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A convergent synthesis of the [4.4]-spiroacetal-γ-lactones cephalosporolides E and F

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ABSTRACT

A short convergent synthesis of the fungal metabolites cephalosporolides E and F is reported. The key step makes use of a chelation-controlled Mukaiyama aldol reaction to access the key acyclic spiroacetal precursor with the required *syn* stereochemistry.

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1. Introduction

Cephalosporolides E (**1a**) and F (**1b**) were first isolated from the fungus *Cephalosporium aphidicola* by Ackland et al. in 1985.[1] At this time only the relative stereochemistry was assigned, however recently the absolute stereochemistry was established as 3*S*,4*S*,6*S*,9*R* for cephalosporolide E and 3*S*,4*S*,6*R*,9*R* for cephalosporolide F by asymmetric synthesis of the enantiomeric compounds.[2] The synthesis of the natural products containing the correct stereochemistry has also recently been achieved by Fernandes et al.[3] In 2004, almost 20 years after their initial isolation, cephalosporolides E and F were independently isolated from the fungus *Cordyceps militaris* together with a proposed furan metabolite.[4] In 2005, the biological linear precursor to cephalosporolides E and F, (+)-bassianolone (**2**) was isolated from the fungus *Beauveria bassiana* and it was also shown that (+)-bassianolone could be converted to a diastereomeric mixture of cephalosporolide E and F by treatment with silica (Fig. 1).[5] (+)-Bassianolone was shown to exhibit significant antimicrobial activity, completely inhibiting the growth of *Staphylococcus aureus* and *Candida albicans*.[5]

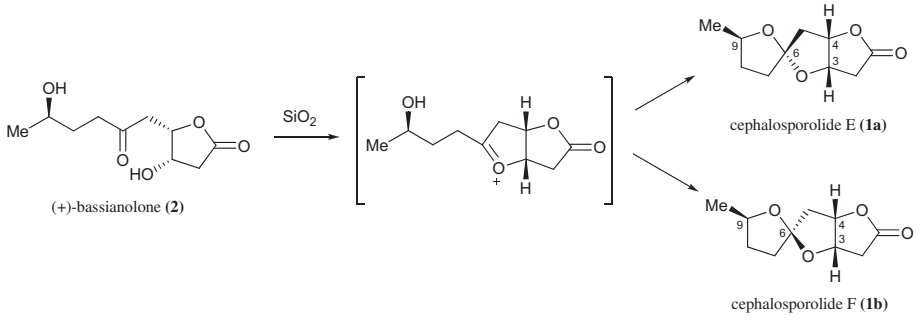

Fig. 1. (+)-Bassianolone (**2**) undergoes silica-catalysed cyclisation to give cephalosporolides E (**1a**) and F (**1b**).[5]

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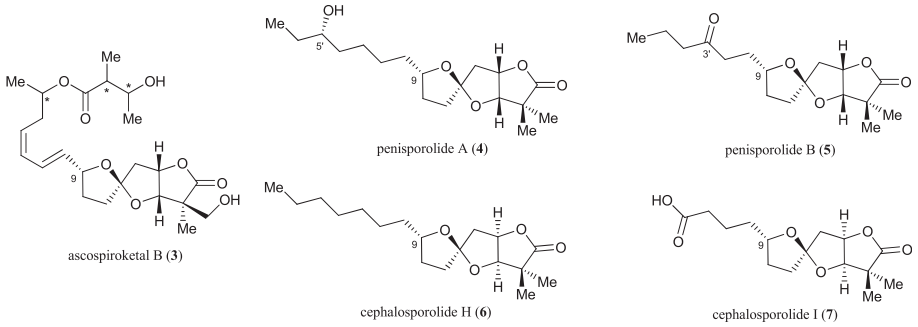
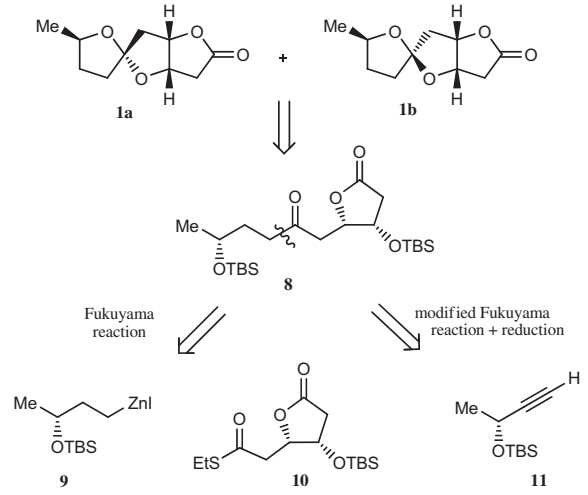


Fig. 2. Natural products containing the tricyclic β,γ-fused-[4.4]-spiroacetal-γ-lactone structural motif.[6–8]

The interesting tricyclic β,γ-fused-[4.4]-spiroacetal-γ-lactone structural motif present in cephalosporolides E (**1a**) and F (**1b**) is also found in five other natural products (Fig. 2). Ascospiroketal B (**3**), isolated in 2007 from the marine fungus *Aschochyta salicorniae*,[6] differs from the cephalosporolides (**1**) by the presence of geminal methyl, hydroxymethylene disubstitution at the position α to the γ-lactone and an elaborate tail of undefined stereochemistry at C-9 in the spiroacetal. Penisporolides A (**4**) and B (**5**), also isolated in 2007, from the marine derived fungus *Penicillium* sp. also possess the same ring system.[7] Penisporolides A and B both contain geminal dimethyl groups at the position α to the γ-lactone with penisporolide A containing a 5′-hydroxyheptyl side chain at C-9 whilst penisporolide B contains a 3′-oxohexyl substituent at C-9. Finally, cephalosporolides H (**6**) and I (**7**),[8] were also isolated in 2007 from the marine derived fungus *Penicillium* sp. Both compounds contain a geminal dimethyl group at the position α to the γ-lactone. Cephalosporolide H bears a saturated heptyl chain at C-9 and cephalosporolide I contains a butanoic acid side chain at C-9.

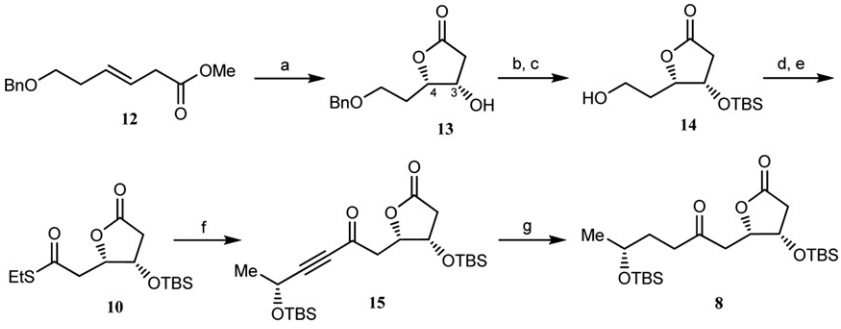


Scheme 1. Retrosynthesis of cephalosporolides E (**1a**) and F (**1b**), using a Fukuyama reaction.[9,10]

2. Results and discussion

Our initial retrosynthesis for cephalosporolides E (**1a**) and F (**1b**) (Scheme 1) hinged on accessing linear precursor **8**. It was intended that the [4.4]-spiroacetal be assembled in the final step via acid-catalysed deprotection and cyclisation of protected ketone **8**. Ketone **8** in turn would be accessed via Fukuyama reaction[9] between alkyl zinc iodide **9** and thioester **10** that bears the preformed γ-lactone functionality. Disappointingly, the initial Fukuyama coupling reaction proved unsuccessful in our hands, however a modified Fukuyama reaction[10] between alkyne **11** and thioester **10** afforded ketone **8** after reduction of the resultant alkyne.

