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Second-Generation Total Synthesis of Haterumalide NA Using *B*-Alkyl Suzuki–Miyaura Coupling

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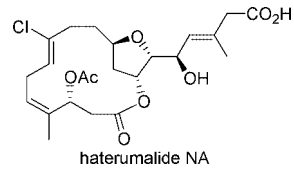
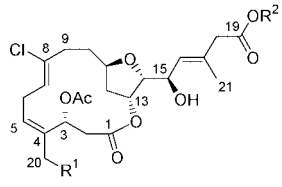
ABSTRACT



haterumalide NA

Second-generation total synthesis of haterumalide NA, a potent cytotoxic marine macrolide, was achieved by using *B*-alkyl Suzuki–Miyaura coupling and Nozaki–Hiyama–Kishi coupling as key steps (1.2% in 33 steps). Compared to our first-generation approach, the second-generation synthesis is much improved in the yield of key intermediate.

Haterumalide NA (**1**) is a macrolide isolated from the Okinawan sponge *Iricinia* sp. by Uemura and co-workers (Figure 1).[1] Haterumalide NA (**1**) exhibits cytotoxicity against P388 cells and moderate acute toxicity against mice. On the other hand, we isolated biselides A–E, which are oxygenated analogues of haterumalides, from the Okinawan ascidian Didemnidae sp.[2a,b] We compared the cytotoxicity of haterumalide NA (**1**), haterumalide NA methyl ester (**2**), biselides A (**3**), B (**4**), and C (**5**), and found that haterumalide NA (**1**), haterumalide NA methyl ester (**2**), biselides A (**3**) and B (**4**) showed stronger cytotoxicity than did anticancer drug cisplatin against human breast cancer MDA-MB-231 and human non-small cell lung cancer NCI-H460.[2b] Interestingly, haterumalide NA (**1**) showed strong toxicity against brine shrimp, with an LD_{50} of 0.6 μg/mL, while haterumalide NA methyl ester (**2**) and biselide A (**3**) are less toxic. These results encouraged us to search for novel anticancer drugs based on these unique lead compounds.



	R^1	R^2
haterumalide NA (**1**)	H	H
haterumalide NA methyl ester (**2**)	H	Me
biselide A (**3**)	OAc	H
biselide B (**4**)	OAc	
biselide C (**5**)	OH	H

Figure 1. Structures of haterumalides and biselides.

The unique structures of haterumalides and biselides, along with their potent biological activity, have made them attractive targets for synthesis.[3] In 2003, we reported the first synthesis of *ent*-haterumalide NA methyl ester (**2**).[4] This synthesis revised the stereochemistry of haterumalide NA

(1) Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309.

(2) (a) Teruya, T.; Shimogawa, H.; Suenaga, K.; Kigoshi, H. *Chem. Lett.* **2004**, *33*, 1184. (b) Teruya, T.; Suenaga, K.; Maruyama, S.; Kurotaki, M.; Kigoshi, H. *Tetrahedron* **2005**, *61*, 6561.

(3) Kigoshi, H.; Hayakawa, I. *Chem. Rec.* **2007**, *7*, 254.

(4) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957.

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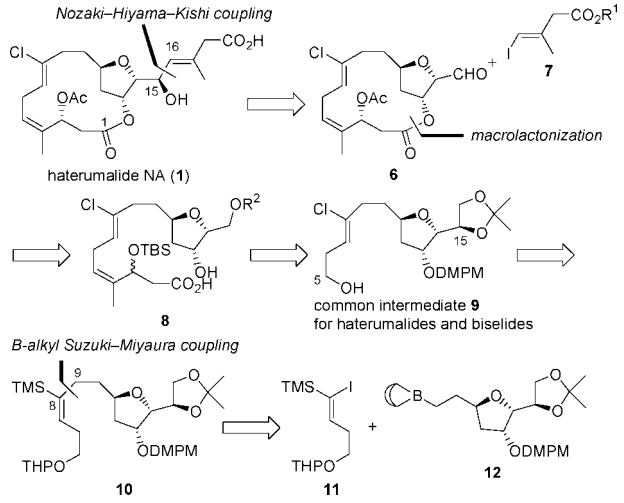
(**1**) and determined its absolute configulation. Snider et al.[5a] and Hoye et al.[5b] synthesized *ent*-haterumalide NA methyl ester (**2**) and haterumalide NA (**1**) itself, respectively. Because our previous route included low-yield steps, we planned to develop an efficient method for the second-generation synthesis of haterumalides, biselides, and their derivatives, which will provide a practical supply for further biological studies.

