Tetrahedron 66 (2010) 6775–6782

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An improved synthesis of (−)-brevisamide, a marine monocyclic ether amide of dinoflagellate origin

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ARTICLE INFO

Article history:
Received 21 April 2010
Received in revised form 23 June 2010
Accepted 23 June 2010
Available online 3 July 2010

Keywords:
Cyclic ether
One-pot lactonization
Suzuki–Miyaura coupling
Dinoflagellate origin

ABSTRACT

An improved synthesis of (−)-brevisamide a marine cyclic ether isolated from the red-tide dinoflagellate *Karenia brevis* was achieved. The ether ring portion was constructed from an unsaturated lactone, which was prepared enantioselectively via an Evans aldol reaction and one-pot lactonization in the presence of excessive base after an Ando reaction. The ether ring and a dienol side chain fragment were connected via Suzuki–Miyaura coupling.

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1. Introduction

Ladder-frame polyethers represent a characteristic group of secondary metabolites produced by numerous marine dinoflagellates.[1] Many of these compounds are potent toxins, which were initially identified as the causative agents in massive fish kills or seafood poisoning events. As a group the ladder-frame polyethers are fascinating not only to chemists for the structural and synthetic challenges they provide, but also to biochemists interested in their biogenesis and potent and selective biological activities. To date, enormous efforts have been conducted to synthesize those complicated molecules,[2] and as a result several synthetic approaches to these ether ring systems have been reported. In contrast, the biosynthetic mechanism leading to formation of the ladder-frame polyethers has been less thoroughly studied and consequently is less well understood, though a general biosynthetic process is beginning to emerge.[3] It is hypothesized that a polyepoxide precursor probably derived from *E*-polyolefin is converted to a ladder-frame polyether via an enzyme mediated cascade of epoxide openings.[4]

The monocyclic ether amide, brevisamide (**1**, Fig. 1)[5] was isolated from the red-tide dinoflagellate *Karenia brevis*, which also produces brevetoxins,[6] brevenal,[7] and brevisin.[8] The structure of **1** was determined based on extensive 2D NMR studies, and was characterized as a single tetrahydropyran ring with a 3,4-dimethylhepta-2,4-dienal side chain and an acetylated terminal amine. This cyclic ether amide is the first nitrogen-containing cyclic ether from *K. brevis* and can be regarded as a truncated analog of brevenal and brevisin containing the A-ring portion and the dienal side chain. In addition to our first total synthesis of **1**,[9] the compound has also been synthesized by 4 independent groups.[10–12] Our original synthesis established the absolute configuration of brevisamide, which has recently been confirmed by a modified Mosher's method.[3] Some steps in our original synthesis resulted in low product yields and it was determined that in order to obtain sufficient material for more extensive biological testing, an improved synthesis was essential.

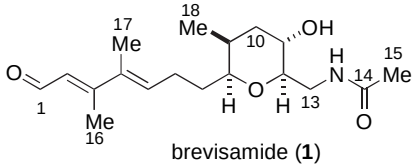

Figure 1. Structure of (−)-brevisamide (**1**).

In our original synthetic approach of a putative biosynthetic precursor of **1**, we reported a concise synthesis of a bromodienol side chain moiety, which was used in a coupling reaction.[13] In this latest study we focused on improving two aspects of the synthesis,

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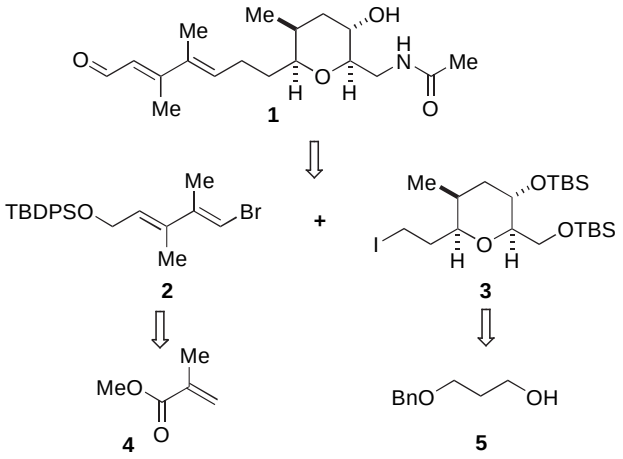
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.074

namely more efficient synthesis of the ether ring fragment and improving the yield of the key Suzuki–Miyaura coupling reaction.[14] To this end, the ether ring fragment was synthesized using an Evans aldol reaction[15] followed by one-pot lactonization in the presence of excessive base after an Ando reaction.[16] The low yield of the Suzuki–Miyaura coupling step was attributed to reduction of the acetamide by 9-BBN-H. In this latest approach, the ether ring fragment contains instead a protected primary alcohol function and following addition of the dienol side chain fragment by Suzuki–Miyaura coupling, the primary alcohol group can be converted to the acetamide. Herein we report an improved total synthesis of **1** via stereo-controlled ether ring construction and a key Suzuki–Miyaura cross coupling reaction.

2. Results and discussion

2.1. Retrosynthetic analysis

Our synthetic strategy is summarized in Scheme 1. The bromodienol fragment **2** was prepared from methyl methacrylate (**4**), and the ether ring fragment **3** was prepared from 3-benzyloxypropan-1-ol (**5**). The fragments **2** and **3** could be linked by the Suzuki–Miyaura cross coupling.



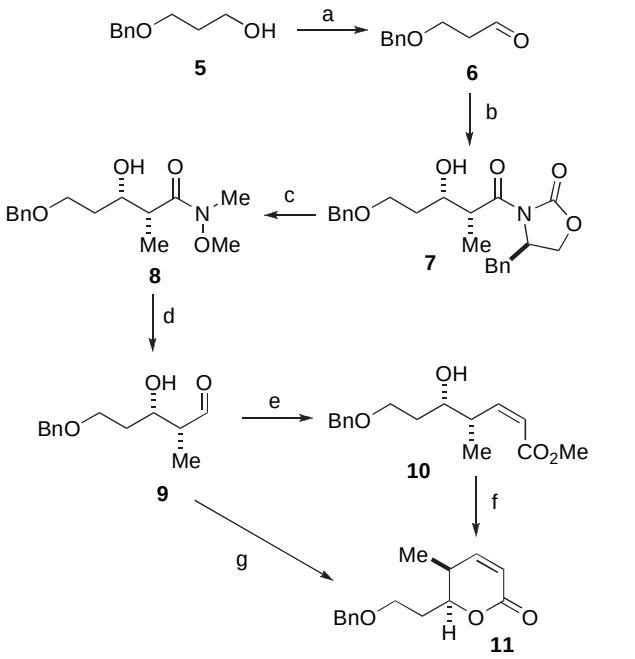
Scheme 1. Retrosynthetic analysis of **1**.

