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TETRAHEDRON

Studies on Stereochemistry of Theonezolides A ~ C[1]: Determination of Absolute Stereochemistry of the C-4 ~ C-17 Fragment

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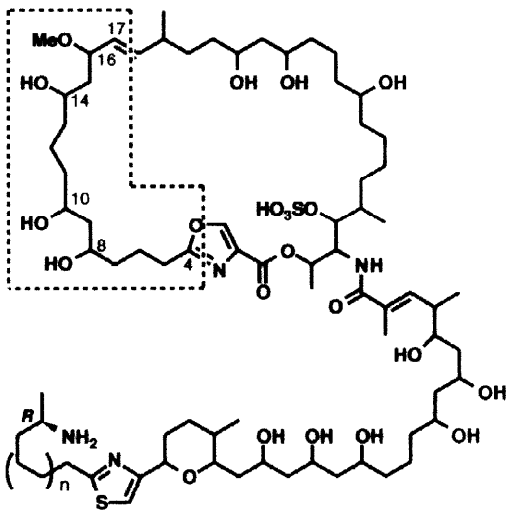
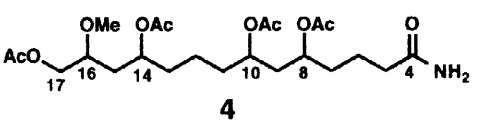
Abstract: The absolute stereochemistry of the C-4 ~ C-17 fragment of theonezolides A ~ C (**1** ~ **3**) was establsihed as 8*S*, 10*R*, 14*S*, 16*S* on the basis of synthesis of the two diastereomers (**4a** and **4b**) suggested from model studies and comparison of their spectral and optical data with those of natural specimen (**4**) obtained from ozonolysis of **1** ~ **3**.

Theonezolides A (**1**), B (**2**), and C (**3**) are novel cytotoxic 37-membered macrolides isolated from the Okinawan marine sponge *Theonella* sp.,[2,3] having unique bioactivity of induction of rabbit platelet shape change and aggregation.[4] Theonezolides A ~ C (**1** ~ **3**) contain 23 chiral centers, among which the absolute configuration of one chiral center at the terminal position (C-75, C-73, and C-77 of **1** ~ **3**, respectively) were determined as all *R* on the basis of synthesis of their ozonolysis products.[3] As to the C-4 ~ C-17 fragment (**4**),[5] which were commonly obtained by ozonolysis of the three macrolides (**1** ~ **3**),[2,3] the relative configurations of two 1,3-diol type moieties (14-OAc/16-OMe and 8-OAc/10-OAc) were investigated on the basis of preparation of model compounds and spectral comparisons with the natural product-derived specimen (**4**). As a result, the two 1,3-diol type moieties were both suggested as *syn*, and four structures (**4a** and **4b** and their enantiomers) remain to be likely out of sixteen possibilities.[1] Here we describe the synthesis of two possible diastereomers (**4a** and **4b**) as optically active forms and comparison of their spectral and optical data with those of the natural specimen (**4**) to establish the absolute configuration of four chiral centers contained in



1: n = 3, 2: n = 2, 3: n = 4



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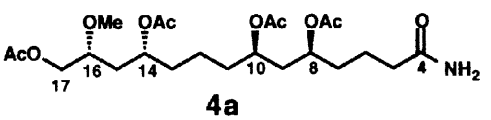
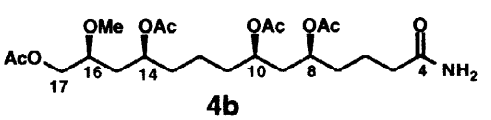
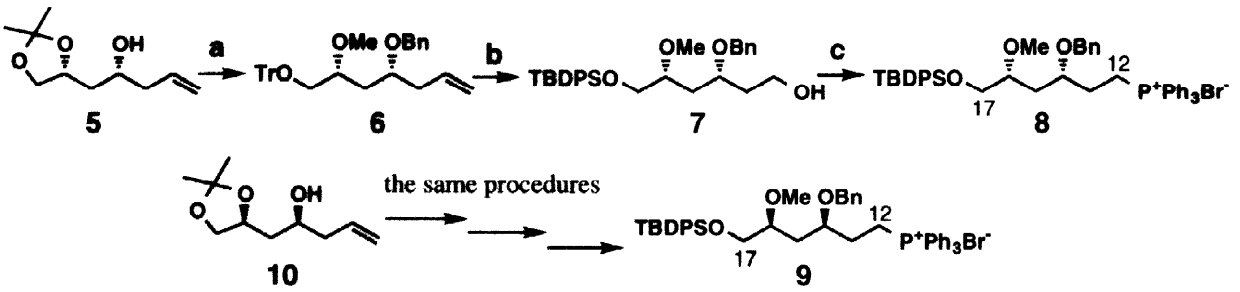


4a



4b

PII: S0040-4020(98)00190-2



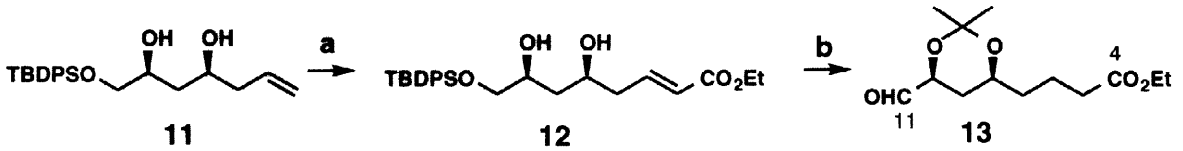
Scheme 1. (a) 1) BnBr, NaH, *n*-Bu_4NI, DMF; 2) 1N HCl, THF; 3) Ph_3CCl, DMAP, pyridine; 4) MeI, KH, THF (76%, 4 steps). (b) 1) 3N HCl, THF (84%); 2) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2 (97%); 3) O_3; 4) $NaBH_4$, MeOH (80%, 2steps); (c) 1) CBr_4, PPh_3 CH_2Cl_2 (97%); 2) PPh_3, CH_3CN (83%).

the C-4 ~ C-17 fragment as 8*S*, 10*R*, 14*S*, 16*S*.

