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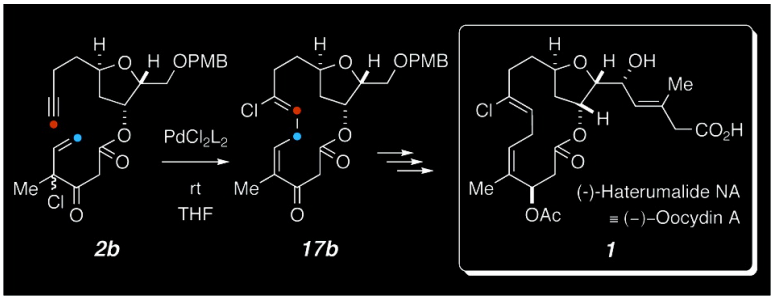
J. Am. Chem. Soc., **2005**, 127 (19), 6950-6951• DOI: 10.1021/ja051749i • Publication Date (Web): 22 April 2005



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Alkyne Haloallylation [with Pd(II)] as a Core Strategy for Macrocycle Synthesis: A Total Synthesis of (−)-Haterumalide NA/(−)-Oocydin A

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Two reports in 1999[1] described the results of parallel studies, each of which led to the identification of the structurally unique, phytopathogenic, and cytotoxic macrolide **1**. The compound isolated from the Okinawan sponge, *Ircinia* sp., was named haterumalide NA, and the one from the bacterium, *Serratia marcescens*, oocydin A. Haterumalide NA/oocydin A (**1**) was subsequently identified in a soil bacterium, *Serratia plymuthica*.[2] It is intriguing that a natural product with this degree of structural complexity is present in such seemingly disparate organisms.

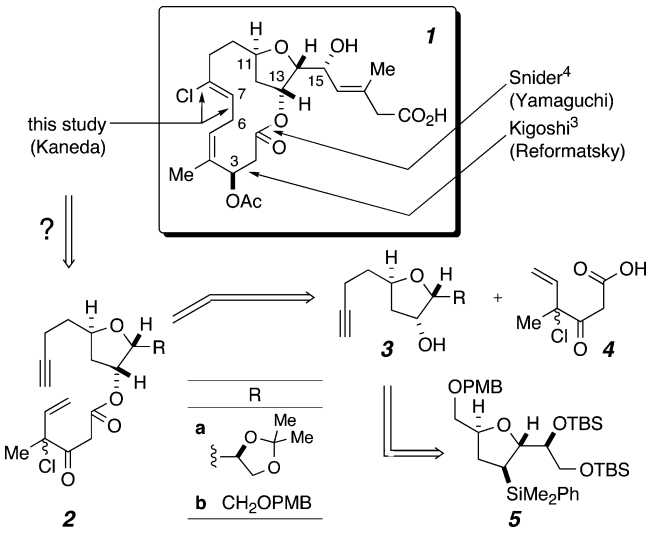
Studies in the Kigoshi[3] and Snider[4] laboratories, each culminating in the synthesis of the *ent*-methyl ester of **1**, led to a revision of the initially assigned relative configuration as well as to the assignment of absolute configuration of haterumalide NA/oocydin A. The 14-membered macrolactone in **1** bridges C11 and C13 on the embedded THF ring in a trans fashion, thereby conferring steric strain. This architecture seemingly places greater demands on macrocyclization reactions used to close the large ring.[5]

A series of reports in the 1970s from the Kaneda/Teranishi laboratory described PdX_2-catalyzed reactions of terminal alkynes (**7**) with allylic chlorides and bromides (**8**) to produce crossed 1:1 adducts **11** (Scheme 2).[6] The predominant products result from net cis-addition of the halogen atom and allylic moiety in **8** across the alkyne with the regiochemistries implied by **11** (and the presumed intermediates **9** and **10**). Even though substantial excesses of the allylic halide partner **8** have usually been employed (to overcome competitive alkyne oligomer formation), we hypothesized that an intramolecular, endocyclic version of this infrequently used reaction[7] could be commandeered to close the large ring in **1** by simultaneous creation of the C7−C8 trisubstituted *Z*-alkene and the C6−C7 bond. The appropriate precursor with which to address this issue took the form of **2** (Scheme 1). We have not found examples where tertiary allylic halides have been used as reaction partners in the Kaneda haloallylation reaction (and only two where secondary[6,7a] were used).

