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Nucleophilic addition of 3,3,3-trifluoropropynyllithium to D-glyceraldimine: Concise synthesis of both enantiomers of 5,5,5-trifluoronorvaline

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Abstract

3,3,3-Trifluoropropynyllithium, *in situ* generated by treatment of 2-bromo-3,3,3-trifluoro-1-propene **1** with 2.0 equiv. of LDA at −78 °C, was trapped with D-glyceraldimine **2** to give trifluoromethylated propargylic amine **4** in 55% yield. Starting from the key intermediate **4**, Boc-protected (*R*)-5,5,5-trifluoronorvaline and (*S*)-5,5,5-trifluoronorvaline were concisely synthesized over three steps in 62% and 63% yield, respectively.

Keywords: Fluorinated amino acids; 3,3,3-Trifluoropropynyllithium; 5,5,5-Trifluoronorvaline

1. Introduction

In recent years, incorporation of trifluoromethyl-containing amino acids (TFAAs) into peptides and proteins has become an important tool in the design of peptides and proteins [1–7]. The importance of TFAAs made the development of new and efficient enantioselective methodologies or strategies to their synthesis a significant and active area of research [8–11]. Among these trifluoromethylated amino acids, 5,5,5-trifluoronorvaline had attracted attention earlier. In 1955, Loncrini and co-workers described that 5,5,5-trifluoronorvaline could inhibit the growth of *Escherichia coli* and may be used as a growth regulatory factor in microbiology [12]. Ojima et al. reported in 1992 that the new methonine–enkephalin analogs bearing (D)-trifluoronorvaline in place of one glycine exhibited ca. 100,000 times enhancement in *in vivo* analgesic activity in comparison with methionine–enkephalin [13]. Therefore, several synthetic routes to 5,5,5-trifluoronorvaline were developed. In most cases racemic mixtures of 5,5,5-trifluoronorvaline were obtained [14–20]. To the best of our knowledge, there was only one report about the stereoselective synthesis of 5,5,5-trifluoronorvaline, in which the fluorinated reagent SF_4 was used [19]. Therefore, the development of efficient and stereoselective route to 5,5,5-trifluoronorvaline was anticipated. Herein we report a concise synthesis of both enantiomers of trifluoronorvaline using nucleophilic addition of 3,3,3-trifluoropropynyllithium to D-glyceraldimine **2** as the key step.

2. Results and discussion

In general, the additions of Grigard reagents or organolithium reagents to imine were found to be rather complicated. However, the additions of Grigard reagents or organolithium reagents to D-glyceraldimine proceeded very well [21], which were attributed to prior formation of a five-membered chelate with the 2-alkoxy group [21–25]. Using this kind of addition reactions, Cativiela et al. [26–28] successfully prepared a number of important unnatural amino acids. Thus, we proposed that the additions of fluoroalkyl substituted organometallic reagents to glyceraldimine should present an efficient synthetic strategy for fluorinated amino acids (Scheme 1) [29].

Tarrant and co-workers described that the addition of 3,3,3-trifluoroisopropenyllithium, *in situ* generated from the reaction of 2-bromo-3,3,3-trifluoro-1-propene and *n*-butyl lithium at

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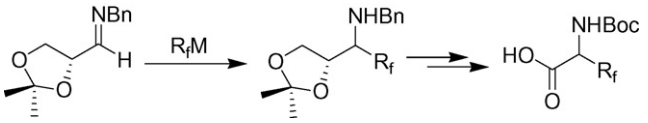
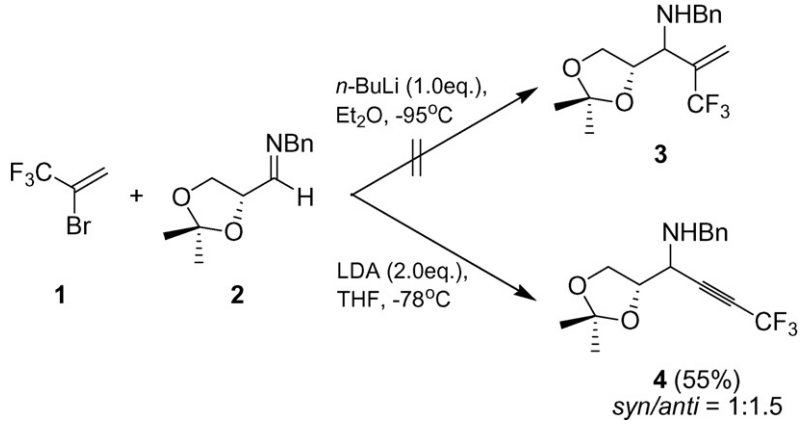


Scheme 1.

