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Asymmetric Synthesis of Four Isomers of 2-*C*-Trifluoromethylerythritol

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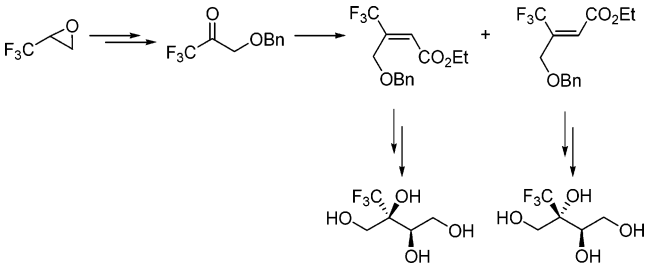
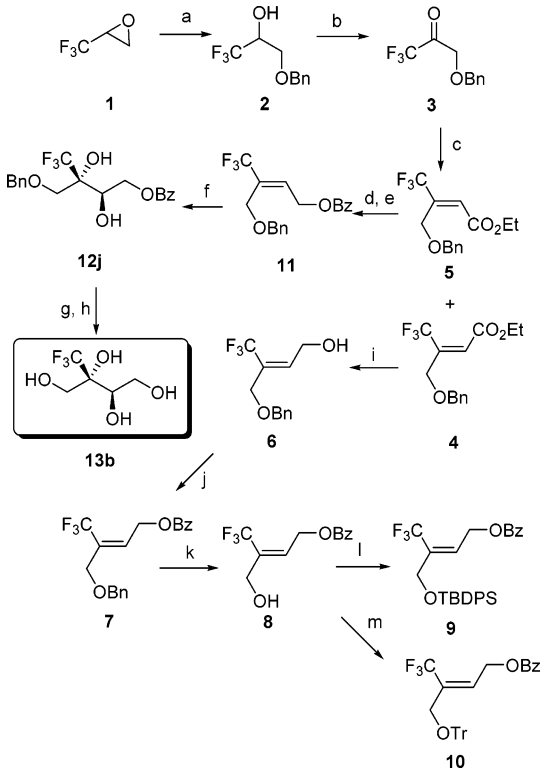


Optically active 2-*C*-trifluoromethylerythritols, analogues of 2-*C*-methylerythritol, which is a key intermediate in the biosynthesis of isoprenoid with a mevalonate-independent route, were conveniently synthesized from 1,1,1-trifluoro-2,3-epoxypropane.

Isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) are important intermediates in the terpenoid biosynthesis. Many studies have accumulated evidence for their existence in Gram-negative bacteria, algae, and plant chloroplasts of a mevalonate-independent pathway (MIP) for the biosynthesis of terpenoids.[1] MIP does not exist in mammals; therefore, it can be a useful target for screening herbicides, antibacterial[2] and antimalarial drugs.[3] The replacement of a methyl group by trifluoromethyl (CF_3) in bioactive compounds has provided many valuable analogues.[4] The introduction of fluorine atoms to organic compounds often results in a dramatic change of their physical, chemical, and biological properties.[5] Therefore, the development of a synthetic methodology for fluorinated 2-*C*-methylerythritol is significant for further studies on MIP. To our knowledge, there is no report concerning the synthesis of fluorinated 2-*C*-methylerythritol analogue. Herein, we wish to present the preparation of 2-*C*-trifluoromethylerythritol.

SCHEME 1[a]



[a] Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, BnOH, 45 °C, 65%; (b) Dess−Martin reagent, rt, 77%; (c) (carbethoxymethyl)triphenylphosphonium bromide, Et_3N, rt, 87% (*E*/*Z* 2:1); (d) DIBAL-H, 0 °C, 87%; (e) BzCl, Et_3N, 89%; (f) 1 mol % of OsO_4, 5 mol % of $(DHQD)_2PHAl$, 1 equiv $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, rt, 78%; (g) K_2CO_3, MeOH, 94%; (h) Pd/C, H_2, MeOH, quant; (i) DIBAL-H, 0 °C, 91%; (j) BzCl, Et_3N, rt, 86%; (k) BCl_3, CH_2Cl_2, MeOH, −78°C, 78%; (l) TBDPSCl, imidazole, DMF, 76%; (m) trityl chloride, 2,6-lutidine, CH_2Cl_2, 87%.

