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Synthesis of optically active β-hydroxy-β-polyfluoromethyl GABAs

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Abstract—A general synthetic route to polyfluoromethyl containing analogues of GABA—β-hydroxy-β-tri- and difluoromethyl GABAs **9a** and **9b** was developed, using the corresponding β-alkoxyvinyl polyfluoromethyl ketones—enones **1a** and **1b** as starting materials. Both enantiomers of the potential biologically active compound **9a** were obtained by chiral resolution with (*R*)- or (*S*)-phenylethylamine.

1. Introduction

GABA (4-aminobutanoic acid, γ-aminobutyric acid) is an important central nervous system (CNS) inhibitory neurotransmitter and is present in the brain in large amounts. GABA is a non-protein amino acid found in virtually all prokaryotic and eukaryotic organisms, including plants.[1] Ever since γ-aminobutyric acid was discovered, the great role it plays in the organism has been shown. GABA influences neurons via a large number of receptor subtypes, which are grouped on the basis of their pharmacology under three classes of receptors: $GABA_a$, $GABA_b$ and $GABA_c$ receptors.[2] GABA arises via decarboxylation of L-glutamate by glutamate decarboxylase (GAD) and is subsequently metabolized via GABA-aminotransferase (GABA-AT) to succinic semialdehyde, which is then oxidized to succinate. Inhibition of this enzyme results in an increased concentration of GABA in the brain and could have therapeutic applications in neurological disorders including epilepsy, Parkinson's disease, Huntington's chorea and Alzheimer's disease.[3]

Several methodologies have already been reported for the synthesis of the derivatives and analogues of GABA and their therapeutic action has been uncovered: baclofen (Lioresal® and Baclon®),[4] gabapentin (GBP, Neurontin®),[5] carnitine,[6] vigabatrin,[7] pregabalin[8] and others[9] (Fig. 1). Thus, the introduction of the hydroxy group to C-3 in the molecule of GABA leads to anticonvulsant activity, methylation of the amino group leads to a decrease in the effect of synaptic prohibition. The chirality also plays an important role. These reasons are why the synthesis of GABA analogues have attracted considerable interest in recent years due to their important biological activities.

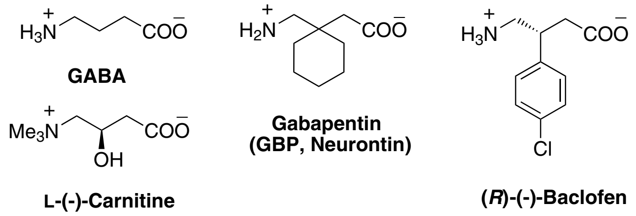

Figure 1. Structures of GABA and its bioactive analogues.

It is well established that the introduction of the fluorine atom or a polyfluoroalkyl group into organic molecules often brings useful and interesting changes into their chemical and physical properties and, of course, influences its biological activity, as was demonstrated for various fluorinated GABAs.[10] Among the fluorinated analogues of GABA, polyfluoroalkyl derivatives are rare and only α-CF_3-substituted α,β-unsaturated GABAs have been synthesized and demonstrated irreversible inhibition of GABA-AT.[11] We supposed that the combination of two pharmacophoric groups, such as an hydroxy and polyfluoromethyl at the same β-carbon atom of GABA skeleton, had to change their biological activity drastically.

For the starting material, we used readily available polyfluoromethyl containing enone **1**, which is widely used as

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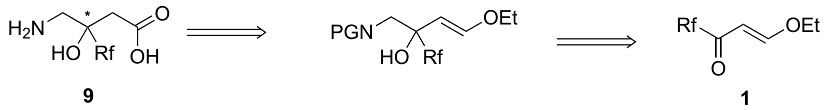


Rf = CF_3, CHF_2; PGN = protected amino group.

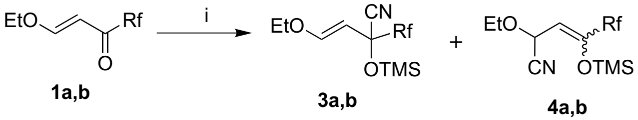
Figure 2. Retrosynthetic steps to β-polyfluoromethyl-β-hydroxy-γ-aminobutyric acids.

a fluorinated building block,[12] due to an interesting reaction profile of the compact molecule. In our laboratory, it has been used in the synthesis of various polyfluoromethyl containing compounds, most of which are trifluoromethyl containing heterocycles,[13] aliphatic polyfunctional products[14] and also enone **1a** (Rf = CF_3) as a protective reagent in peptide synthesis.

It is easy to see from Figure 2 that compound **1**[15,16] is a convenient starting compound for obtaining β-hydroxy-β-polyfluoromethyl GABAs via a few transformations. The polyfluoromethyl fragment presence in molecule **1** and its carbonyl group allowed us to carry out the addition of TMSCN, followed by reduction to the amino group. Alkoxyvinyl group easily hydrolyzes to an aldehyde group, which can be easily converted to carboxylic acid using oxidation as a final step. Herein we report the development of a new, convenient and effective synthesis of racemic and enantiomerically pure β-tri- and difluoromethyl-β-hydroxy-γ-aminobutyric **9a** and **9b** from readily available enones **1**.

