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A Hetero-Diels–Alder Approach to Complex Pyrones: An Improved Synthesis of the Spongistatin AB Spiroketal

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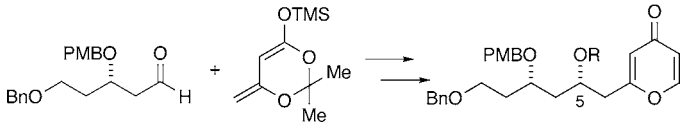
ABSTRACT



The conversion of a substituted dioxinone to a pyrone was used in an improved synthesis of the AB spiroketal subunit of the spongistatins. This transformation occurred via a hetero-Diels–Alder reaction of an acyl ketene with butyl vinyl ether. A double diastereoselective Mukaiyama aldol reaction is used to provide the hetero-Diels–Alder precursor.

The spongistatins (Figure 1) are potent antitumor agents[1] initially isolated in 1993 from marine sponges of the genus *Spongia*.[2] The potenial clinical importance of the spongistatins has created substantial interest in their synthesis, and several total syntheses have been accomplished.[3] The total synthesis of spongistatins 1 and 2 (**1**, **2**) from our laboratory was based on the assembly of three fragments including the C1−13 AB spiroketal **3** (Figure 1).[4]

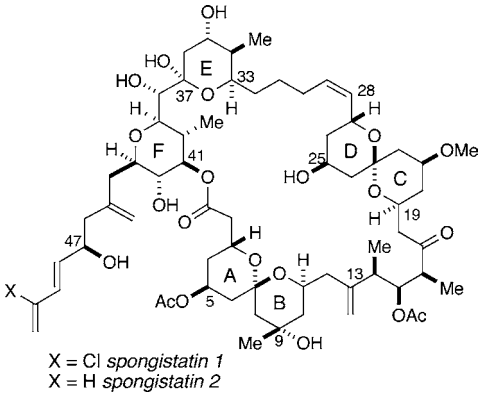


Figure 1. Spongistatins.

Our original synthesis of the AB spiroketal (Scheme 1) centered on the preparation of pyrone **4** through addition of a metalated pyrone to an aldehyde. As shown in Scheme 1, deprotonation of pyrone **5** with LiHMDS followed by

(1) (a) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol.* **1993**, *44*, 757−66. (b) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714−21.

(2) (a) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Byd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem Soc., Chem. Commun.* **1993**, 1805−7. (b) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem Soc., Chem. Commun.* **1994**, 1605−6. (c) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem Soc., Chem. Commun.* **1993**, 1166−8. (d) Pettit, G. R.; Chicacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302−4.

(3) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237−4313. For other recent synthetic efforts, see: Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637−40 and references therein.

(4) (a) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661−3. Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949−952. (b) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957−60. (c) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487−90.

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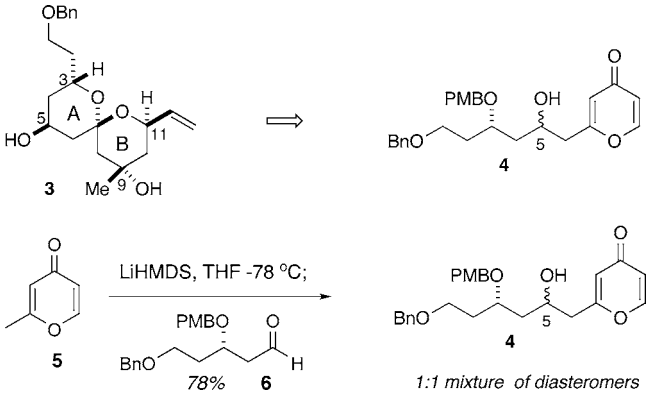
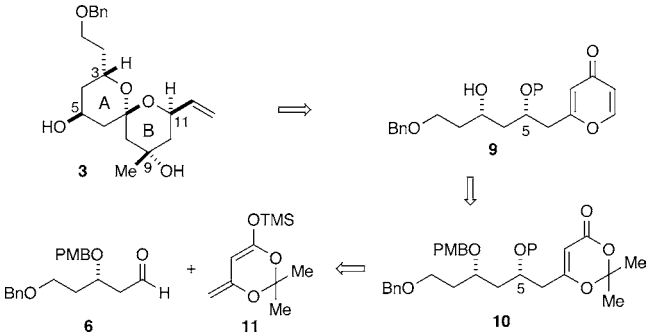
Scheme 1. Addition of Metalated Pyrones to Aldehydes



