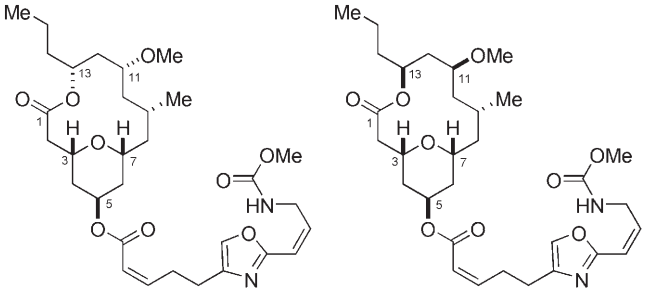
Natural Products Synthesis

DOI: 10.1002/ange.200801399

Total Synthesis of (+)-Neopeltolide**

Haruhiko Fuwa, Shinya Naito, Tomomi Goto, and Makoto Sasaki**

Neopeltolide is a marine macrolide that was isolated from a deep-sea sponge of the Neopeltidae family by Wright and coworkers (Scheme 1).[1] The gross structure, including the relative stereochemistry, was determined based on extensive 2D-NMR analysis. Recently, two independent total syntheses of this natural product, from the research groups of Panek[2] and Scheidt,[3] have resulted in the stereochemical reassignment of the originally proposed structure **1** and the unambiguous determination of the absolute stereostructure, as represented by structure **2** (Scheme 1). Two additional reports on



Scheme 1. The proposed and revised structures of neopeltolide.

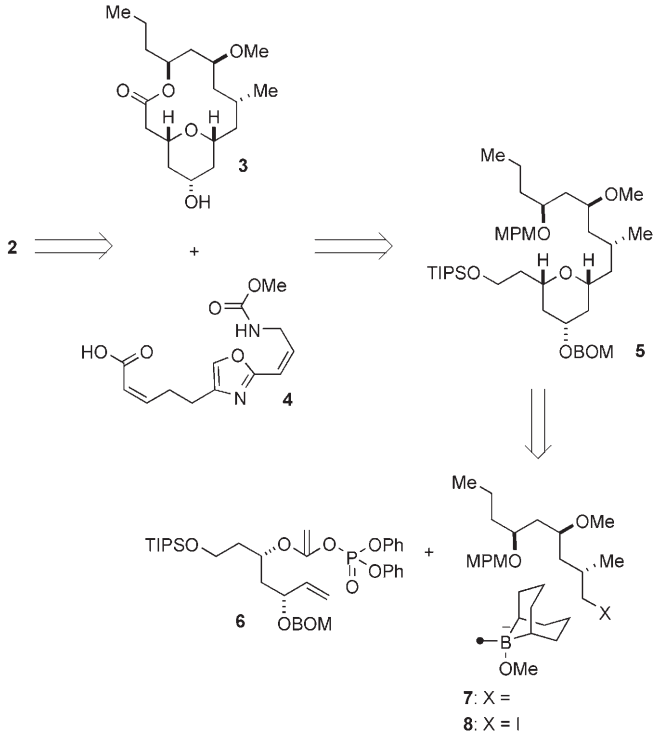
the total synthesis of **2** have appeared to date.[4,5] The intriguing biological activity of **2** includes extremely potent inhibition of the in vitro proliferation of the A-549 human lung adenocarcinoma, the NCI-ADR-RES human ovarian sarcoma, and the P388 murine leukemia cell lines with nanomolar IC_{50} values. Additionally, this natural product is a potent inhibitor of the growth of the fungal pathogen *Candida albicans* (MIC 0.62 $\mu g\,mL^{-1}$). However, the molecular mode of action of this intriguing natural product has yet to be elucidated because of its limited supply from the natural sources. Herein we report an efficient total synthesis of (+)-neopeltolide (**2**) that exploits a Suzuki–Miyaura coupling/ring-closing metathesis (RCM) sequence for the synthesis of 2,4,6-trisubstituted tetrahydropyrans.[6,7]

[*] Dr. H. Fuwa, S. Naito, T. Goto, Prof. Dr. M. Sasaki
Laboratory of Biostructural Chemistry
Graduate School of Life Sciences, Tohoku University
1-1 Tsutsumidori-amamiya, Aoba-ku, Sendai 981-8555 (Japan)
Fax: (+81) 22-717-8896
E-mail: hfuwa@bios.tohoku.ac.jp

