

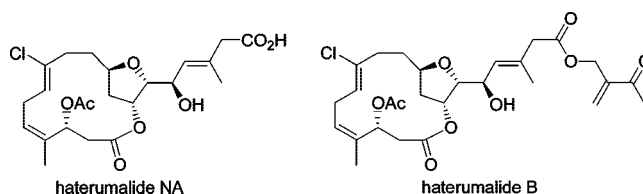
## Total Synthesis and Cytotoxicity of Haterumalides NA and B and Their Artificial Analogues

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The total synthesis of haterumalides NA and B, potent cytotoxic marine macrolides, was achieved by using *B*-alkyl Suzuki–Miyaura coupling and Nozaki–Hiyama–Kishi coupling as key steps. Compared to our first-generation approach for *ent*-haterumalide NA methyl ester, this second-generation synthesis yielded much more of the key intermediate. This synthesis established the relative stereochemistry of haterumalide B. Furthermore, the structure–cytotoxicity relationships of haterumalides were investigated. The combination of macrolide and side chain parts proved to be important to the cytotoxicity.

### Introduction

In 1999, haterumalide B (**1**) was isolated from the Okinawan ascidian *Lissoclinum* sp. by Ueda and Hu.<sup>1</sup> At the same time, haterumalides NA (**2**)–NE (**6**) were isolated from the Okinawan sponge *Iricinia* sp. by Uemura and co-workers.<sup>2</sup> Haterumalide NA (**2**) exhibited cytotoxicity against P388 cells with an IC<sub>50</sub> of 0.32 μg/mL, and moderate acute toxicity against mice with an LD<sub>50</sub> of 0.24 g/kg. Also, haterumalide B (**1**) completely inhibited the first cleavage of fertilized sea urchin eggs at a concentration of 0.01 μg/mL.<sup>1</sup> Oocydin A<sup>3a</sup> and haterumalide A<sup>3b</sup> were also isolated from the South American epiphyte *Serratia marcescens* and the soil bacterium *Serratia plymuthica*, respectively, and they were found to have the same gross

structure as haterumalide NA (**2**). In 2004, we isolated biselides A (**8**) and B (**9**) from the Okinawan ascidian *Didemnidae* sp. and determined their structures to be oxygenated analogues of haterumalides (Figure 1).<sup>4a</sup> The next year, we reported the isolation of three analogues, biselides C (**10**)–E (**12**), and compared the cytotoxicity of haterumalide NA (**2**), haterumalide NA methyl ester (**7**), and biselides A (**8**), B (**9**), and C (**10**).<sup>4b</sup> Among the tested cell lines, haterumalide NA (**2**), haterumalide NA methyl ester (**7**), and biselides A (**8**) and B (**9**) showed stronger cytotoxicity than did anticancer drug cisplatin against human breast cancer MDA-MB-231 and human nonsmall cell lung cancer NCI-H460.<sup>4b</sup> Interestingly, haterumalide NA (**2**) showed strong toxicity against brine shrimp, with an LD<sub>50</sub> of 0.6 μg/mL, while biselides A (**8**) and C (**10**) and haterumalide NA methyl ester (**7**) exhibited no toxicity against this animal, even at 50 μg/mL. In 2005, researchers at Fujisawa Pharmaceutical Company isolated an antimicrobial component FR177391, the enantiomer of haterumalide NA (**2**), from the soil bacterium *Serratia liquefaciens*.<sup>5a</sup> In addition, they identified its molecular target as protein phosphatase 2A (PP2A).<sup>5b–d</sup>

The unique structures of haterumalides and biselides, in conjunction with their potent biological activities, have made them attractive synthetic targets.<sup>6</sup> Several groups have reported approaches to synthesize the haterumalide NA (**2**). In 2003, Snider and Gu synthesized *ent*-haterumalide NA methyl ester (**7**).<sup>7a</sup> Their strategy involved a key fragment coupling at

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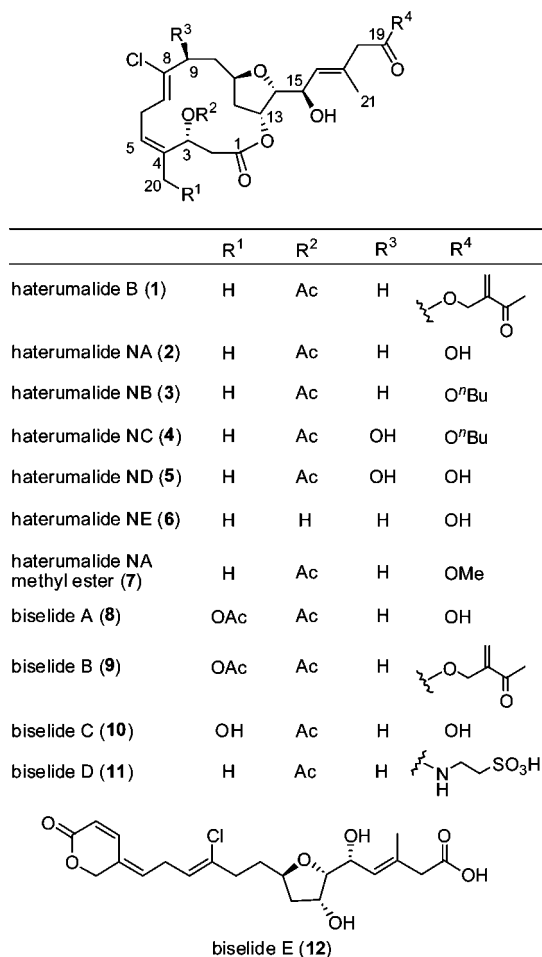
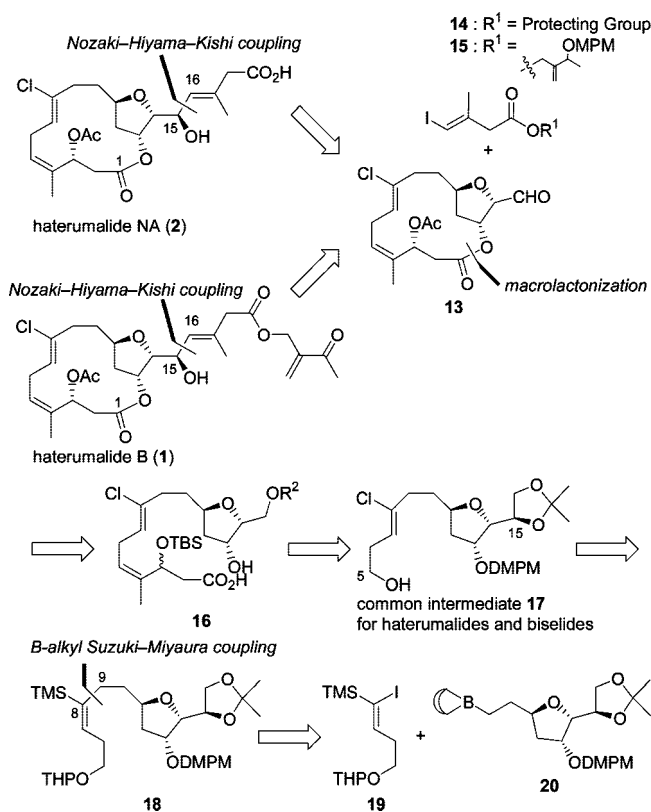


FIGURE 1. Structures of haterumalides and biselides.