addition of aldehyde **6** led to the generation of a 1:1 mixture of diastereomers. All attempts to improve the diastereoselection of the addition by changing the counterion, solvents, and additives were unsatisfactory.[5] Additionally, attempts to prepare the enol silyl ether of pyrone **5** to investigate Mukaiyama-type additions to aldehyde **6** were thwarted since all silylating conditions led to C-silylation of pyrone **5**. The lack of stereocontrol at C5 required a four-step sequence to correct and could not be accomplished until after the spiroketalization event, thus requiring that both diastereomers be carried forward several steps prior to convergence. An improvement in the preparation of the pyrone precursor to the spiroketal which overcomes this stereochemical shortcoming is reported herein.

Retrosynthetically, the AB spiroketal subunit was envisioned to come from an acid-catalyzed cyclization[6] of pyrone **9** (Scheme 2), which would be formed through a hetero-

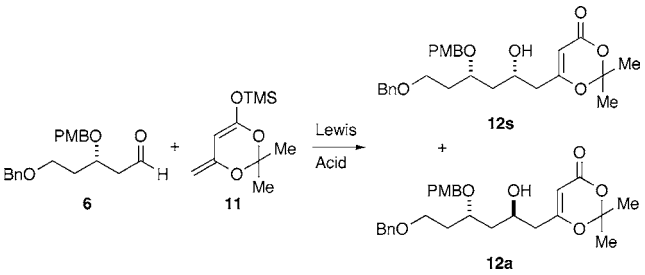
Scheme 2. Hetero-Diels−Alder Cycloaddition Strategy



Diels−Alder cycloaddition−elimination sequence from dioxinone **10**. The dioxinone would derive from a selective Mukaiyama aldol addition of silyl dienolate **11** to aldehyde **6**.

To improve the synthesis of the AB spiroketal, a general method to selectively access the Mukaiyama aldol adduct of silyl dienolate **11** with aldehyde **6** was needed. First attempts to achieve this goal focused on the use of different Lewis acids to take advantage of the potential directing ability of the β-alkoxyaldehyde. The use of a common Lewis acid, $BF_3{\cdot}OEt_2$ (Table 1, entry 1), proved nonselective, albeit

Table 1. Use of Lewis Acids in Addition to Aldehyde



	Lewis acid	ligand	yield (%)	selectivity (**12a/12s**)
1	$BF_3{\cdot}OEt_2$		90	1:1
2	Me_2AlCl		45	1.3:1
3	$TiCl_4$		61	1.5:1
4	Ti(O-*i*-Pr)$_4$		0	
5	Ti(O-*i*-Pr)Cl_3		82	2.0:1
6	Ti(O-*i*-Pr)$_2Cl_2$		89	3.3:1
7	Ti(O-*i*-Pr)$_3$Cl		21	2.4:1
8	Ti(O-*i*-Pr)$_4$	*S*-BINOL	28	1:1
9	Ti(O-*i*-Pr)$_2Cl_2$	(*S*,*S*)-(+)-TADDOL	64	1:5
10	Ti(O-*i*-Pr)$_2Cl_2$	(*R*,*R*)-(−)-TADDOL	60	1:2.1
11	Ti(O-*i*-Pr)$_4$	(−)-**13**	81	8.6:1
12	Ti(O-*i*-Pr)$_4$	(+)-**13**	95	1:10

high yielding. We next investigated the use of stronger chelating Lewis acids, such as Me_2AlCl (entry 2), which has been used in similar cases to achieve rigid chelating transition states with β-alkoxyaldehydes and addition of silyl enol ethers leading to high *anti* selectivity.[7] Unfortunately, only a slight preference (1.3:1) in favor of the *anti* diastereomer was observed. The use of titanium Lewis acids (entries 3−7) slightly improved the *anti* selectivity, but the best case with titanium(IV) dichlorodiisopropoxide (entry 6) provided only a 3.3:1 preference for the *anti* diastereomer.

