JOC*Note*

Regioselective and Stereoselective Nucleophilic Ring Opening of Trifluoromethylated Cyclic Sulfates: Asymmetric Synthesis of Both Enantiomers of *syn*-(3-Trifluoromethyl)isoserine

Zhong-Xing Jiang[†] 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 College of Chemistry and Chemistry Engineering, Donghua University, 1882 West Yanan Lu, Shanghai 200051, China

flq@mail.sioc.ac.cn

Received February 11, 2004

Abstract: A novel and efficient enantioselective synthesis of both enantiomers of *syn*-(3-trifluoromethyl)isoserine was achieved. Ring opening of trifluoromethylated cyclic sulfates **3**, derived from enantiopure trifluoromethylated vicinal diols **2**, with various nucleophiles occurred exclusively at C2 with inversion of chirality. Treatment of **4c** and **4d**, obtained by nucleophilic opening of **3a** and **3b** with $PhCO_2NH_4$, with $(CF_3SO_2)_2O$ followed by substitution with sodium azide, Jones oxidation, and hydrogenolysis furnished (2*S*,3*S*)-(*N*-benzoyl)-3-(trifluoromethyl)isoserine **9a** and (2*R*,3*R*)-(*N*-benzoyl)-3-(trifluoromethyl)isoserine **9b**, respectively.

β-Amino acids and their derivatives are valuable intermediates in the synthesis of β-lactams, Taxol semisynthetic analogues, and peptidomimetic units.[1] Because of the importance of fluorine-containing molecules in chemical and pharmaceutical research,[2] fluorinated analogues of nonproteinogenic β-amino acids have attracted a great deal of attention in the past few years.[3] Among these fluorine-containing amino acids, a special interest has been put to (3-trifluoromethyl)isoserine. One notable example is that Ojima synthesized a class of novel taxoids with a *syn*-(3-trifluoromethyl)isoserine side chain which exhibited greatly enhanced activities against several different human cancer cell lines as compared to those of paclitaxel and docetaxel, in particular against a drug-resistant breast cancer cell line, MCF 7-R.[4] These trifluoromethylated taxoids were also used by the same author for investigation on the bioactive conformations of taxiods by ^{19}F NMR. The first synthesis of racemic methyl *syn*-(3-trifluoromethyl)isoserine by ring opening of the trifluoromethyl-substituted β-lactam was published in 1996 by Begue et al.[5] Uneyama et al.[6a] and Burger et al.[6b] prepared racemic *anti*-(3-trifluoromethyl)isoserine via intramolecular rearrangement of trifluoromethylated imino ether starting from *N*-acyl-1-chloro-2,2,2-trifluoroethylamine, respectively. However, the synthesis of enantiomerically pure *syn*/*anti*-(3-trifluoromethyl)isoserine required the resolution of racemic aziridines[7] and the separation of diastereoisomeric azetidinones.[8] Therefore, it is of great importance to develop new routes to enantiomerically pure (3-trifluoromethyl)isoserine. Herein, we report a novel and efficient enantioselective synthesis of both enantiomers of *syn*-(3-trifluoromethyl)isoserine based upon regioselective and stereoselective nucleophilic ring opening of trifluoromethylated cyclic sulfates.

Recently, we have reported that the Sharpless asymmetric dihydroxylation (AD) of **1** provided both enantiomers of 1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **2a** and **2b** in good yield and high enantioselectivity, and the resulting diols **2a** and **2b** were converted to sulfates **3a** and **3b** in excellent yield, respectively (Scheme 1).[9] However, the Sharpless AD reaction of **1** proceeded quite slowly (3−4 days) under standard AD conditions due to the strong electron-withdrawing effect of the trifluoromethyl group (Table 1, entries 1 and 2). We were pleased to find that a dramatic increase of the reaction rate can be achieved by doubling the amount of both OsO_4 and ligand (Table 1, entries 3 and 4).[10] Both isomers of high enantiomerically pure 1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **2a** and **2b** can be prepared on a 10 g scale through Sharpless AD reaction of **1**.

