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# Ring-contracted artemisinin derivatives: stereoselective reaction of anhydrodihydroartemisinin towards halogenating reagents

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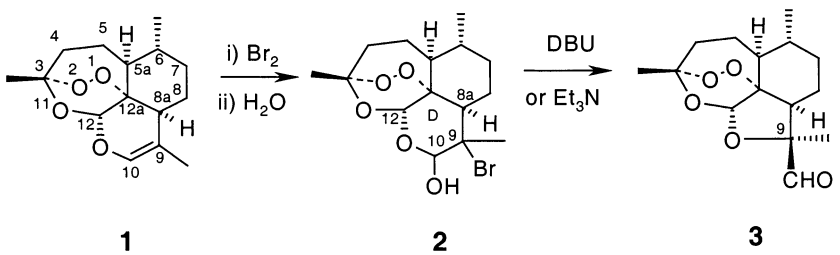
**Abstract**—Reaction of anhydrodihydroartemisinin **1** with halogenating reagents and further rearrangement of adducts into ring-contracted aldehydes has been revisited. The stereochemistry of reactions with iodine is opposite to that with bromine, and allowed the preparation of the new aldehyde **4** with conservation of the configuration of starting artemisinin at C-9. 

Since the discovery of artemisinin, a potent antimalarial agent isolated from the plant *Artemisia annua*, great efforts have been focused on its chemical modifications in order to improve its efficacy and pharmaceutical profile.[1] Among these studies, Venugopalan et al. described an access to a series of novel ring-contracted artemisinin derivatives from glycal **1**,[2] prepared from artemisinin[3] (Scheme 1). Addition of bromine onto **1** and further reaction with water gave the bromoacetal **2**, which underwent a rearrangement under basic conditions leading in high yield to the aldehyde **3** isolated as a single isomer where the methyl at C-9 is α. This aldehyde **3** is precursor of a variety of new artemisinin derivatives, among them some exhibit high antimalarial activities against chloroquine sensitive and chloroquine resistant strains of *Plasmodium*.[4] Considering the great influence of the configuration on biological activity of a molecule we searched for an approach to the aldehyde **4**, where the methyl at C-9 is β, as in artemisinin, and we report here our results.

From an examination of several studies on electrophilic addition reactions performed with anhydrodihydroartemisinin **1** (bromination,[3,5] dihydroxylation,[6] epoxidation[7]), it appears that the stereochemistry of these reactions is not always clear and that selectivities are very sensitive to reaction conditions. For example, Lin et al. also performed the addition of $Br_2$ onto glycal **1**, and a further substitution with aromatic amines provided new artemisinin derivatives, in some cases as a mixture of epimers at C-9.[5] Consequently, we decided to investigate the reactivity of glycal **1** towards different halogenating agents, with the hope of finding conditions avoiding the inversion of the configuration at C-9, and providing the aldehyde **4**, isomer of **3**.

Initially we revisited the preparation and the reactivity of bromoacetals **2**.[3,4] The addition of bromine to the glycal **1** at 0°C in $CCl_4$, followed by addition of water, afforded a ~60/40 mixture of two bromoacetals **2** (out of the four possible stereoisomers) which were not




**1** **2** **3**

**Scheme 1.**

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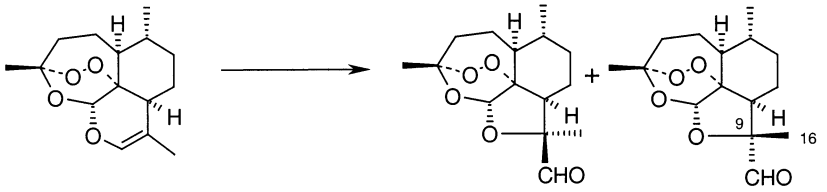

| 1 | 3 | 4 | (3 + 4)[a,b] |
|---|---|---|---|
| i) $Br_2$, $CCl_4$; ii) $H_2O$; iii) $Et_3N$ | 100 % | 0 % | (92 %) |
| i) NBS, $H_2O$/DME, ii) $Et_3N$ | 80 % | 20 % | (76 %) |
| i) NBS, $H_2O$/DME, ii) $AgCF_3COO$/HFIP | 80 % | 20 % | (82 %) |
| NIS, $H_2O$, DME | 20 % | 80 % | (75 %) |
| $I_2$, phosphate buffer, $H_2O$, tBuOH | 0 % | 100 % | (57 %) |

[a] isolated yield
[b] no starting material recovered

**Scheme 2.**

separated. After reaction of this mixture **2** with triethylamine, the aldehyde **3** was obtained in a 92% yield. According to authors,[4] it is assumed that addition of bromine occurs stereoselectively from the α-face and that the mechanism of rearrangement is a D-ring opening and the nucleophilic substitution of bromine at C-9 by the produced alkoxide, occurring with inversion of configuration. We first expected to modify the process of rearrangement and favour a cationic process, by using $CF_3COOAg$ in hexafluoro-2-propanol. However, under these conditions, only the same aldehyde **3** was obtained.