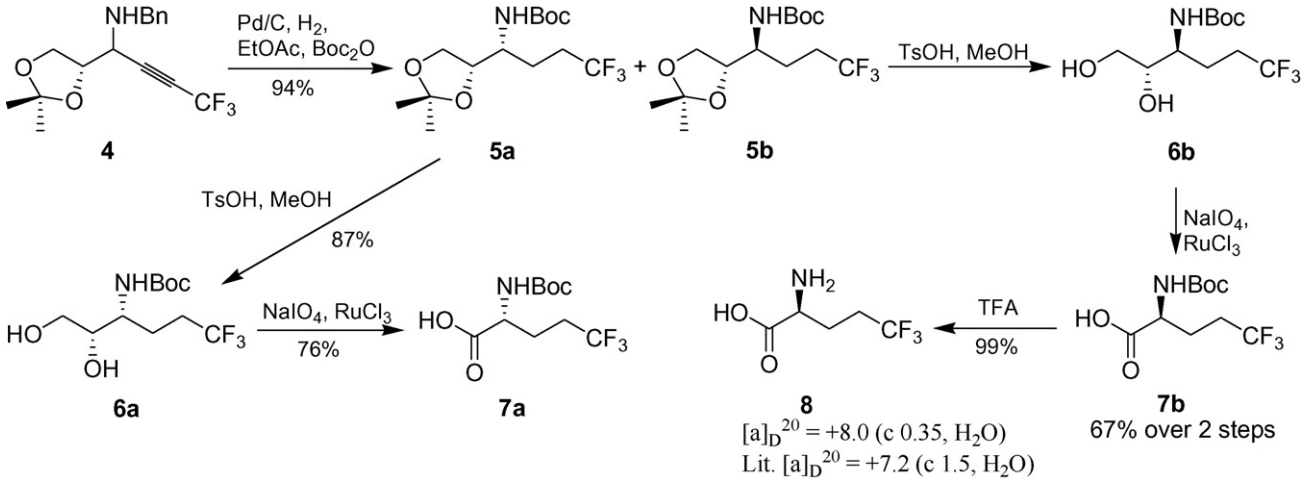
low temperature, to carbonyl compounds gave trifluoromethylated alcohols in moderate yields [30]. Recently, Ichikawa re-examined the reaction of 2-bromo-3,3,3-trifluoro-1-propene with butyl lithium and succeeded in efficiently trapping highly unstable 3,3,3-trifluoroisopropenyllithium by strained cyclic ethers [31]. We were interested in extending Tarrant's reaction to glyceraldimine. Initially treatment of D-glyceraldimine **2** with *in sit*u generated 3,3,3-trifluoroisopropenyllithium in Et_2O at −95 °C was complicated and the desired allylic amine **3** was not obtained (Scheme 2). When THF was used as solvent instead of Et_2O, the trifluoromethylated propargylic amine **4** (*syn*/*anti* = 1: 2.5) was isolated in 13% yield. In our opinion, the formation of trifluoromethylated propargylic amine **4** resulted from the addition of *in situ* generated trifluoropropynyllithium to D-glyceraldimine **2** [32]. The generation of trifluoropropynyllithium indicated 2-bromo-3,3,3-trifluoro-1-propene upon treatment with *n*BuLi in THF underwent partly a dehydrobromination reaction to form 3,3,3-trifluoropropynyl anion, although the lithium–bromine exchange followed by lithium fluoride elimination was major pathway of the reaction of 2-bromo-3,3,3-trifluoro-1-propene with *n*BuLi [30,31]. This result promoted us to further study the reaction between 3,3,3-trifluoropropynyllithium and D-glyceraldimine for improving the yield of compound **4**, because propargylic amine **4** is a potential precursor for the synthesis of trifluoromethylated amino acids. Yamazaki et al. reported that the convenient generation of 3,3,3-trifluoropropynyl anion was realized from 2-bromo-3,3,3-trifluoro-1-propene in the presence of less nucleophilic LDA [32]. Accordingly, the addition of 3,3,3-trifluoropropynyllithium, *in situ* generated from the reaction of 2-bromo-3,3,3-trifluoro-1-propene with 2.0 equiv. of LDA in THF at −78 °C, to D-glyceraldimine **2** was carried out (Scheme 2). We were pleased to find that the reaction proceeded smoothly and the isolated yield of trifluoromethylated propargylic amine **4** was increased to 55%. The ratio of two diastereomers of compound **4** was 1:1.5. The two diastereomers could not be separated by flash column chromatography. We noticed that Yamazaki et al. described the failure of the reaction of the trifluoropropynyllithium with imines due to the less active imine carbon, but the structures of imines were not given [32]. The successful reaction between trifluoropropynyllithium and glyceraldimine was attributed to prior formation of a five-membered chelate with the 2-alkoxy group [21–25], which lowers the transition state energy and thus increase the reaction rate [21–25]. Probably, this intermolecular chelation also stabilized the lithium reagent.

