

Studies on the Stereochemistry of Amphidinolides¹⁾: Synthesis of a Diastereomer of the C-1—C-9 Fragment of Amphidinolide C

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A diastereomer of the C-1—C-9 fragment of amphidinolide C, a potent cytotoxic 25-membered macrolide isolated from a marine dinoflagellate, *Amphidinium* sp., has been synthesized to provide an authentic sample for use in studies on the degradation of amphidinolide C.

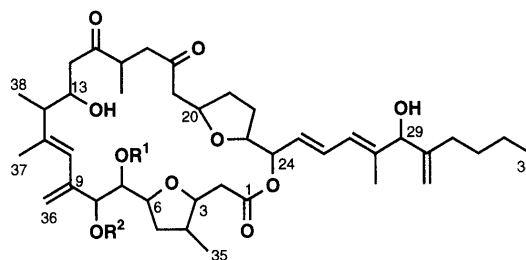
Key words dinoflagellate; *Amphidinium* sp.; macrolide; amphidinolide C; stereochemistry

Amphidinolides are a series of cytotoxic macrolides possessing unique structural features isolated from a laboratory-cultured marine dinoflagellates, *Amphidinium* sp.²⁾ During our studies on the stereochemistry of these unique macrolides based on synthesis and degradation,³⁾ we currently initiated investigation on the stereochemistry of amphidinolide C (**1**), a potent cytotoxic 25-membered macrolide first isolated in 1988 by us.⁴⁾ We previously proposed²⁾ the relative stereochemistry of the two tetrahydrofuran (THF) moieties of **1** based on the nuclear Overhauser effect spectroscopy (NOESY) spectral data of **1**. This paper mainly deals with studies on the stereochemistry of the C-1—C-9 moiety of **1**, which contains five chiral centers.

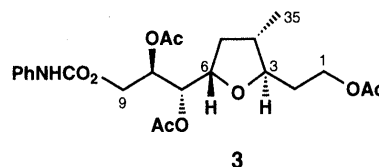
Amphidinolide C (**1**) was isolated in approximately 0.001% yield (wet weight) from the harvested algal cells of the dinoflagellate *Amphidinium* sp. (strain Y-5), which is a symbiont of the Okinawan marine flatworm *Amphiscolops* sp.^{2,4)} The NOESY spectrum of amphidinolide C (**1**) in C₆D₆ solution was recorded and the relative stereochemistries of the oxymethine protons of the two THF moieties of **1** (H-3/H-6, H-20/H-23) were both suggested to be *anti* and the methyl group on C-4 (C-35) was inferred to be *syn* to H-3, since NOESY cross-peaks were clearly observed for H-3/H₃-35, H₃-35/H-7, and H-20/H-24 with no correlation being observed for H-3/H-6 or H-20/H-23. The NOESY spectrum of amphidinolide C (**1**) also revealed substantial cross-peaks for H-7/H-8, H-7/H-10, H-36b/H₃-37, H-10/H-12, and H₃-37/H₃-38. From these cross-peaks we tentatively considered the relative configurations of the C-2—C-12 moiety of **1** as 3*R**, 4*S**, 6*S**, 7*S**, and 8*R**, with the *S*-*cis* conformation for the C-9—C-11 diene moiety; the cross-peaks observed for H-7/H-10 and H-10/H-12 implied that these hydrogens were likely to be oriented to the inside of the macrocycle. In addition, the 7,8-*O*-isopropylidene derivative (**2**) was prepared from **1** by treatment with dimethoxypropane (DMP) in the presence of pyridinium *p*-toluenesulfonate (PPTS), and the NOESY spectrum of **2** revealed significant correlations for H-4/H-6, H-5 α /H-6, H-5 β /H-7, and H-7/H-8, which appeared to be consistent with the relative stereochemistry proposed above for the C-2—C-12 moiety of **1**, including the *erythro*-relationship of the 7,8-diol. This proposal, however, requires further support. We therefore planned the synthesis of a diastereomer (**3**) with 3*R*,4*S*,6*S*,7*S*,8*R*-configurations,⁵⁾ corresponding to

the C-1—C-9 moiety of **1** to afford an authentic sample corresponding to one of the oxidative degradation products of **1**.

The diastereomer (**3**) was synthesized as shown in Chart 1, starting with the known epoxy alcohol **4** possessing 2*S*,3*S*,4*S*-configurations.⁵⁾ Compound **4** was readily prepared from (+)-methyl 3-hydroxy-2(*S*)-methylpropionate according to the literature procedures.⁶⁾ Reduction of the epoxide of **4** with sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) selectively afforded the 1,3-diol,⁷⁾ the acetone (**5**) of which was converted into an ester (**6**) in five steps. Reduction of **6** with diisobutylaluminum hydride (DIBAL) afforded the corresponding allyl alcohol, which was subjected to Sharpless asymmetric epoxidation⁸⁾ using (–)-diethyl tartrate (DET) to furnish an epoxy alcohol (**7**) along with a THF-bearing triol (**8**) in a ratio of 4.1 : 1. The acetone epoxy alcohol (**7**) proved to be readily transformed into the triol (**8**) by treatment with 1 *N* H₂SO₄. The relative stereochemistry relevant to the THF ring moiety of **8** was verified by the NOESY spectrum of the corresponding monopivaloyl ester (**9**)⁹⁾ prepared from **7** in two steps, showing substantial correlations for H-3/H₃-35, H-3/H-5 α , H-5 α /H₃-35,



