Synthesis of the C-14–C-26 segment of amphidinolide B

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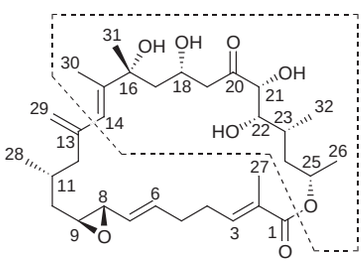
Received (in Cambridge) 3rd February 1999, Accepted 19th March 1999

The C-14–C-26 segment **2** of amphidinolide B **1**, a potent cytotoxic 26-membered macrolide, has been synthesized.

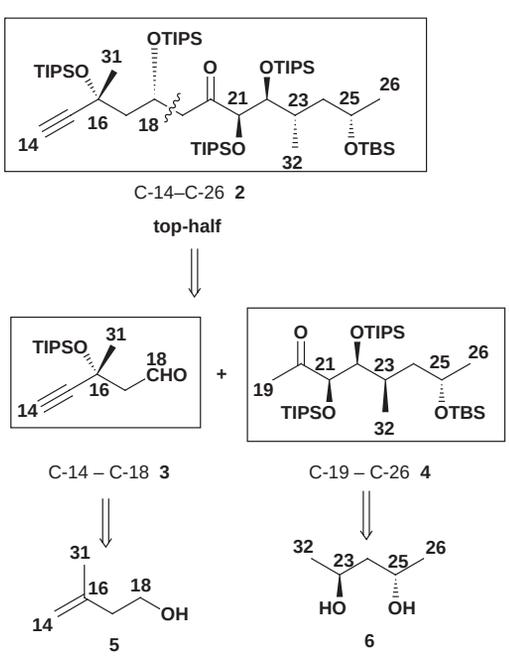
Amphidinolide B[1,2] **1**, isolated from the culture of a symbiotic marine dinoflagellate *Amphidinium* sp. (strain Y-5), is a potent cytotoxic 26-membered macrolide possessing nine chiral centers as well as unique partial structures such as an allyl epoxide and an s-*cis* diene. Since the absolute stereochemistry of nine chiral centers in **1** was determined by X-ray crystal analysis[3] and synthesis of the C-22–C-26 segment,[4] this macrolide has attracted great interest as one of the challenging targets for total synthesis.[5–8] Here we describe the stereoselective synthesis of the C-14–C-26 segment **2** of amphidinolide B **1**.



Amphidinolide B (1)

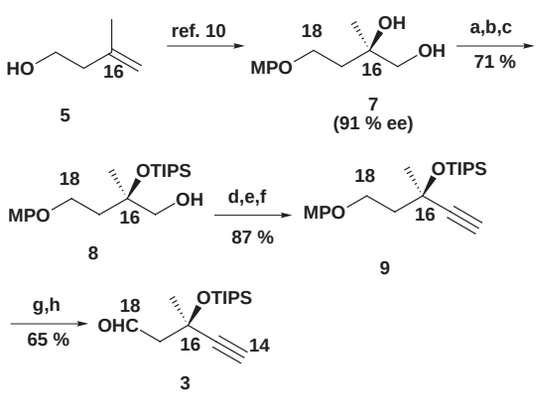
Results and discussion

We planned to synthesize the C-14–C-26 segment **2** by a convergent strategy through an aldol coupling reaction between the C-14–C-18 **3** and C-19–C-26 **4** units (Scheme 1). Unit **3** could be derived from commercially available 3-methylbut-3-en-1-ol **5** *via* asymmetric dihydroxylation using hydroquinidine pyridazine-1,4-diyl diether $[(DHQD)_2PYDZ]\cdot OsO_4$ catalyst[9,10] followed by C1-homologation using carbon tetrabromide.[11] On the other hand, unit **4** could be synthesized from (2*S*,4*S*)-pentane-2,4-diol **6** through a Horner–Wadsworth–Emmons reaction and Sharpless asymmetric dihydroxylation.[12] Triisopropylsilyl (TIPS) ether was selected as a protective group for the hydroxy groups at C-16, C-18, C-21 and C-22, while the hydroxy group at C-25 was protected with a *tert*-butyldimethylsilyl (TBS) ether.