[**] This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Sports, Culture, Science and Technology (Japan).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

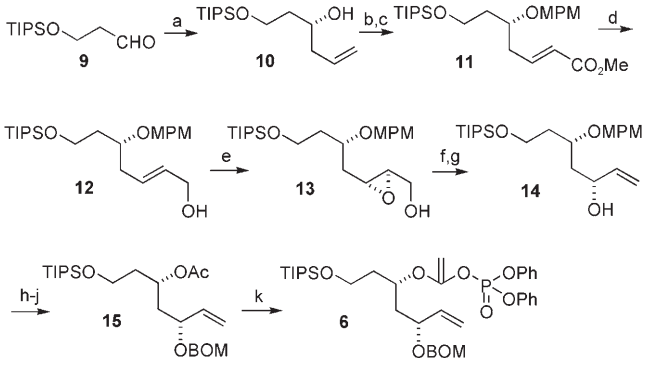
Our plan for the synthesis of **2** is summarized in Scheme 2. Mitsunobu reaction[8] of macrolactone **3** with oxazole-containing carboxylic acid **4**[9] accompanied by inversion of the configuration at C5 would afford **2**. In turn, **3** could be derived



Scheme 2. Retrosynthetic analysis of (+)-neopeltolide (**2**). BOM = benzyloxymethyl, MPM = 4-methoxyphenylmethyl, TIPS = triisopropylsilyl.

from tetrahydropyran **5** through macrolactonization under the Yamaguchi conditions.[10] For the construction of the 2,4,6-trisubstituted tetrahydropyran substructure found in **5**, all of the previous total syntheses of **2** involved either intra- or intermolecular cyclization reaction via an oxocarbenium ion. In contrast, we envisioned that **5** could be constructed by Suzuki–Miyaura coupling of enol phosphate **6** and alkylborate **7** (generated in situ from iodide **8**)[11] and subsequent RCM.[12] Therefore, the highly functionalized tetrahydropyran **5** could be rapidly elaborated from the readily available acyclic precursors **6** and **8**.

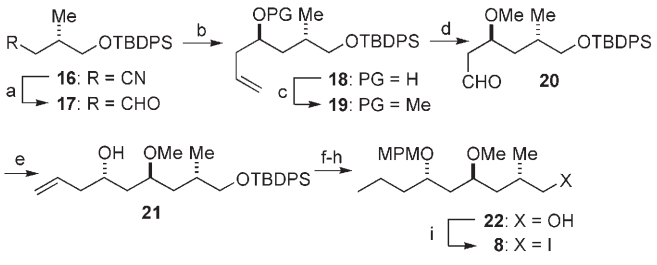
The synthesis of enol phosphate **6** started with the asymmetric allylation[13] of aldehyde **9**, giving alcohol **10** in 98% yield (Scheme 3). Protection of **10** as its MPM ether was followed by olefin cross-metathesis,[14] providing enoate **11** in 58% yield. After reduction of **11** to allylic alcohol **12** (80%), Sharpless asymmetric epoxidation delivered epoxide **13** in 97% yield as a single diastereomer, which was elaborated to



Scheme 3. Reagents and conditions: a) (+)-Ipc$_2$BOMe, allylMgBr, Et_2O, −78 °C; then aqueous NaOH, H_2O_2, RT, 98%; b) MPMOC(=NH)CCl_3, La(OTf)$_3$, toluene, RT; c) methyl acrylate, Grubbs II catalyst (3 mol%), CH_2Cl_2, 40 °C, 58% (over 2 steps); d) DIBALH, CH_2Cl_2, −78 °C, 80%; e) (−)-DET, Ti(O*i*Pr)$_4$, *t*BuOOH, 4 Å M.S., CH_2Cl_2, −20 °C, 97%; f) I_2, PPh_3, imidazole, THF, RT; g) Zn, AcOH, EtOH, RT, 75% (over 2 steps); h) BOMCl, *i*Pr$_2$NEt, CH_2Cl_2, RT; i) DDQ, CH_2Cl_2/pH 7 buffer, RT, 72% (over 2 steps); j) Ac_2O, Et_3N, DMAP, THF, RT, 99%; k) KHMDS, (PhO)$_2$P(O)Cl, THF/HMPA (1:1), −78 °C. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DET = diethyl tartrate; DIBALH = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; HMDS = hexamethyldisilazane; HMPA = hexamethylphosphoramide; Ipc = isopinocampheyl; M.S. = molecular sieves; Tf = trifluoromethanesulfonyl.

allylic alcohol **14** by an iodination/reductive ring-opening sequence. Protection of **14** (BOMCl, *i*Pr$_2$NEt), oxidative cleavage of the MPM ether, and subsequent acetylation gave acetate **15** in good overall yield. Enolization of **15** with KHMDS in the presence of (PhO)$_2$P(O)Cl furnished enol phosphate **6**.

