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Note

Microwave and ultrasound assisted synthesis of 16-methyl-8(*Z*)-heptadecenoic and 16-methyl-6(*Z*)-heptadecenoic acids

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The first total synthesis of two novel iso-branched heptadecenoic acids, the major components in a species of bacterium, *Micrococcus*, has been carried out using a rapid, simple and clean process utilizing microwave and ultrasound radiations.

Keywords: Microwaves, ultrasound, eco-friendly, total synthesis, heptadecenoic acid

Mono-unsaturated fatty acids with double bonds at Δ^6 and Δ^8 are quiet uncommon compared to their Δ^5 and Δ^9 counterparts[1], of the former. The branched chain Δ^6 and Δ^8 mono-unsaturated fatty acids are rarer than the normal-chain analogues and are the components of several marine organisms. They have found in the phospholipids of the sponge *Tethya aurantia*[2] and in fresh water mussels *Unio tumidus*[3].

Carballeira *et al* [4] have isolated and identified two novel fatty acids **1** and **2** for the first time in a species of bacterium *Micrococcus*, isolated from Lake Pomorie in Bulgaria, thus establishing for the first time a bacterial origin for the Δ^6 fatty acid.

In continuation of our earlier work [5] on the development of greener as well as clean technologies and their adaptation towards the synthesis of naturally occurring compounds, we herein report the synthesis of the title compounds **1** and **2** (**Scheme I**) using microwave irradiation (MWI) and ultrasound as the key steps in both the synthesis. These eco-friendly methodologies provide enhanced yields, solvent less conditions or minimal amount of solvents, involve operational simplicity and are more atom efficient, which helps in reduction of waste disposal problems and the reaction time.

