DOI: 10.1002/hlca.202000081

FULL PAPER

HELVETICA chimica acta

Chiral α-Amino Acid-Based NMR Solvating Agents

Anikó Nemes,*[a] Tamás Csóka,[a] Szabolcs Béni,[b] Zsófia Garádi,[b] Dénes Szabó,[a] and József Rábai[a]

[a] Institute of Chemistry, Eötvös Loránd University, Pázmány Péter sétány 1/A, HU-1117 Budapest, Hungary, e-mail: neagaft@caesar.elte.hu

[b] Department of Pharmacognosy, Semmelweis University, Üllői út 26, HU-1085 Budapest, Hungary

Dedicated to *Prof. Antonio Togni* on the occasion of his 65th birthday

Four new chiral α-(nonafluoro-*tert*-butoxy)carboxylic acids were synthesized from naturally occurring α-amino acids (alanine, valine, leucine and isoleucine, respectively), and tested in ^{1}H- and ^{19}F-NMR experiments as chiral NMR shift reagents. The NMR studies were carried out at room temperature, using $CDCl_3$ and C_6D_6 as solvents, and (*RS*)-α-phenylethylamine and (*RS*)-α-(1-naphthyl)ethylamine as racemic model compounds. To demonstrate the applicability of the reagents, the racemic drugs ketamine and prasugrel were also tested.

Keywords: amino acids, carboxylic acids, enantioselectivity, chiral pool.

Introduction

Since most of the active pharmaceutical ingredients (APIs) are optically active molecules, the pharmaceutical industry needs simple, fast and accurate analytical methods for determining enantiomeric ratios. Chiral analytical techniques include 1) chromatography (GC,[1] HPLC) with the use of chiral stationary phases[2] or achiral stationary phases after chiral derivatization,[3] 2) capillary electrophoresis (CE),[4] and 3) chiral spectroscopies.[5] Disadvantage of chromatography resides in the lengthy optimization processes, while spectroscopic methods, such as ECD, VCD and ROA require special equipment, therefore they are relatively rarely used as routine measurements.

NMR Spectroscopy offers an advantageous possibility for chiral discrimination,[6–9] because NMR instruments are usually available for routine structure determinations. The ee determination by NMR spectroscopy is based on diastereomer formation, either as 1) derivatization in a separate step before the measurement, or 2) *in situ* complex formation (using lanthanide shift reagents or chiral solvating agents). These latter procedures have the advantage of fast optimization and data processing, as well as lacking racemization and purification.

The complex formation required for the stereodiscrimination can be based on host-guest interactions, for example, cyclodextrins (CDs) and crown ethers. In the case of CDs the chemical shift difference ($\Delta\delta$) of the analyte ^{1}H resonances are in the 0.005–0.120 ppm range, typically 0.02–0.05 ppm.[10–12] Using crown ethers as CSA, the hydrogens of the analyte show around 0.009–0.250 ppm chemical shift differences.[13,14]

More often, the complex formation takes place using diverse donor–acceptor interactions, for example hydrogen bonding, dipole–dipole interaction, π–π interaction between aromatic rings or steric repulsion.[15] The most widely used salt forming chiral solvating agents are mandelic acid derivatives, such as the *Mosher*'s acid (MTPA)[16–18] and aromatic benzyl alcohols, such as *Pirkle*'s alcohol.[19,20] Both reagents show around 0.020–0.075 ppm $\Delta\delta$ in ^{1}H-NMR, and 0–0.010 ppm in ^{19}F-NMR as chiral solvating agents.

In our previous work, we showed that α-(nonafluoro-*tert*-butoxy)carboxylic acids, based on lactic acid (*R*)-**1**, mandelic acid (*RS*)-**2** and 3-phenyllactic acid (*R*)-**3**, display good chiral discrimination properties to-

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.202000081

wards chiral amines. The chemical shift differences of these compounds are comparable with the literature values of other shift reagents, namely 0.011–0.190 ppm in ^{1}H-NMR and 0.006–0.063 ppm in ^{19}F-NMR in case of (*RS*)-α-phenylethylamine, as test analyte. We also observed chemical shift differences in ^{19}F-NMR in the case of racemic ephedrine (0.008–0.010 ppm).[21,22] To extend these experiments, we synthesized four new chiral carboxylic acid derivatives with similar structures, starting from natural α-amino acids. To introduce the nonafluoro-*tert*-butoxy moiety, the amino group was replaced by stereospecific nucleophilic substitution. In this article, we present the synthesis and chiral discrimination studies of carboxylic acids (*R*)-**1**, (*R*)-**4**, (*R*)-**5** and (2*R*,3*S*)-**6** (*Figure 1*).

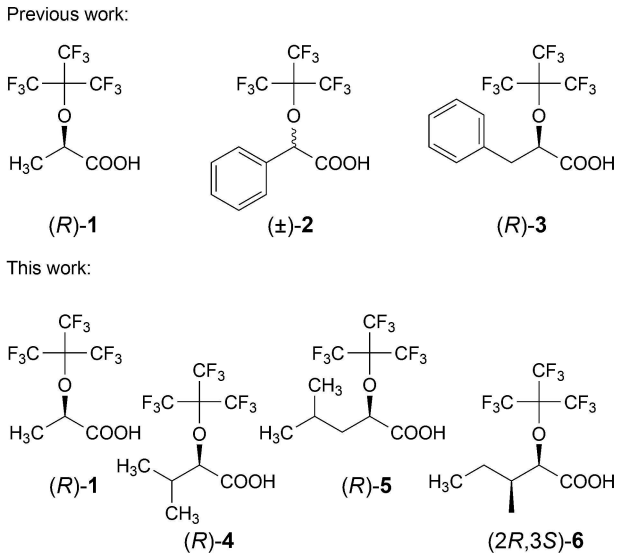
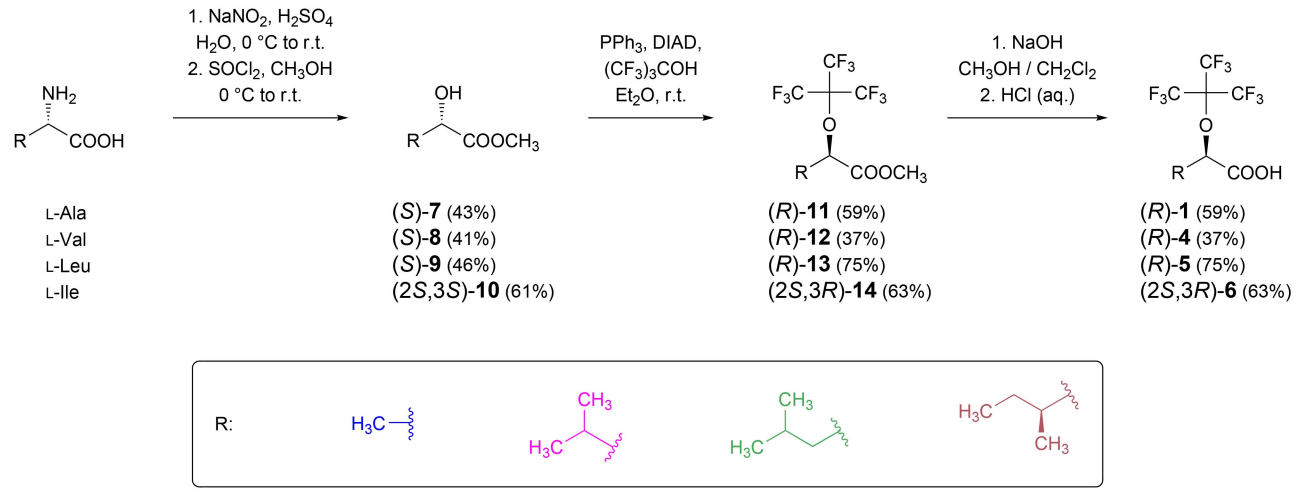


