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Chemical deracemization and (*S*) to (*R*) interconversion of some fluorine-containing α-amino acids

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ABSTRACT

Several ω-CF_3-substituted α-amino acids have been prepared in optically pure form via two complementary approaches. Racemic fluorinated derivatives of 2-aminobutanoic acid, norvaline and norleucine were chemically deracemized by complexation with a Ni(II) salt and a chiral reagent derived from α-(phenyl)ethylamine. Additionally this procedure also allowed the conversion of readily available L-amino acids, CF_3-analogs of cysteine and methionine, into the corresponding unnatural D-series. Optically pure amino acids are obtained upon disassembly of the Ni(II) complexes with recovery of the chiral ligand.

1. Introduction

Due to the paramount importance of amino acids in the numerous fields of biology and medicine, the development of synthetic methods for the preparation of their fluorinated analogs has been one of the most actively pursued research areas [1,2]. Taking into account that the biological activity of amino acids is a function of their stereochemistry, preparation of fluorinated amino acids in enantiomerically pure form has received particular attention. Thus, two major approaches – asymmetric synthesis and enzymatic resolutions of racemic amino acids – have been extensively explored and many practical methods have been developed [1–5]. On the other hand, chemical resolution, deracemization, of racemic fluorinated amino acids under the action of chiral reagents [6] remains a virtually unexplored area of fluoro-amino acids chemistry. One particular type of fluorine-containing α-amino acids, linear ω-trifluoromethyl derivatives **1a–c** and **2a**,**b** (Fig. 1), is of considerable interest for peptide design due to the strong steric [7] and electrostatic [8] requirements of the trifluoromethyl group. Amino acids **1a–c** and **2a**,**b** have been prepared in enantiomerically pure form via asymmetric synthesis [9] and enzymatic resolutions [10]. In this work, we report preparation of (*S*)- and (*R*)-**1a–c** via deracemization of the corresponding racemic derivatives and synthesis of (*S*)-**2a** and (*R*)-2**b** (D-amino acids) via (*S*) to (*R*) interconversion, using new chiral reagents (*S*)- and (*R*)-**3** (Fig. 2).

During our studies of the chemistry of achiral [11,12] and chiral [13,14] Ni(II)-complexes of amino acid Schiff bases and their applications for general [15] asymmetric synthesis of α-amino acids, we discovered a modular approach to the design [16] of a new generation of Ni(II) complexes with the general structure **4** (Fig. 2) [17]. We demonstrated that the rational combination of four structural modules (phenone, acid, amine and amino acid) allows for the complete control of reactivity as well as physicochemical properties of derivatives **4**. In particular, the chiral reagent **3** [18] can be easily assembled using very

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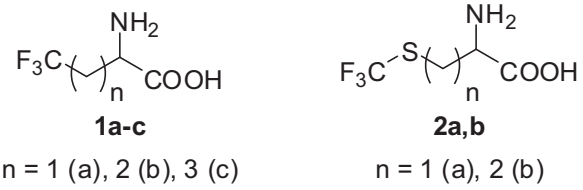


Fig. 1. Linear ω-trifluoromethyl amino acids **1a–c** and **2a**,**b** used in this study.

Fig. 2. Modular Ni(II) complexes **4** and chiral reagent **3**.

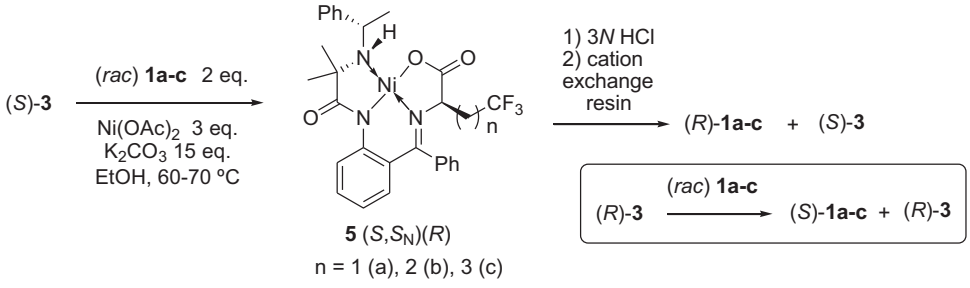
inexpensive 2-bromoisobutyric acid, 2-aminobenzophenone and α-(phenyl)ethylamine, as a source of chirality which is readily available in both enantiomerically pure forms [19].

