Synthesis of 2-hydroxy-5-methyl-3-hexanone

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2-Hydroxy-5-methyl-3-hexanone, which is a characteristic component of eucalyptus honeys, was synthesised by oxidation of the silyl enol ether of 5-methyl-3-hexanone. 5-Methyl-3-hexanone was prepared by Grignard reaction and oxidation starting from isovaleraldehyde and ethylmagnesium bromide. The desired silyl enol ether was produced with high selectivity by deprotonation of 5-methyl-3-hexanone with NaHMDS in n-hexane followed by reaction with chlorotrimethylsilane and then oxidised by MCPBA to give pure 2-hydroxy-5-methyl-3-hexanone in about 77% yield after purification by flash chromatography. 2-Hydroxy-5-methyl-3-hexanone has a cheese and sour milk odour.

Keywords: 2-hydroxy-5-methyl-3-hexanone, 5-methyl-3-hexanone, silyl enol ether

2-Hydroxy-5-methyl-3-hexanone shares the same FEMA (Flavour and Extract Manufacturers Association) number 3989 with its isomer 3-hydroxy-5-methyl-2-hexanone.[1] It has a cheesy and sour milk aroma and can be used in various flavouring formulations for alcoholic beverages, frozen dairy products and puddings. It has been identified in sherry and honey and to be a characteristic of eucalyptus honey.[2–5] There are two methods reported for producing 2-hydroxy-5-methyl-3-hexanone. One method includes reacting 5-methyl-2-hexanone with sulfuryl chloride to produce 3-chloro-5-methyl-2-hexanone, forming 3-acetoxy ketone from 3-chloro-5-methyl-2-hexanone, and hydrolysing the 3-acetoxyketone to form the mixture of 2-hydroxy-5-methyl-3-hexanone and 3-hydroxy-5-methyl-2-hexanone with a ratio of 22/78.[6] The other method is enzymatic synthesis. In order to identify 2-hydroxy-5-methyl-3-hexanone and 3-hydroxy-5-methyl-2-hexanone found in eucalyptus honeys, Fuente *et al.* prepared these two compounds following a method developed by Neruser *et al.*[7] The reaction of acetaldehyde and α-ketoisocaproic acid produced 2-hydroxy-5-methyl-3-hexanone as the major product together with 20% of a by-product 3-hydroxy-5-methyl-2-hexanone. The common disadvantage of these two synthetic methods is that they produce a mixture of 2-hydroxy-5-methyl-3-hexanone and its isomer 3-hydroxy-5-methyl-2-hexanone. As far as we know, no methods have been reported to produce 2-hydroxy-5-methyl-3-hexanone with high selectivity. We now report that it can be obtained by oxidation of the preformed silyl enol ether of 5-methyl-3-hexanone (Fig. 1).

Results and discussion

5-Methyl-3-hexanone was prepared by a Grignard reaction and oxidation starting from isovaleraldehyde and ethyl bromide. The addition of silica gel was necessary for the reaction to go smoothly, and prevent clump formation in the reaction mixture, when 5-methyl-3-hexanol was subsequently oxidised by PCC to produce 5-methyl-3-hexanone.

