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ARTICLE

Synthesis and physical chemical properties of 2-amino-4-(trifluoromethoxy)butanoic acid – CF_3O-containing analogue of natural lipophilic amino acids.

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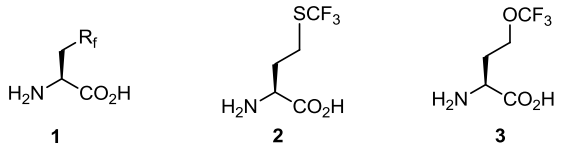
Ivan S. Kondratov,*[a,b] Ivan G. Logvinenko,[a,b] Natalyia A. Tolmachova,[a,b] Roman N. Morev,[a] Maria A. Kliachyna,[a] Florian Clausen,[c] Constantin G. Daniliuc[c] and Günter Haufe*[c,d]

2-Amino-2-(trifluoromethoxy)butanoic acid (*O*-trifluoromethyl homoserine) was synthesized as a racemate and in both enantiomeric forms. Measured pK_a and log*D* values establish the compound as promising analogue of natural aliphatic amino acids.

Fluorinated amino acids are a remarkable class of organofluorine compounds, which attract widespread attention of researchers in various fields such as medicinal chemistry and enzymology [1,2]. These compounds as well as their derivatives exhibit a broad spectrum of biological activities [3] and the corresponding F-18 labelled isotopomers are applied for PET-imaging [4]. They are also useful building blocks for synthesis of biologically active peptidomimetics and model peptides [5]. For instance, Koksch et al. incorporated different α-amino acids of general structure **1** containing fluoroalkyl chains into peptides as analogues of valine, leucine, and isoleucine (Fig. 1). Structural and functional upgrading of peptides and proteins was demonstrated [6].



1 **2** **3**

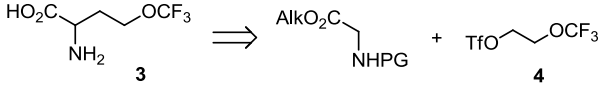
R_f = CH_2F, CHF_2, CF_3, etc.

Fig. 1 Compounds **1-3** as fluorinated analogues of lipophilic aminoacids.

Another lipophilic amino acid, trifluoromethionine (**2**) [7], was also incorporated into different peptides to replace methionine [8] and exhibited significant activity as anti-infective agent [9].

Properties of the CF_3O-group make it also attractive for introduction into α-amino acid's side chain. Thus, according to literature data the lipophilicity of the CF_3O-group in aromatic systems is comparable to that of CF_3- and CF_3S-groups [10,11]. Moreover, it is worth mentioning that the CF_3O substituent is thermally stable and chemically resistant towards acids and bases, reducing and oxidizing agents, and organometallic species [12]. The electronic properties of this substituent are determined by the fact that n-electron pairs of the oxygen are delocalized into the σ*-orbitals of the adjacent C-F bonds [10]. Different approaches to CF_3O-containing compounds (mostly aromatic) were developed [10]. Recent achievements to introduce a CF_3O-group into aliphatic position involve the oxidative trifluoromethylation of alcohols using Ruppert-Prakash reagent [13], the nucleophilic trifluoromethoxylation using various generators of trifluoromethoxide [14] and trifluoromethoxylation promoted by transition metals [15]. Nevertheless, compounds bearing a CF_3O-group in aliphatic or alicyclic positions are still rather rare. This might be due to the limited number of synthetic methods for direct incorporation of this group and by the low accessibility of CF_3O-containing building blocks. For instance, almost no data are available for CF_3O-containing α-amino acids except the recently reported syntheses of several protected derivatives by Qing et al. [13].

This communication presents a straightforward synthesis and physical chemical data of 2-amino-4-trifluoromethoxy-butanoic acid (*O*-trifluoromethyl homoserine, **3**) as an analogue of lipophilic natural amino acids. Retrosynthesis implies alkylation of a protected glycine derivative with the CF_3O-substituted triflate **4** (Scheme 1).

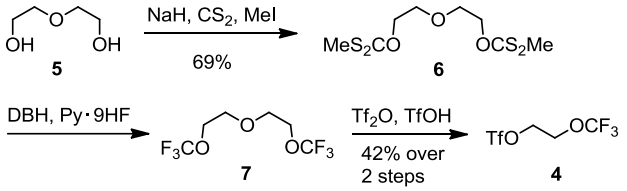


Scheme 1 Retrosynthesis of compound **3** starting from triflate **4**.

[a] Enamine Ltd, Chervonotkatska St 78, Kyiv, 02094, Ukraine.
[b] Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska Str. 1, Kyiv, 02660, Ukraine
[c] Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, Münster 48149, Germany.
[d] Cells-in-Motion Cluster of Excellence, Universität Münster, Waldeyerstraße 15, 48149 Münster, Germany.

