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# Towards the Synthesis of Epothilone A: Enantioselective Preparation of the Thiazole Sidechain and Macrocyclic Ring Closure

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***Abstract***: *A synthetic approach to a new class of microtubule-stabilizing natural products is described which employs a macrocyclic olefination strategy to cyclize the 16-membered lactone ring. The C13-C19 thiazole subunit of epothilone A and B is prepared in high enantioselectivity using a catalytic asymmetric allylation reaction.* © 1997 Elsevier Science Ltd.

Our continued interested in the anticancer agent, Taxol® is driven by the pursuit to understand the structural features and spatial arrangement necessary for tubulin binding[2] and the stabilization of microtubule dynamics.[3] The recently reported class of natural products, epothilone, now provides us with compounds structurally distinct from taxol and taxol analogues but with similar biological activity. In addition, epothilones have much greater activity against multi-drug resistant cell lines.[4]

Early in our effort, we determined the relative stereochemistry of each of the stereogenic centers of epothilone A except for C12 and C13, the *cis*-epoxide using high-field NMR and molecular modeling techniques.[5] Thus, our initial retrosynthetic plan, began with the simplification of the target molecule by replacement of the C12-C13 *cis*-epoxide with a Z-olefin. Figure 1 outlines the connectivity analysis which directs our synthetic efforts. Simplification of the 16-membered lactone was considered through three strategic disconnections. First, the C5-C7 β-hydroxy ketone could be formed, in a synthetic direction from an aldol condensation between the enolate of the C5 ketone and a C7 chiral aldehyde. An additional disconnection through the C12-C13 olefin reveals the necessary chiral aldehyde **A** for the C7-C12 fragment. Retrosynthetic disconnection of the ester (lactone) linkage then exposes a C1-C6 fragment such as chiral ketone **B** for the C1-C6 unit. These two disconnections then leave behind our choice for the epothilone thiazole sidechain **C**. It should be noted that these disconnections not only lead to well precedented synthetic transformations in the forward direction but also three individual target molecules of comparable size and complexity. Each containing a single stereoisomeric center, an attribute necessitated by the lack of absolute stereochemical information when we began our effort. When we initiated our synthetic work, a macrocyclic olefin metathesis closure was chosen for the preparation of epothilone A.[6-8] The Nicolaou group has recently reported[7b] a similar synthetic strategy prompting us to disclose some of our preliminary results. More importantly, this synthetic route will provide access to analogues with significant potential for reaching our long range goals; understanding the conformational properties of epothilone both in solution and while bound to the receptor. Herein we report the enantioselective synthesis of thiazole subunit **C** and a successful closure of a 16-membered ring in a model system.

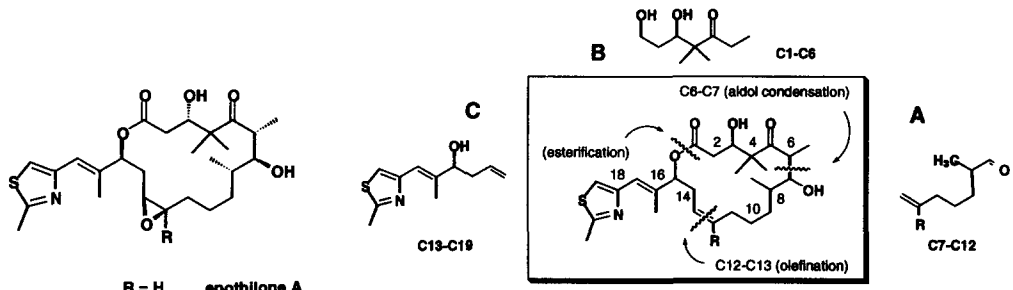
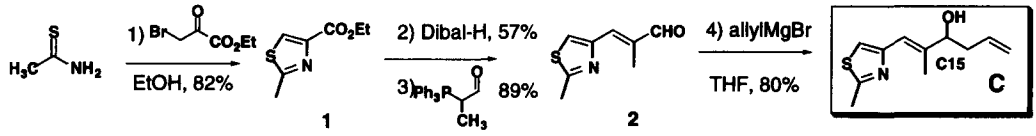



**Figure 1.** Connectivity Analysis of Deoxy-epothilone A

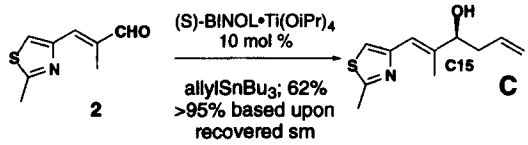
Our initial sub-goal of the synthetic effort was target thiazole **C**, Scheme I. This was readily accomplished in an efficient four step sequence. First, condensation of thioacetamide and bromoethylpyruvate provided thiazole ester **1** in 82% yield. After conversion of the ethyl ester to an aldehyde by reduction with DIBAL-H, homologation to the trisubstituted olefin **2** with triphenylphosphorane propionaldehyde proceeded with excellent control of olefin geometry (>95%) in 89% yield. The two step reduction-oxidation (LAH; Swern) for the conversion of the ester to the aldehyde proceeds in >85% yield is used routinely for material throughput. The synthesis of racemic thiazole **C** was completed by condensation of aldehyde **2** with allylmagnesium chloride in good yield.

