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Divergent Synthesis of Complex Polyketide-Like Macrolides from a Simple Polyol Fragment

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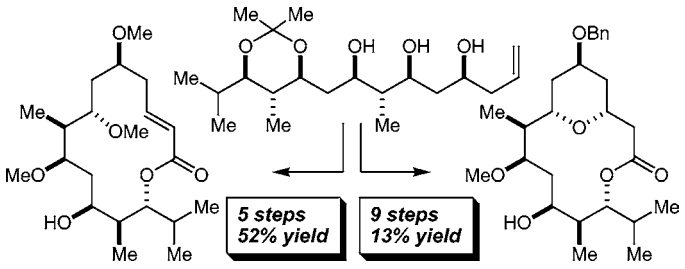
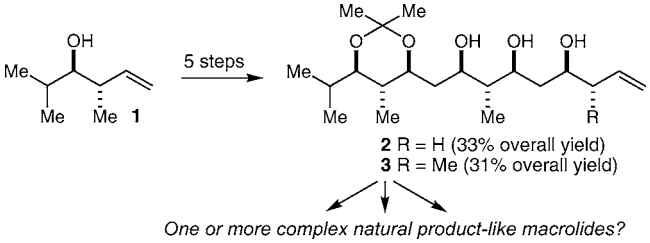
ABSTRACT



Three stereochemically and structurally complex non-natural polyketide macrolides have been synthesized from the same simple polyol precursor. That this polyol fragment is rapidly available in quantity is key to the practicality of these syntheses and allows the targeting of more highly complex and "natural product-like" macrolides.

Polyketide natural products have for decades served as a rich source of structurally and stereochemically complex drugs and drug leads. As a result, enormous effort has been devoted to the development of methods for their synthesis. Despite the wealth of elegant and truly enabling synthetic chemistry to arise from these efforts, the gram-scale (or larger) synthesis of complex polyketide natural products still requires enormous effort and expense.[1] Ever greater reductions in step counts, while employing easily scalable and inexpensive methods and all the while maintaining exquisite stereochemical control, have therefore become the central goal for many laboratories. An example of our own work toward this goal is the five-step conversion of alcohol **1** to polyol fragments **2** and **3** in 33% and 31% overall yields, respectively, employing two iterations of the tandem silylformylation−allylsilylation reaction (Scheme 1).[2] While we have employed and continue to employ such reactions in the synthesis of polyketide natural products,[3] our ability to produce multigram quantities of **2** and **3** in a matter of days inspired a question along different lines: Could **2** and/or **3**, quickly and using only a small number of relatively straightforward chemical steps, be converted into one or more macrolides that more closely resemble—in terms of structural complexity—biologically interesting macrolide natural products? This approach to the generation of natural product-like macrolides places a premium not on large numbers of such structures but rather on smaller numbers of relatively more complex

Scheme 1



(1) The large-scale synthesis of discodermolide is illustrative. See: Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 122.

(2) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890.

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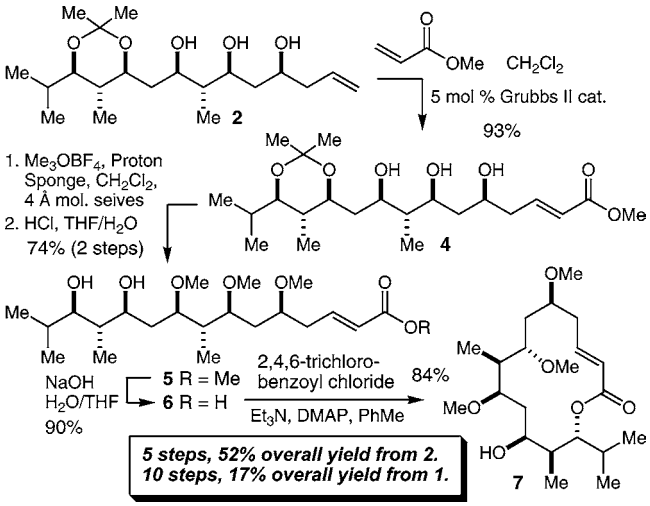
structures.[4] Further, each structure thus generated is to be viewed not as an end goal in itself, but rather as a core structure for further derivitization and diversification[5,6] through simple functionalizations (acylation, glycosylation, etc.) of alcohol groups. As a preliminary assessment of the first part of this strategy, we herein report the straightforward and efficient generation of two structurally complex and natural product-like macrolides from polyol fragment **2** and a third from a simpler polyol precursor.

