JOURNAL OF NATURAL PRODUCTS

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Confirmation of the Absolute Configuration at C45 of Amphidinol 3

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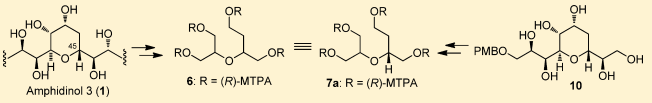
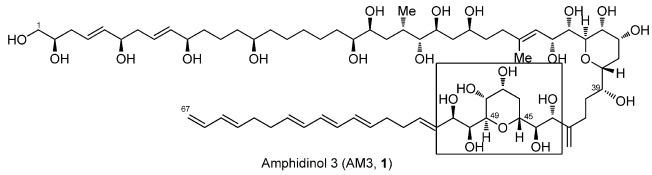
Supporting Information

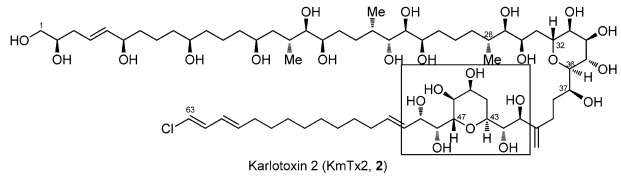
ABSTRACT: Amphidinol 3 (AM3), a membrane-active agent isolated from the dinoflagellate *Amphidinium klebsii*, consists of a long carbon chain containing 25 stereogenic centers. Although the absolute configuration of AM3 was determined by extensive NMR analysis and degradation of the natural product, the partial structure corresponding to the tetrahydropyran ring system was found to be antipodal to that of karlotoxin 2, a structurally related compound recently isolated from the dinoflagellate *Karlodinium veneficum*. By extensive degradation of the natural product and conversion of the resulting alcohol to an MTPA ester, the absolute configuration at C45 of AM3 was confirmed to be *R*, supporting the originally proposed structure.



Amphidinol 3 (AM3, **1**), a marine natural product produced by the dinoflagellate *Amphidinium klebsii*, elicits high antifungal efficacy with submicromolar IC_{50} values, although this is offset by relatively potent hemolytic activity (EC_{50} = 0.25 μM/kg).[1] The biological activities can be accounted for by the formation of ion-permeable pores in a sterol-dependent manner.[2] Although a number of congeners of amphidinol have been identified,[3,4] AM3 is the only example where the absolute configuration was determined by extensive NMR analysis based on the *J*-based configuration analysis (JBCA) method,[5] in combination with the modified Mosher's method,[6] and HPLC analysis of the degradation products of the natural product.[1,7] Distinct structural features represented by the amphidinols are a long hydrophilic polyol chain, highly substituted tetrahydropyran (THP) ring systems, and a hydrophobic polyene unit. The central part containing the two THP rings is a highly conserved region among the congeners. Recently, a structurally related compound, karlotoxin 2 (KmTx2, **2**), was isolated from the dinoflagellate *Karlodinium veneficum* and found to be a potent fish-killing toxin.[8] Although the partial structure corresponding to C41−C49 of KmTx2 possesses identical relative configurations to the C43−C52 part of AM3, the absolute configuration is reported to be antipodal to AM3. Herein, we report confirmation of the absolute configuration at C45 of AM3 by extensive degradation of the natural product followed by conversion to an MTPA ester and comparison of the ^{1}H NMR data with those of synthetic specimens.

Previously, the relative configurations of the C39−C51 part of AM3 were determined by the JBCA method[5] (Scheme 1), and the absolute configuration at C39 of AM3 was determined to be *R* by the modified Mosher's method[6] using MTPA esters **4a** and **4b** derived from the degradation product **3** obtained by treatment of the natural product with HIO_4 and $NaBH_4$.[1] On the basis of the correlation with C39, the absolute configurations at C43, C44, C45, C47, C48, C49, C50, and C51 were determined as depicted in **1**. To confirm the absolute configuration of the THP ring of AM3 unambiguously, we planned to obtain tetraol **5**, which would be derived through extensive degradation of AM3 via intermediate **3**.[1] Comparison of the ^{1}H NMR data of the (*R*)-MTPA ester **6** derived from **5** with those of authentic samples (*R*)-MTPA ester **7a** and (*S*)-MTPA ester **7b** would verify the absolute configuration at C45. However, it remained uncertain whether the 1,2-diol moiety at C43−C44 could be cleaved under the standard conditions, because it remained intact in the previous degradation studies.[1]

