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Enantioselective Synthesis of 15-*epi*-Haterumalide NA Methyl Ester and Revised Structure of Haterumalide NA

Hideo Kigoshi,* Masaki Kita, Seiji Ogawa, Masahiro Itoh, and Daisuke Uemura

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan, and Research Center for Materials Science and Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

kigoshi@chem.tsukuba.ac.jp

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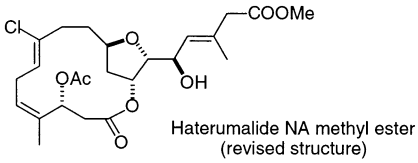
ABSTRACT



The enantioselective synthesis of the enantiomer of the haterumalide NA methyl ester, a cytotoxic macrolide from an Okinawan sponge, was achieved from the threitol derivative in 26 steps. The key steps are the stereoselective construction of a chloroolefin unit and the intramolecular Reformatsky-type reaction. This synthesis revised the absolute stereochemistry of haterumalide NA.

Haterumalide NA is a macrolide isolated from the Okinawan sponge *Ircinia* sp. This compound exhibited a cytotoxicity against P388 cells with an IC_{50} of 0.32 μg/mL.[1] The gross structure and stereochemistry were elucidated by the spectroscopic analysis and the modified Mosher's method as structural formula **1** (R = H). The structural features of this compound are a 14-membered macrolide involving a *trans*-disubstituted tetrahydrofuran ring, a *Z*-chloroolefin, and a β,γ-unsaturated acid moiety. The structurally related haterumalide B[2] and oocydin A[3] were isolated from an Okinawan ascidian and a South American epiphyte, respectively, and their stereostructures have not been fully established. It is noteworthy that haterumalide NA was recently isolated from a soil bacterium.[4] We describe herein the enantioselective synthesis of the *ent*-haterumalide NA methyl ester, which revises the initially assigned stereostructure.

The haterumalide NA methyl ester (**1**: R = Me) can be logically divided into the macrolide unit **3** and the side chain unit **2** (Scheme 1). The side chain unit **2** can be easily prepared from the corresponding carboxylic acid **30** (see Scheme 4).[5] The macrocyclic structure of **3** can be established by lactonization of the seco acid **5** or by the intramolecular Reformatsky-type reaction of the bromo ester derivative **4**. These precursors, **4** and **5**, can be synthesized from a common intermediate **6**, which can be prepared from the tetrahydrofuran unit **8** by a coupling reaction with **7**.

Scheme 2 summarizes the synthesis of the tetrahydrofuran unit **8**. The mono-MPM ether **9** was synthesized from commercially available (+)-2,3-*O*-isopropylidene-L-threitol.[6] After transformation into the corresponding iodide, C1 homologation was effected by using the FAMSO[7] carbanion

* Address correspondence to this author at the University of Tsukuba.

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

(2) Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305.

(3) Strobel, G.; Li, J.-Y.; Sugawara, F.; Koshino, H.; Harper, J.; Hess, W. M. *Microbiology* **1999,** *145*, 3557.

(4) Thaning, C.; Welch, C. J.; Borowicz, J. J.; Hedman, R.; Gerhardson, B. *Soil Biol. Biochem.* **2001**, *33*, 1817.

(5) Thibonnet, J.; Launay, V.; Abarbri, M.; Duchene, A.; Parrain, J.-L. *Tetrahedron Lett.* **1998**, *39*, 4277. We synthesized **30** from 3-butyn-1-ol in 2 steps: (1) Cp_2ZrCl_2, Me_3Al then I_2 and (2) Jones oxidation.

(6) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033.

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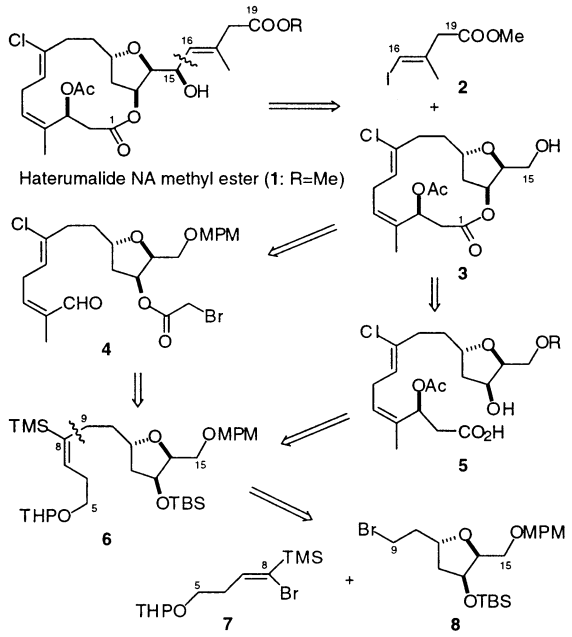
Scheme 1. Retrosynthetic Analysis of Haterumalide NA Methyl Ester

