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Stereoselective Total Synthesis of Umuravumbolide

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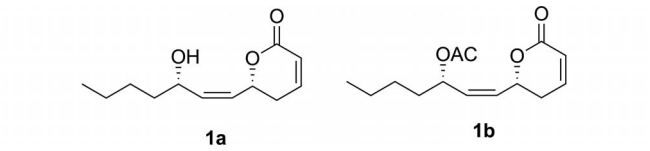
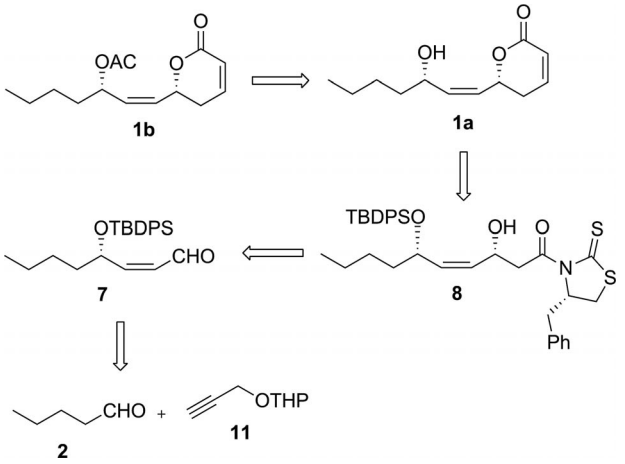
A simple and efficient stereoselective total synthesis of desacetylumuravumbolide (**1a**) and umuravumbolide (**1b**), starting from commercially available valeraldehyde has been described. The synthetic strategy involves a highly enantioselective zinc-mediated addition of protected 2 alkyn-1-ol to aldehyde, a Crimmins aldol reaction, and Horner–Wadsworth–Emmons olefination as key steps.

Introduction

5,6-Dihydro-α-pyrone-containing natural products having a substituted alkyl side chain at the C-6 position have attracted much attention over the last decade due to the Michael acceptor nature of the α,β-unsaturated α-pyrones for the amino acid residues of receptors.[1] These pyrones show various biological activities, including the inhibition of HIV protease[2] and the inducing of apoptosis,[3] and they act as antileukemic[4] and anticancer agents,[5] plant growth inhibitors, pheromones, and antifeedent, antifungal, antibacterial, and antitumor agents.[6] Compounds having the 5,6-dihydro-α-pyrone moiety, desacetylumuravumbolide (**1a**) and umuravumbolide (**1b**),[7] were isolated from *Tetradenia riparia* of the Lamiaceae family from central and southern Africa. The structures of **1a** and **1b** were revised by Davies–Coleman and Rivett. They determined the absolute configuration on the basis of NMR and CD spectral studies and also reported the optical rotations of these compounds.[8] Our continued interest towards the total synthesis of lactone-containing natural products[9] prompted us to undertake the synthesis of demanding targets **1a** and **1b**. To the best of our knowledge, there is only one report on the synthesis of these natural products by Ramachandran et al.[10] who used asymmetric reduction, allylboration, and ring-closing metathesis.



Herein, we report a simple and practical synthesis of desacetylumuravumbolide (**1a**) and umuravumbolide (**1b**) from commercially available valeraldehyde. In our synthesis, the stereogenic centers can easily be established by zinc-mediated addition of protected 2 alkyn-1-ol to the aldehyde and a Crimmins aldol reaction. Our synthetic strategy for the synthesis of **1b** is outlined in Scheme 1. Desacetylumuravumbolide (**1a**) could be derived from β-hydroxyamide **8** through Horner–Wadsworth–Emmons olefination, followed by global deprotection of the silyl and methoxymethyl (MOM) groups and concomitant cyclization. Compound **8** could be obtained from aldehyde **7**, which could be obtained from valeraldehyde (**2**) by through the highly enantioselective zinc-mediated addition of THP-protected propargyl alcohol **11** to **2**.



Scheme 1. Retrosynthetic route for umuravumbolide.

