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Synthesis and revision of the stereochemistry of a cyclopentenone natural product isolated from ascomycete strain A23-98

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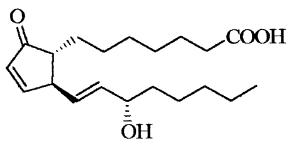
Abstract—The 2-propenyl-4,5-dihydroxycyclopent-2-enones **4**, **10** and **14** have been synthesised in optically active form. NMR data suggest the compounds **10** and **14** (but not **4**) correspond to compounds isolated from ascomycete strain A23-98.

1. Introduction and background information

The cyclopentenone prostaglandins, for example, prostaglandin A_1 **1** display anti-viral and anti-inflammatory properties in vitro and in vivo as well as anti-cancer activity in vitro.[1] These properties have been linked to the ability of prostaglandins -A and -J to activate heat shock factors (HSFs) and thus to potentiate the production of heat shock proteins (HSPs; in particular HSP-70) and to inhibit the formation of nuclear transcription factor NF-κB.[2]



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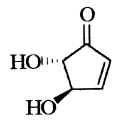

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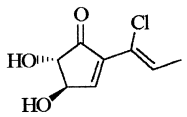
It has also been shown that cyclopentenone[3] itself and the dihydroxy compound **2**[4] activate HSF and/or inhibit NF-κB with weak to modest potency, respectively.

More recently, ((*Z*)-1-chloro-propenyl)-4,5-dihydroxy-cyclopent-2-enone **3** was isolated from ascomycete strain A23-98 and shown to possess NF-κB inhibitory activity.[5] A dechloro compound was also isolated and given the structure **4**, based on NMR evidence. It is noteworthy that compound **4** comprised a mixture of *syn*- and *anti*-C(4) epimers and was reported to possess NF-κB inhibitory activity.



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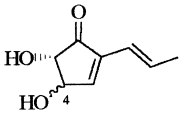

4

The NMR evidence regarding the geometry of the *exo*-cyclic alkene unit in **4** was based on the lack of a NOESY correlation between H-C(3) and the methyl group. The coupling constant between the alkene protons could not be observed because of overlapping peaks in the ^{1}H NMR spectrum.

We set out to synthesise *syn*-**4** and *anti*-**4** (i.e., the *cis*- and *trans*-diols) in order to confirm the structure of the compounds.

2. Results and discussion

Retrosynthetic analysis suggested cleavage of the C(2) bond as shown (Fig. 1). It was envisaged that, in the forward sense this bond could be made via a palladium-catalysed Stille-type reaction between a stannane and vinyl iodide **5**.[6]

Further retrosynthesis reveals the cyclopentenone **6**; the dextrorotatory enantiomer is available in 6 steps from D-ribose **7** while (−)-**6** is prepared from D-ribose **7** by varying the order of the steps (Scheme 1).[7] In our hands D-ribose **7** was converted into (+)-**6** in 40% overall yield, while (−)-**6** was prepared from **7** in 29% overall yield. Halogenation of (+)-**6** using iodine in a mixture of pyridine and carbon tetrachloride, furnished the 2-iodo-compound **5** (Scheme 2).

Palladium-catalysed Stille reaction between vinyl iodide **5**

Keywords: 2-Alkenyl-4,5-dihydroxycyclopent-2-enones; Stille-type reaction; *cis*-Tributylpropenyl Stannane.
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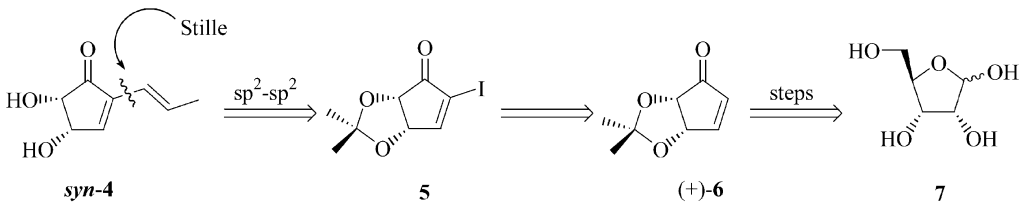