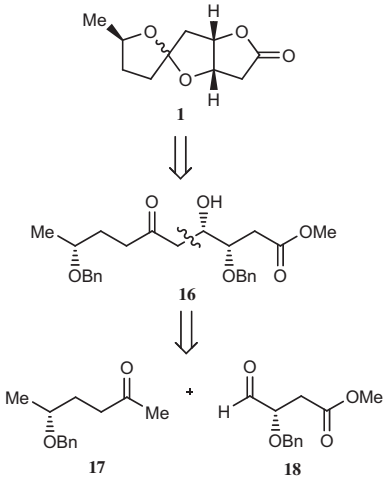
Applying the retrosynthesis summarised in Scheme 1, the common thioester intermediate **10** was prepared in nine steps starting from butane-1,4-diol. Butane-1,4-diol was converted to known β,γ-unsaturated methyl ester **12**,[11] the substrate required for the key Sharpless asymmetric dihydroxylation[12] that allowed installation of the key stereocentres at C-3 and C-4 (Scheme 2). Sharpless asymmetric dihydroxylation using $(DHQ)_2Phal$, followed by in situ lactonisation directly afforded lactone **13** in 86% yield with >95% ee.[13] Protection of the secondary alcohol **13** followed by removal of the benzyl group by hydrogenation afforded primary alcohol **14**. Oxidation to the carboxylic acid using TEMPO[14] and conversion to the desired thioester **10** then proceeded optimally using DIC, ethanethiol and HOBt in dichloromethane. The formation of side products, presumably resulting from E1cB elimination of the secondary OTBS group and E1cB opening of the lactone ring, originating by deprotonation α to the thioester, contributed to the moderate yields obtained for this step.



Scheme 2. Modified Fukuyama reaction and attempted global TBS deprotection of **8**. Reagents and conditions: (a) $(DHQ)_2Phal$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, OsO_4, $^tBuOH/H_2O$, 0 °C, 86%, >95% ee; (b) TBSCl, NEt_3, DMAP, CH_2Cl_2, rt, 3 days, 72%; (c) H_2 (60 psi), Pd/C, EtOH, rt, 6 h, 95%; (d) TEMPO, $NaClO_2$, NaOCl, MeCN, pH 6.7 phosphate buffer, 35 °C, 3 h, 95%; (e) DIC, HOBt, EtSH, CH_2Cl_2, 0 °C→rt, 52%; (f) CuI (2.2 equiv), $PdCl_2(dppf)$ (0.1 equiv), P(2-furyl)$_3$ (0.25 equiv), DMF, NEt_3, alkyne **11**, 34%; (g) Pd/C, H_2, EtOAc, 60 psi, 2 h, 75%.

Initial attempts to access saturated ketone **8** directly, by reaction of thioester **10** with zinc iodide **9** using the Fukuyama reaction[9] were unsuccessful. Alternatively, TBS protected alkyne **11** was coupled with thioester **10** using a modified Fukuyama strategy[10] to provide ynone **15** albeit in only 34% yield. Complete reduction of the alkyne moiety afforded the desired cyclisation precursor, ketone **8**. Due to the sensitivity of keto-γ-lactone **8**, all attempts to effect double TBS deprotection to form (+)-bassianolone (**2**) only afforded complex mixtures of undesired products.

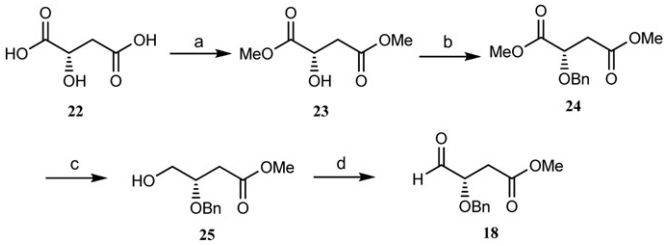
Analogous compounds were synthesised using a methoxymethyl (MOM) protecting group strategy in place of OTBS, however the final acid-catalysed deprotection and cyclisation to afford (+)-bassianolone (**2**) or cephalosporolides E (**1a**) or F (**1b**) proved unrewarding. To circumvent these problems, an alternative synthetic strategy was devised in which the two secondary hydroxyl protecting groups could be removed under neutral conditions with the sensitive lactone functionality installed in the final stages of the synthesis. It was thus anticipated that cephalosporolides E (**1a**) and F (**1b**) could be obtained as a separable mixture of diastereomers upon debenzylation, in situ spirocyclisation, followed by lactonisation of the acyclic precursor **16** (Scheme 3). The 3,4-*syn* stereochemistry in β-hydroxyketone **16** would be installed by *syn* selective Mukaiyama aldol reaction[15] between the silyl enol ether derivative of methyl ketone **17** with aldehyde **18**.[16]



Scheme 3. Revised retrosynthesis of cephalosporolides E (**1a**) and F (**1b**).

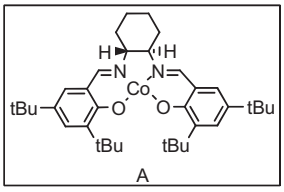
The synthesis of methyl ketone **17** began with hydrolytic kinetic resolution (HKR) of propylene oxide **19** (Scheme 4).[17] Treatment of terminal epoxide **19** with the (*R*,*R*)-cobalt salen complex **A**[17] provided enantioenriched (*R*)-epoxide **20** that could easily be separated from the (*S*)-diol by distillation at atmospheric pressure. The enantiomeric excess of the HKR was established at a later stage by chiral HPLC analysis of methyl ketone **17** (vide infra). Epoxide **20** was opened at the terminal position by the addition of an allyl cuprate reagent and the newly-formed secondary alcohol treated with sodium hydride and benzyl bromide to afford benzyl ether **21** (60% for two steps). Terminal olefin **21** was then subjected to Wacker oxidation ($PdCl_2$, CuCl, O_2)[18] to afford methyl ketone **17** in 93% ee as determined by chiral HPLC analysis.

