

Synthesis of Boc-protected *cis*- and *trans*-4-trifluoromethyl-D-prolines

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Both Boc-protected *trans*- and *cis*-4-trifluoromethyl prolines were synthesized starting from L-serine simultaneously. In our synthetic route, the key intermediate **4** was obtained through the reaction of Garner's aldehyde **1** with ylide **2** followed by trifluoromethylation with FSO₂CF₂COOMe–CuI. After hydrogenation followed by reduction of **4**, the alcohol **5** was obtained in low diastereoselectivity, however, the two diastereoisomers could be separated easily by flash chromatography in the following steps. The bromide **8b** obtained from the alcohol **5** in a straightforward fashion could not afford the desired cyclization product because of the strong electron-withdrawing properties of the trifluoromethyl group and the low ability of bromide as a leaving group. Instead, mesylation of alcohols **12a** and **12b** followed by treatment with potassium bis(trimethylsilyl)amide (KHMDs) afforded the desired cyclization products **13a** and **13b** respectively, which were transformed into Boc-protected *cis*- and *trans*-4-trifluoromethyl-D-prolines in a straightforward fashion.

Introduction

Amino acids have excited interest for many years and are still an area of current interest in the twenty-first century. Investigations into the biological properties of amino acids have been intensively prosecuted and have resulted in a dramatic acceleration of activity and interest in synthesis of unusual amino acids directed, first of all, at the creation of new medicines and fine biochemicals.¹ Among these unusual amino acids, fluorine-containing amino acids attract a great deal of attention because of the similar geometry of fluorine-containing amino acids to hydrocarbon patterns, the opposite polarization of C–H and C–F bonds, the greater energy of the latter and the similar size of F (1.35) to O (1.40) and H (1.20).² Once introduced, the strong carbon–fluorine bond is particularly resistant to metabolic transformation and the electronegativity of fluorine can have a significant effect on the basicity or acidity of neighboring groups and on the reactivity and stability of a molecule.³ In addition, as well as being used as biological tracers and mechanistic probes for investigations on the structures and properties of enzymes,³ fluorinated amino acids also play an important role in the control of blood pressure, allergies and tumor growth⁴ and incorporation of fluorine-containing amino acids provides a route to proteins and peptides with unique structural and chemical features.⁵ For example, Tirrell⁶ and Kumar⁷ recently found that a fluorinated coil-coiled protein prepared from trifluoroleucine had enhanced thermal and chemical stability. Therefore, there is much literature describing methods for the synthesis of fluorinated amino acids.^{8–10}

Proline and substituted prolines are interesting targets as they are considered to be constrained analogues of natural amino acids¹¹ and they are key amino acids in many naturally occurring bioactive peptides such as gramicidin¹² and have been extensively used in the pharmaceutical industry, for instance as angiotensin-converting enzyme (ACE) inhibitors,

including Captopril¹³ and Enalapril.¹⁴ Their incorporation into bioactive peptides and proteins leads to constrained conformations which are useful tools for establishing structure–bioactivity relationships and for understanding biological processes.¹¹

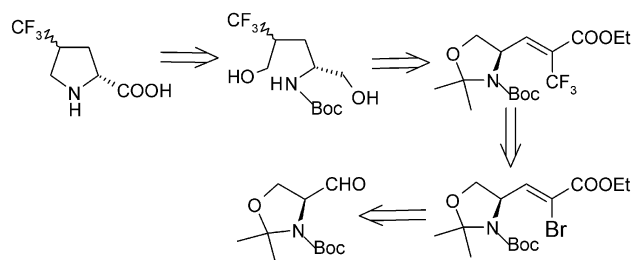
Besides efficient asymmetric syntheses of 3-, 4-, 5-alkyl- and aryl-substituted prolines,^{11,15} there are a number of methods describing the preparation of fluorine-substituted prolines, especially optically pure 4-fluoro and 4,4-difluoroproline, most of which were realized by fluorination of 4-hydroxyproline and 4-oxoproline with DAST.¹⁶ However, to the best of our knowledge, except that Wakselman *et al.*¹⁷ reported the synthesis of racemic methyl *N*-tert-butyl-4-trifluoromethyl-L-proline by means of a [2+3] cycloaddition, there are few reports of enantiomerically pure syntheses of 4-trifluoromethylproline because of the difficulties in stereospecific incorporation of a trifluoromethyl group into proline.¹⁸

Recently, our attention has been focused on the preparation of enantiomerically pure fluorine-containing amino acids starting from abundantly available natural products and on the incorporation of these fluorine-containing amino acids into peptides. In connection with our studies and the situation mentioned above, we were challenged to develop a new, simple synthetic strategy for Boc-protected *trans*- and *cis*-4-trifluoromethylprolines.¹⁹ Herein we describe the synthesis of Boc-protected *trans*- and *cis*-4-trifluoromethyl-D-prolines.

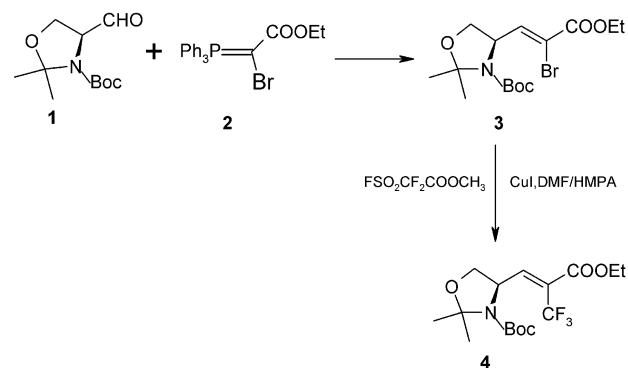
Results and discussion

On the basis of retrosynthetic analysis, the 4-trifluoromethylproline structure can be reached from α -trifluoromethyl- α,β -unsaturated esters obtained through trifluoromethylation of a serine-derived α -bromoenoate, as outlined in Scheme 1.

