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Total Synthesis of (+)-Seimatopolide A

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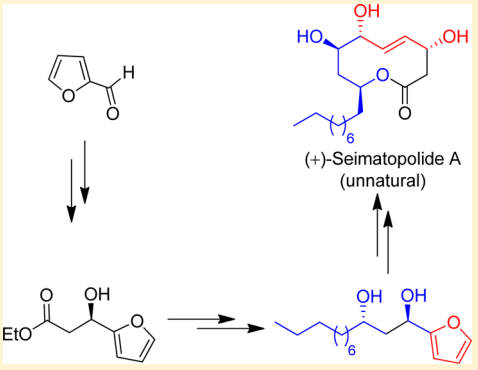
Supporting Information

ABSTRACT: Total synthesis of 10-membered lactone (+)-seimatopolide A is presented from furfural. Key reactions in the present strategy include the effective use of furan as a *E*-but-2-ene-1,4-dione surrogate, Nagao acetate aldol reaction, and Shiina lactonization.



(−)-Seimatopolides A ((−)-**1**) and B ((−)-**2**) (Figure 1) are 10-membered lactones isolated from the fungus *Seimatosporium*

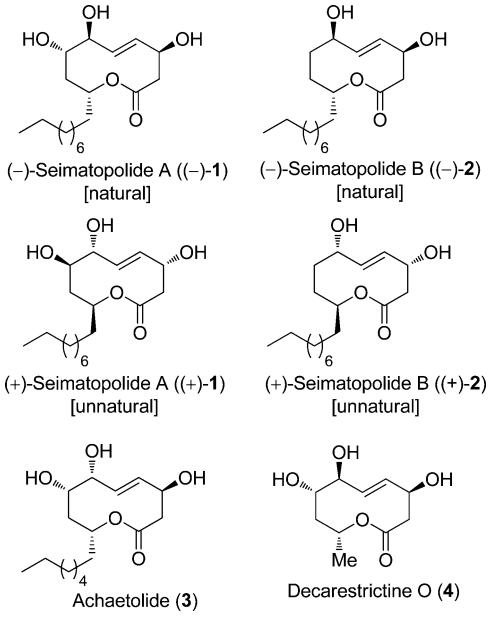


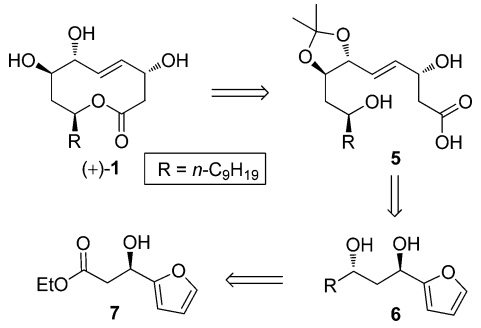
Figure 1. Bioactive 10-membered lactones.

discosioides by Hiep et al. in 2012.[1] Seimatopolides are structurally similar to other 10-membered lactone natural products such as achaetolide (**3**), decarestrictine O (**4**). Seimatopolides are shown to activate the γ-subtype peroxysome prolifirator-activated receptors (PPAR-γ), which is an apparent pivotal process in the regulation of type 2 diabetes.

Hitherto four total syntheses were reported for seimatopolide A.[2] All the reported syntheses for seimatopolide A involve ring closing metathesis (RCM) as the key step for the construction of the macrolactone as well as for the installation of the key *E*-double bond at the C4-position. We have been interested in the synthesis of bioactive lactone containing natural products including macrolactones of varied ring size.[3] Recently, we employed a strategy involving the use of furan as an excellent surrogate for the *E*-but-2-ene-1,4-dione unit in our synthesis of natural products. This synthetic transformation, which was employed first by Kobayashi's group,[4] has been dormant for a while, and we renewed the utility of this reaction in our synthesis of marine macrolide palmerolide A[5] and in the synthesis of pinellic acid, a natural product with anti-influenza property.[6] In continuation of our efforts in the use of furan in natural product synthesis, herein we report the total synthesis of seimatopolide A from furfural.

Our approach for the synthesis of (+)-**1** is shown in Scheme 1. We planned the construction of the macrolactone by Shiina lactonization of the hydroxy acid **5**. Synthesis of the hydroxy

