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DEPOXIDATION OF ARTEANNUIN B WITH
CHLOROTRIMETHYLSILANE AND SODIUM IODIDE¹

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ABSTRACT.—The deepoxidation of arteannuin B [**1**] with chlorotrimethylsilane and sodium iodide resulted in 6 α -hydroxyisoannulide [**2**] which was also isolated from *Artemisia annua*. Lithium borohydride reduction of arteannuin B [**1**] gave a mixture of compound **2** and a dihydro compound [**3**].

Iodotrimethylsilane [chlorotrimethylsilane (CTMS) and sodium iodide] is known to be an effective reagent for deoxygenation of oxiranes (1,2). Deepoxidation of arteannuin B [**1**], one of the major sesquiterpenes in *Artemisia annua* L. (Asteraceae), with CTMS/NaI has resulted in an unexpected product [**2**] in 90% yield in which the double bond is positioned between C-3 and C-4 instead of C-4 and C-5. Compound **2**, which was earlier reported as an acid hydrolysis product of arteannuin B (**3**), has now been isolated from *A. annua* for the first time. The TLC analysis of a crude extract from the plant indicated the presence of **2**, thus eliminating the possibility of the compound being an artifact.

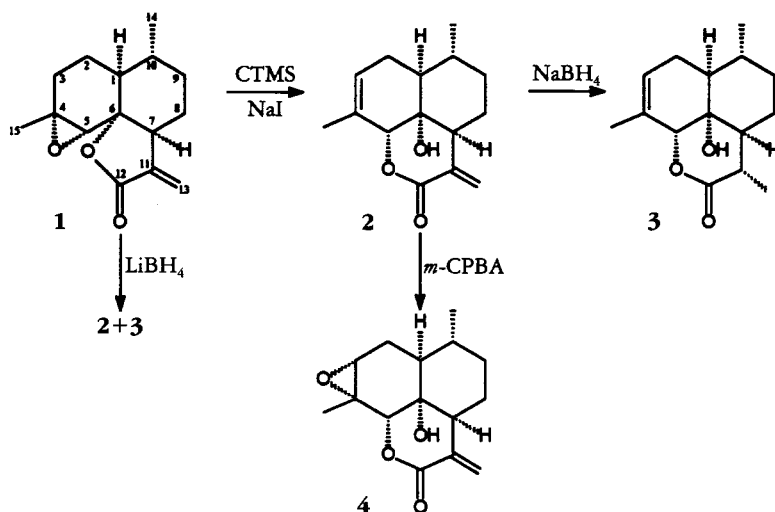
The IR spectrum of **2** showed bands due to a tertiary hydroxyl group and a six-membered ring δ -lactone. Its mass spectrum showed the $[M]^+$ at m/z 248, satisfying the molecular formula $C_{15}H_{20}O_3$, which was also supported by DEPT NMR experiments showing 4 \times C, 5 \times CH, 4 \times CH₂, and 2 \times CH₃ signals. The ¹H-NMR spectrum of **2** showed exomethylene protons at δ 6.48 and 5.62 as weakly coupled signals ($J=1.7$ Hz), one proton signal attached to an oxygenated carbon at δ 4.95, two sets of methyl protons, one proton at an sp² carbon at δ 5.50, and other less resolved signals. The ¹H-NMR data obtained compared well with reported values (**3**). The multiplicity of each carbon atom was ascertained by ¹³C-

DEPT NMR. These carbon atoms were then completely assigned by ¹H-¹³C correlations (HETCOR and long-range HETCOR) (4). Following the establishment of ¹H-¹³C correlations, assignments of the positions of all individual methine and methylene units in this cadinenolide system could be made on the basis of correlations observed in the ¹H-COSY NMR spectrum.

Compound **2**, which has the trivial name 6 α -hydroxyisoannulide (**5**), has a cadinene skeleton with a six-membered lactone bridge between C-5 and C-7 and an α -OH at C-6. The ¹³C-NMR data being reported for the first time were also compared with those published for the other cadinene derivatives arteannuin B (**6**), deoxyarteannuin B (**7**), annulide, and isoannulide (**5**).

The reduction of compound **2** with NaBH₄ furnished the dihydro compound **3**. The NMR spectral data of **3** displayed two secondary methyl groups (¹H NMR, δ 1.35 and 0.92; ¹³C NMR, δ 20.30 and 18.57) instead of one as in **2**, and the signals due to exocyclic olefinic methylene resonances were found to be absent. These features were consistent with the fact that NaBH₄ has reduced only the disubstituted olefinic bond at the C-11 position. The stereochemistry of the C-11 methyl was assigned as α on the basis of its chemical shift and J values (8,9). Treatment of **2** with *m*-CPBA resulted in the introduction of an oxirane ring at C-3 and C-4 as these resonances were observed at δ 60.55 (CH) and 60.36 (C), respectively, in the ¹³C-NMR spectrum,

