Asian Journal of Chemistry; Vol. 26, No. 13 (2014), 3958-3962

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16089

Synthesis of Novel Fragrant Molecules 6-Methoxy-2,6-dimethyl Heptanol Derivatives

XIAODAN GUO, QUAN LI, ZHIJIAN WANG and WEIMIN JIA*

School of Perfume and Aroma Technology, Shanghai Institute of Technology, Shanghai, P.R. China

*Corresponding author: Fax: +86 21 34020519; E-mail: jiawm1964@163.com; 15618492372@163.com

Received: 23 July 2013; *Accepted*: 4 September 2013; *Published online*: 23 June 2014; AJC-15382

Methoxy elgenol as an important class of monomeric spices, has rich and pleasing aroma of sandalwood and flowers. We have synthesized a series of derivatives of methoxy elgenol, which have the similar structure of $(CH_3)_2COCH_3(CH_2)_3CHCH_3CHROH$, expecting sandalwood odor molecules. Actually, the novel compounds possess a wide odor range, different from methoxy elgenol, from typically melon odorants to derivatives with floral, marine, fruity, faint scent or even metallic aroma. This work describes the methoxylation of methyl heptenone and Darzens condensation to form 6-methoxy-2,6-dimethyl-heptanol (**4**), which is an important starting material for synthesizing the derivatives of 6-methoxy-2,6-dimethyl-heptanol (**5**), namely 8-methoxy-4,8-dimethylnoman-3-ol (**5a**), 9-methoxy-5,9-dimethyldecan-4-ol (**5b**), 8-methoxy-2,4,8-dimethyl-decan-3-ol (**5c**), 10-methoxy-6,10-dimethylundecan-5-ol (**5d**), 9-meth-oxy-2,5,9-trimethyldecan-4-ol (**5e**), 10-methoxy-2,6,10-trimethylundecan-5-ol (**5f**), 1-cyclopentyl-6-methoxy-2,6-dimethyl-heptan-1-ol (**5g**), 2-methoxy-2,6-dimethyltridecan-7-ol (**5h**), 1-cyclohexyl-6-methoxy-2,6-dimethylheptan-1-ol (**5i**), 9-methoxy-5,9-dimethyldec-1-en-4-ol (**5j**), pleasant smell emanating from 10-methoxy-2,6,10-trimethylundecan-5-ol (**5f**) with elegant melon and delicatesea breeze, 2-methoxy-2,6-dimethyltridecan-7-ol (**5h**) with faint scent, fruity and oce-an-like taste and 9-methoxy-5,9-dimethyldec-1-en-4-ol (**5j**) with melon and elegant floral.

Keywords: 6-Methoxy-2,6-dimethyl-heptanol derivatives, Novel compounds, Fragrance, Synthesis.

INTRODUCTION

Discovering interesting new fragance ingredients in each family of odorants and being highly innovative in an extremely competitive environment is a real challenge for small companies today[1]. Synthetic organic chemistry has provided perfumers with novel ingredients that are cheaper and more stable than many natural materials over the years[2].

Due to the current scarcity of natural sandalwood resources, the development of synthetic sandalwood spices are increasingly active. Molecular modeling studies were performed to develop a theoretical model of sandalwood odor compounds in order to explain the ol-factory recognition as well as to predict, if a new compound might possess sandalwood scent[3]. With the help of such comparisons a model for sandalwood fragrance molecules was developed[4]. 7-Methoxy-3,7-dimethyloctan-2-ol (methoxy elgenol) usually exhibits sandalwood-type and it was also our initial aim when we synthesized the new derivatives.

It is well known that certain prerequisites need to be met to obtain a sandalwood odor[1], such as an optimal distance between a bulky group and the osmophore group, the most polar functional group, which, in most cases, bears an O-atom, which in the sandalwood family most often is a OH function[5,6,7]. Although 6-methoxy-2,6-dimethyl-heptanol derivatives have similar structure with methoxy elgenol, structure-activity relationships of sandalwood odorants do not obtain. On the contrary, this project affords some new molecules, with a wide odor range, from typically melon odorants to derivatives with floral, marine, fruity, faint scent or even metallic aroma.