Different bases were compared in the transformation of 5-methyl-3-hexanone to the corresponding silyl enol ether in order to obtain the desired silyl enol ether **3** with high regioselectivity (Fig. 2). The results are shown in Table 1. The results indicated that deprotonation occurred mainly on the less bulky carbon to produce the silyl enol ether **3** as the major product whichever base was used in the deprotonation of 5-methyl-3-hexanone and the ratio of silyl enol ether **3** to **3'** was about 3/1. The solvent that was used seemed to have significant impact on the regioselectivity when NaHMDS was used to deprotonate 5-methyl-3-hexanone. The ratio of silyl enol ether **3** to **3'** was improved from 2.5/1 to 7/1 when the reaction was carried out in n-hexane instead of THF. The stereoselectivity of the major product **3** was determined by GC and ^{1}H NMR. The silyl enol ether Z-**3** was formed preferentially when Et_3N or $LiNPh_2$ was used, and $LiNPh_2$ gave Z-**3** with a very high stereoselectivity of 12/1. In contrast, the silyl enol ether E-**3** predominated when LDA or NaHMDS was used. The ratio of E-**3** to Z-**3** reached 7.5/1 when deprotonation occurred at the presence of NaHMDS in n-hexane. The effect of bases on this regio- and stereoselectivity has often been reported.[8–10] 5-Methyl-3-hexanone was deprotonated by NaHMDS to react with TMSCl to give the silyl enol ether **3** in about 86% yield. The mixture of E-**3** and Z-**3** together with small amount of silyl enol ether **3'** was oxidised directly by MCPBA without separation to give

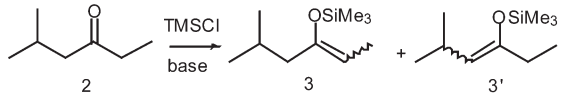

Fig. 2 Regioselectivity in the preparation of silyl enol ether.

Table 1 Regioselectivity and stereoselectivity in the preparation of silyl enol ether

Entry	Base[a]	Solvent	Ratio of **3** to **3'**[c]	Ratio of E-**3** to Z-**3**[c]
1	Et_3N	CH_3CN	3:1	1:2
2	LDA	THF	3:1	1.5:1
3	NaHMDS	THF	2.5:1	1.2:1
4	NaHMDS	n-Hexane	7:1	7.5:1
5	$LiNPh_2$[b]	THF	3:1	1:12

[a]The reaction was performed according to Method A when Et_3N was used, while Method B was adopted when other bases were used; [b]the preparation of $LiNPh_2$ followed the procedure in literature;[10] [c]the ratio was determined by GC and ^{1}H NMR.

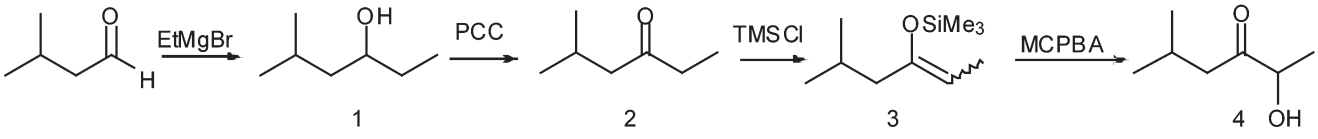

Fig. 1 Synthesis of 2-hydroxy-5-methyl-3-hexanone.

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2-hydroxy-5-methyl-3-hexanone in about 77% yield. The product had a cheese and sour milk odour as described in the literature.

In summary, 2-hydroxy-5-methyl-3-hexanone was synthesised by oxidation of the corresponding silyl enol ether of 5-methyl-3-hexanone. The regio- and stereoselectivity in the formation of silyl enol ether from 5-methyl-3-hexone varied with the bases used in the reaction. 5-Methyl-3-hexanone was deprotonated by NaHMDS in n-hexane to give the desired silyl enol ether with high regio- and stereoselectivity. The resultant silyl enol ether was oxidised by MCPBA to give pure 2-hydroxy-5-methyl-3-hexanone after purification by flash chromatography.

Experimental

Pyridinium chlorochromate (PCC, 98%), Lithium diisopropyl amide (LDA, 2 M solution in THF/n-heptane/ethylbenzene), sodium bis(trimethylsilyl)amide (NaHDMS, 2 M solution in THF), Chlorotrimethylsilane (TMSCl, 98%), 3-chloroperoxybenzoic acid (MCPBA, 70%) were obtained from Beijing Bailingwei Science and Technology Company and the others were purchased from Beijing Huaxue Shiji Company. NMR spectra were obtained with a Bruker AV300 MHz.

