Natural Products

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Total Synthesis of (+)-Neopeltolide by a Prins Macrocyclization**

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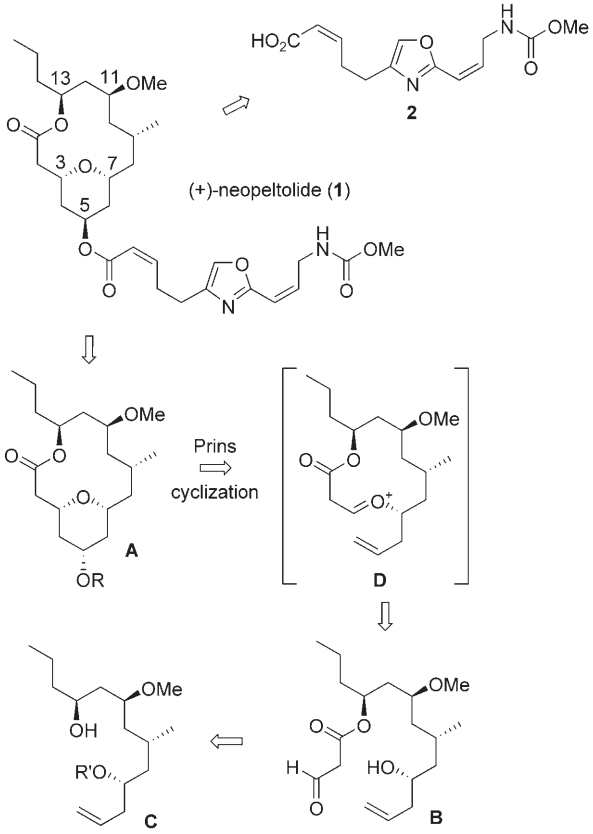
Neopeltolide (**1**) is a 12-membered macrolide from a Lithistid sponge of the Neopeltidae family.[1] It is a potent inhibitor of tumor cell proliferation with IC_{50} values of 1.2, 5.1, and 0.56 nM against human lung adenocarcinoma (A549), human ovarian sarcoma (NCI/ADR-RES), and murine leukemia (P388), respectively, and it is also a potent antifungal agent. A 2,4,6-trisubstituted oxane ring is an integral part of the macrolactone framework and the substituent at the 4-position features an oxazole-bearing carboxylate group identical to that found in leucascandrolide A.[2] A recent total synthesis of **1**[3] by Panek and co-workers corrected the stereochemical assignments at C11 and C13, and a second total synthesis[4] by Scheidt and co-workers confirmed the revised structure. We report herein results of our recent efforts on the total synthesis of **1**.

For the expedient construction of 2,4,6-trisubstituted oxane fragments, a Prins cyclization involving an aldehyde and a homoallylic alcohol partner appeared to be feasible. In the retrosynthetic analysis for **1**, an intramolecular Prins cyclization was envisioned; macrolactone **A** could be prepared from aldehydic homoallylic alcohol **B** through cyclic oxocarbenium ion **D** (Scheme 1). This reaction, if successful, would lead to the bicyclic macrolactone **A** in a single step. This type of cyclization reaction is reported in the literature,[5] but it has been relatively unexplored for the synthesis of complex natural products until recently.[6] The homoallylic alcohol fragment (**C**) would serve as the precursor for **B**.

For the synthesis of fragment **C**, aldehyde **5** was obtained from butanal (**3**) by a reaction sequence involving an asymmetric crotyl transfer reaction,[7] protection of the alcohol group with a benzyl group, and ozonolysis (Scheme 2). Titanium(IV) chloride mediated methallylation proceeded stereoselectively to produce a homoallylic alcohol, from which ester **7** was obtained by esterification with 2-diphenylphosphinobenzoic acid (**6**). The substrate-directed hydroformylation[8] of **7** preferentially produced desired aldehyde **8** in a 5:1 ratio. Dimethyl acetal formation, hydrolysis, and O methylation yielded dimethyl acetal **9**.



Scheme 1. Retrosynthetic analysis.

The aldehyde obtained from **9** was preferentially transformed into desired homoallylic alcohol **10** in a 5.5:1 ratio of isomers by using the method of Brown for the allylation (Scheme 3).[9] Intermediate **11** was prepared from **10** by a sequence involving protecting the alcohol with a *tert*-butyldimethysilyl (TBS) group, cleaving the benzyl group by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and esterifying with 3,3-diethoxypropanoic acid. Compound **11** was reacted with triethylsilyl trifluoromethanesulfonate (TESOTf) in acetic acid in the presence of trimethylsilyl acetate (TMSOAc),[10] and subsequently treated under basic conditions to yield bicyclic macrolactone **12**. Approximately 10% racemization[11] was observed by careful spectroscopic analysis of **12**.

