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AN EFFICIENT SYNTHESIS OF NEW ANALOGS OF WATER-SOLUBLE AND HYDROLYTICALLY STABLE DEOXOARTEMISININ

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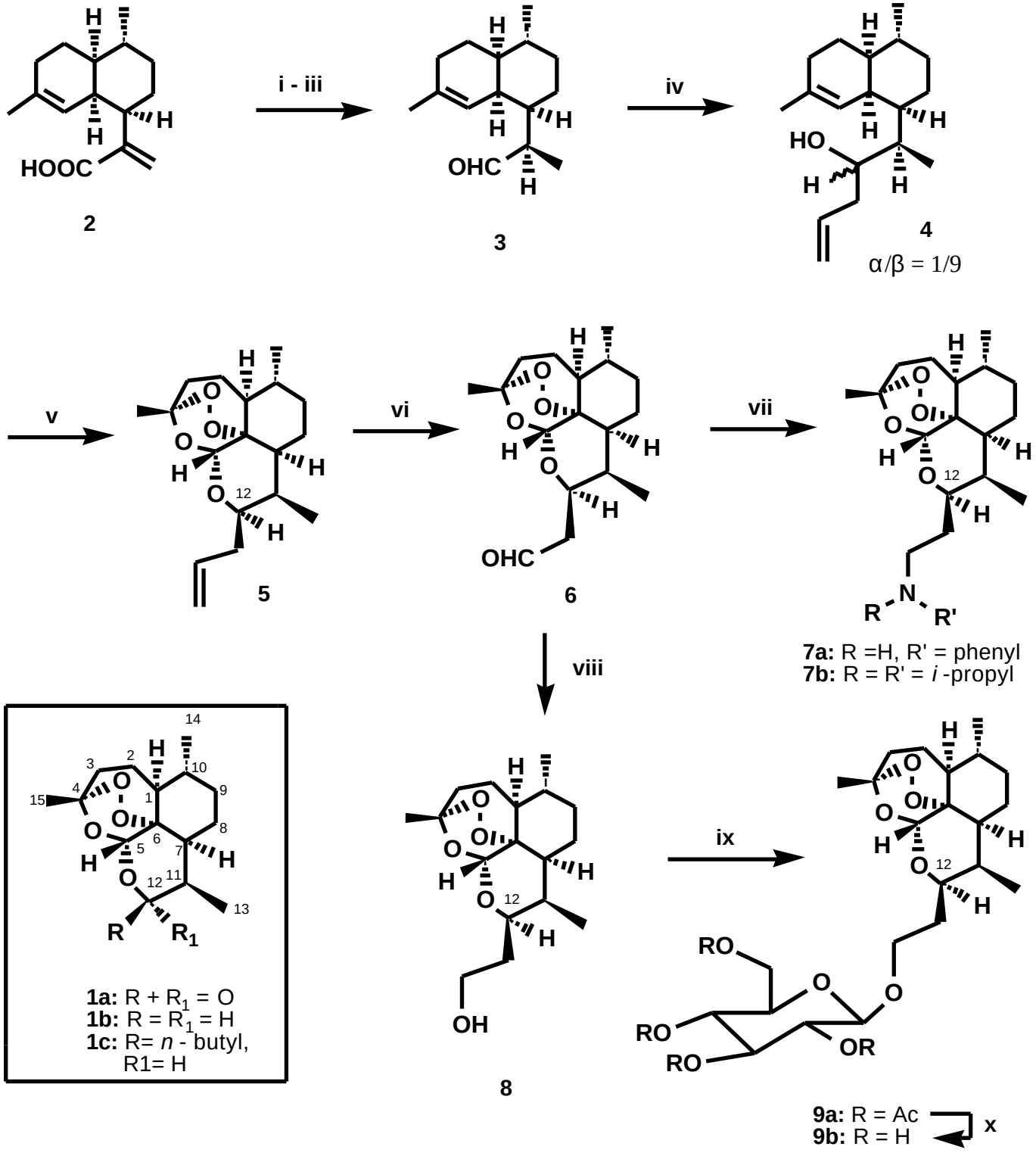
Abstract -Water-soluble and hydrolytically stable novel analogs of deoxoartemisinin were prepared from artemisinic acid in natural configuration.

