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Ethyl-4,4,4-trifluoroacetoacetate (ETFAA), a powerful building block for enantiopure chirons in trifluoromethyl-β-amino acid series

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Abstract

Herein are studied new transformations of ethyl-4,4,4-trifluoroacetoacetate (ETFAA), giving access to a series of enantiopure chirons bearing both a trifluoromethyl group and an amino moiety. The key intermediate is obtained optically pure by a resolution procedure.

Keywords: Trifluoromethyl compounds; β-Amino acids and derivatives; Resolution

1. Introduction

The biological and pharmacological activities of a molecule are strongly modified by the presence of fluorine atoms [1]. Today, the number of drugs containing at least one fluorine atom is reaching about 20–25% [2].

A fluorinated organic compound can be obtained by introduction of fluorine at a late stage of the synthesis using fluorinating methodologies. However, an easier way is to use fluorine containing starting materials such as ethyl-4,4,4-trifluoroacetoacetate (ETFAA) that is commercially available and easy to handle [3]. On the other hand, β-amino acids show interesting pharmacological properties. Therefore, considering the benefits of fluorine substitution for hydrogen, we targeted enantiopure β-amino acid derivatives starting from ETFAA.

In a previous study, we had already reported results regarding the enantioselective [1,3] proton shift reaction of ETFAA amino derivatives. When catalyzed by an appropriate chiral base, e.e.'s as high as 71% were observed [4]. We now would like to report how the racemic mixture of the β-trifluoromethyl-β-amino ester **2** derived from ETFAA was successfully resolved and then used for the construction of enantiopure amino trifluoromethyl chirons (Fig. 1).

2. Results and discussion

2.1. Synthesis of β-aminoester 2 from ETFAA

In order to obtain β-trifluoromethyl-β-aminoester **2** from ETFAA, a reductive amination reaction was performed. Enamine **1** was first synthesized following the Soloshonok's conditions [5]. We then directly obtained the β-aminoester **2** by conducting hydrogenation under pressure (Scheme 1). By this way, in a same step, the double bond was hydrogenated and the (*N*)-benzyl protective group was removed. After having tested various conditions, we observed best results with 3% in mass of Pd/C (10%) as catalyst, with a 300 g L^{-1} concentration of **1** in absolute ethanol and at a temperature of 100 °C, under a 15 bar hydrogen pressure [6].

2.2. Resolution of β-amino ester 2 by chiral acids

In order to obtain compound **2** in enantiomerically pure form, we examined its resolution by several chiral acids (*AH) (Scheme 2).

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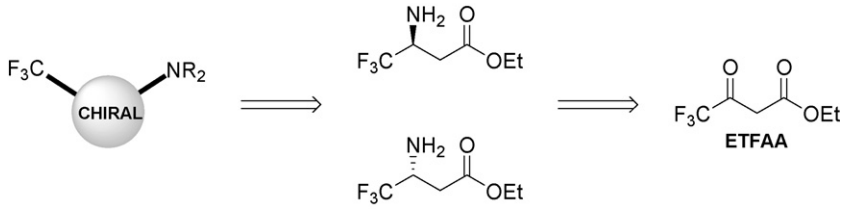
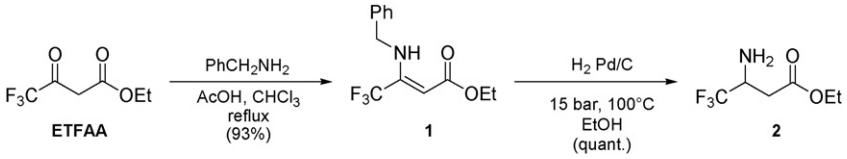


Fig. 1. General strategy to obtain trifluomethyl amino derivatives from ETFAA.



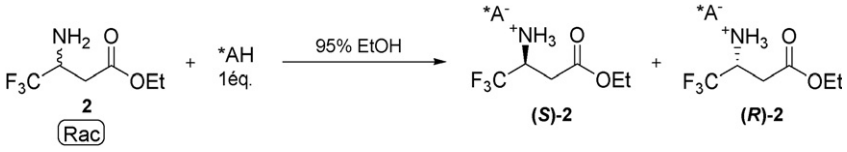
Scheme 1. Synthesis of β-amino ester **2** from ETFAA.

In a first set of experiments, to amino ester **2** was added one equivalent of chiral acid diluted in 95% ethanol, under strirring at room temperature. Various chiral acids were tested (Fig. 2).

In all cases, diastereomeric salts were formed but a precipitate was only observed when tartaric acid was used. For this first experiment, after filtration and basic treatment of the precipitate with a 1 M solution of Na_2CO_3, enantiomeric excess measured by chiral GC was 69% for the recovered amino ester. Having this promising result, we kept tartaric acid but changed the procedure in order to slow down the formation of the precipitate in hope of increasing enantiomeric excess. Therefore, diastereomeric salts were formed in refluxing ethanol and reaction mixture was allowed to cool down at room temperature under stirring. Different concentrations of **2** were tested and after basic treatment, enantiomeric excesses of precipitates were measured. Results are summarized in Table 1.

