An efficient synthesis of 7-methoxy-8-methyl-α-tetralone

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The commercially available 7-methoxy-α-tetralone was subjected to bromination, reduction and protection respectively to obtain the *tert*-butyldimethylsilyl derivative compound whose conversion into the title compound tetralone was accomplished in three steps (methylation, deprotection and oxidation).

Key words: tetralone, bromination, reduction, *tert*-butyldimethylsilyl chloride

The title compound tetralone **7** which is a potential intermediate in the preparation of lactones[1] related to desmotroposantonin has been synthesised[2] by Chatterjee and Banerjee. The starting material selected by these authors is not easily accessible. During its transformation to the tetralone **7** most of the intermediate steps produced isomeric products and thus required very careful purification to give the pure intermediates. The yield of the penultimate product was also not high. Our recent studies[3] on the transformation of 6-methoxytetralin prompted us to explore an alternative route for the title compound.

Results and discussion

The commercially available 7-methoxy-α-tetralone **1** on bromination[4] with N-bromosuccinimide (NBS) in acetone yielded the bromotetralone **2** in 67% yield.

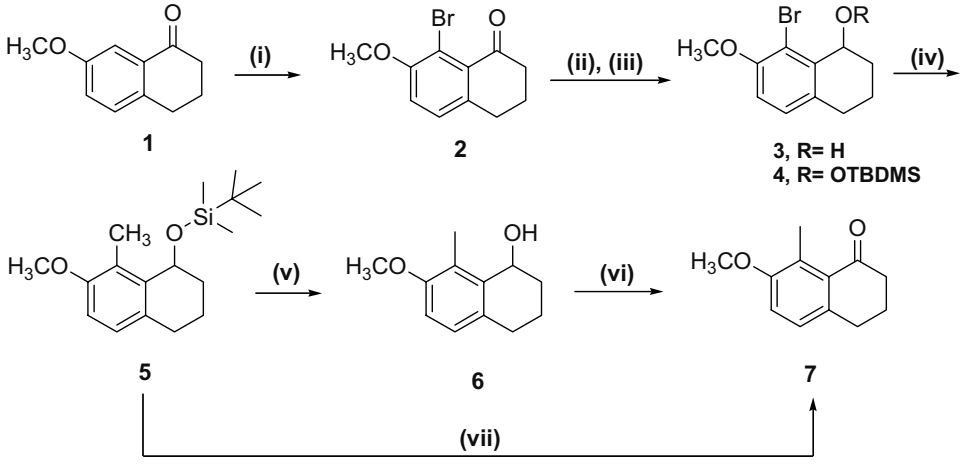
The bromotetralone **2** was obtained in 37% yield when the bromination was carried out with NBS in water under solvent free condition.[5] Reduction of **2** with sodium borohydride in anhydrous ethanol afforded the tetrahydronaphthol **3** in 94% yield. The *tert*-butyldimethylsilyl (OTBDMS) derivative **4** was then prepared in 61% yield by treatment of the naphthol **3** with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide. It was methylated[6] with methyl iodide in presence of *n*-butyl lithium and *t*-butylmethylether to obtain the compound **5** in 83% yield which is the penultimate intermediate in the synthesis of the title compound. The conversion of the compound **5** to the desired tetralone **7** was achieved in two steps: (i) desilylation and (ii) oxidation. Desilylation[7] of **5** with zirconium tetrachloride in methanol furnished the alcohol **6** in 58% yield whose conversion to the desired tetralone **7** in 66% yield was achieved by oxidation with Jones reagent. The conversion of the compound **5** to the target molecule **7** in 64% yield was also achieved by employing different condition[8] which involved the addition of a solution of chromic acid and periodic acid in acetonitrile to solution of the compound **5** in dichloromethane. These conditions not only led to desilylation but also oxidation of the resulting alcohol, thus shortening the reaction sequence by one step.