Chiral ligands were then explored in an attempt to use reagent control to influence the diastereoselectivity of the reaction. BINOL in conjunction with Ti(*i*-PrO)$_4$ has been reported to result in good selectivity in Mukaiyama aldol additions,[8] but when applied to the case at hand (entry 8), low yield and poor selectivity were observed. TADDOL has also been shown to provide high levels of reagent conrol in Lewis acid-catalyzed aldol additions.[9] Exposure of dienolate **11** and aldehyde **6** to titanium(IV) dichlorodiisopropoxide

(5) Crimmins, M. T.; Washburn, D. G.; Katz, J. D.; Zawacki, F. J. *Tetrahedron Lett.* **1998**, *39*, 3439−42.
(6) Crimmins, M. T.; O'Mahony, R. *J. Org. Chem.* **1990**, *55*, 5894−900.
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(8) (a) De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187−95. (b) De Rosa, M.; Acocella, M. R.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1529−31.
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and *S,S*-TADDOL (entry 9) delivered a 5:1 mixture favoring the *anti* diastereomer. Unfortunately, *R,R*-TADDOL gave only a 2:1 preference for the *syn* diastereomer (entry 10).

Satisfactory diastereoselection was ultimately obtained taking advantage of Carreira's catalyst (Figure 2),[10] which

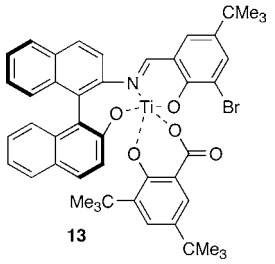


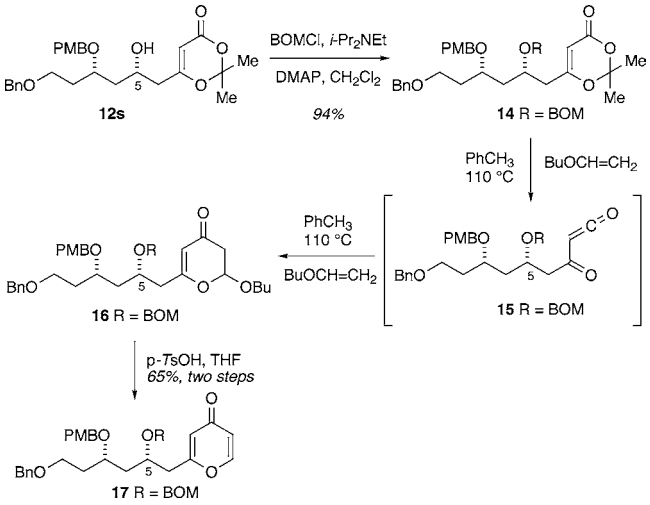
Figure 2. Carreira's catalyst.

has been reported to effect enantioselective Mukiayama aldol additions of silyl dienolate **11** with a variety of achiral aldehydes. Use of the Carreira protocol with dienolate **11** and aldehyde **6** allowed access to either the *syn* diastereomer **12s** or *anti* diastereomer **12a** in high yield and selectivity with low catalyst loadings. Using the (+)-enantiomer of **13** (entry 12) led to formation of a 10:1 mixture of aldol adducts favoring the desired *syn* diastereomer **12s** (95% yield), while (−)-**13** produced the *anti* diastereomer **12a** (entry 11) as the major product (8.6:1 dr, 81% yield).

Having accomplished an efficient synthesis of the desired dioxinone **12s**, its conversion to the required pyrone was investigated. An extension of the method reported by Coleman and Grant[11] to include more complex substrates, by performing a hetero-Diels−Alder reaction of an acyl ketene with butyl vinyl ether, was envisioned for conversion of dioxinone **12s** to the desired pyrone. To this end, the C5 hydroxyl was readily protected as a benzyloxymethyl ether to provide hetero-Diels−Alder precursor **14** (Scheme 3). Heating dioxinone **14** in toluene in the presence of butyl vinyl ether led to formation of butyl acetal **16** presumably through a hetero-Diels−Alder reaction of intermediate acyl ketene **15** with butyl vinyl ether. Immediate exposure of the butyl acetal to *p*-TsOH in THF led to rapid elimination of butanol to produce pyrone **17** (65% over two steps).[12]