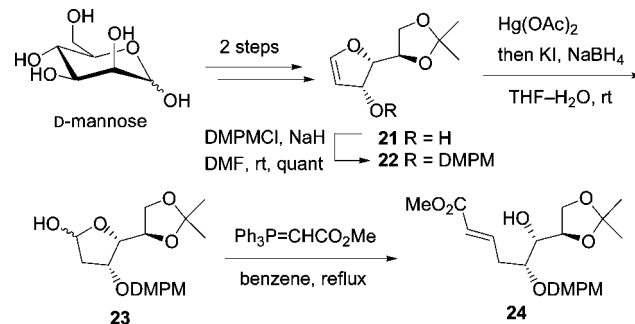
C-5–C-6 using a Stille reaction. Hoyer and Wang achieved the first total synthesis of haterumalide NA (2) itself.<sup>7b</sup> Their synthetic route involved a key intramolecular cyclization at C-6–C-7, based on the Kaneda reaction. Recently, Schomaker and Borhan synthesized haterumalides NA (2) and NC (4) by using chromium-mediated macrocyclization.<sup>7c</sup> Prior to those reports, we reported the first synthesis of *ent*-haterumalide NA methyl ester (7).<sup>8</sup> This synthesis revised the stereochemistry of haterumalide NA (2) and determined its absolute configuration. However, because our previous synthetic route included low-yield steps, we planned to develop an efficient second-generation method for synthesizing haterumalides, biselides, and their derivatives, which will provide a practical supply for further biological studies. The second-generation synthesis of haterumalide NA was preliminarily reported.<sup>9</sup>

We describe in detail the synthesis of haterumalides NA (2) and B (1) by using a convergent synthetic methodology with a *B*-alkyl Suzuki–Miyaura coupling.<sup>10</sup> Very recently, Roulland reported the total synthesis of haterumalide NA (2) using a similar cross-coupling strategy.<sup>7d</sup>

## SCHEME 1. Retrosynthetic Analyses of Haterumalides B (1) and NA (2)



## SCHEME 2. Synthesis of $\alpha,\beta$ -Unsaturated Ester 24



## Results and Discussion

Our retrosynthetic analyses of haterumalides NA (2) and B (1) are shown in Scheme 1. Our strategy involved a key fragment coupling between macrolactone 13 and the appropriately protected side chain unit 14 or 15 using Nozaki–Hiyama–Kishi coupling. We expected that macrolactonization of seco acid 16 provided macrolactone 13. Seco acid 16 might be obtained from a common intermediate 17 for haterumalides and biselides. The synthetic route to a common intermediate 17 for haterumalides and biselides involved the *B*-alkyl Suzuki–Miyaura coupling<sup>10</sup> between the alkenylsilane segment 19<sup>11</sup> and alkyborane 20, with subsequent stereoselective construction of a chloroolefin part from alkenylsilane 18.

The starting point for this work was the construction of the common intermediate 17 (Scheme 2). The known glycal 21 was

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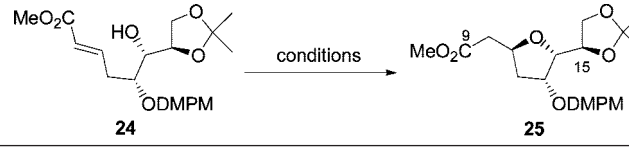
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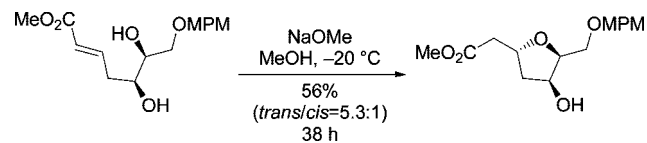
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**TABLE 1.** Study of Intramolecular Oxy-Michael Cyclization of  $\alpha,\beta$ -Unsaturated Ester **24**


entry	conditions	yield <sup>a</sup> (%)
1	NaOMe, MeOH, 0 °C → rt, 30 min	80% (trans:cis = 9:1)
2	Triton B, MeOH, 0 °C → rt, 15 min	87% (single diastereomer)

<sup>a</sup> Isolated yields calculated from dihydrofuran **22** (in 3 steps).

**SCHEME 3.** Intramolecular Oxy-Michael Cyclization in the Previous Work<sup>8</sup>

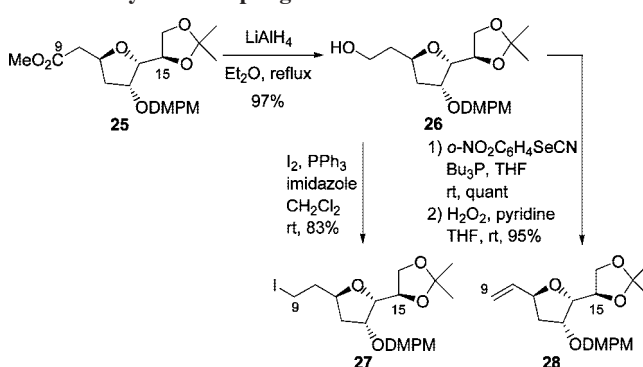
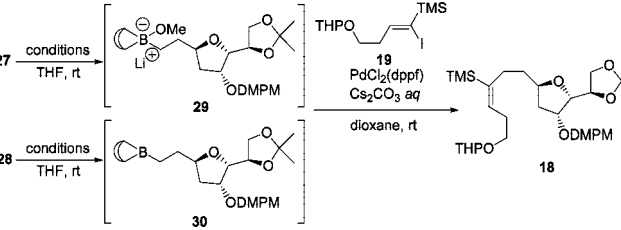
synthesized from commercially available D-mannose.<sup>12</sup> The hydroxy group of glycal **21** was protected to give the 3,4-dimethoxybenzyl (DMPM) ether **22**. The DMPM ether **22** was transformed into the hemiacetal **23** by the oxymercuration–reduction sequence.<sup>13</sup> The hemiacetal **23** was converted into  $\alpha,\beta$ -unsaturated ester **24** by the Wittig reaction.

Table 1 summarizes our attempts toward the intramolecular oxy-Michael cyclization of  $\alpha,\beta$ -unsaturated ester **24**. In our previous report,<sup>8</sup> similar intramolecular oxy-Michael cyclization was carried out by using NaOMe in MeOH, but the yield and stereoselectivity were not so high (56%, trans/cis = 5.3:1) (Scheme 3).

