JOC*Article*

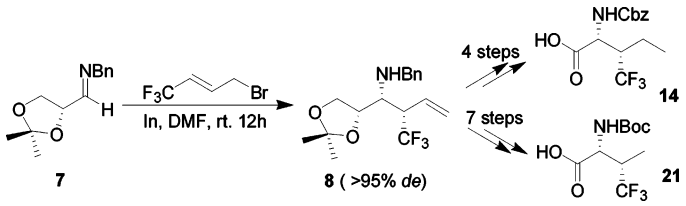
Indium-Mediated Diastereoselective Allylation of D- and L-Glyceraldimines with 4-Bromo-1,1,1-trifluoro-2-butene: Highly Stereoselective Synthesis of 4,4,4-Trifluoroisoleucines and 4,4,4-Trifluorovaline

Qi Chen,[†] Xiao-Long Qiu,[†] and Feng-Ling Qing*[,†,‡]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, China, and Institute of Biological Sciences and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

flq@mail.sioc.ac.cn

Received January 19, 2006



A practical and efficient route for the stereoselective synthesis of (2*R*,3*S*)- and (2*S*,3*R*)-4,4,4-trifluoroisoleucines and (2*R*,3*S*)-4,4,4-trifluorovaline was developed. Indium-mediated allylation of (*R*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine **7** with 4-bromo-1,1,1-trifluoro-2-butene **4** gave the desired homoallylic amine **8** in high diastereoselectivity (>95% de) with moderate yield. The Cbz-protected (2*R*,3*S*)-4,4,4-trifluoroisoleucine **14** and Boc-protected (2*R*,3*S*)-4,4,4-trifluorovaline **21** were then readily prepared from **8**. In addition, following the same procedure, Cbz-protected (2*S*,3*R*)-4,4,4-trifluoroisoleucine **28**, the enantiomer of **14**, was prepared starting from (*S*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine **24**.

Introduction

Recently, fluorinated amino acids have attracted increasing attention because of their extensive utilization as inhibitors of enzymes,[1] antitumor and antibacterial agents,[2] probes to follow biochemical reactions,[3] valuable building blocks for the design of hyperstable protein folds, as well as directing highly specific protein−protein interactions.[4] There has been a special interest in trifluoromethyl-containing amino acids (TFAAs) in peptide and protein design, because the replacement of methyl with trifluoromethyl groups is accompanied by a substantial increase in hydrophobicity, owing to the low polarizability of the fluorine atoms.[5] It must be emphasized that enantiomerically pure TFAAs are highly desirable for peptide synthesis to avoid compositional heterogeneity of samples and for exploration of stereoelectronic and packing effects.[6] Therefore, the development of an efficient and highly stereoselective route to enantiomerically pure TFAAs promotes both synthetic and biological research.

Isoleucine and valine are important natural amino acids; their trifluoromethylated analogues were used in peptide and protein design. Kumar and co-workers[5c] reported a peptide system based on the coiled coil region of the transcriptional activator GCN4

* To whom correspondence should be addressed. Fax: 86-21-64166128.
[†] Shanghai Institute of Organic Chemistry.
[‡] Donghua University.

(1) Kollonitsch, J.; Patchett, A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D. *Nature* **1978**, *274*, 906.

(2) Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N.; Shiratori, O.; Hirata, M. *Tetrahedron* **1988**, *44*, 5375.

(3) (a) Dubios, J.; Dugave, C.; Foures, C.; Kaminsky, M.; Tabet, J. C.; Bory, S.; Gaudry, M.; Marquet, A. *Biochemistry* **1991**, *30*, 10506. (b) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.

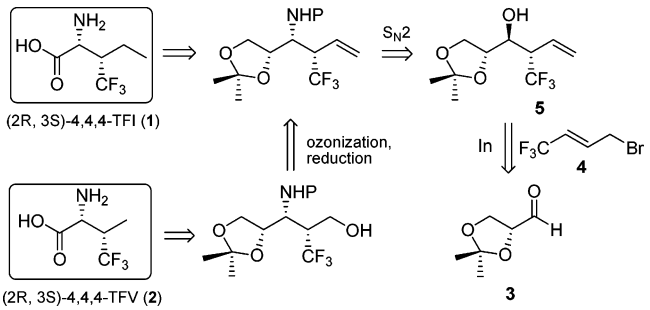
(4) (a) Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335. (b) Neil, E.; Marsh, G. *Chem. Biol.* **2000**, *7*, R153.

(5) (a) Wang, P.; Fichera, A.; Kumar, K.; Tirrell, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3664. (b) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900. (c) Bilgiçer, B.; Fichera, A.; Kumar, K. *J. Am. Chem. Soc.* **2001**, *123*, 4393. (d) Tang, Y.; Ghirlanda, G. W.; Petka, A.; Nakajima, T.; DeGrado, W. F.; Tirrell, D. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1494. (e) Xing, X.; Fichera, A.; Kumar, K. *Org. Lett.* **2001**, *3*, 1285 and references therein.

(6) (a) Xing, X.; Fichera, A.; Kumar, K. *J. Org. Chem.* **2002**, *67*, 1722. (b) Xing, X.; Fichera, A.; Kumar, K. *J. Org. Chem.* **2002**, *67*, 8290.