With the propargylic amine **4** in hand, both enantiomers of trifluoronorvaline were synthesized in a straightforward fashion (Scheme 3). Reduction of the triple bond and removal of the benzyl group of compound **4** by hydrogenation in the presence of 5% Pd/C and protection of the resultant amino group with Boc_2O were accomplished in a one-pot process to give the compounds **5a** and **5b** in 94% yield (**5a/5b** = 1:1.5). Compounds **5a** and **5b** were easily separated by flash column chromatography. Treatment of **5a** with TsOH/MeOH afforded the diol **6a** in 87% yield. Finally, oxidation of the dihydroxyl moiety with $RuCl_3/NaIO_4$ successfully provided the desired Boc-protected (*R*)-5,5,5-trifluoronorvaline **7a** in 76% yield. In addition, Boc-protected (*S*)-5,5,5-trifluorovaline **7b** was also obtained in 67% yield over two steps from **5b** using the same procedure. Treatment of **7b** with trifluoroacetic acid at room temperature gave free amino acid (*S*)-5,5,5-trifluoronorvaline **8** in quantitative yield. The optical rotation of **8** ($[\alpha]_D^{20}$ = +8.0 (c 0.35, H_2O)) is in accordance with its reported value ($[\alpha]_D^{20}$ = +7.2 (c 1.5, H_2O)) [20]. Therefore, the absolute configuration of Boc-protected (*S*)-5,5,5-trifluorovaline **7b** was confirmed.

In conclusion, we found that the nucleophilic addition of 3,3,3-trifluoropropynyllithium to D-glyceraldimine gave the corresponding trifluoromethylated propargylic amine **4** in moderate yield (55%). Starting from the compound **4**, a concise synthetic approach to both enantiomers of 5,5,5-trifluoronorvaline was developed.



Scheme 2.



Scheme 3.

3. Experimental

3.1. General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum flame-dried glasswares under nitrogen atmosphere. NMR spectra were recorded on either 300 MHz (^{1}H NMR), 75 MHz (^{13}C NMR) or 282 MHz (^{19}F NMR, $FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz.

3.2. *N*-Benzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4,4-trifluorobut-2-yn-1-amine (**4**)

To a solution of LDA (8.6 mmol) in THF (4 mL) was added dropwise a solution of 2-bromo-3,3,3-trifluoropropene 1 (710 mg, 4.0 mmol) in THF (4 mL) at −78 °C. After the mixture was stirred for 15 min, a solution of D-glyceraldimine **2** (876 mg, 4.0 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. The reaction mixture was quenched with 1N HCl (10 mL) and extracted with EtOAc three times. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column (petroleum ether/ethyl acetate = 5/1) to afford the compound **4** (500 mg, 55%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H) 4.30–4.22 (m, 1H), 4.11–4.04 (m, 2H), 3.97–3.80 (m, 2H), 3.56–3.47 (m, 1H), 2.26 (br, 1H), 1.45–1.35 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −50.17 (s, 1.2F), −50.38 (s, 1.8F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7, 138.6, 128.5, 128.3, 128.2, 127.4, 114.0 (q, J = 154.5 Hz), 113.9 (q, J = 154.7 Hz), 110.3, 110.2, 86.4 (q, J = 3.7 Hz), 86.1 (q, J = 3.7 Hz), 76.9, 76.6, 72.5 (q, J = 31.3 Hz), 72.2 (q, J = 31.7 Hz), 66.7, 66.3, 51.9, 51.3, 51.2, 26.4, 26.2, 25.1, 25.0; IR (thin film) ν_{max} 3327, 2991, 2270, 1456, 1374, 1278, 1142, 847 cm^{-1}; MS (ESI) m/z 314 $(M + H)^+$; HRMS calcd for $C_{16}H_{19}F_3NO_2$: 314.1362. Found: 314.1372.