Scheme 1. Retrosynthesis for Seimatopolide A 1



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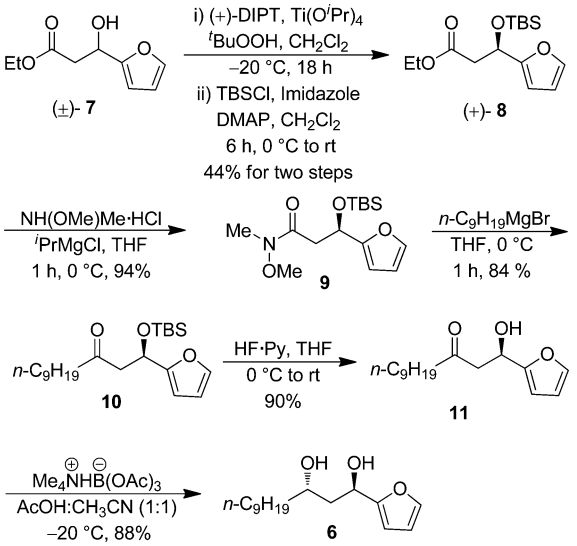
acid **5** is envisaged from the 1,3-diol **6**, by oxidative cleavage of the furan to the *E*-but-2-ene-1,4-dione unit and further elaboration. Synthesis of the 1,3-diol **6** is anticipated from the *β*-hydroxy ester **7**, which can be accessed in enantiopure form by kinetic resolution of the corresponding racemic hydroxy ester or by a standard asymmetric aldol reaction of furfural.

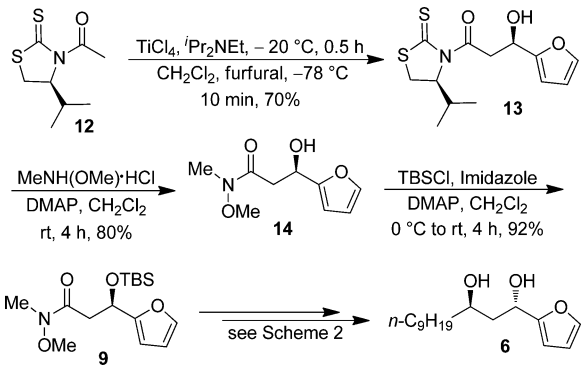
Accordingly the synthetic sequence began with the large scale synthesis of (+)-**7**, through a known procedure involving Sharpless' kinetic resolution of the racemic-hydroxy ester.[7] The formed (+)-**7** was isolated as an inseparable mixture with L-(+)-diisopropyl tartrate used in the reaction; hence, it was converted to the silyl ether **8**, which was isolated as a pure compound in 44% yield for two steps from racemic *β*-hydroxy ester **7**. Conversion of the ester **8** to the Weinreb amide **9**[8] is accomplished in 94% yield, which on reaction with *n*-nonylmagnesium bromide afforded the *β*-silyloxy ketone **10** in 84% yield. Deprotection of the silyl group in **10** is accomplished by reaction with HF·pyridine and the hydroxy ketone **11** is isolated in 90% yield.[9] Reduction of the hydroxy ketone **11** with tetramethylammonium triacetoxyborohydride[10] cleanly furnished the 1,3-diol **6** in 88% yield (Scheme 2).

Scheme 2. Synthesis of the 1,3-Diol 6



In an alternate approach for the 1,3-diol **6**, the following synthetic strategy (Scheme 3) based on acetate aldol reaction was also explored. Thus Nagao acetate aldol[11] reaction of furfural with the thiazolidinonethione **12** derived from valine furnished the aldol product **13** in 70% yield.[12] Treatment of **13** with Weinreb amine (*N*,*O*-dimethylhydroxylamine) hydrochloride in presence of DMAP furnished the *β*-hydroxy Weinreb amide **14** in 80% yield. However, our attempts to synthesize the hydroxy ketone **11** by direct addition of *n*-nonylmagensium bromide to the *β*-hydroxy Weinreb amide **14** were futile. Hence, the hydroxy group in **14** was transformed to the corresponding silyl ether **9**, and following the procedure that is described in Scheme 2, 1,3-diol **6** was synthesized in comparable overall yield.[13]

Scheme 3. Synthesis of 1,3-Diol 6 Using Nagao Acetate Aldol Reaction



The 1,3-diol **6** is converted to the *bis*-silyl ether **15** under standard reaction conditions in 92% yield. NBS-mediated oxidation of the furan in **15** proceeded smoothly to yield **16** in 89% yield. Stereoselective reduction of the keto group in **16** to the alcohol with concomitant reduction of the aldehyde was accomplished with $CeCl_3 \cdot 7H_2O/NaBH_4$ to afford the diol **17** in 87% yield in ≥95:5 diastereomeric ratio. Deprotection of the silyl groups in **17** with concomitant formation of the isopropylidine from the vicinal diol **18** is accomplished in 77% yield by reacting with 2.1 equiv of 2,2-dimethoxypropane (2,2-DMP) in presence of catalytic amount of *p*-TSA. Selective oxidation of the primary allylic alcohol in **18** with MnO_2 afforded the aldehyde **19** which on Nagao acetate aldol reaction furnished **20** as a single diastereomer in 69% yield. Cleavage of the thioazolidinone in **20** to the corresponding acid **5** is accomplished by reaction with $LiOH/H_2O_2$, which on Shiina lactonization[14] afforded the macrolactone **21** in 60% yield. Deprotection of the acetonide in lactone **21** furnished (+)-seimatopolide A (+)-**1** in 63% yield (Scheme 4). The physical and spectroscopic data[15] of the synthesized sample is in complete agreement with that reported in literature.[2c,d]

In conclusion, a facile linear strategy for the total synthesis of 10-membered lactone (+)-seimatopolide A is presented from furfural in 14 steps excluding the optical resolution of the hydroxy ester in 7.8% overall yield. Key strategies in the synthesis include an effective use of furan as a *E*-but-2-ene-1,4-dione surrogate, Nagao acetate aldol reaction, and Shiina lactonization. The strategy depicted is useful for the synthesis of structurally similar macrolactones.

