Total Synthesis of the Antiproliferative Macrolide (+)-Neopeltolide
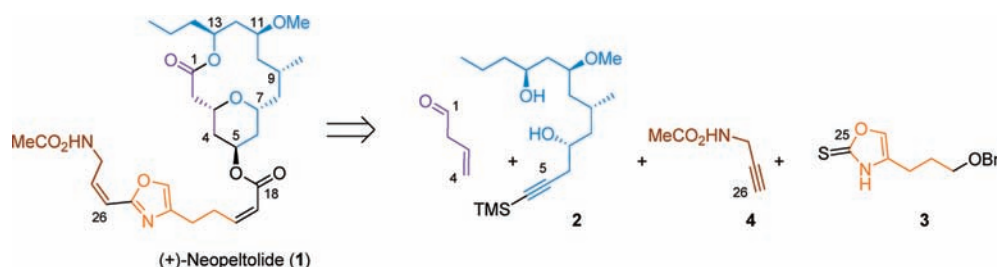
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ABSTRACT

A concise total synthesis of the very promising antiproliferative macrolide (+)-neopeltolide (1) has been performed in 16 steps. The main steps of this approach are a Ru[II]-catalyzed alkyne−enal coupling, a Pd[0]-catalyzed desulfurative cross-coupling, and a stereoselective In[III]-catalyzed propargylation. Four stereogenic centers out of six have been set thanks to substrate-controlled diastereoselective reactions with minimal reliance on protecting groups.

(+)-Neopeltolide (**1**) is a marine macrolide isolated in 2006 by Wright et al.[1] from a sponge of the Neopeltidae family. Beyond the synthetic challenge, (+)-**1** has a great intrinsic value as it is endowed with a nanomolar level of activity against proliferation of various cancer cell lines (A549 human lung adenocarcinoma, NCI/ADR-RES ovarian sarcoma, and P388 murine leukemia with IC_{50} of 1.2, 5.1, and 0.56 nM, respectively) as well as on DLD-1 colorectal cell lines or on the treatmentless PANC-1 pancreatic cell lines.[1] (+)-Neopeltolide (**1**) also shows effective activity against fungal pathogens such as *Candida albicans*.[1] One must notice that (+)-**1** shares common biological properties with (+)-leucascandrolide A,[2] a structurally homologous marine natural product. Furthermore, Kozmin[3] suggested that both compounds target cytochrome *b*c1, resulting in the inhibition of
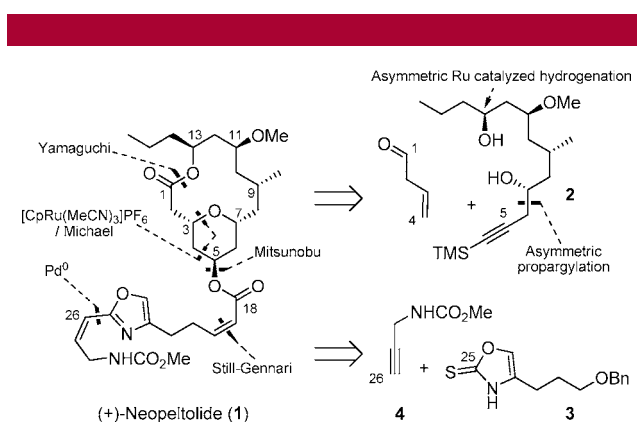

Figure 1. Retrosynthesis.

mitochondrial ATP synthesis. It is noteworthy that the relative configuration initially proposed by Wright et al.[1] for (+)-**1**, which arose from advanced NMR studies, was