1 R¹=R²=H
2 R¹, R²=–C(CH₃)₂–



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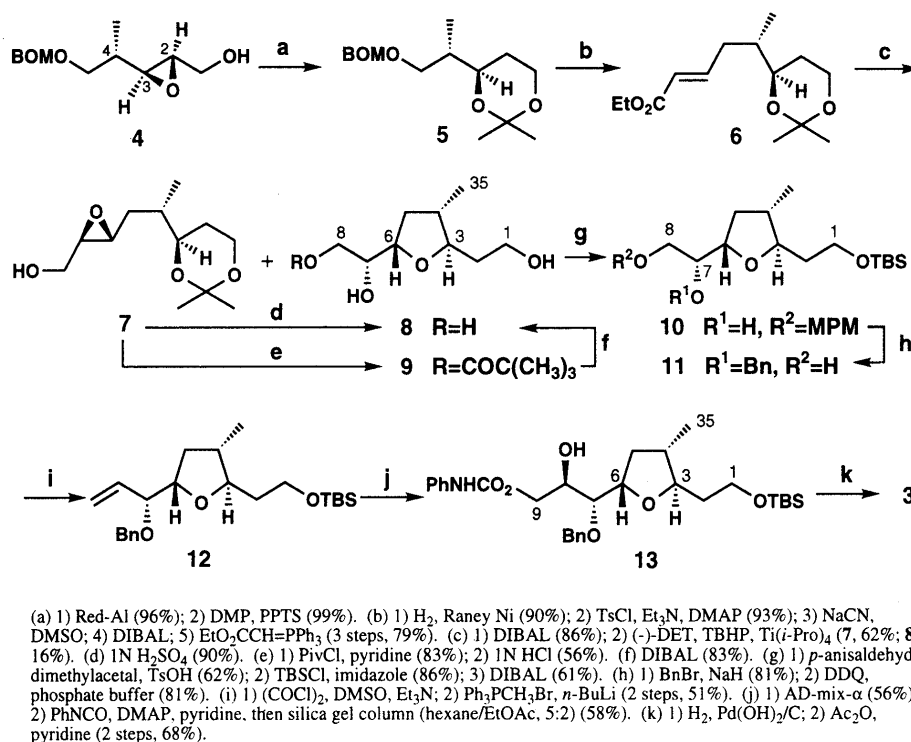


Chart 1

H-4/H-6, H-4/H-5 β , and H-5 β /H-6.⁵⁾ Two primary hydroxyl groups of **8** at the C-1 and C-8 positions were selectively protected in three steps with *tert*-butyldimethylsilyl (TBS) and *p*-methoxyphenylmethyl (MPM) groups, respectively, to give the 7-ol (**10**), which was converted in two steps into an 8-ol (**11**). Swern oxidation of **11** followed by Wittig reaction afforded an olefin (**12**), which was subjected to asymmetric dihydroxylation¹⁰⁾ using AD-mix- α to provide a mixture of *erythro*- and *threo*-diols in a ratio of 7 : 1. The diastereomeric mixture was treated with phenyl isocyanate to give *N*-phenylcarbamates, the *threo*-isomer of which was removed by silica gel column chromatography. The *erythro*-*N*-phenylcarbamate (**13**) thus obtained was then subjected to hydrogenolysis in the presence of palladium hydroxide on carbon, resulting in deprotection of both benzyl and TBS groups to give a triol, which was finally acetylated to furnish the triacetate (**3**).

The required molecule was thus obtained stereoselectively by practical procedures. An oxidative degradation procedure of amphidinolide C (**1**) was designed so that the *N*-phenylcarbamoyl chromophore would be introduced, to assist chromatographic purification of the products. Large-scale culturing of the dinoflagellate *Amphidinium* sp. (Y-5) is in progress to provide an adequate quantity of the macrolide (**1**) for degradation experiments.

Experimental

General Methods Optical rotations were determined on a JASCO DIP-370 digital polarimeter and IR spectra were taken on a JASCO Report-100 IR spectrometer. ¹H- and ¹³C-NMR spectra were recorded on Bruker ARX-500 and/or AMX-600 spectrometers. Electron impact (EI) and FAB mass spectra were obtained on JEOL DX-303 and HX-110 spectrometers, respectively.