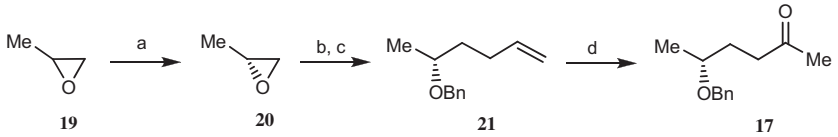
With methyl ketone **17** in hand, attention turned to the synthesis of the aldol coupling partner, namely aldehyde **18** (Scheme 5). Aldehyde **18** was prepared in four steps from (*S*)-malic acid **22**. The base sensitive β-hydroxy ester **23** dictated the use of acid-catalysed benzyl protection conditions, hence alcohol **23** was treated with benzyl trichloroacetimidate in the presence of TfOH to afford benzyl ether **24**.[19] The best results were achieved by reaction of alcohol **23** with freshly prepared benzyl trichloroacetimidate[20] in the presence of a catalytic quantity (10 mol %) of TfOH for 2 days at room temperature. Chelation-controlled reduction of 24 using DIBAL (2.5 equiv) in the presence of $MgBr_2 \cdot OEt_2$ at −8 °C selectively reduced the methyl ester α to the neighbouring alkoxy group thus affording alcohol **25** exclusively. The use of more than 2.5 equiv of DIBAL resulted in undesired reduction of the second methyl ester. Direct formation of aldehyde **18** by conducting the reaction at −90 °C using 1.0 equiv of DIBAL did not proceed cleanly and only a mixture of alcohol **25** and aldehyde **18** was observed.[21] Oxidation of primary alcohol **25** proved to be problematic, however aldehyde **18** was finally obtained using a TEMPO-catalysed oxidation procedure; PCC, Swern, DMP and IBX oxidation conditions were all unsuccessful. The highly sensitive nature of similar α-alkoxy aldehydes has previously been reported by other groups.[22]



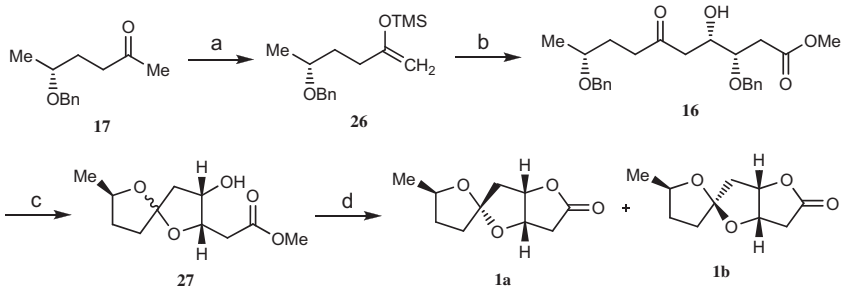
Scheme 5. Synthesis of aldol coupling partner aldehyde **18**. Reagents and conditions: (a) MeOH, AcCl, rt, 18 h, 80%; (b) benzyl trichloroacetimidate, CH_2Cl_2, cyclohexane, TfOH, rt, 24 h, 74%; (c) DIBAL-H, (2.5 equiv), CH_2Cl_2, $MgBr_2 \cdot Et_2O$, −78 °C→0 °C, 2 h, 53%; (d) TEMPO, TCIA, $NaHCO_3$, −5 °C, 1 h, 70%.

Armed with aldol coupling partners **17** and **18**, attention turned to the key stereoselective aldol reaction (Scheme 6).[15] After initial failure to effect a direct aldol reaction using LDA or LHMDS, the TMS enol ether **26** was prepared by exposure of ketone **17** to TMSOTf in the presence of triethylamine.[23] Use of TMSCl under a variety of conditions was unsuccessful. Gratifyingly, subsequent Mukaiyama





Scheme 4. Synthesis of methyl ketone **17**. Reagents and conditions: (a) (*R*,*R*)-salen Co^{II} complex **A**, AcOH (2.1 equiv), H_2O (0.55 equiv); 0 °C→rt, 12 h, 48% (max 50%); (b) CuI, THF, allylmagnesium bromide (1 M in Et_2O), −30 °C, 4 h; (c) NaH, THF, BnBr, TBAI, rt, 15 h; 60% (two steps); (d) $PdCl_2$, CuCl, DMF, O_2, rt, 4 h, 71%.



Scheme 6. Synthesis of cephalosporolides E (**1a**) and F (**1b**). Reagents and conditions: (a) TMSOTf, NEt_3, CH_2Cl_2, 30 min, 0 °C; (b) aldehyde **18**, CH_2Cl_2, $MgBr_2{\cdot}Et_2O$, 2 h, −78 °C→0 °C, 30%; (c) Pd/C, H_2, MeOH, 60 psi, 12 h; (d) Amberlyst-15, CH_2Cl_2, rt, 12 h, 86% (two steps), **1a**:**1b** (3:2).

aldol reaction with aldehyde **18** proceeded under chelation control in the presence of $MgBr_2{\cdot}OEt_2$ at −78 °C in dichloromethane to afford 3,4-*syn* alcohol 16 in >95% de (no other diastereomers were observed by ^{1}H NMR) in moderate yield. Aldol product **16** proved stable to the aldol reaction conditions and careful purification by flash chromatography buffered with 0.25% triethylamine did not effect lactone formation or elimination to the α,β-unsaturated ketone. High pressure hydrogenation was required to effect clean double debenzylation with concomitant in situ spiroketalisation, affording the desired [4.4]-spiroketal **27** as an inseparable (1:1) mixture of diastereomers. Finally acid-catalysed lactonisation was effected by exposure of hydroxy ester **27** to Amberlyst-15 affording γ-lactones (**1**) as a 3:2 mixture of diastereomers, thereby completing the synthesis of cephalosporolides E and F. The two [4.4]-spiroacetal diastereomers were carefully separated by flash column chromatography, affording pure samples of cephalosporolides E and F.

3. Conclusion

In conclusion, we have successfully synthesised 3*S*,4*S*,6*S*,9*R*-(+)-cephalosporolide E (**1a**) and 3*S*,4*S*,6*R*,9*R*-(−)-cephalosporolide F (**1b**) in 12 steps using a diastereoselective Mukaiyama aldol reaction to establish the *syn*-stereocentres in the spirocyclisation precursor **16**. The sensitive [4.4]-spiroacetal-γ-fused lactone ring system was introduced in the final steps of the synthesis. This synthetic strategy should prove amenable to the synthesis of other members of this structural class of natural products.

4. Experimental

4.1. General methods

All reactions were carried out in oven-dried glassware, which was further dried under high vacuum whilst heating with a heat gun. Reactions were carried out under an atmosphere of argon or nitrogen dried by passing through a cylinder of calcium chloride. Solvents were dried under standard conditions. Thin layer chromatography was carried out using Merck 0.2 mm silica gel 60 F_{254} aluminium plates. Flash column chromatography was carried out using 40–63 μm, 230–430 mesh silica gel with the solvent indicated. Mass spectra were obtained on a VG-70SE spectrometer. Prominent fragments are recorded as *m* (*n*) where *m* is the mass to charge ratio and *n* is the percentage abundance relative to the base peak. Infrared spectra were obtained on a Perkin–Elmer Spectrum One Universal ATR Sampling Accessory Fourier Transform IR spectrometer, neat, over a crystal plate or using a Perkin–Elmer Spectrum 1000 series Fourier Transform IR spectrometer as a thin film between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations of chiral compounds were obtained using a Perkin–Elmer 341 polarimeter in the solvent indicated. NMR spectra were recorded on either a Bruker AV300 spectrometer operating at 300 MHz for the ^{1}H nuclei and 75 MHz for the ^{13}C nuclei or a Bruker DRX400 spectrometer operating at 400 MHz for the ^{1}H nuclei and 100 MHz for the ^{13}C nuclei. All chemical shifts are recorded in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or deuterated chloroform (δ 7.26 ppm or δ 77.0 ppm). Coupling constant *J* values are given in Hertz (Hz).