Previous studies²⁰ carried out in our laboratory on the synthesis of α -trifluoromethyl- α,β -unsaturated esters showed that



Scheme 1

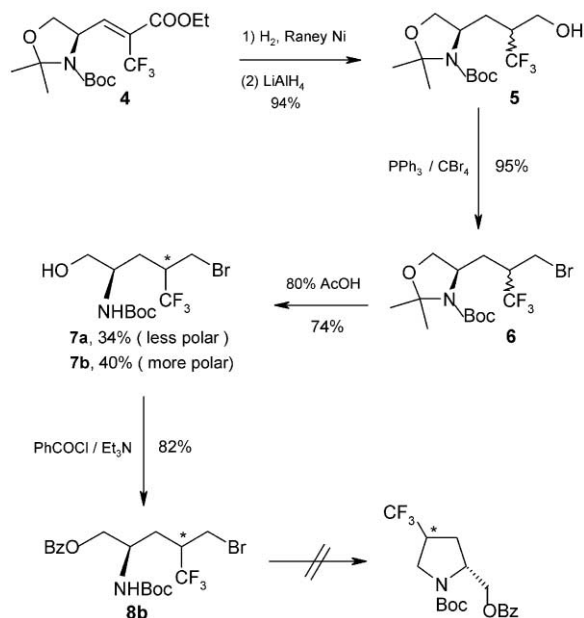


Scheme 2

the key intermediate **4** could easily be reached through trifluoromethylation²¹ of α -bromo- α,β -unsaturated ester **3** obtained through a Wittig reaction between bromo phosphorane **2**²² and Garner's aldehyde²³ (Scheme 2).

With **4** in hand, reduction of the ester with DIBAL-H in toluene at -50°C to the alcohol was carried out, however, the yield was low (30%). In our opinion, the trifluoromethyl group seemed to be responsible for the low yield because it could cause defluorination through a similar Michael addition reaction.²⁴ Fortunately, initial hydrogenation of the double bond of **4** with Raney-Ni followed by reduction²⁵ of the ester group with lithium aluminium hydride (LAH) afforded the desired product **5** in 94% yield. The *syn/anti* ratio was determined to 35/65 according to ^{19}F NMR. Replacement of the hydroxy functionality of **5** by bromide (PPh_3 , Et_3N , CBr_4 , THF)²⁶ was performed and **6** was obtained in 95% yield. The hydrolysis of the hemiaminal moiety of **6** was investigated. Initially, treatment of **6** with I_2 -MeOH²⁷ and $\text{TsOH}\cdot\text{H}_2\text{O}$ -MeOH²⁸ afforded the product **7** in low yield. We were pleased to find that the reaction of **6** with acetic acid (80% aqueous solution)^{11,29} at 50°C for 24 h gave the product **7** in 74% yield. Slightly surprisingly, the two diastereoisomers of **7** could be easily separated by flash chromatography (hexane-ethyl acetate 10 : 1 then 5 : 1). Benzoylation of the alcohol group of **7b** gave the cyclization precursor **8b** as a white solid in 82% yield. However, cyclization of **8b** did not occur in THF at 0°C or room temperature, using KHMDS and LiHMDS as the base. When stronger bases, NaH and *t*-BuOK, were used, hydrolysis of the ester group and dehydrobromination occurred. In our opinion, the strong electron-withdrawing properties of the trifluoromethyl group and the weak ability of bromide as a leaving group seemed to be responsible for the failure of the cyclization of **8b** (Scheme 3).

In view of the failure of the cyclization of bromide **8b**, we envisioned that the mesylate as the leaving group should probably afford the cyclization product (Scheme 4). Thus, benzoylation of the alcohol group of **5** yielded **9** in 95% yield. Hydrolysis of the hemiaminal moiety of **9** with 80% AcOH at 50°C for 24 h afforded the alcohol **10** in 77% yield. The alcohol group of **10** was protected as the *tert*-butyldimethylsilyl (TBDMS) ether to give **11** in 87% yield and fortunately the two diastereoisomers could be separated by flash chromatography (hexane-ethyl acetate 50 : 1, 20 : 1, then 5 : 1). The hydro-



Scheme 3

genations of **11a** and **11b** were carried out on 10% Pd/C to give the alcohols **12a** (99% yield) and **12b** (91% yield) respectively. As we expected, after mesylation of the alcohol groups of **12a** and **12b**,³⁰ the resulting mesylates were treated with KHMDS to yield the desired cyclization products **13a** (83% yield in two steps) and **13b** (80% yield in two steps) respectively. Removal of the *tert*-butyldimethylsilyl groups in **13a** and **13b** with tetrabutylammonium fluoride (TBAF) in THF afforded the alcohols **14a** and **14b** respectively. Finally, oxidation³¹ of the hydroxymethyl moieties of **14a** and **14b** to carboxylic acids with Jones reagent in acetone provided Boc-protected *trans*-4-trifluoromethyl-D-proline **15a** (56% yield) and *cis*-4-trifluoromethyl-D-proline **15b** (68% yield) respectively. The absolute configurations of **15a** and **15b** could be deduced from Boc-protected *cis*-4-trifluoromethyl-L-proline^{18,19} whose absolute configuration was determined by X-ray and NOE studies. ^1H NMR, ^{19}F NMR, ^{13}C NMR, IR, MS of **15b** were identical to those of Boc-protected *cis*-4-trifluoromethyl-L-proline, but the optical rotation of **15b** ($[\alpha]_{\text{D}}^{20} = +79$ (*c* 0.98, CHCl_3)) was opposite to that of Boc-protected *cis*-4-trifluoromethyl-L-proline ($[\alpha]_{\text{D}}^{20} = -77.6$ (*c* 0.70, CHCl_3))¹⁹ which demonstrated that they are enantiomers. Furthermore, NOESY experiments on **15a** showed that the 2-H was *trans* to 4-H.