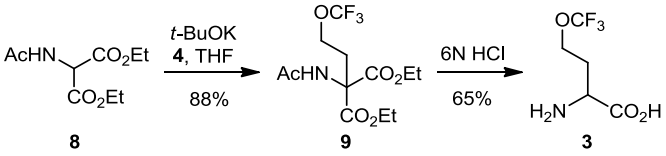
† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterization data and copies of NMR spectra of new compounds are given in the Electronic Supplementary Information. See DOI: 10.1039/x0xx00000x

Triflate **4** has been previously synthesized by Wakselman et al. [16] from diethylene glycol (**5**) in three steps via **6** and **7**. We adapted this approach for multigram synthesis and obtained 31g of compound **4** (29% yield over three steps, Scheme 2).



Scheme 2 Synthesis of triflate **4**.

The racemic amino acid **3** was prepared by alkylation of *N*-acetyl diethyl malonate (**8**) with **4** using potassium *tert*-butoxide as the base to give **9** (88% yield), which was easily hydrolysed with subsequent decarboxylation by refluxing with 6N HCl to give the target amino acid **3** in 65% yield (Scheme 3). Remarkably, the CF_3O-group tolerated these harsh conditions: not any by-products resulting from CF_3O-group decomposition were observed.



Scheme 3 Synthesis of racemc amino acid **3**.

For asymmetric synthesis of enantiomers (+)- and (–)-**3**, imino *tert*-butylesters (+)-**13** and (–)-**13** were prepared from enantiomeric α-pinenes via (+)-(*R,R,R*)-2-hydroxy-3-pinanone ((+)-**12**) and (–)-(*S,S,S*)-2-hydroxy-3-pinanone ((–)-**12**), respectively, following a known protocol [17] (Scheme 4). These auxiliaries were used for the first time by Yamada et al. for asymmetric synthesis of α-amino acids [18]. Later many other groups utilized these imino esters for different diastereoselective alkylations and aldol-type reactions [19,20] including some syntheses of fluorine containing amino acids [21]. Alkylation of the enantiomers **13** with the triflate **4** proceeded diastereoselectively to give (+)-**14** and (–)-**14** with 67 and 60% de, respectively (by ^{19}F NMR and GC). In both cases the major isomers (+)-**14** and (–)-**14** were separated from the minor ones with >95% de by column chromatography (1% Et_3N in EtOAc/cyclohexane, 1:6) contaminated with the starting ketones (–)- or (+)-2-hydroxy-3-pinanone (+)-**12** and (–)-**12** (~40 and ~20%, respectively) due to the close R_f-values. Hydrolysis with 6N HCl was executed starting from these mixtures. As in the case of compound **9**, the hydrolysis of (+)-**14** and (–)-**14** proceeded smoothly giving the amino acid hydrochlorides (+)-**3** and (–)-**3** with 13% and 36% overall yields, respectively (>95% ee). Again we did not observe any products of CF_3O-group decomposition.

The absolute configuration of compound (+)-**3** was confirmed by X-ray analysis (Fig. 2) [22]: as all natural lipophilic (+)-amino acids it has (*S*)-(or L)-configuration. According to the X-ray, the crystal contains a 1:1 mixture of the hydrochloride and the betaine form. The CO_2H and CO_2^- groups do interact through a hydrogen bond. Another remarkable property is the folded conformation of the chain containing the CF_3O-group, which has a *gauche*-orientation with regard to the C1-C2-bond.

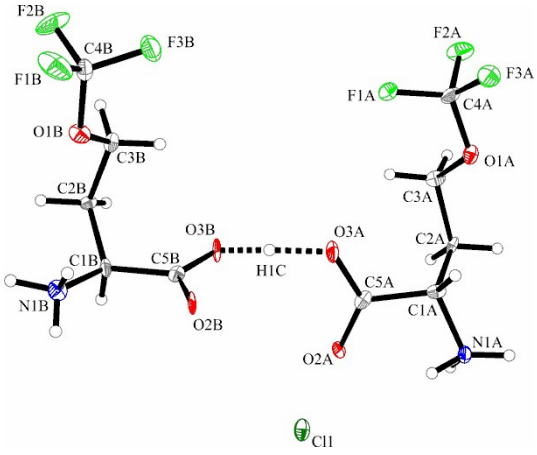
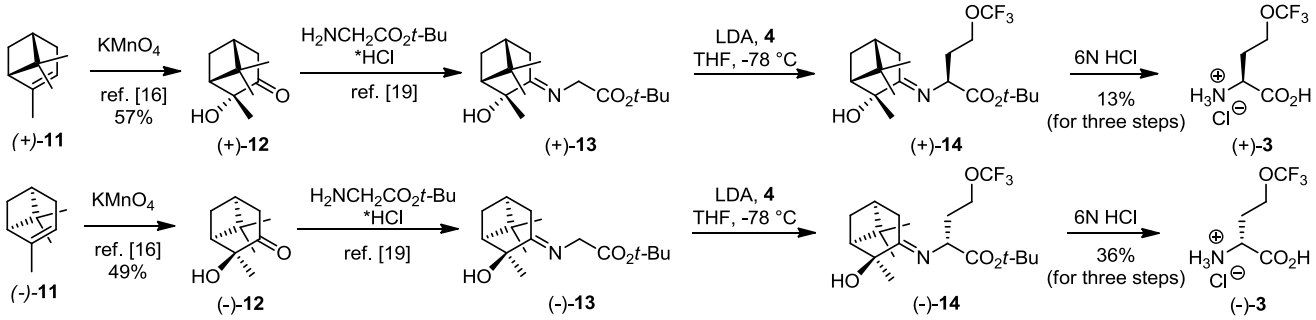


Fig.2 Crystal structure of compound (+)-**3a** [22]. Thermal ellipsoids are shown at 30% probability



Scheme 4 Synthesis the enantiopure CF_3O-containing amino acids (+)- and (-)-**3**.