*4.1.1. (4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(2′-hydroxyethyl)dihydrofuran-2(3H)-one **14**.* To a stirred solution of alcohol **13** (542 mg, 2.29 mmol) in CH_2Cl_2 (12 mL) at room temperature was added triethylamine (1.60 mL, 11.4 mmol), *tert*-butyldimethylsilyl chloride (1.21 g, 8.02 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (55 mg, 0.46 mmol). After 24 h, the reaction mixture was quenched by the addition of 1 M HCl (50 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated, the aqueous fraction extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resultant crude residue purified by flash column chromatography using a gradient elution of hexane/ethyl acetate (9:1→4:1) as eluent to afford the corresponding silyl ether (576 mg, 72%) as a colourless liquid. R_f (20% EtOAc/hexanes) 0.42; $[\alpha]_D^{20}$ −33.5 (*c* 1.30 in $CHCl_3$); ν_{max} (cm^{-1}): 2952, 2929, 2858, 1779 (C≡O), 1362, 1255, 1203, 1159, 1095, 1076; δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.05 (3H, s, Si*CH*$_3$), 0.06 (3H, s, Si*CH*$_3$), 0.88 (9H, s, Si^t*Bu*), 1.88–1.96 (1H, m, H-1′a), 2.06–2.14 (1H, m, H-1′b), 2.42 (1H, dd, *J* 17.3, 1.0 Hz, H-3a), 2.72 (1H, dd, *J* 17.3, 5.3 Hz, H-3b), 3.65 (2H, dd, *J* 7.6, 4.7 Hz, H-2′), 4.38 (1H, ddd, *J* 5.3, 4.0, 1.0 Hz, H-4), 4.47 (1H, d, *J* 11.7 Hz, C*H*$_2$Ar), 4.55 (1H, d, *J* 11.7 Hz, C*H*$_2$Ar), 4.61–4.64 (1H, dt, *J* 6.9, 4.0 Hz, H-5), 7.27–7.36 (5H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si): −5.2 (CH_3, Si*CH*$_3$), −4.8 (CH_3, Si*CH*$_3$), 17.9 (C, Si^t*Bu*), 25.6 (CH_3, Si^t*Bu*), 29.6 (CH_2, C-1′), 39.8 (CH_2, C-3), 66.4 (CH_2, C-2′), 69.8 (CH, C-4), 73.2 (CH_2, *C*H$_2$Ar), 81.9 (CH, C-5), 127.7 (CH, Ar–H), 127.7 (CH, Ar–H), 128.4 (CH, Ar–H), 138.1 (C, Ar), 175.4 (C=O, C-2); *m*/*z* (EI, CI^+, NH_3): 351.1987 (MH^+, $C_{19}H_{31}O_4Si$ requires 351.1992), 368 (MNH_4^+, 0.5%), 351 (MH^+, 2%), 218 (2), 145 (6), 131 (4), 105 (11), 101 (9), 105 (19), 91 (CH_2Ph, 100), 77 (8), 75 (11).

To a stirred solution of the above silyl ether (550 mg, 1.57 mmol) in freshly distilled ethanol (10 mL) was added palladium on carbon (10 wt %, 10 mg, 0.08 mmol). The reaction mixture was stirred vigorously under an atmosphere of hydrogen. After 2.5 h, the reaction mixture was filtered through a plug of Celite and washed through with a solution of hexane/ethyl acetate (3:2) (150 mL). The solvent was evaporated under reduced pressure and the resultant crude residue purified by flash column chromatography using hexane/ethyl acetate (2:3) as eluent to afford the *title compound* **14** (389 mg, 95%) as a colourless solid. Mp 57–59 °C; $[\alpha]_D^{20}$ −35.4 (*c* 2.00 in $CHCl_3$); ν_{max} (cm^{-1}): 3422 (OH), 2956, 2930, 2887, 2858, 1776 (C=O), 1362, 1255, 1161, 1065; δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.03 (6H, s, Si*CH*$_3$), 0.83 (9H, s, Si^t*Bu*), 1.75–1.83 (1H, m, H-1′a), 1.96–2.05 (1H, m, H-1′b), 2.37–2.42 (2H, m, H-3a, O–*H*), 2.72 (1H, dd, *J* 17.3, 5.0 Hz, H-3b), 3.75 (2H, dd, *J* 7.0, 5.0 Hz, H-2′), 4.41 (1H,

ddd, *J* 5.0, 3.6, 0.8 Hz, H-4), 4.59 (1H, dt, *J* 9.6, 3.6 Hz, H-5); δ_C (75 MHz; $CDCl_3$; Me_4Si): −5.2 (CH_3, Si*C*H_3), −4.9 (CH_3, Si*C*H_3), 17.8 (C, Si*C*(*Bu*)), 25.5 (CH_3, Si*C*(*Bu*)), 31.8 (CH_2, C-1′), 39.7 (CH_2, C-3), 58.8 (CH_2, C-2′) 69.8 (CH, C-4), 82.2 (CH, C-5), 175.7 (C=O, C-2); *m*/*z* (EI, CI, NH_3): 261.1524 (MH^+, $C_{12}H_{25}O_4Si$ requires 261.1522), 278 (MNH_4^+, 16%), 261 (MH^+, 22%), 203 (21), 173 (20), 161 (27), 157 (24), 131 (43), 129 (39), 111 (30), 92 (19), 75 (100).

4.1.2. S-Ethyl 2-((2S,3S)-3-(tert-butyldimethylsilyloxy)-5-oxotetrahydrofuran-2-yl)ethanethioate ***10***. To a stirred solution of alcohol **14** (1.30 g, 5.00 mmol) in acetonitrile (30 mL) and aqueous phosphate buffer (25 mL, pH 6.7, 1 mol L^{-1}) at room temperature was added 2,2,6,6-tetramethylpiperidin-1-oxyl (109 mg, 0.70 mmol). The reaction mixture was warmed to 35 °C and solutions of sodium chlorite (1.81 g, 20 mmol) in water (14 mL) and sodium hypochlorite (360 μL) in water (8 mL) were added simultaneously over 2 h. The reaction was stirred for 4 h, diluted with water (15 mL) and diethyl ether (30 mL), and the pH adjusted to 9 with NaOH (2 mol L^{-1}). The reaction was quenched by pouring into saturated $Na_2S_2O_3$, cooled to 0 °C and stirred for 20 min. The layers were separated, the organic layer discarded, the aqueous layer adjusted to pH 3 using 2 M HCl and the mixture extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The solvent was evaporated under reduced pressure to afford the corresponding carboxylic acid (1.30 g, 95%) as a colourless solid. R_f (60% EtOAc/hexanes) 0.20; mp 83–88 °C; $[\alpha]_D^{20}$ +3.3 (*c* 1.73 in $CHCl_3$); ν_{max} (cm^{-1}): 2930, 2928, 2857, 1784 (lactone C=O), 1729 (acid C=O), 1186, 1158, 1042, 834, 774; δ_H (300 MHz; $CDCl_3$; Me_4Si): 0.11 (3H, s, Si*C*H_3), 0.13 (3H, s, Si*C*H_3), 0.89 (9H, s, Si*C*(*Bu*)), 2.48 (1H, dd, *J* 17.5, 1.4 Hz, H-4′a), 2.77 (1H, dd, *J* 17.5, 5.5 Hz, H-4′b), 2.92 (2H, d, *J* 6.9 Hz, H-2), 4.62 (1H, ddd, *J* 5.5, 4.0, 1.4 Hz, H-3′), 4.81 (1H, td, *J* 6.9, 4.0 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si): −5.2 (CH_3, Si*C*H_3), −4.6 (CH_3, Si*C*H_3), 17.6 (C, Si*C*(*Bu*)), 25.3 (CH_3, Si*C*(*Bu*)), 33.1 (CH_2, C-2), 39.0 (CH_2, C-4′), 68.8 (CH, C-3′) 80.1 (CH, C-2′), 175.1 (C=O, C-5′), 175.2 (C=O, C-1); *m*/*z* (EI, CI, NH_3): 292.1578 (MNH_4^+, $C_{12}H_{26}NO_5Si$ requires 292.1580), 292 (MNH_4^+, 100%), 275 (MH^+, 22%), 257 (11), 234 (7), 217 (19), 173 (5), 160 (7), 129 (6), 92(19), 74 (31).

