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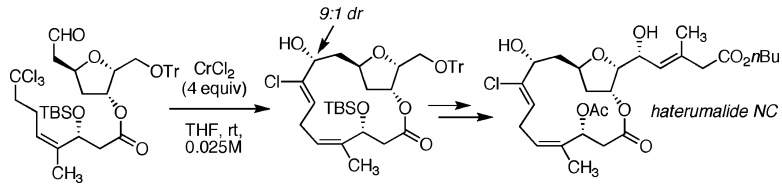


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# Total Synthesis of Haterumalides NA and NC via a Chromium-Mediated Macrocyclization

Jennifer M. Schomaker and Babak Borhan*

*Department of Chemistry, Michigan State University, East Lansing, Michigan 48824*

Received June 9, 2008; E-mail: babak@chemistry.msu.edu

The haterumalides are a series of chlorinated macrolides isolated from an Okinawan sea sponge of the species *Ircinia* (Figure 1).[1,2] Kigoshi's synthesis of haterumalide NA led to its structural revision.[3] The stereochemistry of the remaining haterumalides is assumed to mimic that of haterumalide NA, and the stereochemistries in Figure 1 have been changed to reflect the corrections made to the initial structure of haterumalide NA.

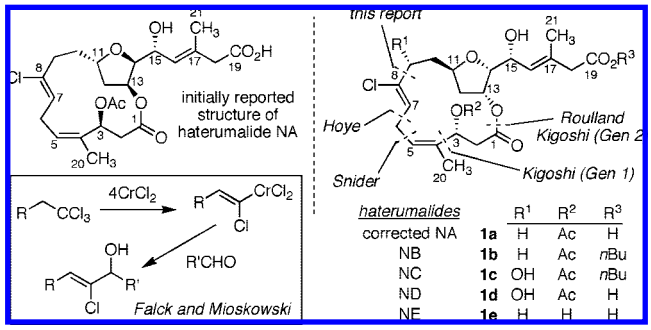



***Figure 1.*** Structure of the haterumalides.

Figure 1 summarizes previous synthetic approaches to haterumalide NA. Kigoshi and co-workers utilized an intramolecular Reformatsky reaction as a key step to form the macrolide.[3] Snider and Gu used an intermolecular Stille coupling reaction followed by a Yamaguchi macrolactonization.[4] Hoye and Wang reported the first total synthesis of the correct enantiomer of haterumalide NA using a Pd-mediated alkyne haloallylation reaction.[5] Most recently, Roulland and Kigoshi, in two separate reports, described the use of variants of Suzuki−Miyaura cross-coupling along with macrolactonizations to achieve the synthesis of haterumalide NA.[6,7] Our approach entailed the construction of the C8−C9 bond, such that any member of the haterumalide family could be accessed. Critical to this assembly would be the ability to construct a nucleophilic *Z*-vinyl chloride moiety that would participate in a macrocyclization event with a pendant aldehyde. Thus, we explored the utility of the chlorovinylidene chromium carbenoids developed by Falck and Mioskowski (see Figure 1, box).[8,9] To the best of our knowledge, this chemistry has not been utilized in a natural product synthesis and its participation in a macrocyclization has not been reported.

Synthesis of **1c** commenced with preparation of the tetrahydrofuran-containing aldehyde for intramolecular $CrCl_2$-mediated coupling (Scheme 1). 2-Deoxy-D-ribose **2** was converted to the disilylated methyl acetal **3** in high yield. Addition of allyltrimethylsilane to **3** in the presence of tin tetrabromide by the method of Woerpel and co-workers gave the allylated product in excellent diastereoselectivity.[10,11] Desilylation to yield **4** was followed by protection of the primary alcohol as a trityl group, yielding **5** poised for Mitsunobu esterification with carboxylic acid **9c**.

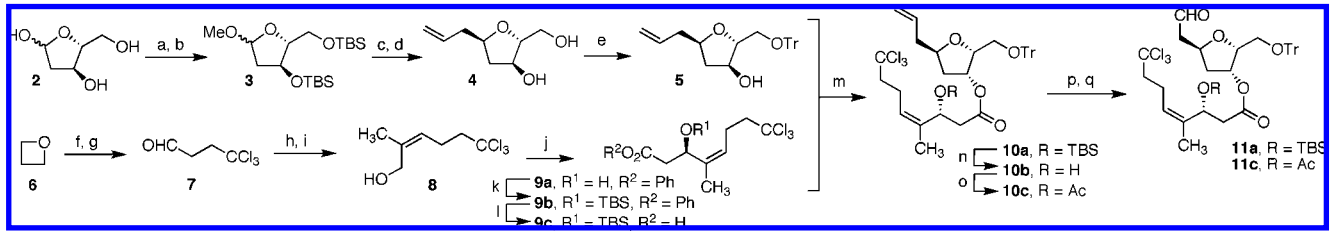
Preparation of **9c** began with the ring-opening of **6** with the anion of chloroform to yield the corresponding alcohol.[12] DMP oxidation furnished the unstable, reactive, and volatile aldehyde **7**, which was immediately subjected to a Still−Gennari olefination to yield the desired *Z*-acrylate.[13] Reduction of the ester to the allylic alcohol **8** was followed by a rapid oxidation to the unsaturated aldehyde and an immediate asymmetric Mukaiyama aldol reaction to furnish **9a**.[14] The secondary alcohol was protected as a TBS ether, and the phenyl ester was hydrolyzed to give the desired 1,1,1-trichloroalkane substrate **9c**.

