Paper

A Concise and Stereoselective Total Synthesis of Pestalotioprolide C Using Ring-Closing Metathesis

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Abstract The stereoselective total synthesis of the pestalotioprolide C is disclosed in 13 linear steps in 4% overall yield. The key steps in this approach are a ring-closing-metathesis protocol for the construction of the 14-membered macrolide with *E*-olefinic bond, a Keck allylation, and a Sharpless kinetic resolution for the installation of desired stereocenters at C4 and C7.

Key words pestalotioprolide C, 14-membered macrolide, Keck allylation, Sharpless kinetic resolution, ring-closing metathesis

Fourteen-membered macrolides have received a lot of attention from researchers because of their prominent biological activities like antibacterial,¹ antifungal,² and cytocidal³ properties. Some of the 14-membered lactones are used in the treatment of bacterial infections (erythromycin,⁴ clarithromycin⁵). Recently, new 14-membered macrolides, pestalotioprolide B-H (Figure 1) were isolated from the Mangrove derived endophytic fungus Pestalotiopsis microspora by Liu and Prokch.⁶ Amongst these pestalosprolides, structurally pestalotioprolide C (1) is endowed with three stereogenic centers at C4, C7, C13 and an E-olefinic bond, which is in conjugation with an acid functional group that is locked in the form of a macrolide. The absolute stereochemistry at three stereocenters of pestalotioprolide C was determined as 4S, 7S, and 13S by X-ray crystal structure analysis. The key structural features and the potential biological activities of this group of macrolides motivated us to take up their synthesis.

Recently Sabitha et al.⁷ reported the first synthesis of pestalotioprolide C and its C7 epimer using Shinna macrolactonization as the key step. Our approach is strategically different, which involved ring-closing metathesis (RCM) as



the key step to assemble the macrolactone while Keck allylation and Sharpless kinetic resolution were invoked to acquire the required C7, C4 stereogenic centers and C13 was achieved through commercially available (*S*)-propylene oxide.

The retrosynthetic analysis of macrolide **1** is depicted in Scheme 1. RCM was envisioned to be the key macrocyclization strategy. The RCM precursor diene **8** could be realized from **9** by silyl deprotection, followed by acryloylation. Compound **9** could be generated from **10** by sequential transformations such as hydroboration, oxidation, vinylation, and Sharpless kinetic resolution. Further, the homoallylic alcohol **10** can be synthesized from **11** by hydroboration, and oxidation followed by Keck allylation. The alcohol **11** could be accessed from regioselective ring-opening reaction of epoxide **13** with 5-bromopent-1-ene (**12**).

Accordingly, to begin our synthesis, the commercially available starting material (S)-propylene oxide (**13**) on regioselective ring-opening reaction with freshly prepared pent-4-en-1-ylmagnesium bromide [generated in situ from



В

5-bromopent-1-ene (**12**) and Mg] in the presence of catalytic amount of Cul (10 mol%)^{8a} in anhydrous THF furnished **14**^{8b} in 86% yield (Scheme 2). Next, protection of the ensuing hydroxyl group of olefinic alcohol **14** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in CH₂Cl₂ and imidazole afforded **11** in 91% yield. Subsequently, the terminal olefin in compound **11** was transformed into primary alcohol by hydroboration-oxidation⁹ reaction set with 9-BBN and hydrogen peroxide to result in **15** (79% yield). The thus generated primary alcohol **15** was oxidized using IBX and DMSO in CH₂Cl₂ at 0 °C to room temperature for 2 hours to provide the corresponding aldehyde. Immediately, this aldehyde was subjected to asymmetric Keck allylation¹⁰ [(*R*)-BINOL, Ti(O*i*-Pr)₄ and allyltributyltin in CH₂Cl₂ at -20 °C, 36 h] to afford the homoallylic alcohol **10** in 76% yield with high

diastereoselectivity (dr 96:4 as determined by HPLC). The stereochemical outcome of this reaction is consistent with the model for Keck allylation, wherein (R)-BINOL provides the *S*-enantiomer of the homoallylic alcohol,¹⁰ which was confirmed by Mosher ester analysis¹¹ (see the Supporting Information for details).

After establishing the stereochemistry, protection of the homoallylic hydroxy group in **10** as its MOM ether was accomplished by the treating with MOM-Cl and DIPEA in CH_2Cl_2 at 0 °C to room temperature to afford **16** in 87% yield. Next, the terminal olefin **16** was subjected to hydroboration-oxidation with 9-BBN and hydrogen peroxide to afford primary alcohol **17** in 80% yield. The thus obtained primary alcohol **17** was oxidized using Dess-Martin reagent to offer the corresponding aldehyde, which was treated with



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Scheme 2 Reagents and conditions: a) pent-4-en-1-yl magnesium bromide, Cul, anhyd THF, -78 °C to r.t., 3 h, 86%; b) TBDPSCl, imidazole, CH₂Cl₂, 0 °C to r.t., 12 h, 91%; c) 9-BBN, THF, NaOH, H₂O₂, 0 °C to r.t., 8 h, 79%; d) (i) IBX, DMSO, CH₂Cl₂, 0 °C to r.t., 2 h; (ii) (*R*)-BINOL, allyltributyltin, Ti(O*i*-Pr)₄, -78 °C, 36 h, 76% (over two steps); e) MOM-Cl, DIPEA, CH₂Cl₂, 0 °C to r.t., 4 h, 87%; f) 9-BBN, THF, NaOH, H₂O₂, 0 °C to r.t., 8 h, 80%; g) (i) DMP, CH₂Cl₂, 0 °C to r.t., 2 h, (ii) vinylmagnesium bromide, THF, -78 °C, 1 h, 75% (over two steps).



