A CONCISE SYNTHESIS OF NOVEL AROMATIC ANALOGS OF ARTEMISININ

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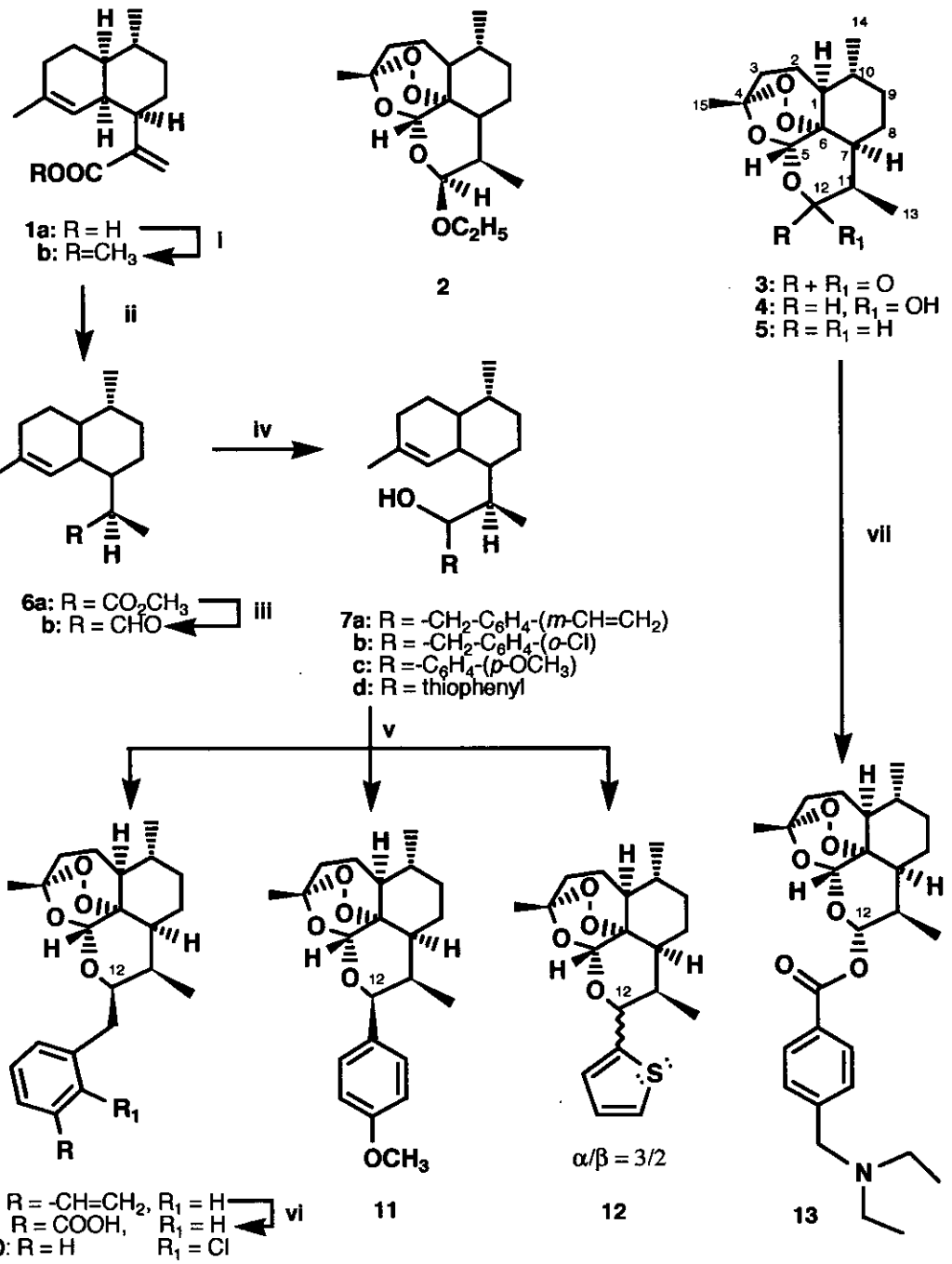
Abstract - Aromatic analogs of deoxoartemisinin were prepared from artemisinic acid *via* photooxygenative cyclization as a key step.

