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Synthesis of *O*-Aminodihydroartemisinin via TMS Triflate Catalyzed C−O Coupling Reaction

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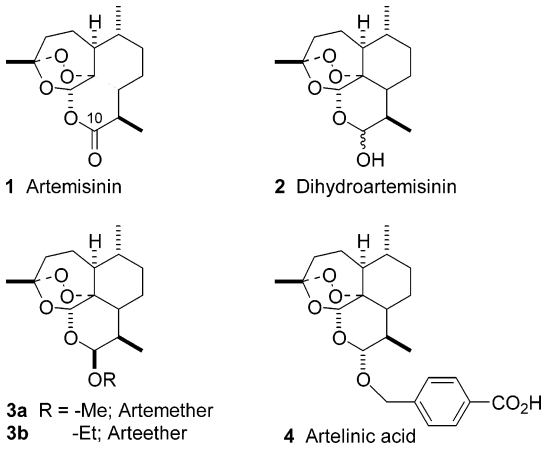
Received January 21, 2004

Abstract: *O*-Aminodihydroartemisinin was synthesized for the first time via TMS triflate catalyzed coupling reaction of *O*-acetylartemisinin. The reaction proceeds with high yield without losing the endoperoxide of the artemisinin backbone. The new coupling reaction was employed to prepare artemisinin *O*-glycosides with improved water solubility. *O*-Aminodihydroartemisinin reacts readily with benzaldehyde to give the corresponding oxime derivative, demonstrating the potential of this compound for the preparation of various artemisinin conjugates.

Artemisinin (**1**) and its derivatives (Scheme 1) have been known for their remarkable toxicities toward protozoan parasite *Plasmodium falciparum* which causes an endemic infectious disease, i.e., malaria.[1] Artemisinin derivatives form free radicals by interaction of the endoperoxide functionality with heme or free iron.[2,3] The antimalaria activity of artemisinin is believed to be associated with these toxic radical species that can damage surrounding cellular structures. There has been tremendous growth in the number of publications of antimalarial research with artemisinin derivatives since 1979. Artemisinin analogues also show antitumor activity whose mechanism likely involves a similar metal-induced free-radical formation.[2,4] The biological activities of artemisinin could greatly be improved by conjugating it to suitable targeting molecules.[5] The aminoxy group has been widely used for the preparation of many medicinally useful bioconjugate molecules.[6a] The aminoxy group reacts with an aldehyde or a ketone to form an *O*-alkyl oxime bond in a near-quantitative yield. The *O*-alkyl oxime linkage is found in many drugs and drug candidates.[6b] However, no artemisinin derivatives with an aminoxy group have been reported. A common strategy to functionalize DHA involves an acid-catalyzed glycosylation reaction at C10. The coupling yield is, however, not always good with a conventional reagent such as BF_3·OEt_2. Our initial attempts to couple DHA with *N*-hydroxyphthalimide also failed with BF_3·OEt_2.[7]

SCHEME 1



Here we wish to report the synthesis of *O*-amino DHA, **6** (Scheme 3), and improved C−O coupling reactions at C-10 position of dihydroartemisinin.

We initially attempted to obtain compounds **5C**−**E** by the reaction between dihydroartemisinin, DHA (**2**) and alcohols (R′OH; **C**, **D**, **E**) in the presence of BF_3·OEt_2 in chloroform or dichloromethane at 0 °C to ambient temperature.[7] A number of C-10-modified artemisinin derivatives have been obtained by this method. Unfortunately, the above reaction did not give the desired products with our hands and resulted in the formation of anhydroartemisinin, AHA, and other side products.[8,9c] It should be possible to generate the intermediate oxo-

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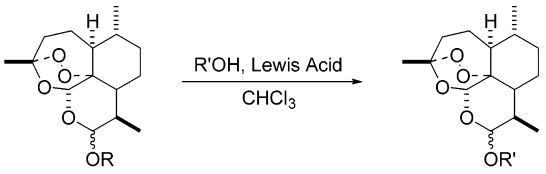
(8) The BF_3 catalyzed C−O coupling reaction of DHA gave only a trace amount (under 10% yield) of the target product, **5D**, which was judged by NMR.