С

vinylmagnesium bromide (1 M solution in THF) at -78 °C to furnish a mixture of diastereomers **18** (*dr* 48:52 as determined by HPLC).

Interestingly, both the diastreomers were found to have same R_f values and our attempts to separate them were unsuccessful. Alternatively, allylic alcohol **18** was protected as its MOM ether in an effort to facilitate the separation of diasteromers, however, their separation could not be realized. Therefore, we resorted to the Sharpless kinetic resolution to garner the *S*-configured allylic alcohol in optically pure form. Thus, alcohol **18** (Scheme 3) was resolved under Sharpless kinetic resolution¹² [Ti(Oi-Pr)₄, (–)-DIPT and TBHP in CH₂Cl₂ at –20 °C, 16 h] conditions to afford the allylic alcohol **18a** (*dr* 97:3 by HPLC analysis) in 44% yield, which was separated from epoxy alcohol **19**. Later, the absolute stereochemistry of the thus-generated stereocenter in allylic alcohol **18a** was established on completion of the total synthesis and correlating with the reported data.^{6,7}

Next, the allylic alcohol **18a** (Scheme 4) was protected as its MOM ether (MOM-Cl and DIPEA in CH_2Cl_2 at 0 °C to r.t.) to furnish the MOM protected olefin **9** in 85% yield. Then deprotection of the silyl group by TBAF in THF gave the secondary alcohol **20** in 89% yield. Esterification of secondary alcohol **20** with acryloyl chloride and triethylamine in CH_2Cl_2 provided the RCM precursor diene **8** in 86% yield. Our next task is the construction of macrolactone by invoking the ring-closing metathesis reaction. Thus, initially we tried RCM with G-I catalyst in CH_2Cl_2 at room temperature conditions. However, under these conditions, the diene **8** remained inert and it was observed that the reaction was not initiated even at longer reaction times. Next, when the reaction mixture was run at higher temperature for 12 hours, lower yields (<30%) of the cyclized product was obtained. Higher catalyst loading of G-I (up to 10 mol%) did not improve the yield. To enhance the yield of macrocycle product, next we conducted the RCM¹³ reaction of diene **8** under G-II conditions at reflux for 12 hours to furnish **21** with an *E*-olefinic bond (J = 15.8 Hz) in 65% yield. Finally, the deprotection of MOM groups on exposure to 6 N HCl afforded the target compound **1** in 88% yield.

The ¹H and ¹³C NMR data of synthetic compound **1** were in agreement with the natural product and the optical rotation has shown equal sign to that of natural product.⁶ In summary, we have accomplished the stereoselective total synthesis of pestalotioprolide C(1) in 13 linear steps by invoking Keck allylation, Sharpless kinetic resolution, and ring-closing metathesis as key steps in an overall yield of 4%.

¹H NMR spectra were recorded at 300/400/ 500 MHz, as specified, ¹³C NMR spectra were recorded at 100 or 125 MHz, as specified. ¹H and ¹³C NMR spectra were obtained from CDCl₃ or CD₃OD as solvent. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, *J*, are in hertz (Hz). Reactions were carried out under N₂ in anhydrous solvents. Air-sensitive reagents were transferred by syringe and double-ended needle. All reactions were monitored by TLC and silica-coated plates were visualized by exposure to ultraviolet light and/or α -naphthol charring. Organic solutions were dried (Na₂SO₄) and concentrated below 40 °C under reduced pressure. All column chromatographic (CC) separations were





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G. R. Kundoor et al.

performed using silica gel (SiO₂; 60–120 mesh) with EtOAc and *n*-hexane as eluents. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials. IR spectra were recorded on a Bruker alpha spectrometer. Optical rotations were measured with a JASCO P-2000 instrument and [α]_D values were in units of 10⁻¹ deg cm² g⁻¹ at 20 °C, Elemental analysis was performed with an Elemental Micro Qube CHN analyzer and High-resolution mass spectra were recorded by using a Thermo Scientific Orbitrap.

Chromatography was carried out using a Shimadzu HPLC system (20AD Japan), consisting of a Binary Pump and Degasser. The separation of analytes was performed on C18 (250 mm × 4.6 mm i.d, 5 μ m) using a mobile phase consisting of MeCN/H₂O (90:10, v/v), pumped at a flow rate of 1.0 mL/min. The injection volume was 20 μ L and the total analysis time per sample was 15 min.

