1745, 1240 (OAc); MS *m/z* (rel. int.): 322.142 $[M-H_2O]^+$ (4) (calc. for $C_{17}H_{22}O_6$: 322.142), 307 $[322-Me]^+$ (7), 304 $[322-H_2O]^+$ (3), 262 $[322-HOAc]^+$ (12), 223 (36), 221 (32), 205 (80), 191 (100), 164 (56).

3β,13-Diacetoxy-1β,4α-dihydroxyeudesm-7(11)-en-6α,12-olide (**11**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1770 (γ-lactone), 1740, 1240 (OAc); MS *m/z* (rel. int.): 364.153 $[M-H_2O]^+$ (7) (calc. for $C_{19}H_{24}O_7$: 364.153), 349 $[364-Me]^+$ (6), 304 $[364-HOAc]^+$ (9), 244 $[304-HOAc]^+$ (32), 206 (90), 205 (81), 191 (100), 164 (63).

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SYNTHESIS OF *EPI*-DEOXY- AND DEOXYARTEANNUIN B

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Key Word Index—*Artemisia annua*; Compositae; sesquiterpene lactones; photooxidation.

Abstract—Arteannuic acid has been converted into *epi*-deoxy- and deoxyarteannuin B in a rational synthesis and in good yield via a hydroperoxide.

INTRODUCTION

Artemisinin (qinghaosu, **1**) is an antimalarial drug isolated from *Artemisia annua* [1]. Other constituents of *A. annua* are of interest because they may be on a common biosynthetic pathway to artemisinin [2] and because they may be synthetic precursors to artemisinin in the laboratory. One such compound is arteannuic acid, **2**, a relatively abundant and easily isolable plant constituent [3]. Others have reported the chemical conversion of **2** into **1** by a seven step route in *ca* 7% overall yield [4].

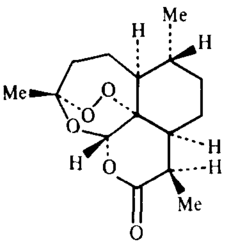
epi-Deoxyarteannuin B (**3a**) and arteannuin B (α-epoxide of deoxyarteannuin B, **3b**), both known constituents of *A. annua* [5, 6], have been produced in the laboratory upon photooxidation of arteannuic acid [7–10]. The relative yield of each of these compounds varies considerably with photolysis conditions, and the reported yield of **3a** has been low. The photooxidation is presumed to occur via the hydroperoxide **4a**, but this compound was not isolated.

RESULTS AND DISCUSSION

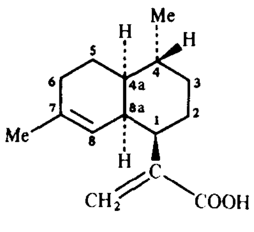
We find that low temperature photooxidation of **2** (−78°, CH_2Cl_2, Methylene Blue) affords hydroperoxide **4a** with only trace amounts of either arteannuin B or **3a** evident by liquid chromatography. On standing in chloroform-d_1 hydroperoxide **4a** produces arteannuin B in 28% yield. More interesting, however, is that **4a** can be converted into either **3a** or **3b** uncontaminated with arteannuin B as follows.

Treatment of the photooxidation reaction mixture with one equivalent of triphenylphosphine or triethyl phosphite effected deoxygenation of the hydroperoxide to the corresponding alcohol **4b**. To prepare **3a**, this alcohol acid was not isolated, but was extracted into aqueous sodium carbonate. Heating the carbonate solution (100°, 2 hr), then acidifying, afforded, after extraction and bulb-to-bulb distillation, a 72% yield (from arteannuic acid) of **3a**. Thus **3a** can be obtained from *A. annua* via **2** with no chromatographic separations required.

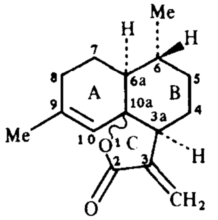
On treatment with trifluoroacetic acid, **4b** rapidly dehydrates to the conjugated 1,8a-dehydroarteannuic acid (Acton, N., unpublished results). However, allowing **4b** to stand at 30–40° in $CDCl_3$ resulted in conversion to **3b**, a labile compound which was reported as the last intermediate in the synthesis of (racemic) arteannuin B [11]. The identity of **3b** was confirmed by epoxidation to give arteannuin B which was identical with the natural product by ^1H NMR, IR, HPLC, TLC, and optical rotation.



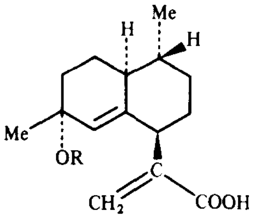
1



2



3a *cis* B/C
3b *trans* B/C



4a R = OH
4b R = H

The lability of **3b** (see experimental) suggests the possibility that **3b**, which has the expected stereochemistry for the product of an S_N2' lactonization, is in fact the initial product from dehydration of **4b**, and that **3a** may arise subsequently both in this experiment and in the plant. These lactones are now being investigated as precursors to artemisinin.