Treatment of  $\alpha,\beta$ -unsaturated ester **24** under the same conditions gave the desired tetrahydrofuran **25** (80% in 3 steps, trans/cis = 9:1) (entry 1). Next, oxy-Michael cyclization was performed with Triton B in MeOH (entry 2).<sup>14</sup> This cyclization improved the stereoselectivity and enhanced the reaction rate. The success of oxy-Michael cyclization of the  $\alpha,\beta$ -unsaturated ester **24** might be due to two factors: (1) steric hindrance of the acetonide group in **24** directed the addition and (2) Triton B was more effective in promoting oxy-Michael cyclization and the reaction was completed at lower temperature.

The LiAlH<sub>4</sub> reduction of **25** gave alcohol **26** (Scheme 4). Alcohol **26** was converted to iodide **27**, a precursor of the requisite boronate. On the other hand, the primary alcohol of **26** was converted to the corresponding selenoether. Upon treatment with H<sub>2</sub>O<sub>2</sub> and pyridine, the selenoether was oxidized and then eliminated to form the terminal olefin **28**.<sup>15</sup>

With iodide **27** and terminal olefin **28** in hand, we attempted *B*-alkyl Suzuki–Miyaura coupling, as depicted in Table 2. The alkylboronate **29** generated in situ from iodide **27**<sup>16</sup> participated in the cross-coupling reaction with alkenylsilane **19**<sup>11</sup> to provide the desired coupling compound **18** in 32% yield (entry 1). We next tried *B*-alkyl Suzuki–Miyaura coupling with terminal olefin **28**. Hydroboration of the terminal olefin **28** with 9-BBN-H/

**SCHEME 4.** Synthesis of the Precursors of *B*-Alkyl Suzuki–Miyaura Coupling**TABLE 2.** Study of *B*-Alkyl Suzuki–Miyaura Coupling


entry	precursor	reagent	yield (%)
1	<b>27</b>	<i>t</i> -BuLi, 9-BBN-OMe	32
2	<b>28</b>	9-BBN-H/THF	0
3	<b>28</b>	9-BBN-H dimer	quant

THF, followed by the addition of PdCl<sub>2</sub>(dppf) and alkenylsilane **19**, did not give the coupling compound **18** (entry 2). In this reaction, the hydroboration step was slow, and the intermediate borane decomposed gradually. The use of 9-BBN-H dimer instead of 9-BBN-H/THF gave the best result, maybe because of the concentrated conditions (entry 3).

We next tried to construct a chloroolefin part stereoselectively from the alkenylsilane **18**. In our previous report,<sup>8</sup> a chloroolefin part was stereoselectively constructed from an alkenylsilane **18** by a modification of Tamao's procedure.<sup>17</sup> We reported that the addition of a small amount of water was important for the reaction to be reproducible. In this study, we attempted the same conditions with the alkenylsilane **18** but obtained a low and irreproducible yield. Thus, preparation of the chloroolefin **31** required optimization (Table 3). Chlorination of the alkenylsilane **18** without water gave the desired chloroolefin **31** and recovery of the alkenylsilane **18**, but the yield was low (35%) (entry 1). We expected that a small amount of base would be neutralized in this reaction system. So we attempted the chlorination of the alkenylsilane **18** by NCS with a base. The reaction with CaCO<sub>3</sub> did not give chloroolefin **31** (entry 2). An attempt at chlorination with KF afforded the desired chloroolefin **31** in 25% yield (entry 3). However, the reaction at higher temperature did not afford the desired chloroolefin **31** (entry 4). Treatment of alkenylsilane **18** with NCS-K<sub>2</sub>CO<sub>3</sub> (1.0 equiv) did not further the reaction (entry 5). However, the chlorination was most efficiently effected by NCS (2.0 equiv) in DMF at 50 °C in the presence of K<sub>2</sub>CO<sub>3</sub> (0.5 equiv) as a base (entry 6). This modification increased the yield of the desired chloroolefin to 58%, reproducibly.

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(13) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Bull. Chem. Soc. Jpn.* **2002**, 75, 1927.

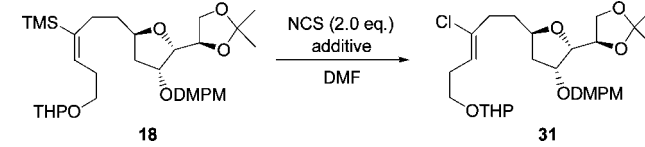
(14) (a) Ko, S.; Klein, L.; Pfaff, K.; Kishi, Y. *Tetrahedron Lett.* **1982**, 23, 4415. (b) The stereochemistry was determined by NOESY correlations.

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(16) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, 63, 7885.

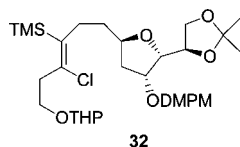
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TABLE 3. Study of Stereoselective Construction of Chloroolefin

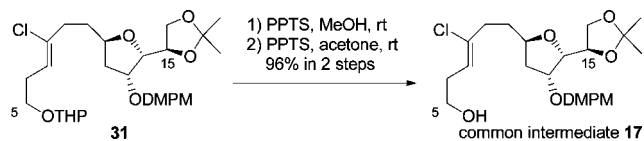


entry	additive	temp, °C	yield, %	recovery of 18, %
1	none	50	35	<40
2	CaCO <sub>3</sub> (2.0 equiv)	50		complex mixture
3	KF (1.0 equiv)	50	25	<42
4	KF (1.0 equiv)	100		complex mixture
5	K <sub>2</sub> CO <sub>3</sub> (1.0 equiv)	50		no reaction
6	K <sub>2</sub> CO <sub>3</sub> (0.5 equiv)	50	58	<29 <sup>a</sup>

<sup>a</sup> This compound contained byproduct such as **32**, which could not be isolated.



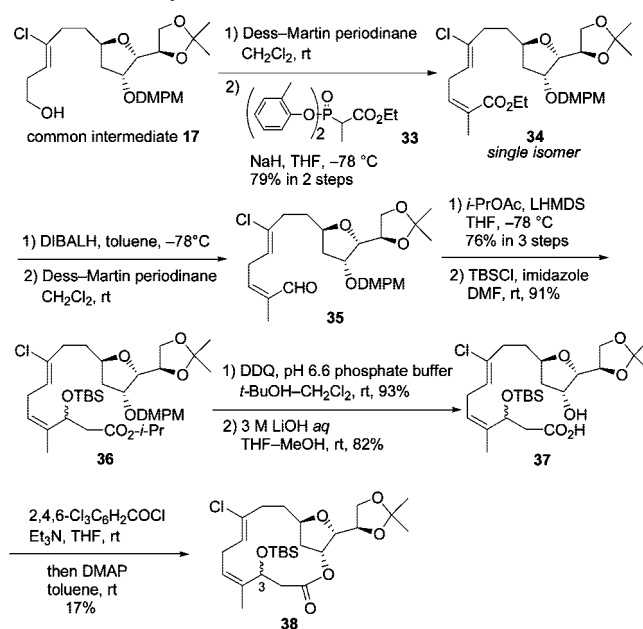
SCHEME 5. Synthesis of Common Intermediate 17 for Haterumalides and Biselides



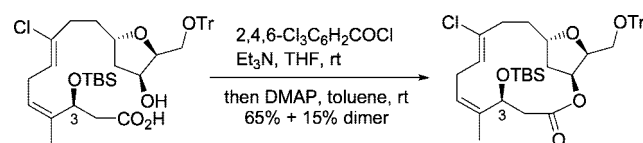
Treatment of chloroolefin **31** with PPTS provided a triol, the 1,2-diol group of which was reprotected as an acetonide group to afford the common intermediate **17** for haterumalides and biselides (Scheme 5). The overall sequence proceeded in 13 steps from D-mannose and in 32% overall yield, and thus the common intermediate **17** could be synthesized in multigram quantities.

