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Synthesis of Two Diastereomers of C-1 ~ C-14 Segment in Amphidinolide L

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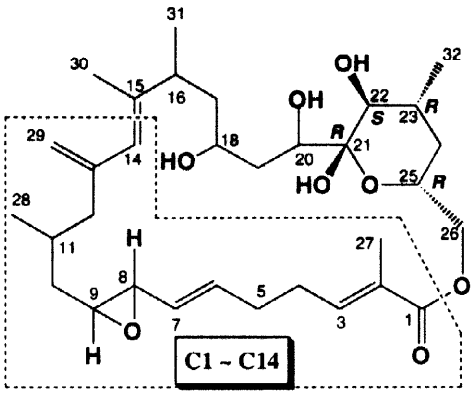
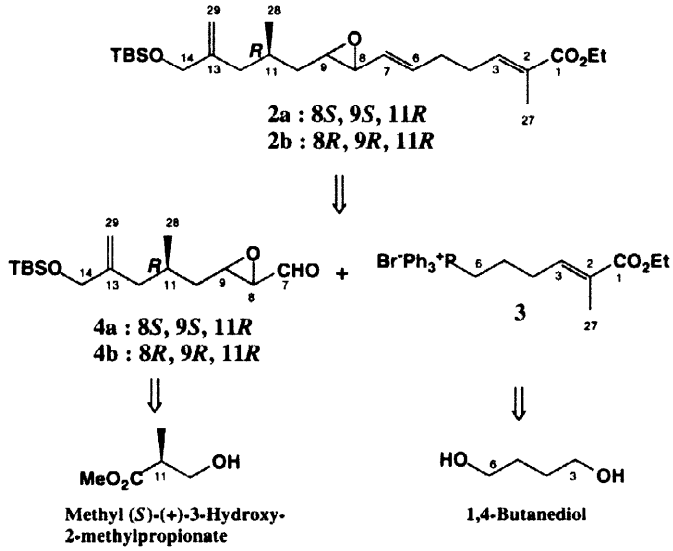
Abstract: In order to determine the stereochemistry of amphidinolide L (**1**), a cytotoxic macrolide from a marine dinoflagellate, (8*S*,9*S*,11*R*)-**2a** and (8*R*,9*R*,11*R*)-**2b**, two diastereomers of the C-1 ~ C-14 segment and (8*S*,9*S*,11*R*)-**4a** and (8*R*,9*R*,11*R*)-**4b**, two diastereomers of the C-7 ~ C-14 segment have been synthesized, providing authentic samples for degradation products of **1**.

During our continuing studies on bioactive substances from marine dinoflagellates,[1] we have isolated a cytotoxic 27-membered macrolide, amphidinolide L (**1**), from culture of the dinoflagellate *Amphidinium* sp. (strain Y-25), which was separated from the Okinawan marine flatworm *Amphiscolops breviviridis*.[2] Amphidinolide L (**1**) exhibited cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells in vitro (IC_{50} 0.092 and 0.1 μg/mL, respectively). The relative stereochemistries of the epoxide and tetrahydropyran ring in **1** have been elucidated on the basis of NOE data, and the absolute configurations at C-21, C-22, C-23, and C-25 have been established by enantioselective synthesis of two diastereomers of the C-21 ~ C-26 segment.[2] In order to determine the absolute configurations at C-16, C-18, and C-20 in **1**, we have synthesized one of eight possible diastereomers of the C-15 ~ C-26 segment as an



Amphidinolide L (1)

Scheme 1

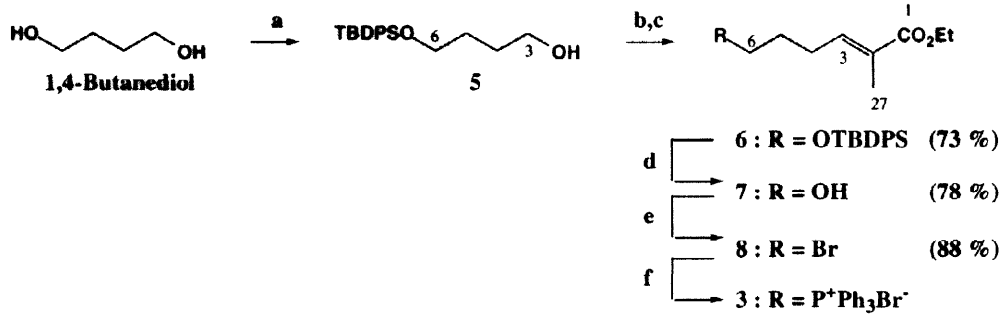


Methyl (*S*)-(+)-3-Hydroxy-2-methylpropionate

1,4-Butanediol

PII: S0040-4020(97)10293-9

Scheme 2



[a] TBDPSCl, imidazole, CH_2Cl_2, rt, 11 h; [b] DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 1 h, then Et_3N, -50 °C; [c] $(i\text{-PrO})_2POCH(CH_3)CO_2Et$, *t*-BuOK, THF, -78 °C, 45 min and then rt, 30 min; [d] TBAF, THF, rt, 1.5 h; [e] CBr_4, Ph_3P, CH_2Cl_2, rt, 12 h; [f] Ph_3P, CH_3CN, 80 °C, 2 h

authentic sample for degradation products of **1**.[3] Furthermore, (8*S*,9*S*,11*R*)-**2a** and (8*R*,9*R*,11*R*)-**2b**, two diastereomers of the C-1 ~ C-14 segment and (8*S*,9*S*,11*R*)-**4a** and (8*R*,9*R*,11*R*)-**4b**, two diastereomers of the C-7 ~ C-14 segment in **1** have been synthesized in order to clarify the stereochemistry at C-8, C-9, and C-11 in **1**. Here we describe the synthesis of **2a** and **2b** and **4a** and **4b** and comparison of the ^1H and ^{13}C NMR data of **1** with those of **2a** and **2b**.