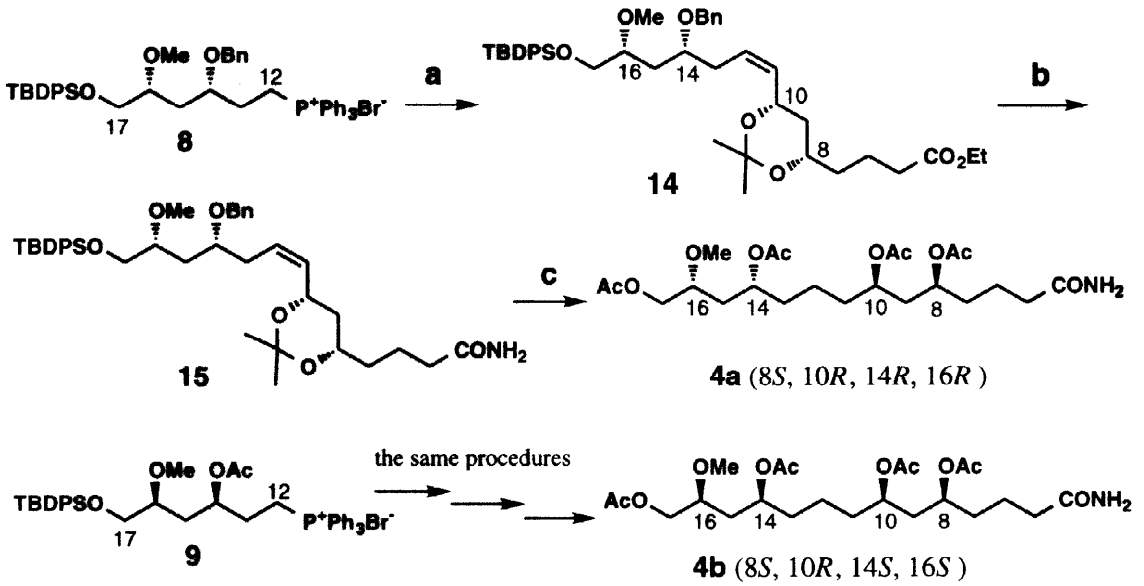
The C-12 ~ C-17 moiety of the diastereomer **4a** was prepared as follows (Scheme 1). The *syn*-homoallylalcohol (**5**), prepared from (+)-(*R*)-malic acid by the literature procedure,[6] was converted into the triphenylmethyl (Tr) ether (**6**) in 4 steps.[1] The Tr group was then replaced by *tert*-butyldiphenylsilyl (TBDPS) group, and ozonolysis of the double bond followed by $NaBH_4$ reduction gave an alcohol (**7**). The hydroxyl group of **7** was substituted with bromine, and the resulting bromide was then treated with triphenylphosphine in acetonitrile to afford a phosphonium salt (**8**), which corresponded to the C-12 ~ C-17 moiety of the diastereomer **4a**. The enantiomeric phosphonium salt (**9**) corresponding to the C-12 ~ C-17 moiety of the diastereomer **4b** was also prepared through the same procedures from the *syn*-homoallylalcohol (**10**) obtained from (-)-(*S*)-malic acid.[1,6]

On the other hand, the C-4 ~ C-11 moiety, which was common to both diastereomers **4a** and **4b**, was synthesized as shown in Scheme 2. The TBDPS ether (**11**),[1] prepared from the homoallylalcohol (**10**, Scheme 1), was subjected to ozonolysis followed by treatment with triphenylcarbethoxymethylene phosphorane to give an ethyl ester (**12**). This ester (**12**) was then converted by 4-step reactions [(1) hydrogenation; (2) protection of 1,3-diol; (3) deprotection of TBDPS group; (4) PCC oxidation] into an aldehyde (**13**), which corresponded to the C-4 ~ C-11 moiety of both diastereomers **4a** and **4b**.

Assemblage of the C-4 ~ C-11 and C-12 ~ C-17 moieties was then carried out as illustrated in Scheme 3. The phosphorus ylid, prepared from the phosphonium salt (**8**) by treatment with lithium bis(trimethylsilyl)amide in THF at rt, was coupled with the aldehyde (**13**) to give a *Z*-olefin (**14**), which was converted to a corresponding amide (**15**) in 3 steps.[3] This amide (**15**) was finally subjected to 5-step reactions (Scheme 3) to give the tetraacetate (**4a**), the 8*S*, 10*R*, 14*R*, 16*R*-isomer of the C-4 ~ C-17 fragment (**4**). The another diastereomer (**4b**), the 8*S*, 10*R*, 14*S*, 16*S*-isomer of **4**, was also synthesized by the similar procedures from the enantiomeric phosphonium salt (**9**) and the aldehyde (**13**).



