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Synthesis of the (1*S*,2*S*)- and (1*R*,2*S*)-stereoisomers of the respective *E*- and *Z*-isomers of ethyl 4-[(2-hydroxycyclohexyl)methyl]phenoxy-3-methyl-2-butenoate using yeast whole cell bioreduction of the parent ketones

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Abstract—*Saccharomyces cerevisiae*, strain DBM 2115, was successfully employed in the reduction of the separated *Z*- and *E*-isomers of ethyl 4-[(2-oxocyclohexyl)methyl]phenoxy-3-methyl-2-butenoates **1** and **2**, in order to prepare the (1*S*,2*S*)- and (1*R*,2*S*)-enantiomers of the corresponding ethyl 4-[(2-hydroxycyclohexyl)methyl]phenoxy-3-methyl-2-butenoates **3**–**6**. The products were obtained with the required absolute configuration: (1*S*,2*S*)-**3** (ee = 98%; yield 48%), (1*R*,2*S*)-**4** (ee = >99%; yield 45%), (1*S*,2*S*)-**5** (ee = 98.5%; yield 47%), and (1*R*,2*S*)-**6** (ee = >99%; chemical yield 44%).

1. Introduction

We have previously studied reductions of different prochiral substrates bearing ketone functionalities in their molecules to the corresponding chiral alcohols, using yeast whole cell bioreactors.[1] Enzymes and microorganisms represent valuable chiral biocatalysts in this synthesis, because they usually give products in high enantiomeric excess.[2] When compared with the use of chiral reagents, most enzymic or microorganism-mediated reductions are less difficult processes. There are some limitations in the application of microbial whole cell systems: the stereoselectivity of the reduction process can be lower in comparison to a process in which a pure enzyme is used due to the existence of different types of alcohol dehydrogenases (reductases; EC 1.1.1.1) showing different stereoselectivities. To employ whole cell systems for the transformation of prochiral organic molecules into non-racemic chiral products, we have developed easy and convenient procedures, which have enabled us to afford chiral products in high chemical yields and enantiomeric purities.[1]

Herein, we have employed the cells of *Saccharomyces cerevisiae*, strain DBM 2115, in the reduction of the separated *E*- and *Z*-isomers of ethyl 4-[(2-oxocyclohexyl)methyl]phenoxy-3-methyl-2-butenoates **1** and **2** to the corresponding (1*S*,2*S*)- and (1*R*,2*S*)-stereoisomers of ethyl 4-[(2-hydroxycyclohexyl)methyl]phenoxy-3-methyl-2-butenoates **3**–**6** (Scheme 1).

Compounds **1** and **2** were first synthesized in the early 1980's,[3] at which time only simple ^{1}H NMR spectra on a 60 or 100 MHz instrument could be taken. To update these data under the same conditions (cf. Section 4), as for products **3**–**6** herein, Table 1 shows newly recorded ^{1}H and ^{13}C NMR data of **1** and **2** as well. The racemic forms of all the above-mentioned compounds **1**–**6** act as hormonomimetic compounds, displaying an analogous mode of action on insects as natural insect juvenile hormones, that is they affect insect morphology and reproduction, and can be used as environmentally safe insect pest management agents. To proceed with this research, individual stereoisomers of ethyl 4-[(2-hydroxycyclohexyl)methyl]phenoxy-3-methyl-2-butenoates have been requested.

A number of experiments[1] with different strains of *S. cerevisiae* and *Geotrichum candidum* led to the conclusion that the preferred course of the reduction mediated by the tested strains of these two yeasts led to a synthesis