Figure 1. Structure of α-(nonafluoro-*tert*-butoxy)carboxylic acids.

Results and Discussion

The starting materials of the synthesis of α-(nonafluoro-*tert*-butoxy)carboxylic acids are the natural amino acids alanine, valine, leucine and isoleucine. The first step is diazotation of the amino group followed by hydrolysis to yield the optically active α-hydroxycarboxylic acids.[23] In this reaction, double inversion of configuration occurs in a stereospecific way. The first reaction step is a diazotation, which is followed by a lactone formation, as the carboxyl group attacks the α-carbon atom, therefore the overall process results in the inversion of configuration.[24] Then, the formed α-lactone hydrolyzes *in situ* also with inversion.[25] The obtained carboxylic acids were reacted with $SOCl_2$ in the presence of methanol, to give the methyl α-hydroxycarboxylate intermediates (*S*)-**7**, (*S*)-**8**, (*S*)-**9** and (2*S*,3*S*)-**10**. Based on our previous experiments, the ether bonds were formed with nonafluoro-*tert*-butanol under *Mitsunobu* reaction conditions[26–29] which took place with complete inversion of configuration. In the last step the ester protecting group was hydrolyzed with NaOH in a MeOH/CH_2Cl_2 solvent mixture, to give the target α-(nonafluoro-*tert*-butoxy)carboxylic acids (*R*)-**1**, (*R*)-**4**, (*R*)-**5** and (2*R*,3*S*)-**6** (*Scheme 1*).

In our NMR experiments, diastereomeric salt formation was investigated between (*R*)-**1**, (*R*)-**4**, (*R*)-**5** and (2*R*,3*S*)-**6** carboxylic acids and racemic α-phenylethylamine (PEA) and α-(1-naphthyl)ethylamine (NEA) as test analytes. In apolar solvents ($CDCl_3$ and C_6D_6),



Scheme 1. Synthesis of optically active α-(nonafluoro-*tert*-butoxy)carboxylic acids.

the diastereomeric salts are present as tight ion pairs, thus the recorded chemical shifts are weighted averages of the free and the protonated amines, which are present in the tight diastereomeric complex. The amounts of the enantiomers can be calculated from the integrals of the signals in ^{1}H- and ^{19}F-NMR spectra. Our first attempt was to observe the enantiorecognition on the ^{1}H and ^{19}F nuclei of the racemic α-phenylethylamine, using α-(nonafluoro-*tert*-butoxy) carboxylic acids (**1**, **4**, **5**, **6**) as chiral solvating agents. Spectra were recorded in 54 mM using $CDCl_3$ as solvent (*Table 1*, *Figure 2*). In the cases of (*RS*)-PEA as analyte, the methyl hydrogens of the amine (*doublets*, *ca.* 1.6 ppm) did not show measurable differences in the chemical shifts of the ^{1}H-NMR resonances. However, the methine hydrogens (*quartets*, *ca.* 4.25 ppm), which are attached directly to the stereogenic carbon atom, exhibited distinguishable chemical shift difference ($\Delta\delta$) in the range of 0.035–0.045 ppm for (*R*)-**1**, (*R*)-**4** and (*R*)-**5**. Concurrently (2*R*,3*S*)-**6**×(*RS*)-PEA has broad signals in the spectrum due to solubility problems, thus the enantiorecognition phenomena cannot be proved under these conditions. It is worthy to note that these *quartet* signals were overlapping, thus exact determination of the relative amounts of enantiomers was not possible.

Table 1. Chemical shift differences ($\Delta\delta$s) of (*RS*)-PEA hydrogens.

Solvating agent	Solvent	$\Delta\delta$ (CH) [ppm]	$\Delta\delta$ (CH_3) [ppm]
(*R*)-**1**	$CDCl_3$	0.045	0
(*R*)-**4**	$CDCl_3$	0.035	0
(*R*)-**5**	$CDCl_3$	0.040	0
(2*R*,3*S*)-**6**	$CDCl_3$	broad signals	0
(*R*)-**1**	C_6D_6	0.010	0.035
(*R*)-**4**	C_6D_6	0	0.030
(*R*)-**5**	C_6D_6	0	0.035
(2*R*,3*S*)-**6**	C_6D_6	0	0.025

In a second set of experiments the same measurements were performed using C_6D_6 as solvent (*Table 1*, *Figure 3*). In these cases, methyl hydrogens (*ca.* 1.5 ppm) have significant $\Delta\delta$ in the range of 0.025–0.035 ppm and due to the smaller peak widths of these *doublets*, their integrals can be used for enantiomeric ratio determination. Surprisingly, the methine hydrogens directly attached to the stereogenic center (*ca.* 4.05 ppm) did not give significant $\Delta\delta$, only (*R*)-**1**× (*RS*)-PEA has a small 0.010 ppm anisochrony. Unfortunately, ^{19}F-NMR measurements failed to show $\Delta\delta$ in any of the above cases.

Similar to the experiments presented above, NMR measurements were also performed with racemic α-(1-naphthyl)ethylamine as the analyte. In $CDCl_3$ solution using (*R*)-**4** and (2*R*,3*S*)-**6** as chiral solvating agents the methyl hydrogens (*ca.* 1.7 ppm) of the (*RS*)-NEA showed distinguishable chemical shift differences (0.015 and 0.020 ppm), while the methine hydrogens (*ca.* 5.15 ppm) resulted in smaller $\Delta\delta$ values (0.015–0.030 ppm) than in the case of (*RS*)-PEA (*Table 2*, *Figure 4*). Unfortunately, diastereomeric complexes of the carboxylic acids (**1**, **4**, **5**, **6**) and (*RS*)-NEA have low solubility in the apolar C_6D_6, thus NMR spectra could not be evaluated in this solvent. Under these conditions ^{19}F nuclei also did not show difference in their chemical shifts.

