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Insect pest control agents: Novel chiral butanoate esters (juvenogens)

Zdeněk Wimmer,[a,*] Alexandra J. F. D. M. Floro,[b] Marie Zarevúcka,[c] Martina Wimmerová,[a] Guido Sello[d] and Fulvia Orsini[d]

[a]*Institute of Experimental Botany AS CR, Laboratory of Chemistry, Vídeňská 1083, 14220 Prague 4, Czech Republic*
[b]*University of Algarve, School of Technology, Food Engineering, Campus da Penha, 8000-117 Faro, Portugal*
[c]*Institute of Organic Chemistry and Biochemistry AS CR, Flemingovo náměstí 2, 16610 Prague 6, Czech Republic*
[d]*University of Milan, Via Venezian 21, 20133 Milan, Italy*

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Abstract—During the investigation of ester derivatives (juvenogens, biochemically activated insect hormonogenic compounds) of biologically active alcohols with potential application in insect pest control, a need for availability of all existing stereoisomers of ethyl *N*-{2-[4-(2-butanoyloxycyclohexyl)methyl]phenoxy}ethyl carbamate occurred. They were synthesized from their chiral precursors, the corresponding stereoisomers of 2-(4-methoxybenzyl)cyclohexyl butanoate, by removing their protecting group (methyl), and by subsequent condensation of the aromatic hydroxyl moiety with ethyl *N*-(2-bromoethyl) carbamate. The requested enantiomers of 2-(4-methoxybenzyl)cyclohexyl butanoate were obtained by a *Candida antarctica* lipase-mediated transesterification and chiral resolution of the respective racemic cis- and trans-isomers of 2-(4-methoxybenzyl)cyclohexanol either directly or after a subsequent chemical esterification of the chiral precursor. In this synthesis, two convenient butanoic acid activating esters, vinyl butanoate and 2,2,2-trifluoroethyl butanoate, were employed, and the chiral precursors in the synthesis of the target molecules were obtained in 41–48% yields (i.e., 82–96% conversion), and with enantiomeric purity ee = 96–98%, respectively. The enantiomeric purity of the products was determined by chiral HPLC analysis, and their absolute configuration was assigned on the basis of analyzing the ^{1}H and ^{19}F NMR spectra of their diastereoisomeric Mosher acid (3,3,3-trifluoromethyl-2-methoxy-2-phenylpropanoic acid) esters.

1. Introduction

Several years ago, a series of fatty acid esters derived from racemic ethyl *N*-{2-[4-(2-hydroxycyclohexyl)methyl]phenoxy}ethyl carbamate was synthesized and subjected to a detailed laboratory screening tests against the termite (*Prorhinotermes simplex*) and the blowfly (*Neobellieria bullata*).[1] Selected esters from that series (butanoate and hexadecanoate esters) were subsequently subjected to the field trials against termites in Australia.[2] Butanoate esters seemed to receive priority attention, and, therefore, their pure enantiomers were requested for basic laboratory screening tests. To obtain these compounds, chemoenzymic approach was employed in this synthetic procedure.

Enzymic reactions mediated by lipases (triacylglycerol hydrolases, EC 3.1.1.3) in non-aqueous media, including transesterification reactions, have received considerable attention over the past decade.[3] Enantiomerically pure compounds of biological interest or convenient enantiomerically pure synthons are usually easily available in high yields.[4] In our past and current projects, the lipase-mediated resolution of racemic 2-substituted cycloalkanols, precursors of the insect juvenile hormone bioanalogs, a series of insect pest management agents, has been extensively studied.[5] Among the lipases tested to date, lipase B from *Candida antarctica* was able to resolve both separated racemic isomers of 2-(4-methoxybenzyl)cyclohexanol with almost quantitative enantiomeric purity (ee > 99%) of the products, 2-(4-methoxybenzyl)cyclohexyl acetates[5], in the process of transesterification. Therefore, this enzyme has been

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* Corresponding author. Tel.: +420 241 062 381; fax: +420 241 062 111; e-mail: wimmer@ueb.cas.cz