Scheme 1

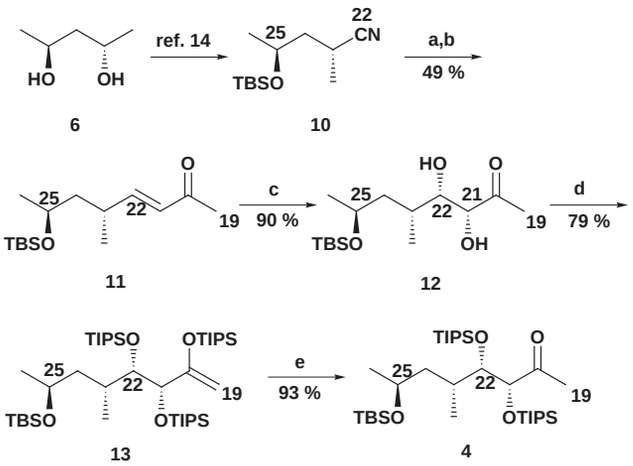
Protection of the primary hydroxy group in the chiral diol **7** (91% ee),[10] derived from 3-methylbut-3-en-1-ol through asymmetric dihydroxylation, afforded a pivaloyl ester (94%). The tertiary hydroxy group was converted into a TIPS ether (93%), and then the pivaloyl ester was deprotected using DIBAL-H reduction to afford the primary alcohol **8** in 81% yield (Scheme 2). Swern oxidation of **8** followed by treatment of



Scheme 2 *Reagents and conditions*: a PivCl, pyridine–CH_2Cl_2 (1 : 1), rt, 12 h; b TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 12 h; c DIBAL-H, CH_2Cl_2, −78 °C, 30 min; d $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 45 min, then Et_3N, −50 °C, 30 min; e CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 50 °C, 1 h; f EtMgBr, THF, 0 °C, 1 h; g CAN, CH_3CN–water (4 : 1), rt, 5 min; h Dess–Martin periodinane, pyridine–CH_2Cl_2 (1 : 1), rt, 2 h.

the corresponding aldehyde with carbon tetrabromide gave the dibromoolefin in 90% yield,[11] which was treated with 4.1 equivalents of ethylmagnesium bromide in THF at 0 °C to afford the acetylene **9** in 97% yield. The *p*-methoxyphenyl (MP) group of **9** was removed by ceric ammonium nitrate (CAN) and then the hydroxy group at C-18 was oxidized by Dess–Martin periodinane[13] in CH_2Cl_2–pyridine (1 : 1) to afford the aldehyde **3**, corresponding to the C-14–C-18 segment, in 65% yield in two steps.

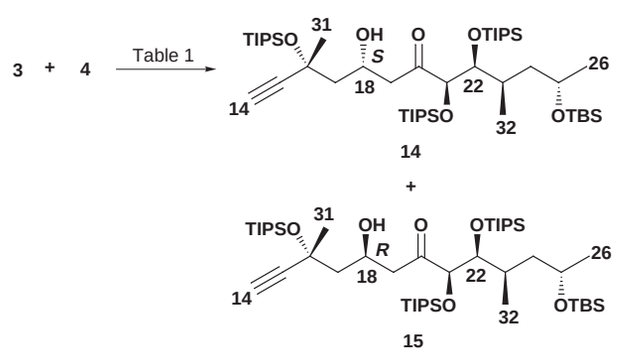
On the other hand, cyanide[14] **10**, prepared from (2*S*,4*S*)-pentane-2,4-diol **6** in three steps, was converted into the α,β-unsaturated ketone **11** by DIBAL-H reduction and then Horner–Wadsworth–Emmons reaction with diethyl (2-oxopropyl)phosphonate in 49% yield (Scheme 3). Sharpless asym-



Scheme 3 *Reagents and conditions*: a DIBAL-H, CH_2Cl_2, −20 °C, 30 min, then aq. NH_4Cl, rt, 20 min; b $(EtO)_2P(O)CHCOCH_3$, NaH, 0 °C, 20 min, and then rt, 8.5 h; c AD-mix-α, $K_2OsO_4{\cdot}2H_2O$, $NaHCO_3$, $CH_3SO_2NH_2$, *t*-BuOH–H_2O, (1 : 1), rt, 10 h; d TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 9 h; e PPTS, CH_2Cl_2, rt, 10 h.

