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Improved Synthesis of (*S*, *E*)-(+)-5-Methylhept-2-en-4-one, the Major Aroma Compound of Hazelnuts

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Abstract

An improved synthesis of enantiomerically pure (*S*, *E*)-(+)-5-methylhept-2-en-4-one from (*S*)-(+)-2-methyl-1-butanol in four steps is reported.

Keywords: Flavours and fragrances; Asymmetric synthesis; Ketones;

1. Introduction

Recently, Emberger et al. reported on the isolation of (*E*)-5-methyl-hept-2-ene-4-one, filbertone, the major aroma compound of hazelnuts[1]. Previously, we reported on the enantiomeric composition and absolute configuration of natural filbertone, and the synthesis of (*S*)-(-)-filbertone[2]. Blanch et al.[3] showed that the enantiomeric composition of natural filbertone depends on the conditions of its isolation (i. e. steam distillation). In this regard, the synthesis of enantiomerically pure (*S*)-filbertone was of interest as reference compound and as synthetic substitute for the natural product. Here we wish to report full experimental details of an improved synthesis of (*S*, *E*)-5-methyl-hept-2-en-4-one (**8**).

2. Results and discussion

Our synthesis (Scheme 1) starts from the commercially available (*S*)-2-methyl-butanol-1 (**1**), which was converted to (*S*)-2-methyl butyraldehyde (**2**) through oxidation with NaOCl/TEMPO

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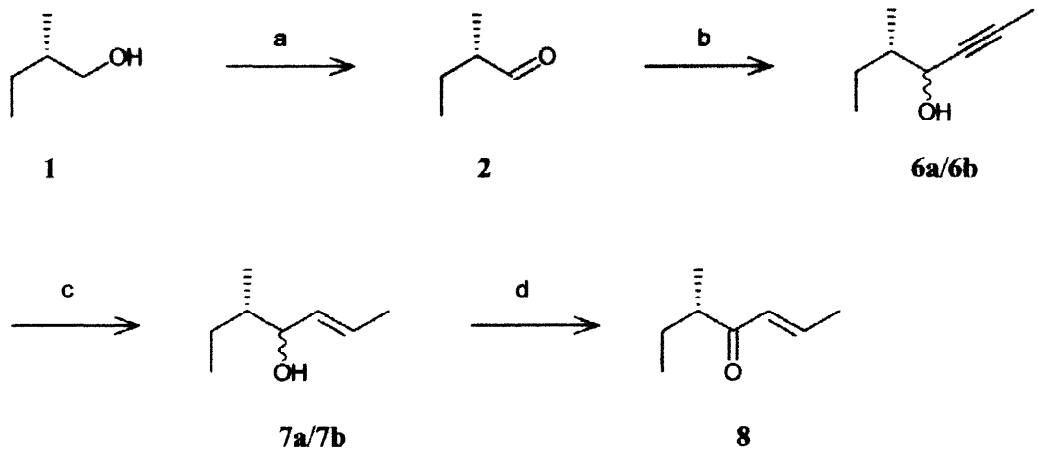
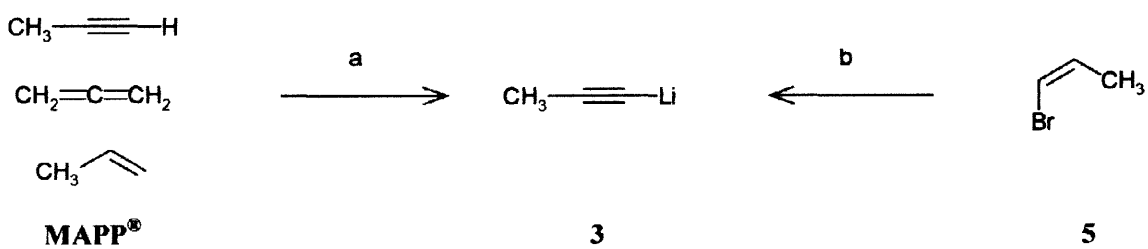
according to Quici et al.[4, 5, 6] To obtain good yields in this first step careful distillation through a 40 cm Vigreux column with a high reflux ratio is highly recommended.



a) NaOCl, TEMPO cat., KBr, $NaHCO_3$, 0 °C, 35 min, 59%. b) 3, THF, -78 °C to r.t., 95%. c) LAH, THF, reflux, 3 h, 88%. d) MnO_2, pentane, r.t., 8 h, 81%.

Scheme 1. Synthesis of filbertone (**8**).