(S)-tert-Butyl(oct-7-en-2-yloxy)diphenylsilane (11)

To a solution of alcohol **14**^{8b} (2 g, 15.62 mmol) in anhyd CH₂Cl₂ (45 mL) was added imidazole (2.1 g, 31.17 mmol) at 0 °C and the mixture was stirred for 15 min. Then TBDPSCI (5.1 mL, 18.69 mmol) was added and the mixture was stirred at r.t. for 12 h. After completion of the reaction, the solvent was evaporated and the residue purified by column chromatography on silica gel (15:1, hexane/EtOAc) to afford **11** (5.2 g, 91%) as a colorless oil; $[\alpha]_D^{25}$ – 5.4 (*c* 0.9, CHCl₃).

IR (neat): 2930, 2857, 1468, 1437, 1106 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.69–7.66 (m, 4 H), 7.41–7.34 (m, 6 H), 5.76 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 4.99–4.88 (m, 2 H), 3.85–3.81 (m, 1 H), 1.96 (t, *J* = 6.8 Hz, 2 H), 1.51–1.24 (m, 6 H), 1.06–1.03 (m, 12 H). ¹³C NMR (100 MHz, CDCl₃): δ = 139.1, 135.9, 135.0, 134.6, 129.4, 129.4, 127.5, 127.4, 114.2, 69.6, 39.3, 33.7, 28.9, 27.1, 24.8, 23.2, 19.3. Anal. Calcd for $C_{24}H_{34}$ OSi: C, 78.63; H, 9.35. Found: C, 78.32; H, 9.42.

(S)-7-[(tert-Butyldiphenylsilyl)oxy]octan-1-ol (15)

To a stirred solution of terminal olefin **11** (4.6 g, 12.56 mmol) in anhyd THF (20 mL) at 0 °C was added 9-BBN (0.5 M in THF, 37.0 mL, 18.85 mmol) dropwise over 10 min. After 6 h at r.t., a solution of aq 3 M NaOH (20 mL) and 35% H₂O₂ (20 mL) was added portionwise at 0 °C. After 2 h at r.t., the reaction mixture was poured into brine (50 mL) and extracted with Et₂O (2 × 100 mL). The combined organic layers were dried (Na₂SO₄), concentrated, and the residue was purified by flash chromatography on silica gel (9:1, hexane/EtOAc) to afford alcohol **15** (3.8 g, 79%) as a colorless oil; $[\alpha]_D^{20}$ –40.9 (*c* 0.9, CHCl₃).

IR (neat): 3363, 2927, 2856, 1447, 1167, 1107, 1052, 754 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.71–7.64 (m, 4 H), 7.46–7.32 (m, 6 H), 3.90–3.77 (m, 1 H), 3.60 (t, J = 6.6 Hz, 2 H), 1.52–1.20 (m, 10 H), 1.08–1.00 (m, 12 H).

¹³C NMR (100 MHz, CDCl₃): δ = 135.9, 134.9, 134.7, 129.4, 129.4, 127.4, 127.4, 69.6, 63.1, 39.4, 32.7, 29.4, 27.1, 25.7, 25.2, 23.2, 19.3. HRMS: *m/z* [M + Na]⁺ calcd for C₂₄H₃₆O₂SiNa: 407.2382; found: 407.2390.

(4S,10S)-10-[(tert-Butyldiphenylsilyl)oxy]undec-1-en-4-ol (10)

To an ice-cooled solution of IBX (3.6 g, 12.85 mmol) in DMSO (2.9 mL, 38.58 mmol) and CH_2Cl_2 (25 mL) was added a solution of alcohol **15** (3.3 g, 8.59 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad and washed with CH_2Cl_2 (3 × 25 mL). The organic filtrate was sequentially washed with H_2O (25 mL) and brine (25 mL), later dried (Na₂SO₄), and concentrated in vacuo. The crude aldehyde (3 g, 90%, viscous liquid) was immediately subjected to the next reaction without further purification.

To a mixture of (*R*)-BINOL (0.43 g, 1.56 mmol), molecular sieves (4Å) in CH₂Cl₂ (25 mL) was added Ti(Oi-Pr)₄ (0.23 mL, 0.78 mmol), and the resultant mixture was heated under reflux for 1 h. To the reaction mixture at r.t. was added the above prepared aldehyde (3 g, 7.85 mmol) in CH₂Cl₂ (6 mL), and the resultant mixture was stirred for 10 min. The mixture was cooled to -78 °C and treated with allyltributyltin (2.6 mL, 8.57 mmol). The resultant mixture was stirred at -20 °C for 76 h. The mixture was quenched with sat. aq NaHCO₃ at -78 °C. The resultant mixture was diluted with CH₂Cl₂ (25 mL), allowed to warm to r.t. over 1.5 h, and filtered through a pad of Celite. The filtrate was extracted with CH₂Cl₂ (3 × 30 mL), and the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (9:1, hexane/EtOAc) to afford the homoallylic alcohol **10** (2.52 g, 76%) as a pale yellow oil; $[\alpha]_D^{20} - 7.1$ (*c* 0.4, CHCl₃).