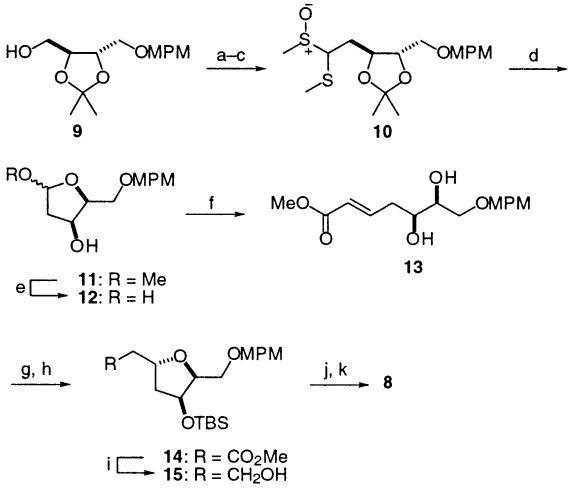


to afford sulfoxide **10** (81%). Sequential acidic methanolysis[8] and hydrolysis afforded the hemiacetal **12** in 57% yield. Wittig reaction of **12** and cyclization provided the 5.3:1 diastereomeric mixture of tetrahydrofurans, which could be separated after silylation to afford the desired *trans*-tetrahydrofuran **14** (70%) and the *cis*-isomer. The latter could be isomerized into the 1:1 mixture (isolation yield of **14**: 42%).[9] The desired *trans*-tetrahydrofuran **14** was quantitatively converted into the bromide **8** in three steps.

3-Butyn-1-ol (**16**) was transformed into the *E*-alkenylsilane **18** (67%) following a reported procedure[10] (Scheme 3). The *E*-alkenylsilane **18** was photochemically isomerized to the *Z*-isomer **7** in 99% yield. The coupling reaction between the tetrahydrofuran unit **8** and the carbanion generated from the *Z*-alkenylsilane **7** and *sec*-butyllithium was accomplished to give compound **6** in 68% yield.

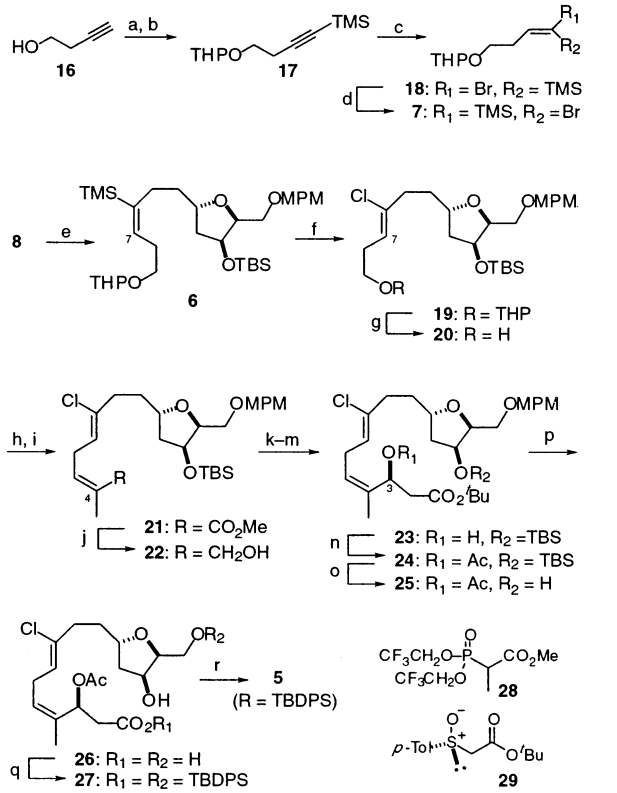
There are only a few published procedures for the stereoselective preparation of chloroolefins. We modified the

Scheme 2. Synthesis of *trans*-2,5-Dialkyl Tetrahydrofuran Unit **8**[a]



[a] Reagents and conditions: (a) *p*-TsCl, pyridine. (b) NaI, $CaCO_3$, acetone (93%, 2 steps). (c) FAMSO, *n*-BuLi, THF−hexanes (87%). (d) concentrated HCl, MeOH (8:92) (58%). (e) 1 M HCl aq, THF (1:1) (99%). (f) $Ph_3P{=}CHCO_2Me$, MeCN. (g) NaOMe, MeOH. (h) TBSCl, imidazole (70%, 3 steps). (i) $LiAlH_4$, THF (100%). (j) *p*-TsCl, pyridine. (k) LiBr, DMF (100%, 2 steps).

