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A convenient preparation of 3-isopropyl-1-methylcyclopentylmethanol and 1-isopropyl-3-methylcyclopentylmethanol via Favorskii rearrangement

Martino Ambrosini [a], Nikla Baricordi [a], Simonetta Benetti [a,*], Carmela De Risi [b], Gian P. Pollini [b], Vinicio Zanirato [b]

[a] *Dipartimento di Chimica, via L. Borsari 46, 44100 Ferrara, Italy*
[b] *Dipartimento di Scienze Farmaceutiche, via Fossato di Mortara 19, 44100 Ferrara, Italy*

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ABSTRACT

The Favorskii rearrangement of suitable α-chloro derivatives of commercially available (+)- and (−)-carvone, and (−)-menthone served efficiently to prepare the title compounds featuring delicious fruity, floral olfactory notes.

1. Introduction

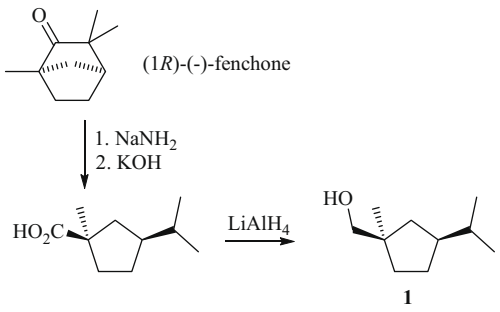
Compounds with particular fruit or flower fragrances characterize a large number of chemical compounds and are widely used in the food, perfume, cosmetic, detergent and other industries. Fruity odours are quite popular in perfumery, almost all feminine perfumes and more and more masculine ones possess fruity notes. Moreover, in the fragrance industry there is a constant demand for new compounds which could enhance or improve odour notes, or impart new odour notes.

Accordingly, perfumers and flavourists are continually looking for new compounds having floral and/or fruit-like qualities which may find use in practically all fields of flavour and fragrance applications.

In the patent literature, it has been recently reported that certain 3-isopropyl-1-methylcyclopentyl derivatives are relevant as fragrance and flavour compounds, having floral, fruity and woody odour notes.[1,2]

Cyclopentyl alcohol derivatives have for a long time been of particular interest as perfumery and aromatic chemicals,[3] as they are relatively simple and easy to prepare starting from readily available, inexpensive and naturally occurring starting materials.[4] Most of the new compounds present interesting olfactory properties, mainly fruity character, associated in several cases with floral and green notes. Particular attention has been devoted to [(*1R*,*3S*)-3-isopropyl-1-methylcyclopentyl]methanol **1** and its enantiomer *ent*-**1**, which could be prepared through elaboration of enantiomerically pure fenchone.[1,2]

Sodium amide-induced C_1–C_2 bond cleavage of the bicyclo[2.2.1]heptan-2-one nucleus of (1*R*)-(−)-fenchone produces a substituted cyclopentanecarboxylic acid amide which can easily be transformed into the corresponding acid through basic hydrolysis.[5] The reduction of the carboxylic functional group gives the odorous compound **1** (Scheme 1). Similarly, the preparation of *ent*-**1** has been accomplished starting from (1*S*)-(+)-fenchone.



Scheme 1.

The cleavage of ketones by sodium amide is usually referred to as the Haller–Bauer reaction,[6,7] a transformation originally reported by Semmler[8] in connection with his investigations on the structure of fenchone.

Although the cleavage reactions of non-enolisable ketones have previously been observed under a variety of conditions, the only thoroughly investigated general method for ketone cleavage is the classical Haller–Bauer reaction. Gassman et al.[9] systematically investigated the C–C bond cleavage reaction in several norbornanone derivatives and also explored various reaction media to impart preparative efficiency to this reaction. Thus, ring cleavage of 2-norbornanone derivatives offers a good methodology to obtain *cis*-1,3-disubstituted cyclopentanes.[10]

* Corresponding author. Tel.: +39 0532455174; fax: +39 053240709.
E-mail address: bns@unife.it (S. Benetti).