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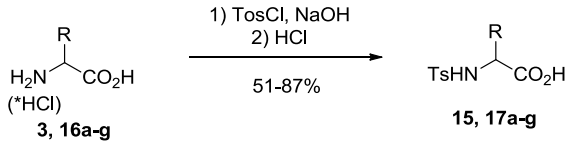
With amino acid **3** in hand, its pK_a values as well as pK_a values of some natural [23] and non-natural lipophilic amino acids **16a-g** were measured for comparison (see Table 1). Remarkably the pK_a values of compound **3** are close to those of valine and leucine but quite different from most of the other measured amino acids. The data show that the CF_3O-group has minor impact on the pK_a values in comparison with MeS-, MeO- and CF_3-groups in the same distance from the functional groups (Table 1, entries 2, 5 and 8).

Furthermore, we compared the lipophilicity of *N*-tosyl derivatives of amino acids **3** and **16a-g** in order to estimate the impact of the CF_3O-group. Effect of fluorine on lipophilicity is extremely important for drug discovery and was extensively studied during the past decade [11,24,25]. Recently, lipophilicity of CF_3O-containing aromatics was investigated [10,11], while no investigation for CF_3O-containing aliphatic molecules was found in the literature. Since amino acids themselves are not suitable for log*D* measurements because of their ionic character [25,26], we investigated *N*-tosyl derivatives **15** and **17a-g** [27-29] (Scheme 5, Table 1).

The measured Log*D* value of *N*-tosyl amino acid **15** (entry 1) is similar to methionine derivative **17a** (entry 2) while tosylates of valine **17b** and leucine **17c** (entries 3,4) are more hydrophilic. Comparison of **15** with the non-fluorinated analogue **17d** demonstrates remarkable increase of Log*D* value (ΔLog*D* = 1.36), which is in agreement with observed ΔLog*P* in case of replacement of CH_3O- by CF_3O-group in aromatic compounds [11]. It is also interesting to compare compound **15** with known fluorinated amino acids **17e-g**. The parent amino acids were previously used as "surrogates" of valine, leucine and isoleucine [6,25]. As expected difluoro- and trifluoroethyl glycine derivatives **17e,f** (entries 6,7) are less lipophilic than **15**. On the other hand the trifluoropropyl glycine derivative **17g** (entry 8) has almost the same lipohilicity value as amino acid **15**. Only minor differences in lipophilicity therefore arise from the replacement of CF_3- with CF_3O-group.

In summary, the first unprotected aliphatic CF_3O-containing amino acid **3** has been synthesised both as racemate and pure enantiomers. The absolute configuration of (+)-enantiomer was confirmed by X-ray analysis which also demonstrates an unusually folded conformation of the lipophilic chain. The pK_a value is close to those of natural neutral amino acids and log*D* measurements of *N*-tosyl derivatives demonstrate remarkable lipophilicity similar to that of methionine and trifluoropropyl glycine derivatives **17a** and **17g**. Therefore amino acid **3** is a promising building block for incorporation into peptides replacing natural lipophilic amino acids.



Scheme 5. Synthesis of *N*-tosyl amino acids **15**, **17a-g** (see Table 1 for R).

Table 1 Measured pK_a values of amino acids **3**, **16a-g** [23] and log*D* values for *N*-tosyl derivatives **15**, **17a-g**.

Entry	Starting amino acid	R	pK_a values of amino acids **3**, **16**	*N*-tosyl amino acid (yield)	log*D* of **15**, **17**
1	**3**	$(CH_2)_2OCF_3$	9.70/2.40	**15** (73)	-0.10
2	**16a**	$(CH_2)_2SMe$	9.24/2.20	**17a** (67)	-0.33
3	**16b**	*i*-Pr	9.72/2.26	**17b** (87)	-1.18
4	**16c**	*i*-Bu	9.69/2.27	**17c** (77)	-0.71
5	**16d**	$(CH_2)_2OMe$	8.88/2.10	**17d** (54)	-1.46
6	**16e**	CH_2CHF_2	9.48/2.21	**17e** (51)	-1.18
7	**16f**	CH_2CF_3	8.05/2.33	**17f** (66)	-1.12
8	**16g**	$(CH_2)_2CF_3$	8.86/2.21	**17g** (72)	-0.12

Experimental section

General

Solvents were purified according to standard procedures. Starting materials including (+) and (-)-α-pinenes (+)-**11** and (-)-**11** and amino acids **16a-g** were purchased from Acros, Sigma-Aldrich, Merck and Enamine at the highest commercial quality and were used without further purification. Melting points are uncorrected. NMR spectra were recorded on Bruker Avance DRX at 500 MHz (^{1}H), 128 MHz (^{13}C) and 470 MHz (^{19}F) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltonics. The progress of reactions was monitored by TLC-plates (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Elemental analyses are correct within the limits of ± 0.3% for C, H, and N.

