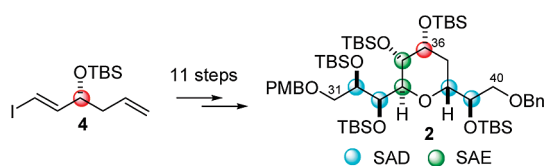## Stereoselective Synthesis of the C31−C40/C43−C52 Unit of Amphidinol 3

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A concise synthesis of a tetrahydropyran ring system corresponding to the C31−C40 and C43−C52 units of amphidinol 3 is described. Successive chemoselective reactions, i.e., cross-metathesis to differentiate the iodoolefin from the terminal olefin and Sharpless asymmetric dihydroxylation on the resulting *E*-olefin, resulted in expeditious synthesis of an intermediate that was then cross-coupled to afford an *E,E*-diene system. Four contiguous stereogenic centers were installed via construction of the tetrahydropyran ring by means of Katsuki−Sharpless asymmetric epoxidation, 6-*endo-tet* cyclization, and Sharpless asymmetric dihydroxylation.

Marine dinoflagellates are a rich source of biologically and structurally unique secondary metabolites.[1] Amphidinol 3 (AM3, **1**), produced by the dinoflagellate *Amphidinium klebsii*, elicits potent antifungal activity (Figure 1).[2] The biological activity can be accounted for by formation of ion-permeable

pores in a sterol dependent manner.[3] The *Amphidinium* sp. are known to produce a number of congeners,[4] in which AM3 is the most potent antifungal. The molecular structure of AM3 was determined in 1999 based on the JBCA method,[5] modified Mosher method,[6] and degradation of the natural product via oxidative cleavage,[2b] and the absolute configuration at C2 has recently been revised to be *R*, based on the chemical synthesis of partial structures corresponding to the C1−C14 moiety, and GC-MS analysis using a chiral capillary column of a degradation product derived from olefin cross-metathesis.[7] Distinct structural features represented by the amphidinols are a long hydrophilic polyol chain, substituted tetrahydropyran (THP) ring systems, and a hydrophobic polyene unit. The middle portion containing the two THP rings is highly conserved among the congeners, and structural diversity arises from the polyol and polyene moieties. These structural features of AM3 have attracted considerable attention from the synthetic community, and a number of synthetic studies of AM3 have been reported.[8−12] Herein we report a concise synthesis of a THP ring system corresponding to the C31−C40/C43−C52 unit of AM3.
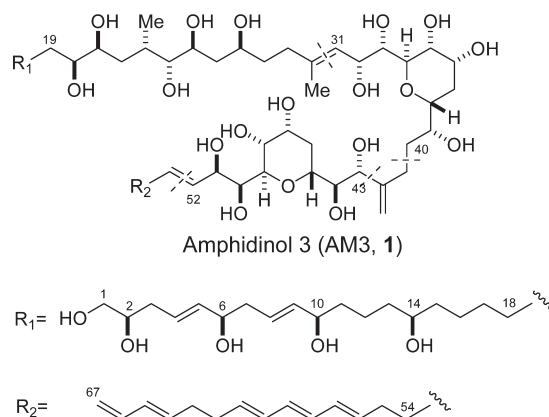

FIGURE 1. Structure of amphidinol 3 (AM3, **1**).

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Although syntheses of the THP ring moieties of AM3 have been reported by Roush,[9b] Rychnovsky,[10a] Paquette,[11b] and Markó,[12] we envisaged a novel strategy for synthesizing **2** as shown in Scheme 1. The stereogenic centers of **2** would be installed by means of Sharpless asymmetric dihydroxylation (SAD)[13] with respect to C32−C33 (C51−C50) and C38−C39 (C45−C44), and Katsuki−Sharpless asymmetric epoxidation (SAE)[14] at C34−C35 (C49−C48) via 6-*endo-tet* cyclization.[15] The remaining stereogenic center corresponding to C36 (C47) was to be derived from iodoolefin **4** via its attachment to building blocks **5** and **3** by means of cross-metathesis and cross-coupling reactions, respectively.