For further exploration of the potential of using (*R*)-**1**, (*R*)-**4**, (*R*)-**5** and (2*R*,3*S*)-**6** as chiral NMR shift reagents

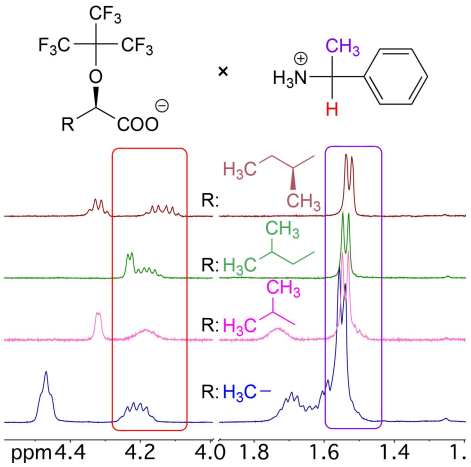


Figure 2. Partial ^{1}H-NMR spectra of α-(nonafluoro-*tert*-butoxy)-carboxylic acids with (*RS*)-PEA in $CDCl_3$.

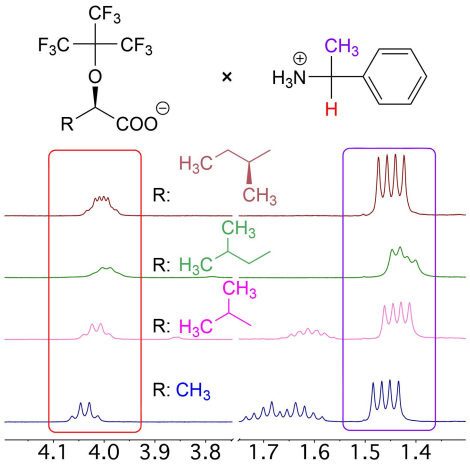


Figure 3. Partial ^{1}H-NMR spectra of α-(nonafluoro-*tert*-butoxy)-carboxylic acids with (*RS*)-PEA in C_6D_6.

Table 2. Chemical shift differences ($\Delta\delta$s) of (*RS*)-NEA hydrogens in $CDCl_3$.

Solvating agent	$\Delta\delta$ (CH) [ppm]	$\Delta\delta$ (CH_3) [ppm]
(*R*)-**1**	0.030	0
(*R*)-**4**	0.015	0.015
(*R*)-**5**	broad signals	broad signals
(2*R*,3*S*)-**6**	0.015	0.020

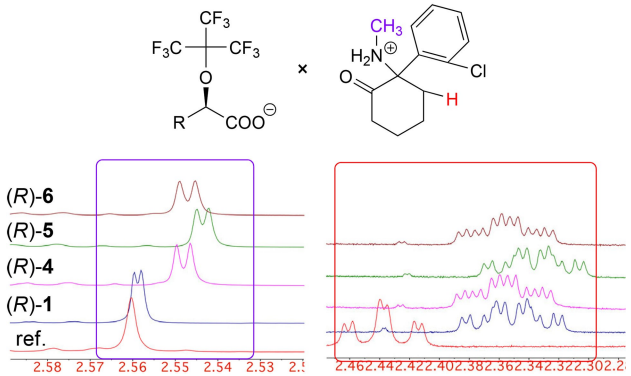


Figure 4. Selected ^{1}H-NMR resonances of (*RS*)-ketamine (bottom) and the same resonances after the addition of equimolar amounts of various α-(nonafluoro-*tert*-butoxy)carboxylic acids in $CDCl_3$.

their applicability has also been tested using the secondary amine ketamine and the tertiary amine prasugrel as active pharmaceutical ingredients, respectively. Both racemic compounds showed the chiral recognition phenomena in ^{1}H-NMR measurements.

First the ^{1}H-NMR spectra of the diastereomeric salts of ketamine were recorded in $CDCl_3$. Significant chemical shift differences were observed in the case of the methylene resonances of the cyclohexanone ring adjacent to the chiral center 0.011–0.015 ppm. Small $\Delta\delta$s (0.002–0.004 ppm) were recognized for the *N*-methyl hydrogens (*Table 3*, *Figure 4*). To obtain better resolution between the hydrogen signals of the diastereomeric complexes the more apolar solvent C_6D_6 was also tested. Unfortunately, these experiments failed, due to the low solubility of the compounds.

Table 3. ^{1}H-NMR chemical shift differences ($\Delta\delta$s) of (*RS*)-ketamine in the presence of various α-(nonafluoro-*tert*-butoxy)-carboxylic acids in $CDCl_3$.

Solvating agent	$\Delta\delta$ (H_a) [ppm]	$\Delta\delta$ (H_b) [ppm]
(*R*)-**1**	0.015	0.002
(*R*)-**4**	0.011	0.004
(*R*)-**5**	0.014	0.003
(2*R*,3*S*)-**6**	0.011	0.004

Then the optically active α-(nonafluoro-*tert*-butoxy) carboxylic acids were used as CSAs for the racemic prasugrel in $CDCl_3$. ^{1}H resonances relatively close to the chiral center show substantial anisochrony 0.035–0.050 ppm for H_a and 0.060–0.086 ppm H_b, respectively. The aromatic ^{1}H resonances separated by four covalent bonds from the stereocenter (H_c and H_d) still exhibit recognizable chemical shift differences (*Table 4*, *Figure 5*).

The ^{1}H-NMR spectra of prasugrel along with the new NMR shift reagents were also recorded in C_6D_6. In these cases, the magnitude of the observed chemical shift differences was comparable with those of $\Delta\delta$s measured in $CDCl_3$. Due to some spectral overlap in C_6D_6 the $\Delta\delta$s were observed for the following

Table 4. ^{1}H-NMR chemical shift differences ($\Delta\delta$s) of (*RS*)-prasugrel in the presence of various α-(nonafluoro-*tert*-butoxy)-carboxylic acids in $CDCl_3$.