metric dihydroxylation of **11** with AD-mix-α[12] in *t*-BuOH–H_2O (1 : 1) followed by silica gel column chromatography (hexane–$CHCl_3$–acetone–MeOH, 45 : 46 : 5 : 4) gave a 21,22-diol **12** in 90% yield. The absolute configurations at C-21 and C-22 of **12** were assigned as *R* and *S*, respectively, on the basis of the modified Mosher method[15] using 22-(*S*)- and 22-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) esters of **12**.† Although protection of the two hydroxy groups of **12** using TIPSCl and $(i\text{-Pr})_2NEt$ failed, treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and 2,6-lutidine (2,6-dimethylpyridine) in CH_2Cl_2 led to the protection of the hydroxy groups as a bis-TIPS ether and the 20-ketone carbonyl as a TIPS enol ether. The silyl enol ether **13** was transformed into the methyl ketone (**4**, 93% yield), corresponding to the C-19–C-26 unit, by treatment with pyridinium toluene-*p*-sulfonate (PPTS) in 93% yield.

The coupling reactions between the C-14–C-18 **3** and the C-19–C-26 **4** units (Scheme 4) are summarized in Table 1. The

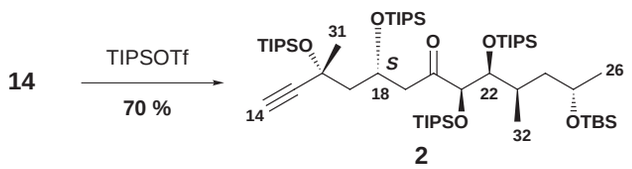


Scheme 4

aldol reaction between aldehyde **3** and the enolate generated from potassium hexamethyldisilazane (KHMDS) and the ketone **4** afforded the desired product **14** and its diastereomer **15** in 30 and 20% yields, respectively. On the other hand, aldehyde **3** was added to a THF solution of the zinc enolate of **4**, which was generated using LiHMDS and zinc chloride at −50 °C to give compounds **14** and **15** in 9 and 26% yields, respectively, while the aldol reaction using NaHMDS gave **14** and **15** in 25 and 27% yields, respectively. The stereochemistry at C-18 of compound **14** is believed to be the desired

Table 1

Reagent	Temperature/ °C	Time/h	Yield (%) **14**	**15**
KHMDS	−78	0.5	30	20
NaHMDS	−78	0.5	25	27
LiHMDS, $ZnCl_2$	−50	1	9	26



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S-configuration, since 18*R*-configuration of **15** was assigned by the modified Mosher method.‡ Finally, treatment of **14** with TIPSOTf afforded the C-14–C-26 segment **2** in 70% yield.

Thus the synthesis of the C-14–C-26 segment **2** lacking C-30 of amphidinolide B **1** has been completed. The synthesis of the C-1–C-13 segment and total synthesis of amphidinolide B **1** are under investigation.

Experimental

General methods

All moisture and air sensitive reactions were performed in flamed dried glassware equipped with rubber septa under a positive pressure of nitrogen or argon. Et_2O and THF were distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2, toluene, benzene, and pyridine were distilled from CaH_2, while DMSO was dried over molecular sieves (4 Å). All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. The work-up procedure involved extraction with EtOAc or ether or $CHCl_3$, washing of the organic extract with water and brine, drying (anhydrous Na_2SO_4), and evaporation of the solvent at aspirator pressure. Optical rotations were measured on a JASCO DIP-370 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on Bruker ARX-500 or JEOL EX-400 spectrometers in $CDCl_3$; ^1H NMR spectra were recorded in ppm in relation to the residual $CHCl_3$ signal (δ 7.26) as an internal standard, while ^{13}C NMR spectra were recorded in ppm relative to the $CDCl_3$ signal (δ 77.0). Multiplicity of each carbon signal was assigned on the basis of DEPT spectra. EI and FAB mass spectra were obtained on JEOL DX-303 and JMX-HX110 spectrometers, respectively.

(2*R*)-4-(4-Methoxyphenoxy)-2-methyl-2-(triisopropylsilyloxy)-butan-1-ol (8)

To a solution of the diol **7**[10] (517 mg, 2.28 mmol) in pyridine–CH_2Cl_2 (1 : 1, 5 mL) was slowly added pivaloyl chloride (337 mL, 2.74 mmol) at 0 °C, and stirring was continued at room temp. for 12 h. After addition of 2 M HCl (20 mL), the reaction mixture was worked-up with EtOAc (40 mL × 3). The residue was purified by silica gel column chromatography (hexane–acetone, 8 : 1→4 : 1) to yield a pivaloyl ester (667 mg, 2.15 mmol, 94%). A solution of the pivaloyl ester in CH_2Cl_2 (2 mL) was treated with 2,6-lutidine (501 mg, 4.3 mmol) and TIPSOTf (867 μL, 3.2 mmol) at room temp. for 12 h. After addition of saturated aqueous NH_4Cl (10 mL), the reaction mixture was worked-up with ether (20 mL × 3). The residue was purified by silica gel

† $\Delta\delta$ value [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for 22-(*S*)- and 22-(*R*)-MTPA esters of **12** are as follows: H_3-19, +0.03; H-21, +0.03; H-22, −0.04; H-25, −0.05; H_3-26, −0.07; H_3-32, −0.12.

