

Studies Toward the Construction of the Allyltrisulfide Component in Esperamicin-A₁ From 5-Ketoshikimic Acid Derivatives: Part 2

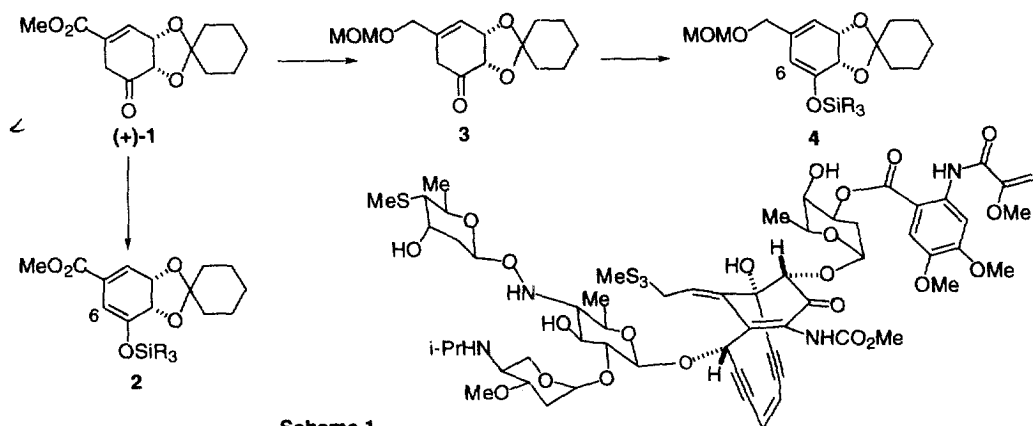
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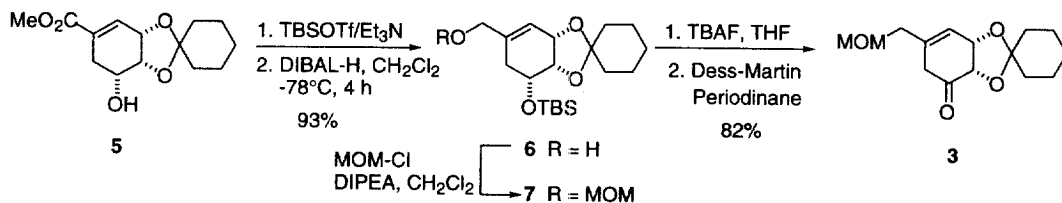
Abstract: The MOM protected keto alcohol **7** was successfully converted to the silyl enol ether **4** by reaction with BSA. Reaction of this intermediate with dioxirane led to formation of allylic alcohol **10**. Lactone **15** was obtained by reaction of tosylate **14** with the cuprate reagent derived from ethyl bromoacetate. Through a short sequence of reactions this 5-membered lactone was isomerized to the target lactone product **18**. © 1998 Elsevier Science Ltd. All rights reserved.

In the preceding communication,¹ a highly efficient and rapid base/silylating agent promoted dimerization reaction of the 5-ketoshikimic acid derivative **1** was described, which thwarted efforts to employ the conjugated enol ether **2** as a vehicle for introduction of functionality at the C-6 position in this molecule. This operation is crucial to our synthetic endeavour to construct the esperamicin A₁ aglycone.² As the ester function in **1** contributes strongly to the acidity of the hydrogens at C-6, further experiments were directed toward the preparation of the corresponding enol silyl ether **4** from the *O*-protected keto-alcohol **3**, and to the development of methodology for conversion of **4** to cyclic lactone **20** (Schemes 1 and 3).



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To begin with, compound **3** was prepared by *O*-TBS protection of the alcohol function and reduction of the ester group in **5**,² followed by conversion of **6** to its *O*-MOM derivative **7**, liberation of the secondary alcohol, and Dess-Martin oxidation (82% overall) (Scheme 2).