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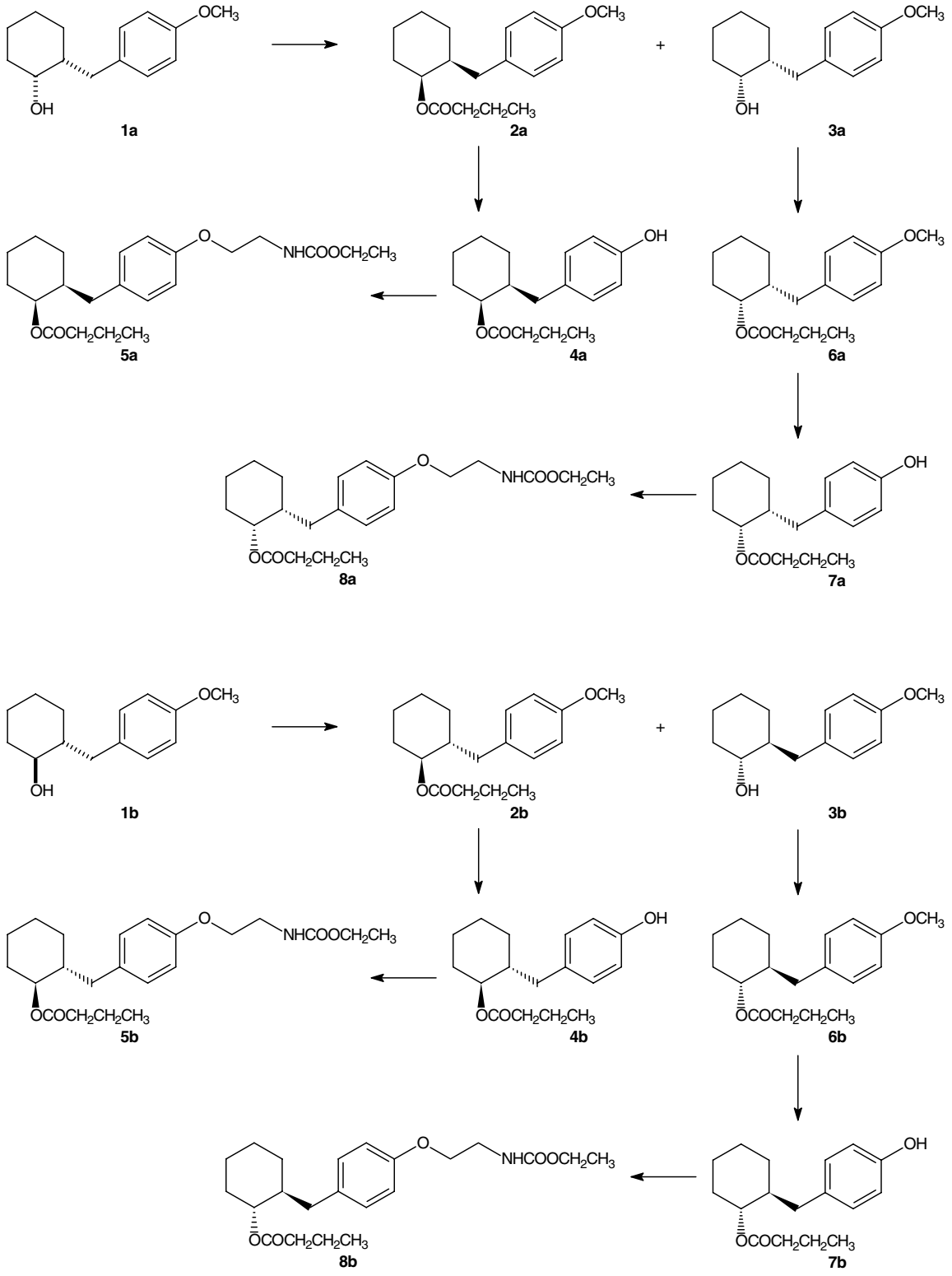
selected for this chemoenzymic synthesis, which choice turned to be an advantageous decision.