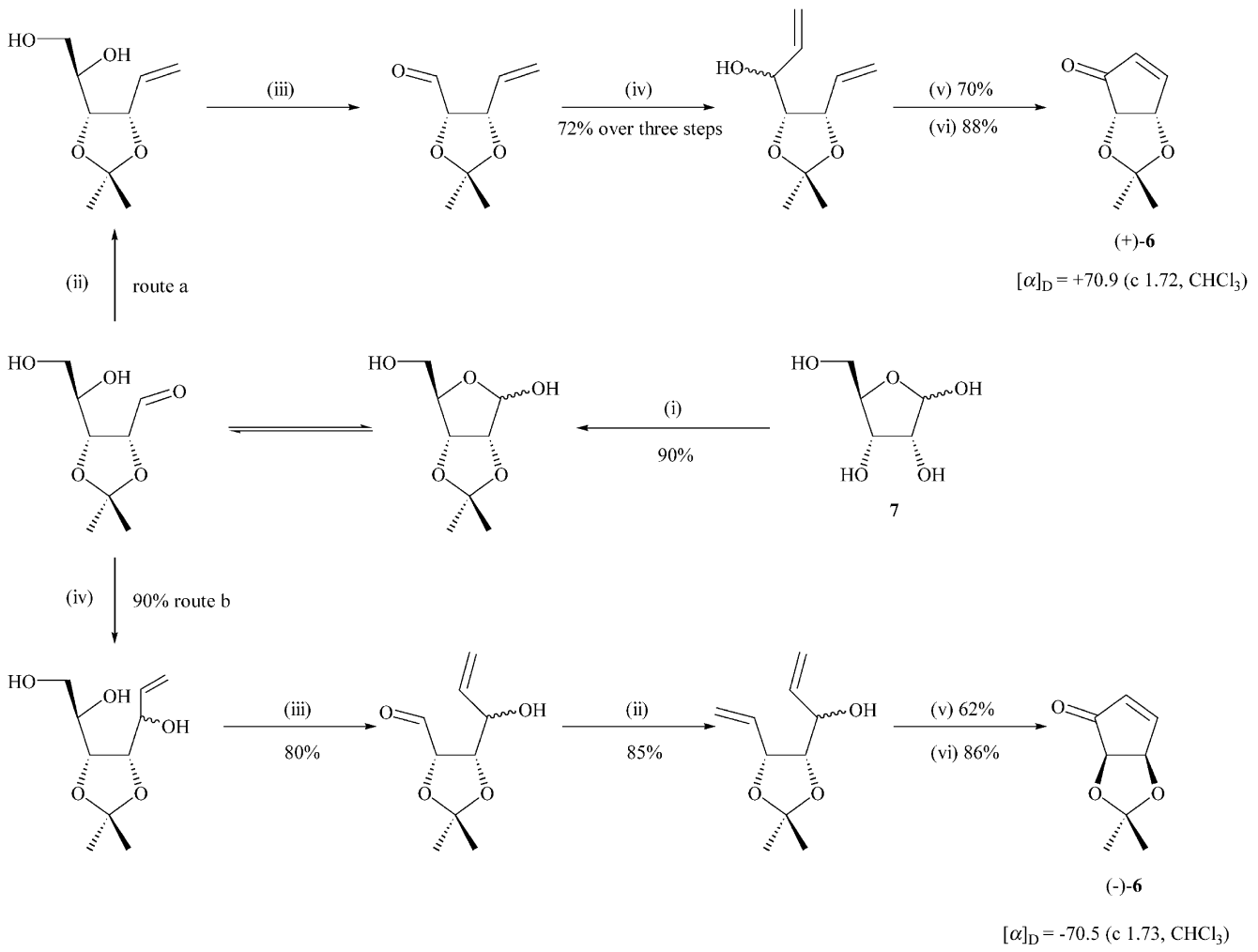
Figure 1.

and *trans*-tributylpropenylstannane[8] gave a crude sample of the compound **8**. Deprotection of **8** with PPTS in methanol gave (+)-*syn*-**4**. The ^{1}H NMR spectrum of **4** showed two distinct signals for the *exo*-cyclic alkene protons in contrast to the literature data for the natural compound which stipulated these protons produced an AA′ spin system centred at 6.05 ppm.

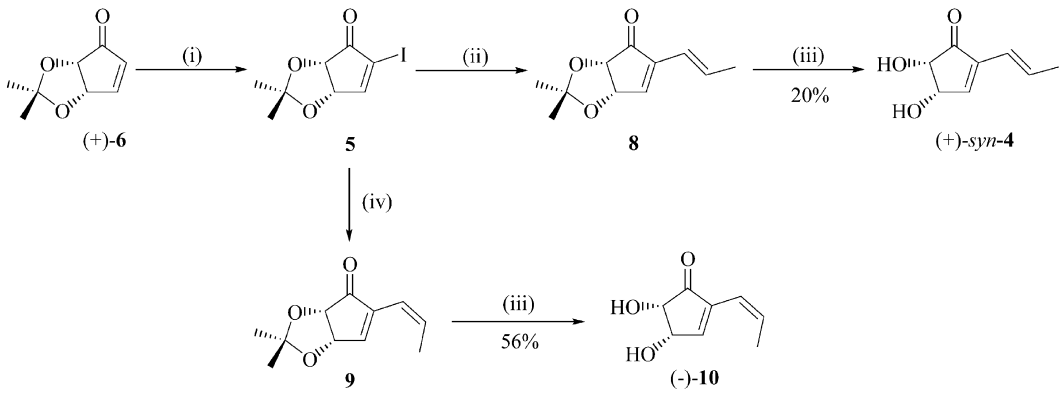
Employing *cis*-tributylpropenyl stannane[9] in the Stille coupling reaction gave the corresponding (*Z*)-propenyl-cyclopent-2-enone **9** in 93% yield. Deprotection with PPTS in methanol gave the diol (−)-**10**, the structure of which was confirmed by X-ray crystallography (Fig. 2).[10]

(+)-Cyclopentenone **10** was obtained from (−)-**6** using the same methodology in an overall yield of 38%. The diol **10** gave an NMR spectrum that was identical to that described for the natural product;[5] to illustrate the point the distinctive alkene signals for **4** and **10** are shown in Figure 3.

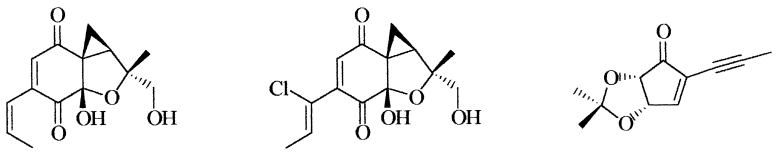
Interestingly, by way of an analogy, Smith et al. have shown previously that the alkenyl side-chain of dechloromikrolin **11** possessed a (*Z*)-alkene unit and not an (*E*)-alkene side-chain as predicted by NMR studies and correlation with mikrolin **12**. This led to a revision of the proposed biosynthetic pathway, in particular the step at which chlorination took place.[11]



Scheme 1. Reagents and conditions: (i) acetone, H_2SO_4, rt, 90%; (ii) CH_3PPh_3Br, NaH/DMSO, THF, rt (route a) or CH_3PPh_3Br, *t*BuOK, THF, reflux (route b); (iii) $NaIO_4$, DCM, H_2O, rt; (iv) vinylmagnesium bromide, THF −78 °C; (v) Grubbs' catalyst, $CHCl_3$, rt; (vi) PDC, DCM, rt.



Scheme 2. Reagents and conditions: (i) I_2, pyr./CCl_4, 97%; (ii) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, *trans*-tributylpropenyl stannane, 73%; (iii) PPTS, MeOH, reflux; (iv) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, *cis*-tributylpropenyl stannane, 93%.