7,8-O-Isopropylideneamphidinolide C (2) Amphidinolide C (**1**, 1 mg) was treated with DMP (0.3 ml) and PPTS (0.3 ml) in CH₂Cl₂ (2.0 ml) at room temperature for 8.5 h. After evaporation of the solvent, the residue was purified on a silica gel column (hexane-EtOAc, 6 : 1) to give an acetone (**2**, 0.49 mg, 46%). ¹H-NMR (C₆D₆) δ : 0.82 (3H, d, *J* = 6.8 Hz, H₃-35), 0.89 (3H, t, *J* = 7.4 Hz, H₃-34), 1.06 (3H, d, *J* = 7.0 Hz, H₃-38), 1.06 (3H, d, *J* = 7.0 Hz, H₃-39), 1.19 (1H, m, H-5'), 1.55 (1H, m, H-4), 1.66 (3H, s, H₃-40), 1.85 (3H, s, H₃-37), 1.97 (1H, m, H-5), 2.69 (1H, m, H-2), 2.74 (1H, m, H-2'), 4.01 (1H, m, H-23), 4.01 (1H, m, H-7), 4.17 (1H, m, H-6), 4.49 (1H, m, H-8), 5.04 (2H, s, H₂-41), 5.14 (1H, s, H-36), 5.31 (1H, s, H-36'), 5.59 (1H, m, H-24), 5.83 (1H, dd, *J* = 8.5, 15.3 Hz, H-25), 6.31 (1H, dd, *J* = 10.4 Hz, H-27), 6.79 (1H, dd, *J* = 10.4, 15.3 Hz, H-26).

(2S,3R)-1-Benzyloxymethoxy-3,5-O-isopropylidene-2-methylpentane-3,5-diol (5) A solution of the epoxy alcohol (**4**)⁶⁾ (7.49 g, 29.7 mmol) in THF (200 ml) was treated dropwise with 13.0 ml (44.2 mmol) of 65% Red-Al solution in toluene at 0 °C. The mixture was stirred at room temperature for 2 h, then MeOH (2.4 ml) was added and stirring was continued for 30 min at 0 °C. After addition of ether (200 ml) and Rochelle solution (saturated potassium sodium tartrate aqueous solution, 50 ml), the mixture was stirred for another hour, then extracted with EtOAc (200 ml $\times$ 8), and the organic phase was evaporated under reduced pressure to afford a residue, which was purified on a silica gel column (hexane-EtOAc, 1 : 2) to give the 1,3-diol (7.23 g, 28.4 mmol, 96%). The 1,3-diol (7.21 g, 28.3 mmol) was dissolved in CH₂Cl₂ (75 ml), then DMP (17.8 ml, 145 mmol) and PPTS (1.8 g, 7.2 mmol) were added at 0 °C, and the mixture was stirred for 2 h. After addition of saturated aqueous NaHCO₃ (30 ml), the reaction mixture was extracted with CH₂Cl₂ (60 ml $\times$ 2). The organic solution was washed with brine, dried over MgSO₄, and evaporated under reduced pressure to give a residue, which was purified on a silica gel column (hexane-EtOAc, 9 : 1) to give the acetone (**5**, 8.20 g, 27.9 mmol, 99%): colorless oil; [α]_D²⁸ -18° (*c* = 1.2, CHCl₃). IR (neat): 1100, 1060 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.96 (3H, d, *J* = 6.9 Hz), 1.37 (3H, s), 1.42 (3H, s), 1.44 (1H, m), 1.61 (1H, m), 1.81 (1H, m), 3.55 (1H, dd, *J* = 6.2, 9.4 Hz), 3.74 (1H, dd, *J* = 4.5, 9.4 Hz), 3.80 (1H, m), 3.86 (1H, ddd, *J* = 1.4, 5.4, 11.6 Hz), 3.95 (1H, dt, *J* = 2.8, 12.0 Hz), 4.60 (2H, s), 4.75 (2H, s), 7.27 (1H, m), 7.36 (4H, m). FAB-MS *m/z*: 295 (M + H)⁺, 187. HR-FAB-MS, Found *m/z*: 295.1935, Calcd for C₁₇H₂₇O₄ (M + H) 295.1909.

Ethyl (2E,5S,6R)-5-Methyl-6,8-O-isopropylidene-6,8-dihydroxy-2-octenoate (6) A suspension of 8.4 g of Raney Ni (W-2) in ethanol (20 ml) was added to a solution of the acetone (**5**, 4.00 g, 13.6 mmol) in ethanol

