HETEROCYCLES, Vol. 89, No. 2, 2014, pp. 515 - 522. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 2nd December, 2013, Accepted, 17th December, 2013, Published online, 18th December, 2013
DOI: 10.3987/COM-13-12905

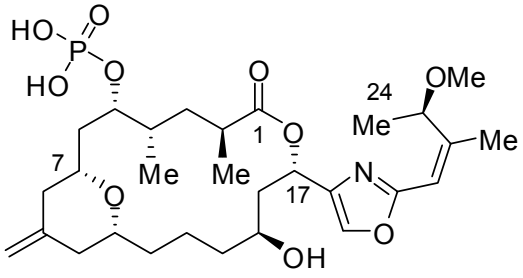
STEREOCONTROLLED SYNTHESIS OF THE C1-C7 FRAGMENT OF ENIGMAZOLE A

Takayuki Kishi, Yuka Fujisawa, Hiroyoshi Takamura, and Isao Kadota*

Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kitaku, Okayama 700-8530, Japan
e-mail: kadota-i@okayama-u.ac.jp

Abstract – An enantio- and stereoselective synthesis of the C1-C7 fragment of enigmazole A is described. The three asymmetric centers of the molecule were constructed efficiently by using Evans chiral auxiliary protocol.

Enigmazole A (**1**), an 18-membered macrolide, was isolated from the sponge *Cinachyrella enigmatica* as the first family of marine phosphomacrolide in 2010.[1] This compound shows potent cytotoxicity against the 60 human tumor cell lines. The unique structural features, including a phosphate, an exomethylenetetrahydropyran, and a 2,4-disubstituted oxazole ring make the molecule an attractive synthetic target.[2] The first total synthesis of **1** was reported by Molinski and co-workers in 2010.[3] In this paper, we wish to describe the stereocontrolled synthesis of the C1-C7 fragment of enigmazole A (**1**) as a part of total synthetic study of **1**.

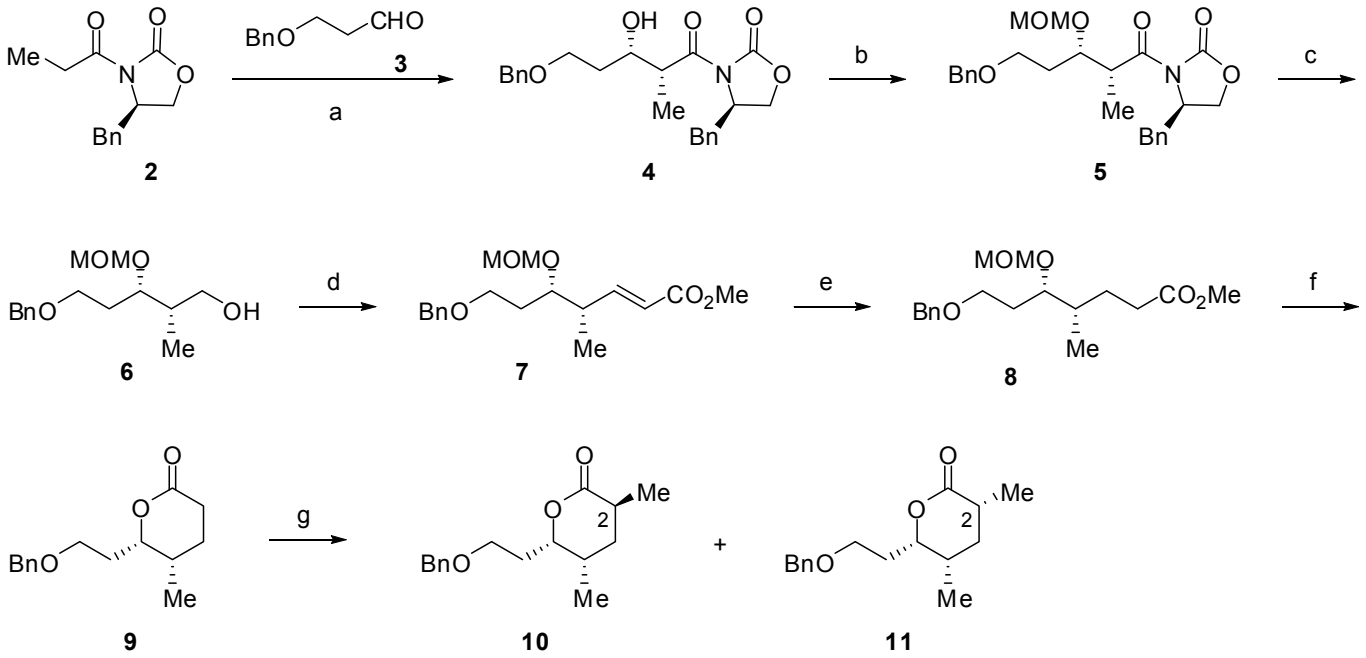


enigmazole A (**1**)

