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Studies Toward the Construction of the Allyltrisulfide Component in Esperamicin-A1 From 5-Ketoshikimic Acid Derivatives: Part 1

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Abstract: *The conversion of keto ester* ***1****, obtained in either enantiomeric form from (-)-quinic acid, to its corresponding enol silyl ether* ***4*** *was examined as the first step to construct the allyl trisulfide unit found in esperamicin* A_1*. Under different conditions a very facile dimerization of either* ***4*** *or enolate* ***10*** *to give compound* ***14*** *was observed.*
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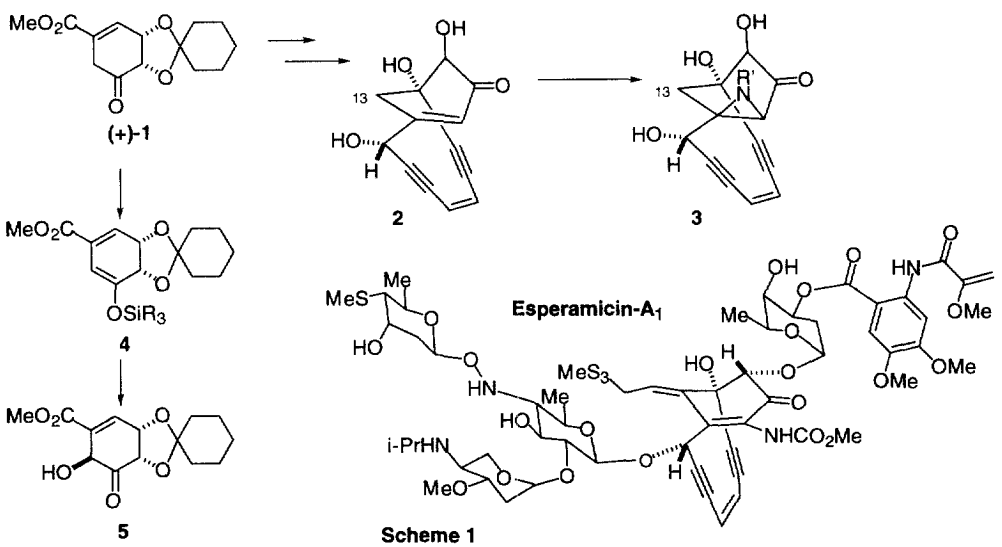
In a project to synthesize the antitumor antibiotic esperamicin-A_1, the keto-ester **1** derived from (-)-quinic acid was employed as a pivotal intermediate in the construction of the bicyclic enediyne **3**.[1] Of the remaining operations necessary for the conversion of **3** to the esperamicin aglycone, the stereoselective introduction of the allyl trisulfide system is perhaps the most challenging. This requires some sort of activation of the C-13 center in either **3** or its enone precursor **2**. One straightforward means whereby this could be achieved is to effect an allylic oxidation.[2] However, the results of the reaction of **2** with selenium based reagents were not encouraging.

For this reason we returned to keto ester synthon **1**, to determine whether it could be converted to enol silyl ether **4**, and from there to **5** via epoxidation/ring opening.[3] Enol ether **4** is a potentially versatile intermediate for aldol type C-C bond forming reactions to introduce functionality at "C-13" prior to enediyne construction, while the 6-hydroxyshikimic acid derivative **5** could be used for the elaboration of **2/3**, bearing a hydroxyl group at C-13.



