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Anionic cyclizations of aromatic ester dithioacetals with facially biased α,β-unsaturated ketones

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ABSTRACT

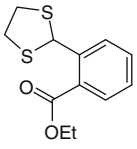
Cyclopent-2-enones bearing a plane-nonsymmetric oxygen function on C-4 reacted efficiently with anions derived from aromatic ester dithioacetals to provide annulated products in a highly diastereoselective fashion. Whereas the anion of a dimethoxy aromatic ester dithiolane more rapidly reacted by an alternative intramolecular pathway, the anion of the corresponding aromatic ester dithiane was suitable for the intermolecular cyclization.

Ozaki et al.[1] showed that the anion derived from the aromatic dithiolane-ester **1** reacts with simple α,β-unsaturated esters and ketones by a Michael addition followed by a Claisen-like ring closure. This method of ring-formation is particularly attractive because the product has two additional ketone functions, of which one is protected as the dithiolane. We wished to assess this cyclization process with more complex α,β-unsaturated ketones and with an analogue of **1** bearing additional functionality on the benzoate moiety.

Spiroannulated cyclopentenones substituted in the γ-position by an oxygen function were chosen as test substrates because the products of cyclization would resemble four of the six rings of the antibiotic fredericamycin A (**2**).[2] Anionic cyclizations have been used in synthetic approaches to **2**, but these involved lactones **3**[3] and **4**.[4,5] Furthermore, an anion derived from a homophthalic anhydride was cyclized onto an activated cyclopentenedione derivative in Kita's elegant asymmetric synthesis of **2**.[6]

Treatment of **1** with LDA in the presence of HMPA followed by addition of the spiro compound **5** or **6** led to the formation of only one cyclized product **7** or **8** in very good yield (Scheme 1). In both instances the dithiolane-anion had attacked the enone exclusively *anti* to the OR group of the enone moiety of the substrate. Addition of the anion of **1** to even the unprotected hydroxy-enone **9** gave only one cyclized product **10**, albeit in low yield.

The next stage was to explore further the cyclization process with a more elaborate α,β-unsaturated ketone. A tricyclic enone was assembled following the sequence included in Scheme 2. Hydrindanone **11**, which had been obtained by the Fries rearrangement[7] of the 2-chloropropionyl ester of *m*-cresol, was converted to the methyl ether **12**. Geminal acylation of the ketone function of **12** with 1,2-bis(trimethylsilyloxy)cyclobutene (**13**) did not proceed to a significant extent under the usual conditions with $BF_3{\cdot}Et_2O$ as the catalyst.[8] The use of $TiCl_4$ as the Lewis acid did provide **14**, but in only 17% yield (56% based on recovered **12**). An acceptable yield of **14** was realized only when large amounts of **13** and of $BF_3{\cdot}Et_2O$ were added in two portions, with many hours between additions, to the solution of **12**. Dehydrogenation of **14** to the enedione was accomplished with benzeneseleninic anhydride, and reduction of one ketone with sodium borohydride in the presence of $CeCl_3$ gave the diastereomeric monoalcohols **15a** and **15b** in a 1:1.8 ratio. The ^1H NMR data for **15b** included a significant NOE of the signal for the methoxy group upon saturation of the signal for the hydrogen on the alcohol carbon. Thus, the major epimer was **15b**, which had arisen by delivery of hydride onto the face of the carbonyl *syn* to the aromatic ring. Compound **15b** was protected as the trimethylsilyl ether **16**. Enone **16** was added



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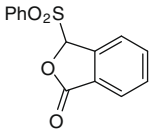

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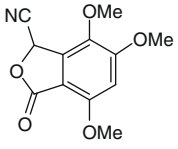

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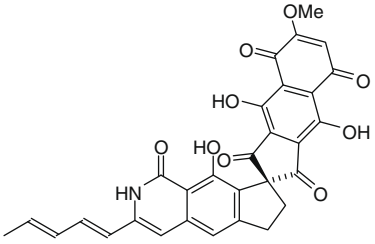

