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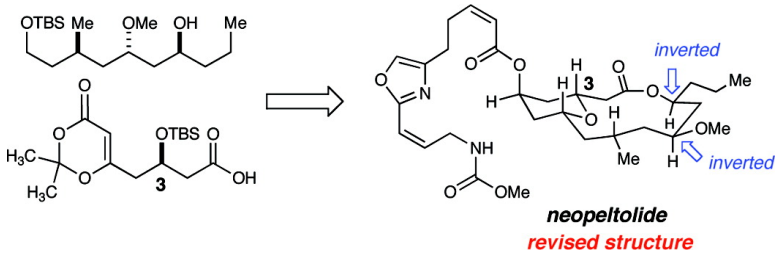
J. Am. Chem. Soc., **2008**, 130 (3), 804-805 • DOI: 10.1021/ja710080q



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Published on Web 12/28/2007

Total Synthesis and Structural Revision of the Marine Macrolide Neopeltolide

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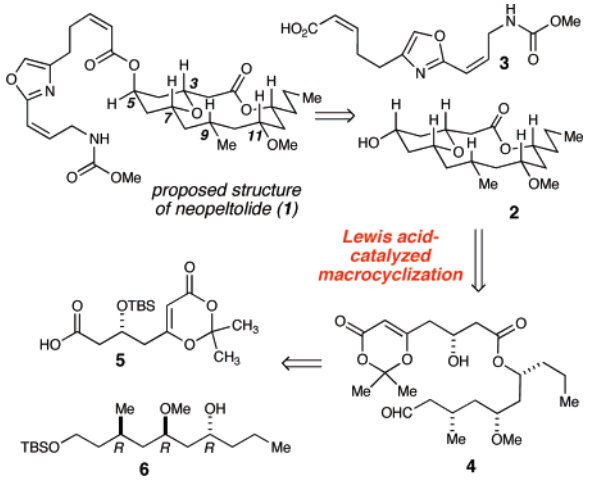
Bioactive marine natural products continue to be a source of potential therapeutic compounds as well as inspiration to develop new synthetic strategies for their construction.[1] Rich sources of promising compounds are the marine sponges from the order Lithistida that are found in warm water environments.[2] Recently, Wright and co-workers reported the isolation and structure elucidation of the marine macrolide neopeltolide (**1**) from sponges most closely related to the genus *Daedalopelta Sollas*.[3] Neopeltolide is an extremely potent inhibitor of tumor cell proliferation with IC_{50} values against lung adenocarcinoma (A549), ovarian sarcoma (NCI/ADR-RES), and murine leukemia (P388) of 1.2, 5.1, and 0.56 nM, respectively. The molecular formula and tricyclic nature of neopeltolide was determined by ^{13}C NMR spectroscopy and mass spectrometry. The planar structure was proposed on the basis of one- (1D) and two-dimensional (2D) ^1H NMR techniques, including advanced TOCSY and COSY experiments. A foreshadowing of the problems regarding the structure included HMBC experiments which surprisingly did not connect the C2−C8 and C9−C16 spin systems. The relative stereochemistry of **1** was assigned on the basis of coupling constants, advanced 1D NOE and 2D NOESY experiments, but the absolute stereochemistry of neopeltolide was not reported.

The key structural attributes of neopeltolide include a 2,6-*cis*-tetrahydropyran unit encircled by a 14-membered macrolactone and an oxazole side chain at C5 that is found in the natural product leucascandrolide A. We were immediately drawn to neopeltolide because we envisioned the embedded tetrahydropyran could be constructed using our recently developed Lewis acid-catalyzed cyclization.[4] The plan was to utilize this stereoselective process as the key bond-forming event, thereby constructing the tetrahydropyran ring and the macrolactone simultaneously (Scheme 1). Since our previous intermolecular reactions were highly diastereoselective, we anticipated that the configuration of C3 would control the cyclization to deliver diequatorial substituents at C3 and C7. The linear precursor to this macrocyclization (**4**) would be constructed from dioxinone acid **5** and alcohol **6**. We did not fully appreciate the convergency of our plan until questions regarding stereochemistry of **1** arose.

