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Stereoselective Synthesis of the Macrolactone Core of (+)-Neopeltolide

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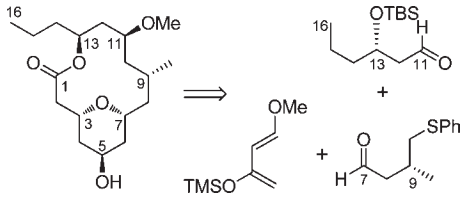
ABSTRACT



A stereoselective synthesis of the macrolactone core of the potent anticancer agent neopeltolide is disclosed. The key steps of the synthesis include asymmetric allylation using Krische' protocol, conjugate reduction using MacMillan's methodology, and an asymmetric hetero-Diels–Alder reaction using Jacobsen's catalyst. Substrate controlled diastereoselective 1,3-*anti* reduction of a keto alcohol, Luche reduction followed by Ireland–Claisen rearrangement, oxymercuration, and reductive lithiation are other key steps.

Neopeltolide **1** is a macrolide isolated by Wright and co-workers in 2007 from a Caribbean sponge of the neopeltolide family collected off the Jamaican coast.[1] Neopeltolide exhibits potent cytotoxic activity against several cancer cell lines (e.g., IC_{50} 0.56, 1.2, and 5.1 nM against P388 murine leukemia, A-549 human lung adenocarcinoma, and NCI-ADR-RES human ovarian sarcoma respectively) as well as DLD-1 colorectal cell lines and the PAWC-1 pancreatic cell line[1,2] in addition to inhibiting the growth of the fungal pathogenic yeast *Candida albicans* with an MIC value of 0.62 μg mL^{-1} in liquid cultures. The key structural characteristics of neopeltolide include a 2,4,6-trisubstituted tetrahydropyran ring contained in a 14-membered macrolactone framework, an oxazole having an unsaturated chain appended through an ester linkage, and six stereogenic centers.

The complex macrolide structure and potent biological activity of neopeltolide have stimulated extensive enthusiasm among synthetic chemists, and several total[3] and formal[4] synthesis have been reported. The initial independent reports of Panek[3a] and Scheidt[3b] led to a revision of the original stereochemical configuration at C11 and C13. Kozmin and co-workers,[5] on the basis of biological testing of neopeltolide and of a simplified analogue, identified cytochrome bc_1 complex as the cellular target.

Herein, we report a new synthesis of the macrolactone core of (+)-neopeltolide adopting a strategy wherein three of the six stereocenters were introduced using organocatalytic or metal complex promoted catalytic asymmetric transformations

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(2) Wright, A. E.; Pomponi, S. A.; McCarthy, P. J. U.S. Patent 7179828B2, 2007, European Patent 1644380, 2007.

(3) For the total synthesis of neopeltolide, see: (a) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211. (b) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804. (c) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242. (d) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708. (e) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737. (f) Guinchard, X.; Roulland, E. *Org. Lett.* **2009**, *11*, 4700.

