

Concise Formal Synthesis of (+)-Neopeltolide

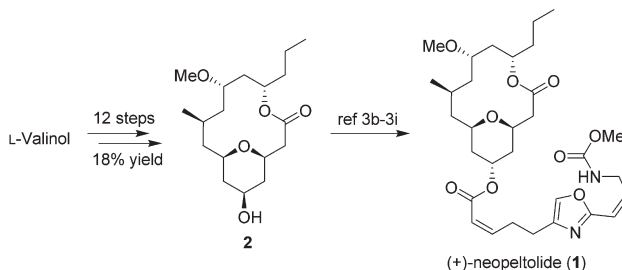
Zhen Yang,[†] Bingbin Zhang,[†] Gaoyuan Zhao,[†] Juan Yang,[†] Xingang Xie,^{*,†} and Xuegong She^{*,†,‡}

State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China

xiexg@lzu.edu.cn; shexg@lzu.edu.cn

Received September 22, 2011

ABSTRACT



A concise formal synthesis of (+)-neopeltolide (1) has been accomplished. The synthesis demonstrated high atom efficiency employing only one step of functional group protection. Key steps involved iridium-catalyzed double asymmetric carbonyl allylation, palladium-catalyzed intramolecular alkoxy carbonylation, ruthenium-catalyzed olefin isomerization, and ring-closing metathesis.

Marine sponges of the polyphyletic order “Lithistida” have been the source of a wealth of natural products with various biological activities.¹ Neopeltolide (1) was isolated from a deep-water sponge of the family Neopeltidae by Wright and co-workers in 2007 (Figure 1).² Bioactivity studies by Wright’s group showed that neopeltolide (1) exhibits significantly potent in vitro cytotoxicity toward several different cancer cell lines, including A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines, with IC₅₀s of 1.2, 5.1, and 0.56 nM, respectively. Neopeltolide (1) also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/mL. In the PANC-1 pancreatic cancer cell line and the DLD-1 colorectal adenocarcinoma cell line, both with p53 mutations, neopeltolide (1) showed strong inhibition of cell proliferation at nanomolar concentrations but did not give

the typical sigmoidal curve, and instead showed 50% cell kill over an extended dose range. Accordingly, it may be cytostatic to these cell lines rather than cytotoxic.²

The structural features of neopeltolide (1) include a 14-membered macrolactone, embedding with a tetrahydropyran ring, and six stereogenic centers. The relative stereochemistry of neopeltolide (1) was determined by combined

(3) For the total synthesis of neopeltolide, see: (a) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211. (b) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804. (c) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242. (d) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708. (e) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737. (f) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.—Eur. J.* **2008**, *14*, 11132. (g) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406. (h) Fuwa, H.; Saito, A.; Naito, S.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. *Chem.—Eur. J.* **2009**, *15*, 12807. (i) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3041. (j) 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.

(4) For the formal synthesis of neopeltolide, see: (a) Vintonyak, V. V.; Maier, M. E. *Org. Lett.* **2008**, *10*, 1239. (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047. (c) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (d) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577. (e) Guinchard, X.; Roulland, E. *Org. Lett.* **2009**, *11*, 4700. (f) Yadav, J. S.; Kumar, G. G. K. S. N. *Tetrahedron* **2010**, *66*, 480.

[†] Lanzhou University.

[‡] Chinese Academy of Sciences.

(1) Bewley, C. A.; Faulkner, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *37*, 2163.

(2) Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412.

spectroscopic analysis. Shortly afterward, the absolute stereochemistry was revised via two total syntheses by Panek^{3a} and Scheidt,^{3b} respectively.