Scheme 2. (a) 1) O_3; 2) Me_2S, MeOH; 3) $Ph_3P{=}CHCO_2Et$ (79%, 3 steps). (b) 1) H_2, Raney Ni (W-2) (98%); 2) $(CH_3)_2C(OCH_3)_2$, PPTS, CH_2Cl_2 (92%); 3) *n*-BuN_4F, THF (97%); 4) PCC, MS3Å, CH_2Cl_2.



Scheme 3. (a) 1) LHMDS, THF; 2) **13**, THF (18%, 2 steps). (b) 1) KOH, dioxane (81%); 2) *N,N'*-dicarbonylimidazole, CH_2Cl_2; 3) NH_3 (gas) (96%, 2 steps). (c) 1) *n*-Bu_4NF, THF; 2) AcOH-H_2O (7:3); 3) Ac_2O, pyridine (66%, 3 steps); 4) H_2, 10% Pd/C, EtOH; 5) Ac_2O, pyridine (49%, 2 steps).

The ^1H and ^{13}C NMR spectra of two synthetic diastereomers (**4a** and **4b**) were then carefully examined. Though two diastereomers (**4a** and **4b**) exihibited very similar NMR data, significant differences were observed in the signals due to acetoxy groups (Figure 1). Figure 2 also shows differences in the ^1H and ^{13}C NMR chemical shifts between two synthetic diastereomers (**4a** and **4b**) and natural product-derived specimen (**4**). These NMR data clearly indicated that relative stereochemistry of the diastereomer (**4b**), the 8*S*, 10*R*, 14*S*, 16*S*-isomer, was identical with that of the natural specimen (**4**). The optical rotation of the synthetic sample (**4b**, $[\alpha]_D$ -15.5° (*c* 0.25, $CHCl_3$)) proved to be identical with that of the natural specimen (**4**, $[\alpha]_D$ -15.3°(*c* 0.25, $CHCl_3$)). Thus, the absolute configurations of the C-4 ~ C-17 fragment (**4**) of theonezolides A ~ C (**1** ~ **3**) were established as 8*S*, 10*R*, 14*S*, and 16*S*. Further investigations on the absolute stereochemistry of other chiral centers contained in theonezolides A ~ C (**1** ~ **3**) are currently underway in our laboratory.

EXPERIMENTAL

General methods. Optical rotations were determined on a JASCO DIP-370 digital polarimeter, and UV and IR spectra were obtained on JASCO Ubest-35 and JASCO FT/IR-5300 spectrophotometers, respectively. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX-500 and/or JEOL EX-400 spectrometers. EI and FAB mass spectra were obtained on JEOL DX-303 and JEOL HX-110 spectrometers, respectively.

(2*R*,4*R*)-4-*O*-Benzyl-2-*O*-methyl-1-*O*-triphenylmethyl-6-heptene-1,2,4-triol (6). To a suspension of NaH (1.06 g, 60% oil dispersion) in DMF (10 mL) was added a solution of homoallylalcohol (**5**, 2.30 g, 12.4 mmol) at 0 °C. After stirring at 0 °C for 20 min, benzyl bromide (5.0 mL) and tetrabutylammonium iodide (120 mg) were added, and the mixture was stirred at rt for 24 h. After addition of saturated aqueous NH_4Cl (10 mL) at 0 °C, the mixture was extracted with EtOAc. The organic phase was concentrated and purifed by silica gel column chromatography (hexane/EtOAc, 9:1) to give a benzyl ether (3.40 g, 12.4 mmol). This benzyl ether (6.07 g, 22.0 mmol) was treated with 1N HCl (30 mL) in THF (60 mL) at rt

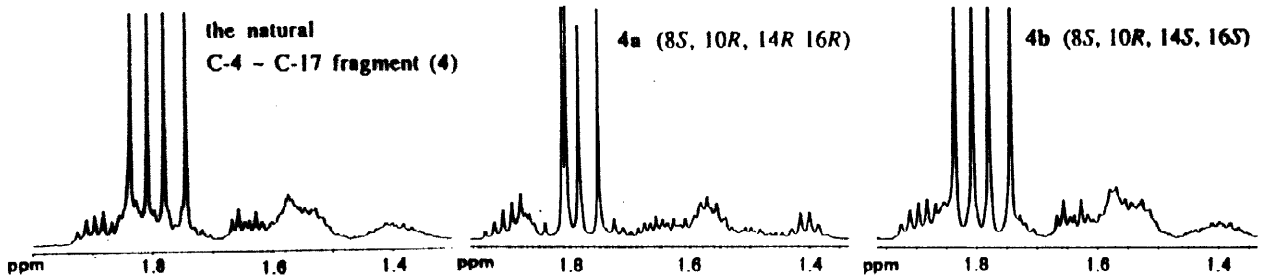


Figure 1. Acetoxy group regions of ^1H NMR spectra (500 MHz, C_6D_6) of natural (**4**) and synthetic (**4a/4b**) fragments.

