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Enantioselective synthesis of methyl-5(*R*)-fluorohept-6-ynoate

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Abstract—The asymmetric synthesis of propargylic fluorides, (+)-**6** and (+)-**3** with ee's >95%, is reported. The first key step involves an asymmetric transfer hydrogenation of the propargylic ketone **11**, using Noyori's catalyst, to give alcohol (+)-**10**. The second important step is the highly stereoselective DAST mediated fluorination of the propargylic alcohol (−)-**5**. The ee determinations were performed using both NMR in chiral solvents and chiral GC. These propargylic fluorides appear to be useful intermediates in the preparation of fluorinated analogues of bioactive chiral molecules.

1. Introduction

The introduction of fluorine atom(s) significantly modifies the physical, chemical, and biological properties of molecules.[1] Therefore, fluorinated compounds have been extensively studied and developed in many areas such as pharmaceuticals and agrochemicals. In fluorobioorganic chemistry, the selective replacement of strategic C–H or C–OH bonds by C–F, as well as the exchange of $–CH_2–$ or –O– by $–CF_2–$ moieties, can lead to important information regarding the structure and mechanism of action of enzymatic systems. This can result in obtaining compounds, which are more stable and/or have a better bioactivity.[2,3] We have recently been involved in a programme dealing with the asymmetric synthesis of monofluorinated compounds having the fluorine atom vicinal to π-systems.[4] This led us to develop a novel propargylic route for the preparation of this type of molecules.[5] In parallel, this strategy was used for the stereoselective synthesis and the biological evaluation of fluorinated analogues of polyunsaturated fatty acid metabolites, such as (+)-**1**, which is the fluorinated analogue of 13-hydroxyoctadecadienoic acid (13-HODE).[6] It has also been extended to the preparation of *gem*-difluorinated compounds, such as the 5,5-difluoro 12(*R*)-leukotriene B_3, (−)-**2** (Fig. 1).[7]

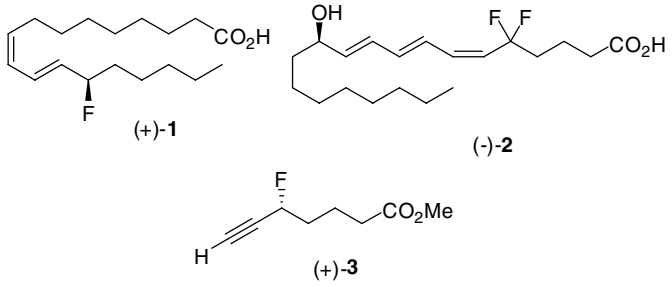

Figure 1.

The next step in these studies required the preparation of methyl-5(*R*)-fluorohept-6-ynoate, (+)-**3**, a key intermediate for the asymmetric synthesis of the monofluoroleukotrienes, as well as for the preparation of various types of bioactive molecules.

Herein, we report the first successful synthesis of fluoride (+)-**3** in a very high enantiomeric excess (ee = 96%).

2. Results and discussion

The most straightforward approach to synthesize our target molecule (+)-**3** is the direct fluorination of the corresponding propargylic alcohol **4**.[8] However, all our attempts to perform this reaction using diethylaminosulfurtrifluoride (DAST) or Deoxofluor®,[9] failed. Indeed, whatever the reaction conditions (solvent, temperature,