Mitsunobu esterification of alcohol **5** and carboxylic acid **9c** yielded **10a** without incident. Both TBS-protected and acetylated C3-OH compounds (**10a** and **10c**) were carried forward for comparative studies in later stages. Selective dihydroxylation of the terminal alkene was followed by oxidative cleavage of the diol with sodium periodate in a mixture of dioxane and water, yielding aldehydes **11a** and **11c**. Presumably, the TBS and acetyl protecting groups provide enough steric hindrance to prevent any undesired oxidation of the trisubstituted olefin.

With the substrates **11a** and **11c** in hand, studies directed toward the intramolecular $CrCl_2$-mediated coupling were pursued (Scheme 2). Several different concentrations were screened, as studies with an intermolecular approach (Cr-mediated coupling, followed by intramolecular Mitsunobu lactonization, not shown) proved that higher reaction concentrations gave much better yields, presumably due to an increased rate in the desired reaction compared to the competing side reaction caused by quenching of the vinylidene chromium carbenoid with water or other proton sources present in the reaction (despite precautions taken to dry all reagents and solvents carefully).

Gratifyingly, treatment of the substrates shown in Scheme 2 with 4.0 equiv of $CrCl_2$ at the indicated concentrations gave the desired

***Scheme 1.*** Synthesis of **11a** and **11c**[a]

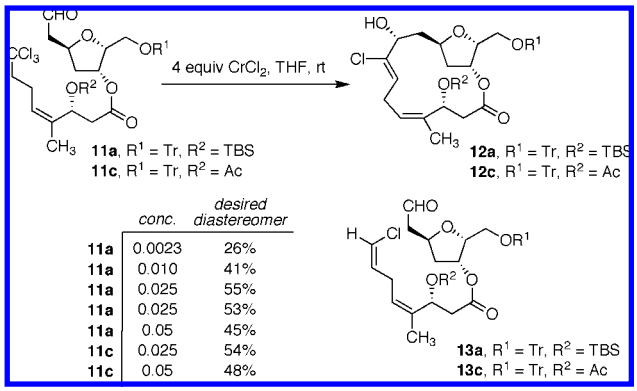



[a] (a) MeOH, cat. HCl, quant.; (b) TBSCl, imid, DMF, 98%; (c) allyltrimethylsilane, $SnBr_4$, $CH_2Cl_2$, −78 °C, 93%, dr > 95:5; (d) TBAF, THF, 90%; (e) TrCl, py, DMAP, $CH_2Cl_2$, rt, 87%; (f) *n*BuLi, $CHCl_3$, $BF_3 \cdot OEt_2$, THF, −94 °C, 96%; (g) DMP, $NaHCO_3$, 0 °C, 86%; (h) $(TFEO)_2P(O)CH(CH_3)CO_2Et$, KHMDS, 18-crown-6, THF, −78 °C, 91%; (i) DIBAL, THF, −20 °C, 93%; (j) $MnO_2$, $CH_2Cl_2$, then add to D-*N*-Ts-valine, $BH_3 \cdot$THF, $CH_2C(OPh)OTMS$, 64%, 80% ee; (k) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 89%; (l) KOH, $^t$BuOH, $H_2O$, 90%; (m) DIAD, $PPh_3$, THF, 74%; (n) TBAF, THF, 0 °C, 88%; (o) $Ac_2O$, py, DMAP, $CH_2Cl_2$, 99%; (p) AD-mix α, *t*BuOH/$H_2O$, rt, 90% for **10a**, 88% for **10c**; (q) $NaIO_4$, dioxane/$H_2O$, 78% for **11a**, 87% for **11c**.



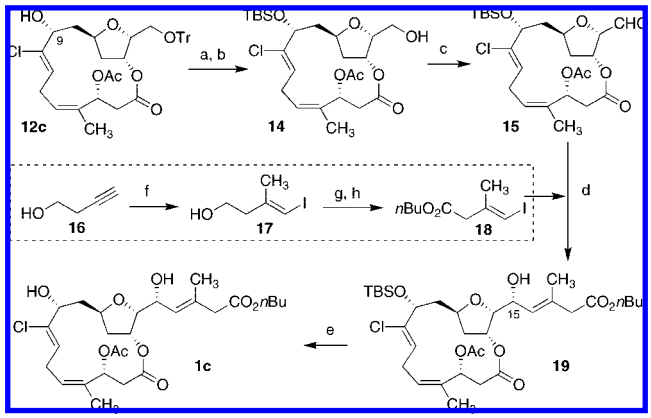
10.1021/ja8043695 CCC: $40.75 

***Scheme 2.*** Chromium Carbenoid-Mediated Macrocyclization




| | conc. | desired diastereomer |
|---|---|---|
| **11a** | 0.0023 | 26% |
| **11a** | 0.010 | 41% |
| **11a** | 0.025 | 55% |
| **11a** | 0.025 | 53% |
| **11a** | 0.05 | 45% |
| **11c** | 0.025 | 54% |
| **11c** | 0.05 | 48% |

