent 89% yield over the two steps. Addition of methyllithium to a solution of **21** in THF at −78 °C next gave rise to a mixture of anomers of the corresponding cyclic hemiketal **22** together with the ketone tautomer **23a**.[24] The mixture was treated immediately with *t*-BuMe_2SiCl and imidazole leading to the differentially protected triol substituted δ-unsaturated methyl ketone **23b** in a modest 54% yield over the two steps.

Methylenation of the methyl ketone **23b**, using Nysted's reagent[25] and $TiCl_4$ in THF, next gave the corresponding 1,6-diene **24** with no evidence of any racemisation at the neighbouring α-chiral centre. Finally, treatment of a solution of the 1,6-diene **24** in benzene at 80 °C with 20 mol% of Grubbs' second generation catalyst,[26] dropwise over 30 h, led to the cyclopentene **25** in 90% yield. Deprotection of the silyl ether group in **25**, then led to the cyclopentenol **26** in readiness for further elaboration to the substituted cyclopentane ring in viridenomycin, via our tandem radical cyclisation–trapping strategy (cf. Scheme 1).

Treatment of the cyclopentenol **26** with (bromomethyl)-chlorodimethylsilane gave the α-bromosilyl ether **27** in good yield (Scheme 4). However, when **27** was irradiated with UV light in the presence of allyltri-*n*-butylstannane and hexa-*n*-butyldistannane, under the conditions used successfully to convert **14** into **16**, only starting material was recovered. This problem was eventually overcome using the alternative radical initiator 1,1′-azobis(cyclohexanecarbonitrile) in *n*-heptane at 100 °C,[27] described by Zard et al.[18] in their synthesis of the pleuromutilin ring system. The



Scheme 1. Retrosynthetic analysis of the substituted cyclopentene **9**.



Scheme 3. Reagents and conditions: (i) EtOH, HCl in dioxane, 60 °C (91%); (ii) BnBr, NaH, DMF, 0 °C (89%); (iii) AcOH, H_2O (98%); (iv) DMSO, Ac_2O (91%); (v) MeLi, THF, −78 °C; (vi) TBSCl, imidazole, DMF (54% over 2 steps); (vii) {*cyclo*-dibromodi-μ-methylene[μ-(tetrahydrofuran)] trizinc}, $TiCl_4$ THF, 0 °C→rt (98%); (viii) 1,3-(bis(mesityl)-2-imidazolidinylidene)-dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium, benzene, 80 °C (90%); (ix) TBAF, THF (80%).

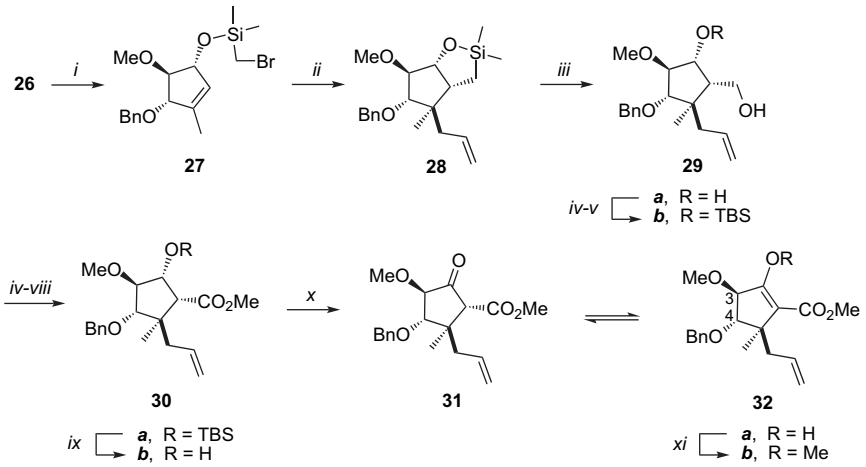
crude product, containing the silacycle **28**, was subjected to the Tamao–Fleming oxidation conditions[21] to give the cyclopentane-substituted diol **29a** containing five contiguous chiral centres in 50% overall yield. The stereochemistry of **29a** followed unambiguously from NOE studies in the ^{1}H NMR spectrum (see Section 4).

The 1,3-diol unit in the cyclopentane **29a** was converted into the methyl enol ether of the corresponding β-keto ester residue in the target, i.e., **32b**, by initial protection of the secondary hydroxyl group in **29a** as its TBS ether followed by oxidation of the primary alcohol group in **29b** to the corresponding methyl ester **30a**, using a three-step sequence (Scheme 4). The oxidation of the secondary alcohol **30b** derived from **30a** to the corresponding β-keto ester **31** turned out to be problematic. Eventually, however, use of a modified Pfitzner–Moffatt oxidation (DMSO, EDC, C_5H_5N, TFA)[28] converted the alcohol **30b** into **31**, which existed exclusively as the enol ester tautomer **32a**, in 89% yield. The substituted cyclopentene **32a** contains all the necessary functionalisation with the correct stereochemistry for elaboration to an appropriate intermediate, cf. **6**, en route to viridenomycin.

Comparison of the ^{1}H NMR spectroscopic data for **32a** with those of natural viridenomycin showed excellent correlation in their chemical shift and coupling data for resonances associated with the cyclopentene ring units. For completeness, the enol ester **32a** was converted into the corresponding methyl ether **32b**, using Me_2SO_4/K_2CO_3. The chemical shift and coupling data in the ^{1}H NMR spectrum of **32b** showed close agreement with similar data published for the substituted cyclopentenes **6** and **7** synthesised by Meyers et al.[11] and Tadano et al.,[12] respectively (Table 1).

