An Alternative Stereoselective Synthesis of (*R*)- and (*S*)-Rosaphen® via Asymmetric Catalytic Hydrogenation

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ABSTRACT We report an alternative synthesis of the two enantiomers of the floral fragrance Rosaphen®. The key intermediate 2-methyl-5-phenylpentanoic acid **3** is synthesized via asymmetric hydrogenation (*ee* up to 99%) in the presence of an in situ prepared ruthenium catalyst containing the chiral ferrocenyl phosphine Mandyphos-4. *Chirality 23:779–783, 2011.*

KEY WORDS: fragrances; ruthenium; Mandyphos-4; enantioselective hydrogenation; MeOBIPHEP

INTRODUCTION

It is now well recognized that human nose may perceive in a different way the enantiomers of a chiral odorant; in other words, the olfactory notes of two enantiomers may be different both in quality and in intensity.[1–6] This phenomenon is not only of great scientific interest, but also of primary practical importance for at least three main reasons: (i) in perfumery there is an increasing demand for odorants to create new unique olfactive notes; (ii) there are environmental and safety concerns arising from the increasing use of odorants and their interaction with the ecosystem and human beings; and (iii) the synthesis of single enantiomer is patentable.[7]

The odorants displaying floral notes (rose, jasmine, lily-of-the-valley, etc.) are of particular interest in perfumery as they are very much appreciated and widely used.[8,9] Rosaphen® [2-methyl-5-phenyl-1-pentanol], which belongs to this class of fragrances, is at present merchandized as racemate by Symrise.

Only very recently, while the present manuscript was in preparation, an enzymatic synthesis of the two enantiomers of Rosaphen has been published by Kawasaki et al., who also reported the description of their olfactive notes, albeit the relevant odor thresholds were not determined.[10]

Besides the work by Kawasaki et al. in the literature, there are a few reports dealing with the asymmetric synthesis of 2-methyl-5-phenyl-1-pentanol and all concern the preparation of the (*R*)-isomer[11–13] for which the absolute configuration–optical rotation relationship is reported by Santini et al.[11] It is worth mentioning that the synthesis reported by Owston and Fu[13] is a rare example of an asymmetric Suzuki reaction.

Transition metal asymmetric catalysis is among the most powerful tools suitable for the synthesis of enantiomerically enriched substances on practical scale[14] and our research group has been for years involved in the application of homogeneous asymmetric catalysis[7] to the synthesis of enantiomerically enriched fragrances such as Galaxolide®,[15] Florydral®,[16,17] Citralis Nitrile®,[18] and Phenoxanol®.[19] We wish to report here a new approach to the enantioselective synthesis of (*R*)- and (*S*)-Rosaphen based on the catalytic asymmetric hydrogenation of 2-methyl-5-phenylpent-2-enoic acid. A description of the odor profiles of the single stereomers is also reported together with their odor thresholds.

EXPERIMENTAL

General Information

All manipulations were carried out under nitrogen by using standard Schlenk techniques. Solvents and NEt_3 were purchased from Aldrich and purified according to literature procedures.[20] All other reagents (Aldrich) were used without further purification. (*R*)-MeOBIPHEP, (*R*,*S*)-Mandyphos-4, and (*S*,*R*)-Mandyphos-4 were kind gifts from Solvias. $[RuCl_2(benzene)]_2$[21] and 2-(diethoxyphosphoryl)propanoic acid[22] were prepared as described in the literature.

All products were characterized by ^1H NMR, ^{13}C NMR, and mass spectrometry. ^1H 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 Flame Ionization Detector (FID). The enantiomeric excesses (*ee*s) 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).

