An Efficient Method for the Synthesis of 10-Aminoartemisinin Derivative

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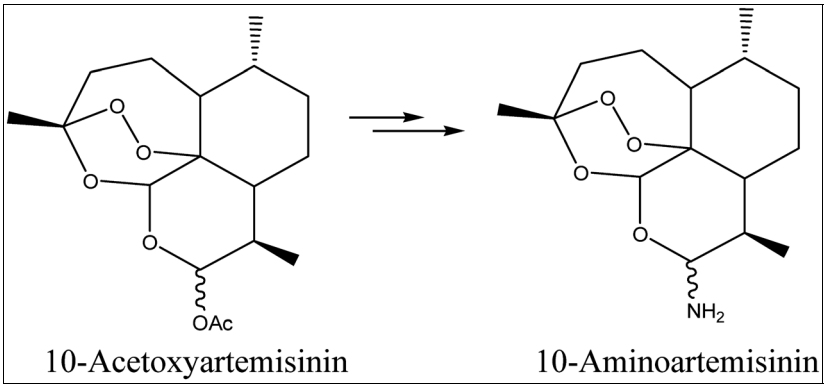

An efficient method for the synthesis of 10-aminoartemisinin derivative has been developed from 10-acetoxyartemisinin and acetonitrile catalyzed by trimethylsilyltrifluoromethanesulfonate in good yield.

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INTRODUCTION

Artemisinin **1** and its derivatives such as dihydroartemisinin **2**, arteether **3**–**4** (Fig. 1) show antimalarial activity [1]. The biological activity of artemisinin can be greatly increased by manipulating the artemisinin molecule [2]. The main disadvantage of artemisinin to use as antimalarial therapy is its low-solubility both in oil and water [3]. The amino group has been widely used in many pharmaceuticals [4]. 10-arylaminoartemisinins [5], artemisone [6], 11-azaartemisinin [7], 14-substituted artemisinin [8], and fluorinated artemisinin [9] have been found to have high antimalarial activity. 10-aminoartemisinin derivatives have greater stability than arteethers **3-4** at physiological pH [5c]. Apart from these, their solubility in oil and water is higher than the artemisinin **1** [5]. They are prepared from dihydroartemisinin (DHA) and arylamines by phase transfer method. Similarly, O-aminodihydroartemisinins have been prepared from DHA and its acetate catalyzed by TMS triflate [10]. Here we wish to report the synthesis of 10-aminoartemisinin derivative from 10-acetoxyartemisinin catalyzed by Lewis acids.

RESULTS AND DISCUSSION

In our recent work we have generated oxocarbenium ion and then trapped by nucleophiles such as arene [11]. Our initial attempt to generate oxocarbenium ion from DHA using $BF_3{\cdot}Et_2O$ and then trap by nucleophiles such as acetonitrile and arene failed (Scheme 1). Instead of desired product, anhydroartemisinin (AHA) and other side products were obtained. It is reported that oxocarbenium ion intermediate can be generated by the treatment of a simple Lewis acid catalyst, such as TMS triflate, and a suitable DHA derivative [12]. We envisioned that if the intermediate oxocarbenium ion undergo S_N1 reaction with acetonitrile and simultaneously hydrolyze, it would give desired product 10-acetamidoartemisinin. First, we performed the reaction of 10-acetoxyartemisinin [13] **5** with acetonitrile in the presence of $BF_3{\cdot}Et_2O$. The results are shown in Table 1. It was observed that although the formation of AHA is reduced the desired product 10-acetamidoartemisinin is not formed. Instead of formation of 10-acetamidoartemisinin its hydrolysis product 10-aminoartemisinin **6a/b** with a ratio of 1:2 and dehydroartemisinin **7** as a major by-product, were formed. The isomers were separated by preparative TLC using hexane/ethyl acetate (4:1) solvent system. The best result was obtained when 10 mol % of TMS triflate was used as Lewis acid (Table 1). The presence of the amino group at 10 position was confirmed by NMR and single crystal X-Ray crystallography (Fig. 2) [14]. This is in contrast to Ritter reaction where carbocation was trapped by acetonitrile to give acetamide [15]. This might be due to the presence of the oxygen at 11 position, which facilitate further hydrolysis of acetamide. It may be mentioned here that there is an equilibrium in solution between the two isomers (α and β) as evident from the fact that during NMR analysis the β-isomer, as time passes, gives NMR signals for both **6a** and **6b** (α and β) in ^1H and ^{13}C NMR. The proposed mechanism for the TMS triflate catalyzed amination reaction of 10-acetoxyartemisinin is shown in Scheme 2. The Lewis acid generates the oxocarbenium ion **8** from 10-acetoxyartemisinin **5**, which is trapped by acetonitrile to give intermediate **9**. Intermediate **9**, after