A general figure can be pointed out: with a low concentration of amino ester **2**, enantiomeric excess is high but yield is moderate. On the opposite, a high concentration of amino ester **2** leads to better yield but lowers enantiomeric excess. We therefore conclude from those results that tartaric acid do not exert any enantiodiscrimination between enantiomers of **2**: when 0.5 equiv. of tartaric acid is engaged enantiomeric excess of the precipitate is not improved (Table 1, entry 6). The solubility in ethanol of diastereomeric salts is thus the crucial factor for efficient resolution.

Using this procedure with a low concentration of amino ester **2**, enantiomeric excess is high and a single recrystallization



Scheme 2. Resolution of enantiomers of **2** by chiral acids.

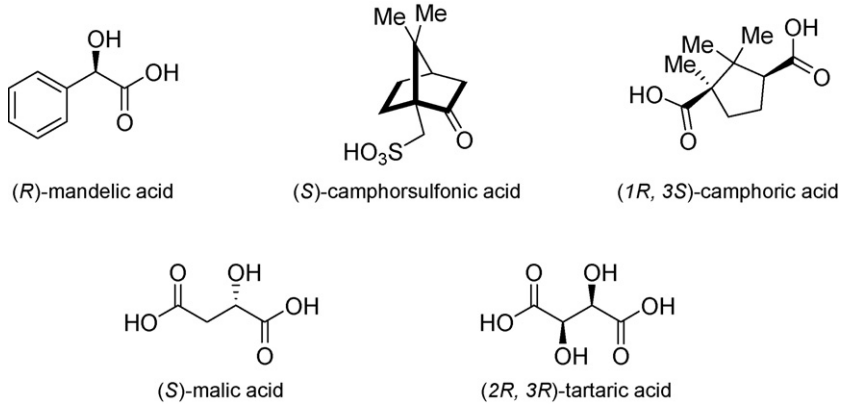


Fig. 2. Chiral acids tested.

Table 1
Resolution by (2*R*, 3*R*)-tartaric acid in refluxing ethanol, influence of concentration of **2**

Entry	C_2 (g L^{-1})	$Yield_{precipitate}$ [a] (%)	$e.e._{precipitate}$ (%)
1	14.3	26	>90
2	20	30	81
3	30	42	77
4	40	48	73
5	56.2	49	61
6[b]	20	11	78

[a] Yield $_{precipitate}$: mass of dry precipitate/(mass $_{amino\ ester}$ + mass $_{(2R,\ 3R)\text{-tartaric acid}}$).
[b] 0.5 equiv. of tartaric acid engaged.

leads to enantiomerically pure amino ester **2**. On the other hand, filtrate recovered after the first resolution is treated with basic solution of Na_2CO_3 and an equivalent of the (2*S*, 3*S*)-tartaric acid is then added. The other enantiomer of amino ester **2** is therefore obtained. By successive resolution using alternatively both enantiomers of tartaric acid, the whole racemic mixture is resolved. We carried out this experiment with a quantity of racemic mixture up to 3 g and the whole procedure is in this case described in Fig. 3.

2.3. Determination of the absolute configuration of enantiomers of 2

In the literature, the absolute configuration of the corresponding amino acid **3** is known [7]. After resolution using tartaric acid, both enantiomers of **2** were therefore hydrolysed in acidic conditions (6 M HCl, reflux, 4 h). Optical rotations of corresponding amino acids obtained were then measured and compared with literature data. We conclude that resolution using (2*R*, 3*R*)-tartaric acid leads to (*R*) isomer of amino ester **2** whereas with (2*S*, 3*S*)-tartaric acid (*S*) isomer of **2** is separated (Scheme 3).

Having obtained **2** in enantiomerically pure form, we then elaborated synthetic ways for the construction of enantiopure amino trifluoromethyl chirons.

2.4. Construction of enantiopure amino trifluoromethyl chirons from 2

We first considered the carbonyl function of amino ester **2**. γ-Amino alcohols are interesting compounds because of their biological activity [8]. We easily obtained the γ-amino alcohol derived from ETFAA by reducing the carbonyl function of amino ester **2**. After several experiments, the best reaction conditions were found using $LiAlH_4$ as reducting agent in THF at −15 °C during 2 h. By this way, γ-trifluoromethyl-γ-amino alcohol **4** was synthesized in both racemic and enantiomerically pure form as confirmed by chiral GC analysis (Fig. 4.).