3. Summary and conclusion

In summary, we have developed an intramolecular, silicon-tethered, *5-exo-trig* radical cyclisation, followed by in situ trapping



Scheme 4. Reagents and conditions: (i) Et_3N, $(CH_3)_2Si(CH_2Br)Cl$, DMAP, CH_2Cl_2 (80%); (ii) ACCN, *n*-heptane, 100 °C, allyltri-*n*-butylstannane; (iii) H_2O_2, KF, $KHCO_3$, MeOH, THF, 80 °C (50% over two steps); (iv) TBSCl, imidazole, DMF (92%); (v) PPTS, EtOH (71%, based on recovered starting material); (vi) Dess–Martin periodinane, pyridine, CH_2Cl_2; (vii) $NaClO_2$, KH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene; (viii) $TMSCHN_2$, benzene, MeOH; (ix) TBAF, THF (69% over four steps); (x) EDC, DMSO, Py·TFA, DMAP (89%); (xi) Me_2SO_4, DMSO, K_2CO_3 (97%).

Table 1
Relevant comparative ^{1}H NMR spectroscopic data for the substituted cyclopentenes **6**, **7** and **32b**[a]

	6	7	32b
C3–H	δ 4.31 d (J=6.3 Hz)	δ 4.32 d (J=6.7 Hz)	δ 4.47 d (J=5.5 Hz)
C4–H	δ 4.07 d (J=6.3 Hz)	δ 4.10 d (J=6.7 Hz)	δ 3.87 d (J=5.5 Hz)

[a] Corresponding ^{1}H NMR spectroscopic data for the cyclopentene **8**, described by Trost and Jiang,[13] are C3–H δ 3.74 d (J=9.8 Hz) and C4–H δ 3.35 d (J=9.8 Hz). The large vicinal coupling (J=9.8 Hz) reported between C3–H and C4–H in **8** is more consistent with a *syn*-relationship between these hydrogen atoms.

of the product radical centre to install the quaternary carbon centre, in addition to the four contiguous chiral centres, in the cyclopentene unit **32** in viridenomycin. The silicon-tethered radical cyclisation precursor **27** was conveniently produced from the commercially available glucofuranose **18** via the cyclopentenol **26** whose synthesis featured ring-closing metathesis from the 1,6-diene intermediate **24**.

4. Experimental

4.1. General details

For general details see Ref. 29.

*4.1.1. 1,2-O-Isopropylidene-3-O-methyl-α-D-xylo-hex-5-enofuranose (**19**)*

The substituted tetrahydrofuran was prepared from the α-D-glucofuranose **18** according to the literature procedures.[23] $[\alpha]_D^{23}$ −85.0 (*c* 1.0, $CHCl_3$) (lit.[23] $[\alpha]_D^{23}$ −70 (*c* 1.0, $CHCl_3$)); ν_{max} ($CHCl_3$) 2984, 2937, 1646, 1455, 1384, 1376, 1134, 1074 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.98 (1H, ddd, J=6.8, 10.5, 17.5 Hz, C*H*=CH$_2$), 5.97 (1H, d, J=3.8 Hz, OC*H*), 5.47 (1H, d, J=17.5 Hz, CH=CH*H*), 5.32 (1H, d, J=10.5 Hz, CH=C*H*H), 4.64 (1H, dd, J=6.8, 3.2 Hz, OC*H*), 4.63 (1H, d, J=3.8 Hz, OC*H*), 3.70 (1H, d, J=3.2 Hz, C*H*OMe), 3.44 (3H, s, OCH_3), 1.54 (3H, s, CH_3), 1.35 (3H, s, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ_C 131.9 (d), 118.7 (t), 111.4 (s), 104.3 (d), 85.8 (d), 82.0 (d), 81.2 (d), 58.1 (q), 26.7 (q), 26.1 (q); *m*/*z* (ES) found 223.0955 (M+Na$^+$, $C_{10}H_{16}O_4Na$ requires 223.0946).

*4.1.2. (2R,3S,4R)-2-Benzyloxy-1-ethoxy-3-methoxy-4-vinyl-tetrahydro-furan (**20b**)*