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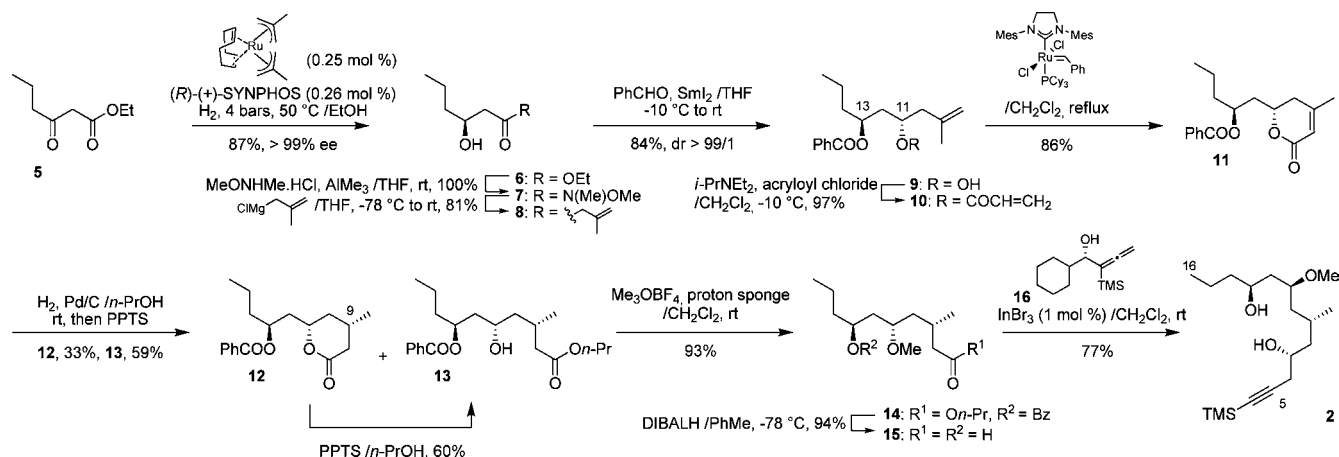
corrected thanks to total syntheses by Panek[4] and Scheidt.[5] They thus established the right relative configurations for C11 and C13 and accordingly determined the absolute configuration of (+)-neopeltolide (1). Since then, this molecule has strongly inspired the organic chemist community leading to four more total asymmetric syntheses,[6] one racemic approach[3] and three formal syntheses,[7] along with the synthesis of neopeltolide analogues.[6d,8]

The main features of the (+)-neopeltolide (1) structure include six asymmetric centers, a macrolactonic ring fused with a trisubstituted tetrahydropyran ring to which is attached an oxazole-containing side chain, which is identical to that of (+)-leucascandrolide A. This original structure attracted our attention and teased our imagination leading to the retrosynthetic plan shown in Figure 1. Inspired by the work of Trost,[9] we imagined performing a rapid and stereoselective elaboration of the tetrahydropyran ring of (+)-1 in the course of a [CpRu(MeCN)₃]PF₆-catalyzed tandem alkyne−enal coupling/Michael addition sequence. This key step would allow assemblage of the silylated alkyne 2 with 3-butenal, an "ene" cross-coupling partner never used in this type of reaction before. Considering that the use of asymmetric

reagents and catalysts increases the cost of syntheses, we designed a strategy restricting their use only to control two centers (C13 and C7) out of six, the four remaining centers (C3, C5, C9, C11) being set by substrate-controlled diastereoselective reactions. Furthermore, a minimal reliance on protective groups was targeted, leading to atom economy and reduced costs. The C18−C28 oxazole-containing side chain has also attracted our attention, and we thought it possible to develop a synthesis more straightforward than those already reported.[6b,d,10] For this goal, a Pd⁰-catalyzed desulfurative Sonogashira-like cross-coupling would allow assemblage of the oxazolethione 3 with alkyne 4.[11]

The route toward the key C5−C16 fragment 2 commenced (Scheme 1) by the ruthenium-catalyzed asymmetric hydrogenation of β-ketoesters developed by Genêt et al.[12] providing alcohol 6 from compound 5 with a full control of the C13 stereogenic center. After transformation into the Weinreb amide[13] 7, a reaction with (2-methylallyl)magnesium chloride led to β,γ-unsaturated ketone 8. An Evans−Tishchenko reaction[14] on ketone 8 allowed to control the C11 configuration providing the *anti* 1,3-diol 9 (84% yield) as a sole detectable diastereoisomer while installing a strategically useful benzoate ester at C13. The alcohol function that remained free at C11 was allowed to react with acryloyl chloride yielding the diene 10. The ring closure metathesis of the latter using second-generation Grubbs' catalyst,[15] led to the α,β-unsaturated lactone 11 in 86% yield. Then, the C9 stereogenic center was controlled by a simple Pd/C-catalyzed hydrogenation that turned out to be totally diastereoselective but with solvolysis leading to an equilibrated mixture of lactone 12 and *seco*-ester 13 (ratio: 1/2). Lactone 12 could be nevertheless cleanly reconverted into 13 using

