

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

Yasuhiro Imakura,* Katsutoshi Hachiya,^{1a} Tomomi Ikemoto,^{1b}

Shigeru Kobayashi,^{1c} and Shinsuke Yamashita

Faculty of Sciences, Naruto University of Education, Takashima, Naruto-shi, Tokushima 772, Japan

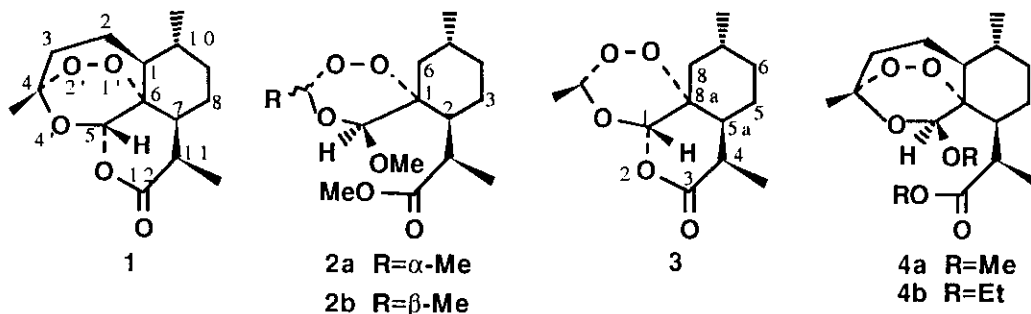
Jinsaku Sakakibara, Forrest T. Smith, and Kuo-Hsiung Lee

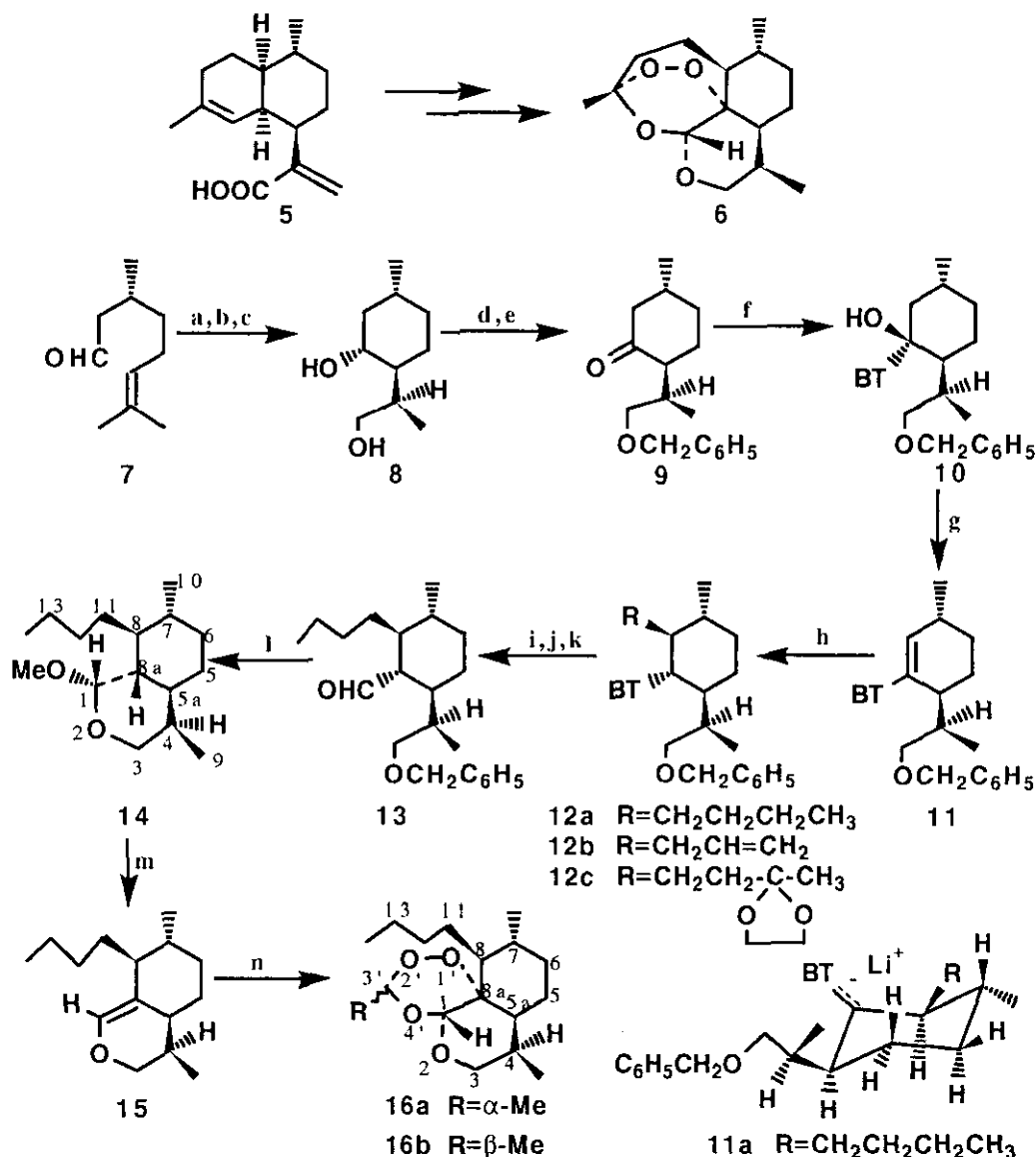
Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, U.S.A.

