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Concise Enantioselective Total Synthesis of Neopeltolide Macrolactone Highlighted by Ether Transfer

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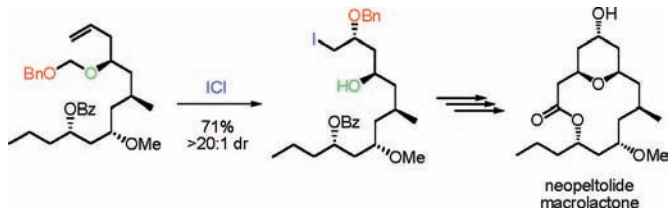
ABSTRACT



A concise total synthesis of neopeltolide macrolactone has been accomplished in 14 steps in the longest linear sequence, 15 steps overall from commercially available materials. The present synthesis was highlighted by successful exploitation of ether transfer methodology and a radical cyclization reaction to directly establish the requisite stereochemistry of the tetrahydropyran core.

Polyketide natural products are biosynthesized by microorganisms for their antibiotic activity and thus create an environmental advantage for the producing organism. Their structures evolve during the ancestral history of the producing organism through modification in the PKS gene clusters and the development or sequestration of post-PKS processing enzymes. Our laboratory is particularly interested in the correlation between unique polyketide structures and their corresponding biological activities. Many cyanobacteria-derived polyketides contain methyl substitution at odd-number carbons proposedly due to an HMG-CoA synthase embedded in the PKS gene cluster.[1] This unique structural feature presumably evolved as an additional conformational control element and to enhance structural diversity.

Neopeltolide **1** is one example of these interesting compounds. In 2007, Wright and co-workers reported the isolation of neopeltolide from a deepwater sponge of the family Neopeltidae collected off the north Jamaican coast.[2] Although the exact species of the specimen was not identified, the sponge was most closely related to *Daedalopelta sollas*. Neopeltolide is a fully saturated, tetrahydropyran-containing 14-membered macrolide exhibiting ornamentation at C5 hydroxyl with a pendant oxazole carbamate side chain identical to that of leucascandrolide A **2**.[3] The original stereochemical configuration of the neopeltolide macrolactone was revised by recent total syntheses.[4−6]

[†] Undergraduate research participant.

(1) Calderone, C. T. *Nat. Prod. Rep.* **2008**, *25*, 845–853.

(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*, 412–416.

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(4) (a) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211−9214; *Angew. Chem.* **2007**, *119*, 9371−9374. (b) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804–805.

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Neopeltolide (Figure 1) has demonstrated cytotoxic activity against several cancer lines, including P388 murine leukemia, A-549 human lung adenocarcinoma, and NCI-ADR-RES human ovarian sarcoma, with their respective IC_{50} values of 0.56, 1.2, and 5.1 nM.[2] Recent efforts by Kozmin and co-workers have suggested that the mode of action of neopeltolide may involve inhibition of mitochondrial ATP synthesis with cytochrome bc_1 complex as the primary cellular target.[6] A related biological activity of leuscandrolide A offers circumstantial support that their inherent activity is primarily associated with their common oxazole carbamate side chain.

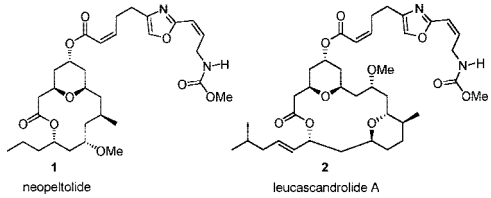


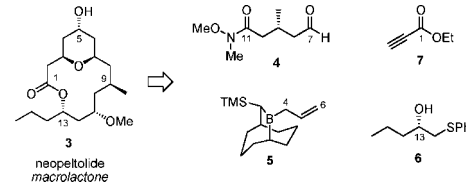
Figure 1. Neopeltolide and Leucascandrolide A.

Biosynthetically, the C5 side chain is likely incorporated by a post-PKS process. As post-PKS genes develop late in the evolutionary history of the producing organism,[7] we are particularly interested in the structural significance of this oxazole-containing side chain and the inherent activity of the polyketide core. From the seven published total syntheses of neopeltolide, only Panek's route directly accessed the natural stereochemistry of the neopeltolide macrolactone.[4a] Alternatively, the rest involved the production of the C5 epimer followed by stereochemical inversion upon installation of the oxazole carbamate side chain by the method of Mitsunobu.[4b,5,6]

We envisioned an assembly of four simple fragments **4**−**7** for the construction of macrolide **3** (Scheme 1), with ethyl propiolate **7** serving as a lynchpin for the macrolactonization. The present total synthesis will be highlighted by the utilization of our ether transfer methodology,[8] which directs the stereochemistry embedded within the tetrahydropyran ring.[9] More importantly, we have successfully implemented a strategy that minimizes protecting group manipulation in a unique fashion, a common and unavoidable practice in polyketide syntheses. The result is a remarkably efficient, 14-step (longest linear sequence, 15 total steps) synthesis of the neopeltolide core which will enable full biological profiling.