X-Ray diffraction

Data sets for the compound (+)-**3a** were collected with a D8 Venture CMOS diffractometer. Programs used: data collection: APEX2 V2014.5-0 [30]; cell refinement: SAINT V8.34A [30];

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data reduction: SAINT V8.34A [30]; absorption correction, SADABS V2014/2 [30]; structure solution SHELXT-2014 [31]; structure refinement SHELXL-2014 [31]. *R*-values are given for observed reflections, and wR^2 values are given for all reflections. The hydrogen atom positions H1C (between the O3A and O3B atoms) and the hydrogen atom positions at N1A and N1B atoms were refined freely, but with N-H distance restraints (N1A: DFIX and U-fixed value; N1B: U-fixed value).

Measurement of pK_a values

The measurements were based on the technical protocols for pK_a measurement provided by Pion, Inc. and Sirius Analytical, Inc. Acquisition and analysis of the data were performed using SmartLogger II 1.0.14 software (Beckman Coulter). The recording pH-meter (Beckman Coulter pHi510) was calibrated before the measurements using calibration standards with pH 1.68 and 10.01. Data analysis was done using GraphPad Prism 5.01, and Excel 2010 software.

pK_a values of compounds **3** and **16a-g** were determined by pH-metric method based on potentiometric acid-base titration at 25 °C. The compounds were dissolved in acidified (HCl) solution of NaCl (150 mM, pH 1.9) and slowly titrated with 75 mM sodium hydroxide solution, while recording pH of the solution as a function of NaOH volume used during the titration (construction of the titration curve). Titration of acidified NaCl solution in absence of any compounds is used for blank plotting. The titration assembly was based on Graseby MS16A Hourly Rate Syringe Driver (Smiths Medical) and a system of tubing and syringes.

Buffering capacity was calculated in each point of titration curve as the ratio of the NaOH flow (constant) to the pH rise velocity. The pK_a value was determined from resulting plot of buffering capacity versus pH as the maximum of buffering capacity.

Log*D* measurements

The log*D* values of **15** and **17a-g** were measured using a miniaturized shake-flask method. Compounds were dissolved in the previously mutually saturated mixture containing 990 µL of phosphate-buffered saline (PBS, pH 7.4) and 100 µL of *n*-octanol, followed by mixing on a rotator for 1 hour at 30 rpm. Equilibrium distribution of each compound between the phases was determined using LC-MS (Shimadzu VP HPLC system, API3000 mass-detector, AB Sciex). Analyte concentrations were measured in both phases, in duplicates.

Synthesis of compound 4 (optimized procedure)

The synthesis was carried out based on a literature approach [16] modified for multigram synthesis.

S,S'-Dimethyl O,O'-[oxybis(ethane-2,1-diyl)]dicarbonodithioate (6). A suspension of sodium hydride (60% oil, 113.0 g, 2.83 mol) in dry THF (600 mL) in a three-necked 2 L round-bottomed flask equipped with a magnetic stir bar, with a bubble counter, thermometer and dropping funnel was cooled to 5-10 °C. Then diethylene glycol **5** (100.0 g, 0.942 mol) in THF (100 mL) was added dropwise under vigorous stirring so that the temperature did not exceed 25 °C. Liberation of hydrogen gas was controlled by bubble counter. When the addition completed stirring at r.t. was continued for 3 h. Then the mixture was cooled to 0 °C and carbon disulfide (143.5 g, 1.88 mol) was added dropwise under stirring. After 1 h, another portion of carbon disulfide (143.5 g, 1.88 mol) was added. The mixture was stirred at r.t. overnight, cooled to 0 °C and iodomethane (401.1 g, 2.83 mol) was added dropwise. The mixture was stirred at r.t. for 2 h, then cooled to 0 °C and carefully treated with water (100 mL) and then with ice-water mixture (1 L). The formed precipitate was filtered off, washed with water (2 × 150 mL), hexanes (2 × 150 mL) and dried giving the pure target compound **6** as pale yellow solid. Yield: 181.2 g (69%). M.p. 61-62 °C (Lit. [16]: 62.5-62.9 °C).