(20 ml) at room temperature, and the mixture was stirred for 48 h under a hydrogen atmosphere. Insoluble material was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified on a silica gel column (CH₂Cl₂–acetone, 15:1) to afford an alcohol (2.13 g, 12.2 mmol, 90%), which was treated with TsCl (4.75 g, 25.0 mmol), triethylamine (10.0 ml, 70.5 mmol), and 4-dimethylaminopyridine (DMAP, 250 mg, 2.02 mmol) in CH₂Cl₂ (38 ml) at room temperature for 18 h under argon. After addition of MeOH (4.0 ml) and water (40 ml), the reaction mixture was extracted with CH₂Cl₂ (40 ml × 3) and the organic phase was chromatographed on silica gel (hexane–EtOAc, 6:1) to give a tosylate (3.72 g, 11.3 mmol, 93%). A solution of the tosylate (3.68 g, 11.2 mmol) in dimethyl sulfoxide (DMSO) (90 ml) was treated with sodium cyanide (1.72 g, 35.1 mmol). The mixture was stirred at 60 °C for 1.5 h, then 300 ml of water and 800 ml of ether were added and the mixture was extracted with ether (800 × 2 ml). The organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified on a silica gel column (hexane–EtOAc, 6:1) to give a nitrile, which was dissolved in CH₂Cl₂ (38 ml), then a 0.93 M DIBAL solution in hexane (14.0 ml, 13.0 mmol) was slowly added with stirring at –78 °C. Stirring was continued for 1 h, MeOH (150 μl) was added, and stirring was further continued for 20 min at –78 °C with gradually warming to room temperature. After addition of saturated NH₄Cl solution (20 ml) and stirring for 20 min, saturated Rochelle solution (60 ml) was added and the whole was stirred for another hour at room temperature. Extraction with CH₂Cl₂ (200 ml × 3) followed by drying over MgSO₄ and evaporation under reduced pressure afforded a crude aldehyde (2.26 g), which was treated with ethyl (triphenylphosphoranylidene)acetate (6.06 g, 17.4 mmol) in CH₂Cl₂ (20 ml) at room temperature for 13.5 h. The solvent was removed by evaporation and the residue was subjected to silica gel column chromatography (hexane–EtOAc, 8:1) to give the ethyl ester (6, 2.26 g, 8.82 mmol, 79% in 3 steps): colorless oil; $[\alpha]_D^{29} -18^\circ$ ($c=1.7$, CHCl₃). IR (neat): 1730, 1180 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.86 (3H, d, $J=6.9$ Hz), 1.28 (3H, t, $J=7.2$ Hz), 1.37 (3H, s), 1.41 (3H, s), 1.45 (1H, m), 1.55 (1H, m), 1.68 (1H, m), 2.10 (1H, m), 2.42 (1H, m), 3.55 (1H, m), 3.84 (1H, ddd, $J=1.7, 5.5, 11.8$ Hz), 3.92 (1H, dt, $J=3.0, 12.0$ Hz), 4.18 (2H, q, $J=7.2$ Hz), 5.18 (1H, d, $J=15.4$ Hz), 6.94 (1H, ddd, $J=7.0, 8.3, 15.4$ Hz). FAB-MS m/z : 257 (M+H)⁺, 241. HR-FAB-MS, Found m/z : 257.1741, Calcd for C₁₄H₂₅O₄ (M+H) 257.1753.

(2R,3R,5S,6R)-2,3-Epoxy-6,8-O-isopropylidene-5-methyloctane-1,6,8-triol (7) The ethyl ester (6, 2.25 g, 8.78 mmol) was dissolved in CH₂Cl₂ (20 ml), and 18.9 ml (17.6 mmol) of 0.93 M DIBAL (in hexane) was slowly added to the solution at –78 °C. The mixture was stirred at –78 °C for 30 min, then MeOH (0.72 ml) was added and stirring was continued for 30 min at room temperature. After addition of ether (250 ml) and saturated Rochelle solution (50 ml), the whole was stirred for 1 h. Extraction with ether (150 ml × 2) and EtOAc (150 ml × 3) followed by evaporation of the combined organic solution under reduced pressure afforded a residue, which was purified on a silica gel column (hexane–EtOAc, 1:2) to give an allyl alcohol (1.62 g, 7.56 mmol, 86%). Titanium(IV) isopropoxide (0.65 ml, 2.78 mmol) was added to a stirred suspension of crushed molecular sieves 4A (1.00 g) in CH₂Cl₂ (6.0 ml) containing diethyl (–)-tartrate (DET, 446 mg, 2.16 mmol) at –20 °C under argon. After 10 min, a solution of the allyl alcohol (928 mg, 4.33 mmol) in CH₂Cl₂ (4.0 ml) was added dropwise, and the mixture was stirred for 30 min. Then a 3.6 M toluene solution of *tert*-butyl hydroperoxide (TBHP, 3.6 ml, 13.0 mmol) was added and the whole was stirred for 21 h at –20 °C, and poured into a cold solution of FeSO₄·7H₂O (1.1 g) and tartaric acid (343 mg) in H₂O (5 ml). The mixture was stirred at 0 °C for 15 min, insoluble materials were filtered off, and a 30% aqueous solution of NaOH saturated with sodium chloride (4.5 ml) was added to the filtrate. This mixture was further stirred for 1 h at 0 °C, then extracted with CH₂Cl₂ (10 ml × 3). The combined organic extracts were washed with H₂O and brine, dried over MgSO₄, and concentrated *in vacuo* to give a residue. The aqueous layers were combined, extracted with EtOAc (50 ml × 10), and concentrated *in vacuo* to give another residue. The combined residues were purified on a silica gel column (hexane–EtOAc, 2:1 and hexane–acetone, 1:3) to afford an epoxy alcohol (7, 616 mg, 2.67 mmol, 62%) together with a triol (8, 134 mg, 0.70 mmol, 16%; *vide infra*). 7: colorless oil; $[\alpha]_D^{29} +11^\circ$ ($c=0.46$, CHCl₃). IR (neat): 3450, 1210 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.98 (3H, d $J=6.9$ Hz), 1.36 (3H, s), 1.39 (1H, m), 1.42 (3H, s), 1.47 (1H, m), 1.55 (1H, m), 1.65 (1H, br t, $J=6.3$ Hz), 1.70 (1H, m), 1.86 (1H, dt, $J=4.7, 14.1$ Hz), 2.88 (1H, m), 3.01 (1H, m), 3.59 (1H, m), 3.64 (1H, m), 3.85 (1H, ddd, $J=1.2,$

