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Establishment of Relative and Absolute Configurations of Phaeosphaeride A: Total Synthesis of *ent*-Phaeosphaeride A

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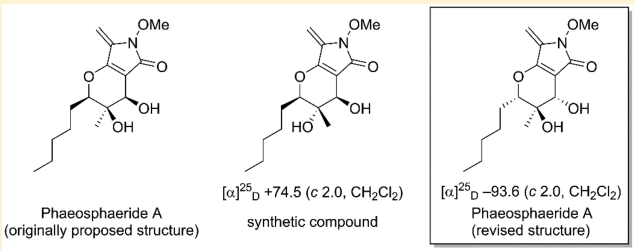
Supporting Information

ABSTRACT: The relative and absolute configurations of phaeosphaeride A have been established via the first total synthesis of *ent*-phaeosphaeride A. The three contiguous stereogenic centers were installed by Sharpless asymmetric dihydroxylation and a stereoselective intramolecular vinyl anion aldol reaction. This synthesis has altered the originally proposed structure of natural phaeosphaeride A.



Many drug candidates for treating human diseases have been discovered from natural sources.[1] In research aimed at finding new cancer chemotherapeutic agents, Clardy and co-workers isolated phaeosphaeride A (proposed structure **1a**), an inhibitor of signal transducer and activator of transcription 3 (STAT3)-dependent signaling, and its inactive stereoisomer, phaeosphaeride B (proposed structure **1b**), from an endophytic fungus in 2006 (Figure 1).[2]

STAT3 has been recently recognized to contribute to oncogenesis;[3] therefore, it is considered to be an attractive target protein in anticancer drug discovery.[4] Phaeosphaeride A (**1a**) inhibits cell growth in STAT3-dependent U266 multiple myeloma cells with an IC_{50} of 6.7 μM *in vitro*,[2] and consequently, **1a** is expected to represent a new class of drug candidates for cancer treatment.

In our previous paper, we reported the first total synthesis of the proposed structure of phaeosphaeride A (**1a**).[5] However, ^{1}H and ^{13}C NMR data for synthetic compound **1a** were not identical to those reported for the natural product, suggesting that the structure of natural phaeosphaeride A was misassigned. Our prior work[5] and recent work by Sarli and co-workers[6] implied that the correct structure of phaeosphaeride A was the C-7 epimer (**1c**) of the originally proposed structure (**1a**) or its enantiomer (**1d**) (Figure 1).

We report the first total synthesis of **1c** (*ent*-phaeosphaeride A) and the reassignment of the relative and absolute stereochemistry of natural phaeosphaeride A (**1d**, correct structure).

Our previous synthesis of **1a** included the Sharpless asymmetric dihydroxylation[7] of *E*-configured unsaturated ester (*E*)-**2** and the intramolecular vinyl anion aldol reaction of **4** to form the three contiguous stereogenic centers (C-6, 7, and 8) (Scheme 1).[5]

To synthesize the C-7 epimer of **1a**, we planned to use the *Z*-configured unsaturated ester instead of (*E*)-**2** and we follow our synthetic scheme for **1a** with minor modifications.

Thus, we initially prepared Still–Gennari phosphonate **7**[8] and used the Horner–Wadsworth–Emmons reaction of hexanal (**6**) with **7** to get (*Z*)-α,β-unsaturated ester **2** in 75% yield with complete stereoselectivity (Scheme 2). Ester (*Z*)-**2** was subjected to Sharpless asymmetric dihydroxylation[7] using AD-mix-β to afford the desired diol **8** in excellent yield (96%) and enantioselectivity (98% ee, determined by modified Mosher's method).[9] Following our previous synthesis,[5] benzyl protection of the secondary alcohol in **8** with BnBr/NaH was first carried out to form benzyl ether **9a** in only 8% yield. We then adopted Kunishima and co-worker's method using 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT)[10] to obtain product **9a** (53%), bis-benzyl ether **9b** (14%), and unreacted **8** (30%). Recovered **8** was retreated with TriBOT to produce **9a** (55%), **9b** (17%), and **8** (28%). In addition, the overreacted bis-benzyl ether (**9b**) was easily converted to starting diol **8** (88%) by Pd/C catalyzed hydrogenation; this recycling can improve the yield of the desired mono-benzyl ether **9a**.

After MOM protection of the tertiary alcohol in **9a**, the ester group was reduced with DIBALH to deliver primary alcohol **10**, which was then protected as a TIPS ether, and subsequent deprotection of the benzyl group gave secondary alcohol **11** (Scheme 3).

Next, we used oxy-Michael addition of alcohol **11** to dimethyl dicarboxylate **12** in the presence of a catalytic amount of *n*-BuLi[11] to get (*E*)-**13** (83%) and (*Z*)-**13** (4%). The stereoselectivity of this reaction was greatly improved compared with our previous work (4.2:1 to 21:1).[5] Major isomer (*E*)-**13** was then treated with HF·py to afford an alcohol in quantitative yield, which was oxidized with Dess–Martin periodinane to produce cyclization precursor **14** in 92% yield.