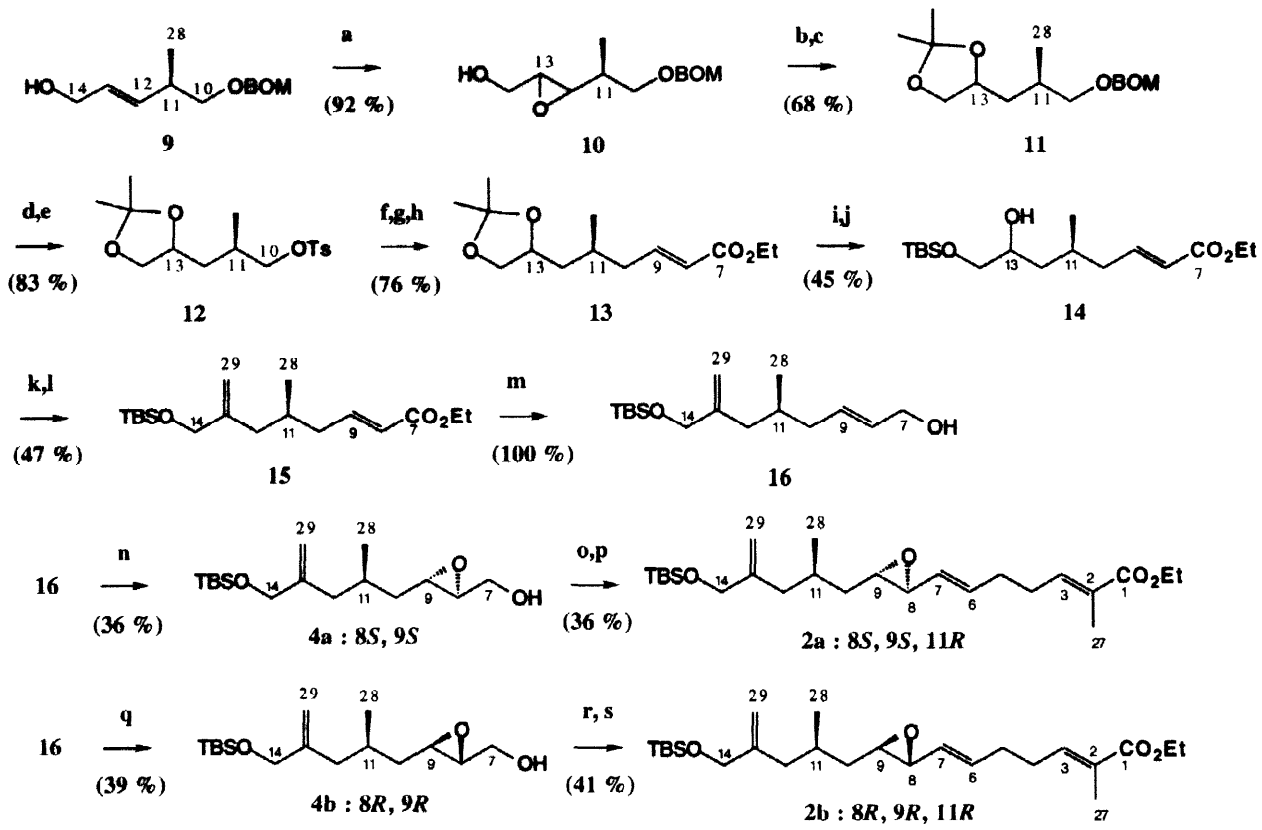
The synthetic route of **2a** and **2b** was based on a convergent strategy through Wittig reaction between the phosphonium salt (**3**) and the aldehyde (**4a** or **4b**) (Scheme 1), which can be derived from 1,4-butanediol and methyl (*S*)-(+)-3-hydroxy-2-methylpropionate, respectively, commercially available.

The monoprotected diol (**5**) was subjected to Swern oxidation and then Horner-Emmons reaction to yield the *E*-unsaturated ester (**6**), predominantly (Scheme 2). Deprotection of **6** and then bromination gave the bromide (**8**), which was treated with triphenylphosphine to afford the phosphonium salt (**3**).

The (11*R*)-allyl alcohol (**9**),[4] prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by five steps, was oxidized with *m*-chloroperbenzoic acid (MCPBA) to yield a 3:2 mixture of the α- and β-epoxides (**10**) (Scheme 3). After four step conversion of this mixture, the tosylate (**12**) was obtained in 56 % yield. Three carbon homologation of **12** was performed by treatment with NaCN and then Wittig reaction to give the unsaturated ester (**13**). Deprotection of the acetonide in **13** and subsequent protection of the primary hydroxy group yielded compound **14**, which was oxidized with tetrapropylammonium perruthenate (TPAP)[5] and then subjected to Wittig reaction with methyltriphenylphosphonium bromide to afford compound **15**. After reduction of **15** with DIBAL, Sharpless asymmetric epoxidation[6] of the allyl alcohol (**16**) with (+)-DET led to 8*S*,9*S*- and 8*R*,9*R*-epoxy alcohols (**4a** and **4b**) in the ratio of ca. 9:1, while epoxidation with (-)-DET afforded **4a** and **4b** in the ratio of ca. 1:10. Coupling reaction of the aldehyde obtained by oxidation of **4a** and the phosphonium salt (**3**) afforded (8*S*, 9*S*, and 11*R*)-**2a** (36 %) together with its 6*Z*-isomer (27 %). Coupling reaction of **3** and the aldehyde derived from **4b** yielded (8*R*, 9*R*, and 11*R*)-**2b** and its 6*Z*-isomer (41 % and 29 %, respectively).