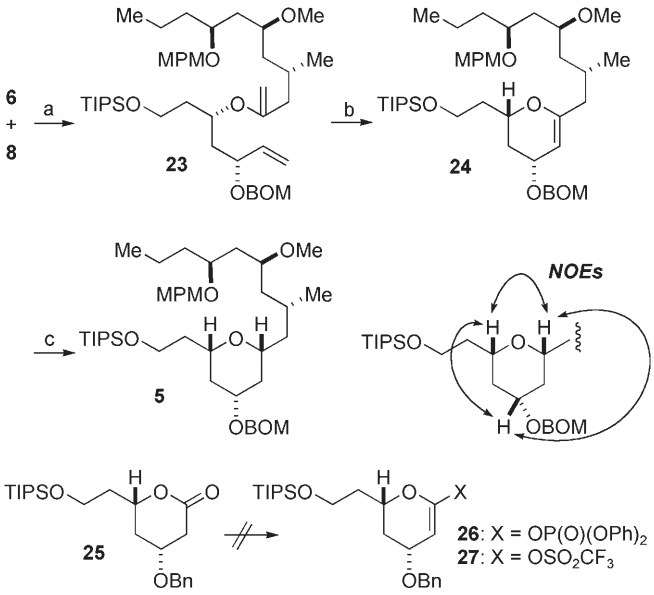
The synthesis of iodide **8** commenced with the known nitrile **16**[15] (Scheme 4). DIBALH reduction of **16** (94%), followed by asymmetric allylation[13] of the derived aldehyde **17**, afforded alcohol **18** in 87% yield as a single diastereomer. Methylation of **18** gave methyl ether **19**. Ozonolysis of the double bond delivered aldehyde **20** (85%), which was subsequently subjected to asymmetric allylation[13] to provide alcohol **21** in 96% yield as a single diastereomer. Hydrogenation of **21**, protection of the remaining hydroxy group as



Scheme 4. Reagents and conditions: a) DIBALH, CH_2Cl_2, −78 °C, 94%; b) (+)-Ipc$_2$BOMe, allylMgBr, Et_2O, −78 °C; then aqueous NaOH, H_2O_2, RT, 87%; c) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, RT, 88%; d) O_3, CH_2Cl_2, −78 °C; then PPh_3, RT, 85%; e) (−)-Ipc$_2$BOMe, allylMgBr, Et_2O, −78 °C; then aqueous NaOH, H_2O_2, RT, 96%; f) H_2, Pd/C, EtOAc, RT, 100%; g) MPMOC(=NH)CCl_3, La(OTf)$_3$, toluene, RT, 75%; h) TBAF, THF, 50 °C, 87%; i) I_2, PPh_3, imidazole, THF, RT, 76%. PG = protecting group; TBAF = tetra-*n*-butylammonium fluoride; TBDPS = *tert*-butyldiphenylsilyl.

its MPM ether, and desilylation afforded alcohol **22**. Iodination under standard conditions then furnished iodide **8** in 76% yield.

