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MODEL STUDIES DIRECTED TOWARD THE AVERMECTINS: A ROUTE TO THE OXAHYDRINDENE SUBUNIT

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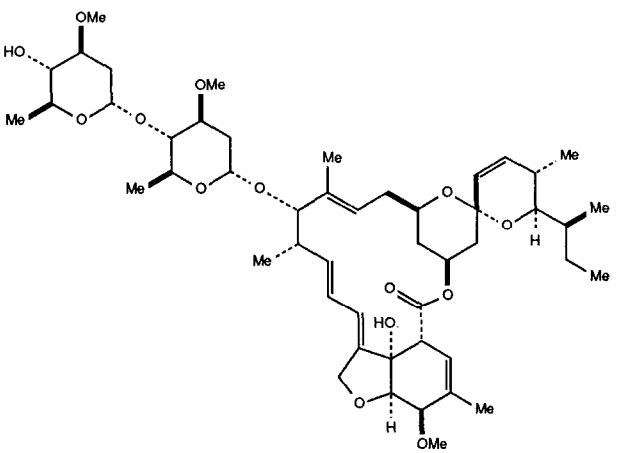
Abstract: A Michael-Aldol sequence of an enoate-ketone triggered by the action of an aluminum thiophenoxy "ate" complex leads to the oxahydrindene subunit of the avermectins.

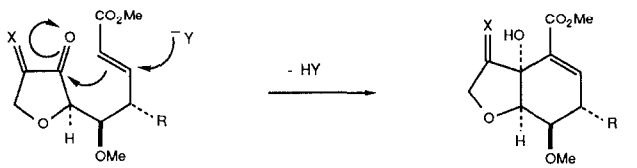
The avermectins, discovered and developed by the Merck laboratories, comprise a family of macrolide-like antibiotics.[1] The novel structures of these compounds in conjunction with their emerging applications against a variety of parasites has stimulated a great deal of interest in their chemical synthesis. We have identified Avermectin A_{1a} as our initial goal compound in this area.



Avermectin A_{1a}

Not the least challenging component to be addressed in such an exploration is that of the extensively functionalized oxahydrindene system. While this type of subunit has been synthesized, there is still room for new solutions to this problem.[2] Particularly at a premium are solutions which produce the relevant antipode in a reasonably expeditious fashion. Hopefully such solutions will prove to be responsive to the larger realities of a total synthesis objective.

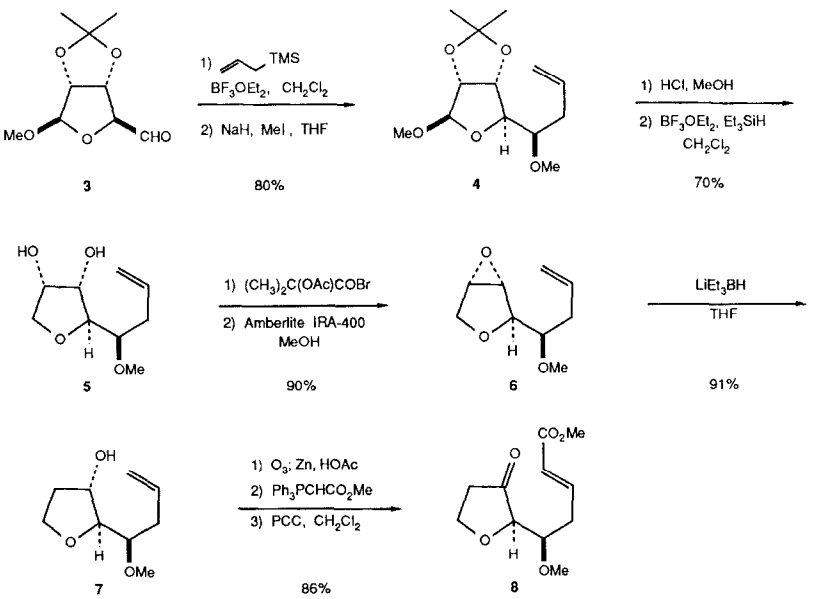
With these considerations well in mind, we investigated the possibilities implied in the transformation of **1** to **2**. The successful reduction to practice of this simple approach is described below.



1a,b **2a,b**

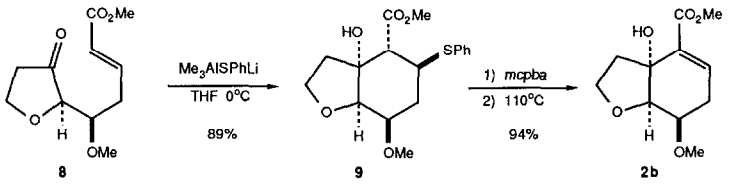
a : X = CHR' R = Me
b : X = H_2 R = H

Our synthesis started with aldehyde **3**, readily available from D-ribose. As previously described,[3] reaction of this aldehyde with allyltrimethylsilane afforded substantially a single homoallylic alcohol which, upon methylation ,provided **4**.[4] The anomeric center was de-oxygenated according to the general procedure of Gray[5] and the resultant diol **5** was converted to the corresponding epoxide, **6**, following the protocol of Robins.[6] This compound was regioselectively reduced with lithium triethylborohydride to produce, cleanly, alcohol **7.** The latter, after a sequence consisting of (i) ozonolysis, (ii) olefination with methyl (triphenylphosphoranylidene)acetate and (iii) oxidation with PCC[7] afforded the keto ester **8**. The setting to test the crucial model reaction was at hand.



3 **4** **5** **6** **7** **8**

In the event, reaction of the keto enoate with the "ate" species generated from the reaction of trimethylaluminum with lithium thiophenoxide produced a high yield of **9** as a single diastereomer. ^{1}H NMR analysis revealed the methoxy, thiophenoxy and carbomethoxy groups, as well as the junction proton, to be equatorial (to the 6-membered ring). The stereochemistry is thus defined as shown. Oxidative de- sulfenylation afforded a high yield of **2b**.



Thus, a Nozaki like reaction has been used to fashion model system **2b**.[8] This chemistry, with some variation, has been successfully adapted to more elaborate systems shown under **1a** and more relevant products of the type **2a** have been obtained. Indeed this chemistry is a central element of our fully synthetic route to the avermectin family.

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