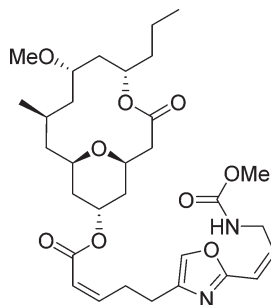
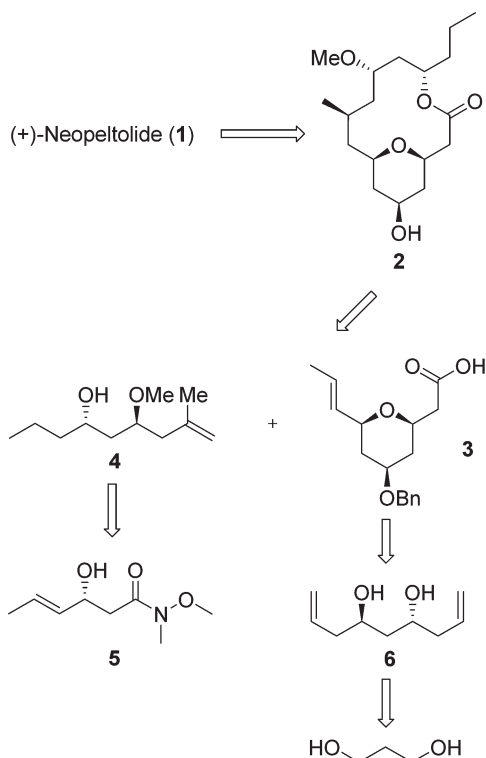


Figure 1. Structure of (+)-neopeltolide (**1**).

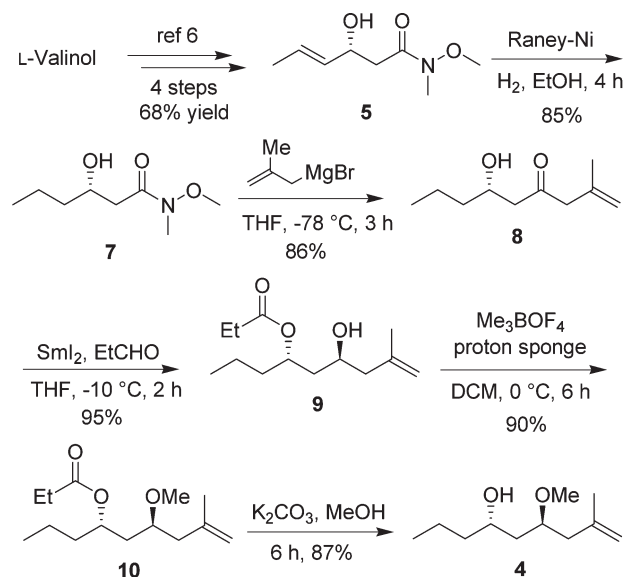
Due to its highly potent anticancer activity, considerable effects have proceeded in the synthetic community.^{3,4} The first total synthesis and stereochemical reassignment of (+)-neopeltolide (**1**) was reported by Panek and co-workers^{3a} using a [4 + 2]-allylsilane annulation to construct the pyran system. The most recent synthetic study by Fuwa³ⁱ is so far the shortest synthesis of neopeltolide (**1**) within 13 linear steps. Our group also aimed to develop an efficient synthetic route for neopeltolide (**1**), which might serve for further biological study and medicinal purposes. Herein, we reported a concise formal synthesis of (+)-neopeltolide (**1**).

Scheme 1. Retrosynthetic Analysis of (+)-Neopeltolide (**1**)



Inspired by Fuwa's work,³ⁱ our retrosynthetic analysis is briefly illustrated in Scheme 1. We envisioned that the central macrolactone core **2** might be constructed by the fragmental assembly of alcohol **4** and acid **3** via intermolecular esterification and a ring-closing metathesis reaction. Alcohol **4** could be prepared with the absence of protecting groups from the known Weinreb amide **5**, exploiting the SmI₂-promoted Evans–Tishchenko reaction. The tetrahydropyran ring in acid **3** could be obtained by means of palladium-catalyzed⁵ intramolecular alkoxyacylation of the diol **6**, which was derived from 1,3-propanediol via iridium-catalyzed asymmetric carbonyl allylation.

Scheme 2. Synthesis of Alcohol **4**



We began the efficient synthesis of alcohol **4** with the known Weinreb amide **5**, which was easily prepared according to the literature⁶ (Scheme 2). Hydrogenation of **5** with the freshly prepared Raney-Ni followed by treatment with (2-methylallyl)magnesium bromide afforded the known β -hydroxy ketone **8** in 73% yield for two steps.^{4c} SmI₂-promoted Evans–Tishchenko reduction⁷ was employed to ketone **8** generating alcohol **9** with high stereoselectivity (*anti/syn* > 95:5). Sequential O-methylation and ester hydrolysis of **9** gave alcohol **4** in excellent yield.⁸ We were pleased with the utilization of the protection group free

(5) For recent reviews of palladium(II)-catalyzed alkene functionalization, see: (a) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (e) Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (g) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854. (h) McDonald, R. I.; Liu, G. S.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

(6) (a) Gálvez, E.; Romea, P.; Urpi, F. *Org. Synth.* **2009**, *86*, 70. (b) Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148. (c) Smith, A. B.; Simov, V. *Org. Lett.* **2006**, *8*, 3315.

