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

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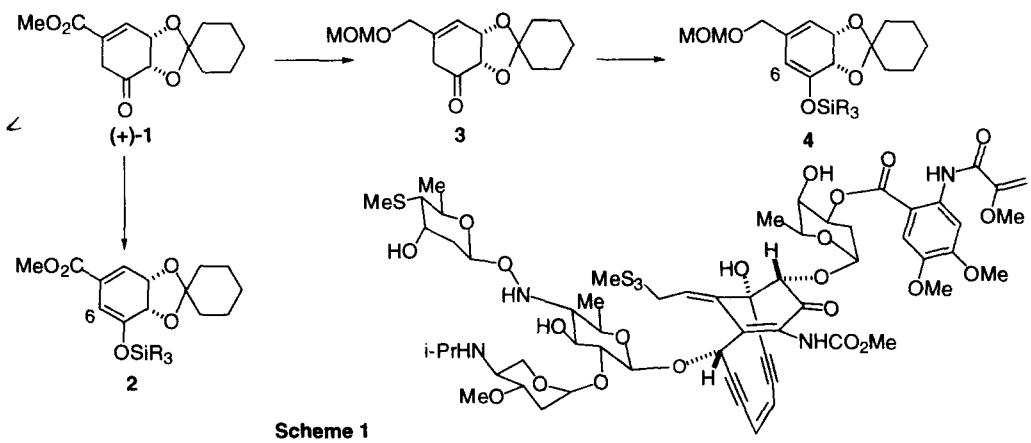
Abstract: *The MOM protected keto alcohol 7 was successfully converted to the silyl enol ether 4 by reaction with BSA. Reaction of this intermediate with dioxirane led to formation of allylic alcohol 10. Lactone 15 was obtained by reaction of tosylate 14 with the cuprate reagent derived from ethyl bromoacetate.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

In the preceeding 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 A_1 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).



Scheme 1

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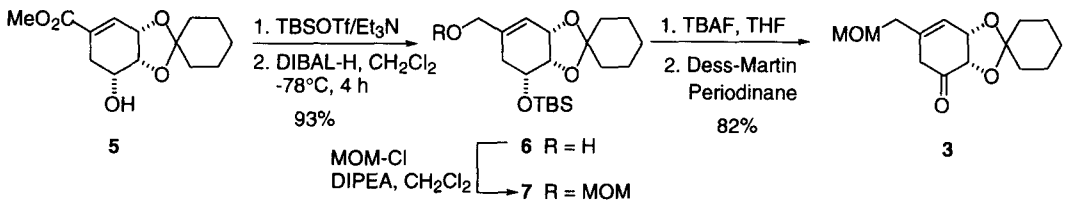
To begin with, compound **3** was prepared by *O*-TBS protection of the alcohol function and reduction of the ester group in **5**,[2] followed by conversion of **6** to its *O*-MOM derivative **7**, liberation of the secondary alcohol, and Dess-Martin oxidation (82% overall) (Scheme 2).