Our first attempt to synthesize 2-*C*-trifluoromethylerythritol is outlined in Scheme 1. The reaction of trifluorooxacylopropane (**1**) with benzyl alcohol gave 3-benzyloxy-1,1,1-trifluoropropan-2-ol (**2**) in 65% yield.[6] Compound **2** was further oxidized by Dess−Martin reagent to provide the 3-benzyloxy-1,1,1-trifluoropropan-2-one (**3**) in 77% yield.[7] Compound **3** reacted with (carbethoxymethyl)triphenylphosphonium bromide to form CF_3-substituted olefin as a pair of isomers **4** and **5** in a 1:2 ratio, which were separable by chromatography. The *E*-isomer **5** was reduced with DIBAL-H to provide the allylic alcohol. Followed by the protection of hydroxyl group with BzCl, intermediate **11** was obtained in 89% yield.

Poulter has reported the synthesis of 4-diphosphocytidyl-2-*C*-methyl-D-erythritol.[8] Using that process, the enantioselective target molecule was obtained in 50% ee after the dihydroxylation of allylic phosphate. Optimizing the reaction conditions indicated that 1 mol % of OsO_4, 5 mol % of ligand, 1 equiv $MeSO_2NH_2$, and room temperature were essential for the asymmetric

(1) (a) Flesch, G.; Rohmer, M. *Eur. J. Biochem.* **1988**, *175*, 405−411. (b) Rohmer, M.; Knani, M.; Simonin, P.; Sutter, B.; Sahm, H. *Biochem. J.* **1993**, *295*, 517−524. (c) Lichtenthaler, H. K.; Schwender, J.; Disch, A.; Rohmer, M. *Biochem. J.* **1996**, *316*, 73−80.

(2) Takahashi, S.; Kuzuyama, T.; Watanabe, H.; Seto, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9879−9884.

(3) Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Turbachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati D.; Beck, E. *Science* **1999**, *285*, 1573−1576.

(4) (a) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H.; Tong, W. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 2899−2901. (b) Rivkin, A.; Biswas, K.; Chou, T. C.; Danishefsky, S. J. *Org. Lett.* **2003**, *4*, 4081−4084.

(5) (a) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994. (b) Welch, J. T.; Eswaraksrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996.

(6) Sznaidman, M. L.; Beauchamp, L. M. *Nucleosides Nucleotides* **1996**, *15*, 1315−1321.

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TABLE 1. Substituent Influence on the Asymmetric Dihydroxylation[a]

entry	substrate	ligand	product	yield (%)	ee[c] (%)
1	**6**	$(DHQD)_2PHAl$	**12c**	81	<5
2	**8**	$(DHQD)_2PHAl$	**12e**	76	<5
3	**9**	$(DHQD)_2PHAl$	**12f**	81	<5
4	**10**	$(DHQD)_2PHAl$	**12g**	83	<5
5	**7**	$(DHQD)_2PHAl$	**12d**	81	27
6	**4**	$(DHQD)_2PHAl$	**12a**[b]	81	86
7	**4**	$(DHQ)_2PHAl$	**12b**	77	55
8	**5**	$(DHQD)_2PHAl$	**12h**	87	83
9	**5**	$(DHQ)_2PHAl$	**12i**	79	50

[a] Reaction are performed with 1 mol % of OsO_4 and 5 mol % of $(DHQD)_2PHAl$ catalyst at room temperature. [b] ee value of **12a** was measured as 99% after one-step recrystallization from hexane. [c] Determined by HPLC analysis.

dihydroxylation of **11** to **12j**. Otherwise, the reaction proceeded rather slowly. Under these conditions, **12j** was obtained in 81% yield, though disappointingly with less than 5% ee. Finally, the deprotection of **12j** gave the racemic **13b** in 94% yield. To increase the selectivity of the asymmetric dihydroxylation, a new strategy was discussed for the preparation of 2-*C*-trifluoromethylerythritol. First, we studied the influence of different protecting groups on the dihydroxylation of the olefins. A series of CF_3-substituted olefins were synthesized according to Scheme 1, and a modified procedure was used for the preparation of **12**. The preliminary results of the asymmetric dihydroxylation are summarized in Table 1.[9]