Figure 1. Structure of enigmazole (**1**)

Stereoselective aldol reaction of chiral oxazolidinone **2** and aldehyde **3** was carried out with *n*-Bu_2BOTf/Et_3N to furnish the known compound **4**[4] as a single stereoisomer in 97% yield.[5] Protection

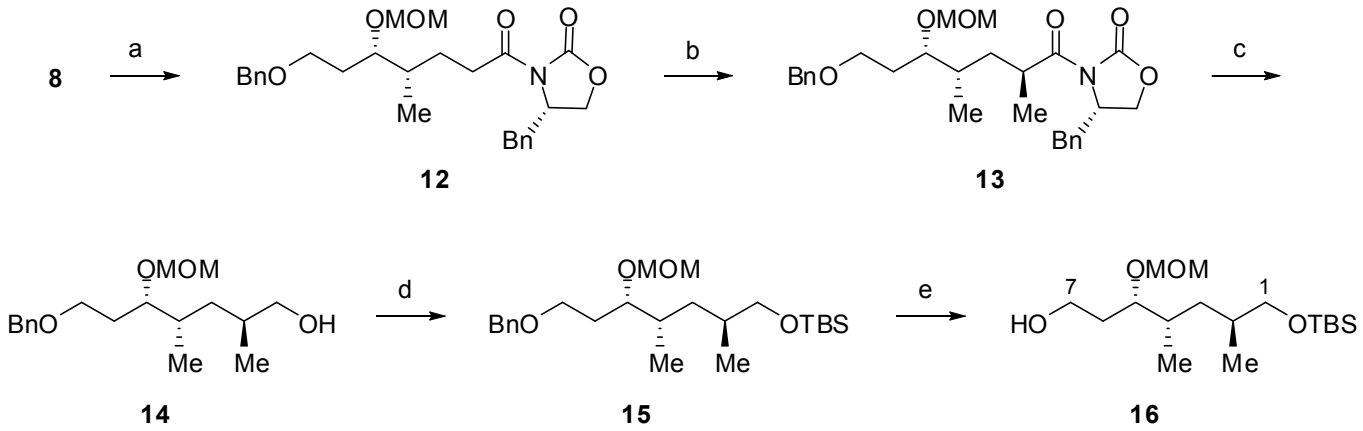
of the hydroxy group of **4** with MOMCl/*i*-Pr_2NEt/DMAP gave **5** in 98% yield. Reductive removal of the chiral auxiliary of **5** with $LiBH_4$ afforded alcohol **6** in 91% yield.[6] Oxidation of **6** with TEMPO/$PhI(OAc)_2$,[7] followed by the Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ provided α,β-unsaturated ester **7** in 88% overall yield. Hydrogenation of **7** with H_2/Pd-C gave **8** in 96% yield. Deprotection of the MOM group of the ester **8** and subsequent lactonization were performed with a catalytic amount of CSA in refluxing benzene to furnish lactone **9** in 84% yield. As an initial attempt, we tested the substrate-controlled installation of the C2 methyl group at this stage. Thus, the lactone **9** was treated with KHMDS in the presence of DMPU followed by MeI. Unfortunately, the product was obtained as a 5:1 inseparable mixture of desired compound **10** and its diastereoisomer **11** in 37% yield. Since several attempts to improve this process resulted in failure, we next examined an alternative approach, the auxiliary-controlled alkylation.



Scheme 1. Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 ºC, then **3**, -78 to 0 ºC, 97%; (b) MOMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 30 ºC, 98%; (c) $LiBH_4$, Et_2O/H_2O, 0 ºC to rt, 91%; (d) (i) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt; (ii) $Ph_3P{=}CHCO_2Me$, benzene, 80 ºC, 88% (2 steps); (e) H_2, Pd-C, THF, rt, 96%; (f) CSA, benzene, reflux, 84%; (g) KHMDS, DMPU, THF, -78 ºC, then MeI, -78 ºC to rt, 37% (**10**:**11** = ca. 5:1).