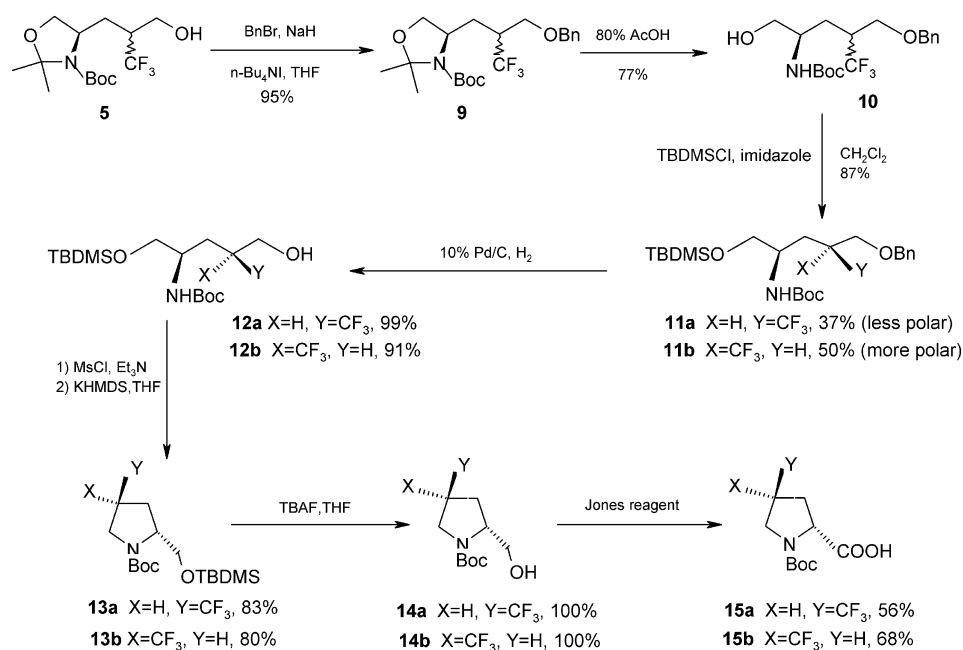
In summary, we have developed a methodology for the first preparation of both *cis*- and *trans*-4-trifluoromethyl-D-proline simultaneously. Most noteworthy is the use of α -trifluoromethyl- α,β -unsaturated ester **4** as the key intermediate and that the replacement of bromide by mesylate as the leaving group successfully provided the cyclization products **13a**, **13b** in good yield. The studies on incorporation of the two fluorine-containing amino acids into peptides are in progress.

Experimental

Compound **4** was prepared according to the literature procedures.³²

2-Trifluoromethyl-3-[(4*R*)-*N*-(1,1-dimethylethoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]propanol (**5**)

To a solution of **4** (2.75 g, 7.49 mmol) in MeOH (260 ml) was added Raney-Ni (8 g, 50% w/w slurry in water, 50% mol). The mixture was hydrogenated at room temperature overnight and filtered through a pad of Celite, and the solvent was removed *in vacuo*. The residue was taken up in Et_2O (3×100 ml) and the combined organic phase was washed with H_2O and brine.



Scheme 4

After the organic phase was dried over anhydrous Na₂SO₄ and filtered, the solvent was removed *in vacuo* to afford an oil which was used without further purification. To a cooled solution of LAH (0.76 g, 20 mmol) in 100 ml ether, the oil obtained above in 100 ml ether was added slowly. The mixture was stirred at 0 °C until the reaction was shown to be complete by TLC and the reaction was quenched by addition of 50 ml water. The mixture was filtered and the filtrate was extracted with ether (3 × 200 ml). The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography (hexane–ethyl acetate, 10 : 1) to give **5** as a white solid (2.30 g, 94%). Mp = 47–49 °C; ¹H NMR (CDCl₃, 300 MHz) δ 1.45–1.49 (m, 12H), 1.57–1.63 (m, 3H), 1.83–2.19 (m, 3H), 3.72–3.75 (m, 2H), 3.96–4.01 (dd, *J* = 4.8, 5.1 Hz, 2H), 4.27–4.29 (br s, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –69.7 (d, *J* = 9.3 Hz), –70.8 (d, *J* = 9.3 Hz); IR (KBr) 3473, 2983, 1690 cm^{–1}; EI-MS *m/z* 312 (M⁺ + 2, <1%), 212 (52), 57 (100); Found: C, 51.33; H, 7.44; N, 4.17. C₁₄H₂₄F₃NO₄ requires C, 51.38; H, 7.34; N, 4.28%.

1-Bromo-2-trifluoromethyl-3-[(4*R*)-*N*-(1,1-dimethylethoxy-carbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (**6**)

To CBr₄ (5.80 g, 17.5 mmol) and Ph₃P (4.80 g, 18.3 mmol), **5** (2.30 g, 7 mmol) in THF (70 ml) was added slowly, followed by Et₃N (5 ml, 35 mmol). The mixture was stirred at room temperature overnight. The resulted red solution was diluted with Et₂O (100 ml) and H₃PO₄ (0.167 M, 50 ml). The aqueous layer was extracted with Et₂O (3 × 100 ml) and the combined organic phases were washed with saturated aqueous Na₂CO₃ (2 × 50 ml) and brine and dried over anhydrous Na₂SO₄. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography (hexane–ethyl acetate, 15 : 1) to give **6** as a clear oil (2.59 g, 95%). ¹H NMR (CDCl₃, 300 MHz) δ 1.41–1.48 (m, 12H), 1.56–1.61 (m, 3H), 1.89–2.07 (m, 2H), 2.60, 2.76 (2 br s, 1H), 3.34–3.45 (m, 1H), 3.53–3.58 (dd, *J* = 4.5, 4.2 Hz, 1H), 3.72–3.75 (d, *J* = 9.0 Hz, 1H), 3.97–4.02 (dd, *J* = 5.4, 4.5 Hz, 1H), 4.13 (br s, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.5 (d, *J* = 9 Hz), –70.8 (d, *J* = 9 Hz); IR (thin film) 2966, 1701, 1390, 1099 cm^{–1}; EI-MS *m/z* 392 (M⁺ + 2, 6%), 391 (M⁺ + 1, 5), 390 (M⁺, 6), 389 (M⁺ – 1, 5), 292 (50), 292 (56), 57 (100); Found: C, 42.64; H, 6.03; N, 3.30. C₁₄H₂₃F₃NO₃Br requires C, 43.07; H, 5.90; N, 3.59%.