EXPERIMENTAL SECTION

General Procedures. Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded either on a 400 MHz machine in $CDCl_3$ as solvent with TMS as reference. (±)-**7** was prepared according to the procedure described in literature.[16] HRMS was obtained using a micromass-QTOF spectrometer using electrospray ionization (ESI).

Preparation of (*R*)-(+)-Ethyl 3-(furan-2-yl)-3-hydroxypropanoate (7). Resolution of (±)-**7** was performed according to the procedure described earlier by Kusakabe et al.[7] Resolution of (±)-**7** (12.8 g, 69.5 mmol) afforded (+)-**7** (7.92 g) as an inseparable mixture with L-(+)-diisopropyl tartrate (DIPT) (**7**: DIPT 1:0.27). Since the compound contains DIPT, it was used as such without further purification in the next step.

Preparation of 8. To a stirred solution of the hydroxy ester (+)-**7** admixed with L-(+) DIPT (7.92 g) obtained above (**7**:DIPT1:0.27) in CH_2Cl_2 (10 mL) cooled to 0 °C were added imidazole (7.54 g, 112 mmol), 4-(dimethylamino)pyridine (0.90 g, 7.4 mmol) and TBSCl (11.14 g, 74 mmol) successively. The reaction mixture was warmed to

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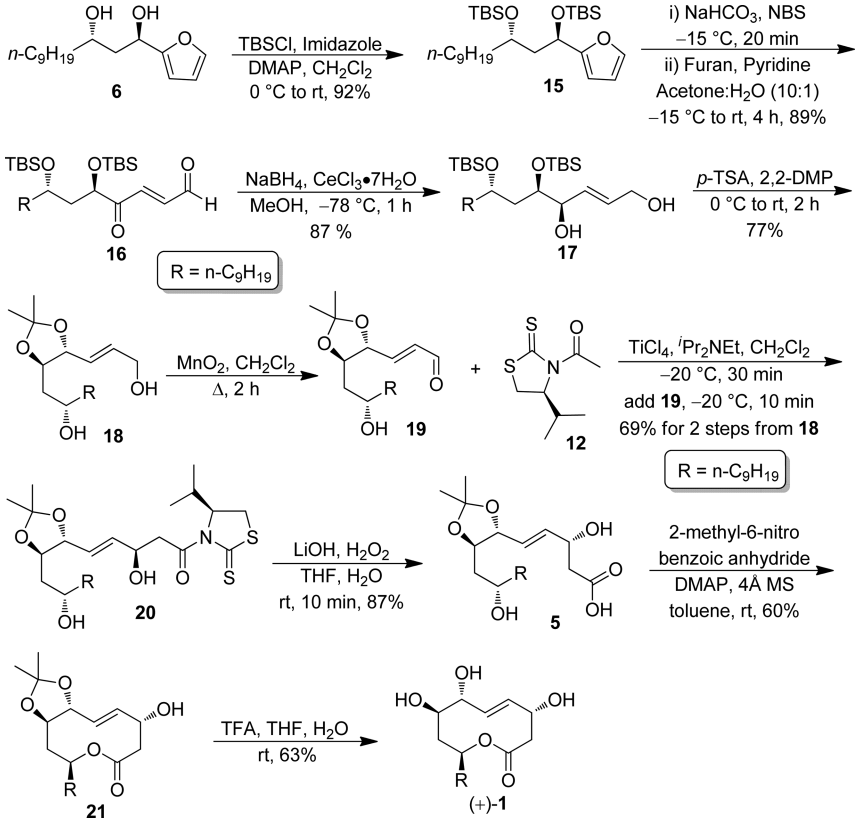
Scheme 4. Total Synthesis of Seimatopolide A



rt and was stirred for 6 h. After completion of the reaction (TLC), it was poured into water (50 mL) and was extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with brine (50 mL) and dried (Na_2SO_4). Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:-EtOAc (19:1) as eluent afforded **8** (9.06 g, 44% for 2 steps from *rac*-7) as a colorless oil: $[\alpha]_D^{24}$ +55.7 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2957, 2859, 1741, 1255, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 1.6 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 5.19 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.30–4.0 (m, 2H), 2.86 (dd, *J* = 14.8, 8.8 Hz, 1H), 2.71 (dd, *J* = 14.8, 4.8 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.06 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 155.6, 141.7, 110.0, 106.1, 65.4, 60.5, 42.4, 25.6 (3 × C), 18.0, 14.1, −5.0, −5.4; HRMS *m*/*z* calcd for $C_{15}H_{26}O_4Si$+Na 321.1498, found 321.1498.

