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Stereoselective Oxidations of a β-Methylglycal, Anhydrodihydroartemisinin

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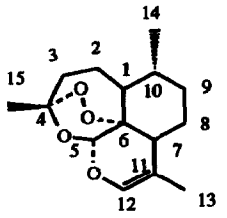
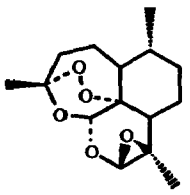
Abstract: Anhydrodihydroartemisinin (**1**) was epoxidized with MCPBA-2KF and the resulting 11β,12β-epoxide (**2**) treated with acidic aqueous acetone to yield 11β-hydroxydihydroepiartemisinin (**5**). The major product of the reaction of **1** with catalytic quantities of osmium tetroxide using NMO as a co-oxidant was 11α-hydroxydihydroartemisinin (**4**). Both **4** and **5** were oxidized to the corresponding 11-hydroxyartemisinins.

Recent interest in the use of glycals for the preparation of 2-deoxyglucosides,[1] as intermediates in the synthesis of trisaccharides[2] and as strategic components in the solid-phase synthesis of oligosaccharides[3] prompts us to report our studies on an unusual β-methyl glycal, anhydrodihydroartemisinin (**1**). In their proposed solid phase synthesis Danishefsky *et al.* [2,3] converted glucals into oxiranes, which were reacted with alcohols, sugars etc. The stereochemistry of the oxirane therefore determined the configuration at the β-carbon of the glucoside. Thus, a mixture of oxiranes produces complex isomeric mixtures of disaccharides. Here we report on the use of a difference in the reactivities of a mixture of isomeric oxiranes (**2** and **3**) to purify **2** and in the stereoselective synthesis of a diol (**4**) possessing the opposite stereochemistry at the β–methyl group of the glycal. The diol is therefore a possible precursor of the less stable oxirane (**3**).



1



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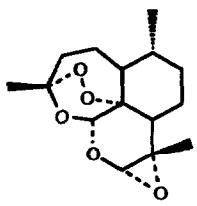

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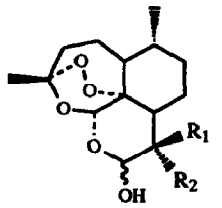
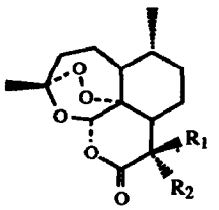
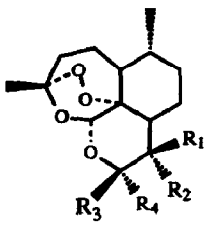


4. $R_1 = CH_3$, $R_2 = OH$
5. $R_1 = OH$, $R_2 = CH_3$
8. $R_1 = CH_3$, $R_2 = H$



6. $R_1 = CH_3$, $R_2 = OH$
7. $R_1 = OH$, $R_2 = CH_3$
14. $R_1 = CH_3$, $R_2 = H$



9. $R_1 = CH_3$, $R_2 = H$, $R_3 = OC_2H_5$, $R_4 = H$
10. $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = OC_2H_5$
11. $R_1 = OH$, $R_2 = CH_3$, $R_3 = OC_2H_5$, $R_4 = H$
12. $R_1 = CH_3$, $R_2 = OH$, $R_3 = OC_2H_5$, $R_4 = H$
13. $R_1 = CH_3$, $R_2 = OH$, $R_3 = H$, $R_4 = OC_2H_5$