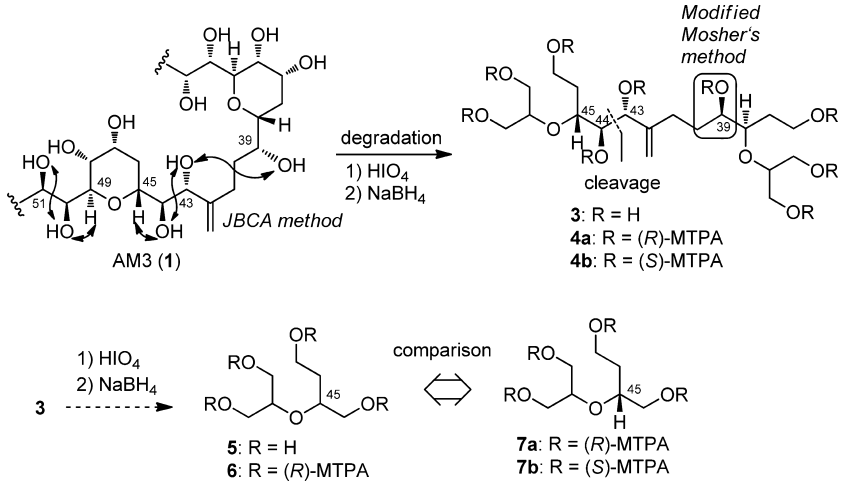




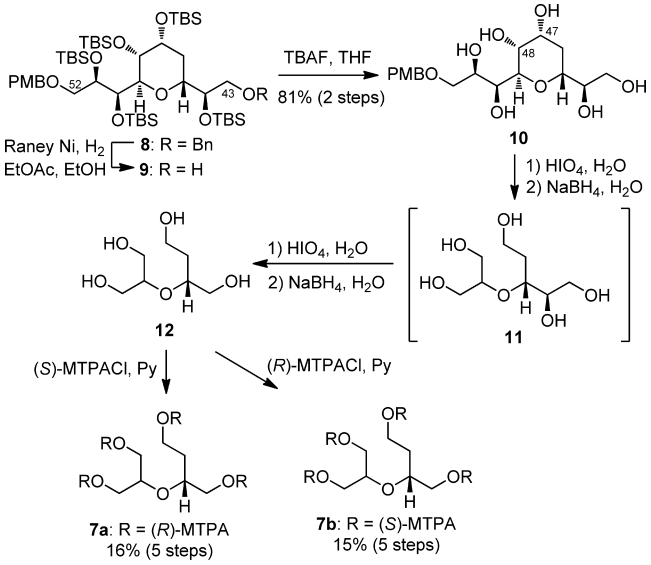
Preparation of the authentic samples **7a** and **7b** commenced with deprotection of the known compound **8** corresponding to the C43−C52 part of AM3 with a C45 *R* configuration (Scheme 2).[9] Hydrogenolysis of the benzyl ether **8** with Raney Ni under hydrogen atmosphere, followed by removal of the TBS groups of **9** with TBAF, afforded hexaol **10**. Treatment of **10** with HIO_4 followed by reduction with $NaBH_4$ resulted in the formation of pentaol **11** as previously reported.[1] The reason that the 1,2-diol moiety in **11** remained intact could be

Received: September 2, 2012
Published: November 6, 2012

Scheme 1. Previous Method for Determination of the Absolute Configuration at C45 by Using the JBCA Method and Modified Mosher's Method (top) and Present Strategy Based on Further Degradation of AM3 and Derivatization to MTPA Esters



