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Total Synthesis of Umuravumbolide and Hyptolide Through Silicon-Tethered Ring-Closing Metathesis

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The total synthesis of umuravumbolide and hyptolide has been achieved in a efficient manner by using temporary silicon-tethered ring-closing metathesis and cross-coupling reactions as key steps. The stereogenic centres were generated by means of proline-catalysed α-aminoxylation of aldehydes and Brown's asymmetric allylation method.

Introduction

Desacetylumuravumbolide[1a] (**1a**) and umuravumbolide[1a] (**1b**) and structurally related hyptolide[1b] (**2**), isolated from species of *Tetradenia* and *Hyptis*, are representative members of the Lamiaceae family (Figure 1). These compounds have a common structural feature, the polyacylated-6-heptenyl-5,6-dihydro-2*H*-pyran-2-one framework, containing an α,β-unsaturated δ-lactone that is known to bind protein thiol groups as a result of their ability to act as a Michael acceptor. These compounds show a wide range of pharmacological activities such as cytotoxicity against human tumour cells, and antimicrobial and antifungal activity. Furthermore, several compounds from the Lamiaceae family have been shown to be an emetic that can be used to treat loss of appetite.

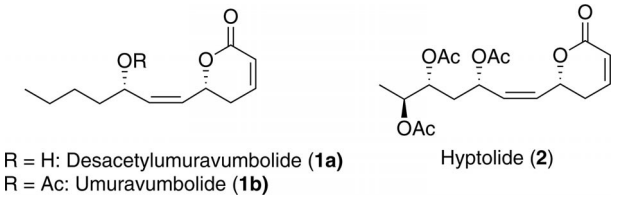
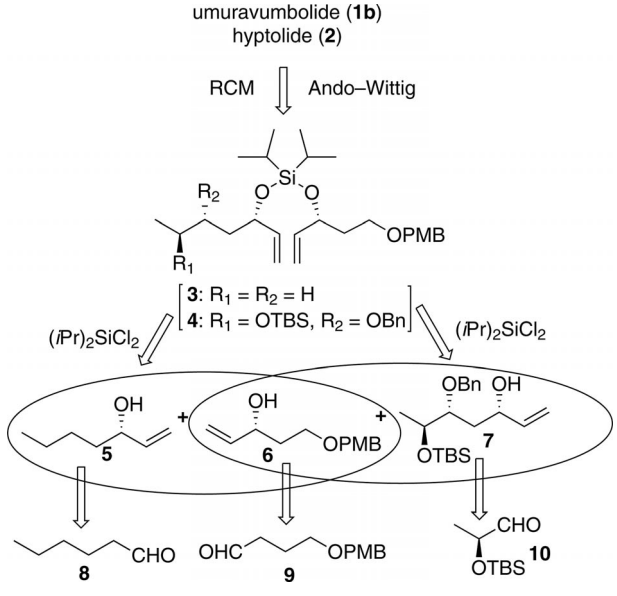


Figure 1. Structures of deacetylumuravumbolide (**1a**), umuravumbolide (**1b**) and hyptolide (**2**).

Synthetic studies toward **1** and **2** have been reported by Ramachandran,[2a] Marco,[2b] Chakraborty,[2c] Venkateswarlu[2d] and Sabitha[2e] et al. However, to the best of our knowledge, all attempts have involved linear approaches involving semihydrogenation of the alkyne part using Lind-Alar's catalyst to generate the side chain olefin, and ring-closing metathesis reaction for construction of the lactone ring.

As a part of our current interest in naturally occurring pharmacologically active α,β-unsaturated δ-lactones,[3] we have accomplished the total synthesis of umuravumbolide (**1b**) and hyptolide (**2**) by a highly convergent strategy.

We note in advance that our approach is both concise and versatile, exploiting temporary silicon-tethered ring-closing metathesis (TST-RCM)[4] and Ando's protocol[5] to construct the olefins. Furthermore, the strategy provides convergent synthetic access to all members of the Lamiaceae family. The general retrosynthetic analysis is depicted in Scheme 1. We aimed to construct the side chain *Z*-olefin of both umuravumbolide **1b** and hyptolide **2** through ring-closing metathesis of bis-siloxane intermediates **3** and **4**, respectively. The latter intermediates would



Scheme 1. Retrosynthetic analysis of umuravumbolide (**1b**) and hyptolide (**2**).

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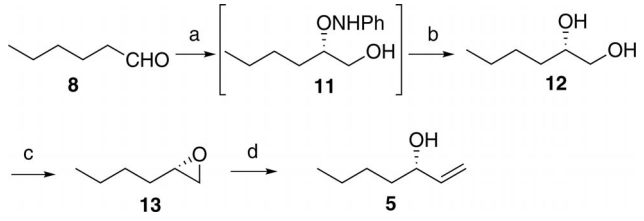
originate from coupling of allylic alcohols **5**, **6** and **6**, **7**, respectively, whereas the requisite fragments **5**–**7** could be prepared from hexanal **8**, 4-(4-methoxybenzyloxy)butanal (**9**)[6] and TBS-protected L-lactaldehyde **10**, respectively.

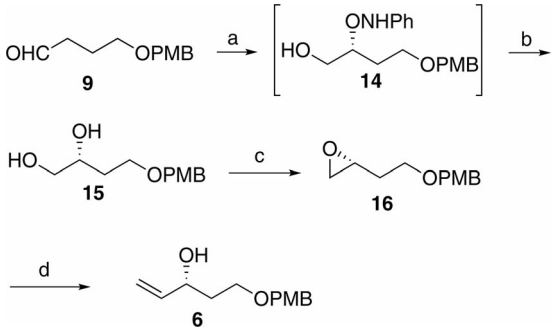
Results and Discussion

Our synthesis started with the preparation of fragment **5**. The sequence developed to prepare fragment **5** is summarized in Scheme 2. Thus, aldehyde **8** was exposed to sequential α-aminoxylation[7] catalyzed by D-proline, followed by reduction in situ using $NaBH_4$ to furnish O-amino-substituted diol **11**. Compound **11** was subjected to reductive hydrogenation conditions to afford the known diol **12**[8] in 85% yield, which, on selective monotosylation and base treatment, furnished epoxide **13**[8] in 80% yield. Finally, dimethylsulfonium methylide mediated[9] ring opening of epoxide **13** generated fragment **5**[10] in 72% yield.



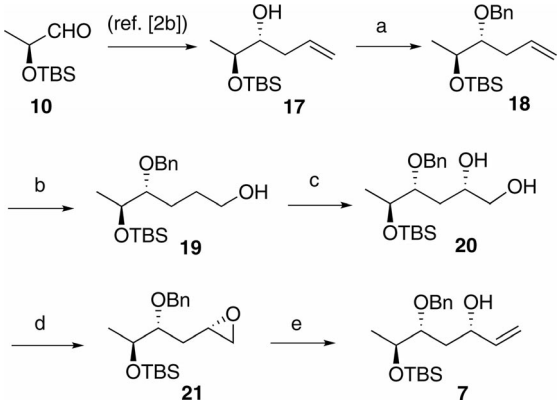
Scheme 2. *Reagents and conditions:* (a) i. D-proline, nitrosobenzene, DMSO; ii. $NaBH_4$, MeOH, 0.5 h; (b) H_2/Pd-C, EtOAc, 8 h, 85% (over two steps); (c) i. TsCl, Bu_2SnO, Et_3N, 2 h; ii. K_2CO_3, MeOH, room temp., 1 h, 80%; (d) $(CH_3)_3SI$, 2 h, *n*BuLi, THF, 72%.