Hydrochloric acid (4 M in dioxane, 3 mL) was added in one portion to a stirred solution of the acetonide **19** (2.00 g, 10.0 mmol) in absolute ethanol (30 mL). The mixture was heated to 60 °C and stirred at this temperature for 15 h, then cooled to room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the resulting suspension was concentrated in vacuo to approximately 20 mL. The aqueous residue was extracted with ethyl acetate (2×60 mL) and the combined organic extracts were then washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to leave the ethyl glycoside **20a** (1.71 g, 91%) as a mixture of anomers. Sodium hydride (3.83 g, 97.8 mmol, 60% in mineral oil) was added in one portion to a stirred solution of the ethyl glycoside (9.96 g, 52.9 mmol) in anhydrous DMF (175 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 20 min and then benzyl bromide (13.1 g, 76.7 mmol) was added in one portion. The mixture was stirred at 0 °C for 2 h, methanol (5 mL) was then added and the solution was stirred at room temperature for a further 30 min. The mixture was poured into diethyl ether (500 mL) and the solution was then washed with water (2×400 mL) followed by brine (50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to leave the crude benzyl ether as a yellow oil, which was purified by flash chromatography, using diethyl ether–pentane (1:12) as eluent, to give: (i) the *β-anomer of the benzyl ether* (eluted first) as a pale yellow oil. $[\alpha]_D^{23}$ −30.1 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2979, 2931, 2902, 1454, 1375, 1351, 1099, 1043 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 6.05 (1H, ddd, J=7.9, 10.3, 17.2 Hz, C*H*=CH$_2$), 5.38 (1H, br d, J=17.2 Hz, CH=CH*H*), 5.28 (1H, br d, J=10.3 Hz, CH=CH*H*), 5.02 (1H, d, J=2.2 Hz, C*H*OEt), 4.65–4.61 (3H, m, CH_2Ph, OC*H*), 4.02 (1H, dd, J=2.2, 3.6 Hz, C*H*OBn), 3.88 (1H, dd, J=3.6, 6.0 Hz, C*H*OMe), 3.85 (1H, qd, J=7.0, 9.2 Hz, OC*H*HCH$_3$), 3.54 (1H, qd, J=7.0, 9.2 Hz, OCH*H*CH$_3$), 3.36 (1H, s, OCH_3), 1.23 (3H, t, J=7.0 Hz, CH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.7 (s), 134. 7 (d), 128.4 (d)×2, 127.8 (d)×2, 127.7 (d), 118.3 (t), 106.6 (d), 87.0 (d), 85.3 (d), 82.0 (d), 72.2 (t), 63.8 (t), 58.1 (q), 15.1 (q); *m*/*z* (ES) found 301.1433 (M+Na, $C_{16}H_{22}O_4Na$ requires 301.1416); and (ii) the *α-anomer of the benzyl ether* (combined yield 13.10 g, 89%) as a pale yellow oil. $[\alpha]_D^{23}$ +99.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2979, 2931, 1454, 1374, 1096, 1053, 989 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43–7.30 (5H, m, Ar*H*), 5.94 (1H, ddd, J=7.1, 10.3, 17.2 Hz, C*H*=CH$_2$), 5.37 (1H, br d, J=17.2 Hz, CH=CH*H*), 5.31 (1H, br d, J=10.3 Hz, CH=CH*H*), 4.95 (1H, d, J=4.3 Hz, C*H*OEt), 4.67–4.64 (3H, m, CH_2Ph, OC*H*), 4.10 (1H, dd, J=6.1, 6.3 Hz, C*H*OMe), 3.82 (1H, dd, J=4.3, 6.3 Hz, C*H*OBn), 3.82 (1H, qd, J=7.1, 9.9 Hz, OC*H*HCH$_3$), 3.53 (1H, qd, J=7.1, 9.9 Hz, OCH*H*CH$_3$), 3.40 (1H, s, OCH_3), 1.29 (3H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.8 (s), 133.9 (d), 128.3 (d)×2, 128.1 (d)×2, 127.7 (d), 118.3 (t), 99.2 (d), 84.5 (d), 83.4 (d), 78.3 (d), 72.5 (t), 63.5 (t), 58.2 (q), 15.2 (q); *m*/*z* (ES) found 301.1409 (M+Na$^+$, $C_{16}H_{22}O_4Na$ requires 301.1416).

*4.1.3. (2R,3S,4R)-2-Benzyloxy-3-methoxy-4-vinyl-dihydro-furan-1-one (**21**)*

A solution of the ethyl glycoside anomer **20b** (4.44 g, 16.0 mmol) in acetic acid–water (3:1, 100 mL) was stirred at 65 °C for 3 days. The mixture was concentrated in vacuo and the residue was then azeotroped with toluene. The residue was dried under vacuum to leave the corresponding hemiacetal (4.0 g, 98%) as a yellow oil, which was used in the next reaction without further purification.

A solution of the hemiacetal (1.50 g 6.0 mmol) in anhydrous DMSO (16 mL) and acetic anhydride (9.6 mL) was stirred at room temperature for 18 h under a nitrogen atmosphere. The mixture was quenched with water (60 mL) and was then stirred at room temperature for a further 15 min during which time the product precipitated. The mixture was diluted with dichloromethane (20 mL) and the separated aqueous phase was then extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with water (2×20 mL) and brine (20 mL), then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography, using ethyl acetate–pentane (1:7) as eluent, to give the *lactone* (1.36 g, 91%) as a colourless oil. $[\alpha]_D^{27}$ +153.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2937, 2886, 1790 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42–7.30 (5H, m, Ar*H*), 5.95 (1H, ddd, J=6.4, 10.3, 17.2 Hz, C*H*=CH$_2$), 5.46 (1H, app. dt, J=1.2, 17.2 Hz, CH=CH*H*), 5.39 (1H, app. dt, J=1.2, 10.3 Hz, CH=CH*H*), 5.07 (1H, ddt, J=1.2, 6.2, 6.4 Hz, OC*H*), 5.03 (1H, d, J=11.5 Hz, C*H*HPh), 4.76 (1H, d, J=11.5 Hz, CH*H*Ph), 4.18 (1H, d, J=6.2 Hz, C*H*OBn), 4.08 (1H, app. t, J=6.2 Hz, C*H*OMe), 3.41 (1H, s, OCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.5 (s), 136.6 (s), 130.9 (d), 128.5 (d)×2, 128.2 (d)×2, 128.1 (d), 119.7 (t), 82.0 (d), 79.5 (d), 76.4 (d), 72.5 (t), 58.2 (q); *m*/*z* (ES) found 271.0970 (M+Na$^+$, $C_{14}H_{16}O_4Na$ requires 271.0970).

*4.1.4. (3R,4R,5R)-3-Benzyloxy-5-(tert-butyl-dimethyl-silanyloxy)-4-methoxy-hept-6-en-2-one (**23b**)*

A solution of methyllithium (2.1 mL, 3.4 mmol, 1.6 M in diethyl ether) was added dropwise over 5 min to a stirred solution of the lactone **21** (0.5 g, 1.9 mmol) in anhydrous THF (20 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 15 min, then a saturated solution of aqueous ammonium chloride (20 mL) was added and the mixture was allowed to warm gradually to room temperature. The mixture was diluted with dichloromethane (40 mL) and the separated aqueous phase was extracted

with dichloromethane (2×20 mL). The combined organic extracts were washed with brine (10 mL), then dried over $MgSO_4$ and concentrated in vacuo to leave the crude lactol **22** as a mixture of anomers, together with the ketone tautomer **23a**.