‡ $\Delta\delta$ value [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for 22-(*S*)- and 22-(*R*)-MTPA esters of **15** are as follows: H-14, +0.09; H_2-17, +0.01 and +0.01; H-18, +0.07; H_2-19, −0.07 and −0.05; H-21, −0.01; H-22, 0.01; H-25, −0.01; H_3-26, −0.03.

column chromatography (hexane–EtOAc, 20:1→15:1) to afford a TIPS ether (931 mg, 1.99 mmol, 93%). The TIPS ether (882 mg, 1.89 mmol) in CH_2Cl_2 (5 mL) was treated with 0.95 M DIBAL-H solution in hexane (4.5 mL, 4.3 mmol) at −78 °C for 30 min. After addition of saturated aqueous potassium sodium tartrate (10 mL) and Et_2O (20 mL) to the mixture, the reaction mixture was stirred vigorously at room temp. for 1 h. The reaction mixture was worked-up with EtOAc (20 mL × 3). The residue was eluted through a silica gel column (hexane–EtOAc, 10:1→8.1) to give a primary alcohol **8** (590 mg, 1.54 mmol, 81%) as a colorless oil; $[\alpha]_D^{26}$ −11 (*c* 1.07, $CHCl_3$); ν_{max}/cm^{-1} 3480, 1590, 1230, 1040 and 825; $\delta_H(CDCl_3)$ 1.05, (21H, m), 1.33 (3H, s), 2.05 (2H, m), 3.42 (1H, dd, *J* = 9.0 and 10.9 Hz), 3.51 (1H, dd, *J* = 5.0 and 10.9 Hz), 3.75 (3H, s), 3.97 (1H, m), 4.09 (1H, m) and 6.81 (4H, m); $\delta_C(CDCl_3)$ 13.4 (3C, d), 18.3 (6C, q), 25.8 (q), 39.3 (t), 55.7 (q), 65.0 (t), 70.0 (t), 75.2 (s), 114.7 (2C, d), 115.4 (2C, d), 152.7 (s) and 154.0 (s); *m/z* (FABMS) 383 $(M + H)^+$; *m/z* (HRFABMS) 383.2629 $[(M + H)^+$. Calc. for $C_{21}H_{39}O_4Si$: 383.2617].

(3*R*)-5-(4-Methoxyphenoxy)-3-methyl-3-(triisopropylsilyloxy)-pent-1-yne (9)

To a solution of oxalyl chloride (224 μL, 2.56 mmol) and DMSO (275 μL, 3.87 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of the alcohol **8** (490 mg, 1.34 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After being stirred at −78 °C for 45 min, the mixture was treated with triethylamine (915 μL, 6.41 mmol) and allowed to warm to −50 °C, and stirring was continued for 30 min. After addition of saturated aqueous NH_4Cl (20 mL), the reaction mixture was worked-up with Et_2O (40 mL × 3) to afford a crude aldehyde (500 mg), which was used for the following reaction without separation. To a solution of the crude aldehyde (600 mg) in toluene (20 mL) were added triethylamine (1.8 mL, 12 mmol), carbon tetrabromide (2.05 g, 6.2 mmol), and triphenylphosphine (3.14 g, 12 mmol), the mixture was stirred at 50 °C for 1 h. After addition of water (20 mL), the reaction mixture was worked-up with $CHCl_3$ (40 mL × 3). The residue was eluted through a silica gel column (hexane–$CHCl_3$, 8:1) to yield a dibrominated olefin (739 mg, 1.38 mmol, 90%). A solution of the olefin (1.04 g, 1.93 mmol) in THF (10 mL) was treated with 1 M THF solution of EtMgBr (8 mL, 8 mmol) at 0 °C for 1 h. After addition of saturated aqueous NH_4Cl (20 mL), the reaction mixture was worked-up with EtOAc (40 mL × 3). The residue was purified by silica gel column chromatography (hexane–EtOAc, 8:1) to afford acetylene **9** (709 mg, 1.88 mmol, 97%) as a colorless oil; $[\alpha]_D^{25}$ −0.66 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} 1590, 1230, 1045 and 825; $\delta_H(CDCl_3)$ 1.07, (21H, m), 1.57 (3H, s), 2.19 (2H, m), 2.42 (1H, s), 3.75 (3H, s), 4.16 (2H, m) and 6.82 (4H, m); $\delta_C(CDCl_3)$ 13.1 (3C, d), 18.4 (6C, q), 31.3 (q), 44.3 (t), 55.7 (q), 65.1 (t), 67.6 (d), 72.1 (s), 87.6 (s), 114.5 (2C, d), 115.2 (2C, d), 152.9 (s) and 153.6 (s); *m/z* (FABMS) 361 $(M + H)^+$; *m/z* (HRFABMS) 361.2579 $[(M + H)^+$. Calc. for $C_{22}H_{37}O_2Si$: 361.2563].

