Bioorganic & Medicinal Chemistry Letters, Vol.1, No.12, pp. 741-744, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

A CONCISE SYNTHESIS OF 12-(3'-HYDROXY-n-PROPYL)-DEOXOARTEMISININ

Mankil Jung* [a,b], Duyi Yu[a], Daniel Bustos[a], Hala N. ElSohly[a], and James D. McChesney[a,c]

[a] Research Institute of Pharmaceutical Sciences,
Departments of [b] Medicinal Chemistry and [c] Pharmacognosy,
School of Pharmacy,
University of Mississippi, University, MS 38677

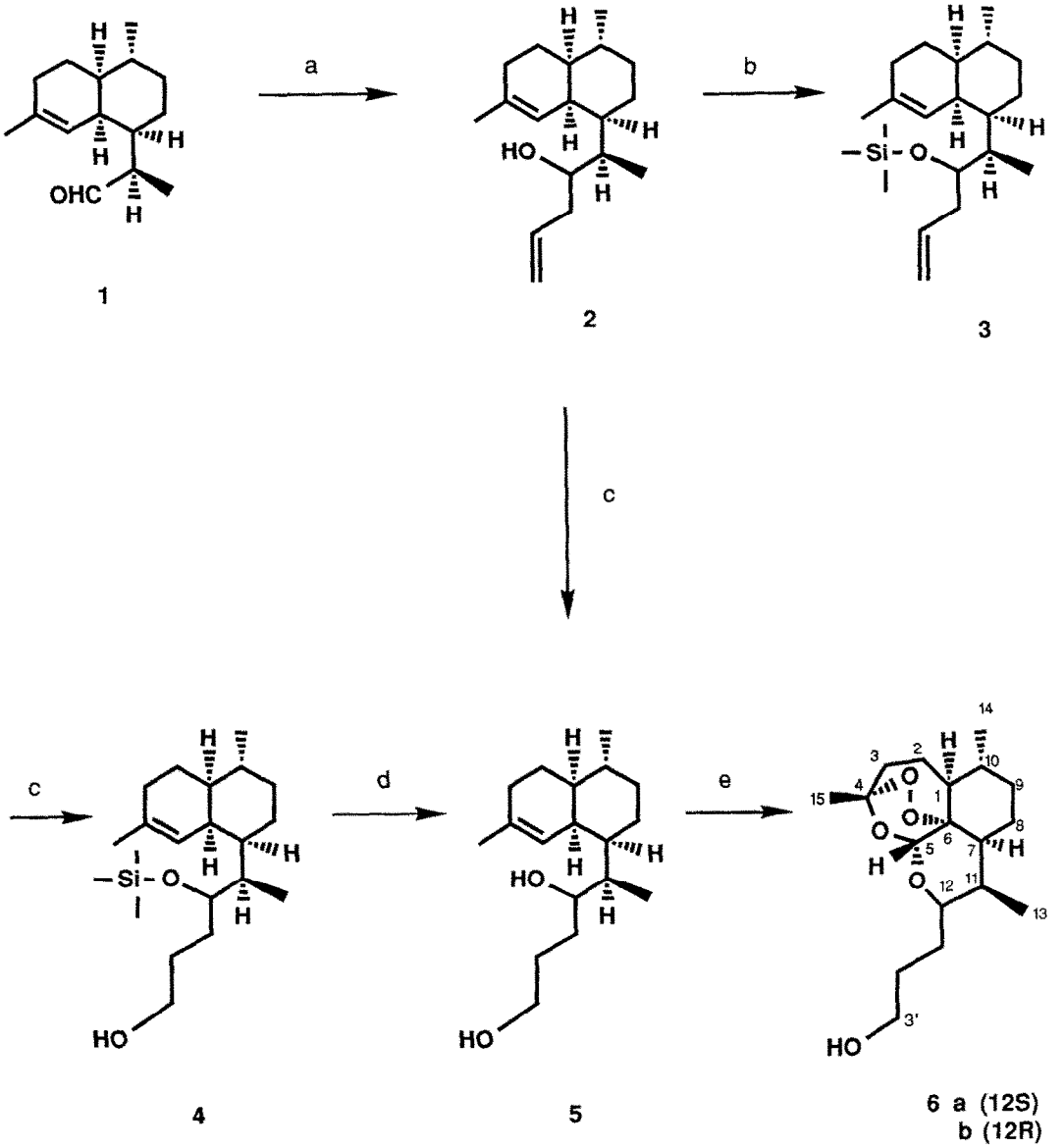
(*Received* 6 *September* 1991)

Abstract: The 12-(3'-hydroxy-n-propyl)-deoxoartemisinin was synthesized from artemisinic acid *via* photooxidative cyclization as a key step. The title compound **6a** is found to show five times greater *in vitro* antimalarial activity compared to artemisinin.