Next, **2** is coupled with propynyl lithium (**3**), which could be prepared in two ways (Scheme 2). The first method employs the cheap welding gas mixture MAPP®, which contains about 13.5% methyl acetylene (= propyne) (**4**), propadiene (1%) and propene (85.5%). When this mixture is bubbled through a solution of MeLi in THF at –20 °C, propyne is converted into its lithium derivative **3** and the other components (propadiene and propene) leave the solution unchanged. The second method which was developed by Suffert et al.[7] is based on HBr elimination from (*Z*)-1-bromo-1-propene (**5**) with *n*-BuLi at –78 °C in THF. Both methods are equally effective. Addition of **3** to **2** gives a 1:1 mixture of diastereomers **6a** and **6b** (NMR), which could not be separated by GC on an capillary column coated with methylpolysiloxane SE30.



a) MeLi, THF, Et_2O, -20 °C. b) *n*BuLi, THF, -78 °C.

Scheme 2. Synthesis of propynyllithium (**3**).

In the third step the mixture of propargylic alcohols **6a/6b** is reduced to a mixture of allylic alcohols **7a** and **7b** by reaction with lithium aluminium hydride in THF at reflux.[8] Careful hydrolysis and extraction of the inorganic residues with THF is important to obtain a quantitative yield of **7a/7b**.

The synthesis is completed by oxidation of the mixture of **7a/7b** with activated MnO_2[9] to (*S*, *E*)-(+)-5-methylhept-2-en-4-one (**8**) in 70% yield after careful distillation.

Enantiomeric composition of **2** was determined by gas chromatography on a heptakis-(2,3-di-O-acetyl-6-O-tert.butyldimethylsilyl)-β-cyclodextrin column[10, 11] (50% in PS 86, 250 nm film, 10 m, 250 μm i.d., 60 °C, 0.25 bar H_2) giving an ee = 92% which is in agreement with the optical rotation.[5]

Determination of the enantiomeric composition of **6a/6b** and **7a/7b** by GC using various chiral stationary phases[12, 13, 14, 15, 16, 17] is rather difficult since base line separation of the diastereomers and enantiomers could not be achieved.

For analysis of the enantiomeric composition of **8** gas chromatography on a heptakis-(2,3-di-O-acetyl-6-O-tert.butyldimethylsilyl)-β-cyclodextrin column[10, 11] (Figure 1) was used. The corresponding chromatogramm is shown in Figure 1. Starting from aldehyde **2** with ee = 92% leads to **8** with the same ee, indicating that no racemization during synthesis of **8** occurred.

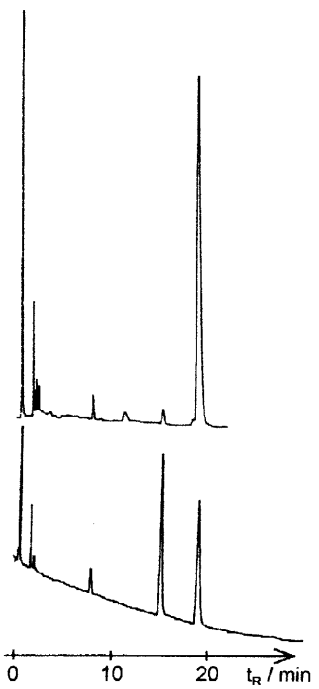


Figure 1. bottom: racemic filbertone, top: synthetic (*S*)-(+)-filbertone. Conditions: heptakis-(2,3-di-O-acetyl-6-O-tert.butyldimethylsilyl)-β-cyclodextrin, 10 m, 250 μm i.d., 60°C, 0.25 bar H_2.

3. Experimental

General. Tetrahydrofuran and diethyl ether were distilled from potassium/benzophenone. *n*-Pentane and dichloromethane were used without further purification. Activated manganese-dioxide was prepared according to ref.[9] (*S*)-2-Methyl-1-butanol was purchased from Fluka, Neu-Ulm, Germany and (*Z*)-1-bromo-1-propene was purchased from Aldrich, Steinheim, Germany and used as received. MAPP® was purchased from Messer Griesheim, Frankfurt, Germany. ^{1}H NMR and ^{13}C NMR spectra were obtained on an Bruker AMX 360. Chemical shifts are reported in ppm relative to $CHCl_3$ (δ = 7.25 ppm for ^{1}H) and relative to $CDCl_3$ (δ = 77.0 ppm for ^{13}C). Mass spectra were recorded on an Finnigan MAT 8200 in EI mode.