C-14–C-18 unit: (3*R*)-3-(triisopropylsilyloxy)-3-methylpent-4-ynal (3)

Acetylene **9** (70.5 mg, 187 μmol) in acetonitrile–water (4:1, 2.5 mL) was treated with ceric ammonium nitrate (260 mg, 474 μmol) at room temp. for 5 min. After addition of saturated aqueous $NaHCO_3$ (5 mL), the reaction mixture was worked-up with EtOAc (50 mL × 3). The residue was purified by silica gel column chromatography (hexane–EtOAc, 6:1) to give an alcohol (44.7 mg, 165 mmol, 88%). To a solution of the alcohol (45 mg, 166 μmol) in pyridine–CH_2Cl_2 (1:1, 1.6 mL) was added Dess–Martin periodinane (106 mg, 248 μmol), and stirring was continued at room temp. for 2 h. After addition of saturated aqueous Na_2SO_3 (4 mL), the mixture was worked-up with EtOAc (15 mL × 3). The residue was subjected to a silica gel column (hexane–EtOAc, 10:1) to yield aldehyde **3** (33 mg, 123 μmol, 74%) as a colorless oil; $\delta_H(CDCl_3)$ 1.07 (18H, m), 1.17 (3H, m), 1.64 (3H, s), 2.56 (1H, s), 2.69 (2H, m) and 9.93 (1H, br s); $\delta_C(CDCl_3)$ 12.9 (3C, d), 18.2 (3C, q), 18.3 (3C, q), 31.3 (q), 57.5 (t), 66.5 (d), 73.5 (s), 86.6 (s) and 201.3 (d); *mz* (FABMS) 269 $(M + H)^+$; *m/z* (HRFABMS) 269.1913 $[(M + H)^+$. Calc. for $C_{15}H_{29}O_2Si$: 269.1889].

(3*E*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methyloct-3-en-2-one (11)

To a solution of the cyanide **10** (6.69 g, 29.4 mmol) in CH_2Cl_2 (150 mL) was added a 0.95 M hexane solution of DIBAL-H (41 mL, 39 mmol) at −20 °C, and the mixture was stirred at −20 °C for 30 min. MeOH (380 μL) was added to the reaction mixture, and stirring was continued at 0 °C for 10 min. After addition of saturated aqueous NH_4Cl (34 mL), the mixture was stirred at room temp. for 20 min. After addition of saturated aqueous potassium sodium tartrate (60 mL) and then Et_2O (120 mL), the reaction mixture was stirred vigorously at room temp. for 1 h. The reaction mixture was worked-up with Et_2O (400 mL × 3) to afford a crude aldehyde (6.64 g), which was used for the following reaction without separation. To a suspension of NaH (3.0 g, 74 mmol) in THF (100 mL) was added diethyl (2-oxopropyl)phosphonate (14.2 g, 74 mmol) in THF (100 mL) at 0 °C, and the mixture was stirred at room temp. for 1 h. To this mixture was added a solution of the crude aldehyde (6.64 g) in THF (50 mL) at 0 °C, and stirring was continued at room temp. for 8.5 h. After addition of saturated aqueous NH_4Cl (120 mL), the mixture was worked-up with ether (250 mL × 3). The residue was purified by silica gel column chromatography (hexane–Et_2O, 8:1–5:1) to give an α,β-unsaturated ketone **11** (3.89 g, 14.4 mmol, 49% in two steps) as a colorless oil; $[\alpha]_D^{26}$ −7.7 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 1700, 1680, 1255 and 835; $\delta_H(CDCl_3)$ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 1.04 (3H, d, *J* = 6.6 Hz), 1.11 (3H, d, *J* = 6.1 Hz), 1.31 (1H, m), 1.58 (1H, m), 2.22 (3H, s), 2.47 (1H, m), 3.81 (1H, m), 6.01 (1H, d, *J* = 15.9 Hz) and 6.70 (1H, dd, *J* = 7.3 and 15.9 Hz); $\delta_C(CDCl_3)$ −5.01 (q), −4.36 (q), 17.8 (s), 18.6 (q), 23.8 (q), 25.6 (3C, q), 26.6 (d), 32.9 (q), 45.6 (t), 65.8 (d), 128.8 (d), 153.6 (d) and 198.5 (s); *m/z* (EIMS) 270 (M^+); *m/z* (HREIMS) 270.2020 $(M^+$. Calc. for $C_{15}H_{30}O_2Si$: 270.2025).