2.2. Synthesis of the ether ring fragment

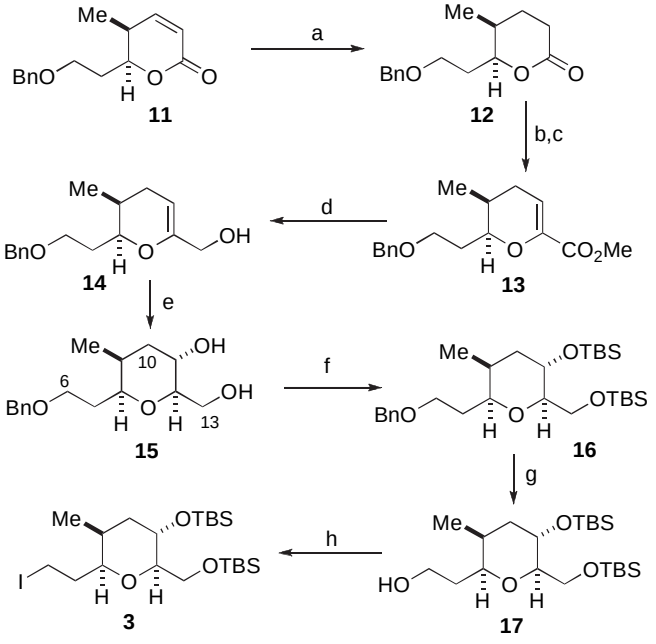
A synthesis of an α,β-unsaturated lactone **11**, a key intermediate of **3** started from 3-benzyloxypropan-1-ol (**5**) (Scheme 2). The alcohol was oxidized to an aldehyde **6** with TEMPO. An aldol addition of the enolborate derived from (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone to the aldehyde **6** gave a *syn* aldol adduct **7** in 92% yield.[15] The aldol adduct **7** was converted to a Weinreb amide **8** with NH(OMe)Me·HCl and $AlMe_3$ in 93% yield. The amide **8** was reduced to a β-hydroxyaldehyde **9** with $LiAlH_4$ in 85% yield.[17] Then **9** was treated with $(PhO)_2P(O)CH_2COOMe$[16] (1.2 equiv) and excessive amounts of NaH (1.5 equiv) in THF. In this operation, when reaction temperature was elevated from −78 to 0 °C, an α,β-unsaturated six-membered lactone **11** was obtained in 71% yield. Although this annulation can be ordinarily carried out via two steps (e and f), the one-pot method is obviously superior to the two-step method because of time savings and comparable yields.

Following successful lactone formation, we focused next on conversion of **11** to the ether ring moiety **3** (Scheme 3).

After hydrogenation of **11** in 98% yield, treatment of **12** with $PhNTf_2$, KHMDS, and DMPU gave a ketene acetal triflate, followed by Pd(0)-catalyzed carbonylation with CO, Et_3N, and MeOH



Scheme 2. Reagents and conditions: (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 94%; (b) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; then MeOH/30% H_2O_2 aq, rt, 92%; (c) NH(OMe)Me·HCl, $AlMe_3$, CH_2Cl_2, −15 to 0 °C; (d) $LiAlH_4$, THF, 0 °C, 85%; (e) $(PhO)_2P(O)CH_2COOMe$ (1.4 equiv), NaH (1.3 equiv), THF, −78 °C, 69%; (f) PPTS, benzene, reflux, 97%; (g) $(PhO)_2P(O)CH_2COOMe$ (1.2 equiv), NaH (1.5 equiv), THF, −78 to 0 °C, 71%.



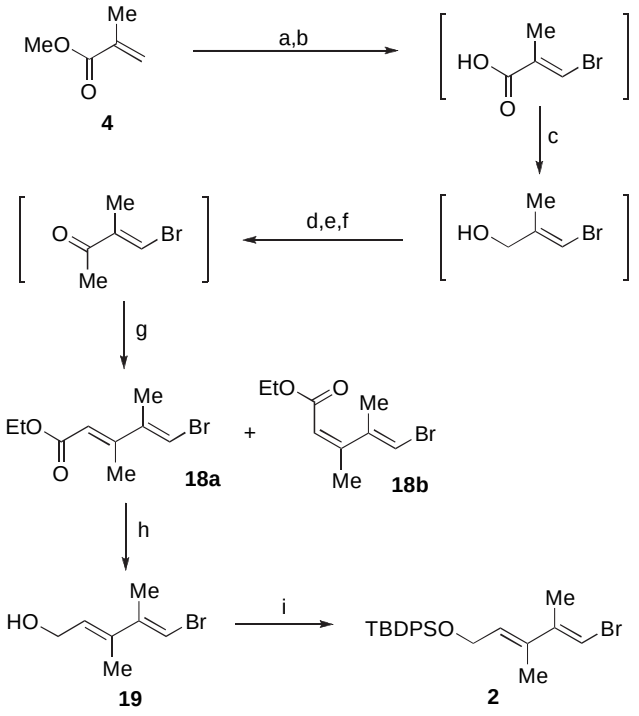
Scheme 3. Reagents and conditions: (a) H_2, Pd/C, EtOAc, rt, 98%; (b) $PhNTf_2$, KHMDS, DMPU, THF, −78 to 0 °C; (c) CO, Et_3N, $Pd(PPh_3)_4$, DMF/MeOH, rt, 88% for two steps; (d) DIBALH, CH_2Cl_2, −78 to 0 °C, 88%; (e) $BH_3·SMe_2$, THF, 0 °C; then 3 M NaOH aq, 30% H_2O_2 aq, 45 °C, 86%; (f) TBSCl, imidazole, DMF, rt, 95%; (g) LiDBB, THF, −78 °C, 82%; (h) I_2, PPh_3, imidazole, toluene, rt, 91%.

afforded an oxene carboxylate **13** in 88% yield after two steps. The methyl ester **13** was reduced with DIBALH, and subsequent hydroboration gave a diol **15** as a single isomer in 86% yield. Steric interaction between $BH_3·SMe_2$ and the C-9 axial methyl group generated the desired stereoselectivity of hydroboration. The stereostructure of the ether ring was assigned at this stage by NOE correlations and $^3J_{H,H}$ coupling constants. NOE correlations

between the C-9 methyl and H-11, and the C-9 methyl and H-10 suggested an axial orientation of the C-9 methyl and H-11 and an equatorial orientation of H-10. An NOE correlation and small coupling constant (J=3 Hz) between H-9 and H-8 confirmed an axial direction of H-8. The resultant diol **15** was protected with TBSCl and followed by treatment with LiDBB to generate primary alcohol **17**. The primary alcohol **17** was converted to iodide with I_2, PPh_3, and imidazole to give rise to the ether ring fragment **3** in 91% yield.

2.3. Synthesis of the bromodienol side chain fragment

In this approach, the dienol fragment **2** was prepared from methyl methacrylate (**4**) (Scheme 4). Bromination of **4**, followed by dehydrobromination and concomitant hydrolysis of the ester afforded a carboxylic acid, which was then reduced to an allylic alcohol.[18] The allylic alcohol was oxidized to an aldehyde, and subsequent addition of Grignard reagent, followed by oxidation of the resultant secondary alcohol gave the known bromoenone.[19] Horner–Wadsworth–Emmons reaction of this bromoenone with $(EtO)_2P(O)CH_2CO_2Et$ in the presence of n-BuLi gave (*E*,*E*)-bromodienoate **18a** and undesired (*Z*,*E*)-bromodienoate **18b** in a highly stereoselective fashion (5:1). It should be noted that **18a** was obtained in a good yield (31% from **4**) without purification until HWE reaction. Reduction of the desired (*E*,*E*)-dienoate **18a** with DIBALH, followed by protection of the resultant hydroxy group with TBDPS afforded the bromodienol side chain fragment **2** in 99% yield.