Solvating agent	$\Delta\delta$ (H_a) [ppm]	$\Delta\delta$ (H_b) [ppm]	$\Delta\delta$ (H_c) [ppm]	$\Delta\delta$ (H_d) [ppm]
(*R*)-**1**	0.035	0.060	0.008	0.007
(*R*)-**4**	0.042	0.064	0.009	0.008
(*R*)-**5**	0.050	0.086	0.014	0.003
(2*R*,3*S*)-**6**	0.041	0.066	0.010	0.010

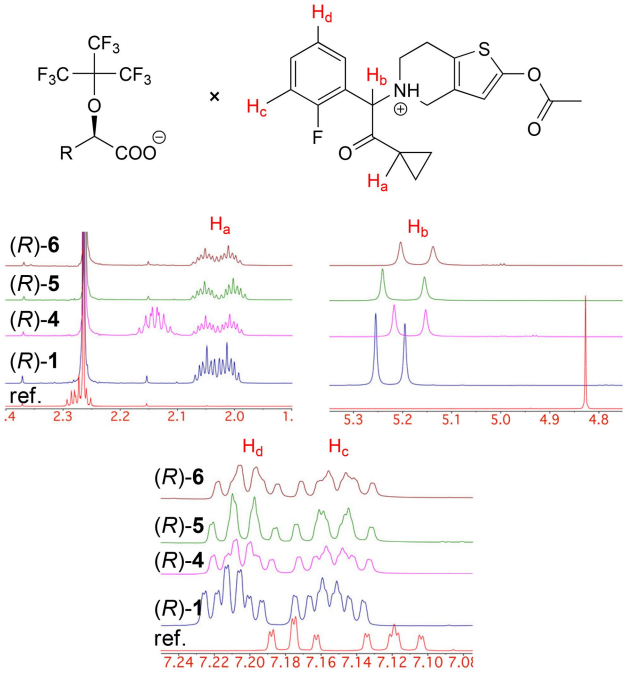


Figure 5. Selected ^{1}H-NMR resonances of (*RS*)-prasugrel (bottom) and the same resonances after the addition of equimolar amounts of various α-(nonafluoro-*tert*-butoxy)carboxylic acids in $CDCl_3$.

resonances: H_e, H_f, H_g (see *Figure 6*). It is worthy to note that in C_6D_6 even H_f resonances exhibit significant anisochrony 0.004–0.008 ppm (separated by five bonds from the chiral center) compared with that of registered in $CDCl_3$. The chemical shift anisochronies of H_b were 0.046–0.077 ppm, somewhat smaller than that observed in $CDCl_3$. The aromatic ^1H resonance H_g also exhibited 0.018–0.037 ppm anisochrony (*Table 5*, *Figure 6*).

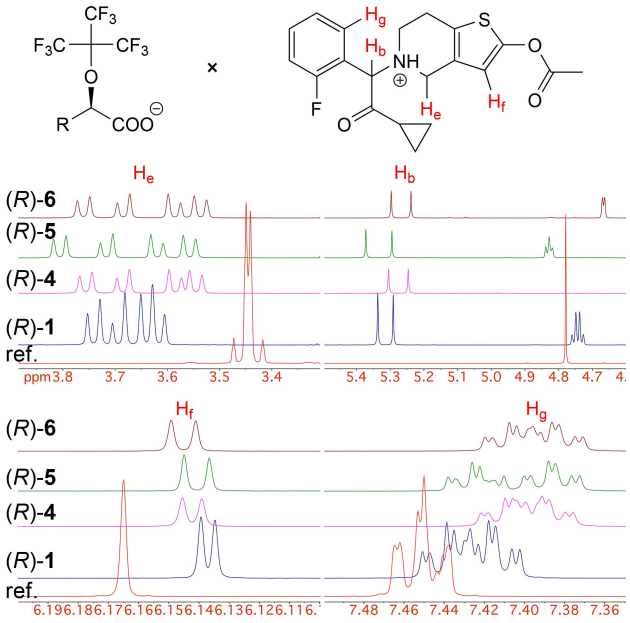


Figure 6. Selected ^1H-NMR resonances of (*RS*)-prasugrel (bottom) and the same resonances after the addition of equimolar amounts of various α-(nonafluoro-*tert*-butoxy)carboxylic acids in C_6D_6.

Table 5. ^1H-NMR chemical shift differences ($\Delta\delta$s) of (*RS*)-prasugrel in the presence of various α-(nonafluoro-*tert*-butoxy)-carboxylic acids in C_6D_6.

Solvating agent	$\Delta\delta$ (H_e) [ppm]	$\Delta\delta$ (H_b) [ppm]	$\Delta\delta$ (H_f) [ppm]	$\Delta\delta$ (H_g) [ppm]
(*R*)-**1**	overlapping resonances	0.046	0.004	0.021
(*R*)-**4**	overlapping resonances	0.059	0.006	0.018
(*R*)-**5**	overlapping resonances	0.077	0.008	0.037
(2*R*,3*S*)-**6**	overlapping resonances	0.059	0.008	0.021

Conclusions

In conclusion, α-(nonafluoro-*tert*-butoxy)carboxylic acids (**1**, **4**, **5**, **6**) exhibit chiral recognition ability toward racemic amines in apolar solvents. The enantiomers of the racemic analyte and the chiral solvating agents formed diastereomeric complexes, which were distinguishable by NMR spectroscopy. In $CDCl_3$, the chemical shift difference of methine hydrogens allow the discrimination of the enantiomers present, while in C_6D_6, the methyl hydrogens are also distinguishable. The measured $\Delta\delta$ values were 0.004–0.086 ppm, which are comparable to those of known chiral NMR shift reagents.

Experimental Section

General

The precursor amino acids and solvents were purchased from *Reanal Laborvegyszer Kft.*, while the other reagents from *VWR International Kft.* FT-IR spectra were obtained on a *Bruker Alpha* FT-IR equipped with diamond ATR. For known compounds ^1H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on *Bruker Avance 250* spectrometer using 5 mm inverse $^1H/^{13}C/^{31}P/^{19}F$ probe head at room temperature. New compounds were characterized by a 600 MHz *Varian DDR* NMR spectrometer equipped with a 5 mm inverse-detection gradient (IDPFG) probe head. Standard pulse sequences and processing routines available in VnmrJ 3.2C/Chempack 5.1 were used. ^1H (400 MHz) and ^{19}F (376 MHz) spectra for enantiomeric excess determination were recorded on a *Varian Mercury Plus* spectrometer. Chemical shifts (δ) are given in ppm units relative to the internal standards: TMS ($\delta = 0.00$ ppm for ^1H). For obtaining high resolution mass spectrometric data an *Orbitrap Q Exactive Focus* mass spectrometer equipped with electrospray ionization (*Thermo Fischer Scientific*, Waltham, MA, USA) was used. Melting points were determined by *Boetius*-micro melting point apparatus, are uncorrected. Optical rotations were determined on a *Carl Zeiss Polamat A* polarimeter with a 1 dm cell at 25 °C.

