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Synthesis and olfactory evaluation of all stereoisomers of the fragrance *Nectaryl*®

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Abstract—The fragrance *Nectaryl*® **1** was prepared by the radical addition of cyclopentanone to (+)-limonene. All the four stereoisomers of this fragrance were prepared by the enzymatic acetylation of the corresponding alcohols in good de. The absolute configurations have been unambiguously assigned by the chemical correlation and X-ray crystal structure of a dinitrobenzoate derivate. The olfactory evaluation is also reported. The odour perception is mainly related to the configuration at the stereocentre α to the carbonyl group. Chiral protonations of the lithium enolate or the enolester of **1** to give a diastereomeric enriched mixture of **1** are reported.

1. Introduction

The preparation of fragrances in their enantiomerically pure forms is an emerging area of synthetic chemistry.[1] Indeed, the relationship between the stereochemistry of chiral odorant molecules and their human perception is still not well understood.[2] Thus, over the last decade we were interested in the synthesis and olfactory evaluation of the enantiomers of many commercial fragrances[3] (see Fig. 1).

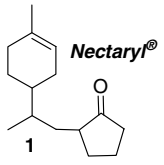
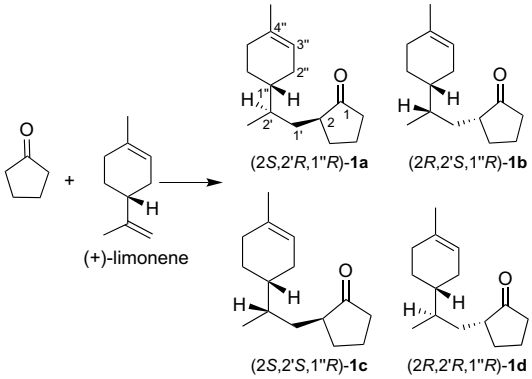


Figure 1. Chemical structure of commercial *Nectaryl*®.

Herein, we report the preparation and the olfactory evaluation of the stereoisomers of the commercial fragrance *Nectaryl*® **1**.

2. Results and discussion

The fragrance *Nectaryl*® produces a pleasant scent of peach and apricot. Its structure is composed of a monoterpene unit attached α to the carbonyl group of cyclopentanone. This fragrance has found several applications as an ingredient of cosmetic formulations and of laundry powders. Hence, we prepared **1** by the radical addition of cyclopentanone to (+)-limonene, catalyzed by $Mn(OAc)_2$ combined with $Co(OAc)_2$ under O_2 atmosphere, in 72% yield (Scheme 1).[4] The cyclopentanone radical adds regioselectively to the exocyclic double bond of the limonene.



Scheme 1. Reagents and conditions: O_2, cat. $Mn(OAc)_2$ and cat. $Co(OAc)_2$, refluxing AcOH.

A comparison of the specific rotation value of **1** prepared by our method $\{[\alpha]_D^{20} = +228$ (c 1, $CHCl_3$)$\}$ with that of

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the commercial *Nectaryl*® {$[\alpha]_D^{20} = +235$ (c 1, $CHCl_3$)} indicates that the latter is prepared starting from (+)-limonene.

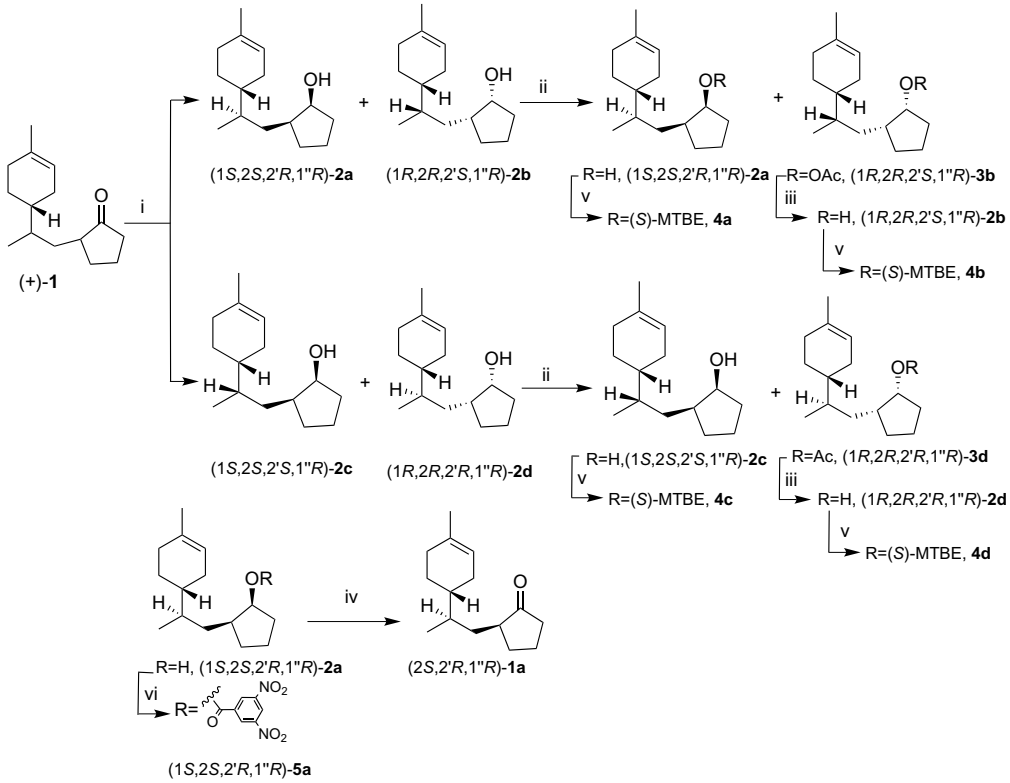
Moreover, the ^{13}C NMR spectra of **1** shows the presence of an equimolar mixture of all four possible stereoisomers of **1**, respectively, (2*S*,2′*R*,1″*R*)-**1a**, (2*R*,2′*S*,1″*R*)-**1b**, (2*S*,2′*S*,1″*R*)-**1c** and (2*R*,2′*R*,1″*R*)-**1d** (Fig. 3).