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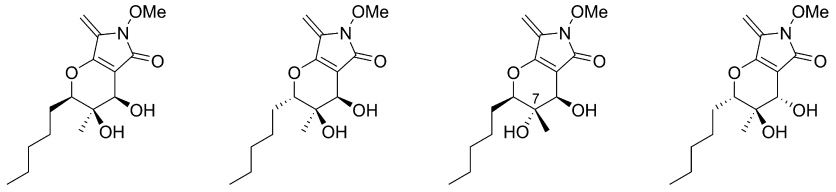
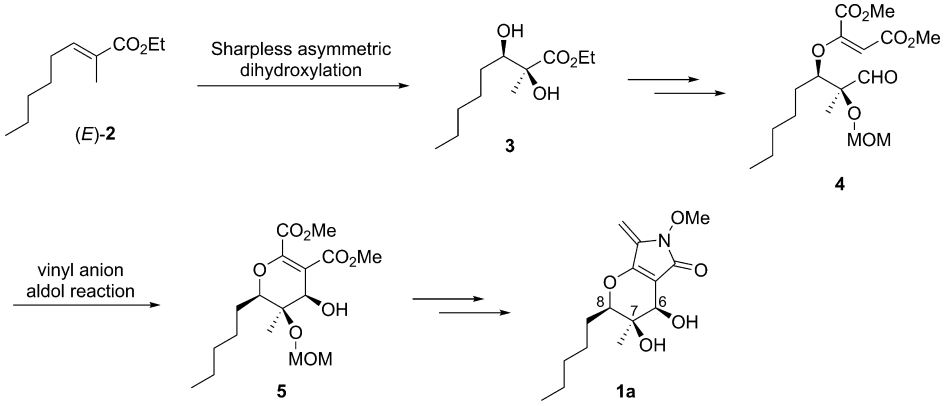
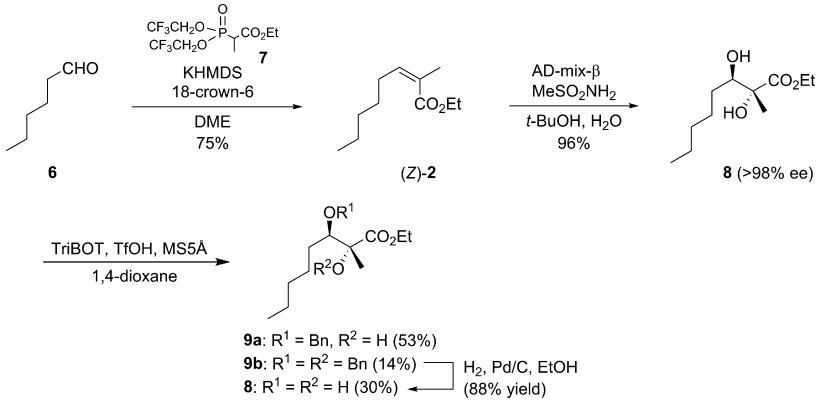


Figure 1. Structures of Phaeosphaerides.

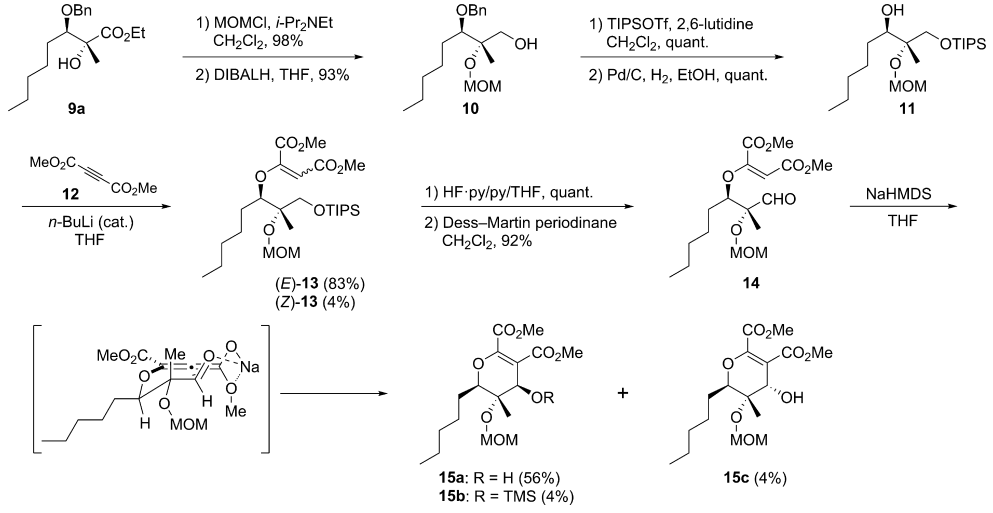
Scheme 1. Our Previous Synthetic Scheme for 1a



Scheme 2. Synthesis of Benzyl Ether 9a



Scheme 3. Synthesis of Dihydropyran Derivatives 15a–c



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The crucial six-membered ring formation was achieved by reaction of **14** with NaHMDS[12] at −78 °C to deliver the desired product **15a** (56%), its TMS protected alcohol **15b** (4%),[13] and undesired isomer **15c** (4%). The stereochemistry of the resulting stereocenter C-6 in **15a** and **15b** was confirmed by observation of W-type long-range coupling between H-6 and H-8 in the ^{1}H NMR spectra (Figure 2). During this reaction,

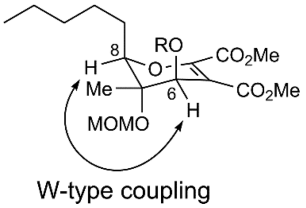


Figure 2. Stereochemistry of **15a** and **15b**.

the *n*-pentyl and the MOM-oxy groups are expected to adopt a pseudo-equatorial orientation, and the formyl group was presumably oriented by intramolecular chelation with the sodium ion of the allenic enolate, which caused the stereoselective ring formation (possible transition state leading to **15a** and **15b** is shown in parentheses, Scheme 3).