1-(Trifluoromethoxy)-2-[2-(trifluoromethoxy)ethoxy]ethane (7). Under an argon atmosphere a mixture of 1,3-dibromo-5,5-dimethylhydantoin (DBH, 219.6 g, 0.77 mol) in dichloromethane (1 L) was cooled to –78 °C in a 2 L Teflon reactor, equipped with overhead stirrer and bubble counter. Then pyridine·9HF (152.5 mL) was added via a polyethylene syringe followed by a solution of compound **6** (40.0 g, 0.14 mol) in dichloromethane (100 mL). The cooling bath was removed and the reaction mixture was stirred at r.t. for 3 h. The mixture was poured into ice water (1 L), the organic layer was separated and the aqueous phase was extracted with dichloromethane (2 × 150 mL). Combined organic layers were washed successively with a cold 37% solution of sodium bisulfite (400 mL), water (400 mL) and brine (400 mL) and dried with Na_2SO_4. Then the mixture was concentrated under reduced pressure giving 34.5 g of the crude product **7**, which was used for the next step without purification.

2-(Trifluoromethoxy)ethyl trifluoromethanesulfonate (4). A mixture of triflic anhydride (85 mL), triflic acid (3 mL) and crude compound **7** (34.5 g) was stirred at 60 °C under an argon atmosphere for 2 days. After full conversion (the reaction was monitored by NMR), the mixture was concentrated under reduced pressure and the residue was diluted with dichloromethane (150 mL), carefully washed with ice water (50 mL), brine (50 mL) and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue was distilled (b.p. 62-65 °C/20 mbar) giving compound **4** as colourless liquid, which was used for the next step without additional purification. Yield: 31 g (42% over 2 steps).

Spectral data of compounds **4, 6** and **7** coincide with the literature data [16]

Synthesis of racemic 2-amino-4-(trifluoromethoxy)butanoic acid (3)

Diethyl 2-acetamido-2-[2-(trifluoromethoxy)ethyl]malonate (9). To a solution of potassium *tert*-butoxide (13.4 g, 0.12 mol) in THF (200 mL) diethyl 2-acetamidomalonate (21.7 g, 0.1 mol) was added portion-wise under vigorous stirring at 0-5 °C. After 30 min a solution of compound **4** (28.8 g, 0.11 mmol) in THF (200 mL) was added dropwise and the mixture was left stirring

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at ambient temperature for 6 h. The mixture was poured into water (800 mL), extracted with EtOAc (3 × 300 mL), washed with brine and dried with $MgSO_4$. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/c-hex, 2:1, R_f = 0.45) giving compound **9** as colourless oil. Yield: 31.9 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 6H), 2.07 (s, 3H), 2.80 (t, *J* = 5.7 Hz, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 4H), 6.96 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.9, 31.3, 62.9, 64.0, 70.6, 121.2 (q, J = 256.1 Hz), 167.5, 169.7; ^{19}F NMR (283 MHz, $CDCl_3$) δ –61.91 (s); HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{12}H_{18}F_3NNaO_6$ 352.0978, found 352.0997; anal calcd for $C_{12}H_{18}F_3NO_6$ (329.27): C 43.77, H 5.51, N 4.25, found C 43.42, H 5.77, N 4.02%.

***rac*-2-Amino-4-(trifluoromethoxy)butanoic acid hydrochloride (3).** A mixture of compound **9** (3.2 g, 9.7 mmol) and 6N HCl (30 mL) was stirred under reflux for 5 h. Then the mixture was cooled and extracted with EtOAc (3 × 30 mL). The aqueous layer was concentrated under reduced pressure and the residue was crystallized from acetonitrile giving compound **3**. Yield: 1.41 g (65%). Colourless solid, m.p. 190-191 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 2.12–2.45 (m, 2H), 3.93 (t, *J* = 6.2 Hz, 1H), 4.20–4.35 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 31.2, 51.6, 66.3, 122.9 (q, *J* = 255 Hz), 171.9; ^{19}F NMR (283 MHz, CD_3OD) δ –60.71 (s). HRMS (ESI-MS) calcd for [M+H$^+$] $C_5H_9F_3NO_3$ 188.0529, found 188.0526; anal calcd for $C_5H_9ClF_3NO_3$ (223.58): C 26.86, H 4.06, N 6.26, found C 26.98, H 3.95, N 6.12%.

Synthesis of enantiopure 2-amino-4-(trifluoromethoxy)butanoic acid 3

(+)-(1R,2R,5R)-2-hydroxy-3-pinanone (+)-12 *and* ***(-)-(1S,2S,5S)-2-hydroxy-3-pinanone (-)-12*** were obtained from commercially available (+)- or (-)-α-pinenes by a described procedure [17] in 57% and 49% yields, respectively.

***tert*-Butyl 2-[(E)-((1R,2R,5R)-2-hydroxy-2,6,6-trimethylbicyclo-[3.1.1]heptan-3-ylidene)amino]acetate (+)-13** was obtained by a reported procedure from *tert*-butyl glycine ester (generated from *tert*-butyl glycine ester hydrochloride (3.36 g, 20.0 mmol) and triethylamine (2.8 mL, 20.0 mmol), (+)-(*1R,2R,5R*)-2-hydroxy-3-pinanone (+)-**12** (2.24 g, 13.3 mmol) and $BF_3{\cdot}Et_2O$ (250 μL) by refluxing in toluene (60 mL) [20]. The obtained crude product (~4.0 g, 75% purity by GC) was used for alkylation. HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{16}H_{27}NNaO_3^+$ 304.1883, found 304.1891.