Preparation of (E)-2-Methyl-5-phenylpent-2-enoic acid ((E)-2)

Under inert atmosphere, to 75 ml of chilled (−60°C) anhydrous THF were sequentially added 19 ml of a 2.7 M solution of *n*-BuLi in hexanes (51.3 mmol), 2-(diethoxyphosphoryl)propanoic acid (5.3 g, 25.2 mmol in 10 ml of THF), and after 1 h of stirring at −60°C, hydrocinnamaldehyde (3.19 g, 23.8 mmol in 10 ml of tetrahydrofuran (THF)). The resulting yellow solution was kept under stirring at −60°C for 3 h, then it was allowed to reach room temperature and kept under stirring overnight. The reaction mixture was then cooled to 0°C, quenched with water (50 ml) and extracted with diethyl ether (3× 50 ml). The combined organic phases were extracted with a 1 M solution of $NaHCO_3$ (3× 20 ml); the combined aqueous layers were then acidified with 50 ml of 1 M HCl and extracted with CH_2Cl_2 (3× 30 ml). The combined organic phases were

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TABLE 1. Asymmetric hydrogenation of (*E*)-2 to 3 in the presence of [$RuCl_2$(benzene)]$_2$/(*R*)-MeOBIPHEP

Entry	*T* (°C)	H_2 (atm)	NEt_3/**2**	*t* (h)	Conv. (%)[a]	*ee* (%)[b]	(Sign)-(Config.)[c]
1	50	50	0	24	100[d]	64	(−)-(*R*)
2	25	50	0	24	100	70	(−)-(*R*)
3	0	50	0	24	74	78	(−)-(*R*)
4	50	50	1/1	6	100	64	(−)-(*R*)
5	25	50	1/1	24	100	48	(−)-(*R*)
6	0	50	1/1	24	100	28	(−)-(*R*)
7	50	20	1/1	6	100	78	(−)-(*R*)

Reaction conditions: substrate: 0.53 mmol, [$RuCl_2$(benzene)]$_2$: 2.65×10^{-3} mmol, substrate/Ru: 100:1 (mol/mol), Ligand/Ru: 1/1 (mol/mol), solvent: CH_3OH (10 ml).[a]Determined by GLC.
[b]Determined on the methyl ester of **3** by chiral GLC (CHIRALDEX G-TA).
[c]The sign–configuration relationship of **3** was determined by polarimetry and comparison with literature data.[12]
[d]Isolated yield: 70%.

finally dried over $MgSO_4$ and, after filtration on a short silica gel column (eluent: diethylether), the solvent was removed in vacuum to give **2** as a pale yellow oil ((*E*)-**2**/(*Z*)-**2** >99%) in 93% yield. The spectroscopic data are in agreement with the literature.[12]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (s, 3H, C*H*$_3$), 2.58 (m, 2H, ArCH$_2$C*H*$_2$), 2.82 (t, 2H, *J* = 7.34 Hz, ArC*H*$_2$CH$_2$), 7.02 (t, 1H, *J* = 7.34 Hz, C*H*=C), 7.21−7.39 (m, 5H, *arom*), 11.80−12.40 (br s, 1H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8, 30.7, 34.5, 126.1, 127.7, 128.3, 128.4, 140.9, 143.8, 173.7. MS (EI): *m/z* (%) = 190 ([M]$^+$, 10), 175 (15), 91 (70), 77 (8), 65 (20).

Asymmetric Hydrogenations with (R)-MeOBIPHEP

The asymmetric hydrogenation experiments were carried out in a 150 ml magnetically stirred stainless steel autoclave. In a typical experiment (entry 1 of Table 1), 100 mg (0.53 mmol) of (*E*)-**2** were introduced in a Schlenk tube together with 10 ml of CH_3OH. Under inert atmosphere, 1.4 mg (2.65×10^{-3} mmol) of [$RuCl_2$(benzene)]$_2$ and 16.7 mg (5.3×10^{-3} mmol) of (*R*)-MeOBIPHEP were added to the solution and kept under stirring for about 30 min. The reaction mixture was then transferred via cannula into the autoclave which was pressurized with 50 atm of H_2 and heated to 50°C. After 24 h the autoclave was cooled to room temperature, the residual gas 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 $MgSO_4$ and, after filtration on a short silica gel column (eluent: diethylether), the solvent was removed in vacuum to give **3** as pale yellow oil in 70% yield. The spectroscopic data are in agreement with the literature.[23]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (d, 3H, *J* = 6.97 Hz, C*H*$_3$), 1.44−1.62 (m, 1H, CH$_2$C*H*$_2$CH), 1.65−1.82 (m, 3H, CH$_2$C*H*$_2$CH and ArCH$_2$C*H*$_2$), 2.50–2.61 (m, 1H, C*H*), 2.70 (t, 2H, *J* = 7.53 Hz, ArC*H*$_2$), 7.21–7.39 (m, 5H, *arom*), 11.10–11.70 (br s, 1H, O*H*). ^{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. MS (EI): *m/z* (%) = 192 ([M]$^+$, 7), 174 (7), 117 (20), 91 (70), 77 (10), 65 (20). Comparison of the optical rotatory power of **3** ($[\alpha]_D^{25}$ = –4.2 (*c* 0.1, CH_3OH)) with the literature data ($[\alpha]_D^{25}$ = –6.6 (*c* 0.1, CH_3OH))[23] allowed us to assign its prevailing configuration as (*R*). A sample of **3** (50 mg, 0.26 mmol) was derivatized to the corresponding methyl ester and analyzed by chiral GLC (Chiraldex GT-A column, *T* = 110°C, N_2: 3.8 ml/min, t_R = 70.93 min, t_S = 71.81 min); the *ee* of the methyl ester of (*R*)-**3** was 64%.