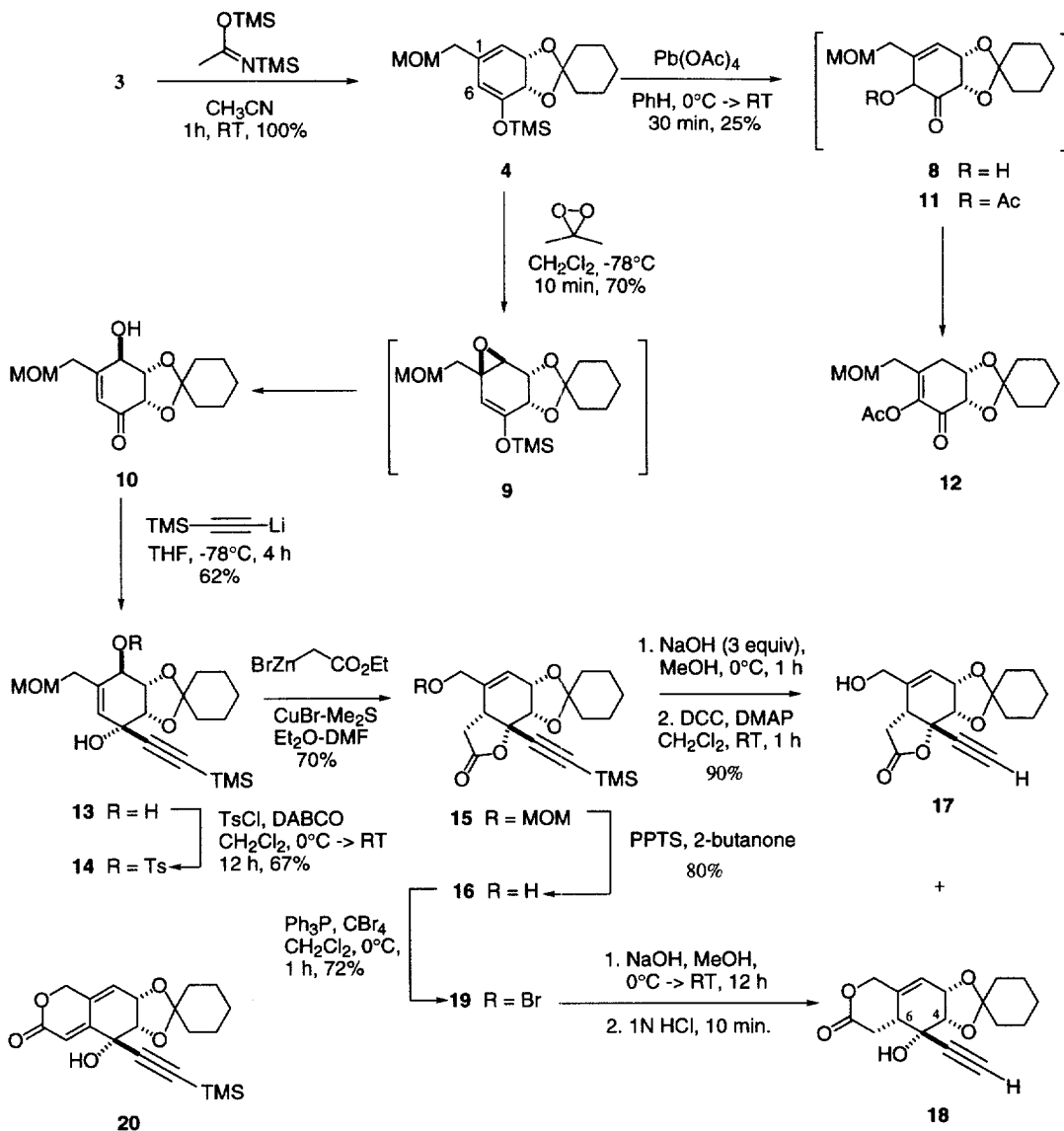


Scheme 2

In contrast to the problems associated with the conversion of keto ester **1** to its corresponding enol ether **2**, the transformation of **3** to enol silyl ether **4** was readily achieved by reaction with *N,O*-bistrimethylsilyl acetamide in MeCN (Scheme 3).^{3,4} Indeed, compound **4** was isolated in quantitative yield after solvent removal *in vacuo* [¹H NMR: δ 5.12 (H-6), 5.51 (H-2); ¹³C 102.4 (C-2), 115.1 (C-6), 133.6 (C-1), 152.4 (C-5)].

With the goal in mind of elaborating compound **20** with the olefin stereochemistry corresponding to the allyl trisulfide unit in esperamicin, efforts were then made to convert silyl enol ether **4** directly to α -hydroxy ketone **8** by reaction with *m*-CPBA.⁵ However, intermediate **4** was rapidly degraded in the presence of *m*-CPBA, even at low temperature. In contrast, it did react in a controlled manner with dioxirane in CH₂Cl₂ at -78°C to give a single product **10** (70%), resulting from initial regio and stereoselective epoxidation of the 1,2-double bond (cf. **9**). In a further experiment it was shown that introduction of an oxygen substituent at C-6 could be achieved by reaction of enol ether **4** with Pb(OAc)₄.⁶ Compound **12** (25%) was isolated from this reaction, indicating that the oxidation step was accompanied by undesired double bond isomerization of **11**.

With ketone **10** available on a gram scale, a reaction sequence was developed whereby its allylic alcohol unit could be exploited to effect C-C bond formation at C-6. To set the stage, **10** was converted to diol **13** (62%) through reaction with lithium trimethylsilylacetylide at -78°C, followed by tosylation of the secondary OH group (TsCl, DABCO; 67%) to give compound **14**. In the key step, reaction of this intermediate with EtO₂CCH₂ZnBr in the presence of CuBr led to selective S_N2' displacement with formation of 5-membered lactone **15** in 70% yield.⁷ In principle, lactone formation could be avoided by protection of the tertiary hydroxyl group prior to the condensation step. However, reaction of tosylate **14** with a variety of silylating agents was met with little success.



Scheme 3

To study the *trans*-lactonization of **15** to **18**, *O*-MOM deprotection was readily achieved by reaction of **15** with PPTS in 2-butanone for 24 h at reflux.⁸ Subsequent treatment of **16** under hydrolysis (NaOH, MeOH) then gave a ring opened diol-acid intermediate which upon reaction with DCC-DMAP gave a mixture of lactones **17** and **18** (2 : 1), the 6-membered lactone product **18** being the minor component. Following a different route, alcohol **16** was converted to the corresponding bromide **19** (Ph₃P, CBr₄; 72%), then sequentially treated with NaOH and 1N HCl. This produced compound **18** in 49% yield, accompanied by small amounts of the five membered

lactone **17**. In the NOESY spectrum for lactone **18** correlations were observed between H₆-H₃ and H₆-H₄, indicating that the absolute configuration at C-6 corresponds to *R*. It follows therefore that the 5-membered lactone **15** is *cis*-fused as indicated. Similarly, since *anti* approach of the cuprate to tosylate **14** is expected in the S_N2' process leading to **15**,⁹ it also follows that the tosylate function in **14** is positioned on the opposite side of the molecule from the protected diol system.

Having shown that the sensitive enol silyl ether **4** can be prepared from keto alcohol **3**, and further that this intermediate can be used to construct lactone **19**, work is currently in progress to employ this methodology to obtain **20**, and ultimately esperamicinone. Application of the reactivity of **3** to the synthesis of other natural products more closely related to shikimic acid is also envisaged.¹⁰

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References and Footnotes

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