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An efficient chiral synthesis of fluoro-containing amino acids: *N*-benzyloxycarbonyl-2-amino-4,4-difluorobutyric acid methyl ester and its analogs

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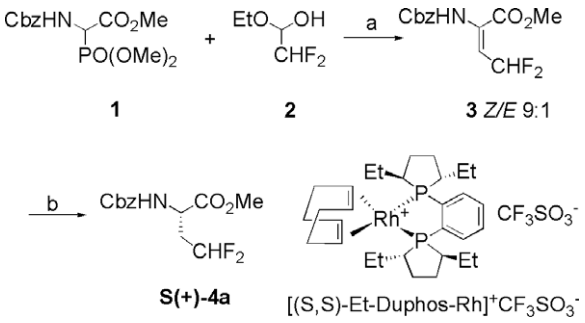
Abstract

Fluoro-containing amino acids, *N*-benzyloxycarbonyl-2-amino-4,4-difluorobutyric acid methyl ester and analogs, were prepared in high enantiomeric excess. Incorporation of 2-amino-4,4-difluoro butyric acid as P1 group provided a potent HCV NS3 protease inhibitor.

Keywords: 2-Amino-4,4-difluorobutyric acid; Fluoro amino acid; HCV protease inhibitor

Fluorinated amino acids possess interesting biological activities, and are frequently used as replacements for natural amino acids in drug discovery.[1] In the process of optimizing a HCV NS3 protease inhibitor, we were in need of (*S*)-2-amino-4,4-difluorobutyric acid (diFAbu) as a replacement for cysteine in the substrate.[2] Literature reports on the preparation of this fluorinated amino acid are limited.[3] In this Letter, we report an efficient two-step synthesis of benzyloxycarbonyl (Cbz) protected (*S*)- and (*R*)-2-amino-4,4-difluorobutyric acid methyl ester and its analogs in high enantiomeric excess.

Scheme 1 outlines the synthesis of *S*(+)-*N*-Cbz-2-amino-4,4-difluoro butyric acid methyl ester. The condensation of commercially available *N*-Cbz-phosphonoglycine trimethyl ester (**1**) with 2,2-difluoroacetaldehyde ethyl hemiacetal (**2**) in the presence of potassium *tert*-butoxide in THF gave methyl 2-Cbz-lamino-4,4-difluorobut-2-enoate (**3**) as a 9:1 *Z*/*E* mixture in 64% yield. When the reaction was performed in dichloromethane, as usually used for this type of reaction, a 4:1 *Z*/*E* mixture of **3** was obtained in 24% yield. Asymmetric hydrogenation of *Z*/*E*-**3** catalyzed by (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(I)trifluoro-methanesulfonate ([Rh(COD)-(*S*,*S*-Et-Duphos)]$^{+}CF_3SO_3^{-}$) provided Cbz protected *S*(+)-diFAbu methyl ester (*S*(+)-**4a**) with excellent enantioselectivity (>98% ee) in quantitative yield. The enantioselectivity is independent of the composition of *Z*/*E* isomers.[4] Similarly, the corresponding *R* isomer of **4a** was obtained using [Rh(COD)(*R*,*R*-Et-Duphos)]$^{+}CF_3SO_3^{-}$ as the catalyst. The asymmetric hydrogenation was



Scheme 1. Reagents and conditions: (a) KO^{t}Bu, THF, −78 °C to rt (64%); (b) H_2, 55 psi, [(*S*,*S*)-Et-Duphos-Rh]$^{+}CF_3SO_3^{-}$, MeOH (>95%).

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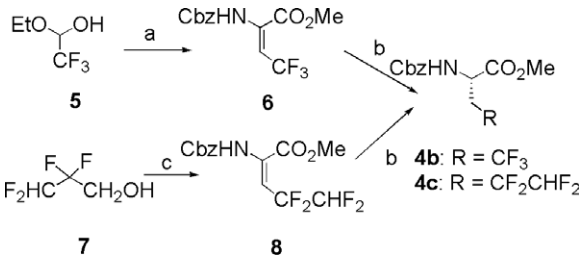
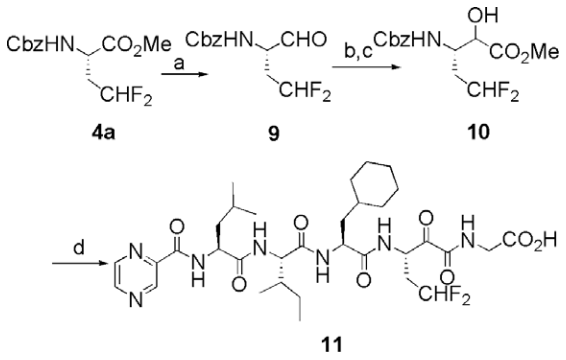