Results and Discussion

As outlined in Scheme 2, the first stereocenter was generated by the highly enantioselective addition of propargyl alcohol **11** to **2** in the presence of Et_2Zn in toluene (1 mmol)

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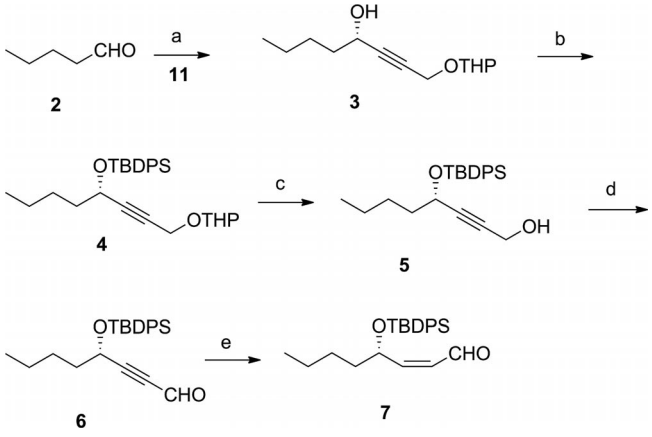
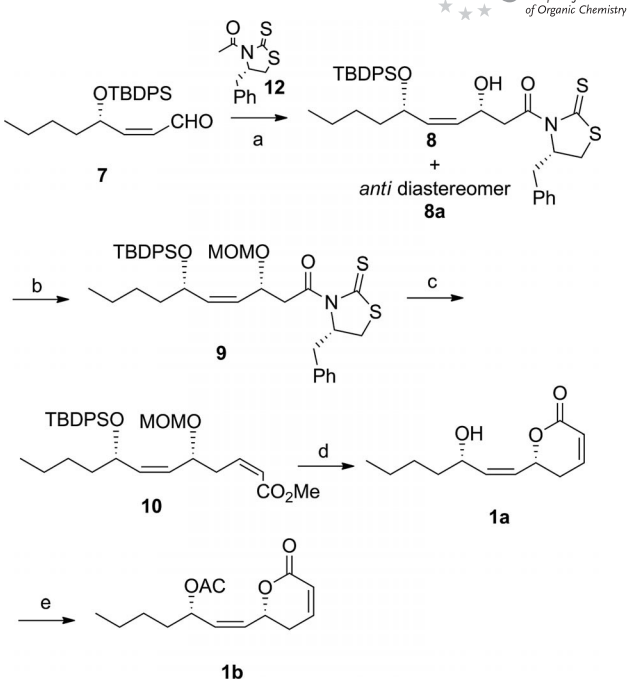
and a catalytic solution of (*R*)-BINOL (0.1 mmol), phenol (0.1 mmol), Ti(*i*PrO)$_4$ (0.25 mmol) in dry ether to give compound **3** in 95% yield[11] with 93%*ee*. The enantiomeric purity was determined by HPLC analysis (see the Experimental Section for details). The secondary hydroxy group in compound **3** was protected with *tert*-butyldiphenylsilyl (TBDPS) chloride as TBDPS ether **4** in 93% yield. The tetrahydropyranyl group in compound **4** was deprotected with pyridinium *p*-toluenesulfonate (PPTS)/MeOH to give compound **5** in 95%, which was oxidized with 2-iodoxybenzoic acid (IBX) in DMSO and dry dichloromethane (DCM) to afford aldehyde **6** in 90% yield. Aldehyde **6** was converted into required (*Z*)-olefinic aldehyde **7** in 85% yield by hydrogenation using Lindlar's catalyst in dry DCM. We synthesized aldehyde **7** in five steps with an overall yield of 65%.



Scheme 2. Reagents and conditions: (a) **11**, Et_2Zn, (*R*)-BINOL, Ti(O*i*Pr)$_4$, PhOH, 95%, 93%*ee*; (b) TBDPSCl, imidazole, dry DCM, 6 h, r.t., 93%; (c) PPTS, MeOH, r.t., 95%; (d) IBX /DMSO, CH_2Cl_2, 0 °C to r.t., 90%; (e) Lindlar's catalyst, DCM, H_2, 8 h, 85%.

