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Synthesis of *ent*-Haterumalide NA (*ent*-Oocydin A) Methyl Ester

Yonghong Gu and Barry B. Snider*

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

snider@brandeis.edu

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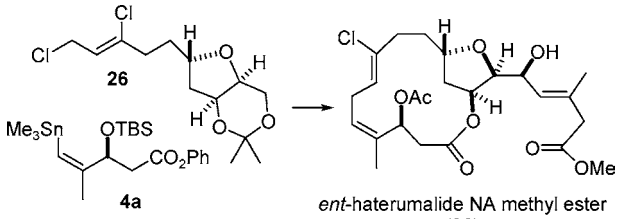
ABSTRACT



Stille coupling of allylic chloride 26 with vinylstannane 4a afforded 65% of 27 with the requisite skipped diene, vinyl chloride, and allylic oxygen functionality. Yamaguchi macrolactonization of 28 provided 65% of 29, which was elaborated to haterumalide NA methyl ester (32) by a Nozaki–Hiyama–Kishi coupling with 31.

The macrolide haterumalide NA (**1**) was isolated in 1999 from an Okinawan sponge *Ircinia* sp.[1] The same macrolide, named oocydin A, was reported contemporaneously from a strain of *Serriatia marcescens* growing as an epiphyte on *Rhyncholacis pedicillata*, in a Venezuelan river,[2] and in 2001 from a soil bacterium *Serratia plymuthica* in Sweden.[3] The closely related ester haterumalide B was isolated from the Okinawan ascidian *Lissoclinum* sp.[4] Haterumalide NA is cytotoxic to P388 cells with an IC_{50} of 0.32 μg/mL,[1] has MICs of approximately 0.03 μg/mL against phytopathogenic oomycetes,[2] and suppresses apothecial formation of the plant pathogen *Sclerotinia sclerotiorum*.[3]

As our work was nearing completion, Kigoshi reported the first synthesis and revision of the structure of haterumalide NA.[5] The stereochemistry at C_{15} of haterumalide NA was revised to that shown in **1**,[1] as was originally proposed for oocydin A.[2] The absolute stereochemistry is also opposite that originally proposed; structure **1** is the enantiomer of haterumalide NA. Kigoshi reported that macrolactonization could not be achieved. The macrolide was formed in 9% yield by an intramolecular Reformatsky reaction of a bromoacetate with an ϵ-chloro-$\alpha,\beta,\delta,\epsilon$-dienal.[5]

We envisioned that the side chain of haterumalide NA (**1**) could be introduced by the Nozaki−Hiyama−Kishi coupling of aldehyde **2** with the appropriate vinyl iodide as shown in Scheme 1. Macrolide **2** should be accessible by macrolactonization of hydroxy acid **3** and adjustment of the oxygen functionality. The key step in our route involved the Stille coupling of allylic halide or acetate **5** with vinylstannane **4** to construct the skipped diene of **3**.[6,7] Finally, **5** should be easily prepared from tetrahydrofuran **6**, which has been prepared by Yoshida by a diastereoselective iodoetherification.[8]

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(7) For applications of this reaction in natural product synthesis, see: (a) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508. (b) White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407. (c) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307.

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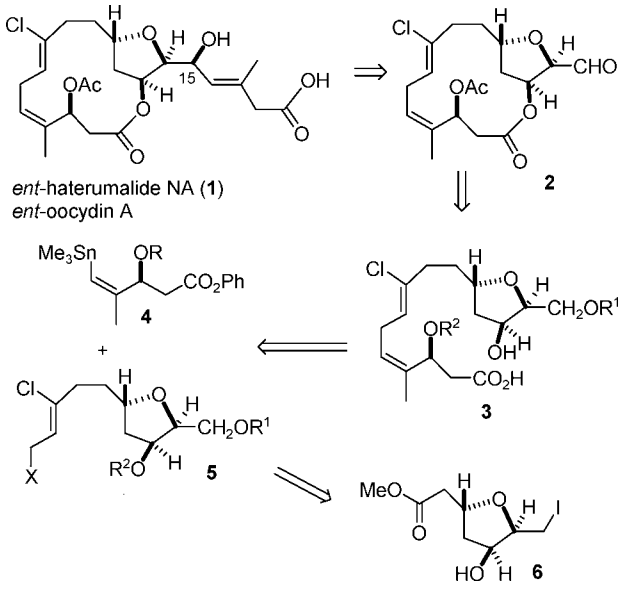
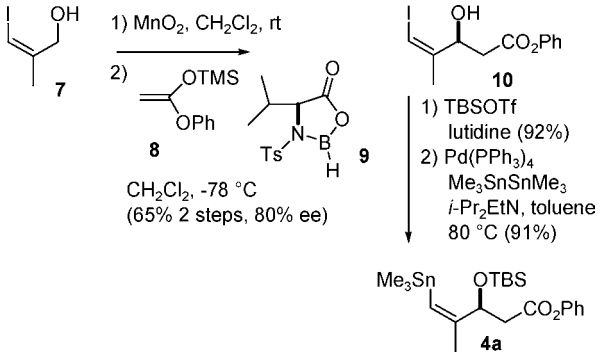
Scheme 1. Retrosynthetic Analysis of Haterumalide NA (**1**)