11 **12** **13**

Palladium-catalysed Sonogashira coupling of the iodide **5** and propyne gave the alkyne **13**. Unfortunately, attempted reduction of **13** to the alkene **9** using Lindlar's catalyst was unsuccessful.

In view of the revision of the structure of the natural product, we changed our second target structure to that of the *anti*-diol **14** (Scheme 3) and styled the approach on the strategy of Takahashi and co-workers.[12] Thus, Weitz–Scheffer oxidation of 4-silanyloxycyclopentenone **15** gave the epoxide **16** (41%) which was converted into the tertiary alcohol **17** in a highly satisfactory 88% yield. Treatment of **17** with Tf_2O in 2,6-lutidine at −78 °C gave a mixture of the desired product **18** in admixture with a second compound, which was tentatively ascribed the structure of the triflate derivative of compound **17**. Treatment of this mixture with Pd(0) and benzoic acid gave rise to two pairs of diastereoisomers **19** and **20**. Protection of the free hydroxyl group as the *tert*-butyldimethylsilyl derivative simplified the situation, furnishing one pair of diastereoisomers **21**.

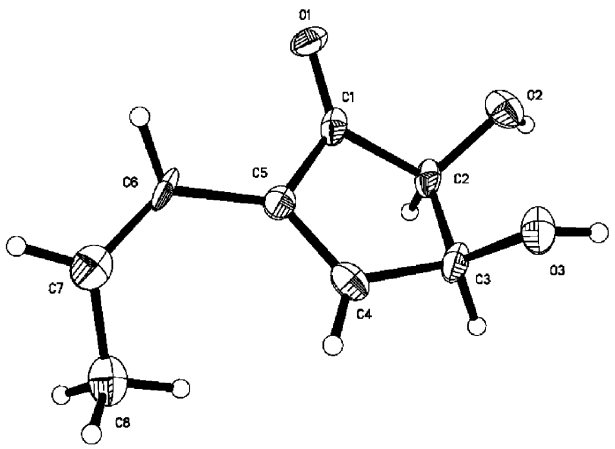


Figure 2. X-ray crystal structure of (−)-**10**.

Reduction of the alkyne moiety proceeded exceedingly well on this occasion, affording diene **22** in 90% yield. Removal of the benzoyl group using DIBAL and oxidation employing PDC furnished compound **23**, whereupon acid-catalysed removal of the silyl protecting groups gave the diol **14** (31% yield for the last three steps). The NMR spectrum of compound **14** showed a coupling constant of 2.8 Hz between H–C(4) and H–C(5) (cf. 5.5 Hz for the *cis*-diol). The *exo*-cyclic alkene protons gave an AA′ signal centred at 6.03 ppm.

3. Conclusions

The non-halogenated compounds isolated from ascomycete strain A23-98 are not *syn*- and *anti*-diols **4**. Instead, the reported physical data fit better to the measurements obtained for the *cis*-alkenes **10** and **14**. While the absolute configurations of the natural products were not ascertained and optical rotations were not reported, $[\alpha]_D$ values are now available for (+)-**10**, (−)-**10** and (+)-**14**, should further information for the natural compounds become available.

The biological activity of the cyclopentenone derivatives described herein will be reported in a separate publication.

4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. Anhydrous THF was distilled under nitrogen from the sodium-benzophenone