Typical aroma compounds of melon odorants, 2,6-dimethyl-5-heptenal and its derivative called 6-methoxy-2,6-dimethyl-5-heptenal, have applied to various kinds of daily chemical essence formula[8]. Hence, the new compounds **5** are synthetized from 6-methoxy-2,6-dimethyl-5-heptenal (**4**), obtained by Darzens glycidic ester condensation of 6-methoxy-6-methyl-2-heptanone (**2**), subsequent hydrolysis and decarboxylation is also presented[9]. And the compound **2** is prepared from 6-methylhept-5-en-2-one (**1**) under the catalysis of concentrated sulfuric acid[10].

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer with TMS as an internal. IR spectra were recorded on a Bruker VERTEX 70 spectrometer. Reagents and chemicals were purchased from commercial resource and used without further purification.

Synthesis of 6-methoxy-6-methyl-2-heptanone (2)[11]: In a 2L round-bottom flask fitted with a thermometer and a stirrer is placed 1100 g methanol and 440 g methyl heptenone (**1**). Then 65 g of concentrated sulfuric acid is dropped into the flask over a period of 1 h while stirring at room temperature. The reaction mixture allows to stand at 50 °C for 22 h. When the reaction is over, 70.4 g sodium carbonate is added to neutralize concentrated sulfuric acid. Then methanol is distilled. The contents of the reaction flask are poured into 500 mL of ice water. After stirring for a while, the organic layer is separated in a glass separator and the aqueous portion is extracted with MTBE. The organic extracts are pumped and the residual oil fractionated in a packed column with an efficiency of approximately 25 theoretical plates. The yield is 319.3 g (58 %) of 6-methoxy-6-methyl-2- heptanone (**2**); b.p. 94 °C (14 mm).

Synthesis of sodium methoxide (3): Sodium (90 g) is placed in a 1 L round-bottom flask, and methyl alcohol is added to the flask slowly. While sodium disappears, the temperature is increased to 160 °C and methyl alcohol is removed to get sodium methoxide powder.

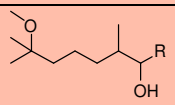
Synthesis of 6-methoxy-2,6-dimethyl-hetanal (4)[12]: Sodium methoxide (15.1g) is added over 2 h to a stirred slurry of 31.6 g of 6-methoxy-6-methyl-2-heptanone (**2**) and 30.6 g ethyl chloroacetate at -10 to -15 °C. The resulting thick slurry is stirred for an additional 2 h at -10 to -15 °C. The solution of 18 g sodium hydroxide in 150 mL methanol is slowly added and the resulting solution is heated at 50 °C for 3 h. Methanol is removed and the reaction mass is then poured into 150 mL water with stirring. The aqueous reaction mass is extracted twice with 100 mL MTBE. The MTBE extracts are discarded and the aqueous layer is acidified (pH 5-6) with concentrated hydrochloric acid (accompanied by evolution of carbondioxide). The aqueous layer is extracted 3 times, each time with 100 mL MTBE. The organic layer are combined and washed with 200 mL of water. The MTBE is removed by distillation at reduced pressure. 0.3 g copper powder is added to the concentrated organic extract[13]. Distillation under vacuum accompanied by release of carbon dioxide affords 6-methoxy-2,6-dimethyl-hetanal (**4**); b.p. 95 °C (18 mm).

6-Methoxy-2,6-dimethyl-heptanol derivatives (5): 6-methoxy-2,6-dimethyl-hetanal, with a faint floral, slightly fruity and citrus characteristic aroma, also, fresh herbs taste and slight melonlike flavor, has been described and used as a fragrance ingredient for a few years. We find that it can be used as a raw material and addition reaction with alkyl magnesium bromide to get alcohols. Astonishingly, the products possessing interesting ol factory properties (Table-1) which can be applied in the perfume industry.

General procedure for the synthesis of 6-methoxy-2,6-dimethyl-heptanol derivatives[14]: Grignard reagents: In a round-bottom flask fitted with a thermometer and a stirrer is placed magnesium, THF and a small amount of bromoalkane and a grain of iodine. The mixture is heated by hair dryer and the reaction is induced quickly. Then, bromoalkane in THF is dropped into the flask. The mixture is kept in an atmosphere of nitrogen for 2 h with stirring at room temperature.