Preparation of 9. To a stirred solution of the ester **8** (6.2 g, 15.7 mmol) in THF (20 mL) cooled to 0 °C was added *N*,*O*-dimethylhydroxylamine hydrochloride (2.31 g, 23.6 mmol). To the resultant suspension ^{i}PrMgCl (47.3 mmol, 67.5 mL of 0.7 M solution in THF) was added dropwise at 0 °C and stirred at the same temperature for 1 h. After completion of the reaction (TLC), it was quenched by addition of sat. NH_4Cl solution (50 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (30 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to furnish **9** (4.63 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ +93.4 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 2957, 2898, 1667,1471, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 1.6 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.29 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 3.27–3.00 (m, 1H), 2.69 (dd, *J* = 14.8, 4.0 Hz, 1H), 0.83 (s, 9H), 0.06 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 156.2, 141.6, 110.0, 106.0, 65.4, 61.4, 39.0, 31.9, 25.7 (3 × C), 18.1, −5.1, −5.3; HRMS *m*/*z* calcd for $C_{15}H_{27}NO_4Si$+Na 336.1607, found 336.1602.

Preparation of 10. To a solution of **9** (1.50 g, 4.8 mmol) in dry THF (10 mL) cooled to 0 °C was added a freshly prepared solution of *n*-$C_9H_{19}MgBr$ (9.6 mL of 0.75 M solution in THF, 7.2 mmol) and stirred at the same temperature for 0.5 h. It was cautiously quenched by addition of sat. NH_4Cl solution (15 mL), poured into water (20 mL) and was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). Evaporation of solvent followed by silica gel column chromatography of the resultant residue with petroleum ether:EtOAc (9:1) as eluent yielded **10** (1.53 g, 84%) as a colorless oil: $[\alpha]_D^{24}$ +67.6 (*c* 1.68, $CHCl_3$); IR (neat) ν_{max} 2956, 2858, 1718, 1470, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.6 Hz, 1H), 6.28 (dd, *J* = 2.8, 1.6 Hz, 1H), 6.17 (d, *J* = 2.8 Hz, 1H), 5.21 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.03 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.67 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.52–2.30 (m, 2H), 1.55 (t, *J* = 6.8 Hz, 2H), 1.25 (bs, 12H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.02 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 156.0, 141.6, 110.0, 106.0, 65.0, 49.3, 44.4, 31.8, 29.4, 29.4, 29.2, 29.1, 25.7 (3 × C), 23.4, 22.6, 18.0, 14.0, −5.1, −5.3; HRMS *m*/*z* calcd for $C_{22}H_{40}O_3Si$+Na 403.2644, found 403.2647.

Preparation of 11. To a solution of **10** (1.43 g, 3.76 mmol) in THF (20 mL) in a Nalgene vial cooled to 0 °C, was added HF·pyridine:pyridine (12.0 mL, 1:1 by volume). It was allowed to warm up to rt and stirred for 2 h. After completion of the reaction (TLC), it was quenched by addition of sat. $NaHCO_3$ solution (25 mL), and was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue obtained after evaporation of the solvent, with petroleum ether:EtOAc (8:2) as eluent, afforded **11** (0.9 g, 90%) as a colorless oil: $[\alpha]_D^{24}$ +27.8 (*c* 1.66, $CHCl_3$); IR (neat) ν_{max} 3445, 2928, 2856, 1716, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.6 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.13 (bd, *J* = 6.4 Hz, 1H), 3.56 (bs, 1H), 2.98 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.85 (dd, *J* = 17.6, 3.2 Hz, 1H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.64–1.45 (m, 2H), 1.23 (bs, 12H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 155.1, 141.8, 110.1, 106.0, 63.6,

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47.1, 43.5, 31.7, 29.3, 29.2, 29.1, 29.0, 23.4, 22.5, 13.9; HRMS m/z calcd for $C_{16}H_{26}O_3$+Na 289.1780, found 289.1782.

Preparation of 6. Tetramethylammoniumtriacetoxy borohydride (0.25 g, 0.95 mmol) was added to a solution of anhydrous acetonitrile and AcOH (1:1, 2 mL) and stirred at rt for 30 min. It was cooled to −20 °C, and a solution of **11** (0.17 g, 0.64 mmol) in acetonitrile:AcOH (1:1, 2 mL) was introduced into this mixture using syringe pump for 1 h. After the addition was complete, the reaction mixture was stirred at −20 °C for additional 4 h. It was quenched by the addition of sat. solution of sodium potassium tartrate (5 mL). The reaction mixture was diluted with EtOAc (10 mL) and was washed with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue obtained was purified by silica gel column chromatography to furnish the diol **6** (0.15 g, 88%) as a white solid: mp 72−73 °C; $[\alpha]_D^{24}$ +22.0 (c 1.9, $CHCl_3$); IR (neat) ν_{max} 3308, 2919, 2852, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.6 Hz, 1H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.27 (d, J = 3.2 Hz, 1H), 5.05 (dd, J = 8.0, 3.2 Hz, 1H), 3.99−3.84 (m, 1H), 2.93 (bs, 1H), 2.07 (ddd, J = 14.4, 8.0, 2.4 Hz, 1H), 1.90 (ddd, J = 14.4, 8.8, 3.2 Hz, 1H), 1.65−1.37 (m, 2H), 1.26 (bs, 14H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 141.8, 110.1, 105.6, 69.2, 65.6, 41.0, 37.5, 31.9, 29.6 (2 × C), 29.5, 29.3, 25.6, 22.6, 14.1; HRMS m/z calcd for $C_{16}H_{28}O_3$+Na 291.1936, found 291.1934.