(*S*)-(+)-2-Methylbutanal (2). In a 500 ml three necked flask were placed 85 ml dichloromethane, 22.03 g (S)-2-methyl-1-butanol (0.25 mol), 0.39 g TEMPO (2.5 mmol) and a solution of 3.00 g KBr (0.025 mol) in 13 ml water. The flask is cooled to 0°C (internal temperature) and 240 ml of a 1.15 M aqueous solution of NaOCl, containing 4.25 g $NaHCO_3$, is added during 30 min such, that the internal temperature is below 15°C. Stirring is continued for 5 min and the orange dichloromethane phase is separated from the aqueous phase. The aqueous phase is extracted twice with 40 ml CH_2Cl_2 and the combined organic phases were washed successively with 50 ml 10% HCl, containing 0.8 g KI, with 30 ml 10% $Na_2S_2O_3$ and 30 ml H_2O and dried over $MgSO_4$. Slow distillation through a 40 cm Vigreux column gave 12.70 g aldehyde **2** (59%), bp 90-91°C/760 Torr. $[\alpha]_D^{20}$ = + 32.9 (ref.[5]: +33.1). ^{1}H NMR ($CDCl_3$, 360 MHz, δ in ppm): 9.57 (d, 2.2 Hz, 1H, H1); 2.23 (sextd, 6.8 Hz, 1.8 Hz, 1 H, H2); 1.69 (m, 1 H, H3); 1.39 (m, 1H, H3); 1.03 (d, 6.8 Hz, 3H, H5); 0.89 (t, 7.1 Hz, 3H, H4). ^{13}C NMR ($CDCl_3$, 90.56 MHz, δ in ppm): 205.2 (d, C1); 41.7 (d, C2); 23.4 (t, C3); 12.7 (q, C5); 11.2 (q, C4).

(4*RS*, 5*S*)-5-Methylhept-2-yn-4-ol (6a/6b). Method A. In a 500 ml three necked flask is placed 100 ml THF and the flask is cooled to -20°C. Then 78 ml MeLi (1.6 M in diethyl ether, 0.125 mol) is added and MAPP is bubbled through the solution at -20°C to -10°C for three to four hours giving a white suspension of **3**. The stirred suspension is cooled to -78°C (internal temperature) and 14.30 g **2** (0.166 mol) in 10 ml THF is added within 20 min. Stirring is continued for 1 h and then the reaction mixture is slowly warmed to room temperature over-night. Hydrolysis with 75 ml saturated aqueous NH_4Cl and extraction of the aqueous phase (4 x 40 ml diethyl ether) folowed by washing the combined organic phases four times with 40 ml brine and drying with $MgSO_4$ gives the crude product which is purified through Kugelrohr distillation (130°C/12 Torr). Yield 12.70 g (81%).

Method B. In a 500 ml three necked flask is placed 75 ml THF under N_2 and 14.00 g of (*Z*)-1-bromo-1-propene (0.120 mol). The flask is cooled to -78°C (internal temperature) and 103.1

ml *n*-BuLi in hexane (1.6 M, 0.165 mol) is added at this temperature. The resulting white suspension is stirred at -78°C for 2 h prior to the addition of a solution of 6.50 g **2** (0.076 mol) in 40 ml THF. Stirring is continued for 1 h and then slowly warmed to room temperature over night. Work up is as described for method A. Yield 9.01 g (95%). ^{1}H NMR ($CDCl_3$, 360 MHz, δ in ppm): 4.20 (dd, 5.3 Hz, 2.2 Hz, 1H, H4); 4.16 (dd, 5.3 Hz, 2.2 Hz, 1H, H4); 2,20 (br s, 1H, OH); 1.80 (s, 3H, H1); 1.79 (s, 3H, H1); 1.63-1.43 (m, 4H, H5, H6); 1.22-1.08 (m, 2H, H6); 0.92 (d, 6.6 Hz, 3H, H8); 0.91 (d, 6.6 Hz, 3H, H8); 0.87 (t, 7.1 Hz, 3H, H7); 0.86 (t, 7.5 Hz, 3H, H7). ^{13}C NMR ($CDCl_3$, 90.56 MHz, δ in ppm): 81.5 (s, C3); 81.2 (s, C3); 79.5 (s, C2); 78.8 (s, C2); 66.8 (d, C4); 66.7 (d, C4); 41.3 (d, C5); 41.1 (d, C5); 25.3 (t, C6); 24.7 (t, C6); 14.4 (q, C8); 14.0 (q, C8); 11.5 (q, C7); 11.4 (q, C7); 3.4 (q, C1). MS (EI): 126 (M^+, 0.5%); 125 ($[M-1]^+$, 1%); 111 ($[M-CH_3]^+$, 12%); 69 ($[M-C_4H_9]^+$, 100%); 57 ($C_4H_9^+$, 10%); 41 ($C_3H_5^+$, 28%). IR (neat, ν in cm^{-1}): 3370 (ν_{OH}, s); 2920-2840 (ν_{CH}, s); 2200 ($\nu_{C\equiv C}$, w); 1460 (δ_{CH}, m); 1380 (δ_{CH}, m); 1160 (m); 1040-1000 (s).