6-Methoxy-2,6-dimethyl-heptanol derivatives[15]: Freshly prepared Grignard reagent (120 % mol) is placed under nitrogen.

TABLE-1
ODOR DESCRIPTIONS OF 6-METHOXY -2,6-DIMETHYL-HEPTANOL DERIVATIVES



Compound	R	Odor description
5a	Ethyl	Rubber odor, slight fruity
5b	*n*-Propyl	Rubber fragrance, ripe melon
5c	*i*-Propyl	Slightly woody (rubber wood), melon
5d	*n*-Butyl	Squashy melon
5e	2-Methyl-propyl	Squashy melon
5f	3-Methyl-butyl	Elegant melon delicate sea breeze, powerful
5g	Cyclopentyl	Metallic aroma, faint scent
5h	*n*-hexyl	Faint scent, fruity, marine, powerful
5i	Cyclohexyl	Faint scent, fruity, marine, melon
5j	Allyl	Melon, elegant floral, powerful

The 6-methoxy-2,6-dimethyl-hetanal in THF are then added dropwise by a syringe at 0 °C. The reaction mixture is allowed to warm to room temperature and tracked by GC. Then, saturated ammonium chloride solution is added to quench the reaction. The organic layer is poured to a distilling flask. Solvent is removed and the target compound is purified by silica gel chromatography. Silica gel is prepared in a column (30 cm length* 3.5 cm i.d.) and conditioned with a mixed solvent (100:10, P/E, v/v). Target compound is collected by elution with a mixed solvent (50:1-100:10, P/E, v/v) and then is concentrated to 20 mL. After vacuum distillation/transfer (HVT), solvent is removed under vacuum. An oil like liquid with an appearance from colourless to yellow was obtained. The reactions are shown in Table-2.

RESULTS AND DISCUSSION

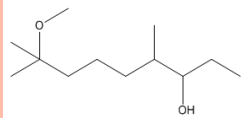
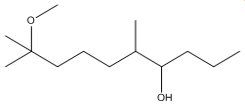
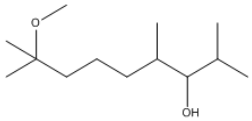
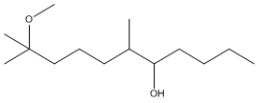
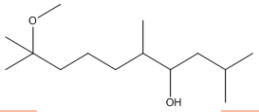
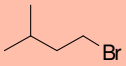
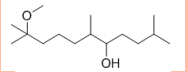
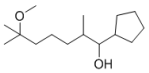
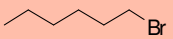
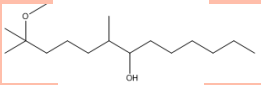
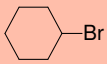
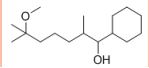
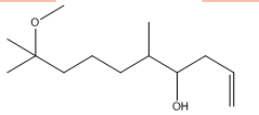
6-Methoxy-2,6-dimethyl-heptanol derivatives [$(CH_3)_2$-$COCH_3(CH_2)_3CHCH_3CHROH$] are novel fragrance compounds, with stable chemical properties, leading us to interesting new insights into the floral, fruity and melon family. Especially, R = allyl, the compound emanates pleasant melon and elegant floral; R = 3-methylbutyl, the compound possesses elegant melon and delicate sea breeze flavor; R = hexyl, the compound possesses faint scent, fruity and oceanlike taste.

Reaction mechanism and effect of reaction conditions: During the course of the methoxylation reaction, which is mediated by concentrated sulfuric acid catalysts, a H-atom and a OCH_3 group are formally added across the C=C bond of an alkene (Fig. 1). Boron trifluoride diethyl etherate and sulfonyl chloride are also employed as catalysts, but the results are not desired. In addition, temperature plays an important role during this reaction, which is related with reaction time and productivity. Table-3 shows the optimum reaction temperature is 50 °C.