Asymmetric Hydrogenations with (R,S)-Mandyphos-4

The asymmetric hydrogenation of (*E*)-**2** for the synthesis of (*R*)-**3** was carried out as described in the previous section. In a typical experiment (entry 4 of Table 2), 100 mg (0.53 mmol) of (*E*)-**2** were introduced in a Schlenk tube together with 20 ml of CH_3OH, then, under inert atmosphere, 1.4 mg (2.65×10^{-3} mmol) of [$RuCl_2$(benzene)]$_2$, 33.3 mg (5.3×10^{-3} mmol) of (*R,S*)-Mandyphos-4, and 75 μl (54 mg, 0.53 mmol) of NEt_3 were added to the solution and kept under stirring for about 1 h. The reaction mixture was then transferred via cannula into the autoclave which was cooled to 0°C and pressurized with 20 atm of H_2. After 24 h, the residual gas was vented off and the reaction mixture was analyzed by GLC to determine the substrate conversion (100%). After the described treatment, enantiopure (*R*)-**3** was recovered in 75% yield.

Synthesis of (S)-2-Methyl-5-phenylpentanoic acid ((S)-3)

The asymmetric hydrogenation of (*E*)-**2** for the synthesis of (*S*)-**3** was carried out as described above for the synthesis of (*R*)-**3** employing (*S,R*)-Mandyphos-4 as ligand. Enantiopure (*S*)-**3** was recovered in 78% yield.

Synthesis of (R)-2-Methyl-5-phenylpentanol ((R)-4)

Under inert atmosphere, a solution of (*R*)-**3** (400 mg, 2.08 mmol in 15 ml of THF, $[\alpha]_D^{25}$ = –6.5 (*c* 0.1, CH_3OH)) was added dropwise under stirring to a solution of $NaBH_4$ (200 mg, 5.40 mmol in 15 ml of THF). Once no more gas evolution was observed, a solution of I_2 (538 mg, 2.10 mmol in 15 ml of THF) was added dropwise and the reaction mixture kept under stirring overnight at reflux temperature.

At room temperature, 50 ml of CH_3OH were added to the mixture and stirred for further 1 h, then the solvent was partially evaporated to precipitate a white solid which was dissolved in 50 ml of an aqueous solution of KOH (20%) and left under stirring for 4 h. Finally, the solution was extracted with CH_2Cl_2 (4× 30 ml); the combined organic phases

TABLE 2. Asymmetric hydrogenation of (*E*)-2 to 3 in the presence of [$RuCl_2$(benzene)]$_2$/(*R,S*)-Mandyphos-4

Entry	*T* (°C)	H_2 (atm)	NEt_3/**2**	*t* (h)	Conv. (%)[a]	*ee* (%)[b]	(Sign)-(Config.)[c]
1	25	20	0	24	97	97	(−)-(*R*)
2	0	20	0	24	50	>99	(−)-(*R*)
3	25	20	1/1	24	100	97	(−)-(*R*)
4	0	20	1/1	24	100[d]	>99	(−)-(*R*)
5	25	100	1/1	1	96	95	(−)-(*R*)