We then turned to other conditions of halogenation of anhydrodihydroartemisinin **1**, and we investigated the direct formation of haloacetal by *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in DME/$H_2O$, according to the procedure recently reported by Mioskowski et al.[8] With NBS, glycal **1** in solution in a DME/$H_2O$ mixture (2:1) provided, after 45 min, a ~45/35/12/8 mixture of bromoacetals (four different signals in $^1H$ NMR for H-10 and H-12). They afforded, under basic or $Ag^+$/hexafluoro-2-propanol (HFIP) treatment, an 80/20 mixture of aldehydes **3** and **4**. This ratio could be reversed by performing the reaction with NIS. In this case, intermediate iodoacetals, although detected by TLC, could not be isolated, and the reaction afforded directly aldehydes. A 20/80 mixture of **3** and **4** could be isolated in a 75% yield (Scheme 2). Formation of the aldehyde **4** is the result of a different stereochemical outcome of the reaction, which could occur at the halogenation step and further reaction with water, or at the rearrangement step. However, the observation of four bromoacetals with NBS, instead of only two with $Br_2$, indicates that the difference in the stereochemistry of this sequence of reactions is due to the first step. In the case of NIS, the major formation of the aldehyde **4** is very surprising. The fast conversion of iodoacetals into aldehydes, without any assistance, strongly suggests a difference of mechanism in this rearrangement step.

Taking in account this great difference of reaction with NBS and NIS, we went back over the first experiment, but using $I_2$ instead of $Br_2$. In $CCl_4$, no reaction occurred. However, under conditions described for glycoside derivatives,[9] with $I_2$ in $t$BuOH/$H_2O$ in the presence of a phosphate buffer (pH 7.2), aldehyde **4** could be exclusively obtained, and isolated in a 57% yield.[10] Structure of **4** was determined by NMR, by comparison with **3**.[11]

So, owing to a remarkable difference of the stereochemical outcome of reactions of brominating and iodinating agents with the glycal **1** of artemisinin, we could find an access to the new aldehyde **4**, where the methyl substituent at C-9 is still β. Analysis of different intermediates in this sequential reaction is under investigation. Aldehyde **4** can be used as precursor of new D-ring contracted artemisinin derivatives, in 16β-Me series.

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10. To a suspension of glycal **1** (200 mg, 0.8 mmol) maintained in the dark in *t*-BuOH (8 mL) was added distilled water (1 mL), and a phosphate buffer solution (20 mL, pH 7.2). $I_2$ (508 mg, 2 mmol., 2.5 equiv.) was then added to the vigorously stirred reaction medium. After 24 h, water was poured, and the mixture was extracted with $Et_2O$. Organic phases were washed with sodium thiosulfate aqueous solution, with aqueous $NaHCO_3$, and brine, and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided a white solid, which was purified on an $SiO_2$ column ($CH_2Cl_2$) to give the pure aldehyde **4** (126 mg, 57%).
11. **(1*S*,4*R*,5*S*,8*R*,9*S*,11*S*,12*S*) - 1,5,9 - Trimethyl - 10,13,14,15-tetraoxatetracyclo[9.3.1.$0^{4,12}$.$0^{8,12}$]pentadecane - 9α - carbaldehyde (4)**. White solid; mp 105°C (AcOEt/petroleum ether); $[\alpha]_D = +131$ (*c* 0.51 MeOH); IR $\nu_{CO}$ 1722 $cm^{-1}$; $^1H$ NMR $\delta$ 0.99 (d, $^3J = 6.5$ Hz, 3H, $CH_3$-15), 1.05 (ddd, $^2J = 13.5$ Hz, $^3J_{H7ax\text{-}H8ax} = 12$ Hz, $^3J_{H7ax\text{-}H6} = 3$ Hz, 1H, H-7ax), 1.18 (s, 3H, $CH_3$-16), 1.25 (m, 1H, H-6), 1.30 (qd, $^2J = {}^3J_{H8ax\text{-}H7ax} = {}^3J_{H8ax\text{-}H8a} = 13.5$ Hz, $^3J_{H8ax\text{-}H7eq} = 3$ Hz, 1H, H-8ax), 1.39 (m, 1H, H-5ax), 1.43 (s, 3H, $CH_3$-14), 1.51 (td, $^3J_{H5a\text{-}H5ax} = {}^3J_{H5a\text{-}H\text{-}6} = 12$ Hz, $^3J_{H5a\text{-}5eq} = 6$ Hz, 1 H, H-5a), 1.68 (qd, $^2J = 13.5$ Hz, $^3J_{H7eq\text{-}H6} = {}^3J_{H7eq\text{-}H8ax} = {}^3J_{H7eq\text{-}H8eq} = 3.5$ Hz, 1H, H-7eq), 1.78 (td, $^2J = 13.5$ Hz, $^3J_{H8eq\text{-}H7eq} = {}^3J_{H8eq\text{-}H7ax} = 3$ Hz, 1H, H-8eq), 1.98 (dddd, $^2J = 14$ Hz, $^3J_{H5eq\text{-}H4ax} = 4$ Hz, $^3J_{H5eq\text{-}H4eq} = 3.5$ Hz, $^3J_{H5eq\text{-}H5a} = 5.5$ Hz, 1H, H-5eq), 2.07 (td, $^2J = 15$ Hz, $^3J_{H4eq\text{-}H5ax} = {}^3J_{H4eq\text{-}H5eq} = 4$ Hz, 1H, H-4eq), 2.25 (dd, $^3J_{H8a\text{-}8ax} = 13.5$ Hz, $^3J_{H8a\text{-}H8eq} = 4$ Hz, 1H, H-8a), 2.29 (dd, $^2J = 13$ Hz, $^3J_{H4ax\text{-}H5eq} = 4$ Hz, 1H, H-4ax), 5.77 (s, 1H, H-12), 9.99 (s, 1H, H-10); $^{13}C$ NMR $\delta$ 17.6 (C-16), 19.5 (C-15), 24.5 (C-5), 24.6 (C-8), 25.2 (C-14), 32.2 (C-7), 36.8 (C-6), 37.0 (C-4), 47.5 (C-5a), 51.8 (C-8a), 86.3 (C-12a), 89.8 (C-9), 96.9 (C-12), 103.5 (C-3), 207.4 (C=O). Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.68; H, 7.91.