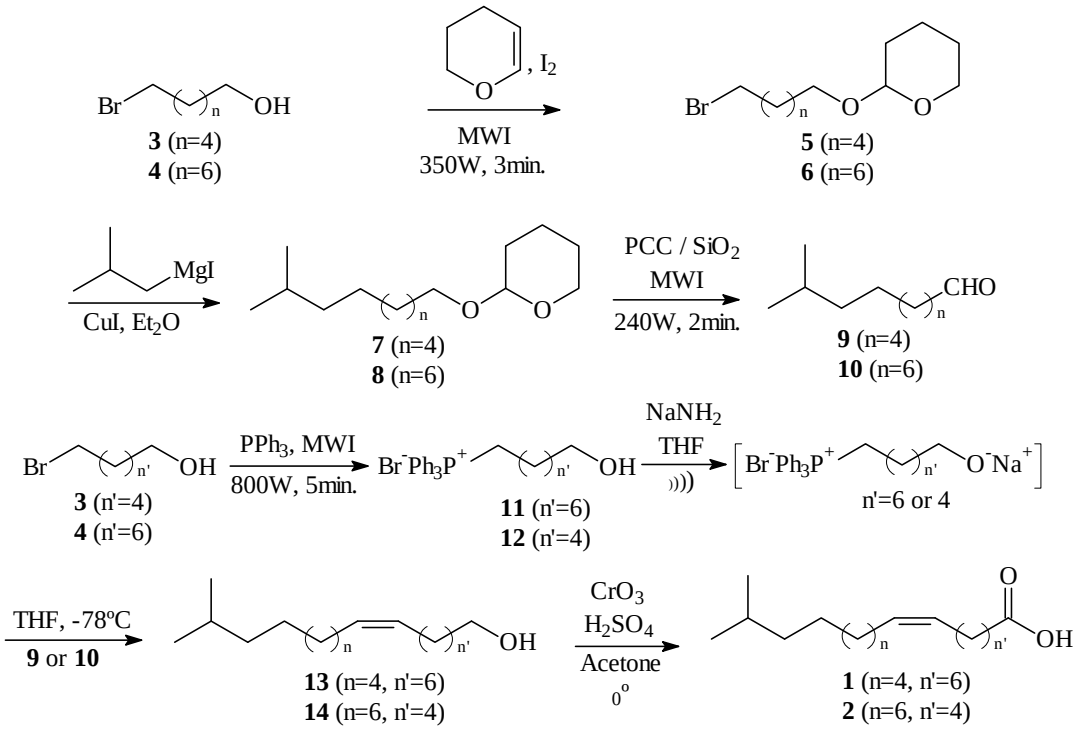
Results and Discussion

Bromoalkanols **3** and **4** prepared from corresponding diol using aqueous HBr (48%) and tetrabutylammonium bromide on microwave irradiation[6] were subjected to iodine catalyzed tetrahydropyranylation [7] under microwave to afford compounds 6-bromo-1-tetrahydropyranyloxyhexane **5** and 8-bromo-1-tetrahydropyranyloxy octane **6**. The bromo-THP ethers (**5** and **6**) were then coupled with 2-methylpropyl magnesium iodide in the presence of catalytic amount of CuI [8] to furnish compounds 8-methyl-1-tetrahydropyranyloxynonane **7** and 10-methyl-1-tetrahydropyranyloxy undecane **8**. Microwave assisted oxidation of **7**, **8** using pyridium chlorochromate doped on silica gel, provided the desired aldehydes 8-methylnonan-1-al **9** and 10-methylundecan-1-al **10**.

Microwave irradiation of a mixture of triphenylphosphine and bromoalcohol (**4**, **3**) at 800W for 5 min. gave corresponding Wittig salts [9] (**11**, **12**) which on sonochemical Schlosser-Wittig olefination [10] with aldehydes **9** and **10** respectively in anhyd. THF, afforded 16-methyl-8(*Z*)-heptadecen-1-ol **13** and 16-methyl-6(*Z*)-heptadecen-1-ol **14**. Subsequent oxidation of **13** and **14** with Jone's reagent [11] in acetone yielded the pure title compounds 16-methyl-8(*Z*)-heptadecenoic acid **1** and 16-methyl-6(*Z*)-heptadecenoic acid **2**. The spectra of both compounds **1** and **2** were found to be consistent with that reported in literature[4].

Experimental Section

The ^{1}H NMR spectra were recorded on Brucker AC 300F, 300MHz Spectrometer. Chemical shift values are expressed as δ value (ppm) downfield from tetramethylsilane (Me_4Si), used as internal standard. The infrared spectra were recorded using a Perkin-Elmer Model RX1 FT-IR spectrophotometer and expressed in cm^{-1}. Column chromatography was performed using silica gel (Acme's Synthetic Chemicals, 100-200 mesh). Reactions assisted by microwave energy were carried out in LG MS-194A (800W) domestic microwave oven. Sonication was carried out using Heat Systems, Probe Sonicator model XL 2015 (20kHz). All reactions were carried



Scheme I

out in oven-dried glassware under dry N_2 atmosphere. During work ups all organic solvents with density less than water were dried over anhyd. Na_2SO_4 and those with density more than water with $CaCl_2$.

6-Bromo-1-tetrahydropyranyloxyhexane 5 and 8-bromo-1-tetrahydropyranyloxy octane 6

To a solution of bromoalcohol (**3** or **4**, 1 mmoles) in dry THF (1 mL) taken in a 50 cm^3 conical flask was added DHP (1.25 mmole) and iodine (0.2 mmole). The conical was covered with a small funnel and subjected to microwave exposure at 350W for 3 min. The reaction mixture was cooled, diluted with $CHCl_3$ (30 mL) and washed with 10% sodium thiosulphate solution (2 × 5 mL), water (2 × 5 mL), brine and dried. Evaporation of solvent under vacuum followed by purification via column chromatography eluting with hexane furnished compounds **5** (0.58 g, 85%) and **6** (0.66 g, 88%) respectively.