3.3. *tert*-Butyl (*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4,4-trifluorobutylcarbamate (**5a**) and *tert*-butyl (*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4,4-trifluorobutylcarbamate (**5b**)

A mixture of 10% palladium on charcoal (500 mg), di-*tert*-butyl dicarbonate (1.37 g, 6.28 mmol) and **4** (982 mg, 3.13 mmol) in ethyl acetate (20 mL) was stirred under 1 atm hydrogen for 8 h at room temperature. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give **5a** (394 mg, 37%) and **5b** (570 mg, 57%) as white solids, respectively. **5a**: mp 65–66 °C; $[\alpha]_D^{20}$ = +46.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (d, J = 9.9 Hz, 1H), 4.16–4.12 (m, 1H), 4.02 (dd, J = 8.4 Hz, 6.6 Hz, 1H), 3.75–3.63 (m, 2H), 2.27–2.11 (m, 2H), 1.84–1.75 (m, 2H), 1.45 (s, 9H), 1.44 (s, 3H), 1.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.44 (t, J = 11.5 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.1, 127.0 (q, J = 276.6 Hz), 109.3, 79.7, 76.6, 66.2, 49.6, 30.8 (q, J = 29.0 Hz), 28.2, 26.3, 26.2 (q, J = 2.9 Hz), 24.8; IR (thin film) ν_{max} 3408, 2992, 1691, 1516, 1370, 1260, 1175, 1047, 848 cm^{-1}; MS (ESI) m/z 350 $(M + Na)^+$; HRMS calcd for $C_{14}H_{24}F_3NO_4Na$: 350.1550. Found: 350.1554. **5b**: mp 121–122 °C; $[\alpha]_D^{20}$ = −25.5 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (d, J = 9.3, 1H), 4.08–4.00 (m, 2H), 3.82–3.76 (m, 1H), 3.70–3.61 (m, 1H), 2.27–2.10 (m, 2H), 2.01–1.92 (m, 1H), 1.58–1.50 (m, 1H), 1.44 (s, 9H), 1.42 (s, 3H), 1.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.42 (t, J = 11.0 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6, 127.1 (q, J = 276.4 Hz), 109.8, 79.7, 76.6, 66.7, 52.3, 30.6 (q, J = 29.0 Hz), 28.2, 26.3, 24.9, 23.7; IR (thin film) ν_{max} 3372, 3012, 2989, 1685, 1522, 1369, 1248, 1173, 1043, 847 cm^{-1}; MS (ESI) m/z 350 $(M + Na)^+$; HRMS calcd for $C_{14}H_{24}F_3NO_4Na$: 350.1549. Found: 350.1554.

3.4. *tert*-Butyl (2*S*,3*R*)-6,6,6-trifluoro-1,2-dihydroxyhexan-3-ylcarbamate (**6a**)

A mixture of **5a** (285 mg, 0.87 mmol) and *p*-toluenesulfonic acid monohydrate (233 mg, 0.87 mmol) in methanol (9 mL)

was stirred overnight. The reaction mixture was quenched with water and extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with water and brine, then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give **6a** (210 mg, 87%) as a white solid. mp 88–89 °C; $[\alpha]_D^{20}$ = +29.1 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, J = 9.6 Hz, 1H), 4.28 (d, J = 4.8 Hz, 1H), 4.03 (t, J = 6.0 Hz, 1H), 3.83–3.69 (m, 2H), 3.53–3.49 (m, 2H), 2.40–2.24 (m, 2H), 1.98–1.79 (m, 2H), 1.46 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.73 (t, J = 11.5 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 157.0, 128.0 (q, J = 275.6 Hz), 78.7, 73.2, 63.4, 50.8, 30.8 (q, J = 27.9 Hz), 27.9, 24.6 (q, J = 2.7 Hz); IR (thin film) ν_{max} 3556, 2918, 1683, 1529, 1255, 1175, 1044 cm^{-1}; MS (ESI) m/z 310 $(M + Na)^+$; HRMS calcd for $C_{11}H_{20}F_3NO_4Na$: 310.1237. Found: 310.1247.