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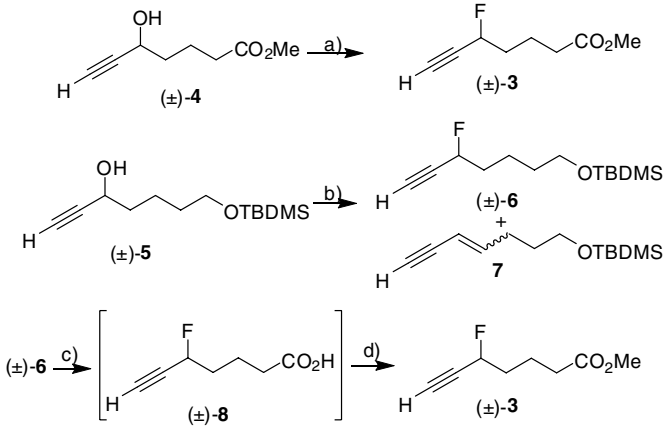
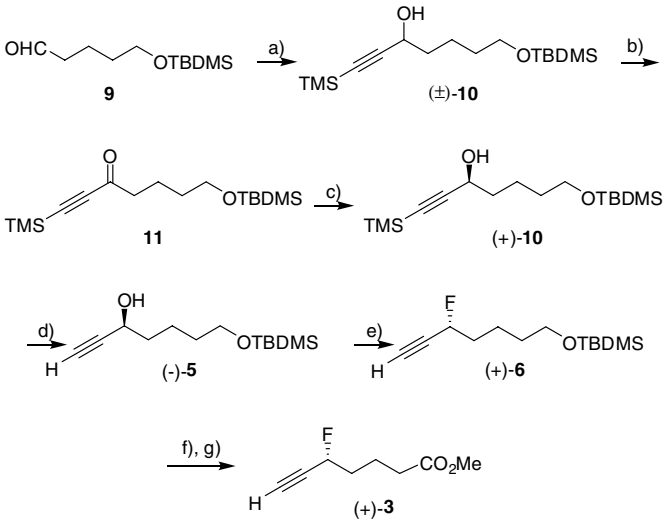
number of equivalents, etc.) only poor yields of **3** (10–20%) were obtained. Furthermore, reproducibility problems have been encountered during this reaction (Scheme 1).



Scheme 1. Reagents and conditions: (a) DAST, CH_2Cl_2, −50 °C, 1 h (10–20%); (b) DAST, CH_2Cl_2, −50 °C, 1 h (59% for **6**); (c) Jones, KF, acetone, 0 °C, 2 h; (d) Amberlyst 15, MeOH, 24 h (62% overall yield for two steps).



Scheme 2. Reagents and conditions: (a) HC≡CTMS, BuLi, THF, −78 °C, 1 h (82%); (b) IBX, $CHCl_3$, 60 °C, 15 h (84%); (c) Noyori's (*S*,*S*) Ru-cat, ^{i}PrOH, 15 h (96%); (d) K_2CO_3, MeOH, 2 h (96%); (e) DAST, CH_2Cl_2, −50 °C, 1 h (59%); (f) Jones, KF, acetone, 0 °C, 2 h; (g) Amberlyst, MeOH, 24 h (62% overall yield).

Considering that efficient fluorinations in propargylic position have been performed,[5] this negative result was rather disappointing. However, it did suggest that the presence of the three carbons chain with the terminal ester group could interfere with the fluorination reaction. Therefore, an indirect route, with another functional group, had to be explored for the synthesis of **3**. Thus, an alcohol function protected by the bulky TBDMS group has been selected. In fact, the racemic propargylic alcohol (±)-**5**[10] was found to react with DAST at −50 °C to give the propargylic fluoride (±)-**6** in fair isolated yield (59%) with only a small amount (12%) of the corresponding enynes **7**. A Jones oxidation reaction[11] gave the corresponding acid (±)-**8**, characterized by NMR spectroscopy and was used directly for the preparation of the desired ester (±)-**3** in 62% overall yield from (±)-**6**.

It is known that the determination of ee's can be difficult with small fluorinated compounds, including propargylic fluorides.[12] However in the case of (±)-**6** and (±)-**3**, extensive analytical studies have shown that both proton-decoupled ^{13}C NMR in chiral liquid crystals (CLC)[13] and chiral GC provided very good spectral or chromatographical separation of the enantiomers, and subsequently determined the enantioselectivity of the fluorination reaction.

The next step involved the preparation of optically active propargylic alcohol (−)-**5**. For that purpose we selected Noyori's asymmetric reduction (Scheme 2). The propargylic alcohol (±)-**10** was obtained in 82% yield by reaction of **9**[10] with the lithium anion of trimethylsilylacetylene. Oxidation with IBX led to the propargylic ketone **11** in 84% yield.