2. Results and discussion

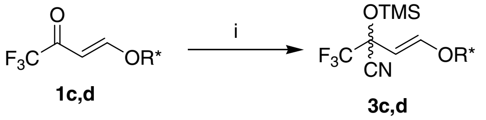
Recently[17] we have found that trimethylsilyl cyanide (TMSCN) easily adds to enone **1** while the regioselectivity of the reaction is very sensitive to conditions. Thus, in the presence of acids 1,4-adducts **4** formed while 1,2-adducts **3** are formed in high yield in the presence of amines (Scheme 1). It is easy to see that adducts **3a** and **3b** can be converted to previously unknown fluorine containing GABAs in several steps, this is why we devoted much time to the peculiarities of performing the reaction 1,2-addition of TMSCN to **1a**, because it will be interesting to carry out the chiral addition of TMSCN to enones **1a** and **1b** in the presence of a catalyst and then to work with enantiopure products. Currently there already is a significant amount of literature regarding chiral addition of TMSCN to carbonyl compounds, most of all at the presence of Lewis acids.[18] However in our case, the use of any acidic catalyst would produce the 1,4-addition product **4**, without the desired product **3** formation.



Rf = CF_3 (**a**), CHF_2 (**b**).

Scheme 1. Reagent: (i) TMSCN.

Our attempts to prepare enantiomerically enriched cyanohydrins **3** were based on chiral enones **1c** and **1d** bearing chiral alkoxy-groups on the vinyl fragment,[19] such as (±)-phenylethoxy, (−)-menthyloxy analogues (Scheme 2).



R* = (±)-CH(Me)Ph (**c**), (-)-Menthyl (**d**).

Scheme 2. Reagents: (i) TMSCN, amine, solvent.

The 1,2-addition of TMSCN was performed in the presence of Et_3N, (−)-sparteine, (−)-*N*,*N*-dimethylphenylethylamine, (−)-cinchonidine, modified cinchona alkaloid—$(DHQ)_2AQN$ and using solvents such as diethyl ether, hexane, dichloromethane and dioxane, with a temperature variation from −20 to +20 °C to study the influence of the reaction conditions on the enantioselectivity of cyanohydrin **3c** and **3d** formation. We analyzed the conversion of the reaction and diastereomeric excess of products **3c** and **3d** by ^{19}F and ^{1}H NMR spectroscopy of the reaction mixture. Thus, in the case of cyanohydrin **3c**, we analyzed the de both by ^{19}F NMR spectra (singlets of CF_3 group of diastereomers **3c** differ on 0.070 ppm) and ^{1}H NMR spectra (the chemical shifts of doublets of vinyl proton R*OC*H* = are δ 6.91 for major diastereomer and δ 6.86 for minor diastereomer). In the case of product **3d**, we analyzed the de only by ^{1}H NMR spectra because the signals of diastereomeric trifluoromethyl groups overlapped in the ^{19}F NMR spectra. Moreover, both the conversion and de of TMSCN addition to (−)-**1d** were essentially lower than for (±)-**1c**, which is why much attention was paid to the corresponding reaction with (±)-**1c**. Some of the results obtained are summarized in Table 1 and it can be seen that the maximal de ratio was obtained with chiral (±)-phenylethoxy auxiliary containing enone **1c** in the presence of Et_3N in ether—25% de. Such a low de can be explained by the large distance between the chiral auxiliary group and the reactive carbonyl group over the *trans*-vinyl fragment. In spite of the poor preliminary results we continued at this stage, looking for suitable catalysts and conditions because enantiomerically pure cyanohydrins **3** are interesting building blocks as corresponding non-fluorinated analogues in organic synthesis.[20]

The next step in our synthetic route was the reduction of cyanohydrins (±)-**3a** and (±)-**3b**. Nitrile group was reduced with $LiAlH_4$ in good yield and the alkoxyvinyl fragment was untouched; however the $SiMe_3$ group was removed

Table 1. Reaction conditions,[a] conversion and diastereomeric excess of the reaction of enone (±)-**1c** with TMSCN

Row	Solvent	T (°C)	Conv.[b] (%)	(±)-**3c**, de[b] (%)
1	Ether	−20	90	20
2	DCM	−20	50	10
3	Hexane	−20	90	15
4	DCM	+20	99	2

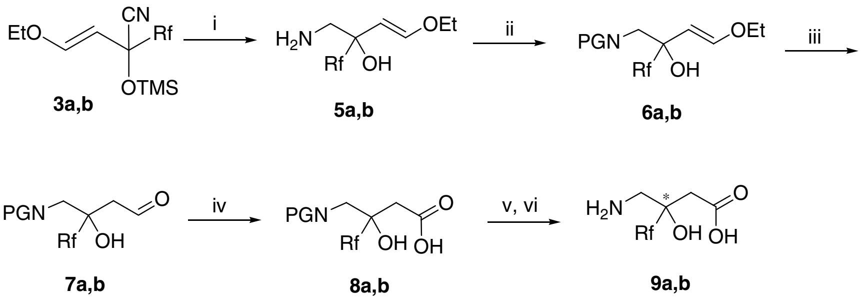
[a] Typical experimental conditions: 0.20 mmol of **1c** was added to the solution of 0.22 mmol of TMSCN and 1–10 mol % of amine in 5 mL of the solvent at predetermined temperature.