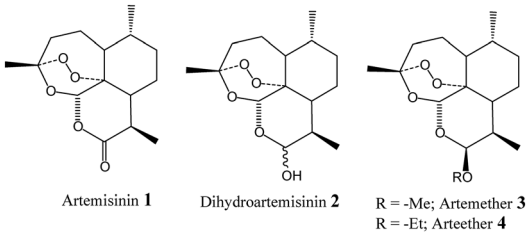


Figure 1. Artemisinin and its derivatives.

hydrolysis gives 10-acetamidoartemisinin **10**, which is again hydrolyzed by TMS triflate to give 10-aminoartemisinin **6a/b**. Unfortunately, we were unable to isolate the intermediate **10**.

The mechanism for epimerization is shown in Scheme 3. Here ring opening of 10-aminoartemisinin **6b** produces compound **12**, which is recyclized to give racemic product **6a/b**. This is similar to the ring opening reaction of DHA [5a].

CONCLUSIONS

In conclusion, 10-aminoartemisinin has been prepared from 10-acetoxyartemisinin with acetonitrile catalyzed by TMS triflate. The introduction of a hydrophilic side chain at the C-10 position should greatly improve the solubility of the artemisinin. Compound 10-aminoartemisinin showed much improved solubility in water as compared to DHA and arteethers.

EXPERIMENTAL

The substrates were prepared by literature procedure. All solvents were distilled before use. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian AS 400 (400 MHz) spectrometer using TMS as internal standard. Mass spectra were recorded on a Perkin Elmer Clarus 500. IR spectra were recorded on a Nicolet Impact 410 spectrometer. Elemental analysis was done on a Perkin Elmer Series II, 2400.

Reaction of 10-acetoxyartemisinin with acetonitrile in presence of BF_3·Et_2O. To a mixture of 10-acetoxyartemisinin (138 mg, 0.42 mmol) in 2 mL acetonitrile was added BF_3·Et_2O (72 mg, 0.51 mmol) at 0°C. The reaction mixture was stirred for 5 h during which temperature was brought to room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent (EA:Hexane: 1:4). After completion of the reaction the product was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by preparative TLC to give 10-aminoartemisinin **6a** (α, 18 mg, 15%), **6b** (β, 36 mg, 30%) (α:β = 1:2) and **7** (39 mg, 35%); **6b:** Solid, m.p. 116–118°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.4 Hz, 3 H, —CH_3), 0.97 (d, J = 6.8 Hz, 3 H, —CH_3), 1.20–1.40 (m, 1 H), 1.43 (s, 3 H, —CH_3), 1.47–1.67 (m, 2 H), 1.80–1.94 (m, 2 H), 2.00–2.10 (m, 2 H), 2.34–2.42 (m, 3 H), 2.62 (brs, 2 H, —NH_2), 2.73–2.74 (m, 2 H), 5.30 (m, 1 H, —CH—), 5.61 (s, 1 H, —CH—).^{13}C NMR (**6a/6b**) (100 MHz, $CDCl_3$): δ 12.94, 13.38, 20.45, 20.57, 22.31, 22.88, 24.75, 24.89 (2C), 26.13, 26.24, 29.89, 30.97, 34.38, 34.93, 36.45, 36.54, 37.54, 37.66, 44.51, 45.62, 51.71, 52.67, 80.63, 81.33, 87.96, 91.43, 94.88, 96.59, 104.33, 104.64. IR (neat): 3379, 2946, 2853, 1378, 1061, 1027, 986, 969, 659 cm^{-1}. HRMS (ES) *m/z* Cald for $C_{15}H_{25}NO_4$ (M^+) 283.1784, found 283.1785. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.62; H, 8.81; N, 4.98.

