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A SHORT AND STEREOSPECIFIC SYNTHESIS OF (+)-DEOXOARTEMISININ AND (-)-DEOXODESOXYARTEMISININ

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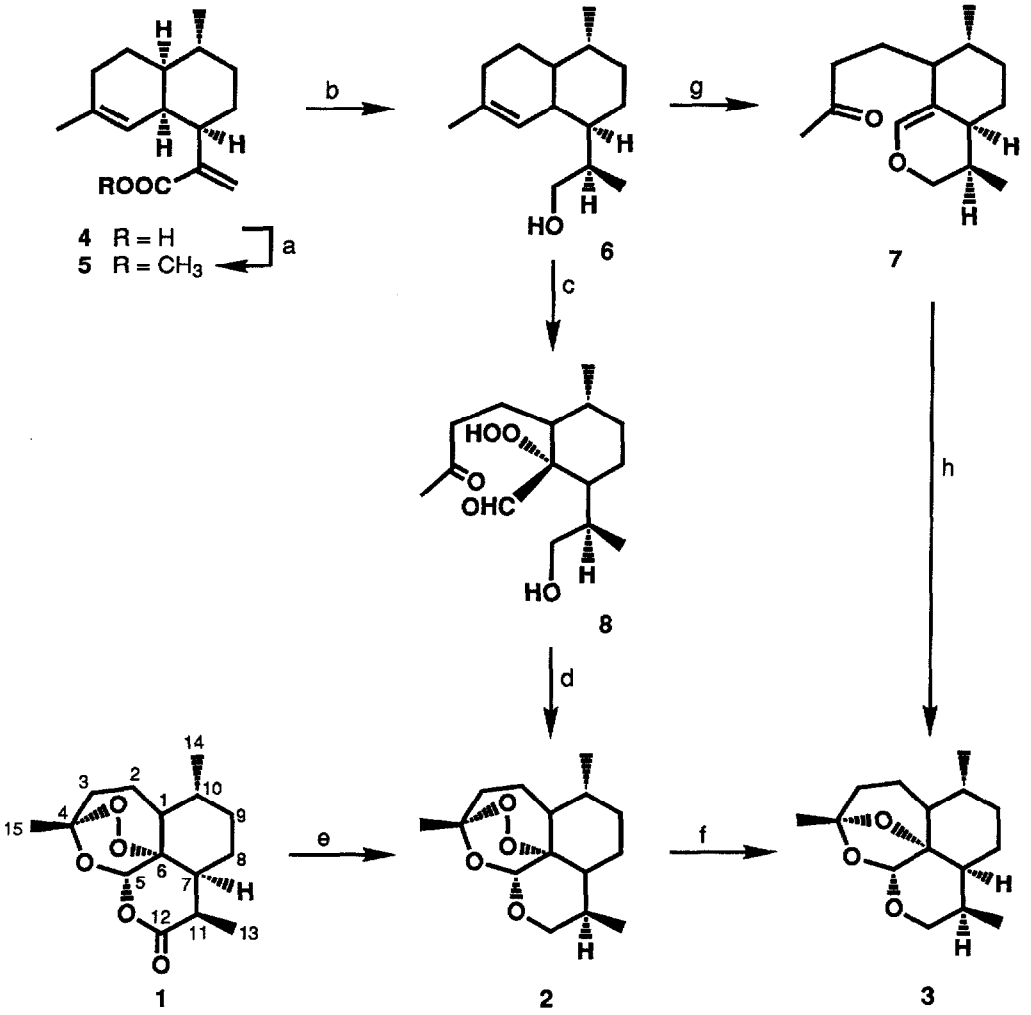
Summary: The synthesis of (+)-deoxoartemisinin and (-)-deoxodesoxyartemisinin was achieved either from artemisinic acid or from artemisinin.

Artemisinin (Qinghaosu, **1**)[1], isolated[2] from Artemisia annua L., has recently received much attention due to its novel structure and clinically useful antimalarial activity against chloroquine-resistant malaria[3]. Total syntheses of artemisinin have been reported[4,5,6]. In continuation of our efforts[7] to find urgently needed new antimalarial agents,[6,8] deoxoartemisinin **2** was prepared for evaluation since it is devoid of the carbonyl function at C-12, while retaining the biologically active endoperoxide. Derivatives of artemisinin lacking the carbonyl function were projected to possess increased stability and thus longer half-life in the body. This note reports a successful synthesis of (+)-deoxoartemisinin and (-)-deoxodesoxyartemisinin **3**, a potential metabolite of deoxoartemisinin.