The ^1H NMR data of **2a** and **2b** in comparison with those of amphidinolide L (**1**) were shown in Table 1. The chemical shifts of H-8 ~ H-11 and C-9, C-11, and C-28 in **1** were similar to those of **2a** rather than those of **2b** (Table 2). Though the stereochemistry at C-8, C-9, and C-11 in **1** seems to be the same as those

Scheme 3



[a] MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 14 h; [b] DIBAL, C_6H_6, 0 °C, 1.5 h; [c] $(CH_3)_2C(OCH_3)_2$, PPTS, CH_2Cl_2, rt, 12 h; [d] Na, *liq.* NH_3, THF, -78 °C, 1 h; [e] TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C and then rt, 13 h; [f] NaCN, DMSO, 80 °C, 2 h; [g] DIBAL, CH_2Cl_2, -78 °C, 30 min; [h] $Ph_3P{=}CHCO_2Et$, C_6H_6, 50 °C, 13 h; [i] 1 N HCl, THF, 40 °C, 19 h; [j] TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; [k] TPAP, NMO, MS-4A, CH_2Cl_2, rt, 17 h; [l] Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C, and then rt, 1 h; [m] DIBAL, CH_2Cl_2, -78 °C, 3 h; [n] (+)-DET, Ti(*i*-PrO)$_4$, *t*-BuOOH, MS-4A, -20 °C, 12 h; [o] Dess-Martin periodinane, DMF, rt, 4 h; [p] 3, *n*-BuLi, THF, -20 °C, 30 min, and then rt, 13 h; [q] (-)-DET, Ti(*i*-PrO)$_4$, *t*-BuOOH, MS-4A, -20 °C, 36 h; [r] Dess-Martin periodinane, DMF, rt, 4 h; [s] 3, *n*-BuLi, THF, -20 °C, 1 h, and then rt, 12 h.

of **2a**, degradation experiments for **1** must be followed to confirm it. Compounds **2a** and **2b** as well as **4a** and **4b** may be useful as authentic samples for degradation products of **1**, although the degradation has not been carried out due to paucity of **1**. Further large-scale cultivation of the dinoflagellate is in progress to provide sufficient quantity of **1** for the degradation experiments.

Experimental Section

General Methods. Optical rotations were recorded on a JASCO DIP-370 polarimeter. The IR and UV spectra were taken on a JASCO FT/IR-230 and JASCO Ubest-35 spectrophotometer, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-500 spectrometer. FAB mass spectra were obtained on a JEOL HX-110 spectrometer using glycerol as a matrix. EI mass spectra were measured on a JEOL DX-303 spectrometer at 70 eV.

6-*tert*-Butyldiphenylsilyloxybutan-1-ol (5). To a solution of 1,4-butanediol (5.00 g, 55.5

Table 1. ^{1}H NMR Data of Amphidinolide L (**1**) and Two Diastereomers (**2a** and **2b**) of the C-1 ~ C-14 Segment in C_6D_6.

positn.	**1**	**2a**	**2b**
3.	6.96 (t, 6.0)	6.94 (t, 5.7)	6.92 (t, 6.3)
4.	1.98 (m)	1.90 (2H, m)	1.87 (2H, m)
	1.95 (m)		
5.	1.94 (m)	1.90 (2H, m)	1.90 (2H, m)
	1.91 (m)		
6.	5.62 (dt, 15,2, 7.2)	5.64 (dt, 15.4, 7.0)	5.60 (dt, 15.2, 7.3)
7.	5.14 (dd, 15.2, 8.1)	5.18 (dd, 15.4, 7.5)	5.25 (dd, 15.2, 7.0)
8.	2.97 (dd, 2.1, 8.1)	3.01 (dd, 2.2, 7.5)	2.81 (dd, 2.2, 7.0)
9.	2.80 (ddd, 2.1, 3.7, 7.0)	2.78 (ddd, 2.2, 4.0, 7.3)	2.83 (ddd, 2.2, 3.3, 7.8)
10.	1.38 (ddd, 5.4, 7.0, 13.4)	1.36 (ddd, 4.7, 7.3, 13.1)	1.48 (ddd, 3.4, 7.8, 13.4)
	1.26 (ddd, 3.7, 9.1, 13.4)	1.27 (ddd, 4.0, 8.0, 13.1)	1.24 (ddd, 3.3, 7.6, 13.4)
11.	1.88 (m)	1.84 (m)	1.72 (m)
12.	2.10 (dd, 6.4, 13.4)	2.07 (dd, 5.4, 14.6)	2.09 (dd, 6.0, 14.3)
	2.05 (dd, 7.5, 13.3)	1.87 (dd, 3.2, 14.6)	1.82 (dd, 4.3, 14.3)
27.	1.90 (brs)	1.91 (brs)	1.90 (brs)
28.	0.93 (d, 6.6)	0.93 (d, 6.3)	0.94 (d, 6.4)
29.	5.05 (d, 2.1)	5.30 (brs)	5.28 (brs)
	4.98 (d, 2.1)	4.88 (brs)	4.87 (brs)

Table 2. ^{13}C NMR Data of Amphidinolide L (**1**) and Two Diastereomers (**2a** and **2b**) of the C-1 ~ C-14 Segment in $CDCl_3$.