[b] The yields and de were determined for reaction mixture by ^{1}H and ^{19}F NMR spectroscopy.

under reaction conditions (Scheme 3). The products of reduction—amino alcohols **5a** and **5b** are easily purified by vacuum distillation as oils, which were crystallized in a refrigerator. Compounds **5** are powerful synthons for further conversions, due to the considerable quantity of functional groups in such a compact molecule. We found that the salt of amine (±)-**5a** with enantiopure tartaric acid (TA) (D- or L-) was easily formed and actually after a third crystallization we obtained a corresponding salt with the high purity de ~98% (Scheme 4). However this method was not successful in the case of amine **5b**, because of the instability of the vinylether fragment under salt formation conditions. We analyzed the enantiomeric excess of the corresponding salts by HPLC method: the co-chromatography with racemic OPA/NBC derivatives under reversed-phase high-performance liquid chromatography (RP-HPLC) was used. The chromatographic procedure consisted of chiral pre-column derivatization of amine **5a** with *o*-phthaldialdehyde (OPA) and *N*-Boc-L-cysteine (NBC) followed by diastereoisomeric isoindol derivative separation by RP-HPLC. At the same time with the resolution of aminoalcohols **5**, we were searching for the possibility to resolve acids **8** by crystallization with chiral amines.

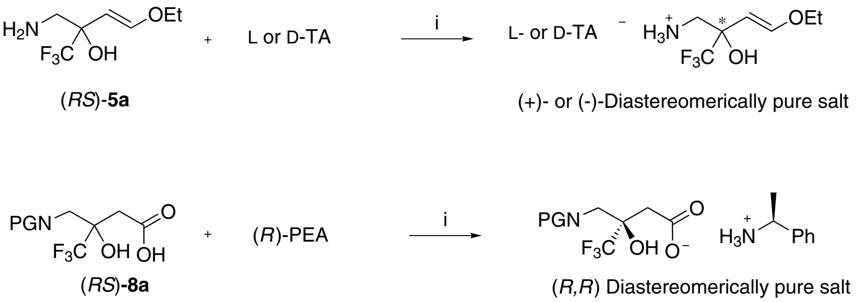
It is known that the alkoxyvinyl group masks the carbonyl group function. We attempted to obtain the intermediate aldehyde by acidic hydrolysis of **5**, but in this case we were unable to obtain the corresponding aminoaldehyde as a consequence of intramolecular condensation of the free amino group and aldehyde functionality. We found that derivatization of the amino group in compounds (±)-**5a** and (±)-**5b** by acylation with either benzoylchloride or other mono-acyl group was not effective enough to prevent the condensation. A good result was obtained by using a phthalimido group for the protection of the amino function and aldehydes **7a** and **7b** were obtained in good yields (Scheme 3). In the case of Rf = CF_3, the reaction proceeds clearly in all stages. In contrast to **6a**, compound **6b** hydrolyzes easily even under weakly acidic conditions to form aldehyde **7b** which was formed without isolation of product **6b**. The corresponding aldehydes **7a** and **7b** were obtained nearly in quantitative yields as oils and involved in the next step without purification.

To oxidize the aldehyde group to carboxylic one, we tried various oxidizing agents[21] and found that the best results



Rf = CF_3 (**a**), CHF_2 (**b**), PGN = N-Phthalimide.

Scheme 3. Reagents and conditions: (i) $LiAlH_4$ in ether, 30% NaOH; (ii) phthalic anhydride, Py, 110 °C; (iii) aq HCl, CH_3CN/H_2O; (iv) Jones' reagent; (v) aq HCl, CH_3COOH, reflux; (vi) Amberlite IR-120.



Scheme 4. Reagents and conditions: (i) crystallized three times from the corresponding solvent (see Experimental).

