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PAPER

Synthesis of the proposed structure of phaeosphaeride A†

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The first total synthesis of the proposed structure of phaeosphaeride A has been achieved *via* six-membered-ring formation by means of an intramolecular vinyl-anion aldol reaction as the key step. This synthesis suggests a revised configurational assignment for phaeosphaeride A.

Introduction

Signal transducer and activator of transcription 3 (STAT3) is a critical protein for cell proliferation and survival. Since STAT3 has an important role in oncogenesis,[1] it has been a novel target protein for treating tumors, and small-molecule inhibitors of STAT3 are considered to be candidate anti-cancer chemotherapeutic agents.[2] Phaeosphaerides A (**1**) and B (**2**) are nitrogen-containing natural products isolated from an endophytic fungus in 2006 by Clardy and co-workers (Fig. 1).[3] Phaeosphaeride A (**1**) inhibits the growth of STAT3-dependent U266 multiple myeloma cells with an IC_{50} of 6.7 μM *in vitro*, whereas phaeosphaeride B (**2**) showed no activity against STAT3. Although the relative stereochemistries of phaeosphaerides A (**1**) and B (**2**) were deduced to be as depicted in Fig. 1 on the basis of NOE experiments, the absolute configurations remained unknown. Captivated by this unique molecular structure and promising biological activity, we launched a synthetic study of phaeosphaeride A. Here, we describe the first total synthesis of the proposed structure **1** of phaeosphaeride A.

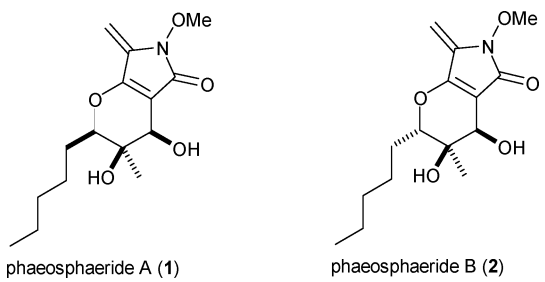
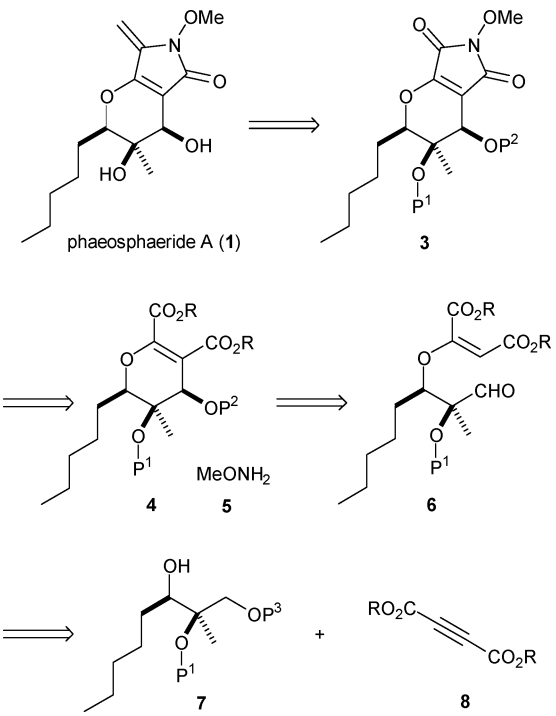


Fig. 1 Proposed structures of phaeosphaerides.

Results and discussion

Our synthetic planning involved oxy-Michael reaction followed by vinyl-anion aldol reaction as shown in the retrosynthetic analysis (Scheme 1). Phaeosphaeride A (**1**) would be obtained by regioselective methylenation of one of the two carbonyl groups in maleimide **3**. The maleimide moiety of **3** can be assembled from diester **4** and methoxyamine (**5**). The dihydropyran ring of **4** might then be constructed by vinyl-anion aldol reaction[4] of the olefinic aldehyde **6**, obtained by oxy-Michael reaction of secondary alcohol **7** with acetylenedicarboxylate (**8**).



Scheme 1 Retrosynthetic analysis of phaeosphaeride A (**1**).

Our investigation was initiated by preparation of alcohol **13**, corresponding to **7**, from hexanal (**9**) (Scheme 2). Thus, Horner–Wadsworth–Emmons reaction of **9** afforded α,β-unsaturated ester (*E*)-**10**[5] (77%) and (*Z*)-**10** (8.5%). As expected,

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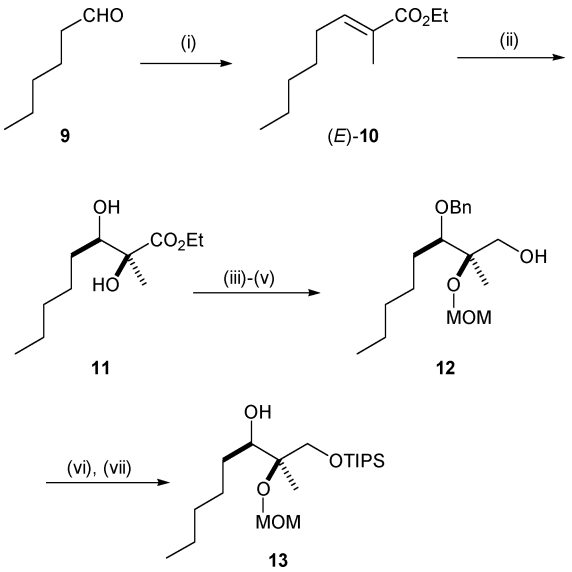
† Electronic supplementary information (ESI) available: CIF file of compound **20** and ^{1}H and ^{13}C-NMR spectra. CCDC reference number 823955. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05612c



Scheme 2 *Reagents and conditions*: (i) $(EtO)_2P(O)CH(CH_3)CO_2Et$, NaH, DME, 77%; (ii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 99%; (iii) NaH, BnBr, THF, 60%; (iv) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 98%; (v) DIBALH, THF, quant.; (vi) TIPSOTf, 2,6-lutidine, CH_2Cl_2, quant.; (vii) H_2, Pd/C, EtOH, 99%.

Sharpless dihydroxylation[6] of (*E*)-**10** provided the requisite α,β-dihydroxyester **11** with high enantioselectivity (98% ee), as determined by the modified Mosher's method (Fig. 2).[7] Benzyl protection of the secondary hydroxy group, MOM protection of the tertiary hydroxy group, and subsequent reduction of the ester group using DIBALH gave primary alcohol **12**. TIPS ether formation of **12** followed by debenzylation provided oxy-Michael precursor alcohol **13**.