SCHEME 1. **Synthesis Plan of the C31−C40/C43−C52 Unit (2) of AM3**
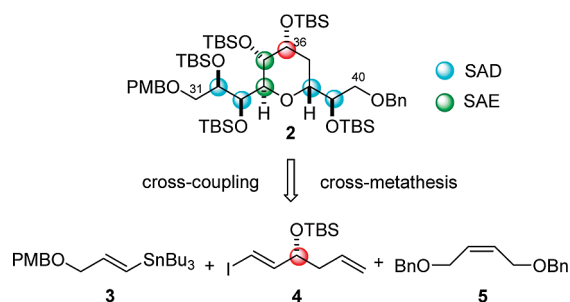
Previously, we reported the synthesis of iodoolefin **4** via lipase-catalyzed kinetic resolution.[7] The iodoolefin **4** was utilized for stereoselective synthesis of the C1−C14 unit of AM3 through chemoselective cross-metathesis[8a,16] as a key step. The method was also applied for coupling with *Z*-olefin **5** as shown in Table 1. The cross-metathesis reaction of the terminal olefin of **4** with 2 or 4 equiv of *Z*-olefin **5**[17] using 10 mol % Grubbs second-generation catalyst **6**[18] in CH$_2$Cl$_2$ at 40 °C (reflux) proceeded selectively in the presence of the iodoolefin to afford diene **7** in 65% and 88% yields as a mixture of *E*- and *Z*-isomers in a 5.0:1 ratio (entries 1 and 2). Attempts to improve the *E/Z* ratio by using solvents of higher boiling points were unsuccessful, e.g., *E/Z* = 4.3:1 in 1,2-dichloroethane at 83 °C (entry 3) and 3.5:1 in toluene at 110 °C (entry 4). The catalyst loading could be reduced to 2 mol % (entry 5); however, the yield of **7** (71%) and the *E/Z* ratio (4.0: 1) were somewhat lower than those in entry 2.

Next, we moved on to the second chemoselective reaction, SAD of **7** using AD-mix-β (Scheme 2). As expected, the less hindered and electron-rich olefin, in the presence of the iodo-olefin, reacted stereoselectively to afford diol **8** in 68% yield,

TABLE 1. **Chemoselective Cross-Metathesis of 4 and 5**

entry	5 /equiv	solvent	temp/°C^a	yield/%	*E/Z* ratio^b
1^c	2	CH$_2$Cl$_2$	40	65	5.0/1
2^c	4	CH$_2$Cl$_2$	40	88	5.0/1
3^c	4	(CH$_2$Cl)$_2$	83	78	4.3/1
4^c	4	toluene	110	76	3.5/1
5^d	4	CH$_2$Cl$_2$	40	71	4.0/1

^{a}The reactions were carried out under reflux. ^{b}Determined by NMR. ^{c}10 mol % of **6** was used. ^{d}2 mol % of **6** was used.

SCHEME 2. **Synthesis of the C31−C40/C43−C52 Segment (2)**
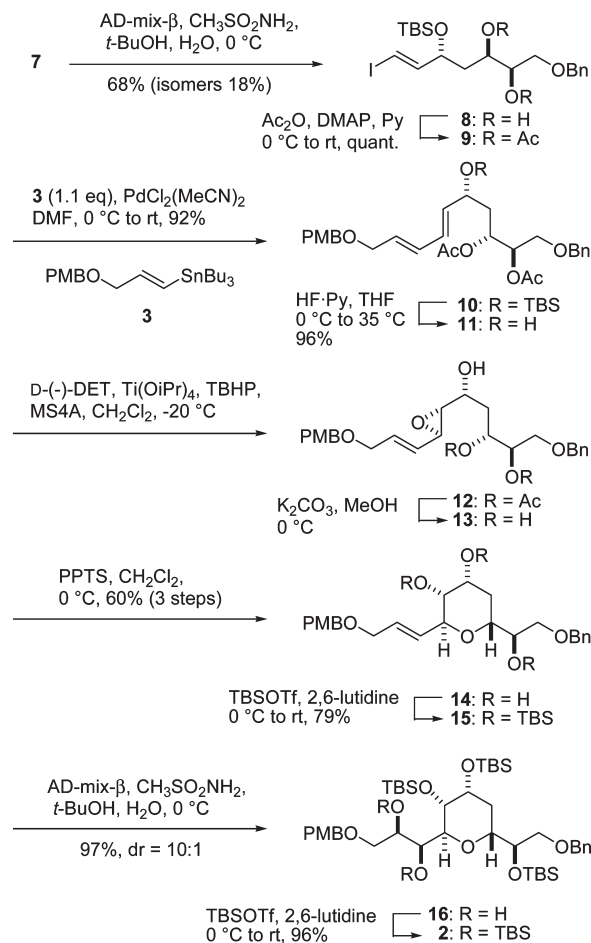
which was separated from the other stereoisomers including the diols derived from the *Z*-olefin (18%). Protection of the hydroxy groups as acetates, followed by Migita−Kosugi−Stille coupling reaction[19] with stannane **3**[20] resulted in the formation of the