Asymmetric reduction using Noyori's conditions [with 5 mol% (*S*,*S*)-TSDPEN Ru catalyst][14] afforded the desired propargylic alcohol (+)-**10** in excellent yield. The (*S*)-absolute configuration was attributed by analogy with the literature.[14] The desilylation process gave key intermediate (−)-**5** in 96% yield.[15] Analysis of this molecule by chiral GC analysis also indicated an ee >98%. Fluorination, with DAST at −50 °C under the previously described reaction conditions, led to the desired propargylic fluoride (+)-**6**. For this enantio-enriched molecule, analysis using ^{13}C–$\{^{1}H\}$ NMR in oriented solutions of poly-γ-benzyl-L-glutamate (PBLG) indicated an ee >95% (Fig. 2). This value has been fully confirmed by the analysis on chiral GC (ee = 96%), thus demonstrating a very high stereoselectivity for this reaction. The same ee was obtained when the fluorination reaction was performed at −20 °C indicating that, with this alcohol, there was no significant effect of temperature on the stereoselectivity of the dehydroxy-fluorination.[12,16,17] Finally, oxidation with the Jones reagent, followed by esterification, gave our target molecule (+)-**3**. Analysis of this derivative by ^{13}C–$\{^{1}H\}$ NMR in PBLG again indicated an ee >95% (Fig. 2), confirmed also by analysis on chiral GC (ee = 96%). This result established that no racemization had occurred during these last steps.

3. Conclusion

In conclusion, we have described a reliable route to functionalized chiral propargylic fluorides, such as (+)-**6** and (+)-**3**. These molecules, which have been synthesized in very high ee's, appear to be useful building blocks for the preparation of not only fluorinated analogues of fatty acid metabolites but also for other series of molecules. This research is currently in development in our group.

4. Experimental

4.1. General information

All reagents were obtained from Aldrich and Acros and used without further purification. Freshly distilled solvents

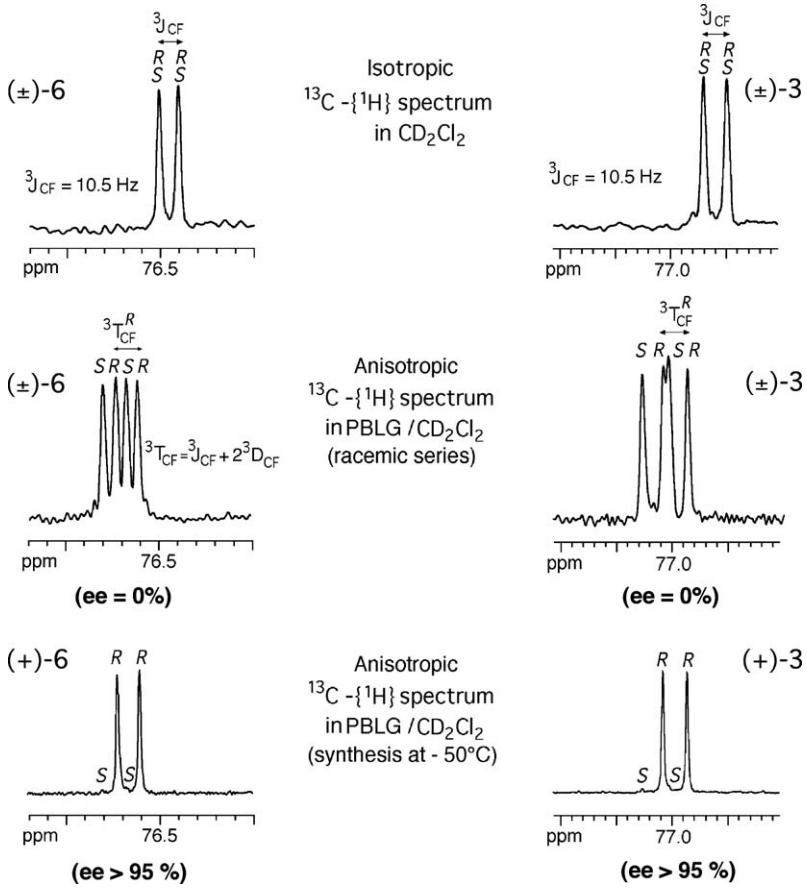


Figure 2. 100.6 MHz ^{13}C–{^{1}H} NMR signals for the terminal acetylenic carbon of **6** and **3** dissolved in CD_2Cl_2 and in the chiral liquid-crystalline phase (PBLG/CD_2Cl_2) at 300 K. The doublets observed in each trace originates from the scalar (^3J) and dipolar (^{3}D) ^{13}C–^{19}F couplings.