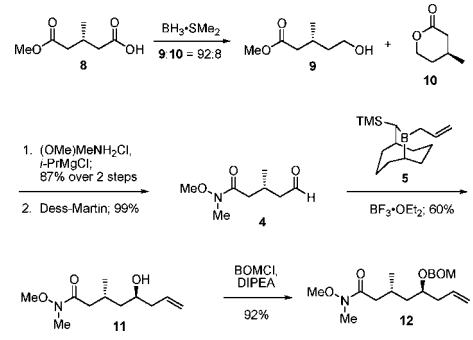
The concise synthesis to neopeltolide macrolactone **3** began with chemoselective reduction of commercially avail-

Scheme 1. Retrosynthetic Analysis



able (*R*)-4-(methoxycarbonyl)-3-methylbutanoic acid[10] **8** with borane dimethylsulfide complex. These conditions yielded a mixture of alcohol **9** and lactone **10** in 92:8 ratio, which were sequentially treated under Weinreb amidation[11] and Dess−Martin oxidation[12] to produce amide−aldehyde **4** in good yields. This compound represents an interesting synthetic intermediate due to its dual electrophilic sites; however, it exhibits an appreciable difference in reactivity. By exploiting the more electrophilic aldehyde functionality, asymmetric allylation should set the C7 stereochemistry necessary for the neopeltolide macrolactone. Upon screening a variety of allylation methods, the transformation to homoallylic alcohol **11** was found most effective with Soderquist's chiral bicyclodecane−allylborane reagent **5**.[13a] Under modified reaction conditions, which included an introduction of a stoichiometric amount of BF_3•OEt_2, homoallylic alcohol **11** was readily produced in 60%.[13b] This external Lewis acid was presumably necessary to sequester the much stronger Lewis basic Weinreb amide functionality. Conversion of **11** to the corresponding benzyloxymethyl (BOM) ether **12**, necessary for the ether transfer, then proceeded in 92% yield (Scheme 2).

Scheme 2. Synthesis of C4−C11 Segment



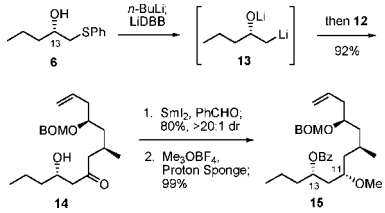
Our synthesis then continued with an installation of the C12−C16 segment by utilizing β-hydroxylsulfide **6**.

(7) Young, J.; Taylor, R. E. *Nat. Prod. Rep.* **2008**, *25*, 651–655.
(8) Liu, K.; Taylor, R. E.; Kartika, R. *Org. Lett.* **2006**, *8*, 5393–5395.
(9) Utilizations of electrophile-induced ether transfer in oxacycle syntheses: (a) Kartika, R.; Taylor, R. E. *Heterocycles* **2007**, *74*, 447–459. (b) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874−6877; *Angew. Chem.* **2007**, *119*, 6998−7001. (c) Kartika, R.; Frein, J. D.; Taylor, R. E. *J. Org. Chem.* **2008**, *73*, 5592–5594.

(10) Commercially available from Aldrich or readily accessible in large scale from enzymatic resolution of dimethyl-3-methylglutarate with porcine liver esterase: Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047–50.
(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(13) (a) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044–8049. (b) The minor diastereomer C7(*R*) was separable by chromatography and isolated in 6% yield.

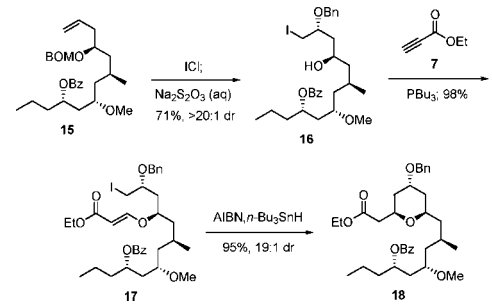
Transformation[14a,b] of **6** to the corresponding dilithio species **13** followed by addition to Weinreb amide **12** according the method of Rychnovsky[14c] cleanly produced β-hydroxy ketone **14** in 92% yield without the necessity for protection at the C13 hydroxy group. Elaboration of the C11 stereochemistry and simultaneous differentiation of the C13 hydroxy group as a benzoate ester was realized by the Evans−Tischenko reaction in 80% yield.[15] Methylation of the resulting C11 hydroxyl with Meerwein's salt in the presence of Proton Sponge then quantitatively afforded methyl ether **15** (Scheme 3).[16]