An Agilent 6890N-5973i was used under the following conditions: capillary column DB-5MS (30 m × 0.25 mm × 0.25 μm); the oven temperature was programmed from 40 to 280 °C at a rate of 20 °C/min; carrier gas, helium; flow rate, 0.8 mL min^{-1}; electron ionization, 70 eV; ion source temperature, 230 °C.

5-Methyl-3-hexanol (**1**): Magnesium turnings (3.6 g, 0.15 mol) were covered by dry diethyl ether (50 mL) and stirred vigorously under an atmosphere of nitrogen. A small crystal of iodine was added, followed by ethyl bromide (0.9 mL, 0.012 mol). The mixture was heated to induce reaction, and a further amount of ethyl bromide (8 mL, 0.108 mol) in diethyl ether (30 mL) was added at such a rate that the solution continued to reflux. After addition, diethyl ether (40 mL) was added and the mixture was kept refluxing for 0.5 h. After cooling to room temperature, the solution of isovaleraldehyde (8.6 g, 0.1 mol) in dry diethyl ether (30 mL) was added dropwise to the solution of ethylmagnesium bromide at *ca* 30 °C. The reaction mixture was stirred for another 1h under reflux after the addition. The mixture was then cooled to room temperature and poured into the mixture of crushed ice and conc. HCl (10 mL) carefully with stirring. And the solution was adjusted to about pH 7. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporator and the residue distilled under vacuum to yield a colourless liquid 5-methyl-3-hexanol **1** (9.3 g, 80% yield): b.p. 83–85 °C (0.01 MPa) [lit.[11] b.p. 146–148 °C (760 mm)]. ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 9H, Me(1), Me(6) and Me–C(5)), 1.26–1.58 (m, 5H, H–C(2), H–C(4) and OH), 1.74 (m, 1H, H–C(5)), 3.59 (m, 1H, H–C(3)).

5-methyl-3-hexanone (**2**): A mixture of PCC (7.5 g, 0.035 mol), 200 mesh silica gel (12 g) and 4 Å molecular sieves (12 g) in CH_2Cl_2 (80 mL) was stirred for about 10 min. A solution of 5-methyl-3-hexanol (2.32 g, 0.02 mol) in CH_2Cl_2 (30 mL) was added to the mixture under nitrogen at 0 °C over a period of 30 min. After the mixture had been strirred at room temperature for 3 h, the mixture was filtered through a short pad of celite followed by washing with diethyl ether. The filtrate was washed successively with water (100 mL) and brine (100 mL), dried with anhydrous $MgSO_4$, and concentrated. The residue was distilled under vacuum to give the 5-methyl-3-hexanone **2** as a colourless oil (1.55 g, 68% yield): b.p. 65–67 °C (0.01 MPa) [lit.[12] b. p. 135 °C (760 mm)]. ^{1}H NMR($CDCl_3$): δ 0.90 (d, *J* = 6.6 Hz, 6H, Me–C(5) and Me(6)), 1.03(t, *J* = 7.5 Hz, 3H, Me(1)), 2.12(m, 1H, H–C(5)), 2.27 (d, *J* = 6.9 Hz, 2H, H–C(4)), 2.4 (q, *J* = 7.5 Hz, 2H, H-C(2)).

Silyl enol ether **3**

Method A. 5-Methyl-3-hexanone (1.71 g, 15 mmol) and triethylamine (3 mL, 22 mmol) was added to a four-necked flask under a nitrogen atmosphere. Chlorotrimethylsilane (2.8 mL, 22.5 mmol) was added dropwise over 10 min to this mixture, stirred at room temperature under nitrogen. The flask was then warmed in a water bath to about 40 °C, and a solution of KI (3.7 g, 22.5 mmol) in acetonitrile (50 mL) was added through a dropping funnel for about 1 h. After the addition, the reaction mixture was stirred for a further 2 h at room temperature. The contents of the flask were then poured into ice-cold water, and the aqueous mixture was extracted three times with pentane. After extraction, the organic layer was dried over anhydrous K_2CO_3. The solvent was removed by rotary evaporation and the residue was distilled under reduced pressure (1.5 KPa, 50–52 °C) to give a mixture of silyl enol ether **3** and **3′** (3/1) (2.5 g, 89% yield). The ratio of E-**3** to Z-**3** was about 1/2.

