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Direct Conversion of Pyranose Anomeric OH→F→R in the Artemisinin Family of Antimalarial Trioxanes

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Summary: Eleven examples form the basis of a short and effective synthetic method for replacement of an anomeric fluorine atom by saturated, unsaturated, aryl and heteroaryl carbon nucleophiles to prepare α- or β-oriented C_{10}-R derivatives of the trioxane 10-deoxoartemisinin.

Chemotherapy of the infectious disease malaria is currently being made more effective through use of the natural antimalarial lactone artemisinin (qinghaosu, **1**) and various semi-synthetic C-10 hydroxyl derivatives of the lactol dihydroartemisinin (**2**).[1] Although many synthetic analogs of trioxane artemisinin have been prepared and much structure-activity information has been generated,[1] relatively few C-10 carbon derivatives have been reported. Begué *et. al.* have shown that 10α-trifluoromethyl-hydroartemisinin, prepared directly from artemisinin, has potent *in vivo* antimalarial activity,[2] and Pu and Ziffer have shown that 10β-allyldeoxoartemisinin, prepared *via* allyltrimethylsilane coupling with dihydroartemisinin (**2**), was easily converted into the saturated 10-*n*-propyl analog that is comparable to the clinically used antimalarial trioxane drug arteether in terms of *in vivo* potency and toxicity.[3] Jung and Lee[4] and Haynes and Vonwiller[5] have demonstrated that several 10-alkyl and 10-aryl analogs of deoxoartemisinin, prepared *via* photooxygenative cyclization starting with natural artemisinic acid, have significant *in vitro* antimalarial activity. Combining our interests in antimalarial trioxanes[1b,6] and in C-glycoside synthesis[7,8] using glycosyl fluorides,[9] we have now developed a direct two-step procedure for replacement of the pyranose anomeric 10-OH group in dihydroartemisinin (**2**) by various carbon nucleophiles without destruction of the antimalarially critical trioxane peroxidic bond. The two steps in this process involve mild DAST fluorination[9] of dihydroartemisinin (**2**) and then facile substitution of the anomeric fluorine atom in pyranosyl fluoride **3** by various alkyl, alkynyl, aryl, and heteroaryl nucleophiles to form either α- or β-oriented C-10 substituted deoxoartemisinins **4** (Scheme I). The shortness and good chemical yields in this direct protocol should make this the method of choice for synthesis of a wide variety of other saturated, unsaturated, and aromatic C-10 analogs.

Several aspects of Scheme I are noteworthy. Fluorination of readily available dihydroartemisinin lactol (**2**) with DAST proceeded in high yield on gram-scale to form a mixture of anomeric fluorides, with the β-fluoride **3** vastly predominating and easily separated from the α-fluoride by immediate application of the crude product mixture to chromatography using a Florisil® column;[10] exposure to water caused hydrolysis of these pyranosyl fluorides back into the reactant lactol **2**. After purification, however, 10β-fluoride **3** is a stable crystalline solid. Coupling of **either** the α-fluoride or the β-fluoride **3** with trimethylaluminum in toluene as solvent gave 10β-methyl derivative **4** with almost complete stereoselectivity, thereby implicating a common oxygen-stabilized C-10 carbocation intermediate. The relative stereochemistry at carbons 9 and 10 was established by the characteristic

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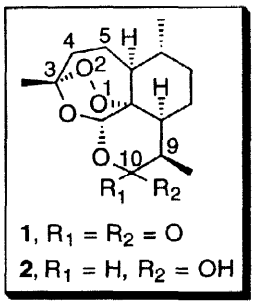
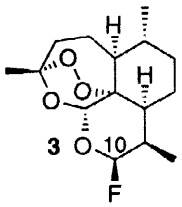
Scheme I.