Scheme 3. Synthesis of Seco Acid **5**[a]



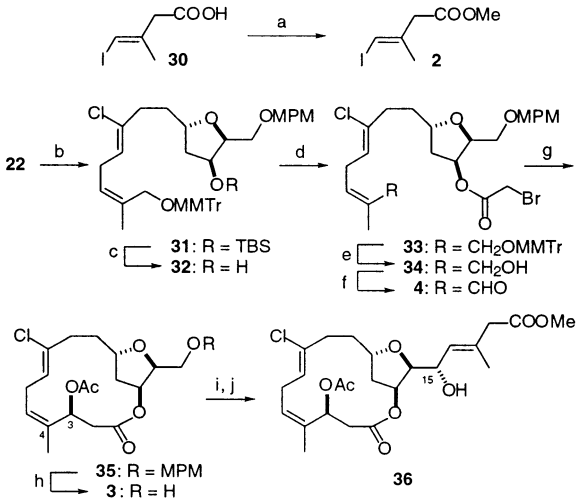
[a] Reagents and conditions: (a) DHP, *p*-TsOH (93%). (b) TMSCl, *n*-BuLi, ether−hexanes (74%). (c) (i) DIBAL, ether−hexanes; (ii) pyridine, ether; (iii) Br_2, CH_2Cl_2 (91%). (d) *hν*, Br_2, pyridine, CH_2Cl_2 (99%). (e) (i) **7**, *s*-BuLi, THF−hexanes; (ii) **8**, HMPA, THF (68%). (f) NCS, H_2O, DMF (45%). (g) AcOH, THF−H_2O (80%). (h) Dess−Martin periodinane, CH_2Cl_2. (i) **28**, KHMDS, 18-crown-6, THF−toluene (75%, 2 steps). (j) DIBAL, toluene (100%). (k) Dess−Martin periodinane, CH_2Cl_2. (l) **29**, *t*-BuMgCl, THF (57%, 3*S*:3*R* = 19:1, 2 steps). (m) Al-Hg, THF−H_2O (86%). (n) Ac_2O, pyridine (99%). (o) HF-py, pyridine, THF (93%). (p) TMSOTf, 2,6-lutidine, CH_2Cl_2 (90%). (q) TBDPSCl, DMAP, Et_3N, CH_2Cl_2. (r) AcOH, THF−H_2O (47%, 2 steps).

(7) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1971**, *34*, 3151.
(8) Dondoni, A.; Fantin, G.; Foganolo, M.; Merino, P. *Tetrahedron Lett.* **1990**, *31*, 4513.
(9) The stereochemistry was determined by the coupling constants from their ^1H NMR data and the NOE experiments.
(10) (a) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1983**, *48*, 4113. (b) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.

procedure[11] for conversion of an alkenylsilane to a bromoolefin for preparation of the chloroolefin **19**. After several attempts, we found that the addition of a catalytic amount of water was important for the reaction to be reproducible. Acidic hydrolysis of **19** gave **20** and subsequent Dess−Martin oxidation afforded a labile aldehyde, which was converted into the *Z*-conjugated ester **21** by using the Still-modified Horner−Emmons reaction[12] (60%, three steps). The DIBAL reduction of **21** gave the allylic alcohol **22** (100%), which was oxidized to a conjugated aldehyde. The asymmetric aldol reaction[13] with Corey's sulfoxide **29**[14] provided a hydroxysulfoxide,[15] amalgam reduction of which gave the desired hydroxy ester **23** (49%, three steps). The absolute stereochemistry of the C-3 hydroxy group in **23** was established by the modified Mosher's method.[16] After acetylation, the protecting groups were removed to give the dihydroxy acid **26** (92%, two steps), the primary hydroxy group of which was protected as the TBDPS ether to afford the seco acid **5** (47%, two steps). Thus, the precursors for the macrolide unit **3** were in hand. However, all attempts at macrolactonization of the dihydroxy acid **26** or the seco acid **5** to **3** failed under the Yamaguchi, Keck, and Mukaiyama-Corey conditions.