3.5. tert-Butyl (2S,3S)-6,6,6-trifluoro-1,2-dihydroxyhexan-3-ylcarbamate (6b)

Using the same procedure described for preparation of compound **6a**. A mixture of **5b** (334 mg, 1.03 mmol) and *p*-toluenesulfonic acid monohydrate (195 mg, 1.04 mmol) in methanol (10 mL) was stirred overnight to give **6b** (242 mg, 82%) as a white solid. mp 107–108 °C; $[\alpha]_D^{20}$ = −20.2 (c 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, J = 8.7 Hz, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.91 (t, J = 6.0 Hz, 1H), 3.67–3.52 (m, 4H), 2.35–2.15 (m, 2H), 2.10–2.00 (m, 1H), 1.75–1.61 (m, 1H), 1.40 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.92 (t, J = 11.0 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 156.3, 127.8 (q, J = 275.6 Hz), 78.4, 74.0, 63.5, 51.4, 30.3 (q, J = 30.0 Hz), 22.9; IR (thin film) ν_{max} 3360, 2984, 1685, 1529, 1254, 1176, 1043 cm^{-1}; MS (ESI) m/z 310 $(M + Na)^+$; HRMS calcd for $C_{11}H_{20}F_3NO_4Na$: 310.1237. Found: 310.1233.

3.6. (R)-2-(tert-Butoxycarbonyl)-5,5,5-trifluoropentanoic acid (7a)

To a stirred mixture of **6a** (96 mg, 0.33 mmol) in CCl_4 (2 mL), CH_3CN (2 mL) and H_2O (3 mL) at room temperature were added $NaIO_4$ (321 mg, 1.50 mmol) and $RuCl_3{\cdot}xH_2O$ (2 mg). The reaction mixture was stirred at room temperature for 6 h. Then, ethyl acetate (20 mL) was added and the mixture was dried over anhydrous Na_2SO_4 directly and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give **7a** (65 mg, 72%) as a white solid. mp 67–68 °C; $[\alpha]_D^{20}$ = −4.1 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 8.02 (s, 1H), 6.36 (d, J = 6.3 Hz, 1H), 4.29–4.24 (m, 1H), 2.50–2.31 (m, 2H), 2.19–2.08 (m, 1H) 2.06–1.90 (m, 1H) 1.42 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.03 (t, J = 10.7 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 172.6, 155.7, 127.5 (q, J = 275.3 Hz), 78.8, 52.3, 30.2 (q, J = 28.2 Hz), 27.9, 24.3 (q, J = 3.0 Hz); IR (thin film) ν_{max} 3413, 3100, 2988, 1728, 1672, 1522, 1257, 1142, 1023 cm^{-1}; MS (ESI) m/z 270 $(M - H)^-$; HRMS calcd for $C_{10}H_{16}F_3NO_4Na$: 294.0924. Found: 294.0925.

3.7. (S)-2-(tert-Butoxycarbonyl)-5,5,5-trifluoropentanoic acid (7b)

Using the same procedure described for preparation of compound **7a**, to a stirred mixture of **6b** (154 mg, 0.54 mmol) in CCl_4 (3 mL), CH_3CN (3 mL) and H_2O (4.5 mL) at room temperature were added $NaIO_4$ (480 mg, 2.24 mmol) and $RuCl_3{\cdot}xH_2O$ (2 mg) to give **7b** (120 mg, 82%) as a white solid. mp 67–68 °C; $[\alpha]_D^{20}$ = +4.3 (c 1.40, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 6.62 (d, J = 5.7 Hz, 1H), 4.54–4.50 (m, 1H), 2.70–2.57 (m, 2H), 2.44–2.35 (m, 1H) 2.26–2.20 (m, 1H) 1.67 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.03 (t, J = 10.7 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 172.7, 155.9, 127.7 (q, J = 275.3 Hz), 78.9, 52.4, 30.2 (q, J = 28.2 Hz), 27.9, 24.5 (q, J = 3.0 Hz); IR (thin film) ν_{max} 3420, 3117 (br), 2988, 1728, 1674, 1521,1257, 1141, 1023 cm^{-1}; MS (ESI) m/z 294 $(M + Na)^+$; HRMS calcd for $C_{10}H_{16}F_3NO_4Na$: 294.0924. Found: 294.0921.

3.8. (S)-2-Amino-5,5,5-trifluoropentanoic acid (8)

To a stirred mixture of **7b** (98 mg, 0.36 mmol) in CH_2Cl_2 (6 mL) at room temperature were added CF_3CO_2H (0.5 mL) dropwise. The mixture was stirred overnight and then concentrated in vacuo. The crude product was washed with petroleum ether three times to give **8** (60 mg, 99%) as a white solid. $[\alpha]_D^{20}$ = +8.0 (c 0.35, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 3.74 (t, J = 6.6 Hz, 1H), 2.38–2.22 (m, 2H), 2.18–2.01 (m, 2H); ^{19}F NMR (282 MHz, D_2O) δ −66.52 (t, J = 10.1 Hz, 3F).

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