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Tetrahedron Letters 46 (2005) 4243–4245
Tetrahedron Letters

A new route to novel 10-deoxoartemisinins

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Received 13 January 2005; revised 15 March 2005; accepted 11 April 2005

Abstract—A series of novel 10-deoxoartemisinin derivatives was synthesized with high regioselectivity and yields using Heck reactions from 10β-allyldeoxoartemisinin. The configuration of the double bond of the product was determined from ^{1}H NMR coupling constants ($J_{2'-3'}$).

In recent years, many efforts have been made to eradicate malaria, the disease, which still affects approximately 2 billion people globally each year. The development of drug resistance, by many strains of *Plasmodium falciparum* to chloroquine **1** and mefloquine **2** has increased the spread of the disease to almost all areas where malaria is endemic. The WHO predicted that without new antimalarial drug intervention, the number of malaria cases will double by the year 2010.[1,2] Therefore, the need for finding new compounds with novel modes of action is urgent. Artemisinin **3** (quinghaosu) and its derivatives such as artemether **5a**, arteether **5b**, and artesunate **5c** are now used for the treatment of malaria (Fig. 1). However, poor bioavailability and rapid clearance are observed with these derivatives, principally as a result of the chemical and metabolic instability of the acetal function present in each. One of the principal routes of metabolism of acetal-containing analogues involves oxidative dealkylation to dihydroartemisinin, a compound associated with toxicity[3] and short half life.[4,5] Aspects of the chemistry, mechanism of action, metabolism, and toxicity of the endoperoxide class of drugs have been recently reviewed by O'Neill et al.[6] The replacement of the oxygen at C-10 with carbon would be expected to produce compounds not only with greater hydrolytic stability but also with a longer half life and potentially lower toxicity. Consequently, new derivatives of artemisinin in which the

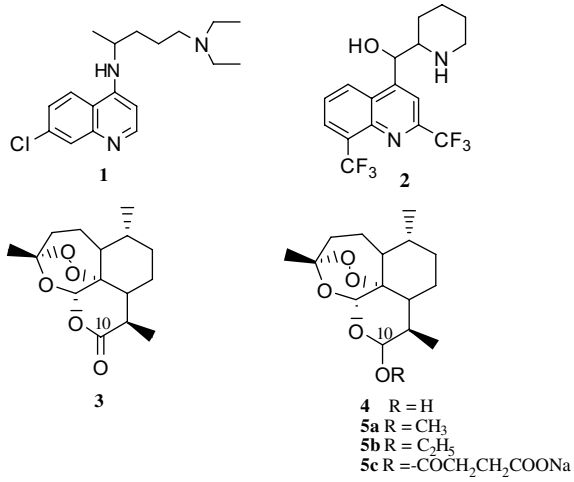

Figure 1.

10-acetal bond is replaced with 10-C–C, the so-called 10-deoxoartemisinins have been synthesized.[7–14]

Recently, we reported the synthesis of novel 10-deoxoartemisinins containing heterocyclic rings, which showed in vitro antimalarial activity, against two *P. falciparum* clones, 10 times more than that of artemisinin.[15] In this letter we present a new route for the synthesis of new 10-deoxoartemisinins containing aromatic rings.

The synthesis of 10-deoxoartemisinins **8a**–**f** is outlined in Scheme 1. The key intermediate, 10β-allyldeoxoartemisinin **7** had been previously synthesized by treatment of dihydroartemisinin **4** with allyltrimethylsilane using catalytic Lewis acids such as boron trifluoride