obtained by us at this stage were with Jones' reagent. The reaction was carried out in the acetone with the excess of Jones' reagent to give the corresponding acid **8**. A disadvantage of this oxidization is that acids **8a** and **8b** are obtained with 90% purity and Cr^{3+} additives are hard to remove. We found that acids **8a** and **8b** gave a crystalline salt with (±)-1-phenylethylamine that we successfully used to purify the protected acids **8**. Moreover, by the use of enantiomerically pure 1-phenylethylamine (*R*)-(+)- or (*S*)-(−)- in forming the salts, we have obtained the corresponding diastereomeric pure salt of **8a** after a third crystallization. The salt of acid **8a** with (*R*)-(+)-1-phenylethylamine was crystallized from dioxane/hexane (4:1) with high de (>99%), while the salt with (*S*)-1-phenylethylamine was crystallized from CH_2Cl_2/hexane (1:1) (Scheme 4). The enantiomeric excess was determined by both ^{19}F NMR and HPLC. However, it was more convenient to control the diastereomeric excess using ^{19}F NMR. In the ^{19}F NMR spectrum of the third crystallized salt samples, the signals of diastereomeric trifluoromethyl groups showed two resonances at δ −80.99 and δ −81.066 (relative to $CFCl_3$) in a ratio of >99:1, respectively, indicating that the enantiomeric purity of the compound was higher than 98%. At the same time, the ^{19}F NMR spectrum of the non-crystallized salt prepared from racemic **8a** with (*R*)-(+) or (*S*)-(−)-1-phenylethylamine showed two resonances of equal intensity, which indicates the successful resolution of the two diastereomers.

The configuration of C-3 in **8a** was determined by X-ray diffraction of enantiomerically pure analytical sample of the salt of (*R*)-**8a** with (*R*)-(+)-1-phenylethylamine obtained by crystallization from acetonitrile. The basic geometry: the length of the bonds O(4)–C(12) 1.266(2) Å and O(5)–C(12) 1.260(2) Å in anion are aligned and are comparable with the lengths in the carboxylate-anion (1.254 Å). The CF_3 group is at the *ap*-position to N(1)–C(9) bond and it is oriented in the direction, which results in sc-conformation of fluorine atom F(2) to C(9)–C(10) torsion angles: N(1)–C(9)–C(10)–C(13) 180.0(2)°, C(9)–C(10)–C(13)–F(2) 61.3(2)° (Fig. 3).

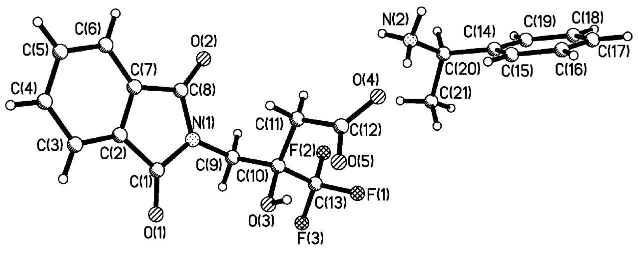


Figure 3. A general view of the X-ray crystallographic structure of diastereomerically pure salt of acid (*R*)-**8a** and (*R*)-(+)-phenylethylamine.

We were unable to obtain the difluoromethyl containing derivative **8b** in good de because it is too complicated to determine the diastereomeric excess. Thus, it is hard to determine de by ^{19}F NMR spectroscopy (because the signals are multiplied), while HPLC analysis is also restricted by pure detection conditions. However, the symmetry of the proton signals of γ-methylene group allows us to derive a conclusion about changing the diastereomeric ratio during crystallization, but it is not enough for exact determination of the ratio.

The free amino acids (±)-**9a** and (±)-**9b** and optically active **9a** were obtained after heating in the mixture of HCl/CH_3COOH[22] (10/1 by volume), then removal of the phthalic acid and purification by ion exchange chromatography.

3. Conclusions

In conclusion, we have developed an effective and original synthetic route to β-hydroxy-β-polyfluoromethyl GABA in racemic and enantiopure forms, starting from a readily available enone **1**. The resolution of the GABA analogues of—β-trifluoromethyl- and β-difluoromethyl-β-hydroxy-γ-aminobutyric acids **9a** and **9b** is based on the fractional crystallization of its *N*-phthalimide derivatives **8a** and **8b** with (*R*)- or (*S*)-1-phenylethylamine. The pharmacology studies of these compounds are currently in a process and will disclosed elsewhere.

4. Experimental

4.1. General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Varian VXR instrument at 300 MHz, Varian Unian Plus at 400 MHz and Bruker Avance DRX at 500 MHz using TMS and CCl_3F as internal standards, respectively. Optical rotations were measured in a 1 dm cell of 1 ml capacity using a PerkinElmer Polarimeter 341. The HPLC experiments were performed on a LKB (Broma, Sweden) liquid chromatographic system consisting of a Model 2150 HPLC pump, a Model 7410 injector, a Model 2140 rapid spectral detector, operating at 340 nm, a Model 2155 column oven and a Model 2200 recording integrator. The column used was Separon SGX C18, 5 μm, 150 × 3.3 mm ID (Tessek, Prague, Czech Republic). The mobile phase was 55:45 (vol.) methanol—2×10^{-2} M phosphate buffer (pH = 6.2), running at 0.3 ml/min. The derivatizing reagent was prepared before analysis by dissolving appropriate amounts of OPA and, freshly reduced, NBC in methanol to form 2.5×10^{-2} M solution. 20 μL of the amine solution (1 mg/mL) was mixed with 50 μL derivatizing reagent and 300 μL 2×10^{-2} M borate buffer (pH = 9.5), and incubated for 3 min in darkness at ambient temperature, after which 15 μL aliquot was injected onto the column.