Afterwards, we considered the reactivity of the amino function of amino ester **2**. We firstly tried to synthesize the lactam **6** from amino ester **2** but none of the conditions tested (strong bases such as DBU and KHMDS, temperature varying from room temperature to 95 °C) were successful and the initial product was always recovered. Finally, taking (*N*)-benzyl

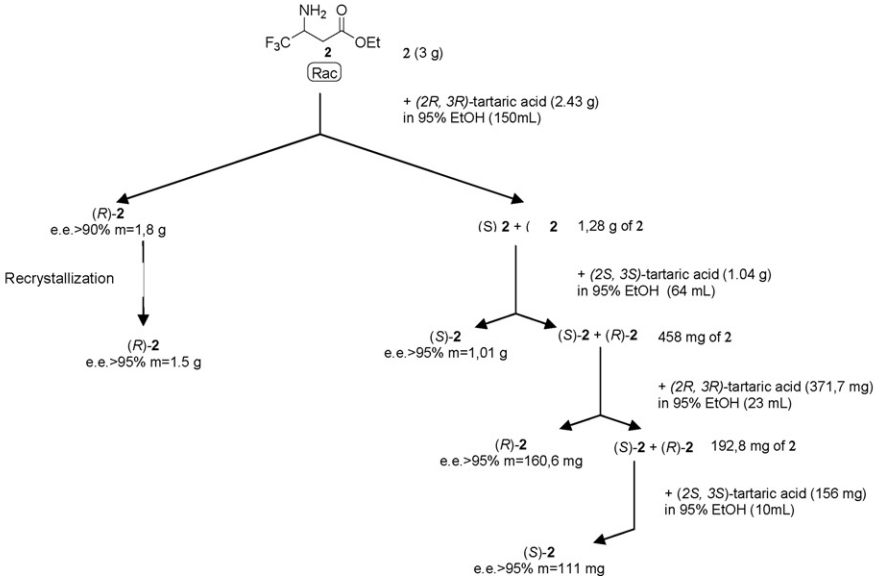
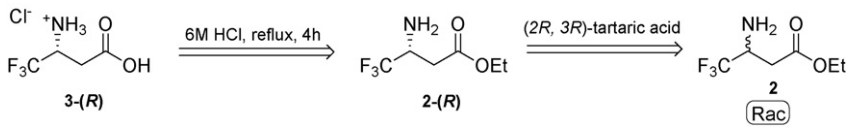


Fig. 3. Successive resolution by both enantiomers of tartaric acid.



Scheme 3. Determination of the absolute configuration of enantiomers of **2**.

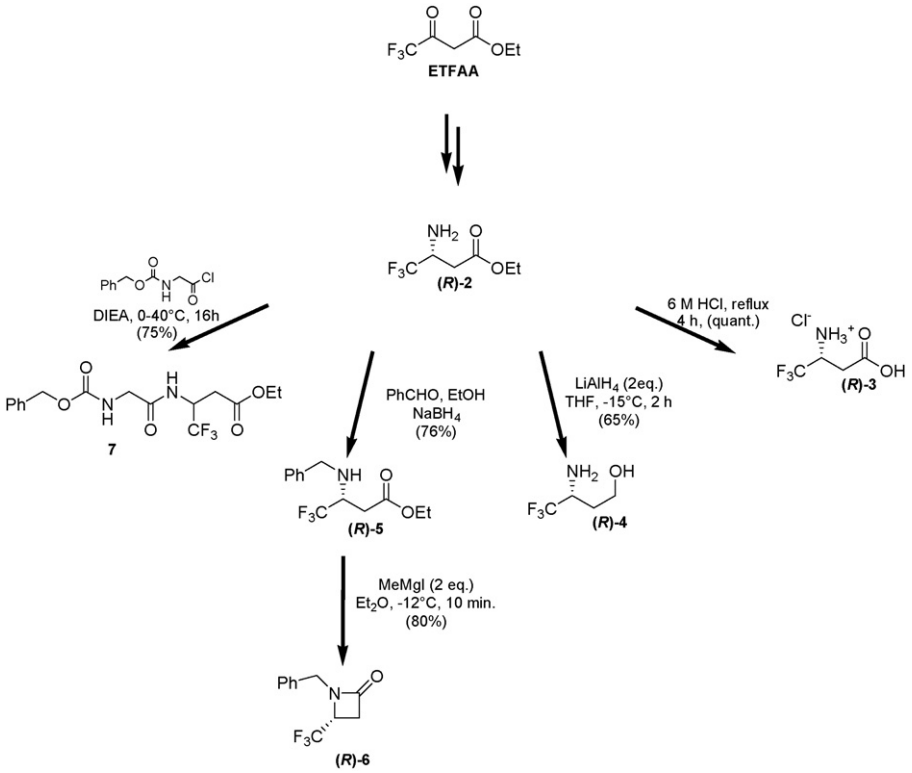
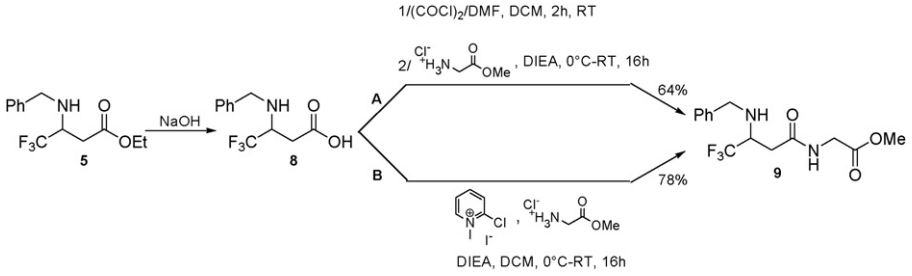


Fig. 4. Construction of amino trifluoromethyl chirons from **2**.