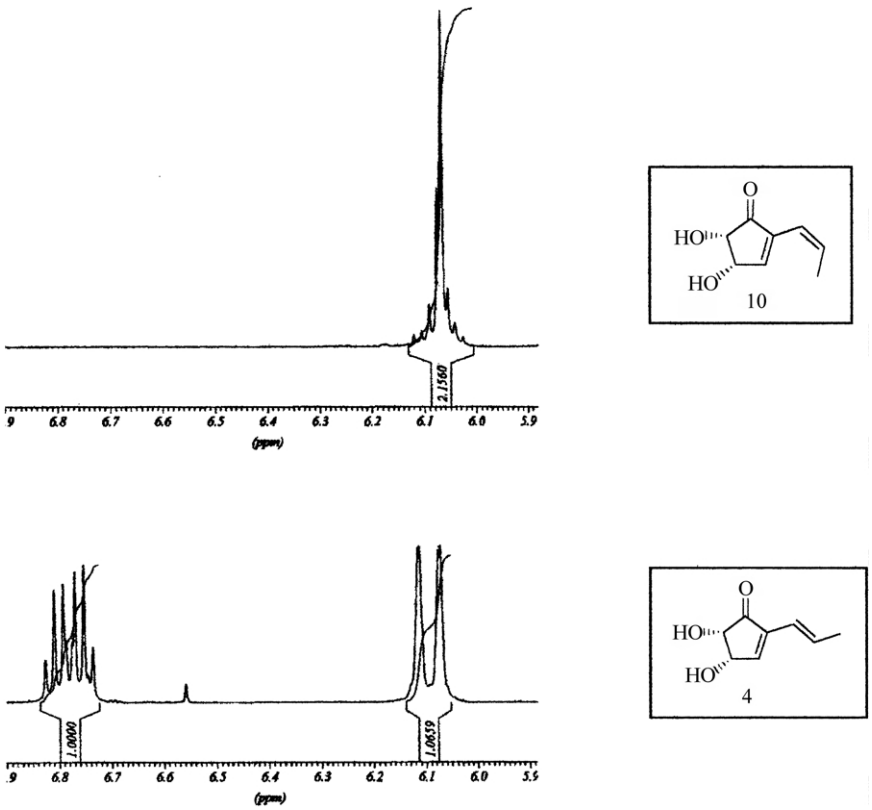


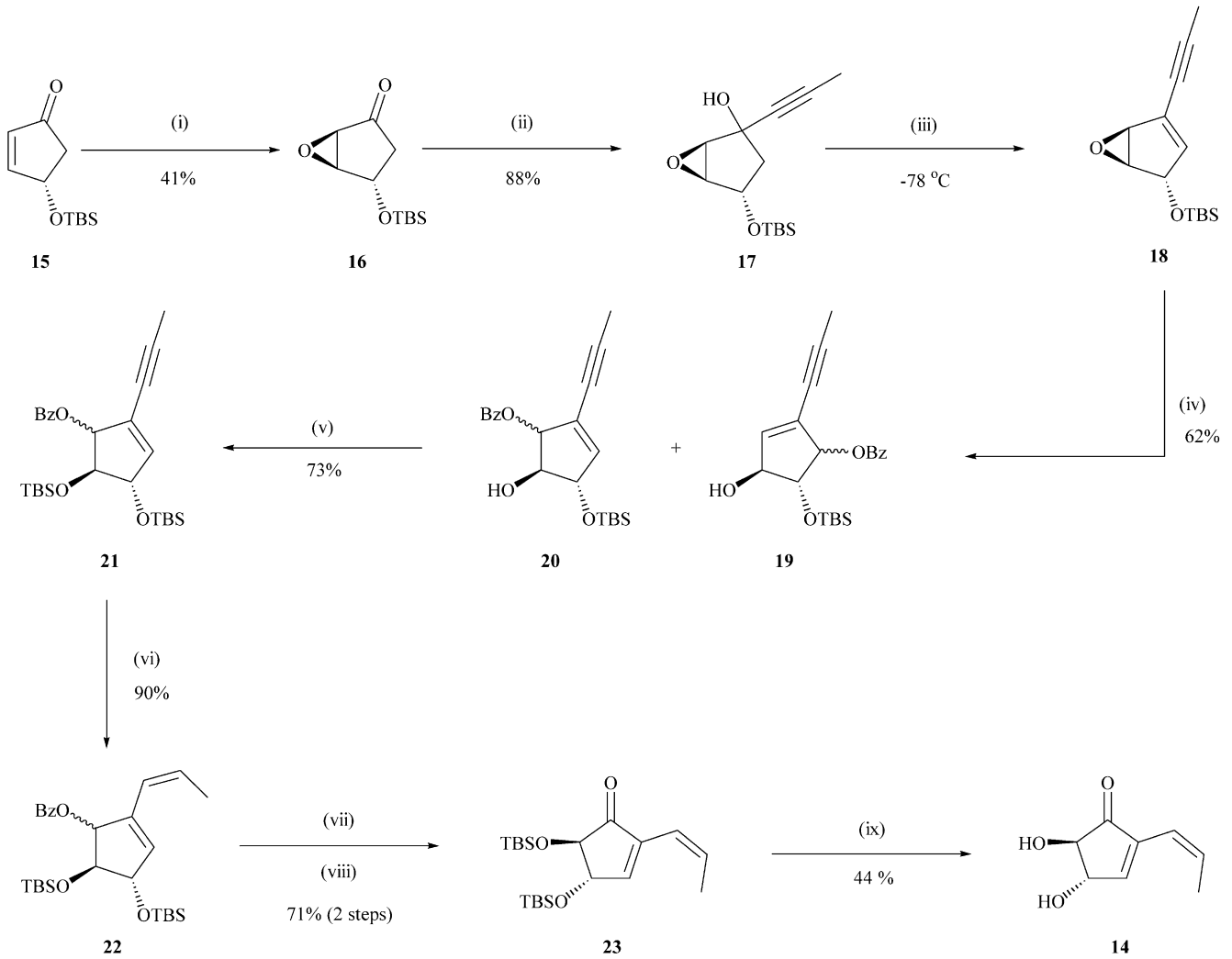
Figure 3.

ketyl radical, DCM was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Infrared spectroscopy was performed on a Perkin–Elmer Paragon 1000 FTIR spectrometer. Optical rotation measurements were recorded using an Optical Activity, Polar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points are uncorrected. Flash column chromatography, under moderate pressure, was performed using silica gel-ICN 32-63, 60 Å.

4.1.1. (3a*S*,6a*S*)-5-Iodo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (5). To a solution of enone (+)-**6** (100 mg, 0.65 mmol) in carbon tetrachloride–pyridine (2.5 ml, 1:1) at 0 °C was added iodine (0.65 g, 2.6 mmol) in carbon tetrachloride–pyridine (2.5 ml, 1:1) dropwise and the reaction stirred for 2.5 h at room temperature under an atmosphere of nitrogen. The reaction was diluted with diethyl ether (25 ml) and water (25 ml) and the layers separated. The aqueous layer was washed with diethyl ether (3×25 ml) and the combined organic layers washed with sat. aq. $Na_2S_2O_3$ (2×50 ml), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:4) to yield the title compound **5** (116 mg, 64%) as a white solid; ν_{max}(film)/cm^{-1} 1380, 1568, 1732, 2356, 2939, 2997; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.53 (1H, d, J=5.6 Hz, C(3a)H), 5.22 (1H, dd, J=2.6, 5.6 Hz, C(6a)H), 7.97 (1H, d, J=2.6 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 26.5, 27.4 (CH_3), 73.8, 79.7 (CH), 105.8, 115.9 (C), 164.8 (CH), 197.4 (C); *m*/*z* (CI) 298 ([M+NH_4]$^+$, 100%); Found: [M+NH_4]$^+$, 297.99380. $C_8H_{13}INO_3$ requires [M+NH_4]$^+$, 297.99405.

4.1.2. *trans*-Tributyl-propenyl-stannane. To a solution of *trans*-1-bromopropene (1.0 g, 8.3 mmol) in anhydrous diethyl ether (23 ml) at −78 °C was added *t*-BuLi (1.7 M in pentane, 10.8 ml, 18.3 mmol) slowly and the reaction stirred for 1 h under an atmosphere of argon. Tributyltin chloride (2.25 ml, 8.3 mmol) was added and the reaction allowed to warm to room temperature over 16 h. The reaction was quenched with methanol (1 ml) and water (50 ml) was added. The product was extracted with ethyl acetate (2×50 ml) and the combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by high vacuum distillation (125 °C, 0.1 mm Hg) to yield the title compound (2.69 g, quant.) as a colourless oil; ν_{max}(film)/cm^{-1} 874, 982, 1376, 1418, 1442, 1464, 1602, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (9H, t, J=7.2 Hz, 3×CH_3), 1.26–1.57 (18H, m, 9×CH_2), 1.84 (3H, d, J=5.4 Hz, CH_3), 5.87–6.03 (2H, m, 2×CH); δ_C (100 MHz, $CDCl_3$, Me_4Si) 9.8 (CH_2), 14.0, 23.9 (CH_3), 27.6, 29.5 (CH_2), 129.3, 144.6 (CH).