Saponification of the ester **8** with LiOH, followed by treatment of the resulting carboxylic acid with PivCl/Et_3N and (*S*)-4-benzyl-2-oxazolidinone/LiCl afforded the corresponding oxazolidinone **12** in 97% overall yield.[8] Stereoselective alkylation of **12** was performed with NaHMDS and MeI to provide **13** as a single stereoisomer in 86% yield.[9] The stereochemistry at the C2 position was unambiguously

confirmed by ^{1}H NMR analysis and NOE experiments on the lactone **10**, prepared from **13** by using LiOH·H_2O in THF/H_2O followed by treatment with 4M HCl in 65% yield, as shown in Figure 2. Removal of the chiral auxiliary of **13** with $LiBH_4$, and protection of the resulting primary alcohol **14** with TBSCl/imidazole gave **15** in 97% overall yield. Debenzylation of **15** was carried out with H_2/Pd-C to furnish the C1-C7 fragment **16** in 98% yield.



Scheme 2. Reagents and conditions: (a) (i) LiOH·H_2O, THF/H_2O, 50 ºC; (ii) PivCl, Et_3N, THF, -20 ºC, then (*S*)-4-benzyl-2-oxazolidinone, LiCl, -20 ºC to rt, 97% (2 steps); (b) NaHMDS, THF, -78 ºC, then MeI, -78 ºC, 86%; (c) $LiBH_4$, Et_2O/H_2O, 0 ºC to rt; (d) TBSCl, imidazole, CH_2Cl_2, rt, 97% (2 steps); (e) H_2, Pd-C, THF, rt, 98%.

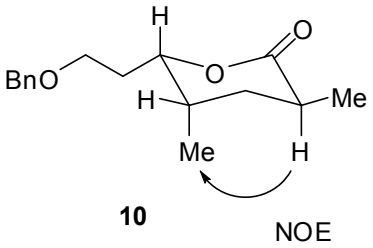


Figure 2. Observed NOE is shown by an arrow.

In conclusion, we have achieved the enantio- and stereoselective synthesis of the C1-C7 fragment of enigmazole A (**1**) via the Evans stereoselective aldol and alkylation methodologies. Further studies towards the the total synthesis of **1** are in progress in our laboratory.

EXPERIMENTAL

All reactions involving air- and/or moisture-sensitive materials were carried out under argon with dry solvents purchased from Wako or Kanto chemicals. On workup, extracts were dried over $MgSO_4$. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates

(60F-254). Column chromatography was performed with Kanto Chemical silica gel 60N (40-100 mesh, spherical, neutral). Yields refer to chromatographically and spectroscopically homogeneous materials. The NMR spectra were recorded on JEOL JNM-AL400 (^{1}H, ^{13}C NMR). Chemical shifts were reported in delta units (δ) relative to chloroform (7.24). IR spectra were recorded on a JASCO FT/IR-460 Plus. Optical rotations were measured by a JASCO DIP-1000. Mass spectra were measured by Micromass LCT (ESI TOF-MS).

MOM Ether 5. To a solution of **4**[4] (103 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) were added DIPEA (0.44 mL, 2.6 mmol), MOMCl (0.17 mL, 2.2 mmol), and DMAP (32 mg, 0.26 mmol). After stirring for 34 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was washed with brine. Concentration and column chromatography (hexane/EtOAc, 5:1) gave **5** (112 mg, 98%): yellow oil; R_f = 0.61 (hexane/EtOAc, 1:1); $[\alpha]^{23}_D$ -83.2 (c 0.92, $CHCl_3$); IR (neat) 2932, 1779, 1697, 1210, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 10H), 4.59 (s, 2H), 4.58-4.52 (m, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.08-3.91 (m, 4H), 3.61-3.52 (m, 2H), 3.31 (s, 3H), 3.26 (dd, *J* = 13.0, 3.2 Hz, 1H), 2.73 (dd, *J* = 13.1, 9.7 Hz, 1H), 2.01-1.85 (m, 2H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 153.0, 138.4, 135.3, 129.3, 128.8, 128.2, 127.6, 127.4, 127.2, 96.7, 76.9, 72.9, 66.7, 66.0, 56.0, 55.7, 41.7, 37.9, 32.7, 12.8; HRMS (ESI TOF) calcd for $C_{25}H_{31}NO_6Na$ $(M+Na)^+$ 464.2049, found 464.2045.