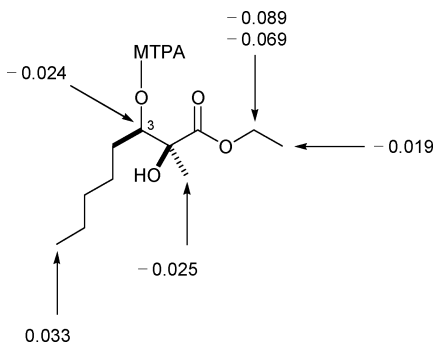
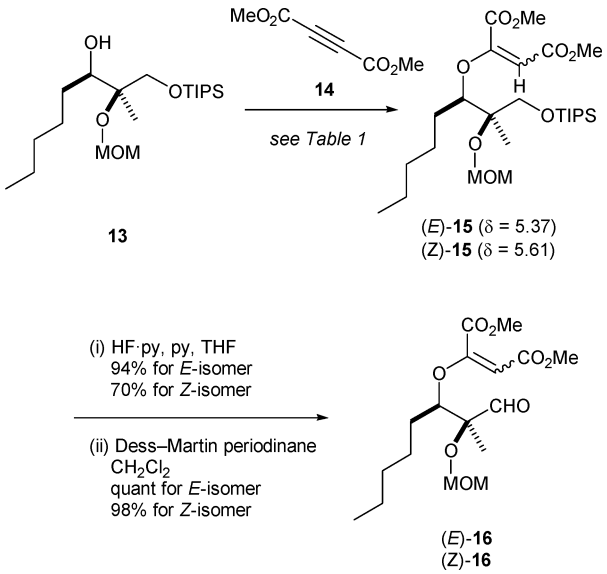


Fig. 2 Modified Mosher's method: differences of the chemical shifts ($\Delta\delta = (\delta_S - \delta_R)$, $CDCl_3$) between (*R*)- and (*S*)-MTPA esters of **11**.

Next we examined oxy-Michael addition of **13** to dimethyl acetylenedicarboxylate (**14**) (Scheme 3, Table 1). After screening several reaction conditions (Table 1, entries 1–5),[8] the use of *n*-BuLi at −78 °C to 0 °C was found to give a good yield of (*E*)-**15** (76%) and (*Z*)-**15** (18%) (entry 6). The stereochemistries of these compounds were confirmed by ^{1}H NMR analysis, which indicated that the olefinic proton signal of (*Z*)-**15** was shifted downfield compared to that of (*E*)-**15**.[9] Desilylation of (*E*)-**15** and (*Z*)-**15** with HF·py followed by Dess–Martin oxidation gave the cyclization precursors (*E*)-**16** and (*Z*)-**16**, respectively.



Scheme 3 Synthesis of aldehydes (*E*)-**16** and (*Z*)-**16**.

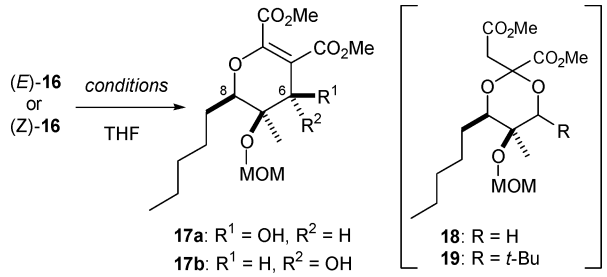
Table 1 Oxy-Michael addition of alcohol **13** to **14**

Entry	Reagent (eq)	Solvent	Temp	Yield (%)[a] (*E*)-**15**	(*Z*)-**15**
1	DABCO (0.1)	CH_2Cl_2	rt to 35 °C	0	0
2	DMAP (0.1)	CH_2Cl_2	rt to 35 °C	0	0
3	AgOTf (0.05)	CH_2Cl_2	rt to 35 °C	0	0
4	LHMDS (0.2)	THF	−78 °C to rt	22	0
5	KHMDS (0.2)	THF	−78 °C to rt	43	0
6	*n*-BuLi (0.2)	THF	−78 °C to 0 °C	76	18

[a] Isolated yield.

The crucial construction of the six-membered-ring by means of a vinyl-anion aldol reaction was next examined (Table 2). First MHMDS (M = Li or Na or K) was examined as a base (Table 2, entries 1–3). Treatment of (*E*)-**16** with LiHMDS provided the desired **17a** (10%) and its diastereomer **17b** (26%) (entry 1). The use of NaHMDS was found to give **17a** in the best yield (43%) accompanied by **17b** in 21% yield (entry 2). When KHMDS was employed, the stereoselectivity and the chemical yield were fairly low (entry 3). Furthermore, reaction of LDA surprisingly afforded **18** as a major product (entry 4), and *t*-BuLi reacted with the formyl group of (*E*)-**16** to give mainly compound **19** (entry 5). In contrast to entry 2, treatment of (*Z*)-**16** with NaHMDS gave only trace amounts of **17a** and **17b**. When **17a** or **17b** was independently treated with NaHMDS at −78 °C, no epimerization at the C-6 stereogenic center occurred. From these results, the present cyclization appears to be a kinetically controlled addition reaction of an allenic enolate.[10] A plausible transition state for the formation of **17a** is depicted in Fig. 3. The ^{1}H NMR spectrum of **17a** showed W-type long-range coupling between H-6 and H-8 (J = 1.3 Hz), whereas the corresponding long-range coupling was not observed for diastereomer **17b**. This observation suggested a pseudo-diequatorial relationship of H-6 and H-8 of **17a**, and hence the stereochemistry of the resulting stereocenter C-6 in **17a** was deduced to be 6*R*.

Table 2 Vinyl-anion aldol reaction of (*E*)-**16** and (*Z*)-**16**



Entry	Substrate	Reagent[a]	Temp	Yield (%)[b] 17a	17b
1	(*E*)-**16**	LiHMDS	−78 °C	10	26
2	(*E*)-**16**	NaHMDS	−78 °C	43	21
3	(*E*)-**16**	KHMDS	−78 °C	12	9
4	(*E*)-**16**	LDA[c]	−78 °C	trace	0
5	(*E*)-**16**	*t*-BuLi[d]	−78 °C	0	0
6	(*Z*)-**16**	NaHMDS	−78 °C	trace	0

[a] All reactions were performed with 1.5 equiv. of the reagent. [b] Isolated yield. [c] Compound **18** was obtained as a major product. [d] Compound **19** was obtained as a major product.

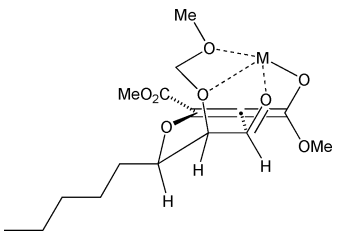
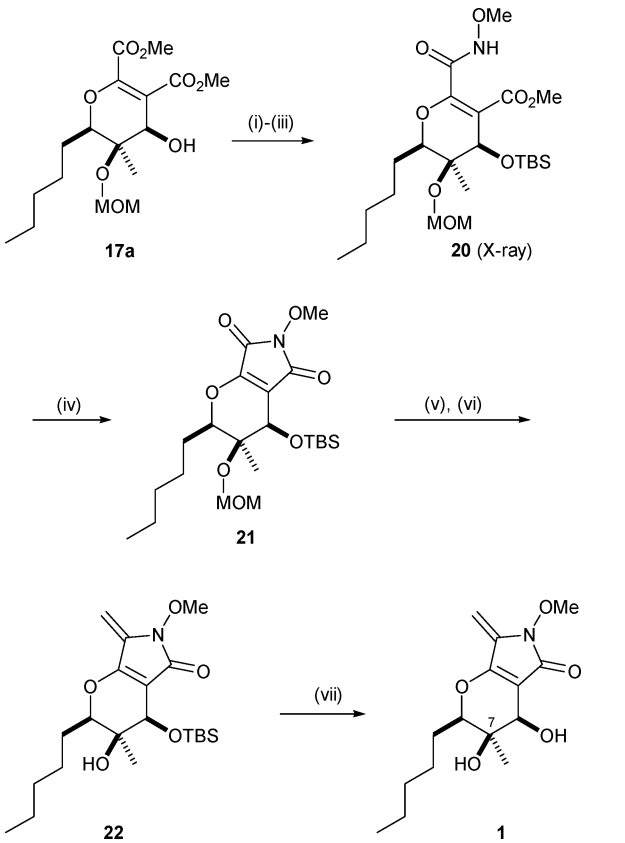


Fig. 3 Plausible transition state for the formation of **17a**.