4.1.3. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*E*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (8). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *trans*-tributyl-propenyl-stannane (0.20 g, 0.6 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml)



Scheme 3. Reagents and conditions: (i) H_2O_2, NaOH, MeOH, 41%; (ii) propynylmagnesium bromide, THF, −78 °C, 88%; (iii) trifluoromethanesulfonic anhydride, 2,6-lutidene, 4 Å molecular sieves, DCM; (iv) $Pd(PPh_3)_4$, benzoic acid, THF, 62%; (v) TBSCl, imid., DMF, 73%; (vi) H_2, Lindlar's cat., quinoline, EtOAc, 90%; (vii) DIBAL, toluene, −78 °C; (viii) PDC, 4 Å molecular sieves, DCM; (ix) acetic acid–water–THF (3:1:1), 60 °C, 44%.

was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (5 ml) and the product washed with aqueous KF (2×5 ml). The combined organic layers were washed with water (10 ml) and the combined aqueous layers back extracted with ethyl acetate (10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:9) to yield the title compound **8** (76 mg, 73%) as a yellow solid; ν_{max}(film)/cm^{-1} 1345, 1374, 1456, 1653, 1717, 2936; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.84 (3H, dd, J=1.4, 6.8 Hz, CH_3) 4.50 (1H, d, J=5.6 Hz, C(3a)H), 5.19 (1H, dd, J=2.6, 5.6 Hz, C(6a)H), 6.08 (1H, dd, J=1.4, 15.7 Hz, C(1′)H), 6.80 (1H, dq, J=6.8, 15.7 Hz, C(2′)H), 7.18 (1H, d, J=2.6 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 19.1, 26.3, 27.6 (CH_3), 76.6, 78.2 (CH), 115.1 (C), 120.5, 135.2 (CH), 141.2 (C), 150.0 (CH), 201.8 (C); *m/z* (CI) 212 ([M+NH_4]$^+$, 30%), 154 ([M−C_3H_6O+NH_4]$^+$, 40), 137 ([M−C_3H_6O+H]$^+$, 100); Found: [M+NH_4]$^+$, 212.12849. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.4. (3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*E*)-enyl-cyclopent-2-enone (*syn*-4). To a solution of acetonide **8** (75 mg, 0.39 mmol) in methanol (3.5 ml) was added pyridinium *p*-toluenesulfonate (15 mg, 0.06 mmol) and the reaction was heated at reflux for 6.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 1:1) to yield the title compound *syn*-**4** (12 mg, 20%) as a pale yellow solid; mp 97–99 °C; $[\alpha]_D$=+38.8 (*c* 1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1158, 1652, 1708, 2956, 3250 br., 3452 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.85 (3H, dd, J=1.4, 6.8 Hz, CH_3) 2.71 (1H, br.s, −OH), 2.99 (1H, br.s, −OH), 4.17 (1H, d, J=5.6 Hz, C(5)H), 4.82–4.84 (1H, m, C(4)H), 6.10 (1H, d, J=16.0 Hz, C(1′)H), 6.74–6.83 (1H, dq, J=6.8, 16.0 Hz, C(2′)H), 7.24 (1H, d, J=3.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 19.2 (CH_3), 67.3, 72.6, 120.5, 135.3 (CH), 140.9 (C), 150.7 (CH), 205.2 (C); *m/z* (CI) 172 ([M+NH_4]$^+$, 100%), 154 ([M]$^+$, 23); Found: [M+NH_4]$^+$, 172.09704. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.5. *cis*-Tributyl-propenyl-stannane. To a solution of

tributyl(propynyl)stannane (500 mg, 1.5 mmol) in anhydrous tetrahydrofuran (35 ml) was added bis(cyclopentadienyl)zirconium chloride hydride (0.77 g, 3 mmol) and the reaction stirred for 30 min. under an atmosphere of nitrogen. The reaction was quenched with water (1 ml) and the reaction mixture stirred for 30 min. Pentane (5 ml) was added and the mixture filtered through a silica plug and the solvent removed in vacuo. The product was purified by high vacuum distillation (125 °C, 0.1 mm Hg) to yield the title compound (0.5 g, 99%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 960, 1072, 1376, 1464, 1601, 2854, 2923, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.87–0.94 (9H, m, 3×CH_3), 1.27–1.54 (18H, m, 9×CH_2), 1.76 (3H, dd, J=1.3, 6.4 Hz, CH_3), 5.80 (1H, dq, J=1.3, 12.4 Hz, CH), 6.59 (1H, dq, J=6.4, 12.4 Hz, CH); δ_C (100 MHz, $CDCl_3$, Me_4Si) 10.5 (CH_2), 14.0, 22.3 (CH_3), 27.7, 29.6 (CH_2), 129.5, 143.6 (CH).