In summary we have developed an alternative route for the synthesis of 7-methoxy- 8-methyl-α-tetralone **1**. The yields of all new compounds are high. The overall yield of our method is 20.4% whereas the overall yield of the published procedure[2] is 16.0%. The experimental conditions selected for the present procedure afforded a very clean product in each step and all the experiments can be reproduced.

Experimental

Unless otherwise stated, IR spectra were obtained with a Nicolet Fourier transform (FT). NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$. Mass spectra were recorded on a Thermo Finnigan TSQ Quantum Ultra AM mass spectrometer. All organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography was carried out on Silica gel 60 (Merck), grade 60, 70–230 mesh, and TLC plates were coated with silica gel 60 F_{254}, layer thickness 0.2 mm and the spots were located by exposing the plate to UV light. Microanalyses were carried out in the Department of Chemistry, IVIC.

8-Bromo-7-methoxy-α-tetralone (**2**); *first approach*: A mixture of 7-methoxy-1-tetralone **1** (4.71 g, 26.78 mmol), *N*-bromosuccinimide (4.76 g, 26.78 mmol) and acetonitrile (25 mL) was stirred at room temperature for 16 h. The solvent was evaporated and chromatographed to give the tetralone **2** (67%, 4.57 g) as a yellow solid, m.p. 92–94 °C, IR (cm^{-1}): 1688 (CO); ^1H NMR δ: 1.89–1.97 (m, 2H, C3-2H), 2.54 (t, 2H, C4-2H, *J* = 6.54 Hz), 2.76 (t, 2H, C2-2H, *J* = 6.24 Hz), 3.76 (s, 3H, OCH_3), 6.88 (d, 1H, ArH, *J* = 8.43 Hz), 7.03 (d, 1H, ArH, *J* = 8.43 Hz);



Reagents: (i) NBS,MeCN; (ii) $NaBH_4$, EtOH; (iii) TBDSCl, imidazole; (iv) MeI, nBuLi, tBuOMe; (v) $ZrCl_4$, MeOH; (vi) Jones, acetone; (vii) CrO_3-H_5IO_6, CH_3CN-CH_2Cl_2.

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^{13}C NMR δ: 22.70, 30.00, 40.05, 56.78, 111.65, 115.89, 129.16, 132.47, 138.63, 155.48, 197.19. EM *m/z*: 256 (M^+ + 1), 255 (M^+), 175 (M^+-Br). Anal. Calcd for $C_{11}H_{11}O_2Br$: C, 51.76; H, 4.31; Br, 31.33. Found: C, 52.04; H, 4.48; Br, 31.58%.

Second approach: A suspension of 7-methoxy-1-tetralone **1** (1.09 g, 6.24 mmol) in water (50 mL) was treated with *N*-bromosuccinimide (1.32 g, 7.41 mmol) and heated to 60 °C. Sulfuric acid (40%, 2 mL) was then added and stirred for 12 h. The reaction mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried, filtered, concentrated and purified by flash chromatography to afford tetralone **2** (37%, 0.58 g) as a yellow solid; m.p. 92–95 °C. Its spectroscopic data were identical with that of obtained by the first approach.

8-Bromo-7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ol (**3**): A solution of ketone **2** (0.79 g, 3.1 mmol) in anhydrous ethanol (10 mL) at 0 °C was treated with sodium borohydride (0.34 g, 8.9 mmol) in portions. The mixture was allowed to reach room temperature and then stirred for 3 h. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by silica flash chromatography (hexanes–ether, 8:2), to give compound **3** as a viscous oil (94%; 0.74 g). IR (cm^{-1}) 3440 (OH), 1597.28 (C=C); ^{1}H NMR δ: 1.70–1.76 (m, 2H, C3-2H), 1.88–2.02 (m, 1H, C2-1H), 2.14–2.19 (m, 1H, C2-1H), 2.55–2.68 (m, 2H, C4-2H), 2.80 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 5.02 (dd, 1H, C1-1H, $J_{ax\text{-}ec}$ = 6.63 Hz, $J_{ax\text{-}ax}$ = 3.42 Hz), 6.78 (d, 1H, C6-1H, *J* = 8.46 Hz), 7.03 (d, 1H, C5-1H, *J* = 8.46 Hz); ^{13}C NMR δ: 17.29, 29.06, 30.71, 56.45, 66.21, 111.68, 114.73, 129.15, 131.65, 138.30, 154.07. EM *m/z*: 258 (M^+ + 1), 256 (M^+-1), 239 (M^+-H_2O), 159 (M^+-H_2O-Br). Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.36; H, 5.05; Br, 31.08. Found: C, 51.63; H, 5.23; Br, 31.36%.