The dihydroxylation of **4**−**10** gave **12a**−**i** in 76−87% yields (Table 1). The hydroxy protecting groups have no significant influence on the enantioselectivity when the hydroxy group is at the position α to the CF_3 (entries 2−4). However, the protecting group for the *β*-OH the affects ee value considerably (entries 5 and 6). For instance, the ee value of **12c** where the hydroxyl is unprotected is less than 5% (entries 1 and 5), and it was increased to 27% upon protection with BzCl. Replacing $-CH_2OBz$ moiety with an ester group further improved the enantioselectivity from 27% ee to 86% ee (entries 5 and 6).

Wipf and co-workers have described an asymmetric dihydroxylation of (*E*)-benzyl-2-(trifluoromethyl)but-2-enoate with 73% ee.[10] Presently, this is the only example for the asymmetric dihydroxylation of olefin where both CF_3 and ester groups attached to the same sp^2 carbon atom. In general, the dihydroxylation is difficult due to the electron-withdrawing nature of both the CF_3 and ester groups.

To synthesize the other two isomers of **12a**,**b**, both **4** and **5** were chosen as the substrates and $(DHQ)_2PHAl$ was used instead of $(DHQD)_2PHAl$. As a result, both **12h** and **12i** were obtained in ca. 87% and 79% yields, with 83% ee and 50% ee, respectively (Table 1).

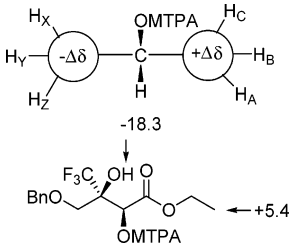
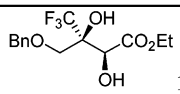
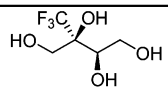
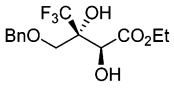
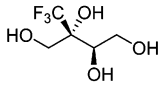
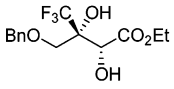
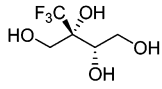
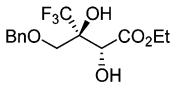
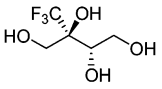


FIGURE 1. Model used to determine the absolute configuration of **12a** and Δδ values ($\delta_S - \delta_R$) obtained for the MTPA ester (300 MHz).

TABLE 2. Results of Deprotection

substrate	product	yield(%)
 **12a**	 **13a**	81
 **12b**	 **13b**	92
 **12h**	 **13c**	94
 **12i**	 **13d**	89

The absolute configuration of **12a** was determined by a single-crystal X-ray diffraction study[11] and the Mosher ester method.[12] The (*R*)- and (*S*)-MTPA derivatives of **12a** were prepared by the treatment of **12a** with (*R*)- and (*S*)-2-methoxy-2-phenyl-2-trifluoromethylacetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2. The Δδ values ($\delta_S - \delta_R$) are summarized and labeled in Figure 1. According to the Δδ, the absolute configuration of **12a** was deduced as (2*S*, 3*R*). These results are in agreement with Sharpless' rule.[9c]

Reduction of **12a** with $LiAlH_4$[13] and then palladium-catalyzed hydrogenation[14] provided the desired product **13a** as an oil. The other three isomers (**13b**, **13c**, and **13d**) were prepared using the same procedure (Table 2).

In conclusion, we have developed an efficient synthesis of 2-*C*-trifluoromethylerythritols from 1,1,1-trifluoro-2,3-epoxypropane. The four stereoisomers were obtained in good yields by an improved asymmetric dihydroxylation with moderate to high ee.