With the dihydropyran derivatives **15a** and **15b** in hand, we turned our attention to completing the total synthesis (Scheme 4). Compound **15a** was regioselectively hydrolyzed to give mono acid **16**, and TMS ether **15b** also gave acid **16** with concomitant cleavage of the TMS group.[14] Mono acid **16** immediately reacted with $MeONH_2$ under standard WSC-mediated amidation conditions to produce maleimide **17** in 49% yield with spontaneous cyclization, and amide **18** in 16% yield. Amide **18** was smoothly converted to maleimide **17** upon heating in DMF at 50 °C in the presence of Et_3N.[15] Finally, the total synthesis was completed by the regioselective addition of the methyl group, and the subsequent dehydration of the resulting hemiaminal and deprotection of the MOM group by treatment with HCl-dioxane to furnish **1c** in 2 steps and 36% yield.

We are delighted that the ^{1}H and ^{13}C NMR data for synthetic compound **1c** correspond to the literature data[2] for natural phaeosphaeride A, and we note that the optical rotations of the synthetic **1c** ($[\alpha]_D^{25}$ +74.5 (*c* 2.0, CH_2Cl_2)) and the natural product ($[\alpha]_D^{25}$ −93.6 (*c* 2.0, CH_2Cl_2)) have opposite signs; therefore, phaeosphaeride A (revised structure **1d**) was assigned as the enantiomer of synthetic **1c**.

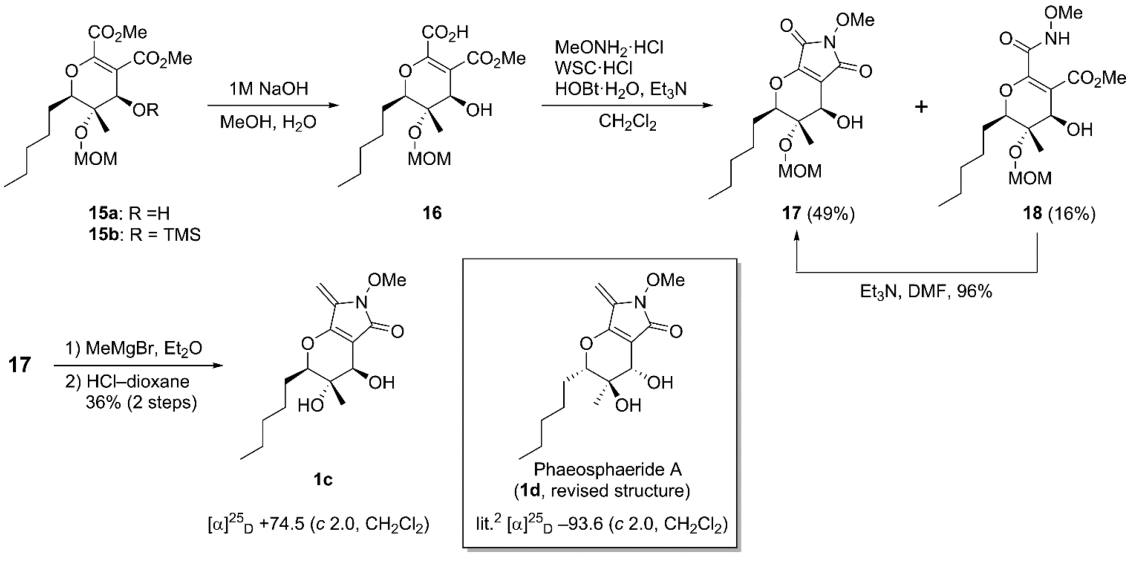
In conclusion, we have accomplished the first total synthesis of *ent*-phaeosphaeride A (**1c**), featuring stereoselective dihydropyran ring formation by an intramolecular vinyl anion aldol reaction, and established the relative and absolute configurations of phaeosphaeride A (**1d**). This synthesis allowed us to identify the correct structure of phaeosphaeride A. Having determined the correct structure of phaeosphaeride A (**1d**), we are now working on its total synthesis, and the results obtained here should provide useful information about structure−activity relationships for developing novel anticancer drugs.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were measured at 300, 400, or 500 MHz. The chemical shifts are expressed in ppm downfield from tetramethylsilane (δ = 0) as an internal standard ($CDCl_3$ or DMSO-d_6 solution). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. ^{13}C NMR spectra were measured at 75, 100, or 125 MHz. The chemical shifts are reported in ppm, relative to the central line of a triplet at 77.0 ppm for $CDCl_3$, or a septet at 39.5 ppm for DMSO-d_6. Infrared spectra (IR) were measured on NaCl plates. High-resolution mass spectra (HRMS) were obtained using an electrostatic sector mass analyzer with FAB ionization. Column chromatography was carried out on silica gel (40−100 mesh). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60-F plates.