tert-Butyldimethylsilyl chloride (0.3 g, 2.2 mmol) and imidazole (0.3 g, 4.4 mmol) were added in one portion to a stirred solution of **22**/**23a** in anhydrous DMF (1.7 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 24 h, then the reaction mixture was purified directly by flash chromatography, using diethyl ether–pentane (1:10) as eluent, to give the *methyl ketone* (370 mg, 54% over two steps) as a colourless oil. $[\alpha]_D^{24}$ +62.9 (*c* 1.3, $CHCl_3$). (Found: C, 66.5; H, 9.1; $C_{21}H_{34}O_4Si$ requires: C, 66.6; H, 9.1); ν_{max} ($CHCl_3$) 2954, 2930, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (5H, m, Ar*H*), 5.79 (1H, ddd, *J*=6.7, 10.4, 17.3 Hz, C*H*=CH_2), 5.63 (1H, d, *J*=17.3 Hz, CH=C*H*H), 5.09 (1H, d, *J*=10.4 Hz, CH=CH*H*), 4.57 (1H, d, *J*=11.5 Hz, C*H*HPh), 4.41 (1H, d, *J*=11.5 Hz, CH*H*Ph), 4.42–4.37 (1H, m, C*H*OTBS), 3.85 (1H, d, *J*=2.6 Hz, C*H*OBn), 3.44 (1H, s, OCH_3), 3.42 (1H, dd, *J*=2.6, 7.3 Hz, C*H*OMe), 2.23 (3H, s, COCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.10 (3H, s, Si(CH_3)(CH_3)), 0.05 (3H, s, Si(CH_3)(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.0 (s), 137.6 (d), 137.1 (s), 128.5 (d)×2, 128.3 (d)×2, 128.1 (d), 116.6 (t), 86.2 (d), 84.5 (d), 74.2 (d), 73.7 (t), 61.0 (q), 27.6 (d), 25.9 (q)×3, 18.2 (s), −4.5 (q), −4.8 (q); *m*/*z* (ES) found 401.2086 ($M+Na^+$, $C_{21}H_{34}O_4NaSi$ requires 401.2124). Some of the lactone **21** (85 mg, 34%) was also recovered.

4.1.5. (3R,4R,5R)-3-Benzyloxy-5-(tert-butyl-dimethyl-silanyloxy)-4-methoxy-2-methyl-hepta-1,6-diene (*24*)

A solution of titanium(IV) tetrachloride (2.0 mL, 2.0 mmol, 1.0 M in dichloromethane) was added dropwise over 5 min to a stirred solution of the Nysted reagent[25] (4.7 mL, 2.4 mmol, 20% in THF) in anhydrous THF (15 mL) at 0 °C under a nitrogen atmosphere. The resulting slurry was stirred at 0 °C for 5 min and then a solution of the methyl ketone **23b** (0.4 g, 1.0 mmol) in anhydrous THF (20 mL, 5 mL wash) was added via cannula. The mixture was allowed to gradually warm to room temperature and held at this temperature for 5 h. The reaction mixture was cooled to 0 °C, and then quenched and neutralised with saturated aqueous sodium hydrogen carbonate solution. The mixture was filtered through a pad of Celite and the separated aqueous phase was then extracted with diethyl ether (3×40 mL). The combined organic extracts were dried over $MgSO_4$, then concentrated in vacuo to leave a colourless oil, which was purified by flash chromatography, using diethyl ether–pentane (1:10) as eluent, to give the *1,6-diene* (266 mg, 98%) as a colourless oil. $[\alpha]_D^{20}$ +37.5 (*c* 0.95, $CHCl_3$). (Found: C, 70.2; H, 9.6; $C_{22}H_{36}O_3Si$ requires C, 70.2; H, 9.6); ν_{max} ($CHCl_3$) 2953, 2929, 2857, 1643, 1455 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34–7.27 (5H, m, Ar*H*), 5.77 (1H, ddd, *J*=6.7, 10.5, 17.2 Hz, C*H*=CH_2), 5.08–5.00 (4H, m, =CH_2, CH=CH_2), 4.54 (1H, d, *J*=11.6 Hz, C*H*HPh), 4.28 (1H, app. tt, *J*=1.1, 6.3 Hz, C*H*OTBS), 4.20 (1H, d, *J*=11.6 Hz, CH*H*Ph), 3.84 (1H, d, *J*=3.2 Hz, C*H*OBn), 3.50 (3H, s, OCH_3), 3.10 (1H, dd, *J*=3.2, 6.3 Hz, C*H*OMe), 1.81 (3H, br s, C(CH_3)=CH_2), 0.90 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, Si(CH_3)(CH_3)), 0.03 (3H, s, Si(CH_3)(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.8 (s), 138.5 (d), 137.1 (s), 128.3 (d)×2, 128.2 (d)×2, 127.4 (d), 115.7 (t), 114.0 (t), 86.9 (d), 81.2 (d), 74.8 (d), 70.6 (t), 61.3 (q), 25.9 (q)×3, 19.0 (q), 18.2 (s), −4.4 (q), −4.8 (q); *m*/*z* (ES) found 399.2357 ($M+Na^+$, $C_{22}H_{36}O_3SiNa$ requires 399.2331).