**Total Synthesis of Haterumalide NA.** Next, we tried to synthesize haterumalide NA (**2**) from the common intermediate **17** (Scheme 6). The primary alcohol of the common intermediate **17** was oxidized to afford an aldehyde, which was converted into the *Z*-conjugated ester **34** by using Ando's modified Horner–Wadsworth–Emmons reaction.<sup>18</sup> Reduction of **34** with DIBALH gave an alcohol, which was converted to aldehyde **35**, a precursor of the aldol reaction. The aldol reaction between aldehyde **35** and isopropyl acetate by LHMDS provided a  $\beta$ -hydroxy ester as a diastereomeric mixture at C-3. The secondary hydroxy group of the  $\beta$ -hydroxy ester was protected as the TBS ether to give **36**. Removal of the DMPM group in **36** by using DDQ in CH<sub>2</sub>Cl<sub>2</sub>–*t*-BuOH–phosphate buffer (pH 6.6) and subsequent hydrolysis of the isopropyl ester group afforded seco acid **37**, a precursor of macrolactonization. The macrolactonization of seco acid **37** under Yamaguchi conditions<sup>19</sup> afforded the corresponding lactone **38**, but the yield was low (17%). An attempt at macrolactonization under Shiina conditions<sup>20</sup> did not afford the desired lactone **38**. On the other hand, Snider and Gu achieved satisfactory macrolactonization of a similar seco acid under Yamaguchi conditions (Scheme 7).<sup>7a</sup> This suggested that steric hindrance of the acetonide group

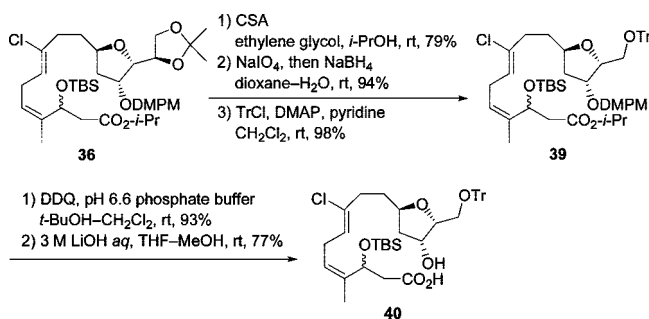
SCHEME 6. Synthesis of Lactone 38



SCHEME 7. Macrolactonization of a Seco Acid by Snider and Gu



SCHEME 8. Synthesis of Seco Acid 40



in our seco acid **37** interfered with macrolactonization. Therefore, we next tried to synthesize a seco acid without an acetonide group.

Removal of the acetonide group in **36** gave the diol, which was converted into a primary alcohol by NaIO<sub>4</sub> oxidation and reduction with NaBH<sub>4</sub> (Scheme 8). The primary hydroxy group was protected as a trityl group to afford compound **39**. Removal of the DMPM group in compound **39** gave an alcohol, and hydrolysis of the isopropyl ester afforded seco acid **40**.

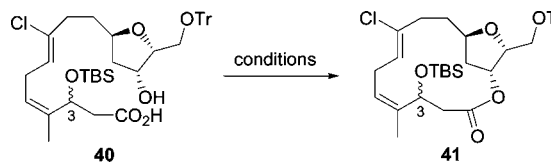
Next, we attempted the macrolactonization of **40**, as depicted in Table 4. The macrolactonization of **40** under Yamaguchi conditions afforded the desired lactone **41** (61%) and the dimer (6%) (entry 1). We next tried the macrolactonization under Shiina conditions. However, the reaction gave only undesired C-3 hydroxy isomer in 12% yield (entry 2).

The TBS group in lactone **41** was removed by TBAF, and the C-3 isomers **42a** and **42b** were separated by silica gel chromatography (Scheme 9). The undesired C-3 isomer **42a** was able to be converted to the desired C-3 isomer **42b** via

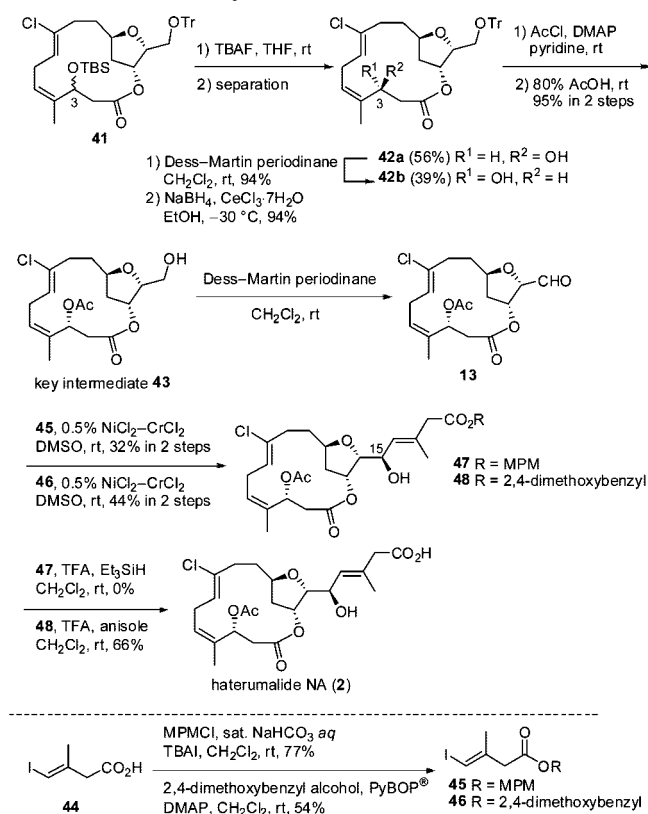
(18) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411.

