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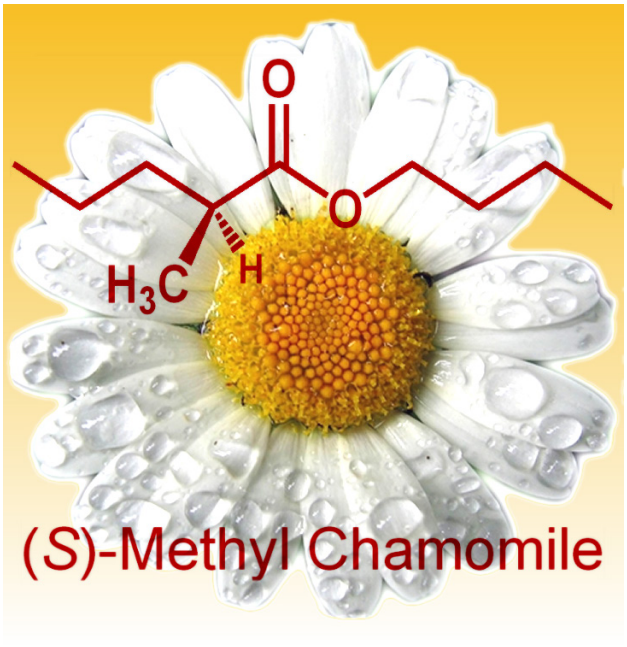

A new challenge: chiral switch to enantiomerically enriched fragrances

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Synthesis of the Chiral Fragrance Methyl Chamomile by Asymmetric Hydrogenation

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Abstract: An alternative synthesis of enantiomerically enriched 2-methylpentanoic butyl ester (Methyl Chamomile) is proposed. The process entails three different steps: the key one is the asymmetric hydrogenation of 2-methylenpentanoic acid catalysed by a Ru(II) complex and a chiral diphosphine.

Keywords: Fragrance synthesis, Palladium catalyst, Carbonylation, Ruthenium, Atropisomeric diphosphine, Asymmetric hydrogenation.

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1. Introduction

Nowadays perfumers can choose among over 3000 fragrances to create a new scent [1]. Nevertheless, this number is in practice reduced by many factors such as price, availability, and safety of the ingredients used. In fact, the problem of safety, in terms of health protection, has become of the utmost importance. A very well-known example is Lilial® (Fig. 1), a fragrance commonly used in a wide number of formulations owing to its pleasant olfactive notes reminiscent of muguet.

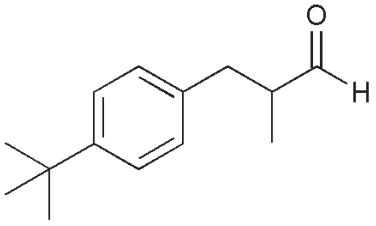
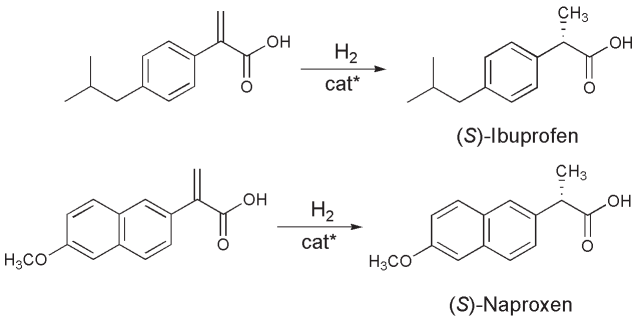


Figure 1. Molecular structure of Lilial®.

