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Stereoselective synthesis of umuravumbolide

T. Vijaya Kumar, G. Venkateswar Reddy, K. Suresh Babu *, J. Madhusudana Rao *

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India

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ABSTRACT

An efficient stereoselective total synthesis of umuravumbolide has been developed. The key features of the synthesis include Jacobsen resolution, Wadsworth Emmons olefination and silyl-tethered ring closing metathesis.

1. Introduction

Desacetylumuravumbolide **1a** and umuravumbolide **1b** were first isolated by Van Puyvelde et al. in 1979 from *Tetradenia riparia* (*Iboza riparia*) of *Lamiaceae* family found in central Africa.[1] Extracts made from this plant are used in traditional medicine as a remedy for malaria, diarrhoea and for several types of fevers and aches.[2] Later, Davies-Coleman and Rivett determined the absolute configuration of **1a** and **1b** based on NMR and CD spectroscopic studies and also reported the specific rotation of these compounds.[3] Structurally, these natural products belong to the 6-substituted 5,6-dihydro-α-pyrone family, which contains an electrophilic α,β-unsaturated-δ-lactone ring attached to a side chain with a *Z*-olefin at the C7–C8 position and hydroxy or acetyl functional groups at C9 (Fig. 1). This class of natural products displays a wide range of biological properties such as antimicrobial, antifungal and phytotoxic activities, as well as cytotoxicity against human tumour cells.[4] Their promising biological profiles as well as interesting structures have attracted significant attention from a number of synthetic chemists.[5]

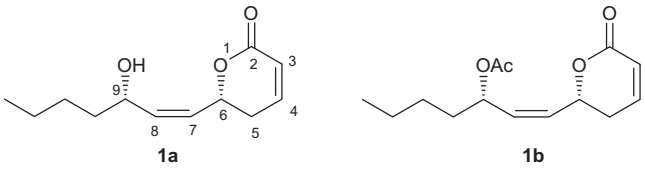

Figure 1. Structures of desacetylumuravumbolide **1a** and umuravumbolide **1b**.

To date, four total syntheses have been reported for **1a** and **1b** in the literature. In an early synthesis reported by Ramachandran et al., asymmetric reduction, allylboration and ring-closing metathesis were used as the key steps in the synthesis.[6a] Recently Sabitha et al. reported on the synthesis and anti tumour activity of **1a** and **1b** involving a Noyori asymmetric reduction and Still–Gennari olefination as key steps[6b] while the other approaches have exploited Crimmins aldol,[6c] and Jacobsen's resolution.[6d] In a continuation of our research program directed towards the synthesis of biologically active natural lactones,[7] we herein report a novel strategy for the synthesis of **1a** and **1b**, which is different from the previously reported syntheses for the installation of the *Z*-olefin, relying on a silyl-tethered ring closing metathesis.

2. Results and discussion

In our synthetic plan, the target molecule was planned from intermediate **2** via ring closing metathesis followed by acid promoted deprotection and lactonization, which in turn, could be obtained from secondary allylic alcohol fragments **3** and **4** through silyl protection followed by *Z*-selective Wittig olefination. Fragments **3** and **4** would be constructed from **5** and **6**, respectively (see Scheme 1).

The synthesis of umuravumbolide started from commercially available 1,2-epoxy hexane **5**, which was subjected to solvent-free hydrolytic kinetic resolution with (acetao)(aqua)(*S*,*S*)-*N*,*N*′bis(3,5-di-*tert*-butylsalicylidene-1,2-cyclohexanediamino)cobalt(III) to afford the required chiral epoxide **7** in 42% yield.[8] The regioselective ring opening of epoxide **7** with dimethylsulfonium methylide ($Me_3S^+I^-$, *n*-BuLi) afforded the required allylic alcohol **3** in 90% yield and with 96% enantioselectivity (Scheme 2).[9] The enantiopurity was determined by chiral HPLC and the absolute configuration was assigned by comparing the specific rotation data with that reported in the literature.[10] With the required fragment **3** in hand, we began the synthesis of the other key fragment **4** with enantiomerically pure (*S*)-2-(2-(4-methoxybenzyloxy)ethyl)oxirane **8**, which was prepared from commercially available L-aspartic acid using the literature procedure.[11] The regioselective ring opening of epoxide **8** with dimethylsulfonium methylide ($Me_3S^+I^-$, *n*-BuLi) afforded the required chiral alcohol **4** in 93% yield and with 98% ee (Scheme 3).[9] The enantiopurity was analysed by chiral HPLC and

