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Copper(I) Catalyzed Conjugate Addition of Grignard Reagents to Acrylic Acids: Homologation of Artemisinic Acid and Subsequent Conversion to 9-Substituted Artemisinin Analogs

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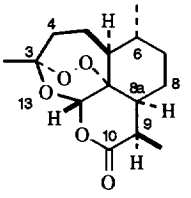
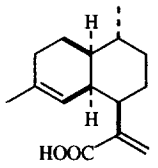
Abstract: A new route to novel 9-substituted-10-deoxoartemisinin analogs (**13, 14**) was developed employing photoxygenation of homologated derivatives of artemisinic acid (**9, 10**). Conjugate addition to the acrylate moiety of artemisinic acid **2** was made possible by *in situ* protection as a silyl ester, Cu(I)-catalyzed 1,4-addition of RMgX, and deprotection.

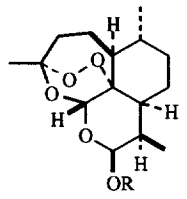
The naturally occurring endoperoxide sesquiterpene (+)-Artemisinin **1**, first isolated in 1972 from *Artemisia annua* L.,[1,2] has been the subject of considerable interest due to its potent *in vitro* activity and novel mechanism of action against drug resistant strains of *Plasmodium falciparum*. Various aspects of this promising antimalarial undergoing intense study include its synthesis, structure-activity relationships, metabolism, biotransformation, mode of action, pharmacokinetics and toxicity.[3-8]



1 Artemisinin



2, Artemisinic Acid



3, R = Me, Artemether
4, R = Et, Arteether
5, R = H, Dihydroartemisinin

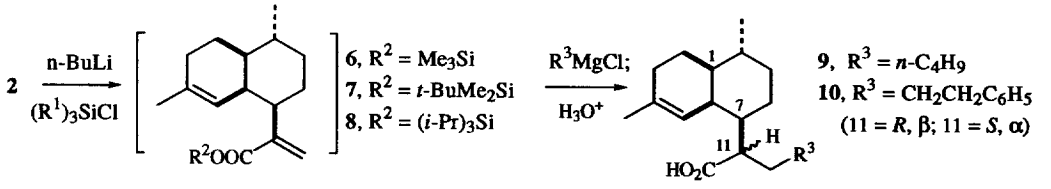
The Chinese Cooperative Research Group reported a high therapeutic index of 4987 for artemisinin when administered intramuscularly (LD_{50} = 3840 mg/kg) leading to the impression that artemisinin analogs could be considered nontoxic.[9] More recently however, it has been shown that artemether **3** and arteether **4** can cause fatal neurotoxicity in animals.[10,11] Since these drugs are rapidly and extensively metabolized, it was believed that a metabolite(s) was the culprit, at least in part, for the toxicity problems.[11] A major metabolite of 10-ether derivatives of artemisinin that was found to be highly neurotoxic both *in vivo* and *in vitro* is dihydroartemisinin **5**.[12] While the endoperoxide grouping appears to be a minimal requirement for this neurotoxicity *in vitro*, other structural features play an important role in this toxicity.[13]

The need for an efficient route to highly potent, yet nontoxic artemisinin analogs lead us to consider the feasibility of producing 9-alkyl-10-deoxo analogs of artemisinin, reported to be highly potent antimalarials lacking the neurotoxic 10-lactol moiety.[14] Artemisinic acid **2** seemed well suited towards this end as: 1) it is a high yielding (2.6% dry weight) natural product from *Artemisia annua L.;* 2) it can be converted to artemisinin

semi-synthetically by singlet oxygenation/acidification;[5] and 3) derivatization of the carboxyl group of **2** has led to the production of 10-substituted artemisinin analogs.[15] Thus, if an efficient method for conjugate addition to the unsaturated carboxylic acid moiety of **2** could be developed, it seemed likely that facile entry to potent 9-alkyl-10-deoxo analogs of artemisinin could be realized.

Traditionally, conjugate addition to α,β-unsaturated carboxylic acids has required three steps: protection, 1,4-addition and deprotection.[16-17] The alternative approach of conducting the conjugate addition on the free acid (carboxylate salt) results in low yields.[18-19] We have developed a novel one-pot conjugate addition to an α,β-unsaturated carboxylic acid that involves both *in situ* protection and deprotection. With this new methodology, the conversion can be accomplished in one flask in good to excellent yields. Artemisinic acid **2** was deprotonated with *n*-butyllithium and the silyl ester[20-23] was formed upon the addition of a trialkylsilyl chloride at 0°C. Upon addition of 10 mole % of copper(I) iodide, a Grignard reagent could then be added to furnish 1,4-addition products (Scheme I).