The synthesis of fragment **6** commenced from 4-(4-methoxybenzyloxy)butanal (**9**) as illustrated in Scheme 3. Aldehyde **9** was subjected to α-aminoxylation catalyzed by L-proline, under a similar set of reaction conditions to those used in Scheme 2, to afford diol **15**[11] in 83% yield and in 97% ee;[12] on selective monotosylation and base treatment of **15**, epoxide **16**[11] was furnished in 83% yield. This epoxide was also opened with dimethylsulfonium methylide to afford the allylic alcohol fragment **6**[13] in 75% yield.



Scheme 3. *Reagents and conditions:* (a) i. L-proline, nitrosobenzene, DMSO; ii. $NaBH_4$, MeOH, 0.5 h; (b) H_2/Pd-C, EtOAc, 7 h, 83% (over two steps); (c) i. TsCl, Bu_2SnO, Et_3N, 2 h; ii. K_2CO_3, MeOH, room temp., 0.5 h, 83%; (d) $(CH_3)_3SI$, 2 h, *n*BuLi, THF, 75%.

The sequence developed to prepare fragment **7** is summarized in Scheme 4. As our point of departure, asymmetric allylation of TBS-protected L-lactaldehyde **10** to generate known homoallylic alcohol **17**[2b] was performed with Brown's B-allyl diisopinocampheylborane, followed by treatment with benzyl bromide (BnBr) to afford **18** in 97% yield. We next examined the proline-catalyzed α-aminoxylation reaction of aldehyde to generate the third stereogenic centre. Towards this end, we converted olefin **18** into alcohol **19** in 95% yield by the hydroboration oxidation technique. Thus, compound **19** was oxidized by using 2-iodoxybenzoic acid (IBX) to furnish the corresponding aldehyde, which was directly subjected to α-aminoxylation catalyzed by D-proline, followed by reduction in situ using $NaBH_4$ to give the required O-amino-substituted diol, which, on treatment with a catalytic amount of copper sulfate, afforded diol **20** in 80% yield along with the minor diastereomer (10%), which could be easily separated by chromatography. The stereochemistry of the major diastereomer **20** was confirmed by ^{13}C NMR spectroscopic analysis.[14] Diol **20**, on selective monotosylation and base treatment, furnished **21** in 90% yield. Finally, dimethylsulfonium methylide mediated (Corey–Chaykovsky's conditions)[9] ring opening of epoxide **21** gave fragment **7** in 80% yield.

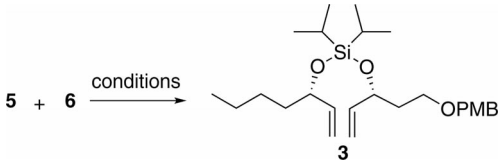


Scheme 4. *Reagents and conditions:* (a) BnBr, NaH, DMF, 0 °C to room temp., 2 h, 97%; (b) BH_3·DMS, THF, room temp., 4 h then H_2O_2, NaOH, EtOH, room temp., 12 h, 95%; (c) i. IBX, EtOAc, reflux, 3 h, ii. D-proline, PhN=O, DMSO then $NaBH_4$, MeOH, 10 min; iii. $CuSO_4$, 80% (over three steps); (d) i. TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 1 h; ii. K_2CO_3, MeOH, room temp., 1 h, 90% (over two steps); (e) $(CH_3)_3SI$, –20 °C, *n*BuLi, THF, 3 h, 80%.

With the cross-coupling partners in hand, the crucial silicon-tethered coupling to construct disiloxane **3** was examined (Table 1). Initial attempts using a range of silicon tethering reagents such as Me_2SiCl_2 and Ph_2SiCl_2 proved unsuccessful. We then considered using $(i\text{Pr})_2SiCl_2$ as the tethering reagent under the reaction conditions reported by Evans and co-workers.[15] Accordingly, the addition of fragment **5** to $(i\text{Pr})_2SiCl_2$ followed by further addition of a second fragment **6** after 24 h, led to the exclusive formation of the homodimer of **5** (Table 1; entry 1). We attributed this failure to the use of excess tethering reagent and to the prolonged reaction time after the addition of the first fragment **5**. Consequently, the reaction was performed with 5 equiv. of tethering reagent, but again with no product formation being observed (entry 2). Nevertheless, we could isolate a

small amount (5%) of coupled product **3** when the amount of tethering reagent was reduced to 1.1 equivalent (entry 3).

Table 1. Optimization of the coupling reaction of fragments **5** and **6**.

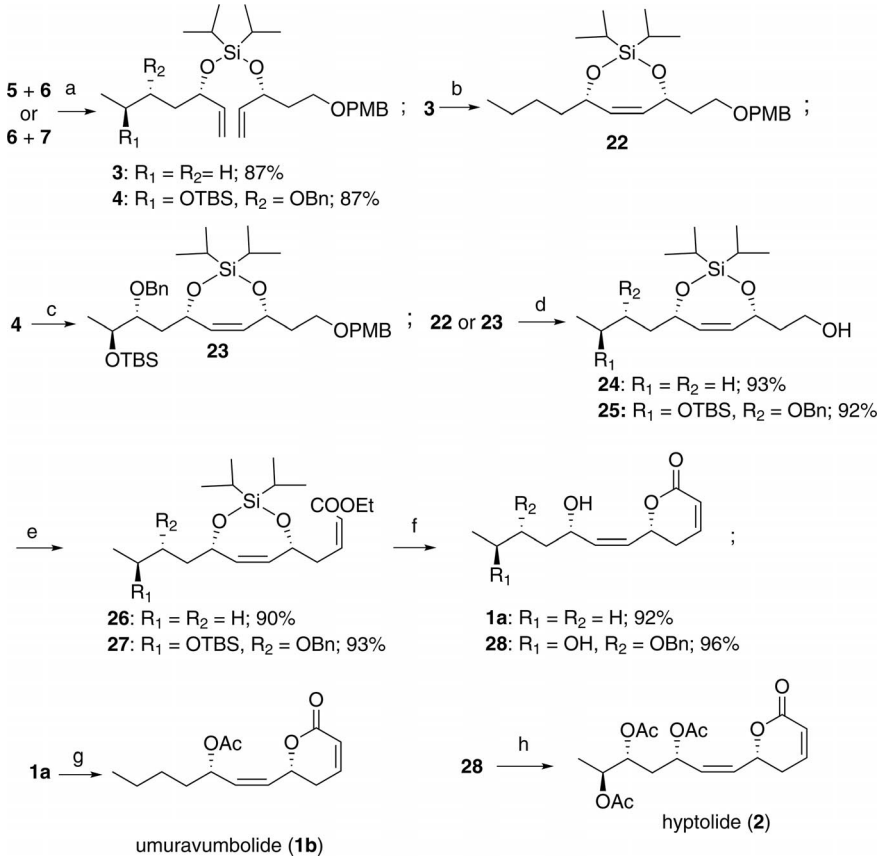


Entry	Fragment **5** [equiv.]	$(i\text{Pr})_2SiCl_2$ [equiv.]	Time[a]	Yield of **3** [%]
1	1	10	24 h	–[b]
2	1	5	24 h	–[b]
3	1	1.1	24 h	5[c]
4	1	1.1	5 h	5[c]
5	1	1.1	1 h	30[c]
6	1	1.1	15 min	87[d]

[a] Time between the addition of first fragment and second fragment. [b] Only homodimer of **5** formed. [c] Obtained along with homodimer of **5**. [d] Obtained along with 5% homodimer of **5** and unreacted **6**.