In our previous study, it was found that the nucleophilic ring opening of trifluoromethylated cyclic sulfates **3a** and **3b** with NaN_3 occurred exclusively at C2 with clean inversion of C2 followed by acidic hydrolysis to provide **4a** and **4b** respectively (Table 2, entries 1 and 2).[9] These results prompted us to investigate the reaction of **3** with other nucleophiles. As shown in Table 2, nucleophilic ring opening of trifluoromethylated cyclic sulfates **3** in an S_N2 fashion with $PhCO_2^-$ ($PhCO_2NH_4$), $PhthN^-$ (potassium phthalimide), and H^- ($NaBH_4$) were generally carried out for 4 h at 80 °C and followed by acidic hydrolysis to provide **4** in excellent yield except for **4e** and **4f**, which may be due to steric effects of the bulky nucleophile. In every case, nucleophilic substitution

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

(1) (a) Cardilllo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128 and references therein. (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377−386.

(2) (a) *Fluorine-containing Amino Acids, Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; J. Wiley and Sons: New York; 1995. (b) *Biomedical Aspect of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo; Elsevier Biomedical: Amsterdam, 1982. (c) *Asymmetric Fluoroorganic Chemistry, Synthesis, Application and Future Directions*; Ramachandran, P. V., Eds.; American Chemical Society: Washington, DC; 2000. (d) *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsenvier: Amsterdam, 1993.

(3) Brovo, P.; Crucianelli, M.; Ono, T.; Zanda, M. *J. Fluorine Chem.* **1999**, *97*, 27−49 and references therein.

(4) (a) Ojima, I.; Slater, J. C. *Chirality* **1997**, *9*, 487−494. (b) Ojima, I.; Slater, J. C.; Perea, P.; Vieth, J. M.; Abouabdellah, A.; Bégué, J. P.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 133−138.

(5) Abouabdellah, A.; Begue, J. P.; Bonnet-Delpon, D. *Synlett* **1996**, 399−400.

(6) (a) Uneyama, K.; Hao, J.; Amii, H. *Tetrahedron. Lett.* **1998**, *39*, 4079−4082. (b) Setgeeva, N. N.; Golubev, A. S.; Hennig, L.; Burger, K. *Synthesis* **2002**, 2579−2584.

(7) Davoli, P.; Forni, A.; Franciosi, C.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2361−2371.

(8) Abouabdellah, A.; Begue, J. P.; Bonnet-Delpon, D.; Nga, T. T. T. *J. Org. Chem.* **1997**, *62*, 8826−8833.

(9) Jiang, Z. X.; Qin, Y. Y.; Qing, F. L. *J. Org. Chem.* **2003**, *68*, 7544−7547.

(10) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

10.1021/jo0497611 CCC: $27.50
Published on Web 07/03/2004

SCHEME 1

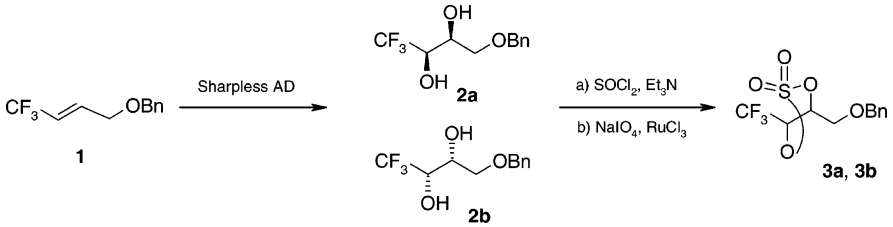


TABLE 1. Sharpless Asymmetric Dihydroxylation of Olefin 1

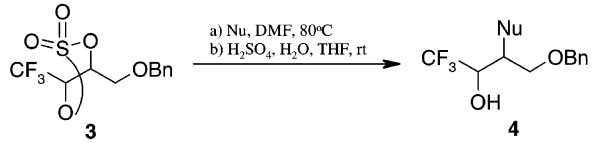
entry	reaction conditions[a]	time (h)	ee[b] (%)	config	product	yield (%)
1	AD-mix-β	72	93	2*S*,3*R*	**2a**	95
2	AD-mix-α	96	93	2*R*,3*S*	**2b**	94
3	(DHQD)PHAL (2% equiv), OsO_4 (0.8% equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv)	48	99.4	2*S*,3*R*	**2a**	96
4	(DHQ)PHAL (2% equiv), OsO_4 (0.8%, equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv)	48	97.5	2*R*,3*S*	**2b**	93