TABLE-3
INFLUENCE OF TEMPERATURE ON THE REACTION

Temperature (°C)	Reaction time (h)	GC conversion Rate (%)	GC purity after reaction (%)
40	28	30.75	13.1
50	22	86.3	64.4
60	21	90.2	57.3

TABLE-2
SYNTHESIS, GC CONTENT, PURITIES, REACTION TEMPERATURE OF 6-METHOXY-2,6-DIMETHYL-HAPTANOL DERIVATIVES

Grignard reagent from	Product	[a]GC Content Isomer 1	Isomer 2 (%)	[b]Purity Isomer 1	Isomer 2 (%)	[c]Reaction temperature (°C)
		61.4	6.9	97.3	1.3	4
		78.5	5.6	97	1.3	4
		43.5	21.2	98.2	0.2	4
		81.2	16.2	94.0	3.5	3
		53.2	1.3	95.6	2.0	4
		39.2	14.1	97.6	0.8	6
		37.5	10.6	96.7	1.2	-40
		32.3	12.8	92.1	2.8	0
		20.1	12.0	89.6	8.1	-40
		86.4	7.6	96.5	3.4	10

[a]GC Content is based on the addition reaction of **4** with the correspondent Grignard reagents. [b]Purity is the GC content after purification. [c]Reaction temperature is not optimized

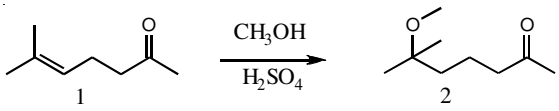


Fig. 1. Synthesis of 6-methoxy-6-methyl-2-heptanone

In the process of synthesis of 6-methoxy-2,6-dimethyl-hetanal **4** (Fig. 2), **2** reacts with ethyl chloroacetate under the catalysis of sodium methoxide **3**, obtaining epoxide carboxylic acid ester, which undergoes saponification, acidification and decarboxylation to afford aldehyde **4**. Wherein, the strongly acidic mixture before decarboxylation will give no product. Therefore, the right amount of sodium hydrogen carbonate is added to neutralize the system to be acidulous. Except for copper powder, we attempt N,N-dimethylaniline to be catalyst of decarboxylation, but with no improvement[16-18].

Present synthesis consisted in preparing the new compounds **5**, which are obtained by reaction of **4** with suitable Grignard reagents (Fig. 3). However, these elegant synthesis are not so easy to perform. As for bromocyclohexane and bromo-cyclopentane[19,20], whose Grignard reagents don't react with 4 in the temperature of 0-10 °C, but undergo coupling

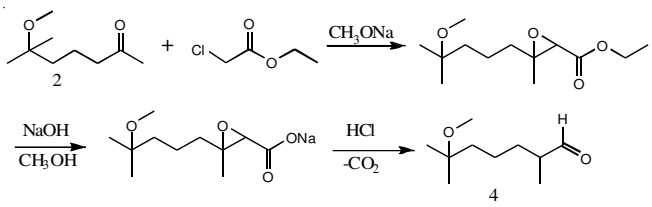


Fig. 2. Synthesis of 6-methoxy-2,6-dimethyl heptanol

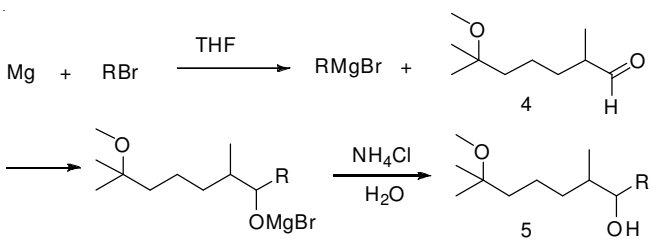


Fig. 3. Synthesis of 6-methoxy-2,6-dimethyl heptanol derivatives

reaction. While the temperature reaches to -40 to -80 °C and the new compounds **5g** and **5i** can be obtained by addition reaction. Allyl bromide is another exception. The results are

