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An "Aprotic" Tamao Oxidation/ *Syn*-Selective Tautomerization Reaction for the Efficient Synthesis of the C(1)–C(9) Fragment of Fludelone

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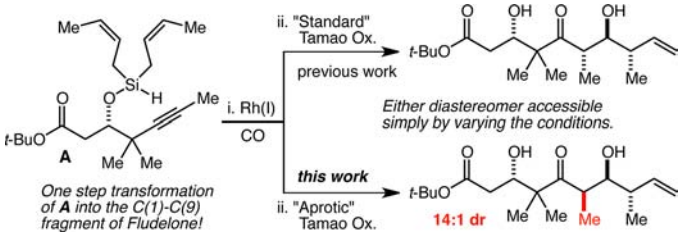
ABSTRACT



An efficient synthesis of the C(1)–C(9) fragment of fludelone has been developed. The key step is a tandem silylformylation–crotylsilylation/ Tamao oxidation sequence that establishes the C(5) ketone, the C(6), C(7), and C(8) stereocenters, and the C(9) alkene in a single operation from a readily accessed starting material. The stereochemical outcome at C(6) depends critically on the development of an "aprotic" Tamao oxidation, which leads to a reversal in the intrinsic diastereoselectivity observed using "standard" Tamao oxidation conditions.

Polyketide natural products continue to influence small molecule drug development efforts. A prominent recent case in point is the epothilone family of natural products (Figure 1), potent anticancer compounds that operate by a microtubule-stabilizing mechanism of action.[1] Significant effort has been devoted to the development of analogs[2] with improved pharmacokinetic profiles, and one of the more promising compounds to emerge from these efforts is fludelone (C(12)-trifluoromethyl-(*E*)-9,10-dehydrodesoxyepothilone B). Developed by Danishefsky and coworkers,[3] this compound is both more potent than epothilone B and more effective *in vivo*, resulting in the shrinking of tumors in mice to the point of nondetectability. Given the extraordinary activity and the structural and stereochemical complexity of fludelone, and given that it is increasingly likely that other polyketide natural product analogs will be developed as drug candidates, it is imperative that ever more efficient synthetic chemistry is advanced to keep pace. The Danishefsky team assembled fludelone in three operations from fragments **1**, **2**, and **3** (Figure 1).[3a] From a stereochemical standpoint, the C(1)–C(9) fragment **1** is the most complex, and its synthesis is the subject of this report.

We have been engaged for some time in the development of tandem reaction strategies for the synthesis of polyketide fragments[4] and recently described the one-step

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(2) For a recent review and lead references, see: Watkins, E. B.; Chittiboyina, A. G.; Avery, M. A. *Eur. J. Org. Chem.* **2006**, 4071.

(3) (a) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T.-C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913. (b) Rivkin, A.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2838.

(4) (a) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587. (b) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915. (c) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890. (d) Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672. (e) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190. (f) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889. (g) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535. (h) Wang, X.; Meng, Q.; Perl, N. R.; Xu, Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12806. (i) Spletstoser, J. T.; Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2008**, *10*, 5593.