IR (neat): 3395, 2930, 2857, 1464, 1427, 1108, 702 cm⁻¹

¹H NMR (500 MHz, $CDCI_3$): δ = 7.70–7.65 (m, 4 H), 7.44–7.33 (m, 6 H), 5.82 (dddd, *J* = 14.3, 9.3, 7.7, 6.8 Hz, 1 H), 5.13 (dd, *J* = 13.7, 1.4 Hz, 2 H), 3.83 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.61 (s, 1 H), 2.33–2.25 (m, 1 H), 2.16–2.08 (m, 1 H), 1.50–1.25 (m, 10 H), 1.06–1.03 (m, 12 H).

 ^{13}C NMR (125 MHz, CDCl_3): δ = 135.9, 134.9, 134.7, 129.5, 129.4, 127.5, 127.4, 118.0, 70.7, 69.6, 42.0, 39.4, 36.8, 29.7, 27.1, 25.6, 25.2, 23.3, 19.3.

HRMS: $m/z [M + NH_4]^*$ calcd for $C_{27}H_{44}NO_2Si$: 442.3136; found: 442.3162.

(4S/R,10S)-10-[(tert-Butyldiphenylsilyl)oxy]undec-1-en-4-ol¹⁴

Conducted Grignard allylation of aldehyde (aldehyde taken from above, which was used for the Keck allylation) to produce homoallylic alcohol (dr 1:1 as determined by HPLC; see Supporting Information).

Mosher Method; General Procedure

Mosher acid (*S* or *R*) (5.4 mg, 0.023 mmol), DCC (4.8 mg, 0.023 mmol), and DMAP (cat.) were added to a solution of **10** (5 mg, 0.011 mmol) in CH_2Cl_2 (2 mL) at r.t. and the reaction mixture was stirred for 4 h. After completion of the reaction (indicated by TLC), the mixture was filtered through a short pad of Celite and the Celite pad was washed with Et_2O (25 mL). Et_2O was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (9.7:0.3, hexane/EtOAc) to afford compound **10a** (if *S*-Mosher acid is used) and **10b** (if *R*-Mosher acid is used).

(4*S*,10*S*)-10-[(*tert*-Butyldiphenylsilyl)oxy]undec-1-en-4-yl (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (10a)

Yield: 6.6 mg (88%); pale yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.69–7.63 (m, 4 H), 7.56–7.51 (m, 2 H), 7.43–7.34 (m, 9 H), 5.75 (ddt, *J* = 16.5, 10.8, 7.0 Hz, 1 H), 5.15–5.08 (m, 3 H), 3.81–3.78 (m, 1 H), 3.55 (s, 3 H), 2.40 (t, *J* = 6.5 Hz, 2 H), 1.54–1.28 (m, 4 H), 1.19–1.06 (m, 6 H), 1.06–1.02 (m, 12 H).

(4*S*,10*S*)-10-[(*tert*-Butyldiphenylsilyl)oxy]undec-1-en-4-yl (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (10b)

Yield: 6.8 mg (91%); pale yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.69–7.65 (m, 4 H), 7.56–7.51 (m, 2 H), 7.42–7.33 (m, 9 H), 5.63 (ddt, *J* = 19.9, 9.6, 7.1 Hz, 1 H), 5.13–5.07 (m, 1 H), 5.04–4.97 (m, 2 H), 3.84–3.80 (m, 1 H), 3.57–3.54 (m, 3 H), 2.33 (t, *J* = 6.2 Hz, 2 H), 1.55–1.30 (m, 4 H), 1.24–1.12 (m, 6 H), 1.07–1.02 (m, 12 H).

G. R. Kundoor et al.

(5*S*,11*S*)-5-Allyl-11,14,14-trimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecane (16)

To a solution of homoallylic alcohol **10** (2.3 g, 5.47 mmol) in anhyd CH₂Cl₂ (15 mL) at 0 °C were successively added DIPEA (2.80 mL, 16.35 mmol), a catalytic amount of DMAP, and MOMCl (0.62 mL, 8.20 mmol). The mixture was stirred for 4 h at r.t., then the reaction was quenched by adding H₂O (8 mL), and the mixture was extracted with CH₂Cl₂ (30 mL). The organic layer was washed with brine (15 mL), dried (Na₂SO₄), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15:1, hexane/EtOAc) to afford **16** (2.2 g, 87%); pale yellow oil; $[\alpha]_{\rm p}^{20}$ –6.6 (*c* 0.6, CHCl₃).

