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Acid Catalyzed Michael Additions to Artemisitene

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Abstract—A series of 14-substituted-artemisinin and 9-epiartemisinin derivatives was prepared by a titanium-tetrachloride catalyzed addition of trimethylsilyl enol ethers to artemisitene. Several compounds were four to seven times more active than artemisinin against *Plasmodium falciparum*. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Malaria continues to be one of the most prevalent and deadly parasitic diseases, infecting some 400 million people and is responsible for 3–4 million deaths each year.[1] The appearance of drug-resistant strains of *Plasmodium falciparum* and the increased cost of new drugs to treat this disease threaten to produce large increases in the number of deaths. Artemisinin (**1a**), is a promising lead compound in the search for new drugs; a great deal of work in the last 20 years has been devoted to increasing its availability and activity, and improving its physical properties (e.g., solubility in oil or water). Avery et al.[2] reported that modification of the group on C-9 increased the activity of derivatives as much as 12-fold and converting the carbonyl of the lactone into a methylene group produced compounds that were 60 times more active than artemisinin. These latter syntheses proceeded from artemisinic acid by alkylation at C-14 and reduction of the lactone to produce a substituted deoxoartemisinin. We wish to describe a new synthesis of C-14 modified artemisinin derivatives from artemisitene and their antimalarial activities.

Avery was able to increase the yields of these compounds by starting with an ester of artemisinic acid.[3] Although significant quantities of artemisinic acid are present in *Artemisia annua*[4] we thought that artemisitene (**2**), which is also present in *A. annua* and has been prepared from artemisinin, was an attractive starting material. Acton et al.[4] isolated artemisitene from impure samples of artemisinin; they established its structure and first attempted to synthesize **2** from **1a**. Later El-Feraly[5] was successful in preparing artemisitene from artemisinin. Thus, large quantities of **2** although not available directly from *A. annua* can be prepared from **1a**.

We had isolated several hundred mg of artemisitene in the course of purifying extracts of *A. annua*.[6] Since one of our objectives was formation of new carbon–carbon bonds with the methylene group, we investigated the use of titanium tetrachloride catalyzed additions of trimethylsilyl enol ethers to artemisitene after Mukaiyama et al.[7] employed a similar reaction sequence with aldehydes and ketones. Baba et al.[8] showed that acyclic α,β-unsaturated esters could also be alkylated in this manner.

The substituents at C-14 in the derivatives prepared by Avery et al.[2] were alkyl or aryl groups. To increase the synthetic utility of the substituents, we chose a route employing the reaction of **2** with a series of silyl enol ethers catalyzed by titanium tetrachloride (Scheme 1). The products thus possessed a carbonyl moiety that in principle could be further modified. Since artemisitene contains a 1,2,4-trioxane as well as an α, β-unsaturated lactone, the report by El-Feraly et al.[9] that the 1,2,4-trioxane in dihydroartemisitene undergoes a rearrangement in the presence of a weak acid raised some question whether the reaction would produce the products we desired. Furthermore, the stereochemistry of the product was uncertain since the group adding to the exocyclic methylene group can become a α or β substituent at C-9.

The reaction between the trimethylsilyl enol ether of methyl *t*-butyl ketone, titanium tetrachloride, and

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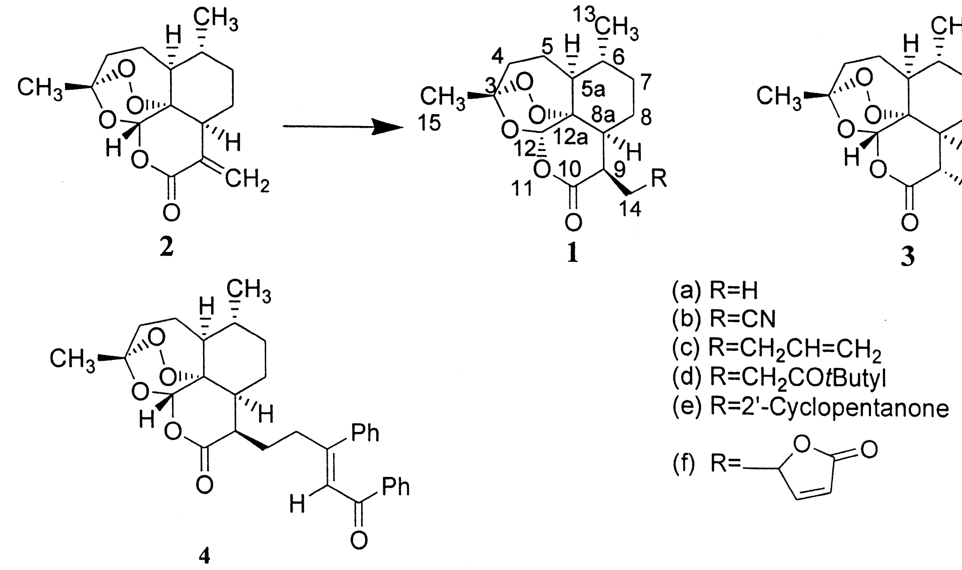