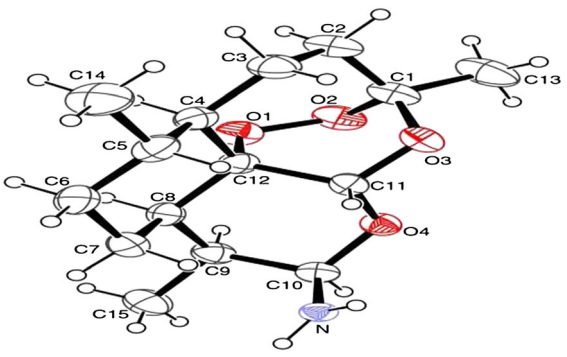


Figure 2. Ortep diagram of 10-aminoartemisinin. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 1. Reaction of dihydroartemisinin with BF_3.Et_2O.

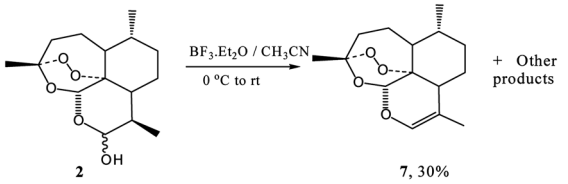
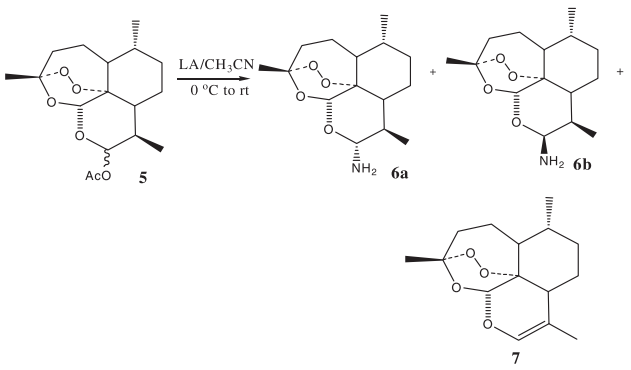


Table 1

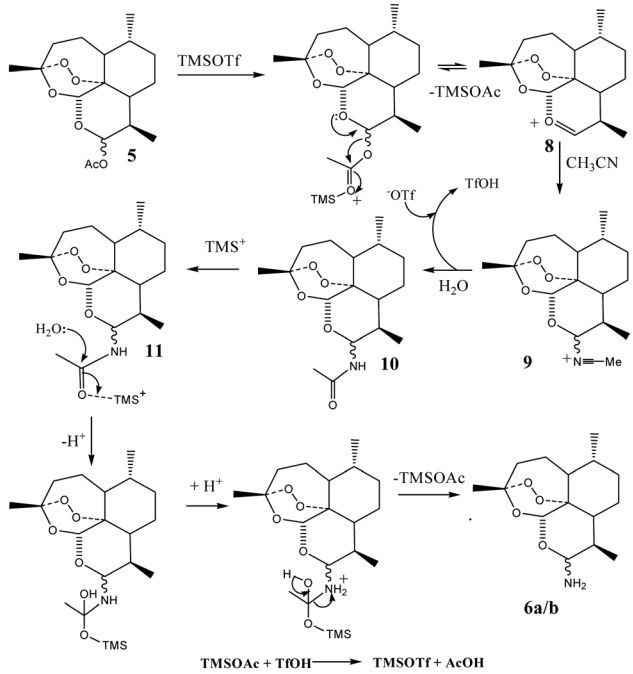
Synthesis of 10-aminoartemisinin.