Aldol adduct **17a** has the correct stereochemistry for phaeosphaeride A (**1**), and elaboration to **1** was now required (Scheme 4). Silylation of alcohol **17a**, regioselective hydrolysis, and subsequent condensation with $MeONH_2$ (**5**) gave the desired amide **20** (78% in 3 steps), of which the structure, including stereochemistry, was unambiguously determined by X-ray diffraction (Fig. 4).† For the formation of the maleimide moiety, the use of NaH[11] or DIPEA as a base in THF proved to be ineffective, and a significant amount of the starting material was recovered. After experimentation, treatment of **20** with Et_3N in DMF at 130 °C was found to afford the desired maleimide **21** in 70% yield. Since direct methylenation of **21** with Tebbe reagent[12] afforded a complex mixture, a stepwise conversion had to be investigated. To our delight, regioselective methylation with MeMgBr followed by treatment with HCl in dioxane led to spontaneous dehydration and removal of the MOM group at C-7 to provide the *exo* methylene compound **22**.[13] Finally, removal of the remaining silyl group on the C-6 hydroxy group with 3HF·Et_3N furnished synthetic **1**.

Surprisingly, the ^1H and ^{13}C NMR data for synthetic **1** were not identical with those reported for the natural sample. In particular, the observed chemical shifts of certain protons (H-6, H-8, and H-15) and carbons (C-6, C-7, and C-8) of synthetic **1** significantly deviated from those reported for natural phaeosphaeride A. Since NOE correlations between H-6 and H-8 for the natural sample were observed,[3] one possibility for the correct structure



Scheme 4 *Reagents and conditions*: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 97%; (ii) 1 M NaOH, MeOH–H_2O, 90%; (iii) $MeONH_2$·HCl, Et_3N, WSC·HCl, HOBt, CH_2Cl_2, 89%; (iv) Et_3N, DMF, 70%; (v) MeMgBr, Et_2O, quant.; (vi) HCl–dioxane, dioxane, 52%; (vii) 3HF·Et_3N, THF, 90%.

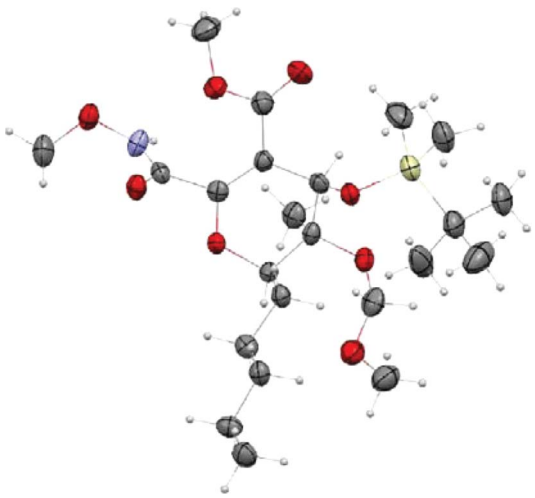


Fig. 4 ORTEP drawing of amide **20**.

of phaeosphaeride A may be the C-7 epimer of the originally proposed **1**.

Conclusion

We have accomplished the first synthesis of the proposed structure of phaeosphaeride A, featuring six-membered-ring formation by means of a vinyl-anion aldol reaction. Although the spectral

properties of synthetic phaeosphaeride A differed from those of the natural product, the result obtained here would be a good starting point for eventual proof of the structure of natural phaeosphaeride A.

Experimental

General

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1020 auto digital polarimeter. Infrared spectra (IR) were recorded with PerkinElmer spectrum 100. ^{1}H NMR spectra were recorded on a JEOL JNM-AL300 (300 MHz) or a Bruker AVANCE 500 (500 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane (δ = 0) as an internal standard ($CDCl_3$ 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 recorded on a JEOL JNM-AL300 (75 MHz), a Bruker AVANCE 500 (125 MHz), or a Bruker AVANCE 600 (150 MHz) spectrometer. The chemical shifts are reported in ppm, relative to the central line of a triplet at 77.0 ppm for $CDCl_3$. Measurements of mass spectra (MS) and high resolution MS (HRMS) were performed with a JEOL JMS SX-102A or a JEOL JMS-T100LP mass spectrometer. Column chromatography was carried out on silica gel (silica gel 40–50 μm neutral, Kanto Chemical Co., Inc.). Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for the TLC analysis. After extractive workup, organic layers were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

Ethyl (*E*)-2-methyl-oct-2-enoate [(*E*)-10] and its (*Z*)-isomer [(*Z*)-10]. To a stirred suspension of NaH (60% in mineral oil, 3.36 g, 84.0 mmol) in DME (120 mL) was added a solution of triethyl 2-phosphonopropionate (20.0 g, 84.0 mmol) in DME (10 mL) at 0 °C. After being stirred at the same temperature for 5 min, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 10 min. The resulting pale yellow solution was cooled to 0 °C, a solution of hexanal (7.01 g, 70.0 mmol) in DME (10 mL) was added slowly, and stirring was continued for 1 h. The reaction mixture was poured into H_2O (420 mL) and extracted with Et_2O (100 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, 49 : 1) to afford (*E*)-**10** (9.95 g, 77%) as a colorless oil and (*Z*)-**10** (1.10 g, 8.5%) as a colorless oil. (*E*)-**10**: IR (film) 2930, 1700, 1648, 1458, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.76 (tq, *J* = 7.5, 1.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.16 (qq, *J* = 7.6, 0.8 Hz, 2H), 1.84–1.82 (m, 3H), 1.49–1.39 (m, 2H), 1.37–1.25 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 142.4, 127.6, 60.3, 31.5, 28.6, 28.2, 22.5, 14.3, 14.0, 12.3; MS (Fab+) *m*/*z* 185 (M+H)$^+$; HRMS calcd for $C_{11}H_{21}O_2$ 185.1542, found 185.1545. (*Z*)-**10**: IR (film) 2928, 1703, 1647, 1457, 1210 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (tq, *J* = 7.5, 1.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.42 (qq, *J* = 7.5, 1.4 Hz, 2H), 1.89 (q, *J* = 1.4 Hz, 3H), 1.45–1.36 (m, 2H), 1.35–1.26 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 143.1, 127.0, 60.0, 31.5, 29.5, 29.1, 22.5, 20.6, 14.2, 14.0; MS (Fab+) *m*/*z* 185 (M+H)$^+$; HRMS calcd for $C_{11}H_{21}O_2$ 185.1542, found 185.1545.