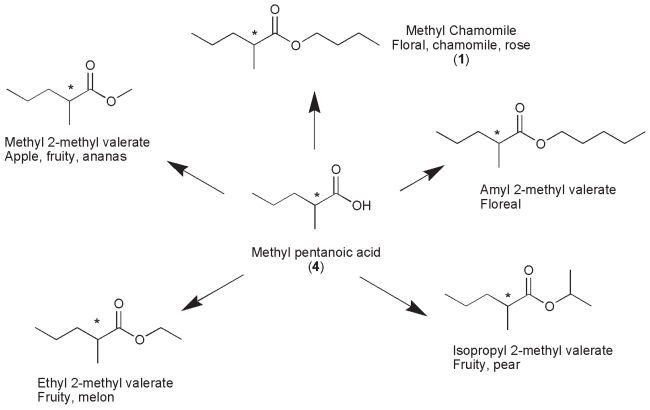
It was already known back in 1983 from tests carried out by the US Environmental Protection Agency (EPA) that this ingredient was responsible for allergic contact dermatitis [2]. Further studies have shown that Lilial® is potentially cytotoxic causing breast cancer [3]; nevertheless, at present, Lilial® is still commercialized although its use is subject to restrictions [4]. According to a study from Global Industry Analysts, the world fragrance and perfume industry is expected to exceed 36 billion of US dollars in 2017, therefore, it will be of crucial importance to reduce the amount of odorants released in the environment. One possibility is the exclusive manufacture and use of the most olfactory active stereoisomer of a perfumery chiral raw material, which would lead to lower consumption and dispersion of these compounds in the environment. It is in fact well-known that the two enantiomers of an odorant may be different in smell, persistence, intensity, etc. [5].

Metal catalyzed asymmetric hydrogenation of prochiral unsaturated substrates is one of the most efficient methodologies in asymmetric catalysis for the synthesis of fragrances [6] and important biologically active compounds [7]. Chiral iridium-, ruthenium-, and rhodium-based catalysts have been employed as precursors in asymmetric hydrogenation of unsaturated prochiral substrates such as alkenes, ketones, imines, etc. [7]. In this connection is worth to note that there are relatively few examples of catalytic asymmetric hydrogenation of α-substituted acrylic acids aimed to the synthesis of biologically active molecules. Two pertinent examples are the syntheses of (*S*)-2-(4-(2-methylpropyl)phenyl)propanoic acid (Ibuprofen®) [8] and (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (Naproxen®) [9] (Scheme 1).



Scheme 1. Asymmetric hydrogenations to Ibuprofen® and Naproxen®.

Our research group has long been interested in the application of homogeneous asymmetric catalysis [10] to the synthesis of enantiomerically enriched fragrances such as Rosaphen, Silvial, etc. [11]. In the present work we wish to report a new synthetic approach to enantiomerically enriched 2-methylpentanoic acid (**4**). We estimate this molecule of particular interest since it can be used as starting product for a quite wide range of esters employed as fragrances (Scheme 2) [10]; among them the most valuable is the butyl ester known as Methyl Chamomile (**1**).

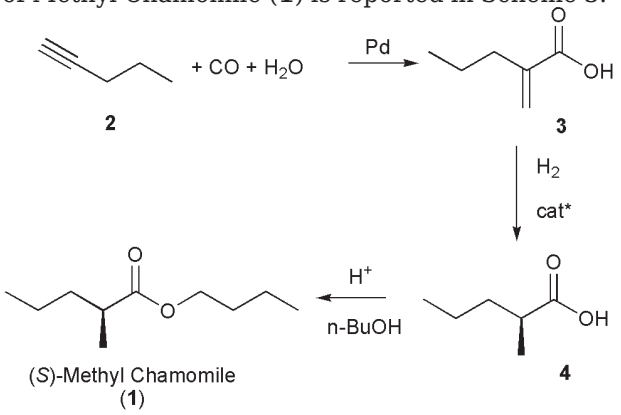


Scheme 2. Synthetic utility of 2-methylpentanoic acid.

Methyl Chamomile, is characterized by an aromatic, fruity, floral odor with the typical herbaceous chamomile flower character. Odorants displaying floral notes (citrus, muguet, chamomile, etc.) are of great interest in perfumery as they are widely appreciated and used [12]. To the best of our knowledge the odor profile of the two enantiomers of Methyl Chamomile has yet to be disclosed and only the racemate is commercialized by TCI Europe, Grau Aromatics, and other companies all over the world.