(+)-Deoxoartemisinin was first prepared from artemisinic acid, **4**, in three steps (Scheme 1). Stereoselective reduction of methyl artemisinate, **5**, gave dihydroalcohol[4], **6**, 81% as crystals after chromatography. Chiral photoxidation (oxygen, methylene blue and irradiation in CH_2Cl_2,-78° for 2 hr) of **6**, followed by in situ treatment of the isolable intermediate **8** with Dowex-resin (strongly acidic) afforded (+)-deoxoartemisinin **2** (18%) in one step and of natural configuration. **2**[9]: m.p. 104-105° (petroleum ether), $[\alpha]_D^{18}$ = + 86.25° (C 0.4, $CHCl_3$). This conversion proves to be a short and stereospecific synthesis of (+)-deoxoartemisinin from naturally more abundant artemisinic acid.

We also evaluated direct conversions of artemisinin, **1**, into deoxoartemisinin **2**. Direct hydrogenolysis of the carbonyl function of **1** was achieved in 71% yield by a slight excess of sodium borohydride in the presence of boron trifluoride etherate in dry tetrahydrofuran (1 hr at 0°, then heat to reflux). The biologically important endo peroxide is left intact under these reductive conditions.

Scheme 1



Key : (a) CH_2N_2, Et_2O, r.t. (b) $LiAlH_4$, $NiCl_2.6H_2O$, CH_3OH, r.t. 3h (c) $^1O_2$, methylene blue, CH_2Cl_2, -78°, 2h (d) Dowex-resin (strongly acidic), hexane, r.t. 4h (e) $NaBH_4$, $BF_3.Et_2O$, THF, 0°, 1h then reflux (f) H_2, 5% $Pd/CaCO_3$, EtOH, r.t. 1h then p-TsOH, toluene (g) O_3, CH_2Cl_2, -78°, 2.5h, p-TsOH, r.t. 2h (h) m-CPBA, $CHCl_3$, 0°, 2h

(-)-Deoxodesoxyartemisinin[10], **3**, a potential metabolite of deoxoartemisinin **2** was synthesized either from artemisinin **1** in two steps (overall yield 70%) or from artemisinic acid **4** in four steps (overall yield 22%) (Scheme 1). Thus, further hydrogenation of **2** with 5% $Pd/CaCO_3$, and subsequent *in situ* treatment with P-TsOH/toluene afforded the deoxodesoxyartemisinin **3**, (yield 98%) **3**[11]:m.p. 97-99° (CH_3CN), $[\alpha]_D^{18}$ = -50.25° (C 0.4, $CHCl_3$). Alternatively, ozonolysis of **6** and *in situ* acid catalyzed cyclization afforded the oily enolether **7**[12,13] in 47% after chromatography and final epoxidative cyclization [m-CPBA (3eq), $CHCl_3$, 0°, 2h] of **7** also afforded **3** cleanly and of natural configuration (93%).

2 and **3** from artemisinin **1** are identical by comparison of mmp, specific rotation, and spectral properties with **2** and **3** from artemisinic acid **4** respectively. Thus, all chiral centers of **1** and **4** were retained in their natural configuration during these manipulations.

(+)-Deoxoartemisinin **2** is found to show approximately eight times the antimalarial activity of artemisinin *in vitro* against chloroquine-resistant malaria.

In conclusion, (+)-deoxoartemisinin, **2**, a new and more active antimalarial agent, and (-)-deoxodesoxyartemisinin **3**, a potential metabolite of **2** were synthesized either from artemisinic acid or from artemisinin.