**Scheme I**




An enantioselective allylation of aldehyde **2** with the protocol developed by Keck and Geraci[10] should provide access to either enantiomer of thiazole **C** with high enantiomeric excess, Scheme II. In fact use of the (S)-BINOL•Ti and allyl tributyltin provided the C15 stereogenic center with the desired (S) configuration necessary for the synthesis of epothilone A and B.[11] The unoptimized enantioselectivity of this reaction was >86% as determined by $^1$H NMR spectroscopy and the Mosher's ester method.[12] Attemps to use other chiral Lewis acid catalysts were unsuccessful presumably due to the presence of the Lewis basic thiazole nitrogen. We are continuing to explore modifications of this reaction in order to increase the observed enantioselectivity.

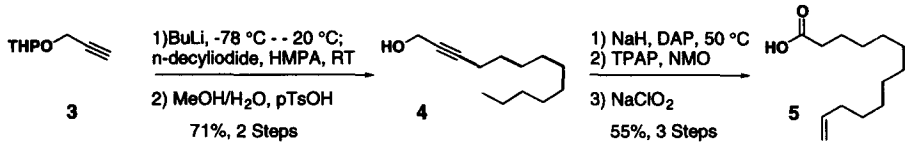
**Scheme II**




Since we have chosen an ambitious synthetic plan which includes a late-stage, macrocyclic ring-closing metathesis reaction, we initially concentrated on the development of this methodology with model systems. However, it was expected that even if successful the olefin metathesis cyclization would provide a mixture of *E* and *Z* isomers. To allow a detailed study of the effect of ring size on geometric isomer distribution we have developed a general sequence for the preparation of α, ω-alkenoic acids. THP-protected

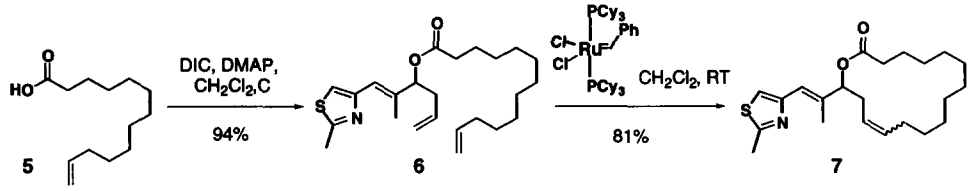
propargyl alcohol was metalated with n-butyllithium at low temperature and alkylated with n-decyl iodide in the presence of HMPA. After deprotection the alcohol was purified by flash chromatography and isolated in 71% yield. The low-melting solid was then exposed to NaH in 1,3-diaminopropane[13] to provide the terminal acetylene in 87% yield. After hydrogenation of the alkyne, the primary hydroxyl was oxidized to the aldehyde with TPAP and then further to the carboxylic acid with sodium chlorite.

**Scheme III**




Acylation of alcohol **C** with carboxylic acid **5** using diisopropyl carbodiimide proceeded in 94% yield to provide the cyclization substrate **6**. Gratifyingly, exposure of *bis*-olefin **6** to a catalytic amount of benzylidene *bis*-tricyclohexyl phosphine Ruthenium dichloride[14] under dilute conditions provided the 16-membered lactone **7**. As expected the reaction selectivity was poor, providing a 3:1 ratio of *E* and *Z* isomers and suggesting the need for general methodology for controlling olefin geometry in olefin metathesis reactions. However, this key cyclization demonstrates the compatibility of the thiazole moiety with the metallocarbene intermediate.

**Scheme IV**




In conclusion, we have developed a practical and efficient enantioselective preparation of a key component towards a convergent synthesis of epothilone A and B.[15] In addition, we have demonstrated the viability of a macrocyclic olefin metathesis reaction for the synthesis of epothilone A and its analogues. Our continued efforts toward the synthesis of epothilone A and B as well as the control of olefin geometry in metathesis macrocyclizations will be reported in due course.

## ACKNOWLEDGEMENT

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