2. Results and Discussion

The synthetic strategy proposed for the synthesis of Methyl Chamomile (**1**) is reported in Scheme 3.



Scheme 3. Designed synthesis of (*S*)-Methyl Chamomile (**1**).

First, pentyne **2** is converted into the prochiral 2-methylenpentanoic acid (**3**) by means of a palladium catalysed hydroxycarbonylation. Then, **3** is hydrogenated in the presence of a chiral transition metal catalyst to give (*R*)- or (*S*)-2-methylpentanoic acid (**4**), which is eventually reacted with *n*-butanol to give the sougth butyl ester. Accordingly, the key step of the designed synthetic strategy is the asymmetric hydrogenation of the α,β-unsaturated carboxylic acid **3**.

In previous works, we have reported the asymmetric hydrogenation of α,β-unsaturated carboxylic acids employing a catalytic system generated *in situ* from $[RuCl_2(benzene)]_2$ and a chiral bidentate phosphine ligand. In fact, this simply assembled catalytic system is readily tuneable by changing the nature of the ligand. A substrate to ruthenium molar ratio of 100/1 was employed in all the hydrogenation experiments. The results of a first set of experiments obtained using the atropisomeric diphosphine (*R*)-MeO-BIPHEP (see Fig. 2) are reported in Table 1.

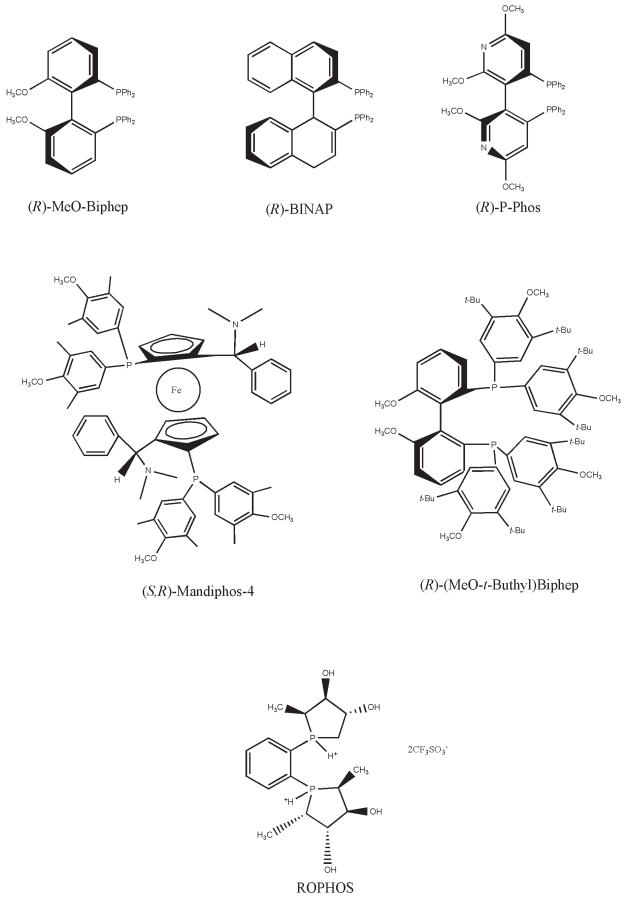


Figure 2. Molecular structure of several commercial diphosphine ligands.

All results reported in Table 1 are the average of two experiments carried out in the same conditions except for runs 1 and 2. In fact, the results of these first two experiments carried out in the same reaction conditions, were highly contradictive giving different conversions and ees.

On the basis of literature data, it is possible to suppose that the contradicting results obtained in runs 1 and 2 may be ascribed to the type of stirring employed during the reaction. In fact Coen et al. report that mass transfer limitations between the liquid and the gas phase may lead to highly pressure dependent reactions, magnetic stirring being inadequate for a correct hydrogen dissolution [13].

It is a common assumption that the dissolution of H_2 in the liquid phase corresponds to the maximum concentration of H_2 at saturation or $[H_2]_{sat}$; however, this assumption holds only when the maximum rate of gas-liquid mass transfer far exceeds the rate of hydrogen consumption by the catalytic reaction. Besides the report of Coen and co-workers, there are in literature several examples dealing with Ru catalysts for which gas transfer interfere with the asymmetric inductions [14].