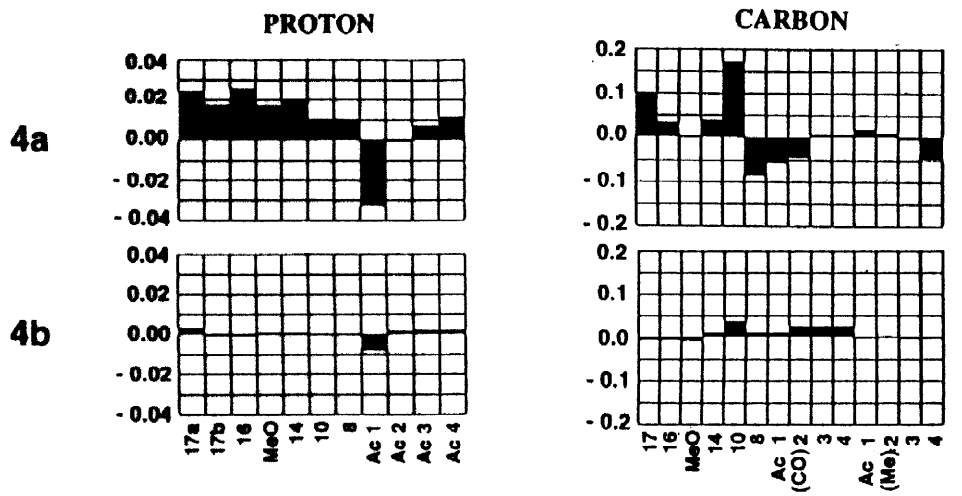


Figure 2. Differences in proton and carbon chemical shifts between natural fragment (**4**) and each of synthetic (**4a/4b**) fragments. The x- and y-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta_{synthetic} - \delta_{natural}$, in ppm), respectively.

for 6 h. After neutralization with solid $NaHCO_3$ at 0 °C and extraction with EtOAc, the organic phase was concentrated and chromatographed on silica gel (EtOAc/MeOH, 9:1) to give a 1,2-diol (4.45 g, 18.9 mmol, 86%). This 1,2-diol (1.59 g, 6.73 mmol) was treated with triphenylmethyl chloride (6.0 g, 22 mmol) and DMAP (40 mg, 0.33 mmol) in pyridine (30 mL) at 60 °C for 1.5 h. After addition of triethylamine (0.5 mL), the mixture was stirred for 10 min then it was concentrated. The residue was diluted with EtOAc (50 mL), washed with sat. aq NH_4Cl and concentrated. The residue was chromatographed on silica gel (hexane/$CHCl_3$, 1:1) to give a triphenylmethyl ether (2.84 g, 5.94 mmol, 88%). This triphenylmethyl ether (2.82 g, 5.89 mmol) in THF (30 mL) was treated with MeI (3.67 mL, 59.0 mmol) and a suspension of KH (6.60 g, 35% oil dispersion) at rt for 11 h. After being cooled at 0°C, the reaction was quenched by the slowly addition of MeOH (5.0 mL) and H_2O (50 mL). The resulting mixture was extracted with EtOAc, and the organic layer was concentrated and purified by a silica gel column chromatography (hexane/$CHCl_3$, 1:1) to give a methyl ether (**6**, 2.90 g, 5.89 mmol) as a colorless oil: $[\alpha]_D^{27}$ -3.3° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 1490, 1450, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.84 (2H, t, *J*=6.3 Hz), 2.31 (2H, t, *J*=7.0 Hz), 3.08 (1H, dd, J=10.0 and 5.1 Hz), 3.21 (1H, dd, *J*=10.0 and 3.8 Hz), 3.38 (3H, s), 3.44 (2H, m), 4.23 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.4 Hz), 5.10 (1H, br d, *J*=10.3Hz), 5.12 (1H, br d, *J*=17.3 Hz), 5.83 (1H, ddt, *J*=17.3, 10.3, and 7.0 Hz), 7.26 (15H, m), and 7.45 (5H, m); ^{13}C NMR ($CDCl_3$) δ_C 35.8, 38.1, 57.3, 64.4, 70.5, 75.6, 77.6, 86.2, 116.9, 126.7 (3C), 127.4, 127.5 (8C), 128.0 (2C), 128.5 (6C), 134.4, 138.4, and 143.8 (3C); HRFABMS *m/z* 515.2564, Calcd for $C_{34}H_{36}O_3Na$: $(M+Na)^+$ 515.2562.