In an ongoing search for new and therapeutically useful antimalarials, we sought to synthesize deoxoartemisinin (deoxoqinghaosu) analog, **6**[1]. Artemisinin analogs lacking the carbonyl function at C-12 are projected to possess increased stability, thus longer half-life in the body[2]. However, it is difficult to prepare **6** from artemisinin by direct derivatization at C-12 due to the chemically labile functional groups within the molecule. In this communication, we wish to report a successful synthesis of **6**.

Because of its greater abundance[3] and suitable stereochemical configuration, artemisinic (qinghao) acid is a useful chiral synthon for the preparation of artemisinin analogs[4]. A strategy for a conversion of (+)-artemisinic acid into 12-(3'-hydroxy-n-propyl)-deoxoartemisinin, **6** is outlined in Scheme 1. Grignard addition to dihydroartemisinylaldehyde **1**, prepared from artemisinic acid[1c], with allylmagnesiumbromide (2.88 eq.) in anhydrous ether (r. t., 30 min.) afforded **2** (12S/12R=1:1) in 62 % yield. Treatment of **2** with t-butyldimethylsilyl chloride (imidazole, DMF, r.t.) gave **3** (93 %) and hydroboration of **3** with 9-BBN in anh. THF (r.t., 24 h.) and subsequent oxidation with 30 % hydrogen peroxide/2N-sodium hydroxide (50 °C, 1 h.) afforded **4** (71 %) with high regioselectivity. The silyl protecting group of the secondary alcohol of **4** was cleanly removed by treatment with tetrabutylammonium fluoride in anh. THF (r.t., 20 h.) to give the diol **5** in high yield (90 %). **5** was also directly prepared from **2** with 9-BBN and subsequently hydrogen peroxide/sodium hydroxide, as described above, in 80 % yield. Chiral photooxidation of **5** with oxygen [irradiation with 450-W medium pressure mercury arc lamp at -78 °C, methylene blue(cat.)] in methylene chloride, followed by acidic Dowex-resin

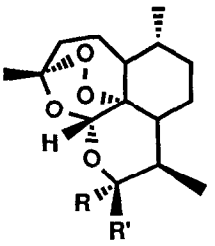
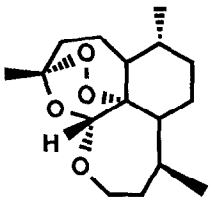
Scheme 1.



a) allyl bromide, Mg, anh. ether, r.t., 30 min. b) TBDMSCl, imidazole, DMF, r. t., 2 h. c) 9-BBN (2.5 eq.), anh. THF, r. t., 24 h. : 30 % H_2O_2 / 2N-NaOH, 50 °C, 1 h. d) n-Bu_4NF, anh. THF, r. t., 20 h. e) oxygen, irradiation at -78 °C, methylene blue (cat.), CH_2Cl_2, 3 h.: Dowex resin (acidic) (cat.), ether, r. t., 18 h.

catalized cyclization (ether, r.t., 18 h.) of the oxygenation intermediates afforded **6a**(12S)[5] and **6b**(12R)[5] of natural configuration in 12 % and 11 % yield, respectively[6]. This conversion proves to be a concise synthesis of the title compound **6a** and its 12-epimer, **6b** from artemisinic acid. The assignments of the ^{1}H NMR and ^{13}C NMR signals were made on the basis of 2D-COSY and HETCOR spectra of 12-(3'-hydroxy-n-propyl)-deoxoartemisinin **6a** and **6b**, respectively. The relative configuration at the new chiral centers, C-4, 5, 6, 11, and 12 was unambiguously determined as depicted in **6a** and **6b**, respectively, by utilization of two dimensional nOe (NOSEY) techniques[7]. Table 1 shows *in vitro* assessment of artemisinin-related analogs. **6a** is found to show five times greater *in vitro* antimalarial activity compared to artemisinin against chloroquine-resistant malaria. **6a** is approximately 80 times more active compared to homoartemisinin **9**[1c]. Due to the lack of the carbonyl function and exo C-O bond at C-12, **6a** is projected to possess increased stability, thus longer half life in the body[2].

Table 1

		IC_{50}(ng/mL) clone of P.falciparum
		
6a: R = $(CH_2)_3$-OH, R' = H	12-(3'-hydroxy-n-propyl)-deoxoartemisinin	0.23
7 : R, R' = O	artemisinin	1.21
8 : R = R' = H	deoxoartemisinin	0.15
		
9	homodeoxoartemisinin	19.02

In conclusion, this communication describes the concise synthesis of 12-(3'-hydroxy-n-propyl)-deoxoartemisinin from artemisinic acid.