Ethyl (2*S*,3*R*)-2,3-dihydroxy-2-methyloctanoate (11). To a stirred solution of AD-mix-β (59.5 g) and methanesulfonamide (4.05 g, 42.6 mmol) in *t*-BuOH (200 mL) and H_2O (200 mL) was added (*E*)-**10** (7.84 g, 42.5 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 6 h. For workup, Na_2SO_3 (63.8 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 (200 mL × 2). The combined extracts were washed with 1 M aqueous NaOH (100 mL × 2) and brine (100 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 **11** (9.17 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +34.8 (*c* 0.50, $CHCl_3$); IR (film) 3513, 2956, 1726, 1378, 1261 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2H), 3.70 (dt, *J* = 1.8, 9.3 Hz, 1H), 3.39 (s, 1H), 1.86 (d, *J* = 9.3 Hz, 1H), 1.66–1.50 (m, 2H), 1.47–1.20 (m, 6H), 1.34 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 77.3, 75.5, 62.1, 31.7, 30.3, 25.5, 22.6, 21.7, 14.1, 14.0; MS (Fab+) *m*/*z* 219 (M+H)$^+$; HRMS 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 **11** were conducted by using modified Mosher's method. Derivatization of **11** to the corresponding (*R*)- or (*S*)-MTPA ester was conducted according to a usual method using the corresponding acid chlorides and pyridine. Since ^{1}H NMR of each crude product did not show the signals of the other diastereomer, the optical purity of **11** was estimated to be more than 98% ee. (*R*)-MTPA ester of **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.53 (m, 2H), 7.46–7.32 (m, 3H), 5.34 (t, *J* = 6.6 Hz, 1H), 4.22 (dq, *J* = 10.5, 7.2 Hz, 1H), 4.12 (dq, *J* = 10.5, 7.2 Hz, 1H), 3.56 (d, *J* = 1.2 Hz, 3H), 3.22 (br s, 1H), 1.74–1.56 (m, 2H), 1.38 (s, 3H), 1.36–1.07 (m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 6.9 Hz, 3H). (*S*)-MTPA ester of **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.53 (m, 2H), 7.46–7.32 (m, 3H), 5.32 (dd, *J* = 8.1, 4.2 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.03 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.51 (d, *J* = 1.2 Hz, 3H), 3.22 (br s, 1H), 1.79–1.64 (m, 2H), 1.38–1.15 (m, 6H), 1.36 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H). The $\Delta\delta$ values for these MTPA esters revealed that the configuration of the secondary alcohol should be *R* (Fig. 2).

Ethyl (2*S*,3*R*)-3-benzyloxy-2-hydroxy-2-methyloctanoate. To a stirred suspension of NaH (60% in mineral oil, 201 mg, 5.01 mmol) in THF (10 mL) was added a solution of **11** (497 mg, 2.28 mmol) in THF (3.0 mL) at 0 °C. After stirring at the same temperature for 1.5 h, BnBr (0.32 mL, 2.7 mmol) was added. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 17 h. The mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (30 mL × 2). The combined extracts were washed with 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) to afford the title compound (423 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ +10.0 (*c* 0.50, $CHCl_3$); IR (film) 3566, 1732, 1456, 1220 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2H), 7.29–7.25 (m, 3H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.68 (dd, *J* = 7.4, 4.5 Hz, 1H), 3.24 (s, 1H), 1.72–1.62

(m, 2H), 1.61–1.51 (m, 1H), 1.42–1.27 (m, 5H), 1.34 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 138.2, 128.3 (2C), 127.6 (3C), 83.6, 77.6, 73.6, 61.6, 32.1, 29.1, 26.1, 22.6, 21.8, 14.1, 14.0; MS (Fab+) m/z 219 $(M+H)^+$; HRMS calcd for $C_{18}H_{29}O_4$ 309.2066, found 309.2066.

Ethyl (2*S*,3*R*)-3-benzyloxy-2-methoxymethoxy-2-methyloctanoate. To a stirred solution of the benzyl ether prepared above (419 mg, 1.36 mmol) in CH_2Cl_2 (10 mL) were added *i*-Pr_2NEt (0.69 mL, 4.1 mmol) and MOMCl (0.26 mL, 3.5 mmol) at 0 °C. The resultant mixture was allowed to warm to 40 °C, and stirring was continued for 4 days. The mixture was diluted with Et_2O (30 mL) and washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–AcOEt, 9 : 1) to afford the title compound (472 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ −3.0 (*c* 0.50, $CHCl_3$); IR (film) 2956, 1730, 1455, 1265 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H), 7.29–7.24 (m, 1H), 4.86 (d, J = 7.2 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.73 (d, J = 7.2 Hz, 1H), 4.62 (d, J = 11.3 Hz, 1H), 4.21 (dq, J = 10.8, 7.1 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 3.74 (dd, J = 9.4, 2.0 Hz, 1H), 3.40 (s, 3H), 1.58–1.48 (m, 2H), 1.46 (s, 3H), 1.37–1.19 (m, 6H), 1.27 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 138.9, 128.2 (2C), 127.7 (2C), 127.4, 92.8, 84.3, 84.0, 74.9, 61.0, 56.1, 31.8, 30.5, 26.3, 22.5, 16.5, 14.1, 14.0; MS (Fab+) m/z 353 $(M+H)^+$; HRMS calcd for $C_{20}H_{33}O_5$ 353.2328, found 353.2331.

(2*R*,3*R*)-3-Benzyloxy-2-methoxymethoxy-2-methyloctan-1-ol (12). To a stirred solution of the MOM ether prepared above (4.33 g, 12.3 mmol) in THF (82 mL) was added DIBAL-H (1.02 M solution in hexane, 36.1 mL, 36.8 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 Rochelle salt (147 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O (50 mL). The organic phase and the extract were combined and washed with brine (50 mL), 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 **12** (3.81 g, quant.) as a colorless oil. $[\alpha]_D^{25}$ +27.4 (*c* 0.50, $CHCl_3$); IR (film) 3465, 2956, 1455, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4H), 7.31–7.25 (m, 1H), 4.82 (d, J = 7.5 Hz, 1H), 4.77 (d, J = 7.5 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 3.65 (dd, J = 12.4, 6.5 Hz, 1H), 3.57 (dd, J = 12.4, 7.3 Hz, 1H), 3.49 (dd, J = 9.3, 2.5 Hz, 1H), 3.43 (s, 3H), 3.12 (dd, J = 7.3, 6.5 Hz, 1H), 1.66–1.54 (m, 2H), 1.53–1.44 (m, 1H), 1.39–1.21 (m, 5H), 1.25 (s, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.3 (2C), 127.7 (2C), 127.5, 91.2, 84.3, 82.5, 74.9, 66.0, 55.5, 32.1, 30.8, 26.6, 22.6, 16.8, 14.0; MS (Fab+) m/z 311 $(M+H)^+$; HRMS calcd for $C_{18}H_{31}O_4$ 311.2222, found 311.2219.