Our retrosynthetic analysis of haterumalide NA (**1**) is shown in Scheme 1. Haterumalide NA (**1**) can be logically

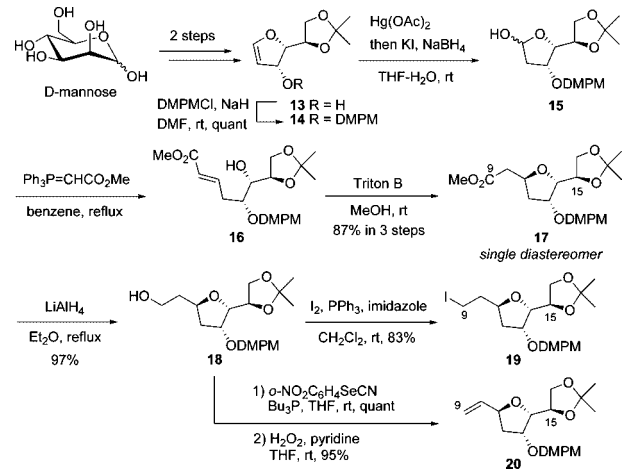
Scheme 1. Retrosynthetic Analysis of Haterumalide NA (**1**)



divided into the macrolactone **6** and the appropriately protected side-chain unit **7**. The macrolactone **6** can be established by the lactonization of the seco acid **8**. Seco acid **8** can be synthesized from a common intermediate **9** for haterumalides and biselides. We planned the practical synthesis of the common intermediate **9** by *B*-alkyl Suzuki–Miyaura coupling[6] between the alkenylsilane segment **11**[7] and alkylborane **12** and subsequent stereoselective construction of a chloroolefin part from alkenylsilane **10**.

Synthesis of the common intermediate **9** started from the known glycal **13** (Scheme 2).[8] The hydroxyl group of **13** was protected as the DMPM ether **14**. The DMPM ether **14** was converted to hemiacetal **15** by the oxymercuration–reduction sequence.[9] The Wittig reaction of hemiacetal **15** afforded the α,β-unsaturated ester **16**. We next tried stereoselective construction of the tetrahydrofuran part by using intramolecular oxy-Michael cyclization. In our previous reports,[4] similar intramolecular oxy-Michael cyclization was

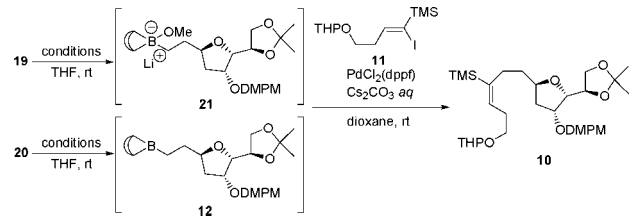
Scheme 2. Synthesis of the Precursor of *B*-Alkyl Suzuki–Miyaura Coupling



carried out by using NaOMe in MeOH, but the yield and stereoselectivity were not so high (56%, *trans*/*cis* = 5.3:1). In this work, the intramolecular oxy-Michael cyclization of **16** was attempted by using Triton B in MeOH to provide tetrahydrofuran **17** as the sole product.[10] This cyclization improved the stereoselectivity and enhanced the reaction rate. Reduction of methyl ester **17** by $LiAlH_4$ gave alcohol **18**. Alcohol **18** was converted to iodide **19**, a precursor of the requisite boranate. On the other hand, alcohol **18** was converted to the terminal olefin **20** via a seleno ether.[11]