Reaction conditions: substrate: 0.53 mmol, [$RuCl_2$(benzene)]$_2$: 2.65×10^{-3} mmol, substrate/cat. = 100/1 (mol/mol), Ligand/Ru = 1/1 (mol/mol), solvent: CH_3OH (10 ml).[a]Determined by GLC.
[b]Determined on the methyl ester of **3** by chiral GLC (CHIRALDEX G-TA).
[c]The sign–configuration relationship of **3** was determined by polarimetry and comparison with literature data.[12]
[d]Isolated yield: 75%.

were dried over $MgSO_4$ and, after filtration on a short silica gel column (eluent: diethyl ether/*n*-hexane 40/60), the solvent was removed in vacuum to give (*R*)-**4** as pale yellow oil in 88% yield.

According to the optical rotatory power data ($[\alpha]_D^{25} = +10.2$ (*c* 1.0, CH_2Cl_2)), the optical purity (o.p.) of (*R*)-**4** was 99% ($[\alpha]_{D,max}^{25} = +10.3$ (*c* 1.0, CH_2Cl_2)).[12] To determine the *ee* value of alcohol **4**, it was oxidized to acid **3** as follows: a solution of **4** in DMF was treated with a solution of pyridinium dichromate in water and the resultant mixture was stirred overnight at room temperature[24]; after standard work up the resulting acid **3** was derivatized and analyzed by chiral GC as described above (*ee* > 99%, Chiraldex GT-A column (0.25 mm × 50 m); nitrogen flow 3.8 ml/min; $T = 110^\circ C$; $t_R = 70.93$ min, $t_S = 71.81$ min).

The spectroscopic data are in agreement with the literature.[12]

^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (d, 3H, $J = 6.59$ Hz, C*H*$_3$), 1.08–1.24 (m, 1H, CH_2CH_2CH), 1.36–1.52 (m, 2H, CH_2CH_2CH and O*H*), 1.56–1.76 (m, 3H, $ArCH_2CH_2$ and C*H*), 2.56–2.64 (m, 2H, $ArCH_2$), 3.40–3.56 (m, 2H, CH_2OH), 7.20–7.40 (m, 5H, *arom*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4, 28.8, 32.7, 35.6, 36.1, 68.2, 125.6, 128.2, 128.3, 142.5. MS (EI): *m/z* (%) = 178 ($[M]^+$, 54), 160 (95), 117 (87), 104 (69), 91 (43).

Synthesis of (S)-2-Methyl-5-phenylpentanol ((S)-4)

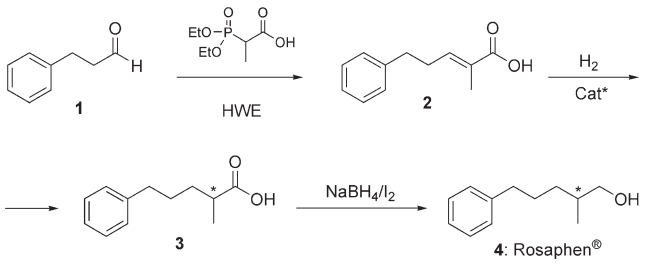
The reduction of (*S*)-**3** was carried out as described above for (*R*)-**3**. Enantiopure (*S*)-**4** was recovered in 90% yield.

RESULTS AND DISCUSSION

In order to synthesize enantiomerically pure Rosaphen, we devised the three steps synthetic strategy reported in Scheme 1. The starting product is the commercially available and inexpensive hydrocinnamaldehyde **1** which is first converted into the prochiral 2-methyl-5-phenylpent-2-enoic acid **2** by means of a Horner–Wadsworth–Emmons (HWE) olefination.[25] Then, **2** is hydrogenated in the presence of a chiral transition metal catalyst to give (*R*)- or (*S*)-2-methyl-5-phenylpentanoic acid, (*R*)- or (*S*)-**3**. In the last step, (*R*)- or (*S*)-**3** is reduced with $NaBH_4/I_2$ to give (*R*)- or (*S*)-2-methyl-5-phenylpentan-1-ol (**4**) ((*R*)- or (*S*)-Rosaphen) with complete retention of the enantiopurity.[26]