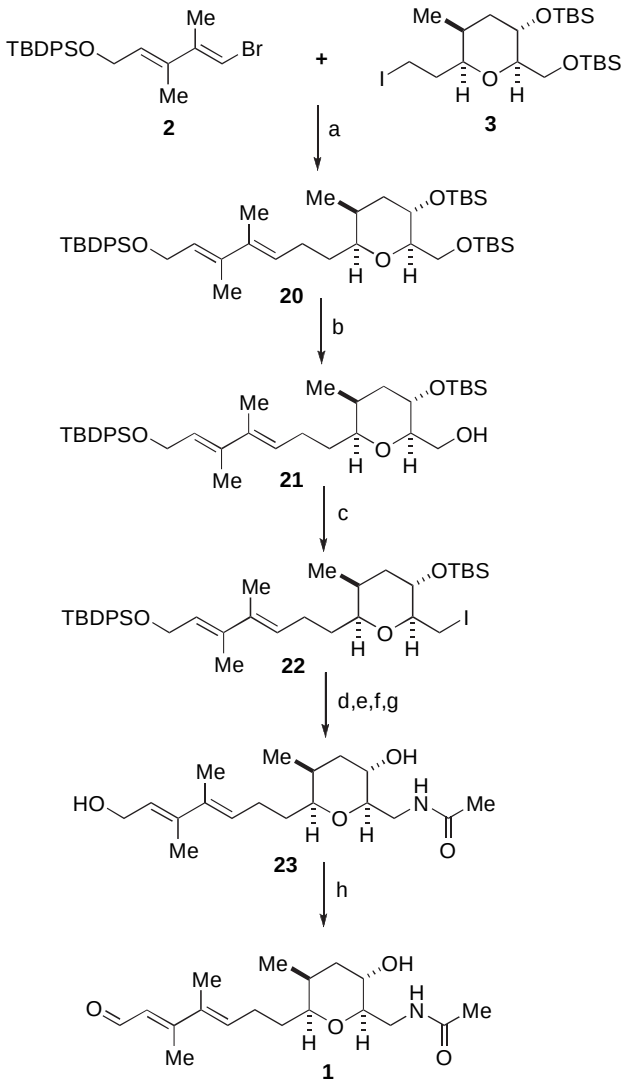


Scheme 4. Reagents and conditions: (a) Br_2, CCl_4, 0 °C to rt; (b) NaOH, THF/H_2O, 0 °C to rt; (c) $LiAlH_4$, ether, 0 °C to rt; (d) MnO_2, ether, rt, (e) MeMgBr, ether, 0 °C; (f) MnO_2, ether, rt; (g) $(EtO)_2P(O)CH_2COOEt$, n-BuLi, THF, 0 °C to rt, **18a** 31%, **18b** 6% for seven steps; (h) DIBALH, CH_2Cl_2, −78 °C, 98%; (i) TBDPSCl, imidazole, DMF, 0 °C to rt, 99%.

2.4. Total synthesis of (−)-brevisamide

Linkage of the bromodienol side chain fragment **2** and the ether ring fragment **3** was accomplished by a Suzuki–Miyaura cross coupling (Scheme 5).

Treatment of **3** with t-BuLi and B-OMe-9-BBN produced a borate intermediate, which was reacted in situ with the bromodienol **2** in the presence of aqueous Cs_2CO_3 and a catalytic amount of Pd(dppf)



Scheme 5. Reagents and conditions: (a) **3**, B-OMe-9-BBN, t-BuLi, ether/THF, −78 °C to rt; then **2**, Pd(dppf)Cl_2, 3 M Cs_2CO_3 aq, DMF, 64%; (b) CSA, CH_2Cl_2/MeOH, 0 °C, 85% brsm; (c) I_2, PPh_3, imidazole, toluene, rt, 90%; (d) NaN_3, DMF, rt; (e) PPh_3, THF, rt; then H_2O, 50 °C; (f) Ac_2O, pyridine, rt; (g) TBAF, THF, 0 °C to rt, 89% for four steps; (h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 88%.

Cl_2 to give rise to a cross-coupled product **20** in 64% yield. The primary TBS group on the ether ring was selectively deprotected with CSA to give a primary alcohol **21**, which was converted to an iodide **22** using I_2, PPh_3, and imidazole. The iodide **22** was converted to an azide with NaN_3 and then reduced to an amine, which was acetylated with acetic anhydride to give an amide. This amide was treated with TBAF to give a dienol **23** in 89% yield over four steps. Finally, chemoselective oxidation of the allylic alcohol at C-1 with TEMPO and $PhI(OAc)_2$ in CH_2Cl_2 gave rise to **1** in 88% yield.

Brevisamide showed weak cytotoxicity against mouse lymphoid P388 cells at more than 30 μg/mL[20] but did not induce any symptoms against mice even at 3 mg/kg.

3. Conclusion

We accomplished the improved synthesis of **1**. The longest linear sequence leading to **1** was 21 steps with overall yield 8.6% and the overall yield of this synthesis was five times as high as that of our previous synthesis (1.6%). In particular, one-pot lactonization in the existence of excessive base after an Ando reaction was found to be an effective method.

4. Experimental section

4.1. General methods

All reactions sensitive to air and/or moisture were carried out in an oven-dried (>100 °C) glassware under argon atmosphere, and under anhydrous conditions otherwise noted. Anhydrous dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc and used without further drying. All other reagents and solvents were purchased at highest commercial grade and used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} plates (0.25-mm thickness). Column chromatography was performed using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral). Optical rotations were recorded on a JASCO DIP-350 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-420 spectrometer. ^1H and ^{13}C NMR spectra were measured on a JEOL ECA-500 and ECX-400 spectrometer, and chemical shift values are reported in parts per million (δ) with reference to internal residual solvent [^1H NMR, $CDCl_3$ (7.24), C_6D_6 (7.16); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (127.0)]. Coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Low- and high-resolution mass spectra were recorded on a JEOL JMS-700P mass spectrometer under fast atom bombardment (FAB) conditions using *m*-nitrobenzyl alcohol (NBA) as a matrix and a JEOL JMS-T100TD mass spectrometer under direct analysis in real time (DART) conditions.

*4.1.1. Aldol adduct (**7**).* To a solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (4.81 g, 20.6 mmol) in CH_2Cl_2 (100 mL) was added *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 22.7 mL, 23 mmol) and Et_3N (3.4 mL) slowly at 0 °C. The reaction mixture was stirred for 1 h and cooled to −78 °C. A solution of **6** (3.38 g, 20.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h then for 2 h at 0 °C. The reaction was quenched with phosphate buffer (pH 7, 40 mL). MeOH/30% aqueous H_2O_2 (60 mL, 30 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. Two layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (70/30 to 60/40 hexane/EtOAc) to afford **7** as a pale yellow oil (7.52 g, 18.9 mmol, 92%). $[\alpha]_D^{26}$ −51.2 (*c* 0.144 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.30 (m, 8H), 7.19 (d, J=6.7 Hz, 2H), 4.67 (dddd, J=10.1, 6.7, 3.4, 3.4 Hz, 1H), 4.50 (s, 2H), 3.80 (td, J=7.1, 3.8 Hz, 1H), 3.69 (ddd, J=9.2, 6.3, 5.0 Hz, 1H), 3.64 (ddd, J=9.2, 7.5, 5.0 Hz, 1H), 3.28 (d, J=2.5 Hz, 1H), 3.24 (dd, J=13.4, 3.4 Hz, 1H), 2.76 (dd, J=13.4, 9.6 Hz, 1H), 2.02 (s, 1H), 1.86 (dddd, J=14.3, 9.6, 7.1, 5.0 Hz, 1H), 1.75–1.70 (m, 1H), 1.26 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 153.0, 138.0, 135.1, 129.4, 128.9, 128.3, 127.7, 127.4, 73.2, 70.4, 68.3, 66.1, 55.2, 42.5, 37.8, 33.7, 11.1; IR (film) ν_{max} cm^{-1} 3512 (br), 2921, 2868, 1778, 1695, 1451, 1386, 1208, 1108, 969, 744, 700; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{15}H_{20}NO_3Na$) 271.1305, found 271.1301.