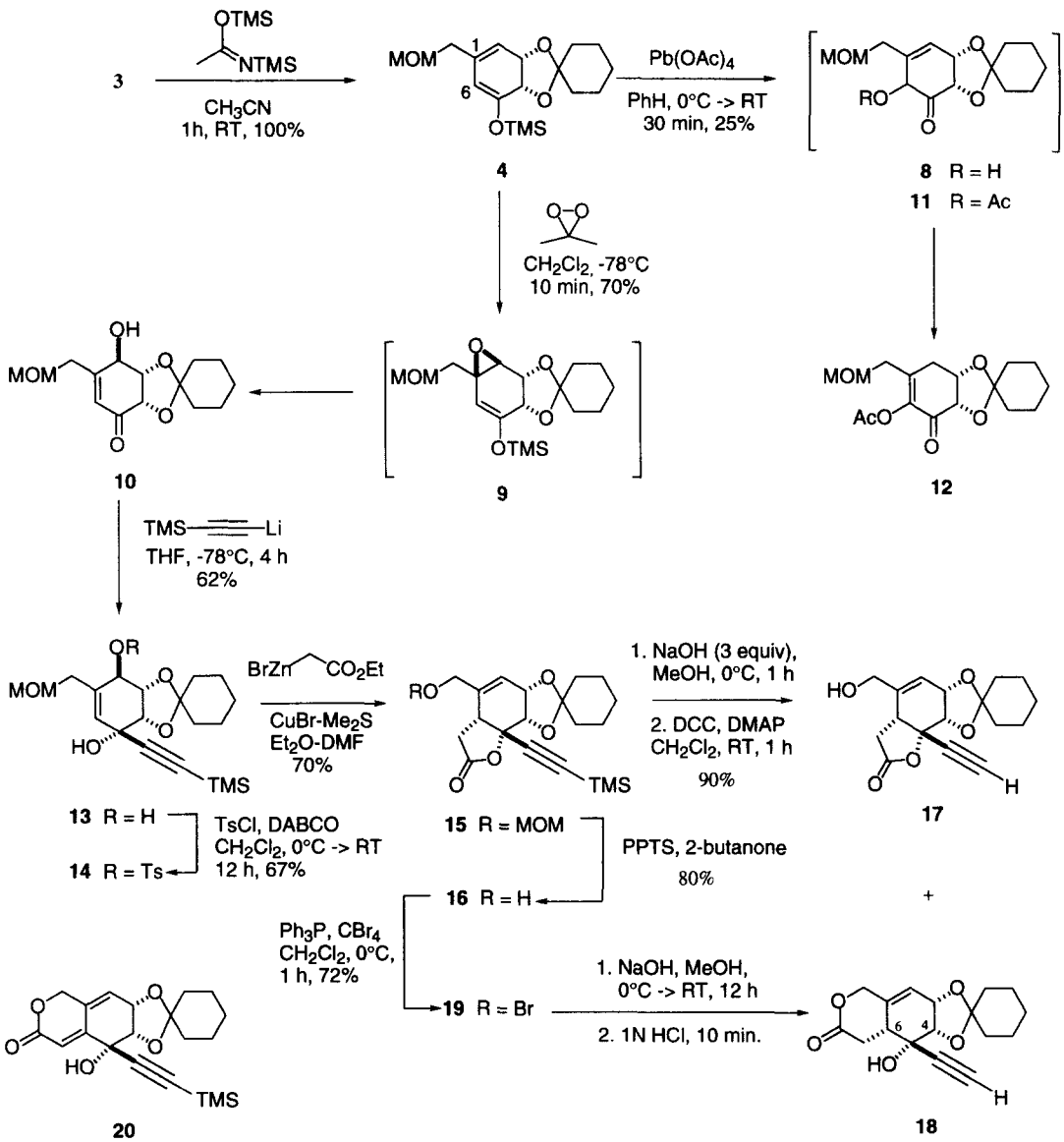


Scheme 2

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* [^{1}H 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 CH_2Cl_2 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 EtO_2CCH_2ZnBr 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** (Ph_3P, CBr_4; 72%), then sequentially treated with NaOHaq 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 H_6-H_3 and H_6-H_4, 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. Similarily, 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

1. Piguel, S.; Ulibarri, G.; Grierson, D.S. *Tetrahedron Letters* **1999**, *40*, 291-294.

2. Ulibarri, G.; Nadler, W.; Skyrdstrup, T.; Audrain, H.; Riche, C.; Chiaroni, A.; Grierson, D.S. *J. Org. Chem.* **1995**, *60*, 2753-2761.

3. Johnson, F.; Pillai, K.M.R.; Grollman, A.P.; Tseng, L. *J. Med. Chem.* **1984**, *27*, 954-958.

4. Reaction of ketone **3** (*O*-bromomethyl acetate instead of MOM derivative) with TMSOTf/triethylamine produced the *s-trans*-isomer of enol ether **4** (28%) wherein the terminal double bond was exocylic to the six membered ring. It is probable that the triethylamine-HOTf salt produced in this reaction acts as a proton source, reacting with the initially formed **4** (or its corresponding enolate) to produce a conjugated enone type intermediate (1,6-double bond) which is then converted to the observed product.

5. a) Rubottom, G.M.; Gruber, J.M.; Boeckman Jr., R.K.; Ramaiah, M.; Medwid, J.B. *Tetrahedron Letters* **1978**, 4603-4606. b) Reddy, K.K.; Falck, J.R.; Capdevila, J. *Tetrahedron Letters* **1993**, *34*, 7869-7872. c) Grieco, P.A.; Nargund, R.P.; Parker, D.T. *J. Am. Chem. Soc.* **1989**, *111*, 6287-6294.

6. Rubottom, G.M.; Gruber, J.M.; Kincaid, K. *Syn. Commun.* **1976**, *6*, 59-62. For same reaction using lead tetrabenzoate; see: Rubottom, G.M.; Gruber, J.M. *J. Org. Chem.* **1977**, *42*, 1051-1056.

7. a) Sekiya, K.; Nakamura, E.*Tetrahedron Letters* **1988**, *29*, 5155-5156. b) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091-3093.

8. Monti, H.; Léandri, G.; Klos-Ringuet, M.; Corriol, C. *Syn. Commun.* **1983**, *13*, 1021-1026.

9. Magid, R.M. *Tetrahedron*, **1980**, *36*, 1901-1930.

10. Tatsuta, K.; Yasuda, S.; Araki, N.; Takahashi, M. Kamiya, Y. *Tetrahedron Letters* **1998**, *39*, 401-402.