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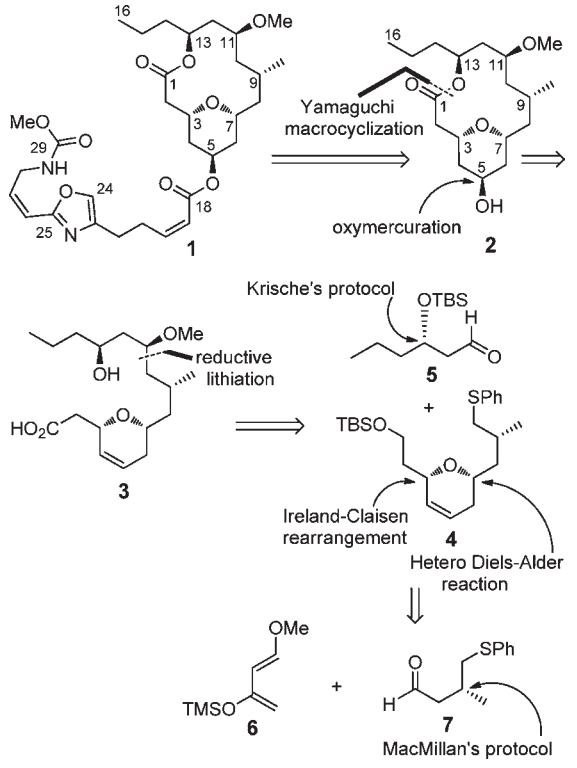
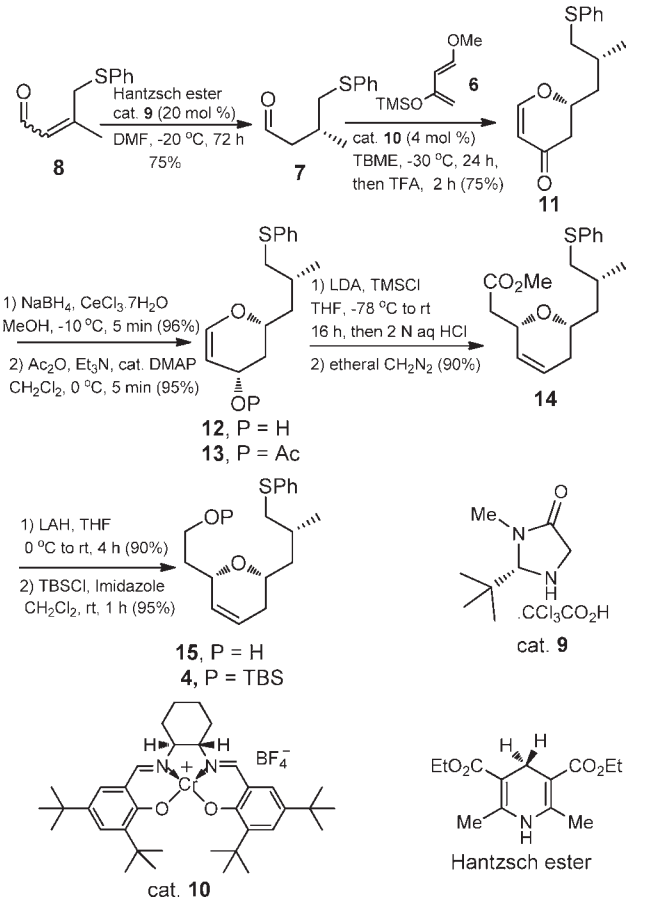
and the remaining three were introduced with excellent stereoselectivity by substrate controlled asymmetric induction. The C5 hydroxy group is accessed with the natural stereochemistry by oxymercuration–demercuration. As outlined in Scheme 1, the hydroxy group at C5 in **2** was envisioned to be introduced after lactonization of *seco* acid **3**, which in turn was envisaged to be obtained by coupling sulphide **4** and aldehyde **5**. Sulphide **4** can be assembled from subunits, diene **6** and aldehyde **7**, taking advantage of the hetero-Diels–Alder reaction.

Scheme 1. Retrosynthetic Analysis of (+)-Neopeltolide



The synthesis commenced with the enantioselective organocatalytic hydride reduction of enal **8**,[6] using MacMillan's protocol.[7] Thus exposure of the mixture of *E*/*Z* isomers of **8** to the trichloroacetic acid salt of (*S*)-2-*tert*-butyl-3-methylimidazolidin-4-one, **9** (20 mol %), and 1.2 equiv of Hantzsch ester resulted in complete conversion to the 1,4-reduction product (75% yield, 95% ee).[8] The pyran ring was constructed by a hetero-Diels–Alder reaction between aldehyde **7** and siloxy diene **6**,[9] in the presence of (*S*,*S*)-Cr(III)-salen-BF_4^+ **10**,[10] to furnish pyranone **11** with high diastereoselectivity (75% yield)[11] after TFA treatment. To the best of our knowledge this is the first example of a hetero-Diels–Alder reaction of an aldehyde possessing a sulfide moiety with diene **6** promoted by Jacobsen's catalyst.[12] Substrate controlled chemoselective reduction of the carbonyl group using Luche's protocol[13] afforded *cis*-2,4-disubstituted pyran derivative **12** (96% yield) exclusively. Acetylation (95% yield) followed by Ireland–Claisen rearrangement[14]of the derived silyl ketene acetal afforded unsaturated ester **14** after esterification of the resulting acid using etheral diazomethane (95% yield for two steps). Reduction of the ester using LAH yielded the primary alcohol **15** (90% yield) that was subsequently protected as its TBS ether **4** (95% yield) under standard conditions, Scheme 2.