It was quickly noted that a cross-metathesis reaction between **2** and an acrylate ester would provide the functionality needed for the generation of a 14-membered macrolide. Thus, treatment of **2** with an excess of methyl acrylate and 5 mol % of the second-generation Grubbs catalyst[7] resulted in a smooth and completely *trans*-selective cross metathesis to give ester **4** in 93% yield (Scheme 2).[8] Permethylation of

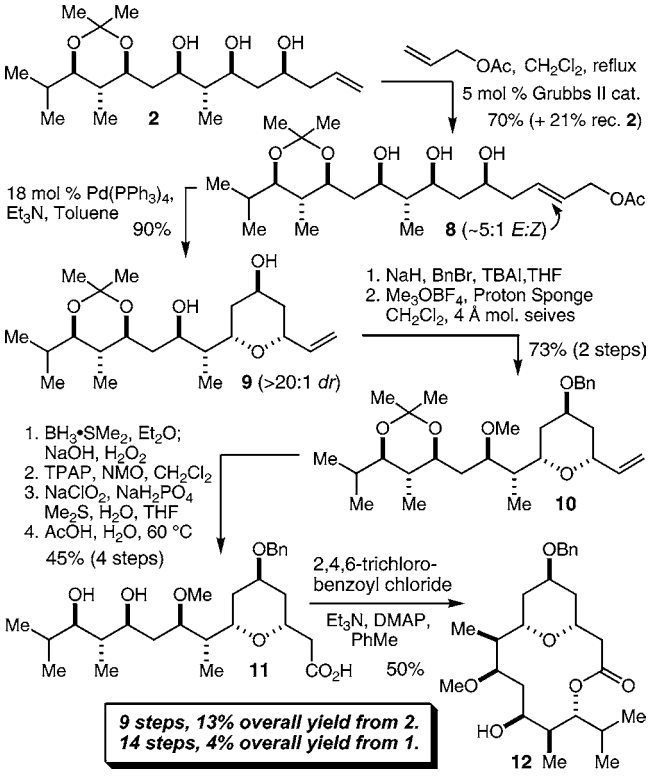
Scheme 2



the triol was then easily achieved with the Meerwein reagent[9] and was followed by acetonide hydrolysis to provide diol **5** in 74% overall yield. Saponification of the ester proceeded in 90% yield, and the resulting diol acid **6** was subjected to the conditions of the Yamaguchi macrolactonization protocol.[10] This highly efficient reaction provided the 14-membered macrolide **7** in 84% yield. The transformation of **2** into **7** required just five simple steps and proceeded in 52% overall yield.

We next targeted the incorporation of a tetrahydropyran ring into a macrolide structure, as this moiety is ubiquitous in biologically active natural products.[11] Our first attempts focused on the simple exposure of ester **4** to basic conditions, and while successful Michael-type cyclization of the C(7)-OH group to give a THP ring was observed, the reaction was not clean and the yields were deemed unacceptably low. We therefore turned our attention to the use of Pd-catalyzed π-allyl chemistry for the stereoselective construction of cyclic ethers.[12] Cross-metathesis of **2** with allyl acetate proceeded smoothly to deliver **8** in 70% yield as a 5:1 *E*/*Z* mixture of alkene isomers (Scheme 3). Exposure of this mixture to the

Scheme 3



action of 18 mol % $Pd(PPh_3)_4$ and Et_3N in toluene led to the

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(6) For discussions and reviews of diversity-oriented synthesis, see: (a) Schreiber, S. L. *Science*, **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271. (d) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163. (e) Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248. (f) Tan, D. S. *Nature Chem. Biol.* **2005**, *1*, 74.

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(11) The phorboxazoles are representative. See: (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.