The objective of the present study (Scheme 1) was (a) to synthesize enantiopure butanoate esters of the studied alcohols applicable as chiral synthons in the synthesis of the target ethyl *N*-{2-[4-(2-butanoyloxycyclohexyl) methyl]phenoxy}ethyl carbamate stereoisomers and (b) to study the ways of enzymic resolution of the isomeric racemates to get both the products and the remaining substrates with as high as possible enantiomeric purity and chemical yields.



Scheme 1. Lipase-mediated resolution of **1a** and **1b**.

2. Results and discussion

Using a chemoenzymic approach, the requested enantiomers of ethyl *N*-{2-[4-(2-butanoyloxycyclohexyl) methyl]phenoxy}ethyl carbamate were synthesized. In the introductory enzymic resolution of racemic substrates **1a** and **1b** (Scheme 1), vinyl butanoate and 2,2,2-trifluoroethyl butanoate were employed as butanoic acid activating derivatives. Lipase B from *C. antarctica* was employed for mediating enzymic transesterification (Scheme 1). The course of the enzymic process was monitored by TLC, and the reactions were finally worked-up after 72 h of stirring in sealed vials at 40 °C. 2,2,2-Trifluoroethyl butanoate afforded **2a** (cis-isomer) with high enantiomeric purity, and vinyl butanoate represented good medium in preparation of **2b** (trans-isomer). The opposite enantiomers of 2-(4-methoxybenzyl)cyclohexanol (**3a** and **3b**) remained unused by the lipase, but enantiomerically resolved, in the reaction mixture (Table 1).

To assign the absolute configuration and the enantiomeric purity of the products **2a**, **2b**, **3a**, and **3b**, chiral HPLC analysis combined with ^{1}H and ^{19}F NMR spectra analysis of diastereoisomeric esters **2c**, **2d**, **3c**, and **3d** derived from the enantiomerically pure 3,3,3-trifluoromethyl-2-methoxy-2-phenylpropanoic acid (Mosher acid; MTPA) were used. Assigning of the absolute configuration at the C(2) chiral center was based on the differences of the chemical shifts of the signals of both hydrogen atoms of the CH_2-Ar (benzyl) group in the ^{1}H NMR spectra, and on the differences of the chemical shift of the signal of the CF_3 group in the ^{19}F NMR spectra.[6] The obtained data were in agreement with the earlier published data of similar compounds bearing the identical key features of chirality.[5] The HPLC analysis performed on a chiral Nucleodex-β-OH column resulted in separation of the enantiomers present in the analyzed samples of the alcohols, the major enantiomers of which are described by the absolute configurations in the formulae **2a**, **2b**, **3a**, and **3b** (Scheme 1). Esterification of the chiral alcohols by the (*S*)-MTPCl (Mosher acid chloride) afforded diastereoisomeric MTPA esters (Fig. 1). The absolute configuration was assigned to the compounds **2a**, **2b**, **3a**, and **3b** on the basis of analyzing the ^{1}H and ^{19}F NMR spectra[5] of the MTPA esters **2c**, **2d**, **3c**, and **3d** (Table 2).

To get the target compounds, the following reaction steps[7] were applied: (a) the methyl group used as a protecting function for the aromatic hydroxyl was removed under acidic conditions; and (b) the aliphatic side chain was introduced into the targeted chiral molecules using their reaction with ethyl *N*-(2-bromoethyl) carbamate under basic conditions in 2-butanone (Scheme 1).