The synthesis of all the single stereoisomers of *Nectaryl*® is summarized in Scheme 2. First, the carbonyl group of **1** was reduced with L-Selectride in THF at −78 °C to give an equimolar mixture of *cis*-cyclopentanol alcohols **2a–d** [by integration of the ^{13}C NMR signals of C(3′)] in 80% yield.[5] Purification by chromatography allowed the separation of the less polar alcohols (1*S*,2*S*,2′*R*,1″*R*)-**2a** and (1*R*,2*R*,2′*S*,1″*R*)-**2b** (ratio 1:1 by GC) from the more polar (1*S*,2*S*,2′*S*,1″*R*)-**2c** and (1*R*,2*R*,2′*R*,1″*R*)-**2d** (ratio 1:1 by ^{13}C NMR). The enzymatic (lipase PS) acetylation of (1*S*,2*S*,2′*R*,1″*R*)-**2a** and (1*R*,2*R*,2′*S*,1″*R*)-**2b** in *t*-butylmethylether (*t*-BuOMe), using vinyl acetate as an acetylating agent, afforded, after 1 day, the acetate (1*R*,2*R*,2′*S*,1″*R*)-**3b** (37% yield, 92% de by ^{13}C NMR) and the non-converted alcohol (1*S*,2*S*,2′*R*,1″*R*)-**2a** (56% yield, 70% de).[6] The latter was separated by column chromatography. Next, the acetate (1*R*,2*R*,2′*S*,1″*R*)-**3b** was hydrolyzed with NaOH in EtOH to give the alcohol (1*R*,2*R*,2′*S*,1″*R*)-**2b** in 94% yield. Since, the de of the recovered alcohol was not sufficiently high, the latter was submitted to the same enzymatic resolution affording (1*S*,2*S*,2′*R*,1″*R*)-**2** with 84% de in 28% yield. The enzymatic acetylation of the other two alcohols, using the same procedure as described above, furnished, respectively, alcohol (1*S*,2*S*,2′*S*,1″*R*)-**2c** (36% yield, de 82%) and (1*R*,2*R*,2′*R*,1″*R*)-**2** (28% yield, 88% de). Finally, the Dess–Martin oxidation of alcohol (1*S*,2*S*,2′*R*,1″*R*)-**2a** in CH_2Cl_2 at 0 °C gave ketone (2*S*,2′*R*,1″*R*)-**1a** (92% yield, de 81% by GC).[7] The other alcohols were oxidized in the same manner giving (2*R*,2′*S*,1″*R*)-**1b** (92% yield, de 89%), (2*S*,2′*S*,1″*R*)-**1c** (92% yield, de 80%) and (2*R*,2′*R*,1″*R*)-**1d** (92% yield, de 86%), respectively.

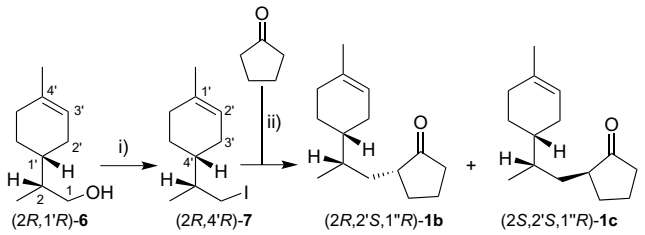
2.1. Absolute stereochemistry assignment

The absolute stereochemical configuration at C(1″) was (*R*) for all the stereoisomers of **1** because, we used the (+)-limonene as the starting material. Regarding the stereochemistry at the C(2′), we prepared a mixture of two diastereoisomers with the (*R*)-configuration at C(1″) and (*S*)-configuration at C(2′), that is, (2*R*,2′*S*,1″*R*)-**1b** and (2*S*,2′*S*,1″*R*)-**1c**. The synthesis of these two diastereoisomers is shown in Scheme 3. The tosyl derivate of alcohol (2*R*,1′*R*)-**6**[8] reacted with NaI in refluxing acetone to give the iodo derivate (2*R*,4′*R*)-**7** in 90% yield. Next, the cyclopentanone enolate, generated with LDA in THF and DMPU at −78 °C, was alkylated at −30 °C with **6** to give **1b** and **1c** in 26% yield (Scheme 3).

The absolute configuration at C(2) was initially assigned by the ^{19}F NMR analysis of the (*S*)-MTPA ester **4a–d** prepared from alcohols **2** (Scheme 2).[9] Since, the relative stereochemistry between C(2) and C(1) is *cis*, the determination of the absolute configuration at C(1) leads



Scheme 2. Reagents and conditions: (i) L-Selectride, −78 °C, THF; (ii) PS Lipase, vinyl acetate, *t*-BuOMe; (iii) NaOH, EtOH; (iv) DMP, CH_2Cl_2, 0 °C; (v) (*S*)-MTPCl, CH_2Cl_2, 0 °C DMAP; (vi) pyridine, 3,5-dinitrobenzoyl chloride.



Scheme 3. Reagents and conditions: (i) (a) TsCl, pyridine; (b) NaI, refluxing acetone; (ii) LDA, DMPU, THF, −30 °C to rt.

to the assignment of the stereochemistry at C(2). The trend observed was similar to the one described for (*S*)-MTPA esters of 2-substituted cyclopentanols. The criteria adopted assigns the (*S*)-configuration to the Mosher's ester with the most shielded CF_3 signal.[10] The ^{19}F NMR data of (*S*)-MTPA esters and the absolute configurations assignments are reported in Table 1.

Table 1. ^{19}F NMR (235.3 MHz) data of (*S*)-MTPA ester derivates **4a–d** of alcohol **2** in $CDCl_3$ and their absolute configuration assignment

Ester	δ (CF_3) (ppm)[a]	AC	Correct stereochemistry
4a	−72.326	(1*R*,2*R*,2′*R*,1″*R*)-**2**	(1*S*,2*S*,2′*R*,1″*R*)-**2a**
4b	−72.436	(1*S*,2*S*,2′*S*,1″*R*)-**2**	(1*R*,2*R*,2′*S*,1″*R*)-**2b**
4c	−72.360	(1*R*,2*R*,2′*S*,1″*R*)-**2**	(1*S*,2*S*,2′*S*,1″*R*)-**2c**
4d	−72.487	(1*S*,2*S*,2′*S*,1″*R*)-**2**	(1*R*,2*R*,2′*R*,1″*R*)-**2d**

[a] C_6F_6 was used as reference $\delta = 0.0$ ppm.