Scheme 1

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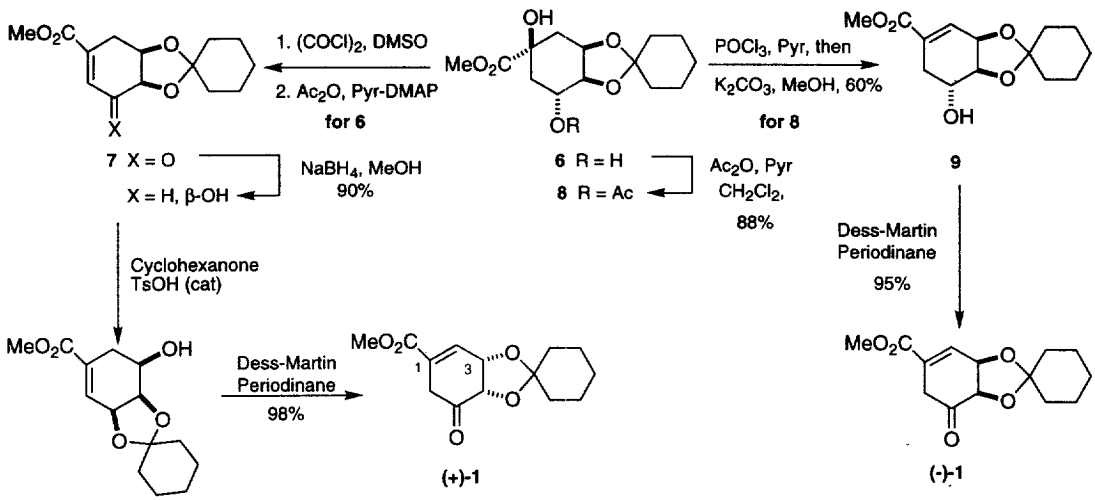
Although keto ester **1**, is available in either enantiomeric form from (-)-quinic acid, for the preparation of (+)-**1**, the conversion of the ester diol **6** to the conjugated ketone **7** on a > 25 gram scale was an operationally difficult transformation (Scheme 2). Inspired by work by Shing *et al.*, a two step procedure was initially employed, involving oxidation of the secondary alcohol function in **6** (PCC/Al_2O_3), followed by acetylation of the remaining tertiary hydroxy group to promote formation of the double bond.[1,4] High yields of ketone **7** could be obtained in this way. However, the necessity on certain occasions to use substantial quantities of PCC/Al_2O_3 to drive the oxidation to completion, plus the accompanying problems of product recovery led us to look at other, more reliable oxidation conditions. In this context, the Swern oxidation [$(COCl)_2$, DMSO, -78°C -> +20°C, 30 min] has proven to be very effective, producing **7** in a consistent fashion in 70-80% yields.

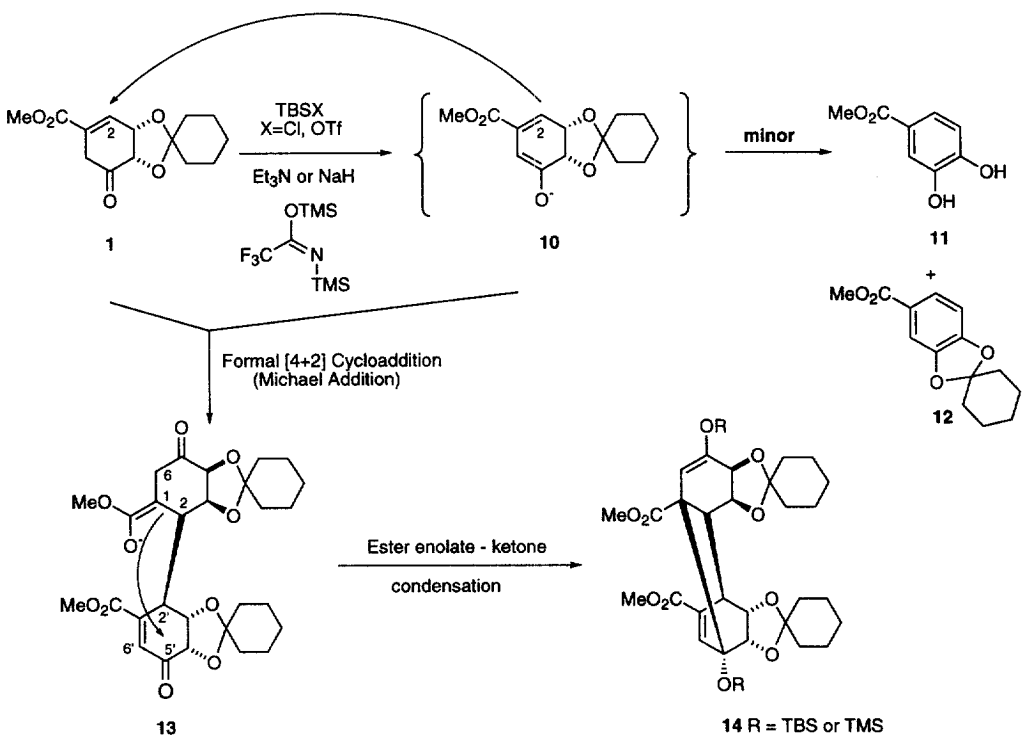
Concerning the synthetic route to (-)-**1**, Gotor *et al.* recently claimed that the transformation of diol **6** to its mono-acetate derivative **8**, and the subsequent conversion of **8** to olefin **9** was not reproducable.[5] In their hands, the latter reaction produced a 1 :1 mixture of the desired product and a rearranged 1,3-ketal side product. Suprized by this report, we have reconfirmed that under our described conditions (Ac_2O-Pyr-CH_2Cl_2), compound **8** is obtained in 88% yield. Further, the reaction of alcohol **8** with good quality (distilled) $POCl_3$ (*2 equivs*, 3 h) leads to regiospecific and reproducable formation of olefin **9** in >60% yield.[1,6] Overall, the conversion of diol **6** to ketoester (-)-**1** was achieved in 50% yield, demonstrating the efficiency of our route to this little studied compound.[7]