5.3, 11.6 Hz), 3.91 (1H, ddd, $J=2.7, 5.1, 12.5$ Hz), 3.94 (1H, dt, $J=2.9, 11.9$ Hz). FAB-MS m/z : 231 (M+H)⁺. HR-FAB-MS, Found m/z : 231.1599, Calcd for C₁₂H₂₃O₄ (M+H) 231.1596.

(2R,3S,5S,6R)-3,6-Epoxy-5-methyloctane-1,2,8-triol (8) A solution of the epoxy alcohol (7, 610 mg, 2.65 mmol) in THF (7.5 ml) was treated with 1 N H₂SO₄ (1.5 ml), and the mixture was stirred at room temperature for 1 h. After addition of saturated NaHCO₃ aqueous solution (15 ml), the whole was extracted with EtOAc (30 ml × 10) and the organic phase was evaporated under reduced pressure. The residue was purified on a silica gel column (hexane–acetone, 1:3) to give the triol (8, 455 mg, 2.39 mmol, 90%): colorless oil; $[\alpha]_D^{29} +9.6^\circ$ ($c=0.30$, CHCl₃). IR (neat): 3400, 1060 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.05 (3H, d, $J=6.5$ Hz), 1.56 (1H, m), 1.65 (1H, m), 1.86 (1H, m), 1.95 (1H, m), 2.08 (1H, m), 2.23 (1H, br s), 2.59 (1H, br s), 2.74 (1H, br s), 3.59 (1H, m), 3.60 (1H, m), 3.70 (1H, m), 3.79 (3H, m), 4.00 (1H, m). FAB-MS m/z : 191 (M+H)⁺. HR-FAB-MS, Found m/z : 191.1255, Calcd for C₉H₁₉O₄ (M+H) 191.1283.

(2R,3S,5S,6R)-3,6-Epoxy-5-methyl-1-trimethylacetoxyoctane-2,8-diol (9) The epoxy alcohol (7, 47 mg, 204 μmol) was treated with pivaloyl chloride (40 μl, 326 μmol) and triethylamine (122 μl, 860 μmol) in the presence of DMAP (3.4 mg, 28 μmol) in CH₂Cl₂ (1 ml) at 0 °C under argon for 2 h. After addition of MeOH (36 μl), the mixture was diluted with H₂O and extracted with CH₂Cl₂. The organic phase was washed with H₂O and brine, dried over MgSO₄, and evaporated *in vacuo*. The residue was purified on a silica gel column (hexane–EtOAc, 6:1) to give a pivaloate (53 mg, 169 μmol, 83%). This pivaloate (47 mg, 150 μmol) was dissolved in THF (2.5 ml), and 1 N HCl (0.5 ml) was added to the solution at 0 °C. The mixture was stirred at room temperature for 1 h, then evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane–EtOAc, 2:1) to yield the THF derivative (9, 22.8 mg, 83 μmol, 56%): colorless oil; $[\alpha]_D^{25} +17^\circ$ ($c=0.82$, CHCl₃). IR (neat): 3400, 1730 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.04 (3H, d, $J=6.5$ Hz), 1.21 (9H, s), 1.59 (1H, m), 1.66 (1H, m), 1.87 (1H, m), 1.96 (1H, m), 2.10 (1H, m), 2.50 (1H, br s), 2.73 (1H, br s), 3.61 (1H, dt $J=2.6, 9.1$ Hz), 3.79 (2H, m), 3.89 (1H, m), 3.99 (1H, dt, $J=5.7, 9.7$ Hz), 4.08 (1H, dd, $J=6.5, 11.6$ Hz), 4.19 (1H, dd, $J=3.8, 11.6$ Hz). EI-MS m/z : 275 (M+H)⁺, 229, 85, 57. HR-EI-MS, Found m/z : 229.1413, Calcd for C₁₂H₂₁O₄ (M–C₂H₄OH) 229.1440.