Artemisinin (Qinghaosu) (**1a**), a sesquiterpene lactone endoperoxide isolated from *Artemisia annua* L. is the first and last natural trioxane to date. This compound has been subjected to a number of reviews[1] because of its novel structure and outstanding *in vitro* and *in vivo* antimalarial activity. Deoxoartemisinin (**1b**), prepared from either artemisinin or artemisinic acid (**2**) by Jung *et al.*[2a] is the first non-acetal type analog of artemisinin and shows more antimalarial activity than that of artemisinin both *in vitro* and *in vivo*.[2b] Non-acetal type analogs of deoxoartemisinins recently draw most attention for better bioavailability such as water solubility and long half life in the body for oral administration. Furthermore, evidence that analogs not possessing exo oxygen at C-12 are less neurotoxic in anaimal studies than acetal-type artemisinin is also emerging, thus bypassing the currently clinically used acetal-type analogs (artemether, arteether, artesunate, and artelinic acid).[3] Since the preparation of 12-n-butyldeoxoartemisinin (**1c**) as the first hydrolytically stable non-acetal type analog[4] containing C-C bond at C-12, a few of derivatives at C-12 have been prepared.[5] Recently some non-acetal type analogs with limited to heteroaryl and unsaturated substituents at C-12 have been also prepared directly from expensive artemisinin in short steps.[6] However, synthesis of the amino- and sugar- non-acetal type alkyl analogs has been unknown. In this communication, we would like to report the efficient synthesis of urgently needed non-acetal type analogs (**7a-b**, **9b**) of deoxoartemisinin as water-soluble and hydrolytically more stable compounds from readily available, cheap artemisinic acid (**2**).

A synthetic strategy for the conversion of (+)-artemisinic acid (**2**) into water-soluble and stable analogs (**7a-b**, **9b**) is outlined in Scheme 1. C-C bond was introduced into the C-12 position during Grignard reaction to increase stability. To improve water solubility, an amino group and a hydrophilic sugar moiety were introduced into at C-12 substituents of deoxoartemisinin. Artemisinic acid (**2**), 10 to 20 times more abundant than artemisinin in *A. annua*,[7] may be used as a versatile chiral synthon to artemisinin[8] and deoxoartemisinin derivatives.[1b] Thus, methyl artemisinate was prepared in 98 % yield from artemisinic acid (**2**) with diazomethane.[9] Reduction of methyl artemisinate by $NaBH_4$ (5.3 equiv.) gave its dihydro compound (93 % yield), which was then exposed to a second reduction with DIBAL-H(1.5 equiv.) to afford the dihydroartemisinylaldehyde (**3**) (70 % yield).[9] Grignard reaction of **3** can introduce the C-C



Scheme 1 : *Reagents and Conditions:* (**i**) CH_2N_2(2.5 equiv.), ether, O^oC, 30 min, 98 %. (ii) $NaBH_4$ [5.3 equiv.), $NiCl_2$ (cat.), CH_3OH, r t, 1.5 h, 93 %. (iii) DIBAL-H (1.5 equiv.), CH_2Cl_2,-78 ^oC, 2 h, 70 %. (iv) allyl bromide (5.4 equiv.) ether, N_2, rt., 1 h, 80 %. (v) oxygen, irradiation, methylene blue, CH_3CN/CH_2Cl_2 (1/1), -23 ^oC, 4 h, then triflic acid, CH_2Cl_2, -23 ^oC to rt, 5 h, 35 %. (vi) O_3, -78 ^oC, CH_2Cl_2, then Zn/HOAc, 53 %. (vii) aniline (3 equiv.), HOAc, THF, 0 ^oC, molecular sieves (4 A^o), $NaBH_3CN$ (2 equiv.), r t, 24 h, 54 % for **7a**. (viii) $NaBH_4$ (2.5 equiv.), CH_3OH/THF (9/1), 0 ^oC, 12 h, 71 %. (ix) acetobromo-D- glucose (6 equiv.), Ag_2CO_3 (3 equiv.), molecular sieves (4 A^o), benzene, rt, 72 h, 54 %. (x) 5N KOH (1.1 equiv.), CH_3OH/H_2O (4/1), 4 h, rt, 81 %.