Vinylstannane **4a** was prepared by the efficient five-step sequence shown in Scheme 2. Addition of MeMgBr and CuI

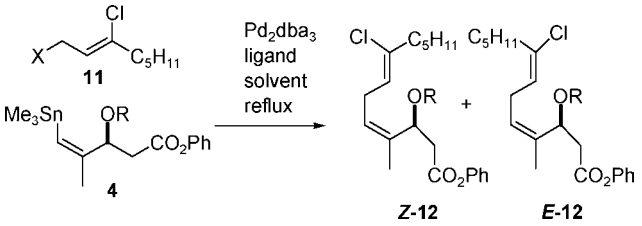
Scheme 2. Synthesis of Vinylstannane **4a**



to propargyl alcohol and trapping with I_2 afforded iodoallylic alcohol **7**,[9] which was oxidized with MnO_2 to yield the unstable β-iodomethacrolein.[10] Aldol reaction of ketene silyl acetal **8** with the iodoaldehyde at −78 °C and oxazaborolidinone **9** by Kiyooka's procedure[11] afforded 65% of **10** in >80% ee.[12] *t*-Butyldimethylsilylation and reaction with $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, and *i*-Pr_2EtN in toluene at 80 °C afforded 91% of vinylstannane **4a**.

There were many questions about the proposed Stille coupling of **4** and **5**. What is the best protecting group for the alcohol of **4**? What is the best leaving group X in **5**? Is the vinyl chloride of **5** compatible with the coupling? Will the stereochemistry of the vinyl chloride be preserved? We therefore carried out a model study, reacting **4** with (*Z*)-3-chloro-2-octen-1-yl compounds **11** as shown in Table 1.

Table 1. Stille Coupling of **4** and **11**



X	R	ligand	solvent	time	yield	*Z*/*E* ratio
Cl	TBS	Ph_3As	THF	17 h	70%	85:15
Cl	TBS	(*o*-furyl)$_3$P	THF	48 h	65%	85:15
Cl	TMS	Ph_3As	THF	42 h	50%	85:15
Cl	TMS	(*o*-furyl)$_3$P	THF	48 h	65%	85:15
Cl	Ac	Ph_3As	THF	48 h	55%	79:21
Cl	Ac	(*o*-furyl)$_3$P	THF	65 h	57%	76:24
Cl	TBS	Ph_3As	C_6H_{12}	14 h	75%	74:26
Br	TBS	Ph_3As	THF	48 h	25%	variable

Reduction of 2-octyn-1-ol with Red-Al at room temperature and quenching with *N*-chlorosuccinimide (NCS)[13] afforded **11**, X = OH. We found that coupling of **4a** with **11**, X = Cl, under Farina conditions[14] using $AsPh_3$ and Pd_2dba_3 afforded 70% of a readily separable 85:15 mixture of the desired product (*Z*)-**12** and the isomerized product (*E*)-**12**. The stereochemistry of the products was established by NOE studies. It is noteworthy that the allylic chloride of **11** reacts rapidly, while the vinyl chloride survives unchanged. Much longer reaction times were required with tri-*o*-furylphosphine. TMS was partially lost during the reaction, and stereocontrol was worse with R = Ac. Much lower yields were obtained with X = Br, and no product was obtained with X = OAc. Reaction in cyclohexane afforded higher yield, but lower stereoselectivity.