The intramolecular Prins cyclization appeared to be a viable solution in the synthesis of compounds like **1**, and we were intrigued by the possibility of an alternative Prins cyclization approach. A second aldehydic homoallylic alcohol (**E**) could also produce macrolactone **A** through cyclic oxocarbenium intermediate **G** under the typical Prins conditions (Scheme 4).

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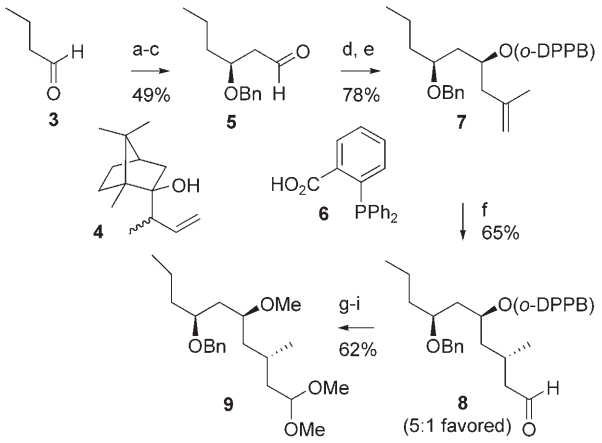
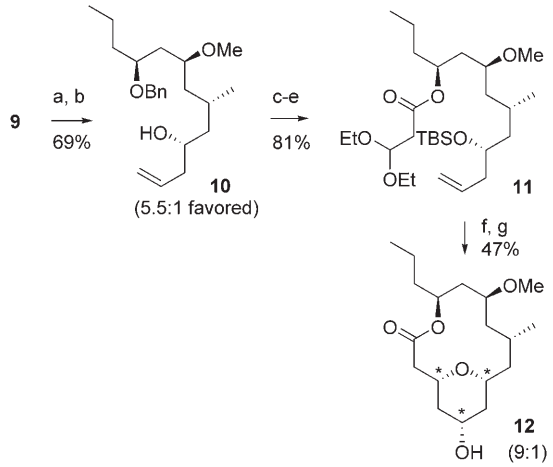
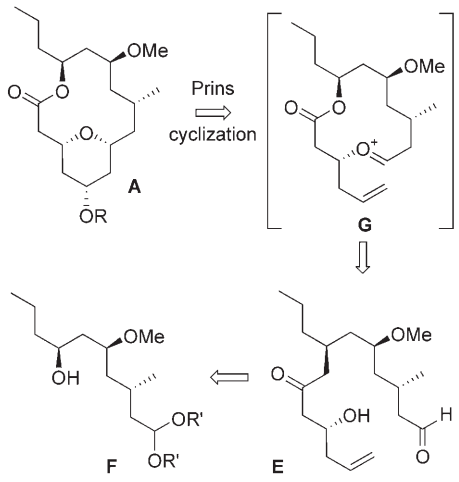


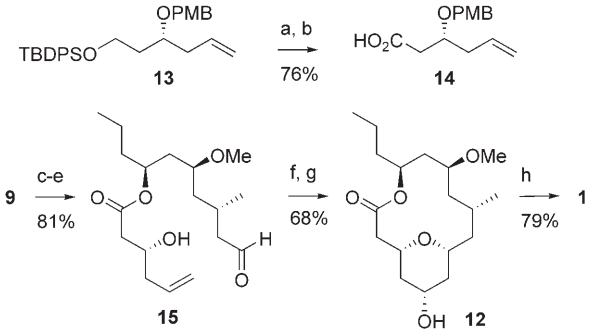
Scheme 2. Preparation of fragment **C**. a) **4**, CSA, CH_2Cl_2; b) NaH, BnBr, TBAI, THF/DMF (5:1); c) O_3, CH_2Cl_2, −78 °C; Ph_3P; d) $CH_2C(CH_3)CH_2TMS$, $TiCl_4$, CH_2Cl_2, −78 °C; e) **6**, DCC, DMAP, CH_2Cl_2; f) $Rh(CO)_2(acac)$, $P(OPh)_3$, 40 bar H_2/CO (1:1), toluene, 30 °C; g) H_2SO_4, $HC(OMe)_3$, MeOH; h) KOH, EtOH, reflux; i) NaH, MeI, THF. CSA = camphorsulfonic acid; TBAI = tetrabutylammonium iodide; TMS = trimethylsilyl; DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine; *o*-DPPB = *o*-diphenylphosphinobenzoyl; acac = acetylacetonate.



Scheme 3. Intramolecular Prins cyclization. a) HCl, acetone; b) $CH_2CHCH_2B(^dIpc)_2$, ether, −78 °C; H_2O_2, NaOH; c) TBSOTf, 2,6-lutidine, CH_2Cl_2; d) DDQ, $ClCH_2CH_2Cl$, pH 7 buffer; e) $(EtO)_2CHCH_2CO_2H$, DCC, DMAP, CH_2Cl_2; f) TESOTf (20 equiv), TMSOAc (30 equiv), AcOH (0.01 M), RT, 30 min; g) K_2CO_3, MeOH. Ipc = isopinocampheyl (superscript *d* implies that it was prepared from (+)-α-pinene), DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBS = *tert*-butyldimethylsilyl, TESOTf = triethylsilyltrifluoromethanesulfonate.