We next tried to cyclize the 14-membered ring using the intramolecular Reformatsky-type reaction (Scheme 4). The

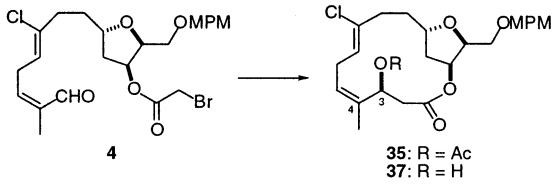
Scheme 4. Synthesis of Haterumalide NA Methyl Ester **36**[a]



[a] Reagents and conditions: (a) $TMSCHN_2$, hexane−benzene−MeOH (74%). (b) MMTrCl, pyridine (100%). (c) TBAF, THF (99%). (d) $BrCH_2COBr$, pyridine, CH_2Cl_2. (e) AcOH, THF−H_2O (82% in 2 steps). (f) Dess−Martin periodinane, CH_2Cl_2 (93%). (g) (i) Et_2Zn, $RhCl(PPh_3)_3$, THF−hexane; (ii) Ac_2O (9%). (h) DDQ, CH_2Cl_2−phosphate buffer (pH 5.9) (88%). (i) Dess−Martin periodinane, CH_2Cl_2. (j) **2**, $CrCl_2$, $NiCl_2$, DMSO (57%, 15*S*:15*R* = 11:1, 2 steps).

hydroxy group of the allylic alcohol **22** was protected as an MMTr ether to quantitatively afford compound **31**. The silyl group in **31** was removed, and the resulting alcohol **32** (99%) was converted into the bromo ester **33**. The MMTr group was removed to give allylic alcohol **34** (82%, two steps), which was oxidized to afford the conjugated aldehyde **4**, a precursor of the intramolecular Reformatsky-type reaction, in 93% yield. Attempts toward the intramolecular Reformatsky-type reaction are summarized in Table 1. The

Table 1. Intramolecular Reformatsky-Type Reaction of Bromoester **4**



entry	conditions	product	(3*S*,4*Z*)/(3*R*,4*Z*)/(4*E*) (yield)
1	SmI_2, 0 °C	**37**	−/−/100 (86%)
2	SmI_2, −100 °C	**37**	−/−/100 (7%)
3	Zn, $B(OMe)_3$, rt	**37**	—[b]
4	Zn, CuBr, Et_2AlCl, −20 °C	**37**	—[c]
5	Et_2Zn−$RhCl(PPh_3)_3$ −20 °C	**37**	—[b]
6[a]	Et_2Zn−$RhCl(PPh_3)_3$ −20 °C	**35**	20/72/8 (45%)

[a] After 4 h, Ac_2O was added to trap the reactive product **37**. [b] Complex mixture. [c] Noncyclized reduced products were obtained: debromo-**4** (65%) and the corresponding debromo-allyl alcohol (23%).

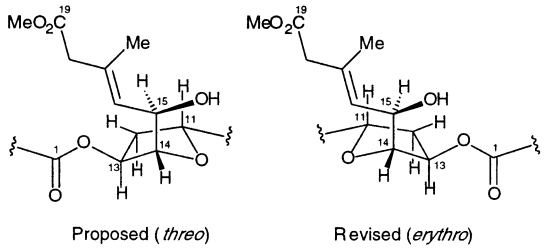
cyclization with SmI_2[17] provided the cyclic compounds in good yields (86%, 3*S*:3*R* = 1:1); however, the stereochemistry of the C-4 double bond was totally isomerized into trans (entry 1). The reaction at lower temperature also gave the same *trans*-products in a lower yield (entry 2). The molecular mechanics calculation indicated that the desired *cis*-compound **35** was less stable (7.5 kJ/mol) than the *trans*-compound.[18] This isomerization might be due to the allylic radical nature of the transition state and/or the reactive intermediates. Therefore, we investigated the cyclization with zinc reagents apt to effect the two-electron reduction. The reactions under the standard conditions[19,20] afforded no cyclized compounds (entries 3 and 4). The reaction under Honda's conditions[21] with Et_2Zn−$RhCl(PPh_3)_3$ resulted in