(2*R*)-2-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-5-bromo-4-trifluoromethylpentanol (**7**)

A solution of **6** (500 mg, 1.28 mmol) in 80% AcOH was stirred overnight at 50 °C, then the solvent was removed *in vacuo* and the residue was diluted with Et₂O (30 ml) and H₂O (20 ml). The aqueous phase was extracted with Et₂O (3 × 20 ml) and the combined organic phases were washed with saturated aqueous NaHCO₃ (20 ml) and brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate, 10 : 1 then 5 : 1) to give **7a** (less polar, 153.5 mg, 34%) as a white solid and **7b** (more polar, 181.4 mg, 40%) as a white solid. **7a** mp = 72–74 °C; [*a*]_D²⁰ = +34.8 (*c* 0.53, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 1.44 (s, 9H), 1.85–1.94 (m, 2H), 2.05 (br s, 1H), 2.59–2.62 (m, 1H), 3.59–3.66 (m, 2H), 3.73–3.81 (m, 3H), 4.79–4.82 (d, *J* = 9 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.8 (d, *J* = 9.9 Hz); IR (KBr) 3338, 3256, 3072, 2976, 1670, 1558, 1175 cm^{–1}; EI-MS *m/z* 352 (M⁺ + 2, <1%), 351 (M⁺ + 1, <1), 350 (M⁺, <1), 349 (M⁺ – 1, <1), 252 (6), 250 (6), 57 (100); Anal. Calcd for C₁₁H₁₉F₃NO₃Br: C, 37.71; H, 5.44; N, 4.01. Found: C, 38.10; H, 5.62; N, 3.87%. **7b** mp = 102–104 °C [*a*]_D²⁰ = +13.0 (*c* 0.26, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 1.46 (s, 9H), 1.89–1.94 (m, 2H), 2.70–2.74 (br s, 1H), 3.34–3.40 (dd, *J* = 7.2, 7.8 Hz, 1H), 3.58–3.63 (dd, *J* = 3.3, 3.3 Hz, 1H), 3.70–3.73 (m, 2H), 3.81–3.82 (m, 1H), 4.82–4.85 (d, *J* = 7.2 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –71.2 (d, *J* = 8.7 Hz); IR (KBr) 3370, 2977, 1681, 1529, 1170 cm^{–1}; EI-MS *m/z* 352 (M⁺ + 2, <1%), 351 (M⁺ + 1, <1), 350 (M⁺, <1), 349 (M⁺ – 1, <1), 252 (6), 250 (6), 57 (100); Found: C, 38.10; H, 5.63; N, 3.85. C₁₁H₁₉F₃NO₃Br requires C, 37.71; H, 5.44; N, 4.01%.

(2*R*)-2-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-1-benzoyloxy-5-bromo-4-trifluoromethylpentane (**8b**)

To a solution of **7b** (206 mg, 0.59 mmol) in dry Et₃N (6 ml), benzoyl chloride (68 μl, 0.59 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h and the solvent was removed *in vacuo*. The residue was diluted with Et₂O (60 ml) and the organic phase was washed with 5% aqueous NaHCO₃ (2 × 10 ml), 3% aqueous hydrogen chloride (2 × 10 ml), and brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate, 15 : 1) to give **8b** as a white solid (219 mg, 82%). Mp = 104.5–106.5 °C; [*a*]_D²⁰ = +30.1

(*c* 0.53, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 1.43 (s, 9H), 1.94–2.03 (m, 2H), 2.75–2.80 (m, 1H), 3.34–3.40 (dd, *J* = 10.5, 8.7 Hz, 1H), 3.62–3.67 (dd, *J* = 3.6, 3.9 Hz, 1H), 4.18–4.22 (m, 1H), 4.34–4.36 (d, *J* = 4.5 Hz, 2H), 4.69–4.72 (d, *J* = 9 Hz, 1H), 7.44–7.50 (t, *J* = 7.8 Hz, 2H), 7.60–7.62 (t, *J* = 7.8 Hz, 1H), 8.03–8.06 (d, *J* = 7.8 Hz, 2H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70 (d, *J* = 66 Hz); IR (KBr) 3362, 2982, 1720, 1711, 1679, 1605, 1531 cm^{–1}; EI-MS *m/z* 252 (6%), 57 (100); ESI-MS *m/z* 456.1 (M⁺ + 2), 454.1 (M⁺); Found: C, 48.00; H, 5.18; N, 3.02. C₁₈H₂₃F₃NO₄Br requires C, 47.58; H, 5.07; N, 3.08%.

1-Benzylloxy-2-trifluoromethyl-3-[(4*R*)-*N*-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (9)

A mixture of Bu₄NI (750 mg, 2.03 mmol) and NaH (950 mg, 60% in oil, 23.75 mmol) was cooled to 0 °C and **5** (4.95 g, 15.13 mmol) in THF (60 ml) was added dropwise. The mixture was stirred for 10 min at 0 °C and then stirred at room temperature for 10 min. The mixture was cooled to 0 °C again and benzyl bromide (2 ml, 16.78 mmol) was added dropwise and the mixture was stirred at room temperature for 5 h. The reaction was quenched with H₂O (20 ml) and the mixture was extracted with Et₂O (3 × 100 ml). The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography (hexane–ethyl acetate, 100 : 1) to give **9** as a clear oil (5.97 g, 95%). ¹H NMR (CDCl₃, 300 MHz) δ 1.44 (s, 9H), 1.55–1.61 (m, 6H), 1.82–2.05 (m, 2H), 2.41 (br s, 1H), 3.46–3.80 (m, 3H), 3.92–3.97 (dd, *J* = 6.6, 5.4 Hz, 1H), 4.08–4.10 (br s, 1H), 4.53–4.55 (m, 2H), 7.27–7.38 (m, 5H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –69.2 (d, *J* = 8.7 Hz), –70.4 (d, *J* = 9.6 Hz); IR (thin film) 2982, 1699, 1497, 1480, 1173 cm^{–1}; EI-MS *m/z* 402 (M⁺ – 15, 2%), 302 (29), 91 (100), 57 (65); Found: C, 60.42; H, 7.20; N, 3.38. C₂₁H₃₀F₃NO₄ requires C, 60.43; H, 7.19; N, 3.36%.