IR (neat): 2931, 2857, 1467, 1428, 1107, 1047, 703 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.70–7.66 (m, 4 H), 7.42–7.34 (m, 6 H), 5.81 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1 H), 5.12–5.03 (m, 2 H), 4.65 (dd, *J* = 18.0, 6.9 Hz, 2 H), 3.84–3.78 (m, 1 H), 3.59–3.55 (m, 1 H), 3.36 (s, 3 H), 2.27 (td, *J* = 5.9, 1.1 Hz, 2 H), 1.46–1.16 (m, 10 H), 1.06–1.03 (m, 12 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 135.9, 135.0, 134.9, 134.6, 129.4, 129.4, 127.4, 127.4, 117.0, 95.4, 69.6, 55.5, 39.4, 38.9, 34.1, 29.7, 27.1, 25.3, 25.2, 23.2, 19.3.

HRMS: m/z [M + Na]⁺ calcd for C₂₉H₄₄O₃SiNa: 491.2951; found: 491.2948.

(4*S*,10*S*)-10-[(*tert*-Butyldiphenylsilyl)oxy]-4-(methoxymethoxy)undecan-1-ol (17)

To a stirred solution of olefin **16** (2.1 g, 4.47 mmol) in anhyd THF (10 mL) at 0 °C was added 9-BBN (0.5 M in THF, 13.42 mL, 6.71 mmol) dropwise over 10 min. After 6 h at r.t., a solution of aq 3 M NaOH (9 mL) and 35% H₂O₂ (9 mL) were added portionwise at 0 °C. After 2 h at r.t., the mixture was poured into brine (40 mL) and extracted with Et₂O (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), concentrated, and the residue was purified by flash chromatography on silica gel (9:1, hexane/EtOAc) to afford alcohol **17** (1.73 g, 80%) as a colorless oil; $[\alpha]_D^{20}$ +18.9 (*c* 0.3, CHCl₃).

IR (neat): 3419, 2930, 2856, 1466, 1427, 1106, 1032, 700 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.73–7.62 (m, 4 H), 7.45–7.33 (m, 6 H), 4.65 (s, 2 H), 3.84–3.79 (m, 1 H), 3.70–3.61 (m, 2 H), 3.60–3.50 (m, 1 H), 3.38 (s, 3 H), 1.65–1.18 (m, 14 H), 1.08–1.03 (m, 12 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 135.9, 134.9, 134.6, 129.4, 129.4, 127.4, 127.4, 95.4, 77.4, 69.6, 63.1, 55.6, 39.4, 34.1, 30.6, 29.8, 28.4, 27.1, 25.3, 25.2, 23.2, 19.3.

HRMS: m/z [M + Na]⁺ calcd for C₂₉H₄₆O₄SiNa: 509.3057; found: 509.3057.

(65,125)-12-[(*tert*-Butyldiphenylsilyl)oxy]-6-(methoxymethoxy)tridec-1-en-3-ol (18)

To a solution of alcohol **17** (1.7 g, 3.49 mmol) in anhyd CH_2Cl_2 (15 mL) cooled to 0 °C was added Dess-Martin periodinane reagent (1.8 g, 4.2 mmol) was added, and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and $NaHCO_3$ (12 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2 - Cl_2 (40 mL). The extract was washed sequentially with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give the corresponding aldehyde, which was used in the next step without further characterization.

To a stirred solution of the above prepared aldehyde (1.6 g, 3.29 mmol) in anhyd THF (15 mL) was added a solution of vinylmagnesium bromide (1 M solution in THF, 4.9 mL, 4.93 mmol) at -78 °C. The

resulting mixture was stirred at –78 °C for 1 h, quenched by the addition of aq NH₄Cl, and then warmed to r.t. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (9:1, hexane/EtOAc) to afford allylic alcohol **18** (1.4 g, 75% over two steps) as a pale yellow oil.

IR (neat): 3434, 2929, 2856, 1427, 1464, 1105, 1034, 701 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.69–7.66 (m, 4 H), 7.42–7.34 (m, 6 H), 5.87 (ddd, J = 17.1, 10.4, 6.0 Hz, 1 H), 5.24 (ddd, J = 17.2, 2.6, 1.3 Hz, 1 H), 5.11 (ddd, J = 10.4, 3.4, 1.4 Hz, 1 H), 4.65–4.63 (m, 2 H), 4.11 (s, 1 H), 3.84–3.79 (m, 1 H), 3.59–3.52 (m, 1 H), 3.37 (dd, J = 1.7, 0.6 Hz, 3 H), 1.54–1.14 (m, 14 H), 1.07–1.03 (m, 12 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 141.2, 141.1, 135.9, 135.0, 134.6, 129.4, 129.4, 127.4, 127.4, 114.7, 114.6, 95.4, 95.3, 77.4, 76.7, 73.3, 73.0, 69.6, 55.6, 39.4, 34.2, 34.1, 32.6, 32.4, 30.1, 29.84, 3.63, 27.1, 25.3, 25.2, 23.2, 19.3.

HRMS: $m/z [M + Na]^+$ calcd for $C_{31}H_{48}O_4SiNa$: 535.3214; found: 535.3213.