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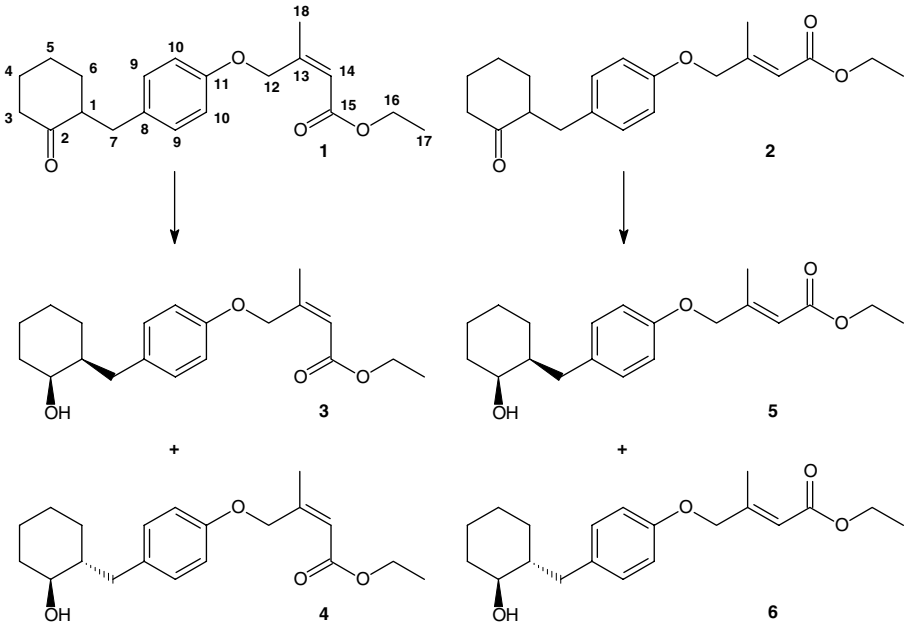

Scheme 1. Reaction pathways. Numbering of the carbon atoms in the structure **1** is introduced for the purpose of assignment of the ^{1}H and ^{13}C NMR signals in Table 1.

of 1-substituted (2*S*)-cycloalkan-2-ol derivatives.[1] These earlier findings have been the basis for predicting the absolute configuration of the products to be obtained through the studied enzymic process.

2. Results and discussion

The used strain DBM 2115 of *S. cerevisiae* reduced the given substrates **1** and **2** with high enantioselectivity and very good chemical yields (details are given in Section 4). Prochiral ketones **1** and **2** afforded diastereoisomeric *cis*- and *trans*-2-substituted cyclohexanols **3**–**6** (Scheme 1). As the products are diastereoisomers, they could be separated by simple column chromatography on silica gel, that is no chiral medium was necessary, and all products **3**–**6** were obtained pure.

To assign their absolute configuration, alcohols **3**–**6** were converted into their esters **7**–**14** (Fig. 1) with (*R*)-(+)- or (*S*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA, Mosher's acid), using (*S*)-(+)- and (*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPCl, Mosher's chloride).[4] Each enantiomer of the Mosher's acid forms diastereoisomeric mixtures of esters with chiral alcohols, while the diastereoisomers of the esters **7**–**14** can be identified on the basis of several signals in their ^{1}H and ^{19}F NMR spectra[5] (Table 2).

The enantiomeric purities and the absolute configurations of alcohols **3**–**6** were determined by this approach. Assignment of the absolute configuration at the C(2) stereogenic center was based on the differences in the chemical shifts of the signals of both hydrogen atoms of the CH_2–Ar (benzyl) group, which are not equivalent due to their chiral environment. A down-field shift of the signals of benzyl hydrogen atoms in the ^{1}H NMR spectra of the diastereoisomeric esters **7**–**14**, when comparing the esters derived from (*R*)-(+)-MTPA **7**, **9**, **11**, and **13** with the esters derived from (*S*)-(−)-MTPA **8**, **10**, **12**, and **14**, was consistent only with the (*S*)-absolute configuration at the C(1) stereogenic center of **3**–**6**.[5] During this study, we observed that the signals of the hydrogen atom at the C(2) carbon center behaved in an opposite fashion. The evaluation of the ^{19}F NMR data of the diastereoisomeric esters **7**–**14** resulted in the same conclusion. A down-field shift of the signal of the CF_3 group in the (*R*)-MTPA esters **7**, **9**, **11**, and **13** in comparison with the same shift observed in the (*S*)-MTPA esters **8**, **10**, **12**, and **14** is in agreement with the expected displacement of the CF_3 group from the eclipsed arrangement with the carbonyl group in consequence of a steric interaction of the bulkier groups, that is of the phenyl group of the MTPA part of esters **7**–**14**, and of the benzyl substituent at C(1) of the alcoholic part of esters **7**–**14**. The selected data are given in Table 2.