4.1.6. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one ((−)-9). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *cis*-tributyl-propenyl-stannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml) was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above afforded the title compound (−)-**9** (97 mg, 93%) as a yellow solid; mp 32–34 °C; $[\alpha]_D$=−73.7 (*c* 1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 1202, 1373, 1637, 1725, 2937, 2990; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.40 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.87 (3H, d, J=5.4 Hz, CH_3) 4.50 (1H, d, J=5.6 Hz, C(3a)H), 5.28 (1H, dd, J=2.7, 5.6 Hz, C(6a)H), 6.05–6.12, (2H, m, C(1′)H and C(2′)H), 7.38 (1H, d, J=2.7 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 16.1, 26.6, 28.0 (CH_3), 76.9, 77.6 (CH), 115.6 (C), 118.1, 134.8 (CH), 141.3 (C), 152.3 (CH), 202.5 (C); *m*/*z* (CI) 212 ([M+NH_4]$^+$, 51%), 154 ([M−C_3H_6O+NH_4]$^+$, 29), 137 ([M−C_3H_6O+H]$^+$, 100); Found: [M+NH_4]$^+$, 212.12812. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.7. (3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone ((−)-10). To a solution of acetonide (−)-**9** (60 mg, 0.31 mmol) in methanol (3.0 ml) was added pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) and the reaction heated at reflux for 5.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 2:3) to yield the title compound (−)-**10** (27 mg, 56%) as a white solid; mp 108–109 °C; $[\alpha]_D$=−17.6 (*c* 1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1153, 1292, 1712, 2939, 3283 br., 3431 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.88 (3H, d, J=5.2 Hz, CH_3), 2.90 (1H, br.s, −OH), 3.16 (1H, br.s, −OH), 4.18 (1H, d, J=5.5 Hz, C(5)H), 4.90 (1H, dd, J=3.2, 5.5 Hz, C(4)H), 6.02–6.12 (2H, m, C(1′)H and C(2′)H), 7.45 (1H, d, J=3.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 15.8 (CH_3), 67.8, 71.2, 117.6, 134.6 (CH), 140.6 (C), 153.3 (CH), 205.7 (C); *m*/*z* (CI) 172 ([M+NH_4]$^+$, 100%), 155 ([M+H]$^+$, 23), 154 ([M]$^+$, 28), 137 ([M−OH]$^+$, 57); Found: [M+NH_4]$^+$, 172.09704. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.8. (3a*R*,6a*R*)-5-Iodo-2,2-dimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (*ent*-5). To a solution of enone (−)-**6** (0.53 g, 3.4 mmol) in carbon tetrachloride–pyridine (12.5 ml, 1:1) at 0 °C was added iodine (3.45 g, 13.6 mmol) in carbon tetrachloride–pyridine (12.5 ml, 1:1) dropwise and the reaction stirred for 1.5 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above furnished the title compound *ent*-**5** (0.69 g, 73%) as a white solid; Found: C, 34.45; H, 3.22. $C_8H_9IO_3$ requires C, 34.31; H, 3.24%; Found: [M+NH_4]$^+$, 297.99408. $C_8H_{13}INO_3$ requires [M+NH_4]$^+$, 297.99405.

4.1.9. (3a*R*,6a*R*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one ((+)-9). To a solution of vinyliodide *ent*-**5** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 ml) was added bis(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper iodide (9.5 mg, 0.05 mmol) and triphenylarsine (15.3 mg, 0.05 mmol). A solution of *cis*-tributyl-propenyl-stannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 ml) was added and the reaction stirred for 16 h at room temperature under an atmosphere of nitrogen. Work-up and chromatography as described above furnished the title compound (+)-**9** (78 mg, 75%) as a yellow solid; mp 32–34 °C; $[\alpha]_D$=+85.6 (*c* 1.4, $CHCl_3$); Found: [M+NH_4]$^+$, 212.12848. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

4.1.10. (3a*R*,6a*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone ((+)-10). To a solution of acetonide (+)-**9** (65 mg, 0.34 mmol) in methanol (3.0 ml) was added pyridinium *p*-toluenesulfonate (13 mg, 0.05 mmol) and the reaction heated at reflux for 6.5 h. The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 2:3) to yield the title compound (+)-**10** (36 mg, 69%) as a white solid; mp 106–108 °C; $[\alpha]_D$=+25.0 (*c* 1.0, MeOH); Found: [M+NH_4]$^+$, 172.09753. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

4.1.11. (3a*S*,6a*S*)-2,2-Dimethyl-5-prop-1-ynyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (13). To a solution of vinyliodide **5** (150 mg, 0.54 mmol) in degassed dimethylformamide (3.0 ml) was added tetrakis(triphenylphosphine)palladium (62 mg, 0.05 mmol), copper iodide (21 mg, 0.1 mmol) and triethylamine (0.15 ml, 1.08 mmol). Propyne was bubbled through the solution for 10 min. and the reaction stirred for 4 h at room temperature under an atmosphere of propyne. The reaction was diluted with water (2 ml) and the product was extracted with diethyl ether (3×10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–petrol, 1:10) to yield the title compound **13** (60 mg, 58%) as a yellow solid; mp 74–76 °C; $[\alpha]_D$=+33.0 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1375, 1603, 1732, 2241, 2936, 2991; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.06 (3H, s, CH_3) 4.51 (1H, d, J=5.6 Hz, C(3a)H), 5.24 (1H, dd, J=2.2, 5.6 Hz, C(6a)H), 7.48 (1H, d, J=2.2 Hz, C(6)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 5.0, 26.6, 27.9 (CH_3), 70.1 (C), 76.9, 77.2 (CH), 96.5, 115.8, 131.1 (C), 157.8 (CH), 199.9 (C); *m*/*z* (CI) 210 ([M+NH_4]$^+$, 100%), 152 ([M−C_3H_6O+NH_4]$^+$,

58), 135 ([M−C_3H_6O+H]$^+$, 71); Found: [M+NH_4]$^+$, 210.11328. $C_{11}H_{16}NO_3$ requires [M+NH_4]$^+$, 210.11301.