(7) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (b) Smith, A. B.; Cox, J. M.; Furuichi, N.; Kenesky, C. S.; Zheng, J. Y.; Atasoylu, O.; Wuest, W. M. *Org. Lett.* **2008**, *10*, 5501.

Scheme 3. Formal Synthesis of (+)-Neopeltolide (**1**)

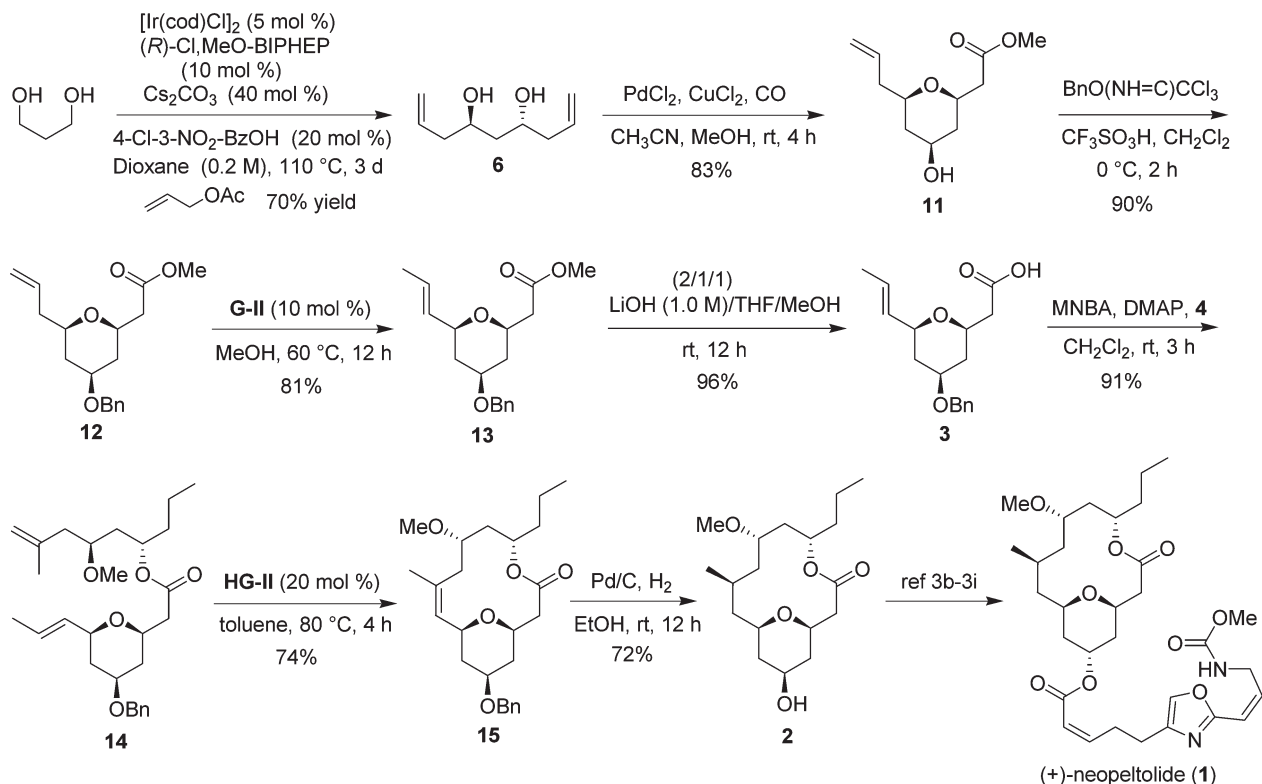


Table 1. Ring-Closing Metathesis of **14**^a

entry	catalyst (20 mol %)	conditions	yield ^c (%)
1	G-II	CH ₂ Cl ₂ , rt, 24 h	N.R.
2	G-II	toluene, 80 °C, 24 h	N.R.
3 ^b	G-II	toluene, 80 °C, 24 h	N.R.
4	HG-II	toluene, rt, 8 h	trace
5	HG-II	toluene, 80 °C, 4 h	74