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whereas the upfield shift of the C-3 signal to δ 3.85 in the ^1H -nmr spectrum supported the epoxidation. The stereochemistry of the epoxide [**4**] was assigned as α on the basis of nOe studies. The signal at δ 4.80 (H-5) showed an nOe (8%) with the signal at δ 1.48 (H₃-15), clearly indicating a β -Me configuration at C-4. The reduction of compound **1** with LiBH_4 furnished a mixture of compounds **2** and **3** which were separated and characterized by mixed mp, co-tlc, and spectral comparison with an authentic sample in each case.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps were determined in open capillaries and are uncorrected. The instruments used in the study were as follows: optical rotation, Jasco DIP-181 digital polarimeter; ir, 399B Perkin Elmer Spectrometer; eims, JEOL JMS 100D Spectrometer at 70 eV; ^1H -nmr spectra, Bruker WM-400, Varian-80 instruments; ^{13}C -nmr spectra, Bruker WM-400 instrument; 2D nmr spectra, Bruker AM-300 with TMS as internal standard and CDCl_3 as solvent. Cc was carried out on E. Merck Si gel (60–120 mesh). Visualization of tlc plates used 10% H_2SO_4 spray reagent.

PLANT MATERIAL.—The plant *Artemisia annua* was collected from CIMAP research farm, Srinagar, India and a voucher specimen (No. 2823 dated March 8, 1992) has been deposited in the Botany Division of the institute.

ISOLATION OF 6α -HYDROXYISOANNULIDE [2].—The hexane extract from the dried plant

material (50 kg) was defatted with MeOH. The filtrate was concentrated under reduced pressure to yield a dark brown residue (2.5 kg), which was subjected to cc over Si gel (25 kg) and eluted with hexane followed by hexane/EtOAc 5%, 10%, 15%, and 20%. The 20% hexane/EtOAc fraction obtained after isolation of artemisinin was concentrated and rechromatographed (300 g) over Si gel (2.5 kg) and elution with 20% hexane/EtOAc afforded 80 mg of **2**: colorless crystals, mp 187–189°; $[\alpha]_D^{25} + 80.48^\circ$ ($c=1.23$, CHCl_3); R_f 0.68 (CHCl_3 -MeOH, 98:2); *anal.*, calcd for $\text{C}_9\text{H}_{20}\text{O}_3$, C 72.55%, H 8.12%, found C 72.47%, H 8.08%; ir (KBr) ν max 3400, 1691, 1620, 1460, 1290, 1215, 1190, 1060, 950, 850 cm^{-1} ; ^1H nmr (CDCl_3 , 400 MHz) δ 6.48 (1H, dd, $J=1.7$ and 1.7 Hz, H-13a), 5.62 (1H, dd, $J=1.7$ and 1.7 Hz, H-13b), 5.50 (1H, br s, H-3), 4.95 (1H, br s, H-5), 2.57 (1H, dd, $J=12$ and 6 Hz, H-7), 2.45 (1H, m, H-2a), 2.18 (1H, dd, $J=19$ and 4 Hz, H-2b), 1.86 (1H, m, H-8a), 1.79 (3H, s, Me-4), 1.74 (1H, m, H-9a), 1.58 (1H, dddd, $J=12$, 12, 12, and 3.5 Hz, H-8b), 1.46 (1H, dd, $J=12$ and 6 Hz, H-1), 1.30 (1H, m, H-10), 1.16 (1H, dddd, $J=12$, 12, 12, and 3.8 Hz, H-9b), 0.89 (3H, d, $J=6.0$ Hz, Me-10); ^{13}C nmr (CDCl_3 , 100 MHz) δ 165.73 (C-12), 138.09 (C-11), 129.92 (C-13), 128.40 (C-4), 123.68 (C-3), 74.64 (C-5), 69.40 (C-6), 47.28 (C-1), 45.49 (C-7), 33.92 (C-9), 32.26 (C-8), 31.83 (C-10), 22.91 (C-2), 20.12 (C-14), 18.37 (C-15); eims (70 eV) m/z [$\text{M}]^+$ 248 (21), 233 (7), 230 (100), 215 (32), 202 (35), 187 (30), 173 (40), 165 (36), 159 (28), 135 (41), 91 (75), 83 (60), 79 (69), 77 (71).

REACTION OF ARTEANNUIN B [1] WITH CHLOROTRIMETHYLSILANE AND SODIUM IODIDE.—To a solution of arteannuin B [**1**] (500 mg) in dry MeCN (5 ml) was added sodium iodide (800 mg) and chlorotrimethylsilane (CTMS) (5 ml) and

stirred for 10 min at room temperature. The reaction was quenched with H₂O (100 ml) and a saturated solution of sodium thiosulphate (20 ml) was added. The mixture was shaken and extracted with CH₂Cl₂ (3×40 ml). The combined organic layer was washed several times with H₂O, dried over Na₂SO₄, and evaporated to give a yellow oily residue (500 mg) which was subjected to cc over neutral Al₂O₃ and 25% hexane/EtOAc, and afforded a white crystalline compound [**2**] (450 mg, 90% yield); mp 187–189°. The compound was compared with authentic **2** by co-tlc, ms, ir, ¹H-nmr, and ¹³C-nmr data.