(3*R*,5*R*)-3-Benzyloxy-6-(*tert*-butyldiphenylsilyloxy)-5-methoxyhexan-1-ol (7). The trityl ether (**6**, 2.71 g, 5.51 mmol) was treated with 3N HCl (5.0 mL) in THF (20 mL) under reflux for 8 h. After neutralization with solid $NaHCO_3$ at 0 °C and extraction with EtOAc, the organic phase was concentrated and chromatographed on silica gel (hexane/$CHCl_3$, 1:1) to give a primary alcohol (1.15 g, 4.60 mmol, 84%). This alcohol (2.86 g, 11.4 mmol) was treated with imidazole (1.50 g, 22.1 mmol), DMAP (120 mg, 0.98 mmol) and *tert*-butyldiphenylsilyl chloride (3.88 mL, 14.9 mmol) in CH_2Cl_2 (60 mL) at rt for 12 h. After addition of MeOH (1 mL) and saturated aqueous NH_4Cl solution, the mixture was extracted with $CHCl_3$, and the organic layer was concentrated and purified by a silica gel column chromatography (hexane/$CHCl_3$, 1:2) to give a TBDPS ether (5.40 g, 11.1 mmol, 97%). A solution of the TBDPS ether (2.01 g, 4.11 mmol) in MeOH (15 mL) was saturated with ozone at -78 °C for 25 min. After removal of ozone with N_2 stream for 10 min, the reaction mixture was treated with $NaBH_4$ (610 mg) in MeOH (5 mL) at 0 °C for 1 h. After addition of 1.0 M phosphate buffer (pH 7), the reaction mixture was concentrated to a low volume, and extracted with $CHCl_3$. The organic layer was concentrated and purified with a silica gel column chromatography ($CHCl_3$) to give a primary alcohol (**7**, 1.61 g, 3.28 mmol, 80%) as a colorless oil: $[\alpha]_D^{27}$ +33° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3570, 1110, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.08 (9H, s), 1.84 (4H, m), 2.51 (1H, br m), 3.34 (3H, s), 3.35 (1H, m), 3.63 (1H, dd, *J*=10.8 and 5.2 Hz), 3.72 (1H, dd, *J*=10.8 and 5.2 Hz), 3.80 (3H, m), 4.46 (1H, d, *J*=11.6 Hz), 4.56 (1H, d, *J*=11.6 Hz), 7.31 (5H, m), 7.42 (6H, m), and 7.68 (4H, m); ^{13}C NMR ($CDCl_3$) δ_C 19.2, 26.9, 35.5, 36.1, 57.7, 60.6, 65.3, 70.6, 75.9, 78.6, 127.6, 127.7, 128.3, 129.6, 133.2, 133.3, 135.4, 135.5, and 138.1; HRFABMS *m/z* 493.2759, Calcd for $C_{30}H_{41}O_4Si$: $(M+H)^+$ 493.2774.

[(2*R*,4*S*)-4-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)-2-methoxyhexyl]-triphenylphosphonium bromide (8). The alcohol (**7**, 2.45 g, 4.99 mmol) was treated with carbon tetrabromide (4.96 g, 15.0 mmol) and triphenylphosphine (3.27 g, 12.5 mmol) in CH_2Cl_2 (40 mL) at rt for 30 min. After addition of saturated aqueous $NaHCO_3$ (40 mL) and extraction with $CHCl_3$, the organic phase was concentrated and chromatographed on silica gel (hexane/EtOAc, 5:1) to give a bromide (2.70 g, 4.86 mmol, 97%). The bromide (50.0 mg, 90.1 μmol) was treated with triphenylphosphine (124 mg, 473 μmol) in acetonitrile (1 mL) under reflux for 16h. After addition of acetonitrile (10 mL), the mixture was washed with hexane (10 mL x 5), concentrated and purified with a silica gel column (hexane/EtOAc, 10:1 → MeOH) to afford a phosphonium salt (**8**, 61.0 mg, 74.6 μmol, 83%) as a white solid: $[\alpha]_D^{29}$ +3.7° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 1440, 1180, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.01 (9H, s), 1.82 (2H, m), 1.96 (2H, m), 3.12 (3H, s), 3.40 (1H, m), 3.53 (1H, dd, *J*=10.6 and 5.3 Hz), 3.59 (1H, m), 3.63 (1H, dd, *J*=10.6 and 4.9 Hz), 4.13 (2H, m), 4.51 (1H, d, *J*=11.4 Hz), 4.61 (1H, d, *J*=11.4 Hz), 7.35 (11H, m), 7.63 (10H, m), and 7.78 (9H, m); HRFABMS *m/z* 737.3571, Calcd for $C_{48}H_{54}O_3SiP$: $(M-Br)^+$ 737.3583.

[(2*S*,4*R*)-4-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)-2-methoxyhexyl]-triphenylphosphonium bromide (9). Starting from the enantiomeric homoallylalcohol (**10**), the same procedures as described for the preparation of compound **8** afforded the enantiomeric phosphonium salt (**9**): $[\alpha]_D^{25}$ -5.1° (*c* 1.0, $CHCl_3$); The IR, ^1H NMR and mass spectral data for **9** were identical with those of its enantiomer **8**.

Ethyl (5*S*,7*S*)-8-*tert*-butyldiphenylsilyloxy-5,7-dihydroxy-2*E*-octenoate (12). The TBDPS ether (**11**,[1] 1.79 g, 4.67 mmol) was treated with ozone in MeOH (20mL) at -78 °C for 50 min. After removal of ozone with N_2 stream for 5 min, the reaction mixture was treated with dimethyl sulfide (0.9 mL) at