8-bromo-1-tert-butyldimethylsilyloxy-7-methoxy-1,2,3,4-tetrahydronaphthalene (**4**): A solution of alcohol **3** (1.89 g, 7.36 mmol) in dimethylformamide (5 mL) was treated with imidazole (1.50 g, 22.15 mmol) and *tert*-butyldimethylsilyl chloride (1.21 g, 8.09 mmol). The solution was stirred for 24 h at room temperature. The reaction mixture was quenched with 1 M HCl and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, concentrated and purified by flash chromatography to afford ether **4** (61%, 1.66 g) as a white solid. m.p. 45–47 °C, IR (cm^{-1}) 843, 832 (Si–C), ^{1}H NMR δ: 0.18 (s, 3H, Si–CH_3), 0.23 (s, 3H, Si–CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.56–1.70 (m, 2H, C3-2H), 2.05–2.13 (m, 2H, C2-2H), 2.59–2.71 (m, 1H, C4-1H), 2.80–2.87 (m, 1H, C4-1H), 3.85 (s, 3H, OCH_3), 5.12–5.14 (m, 1H, C1-1H), 6.78 (d, 1H, C6-1H, *J* = 8.5 Hz), 7.01 (d, 1H, C5-1H, *J* = 8.5 Hz); ^{13}C NMR δ: –4.44, –3.92, 16.37, 18.08, 26.06, 28.50, 31.83, 56.39, 67.52, 111.34, 114.98, 128.77, 131.51, 138.91, 153.82. EM *m/z*: 315(M^+-C_4H_8), 239 (M^+-$C_6H_{16}OSi$), 159 (M^+- $C_6H_{16}OSi$–Br). Anal. Calcd for $C_{17}H_{27}BrO_2Si$: C, 54.98; H, 7.27; Br, 21.53. Found: C, 55.24; H, 7.46; Br, 21.81%.

1- tert-Butyldimethylsilyloxy-7-methoxy-8-methyl-1,2,3,4-tetrahydronaphthalene (**5**): A solution of compound **4** (0.88 g, 2.37 mmol) in *tert*-butyl methyl ether (15 mL) stirred at 0 °C under argon was treated dropwise with methyl iodide (0.30 mL, 4.75 mmol) and *n*-butyllithium (1.3 M, 2.20 mL). The mixture was stirred at 0–15 °C for 1 h and quenched with water. The aqueous mixture was extracted with ether and the combined organic extracts were dried and the solvent was removed under vacuum to leave a compound **5** (83%, 0.60 g) as oil. ^{1}H NMR δ: 0.36 (s, 3H, Si–CH_3), 0.41 (s, 3H, Si–CH_3), 1.15 (s, 9H, $SiC(CH_3)_3$), 1.81–1.92 (m, 2H, C3-2H), 2.21–2.34 (m, 2H, C2-2H), 2.48 (s, 3H, Ar-CH_3), 2.82–2.93 (m, 1H, C4-1H), 3.00-3.07 (m, 1H, C4-1H), 3.96 (s, 3H, OCH_3), 5.22 (s, 1H, C1-1H), 6.93 (d, 1H, C6-1H, *J* = 8.4 Hz), 7.12 (d, 1H, C5-1H, *J* = 8.4 Hz); ^{13}C NMR δ: –4.10, -3.59, 11.33, 17.06, 18.94, 26.12 ($3CH_3$), 29.40, 32.70, 55.60, 65.54, 110.05, 125.76, 127.03, 129.32, 137.77, 155.81. EM *m/z*: 175(M^+-$C_6H_{16}OSi$). Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.58; H, 9.80. Found: C, 70.86; H, 10.02%.

