Natural Product Synthesis

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A Concise Total Synthesis of (+)-Neopeltolide**

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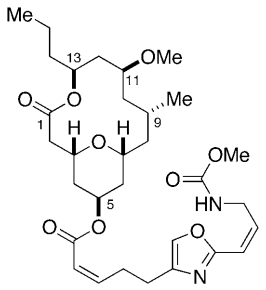
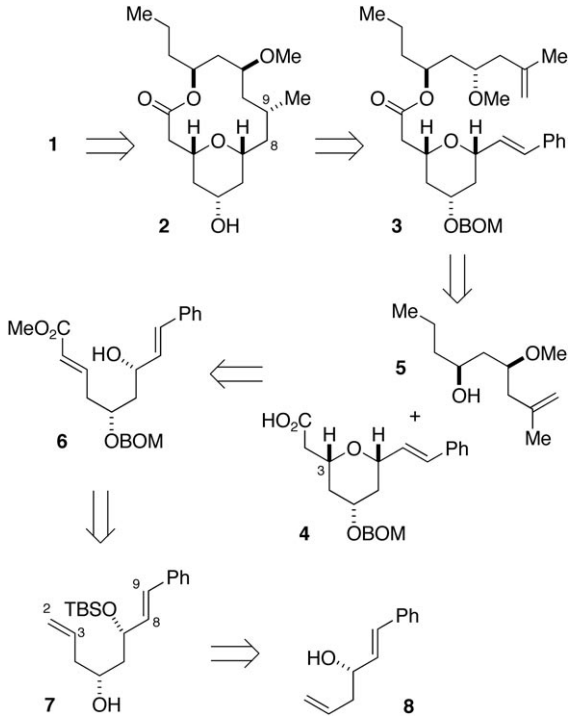
(+)-Neopeltolide (**1**) is a marine macrolide that belongs to the family Neopeltidae, and was isolated from a deep-water sponge collected off the northwest coast of Jamaica by Wright et al.[1] Neopeltolide exhibits highly potent in vitro antiproliferative activity against several cancer cell lines with nanomolar IC_{50} values ($IC_{50} = 1.2$, 5.1, and 0.56 nmol L^{-1} against the A-549 human lung adenocarcinoma, the NCI-ADR-RES human ovarian sarcoma, and the P388 murine leukemia cells, respectively) as well as potent antifungal activity against pathogenic yeast *Candida albicans*. Kozmin and co-workers reported that neopeltolide targets cytochrome bc_1 complex and may inhibit mitochondrial ATP synthesis.[2] The complex molecular architecture coupled with the intriguing biological activity of **1** have spurred the interest of the synthetic community. A number of total syntheses of **1**,[3,4] including the studies from our research group,[5] have been reported.



(+)–neopeltolide (**1**)

Our previous total synthesis of (+)-neopeltolide and its analogues relied on our Suzuki–Miyaura coupling/ring-closing metathesis (RCM) strategy.[5] Unfortunately, our synthesis of **1** necessitated 24 steps (longest linear sequence) owing to the protective group manipulations and oxidation/reduction steps involved. It was necessary to devise a more concise and efficient synthetic entry to **1** and its analogues to facilitate detailed investigations on its structure–activity relationship and biological activity. Herein, we describe a concise total synthesis of **1** based on the strategic application of olefin metathesis reactions. The synthesis proceeds in only 13 linear steps from commercially available (*E*)-cinnamaldehyde, and represents the shortest synthesis of **1** reported to date.

Our retrosynthesis towards **1** is summarized in Scheme 1. On designing the overall strategy, manipulations of oxygen functionalities such as oxidation, reduction, protection, and deprotection steps have to be minimized to maximize the overall efficiency of the plan. Olefin metathesis reactions are particularly attractive in this context owing to the superb chemoselectivity, bond-forming ability, and unnecessary manipulation of oxygen functionalities. Although there was no precedent that utilized RCM[6] for the construction of the neopeltolide macrocycle, we envisioned that the 14-membered lactone **2** could be accessed by a RCM/hydrogenation sequence of diene **3** to forge the C8–C9 bond and define the stereogenic center at C9.[4c] This particular RCM would be challenging because of the pronounced lower reactivity of 1,1-disubstituted alkenes and styryl groups toward olefin metathesis reactions.[6] Furthermore, 2-vinyl-substituted tetrahydropyrans are known to be difficult substrates in RCM.[7] We were also concerned about the stereochemical outcome of the RCM, which would play a key role in determining the



Scheme 1. Retrosynthesis of (+)-neopeltolide (**1**). BOM = benzyloxymethyl, TBS = *tert*-butyldimethylsilyl.