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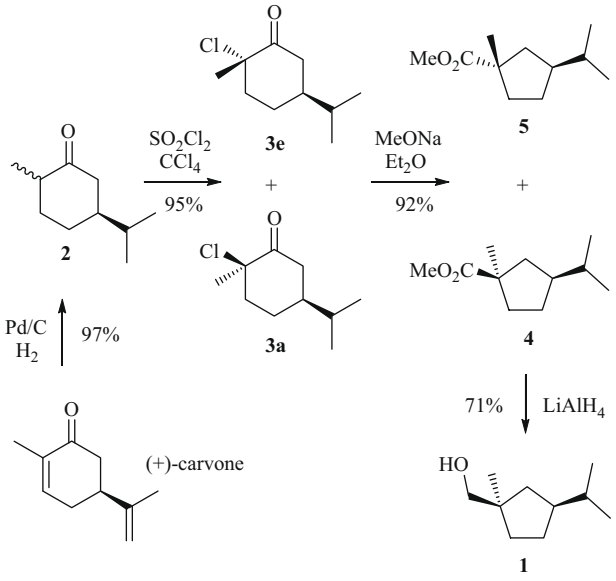
It has also been well established that functionalized cyclopentanecarboxylates can be obtained from the Favorskii rearrangement of α-halocyclohexanone derivatives. This reaction has been subjected to extensive mechanistic studies in order to clarify the stereochemical outcome.[11,12]

Herein, we report a simple, convenient procedure for the stereoselective synthesis of 1-isopropyl-3-methylcyclopentylmethanol and 3-isopropyl-1-methylcyclopentylmethanol through Favorskii rearrangement of suitable α-chlorocyclohexanones, in turn obtained from commercially available starting materials, such as (−)-menthone, and (+)- and (−)-carvone.

2. Results and discussion

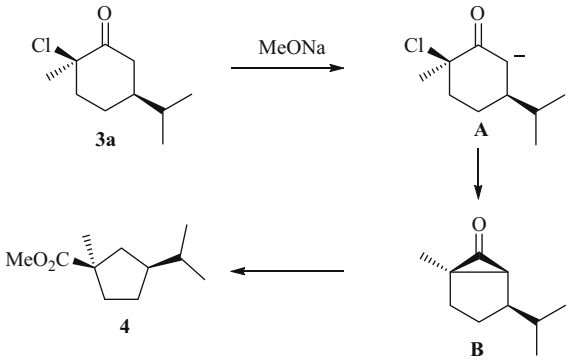
Initially, we wanted a straightforward access to [(1*R*,3*S*)-3-isopropyl-1-methylcyclopentyl]methanol **1** and its enantiomer *ent*-**1** starting from both enantiomerically pure forms of carvone, one of the most common natural monoterpene used as an attractive chiral starting material in the synthesis of natural products.[13,14]

As summarized in Scheme 2, (*S*)-(+)-carvone was hydrogenated to give (5*S*)-carvomenthone **2** as a C-2 epimeric mixture.[15] The subsequent reaction with sulfuryl chloride furnished 2-chloro-2-methyl-(5*S*)-isopropylcyclohexanone **3** as a C-2 epimeric mixture (**3a**/**3e** 4:1 ratio, estimated by ^{1}H NMR), a result matching the already reported chlorination of (5*R*)-carvomenthone which led to *ent*-**3a** (halogen *axial* 77%) and *ent*-**3e** (halogen *equatorial* 23%).[16] A clean Favorskii rearrangement took place easily by treatment of the **3a**/**3e** mixture with sodium methoxide in ether furnishing a 4:1 mixture of C-2 epimeric cyclopentanecarboxylic acid methyl esters **4** and **5** (^{1}H NMR). The major diastereomer **4** could be obtained in a pure state by careful column chromatography and its structure has been confirmed by conversion to the known cyclopentyl alcohol **1**, featuring the fresh clean floral tonality described in the patent literature,[1,2] by reduction with $LiAlH_4$. The same procedure was used to obtain [(1*S*,3*R*)-3-isopropyl-1-methylcyclopentyl]methanol *ent*-**1**, starting from (*R*)-(−)-carvone.



Scheme 2.