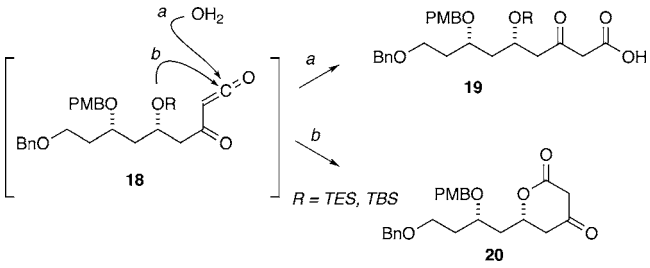
Efficient conversion of the dioxinone **14** to the butyl acetal **16** required that all materials be rigorously dried to avoid trapping of the acyl ketene intermediate by advantitious water. Failure to scrupulously dry the dioxinone, the solvent, or butyl vinyl ether led to formation of β-keto acid **19** (Scheme 4, path a). Additionally, the choice of protecting group on the C5 hydroxyl group was critical. Early attempts

Scheme 3. Hetero-Diels−Alder Cycloaddition



to effect the hetero-Diels−Alder reaction using triethylsilyl[13] and *tert*-butyldimethylsilyl ethers at C5 resulted in formation of β-keto lactone **20** presumably via interception of the acyl ketene by the C5 ether oxygen followed by loss of the labile silicon protecting group (Scheme 4, path b).[14] Incorporating the more robust benzyloxymethyl group precluded formation of the β-keto lactone **20**.

Scheme 4. Side Reactions of Acyl Ketene Intermediate



Taking advantage of the chemistry previously employed in the total synthesis of spongistatin, the *p*-methoxybenzyl group was removed by the action of DDQ to provide the free alcohol at C3 (Scheme 5). Exposure of the hydroxypyrone to catalytic trifluoroacetic acid in benzene provided spiroenone **21** in 64% yield after recycle. The minor diastereomer (<10% which had been introduced in the Mukaiyama aldol addition) could be readily removed after the spiroketalization. Treatment of the spiroenone **21** with the vinyl cuprate reagent formed from vinylmagnesium bromide and tetrakis[copper(I) iodide−tributylphosphine] led to the formation of alkene **22** as the major diastereomer (5:1 dr). The C9 tertiary carbinol was introduced by addition of methylmagnesium iodide to the C9 ketone. Cleavage of the

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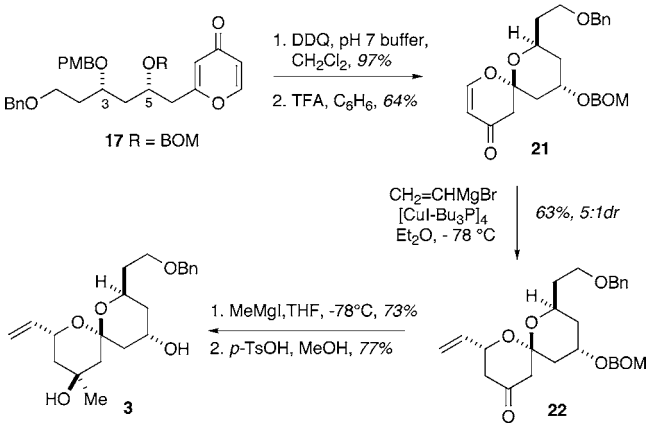
(12) Zawacki, F. J.; Crimmins, M. T. *Tetrahedron Lett.* **1996**, *37*, 6499−6502.

(13) Katz, J. D. Thesis, University of North Carolina.

(14) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435−44. Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839−45.

Scheme 5. Completion of AB Spiroketal



benzyloxymethyl ether occurred upon treatment with acid to provide the desired diol **3**. Comparison of spectral data confirmed the interception of the previously synthesized fragment utilized in the reported total synthesis of spongistatin.[4]

In summary, an improved synthesis of the AB spiroketal subunit of spongistatin has been developed. This synthesis takes advantage of a double diastereoselective Mukaiyama aldol reaction and subsequent hetero-Diels−Alder cycloaddition to contstruct a pyrone precursor for a spiroketalization reaction.

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Supporting Information Available: Copies of ^{1}H NMR spectra and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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