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Toward an Enantioselective Synthesis of (−)-Zampanolide: Preparation of the C9−C20 Region

Matthew R. Wilson and Richard E. Taylor*

Department of Chemistry and Biochemistry and the Walther Cancer Research Center, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556-5670, United States

taylor.61@nd.edu

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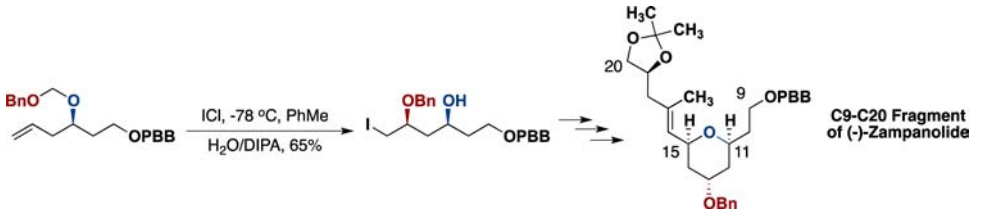
ABSTRACT



Progress toward the synthesis of the microtubule-stabilizing agent, (−)-zampanolide, is reported. Construction of the 2,6-*cis*-tetrahydropyran ring was accomplished utilizing *ether transfer* methodology in conjunction with an intramolecular radical cyclization reaction. Efficient installation of the C16−C20 side chain relied on a one-pot cross-metathesis/olefination sequence, Sharpless epoxidation, and selective reduction of a vinyl epoxide.

Polyketide natural products represent a privileged scaffold for the discovery of novel drugs as their structural features and molecular complexity occupy newly defined regions of chemical space.[1] Resultingly, a great amount of effort has been directed toward developing new synthetic methods for the construction of complex polyketides. Our laboratory has been interested in the use of total synthesis to enable biological evaluation and characterization of their properties at the molecular level.[2] In an effort to provide access to structural units not readily available by known synthetic methods, we have recently developed a protocol for the efficient generation of 1,3-*syn* mono diol ethers from readily accessible alkoxy ether protected homoallylic alcohols.[3] The methodology involves treatment of an alkoxy ether with iodine monochloride (ICl) at low temperature providing a diverse array of orthogonally protected diol ethers upon nucleophilic quench. As an example, a thiophenol quench followed by sulfide oxidation and base-promoted cyclization affords functionalized sulfonyl pyrans which upon subsequent manipulation allows entry to 2,6-*cis* and *trans*-trisubstituted tetrahydropyrans (Figure 1).[4]

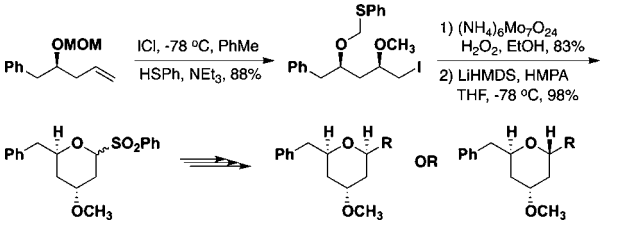


Figure 1. Synthetic approach to 2,6-*cis*- and *trans*-pyrans.[4]

As our ether transfer methodology has successfully been employed for the synthesis of a number of biologically active natural products,[5] a more recent application to alternative structures with unsaturation adjacent to the

(1) Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248–258.
(2) Begaye, A.; Trostel, S.; Zhao, Z.; Taylor, R. E.; Schriemer, D. C.; Sackett, D. L. *Cell Cycle* **2011**, *10*, 3387–3396.
(3) Liu, K.; Taylor, R. E.; Kartika, R. *Org. Lett.* **2006**, *8*, 5393–5395.
(4) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874.
(5) (a) Kartika, R.; Frein, J. R.; Taylor, R. E. *J. Org. Chem.* **2008**, *73*, 5592–5594. (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047–5050. (c) Liu, K.; Arico, J. W.; Taylor, R. E. *J. Org. Chem.* **2010**, *75*, 3953–3975.

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pyran ring warranted the exploration of activating allylic and benzylic alkoxy ethers (Figure 2). In order to investigate the effects of proximal sp^2-hybridization on our methodology, we sought to focus on the highly potent polyketide, (−)-zampanolide **1**.