(2*R*)-2-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-5-benzylloxy-4-trifluoromethylpentanol (10)

The solution of **9** (920 mg, 2.21 mmol) in 80% AcOH (26 ml) was stirred overnight at 50 °C. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (40 ml). The organic phase was washed with saturated aqueous NaHCO₃ (2 × 30 ml) and brine and dried over anhydrous Na₂SO₄. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography (hexane–ethyl acetate, 5 : 1) to give **10** as a clear oil (645 mg, 77%). ¹H NMR (CDCl₃, 300 MHz) δ 1.44 (s, 9H), 1.65–1.98 (m, 2H), 2.28 (br s, 1H), 2.56 (m, 1H), 3.48–3.58 (m, 1H), 3.60–3.65 (m, 2H), 3.68–3.77 (m, 2H), 4.50–4.59 (m, 2H), 4.85, 5.07 (2 br s, 1H), 7.27–7.38 (m, 5H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.1 (d, *J* = 9.3 Hz), –70.4 (d, *J* = 5.6 Hz); IR (thin film) 3423, 2979, 1692, 1509, 1456, 1170 cm^{–1}; EI-MS *m/z* 347 (M⁺ – 30, <1%), 91 (100), 57 (76); C, 57.57; H, 7.05; N, 3.71. C₁₈H₂₆F₃NO₄ requires C, 57.29; H, 6.90; N, 3.71%.

(2*R*,4*S*)-2-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-1-*tert*-butyldimethylsilyloxy-5-benzylloxy-4-trifluoromethylpentane (11a), and (2*R*,4*R*)-2-[*N*-(1,1-dimethyl)ethoxycarbonylamino]-1-*tert*-butyldimethylsilyloxy-5-benzylloxy-4-trifluoromethylpentane (11b)

To a solution of **10** (2.89 g, 7.67 mmol) and imidazole (2.00 g, 29.40 mmol) in CH₂Cl₂ (80 ml), TBDMSCl (2.10 g, 13.93 mmol) in CH₂Cl₂ (40 ml) was added dropwise. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with H₂O (40 ml). The aqueous layer was extracted with CH₂Cl₂ (3 × 100 ml) and the combined organic phases were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate, 50 : 1, 20 : 1, then 5 : 1)

to give **11a** (less polar, 1.41 g, 37%) as a clear oil and **11b** (more polar, 1.88 g, 50%) as a clear oil. **11a** [*a*]_D²⁰ = +39.7 (*c* 0.80, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.43 (s, 9H), 1.76–1.83 (m, 2H), 2.43–2.45 (m, 1H), 3.53–3.58 (dd, *J* = 3.3, 3.3 Hz, 1H), 3.61–3.69 (m, 2H), 3.73–3.77 (dd, *J* = 4.2, 4.8 Hz, 2H), 4.54 (s, 2H), 4.68–4.71 (d, *J* = 9.3 Hz, 1H), 7.30–7.40 (m, 5H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –69.9 (d, *J* = 8.7 Hz); IR (thin film) 3363, 2951, 1716, 1499, 1455 cm^{–1}; EI-MS *m/z* 493 (M⁺ + 2, <1%), 492 (M⁺ + 1, <1), 393 (11), 392 (13), 91 (100), 57 (32); Anal. Calcd for C₂₄H₄₀F₃NO₄Si: C, 58.66; H, 8.15; N, 2.85. Found: C, 58.88; H, 7.92; N, 2.84%. **11b** [*a*]_D²⁰ = +17.7 (*c* 0.75, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 6H), 0.90 (s, 9H), 1.44 (s, 9H), 1.64–1.95 (m, 2H), 2.48–2.51 (m, 1H), 3.51–3.74 (m, 5H), 4.53 (s, 2H), 4.80–4.82 (d, *J* = 7.8 Hz, 1H), 7.31–7.38 (m, 5H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.3 (d, *J* = 8.2 Hz); IR (thin film) 3449, 3067, 3033, 1716, 1499, 1455 cm^{–1}; EI-MS *m/z* 493 (M⁺ + 2, <1%), 492 (M⁺ + 1, <1), 392 (4), 91 (100), 57 (19); Found: C, 58.90; H, 7.87; N, 2.82. C₂₄H₄₀F₃NO₄Si requires C, 58.66; H, 8.15; N, 2.85%.

(2*S*,4*R*)-4-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-5-*tert*-butyldimethylsilyloxy-2-trifluoromethylpentanol (12a)

To a solution of **11a** (1.41 g, 2.86 mmol) in ethanol (80 ml), Pd/C (10% Pd, 150 mg) was added. The mixture was hydrogenated overnight at room temperature and filtered through a pad of Celite, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexane–ethyl acetate, 5 : 1) to give **12a** as a clear oil (1.14 g, 99%). [*a*]_D²⁰ = +22.0 (*c* 0.71, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.45 (s, 9H), 1.66–1.85 (m, 2H), 2.30 (br s, 1H), 3.57–3.61 (dd, *J* = 2.7, 3.0 Hz, 1H), 3.67–3.72 (dd, *J* = 3.6, 3.6 Hz, 1H), 3.78–3.99 (m, 3H), 4.86–4.89 (d, *J* = 9.6 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.5 (d, *J* = 8.7 Hz); IR (thin film) 3447, 3357, 1694, 1505, 1256, 1171, 1124 cm^{–1}; EI-MS *m/z* 302 (M⁺ – Boc, 20%), 57 (100); Found: C, 51.26; H, 8.40; N, 3.51. C₁₇H₃₄F₃NO₄Si requires C, 50.87; H, 8.48; N, 3.49%.

(2*R*,4*R*)-4-[*N*-(1,1-Dimethyl)ethoxycarbonylamino]-5-*tert*-butyldimethylsilyloxy-2-trifluoromethylpentanol (12b)

Compound **12b** (1.40 g, 91%) was prepared as a clear oil from compound **11b** (1.88 g, 3.82 mmol) using the same conditions as for compound **12a**. [*a*]_D²⁰ = +10.5 (*c* 0.44, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.52 (s, 9H), 1.73–1.99 (m, 2H), 2.23–2.26 (br s, 1H), 3.60–3.72 (m, 3H), 3.72–3.86 (dd, *J* = 5.7, 5.7 Hz, 1H), 3.91–3.95 (dd, *J* = 4.5, 4.5 Hz, 1H), 4.96–5.00 (d, *J* = 6 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ –70.6 (d, *J* = 9.3 Hz); IR (thin film) 3447, 3357, 1694, 1505, 1256, 1171, 1124 cm^{–1}; EI-MS *m/z* 302 (M⁺ – Boc, 20%), 57 (100); Found: C, 51.26; H, 8.40; N, 3.51. C₁₇H₃₄F₃NO₄Si requires C, 50.87; H, 8.48; N, 3.49%.

