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Concise Formal Synthesis of (+)-Neopeltolide

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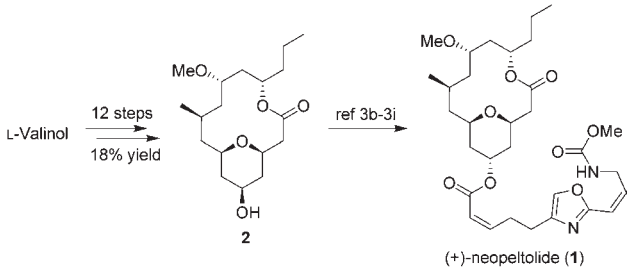
ABSTRACT



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 alkoxycarbonylation, 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

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

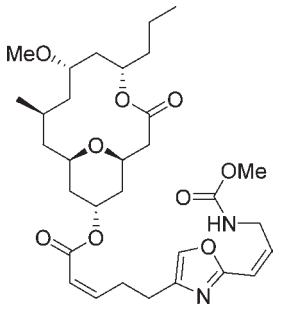
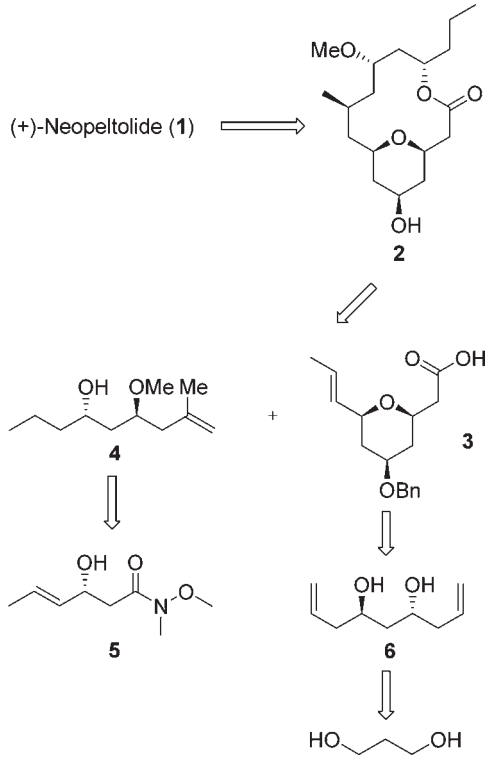


Figure 1. Structure of (+)-neopeltolide (**1**).

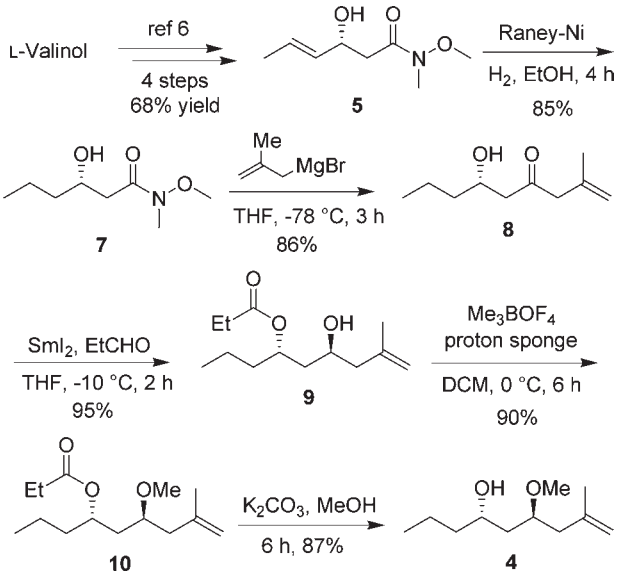
Due to its highly potent anticancer activity, considerable effects have proceeded in the synthetic community.[3,4] The first total synthesis and stereochemical reassignment of (+)-neopeltolide (**1**) was reported by Panek and co-workers[3a] using a [4 + 2]-allylsilane annulation to construct the pyran system. The most recent synthetic study by Fuwa[3i] 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 SmI_2-promoted Evans–Tishchenko reaction. The tetrahydropyran ring in acid **3** could be obtained by means of palladium-catalyzed[5] intramolecular alkoxycarbonylation 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 literature[6] (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.[4e] SmI_2-promoted Evans–Tishchenko reduction[7] 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