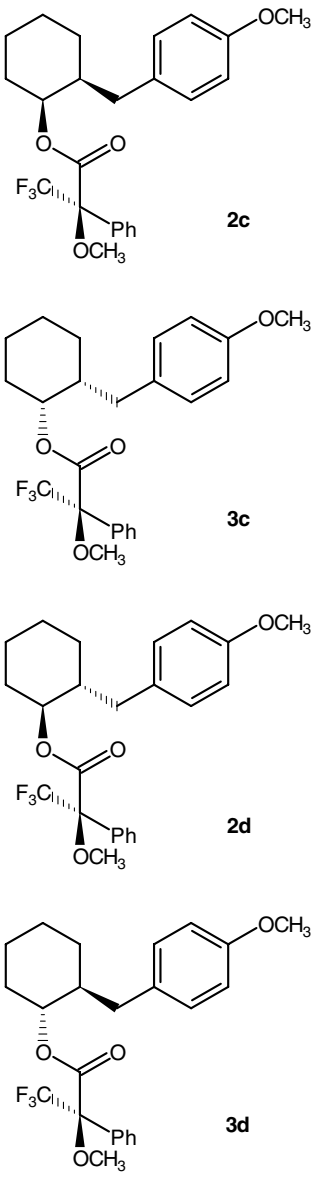


Figure 1. Structures of the (*R*)-MTPA ester derivatives of chiral alcohols.

The NMR data of the products were determined on the basis of both, 1D and 2D NMR experiments. The critical analysis of the 1D ^{1}H NMR and $^{1}H,^{1}H$-PFG-COSY spectra[8] of pure enantiomers allowed assigning the ^{1}H

Table 1. Results of the analysis of the enzymic resolution process

Substrate	Alkyl butanoate	Product (yield [%][a]; absolute configuration; ee [%])	Remaining substrate (yield [%][a]; absolute configuration; ee [%])
1a	Vinyl	**2a** (43; (1*S*,2*S*); 80)	**3a** (44; (1*R*,2*R*); 79)
1a	2,2,2-Trifluoroethyl	**2a** (47; (1*S*,2*S*); 97)	**3a** (46; (1*R*,2*R*); 96)
1b	Vinyl	**2b** (48; (1*S*,2*R*); 98)	**3b** (46; (1*R*,2*S*); 96)
1b	2,2,2-Trifluoroethyl	**2b** (42; (1*S*,2*R*); 84)	**3b** (41; (1*R*,2*S*); 81)

[a] Isolated yield, after chromatographic separation of the product and the resolved substrate.

Table 2. Selected ^{1}H and ^{19}F NMR parameters (signals and coupling constants) of **2c**, **2d**, **3c**, and **3d**

Ester of the (*R*)-MTPA	Parameter					Product (absolute configuration)
	^{1}H NMR				^{19}F NMR	
	δ (H-7a)	δ (H-7b)	J (2,7a)	J (2,7b)	δ (CF_3)	
2c	2.25	2.45	8.1	6.8	−67.13	**2a** (1*S*,2*S*)
2d	2.07	2.70	9.8	3.1	−67.44	**2b** (1*S*,2*R*)
3c	2.33	2.52	8.2	6.7	−67.31	**3a** (1*R*,2*R*)
3d	2.17	2.89	9.9	3.2	−67.55	**3b** (1*R*,2*S*)

chemical shifts and coupling constants. However, positions of the ^{1}H signals of the cyclohexane cycle could be extracted neither directly from the 1D NMR spectra nor from the ^{1}H,^{1}H-PFG-COSY spectra, and it was necessary to estimate these values from the ^{1}H,^{13}C-PFG-HSQC spectra[8] using the knowledge of the ^{13}C NMR chemical shifts from the model compounds with similar structure.[9] The 2D ^{1}H,^{13}C-PFG-HSQC spectra were used for unambiguous assignment of the ^{13}C NMR chemical shifts of the remaining carbon atoms.

Preliminary results of the biological screening tests on the termite *P. simplex* demonstrate the juvenilizing effect of the compounds **5a**, **5b**, **8a**, and **8b**. When the concentration 0.5 mg mL^{-1} of the active ingredient was used in the force feeding test, 65–90% juvenilizing effect was observed under mortality corresponding to the control experiment. Methodology used for screening tests was always normally used in these tests and described earlier.[1]

3. Conclusion

The employed enzymic process represents a convenient way of preparation of **2a** and **3a** using 2,2,2-trifluoroethyl butanoate as butanoic acid activating derivative, and of **2b** and **3b** using vinyl butanoate in high enantiomeric purity (ee = 95–98%) and conversion (92–95%). The target chiral products **5a**, **5b**, **8a**, and **8b** were then prepared by a sequence of the synthetic steps described in Section 2. The products **5a**, **5b**, **8a**, and **8b** have been submitted to entomological screening tests, which will be published separately after completing the tests on several unrelated insect pest species.

4. Experimental

4.1. General

The ^{1}H NMR and the ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 spectrometer (in a FT mode) at 500.1 MHz and 125.8 MHz, respectively, in $CDCl_3$ using either tetramethylsilane (δ = 0.0 for ^{1}H NMR) or a solvent signal ($CDCl_3$—δ = 77.00 for ^{13}C NMR) as internal reference at a temperature of 303 K. The ^{19}F NMR spectra were recorded on a Varian UNITY 500 spectrometer at 470.3 MHz in deuteriochloroform using hexafluorobenzene as external reference (δ = −162.9). The 2D NMR experiments (^{1}H,^{1}H-PFG-COSY and ^{1}H,^{13}C-PFG-HSQC) were performed using standard pulse program delivered by producer of the spectrometer, for unambiguous assignment of both proton and carbon signals in the spectra. IR spectra were recorded in a solution (CCl_4) on a Bruker IFS 88 instrument. Mass spectra (FAB) were recorded on a VG analytical 70–250 SE mass spectrometer, ZAB-EQ (BEQQ configuration) at 70 eV. 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 products were performed on a chiral Nucleodex β-OH column (150 × 4 mm; Macherey-Nagel, Germany) using a methanol/water mixture (9:1, v/v) as mobile phase at 0.3 mL min^{-1}. The eluate was monitored at 220, 254, and 275 nm, and the UV spectra were run from 200 to 300 nm. Optical rotations were measured on an Autopol IV polarimeter (Rudolph Research Analytical, USA). Elemental analyses were performed on a Perkin-Elmer 2400, series II CHNS/O analyzer (USA).

4.2. Enzymic resolution of the racemic isomers of 2-(4-methoxybenzyl)cyclohexanol 1a and 1b

The respective cis- or trans-isomer of 2-(4-methoxybenzyl)cyclohexanol (**1a** or **1b**; 500 mg; 2.27 mmol) was dissolved in either vinyl butanoate or 2,2,2-trifluoroethyl butanoate (10 mL) in a vial and non-immobilized powdered lipase from *C. antarctica* (30 mg; 2.7 U mg^{-1}) was added. The vial was sealed by a screw stopcock equipped with a Teflon-coated rubber seal, and the reaction mixture was stirred at 40 °C for 24 h. The enzyme was filtered off, the solvent was evaporated, and the residue separated by a column chromatography on silica gel using light petroleum/diethyl ether mixture (10:1 to 5:1) as mobile phase. Chemical yields of the products **2a**, **2b**, **3a**, and **3b** are given in Table 1 in relation to the alkyl butanoate used in the reaction.

Compound **2a**: ^{1}H NMR ($CDCl_3$): 1.00 (t, J = 7.4 Hz, 3H), 1.20–1.27 (m, 1H), 1.35–1.42 (m, 1H), 1.40–1.52 (m, 2H), 1.45–1.53 (m, 2H), 1.67–1.72 (m, 1H), 1.71 (m, 1H), 1.72 (m, J = 7.5 Hz, 2H), 1.88–1.94 (m, 1H), 2.35 (t, J = 7.6 Hz, 2H), 2.39 (dd, J = 7.9, 13.7 Hz, 1H), 2.56 (dd, J = 7.8, 13.7 Hz, 1H), 3.78 (s, 3H), 4.92 (dt, J = 2.6, 2.6, 4.4 Hz, 1H), 6.81 (m, 2H), 7.01 (m, 2H); ^{13}C NMR ($CDCl_3$): 13.79 (q), 18.73 (t), 20.87 (t), 25.06 (t), 27.00 (t), 30.00 (t), 36.79 (t), 37.75 (t), 42.57

(d), 55.22 (q), 71.84 (d), 113.72 (d), 129.89 (d), 132.53 (s), 157.83 (s), 173.17 (s); IR (CCl_4): 3464 (w), 3033 (w), 1729 (s), 1612 (w), 1243 (s), 1176 (s), 1095 (m); FAB MS: (*m*/*z*) 291 $[(M+H)]^+$; Calcd for $C_{18}H_{26}O_3$ (290.39): C, 74.44; H, 9.03. Found C, 74.40; H, 9.05; $[\alpha]_D^{20}$ +89 (*c* 0.035, $CHCl_3$).

Compound **2b**: ^1H NMR ($CDCl_3$): 0.95 (t, $J = 7.4$ Hz, 3H), 0.96 (m, 1H), 1.24–1.33 (m, 2H), 1.27–1.32 (m, 1H), 1.57–1.61 (m, 1H), 1.67 (m, $J = 7.4$ Hz, 2H), 1.67–1.74 (m, 3H), 1.97–2.02 (m, 1H), 2.20 (dd, $J = 9.3$, 13.6 Hz, 1H), 2.26 (dt, $J = 0.9$, 7.4, 7.4 Hz, 2H), 2.84 (dd, $J = 3.8$, 13.6 Hz, 1H), 3.78 (s, 3H), 4.57 (dt, $J = 4.5$, 10.1, 10.1 Hz, 1H), 6.81 (m, 2H), 7.03 (m, 2H); ^{13}C NMR ($CDCl_3$): 13.70 (q), 18.60 (t), 24.53 (t), 25.09 (t), 29.92 (t), 31.88 (t), 36.63 (t), 37.83 (t), 43.89 (d), 55.23 (q), 76.52 (d), 113.60 (d), 130.06 (d), 132.32 (s), 157.79 (s), 173.39 (s); **5**: IR (CCl_4): 3464 (w), 3034 (w), 1728 (s), 1612 (w), 1243 (s), 1177 (s), 1101 (m), 1089 (m); FAB MS: (*m*/*z*) 291 $[(M+H)]^+$; Calcd for $C_{18}H_{26}O_3$ (290.39): C, 74.44; H, 9.03. Found C, 74.47; H, 9.01; $[\alpha]_D^{20}$ +124 (*c* 0.046, $CHCl_3$).

Compound **3a**: ^1H NMR ($CDCl_3$): 1.18–1.25 (m, 1H), 1.34–1.44 (m, 2H), 1.42–1.48 (m, 2H), 1.54–1.62 (m, 1H), 1.64–1.70 (m, 2H), 1.73–1.79 (m, 1H), 2.48 (dd, $J = 7.6$, 13.6 Hz, 1H), 2.66 (dd, $J = 7.6$, 13.6 Hz, 1H), 3.78 (s, w = 11, 1H), 3.79 (s, 3H), 6.82 (m, 2H), 7.10 (m, 2H); ^{13}C NMR ($CDCl_3$): 20.34 (t), 25.31 (t), 26.37 (t), 33.27 (t), 37.75 (t), 43.67 (d), 55.23 (q), 68.51 (d), 113.66 (d), 129.95 (d), 133.01 (s), 157.75 (s); IR (CCl_4): 3631 (w), 3501 (w), 3064 (w), 3032 (w), 2934 (s), 2835 (m), 1176 (s), 1041 (s), 974 (m); FAB MS: (*m*/*z*) 220 ($[M]^+$). Calcd for $C_{14}H_{20}O_2$ (220.30): C, 76.32; H, 9.15. Found: C, 76.28; H, 9.13; $[\alpha]_D^{20}$ −33 (*c* 0.036, $CHCl_3$).

Compound **3b**: ^1H NMR ($CDCl_3$): 0.90 (ddt, $J = 3.5$, 11.5, 11.5, 16.5 Hz, 1H), 1.09 (dtt, $J = 3.5$, 3.5, 11.7, 11.7, 15.0 Hz, 1H), 1.19–1.29 (m, 2H) 1.46 (m, 1H), 1.56–1.60 (m, 1H), 1.64 (ddt, $J = 2.0$, 3.5, 3.5, 16.5 Hz, 1H), 1.68–1.73 (m, 1H), 1.95–2.00 (m, 1H), 2.33 (dd, $J = 9.0$, 13.5 Hz, 1H), 3.07 (dd, $J = 4.1$, 13.5 Hz, 1H), 3.28 (dt, $J = 4.3$, 9.9, 9.9 Hz, 1H), 3.79 (s, 3H), 6.82 (m, 2H), 7.10 (m, 2H); ^{13}C NMR ($CDCl_3$): 24.88 (t), 25.43 (t), 30.00 (t), 35.77 (t), 38.07 (d), 47.08 (t), 55.22 (q), 74.51 (d), 113.61 (d), 130.25 (d), 132.67 (s), 157.76 (s); IR (CCl_4): 3624 (w), 3604 (w), 3064 (w), 3033 (w), 2835 (m), 1177 (m), 1042 (s), 1025 (m); FAB MS: (*m*/*z*) 220 ($[M]^+$). Calcd for $C_{14}H_{20}O_2$ (220.30): C, 76.32; H, 9.15. Found: C, 76.36; H, 9.16; $[\alpha]_D^{20}$ +22 (*c* 0.043, $CHCl_3$).

4.3. Synthesis of 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid esters 2c, 2d, 3c, and 3d

A general procedure used for the synthesis of the (*R*)-MTPA (3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid; Mosher's acid) esters on a milligram scale starting from the (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPCl, Mosher's chloride) was already described in details.[5,10] While the chiral alcohols **3a** and **3b** could be directly transformed into their MTPA esters **3c** and **3d**, their enantiomers corresponding to their butanoate esters **2a** and **2b** (104.6 mg; 0.36 mmol) had first to be saponified by heating to reflux with potassium carbonate (150 mg) in a mixture of methanol (20 mL) and water (5 mL) for 2 h. Methanol and water were removed under reduced pressure, the residue was applied onto a silica gel column and purified, affording the pure products in the yields ⩾95%, and subsequently transformed into their MTPA esters **2c** and **2d**. The esters **2c**, **2d**, **3c**, and **3d** (Fig. 1) were obtained in quantitative yields. Their selected ^1H and ^{19}F NMR data, which are important for assignment of the absolute configuration of **2a**, **2b**, **3a**, and **3b**, are given in Table 2.

4.4. Synthesis of the butanoate esters 6a and 6b

A solution of the alcohols **3a** or **3b** (0.884 mmol) in benzene (10 mL) and pyridine (0.4 mL) was cooled to 0 °C under vigorous stirring. A fatty acid chloride (1.06 mmol) was added in one portion by a pipette, and the mixture was stirred at 20 °C for 2–6 h. The reaction course was monitored by TLC. The mixture was then poured onto a mixture of ice (20 mL) and hydrochloric acid (1 mL). The organic layer was extracted with diethyl ether, and the extract was dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the crude residue was purified by column chromatography on silica gel. The products **6a** and **6b** were obtained in 95% yields. Their analytical data were identical with those recorded for **2a** and **2b** with the exception of the optical rotation data: **6a**: $[\alpha]_D^{20}$ −87 (*c* 0.040, $CHCl_3$); **6b**: $[\alpha]_D^{20}$ −120 (*c* 0.037, $CHCl_3$).

4.5. Synthesis of the compounds 5a, 5b, 8a, and 8b

(a) A solution of the respective **2a**, **2b**, **6a** or **6b** (100 mg, 0.4 mmol) in a benzene/ethanol (1:1) mixture (5 mL) was heated to 40 °C in the presence of concentrated hydrobromic acid (0.1 mL) for 12 h. Solvents were evaporated, and the residue was partitioned between water and ether layer. The organic extract was dried over sodium sulfate, and the crude residues (**4a**, **4b**, **7a**, and **7b**) obtained after removal of the solvent were directly used in the following reaction step.

(b) Dry powdered potassium carbonate (1 g) and ethyl *N*-(2-bromoethyl)carbamate (1 g, 5.0 mmol) were added to a solution of the respective chiral **4a**, **4b**, **7a**, and **7b** (0.2 mmol) in 2-butanone (15 mL). The mixture was refluxed for 12 h, cooled, filtered, and the solid material was washed with diethyl ether (30 mL). The filtrate was washed with water (10 mL) and dried over magnesium sulfate. After filtration, the solvents were removed under reduced pressure, and the residues were purified by column chromatography on silica gel, yielding the target products **5a** (90%), **5b** (91%), **8a** (93%), and **8b** (92%).