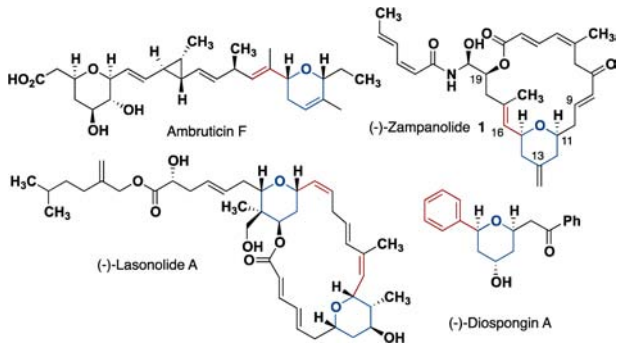
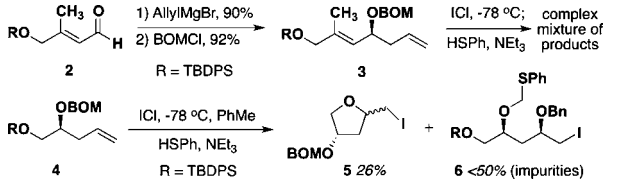


Figure 2. Unsaturated biologically active polyketides.

Zampanolide was initially isolated from the marine sponge *Fasciospongia rimosa* by Tanaka and Higa in 1996.[6] This interesting compound was also found recently by Northcote et al. in the Tongan marine sponge, *Cacospongia mycofijiensis*, along with the well-known polyketides laulimalide and latruncalin A.[7] The latter report demonstrated that zampanolide stabilizes microtubules and blocks cell division in the G2/M phase of the cell cycle similar to paclitaxel, pelorusides, and the epothilones. Moreover, zampanolide exhibits potent cytotoxic activity (1−5 nM) against multiple cancer cell lines including P388, HT29, A549, and MEL28.[8] The impressive biological activity and unique structural features have attracted considerable attention from the synthetic community. In 2001, Smith and co-workers disclosed the first total synthesis of the unnatural (+)-zampanolide and established its absolute and relative stereochemistry.[9] Subsequent syntheses emerged from Hoye,[10] Tanaka,[8] and most recently the Ghosh[11] laboratory. Despite isolation from two marine organisms and several total syntheses, samples of zampanolide remain scarce.[12] Moreover, no analogues have been reported to date. From a structural standpoint, the 20-membered macrolactone contains a *cis*-2,6-trisubstituted tetrahydropyran, ample unsaturation, and an unusual exocyclic *N*-acylhemiaminal side chain that has been documented to be critical for biological activity. Herein, we describe our initial approach toward the C9−C20 fragment of (−)-zampanolide **1**.

Our initial strategy relied on our recently developed methodology to assemble the 4-alkoxy-2,6-*cis*-tetrahydropyran from an advanced sulfonyl pyran fragment. The synthesis commenced with the preparation of benzyloxy methyl ether (BOM) **3** as a model system to assess the viability of our ether transfer methodology with the allylic alkoxy ether (Scheme 1). Allylation of known aldehyde[13] **2** followed by alkylation with commercially available BOMCl provided the model substrate **3** in excellent yield over two steps. Unfortunately, treatment of the allylic ether **3** with ICl at −78 °C did not provide the expected product but gave a complex mixture. This result is in accord with the lack of selectivity observed by Smith and our laboratory with polyolefinic substrates utilizing iodine monobromide for iodocarbonate cyclization.[14] Circumvention of this undesirable reactivity was envisioned by replacing the *E*-trisubstituted olefin as a bulky silyl protected hydroxyl group. However, treatment of BOM ether **4** with ICl resulted in a Bartlett cyclization[15] to afford furan diastereomers **5** and low yields of desired product **6**.[16] Presumably, generation of the intermediate oxonium ion leading to ether transfer may be impeded by the presence of electronegative substituents (sp^2-hybridization in **3** and -OTBDPS in **4**) adjacent to the reacting alkoxymethyl ether.

Scheme 1. Model Systems

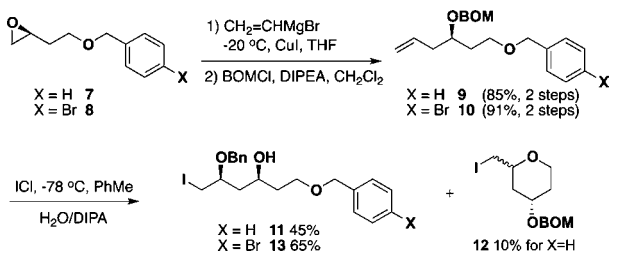


The inefficient ether transfer observed with these two substrates compelled us to revise our synthetic strategy. To this end, we opted to conceal the C8−C9 olefin as a benzyl ether in hopes we could deprotect and install the C13 and C8−C9 alkenes simultaneously as previously reported by