4.1.6. ((1R,4S,5R)-4-Benzyloxy-5-methoxy-3-methyl-cyclopent-2-enyloxy)-tert-butyl-dimethylsilane (*25*)

A solution of 1,3-(bis(mesityl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(trichlorohexenylphosphine)ruthenium (84 mg, 9.3 μmol) in dry degassed benzene (7 mL) was added over 30 h to a stirred solution of the 1,6-diene **24** (0.5 g, 1.3 mmol) in dry degassed benzene (27 mL) at 80 °C under an argon atmosphere. The mixture was stirred at 80 °C for a further 14 h and then cooled to room temperature. Silica was added and the mixture was concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–pentane (1:15) as eluent, to give the *cyclopentene* (415 mg, 90%) as a colourless oil; $[\alpha]_D^{21}$ −47.6 (*c* 1.10, $CHCl_3$); ν_{max} ($CHCl_3$) 2953, 2930, 2857 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 5.40 (1H, br s, =C*H*), 4.70 (1H, d, *J*=11.9 Hz, CH_2Ph), 4.67 (1H, d, *J*=11.9 Hz, CH_2Ph), 4.50 (1H, br s, C*H*OTBS), 4.16 (1H, br s, C*H*OBn), 3.83 (1H, app. t, *J*=3.9 Hz, C*H*OMe), 3.50 (3H, s, OCH_3), 1.76 (3H, d, *J*=1.1 Hz, CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.11 (3H, s, Si(CH_3)(CH_3)), 0.09 (3H, s, Si(CH_3)(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.6 (s), 138.7 (s), 128.8 (d), 128.2 (d)×2, 127.5 (d)×2, 127.4 (d), 96.2 (d), 87.2 (d), 78.9 (d), 71.0 (t), 58.0 (q), 25.7 (q)×3, 17.9 (s), 14.1 (q), −4.2 (q), −4.8 (q); *m*/*z* (ES) found 371.1946 ($M+Na^+$, $C_{20}H_{32}NaO_3Si$ requires 371.2018).

4.1.7. (1R,4S,5R)-4-Benzyloxy-5-methoxy-3-methyl-cyclopent-2-enol (*26*)

A solution of tetrabutylammonium fluoride (3.6 mL, 3.6 mmol, 1.0 M solution in THF) was added dropwise over 5 min to a stirred solution of the TBS ether **25** (0.4 g, 1.2 mmol) in anhydrous THF (5 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 16 h, then diluted with diethyl ether (20 mL) and quenched with water (5 mL). The separated aqueous layer was extracted with diethyl ether (3×20 mL), and the combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–petrol (1:2) as eluent, to give the *alcohol* (222 mg, 80%) as a colourless oil; $[\alpha]_D^{24}$ −3.2 (*c* 1.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3593 (br), 2934, 1602 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 5.50 (1H, br s, =C*H*), 4.72 (1H, d, *J*=11.8 Hz, C*H*HPh), 4.62 (1H, d, *J*=11.8 Hz, CH*H*Ph), 4.48 (1H, br s, C*H*OH), 4.15 (1H, br s, C*H*OBn), 3.78 (1H, app. t, *J*=3.5 Hz, C*H*OMe), 3.52 (3H, s, OCH_3), 1.78 (3H, d, *J*=1.6 Hz, CCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.8 (s), 138.4 (s), 128.4 (d), 128.3 (d)×2, 127.7 (d)×2, 127.6 (d), 95.7 (d), 87.7 (d), 78.9 (d), 71.1 (t), 57.8 (q), 14.2 (q); *m*/*z* (ES) found 217.1240 ($M-OH^-$, $C_{14}H_{17}O_2$ requires 217.1229).

4.1.8. ((1R,4S,5R)-4-Benzyloxy-5-methoxy-3-methyl-cyclopent-2-enyloxy)-bromomethyl-dimethyl-silane (*27*)

(Bromomethyl)chlorodimethylsilane (80 μL, 0.6 mmol) was added in one portion to a stirred solution of the alcohol **26** (69 mg, 0.3 mmol), triethylamine (0.2 mL, 1.2 mmol) and DMAP (3.5 mg, 30 μmol) in anhydrous dichloromethane (2 mL) at 0 °C. The mixture was allowed to warm to room temperature over 12 h and then washed with water (8 mL). The separated aqueous phase was extracted with dichloromethane (3×8 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–pentane (1:9) as eluent, to give the *silyl ether* (79 mg, 80%) as a colourless oil; $[\alpha]_D^{21}$ −44.0 (*c* 0.55, $CHCl_3$). (Found: C, 52.9; H, 6.4; $C_{17}H_{25}BrO_3Si$ requires C, 53.0; H, 6.5); ν_{max} ($CHCl_3$) 2936, 2356, 1662 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.29 (5H, m, Ar*H*), 5.43 (1H, br s, =C*H*), 4.68 (1H, d, *J*=11.8 Hz, CH*H*Ph), 4.62 (1H, d, *J*=11.8 Hz, C*H*HPh), 4.58 (1H, br s, C*H*OSiR_3), 4.17 (1H, br s, C*H*OBn), 3.84 (1H, app. t, *J*=3.8 Hz, C*H*OMe), 4.50 (3H, s, OCH_3), 2.51 (2H, s, Si(CH_3)$_2$CH_2Br), 1.76 (3H, d, *J*=1.1 Hz, CCH_3), 0.32 (3H, s, Si(CH_3)(CH_3)), 0.31 (3H, s, Si(CH_3)(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.8 (s), 138.6 (s), 128.3 (d)×2, 128.2 (d), 127.6 (d)×2, 127.5 (d), 95.6 (d), 87.3 (d), 79.4 (d), 79.1 (t), 57.9 (t), 16.2 (t), 14.2 (q), −2.4 (q)×2; *m*/*z* (ES) found 217.1214 ($M-OSi(CH_3)_2CH_2Br^-$, $C_{14}H_{17}O_2$ requires 217.1229).