Ethyl (*Z*)-2-Methyloct-2-enoate ((*Z*)-2). To a stirred solution of phosphonate 7 (346 mg, 1.00 mmol) in THF (5.0 mL) were added 18-crown-6/CH_3CN (318 mg, 1.04 mmol) and KHMDS (0.5 M solution in toluene, 1.89 mL, 0.95 mmol) at −78 °C. After being stirred at the same temperature for 20 min, hexanal (0.12 mL, 0.95 mmol) was added, and stirring was continued for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated, and the aqueous phase was extracted with Et_2O. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (pentane−Et_2O, 100:1) to afford (*Z*)-**2** (131 mg, 75%) as a pale

Scheme 4. Synthesis of *ent*-Phaeosphaeride A (1c)



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yellow oil. The spectroscopic data for this compound were identical to those reported in the literature.[5]

Ethyl (2*R*,3*R*)-2,3-Dihydroxy-2-methyloctanoate (8). To a stirred solution of AD-mix-β (28.5 g) and methanesulfonamide (1.94 g, 20.4 mmol) in *t*-BuOH (90 mL) and H_2O (102 mL) was added (*Z*)-**2** (3.75 g, 42.5 mmol) in *t*-BuOH (12 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 17 h. For workup, Na_2SO_3 (30.5 g) was added, and the mixture was allowed to warm to room temperature, and stirring was continued for 1 h. The whole was extracted with AcOEt (100 mL × 2). The combined extracts were washed with 1 M aqueous NaOH (80 mL) and brine (80 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 7:3) to afford **8** (4.27 g, 96%) as a colorless oil. $[\alpha]_D^{22}$ +12.5 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3073, 2934, 1726, 1377, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (dq, *J* = 1.2, 6.9 Hz, 2H), 3.35 (ddd, *J* = 9.9, 8.7, 2.1 Hz, 1H), 3.37 (s, 1H), 2.00 (d, *J* = 8.7 Hz, 1H), 1.64−1.48 (m, 2H), 1.45 (s, 3H), 1.41−1.19 (m, 6H), 1.31 (t, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 77.2, 76.1, 62.0, 31.7, 31.6, 25.9, 22.5, 22.5, 14.1, 14.0; HRMS (Fab+) $[M + H]^+$ calcd for $C_{11}H_{23}O_4$ 219.1596, found 219.1600.

Determination of stereochemistry at C-3 and estimation of the optical purity of **8** were conducted by using a modified Mosher's method. Derivatization of **8** to the corresponding (*R*)- or (*S*)-MTPA ester was conducted according to a usual method using the corresponding acid chlorides and pyridine. Since ^1H NMR of each crude product did not show the signals of the other diastereomer, the optical purity of **8** was estimated to be more than 98% ee.

(*S*)-MTPA ester of **8**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.62−7.57 (m, 2H), 7.43−7.37 (m, 3H), 5.31 (dd *J* = 10.0, 2.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.56 (s, 3H), 3.18 (s, 1H), 1.77 (m, 1H), 1.55 (m, 1H), 1.40−1.10 (m, 6H), 1.29 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H). (*R*)-MTPA ester of **8**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.64−7.57 (m, 2H), 7.44−7.37 (m, 3H), 5.29 (dd, *J* = 10.3, 2.8 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.58 (s, 3H), 3.28 (s, 1H), 1.73 (m, 1H), 1.48 (m, 1H), 1.34−1.06 (m, 6H),, 1.38 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H).

Ethyl (2*R*,3*R*)-3-(Benzyloxy)-2-hydroxy-2-methyloctanoate (9a). To a stirred solution of **8** (4.24 g, 19.4 mmol) were added TriBOT (3.11 g, 7.77 mmol) and MS5 Å (2.43 g). TfOH (0.34 mL, 3.8 mmol) was added slowly, and the reaction mixture was stirred for 16 h. The reaction was quenched by addition of Et_3N (1.4 mL), and stirring was continued for 5 min. The mixture was filtered through a pad of Celite, and the residue was washed with AcOEt (30 mL). The filtrate was concentrated *in vacuo*. The residual solid was dissolved in AcOEt (100 mL) and washed with half-saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 19:1 → 9:1 → 17:3 → 7:3) to afford **9a** (3.27 g, 53%) as a colorless oil, **9b** (1.11 g, 14%) as a pale yellow oil, and **8** (1.27 g, 30%) as a pale yellow oil. $[\alpha]_D^{20}$ +8.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3046, 1726, 1455, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 4.68 (s, 2H), 4.24 (dq, *J* = 1.8, 6.9 Hz, 2H), 3.53 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.28 (s, 1H), 1.74−1.38 (m, 4H), 1.44 (s, 3H), 1.37−1.18 (m, 4H), 1.29 (t, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 138.5, 128.3 (2C), 127.7 (2C), 127.6, 84.9, 78.0, 74.8, 61.8, 31.9, 30.9, 26.3, 22.6, 22.5, 17.8, 14.0; HRMS (Fab+) $[M + H]^+$ calcd for $C_{18}H_{29}O_4$ 309.2066, found 309.2069.

Ethyl (2*R*,3*R*)-2,3-Dihydroxy-2-methyloctanoate (8) from 9b. A mixture of **9b** (1.11 g, 2.77 mmol) and 10% Pd on carbon (166 mg) in EtOH (28 mL) was stirred at 35 °C under hydrogen for 17 h. To the reaction mixture was added 10% Pd on carbon (111 mg), and the reaction was continued at 40 °C under hydrogen for 2.5 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 4:1 → 7:3) to afford **8** (533 mg, 88%) as a colorless oil.