To a stirred solution of the above acid (50 mg, 0.18 mmol), 1-hydroxybenzotriazole (28 mg, 0.18 mmol) and ethanethiol (20 μL, 0.27 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added 1,3-diisopropylcarbodiimide (30 μL, 0.18 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h after which the mixture was filtered through a short plug of silica. The solvent was evaporated and the crude residue purified by flash column chromatography using hexane/ethyl acetate (9:1) as eluent to afford the *title compound* **10** (30 mg, 52%) as a colourless liquid. R_f (20% EtOAc/hexanes) 0.45; $[\alpha]_D^{20}$ −3.6 (*c* 1.30 in $CHCl_3$); ν_{max} (cm^{-1}): 2957, 2931, 2888, 2859, 1783 (C=O), 1682 (C=O), 1471, 1408, 1298, 1261; δ_H (300 MHz; $CDCl_3$; Me_4Si): 0.02 (3H, s, Si*C*H_3), 0.05 (3H, s, Si*C*H_3), 0.86 (9H, s, Si*C*(*Bu*)), 1.23 (3H, t, *J* 7.3 Hz, $SCH_2C\mathbf{H}_3$), 2.40 (1H, dd, *J* 17.3, 1.0 Hz, H-4′a), 2.72 (1H, dd, *J* 17.3, 5.2 Hz, H-4′b), 2.87 (2H, q, *J* 7.3 Hz, $SC\mathbf{H}_2CH_3$), 3.05 (2H, d, *J* 6.8 Hz, H-2), 4.54 (1H, ddd, *J* 5.2, 3.9, 1.0 Hz, H-3′), 4.83 (1H, td, *J* 6.8, 3.9 Hz, H-2′); δ_C (75 MHz; $CDCl_3$; Me_4Si): −5.3 (CH_3, Si*C*H_3), −4.8 (CH_3, Si*C*H_3), 14.5 (CH_3, SEt), 17.8 (C, Si*C*(*Bu*)), 23.3 (CH_2, SEt), 25.5 (3×CH_3, Si*C*(*Bu*)), 39.2 (CH_2, C-4′), 42.4 (CH_2, C-2), 69.2 (CH, C-3′), 80.3 (CH, C-2′), 174.5 (C=O, C-5′), 195.9 (C=O, C-1); *m*/*z* (EI, CI, NH_3): 319.1402 (MH^+, $C_{14}H_{27}OSSi$ requires 319.1399), 336 (MNH_4^+, 51%), 319 (MH^+, 22%), 261 (100), 257 (55), 157 (9), 129 (14), 119 (21), 97 (9), 78 (12), 74 (41).

4.1.3. (4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-((R)-5′-(tert-butyldimethylsilyloxy)-2′-oxohex-3′-ynyl)dihydrofuran-2(3H)-one ***15***. To a stirred solution of thioester **10** (34 mg, 0.107 mmol), copper iodide (45 mg, 0.24 mg), P(2-furyl)$_3$ (6 mg, 0.027 mmol), $PdCl_2$(dppf) (9 mg, 0.011 mmol) and triethylamine (150 μL) in dry *N*,*N*-dimethylformamide (750 μL) at room temperature was added neat alkyne **11** (39 mg, 0.214 mmol). The mixture was heated to 50 °C and stirred for 3 h. The reaction was cooled to room temperature, quenched by the addition of brine (3 mL) and diluted with diethyl ether (5 mL). The layers were separated and the aqueous layer extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over $MgSO_4$, the solvent evaporated under reduced pressure and the resultant crude brown residue purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **15** (16 mg, 34%) as a colourless liquid. R_f (10% EtOAc/hexanes) 0.42; $[\alpha]_D^{20}$ +24.5 (*c* 0.75 in $CHCl_3$); ν_{max} (cm^{-1}): 2955, 2929, 2857, 2214 (C≡C), 1787 (lactone C=O), 1678 (ynone C=O), 1254, 1149, 809, 777; δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.04 (3H, s, Si*C*H_3), 0.08 (3H, s, Si*C*H_3), 0.11 (3H, s, Si*C*H_3), 0.14 (3H, s, Si*C*H_3), 0.88 (9H, s, Si*C*(*Bu*)), 0.90 (9H, s, Si*C*(*Bu*)), 1.46 (3H, d, *J* 6.6 Hz, H-6′), 2.44 (1H, dd, *J* 17.8, 3.6 Hz, H-3a), 2.74 (1H, dd, *J* 17.8, 5.2 Hz, H-3b), 3.14 (2H, dd, *J* 5.8, 4.3 Hz, H-1′), 4.59–4.62 (1H, m, H-4), 4.66 (1H, q, *J* 6.6 Hz, H-5′), 4.84–4.89 (1H, m, H-5); δ_C (100 MHz; $CDCl_3$; Me_4Si): −5.3 (CH_3, Si*C*H_3), −5.0 (CH_3, Si*C*H_3), −4.7 (CH_3, Si*C*H_3), −4.7 (CH_3, Si*C*H_3), 17.9 (C, Si*C*(*Bu*)), 18.1 (C, Si*C*(*Bu*)), 24.4 (CH_3, C-6′), 25.6 (3×CH_3, Si*C*(*Bu*)), 25.8 (3×CH_3, Si*C*(*Bu*)), 39.1 (CH_2, C-1′), 43.8 (CH_2, C-3), 58.8 (CH, C-5′), 68.9 (CH, C-4), 79.7 (CH, C-5), 81.8 (C, C-4′), 95.0 (C, C-3′), 174.7 (C=O, C-2), 183.3 (C=O, C-2′);*m*/*z* (EI, CI, NH_3): 441.2496 (MH^+, $C_{22}H_{41}O_5Si_2$ requires 441.2493), 458 (MNH_4^+, 28%), 441 (MH^+, 21%), 383 (100), 313 (20), 309 (18), 255 (30), 209 (9), 171 (14), 90 (16), 73 (68).