* Corresponding authors. Tel.: +91 40 27191881; fax: +91 40 27160512.
E-mail address: suresh@iict.res.in (K.S. Babu).

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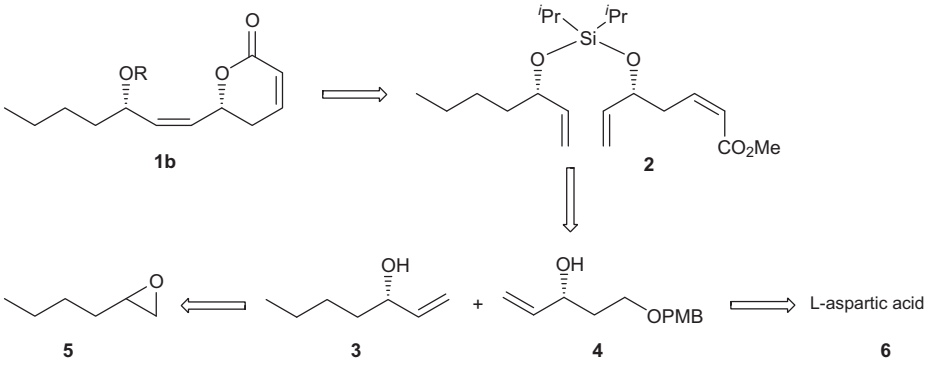
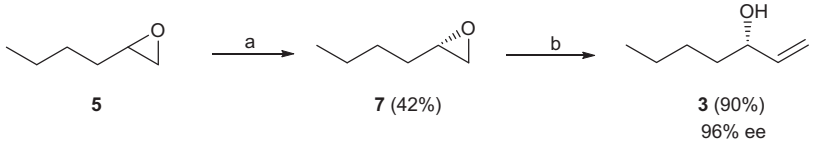
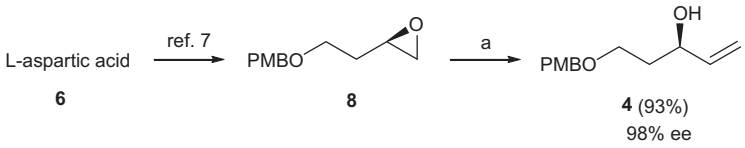


Scheme 1. Retrosynthetic analysis of umuravumbolide **1b**.



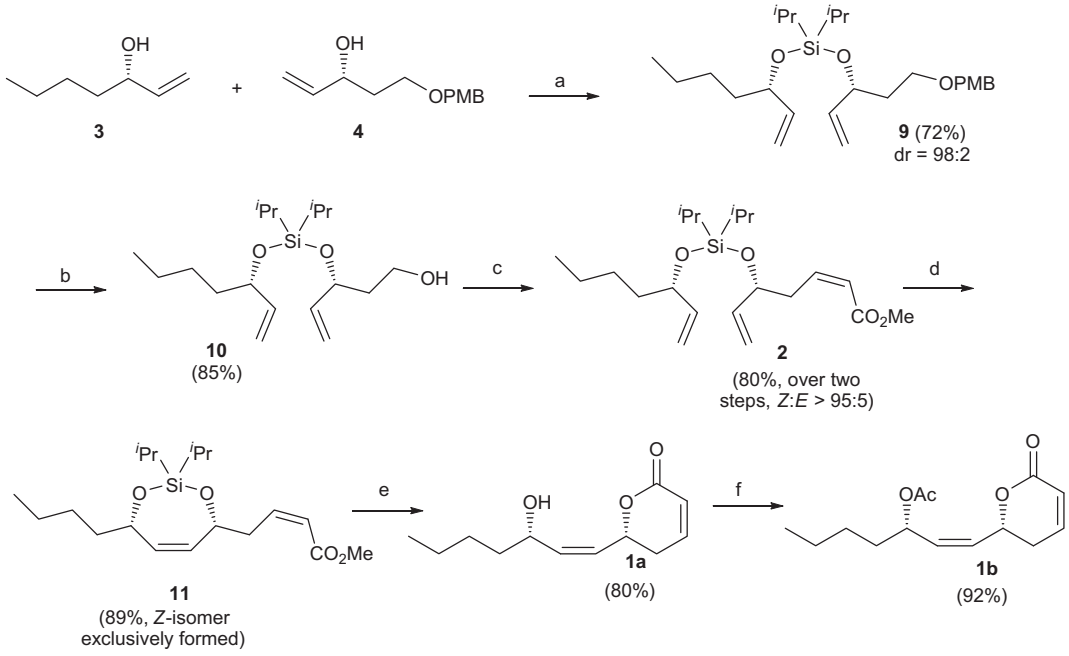
Scheme 2. Reagents and conditions: (a) (*S*,*S*)-(salen)CoIII(OAc), H_2O (0.55 equiv), rt, 16 h; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, −20 °C, 2 h.



Scheme 3. Reagents and conditions: (a) $(CH_3)_3S^+I^-$, *n*-BuLi, −20 °C, 2 h.

the absolute configuration was assigned by comparing the specific rotation data reported in the literature.[12]

With the two secondary allylic alcohol fragments **3** and **4** in hand, we then proceeded with the introduction of the C7–C8, *Z*-olefin via temporary silyl-tethered ring closing metathesis. In order to construct the RCM precursor **2**, allylic alcohol **3** was covalently tethered to **4** through a diisopropylsilyl linker to give disiloxane **9** in 72% yield and with a 98% diastereomeric ratio.[14a] Next, the PMB group was cleaved using DDQ in CH_2Cl_2/H_2O to give alcohol **10** in 85% yield. Subsequent oxidation of the resulting alcohol with Dess–Martin periodinane gave the corresponding aldehyde, which was directly submitted to chain elongation employing the Still



Scheme 4. Reagents and conditions: (a) ^{i}Pr$_2$SiCl$_2$, imidazole, CH_2Cl_2, 0 °C to rt, 4 h; (b) DDQ, CH_2Cl_2/H_2O, 0 °C to rt, 2 h; (c) (i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h; (ii) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, NaH, THF, −78 °C, 1 h; (d) Grubbs-II 9 mol %, 40 °C, CH_2Cl_2, 2 h; (e) 3 M HCl, THF (1:1), 0 °C to rt, 6 h; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h.

Gennari reagent [$(F_3CCH_2O)_2POCH_2CO_2Me$], to afford the corresponding α,β-unsaturated ester **2** (*Z*:*E* >95:5) in 80% yield (over two steps).[13]

At this stage, in order to install C7–C8 olefin with a *Z*-configuration, intermediate **2** was subjected to RCM with Grubbs second generation catalyst (9 mol %, 0.06 M in CH_2Cl_2) at 40 °C, this led to smooth cyclization to exclusively afford compound **11** in 89% yield.[14] One-pot acid promoted desilylation, followed by concomitant lactonization using 3 M HCl/THF (1:1) gave the required lactone desacetylumuravumbolide **1a** in 80% yield. Finally, acetylation of the secondary alcohol afforded umuravumbolide **1b** in 92% yield (Scheme 4). The enantiomeric purity and analytical data (^{1}H NMR, ^{13}C NMR and mass spectra) were in agreement with those reported for the natural product[3] {$[\alpha]_D^{23} = +29$ (*c* 2.2, $CHCl_3$), lit.[3] $[\alpha]_D^{23} = +30$ (*c* 2.1, $CDCl_3$)}.

3. Conclusions

In conclusion, we have accomplished a stereoselective synthesis of umuravumbolide by a combination of Wadsworth Emmons olefination and silyl-tethered ring closing metathesis reactions in a convergent fashion, with eight steps in the longest linear sequence starting from (±)-1,2-epoxyhexane with 12.1% overall yield. This strategy could readily be extended to a diverse range of coupling partners in order to generate novel compound libraries for biological evaluation. Further application of this strategy to the synthesis of other naturally occurring 6-substituted 5,6-dihydro-α-pyrone is currently in progress in our laboratory.

4. Experimental

4.1. General

All reactions were conducted under an atmosphere of nitrogen (IOLAR, Grade I). The apparatuses used for the reactions were oven dried. THF was distilled over sodium benzophenone ketyl before use, dichloromethane was distilled over calcium hydride. All reagents and solvents were reagent grade and used without further purification unless specified otherwise. Column chromatography was carried out with silica gel grade 60–120, and 100–200 mesh. ^{1}H NMR spectra were recorded at 300 and 500 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$. IR spectra were recorded on FT/IR-5700. Mass spectroscopic data were compiled using MS (ESI), HRMS mass spectrometers. Optical rotations were recorded on a polarimeter using 2 mL cell with a 1 dm path length.

4.1.1. (*S*)-2-Butyloxirane 7

A mixture of (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicyclidene-1,2-cyclohexanediamino)cobalt(II) (0.175 g, 0.29 mmol) toluene (5 mL) and AcOH (0.033 mL, 0.59 mmol) was stirred while open to the air for 1 h at room temperature. After 1 h, the toluene and excess acetic acid were removed under reduced pressure and the brown residue was dried over high vacuum, after which (±)-1,2-epoxyhexane (6 g, 59.89 mmol) was then added in one portion, the resultant mixture was stirred for 30 min and cooled in an ice water bath. Water (0.592 mL, 32.93 mmol) was added slowly and the temperature of the reaction mixture was maintained in such a way that it never increased by more than 20 °C (1 h). The slurry was stirred for 16 h and then subjected to distillation. Epoxide **2** was collected at 120 °C (1 atm) (2.52 g, 42%). The recovered epoxide was exhibited $[\alpha]_D^{20} = -8.2$ (*c* 1, $CHCl_3$), reported[8b] $[\alpha]_D^{20} = -9.0$ (*c* 1.0, $CHCl_3$).

4.1.2. (*S*)-Hept-1-en-3-ol 3

To a solution of trimethylsulfonium iodide (8.14 g, 39.94 mmol) in THF (40 mL) at −20 °C was added *n*-BuLi (1.6 M in hexane, 23.7 mL, 37.92 mmol) dropwise and the resulting solution was stirred for 1 h at −20 °C. After being stirred for 1 h, a solution of epoxide **2** (1 g, 9.98 mmol) in THF (6 mL) was added. The resultant cloudy suspension was allowed to warm slowly to 25 °C over 1 h and stirred for another 1 h. After consumption of the starting material (monitored by TLC), the reaction mixture was quenched with water. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc/hexanes) gave 1.030 g (90%) of allylic alcohol **12** as a colourless liquid. $[\alpha]_D^{20} = +9.3$ (*c* 1.5, $CHCl_3$). IR (KBr); 2923, 2852, 1462, 1219, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.81–5.93 (m, 1H), 5.26–5.08 (dd, *J* = 17.37, 10.57 Hz, 2H), 4.10 (q, *J* = 6.79 Hz, 1H), 1.59–1.48 (m, 2H), 1.44–1.21 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.2, 114.3, 73.2, 36.6, 27.4, 22.4, 13.8; MS (EI): *m*/*z* = 96 $[M-H_2O]^+$.

4.1.3. (*R*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol 4

To a solution of trimethylsulfonium iodide (5.8 g, 28.84 mmol) in THF (40 mL) at −20 °C was added *n*-BuLi (1.6 M in hexane, 17.2 mL, 27.4 mmol) dropwise and the resulting solution was stirred for 1 h at −20 °C. After being stirred for 1 h, a solution of epoxide **8** (1.5 g, 7.21 mmol) in THF (10 mL) was added. The resultant cloudy suspension was allowed to slowly warm to 25 °C over 1 h and stirred for another 1 h. After consumption of the starting material (monitored by TLC), the reaction mixture was quenched with water. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) gave 1.5 g (93%) of allylic alcohol **4** as a yellow oil. $[\alpha]_D^{25} = -9.1$ (*c* 1.8, $CHCl_3$); IR (KBr): 3426, 2922, 2859, 1613, 1514, 1465, 1249, 1093, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.83 Hz, 2H), 6.88 (d, *J* = 8.83 Hz, 2H), 5.91–5.84 (m, 1H), 5.27 (d, *J* = 16.5, 1H), 5.1 (d, *J* = 9.93 Hz, 1H), 4.45 (s, 2H), 4.36–4.31 (m, 1H), 3.81 (s, 3H), 3.71–3.66 (m, 1H), 3.64–3.59 (m, 1H), 1.89–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 140.5, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.9, 55.1, 36.2; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{18}O_3Na$: 245.11504; found: 245.11482.

4.1.4. (5*R*,9*S*)-7,7-Diisopropyl-1-(4-methoxyphenyl)-5,9-divinyl-2,6,8-trioxa-7-silatridecane 9

Dichlorodiisopropylsilane (0.85 mL, 4.729 mmol) was added to imidazole (1.53 g, 22.52 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The solution was stirred for 5 min., then allylic alcohol **4** (1 g, 4.504 mmol) in CH_2Cl_2 (10 mL) was added dropwise by a dropping funnel over 1 h at 0 °C. After the mixture was stirred for 10 min at 0 °C, a solution of allylic alcohol **3** (0.513 g, 4.504 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C. The reaction mixture was warmed to the room temperature and stirred for 4 h and then purified directly by silica gel column chromatography (EtOAc/*n*-hexane, 1:49), to afford 1.45 g (72%) of bisalkoxysilane **9** as a colourless oil. $[\alpha]_D^{25} = -36$ (*c* 1.2, $CHCl_3$); IR (KBr): 2933, 2866, 1613, 1513, 1463, 1248, 1094, 993, 921, 682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.30 Hz, 2H), 6.87 (d, *J* = 8.30 Hz, 2H), 5.89–5.74 (m, 2H), 5.20–5.09 (m, 2H), 5.03 (td, *J* = 1.51, 10.57 Hz, 2H), 4.52–4.24 (m, 3H), 3.81 (s, 3H), 3.60–3.45 (m, 2H), 1.97–1.74 (m, 2H), 1.61–1.43 (m, 2H), 1.33–1.23 (m, 5H), 1.06–0.97 (m, 13H), 0.89 (t, *J* = 6.79 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 141.4, 141.1, 130.7, 129.2, 113.9, 113.7, 73.6, 72.6, 70.9, 66.3, 55.2, 37.9, 37.7, 26.8, 22.7, 17.4, 14.1, 12.7; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{44}O_4NaSi$ 471.28964; found: 471.9011.

4.1.5. (*R*)-3-(((*S*)-Hept-1-en-3-yloxy)diisopropylsilyloxy)pent-4-en-1-ol 10

To a solution of PMB ether **9** (1.2 g, 2.67 mmol) in CH_2Cl_2 (15 mL) and water (1.5 mL) at 0 °C was added DDQ (0.912 g,

4.01 mmol), and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL), and the organic layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a light red coloured product. Purification of the crude product by silica gel column chromatography (EtOAc/hexane, 1:19) afforded **10** (0.750 g, 85%) as a colourless liquid $[\alpha]_D^{25} = +13.4$ (*c* 3, $CHCl_3$); IR (KBr): 3409, 2942, 2868, 1465, 1249, 1088, 1033, 921, 885, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.96–5.75 (m, 2H), 5.29–5.06 (m, 4H), 4.65–4.59 (m, 1H), 4.30–4.23 (m, 1H), 3.91–3.81 (m, 1H), 3.72–3.62 (m, 1H), 2.81–2.72 (m, 1H), 1.95–1.84 (m, 1H), 1.70–1.47 (m, 3H), 1.36–1.21 (m, 4H), 1.08–0.96 (m, 14H), 0.89 (t, *J* = 6.79 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 140.7, 114.5, 113.9, 74.3, 71.2, 59.1, 39.4, 37.6, 26.9, 22.6, 17.2, 14.1, 12.6; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{36}O_3NaSi$ 351.23279; found 351.23259.

4.1.6. (*R*,*Z*)-Methyl 5-(((*S*)-hept-1-en-3-yloxy)diisopropylsilyloxy) hepta-2,6-dienoate 2

To a stirred solution of primary alcohol **10** (300 mg, 0.914 mmol) in CH_2Cl_2 (10 mL) was sequentially added solid $NaHCO_3$ (305 mg, 3.658 mmol) and Dess–Martin periodinane (775 mg, 1.829 mmol). After stirring for 2 h at room temperature, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$. The resultant mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, which was directly carried to the next step without further purification. To a stirred suspension of NaH (42.6 mg, 1.779 mmol) in dry THF (10 mL) at 0 °C was added methyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (353 mg, 1.111 mmol) in THF (5 mL) and then allowed to stir for 30 min. The reaction temperature was brought to −78 °C, then a solution of aldehyde (300 mg, 0.914 mmol) in dry THF (3 mL) was added dropwise over a period of 10 min. The resulting mixture was stirred for 1 h at −78 °C. The reaction was quenched with saturated NH_4Cl and warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 8 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and separation of the diastereomers by silica gel column chromatography (EtOAc/hexane, 1:99) yielded *Z*-olefinic ester **2** (280 mg, 80% over two steps) as a colourless oil $[\alpha]_D^{25} = -10.9$ (*c* 1.2, $CHCl_3$); IR (KBr): 3079, 2926, 2866, 1727, 1647, 1463, 1175, 1033, 922, 814, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.37 (td, *J* = 6.29, 10.5 Hz, 1H), 5.86–5.76 (m, 3H), 5.24–5.01 (m, 4 H), 4.53 (q, *J* = 10.49 Hz, 2H), 4.29 (q, *J* = 12.59 Hz, 2H), 3.70 (s, 3H), 3.01–2.88 (m, 2H), 1.61–1.45 (m, 3H), 1.33–1.24 (m, 4H), 1.04–0.99 (m, 13H), 0.88 (t, *J* = 6.29 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 141.3, 140.3, 120.4, 114.3, 113.8, 73.6, 71.8, 50.9, 37.7, 37.0, 26.8, 22.7, 17.4, 14.1, 12.7; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{38}O_4NaSi$: 405.24274; found: 405.24316.

4.1.7. (*Z*)-Methyl 4-((4*R*,7*S*,*Z*)-7-butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)but-2-enoate 11

A solution of compound **2** (200 mg, 0.523 mmol) in CH_2Cl_2 (9 mL, 0.06 M) was degassed after which Grubbs-II generation catalyst (13 mg, 0.0156 mmol, 3 mol %) was added and the solution was again degassed and heated at 35 °C for 30 min. A second batch of catalyst (13 mg, 0.0156 mmol, 3 mol %) was then added and the reaction heated again for 30 min. This process was repeated again, to a total catalyst loading of 9 mol %. The reaction was concentrated in vacuo and purified directly by silica gel column chromatography (EtOAc/hexane, 1:49) to give **11** (165 mg, 89%) as a colourless oil. $[\alpha]_D^{25} = -23.0$ (*c* 1.3, $CHCl_3$); IR (KBr): 2926, 2861, 1728, 1463, 1218, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.07–6.95 (m, 1H), 5.90 (d, 1H, *J* = 11.46 Hz), 5.70–5.45 (m, 2H), 4.77–4.70 (m, 1H), 4.60–4.53 (m, 1H), 3.73 (s, 3H), 2.56–2.45 (m, 2H), 1.62–1.50 (m, 3 H), 1.41–1.26 (m, 4H), 1.06–0.98 (m, 13H), 0.91 (t, *J* = 6.79 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 145.5, 136.4, 133.2, 123.0, 71.4, 69.8, 51.4, 41.2, 27.8, 22.5, 17.3, 17.16, 14.1, 12.9, 12.8; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{34}O_4NaSi$: 377.21240; found: 377.21186.

4.1.8. (*R*)-6-((*S*,*Z*)-3-Hydroxyhept-1-enyl)-5,6-dihydro-2*H*-pyran-2-one 1a (desacetylumuravumbolide)

To a stirred solution of **11** (100 mg, 0.282 mmol) in THF (2 mL) was added 3 M HCl (2 mL) at 0 °C after which the reaction mixture warmed to room temperature and stirred for 6 h. After completion of the reaction, the reaction mixture was quenched by the addition of solid $NaHCO_3$, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 3:7) to afford **1a** as yellow oil (47 mg, 80%). $[\alpha]_D^{25} = -5.6$ (*c* 1, $CHCl_3$); IR (KBr): 3428, 2925, 2854 1718, 1382, 1249, 1024, 817, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94–6.88 (m, 1H), 6.05 (d, *J* = 10.0 Hz, 1H), 5.72–5.59 (m, 2 H), 5.38–5.29 (m, 1H), 4.46–4.38 (m, 1H), 2.52–2.25 (m, 3H), 1.51–1.17 (m, 6 H), 0.90 (t, *J* = 6.79 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 144.7, 137.9, 127.4, 121.4, 73.6, 67.7, 36.7, 29.8, 27.4, 22.6, 14.0; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{12}H_{18}O_3Na$: 233.11494; found: 233.11482.

4.1.9. (*S*,*Z*)-1-((*R*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl)hept-1-en-3-yl acetate 1b (umuravumbolide)

To a stirred solution of compound **1a** (30 mg, 0.142 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.047 mL, 0.342 mmol), acetic anhydride (0.016 mL, 0.171 mmol), DMAP (3.5 mg, 0.0189 mmol) and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction, water was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane, 2:8) afforded **1b** as a yellow oil (33 mg, 92%). $[\alpha]_D^{25} = +29$ (*c* 2.2, $CHCl_3$); IR (KBr): 2921, 2861, 1740, 1711, 1376, 1235, 1022, 815, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.88–6.82 (m, 1H), 6.04 (d, *J* = 9.98 Hz, 1H), 5.74–5.68 (m, 1H), 5.56–5.50 (m, 1H), 5.45–5.36 (m, 2H), 2.49–2.41 (m, 1H), 2.31–2.24 (m, 1H), 2.02 (s, 3H), 1.72–1.64 (m, 1H), 1.56–1.48 (m, 1H), 1.36–1.20 (m, 4H), 0.89 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 163.5, 144.3, 131.6, 130.0, 121.6, 74.0, 69.4, 34.2, 30.0, 27.2, 22.4, 21.1, 13.8; ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{14}H_{20}O_4Na$: 275.12558; found: 275.12538.

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