*4.1.2. Weinreb amide (**8**).* To a solution of NH(OMe)Me·HCl (412 mg, 4.22 mmol) in CH_2Cl_2 (15 mL) was added $AlMe_3$ (2.0 M in heptane, 2.1 mL, 4.2 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature for 1 h then cooled to −15 °C. A solution of **7** (833 mg, 2.10 mmol) in CH_2Cl_2 (5 mL) was added dropwise, and the reaction mixture was warmed to 0 °C and stirred for 40 min. Saturated aqueous potassium sodium tartrate was added, and the reaction mixture was stirred for 1 h. Two layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (70/30 to 60/40 hexane/acetone) to afford **8** as a colorless oil (547 mg, 1.94 mmol, 93%). $[\alpha]_D^{26}$ −14.5 (*c* 0.235 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 4H), 7.27–7.25 (m, 1H), 4.50 (s, 2H), 3.69–3.61 (m, 2H), 3.64 (s, 3H), 3.16 (s, 3H), 1.82 (dddd, J=14.3, 9.2, 6.3, 5.5 Hz, 1H), 1.71–1.65 (m, 1H), 1.18 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 138.1, 128.3, 127.6, 127.6, 73.2, 70.3, 68.3, 61.5, 39.4, 33.9, 31.8, 11.1; IR (film) ν_{max} cm^{-1} 3447 (br), 2933, 2868, 1651, 1636, 1456, 1419, 1387, 1098, 988, 738, 699; HRMS (FAB) calcd for $[M+H]^+$ ($C_{15}H_{24}NO_4$) 282.1700, found 282.1713.

*4.1.3. β-Hydroxyaldehyde (**9**).* To a suspension of $LiAlH_4$ (463 mg, 12.2 mmol) in THF (10 mL) was added a solution of **8** (1.68 g, 5.97 mmol) in THF (50 mL) dropwise via cannula at 0 °C. The reaction mixture was stirred for 1 h before quenching with EtOAc. After aqueous saturated potassium sodium tartrate was added, the reaction mixture was warmed to room temperature and stirred for 50 min. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (60/40 hexane/EtOAc) to afford **9** as a colorless oil (1.13 g, 5.09 mmol, 85%). $[\alpha]_D^{18}$ −20.7 (*c* 0.508 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.36–7.28 (m, 5H), 4.51 (s, 2H), 4.27 (dddd, J=9.6, 4.2, 2.5, 2.5 Hz, 1H), 3.73 (ddd, J=9.2, 5.9, 4.6 Hz, 1H), 3.66 (ddd, J=9.2, 9.2, 3.8 Hz, 1H), 2.46 (qd, J=7.1, 4.2 Hz, 1H),1.85 (dddd, J=14.3, 9.6, 9.2, 4.2 Hz, 1H), 1.68 (dddd, J=14.3, 5.9, 3.8, 2.5 Hz, 1H), 1.11 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 137.6, 128.4, 127.8, 127.6, 73.3, 70.2, 68.9, 51.5, 33.5, 7.7; IR (film) ν_{max} cm^{-1} 3454 (br), 2926, 2863, 2721, 1719, 1454, 1364, 1090, 1024, 741, 696; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{13}H_{18}NaO_3$) 245.1154, found 245.1146.

*4.1.4. α,β-Unsaturated lactone (**11**).* To a solution of NaH (354 mg, 8.9 mmol, 60% dispersion in oil) in THF (40 mL) was added a solution of $(PhO)_2P(O)CH_2COOMe$ (2.27 g, 7.41 mmol) in THF (10 mL) dropwise at 0 °C, and the reaction mixture was stirred for 10 min. The solution was cooled to −78 °C, and a solution of **9** (1.43 g, 6.11 mmol) in THF (10 mL) was added dropwise via cannula. After 80 min the reaction mixture was warmed to 0 °C and stirred for 10 min before quenching with saturated aqueous NH_4Cl. The mixture was concentrated and extracted twice with EtOAc. The organic phase was washed twice with water then with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (95/5 $CHCl_3$/EtOAc) to afford **11** as a colorless oil (1.07 g, 4.34 mmol, 71%). $[\alpha]_D^{22}$ −106 (*c* 0.408 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.92 (dd, J=9.6, 6.4 Hz, 1H), 5.94 (d, J=9.6 Hz, 1H), 4.64 (ddd, J=9.2, 3.7, 3.7 Hz, 1H), 4.51 (d, J=11.9 Hz, 1H), 4.48 (d, J=11.9 Hz, 1H), 3.68 (ddd, J=9.2, 9.2, 5.0 Hz, 1H), 3.62 (ddd, J=9.6, 5.0, 5.0 Hz, 1H), 2.39–2.31 (m, 1H), 2.04 (dddd, J=14.2, 9.6, 5.0, 5.0 Hz, 1H), 1.83 (dddd, J=14.2, 8.7, 5.9, 4.1 Hz, 1H), 1.03 (d, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 151.6, 138.0, 128.3, 127.6, 127.6, 119.8, 76.9, 73.1, 65.7, 32.1, 31.9, 11.3; IR (film) ν_{max} cm^{-1} 2872, 1721, 1454, 1381, 1250, 1094, 985, 823, 739, 698; HRMS (FAB) calcd for $[M+H]^+$ ($C_{15}H_{19}O_3$) 247.1329, found 247.1331.

*4.1.5. Lactone (**12**).* To a solution of **11** (1.04 g, 4.22 mmol) in EtOAc (30 mL) was added a suspension of Pd/C (0.06 g, 5%) in EtOAc (10 mL). The flask was flushed with H_2 and the mixture was stirred for 14 h at room temperature before it was filtered through Celite®. The filtrate was concentrated in vacuo to give **12** as a colorless oil (1.03 g, 4.15 mmol, 98%). $[\alpha]_D^{22}$ −98.4 (*c* 0.606 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 4.52 (ddd, J=9.6, 3.2, 3.2 Hz,

1H), 4.50 (d, *J*=11.9 Hz, 1H), 4.48 (d, *J*=11.9 Hz, 1H), 3.66 (ddd, *J*=9.2, 9.2, 5.0 Hz, 1H), 3.61 (ddd, *J*=9.2, 6.0, 4.6 Hz, 1H), 2.52 (dd, *J*=7.8, 6.9 Hz, 1H), 2.07–1.98 (m, 1H), 1.91 (dddd, *J*=14.2, 10.6, 5.0, 5.0 Hz, 1H), 1.80 (dddd, *J*=14.2, 8.7, 6.0, 3.7 Hz, 1H), 1.64 (ddd, *J*=9.2, 6.9, 6.9 Hz, 1H), 0.95 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.1, 127.7, 127.7, 79.4, 73.2, 66.2, 32.6, 29.5, 26.7, 26.1, 12.6; IR (film) ν_{max} cm^{-1} 2965, 2875, 1734, 1454, 1364, 1239, 1203, 1076, 991, 741, 696; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{15}H_{20}O_3Na$) 271.1305, found 271.1301.