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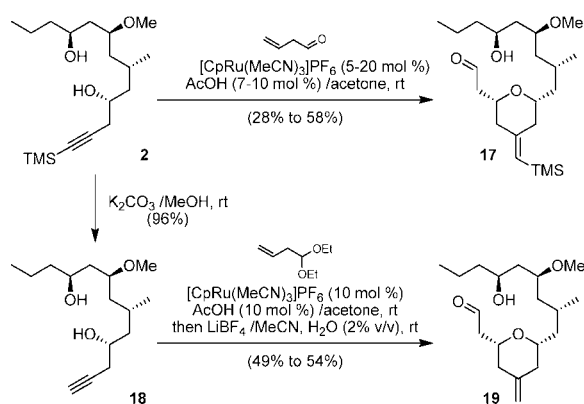(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* 1981, *22*, 3815–3818.

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smooth acidic conditions that left the benzoyl ester untouched. Then, the secondary alcohol functionality at C11 was transformed into a methoxy group using the Meerwein's salt[16] leading to **14**. In the next step, a careful DIBALH addition on diester **14** at low temperature led to aldehyde **15** in 94% yield while removing the benzoyl group inherited from the Evans–Tishchenko step. The second (and last) reaction involving an asymmetric reagent of this total synthesis was used to control the C7 stereogenic center. This step consisted of the In^{III}-catalyzed propargylation reaction[17] in the course of which occurred a fully stereoselective transfer of the trimethylsilylpropynyl group from the asymmetric allenyl alcohol **16**[18] on aldehyde **15** leading to key homopropargylic alcohol **2**.

With homopropargylic alcohol **2** in hand, we investigated Ru-catalyzed reaction conditions (Scheme 2) targeting tetra-

hydropyran **17** by reaction with 3-butenal.[19] To our delight, this key step occurred leading to **17** in the course of the expected Ru-catalyzed tandem alkyne–enal coupling/stereoselective Michael addition sequence. When adding a catalytic amount of AcOH, tetrahydropyran **17** was obtained in better yields and as one sole diastereoisomer (creation of the C3 stereogenic center). Nevertheless, this reaction suffered from poor reproducibility, with yields of **17** varying from 28% to 58%, probably because of the unstable nature of 3-butenal. During the studies on the [CpRu(MeCN)$_3$]PF$_6$-catalyzed ene–yne cross-coupling reactions, Trost demonstrated that the presence of a silicon atom on the alkyne usually strongly favors the formation of branched products, disfavoring linear ones.[20] Nervertheless, there were only scarce examples of nonsilylated terminal alkynes giving branched products with good selectivity.[21] In spite of this, we tried the coupling of the readily obtained desilylated alkyne **18** with 4,4-diethoxybut-1-ene,[22] a protected equivalent of 3-butenal. We were delighted to obtain exclusively the branched product **19** in the course of a fully diastereoselective and reproducible (49% to 54% yield) one-pot, three-step sequence including the now-needed LiBF$_4$·H$_2$O-promoted acetal-hydrolysis/Michael cyclization. Here again, the use of a catalytic amount of AcOH appeared to be instrumental to allow the ene–yne coupling to occur efficiently. One can notice that the reaction also worked well on **18** using [Cp*Ru(MeCN)$_3$]PF$_6$ under the same conditions, leading to **19** in 54% yield with a notably shortened reaction time.