Compound **5a/8a**: ^1H NMR ($CDCl_3$): 1.00 (t, $J = 7.4$ Hz, 3H), 1.20–1.51 (m, 8H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.72 (m, 2H), 1.91 (m, 1H), 2.35 (t, $J = 7.5$ Hz, 2H), 2.39 (dd, $J = 8.2$, 13.6 Hz, 1H), 2.55 (dd, $J = 6.9$, 13.6 Hz, 1H), 3.57 (bq, $J = 5.3$ Hz, 2H), 4.00 (t, $J = 5.3$ Hz, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.91 (dt, $J = 2.6$, 2.6, 4.4 Hz, 1H), 5.11 (bt, $J = 5.3$ Hz, 1H),

6.79 (m, 2H), 7.00 (m, 2H). ^{13}C NMR ($CDCl_3$): 13.78 (q), 14.61 (q), 18.72 (t), 20.86 (t), 25.05 (t), 26.99 (t), 29.99 (t), 36.78 (t), 37.74 (t), 40.52 (t), 42.55 (d), 60.91 (t), 66.99 (t), 71.77 (d), 114.30 (d), 129.97 (d), 133.06 (s), 156.64 (s), 156.74 (s), 173.13 (s). IR (CCl_4): 3464 (w), 3033 (w), 1729 (s), 1612 (w), 1585 (w), 1510(s), 1243 (s), 1176 (s), 1095 (m) cm^{-1}. FAB MS (*m*/*z*) 392 ([M+H]$^+$, 35), 304 (21), 231 (8), 154 (9), 137 (9), 116 (100), 107 (21), 88 (42), 71 (13). Calcd for $C_{22}H_{33}NO_5$ (391.49): C, 67.49; H, 8.50; N, 3.58. Found: C, 67.52; H, 8.47; N, 3.61; Compound **5a**: $[\alpha]_D^{20}$ +80 (*c* 0.031, $CHCl_3$); Compound **8a**: $[\alpha]_D^{20}$ −79 (*c* 0.027, $CHCl_3$).

Compound **5b**/**8b**: ^{1}H NMR ($CDCl_3$): 0.96 (t, J = 7.4 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.26–1.78 (m, 10 H), 2.00 (m, 1H), 2.19 (dd, J = 9.3, 13.6 Hz, 1H), 2.27 (t, J = 7.5 Hz, 2H), 2.84 (dd, J = 3.8, 13.6 Hz, 1H), 3.57 (bq, J = 5.3 Hz, 2H), 4.00 (t, J = 5.3 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 4.56 (dt, J = 4.4, 10.1, 10.1 Hz, 1H), 5.12 (bt, J = 5.3 Hz, 1H), 6.80(m, 2H), 7.03 (m, 2H). ^{13}C NMR ($CDCl_3$): 13.70 (q), 14.61 (q), 18.60 (t), 24.52 (t), 25.09 (t), 29.91 (t), 31.87 (t), 36.64 (t), 37.84 (t), 40.56 (t), 43.89 (d), 60.92 (t), 67.05 (t), 76.48 (d), 114.25 (d), 130.16 (d), 132.90 (s), 156.66 (s), 156.75 (s), 173.35 (s). IR (CCl_4): 3464 (w), 3034 (w), 1728 (s), 1612 (w), 1585 (w), 1509 (s), 1243 (s), 1177 (s), 1101 (m), 1089 (m) cm^{-1}. FAB MS (*m*/*z*) 392 ([M+1]$^+$, 17), 320 (6), 304 (11), 222 (6), 133 (6), 116 (100), 107 (37), 88 (45), 71 (13). Calcd for $C_{22}H_{33}NO_5$ (391.49): C, 67.49; H, 8.50; N, 3.58. Found: C, 67.45; H, 8.47; N, 3.55; Compound **5b**: $[\alpha]_D^{20}$ +109 (*c* 0.033, $CHCl_3$); **8b**: $[\alpha]_D^{20}$ −105 (*c* 0.036, $CHCl_3$).

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