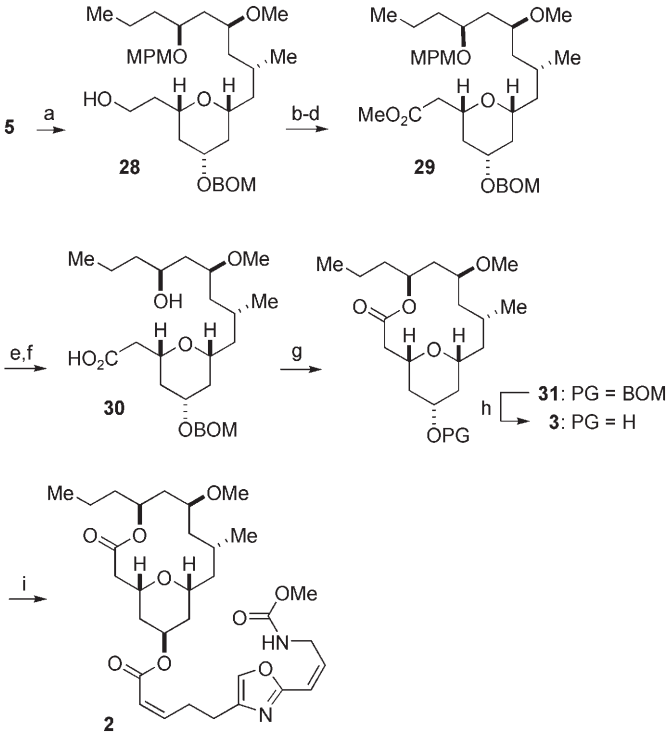
Assembly of the advanced fragments (namely, **6** and **8**) and construction of the 2,4,6-trisubstituted tetrahydropyran substructure are illustrated in Scheme 5. Lithiation of **8** with



Scheme 5. Reagents and conditions: a) **8**, *B*-MeO-9-BBN, *t*BuLi, Et_2O/THF (1:1), −78 °C to RT; then 3 M aqueous Cs_2CO_3, [Pd(PPh$_3$)$_4$] (10 mol%), **6** (1.5 equiv), DMF, RT; b) Grubbs II catalyst (10 mol%), toluene (5 mM), 70 °C, 78% (over 2 steps); c) H_2 (0.8 MPa), Pd/C, EtOAc/MeOH (1:1), RT, 81%. *B*-MeO-9-BBN = *B*-methoxy-9-borabicyclo[3.3.1]nonane; DMF = *N*,*N*-dimethylformamide. NOEs used to establish the stereochemistry of the tetrahydropyran moiety are indicated in the structure next to compound **5**.

*t*BuLi in the presence of *B*-MeO-9-BBN generated the alkylborate **7**, which was reacted in situ with enol phosphate **6** using aqueous Cs_2CO_3 as a base and [Pd(PPh$_3$)$_4$]as a catalyst in DMF at room temperature to give acyclic enol ether **23**. The intermolecular Suzuki–Miyaura coupling of **6** and **7** predominated over the possible intramolecular Heck cyclization of **6**. Subsequent RCM of **23** using the second-generation Grubbs catalyst in toluene (5 mM) furnished the endocyclic enol ether **24** in 78% overall yield from **8**. It was imperative to carry out the cross-coupling process at room temperature, since enol phosphate **6** was found to be rather labile under alkaline conditions. Stereoselective hydrogenation of **24** cleanly afforded tetrahydropyran **5** in 81% yield as a single stereoisomer. The stereochemistry of the tetrahydropyran moiety was established by NOE experiments as shown in Scheme 5. Since we could not prepare the lactone-derived enol phosphate **26** nor its triflate counterpart **27** from lactone **25**,[16] the present Suzuki–Miyaura coupling/RCM sequence would represent an efficient strategy for the synthesis of 2,4,6-trisubstituted tetrahydropyrans.

Completion of the total synthesis of **2** is depicted in Scheme 6. Removal of the TIPS group from **5** gave alcohol **28**. A two-stage oxidation of **28** and ensuing esterification



Scheme 6. Reagents and conditions: a) TBAF, THF, RT, 97%; b) SO_3·Pyr., Et_3N, DMSO/CH_2Cl_2 (1:1), 0°C; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (1:1), RT; d) $TMSCHN_2$, MeOH/benzene (1:1), RT, 89% (over 3 steps); e) DDQ, CH_2Cl_2/pH 7 buffer, RT, 92%; f) TMSOK, Et_2O, RT, 100%; g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, RT; then DMAP, toluene, 80°C, 100%; h) H_2, $Pd(OH)_2$/C, THF/MeOH (1:1), RT, 100%; i) **4**, DIAD, PPh_3, benzene, RT, 61%. DIAD = diisopropylazodicarboxylate, TMS = trimethylsilyl; Pyr = pyridine.

delivered ester **29**. Removal of the MPM group followed by saponification[17] gave hydroxy acid **30**, which was subjected to macrolactonization under the Yamaguchi conditions[10] to furnish macrolactone **31** in quantitative yield. After cleavage of the BOM group by hydrogenolysis, the resultant alcohol **3** was coupled with the known acid **4**[9] under the Mitsunobu conditions to give (+)-neopeltolide (**2**). The spectroscopic properties of the synthetic **2** were in full accordance with the reported data.[3]

In summary, we have accomplished an efficient total synthesis of (+)-neopeltolide (**2**), which was prepared in 25 steps (longest linear sequence) and in an excellent 8.3% overall yield from commercially available methyl (*R*)-(−)-3-hydroxy-2-methylpropiolate via the known compound **16**. The highlight of the present total synthesis is the convergent synthesis of the 2,4,6-trisubstituted tetrahydropyran substructure based on the Suzuki–Miyaura coupling/RCM sequence. Further application of this strategy to the synthesis of other natural products is currently under investigation.