(4*RS*, 5*S*)-5-Methylhept-2-en-4-ol (7a/7b). In a 100 ml three necked flask are placed 2.30 g $LiAlH_4$ (0.061 mol) and 50 ml THF under N_2. 8.00 g of a mixture of **6a/6b** (0.064 mol) is added dropwise durig 10 min and the mixture is refluxed for three hours. After cooling to room temperature, the reaction mixture is carefully hydrolyzed with 4 ml H_2O, 3 ml 15% NaOH and again 8 ml H_2O with vigorous stirring. The precipitate is filtered off and refluxed with 80 ml THF overnight. The combined THF phases are dried with $MgSO_4$ and THF is evaporated at reduced pressure, leaving the pure product (7.40 g, 88%). ^{1}H NMR ($CDCl_3$, 360 MHz, δ in ppm): 5.60 (br quart, 6.7 Hz, 1H, H3); 5.56 (br quart, 6.2 Hz, 1 H, H3); 5.47-5.38 (m, 2 H, H2); 3.82 (br quart, 6.2 Hz, 2H, H4); 1.65 (dd, 6.2 Hz, 1.3 Hz, 3H, H1); 1.64 (dd, 6.2 Hz, 0.9 Hz, 3H, H1); 1.55-1.32 (m, 4H, H6); 1.13-0.96 (m, 6H, H8); 0.85 (br tr, 5.7 Hz, 6H, H7). ^{13}C NMR ($CDCl_3$, 90.56 MHz, δ in ppm): 132.8 (d, C3); 132,2 (d, C3); 127.4 (d, C2); 127.0 (d, C2); 76.6 (d, br, C4); 40.5 (d, C5); 40.3 (d, C5); 25.2 (t, C6); 25.1 (t, C6); 17.6 (q, br, C1); 14.3 (q, C8); 14.1 (q, C8); 11.6 (q, C7); 11.3 (q, C7). MS (EI): 128 (M^+, 0,5%); 110 ($[M-H_2O]^+$, 2%); 71 ($[M-C_4H_9]^+$, 100%); 57 ($[C_4H_9]^+$, 12%); 43 ($[C_3H_7]^+$, 32%). IR (neat, ν in cm^{-1}): 3480 (ν_{OH}, s); 3010 (ν_{CH}, w); 2920-2860 (ν_{CH}, s); 1640 ($\nu_{C=C}$, w); 1460 (δ_{CH}, m); 1370 (δ_{CH}, m); 960 (δ_{CH}, s).

(*S*)-(+)-5-Methylhept-2-en-4-one (8). In a 250 ml round bottom flask are placed 60,00 g activated MnO_2 and 110 ml *n*-pentane. To this suspension is added 6.40 g of a mixture of **7a** and **7b** with vigorous stirring. The reaction mixture is stirred for 20 h at room temperature. Then the MnO_2 is filtered and the *n*-pentane is removed through a 40 cm Vigreux column. The remaining oily residue is distilled in a Kugelrohr oven at 70°C/20 Torr yielding 5.10 g filbertone (**8**) ($[\alpha]_D^{22}$ = +37.3 (c = 2.5, acetone)). ^{1}H NMR ($CDCl_3$, 360 MHz, δ in ppm): 6.81 (dd, 15.7 Hz, 6.6 Hz, 1H, H2); 6.11 (dquart, 15.7 Hz, 1.8 Hz, 1H, H3); 2.59 (sext, 6.6 Hz, 1H,

H5); 1.82 (dd, 6.6 Hz, 1.8 Hz, 3H, H1); 1.61 (sept, 7.1 Hz, 1 H, H6); 1.32 (sept, 7.1 Hz, 1H, H6); 0.99 (d, 7.1 Hz, 3 H, H8); 0.79 (t, 7.5 Hz, 3H, H7). ^{13}C NMR ($CDCl_3$, 90.56 MHz, δ in ppm): 203.6 (s, C4); 142.0 (d, C2); 130.5 (d, C3); 45.2 (d, C5); 26.0 (t, C6); 18.0 (q, C1); 16.0 (q, C8); 11.5 (q, C7). MS (EI): 126 (M^+, 1%); 111 ($[M-CH_3]^+$, 10%); 98 ($[M-C_2H_4]^+$, McLafferty, 10%); 69 ($[M-C_4H_9]^+$, 100%); 41 ($[C_3H_5]^+$, 35%). IR (neat, ν in cm^{-1}): 3020 (ν_{CH}, w); 2980-2860 (ν_{CH}, s); 1650 (ν_{CO}, s); 1620 ($\nu_{C=C}$, s); 1450 (δ_{CH}, s); 1370 (m); 1280 (m); 1200 (w); 980 (δ_{CH}, m).

Acknowledgements

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