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STEREOSELECTIVE SYNTHESIS OF α-ARTEETHER FROM ARTEMISININ[1]

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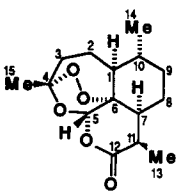
ABSTRACT.—α-Arteether (12α-*O*-ethyldihydroartemisinin), a potent antimalarial drug, has been synthesized stereoselectively from artemisinin (qinghaosu) using Ag_2O catalyst.

Artemisinin [**1**] (qinghaosu), a unique sesquiterpene endoperoxide isolated from the Chinese medicinal plant *Artemisia annua* L. (Compositae), has been found to show significant activity against chloroquine-resistant malaria, with a fast onset of action and remarkably few side effects (1,2). The cyclic hemiacetal dihydroartemisinin [**2**], obtained by $NaBH_4$ reduction of artemisinin, has shown higher antimalarial activity than its parent compound (2). The Chinese workers have prepared a number of ethers and esters of dihydroartemisinin to improve biological activity, stability, and bioavailability of the drug (3). The steering committee of the scientific working group of the World Health Organization (SWG-CHEMAL-WHO) decided in 1985 to develop arteether, the ethyl ether of dihydroartemisinin, as a parenteral formulation for treatment of patients with cerebral malaria (4). The Chinese scientists (5) and later Brossi *et al.* (6) synthesized arteether by Lewis-acid- (boron trifluoride etherate) catalyzed acetal formation from **2**, which yielded a diastereoisomeric mixture of β-arteether [**3**] and α-arteether [**4**] in 75:25 epimeric ratio. The diastereoisomeric arteethers were separated by cc. When individually tested, β- and α-arteether showed comparable antimalarial activity (6–8).



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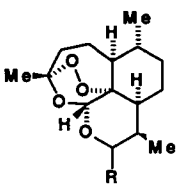

2 R=OH
3 R=β-OEt
4 R=α-OEt

Herein a new efficient and stereoselective method for the preparation of α-arteether [**4**] is reported. Dihydroartemisinin was obtained in 85% yield by $NaBH_4$ reduction of artemisinin in MeOH at 0–5°. The reaction of dihydroartemisinin with ethyl iodide in dry CH_2Cl_2 using freshly prepared Ag_2O at room temperature yielded only α-arteether in quantitative yield. The workup method is simple and involves only filtration and evaporation of the solvent. The ^{1}H-nmr spectra of **4** clearly showed a trans diaxial relationship between H-11 and H-12 (2.40 and 4.44, $J_{11,12} = 9.2$ Hz), and the -OEt group at C-12 was thus assigned an α-equatorial orientation in a half-chair conformation. The nOe spectrum showed 5% nOe between H-5 and H-12, confirming the stereochemistry at C-12.

The reaction, using Koenigs-Knorr-type reaction conditions, represents an unusual case of the preference for the formation of an α-equatorial over a β-axial acetal, which is the thermodynamically expected product. The unexpected equatorial preference can be explained in terms of a reverse anomeric effect (9) for electronegative substituent in a 2-alkoxytetrahydropyran system, and it seems likely that Ag_2O not only functions as an acid acceptor but also stabilizes the kinetically controlled equatorial product by dipole-dipole interaction with the lone pair of electrons of five oxygen atoms that are crowded on

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the same side of the molecule of **4** in an alternate carbon-oxygen chain of $O\text{-}C_{(-12)}\text{-}O\text{-}C_{(-5)}\text{-}O\text{-}C_{(-4)}\text{-}O\text{-}O\text{-}C_{(-6)}$ sequence.

EXPERIMENTAL

Artemisinin [**1**] was isolated from the aerial parts of *A. annua* cultivated in India by the Institute (10). Dihydroartemisinin [**2**] was prepared from artemisinin by a previously reported procedure (6). ^{1}H-nmr spectra were measured on a Bruker WM-400 (400 MHz) spectrometer. The ir spectra were recorded in a 399 B Perkin-Elmer instrument, and mass spectra were determined on a Finnigan MAT and Hitachi RMU 6L mass spectrometer. The optical rotation was measured on a JASCO DIP-181 digital polarimeter. Authentic samples of β-arteether [**3**] and α-arteether [**4**] were synthesized using Brossi's procedure (6).