0°C for 1 h. Evaporation of the solvent under reduced pressure afforded a crude aldehyde, which was used immediately in the next step without purification. The aldehyde was treated with triphenylcarbethoxymethylene phsphorane (3.19 g, 9.17 mmol) in CH_2Cl_2 (6 mL) at rt for 24 h. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/ether, 1:2) to give an ethyl ester (**12**, 1.69 g, 3.71 mmol, 79%) together with its *Z*-isomer (0.219 g, 0.480 mmol, 10%). **12**: colorless oil; $[\alpha]_D^{27}$ +0.87° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3420(br), 1720, 1660, and 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.07 (9H, s), 1.28 (3H, t, *J*=7.2 Hz), 1.45 (2H, m), 2.36 (2H, m), 2.97 (1H, d, *J*=2.9 Hz), 3.50 (1H, dd, *J*=10.1 and 7.4 Hz), 3.61 (1H, dd, *J*=10.1 and 3.7 Hz), 3.65 (1H, m), 4.00 (2H, m), 4.17 (2H, q, *J*=7.2 Hz), 5.87 (1H, d, *J*=15.5 Hz), 6.95 (1H, dt, *J*=15.5 and 7.6 Hz), 7.43 (6H, m), and 7.66 (4H, m); ^{13}C NMR ($CDCl_3$) δ_C 14.2, 19.2, 26.8 (3C), 38.3, 40.3, 60.2, 67.8, 70.6, 72.8, 123.8, 127.8 (4C), 129.9 (2C), 132.9 (2C), 135.5 (4C), 144.8, and 166.3; HRFABMS *m/z* 457.2415, Calcd for $C_{26}H_{37}O_5Si$: $(M+H)^+$ 457.2410.

Ethyl (5*S*,7*S*)-8-oxo-5,7-isopropylidenedioxyoctanoate (13). A mixture (1.909 g, 4.19 mmol) of the ester (**12**) and its *Z*-isomer was treated with hydrogen atomosphere in the presence of Raney Ni (W-2) (15 mL, 50% suspension) in EtOH (10 mL) at rt for 3 h. After filtration of the catalyst, the filtrate was concentrated and purified with silica gel column chromatography (hexane/EtOAc, 1:2) to give a saturated ethyl ester (1.88 g, 4.11 mmol, 98 %). This ester (1.88 g, 4.11 mmol) was treated with pyridinium *p*-toluenesulfonate (15 mg, 60.0 μmol) and 2,2-dimethoxypropane (3.00 mL, 24.5 mmol) in CH_2Cl_2 (15 mL) at rt for 4 h. After addition of saturated aqueous $NaHCO_3$ (60 mL) and extraction with ether, the organic extract was evaporated under reduced presssure to give an acetonide (1.89 g, 3.80 mmol, 92%). This acetonide (1.89g, 3.80 mmol) in THF (15 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (4.2 mL) at rt for 3 h. After addition of saturated aqueous NH_4Cl (50 mL) and extraction with EtOAc, the organic phase was concentrated and chromatographed on silica gel (hexane/EtOAc, 2:1) to afford a primary alcohol (956mg, 3.68 mmol, 97%) as a colorless oil; $[\alpha]_D^{29}$ -0.2° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3470(br), 1740, 1200, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.25 (3H, t, *J*=7.2 Hz), 1.39 (3H, s), 1.44 (3H, s), 1.43 (4H, m), 1.65 (2H, m), 2.01 (1H, dd, *J*=7.1 and 5.6 Hz), 2.30 (2H, t, *J*=7.5 Hz), 3.49 (1H, dt, J=11.4 and 5.6 Hz), 3.59 (1H, ddd, *J*=11.4, 7.1, and 3.3 Hz), 3.85 (1H, m), 3.97 (1H, ddt, *J*=11.6, 6.3, and 3.1 Hz), and 4.12 (2H, q, *J*=7.2 Hz); HRFABMS *m/z* 261.1703, Calcd for $C_{13}H_{25}O_5$: (M+H) 261.1702. This primary alcohol (90.8 mg, 349 μmol) was treated with pyridinium chlorochromate (150 mg, 698 μmol) and molecular sieves 3Å (powdered, 120 mg) in CH_2Cl_2 (3.0 mL) at rt for 1h. The mixture was then diluted with ether (10 mL) and filtered through Florisil column (1.3 g), followed by washing with ether (50 mL). The filtrate was concentrated *in vacuo* to yield an aldehyde (**13**), which was immeadiately used in the next step without any further purification.

Ethyl (5*S*,7*S*,11*R*,13*R*)-11-benzyloxy-14-*tert*-butyldiphenylsilyloxy-5,7-isopropylidenedioxy-13-methoxy-8*Z*-tetradecenoate (14). The phosphonium bromide (**8**, 180 mg, 0.220 mmol) in dry THF (3.0 mL) was treated with 1.0 M lithium bis(trimethylsilyl)amide in THF (0.33 mL) at rt for 30 min. To this solution, the aldehyde (**13**, obtained from 90.8 mg of the corresponding primary alcohol, vide supra) in dry THF (2.0 mL) was added dropwise, and the mixture was stirred at rt for 2 h. After addition of saturated aqueous NH_4Cl and extraction with EtOAc, the organic phase was concentrated and purified by a silica gel column chromatography (hexane/EtOAc, 2:1) to afford a *Z*-olefin (**14**, 27.6 mg, 18%) as a colorless oil: $[\alpha]_D^{26}$ -1.4° (*c* 0.5, $CHCl_3$), UV (MeOH) λ_{max} 213 (ε 18000) and 260 (1000) nm; IR (neat) ν_{max} 1730,