10.1021/jo0601157 CCC: $33.50
Published on Web 04/13/2006

SCHEME 1



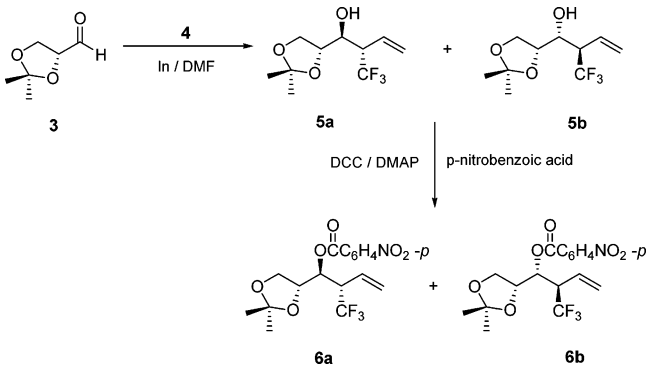
with an unnatural hydrophobic core, prepared by the replacement of four natural leucine and three natural valine residues with unnatural 5,5,5-trifluoroleucine (TFL) and 4,4,4-trifluorovaline (TFV), respectively. The resulting coiled coil structure was more resistant to thermal- and denaturant-induced unfolding than its hydrocarbon counterpart. Tirrell and co-workers[5b] incorporated D,L-trifluoroisoleucine into proteins in vivo and also found that some resulting fluorinated proteins could fold into stable and functional structures. However, Tirrell and co-workers used racemic trifluoroisoleucine (TFI) prepared only in 3% overall yield over seven steps,[5b] and Kumar and co-workers prepared the enantiomerically pure TFL and TFV by enzymatic resolution.[5c] Clearly, the existing approaches for the access of TFI and TFV are insufficient for the procurement of enough quantities for further detailed biological evaluation or the synthesis of other TFI- and TFV-containing compounds. More importantly, to the best of our knowledge, there is no report on stereoselective synthesis of TFI and TFV so far. Herein we report a practical and efficient approach to the highly stereoselective synthesis of TFI and TFV.

Results and Discussion

Several years ago, Loh and Li[7] reported the indium-mediated allylation reaction of aldehydes with 4-bromo-1,1,1-trifluoro-2-butene in water afforded β-trifluoromethylated homoallylic alcohols in high yield and excellent diastereoselectivity. Thus, indium-mediated allylation of chiral pool (*R*)-2,3-*O*-isopropylideneglyceraldehyde **3** with 4-bromo-1,1,1-trifluoro-2-butene **4** was also expected to give β-trifluoromethylated homoallylic alcohol **5** with good yield and high diastereoselectivity. The alcohol **5** should be a key intermediate for the preparation of the two target molecules (Scheme 1). The other key elements in this synthetic approach included the use of S_N2 reaction to install an amino group, cutting a carbon atom via ozonization of double bonds, dehydroxylation via Barton's radical reaction, deisopropylidenation, and then a final oxidation mediated by $RuCl_3/NaIO_4$.

Alkene **4** was prepared on a large scale in 38% overall yield over four steps from commercially available ethyl-4,4,4-trifluoro-3-oxobutanoate.[7,8] However, the reaction of aldehyde **3** with alkene **4** in the presence of indium powder in DMF at room temperature afforded a mixture of homoallylic alcohols **5a** and **5b** in moderate yield (65%) and low diastereoselectivity (dr = 1.5:1), which could not be separated by flash chromatography (Scheme 2). The absolute configuration of **5a** was confirmed by the X-ray diffraction analysis of its *p*-nitrobenzoic ester **6a** (see Supporting Information). Treatment of the mixture of **5a** and **5b** with *p*-nitrobenzoic acid in the presence of DCC and DMAP provided *p*-nitrobenzoic esters **6a** and **6b** in 88% yield. Compounds **6a** and **6b** could be easily separated by flash chromatography on silica gel.

SCHEME 2



In comparison with the indium-mediated allylation of C═O bonds, the allylation of C═N bonds usually achieves better enantioselectivity or diastereoselectivity.[9] Moreover, the amino group of the amino acids could be introduced directly in this way. Accordingly, the reaction between alkene **4** and (*R*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine **7** derived from **3** and benzylamine in the presence of indium powder in THF or MeOH was carried out. However, the reaction was complicated, and the desired product was not obtained. Fortunately, it was found that the allylation reaction proceeded well in DMF (Scheme 3). More strikingly, analysis of the crude reaction mixture by ^{19}F NMR spectroscopy (see Supporting Information) showed that the reaction occurred highly diastereoselectively (>95% de). Only a single diastereomer, **8**, was isolated in 61% yield along with 11% of tertiary amine **9**, which was formed by the allylation of benzylamine. Benzylamine probably came from the hydrolysis of **7**. The amine **8** was further hydrogenated to give primary amine **10** in 89% yield. To confirm the configuration of compound **8**, compound **10** was converted into amide **11**. The configuration of compound **11** was determined by X-ray diffraction analysis (see Supporting Information).

With the intermediate **10** in hand, optically pure (2*R*,3*S*)-4,4,4-trifluoroisoleucine was synthesized in a straightforward fashion (Scheme 4). Treatment of amine **10** with CbzCl gave compound **12** in 93% yield. After the removal of the isopropylidene ketal, the diol **13** was obtained in 94% yield. Finally, oxidation of the dihydroxyl moiety with $RuCl_3/NaIO_4$ successfully provided the desired Cbz-protected (2*R*,3*S*)-4,4,4-trifluoroisoleucine **14** in 76% yield. The ^1H, ^{13}C and ^{19}F NMR spectra of compound **14** showed clearly that no epimerization occurred. Thus, Cbz-protected (2*R*,3*S*)-4,4,4-trifluoroisoleucine was synthesized stereoselectively in 60% overall yield over four steps starting from amine **8**.