We then reduced the time interval between the addition of fragment **5** and fragment **6** from 24 h to 5 h, but this did not lead to any improvement in the yield of coupled product **3** (Table 1, entry 4), yields of more than 25% were obtained when the reaction time was reduced to 1 h (entry 5), and the best yield (87%) was achieved when fragment **6** was added 15 min after the addition of fragment **5** (entry 6).

Thus, coupled product **3** could be synthesized in excellent yield by reducing the amount of tethering reagent from 10 to 1.1 equivalents as well as reducing time interval between the addition of the two fragments from 24 h to 15 min. Clearly, the reduction in the amount of tethering reagent also improves the cost effectiveness of the reaction. With disiloxane intermediates **3** and **4** in hand, we turned our attention to its further elaboration to umuravumbolide (**1b**) and hyptolide (**2**) by transforming the disiloxane moieties (**3** and **4**) into the corresponding cyclic intermediates **22** and **23**, respectively, and subsequent synthetic manipulations (Scheme 5). The ring-closing metathesis reaction of disiloxane **3** using Grubbs' second generation catalyst in toluene at 80 °C proceeded smoothly to generate the required cyclic intermediate **22** in 88% yield. However, cyclisation of **4** under similar conditions furnished the required cyclic interme-



Scheme 5. *Reagents and conditions:* (a) 1st fragment (**5** or **6**), $(i\text{Pr})_2SiCl_2$, imidazole, CH_2Cl_2, 0 °C, 15 min, then 2nd fragment (**6** or **7**), 14 h; (b) Grubbs-II (5 mol-%), 80 °C, toluene, 16 h, 88%; (c) Grubbs–Hoveyda-II (5 mol-%), 80 °C, toluene, 16 h, 75%; (d) DDQ, CH_2Cl_2/H_2O, 0 °C to room temp., 10 min; (e) i. DMP, pyridine, CH_2Cl_2, 0 °C, 0.5 h; ii. $(PhO)_2P(O)CH_2COOEt$, NaH, NaI, THF, –78 °C, 2 h; (f) i. TBAF, THF, room temp. ii.. $Ti(O\text{-}i\text{Pr})_4$, benzene, reflux, 1 h; (g) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, room temp., 9 h, 90%; (h) i. $TiCl_4$, CH_2Cl_2, 0 °C to room temp., 30 min; ii. Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, room temp., overnight, 90% (over two steps).

diate **23** in only low yield. Hence, the ring-closing metathesis (RCM) of disiloxane **4** was examined by using Grubbs catalyst under a variety of reaction conditions; as a result of this study, the *cis*-product was obtained exclusively in appreciable yield (Table 2).

Table 2. Optimization of RCM conditions for disiloxane **4**.

Entry	Catalyst	Solvent	Temp. [°C]	Yield [%]
1	Grubbs II	CH_2Cl_2	40	10
2	Grubbs II	DCE	84	10
3	Grubbs II	toluene	110	20
4	Grubbs–Hoveyda II	toluene	110	75

Our next objective towards the completion of the synthesis was to form the requisite unsaturated lactone rings. Towards this end, compounds **22** and **23** were subjected to removal of the PMB groups using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), producing the corresponding alcohols **24** and **25**, respectively, in excellent yields. Subsequent Dess–Martin periodinane mediated oxidation of the alcohol group led to formation of the corresponding aldehydes, which were directly subjected to two-carbon homologation under Ando conditions[5] to give (*Z*)-unsaturated ester **26** and **27** in 90% and 93% yields, respectively, with excellent stereoselectivity.

With substantial amounts of **26** and **27** in hand, the platform was then set to construct the lactone ring of the target molecules. Initially, simultaneous deprotection of the silyl groups and cyclization to prepare the lactones **1a** and **28** using *p*TSA in MeOH was attempted. However, the reaction led to the formation of some unidentified products. Hence, the clear choice was a two-step procedure; we first deprotected the silyl groups using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) and the crude polyols thus obtained were eventually cyclized to give the six-membered lactones desacetylumuravumbolide (**1a**) and **28** in 92% and 96% yielsd, respectively, upon treatment with a catalytic amount of $Ti(OiPr)_4$ in benzene at reflux. Desacetylumuravumbolide (**1a**) was further acetylated to furnish umuravumbolide **1b**.

The spectroscopic and physical data of desacetylumuravumbolide (**1a**) and umuravumbolide (**1b**) were identical in all respects to those reported in the literature.[1a] Towards the synthesis of target molecule **2**, compound **28** was subjected to debenzylation followed by acetylation of the secondary hydroxyl group to furnish the target molecule hyptolide **2** in excellent yield. The spectroscopic and physical data of compound **2** were identical in all respects to those reported in the literature.[1b]

Conclusions

An efficient synthesis of umuravumbolide (**1b**) and hyptolide (**2**) has been achieved through the application of temporary silicon-tethered ring-closing metathesis (TST-RCM) and Ando olefination reaction. The stereogenic centres were installed by using proline-catalysed α-aminoxylation reactions and by Brown's asymmetric allyl boration. Further application of this methodology to the synthesis of other structurally related biologically active compounds for structure-activity studies is underway in our laboratory.

Experimental Section

General Methods: All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents used for chromatography were distilled at their respective boiling points using known procedures. All commercial reagents were obtained from Sigma–Aldrich Chemical Co. or Lancaster Chemical Co. (UK). Petroleum ether (PE), where used, had a boiling range of 60–90 °C.

Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck silica gel 60 F254). Column chromatography was performed on silica gel 60–120/100–200/230–400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. Standard syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. IR spectra were recorded with a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. ^{1}H NMR spectra were recorded with Bruker AC-200, Bruker AV-400 or Bruker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in ppm; ^{1}H coupling constants (*J*) are reported as absolute values in Hz and multiplicity [broad (br.), singlet (s), doublet (d), triplet (t), multiplet (m)]. ^{13}C NMR spectra were recorded with Bruker AC-200, Bruker AV-400 or Bruker DRX-500 instruments operating at 50, 100 and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). Mass spectra were recorded with a PE SCIEX API QSTAR pulsar (LC-MS) instrument. All melting points were recorded with a Büchi B-540 electrothermal melting point apparatus, yields refer to chromatographically and spectroscopically pure compounds.