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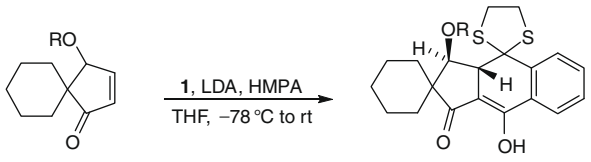
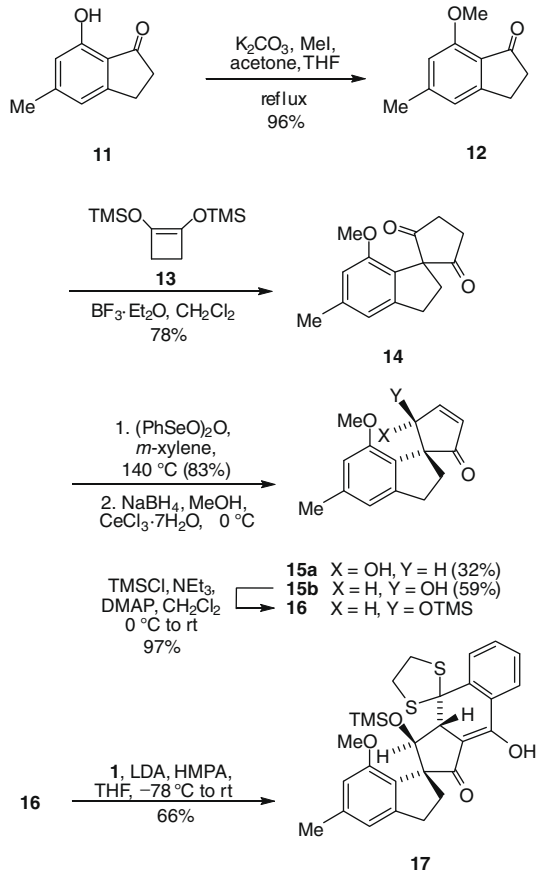


5 R = Ac
6 R = TBS
9 R = H

7 R = Ac (85%)
8 R = TBS (84%)
10 R = H (28%)

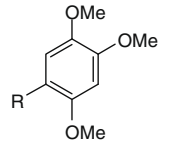
Scheme 1.



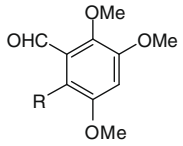
Scheme 2.

to deprotonated **1**. This gave a single diastereomer **17** in 66% yield. It is remarkable that, once again, the anion had added to the face of the enone *anti* to the oxygen function, but in this instance that was *syn* to the aromatic ring of **15b**, even though the aromatic ring bears a methoxy group that one presumes would have presented a significant amount of steric hindrance.

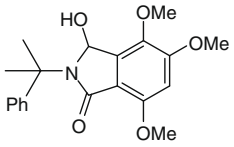
Attention was then directed to an analogue of **1** with additional oxygen functions on its aromatic ring. Initially, a compound with the complete oxygen pattern for the final ring of **2** was targeted, and conversion of commercially available **18** to the trimethoxy-analogue of **1** was attempted. Efforts to carry out directed *ortho*-metallation of this carboxylic acid[9] and of the alcohol **18b**, its methyl- and silyl-protected derivatives gave no products of *ortho*-metallation.[10,11] On the other hand, treatment of the lithiated *N*,*N*-diethylamide[12] **18c** with DMF provided the formylated product **19a** in 53% yield. Directed *ortho*-metallation of **18d**–**f**, which have amide functions with more easily hydrolyzable amide functions,[13–15] also provided formylated products **19b**, **19c**, and **19d,** but the yields of these were low (17%, 27%, and 28%, respectively). The congested aldehyde of **19a** was converted to the dithiolane **20** under catalysis by boron trifluoride etherate.[16] However, attempts to transform the diethyl amide **20** into an ester via hydrolysis or by other means, including by treatment with boiling ethanolic HCl, lithium hydroperoxide,[17] triflic anhydride[18] or aluminum hydrides were completely unsuccessful. It should be noted that when **20** was treated with base, as had been done with **1**, no reaction with an α,β-unsaturated ketone was observed.