(2*R*,3*R*)-3-Benzyloxy-2-methoxymethoxy-2-methyl-1-triisopropylsilyloxyoctane. To a stirred solution of **12** (3.74 g, 12.0 mmol) in CH_2Cl_2 (120 mL) were added 2,6-lutidine (2.5 mL, 22 mmol) and TIPSOTf (3.9 mL, 15 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was washed with H_2O (60 mL) and 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 (5.61 g, quant.) as a colorless oil. $[\alpha]_D^{25}$ +0.4 (*c* 0.50, $CHCl_3$); IR (film) 2945, 1464, 1096, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4H), 7.28–7.23 (m, 1H), 4.95 (d, J = 7.1 Hz, 1H), 4.78 (d, J = 7.1 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 3.88 (d, J = 10.2 Hz, 1H), 3.73 (d, J = 10.2 Hz, 1H), 3.50 (dd, J = 9.5, 2.4 Hz, 1H), 3.37 (s, 3H), 1.68–1.43 (m, 3H), 1.35–1.21 (m, 5H), 1.28 (s, 3H), 1.16–1.00 (m, 21H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 128.2 (2C), 127.7 (2C), 127.3, 91.9, 83.9, 81.9, 74.8, 67.2, 55.3, 32.2, 30.6, 26.8, 22.7, 18.0 (6C), 17.6, 14.1, 12.0 (3C); MS (Fab+) m/z 467 $(M+H)^+$; HRMS calcd for $C_{27}H_{51}O_4Si$ 467.3557, found 467.3569.

(2*R*,3*R*)-2-Methoxymethoxy-2-methyl-1-triisopropylsilyl-oxyoctan-3-ol (13). A mixture of the TIPS ether prepared above (5.49 g, 11.8 mmol) and 10% Pd on charcoal (549 mg) in EtOH (120 mL) was stirred at room temperature 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, 19 : 1) to afford **13** (4.39 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +13.4 (*c* 0.50, $CHCl_3$); IR (film) 3482, 2946, 1464, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (d, J = 7.3 Hz, 1H), 4.78 (d, J = 7.3 Hz, 1H), 3.84 (d, J = 10.3 Hz, 1H), 3.73 (d, J = 10.3 Hz, 1H), 3.69–3.62 (m, 1H), 3.39 (s, 3H), 3.01 (dd, J = 5.9, 0.7 Hz, 1H), 1.71–1.60 (m, 1H), 1.60–1.49 (m, 1H), 1.42–1.23 (m, 6H), 1.21 (s, 3H), 1.16–1.02 (m, 21H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 91.6, 80.8, 74.6, 68.2, 55.4, 32.0, 31.4, 26.4, 22.7, 18.0 (6C), 17.2, 14.1, 11.8 (3C); MS (Fab+) m/z 467 $(M+H)^+$; HRMS calcd for $C_{20}H_{45}O_4Si$ 377.3087, found 377.3088.

Dimethyl (*E*)-2-{(1*R*)-1-[(1*R*)-1-methoxymethoxy-1-methyl-2-triisopropylsilyloxyethyl]hexyloxy}but-2-enedioate [(*E*)-15] and its (*Z*)-isomer [(*Z*)-15]. To a stirred solution of **13** (207 mg, 0.550 mmol) in THF (5.0 mL) was added *n*-BuLi (1.55 M solution in hexane, 0.071 mL, 0.11 mmol) at −78 °C. After stirring at the same temperature for 15 min, a solution of **14** (0.50 M, 1.7 mL, 0.85 mmol) in THF was added 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 quenched with saturated aqueous NH_4Cl (10 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (10 mL). The organic phase and the extract were combined and washed with brine (10 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) to afford (*E*)-**15** (216 mg, 76%) as a colorless solid and (*Z*)-**15** (52.6 mg, 18%) as a colorless oil. (*E*)-**15**: mp 36–37 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +4.8 (*c* 0.50, $CHCl_3$); IR (film) 2952, 1749, 1712, 1622, 1367, 1148 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.81 (d, J = 7.5 Hz, 1H), 4.72 (d, J = 7.5 Hz, 1H), 4.37 (dd, J = 9.9, 2.5 Hz, 1H), 3.87 (s, 3H), 3.80 (d, J = 10.5 Hz, 1H), 3.68 (s, 3H), 3.67 (d, J = 10.6 Hz, 1H), 3.35 (s, 3H), 1.76–1.67 (m, 1H), 1.66–1.55 (m, 1H), 1.54–1.44 (m, 1H), 1.36–1.22 (m, 5H), 1.25 (s, 3H), 1.16–1.00 (m, 21H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.3, 163.2, 93.5, 91.5, 84.4, 80.6, 66.7, 55.3, 52.7, 51.4, 31.9, 29.8, 25.8, 22.4, 17.9 (6C), 16.6, 14.0, 11.9 (3C); MS (Fab+) m/z 519 $(M+H)^+$; HRMS calcd for $C_{26}H_{51}O_8Si$ 519.3353, found 519.3350. (*Z*)-**15**:

$[\alpha]_D^{25}$ −28.8 (*c* 0.50, $CHCl_3$); IR (film) 2952, 1735, 1716, 1626, 1463, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.82 (dd, J = 9.2, 2.4 Hz, 1H), 4.65 (d, J = 7.5 Hz, 1H), 4.63 (d, J = 7.5 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.63 (d, J = 11.2 Hz, 1H), 3.29 (s, 3H), 1.71–1.54 (m, 2H), 1.49–1.38 (m, 1H), 1.37–1.25 (m, 5H), 1.23 (s, 3H), 1.14–0.98 (m, 21H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 163.4, 157.6, 101.7, 91.0, 85.3, 81.4, 66.6, 55.6, 52.2, 51.0, 32.0, 30.1, 26.1, 22.6, 18.0 (3C), 17.9 (3C), 14.2, 14.1, 12.0 (3C); MS (Fab+) m/z 519 $(M+H)^+$; HRMS calcd for $C_{26}H_{51}O_8Si$ 519.3353, found 519.3348.

Dimethyl (*E*)-2-{(1*R*)-1-[(1*R*)-2-hydroxy-1-methoxy-methoxy-1-methylethyl]hexyloxy}but-2-enedioate. A solution of (*E*)-**15** (1.15 g, 2.21 mmol) in HF·pyr.–pyr.–THF (1 : 2 : 2) (20 mL) was stirred at room temperature for 43 h. The reaction mixture was poured into H_2O (200 mL) and extracted with Et_2O (40 mL × 3). The combined extracts were washed successively with 0.1 M aqueous HCl (50 mL), H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–AcOEt, 4 : 1→1:1) to afford the title compound (751 mg, 94%) as a colorless oil. $[\alpha]_D^{25}$ +34.8 (*c* 0.50, $CHCl_3$); IR (film) 3482, 2955, 1748, 1713, 1624, 1439, 1367, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.81 (d, J = 7.6 Hz, 1H), 4.67 (d, J = 7.6 Hz, 1H), 4.34 (dd, J = 9.9, 2.7 Hz, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.61–3.55 (m, 2H), 3.42 (s, 3H), 3.00 (t, J = 7.0 Hz, 1H), 1.72–1.54 (m, 2H), 1.54–1.41 (m, 1H), 1.36–1.22 (m, 5H), 1.20 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 164.2, 163.0, 93.8, 91.0, 84.2, 81.6, 65.5, 55.7, 52.8, 51.4, 31.7, 29.9, 25.6, 22.4, 15.5, 13.9; MS (Fab+) m/z 363 $(M+H)^+$; HRMS calcd for $C_{17}H_{31}O_8$ 363.2019, found 363.2018.