The chromatographic behavior of alcohols **3**–**6**, using a chiral HPLC Nucleodex β-OH column, filled with a chiral β-cyclodextrine-based stationary phase, was studied to confirm the above-described structure assignment. The results obtained from the chiral HPLC analysis were in good agreement with those obtained by analyzing diastereoisomeric esters **7**–**14** of the studied compounds **3**–**6**.

3. Conclusion

The selected strain DBM 2115 of *S. cerevisiae* reduced the parent isomeric compounds **1** and **2** to the requested enantiomers **3**–**6** of the product in high enantioselectivity (ee 98 to >99%), and with very good chemical yields (44–48%).

Table 1. The ^{1}H and ^{13}C NMR data of the starting substrates **1** and **2**, and of the products **3**–**6**[a]

Atom	^{1}H NMR[b]/^{13}C NMR[c] signals					
	1	**2**	**3**[d]	**4**[d]	**5**	**6**
1	2.50 (ddddd; 1.3, 4.9, 5.6, 8.7, 11.8)[b]/52.64 (d)[c]	2.50 (dddt; 1.3, 5.3, 5.3, 8.5, 11.9)[b]/52.62 (d)[c]	1.65 (m)[b]/43.66 (d)[c]	1.48 (m)[b]/47.09 (d)[c]	1.62 (m)[b]/43.64 (d)[c]	1.46 (m)[b]/47.05 (d)[c]
2	—[b]/212.67 (s)[c]	—[b]/212.56 (s)[c]	3.78 (dt; 2.6, 2.6, 4.5)[b]/68.50 (d)[c]	3.28 (dt; 4.2, 9.5, 9.5)[b]/74.51 (d)[c]	3.78 (dt; 2.1, 2.1, 4.5)[b]/68.48 (d)[c]	3.28 (dt; 4.4, 9.8, 9.8)[b]/74.47 (d)[c]
3	2.32 (dddd; 1.3, 6.0, 12.8, 13.6) and 2.42 (dddd; 1.7, 3.4, 4.3, 13.6)[b]/42.14 (t)[c]	2.32 (dddd; 1.3, 6.0, 12.4, 13.5) and 2.44 (dddd; 1.8, 3.4, 4.5, 13.5)[b]/42.15 (t)[c]	1.47 (m) and 1.76 (m)[b]/33.27 (t)[c]	1.26 (m) and 1.97 (m)[b]/35.81 (t)[c]	1.45 (m) and 1.77 (m)[b]/33.28 (t)[c]	1.26 (m) and 1.98 (m)[b]/35.81 (t)[c]
4	1.53–1.73 (m) and 1.83 (m)[b]/25.05 (t)[c]	1.53–1.73 (m) and 1.83 (m)[b]/25.04 (t)[c]	1.48 (m) and 1.59 (m)[b]/20.35 (t)[c]	1.08 (m) and 1.58 (m)[b]/25.45 (t)[c]	1.45 (m) and 1.57 (m)[b]/20.33 (t)[c]	1.09 (m) and 1.58 (m)[b]/25.42 (t)[c]
5	1.53–1.73 (m)[b]/28.03 (t)[c]	1.53–1.73 (m)[b]/28.03 (t)[c]	1.24 (m) and 1.70 (m)[b]/25.31 (t)[c]	1.24 (m) and 1.70 (m)[b]/24.90 (t)[c]	1.23 (m) and 1.68 (m)[b]/25.29 (t)[c]	1.24 (m) and 1.71 (m)[b]/24.88 (t)[c]
6	1.53–1.73 (m) and 1.98–2.09 (m)[b]/33.33 (t)[c]	1.53–1.73 (m) and 1.99–2.05 (m)[b]/33.40 (t)[c]	1.42 (m)[b]/26.37 (t)[c]	1.62 (m) and 0.89 (m)[b]/30.01 (t)[c]	1.43 (m)[b]/26.37 (t)[c]	1.63 (m) and 0.89 (m)[b]/29.96 (t)[c]