(6) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535–5538.
(7) Field, J. J.; Singh, A. J.; Kanakkanthara, A.; Halafihi, T.; Northcote, P. T.; Miller, J. H. *J. Med. Chem.* **2009**, *52*, 7328–7332.
(8) Uenishi, J.; Iwamoto, T.; Tanaka, J. *Org. Lett.* **2009**, *11*, 3262–3265.
(9) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426–12427.
(10) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576–9577.
(11) Ghosh, A. K.; Cheng, X. *Org. Lett.* **2011**, *13*, 4108–4111.
(12) The marine polyketide, (+)-dactylolide, which contains an identical pyran substituted macrocyclic lactone without the acyl hemiaminal side chain, has been synthesized several times: (a) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635–637. (b) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485–3488. (c) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053–3056. (d) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321–2324. (e) Louis, I.; Hungerford, N. L.; Humphries, E. J.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 1117–1120. (f) Ding, F.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 5965–5976. (g) Zurwerra, D.; Gertsch, J.; Altmann, K.-H. *Org. Lett.* **2010**, *12*, 2302–2305. (h) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4261–4263. (i) Lee, K.; Kim, H.; Hong, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5735–5738. For additional synthetic efforts, see: (j) Loh, T.-P.; Yang, J.-Y.; Feng, L.-C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193–7196. (k) Reddy, C. R.; Srikanth, B. *Synlett* **2010**, 1536–1538.
(13) Castagnolo, D.; Botta, L.; Botta, M. *J. Org. Chem.* **2009**, *74*, 3172–3174.
(14) (a) Duan, J. J. W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703–3711. (b) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959–4961.
(15) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.
(16) Alternative protecting groups at this position did not resolve the problem.

McLeod and co-workers in their synthesis of the structurally related polyketide, (−)-dactylolide.[17] Moreover, the BOM ether **9** would serve as an interesting competition experiment to probe the benzyloxy transfer in the presence of an unactivated primary benzyl ether. The synthesis commenced with preparation of the 1,3-*syn* diol monoether **11** as illustrated in Scheme 2.

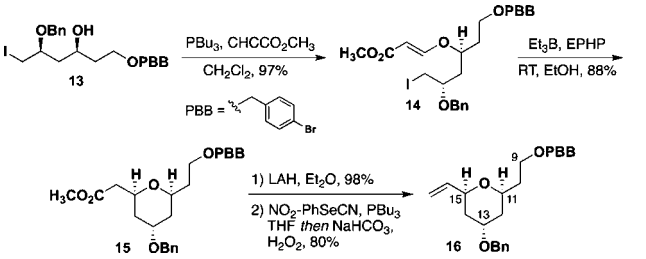
Scheme 2. Synthesis of 1,3-*syn* Diol Mono Ether **13**



The enantiomerically pure epoxide **7** was prepared from (*R*)-aspartic acid via modification of a known procedure previously reported in the literature.[18] Regioselective epoxide opening with vinyl magnesium bromide in the presence of catalytic CuI followed by benzyloxy methyl ether alkylation gave the BOM ether **9** in excellent yield. Electrophilic activation of the resulting ether with ICl at low temperature provided the desired 1,3-*syn* diol monoether **11** in a disappointingly low 45% yield. However, pyran **12** (1:1 *dr*) resulting from Bartlett cyclization[14] of the primary benzyl ether was also isolated in 10% yield. Confronted with a similar problem during their synthesis of (+)-spongistatin 2, it was discovered by Smith and co-workers that use of a *p*-bromobenzyl ether prevented an undesirable cyclization of a neighboring benzyl ether by decreasing the electron density on the oxygen.[19] Inspired by this result, we were pleased to find the reaction of *p*-bromobenzyl **10** with ICl at −78 °C provided upon aqueous workup exclusively 1,3-*syn* diol monoether **13** in 65% yield as an 8:1 mixture of diastereomers.[20]

Our efforts next were directed toward the preparation of the terminal olefin within **16** (Scheme 3). Thus, tributylphosphine-catalyzed conjugate addition[21] of secondary alcohol **13** to methyl propiolate based on previously optimized conditions[5b] yielded *β*-alkoxyacrylate **14**. Intramolecular radical cyclization promoted by triethylborane in the presence of 1-ethylpiperidinium hypophosphate[22] gave pyran methyl ester **15** in excellent yield and diastereoselectivity (> 20:1). Reduction of the methyl ester with LAH followed by Grieco−Sharpless olefination[23] provided **16** in 78% yield, over two steps (Scheme 3). Having secured quantities of olefin **16** necessary for completion of the total synthesis, we turned our attention toward the construction of the C16−C20 fragment.

