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Total Synthesis of the Antiproliferative Macrolide (+)-Neopeltolide

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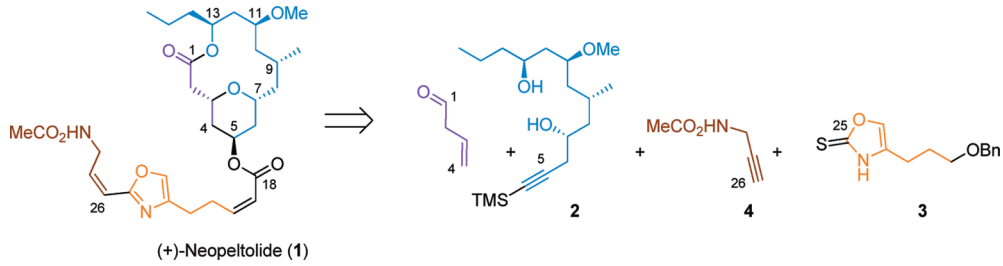
ABSTRACT



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 *bc*1, resulting in the inhibition of 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

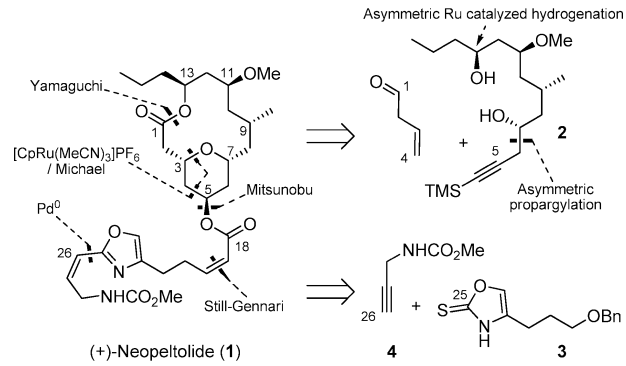


Figure 1. Retrosynthesis.

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(1) (a) Wright, A. E.; Cook Botelho, J.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412–416. (b) Wright, A. E.; Pomponi, S. A.; McCarthy, P. J. U.S. Patent 7179828B2, 2007, European Patent 1644380, 2007.

(2) d'Ambrosio, M.; Tatò, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347–353. Erratum: d'Ambrosio, M.; Tatò, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 1135.

(3) Ulanovskaya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumacker, P. T.; Kron, S. J.; Kozmin, S. A. *Nat. Chem. Biol.* **2008**, *4*, 418–424.

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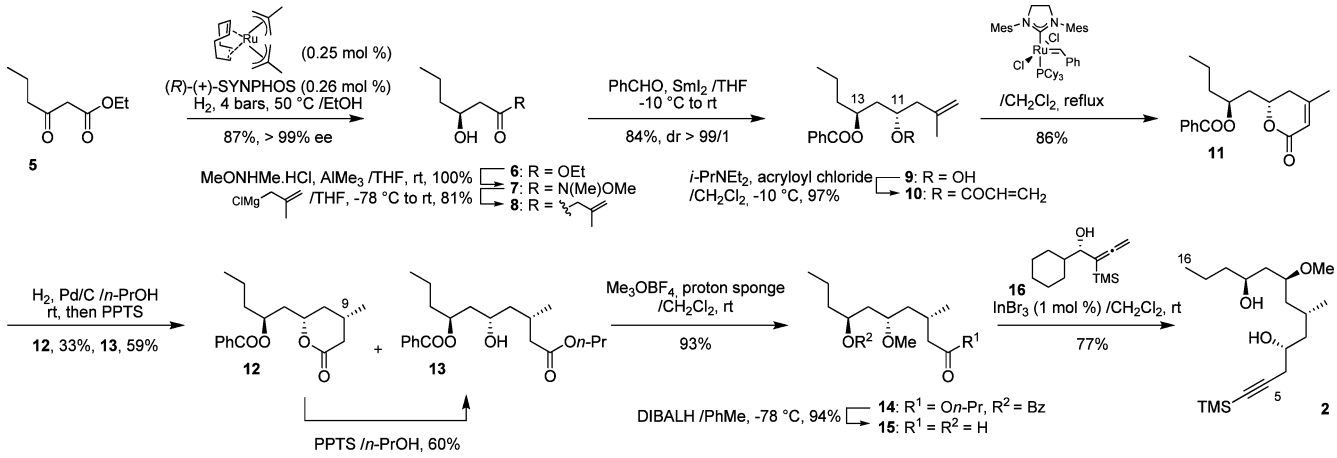
Scheme 1. Synthesis of the C16−C5 Fragment **2**



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)$_3$]PF$_6$-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 Pd^0-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

(4) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211–9214.
(5) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804–805.
(6) (a) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737–4739. (b) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708–4710. (c) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242–3244. (d) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.—Eur. J.* **2008**, *14*, 11132–11140. For a review, see: (e) Gallon, J.; Reymond, S.; Cossy, J. C. R. *Chimie* **2008**, *11*, 1463–1476.
(7) (a) Vintonyak, V. V.; Maier, M. E. *Org. Lett.* **2008**, *10*, 1239–1242. (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047–5050. (c) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567–4571.
(8) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406–12414.
(9) Trost, B. M.; Yang, H.; Wuitschik, G. *Org. Lett.* **2005**, *7*, 4761–4764.
(10) (a) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343–347. (b) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670–13671. (c) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895. (d) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2–24.
(11) Silva, S.; Sylla, B.; Suzenet, F.; Tatibouët, A.; Rauter, A. P.; Rollin, P. *Org. Lett.* **2008**, *10*, 853–856.
(12) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931–1941.
(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(14) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