(*S*)-Hexane-1,2-diol (12): To a stirred solution of aldehyde **8** (1.0 g, 9.98 mmol) and nitrosobenzene (1.06 g, 9.98 mmol) in DMSO (9 mL) was added D-proline (0.23 g, 1.9 mmol, 20 mol-%) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess $NaBH_4$ (1.32 g, 35 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel (EtOAc/PE, 40:60) to give pure aminoxy alcohol **11**. Aminoxy alcohol **11** (1.0 g, 4.7 mmol) was dissolved in EtOAc (10 mL) and 10% Pd/C (0.050 g) was added to the solution and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography (EtOAc/PE, 40:60) to give pure diol **12** (0.48 g, 85%) as a colourless liquid. $[\alpha]_D^{25}$ = –14.3 (*c* = 1.0, methanol) {ref.[8] $[\alpha]_D^{20}$ = –16.4 (*c* = 1.0, methanol)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3372, 2925 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.38–3.36 (m, 5 H), 1.32–1.22 (m, 6 H), 0.84–0.82 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 71.9, 66.2, 33.1, 27.7, 22.6, 13.8 ppm. HRMS (ESI$^+$): *m*/*z* calcd. for $C_6H_{14}O_2$ [M + Na]$^+$ 141.0891; found 141.0893.

(*S*)-2-Butyloxirane (13): To a mixture of diol **12** (0.21 g, 1.77 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dibutyltin oxide (0.008 mg,

0.035 mol) followed by *p*-toluenesulfonyl chloride (0.337 g, 1.77 mmol) and triethylamine (0.25 mL, 1.77 mmol), and reaction was stirred at room temperature under nitrogen and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with water, dried (Na_2SO_4), and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (0.5 g, 3.61 mmol) and the resultant mixture was stirred for 1 h at the same temp. Upon completion of the reaction, as indicated by TLC, the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 × 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography of the crude product (PE/ethyl acetate, 70:30) gave epoxide **13** (0.14 g, 80%) as a colourless liquid. $[\alpha]_D^{25}$ = –16.5 (*c* = 1.0, pentane) {ref.[8] $[\alpha]_D^{24}$ = –18.7 (*c* = 0.93, pentane)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2989, 2925, 2870 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.71–2.67 (m, 1 H), 2.57–2.52 (m, 1 H), 2.28–2.25 (m, 1 H), 1.34–1.10 (m, 6 H), 0.78–0.71 (t, *J* = 6.13 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.9, 46.6, 31.9, 27.8, 22.2, 13.6 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_6H_{12}O$ [M + Na]$^+$ 123.0786; found 123.0784.

(*S*)-Hept-1-en-3-ol (5): To a suspension of trimethylsulfonium iodide (5.44 g, 26.5 mmol) in anhydrous THF (10 mL) at –20 °C was added *n*BuLi (1.6 M in hexane, 16.68 mL, 26.5 mmol) dropwise over 20 min and the mixture was stirred for 30 min. Epoxide **13** (0.5 g, 4.37 mmol) in anhydrous THF (5 mL) was added to the above reaction mixture, which was then slowly warmed to 0 °C over 1 h. The reaction mixture was stirred at ambient temperature for 2 h and, after consumption of the starting material, the reaction was quenched by the addition of H_2O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated. Column chromatography of the crude product (PE/ethyl acetate, 70:30) gave **5** (0.45 g, 80%) as a colourless liquid. $[\alpha]_D^{25}$ = +9.5 (*c* = 1.4, pentane) {ref.[10] $[\alpha]_D^{25}$ = +10.3 (*c* = 1.45, pentane)}; IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3485, 1613, 1586 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.71 (m, 1 H), 5.19–4.99 (m, 1 H), 4.08–3.96 (m, 1 H), 2.34 (s, 1 H), 1.48–1.22 (m, 6 H), 0.88–0.81 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.3, 114.2, 73.0, 36.6, 27.4, 22.5, 13.8 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_7H_{14}O$ [M + Na]$^+$ 137.0942; found 137.0945. $C_{24}H_{50}O_2Si$ (398.74): C 72.29, H 12.64; found C 72.27, H 12.63.

(*R*)-4-(4-Methoxybenzyloxy)butane-1,2-diol (15): Compound **15** was prepared from compound **9** using L-proline as catalyst by following the procedure described for **12**, yield 83%; colourless liquid; $[\alpha]_D^{25}$ = –1.03 (*c* = 1.0, $CHCl_3$) {ref.[11] $[\alpha]_D^{25}$ = –2.6 (*c* = 1.4, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3384, 2934, 1613, 1514, 1249 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.20 (m, 2 H), 6.90–6.84 (m, 2 H), 4.44 (s, 2 H), 3.93–3.82 (m, 1 H), 3.79 (s, 3 H), 3.69–342 (m, 4 H), 1.89–1.62 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 129.8, 129.4, 113.8, 72.9, 71.3, 67.8, 66.5, 55.23, 32.7 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{18}O_4$ [M + Na]$^+$ 249.1103; found 249.1106.

(*R*)-2-[2-(4-Methoxybenzyloxy)ethyl]oxirane (16): Compound **16** was prepared by following the procedure described for **13**, yield 83%; colourless liquid; $[\alpha]_D^{25}$ = +13.82 (*c* = 1.0 $CHCl_3$) {ref.[11] $[\alpha]_D^{25}$ = +12.0 (*c* = 1.0, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2997, 2924, 2860, 1613, 1513 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.24 (m,2 H), 6.91–6.85 (m, 2 H), 4.47 (s, 2 H), 3.81 (s, 3 H), 3.63–3.57 (m, 2 H), 3.11–3.02 (m, 1 H), 2.81–2.76 (m, 1 H), 2.54–2.50 (m, 1 H), 1.99–1.71 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.7, 128.8, 128.5, 112.3, 73.3, 67.5, 55.5, 50.1, 47.3, 33.8 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{16}O_3$ [M + Na]$^+$ 231.0997; found 231.0993.

(*R*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (6): Compound **6** was prepared by following the procedure described for **5**, yield 75%; colourless liquid; $[\alpha]_D^{25}$ = –10.0 (*c* = 1.4, $CHCl_3$) {ref.[12] $[\alpha]_D^{19}$ = –9.2 (*c* 1.0, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3414, 1613, 1586 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 2 H), 6.93–6.86 (m, 2 H), 5.97–5.80 (m, 1 H), 5.33–5.08 (m, 2 H), 4.46 (s, 2 H), 3.82 (s, 3 H), 3.76–3.57 (m, 2 H), 2.99 (s. 1 H), 1.94–1.79 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 140.5, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.8, 55.1, 36.1 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{13}H_{18}O_3$ [M + Na]$^+$ 245.1154; found 245.1158.