differ with the difference of feeding methods[21]. One way, allyl bromide and magnesium react for **3** in the THF to give allyl magnesium bromide, then the mixture are cooled to -10-0 °C and the compound **4** in THF are dropped over 2 h. We find that products are complex and the raw material is remaining. Allyl bromide is so active to generate allylmagnesium in the mixed solvent, which process coupling reaction easily, resulting in low yield. Another way, 20 % of allyl bromide in THF is added into the Grignard reagent just initiated to get a handful of allylmagnesium, then mixture of the remaining allyl bromide and the compound **4** in the THF are dropped into the Grignard reagent under the temperature of 10-20 °C over 2 h. Keeping a little allylmagnesium in the reaction system not only ensure the process of addition reaction, but also decreases the probability of side reaction of coupling, obtaining higher yield of the new compound **5j**.

8-Methoxy-4,8-dimethylnoman-3-ol (5a): Purity (97.3 %) was checked by GC-FID. IR: 735w, 889w, 1082s, 1242s, 1383s, 1467s, 2904w, 2969s, 3668s. ^{1}H NMR ($CDCl_3$): 0.86 (2d, J = 6.5,11.5, 3H); 0.93 (t, J = 6.5, 3H); 1.12 (s, 6H); 1.15-1.20 (m, 9H); 1.76 (s, 1H); 3.15 (s, 3H); 3.25-3.5 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 76.49; 74.60; 48.99; 40.13; 37.79/38.51; 33.90/32.37; 27.24/26.28; 24.95; 24.95; 21.59/21.46; 13.41/15.38; 10.64/10.32.

9-Methoxy-5,9-dimethyldecan-4-ol (5b): Purity (97 %) was checked by GC-FID. IR: 888w, 1064s, 1230s, 1404s, 2895w, 2973s, 3675s. ^{1}H NMR ($CDCl_3$): 0.87-0.9 (2d, J = 7, 12.5, 3H); 0.94 (t, J = 7, 3H); 1.14 (s, 6H); 1.2-1.60 (m, 12H); 3.18 (s,3H); 3.40-3.55 (m,1H). ^{13}C NMR ($CDCl_3$): major isomers: 74.49/75.69; 74.59; 49.03; 40.17; 38.21/38.86; 36.70/35.68; 33.86/32.40; 24.97; 24.97; 21.63/21.51; 19.42/19.23; 14.11/15.31; 13.57.

8-Methoxy-2,4-dimethyldecan-3-ol (5c): Purity (98.2 %) was checked by GC-FID. IR: 879w, 1064s, 1239s, 1375s, 1463s, 2925w, 2973s, 3666s. ^{1}H NMR ($CDCl_3$): 0.75-1.0 (m, 10H); 1.12 (s, 6H); 1.15-1.85 (m, 9H); 3.00-3.10 (m, 1H); 3.15 (s,3 H). ^{13}C NMR ($CDCl_3$): major isomers: 79.99/81.03; 74.57; 48.99; 40.15; 35.00/35.83; 34.73/31.69; 30.93/30.93; 24.93; 24.90; 21.43/21.30; 19.39/20.00; 18.56; 12.96/16.35.

10-methoxy-6,10-dimethylundecan-5-ol (5d): Purity (94.0 %) was checked by GC-FID. IR: 645w, 723w, 869w, 1054s, 1230s, 1385s, 1463s, 2896w, 2984s, 3676s. ^{1}H NMR ($CDCl_3$): 0.82-0.89 (d, J = 7, 3H); 0.89-0.94 (t, J = 7, 3H); 1.15 (s, 6H); 1.18-1.73 (m, 15H); 3.15 (s, 3H); 3.35-3.55 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 75.03/75.94; 74.59; 49.01; 40.15; 38.20/38.83; 34.18/33.15; 33.88/32.39; 28.47/28.28; 24.93; 24.93; 22.76; 21.62/21.50; 14.02/15.32; 13.54.