REDUCTION OF 2 WITH SODIUM BOROHYDRIDE.—To compound **2** (50 mg) in dry MeOH (3 ml) was added NaBH₄ (40 mg) over 5 min with stirring. The mixture was then stirred for 2 h at room temperature. The reaction mixture was diluted with H₂O (50 ml) and extracted with CH₂Cl₂ (3×40 ml). The combined organic layer was dried over Na₂SO₄ and evaporated to give a yellow residue which was purified by prep. tlc (30% hexane/EtOAc) over Si gel G. Recrystallization from CHCl₃/hexane afforded compound **3** as colorless needles (41 mg, 83% yield): mp 152°; [α]²⁵_D +16.8° (c =0.26, CHCl₃); ir (KBr) ν max 3350, 2960, 1750, 1620, 1480, 1400, 1240 cm⁻¹; ¹H nmr (CDCl₃, 400 MHz) δ 5.59 (1H, br s, H-3), 4.83 (1H, s, H-5), 1.82 (3H, s, Me-4), 1.35 (3H, d, J =7.5 Hz, Me-11), 0.92 (3H, d, J =6.5 Hz, Me-10); ¹³C nmr (CDCl₃, 100 MHz) δ 175.08 (C-12), 128.72 (C-4), 124.02 (C-3), 74.91 (C-5), 69.01 (C-6), 47.68, 47.37, 41.57 (C-1, C-7, C-11), 34.17 (C-9), 31.84, 31.64 (C-8, C-10), 22.78 (C-2), 20.30 (C-14), 18.57 (C-13), 18.30 (C-15); eims (70 eV) m/z [M]⁺ 250 (6), 232 (79), 204 (23), 176 (33), 167 (95), 161 (19), 147 (31), 135 (34), 121 (45).

EPOXIDATION OF 2.—A solution of compound **2** (50 mg) in CH₂Cl₂ (3 ml) was stirred at room temperature with *m*-CPBA (100 mg) for 1 h. The reaction mixture was quenched with H₂O (50 ml) and extracted with CH₂Cl₂ (3×40 ml). The CH₂Cl₂ layer was washed with a dilute solution of KI, then sodium thiosulphate, and finally with H₂O, and evaporated to give a yellow oil which was purified by prep. tlc (30% hexane/EtOAc). Recrystallization from CHCl₃ yielded colorless needles [**4**], (40 mg, 80% yield): mp 78°; [α]²⁵_D +5.37° (c =0.8, CHCl₃); ir (KBr) ν max 3280, 1680, 1620, 762 cm⁻¹; ¹H nmr (CDCl₃, 400 MHz) δ 6.45 (1H, dd, J =1.6 and 1.6 Hz, H-13a), 5.59 (1H, dd, H-13b), 4.80 (1H, s, H-5), 4.30 (1H, s, D₂O exchangeable, OH), 3.18 (1H, d, J =4 Hz, H-3), 2.44 (1H, dd, J =4 and 9 Hz, H-7), 2.30 (1H, dd, J =8 and 12 Hz, H-2a), 2.10 (1H, dd, J =8 and

12 Hz, H-2b), 1.48 (3H, s, Me-4), 0.95 (3H, d, J =6.5 Hz, Me-10); ¹³C nmr (CDCl₃, 100 MHz) δ 165.02 (C-12), 138.02 (C-11), 129.86 (C-13), 73.89 (C-5), 70.36 (C-6), 60.55 (C-3), 60.36 (C-4), 47.62 (C-1), 45.84 (C-7), 34.99 (C-9), 32.42 (C-8), 31.84 (C-10), 21.56 (C-2), 20.55 (C-14), 18.85 (C-15); eims (70 eV) m/z [M]⁺ 264 (12), 246 (29), 228 (27), 203 (47), 190 (58), 177 (32), 163 (20), 156 (28), 149 (25), 139 (100).

REDUCTION OF 1 WITH LITHIUM BOROHYDRIDE.—Arteannuin B [**1**] (2 g) was dissolved in MeOH (50 ml) at room temperature and the solution was cooled to 0–5°. LiBH₄ (1.2 g) was added with stirring slowly over a period of 0.5 h and the temperature was maintained at 0–5°. On completion of the addition, the reaction mixture was further stirred for 2 h. The reaction mixture was diluted with H₂O and extracted with Et₂O to give a residue (1.8 g). This was crystallized to give a mixture of compounds (1.2 g), which was purified by prep. tlc (30% hexane/EtOAc) to afford **2** (400 mg) and **3** (300 mg). On purification, compounds **2** and **3** were characterized by direct comparison with their authentic samples.

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