Scheme 4. Peptide coupling with amino acid **8**.

amino ester **5** as substrate and using methyl magnesium iodide as base, we were pleased to obtain the desired product **6** (Fig. 4). It is to note that this compound was successfully synthesized in both racemic and enantiomerically pure form as monitored by chiral GC.

Always in view of studying reactivity of amino function in compound **2** we also considered the peptide coupling between the carboxyl function of Z-glycine and the amino function of compound **2**. Best result was observed when acyl chloride of Z-glycine was firstly formed. Desired pseudopeptide **7** was then obtained with a satisfying 75% yield (Fig. 4). In addition, since peptides containing fluorinated amino acids seem to be more stable than their unfluorinated analogues [9], we also conducted the peptide coupling between glycine methyl ester and **8** derived from **5**. Two procedures can be followed. In the first one, the acyl chloride derived from **8** was formed and the desired pseudopeptide **9** was obtained with a yield reaching 64%. Another method to activate the carboxylic function of **8** is by using a coupling agent like the 2-chloro-1-methylpyridinium iodide and the pseudopeptide **9** was then synthesized with 78% yield (Scheme 4). Since peptide couplings were performed as model reactions in order to test the reactivity of trifluoromethyl β-aminoacids, only racemic starting materials **2** and **5** were examined.

3. Conclusion

A strategy to generate fluorinated organic compounds is to begin the synthesis with a commercial fluorinated molecule. In this view, we had chosen ETFAA as starting material. During this study, the production of the ethyl 3-amino-4,4,4-trifluorobutanoate **2** was performed in large scale. Both enantiomers of this compound were successfully resolved using tartaric acid as chiral counterpart, and their absolute configurations were assigned. The resolution methodology thus remains an excellent alternative strategy with respect to asymmetric synthesis of related compounds [10].

The derivatisation of amino ester **2** was also carried out. Firstly, by considering the carbonyl function of this compound,

we easily accessed to the corresponding γ-amino alcohol **4**. Finally, we also studied the reactivity of the amino function of this compound **2** by conducting the synthesis of both lactam **6** and peptide **7**. Therefore, although the nucleophilicity of the amino function is lowered by the CF_3 group in compound **2**, it is possible in some conditions to make it reactive as nucleophile.

4. Experimental

4.1. General

Thin Layer Chromatography was performed using Silica TLC plates (Silica gel 60 F254, Merck). Products were visualized under UV light (254 nm) and then revealed by potassium permanganate aqueous solution. Flash chromatographies were performed on silica gel column (Silica gel Si 60 0.040–0.063 mm, Merck).

Infra Red spectra were recorded on a Perkin-Elmer 16PCFT-IR and wave numbers are given in cm^{-1}. NMR Spectra were performed on a Bruker Avance 300. Chemical shifts of ^1H NMR (300 MHz) were expressed in ppm downfield from tetramethylsilane external standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR (75.5 MHz) were expressed in ppm downfield from $CDCl_3$ as internal standard ($\delta = 77.16$). Chemical shifts of ^{19}F NMR (282 MHz) were expressed in ppm downfield from $CFCl_3$ as internal standard ($\delta = 0$). Coupling constants are reported in hertz (Hz). Abbreviations used for signals observed are: **s** for singlet, **d** for doublet, **t** for triplet, **q** for quartet, **dd** for double doublet, **dt** for double triplet, **m** for multiplet and **b** for broad. HPLC analyses were carried out on either a HP series 1100 using a HP 3395 integrator or a Waters 600 with a Waters 486 UV detector and a Waters 746 integrator. Chiral columns used are Chiralcel OD-H and Chiralpak AD-H. Gas Chromatography (GC) was performed on a Hewlett Packard HP 5890A series II using a Hewlett Packard HP 3396 series II integrator with either a BETA-DEX 120 (permethylated β-cyclodextrin) column (25 m × 0.25 mm × 0.25 μm thickness of layer) or a Chiral DEX βDA (dialkyl β-cyclodextrin) column (40 m × 0.25 mm × 0.25 μm thickness of layer). Mass spectrometry was performed on a Shimadzu GCMS-QP2010 in EI or CI mode. Elementary Analyses were realised on a CE instruments EA 1110.

4.2. (Z)-Ethyl 3-(benzylamino)-4,4,4-trifluorobut-2-enoate (*1*)

To a solution of glacial acetic acid (1.6 mL, 27.7 mmol) in chloroform (11 mL), benzylamine (3 mL, 27.7 mmoL) was added. After stirring for 5 min, ETFAA (3.6 mL, 24.9 mmol) was added. The resulting mixture was refluxed for 16 h followed by evaporation of the solvent in vacuum. The residue was placed on a short silica gel column and eluted with a mixture of cyclohexane/ethyl acetate (95/5) to afford desired product (6.3 g, 93%) as pale yellow oil.