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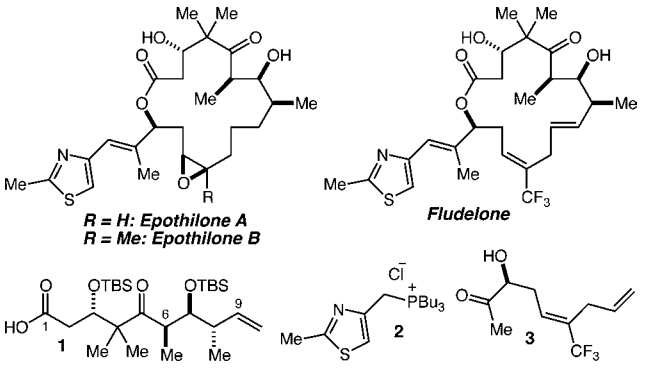
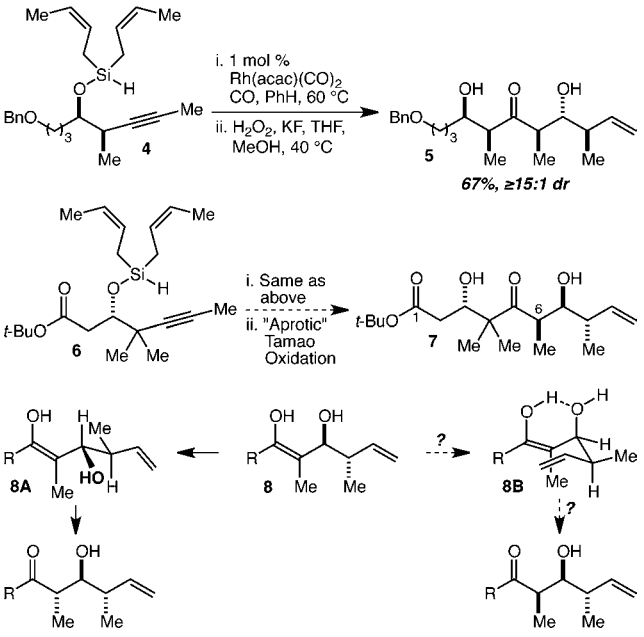


Figure 1. Epothilones A and B, fludelone, and the three principal fragments from which fludelone is assembled.

conversion of **4** to **5** as the centerpiece of an efficient synthesis of zincophorin methyl ester (Scheme 1).[5] This complex series of chemical events transforms a propynyl fragment, a butenyl fragment, a silyl hydride, CO, and H_2O_2 into a six-carbon chain comprised of a ketone, three stereocenters, and an alkene, and it accomplishes this with no external stereochemical control, no protecting group manipulations, and no nonstrategic redox steps.[6] While the possibility that we might apply such a reaction to a synthesis of **1**—wherein the entire C(5)−C(9) segment would be directly installed with everything in the right oxidation state and orientation and without recourse to any protecting groups (cf. **6** to **7**)—was exciting, it was also clear that the reaction would provide the wrong diastereomer at C(6). That stereocenter is established upon tautomerization of the immediate product of the Tamao oxidation,[7] enol **8**, and the observed *anti* selectivity (relative to the vicinal hydroxyl group) is proposed to arise from the illustrated enol conformation **8A** in which allylic 1,3 strain and related considerations dictate that the terminal crotyl unit effectively blocks the back face of the enol and that the highlighted hydroxyl group is well positioned to deliver the proton to the front face of the enol.[4i] Importantly, this model assumes that in the polar, protic environment of the Tamao oxidation conditions (aqueous H_2O_2 and MeOH as solvent), internal hydrogen bonding within **8** does not play a significant role. We hypothesized that if we could develop an "aprotic" Tamao oxidation procedure, the conformation of enol **8** would be dictated by internal hydrogen bonding as in **8B**. If so, tautomerization would then be expected to produce the desired stereochemistry at C(6), by virtue of the back face of the enol being significantly more exposed in this conformation. We describe here the development of an "aprotic" Tamao oxidation and its

Scheme 1. Proposal for a Method to Reverse the Intrinsic Selectivity in the Tandem Tamao Oxidation/Diastereoselective Tautomerization Reaction



application to an efficient synthesis of the fludelone C(1)−C(9) fragment **1**.

Our synthesis of silane **6** commenced from **9**,[8] which was epoxidized with *m*-CPBA to give **10**[9] in 97% yield (Scheme 2). Regioselective opening of epoxide **10** followed the procedure of Pagenkopf[10] to deliver **11**. Removal of the TBS group was followed by oxidative cleavage of the diol to give aldehyde **12**, which was subjected to the enantioselective ketene cycloaddition procedure of Nelson[11] using catalyst **13** to give β-lactone **14** in 56% overall yield (from **10**) and 87% ee. Alcoholysis with *tert*-butanol catalyzed by KCN provided ester **15** in 77% yield, and finally, silane alcoholysis with di-*cis*-crotylsilane[4c] provided **6** in 88% yield. While more step-economical routes to **6** may be imagined, this route served our purposes well in that it provided for reliable access to **6** in 39% overall yield from **9**.