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 studies⁵ 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.





(a) ZnBr₂, 0~5 °C, Benzene; (b) B₂H₆; (c) NaOH, H₂O₂; (d) C₆H₅CH₂Cl, NaH, DMF; (e) Jones oxidation; (f) BT, n-BuLi, -70~-80 °C; (g) MeO₂CN⁻SO₂N⁺Et₃; (h) n-BuLi; (i) MeOSO₂F; (j) NaBH₄; (k) AgNO₃; (l) p-TsOH, (MeO)₃CH, Xylene, Δ; (m) 10% H₂SO₄, Δ; (n) Rose Bengal, MeCHO, ¹O₂, hv, -78 °C.

Scheme 1

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.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; $[\alpha]_D -46.6^\circ$ (*c* 1.0, CHCl₃)]^{8,9} in 44 % yield. Compound (**10**) was converted to a vinyl BT [**11**; mp 80~81 °C; $[\alpha]_D -40.7^\circ$ (*c* 1.0, CHCl₃)]⁹ in 75 % yield upon reacting with the *cis* dehydration reagent, MeOOCN-SO₂N⁺Et₃¹⁰ in dry benzene.

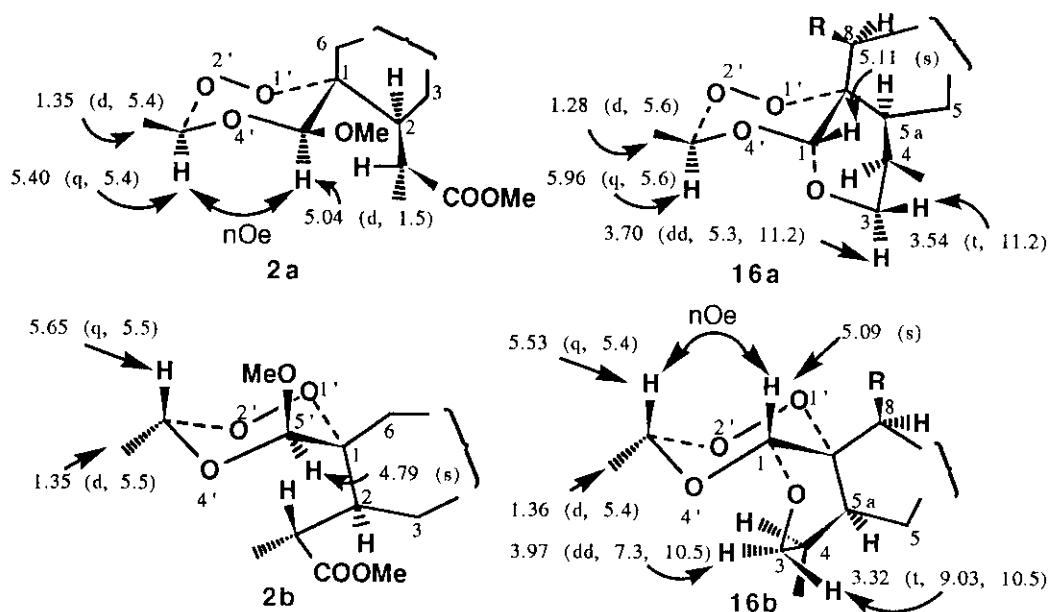
The conjugated addition¹¹ of *n*-BuLi to **11** in dry THF at -78 °C was followed by quenching of the resulting intermediate anion (**11a**) with absolute MeOH at -78 °C to furnish **12a** [mp 76~77 °C; $[\alpha]_D -71.2^\circ$ (*c* 1.0, CHCl₃); 70 % yield]⁹ with both C-2 *n*-butyl and C-3 BT substituents to be *trans* equatorial. The stereochemistry of **12a** was established by the coupling patterns ($J_{2,3} = J_{3,4} = 10.9$ 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; $[\alpha]_D -37.8^\circ$ (*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; $[\alpha]_D -71.5^\circ$ (*c* 0.4, MeOH); 90 % yield].⁹ Compound (**14**) is presumably formed *via* debenylation 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; $[\alpha]_D -53.9^\circ$ (*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; $[\alpha]_D -70.2^\circ(c\ 0.5, \text{MeOH})$]⁹ and **16b** [colorless oil; $[\alpha]_D +65.1^\circ(c\ 0.5, \text{MeOH})$]⁹. The stereochemistries of **16a** and **16b** were established by comparing their ¹H-nmr spectral data (CDCl₃, 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