positn.	**1**		**2a**		**2b**	
3.	141.26	d	142.87	d	142.80	d
4.	27.25	t	28.51	t	28.48	t
5.	30.76	t	31.23	t	31.29	t
6.	134.37	d	133.87	d	132.86	d
7.	129.11	d	130.21	d	131.38	d
8.	59.33	d	59.66	d	60.27	d
9.	59.24	d	58.87	d	57.19	d
10.	38.65	t	38.73	t	38.23	t
11.	29.65	d	29.68	d	30.81	d
12.	46.11	t	40.92	t	40.61	t
28.	19.61	q	19.69	q	20.75	q
29.	114.92	t	110.40	t	110.45	t

mmol) in CH_2Cl_2 were added imidazole (4.15 g, 61.0 mmol) and then *tert*-butyldiphenylchlorosilane (TBDPSCl, 14.8 mL, 55.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 11 h. After addition of MeOH, the reaction mixture was partitioned between Et_2O and saturated aqueous NH_4Cl. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 95:5) to give compound **6** (15.82 g, 48.2 mmol, 87 %) as colorless oil; IR (neat) ν_{max} 3430, 2985, 1600, 1370, 1260, and 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.6 ~ 1.8 (4H, m), 2.00 (1H, brt, J = 7.4 Hz), 3.6 ~ 3.8 (4H, m), 7.35 ~ 7.45 (6H, m), and 7.6 ~ 7.7 (4H, m); EIMS *m/z* 328 (M^+); HREIMS *m/z* 328.1846 M^+, calcd for $C_{20}H_{28}O_2Si$, 328.1859.

Ethyl (2*E*)-6-*tert*-Butyldiphenylsilyloxy-2-methyl-2-hexenoate (6). To a solution of oxalyl chloride (265 μL, 3.04 mmol) in CH_2Cl_2 (5.8 mL), DMSO (323 μL, 4.56 mmol) in CH_2Cl_2 (580 μL) was slowly added at -78 °C, and the mixture was stirred for 10 min. To the reaction mixture was dropwise

added a solution of 4-*tert*-butyldiphenylsilyloxybutan-1-ol (**5**, 500 mg, 1.52 mmol) in CH_2Cl_2 (2.23 mL). After stirring at -78 °C for 1 h, Et_3N (1.05 mL, 7.60 mmol) was added to the reaction mixture, which was allowed to warm to -50 °C. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The organic phase was washed with H_2O and then brine, and dried over $MgSO_4$. The solvent was evaporated to afford a crude aldehyde (514 mg), which was subjected to the following reaction without purification. To a stirred suspension of *t*-BuOK (597 mg, 5.32 mmol) in THF (11 mL) was added diisopropyl (1-ethoxycarbonylethyl)phosphonate (1.44 g, 6.08 mmol) in THF (11 mL) at 0 °C. After stirring for 1 h, to the reaction mixture cooled to -78 °C was added a solution of the crude aldehyde (514 mg) in THF (5.5 mL), and the stirring was continued at -78 °C for 45 min and then room temperature for 30 min. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The organic phase was washed with H_2O and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 95:5) to give compound **6** (450.6 mg, 1.10 mmol, 73 %) as colorless oil; IR (neat) ν_{max} 2985, 1720, 1655, 1455, 1370, 1265, 1175, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.29 (3H, t, J = 7.2 Hz), 1.68 (2H, m), 1.83 (3H, brs), 2.28 (2H, q, J = 7.4 Hz), 3.68 (2H, t, J = 6.1 Hz), 4.19 (2H, q, J = 7.2 Hz), 6.76 (1H, dt, J = 1.1 and 7.4 Hz), 7.35 ~ 7.45 (6H, m), and 7.6 ~ 7.7 (4H, m); EIMS *m/z* 410 (M^+); HREIMS *m/z* 410.2274 M^+, calcd for $C_{25}H_{34}O_3Si$, 410.2277.

Ethyl (2*E*)-6-Hydroxy-2-methyl-2-hexenoate (7). To a solution of the unsaturated ester **6** (427 mg, 1.05 mmol) in THF (3 mL) was added a 1 M THF solution (1.56 mL, 1.56 mmol) of tetrabutylammonium fluoride (TBAF), and the reaction mixture was stirred at room temperature for 1.5 h. After addition of Et_2O and saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O, and the organic layer was washed with H_2O and then brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was subjected to silica gel column chromatography (hexane/EtOAc, 4:1) to afford compound **7** (139.1 mg, 817 μmol, 78 %) as a colorless oil; IR (neat) ν_{max} 3430, 2985, 1720, 1455, 1370, 1265, 1175, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J = 7.2 Hz), 1.42 (1H, brs), 1.68 (2H, m), 1.83 (3H, brs), 2.24 (2H, q, J = 7.4 Hz), 3.66 (2H, brt, J = 6.1 Hz), 4.19 (2H, q, J = 7.2 Hz), and 6.76 (1H, dt, J = 1.1 and 7.4 Hz); EIMS *m/z* 172 (M^+); HREIMS *m/z* 172.1092 M^+, calcd for $C_9H_{16}O_3$, 172.1099.

Ethyl (2*E*)-6-Bromo-2-methyl-2-hexenoate (8). A solution of compound **7** (502 mg, 2.92 mmol) in CH_2Cl_2 (5 mL) was treated with tetrabromomethane (2.90 g, 8.75 mmol) and triphenylphosphine (1.53 g, 5.83 mmol) at room temperature for 12 h. The mixture was diluted with $CHCl_3$ and saturated aqueous $NaHCO_3$, and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was subjected to silica gel column chromatogrphy (hexane/EtOAc, 4:1) to afford compound **8** (606.2 mg, 2.58 mmol, 88 %) as a colorless oil; IR (neat) ν_{max} 2985, 1720, 1460, 1380, 1235, and 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.2 Hz), 1.74 (3H, brs), 1.86 (2H, m), 2.23 (2H, q, J = 7.4 Hz), 3.28 (2H, t, J = 6.1 Hz), 4.08 (2H, q, J = 7.2 Hz), and 6.57 (1H, dt, J = 1.1 and 7.4 Hz); EIMS *m/z* 234 (M^+); HREIMS *m/z* 234.0232 M^+, calcd for $C_9H_{15}O_2{}^{79}Br$, 234.0255.

