

Total Synthesis and Stereochemical Reassignment of (+)-Neopeltolide**

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Neopeltolide (**1b**) is a complex macrolide recently isolated by Wright and co-workers from a deep-water sponge of the family Neopeltidae which was found off the northwest coast of Jamaica (Figure 1).^[1] The species was not identified but was

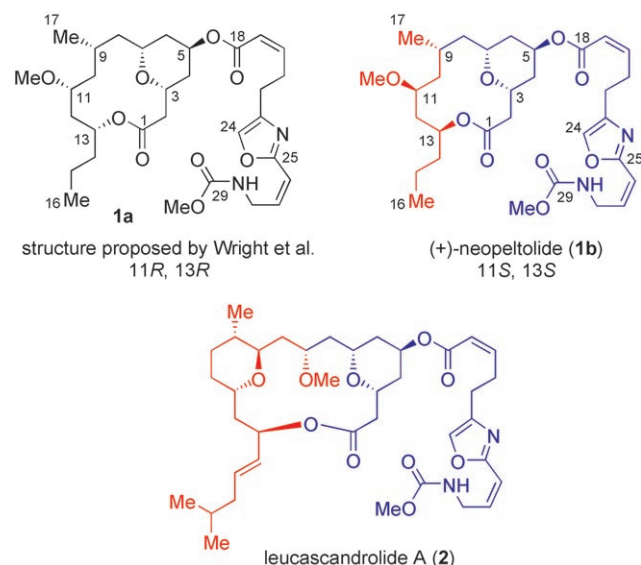


Figure 1. Sponge metabolites: the original neopeltolide structure (**1a**), the correct structure of (+)-neopeltolide (**1b**), and leucascandrolide A (**2**).

described as a member of the genus *Daedalopelta* and a close relative of *Callipelta*, the latter of which have proven to be a rich source of biologically active marine metabolites.^[2] Although neopeltolide is isolated from the sponge, the participation of epibiotic heterotrophic cyanobacteria in its biosynthesis cannot be ruled out.^[1,3]

On the basis of careful spectroscopic studies, the structure of neopeltolide was reported as a 14-membered macrolactone incorporating an *anti* 1,3-oxygenated pattern, an embedded trisubstituted tetrahydropyran, and an oxazole-bearing side chain identical to that found on leucascandrolide A (**2**, Figure 1). Although coupling constant analysis, NOESY, and a series of double-pulsed field gradient spin echo (DPFGSE) NOE experiments permitted determination of the relative stereochemistry, the lack of available material prevented assignment of the absolute stereochemistry.^[1a]

Biological assays of neopeltolide revealed potent *in vitro* cytotoxicity toward several different cancer cell lines including P388 murine leukemia, A-549 human lung adenocarcinoma, and NCI-ADR-RES human ovarian sarcoma (IC₅₀ values of 0.56, 1.2, and 5.1 nM, respectively). Neopeltolide also showed strong inhibitory effects in PANC-1 pancreatic and DLD-1 colorectal cell lines; however, only 50% cell death was observed over an extended dose range, suggesting a cytostatic rather than cytotoxic effect. In addition, **1b** inhibits growth of the pathogenic yeast *Candida albicans* with an MIC value of 0.62 μg mL⁻¹ in liquid cultures.^[1] In comparison, leucascandrolide A has higher IC₅₀ values towards KB and P388 cancer cell lines (0.05 and 0.25 μg mL⁻¹, respectively) but exhibits similar activity against *Candida albicans*.^[4]