***(S)*-tert-Butyl 2-[(E)-((1R,2R,5R)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]-heptan-3-ylidene)amino]-4-(trifluoromethoxy)-butanoate (+)-14.** A 2 M solution of LDA in THF (11.1 mL, 22.2 mmol) was put into flask under argon atmosphere and cooled to –78 °C. Then the crude product (+)-**13** (2.50 g, 8.8 mmol) was added dropwise via syringe and the mixture was stirred for 90 min. Then triflate **4** (2.50 g, 9.5 mmol) was added and the reaction mixture was stirred at –78 °C for 2 h and left stirring at r.t. overnight. Then the mixture was quenched with brine. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried with $MgSO_4$. The solution was concentrated under reduced pressure to give 5.37 g of a crude product. According to GC and ^{19}F NMR the mixture contained ~62% of major diastereomer (+)-**14** (estimated de 67%) which was isolated by column chromatography (eluent: 1% Et_3N in EtOAc/*c*-hexane, 1:6, R_f = 0.65) giving 1.34 g of a mixture of diastereomerically pure (+)-**14** (de >95% by GC and ^{19}F NMR) and ~38% of compound (+)-**12** (by GC and ^{1}H NMR) as a pale yellow oil.
NMR data are provided without signals of compound (+)-**12**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.65 (s, 3H), 1.07 (s, 3H), 1.27 (s, 9H), 1.51 (s, 3H), 1.65–1.69 (m, 1H), 1.75 (d, *J* = 10.5 Hz, 1H), 2.01-2.06 (m, 1H, dt, J_1 = 18.1 Hz, J_2 = 2.9 Hz, 1H), 2.06 (t, *J* = 6.0 Hz, 1H), 2.14–2.21 (m, 2H), 2.25 (dt, J_1 = 18.1 Hz, J_2 = 2.9 Hz, 1H), 2.45 (dd, J_1 = 18.1 Hz, J_2 = 2.0 Hz, 1H), 2.79 (bs, 1H), 3.68–3.75 (m, 2H), 4.17 (dd, J_1 = 10.2 Hz, J_2 = 3.9 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 22.1, 26.9, 27.5, 28.1, 28.3, 33.1, 37.8, 38.3, 42.6, 50.2, 58.44, 64.2 (q, *J* = 3.1 Hz), 76.1, 80.8, 121.9 (q, *J* = 254.0 Hz), 169.3, 180.6; ^{19}F NMR (578 MHz, $CDCl_3$) δ –60.60 (s). HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{19}H_{30}F_3NNaO_4^+$ 416.2019, found 416.2015.

***tert*-Butyl 2-[(E)-((1S,2S,5S)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylidene)amino]acetate (–)-13** was obtained by reported procedure from *tert*-butyl glycine ester (generated from *tert*-butyl glycine ester hydrochloride (3.36 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol), (+)-(*1S,2S,5S*)-2-hydroxy-3-pinanone (-)-**12** (2.24 g, 13.3 mmol) and $BF_3{\cdot}Et_2O$ (250 μL) by refluxing in toluene (60 mL) [20]. The obtained crude product (-)-**13** (4.05 g, 76% purity by GC) was used for alkylation without purification. HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{16}H_{27}NNaO_3^+$ 304.1883, found 304.1890.

***(R)*-tert-Butyl 2-[(E)-((1S,2S,5S)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]-heptan-3-ylidene)amino]-4-(trifluoromethoxy)butanoate (-)-14.** According to the procedure given above, alkylation of (-)-**13** (3.04 g, 10.7 mmol) with triflate **4** (2.37 g, 9.0 mmol) in the presence of 2M LDA in THF (13.5 mL, 27.0 mmol), gave 5.71 g of the crude product (-)-**14**. GC and ^{19}F NMR showed that the mixture contained ~67% of major diastereomer (-)-**14** (estimated de 60%), which was isolated by column chromatography (eluent: 1% Et_3N in EtOAc/c-hexane, 1:6, R_f = 0.65) to give 2.33 g of a mixture of diastereomerically pure (-)-**14** (de >95% by GC and ^{19}F NMR) and ~20% of compound (-)-**12** (by GC and ^{1}H NMR) as a pale yellow oil. NMR spectra of compounds (+)-**14** and (-)-**14** are identical. HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{19}H_{30}F_3NNaO_4^+$ 416.2019, found 416.2013.

***(S)*-2-Amino-4-(trifluoromethoxy)butanoic acid *(+)*-3.** Obtained product (+)-**14** (0.90 g, containing ~40% of compound (+)-**12**) was dissolved in dioxane (10 mL). Then 6N HCl (20 mL) was added and the mixture was refluxed for 3 h. Then the mixture was cooled to r.t. and extracted with EtOAc (3 × 20 mL). The aqueous layer was concentrated under

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reduced pressure and the residue was crystallized from acetonitrile (20 mL) giving compound (+)-**3** as colourless solid. Yield: 0.21 mg (13 % over 3 steps from compound (+)-**12**). Colourless solid, mp 184-185 °C, $[\alpha]_D^{20}$ = +8.8 (H_2O). NMR spectra are identical with those for the racemic compound **3**. HRMS (ESI-MS) calcd for $[M+H^+]$ $C_5H_9F_3NO_3$ 188.0529, found 188.0525.