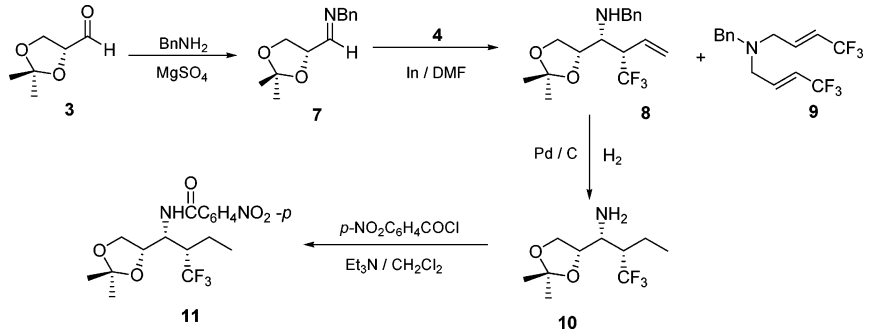
In addition, (2*R*,3*S*)-4,4,4-trifluorovaline was also readily synthesized starting from homoallylic amine **8** (Scheme 5). Exposure of compound **8** to $(CF_3CO)_2O$ provided amine **15** in 97% yield. Ozonization of **15** followed by reduction with $NaBH_4$ gave the desired alcohol **16** in 86% yield. Removal of the benzyl

(7) (a) Loh, T.-P.; Li, X.-R *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 980. (b) Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893.

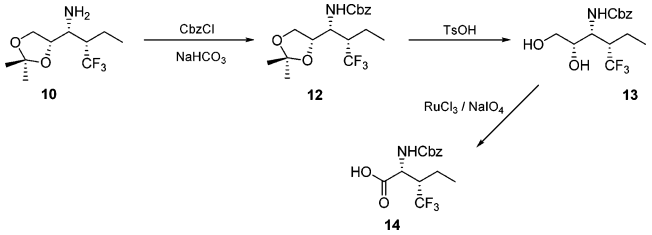
(8) (a) Bevilacqua, P. F.; Keith, D. D.; Roberts, J. L. *J. Org. Chem.* **1984**, *49*, 1430. (b) Mcbee, E. T.; Pierce, O. R.; Smith, D. D. *J. Am. Chem. Soc.* **1954**, *76*, 3722.

(9) (a) Beuchet, P.; Marrec, N. L.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959. (b) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589. (c) For a review, see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

SCHEME 3



SCHEME 4



group via hydrogenation and protection of the resultant amine with Boc_2O were carried out in a one-pot process to provide compound **17** in quantitative yield. Treatment of alcohol **17** with PhOC(S)Cl provided thiocarbonyl derivative **18** in 95% yield. However, exposure of compound **18** to Bu_3SnH (4 equiv)/AIBN (0.8 equiv) in toluene at 80 °C produced the expected product **19** only in 25% yield. Notably, it was reported that raising the reaction temperature as well as prolongation of addition time of Bu_3SnH could efficiently increase the yield of the Barton radical dehydroxylation for the primary hydroxyl substrate.[10] Thus, when the reaction temperature was raised to 140 °C (in xylene) and the addition time of Bu_3SnH was prolonged to 12 h, the dehydroxylation of compound **18** proceeded smoothly to give the desired product **19** in 65% isolated yield. Finally, Boc-protected (2*R*,3*S*)-4,4,4-trifluorovaline **21** was provided in 58% yield over two steps using the same procedures as described for the synthesis of amino acid **14** from **12**. Although the absolute configuration of **21** could be determined from the configuration of homoallylic amine **8**, it was not sufficient because there was the possibility of racemization in the follow-up steps. To further confirm the configuration of compound **21**, treatment of **21** with trifluoroacetic acid at room temperature gave free amino acid (2*R*,3*S*)-4,4,4-trifluorovaline **22** in quantitative yield. The optical rotation of **22** ($[\alpha]^{20}_D = -12.1$ (*c* 0.30, 1 N HCl)) was opposite to that of its reported enantiomer (2*S*,3*R*)-4,4,4-trifluorovaline ($[\alpha]^{20}_D = +12.8$ (*c* 0.50, 1 N HCl)),[6] therefore, the absolute configuration of **21** was further confirmed.

We also wanted to extend this methodology to the synthesis of enantiomer of Cbz-protected (2*R*,3*S*)-4,4,4-trifluoroisoleucine **14**. The indium-mediated reaction of alkene **4** with (*S*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine **24** derived from (*S*)-2,3-*O*-isopropylideneglyceraldehyde **23** and benzylamine also proceeded smoothly to give homoallylic amine **25** in 55% yield and high diastereoselectivity (>95% de) along with byproduct tertiary amine **9** in 9% yield (Scheme 6). Hydrogenation of compound **25** followed by treatment with CbzCl gave compound **26** in 88% yield for two steps. Removal of isopropylidene ketal of **26** in the presence of TsOH in methanol afforded the diol **27** in 93% yield. Finally, oxidation of the dihydroxyl moiety of **27** with $RuCl_3/NaIO_4$ provided Cbz-protected (2*S*,3*R*)-4,4,4-trifluoroisoleucine **28** in 71% yield. The optical rotation of **28** ($[\alpha]^{20}_D = -0.5$ (*c* 0.85, $CHCl_3$)) was opposite to that of its enantiomer Cbz-protected (2*R*,3*S*)-4,4,4-trifluoroisoleucine **14** ($[\alpha]^{20}_D = +0.6$ (*c* 1.10, $CHCl_3$)).

The different stereoselectivity in the allylation reaction of aldehyde **3** and imine **7** could be illustrated by the indium-chelated six-membered transition state (Figure 1). The CF_3 group

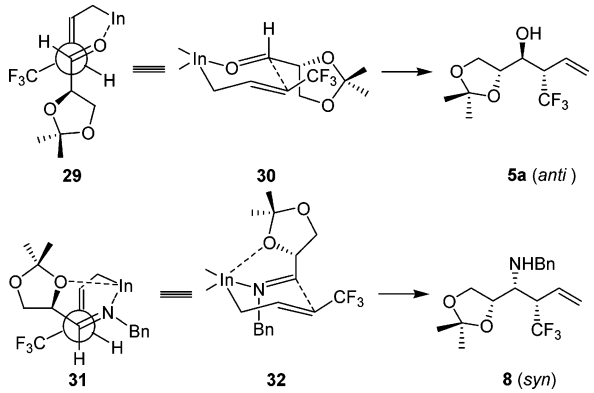


FIGURE 1. Proposed explanation for stereoselectivity.

would be in the equatorial position due to its steric bulkiness.[7,11,12] The chirality of aldehyde **3** would block the *re*-face of itself, thus the indium species would mainly attack the *si*-face. In addition, the isopropylidenyl moiety preferentially favored the equatorial position due to its large steric bulk. All of these factors led to mainly the formation of transition states **29** and **30**, which delivered anti isomer **5a** as the main product. On the other hand, the benzyl group and isopropylidenyl moiety in *E*-imine **7** must adopt orthogonal positions so that indium could efficiently chelate with the nitrogen atom.[13] Another advantage for the orthogonal position of the isopropylidenyl moiety was that five-membered ring chelation between the indium and the oxygen atom could occur.[7,14] Thus, transition state **31** or **32** was predominantly formed, leading to the highly stereoselective generation of syn isomer **8**.

In conclusion, we have developed a practical and efficient route for the stereoselective synthesis of TFI and TFV.

(10) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

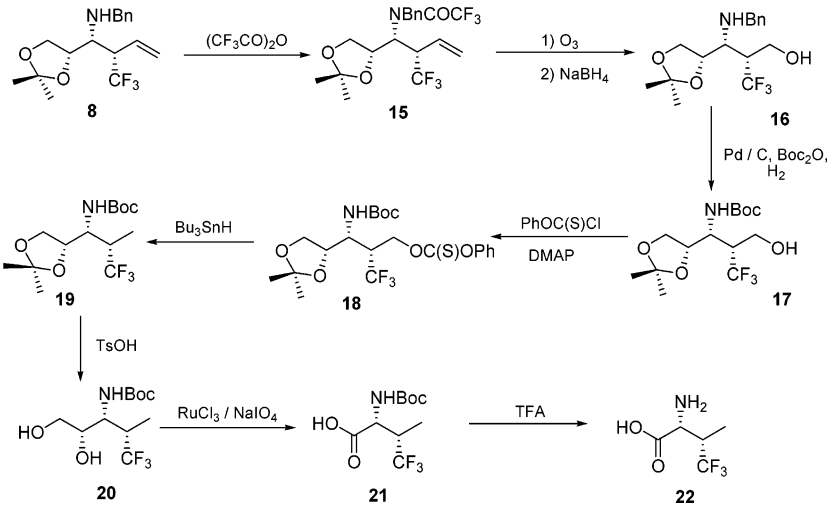
(11) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107.

(12) Konno, T.; Yamazaki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 199.

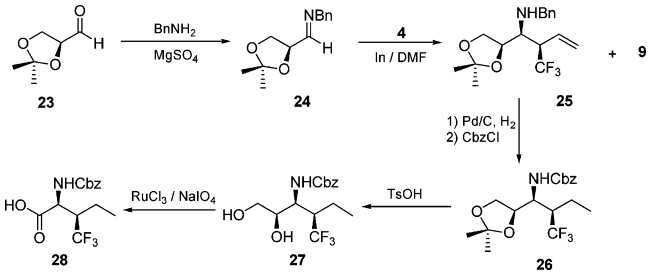
(13) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589.

(14) Bernardi, L.; Ceré, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, *68*, 3348.

SCHEME 5



SCHEME 6



Compared with those reported methods on the synthesis or procurement of racemic or chiral TFI and TFV, the following advantages of our synthetic route are noteworthy: (1) The starting materials could be prepared in large scale. (2) The key indium-mediated allylation reaction was operationally simple and highly stereoselective. (3) The synthesis of β-trifluoromethyl-α-amino acids starting from the trifluoromethylated homoallylic amine was efficient, producing a high yield in a straightforward fashion.

Experimental Section

1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)but-3-en-1-ol (5). To a stirred solution of (*R*)-2,3-*O*-isopropylideneglyceraldehyde **3** (2.7 g, 20.7 mmol) in DMF (35 mL) at room temperature was added 1,1,1-trifluoro-4-bromo-2-butene **4** (6.7 g, 35.5 mmol), followed by indium powder (4.1 g, 35.5 mmol). The resulting mixture was stirred for 48 h at room temperature, treated with 1 N HCl (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to afford **5** (3.24 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00−5.81 (m, 1H), 5.52−5.29 (m, 2H), 4.17−3.71 (m, 4H), 3.22−2.62 (m, 1H), 2.21 (br, 1H), 1.45−1.33 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.97 (d, J = 9.0 Hz, 1.2F), δ −68.12 (d, J = 11.5 Hz, 1.8F); IR (thin film) ν_{max} 3468, 2992, 1375, 1261, 1071, 846 cm^{-1}; MS (ESI) *m*/*z* 241 (M + H)$^+$, 263 (M + Na)$^+$. Anal. Calcd for $C_{10}H_{15}F_3O_3$: C, 50.00; H, 6.29. Found: C, 49.67; H, 6.58.

(1*S*,2*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)but-3-enyl 4-Nitrobenzoate (6a) and (1*R*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)but-3-enyl 4-Nitrobenzoate (6b). A mixture of **5** (177 mg, 0.74 mmol), *p*-nitrobenzoic acid (254 mg, 1.52 mmol), DCC (322 mg, 1.56 mmol), and DMAP (5 mg) in methylene chloride (8 mL) was stirred for 6 h at room temperature. The resulting solid was removed by filtration, and the solvent was evaporated in vacuo. Ether (20 mL) was added to the residue, the additional precipitate of DCU was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30/1) to give **6a** (155 mg, 54%) as a white solid and **6b** (97 mg, 34%) as a clear oil. **6a:** mp 124−125 °C; $[\alpha]^{20}_D$ = +61.7 (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 2H), 8.19 (d, J = 9.0 Hz, 2H), 5.99−5.87 (m, 1H), 5.68−5.55 (m, 3H), 4.22−4.16 (m, 1H), 4.02 (dd, J = 8.7, 5.7 Hz, 1H), 3.89 (dd, J = 8.7, 4.8 Hz, 1H), 3.47−3.35 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.12 (d, J = 9.3 Hz, 3F); IR (thin film) ν_{max} 2989, 1728, 1529, 1348, 1282, 1186, 1112, 1057, 846, 724 cm^{-1}; MS (ESI) *m*/*z* 390 (M + H)$^+$. Anal. Calcd for $C_{17}H_{18}F_3NO_6$: C, 52.45; H, 4.66; N, 3.60. Found: C, 52.68; H, 4.71; N, 3.32. **6b:** $[\alpha]^{20}_D$ = −42.8 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 9.0 Hz, 2H), 5.98−5.86 (m, 1H), 5.67−5.64 (m, 1H), 5.52−5.40 (m, 2H), 4.42−4.36 (m, 1H), 4.10 (dd, J = 8.7, 6.6 Hz, 1H), 3.83 (dd, J = 8.7, 5.7 Hz, 1H), 3.19−3.06 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.46 (d, J = 9.0 Hz, 3F); IR (thin film) ν_{max} 2989, 1728, 1529, 1282, 1186, 1092, 846, 724 cm^{-1}; MS (ESI) *m*/*z* 390 (M + H)$^+$. Anal. Calcd for $C_{17}H_{18}F_3NO_6$: C, 52.45; H, 4.66; N, 3.60. Found: C, 52.19; H, 4.51; N, 3.27.

(1*R*,2*S*)-*N*-Benzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)but-3-en-1-amine (8) and (*E*)-*N*-Benzyl-4,4,4-trifluoro-*N*-((*E*)-4,4,4-trifluorobut-2-enyl)but-2-en-1-amine (9). A mixture of 2,3-*O*-isopropylidene-D-glyceraldehyde (1.05 g, 8.12 mmol), benzylamine (869 mg, 8.12 mmol), and anhydrous $MgSO_4$ (1.47 g, 12.24 mmol) in CH_2Cl_2 (24 mL) was stirred overnight. The white solid was removed by filtration, and the solvent was evaporated in vacuo to afford (*R*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine **7** (1.75 g, 98%), which was used directly in the next step without further purification. To a stirred solution of **7** (1.0 g, 4.6 mmol) in anhydrous DMF (15 mL) at room temperature was added 1,1,1-trifluoro-4-bromo-2-butene **4** (1.72 g, 9.1 mmol), followed by indium powder (780 mg, 6.8 mmol). The resulting mixture was stirred for 15 h at room temperature and then treated with 1 N HCl (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to afford **8** (916 mg, 61%) and **9** (160 mg, 11%). **8:** $[\alpha]^{20}_D$ = −16.1 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.22 (m, 5H), 5.97−5.84 (m,

1H), 5.41−5.32 (m, 2H), 4.36−4.30 (m, 1H), 3.98−3.87 (m, 3H), 3.72−3.68 (m, 1H), 3.28−3.18 (m, 1H), 2.91 (dd, J = 3.9, 2.4 Hz, 1H), 1.70 (br, 1H), 1.38 (s, 3H), 1.33 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.10 (d, J = 9.6 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.9, 129.2, 128.3, 128.1, 127.1, 126.5 (q, J = 168.3 Hz), 122.5, 109.3, 75.4, 66.9, 54.9, 50.9, 50.1 (q, J = 14.7 Hz), 26.3, 25.3; IR (thin film) ν_{max} 3356, 3088, 3031, 2989, 2937, 1456, 1381, 1261, 1125, 850, 742 cm^{-1}; MS (ESI) m/z 330 (M + H)$^+$. Anal. Calcd for $C_{17}H_{22}F_3NO_2$: C, 61.99; H, 6.73; N, 4.25. Found: C, 61.91; H, 6.43; N, 4.15. **9:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37−5.27 (m, 5H), 6.44−6.37 (m, 2H), 5.91−5.79 (m, 2H), 3.61 (s, 2H), 3.20−3.19 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.54 (s, 3F); IR (thin film) ν_{max} 3034, 2928, 1685, 1328, 1122, 981, 741 cm^{-1}; MS (ESI) m/z 324 (M + H)$^+$. Anal. Calcd for $C_{15}H_{15}F_6N$: C, 55.73; H, 4.68; N, 4.33. Found: C, 56.03; H, 4.94; N, 4.08.

(1*R*,2*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)butan-1-amine (10). A mixture of 10% palladium on charcoal (181 mg) and **8** (570 mg, 1.73 mmol) in ethyl acetate (14 mL) was stirred under hydrogen for 4 h at room temperature. Filtration and the removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give **10** (372 mg, 89%) as a yellow oil. **10:** $[\alpha]^{20}_D$ = +2.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26−4.18 (m, 1H), 4.05 (dd, J = 8.1, 6.6 Hz, 1H), 3.73−3.68 (m, 1H), 2.94−2.91 (m, 1H), 2.07−1.94 (m, 1H), 1.75 (dq, J = 14.7, 7.2 Hz, 2H), 1.71 (br, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.01 (d, J = 9.6 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 128.0 (q, J = 281.9 Hz), 109.3, 77.6, 66.8, 52.6, 47.9 (q, J = 23.0 Hz), 26.6, 25.2, 18.8 (q, J = 2.9 Hz), 11.9; IR (thin film) ν_{max} 2988, 2940, 2887, 1373, 1253, 1163, 1064, 861 cm^{-1}; MS (ESI) m/z 242 (M + H)$^+$; HRMS calcd for $C_{10}H_{19}F_3NO_2$, 242.1372; found, 242.1362.