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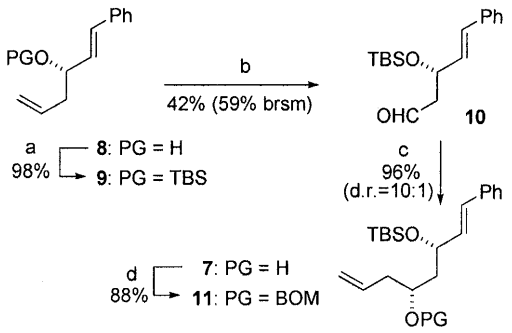
conformation of the RCM product and the facial selectivity of subsequent hydrogenation. Diene **3** would be derived from an esterification of acid **4** and alcohol **5**. The acetic acid appendage at the C3-position of **4** suggested an intramolecular oxa-conjugate addition of **6** would be suitable for the stereoselective construction of the 2,4,6-trisubstituted tetrahydropyran substructure. Enoate **6** would be formed from olefin **7** by means of a chemoselective olefin cross-metathesis (CM) reaction to allow introduction of the enoate functionality, where the phenyl group at C9 and the OTBS group at C7 would block initiation of CM at the C8–C9 double bond.[8] Nonetheless, the CM should still be challenging owing to an intrinsically competitive RCM initiated at the C2–C3 double bond to form a six-membered carbocycle. Finally, substrate **7** would be synthesized from the known homoallylic alcohol **8**,[9] which is available from (*E*)-cinnamaldehyde by an asymmetric allylation.

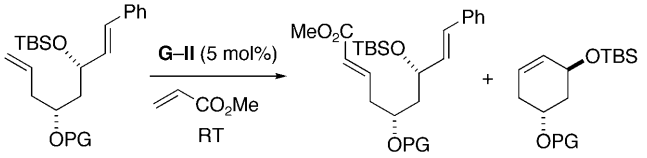
The synthesis commenced with protection of **8** as its TBS ether and gave olefin **9** (Scheme 2). Chemoselective dihydroxylation of **9** and concomitant oxidative cleavage[10] afforded aldehyde **10**. Asymmetric allylation[11] of **10** by using the protocol developed by Brown and Jadav proceeded with good diastereoselectivity, and led to an inseparable mixture of homoallylic alcohol **7** and its diastereomer (d.r. = 10:1) in 96% yield. Protection of **7** as its BOM ether furnished olefin **11**.



Scheme 2. Synthesis of olefins **7** and **11**. a) TBSCl, imidazole, DMF, RT, 98%; b) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O, 0°C, 42% (59% brsm); c) (+)-Ipc_2BOMe, allylMgBr, Et_2O, −78°C; then aq NaOH, 30 wt.% in H_2O, RT, 96% (d.r. = 10:1); d) BOMCl, iPr_2NEt, CH_2Cl_2, RT, 88%. brsm = based on recovered starting material, DMF = *N*,*N*-dimethylformamide, Ipc = isopinocampheyl, PG = protecting group.

Olefin CM of **11** with methyl acrylate (20 equiv) using 5 mol% of the Grubbs second-generation catalyst (**G-II**)[12] in CH_2Cl_2 at room temperature gave the desired (*E*)-enoate **12a**, albeit in 25% yield together with RCM product **12b** in 71% yield (Table 1, entry 1). To overcome the intrinsically competitive RCM, the CM of **11** was investigated under various reaction conditions using **G-II** or the Hoveyda–Grubbs second-generation catalyst (**HG-II**)[13] in CH_2Cl_2, toluene or THF at room temperature. The best result was obtained when **11** was treated with 5 mol% of **G-II** in methyl acrylate/toluene (1:1) at room temperature. The desired (*E*)-enoate

Table 1: Chemoselective olefin cross-metathesis.



