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First total synthesis of the marine natural products clavulolactones II and III.

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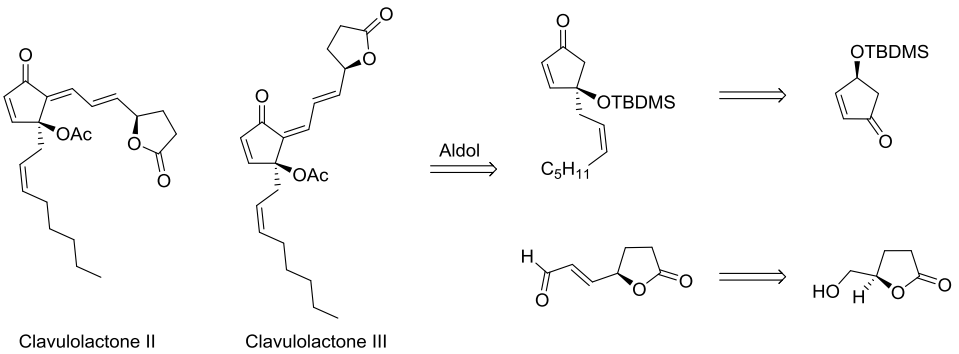
The first total synthesis of the marine prostanoids clavulolactones II and III is presented from an easily accessible chiral, non-racemic cyclopentenone intermediate. Key steps involve selective TBDMS deprotection, selective reduction of the *β*-side chain and aldol condensation. Clavulolactones II and III were successfully prepared from (*S*)-4-((*tert*-butyldimethylsilyl)oxy) cyclopent-2-en-1-one over nine steps, in overall yields of 21 and 7% respectively.



Introduction

Clavulolactones II and III were isolated from the Okinawan soft coral Clavularia viridis by Iguchi et. al. in 1995, with clavulolactone I reported later, in 1999 (Figure 1).[1,2] These compounds are the first examples of natural prostanoids possessing a γ lactone moiety in the α side chain.

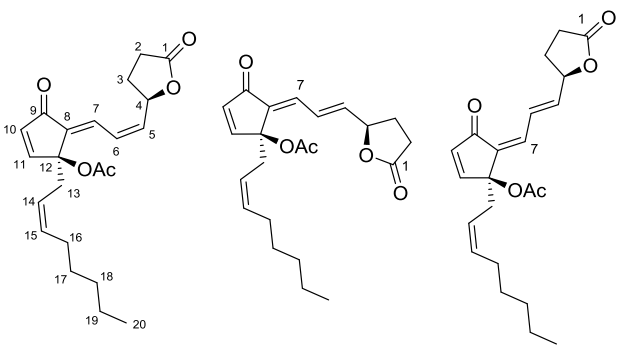


Figure1: Clavulolactones I - III

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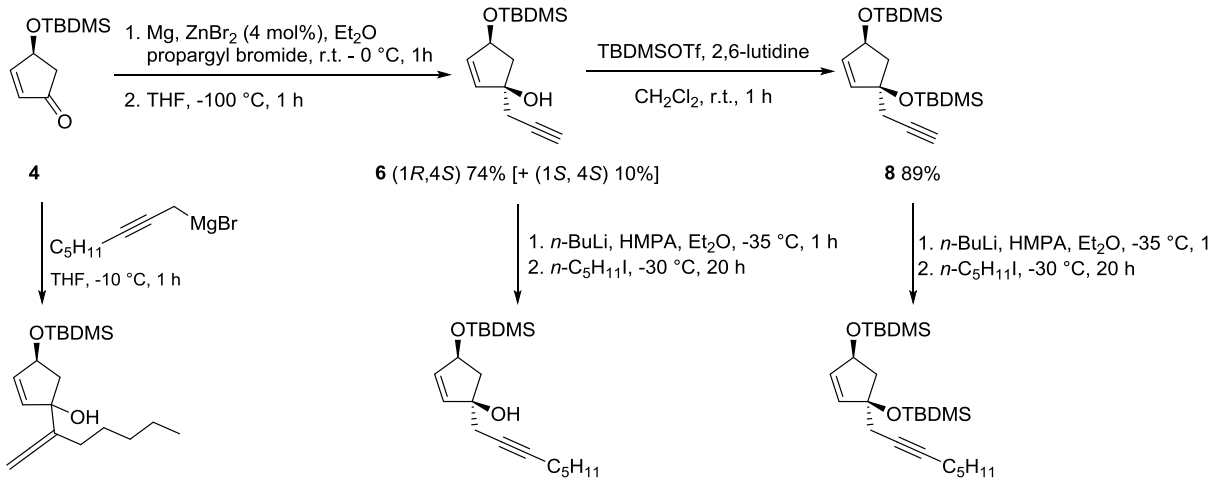
Clavulolactones II and III differ in the alkene configuration at C-7, whereas clavulolactone I has *Z*-configuration at C-5.

C. viridis has been a continuing source of structurally diverse and biologically interesting prostanoids since the early 1980s, with the most recent compounds in the series isolated in 2008.[3] Structurally related prostanoids from C. viridis include clavulones I-III[4,5] and the chlorovulones I-IV.[6] These have been shown to possess antiproliferative and cytotoxic activity in several cancer cell lines as well as antiviral activity.[7–12] It is thought that the efficacy of these compounds may be due to the cyclopentenone core, which is susceptible to attack by sulphur containing amino acids but not by weaker nucleophiles, such as DNA.[13,14]

Given the interesting biological activities of the clavulones and chlorovulones, the total synthesis of the clavulolactones and subsequent biological testing is of significant interest. Here we present the first total synthesis of clavulolactones II and III from an easily accessible chiral, non-racemic cyclopentenone intermediate.

Results and discussion

Our synthetic strategy focused on the key Aldol condensation shown in the graphical abstract, which has previously been utilized in the preparation of the structurally similar prostanoids.[15-20] To begin the synthesis, (*S*)-4-((*tert*-

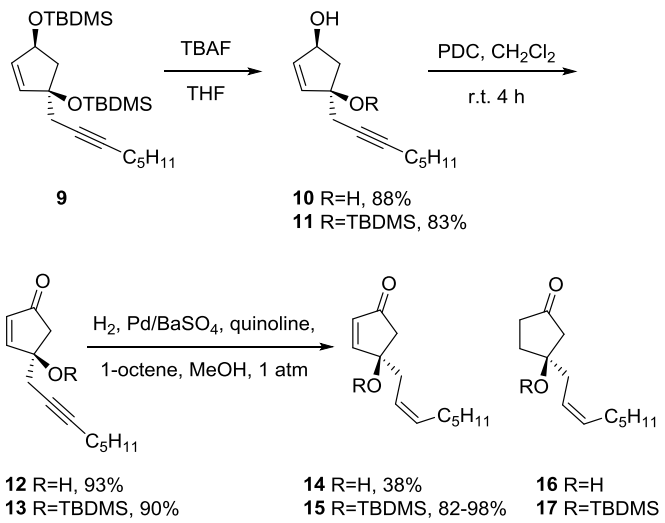


Scheme 1: Introduction of β–side chain

butyldimethylsilyl)oxy) cyclopent-2-en-1-one **4** was prepared in six steps from cyclopentadiene on a multigram scale (*via* literature procedures), with an overall yield of 31%.[21,22] The stereochemistry was determined by Mosher's analysis to be 98% e.e. Next, the Grignard reagent, oct-2-yn-1-ylmagnesium bromide was prepared[23] and reacted with **4**, but the allene **5** was isolated in 97% as a 3.9:1 mixture of diastereoisomers, rather than the desired alkyne **7** (Scheme 1). Such long chain alkynyl-Grignard reagents have previously been reported to preferentially produce allenes, so this reaction was not investigated further. Instead, propargylmagnesium bromide was prepared and the desired terminal alkyne **6** was obtained in 74% yield, along with 10% of the undesired diasteroisomer. These compounds were separable by column chromatography and the stereochemistry was determined by selective nOe experiments of both isomers.