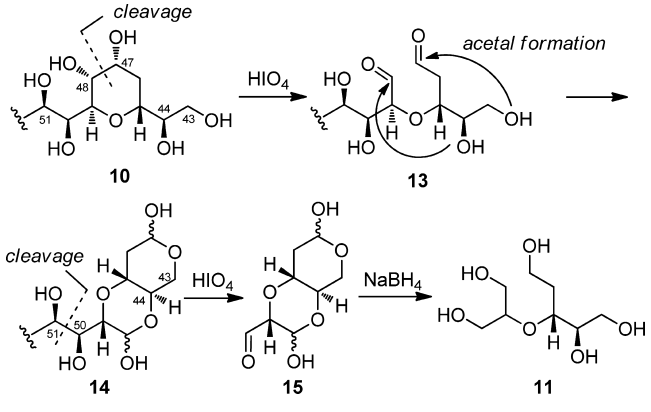
Scheme 2. Preparation of the Authentic Samples 7a and 7b



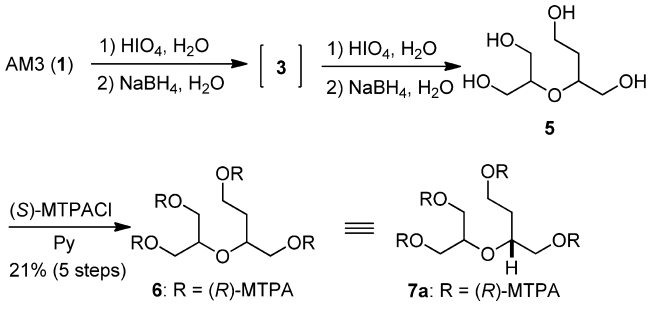
explained as shown in Scheme 3. The 1,2-diol at C47−C48, fixed in the *cis* configuration on the THP ring, would be cleaved faster than the other 1,2-diol moiety. The resultant bis-aldehyde **13** is prone to undergo intramolecular acetal formation to form intermediate **14** as the most stable 6/6-fused bicyclic system, in which cleavage of the 1,2-diol at C43−C44 would be prevented. Next, oxidative cleavage of the C50−C51 diol of **14** followed by reduction of **15** with $NaBH_4$ afforded **11**. Cleavage of the 1,2-diol of **11** was achieved by successive treatment with HIO_4 and $NaBH_4$ again to afford tetraol **12**, which was converted to (*R*)-MTPA ester **7a** and (*S*)-MTPA ester **7b** by acylation of all the hydroxy groups with (*S*)- and (*R*)-MTPACl, respectively (Scheme 2).

In an analogous sequence, AM3 was extensively degraded by treatment with HIO_4 and $NaBH_4$, giving **3**, followed by retreatment with HIO_4 and $NaBH_4$ to afford the degradation product **5**, which was converted to (*R*)-MTPA ester **6** by acylation of all hydroxy groups with (*S*)-MTPACl (Scheme 4).

Scheme 3. Plausible Reaction Pathway of Degradation of 10



Scheme 4. Degradation of AM3 and Conversion to the (*R*)-MTPA Ester 6



Having obtained the MTPA esters, the ^{1}H NMR spectrum of **6** derived from AM3 was compared with those of the authentic samples **7a** and **7b** (see Table S1). Although the chemical shifts of H48 and H50 were indistinguishable, the ^{1}H NMR spectrum of **6** was identical with that of **7a**, but different from that of **7b**. Therefore, the absolute configuration at C45 of AM3 was confirmed to be *R* as previously reported.[1]

In conclusion, all 1,2-diol moieties including those in the C43−C44 part of AM3 were cleaved by two successive treatments with HIO_4 and $NaBH_4$ to give tetraol **5**, which was converted to (*R*)-MTPA ester **6**. By comparing the ^{1}H NMR spectrum of **6** with those of synthetic (*R*)- and (*S*)-MTPA esters (**7a** and **7b**), the absolute configuration at C45 of AM3 was confirmed to be *R*. The present method would also be

