

Article

An Alternative Route for the Synthesis of (E)-(+)-5(S)-Methylhept-2-en-4-one (Filbertone)

Paulo H.G. Zarbin^a, Massami Yonashiro^{b,*}, and Waldir Perissini Jr.^b

^aDepartamento de Química, Universidade Federal do Paraná, Centro Politécnico,
Jardim das Américas, 81539-990 Curitiba - PR, Brazil;

^bDepartamento de Química, Universidade Federal de São Carlos,
Rod. Washington Luiz Km 235, C.P. 676, 13565-905 São Carlos - SP, Brazil

Received: August 13, 1997

Foi estudada uma metodologia alternativa para a obtenção da (+)-Filbertone (**1**), um aromatizante natural isolado de avelãs. Utilizou-se o álcool comercial (-)-2(*S*)-metilbutan-1-ol (**2**) como material de partida, sendo a síntese realizada em quatro etapas com rendimento global de 42%. A rotação óptica e pureza enantiomérica do produto final foram determinados.

We are reporting an alternative methodology to prepare (+)-Filbertone (**1**), a natural flavor isolated from hazelnut extracts. Commercially available (-)-2(*S*)-methylbutan-1-ol (**2**) was used as starting material and the synthesis was carried out in four steps with an overall yield of 42%. The optical rotation and the enantiomeric purity of the final compound were determined.

Keywords: pyridinium chlorocromate, Filbertone, double bond isomerization

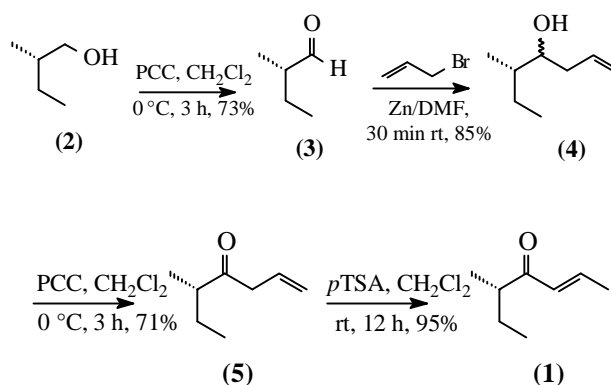
Introduction

The (E)-(+)-5(*S*)-methylhept-2-en-4-one, (+)-Filbertone (**1**), was isolated from hazelnut extracts of a Turkish variety in 1989 by Schurig and co-workers¹. They also carried out the first chiral synthesis of this compound in 20% overall yield, establishing the relationship between chirality and olfaction. The enantiomeric composition and assignment of the absolute configuration was made¹. According to Schurig, the natural product (**1**) exhibits low enantiomeric excess, varying with the origin of hazelnut (54.4-62.6% *ee*). Compound (**1**) is included as GRAS (Generally Recognized As Safe) substances and its FAME (Flavor and Extract Manufacturer's Association) number is 3761 as 5-methyl-2-hepten-4-one².

In this work, we are describing a new methodology to prepare Filbertone (**1**) (Scheme 1), using an easy experimental procedure with four steps and overall yield of 42%.

Results and Discussion

Commercially available (-)-2(*S*)-Methylbutan-1-ol (**2**) (Aldrich) was oxidized with PCC in methylene chloride³ to the known 2(*S*)-methylbutanal (**3**)⁴ in 73% yield. The



Scheme 1. Synthesis of Filbertone (1).

freshly purified aldehyde (**3**) was coupled with allyl bromide using Shono's reaction conditions⁵ to provide the diastereoisomeric mixture of alcohols (**4**) in 85% yield. The mixture of (**4**) was oxidized with PCC in CH₂Cl₂ at 0 °C³ to afford the β,γ unsaturated ketone (**5**) in 71% yield.