Compound **5**: IR (neat) : 2927, 1460, 1280, 1120, 722 and 560 cm^{-1}; ^1H NMR(CCl_4) : δ 1.32-1.71 (m, 14H, saturated methylene protons), 3.35-3.79 (m, 6H, $-CH_2CH_2Br$, $-CH_2CH_2O-$, $-OCH_2CH_2-$), 4.73 (t, *J* = 7Hz, 1H, -OC*H*O-).

Compound **6**: IR(neat) : 2930, 1465, 1275, 1120, 720 and 580 cm^{-1}; ^1H NMR(CCl_4) : δ 1.42-1.81 (m, 18H, saturated methylene protons), 3.28-3.80 (m, 6H, $-CH_2CH_2Br$, $-CH_2CH_2O-$, $-OCH_2CH_2-$), 4.71 (t, *J* = 7Hz, 1H, -OC*H*O-).

8-Methyl-1-tetrahydropyranyloxynonane 7 and 10-methyl-1-tetrahydropyranyloxy undecane 8

To a stirred solution of Grignard reagent, prepared from activated magnesium turnings (10 mmoles) and 1-iodo-2-methylpropane (10 mmoles) in dry diethyl ether (50 mL) was added drop wise a solution of bromotetrahydropyranyloxyalkane (**5** or **6**, 9 mmoles) in dry diethyl ether (30 mL) at -10ºC. After 30 min., the reaction mixture was brought to room temperature and copper(I) iodide (0.02 mmole) was added over 30 min and refluxed. On completion (TLC monitoring), the reaction mixture was cooled, decomposed with saturated solution of NH_4Cl, extracted with diethyl ether (2 × 30 mL) and dried. Evaporation of solvent *in vacuo* followed by purification via silica gel chromatography, eluting with 10% EtOAc in hexane afforded compounds **7** (1.67 g) and **8** (1.79 g) in 74 and 71% yields, respectively.

Compound **7**: IR(neat) : 2930, 2850, 1385, 1367, 1210 and 722 cm^{-1}; ^1H NMR(CCl_4) : δ 0.91 (d, *J* = 6Hz, 6H, $-CH(CH_3)_2$), 1.24-1.62 (m, 18H, saturated methylene protons), 1.70-1.91 (m, 1H, $-CH(CH_3)_2$), 3.29-3.88 (m, 4H, $-CH_2CH_2O-$, $-OCH_2CH_2-$), 4.72 (t, *J* = 7Hz, 1H, -OC*H*O-).

Compound **8**: IR(neat) : 2928, 2850, 1460, 1385, 1360, 1120 and 720 cm^{-1}; ^1H NMR(CCl_4) : δ 1.00 (d, *J* = 6Hz, 6H, -CH(CH_3)$_2$), 1.20-1.61 (m, 22H, saturated methylene protons), 1.74-1.93 (m, 1H, -C*H*(CH_3)$_2$), 3.30-3.92 (m, 4H, -CH_2CH_2O-, -OC$H_2$$CH_2$-), 4.71 (t, *J* = 7Hz, 1H, -OC*H*O-).

8-Methylnonan-1-al 9 and 10-methylundecan-1-al 10

To a mixture of PCC (4.5 mmoles) and silica gel (1 g) was added tetrahydropyranyl ether (**7** or **8**, 3 mmoles) in DCM (2 mL). The mixture was stirred for 5 min. followed by evaporation of the solvent. The resultant free-flowing solid was exposed to MWI at 240W for 2 min. On cooling, the solid was extracted with DCM (20 mL) filtered through a short pad of silica and solvent evaporated *in vacuo* to furnish pure aldehyde (**9**, 0.45 g, 92%) and (**10**, 0.52 g, 90%).

Compound **9**: IR(neat) : 2950, 2860, 2720, 1740, 1383, 1365, 970 and 725 cm^{-1}; ^1H NMR(CCl_4) : δ 1.01 (d, *J* = 6Hz, 6H, -CH(CH_3)$_2$), 1.19-1.71 (m, 10H, saturated methylene protons), 1.81-2.00 (m, 1H, -C*H*(CH_3)$_2$), 2.33 (t, *J* = 7Hz, 2H, -CH_2CH_2CHO), 10.13 (s, 1H, -C*H*O).