The HWE olefination, a modification of the well known Wittig reaction,[27] is preferred because it offers a good control of the *E/Z* diastereoselectivity in the product, *E/Z* isomer ratios higher than 9/1 being usually obtained.[28] Control of the olefin diastereoselectivity is of primary importance because it often occurs such that the asymmetric hydrogenation of the *E* and the Z isomers leads to opposite enantiomers.[19,29,30]

2-(Diethoxyphosphoryl)propanoic acid, prepared by a literature method,[22] is a co-reactant particularly activated in HWE owing to the presence of the electron-withdrawing COOH moiety, so that the sought 2-methyl-5-phenylpent-2-enoic acid **2** is obtained in about 93% isolated yield. In keeping with the adopted strategy, the diastereoselectivity



Scheme 1. The designed synthesis of Rosaphen®.

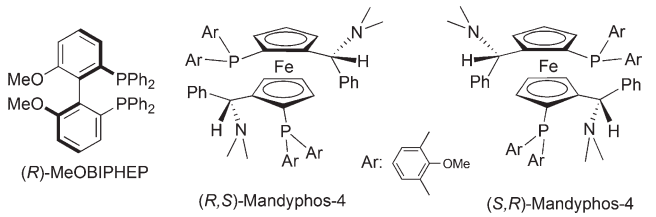


Fig. 1. Molecular structure of (*R*)-MeOBIPHEP, (*R,S*)-Mandyphos-4 and (*S,R*)-Mandyphos-4.

towards (*E*)-**2** is greater than 99% as shown by ^1H NMR spectroscopy.

The asymmetric hydrogenation of the α,β-unsaturated carboxylic acid **2** is the key step of the designed synthetic strategy.[31–35] A very convenient approach for preliminary studies consists in the use of a catalytic system generated in situ from $[RuCl_2(benzene)]_2$ and a chiral bidentate phosphine ligand in the 1/2 molar ratio.[36–38] In fact, this simply assembled catalytic system is readily tunable 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*)-MeOBIPHEP (see Fig. 1) are reported in Table 1. At 50°C and 50 atm of hydrogen, the prochiral olefin **2** is totally hydrogenated in 24 h to give (–)-(*R*)-**3** in fairly good *ee* (64%) (see Experimental section). By lowering the reaction temperature to 25°C, the enantioselectivity increases to 70% with complete conversion of the substrate. Further improvement of the *ee* (78%) is obtained working at 0°C, although the conversion is only 74%.

Thus, we were prompted to evaluate the effect of the addition of triethylamine as promoter on the reaction.

As a matter of fact, it is well known that the rate of the hydrogenation with ruthenium catalysts may be improved by adding an amine as the co-catalyst; although it is worth noting that a positive effect on the reaction rate is not always accompanied by an enhancement in enantioselectivity.[18,39,40]

The data of the experiments with triethylamine (in 1/1 molar ratio with respect to the substrate) are reported in entries 4–7 of Table 1. As expected, addition of amine leads to faster hydrogenation rates (compare entries 3 and 6). By comparing the asymmetric inductions, it appears that at 50°C the presence of the amine has no effect, while at 25°C or 0°C the *ees* obtained with the amine are lower than those obtained without this co-catalyst. It is noteworthy that, as far as the dependence of enantioselectivity on the temperature is concerned, two different trends are found: without amine the selectivity increases on decreasing the temperature, while the opposite behavior is observed using the co-catalyst. 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 4 of Table 1 in 24 h gives the same enantioselection (64% *ee*).

Last row of Table 1 shows the effect of the hydrogen pressure on the reaction: a decrease from 50 to 20 atm (compare entries 4 and 7) leads to a significant increase in the asymmetric induction (*ee* 64% and 78%, respectively), as in other ruthenium catalyzed hydrogenations.[41]

Although under these conditions, we are able to obtain *ee*s up to about 80%, this result was not considered completely

satisfactory. Therefore, deeming that substantial improvements in enantioselectivity could not be achieved by a further fine tuning of the reaction conditions, we decided to test (*R,S*)-Mandyphos-4 [(α*R*,α*R*)-2,2′-bis(α-*N*,*N*-dimethylaminophenylmethyl)-(*S,S*)-1,1′-bis[di(3,5-dimethyl-4-ethoxyphenyl)-phosphino]ferrocene (see Fig. 1)], a completely different ligand belonging to the class of ferrocenyl diphosphines.[42] The results are summarized in Table 2.