Dimethyl (*Z*)-2-{(1*R*)-1-[(1*R*)-2-hydroxy-1-methoxy-methoxy-1-methylethyl]hexyloxy}but-2-enedioate. The title compound (176 mg, 70%, colorless solid) was obtained from (*Z*)-**15** (362 mg, 0.698 mmol) by using a procedure similar to that for the (*E*)-isomer. mp 44–45 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +13.6 (*c* 0.50, $CHCl_3$); IR (film) 3502, 2955, 1734, 1716, 1628, 1436, 1267, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 4.74 (d, J = 7.6 Hz, 1H), 4.73 (dd, J = 9.5, 1.9 Hz, 1H), 4.59 (d, J = 7.6 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.62 (dd, J = 12.4, 6.5 Hz, 1H), 3.47 (dd, J = 12.4, 7.7 Hz, 1H), 3.37 (s, 3H), 3.13 (dd, J = 7.7, 6.5 Hz, 1H), 1.73–1.52 (m, 2H), 1.46–1.37 (m, 1H), 1.36–1.25 (m, 5H), 1.27 (s, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 163.2, 156.4, 103.8, 90.7, 84.6, 82.2, 65.9, 55.6, 52.5, 51.3, 31.7, 30.0, 26.1, 22.5, 14.5, 14.0; MS (Fab+) m/z 363 $(M+H)^+$; HRMS calcd for $C_{17}H_{31}O_8$ 363.2019, found 363.2014.

Dimethyl (*E*)-2-{(1*R*)-1-[(1*S*)-1-methoxymethoxy-1-methyl-2-oxoethyl]hexyloxy}but-2-enedioate [(*E*)-16]. To a stirred solution of the alcohol prepared above [(*E*)-isomer, 7.0 mg, 0.019 mmol] in CH_2Cl_2 (0.5 mL) was added a solution of Dess–Martin periodinane (15%w/w, 62 μL, 0.029 mmol) in CH_2Cl_2 at 0 °C. After being stirred for 15 min, the mixture was allowed to warm to room temperature, and stirring was continued for 1.5 h. Another 0.12 mL (0.057 mmol) of a solution of Dess–Martin periodinane in CH_2Cl_2 was added, and the stirring was continued for another 1 h. The mixture was diluted with Et_2O (10 mL) and washed successively with 5% aqueous $Na_2S_2O_3$ (5.0 mL), saturated aqueous $NaHCO_3$ (5.0 mL), H_2O (5.0 mL), and brine (5.0 mL), 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 (*E*)-**16** (7.0 mg, quant.) as a colorless oil. $[\alpha]_D^{25}$ −11.0 (*c* 0.50, $CHCl_3$); IR (film) 2956, 1747, 1627, 1439, 1271, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 5.37 (s, 1H), 4.82 (d, J = 7.4 Hz, 1H), 4.69 (d, J = 7.4 Hz, 1H), 4.31 (dd, J = 8.9, 3.6 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.40 (s, 3H), 1.70–1.56 (m, 2H), 1.54–1.41 (m, 1H), 1.36 (s, 3H), 1.34–1.20 (m, 5H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 166.5, 163.8, 162.1, 94.8, 92.2, 83.9, 83.3, 56.0, 52.9, 51.6, 31.5, 29.7, 25.4, 22.3, 14.0, 13.9; MS (Fab+) m/z 361 $(M+H)^+$; HRMS calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1846.

Dimethyl (*Z*)-2-{(1*R*)-1-[(1*S*)-1-methoxymethoxy-1-methyl-2-oxoethyl]hexyloxy}but-2-enedioate [(*Z*)-16]. Compound (*Z*)-**16** (122 mg, 98%, colorless oil) was obtained from the alcohol prepared above [(*Z*)-isomer, 125 mg, 0.344 mmol] by using a procedure similar to that for the (*E*)-isomer. $[\alpha]_D^{25}$ −29.6 (*c* 0.50, $CHCl_3$); IR (film) 2955, 1735, 1632, 1436, 1266, 1208, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 5.82 (s, 1H), 4.88 (dd, J = 9.7, 1.9 Hz, 1H), 4.72 (d, J = 7.3 Hz, 1H), 4.52 (d, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.33 (s, 3H), 1.69–1.52 (m, 2H), 1.44–1.19 (m, 6H), 1.42 (s, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 164.8, 163.0, 155.5, 104.9, 91.8, 84.9, 81.9, 55.9, 52.6, 51.3, 31.5, 30.0, 25.7, 22.4, 14.0, 11.4; MS (Fab+) m/z 361 $(M+H)^+$; HRMS calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1848.

Dimethyl (4*R*,5*R*,6*R*)-4-hydroxy-5-methoxymethoxy-5-methyl-6-pentyl-5,6-dihydro-4*H*-pyran-2,3-dicarboxylate (17a) and its (4*S*,5*R*,6*R*)-isomer (17b). To a stirred solution of NaHMDS (1.0 M solution in THF, 0.63 mL, 0.63 mmol) in THF (1.0 mL) was added a solution of (*E*)-**16** (150 mg, 0.417 mmol) in THF (3.0 mL) at −78 °C. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by addition of silica gel (751 mg). The resulting slurry was filtered, and the residue was washed with AcOEt. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–AcOEt, 4 : 1→3:1→7:3) to afford **17a** (64.7 mg, 43%) as a colorless oil and **17b** (31.1 mg, 21%) as a colorless solid. **17a**: $[\alpha]_D^{25}$ +80.2 (*c* 0.50, $CHCl_3$); IR (film) 3356, 2955, 1746, 1635, 1438, 1296, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, J = 7.5 Hz, 1H), 4.76 (d, J = 7.5 Hz, 1H), 4.31 (dd, J = 6.8, 1.3 Hz, 1H), 4.10 (d, J = 6.8 Hz, 1H), 3.94–3.90 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.44 (s, 3H), 2.02–1.90 (m, 1H), 1.76–1.53 (m, 2H), 1.39–1.21 (m, 5H), 1.32 (s, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 163.1, 149.2, 110.5, 91.4, 83.3, 74.4, 68.4, 56.0, 52.7, 52.1, 31.5, 27.2, 25.9, 22.5, 18.6, 14.0; MS (Fab+) m/z 361 $(M+H)^+$; HRMS calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1846. **17b**: mp 45–48 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +167 (*c* 0.50, $CHCl_3$); IR (film) 3502, 2955, 1748, 1706, 1636, 1439, 1283, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 7.8 Hz, 1H), 4.60 (br s, 1H), 3.99 (dd, J = 10.3, 2.4 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.30 (s, 3H), 2.52 (br s, 1H), 1.89 (m, 1H), 1.69–1.55 (m, 2H), 1.44–1.20 (m, 5H), 1.37 (s, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 163.9, 156.2, 105.3, 91.2, 79.8, 74.4, 65.8, 55.7, 52.8, 51.9, 31.7, 27.1, 25.4, 22.5, 17.0, 14.0; MS (Fab+) m/z 361 $(M+H)^+$; HRMS calcd for $C_{17}H_{29}O_8$ 361.1862, found 361.1858.