Received: March 24, 2008
Published online: May 19, 2008

Keywords: macrolides · natural products · ring-closing metathesis · Suzuki–Miyaura coupling · total synthesis

[1] A. E. Wright, J. C. Botelho, E. Guzmán, D. Harmody, P. Linley, P. J. McCarthy, T. P. Pitts, S. A. Pomponi, J. K. Reed, *J. Nat. Prod.* **2007**, *70*, 412.
[2] W. Youngsaye, J. T. Lowe, F. Pohlki, P. Falifo, J. S. Panek, *Angew. Chem.* **2007**, *119*, 9371; *Angew. Chem. Int. Ed.* **2007**, *46*, 9211.
[3] D. W. Custer, T. P. Zabawa, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 804.
[4] V. V. Vintonyak, M. E. Maier, *Org. Lett.* **2008**, *10*, 1239.
[5] S. K. Woo, M. S. Kwon, E. Lee, *Angew. Chem.* **2008**, *120*, 3286; *Angew. Chem. Int. Ed.* **2008**, 47, 3242.
[6] For reviews of Suzuki–Miyaura coupling, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
[7] For reviews of ring-closing metathesis, see: a) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[8] O. Mitsunobu, *Synthesis* **1981**, 1.
[9] Y. Yang, J. Janjic, S. A. Kozmin, *J. Am. Chem. Soc.* **2002**, *124*, 13670.
[10] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
[11] For our successful implementation of enol phosphates in palladium-catalyzed synthesis of heterocycles, see: a) M. Sasaki, H. Fuwa, M. Ishikawa, K. Tachibana, *Org. Lett.* **1999**, *1*, 1075; b) M. Sasaki, M. Ishikawa, H. Fuwa, K. Tachibana, *Tetrahedron* **2002**, *58*, 1889; c) H. Fuwa, N. Kainuma, K. Tachibana, M. Sasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14983; d) C. Tsukano, M. Ebine, M. Sasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4326; e) H. Fuwa, M. Ebine, A. J. Bourdelais, D. G. Baden, M. Sasaki, *J. Am. Chem. Soc.* **2006**, *128*, 16989; f) H. Fuwa, A. Kaneko, Y. Sugimoto, T. Tomita, T. Iwatsubo, M. Sasaki, *Heterocycles* **2006**, *70*, 101; g) H. Fuwa, M. Sasaki, *Org. Biomol. Chem.* **2007**, *5*, 1849; h) H. Fuwa, M. Sasaki, *Chem. Commun.* **2007**, 2876; i) H. Fuwa, M. Sasaki, *Org. Lett.* **2007**, *9*, 3347.
[12] For other examples of the synthesis of endocyclic enol ethers employing RCM, see: a) K. C. Nicolaou, M. H. D. Postema, C. F. Claiborne, *J. Am. Chem. Soc.* **1996**, *118*, 1565; b) J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310; c) D. Calimente, M. H. D. Postema, *J. Org. Chem.* **1999**, *64*, 1770; d) J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, C. Wilson, *Angew. Chem.* **2005**, *117*, 6313; *Angew. Chem. Int. Ed.* **2005**, *44*, 6157.
[13] H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1981**, *105*, 2092.
[14] For a review of olefin cross-metathesis, see: S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
[15] F. Keyling-Bilger, G. Schimitt, A. Beck, B. Luu, *Tetrahedron* **1996**, *52*, 14891.
[16] Treatment of lactone **25** with KHMDS or LHMDS resulted in decomposition of the starting material, even in the presence of $(PhO)_2P(O)Cl$, $PhNTf_2$, or Comins reagent (2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine).
[17] E. D. Laganis, B. L. Chenard, *Tetrahedron Lett.* **1984**, *25*, 5831.