7	2.36 (dd; 8.7, 14.0) and 3.15 (dd; 4.9, 14.0)[b]/34.54 (t)[c]	2.37 (dd; 8.5, 14.0) and 3.15 (dd; 5.1, 14.0)[b]/34.57 (t)[c]	2.48 (dd; 7.6, 13.6) and 2.65 (dd; 7.6, 13.6)[b]/37.76 (t)[c]	2.32 (dd; 8.9, 13.5) and 3.06 (dd; 4.2, 13.5)[b]/38.08 (t)[c]	2.48 (dd; 7.6, 13.6) and 2.65 (dd; 7.6, 13.6)[b]/37.76 (t)[c]	2.33 (dd; 9.0, 13.5) and 3.08 (dd; 4.0, 13.5)[b]/38.08 (t)[c]
8	—[b]/132.60 (s)[c]	—[b]/133.10 (s)[c]	—[b]/133.29 (s)[c]	—[b]/132.96 (s)[c]	—[b]/133.77 (s)[c]	—[b]/133.40 (s)[c]
9	7.05 (m)[b]/130.07 (d)[c]	7.07 (m)[b]/130.12 (d)[c]	7.08 (m)[b]/130.02 (d)[c]	7.08 (m)[b]/130.32 (d)[c]	7.08 (m)[b]/130.07 (d)[c]	7.09 (m)[b]/130.35 (d)[c]
10	6.84 (m)[b]/114.37 (d)[c]	6.81 (m)[b]/114.62 (d)[c]	6.84 (m)[b]/114.35 (d)[c]	6.85 (m)[b]/117.40 (d)[c]	6.84 (m)[b]/114.58 (d)[c]	6.82 (m)[b]/114.48 (d)[c]
11	—[b]/156.28 (s)[c]	—[b]/156.56 (s)[c]	—[b]/156.35 (s)[c]	—[b]/156.35 (s)[c]	—[b]/156.43 (s)[c]	—[b]/156.42 (s)[c]
12	5.17 (dq; 0.8, 0.8, 0.8, 1.8)[b]/67.21 (t)[c]	4.47 (dq; 0.7, 0.7, 0.7, 1.7)[b]/71.78 (t)[c]	5.17 (dq; 0.8, 0.8, 0.8, 1.8)[b]/67.24 (t)[c]	5.17 (dq; 0.8, 0.8, 0.8, 1.8)[b]/67.24 (t)[c]	4.47 (dq; 0.6, 0.6, 0.6, 1.7)[b]/71.80 (t)[c]	4.47 (dq; 0.6, 0.6, 0.6, 1.4)[b]/71.73 (t)[c]
13	—[b]/156.85 (s)[c]	—[b]/152.90 (s)[c]	—[b]/156.73 (s)[c]	—[b]/156.77 (s)[c]	—[b]/152.98 (s)[c]	—[b]/153.01 (s)[c]
14	5.82 (m)[b]/117.42 (d)[c]	6.05 (m)[b]/115.72 (d)[c]	5.82 (m)[b]/117.40 (d)[c]	5.82 (m)[b]/117.40 (d)[c]	6.06 (m)[b]/115.70 (d)[c]	6.06 (m)[b]/115.63 (d)[c]
15	—[b]/165.92 (s)[c]	—[b]/166.51 (s)[c]	—[b]/165.93 (s)[c]	—[b]/165.94 (s)[c]	—[b]/166.54 (s)[c]	—[b]/166.56 (s)[c]
16	4.17 (q; 7.1)[b]/59.97 (t)[c]	4.17 (q; 7.1)[b]/59.81 (t)[c]	4.17 (q; 7.1)[b]/59.97 (t)[c]	4.17 (q; 7.1)[b]/59.97 (t)[c]	4.18 (q; 7.1)[b]/59.81 (t)[c]	4.18 (q; 7.1)[b]/59.82 (t)[c]
17	1.29 (t; 7.1)[b]/14.27 (q)[c]	1.29 (t; 7.1)[b]/14.28 (q)[c]	1.29 (t; 7.1)[b]/14.28 (q)[c]	1.29 (t; 7.1)[b]/14.28 (q)[c]	1.29 (t; 7.1)[b]/14.28 (q)[c]	1.29 (t; 7.1)[b]/14.27 (q)[c]
18	2.01 (dt; 0.8, 0.8, 1.5)[b]/21.31 (q)[c]	2.19 (dt; 0.7, 0.7, 1.4)[b]/15.66 (q)[c]	2.02 (dt; 0.8, 0.8, 1.5)[b]/21.32 (q)[c]	2.02 (dt; 0.8, 0.8, 1.5)[b]/21.33 (q)[c]	2.19 (dt; 0.6, 0.6, 1.4)[b]/15.67 (q)[c]	2.20 (br d; 1.4)[b]/15.68 (q)[c]