Petrov and Ognyanov[4] prepared **2** from **1** using a complex of *m*-chloroperbenzoic acid and KF (MCPBA-2KF). The structure and stereochemistry of **2** were later confirmed by Hufford *et al.* [5] by x-ray crystallography. We repeated Petrov and Ognyanov's synthesis of **2** and an ^{1}H nmr analysis of the crude reaction mixture showed it to be a 4:1 mixture of **2** and **3**. In the course of separating the isomeric oxiranes, we observed that **3** reacted more rapidly with water than did **2**. This difference in reactivities was employed to purify **2** by flash chromatography on silica gel under conditions in which the α-oxirane was converted into 11α-hydroxydihydroartemisinin **4**. The isomeric diol, 11β-hydroxydihydroartemisinin (**5**) was prepared from **2** by reaction with acidic aqueous acetone.[6] Since synthetic procedures for converting diols into oxiranes exist[7], we sought a stereoselective synthesis of **4** from **1**. Hufford *et al.* [5] had reacted **1** with stoichiometric quantities of osmium tetroxide, in the presence of pyridine, and obtained an inseparable 1:1 mixture of **4** and **5**. A reinvestigation of this reaction demonstrated that using catalytic quantities of osmium tetroxide in *t*-butyl alcohol containing a co-oxidant N-methylmorpholine N-oxide (NMO)[8] produced a 10:1 mixture of **4**:**5**. Crystalline **4** was readily isolated from the mixture in 80% yield by flash chromatography. Although we are uncertain why the use of catalytic quantities of osmium tetroxide results in the observed stereoselectivity, it is tempting to speculate that in the absence of pyridine, osmium tetroxide coordinates with and is stabilized by the peroxide moiety facilitating reaction from the α–face of the glycal. Diols **4** and **5** were oxidized with Jones reagent to afford 11α-hydroxyartemisinin **6** and 11β-hydroxy-11-epiartemisinin **7**, respectively. Although **4** was not converted into the less stable oxirane **3** it was transformed into a ketal (dioxalane) using acetone containing sulfuric acid. Published procedures exist for converting dioxalanes into the corresponding oxiranes [9].

In addition to anhydrodihydroartemisinin being an unusual glycal, it is a valuable intermediate for the synthesis of artemisinin derivatives containing an 11-epi configuration[10]. Artemisinin **14** was isolated from a Chinese medicinal herb *Artemisia annua* and has been used to treat patients infected with drug-resistant strains of *Plasmodium falciparum* [11]. Thus, the synthesis and reactions of gram quantities of **2**, **4** and **5** have enabled us to prepare a number of derivatives for structure-activity studies. Dihydroartemisinin **8** was converted into its β-ethyl ether **9** using boron trifluoride etherate and ethanol.[12] Vishwakarma[13] had reported that **8** could be converted into α-arteether **10** on treatment with silver oxide and ethyl iodide in dry methylene chloride. To determine if the presence of a tertiary alcohol at C-11 would interfere with either reaction we reacted **5** and **4** with boron trifluoride and ethanol as well as under the alkaline conditions described by Vishwakarma. Under acidic conditions (boron trifluoride etherate) **5** yielded 11β-hydroxy-11-epi-β-arteether **11** in 40% yield, and **4** yielded 11α-hydroxy-β-arteether **12** in 60% yield. However, under alkaline conditions **4** yielded 11α-hydroxy-α-arteether **13** and **5** was recovered unchanged.

The antimalarial activities of a number of the above compounds were determined and the results are summarized in Table 1. Unfortunately, none of the compounds were more active than artemisinin.

Table 1.

Compound	IC_{50} artemisinin/IC_{50} compd. W-2 Clone	IC_{50} artemisinin/IC_{50} compd. D-6 Clone
2	0.1	0.1
4	0.4	0.6
11	0.06	0.08
12	0.3	0.4
13	0.2	0.2

Acknowledgement We wish to express our thanks to Dr. Robert Miller of the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D. C. 20307-5100 for determining the antimalarial activities of the compounds in Table 1.

