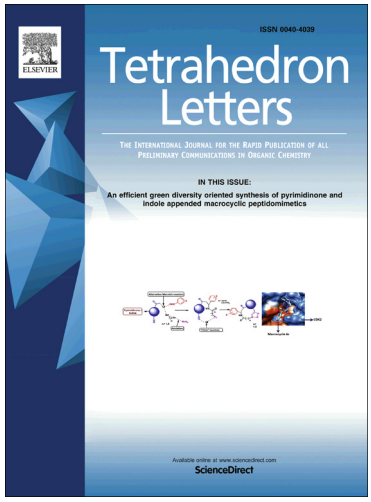


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## Graphical Abstract

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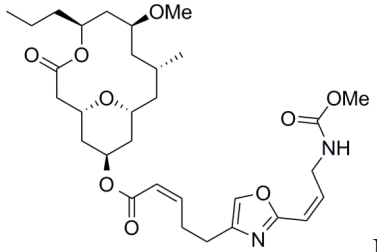


Neopeltolide

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# Stereocontrolled synthesis of the macrolactone core of neopeltolide

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ABSTRACT

A stereoselective synthesis of the macrolactone core of neopeltolide is described. The tetrahydropyran moiety was constructed via the intramolecular allylation of an α-acetoxy ether. A late-stage macrolactonization provided a known synthetic intermediate of neopeltolide.



## Introduction

In 2007, Wright and co-workers isolated the macrolide neopeltolide (**1**) from the deep-water sponge Daedalopelta and elucidated its structure.[1] The first proposed structure was later corrected as shown in Figure 1 based on the total syntheses by Panek and Scheidt groups, independently.[2a,b] The structure of **1** consists of a 14-membered macrolactone including a THP ring, bound to an oxazole-containing side-chain. Biologically, **1** was reported to show high in vitro inhibition of different cancer cell lines in the nanomolar range (0.56 nM for P388 murine leukemia cell lines). Furthermore, the unique structural features have attracted attention of synthetic organic chemists, and various approach to the total synthesis of **1** have been reported over the past decade.[2] In this paper, we wish to describe a convergent approach to the THP macrolactone structure of **1** as a part of synthetic study of THP macrolide derivatives based on the intramolecular allylation methodology.

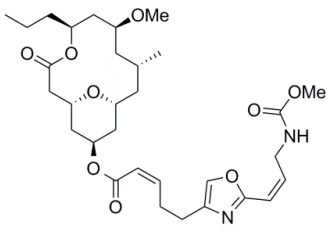
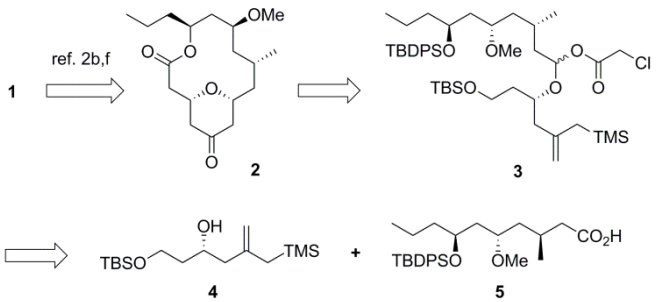


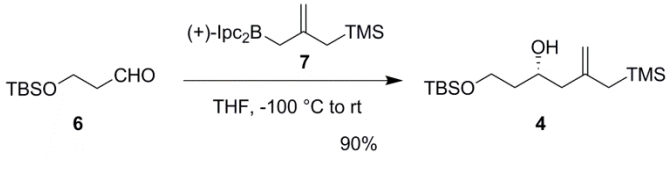

**Figure 1**. Revised structure of neopeltolide (**1**)

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. Scheidt and co-workers published the total synthesis of neopeltolide (**1**) from macrolactone **2**, which we set as our target molecule in this study.[2b] For the construction of the THP ring, we recently reported a stereoselective and convergent synthesis via the intramolecular allylation of $\alpha$-acetxy ether and used this strategy in the convergent total synthesis of dactylolide[3] and formal total synthesis of enigmazole A.[4] According to this strategy, the synthetic intermediate **2** would be synthesized from an $\alpha$-acetoxy ether **3** followed by macrolactonization. The cyclization precursor **3** could be prepared from alcohol fragment **4** and carboxylic acid fragment **5**.