(11) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.
(12) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(13) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, R.; Cho, H.; Hua, D. H. *J. Am. Chem.* Soc. **1980**, *102*, 6613. (b) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227. (c) Solladie, G.; Moghadam, F.-M. *J. Org. Chem.* **1982**, *47*, 91.
(14) Mioskowski, C.; Solladie, G. *Tetrahedron Lett.* **1975**, 3341.
(15) Diastereoselectivity of this aldol reaction was 95:5, and the mixture could be chromatographically separated.
(16) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(17) (a) Tabuchi, T.; Kawamura, K.; Inagawa, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889. (b) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.
(18) The calculations were executed by MacroModel (Version 6.0) with the MM2* force field.
(19) Rathke, M. W.; Lindert, A. *J. Org. Chem.* **1970**, *35*, 3966.
(20) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3301.

the decomposition of the starting material; however, we found by TLC monitoring, the generation of an intermediate, the β-hydroxy lactone **37**, which decomposed upon workup (entry 5). The addition of Ac_2O to trap the reactive products allowed us to isolate the desired cyclized product (3*S*,4*Z*)-**35** in 9% yield along with the (3*R*,4*Z*)- and (4*E*)-isomers (entry 6).[22]

The MPM group in (3*S*,4*Z*)-**35** was removed to give the alcohol **3** in 88% yield, which was oxidized with the Dess−Martin periodinane to afford an unstable aldehyde. The Nozaki−Hiyama−Kishi coupling reaction[23] of the aldehyde and iodide **2**, prepared from **30**,[5] afforded the coupling product **36** (57%, *S*:*R* = 11:1), and the diastereomers were separated with HPLC. The major isomer, (15*S*)-**36**, was found to be identical with the naturally occurring sample upon comparison of their spectral data and chromatographic behavior except for the sign of the CD spectrum (see Supporting Information). Because the stereochemistry of the C-3, C-11, C-13, and C-14 in synthetic **36** was undoubtedly constructed by the organic synthetic method, we unambiguously determined the absolute stereochemistry of C-3, C-11, C-13, and C-14 in natural **1** to be *R*, *R*, *R*, and *R*. On the other hand, since the absolute stereochemistry of C-15 in natural **1** was determined to be *R* by the modified Mosher's method, the total absolute stereochemistry of haterumalide NA was revealed, which revised the previously reported structure.[1] To confirm these results, **36** was converted into the (*R*)-MTPA ester, which was found to be the enantiomer of the (*S*)-MTPA ester of the natural haterumalide NA methyl ester on comparison of their ^{1}H NMR spectra.

In a previous paper,[1] in light of the abnormal $\Delta\delta$ values in the experiments of the modified Mosher's method for **1** (R = Me), we postulated the folded conformation of the side chain in the Mosher esters of **1**, which led us to the wrong conclusion that the stereochemistry at C14−C15 was *threo* (Figure 1). The generally accepted zigzag conformation of the side chain in the Mosher esters of **1** is consistent with the revised stereostructure, in which the stereochemistry at C14−C15 is *erythro*, from the viewpoint of the coupling constants and the NOESY correlations of **1**.



Proposed (*threo*) Revised (*erythro*)

Figure 1. Relative stereochemistry of the C14−C15 part of haterumalide NA (**1**, R = Me).

In summary, the enantioselective synthesis of 15-*epi*-haterumalide NA methyl ester (**36**) has been achieved from the threitol derivative **9** in 26 steps. This synthesis revises the absolute stereochemistry of haterumalide NA. Further biological studies and the synthesis of natural (−)-haterumalide NA are now in progress.

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Supporting Information Available: Spectral data and experimental procedures of key compounds **6**, **7**, **8**, **19**, **35**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549.

(22) The stereochemistry at the C-4 double bond was easily determined by the NOE experiments. On the other hand, the stereochemistry at C-3 was determined by the modified Mosher's method. The minor isomer, (3*S*,4*Z*)-**35**, could not be transformed into the corresponding MTPA esters because of the instability during the methanolysis of the acetyl group. However, the modified Mosher's method could be applied to (3*R*,4*Z*)-**37** that was obtained by methanolysis of the major isomer, (3*R*,4*Z*)-**35**, establishing that the major isomer possessed the undesired stereochemistry 3*R*, i.e., the minor isomer was the desired (3*S*)-compound.

(23) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.