With iodide **19** and terminal olefin **20** in hand, we attempted *B*-alkyl Suzuki–Miyaura coupling,[6] as depicted in Table 1. Boranate **21**, which was prepared from **19** by

Table 1. Study of *B*-Alkyl Suzuki–Miyaura Coupling



entry	precursor	reagent	yield (%)
1	**19**	*t*-BuLi, 9-BBN-OMe	32
2	**20**	9-BBN	-
3	**20**	9-BBN dimer	quant

lithiation and transmetalation,[12] participated in the cross-coupling reaction with alkenylsilane **11**[7] to provide desired coupling compound **10**, but the yield was low (32%) (entry

(5) (a) Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385. (b) Hoye and Wang first achieved the total synthesis of haterumalide NA (**1**) itself. Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950.

(6) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(7) Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* **2002**, *67*, 6082.

(8) Ireland, R.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. *J. Org. Chem.* **1979**, *45*, 48.

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

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

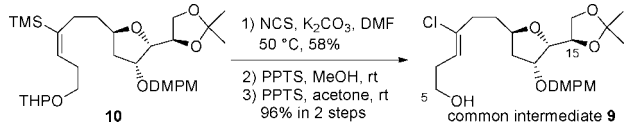
(11) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

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

1). We next investigated *B*-alkyl Suzuki–Miyaura coupling[6] with **20** and **11**. Although hydroboration of the terminal olefin **20** with 9-BBN was followed by the addition of $PdCl_2$(dppf) and alkenylsilane **11**,[7] the desired compound **10** could not be obtained (entry 2). However, the use of 9-BBN dimer instead of 9-BBN gave the best result: a quantitative yield of **10** maybe due to the concentrated conditions (entry 3).

We next tried to stereoselectively construct a chloroolefin part from alkenylsilane **10** (Scheme 3). In our previous

Scheme 3. Synthesis of Common Intermediate **9** of Haterumalides and Biselides

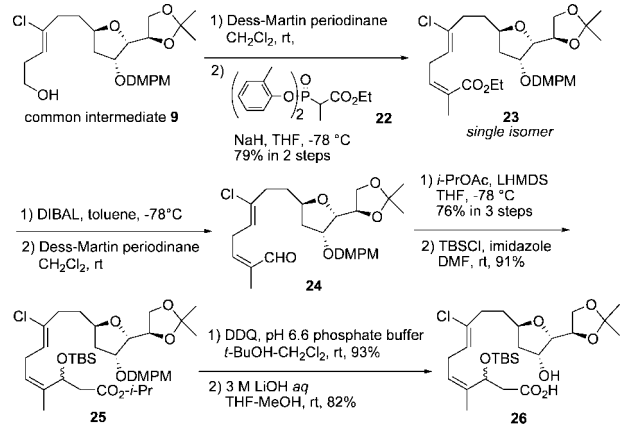


report,[4] a chloroolefin part was stereoselectively constructed from an alkenylsilane by a modification of Tamao's procedure.[13] We reported that the addition of a catalytic amount of water was important for the reaction to be reproducible. In this study, we attempted this reaction condition to alkenylsilane **10** but achieved a low and irreproducible yield, thus prompting us to reexamine the reaction conditions. Extensive examination of this reaction led us to find satisfactory conditions, i.e., NCS (2.0 equiv) in DMF at 50 °C in the presence of K_2CO_3 (0.5 equiv) as a base.[14] This modification increased the yield of the desired chloroolefin to 58% reproducibly.[15] Treatment of chloroolefin under acidic conditions gave a triol, and the resulting 1,2-diol group was reprotected as an acetonide group to afford the common intermediate **9** for haterumalides and biselides. The overall sequence proceeded in 13 steps from D-mannose and in 32% overall yield, and thus, the common intermediate **9** could be synthesized in multigram quantities.