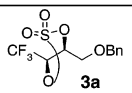
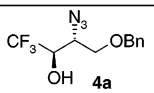
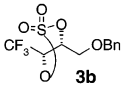
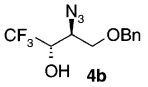
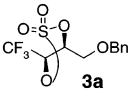
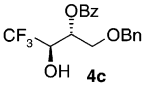
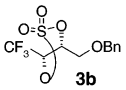
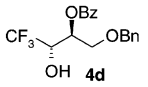
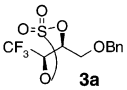
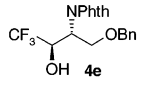
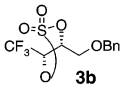
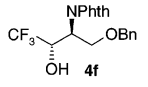
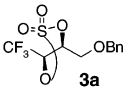
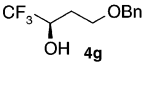
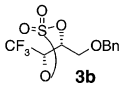
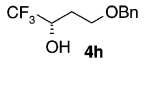
[a] All reactions were carried out in the presence of $MeSO_2NH_2$ (1 equiv) in $H_2O-{}^tBuOH$ at room temperature. [b] Determined by HPLC on Chiralcel OD column.

occurred exclusively at C2 with clean inversion at C2, as only one peak appeared in the ^{19}F NMR of the reaction mixture after acidic hydrolysis. The high regioselectivity is attributed to the strong electron-withdrawing effect of the trifluoromethyl group which destabilizes the transition state for C3 substitution. The structure of **4** was confirmed in many ways. First, it was confirmed by the ^{19}F NMR spectroscopy of **4g**: A doublet peak appeared at −79.80 ppm (J = 8.1 Hz), indicating that the trifluoromethyl group of **4g** is adjacent to a methine group (CH), and not a methylene group (CH_2). Second, we had prepared (2*S*)-2-(*tert*-butoxycarbonyl) amino-4,4,4-trifluorobutanoic acid from **4a** using the radical-based dehydroxylation as the key step.[9] A triplet peak appeared at −65.09 (J = 12.4 Hz) in the ^{19}F NMR spectrum of (2*S*)-2-(*tert*-butoxycarbonyl) amino-4,4,4-trifluorobutanioc acid, which further showed that the trifluoromethyl group of **4** was adjacent to methine group (CH). Furthermore, the absolute configuration of **2** and **4** was determined by comparison the optical rotation data of (2*S*)-2-(*tert*-butoxycarbonyl) amino-4,4,4-trifluorobutanioc acid and (2*S*,3*R*)-4,4,4-trifluorothreonine derived from **4a** with that reported.[9]

With **4c** and **4d** in hand, we sought to apply them to the synthesis of (3-trifluoromethyl)isoserine. The synthesis of (2*S*,3*S*)-*N*-benzoyl-3-(trifluoromethyl)isoserine **9a** commenced with alcohol **4c** (Scheme 2). Alcohol **4c** was treated with trifluoromethanesulfonic anhydride and pyridine at −40 °C to afford trifluoromethanesulfate **5a** in quantitative yield. Exposure of trifluoromethanesulfonate **5a** to sodium azide in dimethyl sulfoxide at 40 °C gave azide **6a** in 94% yield. Removal of the benzyl group with boron trichloride at −78 °C generated primary alcohol **7a** in quantitative yield, which was then oxidized with Jones reagent to give the acid **8a** in good yield. To complete the synthesis of (2*S*,3*S*)-*N*-benzoyl-3-(trifluoromethyl)isoserine **9a**, the azido group had to be reduced to an amino group and the benzoyl group needed to migrate to the amino group. It was anticipated that a migration of the benzoyl group from the oxygen atom to the nitrogen atom would readily occur.[11] As expected,