Ethyl (2*R*,3*R*)-3-(Benzyloxy)-2-(methoxymethoxy)-2-methyloctanoate. To a stirred solution of **9a** (4.64 g, 15.0 mmol) and *i*-Pr_2NEt (7.7 mL, 45 mmol) in CH_2Cl_2 (100 mL) was added MOMCl (2.8 mL, 37 mmol) at 0 °C. The resultant mixture was allowed to warm to 35 °C, and stirring was continued for 4 days. The mixture was diluted with Et_2O (150 mL) and washed with 0.5 M aqueous HCl (50 mL), and then a mixture of saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 93:7 → 9:1) to afford the title compound (5.21 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +7.5 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2932, 1731, 1455, 1231 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 4.83 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.15 (dq, *J* = 10.5, 7.5 Hz, 1H), 4.12 (dq, *J* = 10.5, 7.5 Hz, 1H), 3.78 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.37 (s, 3H), 1.71−1.45 (m, 3H), 1.48 (s, 3H), 1.41−1.22 (m, 5H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 138.7, 128.2 (2C), 127.4 (2C), 127.4, 92.3, 83.7, 81.6, 74.4, 61.1, 56.1, 32.1, 30.5, 26.6, 22.6, 15.4, 14.1, 14.0; HRMS (Fab+) $[M + H]^+$ calcd for $C_{20}H_{33}O_5$ 353.2328, found 353.2321.

(2*R*,3*R*)-3-(Benzyloxy)-2-(methoxymethoxy)-2-methyloctan-1-ol (10). To a stirred solution of the MOM ether prepared above (959 mg, 2.72 mmol) in THF (18 mL) was added DIBALH (1.04 M solution in hexane, 8.0 mL, 8.3 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the mixture was allowed to warm to room temperature, and stirring was continued for 2 h. To the reaction mixture was added 1 M aqueous roschelle salt at 0 °C; the mixture was stirred at room temperature for 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O. The organic phase and the extract were combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 4:1) to afford **10** (788 mg, 93%) as a pale yellow oil. $[\alpha]_D^{20}$ −1.4 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3465, 2931, 1456, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.30 (m, 4H), 7.29−7.23 (m, 1H), 4.81 (d, *J* = 7.5 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 3.70 (dd, *J* = 12.5, 7.5 Hz, 1H), 3.59 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.55 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.43 (s, 3H), 3.24 (dd, *J* = 7.5, 6.0 Hz, 1H), 1.68−1.45 (m, 3H), 1.39−1.23 (m, 5H), 1.13 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.3 (2C), 127.7 (2C), 127.5, 90.9, 81.8, 81.7, 74.7, 65.6, 55.6, 32.2, 30.4, 26.8, 22.6, 15.7, 14.1; HRMS (Fab+) $[M + H]^+$ calcd for $C_{18}H_{31}O_4$ 311.2222, found 311.2230.

(2*S*,3*R*)-3-(Benzyloxy)-2-(methoxymethoxy)-2-methyl-1-triisopropylsilyloxyoctane. To a stirred solution of **10** (3.69 g, 11.9 mmol) in CH_2Cl_2 (119 mL) were added 2,6-lutidine (2.5 mL, 21 mmol) and TIPSOTf (3.8 mL, 14 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. To the reaction mixture were added H_2O (60 mL) and 1 M aqueous HCl (10 mL), and the layers were separated. The organic phase was washed with brine (60 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 19:1) to afford the title compound (5.55 g, quant.) as a colorless oil. $[\alpha]_D^{20}$ −0.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2946, 1457, 1120, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.30 (m, 3H), 7.29−7.23 (m, 2H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 1H), 4.62 (s, 2H), 3.76 (d, *J* = 10.5 Hz, 1H), 3.70 (d, *J* = 10.5 Hz, 1H), 3.51 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.36 (s, 3H), 1.70 (m, 1H), 1.64−1.51 (m, 2H), 1.40−1.24 (m, 5H), 1.31 (s, 3H), 1.15−1.00 (m, 21H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 128.2 (2C), 127.5 (2C), 127.3, 92.0, 82.9, 81.2, 74.6, 67.7, 55.4, 32.3, 30.4, 26.9, 22.7, 18.0 (6C), 17.0, 14.1, 12.0 (3C); HRMS (Fab+) $[M + H]^+$ calcd for $C_{27}H_{51}O_4Si$ 467.3557, found 467.3564.

(2*S*,3*R*)-2-(Methoxymethoxy)-2-methyl-1-((triisopropylsilyl)-oxy)octan-3-ol (11). A mixture of the TIPS ether prepared above (5.49 g, 11.8 mmol) and 10% Pd on carbon (549 mg) in EtOH (118 mL) was stirred at 30 °C under hydrogen for 3 h. To the reaction mixture was added 10% Pd on carbon (549 mg), and the reaction was continued at 30 °C under hydrogen for 2 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt,

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19:1) to afford **11** (4.41 g, quant.) as a colorless oil. $[\alpha]_D^{20}$ +9.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3466, 2947, 1464, 1117, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 10.0 Hz, 1H), 3.75 (d, *J* = 10.0 Hz, 1H), 3.60 (m, 1H), 3.38 (s, 3H), 3.12 (d, *J* = 5.5 Hz, 1H), 1.67−1.50 (m, 2H), 1.42−1.24 (m, 6H), 1.29 (s, 3H), 1.17−1.00 (m, 21H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.4, 80.6, 76.0, 68.5, 55.5, 32.0, 31.1, 26.4, 22.7, 18.0 (6C), 17.0, 14.1, 11.8 (3C); HRMS (Fab+) $[M + H]^+$ calcd for $C_{20}H_{45}O_4Si$ 377.3087, found 377.3093.