Compound **10**: IR(neat) : 2980, 2865, 2710, 1738, 1460, 1387, 1365, 965 and 725 cm^{-1}; ^1H NMR(CCl_4) : δ 1.01 (d, *J* = 6Hz, 6H, -CH(CH_3)$_2$), 1.22-1.70 (m, 14H, saturated methylene protons), 1.81-2.02 (m, 1H, -C*H*(CH_3)$_2$), 2.33 (t, *J* = 7Hz, 2H, -CH_2CH_2CHO), 10.51 (s, 1H, -C*H*O).

8-Hydroxyoctyltriphenylphosphonium bromide 11 and 6-hydroxyhexyltriphenylphosphonium bromide 12

A mixture of bromoalcohol (**4** or **3**, 2.5 mmoles) and triphenylphosphine was taken in a 100 mL Erlenmeyer flask and exposed to microwave radiation at 800W for 5 min. On cooling, the reaction mixture was washed with dry hot toluene (2 × 10 mL) and the crude product was recrystallized from ethanol to afford pure crystals [12] of **11** (0.97 g, 86%, m.p. 130-132ºC) and **12** (1 g, 82%, m.p. 150-153ºC).

Compound **11**: IR(nujol) : 3350, 2910, 1462, 1435, 1210, 1045 and 720 cm^{-1}; ^1H NMR($CDCl_3$) : δ 1.62-2.43 (m, 12H, saturated methylene protons), 2.91 (1bs, 1H, -O*H*, D_2O exchangeable), 3.42-4.11 (m, 4H, -CH_2C$H_2$$P^+Ph_3Br^-$, -$CH_2CH_2$OH), 7.51-8.00 (m, 15H, -Ar*H*).

Compound **12**: IR(nujol) : 3300, 2920, 1495, 1430, 1208, 1057 and 720 cm^{-1}; ^1H NMR($CDCl_3$) : δ 1.62-2.49 (m, 8H, saturated methylene protons), 3.50-4.19 (m, 4H, -CH_2C$H_2$$P^+Ph_3Br^-$, -$CH_2CH_2$OH), 4.31 (bs, 1H, -O*H*, D_2O exchangeable), 7.50-8.00 (m, 15H, -Ar*H*).

16-Methyl-8(*Z*)-heptadecen-1-ol 13 and 16-methyl-6(*Z*)-heptadecen-1-ol 14

A suspension of Wittig salt (**11** or **12**, 4.25 mmoles) and freshly prepared sodamide (4.25 mmoles) in dry THF (50 mL) was sonicated at room temperature for 30 min. under a nitrogen blanket. Once the reaction mixture developed a brick red colour (~15 min.) indicating formation of ylide, it was cooled to -78ºC and a solution of aldehyde (**9** or **10**, 4.1 mmoles) in dry THF (10 mL) was added to it with stirring over a period of 20 min. On addition, slow disappearance of the red colour took place and the reaction was brought to room temperature. The mixture was diluted with ice-cold water (100 mL), extracted with diethyl ether (2 × 30 mL), washed with brine and dried. Evaporation of solvent yielded a gummy residue which was dissolved in hexane:ethyl acetate (9:1) and filtered through a bed of silica gel (20 g) to remove the oil, which on chromatography over silica gel eluting with 5% ethyl acetate in hexane furnished the pure alcohol (**13**, 0.68 g, 62%) and (**14**, 0.52 g, 59%).