Scheme 4. An alternative Prins approach to neopeltolide (**1**).



Scheme 5. Synthesis of neopeltolide (**1**). a) TBAF, THF; b) DMP, CH_2Cl_2; $NaClO_2$, NaH_2PO_4, *t*BuOH-2-methyl-2-butene-H_2O (12:3:2); c) H_2, Pd/C, MeOH; d) **14**, DCC, DMAP, CH_2Cl_2; e) DDQ, pH 7 buffer, CH_2Cl_2; f) TESOTf (20 equiv), TMSOAc (30 equiv), AcOH, RT, 30 min; g) K_2CO_3, MeOH; h) **2**, DIAD, Ph_3P, benzene. TBAF = tetrabutylammonium fluoride; DMP = Dess–Martin periodinane; DIAD = diisopropylazodicarboxylate.

Carboxylic acid **14** was prepared from known olefin **13**[12] by the removal of a silyl group and an oxidation (Scheme 5). Benzyl cleavage of **9**, esterification of the product secondary alcohol with **14**, and then prolonged exposure to DDQ produced aldehydic homoallylic alcohol **15** in good yield. This time, the Prins cyclization of **15** proceeded more efficiently and hydrolysis of the Prins adduct gave macrolide **12** in reasonable yield. The efficiency and stereoselectivity[13] of the Prins reaction was remarkable; the bicyclic oxane/macrolactone system was constructed efficiently with complete stereocontrol at the two new stereogenic centers. Finally, Mitsunobu reaction[4] of **12** with known carboxylic acid **2** (see Scheme 1 for structure)[14] led to neopeltolide (**1**).[15]

In the present synthesis, a macrolactone was generated by a Prins cyclization strategy and it was used successfully in the total synthesis of neopeltolide (**1**). Additional applications of this concept will be reported in due course.

Experimental Section

Macrolide **12**: TMSOAc (0.40 mL, 2.73 mmol) was added to a solution of aldehyde **15** (30 mg, 0.091 mmol) in AcOH (9.0 mL) at room temperature. TESOTf (0.40 mL, 1.82 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into ether (20 mL) and sat. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with ether (20 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The product from the crude reaction mixture was dissolved in MeOH (2 mL) and then K_2CO_3 (125 mg, 0.91 mmol) was added. The reaction mixture was

stirred for 3 h at room temperature and then concentrated. The residue was dissolved in water (5 mL) and ether (5 mL). The layers were separated, and the aqueous layer was extracted with ether (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was separated by flash column chromatography (hexanes/EtOAc, 3:1) to afford macrolide **12** (20.0 mg, 68 %).

$R_f = 0.28$ (hexanes-EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 5.17–5.13 (m, 1H), 3.83–3.76 (m, 1H), 3.76–3.71 (m, 1H), 3.60–3.56 (m, 1H), 3.31 (s, 3H), 3.20–3.15 (m, 1H), 2.62 and 2.43 (ABX, $J_{AB} =$ 14.5 Hz, $J_{AX} = 4.0$ Hz, $J_{BX} = 11.0$ Hz, 2H), 1.99–1.95 (m, 1H), 1.88–1.83 (m, 2H), 1.74–1.67 (m, 2H), 1.61–1.56 (m, 1H), 1.54–1.45 (m, 2H), 1.42–1.41 (m, 1H), 1.39–1.29 (m, 3H), 1.26–1.11 (m, 3H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.94 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.1$, 78.9, 75.8, 73.5, 72.5, 68.3, 56.5, 44.3, 42.5, 42.5, 42.2, 41.0, 40.2, 37.1, 31.5, 25.8, 19.2, 14.1 ppm; IR (neat): $\tilde{\nu}_{max} = 3420$, 2953, 2871, 2351, 2318, 1730, 1647, 1383, 1156, 937, 798, 705 cm^{-1}; MS *m*/*z* (CI, relative intensity): 329 [M^++1, 100], 311 (84), 297 (81), 279 (66), 267 (6), 241 (26), 209 (1), 199 (3), 181 (5), 155 (4), 141 (7), 113 (11), 85 (2); HRMS (CI) calcd. for $C_{18}H_{33}O_5$ [M^++1] 329.2328, found 329.2327; $[\alpha]_D^{29} = +22.2$ deg cm^3 g^{-1} dm^{-1} ($c = 0.01$ g cm^{-3}, $CHCl_3$).

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[15] $[\alpha]_D^{27} = +25.8$ deg cm^3 g^{-1} dm^{-1} ($c = 0.0065$ g cm^{-3}, MeOH). The specific rotation of the natural sample is[1] $[\alpha]_D^{24} = +24.0$ deg cm^3 g^{-1} dm^{-1} ($c = 0.0024$ g cm^{-3}, MeOH).