9-Methoxy-2,5,9-trimethyldecan-4-ol(5e): Purity (95.6 %) was checked by GC-FID. IR: 635w, 733w, 889w, 1074s, 1240s, 1405s, 1463s, 2896w, 2974s, 3675s. ^{1}H NMR ($CDCl_3$): 0.85-0.97 (m, 9H); 1.15 (s, 6H); 1.23-1.85 (m, 12H); 3.15 (s, 3H); 3.45-3.65 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 74.60/73.68; 72.90; 48.99; 43.66/42.49; 40.14/; 38.64/39.92; 33.80/32.44; 24.93/24.96; 24.93/24.90; 24.80/24.69; 23.60/23.88; 21.98/21.69; 21.61/21.52; 13.62/15.17.

10-Methoxy-2,6,10-trimethylundecan-5-ol(5f): Purity (97.6 %) was checked by GC-FID. IR: 869w, 1064s, 1240s, 1404s, 2896w, 2984s, 3686s. ^{1}H NMR ($CDCl_3$): 0.84-0.92 (m, 9H); 1.13 (s, 6H); 1.15-1.58 (m, 13H); 1.65 (s, 1H); 3.18 (s, 3H); 3.42-3.55 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 75.31/76.24; 74.60; 49.02; 40.14; 38.14/38.79; 35.46/35.26; 33.92; 32.28/32.42; 28.12/31.16; 24.94/24.97; 24.94/24.97; 22.65/22.76; 22.52/22.43; 21.6/21.50; 13.50/15.37.

1-Cyclopentyl-6-methoxy-2,6-dimethylheptan-1-ol (5g): Purity (96.7 %) was checked by GC-FID. IR: 626w, 743w, 879w, 1074s, 1230s, 1395s, 1453s, 2876w, 2964s, 3471w, 3666s. ^{1}H NMR ($CDCl_3$): 0.84-0.98 (2d, J = 7, 3H); 1.15 (s, 6H); 1.19-2.10 (m, 17H); 3.17 (s, 3H); 3.22-3.31 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 79.18/80.33;74.60; 49.03; 43.93/43.24; 40.14/40.29; 36.40/37.10; 34.94; 29.93/30.85; 29.17/29.36; 25.52/25.61; 25.43;24.96; 24.94; 21.62/21.58;12.70/16.86.

2-Methoxy-2,6-dimethyl tridecan-7-ol (5h): Purity (92.1 %) was checked by GC-FID. IR: 735w, 889w, 1062s, 1242s, 1383s, 1467s, 2898w, 2974s, 3667s. ^{1}H NMR ($CDCl_3$): 0.89-0.95 (m, 6H); 1.15 (s, 6H); 1.20-1.72 (m, 18H); 3.18 (s, 3H); 3.40-3.60 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 75.03/76.00; 74.60/74.48; 49.05; 40.15/40.00; 38.21/38.83; 34.52; 33.89/33.49; 31.84/32.39; 29.39/29.67; 26.24/26.05; 24.95/24.87; 24.95/24.84; 22.61; 21.63/21.52; 14.04; 13.56. minor isomer: 40.48; 39.38; 36.73; 36.64; 19.48; 18.47; 15.34.

1-Cyclohexyl-6-methoxy-2,6-dimethylheptan-1-ol (5i): purity (89.6 %) was checked by GC-FID. IR: 723w, 889w, 1064s, 1240s, 1414s, 2896w, 2974s, 3676s. ^{1}H NMR ($CDCl_3$): 0.80-0.93 (2d, J = 6.5, 3H); 0.9-1.15 (m, 2H); 1.13 (s, 6H); 1.19-2.10 (m, 17H); 3.17 (s, 3H); 3.05-3.16 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 78.94/80.62; 74.62; 49.04; 40.74/40.27; 40.14/40.21; 34.75/35.02; 34.72/31.33; 29.43/30.15; 29.14/27.24; 26.48/26.54; 26.24/26.19; 26.04; 24.96; 24.92; 21.51/21.36; 12.84/16.51.