*4.1.6. Oxene carboxylate (**13**).* To a solution of **12** (340 mg, 1.37 mmol) in THF (24 mL) was added DMPU (0.21 mL, 1.8 mmol), KHMDS (0.5 M in toluene, 3.6 mL, 1.8 mmol), a solution of $PhNTf_2$ (698 mg, 1.95 mmol) in THF (3.0 mL) at −78 °C, and the mixture was stirred for 30 min. The reaction mixture was warmed to 0 °C and stirred for further 40 min before hexane and phosphate buffer (pH 7) was added. The layers were separated and the aqueous layer was extracted with hexane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford an oil. The product was employed in the next reaction without further purification.

The above enoltriflate was dissolved in DMF (15 mL), MeOH (5.2 mL) at room temperature. Et_3N (0.77 mL, 5.5 mmol), Pd(PPh_3)$_4$ 77 mg (0.067 mmol) was added. The flask was flushed with CO, and the reaction mixture was stirred for 16 h. Additional Pd(PPh_3)$_4$ (86 mg, 0.074 mmol) was added, and the reaction mixture was warmed to 40 °C. After 10 h the reaction mixture was cooled to room temperature, and EtOAc and brine was added. Two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel with hexane/EtOAc/Et_3N (90/10/0.5 to 80/20/0.5) gave **13** as a colorless oil (349 mg, 1.20 mmol, 88% for two steps). $[\alpha]_D^{22}$ −77.8 (*c* 0.445 in benzene); ^{1}H NMR (400 MHz, C_6D_6) δ 7.44–7.15 (m, 5H), 6.11 (dd, *J*=4.1, 4.1 Hz, 1H), 4.39 (d, *J*=12.8 Hz, 1H), 4.38 (d, *J*=12.8 Hz, 1H), 4.10 (ddd, *J*=9.6, 2.7, 2.7 Hz, 1H), 3.70 (ddd, *J*=9.2, 9.2, 5.5 Hz, 1H), 3.55 (ddd, *J*=9.2, 5.5, 5.5 Hz, 1H), 3.48 (s, 3H), 1.99 (ddd, *J*=18.7, 6.4, 3.2 Hz, 1H), 1.92 (ddd, *J*=14.2, 5.0, 5.0 Hz, 1H), 1.68–1.56 (m, 1H), 1.48 (ddd, *J*=18.3, 4.6, 4.6 Hz, 1H), 0.75 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 163.1, 144.0, 139.3, 128.5, 127.7, 127.5, 109.6, 75.8, 73.0, 67.0, 51.3, 31.6, 29.0, 29.0, 13.4; IR (film) ν_{max} cm^{-1} 2954, 1732, 1649, 1437, 1371, 1287, 1253, 1102, 739, 698; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{17}H_{22}O_4Na$) 313.1416, found 313.1425.

*4.1.7. Allylic alcohol (**14**).* To a solution of **13** (258 mg, 0.888 mmol) in CH_2Cl_2 (10 mL) was added DIBALH (1.0 M in hexane, 2.2 mL, 2.2 mmol) dropwise at −78 °C. The reaction mixture was warmed to 0 °C and stirred for 20 min before the reaction was quenched with EtOAc and water. Saturated aqueous potassium sodium tartrate was added, and the mixture was stirred additional 1 h at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (75/25/0.5 to 50/50/0.5 heane/EtOAc/Et_3N) to afford **14** as a colorless oil (205 mg, 0.781 mmol, 88%). $[\alpha]_D^{22}$ −66.6 (*c* 0.322 in benzene); ^{1}H NMR (400 MHz, C_6D_6) δ 7.38–7.16 (m, 5H), 4.64 (s, 1H), 4.42 (d, *J*=12.4 Hz, 1H), 4.41 (d, *J*=12.4 Hz, 1H), 4.12 (ddd, *J*=9.6, 3.2, 3.2 Hz, 1H), 3.96 (s, 2H), 3.59 (ddd, *J*=8.7, 8.7, 5.5 Hz, 1H), 3.50 (ddd, *J*=8.7, 5.5, 5.5 Hz, 1H), 2.07 (ddd, *J*=4.6, 3.2, 1.4 Hz, 1H), 1.92 (dddd, *J*=14.6, 10.1, 5.0, 5.0 Hz, 1H), 1.80–1.71 (m, 1H), 1.64 (dddd, *J*=14.6, 8.7, 6.4, 3.7 Hz, 1H), 1.56 (ddd, *J*=16.9, 4.6, 4.6 Hz, 1H), 0.84 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.5, 139.2, 128.5, 127.8, 127.6, 95.2, 75.4, 73.1, 67.2, 63.2, 30.9, 29.7, 28.1, 13.9; IR (film) ν_{max} cm^{-1} 3409 (br), 2959, 2908, 2868, 2367, 2342, 1683, 1451, 1381, 1367, 1207, 1104, 1077, 1014, 737, 696; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{16}H_{22}O_3Na$) 285.1461, found 285.1461.

*4.1.8. Diol (**15**).* To a solution of **14** (145 mg, 0.553 mmol) in THF (5.0 mL) was added $BH_3\cdot SMe_2$ (2.0 M in THF, 0.55 mL, 1.1 mmol) at 0 °C, and the solution was stirred for 4 h. Aqueous 3 M NaOH (0.7 mL) and aqueous 30% H_2O_2 (0.4 mL) was added, and the reaction mixture was stirred for 30 min at 45 °C. The mixture was extracted twice with EtOAc, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (2/8 to 1/9 hexane/EtOAc) to afford **15** as a white solid (133 mg, 0.476 mmol, 86%). $[\alpha]_D^{22}$ −33.3 (*c* 0.255 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 4.50 (d, *J*=11.7 Hz, 1H), 4.46 (d, *J*=11.7 Hz, 1H), 3.79–3.75 (m, 2H), 3.63 (ddd, *J*=9.2, 4.2, 2.5 Hz, 1H), 3.59–3.48 (m, 2H), 3.11 (ddd, *J*=9.2, 4.6, 4.6 Hz, 1H), 2.49 (dd, br, *J*=18.9, 4.6 Hz, 2H), 1.93 (ddd, *J*=12.6, 4.6, 2.5 Hz, 1H), 1.85–1.79 (m, 1H), 1.75 (dddd, *J*=14.3, 9.2, 5.4, 5.4 Hz, 1H), 1.65–1.58 (m, 2H), 0.93 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 127.6, 81.9, 76.4, 72.9, 67.0, 63.8, 63.4, 40.0, 33.0, 32.7, 12.6; IR (film) ν_{max} cm^{-1} 3392 (br), 2921, 2861, 1454, 1387, 1361, 1100, 1065, 738, 696; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{16}H_{24}O_4Na$) 281.1748, found 281.1761.