TABLE 2. Nucleophilic Opening of Cyclic Sulfates 3

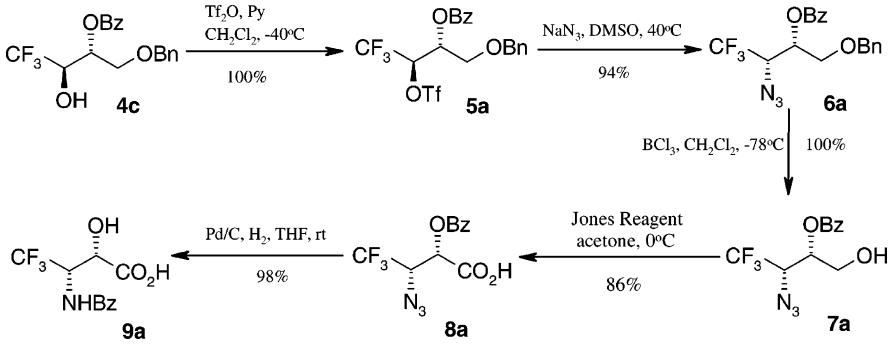


Entry	Substrates	Nucleophiles	Products	Yield (%)
1	 **3a**	NaN_3	 **4a**	96
2	 **3b**	NaN_3	 **4b**	94
3	 **3a**	$PhCO_2NH_4$	 **4c**	100
4	 **3b**	$PhCO_2NH_4$	 **4d**	97
5	 **3a**	PhthNK	 **4e**	70
6	 **3b**	PhthNK	 **4f**	74
7	 **3a**	$NaBH_4$[a]	 **4g**	95
8	 **3b**	$NaBH_4$[a]	 **4h**	98

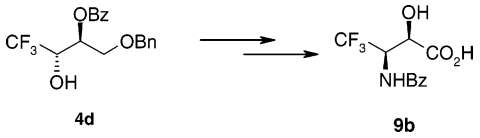
[a] DMAC was used as solvent, at 60 °C.

(11) (a) Bessodes, M.; Abushanab, E.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 5899−5902. (b) Denis, J. N.; Greene, A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 46−50. (c) Gou, D. M.; Liu, Y. C.; Chen, C. S. *J. Org. Chem.* **1993**, *58*, 1287−1289. (d) Bonini, C.; Righi, G. *J. Chem. Soc. Chem. Commun.* **1994**, 2767−2768. (e) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967−9976. (f) Hamamoto, H.; Mamedov, V. A.; Kitamoto, M.; Hayashi, N.; Tsuboi, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4485−4498.

SCHEME 2



SCHEME 3



both the reduction and the migration of the benzoyl group proceeded smoothly under normal palladium catalyzed hydrogenation conditions to give amino acid **9a** in 98% yield from **8a**. The migration of the benzoyl group was confirmed by IR spectroscopy of **9a**: A strong absorption at 1655 cm^{-1} was observed, which is the typical absorption of the amide groups.

The same procedure as described above can smoothly convert **4d** to (2*R*,3*R*)-*N*-benzoyl-3-(trifluoromethyl)isoserine **9b** (Scheme 3).

In summary, we have described an efficient procedure for construction of both enantiomers of trifluoromethylated cyclic sulfates **3**. Nucleophilic ring opening of trifluoromethylated cyclic sulfates **3** with various nucleophiles took place exclusively at C2 with clean inversion of chirality. Both enantiomers of (3-trifluoromethyl)-isoserine were successfully synthesized from the nucleophilic substitution products **4c** and **4d**.

Experimental Section

(2*S*,3*R*)-1-Benzyloxy-4,4,4-trifluoro-2,3-butanediol (2a). To a stirred mixture of *tert*-butyl alcohol (250 mL) and water (250 mL) were added $(DHQD)_2PHAL$ (0.78 g, 2.0 mol %), $K_3Fe(CN)_6$ (49.50 g, 150 mmol), K_2CO_3 (21.00 g, 150 mmol), and OsO_4 (4.00 mL of a 0.1 M solution in toluene, 0.8 mol %) at room temperature. After the solid was dissolved, $MeSO_2NH_2$ (4.75 g, 50 mmol) was added. Then the mixture was cooled to 0 °C. Olefin **1**[9] (10.80 g, 50 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at room temperature for 48 h. Na_2SO_3 was added, and the mixture was stirred for 30 min and then extracted with ethyl acetate. The combined organic layer was washed with 2 N KOH and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **2a** (12.01 g, 96% yield, 99.4% ee): ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.42 (m, 5H), 4.59 (s, 2H), 4.16 (dt, J = 2.1 Hz, 6.0 Hz, 1H), 3.97 (dq, J = 2.1 Hz, 9.0 Hz, 1H), 3.63 (d, J = 6.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.45 (d, J = 9.0 Hz).

(2*R*, 3*S*)-1-Benzyloxy-4,4,4-trifluoro-2,3-butanediol (2b). This compound was prepared from **1** in 93% yield by using the same procedure as described for **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−39 (m, 5H), 4.57 (s, 2H), 4.14 (dt, J = 1.8 Hz, 5.7 Hz, 1H), 3.95 (dq, J = 1.8 Hz, 7.5 Hz, 1H), 3.60 (d, J = 5.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.45 (d, J = 7.5 Hz).

Representative Procedure for the Nucleophilic Ring Opening of Trifluoromethylated Cyclic Sulfates 3. (2*R*,3*R*)-1-Benzyloxy-2-azido-4,4,4-trifluorobutan-3-ol (4a). A solution of cyclic sulfate **3a** (1.80 g, 5.77 mmol) and sodium azide (0.75 g, 11.54 mmol) in DMF (20 mL) was stirred for 4 h at 80 °C. The solvent was carefully removed by distillation under reduced pressure. THF (20 mL), water (54 μL), and sulfuric acid (150 μL) were added, and the resulting suspension was stirred for 1 h. Then $NaHSO_3$ was added. The reaction mixture was stirred for 20 min and filtered on silica gel. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give **4a** (1.53 g, 96%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.42 (m, 5H), 4.62 (s, 2H), 4.18−4.26 (m, 1H), 3.98 (dd, J = 4.2 Hz, 10.2 Hz, 1H), 3.90 (dd, J = 3.3 Hz, 10.2 Hz, 1H), 3.64−3.69 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.90 (d, J = 6.6 Hz).

(2*S*,3*S*)-1-Benzyloxy-2-azido-4,4,4-trifluorobutan-3-ol (4b). This compound was prepared from **3b** in 100% yield by using the same procedure as described for **4a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.39 (m, 5H), 4.58 (s, 2H), 4.10−4.20 (m, 1H), 3.93 (dd, J = 4.9 Hz, 9.4 Hz, 1H), 3.90 (dd, J = 3.1 Hz, 9.4 Hz, 1H), 3.61−3.65 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.53 (d, J = 6.6 Hz).

(2*R*,3*R*)-Benzoic Acid 1-Benzyloxymethyl-3,3,3-trifluoro-2-hydroxypropyl Ester (4c). This compound was prepared from **3a** in 100% yield by using the same procedure as described for **4a**: $[\alpha]^{20}_D$ = −5.14 (*c* 3.315, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08−8.12 (m, 2H), 7.60−7.65 (m, 1H), 7.47−7.52 (m, 2H), 7.33−7.35 (m, 5H), 5.40−5.44 (m, 1H), 4.61 (s, 2H), 4.46−4.50 (m, 1H), 4.06 (dd, J = 3.3 Hz, 10.8 Hz, 1H), 3.92 (dd, J = 3.3 Hz, 11.4 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.73 (d, J = 8.5 Hz); IR (thin film) ν_{max} 3448, 3035, 1719, 1603, 1585, 1497, 1453, 1264, 1145 cm^{-1}. MS (EI) *m*/*z* 354 (M^+, 2), 107 (15), 105 (100), 91 (89), 77 (52), 69 (1). Anal. Calcd for $C_{18}H_{17}O_4F_3$: C, 61.02; H, 4.83. Found: C, 61.47; H, 4.94.