The 3,5-dinitrobenzoate ester **5** of alcohol **2a** gave crystals suitable for *X*-ray structure determination (Fig. 2). However, the absolute configuration obtained from the crystal structure of **5**, fixing the (*R*)-configuration at C(1″) was in disagreement with that obtained by Mosher's ester analysis.

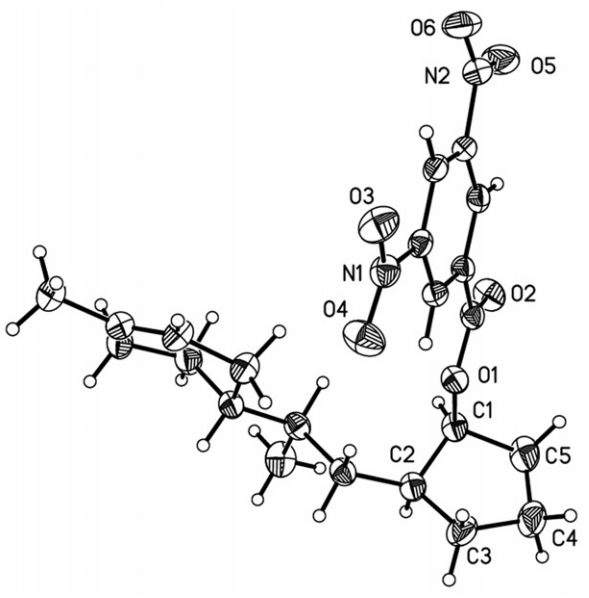


Figure 2. ORTEP draw of **5**.

Finally, we report a selected region of ^{13}C NMR spectra of the C(3′) signals, elucidating the correct absolute configuration assignment of all stereoisomers of *Nectaryl*® (Fig. 3 and Table 1).

2.2. Olfactory evaluation and structure–odour relationships

All the samples of *Nectaryl*® were submitted to professional olfactory evaluation with the following results.

- (+)-*Nectaryl*®: Power in the direction of peach and apricot. Odour threshold: 0.354 ng/L air.
- (2*S*,2′*R*,1″*R*)-**1a**: Rather weak and uncharacteristic fruity-lactonic odour with some additional resemblance of green apple, it does not contribute much to the commercial *Nectaryl*®. Odour threshold: 11.2 ng/L air.
- (2*R*,2′*S*,1″*R*)-**1b**: Powerful, very intense, sweet and dry fruity-lactonic odour in the direction of peach and apricots, with some floral undertone, does contribute much to the overall odour of commercial *Nectaryl*®. Odour threshold: 0.094 ng/L air.
- (2*S*,2′*S*,1″*R*)-**1c**: The same as **1a**. Odour threshold: 14.9 ng/L air.
- (2*R*,2′*R*,1″*R*)-**1d**: The same as **1b**. Odour threshold: 0.112 ng/L air.

2.3. Synthesis of the most odorant diastereoisomers

The olfactory evaluation has shown that the (*R*) configuration at C(2) seems to be crucial for the odour perception of *Nectaryl*®, therefore, it might be interesting to design a selective synthesis for the preparation of those stereoisomers. Due to the low cost of this fragrance, such a synthesis should be simple and straightforward. Keeping this in mind, we envisaged on the enantioselective protonation of prochiral enolates or enol esters to be the shortest way to prepare the target compounds (Scheme 4).[11]

Concerning the chemo- and enantioselective protonation of enolates, among the many reagents so far developed, we have chosen the amino alcohols (+)-**8** and (−)-**8**.[12] Thus, the treatment of the silyl ether (2′*RS*,1′*R*)-**8** with BuLi in THF at 0 °C generated the lithium enolate of **1**. The latter at −78 °C was quenched with a stoichiometric amount of (+)-**8** and after 1 h with 0.1 equiv of Me_3SiCl, gave a mixture of **1** with a low enrichment of the stereoisomers with a (2*S*)-configuration (de_{tot} −21%, Table 2, entry 1), and the recovered (2′*RS*,1′*R*)-**9**.[13]

When using (−)-**8**, as a chiral proton donor, it gave a mixture of **1** with the modest enrichment of (*R*) stereoisomers ($de_{tot} = 41\%$, Table 2, entry 2). Next, we performed the reaction in Et_2O in the presence of 5 equiv of LiBr, since it is known from the literature that the formation of mixed aggregates might increase the enantioselectivity.[14] However, we obtained a mixture of **1** with a low enrichment in the direction of the most odorant stereoisomers. Surprisingly, the chiral protonation of the enolate with a (2′*R*,1″*R*)-configuration gave a mixture of **1** with a 58% de, whereas the enolate with a (2′*R*,1″*R*)-configuration gave a mixture of **1** with −22% de. The reaction was carried out at −50 °C because at the lower temperatures the enolate