(35,65,125)-12-[(*tert*-Butyldiphenylsilyl)oxy]-6-(methoxymethoxy)tridec-1-en-3-ol (18a)

To a suspension of powdered molecular sieves (4Å) in anhyd CH₂Cl₂ (15 mL) were added sequentially Ti(Oi-Pr)₄ (0.3 mL, 2.53 mmol) and (-)-DIPT (0.6 mL, 3.034 mmol) at -20 °C. After stirring for 0.5 h, allyl alcohol 18 (1.3 g, 2.53 mmol) in anhyd CH₂Cl₂ (6 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (5 M, 1.0 mL, 5.06 mmol) was added and after stirring for another 16 h at the same temperature, the reaction mixture was quenched by the addition of H₂O (5 mL). It was then kept at r.t. and stirred for 30 min. After re-cooling to 0 °C, aq NaOH (30% w/v, 5 mL saturated with brine) was added and the mixture was stirred at 0 °C for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried (Na₂-SO₄), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9:1, hexane/EtOAc) to give the allylic alcohol **18a** (0.57 g, 44%) as a pale yellow oil; $[\alpha]_{D}^{20}$ -15.3 (c 0.8, CHCl₂).

IR (neat): 3434, 2929, 2856, 1427, 1464, 1105, 1034, 701 cm⁻¹.

¹H NMR (500 MHz, $CDCI_3$): δ = 7.69–7.66 (m, 4 H), 7.42–7.34 (m, 6 H), 5.92–5.82 (m, 1 H), 5.24 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.11 (dt, *J* = 10.4, 1.3 Hz, 1 H), 4.65 (s, 2 H), 4.14–4.08 (m, 1 H), 3.84–3.78 (m, 1 H), 3.59– 3.52 (m, 1 H), 3.37 (s, 3 H), 1.56–1.21 (m, 14 H), 1.07–1.01 (m, 12 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 141.2, 135.9, 135.0, 134.6, 129.4, 129.4, 127.4, 127.4, 114.6, 95.4, 77.4, 73.2, 69.6, 55.6, 39.4, 34.2, 32.6, 30.1, 29.8, 27.1, 25.3, 25.2, 23.2, 19.3.

HRMS: m/z [M + Na]⁺ calcd for C₃₁H₄₈O₄SiNa: 535.3214; found: 535.3213.

(55,85,145)-8-(Methoxymethoxy)-14,17,17-trimethyl-16,16-diphenyl-5-vinyl-2,4,15-trioxa-16-silaoctadecane (9)

To a solution of allylic alcohol **19** (0.41 g, 0.79 mmol) in anhyd CH_2CI_2 (4 mL) at 0 °C were successively added DIPEA (0.4 mL, 2.33 mmol), a catalytic amount of DMAP, and MOMCI (0.08 mL, 1.18 mmol). The mixture was stirred for 4 h at r.t., then the reaction was quenched by adding H_2O (3 mL), and the mixture was extracted with CH_2CI_2 (3 × 8 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and the solvent was evaporated under reduced pres-

G. R. Kundoor et al.

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sure. The residue was purified by column chromatography on silica gel (15:1, hexane/EtOAc) to afford compound **9** (0.37 g 85%) as a pale yellow oil; $[\alpha]_{D}^{20}$ -31.8 (*c* 0.3, CHCl₃).

IR (neat): 2930, 2856, 1465, 1147, 1101, 1030 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.69–7.66 (m, 4 H), 7.42–7.34 (m, 6 H), 5.67 (ddd, *J* = 17.9, 10.4, 7.7 Hz, 1 H), 5.23–5.17 (m, 2 H), 4.70 (d, *J* = 6.7 Hz, 1 H), 4.64 (s, 2 H), 4.54 (d, *J* = 6.7 Hz, 1 H), 3.98 (dd, *J* = 13.3, 6.5 Hz, 1 H), 3.84–3.78 (m, 1 H), 3.54–3.49 (m, 1 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 1.56–1.14 (m, 14 H), 1.06–1.03 (m, 12 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 138.3, 135.9, 135.0, 134.6, 129.4, 129.4, 127.4, 127.4, 117.3, 95.4, 93.8, 77.6, 69.6, 55.5, 55.5, 39.4, 34.3, 31.1, 30.0, 29.9, 27.1, 25.3, 25.2, 23.2, 19.3.

HRMS: m/z [M + Na]⁺ calcd for C₃₃H₅₂O₅SiNa: 579.3476; found: 579.3464.

(2S,8S,11S)-8,11-Bis(methoxymethoxy)tridec-12-en-2-ol (20)

To compound **9** (0.28 g, 0.50 mmol) was taken in anhyd THF (3 mL) THF was added TBAF (1 M in THF, 0.74 mL, 0.74 mmol) and the reaction mixture was then stirred for 12 h at r.t. THF was then evaporated, and H₂O (2 mL) was added, and the reaction mixture was extracted with EtOAc (20 mL). The organic layer was washed with sat. aq NaH-CO₃ (4 mL) and brine (4 mL), and dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (7:3, hexane/EtOAc) to afford alcohol **20** (0.14 g, 89% yield) as a colorless oil; $[\alpha]_D^{20}$ –26.3 (*c* 0.3, CHCl₃).