Melting points are uncorrected. The conversion of TMSCN addition reaction was monitored by GC on a 'Chrom-5' (Prague, Czechoslovakia) instrument (FID, thermostat temperature: 100–150 °C, gas-carrier—nitrogen (20–30 mL min^{-1}), steel column 3 mm × 2400 mm, stationary phase SE-30 (5%) or by TLC-plates (silica gel 60 F254, Merck). Reagents and solvents were commercially available (Aldrich, Fluka, Merck). All solvents and liquid reagents were distilled before use. Starting materials: 4-ethoxy-1,1,1-trifluoro-but-3-en-2-one,[15] 4-ethoxy-1,1-difluoro-but-3-en-2-one[16] were prepared by literature methods.

4.2. General procedure for the preparation of 1,2-adducts 3a and 3b

To a mixture of 50 mg (0.5 mmol) Et_3N and 1.29 g (13 mmol) TMSCN was added 10 mmol of ketones **1a** and **1b** under stirring and at 0–5 °C. Then the mixture was stirred for 15 min and allowed to stand overnight at room temperature. The product was isolated by vacuum distillation.

4.2.1. (*E*)-2-Trifluoromethyl-4-ethoxy-2-trimethylsiloxy-3-butenenitrile 3a. Yield (80%), bp 84–85 °C/15 mmHg (lit.[17] bp 84–85 °C/15 mmHg); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.26 (s, 9H), 1.32 (t, 3H, $J = 7.1$ Hz), 3.85 (q, 2H, $J = 7.1$ Hz), 4.83 (d, 1H, $J = 12.5$ Hz), 6.98 (d, 1H, $J = 12.5$ Hz); ^{19}F NMR (282.3 MHz, $CDCl_3$) δ: −82.00 (s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 0.78, 14.26, 66.27, 72.51 (q, $J = 35$ Hz), 96.96, 114.82, 121.88 (q, $J = 285.0$ Hz), 157.96.

4.2.2. (*E*)-2-Difluoromethyl-4-ethoxy-2-trimethylsilyloxy-3-butenenitrile 3b. Yield (81%); bp 102–103 °C/14 mmHg (lit.[17] bp 103–105 °C/15 mmHg); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.26 (s, 9H), 1.33 (t, 3H, $J = 7.1$ Hz), 3.85 (q, 2H, $J = 7.1$ Hz), 4.80 (d, 1H, $J = 12.5$ Hz), 5.56 (t, 1H, $J = 56.1$ Hz), 6.90 (d, 1H, $J = 12.5$ Hz); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: −130.77 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz), −125.98 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz).

4.2.3. (*E*)-2-Hydroxy-4-(1-phenylethoxy)-2-trifluoromethyl-2-trimethylsilyloxy-3-butenenitrile 3c. ^1H NMR (500 MHz, $CDCl_3$) δ: the major diastereoisomer: 1.59 (d, 3H, $J = 6.5$ Hz), 4.98 (d, 1H, $J = 12.5$ Hz), 6.93 (d, 1H, $J = 12.5$ Hz); the minor diastereoisomer: 1.61 (d, 3H, $J = 6.5$ Hz), 4.87 (d, 1H, $J = 12.5$ Hz), 6.88 (d, 1H, $J = 12.5$ Hz), other signals are identical: 0.14 (s, 9H), 5.18 (q, 1H, $J = 6.5$ Hz), 7.36 (m, 5H); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: the major diastereoisomer: −82.15 (s); the minor diastereoisomer: −82.08 (s).

4.3. General procedure for the preparation of aminoalcohols 5a and 5b

To a suspension of $LiAlH_4$ (2.03 g, 53.5 mmol) in dry ether (50 mL), adducts **3a** and **3b** (48.6 mmol) were added dropwise under stirring for 30 min at 0–5 °C. The mixture was stirred overnight at room temperature. Excess $LiAlH_4$ was decomposed with 30% NaOH (10 mL) under stirring at 0 °C. The alumina was then filtered off and washed thoroughly with ether (50 mL × 3). The filtrate was dried (Mg_2SO_4) and concentrated under reduced pressure. The rest was purified by vacuum distillation.

4.3.1. (*E*)-1,1,1-Trifluoro-4-ethoxy-2-(aminomethyl)-3-buten-2-ol 5a. Yield (88%); bp 85–90 °C/0.1 mmHg; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.32 (t, 3H, $J = 7.1$ Hz), 2.16 (s, 3H), 2.7 (d, 1H, $J = 13.0$ Hz), 3.12 (d, 1H, $J = 13.0$ Hz), 3.77 (q, 2H, $J = 7.1$ Hz), 4.7 (d, 1H, $J = 12.5$ Hz), 6.75 (d, 1H, $J = 12.5$ Hz); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: −81.60 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.62, 45.3, 65.46, 72.51 (q, $J = 35.0$ Hz), 99.27, 125.86 (q, $J = 285.0$ Hz), 150.9. Anal. Calcd for $C_7H_{12}F_3NO_2$: C, 42.21; H, 6.07; N, 7.03. Found: C, 42.36; H, 6.25; N, 7.01.