4.1.12. (1*R*,4*S*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hexan-2-one (16). To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-cyclopent-2-enone **15** (5.0 g, 23.6 mmol) in methanol (100 ml) at 0 °C was added 30% aqueous hydrogen peroxide (11.5 ml, 113 mmol). Sodium hydroxide (0.4 M, 61 ml, 24.4 mmol) was added dropwise over 10 min., and the reaction stirred at 0 °C for 30 min. The reaction was quenched with sat. aq. Na_2SO_3 (100 ml) and diluted with diethyl ether (100 ml). The layers were separated and the aqueous layer extracted with diethyl ether (3×100 ml), the organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:6) to yield the title compound **16** (2.21 g, 41%) as a colourless oil; $[\alpha]_D$=+21.7 (*c* 0.9, $CHCl_3$); Found: C, 58.12; H, 9.07. $C_{11}H_{20}O_3Si$ requires C, 57.85; H, 8.83%; ν_{max}(film)/cm^{-1} 1260, 1472, 1759, 2858, 2930, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.10 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.95 (1H, d, *J*=18.1 Hz, C*H*H), 2.59 (1H, dd, *J*=5.7, 18.1 Hz, CH*H*), 3.39 (1H, d, *J*=2.2 Hz, C(5)H), 3.78 (1H, d, *J*=2.2 Hz, C(1)H), 4.59 (1H, d, *J*=5.7 Hz, C(4)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.8, −4.76 (CH_3), 18.0 (C), 25.7 (CH_3), 42.3 (CH_2), 54.2, 60.8, 67.7 (CH), 207.9 (C); *m*/*z* (CI) 246 ([M+NH_4]$^+$, 29%), 171 ([M−$C(CH_3)_3$]$^+$, 24); Found: [M+NH_4]$^+$, 246.15305. $C_{11}H_{24}NO_3Si$ requires [M+NH_4]$^+$, 246.15254.

4.1.13. (1*R*,4*S*,5*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (17). To a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hexan-2-one **16** (3.2 g, 14.0 mmol) in anhydrous tetrahydrofuran (140 ml) at −78 °C was added propynylmagnesium bromide (0.5 M in tetrahydrofuran, 42.1 ml, 21.0 mmol) slowly over 15 min. and the reaction stirred at −78 °C for 20 h. The reaction was quenched with sat. aq. NH_4Cl (100 ml) and the reaction mixture diluted with ethyl acetate (100 ml). The layers were separated and the aqueous layer extracted with ethyl acetate (3×100 ml), the organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 4:5) to yield the title compound **17** (3.31 g, 88%) as a colourless oil; ν_{max}(film)/cm^{-1} 1258, 1351, 1473, 2360, 2857, 2929, 2955, 3419 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.83 (1H, dd, *J*=5.3, 13.7 Hz, C*H*H), 1.85 (3H, s, CH_3), 2.09 (1H, d, *J*=13.7 Hz, CH*H*), 3.41 (1H, d, *J*=2.5 Hz, C(5)H), 3.58 (1H, d, *J*=2.5 Hz, C(1)H), 4.38 (1H, d, *J*=5.3 Hz, C(4)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.5, −4.4, 4.0 (CH_3), 18.3 (C), 25.9 (CH_3), 46.6 (CH_2), 59.6, 62.1, 71.7 (CH), 73.4, 79.6, 83.3 (C); *m*/*z* (CI) 286 ([M+NH_4]$^+$, 49%), 269 ([M+H]$^+$, 28), 268 ([M]$^+$, 43), 251 ([M−OH]$^+$, 70); Found: [M+NH_4]$^+$, 286.18363. $C_{14}H_{28}NO_3Si$ requires [M+NH_4]$^+$, 286.18387.

4.1.14. (4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-cyclopent-2-enyl ester (21). A solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-1-ynyl-6-oxa-bicyclo[3.1.0]hexan-2-ol **17** (1.0 g, 3.73 mmol) and 4 Å molecular sieves (1.0 g) in anhydrous dichloromethane (40 ml) at −78 °C was stirred for 1 h under an atmosphere of nitrogen. 2,6-Lutidene (2.17 ml, 18.6 mmol) was added to the solution followed by trifluoromethanesulfonic anhydride (0.92 ml, 5.5 mmol) and the reaction stirred at −78 °C for 1 h. The reaction was quenched with water (10 ml) and the reaction mixture filtered through Celite. The product was extracted with dichloromethane (3×10 ml) and the organic layers combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:6) to yield the eliminated alcohol **18** along with an unseparable, unidentified product (687 mg) as a pale yellow oil (~3:1 in favour of the eliminated alcohol). The mixture was taken onto the next step without further characterisation. A solution of this mixture (425 mg, 1.7 mmol) in anhydrous tetrahydrofuran (0.5 ml) was added to a stirred solution of tetrakis(triphenylphosphine)palladium (98 mg, 0.09 mmol) and benzoic acid (azeotropically dried with toluene, 0.23 g, 1.9 mmol) in anhydrous tetrahydrofuran (2 ml) at 0 °C, under an atmosphere of nitrogen. The reaction was stirred at 0 °C for ten min. followed by 1 h at room temperature. The reaction mixture was passed through a plug of silica and flushed through with diethyl ether and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:10) to yield a mixture of regio- and diastereoisomers of the products **19** and **20** (392 mg, 62% over 2 steps) as a yellow oil. The mixture was taken onto the next step without further characterisation. To a solution of the mixture of alcohols (392 mg, 1.05 mmol) in anhydrous dimethylformamide (10 ml) was added imidazole (143 mg, 2.1 mmol) followed by *tert*-butyldimethylsilyl chloride (191 mg, 1.3 mmol) and the reaction stirred at room temperature for 18 h. The reaction was quenched with water (20 ml) and the product extracted with diethyl ether (30 ml). The organic layer was washed with brine (20 ml), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:10) to yield the title compound **21** (358 mg, 70%) as a colourless oil; ν_{max}(film)/cm^{-1} 1728, 2233, 2856, 2886, 2929, 2954; δ_H (400 MHz; $CDCl_3$; Me_4Si) −0.02 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.81 (3H, s, CH_3), 4.29 (1H, t, *J*=5.0 Hz, C(5)H), 4.57 (1H, m, C(4)H), 5.82 (1H, d, *J*=5.0 Hz, C(1)H), 5.95 (1H, s, C(3)H), 7.45 (2H, dd, *J*=7.5, Ph), 7.57 (1H, tt, *J*=1.5, 7.5 Hz, Ph), 8.10 (2H, d, *J*=7.5 Hz, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.2, −4.15, −4.1, 4.7 (CH_3), 18.3, 18.4 (C), 26.1, 26.2 (CH_3), 73.8 (C), 80.3, 82.3, 86.7 (CH), 90.9, 125.3 (C), 128.7, 130.2 (CH), 130.6 (C), 133.3, 138.6 (CH), 166.1 (C); *m*/*z* (ES+) 509 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 509.2514. $C_{27}H_{42}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 509.2519.