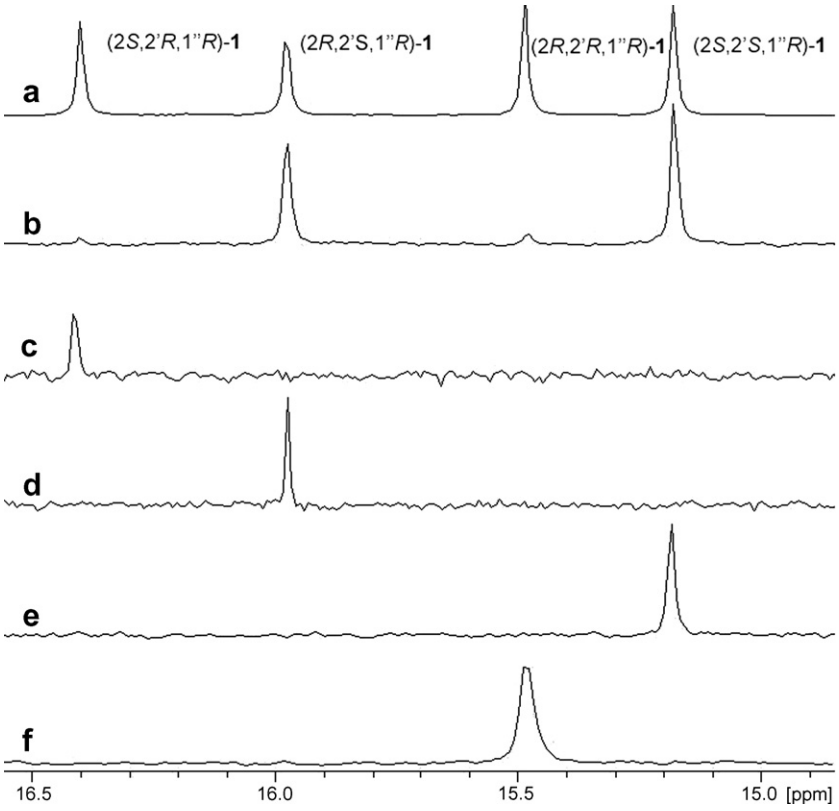
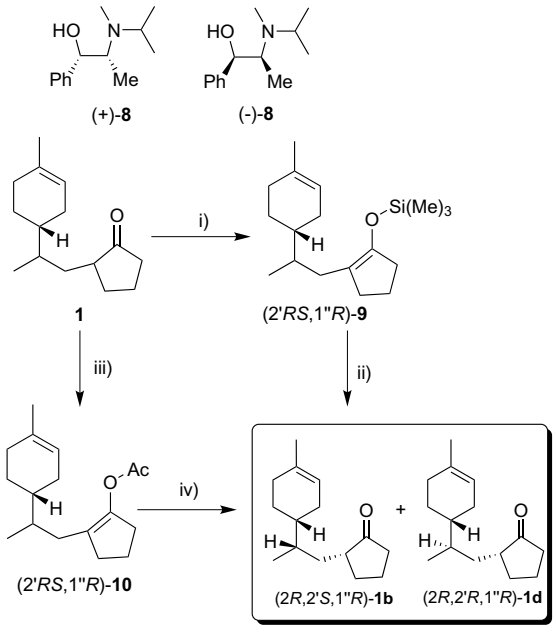


Figure 3. Selected region of ^{13}C NMR (100 MHz) spectra of **1** in $CDCl_3$: (a) *Nectaryl*®. (b) Pair of diastereoisomers **1b** and **1c**. (c) Diastereoisomer **1a** coming from the remaining alcohol **2a** of the enzymatic resolution of the less polar alcohols **2a** and **2b**, stereochemistry (2*S*′,2′*R*,1″*R*) known from an X-ray structure. (d) Diastereoisomer **1b** coming from the acetate **3b** of the enzymatic resolution of the less polar alcohols **2a** and **2b**. (e) Diastereoisomer **1c** coming from the remaining alcohol **2c** of the enzymatic resolution of the most polar alcohols **2c** and **2d**. (f) Diastereoisomer **1d** coming from the acetate **3d** of the enzymatic resolution of the most polar alcohols **2c** and **2d**.



Scheme 4. Reagents and conditions: (i) $Si(Me)_3Cl$, pyridine, NaI, MeCN; (ii) (a) BuLi, 0 °C; (b) 1.1 equiv (+)-**7** or (−)-**7**, see Table 2 for solvent, temp conditions, 0.1 equiv $Si(Me)_3Cl$; (iii) Ac_2O, cat. $HClO_4$, CCl_4; (iv) enzyme, *t*-butylmethylether, EtOH.

precipitated. Finally, we repeated the chiral protonation in THF in the presence of LiBr improving the de_{tot} up to 45%.

The enzymatic hydrolysis of the enolacetate (2′*RS*,1″*R*)-**9**, using EtOH as the proton source in *t*-BuOMe at room temperature, furnished **1** with low de_{tot}. The results are summarized in Table 2.[15] The lipase PS supported on ceramic gave de_{tot} in the direction of the less odorant stereoisomers. As in the case of entry 3 the selectivity was mismatching. Indeed, the enolacetate (2′*R*,1″*R*)-**10** was hydrolyzed to give **1** with −58% de, whereas (2′*R*,1″*R*)-**10** was hydrolyzed to give **1** with 34% de. The similar results were obtained with the enzyme Novazim.

3. Conclusion

The enzymatic acetylation proved to be a simple and efficient method of preparing all of the stereoisomers of *Nectaryl*®.

The olfactory results clearly show that the pleasant apricot and peach odour of *Nectaryl*® are strongly related to the (*R*) configuration of the stereocentre in α to the carbonyl group, indeed, the two diastereoisomers having such configuration are the two orders of magnitude more intense of those having opposite configuration. This difference

Table 2. Asymmetric protonation of lithium enolate with (+)-**8** or (−)-**8**, and asymmetric hydrolysis of enolacetate with enzymes

Entry	Reagents and conditions	Conv.[a] (%)	**1d** versus **1a**	**1b** versus **1c**	de$_t$[c] (%)
			de[b] (%)	de[b] (%)	
1	(+)-**7**, THF, −78 °C, 1 h	89	−33	−8.0	−21
2	(−)-**7**, THF, −78 °C, 1 h	92	31	50	40
3	(−)-**7**, Et_2O, LiBr, −50 °C, 1 h	74	−21	58	18
4	(−)-**7**, THF, LiBr, −50 °C, 1 h	70	44	46	45
5	Lipase-PS CII, *t*-BuOMe, EtOH, rt, 1 d	85	−58	34	−12
6	Novazim, *t*-BuOMe, EtOH, rt, 1 d	50	−33	24	−10

[a] The conversions are determined by GC.
[b] The de has been determined by integration of ^{13}C NMR signals of C(3′) assuming that the relaxation times of diastereoisomers are similar.
[c] The de$_t$ is the average of the de.

might be even greater, because all the stereoisomers prepared are not completely diastereomerically pure. Moreover, the stereochemistry at the other stereocentres does not contribute to the final odour perception. Attempts to prepare the best odorants by means of chiral protonation of the Li-enolate or the enzyme-mediated hydrolysis of the enolester gave the modest results. However, the enzymatic method seems to be the less promising, because all the enzymes tested have exhibited a mismatching selectivity.