Acknowledgments: We gratefully acknowledge the financial support of the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases. We wish to thank Dr. Wilbur K. Milhous at Walter Reed Army Institute of Research for antimalarial tests.

References and Notes:

1. For recent deoxoartemisinin analog work, see a) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D., *Tet. Lett.* **1989**, *30*, 5973. b) Ye, B.; Wu, Y-L., *J. C. S. Chem. Comm.*, **1990**, 726. c) Bustos, D. A.; Jung, M.; ElSohly, H. N.; McChesney, J. D., *Heterocycles* **1989**, *29*, 2273.

2. Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D.; Milhous, W. K., *J. Med. Chem.* **1990**, *33*, 1516.

3. For isolation of artemisinic acid, see a) Tu, Y.; Ni, M.; Zhong, Y.; Li, L.; Cui, S.; Zhang, M.; Wang, X.; Ji, Z., *Planta Medica* **1982**, *44*, 143. b) Roth, R. J.; Acton, N., ibid **1987**, *53*, 501. c) ElSohly, H. N.; Croom Jr., E. M.; ElFeraly, F. S.; ElSherei, M. M., *J. Nat. Prod.* **1990**, *53*, 1560.

4. Jung, M.; ElSohly, H. N.; Croom Jr., E. M.; McPhail, A. T.; McPhail, D. R., *J. Org. Chem.* **1986**, *51*, 5417.

5. For **6a**: $[\alpha]_D^{18}$ = -20.25 ° (c 0.8, $CHCl_3$,): ^1H NMR ($CDCl_3$, 300 MHz) 5.26(s, 1H, C5-H), 3.69(m, 2H, C3'-H), 3.52 (m, 1H, C12-H), 2.42(m, 1H, C11-H), 2.34(ddd, 1H, J=14.96, 4.02, 1.17 Hz, C3α -H), 2.03, and 1.98(dq, 1H, J=14.96, 3.0 Hz, C3β -H), 1.40 (s, 3H, C15-H), 0.95(d, J=6.2 Hz, 3H, C13-H), 0.79(d, J=7.2 Hz, 3H, C14-H): ^{13}C NMR ($CDCl_3$, 75 MHz). 104.18, 92.14, 80.82, 74.05, 63.03, 51.91, 45.97, 37.39, 36.16, 34.16, 30.63, 29.80, 27.64, 25.93, 24.74, 21.44, 20.29, 13.76 ppm. IR ($CHCl_3$) ν max 3440(br.s), 2925, 1505, 1380,1130,1100,1060,1040,880 Cm^{-1}:MS(70eV):m/e,326(M^+, 53.49), 294(M^+-O_2,7.11). For **6b**: $[\alpha]_D^{18}$= +47.25 ° (c 0.4, $CHCl_3$): ^1H NMR ($CDCl_3$, 300 MHz) 5.33(s, 1H, C5-H), 4.23(m, 1H, C12-H), 3.68 (m, 2H, C3'-H), 2.65(m, 1H, C11-H), 2.32(ddd, 1H, J=14.01, 3.96, 4.02 Hz, C3α -H), 2.05 and 2.00(dq, 1H, J=14.01, 3.12, C3β -H), 1.42(s, 3H, C15-H), 0.96(d, J=6 Hz, 3H, C13-H), 0.87 (d, J=7.53 Hz, 3H, C14-H): ^{13}C NMR ($CDCl_3$, 75 MHz) 103.18, 89.20, 81.11, 75.44, 62.77, 52.24, 44.21, 37.48, 36.54, 34.42, 31.22, 30.50, 26.44, 26.00, 24.87, 24.72, 20.16, 12.88: IR ($CHCl_3$) ν max 3440(br.s), 2950, 1450, 1380, 1130, 1070, 1020, 635 Cm^{-1}.

6. For the mechanism of photooxidative cyclization, see ref. 4 and Jung, M.; ElSohly, H. N.; McChesney, J. D., *Planta Medica* **1990**, *56*, 624.

7. For NOESY experiments of artemisinin analogs, see ref. 1c and a) Brossi, A.; Venugopalan, B.; Dominguez Gerpe, L.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W. K.; Peters, W., *J. Med. Chem.*, **1988**, *31*, 645. b) Avery, M. A.; Jennings-White, C.; Chong, W. K. M., *J. Org. Chem.* **1989**, *54*, 1792. c) Baker, J. K.; ElSohly, H. N.; Hufford, C. D., *Spectrosc. Lett.* **1990**, *23*, 111