(9) The formation of AHA has been a problem when moderate excess of TMS triflate or TMSCl are used to activate DHA. (a) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892−897. (b)Toshima, K.; Matsuo, G.; Tatsuta, K. *Tetrahedron Lett.* **1992**, *33*, 2175−2178. (c) O'Neill, P. M.; Miller, A.; Bishop, L. P. D.; Hindley, S.; Maggs, J. L.; Ward, S. A.; Roberts, S. M.; Scheinmann, F.; Stachulski, A. V.; Posner, G. H.; Park, B. K. *J. Med. Chem.* **2001**, *44*, 58−68.

10.1021/jo0498765 CCC: $27.50
Published on Web 04/02/2004

TABLE 1.



R= -H **2** (α:β=1:6)
-Ac **3c** (α:β=1:4.4)

5

Compounds			Results, %		
2, 3c	R'OH		BF_3OEt_2	TMSOTf	α:β[c]
2 **3c**	**A** HO–(CH2)2–Br	**5A**	84[a]	89	1:10 1:9
2 **3c**	**B** HO–(CH2)3–N(phthalimide)	**5B**	32	65	1:7 1:9
2 **3c**	**C** HO–(CH2)2–O–(CH2)2–N(H)–Fmoc	**5C**	trace[b]	69	– 1:9
2 **3c**	**D** HO–N(phthalimide)	**5D**	trace[b]	70	– 1:>20
2 **3c**	**E** HO–(CH2CH2O)2–CH2CH2–N(phthalimide)	**5E**	trace[b]	87	– 1:6

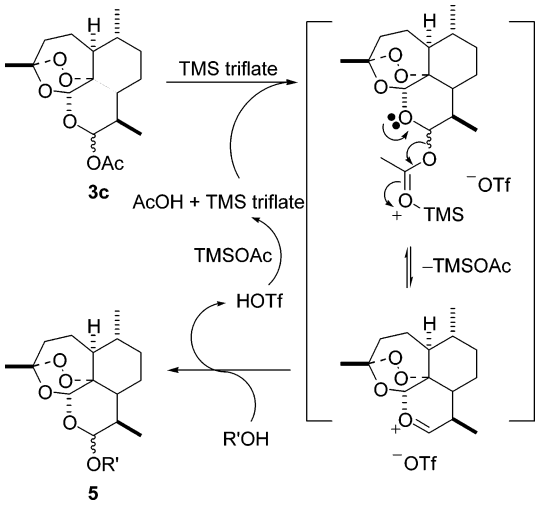
[a] Literature yield, 60%.[7] [b] Under 10%.[8] [c] Determined by ^{1}H NMR spectra. The α- and *β*-anomers were assigned on the basis of the coupling constant, J_{10-9}.[7]

nium ion by the treatment of a simple Lewis acid catalyst, such as TMS triflate, and a suitable DHA derivative.[9] The intermediate oxonium ion can undergo either S_N1 reaction with an alcohol to give the desired product or elimination reaction to give AHA.[7,9] The formation of AHA should be reduced by using a leaving group that would form a weak base.[9] Therefore, we explored the reactions of *O*-acetyl dihydroartemisinin (**3c**) with a series of alcohols in the presence of TMS triflate. The results are summarized in Table 1.

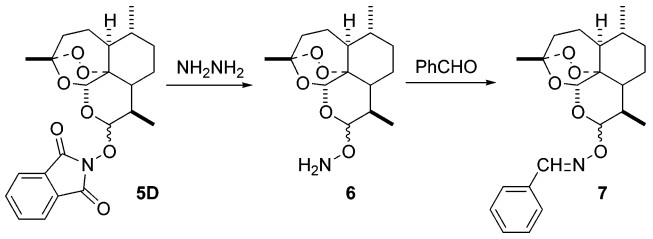
The *O*-glycosylation type reaction between *O*-acetyl dihydroartemisinin (**3c**) and functionalized alcohols (**A**−**E**) in the presence of TMS triflate resulted in good yield,[9,10] including the reaction with *N*-hydroxyphthalimide (**D**). The isomer ratio, α:*β*, was generally from 1:9 to 1:6.