4. Experimental

4.1. General methods

All the solvents and reagents were purchased by the suppliers and used without further purification. *Burkholderia cepacia* lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) was employed in this work. The THF and the Et_2O were distilled on $LiAlH_4$. GC/MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 mm). The following temperature program was employed: 60 °C (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). ^1H NMR spectra were recorded in $CDCl_3$ solutions, on a Bruker spectrometer; DMX (400 ^1H MHz), the ^{19}F spectra have been recorded on a Bruker spectrometer Avance 500 (500 ^1H MHz). The chemical shift scale was based on internal TMS. *J* values are in Hz. The optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates.

4.2. X-ray crystallographic data for 5a

$C_{22}H_{28}N_2O_6$, $M_w = 416.5$, monoclinic, space group $P2_1$, $Z = 2$, $a = 19.104(4)$, $b = 5.914(1)$, $c = 9.834(2)$ Å, $\beta = 91.940(5)°$, $V = 1110.4(2)$ Å^3, $D_x = 1.246$ g cm^{-3}. CCDC 671244 (for **5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

4.3. Synthesis of (+)-*Nectaryl*®

A mixture of cyclopentanone (33.6 g, 0.4 mol), $Mn(OAc)_2$ (0.1 g), $Co(Ac)_2$ (0.1 g) and (+)-limonene (5.4 g, 40 mmol) in AcOH (60 mL) was refluxed for 8 h and bubbled with air. The AcOH and cyclopentanone were evaporated under reduced pressure and the resulting mixture was diluted in Et_2O (200 mL), washed with $NaHCO_3$ (3 × 100 mL) and brine (1 × 100 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting liquid was distilled under reduced pressure to give **1** as a colourless liquid (6.3 g, 72%): 97% chemical purity by GC; $[\alpha]_D^{20} = +228$ (*c* 1.1, $CHCl_3$); for ^1H and ^{13}C NMR data, see the single stereoisomers; GC/MS: $t_r = 22.01$, 22.10, 22.30 min (1:1:2); for the *m*/*z*, see the single stereoisomers.

4.4. Reduction of *Nectaryl*®

To a solution of **1** (6.0 g, 27.0 mmol) in THF at −78 °C was added dropwise a solution of L-Selectride (27.0 mL, 1 M). After 3 h, the reaction mixture was quenched with a solution of satd NH_4Cl (100 mL), and diluted with Et_2O (100 mL). The organic phase was washed with brine (1 × 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil, which was submitted to column chromatography (hexane/AcOEt, 95:5) separation to give in order of elution: **2a** together with **2b** (2.4 g, 40%), and **2c** with **2d** (2.4 g, 40%).

Data for **2a** *and* **2b**: 97% chemical purity by GC; for ^1H and ^{13}C NMR data, see the single stereoisomers; GC/MS: $t_r = 21.98$, 22.02, 22.18 min, (48:48:4); for the *m*/*z* see the single stereoisomers.

Data for **2c** *and* **2d**: 96% chemical purity by GC; for ^1H and ^{13}C NMR data see the single stereoisomers; GC/MS: $t_r = 21.98$, 22.02, 22.18 min, (2:2:96); for the *m*/*z* see the single stereoisomers.

4.5. General procedure for the enzymatic resolution of alcohols 2a–d

To a suspension of the alcohol (1.2 g, 5.4 mmol), lipase PS (3 g), vinyl acetate (5 mL) and *t*-BuOMe (30 mL) were stirred at r.t. until the conversion reached ca. 40% (Checked by GC). The residue obtained by evaporation under reduced pressure of the filtered mixture was submitted to column chromatography (hexane/AcOEt, 9:1) for the separation of the acetate from the alcohol. The recovered alcohol was re-submitted to the same procedure.

4.5.1. Resolution of alcohols 2a and 2b. According to the general procedure, were obtained (1*R*,2*R*,2′*S*,1″*R*)-**3b** (0.53 g, 37%, de 92%) and (1*S*,2*S*,2′*R*,1″*R*)-**2a** (0.35 g, 25%, de 84).

Data for (1*R*,2*R*,2′*S*,1″*R*)-**3b**: 99% chemical purity by GC; $[\alpha]_D^{20} = +43.2$ (*c* 1.1, $CHCl_3$); ^{1}H NMR, $\delta = 5.38$ (m, 1H, CH=), 5.16 (t, $J = 5.5$, 2.0, 1H, H–C(1)), 2.1–1.2 (m, 19H), 0.84 (d, $J = 6.8$, 3H, H-(3′)); ^{13}C NMR $\delta = 170.8$, 134.0, 121.0, 77.3, 42.0, 38.5, 35.6, 33.4, 32.7, 31.0, 30.4, 27.6; 26.9, 23.4, 22.0, 21.2, 16.4. GC/MS: $t_r = 23.15$ min; *m*/*z*: 204 (M^+−60, 10), 148 (60), 121 (100). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.29; H, 10.59.

Data for (1*S*,2*S*,2′*R*,1″*R*)-**2a**: 99% chemical purity by GC; $[\alpha]_D^{20} = +82.8$ (*c* 0.9, $CHCl_3$); ^{1}H NMR, $\delta = 5.38$ (m, 1H, 1H, CH=), 4.12 (br t, 1H, H–C(1)), 2.19–1.16 (m, 19H), 0.89 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 133.8$, 121.0, 74.3, 43.5, 38.6, 35.7, 33.8, 32.2, 30.9, 29.4, 27.6; 25.1, 23.3, 21.7, 16.6. GC/MS: $t_r = 21.98$ min; *m*/*z*: 204 (M^+−18, 10), 148 (90), 121 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H 11.79. Found: C, 81.14; H, 11.69.