Direct introduction of the pentyl chain was attempted several times on the terminal alkyne **6**, however this yielded approximately 1:1 mixtures of starting material and product under various conditions, requiring a laborious separation by column chromatography. It was thought that the presence of the free alcohol may be the source of this problem, so the tertiary alcohol **6** was protected using TBDMS-triflate to give the di-silyl compound **8** in 89% yield. Deprotonation followed by alkylation with 1-iodopentane gave **9** in an excellent yield of 91%.

Removal of both TBDMS groups of **9** was effected with excess TBAF in THF in 88% yield (**10**, Scheme 2). Oxidation to the cyclopentenone **12** proved straightforward (93%), however hydrogenation with Lindlar's catalyst gave a 3:1 mixture of the desired *Z*-alkene **14** and the over-reduced side product **16**. Separation of these compounds by column chromatography was difficult and was only slightly aided by the use of $AgNO_3$ doped silica gel, to give pure **14** in 38% yield. Moreover, when this compound was subjected to the subsequent aldol reaction only trace amounts of the desired products were isolated. These two problematic reactions resulted in a re-thinking of the strategy. Since sufficient amounts of compound **9** had been prepared, we wondered if a selective deprotection of the 2° TBDMS protected alcohol was possible.



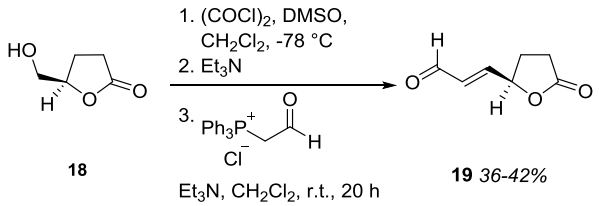
Scheme 2: Selective deprotection and partial reduction

The selective deprotection of 1° TBDMS protected alcohols in the presence of 2° TBDMS protected alcohols has been reported many times in the literature, however reports of 2° TBDMS protected alcohols selectively deprotected in the presence of 3° TBDMS protected alcohols are much less common. To our delight, the gradual portion-wise addition of TBAF to **9** at 0 °C, coupled with TLC monitoring, gave the selectively deprotected compound **11** in 83% yield. This was then oxidized to the cyclopentenone **13** in 90% yield.

Hydrogenation of **13** was initially carried out using Lindlar's catalyst in methanol for 18 hours. As previously, this resulted in

mixtures of the desired product **15** and the over-reduced side product **17**. Switching the catalyst to palladium on barium sulfate with quinoline as poison gave a significant improvement, with **15** isolated in 98% yield after chromatography on one occasion. However these conditions were not always reliable and sometimes a significant amount of side product **17** was also formed. This unusual over-reduction of the cyclopentenone ring was also reported by Zhu *et al.* in the synthesis of clavulones.[17] In our case, the problem was largely overcome by the addition of a sacrificial alkene (1-octene) and careful monitoring of the reaction by TLC. This gave consistent results on repetition and an 82% yield of pure alkene **15**.

The γ-lactone side chain **19** was prepared *via* Swern oxidation[24] of the commercially available enantiopure alcohol **18** and *in situ* Wittig reaction (Scheme 3).

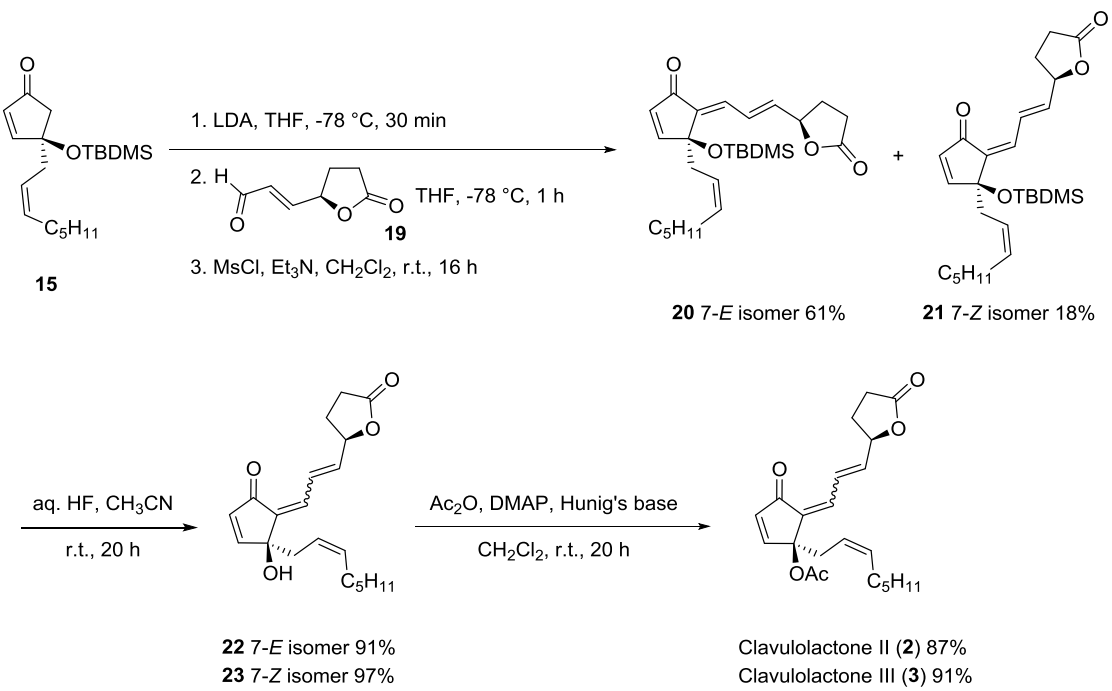


Scheme 3: Preparation of γ-lactone side chain

The aldehyde intermediate was found to be highly unstable and the pre-prepared phosphorus ylide was added directly to the reaction after quenching with triethylamine, giving yields between 36 – 42% after column chromatography. The oxidation of **18** was also attempted with PCC, PDC and Dess-Martin periodinane with no success. Alternatively, Rosenmund reduction[25] of the corresponding acid followed by Wittig reaction gave the aldehyde **19** in yields of 15-20%.

With both the lactone side chain and substituted cyclopentenone in hand, the key aldol condensation was undertaken. The cyclopentenone **15** was deprotonated with LDA over 30 minutes at -78 ˚C, followed by addition of the lactone **19**. After quenching and work-up, the crude mixture of diasteromeric alcohols (ratio 1:1.6 from NMR analysis) was treated with triethylamine and mesyl chloride to afford the C-7 *E* and *Z* isomers **20** and **21**, which were separated by careful column chromatography (61% and 18% respectively). The crude ^{1}H NMR after elimination showed approximately the same ratio of isomers as that of the intermediate alcohols, however, purification of the mixture was challenging, leading to a lower than expected yield of the *Z* isomer **21**.

Removal of the TBDMS groups of **20** and **21** was initially attempted with TBAF in THF, however cleavage of the silyl group was accompanied by partial decomposition, resulting in yields below 30%. Several other methods were attempted but gave no reaction (starting material recovered): AcOH/H_2O/THF;[26] TBAF/AcOH in THF;[27] conc. HCl in THF; CsF in CH_3CN-H_2O;[28] $NaIO_4$ in THF- H_2O;[29] HF-pyr in THF.[30] Other reported methods gave decomposition, including TASF in DMF[31,32] and $BF_3.OEt_2$ in CH_3CN.[33,34] At this point, several methods for direct conversion of TBDMS to acetyl groups were investigated: AcBr in CH_2Cl_2;[35] $FeCl_3/Ac_2O$;[36] $Cu(OTf)_2/Ac_2O$ in CH_2Cl_2;[37] $Sc(OTf)_3/Ac_2O$ in CH_3CN[38] – all were unsuccessful. The deprotection was finally achieved with 40% aqueous HF in CH_3CN,[39] which resulted in excellent yields - 91% of **22** and 97% of **23**.