1170, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.05 (9H, s), 1.25 (3H, t, *J*=7.1 Hz), 1.38 (3H, s), 1.44 (3H, s), 1.15 ~ 1.55 (4H, m), 1.65 (2H, m), 1.79 (2H, t, *J*=6.3 Hz), 2.29 (2H, t, *J*=7.4 Hz), 2.40 (2H, t, *J*=6.3 Hz), 3.33 (3H, s), 3.40 (1H, m), 3.56 (1H, m), 3.64 (2H, d, *J*=4.6 Hz), 3.78 (1H, m), 4.12 (2H, q, *J*=7.1 Hz), 4.40 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=11.5 Hz), 4.65 (1H, ddd, *J*=10.8, 7.8, and 2.5 Hz), 5.45 (1H, dd, *J*=10.8 and 7.8 Hz), 5.57 (1H, dt, *J*=10.8 and 7.2 Hz), 7.28 (5H, m), 7.39 (6H, m), and 7.67 (4H, m); ^{13}C NMR ($CDCl_3$) δ_C 14.3, 19.3, 19.8, 20.6, 26.9, 30.3, 32.3, 34.2, 35.5, 35.7 36.7, 57.6, 60.3, 65.2, 65.6, 68.3, 70.8, 75.9, 78.9, 98.4, 127.5, 127.6, 127.6, 128.2, 128.6, 129.6 132.2, 133.3, 133.4, 135.5, 135.6, 138.5, and 173.4; FABMS *m/z* 739 $(M+Na)^+$, 717 $(M+H)^+$, and 659 $(M-tBu)^+$; HRFABMS *m/z* 717.4176, Calcd for $C_{43}H_{61}O_7Si$: (M+H) 717.4187.

(5*S*,7*S*,11*R*,13*R*)-11-Benzyloxy-14-*tert*-butyldiphenylsilyloxy-5,7-isopropylidenedioxy-13-methoxy-8*Z*-tetradecenamide (15). The ester (**14**, 55.5 mg, 77.4 μmol) in dioxane (2.0 mL) was treated with 1N aqueous KOH solution (1.0 mL) at rt for 3 h. After addition of 10% aqueous citric acid solution (5 mL) and extraction with EtOAc, the organic phase was concentrated *in vacuo* to give a carboxylic acid (43.4 mg, 63.0 μmol, 81%). This acid (43.4 mg, 63.0 μmol) was treated with *N,N'*-carbonyldiimidazole (20.4 mg, 126 μmol) in THF (1.0 mL) at 60 °C for 1 h. After cooling to 0 °C, the mixture was bubbled with NH_3 gas at 0 °C for 5 min, followed by stirring for 30 min. After evaporation of the solvent, the EtOAc-soluble fraction of the residue was purified with a silica gel column chromatography ($CHCl_3$/MeOH, 10:1) to give an amide (**15**, 41.6 mg, 61.7 μmol, 96%) as a colorless oil: $[\alpha]_D^{26}$ -3.6° (*c* 1.0, $CHCl_3$), IR (neat) ν_{max} 3520 ~ 3280, 1670, 1620, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.05 (9H, s), 1.38 (3H, s), 1.45 (3H, s), 1.20 ~ 1.55 (4H, m), 1.72 (2H, m), 1.80 (2H, t, *J*=6.3 Hz), 2.23 (2H, t, *J*=7.3 Hz), 2.40 (2H, t, *J*=6.3 Hz), 3.33 (3H, s), 3.40 (1H, t, *J*=4.6 Hz), 3.56 (1H, t, *J*=5.9 Hz), 3.65 (2H, d, *J*=4.3 Hz), 3.82 (1H, m), 4.40 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=11.5 Hz), 4.66 (1H, ddd, *J*=10.6, 7.9, and 2.6Hz), 5.41 ~ 5.58 (2H, m), 5.45 (1H, dd, *J*=10.9 and 7.9Hz), 5.57 (1H, dt, *J*=10.9 and 7.3Hz), 7.27 (5H, m), 7.39 (6H, m), and 7.66 (4H, m); ^{13}C NMR ($CDCl_3$) δ_C 19.3, 19.9, 21.4, 26.9 (3C), 30.4, 32.3, 35.4, 35.5, 35.7, 36.8, 57.6, 65.2, 65.7, 68.8, 70.9, 75.9, 79.0, 98.6, 127.6, 127.7, 127.7, 128.2, 128.4, 129.7, 132.3, 133.5, 133.6, 135.7, 138.7, and 175.3; FABMS *m/z* 688 $(M+H)^+$ and 630 $(M-tBu)^+$; HRFABMS *m/z* 688.4026, Calcd for $C_{41}H_{58}O_6NSi$: (M+H) 688.4033.

(5*S*,7*R*,11*R*,13*R*)-5,7,11,14-Tetraacetoxy-13-methoxytetradecanamide (4a). A solution of the amide (**15**, 41.6 mg, 61.7 μmol) in THF (1.0 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (0.10 mL) at rt for 2 h. After addition of saturated aqueous NH_4Cl (5 mL) and extraction with EtOAc, the organic phase was evaporated under reduced pressure to give a primary alcohol, which was dissolved in H_2O (0.3 mL) without purification and treated with AcOH (0.7 mL) at rt for 1.5 h. Evaporation of the solvent afforded a crude triol (42.8 mg), which was treated with acetic anhydride (1.0 mL) and pyridine (2.0 mL) at rt for 12 h. After addition of an ice-cooled water (5 mL) and extraction with EtOAc, the organic phase was concentrated and purified with a silica gel column ($CHCl_3$/MeOH, 20:1) to yield a triacetate (21.8 mg, 40.8 μmol, 66% from **15**). This triacetate (21.0 mg, 39.9 μmol) was treated with hydrogen atomosphere in the presence of 10% Pd-C (50 mg) in EtOH (1.0 mL) at rt for 43 h. After filtration of the catalyst, the filtrate was evaporated under reduced pressure to afford a saturated alcohol (18.6 mg), which was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) at rt for 6 h. After evaporation of the solvent, the residue was purified by reversed phase HPLC [Develosil ODS-HG-5 (Nomura Chemical, 4.6 x