[a] See Section 4.1 for experimental details.
[b] ^{1}H NMR signal (type of multiplicity; coupling constants, if applicable).
[c] ^{13}C NMR signal (type of multiplicity).
[d] Data proved by gHSQC experiment[6] (for details, see Section 4.1).

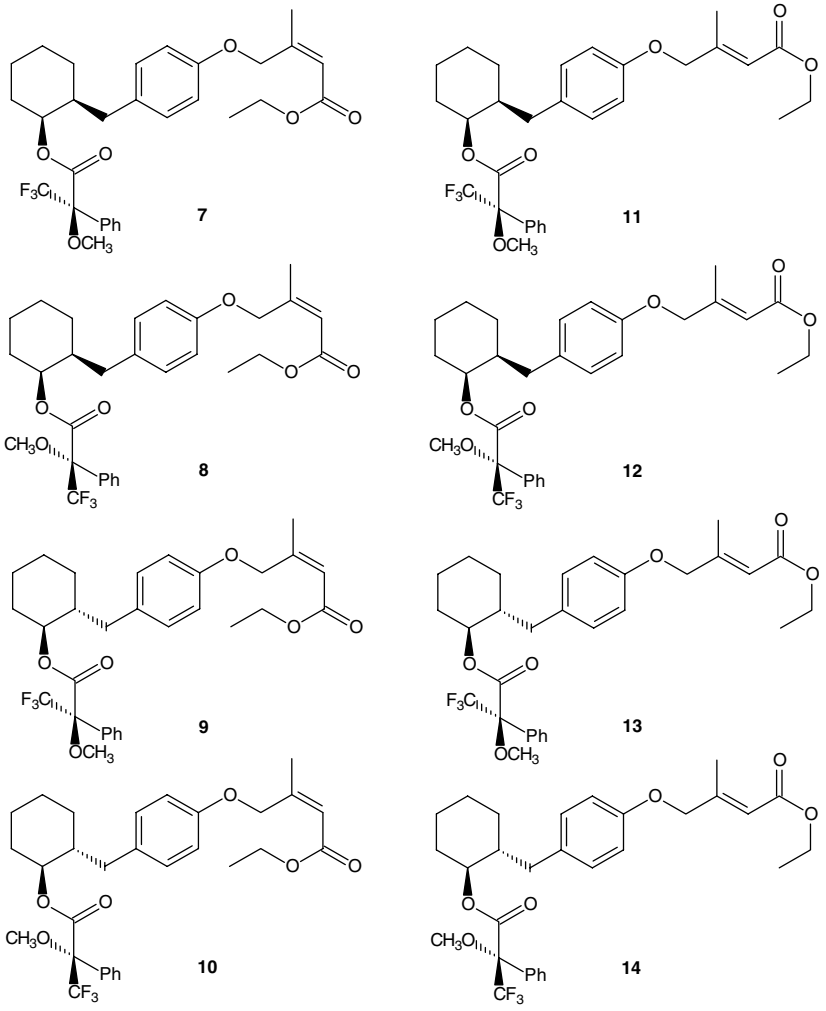

Figure 1. Structures of the MTPA esters **7**–**14**.