Scheme 4: Aldol condensation and completion of synthesis

Finally, acetylation with acetic anhydride, DMAP and Hunig's base proceeded smoothly to give clavulolactone II (87%) and clavulolactone III (91%). ^{1}H & ^{13}C NMR, IR, and specific rotation analyses are all in excellent agreement with those reported by Iguchi *et al.* when the clavulolactones were first isolated.[1]

Conclusions

In summary, clavulolactones II and III have been synthesized for the first time, in 10 linear steps from an easily accessible chiral cyclopentenone intermediate, and in overall yields of 21% and 7% respectively. These interesting natural products will now undergo biological testing in order to elucidate their activities and establish possible leads for future development.

Acknowledgements

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Experimental

General procedures:

The ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AV 600 instrument, at 400 MHz with a Bruker AVII 400 instrument, or at 300 MHz with a Bruker Avance DPX 300 instrument. The decoupled ^{13}C NMR spectra were recorded at 150, 100, or 75 MHz using instruments mentioned previously. All spectra were recorded at room temperature (~20 ºC) in deuterated chloroform ($CDCl_3$). Chemical shifts (δ_H and δ_C) are expressed in parts per million (ppm) relative to the reference peak. Coupling constants (*J*) are expressed in Hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), tt (triplet of triplets) and m (multiplet). COSY (Correlation Spectroscopy) experiments were used to assign ambiguous ^{1}H NMR spectra. ^{13}C NMR spectra were assigned with the aid of DEPT (Distortionless Enhancement by Polarisation Transfer) experiments, HSQC (Heteronuclear Single Quantum Correlation) & HMBC (Heteronuclear Multiple-Bond Correlation) experiments. All spectroscopic details for compounds previously made were in agreement with those previously reported.

Mass spectra under CI conditions were recorded with a VG Prospec instrument. Infrared spectra were recorded as a thin film on sodium chloride plates on a Perkin Elmer Spectrum One FT-IR spectrometer.

Dry tetrahydrofuran (THF), diethyl ether (Et_2O) dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were obtained from a solvent purification system, MB SPS-800, from MBraun, Garching, Germany. Hexane was distilled prior to use and toluene was distilled from CaH_2 and stored over 4Å molecular sieves. Alkyllithium and Grignard reagents were titrated prior to use. All other reagents were commercially available and used as received. Organic phases were dried using anhydrous magnesium sulphate. All flash column chromatography was performed with silica gel 60 from Merck (0.040 – 0.063 mm). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light detection (254 nm) along with vanillin or *p*-anisaldehyde stains.

(1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(prop-2-yn-1-yl)cyclopent-2-en-1-ol 6

Propargylmagnesium bromide was prepared as described by Acharya *et al.*[3] and titrated with menthol and 4-(phenylazo)diphenylamine in tetrahydrofuran. The resulting 0.19 M solution was used within 1 h. (*S*)-4-((*tert*-butyl dimethylsilyl)oxy)cyclopent-2-en-1-one **4** (13.0 g, 61.2 mmol) was dissolved in THF (650 mL) and cooled to −105 °C under Ar. Propargylmagnesium bromide (490 mL, 93.1 mmol, 0.19 M soln.) was added *via* cannula over 30 minutes at a rate to keep the reaction temperature below −90 °C. The mixture was stirred for a further 60 minutes at −100 °C, allowed to warm to −50 °C, and then quenched with sat. aq. NH_4Cl (100 mL) and water (300 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with water (2 × 200 mL) and brine (200 mL), then dried and evaporated. The product was purified by column chromatography with dichloromethane to give the desired product **6** as a colourless oil (11.5 g, 74%) along with a small amount of the minor diasteroisomer (1.57 g, 10%). Compound **6**: ν_{max}/cm^{-1} (film): 3400 (OH, broad), 3311(C≡C−H stretch), 2121 (C≡C), 1721(C=C), 1472, 1367, 1256 (C−O); δ_H (400 MHz, $CDCl_3$): 5.89 [2 H, s C(2)H, C(3)H], 4.75 [1 H, dd, *J* 6.7, 3.9, C(4)H], 2.53 [1 H, dd, *J* 13.8, 6.7, one of C(5)H_2], 2.51 – 2.48 [2 H, m, C(6)H_2], 2.01 [1 H, t, *J* 2.6, C(8)H)], 1.79 [1 H, dd, *J* 13.8, 3.9, one of C(5)H_2], 0.89 [9 H, s, SiC(CH_3)$_3$], 0.09 [6 H, s, Si(CH_3)$_2$]; δ_C (100.6 MHz, $CDCl_3$): 137.5 C(2)H or C(3)H, 136.9 C(2)H or C(3)H, 82.7 C(1), 80.7 C(7), 75.6 C(4)H, 70.2 C(8)H, 48.7 C(5)H_2, 30.6 C(6)H_2, 26.0 SiC($\underline{C}H_3$)$_3$, 18.3 Si$\underline{C}$(CH_3)$_3$, -4.5 Si($\underline{C}H_3$)$_2$; m/z (CI^+): 235 [(M+H–H_2O)$^+$, 100%]; HRMS (CI^+): Exact mass calculated for $C_{14}H_{23}OSi^+$ 235.1518. Found 235.1525. (1*R*, 4*S*) configuration was assigned to compound **6** based on selective nOe experiments of both major and minor products.

(((1*R*,4*S*)-1-(Prop-2-yn-1-yl)cyclopent-2-ene-1,4-diyl)bis(oxy)) bis(*tert*-butyldimethylsilane) 8

(1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(prop-2-yn-1-yl) cyclopent-2-en-1-ol **6** (10.1 g, 39.9 mmol) was dissolved in CH_2Cl_2 (95 mL) and cooled to 0 °C under Ar. 2,6-Lutidine (11.6 mL, 99.75 mmol 2.5 eq.) was added in one portion, followed by drop-wise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (18.3 mL, 79.7 mmol, 2 eq.). The solution was stirred at 0 °C for 1 h and at room temp. for 3 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (500 mL). This was washed with 1M HCl (3 × 200 mL), sat. aq. $NaHCO_3$ (3 × 200 mL), H_2O (2 × 200 mL) and brine (200 mL), then dried and evaporated. Purification by column chromatography with hexane-ethyl acetate (99:1 – 96:4) gave the desired compound as a colourless oil (12.9 g, 89%). Compound **8**: ν_{max}/cm^{-1} (film): 3314 (C≡C−H stretch), 2930 (CH), 2122 (C≡C), 1728 (C=C), 1472, 1255 (C−O); δ_H (400 MHz, $CDCl_3$): 5.79 [2 H, s, C(2)H, C(3)H], 4.75 – 4.63 [1 H, m, C(4)H], 2.57 [1 H, dd, *J* 13.6, 7.2, one of C(5)H_2], 2.42 [2 H, d, *J* 2.5, C(6)H_2], 1.90 [1 H, t, *J* 2.5, C(8)H], 1.83 [1 H, dd, *J* 13.6, 4.9, one of C(5)H_2], 0.86 and 0.89 (18 H, two overlapping singlets, SiC($C\underline{H}_3$)$_3$ × 2], 0.12 – 0.04 (12 H, m, Si($C\underline{H}_3$)$_2$ × 2]; δ_C (100.6 MHz, $CDCl_3$): 137.4 C(2)H or C(3)H, 136.2 C(2)H or C(3)H, 84.7 C(1), 81.5 C(7), 75.4 C(4)H, 69.3

C(8)H, 49.3 C(5)H_2, 33.4 C(6)H_2, 26.0 and 25.9 SiC($\underline{C}H_3)_3$ × 2, 18.2 and 18.2 Si$\underline{C}(CH_3)_3$ × 2, -2.1, -2.4, -4.5 and -4.5 Si($\underline{C}H_3)_2$ × 2; m/z (CI^+): 368 [$(M+H)^+$ 1%], 327 [$(M+H-C_3H_4)^+$ 70%]; HRMS (CI^+): Exact mass calculated for $C_{17}H_{35}O_2Si_2^+$ 327.2175. Found 327.2167.