Compound **13**: IR(neat) : 3370, 3010, 2930, 2860, 1640, 1380, 1365, 1262, 1120, 735 and 668 cm^{-1}; ^1H NMR(CCl_4) : δ 0.91 (d, *J* = 6Hz, 6H, -CH(CH_3)$_2$), 1.13-1.42 (m, 18H, saturated methylene protons), 1.53-1.72 (m, 1H, -C*H*(CH_3)$_2$), 1.81-2.10 (m, 6H, -CH_2CH=CHCH_2-, -C$H_2$$CH_2$OH), 3.63 (t, *J* = 6Hz, 2H, -CH_2CH_2OH), 4.04 (bs, 1H, -O*H*, D_2O exchangeable), 5.12-5.43 (m, 2H, -CH_2C*H*=C*H*CH_2-).

Compound **14**: IR(neat) : 3350, 3012, 2960, 2857, 1641, 1383, 1367, 1210, 1120, 730 and 650 cm^{-1}; ^1H NMR(CCl_4) : δ 1.00 (d, *J* = 6Hz, 6H, -CH(CH_3)$_2$), 1.10-1.42 (bs, 18H, saturated methylene protons), 1.49-1.73 (m, 1H, -C*H*(CH_3)$_2$), 1.82-2.12 (m, 6H, -CH_2CH=CHCH_2-, -C$H_2$$CH_2$OH), 3.00 (bs, 1H, -O*H*, D_2O exchangeable), 3.59 (t, *J* = 6Hz, 2H, -CH_2CH_2OH), 5.13-5.44 (m, 2H, -CH_2C*H*=C*H*CH_2-).

16-Methyl-8(*Z*)-heptadecenoic acid 1 and 16-methyl-6(*Z*)-heptadecenoic acid 2

To a stirred, ice-cooled mixture of alcohol (**13** or **14**, 1.86 mmole) in acetone (50 mL) was added Jone's reagent (5 mL) drop wise over 30 min. The reaction was quenched after 1 hr with isopropyl alcohol and

solvent evaporated under vacuum. The reaction mixture was extracted with diethyl ether (2 × 25 mL), washed with water (2 × 5 mL), brine and dried. The solvent was evaporated *in vacuo* to furnish pure compounds **1** (0.38 g, 72%) and **2** (0.39 g, 74%).

Compound **1**: IR(neat) : 3200, 3010, 2930, 2868, 1715, 1642, 1580, 1381, 1360 and 700 cm^{-1}; ^1H NMR(CCl_4) : δ 0.99 (d, *J* = 6Hz, 6H, -CH(C*H*$_3$)$_2$), 1.13-1.43 (bs, 18H, saturated methylene protons), 1.61-1.82 (m, 1H, -C*H*(CH$_3$)$_2$), 1.94-2.23 (m, 4H, -C*H*$_2$CH=CHC*H*$_2$-), 2.35 (t, *J* = 7Hz, 2H, -C*H*$_2$COOH), 5.11-5.41 (m, 2H, -CH$_2$C*H*=C*H*CH$_2$-), 11.56 (bs, 1H, -COO*H*, D_2O exchangeable).

Compound **2**: IR(neat) : 3250, 3010, 2940, 2852, 1720, 1640, 1590, 1380, 1362, 720 and 695 cm^{-1}; ^1H NMR(CCl_4) : δ 1.03 (d, *J* = 6Hz, 6H, -CH(C*H*$_3$)$_2$), 1.29-1.58 (bs, 18H, saturated methylene protons), 1.64-1.81 (m, 1H, -C*H*(CH$_3$)$_2$), 1.92-2.23 (m, 4H, -C*H*$_2$CH=CHC*H*$_2$-), 2.32 (t, *J* = 6Hz, 2H, -C*H*$_2$COOH), 5.11-5.42 (m, 2H, -CH$_2$C*H*=C*H*CH$_2$-), 11.53 (bs, 1H, -COO*H*, D_2O exchangeable).

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12 Literature reports melting point of 8-hydroxytriphenylphosphonium bromide as 132-134ºC and that of 6-hydroxytriphenylphosphonium bromide as 153-154ºC.