4.5.2. Resolution of alcohols 2c and 2d. According to the general procedure, were obtained (1*R*,2*R*,2′*R*,1″*R*)-**3d** (0.52 g, 36%, de 88%) and (1*S*,2*S*,2′*S*,1″*R*)-**2c** (0.36 g, 28%, de 82%).

Data for (1*R*,2*R*,2′*R*,1″*R*)-**3d**: 99% chemical purity by GC; $[\alpha]_D^{20} = +52.1$ (*c* 1.3, $CHCl_3$); ^{1}H NMR, $\delta = 5.39$ (m, 1H, CH=), 5.16 (dt, $J = 5.5$, 2.0, 1H, H–C(1)), 2.1–1.2 (m, 19H), 0.84 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta =$ 171.1, 134.3, 121.4, 79.0 42.4, 39.3, 35.9, 33.5, 32.8, 31.2, 29.7, 29.6; 25.7, 23.7, 22.3, 21.5, 16.5. GC/MS: $t_r = 23.15$ min; *m*/*z*: 204 (M^+−60, 20), 148 (60), 121 (100). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.23; H, 10.69.

Data for (1*S*,2*S*,2′*S*,1″*R*)-**2c**: 99% chemical purity by GC; $[\alpha]_D^{20} = +62.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR, $\delta = 5.51$ (br t, 1H, H–C(1)), 5.23 (m, 1H, CH=), 2.19–1.16 (m, 20H), 0.89 (d, $J = 6.8$, 3H, H–C(3′)); ^{13}C NMR $\delta = 133.8$, 121.0, 74.3, 43.5, 38.6, 35.7, 33.8, 32.2, 30.9, 29.4, 27.6; 25.1, 23.3, 21.7, 16.6. GC/MS: $t_r = 22.18$ min; *m*/*z*: 204 (M^+−18, 15), 148 (90), 121 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.04; H, 11.63.

4.6. General procedure for the hydrolysis of acetates 3b and 3d

To a solution of acetate (0.5 g, 3.0 mmol) in EtOH (10 mL) was added KOH (0.17 g, 6.0 mmol). After 5 h, the reaction mixture was concentrated under reduced pressure and diluted in Et_2O (30 mL). Then, the organic phase was washed with brine (1 × 20 mL) and the solvent was removed under reduced pressure to give the alcohol as a colourless oil.

4.6.1. (1*R*,2*R*,2′*S*,1″*R*)-2b. According to the general procedure, (1*R*,2*R*,2′*S*,1″*R*)-**2b** was obtained (0.36 g, 92%): 99% chemical purity by GC; $[\alpha]_D^{20} = +42.2$ (*c* 1.1, $CHCl_3$); ^{1}H NMR, $\delta = 5.51$ (br t, 1H, H–C(1)), 5.23 (m, 1H, CH=), 2.19–1.16 (m, 20H), 0.89 (d, $J = 6.8$, 3H, H–C(3′)); ^{13}C NMR $\delta = 133.8$, 121.0, 74.3, 43.5, 38.6, 35.7, 33.8, 32.2, 30.9, 29.4, 27.6; 25.1, 23.3, 21.7, 16.6. GC/MS: $t_r = 22.02$ min; *m*/*z*: 204 (M^+−18, 15), 148 (90), 121 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.04; H, 11.63.

4.6.2. (1*R*,2*R*,2′*R*,1″*R*)-2d. According to the general procedure, was obtained (1*R*,2*R*,2′*R*,1″*R*)-**2d** (0.37 g, 94%): 99% chemical purity by GC; $[\alpha]_D^{20} = +69.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR, $\delta = 5.51$ (br t, 1H, H–C(1)), 5.23 (m, 1H, CH=), 2.19–1.16 (m, 20H), 0.89 (d, $J = 6.8$, 3H, H–C(3′)); ^{13}C NMR $\delta = 133.8$, 121.0, 74.3, 43.5, 38.6, 35.7, 33.8, 32.2, 30.9, 29.4, 27.6; 25.1, 23.3, 21.7, 16.6. GC/MS: $t_r = 22.18$ min; 204 (M^+−18, 15), 148 (90), 121 (100). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.04; H, 11.63.

4.7. General procedure for the oxidation of alcohols 2a–d

To an ice-cold solution of alcohol (0.3 g, 1.35 mmol) in CH_2Cl_2 (10 mL) was added DMP (0.75 g, 1.76 mmol) and stirred at rt until no alcohol was indicated by TLC (2 h). The reaction mixture was then poured in a satd solution of $Na_2S_2O_3$ (30 mL) and after 15 min was extracted with Et_2O (2 × 50 mL). The combined organic phase was washed with a saturated solution of $NaHCO_3$ (1 × 50 mL) and brine solution (1 × 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a liquid residue, which was submitted to the column chromatography purification (hexane/ AcOEt, 95:5) to give the ketone as a liquid. The ketone was then purified by bulb-to-bulb distillation (140–150 °C, 0.15 mm Hg).

4.7.1. Compound (2*S*,2′*R*,1″*R*)-1a. According to the general procedure, the oxidation of alcohol **2a** gave the ketone **1a** (0.28 g, 92% after column chromatography, de 81% by ^{13}C NMR) as a white solid: 99% chemical purity by GC; $[\alpha]_D^{20} = -31.4$ (*c* 1.3, $CHCl_3$); ^{1}H NMR, $\delta = 5.38$ (m, 1H, CH=), 2.4–1.4 (m, 18H), 1.23 (m, 1H), 1.08 (ddd, $J = 7.1$, 8.6, 14, 1H), 0.84 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 221.5$, 134.1, 121.1, 47.5, 37.9, 37.4, 35.1, 34.6, 30.9, 30.7, 29.8, 24.3; 23.4, 20.7, 16.5. GC/MS: $t_r = 22.01$ min; *m*/*z*: 220 (M^+, 12), 202 (50), 121 (100). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.59; H, 10.99.