Experimental

General Procedure for the Synthesis of Methyl α-Hydroxycarboxylates. The solution of α-amino acid (0.15 mol) in 1 M H_2SO_4 (300 ml) was cooled to 0 °C, and the solution of $NaNO_2$ (62.1 g, 0.9 mol) in water (150 ml) was added dropwise, in a rate, that the

temperature remained under 5 °C. The solution was stirred at 0 °C for 1 h, then at r.t. overnight. NaCl (33.0 g) was added to the mixture, and it was extracted with diethyl ether (4×90 ml). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The remaining oil was dissolved in methanol (110 ml), then cooled to 0 °C, and $SOCl_2$ (11.61 ml, 0.15 mol) was added dropwise. The mixture was stirred at r.t. overnight, then, the solvent was removed under reduced pressure and the crude product was purified by vacuum distillation.

Methyl (*S*)-(+)-2-Hydroxypropanoate (=**Methyl (2*S*)-2-Hydroxypropanoate**; (*S*)-**7**). L-Alanine (15.00 g, 0.17 mol) was reacted according to the *General Procedure* to give 7.08 g (43 %) colorless liquid. B.p. 144 °C. (Lit. b.p. 144–145 °C[30]). $[\alpha]_{546}^{25} = +11.6$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.29 (*q*, ^3J(H,H) = 6.9, CH); 4.18 (br. *s*, OH); 3.77 (*s*, $COOCH_3$); 1.41 (*d*, ^3J(H,H) = 6.9, CH_3CH). ^{13}C-NMR (63 MHz, $CDCl_3$): 176.5 ($COOCH_3$); 67.2 (CH); 53.0 ($COOCH_3$); 20.6 (CH_3CH). HR-MS: 104.0474 ($[M+NH_4]^+$, $C_4H_{12}O_3N^+$; calc. 104.0473).

Methyl (*S*)-(+)-2-Hydroxy-3-methylbutanoate (=**Methyl (2*S*)-2-Hydroxy-3-methylbutanoate**; (*S*)-**8**). L-Valine (15.23 g, 0.13 mol) was reacted according to the *General Procedure* to give 7.05 g (41 %) colorless liquid. B.p. 58–59 °C/15 Torr (Lit. b.p. 61–62 °C/15 Torr[25]). $[\alpha]_{546}^{25} = +18.0$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.12 (br. *s*, OH); 4.04 (*d*, ^3J(H,H) = 3.6, CH); 3.77 (*s*, $COOCH_3$); 2.05 (*dtd*, ^3J(H,H) = 13.8, 6.9, 3.6, $(CH_3)_2CH$); 0.99 (*d*, ^3J(H,H) = 6.9, CH_3CH); 0.84 (*d*, ^3J(H,H) = 6.9, CH_3CH). ^{13}C-NMR (63 MHz, $CDCl_3$): 175.7 ($COOCH_3$); 75.5 (CH), 52.8 ($COOCH_3$); 32.4 ($(CH_3)_2CH$); 19.1 (CH_3CH); 16.4 (CH_3CH). HR-MS: 132.0787 ($[M+H]^+$, $C_6H_{13}O_3^+$; calc. 132.0787).

Methyl (*S*)-(+)-2-Hydroxy-4-methylpentanoate (=**Methyl (2*S*)-2-Hydroxy-4-methylpentanoate**; (*S*)-**9**). L-Leucine (15.00 g, 0.11 mol) was reacted according to the *General Procedure* to give 7.63 g (46 %) colorless liquid. B.p. 76–77 °C/15 Torr (Lit. b.p. 69–70 °C/8 Torr[25]). $[\alpha]_{546}^{25} = +10.6$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.19 (*t*, ^3J(H,H) = 6.6, CHOH); 3.75 (*s*, $COOCH_3$); 3.01 (br. *s*, OH); 1.94–1.78 (*m*, $CH(CH_3)_2$); 1.53 (*dd*, ^3J(H,H) = 6.8, 6.8, CH_2); 0.93 (*d*, ^3J(H,H) = 2.2, $CHCH_3$); 0.91 (*d*, ^3J(H,H) = 2.4, $CHCH_3$). ^{13}C-NMR (63 MHz, $CDCl_3$): 176.7 (COO); 69.4 (CHOH); 52.8 ($COOCH_3$); 43.8 (CH_2); 24.7 ($CH(CH_3)_2$); 23.6 ($CHCH_3$); 21.9 ($CHCH_3$). HR-MS: 146.0942 ($[M+H]^+$, $C_7H_{15}O_3^+$; calc. 146.0943).

Methyl (2*S*,3*S*)-(+)-2-Hydroxy-3-methylpentanoate (=**Methyl (2*S*,3*S*)-2-Hydroxy-3-methylpentanoate**; (2*S*,3*S*)-**10**). L-Isoleucine (15.00 g, 0.11 mol) was reacted according to the *General Procedure* to give 10.27 g (61 %) colorless liquid. B.p. 75–77 °C/15 Torr. $[\alpha]_{546}^{25} = +5.3$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.08 (*d*, ^3J(H,H) = 3.8, *CH*OH); 3.77 (*s*, $COOCH_3$); 2.71 (*s*, OH); 1.88–1.71 (*m*, $CHCH_3$); 1.43–1.13 (*m*, CH_2); 0.96 (*d*, ^3J(H,H) = 6.9, $CHCH_3$); 0.88 (*t*, ^3J(H,H) = 7.4, CH_2CH_3). ^{13}C-NMR (63 MHz, $CDCl_3$): 175.8 ($COOCH_3$); 75.2 (CHOH); 52.6 ($COOCH_3$); 39.5 ($CHCH_3$); 24.1 (CH_2); 15.7 (CH_3); 12.1 (CH_3). HR-MS: 146.0941 ($[M+H]^+$, $C_7H_{15}O_3^+$; calc. 146.0943).

General Procedure for the Synthesis of Methyl α-(Nonafluoro-tert-butoxy)carboxylates. The solution of methyl α-hydroxycarboxylate (40 mmol), triphenylphosphine (15.7 g, 60 mmol) and nonafluoro-*tert*-butanol (15.1 g, 64 mmol) in diethyl ether (100 ml) was cooled to 0 °C, and the solution of DIAD (12.1 g, 60 mmol) in diethyl ether (50 ml) was added dropwise. The mixture was stirred at r.t. for 12 h. Then, the solvent was removed under reduced pressure, and the remaining oil was steam-distilled. The organic phase of the distillate was separated and dried over Na_2SO_4. The crude product was purified by vacuum distillation.