The stereospecific course of the Favorskii rearrangement of **3** (*a*/*e* 4:1) leading to the formation of a mixture of **4** and **5** in a 4:1 ratio should be noted. Interestingly, the use of aprotic solvents as well as of heterogeneous reaction media has been claimed[17] to favour a 'Loftfield-type' mechanism (Scheme 3). Thus, the initially formed

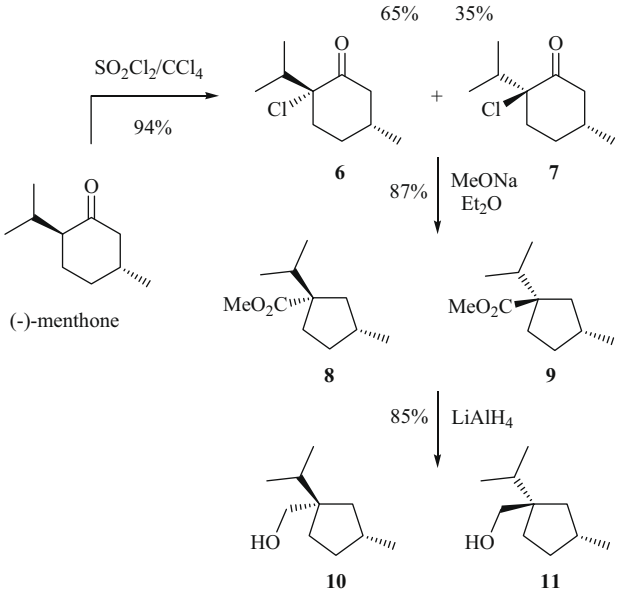


Scheme 3.

enolate **A** promoted an intramolecular displacement of the halogen atom leading to cyclopropanone **B**, which underwent a regioselective ring opening to give **4**.[18]

Accordingly, we extended this protocol to the known[16] α-chlorocyclohexanones **6** and **7**, in turn prepared from (2*S*,5*R*)-(−)-menthone, allowing us to obtain the structurally related cyclopentylmethanols **10** and **11**, both possessing a pleasant floral odour with fresh and clean notes.

In order to validate the stereospecific outcome of the Favorskii reaction, we separated **6** and **7** subjecting them to the ring contraction/reduction sequence (Scheme 4). We found that sodium methoxide-promoted Favorskii rearrangement of the two haloketones epimeric at the halogen-bearing carbon gave rise to the formation of different cyclopentanecarboxylic acid methyl esters. The structures of the corresponding cyclopentylmethanols obtained by reduction with $LiAlH_4$ were inferred on the basis of NOE-difference experiments. In detail, a positive NOE effect observed or the lacking of this effect between H-3 and hydroxymethyl group allowed to assign the (1*R*,3*R*) absolute configuration to **11** and the (1*S*,3*R*) configuration for the diastereomer **10**, respectively. In this way the stereochemistry of the parent cyclopentanecarboxylic acid methyl esters **8** and **9** could also be set.



Scheme 4.

These findings strongly suggest a Favorskii rearrangement occurring through a mechanism entailing on the formation of an intermediate cyclopropanone via an S_N2-like reaction, rather than

the alternative mechanism via a zwitterionic intermediate,[19] the latter requiring that both haloketones **6** and **7** produce the same mixture of esters **8** and **9**.

3. Conclusion

In conclusion, we have described an efficient and convenient preparation of substituted cyclopentyl alcohol derivatives through Favorskii ring contraction of the α-chloroketones in turn prepared from commercially available, optically active (+) and (−)-carvone, and (−)-menthone.

The preparation of (1*R*,3*S*)- and (1*S*,3*R*)-3-isopropyl-1-methylcyclopentylmethanol allowed for comparison of the present methodology with that described in the patent literature in terms of the starting material (carvone vs fenchone), milder reaction conditions (sodium methoxide in diethyl ether vs sodium amide in toluene) and easier reduction of the intermediate (ester vs carboxylic acid) which requires less reducing agent.