Conversion of Pivaloate (9) into Triol (8) The pivaloate (9, 13 mg, 47 μmol) was dissolved in CH₂Cl₂ (1 ml), and 0.2 ml of 0.93 M DIBAL (in hexane) was slowly added to the solution at –78 °C. The mixture was stirred at –78 °C for 40 min, then MeOH (22 μl) was added and stirring was continued for 30 min at room temperature. After addition of saturated Rochelle solution (5 ml), extraction with EtOAc (10 ml × 10) and evaporation of the organic solution under reduced pressure, the residue obtained was purified on a silica gel column (hexane–acetone, 1:2) to give the triol (8, 7.4 mg, 39 μmol, 83%).

(2R,3S,5S,6R)-8-*tert*-Butyldimethylsilyloxy-3,6-epoxy-1-(4-methoxyphenyl)methoxy-5-methyloctan-2-ol (10) The triol (8, 45.5 mg, 239 μmol) was treated with *p*-anisaldehyde dimethylacetal (61 μl, 0.36 mmol) and *p*-toluenesulfonic acid monohydrate (14.2 mg, 0.074 mmol) in THF (4 ml) at room temperature for 18 h. After addition of saturated aqueous NaHCO₃ (8 ml), the reaction mixture was extracted with EtOAc (16 ml × 3). The organic solution was washed with H₂O and brine, dried over MgSO₄, and evaporated under reduced pressure to give a residue. The aqueous layers were combined and further extracted with EtOAc (50 ml × 10); again the organic solution was concentrated *in vacuo* to give another residue. The combined residues were purified on a silica gel column (hexane–EtOAc, 2:1 and hexane–acetone, 1:3) to yield a 7,8-(MPM)dioxo-1-ol⁵⁾ (46.0 mg, 149 μmol, 62%) together with the starting triol (8, 19 μmol, 8%). This reaction was repeated to obtain 464 mg (1.50 mmol) of the 7,8-(MPM)dioxo-1-ol, which was treated with *tert*-butylchlorodimethylsilane (TBSCl, 357 mg, 2.37 mmol) and imidazole (207 mg, 3.04 mmol) in CH₂Cl₂ (5 ml) at 0 °C for 3 h. After addition of saturated NaHCO₃ (5 ml) aqueous solution, the mixture was extracted with EtOAc (10 ml × 3). The combined organic solution was washed with H₂O and brine, dried over MgSO₄, and concentrated *in vacuo*. Purification of the residue on a silica gel column (hexane–EtOAc, 20:1) gave a 7,8-(MPM)dioxo-1-*O*-TBS ether⁵⁾ (545 mg, 1.29 mmol, 86%), a part of which (542 mg, 1.28 mmol) was dissolved in CH₂Cl₂ (5 ml) and treated with 2.9 ml (2.7 mmol) of 0.93 M DIBAL (in hexane) at –78 °C for 4 h. After addition of MeOH (56.7 μl) and further stirring for 30 min at room temperature, saturated Rochelle solution (10 ml) was added and the mixture was stirred for another hour. After extraction with EtOAc

(20 ml $\times$ 3), the organic phase was washed with H₂O and brine, dried over MgSO₄, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane–EtOAc, 4:1) to yield the 7-ol⁵⁾ (**10**, 333 mg, 0.78 mmol, 61%) together with the starting 7,8-(MPM)dioxy-1-*O*-TBS ether⁵⁾ (81 mg, 0.19 mmol, 15%). **10**: colorless oil; $[\alpha]_D^{25} + 35^\circ$ ($c=2.0$, CHCl₃). IR (neat): 3450, 1100 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.06 (6H, s), 0.91 (9H, s), 1.03 (3H, d, $J=6.5$ Hz), 1.55 (1H, m), 1.60 (1H, m), 1.80 (1H, m), 1.89 (1H, m), 2.09 (1H, m), 2.45 (1H, brs), 3.46 (1H, dd, $J=7.1$, 9.5 Hz), 3.51 (1H, dt, $J=2.9$, 8.8 Hz), 3.59 (1H, dd, $J=3.6$, 9.8 Hz), 3.72 (1H, m), 3.77 (1H, m), 3.81 (3H, s), 3.83 (1H, m), 3.92 (1H, m), 4.50 (2H, m), 6.89 (2H, d, $J=8.4$ Hz), 7.27 (2H, d, $J=8.4$ Hz). FAB-MS m/z : 425 (M+H)⁺, 367. HR-FAB-MS, Found m/z : 425.2753, Calcd for C₂₃H₄₁O₅Si (M+H) 425.2724.