Scheme 2. Reagents and conditions: (a) KO^{t}Bu, THF, −78 °C to rt (78%); (b) H_2, 55 psi, [(*S*,*S*)-Et-Duphos-Rh]$^+CF_3SO_3^-$, MeOH (>95%), (i) Dess–Martin, DCM, rt, (ii) KO^{t}Bu, THF, −78 °C to rt (38%).



Scheme 3. Reagents and conditions: (a) DiBAL, CH_2Cl_2, −78 °C, 30 min (89%); (b) LiC(SMe)$_3$, THF, −64 °C to −30 °C, 1 h (85%); (c) $HgCl_2$/HgO, MeOH/H_2O, rt, 2 h (96%); (d) Ref. 2.

efficient for scales up to 200 g with no detectable decreased enantioselectivity.

This approach was applied to the synthesis of other fluoro-containing amino acid analogs. Examples such as *S*(+)- and *R*(−)-*N*-Cbz-2-amino-4,4,4-trifluorobutyric acid methyl ester (**4b**), and *S*(+)-*N*-Cbz-2-amino-4,4,5,5-tetrafluoro-2-pentanoic acid methyl ester (**4c**) were synthesized in high enantiomeric excess (>98% ee) as shown in Scheme 2.[5]

With *S*(+)-**4a** available, we incorporated it as P1 group to our HCV NS3 protease inhibitors. As outlined in Scheme 3, methyl ester **4a** was reduced to the corresponding aldehyde **9**. Aldehyde **9** was treated with tris(methylthio) methyl lithium followed by $HgCl_2$/HgO to provide α-hydroxyl ester **10** in good yield. Using the procedures previously described by us, **10** was then converted to a tetrapeptide-based α-ketoamide HCV NS3 protease inhibitor **11**, which has an IC_{50} of 0.06 μM.[2]

In summary, an efficient chiral method for the synthesis of diFAbu derivative and structural related fluoro-containing analogs was described. DiFAbu was evaluated as P1 group of HCV NS3 protease inhibitor.

