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Synthesis of Acyclic Marine Halogenated Natural Product Analogues from Myrcene

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Synthesis of acyclic halogenated marine natural products such as 1,8-dibromo-3,7-di(bromo methyl)-(Z)-2-octene (**1**), 1,6,7-tribromo-3-bromo methyl-7-methyl-(Z)-2-octene (**2**), 2,3-di(bromo methyl)-6-(1-bromo-1-methyl ethyl) tetrahydro-2H-3-pyranol (**3**), 2,6,7,8- tetrabromo-6-bromo methyl-2-methyl-3-octanol (**4**) was planned from myrcene in view of their good antitumour activity.

INTRODUCTION

Marine natural products[1] have received increasing attention from chemists and pharmacologists during the last two decades. Interested chemists have probed marine organisms as sources of new and unusual organic molecules, while synthetic chemists have followed by targeting these novel structures for development of new analogues, new synthetic methodologies and strategies. Recent studies of marine organisms have focussed on their potential applications, particularly on the treatment of human disease and control of agricultural pests. Nearly all of the marine monoterpenes observed to date are halogenated. This can be contrasted with the fact that no halogenated monoterpenes have been found in terrestrial organisms. This may not be surprising considering that sea water contains high concentrations of chloride (1.99×10^7 μg/L) and bromide (6.8×10^4 μg/L) ions[2], whereas similar concentrations of halide ions are not found in the terrestrial environment. In the present work we have synthesized **1, 2, 3** and **4** starting from myrcene. Synthesis of these compounds exhibited highly differential cytotoxicity. According to US national cancer institute's *in vitro* human tumour cell line screening panel, brain tumor, renal and colon tumor cell lines were most sensitive. These compounds thus served as a substantial point of departure from structure/activity relationship insights. In spite of their promising biological activity, synthesis of these natural product analogues till date has not been reported.

RESULTS AND DISCUSSION

In 1975, Moore *et al.*[3] have isolated three halogenated myrcenes from *Hawauan chondrococcus hornemannii* and proposed that these are formed by

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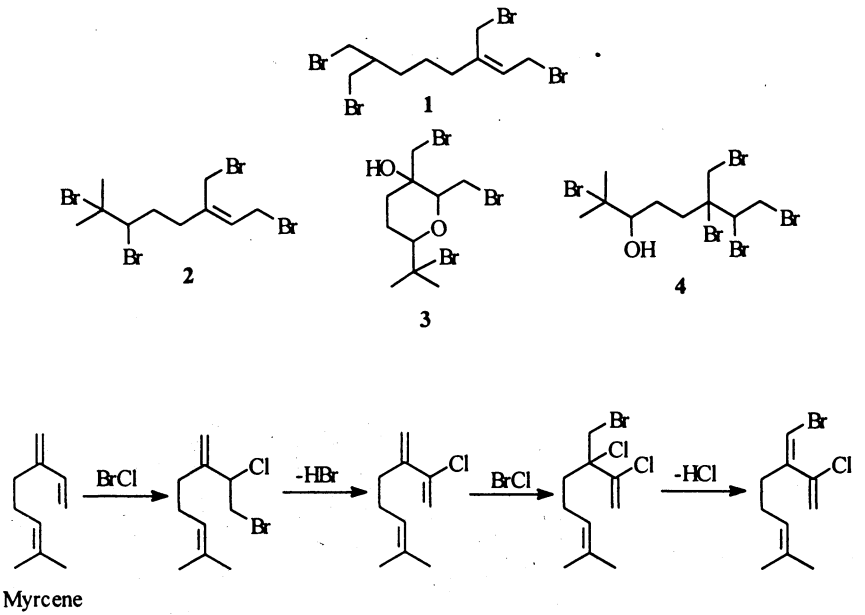
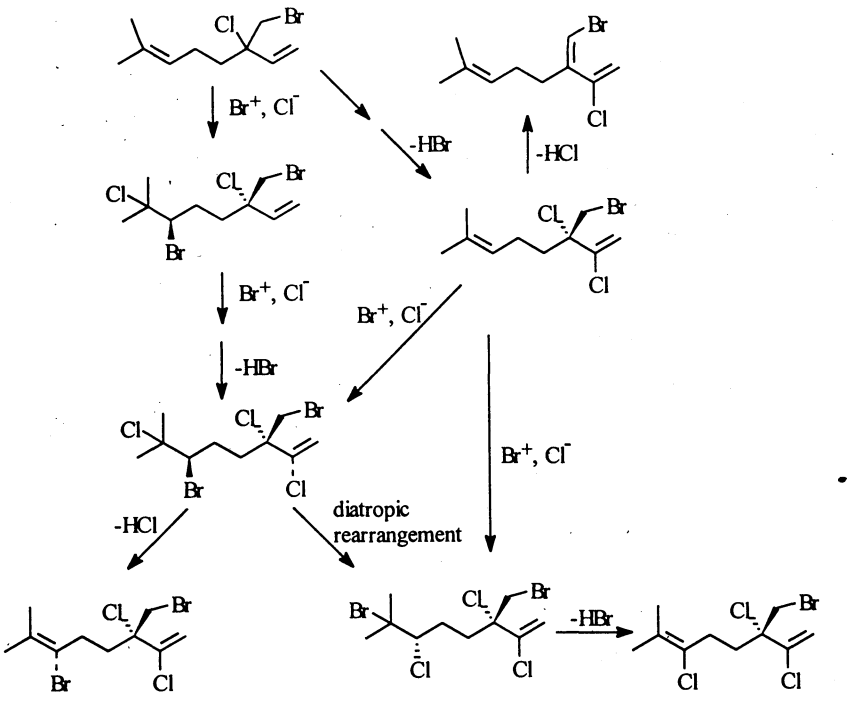