Experimental Section

3-Benzyloxy-1,1,1-trifluoropropan-2-one (3). To a well-stirred solution of 3-benzyloxy-1,1,1-trifluoropropan-2-ol (2.18 g, 10 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin (DM) reagent

(7) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Yoshichika, K.; Yuko, S.; Katsuhiko, I. *Org. Lett.* **2001**, *3*, 457−460. (c) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661−668. (d) Kimura M.; Yamazaki T.; Kitazume T.; Kubota T. *Org. Lett.* **2004**, *6*, 4651−4654

(8) (a) Koppisch, A. T.; Poulter, C. D. *J. Org. Chem.* **2002**, *67*, 5416−5418. (b) Koppisch, A. T.; Blagg, B. S. J.; Poulter, C. D. *Org. Lett.* **2000**, *2*, 215−217.

(9) (a) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079−2082. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278−1291. (c) Kolb, H. C.; VamNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(10) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088−6089.

(11) See the Supporting Information. Crystallographic data of **12a** has been deposited with the Cambridge Crystallographic Centre as CCDC 253465. Copies of the data can be obtained, free of charge, via the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K., e-mail: deposit@ccdc.cam.ac.uk.

(12) (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147. (b) Xiao, L.; Yamazaki, T.; Kitazume, T.; Yonezawa, T.; Sakamoto, Y.; Nogawa, K. *J. Fluorine Chem.* **1997**, *84*, 19−23.

(13) Seebach, D.; Eberle, M. *Synthesis* **1986**, 37−40.

(14) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746−1757.

(5.58 g, 13 mmol). The reaction mixture was stirred at room temperature for 5 h and then diluted with CH_2Cl_2 (30 mL) and poured into a solution of $Na_2S_2O_3$ (0.26 M) in a saturated solution of $NaHCO_3$ (50 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and water (2 × 30 mL). The combined aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The organic phase was combined, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure,, and the residue was purified by a distillation under reduced pressure to afford **3** as a colorless liquid in 77% yield along with a small amount of hydrate (8.8%): bp 45−47 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.53 (s, 2H), 4.70 (s, 2H), 7.28−7.39 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −78.1 (s); ^{13}C NMR ($CDCl_3$) δ 69.9 (s), 73.6 (s), 115.3 (q, J = 292.3 Hz), 128.1 (s), 128.5 (s), 128.7 (s), 136.1 (s) 188.4 (q, J = 34.9 Hz); MS (EI) m/z 218 (M^+, 3.8), 91 ($C_7H_7^+$, 100.0).

2-Benzyloxymethyl-1,1,1-trifluorobut-3-enoic Acid Ethyl Ester (*Z*/*E*) (4/5). To a solution of **3** (2.20 g, 10 mmol) in benzene (20 mL) were added (carbethoxymethyl)triphenylphosphonium bromide (4.29 g, 10 mmol) and Et_3N (2.02 g, 20 mmol). The reaction mixture was stirred at room temperature for 6 h, diluted with 50 mL of petroleum ether, and stirred for a further 30 min. The triphenylphosphine oxide was filtered off, and the filtrate was concentrated in a vacuum. The residue was purified on silica gel (PE/EtOAc = 100/1) to give **5** (R_f = 0.5, 1.393 g) and **4** (R_f = 0.45, 0.712 g) in 87% total yield as a colorless liquid.

4: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.2 Hz), 4.19 (t, 2H, J = 0.5 Hz), 4.25 (q, 2H, J = 7.2 Hz), 4.62 (s, 2H), 6.50 (t, 1H, J = 2.0 Hz), 7.33∼7.39 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 63.4 (s); ^{13}C NMR ($CDCl_3$) δ 13.9 (s), 61.5 (s), 66.4 (q, J = 3.5 Hz), 73.1 (s), 122.0 (q, J = 273.8 Hz), 125.2 (q, J = 3.7 Hz), 127.7 (s), 128.1 (s), 128.6 (s), 135.3 (q, J = 30.9 Hz), 137.0 (s), 164.6 (s); IR (thin film) ν_{max} 3066, 2987, 1740, 1455, 1268 cm^{-1}; MS (EI) m/z 289 (M^+ + 1, 6.7), 259 (M^+ − C_2H_5, 0.6), 91 ($C_7H_7^+$, 100.0). Anal. Calcd for $C_{14}H_{15}O_3F_3$: C, 58.33; H, 5.21. Found: C, 58.21; H, 5.25.

