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A new synthetic route to 10β-alkyldeoxoartemisinins

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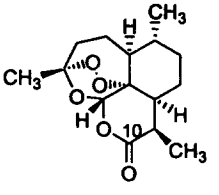
Abstract

Artemisinin was reduced with DIBAL and acetylated to yield 10α-acetoxyartemisinin. The latter compound was treated with titanium tetrachloride and a series of trimethylsiloxyl enol ethers to produce a series of 10β-alkyldeoxoartemisinins. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: artemisinin; lactol acetate; trimethyloxy group; titanium tetrachloride.

Artemisinin **1**, is an important lead compound in the search for new antimalarial drugs to treat drug-resistant strains found in South East Asia, Africa, India, etc.[1] A recent report found that non acetal-type analogs of artemisinin, e.g. 10-deoxoartemisinins, are 15–22 times more stable than acetal type prodrugs of artemisinin in simulated stomach acid.[2] Use of 10-alkyldeoxoartemisinins as oral drugs would greatly facilitate their utilization in combination with older antimalarials, the currently favored approach in treating drug-resistant strains of malaria.[1] We had prepared 10β-allyldeoxoartemisinin **2**, and derivatives from dihydroartemisinin **3**, and shown that the in vitro activity of 10β-propyldeoxoartemisinin was four to five times greater than that of artemisinin against drug resistant clones of *Plasmodium falciparum*.[3] It was also approximately four times more active than artemisinin in vivo in mice infected with *Plasmodium berghei*. These observations and the potential value of these compounds as oral drugs, rekindled our interest in developing a more general synthesis of 10-alkyldeoxoartemisinins.[3] We report here a new, short and efficient synthetic route to 10-substituted deoxoartemisinins.



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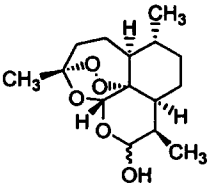

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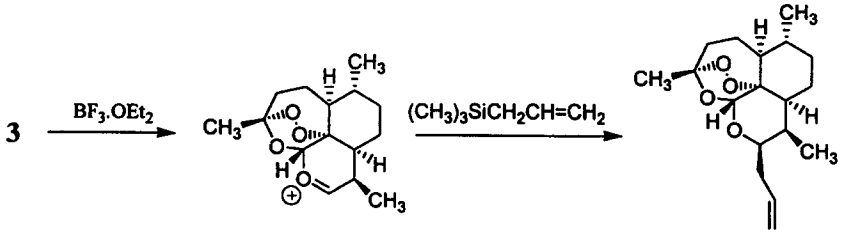
The first preparations of 10-deoxoartemisinins (Jung et al.[4] and Haynes et al.[5]) employed artemisinic acid as the starting material. However, the scarcity of artemisinic acid, the low overall yield for their reaction sequences and the fact that mixtures of the 10α- and 10β- isomers were frequently produced, indicated the need for another approach. Posner et al.[6] prepared a series of 10α- and 10β- carbocyclic and heterocyclic deoxoartemisinins via an intermediate, 10β-fluoroartemisinin, the compounds were orally active. We elected to employ **3** as our starting material for the preparation of 10β-allyldeoxoartemisinin **2**, shown in Scheme 1.[2] The allyl group was converted into other moieties.



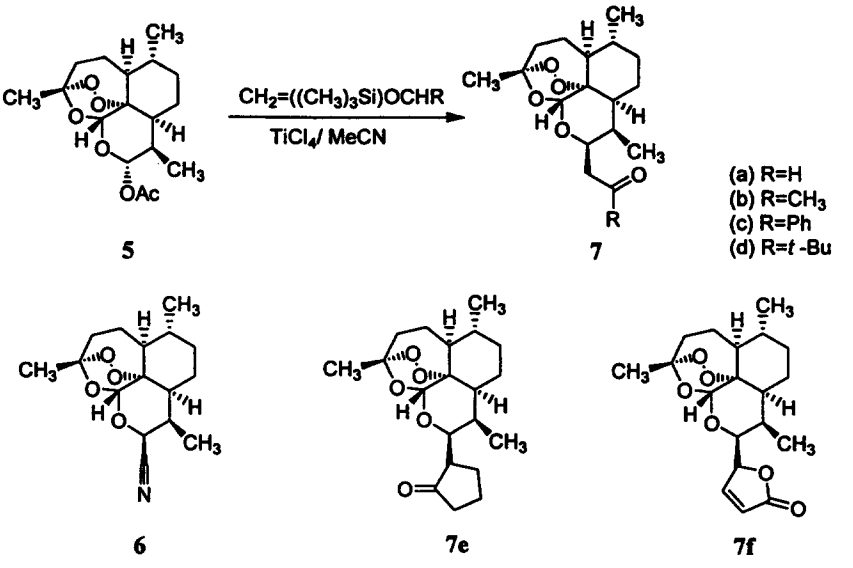
Scheme 1.