Scheme 1a

the enzymatic addition of BrCl (Markovnikov or anti-Markovnikov) to the C-1, C-6, C-3 exomethylene double bonds of 7-methyl-3-methylene-1,6-octadiene (myrcene) followed by the elimination of HCl and/or HBr (Schemes 1a, 1b). Earlier attempts to prepare marine halogenated natural products from geraniol have been unsuccessful. Hence, we looked at the biogenetic scheme of Moore *et al.*[3] to synthesise it and initiated our work in this direction by taking myrcene as the appropriate starting material.

Myrcene on controlled addition reaction with Br_2 (2 mole eq) in CCl_4 at 0°C for 45 min (Scheme 2) gave a mixture of tetrabrominated compounds **1** and **2**. Purification by column chromatography resulted in isolation of **1** (33%) and **2** (40%) respectively. ^1H NMR spectrum of **1** showed $4 \times CH_2Br$ protons betwen δ 3.8–4.0 as multiplet. **2** was characterized from ^1H NMR spectrum from the appearance of $2 \times CH_3$ protons at δ 1.75, δ 1.95; $2 \times CH_2Br$ protons and CHBr as a multiplet between δ 3.85–4.1, while rest of the protons resonated at expected chemical shifts. Assignments were based on reported literature on similar halogenated terpenes[4]. **2** also exhibited a molecular ion peak at M^+ 454. **2** on reaction with cat. OsO_4·NMO in acetone : H_2O[5] (2 : 1) for 12 h gave tribromo pyran **3** in 61% yield. ^1H NMR spectrum of **3** showed $2 \times CH_2Br$ protons as a multiplet between δ 3.70–3.32 and H-6 proton appeared as a multiplet between δ 4.20–4.08. **3** exhibited a molecular ion peak at M^+ 407. Thus, vicinal hydroxylation of **2** resulted in the formation of cyclic derivative **3** due to dehydrobromination. **2** on treatment with *m*-CPBA in $CHCl_3$ at 0°C for 30 min