11: PG = BOM
7: PG = H

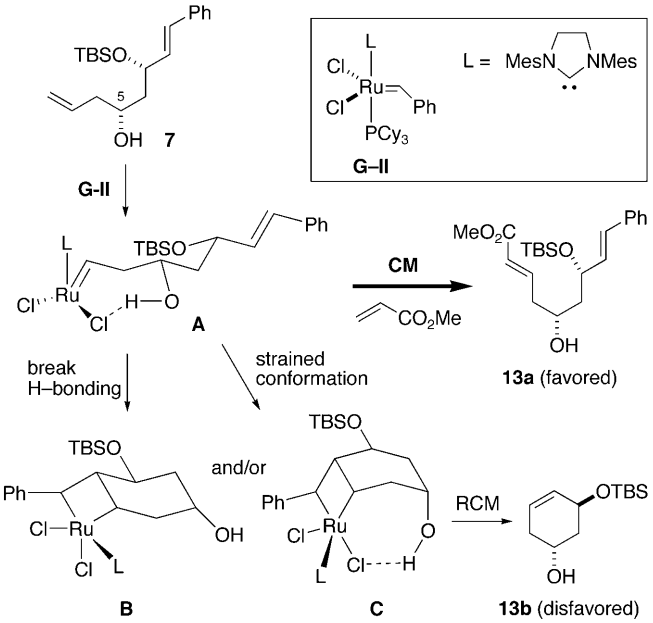
12a: PG = BOM
13a: PG = H

12b: PG = BOM
13b: PG = H

Entry	Substrate	Reagents and conditions	Yield [%]
1	**11**	methyl acrylate (20 equiv), CH_2Cl_2	**12a**, 25 **12b**, 71
2	**11**	methyl acrylate/toluene (1:1)	**12a**, 51 **12b**, 46
3	**7**	methyl acrylate/CH_2Cl_2 (1:1)	**13a**, 77 **13b**, 7
4	**7**	methyl acrylate (30 equiv), CH_2Cl_2	**13a**, 82 **13b**, 7

12a was isolated in 51% yield along with RCM product **12b** in 46% yield under these conditions (entry 2). However, upon scale-up (> 0.1 mmol), the reaction often stalled before reaching completion (ca. 70%–80% conversion), and the product selectivity proved to be capricious. Other conditions examined resulted in lower yields, which could be a consequence of the competitive RCM and/or insufficient conversion of the starting material.

At this stage, we thought that the hydroxy group at C5 of **7** could be exploited as a "directing group" to render the conformation of the molecule unfavorable for the competitive RCM (Scheme 3). A recent report by Hoveyda et al.[14a] and previous literature precedents[14b–h] suggested that the reaction of a homoallylic alcohol with a Grubbs catalyst would generate the corresponding ruthenium alkylidene species, wherein hydrogen bonding between the hydroxy group and the chlorine atom of the catalyst is formed (such as **A**). We



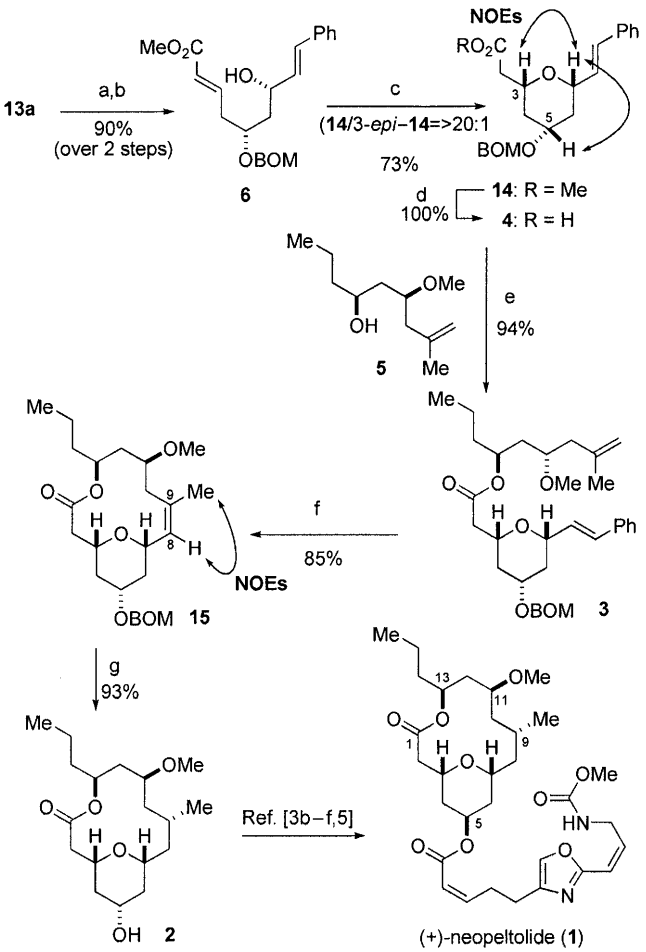
Scheme 3. Olefin metathesis reactions of **7**. Cy = cyclohexyl, Mes = mesityl.