1. Current address: a) Medicinal Chemistry, Ono Pharmaceutical Co. LTD., Sakurai, Misima-gun, Osaka 618, Japan. b) Vitamin and Food Division, Takeda Chemical Ind. Co. LTD., Hikaru-shi, Yamaguchi 743, Japan. c) Faculty of Home Economics, Shikoku Women's University, Furukawa, Ohjin-cho, Tokushima 770, Japan.

2. W. S. Zhou, *Pure and Appl. Chem.*, 1986, **58**, 817, and the literatures cited therein.
3. D. L. Klayman, *Science*, 1985, 1049, and the literatures cited therein.
4. Synthesis of 1: T. Ravindranathan, M. A. Kumar, R. B. Menon, and S. V. Hiremath, *Tetrahedron Lett.*, 1990, **31**, 755; F. Binns and T. Wallace, *Tetrahedron Lett.*, 1989, **30**, 1125; M. A. Avery, C. Jennings-White, and W. Chong, *Tetrahedron Lett.*, 1987, **38**, 4629; X. Xu, J. Zhu, D. Huang, and W. Zhou, *Tetrahedron*, 1986, **42**, 818; G. Clark, M. Nikaido, C. Fair, and J. Lin, *J. Org. Chem.*, 1985, **50**, 1994; G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983, **105**, 624.
Synthesis of analogs related to 1: S. Tani, N. Fukamiya, H. Kiyokawa, H. A. Musallum, R. O. Pick, and K. H. Lee, *J. Med. Chem.*, 1985, **28**, 1743; M. A. Avery, C. Jennings-White, and W. Chong, *J. Org. Chem.*, 1989, **54**, 1792; J. Kepler, A. Philip, Y. Lee, M. Morey, and F. Carroll, *J. Med. Chem.*, 1988, **31**, 713
5. Y. Imakura, T. Yokoi, T. Yamagishi, J. Koyama, H. Hu, D. R. McPhail, and K. H. Lee, *J. Chem. Soc., Chem. Commun.*, 1988, 372; Y. Imakura, K. Hachiya, T. Ikemoto, S. Yamashita, M. Kihara, S. Kobayashi, T. Shingu, W. K. Milhous, and K. H. Lee, *Heterocycles*, 1990, **31**, 1011.
6. M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, and J. D. Mchensney, *Tetrahedron Lett.*, 1989, **30**, 5973.
7. Y. Nakatani and K. Kawashima, *Synthesis*, 1978, 147; K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, 1967, **50**, 153.
8. E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 1978, 5.
9. All new substances exhibited satisfactory spectroscopic (nmr, ir, ms) and elemental analyses or high resolution mass spectral analytical data.
10. E. M. Burgess, H. R. Renton, and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.
11. E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 1978, 9 and 12.
12. In the ^1H -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 : ^1H -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, $\beta\text{H-8a}$), 1.54 (1H, m, $\alpha\text{H-4}$), 1.74 (1H, tt, $J = 11.2, 4.0$ Hz, $\alpha\text{H-8}$), 3.29 (1H, dd, $J = 11.0, 1.2$ Hz, $\beta\text{H-3}$), 3.35 (3H, s, $\alpha\text{MeO-1}$), 3.91 (1H, dd, $J = 11.0, 2.7$ Hz, $\alpha\text{H-3}$), 4.57 (1H, d, $J = 3.5$ Hz, $\beta\text{H-1}$). The nOe enhancement (7~14 %) was observed between OMe-1, $\alpha\text{H-3}$ and $\alpha\text{H-5a}$, establishing that OMe group at C-1 is α .

Received, 7th November, 1990