The best results were obtained when only a catalytic amount (0.1 equiv) of TMS triflate was used. Scheme 2

SCHEME 2



SCHEME 3



shows a proposed mechanism for the TMS triflate-catalyzed glycosylation reaction of **3c**.[10] *O*-Phthalimide dihydroartemisinin **5D** was treated with hydrazine monohydrate in ethanol-methylene chloride (1:1) to give the target **6** with high yield (90%, Scheme 3). The aminoxy compound **6** readily reacted with benzaldehyde in methanol to give the corresponding oxime, **7** (Scheme 3), demonstrating the usefulness of **6** in the preparation of artemisinin conjugates for biomedical applications.

The introduction of a hydrophilic side chain at the C10 position should greatly improve the solubility of the artemisinin derivatives. Compound **5E** was converted to the corresponding amine **8** by a standard hydrazinolysis. The compound **8** showed much improved solubility in water compared to DHA.[11] Antimalarial and antitumor activities of the artemisinin derivatives presented here are currently under investigation in our laboratory.

In conclusion, *O*-aminodihydroartemisinin **6** was prepared by the TMS triflate catalyzed reaction between **3c** and **D** in chloroform at room temperature without deterioration of endoperoxide backbone. The improved reaction conditions should be useful in the preparation of various C10-modified DHA derivatives. The aminoxy artemisinin, **6**, will react with various aldehydes or ketones to quickly generate a large library of artemisinin derivatives for screening a desired biological activity.

Experimental Section

***O*-Acetyl Dihydroartemisinin, 3c.** To a solution of artmesinin (284 mg, 1 mmol) in dry pyridine (2 mL) at 0 °C was slowly added acetic anhydride (2 mL). The reaction mixture was stirred

(10) Artemether (**3a**) was treated with alcohols (**A**−**E**) in the presence of TMS triflate. The result was similar with the BF_3·OEt_2-catalyzed C−O coupling reaction. A similar glycosylation of sugar, which was activated by TMS triflate, has been reported. Our proposed mechanism shows that the stability of the ketals (**3a** and **3c**) and TMS ether (TMSOMe and TMSOAc, and TMSOTMS) could be responsible for the difference in the final coupling yields. (a) Tietze, L. F.; Fisher, R.; Guder, H. T.; Goerlach, A.; Neumann, M.; Krach, T. *Carbohydr. Res.* **1987**, *164*, 177−194. (b) Lin, A. J.; Li, L.; Andersen, S. L.; Klayman, D. L. *J. Med. Chem.* **1992**, *35*, 1639−1642. (c) The coupling of aminosugars catalyzed by TMS triflate was doubly activated by introducing a trichloro-oxazoline group into the substrate. Donohoe, T. J.; Logan, J. G.; Laffan, D. D. P. *Org. Lett.* **2003**, *5*, 4995−4998. (d) The real catalyst may be triflic acid after TMS triflate is consumed.

(11) Compound **8** was soluble in neutral (pH = 7.35) phosphate buffer (>3 mg/mL).

at 0 °C for 1 h, and then a catalytic amount of 4-(dimethylamino)-pyridine (DMAP, 5 mg) was added. The reaction mixture was then allowed to warm to room temperature. The solution was allowed to stir for 2 h. The clear mixture was slowly poured into 10 mL of fast stirring ice−water. The solution was extracted with ethyl acetate (20 mL × 3) and washed with 1 N HCl, water, and brine. After the solution was dried over $MgSO_4$ and filtered, the solvent was removed to give a crude product. Quick purification of the residues through a short silica gel pad with hexanes/EtOAc (4:1) gave the pure product in 99% yield (365 mg; α/β = 1:4.4): ^{1}H NMR (300 MHz, $CDCl_3$) β-isomer δ 6.25 (d, J = 3.6 Hz, 1H), , 5.48 (s, 1H), 2.08 (m, 1H), 2.38 (td, J = 13.5, 3.9 Hz, 1H), 1.42 (s, 3H), 0.98 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 7.5 Hz, 3H); α-isomer δ 5.79 (d, J = 9.9 Hz, 1H), 5.44 (s, 1H); HRMS calcd for $C_{17}H_{26}O_6Na$ 349.1627, found 349.1633.