IR (neat): 3468, 2927, 2854, 1461, 1147, 1059 cm⁻¹.

¹H NMR (500 MHz, $CDCl_3$): δ = 5.67 (ddd, *J* = 17.3, 10.4, 7.7 Hz, 1 H), 5.23–5.17 (m, 2 H), 4.70 (d, *J* = 6.7 Hz, 1 H), 4.65 (s, 2 H), 4.54 (d, *J* = 6.7 Hz, 1 H), 3.98 (dd, *J* = 13.5, 6.4 Hz, 1 H), 3.83–3.75 (m, 1 H), 3.58–3.51 (m, 1 H), 3.38 (s, 3 H), 3.38 (s, 3 H), 1.63–1.32 (m, 14 H), 1.19 (d, *J* = 6.2 Hz, 3 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 138.3, 117.3, 95.4, 93.8, 77.5, 77.2, 68.1, 55.6, 55.5, 39.3, 34.3, 31.1, 30.1, 29.8, 25.7, 25.2, 23.5.

HRMS: m/z [M + Na]⁺ calcd for C₁₇H₃₄O₅Na: 341.2298; found: 341.2276.

(25,85,115)-8,11-Bis(methoxymethoxy)tridec-12-en-2-yl Acrylate (8)

To a cooled (0 °C) solution of alcohol **20** (0.13 mg, 0.40 mmol) in anhyd CH₂Cl₂ (4 mL) were added Et₃N (0.11 mL, 0.80 mmol) and acryloyl chloride (0.04 mL, 0.48 mmol) and stirred at the same temperature for 0.5 h. After completion of the reaction, the reaction mixture was quenched with sat. aq NaHCO₃ (4 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phases were washed with brine (6 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (9:1, hexane/EtOAc) to afford **8** (0.12 g, 86%) as a pale yellow liquid; $[\alpha]_D^{20}$ –45.5 (*c* 0.4, CHCl₃).

IR (neat): 2931, 2859, 1720, 1638, 1198, 1096, 1029 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 6.38$ (dd, J = 17.3, 1.2 Hz, 1 H), 6.10 (dd, J = 17.3, 10.4 Hz, 1 H), 5.79 (dd, J = 10.4, 1.2 Hz, 1 H), 5.67 (ddd, J = 17.8, 10.4, 7.7 Hz, 1 H), 5.24–5.16 (m, 2 H), 5.03–4.93 (m, 1 H), 4.70 (d, J = 6.7 Hz, 1 H), 4.64 (s, 2 H), 4.54 (d, J = 6.7 Hz, 1 H), 3.97 (dd, J = 13.1, 6.5 Hz, 1 H), 3.58–3.49 (m, 1 H), 3.37 (s, 6 H), 1.68–1.58 (m, 4 H), 1.53–1.44 (m, 4 H), 1.42–1.27 (m, 6 H), 1.24 (d, J = 6.3 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 165.9, 138.3, 130.1, 129.1, 117.3, 95.4, 93.8, 77.6, 71.2, 55.5, 55.4, 35.9, 34.2, 31.1, 30.0, 29.6, 25.4, 25.2, 19.9.

HRMS: m/z [M + Na]⁺ calcd for C₂₀H₃₆O₆Na: 395.2404; found: 395.2395.

(55,85,145,E)-5,8-Bis(methoxymethoxy)-14-methyloxacyclotetradec-3-en-2-one (21)

To a solution of diene **8** (0.1 g, 0.26 mmol) in anhyd CH₂Cl₂ (150 mL) was added second-generation Grubbs catalyst (0.02 g, 0.026 mmol) and the mixture was degassed thoroughly under N₂. The mixture was refluxed for 12 h, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (8:2, hexane/EtOAc) to afford **21** (0.06 g, 65%) as a colorless liquid; $[\alpha]_D^{20}$ +1.2 (*c* 0.2, CHCl₃).

IR (neat): 2926, 2855, 1716, 1656, 1149, 1096, 1037 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.79 (dd, *J* = 15.8, 5.8 Hz, 1 H), 6.07 (dd, *J* = 15.8, 1.4 Hz, 1 H), 5.08 (ddd, *J* = 10.1, 6.3, 3.3 Hz, 1 H), 4.68 (d, *J* = 7.0 Hz, 1 H), 4.63 (s, 2 H), 4.59 (d, *J* = 7.0 Hz, 1 H), 4.41 (dt, *J* = 10.2, 4.4 Hz, 1 H), 3.55 (dq, *J* = 12.5, 4.2 Hz, 1 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 1.95–1.87 (m, 1 H), 1.78 (ddd, *J* = 14.1, 8.4, 4.2 Hz, 1 H), 1.75–1.68 (m, 1 H), 1.65–1.60 (m, 1 H), 1.52–1.39 (m, 6 H), 1.35–1.28 (m, 2 H), 1.26 (d, *J* = 6.3 Hz, 3 H), 1.18–1.15 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 165.7, 147.0, 123.5, 94.9, 94.5, 75.3, 74.1, 72.7, 55.5, 55.5, 34.3, 33.0, 29.4, 29.0, 27.2, 26.1, 24.8, 20.6.