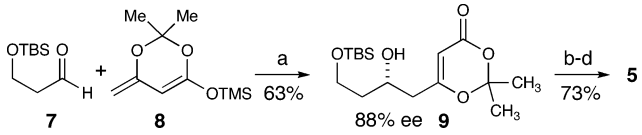
The synthesis of acid **5** began with the Ti(IV)-(*R*)-BINOL-catalyzed aldol reaction between dienoxy silane **8**[5] and the protected saturated aldehyde (**7**) to afford secondary alcohol **9** in 63% yield and 88% ee (Scheme 2).[6] The protection of the alcohol and subsequent two-step conversion of the primary silyl ether to the carboxylic acid furnished the dioxinone acid **5** poised for the fragment assembly acylation (Scheme 4). The synthesis of the target alcohol commenced with the two-step conversion of β-hydroxy ester **10**[7] to Weinreb amide **11**.[8] The addition of the alkyl lithium derived from **12** to this amide afforded the extended ketone **13**.[9,10] The removal of the PMB group and a selective Evans−Tischenko reduction[11] generated alcohol **14** with the requisite *anti* stereochemistry. A careful methylation of **14** and hydrolysis of the benzoate furnished the necessary alcohol **6**.

The fragment coupling of **5** and **6** was accomplished using Yamaguchi's protocol[12] (Scheme 4).The removal of both silyl ethers proceeded smoothly with HF·pyridine, and the resulting diol underwent a selective oxidation of the primary alcohol with TEMPO[13] to generate acyclic aldehyde **4**. In the key step, scandium(III) triflate promoted the macrocyclization of **4** to produce the fully elaborated 14-membered ring. Although the yield for this Prins-type transformation is modest, a high degree of complexity is generated in this single unprecedented step. The tricyclic dioxinone (**15**) was converted to alcohol **2** by heating in wet DMSO followed by a selective reduction of the ketone with $NaBH_4$. Much to our surprise, a Mitsunobu reaction with alcohol **2** and carboxylic acid **3**[14] produced a compound whose spectra were similar, but not identical, to the natural product. At this point, extensive NOE

Scheme 1. Synthetic Plan

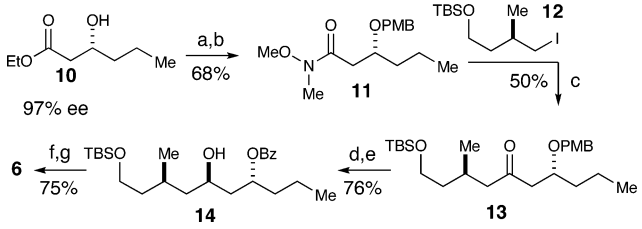


Scheme 2. Dioxinone Fragment Synthesis[a]



[a] Conditions: (a) Ti(*i*-PrO)$_4$, (*R*)-BINOL, 4 Å sieves, CH_2Cl_2. (b) TBS-OTf, 2,6-lutidine, CH_2Cl_2. (c) pPTs, EtOH. (d) PDC, DMF.

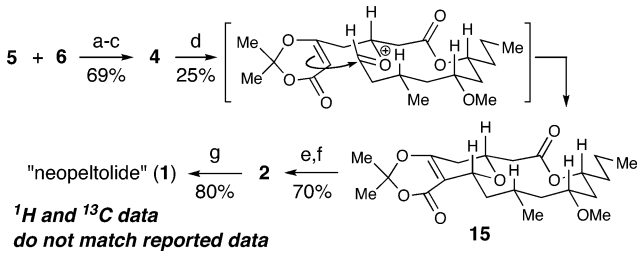
Scheme 3. Alcohol Fragment Synthesis[a]



[a] Conditions: (a) $H_2N(Me)OMe\cdot Cl$, *i*-PrMgBr, THF. (b) PMB−OC(NH)CCl_3, pPTs, cyclohexane/CH_2Cl_2. (c) *t*-BuLi, pentane/Et_2O, −78 °C. (d) DDQ, pH 7 buffer, CH_2Cl_2. (e) SmI_2, PhCHO, THF, 0 °C. (f) MeOTf, DTBMP, CH_2Cl_2. (g) K_2CO_3, MeOH.