Dimethyl 2-(((2*S*,3*R*)-2-(Methoxymethoxy)-2-methyl-1-((triisopropylsilyl)oxy)octan-3-yl)oxy)maleate ((*E*)-13) and Dimethyl 2-(((2*S*,3*R*)-2-(Methoxymethoxy)-2-methyl-1-((triisopropylsilyl)oxy)octan-3-yl)oxy)fumarate ((*Z*)-13). To a stirred solution of **11** (162 mg, 0.431 mmol) in THF (4.0 mL) was added *n*-BuLi (1.6 M solution in hexane, 0.054 mL, 0.11 mmol) at −78 °C. After stirring at the same temperature for 15 min, a solution of freshly distilled **12** (91.9 mg, 0.647 mmol) in THF (1.5 mL) was added slowly at −78 °C. The mixture was stirred at the same temperature for 1 h, and then allowed to warm to 0 °C, and stirring was continued for 1 h. The reaction was qenched with saturated aqueous NH_4Cl (10 mL) and H_2O (5.0 mL). The whole was extracted with Et_2O (20 mL × 3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 19:1 → 93:7) to afford (*E*)-**13** (185 mg, 83%) as a colorless oil and (*Z*)-**13** (9.9 mg, 4%) as a colorless oil. (*E*)-**13**: $[\alpha]_D^{21}$ −16.8 (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 2954, 1750, 1716, 1623, 1369, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.82 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.38 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.87 (s, 3H), 3.70 (d, *J* = 10.0 Hz, 1H), 3.68 (s, 3H), 3.63 (d, *J* = 10.0 Hz, 1H), 3.35 (s, 3H), 1.81−1.67 (m, 2H), 1.49 (m, 1H), 1.37−1.24 (m, 5H), 1.33 (s, 3H), 1.16−0.99 (m, 21H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.2, 163.0, 93.3, 91.8, 83.5, 80.1, 67.3, 55.5, 52.8, 51.4, 32.0, 29.2, 25.8, 22.4, 18.0 (3C), 18.0 (3C), 17.2, 14.0, 11.9 (3C); HRMS (Fab+) $[M + H]^+$ calcd for $C_{26}H_{51}O_8Si$ 519.3353, found 519.3358. (*Z*)-**13**: $[\alpha]_D^{25}$ −8.1 (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 2954, 1735, 1717, 1629, 1463, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.61 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.79 (s, 3H), 3.78 (d, *J* = 10.5 Hz, 1H), 3.75 (d, *J* = 10.5 Hz, 1H), 3.70 (s, 3H), 3.32 (s, 3H), 1.77−1.64 (m, 2H), 1.56 (m, 1H), 1.42−1.21 (m, 5H), 1.35 (s, 3H), 1.15−0.97 (m, 21H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 163.2, 156.3, 104.3, 92.0, 86.1, 80.8, 67.2, 55.4, 52.4, 51.2, 32.0, 30.3, 26.3, 22.5, 18.0 (6C), 17.2, 14.0, 11.9 (3C); HRMS (Fab+) $[M + H]^+$ calcd for $C_{26}H_{51}O_8Si$ 519.3353, found 519.3348.

Dimethyl 2-(((2*S*,3*R*)-1-Hydroxy-2-(methoxymethoxy)-2-methyloctan-3-yl)oxy)maleate. A solution of (*E*)-**13** (237 mg, 0.457 mmol) in HF·pyr./pyr./THF (1:2:2) (5.0 mL) was stirred at room temperature for 24 h and then at 30 °C for 52 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL), and the mixture was stirred for 10 min. The whole was extracted with Et_2O (20 mL × 2), and the combined extracted was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 3:2) to afford the title compound (165 mg, quant.) as a pale yellow oil. $[\alpha]_D^{21}$ −16.2 (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 3517, 2956, 1749, 1712, 1627, 1439, 1371, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 4.84 (d, *J* = 7.6 Hz, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.34 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.55 (dd, *J* = 13.8, 6.8 Hz, 1H), 3.51 (dd, *J* = 13.2, 7.2 Hz, 1H), 3.43 (s, 3H), 3.00 (dd, *J* = 7.2, 6.8 Hz, 1H), 1.77 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.38−1.22 (m, 5H), 1.15 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.3, 162.3, 94.0, 90.8, 81.3, 80.8, 64.4, 55.8, 52.8, 51.5, 31.8, 29.2, 25.8, 22.4, 15.1, 14.0; HRMS (Fab+) $[M + H]^+$ calcd for $C_{17}H_{31}O_8$ 363.2019, found 363.2019.