{[(2*S*,3*R*)-3-(Benzyloxy)hex-5-en-2-yl]oxy}(*tert*-butyl)dimethylsilane (18): To the known homoallylic alcohol **17** (2 g, 8.67 mmol) in DMF (7.5 mL) at 0 °C was added NaH (60% in mineral oil, 0.38 g, 9.54 mmol). After 15 min, benzyl bromide (1.63 g, 1.13 mL, 9.54 mmol) was introduced and the reaction mixture was stirred for 2 h at room temperature. Water was carefully added to the reaction mixture, which was then extracted with diethyl ether, washed with water, and dried (Na_2SO_4). Silica gel column chromatography of the crude product (petroleum ether/EtOAc, 95:5) afforded benzyl-protected compound **18** (2.69 g, 97%). $[\alpha]_D^{25}$ = +10.16 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2933, 2867, 1613, 1514, 1464, 1248, 1039, 920, 885 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.19 (m, 5 H), 5.92–5.75 (m, 1 H), 5.08–4.93 (m, 2 H), 4.64–4.45 (m, 2 H), 3.92–3.61 (m, 1 H), 3.31–3.21 (m, 1 H), 2.25 (t, *J* = 6.53 Hz, 2 H), 1.13 (d, *J* = 6.42 Hz, 3 H), 0.83–0.80 (m, 9 H), –0.01–0.06 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.9, 135.6, 128.2, 127.8, 127.3, 116.6, 83.6, 72.7, 70.4, 35.7, 33.7, 25.9, 19.3, –4.3, –4.7 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{33}O_2Si$ [M + H] 321.2250; found 321.2254.

(4*R*,5*S*)-4-(Benzyloxy)-5-[(*tert*-butyldimethylsilyl)oxy]hexan-1-ol (19): A solution of olefin **18** (2.5 g, 7.8 mmol) in anhydrous THF (30 mL) was treated under N_2 with BH_3·DMS (0.75 mL, 7.8 mmol, d = 0.8 g/mL). The reaction mixture was stirred for 4 h at room temperature and then quenched by addition of MeOH (25 mL), 6 M aqueous NaOH (9 mL), and 30% H_2O_2 (15 mL) and stirred for an additional 12 h. The resulting mixture was stirred for 1 h and worked up (extraction with EtOAc). Column chromatography on silica gel (PE/EtOAc, 90:10) afforded **19** (2.5 g, 95%) as a light-yellow oil. $[\alpha]_D^{25}$ = +9.31 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3377, 3019, 2400, 1501, 1427, 1230, 1070, 993, 857, 725 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.18 (m, 5 H), 4.73–4.37 (m, 2 H), 4.01–3.73 (m, 1 H), 3.63–3.47 (m, 2 H), 3.35–3.15 (m, 1 H), 1.61–1.50 (m, 4 H), 1.11 (d, *J* = 6.19 Hz, 3 H), 0.81–0.79 (m, 9 H), –0.01–0.07 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.7, 128.3, 127.9, 127.5, 83.8, 72.9, 70.8, 63.0, 29.6, 29.0, 27.4, 25.8, 19.2, –4.3, –4.7 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{35}O_3Si$ [M + H] 339.2355; found 339.2354.

(2*S*,4*R*,5*S*)-4-(Benzyloxy)-5-[(*tert*-butyldimethylsilyl)oxy]hexane-1,2-diol (20): To a solution of **19** (2 g, 5.9 mmol) in EtOAc (10 mL) was added IBX (4.6 g, 17.7 mmol) and the mixture was heated to 80 °C for 3 h. The mixture was cooled to room temp. and filtered through a pad of Celite, the filtrate was concentrated, and the crude aldehyde was used for the next step without purification.

To a stirred solution of the above aldehyde (1.5 g, 4.45 mmol) and nitrosobenzene (0.48 g, 4.45 mmol) in DMSO (4 mL) was added D-proline (0.1 g, 0.89 mmol, 20 mol-%) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, the reaction mixture was diluted with anhyd. MeOH (5 mL) and excess $NaBH_4$ (0.6 g, 15.6 mmol) was carefully added. The reaction was quenched after

10 min by addition of satd. NH_4Cl. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel (EtOAc/PE, 40:60) to give pure aminoxy alcohol (1.5 g, 80%). The aminoxy alcohol (1.5 g, 3.5 mmol) was dissolved in MeOH (10 mL) , 3% copper sulfate was added and the reaction mixture was stirred for 12 h. After completion of the reaction (monitored by TLC) it was quenched by addition of satd. NH_4Cl. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by silica gel chromatography (EtOAc/PE, 50:50) to give pure diol **20** (0.66 g, 80%) as a colourless liquid. $[\alpha]_D^{25}$ = +41.86 (c = 0.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3412, 3020, 2978, 1652, 1534, 1248, 1237 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.19 (m, 5 H), 4.77–4.41 (m, 2 H), 3.99–3.78 (m, 3 H), 3.56–3.47 (m, 2 H), 3.41–3.29 (m, 1 H), 1.58–1.54 (m, 2 H), 1.10–1.07 (m, 3 H), 0.82–0.81 (m, 9 H), –0.01 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.0, 128.5, 127.9, 83.0, 72.4, 70.5, 70.1, 66.8, 33.0, 29.6, 25.8, 18.9, –4.8 ppm. HRMS (ESI+): m/z calcd. for $C_{19}H_{35}O_4Si$ [M + H] 355.2305; found 355.2301.

(2*S*,3*R*)-3-(Benzyloxy)-4-[(*S*)-oxiran-2-yl]butan-2-yloxy(*tert*-butyl)dimethylsilane (21): Compound **21** was prepared by following the procedure described for **13**, yield 90%; colourless liquid; $[\alpha]_D^{25}$ = +12.8 (c = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2930, 2856, 1620, 1600, 1557, 1501, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.21 (m, 5 H), 4.74–4.45 (m, 2 H), 3.87–3.79 (m, 1 H), 3.51–3.30 (m, 1 H), 3.05–2.95 (m, 1 H), 2.73–2.61 (m, 1 H), 2.44–2.35 (m, 1 H), 1.92–1.37 (m, 2 H), 1.10 (t, J = 6.22 Hz, 3 H), 0.81–0.79 (m, 9 H), –0.02–0.04 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.8, 135.6, 128.3, 127.8, 127.5, 81.7, 73.1, 70.5, 50.1, 47.8, 34.5, 34.0, 25.8, 19.2, –4.4, –4.7 ppm. HRMS (ESI+): m/z calcd. for $C_{19}H_{33}O_3Si$ [M + H] 337.2199; found 337.2196.

(3*S*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldimethylsilyl)oxy]hept-1-en-3-ol (7): Compound **7** was prepared by following the procedure described for **5**, yield 80%; colourless liquid; $[\alpha]_D^{25}$ = +26.42 (c = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3290, 3032, 2430, 1652, 1561, 1504, 1215, 1012, 901, 876 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.16 (m, 5 H), 5.83–5.67 (m, 1 H), 5.21–4.96 (m, 2 H), 4.77–4.41 (m, 2 H), 4.25–4.18 (m, 1 H), 3.93–3.77 (m, 1 H), 3.56–3.46 (m, 1 H), 1.74–1.59 (m, 2 H), 1.09 (d, J = 6.42 Hz, 3 H), 0.83–0.82 (m, 9 H), –0.01 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.8, 138.2, 128.4, 127.9, 127.7, 114.2, 83.2, 72.5, 71.3, 76.6, 40.1, 37.5, 25.7, 18.9, –4.6, –4.7 ppm. HRMS (ESI+): m/z calcd. for $C_{20}H_{34}O_3Si$ [M + H] 351.2355; found 351.2350.