(2R,3S,5S,6R)-2-Benzoyloxy-8-tert-butylidimethylsilyloxy-3,6-epoxy-5-methyloctan-1-ol (11) A solution of the 7-ol (**10**, 301 mg, 0.709 mmol) in THF (3 ml) was added to a suspension of NaH (60% in oil, 85.0 mg) in THF–DMSO (1:4, 5 ml) at room temperature. The mixture was stirred for 1 h at room temperature, then 169 ml (1.42 mmol) of benzyl bromide was introduced and the resulting mixture was further stirred for 2 h at room temperature. After addition of saturated NH₄Cl aqueous solution, the mixture was extracted with Et₂O (20 ml $\times$ 3), and the organic phase was washed with H₂O and brine, dried over MgSO₄, and evaporated under reduced pressure. The residue was purified on a silica gel column (hexane–EtOAc, 10:1) to yield the 7-*O*-benzyl ether⁵⁾ (296 mg, 575 μ mol, 81%), which was dissolved in CH₂Cl₂ (3.6 ml) and phosphate buffer (pH 7, 0.2 ml) at room temperature. To this solution, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (385 mg, 1.70 mmol) was added. The whole was stirred vigorously for 3 h, then poured into saturated aqueous NaHCO₃ (5 ml) and extracted with EtOAc (10 ml $\times$ 3). The combined organic solution was dried over MgSO₄ and concentrated *in vacuo*. Purification on a silica gel column (hexane–EtOAc, 4:1) gave the 8-ol⁵⁾ (**11**, 183 mg, 0.464 mmol, 81%): colorless oil; $[\alpha]_D^{30} - 7.3^\circ$ ($c=0.67$, CHCl₃). IR (neat): 3450, 1100 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.04 (6H, s), 0.88 (9H, s), 1.03 (3H, d, $J=6.5$ Hz), 1.49 (1H, m), 1.60 (1H, m), 1.79 (1H, m), 1.88 (1H, m), 2.20 (1H, m), 2.30 (1H, br t), 3.49 (1H, m), 3.52 (1H, dt, $J=2.9$, 9.0 Hz), 3.72 (4H, m), 4.03 (1H, m), 4.64 (2H, br s), 7.30 (1H, m), 7.34 (4H, m). FAB-MS m/z : 395 (M+H)⁺, 337. HR-FAB-MS, Found m/z : 395.2597, Calcd for C₂₂H₃₉O₄Si (M+H) 395.2618.

(3R,4S,6S,7R)-3-Benzoyloxy-9-tert-butylidimethylsilyloxy-4,7-epoxy-6-methyl-1-nonene (12) A solution of DMSO (0.15 ml, 2.2 mmol) in CH₂Cl₂ (1 ml) was added to a solution of oxalyl chloride (0.1 ml, 1.2 mmol) in CH₂Cl₂ (2 ml) at -78°C . The mixture was stirred for 5 min, then the 8-ol⁵⁾ (**11**, 46.0 mg, 117 μ mol) in CH₂Cl₂ (2 ml) was added and the whole was stirred for 45 min at -78°C . Triethylamine (0.4 ml, 2.9 mmol) was added and stirring was continued with warming to -20°C over 20 min. After addition of saturated aqueous NH₄Cl solution, the mixture was extracted with ether (10 ml $\times$ 3) and the organic solution was dried over MgSO₄, and concentrated *in vacuo* to give a crude aldehyde, which was used immediately without purification. A solution of the aldehyde in THF (1 ml) was added at -78°C to a solution of triphenylmethylenephosphorane in THF (2 ml), prepared from methyltriphenylphosphonium bromide (328 mg, 0.918 mmol) and 1.6 M *n*-BuLi (0.2 ml, 0.32 mmol). The stirred mixture was gradually warmed to room temperature. The resulting suspension was stirred for 3 h, then diluted with saturated NH₄Cl aqueous solution, and extracted with ether (20 ml $\times$ 3). The organic layer was washed with brine, dried over MgSO₄, and evaporated under reduced pressure. The residue was purified on a silica gel column (hexane–EtOAc, 20:1) to give an olefin (**12**, 23.5 mg, 60 μ mol, 51%): colorless oil; $[\alpha]_D^{28} - 5.5^\circ$ ($c=0.78$, CHCl₃). IR (neat): 1096 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.05 (6H, s), 0.89 (9H, s), 0.99 (3H, d, $J=6.5$ Hz), 1.53 (1H, m), 1.62 (1H, m), 1.79 (1H, m), 1.85 (1H, m), 2.09 (1H, m), 3.51 (1H, dt, $J=3.0$, 8.9 Hz), 3.71 (1H, m), 3.78 (2H, m), 4.03 (1H, m), 4.45 (1H, d, $J=12.2$ Hz), 4.65 (1H, d, $J=12.2$ Hz), 5.28 (1H, d, $J=17.5$ Hz), 5.29 (1H, d, $J=10.2$ Hz), 5.79 (1H, ddd, $J=7.4$, 10.2, 17.5 Hz), 7.27 (1H, m), 7.33 (4H, m). FAB-MS m/z : 391 (M+H)⁺, 333, 283. HR-FAB-MS, Found m/z : 391.2683, Calcd for C₂₃H₃₉O₃Si (M+H) 391.2669.