4.1.4. (4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-((R)-5′-(tert-butyldimethylsilyloxy)-2′-oxohexyl)dihydrofuran-2(3H)-one ***8***. To a solution of ynone **15** (15 mg, 0.034 mmol) dissolved in ethyl acetate (5 mL) was added palladium on carbon (5 mg, 10 wt %, 0.04 mmol). The mixture was subjected to 60 psi H_2 for 16 h until negligible starting material was presented by TLC analysis. The reaction mixture was filtered through a plug of Celite then washed with ethyl acetate (20 mL) and diethyl ether (20 mL). The solvent was evaporated under reduced pressure and the resultant crude yellow residue purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **8** (10 mg, 75%) as a colourless liquid. R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{20}$ −3.8 (*c* 0.50 in $CHCl_3$); ν_{max} (cm^{-1}): 2956, 2929, 2857, 1784 (C=O), 1715 (C=O), 1254, 1093, 1030, 836, 775; δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.01 (3H, s, Si*C*H_3), 0.03 (3H, s, Si*C*H_3), 0.05 (3H, s, Si*C*H_3), 0.06 (3H, s, Si*C*H_3), 0.85 (9H, s, Si*C*(*Bu*)), 0.88 (9H, s, Si*C*(*Bu*)), 1.12 (3H, d, *J* 6.0 Hz, H-6′), 1.67–1.72 (2H, m, H-4′), 2.40–2.48 (2H, m, H-3′), 2.55–2.58 (1H, m, H-3a), 2.73 (1H, dd, *J* 17.6, 5.6 Hz, H-3b), 2.95–2.98 (2H, m, H-1′), 3.81–3.85 (1H, m, H-5′), 4.57–4.59 (1H, m, H-4), 4.80–4.84 (1H, m, H-5); δ_C (100 MHz; $CDCl_3$; Me_4Si): −5.3 (CH_3, Si*C*H_3), −4.8 (CH_3, Si*C*H_3), −4.7 (CH_3, Si*C*H_3), −4.4 (CH_3, Si*C*H_3), 17.9 (C, Si*C*(*Bu*)), 18.1 (C, Si*C*(*Bu*)), 23.5 (CH_3, C-6′), 25.6 (CH_3, Si*C*(*Bu*)), 25.8 (CH_3, Si*C*(*Bu*)), 32.9 (CH_2, C-4′), 39.2 (CH_2, C-1′), 39.4 (CH_2, C-3), 41.2 (CH_2, C-3′), 67.4 (CH, C-4), 69.2 (CH, C-5′), 80.6 (CH, C-5), 174.9 (C=O, C-2), 208.6 (C=O, C-2′);*m*/*z* (EI, CI, NH_3): 445.2797 (MH^+, $C_{22}H_{45}O_5Si_2$ requires 445.2806), 445 (MH^+, 42%), 387 (48), 369 (14), 329 (10), 313 (90), 295 (12), 255 (100), 171 (16), 132 (11), 75 (38).

4.1.5. (S)-Dimethyl malate ***23***. Acetyl chloride (8.21 mL, 116 mmol) was added to methanol (150 mL) at room temperature followed after 10 min by (*S*)-malic acid (25 g, 186 mmol). The solution was stirred at room temperature for 18 h before the volatile components were evaporated under reduced pressure. The resultant residue was purified by flash column chromatography using CH_2Cl_2/MeOH (95:5) as eluent to afford the title compound **23** (22.67 g, 80%) as a yellow oil. The spectroscopic data was in agreement with those reported in the literature.[24] R_f (5% MeOH/CH_2Cl_2) 0.51; $[\alpha]_D^{20}$ +1.6 (*c* 0.80 in $CHCl_3$); lit.[24] $[\alpha]_D^{25}$ +3.1 (*c* in 0.80, $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.72 (2H, dd, *J* 16.4, 4.4 Hz, H-3), 3.35 (1H, br s, OH), 3.61 (3H, s, C-4OMe), 3.67 (3H, s, C-1OMe),

4.42 (1H, dd, *J* 6.3, 4.4 Hz, H-2); δ_C (75 MHz; $CDCl_3$; Me_4Si) 38.4 (CH_2, C-3), 51.9 (CH_3, C-4OMe), 51.6 (CH_3, C-1OMe), 67.2 (CH, C-2) 170.9 (C=O, C-4), 173.6 (C=O, C-1).

4.1.6. (S)-Dimethyl 2-(benzyloxy)succinate ***24***. Benzyl 2,2,2-trichloroacetimidate (16.3 g, 65.0 mmol) was added to a solution of (*S*)-dimethyl malate **23** (7.00 g, 43.0 mmol) in CH_2Cl_2 (35 mL) and cyclohexane (60 mL). Triflic acid (0.97 mL, 6.48 mmol) was then added dropwise. The mixture was stirred at room temperature for 24 h. The mixture was filtered and the filtrate was washed with (aq) $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The resultant crude yellow residue was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the title compound **24** (11.52 g, 74%) as a yellow oil. The spectroscopic data was in agreement with those reported in the literature.[19] R_f (20% EtOAc/hexanes) 0.33; $[\alpha]_D^{20}$ −43.5 (*c* 1.60 in $CHCl_3$); lit.[19] $[\alpha]_D^{20}$ −63.0 (*c* 1.60 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.72–2.76 (2H, m, H-3) 3.60 (3H, s, C-4OMe), 3.69 (3H, s, C-1OMe), 4.38–4.41 (1H, m, H-2), 4.53 (1H, d, *J* 11.5 Hz, C*H*$_2$Ph), 4.76 (1H, d, *J* 11.5 Hz, C*H*$_2$Ph) 7.29–7.32 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$; Me_4Si) 37.4 (CH_2, C-3), 51.6 (CH_3, C-4OMe), 51.8 (CH_3, C-1OMe), 72.7 (CH, C-2) 74.3 (CH_2, *C*H_2Ph) 2×127.7 (CH, Ph–H), 127.9 (CH, Ph–H), 2×128.2 (CH, Ph–H) 137.0 (C, Ph) 170.3 (C=O, C-4) 171.6 (C=O, C-1).

4.1.7. (S)-Methyl 3-(benzyloxy)-4-hydroxybutanoate ***25***. To a solution of diester **24** (1.00 g, 3.96 mmol) in CH_2Cl_2 (50 mL) was added $MgBr_2 \cdot OEt_2$ (1.15 g, 4.48 mmol) and the resultant mixture was stirred at room temperature for 1 h. The solution was then cooled to −78 °C and DIBAL-H (9.92 mL of 1.0 M solution in toluene, 9.92 mmol) was added dropwise over 90 min via syringe pump. After complete addition followed by stirring for 30 min at −78 °C, the reaction was allowed to warm to 0 °C then stirred for a further 2 h. Methanol (5 mL) and saturated (aq) Rochelle's salt solution (30 mL) were then added and the solution was allowed to warm to room temperature and stirred for a further 20 min. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by flash column chromatography using hexane/ethyl acetate (3:2) as eluent to afford the *title compound* **25** (0.45 g, 53%) as a yellow oil. R_f (40% EtOAc/hexanes) 0.28; $[\alpha]_D^{20}$ −2.1 (*c* 1.2 in $CHCl_3$) ν_{max} (film)/cm^{-1} 3436, 1730, 1057, 824, 736, 697; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.55–2.70 (2H, m, H-2), 3.55–3.65 (2H, m, H-4), 3.70 (3H, s, OMe), 3.93–3.97 (1H, m, H-3), 4.46 (1H, d, *J* 11.5 Hz, C*H*$_2$Ph), 4.57 (1H, d, *J* 11.5 Hz, C*H*$_2$Ph), 7.25–7.32 (5H, m, Ph–H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 36.4 (CH_2, C-2) 51.6 (CH_3, C-1OMe) 63.7 (CH_2, C-4) 71.9 (CH, C-3) 76.2 (CH_2, *C*H_2Ph) 2×127.5 (CH, Ph–H),127.7 (CH, Ph–H), 2×128.3 (CH, Ph–H) 137.9 (C, Ph) 171.7 (C=O, C-1); *m*/*z* (EI) 224.0937 (MH^+, $C_{13}H_{18}O_2$ requires 224.1000) 225 (10%), 236 (1), 244 (1), 247 (MNa^+, 100), 248 (15).