Having established by this model study that the Stille coupling of **4** and **5** should be viable, we turned our attention to the preparation of **5** as shown in Scheme 3. Alcohol **13** has been prepared in optically pure form by Carreira's aldol procedure[15] and by kinetic resolution of the racemic alcohol with Sharpless asymmetric epoxidation.[16] Heating **13** in toluene containing MeOH at reflux afforded 85% of the keto ester, which was reduced to give 93% of syn diol **14** with Et_2BOMe and $NaBH_4$ in THF/MeOH at low temperature.

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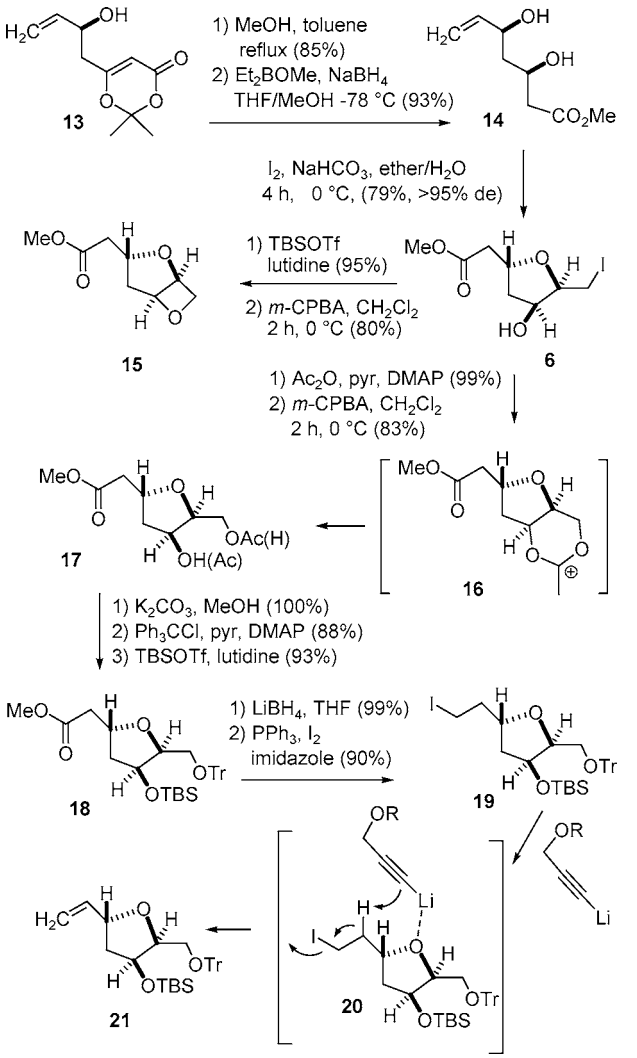
(16) Sugita, Y.; Sakaki, J.-i.; Sato, M.; Kaneko, C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2855.

Scheme 3. Unsuccessful Route to **5**



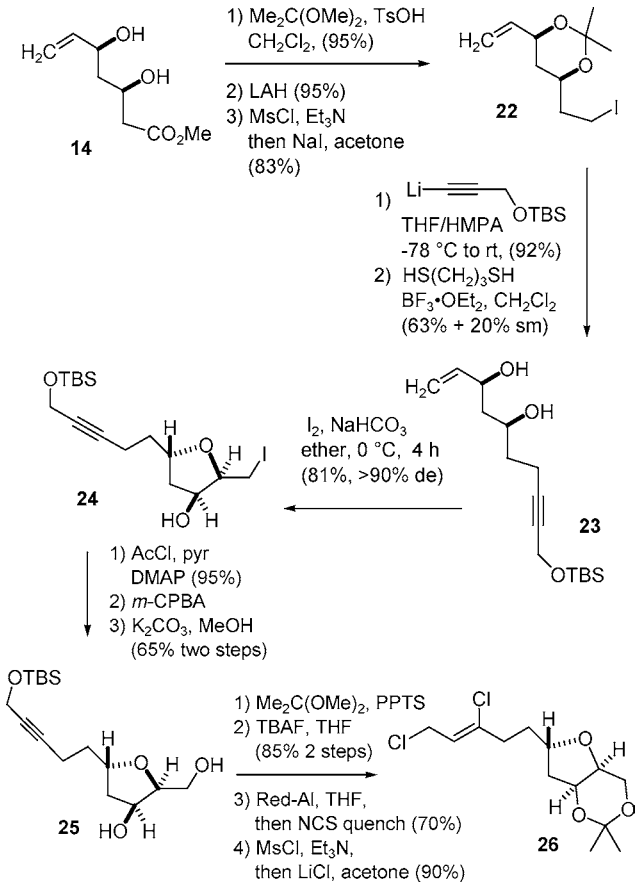
Iodoetherification as described by Yoshida[8] afforded 79% of iodomethyltetrahydrofuran **6** in >95% de.