Preparation of 13. To a stirred solution of **12** (0.2 g, 0.98 mmol) in freshly distilled DCM (4 mL) cooled to −20 °C was added $TiCl_4$ (0.11 mL, 0.98 mmol) dropwise under inert atmosphere and was stirred for 5 min. Diisopropylethylamine (0.34 mL, 1.97 mmol) was introduced into the reaction mixture, and the resulting dark brown solution was stirred for 30 min at −20 °C. It was cooled to −78 °C, and a solution of furfural (0.14 g, 1.48 mmol) in DCM (4 mL) was added dropwise and was stirred at −78 °C. After completion of the reaction (∼10 min), it was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine, and then dried over Na_2SO_4. Residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether:EtOAc (7:3) as eluent to afford **13** (0.20 g, 70%) as a yellow oil: $[\alpha]_D^{24}$ +217.8 (c 0.6, $CHCl_3$); IR (neat) ν_{max} 3458, 2965, 1687, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.6 Hz, 1H), 6.33 (dd, J = 3.2, 1.6 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 5.25 (dd, J = 8.4, 3.6 Hz, 1H), 5.14 (t, J = 6.8 Hz, 1H), 3.82 (dd, J = 17.6, 3.6 Hz, 1H), 3.75 (dd, J = 18.0, 8.4 Hz, 1H), 3.52 (dd, J = 11.6, 8.0 Hz, 1H), 3.26 (bs, 1H), 3.03 (d, J = 11.6 Hz, 1H), 2.35 (octet, 6.8 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 171.9, 154.7, 142.1, 110.2, 106.3, 71.3, 64.0, 43.7, 30.7, 30.7, 19.0, 17.7; HRMS m/z calcd for $C_{13}H_{17}NO_3S_2$+Na 322.0548, found 322.0550.

Minor Isomer 13a. Yield 16%: $[\alpha]_D^{24}$ +317.4 (c 0.65, $CHCl_3$); IR (neat) ν_{max} 3458, 2965, 1687, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 1.6 Hz, 1H), 6.33 (dd, J = 3.2, 1.6 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 5.25−5.11 (m, 2H), 4.04 (dd, J = 17.6, 9.2 Hz, 1H), 3.62 (dd, J = 17.6, 3.2 Hz, 1H), 3.53 (dd, J = 11.6, 8.0 Hz, 1H), 3.05 (d, J = 11.6 Hz, 1H), 2.36 (octet, 6.8 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 172.3, 154.7, 142.2, 110.2, 106.4, 71.3, 64.5, 43.6, 30.7, 30.6, 19.0, 17.7.

Preparation of 14. To a stirred solution of **13** (0.10 g, 0.31 mmol) in dry DCM (2 mL) were added DMAP (0.15 g, 1.25 mmol) followed by *N*,*O*-dimethylhydroxylaminehydrochloride (0.059 g, 0.62 mmol) at room temperature and was stirred for 4 h. It was poured into water (5 mL) and was extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (6:4) as eluent to afford **14** (0.05 g, 80%) as a colorless oil: $[\alpha]_D^{24}$ +53.9 (c 0.92, $CHCl_3$); IR (neat) ν_{max} 3450, 1739, 1638, 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 1.6 Hz, 1H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 5.17 (dd, J = 8.8, 3.2 Hz, 1H), 4.25 (bs, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 3.03 (dd, J = 16.8, 8.8 Hz, 1H), 2.92 (dd, J = 16.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 155.1, 141.9, 110.1, 106.1, 64.1, 61.2, 36.7, 31.8; HRMS m/z calcd for $C_9H_{13}NO_4$+Na 222.0742, found 222.0730.

Preparation of 9 from 14. The hydroxy amide **14** (0.043 g, 0.32 mmol) was converted to the silyloxy amide **9** (0.06 g, 92%) using a procedure described for the preparation of the silyloxyester (+)-**8**.