4.1.8. (S)-Methyl 3-(benzyloxy)-4-oxobutanoate ***18***. To a solution of alcohol **25** (0.20 g, 0.892 mmol) and TEMPO (1.30 mg, 8.92 μmol) in EtOAc (3 mL) was added $NaHCO_3$ (0.225 g, 2.67 mmol). The mixture was cooled to −5 °C and a solution of trichloroisocyanuric acid (0.217 g, 0.938 mmol) in EtOAc (5 mL) was added dropwise over 1 h. After stirring for 1 h at −5 °C, NaI (5 mL of 1 M solution in water) was added. The solution was separated and extracted with EtOAc (3×20 mL). The combined organic layers were washed with (10% aq) Na_2SO_3 (10 mL) and the aqueous layer further extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound **18** (0.14 g, 70%) as a colourless oil. The spectroscopic data was in agreement with those reported in the literature.[21] R_f (40% EtOAc/hexanes) 0.30; $[\alpha]_D^{20}$ −16.7 (*c* 0.70 in $CHCl_3$); lit.[21] $[\alpha]_D$ −56.3 (*c* 0.70 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.55–2.74 (2H, m, H-2), 3.60 (3H, s, OMe), 4.09–4.17 (1H, m, H-3), 4.51 (1H, d, *J* 11.4 Hz, C*H*$_2$Ph), 4.60 (1H, d, *J* 11.4 Hz, C*H*$_2$Ph), 7.25–7.36 (5H, m, Ph–H) 9.64 (1H, s, H-4); δ_C (75 MHz; $CDCl_3$; Me_4Si) 35.6 (CH_2, C-2), 51.9 (CH_3, OMe), 73.0 (CH_2, CH_2Ph) 79.5 (CH, C-3), 127.6 (CH, Ph–H), 127.7 (CH, Ph–H), 128.3 (CH, Ph–H), 2×128.4 (CH, Ph–H), 136.8 (C, Ph), 170.4 (C=O, C-1), 201.8 (C=O, C-4).

4.1.9. (R)-Propylene oxide ***20***. (*R*,*R*–*N*,*N*) Bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (242 mg, 0.40 mmol) was dissolved in toluene (5 mL) and acetic acid (240 μL, 4.2 mmol) was added dropwise. The resultant solution was stirred at room temperature open to air for 30 min resulting in a colour change from orange-red to dark brown. The solution was concentrated in vacuo to yield a crude brown solid. The cobalt(III) complex was dissolved in propylene oxide (11.6 g, 14 mL, 200 mmol), cooled to 0 °C then water (1.98 mL, 110 mmol) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stirred overnight. (*R*)-Propylene oxide **25** was isolated by distillation at 36 °C at atmospheric pressure (5.6 g, 48%).[15]

4.1.10. (R)-5-Benzyloxyhex-1-ene ***21***. Copper(I) iodide (1.14 g, 6.00 mmol) was gently heated under nitrogen until it turned light yellow. THF (100 mL) was added and the resultant solution cooled to −30 °C after which 1 M allylmagnesium bromide in Et_2O (60 mL, 60 mmol) was added dropwise. The reaction was stirred for 5 min after which (*R*)-propylene oxide **20** (2.5 g, 43 mmol) in THF (15 mL) was added and the mixture allowed to stir for 4 h at −30 °C NH_4Cl (aq) was added and the mixture extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure to give (*R*)-hex-5-en-2-ol as a yellow oil, which was used without further purification.

To a solution of NaH (2.82 g, 70 mmol) in dry THF (180 mL) was added (*R*)-hex-5-en-2-ol in THF (25 mL) and the reaction mixture was stirred at room temperature for 30 min. Benzyl bromide (7.75 mL, 65 mmol) and tetra-*n*-butylammonium iodide (75 mg, 0.2 mmol) were then added and stirring continued at room temperature for 15 h. The reaction was then quenched with (aq) NH_4Cl (50 mL), extracted with EtOAc (3×50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (9.9:0.1) as eluent to afford the title compound **21** (5.08 g, 60%) as a yellow oil. The spectroscopic data was in agreement with those reported in the literature.[25] R_f (20% EtOAc/hexanes) 0.84; $[\alpha]_D^{20}$ −15.7 (*c* 1.10 in $CHCl_3$); lit.[25] $[\alpha]_D$ −32.9 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.17 (3H, d, *J* 6.1 Hz, H-6), 1.49–1.53 (1H, m, H-4), 1.67–1.71 (1H, m, H-4), 2.09–2.16 (2H, m, H-3), 3.47–3.52 (1H, m, H-5), 4.44 (1H, d, *J* 11.7 Hz, C*H*$_2$Ph), 4.57 (1H, d, *J* 11.7 Hz, C*H*$_2$Ph) 4.91–5.01 (2H, m, H-1) 5.76–5.80 (1H, m, C-2), 7.25–7.35 (5H, m, Ph–H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 19.5 (CH_3, C-6), 29.7 (CH_2, C-3), 35.8 (CH_2, C-4), 70.3 (CH_2, *C*H_2Ph), 74.2 (CH, C-5), 114.4 (CH_2, C-1), 127.4 (CH, Ph–H), 127.6 (CH, Ph–H), 127.7 (CH, Ph–H), 2×128.3 (CH, Ph–H), 138.6 (C, Ph), 139.1 (CH, C-2).

4.1.11. (R)-5-(Benzyloxy)hexan-2-one ***17***. A solution of alkene **21** (1.00 g, 5.26 mmol) in DMF (7.5 mL) was added to a mixture of $PdCl_2$ (1.00 g, 2.68 mmol) and CuCl (0.67 g, 6.73 mmol) in DMF (15 mL) and water (5 mL). Oxygen gas was bubbled through the solution. The reaction was stirred for 4 h then filtered through a plug of silica that was washed with further EtOAc and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **17** (0.76 g, 71%) as a yellow oil. R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{20}$ −26.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2969, 1714, 1356, 1093, 1063, 743, 697; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.19 (3H, d, *J* 6.1 Hz, H-6), 1.75–1.85 (2H, m, H-3), 2.11 (3H, s, H-1), 2.48–2.54 (2H, m, H-4), 3.49–3.55 (1H, m, H-5), 4.37 (1H, d, *J* 11.7 Hz, C*H*$_2$Ph), 4.54 (1H, d, *J*

11.7 Hz, C*H*$_2$Ph), 7.25–7.35 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$; Me_4Si) 19.2 (CH_3, C-6), 29.5 (CH_3, C-1), 30.1 (CH_2, C-4), 39.0 (CH_2, C-3), 69.9 (CH_2, *C*H$_2$Ph), 73.4 (CH, C-5), 127.1 (CH, Ph–H), 127.5 (CH, Ph–H), 127.7 (CH, Ph–H), 128.4 (CH, Ph–H), 128.5 (CH, Ph–H), 138.5 (C, Ph), 208.1 (C=O, C-2); *m*/*z* (EI) 229.1190 (MH^+, $C_{13}H_{18}NaO_2$ requires 229.1199) 229 (MNa^+, 100%), 230 (10), 231 (1).