4.1.15. (4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-(*Z*)-enyl-cyclopent-2-enyl ester (22). To a solution of alkyne **21** (271 mg, 0.56 mmol) in ethyl acetate (11 ml) was added a solution of quinoline (0.1 M solution in ethyl acetate, 2.8 ml, 0.28 mmol) followed by Lindlar's catalyst (379 mg). The solution was evacuated and backfilled 4 times with hydrogen and the reaction stirred for 40 min. under a balloon of hydrogen. The reaction mixture was filtered through a plug of silica and the solvent removed

in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:15) to yield the title compound **22** (245 mg, 90%) as a colourless oil; ν_{max}(film)/cm^{-1} 1724, 2343, 2360, 2857, 2894, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) −0.01 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 1.80 (3H, d, J=5.7 Hz, C(3′)H), 4.33 (1H, t, J=4.8 Hz, C(5)H), 4.61 (1H, m, C(4)H), 5.68–5.78 (3H, m, C(1)H, C(1′)H and C(2′)H), 5.90 (1H, d, J=4.8 Hz, C(3)H), 7.44 (2H, dd, J=7.5 Hz, Ar), 7.56 (1H, tt, J=1.5, 7.5 Hz, Ar), 8.07 (2H, dd, J=1.5, 7.5 Hz, Ar); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.2, −4.15, −4.04, −4.01, 15.5 (CH_3), 18.3, 18.5 (C), 26.1, 26.3 (CH_3), 80.8, 83.4, 86.7, 122.4, 128.7, 130.1 (CH), 130.5 (C), 131.3, 132.6, 133.3 (CH), 138.2, 166.5 (C); *m/z* (ES+) 511 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 511.2698. $C_{27}H_{44}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 511.2676.

4.1.16. (4*S*,5*R*)-4,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-prop-(*Z*)-enyl-cyclopent-2-enone (23). To a solution of benzoate **22** (365 mg, 0.75 mmol) in anhydrous toluene (8 ml) at −78 °C under an atmosphere of nitrogen was added diisobutylaluminium hydride (1 M solution in hexanes, 1.65 ml, 1.65 mmol) slowly and the reaction stirred for 90 min. The reaction mixture was allowed to warm to room temperature then cooled to −78 °C and quenched with methanol (1 ml) and water (5 ml). The product was extracted with diethyl ether (3×10 ml) and the combined organic layers dried ($MgSO_4$) and the solvent removed in vacuo to yield 350 mg of a crude colourless oil. The crude alcohol (350 mg) was dissolved in dichloromethane (8 ml) and 4 Å molecular sieves (350 mg) added. After 45 min. at room temperature pyridinium dichromate (0.71 g, 1.88 mmol) was added and the reaction was stirred for 16 h. The reaction was filtered through a plug of silica and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–*n*-hexane, 1:15) to yield the title compound **23** (202 mg, 71% over two steps) as a colourless oil; $[\alpha]_D$=+86.2 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1472, 1732, 2359, 2857, 2885, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.15 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.94 (18H, s, 2×$SiC(CH_3)_3$), 1.84 (3H, d, J=5.7 Hz, CH_3), 4.18 (1H, d, J=2.7 Hz, C(5)H), 4.70 (1H, m, C(4)H), 5.94–6.03 (2H, m, C(1′)H and C(2′)H), 7.00 (1H, d, J=1.8 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) −4.6, −4.19, −4.18, −3.9, 16.0 (CH_3), 18.4, 18.7 (C), 26.15, 26.18 (CH_3), 77.4, 83.0, 118.3, 133.5 (CH), 139.3 (C), 152.7 (CH), 202.6 (C); *m/z* (CI) 383 ([M+H]$^+$, 100%), 325 ([M−C$(CH_3)_3$]$^+$, 49), 268 ([M−2×C$(CH_3)_3$]$^+$, 47); Found: [M+H]$^+$, 383.24393. $C_{20}H_{39}O_3Si_2$ requires [M+H]$^+$, 383.24377.

4.1.17. (4*S*,5*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone (14). A solution of *bis*-silylether **23** (200 mg, 0.52 mmol) in acetic acid–water–tetrahydrfuran (2 ml, 3:1:1) was heated at 60 °C for 4 h. Ethyl acetate (10 ml) was added to the cooled reaction mixture and the solution washed with sat. aq. $NaHCO_3$ (5 ml) and brine (5 ml). The aqueous layers were combined and washed with ethyl acetate (3×10 ml) and the organic layers combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; EtOAc–*n*-hexane, 7:3) to yield the title compound **14** (36 mg, 44%) as a white solid; mp 52–56 °C; $[\alpha]_D$=+22.6 (*c* 0.9, MeOH); ν_{max}(film)/cm^{-1} 1050, 1132, 1292, 1417, 1715, 2361, 2921, 3372 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.86 (3H, d, J=4.8 Hz, CH_3), 4.28 (1H, d, J=2.8 Hz, C(5)H), 4.82 (1H, m, C(4)H), 5.98–6.08 (2H, m, C(1′)H and C(2′)H), 7.25 (1H, d, J=2.2 Hz, C(3)H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 15.8 (CH_3), 75.6, 81.6, 117.3, 134.2 (CH), 139.2 (C), 153.2 (CH), 203.6 (C); *m/z* (CI) 172 ([M+NH_4]$^+$, 100%), 155 ([M+H]$^+$, 79), 154 ([M]$^+$, 20); Found: [M+H]$^+$, 155.07109. $C_8H_{11}O_3$ requires [M+H]$^+$, 155.07082.

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8. The *trans*-stannane was prepared from *trans*-1-bromo-1-propene and *t*-BuLi at −78 °C, quenching the vinyl anion with tributyltin chloride.
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