*4.1.9. Bis-TBS ether (**16**).* To a solution of **15** (133 mg, 0.473 mmol) in DMF (2.5 mL) was added imidazole (184 mg, 1.72 mmol) and TBSCl (337 mg, 1.27) at room temperature, and the reaction mixture was stirred for 1.5 h before water was added at 0 °C. The mixture was extracted twice with EtOAc. The combined organic phase was washed twice with water, then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (93/7 hexane/EtOAc) to afford **16** as a colorless oil (230 mg, 0.452 mmol, 95%). $[\alpha]_D^{22}$ +8.23 (*c* 0.417 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.31 (m, 4H), 7.29–7.24 (m, 1H), 4.49 (d, *J*=12.2 Hz, 1H), 4.48 (d, *J*=12.2 Hz, 1H), 3.76–3.68 (m, 3H), 3.60–3.53 (m, 3H), 3.02 (ddd, *J*=9.2, 4.6, 2.1 Hz, 1H), 1.83 (ddd, *J*=12.6, 4.6, 2.5 Hz, 1H), 1.80–1.73 (m, 2H), 1.65–1.56 (m, 2H), 1.93 (ddd, *J*=12.6, 4.6, 2.5 Hz, 1H), 0.93 (d, *J*=7.1 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 83.5, 75.9, 73.0, 67.5, 63.0, 62.9, 41.1, 33.2, 33.1, 25.9, 25.8, 18.4, 17.9, 12.8, −4.3, −4.9, −5.3; IR (film) ν_{max} cm^{-1} 2959, 2929, 2882, 2857, 1461, 1387, 1361, 1252, 1136, 1103, 1017, 866, 836, 776, 731, 696; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{16}H_{24}O_4Na$) 531.3297, found 531.3309.

*4.1.10. Primary alcohol (**17**).* To a solution of **16** (25.9 mg, 0.0509 mmol) in THF (1 mL) was added a pre-made 0.5 M solution of LiDBB in THF (ca. 6 mL) dropwise at −78 °C. The reaction mixture was stirred for 3 h before MeOH and saturated aqueous NH_4Cl was added. The reaction mixture was extracted three times with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification on silica gel chromatography (9/1 to 8/2 hexane/EtOAc) afforded **17** as a colorless oil (17.5 mg, 0.0418 mmol, 82%). $[\alpha]_D^{22}$ +26.5 (*c* 0.243 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.81–3.72 (m, 3H), 3.68–3.59 (m, 3H), 3.16 (ddd, *J*=8.4, 6.3, 2.1 Hz, 2H), 1.87–1.77 (m, 3H), 1.73–1.66 (m, 1H), 1.62 (td, *J*=11.8, 4.6 Hz, 1H), 1.41 (dddd, *J*=14.7, 4.6, 2.1, 2.1 Hz, 1H), 0.96 (d, *J*=6.7 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 81.3, 63.2, 62.8, 40.9, 34.4, 33.5, 25.9, 25.7, 18.3, 17.9, 13.0, −4.2, −5.0, −5.3, −5.4; IR (film) ν_{max} cm^{-1} 3422 (br), 2959, 2930, 2882, 2857, 1469, 1387, 1253, 1104, 1018, 976, 866, 836, 776, 670; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{21}H_{46}O_4Si_2Na$) 441.2827, found 441.2834.

*4.1.11. Ether ring fragment (**3**).* To a solution of **17** (159 mg, 0.379 mmol) in toluene (4 mL) was added imidazole (46.0 mg, 0.675 mmol), PPh_3 (132 mg, 0.503 mmol), I_2 (173 mg, 0.682 mmol)

at room temperature. The flask was wrapped in aluminum foil, and the mixture was stirred for 1 h before aqueous $Na_2S_2O_3$ was added at 0 °C. The reaction mixture was extracted twice with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification on silica gel with (98/2 hexane/EtOAc) afforded **3** as a colorless oil (183 mg, 0.346 mmol, 91%). $[\alpha]_D^{24}$ −4.24 (*c* 0.471 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79–3.68 (m, 3H), 3.49 (ddd, *J*=9.2, 2.5, 2.5 Hz, 1H), 3.30–3.21 (m, 2H), 3.05 (ddd, *J*=9.2, 4.6, 2.1 Hz, 1H), 1.97 (dddd, *J*=14.3, 9.6, 6.7, 5.0 Hz, 1H), 1.83 (ddd, *J*=12.6, 5.0, 2.5 Hz, 1H), 1.79–1.69 (m, 2H), 1.63 (td, *J*=12.2, 4.6 Hz, 1H), 0.93 (d, *J*=7.2 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 78.8, 62.8, 40.9, 36.8, 32.8, 25.9, 25.8, 18.4, 17.9, 13.0, 4.0, −4.3, −4.9, −5.0, −5.3; IR (film) ν_{max} cm^{-1} 2959, 2930, 2882, 2856, 1462, 1387, 1251, 1108, 1016, 866, 836, 776, 667; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{21}H_{45}IO_3Si_2Na$) 551.1845, found 551.1841.

*4.1.12. Bromodienoate (**18a**).* To a solution of **4** (5.0 mL, 46.6 mmol) in CCl_4 (60 mL) at 0 °C was added dropwise bromine (2.4 mL, 46.6 mmol) in CCl_4 (30 mL). After being stirred at room temperature for 80 min, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residual crude dibromide was used in the next reaction without further purification.

To a solution of the above dibromide in THF (40 mL) was added NaOH (7.46 g, 186 mmol) in water (40 mL) at 0 °C. After being stirred at room temperature for 24 h, the reaction mixture was acidified with 1 M HCl aq and diluted with ether. The organic layer was separated, and the aqueous layer was extracted four times with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual crude carboxylic acid, obtained as a white solid, was used in the next reaction without further purification.

To a suspension of $LiAlH_4$ (2.46 g, 65.0 mmol) in ether (150 mL) was slowly added above crude carboxylic acid in ether (45 mL) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with water (2.5 mL), 3 M NaOH aq (2.5 mL), and water (7.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. To the mixture was added anhydrous Na_2SO_4, and the salt was filtered through Celite®. The solution was concentrated in vacuo. The residual crude allylic alcohol was used in the next reaction without further purification.

To a solution of the above crude alcohol in ether (100 mL) was added MnO_2 (59 g) at room temperature. After being stirred for 3 h, additional MnO_2 (29.5 g) was added, and the reaction mixture was stirred for a further 1 h. The mixture was filtered through Celite®. The filtrate containing the resultant aldehyde was used in the next reaction as obtained.

To a solution of the above crude aldehyde in ether was added MeMgBr (3 M in ether, 16.9 mL, 50.8 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted three times with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residual crude secondary alcohol was used in the next reaction without further purification.

To a solution of the above alcohol in ether (56 mL) was added MnO_2 (47.2 g) at room temperature. After being stirred for 9 h, additional MnO_2 (47.2 g) was added, and the reaction mixture was stirred for a further 10 h. The mixture was filtered through Celite® and concentrated in vacuo. The residual crude bromoenone was used in the next reaction without further purification.