under anhydrous conditions were used, unless otherwise mentioned. The reactions were magnetically stirred with Teflon stirrer bars, and the temperatures measured externally. Reactions that require anhydrous conditions, were carried out under nitrogen using oven-dried (120 °C, 24 h) or flame-dried (vacuum <0.5 Torr) glasswares. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials and the reactions were monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F_{254}). The eluents used were mixtures of pentane and diethylether, with detection using UV light, or a *p*-anisaldehyde staining solution. SDS silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. The GC analysis was performed on a Fisons GC 8000 instrument, using a splitless mode and a FID detector. The column was a Restek RT-βDEX sm (30 m × 0.25 mm × 0.25 μm). Rotation data were recorded on a Perkin–Elmer 241 Polarimeter. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 300 spectrometer. ^{1}H NMR spectra: (300 MHz); δ (H) are given in parts per million relative to tetramethylsilane (TMS) as the internal reference. ^{13}C NMR spectra: (75 MHz); δ (C) are given in parts per million relative to TMS signal as the internal reference. ^{19}F NMR spectra: (282.4 MHz); δ (F) are given in ppm relative to CCl_3F signal. Multiplicities were designated as singlet (s), doublet (d), triplet (t), or multiplet (m). The CLC NMR samples of **3** and **6** in racemic and enantio-enriched series were prepared from around 40 mg of chiral material, 100 mg of PBLG ($M_w \approx 204{,}000$ g mol^{-1}), and 420 mg of dry CD_2Cl_2. PBLG is available from Sigma. The oriented sample preparation is described in Ref. 13. NMR experiments were performed on DRX-400 (using a 5 mm QXO probe for ^{13}C). Broad-band ^{1}H decoupling used the WALTZ-16 sequence. ^{13}C–{^{1}H} spectra were recorded at 300 K by adding 4000 scans. A gaussian filtering was applied on racemic mixture spectra to enhance the peak separations. No filtering was applied to enantio-enriched mixture spectra. ^{13}C signal of CD_2Cl_2 was used as internal reference ($\delta = 53.8$ ppm).

4.2. 7-[*tert*-Butyl(dimethyl)silyl]oxy-1-(trimethylsilyl)hept-1-yn-3-one 11

Propargylic alcohol (±)-**10**[10] (1.19 g, 3.49 mmol) was dissolved in $CHCl_3$ (14 mL), and IBX (2.93 g, 10.48 mmol) was added. The resulting suspension was heated in an oil bath set to 60 °C and stirred vigorously. After 15 h (TLC monitoring), the reaction was cooled to room temperature and filtered through Celite. The filter cake was washed with CH_2Cl_2 (3 × 10 mL), and the combined filtrates concentrated and purified by flash chromatography on silica gel with pentane, to afford ketone **11** in 84% yield (0.91 g). $R_f = 0.85$ (10% Et_2O/pentane); ^{1}H NMR ($CDCl_3$,

300 MHz): $\delta = 3.62$ (t, $J = 6.4$ Hz, 2H), 2.58 (t, $J = 7.3$ Hz, 2H), 1.85–1.68 (m, 2H), 1.60–1.52 (m, 2H), 0.88 (s, 9H), 0.23 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 187.80$, 101.98, 97.62, 62.65, 45.00, 31.85, 25.90 (3C), 20.50, 18.25, −0.70 (3C), −5.30 (2C) ppm.