[(4*E*)-5-Carbethoxy-4-hexenyl]triphenylphosphonium Bromide (3). To a solution of the compound **8** (100 mg, 425 μmol) in CH_3CN (1.5 mL) was added triphenylphosphine (123 mg, 468 μmol) and the mixture was stirred at 80 °C for 2 h. The mixture was evaporated *in vacuo* and the residue was washed with hexane to afford the phosphonium salt (**3**, 138 mg), which was used without further purification.

(4*S*)-5-Benzyloxymethyloxy-2,3-epoxy-4-methylpentan-1-ol (10). To a solution of **9** (3.53 g, 14.5 mmol) in CH_2Cl_2 (25 mL) were added $NaHCO_3$ (6.10 g, 72.6 mmol) and *m*-chloroperbenzoic acid (7.10 g, 29.0 mmol) at 0°C, and the mixture was stirred at room temperature for 14 h. After addition of saturated aqueous $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $Na_2S_2O_3$, H_2O, and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (hexane/EtOAc, 4:1) to give a 3:2 mixture of α- and β-epoxides (**10**, 3.37 g, 13.3 mmol, 92 %) as a colorless oil; $[\alpha]_D{}^{25}$ -2.10° (*c* 3.73, $CHCl_3$); IR (neat) ν_{max} 3430, 2930, 1725, 1455, 1380, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) for α-epoxide δ 1.02 (3H, d, J = 7.0 Hz), 1.73 (1H, br.s), 1.76 (1H, m), 2.95 (1H, dd, J = 2.3 and 7.0 Hz), 3.00 (1H, m), 3.54 (1H, m), 3.61 (2H, d, J = 5.6 Hz), 4.61 (2H, s), 4.78 (2H, s), and 7.26 ~ 7.36 (5H, m); ^1H NMR for β-epoxide δ 1.03 (3H, d, J = 7.9 Hz), 1.73 (1H, br.s), 1.76 (1H, m), 2.92 (1H, dd, J = 2.3 and 6.8 Hz), 3.05 (1H, m), 3.61 (2H, d, J = 5.6 Hz), 3.63 (1H, m), 4.56 (2H, s), 4.75 (2H, s), and 7.26 ~ 7.36 (5H, m); FABMS (Pos.) *m/z* 253 $(M+H)^+$; HRFABMS *m/z* 253.1444 $(M+H)^+$, calcd for $C_{14}H_{21}O_4$, 253.1440.

(4*R*)-5-Benzyloxymethoxy-1,2-isopropylidenedioxy-4-methylpentane (11). To a solution of the epoxide **10** (2.41 g, 9.56 mmol) in benzene (40 mL) was dropwise added a 1.01 M toluene

solution of DIBAL (29.4 mL, 29.7 mmol) at 0 °C, and the mixture was stirred for 1.5 h. After addition of MeOH (2 mL) to decompose the excess reagent, the reaction mixture was allowed to warm to room temperature. Et_2O and saturated aqueous potassium sodium tartarate were added and the resulting mixture was stirred vigorously for 1 h. After extraction with Et_2O, the organic phase was washed with H_2O and then brine, and dried over $MgSO_4$. The solvent was evaporated to give a 8:1 mixture of 1,2-diol and 1,3-diol (2.31 g), which was subjected to the following reaction without separation. To a solution of the mixture (2.31 g) in CH_2Cl_2 (38 mL) were added 2,2-dimethoxypropane (2.34 mL, 19.1 mmol) and then pyridinium *p*-toluenesulfonate (240 mg, 956 μmol), and the mixture was stirred at room temperature for 12 h. After addition of H_2O, the reaction mixture was extracted with Et_2O. The organic phase was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 9:1) to give the 1,2-acetonide **11** (1.91 g, 6.50 mmol, 68 % from **10**) as colorless oil; $[\alpha]_D^{26}$ -23.7° (*c* 1.53, $CHCl_3$); IR (neat) ν_{max} 2935, 1455, 1380, 1110, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (1.8H, d, *J* = 6.6 Hz), 1.01 (1.2H, d, *J* = 6.8 Hz), 1.33 (0.6H, ddd, *J* = 5.0, 8.6, and 13.6 Hz), 1.35 (3H, s), 1.40 (3H, s), 1.53 (0.4H, m), 1.64 (0.4H, m), 1.77 (0.6H, ddd, *J* = 5.2, 8.2, and 13.5 Hz), 1.84 (0.4H, m), 1.94 (0.6H, m), 3.4 ~ 3.5 (3H, m), 4.05 (1H, m), 4.19 (1H, m), 4.60 (2H, s), 4.75 (2H, s), and 7.26 ~ 7.36 (5H, m); FABMS (Pos.) *m/z* 295 $(M+H)^+$; HRFABMS *m/z* 295.1930 $(M+H)^+$, calcd for $C_{17}H_{27}O_4$, 295.1909.