(5*R*,9*S*)-7,7-Diisopropyl-1-(4-methoxyphenyl)-5,9-divinyl-2,6,8-trioxa-7-silatridecane (3): Dichlorodiisopropylsilane (0.085 mL, 0.48 mmol) was added to imidazole (0.089 g, 1.31 mmol) in CH_2Cl_2 (0.24 mL) at 0 °C. The solution was stirred for 5 min, then fragment **5** (0.05 g, 0.437 mmol) in CH_2Cl_2 (0.18 mL) was added dropwise over 1 h at 0 °C. The mixture was stirred for a further 15 min at 0 °C, then a solution of fragment **6** (0.097 g, 0.437 mmol) in CH_2Cl_2 (0.035 mL) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 14 h, then filtered and washed with hexane. Concentration in vacuo afforded a crude oil, which was purified by flash chromatography on silica gel (PE/ethyl acetate, 95:5) to afford bis-alkoxysilane **3** (0.196 g, 87%) as a colourless oil. $[\alpha]_D^{25}$ = –1.98 (c = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2933, 2867, 1613, 1514, 1464, 1248, 1089, 1039, 920, 885 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.24 (m, 2 H), 6.92–6.85 (m, 2 H), 5.95–5.74 (m, 2 H), 5.23–5.01 (m, 4 H), 4.55–4.24 (m, 4 H), 3.82 (s, 3 H), 3.63–3.44 (m, 2 H), 2.02–1.76 (m, 2 H), 1.35–1.23 (m, 7 H), 1.05–1.04 (m, 12 H), 0.97–0.93 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 141.4, 141.1, 129.4, 129.2, 113.9, 113.7, 113.7, 73.6, 72.6, 70.9, 66.4, 55.3, 38.0, 37.7, 22.8, 22.6, 17.4, 17.2, 14.3 ppm. HRMS (ESI+): m/z calcd. for $C_{26}H_{44}O_4Si$ [M + Na]$^+$ 471.2907; found 471.2907.

(5*R*,9*S*,11*R*,12*S*)-11-(Benzyloxy)-7,7-diisopropyl-1-(4-methoxyphenyl)-12,14,14,15,15-pentamethyl-5,9-divinyl-2,6,8,13-tetraoxa-7,14-disilahexadecane (4): Compound **4** was prepared from coupling fragments **6** and **7** by following the procedure described for **3**, yield 87%; colourless liquid; $[\alpha]_D^{25}$ = 26.86 (c = 0.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2935, 2856, 1713, 1600, 1504, 1265, 1065, 1071, 920, 885 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.15 (m, 7 H), 6.82–6.77 (m, 2 H), 5.84–5.62 (m, 2 H), 5.12–4.91 (m. 4 H), 4.48–4.19 (m, 6 H), 4.03–3.79 (m, 1 H), 3.73 (s, 3 H), 3.66–3.26 (m, 3 H), 1.68–1.66 (m, 4 H), 1.53–1.33 (m, 2 H), 1.07 (d, J = 6.31 Hz, 3 H), 0.95–0.94 (m, 12 H), 0.83 (s, 9 H), –0.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 140.9, 139.3, 139.1, 130.8, 129.1, 128.2, 127.6, 127.3, 127.2, 114.6, 113.7, 81.6, 72.9, 72.7, 71.6, 71.2, 70.6, 55.2, 39.9, 26.0, 25.8, 18.0, 17.4, 17.3, –4.6, –4.7 ppm. HRMS (ESI+): m/z calcd. for $C_{39}H_{64}6Si_2$ [M + Na]$^+$ 707.4139; found 707.4139.

(4*S*,7*R*)-4-Butyl-2,2-diisopropyl-7-[2-(4-methoxybenzyloxy)ethyl]-4,7-dihydro-1,3,2-dioxasilepine (22): A solution of **3** (0.1 g, 0.22 mmol) in toluene (50 mL) was degassed for 5 min with argon, then Grubbs-II catalyst (0.006 g, 0.006 mmol) was added and the solution was degassed again. The mixture was stirred at 80 °C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (PE/ethyl acetate, 95:5) to give cyclised product **22** (0.082 g, 88%); $[\alpha]_D^{25}$ = +3.00 (c = 0.65, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2929, 2865, 1612, 1513, 1465, 1248, 1092, 884 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.23–7.21 (m, 2 H), 6.91–6.88 (m, 2 H), 5.92–5.45 (m, 2 H), 4.88–4.48 (m, 2 H), 3.79 (s, 3 H), 3.75–3.43 (m, 4 H), 1.40–1.29 (m, 10 H), 1.03 (s, 12 H), 0.89–0.87 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.1, 135.5, 134.8, 133.9, 129.32, 113.7, 72.8, 71.0, 67.9, 66.7, 55.3, 38.6, 38.3, 22.6, 22.5, 17.6, 17.2, 14.1 ppm. HRMS (ESI+): m/z calcd. for $C_{24}H_{41}O_4Si$ [M + H]$^+$421.2774; found 421.2775.

(4*S*,7*R*)-4-{(2*R*,3*S*)-2-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]butyl}-2,2-diisopropyl-7-{2-[(4-methoxybenzyl)oxy]ethyl}-4,7-dihydro-1,3,2-dioxasilepine (23): A solution of **4** (0.075 g, 0.109 mmol) in toluene (18 mL) was degassed for 5 min with argon, then Hoveyda–Grubbs second-generation catalyst (2 mg, 3.28 μmol) was added and the solution was degassed again. The mixture was stirred at 80 °C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (PE/ethyl acetate, 90:10) to give cyclised product **23** (0.054 g, 75%); $[\alpha]_D^{25}$ = 27.98 (c = 0.8, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2931, 2901, 2301, 1800, 1654, 1466, 885, 847, 770, 681 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.18 (m, 7 H), 6.83–6.78 (m, 2 H), 5.60–4.63 (m, 2 H), 4.61–4.36 (m, 4 H), 4.16–3.97 (m, 1 H), 3.87–3.78 (m, 1 H), 3.73 (s, 3 H), 3.65–3.35 (m, 3 H), 2.36–1.46 (m, 7 H), 1.11 (d, J = 6.19 Hz, 3 H), 0.98–0.94 (m, 12 H), 0.83 (s, 9 H), –0.01 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.2, 138.7, 129.4, 128.2, 128.0, 127.8, 127.5, 113.7, 80.9, 72.9, 72.7, 71.0, 68.5, 67.9, 64.9, 55.2, 39.1, 39.0, 30.2, 25.8, 18.0, 17.2, 16.9, –4.5, –4.6 ppm. HRMS (ESI+): m/z calcd. for $C_{37}H_{60}O_6Si2$ [M + H]$^+$ 657.4007; found 657.4007.