dx.doi.org/10.1021/np300604w | *J. Nat. Prod.* 2012, 75, 2003−2006

applicable to other amphidinol congeners to determine the absolute configuration of the THP rings.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were recorded on a JASCO P-1010 polarimeter. IR spectra were recorded on a JASCO FT-IR 4100ST. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA600 spectrometer. Chemical shifts are reported in ppm from reference to internal residual solvent [^{1}H NMR, $CHCl_3$ (7.24); ^{13}C NMR, $CDCl_3$ (77.0) or ^{1}H NMR, CHD_2OD (3.30); ^{13}C NMR, CD_3OD (49.0)]. High-resolution mass spectra (HRMS) were recorded on a Burker micrOTOFfocus under ESI-TOF conditions. All reactions sensitive to air or moisture were performed under an argon atmosphere with dry glassware unless otherwise noted. The dehydrated solvents, tetrahydrofuran (THF) and pyridine, were purchased from Kanto Chemical Co. Inc. or Wako Pure Chemical Industries Ltd. and were used without further dehydration. All other chemicals were obtained from local venders and used as supplied. Thin-layer chromatography (TLC) of E. Merck silica gel 60 F254 precoated plates (0.25 mm thickness) was used for the reaction analyses. For column chromatography, Kanto silica gel 60N (spherical, neutral, 100−210 μm) was used. For preparative TLC, E. Merck silica gel 60 F254 precoated plates (0.25 mm thickness, 10 cm × 10 cm) were used.

Compound 9. Raney nickel W-2 in EtOH (4 mL) was added to a solution of benzyl ether **8** (800 mg, 744 μmol) in EtOAc (2 mL) at room temperature (rt) and stirred at 35 °C for 48 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The combined filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10:1) afforded **9** (740 mg, quant) as a colorless syrup: $[\alpha]^{22}_D$ +20.6 (*c* 0.65, $CHCl_3$); IR (film) ν 3477, 2953, 2929, 2885, 2857, 1251, 1105, 835, 774 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 4.41 (s, 2H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.98 (brs, 1H), 3.96 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.92 (m, 1H), 3.80−3.74 (m, 3H), 3.79 (s, 3H), 3.62 (brd, *J* = 12.6 Hz, 1H), 3.49 (m, 1H), 3.46 (dd, *J* = 8.4, 7.8 Hz, 1H), 3.31 (dd, *J* = 7.8, 5.4 Hz, 1H), 2.62 (brs, 1H), 2.05 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.50 (brd, *J* = 12.0 Hz, 1H), 0.879 (s, 9H), 0.875 (s, 9H), 0.87 (s, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.06 (s, 15H), 0.04 (s, 3H), 0.03 (s, 6H), 0.006 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 130.4, 129.1, 113.7, 79.0, 73.2, 72.7, 72.2, 70.4, 69.8, 69.2, 69.2, 68.6, 63.5, 55.3, 28.4, 26.02, 25.99, 25.8, 25.8, 25.7, 18.4, 18.13, 18.13, 18.11, 17.9, −3.4, −4.0, −4.0, −4.27, −4.29, −4.5, −4.7, −4.8, −4.96, −5.03; HRMS (ESI, positive) *m*/*z* 981.5929 [M + Na]$^+$ (calcd for $C_{48}H_{98}O_9Si_5Na$, 981.5949).

Compound 10. A solution of 1 M TBAF in THF (1.6 mL, 1.6 mmol) was added to a solution of **9** (102.4 mg, 106.7 μmol) in THF (4 mL) at 0 °C. After stirring at rt for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography ($CHCl_3$/MeOH = 3:1), followed by preparative TLC ($CHCl_3$/MeOH = 3:1) to afford **10** (33.7 mg) in 81% yield as a colorless syrup: $[\alpha]^{25}_D$ −8.5 (*c* 0.1, MeOH); IR (film) ν 3322, 2959, 2927, 2874, 1514, 1465, 1371, 1247, 1074 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.48 (s, 2H), 4.02 (brt, *J* = 2.4 Hz, 1H), 3.98 (ddd, *J* = 6.0, 6.0, 1.8 Hz, 1H), 3.95 (m, 1H), 3.93 (m, 1H), 3.87 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.77 (s, 3H), 3.65−3.60 (m, 2H), 3.59−3.50 (m, 4H), 1.91 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.59 (ddd, *J* = 12.6, 4.8, 3.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 160.8, 131.7, 130.5, 114.8, 78.3, 75.2, 74.0, 72.3, 72.2, 69.1, 68.9, 68.6, 67.1, 64.1, 55.7, 31.2; HRMS (ESI, positive) *m*/*z* 411.1624 [M + Na]$^+$ (calcd for $C_{18}H_{28}O_9Na$, 411.1626).