***N*-((1*R*,2*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)butyl)-4-nitrobenzamide (11).** To a suspension of 4-nitrobenzoic acid (100 mg, 0.6 mmol) in methylene chloride (5 mL) was added oxalyl chloride (57 μL) and DMF (10 μL). The resulting suspension was stirred for 2 h at room temperature. The mixture was concentrated. The residue was dissolved in methylene chloride (5 mL) and treated with **10** (144 mg, 0.6 mmol in 2.5 mL methylene chloride) and triethylamine (98 μL). The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with methylene chloride. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 15/1) to give **11** (30 mg, 13%) as a white solid. **11:** mp 122−124 °C; $[\alpha]^{20}_D$ = +34.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 9.0 Hz, 2H), 6.51 (d, J = 9.0 Hz, 1H), 4.60−4.55 (m, 1H), 4.48−4.44 (m, 1H), 4.16−4.10 (m, 1H), 3.72−3.66 (m, 1H), 2.57−2.45 (m, 1H), 1.86−1.74 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.10 (t, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.07 (d, J = 9.9 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.3, 149.8, 139.7, 128.0, 127.5 (q, J = 284.6 Hz), 124.0, 109.8, 74.4, 66.8, 48.6, 46.8 (q, J = 23.8 Hz), 26.4, 24.5, 19.0, 11.8; IR (thin film) ν_{max} 3270, 2925, 1644, 1558, 1351, 1174, 870, 707 cm^{-1}; MS (ESI) m/z 391 (M + H)$^+$; HRMS calcd for $C_{17}H_{21}F_3N_2O_5Na$, 413.1313; found, 413.1295.

Benzyl (1*R*,2*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)butylcarbamate (12). To a stirred solution of **10** (320 mg, 1.33 mmol) in THF (16 mL) was added CbzCl (341 mg, 2.0 mmol), followed by saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give **12** (462 mg, 93%) as a clear oil. **12:** $[\alpha]^{20}_D$ = +28.6 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 5.18−5.08 (m, 3H), 4.33−4.27 (m, 1H), 4.11−4.02 (m, 2H), 3.63 (dd, J = 8.4, 7.2 Hz, 1H), 2.40−2.28 (m, 1H), 1.77−1.67 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.67 (d, J = 9.9 Hz, 3F); IR (thin film) ν_{max} 3452, 3345, 3056, 2988, 2889, 1726, 1512, 1251, 1066, 847, 742 cm^{-1}; MS (ESI) m/z 376 (M + H)$^+$. Anal. Calcd for $C_{18}H_{24}F_3NO_4$: C, 57.59; H, 6.44; N, 3.73. Found: C, 57.99; H, 6.31; N, 3.57.

Benzyl (2*S*,3*R*,4*S*)-1,2-Dihydroxy-4-(trifluoromethyl)hexan-3-ylcarbamate (13). A mixture of **12** (460 mg, 1.23 mmol) and *p*-toluenesulfonic acid monohydrate (233 mg, 1.23 mmol) in methanol (14 mL) was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, 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 **13** (385 mg, 94%) as a white solid. **13:** mp 79−80 °C; $[\alpha]^{20}_D$ = +16.5 (*c* 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.21−5.12 (m, 3H), 4.10−4.04 (m, 1H), 3.94−3.89 (m, 1H), 3.60−3.57 (m, 2H), 2.50−2.45 (m, 1H), 2.19 (br, 2H), 1.76−1.69 (m, 2H), 1.04 (t, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.02 (d, J = 7.9 Hz, 3F); IR (thin film) ν_{max} 3388, 3329, 2974, 2893, 1695, 1504, 1263, 1049, 752, 696 cm^{-1}; MS (ESI) m/z 336 (M + 1). Anal. Calcd for $C_{15}H_{20}F_3NO_4$: C, 53.73; H, 6.01; N, 4.18. Found: C, 53.58; H, 5.88; N, 3.95.

(2*R*,3*S*)-2-(Benzyloxycarbonyl)-3-(trifluoromethyl)pentanoic acid (14). To a stirred mixture of **13** (80 mg, 0.24 mmol) in CCl_4 (1 mL), CH_3CN (1 mL), and H_2O (1.5 mL) at room temperature were added $NaIO_4$ (210 mg, 0.98 mmol) and $RuCl_3 \cdot H_2O$ (2 mg). Stirring was allowed to continue 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 **14** (58 mg, 76%) as a white solid. **14:** mp 90−92 °C; $[\alpha]^{20}_D$ = +0.6 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.27−7.16 (m, 5H), 6.28 (d, J = 9.6 Hz, 1H), 5.04−4.95 (m, 2H), 4.63 (dd, J = 9.3, 3.0 Hz, 1H), 2.88−2.74 (m, 1H), 1.69−1.46 (m, 2H), 0.97 (t, J = 7.8 Hz, 3H); ^{19}F NMR (282 MHz, CD_3COCD_3) δ −61.47 (d, J = 10.7 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 172.2, 158.0, 138.1, 129.6, 129.1, 129.0, 128.6 (q, J = 168.7 Hz), 67.6, 52.6, 48.0 (q, J = 15.6 Hz), 19.7, 12.0; IR (thin film) ν_{max} 3342, 3070 (br), 1725, 1550, 1274, 1145, 1095, 735, 696 cm^{-1}; MS (ESI) m/z 320 (M + H)$^+$; HRMS calcd for $C_{14}H_{16}F_3NO_4Na$, 342.0924; found, 342.0923. Anal. Calcd for $C_{14}H_{16}F_3NO_4$: C, 52.67; H, 5.05; N, 4.39. Found: C, 52.69; H, 5.07; N, 4.16.

