Journal of Natural Products
Vol. 50, No. 5, pp. 972-973, Sep-Oct 1987

ONE-STEP STEREOSPECIFIC SYNTHESIS OF (−)-ARTEANNUIN B

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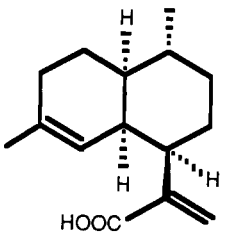
Arteannuin B, first isolated (1) from *Artemisia annua* L. (Compositae) has attracted much interest from synthetic chemists due to its potential antitumor activity (2) as well as its natural scarcity. This sesquiterpene was proposed as a possible biogenetic precursor to artemisinin (3). Its structure and absolute configuration have been determined by spectroscopy and X-ray analysis (1,4), and total syntheses have been achieved in multi steps (5,6). Recently two research groups (7-9) reported conversion of artemisinic acid [**1**] into arteannuin B [**2**] in low yields (9 and 12%, respectively). During our synthetic efforts directed toward artemisinin, we attempted to convert artemisinic acid into arteannuin B according to the known procedure (7,8). Surprisingly and interestingly enough, we found the major product for this photooxidation to be (−)-arteannuin B [**2**] and not (+)-desoxyisoarteannuin B [**3**] as reported in the literature (7,8).

Thus, irradiation of artemisinic acid [**1**] in pyridine and H_2O (9:1) with a high pressure quartz mercury arc lamp (450 watt, Hanovia) for 5 h at room temperature, followed by purification of the reaction mixture, afforded (−)-arteannuin B [**2**] (32%) and (+)-desoxyisoarteannuin B [**3**] (6%). Repeated experiments show the consistent ratio of yields of **2** and **3**. This result is the reverse of that of the known procedure (7,8), which gave (+)-desoxyisoarteannuin B



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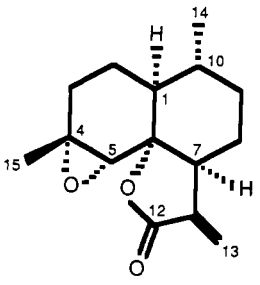

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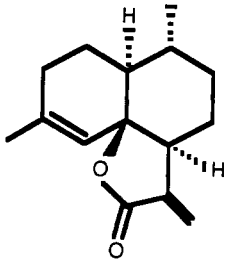

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(20%) as a major product and (−)-arteannuin B (9%) as a minor one, following irradiation with a 200 watt high pressure mercury lamp. Therefore, our

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results indicate irradiation with a 450 watt lamp using pyridine and H_2O as the solvent substantially increases the yield of arteannuin B.

This one-step stereospecific synthesis affords (−)-arteannuin B [**2**] of natural configuration in 32% yield from readily available, optically active, artemisinic acid and, thus, provides this scarce natural product in quantities suitable for more extensive biological evaluation.

EXPERIMENTAL

(−)-ARTEANNUIN B [**2**] AND (+)-DESOXYISOARTEANNUIN B [**3**].—A stream of pure oxygen was admitted through a gas dispersion tube into a solution of artemisinic acid [**1**] (1.0 g, 4.27 mmol) and hematoporphyrin (10 mg, 0.017 mmol) in pyridine (45 ml) and H_2O (5 ml). The mixture was irradiated by high pressure quartz mercury arc lamp (450 watt, Hanovia) during 5 h at room temperature. The solvent was removed in vacuo to give a foam, and H_2O (13 ml) was added. The reaction mixture was extracted with CH_2Cl_2 (25 ml×3), and the organic layer was washed successively with 0.5N HCl (25 ml), then saturated NaCl to pH=7. Drying over $MgSO_4$ and evaporation in vacuo gave a crude product. Purification by column chromatography [Si gel, CH_2Cl_2-EtOAc (9:1) as eluent] afforded (−)-arteannuin B [**2**] (Rf 0.64) and (+)-desoxyisoarteannuin B [**3**] (Rf 0.81). Recrystallization from Et_2O gave **2** as colorless crystals (343 mg, 32%). Desoxyisoarteannuin B [**3**] was further recrystallized from *n*-hexane to afford colorless crystals (60 mg, 6%).

COMPOUND [**2**][3].—$[\alpha]^{18}D$=−72.27° (*c* 0.75, MeOH), lit (7,8), $[\alpha]^{20}D$=−72° (*c* 0.75, MeOH) mp 149-151° (Et_2O), lit (7,8), mp 150-151° (isopropylether); ^1H nmr ($CDCl_3$, TMS) δ 6.14 (1H, d, *J*=3 Hz, 13-CH=), 5.42 (1H, d, *J*=3 Hz, 13-CH=), 2.70 (1H, s, 5-CH), 1.34 (3H, s, 15-CH_3), 0.99 (3H, d, *J*=6 Hz, 14-CH_3).

COMPOUND [**3**][3].—$[\alpha]^{18}D$=+148° (*c* 0.93, MeOH), lit (7,8), $[\alpha]^{10}D$=+153° (*c* 0.93, MeOH) mp 79-80° (*n*-hexane), lit (7,8), mp 81.5-83° (*n*-hexane); ^1H nmr ($CDCl_3$, TMS) δ 6.07 (1H, s, 13-CH=), 5.56 (1H, s, 13-CH=), 5.25 (1H, d, *J*=1.3 Hz, 5-CH=), 1.67 (3H, s, 15-CH_3), 0.98 (3H, d, *J*=6 Hz, 14-CH_3).

ACKNOWLEDGMENTS

This research was supported by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. We express our thanks to Drs. Mahmoud A. El-Sohly and Edward M. Croom for helpful discussions.

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Received 13 April 1987

[3]Synthetic **2** and **3** are identical by comparison of mmp, specific rotation, and spectral properties with the natural arteannuin B and synthetic desoxyisoarteannuin B as reported in the literature (7,8).