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A Highly Stereoselective, Efficient, and Scalable Synthesis of the C(1)−C(9) Fragment of the Epothilones

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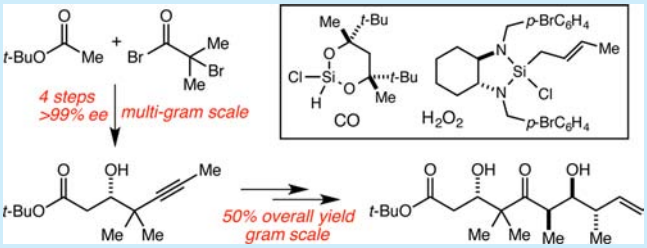
Supporting Information

ABSTRACT: A second-generation synthesis of the C(1)−C(9) fragment of the epothilones is reported. The key tandem intramolecular silylformylation/crotylsilylation/"aprotic" Tamao oxidation sequence has been redeveloped as a stepwise intermolecular variant, allowing excellent levels of diastereoselectivity in the crotylation step and proceeds in 50% overall yield on gram scale. An improved synthesis of the homopropargyl alcohol starting material is also described, which proceeds in four steps and >99% ee from inexpensive starting materials and is amenable to multigram scales.



The epothilone family of natural products (Figure 1) ranks as among the most important and promising of the large collection of microtubule-stabilizing agents (MSAs) known to express their antimitotic activity by binding to the taxane binding site on the interior of microtubules.[1] Epothilone B (epo B) in particular possesses subnanomolar potencies against a variety of cell lines, and in 2007 the FDA approved ixabepilone (the lactam analogue of epo B) for use in the treatment of particularly aggressive and otherwise unresponsive forms of metastatic breast cancer.[2] Extensive SAR studies have been carried out in numerous laboratories,[3] and this has led to several analogues being advanced into clinical trials, most notably sagopilone,[4] whose development has been halted for unspecified reasons despite demonstrating efficacy in several Phase II trials, and iso-fludelone,[5] Danishefsky's designed analogue that has exhibited a remarkably favorable pharmacokinetic profile in an extensive preclinical evaluation and that is currently being evaluated in a Phase I trial. As a prelude to launching our own program in the design, synthesis, and evaluation of epothilone analogues possessing novel functionality, we targeted the development of an efficient, step-economical, and scalable synthesis[6,7] of the C(1)−C(9) fragment that is conserved in every important epothilone derivative to save sagopilone.

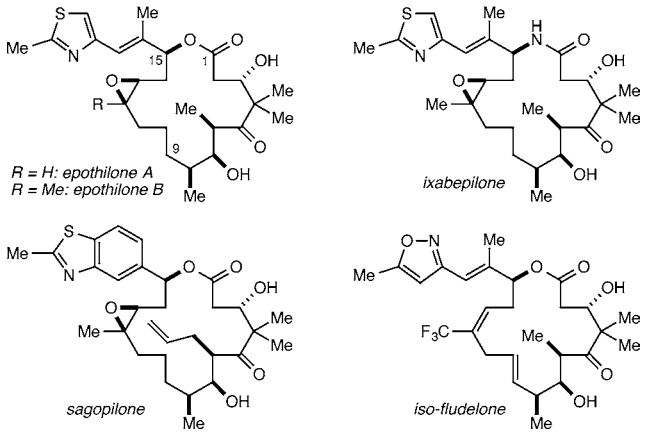


Figure 1. Epothilones A and B and FDA-approved ixabepilone, sagopilone, and iso-fludelone.

In our broader program dedicated to the synthesis and evaluation of novel analogues of bioactive polyketide natural products, we have emphasized the development of step-economical *and* practical and scalable syntheses as it is only this combination that can facilitate the analogue work in a truly time- and resource-efficient manner. To that end, we recently reported a synthesis of the C(1)−C(9) fragment of the epothilones using an application of the one-pot tandem alkyne silylformylation/crotylsilylation and Tamao oxidation/diastereoselective tautomerization reaction sequence[8] to set the C(6), C(7), and C(8) stereocenters in a highly step-economical and gram-scalable way (**2** to **3**, Figure 2).[9] The key methodological innovation developed for that purpose was a set of "aprotic" Tamao oxidation conditions that resulted in a highly (14:1) *syn*-diastereoselective tautomerization step to set the C(6) stereocenter. As excited as we were by the remarkable transformation of **2** to **3**, we felt that other aspects of the route (e.g., the synthesis of **1** and the moderate 1,5-diastereoselectivity of the intramolecular crotylation event) might put limits on the ease with which we could move multigram quantities through the sequence in a time- and resource-efficient manner. We therefore targeted the development of a second-generation synthesis of **1** with significantly improved step-economy, scalability, and enantioselectivity, as well as a modified version of the silylformylation/crotylation/oxidation sequence that would proceed with