General C−O Coupling Procedure. A mixture of *O*-acyldihydroatemisinin **3c** (0.31 mmol) and functionalized alcohol (0.34 mmol, **A**−**E**) in anhydrous chloroform solution (1 mL) was treated with TMS triflate (0.1 equiv) at ambient temperature. After being stirred for 1 h, the reaction was quenched by aq $NaHCO_3$ solution (0.5 mL) and then extracted with chloroform (3 mL × 3). The organic layer was washed with water and dried over $MgSO_4$. After the solvent was removed, quick purification of the residues through a short silica pad with hexanes/EtOAc (7:1 then 4:1) gave the corresponding pure product.

5A:[6] yield 89% (107 mg; α/β = 1:9); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (s, 1H), 4.85 (d, J = 3.0 Hz, 2H), 4.12 (m, 1H), 3.79 (m, 1H), 3.51 (t, J = 6.0 Hz, 2H), 2.65 (m, 1H), 2.36 (td, J = 13.5, 3.9 Hz, 1H), 1.44 (s, 3H), 0.96 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H).

5B:[6] yield 65% (94 mg; α/β = 1:9); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.78 (m, 2H), 7.81−7.89 (m, 2H), 5.44 (s, 1H), 4.79 (d, J = 3.3 Hz, 1H), 3.91 (m, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.43 (m, 1H), 2.63 (m, 1H), 2.37 (td, J = 13.5, 3.6 Hz, 1H), 1.43 (s, 3H), 0.96 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 7.5 Hz, 3H).

5C: yield 69% (125 mg; α/β = 1:9); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.5, 0.9 Hz, 2H), 7.31 (t, J = 7.5, 1.2 Hz, 2H), 5.48 (s, 1H), 5.33 (bs, 1H), 4.40 (d, J = 6.9 Hz, 2H), 4.23 (d, J = 6.9 Hz, 1H), 3.89−3.99 (m, 1H), 3.50−3.70 (m, 5H), 3.40 (b, 2H), 2.63 (m, 1H), 2.36 (td, J = 13.5, 3.9 Hz, 1H), 1.43 (s, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.91 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 144.0, 141.3, 136.3, 127.7, 127.0, 125.0, 120.0, 104.1, 102.2, 87.9, 81.1, 70.5, 67.5, 52.7, 47.3, 44.5, 37.6, 36.4, 34.6, 30.9, 26.1, 24.7, 24.5, 20.4, 13.0; HRMS calcd for $C_{34}H_{43}NO_8Na$ 616.2889, found 616.2891.

5D: yield 70% (301 mg; α/β = 1:>20); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.78 (m, 2H), 7.81−7.89 (m, 2H), 6.14 (s, 1H), 5.48 (d, J = 3.0 Hz, 1H), 2.87 (m, 1H), 2.37 (td, J = 13.5, 3.6 Hz, 1H), 1.39 (s, 3H), 1.21 (d, J = 7.5 Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 134.3, 129.3, 123.4, 107.0, 104.3, 89.1, 80.7, 52.5, 43.9, 37.3, 36.3, 34.6, 30.4, 25.9, 24.61, 24.56, 20.2, 12.6; HRMS calcd for $C_{23}H_{27}NO_7Na$ 452.1685, found 452.1702.

