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Synthesis of Analogue Structures of the *p*-Quinone Methide Moiety of Kendomycin

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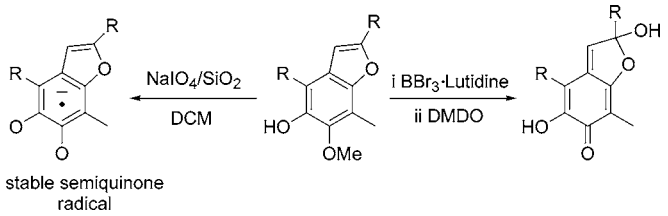
ABSTRACT



The synthesis of two model *p*-quinone methide ring systems of the antibiotic and antiosteoporotic compound kendomycin is reported. Two approaches were examined in detail, and the two-step (i) demethylation and (ii) DMDO oxidation were found to be reliable and generally applicable. Additionally, it was found that oxidation of a benzofuran by $NaIO_4$ on silica produced a long-lived semiquinone radical.

Kendomycin [(−)-TAN 2162] **1**, a novel ansamycin compound isolated from several different *Streptomyces* species, has been shown to be a potent endothelin receptor antagonist and an antiosteoporotic compound with remarkable antibacterial and cytostatic activity.[1] The challenging structure and diverse pharmacological profile of kendomycin has motivated us and other groups to carry out studies toward its synthesis.[2]

The most intriguing feature of kendomycin is the unique and structurally interesting *p*-quinone methide chromophore. As well as being the source of the yellow color of the natural product, it is thought that the highly electrophilic C16 of the quinone methide is crucial for its pharmacological activity.[1d] As part of our ongoing studies toward the synthesis of this challenging natural product, we recently carried out some model work on the construction of this previously unknown quinone methide.

The most common approach for the synthesis of *p*-quinone methides, as developed by Trammel for the synthesis of puupehenone,[3] involves the oxidation of a catechol to an *o*-quinone followed by tautomerization. Initial experiments confirmed our expectations that these and other literature conditions[4] would be unsuitable for the synthesis of the quinone methide moiety found in **1**, mainly because of complications arising from the presence of the hemiketal. It was therefore essential to develop a new strategy specifically designed for our purposes.

As a result of the chemical sensitivity of the quinone methide in **1**, we planned to introduce it late in the total synthesis, perhaps by oxidation of a suitably functionalized benzofuran **2** (Scheme 1). The benzofuran moiety is ideally

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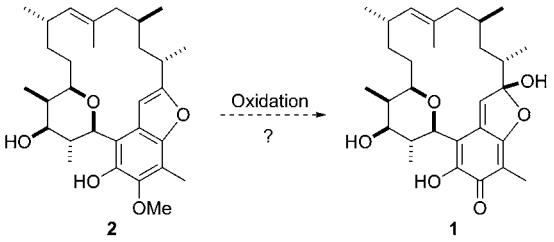
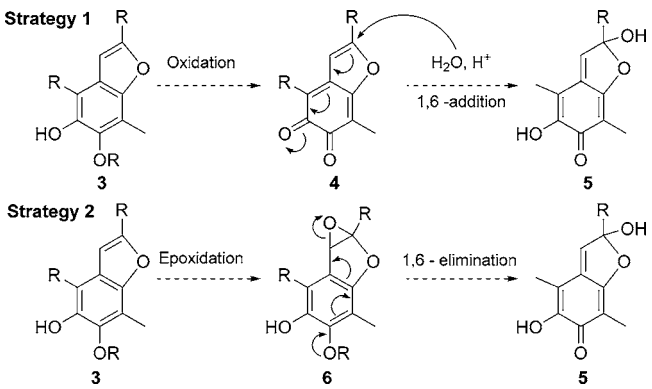
Scheme 1. Benzofuran Oxidation as Last Step in the Synthesis of Kendomycin



suited as a quinone methide precursor because it can be introduced early in our current route to the natural product and should be able to withstand the rest of the synthetic sequence with little requirement for protecting group chemistry.

At the outset of this work, we considered two alternative strategies for the required oxidation (Scheme 2). First, we

Scheme 2. Oxidation Strategies



planned to oxidize an arene such as **3** to an *o*-quinone **4** and have the latter undergo a 1,6-addition of water to give the quinone methide **5**. Alternatively, we proposed that in a Rubottom-type oxidation[5] epoxidation of the furan double bond could be followed by 1,6-elimination to give the quinone methide.

To examine these two approaches in detail we decided to carry out a study using two relatively simple model substrates **7** and **8**. In both cases, the catechol was monomethylated, because this protecting group is used in our current approach to the synthesis of kendomycin.

