# Studies toward a Synthesis of Epothilone A: Stereocontrolled Assembly of the Acyl Region and Models for Macrocyclization

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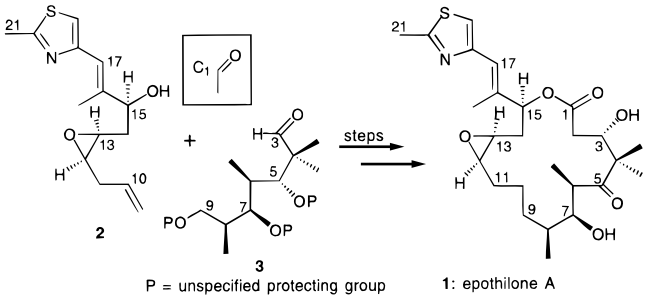
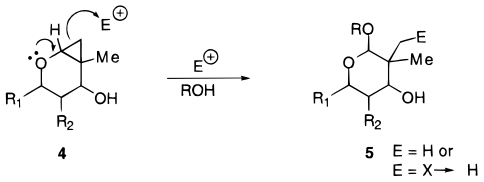
In our previous paper, we described a synthesis of the "alkoxy" segment of epothilone A **1** (see compound **2**, Scheme 1) encompassing carbons 10−21.[1] In this paper, we address the synthesis of another fragment encoding the stereochemical information of acyl section carbons 3−9. It was envisioned that the aldehydo center ($C_3$) of the formal target **3** would serve as an attachment site to a nucleophilic construct derived from compound **2** (requiring placement of a two-carbon insert, as suggested in Scheme 1), through either inter- or intramolecular means. In such a context, it would be necessary to deal independently with the stereochemistry of the secondary alcohol center eventually required at $C_3$. One of the interesting features of system **3** is the presence of geminal methyl groups at carbon 4 (epothilone numbering). It was our hope to again use a dihydropyran strategy to assemble a cyclic matrix corresponding, after appropriate disassembly, to a viable equivalent of system **3**. *We hoped to expand upon our dihydropyran paradigm to include the synthesis of gem dimethyl containing cyclic and acyclic fragments.* The particular reaction type we had in mind for this purpose is generalized under the heading of transformation of **4** → **5** (see Scheme 2). At this juncture, we deliberately avoid commitment as to the nature of the electrophile, E. Accordingly, we leave for the moment unaddressed the question as to whether a reduction would or would not be necessary in going from structure type **5** to reach the intended generalized target **3**.

Once again, our opening step consisted of a stereochemically tunable version of the diene−aldehyde cyclocondensation reaction[2] (Scheme 3)—in this instance drawing upon chelation control in the merger of the readily available enantiomerically homogeneous aldehyde **6** with the known diene **7**.[3] Indeed, as precedent would have it, under the influence of titanium tetrachloride there was produced substantially a single isomer shown as compound **8**.[4] In the usual and stereochemically reliable way,[5] the dihydropyrone was reduced to the corresponding glycal **9**. At this point, we utilized a directed Simmons−Smith reaction for the conversion of glycal **9** to cyclopropane **10**.[6] This compound is indeed an interesting structure in that it corresponds in one sense to a cyclopropano version of a *C*-glycoside. At the same time, the cyclopropane is part of a cyclopropylcarbinyl alcohol system with attendant possibilities for rearrangement.[7] It was our intention to cleave the *C*-glycosidic bond of the cyclopropane in a fashion that would elaborate the geminal methyl groups, leaving in its wake a solvent-derived glycoside with the desired aldehyde oxidation state at C-3 (see hypothesized transformation **4** → **5**, Scheme 2). In early efforts, the nonoxidative version of the projected reaction (*i.e.*, $E^+ = H^+$) could not be reduced to practice. Instead, products clearly attributable to the ring-expanded system **11**[8] were identified.