Artemisinin (Qinghaosu) (**3**), the active constituent of *Artemisia annua* has attracted much interest for synthesis[1-3] and derivatization[4a] due to its novel structure as the first 1, 2, 4-trioxane found in the nature and clinically useful antimalarial activity. Artemisinin analogs containing aromatic ring have never been isolated from *A. annua* and few aromatic analogs of deoxoartemisinin were prepared directly from artemisinin.[4b] Consequently little is known about the effect of an aromatic ring at C-12 on biological activity, particularly antimalarial activity.[4b] Aromatic rings are commonly involved in van der Waals interactions with flat hydrophobic regions of the binding site of the receptors.[5] Replacing the known alkyl groups[6] of deoxoartemisinin analogs with aromatic ring could increase van der Waals bonding, thus interact more efficiently with the clone of *Plasmodium falciparum*. It is of interest to study the effect of aromatic ring of deoxoartemisinin on antimalarial activity against *P. falciparum*. In this communication, we would like to report synthesis of novel aromatic analogs of urgently needed artemisinin-related antimalarial drugs. Artemisinic acid (**1a**) is a precursor in the biosynthesis of artemisinin[7] and may be used as a versatile chiral synthon to artemisinin derivatives.[8] A scheme for conversion of (+)-artemisinic acid (**1a**) into aromatic analogs (**8-13**) is shown in Scheme 1. Thus, methyl artemisinate (**1b**) was prepared in 98 % yield from artemisinic acid with diazomethane.[8] Reduction of **1b** by $LiBH_4$ (5.3 equiv.) gave **6a** in 95 % yield, which was then exposed to a second reduction with DIBALH to afford the dihydroartemisinylaldehyde, (**6b**) (yield 67 %).[6,9] Compound (**6b**) is a versatile chiral intermediate for the synthesis of various novel analogs of artemisinin.[6,9] Grignard reactions of **6b** can introduce the C-C bond at C-12, which at the same time carries aromatic moiety. Coupling of **6b** (11*R*) with the aromatic halides (3-vinylbenzyl bromide for **7a**, 2-chlorobenzyl chloride for **7b**, 4-methoxybenzyl bromide for **7c**, and 2-bromothiophene for **7d**) cleanly afforded aromatic alcohols (**7a-d**) (yields, 62 % for **7a**, 64 % for **7b**, 72 % for **7c** and 55 % for **7d**) respectively. The vinyl group of **7a** and **8** serves as a masked equivalent for the carboxyl group of **9**. Dye-sensitized photooxygenative cyclization[10,11] of the diastereomers of **7a-d** with oxygen, followed by treatment of the intermediate mixture with a catalytic amount of strong acids such as Dowex resin, trifluoroacetic acid,[11] or triflic acid afforded **8**, **10**,[12] and **11**[12] in 21 %, 36 % and 29 % yield, respectively. No 12 α-isomer was detected. The hetero analog (**12**)[12] was prepared in 18 % yield in the ratio of 12 α/ β= 3/2. The predominate 12*R*-α-isomer of **12**[12] was easily separated from their 12*S*-β-



Scheme 1. *Reagents and Conditions*: (i) CH_2N_2 (2.5 equiv.), anhydrous ether, O°C, 30 min,98 %. (ii) $LiBH_4$ (5.3 equiv.), $NiCl_2$ (cat), CH_3OH, rt, 1.5 h, 95 %. (iii) DIBALH (1.5 equiv.), CH_2Cl_2, -78 °C, 2 h, 67 %. (iv) 3-vinylbenzyl bromide (5.1 equiv.) for **7 a**, 2-chlorobenzyl chloride(5.1 equiv.) for **7b**, 4-methoxybenzyl bromide (5.2 equiv.) for **7c**, 2-bromothiophene (5.2 equiv.) for **7 d**, magnesium (2.4 equiv.), anhydrous ether, N_2, rt, 1 h, 55-72 %. (v) oxygen, irradiation, methylene blue, CH_2Cl_2, -23 °C, 2 h, then triflic acid, TFA, or Dowex resin (stronly acidic) (cat.), CH_2Cl_2, -23 °C to rt, 5 h, 18-36 %. (vi) $KMnO_4$ (3.0 equiv.), $NaHCO_3$ (0.5 equiv.), acetone, rt, 4 h, 67 %. (vii) 4-(*N,N*-diethylaminomethyl)benzoic acid (1.02 equiv.), DCC (1.0 equiv.), DMAP (cat.), CH_2Cl_2, rt, 24 h, 82 %.