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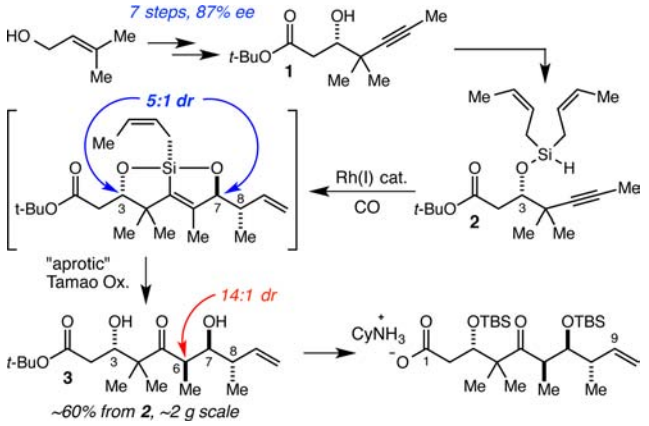


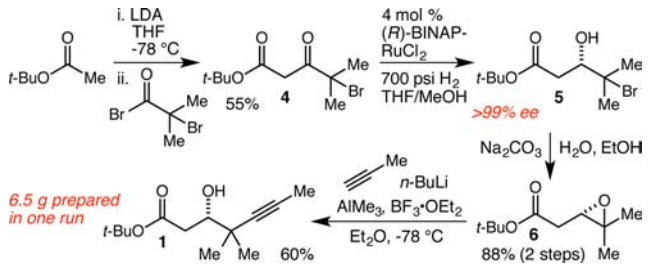
Figure 2. Our first-generation synthesis of the C(1)−C(9) fragment of the epothilones relied on the development of a highly diastereoselective "aprotic" Tamao oxidation/tautomerization reaction.

improved diastereoselectivity in the crotylation event and improved overall efficiency.

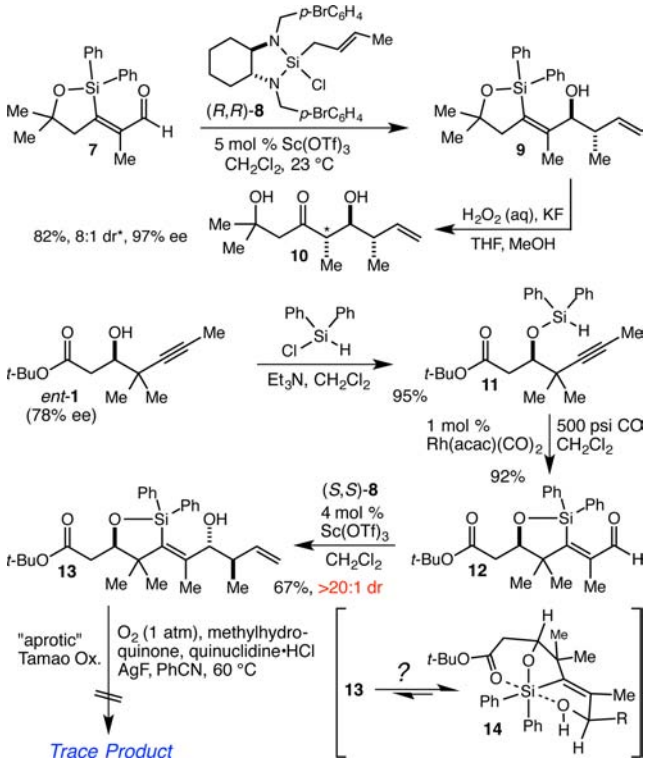
Our first task was the development of a synthesis of **1** that proceeds in fewer, yet more easily scaled steps, and that delivers the target with significantly improved enantiomeric purity. The second-generation synthesis of homopropargyl alcohol **1** that we devised to achieve these goals begins with a Claisen condensation between *t*-butyl acetate and α-bromoisobutyryl bromide (both commercially available and inexpensive) to give β-ketoester **4** in 55% yield on multigram scales. Noyori hydrogenation[10] of **4** proceeds with exceptional efficiency and enantioselectivity to give **5**, which is, without chromatographic purification, treated with Na_2CO_3 to effect the formation of epoxide **6**. This latter reaction required some optimization, as the epoxide, once formed, is susceptible to enolization and elimination. Once optimized, this two-step procedure reliably produced **6** in excellent overall yield (88%) and in >99% ee on multigram scales. Finally, the epoxide opening reaction with propyne according to the Pagenkopf method[11] that we used previously delivers the target homopropargyl alcohol **1** in 60% yield. This four-step procedure is amenable to multigram scales (6.5 g of **1** was produced in one run through the sequence), produces **1** essentially enantiomerically pure, and employs only inexpensive starting materials and reagents.