**Scheme 1. Convergent Strategy for a Total Synthesis of Epothilone A (1)**




**Scheme 2. Glycal Cyclopropane Solvolysis Strategy for the Introduction of Geminal Methyl Groups**




Fortunately, however, the desired sense of cyclopropane opening, under the influence of the ring oxygen, was achieved by subjecting compound **10** to oxidative opening with *N*-iodosuccinimide.[9] The intermediate iodomethyl compound, obtained as a methyl glycoside **12**, when exposed to the action of tri-*n*-butyltin hydride, gave rise to pyran **13** containing the geminal methyl groups. Protection of this alcohol (see **13** → **14**), followed by cleavage of the glycosidic bond, revealed the acyclic dithiane derivative **15** which can serve as a functional version of the hypothetical aldehyde **3**.

We have also begun to explore possible ways of combining fragments relating to **2** and **3** in a fashion to reach epothilone and congeners thereof. Mindful of the pio-

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(1) Meng, D.; Sorensen, E. J.; Bertinato, P.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 7998−7999.

(2) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.

(3) Danishefsky, S. J.; Yan, C.-F.; Singh, R. K. Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(4) (a) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (b) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862.

(5) Danishefsky, S. J. *Chemtracts Org. Chem.* **1989**, *2*, 273.

(6) (a) Winstein, S.; Sonnenberg. J. *J. Am. Chem. Soc*, **1961**, *83*, 3235. (b) Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468. (c) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. For selected examples, see: (d) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337. (e) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831.

(7) Wenkert, E.; Mueller, R. A.; Reardon, E. J., Jr.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428.

(8) For example, exposure of **10** to acidic methanol gave rise to an epimeric mixture of seven- membered mixed acetals, presumably through the addition of methanol to oxocarbenium ion **11**. This most interesting transformation is under active study in our laboratory.

(9) For interesting Hg(II)-induced solvolyses of cyclopropanes that are conceptually similar to the conversion of **10** to **12**, see: (a) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094. (b) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882. Following this precedent, we did, in fact, accomplish a Hg(II)-induced solvolysis of cyclopropane **10**, although this transformation proved to be less efficient than the reaction shown in Scheme 3.

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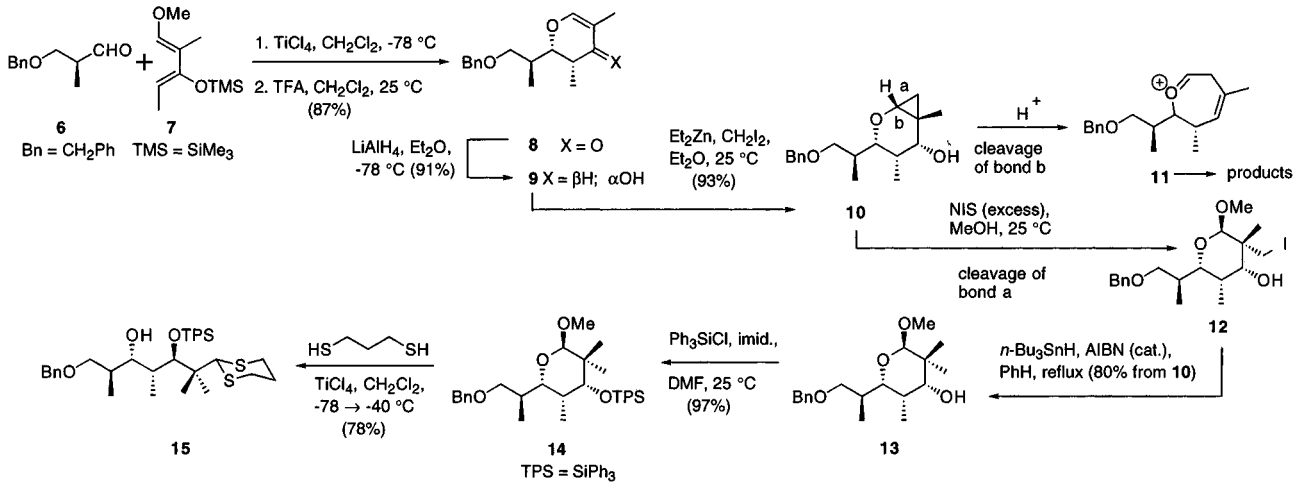
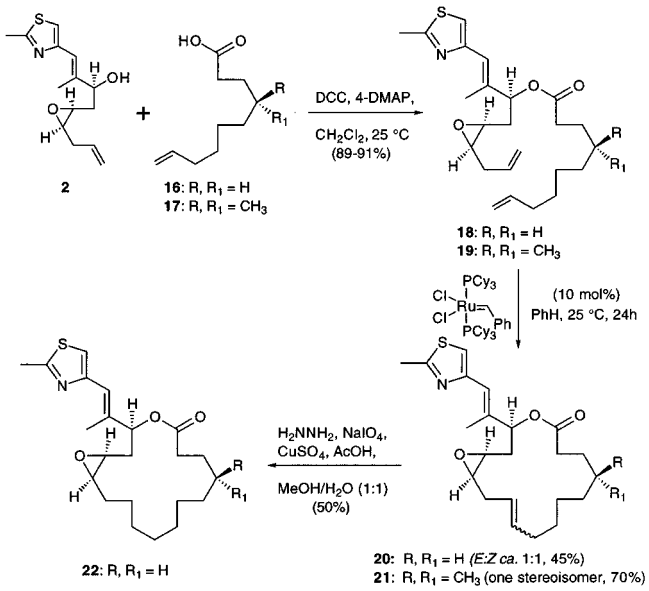
**Scheme 3. Enantioselective Synthesis of Compound 15**