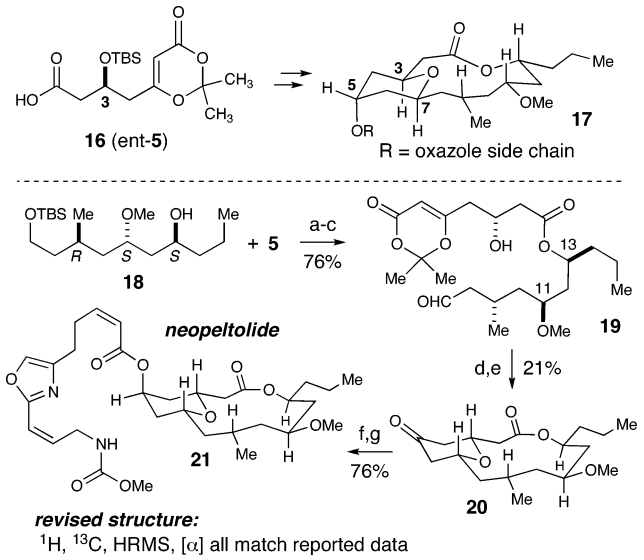
10.1021/ja710080q CCC: $40.75

Scheme 4. Fragment Coupling and Initial Synthesis[a]



[a] Conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, THF. (b) HF·pyridine, THF. (c) TEMPO, $H_5C_6I(OAc)_2$, CH_2Cl_2. (d) $Sc(OTf)_3$, $CaSO_4$, MeCN. (e) DMSO, H_2O, 130 °C. (f) $NaBH_4$, MeOH, 0 °C. (g) DIAD, Ph_3P, **3**, benzene.

Scheme 5. Completion of the Synthesis[a]



[a] Conditions: see conditions for Scheme 4.

experiments on **1** strongly supported the depicted relative stereochemistry system.[15]

The discrepancies between our synthetic **1** and the isolation data prompted us to consider a variety of possibilities. If an oxonia-Cope reaction[16] had intervened in our intramolecular scandium(III) cyclization, then this process could have inverted the configurations at C3, C5, and C7, thereby producing diastereomer **17** instead of neopeltolide (Scheme 5).[17] We decided to test this oxonia-Cope hypothesis by starting with the opposite configuration at C3. If a rapid equilibrium was in effect during the cyclization, **16** (the enantiomer of **5**) would ultimately lead to observable amounts of **1**. Accordingly, **16** was prepared using Ti(IV)-(*S*)-BINOL and then taken through the synthesis. For a second time, the installation of the oxazole side chain did not produce **1**, but diastereomer **17**. An NOE analysis of **17** indicated that the C3, C5, and C7 configurations were indeed inverted relative to **1**, thereby ruling out the oxonia-Cope process and reinforcing our earlier premise that the first route had accessed the original neopeltolide structure.

After careful consideration of the original data in conjunction with our synthetic efforts, we postulated that the correct structure for neopeltolide was the diastereomer with C11 and C13 inverted compared to **1**. Given our convergent approach, testing this hypothesis was straightforward. The desired alcohol **18** with inverted stereochemistry at C11 and C13 was prepared in a similar manner to that for **6**.[15] The esterification, deprotection, and selective oxidation steps proceeded smoothly. After the scandium(III)-promoted macrocyclization, the dioxinone was heated in DMSO to afford the ketone (**20**). The fully elaborated structure (**21**) was assembled by reduction of the carbonyl of **20** to the equatorial alcohol followed by a Mitsunobu reaction with acid **3**. Gratifyingly, the ^1H and ^{13}C spectra of macrocycle **21** match the reported data for neopeltolide. The NOESY and HRMS data and optical rotation confirmed that compound **21** is indeed neopeltolide.[15] It seems that the challenges assigning the relative stereochemistry of this natural product arise from the flexibility of the macrocycle which can orient the C9−C11−C13 methine protons for the original NOE correlations.[18]

In conclusion, the total synthesis of the marine macrolide neopeltolide has been accomplished. The key bond-forming event involves the Lewis acid-catalyzed cyclization between a dioxinone and in situ generated oxocarbenium ion to generate the THP ring and macrocycle concurrently. This macrocyclization strategy is the first of its kind and will be applied to future natural product targets. The route detailed herein is convergent and flexible, thereby allowing for the synthesis of multiple diastereomers that facilitated the structural revision and absolute stereochemistry determination of neopeltolide. These studies reinforce the vital role that total synthesis continues to play in determining the actual structures of promising natural products.

Acknowledgment. This work has been generously supported by the Sloan Foundation, Abbott, Amgen, AstraZeneca, 3M, GlaxoSmithKline and Boehringer-Ingelheim. We thank Dr. Thad Franczyk and Professor Regan Thomson for helpful discussions and Dr. Amy Wright for providing copies of NMR spectra.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA710080Q