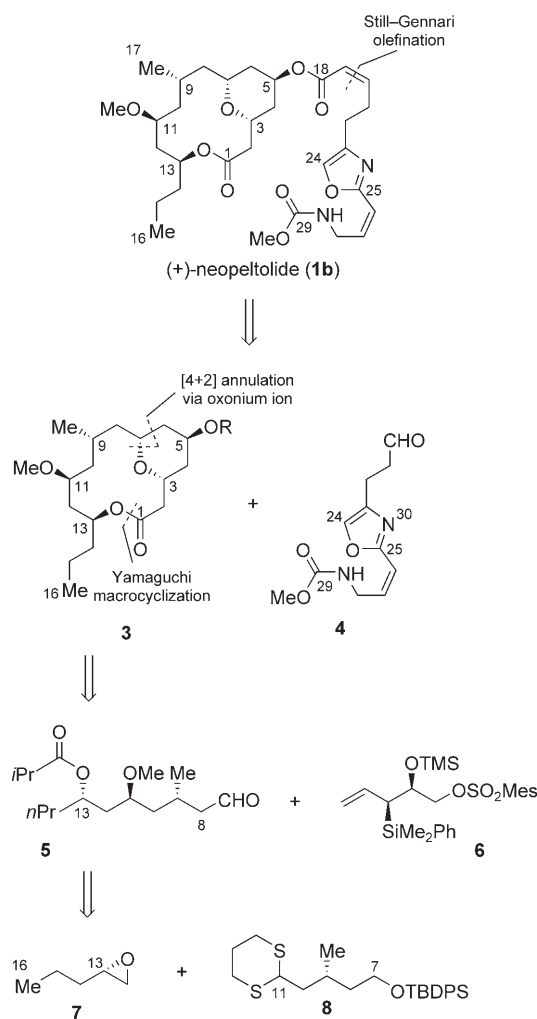
We were attracted to neopeltolide as a synthetic target because of its structural complexity and bioactivity similar to that of leucascandrolide A.^[5] Our initial efforts focused on synthesis of the proposed natural product **1a** and afforded a compound that exhibited several ¹H and ¹³C NMR spectroscopic discrepancies with the corresponding data reported for naturally derived neopeltolide, suggesting a possible stereochemical misassignment.^[6] Upon close inspection of the available spectral data, we undertook the synthesis of a select set of diastereoisomers that would permit identification of the correct stereochemical configuration of neopeltolide. Herein we report the first enantioselective synthesis of (+)-neopeltolide that culminates in a reassignment of the C11 and C13 stereogenic centers and establishes the absolute stereochemistry of the natural product.

Our retrosynthetic strategy began with disconnection of the C19–C20 double bond to reveal the macrolide **3** and the oxazole side chain **4** (see Still–Gennari olefination in Scheme 1). We reasoned that the absolute stereochemistry of **1b**, particularly of the tetrahydropyran moiety, would

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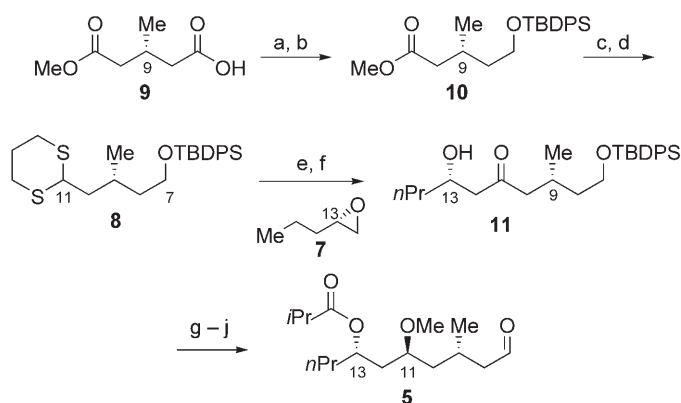


Scheme 1. Retrosynthetic analysis of (+)-neopeltolide (**1b**). Mes = mesitylenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

reflect its structural homology to leucascandrolide A. As such, it was anticipated that installation of the tetrahydropyran unit would be carried out using a [4+2] annulation strategy with allylsilane **6** while macrocyclization would be achieved through Yamaguchi esterification. Allylsilane **6** can be readily prepared in multigram quantities using a six-step sequence from commercially available 3-propyn-1-ol.^[5h] Intermediate **5** would be constructed from the enantio-enriched epoxide **7**^[7] and dithiane **8**. Oxazole **4** could be assembled as previously reported by our group.^[5a]

Preparation of the C7–C11 fragment of neopeltolide began from commercially available methyl (*R*)-(+)-3-methylglutarate (Scheme 2).^[8] Chemoselective reduction of the carboxylic acid using borane/dimethyl sulfide complex^[9] provided the primary alcohol, which was subsequently protected as a TBDPS ether to give **10**. Hydride reduction was followed by an iodine-catalyzed dithioacetalization of the resulting aldehyde to afford dithiane **8** in 68% overall yield.