Scheme 1.

artemesitene (Scheme 1) produced a (2:1) mixture of **1d** and **3d**, which were separated by flash chromatography on silica gel. The structures were tentatively assigned from an analysis of their ^{1}H and ^{13}C NMR spectra. Compounds in which H-9 appears at δ 3.0 or at lower field have been assigned as possessing an α-substituent. Several compounds in which the chemical shift of H-9 occurs at higher field overlapping other signals have been assigned the β configuration. Since the reaction yielded the desired products, the reaction of the trimethylsilyl enol ether of acetone with artemisitene, under the same reaction conditions, was examined. The products were again a mixture of artemisinin and epiartemisinin adducts. If the chemical shift of H-9 can be assigned it is given in Table 1. The reaction of the trimethylsilyl enol ether of acetophenone with artemisitene produced **4**, which had formed from consecutive aldol reactions (i.e., two equivalents of the trimethylsilyl enol ether with **2**). Attempts to stop the reaction after one equivalent of the trimethylsilyl enol ether had reacted with **2** were unsuccessful.

We next turned our attention to the reaction of trimethylsilyl ethers of compounds where the reaction product could possess a new asymmetric center in addition to the α and β epimers at C-9 described above. Because the antimalarial activity observed with the resulting mixtures of diastereomers was not high, the diastereomers were not separated. The products of these reactions are given in Scheme 1 along with their activities.

Table 1. Relative antimalarial activities against two *Plasmodium falciparum* clones

Compound	δ (H-9) ppm	Relative activity[a]	
		D-6	W-2
1b and **3b**		0.17	0.036
1c	3.2	2.3	2.9
1d	3.1	7.4	1.13
3d	2.1	4.5	0.74
1e		0.47	0.29
1f		0.058	0.03
3f		0.33	0.037
4		6.2	0.55

[a]Relative activity = IC_{50} artemisinin/IC_{50} analogue.

In addition to trimethylsilyl enol ethers, the reaction of two trimethylsilyl derivatives with artemisitene were also examined. A 14-cyano adduct (**1b** and **3b**) was prepared in 52% yield from the reaction of trimethyl-silyl cyanide, titanium tetrachloride and artemisitene. The reaction of allyltrimethyl silane with artemisitene yielded a mixture of **1c** and **3c**. The compounds were separated and the activity of **1c** was determined. Thus a broad array of artemisitene adducts can be prepared employing this methodology.

All compounds reported here were purified by chromatography on silica gel and were homogeneous by TLC in two or more solvent systems. Their ^{1}H and ^{13}C spectra did not contain resonances that could be attributed to starting material or isomeric products. CI-MS of the products did not contain peaks that suggested the presence of impurities.

In vitro antimalarial activities of the compounds were determined by a semi-automated microdilution technique.[10] The results are given in Table 1. Several compounds are four to seven times more active than artemisinin.

In summary, these results demonstrate that the chemistry developed by Mukaiyama and others can be employed to form carbon–carbon bonds at the terminus of the α,β-unsaturated lactone in artemisitene without destroying the peroxide grouping essential for antimalarial activity in these compounds. Posner et al.[11] have described other examples of the stability of the peroxide grouping to a variety of reagents. These results confirm earlier findings by Avery et al. that substitution on C-14 in **1a** increases antimalarial activity several folds.

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