Keto ester **1** is a relatively sensitive molecule, especially in basic medium. A major concern in the transformation **1** -> **4** was thus the possibility that deprotonation at C-6 giving enolate **10** would promote eliminative opening of the cyclohexylidene system and formation of the aromatized products **11** and/or **12**. However, when a solution of **1** in THF was treated with NaH at 0°C, followed by addition of TBSCl to trap the *in situ* generated conjugated enolate **10**, only trace amounts of two products were isolated, whose ^1H NMR spectra are consistent with the aromatic structures **11** and **12** (Scheme 3). In fact, under these conditions the major reaction product formed corresponded to the novel dimer **14** (R= TBS) (colourless oil; 52%) (CIMS: MH^+ m/z = 761, IR: 1722 cm^{-1}). The structure of this compound was readily deduced from the ^1H, ^{13}C NMR, ^1H-^1H correlation, and NOESY spectral data. The NOESY spectrum was of particular importance, as it permited confirmation of the spatial proximity of H_6-$H_{6'}$, $H_{6'}$-H_4, $H_{6'}$-H_5, and H_2-$H_{2'}$. Formally, compound **14** corresponds to the product of a Diels-Alder reaction between the starting keto ester **1** and enolate **10**, but, given the facility with which dimer **14** is obtained, a more plausible mechanism involves an intermolecular Michael reaction between these entities to give intermediate **13**, followed by an intramolecular ester enolate-ketone condensation step.

To probe further the reactivity of keto ester **1**, it was envisaged that dimer formation may be suppressed if silylation of the ketone oxygen in **1** were to preceed proton loss at C-6. In this context, the reaction of **1** with TBSOTf/Et_3N in CH_2Cl_2 (0.06 M) was examined both at 0°C and at -78°C.[8] However, at -78°C formation of dimer **14** predominated (40%), and at 0°C dimerization was both rapid and efficient (84% isolated yield). These results suggested that enol ether **4** is not only formed on treatment of **1** with TBSOTf, but that it may also engage in reaction with the starting keto ester to give **14**. In support for this view it was observed that **1** was converted to dimer **14** (R = TMS) in 51% yield employing *N,O*-bistrimethylsilyl trifluoromethylacetamide as the silylating agent in MeCN at room temperature (1 h).[9] In contrast, when TBSCl was used in place of TBSOTf, the role of



Scheme 2



Scheme 3

Et_3N as a reversible base was exacerbated, effecting both deprotonation of **1** and reprotonation of enolate **10** to produce the thermodynamically more stable conjugated enone product *enant*-**7**. This latter reaction illustrates to what point the C-6 hydrogens in keto ester **1** are labile.

Globally, these results indicate that enolate **10**, or the derived enol ether **4**, is too reactive with respect to dimer formation to permit exploitation of keto ester **1** for the synthesis of C-6 functionalized shikimic acid systems via the ketone -> enol ether strategy. As described in the accompanying communication,[10] this problem was resolved by employing the corresponding keto alcohol derivative in which the ester function in **1** is reduced.

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6. Note that using 1.1 equiv only of $POCl_3$ (see ref. 1) followed by OAc hydrolysis, substantial amounts of diol **6** were recovered. Thus it is recommended to use 2 equivalents of this reagent. Furthermore, when 3 equivalents of $POCl_3$ were employed a minor by-product (10-15%) was formed, corresponding to a derivative of **6** bearing a chloro substituent in the place of the tertiary hydroxyl group [CIMS: m/z = 305 and 307; ^{13}C NMR: 62.9 ppm (C-1)]. The ketal rearrangement product reported by Gotor[5] was not observed.

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