4.3. 7-[*tert*-Butyl(dimethyl)silyl]oxy-1-(trimethylsilyl)hept-1-yn-3(*S*)-ol (+)-10

To a magnetically stirred solution of **11** (1.20 g, 3.83 mmol) in *i*-*Pr*OH (10 mL) was added Noyori's (*S*,*S*) Ru-catalyst (0.11 g, 0.19 mmol) in *i*-*Pr*OH (28 mL, with sonication for dissolution) and the reaction mixture was stirred at room temperature under argon for 15 h. Then the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel with 5% Et_2O/pentane to afford alcohol (+)-**10** as a colorless oil in 96% yield (1.16 g). $R_f = 0.40$ (10% Et_2O/pentane); $[\alpha]_D^{21} = +0.6$ (*c* 0.60, $CHCl_3$); Lit. $[\alpha]_D^{22} = +0.7$ (*c* 1.00, $CHCl_3$);[18] ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.35$ (t, $J = 6.4$ Hz, 1H), 3.60 (t, $J = 6.0$ Hz, 2H), 2.15 (br s, 1H), 1.72–1.68 (m, 2H), 1.58–1.45 (m, 4H), 0.90 (s, 9H), 0.18 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 106.85$, 89.25, 63.05, 62.80, 37.40, 32.35, 25.95 (3C), 21.55, 18.35, −0.08 (3C), −5.30 (2C) ppm.

4.4. 7-[*tert*-Butyl(dimethyl)silyloxy]hept-1-yn-3(*S*)-ol (−)-5

To a solution of compound (+)-**10** (1.01 g, 3.21 mmol) in MeOH (32 mL) was added K_2CO_3 (0.57 g, 4.17 mmol) at room temperature. The reaction mixture was stirred for 2 h and MeOH was evaporated under vacuum. The residue was diluted with water and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated under vacuum. The residue was purified by chromatography on silica gel with 5% Et_2O/pentane to afford the propargylic alcohol (−)-**5**, as a colorless oil in 96% yield (0.75 g). $R_f = 0.34$ (10% Et_2O/pentane); $[\alpha]_D^{21} = -1.3$ (*c* 0.60, $CHCl_3$); (Lit. $[\alpha]_D^{21} = -2.1$ (*c* 2.97, $CHCl_3$);[15] ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.35$ (td, $J = 6.4$ Hz, $J = 2.1$ Hz, 1H), 3.63 (t, $J = 6.1$ Hz, 2H), 2.86 (br s, 1H), 2.45 (d, $J = 2.1$ Hz, 1H), 1.79–1.69 (m, 2H), 1.60–1.50 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); NMR ^{13}C ($CDCl_3$, 75 MHz): $\delta = 84.95$, 72.81, 62.98, 62.14, 37.29, 32.25, 25.94 (3C), 21.37, 18.32, −5.35 (2C) ppm. The enantiomeric excess was established by chiral GC (ee >98%), with the following conditions: 90–180 °C, 1 °C/min. Retention time for (−)-**5**: 74.46 min. The retention time for the second enantiomer was 75.89 min.

4.5. *tert*-Butyl[(3(*R*)-fluorohept-1-yn-7-yl)oxy]dimethyl silane (+)-6

To a solution of diethylamino-sulfurtrifluoride (DAST, 0.121 mL, 0.93 mmol) in CH_2Cl_2 (1 mL) was added, dropwise and slowly at −50 °C, the alcohol (−)-**5** (0.15 g, 0.62 mmol). The solution was stirred at the same temperature for 1 h. A saturated Na_2CO_3 solution was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under low vacuum (20–25 mmHg). The residue was purified by column chromatography on silica gel using pentane as eluent to afford the fluoro propargylic compound (+)-**6** as a colorless oil in 59% yield (0.08 g). $[\alpha]_D^{21} = +3.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.06$ (dtd, $J_{H-F} = 48.2$ Hz, $J = 6.1$ Hz, $J = 2.0$ Hz, 1H), 3.68–3.59 (m, 2H), 2.68 (dd, $J_{H-F} = 5.5$ Hz, $J = 2.0$ Hz, 1H), 1.98–1.78 (m, 2H), 1.65–1.52 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 82.38$ (d, $J = 167.2$ Hz,), 80.37 (d, $J = 26.4$ Hz), 76.18 (d, $J = 10.5$ Hz), 62.74, 35.53 (d, $J = 22.2$ Hz), 32.14, 25.93 (3C), 20.80 (d, $J = 4.3$ Hz), 18.31, −5.33 (2C), ^{19}F NMR ($CDCl_3$, 282.4 MHz): $\delta = -175.15$ (dtd, $J = 48.2$ Hz, $J = 20.0$ Hz, $J_{H-F} = 5.6$ Hz) ppm; HRMS: $[M-{}^{\cdot}C_4H_9-HF]^+$ ($C_9H_{15}OSi$): calcd 167.0892, found: 167.0890 (1 ppm). The enantiomeric excess was determined by ^{13}C NMR in chiral liquid crystals (see Fig. 2) and chiral GC (ee = 96%), with the following conditions: 70–180 °C, 1 °C/min. Retention time 69.10 min. The retention time for the second enantiomer was 67.85 min.