isomer ($J_{12,11}$= 6.17 Hz at δ 5.59) by column chromatography (silica gel, hexane and ethyl acetate as eluents). 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. Oxidation of sulfur atom and [1, 4]-cycloaddition to 2,4-diene of thiophene ring of **12** did not occur because of aromaticity of the thiophene. Direct oxidation of the double bond of **8** into **9**[12] was achieved with $KMnO_4$ in one step (yield 67 %).[13] Coupling of dihydroartemisinin (**4**) with 4-(*N*,*N*-diethylaminomethyl)benzoic acid (DCC, DMAP, CH_2Cl_2, rt) afforded a new analog, 12-*p*-(*N*,*N*-diethylaminomethyl)benzoyldeoxoartemisinin (**13**)[12] (82 % yield) (Scheme 1). In this reaction, α-isomer was exclusively obtained ($J_{12,11}$ = 9.8 Hz). This result is consistent with the report that acylation of **4** in alkaline medium led almost exclusively to α-configurated derivatives.[14] The assignment of ^1H NMR and ^{13}C NMR signals was made on the basis of 2D-COSY and HETCOR spectra of **9** and **13**. The relative configuration at the new chiral centers (C-5, 6, 11 and 12) of **9** and **13** was unambiguously determined as depicted in Scheme 1 by utilization of two dimensional nOe (NOESY) techniques. They are of special interst because **9** and **13** are water-soluble as a salt. As compounds (**8**-**12**) lack the carbonyl function and exo C-O bond at C-12, they are projected to possess increased stability, thus longer half-life in the body and they point the way to potential new generation analogs.[6] 12-Thiophenyldeoxoartemisinin (**12**) is the first heterocyclic analog of deoxoartemisinin (**5**).[10] The amino ester (**13**) could be resistant to normal chemical hydrolysis because of the bulky aromatic moiety. Preliminary results reveal that aromatic analogs with electron-donating substituents show five to eight times more *in vitro* antimalarial activity compared to artemisinin (**3**).

In conclusion, this synthesis represents a concise methodology to prepare new aromatic analogs of deoxoartemisinin (**5**)[10] as water-soluble (sodium salt for **9** and ammonium salt for **13**) and chemically more stable antimalarial agents (**8**-**12**). Their aromatic ring effect on antimalarial activity will be reported in due course.

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12. Compound (**9**): oil; $[\alpha]_D^{25}$ +91.05 º (c 0.1, $CHCl_3$); NMR (250 MHz, $CDCl_3$,): δ 8.02(s, 1H, aromatic), 7.95 (d, J=7.7 Hz, 1H, aromatic), 7.61 (d, J= 7.8 Hz, 1H, aromatic), 7.41 (d, J= 7.3 Hz, 1H, aromatic), 5.43 (s, 1H, H-5), 4.70 (ddd, $J_{12,1'}$ = 10.1 Hz, $J_{12,1'}$ = 3.2 Hz, $J_{12,11}$= 3.8 Hz, 1H, H-12), 2.91 (dd, J= 14.55, 3.2 Hz, 2H, benzyl CH_2), 1.27 (s, 3H, 15-CH_3), 1.02 (d, J= 8.4 Hz, 3H, 13-CH_3), 0.99 (d, J= 3.7 Hz, 3H, 14-CH_3); IR ($CHCl_3$), max 3440(OH), 2932, 1692 (C=O), 1452, 1383, 1287, 1097 cm^{-1}; MS m/z: 388 (M^+).