Preparation of 15. Following a procedure described for the synthesis of **8**, reaction of diol **6** (0.736 g, 2.75 mmol) in CH_2Cl_2 (10 mL) with TBDMSCl (1.04 g, 6.9 mmol) at 0 °C in presence of imidazole (0.28 g, 4.11 mmol) and DMAP (0.066 g, 0.55 mmol) afforded the *bis*-silylether **15** (1.25 g, 92%) as a colorless oil: $[\alpha]_D^{24}$ +27.2 (c 0.85, $CHCl_3$); IR (neat) ν_{max} 2926, 285, 1503, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 6.30 (dd, J = 3.2, 1.6 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 4.80 (dd, J = 8.4, 4.8 Hz, 1H), 3.88−3.72 (m, 1H), 2.02 (ddd, J = 13.6, 8.4, 4.4 Hz, 1H), 1.82 (ddd, J = 13.6, 7.2, 4.8 Hz, 1H), 1.52−1.37 (m, 2H), 1.27 (s, 14H), 0.89 (s, 9H), 0.86 (s, 9H), 0.95−0.80 (m, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 141.3, 110.0, 106.1, 69.3, 65.3, 44.5, 37.7, 31.9, 29.7, 29.6, 29.6, 29.3, 25.9 (3 × C), 25.8 (3 × C), 24.9, 22.7, 18.1, 18.1, 14.1, −4.1, −4.3, −4.8, −5.1; HRMS m/z calcd for $C_{28}H_{56}O_3Si_2$+Na 519.3666, found 519.3665.

Preparation of 16. To a stirred solution of **15** (1.12 g, 2.3 mmol) in acetone/H_2O (9:1, 10 mL) cooled to −15 °C was added $NaHCO_3$ (0.38 g, 4.52 mmol) and a solution of NBS (0.48 g, 2.71 mmol) in acetone/H_2O (9:1, 6 mL). It was stirred at −15 °C for 20 min, and furan (0.30 mL, 4.52 mmol) was introduced into the reaction mixture to destroy excess NBS. After stirring for 0.5 h, pyridine (0.18 mL, 2.3 mmol) was introduced at −15 °C, and the reaction mixture was stirred at rt for 4 h. Brine (15 mL) and EtOAc (20 mL) were added to the reaction mixture, and the resulting mixture was acidified with phosphate buffer (pH ∼ 4.0). The separated aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic extracts were dried (Na_2SO_4). The residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether:EtOAc (20:1) as eluent to afford **16** (1.03 g, 89%) as a pale yellow oil: $[\alpha]_D^{24}$ +4.5 (c 0.70, $CHCl_3$); IR (neat) ν_{max} 2945, 2858, 2723, 1702, 1464; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 16.0 Hz, 1H), 6.92 (dd, J = 16.0, 7.6 Hz, 1H), 4.39 (dd, J = 6.8, 5.6 Hz, 1H), 3.67−3.95 (m, 1H), 1.69−1.85 (m, 2H), 1.55−1.40 (m, 2H), 1.25 (bs, 14 H), 0.90 (s, 9H), 0.87 (s, 9H), 0.97−0.80 (m, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 193.0, 140.9, 138.2, 76.1, 69.4, 42.3, 37.6, 31.8, 29.6, 29.6, 29.5, 29.3, 25.9 (3 × C), 25.7 (3 × C), 24.9, 22.6, 18.1 (2 × C), 14.1, −3.9, −4.3, −4.6, −4.8; HRMS m/z calcd for $C_{28}H_{56}O_4Si_2$+Na 535.3615, found 535.3613.

Preparation of 17. To a solution of the keto-aldehyde **16** (0.75 g, 1.46 mmol) in methanol (15 mL) was added $CeCl_3.7H_2O$ (1.90 g, 5.12 mmol) at rt and stirred for 0.5 h. It was cooled to −78 °C, and $NaBH_4$ (0.17 g, 4.38 mmol) was added portionwise over a period of 15 min and was stirred at −78 °C for 1 h. After completion of the reaction (TLC), it was cautiously quenched by addition of water (1 mL). Most of the MeOH was evaporated off, and the crude residue was dissolved in water and was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude residue thus obtained with petroleum ether:EtOAc (4:1) as eluent gave **17** (0.65 g, 87%) as a colorless liquid: $[\alpha]_D^{24}$ +9.6 (c 0.75, $CHCl_3$); IR (neat) ν_{max} 3394, 2929, 2858, 1652, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, J = 15.6, 5.2 Hz, 1H), 5.74 (dd, J = 15.6, 5.2 Hz, 1H), 4.17 (d, J = 5.2 Hz, 2H), 4.03 (bs, 1H), 3.85−3.64 (m, 2H), 2.46 (d, J = 7.2 Hz, 1H, OH, exchangeable with D_2O), 1.85 (pentet, J = 7.2 Hz, 1H), 1.60 (bs, IH, OH, exchangeable with D_2O), 1.54 (dt, J = 14.0, 5.2 Hz, 1H), 1.50−1.35 (m, 2H), 1.26 (bs, 14H), 0.89 (bs, 21H), 0.01−0.15 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 130.6, 73.8, 73.1, 70.3, 63.1, 41.5, 37.8, 31.8, 29.7, 29.6, 29.5, 29.3, 25.9 (3 × C), 25.8 (3 × C), 25.0, 22.6, 18.1, 18.0, 14.1, −4.0, −4.1 (2 × C), −4.4; HRMS m/z calcd for $C_{28}H_{60}O_4Si_2$+Na 539.3928, found 539.3925.