Nuc	10-R	yield of purified product
Me_3Al	β-Me	57%
Me_2AlR	β-C≡C-Ph	70%
Me_2AlR	β-C≡C-PhCl-*p*	69%
Me_2AlR	β-C≡C-C_6H_{13}	77%
Me_2AlR	β-C≡C-$SiMe_3$	80%
Et_3Al	β-Et	51%

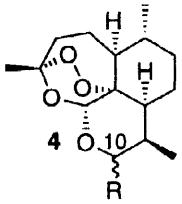
2

82% | Et_2NSF_3 (DAST)

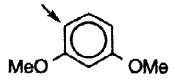
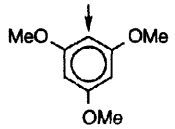
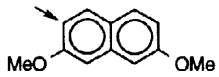
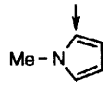
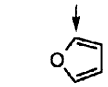


3

Nuc
$BF_3.Et_2O$ (1.2 eq)
-78 °C → -40 °C
(or 0 °C)



4

Aryl Nuc and site of attachment (↓)	10-R	yield of purified product
	α	71%
	α	60%
	α	80%
	α	86%
	α	31%

coupling constants of the methine hydrogen atoms at these positions ($J_{9,10}$ = 10–11 Hz for *trans* and $J_{9,10}$ = 5.6–6.7 Hz for *cis*).[3,4] Based on the characteristic ^1H NMR chemical shifts for analogous C-9,10-disubstituted systems, we conclude that the structure of 10β-methyl derivative **4** (with C-9β-methyl at δ 0.9) is as shown rather than 9α,10α-dimethyl (with C-9α-methyl expected at δ 1.3);[3,4] therefore, this substitution reaction probably does not proceed *via* the intermediacy of a C-9,10-olefin (*i.e. via* the dehydrofluorinated intermediate). Several dimethylaluminum acetylides, prepared from Me_2AlCl and the corresponding lithium acetylides, coupled smoothly in the presence of boron trifluoride-etherate at -78 °C for 2 hours and then slowly warmed to 0 °C for 3 hours to form exclusively the 10β-acetylenic derivatives **4**. Di- and tri-methoxylated aromatics[11] and heteroaromatic N-methylpyrrole[12] and furan coupled to produce exclusively, in stereochemical contrast, the 10α-oriented derivatives **4**.[13,14] Apparently, relatively small nucleophiles approach the intermediate cation from the β-face of the molecule, whereas relatively large aryl and heteroaryl nucleophiles approach from the α-face (*i.e.* directed by and *trans* to the C-9 methyl group). Coupling of pyranosyl fluoride **3** with N-methylpyrrole proceeded equally well on 400 mg scale as on 20 mg scale, and larger scale executions of this and of the other coupling reactions reported here are not expected to be a problem.

In the course of these studies, we found that dihydroartemisinin (**2**) itself, like many 1-hydroxy carbohydrates,[8] can be used directly as an electrophilic donor in the presence of boron trifluoride-etherate for

Friedel-Crafts arylation of reactive aromatics; C-10α-glycoside formation using this procedure proceeded in 56% yield with 1,3-dimethoxybenzene (*vs.* 71% using glycosyl fluoride **3**) and in 75% yield with N-methylpyrrole (*vs.* 86% using glycosyl fluoride **3**). Although furan did not couple with lactol **2**, furan did couple in 31% yield with fluoride **3**. Neither lactol **2** nor fluoride **3**, however, coupled with thiophene.

In summary, recognition of dihydroartemisinin lactol (**2**) as a pyranose sugar with a free anomeric hydroxyl group has led to this two-step protocol involving direct fluorination of readily available lactol **2** and then C-glycoside formation for easy semi-synthesis of various artemisinin C-10 derivatives. These C-10 carbon-substituted trioxanes are expected to be considerably more stable toward hydrolysis[3-5] than the corresponding ether and ester derivatives (C-10 acetals) of dihydroartemisinin that are currently used clinically as chemotherapeutic antimalarial drugs. The biological activities of these new C-10 carbon-substituted trioxanes **4** will be reported in due course.