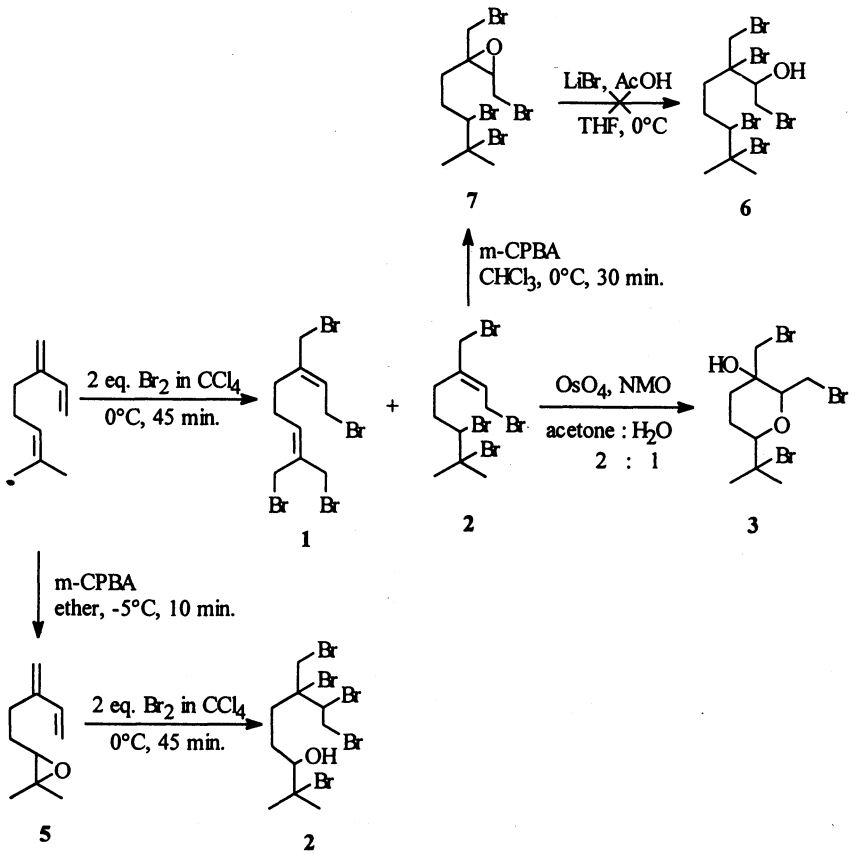


Scheme 1b

gave **6** in 72% yield. ^{1}H NMR spectrum **6** showed 2 × CH_2Br protons as a multiple between δ 3.2–3.6 and epoxy proton signal also as a multiplet between δ 4.1–4.3. Reaction of **6** with LiBr in AcOH-THF to get penta brominated compounds **7** was unsuccessful. Myrcene was converted to epoxide with *m*-CPBA in ether at –5°C[6] for 10 min to **5** in 54% yield. ^{1}H NMR spectrum of **5** revealed the appearance of a triplet at δ 2.7 (1H) ($J_{5,6}$ = 6 Hz) due to epoxy proton. **5** on treatment with Br_2 (2 mole eq) in CCl_4 at 0°C for 45 min gave pentabrominated compound **4** in 46% yield. **4** was characterized from ^{1}H NMR spectrum analogous to **2** from the appearance of 2 × CH_2Br protons and CHBr proton as a multiplet between δ 3.5–4.0, while rest of the protons resonated at expected chemical shifts. IR spectrum of **4** showed absorption at 3500 cm^{-1} due to presence of secondary hydroxyl group.

EXPERIMENTAL

Proton Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini) and Unity-400 MHz spectrometers using tetramethyl silane (TMS) as the internal standard. Infrared spectra were scanned on Perkin-Elmer 683 or 1310 spectrometer with sodium chloride optics. Mass spectra were recorded on a VG Micromass 7070 H and Finnigan Mat 1020 B Mass spectrometer operating at 70 eV using a direct inlet probe. All solvents and reagents were purified and



Scheme 2

dried according to procedure given in Vogel's Textbook of Practical Organic Chemistry.

1,8-Dibromo-3,7-di(bromomethyl)-(Z)-2-octene (1) and 1,6,7-tribromo-3-bromomethyl-7-methyl-(Z)-2-octene (2): To a solution of myrcene (3 g, 22.0 mmol) in carbon tetrachloride (5 mL) was added bromine (3.5 g, 66.0 mmol) in carbon tetrachloride (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 45 min. Progress of the reaction was monitored by TLC. When the reaction was complete, the reaction mixture was diluted with water (10 mL) and extracted into dichloromethane (2 × 100 mL). Combined dichloromethane layers were washed with water, dried (Na_2SO_4) and concentrated to obtain a residue which was purified by column chromatography (SiO_2, 30–120 mesh; hexane : ethyl acetate, 45 : 2) to elute first **1** (3.5 g) in 34% yield as a syrup.

^{1}H NMR ($CDCl_3$): δ 6.0–5.8 (m, 1H, H-2), 4.0–3.8 (m, 8H, 4 × CH_2Br), 2.45–2.10 (m, 4H, H-4, 4′, 5, 5′), 1.90–1.75 (m, 2H, 6, 6′); Anal., calcd. for $C_{10}H_{16}Br_4$: C, 26.35; H, 3.54; found: C, 26.55; H, 3.68%.

This followed by **2** (4.02 g) in 40% yield as a syrup.

^{1}H NMR ($CDCl_3$): δ 5.95 (t, 1H, H-2), 4.10–3.85 (m, 5H, 2 × CH_2Br, CHBr), 2.70–2.55 (m, 4H, H-4, 4′, 5, 5′), 1.95–1.75 (2s, 6H, 2 × CH_3); *MS (m/z)*: 454; Anal., calcd. for $C_{10}H_{16}Br_4$: C, 26.35; H, 3.54. Found: C, 26.48; H, 3.62%.