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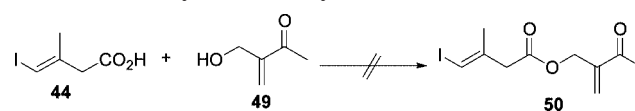
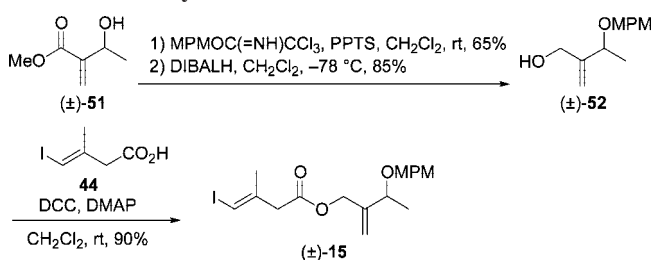
TABLE 4. Study of Macrolactonization of Seco Acid **40**


entry	conditions	results
1	2,4,6-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> COCl, Et <sub>3</sub> N, THF, rt then DMAP, toluene, rt	<b>41</b> : 61% dimer: 6%
2	2-methyl-6-nitrobenzoic anhydride, Et <sub>3</sub> N, DMAP, toluene, rt	<b>41</b> : 12% (only undesired C-3 hydroxy isomer) dimer: 11% recovered <b>40</b> : 14%

SCHEME 9. Total Synthesis of Haterumalide NA (**2**)

Dess–Martin oxidation<sup>21</sup> followed by Luche reduction.<sup>22</sup> To convert **42b** to **43**, we followed the reported procedure by Snider and Gu.<sup>7a</sup> Thus, acetylation of the hydroxy group at C-3 in **42b** and removal of the trityl group gave the primary alcohol **43**, which is the natural enantiomer of the key intermediate of our previous total synthesis of *ent*-haterumalide NA methyl ester (**7**).<sup>8,23</sup> The stereochemistry at C-3 was determined by comparison of the <sup>1</sup>H NMR spectra with those of our authentic sample.<sup>8</sup> To convert **43** into haterumalide NA (**2**), we followed our first-generation synthesis with modification by Hoye and Wang.<sup>7b</sup> The Nozaki–Hiyama–Kishi coupling reaction<sup>24</sup> of

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(22) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.  
(23) The alcohol **43** gave spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS) in full agreement with the authentic sample. The optical rotation of our sample **43** {[α]<sub>D</sub><sup>23</sup> –11.7 (c 0.18, CHCl<sub>3</sub>)} corresponded to the reported values (+10.7 for *ent*-**43**<sup>7a</sup> and –16.0 for **43**<sup>7b</sup>).  
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SCHEME 10. Synthetic Study of Ester **50**SCHEME 11. Synthesis of Iodide **15**

iodide **45**<sup>7b</sup> and aldehyde **13**, derived from **43** by Dess–Martin periodinane,<sup>21</sup> afforded the coupling product **47**. However, we could not remove the 4-methoxybenzyl (MPM) ester in **47** under reported conditions (TFA, Et<sub>3</sub>SiH).<sup>25</sup> Therefore, we next tried Nozaki–Hiyama–Kishi coupling with 2,4-dimethoxybenzyl ester **46** instead of the MPM ester **45**. The Nozaki–Hiyama–Kishi coupling with iodide **46**, prepared from **44**,<sup>8</sup> afforded haterumalide NA 2,4-dimethoxybenzyl ester **48**.<sup>26</sup> Removal of the 2,4-dimethoxybenzyl group with TFA and anisole gave haterumalide NA (**2**).<sup>27</sup> Synthetic haterumalide NA (**2**) gave spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS, and CD<sup>28</sup>) in full agreement with those of the natural one,<sup>2</sup> completing the total synthesis.

**Total Synthesis of Haterumalide B.** We next tried the synthesis of haterumalide B (**1**) from aldehyde **13**. To the best of our knowledge, there are few natural products with the 2-methylene-3-oxobutyl ester group and no total synthesis has been reported about these types of natural products. First we tried to synthesize the side chain unit of haterumalide B (**1**) for Nozaki–Hiyama–Kishi coupling. We attempted to prepare iodide **50** from carboxylic acid **44** and allylic alcohol **49**<sup>29</sup> by DCC–DMAP, Yamaguchi conditions, Shiina conditions, and (COCl)<sub>2</sub> (Scheme 10). However, the desired iodide **50** could not be obtained because it is unstable. Therefore, we next tried to synthesize iodide with a masked enone group.

The secondary hydroxy group in (±)-**51**<sup>30</sup> was protected as an MPM ether, and methyl ester was reduced by DIBALH to give allylic alcohol (±)-**52** (Scheme 11). Esterification between iodide **44** and allylic alcohol (±)-**52** by DCC–DMAP afforded the desired iodide (±)-**15**.

The Nozaki–Hiyama–Kishi coupling reaction of aldehyde **13** and iodide (±)-**15** afforded the coupling product **53** (48%, 5.5:1 ratio of **53**:15-*epi*-**53**) (Scheme 12). The newly generated C-15 stereochemistry of **53** has been determined by modified Mosher's method.<sup>31</sup> Removal of the MPM group and subsequent selective oxidation of C-22 allylic alcohol with MnO<sub>2</sub> afforded

(25) Hoye et al.<sup>7b</sup> and Roulland<sup>7d</sup> successfully cleaved under this condition.  
(26) Due to the small reaction scale of Nozaki–Hiyama–Kishi coupling, we could not isolate the minor isomer at C-15.

(27) Kobayashi et al. have reported removal of the 2,4-dimethoxybenzyl group in similar esters.<sup>5c</sup>

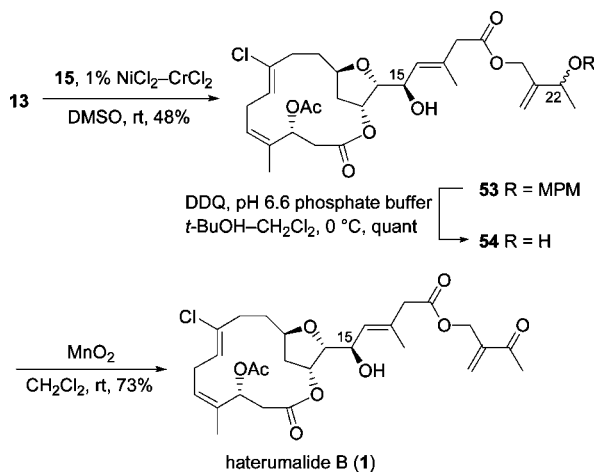
(28) Comparison of the CD spectra of synthetic and natural samples identified absolute configuration. The CD spectral data of the synthetic sample, CD (MeOH) λ<sub>ext</sub> 220 nm, Δε +0.12, was the same sign as the natural sample [CD (MeOH) λ<sub>ext</sub> 220 nm, Δε +0.10].

(29) İşeri, R.; Küsefoğlu, S. H. *J. Appl. Polym. Sci.* **2000**, *77*, 509.

(30) Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett.* **1996**, *37*, 5487.

(31) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) The detailed experimental procedures of MTPA esters of **53** are given in the Supporting Information.