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10. A representative fluorination is as follows:

A 250 mL flame-dried round-bottomed flask was charged with lactol **2** (1.30 g, 4.57 mmole) and dry tetrahydrofuran (100 mL). To this mixture at -30 °C was added diethylaminosulfur trifluoride (DAST, 1.34 mL, 6.82 mmole). The resulting reaction mixture was stirred at -30 °C for 15 min, slowly warmed up to room temperature and stirred for 1 h. The reaction was concentrated under reduced pressure. The crude product was purified by column chromatography (Florisil®, 1%→5% ethyl acetate/hexanes) to give 10β-fluoride **3** (1.08 g, 3.75 mmole, 82%) and 10α-fluoride (0.102 g, 0.366 mmole, 8%) as white solids.

10β-fluoride **3**: mp = 108.0-109.0 °C; $[\alpha]_D^{25}$ = +136.0 (*c* = 1.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (dd, J_{H-F} = 54.4 Hz, J_{H-H} = 2.3 Hz, 1 H), 5.56 (d, J_{H-F} = 1.9 Hz, 1 H), 2.63 (d of m, J_{H-F} = 33.3 Hz, 1 H), 2.38 (m, 1 H), 2.03 (m, 1 H), 1.93–1.80 (m, 2 H), 1.73–1.21 (m, 7 H), 1.43 (s, 3 H), 1.00 (d, *J* = 7.4 Hz, 3 H), 0.96 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.2 (d, J_{C-F} = 223 Hz), 104.9, 89.1, 80.9, 52.6, 43.8 (d, J_{C-F} = 1.8 Hz), 37.8, 36.6, 34.9, 31.1 (d, J_{C-F} = 22.7 Hz), 26.2, 25.0, 24.6 (d, J_{C-F} = 5.9 Hz), 20.6, 12.7; ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ (ex)) δ -134.7 (dd, *J* = 53.7, 36.7 Hz); IR (KBr) 2947, 2871, 1453, 1381, 1181, 1116, 1040, 982, 950, 914, 867 cm^{-1}; Anal. calcd for $C_{15}H_{23}O_4F$: C 62.92, H 8.10, found: C 63.10, H 8.17.

10α-fluoride: mp = 99.0-100.0 °C; $[\alpha]_D^{25}$ = +115.1 (*c* = 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 5.27 (dd, J_{H-F} = 53.6 Hz, J_{H-H} = 9.1 Hz, 1 H), 2.53 (m, 1 H), 2.40 (m, 1 H), 2.03 (m, 1 H), 1.94–1.05 (m, 9 H), 1.46 (s, 3 H), 0.99 (d, *J* = 7.1 Hz, 3 H), 0.96 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8 (d, J_{C-F} = 209 Hz), 105.0, 91.7 (d, J_{C-F} = 5.8 Hz), 80.2, 51.7, 45.4 (d, J_{C-F} = 9.6 Hz), 37.7, 36.5, 34.5, 33.2 (d, J_{C-F} = 19.0 Hz), 26.2, 25.0, 22.5, 20.6, 12.0; ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ (ex)) δ -140.7 (ddd, *J* = 53.7, 10.8, 4.6 Hz); IR (KBr) 2946, 2880, 1456, 1380, 1205, 1111, 1042, 878, 846 cm^{-1}.

11. A representative example is as follows:

A flame-dried 10 mL round-bottomed flask was charged with 2,7-dimethoxynaphthalene (0.113 g, 0.601 mmole) and fluoride **3** (0.034 g, 0.119 mmole) in dried dichloromethane (1 mL). To this mixture at -78 °C was added boron trifluoride diethyl etherate (0.018 mL, 0.143 mmole) via gas-tight syringe. The mixture turned bright yellow and then dark orange in 20 min at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. TLC indicated no starting material fluoride. The reaction was quenched at -78 °C with distilled water (2 mL) and diluted with chloroform (4 mL). The two layers were separated and the aqueous phase was extracted with chloroform (4 mL x 3). The combined organic layers were washed with brine (2 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (flash gel, 1%→5% ehtyl acetate/hexanes) to give the product (0.044 g, 0.095 mmole, 80%) with ^1H NMR identical to that of subsequent material after HPLC.