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E,E-diene in 92% yield. Removal of the TBS group with HF·Py at 0 to 35 °C in THF provided allylic alcohol **11**, which was subjected to SAE, using D-(−)-DET to furnish vinyl epoxide **12**. Solvolysis of the acetate with K_2CO_3 in MeOH, and successive treatment of the resulting epoxy alcohol **13** with PPTS resulted in 6-*endo-tet* cyclization to afford the THP ring **14** in 60% yield for three steps. The structure of **14** was confirmed by NOE experiments of the corresponding triacetate **17** (Figure 2), i.e., NOEs between H38 and H33, and H38 and H36 were observed, in which H36 and H38 occupied 1,3-diaxial positions ($J_{H36-H37ax}$ = 12.0 Hz, $J_{H37ax-H38}$ = 12.0 Hz). Protection of the triol **14** as TBS ethers with TBSOTf/2,6-lutidine furnished **15** in 79% yield. SAD of **15** with AD-mix-β proceeded stereoselectively to afford the desired diol **16** in 97% yield (dr = 10: 1), and protection of the resulting vicinal diol as TBS ethers provided **2**. The overall yield of **2** from the iodoolefin **4** was 20% over 11 steps. The fully protected **2** would be a key intermediate corresponding to both the C31−C40 and C43−C52 units of AM3, in which protecting groups of the primary alcohols can be selectively removed under oxidative (for PMB ether) or reductive (for benzyl ether) conditions in the presence of TBS ethers.
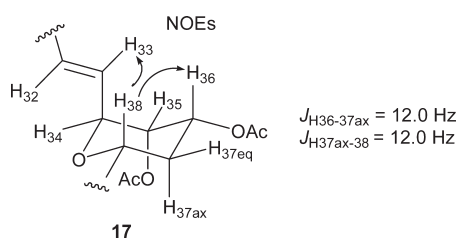

FIGURE 2. Structure determination of **17** by NMR analysis.

In conclusion, a concise synthesis of the tetrahydropyran ring system **2**, corresponding to the C31−40/C43−C52 unit of AM3, was achieved based on chemoselective cross-metathesis, regioselective dihydroxylation, and 6-*endo-tet* cyclization. On the basis of the present method, it would be possible to synthesize an enantiomer of **2** from an enantiomer of **4** by changing the ligands used in SAD and SAE.