Table 1. Asymmetric hydrogenation of 2-methylenpentanoic acid (**3**) in the presence of $[RuCl_2(benzene)]_2$ and (*R*)-MeO-BIPHEP[a].

Entry	$P(H_2)$ (atm)	Speed (rpm)	NEt_3/Ru (mol/mol)	Conv. (%)[b]	ee (%) [c,d]
1[e]	10	n.d.	100/1	7	18
2[e]	10	n.d.	100/1	42	35
3	10	700	100/1	56	51
4	10	700	0	6	30
5	10	1500	0	26	40
6	30	700	100/1	100	66
7	30	700	0	15	51
8	30	1500	0	40	57
9	50	700	100/1	100	76
10	50	350	0	76	65
11	50	700	0	82	67
12	50	1500	0	100	70
13	70	700	100/1	100	80
14	70	700	0	100	76
15	70	1500	0	100	75
16[f]	70	700	100/1	100	76
17[g]	70	700	100/1	77	81

[a] Reaction conditions: substrate = 1.17 mmol, substrate/Ru = 100/1 (mol/mol), ligand/Ru = 1/1 (mol/mol), time = 1 h, solvent = CH_3OH (20 mL), naphthalene: 0.5 mmol, T = 0 °C, $p(H_2)$ = 10 atm, mechanical stirring (700 rpm). [b] Determined by GLC with internal standard (naphthalene). [c] Determined on the methyl ester of **4** by chiral GLC (CHIRALDEX G-TA). [d] (*R*)-isomer. The sign-configuration relationship of **4** was determined by polarimetry and compared with literature data [15]. [e] Magnetic stirring. [f] T = 20 °C. [g] T = -10 °C.

Assuming that also for the hydrogenation of **3** magnetic stirring could be inadequate, the reaction was repeated under mechanical stirring (run 3, average of three experiments) giving (*R*)-2-methylpentanoic acid (**4**) in a reproducible manner and with higher conversion and enantiomeric induction compared to magnetic stirring (compare runs 1-3 of Table 1). To further understand the influence of the stirring speed, a set of experiments was carried out at 700 and 1500 rpm (speed limit of the employed mechanical stirrer).The influence of the stirring speed on conversion and asymmetric induction at different $p(H_2)$ is reported in Fig. 3.

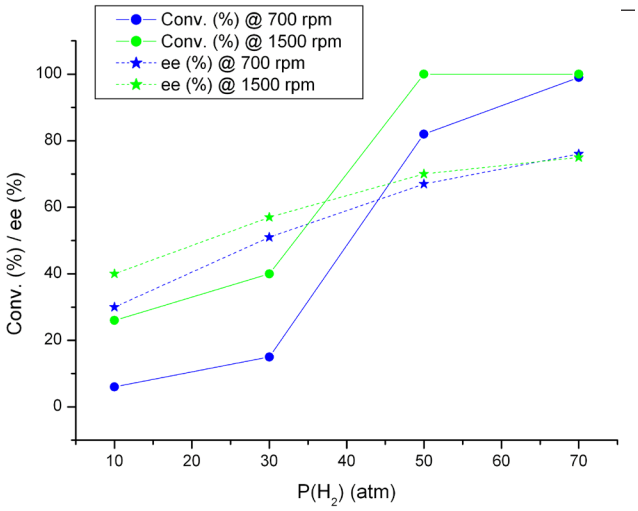


Figure 3. Influence of the stirring speed on conversion and asymmetric induction at different $p(H_2)$.

