Synthesis of Melithasterol A, a 5α,6α-Epoxy-7α-hydroxy Δ⁸-Steroid†

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A short, first synthesis of melithasterol A (**3**) utilizing microwave irradiation-induced isomerization of 5α,8α-epidioxy steroid (**1**) as the key step has been achieved in 80% yield.

A number of interesting microwave-assisted organic reactions have been reported.[1] Polyhydroxy steroids from marine organisms[2,3] are a growing group of secondary metabolites with potentially interesting biological and pharmacological activities. A literature survey revealed that 5α,8α-epidioxy steroids have been subjected to ozonolysis,[4] Birch reduction,[5] thermolysis in acetic acid,[6,7] and thermolysis in kerosene[8] to afford secocholestane diones, Δ⁷-sterols 5,10:8,9-disecosteroids, and 5α,6α-epoxy-7α-hydroxy Δ⁸ and Δ⁸⁽¹⁴⁾ 5α,6α-epoxy-7-keto steroids, respectively. To utilize sterol endo peroxides for further conversions, we irradiated compound **1a**[9] in a microwave oven for 10 min, to afford 5α,6α-epoxy-7α-hydroxy-cholest-8-en-3β-acetate (**2**) in 80% yield.

The formation of compound **2** was readily recognized by the presence of characteristic ^{1}H NMR chemical shifts for a trisubstituted epoxy methine hydrogen at δ 3.30 (1H, d, J = 2.5 Hz), a methine hydrogen on a carbon bearing a hydroxyl group at δ 4.21 (1H, br s), and methine proton on an acetoxy carrying carbon at δ 4.98 (1H, m). Further, the high-field portion of the spectrum displayed five methyl signals at δ 0.58 (3H, s, H-18), 0.87 (3H, d, J = 6.5 Hz H-26), 0.89 (3H, d, J = 6.5 Hz, H-27), 0.90 (3H, d, J = 6.5 Hz, H-21), and 1.15 (3H, s, H-19). Of the two possibilities for the fully substituted double bond [Δ⁸ or Δ⁸⁽¹⁴⁾] in compound **2**, the Δ⁸-containing nucleus was established as the calculated chemical shifts[10] for H-18 and H-19 (H-18, δ_H 0.57, H-19, δ_H 1.17) of the 3β,7α-dihydroxy-5α,6α-epoxy-Δ⁸-steroid are very close to those found in compound **2** (18-H δ_H 0.58; 19-H, δ_H 1.15), in contrast to the chemical shifts of its Δ⁸⁽¹⁴⁾ isomer (18-H, δ_H 0.83; 19-H, δ_H 0.93). Compound **2** was acetylated (Ac_2O/Pyr) to give diacetate **2a**, which further confirmed the presence of two acetoxy groups. Compound **2** was hydrolyzed (10% KOH/MeOH) to give melithasterol A (**3**) (see Scheme 1).[11] The ^{1}H NMR spectral data of **2** are in agreement with those of 3β-acetoxy-7α-hydroxy-5α,6α-epoxy-Δ⁸-steroids.[11] The physical and spectral data of synthetically prepared compound **3** are identical in all respects with those of melithasterol A isolated from a gorgonian coral *Melithaea ocracea*.[11]

A tentative mechanism[8] can be proposed to explain the formation of **2**. Homolytic rupture of the peroxide bridge, followed by formation of two oxirane rings between C-5 and C-6, and C-7 and C-8. Further, the oxirane ring between C-7 and C-8 opens to give oxygen radical at C-7, which would abstract H_α-9 involving a five-centered cyclic transition state in which C-7, C-8, C-9, the oxygen radical at C-7, and the hydrogen at C-9 participate in a concerted process to give the 5α,6α-epoxy-Δ⁸-7α-hydroxy steroid (**2**) (Scheme 2). To the best of our knowledge this is the first report of microwave irradiation of endoperoxides.