Experimental Section

(3R,1E,5E)-7-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-1-iodohepta-1,5-diene (7). To a solution of **4** (5.01 g, 14.8 mmol) and **5** (15.9 g, 59.2 mmol) in CH_2Cl_2 (48 mL) under reflux was added a solution of Grubbs catalyst **6** (251 mg, 0.296 mmol, 2 mol %) in CH_2Cl_2 (1.0 mL). After being stirred for 6 h, the reaction mixture was cooled to 0 °C, quenched with Et_3N, and allowed to warm to room temperature over 1 h, then the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/0 → 20/1 → 10/1) afforded a mixture of **7** and allyl benzyl ether. The allyl benzyl ether was removed under reduced pressure at 90 °C for 1 h to provide **7** (4.81 g, 71%) as a yellow oil: $[\alpha]^{26}_D$ +6.84 (*c* 1.05, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 10/1); IR (film) ν 2953, 2928, 2884, 2856, 1606, 1471, 1361, 1254, 1088, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 6.51 (dd, J = 14.3, 6.0 Hz, 1H), 6.21 (dd, J = 14.3, 1.3 Hz, 1H), 5.74−5.54 (m, 2H), 4.41 (s, 2H), 4.11 (tdd, J = 6.0, 6.0, 1.3 Hz, 1H), 3.96 (d, J = 6.0 Hz, 2H), 2.24 (t, J = 6.0 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 138.4, 129.7, 129.2, 128.4, 127.7, 127.5, 76.0, 74.8, 71.9, 70.6, 65.8, 40.6, 35.9, 25.8, 18.1, −4.6, −4.9; HRMS (ESI-TOF) calcd for $C_{20}H_{31}IO_2$-SiNa [(M + Na)$^+$] 481.1036, found 481.1033.

(2R,3R,5R,E)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-7-iodohept-6-ene-2,3-diol (8). A mixture of $K_2OsO_4·2H_2O$ (31.3 mg, 0.0851 mmol), (DHQD)$_2$PHAL (331 mg, 0.425 mmol), $K_3Fe(CN)_6$ (8.40 g, 25.5 mmol), K_2CO_3 (3.52 g, 25.5 mmol), and $MeSO_2NH_2$ (2.42 g, 25.5 mmol) in *t*-BuOH (18 mL) and H_2O (28 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resulting suspension was added a solution of **7** (3.87 g, 8.51 mmol) in *t*-BuOH (10 mL). After being stirred for 36 h at 0 °C, the resulting mixture was quenched with solid $Na_2S_2O_3·5H_2O$ (8.0 g) and allowed to warm to room temperature over 1 h. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1 → 2/1) afforded **8** (2.27 g, 68%) as a yellow syrup: $[\alpha]^{27}_D$ +37.8 (*c* 0.89, $CHCl_3$); R_f 0.40 (hexane/EtOAc = 2/1); IR (film) ν 3433, 2953, 2928, 2888, 2856, 1253, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.54 (dd, J = 14.4, 5.8 Hz, 1H), 6.27 (dd, J = 14.4, 1.2 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.42 (m, 1H), 3.89 (d, J = 10.5 Hz, 1H), 3.59−3.51 (m, 3H), 3.09 (br s, 1H), 2.62 (br s, 1H), 1.79 (ddd, J = 14.2, 10.5, 3.4 Hz, 1H), 1.53 (ddd, J = 14.2, 7.2, 2.2 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 137.7, 128.5, 127.9, 127.8, 76.3, 73.6, 72.9, 72.1, 68.5, 40.2, 25.8, 18.1, −4.6, −5.2; HRMS (ESI-TOF) calcd for $C_{20}H_{33}IO_4SiNa$ [(M + Na)$^+$] 515.1091, found 515.1102.

(2R,3R,5R,6E,8E)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)deca-6,8-diene-2,3-diyl Diacetate (10). To a solution of **9** (3.28 g, 5.68 mmol) and **3** (2.92 g, 6.25 mmol) in DMF (18.9 mL) was added $PdCl_2(MeCN)_2$ (36.8 mg, 0.142 mmol, 2.5 mol %) at 0 °C then the mixture was stirred at room temperature for 7 h. The resulting mixture was quenched with aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 8/1 → 4/1) afforded **10** (3.29 g, 92%) as a colorless syrup: $[\alpha]^{26}_D$ +8.92 (*c* 0.75, $CHCl_3$); R_f 0.48 (hexane/EtOAc = 2/1); IR (film) ν 2954, 2929, 2857, 1744, 1513, 1372, 1250, 1224, 1097, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.23 (m, 7H), 6.86 (m, 2H), 6.19 (dd, J = 15.0, 10.6 Hz, 1H), 6.11 (dd, J = 15.0, 10.6 Hz, 1H), 5.75 (dt, J = 15.0, 6.0 Hz, 1H), 5.58 (dd, J = 15.0, 7.4 Hz, 1H), 5.29 (ddd, J = 8.4, 4.0, 4.0 Hz, 1H), 5.16 (m, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.43 (s, 2H), 4.13 (m, 1H), 4.00 (d, J = 6.0 Hz, 2H), 3.78 (s, 3H), 3.53 (dd, J = 10.5, 4.6 Hz, 1H), 3.50 (dd, J = 10.5, 6.0 Hz, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.74 (ddd, J = 14.2, 7.9, 4.0 Hz, 1H), 1.69 (ddd, J = 14.2, 8.4, 4.6 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.0, 159.1, 137.7, 136.4, 131.7, 130.2, 129.9, 129.4, 129.3, 128.2, 127.6, 113.7, 73.0, 72.7, 71.8, 70.1, 69.9, 69.1, 68.5, 55.2, 39.5, 25.8, 20.9. 20.8, 18.0, −4.0, −5.1; HRMS (ESI-TOF) calcd for $C_{35}H_{50}O_8SiNa$ [(M + Na)$^+$] 649.3173, found 649.3193.