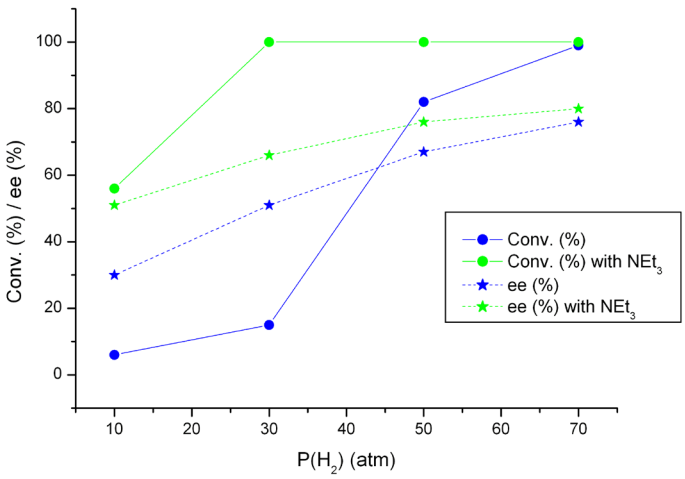


Figure 4. Influence of the amine on conversion and asymmetric induction at different $p(H_2)$.

At low hydrogen pressures (10-30 atm) both conversion and ee are highly influenced by the stirring speed indicating that in these conditions the rate determining step is the mass transfer of hydrogen from the gas to the liquid phase. At 50 atm there is no significant change neither in the conversion nor in enantioselectivity, thus we may assume that at $p(H_2)>50$ atm $[H_2]\approx[H_2]_{sat}$. According to these findings all further experiments were carried out under magnetic stirring at 700 rpm.

According to our previous study on asymmetric hydrogenations in the presence of ruthenium catalysts we investigated the effect of the addition of triethylamine as promoter on the reaction course. In fact, it is well known that on one hand the rate of the hydrogenation with ruthenium catalysts may be improved by the presence of an amine, but on the other hand the influence of the amine on the enantioselectivity is not always positive [11b,16]. In our case, addition of triethylamine leads both to faster hydrogenation rates and higher ees (compare entries 3 and 4). A set of experiments carried out at increasing pressures with and without the NEt_3 show a plateau trend reaching maximum conversion and asymmetric induction at 70 atm (see Fig. 4).

The dependence of the conversion and enantioselectivity on changing the $p(H_2)$ has a similar trend both in the presence and in the absence of the amine, giving at all pressures tested better results when NEt_3 is present. In this connection, it should be noted that the enantioselectivity in the presence of the amine does not depend on the reaction time. In fact, an experiment carried out under the same conditions of entry 9 of Table 1 in 30, 60, 90 min and 18 h gives the same enantioselectivity (76% ee) (data not reported in Table 1).

Although under these conditions, we are able to obtain **4** with ees up to about 80%, this result was not considered completely satisfactory. Therefore, believing that substantial improvements in enantioselectivity could not be achieved by a further fine tuning of the reaction conditions, we decided to test other commercially available phosphine ligands. The results are summarized in Table 2.

Table 2. Asymmetric hydrogenation of 2-methylenpentanoic acid (**3**) in the presence of $[RuCl_2(benzene)]_2$ and a diphosphine ligand[a].

Run	Ligand	Conv. (%)[b]	ee (%)[c, d]
1	(*R*)-(*tert*-Butyl)-MeO-BIPHEP	72	71
2	(*S*,*R*)-Mandiphos-4	100	56
3	(*R*)-BINAP	64	68
4	(*R*)-P-Phos	72	66
5[e]	(*R*)-P-Phos	100	60
6	ROPHOS	10	10

[a] Reaction conditions: substrate = 1.17 mmol, substrate/NEt_3 =

1/1 (mol/mol), substrate/Ru = 100/1 (mol/mol), ligand/Ru = 1/1 (mol/mol), time = 1 h, solvent = CH_3OH (20 mL), naphthalene: 0.5 mmol, T = 0 °C, p(H_2) = 10 atm, mechanical stirring (700 rpm). [(b)] Determined by GLC with internal standard (naphthalene). [(c)] Determined on the methyl ester of **4** by chiral GLC (CHIRALDEX G-TA). [(d)] (*R*)-isomer. The sign-configuration relationship of **4** was determined by polarimetry and compared with literature data [15]. [(e)] No NEt_3 added.