(2*R*,4*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-4-trifluoromethyl-*N*-(1,1-dimethyl)ethoxycarbonylpyrrolidine (13a)

A mixture of **12a** (1.14 g, 2.84 mmol), methanesulfonyl chloride (4 ml, 51.68 mmol) and Et₃N (15 ml, 107.9 mmol) in CH₂Cl₂ (30 ml) was stirred overnight at room temperature. After dilution with H₂O, the aqueous layer was extracted with CH₂Cl₂ (3 × 40 ml) and the combined organic phases were washed with saturated aqueous NaHCO₃, H₂O and brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was treated with KHMDS (3.0 ml, 20% in toluene) in THF (200 ml) at 0 °C for 24 h. The reaction was quenched with saturated aqueous NH₄Cl (40 ml) and the aqueous layer was extracted with Et₂O (3 × 50 ml). The combined organic phases were washed with H₂O (50 ml), brine and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate, 100 : 1) to give

13a (904 mg, 83%) as a clear oil. $[\alpha]_{\text{D}}^{20} = +40.8$ (c 1.93, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.45 (s, 9H), 2.05–2.15 (m, 2H), 3.08–3.22 (m, 1H), 3.37–3.68 (m, 3H), 3.86–3.90 (dd, $J = 3.6, 3.3$ Hz, 1H), 4.00–4.01 (br s, 1H); ^{19}F NMR (CDCl_3 , 282 MHz) δ –72.6 (t, $J = 8.6$ Hz); IR (thin film) 2961, 1704, 1473, 1391, 1262, 1137 cm^{-1} ; EI-MS m/z 384 ($\text{M}^+ + 1$, 15%), 284 (100), 57 (66); ESI-HRMS m/z 406.1996 ($\text{M}^+ + \text{Na}$, $\text{C}_{17}\text{H}_{32}\text{F}_3\text{NO}_3\text{NaSi}$ requires 406.1933); Found: C, 53.27; H, 8.28; N, 4.07. $\text{C}_{17}\text{H}_{32}\text{F}_3\text{NO}_3\text{Si}$ requires C, 53.26; H, 8.36; N, 3.66%.

(2R,4R)-2-(tert-Butyldimethylsilyloxymethyl)-4-trifluoromethyl-N-[(1,1-dimethyl)ethoxycarbonyl]pyrrolidine (13b)

Compound **13b** (1.07 g, 80%) was prepared as a clear oil from compound **12b** (1.40 g, 3.49 mmol) using the same conditions as for compound **13a**. $[\alpha]_{\text{D}}^{20} = +58.0$ (c 1.21, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.46 (s, 9H), 2.20–2.25 (m, 2H), 2.76–2.84 (m, 1H), 3.19–3.26 (t, $J = 10.2$ Hz, 1H), 3.62–3.97 (m, 4H); ^{19}F NMR (CDCl_3 , 282 MHz) δ –71.6 (t, $J = 7.0$ Hz); IR (thin film) 2957, 1702, 1474, 1392, 1167 cm^{-1} ; EI-MS m/z 385 ($\text{M}^+ + 2$, 5%), 384 ($\text{M}^+ + 1$, 4), 271 (100), 57 (66); Found: C, 53.39; H, 8.16; N, 3.65. $\text{C}_{17}\text{H}_{32}\text{F}_3\text{NO}_3\text{Si}$ requires C, 53.26; H, 8.36; N, 3.66%.

(2R,4S)-2-Hydroxymethyl-4-trifluoromethyl-N-[(1,1-dimethyl)ethoxycarbonyl]pyrrolidine (14a)

To a cooled solution of **13a** (395 mg, 1.03 mmol) in THF (10 ml), TBAF (1.1 ml, 1.1 M in THF, 1.1 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (5 ml) and Et_2O (20 ml) was added. The aqueous layer was extracted with Et_2O (3×20 ml) and the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate 10 : 1 then 5 : 1) to give **14a** (280 mg, 100%) as a clear oil. $[\alpha]_{\text{D}}^{20} = +26.8$ (c 1.47, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 1.45 (s, 9H), 1.94–2.01 (br s, 1H), 2.16–2.27 (m, 1H), 2.97–3.06 (br s, 1H), 2.97–3.05 (m, 1H), 3.57–3.63 (m, 3H), 3.70–3.75 (dd, $J = 3.3, 3.9$ Hz, 1H), 4.09–4.10 (br s, 1H); ^{19}F NMR (CDCl_3 , 282 MHz) δ –72.7 (d, $J = 7$ Hz); IR (thin film) 3437, 2980, 1699, 1678, 1480, 1134 cm^{-1} ; EI-MS m/z 238 ($\text{M}^+ - 31$, 8%), 138 (34), 57 (100); Found: C, 49.33; H, 7.14; N, 5.08. $\text{C}_{11}\text{H}_{18}\text{F}_3\text{NO}_3$ requires C, 49.07; H, 6.69; N, 5.20%.

(2R,4R)-2-Hydroxymethyl-4-trifluoromethyl-N-[(1,1-dimethyl)ethoxycarbonyl]pyrrolidine (14b)

Compound **14b** (600 mg, 100%) was prepared as a clear oil from compound **13b** (857 mg, 2.23 mmol) using the same conditions as for compound **14a**. $[\alpha]_{\text{D}}^{20} = +43.8$ (c 0.99, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 1.48 (s, 9H), 1.65–1.71 (m, 1H), 2.25–2.34 (m, 1H), 2.81–2.90 (m, 1H), 3.30–3.37 (t, $J = 10.8$ Hz, 1H), 3.62–3.71 (m, 2H), 3.75–3.84 (m, 1H), 3.97–4.05 (m, 1H); ^{19}F NMR (CDCl_3 , 282 MHz) δ –71.9 (d, $J = 4.8$ Hz); IR (thin film) 3427, 2981, 1697, 1679, 1396, 1137 cm^{-1} ; EI-MS m/z 271 ($\text{M}^+ + 2$, 5%), 270 ($\text{M}^+ + 1$, 5), 238 ($\text{M}^+ - 31$, 2), 57 (100); Found: C, 49.30; H, 7.14; N, 5.10. $\text{C}_{11}\text{H}_{18}\text{F}_3\text{NO}_3$ requires C, 49.07; H, 6.69; N, 5.20%.