Aldehyde **7** was subjected to an aldol reaction with chiral (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (**12**) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) and titanium tetrachloride in dry DCM under the Crimmins protocol[12] to give a mixture of diastereomers in 77% yield (Scheme 3). The diastereomers of the β-hydroxy amide were easily separable (*syn*/*anti* = 8.5:1.5). The diastereoselectivity of the Crimmins aldol reaction was determined by HPLC (see the Experimental Section for details). The hydroxy group in **8** was protected as MOM ether **9** in 95% yield by using DEIPA and MOMCl in dry DCM. Amide **9** was treated with DIBAL-H to give the aldehyde, which was subjected to Horner–Wadsworth–Emmons olefination by employing bis(2,2,2-trifluoromethyl)(methoxycarbonylmethyl)phosphonate[13] to give *cis*-olefinic ester **10** in 82% yield.

With *cis*-olefinic ester **10** in hand, we proceeded further to the one-pot deprotection of the protecting groups with concomitant cyclization of the ester and alcohol functionalities with 3.0 M HCl/THF (1:1) at room temperature to afford **1a** {$[a]_D^{25}$ = –5.4 (*c* = 1, $CHCl_3$)} in 60% yield. Further, in a separate experiment, **1a** was acetylated by using acetic anhydride/pyridine to afford **1b** {$[a]_D^{25}$ = +33.4 (*c* = 1, $CHCl_3$)} in 97% yield (Scheme 3). The physical and spectroscopic data of **1a** and **1b** were in full agreement with those of reported natural product.[8]



Scheme 3. Reagents and conditions: (a) **12**, $TiCl_4$, DIPEA, dry DCM, –78 °C, 77%; (b) MOMCl, DIPEA, 7 h, 0 °C to r.t., 95%; (c) 1. DIBAL-H, dry DCM, –78 °C, 5 min; 2. NaH/THF, –78 °C, 30 min, then $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, THF, 30–45 min, 82%; (d) 3 M HCl, THF (1:1), 3 h, r.t.; (e) Ac_2O, pyridine, DCM, 18 h, 97%.

Conclusions

A stereoselective total synthesis of umuravumbolide from valeraldehyde with a high overall yield of 22% has been demonstrated. In our synthesis, the stereogenic centers can be easily established by zinc-mediated addition of protected 2 alkyn-1-ol to the aldehyde and a Crimmins aldol reaction.

Experimental Section

General Methods: All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 and 100–200 mesh. FTIR spectra were measured with a Thermo Nicolet Nexus 670 spectrometer. Optical rotations were recorded with a Horiba high sensitive polarimeter in a 10 mm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a Bruker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Mass spectra were acquired with a Micro mass Quattro Micro API (Waters) mass spectrometer. HPLC chiral analyses were performed with a Shimadzu LC-20 AT apparatus equipped with a UV detector by using a 25 cm × 4.6 mm DAICEL Chiracel AD-H column. HPLC were measured with an Agilent 1100 series apparatus equipped with a DAD detector by using 150 × 4.6 mm ZORBAX SBC-3 columns.

(4*S*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)oct-2-yn-4-ol (3): A solution of Et_2Zn (1.1 M) in toluene (10 mL, 10.0 mmol) was added at room temperature to a solution of **11** (1.24 g, 10.0 mmol) in dry toluene (1 mL), and the mixture was heated at reflux for 1 h. A catalyst solution of (*R*)-BINOL (286 mg, 1.0 mmol), phenol (94 mg, 1.0 mmol), and Ti(*i*PrO)$_4$ (0.74 mL, 2.5 mmol) in anhydrous Et_2O (3 mL) was stirred for 30 min. This solution was added to the reaction mixture, and the mixture was stirred for 1 h at room temperature before adding valeraldehyde (**2**; 0.26 mL, 2.5 mmol). The entire reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, the reaction was quenched with NH_4Cl (15 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with 2 N HCl (2 × 5 mL), $NaHCO_3$ (2 × 5 mL), and brine (10 mL), dried with $MgSO_4$, and evaporated under reduced pressure. Thus obtained crude residue was purified over silica gel (CH_2Cl_2/MeOH, 99:1) to give **3** (504 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ = –6.76 (*c* = 2.25, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3414, 2942, 2864, 1623, 1120, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.78 (dd, *J* = 3.0, 0.8 Hz, 1 H, OCHO), 4.35 (t, *J* = 6.0 Hz, 1 H, CHOH), 4.25 (d, *J* = 1.5 Hz, 1 H, OCHC), 4.23 (d, *J* = 2.3 Hz, 1 H, OCHC), 3.84–3.76 (m, 1 H, C≡CHOC), 3.55–3.48 (m, 1 H, C≡CHOC), 1.88–1.31 (m, 12 H), 0.93 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 96.7, 87.2, 80.5, 62.3, 62.0, 54.22, 37.3, 30.1, 27.2, 25.2, 22.2, 18.9, 13.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}NaO_3$ [M + Na]$^+$ 249.1461; found 249.1472. HPLC (DAICEL Chiralpak AD-H, hexane/*i*PrOH = 90:10, flow rate = 1.0 mL/ min, λ = 210 nm): t_R = 10.3 (major), 11.7 min (minor); 93% *ee*.