Sl. no.	Lewis acid	Yield (%)[a] 6a	6b	7
1	BF_3.Et_2O (1 equiv.)	15	30	35
2	TMSOTf (10 mol %)	25	51	5

[a]Yield refers to isolated yield. Compounds are characterized by NMR, IR, and mass spectroscopy.

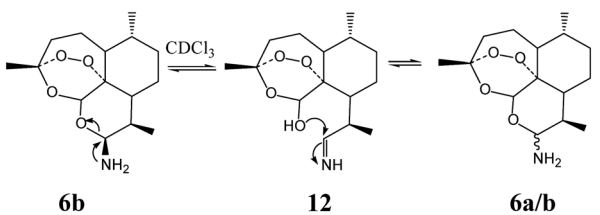
Scheme 2. Proposed mechanism of the reaction.



6a: Gum. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.8 Hz, 3 H, —CH_3), 0.97 (d, J = 6.8 Hz, 3 H, —CH_3), 1.20–1.40 (m, 1 H), 1.45 (s, 3 H, —CH_3), 1.47–1.67 (m, 1H), 1.71–1.83 (m, 2H), 1.85–1.98 (m, 2H), 2.00–2.10 (m, 2H), 2.25–2.41 (m, 3H), 2.56–2.66 (m, 1H), 3.35 (brs, 2H, —NH_2), 4.90 (m, 1H, —CH—), 5.51 (s, 1H, —CH—). IR (neat): 3375, 2924, 2852, 1456, 1377, 1093, 1024, 986, 969, 659 cm^{-1}. HRMS (ES) *m/z* Cald for $C_{15}H_{25}NO_4$ (M^+) 283.1784, found 283.1785. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.61; H, 8.83; N, 4.96.

Preparation of 10-aminoartemisinin using TMS triflate. To a mixture of 10-acetoxyartemisinin (200 mg, 0.62 mmol) in acetonitrile (2 mL) was added TMSOTf (14 mg, 0.06 mmol) at 0°C. The reaction mixture was stirred at same temperature for 1 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent (EA:Hexane; 1:4). After completion of the reaction the mixture was neutralized with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by preparative TLC to give 10-aminoartemisinin **6a** (44 mg, 25%), **6b** (90 mg, 51%), and **7** (8 mg, 5%).

Scheme 3. Proposed mechanism of epimerization.



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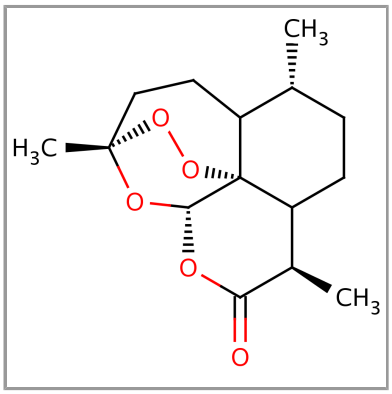

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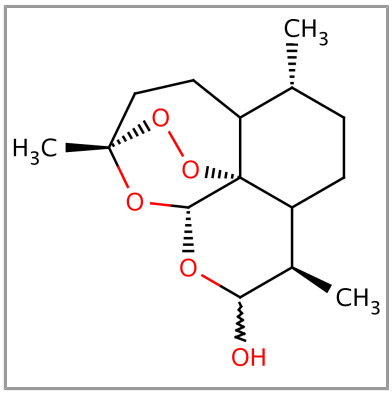