$C_{13}H_{14}F_3NO_2$, $M_W = 273.25$, yellow oil; IR (cm^{-1}): 3283 (NH); 3031 (CH_{Aro}); 2982 (CH_3); 2936 (CH_2); 1672 (db_{CIS}); 1632 (CO); NMR ^{19}F ($CDCl_3$): −67.0 (3F, s); NMR ^1H ($CDCl_3$): 1.18 (3H, t, $J = 7.1$), 4.05 (2H, q, $J = 7.1$), 4.39 (2H, d, $J = 6.4$), 5.08 (1H, s), 7.21 (5H, m), 8.37 (1H, b); NMR ^{13}C ($CDCl_3$): 14.3, 48.1, 59.8, 85.3 (q, $J = 5.9$), 120.4 (q, $J = 277$), 127.3, 127.9, 128.9, 137.8, 148.2 (q, $J = 31.0$), 169.9; HPLC (Chiracel OD-H, Hexane/*i*-PrOH, 99.9/0.1, 1 mL min^{-1}, 254 nm): 14.4 min; GC (BPX5, 23 m, 40 °C (5 min), 8 °C/min, 280 °C): 16.6 min; GC–MS (EI): 91(100), 200(52), 273($M^{\bullet+}$); Anal. Calcd. for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13; found: C, 57.06; H, 4.98; N, 5.39.

4.3. Ethyl 3-amino-4,4,4-trifluorobutanoate (*2*)

A suspension of 10% Pd/C (3 wt%) and **1** in absolute ethanol ($C_1 = 300$ g L^{-1}) was hydrogenated at 15 bars and stirred for 3 h at 100 °C. The catalyst was then removed by filtration and the ethanolic filtrate was condensed in vacuum to give the desired product as colourless oil.

$C_6H_{10}F_3NO_2$, $M_W = 185.14$, colourless oil; IR (cm^{-1}): 3333 (NH); 2987 (CH_3); 2945 (CH_2); 1633 (CO); NMR ^{19}F ($CDCl_3$): −79.4 (3F, d, $J = 6.8$); NMR ^1H ($CDCl_3$): 1.26 (3H, t, $J = 7.1$), 1.53 (2H, b), 2.41 (1H, dd, $J = 10.2$, $J = 16.2$), 2.69 (1H, dd, $J = 3.4$, $J = 16.2$), 3.70 (1H, m), 4.17 (2H, q, $J = 7.1$); NMR ^{13}C ($CDCl_3$): 13.7, 35.4, 50.9 (q, $J = 30.4$), 60.8, 126.0 (q, $J = 281.3$), 170.0; GC (BETA DEX 120, 15 m, 60 °C): (*S*): 8.76 min; (*R*): 9.53 min; Anal. Calcd. for $C_6H_{10}F_3NO_2$: C, 38.92; H, 5.44; N, 7.57; found: C, 38.86; H, 5.19; N, 7.67; optical rotation ($c = 1$, $CHCl_3$, 25 °C): (*R*): $[\alpha]_D = +21.0$; $[\alpha]_{365} = +62.4$; $[\alpha]_{436} = +41.4$; $[\alpha]_{546} = +24.8$; $[\alpha]_{578} = +22.2$; (*S*): $[\alpha]_D = -21.1$; $[\alpha]_{365} = -60.7$; $[\alpha]_{436} = -40.1$; $[\alpha]_{546} = -24.5$; $[\alpha]_{578} = -21.5$.

4.4. General procedure for resolution of (*2*)

To a solution of (2*R*, 3*R*)-tartaric acid (2.43 g) in refluxing ethanol 95% (75 mL), ethyl 3-amino-4,4,4-trifluorobutanoate **2** (3 g) diluted in ethanol 95% (75 mL) was added. The resulting mixture was stirred at reflux during 5 min and then allowed to cool to room temperature under stirring. After filtration, 1.8 g of precipitate was recovered. Mixture of enantiomers contained in the filtrate was released by basic treatment with an aqueous solution of Na_2CO_3 1 M. After extraction with dichloromethane and evaporation of solvent in vacuum, 1.28 g was recovered and added at reflux to (2*S*, 3*S*)-tartaric acid (1.04 g) in solution in ethanol 95% (64 mL). Resulting mixture was stirred at reflux during 5 min and then allowed to cool to room temperature under stirring. After filtration, 1.01 g of precipitate was recovered.

4.5. 3-Amino-4,4,4-trifluorobutanoic acid hydrochloride (*3*)

Ethyl 3-amino-4,4,4-trifluorobutanoate **2** (0.2 g, 1.08 mmol) was diluted in an aqueous solution of HCl 2 M (3 mL). Resulting mixture was stirred at reflux for 4 h. The solvent was then evaporated in vacuum to afford desired product as white solid with a quantitative yield.