5: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 4.25 (q, 2H, J = 7.2 Hz), 4.80 (s, 2H), 4.86 (s, 2H), 6.53 (t, 1H, J = 0.6 Hz), 7.28∼7.39 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 67.5 (s); ^{13}C NMR ($CDCl_3$) δ 14.0 (s), 61.4 (s), 62.6 (s), 73.1 (s), 122.8 (q, J = 273.9 Hz), 125.9 (q, J = 6.9 Hz), 127.8 (s), 127.83 (s), 128.4 (s), 137.5 (s), 140.3 (q, J = 29.1 Hz), 164.2 (s); IR (thin film) ν_{max} 2987, 1731, 1307, 1207, 1180 cm^{-1}; MS (EI) m/z 289 (M^+ + 1, 8.2), 259 (M^+ − C_2H_5, 0.6), 91 ($C_7H_7^+$, 100.0). Anal. Calcd for $C_{14}H_{15}O_3F_3$: C, 58.33; H, 5.21. Found: C, 58.04; H, 5.30.

(*Z*)-2-Benzyloxymethyl-1,1,1-trifluorobut-3-en-4-ol (6). A solution of DIBAL-H (1 M in toluene, 4.4 mL) was slowly added to a well-stirred solution of **4** (576 mg, 2 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched with HCl (1 M, 5 mL). The mixture was stirred for 30 min, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified on silica gel (PE/EtOAc = 7:1, R_f = 0.3) to afford **6** (422 mg, 87% yield) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.83−2.02 (m, 1H), 4.11 (s, 2H), 4.46 (s, 2H), 4.54 (s, 2H), 6.25 (t, 1H, J = 5.8 Hz), 7.29−7.40 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 61.1 (s); ^{13}C NMR ($CDCl_3$) δ 58.9 (q, J = 2.7 Hz), 68.3 (q, J = 2.7 Hz), 72.6 (s), 123.2 (q, J = 274.1 Hz), 126.7 (q, J = 27.9 Hz), 127.7 (s), 127.9 (s), 128.9 (s), 137.5 (s), 139.5 (q, J = 3.5 Hz); IR (thin film) υ_{max} 3387, 2929, 1456, 1387, 1170 cm^{-1}; MS (EI) m/z 246 (M^+, 0.9), 91 ($C_7H_7^+$, 100.0). Anal. Calcd for $C_{12}H_{13}O_2F_3$: C, 58.54; H, 5.28. Found: C, 58.47; H, 5.34.

(*Z*)-Benzoic Acid 2-Benzyloxymethyl-1,1,1-trifluorobut-3-enyl Ester (7). To a solution of **6** (492 mg, 2 mmol) and BzCl (214 mg, 2 mmol) in CH_2Cl_2 (4 mL) was slowly added Et_3N (404 mg, 2 mmol) at 0 °C in 30 min. The reaction mixture was stirred for 4 h, diluted with 10 mL of CH_2Cl_2, and washed with water (3 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated in a vacuum. The residue was purified on silica gel (PE/EtOAc = 4/1, R_f = 0.4) to afford **7** (624 mg, 89% yield) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2H), 4.59 (s, 2H), 5.16 (q, 2H, J = 2.4 Hz), 6.32 (t, 1H, J = 6.0 Hz), 7.30−7.37 (m, 5H), 7.48 (t, 2H, J = 7.8 Hz), 7.63 (t, 1H, J = 6.9 Hz), 8.09 (d, 2H, J = 8.1 Hz); ^{19}F NMR ($CDCl_3$) δ 61.5 (s); ^{13}C NMR ($CDCl_3$) δ 60.9 (s), 67.9 (q, J = 3.2 Hz), 72.7 (s), 123.3 (q, J = 274.8 Hz), 127.9 (s), 128.0 (s), 128.3 (s), 128.6 (s), 129.8 (s), 133.1 (s), 133.4 (s), 133.8 (q, J = 7.1 Hz), 137.3 (s), 166.2 (s); IR (thin film) ν_{max} 3067, 2868, 1725, 1453, 1276 cm^{-1}; MS (EI): m/z 244 (M^+ − 106). Anal. Calcd for $C_{19}H_{17}O_3F_3$: C, 65.14; H, 4.86. Found: C, 65.31; H, 5.04.