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer with $CDCl_3$ as a solvent. Chemical shifts (δ) are given in parts per million (ppm) downfield from TMS as an internal standard. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sp = septuplet, and m = multiplet. Optical rotations were carried out with a Perkin–Elmer 241 MC polarimeter. Silica gel for column chromatography (Merck, 230–400 mesh) was used for chromatographic purifications. (2*S*,5*R*)-(−)-Menthone, purchased from Fluka, was claimed to be >98% ee by GC. (*S*)-(+)-Carvone and (*R*)-(−)-carvone were purchased from Aldrich and reduced to the corresponding tetrahydro derivatives following literature directions.[15] (1*RS*,5*S*)-2-Chloro-2-methyl-5-isopropylcyclohexanones **3**, (2*R*,5*R*)-(+)-2-chloro-2-isopropyl-5-methylcyclohexanone **6** and (2*S*,5*R*)-(+)-2-chloro-2-isopropyl-5-methylcyclohexanone **7** were prepared as described in the literature.[16]

4.2. Preparation procedures

4.2.1. Methyl (1*R*,3*S*)-3-isopropyl-1-methyl-cyclopentane-carboxylate 4

A solution of the mixture of **3a** and **3e** (4.2 g, 22.34 mmol) in dry ether (10 mL) was added dropwise over a period of 10 min to an ice-cooled and stirred slurry of NaOMe (prepared from 0.6 g of Na). During the addition, a precipitate was formed and the temperature of the reaction was maintained below 15 °C. The reaction mixture was stirred for a further 15 min, then water (30 mL) was added and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure, to yield the crude mixture of **4** and **5** (3.8 g, 92%) which was purified by silica gel chromatography (EtOAc/cyclohexane, 1:9) to give pure **4**. $[\alpha]_D^{25} = -7.8$ (*c* 1, $CHCl_3$); IR ν_{max} 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.80–0.90 (m, 6H), 1.20 (s, 3H), 1.20–1.95 (m, 5H), 2.00–2.50 (m, 3H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3 ($2CH_3$), 22.8 (CH_3), 30.2 (CH_2), 30.5 (CH_2), 31.8 (CH), 42.7 (CH), 46.6 (CH_2), 51.6 (C), 52.3 ($COOCH_3$), 178.7 ($COOCH_3$). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.65; H, 11.00.

4.2.2. [(1*R*,3*S*)-3-Isopropyl-1-methylcyclopentyl]-methanol 1

A solution of **4** (2 g, 10.87 mmol) in dry THF (10 mL) was added dropwise to an ice-cooled mixture of $LiAlH_4$ (0.45 g, 11.96 mmol) in dry THF (20 mL) over a period of 10 min. After the reaction mixture was stirred for 2 h at room temperature, water (1 mL) was carefully added under ice-cooling, followed by 4 M NaOH solution (1 mL) and water (4 mL). After being stirred for 30 min the reaction mixture was filtered to remove the inorganic salts, which were carefully washed with dichloromethane (20 mL). The filtrate was dried with Na_2SO_4, filtered and evaporated under reduced pressure. Distillation gave pure **1** (1.2 g, 71%), bp 96–98 °C (10 mbar). $[\alpha]_D^{25} = -11.4$ (*c* 1, $CHCl_3$) {Lit.[1]: $[\alpha]_D^{22} = -12.0$ (*c* 1, EtOH)}; IR ν_{max} 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz), 0.98 (s, 3H), 1.30–2.10 (m, 8H), 3.30–3.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 ($2CH_3$), 20.3 (CH_3), 31.8 (CH_2), 32.1 (CH), 35.1 (CH_2), 35.5 (CH), 41.0 (CH_2), 50.0 (C), 70.0 (CH_2OH). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.80; H, 13.00.