Methyl (*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)propanoate (=**Methyl (2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}propanoate**; (*R*)-**11**). Compound (*S*)-**7** (3.30 g, 32 mmol) was reacted according to the *General Procedure* to give 6.60 g (59 %) colorless liquid. B.p. 131–135 °C. $[\alpha]_{546}^{25} = +32.9$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.71 (*q*, ^3J(H,H) = 6.6, CH); 3.78 (*s*, $COOCH_3$); 1.54 (*d*, ^3J(H,H) = 6.8, CH_3CH). ^{13}C-NMR (63 MHz, $CDCl_3$): 171.0 (COO); 120.5 (*q*, ^1J(C,F) = 292, CF_3); 74.4 (CH); 52.4 ($COOCH_3$); 19.7 (CH_3CH). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.68 (CF_3). HR-MS: 322.0249 ($[M+H]^+$, $C_8H_8O_3F_9^+$; calc. 322.0251).

Methyl (*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-3-methylbutanoate (=**Methyl (2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}-3-methylbutanoate**; (*R*)-**12**). Compound (*S*)-**8** (7.05 g, 53 mmol) was reacted according to the *General Procedure* to give 6.60 g (37 %) colorless liquid. B.p. 153–157 °C. $[\alpha]_{546}^{25} = +16.7$ ($c = 2$, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.41 (*d*, ^3J(H,H) = 5.3, *CH*$COOCH_3$); 3.77 (*s*, $COOCH_3$); 1.65–1.78 (*m*, $CH_2CH(CH_3)_2$); 0.94 (*d*, ^3J(H,H) = 6.2, 2 CH_3). ^{13}C-NMR (63 MHz, $CDCl_3$): 170.5 ($COOCH_3$); 120.5 (*q*, ^1J(C,F)

= 292.4, CF_3); 82.5 (*C*HCOOH); 77.2 (*q*, ^2J(C,F) = 120.5, *C*(CF_3)$_3$); 33.1 (*C*H(CH_3)$_2$); 18.0 (CH_3); 17.8 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.80 (CF_3). HR-MS: 350.0559 ([*M* + H]$^+$, $C_{10}H_{12}O_3F_9^+$; calc. 350.0564).

Methyl (*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-4-methylpentanoate (= **Methyl (2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}-4-methylpentanoate**; (*R*)-**13**). Compound (*R*)-**9** (7.00 g, 48 mmol) was reacted according to the *General Procedure* to give 13.125 g (75%) colorless liquid. B.p. 170–172 °C. $[\alpha]_{546}^{25}$ = +18.1 (*c* = 2, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.65 (*t*, ^3J(H,H) = 6.2, *CH*COOCH$_3$); 3.76 (*s*, COOC*H*$_3$); 2.24–2.08 (*m*, *CH*(CH_3)$_2$); 1.01 (*d*, ^3J(H,H) = 7.0, CH_3); 0.98 (*d*, ^3J(H,H) = 6.9, CH_3). ^{13}C-NMR (63 MHz, $CDCl_3$): 169.6 (*C*OOCH$_3$); 120.5 (*q*, ^1J(C,F) = 292, 2 CF_3); 82.5 (*C*HCOOCH$_3$); 75.4 (*q*, ^2J(C,F) = 293, *C*(CF_3)$_3$); 33.1 (*C*H(CH_3)$_2$); 18.0 (CH_3); 17.8 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.54 (CF_3). HR-MS: 364.0718 ([*M* + H]$^+$, $C_{11}H_{14}O_3F_9^+$; calc. 364.0721).

Methyl (2*R*,3*S*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-3-methylpentanoate (= **Methyl (2*R*,3*S*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}-3-methylpentanoate**; (2*R*,3*S*)-**14**). Compound (2*S*,3*S*)-**10** (9.05 g, 65 mmol) was reacted according to the *General Procedure* to give 14.846 g (63%) colorless liquid. B.p. 168–171 °C. $[\alpha]_{546}^{25}$ = +17.6 (*c* = 2, methanol). ^{1}H-NMR (250 MHz, $CDCl_3$): 4.38 (*d*, ^3J(H,H) = 4.5, *CH*OC(CF_3)$_3$); 3.64 (*s*, COOCH$_3$); 1.81–1.73, 1.51–1.40, 1.15–0.95 (3*m*, CH_2CH); 0.88 (*d*, ^3J(H,H) = 7.0, *CH*$_3$CH); 0.81 (*d*, ^3J(H,H) = 7.4, *CH*$_3$CH). ^{13}C-NMR (63 MHz, $CDCl_3$): 169.7 (*C*OOCH$_3$); 120.5 (*q*, ^1J(C,F) = 294, CF_3); 81.7 (*C*(CF_3)$_3$); 75.2 (*C*HOC(CF_3)$_3$); 52.3 (COO*C*H$_3$); 39.8 (CH_2*CH*); 24.9 (CH_2); 14.5 (CH_3); 11.9 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.6(CF_3). HR-MS: 364.0715 ([*M* + H]$^+$, $C_{11}H_{14}O_3F_9^+$; calc. 364.0721).

General Procedure for the Synthesis of α-(Nonafluoro-tert-butoxy)carboxylic Acids. To the solution of α-(nonafluoro-*tert*-butoxy)carboxylate (30 mmol) in CH_2Cl_2 1.2 M NaOH in MeOH (75 ml) was added, and the mixture was stirred at r.t. for 2 h. Then, the solvent was removed under reduced pressure, and the remaining material was dissolved in water (35 ml). The solution was cooled to 0 °C and acidified with HCl to pH = 2. After standing for an additional 1 h, crystals were filtered, washed with water and dried. The crude product was recrystallized from hexane.

(*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)propanoic Acid (= **(2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}propanoic Acid**; (*R*)-**1**). Compound (*R*)-**11** (6.08 g, 19 mmol) was reacted according to the *General Procedure* to give 4.57 g (79%) white solid material. M.p. 52–54 °C. $[\alpha]_{546}^{25}$ = +33.6 (*c* = 2, methanol). IR (ATR): 487, 539, 633, 696, 724, 769, 838, 885, 967, 989, 1030, 1091, 1122, 1156, 1227, 1249, 1357, 1423, 1457, 1733, 2955. ^{1}H-NMR (600 MHz, $CDCl_3$): 10.22 (br. *s*, COOH); 4.75 (*q*, ^3J(H,H) = 6.8, CH); 1.61 (*d*, ^3J(H,H) = 6.8, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.4 (COOH); 122.7 (*q*, ^1J(C,F) = 293, CF_3); 76.0 (CH); 22.0 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.9 (CF_3). HR-MS: 308.0105 ([*M* + H]$^+$, $C_7H_5O_3F_9^+$; calc. 308.0095).

(*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-3-methylbutanoic Acid (= **(2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)-propan-2-yl]oxy}-3-methylbutanoic Acid**; (*R*)-**4**). Compound (*R*)-**12** (5.95 g, 17 mmol) was reacted according to the *General Procedure* to give 4.12 g (72%) white solid material. M.p. 57–60 °C. $[\alpha]_{546}^{25}$ = +21.6 (*c* = 2, methanol). IR (ATR): 424, 536, 634, 660, 727, 893, 966, 987, 1008, 1023, 1144, 1184, 1247, 1374, 1434, 1650, 1720, 2977. ^{1}H-NMR (600 MHz, $CDCl_3$): 9.20 (br. *s*, COOH); 4.46 (*d*, ^3J(H,H) = 4.9, *CH*COOH); 2.22 (*td*, ^3J(H,H) = 13.7, 6.9, *CH*(CH_3)$_2$); 1.05 (*d*, ^3J(H,H) = 7.1, CH_3); 1.04 (*d*, ^3J(H,H) = 6.9, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.8 (COOH); 122.7 (*q*, ^1J(C,F) = 293, CF_3); 84.1 (CH); 34.3 (*C*H(CH_3)$_2$); 20.2 (CH_3); 20.0 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.45 (CF_3). HR-MS: 336.0418 ([*M* + H]$^+$, $C_9H_8O_3F_9^+$; calc. 336.0408).

(*R*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-4-methylpentanoic Acid (= **(2*R*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}-4-methylpentanoic Acid**; (*R*)-**5**). Compound (*R*)-**13** (9.00 g, 25 mmol) was reacted according to the *General Procedure*. The acidified mixture was an emulsion, which was extracted with diethyl ether (3 × 30 ml), and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure, to give 4.87 g (56%) colorless liquid. $[\alpha]_{546}^{25}$ = +13.0 (*c* = 2, methanol). IR (ATR): 539, 637, 728, 969, 1014, 1154, 1248, 1371, 1471, 1735, 2966. ^{1}H-NMR (600 MHz, $CDCl_3$): 9.54 (br. *s*, COOH); 4.54 (*d*, ^3J(H,H) = 4.1, *CH*COOH); 1.77–1.69 (*m*, $CHCH_2$); 0.99 (*d*, ^3J(H,H) = 7.1, CHC*H*$_3$); 0.98 (*t*, ^3J(H,H) = 7.4, CH_2CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.8 (COOH); 122.7 (*q*, ^1J(C,F) = 293, CF_3); 84.1 (CH); 34.3 (CH(CH_3)$_2$); 20.2 (CH_3); 20.0 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$):

−70.55 (CF_3). HR-MS: 350.0573 ($[M+H]^+$, $C_{10}H_{10}O_3F_9^+$; calc. 350.0564).

(2*R*,3*S*)-(+)-2-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-3-methylpentanoic Acid (=(2*R*,3*S*)-2-{[1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl]oxy}-3-methylpentanoic Acid; (2*R*,3*S*)-**6**). Compound (2*R*,3*S*)-**14** (12.00 g, 33 mmol) was reacted according to the *General Procedure* to give 8.18 g (71%) white solid material. M.p. 52–55 °C. $[\alpha]_{546}^{25} = +8.3$ ($c = 2$, methanol). IR (ATR): 430, 480, 512, 538, 672, 727, 903, 966, 1004, 1106, 1139, 1177, 1248, 1372, 1434, 1641, 1717, 2974. ^{1}H-NMR (600 MHz, $CDCl_3$): 8.45 (br. *s*, COOH); 4.62 (*t*, ^3J(H,H) = 6.0, C*H*COOH); 1.74 (*dd*, ^3J(H,H) = 5.6, ^3J(H,H) = 2.6, CH_2); 1.68–1.77 (*m*, $CH(CH_3)_2$); 0.90 (*d*, ^3J(H,H) = 2.3, CH_3); 0.89 (*d*, ^3J(H,H) = 2.3, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 174.3 (COOH); 119.1 (*q*, ^1J(C,F) = 293, CF_3); 79.0 (*q*, ^2J(C,F) = 293, $C(CF_3)_3$); 75.2 (CHCOOH); 41.5 (CH_2); 22.9 ($CH(CH_3)_2$); 21.5 (CH_3); 21.4 (CH_3). ^{19}F-NMR (235 MHz, $CDCl_3$): −70.73 (CF_3). HR-MS: 350.0574 ($[M+H]^+$, $C_{10}H_{10}O_3F_9^+$; calc. 350.0564).

NMR Experiments

NMR sample solutions were made as follows: 0.027 mmol carboxylic acid was dissolved in 600 μL of deuterated solvent. After ^{1}H- and ^{19}F-NMR measurements, 0.027 mmol amine were added, and the NMR spectra were recorded. All measurements were carried out at 298 K.

Acknowledgements

The authors thank the National Research, Development and Innovation Office (K115764) for supporting this work. This work was partially supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences and by the Bolyai + New National Excellence Program (grant number: ÚNKP-19-4-SE-53) of the Ministry of Human Capacities (*Sz. B.*).

Author Contribution Statement

A. N. and *T. Cs.* designed experiments and made preliminary syntheses. *A. N.* and *D. Sz.* improved them to the laboratory scale and wrote the manuscript. *A. N.*, *Sz. B.* and *Zs. G.* made the one- and two-dimensional NMR measurements along with chiral discrimination experiments, *Zs. G.* recorded the IR and MS spectra, resp. *J. R.* surveyed the literature on fluorous chemistry. All authors commented on manuscript.