## SCHEME 12. Total Synthesis of Haterumalide B (1)



haterumalide B (**1**), which is identical in all respects to the natural product.<sup>1</sup> Therefore, this synthesis established the relative stereochemistry of haterumalide B (**1**).<sup>32</sup>

**Synthesis of Artificial Analogues of Haterumalides.** To investigate the structure–cytotoxicity relationships of haterumalides, three analogues **55**, **56**, and **57** were synthesized (Figure 2).

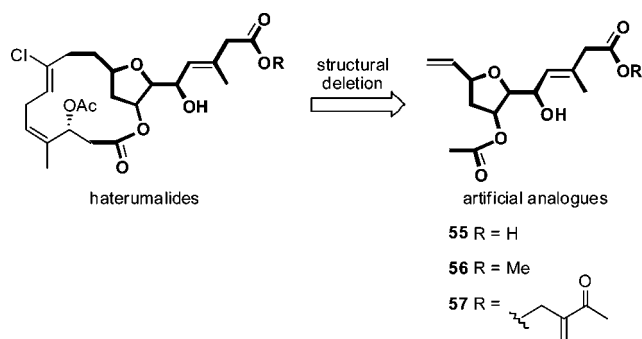


FIGURE 2. Artificial analogues of haterumalides.

These artificial analogues were prepared from synthetic intermediate **28** by a strategy similar to that used for haterumalides NA (**2**), NA methyl ester (**7**),<sup>8</sup> and B (**1**), respectively (Scheme 13). The DMPM group in **28** was removed by using DDQ to give a secondary alcohol, which was converted into acetate **58**. Acidic hydrolysis of **58** gave a diol. Oxidative cleavage of the diol group by NaIO<sub>4</sub> afforded aldehyde **59**. The Nozaki–Hiyama–Kishi coupling of aldehyde **59** and 2,4-dimethoxybenzyl ester **46** afforded the coupling product **61**. The 2,4-dimethoxybenzyl group in **61** was removed by using TFA and anisole to give the artificial analogue **55** of haterumalide NA. The artificial analogue **56** of haterumalide NA methyl ester was prepared from aldehyde **59** and iodide **60**<sup>8</sup> by Nozaki–Hiyama–Kishi coupling. We next tried to synthesize the artificial analogue **57** of haterumalide B. The Nozaki–Hiyama–Kishi coupling reaction of aldehyde **59** and iodide **15** afforded the coupling product **62**. The MPM group in **62** was removed by using DDQ to give an allylic alcohol **63**. Selective oxidation of

(32) The optical rotation of natural haterumalide B (**1**) was reported. However, the value of the optical rotation was too small [ $[\alpha]_D^{23} = -0.002$  (*c* 0.08, CHCl<sub>3</sub>)]<sup>1</sup> to determine the absolute stereochemistry. We measured the CD spectrum of synthetic **1**; however, the spectrum of the natural one was not reported.

## SCHEME 13. Synthesis of Artificial Analogues of Haterumalides

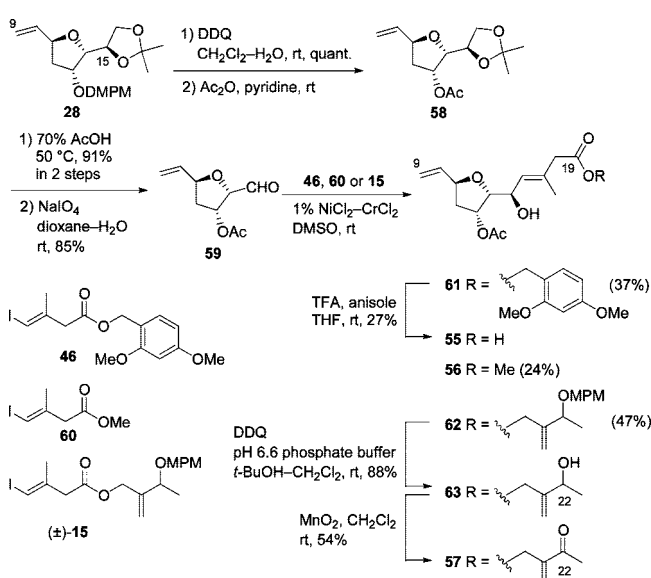


TABLE 5. Cytotoxicity Against HeLa S<sub>3</sub> Cells of Haterumalides and the Artificial Analogues

	IC <sub>50</sub> values, μg/mL
haterumalide NA ( <b>2</b> ) (natural)	0.019
haterumalide NA ( <b>2</b> ) (synthetic)	0.024
haterumalide NA methyl ester ( <b>7</b> )	0.023
haterumalide B ( <b>1</b> ) <sup>a</sup>	0.021
lactone part of haterumalides ( <b>43</b> )	93.2
artificial analogue of haterumalide NA ( <b>55</b> )	81.6
artificial analogue of haterumalide NA methyl ester ( <b>56</b> )	405
artificial analogue of haterumalide B ( <b>57</b> )	2.87

<sup>a</sup> A diastereomeric mixture {4:1 ratio of haterumalide B (**1**):15-*epi*-haterumalide B (**1**)} was used for the cytotoxicity assay.

C-22 allylic alcohol with MnO<sub>2</sub> afforded artificial analogue **57** of haterumalide B.

**Structure–Cytotoxicity Relationships of Haterumalides.** Table 5 summarizes the cytotoxicity of haterumalides NA (**2**), NA methyl ester (**7**), B (**1**), lactone part (synthetic intermediate) **43** of haterumalides, and artificial analogues **55**, **56**, and **57** of haterumalides against HeLa S<sub>3</sub> cells. The cytotoxic activity of synthetic haterumalide NA (**2**) against HeLa S<sub>3</sub> cells had the same IC<sub>50</sub> value as that of natural haterumalide NA (**2**). Haterumalide NA methyl ester (**7**) and haterumalide B (**1**) showed cytotoxicity with IC<sub>50</sub> of 0.023 and 0.021 μg/mL, respectively. From these results, the carboxylic acid group at the side chain of haterumalide NA (**2**) was shown to be unimportant for the strong cytotoxicity of haterumalide NA (**2**). The lactone part **43** of haterumalides showed a very weak cytotoxicity, indicating the importance of the side chain part to cytotoxicity. However, side chain analogues **55**, **56**, and **57** of haterumalides were much less cytotoxic than the corresponding haterumalides. These results showed that the combination of lactone and side chain parts is essential for the strong cytotoxicity of haterumalides. It is of worth noting that analogue **57** of haterumalide B was more cytotoxic than analogues **55** and **56** of haterumalide NA. These results indicated that the conjugated ketone moiety was somewhat responsible for the cytotoxicity.