(((1*R*,4*S*)-1-(Oct-2-yn-1-yl)cyclopent-2-ene-1,4-diyl)bis(oxy))bis (*tert*-butyldimethylsilane) 9

A solution of (((1*R*,4*S*)-1-(prop-2-yn-1-yl)cyclopent-2-ene-1,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) **8** (7.62 g, 20.8 mmol) in diethyl ether (270 mL) at −40 °C under Ar was treated with HMPA (44 mL, 253 mmol, 12 eq.) and then *n*-BuLi (12.5 mL, 31.13 mmol, 1.5 eq., 2.49 M soln.). After stirring at −35 °C for 1 h, 1-iodopentane (8.1 mL, 62.0 mmol, 3 eq.) was added and the mixture was stirred at −30 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and then H_2O (200 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were washed with water (7 × 200 mL, excess used to remove HMPA) and brine (200 mL), then dried and evaporated. The product was purified by dry flash column chromatography with hexane (600 mL) followed by hexane – ethyl acetate (98:2) to give the desired product **9** as a colourless oil (8.77 g, 97%). Compound **9**: ν_{max}/cm^{-1} (film): 2956 (CH), 2858 (CH), 2213 (C≡C), 1717 (C=C), 1472, 1367, 1252 (C−O); δ_H (400 MHz, $CDCl_3$): 5.77 [2 H, s, C(2)H, C(3)H], 4.69 [1 H, dd, *J* 7.1, 5.1, C(4)H], 2.56 [1 H, dd, *J* 13.4, 7.1, one of C(5)H_2], 2.38 [2 H, t, *J* 2.3, C(6)H_2], 2.11 [2 H, tt, *J* 7.1, 2.3, C(9)H_2], 1.79 [1 H, dd, *J* 13.4, 5.1, one of C(5)H_2], 1.50 – 1.28 [6 H, m, C(10)H_2, C(11)H_2, C(12)H_2], 0.93 – 0.82 [21 H, m, C(13)H_3, SiC($C\underline{H}_3)_3$ × 2], 0.11 – 0.04 [12 H, m, Si($C\underline{H}_3)_2$ × 2]; δ_C (100.6 MHz, $CDCl_3$): 137.8 C(2)H or C(3)H, 135.8 C(2)H or C(3)H, 85.1 C(1), 81.4 C(8), 77.4 C(7), 75.5 C(4)H, 49.5 C(5)H_2, 33.6 C(6)H_2, 31.3 C(11)H_2, 29.0 C(10)H_2, 26.0 and 25.9 SiC($\underline{C}H_3)_3$ × 2, 22.4 C(12)H_2, 18.9 C(9)H_2, 18.3 and 18.2 Si$\underline{C}(CH_3)_3$ × 2, 14.2 C(13)H_2, -2.1, -2.4, -4.4, -4.5 Si($\underline{C}H_3)_2$ × 2; m/z (CI^+): 421 [$(M+H-CH_3)^+$ 80%] 379 (100%); HRMS (CI^+): Exact mass calculated for $C_{24}H_{45}O_2Si_2^+$ 421.2958. Found 421.2944.

(1*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-(oct-2-yn-1-yl) cyclopent-2-en-1-ol 11

A solution of (((1*R*,4*S*)-1-(oct-2-yn-1-yl)cyclopent-2-ene-1,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) **9** (5.16 g, 11.8 mmol) in THF (65 mL) was cooled to 0 °C under Ar and treated with TBAF (11.8 mL, 11.8 mmol, 1 eq., 1 M soln.). The mixture was stirred at r.t. and monitored by TLC. Two additional portions of TBAF (4.7 mL + 4.7 mL) were added at 2 h and 4 h based on TLC analysis. After 5 h the reaction was quenched with sat. aq. NH_4Cl (5 mL) and then H_2O (100 mL) and EtOAc (100 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (2 × 200 mL) and brine (200 mL), then dried and evaporated. The product was purified by column chromatography with hexane – EtOAc (99:1 – 60:40) to give the pure product **11** (2.805 g, 74%) and unreacted starting material **9** (0.579 g, 11% recovery) – 83% yield of **11** taking recovered starting material into consideration. Compound **11**: ν_{max}/cm^{-1} (film): 3430 (OH), 2956 (CH), 2858 (CH), 2215 (C≡C), 1726 (C=C), 1463, 1253 (C−O); δ_H (400 MHz, $CDCl_3$): 5.91 [1 H, dd, *J* 5.6, 1.7, C(2)H], 5.88 [1 H, dd, *J* 5.6, 0.9, C(3)H], 4.69 [1 H, br s, C(1)H], 2.66 [1 H, dd, *J* 13.7, 7.2, one of C(5)H_2], 2.48 – 2.36 [2 H, m, C(6)H_2], 2.10 [2 H, tt, *J* 7.1, 2.4, C(9)H_2], 1.76 [1 H, dd, *J* 13.7, 4.7, one of C(5)H_2], 1.56 [1 H, br s, C(1)OH], 1.50 – 1.40 [2 H, m, C(10)H_2], 1.38 – 1.26 [4 H, m, C(11)H_2, C(12)H_2], 0.93 – 0.83 [12 H, m, C(13)H_3, SiC($C\underline{H}_3)_3$], 0.10 [3 H, s, one of Si($C\underline{H}_3)_2$], 0.10 [3 H, s, one of Si($C\underline{H}_3)_2$]; δ_C (100.6 MHz, $CDCl_3$): 139.5 C(3)H, 135.1 C(2)H, 85.3 C(4), 81.8 C(8), 76.5 C(7), 75.7 C(1)H, 49.4 C(5)H_2, 33.1 C(6)H_2, 31.2 C(11)H_2, 28.8 C(10)H_2, 25.8 SiC($\underline{C}H_3)_3$, 22.4 C(12)H_2, 18.8 C(9)H_2, 18.1 Si$\underline{C}(CH_3)_3$, 14.2 C(13)H_2, -2.1 one of Si($\underline{C}H_3)_2$, -2.2 one of Si($\underline{C}H_3)_2$; m/z (CI^+): 323 [$(M+H)^+$ 20%], 305 (100%); HRMS (ESI^+): Exact mass calculated for $C_{19}H_{35}O_2Si^+$ 323.2406. Found 323.2393.

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-(oct-2-yn-1-yl)cyclopent-2-en-1-one 13