Our proposed solution to the moderate 1,5-diastereoselectivity of the crotylation step in the reaction sequence described in Figure 2 was to simply perform it as an intermolecular externally controlled reaction following silylformylation with a diphenylsilyl group in place of the di-*cis*-crotylsilyl group.[12] Indeed, we had every reason to expect that this would be a straightforward solution based on our previous demonstration of the efficient and highly enantioselective $Sc(OTf)_3$-catalyzed crotylation of **7** with *trans*-crotylsilane **8** to give **9**, while the subsequent transformation of **9** to **10** using the "standard" *anti*-diastereoselective Tamao oxidation/tautomerization conditions established that a structure of this type was a viable oxidation substrate (Scheme 2).[13] Thus, silylation of *ent*-**1** (the exploratory reactions we conducted to test this idea were carried out prior to the development of the chemistry described in Scheme 1 using a sample of *ent*-**1** that was prepared in 78% ee) with diphenylchlorosilane provided **11** in 95% yield, and Rh(I)-catalyzed silylformylation[14] then produced aldehyde **12** in 92% yield. As expected, $Sc(OTf)_3$-catalyzed crotylation[13] of **12** with silane **8**[15] proceeded highly diastereoselectively to give **13** in 67%

Scheme 1. Efficient, Scalable, and Highly Enantioselective Synthesis of Homopropargylic Alcohol 1



Scheme 2. Exploration of the Stepwise Silylformylation/Crotylation/Oxidation Sequence



yield (after chromatographic separation of the minor diastereomer that resulted from crotylation of the small amount of *ent*-**12**). Unfortunately, our satisfaction was short-lived as subjection of **13** to the aprotic Tamao oxidation conditions unexpectedly produced only trace amounts of any oxidation products. Even more surprisingly given the success of the transformation of **9** to **10**, the standard Tamao oxidation conditions also failed to produce any meaningful amounts of oxidation products. This result seemed to implicate the *t*-butyl ester as playing a key role in the inertness of **13** to either set of oxidation conditions, as the presence or absence of the ester appears to be the only significant difference between substrates **9** and **13**. Based on this analysis, we speculate that at least under the conditions of the oxidation reactions, **13** may exist as hexa-coordinate silane **14** thereby preventing fluoride displacement of the alkoxide, the presumed prerequisite for the oxidation step to occur, and note that Hoveyda advanced a related hypothesis to explain the recalcitrance of a β-hydroxy siloxane to undergo protodesilylation with *n*-Bu_4NF.[16]

Regardless of the mechanistic basis for the surprising inertness of **13** to Tamao-type oxidation, we decided to examine whether

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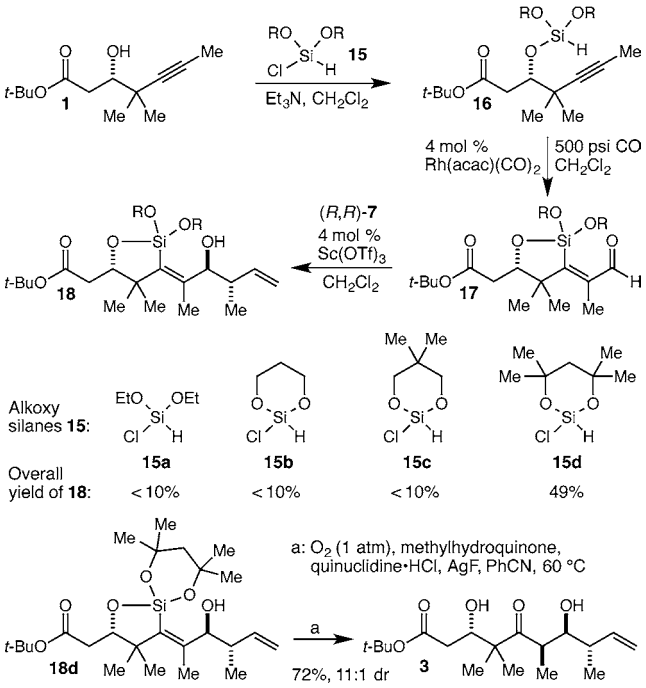
we could achieve greater electronic activation of the silane by replacement of the phenyl groups with alkoxy groups. While we were hopeful that this would allow for a productive oxidation notwithstanding our speculation regarding hexa-coordinate silane **14**, we were also concerned about the hydrolytic stability of alkoxysilanes, which would have to survive the silylformylation/crotylation sequence and more specifically the workup and isolation procedures following the crotylation step. A series of dialkoxychlorosilanes with varying degrees of steric hindrance (**15a–d**) were prepared and used to silylate alcohol **1** (Scheme 3). As feared, the hydrolytic instability of silanes **15a–c** made