(2R,3R,4S,6S,7R)-3-Benzoyloxy-9-tert-butylidimethylsilyloxy-4,7-epoxy-1-(*N*-phenylcarbamoyloxy-6-methylnonan-2-ol (13) AD-mix- α ¹⁰⁾ (301 mg) was stirred in 2-methyl-2-propanol–water (1:2, 1.5 ml) at room temperature for 30 min. To this mixture was added 55 mg (0.66 mmol) of NaHCO₃, and the solution was cooled to 0°C . Then the olefin (**12**, 15 mg, 38 μ mol) in 2-methyl-2-propanol (0.5 ml) was introduced, and the mixture was stirred at 4°C for 24 h. The reaction was quenched by the

addition of 325 mg (2.6 mmol) of Na₂SO₃, and the whole was stirred at 0°C for another 30 min then extracted with EtOAc (2 ml $\times$ 5). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified on a silica gel column (hexane–EtOAc, 2:1) to give a mixture of *erythro*- and *threo*-diol (8.7 mg, 21 μ mol, 55%) in a ratio of 7:1, together with the starting olefin (**12**, 2.7 mg, 6.9 μ mol, 18%). A part of the diol mixture (3.1 mg, 7.3 μ mol) was treated with phenyl isocyanate (1 μ l, 9 μ mol) in pyridine (1 ml) in the presence of DMAP (2.1 mg) at room temperature for 4 d; 10 μ l of PhNCO was added each day. After evaporation of the solvent, purification of the residue on a silica gel column (hexane–EtOAc, 5:2) to remove the *threo*-isomer afforded the *erythro*-carbamate (**13**, 2.3 mg, 4.2 μ mol, 58%): white amorphous powder; $[\alpha]_D^{23} + 13^\circ$ ($c=0.23$, CHCl₃). IR (film): 3300, 1700 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.04 (6H, s), 0.88 (9H, s), 1.04 (3H, d, $J=6.5$ Hz), 1.57 (2H, m), 1.80 (1H, m), 1.91 (1H, m), 2.26 (1H, m), 3.45 (1H, br d, $J=3.1$ Hz), 3.53 (1H, m), 3.57 (1H, dt, $J=2.7$, 8.8 Hz), 3.70 (1H, m), 3.76 (1H, m), 3.96 (1H, m), 4.17 (1H, m), 4.32 (1H, dd, $J=5.8$, 11.6 Hz), 4.43 (1H, dd, $J=1.4$, 11.6 Hz), 4.64 (1H, d, $J=11.1$ Hz), 4.70 (1H, d, $J=11.1$ Hz), 6.55 (1H, br s), 7.07 (1H, t, $J=7.4$ Hz), 7.30 (1H, m), 7.36 (8H, m). FAB-MS m/z : 544 (M+H)⁺, 486, 425, 407. HR-FAB-MS, Found m/z : 544.3091, Calcd for C₃₀H₄₆NO₆Si (M+H) 544.3095.

(2R,3S,4S,6S,7R)-4,7-Epoxy-1-(*N*-phenylcarbamoyloxy-6-methyl-2,3,9-triacetoxynonane (3) The carbamate (**13**, 1.2 mg, 2.2 μ mol) was dissolved in EtOH (2 ml), and the solution was vigorously stirred under a hydrogen atmosphere in the presence of Pd(OH)₂ on carbon (1.4 mg) at room temperature for 4 h. To this mixture, 7.9 mg of Pd(OH)₂ on carbon was further added and stirring was continued for another hour. The mixture was filtered to remove the catalyst and the filtrate was evaporated under reduced pressure. The residue was treated with acetic anhydride (0.5 ml) and pyridine (1.0 ml) at room temperature for 12 h. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column (hexane–EtOAc, 2:2) to afford the triacetate (**3**, 0.7 mg, 1.5 μ mol, 68%): white amorphous powder; $[\alpha]_D^{24} + 12^\circ$ ($c=0.15$, CHCl₃). IR (film): 3340, 1740, 1220 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.02 (3H, d, $J=6.4$ Hz), 1.45 (1H, m), 1.63 (1H, m), 1.70 (1H, m), 1.89 (1H, m), 2.05 (3H, s), 2.07 (1H, 3H, s), 2.08 (3H, s), 2.18 (1H, m), 3.51 (1H, dt, $J=2.9$, 9.0 Hz), 4.12 (1H, m), 4.16 (1H, m), 4.23 (1H, m), 4.33 (1H, m), 4.46 (1H, dd, $J=3.1$, 12.0 Hz), 5.14 (1H, dd, $J=4.0$, 6.9 Hz), 5.39 (1H, m), 6.78 (1H, br s), 7.06 (1H, t, $J=7.5$ Hz), 7.33 (4H, m). EI-MS m/z : 465 (M⁺), 329, 268, 143, 119, 111, 93, 43. HR-EI-MS, Found m/z : 465.2010, Calcd for C₂₃H₃₁NO₉ (M) 465.1999.

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