Scheme I



The effect of a Lewis acid accelerant was examined in certain cases by addition of trimethylsilyl chloride (or triflate in one case) prior to addition of copper iodide as shown in Table 1.[24-26]

Table 1. Cu(I) Catalyzed Addition of Grignards to Transiently Silylated Vinyl Acids.[27]

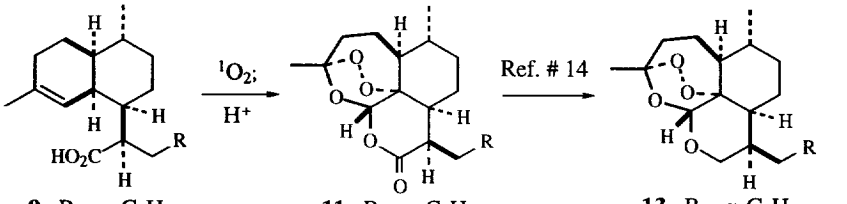
Silyl Ester	RMgBr	Accelerant	Product Ratio (11-*R*/*S*)	HPLC Yield	Isolated Yield
Me_3Si	*n*-C_4H_9	----	1.0	25	----
(*i*-Pr)$_3$Si	*n*-C_4H_9	----	1.8	8	----
t-BuMe_2Si	*n*-C_4H_9	----	1.8	33	----
Me_3Si	*n*-C_4H_9	Me_3SiOTf	1.7	82	----
Me_3Si	*n*-C_4H_9	Me_3SiCl	1.9	66	88
(*i*-Pr)$_3$Si	*n*-C_4H_9	Me_3SiCl	2.55	79	----
t-BuMe_2Si	*n*-C_4H_9	Me_3SiCl	2.0	100	----
Me_3Si	$C_6H_5CH_2CH_2$	----	13.0	66	----
(*i*-Pr)$_3$Si	$C_6H_5CH_2CH_2$	----	9.4	20	----
t-BuMe_2Si	$C_6H_5CH_2CH_2$	----	11.2	12	----
Me_3Si	$C_6H_5CH_2CH_2$	Me_3SiCl	β only	68	68
(*i*-Pr)$_3$Si	$C_6H_5CH_2CH_2$	Me_3SiCl	5.1	16	----
t-BuMe_2Si	$C_6H_5CH_2CH_2$	Me_3SiCl	3.6	16	----

The catalytic cuprate reaction was monitored by TLC, quenched cold with 10 equivalents of glacial acetic acid and was warmed to ambient temperature and stirred overnight. Acidification insured complete removal of the more hindered silyl esters (such as TIPS) leaving the free acid. The accelerant dramatically improved the yields in the conjugate addition of butyl but had little effect on the yield of the phenethyl Grignard. From the standpoint of artemisinin structure-activity relationships, the β-isomer (11 position = *R*) was desired since later

oxidative conversion to artemisinin analogs would result in more potent, 9β-substituted products. The larger the silyl group the higher the β/α ratio (or the 11-*R/S* ratio) in the butyl adduct **9** while added accelerant gave a slight improvement over the reactions without accelerant. In the phenethyl case, the accelerant actually decreased the β/α ratio. As a control experiment, simple quench of the reactions without acid treatment led to the same product ratios, clearly demonstrating that product ratios were not a spurious artifact of the acidification step.

Singlet oxygenation of pentyl acid **9** and phenylpropyl acid **10** followed by acid treatment with Amberlyst-15 gave 9β-pentyl artemisinin **11** in 40% yield and 9β-propylphenyl artemisinin **12** in a 38% yield (Scheme II). Conversion to their 10-deoxo counterparts has recently been reported.[14] Starting from artemisinic acid **2**, 10-deoxo-9β-pentyl artemisinin **13** can be synthesized in 33% overall yield; compared to less than 4% when prepared by total synthesis.[8,28]

Scheme II



9, R = *n*-C_4H_9
10, R = $(CH_2)_2C_6H_5$

11, R = *n*-C_4H_9
12, R = $(CH_2)_2C_6H_5$

13, R = *n*-C_4H_9
14, R = $(CH_2)_2C_6H_5$

Pyrans **13** and **14** demonstrate weak neurotoxicity relative to dihydroartemisinin **5** in preliminary *in vitro* bioassay, suggesting that metabolism to lactols does not occur *in vitro*. The results of neurotoxic bioassay will be reported separately.

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27. **General Procedure for 9 and 10**: Under anhydrous conditions, artemisinic acid **2** (250 mg, 1.07 mmol) dissolved in THF (5 mL) was cooled to 0°C and 2.5 M *n*-BuLi was added (450 μL or 1.12 mmol). After 15 min, trimethylsilyl chloride was added (145 μL or 1.12 mmol). After another 15 minutes, the solution was cooled to -78°C and additional trimethylsilyl chloride was added (270 μL or 2.14 mmol) followed succesively by CuI (30 mg or 0.16 mmol) and 2.0 M *n*-BuMgCl (600 μL or 1.18 mmol). Upon completion, cold glacial acetic acid (0.5 mL or 11 mmol) was added and the mixture was allowed to stir overnight at room temperature. After standard aqueous workup, each isomer (11-α or *S* and 11-β or *R*) of **9** and **10** were separated by reverse phase semipreparative HPLC and calibration curves were run for all four isomers on analytical reverse phase HPLC. The identity of each isomer was established by conversion to known artemisinin analogs **11** and **12**, where the alternate isomers were assumed to be the corresponding α-epimers (11-*S*).[28] Known quantities from each run of dried, crude reaction product were then analyzed by HPLC and the yield and isomer ratios were quantitated relative to controls. In two examples, isolated yields (silica gel flash chromatography, 20% EtOAc/hexane) were determined in order to validate the HPLC method (Table 1). All compounds displayed satisfactory spectral and analytical data.

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