Next, we tried to synthesize haterumalide NA (**1**) from the common intermediate **9** (Scheme 4). Oxidation of **9** by Dess–Martin periodinane afforded a labile aldehyde, which was converted into the *Z*-conjugated ester **23** by using Ando's modified Horner–Wadsworth–Emmons reaction.[16] The DIBAL reduction of **23** gave an allylic alcohol, which was oxidized to the conjugated aldehyde **24**. The aldol reaction of **24** with isopropyl acetate provided a β-hydroxy ester as a diastereomeric mixture of the hydroxyl group at C-3. The resulting secondary hydroxyl group was protected as a TBS ether to afford compound **25**. The DMPM group in **25** was removed, and hydrolysis of the isopropyl ester afforded seco acid **26**, a precursor of the macrolactonization.

Thus, the precursor for the macrolactonization was in hand. However, attempts to macrolactonize seco acid **26** to

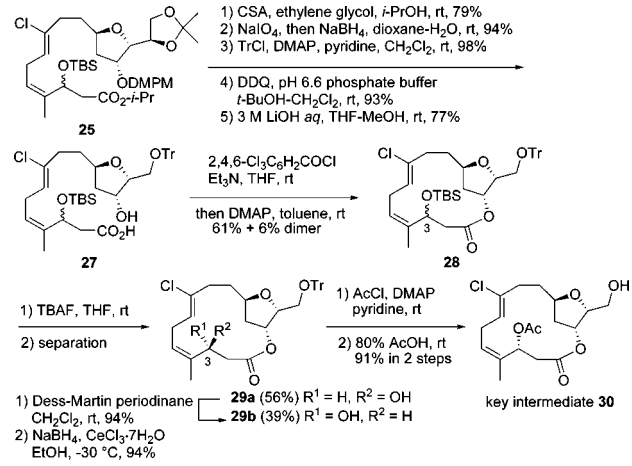
Scheme 4. Synthesis of Seco Acid **26**



macrolactone produced low yields (17%) under the Yamaguchi conditions.[17] On the other hand, Snider and Gu achieved satisfactory macrolactonization of a similar seco acid under the same condition.[5a] This suggested that steric hindrance of the acetonide group in our seco acid **26** interfered with macrolactonization. Therefore, we next tried macrolactonization using seco acid without an acetonide group.

The acetonide group in **25** was removed by using CSA to give a diol (Scheme 5). Oxidative cleavage of the diol by

Scheme 5. Synthesis of Key Intermediate **30**



$NaIO_4$ followed by reductive workup with $NaBH_4$ afforded an alcohol. The primary hydroxyl group was protected as a trityl group, and the DMPM group was removed. Hydrolysis of the isopropyl ester afforded seco acid **27**. The macrolactonization of **27** was accomplished by the Yamaguchi conditions[17] to give the desired lactone **28** along with the dimer (6%).[18] After the TBS group in **28** was removed by TBAF, the C-3 isomers **29a** and **29b** were separated by silica

(13) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.

(14) Addition of KF showed little improvement, and addition of $CaCO_3$ had no effect in this case.

(15) We could not recover alkenylsilane **10** under the previous conditions.

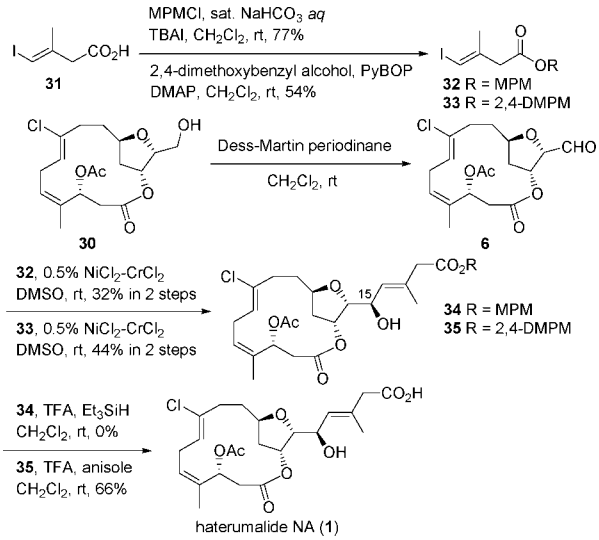
(16) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411.