We deemed it possible to achieve better results with the more hindered (*R*)-(*tert*-Butyl)-MeO-BIPHEP which has been previously used with excellent results for the hydrogenation of similar substrates [11b]. A first experiment was carried out in the best reaction conditions employed with (*R*)-MeO-BIPHEP, nevertheless conversions and asymmetric induction resulted to be lower than those obtained with (*R*)-MeO-BIPHEP (compare entry 13 of Table 1 and entry 1 of Table 2).

Another class of ligands which are commonly employed in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids, are ferrocenyl ligands such as (*R*,*S*)-Mandyphos-4 (Fig. 2) or (α*R*,α'*R*)-2,2'-bis(α-*N*,*N*-dimethylamino-phenyl-methyl)-(*S*,*S*)-1,1'-bis[di(3,5-dimethyl-4-methoxy-phenyl)phosphine] ferrocene] [17]; the asymmetric hydrogenation of carried out in the presence of (*R*,*S*)-Mandyphos-4 gave quantitative conversions as with (*R*)-MeO-BIPHEP but the ees were lower.

Further experiments carried out with different chiral ligands gave unsatisfactory results (see entries 3-6 in Table 2).

In conclusion, in this work we report a new synthesis to enantiomerically enriched (*R*)-2-methylpentanoic acid **4** with total conversion and, in best conditions, 80% ee. Although we were unsuccessful in preparing enantiopure carboxylic acid **4** for the determination of the odor profiles and thresholds of the two stereoisomers, in our opinion the synthetic approach here reported is a valuable alternative for the preparation of Methyl Chamomile. In fact, from an environmental point of view, a 90:10 ratio between the two enantiomers corresponding to an ee of 80%, may be a good compromise in the aim to reduce the overall amount of fragrance release in the environment.

3. Experimental

3.1. General materials and methods

Solvents were purchased from Aldrich and purified according to literature [18]. All other reagents (Aldrich) were used without further purification. All products were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AC300 spectrometer operating at 300.21 and 75.44 MHz, respectively. Gas Chromatography-Mass Spectrometry (GC-MS) analyses were performed on a Hewlett-Packard 5890 SERIES II gas chromatograph interfaced with a HP 5971 quadrupole mass detector. Gas Liquid Chromatography (GLC) analyses were performed on an Agilent 6850 gas chromatograph equipped with a Flame Ionization Detector (FID). The enantiomeric excesses (ees) were determined by chiral GLC using a Chiraldex G-TA column (50 m × 0.25 mm) installed on an Agilent 6850 gas chromatograph with a FID detector. Optical rotatory power values (α) were determined using a Perkin-Elmer 241 polarimeter (Na lamp at 25 °C).

The carbonylation step and hydrogenations experiments of runs 1 and 2 were carried out in a magnetically stirred stainless steel autoclave (total volume ca. 150 mL). All other hydrogenation experiments were carried out in stirred stainless steel autoclave (total volume ca. 200 mL) equipped with a mechanical stirrer Büchi drive bmd 075 and cyclone 075.

3.2 Synthesis of 2-methylenpentanoic acid (3)

In a typical experiment, the magnetically stirred reactor was charged under nitrogen with a mixture of THF/H_2O (30 mL/5 mL), 2-pyridyldiphenylphosphine (0.42 g, 1.60 mmol), $Pd(OCOCH_3)_2$ (9.0 mg, 0.04 mmol), 3.0 mL of pentyne (2.07 g, 30.0 mmol), and 0.2 mL of CH_3SO_3H (0.31 g, 3.20 mmol), then pressurized with CO (30 atm) and heated with a thermostatic bath at 50 °C.

After 24 h, the reactor was cooled and the residual gas vented off. The crude reaction mixture was analysed by GLC to determine the conversion and the selectivity of the reaction. The reaction solvent was then evaporated and the solid obtained treated with a 1 M solution of $NaHCO_3$ (3 × 20 mL); the combined aqueous layers were then acidified with 1 M HCl (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were finally dried over $MgSO_4$, filtered and the solvent was removed in vacuum to give **3** as a pale yellow oil in 93% yield. The spectroscopic data are in agreement with the literature [19].