(2S,3R,4R,6R)-6-[(1R)-2-Benzyloxy-1-hydroxyethyl]-2-[(E)-3-(4-methoxybenzyloxy)prop-1-enyl]tetrahydropyran-3,4-diol (14). To a mixture of powdered MS4A (450 mg) in CH_2Cl_2 (8 mL) were added D-(−)-DET (127 μL, 0.732 mmol) and Ti(O*i*-Pr)$_4$ (174 μL, 0.585 mmol) at −25 °C. After the mixture was stirred for 30 min, a solution of **11** (1.50 g, 2.96 mmol) in CH_2Cl_2 (6 mL) was added. After an additional 30 min of stirring, a solution of 2.8 M TBHP in CH_2Cl_2 (2.1 mL, 5.85 mmol) was added. Then after being stirred for 18 h at −20 °C, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$, diluted with EtOAc, and allowed to warm to room temperature. The

Kanemoto et al.

precipitates were removed by filtration through a Celite pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a mixture of **12** and D-(−)-DET as a yellow oil.

To a solution of the above mixture of **12** and D-(−)-DET in MeOH (30 mL) was added K_2CO_3 (80 mg, 0.585 mmol) at 0 °C. After being stirred for 3 h at 0 °C, the resulting mixture was quenched with pH 7.0 phosphate buffer, then MeOH was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide **13**. This crude **13** was used for the next step without further purification.

To a solution of the above crude **13** in CH_2Cl_2 (29 mL) was added PPTS (73.2 mg, 0.292 mmol) at 0 °C then the solution was stirred for 19 h. The resulting mixture was quenched with Et_3N and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/MeOH = 1/0 → 30/1 → 20/1 → 10/1) afforded **14** (782 mg, 60% for 3 steps) as a colorless syrup: $[\alpha]^{26}_D$ −23.7 (c 0.75, CHCl$_3$); R_f 0.30 (hexane/EtOAc = 3/1);

IR (film) ν 3387, 2910, 2864, 1612, 1513, 1454, 1248, 1096 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31−7.19 (m, 7H), 6.86−6.82 (m, 2H), 5.79 (dt, J = 15.9, 5.4, 1.2 Hz, 1H), 5.65 (dd, J = 15.9, 4.4 Hz, 1H), 4.51 (br s, 1H), 4.49 (s, 2H), 4.39 (s, 2H), 3.92 (d, J = 5.4 Hz, 2H), 3.81−3.74 (m, 2H), 3.76 (s, 3H), 3.71−3.68 (m, 2H), 3.54 (d, J = 6.0 Hz, 2H), 1.93 (ddd, J = 12.6, 12.6, 12.6 Hz, 1H), 1.61 (br d, J = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 137.9, 130.4, 130.0, 129.4, 128.4, 128.2, 127.7, 127.7, 76.9, 73.4, 72.4, 72.1, 71.0, 70.6, 69.7, 69.4, 65.9, 55.2, 30.9; HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_7Na$ [(M + Na)$^+$] 467.2046, found 467.2036.

Supporting Information Available: General experimental methods, additional experimental procedures, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.