4.1.9. (1R,2S,3R,4S,5S)-3-Allyl-4-benzyloxy-2-hydroxymethyl-5-methoxy-3-methyl-cyclopentanol (*29a*)

Azobis(cyclohexanecarbonitrile) (41.0 mg, 0.17 mmol) was added in one portion to a degassed solution of the α-bromosilyl

ether **27** (128 mg, 0.33 mmol) and allyltri-*n*-butylstannane (311 mg, 1.00 mmol) in *n*-heptane. The mixture was heated at 100 °C for 24 h, then cooled to room temperature and concentrated in vacuo. The residue, containing the silacycle **28**, was dissolved in methanol–tetrahydrofuran (14 mL, 1:1) and the solution was treated with potassium hydrogen carbonate (670 mg, 6.67 mmol), potassium fluoride (390 mg, 6.67 mmol) and aqueous hydrogen peroxide solution (7 mL, 35%) at room temperature. The mixture was heated at 80 °C for 3 h, then cooled to room temperature and concentrated in vacuo. The residue was diluted with ethyl acetate (30 mL) and the solution was filtered through Celite. The separated aqueous layer was extracted with ethyl acetate (2×10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using ethyl acetate–pentane (1:9) then ethyl acetate as eluent, to give the *diol* (51 mg, 50%) as a colourless oil; $[\alpha]_D^{23}$ −4.46 (*c* 1.53, $CHCl_3$); ν_{max} ($CHCl_3$) 3615, 3413, 2930, 1454, 1097 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m, Ar*H*), 5.74 (1H, dddd, *J*=4.8, 7.4, 10.2, 17.1 Hz, C*H*=CH_2), 5.06 (1H, dd, *J*=1.2, 10.2 Hz, CH=C*H*H), 5.01 (1H, dd, *J*=1.2, 17.1 Hz, CH=C*H*H), 4.76 (1H, d, *J*=11.8 Hz, C*H*HPh), 4.57 (1H, d, *J*=11.8 Hz, CH*H*Ph), 4.26 (1H, dd, *J*=3.6, 7.8 Hz, C*H*OH), 3.87 (1H, dd, *J*=7.5, 11.2 Hz, CH_2OH), 3.78 (1H, dd, *J*=4.8, 11.2 Hz, CH_2OH), 3.74 (1H, dd, *J*=3.6, 5.0 Hz, C*H*OMe), 3.47 (3H, s, OCH_3), 3.44 (1H, d, *J*=5.0 Hz, C*H*OBn), 2.12–2.04 (3H, m, C*H*CH_2OH, CH_2CH=CH_2), 1.03 (3H, s, CCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.3 (s), 134.0 (d), 128.4 (d), 128.3 (d)×2, 127.6 (d)×2, 118.3 (t), 95.1 (d), 87.0 (d), 76.8 (d), 72.2 (t), 59.0 (t), 57.7 (q), 48.3 (d), 45.0 (s), 43.5 (t), 17.3 (q); *m*/*z* (ES) found 329.1707 ($M+Na^+$, $C_{18}H_{26}O_4Na$ requires 329.1729). In an NOE experiment (^1H NMR, 360 MHz, $CDCl_3$) irradiation at δ 1.03 (CMe) gave enhancements of 5.1% at δ 3.78 (CH_2OH) and 5.3% at δ 3.87 (CH_2OH). In addition, irradiation at δ 4.26 (C*H*CH_2OH) gave an enhancement of 2.1% at δ 2.1 (CH_2CH=CH_2).

4.1.10. [(1S,2R,3S,4R,5R)-2-Allyl-3-benzyloxy-5-(tert-butyldimethyl-silanyloxy)-4-methoxy-2-methyl-cyclopentyl]-methanol (**29b**)

tert-Butyldimethylsilyl chloride (60 mg, 0.4 mmol) and imidazole (50 mg, 0.8 mmol) were added portionwise to a stirred solution of the diol **29a** (28 mg, 91 μmol) in anhydrous DMF (200 μL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 2 days and then more *tert*-butyldimethylsilyl chloride (60 mg, 0.4 mmol) and imidazole (50 mg, 0.8 mmol) were added and the solution was stirred for a further 3 days. The mixture was purified directly by flash chromatography, using diethyl ether–petrol (1:30) as eluent, to give the corresponding *bis-silyl ether* (45 mg, 92%) as a colourless oil; $[\alpha]_D^{24}$ +16.9 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2856, 1602 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 5.82 (1H, dddd, *J*=7.0, 7.7, 10.2, 17.0 Hz, C*H*=CH_2), 5.03 (1H, dd, *J*=1.2, 10.2 Hz, CH=CH*H*), 4.96 (1H, dd, *J*=1.2, 17.0 Hz, CH=C*H*H), 4.69 (1H, d, *J*=11.9 Hz, CH*H*Ph), 4.60 (1H, d, *J*=11.9 Hz, C*H*HPh), 4.04 (1H, dd, *J*=1.5, 6.2 Hz, C*H*OTBS), 3.79 (1H, dd, *J*=7.9, 10.2 Hz, C*H*HOTBS), 3.67 (1H, dd, *J*=6.0, 10.2 Hz, CH*H*OTBS), 3.63 (1H, dd, *J*=1.5, 5.4 Hz, C*H*OMe), 3.46 (1H, d, *J*=5.4 Hz, C*H*OBn), 3.42 (3H, s, OCH_3), 2.17–2.11 (2H, m, CH_2CH=CH_2), 1.65 (1H, ddd, *J*=6.0, 6.2, 7.9 Hz, C*H*CH_2OTBS), 1.03 (3H, s, CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, Si(CH_3)), 0.04 (3H, s, Si(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 139.2 (s), 135.2 (d), 128.3 (d)×2, 127.5 (d)×2, 127.4 (d), 117.6 (t), 95.0 (d), 89.2 (d), 77.3 (d), 72.2 (t), 59.0 (t), 57.7 (q), 48.3 (s), 45.0 (d), 43.5 (t), 26.1 (q)×3, 26.0 (q)×3, 18.3 (s), 18.2 (s), 17.3 (q), −4.4 (q), −4.9 (q), −5.2 (q)×2; *m*/*z* (ES) found 535.3644 ($M+H^+$, $C_{30}H_{55}O_4Si_2$ requires 535.3634).