Compound 12. A solution of 0.1 M HIO_4 in H_2O (3 mL, 300 μmol) was added to compound **10** (18.5 mg, 47.6 μmol) in a flask, and the reaction mixture was stirred at rt for 30 min. After cooling to 0 °C, a solution of 1 M $NaBH_4$ in H_2O (1.2 mL, 1.2 mmol) was added. After stirring for 30 min, the reaction was quenched with two drops of AcOH, and the reaction mixture was concentrated under reduced pressure. A solution of 0.1 M HIO_4 in H_2O (3 mL, 0.3 mmol) was added to the resultant residue again, and the reaction mixture was stirred at rt for 30 min. After cooling to 0 °C, a solution of 1 M $NaBH_4$ in H_2O (1.2 mL, 1.2 mmol) was added. After stirring for 30 min, the reaction was quenched with two drops of AcOH, and the reaction mixture was concentrated under reduced pressure. The resultant mixture was roughly purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1 to 2:1) to give crude **12** (19.3 mg) as a colorless syrup, which was used for the next reaction without further purification.

Compound 7a. To a solution of (*R*)-MTPA acid (100 mg, 0.426 mmol) in hexane (1 mL) were added oxalyl chloride (5.6 μL, 0.64 mmol) and DMF (6.6 μL, 86 μmol). After stirring for 1 h at rt, the solution was concentrated under reduced pressure to give (*S*)-MTPACl.[10] (*S*)-MTPACl (35.0 mg, 139 μmol) was added to a solution of the crude **12** (9.7 mg) in pyridine (346 μL). After stirring for 1 h at rt, the reaction mixture was diluted with hexane and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane three times, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative TLC (hexane/EtOAc = 3:1) afforded (*R*)-MTPA ester **7a** (3.9 mg, 3.7 μmol) in 16% yield in five steps as a colorless syrup: $[\alpha]^{26}_D$ +45.8 (*c* 0.20, $CHCl_3$); IR (film) ν 2953, 2921, 2850, 1751, 1452, 1271, 1240, 1168, 1121, 1022, 719 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47−7.41 (m, 8H), 7.39−7.31 (m, 12H), 4.27 (m, 1H), 4.26 (m, 1H), 4.25 (m, 1H), 4.17 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.13 (ddd, *J* = 10.8, 5.4, 2.4 Hz, 1H), 4.01 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.96 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.91 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.57 (m, 1H), 3.48 (m, 1H), 3.47 (s, 3H), 3.46 (s, 6H), 3.45 (s, 3H), 1.71 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 166.2, 166.1, 132.1, 132.0, 129.9, 128.6, 127.3, 123.3 (q, *J* = 287.3 Hz), 123.2 (q, *J* = 287.1 Hz), 84.66 (q, *J* = 28.8 Hz), 84.62 (q, *J* = 28.8 Hz), 84.58 (q, *J* = 28.2 Hz), 73.9, 67.4, 64.1, 64.0, 63.9, 61.9, 55.4, 55.44, 55.38, 55.30, 30.9; HRMS (ESI, positive) *m*/*z* [M + Na]$^+$ calcd for $C_{47}H_{44}O_{13}F_{12}Na$, 1067.2483, found 1067.2481.

