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.
Recently, Jung et al.\(^6\) reported the conversion of artemisinic acid (5), obtained from *A. annua*, into (+)-deoxyartemisinin (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. 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; [α]D -46.6°(c 1.0, CHCl3)]8,9 in 44 % yield. Compound (10) was converted to a vinyl BT [11; mp 80-81 °C; [α]D -40.7°(c 1.0, CHCl3)]9 in 75 % yield upon reacting with the cis dehydration reagent, MeOOCN-SO2N+Et310 in dry benzene.

The conjugated addition11 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; [α]D -71.2°(c 1.0, CHCl3); 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 (J2,3 = J3,4 = 10.9 Hz) between H-2, H-3 and H-4 in the 1H-nmr (1H-1H COSY spectrum), and by conversion to the corresponding trans-substituted aldehyde (13) as shown below.

Methylation of 12a (2.0 mmol) with MeOSO2F (2.5 mmol, 2.5 h, CH2Cl2) followed by NaBH4 reduction (9.5 mmol, -20 °C, 30 min, EtOH) and AgNO3 hydrolysis gave trans-substituted aldehyde (13) [colorless oil; [α]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·H2O (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; [α]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 1H-nmr spectrum.13

Removal of a molecule of methanol from 14 by heating with 10 % H2SO4 at 130 °C gave 15 [pale yellow oil; [α]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 1H-nmr analysis).
which was separated by silica gel column chromatography (n-hexane:Et2O = 10:1) to give pure 16a [colorless oil; [α]D$^\text{D}$ -70.2°(c 0.5, MeOH)$^9$] and 16b [colorless oil; [α]D$^\text{D}$ +65.1°(c 0.5, MeOH)$^9$].

The stereochemistries of 16a and 16b were established by comparing their $^1$H-nmr spectral data (CDCl$_3$, 5) 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 stereostuctures 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.


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 (CDCl3): 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, $\beta$H-8a), 1.54 (1H, m, $\alpha$H-4), 1.74 (1H, tt, $J = 11.2, 4.0$ Hz, $\alpha$H-8), 3.29 (1H, dd, $J = 11.0, 1.2$ Hz, $\beta$H-3), 3.35 (3H, s, $\alpha$MeO-1), 3.91 (1H, dd, $J = 11.0, 2.7$ Hz, $\alpha$H-3), 4.57 (1H, d, $J = 3.5$ Hz, $\beta$H-1). The nOe enhancement (7–14 %) was observed between OMe-1, $\alpha$H-3 and $\alpha$H-5a, establishing that OMe group at C-1 is $\alpha$.

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