A solution of pyridinium *para*-toluenesulphonate (11.2 mg, 44.0 μmol) in water (220 μL) was added in one portion to a stirred solution of the bis-silyl ether (119 mg, 220 μmol) in ethanol (2.2 mL). The mixture was stirred at room temperature for 60 h, then brine was added (4 mL) and the mixture was extracted with diethyl ether (3×8 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–petrol (1:9) as eluent, to give the *alcohol* (53.7 mg, 58%) as a colourless oil; $[\alpha]_D^{28}$ −6.8 (*c* 0.15, $CHCl_3$); ν_{max} ($CHCl_3$) 3626, 3521, 2930, 2858, 1602 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m, Ar*H*), 5.82 (1H, dddd, *J*=7.1, 7.7, 10.2, 17.3 Hz, C*H*=CH_2), 5.07 (1H, br d, *J*=10.2 Hz, CH=C*H*H), 5.02 (1H, br d, *J*=17.3 Hz, CH=CH*H*), 4.68 (1H, d, *J*=11.8 Hz, C*H*HPh), 4.59 (1H, d, *J*=11.8 Hz, CH*H*Ph), 4.17 (1H, dd, *J*=3.4, 6.8 Hz, C*H*OTBS), 3.88 (1H, dd, *J*=8.4, 11.0 Hz, CH_2OH), 3.71 (1H, dd, *J*=3.9, 6.8 Hz, C*H*OMe), 3.70 (1H, dd, *J*=4.3, 8.4 Hz, CH_2OH), 3.45 (1H, d, *J*=3.9 Hz, C*H*OBn), 3.44 (3H, s, OCH_3), 2.17 (1H, dd, *J*=7.7, 14.1 Hz, C*H*HCH=CH_2), 2.08 (1H, dd, *J*=7.1, 14.1 Hz, CH*H*CH=CH_2), 1.94 (1H, ddd, *J*=3.4, 4.3, 11.0 Hz, C*H*CH_2OH), 1.06 (3H, s, CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.14 (3H, s, Si(CH_3)(CH_3)), 0.13 (3H, s, Si(CH_3)(CH_3)); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.8 (s), 134.5 (d), 128.4 (d)×2, 127.5 (d), 127.4×2, 118.2 (t), 94.1 (d), 88.7 (d), 77.2 (d), 72.6 (t), 59.0 (t), 57.7 (q), 48.3 (s), 45.2 (d), 44.4 (t), 25.9 (q)×3, 18.1 (s), 17.3 (q), −4.4 (q), −5.0 (q); *m*/*z* (ES) found 443.2536 ($M+Na^+$, $C_{24}H_{40}NaO_4Si$ requires 443.2594).

4.1.11. (1R,2R,3S,4S,5R)-2-Allyl-3-benzyloxy-5-hydroxy-4-methoxy-2-methyl-cyclopentanecarboxylic acid methyl ester (**30b**)

Dess–Martin periodinane (81.3 mg, 0.19 mmol) was added to a stirred solution of the alcohol **29b** in anhydrous dichloromethane (2.6 mL) and pyridine (260 μL), and the suspension was then stirred at room temperature for 4 h. The mixture was diluted with diethyl ether, then saturated aqueous solutions of sodium thiosulfate (2.5 mL) and sodium hydrogen carbonate (2.5 mL) were added and the mixture was stirred at room temperature for a further 0.5 h. The separated aqueous layer was extracted with diethyl ether (3×5 mL), and the combined ether extracts were then dried over $MgSO_4$ and concentrated in vacuo to leave the corresponding aldehyde, which was used without further purification.

Sodium chlorite (58.0 mg, 0.64 mmol) and a solution of potassium dihydrogen phosphate (87.0 mg, 0.64 mmol) in water (0.6 mL) were added to a stirred solution of the crude aldehyde in *tert*-butanol (2.5 mL) and 2,3-dimethylbut-2-ene (2.5 mL). The mixture was stirred at room temperature for 15 h, and was then diluted with dichloromethane (14 mL) and water (7 mL). The separated aqueous layer was extracted with dichloromethane (2×7 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to leave the corresponding carboxylic acid. A solution of trimethylsilyldiazomethane (100 μL, 200 μmol, 2 M in dichloromethane) was added dropwise to a stirred solution of the carboxylic acid in dry methanol–benzene (1:2, 3 mL), under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, and then concentrated in vacuo to leave the crude methyl ester **30a**, which was used without further purification. Tetrabutylammonium fluoride (81.0 mg, 0.26 mmol) was added to a stirred solution of the methyl ester in anhydrous THF (2.6 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 26 h, and then diluted with diethyl ether (12 mL) and water (3 mL). The separated aqueous layer was extracted with diethyl ether (3×12 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–petrol (2:1) as eluent, to give the *β-hydroxy ester* (29.5 mg, 69% over four steps) as a colourless oil; $[\alpha]_D^{26}$ +37.6 (*c* 0.17, $CHCl_3$); ν_{max} ($CHCl_3$) 3483 (br), 2934, 2902, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38–7.27 (5H, Ar*H*), 5.71 (1H, dddd, *J*=4.8, 7.5, 10.2, 17.0 Hz, C*H*=CH_2), 5.06 (1H, dd, *J*=2.3, 10.2 Hz, CH=C*H*H), 4.76 (1H, br d, *J*=17.0 Hz, CH=CH*H*), 4.76 (1H, d, *J*=12.0 Hz, C*H*HPh), 4.57 (1H, d, *J*=12.0 Hz, CH*H*Ph), 4.19 (1H, dd, *J*=2.1, 6.2 Hz, C*H*OH), 3.78 (1H, dd, *J*=2.1, 6.2 Hz, C*H*OMe), 3.77 (3H, s, CO_2CH_3), 3.50 (1H, d, *J*=6.2 Hz, C*H*OBn), 3.44 (3H, s, OCH_3), 2.70 (1H, d, *J*=6.2 Hz,