Method B. A dry flask (250 mL) under nitrogen was charged with THF or n-hexane (100 mL) and LDA or NaHMDS (18 mmol) and cooled to –78 °C. 5-Methyl-3-hexanone (1.71 g, 15 mmol) was added by syringe followed by stirring about 10 min. Freshly distilled TMSCl (2.3 mL, 18 mmol) was added. The reaction mixture was stirred 0.5 h at –78 °C and then allowed to rise to room temperature. The work-up procedure was the same as Method A. A mixture of silyl enol ether **3** and **3′** was obtained in about 86% yield (2.4 g), among which E-5-methyl-3-trimethylsilyloxy-2-hexene was the major product. E-5-methyl-3-trimethylsilyloxy-2-hexene, ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 9H, Me-Si), 0.88 (d, *J* = 6.3 Hz, 6H, Me(6) and Me-C(5)), 1.52 (d, *J* = 6.9 Hz, 3H, Me(1)), 1.86 (m, 1H, H–C(5)), 2.1 (d, *J* = 5.7 Hz, 2H, H–C(4)), 4.7 (q, *J* = 6.9 Hz, 1H, H–C(2)). ^{13}C NMR ($CDCl_3$): δ 0.3 (Me–Si), 12.1 (C(1)), 22.3 (Me(6) and Me-C(5)), 26.1(C(5)), 40.0 (C(4)), 101.9 (C(2)), 151.1 (C(3)). GC/MS (EI): *m/z* 186 (16, M^+), 171 (35), 157 (10), 144 (100), 129 (88), 75 (71), 73 (90), 45 (21).

2-Hydroxy-5-methyl-3-hexanone (**4**): A solution of MCPBA (1.8 g, 70%, 7.2 mmol) in CH_2Cl_2 (25 mL) was added to a solution of the silyl enol ether **3** (1.1 g, 6 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at –25 °C for 5 h and then slowly warmed to room temperature. Triethylamine (1 mL, 7.2 mmol) was added and the mixture was stirred for about 15 min. The reaction mixture was washed with water and the organic layer was separated. The solution of HCl–MeOH (6 mol L^{-1}, 5 mL) was added to the organic layer and the resulting mixture was heated to reflux for 30 min. The reaction mixture was diluted with water and neutralised with 10% $NaHCO_3$. The organic layer was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed by distillation and the residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 8/1) to afford product **4** (0.6 g, 77% yield). ^{1}H NMR ($CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H, Me(6)), 0.92 (d, *J* = 6.6 Hz, 3H, Me-C(5)), 1.34 (d, *J* = 7.2 Hz, 3H, Me(1)), 2.18 (m, 1H, H–C(5)), 2.27 (overlapping dd, *J* = 6.3, 16.2 Hz, H–C(4)), 2.35 (overlapping dd, *J* = 7.2, 16.2 Hz, H–C(4)), 3.60 (br, 1H, OH), 4.18 (q, *J* = 7.2 Hz, 1H, H–C(2)). ^{13}C NMR ($CDCl_3$): δ 19.7 (C(1)), 22.5 (C(6)), 22.6 (Me–C(5)), 24.5 (C(5)), 46.4 (C(4)), 72.8 (C(2)), 212.3 (C=O). GC/MS (EI): *m/z* 130 (1, M^+), 85 (64), 74 (9), 69 (11), 57 (100), 45 (80), 41 (35), 29 (15). The mass fragments matched those reported by Nerser *et al.*[7]

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