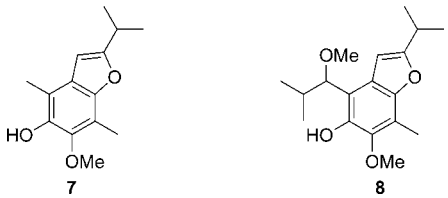
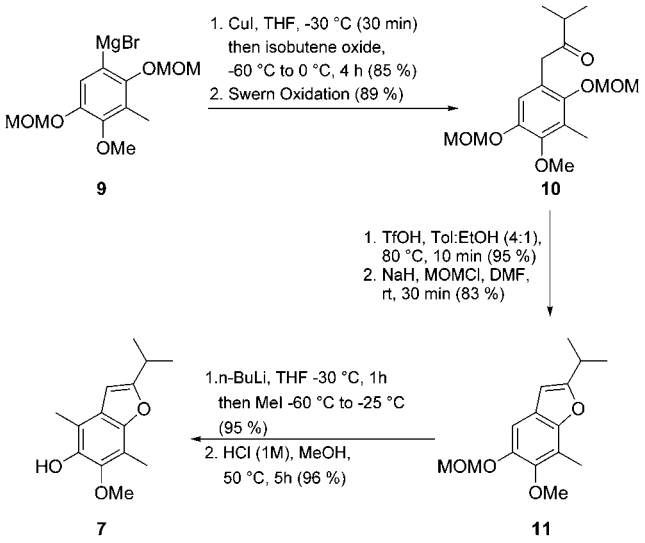


Figure 1. Substrates chosen for model study.

Our model study began with the synthesis of substrate **7** from known aryl Grignard **9**.[2c] Reaction with isobutene oxide in the presence of copper iodide gave ketone **10** after Swern oxidation. Acid-catalyzed MOM deprotection and benzofuran formation of **10** was followed by reprotection of the phenolic OH to give **11**. *ortho*-Lithiation of **11** and reaction with methyl iodide then gave **7** after MOM deprotection (Scheme 3).

Scheme 3. Synthesis of Benzofuranes



Various conditions for the direct oxidation of **7** to the corresponding *o*-quinone **13** were studied. Unfortunately, our initial efforts to apply several known procedures for the oxidation of monoquinol ethers and monocatechol ethers to quinones, including CAN,[6] DDQ,[7] AgO,[8] and $NaIO_4$,[9] resulted in complex mixtures of products. Upon further examination of the literature we found a report that sodium periodate adsorbed onto silica could be used for the oxidation of quinols and catechols to quinones.[10] Application of these conditions to the oxidation of **7** resulted in conversion of the starting material to a strongly blue colored compound. Although we were unable to purify this compound, ^{1}H NMR analysis of the crude material showed that the phenolic OMe had been removed and that the signal for the furan proton had shifted from 6.3 to 5.8 ppm. This initially led us to believe that we had produced the desired *o*-quinone; however, this did not explain the strong blue color observed. We realized at this point that we might have in fact produced a stable semiquinone radical **12** resulting from single-electron oxidation with $NaIO_4$. Evidence for this hypothesis came from the EPR spectrum, which clearly showed the presence of a radical (Figure 2).

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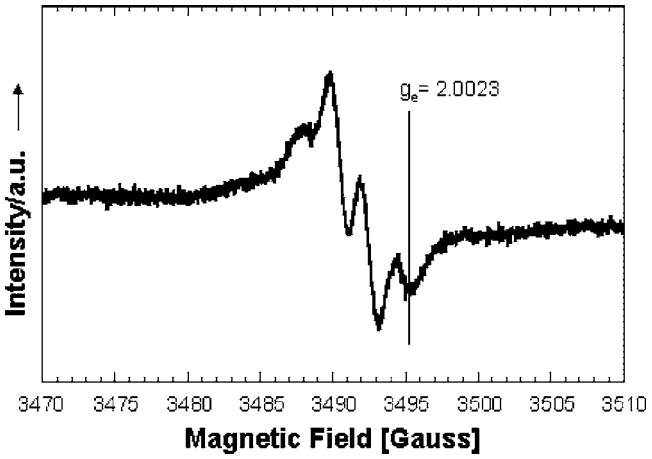
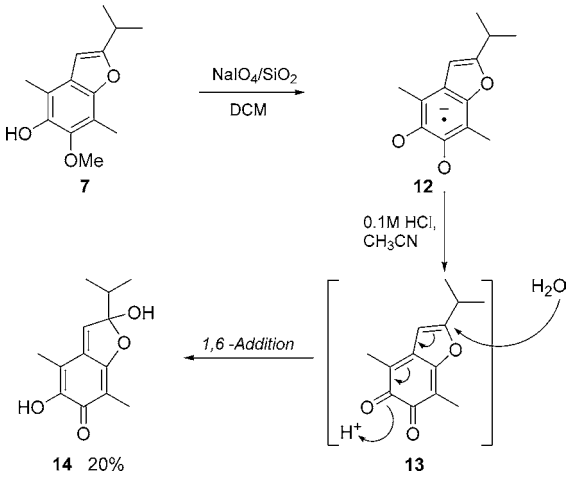


Figure 2. EPR spectrum of semiquinone radical **12**.