C*H*CO_2Me), 2.26–2.18 (2H, m, CH_2CH=CH_2), 0.93 (3H, s, CCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.8 (s), 138.9 (d), 133.8 (s), 128.3 (d)×2, 127.7 (d)×2, 127.5 (d), 119.1 (t), 93.1 (d), 85.5 (d), 74.2 (d), 72.2 (t), 57.6 (q), 51.9 (q), 49.6 (d), 46.8 (s), 42.5 (t), 18.9 (q); *m*/*z* (ES) found 357.1649 (M+Na^+, $C_{19}H_{26}NaO_5$ requires 357.1678).

*4.1.12. (3R,4S,5R)-5-Allyl-4-benzyloxy-2-hydroxy-3-methoxy-5-methyl-cyclopent-1-enecarboxylic acid methyl ester (**32a**)*

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12 mg, 61 μmol), 4-dimethyl aminopyridine (1.2 mg, 10 μmol, DMAP), then pyridine trifluoroacetate (7.9 mg, 41 μmol) were added to a stirred solution of the β-hydroxy ester **30b** (3.4 mg, 10 μmol) in dry DMSO (300 μL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 3 days, then water (500 μL) was added and the mixture was extracted with diethyl ether (5×500 μL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, using diethyl ether–pentane (1:6) as eluent, to give the *enol ester* (3.0 mg, 89%) as a colourless film; $[\alpha]_D^{20}$ +52.6 (*c* 0.19, $CHCl_3$); ν_{max} ($CHCl_3$) 2977, 2874, 1661, 1619 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.55 (1H, s, O*H*), 7.42–7.27 (5H, m, Ar*H*), 5.59 (1H, dddd, *J*=6.2, 8.5, 10.1, 16.4 Hz, C*H*=CH_2), 4.99 (1H, br d, *J*=10.1 Hz, CH=C*H*H), 4.85 (1H, br d, *J*=16.4 Hz, CH=CH*H*), 4.78 (1H, d, *J*=11.9 Hz, C*H*HPh), 4.68 (1H, d, *J*=11.9 Hz, CH*H*Ph), 4.37 (1H, d, *J*=6.5 Hz, C*H*OMe), 3.83 (1H, d, *J*=6.5 Hz, C*H*OBn), 3.82 (3H, s, CO_2CH_3), 2.52 (1H, dd, *J*=6.2, 14.0 Hz, C*H*HCH=CH_2), 2.23 (1H, dd, *J*=8.5, 14.0 Hz, CH*H*CH=CH_2), 1.16 (3H, s, CCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.8 (s), 169.9 (s), 138.5 (d), 135.1 (s), 128.2 (d)×2, 127.7 (d)×2, 127.5 (d), 117.7 (t), 85.7 (d), 84.1 (d), 77.2 (d), 72.6 (t), 58.5 (q), 51.2 (q), 44.4 (t), 42.1 (s), 21.7 (q); *m*/*z* (ES) found 355.1573 (M+Na^+, $C_{19}H_{24}NaO_5$ requires 355.1521).

*4.1.13. (3R,4S,5R)-5-Allyl-4-benzyloxy-2,3-dimethoxy-5-methyl-cyclopent-1-enecarboxylic acid methyl ester (**32b**)*

Potassium carbonate (13 mg, 95 μmol) and dimethyl sulfate (9.5 mg, 76 μmol) were added portionwise to a stirred solution of the enol ester **32a** (6.3 mg, 19 μmol) in dry DMSO (300 μL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 16 h, then water (300 μL) was added and the mixture was extracted with diethyl ether (5×500 μL). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo to leave the *methyl enol ether* (6.4 mg, 97%) as a colourless film; $[\alpha]_D^{22}$ +35.5 (*c* 0.58, $CHCl_3$); ν_{max} ($CHCl_3$) 2949, 1698, 1627 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42–7.27 (5H, m, Ar*H*), 5.59 (1H, dddd, *J*=6.1, 8.6, 10.1, 17.1 Hz, C*H*=CH_2), 5.00 (1H, br d, *J*=10.1 Hz, CH=C*H*H), 4.87 (1H, br d, *J*=17.1 Hz, CH=CH*H*), 4.73 (1H, d, *J*=11.7 Hz, C*H*HPh), 4.67 (1H, d, *J*=11.7 Hz, CH*H*Ph), 4.47 (1H, d, *J*=5.5 Hz, C*H*OMe), 3.89 (3H, s, OCH_3), 3.87 (1H, d, *J*=5.5 Hz, C*H*OBn), 3.73 (3H, s, CO_2CH_3), 3.40 (3H, s, OCH_3), 2.55 (1H, dd, *J*=6.1, 14.0 Hz, C*H*HCH=CH_2), 2.22 (1H, dd, *J*=8.6, 14.0 Hz, CH*H*CH=CH_2), 1.16 (3H, s, CCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.30 (s), 161.8 (s), 138.5 (s), 135.5 (d), 128.2 (d)×2, 127.7 (d)×2, 117.9 (t), 112.7 (s), 85.5 (d), 84.1 (d), 77.3 (d), 72.7 (t), 58.3 (q), 56.1 (q), 51.2 (q), 46.6 (q), 42.8 (t), 21.8 (q); *m*/*z* (ES) found 369.1677 (M+Na^+, $C_{20}H_{26}NaO_5$ requires 369.1678).

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