9-Methoxy-5,9-dimethyl dec-1-en-4-ol (5j): Purity (96.5 %) was checked by GC-FID. IR: 635w, 743w, 889w, 918s, 1094s, 1250s, 1395s, 1454s, 1649s, 2906w, 2993s, 3461s, 3676s. ^{1}H NMR ($CDCl_3$): 0.85-0.95 (m, 3H); 1.14 (s, 6H); 1.21-2.39 (m, 10H); 3.15 (s, 3H); 3.40-3.60 (m, 1H); 5.10 (m, 2H); 5.85 (m, 1H). ^{13}C NMR ($CDCl_3$): major isomers: 135.59; 117.58; 74.57/74.49; 73.04; 49.01; 40.14/39.12; 38.29/37.85; 33.70/32.64; 24.95/24.97; 24.91; 24.91;21.55/21.39; 13.83/15.22.

Conclusion

We have synthesized novel fragrant molecules 6-methoxy-2,6-dimethylheptanol derivatives. These compounds are first synthesized, possessing a wide odor range, from typically melon odorants to derivatives with floral, marine, fruity, faint scent or even metallic aroma. It provides a series of new flavors for spices industry and have the potential to be applied to the Daily Chemical Essence Industry.

ACKNOWLEDGEMENTS

The authors thank Qingsheng Guo for the ^{1}H NMR and C NMR structure. Thanks are also due to Suning Zhang for IR interpretation.

REFERENCES

1. P. Kraft, J.A. Bajgrowicz, C. Denis and G. Fráter, *Angew. Chem. Int. Ed.*, **39**, 2980 (2000).
2. A.-D. Fortineau, *J. Chem. Educ.*, **81**, 45 (2004).
3. G. Buchbauer, F. Zcchmeister-Machhart, P. Weiß-Greilar and P. Wolschann, *Arch. Pharm. Pharm. Med. Chem.*, **330**, 112 (1997).

4. G. Buchbauer, A. Hillisch, K. Mraz and P. Wolschann, *Helv. Chim. Acta*, **77**, 2286 (1994).
5. D.I. Hadaruga, N.G. Hadaruga and S. Muresan, *Chem. Bull. Politehnica Univ*., **52**, 1 (2007).
6. T. Hasegawa, H. Izumi, Y. Tajima and H. Yamada, *Molecules*, **17**, 11292 (2012).
7. C. Plessis, *Biodiversity*, **5**, 1083 (2008).
8. H. Mao, *Domestic-Overseas Flavor Fragrance Cosmetic Inform.*, **2**, 16 (2003).
9. J. P. Munch, *Acta Chem. Scand*., **7**, 1041 (1953).
10. J.D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).
11. J.D. Surmatis and C. West, US Patent 3156714 (1964).
12. M.A. Sprecker, R.W. Trenkle, B.D. Mookherjee, M.H. Vock, J.F. Vinals, J. Kiwala and F.L. Schmitt, US Patent 4,281,177 (1981).
13. S.J. William, J.S. Belew, L.J. Chinn and R.H. Hunt, *J. Am. Chem. Soc*., **75**, 4995 (1953).
14. S. Tartaglia, F. Pace, P. Scafato and C. Rosini, *Org. Lett*., **10**, 3421 (2008).
15. P. Anbarasan, Ph.D. Thesis, Enantioselective Synthesis of Bio-Active Bicyclic Acetals, Cyclic Ethers and Lactones, Indian Institute of Science, Bangalore, India (2007).
16. J.A. Waters and B. Witkop, *J. Org. Chem*., **36**, 3232 (1971).
17. S.P. Singh and J. Kagan, *J. Org. Chem*., **35**, 2203 (1970).
18. N.K. Nelson and H.H. Morris, *J. Am. Chem. Soc*., **75**, 3337 (1953).
19. J. Clayden, M. Pickworth and L.H. Jones, *Chem. Commun*., **5**, 547 (2009).
20. A.R. Hudson, S.L. Roach, R.I. Higuchi, D.P. Phillips, R.P. Bissonnette, W.W. Lamph, J. Yen, Y. Li, M.E. Adams, L.J. Valdez, A. Vassar, C. Cuervo, E.A. Kallel, C.J. Gharbaoui, D.E. Mais, J.N. Miner, K.B. Marschke, D. Rungta, A. Negro-Vilar and L. Zhi, *J. Med. Chem*., **50**, 4699 (2007).
21. M. Chen, C. Xu and X. Zhu, *J. Jiangsu Polytech. Univ*., **21**, 8 (2009).