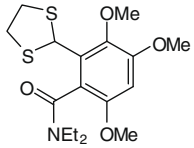
18a R = CO_2H
18b R = CH_2OH
18c R = $CONEt_2$
18d R = $CONEt(CH_2)_2NEt_2$
18e R = CON*t*-BuMe
18f R = $CONHCMe_2Ph$



19a R = $CONEt_2$
19b R = $CONEt(CH_2)_2NEt_2$
19c R = CON*t*-BuMe

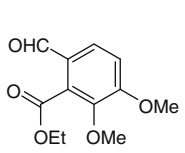


19d

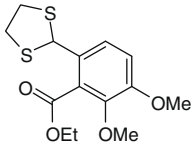


20

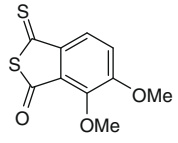
This failure to produce an ester corresponding to **20** prompted us to consider a more modestly substituted analogue of **1**. We had reported the preparation of **22** from the aldehyde **21**.[19] Treatment of **22** with LDA (in THF with HMPA, −78 °C to room temperature) had produced the thiothionoanhydride **23**. Under the same conditions, but in the absence of a Michael acceptor, generation of the anion of **1** led to the formation of this unusual functional group, also. In an effort to intercept the anion before the formation of the thiothionoanhydride, **16** was added quickly after the LDA was added to **22**, but **23** was once again the exclusive product. Thus, in contrast with **1**, for **22** the unimolecular pathway to **23** appears to be significantly faster than the bimolecular cyclization reaction.



21



22

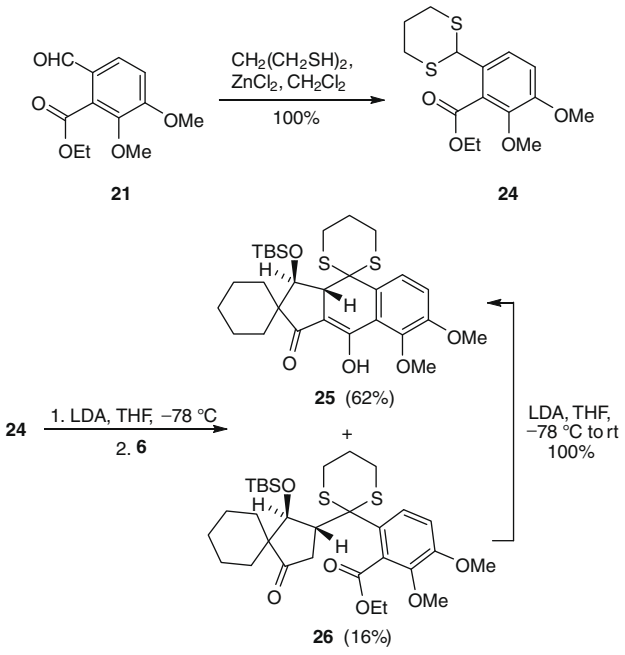


23

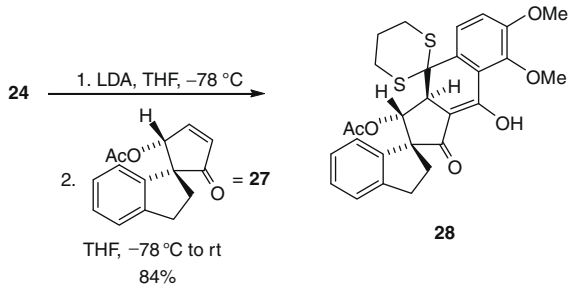
The formation of the thiothionoanhydride could be thwarted completely by the use of the dithiane **24** in the place of the dithiolane **22**. Now creation of the anion with LDA followed by addition of **6** gave a 62% yield of the cyclized product **25**, as a single diastereomer (Scheme 3). However, this process had not involved allowing the reaction mixture to warm to room temperature before the reaction was quenched, and 16% of a by-product was obtained. This proved to be **26**, which was the result of just the Michael reaction. The by-product could be converted completely to **25** with LDA.

Finally, the tricyclic enone-acetate **27** was added to the anion of **24**, and the only product was the pentacyclic compound **28**, in which the anion had added exclusively to one face of the enone (Scheme 4).

In summary, cyclization onto an α,β-unsaturated carbonyl with an aromatic dithiane-ester such as **24** is a more generally applicable process than with the corresponding dithiolane-ester. Yields of the cyclized product are very good, and the facial selectivity can be controlled efficiently by a plane-nonsymmetric moiety on the



Scheme 3.



Scheme 4.

α,β-unsaturated system. We anticipate that dithiane-ester cyclizations may be useful for the synthesis of analogues of antibiotics such as **2**.[20]

Acknowledgment

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Supplementary data

Experimental procedures and characterization data for compounds **1**, **7**, **8**, **10**–**12**, **14**–**17**, **19a**–**d**, **20**, **24**–**28** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.162.

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