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DEEPOXIDATION OF ARTEANNUIN B WITH CHLOROTRIMETHYLSILANE AND SODIUM IODIDE[1]

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ABSTRACT.—The deepoxidation of arteannuin B [**1**] with chlorotrimethylsilane and sodium iodide resulted in 6α-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 4xC, 5xCH, 4xCH_2, and 2xCH_3 signals. The ^{1}H-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 sp^2 carbon at δ 5.50, and other less resolved signals. The ^{1}H-nmr data obtained compared well with reported values (3). The multiplicity of each carbon atom was ascertained by ^{13}C-DEPT nmr. These carbon atoms were then completely assigned by ^{1}H-^{13}C correlations (HETCOR and long-range HETCOR) (4). Following the establishment of ^{1}H-^{13}C correlations, assignments of the positions of all individual methine and methylene units in this cadinenoloide system could be made on the basis of correlations observed in the ^{1}H-COSY nmr spectrum.

Compound **2**, which has the trivial name 6α-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 ^{13}C-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 $NaBH_4$ furnished the dihydro compound **3**. The nmr spectral data of **3** displayed two secondary methyl groups (^{1}H nmr, δ 1.35 and 0.92; ^{13}C 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 $NaBH_4$ 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 ^{13}C-nmr spectrum,

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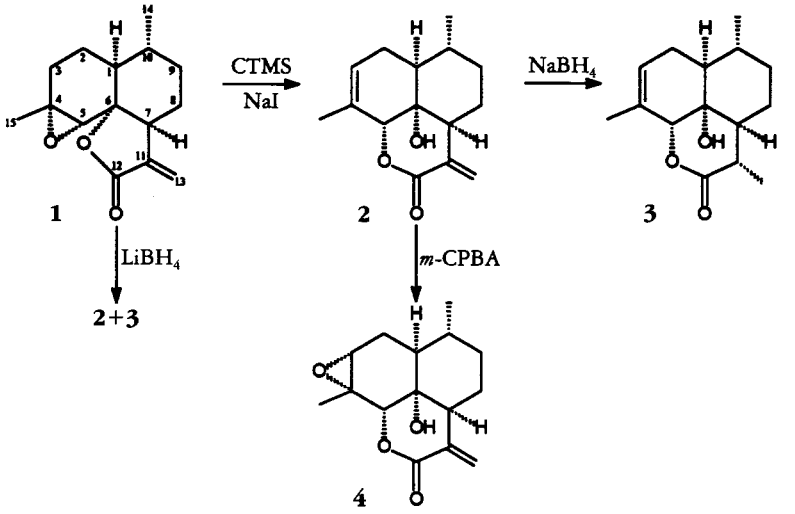

whereas the upfield shift of the C-3 signal to δ 3.85 in the ^{1}H-nmr spectrum supported the epoxidation. The stereochemistry of the epoxide [**4**] was assigned as α on the basis of nOe studies. The signal at δ 4.80 (H-5) showed an nOe (8%) with the signal at δ 1.48 (H_3-15), clearly indicating a β-Me 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; ^{1}H-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°; $[\alpha]^{25}D$ +80.48° (c=1.23, $CHCl_3$); R_f 0.68 ($CHCl_3$-MeOH, 98:2); *anal.*, calcd for $C_{15}H_{20}O_3$, 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}; ^{1}H 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 [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 H_2O (100 ml) and a saturated solution of sodium thiosulphate (20 ml) was added. The mixture was shaken and extracted with CH_2Cl_2 (3×40 ml). The combined organic layer was washed several times with H_2O, dried over Na_2SO_4, and evaporated to give a yellow oily residue (500 mg) which was subjected to cc over neutral Al_2O_3 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, ^{1}H-nmr, and ^{13}C-nmr data.

REDUCTION OF **2** WITH SODIUM BOROHYDRIDE.—To compound **2** (50 mg) in dry MeOH (3 ml) was added $NaBH_4$ (40 mg) over 5 min with stirring. The mixture was then stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3×40 ml). The combined organic layer was dried over Na_2SO_4 and evaporated to give a yellow residue which was purified by prep. tlc (30% hexane/EtOAc) over Si gel G. Recrystallization from $CHCl_3$/hexane afforded compound **3** as colorless needles (41 mg, 83% yield): mp 152°; $[\alpha]^{25}D$ +16.8° (c=0.26, $CHCl_3$); ir (KBr) ν max 3350, 2960, 1750, 1620, 1480, 1400, 1240 cm^{-1}; ^{1}H nmr ($CDCl_3$, 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); ^{13}C nmr ($CDCl_3$, 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 CH_2Cl_2 (3 ml) was stirred at room temperature with *m*-CPBA (100 mg) for 1 h. The reaction mixture was quenched with H_2O (50 ml) and extracted with CH_2Cl_2 (3×40 ml). The CH_2Cl_2 layer was washed with a dilute solution of KI, then sodium thiosulphate, and finally with H_2O, and evaporated to give a yellow oil which was purified by prep. tlc (30% hexane/EtOAc). Recrystallization from $CHCl_3$ yielded colorless needles [**4**], (40 mg, 80% yield): mp 78°; $[\alpha]^{25}D$ +5.37° (c=0.8, $CHCl_3$); ir (KBr) ν max 3280, 1680, 1620, 762 cm^{-1}; ^{1}H nmr ($CDCl_3$, 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, D_2O 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); ^{13}C nmr ($CDCl_3$, 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°. $LiBH_4$ (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 H_2O and extracted with Et_2O 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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