References and notes

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5. *Procedures: N-Benzyloxycarbonyl-2-amino-4,4-difluoro-2-butenoic acid methyl ester* (**3**): *N-Z*-Phosphonoglycine trimethyl ester (35.5 g, 107 mmol) was added to a solution of potassium *tert*-butoxide (13.2 g, 118 mmol) in THF (200 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 20 min, and 2,2-difluoroacetaldehyde ethyl hemiacetal (**2**) (15.0 g, 119 mmol) was added slowly. The reaction was warmed up to room temperature slowly and stirred for 22 h. The mixture was poured into ethyl acetate, washed with cold water. The organic phase was separated and dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–15% ethyl acetate–hexanes) to give a 9:1 *Z*/*E* mixture of the desired product as a clear oil 19.63 g (64%). Isomer *Z*: ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.84 (s, 3H), 5.18 (s, 2H), 6.32 (dt, 1H, J = 10.8 Hz, 5.4 Hz), 6.70 (dt, 1H, J = 55.2 Hz, 5.4 Hz), 7.02 (b, 1H), 7.38 (b, 5H). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −115.50 (dd, 2F, J = 55.0 Hz, 10.7 Hz). Isomer *E*: ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 3.91 (s, 3H), 5.17 (s, 2H), 7.00 (dt, 1H, J = 56.1 Hz, 6.9 Hz), 7.09 (dt, 1H, J = 10.4 Hz, 6.9 Hz), 7.22 (b, 1H), 7.38 (b, 5H). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −108.28 (dd, 2F, J = 56.4 Hz, 10.7 Hz). *(S)-(+)-N-Benzyloxycarbonyl-2-amino-4,4-difluorobutyric acid methyl ester* (*S*(+)-**4a**): A solution of **3** (0.90 g, 3.16 mmol) in MeOH (20 mL) was degassed with nitrogen, and Rh(COD)(*S*,*S*-Et-Duphos)]$^+$ $CF_3SO_3^-$ (25 mg, 1 mol %) was added. The solution was stirred under hydrogen (55 psi) for 15 h. The solvent was removed under reduced pressure and the residue was passed through a pad of silica gel eluting with 30% EtOAc in hexanes to remove small amount of catalyst to leave a product as a white solid, 0.91 g (100%). $[\alpha]^{25}$ +3.0 (c = 0.362, chloroform). ee% 98.5. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.20–2.55 (m, 2H), 3.78 (s, 3H), 4.56 (dd, 1H, J = 12.9 Hz, 7.2 Hz), 5.13 (s, 2H), 5.51 (d, 1H, J = 6.9 Hz), 5.94 (tt, 1H, J = 56.1 Hz, 4.8 Hz), 7.36 (b, 5H). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −116.63 (dt, 2F, J = 56.4 Hz, 16.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 36.67 (t, J = 22.44 Hz), 49.43, 52.85, 67.28, 115.13 (t, J = 239.56 Hz), 128.11, 128.29, 128.55, 135.96, 155.76, 171.20. Anal. Calcd for $C_{13}H_{15}F_2NO_4$: C, 54.36; H, 5.26; N, 4.88. Found: C, 54.62; H, 5.38; N, 4.68. *R*(−)-**4a**: $[\alpha]^{25}$ −2.7 (c = 0.942, chloroform). ee% 95.5. *S*(+)-*N*-Benzyloxycarbonyl-2-amino-4,4,4-trifluoro-2-butyric acid methyl ester (*S*(+)-**4b**) $[\alpha]^{25}$ +6.2 (c = 0.280, chloroform). ee% 97.1. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.62–2.85 (m, 2H), 3.79 (s, 3H), 4.64 (q, 1H, J = 12.6 Hz, 6.3 Hz), 5.13 (s, 2H), 5.51 (d, 1H, J = 7.8 Hz), 7.36 (b, 5H). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −63.58 (t, 3F, J = 9.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 35.62 (q, J = 28.3 Hz), 48.99, 52.96, 67.27, 125.51 (q, J = 277.58 Hz), 128.03, 128.26, 128.53, 135.97, 155.56, 170.26. Anal. Calcd for $C_{13}H_{14}F_3NO_4$: C, 51.15; H, 4.62; N, 4.60. Found: C, 51.06; H, 4.58; N, 4.55. *R*(−)-**4b**: $[\alpha]^{25}$ −6.4 (c = 0.168, $CHCl_3$). ee% 98.3. Anal. Calcd for $C_{13}H_{14}F_3NO_4$: C, 51.15; H, 4.62; N, 4.60. Found: C, 51.22; H, 4.60; N, 4.53. (*S*)-(+)-*N*-Benzyloxycarbonyl-2-amino-4,4,5,5-tetrafluoropentanoic acid methyl ester (*S*(+)-**4c**) $[\alpha]^{25}$ +5.4 (c = 0.968, chloroform). ee% 98.4. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.46–2.70 (m, 2H), 3.77 (s, 3H), 4.70 (dd, 1H, J = 12.3 Hz, 7.5 Hz), 5.13 (s, 2H), 5.63 (d, 1H, J = 8.1 Hz), 5.74 (tt, 53.7 Hz, 2.7 Hz), 7.35 (b, 5H). ^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ −115.31 (m, 2F), −136.09 (dd, 2F, J = 53.4 Hz, 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 31.79 (t, J = 21.4 Hz), 48.46, 52.91, 67.25, 109.70 (tt, J = 150.0 Hz, 40.1 Hz), 117.19 (tt, J = 248.5 Hz, 29.6 Hz), 128.03, 128.24, 128.52, 136.00, 155.61, 170.86. Anal. Calcd for $C_{13}H_{14}F_3NO_4$: C, 49.86; H, 4.48; N, 4.15. Found: C, 49.85; H, 4.42; N, 3.97.