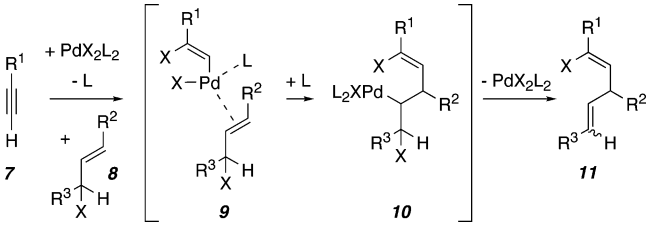
The synthesis of esters **2a** and **2b** evolved as summarized retrosynthetically in Scheme 1. The absolute and relative stereochemical properties of the 3-hydroxytetrahydrofuran **3a** were established in **5**, which was constructed in an efficient fashion by the method of Roush and Micalizio.[8,9]

Coupling reactions for joining two complex and valuable fragments must be efficient at a nearly equimolar ratio of the two reaction partners. This requirement pertains to both inter- and intramolecular versions. With this need as a guiding principle, we examined the intermolecular couplings shown in Scheme 3. The alkyne substrate for these studies, **13**, is the TIPS ether of **3a**; three *tertiary* allylic chlorides, **12a**−**c**, were examined. The results were similar regardless of whether a 5-fold (**12a**,**b**) or a 1.5-fold excess (**12c**) of the chloride (relative to alkyne **13**) was used. Slow addition of the alkyne[6,7f,g] was clearly advantageous. Only *Z*-$\Delta^{7,8}$-chloroalkene geometry was observed (NOE H7−H9). Separable mixtures of *Z*- and *E*-$\Delta^{4,5}$-alkenes (∼2:1; NOE Me4−H5) were generated. Isolated yields were >50% even though some loss due to acetonide cleavage[10] was always observed. Excess **12** could be recovered and did not isomerize to its allylomeric primary chloride under the reaction conditions.[6]

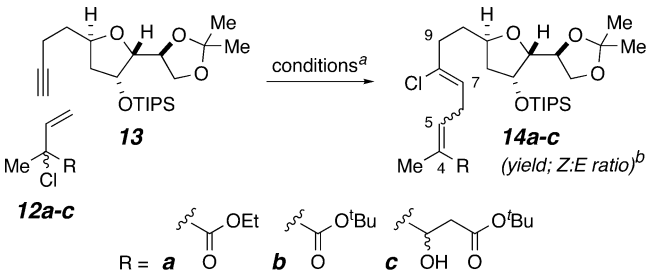
Scheme 1



Scheme 2



Scheme 3

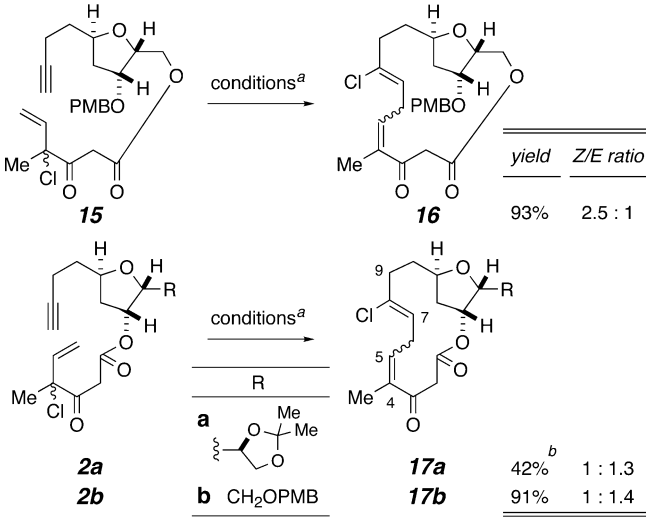


[a] $PdCl_2(PhCN)_2$ (∼20 mol %), THF, RT, **12**:**13** molar ratio 5:1 (for **12a**,**b**) or 1.5:1 (for **12c**); alkyne added last by syringe pump over 10−60 min; conversion complete upon addition; $[\mathbf{13}]_{final} = 0.01$ M. [b]Percent yield; **14Z** + **14E** = 50−67%; **14Z**:**14E** 1.8−2.5:1. After MPLC purification SiO_2; varying amounts of a 1,2-diol byproduct arising from acetonide cleavage were observed (TLC for **14b** and **14c**) and isolated (∼10%, for **14a**).

Encouraged by these results, we examined the alkynyl allylic chlorides **15**, **2a**, and **2b** as substrates for intramolecular macrocyclization (Scheme 4). Each of these allylic chlorides smoothly underwent cyclization when exposed to $PdCl_2(PhCN)_2$. The yield from the PMB-containing substrates **15** and **2b** was excellent,

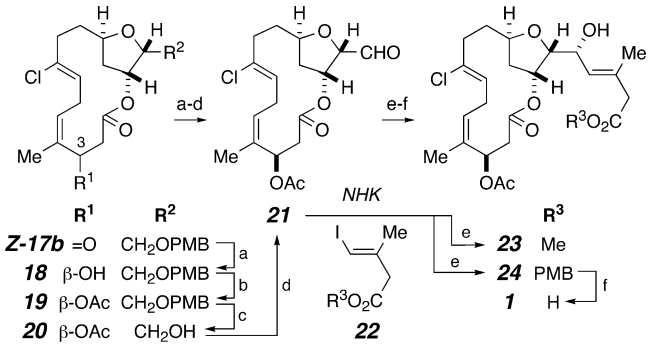
10.1021/ja051749i CCC: $30.25

Scheme 4



[a] $PdCl_2(PhCN)_2$ (~20−30 mol %), THF, RT, slow addition over 2 h; [enyne substrate]$_{final}$ = ~0.3 mM. [b]Plus the diol from acetonide cleavage.[10]