(1*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-(oct-2-yn-1-yl) cyclopent-2-en-1-ol **11** (2.78 g, 8.61 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with PDC (4.86 g, 12.9 mmol, 1.5 eq.). The reaction was stirred at r.t. under Ar for 3.5 h, at which point TLC indicated complete consumption of starting material. The mixture was filtered through a well packed bed of Celite and washed with CH_2Cl_2 (500 mL). Further purification was carried out using a short column (6 cm), eluting with 90:10 hexane – EtOAc and collecting in 3 × 500 mL fractions to give the pure product **13** as a colourless oil (2.49 g, 90%). Compund **13**: ν_{max}/cm^{-1} (film): 2956 (CH), 2859 (CH), 2216 (C≡C), 1727 (C=O), 1680, 1472, 1254 (C−O); δ_H (400 MHz, $CDCl_3$): 7.39 [1 H, d, *J* 5.7, C(3)H], 6.15 [1 H, d, *J* 5.7, C(2)H], 2.70 [1 H, d, *J* 18.2, one of C(5)H_2], 2.66 – 2.53 [2 H, m, C(6)H_2], 2.42 [1 H, d, *J* 18.2, one of C(5)H_2], 2.07 [2 H, t, *J* 7.0, C(9)H_2], 1.47 – 1.36 [2 H, m, C(10)H_2], 1.34 – 1.23 [4 H, m, C(11)H_2, C(12)H_2], 0.93 – 0.82 [12 H, m, C(13)H_3, SiC($C\underline{H}_3)_3$], 0.07 [3 H, s, one of Si($C\underline{H}_3)_2$], 0.06 [3 H, s, one of Si($C\underline{H}_3)_2$]; δ_C (100.6 MHz, $CDCl_3$): 206.4 C(1)=O, 165.3 C(3)H, 133.8 C(2)H, 83.7 C(8), 80.7 C(4), 75.1 C(7), 49.1 C(5)H_2, 32.6 C(6)H_2, 31.2 C(11)H_2, 28.6 C(10)H_2, 25.7 SiC($\underline{C}H_3)_3$, 22.3 C(12)H_2, 18.7 C(9)H_2, 18.1 Si$\underline{C}(CH_3)_3$, 14.1 C(13)H_2, -2.3 one of Si($\underline{C}H_3)_2$, -2.5 one of Si($\underline{C}H_3)_2$; m/z (CI^+): 321[$(M+H)^+$ 60%] 263 (100%); HRMS (CI^+): Exact mass calculated for $C_{19}H_{33}O_2Si^+$ 321.2249. Found 321.2242.

(*R*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-(oct-2-en-1-yl)cyclopent-2-en-1-one 15

See results and discussion section for details on advantages of method 2 over method 1.

Method 1: A degassed solution of (*R*)-4-((*tert*-butyldimethylsilyl)oxy)-4-(oct-2-yn-1-yl)cyclopent-2-en-1-one **13** (0.794 g, 2.48 mmol) in methanol (39 mL) was treated with quinolone (72 µL, 10% w/w) and $Pd/BaSO_4$ (79 mg, 10% w/w) and then rapidly stirred under H_2 at approx. 1 atm for 1.5 h. The mixture was filtered through Celite, washed with methanol (20 mL) and concentrated. Purification by column chromatography with 30:70 heaxane – CH_2Cl_2 gave **15** as a colourless oil (782 mg, 98%). Analysis identical to that given below.

Method 2: Quinolone (0.24 mL), 1-octene (2.4 mL) and $Pd/BaSO_4$ (47 mg, 10% w/w) were added to (*R*)-4-((*tert*-butyldimethylsilyl)oxy)-4-(oct-2-yn-1-yl)cyclopent-2-en-1-one **13** (474 mg, 1.48 mmol) in degassed methanol (24 mL) and stirred under H_2 for 1.25 hours. The reaction was monitored by TLC using a microliter syringe to withdraw approx. 5 µL of reaction mixture and adding to approx. 3 drops of CH_2Cl_2.

When the starting material had been consumed, the mixture was filtered through Celite, washed with methanol (40 mL) and evaporated. Purification by column chromatography with hexane – EtOAc on 10% w/w $AgNO_3$ doped silica gel gave the pure alkene **15** as a colourless oil (392 mg, 82%). Compound **15**: ν_{max}/cm^{-1} (film): 2956 (CH), 2858 (CH), 1724 (C=O), 1406, 1360, 1252 (C-O); δ_H (400 MHz, $CDCl_3$): 7.40 [1 H, d, *J* 5.7, C(3)H], 6.10 [1 H, d, *J* 5.7, C(2)H], 5.57 – 5.48 [1 H, m, C(8)H], 5.40 – 5.31 [1 H, m, C(7)H], 2.54 – 2.38 [4 H, m, $C(5)H_2$, $C(6)H_2$], 2.03 – 1.94 [2 H, m, $C(9)H_2$], 1.38 – 1.22 [6 H, m, $C(10)H_2$, $C(11)H_2$, $C(12)H_2$], 0.93 – 0.85 [12 H, m, $C(13)H_3$, $SiC(C\underline{H}_3)_3$], 0.07 [3 H, s, one of $Si(C\underline{H}_3)_2$], 0.05 [3 H, s, one of $Si(C\underline{H}_3)_2$]; δ_C (100.6 MHz, $CDCl_3$): 206.8 C(1)=O, 166.6 C(3)H, 133.7 C(8)H, 133.2 C(2)H, 123.3 C(7)H, 81.1 C(4), 49.2 $C(5)H_2$, 39.7 $C(6)H_2$, 31.7 $C(11)H_2$, 29.3 $C(10)H_2$, 27.6 $C(9)H_2$, 25.8 $SiC(\underline{C}H_3)_3$, 22.7 $C(12)H_2$, 18.2 $Si\underline{C}(CH_3)_3$, 14.2 $C(13)H_2$, -2.2 one of $Si(\underline{C}H_3)_2$, -2.4 one of $Si(\underline{C}H_3)_2$; m/z (CI^+): 323 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_{19}H_{35}O_2Si^+$ 323.2406. Found 323.2413.

(*R*,*E*)-3-(5-Oxotetrahydrofuran-2-yl)acrylaldehyde 19

Formylmethyltriphenylphosphonium chloride (865 mg, 2.54 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.37 mL, 2.65 mmol) and stirred at r.t. for 1 h.
In a separate flask, CH_2Cl_2 (7 mL) was cooled to −78 °C under Ar and treated with oxalyl chloride (343 μL, 4.06 mmol, 1.2 eq.), followed by drop-wise addition of DMSO (0.60 mL, 8.45 mmol, 2.5 eq.). The mixture was stirred at −78 °C for 5 minutes and (*R*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (393 mg, 3.38 mmol) was added drop-wise in CH_2Cl_2 (5 mL). The reaction was stirred at −78 °C for 30 minutes, quenched with Et_3N (2.35 mL, 16.9 mmol, 5 eq.) and allowed to warm to −20 °C. The solution of phosphorus ylide was added and stirred at r.t. for 18 h. The solvent was evaporated and purified by column chromatography, first with CH_2Cl_2 – MeOH (98:2) to remove triphenylphosphine oxide and a second time with hexane – EtOAc (40:60) to give the pure product **19** as a pale yellow oil (200 mg, 42%). Compound **19**: ν_{max}/cm^{-1} (film): 2932 (CH), 1775 (C=O lactone), 1691 (C=O aldehyde), 1180 (C-O lactone); δ_H (400 MHz, $CDCl_3$): 9.60 (1 H, d, *J* 7.5, C<u>H</u>O), 6.79 [1 H, dd, *J* 15.8, 4.7, C(5)H], 6.32 [1 H, ddd, *J* 15.8, 7.5, 1.5, C(6)H], 5.29 – 5.13 [1 H, m, C(4)H], 2.63 – 2.52 [3 H, m, $C(2)H_2$, one of $C(3)H_2$], 2.15 – 2.02 [1 H, m, one of $C(3)H_2$]; δ_C (100.6 MHz, $CDCl_3$): 192.4 CHO, 175.8 C=O lactone, 151.2 C(5)H, 131.8 C(6)H, 77.6 C(4)H, 27.9 $C(2)H_2$ and $C(3)H_2$; m/z (CI^+): 141 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_7H_9O_3^+$ 141.0551. Found 141.0553.