MS (EI): *m/z* (%) 114 [M]+, 99, 85, 69, 55.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, 3H, *J* = 7.2 Hz, CH_3), 1.46-1.58 (m, 2H, CH_2), 2.29 (t, 2H, *J* = 7.2

Hz, CH_2), 5.65 (s, 1H, C=CH_2), 6.30 (s, 1H, C=CH_2), 11.00-11.70 (br s, 1H, OH).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 21.5, 33.5, 127.1, 140.0, 172.9.

3.3 Synthesis of 2-methylpentanoic acid (4)

In a typical experiment (entry 3 of Table 1), 130 mg of **3** (1.17 mmol) were introduced in a Schlenk tube together with 20 mL of anhydrous CH_3OH. Under inert atmosphere, 6.8 mg of (*R*)-MeO-BIPHEP (1.2×10^{-2} mmol), 2.93 mg of $[RuCl_2(benzene)]_2$ (5.9×10^{-3} mmol), 72 mg of naphthalene (0.6 mmol) and 0.16 mL of NEt_3 (0.12 g, 1.2 mmol) were added to the solution and kept under stirring for about 30 min. The reaction mixture was then transferred *via canula* into the autoclave which was pressurized with 10 atm of H_2 at 0 °C.

After 1 h, the residual gas was vented off and the reaction mixture analyzed by GLC to determine the substrate conversion. The raw reaction mixture was taken to dryness and then treated with a 1 M solution of $NaHCO_3$ (3 × 20 mL); the combined aqueous layers were acidified to pH 1 with 1 M HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were finally dried over $MgSO_4$, filtered and the solvent was removed in vacuum to give **4** as pale yellow oil in 70% yield. The spectroscopic data are in agreement with the literature [15].
MS (EI): *m/z* (%) 116 [M]+, 101, 87, 74, 56.
^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, 3H, *J* = 7.1 Hz, CH_3), 1.15 (d, 3H, *J* = 7.1 Hz, CH_3), 1.31-1.44 (m, 3H), 1.62-1.72 (m, 1H), 2.42-2.49 (m, 1H, CH), 11.10-11.70 (br s, 1H, OH).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.8, 28.9, 33.0, 35.7, 39.2, 125.7, 128.2, 128.3, 142.0, 183.1.

Comparison of the optical rotatory power of ($[\alpha]^{25}_D$ = -9.4 neat) with the literature data ($[\alpha]^{25}_D$ = -18.4 neat) [15] allowed us to assign its prevailing configuration as (*R*). A sample of (50 mg, 0.43 mmol) was derivatized to the corresponding methyl ester [11b] and analyzed by chiral GLC (Chiraldex GT-A column, T = 70 °C, N_2: 2.8 mL/min, t_R = 9.716 min, t_S = 9.106 min); the ee of the methyl ester of (*R*)- was 51%.

4. References

[1] C.S. Sell, *The Chemistry of Fragrances: From Perfumer to Consumer*, Cambridge (UK), RSC, **2006**.

[2] a) E.G. Arnau, K.E. Andersen, M. Bruze, P.J. Frosch, J.D. Johansen, T. Menné, S.C. Rastogi, I.R. White, J.P. Lepoittevin, *Contact Dermatitis* **2000**, *43*, 351-358; b) W.G. Larsen *Contact Dermatitis*, **1983**, *9*, 158-159.

[3] a) A.K. Charles, P.D. Darbre, *J. Appl. Toxicol.* **2009**, *29*, 422-434; b) J. Usta, Y. Hachem, O. El-Rifai, Y. Bou-Moughlabey, K. Echtay, D. Griffiths, H. Nakkash-Chmaisse, R.F. Makki, *Toxicology in Vitro* **2013**, *27*, 339-348.

[4] `http://www.ewg.org/skindeep/site/about.php#5`

[5] M.H. Boelens, L.J. van Gemert, *Perfumer & Flavorist* **1993**, *3*, 2-16.