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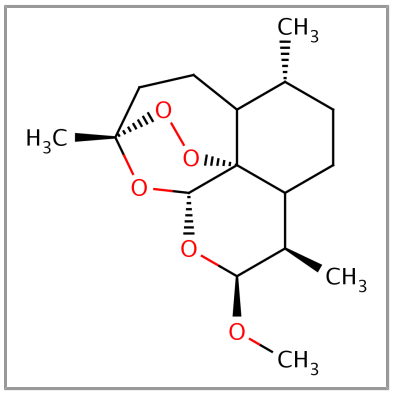

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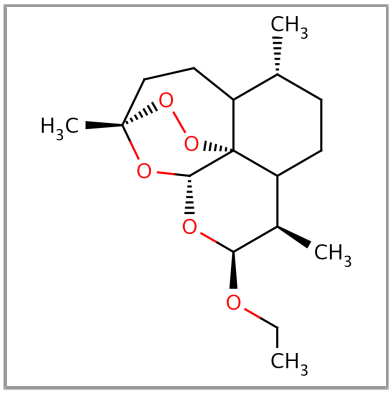

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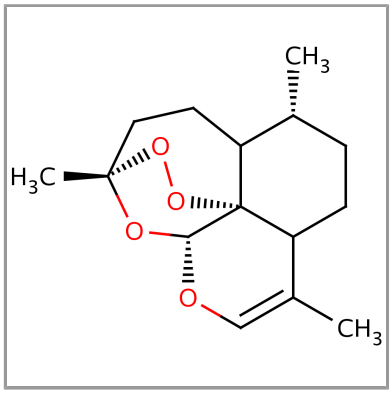

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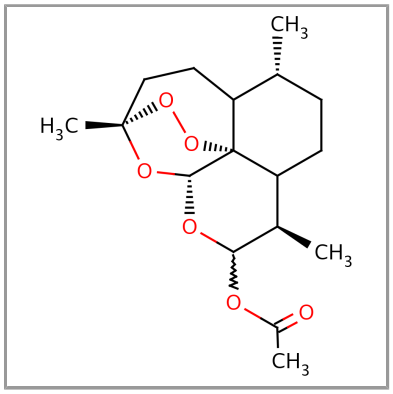

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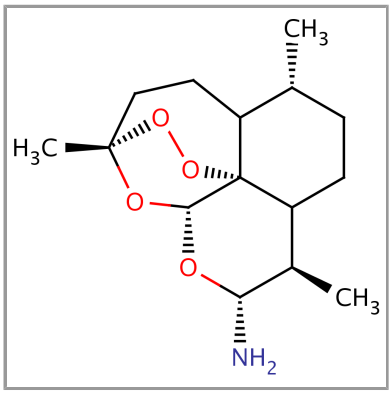
6a



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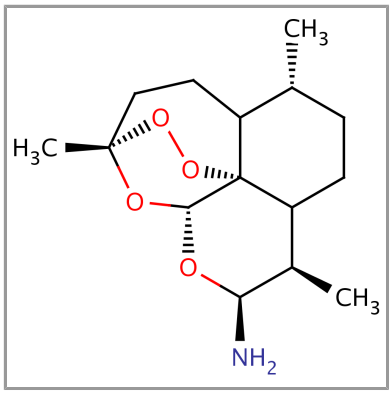
6b



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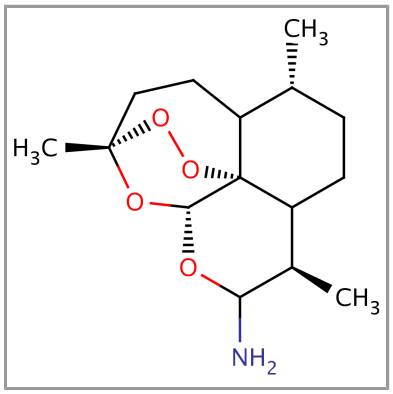
6a/b



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