***(R)*-2-Amino-4-(trifluoromethoxy)butanoic acid *(-)*-3** was obtained by the same procedure as compound (+)-**3** from product (-)-**14** (2.10 g, containing ~20% of compound (-)-12) in dioxane (20 mL) and 6N HCl (35 mL). Yield: 0.91 g (36% over 3 steps from compound (-)-**12**). Colourless solid, mp 182-184 °C. $[\alpha]_D^{20}$ = –9.3 (H_2O). NMR spectra are identical with those for the racemic compound **3**.
HRMS (ESI-MS) calcd for $[M+H^+]$ $C_5H_9F_3NO_3$ 188.0529, found 188.0526.

Synthesis of *N*-tosyl amino acids 15, 17a-g. General procedure.

To a solution of the amino acid or the corresponding hydrochloride (1 mmol) in H_2O (5 mL) were added NaOH (88 mg, 2.2 mmol or 132 mg, 3.3 mmol in the case of hydrochlorides) and TosCl (210 mg, 1.1 mmol). The reaction mixture was stirred at r.t. overnight. Then the solution was acidified with 1 M aqueous HCl until pH ~1 and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by crystallization from MeOH/water.

***rac*-2-(4-Methylphenylsulfonamido)-4-(trifluoromethoxy)-butanoic acid 15** was obtained by general procedure starting from *rac*-**3** (223 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (133 mg, 3.3 mmol). Yield: 249 mg (73%). Colourless solid, m.p. 129-131 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32–2.06 (m, 2H), 2.36 (s, 3H), 3.74–3.84 (m, 1H), 3.92–4.04 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 12.23–13.10 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ 20.9, 31.1, 51.9, 64.1 (q, *J* = 3.5 Hz), 121.0 (q, *J* = 254.0 Hz), 126.4, 129.3, 138.0, 142.5, 172; ^{19}F NMR (376 MHz, DMSO-d_6) δ –58.71 (s); HRMS (ESI-MS) calcd for $[M+Na^+]$ $C_{12}H_{14}F_3NNaO_5S^+$ 364.0437, found 364.0428; anal calcd for $C_{12}H_{14}F_3NO_5S$ (341.30): C 42.23, H 4.13, N 4.10, found C 42.01, H 4.28, N 3.97%.

***(S)*-2-(4-Methylphenylsulfonamido)-4-(methylthio)butanoic acid 17a** was obtained by general procedure starting from *L*-methionine (150 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 203 mg (67%).
Colourless solid, m.p. 77-79 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.66–1.86 (m, 2H), 1.93 (s, 3H), 2.25–2.45 (m, 5H), 3.77–3.84 (m, 1H), 7,36 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 8.04 (br s, 1H), 12.79 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ 14.8, 21.4, 29.7, 32.1, 54.9, 127.0, 129.9, 138.9, 142.9, 173.0; HRMS (ESI-MS) calcd for $[M+Na^+]$ $C_{12}H_{17}NNaO_4S_2^+$ 326.0491; found 326.0497; anal calcd for $C_{12}H_{17}NO_4S_2$ (303.40): C 47.50, H 5.65, N 4.62%; found C 47.28, H 5.60, N 4.79%.

***(S)*-3-Methyl-2-(4-methylphenylsulfonamido)butanoic acid 17b** was obtained by general procedure starting from *L*-valine (117 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 236 mg (87%). Colourless solid, m.p. 143-145 °C. NMR spectra coincide with the literature data [27].

***(S)*-4-Methyl-2-(4-methylphenylsulfonamido)pentanoic acid 17c** was obtained by general procedure starting from *L*-leucine (131 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 219 mg (77%). Colourless solid, m.p. 113-115 °C. NMR spectra coincide with the literature data [28].

4-Methoxy-2-(4-methylphenylsulfonamido)butanoic acid 17d was obtained by general procedure starting from *rac*-2-amino-4-methoxybutanoic acid **16d** (132 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 155 mg (54%). Colourless solid, m.p. 106-108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47–1.97 (m, 2H), 2.37 (s, 3H), 3.05 (s, 3H), 3.11–3.32 (m, 2H), 3.70–3.85 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 8.02 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ 21.5, 32.7, 53.2, 58.3, 68.1, 127.0, 130.0, 139.0, 143.6, 173.5; HRMS (ESI-MS) calcd for $[M+Na^+]$ $C_{12}H_{17}NNaO_5S^+$: 310.0720, found 310.0708; anal calcd for $C_{12}H_{17}NO_5S$ (287.33): C 50.16, H 5.96, N, 4.87%; found C 50.03, H 6.02, N 4.98%.