***N*-Benzyl-*N*-((1*R*,2*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)but-3-enyl)-2,2,2-trifluoroacetamide (15).** To a stirred solution of **8** (200 mg, 0.60 mmol) in methylene chloride (8 mL) was added trifluoroacetic anhydride (277 mg, 1.32 mmol) dropwise. The reaction mixture was stirred for 1 h at room temperature. The mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give **15** (249 mg, 97%) as a rotamer. **15:** $[\alpha]^{20}_D$ = −1.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 5.51−5.29 (m, 3H), 4.97−4.80 (m, 2H), 4.57−4.31 (m, 2H), 4.06−4.01 (m, 2H), 3.44−3.31 (m, 2H), 1.34−1.19 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.81 (m, 0.37F), −67.41 (s, 2.63F), −68.71 (m, 0.37F), −69.04 (s, 2.63F); IR (thin film) ν_{max} 3034, 2991, 1695, 1453, 1250, 1151, 1074 cm^{-1}; MS (ESI) m/z 426 (M + H)$^+$. Anal. Calcd for $C_{19}H_{21}F_6NO_3$: C, 53.65; H, 4.98; N, 3.29. Found: C, 53.82; H, 5.13; N, 3.27.

(*R*)-2-((*R*)-(Benzylamino)-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl)-3,3,3-trifluoropropan-1-ol (16). Ozone was bubbled through a solution of **15** (240 mg, 0.56 mmol) in methylene chloride (30 mL) at −78 °C. The reaction was monitored by TLC, and

$NaBH_4$ (372 mg, 9.8 mmol) in ethanol (15 mL, 95%) was then added. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with water and extracted with methylene chloride (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give **16** (160 mg, 86%) as a clear oil. **16:** $[\alpha]^{20}_D = -12.0$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 4.55−4.40 (m, 1H), 4.12−3.92 (m, 4H), 3.79−3.69 (m, 2H), 3.05−3.03 (m, 1H), 2.81−2.67 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.79 (d, J = 9.3 Hz, 3F); IR (thin film) ν_{max} 3363, 2989, 1456, 1382, 1054, 857, 741 cm^{-1}; MS (ESI) *m*/*z* 334 $(M + H)^+$. Anal. Calcd for $C_{16}H_{22}F_3NO_3$: C, 57.65; H, 6.65; N, 4.20. Found: C, 57.49; H, 6.80; N, 3.92.

***tert*-Butyl (1*R*,2*R*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3,3-trifluoro-2-(hydroxymethyl)propylcarbamate (17).** A mixture of 10% palladium on charcoal (116 mg), di-*tert*-butyl dicarbonate (131 mg, 0.60 mmol) and **16** (135 mg, 0.41 mmol) in ethyl acetate (10 mL) was stirred under hydrogen for 4 h at room temperature. Filtration and the removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give **17** (140 mg, 100%) as a white solid. **17:** mp 81−82 °C; $[\alpha]^{20}_D = +17.8$ (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, J = 9.9 Hz, 1H), 4.41−4.36 (m, 1H), 4.21−4.15 (m, 1H), 4.11 (dd, J = 12.3, 6.6 Hz, 1H), 3.96−3.80 (m, 2H), 3.73−3.67 (m, 1H), 2.62−2.49 (m, 1H), 1.45 (s, 12H), 1.38 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.42 (d, J = 10.4 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.5, 126.2 (d, J = 169.0 Hz), 110.0, 80.6, 74.9, 67.0, 57.4, 48.6 (q, J = 14.0 Hz), 47.8, 28.2, 26.2, 25.2; IR (thin film) ν_{max} 3297, 2986, 1678, 1559, 1124, 1059 cm^{-1}; MS (ESI) *m*/*z* 366 $(M + Na)^+$; HRMS calcd for $C_{14}H_{24}F_3NO_5Na$, 366.1497; found, 366.1498.

***O*-Benzyl *O*-(*R*)-2-((*R*)-(*tert*-Butoxycarbonyl)-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3,3,3-trifluoropropyl Carbonothioate (18).** To a stirred mixture of **17** (225 mg, 0.66 mmol), pyridine (0.14 mL), and DMAP (18 mg) in methylene chloride (18 mL) at room temperature was added dropwise phenyl chlorothionoformate (227 mg, 1.32 mmol). The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched with water and washed with water and brine. The organic layers was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give **18** (298 mg, 95%) as a clear oil. **18:** $[\alpha]^{20}_D = -9.6$ (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.40 (m, 2H), 7.33−7.26 (m, 1H), 7.12−7.09 (m, 2H), 5.03 (d, J = 9.6 Hz, 1H), 4.91 (dd, J = 12.0, 4.5 Hz, 1H), 4.79 (dd, J = 12.3, 6.6 Hz, 1H), 4.42−4.37 (m, 1H), 4.23 (dd, J = 8.7, 4.8 Hz, 1H), 4.08 (dd, J = 8.4, 7.2 Hz, 1H), 3.74−3.68 (m, 1H), 3.16−3.05 (m, 1H), 1.48 (s, 3H), 1.45 (s, 9H), 1.36 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.52 (d, J = 8.7 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 194.4, 155.4, 153.3, 129.6, 126.7, 125.8 (q, J = 281.8 Hz), 121.8, 109.9, 80.4, 73.9, 68.2, 66.5, 47.9, 45.8 (q, J = 24.9 Hz), 28.3, 26.2, 24.7; IR (thin film) ν_{max} 3453, 2984, 2936, 1718, 1492, 1161, 771 cm^{-1}; MS (ESI) *m*/*z* 502 $(M + Na)^+$; HRMS calcd for $C_{21}H_{28}F_3NO_6SNa$, 502.1487; found, 502.1481.