Dimethyl 2-(((2*R*,3*R*)-2-(Methoxymethoxy)-2-methyl-1-oxooctan-3-yl)oxy)maleate (14). To a stirred solution of the alcohol prepared above (940 mg, 2.59 mmol) in CH_2Cl_2 (26 mL) was added Dess−Martin periodinane (2.20 g, 5.19 mmol) at room temperature. The reaction mixture was stirred for 2 h and poured into a mixture of 5% aqueous Na_2SO_3 (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (30 mL), and stirred for 10 min. The whole was extracted with Et_2O (50 mL, 30 mL × 2). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 4:1 → 3:1) to afford **14** (857 mg, 92%) as a pale yellow oil. $[\alpha]_D^{21}$ +9.7 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 2956, 1747, 1626 1439, 1295, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 5.35 (s, 1H), 4.86 (d, *J* = 7.2 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 1H), 4.33 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.41 (s, 3H), 1.77−1.53 (m, 3H), 1.41−1.15 (m, 5H), 1.36 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 166.4, 163.7, 162.0, 94.6, 92.0, 83.8, 83.3, 55.9, 52.9, 51.6, 31.6, 29.7, 25.3, 22.3, 14.6, 13.9; HRMS (Fab+) $[M + H]^+$ calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1856.

Dimethyl (2*R*,3*S*,4*R*)-4-Hydroxy-3-(methoxymethoxy)-3-methyl-2-pentyl-3,4-dihydro-2*H*-pyran-5,6-dicarboxylate (15a) and Dimethyl (2*R*,3*R*,4*R*)-3-(Methoxymethoxy)-3-methyl-2-pentyl-4-((trimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-5,6-dicarboxylate (15b) and Dimethyl (2*R*,3*S*,4*S*)-4-Hydroxy-3-(methoxymethoxy)-3-methyl-2-pentyl-3,4-dihydro-2*H*-pyran-5,6-dicarboxylate (15c). To a stirred solution of NaHMDS (1.0 M solution in THF, 2.4 mL, 2.4 mmol) in THF (10 mL) was added a solution of **14** (574 mg, 1.59 mmol) in THF (6.0 mL) at −78 °C, and the mixture was stirred at the same temperature for 45 min. To the reaction mixture were added saturated aqueous NH_4Cl (10 mL) and H_2O (20 mL). The whole was extracted with Et_2O (20 mL × 2), and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane−AcOEt, 3:1) to afford **15a** (321 mg, 56%) as a colorless oil, **15b** (30.1 mg, 4%) as a colorless oil, and **15c** (23.5 mg, 4%) as a colorless oil. **15a**: $[\alpha]_D^{25}$ +24.1 (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 3421, 2956, 1749, 1636, 1439, 1300, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, *J* = 7.0 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.54 (d, *J* = 3.0 Hz, 1H), 3.98 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.64 (br s, 1H), 3.41 (s, 3H), 1.81−1.67 (m, 2H), 1.66−1.50 (m, 1H), 1.41−1.24 (m, 5H), 1.30 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 163.2, 151.3, 109.1, 91.4, 82.7, 75.6, 69.9, 55.9, 52.7, 52.1, 31.5, 27.4, 26.1, 22.5, 14.0, 12.1; HRMS (Fab+) $[M + H]^+$ calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1863. **15b**: $[\alpha]_D^{27}$ +34.0 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 2956, 1749, 1634 1438, 1298, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, *J* = 7.5 Hz, 1H), 4.75 (d, *J* = 7.5 Hz, 1H), 4.41 (d, *J* = 2.5 Hz, 1H), 4.27 (dt, *J* = 11.0, 2.5 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.34 (s, 3H), 2.10 (m, 1H), 1.56 (m, 1H), 1.43−1.18 (m, 6H), 1.36 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 164.2, 152.6, 106.6, 91.1, 82.5, 76.3, 67.5, 55.8, 52.7, 51.5, 31.4, 28.3, 26.6, 22.5, 17.4, 14.0, 0.22 (3C); HRMS (Fab+) $[M + H]^+$ calcd for $C_{20}H_{37}O_8Si$ 433.2258, found 433.2252. **15c**: $[\alpha]_D^{25}$ +58.7 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3460, 2956, 1749, 1714, 1636, 1439, 1302, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, *J* = 7.2 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 2.8 Hz, 1H), 4.11 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.60 (d, *J* = 2.8 Hz, 1H), 3.45 (s, 3H), 1.79 (m, 1H), 1.70−1.17 (m, 7H), 1.10 (s, 3H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 163.6, 155.8, 105.7, 91.3, 77.7, 76.2, 66.4, 56.0, 52.8, 52.0, 31.7, 27.2, 25.8, 22.5, 14.4, 14.0; HRMS (Fab+) $[M + H]^+$ calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1868.

(2*R*,3*S*,4*R*)-4-Hydroxy-6-methoxy-3-(methoxymethoxy)-3-methyl-2-pentyl-3,4-dihydropyrano[2,3-*c*]pyrrole-5,7(2*H*,6*H*)-dione (17) and Methyl (2*R*,3*S*,4*R*)-4-Hydroxy-6-(methoxycarbamoyl)-3-(methoxymethoxy)-3-methyl-2-pentyl-3,4-dihydro-2*H*-pyran-5-carboxylate (18). To a stirred solution of **15a** (315 mg, 0.875 mmol) in MeOH (10 mL) was added 1.0 M aqueous NaOH (1.3 mL, 1.3 mmol) at room temperature. The resulting mixture was stirred at 35 °C for 15 h and then concentrated *in vacuo*. The residual oil was dissolved in H_2O (13 mL), and 1 M aqueous HCl (3.9 mL) was added to this solution. The whole was extracted with AcOEt (20 mL × 2), and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude acid **16** was carried forward without further purification.