(2*R*)-4,5-Isopropylidenedioxy-2-methylpentyl *p*-toluenesulfonate (12). Sodium (2.98 g, 129 mmol) was added to liq. NH_3 (120 mL) at -78 °C, and the mixture was stirred for 10 min. To the mixture was dropwise added a solution of **11** (1.91 g, 6.48 mmol) in THF (30 mL) at -78 °C, and stirring was continued for 1 h. After dilution with Et_2O, NH_4Cl was added to the reaction mixture until blue color of the solution disappeared. After insoluble materials were filtered, the solvent was evaporaed to give a residue, which was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give the alcohol (1.00 g, 5.74 mmol, 88 %). To a solution of the alcohol (1.00 g, 5.74 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (2.42 mL, 17.2 mmol), DMAP (70 mg, 574 μmol), and *p*-toluenesulfonyl chloride (2.19 g, 11.5 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 13 h. To the reaction mixture was added MeOH (3 mL), stirring was continued for 30 min. After dilution with Et_2O, 1 N HCl was added and the mixture was extracted with Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/$CHCl_3$, 2:1) to give the tosylate **12** (1.77 g, 5.40 mmol, 94 %) as a colorless oil; $[\alpha]_D^{26}$ -15.2° (*c* 0.30, $CHCl_3$); IR (neat) ν_{max} 2940, 1455, 1360, 1170, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (1.8H, d, *J* = 7.0 Hz), 0.97 (1.2H, d, *J* = 7.7 Hz), 1.30 (3H, s), 1.31 (3H, s), 1.60 ~ 1.75 (2H, m), 1.96 (0.4H, m), 2.02 (0.6H, m), 2.45 (3H, s), 3.43 (1H, m), 3.8 ~ 4.1 (4H, m), 7.34 (2H, d, *J* = 8.1 Hz), and 7.79 (2H, d, *J* = 8.3 Hz); FABMS (Pos.) *m/z* 329 $(M+H)^+$; HRFABMS *m/z* 329.1436 $(M+H)^+$, calcd for $C_{16}H_{25}O_5S$, 329.1422.

Ethyl (2*E*,5*S*)-7,8-Isopropylidenedioxy-5-methyl-2-octenoate (13). To a solution of the tosylate **12** (1.75 g, 5.33 mmol) in DMSO (38 mL) was added NaCN (523 mg, 10.7 mmol), and the reaction mixture was stirred at 80 °C for 2 h. After dilution with H_2O, the reaction mixture was extracted with Et_2O. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated to give a crude cyanide (1.23 g). To a solution of the cyanide in CH_2Cl_2 (20 mL) was dropwise added a 0.95 M hexane solution of DIBAL (11.5 mL, 10.9 mmol) at -78 °C, and the mixture was stirred for 30 min. After addition of MeOH (2 mL) to decompose the excess reagent, the reaction mixture was allowed to warm to room temperature. Et_2O and saturated aqueous potassium sodium tartarate were added and the resulting mixture was stirred vigorously for 1 h. After extraction with EtOAc, the organic phase was washed with H_2O and then brine, and dried over $MgSO_4$. The solvent was evaporated to give the crude aldehyde (1.09 g), which was subjected to the following reaction without separation. To a solution of the aldehyde in benzene (20 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (2.79 g, 8.00 mmol), and the mixture was stirred at 50 °C for 13 h. The solvent was removed *in vacuo* and then the residue was purified by silica gel column chromatography (hexane/EtOAc, 19:1) to give compound **13** (758 mg, 4.07 mmol, 76% from **12**) together with the *cis*-isomer (55 mg, 0.21 mmol, 4 %). **13:** a colorless oil; $[\alpha]_D^{27}$ -3.61° (*c* 6.33, $CHCl_3$); IR (neat) ν_{max} 2985, 1720, 1655, 1455, 1370, 1265, 1175, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (1.8H, d, *J* = 6.7 Hz), 0.97 (1.2H, d, *J* = 6.7 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 1.35 (3H, s), 1.40 (3H, s), 1.49 (0.4H, m), 1.56 (0.6H, m), 1.66 (1H, m), 1.77 (1H, m), 2.10 (1H, m), 2.26 (1H, m), 3.47 (1H, q, *J* = 6.0 Hz), 4.04 (1H, m), 4.15 (1H, m), 4.18 (2H, q, *J* = 7.2 Hz), 5.83 (1H, d, *J* = 15.6 Hz), and 6.93 (1H, m); FABMS (Pos.) *m/z* 257 $(M+H)^+$; HRFABMS *m/z* 257.1747 $(M+H)^+$, calcd for $C_{14}H_{25}O_4$, 257.1753.

Ethyl (2*E*,5*S*)-8-(*t*-Butyldimethylsilyloxy)-7-hydroxyl-5-methyl-2-octenoate (14). The compound **13** (420 mg, 1.64 mmol) was dissolved in THF (5 mL), 1 N HCl (820 μL) was added to this

mixture with stirring and the stirring was continued at 40 °C for 19 h. After addition of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with Et_2O and then washed with H_2O and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to give 7,8-diol (340.5 mg, 1.57 mmol, 96 %) as a colorless oil. To a solution of the diol (168 mg, 777 μmol) in CH_2Cl_2 (1.5 mL) were added Et_3N (120 μL, 854 μmol), DMAP (3.8 mg, 31.1 μmol), and *t*-butyldimethylsilyl chloride (129 mg, 854 μmol), and the reaction mixture was stirred at room temperature for 1 h. After dilution with Et_2O, 1 N HCl was added and the mixture was extracted with Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, and then brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 95:5) to give the alcohol **14** (121 mg, 366 μmol, 47 %) as a colorless oil, and 19 % of the diol (31 mg, 144 μmol) was recovered. **14**; $[\alpha]_D^{23}$ -1.51° (*c* 4.07, $CHCl_3$); IR (neat) ν_{max} 3500, 2955, 1720, 1650, 1255, and 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 0.94 (1.8H, d, *J* = 6.4 Hz), 0.95 (1.2H, d, *J* = 6.8 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 1.33 (1H, m), 1.8 ~ 2.45 (4H, m), 3.34 (1H, m), 3.57 (1H, m), 3.71 (1H, m), 4.17 (2H, q, *J* = 7.1 Hz), 5.78 (1H, d, *J* = 15.2 Hz), 5.84 (1H, d, *J* = 15.2 Hz), and 6.92 (1H, m); FABMS (Pos.) *m/z* 331 $(M+H)^+$; HRFABMS *m/z* 331.2291 $(M+H)^+$, calcd for $C_{17}H_{35}O_4Si$, 331.2276.