With access to **6** secured we were poised to develop a *syn*-selective Tamao oxidation/tautomerization reaction. Because unraveling the complex diastereoselectivity of these tandem reactions is not trivial, however, it was important first to examine in detail the performance of **6** in the tandem silylformylation/crotylsilylation reaction. Thus, when **6** was subjected to the silylformylation reaction conditions and the resulting mixture was treated with

(5) Harrison, T. J.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7308.
(6) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
(7) (a) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
(8) Volkert, M.; Uwai, K.; Tebbe, A.; Popkirova, B.; Wagner, M.; Kuhlmann, J.; Waldmann, H. *J. Am. Chem. Soc.* **2003**, *125*, 12749.
(9) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.
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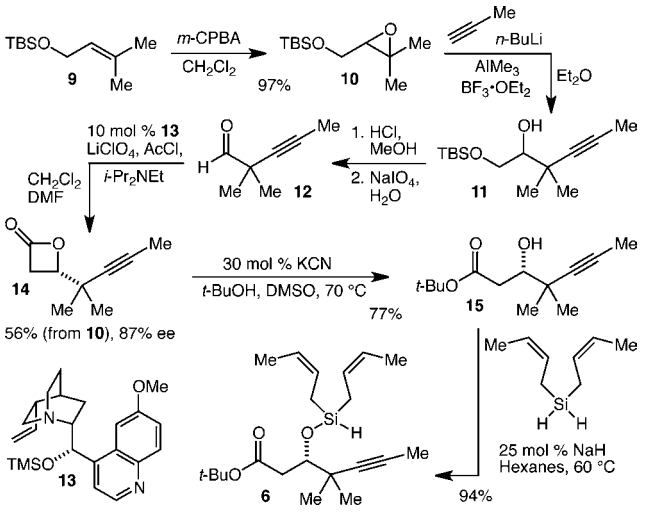
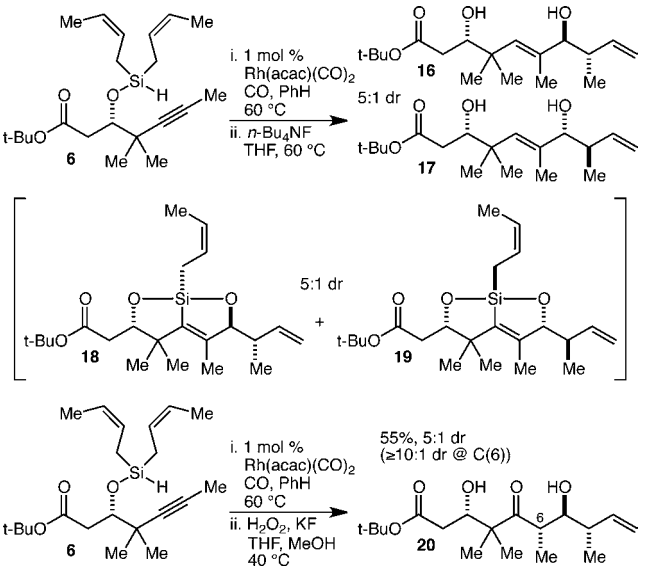
(11) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.

Scheme 2. Synthesis of Di-*cis*-crotylsilyl Ether **6**



Scheme 3. Performance of **6** in the Tandem Silylformylation/Crotylsilylation Reaction and in the Tandem Tamao Oxidation/Diastereoselective Tautomerization Reaction



n-Bu_4NF, a 5:1 mixture of protodesilylated products **16** and **17** was produced, by way of a 5:1 mixture of initial products **18** and **19** (Scheme 3). The 5:1 mixture of **18** and **19** was therefore to be the starting point for our survey of Tamao oxidation conditions. In principle, Tamao oxidation of this mixture can produce four diastereomers, complicating our efforts to directly and clearly measure the selectivity of the Tamao oxidation/tautomerization of **18**. When our "standard" oxidation conditions were employed and resulted in the production of **20** as the major product of a 5:1 mixture of diastereomers, it was clear that, as expected, **18** had been transformed into **20** with high levels of *anti*-diastereoselectivity, at C(6). Once we obtained a sample of **7** (see below), we were then able to develop a simple ^1H NMR assay for the reaction of **18** without interference from the presence of the oxidation product(s) of **19**.