Acknowledgements

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References

1. For comprehensive review, see
a) D.L. Klayman, Science (1985), **228**, 1049.
b) X.D. Luo and C.C. Shen, Med. Res. Rev. (1987), **7**, 29

2. Cooperative Research Group on Qinghaosu, Yaoxue Tongbao (1979) **14**, 49.

3. Qinghaosu Antimalaria Coordinating Research Group, Chin. Med. J. (1979),92.

4. X. Xu, J. Zhu, D. Huang and W. Zhou, a) Acta. Chim. Sin. (1983), **41**, 574, b) Tetrahedron (1986), **42**, 818.

5. G. Schmid, W. Hofheinz, J. Am. Chem. Soc. (1983), **105**, 624.

6. M.A. Avery, C. Jennings - White, and W.K.M. Chong, Tet. Lett. (1987), **28**, 4629.

7. M. Jung, H.N. ElSohly, E.M. Croom, A.T. McPhail, and D.R. McPhail, J. Org. Chem. (1986) **51**, 5417.

8. (a) China Cooperative Research Group on Qinghaosu, J. Trad. Chin. Med. (1982), **2**, 9. (b) W.S. Zhou, Pure & Appl. Chem. (1986), **58**, 817. (c) A. J. Lin, D.L. Klayman,and W.K.Milhous, J. Med. Chem. (1987), **30**, 2147. (d) Y. Imakura, T. Yokoi, T. Yamagishi, J. Koyama, H.Hu, D.R. McPhail, A.T. McPhail and K.H. Lee, J.C.S. Chem. Comm. (1988), 372

9. Compound **2**: H^1-NMR ($CDCl_3$, 300 MHz); 5.19 (s,1H, 5-CH), 3.72(dd, J=4.2, 11.7Hz, 1H, 12-

CH), 3.44(t, J=11.7 Hz, 1H, 12-CH), 2.64 (m, 1H, 11-CH), 2.37 (2dd, J=4.2, 1.2Hz, 1H, 7-CH), 1.43(s,3H, 15-CH_3), 0.96(d,J=6.3 Hz, CH_3), 0.77(d, J=7.2 Hz, CH_3). IR (KBr); 2950, 2860, 1500, 1340, 1060, 875 Cm^{-1} MS (70eV): m/e 268 (M+), 250 (M+ - H_2O), 236 (M+-O_2), 178, 164, 137. Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.16; H, 8.96; O, 23.88. Found: C, 67.34; H, 9.17; O, 23.58.
For the mechanism for conversion of **6** to **2** see reference 7.

10. 7-Epi-deoxodesoxyartemisinin was previously synthesized in nine steps (overall yield, about 5%) from artemisinin: See W.S. Zhou, J.M. Shen, C.H. Cheng, and Z.H. Wu, Scientia Sinica(B), (1984), 150.

11. Compound **3**: H'-NMR($CDCl_3$,300 MHz): 5.25 (s,1H, 5-CH), 3.94 (dd, J=6.6, 12.3 Hz, 1H, 12-CH), 3.28 (dd, J=4.5, 12.1Hz, 1H, 12-CH), 2.27 (m, 1H, 11-CH), 1.53 (s, 3H, 15-CH_3), 0.92 (d, J=7.5 Hz, CH_3), 0.89 (d, J=6.0 Hz, CH_3). IR (KBr): 2920, 1500, 1380, 1109, 991, 880 cm^{-1}. MS (70eV); m/e 252 (M+), 237, 191, 181, 164, 149, 106. Anal. Calcd. for $C_{15}H_{24}O_3$; C, 71.42; H, 9.52; O, 19.06. Found; C, 70.82; H, 9.47; O, 19.71

12. Compound **7**: H^1-NMR ($CDCl_3$): 6.16 and 6.09 (2bs, 1H, olefinic H), 3.60 (m,2H, OCH_2), 2.54 (m, 2H, CH_2CO), 2.12 (s, 3H, CH_3CO), 0.96 (d, J=6Hz, 3H, CH_3), 0.89 (d, J=7.0 Hz, CH_3). IR (neat); 2910, 1705 (C=0), 1645, 1450, 1150, 750 cm^{-1}. MS (70eV); m/e 236 (M+).

13. Treatment of **7** with triphenylphosphite-ozone adduct $(PhO)_3P$, O_3, -78° to -23°, CH_2Cl_2) gave (+)-deoxoartemisinin, **2**, in low yield (4%) and attempted photooxidation of **7** (oxygen, light and photosensitizer) afforded only deoxodesoxyartemisinin **3** (23% yield) but no deoxoartemisinin **2**.

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