Alcohol 6. To a solution of **5** (247 mg, 0.56 mmol) in ether (6 mL) and H_2O (30 μL) at 0 °C was added $LiBH_4$ (39 mg, 1.8 mmol). After stirring for 70 min at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C. The mixture was extracted with ether, and the organic layer was washed with brine. Concentration and column chromatography (hexane/EtOAc, 5:1) gave **6** (136 mg, 91%): colorless oil; R_f = 0.31 (hexane/EtOAc, 1:1); $[\alpha]^{23}_D$ +22.1 (c 1.37, $CHCl_3$); IR (neat) 3434, 3030, 1496, 1208, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.17 (m, 5H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.41 (s, 2H), 3.84-3.80 (m, 1H), 3.56-3.41 (m, 4H), 3.30 (s, 3H), 2.62 (dd, *J* = 7.3, 4.9 Hz, 1H), 1.90-1.67 (m, 2 H), 0.76 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.5, 97.1, 77.2, 73.1, 67.0, 65.2, 55.9, 38.7, 31.9, 11.3; HRMS (ESI TOF) calcd for $C_{15}H_{24}O_4Na$ $(M+Na)^+$ 291.1572, found 291.1579.

α,β-Unsaturated Ester 7. To a solution of **6** (472 mg, 1.76 mmol) in CH_2Cl_2 (17.6 mL) at room temperature were added $PhI(OAc)_2$ (1.42 g, 4.41 mmol) and TEMPO (45 mg, 0.29 mmol). After stirring for 4.5 h at room temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, water, and brine. Concentration gave the corresponding aldehyde which was used for the next reaction directly.

To a solution of the crude aldehyde obtained in benzene (9 mL) was added $Ph_3P{=}CHCO_2Me$ (380 mg,

1.14 mmol), and the mixture was refluxed for 6.5 h. Concentration and column chromatography (hexane/EtOAc, 7.5:1) gave **7** (178 mg, 88%): colorless oil; R_f = 0.23 (hexane/EtOAc, 4:1); $[\alpha]^{24}_D$ -66.9 (c 1.12, $CHCl_3$); IR (neat) 2950, 1724, 1655, 1273, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 7.03 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.82 (dd, *J* = 15.9, 1.5 Hz, 1H), 4.61 (s, 2H), 4.47 (s, 2H), 3.74 (s, 3H), 3.71-3.67 (m, 1H), 3.54 (dd, *J* = 7.3, 5.3 Hz, 2H), 3.34 (s, 3H), 2.64 (dd, *J* = 12.3, 5.3 Hz, 1H), 1.84-1.76 (m, 1H), 1.71-1.62(m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.7, 138.3, 128.3, 127.6, 127.5, 121.1, 96.6, 78.3, 73.0, 66.8, 55.8, 51.4, 40.2, 31.8, 14.6; HRMS (ESI TOF) calcd for $C_{18}H_{26}O_5Na$ $(M+Na)^+$ 345.1678, found 345.1681.

Ester 8. A mixture of **7** (2.55 g, 7.90 mmol) and a catalytic amount of 10% Pd-C in THF (80 mL) was stirred for 1 h under H_2 atmosphere. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **8** (3.39 g, 96%): colorless oil; R_f = 0.23 (hexane/EtOAc, 4:1); $[\alpha]^{24}_D$ -24.4 (c 0.40, $CHCl_3$); IR (neat) 3029, 2951, 1737, 1496, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 4.60 (s, 2H), 4.48 (s, 2H), 3.64 (s, 3H), 3.62-3.58 (m, 1H), 3.55-3.51 (m, 2H), 3.33 (s, 3H), 2.41-2.25 (m, 2H), 1.91-1.82 (m, 1H), 1.79-1.65 (m, 3H), 1.48-1.39 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.4, 128.3, 127.6, 127.5, 96.3, 78.7, 73.0, 67.3, 55.7, 51.5, 36.0, 32.4, 31.2, 27.4, 14.8; HRMS (ESI TOF) calcd for $C_{18}H_{28}O_5Na$ $(M+Na)^+$ 347.1834, found 347.1835.

Oxazolidinone 12. To a solution of **8** (3.39 g, 10.5 mmol) in THF (18 mL) and H_2O (6 mL) was added $LiOH·H_2O$ (660 mg, 16 mmol). After stirring for 2.0 h at 50 °C, the reaction mixture was cooled to 0 °C, and acidified with 1M HCl. The mixture was extracted with EtOAc, and the organic layer was washed with brine. Concentration gave the corresponding carboxylic acid which was used for the next reaction directly.