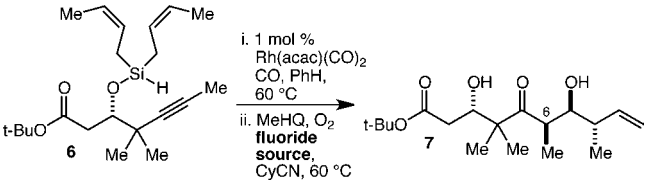
As discussed in detail above, our central hypothesis was that if the oxidation was carried out in an aprotic and nonpolar environment, the enol resulting from oxidation of **18** would undergo tautomerization from a hydrogen-bonded conformation such as **8B**, leading to desired product **7**. The first task was to identify an oxidant that could be generated safely in a nonaqueous solution and that would be effective in a relatively nonpolar solvent, and we were intrigued by a report from Tamao that small amounts of H_2O_2 could be generated in a controlled fashion by the use of methylhydroquinone (MeHQ) in concert with 1 atm of O_2.[12] When this procedure was employed under otherwise "normal" Tamao conditions (with *n*-Bu_4NF in THF), we were delighted to find that the near-total selectivity for **20** had indeed been reversed with **7** produced as the major product with 2:1 selectivity, albeit with poor efficiency (Table 1, entry 1). We were unable to perturb this ratio significantly in an extensive solvent screen, but we did find that nonpolar solvents generally led to significantly more efficient reactions and eventually settled on cyclohexane/carbonitrile[13] (CyCN) as our standard solvent (entry 2). That left the fluoride source as the remaining variable, and it was found that the use of tetrabutylphosphonium fluoride (formed *in situ* from tetrabutylphosphonium chloride and silver(I) fluoride[14]) reproducibly led to slightly improved selectivity (entry 3). We decided to prepare a series of phosphonium salts with bulkier alkyl groups, and although this line of inquiry did result in improved selectivity (entries 4 and 5), we could achieve no better than ~5:1 dr. The breakthrough came when a repeat of entry 4 gave a 6:1 dr, and we determined that the phosphonium salt used in that experiment was contaminated with PCy_3•HCl. Among other things, this led us to examine amine•HF salts,[14] and we were delighted to find that Et_3N•HF resulted in a 6.5:1 dr (entry 6). It quickly became apparent that the structure of the amine had a direct and significant impact on the diastereoselectivity, with the HF salts of *i*-Pr_2NEt and other bulkier amines giving reduced selectivities. Me_3N•HF was therefore examined, and our delight at the improved (10:1) selectivity was tempered only by a dramatic reduction in reaction efficiency (entry 7). Reasoning that the poor oxidation efficiency in this case was likely due to poor

(12) Tamao, K.; Hayashi, T.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6533.

(13) It is interesting to note that nitriles and H_2O_2 can combine to form peroxyimidic acids (with PhCN, the product is Payne's reagent; see: Payne, G. B. *Tetrahedron* **1962**, *18*, 763). Because the formation of the peroxyimidic acid seems to require mildly basic conditions (pH 8), and because we have never observed any epoxidation of the terminal alkene in these reactions, we do not believe this is relevant to the present oxidation reaction, but we cannot definitively rule it out.

(14) For convenience, the phosphonium and ammonium fluoride salts were in every case formed *in situ* by using the corresponding chloride salts in combination with AgF. Control experiments established that the oxidation reactions do not work at all in the absence of either component.