4,4-Difluoro-2-(4-methylphenylsulfonamido)butanoic acid 17e was obtained by general procedure starting from *rac*-2-amino-4,4-difluorobutanoic acid **16e** (139 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 150 mg (51%). Colourless solid, m.p. 134-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94–2.27 (m, 2H), 2.36 (s, 3H), 3.75–3.87 (m, 1H), 5.97 (tt, J_1 = 56.0, J_2 = 4.0 Hz, 1H), 7.36 (d, 2H, *J* = 8.1 Hz), 7.65 (d, 2H, *J* = 8.1 Hz), 8.20 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ 21.4, 37.0 (t, *J* = 21.8 Hz), 51.3 (t, *J* = 5.0 Hz), 116.1 (t, *J* = 238.5 Hz), 127.0, 130.0, 138.3, 143.2, 171.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ –116.78-–116.78 (m); HRMS (ESI-MS) calcd for $[M+Na^+]$ $C_{11}H_{13}F_2NNaO_4S^+$ 316.0426; found 316.0433; anal calcd for $C_{11}H_{13}F_2NO_4S$ (293.29): C 45.05, H 4.47, N 4.78%; found C 44.89, H 4.58, N 4.92%.

4,4,4-Trifluoro-2-(4-methylphenylsulfonamido)butanoic acid 17f was obtained by general procedure starting from *rac*-2-amino-4,4,4-trifluorobutanoic acid **16f** (157 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 205 mg (66%). Colourless solid, mp 168-170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 2.48–2.64 (m, 1H), 2.68–2.84 (m, 1H), 3.98–4.08 (m, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 8.33 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ =20.9, 35.5 (q, *J* = 28.0 Hz), 50.4, 125.6 (q, *J* = 276.7 Hz), 126.5, 129.3, 138.0, 142.6, 170.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ –63.04 (t, *J* = 10.5 Hz); HRMS (ESI-MS) calcd for $[M+Na^+]$ $C_{11}H_{12}F_3NNaO_4S^+$ 334.0331; found 334.0341; anal calcd for

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$C_{11}H_{12}F_3NO_4S$ (311.28): C 42.44, H 3.89, N 4.50%; found C 42.37, H 4.02, N 4.41%.

5,5,5-Trifluoro-2-(4-methylphenylsulfonamido)pentanoic acid 17g was obtained by general procedure starting from *rac*-2-amino-5,5,5-trifluoropentanoic acid **16g** (171 mg, 1 mmol), tosyl chloride (210 mg, 1.1 mmol) and NaOH (88 mg, 2.2 mmol). Yield: 234 mg (72%). Colourless solid, mp 137-139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.61–1.88 (m, 2H), 2.08–2.27 (m, 2H), 2.37 (s, 3H), 3.78–3.88 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 2H), 8.16 (br s), 12.27–13.34 (br s, 1H); ^{13}C NMR (128 MHz, DMSO-d_6) δ 21.5, 25.2, 29.7 (q, *J* = 27.8 Hz), 54.8, 127.1, 127.8 (q, *J* = 235.0 Hz), 130.0, 138.9, 143.2, 172.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ –64.55 (t, *J* = 11.5 Hz) ppm. HRMS (ESI-MS) calcd for [M+Na$^+$] $C_{11}H_{12}F_3NNaO_4S^+$ 334.0331; found 334.0341; anal calcd for: $C_{12}H_{14}F_3NO_4S$ (325.30): C 44.31, H 4.34, N 4.31%; found: C 44.19, H 4.28, N 4.50%.

X-ray crystal structure of compound (+)-3

A colourless needle-like specimen of $C_{10}H_{17}ClF_6N_2O_6$, dimensions 0.055 mm x 0.072 mm x 0.228 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 923 frames were collected. The total exposure time was 24.10 hours. The frames were integrated with the Bruker SAINT software-package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 7433 reflections to a maximum θ angle of 63.65° (0.86 Å resolution), of which 2417 were independent (average redundancy 3.075, completeness = 95.0%, R_{int} = 14.73%, R_{sig} = 13.43%) and 1807 (74.76%) were greater than 2σ(F^2). The final cell constants of a = 11.0208(8) Å, b = 5.0952(4) Å, c = 14.7276(11) Å, β = 103.403(6)°, volume = 804.48(11) Å^3, are based upon the refinement of the XYZ-centroids of 2344 reflections above 20 σ(I) with 8.247° < 2θ < 136.3°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.793. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5420 and 0.8500. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 2 for the formula unit, $C_{10}H_{17}ClF_6N_2O_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 248 variables converged at R1 = 9.18%, for the observed data and wR2 = 16.90% for all data. The goodness-of-fit was 1.191. The largest peak in the final difference electron density synthesis was 0.466 e$^-$/Å^3 and the largest hole was -0.548 e$^-$/Å^3 with an RMS deviation of 0.115 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.695 g/cm^3 and F(000), 420 e$^-$. Flack parameter: 0.12(4).

Notes and references

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For table of contents:

According to their pK_a values and lipophilicity the new enantiopure CF_3O-homoserines might be promising surrogates of natural α-amino acids

Graphical abstract: