ANTIMALARIAL ARTEMISININ ANALOGS: SYNTHESIS OF 2,3-DESETHANO-12-DEOXOARTEMISININ-RELATED COMPOUNDS

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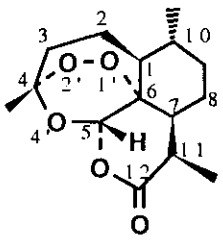
Abstract-----2,3-Desethano-12-deoxoartemisinin-related compounds ((+)-**16a**) and ((-)-**16b**) have been synthesized from *R*-(+)-citronellal (**7**) by a stereoselective manner, which is applied to the synthesis of various novel antimalarial artemisinin analogs.

Artemisinin (qinghaosu, **1**) is a clinically useful antimalarial sesquiterpene lactone endoperoxide isolated from the Chinese drug "Qing Hao" (*Artemisia annua* L.).[2,3] Its potent biological activity and novel chemical structure, coupled with the low yield from natural sources, have prompted syntheses of **1** and its analogs by many laboratories.[4]

Our previous studies [5] on the synthesis and structure-activity relationships among analogs of **1**, such as **2a**, **2b**, **3**, **4a** and **4b**, have indicated the importance of a steric environment of the 1',2',4'-trioxane ring system as found in **1**, **4a** and **4b** in contributing to the antimalarial activity.



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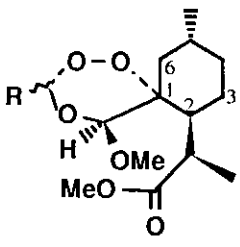
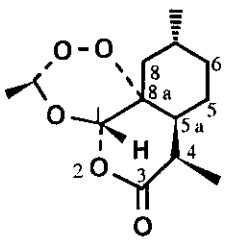


2a R=α-Me
2b R=β-Me



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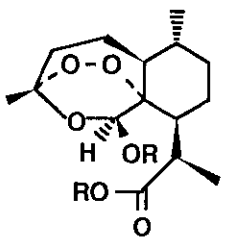
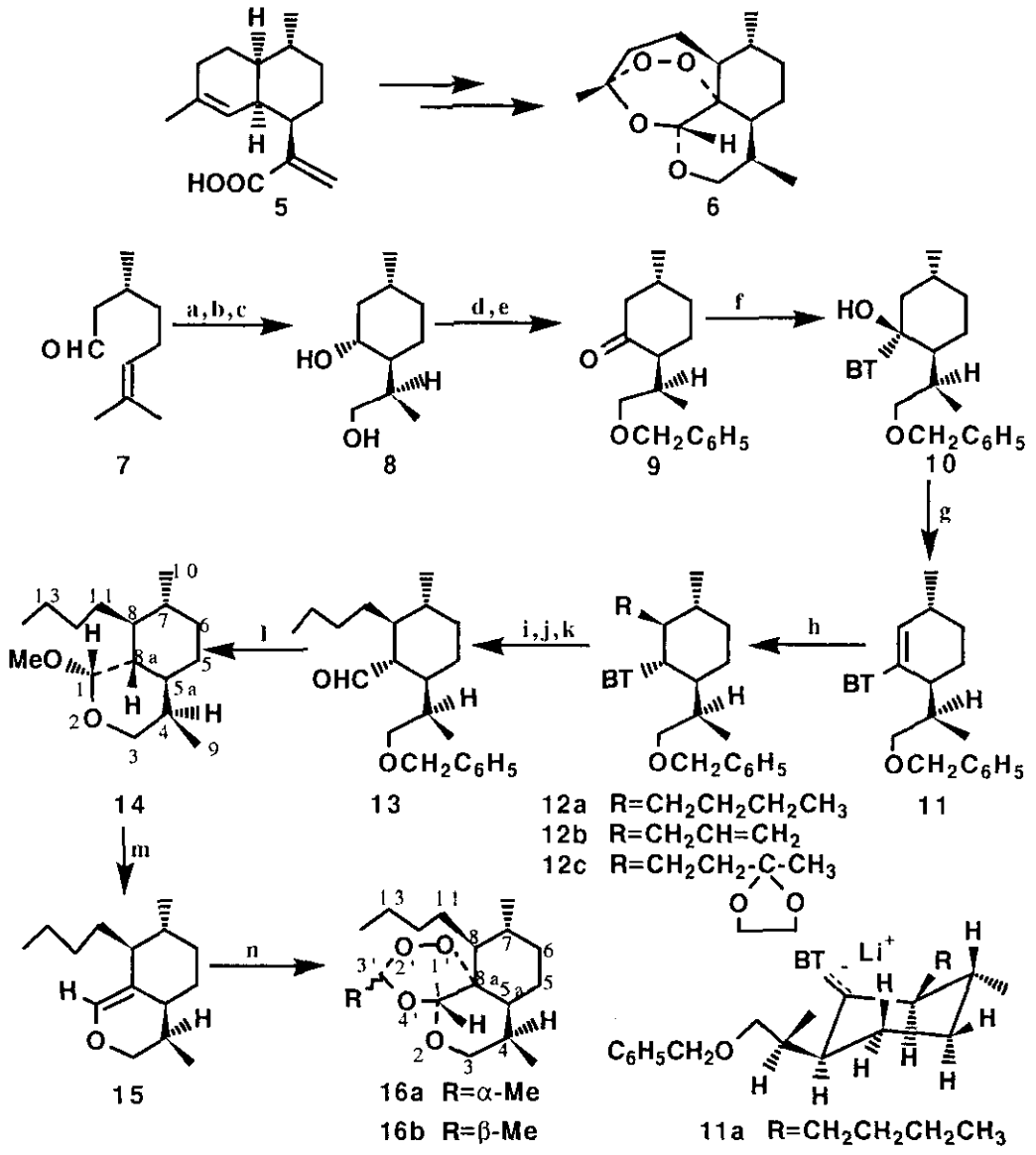


4a R=Me
4b R=Et



(a) $ZnBr_2$, 0~5 °C, Benzene; (b) B_2H_6; (c) NaOH, H_2O_2; (d) $C_6H_5CH_2Cl$, NaH, DMF; (e) Jones oxidation; (f) BT, n-BuLi, -70~-80 °C;. (g) $MeO_2CN^-SO_2N^+Et_3$; (h) n-BuLi; (i) $MeOSO_2F$; (j) $NaBH_4$; (k) $AgNO_3$; (l) p-TsOH, $(MeO)_3CH$, Xylene, Δ ; (m) 10% H_2SO_4, Δ ; (n) Rose Bengal, MeCHO, $^1O_2$, hν , -78 °C.

Scheme 1

Recently, Jung et al.[6] reported the conversion of artemisinic acid (**5**), obtained from *A. annua*, into (+)-deoxoartemisinin (**6**), which showed several fold more activity than **1** in the *in vitro* antimalarial assay against the chloroquine-resistant *Plasmodium falciparum*. As a result of our studies aimed at the development of a more practical and stereoselective synthesis of **1** and **6**,

and their analogs, we report herein on the stereoselective synthesis of **16a** and **16b** that possess an n-butyl group at C-1 instead of an ethane bridge between C-1 and C-4 as seen in **6** from *R*-(+)-citronellal (**7**).

As shown in Scheme 1, the dihydroxy compound (**8**) was prepared from **7** by the known procedures.[7] Partial benzylation of **8** with benzyl chloride and sodium hydride at 0 °C in DMF followed by oxidation with Jones reagent gave the ketobenzyl derivative (**9**) in 50 % yield. Treatment of **9** with benzothiazole (BT) and *n-BuLi* at -78 °C gave the BT carbinol [**10**; mp 104~105 °C; $[\alpha]_D$ -46.6°(*c* 1.0, $CHCl_3$)][8,9] in 44 % yield. Compound (**10**) was converted to a vinyl BT [**11**; mp 80~81 °C; $[\alpha]_D$ -40.7°(*c* 1.0, $CHCl_3$)][9] in 75 % yield upon reacting with the *cis* dehydration reagent, $MeOOCN^-SO_2N^+Et_3$[10] in dry benzene.

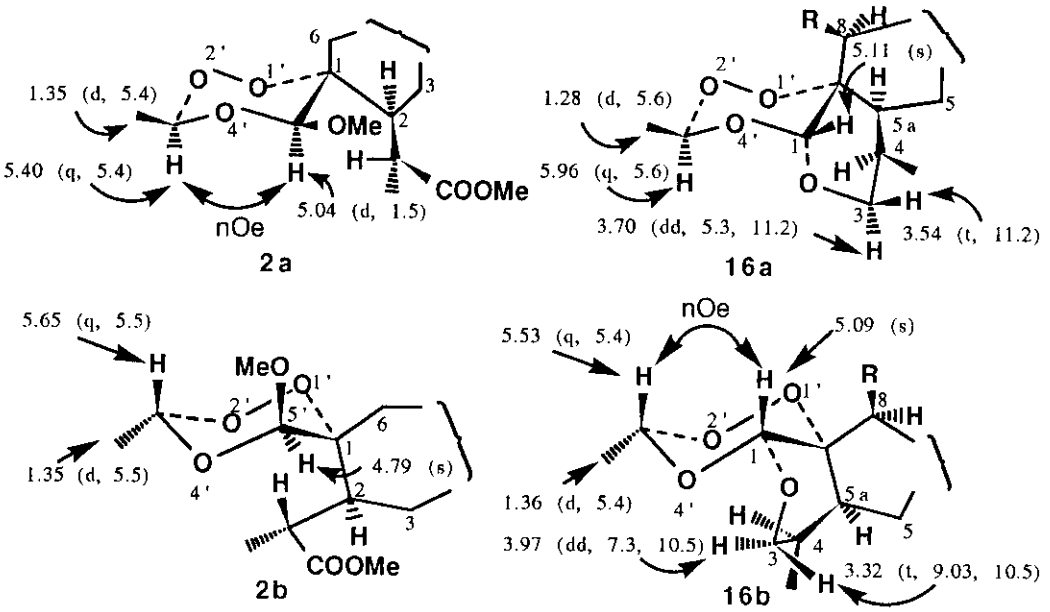
The conjugated addition[11] of n-BuLi to **11** in dry THF at -78 °C was followed by quenching of the resulting intermediate anion (**11a**) with absolute MeOH at -78 °C to furnish **12a** [mp 76~77 °C; $[\alpha]_D$ -71.2°(*c* 1.0, $CHCl_3$); 70 % yield][9] with both C-2 n-butyl and C-3 BT substituents to be *trans* equatorial. The stereochemistry of **12a** was established by the coupling patterns ($J_{2,3}$ = $J_{3,4}$ = 10.9 Hz) between H-2, H-3 and H-4 in the ^{1}H-nmr (^{1}H-^{1}H COSY spectrum), and by conversion to the corresponding *trans*-substituted aldehyde (**13**) as shown below.

Methylation of **12a** (2.0 mmol) with $MeOSO_2F$ (2.5 mmol, 2.5 h, CH_2Cl_2) followed by $NaBH_4$ reduction (9.5 mmol, -20 °C, 30 min, EtOH) and $AgNO_3$ hydrolysis gave *trans*-substituted aldehyde (**13**) [colorless oil; $[\alpha]_D$ -37.8°(*c* 0.5, MeOH)][9,12] in 60 % yield, which confirmed the assigned stereochemistry for **12a**. In the cases where the allyl position of the vinyl BT compound is not substituted by a methyl group, it is known that such conjugated addition would normally give rise to a *cis*-substituted BT compound as the major product.[11] Thus, the conjugate *trans* addition of the n-butyl group to the C-2 of **11** with the introduction of one axial proton from MeOH at C-3 indicates that a β-side attack of the n-butyl group is highly favored, due to the steric hindrance of the α-methyl group at C-1.