Scheme 2. Synthesis of Dihydropyran **4**



(6) Preparation of enal **8** was achieved in three high yielding steps from commercially available chloro acetone; see: Supporting Information for a detailed experimental protocol.

(7) Ouellet, S. G.; Tuttle, J. B.; MacMillan., D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

(8) The enantiomeric ratio was determined by HPLC of the benzoate prepared in two steps from **7**, (a) reduction with $NaBH_4$ to furnish the alcohol and (b) treatment with benzoyl chloride in the presence of a base. Chiralcel OD-H ((0.46 mm × 25 cm) isocratic 5% EtOH in hexane, 1.0 mL/min, 25 °C); (*R*) isomer t_r = 5.167 min and (*S*) isomer t_r = 6.475 min. See Supporting Information. The enantiomeric alcohol is reported; see: Sato, T.; Hanayama, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 2199.

(9) For reviews, see: (a) Danishefsky, S. J. *Chemtracts* **1989**, 273. (b) Danishefsky, S. J.; De Ninno, M . P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

(10) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.

(11) The diastereomeric adduct epimeric at C7 was not observed.

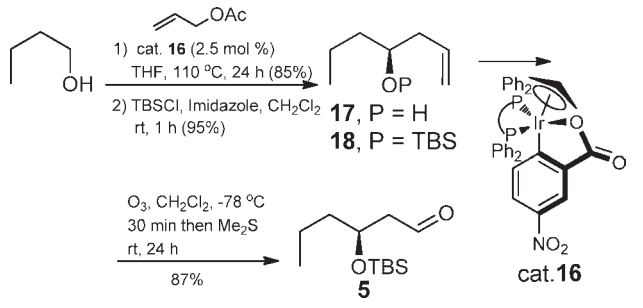
(12) The hetero–Diels–Alder reaction of the sulfoxide and sulfone corresponding to **7** with diene **6** failed under identical conditions.

(13) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(14) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

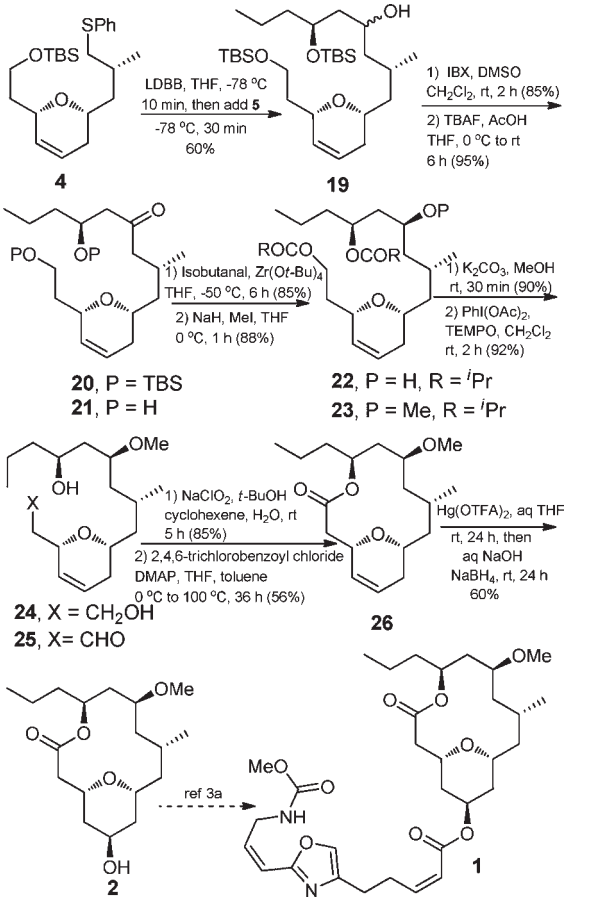
The C13 stereogenic center was created by an asymmetric allylation of *n*-butanol using the chemistry developed by Krische.[15] Thus iridium complex **16** (2.5 mol %) catalyzed reaction of allyl acetate with *n*-butanol in the presence of (*R*)-BINAP yielded homoallyl alcohol **17** (85% yield, 97% ee).[16] Protection of the hydroxy group as its silyl ether afforded compound **18** (95% yield) which on ozonolysis furnished aldehyde **5** (87% yield), Scheme 3.