(2R,4S)-N-[(1,1-Dimethyl)ethoxycarbonyl]-4-trifluoromethyl-D-proline (15a)

To a 0°C solution of **14a** (220 mg, 0.82 mmol) in acetone (20 ml), Jones reagent (10 ml) was added dropwise. The mixture was stirred at 0°C for 7 h. After the remaining oxidant was decomposed by the addition of propan-2-ol (5 ml), the solvent was removed *in vacuo* and the residue was diluted with ether and water. The organic layer was separated and the aqueous phase was extracted with ether (3×30 ml). The combined organic phases were washed with brine and dried over

anhydrous Na_2SO_4 . After removal of the solvent, the residue was purified by flash chromatography (hexane–ethyl acetate 5 : 1 then 0 : 100) to give **15a** (130 mg, 56%) as a white solid. $\text{Mp} = 113\text{--}115^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} = +70.0$ (c 0.45, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 1.38, 1.44 (2s, 9H), 2.19–2.30 (m, 1H), 2.35–2.47 (m, 1H), 2.97–3.08 (m, 1H), 3.43–3.57 (m, 1H), 3.64–3.77 (2 \times dd, $J = 8.7, 8.4, 8.4, 9.0$ Hz, 1H), 4.34–4.47 (2 \times dd, $J = 2.7, 2.4, 2.4, 2.7$ Hz, 1H), 8.38–8.51 (m, 1H); ^{19}F NMR (CDCl_3 , 282 MHz) δ –72.4 (d, $J = 36.7$ Hz); IR (KBr) 3000–2500, 1759, 1673, 1399, 1144 cm^{-1} ; EI-MS m/z 239 ($\text{M}^+ - 44$, 3%), 138 (94), 57 (100); Found: C, 46.71; H, 5.74; N, 4.94. $\text{C}_{11}\text{H}_{16}\text{F}_3\text{NO}_4$ requires C, 46.64; H, 5.65; N, 4.95%.

(2R,4R)-N-[(1,1-Dimethyl)ethoxycarbonyl]-4-trifluoromethyl-D-proline (15b)

Compound **15b** (258 mg, 68%) was prepared as a white solid from compound **14b** (360 mg, 1.34 mmol) using the same conditions as for compound **15a**. $\text{Mp} = 124\text{--}126^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} = +79.0$ (c 0.98, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 1.44, 1.50 (2s, 9H), 2.19–2.42 (m, 1H), 2.54–2.64 (m, 1H), 2.94–3.02 (m, 1H), 3.47–3.52 (m, 1H), 3.83–3.97 (m, 1H), 4.34–4.48 (dt, $J = 28.8, 7.6$ Hz, 1H), 8.87 (br s, 1H); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 177.3, 175.7, 154.6, 153.4, 127.6, 123.9, 81.7, 81.4, 58.3, 58.2, 45.9, 45.6, 41.8, 41.5, 41.2, 40.8, 29.9, 28.6, 28.2, 28.0; ^{19}F NMR (CDCl_3 , 282 MHz) δ –71.0 (d, $J = 7.05$ Hz); IR (KBr) 3000–2500, 1750, 1648, 1440, 1182 cm^{-1} ; EI-MS m/z 238 ($\text{M}^+ - 45$, 4%), 138 (38), 57 (100); Found: C, 46.66; H, 5.74; N, 4.81. $\text{C}_{11}\text{H}_{16}\text{F}_3\text{NO}_4$ requires C, 46.64; H, 5.65; N, 4.95%.

References

- 1 R. P. Kukhá and V. A. Soloshonok, *Fluorine-containing Amino Acids*, Wiley & Sons, New York, 1997.
- 2 (a) D. B. Harper and D. O'Hagan, *Nat. Prod. Rep.*, 1994, **11**, 123; (b) B. E. Smart, in *Molecular Structure and Energetics*, ed. J. L. Liebman and A. Greenberg, VCH Publishers Inc., Deerfield Park, Florida, 1986, vol. 3, p. 141.
- 3 (a) S. M. Hecht, *Acc. Chem. Res.*, 1992, **25**, 545; (b) V. W. Cornish, D. Mende and P. G. Schultz, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 621; (c) D. R. Liu, T. J. Magliery, M. Pastrnak and P. G. Schultz, *Proc. Natl. Acad. Sci. USA*, 1997, **94**, 10092; (d) R. Furter, *Protein Sci.*, 1998, **7**, 419; (e) D. R. Liu and P. G. Schultz, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 4780.
- 4 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991.
- 5 (a) C. T. Walsh, *Annu. Rev. Biochem.*, 1984, **53**, 493; (b) R. Filler, Y. Kobayashi and L. M. Yagupolskii, *Biomedical Aspects of Fluorine Chemistry*, Elsevier, Amsterdam, 1993, p. 241.
- 6 (a) A. Niemz and D. A. Tirrell, *J. Am. Chem. Soc.*, 2001, **123**, 7407; (b) Y. Tang, G. Ghirlanda, W. Petka, T. Nakajima, W. Degradó and D. A. Tirrell, *Angew. Chem., Int. Ed.*, 2001, **40**, 1494.
- 7 (a) B. Bilgiçer, A. Fichera and K. Kumar, *J. Am. Chem. Soc.*, 2001, **123**, 4393; (b) B. Bilgiçer, X. Xing and K. Kumar, *J. Am. Chem. Soc.*, 2001, **123**, 11815.
- 8 *Fluorine-containing Amino Acids, Synthesis and Properties*, ed. V. P. Kukhar' and V. A. Soloshonok, Wiley, Chichester, 1995.
- 9 A. Sutherland and C. L. Willis, *Nat. Prod. Rep.*, 2000, **17**, 621.
- 10 For recent examples, see: (a) D. W. Konas and J. K. Coward, *J. Org. Chem.*, 2001, **66**, 8831; (b) X. Xing, A. Fichera and K. Kumar, *Org. Lett.*, 2001, **3**, 1285; (c) S. Fustero, A. Navarro, B. Pina, J. G. Soler, A. Bartolomé, A. Asensio, A. Simón, P. Bravo, G. Fronza, A. Volonterio and M. Zanda, *Org. Lett.*, 2001, **3**, 2621; (d) H. Abe, H. Amii and K. Uneyama, *Org. Lett.*, 2001, **3**, 313; (e) N. Lebouvier, C. Laroche, F. Huguenot and T. Brigaud, *Tetrahedron Lett.*, 2002, **43**, 2827; (f) X. Xing, A. Fichera and K. Kumar, *J. Org. Chem.*, 2002, **67**, 1722.
- 11 M. Nevalainen, P. M. Kauppinen and A. M. P. Koskinen, *J. Org. Chem.*, 2001, **66**, 2061.
- 12 M. Tamaki, T. Okitsu, M. Araki, H. Sakamoto, M. Takimoto and I. Muramatsu, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 531.
- 13 M. A. Ondetti, B. Rubin and D. W. Cushman, *Science*, 1977, **196**, 441.
- 14 A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. T. Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr,