4.7.2. Compound (2*R*,2′*S*,1″*R*)-1b. According to the general procedure, the oxidation of alcohol **2b** gave ketone **1b** (0.28 g, 92% after column chromatography, de 89% by ^{13}C NMR) as a colourless liquid: 99% chemical purity by GC; $[\alpha]_D^{20} = +197.4$ (*c* 0.8, $CHCl_3$); ^{1}H NMR, $\delta = 5.30$ (m, 1H, CH=), 2.3–1.2 (m, 19H), 0.99 (ddd, $J = 7.1$, 8.6, 14, 1H), 0.78 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 221.4$, 133.9, 120.9, 47.3, 37.9, 37.1, 35.4, 34.8, 31.1, 30.7, 27.6, 26.4; 23.4, 20.7, 16.1. GC/MS: $t_r = 22.10$ min; *m*/*z*: 220 (M^+, 10), 202 (60), 121 (100). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.69; H, 10.90.

4.7.3. (2*S*,2′*S*,1″*R*)-1c. According to the general procedure, the oxidation of alcohol **2c** gave ketone **1c** (0.28 g,

92% after column chromatography, de 80% by ^{13}C NMR) as a colourless liquid: 99% chemical purity by GC; $[\alpha]_D^{20} = -71.7$ (*c* 1.4, $CHCl_3$); ^1H NMR, $\delta = 5.37$ (m, 1H, CH=), 2.4–1.2 (m, 20H), 0.85 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 221.9$, 134.0, 120.8, 47.3, 39.1, 38.1, 35.2, 34.4, 30.9, 29.9, 27.8, 26.8; 23.4, 20.7, 15.3. GC/MS: $t_r = 22.30$ min; *m*/*z*: 220 (M^+, 8), 202 (60), 121 (100). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.73; H, 10.88.

4.7.4. (2*R*,2′*R*,1″*R*)-1d. According to the general procedure, the oxidation of alcohol **2d** gave ketone **1d** (0.28 g, 92% after column chromatography, de 86% by ^{13}C NMR) as a colourless liquid: 99% chemical purity by GC; $[\alpha]_D^{20} = +238.2$ (*c* 1.1, $CHCl_3$); ^1H NMR, $\delta = 5.36$ (m, 1H, CH=), 2.31 (m, 1H), 2.23 (m, 1H), 2.16–1.89 (m, 6H), 1.83–1.65 (m, 4H), 1.63 (s, 3H, CH_3C=), 1.50–1.35 (m, 3H), 1.30–1.20 (m, 2H), 0.87 (d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 221.9$, 133.9, 120.9, 47.4, 39.2, 38.1, 35.1, 34.1, 30.8, 29.8, 29.2, 25.7, 23.4, 20.7, 15.5. GC/MS: $t_r = 22.30$ min; *m*/*z*: 220 (M^+, 8), 202 (60), 121 (100). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.69; H, 10.90.

4.8. (1*S*,2*S*)-2-[(*R*)-2-[(*R*)-4-Methylcyclohex-3-enyl]propyl]cyclopentyl 3,5-dinitrobenzoate-(1*S*,2*S*,2′*R*,1″*R*)-5

To a stirred solution of **2a** (0.5 g, 2.3 mmol) in CH_2Cl_2 (5 mL) and pyridine (1 mL) was added portionwise the 3,5-dinitrobenzoylchloride (0.6 g, 2.6 mmol). After 4 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with an aqueous solution of HCl (0.1 M, 2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a yellow oil, which was purified on a pad of silica gel, using hexane/AcOEt (8:2) affording (1*S*,2*S*,2′*R*,1″*R*)-**5** as a yellow-white powder (0.86 g, 90%): 99% chemical purity by GC; $[\alpha]_D^{20} = +114.8$ (*c* 1.0, $CHCl_3$); ^1H NMR, $\delta = 9.20$, (t, $J = 2.0$, 1H, ArH), 9.10 (d, $J = 2.0$, 2H, ArH), 5.51 (br t, 1H, H–C(1)), 5.23 (m, 1H, CH=), 2.19–1.16 (m, 20H), 0.89 (d, $J = 6.8$, 3H, H–C(3′)); ^{13}C NMR $\delta = 162.1$, 148.7, 134.6, 134.0, 129.2, 122.2, 120.7, 80.8, 42.6, 38.6, 35.5, 33.4, 32.8, 30.7, 30.6, 29.2, 25.3, 23.3, 22.0, 16.7; Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78. Found: C, 63.45; H, 6.81.

4.9. (*R*)-4-((*R*)-1-Iodopropan-2-yl)-1-methylcyclohex-1-ene (2*R*,4′*R*)-7

To an ice-cold solution of (2*R*,1′*R*)-**6** (1.3 g, 8.4 mmol) in pyridine (10 mL) was added TsCl (1.9 g, 10.0 mmol). After 4 h, the reaction mixture was concentrated under reduced pressure, diluted in Et_2O (50 mL), and washed with a solution of $NaHCO_3$ (0.1 M, 1 × 50 mL), HCl dil. (1 M, 2 × 50 mL) and brine (1 × 50 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the tosyl derivate in sufficient purity. A mixture of the tosyl derivate and NaI (5 g) in acetone (50 mL) was stirred at reflux for 5 h. Then, the solvent was concentrated under reduced pressure, diluted with Et_2O (850 mL), washed with dil HCl (1 M, 50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue, which after bulb-to-bulb distillation furnished (2*R*,4′*R*)-**7** (1.75 g, 79%): 99% chemical purity by GC; $[\alpha]_D^{20} = +37.5$ (*c* 2.0, $CHCl_3$); ^1H NMR, $\delta = 5.36$, (m, 1H, H–C(2′)), 3.25 (AB, 2H, CH_2I), 2.1 (m, 3H), 1.8–1.7 (m, 2H), 1.64 (s, CH_3C=), 1.54 (m, 1H), 1.42 (m, 1H), 1.28 (m, 1H), 0.99 (d, $J = 6.6$, 3H, H–C(3′)); ^{13}C NMR $\delta = 137.9$, 120.3, 39.2, 38.0, 30.4, 27.7, 26.9, 23.3, 17.4, 16.0. GC/MS: $t_r = 17.33$ min; *m*/*z*: 264 (M, 10), 137 (20), 95 (100). Anal. Calcd for $C_{10}H_{17}I$: C, 45.47; H, 6.49. Found: C, 45.45; H, 6.51.