The α,β-unsaturated ketone (**1**) was obtained in 95% yield by isomerization of the double bond of ketone (**5**) using *p*-TsOH in CH₂Cl₂. The ¹H-NMR analysis of ketone

(1), showed a coupling constant ($J = 16.2$ Hz) for the vinylic protons. The enantiomeric purity of Filbertone (1) was determined by GC chiral column (75% *ee* of (*E*)-(+)-5*S*-methylhept-2-en-4-one) (Fig. 1) and the optical rotation in ethyl acetate solution shows a value of $[\alpha]_D^{23} +12.5^\circ$. We believe that the partial isomerization of the stereocenter was occurred during the double bond conjugation step.

Experimental

All boiling points are uncorrected. The IR spectra refer to films and were measured on a Bomem M-102 spectrometer. The $^1\text{H-NMR}$ spectras were recorded with TMS as an internal standard at 60 MHz on a Hitachi Perkin-Elmer R-24A spectrometer and at 80 MHz on a Varian FT-80A spectrometer. The $^{13}\text{C-NMR}$ spectra was recorded with TMS as an internal standard at 20 MHz on a Varian FT-80A spectrometer. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. Chiral separation was obtained by GC on a cyclodextrin-based capillary column, CD-5 (10 m x 0.25 mm x 0.28 μm ; Laboratório de Cromatografia USP/IFQSC/DQFM) using a HP 5890 series II gas chromatograph (equipped with FID) with H_2 as carrier (37.8 cm/s), operating at 40 $^\circ\text{C}$. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art.-Nr. 7734.

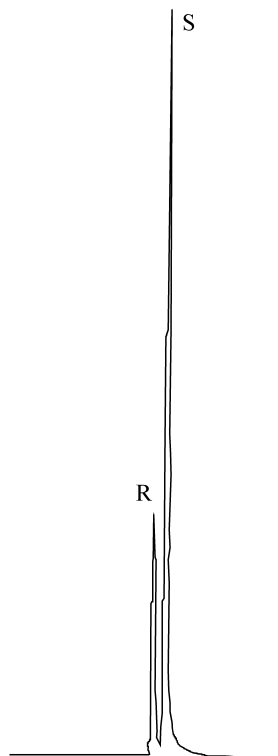


Figure 1. Enantiomeric separation of (*E*)-5-methylhept-2-en-4-one (1) by CD-5 chiral capillary column. t_R (R) = 11.86 min; t_R (S) = 12.90 min.

2(*S*)-methylbutanal (3)

Alcohol (2) (0.82 g, 9.30 mmol) was added to a suspension of PCC (4.0 g, 18.60 mmol) in dry CH_2Cl_2 (20 mL) at 0 $^\circ\text{C}$. After 3 h, dry ether (10 mL) was added and the mixture of ether and methylene chloride was filtered through Celite, silica gel and charcoal. The solvent was removed by distillation and the residue obtained was quickly purified in a short chromatography column (hexane : ethyl acetate, 9:1) to afford the aldehyde (3) in 73% yield (0.58 g). IR ($\bar{\nu}_{\text{max}}$, film cm^{-1}): 2963, 1713, 1461, 1230, 948. $^1\text{H-NMR}$ (60 MHz, CDCl_3): δ 0.85 (d, $J = 6$ Hz, 3H); 1.0 (t, $J = 6$ Hz, 3H); 1.20-1.80 (m, 2H); 1.80-2.40 (m, 1H); 9.5 (br s, 1H).