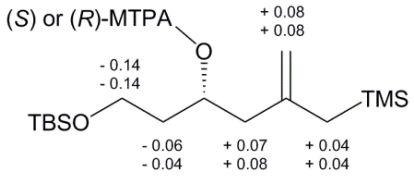



**Scheme 1.** Retrosynthetic analysis of neopeltolide (**1**).

Prepapration of the alcohol fragment **4** is illustrated in Scheme 2. The asymmetric allylboration of aldehyde **6**[5] with the chiral allylborane **7** gave **4** in 90% yield.[3]



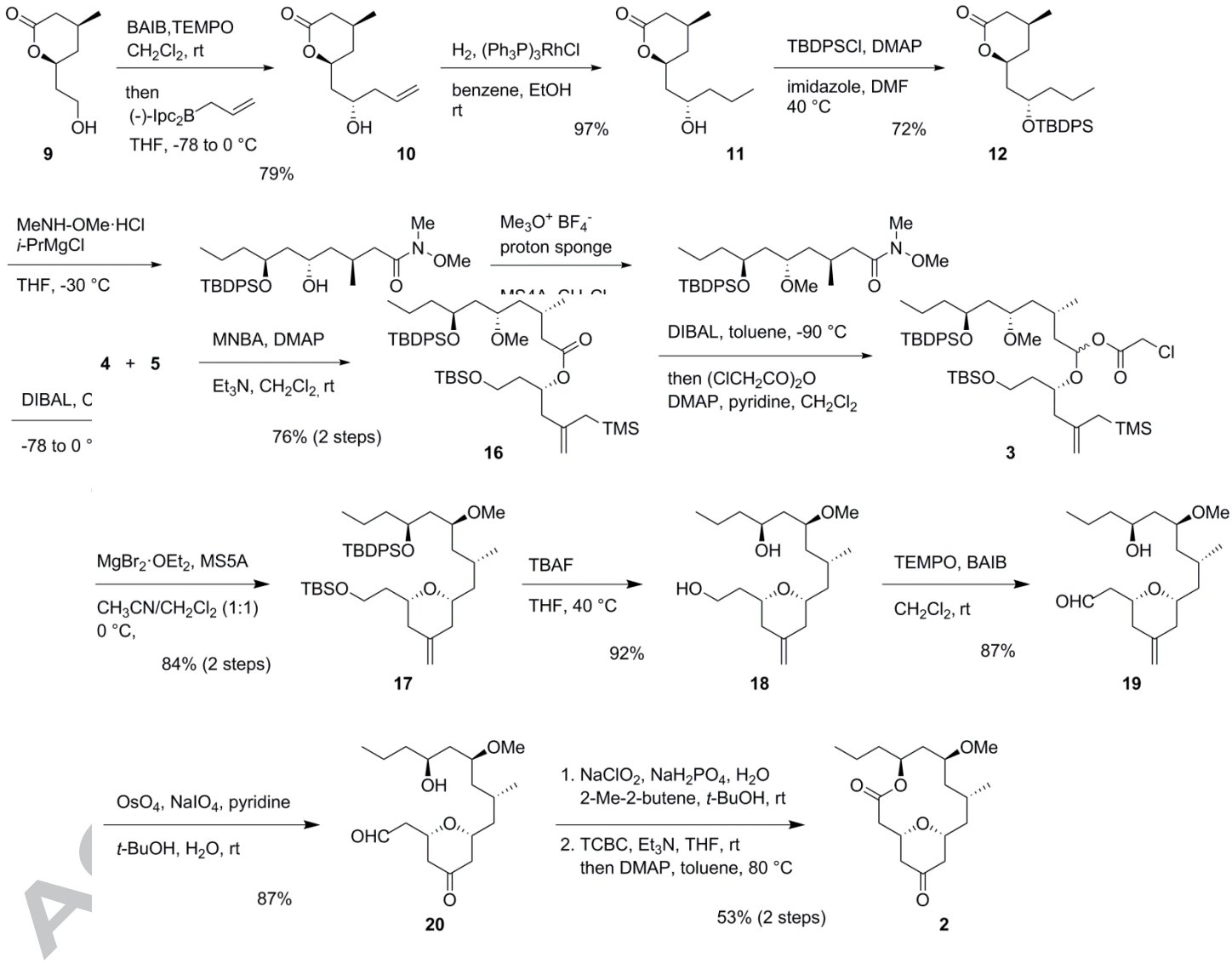

**Scheme 2.** Synthesis of the alcohol fragment **4**.




**8**

**Figure 2.** Chemical shift differences ($\Delta\delta_{S-R}$) of MTPA esters **8** derived from **4**.

The synthesis of the carboxylic acid fragment **5** was started from hydroxy lactone **9**, prepared by the reported procedure (Scheme 3).[7] Stereoselective installation of the propyl group was performed by three step sequence. Thus, oxidation of **9** with TEMPO/BAIB followed by Brown's allylation with a chiral allylic borane reagent gave homoallylic alcohol **10** in 79%, stereoselectively.[8] The diastereomeric purity was higher than 95% as determined by Mosher`s ester analysis.[6] Hydrogenation of the olefin **10** with $H_2$/Wilkinson catalyst provided **11** in 97% yield.[9] The alcohol **11** was protected with TBDPSCl/imidazole to give silyl ether **12** in 72% yield. Treatment of **12** with MeNH-OMe/*i*-PrMgCl opened the lactone to give Weinreb amide **13** in



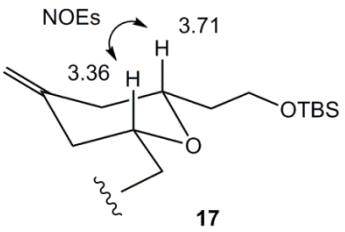

**Scheme 4.** Synthesis of the macrolactone **2**.

The absolute configuration of the hydroxyl group of **4** was confirmed by the modified Mosher's analysis on the MTPA ester derivatives **8** as shown in Figure 2.[6]

90%. Reaction of **13** with Meerwein reagent/proton sponge delivered methyl ether **14** in 76%.[10] Since the hydrolysis of Weinreb amide tend to require harsh conditions such as strong base or microwave irradiation,[11] the Weinreb amide **14** was converted to the carboxylic acid **5** via two-step sequence. Thus, partial reduction of **14** with DIBAL-H giving aldehyde **15** (92%) followed by the Pinnick oxidation to furnish the carboxylic acid fragment **5**.

Esterification of the alcohol **4** and carboxylic acid **5** was carried out under the Shiina conditions to give ester **16** in 76% overall yield (Scheme 4).[12] Partial reduction of the ester **15** with