2-[(4*R*,7*S*)-7-Butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl]ethanol (24): To a stirring solution of PMB ether **22** (0.070 g, 0.164 mmol) in CH_2Cl_2/H_2O (0.5:0.03) was added DDQ (0.046 g, 0.199 mmol). The resulting mixture was stirred for 10 min at room

temp., then the mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as a yellow oil. Silica gel column chromatography of the crude product (PE/ethyl acetate, 80:20) gave **24** (0.046 g, 93%); $[a]_D^{25}$ = –6.18 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3456, 2929, 2865, 1465, 1248, 1092, 884 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.68–5.45 (m, 2 H), 3.89–3.83 (m, 2 H), 3.66–3.62 (m, 2 H), 1.35–1.29 (m, 10 H), 0.92–0.80 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 135.2, 132.8, 71.8, 71.0, 61.3, 39.1, 37.7, 22.7, 22.6, 19.8, 17.2, 14.1 ppm. LC–MS: *m*/*z* = 323 $[M + Na]^+$. HRMS (ESI+): *m*/*z* calcd. for $C_{16}H_{32}O_3Si$ $[M + Na]^+$ 323.2018; found 323.2018.

2-((4*R*,7*S*)-7-{(2*R*,3*S*)-2-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]butyl}-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)ethanol (25): Compound **25** was prepared from **23** by following the procedure described for **24**, yield 92%; colourless liquid; $[a]_D^{25}$ = 12.43 (*c* = 0.8, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2967, 2861, 1582, 1513, 1445, 1348, 1092, 889 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.25 (m, 5 H), 5.70–5.46 (m, 2 H), 5.00–4.82 (m, 2 H), 4.78–4.63 (m, 1 H), 4.60–4.45 (m, 1 H), 3.94–3.83 (m, 3 H), 3.76–3.40 (m, 1 H), 1.96–1.58 (m, 6 H), 1.18–1.15 (m, 3 H), 1.06–0.99 (m, 12 H), 0.89 (s, 9 H), 0.06–0.01 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 120 MHz): δ = 138.9, 135.7, 135.4, 134.9, 128.2, 127.8, 80.5, 73.3, 72.5, 69.3, 68.4, 61.3, 39.4, 39.2, 29.7, 25.8, 18.5, 17.4, 17.1, –4.5, –4.7 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{52}O_5Si_2$ $[M + Na]^+$ 559.3251; found 559.3252.

(*Z*)-Ethyl 4-[(4*R*,7*S*)-7-Butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl]but-2-enoate (26): Dess–Martin periodinane (0.046 g, 0.109 mmol) was added to a solution of **24** (0.030 g, 0.099 mmol) and pyridine (0.04 mL, 0.49 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C. The reaction was stirred at room temp. for 30 min, then quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with satd NaCl solution, dried with Na_2SO_4, and concentrated to afford the aldehyde, which was used immediately in the next step without further purification.

To a solution of $(PhO)_2P(O)CH_2COOEt$ (0.043 g, 0.108 mmol) in THF (0.6 mL) at 0 °C was added NaI (0.012 g, 0.084 mmol). After 5 min, NaH (60% dispersion in mineral oil, 0.002 g, 0.108 mmol) was added, and the resulting solution was cooled to –78 °C. The aldehyde (0.026 g, 0.084 mmol) dissolved in THF (0.6 mL) was then added dropwise. After 2 h at –78 °C, saturated NH_4Cl (0.7 mL) was added and the reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (PE/ethyl acetate, 85:15) to give **26** (0.033 g, 90%). $[a]_D^{25}$ = –7.60 (*c* = 0.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2930, 2861, 1650, 1610, 1512, 1460, 1241, 1092, 885 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.46–6.39 (m, 1 H), 5.87–5.84 (m, 1 H), 5.66–5.58 (m, 1 H), 5.51–5.44 (m, 1 H), 4.82–4.54 (m, 2 H), 4.18–4.14 (m, 2 H), 3.08–2.99 (m, 1 H), 2.90–2.80 (m, 1 H), 1.32–1.26 (m, 1 H), 1.03–0.98 (m, 12 H), 0.90–0.88 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.5, 146.5, 135.1, 132.9, 120.9, 71.1, 70.2, 59.9, 38.3, 37.3, 22.7, 22.5, 17.6, 17.1, 14.3, 14.1 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{37}O_4Si$ $[M + H]^+$ 369.2461; found 369.2464.

(*Z*)-Ethyl 4-((4*R*,7*S*)-7-{(2*R*,3*S*)-2-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]butyl}-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)but-2-enoate (27): Compound **27** was prepared from **25** by following the procedure described for **26**, yield 93%; colourless liquid; $[a]_D^{25}$ = 18.06 (*c* = 0.6, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2932, 2867, 1742, 1705, 1422, 1302, 1274, 1101, 965, 889, 773 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.25 (m, 5 H), 6.46–6.36 (m, 1 H), 5.86 (d, *J* = 11.76 Hz, 1 H), 5.67–5.48 (m, 2 H), 4.92–4.46 (m, 5 H), 4.16 (q, *J* = 7.15 Hz, 2 H), 3.94–3.83 (m, 1 H), 1.79–1.57 (m, 4 H), 1.27–1.24 (m, 5 H), 1.18–1.15 (m, 3 H), 1.02–098 (m, 12 H), 0.88 (s, 9 H), 0.06 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 146.3, 139.0, 128.2, 127.8, 127.7, 127.4, 121.0, 80.5, 72.5, 70.2, 68.4, 59.8, 40.8, 37.5, 29.7, 25.8, 19.1, 17.4, 17.2, 14.3, –4.5, –4.7 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{56}O_6Si_2$ $[M + H]^+$ 605.3694; found 605.3696.

Desacetylumuravumbolide (1a): To a stirred solution of compound **26** (25 mg, 67.8 μmol) in THF (0.6 mL) was added TBAF (40 μL, 0.13 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated to give the crude triol, which was used for the next step without purification.

The diol was dissolved in benzene (0.4 mL) and $Ti(OiPr)_4$ (2 μL, 6 μmol) was added. The yellow solution was heated to reflux for 1 h, then the solution was cooled to room temp. and the solvent was removed in vacuo. The residue was purified by flash chromatography (100 g silica gel; CH_2Cl_2/MeOH, 98:2) to give lactone **1a** (16 mg, 92%) as a colourless oil; $[a]_D^{25}$ = –2.3 (*c* = 0.5, $CHCl_3$) {ref.[2] $[a]_D^{25}$ = –5.3 (*c* = 1.3, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3456, 1720, 1685, 1390, 1060 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.89–6.87 (m, 1 H), 6.00–5.97 (m, 1 H), 5.78–5.65 (m, 1 H), 4.62–4.34 (m, 1 H), 2.41–2.19 (m. 2 H), 1.56–1.47 (m, 2 H), 1.45–1.26 (m, 4 H), 0.93 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.1, 146.6, 135.8, 127.4, 123.1, 72.8, 67.2, 37.0, 29.9, 27.0, 23.1, 14.0 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{18}O_3$ $[M + Na]^+$ 233.1154; found 233.1155.