(3*R*,4*S*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-3,4-dihydroxy-5-methyloctan-2-one (12)

To a suspension of AD-mix-α (21 g) in *t*-BuOH–water (1:1, 100 mL) were added potassium osmate dihydrate (44 mg, 120 μmol), $NaHCO_3$ (2.52 g, 30 mmol), and methanesulfonanide (3.6 g, 38 mmol) at room temp., and the mixture was stirred for 10 min. To the mixture was added a solution of compound **11** (2.707 g, 10.0 mmol) in *t*-BuOH–water (1:1, 20 mL) at 4 °C, and stirring was continued at 4 °C for 13 h. After addition of Na_2SO_3 (3.78 g, 30 mmol), stirring was further continued at room temp. for 1 h. The mixture was worked-up with EtOAc (300 mL × 3). The residue was eluted on a silica gel column (hexane–$CHCl_3$–acetone–MeOH, 45:46:5:4) to yield a diol **12** (2.74 g, 9.00 mmol, 90%) as a colorless oil; $[\alpha]_D^{26}$ −2.1 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 3445, 1715 and 835; $\delta_H(CDCl_3)$ 0.07 (6H, s), 0.89 (9H, s), 1.04 (3H, d, *J* = 6.6 Hz), 1.14 (3H, d, *J* = 6.1 Hz), 1.23 (1H, m), 1.64 (1H, m), 2.10 (1H, m), 2.27 (3H, s), 3.66 (1H, m), 3.93 (1H, m) and 4.23 (1H, s); $\delta_C(CDCl_3)$ −4.30 (q), −3.73 (q), 15.8 (s), 18.4 (q), 24.8 (q), 25.2 (q), 25.6 (3C, q), 33.7 (d), 43.6 (t), 66.5 (d), 76.0 (d), 78.0 (d) and 212.0 (s); *m/z* (FABMS) 305 $(M + H)^+$; *m/z* (HRFABMS) 305.2173 $[(M + H)^+$. Calc. for $C_{15}H_{33}O_4Si$: 305.2148].

(3*R*,4*S*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methyl-2,3,4-tris(triisopropylsilyloxy)oct-1-ene (13)

To a solution of the diol **12** (49.5 mg, 242 μmol) in CH_2Cl_2 (0.4 mL) were added 2,6-lutidine (0.18 mL, 2.18 mmol) and triiso-

propylsilyl trifluoromethanesulfonate (0.27 mL, 1.45 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 9 h. After addition of aqueous saturated NH_4Cl (3 mL), the mixture was worked-up with Et_2O (5 mL × 3). The residue was purified by silica gel column chromatography (hexane) to afford a silyl enol ether **13** (147 mg, 191 μmol, 79%) as a colorless oil; $[\alpha]_D^{26}$ −0.48 (*c* 1.03, $CHCl_3$); ν_{max}/cm^{-1} 1625, 1465, 885 and 835; δ_H($CDCl_3$) 0.02 (3H, s), 0.22 (3H, s), 0.85 (9H, s), 1.07 (57H, m), 1.14 (3H, d, *J* = 6.1 Hz), 1.23 (9H, m), 1.24 (1H, m), 1.74 (1H, m), 2.08 (1H, m), 3.78 (1H, br s), 3.87 (1H, m), 4.13 (1H, br s), 4.20 (1H, s) and 4.50 (1H, s); δ_C($CDCl_3$) −4.51 (q), −4.18 (q), 12.9 (3C, d), 13.0 (3C, d), 13.6 (3C, d), 15.3 (s), 18.3 (12C, q), 18.5 (6C, q), 22.7 (q), 26.0 (3C, q), 32.7 (d), 44.0 (t), 66.2 (d), 75.4 (d), 78.8 (d), 90.1 (t) and 159.4 (s); *m*/*z* (FABMS) 773 (M^+); *m*/*z* (HRFABMS) 773.5365 (M^+. Calc. for $C_{42}H_{92}O_4Si_4$: 773.5321).