Scheme 5 [a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −30 °C (90%); (b) Ac_2O, Et_3N, DMAP, DCM, 0 °C (99%); (c) DDQ, DCM, H_2O, 0 °C (94%); (d) DMP, DCM, 0 °C; (e) **21** + **22** in DMSO, rt, then add $CrCl_2/NiCl_2$ (0.30 wt % $NiCl_2$) in drybox, 5−10 h (two steps: 50% for R^3 = PMB; 10:1 ratio of **24**:15-*epi*-**24**[12]); (f) TFA, Et_3SiH, DCM, 0 °C, 1 h.

regardless of whether the more relaxed, 15-membered (**16**) or the 14-membered macrolactone (**17b**) was being generated. Again, only the *Z*-$\Delta^{7,8}$-alkene was observed, but the $\Delta^{4,5}$-alkene was produced as a separable mixture of alkene isomers. This result raises the intriguing possibility that these intramolecular haloallylations are stereospecific—that each of the epimeric allylic chlorides engenders a single C4−C5 alkene geometry. This hypothesis will be explored.

To complete the synthesis of **1**, Luche reduction (Scheme 5) of the C3-ketone in the *Z*-isomer of **17b** provided **18** as a single alcohol having the 3*R* configuration (MTPA). This extremely high preference for the natural configuration is in contrast to that observed for reduction of the conformationally relaxed, larger ketolactone **16**. This substrate gave a ca. 2:1 mixture of epimeric alcohols under similar conditions. Acetylation of **18** (to **19**) and PMB removal (to **20**) were uneventful. Careful Dess−Martin oxidation at 0 °C provided aldehyde **21**. The Cr(II)/Ni^0-mediated Nozaki−Hiyama−Kishi (NHK) reaction[11] gave the methyl ester **23**[3,4] and, ultimately, the PMB ester **24**.[12] Consistent with others' experience,[3,4] ester **23** could not be successfully hydrolyzed under basic nor essentially neutral (Me_3SnOH, DCE[13]) conditions. However, the PMB ester in **24** was cleanly cleaved (TFA, Et_3SiH)[14] to the acid **1**, completing this first synthesis of haterumalide NA/oocydin A (**1**). Key to our success were the Pd(II)-mediated chloroallylative cyclization of **2b** to close the strained macrocycle in **17b** and the choice of the acid-labile PMB ester in **24**.

Acknowledgment. This investigation was supported by a grant awarded by the DHHS (GM-65597). We thank Professors G. Strobel (sample of **1**), H. Kigoshi (NMR data), and B. Snider (NMR and experimental data) for their very helpful assistance.

Supporting Information Available: Spectroscopic data for compounds **1**−**5**, **13**−**21**, **23**, and **24**; PDFs of ^1H NMR spectra for **1**, **2**, **17**−**21**, and **24**; and representative procedures for inter- and intramolecular chloroallylation (56 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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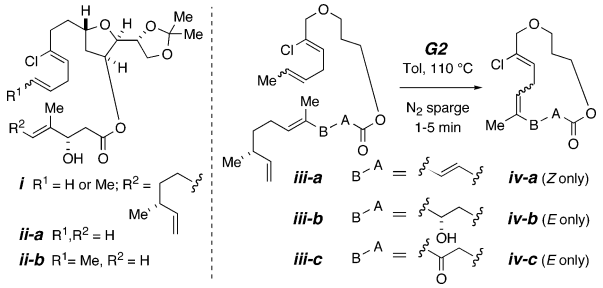
(5) (a) In the Kigoshi synthesis,[3] the macrocycle was closed by a Reformatsky-like reaction in 9% yield. In the Snider synthesis,[4] Yamaguchi macrolactonization was accompanied by competitive dimer and trimer formation. Our studies[5c] of a relay ring closing metathesis (RRCM) process[5b] can also be interpreted as evidence for strain in the bridged bicycle of **1**. Collectively, these results reinforce that the macrocycle in **1** is a challenging one to close in a substrate with an intact THF ring. (b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211. (c) Relay substrates **i** gave only the products of truncation **ii** upon treatment with the Grubbs metathesis initiator **G2** (i.e., the metathesis relay, but not the subsequent ring closing event occurred). By contrast and under the same conditions, each of the "relaxed" substrates **iii** closed efficiently to the 14-membered lactones **iv**, suggesting that the ring-closing event was faster than (bimolecular) truncation.[9]



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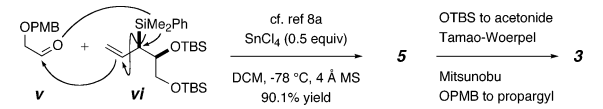

(9) Details of the conversion of **5** into **3a** and **3b**[8b] as well as of the syntheses of (±)-**4** and the three cyclization substrates **2a**, **2b**, and **15** (Scheme 4) are described: Wang, J. Ph.D. Thesis, University of Minnesota, 2005.

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JA051749I