2. Results and discussion

First, we studied deracemization of amino acids **1a**-**c**. These amino acids are readily available in racemic form via alkylation of amino malonic acid esters with the corresponding ω-CF_3-alkyl iodides [20]. As shown in Scheme 1, the reactions of reagent (*S*)-**3** with amino acids (*rac*)-**1a–c** were conducted in ethanol in the presence of excess $Ni(OAc)_2$ and K_2CO_3 while heating. Monitoring the reaction progress by TLC revealed that initially, under kinetically controlled conditions, a mixture of diastereomeric products is produced. However, after allowing the reaction mixture to continue mixing under heat for approximately 24 h effectively provided only the thermodynamically controlled products **5**. Absolute configuration of products **5a–c** was determined to be (S,S_N)(R) based on the chiroptical properties of the complexes **5a–c** and by analogy with the previous results of the reactions of reagent (*S*)-**3** with linear non-fluorinated amino acids [18]. Compounds **5a–c** were obtained in good chemical yields (Table 1, entries 1–3). The yield of product **5a** was slightly lower as compared with that of **5b** and **5c**, which can be explained by the more profound effect of the CF_3-group on the basicity of amino group in **1a** [21]. Compounds (S,S_N)(R)-**5a–c** were purified by column chromatography to yield chemically and diastereomerically pure materials. Free amino acids (*R*)-**1a–c** were obtained via standard disassembly of complexes **5a–c** under acidic conditions [22] along with quantitative recovery of the chiral reagent (*S*)-**3**.

Similar results were obtained with application of reagent **3** derived from (*R*)-α-(phenyl)ethylamine. In this case the major diastereomeric products **5a–c** had (R,R_N)(S) absolute configuration (Table 1, entries 4–6). Complex (R,R_N)(S)-**5c** was purified by column chromatography and upon disassembling gave rise to α-(*S*) configured amino acid **1c** in good chemical yield. Chiroptical and spectral properties of the free amino acid (*S*)-**1c** matched the literature data reported for this compound [9a].

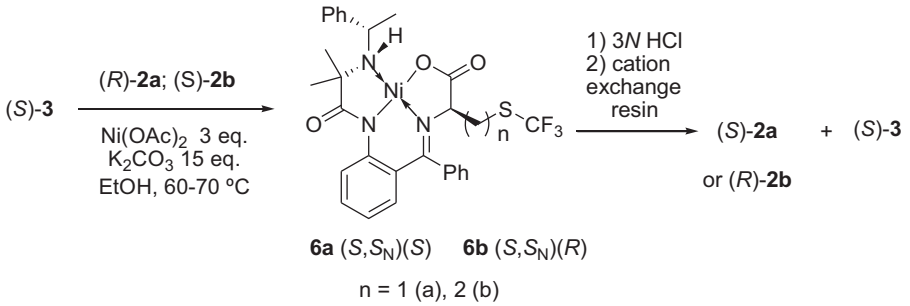
Our second goal was to study the application of reagents (*S*)- and (*R*)-**3** for (*S*) to (*R*) interconversion of fluorinated amino acids. As an example, we chose CF_3-containing (*R*)-cysteine **2a** and (*S*)-methionine **2b**. It should be noted that both amino acids **2a** and **2b** are of the same relative configuration (L-series) and the difference of their absolute configurations is the result of CIP rules [23]. Amino acids **2a**,**b** can be easily prepared form naturally occurring derivatives and therefore are readily available in their L-configuration [9e]. On the other hand, the corresponding compounds of the D-series [(*S*)-**2a** and (*R*)-**2b**] have never been reported in the literature. Considering the importance of D-amino acids in biochemical sciences [24], preparation of D-enantiomers of trifluoromethyl cysteine **2a** and trifluoro-methionine **2b** seems to be of great interest. To this end, we conducted the reactions of enantiomerically pure amino acids L-**2a**,**b** with reagent (*S*)-**3**. As shown in Scheme 2, heating a mixture of L-**2a**,**b** with (*S*)-**3** and $Ni(OAc)_2$ gave rise to thermodynamically controlled products **6a**,**b** in good chemical yield (Table 1, entries 7 and 8). Complexes **6a**,**b** were purified by



Scheme 1. Deracemization of racemic amino acids **1a–c**.

Table 1
Reactions of reagent **3** with amino acids **1a–c** and **2a**,**b**.

Entry	Amino acid	Ligand **3**	**5a–c**/**6a**,**b** (config.)	**5a–c** yield (%)	**6a**,**b** yield (%)	Amino acid (yield, %)
1	*rac*-**1a**	(*S*)-**3**	**5a** (S,S_N)(R)	75	N/A	(*R*)-**1a** (63)
2	*rac*-**1b**	(*S*)-**3**	**5b** (S,S_N)(R)	79	N/A	(*R*)-**1b** (60)
3	*rac*-**1c**	(*S*)-**3**	**5c** (S,S_N)(R)	79	N/A	(*R*)-**1c** (66)
4	*rac*-**1a**	(*R*)-**3**	**5a** (R,R_N)(S)	74	N/A	N/A
5	*rac*-**1b**	(*R*)-**3**	**5b** (R,R_N)(S)	78	N/A	N/A
6	*rac*-**1c**	(*R*)-**3**	**5c** (R,R_N)(S)	80	N/A	(*S*)-**1c** (69)
7	(*R*)-**2a**	(*S*)-**3**	**6a** (S,S_N)(S)	N/A	87	(*S*)-**2a** (73)
8	(*S*)-**2b**	(*S*)-**3**	**6b** (S,S_N)(R)	N/A	90	(*R*)-**2b** (74)



Scheme 2. (*S*) to (*R*) inversion of amino acids **2a**,**b**.

column chromatography and disassembled to afford free amino acids (*S*)-**2a** and (*R*)-**2b**. It should be noted that S-CF_3 containing amino acids **2a**,**b** possess relatively high volatility and therefore present quite interesting models for investigations of self-disproportionation of enantiomers (SDE) via achiral chromatography [25] and sublimation [26], which are currently under study in our laboratories.

3. Conclusions

In conclusion, the chemical approach for deracemization and (*S*) to (*R*) inversion of a series of ω-CF_3 and ω-S-CF_3 amino acids has been successfully developed with the application of new chiral reagent (*S*)- or (*R*)-**3**. Good chemical yields and simple reaction conditions render this method as a synthetically valuable alternative to asymmetric synthesis and/or enzymatic resolutions for preparation of these fluorinated amino acids in enantiomerically pure form.

4. Experimental

*4.1. General procedure for preparation of Ni(II)-complexes **5a–c** and **6a**,**b** by the reaction of (S)- or (R)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)acetamide **3** with corresponding amino acids **1a–c** and **2a**,**b***

To a flask containing ethanol solution of reagent **3** (1 equiv.), $Ni(OAc)_2{\cdot}4H_2O$ (4 equiv.), racemic amino acid (2.0 equiv.), was added K_2CO_3 (15 equiv.), and the reaction mixture was stirred at 60–70 °C. The progress of the reaction was monitored by TLC and upon completion (consumption of the reagent **3**), the reaction mixture was poured into ice water. The target product was extracted several times with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum. After evaporation of the solvents and silica–gel column chromatography, the target complexes **5a–c** and **6a**,**b** were obtained in diastereomerically pure form.

*4.1.1. Ni(II) complex of (R)-2-amino-4,4,4-trifluorobutanoic acid Schiff base with (S)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5a***

M.p. 275.5 °C (decomp.). $[\alpha]_D^{25}$ −767.6 (*c* 1.11, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (3H, s), 1.67 (3H, d, *J* = 6.7 Hz), 2.53 (1H, bm), 2.85–3.01 (2H, m), 2.95 (3H, s), 3.89 (1H, m), 4.28 (1H, dd, *J* = 7.4, 5.6 Hz), 6.57 (1H, m), 6.68 (1H, m), 6.83 (1H, bd, *J* = 7.9 Hz), 7.04–7.14 (2H, m), 7.17–7.27 (4H, m), 7.40–7.56 (3H, m), 8.03 (1H, d, *J* = 8.8 Hz), 8.21 (2H, bd, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.1, 22.5, 33.3, 40.1 (q, *J* = 30.7 Hz), 57.6, 64.9, 65.0, 120.2, 123.3, 126.8, 127.4, 127.7, 128.3, 128.6, 128.8, 129.2, 129.4, 129.8 (q, *J* = 277.8 Hz), 131.8, 132.8, 133.8, 140.1, 142.2, 169.7, 180.5, 181.0. HRMS [M+Na^+] found *m*/*z* 604.1358, calcd for $C_{29}H_{28}F_3N_3NaNiO_3$ 604.1334.

*4.1.2. Ni(II) complex of (R)-2-amino-5,5,5-trifluoropentanoic acid Schiff base with (S)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5b***

M.p. 251.0 °C (decomp.). $[\alpha]_D^{25}$ −811.6 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (3H, s), 1.63 (3H, d, *J* = 6.7 Hz), 2.64 (1H, bm), 2.60–3.00 (4H, m), 2.88 (3H, s), 3.79 (1H, m), 4.33 (1H, bt, *J* = 6.3 Hz), 6.61 (1H, m), 6.73 (1H, m), 6.84 (1H, bd, *J* = 7.9 Hz), 7.07–7.12 (2H, m), 7.14–7.29 (4H, m), 7.41–7.60 (3H, m), 8.03 (1H, d, *J* = 8.8 Hz), 8.22 (2H, bd, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.3, 22.6, 29.8, 33.3, 34.0 (q, *J* = 27.1 Hz), 57.7, 65.0, 65.2, 120.3, 123.1, 126.6, 127.7, 128.1, 128.3, 128.8, 128.9, 129.3, 129.6, 131.2 (q, *J* = 275.1 Hz), 131.6, 133.8, 133.9, 140.2, 143.3, 170.7, 181.3, 183.0. HRMS [M+Na^+] found *m*/*z* 618.1502, calcd for $C_{30}H_{30}F_3N_3NaNiO_3$ 618.1490.

*4.1.3. Ni(II) complex of (R)-2-amino-6,6,6-trifluorohexanoic acid Schiff base with (S)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5c***

M.p. 264.0 °C (decomp.). $[\alpha]_D^{25}$ −921.0 (*c* 1.12, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (3H, s), 1.55–1.61 (2H, m), 1.67 (3H, d, *J* = 6.6 Hz), 1.81–1.90 (2H, m), 2.71 (1H, bm), 2.55–2.63 (2H, m), 2.88 (3H, s), 3.79 (1H, m), 4.01 (1H, dd, *J* = 8.5, 3.7 Hz), 6.63 (1H, m), 6.75 (1H, m), 6.83 (1H, bd, *J* = 7.9 Hz), 7.06–7.14 (2H, m), 7.14–7.29 (4H, m), 7.44–7.59 (3H, m), 8.02 (1H, d, *J* = 8.7 Hz), 8.23 (2H, bd, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.0, 21.3, 29.8, 33.2 (q, *J* = 28.8 Hz), 33.9, 57.9, 65.4, 65.9, 120.6, 123.8, 126.5 (q, *J* = 277.0 Hz), 126.9, 127.8, 127.9, 128.5, 128.7, 128.8, 129.2, 129.9, 131.3, 134.0, 135.8, 141.1, 142.4, 169.9, 180.7, 183.5. HRMS [M+Na^+] found *m*/*z* 632.1655, calcd for $C_{31}H_{32}F_3N_3NaNiO_3$ 632.1647.

*4.1.4. Ni(II) complex of (S)-2-amino-4,4,4-trifluorobutanoic acid Schiff base with (R)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5a***

M.p. 264.0 °C (decomp.). $[\alpha]_D^{25}$ +761.3 (*c* 1.10, $CHCl_3$). The NMR spectra are identical to that of (*R*),(*S*)-**5a** enantiomer.

*4.1.5. Ni(II) complex of (S)-2-amino-5,5,5-trifluoropentanoic acid Schiff base with (R)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5b***

M.p. 259.5 °C (decomp.). $[\alpha]_D^{25}$ +817.0 (*c* 1.15, $CHCl_3$). The NMR spectra are identical to that of (*R*),(*S*)-**5b** enantiomer.

*4.1.6. Ni(II) complex of (S)-2-amino-6,6,6-trifluorohexanoic acid Schiff base with (R)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **5c***

M.p. 258.0 °C (decomp.). $[\alpha]_D^{25}$ +915.4 (*c* 1.13, $CHCl_3$). The NMR spectra are identical to that of (*R*),(*S*)-**5c** enantiomer.

*4.1.7. Ni(II) complex of (S)-2-amino-3-(trifluoromethylthio)propanoic acid Schiff base with (S)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **6a***

M.p. 221.0 °C (decomp.). $[\alpha]_D^{25}$ −1005.8 (*c* 1.13, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (3H, s), 1.67 (3H, d, *J* = 6.7 Hz), 2.53

(1H, bm), 2.95 (3H, s), 3.44–3.71 (2H, m), 3.89 (1H, m), 4.38 (1H, dd, J = 7.2, 4.7 Hz), 6.55 (1H, m), 6.72 (1H, m), 6.78 (1H, bd, J = 7.9 Hz), 7.05–7.15 (2H, m), 7.14–7.30 (4H, m), 7.37–7.57 (3H, m), 8.02 (1H, d, J = 8.8 Hz), 8.23 (2H, bd, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.1, 22.5, 30.6, 54.7, 63.9, 65.5, 121.2, 122.1, 124.5, 126.9, 127.7, 128.4, 128.7, 128.8, 129.5, 129.7, 130.3 (q, J = 305.5 Hz), 131.8, 132.4, 134.7, 140.8, 142.9, 173.7, 182.5, 183.0. HRMS [M+Na$^+$] found m/z 636.1014, calcd for $C_{29}H_{28}F_3N_3NaNiO_3S$ 636.1055.

4.1.8. Ni(II) complex of (R)-2-amino-4-(trifluoromethylthio)butanoic acid Schiff base with (S)-N-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide ***6b***

M.p. 197.5 °C (decomp.). $[\alpha]_D^{25}$ −984.5 (c 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (3H, s), 1.67 (3H, d, J = 6.7 Hz), 1.95–2.40 (2H, m), 2.53 (1H, bm), 2.95 (3H, s), 3.00–3.05 (2H, m), 3.89 (1H, m), 4.11 (1H, m), 6.55 (1H, m), 6.72 (1H, m), 6.78 (1H, bd, J = 7.9 Hz), 7.05–7.15 (2H, m), 7.14–7.30 (4H, m), 7.37–7.57 (3H, m), 8.02 (1H, d, J = 8.8 Hz), 8.23 (2H, bd, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.3, 22.4, 25.0, 30.7, 54.8, 62.4, 64.3, 121.0, 123.5, 126.9, 126.9, 128.0, 127.9, 128.9, 128.3, 129.4, 129.6, 130.1 (q, J = 305.0 Hz), 132.0, 133.0, 134.0, 140.5, 142.3, 171.9, 180.8, 181.2. HRMS [M+Na$^+$] found m/z 650.1244, calcd for $C_{30}H_{30}F_3N_3NaNiO_3S$ 650.1211.

4.2. General procedure for decomposition of complexes ***5*** *and* ***6****, isolation of target amino acids* ***1*** *and* ***2****, and recovery of chiral reagent* ***3***

A solution of diastereomerically pure complex **5** or **6** (25 mmol) in MeOH (50 mL) was added to a stirring solution of 3 N HCl in MeOH (90 mL, ratio 1:1, acid:MeOH) at 70 °C. Upon disappearance of the red color (about 5–10 min), the reaction mixture was evaporated in vacuum. Water (85 mL) was added and the resultant mixture was treated with an excess of concentrated ammonium hydroxide and extracted with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and evaporated in vacuum to give (>95%) ligand **3**. The aqueous solution was evaporated in vacuum, dissolved in a minimum amount of water, and passed through cation exchange resin Dowex 50 × 2 100 to afford analytically pure samples of the target amino acids (91–95%) **1** and **2**. The enantiomeric purity of thus prepared amino acids **1** and **2** was determined to be >98% ee by the chiral HPLC analysis using chiral stationary phase containing hydroxyproline residues. For details, see Ref. [27].

4.2.1. (R)-2-amino-4,4,4-trifluorobutanoic acid ***1a***

M.p. 201–203 °C (decomp.). $[\alpha]_D^{25}$ −9.9 (c 1.01, 6 N HCl). ^{1}H NMR (D_2O, 300 MHz) δ 2.45–3.10 (2H, m), 4.19 (1H, dd, J = 7.5, 5.5 Hz).

4.2.2. (R)-2-amino-5,5,5-trifluoropentanoic acid ***1b***

M.p. 207–209 °C (decomp.). $[\alpha]_D^{25}$ −10.3 (c 0.93, 6 N HCl). ^{1}H NMR (D_2O, 300 MHz) δ 2.40–3.17 (4H, m), 4.24 (1H, t, J = 6.1 Hz).

4.2.3. (R)-2-amino-6,6,6-trifluorohexanoic acid ***1c***

M.p. 194–195 °C. $[\alpha]_D^{25}$ −7.7 (c 1.12, 6 N HCl). ^{1}H NMR (D_2O, 300 MHz) δ 1.52–1.62 (m, 2H), 1.81–1.87 (m, 2H), 2.06–2.21 (m, 2H), 3.73–3.77 (m, 1H).

4.2.4. (S)-2-amino-6,6,6-trifluorohexanoic acid ***1c***

M.p. 194–195 °C. $[\alpha]_D^{25}$ +7.9 (c 1.07, 6 N HCl). ^{1}H NMR (D_2O, 300 MHz) δ 1.51–1.62 (m, 2H), 1.81–1.86 (m, 2H), 2.05–2.20 (m, 2H), 3.74–3.77 (m, 1H).

4.2.5. (S)-2-amino-3-(trifluoromethylthio)propanoic acid ***2a***

M.p. 233–235 °C. $[\alpha]_D^{25}$ +26.7 (c 0.9, H_2O). ^{1}H NMR (D_2O, 300 MHz) δ 3.47 (dd, J = 7.2, 15.5 Hz, 1H), 3.64 (dd, J = 4.5, 15.5 Hz, 1H), 4.34 (dd, J = 4.5, 7.2 Hz, 1H). ^{19}F NMR (282 MHz, D_2O) −41.4 (s, 3F). ^{13}C NMR (150.9 MHz, D_2O) δ 30.5, 54.7, 131.0 (q, J = 307 Hz), 172.0.

4.2.6. (R)-2-amino-4-(trifluoromethylthio)butanoic ***2b***

M.p. 227–230 °C. $[\alpha]_D^{25}$ −23.9 (c 1.07, 4 N HCl). ^{1}H NMR (D_2O, 200 MHz) δ 1.95–2.40 (2H, m), 3.04 (2H, t, J = 8.3 Hz), 4.11 (1H, t, J = 6.6 Hz). ^{19}F NMR (D_2O, 188 MHz) δ −41.5 (s, 3F). ^{13}C NMR (D_2O, 75.5 MHz) δ 25.2, 30.1, 51.3, 130.4 (q, J = 306 Hz), 170.8.

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