4.3.2. (*E*)-1,1-Difluoro-4-ethoxy-2-(aminomethyl)-3-buten-2-ol 5b. Yield (80%); bp 90–95 °C/0.1 mmHg; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, 3H, $J = 7.1$ Hz), 2.28 (s, 3H), 2.73 (d, 1H, $J = 13.0$ Hz), 3.05 (d, 1H, $J = 13.0$ Hz), 3.77 (q, 2H, $J = 7.1$ Hz), 4.69 (d, 1H, $J = 12.5$ Hz), 5.57 (t, 1H, $J = 56.1$ Hz), 6.68 (d, 1H, $J = 12.5$ Hz); ^{19}F NMR (470.5, $CDCl_3$) δ: −130.77 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz), −125.98 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.58, 44.91, 65.24, 72.61 (t, $J = 21.5$ Hz), 100.46, 117.34 (t, $J = 248.5$ Hz), 150.24. Anal. Calcd for $C_7H_{13}F_2NO_2$: C, 46.40; H, 7.23; N, 7.73. Found: C, 46.29; H, 7.34; N, 7.65.

4.4. (*E*)-4-Ethoxy-2-hydroxy-2-trifluoromethyl-but-3-enyl-isoindole-1,3-dione 6a

A solution of phthalic anhydride (6.32 g, 42.6 mmol) and amine **5a** (8.5 g, 42.6 mmol) in dry pyridine (30 mL) was stirred for 12 h at 35–40 °C and then heated at reflux for 24 h. The reaction mixture was cooled to ambient temperature and evaporated under reduced pressure, after which 20 mL of methylene chloride was added. The solution was washed with 1% HCl and with H_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by crystallization from ether/hexane (2:1) and phthalimide **6a** was obtained as white crystals (10 g, 71%), mp 77 °C; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.21 (t, 3H, $J = 7.1$ Hz), 3.69 (q, 2H, $J = 7.1$ Hz), 4.01 (d, 1H, $J = 14.5$ Hz), 4.11 (d, 1H, $J = 14.5$ Hz), 4.68 (d, 1H, $J = 12.5$ Hz), 6.73 (d, 1H, $J = 12.5$ Hz), 7.77 (m, 2H), 7.89 (m, 2H); ^{19}F NMR (470.5, $CDCl_3$) δ: −81.64 (s); Anal. Calcd for $C_{15}H_{14}F_3NO_4$: C, 54.72; H, 4.29; N, 4.25; Found: C, 54.70; H, 4.38; N, 4.28.

4.5. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-butyraldehyde 7a

To a solution of **7a** (2 g, 6 mmol) in a mixture of acetonitrile (4 mL) and water (2 mL) was added 5% HCl (1 mL). The mixture was made to stand at room temperature over 2 days. The solvents were evaporated in vacuum and the crude product was obtained (1.8 g, 98%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.69 (d, 1H, $J = 16.5$), 2.85 (d, 1H, $J = 16.5$ Hz), 4.07 (d, 1H, $J = 14.5$ Hz), 4.14 (d, 1H, $J = 14.5$ Hz), 7.80 (m, 2H), 7.91 (m, 2H), 9.82 (s, 1H); ^{19}F NMR (470.5, $CDCl_3$) δ: −80.64 (s).

4.5.1. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,4-difluoro-3-hydroxy-butyraldehyde 7b. Aldehyde **7b** was obtained from amine **5b** by the same procedure as for **6a**, without the isolation of **6b**, because product **6b** easily hydrolyzes (90%, yellow oil). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.71 (d, 1H, $J = 17.0$ Hz), 2.81 (d, 1H, $J = 17.0$ Hz), 3.99 (s, 2H), 5.89 (t, 1H, 56.1 Hz), 7.75 (m, 2H), 7.86 (m, 2H), 9.78 (s, 1H). ^{19}F NMR (470.5, $CDCl_3$) δ: −132.63 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz), −131.70 (dd, 1F, $J_{FF} = 272.1$ Hz, $J_{FH} = 56.1$ Hz).

4.6. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-butyric acid 8a

The solution of aldehyde **7a** (1.8 g, 5.9 mmol) in acetone (10 mL) was added dropwise to a solution of Jones' reagent (5 mL) under room temperature while stirring. The mixture was stirred over 5 h, after which the excess of Jones' reagent was decomposed with isopropanol (5 mL) and the rest was treated with methylene chloride (2 × 100 mL). The solution was washed with water (200 mL) and dried over Mg_2SO_4. The organic phase was concentrated in vacuum to give compound **8a** (1.5 g, 80%) as a slightly green solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.77 (d, 1H, $J = 16.5$ Hz), 2.91 (d, 1H, $J = 16.5$ Hz), 4.11 (d, 1H, $J = 14.5$ Hz), 4.21 (d, 1H, $J = 14.5$ Hz), 7.77 (m, 2H), 7.89 (m, 2H); ^{19}F NMR (470.5, $CDCl_3$) δ: −80.90 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 36.08, 41.24, 74.29 (q, $J = 28.8$ Hz), 123.45 (q, $J = 285$ Hz), 123.91, 131.55, 134.65, 168.67, 174.54. Anal. Calcd for $C_{13}H_{10}F_3NO_5$: C, 49.22; H, 3.18; N, 4.42. Found: C, 49.12; H, 3.25; N, 4.33.