$C_4H_7ClF_3NO_2$, $M_W = 193.55$, white solid, mp = 168–170 °C; IR (cm^{-1}): 3400 (OH); 2907 (NH); 1731 (CO); 1418 (C–O); NMR ^{19}F (CD_3OD): −74.3 (3F, d, $J = 6.8$); NMR

^{1}H (CD_3OD): 2.88 (1H, dd, J = 8.7, J = 17.7), 3.05 (1H, dd, J = 4.1, J = 17.7), 4.52 (1H, m), 5.25 (4H, b); NMR ^{13}C ($CDCl_3$): 31.9, 50.7 (q, J = 32.5), 125.1 (q, J = 279.9), 171.2; Anal. Calcd. for $C_4H_7ClF_3NO_2$: C, 24.82; H, 3.65; N, 7.24; found: C, 24.84; H, 3.73; N, 7.18; optical rotation (c = 1.00, HCl 6N, 25 °C): (*R*): $[\alpha]_D$ = +21.5; $[\alpha]_{365}$ = +65.7; $[\alpha]_{546}$ = +26.4; $[\alpha]_{578}$ = +23.5; (*S*) $[\alpha]_D$ = −21.6; $[\alpha]_{365}$ = −60.0; $[\alpha]_{546}$ = −24.1; $[\alpha]_{578}$ = −21.3.

4.6. 3-Amino-4,4,4-trifluorobutan-1-ol (*4*)

To a suspension of $LiAlH_4$ (0.205 g, 5.4 mmol) in dry THF (17 mL), ethyl 3-amino-4,4,4-trifluorobutanoate **2** (0.5 g, 2.7 mmol) was added at −15 °C. Resulting mixture was stirred for 2 h at −15 °C. Reaction was then quenched with iced water and after stirring for 20 min at room temperature, mixture was filtrated and extracted several times with diethyl ether. Solvent was evaporated and crude product was purified on silica gel column with a mixture of dichloromethane/methanol (97/3) as eluent to afford desired product (0.251 g, 65%), as colourless oil.

$C_4H_8F_3NO$, M_W = 143.11, colourless oil; NMR ^{19}F ($CDCl_3$): −80.2 (3F, d, J = 6.9); NMR ^{1}H ($CDCl_3$): 1.61 (1H, m), 1.86 (1H, m), 2.30 (1H, b), 3.34 (1H, m), 3.82 (2H, m); NMR ^{13}C ($CDCl_3$): 31.0, 53.8 (q, J = 29.7), 60.9, 126.2 (q, J = 281.3); GC (BETA DEX 120, 15 m, 60 °C): (*S*): 12.6 min; (*R*): 13.5 min; Anal. Calcd. for $C_4H_8F_3NO$: C, 33.57; H, 5.63; N, 9.79; found: C, 33.46; H, 5.79; N, 9.83; optical rotation (c = 1.5, $CHCl_3$, 25 °C): (*R*): $[\alpha]_D$ = +44.0; $[\alpha]_{365}$ = +134.1; $[\alpha]_{436}$ = +89.0; $[\alpha]_{546}$ = +53.7; $[\alpha]_{578}$ = +47.7.

4.7. (R)-Ethyl 3-(benzylamino)-4,4,4-trifluorobutanoate (*5*)

Freshly distilled benzaldehyde (329 mL, 3.24 mmol) was added dropwise to a solution of (*R*)-ethyl 3-amino-4,4,4-trifluorobutanoate **2** (0.4 g, 2.16 mmol) in a mixture of ethanol (14 mL) and glacial acetic acid (3.5 mL). The resultant mixture was stirred at room temperature for 1.5 h. After cooling to 0 °C, sodium borohydride (0.144 g, 3.78 mmol) was added in portions. After being stirred for an additional 15 min, the reaction mixture was partitioned between saturated $NaHCO_3$ and dichloromethane, the aqueous phase was twice extracted with dichloromethane. Organic layers were combined, dried over Na_2SO_4, and condensed in vacuum. The residue was placed on silica gel column and eluted with a mixture of cyclohexane/ethyl acetate (90/10) to afford desired product (0.209 g, 76%) as colourless oil.

$C_{13}H_{16}F_3NO_2$, M_W = 275.27, colourless oil; IR (cm^{-1}): 3355 (NH); 3030 (CH_{Aro}); 2984 (CH_3); 2937 (CH_2); 1740 (CO); 1603 (db_{Aro}); NMR ^{19}F ($CDCl_3$): −75.3 (3F, d, J = 6.8); NMR ^{1}H ($CDCl_3$): 1.08 (3H, t, J = 7.2), 1.56 (1H, bs), 2.30 (1H, dd, J = 9.8, J = 15.5), 2.52 (1H, dd, J = 4.1, J = 15.5), 3.50 (1H, m), 3.70 (1H, d, J = 12.8), 3.80 (1H, d, J = 12.8), 4.05 (2H, m), 7.10 (5H, m); NMR ^{13}C ($CDCl_3$): 14.0, 35.0, 52.0, 56.2 (q, J = 28.4), 61.0, 126.3 (q, J = 284.0), 127.3, 128.2, 128.4, 139.5, 170.0; GC (BPX5, 23 m, 40 °C (5 min), 8 °C/min, 280 °C): 16.1 min; GC–MS (EI): 91(100); 106(95); 188(9); 275($M^{\bullet+}$); anal. calcd. for $C_{13}H_{16}F_3NO_2$: C, 56.72; H, 5.86; N, 5.09; found: C, 56.69; H, 5.68; N, 5.54; optical rotation (c = 1, $CHCl_3$, 25 °C): (*R*): $[\alpha]_D$ = +22.6; $[\alpha]_{436}$ = +53.8; $[\alpha]_{546}$ = +31.5; $[\alpha]_{578}$ = +27.6.

4.8. 1-Benzyl-4-(trifluoromethyl)azetidin-2-one (*6*)

Under inert atmosphere, at −12 °C, a freshly prepared solution of methyl magnesium iodide in anhydrous diethyl ether (1.3 mmol) was slowly added to a stirred solution of (*R*) or (*Rac.*) ethyl 3-(benzylamino)-4,4,4-trifluorobutanoate **5** (0.170 g, 0.6 mmol) in anhydrous diethyl ether (2 mL). Once the addition was finished, the reaction mixture was stirred at −12 °C for 15 min more. Thereafter, the slurry was quenched with saturated aqueous solution of NH_4Cl and extracted 3 times with diethyl ether. Organic phases were combined, washed with aqueous $NaHCO_3$, water and dried over Na_2SO_4. The filtered solution was concentrated in vacuum. The residue was purified by column chromatography with cyclohexane/ethyl acetate (6/1) to yield desired product (0.112 g, 80%) as white solid.

$C_{11}H_{10}F_3NO$, M_W = 229.20, white solid, mp = 58–60 °C; IR (cm^{-1}): 3033 (CH_{Aro}); 2940 (CH_2); 1775 (CO_{lactam}); NMR ^{19}F (CD_3OD): −75.3 (d, J = 5.72); NMR ^{1}H (CD_3OD): 2.97 (1H, dd, J = 15.1, J = 2.6), 3.05 (1H, dd, J = 15.1, J = 5.28), 3.75 (1H, m), 4.75 (1H, d, J = 15.1), 4.80 (1H, d, J = 15.1), 7.18–7.33 (5H, m); NMR ^{13}C (CD_3OD): 38.7, 45.9, 49.8 (q, J = 35.3), 124.6 (q, J = 279.0), 128.3, 128.6, 129.1, 134.7, 165.3; GC (Chiral DEX βDA, 40 m, 120 °C): (*R*): 14.0 min; (*S*): 14.5 min; anal. calcd. for $C_{11}H_{10}F_3NO$: C, 57.64; H, 4.40; N, 6.11; found: C, 57.62; H, 4.44; N, 6.26; optical rotation (c = 1, $CHCl_3$, 25 °C): (*R*): $[\alpha]_D$ = −108.7; $[\alpha]_{365}$ = −414.9; $[\alpha]_{436}$ = −239.6; $[\alpha]_{546}$ = −131.5; $[\alpha]_{578}$ = −113.8.

4.9. N-[(Z)-Gly]-ethyl 3-amino 4,4,4-trifluorobutanoate (*7*)

To a stirred solution of Z-glycine (0.31 g, 1.48 mmol) in distilled dichloromethane (20 mL), oxalyl dichloride (150 μL, 1.76 mmol) and a drop of distilled DMF were added dropwise at 0 °C. After 2 h stirring at room temperature, ethyl 3-amino-4,4,4-trifluorobutanoate **2** (0.3 g, 1.62 mmol) was first added and then DIEA (0.84 mL, 4.8 mmol) was added dropwise at 0 °C. Once the addition was finished, the mixture was heated at 40 °C for 16 h. Thereafter, dichloromethane was added and the mixture was washed twice with aqueous solution of $NaHCO_3$ 1 M, twice with aqueous solution of citric acid (5%) and finally twice with distilled water. Organic phase was dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by recrystallization (ethyl acetate/hexane) to yield the desired product (0.41 g, 75%) as white solid.