(2*S*,3*S*)-Benzoic Acid 1-Benzyloxymethyl-3,3,3-trifluoro-2-hydroxypropyl Ester (4d). This compound was prepared from **3b** in 97% yield by using the same procedure as described for **4a**: $[\alpha]^{20}_D$ = +5.20 (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.11 (m, 2H), 7.60−7.65 (m, 1H), 7.46−7.52 (m, 2H), 7.31−7.35 (m, 5H), 5.39−5.43 (m, 1H), 4.61 (s, 2H), 4.46−4.50 (m, 1H), 4.06 (dd, J = 3.3 Hz, 10.8 Hz, 1H), 3.92 (dd, J = 3.3 Hz, 11.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.73 (d, J = 8.5 Hz); IR (thin film) ν_{max} 3442, 3035, 1725, 1603, 1586, 1490, 1454, 1279, 1141 cm^{-1}; MS (EI) *m*/*z* 354 (M^+, 1), 107 (14), 105 (100), 91 (87), 77 (48), 69 (1). Anal. Calcd for $C_{18}H_{17}O_4F_3$: C, 61.02; H, 4.83. Found: C, 61.33; H, 4.80.

(2*R*,3*R*)-2-(1-Benzyloxymethyl-3,3,3-trifluoro-2-hydroxypropyl)isoindole-1,3-dione (4e). This compound was prepared from **3a** in 70% yield by using the same procedure as described for **4a**: $[\alpha]^{20}_D$ = −27.2 (*c* 0.750 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84−7.90 (m, 2H), 7.76−7.80 (m, 2H), 7.18−7.26 (m, 5H), 4.89 (qd, J = 6.9 Hz, 2.7 Hz, 1H), 4.63−4.71 (m, 1H), 4.60 (d, J = 12 Hz, 1H), 4.45 (d, J = 12 Hz, 1H), 3.98−4.09 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.49 (d, J = 6.9 Hz); IR (thin film) ν_{max} 3473, 2885, 1778, 1716, 1614, 1498, 1470, 1456, 1390, 1178 cm^{-1}; MS (EI) *m*/*z* 380 (M + 1, <1), 379 (M^+, 1), 174 (100), 146 (2), 107 (7), 91 (94), 77 (11), 69 (1). Anal. Calcd for

$C_{19}H_{16}O_4F_3N$: C, 60.16; H, 4.25; N, 3.69. Found: C, 59.79; H, 4.45; N, 3.53.

(2*S*,3*S*)-2-(1-Benzyloxymethyl-3,3,3-trifluoro-2-hydroxypropyl)isoindole-1,3-dione (4f). This compound was prepared from **3b** in 74% yield by using the same procedure as described for **4a**: $[\alpha]^{20}_D = +26.4$ (*c* 1.100 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.90 (m, 2H), 7.75−7.80 (m, 2H), 7.17−7.27 (m, 5H), 4.89 (qd, J = 6.9 Hz, 2.7 Hz, 1H), 4.65−4.70 (m, 1H), 4.59 (d, J = 12 Hz, 1H), 4.44 (d, J = 12 Hz, 1H), 3.98−4.09 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.49 (d, J = 6.9 Hz); IR (thin film) ν_{max} 3464, 2885, 1777, 1716, 1609, 1498, 1470, 1456, 1389, 1179 cm^{-1}; MS (EI) *m*/*z* 380 (M + 1, 3), 379 (M^+, 2), 174 (95), 147 (60), 107 (7), 91 (100), 77 (17), 69 (1). Anal. Calcd for $C_{19}H_{16}O_4F_3N$: C, 60.16; H, 4.25; N, 3.69. Found: C, 60.49; H, 4.10; N, 4.07.