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

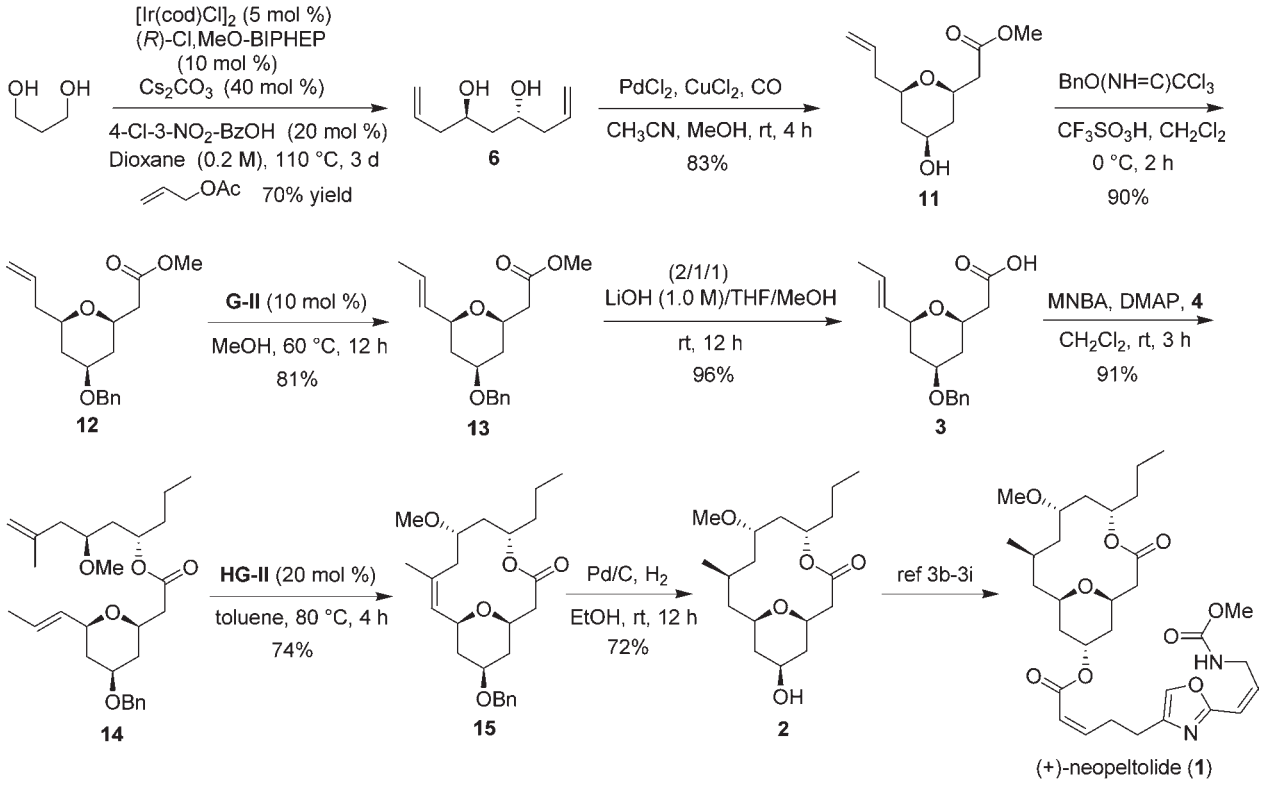
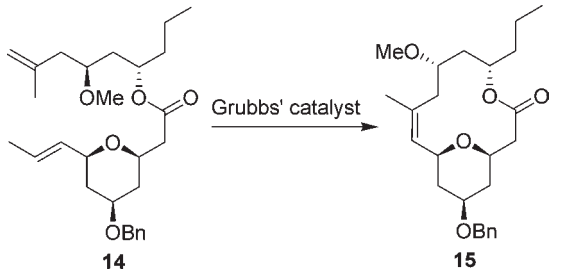


Table 1. Ring-Closing Metathesis of **14**[a]



entry	catalyst (20 mol %)	conditions	yield[c] (%)
1	**G-II**	CH_2Cl_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 C_2-symmetric diol **6** in 70% yield.[9] Subjecting diol **6** to the palladium-catalyzed intramolecular alkoxycarbonylation reaction[10] 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 methanol[12] 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]

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Intermolecular esterification between alcohol **4** and acid **3** was examined. To our delight, esterification under Shiina's (MNBA = 2-methyl-6- nitrobenzoic anhydride) conditions[14] smoothly provided diene **14** in 91% yield. Ring-closing metathesis[15] 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 (+)-macrolactone **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.

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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.

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