Preparation of 18. To a stirred solution of the diol **17** (0.43 g, 0.82 mmol) in 2,2-dimethoxypropane (3 mL) was added *p*-TSA (0.33

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g, 1.74 mmol) at rt in a single portion and was stirred at rt for 2 h. After completion of the reaction (TLC), it was quenched by addition of sat. $NaHCO_3$ solution (5 mL), and was extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the residue obtained with petroleum ether:EtOAc (1:1) as eluent afforded **18** (0.21 g, 77%) as a colorless liquid: $[\alpha]_D^{24}$ +7.6 (*c* 0.85, $CHCl_3$); IR (neat) ν_{max} 3389, 2986, 2856, 1462, 1375; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 15.2, 4.8 Hz, 1H), 5.64 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.08 (d, *J* = 3.6 Hz, 2H), 4.02 (t, *J* = 8.4 Hz, 1H), 3.96−3.81 (m, 1H), 3.65−3.82 (bm, 1H), 3.31 (bs, 1H), 3.06 (bs, 1H), 1.59 (t, *J* = 5.6 Hz, 2H), 1.38 (bs, 16H), 1.22 (s, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 127.1, 108.7, 81.4, 77.8, 68.6, 62.1, 38.2, 37.8, 31.8, 29.5, 29.5, 29.5, 29.2, 27.2, 26.9, 25.5, 22.6, 14.0; HRMS *m*/*z* calcd for $C_{19}H_{36}O_4Na$ 351.2511, found 351.2518.

Preparation of 20. To a stirred solution of the diol **18** (0.21 g, 0.64 mmol) in dichloromethane was added MnO_2 (0.56 g, 6.46 mmol) at rt, and the resulting suspension was refluxed for 2 h. It was filtered through a Celite pad and was concentrated to afford the crude aldehyde **19**, which was used in the next step without further purification.

Aldol reaction of the above aldehyde with **12** (0.33 g, 1.6 mmol) using a procedure described for the synthesis of **13** afforded **20** (0.22 g, 69%) as a colorless oil: $[\alpha]_D^{24}$ +180.1 (*c* 0.7, $CHCl_3$); IR (neat) ν_{max} 3448, 2958, 2856, 1686, 1370; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 15.6, 5.2 Hz, 1H), 5.75, (dd, *J* = 15.6, 7.2 Hz, 1H), 5.14 (t, *J* = 6.8 Hz, 1H), 4.80−4.60 (bm, 1H), 4.09 (t, *J* = 8.0 Hz, 1H), 4.01−3.89 (m, 1H), 3.84 (bs, 1H), 3.68 (dd, *J* = 17.6, 3.2 Hz, 1H), 3.53 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.27 (dd, *J* = 17.6, 8.8 Hz, 1H), 3.03 (dd, *J* = 11.6, 0.8 Hz, 1H), 3.0 (d, 4.4 Hz, 1H, OH exchangeable with D_2O), 2.34 (octet, 6.8 Hz, 1H), 2.31 (bs, 1H, OH, exchangeable with D_2O), 1.57−1.78 (m, 2H), 1.55−1.35 (m, 2H), 1.41 (apparent d, *J* = 4.0 Hz, 6H), 1.26 (bs, 14H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 172.2, 135.5, 127.5, 108.8, 81.2, 78.0, 71.3, 68.9, 67.8, 45.0, 37.8, 37.6, 31.8, 30.8, 30.6, 29.6, 29.6, 29.5, 29.3, 27.2, 26.9, 25.6, 22.6, 19.0, 17.8, 14.1; HRMS *m*/*z* calcd for $C_{27}H_{47}NO_5S_2$+Na 552.2793, found 552.2791.

Preparation of 5. To a stirred solution of **20** (0.032 g, 0.061 mmol) in THF (1 mL) at 0 °C were added LiOH (0.3 mmol, 0.3 mL of 1.0 M solution in H_2O) followed by H_2O_2 (1.0 mL of 30% w/v solution in water). The reaction mixture was stirred for 10 min at 0 °C, and was acidified carefully to pH = 7 with 2 N HCl. It was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine (5 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by silica gel column chromatography using EtOAc as eluent to afford **5** (0.027 g) in 87% yield: $[\alpha]_D^{24}$ +15.9 (*c* 1.0, MeOH); IR (neat) ν_{max} 3448, 2925, 2600, 1718, 1707, 1380; ^{1}H NMR (400 MHz, CD_3OD) δ 5.80 (dd, *J* = 15.6, 5.6 Hz, 1H), 5.62 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.43 (bs, 1H), 3.91(t, *J* = 7.6 Hz, 1H), 3.87−3.75 (m, 1H), 3.77−3.55 (m, 1H), 2.47−2.31 (m, 2H), 1.49 (t, *J* = 5.6 Hz, 2H), 1.40−1.32 (bm, 2H), 1.29 (bs, 6H), 1.21 (bs, 14H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 135.3, 127.9, 108.9, 81.4, 77.9, 69.2, 68.0, 38.7, 37.9, 31.9, 29.6, 29.6, 29.3, 27.3, 27.0, 25.7, 22.7, 14.1; HRMS *m*/*z* calcd for $C_{21}H_{38}O_6Na$ 409.2566, found 409.2562.