HRMS: m/z [M + Na]⁺ calcd for C₁₈H₃₂O₆Na: 367.2091; found: 367.2081.

(55,85,145,E)-5,8-Dihydroxy-14-methyloxacyclotetradec-3-en-2one (Pestalotioprolide C, 1)^{6,7}

To a stirred solution of **21** (52 mg, 0.15 mmol) in THF (1.5 mL) was added aq 6 N HCl (0.1 mL) and stirred for 2 h. After completion of reaction, the mixture was quenched with solid NaHCO₃ (0.1 g) at 0 °C and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (3:7, hexane/EtOAc) to give the desired compound **1** (34 mg, 88%) as a colorless solid; mp 122–124 °C; $[\alpha]_D^{20}$ +36.8 (*c* 0.2, MeOH); $[\alpha]_D$ for natural product:⁶ $[\alpha]_D^{20}$ +40 (*c* 1.4, MeOH).

IR (neat): 3432, 2925, 2854, 1714, 1458, 1266, 1108 cm⁻¹.

¹H NMR (500 MHz, CD₃OD): δ = 6.98 (dd, *J* = 15.7, 4.2 Hz, 1 H), 6.02 (dd, *J* = 15.7, 1.8 Hz, 1 H), 5.05–5.00 (m, 1 H), 4.52–4.47 (m, 1 H), 3.63–3.55 (m, 1 H), 1.98–1.90 (m, 1 H), 1.80–1.71 (m, 2 H), 1.62–1.32 (m, 9 H), 1.29 (d, *J* = 6.3 Hz, 3 H), 1.28–1.18 (m, 2 H).

 ^{13}C NMR (100 MHz, CD₃OD): δ = 167.8, 152.0, 121.8, 73.7, 70.7, 70.7, 36.2, 35.8, 32.6, 30.4, 29.6, 26.2, 25.0, 21.0.

HRMS: *m*/*z* [M + H]⁺ calcd for C₁₄H₂₅O₄: 257.1747; found: 257.1748.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589152.

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G. R. Kundoor et al.

References

- McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. Antibiot. Chemother. **1952**, *2*, 281.
- (2) (a) Yang, S. W.; Chan, T. M.; Terracciano, J.; Loebenberg, D.; Patel, M.; Chu, M. J. Antibiot. 2005, 58, 535. (b) Mandala, S. M.; Thornton, R. A.; Milligan, J.; Rosenbach, M.; Calvo, M. G.; Bull, H. G.; Harris, G.; Abruzzo, G. K.; Flattery, A. M.; Gill, C. J.; Bartizal, K.; Dreikorn, S.; Kurtz, M. B. J. Biol. Chem. 1998, 273, 14942.
- (3) Kim, Y. J.; Furihata, K.; Shimazu, A.; Furihata, K.; Seto, H. J. Antibiot. **1991**, 44, 1280.
- (4) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/ 050611s027lbl.pdf.
- (5) https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/ 050662s044s050,50698s026s030,050775s015s019lbl.pdf.
- (6) Liu, S.; Dai, H.; Makhlonfi, G. J. Nat. Prod. 2016, 79, 2332.
- (7) Sabitha, G.; Nagi Reddy, K. S. Tetrahedron Lett. 2017, 58, 1198.
- (8) (a) Zhou, Y.; Yang, P.; Li, S.; Wang, L.; Yin, J.; Zhong, J.; Dong, Y.;
- Liu, S.; Wang, M.; Bian, Q. *Tetrahedron: Asymmetry* **2017**, *28*, 338. (b) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

- (9) Joseph, D. P.; Stephen, P. W. J. Org. Lett. 2009, 11, 5086.
- (10) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. J. Am. Chem. Soc. 1993, 115, 8467. (b) Radha Krishna, P.; Karunakar Reddy, P.; Srinivas, P. Tetrahedron 2012, 68, 841. (c) Bhoite, S. P.; Kamble, R. B.; Suryavanshi, G. M. Tetrahedron Lett. 2015, 56, 4704.

Paper

- (11) (a) Hoye, T. R.; Jeffery, C. S.; Shao, F. Nat. Protoc. 2007, 2, 2451.
 (b) Dale, J. A.; Dull, D. A.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543.
- (12) (a) Sharpless, K. B.; Behrens, H. C.; Katsuki, T.; Lee, M. W. A.; Martin, S. V.; Takatani, M.; Viti, M. S.; Walker, J. F.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. (b) Show, K.; Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1212.
- (13) Seetharamsingh, B.; Pankaj, V. K.; Srinivasa Reddy, D. J. Org. Chem. 2016, 81, 290.
- (14) This experiment was conducted based on the referees' suggestions in order to verify the $t_{\rm R}$ of the minor isomer in compound **10** on HPLC.