The *exo*-methylene functions of either compounds **17** or **19** was oxidized by OsO$_4$ and NaIO$_4$ leading to ketone **20** (Scheme 3), which was then transformed into the known
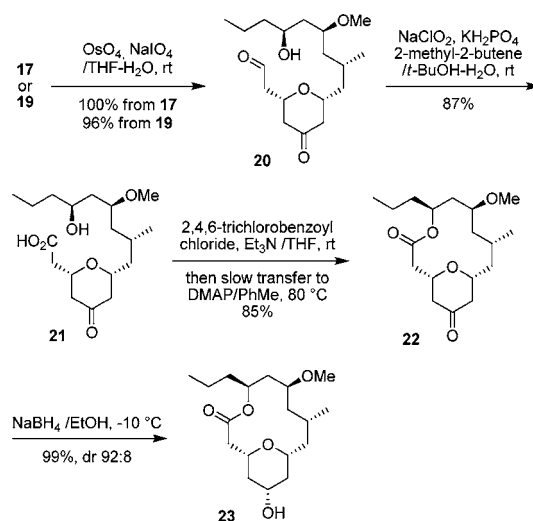
carboxylic acid **21**[6b] using the Pinnick oxidation.[23] The macrocycle was then closed using classical Yamaguchi macrolactonization conditions[24] affording **22** in high yield. As described by Scheidt,[5] the ketone **22** was reduced by NaBH$_4$ into the key alcohol **23** with a good diastereoselectivity.

Concerning the synthesis of the oxazole-containing side chain, we started from oxazolethione derivative **3** (Scheme 4), which was easily accessed by reaction of KSCN[25] with the known α-hydroxyketone **24**.[26] Using the palladium-catalyzed copper-induced desulfurative cross-coupling conditions described by Tatibouët,[11] we coupled oxazolethione **3** with alkyne **4** yielding oxazole **25**, comprising the first use of this methodology in the natural product synthesis context. The alkyne functionality of **25** was then partially hydrogenated using Lindlar catalyst leading to the *Z* alkene **26**. The

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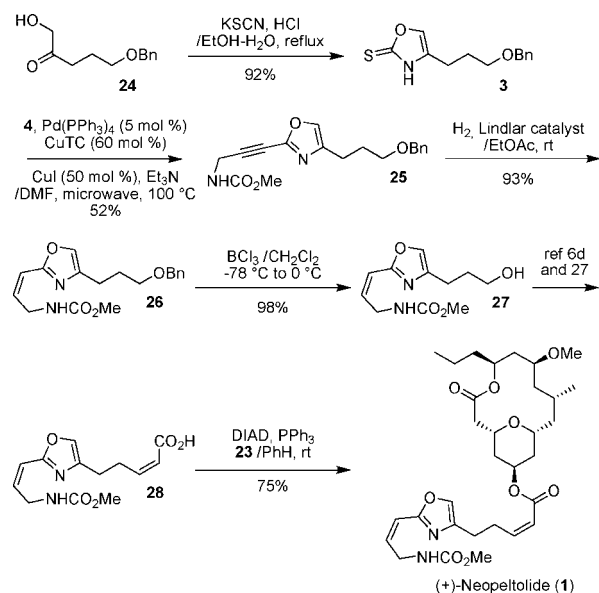(18) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131.

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Scheme 4. Synthesis of the Oxazole-Containing Side Chain **28** and Final Coupling

This final step supplied (+)-neopeltolide (**1**), the chemical data of which are identical with those reported for the naturally occurring compound [[α]$^{20}_D$ +24.4 (*c* 0.24, MeOH) (lit.[1a] [α]$^{20}_D$ +24.0 (*c* 0.24, MeOH)].

In conclusion, we have achieved one of the shortest and most straightforward (16 steps from **5**, 6.2% overall yield) total syntheses of (+)-neopeltolide (**1**), a novel biologically highly important cytotoxic marine natural product. In the course of this synthesis, four stereogenic centers out of six have been set, thanks to substrate-controlled diastereoselective reactions, and our strategy also allowed us to minimize the use of protective groups. We also performed a new and straightforward synthesis of the oxazole-containing C20−C28 chain also found in other natural products.

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

benzyl group was then removed leading to known alcohol **27**.[27] Finally, we obtained acid **28** by following the route described by Panek[27] and Maier.[6d]

For the end game, we coupled alcohol **23** with acid **28** in Mitsunobu conditions, following the Scheidt strategy,[5] this reaction setting then the right C5 configuration (Scheme 4).

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