(*Z*)-Benzoic Acid 1,1,1-Trifluoro-2-hydroxymethylbut-3-enyl Ester (8). A solution of BCl_3 in *n*-hexane (1 M) was added to mixture of **7** (350 mg, 1 mmol) in CH_2Cl_2 at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and quenched with methanol. The reaction mixture was allowed to warm to ambient temperature, and 5 mL of 5% aq $NaHCO_3$ was carefully added. After being washed with water (3 × 10 mL), the organic phase was dried over Na_2SO_4 and concentrated in a vacuum. The residue was purified on silica gel (PE/EtOAc = 4:1, R_f = 0.4) to afford **8** (202 mg, 78% yield) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 1H), 4.33 (s, 2H), 5.14 (q, 2H, J = 2.4 Hz), 6.31 (t, 1H, J = 6.0 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.60 (t, 1H, J = 6.9 Hz), 8.07 (d, 2H, J = 7.2 Hz); ^{19}F NMR ($CDCl_3$) δ −61.4 (s); ^{13}C NMR ($CDCl_3$) δ 60.9 (q, J = 2.9 Hz), 61.2 (t, J = 2.4 Hz), 123.8 (q, J = 280.3 Hz), 128.5 (s), 129.7 (s), 130.4 (s), 132.5 (q, J = 1.7 Hz), 133.4 (s), 166.3 (s); IR (thin film) ν_{max} 3434, 1724, 1603, 1278 cm^{-1}; MS (EI) m/z 260 (M^+, 3.9). Anal. Calcd for $C_{12}H_{11}O_3F_3$: C, 55.39; H, 4.26. Found: C, 55.55; H, 4.30.

(*Z*)-Benzoic Acid 2-(*tert*-Butyldiphenyl-ilanyloxymethyl)-1,1,1-trifluorobut-3-enyl Ester (9). To a well-stirred solution of **8** (160 mg, 0.62 mmol) and imidazole (64 mg, 0.94 mmol) in 2 mL of DMF was added TBDPSCl (205 mg, 0.74 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), the reaction was quenched with 5 mL of water. The mixture was stirred for 30 min, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel (PE/EtOAc = 100:1 R_f = 0.4) to afford **9** (233 mg, 76% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 2H), 5.10−5.13 (m, 2H), 6.34 (t, 1H, J = 6.0 Hz), 7.7.237.46 (m, 8H), 7.567.64 (m, 1H), 7.647.68 (m, 4H), 8.058.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 61.9 (s), 60.8 (q, J = 2.4 Hz), 61.7 (q, J = 2.3 Hz), 123.3 (q, J = 274.4 Hz), 128.4 (s) 128.8 (s), 129.7 (s), 129.9 (s), 130.0 (s), 130.4 (s), 130.8 (s), 131.1 (q, J = 6.4 Hz), 131.6 (s), 132.8 (s), 133.2 (s), 135.5 (s), 166.1 (s); ^{19}F NMR ($CDCl_3$) δ −61.5 (s); IR (thin film) ν_{max} 3074, 2934, 1727, 1429, 1274, 1115 cm^{-1}; MS (EI) m/z 441 (M^+ − 57, 3.7). Anal. Calcd for $C_{28}H_{29}O_3F_3$: C, 67.47; H, 5.82. Found: C, 67.44; H, 5.83.