DIBAL-H followed by trapping of the acetal intermediate with $(CH_2ClCO)_2O$/DMAP/pyridine gave α-acetoxy ether **3**.[13,14] The cyclization precursor **3** obtained was then subjected to the intramolecular allylation using $MgBr_2 \cdot OEt_2$ as a Lewis acid and MS5A in $CH_3CN/CH_2Cl_2$ (1:1) yielding the desired methylene THP derivative **17** as a single stereoisomer in 84% overall yield. The stereochemistry of the methylene THP ring moiety newly generated was confirmed by the $^1H$ NMR analysis and NOE experiments as shown in Figure 3. Both of the TBDPS and TBS groups were removed using TBAF at elevated temperature to give diol **18** in 92% yield. Selective oxidation of the primary hydroxyl group of **18** was performed with TEMPO/BAIB to provide aldehyde **19** in 87% yield. According to a reported procedure, the olefin of **19** was subjected to oxidative cleavage with $OsO_4/NaIO_4$ to yield **20** in 87% yield.[2f] Pinnick oxidation of the aldehyde **20** followed by macrolactonization under the Yamaguchi conditions furnished the lactone **2** in 53% overall yield.[15] The spectroscopic data ($^1H$ and $^{13}C$ NMR) and optical rotation ($[\alpha]_D^{21}$ +18.0 (c 0.16, $CHCl_3$), lit.[2b] $[\alpha]_D^{25}$ +32.6 (c 0.1, $CHCl_3$), lit.[2f] $[\alpha]_D^{21}$ +18.0 (c 0.4, $CHCl_3$)) of the synthetic material **2** were in good agreement with those reported previously.




**17**

**Figure 3.** Observed NOEs are shown by arrows.

## Conclusion

In conclusion, we have achieved the stereocontrolled synthesis of the macrolactone core of neopeltolide via the intramolecular allylation methodology. The current work demonstrates the ability of our methodology for the synthesis of methylene THP macrolide derivatives. Further application of the methodology to the total syntheses of natural products is in progress.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://

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## Highlights

Reporting a stereocontolled synthesis of the macrolide core of neopeltlide, a cytotoxic macrolide.

The 2,6-disubstituted THP ring moiety was constructed by the intramolecular allylation of an α-acetoxy ether derivative.

A stereocontrolled synthesis of the macrolide core of neopeltlide was accomplished.