Table 2. Selected signals of MTPA esters **7**–**14** in ^{1}H and ^{19}F NMR spectra

MTPA ester (major)	Source MTPA (AC)[a]	^{1}H NMR									^{19}F NMR	Chiral product (AC)[a]
		*H*CH-C(1)	HC*H*-C(1)	*H*-C(2)	*H* (Ar)	*H* (Ar)	OCH_2C=C	CH_3C=C	C=C*H*	OCH_3 (MTPA)	CF_3	
7	*R*	2.237	2.448	5.188	6.810	6.902	5.160	2.014	5.818	3.604	−70.954	**3**
8	*S*	2.326	2.505	5.154	6.825	6.930	5.165	2.016	5.819	3.571	−71.072	(1*S*,2*S*)
9	*R*	2.067	2.696	4.798	6.798	6.865	5.154	2.012	5.815	3.604	−71.269	**4**
10	*S*	2.167	2.881	4.783	6.832	6.958	5.167	2.016	5.818	3.578	−71.354	(1*R*,2*S*)
11	*R*	2.246	2.454	5.189	6.785	6.919	4.462	2.195	6.055	3.591	−70.906	**5**
12	*S*	2.335	2.508	5.153	6.798	6.942	4.466	2.195	6.057	3.573	−71.072	(1*S*,2*S*)
13	*R*	2.080	2.703	4.801	6.772	6.883	4.457	2.190	6.051	3.602	−71.248	**6**
14	*S*	2.182	2.886	4.785	6.806	6.976	4.469	2.195	6.056	3.578	−71.354	(1*R*,2*S*)

[a] AC = absolute configuration.

4. Experimental

4.1. General

A Unimax 1010 incubator (Heidolph, Germany) equipped with controlled heating and shaking plate for up to five shake-flasks (250 ml size) was used for performing the reactions mediated by yeasts. The ^{1}H NMR and the ^{13}C NMR spectra were recorded on a Bruker AVANCE spectrometer (in a FT mode) at respectively, 500.13 and 125.8 MHz in deuteriochloroform using tetramethylsilane (δ 0.0 for ^{1}H) and central line of signal of the solvent (δ 77.0 for ^{13}C) as internal reference. The ^{19}F NMR spectra were recorded on a

Varian UNITY 500 spectrometer at 470.3 MHz in deuteriochloroform using hexafluorobenzene as the external reference (δ −162.9). For unambiguous assignment of the signals, the gHSQC experiments were performed, using the standard pulse program delivered by the producer of the spectrometer. IR spectra were recorded in chloroform on a Bruker IFS 88 instrument. MS (FAB) were recorded on a VG analytical 70–250 SE mass spectrometer, ZAB-EQ (BEQQ configuration) at 70 eV. Optical rotations were measured on an Autopol IV polarimeter (Rudolph Research Analytical, USA). Preparative column chromatography was performed on a silica gel type 60 (particle size 0.04–0.063 mm; Fluka, Switzerland). TLC was performed on aluminum sheets precoated with silica gel 60 (Merck, Germany). Analytical HPLC was carried out on a TSP (Thermoseparation Products, USA) instrument equipped with a ConstaMetric 4100 Bio pump and a SpectroMonitor 5000 UV DAD. The analyses of the chiral products were performed on a chiral Nucleodex β-OH column (150 × 4 mm; Macherey-Nagel, Germany) using methanol/water (4:1, v/v) as mobile phase at 0.3 ml min^{-1}. The eluate was monitored at 220, 254, and 275 nm and UV spectra were run from 200 to 300 nm.

4.2. *S. cerevisiae*

S. cerevisiae, strain DBM 2115, was obtained from the Research Institute of Fermentation Industry (Prague, Czech Republic). Yeasts were grown on a medium which consisted of glucose (30 g l^{-1}), $MgSO_4 \cdot 7H_2O$ (0.5 g l^{-1}), corn steep (10 g l^{-1}), KH_2PO_4 (1 g l^{-1}), K_2HPO_4 (1 g l^{-1}), $NaNO_3$ (2 g l^{-1}), KCl (0.5 g l^{-1}), and $FeSO_4 \cdot 7H_2O$ (0.02 g l^{-1}).