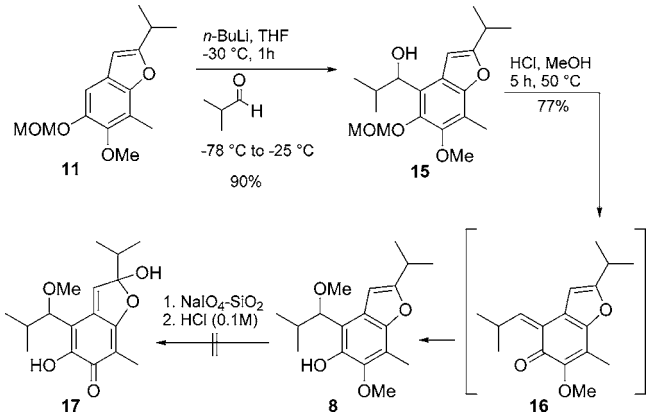
We found that the redox potential of semiquinone radical is dependent on pH, as on treatment of an acetonitrile solution of the radical species with aqueous 0.1 N HCl we observed a rapid color change from blue to yellow. After workup we were able to isolate the quinone methide **14** in a moderate 20% yield. Presumably, formation of the *o*-quinone **13** occurs through either auto-oxidation or disproportionation of the semiquinone radical, followed by acid-catalyzed 1,6-addition of water to the quinone to give the *p*-quinone methide **14** (Scheme 4).

Scheme 4. Quinone Methide Formation via *o*-Quinone



Having fortuitously achieved a first synthesis of the desired quinone methide, we then sought to apply these conditions to the slightly more complex model substrate **8**. We were able to access the model system using conditions similar to those before. In this case though, MOM deprotection with aqueous HCl in the presence of methanol was accompanied by exchange of the benzylic alcohol with OMe via the intermediate *ortho*-quinone methide **16** (Scheme 5). Upon

Scheme 5. Synthesis of Benzofuran **8**

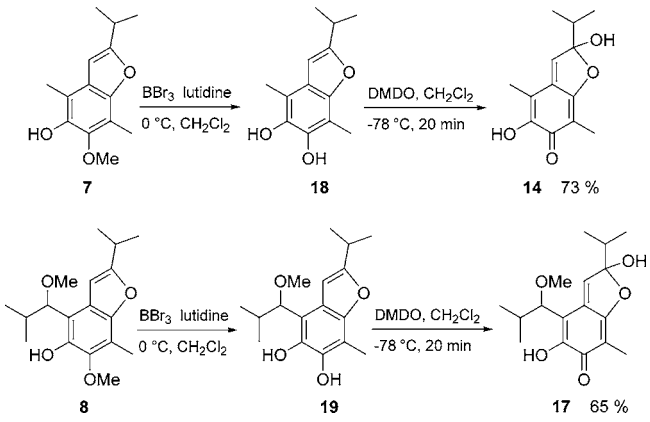


treatment with this model substrate with $NaIO_4$ on SiO_2 a blue color was once again observed, although it was apparent from ^{1}H NMR spectroscopy that a complex mixture of products had been produced. Attempted acid-catalyzed oxidation and hydrolysis, as used previously, resulted in loss of the blue color, but no *p*-quinone methide **17** could be identified.

Given the low yield for the formation of **14** and the unsuccessful conversion of **8** to quinone methide **17**, we continued to seek a general procedure for the required benzofuran oxidation. As stated earlier, we believed that it would be possible to functionalize the furan double bond of the benzofuran by epoxidation. This would be followed by rearrangement to give the quinone methide. There was some precedent for this transformation in the literature in which Adam et al.[11] converted a range of benzofurans into their corresponding epoxides by treatment with dimethyldioxirane (DMDO) at −78 °C. The resulting strained epoxides were found to be unstable and rapidly decomposed above −20 °C.

Preliminary experiments in which our monomethylated model substrates **7** and **8** were treated with DMDO[12] or *m*-CPBA at various temperatures resulted only in the

Scheme 6. Quinone Methide Formation by Rubottom Oxidation



decomposition of starting material. We then sought to remove the OMe protecting group, which we believed was preventing the necessary rearrangement reaction. After numerous experiments we found that the demethylation of both of these substrates could be carried out cleanly by treatment with a 1:1 mixture of boron tribromide and 2,6-lutidine in CH_2Cl_2 at 0 °C for 10 h (Scheme 6).[13] The resulting catechols **18** and **19** were quite unstable with respect to column chromatography on silica and were therefore used in crude form for the next reaction. To our delight, treatment of **18** and **19** with DMDO at −78 °C for 20 min resulted in the expected epoxidation and spontaneous rearrangement reactions to give the yellow colored kendomycin-like *p*-quinone methides **14** and **17** in good yields over two steps.

In summary, we have developed a novel and reliable two-step procedure for the synthesis of *p*-quinone methide ring systems similar to that found in kendomycin. We are now examining its application to the total synthesis of kendomycin and these results will be published in due course.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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