***tert*-Butyl (1*R*,2*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3,3-trifluoro-2-methylpropylcarbamate (19).** Tributylstannane (0.64 mL, 2.10 mmol) in xylene (12 mL) is added during 12 h to **18** (210 mg, 0.44 mmol) in xylene (6 mL) at 140 °C under nitrogen. After heating for an additional 12 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give **19** (93 mg, 65% yield) as a white solid. **19:** mp 60−61 °C; $[\alpha]^{20}_D = +27.5$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, J = 9.9 Hz, 1H), 4.36−4.31 (m, 1H), 4.03 (dd, J = 8.1, 6.6 Hz, 1H), 3.96−3.91 (m, 1H), 3.67−3.62 (m, 1H), 3.58−3.45 (m, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.34 (s, 3H), 1.21 (d, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.19 (d, J = 9.3 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5, 127.4 (q, J = 280.7 Hz), 109.5, 79.9, 74.1, 66.5, 49.4, 41.2 (q, J = 24.8 Hz), 28.3, 26.2, 24.9, 10.1; IR (thin film) ν_{max} 3383, 2988, 1687, 1533, 1175, 1069, 867 cm^{-1}; MS (ESI) *m*/*z* 350 $(M + Na)^+$; HRMS calcd for $C_{14}H_{25}F_3NO_4$, 328.1733; found, 328.1730.

***tert*-Butyl (2*S*,3*R*,4*S*)-1,1,1-Trifluoro-4,5-dihydroxy-2-methylpentan-3-ylcarbamate (20).** A mixture of **19** (86 mg, 0.26 mmol) and *p*-toluenesulfonic acid monohydrate (24 mg, 0.13 mmol) in methanol (5 mL) was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, 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 **20** (62 mg, 83%) as a white solid. **20:** mp 102−103 °C; $[\alpha]^{20}_D = +18.3$ (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 5.89 (d, J = 9.9 Hz, 1H), 4.20−4.18 (m, 1H), 3.95−3.84 (m, 3H), 3.46 (br, 2H), 2.79−2.64 (m, 1H), 1.42 (s, 9H), 1.24 (d, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, CD_3COCD_3) δ −65.11 (d, J = 9.0 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 156.2, 128.4 (q, J = 280.2 Hz), 78.6, 70.2, 63.2, 50.3, 39.6 (q, J = 24.4 Hz), 27.6, 10.1 (q, J = 3.2 Hz); IR (thin film) ν_{max} 3338, 2926, 1723, 1679, 1270, 1168 cm^{-1}; MS (ESI) *m*/*z* 310 $(M + Na)^+$; HRMS calcd for $C_{11}H_{20}F_3NO_4Na$, 310.1237; found, 310.1236.

(2*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-4,4,4-trifluoro-3-methylbutanoic Acid (21). To a stirred mixture of **20** (87 mg, 0.30 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 $RuCl_3 \cdot H_2O$ (2 mg). Stirring was allowed to continue for 12 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 dissolved in saturated $NaHCO_3$, and the aqueous phase was washed with ethyl acetate, acidified with saturated $NaHSO_4$, and extracted again with ethyl acetate. The organic phase was then dried and evaporated. The residue was recrystallized from petroleum ether to give **21** (58 mg, 71%) as a white solid. **21:** mp 85−86 °C; $[\alpha]^{20}_D = -13.2$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 6.28 (d, J = 9.0 Hz, 1H), 4.75 (dd, J = 9.3, 5.4 Hz, 1H), 3.34−3.22 (m, 1H), 1.65 (s, 9H), 1.47 (d, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, CD_3COCD_3) δ −69.11 (d, J = 9.3 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 170.6, 155.5, 127.4 (q, J = 279.1 Hz), 79.1, 53.2, 40.0 (q, J = 25.4 Hz), 27.5, 10.3 (q, J = 2.5 Hz); IR (thin film) ν_{max} 3370, 2983 (br), 1737, 1643, 1263, 1177, 1026 cm^{-1}; MS (ESI) *m*/*z* 270 $(M - H)^-$; HRMS calcd for $C_{10}H_{16}F_3NO_4Na$, 294.0918; found, 294.0923.

(2*R*,3*S*)-4,4,4-Trifluorovaline (22). To a stirred mixture of **21** (78 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) at room temperature was added CF_3COOH (0.4 mL) dropwise. The mixture was stirred overnight and then concentrated in vacuo to give **22** (49 mg, 100%) as a white solid. **22:** $[\alpha]^{20}_D = -12.1$ (*c* 0.30, 1 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 3.78 (d, J = 4.5 Hz, 1H), 3.04−2.92 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, D_2O) δ −69.17 (d, J = 9.0 Hz, 3F).

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20325210, 20472105), Ministry of Education of China, and Shanghai Municipal Scientific Committee for funding this work.

Supporting Information Available: Experimental procedures and characterization data for compound **25**−**28**, ^{1}H NMR spectra for all compounds, ^{13}C NMR spectra for compounds **8**, **10**, **11**, **14**, **17**−**21**, **25**, and **28**, ^{19}F NMR spectra for compounds **8**, **14**, **21**, **25**, and **28**, and ^{19}F NMR spectrum of analysis for the reaction of compounds **4** and **7**. ORTEP drawing of the X-ray structure of compounds **6a** and **11** and X-ray crystallographic details for compounds **6a** and **11** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0601157