Further purification by HPLC (silica, 15% ethyl acetate/hexanes, 3.0 mL/min, 264 nm, t_R = 11.1 min) afforded white solid 10α-(2′,7′-dimethoxynaphth-3′-yl)deoxoartemisinin: mp = 149.0-151.0 °C; $[\alpha]_D^{25}$ = +246.4 (*c* = 1.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.4 Hz, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.69 (d, *J* = 11.2 Hz, 1 H), 5.50 (s, 1 H), 4.02 (s, 3 H), 3.90 (s, 3 H), 3.38 (m, 1 H), 2.43 (apparent dt, *J* = 4.0, 14.0 Hz, 1 H), 2.09 (ddd, *J* = 16.0, 4.0, 2.8 Hz, 1 H), 1.94 (m, 1 H), 1.82–1.54 (m, 7 H), 1.44 (s, 3 H), 1.35 (m, 1 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 0.47 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 155.3, 134.0, 129.52, 129.48, 125.4, 119.3, 116.9, 110.2, 104.6, 104.1, 93.0, 81.3, 70.2, 56.7, 56.1, 52.4, 46.3, 37.4, 36.4, 34.3, 30.4, 26.2, 24.8, 21.3, 20.4, 13.2; IR ($CHCl_3$) 3011, 2930, 2883, 1627, 1248, 1216, 1210, 1043, 784, 768, 748 cm^{-1}; Anal. calcd for $C_{27}H_{34}O_6$: C 71.34, H 7.54, found: C 71.27, H 7.52.

12. A representative example is as follows:

Fluoride **3** (0.400 g, 1.40 mmol) and N-methylpyrrole (0.568 g, 7.00 mmol) were dissolved in dry dichloromethane (25 mL) and the solution was cooled to -78 °C. Boron trifluoride diethyl etherate (0.238 g, 0.206 mL, 1.68 mmol) was added slowly by syringe. The reaction was stirred for 30 min at -78 °C and then the temperature was raised to -40 °C. After 5 h at -40 °C, the reaction was quenched with distilled water (10 mL). The aqueous phase was separated and extracted with dichloromethane (10 mL x 2). The combined organic solution was dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by column chromatography (Florisil®, 10% ethyl acetate/hexanes) to provide the product (0.417 g, 1.20 mmol, 86%) 10α-(N-methylpyrrol-2′-yl)deoxoartemisinin as a white foam: $[\alpha]_D^{25}$ = +105.8 (*c* = 1.65, $CHCl_3$); HPLC: silica, 10% ethyl acetate/hexanes, 3 mL/min, 254 nm, t_R = 12.5 min; ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 2.0, 2.4 Hz, 1 H), 6.00–5.97 (m, 2 H), 5.39 (s, 1 H), 4.50 (d, *J* = 11.2 Hz, 1 H), 3.84 (s, 3 H), 2.90–2.78 (m, 1 H), 2.39 (dt, *J* = 4.0, 14.0 Hz, 1 H), 2.04 (ddd, *J* = 14.4, 4.8, 2.8 Hz, 1 H), 1.94–1.87 (m, 1 H), 1.40 (s, 3 H), 0.99 (d, *J* = 6.4 Hz, 3 H), 1.80–0.80 (m, 8 H), 0.61 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.6, 123.6, 109.4, 106.0, 104.0, 91.8, 80.6, 72.4, 51.9, 45.8, 37.3, 36.2, 35.0, 34.1, 30.8, 26.0, 24.7, 20.9, 20.3, 14.3; IR ($CHCl_3$) 2927, 1454, 1377, 1321, 1042, 927, 880, 828 cm^{-1}.

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