To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (17 mL, 85.2 mmol) in THF (140 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexane, 35.5 mL, 57 mmol). After being stirred at 0 °C for 30 min, a solution of the above crude bromoenone in THF (27 mL) was added. The reaction mixture was stirred at room temperature for 12 h, and then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to column chromatography (99/1 to 98/2 hexane/EtOAc) to give the mixture of **18a** and **18b** (4.00 g, 17.2 mmol, 37% for seven steps) as a colorless oil. The ratio of **18a** and **18b** was calculated to be 5:1 based on the ^{1}H NMR integration values. Pure **18a** obtained after repetitive column chromatography was used in the next reaction. Spectroscopic data for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 5.89 (s, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 1.98 (s, 3H), 1.26 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.1, 142.5, 116.9, 110.8, 60.0, 17.5, 15.6, 14.2; IR (film) ν_{max} cm^{-1} 3100, 2980, 1715, 1617, 1444, 1375, 1345, 1302, 1227, 1165, 1096, 1050, 1020, 978, 871, 792, 732; HRMS (DART) calcd for $[M+H]^+$ ($C_9H_{14}{}^{79}BrO_2$) 233.0177, found 233.0174. Spectroscopic data for **18b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.63 (d, *J*=1.2 Hz, 1H), 4.07 (q, *J*=7.2 Hz, 2H), 1.92 (s, 3H), 1.90 (d, *J*=1.2 Hz, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.8, 141.8, 139.9, 118.2, 103.3, 60.0, 24.3, 18.7, 14.1; IR (film) ν_{max} cm^{-1} 3077, 2980, 1720, 1643, 1617, 1443, 1373, 1347, 1274, 1216, 1154, 1095, 1051, 984, 868, 793, 716.

*4.1.13. Bromodienol (**19**).* To a solution of **18a** (1.13 g, 4.85 mmol) in CH_2Cl_2 45 mL at −78 °C was added DIBALH (1.03 M in hexane, 11.3 mL, 11.6 mmol). After being stirred for 1 h, the reaction mixture was quenched with MeOH, allowed to warm to room temperature, and diluted with EtOAc and saturated aqueous potassium sodium tartrate. The resultant mixture was stirred at room temperature until the layers became clear. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to column chromatography (75/25 hexane/EtOAc) to give the bromodienol **19** (910 mg, 4.76 mmol, 98%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.77 (t, *J*=6.3 Hz, 1H), 4.25 (d, *J*=6.3 Hz, 2H), 1.97 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 136.6, 126.9, 106.2, 59.7, 17.4, 14.3; IR (film) ν_{max} cm^{-1} 3319, 2924, 2862, 1442, 1377, 1287, 1205, 1116, 1079, 1003, 764, 732; HRMS (DART) calcd for $[M-H_2O+H]^+$ ($C_7H_{10}{}^{79}Br$) 172.9966, found 172.9970.

*4.1.14. Bromodienol fragment (**2**).* To a solution of **19** (357 mg, 1.86 mmol) in DMF (20 mL) at 0 °C were added imidazole (201 mg, 2.95 mmol) and TBDPSCl (0.74 mL, 2.8 mmol). After being stirred at room temperature for 3.5 h, the reaction mixture was quenched with water at 0 °C. The mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to column chromatography (97/3 hexane/EtOAc) to give **2** (789 mg, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.43–7.35 (m, 6H), 6.21 (s, 1H), 5.75 (t, *J*=5.9 Hz, 1H), 4.30 (d, *J*=5.9 Hz, 2H), 1.92 (s, 3H), 1.56 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 135.6, 134.7, 133.7, 129.6, 127.7, 105.5, 61.4, 26.8, 19.1, 17.4, 14.3; IR (film) ν_{max} cm^{-1} 3319, 2924, 2862, 1442, 1377, 1287, 1205, 1116, 1079, 1003, 764, 732; HRMS (DART) calcd for ($C_{23}H_{28}{}^{79}BrOSi$) $[M+Na]^+$ 427.1090, found 427.1093.

*4.1.15. Cross-coupled product (**20**).* The ether ring fragment **3** (36.4 mg, 0.0688 mmol) was dissolved in ether (1 mL) and the solution was cooled to −78 °C. To this solution was added a *B*-OMe-9-BBN (1.0 M, 0.19 mL in hexane, 0.19 mol) and *t*-BuLi (1.58 M, 0.17 mL

in pentane, 0.27 mol). After 15 min, THF (1 mL) was added, and the solution was stirred for 5 min at −78 °C then for 1 h at room temperature. Aqueous Cs_2CO_3 (3 M aqueous solution, 0.3 mL, 0.9 mmol) was then added followed by addition of **2** (50.0 mg, 0.116 mmol) in DMF (1 mL). Pd(dppf)Cl_2 (9.9 mg, 0.012 mmol) was added and the resulting mixture was warmed to 45 °C and stirred for 17 h. The reaction was quenched with saturated NH_4Cl at 0 °C. The organic layer was extracted twice with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification on silica gel chromatography (99/1 to 96/4 hexane/ether) gave **20** as a colorless oil (32.9 mg, 0.0438 mmol, 64%). $[\alpha]_D^{25}$ +8.01 (*c* 0.220 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J*=8.0, 1.7 Hz, 4H), 7.42–7.35 (m, 6H), 5.65 (t, *J*=5.9 Hz, 1H), 5.48 (t, *J*=7.1 Hz, 1H), 4.36 (d, *J*=5.9 Hz, 2H), 3.81–3.71 (m, 3H), 3.32 (ddd, *J*=8.8, 4.2, 2.5 Hz, 1H), 3.01 (ddd, *J*=9.2, 4.6, 2.1 Hz, 1H), 2.24–2.13 (m, 2H), 1.83 (ddd, *J*=12.6, 4.2, 2.5 Hz, 1H), 1.75 (s, 3H), 1.63–1.55 (m, 2H), 1.58 (s, 3H), 1.29 (dddd, *J*=13.0, 8.8, 7.6, 4.6 Hz, 1H), 1.04 (s, 9H), 0.93 (d, *J*=7.2 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.0, 135.6, 129.5, 127.6, 126.6, 125.1, 83.6, 78.5, 63.0, 61.9, 41.1, 33.0, 32.8, 26.8, 25.9, 25.8, 25.2, 19.2, 18.4, 18.0, 14.2, 13.8, 12.8, −4.3, −4.9, −5.0, −5.2; IR ν_{max} cm^{-1} 2959, 2930, 2882, 2856, 1462, 1387, 1251, 1108, 1016, 866, 836, 776, 667; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{44}H_{74}NaO_4Si_3$) 773.4787, found 773.4777.