Dimethyl (4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-5-methoxymethoxy-5-methyl-6-pentyl-5,6-dihydro-4*H*-pyran-2,3-dicarboxylate. To a stirred solution of **17a** (674 mg, 1.87 mmol) in CH_2Cl_2 (19 mL) were added 2,6-lutidine (0.87 mL, 7.5 mmol) and TBSOTf (0.86 mL, 3.7 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 1 h, and then was allowed to warm to 35 °C, and stirring was continued for 2 h. The reaction mixture was diluted with Et_2O (50 mL) and washed successively with 1 M aqueous HCl (20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (60 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–AcOEt, 9 : 1) to afford the title compound (856 mg, 97%) as a colorless oil. $[\alpha]_D^{25}$ +80.2 (*c* 0.50, $CHCl_3$); IR (film) 2954, 1748, 1714, 1633, 1438, 1295, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, *J* = 7.5 Hz, 1H), 4.65 (d, *J* = 7.5 Hz, 1H), 4.33 (d, *J* = 1.8 Hz, 1H), 4.13 (dt, *J* = 11.1, 1.8 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.39 (s, 3H), 2.12–2.01 (m, 1H), 1.84–1.74 (m, 1H), 1.60–1.50 (m, 1H), 1.37–1.22 (m, 5H), 1.28 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 164.0, 150.8, 108.8, 91.4, 83.8, 74.6, 68.5, 56.0, 52.8, 51.7, 31.6, 27.8, 27.0, 25.8 (3C), 22.5, 21.1, 18.4, 14.0, –4.6, –5.2; MS (Fab+) *m*/*z* 475 $(M+H)^+$; HRMS calcd for $C_{23}H_{43}O_8Si$ 475.2727, found 475.2712.

(4*R*,5*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methoxy-carbonyl-5-methoxymethoxy-5-methyl-6-pentyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid. To a stirred solution of the TBS ether prepared above (805 mg, 1.70 mmol) in MeOH (20 mL) was added 1.0 M aqueous NaOH (2.5 mL, 2.5 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 1 h, and then was allowed to warm to 35 °C, and stirring was continued for 17 h. The reaction was quenched by addition of Amberlite® IR-120. After being stirred for 10 min, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 4 : 1) to afford the title compound (703 mg, 90%) as a pale yellow syrup. $[\alpha]_D^{25}$ +20.6 (*c* 0.50, $CHCl_3$); IR (film) 3525, 2955, 1715, 1625, 1295, 1094 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.81 (d, *J* = 7.3 Hz, 1H), 4.68 (d, *J* = 7.3 Hz, 1H), 4.25 (d, *J* = 1.7 Hz, 1H), 4.08 (br d, *J* = 10.8 Hz, 1H), 3.55 (s, 3H), 3.29 (s, 3H), 1.98–1.85 (m, 1H), 1.75–1.63 (m, 1H), 1.51–1.37 (m, 1H), 1.31–1.14 (m, 5H), 1.16 (s, 3H), 0.84 (t, *J* = 6.9 Hz, 3H), 0.80 (s, 9H), 0.07 (s, 3H), –0.01 (s, 3H). A signal due to one proton (COOH) was not observed; ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 164.8, 154.7, 104.4, 90.9, 81.7, 73.9, 68.5, 55.3, 51.1, 31.2, 27.3, 26.3, 25.7 (3C), 21.9, 20.7, 18.1, 13.8, –4.7, –5.2; MS (Fab+) *m*/*z* 483 $(M+Na)^+$; HRMS calcd for $C_{22}H_{40}NaO_8Si$ 483.2390, found 483.2391.

Methyl (4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-2-methoxycarbamoyl-5-methoxymethoxy-5-methyl-6-pentyl-5,6-dihydro-4*H*-pyran-3-carboxylate (20). To a stirred solution of the carboxylic acid prepared above (683 mg, 1.48 mmol) in CH_2Cl_2 (15 mL) were added $MeONH_2$·HCl (296 mg, 3.54 mmol), Et_3N (0.79 mL, 5.7 mmol), 1-hydroxybenzotriazole monohydrate (434 mg, 2.83 mmol), and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (543 mg, 2.83 mmol) at room temperature, and the mixture was stirred for 5 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane–AcOEt, 7 : 3) to afford **20** (649 mg, 89%) as a colorless solid. mp 89–90 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +8.4 (*c* 0.50, $CHCl_3$); IR (film) 3403, 2930, 1714, 1653, 1627, 1558, 1465, 1254, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 4.95 (d, *J* = 7.5 Hz, 1H), 4.64 (d, *J* = 7.5 Hz, 1H), 4.28 (br s, 1H), 4.05 (br d, *J* = 10.4 Hz, 1H), 3.82 (br s, 3H), 3.75 (s, 3H), 3.39 (s, 3H), 2.08–1.93 (m, 1H), 1.86–1.71 (m, 1H), 1.55–1.40 (m, 1H), 1.38–1.21 (m, 5H), 1.28 (s, 3H), 0.90 (br t, *J* = 6.7 Hz, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 160.2, 145.4, 113.6, 91.6, 83.3, 74.3, 70.0, 64.5, 56.1, 52.2, 31.6, 27.2, 27.2, 25.7 (3C), 22.6, 20.7, 18.3, 14.0, –4.4, –5.2; MS (Fab+) *m*/*z* 490 $(M+H)^+$; HRMS calcd for $C_{23}H_{44}NO_8Si$ 490.2836, found 490.2840. Crystal data† for amide **20**: C23H43NO8Si, M_w = 489.67, orthorhombic, $P2_12_12_1$, *a* = 9.0593(3), *b* = 15.3579(5), *c* = 19.9706(6), *V* = 2778.55(15), *R* = 0.0569, *wR* = 0.1255, *S* = 1.018

(2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-3-methoxymethoxy-3-methyl-2-pentyl-3,4-dihydro-2*H*-pyrano[2,3-*c*]pyrrole-5,7-dione (21). A solution of **20** (403 mg, 0.822 mmol) and Et_3N (0.34 mL, 2.4 mmol) in DMF (10 mL) was stirred at 130 °C for 4 h. After being cooled to room temperature, the mixture was diluted with Et_2O (50 mL) and washed successively with H_2O (25 mL × 3) and brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–AcOEt, 9 : 1) to afford **21** (262 mg, 70%) as a colorless solid. mp 54–55 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +29.4 (*c* 0.50, $CHCl_3$); IR (film) 2931, 1738, 1663, 1417, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (br s, 1H), 4.64 (d, *J* = 7.5 Hz, 1H), 4.26 (br s, 2H), 3.97 (s, 3H), 3.40 (s, 3H), 2.00–1.84 (m, 2H), 1.67–1.52 (m, 1H), 1.41–1.21 (m, 5H), 1.30 (s, 3H), 0.96–0.82 (m, 3H), 0.90 (s, 9H), 0.17 (br s, 3H), 0.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 161.0, 152.0, 109.6, 92.0, 87.4, 75.2, 66.1, 65.0, 56.0, 31.6, 28.2, 26.6, 25.8 (3C), 22.5, 20.6, 18.2, 14.0, –4.7, –4.9; MS (Fab+) *m*/*z* 458 $(M+H)^+$; HRMS calcd for $C_{22}H_{40}NO_7Si$ 458.2574, found 458.2576.