***Scheme 3.*** Synthesis of Haterumalide NC (**1c**)[a]



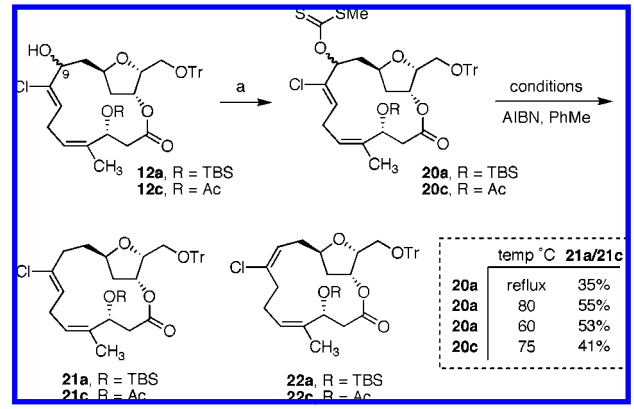

[a] (a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 94%; (b) 80% AcOH, 40 °C, 63%; (c) DMP, $NaHCO_3$, $CH_2Cl_2$; (d) $CrCl_2$, cat. $NiCl_2$, DMSO, rt, 52%, 9:1 dr; (e) HF/py, THF, 91%; (f) $AlMe_3$, $Cp_2ZrCl_2$ (cat.), $I_2$, 84%; (g) DMP, $NaHCO_3$, $CH_2Cl_2$, rt; (h) *n*BuOH, $CrO_3$, $AcOH/H_2SO_4$, 0 °C, 51%.

C−C bond formation, with 0.025 M leading to the highest yields. Most importantly, the macrocyclization products **12a** and **12c** were obtained as one major diastereomer (9:1 for **12a**, 4:1 for **12c**), with minor side products **13a** and **13c** resulting from proto-demetalation. The stereochemistry of the newly generated C9 center matched the stereochemistry of the natural product, haterumalide NC, according to the chemical shift data obtained via $^1$H NMR.[2] This was further verified through modified Mosher ester analysis of the products (Supporting Information).

The final piece for installation of the side chain of haterumalide NC was prepared as illustrated in Scheme 3 in a fashion similar to that reported in prior syntheses for haterumalide NA. Treatment of 3-butyn-1-ol (**16**) under Negishi's conditions gave the desired *E*-iodoalkene **17**.[15] Conversion of the alcohol to aldehyde with DMP in the presence of excess $NaHCO_3$ was immediately followed by further oxidation to the *n*-butyl ester **18**. The macrocycle **12c** was prepared for the upcoming NHK coupling by protection of the C9 alcohol with TBSOTf, removal of the trityl group, and oxidation of the primary alcohol to the aldehyde with DMP. The crude aldehyde **15** was immediately subjected to NHK coupling with the vinyl iodide **18** to give the alcohol **19** as a 9:1 mixture of diastereomers at C15.[3−5] Deprotection of the C9 TBS group with HF/py in THF provided haterumalide NC (**1c**).

Next, we turned our attention toward the deoxygenation of the C9-OH, which would lead to haterumalide NA. Xanthates **20a** and **20c** were synthesized as illustrated in Scheme 4.[16] Radical-induced fragmentation of **20a** with AIBN in refluxing toluene led to a low

***Scheme 4.*** Formal Synthesis of Haterumalide NA (**1a**)[a]




| | temp °C | **21a**/**21c** |
|---|---|---|
| **20a** | reflux | 35% |
| **20a** | 80 | 55% |
| **20a** | 60 | 53% |
| **20c** | 75 | 41% |

[a] (a) NaH, THF, $CS_2$, then MeI, 98% for **12a**, 95% for **12c**.

yield of **21a**, along with several unidentifiable byproducts (Scheme 4). Lowering the reaction temperature to 80 °C improved the yield substantially; however, no further gains were observed at 60 °C. Compounds **21a** and **21c** were obtained as the major product of the deoxygenation, along with olefin-isomerized **22a** or **22c** as side products. Compound **21a** constitutes a formal synthesis of haterumalide NA.[4]

In summary, the first total synthesis of haterumalide NC was accomplished in 16 linear steps (longest route) with an overall yield of 6.2% via an unprecedented macrocyclization of an aldehyde and a chlorovinylidene chromium carbenoid to construct the C8−C9 bond. Deoxygenation of the latter product led to the formal synthesis of haterumalide NA.

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**Supporting Information Available:** Experimental procedures and spectral data for **1c**−**21c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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