Scheme 3. Synthesis of Aldehyde **5**



With aldehyde **5** in hand, we turned our attention to its coupling with the organolithium derivative obtained from the reductive cleavage of the alkyl carbon−sulfur bond of phenyl thioether **4** performed using a single electron transfer (SET) reaction. Thus treatment of **4** with lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB)[17] followed by addition of aldehyde **5** furnished an epimeric mixture of alcohols **19** (65% yield) that was subjected to IBX oxidation[18] to yield ketone **20** (85% yield). Deprotection of the TBS ether using TBAF under buffered conditions yielded the diol **21** (95% yield). Diastereoselective reduction of the carbonyl group in the presence of an excess of isobutyraldehyde and zirconium *tert*-butoxide following the modified Evans−Tishchenko protocol[19] afforded the *anti*-1,3-diol derivative[20] **22** (85% yield, 98:2 *anti*/*syn*), possessing five of the six stereocenters of the target. Curiously, under the reaction conditions the free primary hydroxy group was also protected as its ester, probably via an intermolecular redox reaction. O-Methylation using sodium hydride and methyl iodide yielded methyl ether **23** (88% yield), Scheme 4.

Scheme 4. Formal Synthesis of Neopeltolide **1**



The diester was hydrolyzed to furnish diol **24** (90% yield). Selective oxidation of the primary hydroxy group[21] in **24** using $PhI(OAc)_2$/TEMPO to the aldehyde **25** followed by Pinnick oxidation furnished *seco* acid **3** (85% overall yield). Cyclization of **3** under Yamaguchi's conditions[22] provided the 14-membered macrolactone **26** (56% yield). It only remained to introduce the C5 hydroxy group to complete the formal synthesis of neopeltolide. This was accomplished by oxymercuration−demercuration as originally reported by Panek and co-workers[3a] to selectively furnish the macrolactone **2** (60% yield). The spectroscopic data of our synthetic material were found to be in complete agreement with those presented by Panek. Considering Panek's two-step conversion of **2** to (+)-neopeltolide, the present route represents a formal total synthesis.

In summary, we have disclosed a new stereoselective route to (+)-neopeltolide (3.83% overall yield in 16 steps by the longest linear sequence) exploiting catalytic asymmetric reactions. The synthetic route is characterized by high stereoselectivity in the creation of the stereogenic

(15) Kim, l. S.; Ngai, M. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

(16) The enantiomeric ratio was determined by HPLC, and the configuration was determined by comparing the ^{1}H NMR spectra of the mandelate esters of homo allyl alcohol **17**. See: Supporting Information for a detailed experimental protocol.

(17) For a review, see: Foubelo, F.; Yus, M. *Chem. Soc. Rev.* **2008**, *37*, 2620.

(18) For the first use of IBX as a selective oxidant for alcohols, see: (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. For Nicolaou's excellent work with IBX, see: (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Barluenga, Z. S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233.

(19) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (b) Schneider, C.; Klapa, K.; Hansch, M. *Synlett* **2005**, 91. (c) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 2602.

(20) The *anti* relationship of the C13 and C11 centers was determined by ^{13}C NMR spectroscopic analysis of the acetonide derived from the diol product obtained after hydrolysis of C13 and C1 acyl protecting groups. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(21) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

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

centers by reagent or substrate control, readily available starting materials, mild reaction conditions, and its potential to prepare analogs.

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Note Added after ASAP Publication. In the version published ASAP on April 19, 2012, reference 4e did not detail a formal synthesis but instead a total synthesis of neopeltolide, it has been relocated as reference 3f. The correct version reposted on April 24, 2012.

Supporting Information Available. Detailed experimental procedure and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.