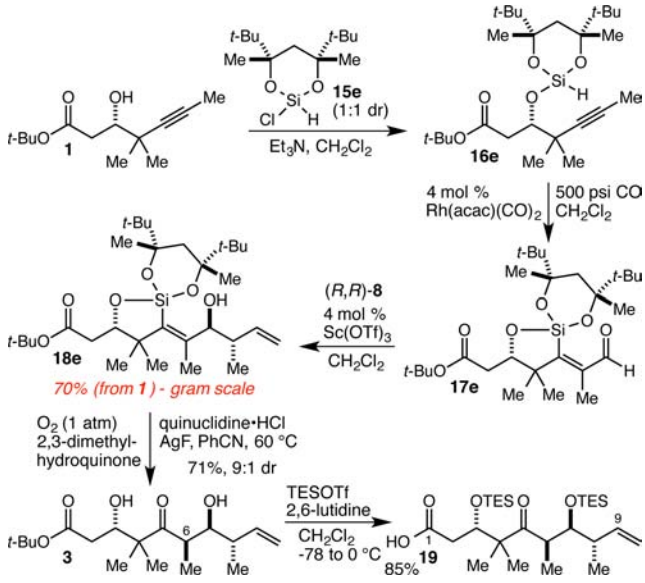
Scheme 3. Silylformylation/Crotylation/Oxidation Sequence with Alkoxysilanes 15



handling of the intermediates **16a–c** and **17a–c** difficult, and more importantly rendered the isolation of crotylation products **18a–c** impracticable in anything greater than trace amounts. This led us to use the significantly more hindered dialkoxysilane **15d**, which had the desired effect of imparting hydrolytic stability to the intermediates in the sequence and allowed for the isolation of **18d** in 49% overall yield from **1**. Gratifyingly, **18d** proved to be a viable substrate for the aprotic Tamao oxidation using the previously developed conditions, giving **3** in 72% yield and with 11:1 diastereoselectivity at C(6). It is not entirely clear that this result is consistent with our hypothesis regarding the inertness of diphenylsilane **13**, but we note that it is possible that the steric hindrance of dialkoxysilane **18d** might destabilize the hexa-coordinate silane corresponding to **14**. Regardless, the successful transformation of **16d** to **3** constituted an encouraging proof-of-concept result.

Final optimization of the conversion of **1** to **3** focused on even more sterically hindered dialkoxysilanes, and to that end silane **15e** was prepared as an inconsequential 1:1 mixture of diastereomers (Scheme 4). The silylformylation/crotylation sequence was then repeated using silane **15e**, and we were delighted to find that it proved efficient, robust, and scalable as **18e** was isolated in 70% overall yield from **1** on a gramscale (**16e**, **17e**, and **18e** were all produced as an inconsequential ~1.6:1

Scheme 4. Efficient and Scalable Synthesis of the C(1)–C(9) Fragment of the Epothilones



mixture of diastereomers at silicon). Unfortunately, our satisfaction was once again short-lived as the steric hindrance that rendered this sequence so efficient and practicable now rendered the aprotic Tamao oxidation sluggish and inefficient. We wondered whether this problem could be addressed with a higher concentration of the active oxidant and noted that in his original report Tamao had shown that 2,3-dimethylhydroquinone reacted with O_2 to generate H_2O_2 at a faster rate than did methylhydroquinone.[17] Indeed, we were gratified to find that this modification to the aprotic Tamao oxidation conditions restored the lost reactivity[18] and led to the conversion of **18e** to **3** in 71% yield as a 9:1 mixture of diastereomers at C(6). Treatment of **3** with triethylsilyl triflate (TESOTf) completed the synthesis of the fully elaborated C(1)–C(9) fragment and gave acid **19** in 85% yield.

We have devised a second-generation synthesis of the C(1)–C(9) fragment of the epothilone family of natural products with significantly improved step-economy, stereoselectivity, robustness, and scalability. Along the way, we encountered an unexpected failure of the previously developed and *syn*-selective aprotic Tamao oxidation/tautomerization conditions, and devised a more highly activated hydrosilane that was both compatible with the silylformylation/crotylation sequence and that also allowed for a successful and diastereoselective application of the aprotic Tamao oxidation/tautomerization reaction. The synthesis begins with *t*-butyl acetate and *α*-bromoisobutyryl bromide and proceeds in 12% overall yield to completed fragment **19** by way of a nine-step/eight-pot sequence that is experimentally simple and robust, proceeds with high levels of diastereo- and enantioselectivity, and is amenable to being carried out on gram/multigram scales. Importantly, the practicality and scalability of the route allow the rapid stockpiling of intermediates, and it is our expectation that this will greatly facilitate the synthesis and exploration of novel and functional epothilone analogues.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and spectroscopic and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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