4.6. Methyl-5-(*R*)-fluorohept-6-ynoate (+)-3

To a solution of (+)-**6** (0.20 g, 0.82 mmol) in acetone (5 mL) were added at 0 °C, KF (0.95, 1.96 mmol), and freshly prepared 8 N Jones reagent (0.41 mL). The mixture was stirred at 0 °C for 2 h, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (4 × 10 mL). The organic solution was washed with H_2O, dried on $MgSO_4$, filtered, and concentrated under low vacuum. The residue was purified on silica gel eluting with 15% Et_2O/pentane affording the crude acid **8** (0.08 g). This compound was characterized by NMR and HRMS and used directly for the next step. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 10.84$ (br s, 1H); 5.14 (dtd, $J_{H-F} = 48.7$ Hz, $J = 6.0$ Hz, $J = 2.0$ Hz, 1H); 2.71 (dd, $J_{H-F} = 5.5$ Hz, $J = 2.1$ Hz, 1H); 2.46 (t, $J = 7.3$ Hz, 2H); 2.02–1.80 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 179.54$; 81.88 (d, $J = 168.0$ Hz); 79.78 (d, $J = 26.0$ Hz); 76.68 (d, $J = 10.5$ Hz); 34.78 (d, $J = 22.6$ Hz); 33.24; 19.50 (d, $J = 4.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): $\delta = -175.71$ (dtd, $J = 48.0$ Hz, $J = 20.7$ Hz, $J = 5.5$ Hz) ppm. HRMS: $[M-HF]^+$ $C_7H_8O_2$ calculated 124.0524; found: 124.0513 (8 ppm).

To a magnetically stirred solution of the preceding crude fluoroheptynoic acid **8** (0.08 g) in MeOH (4 mL) was added Amberlyst 15 (0.16 g), and the reaction mixture stirred at room temperature under nitrogen for 24 h. The resulting reaction mixture was filtered over Celite, the filter cake was washed with MeOH (3 × 5 mL) and the combined filtrates were concentrated under low vacuum (20–25 mmHg). The residue was purified by column chromatography on silica gel (10% Et_2O/pentane) to afford propargylic fluoride (+)-**3** as a colorless oil in 62% overall yield from (+)-**6** (0.08 g). $[\alpha]_D^{21} = +14.5$ (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.11$ (dtd, $J_{H-F} = 48.0$ Hz, $J = 5.6$ Hz, $J = 2.0$ Hz, 1H), 3.67 (s, 3H), 2.69 (dd, $J_{H-F} = 5.5$ Hz, $J = 2.0$ Hz, 1H), 2.38 (t, $J = 7.4$ Hz, 2H), 1.96–1.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 173.37$, 81.90 (d, $J = 168.0$ Hz), 79.84 (d, $J = 26.0$ Hz), 76.56 (d, $J = 10.5$ Hz), 51.53, 34.90 (d, $J = 22.5$ Hz), 33.19, 19.77 (d, $J = 4.3$ Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz): $\delta = -175.65$ (dtd, $J = 48.6$ Hz, $J = 20.6$ Hz, $J = 5.6$ Hz) ppm. Anal. Calcd for $C_8H_{11}FO_2$: C, 60.75;

H, 7.01. Found: C, 61.04; H, 7.13. The enantiomeric excess was determined by ^{13}C–$\{^{1}H\}$ NMR in chiral liquid crystals (see Fig. 2) and chiral GC, using the following conditions: 70–180 °C, 1 °C/min. The target molecule (+)-**3** was obtained in 96% ee and its retention time was 45.33 min. The retention time for the (*S*) enantiomer was 44.85 min.

Acknowledgments

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