(2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-6-methoxy-3-methoxymethoxy-3,7-dimethyl-2-pentyl-3,4,6,7-tetrahydro-2*H*-pyrano[2,3-*c*]pyrrol-5-one. To a stirred solution of **21** (159 mg, 0.346 mmol) was added MeMgBr (3.0 M solution in Et_2O, 0.23 mL, 0.69 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min, and then poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (30 mL). The combined extracts were washed with brine (20 mL), 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 the title compound (164 mg, quant.) as a colorless oil. $[\alpha]_D^{25}$ +2.2 (*c* 0.50, $CHCl_3$); IR (film) 2930, 1727, 1669, 1416, 1219, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 [4.95] (d, *J* = 7.5 Hz, 1H), 4.67 [4.64] (d, *J* = 7.5 Hz, 1H), 4.25–4.12 (m, 2H), 3.94 [3.94] (s, 3H), 3.39 (s, 3H), 3.34 [2.09] (br s, 1H), 1.99–1.85 (m, 2H), 1.59–1.48 (m, 1H), 1.53 [1.60] (s, 3H), 1.38–1.23 (m, 5H), 1.25 [1.22] (s, 3H), 0.94–0.82 (m, 3H), 0.88 [0.87] (s, 9H), 0.16 [0.16 and 0.13] (s, 6H) (the minor counterpart of doubled signals in the ratios of 1.2 : 1 are in brackets); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 [169.4], 167.4 [167.1], 103.6, 91.8 [91.8], 86.7 [87.0], 86.4 [86.2], 77.2 [75.5], 65.9 [66.1], 64.5, 55.8, 31.6 [31.6], 28.1 [28.3], 26.9 [26.8], 25.8 [25.8] (3C), 22.4 [22.5], 21.3, 21.1 [20.1], 18.2, 14.0 [13.9], –4.7 [–4.7], –5.2 (the minor counterpart of doubled signals in the ratios of 1.2 : 1 are in brackets); MS (Fab+) *m*/*z* 474 $(M+H)^+$; HRMS calcd for $C_{23}H_{44}NO_7Si$ 474.2887, found 474.2884.

(2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-6-methoxy-3-methyl-7-methylene-2-pentyl-3,4,6,7-tetrahydro-2*H*-pyrano-[2,3-*c*]pyrrol-5-one (22). To a stirred solution of the hemiaminal prepared above (142 mg, 0.299 mmol) in 1,4-dioxane (3.0 mL) was added a solution of HCl (*ca.* 4 mol L^{-1}, 3.0 mL) in 1,4-dioxane at room temperature. The mixture was stirred at the same temperature for 1 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane–AcOEt, 9 : 1→17:3→4:1→3:1) to afford **22** (63.5 mg, 52%) as a colorless oil. $[\alpha]_D^{25}$ +59.8 (*c* 0.72, $CHCl_3$); IR (film) 3526, 2931, 1738, 1666, 1421, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (d, J = 1.7 Hz, 1H), 4.99 (d, J = 1.7 Hz, 1H), 4.12 (d, J = 1.2 Hz, 1H), 4.03 (dt, J = 10.9, 1.4 Hz, 1H), 3.92 (s, 3H), 3.19 (s, 1H), 1.99–1.85 (m, 1H), 1.79–1.67 (m, 1H), 1.58–1.46 (m, 1H), 1.41–1.25 (m, 5H), 1.23 (s, 3H), 0.95–0.83 (m, 3H), 0.90 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 156.4, 136.9, 103.3, 91.8, 86.1, 69.9, 65.6, 64.3, 31.5, 27.5, 26.7, 25.9 (3C), 24.0, 22.5, 18.2, 14.0, −4.5, −5.4; MS (Fab+) *m*/*z* 412 $(M+H)^+$; HRMS calcd for $C_{21}H_{38}NO_5Si$ 412.2519, found 412.22514.

Proposed structure of phaeosphaeride A (1). A solution of **22** (61.5 mg, 0.149 mmol) and $3HF{\cdot}Et_3N$ (0.49 mL) in THF (2.0 mL) was stirred at room temperature for 10 h. After concentration, the crude product was purified by column chromatography on silica gel (hexane–AcOEt, 1 : 1) to afford the proposed structure of phaeosphaeride A (**1**) (39.9 mg, 90%) as colorless crystals. mp 135–136 °C (hexane–AcOEt); $[\alpha]_D^{25}$ +95.4 (*c* 0.50, $CHCl_3$); IR (film) 3420, 2959, 1703, 1636, 1448, 1173 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.17 (d, J = 7.0 Hz, 1H), 4.96 (d, J = 1.7 Hz, 1H), 4.94 (d, J = 1.7 Hz, 1H), 4.51 (br s, 1H), 4.02 (d, J = 7.0 Hz, 1H), 3.99 (dd, J = 10.7, 2.2 Hz, 1H), 3.76 (s, 3H), 1.86–1.75 (m, 1H), 1.75–1.64 (m, 1H), 1.57–1.45 (m, 1H), 1.38–1.21 (m, 5H), 1.07 (s, 3H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.9, 156.4, 136.7, 104.9, 90.9, 85.0, 68.8, 64.7, 63.7, 31.1, 27.0, 25.2, 22.6, 22.0, 13.9; MS (Fab+) *m*/*z* 298 $(M+H)^+$; HRMS calcd for $C_{15}H_{24}NO_5$ 298.1654, found 298.1655. Reported data[3] for natural phaeosphaeride: ^1H NMR (500 MHz, DMSO-d_6) δ 5.44 (d, J = 5.5 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 4.96 (d, J = 1.8 Hz, 1H), 4.92 (s, 1H), 4.07 (d, J = 11.5 Hz, 1H), 3.86 (d, J = 5.5 Hz, 1H), 3.79 (s, 3H), 1.82 (m, 1H), 1.51 (m, 1H), 1.44 (m, 2H), 1.28 (m, 2H), 1.27 (m, 2H), 1.18 (s, 3H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.5, 155.2, 137.0, 104.7, 90.8, 86.2, 70.8, 64.1, 63.7, 30.8, 27.5, 25.9, 21.9, 20.5, 13.8.

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