$C_{16}H_{19}F_3N_2O_5$, M_W = 376.33, white solid, mp = 110 °C; IR (cm^{-1}): 3416 (NH); 3074 (CH_{Aro}); 2981 (CH_2); 1728 (CO_{ester}); 1695, 1682 (CO_{amide}); NMR ^{19}F (CD_3OD): −76.3 (3F, d, J = 6.8); NMR ^{1}H (CD_3OD): 1.24 (3H, t, J = 7.2), 2.66 (2H, 2dd, J = 15.8, J = 7.2, J = 3.7), 3.91 (2H, d, J = 5.3), 4.15 (2H, q, J = 7.2), 5.02 (1H, m), 5.12 (2H, s), 5.56 (1H, bs), 7.23 (1H, bs), 7.34 (5H, m); NMR ^{13}C (CD_3OD): 14.1, 33.1, 44.7, 47.6 (q, J = 31.8), 61.7, 67.5, 124.6 (q, J = 282.0), 128.2, 128.5, 128.7,

136.1, 156.8, 169.2, 169.4; anal. calcd. for $C_{16}H_{19}F_3N_2O_5$: C, 51.06; H, 5.09; N, 7.44; found: C, 51.09; H, 5.03; N, 7.42.

4.10. 3-(Benzylamino)-4,4,4-trifluorobutanoic acid (**8**)

Ethyl 3-(benzylamino)-4,4,4-trifluorobutanoate **5** (1.5 g, 5.45 mmol) was added at room temperature to a mixture of *i*PrOH (42 mL) and water (14 mL). The resulting mixture was stirred at room temperature for 15 min. Aqueous solution of NaOH 1 M (0.0164 g, 16.4 mmol) was then added dropwise at 0 °C. The resulting mixture was allowed to room temperature and stirred for a night followed by evaporation of the solvent in vacuum. The residue was dissolved with a saturated aqueous solution of NH_4Cl and the pH of the mixture was adjusted down to 1 by addition of an aqueous solution of HCl (2 M). The mixture was extracted with diethyl ether, organic layers were combined, dried over $MgSO_4$ and condensed in vacuum. The desired product was obtained as white solid (1.28 g, 95%).

$C_{11}H_{12}F_3NO_2$, M_W = 247.21, white solid, mp = 106 °C; IR (cm^{-1}): 3423 (bb, NH, OH); 1714 (CO); 1639 (db_{Aro}); NMR ^{19}F (CD_3OD): −74.4 (3F, d, J = 6.8); NMR ^1H (CD_3OD): 2.74 (1H, dd, J = 14.9, J = 7.8), 2.88 (1H, dd, J = 14.9, J = 4.2), 3.86 (1H, m), 4.09 (1H, d, J = 12.4), 4.17 (1H, d, J = 12.4), 7.50 (5H, m); NMR ^{13}C (CD_3OD): 34.9, 52.7, 57.2 (q, J = 29.0), 127.8 (q, J = 283.4), 129.5, 129.4, 128.3, 140.3, 173.6; anal. calcd. for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67; found: C, 53.47; H, 5.04; N, 5.59.

4.11. 2-[3-(Benzylamino) 4,4,4-trifluoro]-butanamide-methylacetate (**9**)

In a flask, 3-(benzylamino)-4,4,4-trifluorobutanoic acid **8** (0.150 g, 0.6 mmol), 2-chloro-1-methylpyridinium iodide (0.184 g, 0.73 mmol) and dichloromethane (8 mL) were introduced and put under inert atmosphere. The mixture was stirred 15 min at room temperature. Methyl glycinate hydrochloride (0.083 g, 0.66 mmol) first and then, dropwise, diisopropyl ethyl amine (350 μL, 1.98 mmol) were added at 0 °C. Once the addition was finished, the resultant mixture was stirred overnight at room temperature. Dichloromethane was then added and the mixture was washed twice with an aqueous solution of $NaHCO_3$ 1 M, twice with an aqueous solution of citric acid (5%), and finally twice with distilled water. Organic layer were combined, dried over Na_2SO_4, filtrated and condensed in vacuum. The residue was placed on short silica gel column and eluted with a mixture of dichloromethane/methanol (99/1) to afford the desired product (0.150 g, 78%) as yellow pale oil.

$C_{14}H_{17}F_3N_2O_3$, M_W = 318.29, pale yellow oil; IR (cm^{-1}): 3320 (NH); 3065 (CH_{Aro}); 3030 (CH_{Aro}); 2954 (CH_3); 2855 (CH_2); 1750 (CO_{ester}); 1658 (CO_{amide}); 1547 (NH_{amide}); NMR ^{19}F (CD_3OD): −74.9 (3F, d, J = 6.8); NMR ^1H (CD_3OD): 1.84 (1H, bs), 2.38 (1H, dd, J = 10.2, J = 15.4), 2.38 (1H, dd, J = 3.0, J = 15.4), 3.59 (1H, m), 3.71 (3H, s), 3.85 (1H, d, J = 12.8), 3.96 (2H, d, J = 5.6), 4.00 (1H, d, J = 12.8), 7.22–7.30 (6H, m); NMR ^{13}C (CD_3OD): 35.3, 41.2, 51.8, 52.4, 56.2 (q, J = 28.3), 126.4 (q, J = 284.8), 127.5, 128.4, 128.6, 139.1, 169.6, 170.3; anal. calcd. for $C_{14}H_{17}F_3N_2O_3$: C, 52.83; H, 5.38; N, 8.80; found: C, 52.81; H, 5.37; N, 8.71.

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