Ethyl (2*E*,5*S*)-7-(*t*-Butyldimethylsilyloxymethyl)-5-methyl-2,7-octadienoate (15). To a solution of the alcohol **14** (121 mg, 366 μmol) in CH_2Cl_2 (1.5 mL) were added molecular sieves 4A (183 mg) and 4-methylmorpholine *N*-oxide (64.3 mg, 549 μmol). After the mixture was stirred at room temperature for 10 min, tetrapropylammonium perruthenate (6.4 mg, 18.2 μmol) was added to the reaction mixture and stirring was continued at room temperature for 17 h. After insoluble materials were filtered off, the solvent was evaporated *in vacuo* to afford a crude ketone, which was subjected to the following reaction without purification. To a solution of methyltriphenylphosphonium bromide (261 mg, 732 μmol) in THF (7 mL) was added a 1.6 M hexane solution of *n*-BuLi (435 μL, 695 μmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The crude ketone (108 mg) in THF (4 mL) was added to the mixture at 0 °C, and the reaction mixture was stirred at room temeprature for 1 h. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The organic phase was washed with H_2O and then brine, and dried over $MgSO_4$. After evaporation, the residue was purified by a silica gel column (hexane/EtOAc, 49:1) to afford **15** (56.1 mg, 173 μmol, 47 % from **14**) as a colorless oil; $[\alpha]_D^{23}$ -2.64° (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06, (6H, s), 0.89 (3H, d, *J* = 6.0 Hz), 0.91 (9H, s), 1.28 (3H, t, *J* = 7.0 Hz), 1.75-1.90 (2H, m), 1.95-2.05 (2H, m), 2.24 (1H, m), 4.03 (2H, s), 4.18 (2H, q, *J* = 7.1 Hz), 4.80 (1H, s), 5.08 (1H, s), 5.80 (1H, dt, *J* = 1.2 and 13.6 Hz), and 6.93 (1H, m); ^{13}C NMR ($CDCl_3$) δ -5.45 (2C), 12.21, 18.30, 19.48, 25.85 (3C), 30.66, 39.33, 40.39, 60.04, 65.70, 110.45, 122.64, 146.56, 147.66, and 166.44; FABMS (Pos.) *m/z* 327 $(M+H)^+$; HRFABMS *m/z* 327.2376 $(M+H)^+$, calcd for $C_{18}H_{35}O_3Si$, 327.2356.

(2*E*,5*S*)-7-(*t*-Butyldimethylsilyloxymethyl)-5-methyl-2,7-octadien-1-ol (16). To a solution of compound **15** (51.4 mg, 158 μmol) in CH_2Cl_2 (1 mL) was dropwise added a 0.95 M CH_2Cl_2 solution of DIBAL (664 μL, 630 μmol), and the mixture was stirred at -78 °C for 3 h. After addition of MeOH (100 μL) to decompose the excess reagent, the reaction mixture was allowed to warm to room temperature. Et_2O and saturated aqueous potassium sodium tartrate were added to the reaction mixture, which was stirred vigorously for 1 h. After extraction with EtOAc, the organic phase was washed with H_2O and then brine and dried over $MgSO_4$. The solvent was evaporated to give a residue, which was subjected to silica gel column chromatography (hexane/EtOAc, 19:1) to afford the allyl alcohol (**16**, 44.9 mg 158 μmol, 100 %) as a colorless oil; $[\alpha]_D^{24}$ -3.45° (*c* 1.15, $CHCl_3$); IR (neat) ν_{max} 3340, 2955, 1460, 1255, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06, (6H, s), 0.86 (3H, d, *J* = 6.5 Hz), 0.91 (9H, s), 1.55 (1H, br.s), 1.68 (1H, m), 1.80 (1H, dd, *J* = 8.3 and 13.9 Hz), 1.87 (1H, m), 2.0 ~ 2.1 (2H, m), 4.03 (2H, s), 4.08 (2H, d, *J* = 4.7 Hz), 4.79 (1H, s), 5.07 (1H, d, *J* = 1.6 Hz), and 5.64 (2H, m); ^{13}C NMR ($CDCl_3$) δ -5.41 (2C), 18.36, 19.43, 25.89 (3C), 31.16, 39.56, 40.37, 63.38, 65.78, 110.03, 130.51, 131.43, and 147.00; FABMS (Pos.) *m/z* 285 $(M+H)^+$; HRFABMS *m/z* 285.2274 $(M+H)^+$, calcd for $C_{16}H_{33}O_2Si$, 285.2250.

(2*S*,3*S*,5*R*)-7-(*t*-Butyldimethylsilyloxymethyl)-2,3-epoxy-5-methyl-7-octen-1-ol (4a). To a stirred suspension of molecular sieves 4A (20 mg) in CH_2Cl_2 (150 μL) containing diethyl (+)-tartrate (130 mg, 630 μmol) was added titanium tetraisopropoxide (15 μL, 50 μmol) at -20 °C, and successively a solution of the alcohol **16** (35 mg, 123 μmol) in CH_2Cl_2 (300 μL) was dropwise added. After stirring for 30 min, a 3.0 M 2,2,4-trimethylpentane solution of *tert*-butyl hydroperoxide (123 μL, 369 μmol) was added and the resulting mixture was stirred at -20 °C for 12 h. The reaction mixture was poured into a cold and stirring solution of $FeSO_4 \cdot 7H_2O$ (70 mg) and tartaric acid (20 mg) in H_2O (200 μL). After insoluble materials were filtered, 30% NaOH in brine was added to the filtrate, and stirring was continued at 0 °C for 1 h. The mixture was extracted with CH_2Cl_2 and washed with H_2O and then brine and dried over

$MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc, 9:1) to afford compound **4a** (13.3 mg, 44.3 μmol, 36 %) and **4b** (1.5 mg, 5.0 μmol, 4 %), and 49 % of **16** (17.2 mg, 60.5 μmol) was recovered. **4a**: a colorless oil; $[\alpha]_D^{25}$ -18.9° (c 1.23, $CHCl_3$); IR (neat) ν_{max} 3445, 2955, 1460, 1255, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07, (6H, s), 0.91 (9H, s), 0.96 (3H, d, *J* = 6.6 Hz), 1.33 (1H, ddd, *J* = 5.4, 8.3, and 10.2 Hz), 1.63 (1H, ddd, *J* = 4.5, 6.5, and 13.8 Hz), 1.73 (1H, br.s), 1.8 ~ 2.0 (2H, m), 2.08 (1H, dd, *J* = 6.1 and 13.5 Hz), 2.90 (1H, m), 2.99 (1H, m), 3.64 (1H, dd, *J* = 3.5 and 12.3 Hz), 3.90 (1H, dd, *J* = 1.8 and 12.5 Hz), 4.05 (2H, s), 4.81 (1H, s), and 5.09 (1H, d, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ -5.39 (2C), 18.38, 19.63, 25.91 (3C), 29.06, 38.67, 40.97, 54.55, 58.79, 61.58, 65.72, 110.40, and 146.58; FABMS (Pos.) *m/z* 301 $(M+H)^+$; HRFABMS *m/z* 301.2174 $(M+H)^+$, calcd for $C_{16}H_{33}O_3Si$, 301.2199.

"(2*R*,3*R*,5*R*)-7-(*t*-Butyldimethylsilyloxymethyl)-2,3-epoxy-5-methyl-7-octen-1-ol (4b). The compound **4b** (14.5 mg, 48.3 μmol, 39 %) was prepared from the alcohol **16** (35 mg, 124 μmol) under the similar procedure except using (-)-DET described above together with **4a** (1.4 mg, 4.7 μmol, 4 %), and 45 % of **16** (16.7 mg, 55.8 μmol) was recovered. **4b**: a colorless oil; $[\alpha]_D^{25}$ +16.7° (*c* 1.44, $CHCl_3$); IR (neat) ν_{max} 3445, 2955, 1460, 1255, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07, (6H, s), 0.91 (9H, s), 0.98 (3H, d, *J* = 6.3 Hz), 1.40 (1H, m), 1.61 (1H, m), 1.8 ~ 1.95 (2H, m), 2.09 (1H, m), 2.87 (1H, m), 2.90 (1H, m), 2.98 (1H, m), 3.60 (1H, br.d, *J* = 18.8 Hz), 3.90 (1H, br.d, *J* = 12.6 Hz), 4.05 (2H, s), 4.81 (1H, s), and 5.89 (1H, d, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ -5.40 (2C), 18.36, 20.11, 25.90 (3C), 29.74, 38.75, 40.67, 54.83, 58.19, 61.60, 65.78, 110.45, and 146.65; FABMS (Pos.) *m/z* 301 $(M+H)^+$; HRFABMS *m/z* 301.2185 $(M+H)^+$, calcd for $C_{16}H_{33}O_3Si$, 301.2199.

Ethyl (2*E*,6*E*,8*S*,9*S*,11*R*)-13-(*t*-Butyldimethylsilyloxymethyl)-2,11-dimethyl-8,9-epoxy-2,6,13-tetradecatrienoate (2a). To a suspension of Dess-Martin periodinane (21.2 mg, 50.0 μmol) in DMF (50 μL) was added the epoxy alcohol **4a** (10.0 mg, 33.3 μmol) in DMF (50 μL). The mixture was stirred at room temperature for 4 h. After addition of 10 % $Na_2S_2O_3$-saturated $NaHCO_3$ aqueous solution, the reaction mixture was extracted with Et_2O. The organic phase was washed with H_2O and then brine and dried over $MgSO_4$. The solvent was evaporated to afford an aldehyde (10.4 mg), which was subjected to the following reaction without purification. To a solution of compound **3** (50 mg, 100 μmol) in THF (11 mL) was added 1.6 M *n*-BuLi in hexane (60 μL, 96 μmol) at -78 °C. After stirring for 2 h, a solution of the aldehyde (10.4 mg) in THF (100 μL) was added with stirring and the stirring was continued at -20 °C for 30 min and then room temperature for 13 h. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with Et_2O. The organic phase was washed with H_2O and then brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/EtOAc, 95:5) to give compound **2a** (5.3 mg, 12 μmol, 36 %) and its *cis*-isomer (3.9 mg, 9.0 μmol, 27 %). **2a**: $[\alpha]_D^{26}$ -12.6° (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 2955, 1720, 1460, 1255, and 1085 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FABMS (Pos.) *m/z* 437 $(M+H)^+$; HRFABMS *m/z* 437.3065 $(M+H)^+$, calcd for $C_{25}H_{45}O_4Si$, 437.3087.

Ethyl (2*E*,6*E*,8*R*,9*R*,11*R*)-13-(*t*-Butyldimethylsilyloxymethyl)-2,11-dimethyl-8,9-epoxy-2,6,13-tetradecatrienoate (2b). The compound **2b** (5.9 mg, 13.6 μmol, 41 %) and its *cis*-isomer (4.2 mg, 9.7 μmol, 29 %) were prepared from the epoxy alcohol **4b** (10.0 mg, 33.3 μmol) essentially by the similar procedure described above. **2b**: $[\alpha]_D^{26}$ +20.5° (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 2955, 1720, 1460, 1255, and 1085 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); FABMS (Pos.) *m/z* 437 $(M+H)^+$; HRFABMS *m/z* 437.3115 $(M+H)^+$, calcd for $C_{25}H_{45}O_4Si$, 437.3087.

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