***tert*-Butyldiphenyl[(4*S*)-1-(tetrahydro-2*H*-pyran-2-yloxy)oct-2-yn-4-yloxy]silane (4):** To a cooled (0 °C) solution of **3** (1.4 g, 6.2 mmol) and imidazole (1.3 g, 19.1 mmol) in dry DCM (30 mL) was added *tert*-butyldiphenylsilyl chloride (2.0 g, 7.44 mmol) dropwise, and the mixture was stirred for 4 h. After the completion of reaction, the reaction mixture was diluted with water (20 mL) and extracted into DCM (3 × 30 mL). The combined organic layer was washed with brine (10 mL), dried with anhydrous Na_2SO_4, and concentrated under vacuum to furnish the crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 5:95) to give **4** (2.6 g, 93%) as a yellow liquid. $[\alpha]_D^{25}$ = –46.99 (*c* = 2.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2936, 2859, 1428, 1112, 1026, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.64 (m, 4 H, ArH), 7.41–7.30 (m, 6 H, ArH), 4.64 (dt, *J* = 9.8, 6.8, 3.0 Hz, 1 H, OCHO), 4.34 (tt, *J* = 1.5 Hz, 1 H, CHOTBDPS), 4.07 (d, *J* = 2.3 Hz, 2 H, OCHC), 3.79–3.69 (m, 1 H, C≡CHOC), 3.49–3.40 (m, 1 H, C≡CHOC), 1.69–1.46 (m, 6 H), 1.42–1.19 (m, 4 H), 1.06 [s, 9 H, $Si(CH_3)_3$], 0.86 (t, *J* = 6.79 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.8, 135.3, 133.7, 129.6, 129.4, 127.5, 127.3, 96.4, 87.3, 80.6, 63.8, 61.9, 54.1, 38.0, 30.2, 27.0, 26.9, 25.3, 22.3, 19.2, 19.0, 14.0 ppm. MS (ESI): *m*/*z* = 487 [M + Na]$^+$.

(4*S*)-4-(*tert*-Butyldiphenylsilyloxy)oct-2-yn-1-ol (5): To a cooled (0 °C) solution of compound **4** (2 g, 4.4 mmol) in methanol (10 mL) was added a catalytic amount of PPTS (30 mg), and the mixture was stirred for 5 h. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ and extracted into ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 8:2) to afford pure compound **5** (1.55 g, 95%) as a clear liquid. $[\alpha]_D^{25}$ = –52.8 (*c* = 1.75, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3376, 2933, 2860, 1427, 1109, 1074, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 4 H, ArH), 7.40–7.30 (m, 6 H, ArH), 4.36 (tt, *J* = 1.5 Hz, 1 H, CHOTBDPS), 3.95 (dd, *J* = 3.7 Hz, 2 H, CH_2OH), 2.03 (s, 1 H, OH), 1.71–1.62 (m, 2 H), 1.45–1.22 (m, 4 H), 1.06 [s, 9 H, $Si(CH_3)_3$], 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.0, 135.8, 134.7,134.1, 129.6, 129.4, 127.5, 127.1, 87.3, 83.0, 63.8, 51.0, 37.9, 27.0, 26.9, 26.5, 19.3, 14.0·ppm. MS (ESI): *m*/*z* = 398 [M + NH_4]$^+$.

(4*S*)-4-(*tert*-Butyldiphenylsilyloxy)oct-2-ynal (6): To a stirred solution of IBX (635 mg, 2.3 mmol) in dry DMSO (5 mL) was added a solution of **5** (0.35 g, 1.5 mmol) in DCM (10 mL) at room temperature, and the mixture was stirred for 5 h at room temperature. After completion of the reaction, the mixture was filtered, diluted with water (5 mL), and extracted into DCM (2 × 10 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the crude aldehyde, which was purified by column chromatography (hexane/EtOAc, 9:1) to give **6** (519 mg, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = –23.5 (*c* = 2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2956, 2932, 2859, 2208, 1670, 1109, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1 H, CHO), 7.73–7.57 (m, 4 H, ArH), 7.48–7.28 (m, 6 H, ArH), 4.52–4.45 (m, 1 H, CHOTBDPS), 1.78–1.64 (m, 1 H), 1.54–1.19 (m, 5 H), 1.09 [s, 9 H, $Si(CH_3)_3$], 0.86 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 135.9, 135.7, 132.9, 132.8, 129.9, 129.8, 127.79, 127.5, 97.8, 84.1, 63.6, 37.1, 26.8, 26.5, 22.2, 19.2, 13.8 ppm.

(*Z*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)oct-2-enal (7): To a solution of aldehyde **6** (1.88 g, 5.0 mmol) in dry DCM (20 mL) was added Lindlar's catalyst (0.5 g), and the mixture was stirred under a hydrogen atmosphere. The reaction was monitored by TLC. After completion of the reaction (10 h), the reaction mixture was filtered through a silica gel pad; the solvent was removed, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 9:1) to afford **7** (1.6 g, 85%) of as a liquid. $[\alpha]_D^{25}$ = +15.1 (*c* = 1.65, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2957, 2932, 2859, 1688, 1466, 1428, 1109, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.29 (d, *J* = 8.0 Hz, 1 H, CHO), 7.65–7.57 (m, 4 H, ArH), 7.42–7.30 (m, 6 H, ArH), 6.39 (dd, *J* = 11.2, 8.8 Hz, 1 H, CH=C), 5.64 (dd, *J* = 11.2, 7.2 Hz, 1 H, =CHCHO), 4.92 (q, *J* = 15.2, 6.4 Hz, 1 H, CHOTBDPS), 1.75–1.45 (m, 2 H), 1.28–1.17 (m, 4 H), 1.06 [s, 9 H, $Si(CH_3)_3$], 0.86 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.4, 153.1, 135.7, 135.6, 133.3, 133.2, 130.8, 129.9, 129.4, 128.1, 127.6, 127.5, 68.8, 37.4, 26.8, 22.3, 19.1, 13.8 ppm.

(3*R*,6*S*,*Z*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-6-*tert*-butyldiphenylsilyloxy]-3-hydroxydec-4-en-1-one (8): To cooled (0 °C) solution of **12** (0.6 mmol) in dry CH_2Cl_2 (6 mL) was added titanium(IV) chloride (1.32 mmol, 0.2 mL) dropwise, and the solution was allowed to stir for 5 min, after which the solution turned yellow in color. Then DIPEA (0.6 mmol, 0.11 mL) was added. The yellow slurry or suspension turned dark red and was stirred for 20 min at 0 °C. To this dark red solution was added **7** (0.55 mmol, 200 mg) in dry DCM (10 mL) dropwise, and the reaction mixture was stirred for 1 h at 0 °C. After completion of the reaction, the reaction was quenched with ammonium chloride solution (6 mL) and then extracted into DCM (3 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 8:2) to afford **8** (217 mg, 66%) along with *anti*-**8a** (37 mg, 11%). $[\alpha]_D^{25}$ = –15.14 (*c* = 1.75, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3447, 2930, 2857, 1699, 1634, 1035, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.63 (m, 4 H, ArH), 7.46–7.27 (m, 11 H, ArH), 5.62–5.46 (m, 1 H, CH=C), 5.36–5.15 (m, 2 H, =CHCHO, NCHBn), 4.57–4.32 [m, 2 H, (CHOTBDPS, CHOH)], 3.40–3.29 (m, 1 H, CHS), 3.25–3.14 [m, 2 H, (CHS, CHPh)], 3.04–2.98 [m, 2 H, (CHPh, CHCO)], 2.92–2.83

(m, 1 H, CHCO), 2.27 (s, 1 H, OH), 1.48–1.37 (m, 1 H),1.33–1.15 (m, 5 H), 1.04 [s, 9 H, $Si(CH_3)_3$], 0.85 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 171.4, 136.4, 136.1, 135.9, 135.8, 134.7, 134.1, 134.2, 129.6, 129.3, 128.8, 128.4, 127.5, 127.4, 127.2, 69.3, 68.4, 63.7, 45.3, 38.0, 36.7, 32.0, 27.1, 26.9, 22.67, 19.2, 14.06 ppm. HRMS (ESI): calcd. for $C_{36}H_{45}NNaO_3S_2Si$ $[M + Na]^+$ 654.2502; found 654.2520. HPLC (ZORBAX SBC-3, acetonitrile/water = 70:30, flow rate = 1.0 mL/ min, λ = 210 nm): t_R = 10.9 (major, 85%), 9.9 min (minor, 15%).

(*Z*,3*R*,6*S*)-1-[(4*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-6-(*tert*-butyldiphenylsilyloxy)-3-(methoxymethoxy)dec-4-en-1-one (9): To a stirred solution of **8** (470 mg, 0.80 mmol) and DIPEA (0.43 mL, 2.4 mmol) in dry DCM (20 mL) was added MOMCl (0.13 mL, 1.6 mmol) at 0 °C, and the mixture was stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, water was added, and the reaction mixture was extracted into DCM (3 × 20 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 9:1) to afford **9** (480 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ = –1.11 (c = 0.77, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2930, 2858, 1690, 1350, 1160, 1047, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.62 (m, 4 H, ArH), 7.42–7.27 (m, 11 H, ArH), 5.74 (dd, J = 11.3, 9.0 Hz, 1 H, CH=C), 5.33–5.21 [m, 2 H, (=CHCHOMOM, NCHBn], 4.75–4.54 [m, 2 H, (CHOTBDPS, CHOMOM)], 4.25 (s, 2 H, OCH_2O), 3.63–3.52 (m, 1 H, CHS), 3.42–3.26 [m, 2 H, (CHS, CHPh)], 3.23 (s, 3 H, OCH_3), 3.10–2.95 [m, 2 H, (CHPh, CHCO)], 2.89–2.83 (m, 1 H, CHCO), 1.46–1.38 (m, 1 H), 1.32–1.10 (m, 5 H), 1.05 [s, 9 H, $Si(CH_3)_3$], 0.85 (t, J = 6.7 Hz 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 170.5, 137.5, 137.2, 136.0, 135.9, 129.6, 129.5, 129.4, 129.3, 128.8, 127.6, 127.5, 127.1, 127.4, 127.2, 94.3, 69.7, 68.6, 68.1, 55.6, 44.5, 37.8, 36.4, 32.1, 27.0, 26.8, 22.5, 19.3, 14.0 ppm. HRMS (ESI): calcd. for $C_{38}H_{49}NNaO_4S_2Si$ $[M + Na]^+$ 698.2764; found 698.2789.

Methyl (2*Z*,5*R*,6*Z*,8*S*)-8-(*tert*-butyldiphenylsilyloxy)-5-(methoxymethoxy)dodeca-2,6-dienoate (10): To a cooled (–78 °C) solution of **9** (330 mg, 0.52 mmol) in dry CH_2Cl_2 (6 mL) was added DIBAL-H (0.46 mL, 0.471 mmol, 20% in toluene), and the reaction mixture was allowed to stir at –78 °C for 5–10 min. After completion of the reaction, the reaction was quenched with sodium potassium tartarate solution (1 mL). The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated to afford the crude aldehyde. This crude aldehyde was directly used for the next reaction. To a cooled (0 °C) stirred suspension of NaH (36 mg, 1.55 mmol) in dry THF (6 mL) under a nitrogen atmosphere was added bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (270 mg, 0.84 mmol) in dry THF (3 mL), and the mixture was stirred for 30 min at 0 °C. The reaction temperature was brought to –78 °C, and then a solution of aldehyde (351 mg, 0.77 mmol) in dry THF (5 mL) was added dropwise and stirred for 1 h. After completion of the reaction, the reaction was diluted with Et_2O (5 mL) and quenched by the slow addition of water (3 mL) and extracted into Et_2O (3 × 10 mL). The organic extract was washed with brine solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to yield a crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 9:1) to give **10** (320 mg, 82%) as a viscous liquid. $[\alpha]_D^{25}$ = +43.1 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.64 (m, 4 H, ArH), 7.44–7.32 (m, 6 H, ArH), 6.86 (dd, J = 11.5, 8.3 Hz, 1 H, $CH=CHCOCH_3$), 5.78 (dd, J = 11.5, 8.6 Hz, 1 H, $=CHCOCH_3$), 5.71 (d, J = 10.6 Hz, 1 H, CH=C), 5.16 (dt, J = 10.6 Hz, 1 H, =CHCHOMOM), 4.45–4.40 (m, 1 H, CHOTBDPS), 4.12 (s, 2 H, OCH_2O), 3.90 (dd, J = 9.6, 4.8 Hz, 1 H, CHOMOM), 3.70 (s, 3 H, $COCH_3$), 3.18 (s, 3 H, OCH_3), 2.39–2.27 (m, 2 H, $CH_2CH=CH$), 1.56–1.40 (m, 2 H), 1.38–1.1 (m, 4 H), 1.03 [s, 9 H $Si(CH_3)_3$], 0.78 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.8, 138.4, 136.1, 136.0, 129.5, 129.4, 127.5, 127.3, 126.5, 121.0, 93.5, 73.5, 69.3, 55.4, 51.4, 41.6, 38.5, 38.1, 29.7, 27.0, 26.6, 26.9, 22.6, 19.3, 14.0 ppm. MS (ESI): m/z = 547 $[M + Na]^+$.

Desacetylumuravumbolide (1a): To a solution of **10** (130 mg, 0.27 mmol) was added 3 M HCl/THF (1:1, 2 mL of 3 M HCL + 2 mL of THF), and the solution was stirred for 3 h at room temperature. After completion of the reaction, the reaction medium was washed with sat. $NaHCO_3$ solution and extracted into EtOAc. The respective organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated to give a crude residue, which was purified by silica gel column chromatography (hexane/EtOAc, 6:4) to afford **1a** (30 mg, 60%). $[\alpha]_D^{25}$ = –5.4 (c = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3429, 2924, 2855, 1726, 1377, 1243, 1082 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.88 (m, 1 H, CH=CHCOO), 6.0 (dd, J = 9.8, 2.2 Hz, 1 H, =CHCOO), 5.60–5.73 (m, 2 H, CH=CH), 5.25–5.36 (m, 1 H, CHOCO), 4.33–4.47 (m, 1 H, CHOH), 2.34–2.51 (m, 2H $CH_2CH=CH$), 2.2 (s, 1 H, OH), 1.45–1.70 (m, 2 H), 1.20–1.42 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 144.9, 137.9, 127.4, 121.4, 73.7, 67.7, 36.8, 29.9, 27.5, 22.6, 14.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}O_3$ $[M + H]^+$ 211.1329; found 211.1323.

Umuravumbolide (1b): To solution of compound **1a** (52 mg, 0.25 mmol) and pyridine (80 mg, 1 mmol) in DCM (1 mL) was added Ac_2O (0.05 g, 0.5 mmol), and the solution was stirred for 18 h. After completion of the reaction, the reaction was diluted with cold water and extracted into DCM (3 × 15 mL). The combined extract was dried with anhydrous Na_2SO_4 and concentrated to yield a crude residue, which was purified by silica gel chromatography (hexane/EtOAc, 8:2) to yield **1b** (61 mg, 97%). $[\alpha]_D^{25}$ = +33.4 (c = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2929, 2860, 1747, 1730, 1242 cm^{-1}. ^1H NMR (300 MHz, CDCl3): δ = 6.88 (m, 1 H, CH=CHCOO), 6.01 (dd, J = 9.8, 2.2 Hz, 1 H, =CHCOO), 5.71 (dd, J = 11.1, 8.0 Hz, 1 H, CH=CH), 5.31–5.56 (m, 3 H, =CH, CHOCO, $CHOCOCH_3$), 2.28–2.57 (m, 2 H, $CH_2CH=CH$), 2.02 (s, 3 H, $COCH_3$), 1.44–1.75 (m, 2 H), 1.20–1.43 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 163.4, 144.2, 131.7, 130.0, 121.7, 74.0, 69.5, 34.3, 30.1, 27.3, 22.5, 22.2, 17.0, 14.0 ppm. MS (ESI): m/z = 253 $[M + H]^+$.

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