Umuravumbolide (1b): Prepared from desacetylumuravumbolide **(1a)** according to ref.[2a] $[a]_D^{25}$ = +15 (*c* = 0.3, $CHCl_3$) {ref.[2] $[a]_D^{25}$ = +30 (*c* = 2.1, $CDCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1745, 1730, 1685, 1256 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.88–6.86 (m, 1 H), 6.03–5.99 (m, 1 H), 5.93–5.66 (m, 1 H), 5.42–5.08 (m, 3 H), 2.31–2.29 (m, 2 H), 2.02 (s, 3 H), 1.41–1.35 (m, 6 H), 0.87 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.7, 163.5, 146.4, 130.9, 130.5, 123.7, 72.8, 69.9, 34.5, 30.2, 28.9, 22.2, 21.9, 14.0 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{20}O_4$ $[M + Na]^+$ 275.1259; found 275.1258.

(*R*)-6-[(3*S*,5*R*,6*S*,*Z*)-5-(Benzyloxy)-3,6-dihydroxyhept-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (28): Prepared from **27** by following the procedure described for **1a**, yield 96%; colourless liquid; $[a]_D^{25}$ = –1.7 (*c* = 0.7, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3330, 2937, 1823, 1470, 1320, 1245, 1076, 872 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.23 (m, 5 H), 6.40–6.31 (m, 1 H), 5.80 (d, *J* = 11.87 Hz, 1 H), 5.62–5.43 (m, 2 H), 4.87–4.54 (m, 3 H), 3.88–3.79 (m, 1 H), 1.74–1.52 (m, 4 H), 1.13–1.10 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.6, 144.2, 139.0, 130.7, 129.8, 128.5, 127.9, 127.7, 127.6, 126.7, 84.0, 70.3, 67.1, 66.6, 64.7, 41.6, 31.6, 22.4 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{24}O_5$ $[M + Na]^+$ 355.1521; found 355.1521.

Hyptolide (2): To a solution of **28** (10 mg, 30 μmol) in anhydrous CH_2Cl_2 (0.35 mL) under nitrogen at 0 °C was added $TiCl_4$ (28 mg, 16 μL, 0.15 mmol). After 20 min, excess reagent was quenched by the addition of water, and the mixture was extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4), and evaporated to afford the triol, which was used immediately in the next step without further purification.

The triol was then dissolved in anhydrous CH_2Cl_2 (0.12 mL) and treated with Et_3N (33 μL, 0.24 mmol), acetic anhydride (20 μL, 0.2 mmol) and DMAP (1.4 mg, 12 μmol). After stirring overnight, the reaction mixture was worked up (extraction with CH_2Cl_2) and purified by chromatography on a silica gel column (PE/ethyl acetate, 70:30) to give hyptolide **2** (7 mg, 90%) as a colourless solid; m.p. 83–86 °C (ref.[2b] m.p. 87–88 °C); $[a]_D^{25}$ = +12.3 (*c* = 0.7, $CHCl_3$) {ref.[2b] $[a]_D^{25}$ = +11.2 (*c* = 0.6, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1737, 1645, 1280 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.86–6.84 (m, 1 H), 6.09–6.03 (m, 1 H), 5.73–5.71 (m, 1 H), 5.52–5.50 (m, 2 H), 5.11–5.07 (m, 1 H), 5.03–4.80 (m, 2 H), 2.36–2.33 (m, 2 H), 2.04–2.02 (m, 10 H), 1.81 (s, 1 H), 1.15–1.11 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.7, 169.0, 164.8, 139.2, 129.5, 126.5, 124.0, 72.8, 70.5, 69.9, 67.2, 61.5, 33.7, 22.6, 14.0 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{24}O_8$ $[M + Na]^+$ 511.2492; found 511.2495.

***tert*-Butyl{(*S*)-1-[(4*R*,6*S*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]ethoxy}dimethylsilane (29):** To a dark-blue solution of sodium-ammonia prepared from excess sodium and liquid ammonia (30 mL), was added a solution of **7** (0.05 g, 0.14 mmol) in THF (5 mL) at –78 °C. The solution was warmed to –50 °C and stirred for 1 h. The reaction was quenched by the addition of ammonium chloride. The cooling bath was removed and, after all ammonia was evaporated, the mixture was diluted with water and the aqueous layer was extracted with EtOAc. The extract was washed with water and concentrated under reduced pressure.

To a solution of the above compound in CH_2Cl_2 (5 mL) at 25 °C was added 2-methoxy-propene (40 μL, 0.42 mmol), followed by PPTS (2.5 mg, 10 μmol) portionwise. The reaction mixture was stirred at 25 °C for 15 min, then quenched by the addition of solid $NaHCO_3$ and stirred for 30 min. The reaction mixture was filtered through a pad of Celite and concentrated. Silica gel column chromatography (PE/ethyl acetate, 24:1) gave **29** (0.036 g, 85%) as a colourless liquid; $[a]_D^{25}$ = +11.50 (*c* = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2901, 2823, 1580, 1545, 1309, 745 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.92–5.79 (m, 1 H), 5.27–5.18 (m, 1 H), 5.13–5.04 (m, 1 H), 4.39–4.18 (m, 1 H), 3.98–3.70 (m, 1 H), 3.64–3.55 (m, 1 H), 1.92–1.64 (m, 2 H), 1.57 (s, 6 H), 1.15–1.11 (m, 3 H), 0.88–0.86 (m, 9 H), 0.05 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.0, 115.3, 114.2, 98.5, 73.4, 71.3, 70.2, 32.7, 30.1, 29.7, 25.8, 19.9, –4.4, –4.6 ppm. HRMS (ESI+): *m*/*z* calcd. for $C_{16}H_{33}O_3Si$ [M + H] 301.2199; found 303.2197.

Supporting Information (see footnote on the first page of this article): Characterization data of synthetic intermediates of umuravumbolide **1b** and hyptolide **2**, and ^1H and ^{13}C NMR spectra of all new compounds.

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[12] The enantiomeric excess of diol **15** was determined by converting its derivative allylic alcohol **6** into the Mosher ester and analyzing the ^{19}F NMR spectrum (see the Supporting Information).

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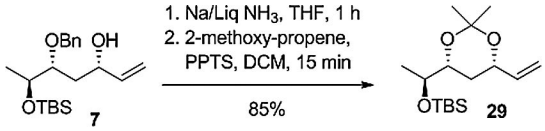
[14] The stereochemistry of **20** was confirmed on the basis of ^{13}C NMR spectra by converting **7** (derived from **20**, Scheme 4) into compound **29** through the following sequence of reaction. Compound **7** was subjected to Birch reaction conditions followed by acetonide protection of 1,3-diol to give the cyclic moiety **29**. The appearance of methyl resonance peaks at δ = 19.8 and 30.0 ppm and the acetal carbon resonating at δ = 98.5 ppm (see the Supporting Information) confirmed the presence of *syn*-acetonide **29**.



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