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To a stirred solution of the crude product (296 mg) in CH_2Cl_2 (29 mL) were added $MeONH_2$·HCl (183 mg, 2.19 mmol), Et_3N (0.49 mL, 3.5 mmol), HOBt·H_2O (268 mg, 1.75 mmol), and WSC·HCl (336 mg, 1.75 mmol) at room temperature, and the mixture was stirred for 14 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane−AcOEt, 13:7 → 7:13) to afford **17** (146 mg, 49%) as a pale yellow oil and **18** (51.7 mg, 16%) as a colorless oil. **17**: $[\alpha]_D^{25}$ +46.3 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3413, 2934, 1739, 1672, 1559, 1457, 1233, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 1H), 4.57 (br s, 1H), 4.13 (m, 1H), 3.96 (s, 3H), 3.44 (s, 3H), 1.89−1.60 (m, 3H), 1.44−1.18 (m, 6H), 1.26 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 160.4, 152.7, 109.3, 91.2, 85.9, 76.9, 67.9, 66.0, 56.1, 31.5, 27.7, 26.0, 22.4, 14.0, 10.9; HRMS (Fab+) $[M + H]^+$ calcd for $C_{16}H_{26}NO_7$ 344.1709, found 344.1706. **18**: $[\alpha]_D^{27}$ +10.9 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 3407, 2934, 1705, 1668, 1635, 1540, 1468, 1290, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 4.92 (d, *J* = 7.0 Hz, 1H), 4.70 (m, 1H), 4.55 (s, 1H), 4.03 (br s, 1H), 3.89 (m, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.42 (s, 3H), 1.92 (m, 1H), 1.78 (m, 1H), 1.60 (m, 1H), 1.43−1.16 (m, 4H), 1.24 (s, 3H), 1.00−0.81 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 159.4, 146.5, 113.4, 91.2, 82.3, 75.6, 71.3, 64.5, 55.9, 52.3, 31.5, 27.3, 26.1, 22.4, 13.9, 10.6; HRMS (Fab+) $[M + H]^+$ calcd for $C_{17}H_{29}NO_8$ 376.1971, found 376.1978.

(2*R*,3*S*,4*R*)-4-Hydroxy-6-methoxy-3-(methoxymethoxy)-3-methyl-2-pentyl-3,4-dihydropyrano[2,3-*c*]pyrrole-5,7(2*H*,6*H*)-dione (17) from 18. A solution of **18** (47.3 mg, 0.126 mmol) and Et_3N (53 μL, 0.38 mmol) in DMF (1.3 mL) was stirred at 50 °C for 6 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane−AcOEt, 7:3 → 13:7) to afford **17** (41.7 mg, 96%) as a pale yellow oil.

***ent*-Phaeosphaeride A (1c).** To a stirred solution of **17** (21.3 mg, 0.062 mmol) in Et_2O (1.0 mL) was added MeMgBr (0.5 M solution in Et_2O, 0.31 mL, 0.16 mmol) at −78 °C. The mixture was stirred at the same temperature for 30 min. To the reaction mixture was added MeMgBr (0.5 M solution in Et_2O, 0.10 mL, 0.050 mmol), and the stirring was continued for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (10 mL × 2). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude hemiaminal was carried forward without further purification.

The crude product was dissolved in a solution of HCl (ca. 4 mol/L solution in 1,4-dioxane, 1.0 mL) at room temperature. The reaction mixture was stirred at the same temperature for 1.5 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane−AcOEt, 3:2 → 1:1) to afford **1c** (6.6 mg, 36%) as a colorless oil. $[\alpha]_D^{25}$ +74.5 (*c* 2.00, CH_2Cl_2); IR ($CHCl_3$) 3420, 2932, 2862, 1707, 1637, 1441, 1085, 1064 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.42 (d, *J* = 5.5 Hz, 1H), 4.97 (s, 2H), 4.90 (s, 1H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.87 (d, *J* = 5.5 Hz, 1H), 3.79 (s, 3H), 1.82 (m, 1H), 1.57−1.39 (m, 3H), 1.36−1.10 (m, 4H), 1.18 (s, 3H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 155.3, 137.1, 104.8, 90.7, 86.2, 70.9, 64.3, 63.7, 30.9, 27.6, 26.1, 21.9, 20.3, 13.8; HRMS (Fab+) $[M + H]^+$ calcd for $C_{15}H_{24}NO_5$ 298.1654, found 298.1652.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all 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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(11) The use of *n*-BuLi gave the best result in our previous synthesis of **1a**; see ref 5.
(12) (a) Tatsuta, K.; Suzuki, Y.; Furuyama, A.; Ikegami, H. *Tetrahedron Lett.* **2006**, *47*, 3595. (b) NaHMDS gave the best yield and stereoselectivity in our studies on **1a**; see ref 5.
(13) The TMS group in **15b** was apparently derived from NaHMDS.
(14) Although we examined TBS protection of **15a** based on our preceding work (see ref 5), the yield of the reaction was only 14%.
(15) In the synthesis of **1a** (see ref 5), a higher reaction temperature (130 °C) was needed to form a maleimide (corresponding to **17**) from an amide (corresponding to **18**). The high reactivity of **18** toward the maleimide formation seemed to result from the lack of a TBS group.

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