4.2.3. Methyl (1*S*,3*R*)-1-isopropyl-3-methylcyclopentane-carboxylate 8

A solution of **6** (5.38 g, 28.6 mmol) in dry ether (10 mL) was added dropwise over a period of 10 min to an ice-cooled and stirred suspension of NaOMe (prepared from 0.76 g of Na). After 15 min, the ice-bath was removed and the reaction mixture stirred for 9 h at room temperature. The ether solution was filtered, washed with water (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by flash-chromatography (pentane/CH_2Cl_2, 60:40) and the ester **8** (4.6 g, 87%) was obtained as a light yellow oil. $[\alpha]_D^{25} = -16.3$ (*c* 1, $CHCl_3$); IR ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (d, 3H, *J* = 6.7 Hz), 0.88 (d, 3H, *J* = 6.7 Hz), 1.00 (d, 3H, *J* = 6.4 Hz), 1.01–1.15 (m, 1H), 1.40–1.50 (m, 1H), 1.60–1.70 (m, 1H), 1.70–1.95 (m, 3H), 1.98 (sp, 1H, *J* = 6.7 Hz), 2.02–2.30 (m, 1H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4 (CH_3), 18.8 (CH_3), 20.2 (CH_3), 33.3 (CH_2), 33.7 (CH_2), 33.8 (CH), 35.4 (CH), 41.4 (CH_2), 51.5 ($COOCH_3$), 59.0 (C), 178.1 ($COOCH_3$). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.65; H, 11.00.

4.2.4. Methyl (1*R*,3*R*)-1-isopropyl-3-methyl-cyclopentane-carboxylate 9

Compound **9** was obtained from **7** according to the procedure described for the preparation of **8**. $[\alpha]_D^{25} = +3.8$ (*c* 1, $CHCl_3$); IR ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, 3H, *J* = 6.8 Hz), 0.86 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.4 Hz), 1.04–1.20 (m, 1H), 1.42–1.52 (m, 1H), 1.59–1.66 (m, 1H), 1.70–1.92 (m, 3H), 1.96 (sp, 1H, *J* = 6.8 Hz), 2.19–2.22 (m, 1H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 18.7 (CH_3), 20.1 (CH_3), 32.3 (CH_2), 35.5 (CH), 34.9 (CH_2), 35.0 (CH), 41.8 (CH_2), 51.5 (C), 58.1 (CH_3), 178.6 (CO). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.65; H, 11.00.

4.2.5. [(1*S*,3*R*)-3-Methyl-1-isopropylcyclopentyl]-methanol 10

To an ice-cooled suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in dry ether (20 mL), a solution of **8** (0.97 g, 5.27 mmol) in dry ether (10 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred for 2 h at room temperature, then water (1 mL) was carefully added under ice-cooling, followed by 4 M NaOH solution (4 mL). After stirring for 30 min, the reaction mixture was filtered to remove the inorganic precipitate, which was carefully washed with ether (20 mL). The dried filtrate (Na_2SO_4) was evaporated under reduced pressure and the residual oil purified by flash-chromatography (pentane/CH_2Cl_2, 60:40). Alcohol **10** (0.70 g, 85%) was obtained as a light yellow oil. $[\alpha]_D^{25} = +15.6$ (*c* 1, $CHCl_3$); IR ν_{max} 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (d, 3H, *J* = 6.7 Hz), 0.89 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.00–

1.10 (m, 1H), 1.22–1.38 (m, 1H), 1.40–1.50 (m, 1H), 1.50–1.60 (m, 2H), 1.62–1.80 (m, 2H), 1.80–1.97 (m, 1H), 3.42 (d, 1H, J = 10.7 Hz), 3.47 (d, 1H, J = 10.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0 ($2CH_3$), 20.2 (CH_3), 31.7 (CH_2), 32.0 (CH), 35.1 (CH_2), 35.5 (CH), 40.9 (CH_2), 50.0 (C), 69.0 (CH_2). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.80; H, 13.00.

4.2.6. [(1*R*,3*R*)-3-Methyl-1-isopropylcyclopentyl]-methanol 11

Compound **11** was obtained from **9** according to the procedure described for the preparation of **10**. $[\alpha]_D^{25} = +10.9$ (c 1, $CHCl_3$); IR ν_{max} 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.00–1.20 (m, 2H), 1.40–1.50 (m, 3H), 1.70–1.90 (m, 3H), 3.41 (d, 1H, J = 10.7 Hz), 3.47 (d, 1H, J = 10.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0 ($2CH_3$), 20.2 (CH_3), 31.7 (CH_2), 32.0 (CH), 35.1 (CH_2), 35.5 (CH), 40.9 (CH_2), 50.0 (C), 69.0 (CH_2). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.80; H, 13.00.

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