5(*S*)-Methylhept-1-en-4(*R/S*)-ol (4)

A solution of aldehyde (4) (1.30 g; 15.11 mmol) and allyl bromide (2.15 g, 22.20 mmol) in DMF (15 mL) was stirred at room temperature for 5 min. Zinc powder (1.50 g, 23.10 mmol) was added to the solution and a very strong exothermic reaction started after 10 min and finished in 30 min. A solution of saturated NH_4Cl was added (100 mL) and the reaction mixture was extracted with ether, dried (Na_2SO_4) and concentrated. The crude product was chromatographed over silica gel (hexane:ethyl acetate, 8:2) and the homoallylic alcohol (4) was obtained in 85% yield (1.60 g). IR (ν_{max} , film cm^{-1}): 3409, 3074, 2961, 1642. $^1\text{H-NMR}$ (80 MHz, CDCl_3): δ 0.70-0.80 (m, 6H); 1.10-1.70 (m, 3H); 1.85 (br s, 1H); 2.10-2.25 (m, 2H); 3.25-3.60 (m, 1H); 5.00 (dd, $J_1 = 15$ Hz, $J_2 = 5$ Hz, 2H); 5.50-6.10 (m, 1H). $^{13}\text{C-NMR}$ (20 MHz, CDCl_3): δ (11.2, 11.4); (13.1, 14.4); (21.5, 25.6); (38.0, 38.9); (39.4, 39.7); (73.5, 74.1); (117.0, 117.2); 135.1.

5(*S*)-Methylhept-1-en-4-one (5)

The mixture of homoallylic alcohols (4) (2.0 g, 15.60 mmol) was added to a suspension of PCC (6.7 g, 31.0 mmol) in dry CH_2Cl_2 (100 mL) at 0 $^\circ\text{C}$. After 3 h, dry ether (40 mL) was added and the mixture of ether and CH_2Cl_2 was filtered through Celite, silica gel and charcoal. The solvent was removed by distillation and the residue obtained (1.40 g, 71% yield) was used in the next step without further purification. The ketone (5) was found to be highly volatile.

5(*S*)-Methylhept-2-en-4-one (1)

A solution of compound (5) (1.0 g, 7.9 mmol) and *p*-TsOH (0.1 g) in dry methylene chloride (40 mL) was magnetically stirred over night at room temperature. A solution of saturated NaCl (20 mL) was added and the mixture was extract with CH_2Cl_2 . The organic layer was dried (MgSO_4) and concentrated *in vacuo*. The crude product obtained was purified in a Kugelrohr (55 $^\circ\text{C}$, 2.2 mmHg) to afford Filbertone (1) (0.95 g) in 95% yield.

$[\alpha]_D^{23} + 12.5^\circ$ (c 3.0, EtOAc) IR (ν_{\max} , film cm^{-1}): 2950, 1675, 1631, 1450, 1200. $^1\text{H-NMR}$ (80 MHz, CDCl_3): δ 0.75 (t, $J = 7.5$ Hz, 3H); 1.00 (d, $J = 7.5$ Hz, 3H); 1.25-1.75 (m, 2H); 1.80 (dd, $J_1 = 7.5$ Hz, $J_2 = 2.5$ Hz, 3H); 2.60 (sext, $J = 7.25$ Hz, 1H); 6.15 (dq, $J_1 = 16.2$ Hz, $J_2 = 2.5$ Hz, 1H); 6.75 (dq, $J_1 = 16.2$ Hz; $J_2 = 7.5$ Hz, 1H). $^{13}\text{C-NMR}$ (20 MHz, CDCl_3): δ 11.3; 15.8; 17.8; 26.0; 45.0; 130.4; 141.7; 203.2.

Acknowledgments

The authors are grateful to FAPESP for financial support.

References

1. Jauch, J.; Schmalzing, D.; Schurig, V.; Emberger, R.; Hopp, R.; Kopsel, M.; Silberzahan, W.; Werkhoff, P. *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1022.
2. Burdock, G.A.; Wagner, B.M.; Smith, R.L.; Munro, I.C.; Newberne, P.M. In *Food Technology* 1990, 78.
3. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647.
4. Seebach, D.; Ehrig, V.; Teschner, M. *Justus Liebigs Ann. Chem.* **1976**, 1357.
5. Shono, T.; Ishifune, M.; Kishimura, S. *Chem. Lett.* **1990**, 449-452.

FAPESP helped in meeting the publication costs of this article