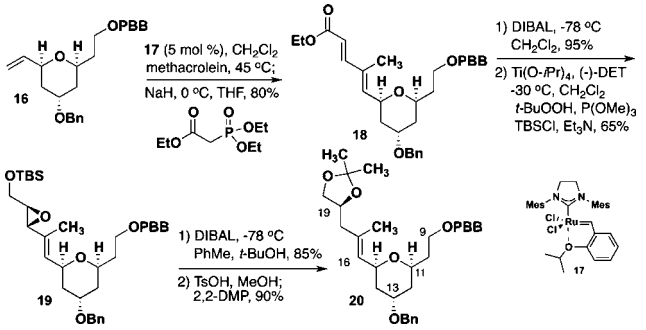
Scheme 3. Synthesis of Terminal Olefin **18**



Here we anticipated utilizing a geometrically selective cross-metathesis reaction to construct the C16−C17 *E*-trisubstituted olefin. Previous efforts[11] exploiting a cross-metathesis approach with terminal and 1,1-disubstituted olefin coupling partners often lacked *E*/*Z*-selectivity requiring the use of isomerization to regenerate the desired *E*-olefin geometry.[24] With this in mind, we opted to use methacrolein as a coupling partner to secure the desired *trans*-olefin geometry and provide a reactive functional handle for installation of the remaining two carbons. The recent emergence of tandem catalysis with Grubbs' and Hoveyda ruthenium alkylidene catalysts encouraged us to explore a sequential cross-metathesis/olefination sequence[25] for installation of all four carbons in a single step. Much to our delight, exposure of terminal olefin **16** to excess methacrolein in the presence of Hoveyda−Grubbs' second-generation catalyst **17** (5 mol %) followed by Horner−Wadsworth−Emmons olefination of the intermediate aldehyde gave dienonate **18** in high yield as a single geometrical isomer (*E*,*E* > 20:1) (Scheme 4). The C19-stereocenter was envisioned to arise from Sharpless epoxidation[26] of a dienol fragment followed by selective reduction at the most electrophilic carbon to unveil the enantiomerically pure secondary alcohol. Reduction of the dienoate with DIBAL-H followed by SAE and in situ silyl protection gave the TBS-protected 2,3-epoxy alcohol **19** in 62% yield, over three steps, with excellent diastereoselectivity. Interestingly, it proved imperative to in situ protect the resulting 2,3-epoxy alcohol due to difficulty

(17) Ignace, L.; Hungerford, N. L.; Humphries, E. J.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 1117–1120.
(18) Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621–623.
(19) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Boldi, A. M.; Murase, N.; Moser, W. H.; Brook, C. S.; Bennett, C. S.; Nakayama, K.; Sobukawa, M.; Trout, R. E. *Tetrahedron* **2009**, *65*, 6470–6488.
(20) While the thiophenol trapping conditions work well in this system, the hydrolytic workup providing **13** is a more appropriate intermediate for this synthetic sequence.
(21) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244.
(22) Lee, E.; Han, H. O. *Tetrahedron Lett.* **2002**, *43*, 7295–7296.
(23) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
(24) (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753. (b) Ghosh, A. K.; Cheng, X. *Org. Lett.* **2011**, *13*, 4108–4111.
(25) (a) Chatterjee, A. K.; Choi, T. -L.; Sanders, D. P. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Murelli, R. P.; Snapper, M. L. *Org. Lett.* **2007**, *9*, 1749–1752. (c) Sirasani, G.; Paul, T.; Andrade, R. B. *Tetrahedron* **2011**, *67*, 2197–2205.
(26) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
(27) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. J. *J. Org. Chem.* **1998**, *63*, 2948–2953.

Scheme 4. Completion of C16−C20 Fragment



isolating the unstable vinyl epoxide on silica gel.[27] Completion of the C9−C20 fragment was accomplished via regioselective opening of the vinyl epoxide with DIBAL-H[28] at low temperature. Desilylation followed by acetonide formation provided **20** in 77% yield for the one-pot process.

In summary, we have developed an efficient, enantioselective route to a protected C9−C20 fragment of (−)-zampanolide utilizing our electrophile-induced ether transfer methodology. The route is highlighted by a radical cyclization, one-pot cross-metathesis/olefination sequence, Sharpless epoxidation, and regioselective reduction of a vinyl epoxide. Coupling of the advanced C9−C20 intermediate to a previously prepared C1−C8 fragment and conversion to (−)-zampanolide are currently underway in our laboratory. Moreover, further studies investigating the ether transfer of allylic and benzylic substrates is in progress. Results along these lines will be reported in due course.

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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.

(28) (a) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719–2722. (b) Furstner, A.; Bouchez, L. C.; Morency, L.; Funel, J. A.; Liepins, V.; Poree, F. H.; Gilmour, R.; Laurich, D.; Beaufils, F.; Tamiya, M. *Chem.—Eur. J.* **2009**, *15*, 3983.

The authors declare no competing financial interest.