Preparation of 21. In a 100-mL two necked flask was placed powdered flame-dried molecular sieves (4 Å, 800 mg), DMAP (32 mg, 0.26 mmol) and 2-methyl-6-nitrobenzoicanhydride (23 mg, 0.066 mmol) under a steady stream of Argon. The flask was charged with dry toluene (14 mL), and a solution of **5** (0.016 g, 0.044 mmol) in dry toluene (10 mL) was added to this suspension using syringe pump (0.80 mL/h). After the addition was complete, it was stirred for another 6 h at rt. The reaction mixture was diluted with EtOAc (25 mL) and was filtered. The organic phase was washed with sat. $NaHCO_3$ (2 × 10), brine (10 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to furnish **21** (0.009 g, 60%) as a colorless liquid: $[\alpha]_D^{24}$ +19.4 (*c* 0.18, CH_2Cl_2); IR (neat) ν_{max} 3463, 2984, 2857, 1733, 1461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91(dd, *J* = 15.6, 2.4 Hz, 1H), 5.63 (dd, *J* = 15.6, 9.2 Hz, 1H), 5.06 (dt, *J* = 10.0, 6.4 Hz, 1H), 4.71 (bs, 1H), 4.06 (t, *J* = 8.8 Hz, 1H), 3.65 (t, *J* = 8.8 Hz, 1H), 2.64 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.54 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.49 (d, *J* = 7.2 Hz, 1H), 2.07 (d, *J* = 15.6 Hz, 1H), 1.89 (dt, *J* = 14.4, 10.0 Hz, 1H), 1.59−1.45 (m, 2H), 1.4 (s, 6H), 1.24 (bs, 14H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 136.8, 123.1, 108.1, 83.9, 81.7, 73.0, 67.3, 44.4, 36.9, 36.0, 31.8, 29.4, 29.4, 29.3, 29.2, 27.0, 26.9, 25.2, 22.6, 14.0; HRMS *m*/*z* calcd for $C_{21}H_{36}O_5Na$ 391.2460, found 391.2458.

Preparation of (+)-Seimatopolide A [(+)-1]. Synthesis of **1** was carried out using a procedure described for the same compound by Schmidt et al.[2d] Accordingly, reaction of **21** (0.009 g, 0.024 mmol) with TFA furnished seimatopolide A ((+)-**1**) (0.005 g) as a white powder in 63% yield: $[\alpha]_D^{24}$ +21.7 (*c* 0.06, MeOH); IR (KBr) ν_{max} 3342, 2920, 2850, 1662, 1446; ^{1}H NMR (400 MHz, CD_3OD) δ 5.83 (dd, *J* = 15.6, 2.8 Hz, 1H), 5.48 (dd, *J* = 15.6, 9.6 Hz, 1H), 4.62 (dd, *J* = 12.9, 6.6 Hz, 1H), 4.55 (bs, 1H), 3.67 (t, *J* = 9.2 Hz, 1H), 3.29 (t, *J* = 8.8 Hz, 1H), 2.48 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.38 (dd, *J* = 12.0, 3.2 Hz, 1H), 1.84−1.65 (m, 2H), 1.53−1.35 (m, 2H), 1.20 (bs, 14H), 0.81 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.1, 137.2, 127.3, 80.1, 77.4, 74.5, 67.9, 44.5, 42.5, 38.1, 33.2, 30.8 (2 × C), 30.7, 30.6, 26.2, 23.9, 14.4; ^{13}C NMR (100 MHz, pyridine-d_5) δ 170.8, 136.8, 128.5, 80.1, 77.5, 73.8, 67.7, 45.1, 42.6, 37.9, 32.5, 30.32, 30.3, 30.2, 30.0, 26.0, 23.4, 14.7; HRMS *m*/*z* calcd for $C_{18}H_{32}O_5Na$ 351.2147, found 351.2142.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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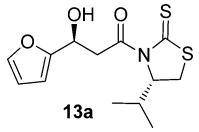

13a

(13) We have also explored the synthesis of the 1,3-anti-diol **6** by Ipc_2BCl mediated direct aldol reaction (Paterson aldol reaction)/ reduction sequence using 2-acetyl furan and *n*-decanal following a procedure recently described for the synthesis of 1,3-anti-diols by Dieckmann and Menche. Dieckmann, M.; Menche, D. *Org. Lett.* **2013**, *15*, 228−231. However, we were not able to isolate any appreciable amount of the product in the reaction. No efforts were made to optimize the reaction conditions.
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