[6] L.A. Saudan, *Acc. Chem. Res.* **2007**, *40*, 1309-1319.

[7] a) P. Etayo, A. Vidal-Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728-754; b) D.J. Ager, A.H.M. de Vries, J.G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340-3380; c) Z. Yu, W. Yin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060-6072; d) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557-2590; e) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126-4140; f) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713-1760; g) K. Gopalaiah, H.B. Kagan, *Chem. Rev.* **2011**, *111*, 4599-4657; h) S.-F. Zhu, Y.-B. Yu, S. Li, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8872-8875.

[8] L. Qiu, Y.M. Li, F.Y. Kwong, W.Y. Yu, Q.H. Fan, A.S.C. Chan, *Adv. Synth. Catal.* **2007**, *349*, 517-520.

[9] P.-J. Harrington, E. Lodewijk, *Org. Process Res. Dev.* **1997**, *1*, 72-76.

[10] A. Ciappa, S. Bovo, M. Bertoldini, A. Scrivanti, U. Matteoli, *Chem. Biodivers.* **2008**, *5*, 1058-1069.

[11] a) V. Beghetto, U. Matteoli, A. Scrivanti, M. Bertoldini, *Sciences at Ca' Foscari* **2012**, 14-19; b) U. Matteoli, V. Beghetto, A. Scrivanti, M. Aversa, M. Bertoldini, S. Bovo, *Chirality* **2011**, *23*, 779-783; c) U. Matteoli, A. Ciappa, S. Bovo, M. Bertoldini, A. Scrivanti, *Tetrahedron: Asymmetry* **2007**, *18*, 797-802.

[12] a) H. Surburg, J. Panten in *Common fragrance and flavour materials: preparation, properties and uses*, 5th ed., Weinheim, Wiley-VCH, **2006**, 330; b) A.M. Peck, K.C. Hornbuckle, *Atmos. Environ.* **2006**, *40*, 6101-6111.

[13] G. Combes, E. Coen, F. Dehghani, N. Foster, *Ind. Eng. Chem. Res.* **2006**, *45*, 1281-1290.

[14] a) Y. Sun, R.N. Landau, J. Wang, C. LeBlond, D.G. Blackmond, *J. Am. Chem. Soc.* **1996**, *118*, 1348-1353; b) H. Takaya, T. Ohta, S.-I. Inoue, M. Tokunaga, M. Kitamura, R. Noyori, *Org. Synth.* **1993**, *72*, 74-81; c) Y. Sun, J. Wang, C. LeBlond, R.A. Reamer, J. Laquidara, J.R. Sowa Jr., D.G. Blackmond, *J. Organomet. Chem.* **1997**, *548*, 65-72.

[15] R. Morrone, M. Piattelli, G. Nicolasi, *Eur. J. Org. Chem.* **2001**, 1441-1443.

[16] a) A. Scrivanti, S. Bovo, A. Ciappa, U. Matteoli, *Tetrahedron Lett.* **2006**, *47*, 9261-9265; b) G.S. Forman, T. Ohkuma, W.P. Hems, R. Noyori, *Tetrahedron Lett.* **2000**, *41*, 9471-9475; c) G.A. Grasa, A. Zanotti-Gerosa, S. Ghosh, C.A. Teleha, W.A. Kinney, B.E. Maryanoff, *Tetrahedron Lett.* **2008**, *49*, 5328-5331.

[17] F. Spindler, C. Malan, M. Lotz, M. Kessenlgruber, U. Pittelkow, A. Rivas-Nass, O. Briel, H.U. Blaser, *Tetrahedron: Asymmetry* **2004**, *15*, 2299-2306.

[18] W.L.F. Armarego, D.D. Perrin in *Purification of laboratory chemicals*, 4th ed., Oxford, Butterworth-Heinemann, **1996**.

[19] K. Borszeky, T. Mallat, A. Baiker, *Tetrahedron Asymmetry* **1977**, *8*, 3745-3753.