After stirring **13** (2.8 mmol) with $(MeO)_3CH$ (3 ml) and p-$TsOH{\cdot}H_2O$ (100 mg) in MeOH (6 ml) for 2 h at room temperature, xylene (3 ml) was added, and the mixture was further refluxed for 2 h to yield **14** [pale yellow oil; $[\alpha]_D$ -71.5°(*c* 0.4, MeOH); 90 % yield].[9] Compound (**14**) is presumably formed *via* debenzylation after forming dimethyl acetal from **13**, and its relative configuration at C-1, C-4, C-5a, C-8, and C-8a was unambiguously determined by use of nOe and decoupling techniques from its ^{1}H-nmr spectrum.[13]

Removal of a molecule of methanol from **14** by heating with 10 % H_2SO_4 at 130 °C gave **15** [pale yellow oil; $[\alpha]_D$ -53.9°(*c* 0.5, MeOH)][9] in 62 % yield. Photooxygenation of **15** with MeCHO in the presence of Rose Bengal at -70~-78 °C under a bubbling stream of oxygen afforded a 31 % yield of a mixture of diastereomers [**16a** and **16b**; **16a**:**16b** = 1.3:1.0, based upon a ^{1}H-nmr analysis),

which was separated by silica gel column chromatography (n-hexane:Et_2O = 10:1) to give pure **16a** [colorless oil; $[\alpha]_D$ -70.2°(*c* 0.5, MeOH)][9] and **16b** [colorless oil; $[\alpha]_D$ +65.1°(*c* 0.5, MeOH)].[9] The stereochemistries of **16a** and **16b** were established by comparing their ^{1}H-nmr spectral data ($CDCl_3$, δ) with those of **2a** and **2b**, prepared previously.[5]



Scheme 2

As shown in Scheme 2, the H-3' signal in **16a** shows a downfield shift by 0.43 ppm compared to that in **16b**, indicating that H-3' and O-1 are in a 1,3-diaxial relationship, which are found for the H-3' and OMe-5' of **2b**. On the other hand, the nOe enhancement (10 %) observed between H-1 and H-3' in **16b**, established their 1,3-diaxial relationship, which is also seen for H-3' and H-5' of **2a**. Consequently, the stereostructures of **16a** and **16b** were established as those depicted in Schemes 1 and 2.

The *in vitro* antimalarial bioassay of **16a** and **16b** , and the stereoselective total synthesis of 1 and 6 as well as their analogues *via* minor modifications of the synthetic sequence, such as the formation of **12b** and **12c**, involved in Scheme 1 are in progress.

References and Notes

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9. All new substances exhibited satisfactory spectroscopic (nmr, ir, ms) and elemental analyses or high resolution mass spectral analytical data.

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12. In the ^{1}H-nmr spectrum of **13**, large coupling constants ($J_{2,3}$ = $J_{3,4}$ = 10.6 Hz) were observed between H-2, H-3 and H-4, indicating their axial-orientation.

13. **14** : ^{1}H-Nmr ($CDCl_3$): δ 0.83 (3H, d, J = 5.9 Hz, Me-7), 0.90 (3H, t, J = 6.6 Hz, Me-13), 0.99 (3H, d, J = 7.0 Hz, Me-4), 1.53 (1H, dt, J = 11.2, 3.5 Hz, βH-8a), 1.54 (1H, m, αH-4), 1.74 (1H, tt, J = 11.2, 4.0 Hz, αH-8), 3.29 (1H, dd, J = 11.0, 1.2 Hz, βH-3), 3.35 (3H, s, αMeO-1), 3.91 (1H, dd, J = 11.0, 2.7 Hz, αH-3), 4.57 (1H, d, J = 3.5 Hz, βH-1). The nOe enhancement (7~14 %) was observed between OMe-1, αH-3 and αH-5a, establishing that OMe group at C-1 is α.

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