2,3-Di(bromomethyl)-6-(1-bromo-1-methyl ethyl)-tetrahydro-2H-3-pyranol (3): To a stirred solution of compound **2** (2 g, 4.4 mmol) in acetone: water (10 mL, 2 : 1), N-methyl morpholine N-oxide (60% in water, 1.8 mL, 5.3 mmol), 2% osmium tetroxide in toluene (1 mL, 0.03 mmol) were sequentially added and stirred at room temperature for 24 h. After completion of the reaction solid $Na_2S_2O_5$ (2.6 g) was added to the reaction mixture and stirred for 10 min. CH_2Cl_2 (50 mL) was then added to the above reaction mixture and filtered on celite. Solvent was concentrated *in vacuo* to a residue which on chromatographic purification (SiO_2, 60–120 mesh; hexane : ethyl acetate, 4 : 1) to obtain **3** (1.3 g) in 61% yield as a syrup.

^{1}H NMR ($CDCl_3$): δ 4.20–4.08 (m, 1H, H-6), 3.90–3.75 (m, 1H, H-2), 3.7–3.3 (m, 4H, 4H, 2 × CH_2Br), 2.6–2.2 (m, 4H, H-4, 4′, 5, 5′), 1.9–1.75 (2s, 6H, 2 × CH_3); MS (m/z): 407. Anal., calcd. for $C_{10}H_{17}Br_3O_2$: C, 29.37; H, 4.19; Found: C, 29.58; H, 4.34%.

2,3-Di(bromomethyl)-2-(3,4-dibromo-4-methyl pentyl)-oxirane (6): To a solution of **2** (2 g, 4.38 mmoi) in chloroform (10 mL) at 0°C was added *m*-CPBA (1.1 g, 6.6 mmol) and stirred at room temperature. After 1 h the mixture was diluted with chloroform (50 mL) and washed with saturated aqueous $NaHCO_3$ solution and water. Organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to a residue that was purified by column chromatography (SiO_2, 60–120 mesh; hexane : ethyl acetate, 45 : 2) to obtain **6** (1.48 g) in 72% yield as a syrup.

^{1}H NMR ($CDCl_3$): δ 4.3–4.1 (t, 1H, H-2), 3.6–3.2 (m, 5H, 2 × CH_2Br, CHBr), 2.75–2.10 (m, 4H, H-1, 1′, 2, 2′), 1.95–1.75 (2s, 6H, 2 × CH_3). Anal., calcd. for $C_{10}H_{16}Br_4O$: C, 25.46; H, 3.42; found: C, 25.38; H, 3.52%.

(6,7)-Epoxy-7-methyl-3-methylene-octa-1-ene (5): Experimetnal procedure as described for **6**. Reaction of myrcene (1 g, 7.4 mmol) with 80% *m*-CPBA (1.9g, 11.0 mmol) in ether (200 mL) for 10 min at –5°C, after purification by column chromatography (SiO_2, 60–120 mesh; hexane : ethyl acetate, 9 : 1) gave **5** (0.6 g) in 54% yield as syrup.

^{1}H NMR ($CDCl_3$): δ 6.35 (dd, 1H, $J_{1,2}$ = 10.4 Hz, $J_{1,2}$ = 1.8 Hz, H-2), 5.3–5.0 (9m, 4H, H-1,1′, methylene), 2.75 (t, 1H, $J_{5,6}$ = 6.0 Hz, H-6), 2.5–2.2 (m, 2H, H-4, 4′), 1.75 (q, 2H, $J_{4,5}$ = 6.0 Hz, H-5, 5′), 1.30-1.25 (2s, 6H, 2 × CH_3). Anal., calcd. for $C_{10}H_{16}O$: C, 71.39; H, 9.59; found: C, 71.48; H, 9.68%.

2,6,7,8-Tetrabromo-6-bromomethyl-2-methyl-3-octanol (4): Experimental procedure as described for **1**. To a solution of the epoxide **5** (0.5 g, 3.2 mmol) in carbon tetrachloride (2 mL) was added bromine (1.5 g, 9.7 mmol) in carbon tetra chloride (5 mL) at 0°C and stirred for 45 min. Purification by column chromatography (SiO_2, 60–120 mesh; hexane: ethyl acetate, 8 : 2) gave **4** (0.85 g) in 46% yield as a syrup.

^{1}H NMR ($CDCl_3$): δ 4.1–3.5 (m, 6H, 2 × CH_2Br, CHBr, CHOH), 2.45–1.90 (m, 4H, H-4, 4′, 5, 5′), 1.8–1.7 (2s, 6H, 2 × CH_3); IR (Neat): 3500 cm^{-1}; Anal. calcd. for $C_{10}H_{16}Br_5Cl$: C, 21.03; H, 2.82; found: C, 21.21; H, 2.88%.

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