α-ARTEETHER [**4**].—To a magnetically stirred suspension of dihydroartemisinin (5.68 g, 0.02 mol), freshly prepared Ag_2O (4 g, 0.017 mol) in dry CH_2Cl_2 (50 ml) and ethyl iodide (10 ml, 0.12 mol, excess) were added. The reaction mixture was stirred for 5 h and filtered, and the filtrate was washed with H_2O, dried (Na_2SO_4), and evaporated to afford pure α-arteether [**4**] as a colorless oil (5.60 g, 90%), $[\alpha]^{21}D$ −2.2° (c = 1.0, $CHCl_3$). The chemical purity of **4** was checked by tlc on Si gel G plates by comparison with the authentic samples of α-arteether [**4**] and β-arteether [**3**]. ^{1}H nmr ($CDCl_3$) 0.88 (3H, d, J = 7.6 Hz, H-13), 0.96 (3H, d, J = 5.9 Hz, H-14), 1.21 (3H, t, J = 7.0 Hz, H-17), 1.44 (3H, s, H-15), 1.10–2.20 (10H, m), 2.38 (1H, m, J_{gem} = 14.7, $J_{3,2}$ = 4.1, $J_{3,2'}$ = 10.6 Hz, H-3), 2.02 (1H, m, J_{gem} = 14.7, $J_{3',2}$ = 2.9, $J_{3',2'}$ = 5.3 Hz, H-3'), 2.40 (1H, dd, $J_{11,13}$ = 7.6, $J_{11,12}$ = 9.4 Hz, H-11), 3.49 (1H, dd, J_{gem} = 8.2, $J_{16,17}$ = 7.0 Hz, H-16'), 4.00 (1H, dd, J_{gem} = 8.2, $J_{16,17}$ = 7.0 Hz, H-16), 4.44 (1H, d, J = 9.4 Hz, H-12), 5.34 (1H, s, H-5); ir ($CHCl_3$) ν max 2930, 2880, 1380, 1050, 1016, 877 cm^{-1}; ms m/z $[M + 1]^+$ 313.

LITERATURE CITED

1. D.L. Klayman, *Science (Washington, D.C.)*, **228**, 1049 (1085).
2. X.D. Luo and C.C. Shen, *Med. Res. Rev.*, **7**, 29 (1987).
3. China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, *J. Trad. Chin. Med.*, **2**, 9 (1982).
4. World Health Organization, Scientific Working Group on Chemotherapy of Malaria, TDR/CHEMAL/WHO/85.3 (1985).
5. Y. Li, P.L. Yu, Y.X. Chen, L.Q. Li, Y.S. Gai, D.S. Wang, and Y.P. Zheng, *Yaoxue Xuebao*, **16**, 429 (1981); *Chem. Abstr.*, **97**, 922245n (1982).
6. A. Brossi, B. Venugopalan, L. Dominguez Gerpe, H.J.C. Yeh, J.L. Flippen-Anderson, P. Buchs, X.D. Luo, W. Milhous, and W. Peters, *J. Med. Chem.*, **31**, 645 (1988).
7. G.P. Dutta, R. Bajpai, and R.A. Vishwakarma, *Indian J. Parasitol.*, **11**, 253 (1987).
8. G.P. Dutta, R. Bajpai, and R.A. Vishwakarma, *Indian J. Parasitol.*, **12**, 212 (1988).
9. H. Booth, K.A. Khedhair, and S.A. Readshaw, *Tetrahedron*, **44**, 7027 (1988).
10. A. Singh, R.A. Vishwakarma, and A. Husain, *Planta Med.*, **54**, 475 (1988).

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