Coupling of dithiane **8** with epoxide **7** provided the complete carbon framework of the C7–C16 fragment of neopeltolide. Removal of the dithioacetal protecting group

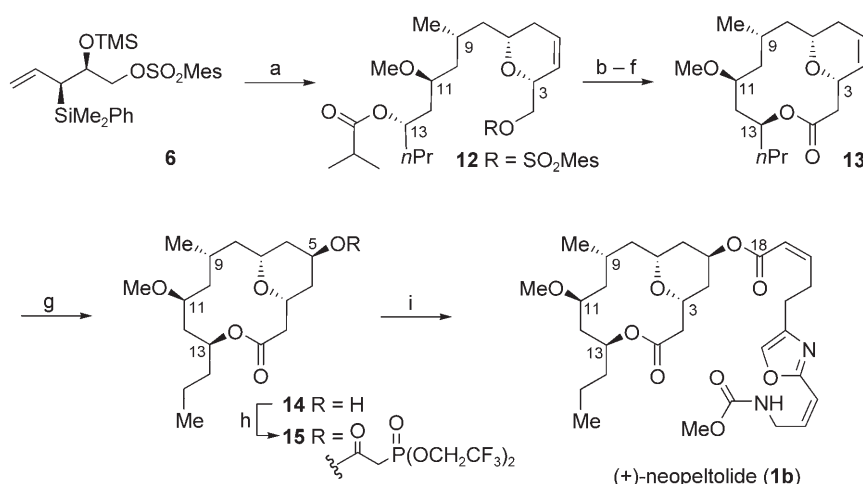


Scheme 2. Synthesis of the C7–C16 fragment **5**. a) $\text{BH}_3\cdot\text{SMe}_2$, THF, 0°C to RT; b) TBDPSCI, imidazole, DMF, 0°C to RT, 80% (over 2 steps); c) DIBAL-H, diethyl ether, –78°C; d) 1,3-propanedithiol, I_2 , CHCl_3 , RT, 85% (over 2 steps); e) *tert*-butyllithium, HMPA, THF, 7, –78°C, 68%; f) CaCO_3 , MeI, MeCN/ H_2O , RT, 73%; g) $\text{Zr}(\text{OtBu})_4$, *i*PrCHO, toluene, –78°C; h) Me_3OBF_4 , Proton Sponge, 4 Å molecular sieves, CH_2Cl_2 , RT, 90% (over 2 steps); i) 49% HF in H_2O , MeCN, RT, 91%; j) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , Et_3N , –78°C to RT, 89%. DMF = *N,N*-dimethylformamide, DIBAL-H = diisobutylaluminum hydride, HMPA = hexamethylphosphoramide, Proton Sponge = 1,8-bis(dimethylamino)naphthalene, DMSO = dimethyl sulfoxide.

with CaCO_3/MeI unmasked the desired ketone **11** (Scheme 2). A modified Evans–Tishchenko reduction^[10] (d.r. 14:1) provided the *anti* stereochemical relationship^[11] required for the C11 and C13 centers, in addition to installing an isobutyrate protecting group, thereby differentiating the *anti* 1,3-diol. The remaining secondary alcohol was treated with Meerwein's reagent^[12] to give the C11 methyl ether. Deprotection of the silyl ether by using aqueous HF released the primary alcohol, which was immediately oxidized using Swern conditions^[13] to provide aldehyde **5**.