4.10. Preparation of (2*R*,2′*S*,1″*R*)-1b and (2*S*,2′*S*,1″*R*)-1c

To an ice-cold solution of DIPA (0.5 g, 5.0 mmol) in THF (10 mL) under a nitrogen atmosphere was added a solution of BuLi in hexane (2.0 mL, 2.5 M). After 1 h, the temperature was lowered to −78 °C and was added dropwise a solution of cyclopentanone (0.35 g, 4.1 mmol) in THF (2 mL). After 1 h, the solution was warmed to −30 °C and DMPU and a solution of **6** (1.3 g, 5.0 mmol) were added. After 1 h, the reaction mixture was quenched with satd solution of NH_4Cl (20 mL) and washed with Et_2O (2 × 50 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (hexane/AcOEt, 9:1) to give a liquid. Then, the liquid was purified by bulb-to-bulb distillation (140–150 °C, 0.15 mm Hg) to give **1b** and **1c** (0.23 g, 26%): 95% chemical purity by GC. For ^1H and ^{13}C NMR data, see the single stereoisomers.

4.11. Trimethyl(2-((*R*,*S*)-2-((*R*)-4-methylcyclohex-3-enyl)propyl)cyclopent-1-enyloxy)silane (2′*R S*,1′*R*)-9

To a stirred and ice-cold mixture of **1** (5.0 g, 22.7 mmol), NaI (2.2 g, 28.3 mmol) and pyridine (2.23 g, 28.3 mmol) in MeCN (30 mL), was added dropwise TMSiCl (3.05 g, 28.3 mmol). After 8 h, the reaction mixture was poured into an ice-cold solution of satd NH_4Cl (20 mL) and washed with hexane (2 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow liquid which was distilled (150–170 °C, 0.5 mmHg) to give (2′*RS*,1′*R*)-**9** (6.0 g, 90%) as a colourless liquid: 95% chemical purity by GC (1% of **1** and 4% of the other regioisomers of **9**); ^1H NMR, $\delta = 5.37$ (m, 1H, CH=), 2.4–1.2 (m, 19H), 0.79 (d+d, $J = 6.8$, 3H, H–(C3′)), 0.17 (s+s, 9H); ^{13}C NMR $\delta = 147.2$, 147.1, 134.0, 133.8, 121.3, 116.2, 53.3, 38.3, 38.2, 35.8, 35.6, 33.7, 31.5, 31.2, 31.1, 31.0, 29.8, 27.5, 27.4, 25.1, 23.4, 20.0, 16.3, 16.0, 0.69. GC/MS: $t_r =$ 22.52 min; *m*/*z*: 292 (M^+, 10), 202 (15), 169 (100). Anal. Calcd for $C_{18}H_{32}OSi$: C, 73.90; H, 11.03. Found: C, 73.83; H, 10.88.

4.12. 2-((*R*,*S*)-2-((R)-4-Methylcyclohex-3-enyl)propyl)-cyclopent-1-enyl acetate (2*RS*,1′*R*)-10

To a stirred and ice-cold solution of **1** (3.0 g, 13.6 mmol) and acetic anhydride (3.0 g, 27.2 mmol) in CCl_4 (10 mL)

was added a cat. amount of $HClO_4$. After 3 h, the reaction mixture was quenched with ice (50 g), and washed with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow liquid, which was purified by column chromatography (hexane/AcOEt, 8:2) to give (2′*RS*,1′*R*)-**10** as a slightly yellow oil: 95% chemical purity by GC; ^{1}H NMR, $\delta = 5.37$ (m, 1H, CH=), 2.47 (br t, 2H), 2.3–1.2 (m, 20H), 0.79 (d+d, $J = 6.8$, 3H, H–(C3′)); ^{13}C NMR $\delta = 168.4$, 145.0, 144.9, 137.0, 133.6, 125.8, 120.8, 120.7, 38.2, 37.9, 35.5, 35.1, 31.4, 31.3, 31.2, 31.0, 30.8, 30.7, 29.6, 27.5, 27.4, 24.9, 23.2, 20.5, 19.9, 16.0, 16.0, 15.8. GC/MS: $t_r = 22.92$ min; *m*/*z*: 262 (M^+, 1), 220 (15), 202 (100). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.93; H, 9.79.

4.13. Typical procedure for chemo enantioselective protonation of 9

To a stirred and ice-cold solution of **9** (0.7 g, 2.37 mmol) in THF (5 mL) was added dropwise BuLi (2.5 M, 1.05 mL, 2.6 mmol) under a nitrogen atmosphere. After 1 h, the reaction mixture was brought at −78 °C, and was added a solution of (−)-**7** (0.56 g, 2.6 mmol), in THF (1 mL). After 1 h, TMSiCl (0.3 g) was added and the reaction mixture was left to reach 0 °C. Then, it was quenched with an ice-cold solution of satd NH_4Cl (20 mL) and washed with hexane (2 × 30 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to give a liquid, which was purified by column chromatography (hexane/AcOEt, 95:5, 0.1% NEt_3) to give a diastereomeric enriched mixture of **1** (0.45 g, 79%) and recovered **9**. The conversion was analyzed by GC. The de (see Table 2) was determined by ^{13}C NMR on the reaction mixture.

4.14. General procedure for enzymatic enantioselective protonation of 10

A mixture of **10** (0.18 g, 0.69), enzyme (20 mg), in *t*-BuOMe was added to EtOH (400 mL, 6.4 mmol). After 1 day, the mixture was filtered, and the filtrate was concentrated under reduced pressure to give a mixture of **1** and **9**. The conversion was analyzed by GC. The de was determined by ^{13}C NMR on the not purified compound (see Table 2).

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