Compound 7b. To a solution of (*S*)-MTPA acid (100 mg, 0.426 mmol) in hexane (1 mL) were added oxalyl chloride (5.6 μL, 0.64 mmol) and DMF (6.6 μL, 86 μmol). After stirring for 1 h at rt, the solution was concentrated under reduced pressure to give (*R*)-MTPACl.[10] (*R*)-MTPACl (35.0 mg, 139 μmol) was added to a solution of the crude **12** (9.7 mg) in pyridine (346 μL). After stirring for 1 h at rt, the reaction mixture was diluted with hexane and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane three times, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative TLC (hexane/EtOAc = 3:1) afforded (*S*)-MTPA ester **7b** (3.6 mg, 3.4 μmol) in 15% yield in five steps as a colorless syrup: $[\alpha]^{26}_D$ −42.7 (*c* 0.20, $CHCl_3$); IR (film) ν 2953, 2922, 2849, 1751, 1452, 1270, 1241, 1168, 1121, 1023, 719 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48−7.42 (m, 8H), 7.39−7.32 (m, 12H), 4.33 (ddd, *J* = 10.8, 5.4, 5.4 Hz, 1H), 4.23 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.21 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.18 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.07 (m, 1H), 4.06 (m, 1H), 3.99 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.97 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.72 (dddd, *J* = 4.8, 4.8, 4.8, 4.8 Hz, 1H), 3.53 (m, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 3.454 (s, 3H), 3.450 (s, 3H), 1.73 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.22, 166.18, 166.1, 165.9, 132.1, 131.9, 129.8, 129.7, 128.5, 127.3, 127.2, 123.3 (q, *J* = 287.3 Hz), 123.2 (q, *J* = 287.3 Hz), 84.7 (q, *J* = 28.8 Hz), 84.5 (q, *J* = 28.8 Hz), 73.7, 73.3, 67.2, 63.9, 63.5, 61.7, 55.3, 30.9; HRMS (ESI, positive) *m*/*z* 1067.2485 [M + Na]$^+$ (calcd for $C_{47}H_{44}O_{13}F_{12}Na$, 1067.2483).

Compound 6. A solution of 0.1 M HIO_4 in H_2O (20 μL, 2 μmol) was added to AM3 (0.125 μmol, estimated by ^{1}H NMR using DMF as an internal standard) in a vial, and the reaction mixture was stirred at rt for 30 min. After cooling to 0 °C, a solution of 1 M $NaBH_4$ in H_2O (8 μL, 8 μmol) was added. After stirring for 30 min, the reaction was quenched with one drop of AcOH, and the reaction mixture was concentrated under reduced pressure. A solution of 0.1 M HIO_4 in H_2O (20 μL, 2 μmol) was added to the resultant residue again, and the reaction mixture was stirred at rt for 30 min. After cooling to 0 °C, a

dx.doi.org/10.1021/np300604w | J. Nat. Prod. 2012, 75, 2003−2006

solution of 1 M $NaBH_4$ in H_2O (8 μL, 8 μmol) was added. After stirring for 30 min, the reaction was quenched with one drop of AcOH, and the reaction mixture was concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1 to 2:1) to give crude **5** as a colorless syrup, which was used for next reaction without further purification. (*S*)-MTPACl (35.0 mg, 139 μmol) was added to a solution of the crude **5** in pyridine (346 μL). After stirring for 1 h at rt, the reaction mixture was diluted with hexane and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparative TLC (hexane/EtOAc = 3:1) afforded (*R*)-MTPA ester **6** (0.025 μmol, estimated by ^1H NMR using acetone as an internal standard) in 21% yield in five steps: HRMS (ESI, positive) *m*/*z* 1067.2483 $[M + Na]^+$ (calcd for $C_{47}H_{44}O_{13}F_{12}Na$, 1067.2483).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for compounds **9**, **10**, **7a**, **7b**, and **6** are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Prof. T. Katsuki and T. Uchida, Kyushu University, for measurement of mass spectra. We thank Dr. K. Torikai for helpful discussion. This work was supported in part by a fund from Kyushu University, Funds for the Development of Human Resources in Science and Technology originating from Ministry of Education, Culture, Sports, Science and Technology (MEXT), and by a Grant-in-Aid for Young Scientists (B) (No. 24750092) from the Japan Society for the Promotion of Science (JSPS).

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