Keywords: Antimalarial; Artemisinin; Dihydroartemisinin; Artemether; Arteether.
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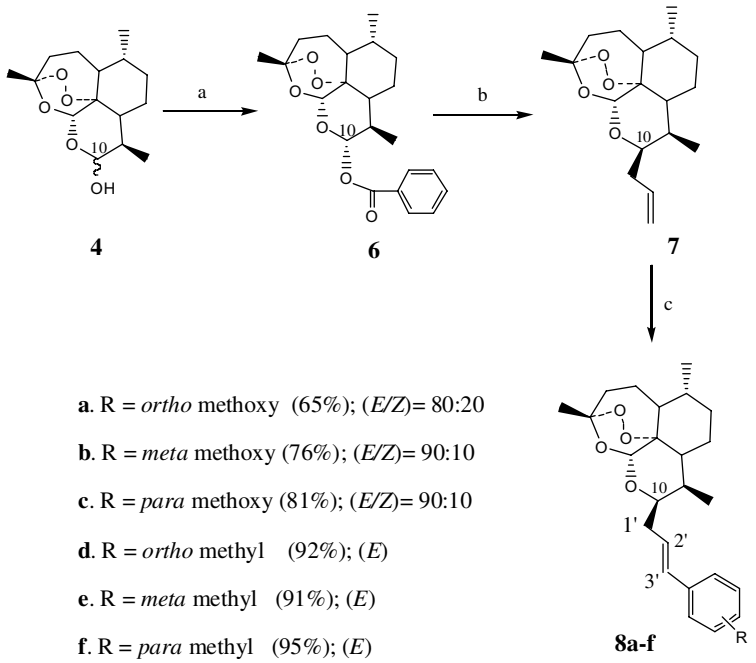
doi:10.1016/j.tetlet.2005.04.042



Scheme 1. Reagents and conditions: (a) benzoyl chloride, pyridine, CH_2Cl_2, rt, 16 h, 97%; (b) allyltrimethylsilane, $ZnCl_2$, molecular sieves, 1,2-dichloroethane, 0 °C, 1 h, 90%; (c) aryl iodides, DMF, $Pd(OAc)_2$, PEG 4600, NEt_3, 80 °C, 2–6 h (65–95%).

etherate[14,16] or tin tetrachloride.[15] We synthesized **7** in excellent yield from **6** according to a known procedure.[17] Compound **7** was then reacted with aryl iodides in dimethylformamide[18] at 80 °C in the presence of palladium acetate, PEG 4600 and triethylamine to afford a series of novel 10-deoxoartemisinins **8a**–**f**[19] in good to excellent yields with high regioselectivity at C-3′. The (*E*) configuration of the double bond was determined from ^{1}H NMR coupling constant ($J_{2'\text{-}3'}$). One hundred percent regioselectivity was obtained with iodotoluene, and high selectivity was obtained with the iodoanisoles. The *E*/*Z* isomer ratios were based on ^{1}H NMR integrals.

In conclusion we have presented a new route to novel 10-deoxoartemisinin derivatives. Study on the antimalarial activity of these derivatives is in progress.

Acknowledgements

We thank the International Foundation for Science (IFS), Stockholm, Sweden for financial support through a grant to T.K.Vu.

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19. General procedure for the synthesis of **8a**–**f**. A mixture of aryl iodide (0.4 mmol), 10β-allyldeoxoartemisinin (0.4 mmol), PEG- 4600 (2 g), $Pd(OAc)_2$ (0.02 mmol), and triethylamine (0.4 mmol) was stirred in anhydrous dimethylformamide (15 mL) at 80 °C under nitrogen for 2–6 h. After completion of the reaction, the reaction mixture was cooled and extracted with cold diethyl ether and purified by column chromatography on silica gel to give the products **8a**–**f**. *10β-[(E)-3′-ortho-Methylphenyl-prop-2′-enyl]deoxoartemisinin* **8d**. Yield: 92%; mp 64–66 °C; IR (KBr); *v* (cm^{-1}): 2948, 2848, 1642, 1454, 1375, 1205, 1052, 1009, 965, 744; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, *J* = 7.0 Hz, 1H), 7.14–7.09 (m, 3H), 6.67 (d, *J* = 15.5 Hz, 1H), 6.23–6.17 (m, 1H), 5.38 (s, 1H), 4.41–4.37 (m, 1H),

2.69 (m, 1H), 2.61–2.54 (m, 1H), 2.42–2.32 (m, 4H), 2.05–2.01 (m, 1H), 1.94–1.90 (m, 1H), 1.89–1.80 (m, 1H), 1.70–1.64 (m, 2H), 1.57 (s, 2H), 1.47–1.43 (m, 1H), 1.41 (s, 3H), 1.39–1.30 (m, 2H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.94 (d, $J = 7.5$ Hz, 3H), 0.89 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.9, 134.9, 129.8, 129.2, 126.8, 125.9, 125.7, 103.1, 89.3, 81.1, 75.0, 52.3, 44.3, 37.5, 36.6, 34.5, 33.9, 30.3, 26.0, 24.9, 24.7, 20.2, 19.8, 13.0; CIMS: m/z 399 $[M+H]^+$. Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60; O, 16.06. Found: C, 75.29; H, 8.57; O, 15.98.