C-19–C-26 unit: (3*R*,4*S*, 5*R*,7*S*)-3,4-bis(triisopropylsilyloxy)-7-(*tert*-butyldimethylsilyloxy)-5-methyloctan-2-one (4)

Compound **13** (155.3 mg, 201 μmol) in CH_2Cl_2 (2 mL) was treated with pyridinium toluene-*p*-sulfonate (53 mg, 207 μmol) at room temp. for 10 h. After addition of water (10 mL), the reaction mixture was worked-up with Et_2O (15 mL × 3). The residue was purified by silica gel column chromatography (hexane–Et_2O, 8 : 1–5 : 1) to give a ketone **4** (114.7 mg, 186 μmol, 93%) as a colorless oil; $[\alpha]_D^{24}$ −34.4 (*c* 1.07, $CHCl_3$); ν_{max}/cm^{-1} 1725 and 835; δ_H($CDCl_3$) 0.00 (3H, s), 0.01 (3H, s), 0.79 (6H, d, *J* = 5.6 Hz), 0.85 (9H, s), 1.06 (21H, m), 1.15 (21H, m), 1.22 (1H, m), 1.60 (1H, m), 2.12 (1H, m), 2.24 (3H, s), 3.83 (1H, m), 3.90 (1H, m) and 4.34 (1H, d, *J* = 4.6 Hz); δ_C($CDCl_3$) −4.7 (q), −4.1 (q), 12.5 (3C, d), 13.0 (3C, d), 14.5 (s), 17.8 (q), 18.15 (6C, q), 18.18 (4C, q), 18.4 (2C, q), 24.7 (q), 25.9 (3C, q), 29.2 (q), 31.0 (d), 44.9 (d), 66.0 (d), 80.0 (d), 81.7 (d) and 208.6 (s); *m*/*z* (FABMS) 617 $(M + H)^+$; *m*/*z* (HRFABMS) 617.4832 $[(M + H)^+$. Calc. for $C_{33}H_{73}O_4Si$: 617.4817].

Aldol coupling between C-14–C18 (3) and C-19–C-26 (4) units

To a stirring solution of the ketone **4** (120.6 mg, 196 μmol) in THF (2 mL) was added 0.5 M potassium hexamethyldisilazide in THF (570 μL, 285 μmol) at −78 °C. After being stirred at −78 °C for 30 min, the mixture was added to a solution of aldehyde **3** (43.7 mg, 163 μmol) in THF (2 mL) at −78 °C, and the mixture was stirred at −78 °C for 30 min. After addition of 1 M phosphate buffer (pH 7.3, 2 mL), the reaction mixture was worked-up with EtOAc (10 mL × 3). The residue was eluted on a silica gel column (hexane–$CHCl_3$, 2 : 1) to yield (3*S*,5*S*,8*R*,9*S*,10*R*,12*S*)-12-(*tert*-butyldimethylsilyloxy)-3,10-dimethyl-5-hydroxy-3,8,9-tris(triisopropylsilyoxy)tridec-1-yn-7-one **14** (43.3 mg, 48.9 μmol, 30%) and its 5*R*-isomer **15** (28.9 mg, 32.6 μmol, 20%), and the ketone **4** (55.4 mg, 89.8 μmol, 46%). **14**: a colorless oil; $[\alpha]_D^{25}$ −15 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} 1720 and 835; δ_H($CDCl_3$) 0.02 (3H, s), 0.03 (3H, s), 0.79 (9H, d, *J* = 5.6 Hz), 0.87 (9H, s), 1.11 (61H, m), 1.59 (1H, m), 1.80 (1H, dd, *J* = 1.7 and 14.1 Hz), 1.95 (1H, dd, *J* = 8.9 and 14.1 Hz), 1.63 (3H, s), 2.17 (1H, m), 2.43 (1H, s), 2.69 (1H, dd, *J* = 2.5 and 18.4 Hz), 3.00 (1H, dd, *J* = 8.1 and 18.4 Hz), 3.46 (1H, d, *J* = 1.9 Hz), 3.84 (1H, m), 3.97 (1H, m) and 4.41 (2H, m); δ_C($CDCl_3$) −4.6 (q), −4.1 (q), 12.5 (6C, d), 13.1 (3C, d), 14.5 (s), 18.1 (4C, q), 18.2 (6C, q), 18.3 (3C, q), 18.4 (6C, q), 24.7 (q), 25.9 (3C, q), 30.5 (d), 30.6 (q), 45.3 (t), 49.0 (t), 51.1 (t), 64.6 (d), 66.0 (d), 69.0 (d), 72.4 (s), 80.0 (d), 81.2 (d), 88.0 (s) and 210.7 (s); *m*/*z* (FABMS) 907 $(M + Na)^+$; *m*/*z* (HRFABMS) 907.6491 $[(M + Na)^+$. Calc. for $C_{48}H_{100}O_6Si_4Na$: 907.6494]. **15**: a colorless oil; $[\alpha]_D^{27}$ −45 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3530, 1720 and 835; δ_H($CDCl_3$) 0.02 (3H, s), 0.03 (3H, s), 0.78 (9H, m), 0.86 (9H, s), 1.12 (61H, m), 1.59 (1H, m), 1.60 (3H, s), 1.77 (1H, m), 1.89 (1H, dd, *J* = 9.5 and 14.2 Hz), 2.11 (1H, m), 2.45 (1H, s), 2.80 (2H, m), 3.52 (1H, m), 3.83 (1H, m), 3.96 (1H, m) and 4.49 (2H, m); *m*/*z* (FABMS) 907 $(M + Na)^+$; *m*/*z* (HRFABMS) 907.6497 $[(M + Na)^+$. Calc. for $C_{48}H_{100}O_6Si_4Na$, 907.6494].