In entries 1 and 2 are reported the experiments carried out using $[RuCl_2(benzene)]_2$/(*R,S*)-Mandyphos-4 in the absence of co-catalyst. At once, this new system appears much more stereoselective than the one based on (*R*)-MeOBIPHEP since at room temperature under 20 atm of hydrogen the reaction proceeds with complete substrate conversion giving (*R*)-**3** in 97% *ee*. When the temperature is lowered to 0°C almost complete enantioselectivity is obtained (>99%); unfortunately, under these conditions the reaction rate is depressed and only 50% of the substrate is hydrogenated in 24 h (entries 1 and 2 of Table 2).

The data reported in entries 3–5 are obtained using triethylamine as co-catalyst. In entries 3 and 4, carried out under 20 atm of hydrogen, the enantioselectivity remains unaffected while a strong enhancement in the reaction rate is observed. When the hydrogen pressure is increased to 100 atm (entry 5), very high reaction rates are obtained, but, adversely, this is accompanied by a small decrease in the enantioselectivity.

By comparing the data in Table 2, it appears that the most suitable conditions for the asymmetric hydrogenation are those of entry 4. Therefore, these conditions were adopted to prepare about 0.5 g of practically enantiopure (*R*)-**3**. Analogously, enantiopure (*S*)-**3** was synthesized employing (*S,R*)-Mandyphos-4.

According to the last step of the planned synthesis (Scheme 1), pure samples of (*R*)- or (*S*)-**3** were reduced with $NaBH_4/I_2$[26] with complete retention of enantioselectivity to give (*R*)- or (*S*)-**4**, in about 90% isolated yield.

Samples of (*R*)- and (*S*)-Rosaphen were submitted to a panel of skilled perfumers (Givaudan) for the evaluation of the odor profiles. The following description was obtained for (−)-(*S*)-Rosaphen: floral rosy odor in the direction of phenylethyl esters, with green, powdery, honey-like, and slightly animalic aspects (odor threshold: 3.45 ng/l); while for (+)-(*R*)-Rosaphen the description is: transparent floral rosy and watery odor in the direction of citronellol and mefrosol (3-methyl-5-phenylpentan-1-ol) (odour threshold: 9.95 ng/l).

CONCLUSIONS

In conclusion, we have developed a new three-step synthesis of the single enantiomers of Rosaphen which allowed us to evaluate the odor profiles of the single stereomers and determine their odor thresholds. Even if no particular striking differences were perceived in the odor profiles or in their intensities, it is worth to mention that (*R*)-Rosaphen presents the more complex and interesting olfactive notes.

In the devised synthetic approach, the critical step is represented by the asymmetric hydrogenation of the (*E*)-2-methyl-5-phenylpent-2-enoic acid **2**. The enantiomeric excesses obtained with the catalyst prepared by mixing $[RuCl_2(benzene)]_2$ and (*R,S*)-Mandyphos-4 or (*R,S*)-Mandyphos-4 are excellent (99%) and comparable with the ones achieved by enzymatic approaches.[10]

In order to turn the process into a practically feasible one, a more sustainable reduction of acid **3** to alcohol **4** should be developed. Indeed, a straight **3** to **4** transformation could be accomplished by catalytic hydrogenation of the carboxylic moiety; either homogeneous[43,44] or heterogeneous[45] catalysts might be employed.

In the devised synthesis, a further weakness is the HWE olefination which does not meet the concept of atom efficiency and has to be carried out at low temperatures. As suggested by an anonymous reviewer, alternative precursors of **3** or **4** such as α,β-unsaturated acids, aldehydes, or allyl alkohols could be synthesized by Mannich or aldol reactions which are more atom efficient than HWE olefination and feasible at ordinary temperatures. A variety of asymmetric hydrogenations of such intermediates either enzymatic[46–51] or catalytic[18,52] are available and have been the subject of a recent review by Saudan.[53]

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