To a solution of the crude carboxylic acid obtained in THF (100 mL) at -20 °C were added Et_3N (4.4 mL, 31.5 mmol) and PivCl (1.4 mL, 11.6 mmol). After stirring for 2 h at the same temperature, LiCl (670 mg, 15.8 mmol) and (*S*)-4-benzyl-2-oxazolidinone (1.86 g, 10.5 mmol) were added, and the resulting mixture was stirred for an additional 4 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C, and extracted with EtOAc. The organic layer was washed with brine. Concentration and column chromatography (hexane/EtOAc, 4:1 to 3:1) gave **12** (4.76 g, 97% from **8**): colorless oil; R_f = 0.35 (hexane/EtOAc, 2:1); $[\alpha]^{22}_D$ +8.7 (c 2.05, $CHCl_3$); IR (neat) 3028, 1782, 1698, 1212, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10H), 4.71-4.65 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.54 (s, 2H), 4.23-4.16 (m, 2H), 4.23-4.16 (m, 2H), 3.70-3.66 (m, 1H), 3.62-3.59 (m, 2H), 3.40 (s, 3H), 3.32 (dd, *J* = 13.1, 3.2 Hz, 1H), 3.04-2.99 (m, 2H), 2.79 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.04-1.95 (m, 1H), 1.87-1.81 (m, 3H), 1.59-1.48 (m, 1H), 0.97 (d, *J* = 6.8

Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 153.3, 138.4, 135.2, 129.3, 128.9, 128.3, 127.6, 127.4, 127.2, 96.4, 78.8, 73.0, 67.3, 66.1, 55.7, 55.2, 38.0, 36.0, 33.8, 31.2, 26.8, 15.0; HRMS (ESI TOF) calcd for $C_{27}H_{35}NO_6Na$ $(M+Na)^+$ 492.2362, found 492.2361.

Synthesis of 13. To a solution of **12** (122 mg, 0.26 mmol) in THF (1.0 mL) at -78 °C was added NaHMDS (1 M in THF, 0.4 mL, 0.4 mmol), and the mixture was stirred for 30 min at the same temperature. To the resulting mixture, MeI (48.6 μL, 0.780 mmol) was added, and stirring was continued for 3.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine. Concentration and column chromatography (hexane/EtOAc, 4:1) gave **13** (108 mg, 86%): colorless oil; R_f = 0.56 (hexane/EtOAc, 1:1); $[\alpha]^{24}_D$ +20.1 (c 1.62, $CHCl_3$); IR (neat) 3029, 2931, 1779, 1697, 1209 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 10H), 4.68-4.63 (m, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 4.16 (d, *J* = 5.1 Hz, 2H), 3.92-3.83 (m, 1H), 3.63-3.52 (m, 3H), 3.37 (s, 3H), 3.28 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.91-1.72 (m, 3H), 1.65 (t, *J* = 7.1 Hz, 2H) 1.23 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 152.8, 138.4, 135.3, 129.3, 128.8, 128.2, 127.6, 127.4, 127.2, 96.4, 79.1, 72.9, 65.9, 55.7, 67.3, 55.4, 37.9, 35.3, 33.8, 31.0, 17.2, 15.2; HRMS (ESI TOF) calcd for $C_{28}H_{37}NO_6Na$ $(M+Na)^+$ 506.2519, found 506.2516.

Lactone 10. To a mixture of **13** (7.1 mg, 15 μmol) in THF (0.5 mL) and H_2O (0.5 mL) at 0 °C was added $LiOH·H_2O$ (2.5 mg, 60 μmol), and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was cooled to 0 °C and acidified by adding 4M HCl. After strring for 15 h at 80 °C, the mixture was diluted with ether, then washed with water and brine. Concentration and column chromatography (hexane/EtOAc, 4:1) gave **10** (108 mg, 86%): colorless oil; R_f = 0.59 (hexane/EtOAc, 1:1); IR (neat) 1731, 1198, 1100 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.29-7.24 (m, 2 H), 7.22-7.16 (m, 2 H), 7.12-7.06 (m, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.23-4.18 (m, 1H), 3.48 (ddd, *J* = 9.0, 9.0, 5.0 Hz, 1H), 3.38-3.30 (m, 1H), 2.25-2.12 (m, 1H), 1.71-1.60 (m, 1H), 1.52-1.41 (m, 1H), 1.37-1.26 (m, 1H), 1.24-1.15 (m, 1H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.08-1.01 (m, 1H), 0.53 (d, *J* = 7.3 Hz, 3H); HRMS (ESI TOF) calcd for $C_{16}H_{22}O_3Na$ $(M+Na)^+$ 285.1467, found 285.1467.