4.1.12. (R)-5-(Benzyloxy)-2-trimethylsilyloxyhex-1-ene ***26****.* Et_3N (1.11 mL, 8.01 mmol) and TMSOTf (0.73 mL, 4.00 mmol) were added to a solution of ketone **17** (0.55 g, 2.67 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min the reaction was quenched by the addition of (aq) NH_4Cl (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL) and dried over Na_2SO_4. Concentration under reduced pressure afforded the crude silyl enol ether **26** as a yellow oil, which was used in the next step without further purification.

4.1.13. (3S,4S,9R)-Methyl 3,9 bis(benzyloxy)-4-hydroxy-6-oxodecanoate ***16****.* To a solution of aldehyde **18** (0.25 g, 1.12 mmol) in CH_2Cl_2 (5 mL) was added $MgBr_2 \cdot OEt_2$ (1.74 g, 6.76 mmol) at −78 °C. (*R*)-5-(Benzyloxy)-2-trimethylsilyloxyhex-1-ene **26** (0.64 g, 2.30 mmol) in CH_2Cl_2 (2 mL) was added and the reaction allowed to warm to 0 °C. The reaction was stirred at 0 °C for 2 h after which it was quenched with pH 7 phosphate buffer (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic phases were then washed with brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the *title compound* **16** (0.15 g, 30%) as a colourless oil. R_f (20% EtOAc/hexanes) 0.11; $[\alpha]_D^{20}$ −19.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3457, 2928, 1713, 1454, 1167, 1068, 736, 697; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* 6.1 Hz, H-10), 1.63–1.73 (2H, m, H-8) 2.38–2.44 (2H, m, H-7) 2.45–2.52 (2H, m, H-5), 2.54–2.59 (2H, m, H-2), 3.40–3.45 (1H, m, H-9), 3.71 (3H, s, C-1OMe), 3.81–3.85 (1H, m, H-3), 4.04–4.06 (1H, m, H-4), 4.25 (2H, m, C*H*$_2$Ph), 4.43 (2H, m, C*H*$_2$Ph), 4.52 (1H, d, *J* 5.7 Hz, OH) 7.20–7.35 (10H, m, Ph–H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 19.3 (CH_3, C-10), 30.1 (CH_2, C-8) 34.7 (CH_2, C-2) 39.3 (CH_2, C-7), 44.5 (CH_2, C-5), 51.6 (CH_3, OMe), 68.1 (CH, C-4), 70.1 (CH_2, *C*H$_2$Ph), 72.6 (CH_2, *C*H$_2$Ph), 73.7 (CH, C-3), 77.3 (CH, C-9), 127.2 (CH, Ph–H), 127.3 (CH, Ph–H), 2×127.5 (CH, Ph–H), 127.6 (CH, Ph–H), 127.7 (CH, Ph–H), 127.9 (CH, Ph–H), 128.1 (CH, Ph–H), 128.2 (CH, Ph–H), 128.4 (CH, Ph–H), 136.8 (C, Ph), 137.8 (C, Ph), 172.0 (C=O, C-1), 210.8 (C=O, C-6); *m*/*z* (EI) 451.2105 (M+, $C_{25}H_{32}NaO_6$ requires 451.2091) 429 (25%), 446 (30), 451 (MNa^+, 100), 467 (31).

*4.1.14. Cephalosporolide E (****1a****) and cephalosporolide F (****1b****).* To a solution of bis-benzyl ether **16** (0.30 g, 0.70 mmol) in MeOH (5 mL) was added Pd/C (0.05 g, 0.05 mmol) and the mixture was placed overnight in a Parr hydrogenator at 60 psi. The solution was filtered through a plug of Celite, washed with EtOAc (3×5 mL) and concentrated under reduced pressure to give a crude yellow oil.

To a solution of the above crude material in CH_2Cl_2 (5 mL) was added Amberlyst-15 (0.05 g) and the mixture was stirred at room temperature overnight. The solution was filtered, washed with CH_2Cl_2 (3×10 mL) and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography using 3:2 hexane/ethyl acetate as eluent to afford a 3:2 separable mixture of cephalosporolide E (**1a**) and cephalosporolide F (**1b**), respectively (44.0 mg, 86%) over two steps. The spectroscopic data was in agreement with that reported in the literature.[1]

*4.1.15. Cephalosporolide E (****1a****).* R_f (40% EtOAc/hexanes) 0.30; $[\alpha]_D^{25}$ +27.3 (*c* 0.41 in $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ +49.2 (*c* 0.25 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3498, 2934, 1781, 1375, 1165, 1056, 925, 715; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* 6.2 Hz, H-10), 1.31–1.50 (1H, m, H-8), 2.00–2.05 (1H, m, H-8), 2.07–2.15 (2H, m, H-7), 2.15–2.18 (1H, m, H-5), 2.44 (1H, d, *J* 14.2 Hz, H-5), 2.67 (1H, d, *J* 18.8 Hz, H-2), 2.71 (1H, dd, *J* 7.4, 18.8 Hz, H-2), 4.15–4.21 (1H, m, H-9), 4.86–4.91 (1H, m, H-3), 5.15 (1H, t, *J* 5.9 Hz, H-4); δ_C (75 MHz; $CDCl_3$; Me_4Si) 20.5 (CH_3, C-10), 31.3 (CH_2, C-8), 34.1 (CH_2, C-7), 37.3 (CH_2, C-5), 41.6 (CH_2, C-2), 75.1 (CH, C-9), 77.3 (CH, C-3), 83.4 (CH, C-4), 115.1 (C, C-6), 175.9 (C=O, C-1); *m*/*z* (EI) 221.0792 (MH^+, $C_{10}H_{14}NaO_4$ requires 221.0784) 221 (MNa^+, 100%), 222 (20), 223 (1), 224 (10).

*4.1.16. Cephalosporolide F (****1b****).* R_f (40% EtOAc/hexanes) 0.15; $[\alpha]_D^{20}$ −33.9 (*c* 0.79 in $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ −33.3 (*c* 0.79 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3529, 2969, 1774, 1347, 1152, 1054, 917, 700; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.27 (3H, d, *J* 6.2 Hz, H-10), 1.67–1.76 (1H, m, H-8), 1.99–2.05 (1H, m, H-8), 2.06–2.18 (2H, m, H-7), 2.32 (1H, dd, *J* 14.8, 2.2 Hz, H-5) 2.51 (1H, dd, *J* 14.8, 6.8 Hz, H-5), 2.67 (1H, d, *J* 17.8 Hz, H-2), 2.74 (1H, dd, *J* 5.3 Hz, 17.8, H-2), 4.11–4.16 (1H, m, H-9), 4.72 (1H, t, *J* 5.0 Hz, H-3), 5.06–5.10 (1H, m, H-4); δ_C (75 MHz; $CDCl_3$; Me_4Si) 22.7 (CH_3, C-10), 32.4 (CH_2, C-8), 36.0 (CH_2, C-7), 36.9 (CH_2, C-5), 42.1 (CH_2, C-2), 76.5 (CH, C-9), 79.9 (CH, C-3), 83.8 (CH, C-4), 115.5 (C, C-6), 175.5 (C=O, C1); *m*/*z* (EI) 221.0790 (MH^+, $C_{10}H_{14}NaO_4$ requires 221.0784) 221 (MNa^+, 100%), 222 (20), 223 (1), 224 (10).

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