(*R*)-5-((1*E*,3*E*)-3-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one 20 and (*R*)-5-((1*E*,3*Z*)-3-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one 21

n-Butyllithium (1.18 mL, 2.78 mmol, 2.35 M soln.) was added drop-wise to a solution of diisopropylamine (0.45 mL, 3.21 mmol) in THF (8 mL) under Ar at −78 °C and stirred for 15 minutes. (*R*,*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-4-(oct-2-en-1-yl)cyclopent-2-en-1-one **15** (691 mg, 2.14 mmol) in THF (10 mL) was added drop-wise over 10 minutes. After stirring at −78 °C for a further 30 minutes, (*R*,*E*)-3-(5-oxotetrahydrofuran-2-yl)acrylaldehyde **19** (430 mg, 3.07 mmol) in THF (10 mL) was added drop-wise. The reaction was stirred at −78 °C for 1 hour and then allowed to warm to −20 °C before quenching with sat. aq. NH_4Cl (5 mL). Water (20 mL) was added and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), then dried and evaporated to give the intermediate alcohol as a mixture of diasteromers (1:1.6 ratio from ^1H NMR). This material was immediately dissolved in CH_2Cl_2 (25 mL), cooled to 0 °C and treated with triethylamine (0.6 mL, 4.28 mmol) and methanesulfonyl chloride (0.25 mL, 3.21 mmol). The mixture was heated to reflux and monitored by TLC. After 2 hours additional MsCl (0.25 mL, 3.21 mmol) was added and the reaction was heated to reflux for a further hour. The reaction mixture was cooled and water (20 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL), then dried and evaporated to give the crude product. Careful purification by column chromatography with hexane – EtOAc (90:10 – 60:40) gave **21** first (167 mg, 18%), followed by **20** (582 mg, 61%).
Compound **20**: ν_{max}/cm^{-1} (film): 2955 (CH), 2856 (CH), 1783 (C=O lactone), 1701 (C=O cyclopentenone), 1642 (C=C), 1462, 1252, 1169; δ_H (400 MHz, $CDCl_3$): 7.34 [1 H, d, *J* 6.0, C(11)H)], 7.04 [1 H, dd, *J* 15.2, 11.9, C(6)H], 6.89 [1 H, d, *J* 11.9, C(7)H], 6.35 [1 H, d, *J* 6.0, C(10)H], 6.15 [1 H, dd, *J* 15.2, 5.8, C(5)H], 5.51 – 5.42 [1 H, m, C(15)H], 5.31 – 5.22 [1 H, m, C(14)H], 5.11 – 5.03 [1 H, m, C(4)H], 2.70 [1 H, dd, *J* 14.4, 6.4, one of $C(13)H_2$], 2.63 – 2.44 [4 H, m, one of $C(13)H_2$, $C(2)H_2$, one of $C(3)H_2$], 2.08 – 1.99 [1 H, m, one of $C(3)H_2$], 1.95 – 1.88 [2 H, m, $C(16)H_2$], 1.32 – 1.19 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.91 – 0.83 [12 H, m, $C(20)H_3$, $SiC(C\underline{H}_3)_3$], 0.00 [3 H, s, one of $Si(C\underline{H}_3)_2$], -0.14 [3 H, s, one of $Si(C\underline{H}_3)_2$]; δ_C (100.6 MHz, $CDCl_3$): 194.9 C(9)=O, 176.3 C(1)=O, 162.2 C(11)H, 141.1 C(8), 139.8 C(5)H, 134.6 C(10)H, 133.8 C(15)H, 129.6 C(7)H, 127.2 C(6)H, 122.9 C(14)H, 81.2 C(12), 79.4 C(4)H, 39.6 $C(13)H_2$, 31.7 $C(18)H_2$, 29.3 $C(17)H_2$, 28.7 $C(3)H_2$, 28.5 $C(2)H_2$, 27.6 $C(16)H_2$, 25.9 $SiC(\underline{C}H_3)_3$, 22.7 $C(19)H_2$, 18.3 $Si\underline{C}(CH_3)_3$, 14.2 $C(20)H_3$, -2.0 one of $Si(\underline{C}H_3)_2$, -3.0 one of $Si(\underline{C}H_3)_2$; m/z (CI^+): 445 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_{26}H_{41}O_4Si^+$ 445.2774. Found 445.2766.
Compound **21**: ν_{max}/cm^{-1} (film): 2955 (CH), 2857 (CH), 1781 (C=O lactone), 1697 (C=O cyclopentenone), 1641 (C=C), 1463, 1251, 1166; δ_H (400 MHz, $CDCl_3$): 7.80 [1 H, dd, *J* 15.3, 11.5, C(6)H], 7.28 [1 H, d, *J* 6.0, C(11)H)], 6.51 [1 H, d, *J* 11.5, C(7)H], 6.28 [1 H, d, *J* 6.0, C(10)H], 6.07 [1 H, dd, *J* 15.3, 6.8, C(5)H], 5.54 – 5.44 [1 H, m, C(15)H], 5.39 – 5.30 [1 H, m, C(14)H], 5.15 – 5.06 [1 H, m, C(4)H], 2.64 – 2.42 [5 H, m, $C(13)H_2$, $C(2)H_2$, one of $C(3)H_2$], 2.13 – 2.03 [1 H, m, one of $C(3)H_2$], 1.98 – 1.88 [2 H, m, $C(16)H_2$], 1.33 – 1.20 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.89 – 0.85 [12 H, m, $C(20)H_3$, $SiC(C\underline{H}_3)_3$], -0.03 [3 H, s, one of $Si(C\underline{H}_3)_2$], -0.12 [3 H, s one of $Si(C\underline{H}_3)_2$]; δ_C (100.6 MHz, $CDCl_3$): 195.4 C(9)=O, 176.6 C(1)=O, 160.8 C(11)H, 140.6 C(8), 139.2 C(5)H, 135.8 C(10)H, 133.7 C(15)H, 133.2 C(7)H, 128.0 C(6)H, 123.2 C(14)H, 80.6 C(12), 80.1 C(4)H, 40.0 $C(13)H_2$, 31.7 $C(18)H_2$ or $C(19)H_2$, 29.3 $C(17)H_2$, 28.8 two overlapping peaks $C(3)H_2$ and $C(2)H_2$, 27.5 $C(16)H_2$, 25.8 $SiC(\underline{C}H_3)_3$, 22.7 $C(18)H_2$ or $C(19)H_2$, 18.2 $Si\underline{C}(CH_3)_3$, 14.2 $C(20)H_3$, -2.3 one of $Si(\underline{C}H_3)_2$, -2.7 one of $Si(\underline{C}H_3)_2$; m/z (CI^+): 445 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_{26}H_{41}O_4Si^+$ 445.2774. Found 445.2768.

(*R*)-5-((1*E*,3*E*)-3-((*S*)-2-Hydroxy-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one 22

(*R*)-5-((1*E*,3*E*)-3-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one **20** (31 mg, 0.070 mmol) in acetonitrile (0.3 mL) was carefully treated with 40% aq. HF solution (130 µL) and stirred at r.t. for 20 h. The reaction was slowly quenched with sat. aq. $NaHCO_3$ (4 mL) and extracted with diethyl ether (3 × 4 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), then dried and evaporated to give a yellow oil. Purification by column chromatography with hexane – EtOAc (50:50 – 30:70) gave **22** as a colourless oil (21 mg, 91%). Compound **22**: δ_H (400 MHz, $CDCl_3$): 7.33 [1 H, dd, *J* 6.0, 0.7, C(11)H)], 7.05 [1 H, ddd, *J* 15.0, 11.9, 1.2, C(6)H], 6.88 [1 H, d, *J* 11.9, C(7)H], 6.34 [1 H, d, *J* 6.0, C(10)H], 6.16 [1 H, dd, *J* 15.0, 6.4, C(5)H], 5.58 – 5.45 [1 H, m, C(15)H], 5.27 – 5.13 [1 H, m, C(14)H], 5.13 – 5.03 [1 H, m, C(4)H], 2.84 – 2.29 [6 H, m, $C(13)H_2$, $C(2)H_2$, one of $C(3)H_2$, C(12)OH], 2.14 – 2.01 [1 H, m, one of $C(3)H_2$], 2.00 – 1.90 [2 H, m, $C(16)H_2$], 1.35 – 1.23 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.87 [3 H, t, *J* 6.8, $C(20)H_3$]; δ_C (100.6 MHz, $CDCl_3$): 195.1 C(9)=O, 176.5 C(1)=O, 161.6 C(11)H, 140.5 C(5)H, 140.4 C(8), 134.9 broad (two overlapping peaks) C(10)H and C(15)H, 130.0 C(7)H, 126.8 C(6)H, 122.1 C(14)H, 79.6 C(4)H, 37.0 $C(13)H_2$, 31.7 $C(18)H_2$, 29.3 $C(17)H_2$, 28.7 $C(2)H_2$ or $C(3)H_2$, 28.5 $C(2)H_2$ or $C(3)H_2$, 27.6 $C(16)H_2$, 22.7 $C(19)H_2$, 14.2 $C(20)H_3$; $[\alpha]^{20}_D$ -45.3° (c=0.3, $CHCl_3$); m/z (CI^+): 331 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_{20}H_{27}O_4^+$ 331.1909. Found 331.1902.