TBS Ether 15. To a mixture of **13** (178 mg, 37 μmol) in ether (0.4 mL) and H_2O (2 μL) at 0 °C was added $LiBH_4$ (2.4 mg, 0.11 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C, and extracted with ether. The organic layer was washed with brine. Concentration and short column chromatography gave the crude alcohol **14** which was used for the next reaction without further purification.

To a mixture of the alcohol **14** obtained above in CH_2Cl_2 (0.4 mL) at room temperature were added imidazole (7.5 mg, 0.11 mmol) and TBSCl (11 mg, 70 μmol). After stirring for 2 h, the reaction mixture

was quenched with MeOH, diluted with ether, then washed with water and brine. Concentration and column chromatography (hexane/EtOAc, 4:1) gave **15** (15 mg, 97% from **13**): colorless oil; R_f = 0.53 (hexane/EtOAc, 4:1); $[\alpha]^{26}_D$ -35.7 (c 1.24, $CHCl_3$); IR (neat) 2955, 2928, 1208, 1152, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 5H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.48 (s, 2H), 3.57-3.52 (m, 3H), 3.41-3.32 (m, 2H), 3.33 (s, 3H), 1.84-1.59 (m, 4H), 1.21-1.12 (m, 1H), 1.10-1.02 (m, 1H), 0.87 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 127.6, 127.4, 96.4, 79.8, 73.0, 69.2, 67.5, 55.7, 35.2, 33.3, 31.3, 26.0, 18.4, 16.2, 15.0, -5.2; HRMS (ESI TOF) calcd for $C_{24}H_{44}O_4SiNa$ $(M+Na)^+$ 447.2906, found 447.2909.

Alcohol 16. A mixture of **15** (36 mg, 84 μmol) and a catalytic amount of 10% $Pd(OH)_2$-C in THF (0.8 mL) was stirred for 2 h under H_2 atmosphere. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **16** (28 mg, 98%): colorless oil; R_f = 0.28 (hexane/EtOAc, 2:1); $[\alpha]^{26}_D$ -79.9 (c 1.29, $CHCl_3$); IR (neat) 3433, 2955, 2857, 1215, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.81-3.68 (m, 2H), 3.64-3.57 (m, 1H), 3.40 (s, 3H), 3.37 (dd, *J* = 6.3, 2.7 Hz, 2H), 2.39 (s, 1H), 1.85-1.74 (m, 1H), 1.72-1.60 (m, 3H), 1.27-1.19 (m, 1H), 1.17-1.08 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.7, 81.2, 69.2, 60.3, 56.0, 35.1, 33.6, 33.3, 33.2, 26.0, 18.4, 16.1, 15.2, -5.2; HRMS (ESI TOF) calcd for $C_{17}H_{38}O_4SiNa$ $(M+Na)^+$ 357.2437, found 357.2435.

ACKNOWLEDGEMENTS

This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES

1. N. Oku, K. Takeda, R. W. Fuller, J. A. Wilson, M. L. Peach, L. K. Pannell, J. B. McMahon, and K. R. Gustafson, *J. Am. Chem. Soc.*, 2010, **132**, 10278.
2. For an example of the synthesis of the macrolide framework of enigmazole A, see: P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh, and A. Fürstner, *Chem. Eur. J.*, 2013, **19**, 13047.
3. C. K. Skepper, T. Quach, and T. F. Molinski, *J. Am. Chem. Soc.*, 2010, **132**, 10286.
4. V. Rauhala, K. Nättinen, K. Rissanen, and A. M. P. Koskinen, *Eur. J. Org. Chem.*, 2005, 4119.
5. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
6. T. D. Penning, S. W. Djuric, R. A. Haack, V. J. Kalish, J. M. Miyashiro, B. W. Rowell, and S. S. Yu, *Synth. Commun*., 1990, 307.

7. T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, and C. J. Forsyth, *Tetrahedron Lett.*, 2003, **44**, 57.
8. T. K. Chakraborty and V. R. Suresh, *Tetrahedron Lett.*, 1998, **39**, 7775.
9. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.