## Conclusion

In conclusion, we have achieved the total synthesis of haterumalides NA (**2**) (1.3% overall yield in 33 steps) and B (**1**) (1.5% overall yield in 34 steps). From this synthetic work, we determined the relative stereochemistry of haterumalide B (**1**). Furthermore, we have investigated the structure–cytotoxicity relationships and revealed that the combination of lactone and side chain parts is important to the strong cytotoxicity of haterumalides. This strategy is being applied to the synthesis of biselides and probe molecules for searching target biomolecules. Further investigation into the structure–activity relationship and synthetic studies of biselides by using intermediate **17** are in progress.

## Experimental Section

**Allylic Alcohol (±)-52.** To a stirred solution of alcohol (±)-**51** (578 mg, 4.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added a solution of MPM 2,2,2-trichloroacetimidate (2.13 g, 7.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and PPTS (53 mg, 5 mol %) at 0 °C. The mixture was stirred at room temperature for 19 h, diluted with saturated aqueous NaHCO<sub>3</sub> (6 mL), and extracted with EtOAc. The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue oil was purified by column chromatography on silica gel (50 g, hexane–EtOAc 20:1) to give an MPM ether (721 mg, 65%) as a colorless oil: IR (film) 2976, 2952, 1716, 1612, 1514, 1290, 1248, 1097 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 1.4 Hz, 1H), 5.96 (dd, *J* = 1.4, 1.4 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 4.42 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 166.6, 159.0, 142.3, 130.4, 129.1 (2C), 124.3, 113.7 (2C), 72.9, 70.5, 55.3, 51.8, 22.0; HRMS (ESI) *m/z* 273.1111, calcd for C<sub>14</sub>H<sub>18</sub>NaO<sub>4</sub> [M + Na]<sup>+</sup> 273.1103.

To a stirred solution of the MPM ether (353 mg, 1.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added DIBALH (0.94 M solution in hexane, 3.8 mL, 3.57 mmol) at -78 °C. The mixture was stirred at the same temperature for 3 h, diluted with saturated aqueous Na/K tartrate (7.5 mL) at 0 °C, and filtrated through a pad of Celite. The aqueous mixture was extracted with EtOAc. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–EtOAc 5:1) to give allylic alcohol (±)-**52** (269 mg, 85%) as a colorless oil: IR (film) 3390, 2976, 2866, 1612, 1514, 1302, 1248, 1092, 1034, 912, 822 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.21 (dd, *J* = 3.0, 1.4 Hz, 1H), 5.11 (s, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.28 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.16 (dd, *J* = 13.8, 6.5 Hz, 1H), 4.09 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 2.17 (t, *J* = 5.7 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 159.0, 148.6, 130.2, 129.2 (2C), 113.8 (2C), 112.5, 77.0, 69.9, 63.1, 55.3, 20.3; HRMS (ESI) *m/z* 245.1155, calcd for C<sub>13</sub>H<sub>18</sub>NaO<sub>3</sub> [M + Na]<sup>+</sup> 245.1154.

**Iodo Ester (±)-15.** To a stirred solution of carboxylic acid **44** (120 mg, 530 μmol) and alcohol (±)-**52** (354 mg, 1.59 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.1 mL) were added DMAP (19.5 mg, 159 μmol) and DCC (220 mg, 1.06 mmol) at 0 °C. The mixture was stirred at room temperature for 21 h, diluted with saturated aqueous NH<sub>4</sub>Cl (6 mL), and extracted with EtOAc (3 × 6 mL). The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was purified by column chromatography on silica gel (18.8 g, hexane–EtOAc 20:1 → 10:1 → 5:1) to give iodo ester (±)-**15** (206 mg, 90%) as a colorless oil: IR (film) 2976, 2866, 1738, 1612, 1514, 1302, 1248, 1173, 1144, 1034, 918, 822 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.16 (q, *J* = 1.1 Hz, 1H), 5.23 (s, 1H), 5.20 (d, *J* = 1.4 Hz, 1H), 4.67 (s, 2H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.28 (d, *J* = 11.3,

1H), 4.01 (q, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.23 (d, *J* = 1.1 Hz, 2H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 169.4, 159.0, 144.4, 140.1, 130.4, 129.2 (2C), 114.3, 113.7 (2C), 79.8, 76.0, 69.9, 63.9, 55.3, 44.2, 24.1; HRMS (ESI) *m/z* 453.0543, calcd for C<sub>18</sub>H<sub>23</sub>INaO<sub>4</sub> [M + Na]<sup>+</sup> 453.0539.

**MPM Ether 53.** DMSO was degassed by freeze–thawing. To a stirred solution of aldehyde **13** (7.1 mg, 19.1 μmol) and iodide (±)-**15** (60.8 mg, 141 μmol) in DMSO (1.9 mL) was added CrCl<sub>2</sub> doped with 1% NiCl<sub>2</sub> (49.5 mg, CrCl<sub>2</sub>: 399 μmol, NiCl<sub>2</sub>: 3.82 μmol) at room temperature in a glovebox. The mixture was stirred at room temperature for 28 h, diluted with Et<sub>2</sub>O (10 mL) and H<sub>2</sub>O (3 mL), and extracted with Et<sub>2</sub>O (7 × 6 mL). The combined extracts were dried (MgSO<sub>4</sub>) and concentrated. The residual oil was purified by column chromatography on silica gel (1.6 g, hexane–EtOAc 2:1 → 1:1 → 1:2) to give MPM ether **53** (6.2 mg, 48%) as a colorless oil: IR (film) 3456, 2931, 1738, 1652, 1371, 1246, 1149, 1065, 1020, 821, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.77 (dd, *J* = 11.0, 5.0 Hz, 1H), 5.67 (dd, *J* = 10.0, 7.5 Hz, 1H), 5.44 (m, 1H), 5.33 (ddd, *J* = 6.4, 3.3, 3.3 Hz, 1H), 5.21 (s, 2H), 5.21 (m, 1H), 4.66 (s, 2H), 4.63 (m, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.04–3.90 (m, 3H), 3.80 (s, 3H), 3.54 (ddd, *J* = 17.8, 10.1, 7.7 Hz, 1H), 3.11 (br s, 2H), 2.80 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.76 (dd, *J* = 11.6, 4.7 Hz, 1H), 2.56–2.48 (m, 2H), 2.39 (m, 1H), 2.17 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.13 (m, 1H), 2.04 (s, 3H), 1.89 (s, 3H), 1.87 (s, 3H), 1.50–1.37 (m, 2H), 1.32 (d, *J* = 2.5 Hz, 1.5H), 1.31 (d, *J* = 2.5 Hz, 1.5H), a signal due to one proton (OH) was not observed; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.0, 169.5, 168.0, 159.1, 144.6 (0.5C), 144.5 (0.5C), 134.4, 133.2, 132.0, 130.5, 129.9, 129.5, 129.3 (0.5C), 129.3 (0.5C), 125.5, 114.3 (0.5C), 114.1 (0.5C), 113.8 (2C), 82.7, 76.1, 76.0, 75.8, 69.9 (0.5C), 69.8 (0.5C), 67.4, 66.4 (0.5C), 66.4 (0.5C), 63.6 (0.5C), 63.6 (0.5C), 55.3, 45.0, 38.0, 37.8, 34.8, 27.9, 26.7, 21.1, 20.5, 18.3, 17.6; HRMS (ESI) *m/z* 697.2759, calcd for C<sub>36</sub>H<sub>47</sub><sup>35</sup>ClNaO<sub>10</sub> [M + Na]<sup>+</sup> 697.2755.