Compound (**10**): oil; $[\alpha]_D^{25}$ -6.25 º (c 0.24, $CHCl_3$); NMR (250 MHz, $CDCl_3$,): δ 7.4-7.1 (m, 4H, benzene), 5.23 (s, 1H, H-5), 4.54 (ddd, $J_{12,1'}$ = 8.8 Hz, $J_{12,1'}$ = 3.2 Hz, $J_{12,11}$= 3.1 Hz, 1H, H-12), 2.92 (dd, J= 15.2, 3.2 Hz, 2H, benzyl CH_2), 1.46 (s, 3H, 15-CH_3), 1.02 (d, J= 7.6 Hz, 3H, 13-CH_3), 0.89 (d, J= 5.2 Hz, 3H, 14-CH_3); IR (benzene), max 2932, 1713, 1601, 1424, 1216, 1097 cm^{-1}; MS m/z: 376 (M^+-16), 358.
Compound (**11**): mp 196-197 ºC; $[\alpha]_D^{25}$ + 156 º (c 0.1, $CHCl_3$); NMR (250 MHz, $CDCl_3$,): δ 7.19 (d, J= 8.7 Hz, 2H, benzene-3', 5'), 6.84 (d, J=6.7 Hz, 2H, benzene-2', 6'), 5.47 (s, 1H, 5-H), 5.26 (d, $J_{12,11}$= 7.7 Hz, 1H, H-12), 3.81 (s, 3H, OCH_3), 1.59 (s, 3H, 15-CH_3), 1.00 (d, J= 3.2 Hz, 3H, 13-CH_3), 0.48 (d, J= 7.7 Hz, 3H, 14-CH_3); IR (KBr), max 2944, 2872, 1614, 1523, 1459, 1382, 1304, 1242, 1178, 1152, 1004, 979, 954 cm^{-1}; MS m/z: 358 (M^+-16), 340.
Compound (**12**) α-isomer: oil; $[\alpha]_D^{25}$ +22.8 º (c 0.47, $CHCl_3$); NMR (250 MHz, $CDCl_3$,): δ 5.41 (s, 1H, H-5), 4.66 (d, $J_{12,11}$ = 10.6 Hz, 1H, H-12), 2.63 (m, 1H, H-11), 1.42 (s, 3H, 15-CH_3), 0.98 (d, J= 6.0 Hz, 3H, 13-CH_3), 0.87 (d, J= 7.0 Hz, 3H, 14-CH_3); IR ($CHCl_3$), max 2928, 2873, 1734, 1659, 1453, 1378; 1220, 1045 cm^{-1}; MS m/z: (M-16, 334), 262.
Compound (**13**): oil; $[\alpha]_D^{25}$ - 45.30 º (c 0.05, $CHCl_3$); NMR (250 MHz, $CDCl_3$,): δ 8.05 (d, J= 8.4 Hz, 2H), 7.42 (d, J= 8.4 Hz, 2H), 6.01 (d, $J_{12,11}$ = 9.8 Hz, 1H, H-12), 5.52 (s, 1H, H-5), 3.61 (s, 2H, benzyl CH_2), 2.74 (m, 1H, H-11), 2.51 (q, J= 11.25, 4.05 Hz, 4H, 2ethyl), 2.38 (ddd, J= 3.75, 5.2, 4.15 Hz, 1H, H-2α), 2.03 (m, 1H, H-2β), 1.42 (s, 3H, 15-CH_3), 1.04 (t, J= 7.15 Hz, 6H, $2CH_3$), 0.98 (d, J= 5.95 Hz, 3H, 13-CH_3), 0.92 (d, J= 7.2 Hz, 3H, 14-CH_3); IR ($CHCl_3$): max 3400, 2934, 2876, 1739(C=O), 1612, 1453, 1267, 1031, 880 (peroxide) cm^{-1}; MS m/z: 473 (M^+).
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