**Scheme 4. Construction of Epothilone Model Systems 20−22 by Ring-Closing Olefin Metathesis**




neering studies of Schrock[10a] and Grubbs[10b] and the recent ground-breaking disclosure of Hoveyda,[11] we wondered about the possibility of realizing such an approach *en route* to our goal.[12] The matter was first examined with two model *ω*-unsaturated acids **16** and **17** that were used to acylate alcohol **2** to provide esters **18** and **19**, respectively (see Scheme 4). These compounds did indeed undergo olefin metathesis macrocyclization in the desired manner under the conditions shown. In the case of substrate **18**, **20** was obtained as a mixture of *E*- and *Z*- stereoisomers (*ca.* 1:1). Diimide reduction of **20** was then conducted to provide homogeneous **22** in 50% yield. The olefin metathesis reaction was also extended to compound **19** bearing geminal methyl groups corresponding to their placement at C4 of epothilone A. Once again, olefin metathesis occurred, this time curiously producing olefin **21** as a single entity in 70% yield (stereochemisty tentatively assigned as *Z*). Substantially identical results were obtained through the use of Schrock's molybdenum alkylidene metathesis catalyst.

Having shown that olefin metathesis is equal, in principle, to the challenge of constructing the 16-membered ring containing both the required epoxy and thiazolyl functions of our target system, we have started to project a synthesis of epothilone A itself. Clearly, with these fragments in hand, a variety of strategies for their combination, culminating in either carbon−carbon bond formation or macrolactonization, can be entertained, and these are being evaluated. At the present writing, however, it is appropriate to point out that no successful olefin metathesis reaction has yet been realized from *seco*-systems bearing a full compliment of functionality required to reach epothilone. These negative outcomes may merely reflect a failure to identify, as yet, a suitable functional group constraint pattern appropriate for macrocylization.[13] Many possibilities remain to be screened. Accordingly, intramolecular olefin metathesis is still included in a variety of ring-forming options currently being evaluated for reaching epothilone A.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for the compounds illustrated in the schemes (compounds **8**−**10**, **12**−**16**, and **18**−**22**) (6 pages).

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(10) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. For reviews of ring-closing metathesis, see: (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (d) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833.

(11) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.

(12) For recent examples of ring-closing metathesis, see: (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (b) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942.

(13) Substrates containing the full complement of oxygenated functionality, including the trisubstituted olefin and thiazolyl moiety, were screened for ring-closing olefin metathesis. In an effort to favor ring closure through the rigidification of the carbon backbone, a *seco* structure possessing a cyclic isopropylidene ketal bridging a C3−C5 diol relationship was prepared and subjected to ring-closing metathesis. In one instance, we also screened a substrate containing functionality that would lead to the C12−C13 epoxide, but lacking this function, *per se*. In spite of these setbacks, efforts to fashion the macrolide of epothilone A through ring-closing metathesis are continuing A full account of these studies will be disclosed in due course.