4.6.1. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,4-difluoro-3-hydroxy-butyric acid 8b. The compound was obtained by adopting the same procedure as that adopted for acid **8a** from aldehyde **7b**, 80% as a slightly green solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.68 (d, 1H, $J = 16.8$ Hz), 2.82 (d, 1H, $J = 16.8$ Hz), 4.06 (s, 2H), 6.01 (t, 1H, $J = 56.1$ Hz), 7.76 (m, 2H), 7.88 (m, 2H). ^{19}F NMR (470.5, $CDCl_3$) δ: −133.11 (dd, 1F, $J_{FF} = 286.4$ Hz, $J_{FH} = 55.4$ Hz), −132.20 (dd, 1F, $J_{FF} = 286.4$ Hz, $J_{FH} = 55.4$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.93, 41.00, 73.53 (t, $J = 21.5$ Hz), 115.28 (t, $J = 248.5$ Hz), 123.80, 131.66, 134.53, 168.93, 175.09. Anal. Calcd for $C_{13}H_{11}F_2NO_5$: C, 52.18; H, 3.71, N, 4.68. Found: C, 52.27; H, 3.90; N, 4.58.

4.7. General procedure for the preparation of diastereomeric salts

The resolution of amine **5a** is as follows: to a 50 mL flask were added (*RS*)-**5a** (1.0 g, 5.02 mmol) in acetonitrile and (*R*)- or (*S*)-TA (tartaric acid) (0.75 g, 5.02 mmol); the mixture was heated to about 50 °C to give a clear solution, after which the solvent was evaporated and the rest crystallized from dioxane/hexane (1/1). After a third crystallization, the diastereomerically pure salt of **5a** was obtained, as white crystals; mp 125 °C for the racemic salt and 130–135 °C for diastereomeric pure salts correspondingly (0.45 g, 1.36 mmol, 27% yield, 98% de).

The resolution of acid **8a** is as follows: (*S*)- or (*R*)-1-phenylethylamine (0.57 g, 4.73 mmol) and (*RS*)-**8a** (1.5 g, 4.73 mmol) were combined in methylene chloride (10 mL). After standing at room temperature for 15 min, the solvent was evaporated and the rest was crystallized from dioxane/hexane (2/1) in the case of (*R*)- and from methylene chloride/ether (1.5/1) for (*S*)-1-phenylethylamine, correspondingly. After a third crystallization, we obtained diastereomerically pure salt in the form of white crystals. Mp 150 °C for the racemic salt and 160–165 °C for diastereomeric pure salts (0.6 g, 30.6%, >99% de).

4.7.1. Crystallographic analysis for the salt of acid 8a and (*R*)-1-phenylethylamine. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-623404. CCDC-623404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.

4.8. General procedure for the preparation of β-hydroxy-β-polyfluoromethyl-γ-aminobutyric acid 9a,b

A mixture of *N*-protected amino acids **8a** and **8b** (1.0 mmol), acetic acid (3.0 mL) and 6 M HCl (30 mL) was heated for 3–4 h at 120 °C (bath temperature) (monitoring by TLC). The mixture was allowed to cool to room temperature and the solvents were evaporated in vacuum. Water (30 mL) was added to the residue and extracted with ethyl acetate (2 × 30 mL). The aqueous phase was concentrated in vacuum, passed through Amberlite IR-120 ion exchange resin and the resin was washed with distilled water. Elution of the resin with 3% aq NH_4OH furnished racemic and (*R*) or (*S*) amino acid **9a**,**b**, correspondingly to optical purity of starting acids **8a**,**b**.

4.8.1. 4,4,4-Trifluoro-3-hydroxy-3-(aminomethyl)-butanoic acid 9a. Yield (90%) as a white solid, (*R*)-**8a**: $[\alpha]_D^{25} = +32.2$ (*c* 0.8, 1% NH_3). ^1H NMR (500 MHz, D_2O) δ: 2.60 (s, 2H), 3.25 (d, 1H, $J = 13.9$ Hz), 3.32 (d, 1H, $J = 13.9$ Hz); ^{19}F NMR (470.5, D_2O) δ: −81.29 (s); ^{13}C NMR (125 MHz, D_2O) δ: 37.75, 41.84, 71.38 (q, $J = 28.8$ Hz), 126.15 (q, $J = 285.0$ Hz), 176.34. Anal. Calcd for $C_5H_8F_3NO_3$: C, 32.09, H, 4.31, N, 7.49. Found: C, 32.07, H, 4.48, N, 7.45.