^a Reactions were run in the indicated solvent (0.005 M) under argon, and the catalysts were added in one portion. ^b 1.0 equiv of 1,4-benzoquinone was used as the additive, and the catalyst was added over 6 h (see ref 3i). ^c N.R. = no reaction.

strategy to prepare alcohol **4** from Weinreb amide **5** in 54% yield over five steps.

With alcohol **4** in hand, we turned our attention to the synthesis of the macrolactone core **2** of (+)-neopeltolide (**1**)

(Scheme 3). Iridium-catalyzed double asymmetric carbonyl allylation of 1,3-propanediol furnished the C₂-symmetric diol **6** in 70% yield.⁹ Subjecting diol **6** to the palladium-catalyzed intramolecular alkoxy carbonylation reaction¹⁰ smoothly provided tetrahydropyran **11** in 83% isolated yield (d.r. > 20:1). The free secondary hydroxy group in **11** further underwent protection as the corresponding benzyl ether **12** in 90% yield.¹¹ Isomerization of the terminal olefin in **12** using Grubbs' second generation catalyst (**G-II**) in methanol¹² gave alkene **13** (*E/Z* = 8:1). Hydrolysis of the methyl ester group in **13** under basic conditions afforded carboxylic acid **3** in nearly quantitative yield.¹³

(8) (a) Smith, A. B.; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625. (b) Paterson, I.; Gibson, L. J.; Kan, S. B. *J. Org. Lett.* **2010**, *12*, 5530.

(9) (a) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (b) Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559.

(10) (a) Yang, Z.; Xie, X. G.; Jing, P.; Zhao, G. Y.; Zheng, J. Y.; Zhao, C. G.; She, X. G. *Org. Biomol. Chem.* **2011**, *9*, 984. (b) White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463. (c) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.

(11) (a) White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624. (b) Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619.

(12) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481. (c) Seden, P. T.; Charmant, J. P. H.; Willis, C. L. *Org. Lett.* **2008**, *10*, 1637.

(13) (a) Smith, A. B.; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. *Org. Lett.* **2005**, *7*, 5075. (b) Smith, A. B.; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665.

Intermolecular esterification between alcohol **4** and acid **3** was examined. To our delight, esterification under Shiina's (MNBA = 2-methyl-6-nitrobenzoic anhydride) conditions¹⁴ smoothly provided diene **14** in 91% yield. Ring-closing metathesis¹⁵ of diene **14** was tested using various conditions, and the results are summarized in Table 1. Hoveyda–Grubbs' second generation catalyst (**HG-II**) was found as the only effective one while **G-II** showed no activity. Finally, a metathesis reaction of diene **14** in toluene at 80 °C provided the macrolactone **15** as a (*Z*)-isomer in 74% yield.¹⁶ The ensuing hydrogenation of the double bond in the presence of a catalytic amount of Pd/C and at the same time removal of the C5 benzyl ether, thus, completed our synthesis of (+)-macro-

lactone **2**, which would be easily transformed into (+)-neopeltolide (**1**) according to the previous reports.^{3b–i}

In summary, a concise formal synthesis of (+)-neopeltolide (**1**) has been achieved in 12 steps (longest linear sequence) and 18% overall yield from commercially available L-valinol. Notable features include high atom economy with minimized protective group manipulation, iridium-catalyzed double asymmetric carbonyl allylation, palladium-catalyzed intramolecular alkoxycarbonylation, ruthenium-catalyzed olefin isomerization, and ring-closing metathesis. This efficient pathway would enable large scale preparation of (+)-neopeltolide (**1**) offering convenience for further studies.

(14) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.

(15) For reviews, see: (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (c) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012 and references therein.

(16) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Smith, A. B.; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872.

Acknowledgment. We are grateful for the generous financial support by the MOST (2010CB833200), the NSFC (20872054, 20732002, 21072086), and program 111.

Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.