*4.1.16. Primary alcohol (**21**).* To a solution of **20** (17.0 mg, 0.0226 mmol) in CH_2Cl_2 (1 mL), MeOH (1 mL) under air was added CSA (2.1 mg, 0.0090 mmol) at 0 °C. After 1 h, the reaction was quenched with Et_3N, and the mixture was concentrated in vacuo and purified by silica gel column chromatography (96/4 to 90/10 hexane/EtOAc) to afford **21** as a colorless oil (9.1 mg, 0.014 mmol, 63%). The starting material was recovered (4.2 mg, 0.0056 mmol, 25%). $[\alpha]_D^{25}$ +5.90 (*c* 0.420 in $CDCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.69 (dd, *J*=8.0, 1.7 Hz, 4H), 7.42–7.35 (m, 6H), 5.66 (t, *J*=5.9 Hz, 1H), 5.47 (t, *J*=7.1 Hz, 1H), 4.36 (d, *J*=5.9 Hz, 2H), 3.81 (d, *J*=10.9 Hz, 1H), 3.69 (ddd, *J*=10.9, 9.2, 5.0 Hz, 1H), 3.60 (dd, *J*=10.9, 5.5 Hz, 1H), 3.42 (ddd, *J*=8.8, 4.6, 2.5 Hz, 1H), 3.15 (ddd, *J*=9.2, 5.9, 2.9 Hz, 1H), 2.18 (dt, *J*=7.5, 7.5 Hz, 2H), 2.08 (br, 1H), 1.87 (ddd, *J*=12.6, 4.6, 2.5 Hz, 1H), 1.81 (ddd, *J*=9.6, 4.6, 2.5 Hz, 1H), 1.75 (s, 3H), 1.66–1.60 (m, 2H), 1.58 (s, 3H), 1.39–1.32 (m, 1H), 1.05 (s, 9H), 0.94 (d, *J*=7.1 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 136.2, 134.8, 133.9, 129.5, 128.3, 127.6, 126.2, 125.4, 82.5, 78.9, 64.2, 63.2, 61.9, 40.9, 32.8, 32.6, 26.8, 26.5, 25.7, 25.2, 19.2, 17.9, 14.1, 13.9, 12.7, −4.2, −4.9; IR (film) ν_{max} cm^{-1} 3512 (br), 2930, 2856, 1470, 1458, 1425, 1387, 1252, 1107, 1039, 866, 836, 776, 738, 703; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{38}H_{60}NaO_4Si_2$) 659.3923, found 659.3929.

*4.1.17. Iodide (**22**).* To a solution of **21** (37.0 mg, 0.0581 mmol) in toluene (2 mL) were added imidazole (31.3 mg, 0.460 mmol), PPh_3 (68.8 mg, 0.262 mmol), and I_2 (107 mg, 0.422 mmol) at room temperature, and the reaction mixture was stirred for 50 min before saturated aqueous $Na_2S_2O_3$ was added. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification on silica gel with hexane/EtOAc (96/4) gave **22** as a colorless oil (39.0 mg, 0.0522 mmol, 90%). $[\alpha]_D^{26}$ +11.8 (*c* 0.309 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J*=8.0, 1.7 Hz, 4H), 7.43–7.35 (m, 6H), 5.66 (t, *J*=5.9 Hz, 1H), 5.51 (t, *J*=7.1 Hz, 1H), 4.37 (d, *J*=5.9 Hz, 2H), 3.57 (ddd, *J*=10.9, 8.8, 5.0 Hz, 1H), 3.52 (dd, *J*=10.1, 2.5 Hz, 1H), 3.43 (ddd, *J*=9.2, 4.2, 2.1 Hz, 1H), 3.26 (dd, *J*=10.5, 6.7 Hz, 1H), 2.31–2.18 (m, 2H), 2.08 (br, 1H), 1.84 (ddd, *J*=12.6, 4.6, 2.5 Hz, 1H), 1.78 (s, 3H), 1.68–1.61 (m, 2H), 1.59 (s, 3H), 1.37–1.31 (m, 1H), 1.05 (s, 9H), 0.97 (d, *J*=7.1 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.2, 135.6, 133.9, 129.5, 128.3, 127.6, 126.5, 125.2, 81.3, 79.2, 68.0, 61.9, 40.9, 33.2, 32.6, 26.8, 25.2, 19.2, 17.8, 14.2, 14.0, 13.0, 9.6, −4.0, −4.5; IR (film) ν_{max} cm^{-1} 3512 (br), 2959, 2930, 2882, 2856, 1469, 1429, 1384, 1253, 1108, 1043, 863, 776, 740, 703; HRMS (FAB) not detected.

*4.1.18. Dienol (**23**).* To a solution of **22** (25.0 mg, 0.0335 mmol) in DMF (0.60 mL) was added NaN_3 (21.6 mg, 0.332 mmol) at room temperature, and the solution was stirred for 7 h. NaN_3 (24.2 mg, 0.372 mmol) was added, and the solution was stirred for 3.5 h. NaN_3 (38.9 mg, 0.598 mmol) was added, and the solution was stirred for 12 h before adding water and ether. Two layers were separated, and the aqueous layer was extracted with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was used in the next step without further purification.

The above obtained azide was dissolved in THF (1.0 mL) and PPh_3 (11.0 mg, 0.0419 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 17 h before water (50 μL) was added. The reaction mixture was stirred for 72 h before PPh_3 (10.6 mg, 0.0404 mmol) and THF (0.50 mL) were added. The reaction mixture was stirred for 1 h before water (0.10 mL) was added. Then the reaction mixture was warmed to 50 °C and stirred for 9 h. The reaction mixture was cooled to room temperature and saturated $NaHCO_3$ was added. The mixture was extracted twice with EtOAc, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was used in the next step without further purification.

The above obtained amine was dissolved in Ac_2O (1.0 mL) and pyridine (1.0 mL), and the reaction mixture was stirred for 15 h at room temperature. The mixture was concentrated in vacuo and subjected to silica gel column chromatography (99/1 to 98/2 $CHCl_3$/MeOH) to afford crude acetamide as a colorless oil. The crude product was used in the next step without further purification.

The above obtained acetamide was dissolved in THF (2.0 mL) and TBAF (1 M, 2.0 mL in THF 20 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4.5 h before the reaction was quenched with saturated NH_4Cl aqueous at 0 °C. The mixture was extracted three times with EtOAc, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel with $CHCl_3$/MeOH (93/7 to 9/1) gave **23** as a colorless amorphous (8.9 mg, 0.0273 mmol, 89% for four steps). Spectroscopic data were identified with reported compound.

*4.1.19. (−)-Brevisamide (**1**).* To a solution of **23** (8.9 mg, 0.0273 mmol) in CH_2Cl_2 (1.5 mL) was added PhI(OAc)$_2$ (19.0 mg, 0.0590 mmol) and TEMPO (1.9 mg, 0.012 mmol) at room temperature. After 3 h the reaction was quenched with saturated $Na_2S_2O_3$ aqueous at 0 °C, and the mixture was extracted twice with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification on silica gel column chromatography (95/5 $CHCl_3$/MeOH) gave brevisamide (**1**) as a yellow oil (7.8 mg, 0.0241 mmol, 88%). Spectroscopic data were identified with reported compound.

Acknowledgements

We are grateful to Mr. T. Shirai for significant contribution to the synthesis of **2**. This work was financially supported by KAKENHI (No. 2061102) and the Global COE Program for Chemistry Innovation, the University of Tokyo. T.K. is grateful for a SUNBOR Scholarship. The natural brevisamide was isolated from the cultures maintained under grants P01 ES 10594 (NIEHS, DHHS) and MARBIONC, Marine Biotechnology in North Carolina. J.L.C.W. acknowledges funding from NOAA-ECOHAB (MML-106390A) and NCDHHS (01515-04).

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20. Mouse lymphoid cells (P388) were seeded onto 96-well plates and then test solutions were added. Cells were incubated for 96 h at 37 °C in 5% CO_2 atmosphere. After incubation, MTT reagents were added and the cells were maintained in a CO_2 incubator for another 4 h. The plates were read at 490 nm using a microplate reader.