(*R*)-5-((1*E*,3*Z*)-3-((*S*)-2-Hydroxy-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one 23

Prepared and purified as described for compound **22** from *(R)*-5-((1*E*,3*Z*)-3-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one **21** (19 mg, 0.043 mmol) giving **23** as a colourless oil (13.7 mg, 97%). Compound **23**: δ_H (400 MHz, $CDCl_3$): 7.78 [1 H, ddd, *J* 15.5, 11.3, 1.1, C(6)H], 7.29 [1 H, d, *J* 6.0, C(11)H)], 6.61 [1 H, d, *J* 11.3, C(7)H], 6.30 [1 H, d, *J* 6.0, C(10)H], 6.08 [1 H, dd, *J* 15.5, 7.2, C(5)H], 5.61 – 5.50 [1 H, m, C(15)H], 5.35 – 5.23 [1 H, m, C(14)H], 5.09 [1 H, m, C(4)H], 2.67 – 2.52 [4 H, m, $C(13)H_2$, $C(2)H_2$], 2.52 – 2.40 [1 H, m, one of $C(3)H_2$], 2.27 [1 H, s, C(12)OH], 2.12 – 2.03 [1 H, m, one of $C(3)H_2$], 2.03 – 1.93 [2 H, m, $C(16)H_2$], 1.36 – 1.20 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.87 [3 H, t, *J* 6.9, $C(20)H_3$]; δ_C (100.6 MHz, $CDCl_3$): 195.38 C(9)=O, 176.72 C(1)=O, 160.05 C(11)H, 140.27 C(8), 139.65 C(5)H, 136.26 C(10)H 134.88 C(15)H 133.01 C(7)H, 127.93 C(6)H, 122.26 C(14)H, 80.23 C(4)H, 79.00 C(12), 37.38 $C(13)H_2$, 31.65 $C(18)H_2$, 29.25 $C(17)H_2$, 28.73 broad (two overlapping peaks) $C(2)H_2$ and $C(3)H_2$, 27.50 $C(16)H_2$, 22.66 $C(19)H_2$, 14.18 $C(20)H_3$; $[\alpha]^{20}_D$ -14.2° (c=0.3, $CHCl_3$); m/z (CI^+): 331 [$(M+H)^+$ 100%]; HRMS (CI^+): Exact mass calculated for $C_{20}H_{27}O_4^+$ 331.1909. Found 331.1900.

Clavulolactone II, (*S,E*)-1-((*Z*)-oct-2-en-1-yl)-4-oxo-5-((*E*)-3-((*R*)-5-oxotetrahydrofuran-2-yl)allylidene)cyclopent-2-en-1-yl acetate 2

R)-5-((1*E*,3*E*)-3-((*S*)-2-Hydroxy-2-((*Z*)-oct-2-en-1-yl)-5-oxo cyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one **22** (34.6 mg, 0.105 mmol) was dissolved in CH_2Cl_2 (0.15 mL) under Ar. Hünigs base (33 µL, 0.189 mmol, 1.8 eq), Ac_2O (17 µL, 0.180 mmol, 1.7 eq) and DMAP (0.6 mg, 0.005 mmol, 0.05 eq) were added and the reaction was stirred at r.t. under Ar for 18 h. The reaction was quenched with 0.5 M HCl (1 mL), followed by addition of H_2O (2 mL) and CH_2Cl_2 (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with 0.5 M HCl (3 mL), sat. aq. $NaHCO_3$ (3 mL) and brine (3 mL), then dried and evaporated to give the crude product. Purification by column chromatography with hexane – EtOAc (60:40) gave **2** as a clear oil (13 mg, 92%). Compound **2**: ν_{max}/cm^{-1} (film): 2929 (CH), 2857 (CH), 1779 (C=O), 1745 (C=O), 1704 (C=O), 1644 (C=C), 1368, 1231, 1170; δ_H (400 MHz, $CDCl_3$): 7.49 [1 H, d, *J* 6.1, C(11)H)], 6.91 [1 H, d, *J* 12.0, C(7)H], 6.82 [1 H, ddd, *J* 14.8, 12.0, 1.5, C(6)H], 6.41 [1 H, d, *J* 6.1, C(10)H], 6.17 [1 H, dd, *J* 14.8, 4.8, C(5)H], 5.58 – 5.44 [1 H, m, C(15)H], 5.20 – 5.08 [2 H, m, C(14)H, C(4)H], 2.92 [1 H, dd, *J* 14.2, 6.9, one of $C(13)H_2$], 2.70 [1 H, dd, *J* 14.2, 8.2, one of $C(13)H_2$], 2.63 – 2.43 [3 H, m, $C(2)H_2$, one of $C(3)H_2$], 2.10 – 1.99 [4 H, m, $C(22)H_3$, one of $C(3)H_2$], 1.97 – 1.88 [2 H, m, $C(16)H_2$], 1.34 – 1.19 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.87 [3 H, t, *J* 6.9, $C(20)H_3$]; δ_C (100.6 MHz, $CDCl_3$): 193.5 C(9)=O, 176.4 C(1)=O, 169.5 C(21)=O, 158.2 C(11)H, 141.0 C(5)H, 137.3 C(8), 135.3 C(10)H or C(15)H, 135.2 C(10)H or C(15)H, 129.0 C(7)H, 125.1 C(6)H, 121.1 C(14)H, 85.3 C(12), 78.8 C(4)H, 36.0 $C(13)H_2$, 31.6 $C(18)H_2$, 29.2 $C(17)H_2$, 28.4 $C(3)H_2$, 27.9 $C(2)H_2$, 27.6 $C(16)H_2$, 22.6 $C(19)H_2$, 21.4 $C(22)H_3$, 14.2 $C(20)H_3$; $[\alpha]^{20}_D$ -25.7° (c=0.26, $CHCl_3$); m/z (CI^+): 373 [$(M+H)^+$ 15%], 313 (100%); HRMS (CI^+): Exact mass calculated for $C_{22}H_{29}O_5^+$ 373.2015. Found 373.2007.