References

[1] L. He, T. E. Beesley, 'Applications of Enantiomeric Gas Chromatography: A Review', *J. Liq. Chromatogr. Relat. Technol.* **2005**, *28*, 1075–1114.
[2] E. Badaloni, W. Cabri, A. Ciogli, R. Deias, F. Gasparrini, F. Giorgi, A. Vigevani, C. Villani, 'Combination of HPLC 'Inverted Chirality Columns Approach' and MS/MS Detection for Extreme Enantiomeric Excess Determination Even in Absence of Reference Samples. Application to Camptothecin Derivatives', *Anal. Chem.* **2007**, *79*, 6013–6019.
[3] I. Ilisz, R. Berkecz, A. Péter, 'Application of chiral derivatizing agents in the high-performance liquid chromatographic separation of amino acid enantiomers: A review', *J. Pharm. Biomed. Anal.* **2008**, *47*, 1–15.
[4] L. G. Blomberg, H. Wan, 'Determination of enantiomeric excess by capillary electrophoresis', *Electrophoresis* **2000**, *21*, 1940–1952.
[5] D. Leung, S. O. Kang, E. V. Anslyn, 'Rapid determination of enantiomeric excess: a focus on optical approaches' *Chem. Soc. Rev.* **2012**, *41*, 448–479.
[6] T. J. Wenzel, 'Discrimination of Chiral Compounds Using NMR Spectroscopy', John Wiley & Sons, Inc. Hoboken, New Jersey, 2007.
[7] D. Parker, 'NMR determination of enantiomeric purity', *Chem. Rev.* **1991**, *91*, 1441–1457.
[8] J. M. Seco, E. Quiñoá, R. Riguera, 'The Assignment of Absolute Configuration by NMR', *Chem. Rev.* **2004**, *104*, 17–118.
[9] J. M. Seco, E. Quiñoá, R. Riguera, 'Assignment of the Absolute Configuration of Polyfunctional Compounds by NMR Using Chiral Derivatizing Agents', *Chem. Rev.* **2012**, *112*, 4603–4641.
[10] H. Dodziuk, A. Ejchart, O. Lukin, M. O. Vysotsky, '^{1}H and ^{13}C NMR and Molecular Dynamics Study of Chiral Recognition of Camphor Enantiomers by α-Cyclodextrin', *J. Org. Chem.* **1999**, *64*, 1503–1507.
[11] M. Bernabé, J. Jiménez-Barbero, M. Martin-Lomas, S. Penadés, C. Vicent, 'Chiral recognition of 1-*O*-allyl- and 1-*O*-benzyl-D- and -L-*myo*-inositol by cyclomalto-hexaose and -heptaose (α- and β-cyclodextrin)', *Carbohydr. Res.* **1990**, *208*, 255–259.
[12] Z. Aturki, C. Desiderio, L. Mannina, S. Fanali, 'Chiral separations by capillary zone electrophoresis with the use of cyanoethylated-β-cyclodextrin as chiral selector', *J. Chromatogr. A* **1998**, *817*, 91–104.
[13] Y. Nakatsuji, Y. Nakahara, A. Muramatsu, T. Kida, M. Akashi, 'Novel C_2-symmetric chiral 18-crown-6 derivatives with two aromatic sidearms as chiral NMR discriminating agents', *Tetrahedron Lett.* **2005**, *46*, 4331–4335.
[14] D. J. Chadwick, I. A. Cliffe, I. O. Sutherland, R. F. Newton, 'The formation of complexes between aza derivatives of crown ethers and primary alkylammonium salts. Part 7. Chiral derivatives of aza crown ethers', *J. Chem. Soc., Perkin Trans. 1* **1984**, 1707–1717.

[15] T. J. Wenzel, J. D. Wilcox, 'Chiral reagents for the determination of enantiomeric excess and absolute configuration using NMR spectroscopy', *Chirality* **2003**, *15*, 256–270.
[16] C. A. R. Baxter, H. C. Richards, 'Substituted 1,2,3,4-tetrahydroquinolines. Measurement of optical purity by nuclear magnetic resonance spectroscopy', *Tetrahedron Lett.* **1972**, *13*, 3357–3358.
[17] H. Navrátilová, 'Use of S-mosher acid as a chiral solvating agent for enantiomeric analysis of some trans-4-(4-fluorophenyl)-3-substituted-1-methylpiperidines by means of NMR spectroscopy', *Chirality* **2002**, 731–735.
[18] K. Y. Y. Lao, D. J. Hodgson, B. Dawson, P. H. Buist, 'A micromethod for the stereochemical analysis of fatty acid desaturase-mediated sulfoxidation reactions', *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2799–2802.
[19] W. H. Pirkle, S. D. Beare, 'Optically active solvents in nuclear magnetic resonance spectroscopy. IX. Direct determinations of optical purities and correlations of absolute configurations of α-amino acids', *J. Am. Chem. Soc.* **1969**, *91*, 5150–5155.
[20] M. de Moragas, E. Cervelló, A. Port, C. Jaime, A. Virgili, B. Ancian, 'Behavior of the 9-Anthryl-*tert*-butylcarbinol as a Chiral Solvating Agent. Study of Diastereochemical Association by Intermolecular NOE and Molecular Dynamics Calculations', *J. Org. Chem.* **1998**, *63*, 8689–8695.
[21] T. Csóka, A. Nemes, D. Szabó, 'Synthesis of optically active α-(nonafluoro-*tert*-butoxy)carboxylic acids', *Tetrahedron Lett.* **2013**, *54*, 1730–1733.
[22] A. Nemes, T. Csóka, S. Béni, V. Farkas, J. Rábai, D. Szabó, 'Chiral Recognition Studies of α-(Nonafluoro-*tert*-butoxy) carboxylic Acids by NMR Spectroscopy', *J. Org. Chem.* **2015**, *80*, 6267–6274.
[23] M. del Pilar García-Santos, E. Calle, J. Casado, 'Amino Acid Nitrosation Products as Alkylating Agents', *J. Am. Chem. Soc.* **2001**, *123*, 7506–7510.
[24] F. Degerbeck, B. Fransson, L. Grehn, U. Ragnarsson, 'Synthesis of ^{15}N-labelled chiral Boc-amino acids from triflates: enantiomers of leucine and phenylalanine', *J. Chem. Soc., Perkin Trans. 1* **1993**, 11–14.
[25] M. Poterała, J. Plenkiewicz, 'Synthesis of new chiral ionic liquids from α-hydroxycarboxylic acids', *Tetrahedron Asymmetry* **2011**, *22*, 294–299.
[26] O. Mitsunobu, M. Yamada, 'Preparation of Esters of Carboxylic and Phosphoric Acids *via* Quaternary Phosphonium Salts', *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.
[27] K. C. Kumara Swamy, N. N. Bhuvan Kumar, E. Balaraman, K. V. P. Pavan Kumar, 'Mitsunobu and Related Reactions: Advances and Applications', *Chem. Rev.* **2009**, *109*, 2551–2651.
[28] A.-M. Bálint, A. Bodor, Á. Gömöry, K. Vékey, D. Szabó, J. Rábai, 'Mitsunobu synthesis of symmetrical alkyl and polyfluoroalkyl secondary amines', *J. Fluorine Chem.* **2005**, *126*, 1524–1530.
[29] D. Szabó, A.-M. Bonto, I. Kövesdi, Á. Gömöry, J. Rábai, 'Synthesis of novel lipophilic and/or fluorophilic ethers of perfluoro-*tert*-butyl alcohol, perfluoropinacol and hexafluoroacetone hydrate via a Mitsunobu reaction: Typical cases of ideal product separation', *J. Fluorine Chem.* **2005**, *126*, 641–652.
[30] M. J. O'Neil, 'The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge', UK, Royal Society of Chemistry, 2013, p. 1130.

Received April 20, 2020
Accepted June 30, 2020