5E: yield 87% (145 mg; α/β = 1:6); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.78 (m, 2H), 7.81−7.89 (m, 2H), 5.41 (s, 1H), 4.79 (d, J = 3.3 Hz, 1H), 3.90 (t, J = 5.7 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 3.48−3.68 (m, 8H), 2.60 (m, 1H), 2.36 (td, J = 13.5, 3.6 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 133.9, 132.1, 123.2, 104.0, 102.1, 87.8, 81.1, 70.5, 70.1, 68.0, 67.4, 52.6, 44.5, 37.4, 37.2, 36.4, 34.7, 30.9, 26.2, 24.7, 24.4, 20.3, 12.9; HRMS calcd for $C_{29}H_{39}NO_9Na$ 568.2523, found 568.2524.

***O*-Aminodihydroartemisinin, 6.** Compound **5D** (100 mg, 0.23 mmol) was treated with excess hydrazine monohydrate (0.5 mL) in ethanol−CH_2Cl_2 (1:1, 1 mL) at room temperature for 3 h. After the solvent was removed under reduced pressure, the residues were extracted with diisopropyl ether (5 mL × 3) and then washed with water (1 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (chloroform/MeOH = 15:1): yield 90% (63 mg); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (bs, 2H), 5.44 (s, 1H), 4.93 (d, J = 3.6 Hz, 1H), 2.70 (m, 1H), 2.38 (td, J = 13.5, 3.9 Hz, 1H), 1.45 (s, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.6, 104.2, 87.9, 80.9, 52.4, 44.2, 37.4, 36.3, 34.4, 30.6, 26.1, 24.67, 24.59, 20.3, 12.8; IR (KBr) 3155 cm^{-1}; HRMS calcd for $C_{15}H_{25}NO_5Na$ 322.1630, found 322.1628.

Benzaldoxime of *O*-Aminodihydroartemisinin, 7. To a solution of *O*-aminodihydroartmesinin (10 mg, 0.033 mmol) in methanol (0.5 mL) was added distilled benzaldehyde (5 μL, 0.04 mmol) at room temperature for 1 h. After the solvent was removed, quick purification of the residues through a short silica pad with hexanes/EtOAc (7:1) gave the corresponding pure product: yield 98% (13 mg); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.58−7.66 (m, 2H), 7.32−7.40 (m, 3H), 5.63 (d, J = 3.6 Hz, 1H), 5.50 (s, 1H), 2.83 (m, 1H), 2.38 (td, J = 13.5, 3.9 Hz, 1H), 1.44 (s, 3H), 1.01 (d, J = 7.5 Hz, 1H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 131.9, 130.0, 128.6, 127.4, 104.5, 104.2, 88.1, 80.9, 52.6, 44.3, 37.5, 36.4, 34.6, 30.4, 26.1, 24.7, 20.3, 12.9; ESI-MS m/z [M + H$^+$] 388.4; HRMS calcd for $C_{22}H_{29}NO_5Na$ 410.1943, found 410.1926.

8. Compound **5E** (1.44 g, 2.64 mmol) was treated with excess hydrazine monohydrate (3 mL) in ethanol−CH_2Cl_2 (1:1, 8 mL) at room temperature for 3 h. After the solvent was removed under reduced pressure, the residues were extracted with diisopropyl ether (20 mL × 3) and then washed with water (3 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (chloroform/MeOH = 4:1): yield 63% (690 mg, 2.6 mmol scale); β-isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.83 (d, J = 3.0 Hz, 1H), 3.90−4.00 (m, 1H), 3.55−3.73 (m, 8H), 3.51 (t, J = 5.4 Hz, 2H), 2.87 (t, J = 4.8 Hz, 2H), 2.62 (m, 1H), 2.37 (td, J = 13.5, 3.9 Hz, 1H), 1.43 (s, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 7.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 104.0, 102.1, 87.9, 81.1, 73.5, 70.5, 67.4, 52.6, 44.5, 41.8, 37.5, 36.5, 34.7, 30.9, 26.2, 24.7, 24.4, 20.4, 13.0; HRMS calcd for $C_{21}H_{38}NO_7$ 416.2648, found 416.2634.

Acknowledgment. This research was supported by the Akibene Foundation.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **5C**−**E** and **6**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0498765