Clavulolactone III, (*S,Z)*-1-((*Z*)-oct-2-en-1-yl)-4-oxo-5-((*E*)-3-((*R*)-5-oxotetrahydrofuran-2-yl)allylidene)cyclopent-2-en-1-yl acetate 3

Prepared and purified as described for compound **2** from (*R*)-5-((1*E*,3*Z*)-3-((*S*)-2-hydroxy-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)prop-1-en-1-yl)dihydrofuran-2(3*H*)-one **23** (34.6 mg, 0.105 mmol) giving **3** as a colourless oil (34 mg, 87%). Compound **3**: ν_{max}/cm^{-1} (film): 2929 (CH), 2857 (CH), 1778 (C=O), 1743 (C=O), 1702 (C=O), 1644 (C=C), 1626 (C=C), 1231, 1170; δ_H (400 MHz, $CDCl_3$): 7.82 [1 H, dd, *J* 15.6, 11.2, C(6)H], 7.49 [1 H, d, *J* 6.1, C(11)H)], 6.53 [1 H, d, *J* 11.2, C(7)H], 6.38 [1 H, d, *J* 6.1, C(10)H], 6.08 [1 H, dd, *J* 15.6, 7.2, C(5)H], 5.60 – 5.43 [1 H, m, C(15)H], 5.28 – 5.15 [1 H, m, C(14)H], 5.15 – 5.05 [1 H, m, C(4)H], 2.84 [1 H, dd, *J* 14.4, 7.4, one of $C(13)H_2$], 2.71 – 2.40 [4 H, m, $C(2)H_2$, one of $C(3)H_2$, one of $C(13)H_2$], 2.14 – 2.01 [4 H, m, one of $C(3)H_2$, $C(22)H_3$], 2.01 – 1.91 [2 H, m, $C(16)H_2$], 1.35 – 1.19 [6 H, m, $C(17)H_2$, $C(18)H_2$, $C(19)H_2$], 0.88 [3 H, t, *J* 6.8, $C(20)H_3$]; δ_C (100.6 MHz, $CDCl_3$): 194.2 C(9)=O, 176.6 C(1)=O, 169.8 C(21)=O, 156.5 C(11)H, 140.0 C(5)H, 136.8 C(10)H, 136.8 C(8), 135.2 C(15)H, 132.6 C(7)H, 127.8 C(6)H, 121.3 C(14)H, 85.2 C(12), 80.2 C(4)H, 35.9 $C(13)H_2$, 31.7 $C(18)H_2$, 29.2 $C(17)H_2$, 28.8 $C(2)H_2$, 28.8 $C(3)H_2$, 27.6 $C(16)H_2$, 22.7 $C(19)H_2$, 21.8 $C(22)H_3$, 14.2 $C(20)H_3$; $[\alpha]^{20}_D$ -7.8° (c=0.20, $CHCl_3$); m/z (CI^+): 373 [$(M+H)^+$ 20%], 313 (100%); HRMS (CI^+): Exact mass calculated for $C_{22}H_{29}O_5^+$ 373.2015. Found 373.2019.

Note: Analysis for both Clavulolactone II and III is in excellent agreement with that reported by Iguchi *et al.*[1]

Notes and references

1 K. Iguchi, M. Iwashima, K. Watanabe, *J. Nat. Prod.* 1995, **58**, 790.
2 M. Iwashima, K. Okamoto, F. Konno, K. Iguchi, K. *J. Nat. Prod.* 1999, **62**, 352.
3 Y.-S. Lin, A. Taha Khalil, S.-H. Chiou, Y.-C. Kuo, Y.-B. Cheng, C.-C. Liaw, Y.-C. Shen, *Chem. Biodiversity* 2008, **5**, 784.
4 H. Kikuchi, Y. Tsukitani, K. Iguchi, Y. Yamada, *Tetrahedron Lett.* 1982, **23**, 5171.
5 M. Kobayashi, T. Yasuzawa, M. Yoshihara, H. Akutsu, Y. Kyogoku, I. Kitagawa, *Tetrahedron Lett.* 1982, **23**, 5331.
6 K. Iguchi, S. Kaneta, K. Mori, Y. Yamada, A. Honda, Y. Mori, *Tetrahedron Lett.* 1985, **26**, 5787.
7 A. Honda, Y. Yamamoto, Y. Mori, Y. Yamada, H. Kikuchi, *Biochem. Biophys. Res. Comm.* 1985, **130**, 515.
8 A. Honda, Y. Mori, K. Iguchi, Y. Yamada, *Mol. Pharmacol.* 1987, **32**, 530.
9 A. Honda, Y. Mori, K. Iguchi, Y. Yamada, *Prostaglandins* 1988, **36**, 621.
10 Y.-C. Shen, Y.-B. Cheng, Y.-C. Lin, J.-H. Guh, C.-M. Teng, C.-L. Ko, *J. Nat. Prod.* 2004, **67**, 542.
11 Y.-C. Huang, J.-H. Guh, Y.-C. Shen, C.-M. Teng, *J. Biomed. Sci.* 2005, **12**, 335.
12 T. Bader, Y. Yamada, H. Ankel, *Antiviral Res.* 1991, **16**, 341.
13 M. Rosetti, M. Frasnelli, F. Fabbri, C. Arienti, I. Vannini, A. Tesei, W. Zoli, M. Conti, *Anticancer Res.* 2008, **28**, 315.
14 M. Conti, *Expert Opin. Drug Discov.* 2007, **2**, 1153.
15 E. J. Corey, M. M. Mehrotra, *J. Am. Chem. Soc.* 1984, **106**, 3384.
16 H. Nagaoka, T. Miyakoshi, Y. Yamada, *Tetrahedron Lett.* 1984, **25**, 3621.
17 J. Zhu, J.-Y. Yang, A. J. H. Klunder, Z.-Y. Liu, B. Zwanenburg, *Tetrahedron* 1995, **51**, 5847.
18 M. Suzuki, Y. Morita, A. Yanagisawa, R. Noyori, B. J. Baker, P. J. Scheuer, *J. Am. Chem. Soc.* 1986, **108**, 5021.
19 H. Nagaoka, H. Miyaoka, T. Miyakoshi, Y. Yamada, *J. Am. Chem. Soc.* 1986, **108**, 5019.
20 K. Mori, T. Takeuchi, *Tetraheron* 1988, **44**, 333.
21 L. Tietze, C. Stadler, N. Böhnke, G. Brasche, A Grube, *Synlett* 2007, **3**, 485.
22 M. Le Liepvre, J. Ollivier, D. J. Aitken, *Eur. J. Org. Chem.* 2009, **34**, 5953.
23 H. P. Acharya, K. Miyoshi, Y. Kobayashi, *Org. Lett.* 2007, **9**, 3535.
24 S.-K. Kang, D.-S. Shin, J.-O. Lee, H.-G. Goh, *Bull. Korean Chem. Soc.* 1986, **7**, 444.
25 R. E. Doolittle, J. H. Tumlinson, A. T. Proveaux, R. R. Hwath, *J. Chem. Ecology* 1980, **6**, 473.
26 E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* 1972, **94**, 6190.
27 A. B. Smith, G. R. Ott, *J. Am. Chem. Soc.* 1996, **118**, 13095.
28 P. F. Cirillo, J. S. Panek, *J. Org. Chem.* 1990, **55**, 6071.
29 M. Wang, C. Li, D. Yin, X.-T. Liang, *Tetrahedron Lett.* 2002, **43**, 8727.
30 S. Masamune, L. D. L. Lu, W. P. Jackson, T. Kaiho, T. Toyoda, *J. Am. Chem. Soc.* 1982, **104**, 5523.
31 K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* 1998, **63**, 6436.
32 K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley, W. R. Roush, *J. Am. Chem. Soc.* 2002, **124**, 6981.
33 S. A. King, B. Pipik, A. S. Thompson, A DeCamp, T. R. Verhoeven, *Tetrahedron Lett.* 1995, **36**, 4563.
34 M. Eggen, S. K. Nair, G. I. Georg, *Org. Lett.* 2001, **3**, 1813.
35 T. Oriyama, M. Oda, J. Gono, G. Koga, *Tetrahedron Lett.* 1994, **35**, 2027.
36 B. Ganem, V. R. Small, *J. Org. Chem.* 1974, **39**, 3728.
37 K. L. Chandra, P. Saravanan, V. K. Singh, *Tetrahedron Lett.* 2001, **42**, 5309.
38 Q. Xiao, W.-W. Ren, Z.-X. Chen, T.-W. Sun, Y. Li, Q.-D. Ye, J.-X. Gong, F.-K. Meng, L. You, Y.-F. Liu, M.-Z. Zhao, L.-M. Xu, Z.-H. Shan, Y. Shi, Y.-F. Tang, J.-H. Chen, Z. Yang, *Angew. Chem. Int. Ed.* 2011, **50**, 7373.
39 R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, S. M. Roberts, *Tetrahedron Lett.* 1979, **20**, 3981.