To our surprise, displacement of the iodide of **6** with an oxygen nucleophile proved to be surprisingly difficult. Mixtures of substitution and elimination products were obtained under most conditions. Eventually, we found that Reich's oxidative substitution protocol[17] effected substitution without elimination. Oxidation of the TBS ether of **6** with *m*-CPBA in CH_2Cl_2 generated the reactive iodoso compound that was displaced by the OTBS oxygen to give 80% of oxetane **15** after loss of the TBS group. We reasoned that changing the protecting group could prevent formation of the oxetane. The analogous oxidation of the acetate of **6** led to cation **16**, which reacted with water to give 82% of a mixture of hydroxy acetates **17**. Basic hydrolysis of this mixture (100%), tritylation of the primary alcohol (88%), and silylation of the secondary alcohol (93%) afforded **18**.

$LiBH_4$ reduction of the ester of **18** (99%) and reaction of the primary alcohol with PPh_3, I_2, and imidazole (90%) afforded primary iodide **19**. Unfortunately, all attempts to displace the iodide with a lithium acetylide led only to elimination product **21**. We hypothesized that the basic tetrahydrofuran oxygen of **19** complexed to the lithium acetylide to give complex **20** in which the acetylide is positioned to effect elimination to give **21**, rather than the desired substitution to generate the carbon skeleton of **5**.

If this analysis is correct, changing the order of the steps so that the propargylic alcohol is introduced before the iodoetherification forms the tetrahydrofuran should solve this problem. Protection of the diol of **14** as the acetonide (95%), reduction of the ester with LAH (95%), and reaction with MsCl and Et_3N and then NaI in acetone (83%) afforded iodide **22** (see Scheme 4). The propargylic alcohol was now

Scheme 4. Preparation of Stille Coupling Precursor **26**



successfully introduced in 92% yield by displacement with $LiC{\equiv}CCH_2OTBS$ in THF/HMPA and resilylation of the partially deprotected primary alcohol. Deprotection of the acetonide with $BF_3{\cdot}Et_2O$ and propanedithiol[18] afforded 79% of diol **23** at 80% conversion.

Iodoetherification of **23** afforded 81% of iodomethyltetrahydrofuran **24** in >90% de. Acetylation (95%), oxidation with *m*-CPBA,[17] and hydrolysis of the hydroxyacetate mixture (65% two steps) afforded diol **25**. Formation of the

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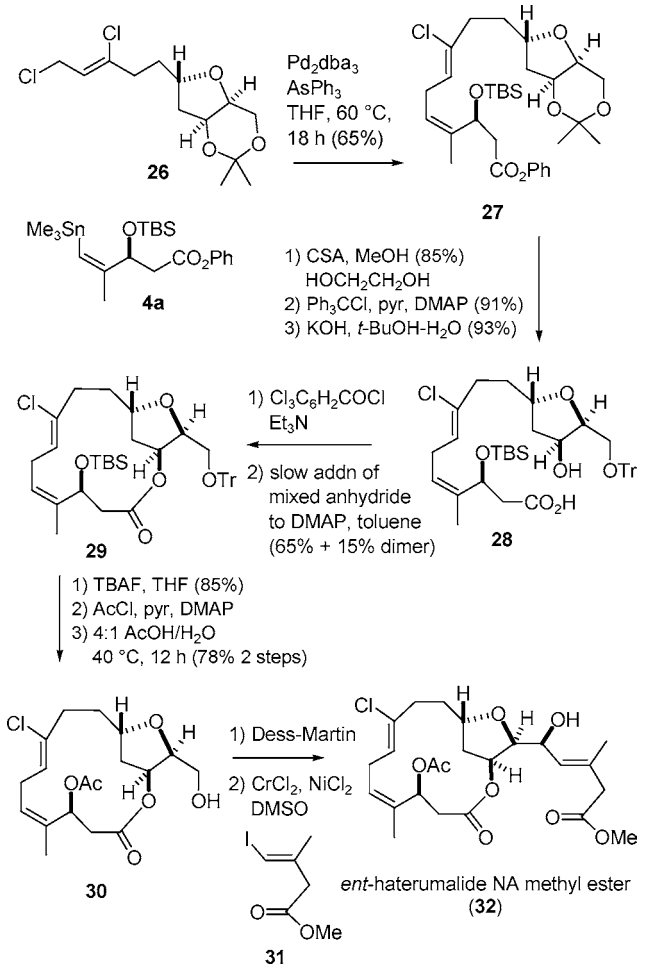
acetonide, cleavage of the TBS ether with TBAF (85% two steps), reduction of the propargylic alcohol with Red-Al followed by NCS quench (70%),[13] and conversion of the allylic alcohol to the chloride with MsCl, Et_3N, and then LiCl in acetone (90%) afforded the required Stille coupling precursor **26**.