(*Z*)-Benzoic Acid 1,1,1-Trifluoro-2-trityloxymethylbut-3-enyl Ester (10). To a well-stirred solution of **8** (160 mg, 0.62 mmol) and trityl chloride (259 mg, 0.94 mmol) in 2 mL of CH_2Cl_2 was added 1 mL of 2,6-lutidine at 0 °C in 30 min. The reaction mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 5 mL of water. The mixture was stirred for 30 min and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried with Na_2SO_4 and concentrated. The residue was subjected to silica gel (PE/EtOAc = 100:1, R_f = 0.3) to afford **10** (251 mg, 86.7% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 5.04 (s, 2H), 6.29 (t, 1H, J = 6.3 Hz), 7.13−7.24 (m, 9H), 7.35−7.40 (m, 8H), 7.50 (t, 1H, J = 6.0 Hz), 8.01 (t, 2H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 60.9 (q, J = 3.2 Hz), 62.0 (q, J = 1.6 Hz), 87.7 (s), 123.3 (q, J = 273.9 Hz), 127.5 (s), 127.8 (s), 128.0 (s), 128.2 (s), 128.5 (s), 128.6 (s), 128.8 (s), 129.0 (s), 129.4 (s), 129.8 (s), 129.9 (s), 132.4 (q, J = 2.4 Hz), 133.2 (s), 143.5 (s), 166.1 (s); ^{19}F NMR ($CDCl_3$) δ −75.5 (s); IR (thin film) ν_{max} 3066, 2875, 1721, 1450, 1273 cm^{-1}; MS (EI) m/z 502 (M^+, 0.1). Anal. Calcd for $C_{31}H_{25}O_3F_3$: C, 74.10; H, 4.98. Found: C, 74.15; H, 5.11.

(2*R*,3*S*)-2-Benzyloxymethyl-1,1,1-trifluoro-2,3-dihydroxybutyric Acid Ethyl Ester (12a). Compound **4** (140 mg, 0.5 mmol) was added in one portion to a mixture consisting of $K_3Fe(CN)_6$ (493 mg, 1.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol), OsO_4 (0.1 M in H_2O, 0.05 mL, 0.005 mmol), $(DHQD)_2PHAL$ (20 mg, 0.02 mmol), and $MeSO_2NH_2$ (46 mg, 0.5 mmol) in 1:1 *tert*-butyl alcohol/water (5 mL) at 0 °C. The mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 5 mL of saturated $NaHSO_3$. The mixture was stirred for 30 min and extracted with EtOAc (3 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel (PE/EtOAc = 3:1, R_f = 0.3) to afford **12a** (130 mg) as a white solid in 81% yield: mp 63.5−64.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.2 Hz), 3.37 (d, 1H, J = 6.0 Hz), 3.71 (d, 1H, J = 9.3 Hz), 3.88 (d, 1H, J = 9.9 Hz), 4.05−4.19 (m, 3H), 4.47 (s, 1H), 4.49−4.62 (m, 2H), 7.33−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8 (s), 62.9 (s), 67.1 (s), 69.2 (s), 74.2 (s), 76.5 (q, J = 29.7 Hz), 124.3 (q, J = 284.9 Hz), 128.1 (s), 128.2 (s), 128.5 (s), 136.9 (s), 171.7 (s); ^{19}F NMR ($CDCl_3$) δ −77.4 (s); IR (thin film) ν_{max} 3497, 3430, 1738, 1250, 1099 cm^{-1}; MS (EI) *m*/*z* 322 (M^+, 0.6). Anal. Calcd for $C_{14}H_{17}O_5F_3$: C, 52.17; H, 5.28. Found: C, 52.21; H, 5.33; $[\alpha]^{20}_D$ +20.0 (*c* 0.81, $CHCl_3$); t_R (2*R*,3*S*) = 23.97min, t_R (2*S*,3*R*) = 25.87min (Chiralpak AS, column no. AS00CE-JG019, λ = 220 nm, Hex/*i*-PrOH = 95:5, 0.7 mL/min).

(2*R*,3*R*)-2-*C*-Trifluoromethylerythritol (13a): oil, in 91% yield; ^{1}H NMR (MeOH-d_4) δ 3.70−3.84 (m, 4H), 3.92−3.95 (m, 1H); ^{13}C NMR (MeOH-d_4) δ 60.0 (s), 62.1 (s), 71.0 (s), 76.0 (q, J = 24.0 Hz), 126.1 (q, J = 285.6 Hz); ^{19}F NMR (MeOH-d_4) δ −77.7 (s); IR (thin film) ν_{max} 3391, 2908, 1641, 1180, 1147, 1045 cm^{-1}; MS (ESI) *m*/*z* 191.1 (M + H^+); HRMS (M + Na^+) calcd for $C_5H_9O_4F_3Na$ 213.0353, found 213.0345; $[\alpha]^{20}_D$ +7.9 (*c* 0.6, MeOH).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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