4.3. Enzymic reduction of the separated *E*- and *Z*-isomers of ethyl 4-[(2-oxocyclohexyl)-methyl]phenoxy-3-methyl-2-butenoates 1 and 2

S. cerevisiae was cultivated in the cultivation medium (100 ml) at 27 ± 1 °C for 48 h. The respective *E*- and *Z*-isomers of ethyl 4-[(2-oxocyclohexyl)methyl]phenoxy-3-methyl-2-butenoates **1** or **2** (150 mg per flask; 0.454 mmol), dissolved in ethanol (0.5 ml), were added to the yeast cells using five Erlenmeyer flasks. Substrate **1** or **2** was added directly to the original suspension of the yeast cells in the cultivation medium. Then the reaction was maintained under shaking at 27 ± 1 °C for 7 days in 250-ml shake-flasks using a Unimax incubator. Thereafter, the organic compounds were extracted with ether (four times, 100 ml). The extracts were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was applied on the top of a column filled with silica gel, and the respective diastereoisomeric products **3** and **4**, or **5** and **6** (cf. Scheme 1) were separated. Yields: **3** (48%), **4** (45%), **5** (47%), and **6** (44%). Both ^1H and the ^{13}C NMR data of substrates **1** and **2** as well as products **3**–**6** are presented in Table 1. For unambiguous assignment of signals, the gHSQC experiments (see remarks in Table 1) were performed using the standard pulse program.[6] Other analytical data of the products **3**–**6** are summarized below:

(1*S*,2*S*)-**3**: IR (CCl_4): 3631 (w), 3556 (w), 1715 (s), 1648 (m), 1612 (m) 1511 (s), 1446 (s), 1340 (m), 1238 (s), 1210 (s), 1177 (s), 1151 (s), 898 (w) cm^{-1}; MS (FAB): *m*/*z* 332 ($[M]^+$, 2), 315 (1), 287 (2), 269 (3), 233 (3), 203 (1), 187 (6), 127 (100), 99 (76); $[\alpha]_D^{20} = +27.3$ (*c* 0.079, $CHCl_3$); absolute configuration: (1*S*,2*S*); ee = 98%.

(1*R*,2*S*)-**4**: IR (CCl_4): 3625 (w), 3555 (w), 1715 (s), 1648 (m), 1612 (m), 1511 (s), 1447 (s), 1340 (m), 1238 (s), 1211 (s), 1177 (s), 1151 (s), 1020 (m) cm^{-1}; MS (FAB): *m*/*z* 333 ($[M+H]^+$, 3), 315 (1), 287 (1), 269 (4), 233 (4), 203 (1), 187 (8), 127 (100), 99 (86); $[\alpha]_D^{20} = +52.7$ (*c* 0.084, $CHCl_3$); absolute configuration: (1*R*,2*S*); ee = >99%.

(1*S*,2*S*)-**5**: IR (CCl_4): 3630 (w), 3546 (w), 1719 (s), 1665 (m), 1612 (m), 1511 (s), 1327 (m), 1224 (s), 1149 (s), 975 (m), 898 (w) cm^{-1}; MS (FAB): *m*/*z* 332 ($[M]^+$, 5), 315 (7), 268 (3), 205 (3), 187 (20), 127 (26), 107 (72), 99 (100); $[\alpha]_D^{20} = +17.3$ (*c* 0.081, $CHCl_3$); absolute configuration: (1*S*,2*S*); ee = 98.5%.

(1*R*,2*S*)-**6**: IR (CCl_4): 3629 (w), 3447 (w), 1720 (s), 1665 (w), 1612 (w), 1511 (s), 1327 (m), 1225 (s), 1149 (s), 1054 (m), 920 (w), 878 (w) cm^{-1}; MS (FAB): *m*/*z* 333 ($[M+H]^+$, 21), 315 (8), 269 (3), 201 (7), 187 (9), 127 (20), 107 (41), 99 (100); $[\alpha]_D^{24} = +12.5$ (*c* 0.087, $CHCl_3$); absolute configuration: (1*R*,2*S*); ee = >99%.

4.4. Synthesis of 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid esters 7–14

A general procedure used for the synthesis of the (*R*)- and (*S*)-MTPA (3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid; Mosher's acid) esters on a milligram scale starting from the (*S*)-(+)- or (*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPCl, Mosher's chloride) has already been described in detail.[1,4] Esters **7**–**14** (Fig. 1) were obtained in quantitative yields. Their selected ^1H and ^{19}F NMR data, which are important for the assignment of the absolute configuration of the parent major enantiomers **3**–**6** of ethyl 4-[(2-hydroxycyclohexyl)methyl]phenoxy-3-methyl-2-butenoates, are given in Table 2 and discussed in Section 2.

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