4.8.2. 4,4-Difluoro-3-hydroxy-3-(aminomethyl)-butanoic acid 9b. Yield (92%) as a light brown solid. ^1H NMR (500 MHz, D_2O) δ: 2.71 (d, 1H, $J = 16.5$ Hz), 2.75 (d, 1H, $J = 16.5$ Hz), 3.28 (d, 1H, $J = 14.2$ Hz), 3.32 (d, 1H, $J = 14.2$ Hz), 5.99 (t, 1H, $J = 56.1$ Hz); ^{19}F NMR (470.5, D_2O) δ: −132.9 (dd, 1F, $J_{FF} = 286.4$ Hz, $J_{FH} = 55.4$ Hz), −131.81 (dd, 1F, $J_{FF} = 286.4$ Hz, $J_{FH} = 55.4$ Hz); ^{13}C NMR (125 MHz, D_2O) δ: 38.77, 41.67, 70.42 (t, $J = 21.5$ Hz), 116.15 (t, $J = 248.5$ Hz), 176.94. Anal. Calcd for $C_5H_9F_2NO_3$: C, 35.51, H, 5.36, N, 8.28. Found: C, 35.75, H, 5.44, N, 8.22.

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References

1. Waagepetersen, H. S.; Sonnewald, U.; Schousboe, A.. *J. Neurochem.* **1999**, *73*, 1335–1342.
2. Chebib, M.; Johnoston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1428–1447.
3. Nanavati, S. M.; Silverman, R. B. *J. Med. Chem.* **1989**, *32*, 2413–2421.
4. Felluga, F.; Gombac, V.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1341–1345; Moglioni, A. G. *Tetrahedron: Asymmetry* **2002**, *13*, 451–454.
5. Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149–177.
6. Comber, R. N.; Hoster, C. A.; Brouilette, W. J. *J. Org. Chem.* **1985**, *50*, 3627–3631; Jain, R. P.; Williams, R. M. *Tetrahedron* **2001**, *57*, 6505–6509; Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133–141.
7. Wei, Z.-Y.; Knaus, E. E. *Synlett* **1993**, *4*, 295–296.
8. Beliotti, T. R.; Caparis, T.; Ekhato, V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhu-Su, T.; Weber, M. L.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 2294–2307.
9. Silverman, R. B.; Levy, M. A. *J. Biol. Chem.* **1981**, *256*, 11565–11568; Kolb, M.; Barth, J.; Heydt, J.; Jung, M. J. *J. Med. Chem.* **1987**, *30*, 267–272; Andruszkiewicz, R.; Silverman, R. B. *J. Biol. Chem.* **1990**, *265*, 22288–22291; Duke, R. K.; Chebib, M.; Hibbs, D. E.; Johnston, M. G. A. R. *Tetrahedron: Asymmetry* **2004**, *15*, 1745–1751; Aguirre, D.; Cativiela, C.; Dıaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **2006**, *62*, 8142–8146.
10. Wang, Z.; Silverman, R. B. *Bioorg. Med. Chem.* **2006**, *14*, 2242–2252.
11. Jonson, T. R.; Silverman, R. B. *Bioorg. Med. Chem.* **1999**, *7*, 1625–1636.
12. Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 483–505.
13. Gerus, I. I.; Vdovenko, S. I.; Gorbunova, M. G.; Kukhar, V. P. *Khim. Heterocycl. Soed.* **1991**, *4*, 502–511; Gerus, I. I.; Gorbunova, M. G.; Kukhar, V. P.; Schmutzler, R. *J. Fluorine Chem.* **1998**, *90*, 1–3; Kacharova, L. M.; Gerus, I. I.; Kacharov, A. D. *J. Fluorine Chem.* **2002**, *117*, 193–197; Lyutenko, N. V.; Gerus, I. I.; Kacharov, A. D.; Kukhar, V. P. *Tetrahedron* **2003**, *59*, 1731–1738.
14. *Fluorine-containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley: New York, 1996.
15. Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, *5*, 499–502.
16. Gorbunova, M. G.; Gerus, I. I.; Kukhar, V. P. *Synthesis* **2000**, *5*, 738–742.
17. Gerus, I. I.; Kruchok, I. S.; Kukhar, V. P. *Tetrahedron Lett.* **1999**, *40*, 5923–5926; Kruchok, I. S.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **2000**, *56*, 6533–6539.
18. Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694.
19. Kondratov, I. S.; Gerus, I. I.; Kacharov, A. D.; Gorbunova, M. G.; Kukhar, V. P.; Fröhlich, R. *J. Fluorine Chem.* **2005**, *126*, 543–550.
20. Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; North, M. *Synlett* **1993**, 807–820.
21. *Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; John Wiley: New York, 1999.
22. Camps, P.; Perez, F.; Soldevilla, N.; Borrego, M. A. *Tetrahedron: Asymmetry* **1999**, *10*, 493–509.