7-Methoxy-8-methyl-1,2,3,4-tetrahydronaphthalenol (**6**): A solution of TBDMS ether **5** (1.04 g, 3.40 mmol) in methanol (10 mL) was treated with $ZrCl_4$ (0.15 g, 0.68 mmol) and stirred at room temperature for 12 h. The reaction mixture was evaporated and purified by flash chromatography (hexane/ether 8:2) to furnish the desilylated product **6** (58%, 0.37 g) as needles solid. m.p. 59–61 °C. IR(cm^{-1}) 3297 (OH), 1600 (C=C); ^{1}H NMRδ: 1.65 (s, 1H, OH), 1.65–1.79 (m, 2H, C3-2H), 1.82–1.93 (m, 1H, C2-1H), 2.09–2.13 (m, 1H, C2-1H), 2.29 (s, 3H, Ar-CH_3), 2.58–2.79 (m, 2H, C4-2H), 3.79 (s, 3H, OCH_3), 4.92–4.94 (m, 1H, C1-1H), 6.76 (d, 1H, C6-1H, *J* = 8.43z), 6.93 1H, C5-1H, *J* = 8.43z); ^{13}C NMR δ: 10.79, 17.21, 29.31, 32.01, 55.75, 64.42, 110.50, 125.85, 127.09, 129.35, 136.90, 156.04. EM *m/z*: 192(M^+), 175 (M^+-OH), 174 (M^+-H_2O). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.16; H, 8.61%.

7-methoxy-8-methyl-α-tetralone (**7**): *first approach:* CrO_3 (1.43 mg, 0.14 mmol) and periodic acid (0.97 g, 4.31 mmol) were dissolved in acetonitrile (12 mL) by stirring at room temperature for 1 h. The resulting solution was added to a solution of compound **5** (0.43 g, 1.43 mmol) in dichloromethane (12 mL) at 0 °C over a period of 15 min. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h, quenched with saturated $Na_2S_2O_3$, extracted with dichloromethane and the combined organic extracts were dried. The solvent was removed under reduced pressure and the residue was chromatographed (hexane-ether, 8:2) to obtain the tetralone **7** (64%, 0.17 g) as a yellow solid. M.p. 43–45 °C. IR (cm^{-1}) 1680 (CO), ^{1}H NMR δ: 1.96–2.04 (m, 2H, C3-2H), 2.49 (s, 3H, Ar-CH_3), 2.58 (t, 2H, C4-2H, *J* = 6.5 Hz), 2.83 (t, 2H, C2-2H, *J* = 6.2 Hz), 3.77 (s, 3H, OCH_3), 6.93 (d, 1H, ArH, *J* = 8.4 Hz), 7.01 (d, 1H, ArH, *J* = 8.4 Hz); ^{13}C NMR δ: 13.16, 23.20, 30.35, 41.09, 56.07, 114.99, 126.60, 129.54, 132.31, 137.28, 156.58, 200.75. EM *m/z*: 190 (M^+), 161 (M^+-COH); HRMS calculated for $C_{12}H_{14}O_2$ (M +1) 191.242, found 191.182. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.88; H, 7.51%.

Second approach: A solution of alcohol **6** (0.137 g, 0.717 mmol) in acetone (5 mL) magnetically stirred and cooled to 0 °C and treated dropwise with Jones reagent (8 N, 0.38 mL). The mixture was stirred at 0–15 °C for 20 min and isopropyl alcohol (2 mL) was then added to destroy the excess Jones reagent. The solvent was removed under pressure and the crude was purified by flash chromatography (hexane/ether 9:1) to furnish the tetralone **7** (66%, 89.91 mg). Its spectroscopic data were identical with that of obtained by the first method.

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