bond at C-12, which at the same time carries allyl moiety. Coupling of **3** (11*R*) with the allyl bromide (5.4 eq.) cleanly afforded allylic alcohol (**4**) (80 % yield). The stereoselectivity at C-12 was dependant on the reaction temperature (12 α/ β = 1/9 at 0 ºC, 1/1 at room temperature). The allyl group of **4** serves as a masked equivalent for the formyl group of **6**. Dye-sensitized photooxygenative cyclization[2a] of a mixture (12 α/ β = 1/9) of the diastereomers (**4**) with oxygen, followed by *in situ* treatment of the intermediate mixture with a catalytic amount of strong acids such as Dowex resin, trifluoroacetic acid,[7] or triflic acid afforded 12-β-allyldeoxoartemisinin (**5**)[6a,9] (mp 75-77 ºC), [α]$_D^{25}$ +66 º (c 0.47, $CHCl_3$) in 35 % yield. This chiral oxidation of **4** led almost exclusively to β-configurated derivative (**5**). Although the yield for this key step was only moderate, this reaction represents one of the best methods to prepare these novel compounds in one step. Direct ozonolysis of the double bond of **5** into 12-β-(formylmethyl)-deoxoartemisinin (**6**)[6a,10] (oil), [α]$_D^{24}$ +41.6º (c 0.375, $CHCl_3$) was achieved with ozone (53 % yield). **6** is a versatile chiral intermediate for the synthesis of various novel analogs of artemisinin. Direct reductive amination of **6** with aniline (3 eq.) following *in situ* reduction with $NaBH_3CN$ (2 eq.) afforded 12-β-(2'-*N*-phenylaminoethyl)deoxoartemisinin (**7a**)[10] (oil) in 54 % yield in one step. Similar reductive amination of **6** with diisopropylamine (1 eq.) and $NaBH(OAc)_3$ (1.4 eq.) gave 12-β-(2'-*N, N'*-diisopropylaminoethyl)deoxoartemisinin (**7b**) in 78 % yield. Further reduction of **6** with $NaBH_4$ (2.5 eq.) gave 12-β-(2'-hydroxyethyl)deoxoartemisinin (**8**)[6a,10] (mp 102-104 ºC), [α]$_D^{25}$ +51º (c 0.35, $CHCl_3$) in 71 % yield. Direct conversion of **5** into **8** was achieved by treatment with ozone followed by *in situ* reduction with $NaBH_4$ (2.5 eq.). The endoperoxide of **6** was intact and not cleaved through both reduction with $NaBH_4$. This remarkable intactness could be explained on the basis of the deep location of the peroxide sterically hindered within the molecule. To improve the water solubility, hydrophilic sugar was introduced into **8**. Glycosidation of **8** with commercialy availableacetobromo-α-D-glucose (6 eq.) in the presence of silver carbonate (3 eq.) as a coupling agent afforded cleanly the glycoside (**9a**)[10] of deoxoartemisinin in 54 % yield. In this reaction, β-anomer was exclusively obtained. The NMR proton at anomeric center shows as a doublet ($J_{1',2'}$ = 13 Hz) at 4.5 ppm, which thus confirms the β-configuraion of the sugar moiety. Deacetylation of **9a** with KOH in CH_3OH finally gave the glycoside **9b**[10] of deoxoartemisinin in 81 % yield. The nine times increased water solubility of the glycoside (**9b**) was confirmed in > 4 mg/mL compared to 0.46 mg/mL[11] at 37 ºC of artemisinin. All new compounds (**6-9**)[10] and their stereochemistry were fully and satisfactorily characterized by spectral data as shown in the Scheme 1. β-configuraion at the C-12 position of compound (**5**) was retained during the manipulation to the target molecules (**7a-b**) and (**9b**). Because **7a-b** and **9b** are water-soluble and possess the exo C-C bond at C-12 resistant to normal chemical hydrolysis, they are projected to possess the increased stability as experimentally proven for the non-acetal anlogs,[12] and they point the way to potential new generation analogs.[4] **7a-b** are the first aminoalkyl analogs, whose synthesis has been awaited for a long time. In the preliminary result, the *in vitro* antimalarial activities of **7a** and **9b** are comparable to that of artemisinin. In conclusion, this synthesis represents a concise methodology to prepare new analogs of deoxoartemisinin as water-soluble (HCl salt for **7a-b**) and hydrolytically more stable antimalarial agents (**6-9**).

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10. All new compounds gave satisfactory analytical and spectral data. Selected spectral data for (**7a**): oil; $[\alpha]_D^{24}$ +29.9 º (c 0.215, $CHCl_3$); ^{1}H -NMR (250 MHz, $CDCl_3$,): δ7.15(m, 2H, phenyl), 6.66-6.61 (m, 3H, phenyl), 5.29 (s, 1H, H-5), 4.30 (m, 1H, H-12), 3.27 (dt, 2H, J= 6.8 Hz, 3.05 Hz, 2'-H), 2.25(m, 2H, 1'-H), 1.50 (s, 3H, 15-CH_3), 0.89 (d, J= 5.2 Hz, 3H, 13-CH_3), 0.86 (d, J= 7.45 Hz, 3H, 14-CH_3); IR (neat), max 3381(NH), 3043, 2934, 2870, 1605, 1499, 1459, 1078, 1043, 872, 739 $cm^{-1;}$ MS m/z: 389 (M^+). (**9b**): oil; $[\alpha]_D^{25}$ +26.0 º (c 0.2, CH_3OH); ^{1}H -NMR (250 MHz, D_2O): δ5.49(s, 1H, H-5), 4.69 (m, 1H, H-12), 4.36 (d, $J_{1',2'}$ = 7.94 Hz, 1H, H-1'), 4.12-3.37 (m, 4H, H-2', 3', 4', 5'), 3.14 (t, J= 9.06, 2H, H-6'), 2.55 (m, 1H, H-11), 1.28 (s, 3H, 15-CH_3), 0.82 (d, J= 5.62 Hz, 3H, 14-CH_3), 0.76 (d, J= 7.50 Hz, 3H, 14-CH_3); IR (neat), max 3440, 2920, 2869, 1190, 1046, 912 cm^{-1}; MS m/z: 472 (M^+).
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