In searching for a new general approach, we considered potential reactions of the oxonium intermediate **4**, in our earlier synthesis of 10β-allyldeoxoartemisinin. To investigate the possibility of a reaction via an oxonium intermediate we reacted dihydroartemisinin with trimethylsilyl cyanide, boron trifluoride etherate but were unable to isolate any 10-cyanodeoxoartemisinin. Dahanukar and Rychnovsky[7] have used lactol acetates for the preparation of C-glycosides. In their synthesis[7] several α-cyanoethers were prepared from the corresponding hemiacetal acetates. The stereochemistry of one of their products was consistent with a reaction mechanism that proceeded by axial addition of the nucleophile to a cyclic oxonium ion. An oxonium intermediate **4**, had been invoked in our earlier preparation of **2**. We therefore prepared 10α-acetoxyartemisinin **5**, and reacted it with titanium tetrachloride and trimethylsilyl cyanide as shown in Scheme 2.[8] The desired 10-cyanodeoxoartemisinin **6**, was isolated in 60% yield. When **3** was employed in the reaction instead of the corresponding acetate, the cyano derivative was not formed, consistent with Dahanukar and Rychnovsky's[7] reasoning that a better leaving group was required to generate the oxonium salt. We also prepared 10β-acetoxyartemisinin and demonstrated that it was also converted into **6**, in approximately the same yield, as was 10α-acetoxydeoxoartemisinin, under the same reaction conditions. The data is consistent with formation of a common oxonium ion from the isomeric acetates, which reacts with trimethyl silyl cyanide to form **6**.

The successful conversion of **5** into a cyano derivative prompted us to examine its reactivity with several trimethylsiloxyl olefins. The reaction yielded a series of 10β-alkyldeoxoartemisinins in 60–70% yield shown in Scheme 2.[9] Each of the trimethylsiloxyl olefins had an exomethylene and thus the only asymmetric center formed in the reaction occurs at C-10. In each of the products, addition occurred from the β-face of the oxonium salt. In addition to acyclic olefins we also examined the products obtained from trimethylsiloxyl groups of cyclic olefins. The reaction of trimethylsiloxyl cyclopentene with **5** yielded a single product **7e**. However, mixtures were obtained from trimethylsiloxyl cyclohexene and **5**. We were unable to separate the latter products or to assign their stereochemistry.

To determine whether reaction occurs on a carbon adjacent to the trimethylsiloxyl group or on the terminal carbon in a conjugated system, we examined the reaction of **5** with 2-(trimethylsiloxyl)furan. A single product was formed whose structure we tentatively assigned as **7f** by NMR.

The above syntheses complement the earlier preparations of 10-alkyl or aryl deoxoartemisinins and thus makes it possible to synthesize a wider variety of potential drugs. Our syntheses provide



Scheme 2.

derivatives containing functionalized substituents, employable as intermediates in the preparation of other derivatives. The antimalarial activities of the above compounds are currently under study. Their in vivo activities and bioavailabilities will also be determined.

Acknowledgements

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8. Procedure for generation of **6** from **5**. To a solution of **5** (220 mg, 0.67 mmol) in acetonitrile was added trimethylsilyl cyanide (200 mg, 2 mmol) followed by the solution of titanium chloride in CH_2Cl_2 (1.3 ml, 1.3 mmol) at –40°C under N2. The reaction mixture was stirred for 3 h, then 10% HCl was added. The solution was extracted with CH_2Cl_2, the organic phase was washed with water and saturated $NaHCO_3$ solution, dried and evaporated. The residue was purified by chromatography on silica gel to give 150 mg white solid in 76% yield.
9. All new compounds gave satisfactory $^{13}C/^{1}H$ NMR spectra, mass spectra and microanalysis or high solution mass spectra.