Stille coupling of **26** with **4a** using the conditions developed in the model study with Pd_2dba_3 and $AsPh_3$ in THF at 60 °C afforded 65% of **27** and 10% of the corresponding (*E*)-isomer (see Scheme 5). Hydrolysis of the

Scheme 5. Completion of the Synthesis of Haterumalide NA Methyl Ester (**32**)



acetonide of **27** with CSA (85%), tritylation of the primary alcohol (91%), and basic hydrolysis of the phenyl ester (93%) afforded hydroxy acid **28**.

Macrolactonization was achieved efficiently by the Yamaguchi protocol.[19] Addition of trichlorobenzoyl chloride and Et_3N afforded the mixed anhydride, which was added over 15 h to a solution of DMAP in toluene at 25 °C to give 65% of the desired macrolide **29** and 15% of dimer and trimer.[20] Addition of the mixed anhydride to DMAP in toluene at higher temperatures afforded no dimer and trimer but gave a lower yield of **29**, suggesting that it is thermally unstable. If DMAP was added to the mixed anhydride, only 15−20% of **29** was formed, with dimer and trimer being the major products formed in 50−60% yield.

Kigoshi reported that he was unable to effect macrolactonization of a substrate that differs from **28** only in that the primary alcohol is protected as a TBDPS rather than a trityl ether and the secondary alcohol is protected as an acetate rather than a TBS ether.[5] Clearly the choice of protecting groups is crucial for the success of the macrolactonization. The β-acetoxy mixed anhydride may undergo elimination. The primary TBDPS ether may undergo migration.

Hydrolysis of the TBS ether of **29** with TBAF in THF (85%), acetylation of the alcohol (AcCl, pyr, DMAP), and hydrolysis of the trityl ether in 80% AcOH at 40 °C for 12 h (78% for two steps) afforded primary alcohol **30**. The ^{1}H NMR spectrum of **30** is identical to that kindly provided by Prof. Kigoshi.

The synthesis of haterumalide NA methyl ester (**32**) was completed as described by Kigoshi.[5] Oxidation with Dess−Martin periodinane and Nozaki−Hiyama−Kishi coupling with iodide **31**[5,21] afforded 30−40% of haterumalide NA methyl ester after HPLC purification. The ^{1}H NMR and CD spectra of **32** are identical to those reported by Kigoshi for *ent*-haterumalide NA methyl ester.

In conclusion, we have completed an efficient, convergent synthesis of haterumalide NA methyl ester (**32**) that will be equally suitable for the preparation of the natural enantiomer. The key step is the Stille coupling of **4a** with **26** to give 65% of **27** containing the desired skipped diene, vinylic chloride, and allylic oxygen functionality. The successful Yamaguchi macrolactonization of **28** to give **29**, despite earlier reports to the contrary with similar substrates,[5] demonstrates the critical effect of protecting groups on the success of the cyclization.

Acknowledgment. We thank the National Institutes of Health (GM-50151) for financial support. We thank Prof. H. Kigoshi for a copy of the ^{1}H NMR spectrum of macrolide alcohol **30**.

Supporting Information Available: Full experimental details and copies of ^{1}H and ^{13} C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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