250 mm); eluent: 45% CH_3CN/H_2O (0 min) → 85% CH_3CN/H_2O (15 min), linear gradient; flow rate: 0.8 mL/min; UV detection at 215 nm] to afford a tetraacetate (**4a**, t_R 6.5 min,[7] 9.5 mg, 19.4 μmol, 49%) as colorless oils: $[\alpha]_D^{27}$ -8.1° (*c* 0.10, $CHCl_3$), IR (neat) ν_{max} 3580, 1730, and 1240 cm^{-1}; ^1H NMR (C_6D_6) δ_H 1.40 (3H, m), 1.58 (7H, m), 1.64 (2H, m), 1.75 (3H, s), 1.79 (3H, s), 1.806 (3H, s), 1.812 (3H, s), 1.89 (4H, m), 3.21 (3H, s), 3.42 (1H, m), 4.10 (1H, dd, *J*=11.8 and 5.0 Hz), 4.26 (1H, dd, *J*=11.8 and 3.9 Hz), 4.78 (1H, br m), 5.13 (2H, m), 5.25 (1H, m), and 5.55 (1H, br m); ^{13}C NMR (C_6D_6) δ_C 20.5, 20.84, 20.86, 20.90, 21.2 (2C), 33.9, 34.2, 34.3, 34.8, 36.5, 39.4, 56.9, 65.0, 70.7, 70.8, 71.0, 76.6, 170.1, 170.2, 170.3 (2C), and 173.9; FABMS *m/z* 490 $(M+H)^+$ and 430 $(M-OAc)^+$; HRFABMS *m/z* 490.2673, Calcd for $C_{23}H_{40}O_{10}N$: (M+H) 490.2652.

(5*S*,7*R*,11*S*,13*S*)-5,7,11,14-Tetraacetoxy-13-methoxytetradecanamide (4b). Starting from the coupling between the enantiomeric phosphonium bromide (**9**) and the aldehyde (**13**), the diastereomer (**4b**) was obtained through essentially the same procedures as described for the preparation of compound **4a**, and was finally purified with reversed phase HPLC (the same linear-gradient conditions for compound **4a**, vide supra; t_R of **4b**, 6.8 min[7]). **4b**: $[\alpha]_D^{27}$ -15.5° (*c* 0.25, $CHCl_3$); ^1H NMR (C_6D_6) δ_H 1.40 (3H, m), 1.58 (7H, m), 1.63 (2H, m), 1.74 (3H, s), 1.78 (3H, s), 1.81 (3H, s), 1.84 (3H, s), 1.88 (4H, m), 3.20 (3H, s), 3.40 (1H, m), 4.08 (1H, dd, *J*=11.7 and 5.0 Hz), 4.24 (1H, dd, *J*=11.7 and 4.0 Hz), 4.61 (1H, m), 4.98 (1H, m), 5.12 (2H, m), and 5.23 (1H, m); ^{13}C NMR (C_6D_6) δ_C 20.5, 20.83, 20.86, 20.94, 21.09, 21.3, 33.7, 34.2, 34.3, 34.6, 36.5, 39.3, 56.9, 64.9, 70.5, 70.9, 71.1, 76.6, 170.2, 170.3 (3C), and 173.8; HRFABMS *m/z* 490.2633, Calcd for $C_{23}H_{40}O_{10}N$: $(M+H)^+$ 490.2652.

The C-11 ~ C-17 Fragment (4). The C-11 ~ C-17 fragment (**4**) derived from degradation of the natural products (**1** ~ **3**)[2,3] was purified by reversed phase HPLC (the same linear-gradient conditions for compound **4a**, vide supra; t_R of **4**, 6.8 min[7]), and the ^1H and ^{13}C NMR spectral data and the optical rotation were reexamined as follows. **4**: $[\alpha]_D$ -15.3°(*c* 0.25, $CHCl_3$); ^1H NMR (C_6D_6) δ_H 1.40 (3H, m), 1.58 (7H, m), 1.64 (2H, m), 1.74 (3H, s), 1.78 (3H, s), 1.81 (3H, s), 1.83 (3H, s), 1.89 (4H, m), 3.19 (3H, s), 3.40 (1H, m), 4.08 (1H, dd, *J*=11.7 and 5.1 Hz), 4.24 (1H, dd, *J*=11.7 and 4.1 Hz), 4.50 (1H, m), 4.66 (1H, m), 5.12 (2H, m), and 5.23 (1H, m); ^{13}C NMR (C_6D_6) δ_C 20.5, 20.83, 20.87, 20.95, 21.08, 21.3, 33.8, 34.2, 34.4, 34.6, 36.5, 39.3, 56.9, 64.9, 70.5, 70.9, 71.0, 76.6, 170.2, 170.3 (3C), and 173.4.

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References and Notes

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5. The numberings of the carbons of compound **4** and other compounds described here corresponded to those of the parent natural product, theonezolide A (**1**).
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7. These HPLC analyses also showed that **4a** and **4b** are distinguishable and **4b** is identical with **4**.