Aldehyde **5** was combined with allylsilane **6** in a triflic acid promoted [4+2] annulation to access dihydropyran **12** in good yield and diastereoselectivity (75%, d.r. 10:1, Scheme 3).^[5h] The sulfonate group of **12** was replaced with a nitrile moiety through an $\text{S}_{\text{N}}2$ displacement upon exposure to DIBAL-H, and the acyl protecting group was cleaved to restore the C13 alcohol. The nitrile functionality was converted to the corresponding aldehyde using DIBAL-H and was subsequently transformed to the carboxylic acid through Pinnick oxidation.^[14] Macrocyclization was effected through Yamaguchi esterification of the seco acid intermediate to form macrolide **13** in 44% yield.

Selective oxymercuration of the pyran olefin yielded the axial C5 alcohol **14** as a single stereoisomer.^[5h] Based on our previous studies of leucascandrolide A, direct coupling of **14** with the corresponding acid of intermediate **4** was not attempted.^[5f] Instead, Still–Gennari olefination was used to establish the *cis* enoate of the side chain.^[5a] Acylation of alcohol **14** with bis(2,2,2-trifluoroethyl)phosphonoacetic acid^[15] gave phosphonoacetate **15**, which was immediately deprotonated with KHMDS at –78°C in THF in the presence of [18]crown-6 ether; further treatment of the resulting anion with side-chain aldehyde **4** at –85°C successfully provided a 7:1 mixture of neopeltolide **1b** and the corresponding *E* olefin



Scheme 3. Completion of (+)-neopeltolide (**1b**) synthesis. a) **5**, TFOH, CH₂Cl₂/benzene (3:1), –78 °C, 75 % (d.r. 10:1); b) NaCN, DMF, 60 °C, 84 %; c) DIBAL-H, diethyl ether, –78 °C, 96 %; d) DIBAL-H, CH₂Cl₂, –78 °C, 60 %; e) NaClO₂, 2-methyl-2-butene, NaH₂PO₄·H₂O, tBuOH, H₂O, 85 %; f) 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, Et₃N, 44 %; g) Hg(O₂CCF₃)₂ then HOBT·H₂O, CH₂Cl₂, 99 %; h) **15**, [18]crown-6, KHMDS, –78 °C, then **4**, –85 °C, 62 %. TFOH = triflic acid, DMAP = 4-dimethylaminopyridine, EDCI = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, HOBT = 1-hydroxy-1H-benzotriazole, KHMDS = potassium bis(trimethylsilyl)amide.

in 62 % overall yield. The spectroscopic data of our synthetic material were in complete agreement with those reported for naturally derived neopeltolide (¹H, ¹³C NMR spectroscopy, mass spectrometry, infrared spectroscopy, and [α]_D²⁰ = +29.5 (*c* = 0.47, MeOH)), thus allowing confident reassignment of the relative and absolute configurations.^[16]

In summary, the first enantioselective total synthesis, with reassigned stereochemical and absolute configurations, for the metabolite (+)-neopeltolide has been reported. The longest linear sequence required 19 steps with an overall yield of 1.3 %.^[17] Highlights of this route include a modified Evans–Tishchenko reduction to introduce the C11 stereocenter, [4+2]-allylsilane annulation to construct the pyran system, and a Still–Gennari olefination to install the oxazole side chain. Investigations into the preparation of structural analogues of (+)-neopeltolide to help identify in vivo biological targets and elucidate its mode of action are in progress and will be reported in due course.

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- [16] In comparison, the specific rotation reported for natural neopeltolide by Wright (Ref. [1a]) was $[\alpha]_{\text{D}}^{20} = +24.0$ ($c = 0.24$, MeOH) while the observed specific rotation for **1a** was $[\alpha]_{\text{D}}^{20} = +12.4$ ($c = 0.63$, MeOH). For ^1H and ^{13}C NMR spectra of **1b** and **1a**, see the Supporting Information.
- [17] Starting from commercially available methyl (*R*)-(+)-3-methylglutarate **9**.