Experimental Section

General Experimental Procedures. The melting points were measured on Fisher-Johns instrument and are uncorrected. Optical rotations were measured on JASCO DIP-370 polarimeter. IR spectra were recorded on Schimadzu 240-C instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 MHz or a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Chemical shifts are reported in parts per million (ppm), and coupling constants (J) are expressed in hertz. The mass spectra were recorded on a VG Auto Spec-M instrument.

3β-Acetoxy-5α,8α-epidioxy-cholest-6-ene (1a). A solution of **1** (100 mg) in Ac_2O/pyridine (1 mL) was allowed to stand at room temperature overnight. After the usual workup, the crude product was chromatographed on Si gel to give the monoacetate **1a**: IR (neat) ν_{max} 1745, 1620, 1360; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82 (3H, s), 0.85 (3H, d, J = 6.5 Hz), 0.86 (3H, d, J = 6.5 Hz), 0.90 (3H, s), 0.92 (3H, s), 2.05 (3H, s), 4.95 (1H, m), 6.2 (1H, d, J = 8 Hz), 6.48 (1H, d, J = 8 Hz); EIMS m/z 458 $[M]^+$, 398, 366, 351, 253, 211.

Melithasterol A 3-Acetate (2). Compound **1a** (50 mg) in an Erlenmeyer flask was placed in a commercial microwave oven (BPL BMO 700 T) and irradiated (233 W) for 10 min. The reaction mixture was removed and cooled to room temperature. The reaction mixture was purified by column chromatography over Si gel, eluting with hexane−ethyl acetate mixtures to afford compounds **1a** (25 mg) and **2** (20 mg): IR (neat) ν_{max} 3500, 1740, 1615, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.58 (3H, s, 18-H), 0.87, 0.89 (each 3H, d, J = 6.5 Hz 26, 27-H), 0.90 (3H, d, J = 6.5 Hz, 21-H), 1.15 (3H, s, 19-H), 2.08 (3H, s), 3.30 (1H, d, J = 2.5 Hz, 6-H), 4.21 (1H, br s, 7-H), 4.98 (1H, m, 3-H); FABMS m/z 441 $[(M^+ + 1) - H_2O]$ (15), 381 (100), 365 (50), 267 (35), and 225 (25).

Melithasterol A (3). To a clear solution of compound **2** (10 mg) in dry dichloromethane (3 mL) was added 10% KOH/MeOH (1 mL), and the resulting mixture was stirred for 3 h. After the usual workup, the crude product was chromatographed on Si gel to give melithasterol A (**3**): mp 176 °C;[11] $[\alpha]^{25}_D$ −68° (c 2.5, $CHCl_3$);[11] IR (neat) ν_{max} 3500, 1615, 1075 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.57 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J = 6.5 Hz 26, 27-H), 0.92 (3H, d, J = 6.5 Hz, 21-H), 1.14 (3H, s, 19-H), 3.32 (1H, d, J = 2.5 Hz, 6-H), 3.95 (1H, m, 7-H), 4.22 (1H, m, 3-H); EIMS m/z 416 $[M]^+$, 398, 383, 380, 365, 355, 337, 313, 295, 285, 267.

Melithasterol A Diacetate (2a). A solution of 2 (10 mg) in Ac_2O/pyridine (0.5 mL) was allowed to stand at room