Table 1. Optimization of a *Syn*-Selective Tamao Oxidation/Diastereoselective Tautomerization Reaction



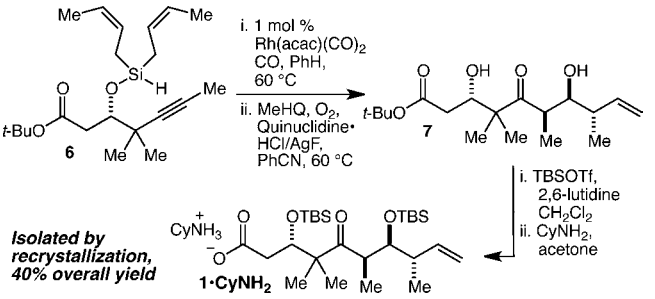
entry	fluoride source	conversion/efficiency[b]	dr (**7:20**)[c]
1[a]	*n*-Bu_4NF	poor	2:1
2	*n*-Bu_4NF	good	2:1
3	*n*-Bu_4PCl/AgF	good	3:1
4	Cy_3PBuCl/AgF	good	4.5:1
5	$Cy_3PCH_2CH(Et)_2Cl$/AgF	good	5:1
6	$Et_3N\cdot HCl$/AgF	good	6.5:1
7	$Me_3N\cdot HCl$/AgF	poor	10:1
8	**quinuclidine HCl/AgF**	**good**	**14:1**

[a] This reaction was performed in THF. [b] Qualitative measure as judged by ^1H NMR analysis of the unpurified product mixture. [c] Determined by ^1H NMR analysis of the unpurified product mixture.

solubility of the amine salt and that we therefore needed a sterically small yet more hydrophobic amine, we turned finally to the HF salt of quinuclidine and were gratified to find that this led to a highly diastereoselective (14:1) and efficient reaction in favor of the desired product **7** (entry 8). Although these results suggest that the origins of the diastereoselectivity are more complex than the hypothesis presented in Scheme 1, it is nevertheless true that that hypothesis was the origin of these experiments, and we believe that the idea regarding hydrogen-bonded enol conformation **8B** may well be sound.

We next employed the optimized oxidation conditions in a preparative reaction (Scheme 4). Thus, **6** was subjected to the tandem silylformylation–crotylsilylation reaction, and this was followed without purification by the optimized "aprotic" Tamao oxidation (in preparative scale reactions, it proved practically advantageous to use PhCN as the solvent instead of CyCN in the oxidation reaction; no significant difference in reaction efficiency or selectivity was noted[13]). After filtration through a plug of silica gel, **7** was obtained as the major product of a mixture of diastereomers (**7**, **20**, and the oxidation product(s) derived from **19**). We were able to confirm at this point that the selectivity at C(6) for the major diastereomer from the first part of the reaction (**18**) was 14:1. Treatment of this mixture with TBSOTf resulted in TBS protection of both alcohols and *t*-Bu ester cleavage to give acid **1**. For convenient purification and isolation, we then prepared the salt **1•CyNH$_2$** and isolated it by recrystallization in

Scheme 4. Application of Optimized Conditions to Silane **6** for the Direct and Efficient Synthesis of the C(1)–C(9) Fragment of Fludelone



40% overall yield from **6**. Based on experiments in which **7** was purified by more careful chromatography, we can estimate that the yield for the transformation of **6** to **7** is ~60%. Given the number of chemical bond making and breaking events in the former transformation, we view the 60% yield as being a quite reasonable level of efficiency, and we believe this transformation could serve as the basis for a step-economical and scalable synthesis of acid **1**/**1•CyNH$_2$**.

The tandem silylformylation–crotylsilylation/Tamao oxidation reaction allows the rapid buildup of molecular complexity relevant to precious polyketide targets from very simple building blocks (an alkyne, crotylsilanes, and carbon monoxide). Prior to the work reported here, however, only one stereochemical permutation (*anti*) was accessible. We have now identified an alternate set of Tamao oxidation conditions that allow access to the corresponding *syn* isomer highly selectively with a substrate that is directly relevant to the C(1)–C(9) fragment of fludelone. Notably, this constitutes a rare example of the ability to select for either diastereomer in a substrate-controlled reaction with no external stereochemical influence simply by varying the reaction conditions.

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Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs as well as X-ray crystallographic data for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.