**Allylic Alcohol 54.** To a stirred solution of MPM ether **53** (4.8 mg, 7.1 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.9 mL), *t*-BuOH (0.11 mL), and pH 6.6 phosphate buffer (0.11 mL) was added DDQ (2.3 mg, 10.1 μmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, and pH 6.6 phosphate buffer (0.11 mL) and DDQ (2.7 mg, 11.9 μmol) were added. The mixture was stirred at 0 °C for 2 h, and pH 6.6 phosphate buffer (0.11 mL) and DDQ (2.3 mg, 10.1 μmol) were added. The mixture was stirred at 0 °C for 2 h, and pH 6.6 phosphate buffer (0.11 mL) and DDQ (2.3 mg, 10.1 μmol) were added. The mixture was stirred at 0 °C for 15 h, diluted with saturated aqueous NaHCO<sub>3</sub> (2 mL), and extracted with EtOAc (3 × 4 mL). The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane–EtOAc 1:3 → 1:4) to give allylic alcohol **54** (3.9 mg, quant) as a colorless oil: IR (film) 3436, 2929, 1734, 1370, 1231, 1149, 1069, 1019, 757 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.77 (dd, *J* = 10.8, 5.1 Hz, 1H), 5.67 (dd, *J* = 10.1, 7.1 Hz, 1H), 5.45 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.33 (dd, *J* = 3.4, 3.4 Hz, 1H), 5.24 (s, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.15 (s, 1H), 4.73 (dd, *J* = 12.2, 12.2 Hz, 1H), 4.67–4.58 (m, 2H), 4.36 (dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 3.98–3.91 (m, 2H), 3.54 (ddd, *J* = 18.0, 10.0, 8.0 Hz, 1H), 3.09 (s, 2H), 2.82–2.75 (m, 2H), 2.56–2.49 (m, 2H), 2.37 (m, 1H), 2.19–2.11 (m, 2H), 2.05 (s, 3H), 1.89 (s, 3H), 1.86 (s, 3H), 1.51–1.39 (m, 2H), 1.33 (d, *J* = 6.5 Hz, 3H), signals due to two protons (OH) were not observed; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 170.9, 169.6, 168.0, 147.1 (0.5C), 147.0 (0.5C), 134.4 (0.5C), 134.4 (0.5C), 133.1, 132.0, 129.8, 129.5 (0.5C), 129.5 (0.5C), 125.6, 113.9 (0.5C), 113.7 (0.5C), 82.7 (0.5C), 82.7 (0.5C), 75.7 (0.5C), 75.7 (0.5C), 68.8, 68.7, 67.4, 66.3 (0.5C), 66.2 (0.5C), 64.8 (0.5C), 64.8 (0.5C), 45.1, 38.0, 37.8, 34.8, 27.9, 26.7, 21.9, 21.1, 18.3, 17.6; HRMS (ESI) *m/z* 577.2177, calcd for C<sub>28</sub>H<sub>39</sub><sup>35</sup>ClNaO<sub>9</sub> [M + Na]<sup>+</sup> 577.2180.

**Haterumalide B (1).** To a stirred solution of allylic alcohol **54** (3.0 mg, 5.4 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.55 mL) was added MnO<sub>2</sub> (20.0

mg, 230  $\mu$ mol) at 0 °C. The mixture was stirred at room temperature for 11 h, and MnO<sub>2</sub> (9.4 mg, 108  $\mu$ mol) was added. The mixture was stirred at room temperature for 6.5 h and filtrated through a pad of Celite. The filtrate was concentrated, and the residual oil was purified by column chromatography on silica gel (0.6 g, hexane–EtOAc 1:1 → 1:2) to give haterumalide B (**1**) (2.2 mg, 73%) as a colorless oil. This sample contained a small amount of byproduct, maybe the C-15 epimer. An attempt to separate this sample by HPLC (Develosil ODS-HG-5 250 × 20 mm, flow rate 5 mL/min; detection, UV 215 nm; solvent 63% MeOH) resulted in the decomposition of product: CD (MeOH)  $\lambda_{\text{ext}}$  218 nm,  $\Delta\epsilon$  +0.31; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  6.19 (s, 1H), 6.03 (t,  $J$  = 1.5 Hz, 1H), 5.78 (dd,  $J$  = 11.1, 4.8 Hz, 1H), 5.68 (m, 1H), 5.46 (dd,  $J$  = 8.3, 1.1 Hz, 1H), 5.34 (t,  $J$  = 3.4 Hz, 1H), 5.21 (m, 1H), 4.81 (br s, 2H), 4.61 (t,  $J$  = 8.1 Hz, 1H), 3.96 (m, 1H), 3.96 (dd,  $J$  = 8.1, 3.8 Hz, 1H), 3.54 (m, 1H), 3.11 (br s, 2H), 2.80 (dd,  $J$  = 11.3, 11.3 Hz, 1H), 2.77 (dd,  $J$  = 11.3, 4.8 Hz, 1H), 2.56–2.49 (m, 2H), 2.38 (m, 1H), 2.37 (s, 3H), 2.18 (dd,  $J$  = 12.7, 5.5 Hz, 1H), 2.13 (dd,  $J$  = 13.0, 3.0 Hz, 1H), 2.05 (s, 3H), 1.89 (br s, 3H), 1.86 (d,  $J$  = 1.3 Hz, 3H), 1.48 (ddd,  $J$  = 12.5, 12.5, 3.2 Hz, 1H), 1.41 (m, 1H), a signal due to one proton (OH) was not observed; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  198.1, 170.7, 169.5, 168.0, 143.2, 134.3, 133.2, 132.0, 129.8, 129.6, 126.9, 125.6, 82.7, 76.5, 75.8, 67.4, 66.4, 62.3, 44.9, 38.0, 37.8, 34.8, 28.0, 26.7, 25.9, 21.1, 18.3,

17.4; HRMS (ESI)  $m/z$  575.2024, calcd for C<sub>28</sub>H<sub>37</sub><sup>35</sup>ClNaO<sub>9</sub> [M + Na]<sup>+</sup> 575.2024.

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**Supporting Information Available:** Experimental procedures and copies of the <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **2**, **13**, **17–18**, **22–26**, **28**, **31**, **34–36**, **39–43**, **46**, **48**, **55–59**, and **61–63**, and copies of the <sup>1</sup>H and <sup>13</sup>C NMR spectra for **1**, **15**, and **52–54**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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