envisaged that the CM of **7** would be more facile than the competitive RCM, because the latter process has to proceed through energetically demanding pathway(s). Thus, formation of a ruthenacyclobutane **B** by breaking the hydrogen bonding in **A** or a conformationally strained ruthenacyclobutane **C** would be necessary for the RCM of **7** to give **13b**. In the event, we were delighted to find that treatment of **7** with **G-II** (5 mol%) in methyl acrylate/CH_2Cl_2 (1:1) at room temperature afforded (*E*)-enoate **13a** in a gratifying 77% yield, and the cyclohexene-derivative RCM product **13b** was isolated in only 7% yield (entry 3). Moreover, we could lower the amount of methyl acrylate used in the reaction without affecting the product selectivity (entry 4). Therefore, the intramolecular hydrogen bonding formed within ruthenium alkylidene **A** plays a key role in determining the reaction pathway. Consequently, we were able to reproducibly prepare **13a** in good yield.

Completion of the total synthesis of **1** is illustrated in Scheme 4. Protection of **13a** as its BOM ether and subsequent desilylation provided alcohol **6**. The intramolecular oxa-conjugate addition of **6** was best accomplished by treatment with DBU in toluene at 100°C which afforded the thermodynamically favored **14** in 73% yield (**14**/3-*epi*-**14** = > 20:1). At this stage, the minor C5 diastereoisomer could be separated by flash chromatography on silica gel.[15] Hydrolysis of **14** using TMSOK[16] provided acid **4** quantitatively. Esterification of **4** with alcohol **5**[17] under Yamaguchi conditions[18] delivered ester **3** in 94% yield.

As expected, the construction of the 14-membered macrocycle **2** by the RCM of **3** was a significant challenge. After extensive investigations, we eventually found that treatment of **3** with **G-II** (30 mol%) in the presence of 1,4-benzoquinone[7c,19] in toluene at 100°C afforded the 14-membered macrocycle **15** in 85% yield. As a result of the high reaction temperature, slow addition of the **G-II** complex was important to achieve a satisfactory conversion.[20] Gratifyingly, **15** was isolated solely as the desired *Z* isomer, whose hydrogenation was anticipated to occur from the less hindered *Re* face of the molecule to give neopeltolide macrolactone **2** with the desired configuration at C9. This outcome was suggested by molecular modeling and by a recent related report by Tu and Floreancig.[4c,21] In the event, the stereoselective hydrogenation of the C8–C9 double bond with concomitant hydrogenolysis of the BOM group afforded **2** in 93% yield as a single diastereomer, which has previously been transformed into **1** by us[5] and other research groups.[3b–f]

In conclusion, we have completed a concise total synthesis of (+)-neopeltolide (**1**), which proceeded in only 13 steps (longest linear sequence) from commercially available (*E*)-cinnamaldehyde. The present synthesis represents the shortest asymmetric synthesis of **1** reported to date. Highlights of the present synthesis are: 1) a highly chemoselective CM of **7** by exploiting hydrogen bonding, 2) a stereoselective intramolecular oxa-conjugate addition of **6** under thermodynamic conditions to forge the 2,4,6-trisubstituted tetrahydropyran subunit, and 3) a macrocyclization of **3** through a stereoselective RCM/hydrogenation sequence. Significantly, our newly developed olefin metathesis-based strategy should be generally applicable to the rapid assembly of tetrahydropyran-containing macrolide natural products and their analogues.



Scheme 4. Completion of the total synthesis of **1**. a) BOMCl, *i*Pr_2NEt, *n*Bu_4NI, 1,2-dichloroethane, 50°C; b) TBAF, AcOH, THF, 35°C, 90% (over 2 steps); c) DBU, toluene, 100°C, 73% (d.r. > 20:1); d) TMSOK, Et_2O, RT, 100%; e) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, RT; then **5**, DMAP, toluene, RT, 94%; f) **G-II** (30 mol%), 1,4-benzoquinone, toluene, 100°C, 85%; g) H_2 (0.8 MPa), Pd/C, $Pd(OH)_2$/C, EtOH, RT, 93%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, TMS = trimethylsilyl.

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[20] The addition of **G-II** complex in several portions was less effective in our hands; for example, portionwise addition of 60 mol % of **G-II** in toluene at 100 °C for 3 days gave **15** in 50 % yield together with recovered **3** in 28 % yield. Meanwhile, **HG-II**, a more reactive and air-stable complex, was ineffective for the present RCM, presumably as a result of the steric bulk.

[21] In contrast, the *Re* face of the corresponding *E* isomer was predicted to be oriented towards the inside of the macrocyclic cavity of the molecule, which suggested that hydrogenation would occur from the *Si* face to afford the C9 epimer of **2**. Fortunately, no trace amounts of the undesired *E* isomer were observed in the RCM of **3**.