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

gel chromatography. The undesired isomer **29a** was transformed into the desired isomer **29b** by oxidation and Luche reduction.[19] To convert **29b** to **30**, we followed the procedure reported by Snider and Gu.[5a] Acetylation of the hydroxyl group at C-3 and removal of the trityl group gave alcohol **30**,[20] which is the enantiomer of the key intermediate of our previous total synthesis of *ent*-haterumalide NA methyl ester (**2**).[4]

To convert **30** into haterumalide NA (**1**), we followed our first-generation synthesis with modification by Hoye (Scheme 6).[4,5b] Oxidation with Dess–Martin periodinane and Nozaki–Hiyama–Kishi coupling[21] with iodide **32**, prepared from **31**,[4] afforded haterumalide NA MPM ester (**34**). However, the MPM ester in **34** could not be successfully cleaved under reported conditions (TFA, Et_3SiH).[5b] We next tried the total synthesis via 2,4-dimethoxybenzyl ester **35**. Nozaki–Hiyama–Kishi coupling[21] with 2,4-dimethoxybenzyl **33** afforded the coupling product **35**.[22] The 2,4-dimethoxybenzyl ester in **35** was cleaved with TFA and anisole to afford haterumalide NA (**1**).[23] Synthetic haterumalide NA (**1**) gave spectral data (^{1}H NMR, ^{13}C NMR, HRMS, and CD[24]) in full agreement with those of the natural one,[1] completing the total synthesis.

Scheme 6. Total Synthesis of Haterumalide NA (**1**)



In conclusion, we have achieved the second-generation total synthesis of haterumalide NA (**1**). Practical synthesis of the common intermediate **9** for haterumalides and biselides has been achieved on the basis of *B*-alkyl Suzuki–Miyaura coupling[6] as a key step in multigram quantities. Compared to our first-generation approach,[4] which required 25 steps (longest linear sequence) and proceeded in 0.22% overall yield, the second-generation synthesis is much improved in the yield of key intermediate. Also, we achieved total synthesis of haterumalide NA (**1**) itself (1.2% in 33 steps) by using Nozaki–Hiyama–Kishi coupling[21] with a modification of our first-generation procedure. This strategy is now being applied to the synthesis of other haterumalides, biselides, and their derivatives, and further structure−activity relationship studies are in progress.

Acknowledgment. We thank Nippon Kayaku Co., Ltd., for its financial support. This work was supported in part by Grants-in-Aid for Young Scientists (B), Scientific Research on Priority Area "Creation of Biologically Functional Molecules"; and by the 21st COE program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We would like to thank Professors Akira Sekiguchi, Tatsuya Nabeshima, Masaaki Ichinohe, and Shigehisa Akine (University of Tsukuba) for APCI mass analysis and CD spectrum analysis.

Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Another macrolactonization, the Shiina conditions, gave only undesired C-3 hydroxyl isomer (12%), see: Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.

(19) Gemal, A. L.; Luche, J-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(20) The alcohol **30** gave spectral data (^{1}H NMR, ^{13}C NMR and HRMS) in full agreement with the authentic sample. The optical rotation of our sample **30** corresponded to the reported values (−11.7 compared with +10.7 for *ent*-**30**[5a] and −16.0 for **30**[5b]).

(21) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(22) Due to the small reaction scale of Nozaki–Hiyama–Kishi coupling, we could not isolate the minor isomer at C-15.

(23) Kobayashi et al. have reported removal of the 2,4-dimethoxybenzyl group in similar esters. Kobayashi, M.; Sato, K.; Yoshimura, S.; Yamaoka, M.; Takase, S.; Ohkubo, M.; Fujii, T.; Nakajima, H. *J. Antibiot.* **2005**, *58*, 648.

(24) Comparison of the CD spectra of synthetic and natural samples identified absolute configuration. The CD spectral data of synthetic sample, CD (MeOH) λ_{ext} 220 nm, $\Delta\epsilon$ +0.12, was the same sign as natural sample [CD (MeOH) λ_{ext} 220 nm, $\Delta\epsilon$ +0.10].