Scheme 3. Preparation of Ether Transfer Precursor **15**



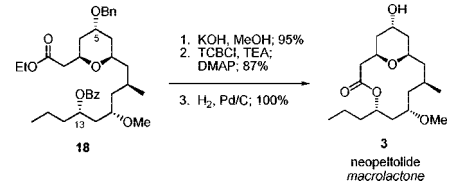
The highlight of the present total synthesis resides in the utilization of our ether transfer technology which directly installed the requisite C5 stereochemistry as a benzyl-protected ether. This was accomplished by simply treating homoallylic BOM ether **15** with iodine monochloride.[8] Upon aqueous workup, 1,3-*syn*-diol monoether **16** was liberated in 71% yield with excellent stereocontrol. In addition to our previous work in phorboxazole A,[9b] this transformation once again exemplifies the versatility and applicability of the ether transfer reaction to complex substrates. The completion to the carbon skeleton of neopeltolide macrolactone was realized via tributylphosphine-promoted conjugate addition of the C7 hydroxyl to ethyl propiolate **7**.[17a] This reaction proved challenging since, under the established reaction conditions,[17a,18] the alternative tetrahydrofuran cyclization event of alcohol **16** was highly competitive. However, upon optimization,[17b] the desired β-alkoxyacrylate **17** was selectively produced in 98% yield. The ensuing construction of the tetrahydropyran core was executed via radical cyclization with AIBN and *n*-Bu_3SnH in refluxing toluene (Scheme 4).[19] These conditions afforded **18** in 95% yield as nearly a single diastereomer.

Scheme 4. Construction of the Tetrahydropyran Core



The endgame strategy to neopeltolide macrolactone was straightforward. Exposure of tetrahydropyran **18** to a mixture of aqueous KOH and methanol saponified the ethyl ester group to the corresponding carboxylic acid and at the same time cleaved the C13 benzoate ester (Scheme 5). Macrolactonization of the resulting seco acid was then realized under the Yamaguchi protocol;[20] both steps proceeded in good yields. The ensuing hydrogenolysis in the presence of a catalytic amount of Pd/C removed the C5 benzyl ether and thus completed our total synthesis of neopeltolide macrolactone **3**. The spectroscopic analyses of our synthetic material were found in a complete agreement with those presented by Panek.[21] Considering Panek's two-step conversion of **3** to neopeltolide, the present route represents a formal total synthesis.

Scheme 5. Endgame to Neopeltolide Macrolactone



In summary, we have accomplished a concise total synthesis of neopeltolide macrolactone **3** with only 14 steps in the longest linear sequence and 15 steps[22] overall from commercially available materials. The highly efficient route outlined in this communication successfully implemented a strategy that utilized sequential ether transfer and radical cyclization reactions to directly install the requisite stereochemistry within the tetrahydropyran ring. In addition, our present route readily minimized protecting group manipula-

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(16) (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171–7172. (b) It was essential to immediately methylate the Evans−Tischenko product upon isolation to prevent the facile C11−C13 benzoate migration.

(17) (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244. (b) The reaction was optimized by simultaneous dropwise addition of stoichiometric amounts of PBu_3 and ethyl propiolate to a dilute solution of β-alkoxyacrylate **17**; see Supporting Information for a detailed experimental protocol.

(18) The use of amine-based promoters, such as DMAP, DABCO, TEA, and NMM, also predominantly led to the tetrahydrofuran cyclization event.

(19) A recent review of β-alkoxyacrylate radical cyclization to oxacycle systems in total syntheses: Lee, E. *Pure Appl. Chem.* **2005**, *77*, 2073–2081.

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

(21) We thank Professor James Panek for kindly providing us with their NMR spectra for neopeltolide macrolactone **3**.

(22) Preparation of β-hydroxysulfide **6** was achieved in one step via addition of sodium thiophenoxide to commercially available (*S*)-2-propyloxirane; see Supporting Information for a detailed experimental protocol.

tion. In fact, the two protecting groups (C5 benzyl ether and C13 benzoate ester) were produced simultaneously upon generation of a specific stereogenic center and, thus, allowed differentiation of the resulting 1,3-diol products. The significant quantities of material prepared by the route, >300 mg, will allow for detailed biological analysis of **3** as well as analogues. Moreover, extensive conformational analyses[23] are currently underway in our laboratories and will be reported in due course.

(23) Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224–7228.

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Supporting Information Available: Full experimental 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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