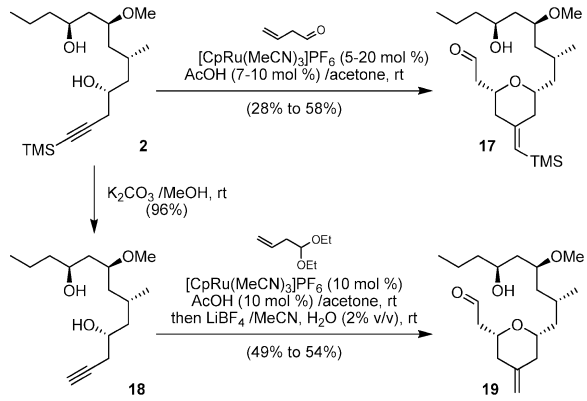
smooth acidic conditions that left the benzoyl ester untouched. Then, the secondary alcohol functionality at C11 was transformed into a methoxy group using the Meerwein's salt[16] leading to **14**. In the next step, a careful DIBALH addition on diester **14** at low temperature led to aldehyde **15** 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 tetrahydropyran **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 $LiBF_4{\cdot}H_2O$-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.

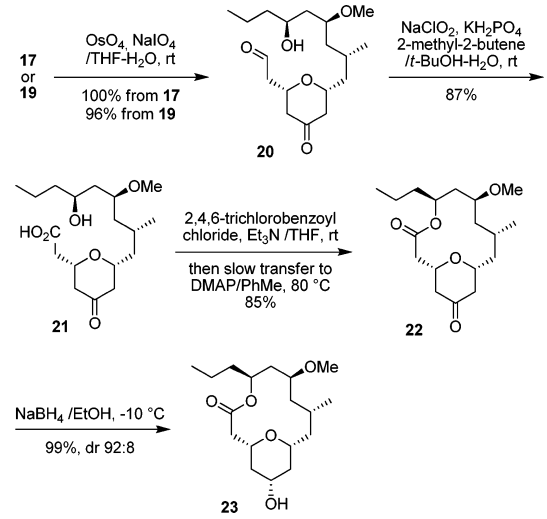
The *exo*-methylene functions of either compounds **17** or **19** was oxidized by OsO_4 and $NaIO_4$ leading to ketone **20** (Scheme 3), which was then transformed into the known carboxylic acid **21**[6b] using the Pinnick oxidation.[23] The macrocycle was then closed using classical Yamaguchi macrolactonization 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

Scheme 2. Ru^{II}-Catalyzed Ene−Yne Coupling Trials



Scheme 3. Synthesis of Key Macrolactone **23**



(16) Curphey T. J. In *Organic Synthesis*; Noland, W. E., Ed.; Wiley: New York, 1988; Vol. 6, pp 1019−1023.

(17) Lee, K.-C.; Lin, M.-J.; Loh, T.-P. *Chem. Commun.* **2004**, 2456–2457.

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

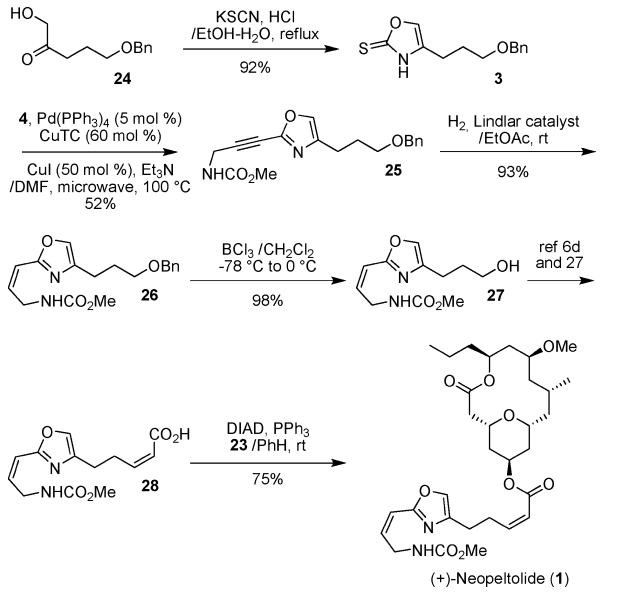
(19) Vugts, D. J.; Veum, L.; al-Mafraji, K.; Lemmens, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Hanefeld, U.; Orru, R. V. A. *Eur. J. Org. Chem.* **2006**, 1672–1677.

(20) Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761–1764.

(21) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504–12509.

(22) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

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



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).

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

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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.

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(23) (a) Bal, P. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096. (b) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465–9467.

(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(25) Leconte, N.; Silva, S.; Tatibouët, A.; Rauter, A. P.; Rollin, P. *Synlett* **2006**, 301–305.

(26) (a) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485–2488. (b) Hydroxy ketone **24** was accessed by oxidation of the corresponding alkene using the procedure described in: Bonini, C.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Pullez, M. *Eur. J. Org. Chem.* **2006**, 80–83.

(27) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812–6815.