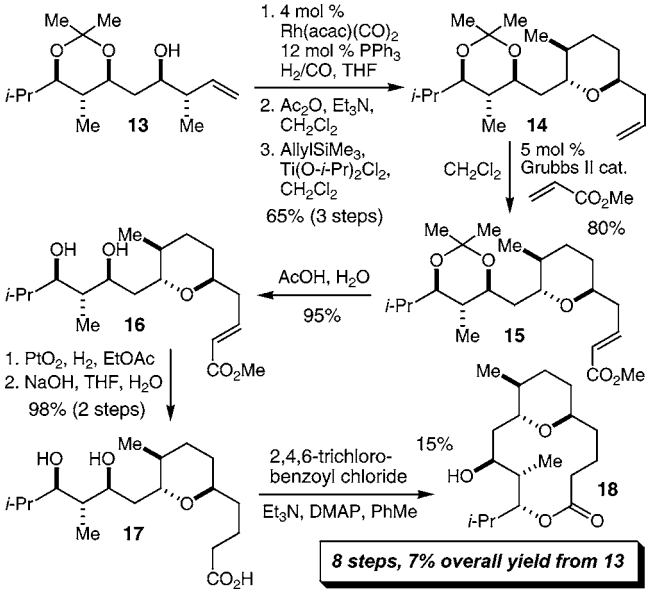
(12) (a) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. (b) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. **1983**, *105*, 1964. (c) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927. (d) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915.

diastereoselective (>20:1) formation of tetrahydropyran **9** in 90% yield. While attempting to protect the alcohols in **9**, it was discovered that the axial alcohol on the THP ring could be alkylated (benzylated) selectively, and following methylation of the remaining alcohol, **10** was obtained in 73% overall yield from **9**. A simple series of functional group transformations (hydroboration, two-stage alcohol oxidation, and acetonide hydrolysis) then provided putative macrolactonization candidate **11** in 45% overall yield. Subjection of **11** to the Yamaguchi conditions as before led to the isolation of macrolide **12** in 50% yield. This somewhat less efficient macrolactonization may be attributed to the formation of the dimeric macrodiolide as identified by mass spectrometry. Although this sequence was less efficient relative to the synthesis of **7** (in large part due to the three step oxidation sequence), it will be noted that **12** is a more complex structure not only because of the THP ring but also because of the differential protection/derivatization of the alcohols.

Alcohol **13** is an intermediate in the synthesis of **2** and **3** and is available in quantity from **1** in just three steps. Hydroformylation of **13**, acetylation of the resulting hemiacetal, and Lewis acid promoted allylation[13] provided tetrahydropyran **14** as a single diastereomer in 65% overall yield from **13**. Cross-metathesis, as above, allowed the straightforward incorporation of the functionality required for a macrolide and gave **15** in 80% yield. Acetonide hydrolysis provided diol **16** in 95% yield and was followed by alkene hydrogenation and ester saponification to give acid **17** in 98% yield (two steps). In this case, the macrolactonization under the Yamaguchi conditions was not straightforward and was accompanied by significant decomposition. Nevertheless, the reaction did provide macrolide **18**, albeit in only 15% yield. Despite this inefficient reaction, **18** was obtained in just eight steps and 7% overall yield from **13** (Scheme 4).

For all three macrolide syntheses described above, we had a general idea about what the ultimate target would look like and a synthetic plan to get there. That is not to say, however, that no pitfalls were encountered. While the synthesis of **7** was indeed pitfall-free and was accomplished as planned in a matter of days, the syntheses of **12** and **18** were not quite as smooth and did require a little more experimentation. In the case of **12**, we first investigated the macrolactonization of a triol (OH in place of OMe), and while a macrolide was obtained, the reaction was found to be both inefficient and irreproducible. In the case of **18**, initial attempts omitted the alkene hydrogenation step, and the corresponding unsaturated acid did not macrolactonize. These

Scheme 4



setbacks were minor and not particularly time-consuming, however, and we believe it is noteworthy that, albeit with differing levels of efficiency, each projected macrolactonization was accomplished. It is also noteworthy that no 12-membered macrolides were produced in any of the three macrolactonization reactions.

Given that each of these three macrolides could readily serve as the basis for a library of tens or hundreds of compounds, we conclude that, at least on the synthetic side, the effort required to synthesize more complex macrolide cores of this type is not prohibitive. Of course, the larger and more important question of whether this emphasis on smaller numbers of more complex natural product-like macrolide cores provides any advantages (relative to simpler macrolide libraries) on either the "hit-rate" or "hit-quality" can only begin to be answered by the preparation, and biological assaying, of several such libraries.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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