C-14–C-26 segment: (3*S*,5*S*,8*R*,9*S*,10*R*,12*S*)-12-(*tert*-butyldimethylsilyloxy)-3,10-dimethyl-3,5,8,9-tetrakis(triisopropylsilyloxy)tridec-1-yn-7-one (2)

A solution of compound **14** (18 mg, 20.4 μmol) in CH_2Cl_2 was treated with triisopropylsilyl trifluoromethanesulfonate (40 μL, 215 μmol) and 2,6-lutidine (35 μL, 300 μmol) at room temp. for 36 h. After addition of H_2O (1 mL), the mixture was worked-up with EtOAc (2 mL × 3). The residue was purified by silica gel column chromatography (hexane) to give the C-14–C-26 segment **2** (15 mg, 14.4 μmol, 70%) as a colorless oil; $[\alpha]_D^{27}$ −9.2 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3310, 1725 and 835; δ_H($CDCl_3$) 0.03 (3H, s), 0.04 (3H, s), 0.81 (12H, d, *J* = 6.8 Hz), 0.87 (9H, s), 1.12 (79H, m), 1.58 (3H, s), 1.60 (1H, m), 1.80 (1H, dd, *J* = 5.6 and 13.5 Hz), 2.07 (1H, dd, *J* = 5.6 and 13.5 Hz), 2.14 (1H, m), 2.43 (1H, s), 3.02 (2H, m), 3.84 (1H, m), 3.92 (1H, m), 4.35 (1H, d, *J* = 4.7 Hz) and 4.66 (1H, m); δ_C($CDCl_3$) −4.23 (q), −4.18 (q), 12.5 (6C, d), 13.1 (3C, d), 13.8 (3C, d), 15.0 (s), 17.9 (q), 18.1 (3C, q), 18.2 (6C, q), 18.3 (3C, q), 18.4 (6C, q), 18.5 (6C, s), 24.6 (q), 26.0 (3C, q), 30.4 (d), 30.5 (q), 45.2 (t), 50.0 (t), 52.5 (t), 66.2 (d), 68.3 (d), 73.2 (s), 80.1 (d), 88.1 (s) and 206.9 (s); *m*/*z* (FABMS) 1041 $(M + H)^+$; *m*/*z* (HRFABMS) 1041.7990 $[(M + H)^+$. Calc. for $C_{57}H_{121}O_6Si_5$: 1041.8010].

Acknowledgements

We are grateful to Professor M. Ishibashi, Chiba University, for helpful discussions. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan. H. I. thanks Research Fellowships of the Japanese Society for the Promotion of Science for Young Scientists.

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