(3*R*)-4-Benzyloxy-1,1,1-trifluorobutan-2-ol (4g). This compound was prepared from **3a** in 95% yield by using the same procedure as described for **4a** (DMAC was used as solvent, at 60 °C): $[\alpha]^{20}_D = -14.4$ (*c* 0.825 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.41 (m, 5H), 4.56 (s, 2H), 4.18−4.24 (m, 1H), 3.79−3.86 (m, 1H), 3.68−3.75 (m, 1H), 1.91−2.09 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.80 (d, J = 8.1 Hz); IR (thin film) ν_{max} 3413, 2874, 1497, 1456, 1278, 1170 cm^{-1}; MS (EI) *m*/*z* 234 (M^+, 7), 107 (65), 91 (100), 69 (2). Anal. Calcd for $C_{11}H_{13}O_2F_3$: C, 56.41; H, 5.60. Found: C, 56.83; H, 5.98.

(3*S*)-4-Benzyloxy-1,1,1-trifluorobutan-2-ol (4h). This compound was prepared from **3b** in 98% yield by using the same procedure as described for **4a** (DMAC was used as solvent, at 60 °C): $[\alpha]^{20}_D = +14.5$ (*c* 1.030 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.41 (m, 5H), 4.55 (s, 2H), 4.17−4.23 (m, 1H), 3.78−3.85 (m, 1H), 3.67−3.74 (m, 1H), 1.90−2.07 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.09 (d, J = 8.1 Hz); IR (thin film) ν_{max} 3413, 2874, 1497, 1456, 1278, 1170 cm^{-1}; MS (EI) *m*/*z* 234 (M^+, 17), 107 (28), 91 (100), 69 (1); HRMS (EI) calcd for $C_{11}H_{13}O_2F_3$ 234.08677, found 234.08804.

(2*R*,3*R*)-Benzoic Acid 1-Benzyloxymethyl-3,3,3-trifluoro-2-trifluoromethanesulfinyloxypropyl Ester (5a). To a stirred solution of **4c** (1.42 g, 4 mmol) and pyridine (0.63 g, 8 mmol) in methylene chloride (25 mL) at −40 °C was added dropwise trifluoromethanesulfonic anhydride (1.24 g, 4.4 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 1 h at −40 °C. The solution was then washed with brine. After the layers were separated, the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 25:1) to give **5a** (1.95 g, 100%): $[\alpha]^{20}_D = +13.4$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−8.09 (m, 2H), 7.62−7.67 (m, 1H), 7.47−7.52 (m, 2H), 7.32−7.33 (m, 5H), 5.75 (q, J = 4.9 Hz, 1H), 5.57 (qd, J = 4.9 Hz, 6.0 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H) 3.87 (d, J = 4.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.09 (m, 3F), −74.16 (m, 3F); IR (thin film) ν_{max} 3036, 1734, 1604, 1587, 1497, 1454, 1263, 1199, 1139 cm^{-1}; MS (EI) *m*/*z* 486 (M^+, 6), 379 (49), 107 (29), 105 (100), 91 (86), 77 (36), 69 (7). Anal. Calcd for $C_{19}H_{16}O_6F_6S$: C, 46.92; H, 3.32. Found: C, 46.96; H, 3.30.

(2*S*,3*S*)-Benzoic Acid 2-Azido-1-benzyloxymethyl-3,3,3-trifluoropropyl Ester (6a). A solution of **5a** (1.70 g, 3.5 mmol) and sodium azide (455 mg, 7.0 mmol) in DMSO (15 mL) was stirred for 6 h at 40 °C. The resulting suspension was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) to give **6a** (1.25 g, 94%): $[\alpha]^{20}_D = +12.5$ (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−8.07 (m, 2H), 7.58−7.64 (m, 1H), 7.42−7.50 (m, 2H), 7.31−7.34 (m, 5H), 5.71 (qd, J = 5.4 Hz, 2.7 Hz, 1H), 4.57−4.66 (m, 2H), 4.26 (ddd, J = 3.0 Hz, 7.2 Hz, 14.7 Hz, 1H), 3.72−3.81 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.77 (d, J = 5.4 Hz); IR (thin film) ν_{max} 2119, 1731, 1602, 1587, 1496, 1454, 1266, 1108 cm^{-1}; MS (EI) *m*/*z* 380 (M^+, 1), 216 (22), 107 (3), 105 (100), 91 (70), 77 (24), 69 (2). Anal. Calcd for $C_{18}H_6O_3F_3N_3$: C, 56.99; H, 4.25; N, 11.08. Found: C, 56.91; H, 4.21; N, 10.86.