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6. **11β-hydroxydihydro-epiartemisinin (5).** To a solution of **2** (500mg, 1.77 mmole) in acetone (120 mL) and water (40 mL) was added 1M H_2SO_4 (0.10 mL). The solution was stirred at room temperature for 5 min and extracted with CH_2Cl_2. The extract was washed with 1% aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporate to dryness. Flash chromatography on silica gel (TLC grade) with hexane:acetone (3:1) as eluant yielded **5** (430 mg, 80%). mp 133-135 °C; $[\alpha]_{589}$= +70° (*c* 0.30, $CHCl_3$); CI-MS (NH_3) 318 (M+ NH_4^+, 40%), 300 (M+ NH_4^+ -H_2O, 60%); δ_H ($CDCl_3$) 12α–epimer: 5.37 (1H, s, 5-CH), 4.95 (1H, s, 12-CH), 3.35, 2.30 (2H, s, D_2O exchangeable, 12-OH and 11-OH), 2.4-0.9 (11H, overlapping carbon skeleton protons), 1.53 (3H, s, 13-CH_3), 1.40 (3H, s, 15-CH_3), 0.94 (3H, d, J=5.8Hz, 14-CH_3); δ_C ($CDCl_3$) 20.1, 23.3, 24.5, 25.7, 28.1, 34.1, 36.5, 37.4, 50.5, 52.2, 70.7, 81.8, 88.6, 96.1, 103.5; 12β-epimer: 5.51 (1H, s, 5-CH), 5.26 (1H, s, 12-CH), 3.80, 2.30 (2H, s, D_2O exchangeable, 12-OH and 11-OH), 2.4-0.9 (11H, overlapping carbon skeleton protons), 1.45 (3H, s, 13-CH_3), 1.40 (3H, s, 15-CH_3), 0.94 (3H, d, J=5.8 Hz, 14-CH_3); δ_C 20.2,

23.0, 24.4 , 25.5, 29.7, 34.0, 36.3, 37.4, 50.6, 52.0, 71.3, 82.0, 91.7, 93.7, 104.4; FT-IR (KBr Pellet) 3430 (br.), 2964, 1040, 978cm^{-1}; Anal. for $C_{15}H_{24}O_6$; C% 59.98, H% 8.05; found 60.11, 8.10.

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8. **11α-hydroxydihydroartemisinin (4).** To a solution of 1 (1.1g, 4.13 mmole) and NMO (510 mg, 4.36 mmole) in *t*-butyl alcohol (60 mL) and water (5.0 mL) was introduced 1% OsO_4 t-butyl alcohol solution (4.0 mL, 0.16 mmole). The solution was stirred at rt for 4 h, then transferred to 200 mL of $CHCl_3$. The separated organic layer washed with water, dried over Na_2SO_4 and concentrated. Flash chromatography on a 150 mL Buchner funnel tightly packed with TLC grade silica gel (hexane:chloroform:acetone = 7:2:1) afforded 1.0 g of pure 4 (80%). mp 145-150°C; $[\alpha]_{589}$=+82° (*c* 0.22, $CHCl_3$); CI-MS (NH_3) 318 (M+ NH_4^+, 100%), 300 (M+ NH_4^+ -H_2O, 75%); δ_H ($CDCl_3$) 12α-epimer: 5.40 (1H, s, 5-CH), 4.76 (1H, s, 12-CH), 4.36, 3.86 (2H, s, D_2O exchangeable, 11-OH and 12-OH), 2.4-0.9 (11H, overlapping carbon skeleton protons), 1.46 (3H, s, 15-CH_3), 1.12 (3H, s, 13-CH_3), 0.97 (3H, d, J=5.8Hz, 14-CH_3); δ_C ($CDCl_3$) 20.3, 22.7, 24.5, 25.5, 25.9, 34.4, 36.4, 37.4, 49.2, 52.3, 71.0 , 83.4, 87.4, 100.1, 104.3; 12β-epimer: 5.69 (1H, s, 5-CH), 5.12 (1H, s, 12-CH), 4.68, 3.0 (2H, s, D_2O exchangeable, 11-OH and 12-OH), 2.4-0.9 (11H, overlapping carbon skeleton protons), 1.46(3H, s, 15-CH_3), 1.21 (3H, s , 13-CH_3), 0.96 (3H, d, J=5.8 Hz, 14-CH_3); δ_C 20.2, 22.1 , 24.5, 25.1, 25.9, 34.0, 36.2, 37.4, 49.5, 51.4, 71.9, 83.0, 90.8, 93.8, 104.5; FT-IR (KBr Pellet) 3500, 3330 (br.), 2964, 1050, 990 cm^{-1}; Anal. for $C_{15}H_{24}O_6$; C% 59.98, H% 8.05; found 60.25, 8.08.

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