- R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil and C. A. Stone, *Nature*, 1980, **288**, 280.
- 15 (a) N. A. Sasaki, M. Dockner, A. Chiaroni, C. Riche and P. Potier, *J. Org. Chem.*, 1997, **62**, 765; (b) M. Dockner, N. A. Sasaki and P. Potier, *Heterocycles*, 1996, **42**, 529; (c) M. Tamaki, G. Han and V. J. Hruby, *J. Org. Chem.*, 2001, **66**, 3593.
- 16 (a) F. N. Shirota, H. T. Nagasawa and J. A. Elberling, *J. Med. Chem.*, 1977, **20**, 1176; (b) A. Gottlieb, Y. Fujita, S. Underfriend and B. Witkop, *Biochemistry*, 1965, **4**, 2507; (c) E. M. Smith, G. F. Swiss, B. R. Neustadt, E. H. Gold, J. A. Sommer, A. D. Brown, P. J. S. Chiu, R. Moran, E. J. Sybertz and T. Baum, *J. Med. Chem.*, 1988, **31**, 875; (d) M. Hudlický and J. S. Merola, *Tetrahedron Lett.*, 1990, **31**, 7403; (e) D. R. Kronenthal, R. H. Mueller, P. L. Kuester, T. P. Kissick and E. J. Johnson, *Tetrahedron Lett.*, 1990, **31**, 1241; (f) A. G. Avent, A. N. Bowler, P. M. Doyle, C. M. Marchand and D. W. Young, *Tetrahedron Lett.*, 1992, **33**, 1509; (g) M. Hudlický, *J. Fluorine Chem.*, 1993, **60**, 193; (h) B. P. Hart and J. K. Coward, *Tetrahedron Lett.*, 1993, **34**, 4917; (i) K. Burger, M. Rudolph, S. Fehn and N. Sewald, *J. Fluorine Chem.*, 1994, **66**, 87; (j) T. T. Tran, N. Patino, R. Condom, T. Frogier and R. Guedj, *J. Fluorine Chem.*, 1997, **82**, 125; (k) M. Tandon, M. Wu and T. P. Begley, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1139; (l) L. Demange, A. Ménez and C. Dugave, *Tetrahedron Lett.*, 1998, **39**, 1169; (m) L. Demange, J. Cluzeau, A. Ménez and C. Dugave, *Tetrahedron Lett.*, 2001, **42**, 651.
- 17 J. Leroy and C. Wakselman, *Can. J. Chem.*, 1976, **54**, 218.
- 18 During the preparation of this manuscript, Goodman *et. al.* reported the stereoselective synthesis of *cis* and *trans*-4-trifluoromethyl-L-prolines by asymmetric hydrogenation. J. R. Del Valle and M. Goodman, *Angew. Chem., Int. Ed.*, 2002, **41**, 1600.
- 19 Our group recently prepared Boc-protected *cis*-4-trifluoromethyl-L-proline starting from 4-hydroxy-L-proline using the methodology being similar to Goodman's. X. L. Qui and F. L. Qing, *J. Org. Chem.*, 2002, in the press.
- 20 X. Zhang, F.-L. Qing, Y. Yang, J. Yu and X.-K. Fu, *Tetrahedron Lett.*, 2000, **41**, 2953.
- 21 Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc., Chem. Commun.*, 1989, 705.
- 22 D. B. Denney and S. T. Ross, *J. Org. Chem.*, 1962, **27**, 998.
- 23 (a) P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361; (b) P. Garner and J. M. Park, *Org. Synth.*, 1992, **70**, 18.
- 24 (a) T. Kitazume, T. Ohnogi, H. Miyauchi and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 5603; (b) T. Yamazaki, S. Hiraoka and T. Kitazume, *J. Org. Chem.*, 1994, **59**, 5100.
- 25 I. Kadota, S. Saya and Y. Yamamoto, *Heterocycles*, 1997, **46**, 335.
- 26 (a) S. Watanabe and Y. Sakai, *J. Fluorine Chem.*, 1994, **67**, 149; (b) T. Konno, H. Nakano and T. Kitazume, *J. Fluorine Chem.*, 1997, **86**, 81; (c) T. Konno, H. Umetani and T. Kitazume, *J. Org. Chem.*, 1997, **62**, 137.
- 27 (a) W. A. Szarek, A. Zamojski, K. N. Tiwari and E. R. Ison, *Tetrahedron Lett.*, 1986, **27**, 3827; (b) F.-L. Qing, S. Peng and C.-M. Hu, *J. Fluorine Chem.*, 1998, **88**, 79.
- 28 X. Xing, A. Fichera and K. Kumar, *Org. Lett.*, 2001, **3**, 1285.
- 29 A. M. P. Koskinen and L. A. Otsomaa, *Tetrahedron*, 1997, **53**, 6473.
- 30 (a) N. Ikota, *Heterocycles*, 1995, **41**, 983; (b) N. Ikota, H. Nakagawa, S. Ohno, K. Noguchi and K. Okuyama, *Tetrahedron*, 1998, **54**, 8985; (c) M. Yokoyama, T. Ikenogami and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2067.
- 31 (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39; (b) A. Barco, S. Benetti, G. Spalluto, A. Casolari, G. P. Pollini and V. Zanirato, *J. Org. Chem.*, 1992, **57**, 6279.
- 32 X. Zhang, F.-L. Qing and Y. Yu, *J. Org. Chem.*, 2000, **65**, 7075.