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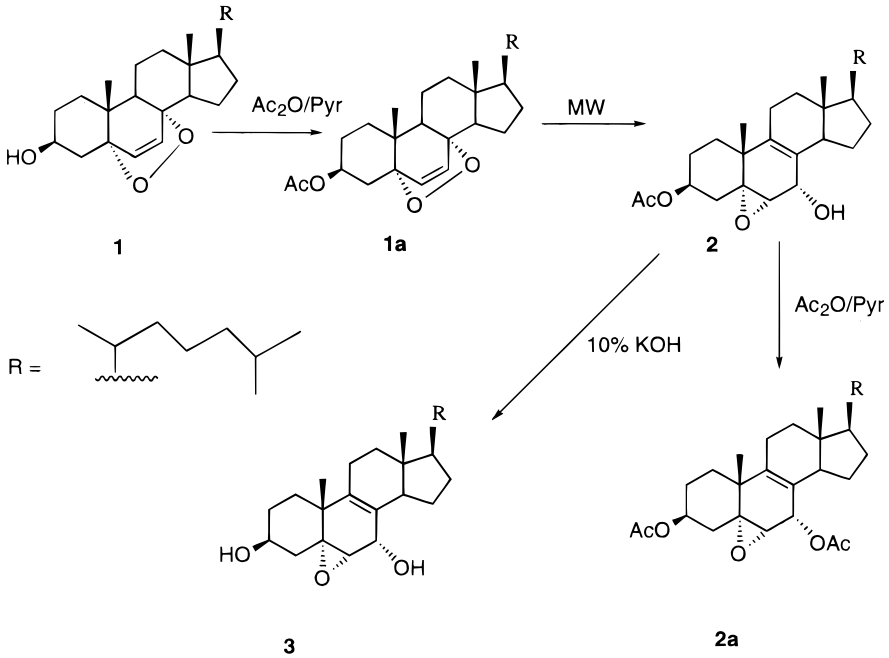
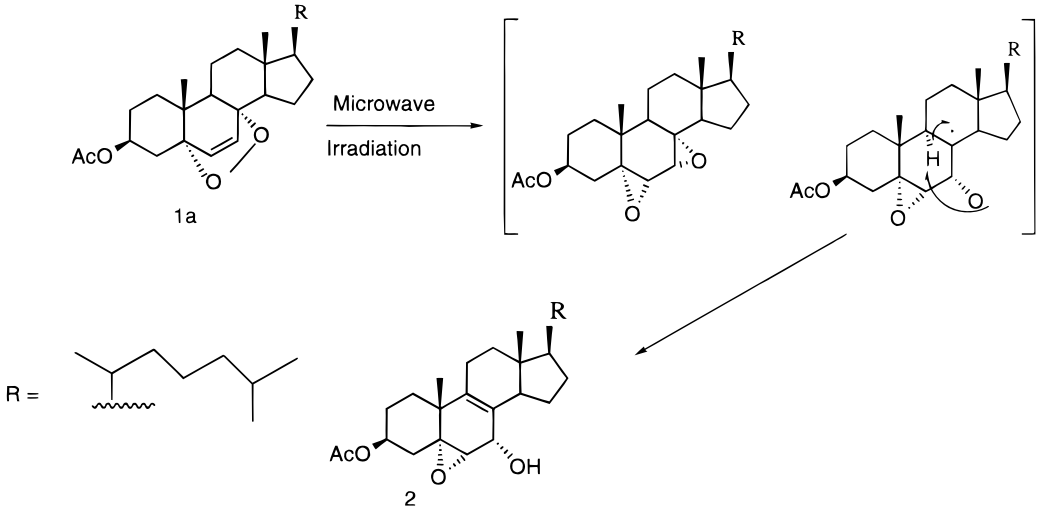
Scheme 1



Scheme 2



temperature overnight. After the usual workup, the crude product was chromatographed on Si gel to give the diacetate **2a**: IR (neat) ν_{max} 1740, 1620, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.56 (3H, s, 18-H), 0.86 and 0.87 (each 3H, d, J = 6.5 Hz, 26-, 27-H), 0.92 (3H, d, J = 6.5 Hz, 21-H), 1.17 (3H, s, 19-H), 2.02 (3H, s), 2.13 (3H, s), 3.37 (1H, d, J = 2.5 Hz, 6-H), 4.95 (1H, m, 3-H), 5.53 (1H, br s, $W_{1/2}$ = 6 Hz, 7-H); FABMS m/z 441 [(M^++1) − HOAc] (20), 381 (100), 365 (30), 267 (40), and 225 (30).

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