(2*S*,3*S*)-Benzoic Acid 2-Azido-3,3,3-trifluoro-1-hydroxymethylpropyl Ester (7a). To a stirred solution of **6a** (1.20 mg, 3.15 mmol) in anhydrous methylene chloride (60 mL) at −78 °C was added dropwise boron trichloride (6.30 mL of 1 M solution in methylene chloride, 6.30 mmol). The reaction mixture was stirred for 2 h at −78 °C, and then methanol (8 mL) was added. The solution was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to give **7a** (910 mg, 100%): $[\alpha]^{20}_D = +6.5$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−8.07 (m, 2H), 7.59−7.65 (m, 1H), 7.45−7.51 (m, 2H), 5.56−5.61 (m, 1H), 4.26 (qd, J = 6.9 Hz, 3.0 Hz, 1H), 4.00 (dd, J = 11.4 Hz, 2.7 Hz, 1H), 3.90 (dd, J = 11.4 Hz, 7.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.72 (d, J = 6.9 Hz); IR (thin film) ν_{max} 3456, 2121, 1727, 1603, 1454, 1272, 1143 cm^{-1}; MS (EI) *m*/*z* 290 (M + 1, 4), 272 (8), 123 (11), 105 (100), 77 (23), 69 (2). Anal. Calcd for $C_{11}H_0O_3F_3N_3$: C, 45.68; H, 3.49; N, 14.53. Found: C, 45.56; H, 3.58; N, 14.53.

(2*S*,3*S*)-Benzoic Acid 2-Azido-1-carboxy-3,3,3-trifluoropropyl Ester (8a). To a mixture of **7a** (549 mg, 1.9 mmol) in acetone (60 mL) at 0 °C was added Jones reagent (1 M, 15 mL, 15 mmol). The mixture was stirred for 20 min at 0 °C under nitrogen. The reaction was quenched with isopropyl alcohol (7 mL) and then diluted with water (60 mL) and ethyl acetate (60 mL). The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to give **8a** (495 mg, 86%): $[\alpha]^{20}_D = -22.9$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−8.12 (m, 2H), 7.62−7.68 (m, 1H), 7.48−7.53 (m, 2H), 5.91 (d, J = 2.4 Hz, 1H), 4.40 (qd, J = 7.2 Hz, 2.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.62 (d, J = 7.2 Hz); IR (thin film) ν_{max} 3300, 2120, 1729, 1603, 1454, 1266, 1145 cm^{-1}; MS (EI) *m*/*z* 303 (M^+, 1), 284 (1), 105 (100), 77 (28) 69 (3); HRMS (EI) calcd for $C_{11}H_8O_4F_3N_3$ 303.04669, found 303.04698.

(2*S*,3*S*)-3-Benzoylamino-4,4,4-trifluoro-2-hydroxybutyric Acid (9a). A mixture of 10% palladium on charcoal (73 mg) and **8a** (364 mg, 1.2 mmol) in THF (15 mL) was stirred under hydrogen at room temperature for 16 h. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to give **9a** (326 mg, 98%): $[\alpha]^{20}_D = -14.9$ (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−8.05 (m, 2H), 7.57−7.61 (m, 1H), 7.45−7.50 (m, 2H), 5.19−5.20 (m, 1H), 4.98−5.02 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.53 (d, J = 5.0 Hz); IR (thin film) ν_{max} 3350, 1734, 1655, 1603,1523, 1491,1454, 1268, 1135 cm^{-1}; MS (EI) *m*/*z* 277 (M^+, 1), 259 (7), 239 (26), 202 (5), 105 (100), 77 (47) 69 (5); HRMS (ESI) calcd for $C_{11}H_{10}O_4F_3NNa$ 300.04541, found 300.04516.

Acknowledgment. We thank the National Natural Science Foundation of China, Ministry of Education of China, and Shanghai Municipal Scientific Committee for funding this work.

Supporting Information Available: Experimental procedures and characterization data for **5b**, **6b**, **7b**, **8b**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0497611