EXPERIMENTAL

General. NMR: $CDCl_3$, TMS int. standard. HPLC analyses were performed using electrochemical (ECLC) [12] and ultraviolet (UVLC) [5] detection as previously described.

epi-*Deoxyarteannuin B* (**3a**). O_2 was passed through a −78° soln of **2** (500 mg, 2.1 mmol) and Methylene Blue (9 mg) in CH_2Cl_2 (50 ml) while irradiating with a Westinghouse Ceramalux high intensity C400S51 electric discharge street lamp. After 2.5 hr, triphenylphosphine (550 mg, 2.1 mmol) was added, and the soln allowed to warm to *ca* −15° during 30 min. The resulting **4b** was extracted into 5% aq. Na_2CO_3 (3 × 50 ml) and the carbonate soln washed with CH_2Cl_2 to remove triphenylphosphine and triphenylphosphine oxide. This aq. soln was then heated at 100° for 2 hr. After washing with Et_2O (2 × 50 ml), the soln was acidified with 10% aq. HCl, and the product extracted into Et_2O (3 × 50 ml). The extract was washed with 5% aq. Na_2CO_3 (3 × 25 ml, to remove residual **2**), then H_2O (1 × 50 ml), then brine (1 × 25 ml). After drying ($MgSO_4$) and removal of solvent, bulb-to-bulb distillation at 120° afforded 360 mg (72%) of **3a**, identical by IR and by ^1H and ^{13}C NMR with material isolated from *A. annua* [5], but with slightly lower specific rotation, $[\alpha]_D^{23}$: +134° (MeOH; *c* 2), vs +142° [5]; UVLC: 14 min.

Hydroperoxide **4a**. A sample of photolysate was flash chromatographed on silica gel (hexane–EtOAc 1:1) to afford **4a** as a colourless foam, IR ν_{max}^{neat} cm^{-1} 3352, 2970, 2927, 2868, 1694, 1626. ^1H NMR: δ 0.98 (3H, *d*, $J = 1.5$ Hz, 6-Me), 1.21 (3H, *s*, 9-Me), 1.2–2.2 (10 H, *m*'s), 3.13 (1H, *br d*, $J = 10$ Hz, H-3a), 5.05, 5.65, 6.47 (1H ea, *br s*'s, olefinic), 9.26 (2H, *br s*, OOH and COOH). ^{13}C NMR: 19.9 *q*, 24.1 and 24.2 *t* and *q*, 29.8 *t*, 31.8 *t*, 35.3 *t*, 39.5 *d*, 44.4 *d*, 44.8 *d*, 81.4 *s*, 122.1 *d*, 126.9 *d* of *d*, 141.9 *s*, 147.3 *s*, 172.4 *s*; UVLC: 6.0, ECLC: 1.5 min.

Alcohol **4b**. CH_2Cl_2 was evapd from the crude hydroperoxide soln obtained from 500 mg (2.1 mmol) of **2**. The residue was dissolved in Et_2O–petrol (1:1, 50 ml), and $(EtO)_3P$ (355 mg, 2.1 mmol) was added. After standing for 30 min at room temp., a soln of H_2O_2 in *t*-BuOH (2 ml of *ca* 6% H_2O_2) was added to oxidize excess $(EtO)_3P$. The resulting soln was washed with H_2O (5 × 50 ml), dried ($MgSO_4$), filtered and the solvent evapd to yield 410 mg of crude **4b**. Silica gel chromatography or distillation of this alcohol resulted in destruction of a large portion of the material. IR ν_{max}^{neat} cm^{-1} 3439, 2926, 2851, 1699, 1627, 1450. ^1H NMR: δ 0.98 (3H, *d*, $J = 2$ Hz, 6-Me), 1.21 (3H, *s*, 9-Me), 1.2–2.0 (10 H, *m*'s), 3.14 (1H, *br d*, $J = 11$ Hz, H-3a), 5.04, 5.59, 6.42 (1H ea, *br s*'s, olefinic), 5.69 (2H, *br s*, OH and COOH). ^{13}C NMR: 19.7, 24.0, 28.0, 31.7, 35.1, 35.3, 38.9, 44.0, 44.2, 69.0, 125.5, 125.8, 142:0, 143.3, 170.3; UVLC: 12.5 min.

Deoxyarteannuin B **3b**. Chromatographically purified (silica gel, hexane–EtOAc, 1:1) **4b** (50 mg, 0.2 mmol) in 0.5 ml of $CDCl_3$ was let stand 18 hr at 30°. Flash chromatography on silica gel (10 g, hexane–EtOAc 2:1) afforded a 54% yield of **3b** estimated by ^1H NMR to be >90% pure. $[\alpha]_D^{29}$: −167° (MeOH; *c* 1); IR ν_{max}^{neat} cm^{-1} 2931, 2870, 1766, 1723, 1668, 1448, 1378, 1259, 1238, 1216, 1198, 1158, 1134, 1108, 1074, 940, 928, 909. ^1H NMR: δ 0.99 (3H, *d*, $J = 5.4$ Hz, 6-Me), 1.66 (3H, *s*, 9-Me), 2.70 (1H, *m*), 5.13 (1H, *br s*, H-10), 5.36 (1H, *d*, $J = 3.2$ Hz, $=CH_2$), 6.09 (1H, *d*, $J = 3.2$ Hz, $=CH_2$). ^{13}C NMR: 19.8, 20.0, 22.1, 23.6, 26.2 *t*, 30.7 *d*, 34.4 *t*, 44.9 *d*, 52.6 *d*, 84.3 *s*, 116.7 *d* of *d*, 118.9 *d*, 140.0 *s*, 142.4 *s*, 170.7 *s*. UVLC: 14.0 min. Attempted distillation of **3b** (100°, 0.1 mm) converted it into 1,8a-dehydroarteannuic acid. Chromatography on large amounts of silica gel partially converted **3b** into **3a**, as did gas and counter current chromatography.

Epoxidation of **3b** with *meta*-chloroperbenzoic acid as described for the racemic material [12], after flash chromatography on silica gel (cyclohexane–Et_2O, 1:1), afforded a 36% yield of arteannuin B, mp 145–146° (uncorr.), $[\alpha]_D^{28}$ −72.5° (MeOH; *c* 1) after crystallization from Et_2O; lit. mp 152–152.5°, $[\alpha]_D^{25}$ −72.2° (13). IR and ^1H NMR identical with the natural product.

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