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Diastereospecific Cyclization of Optically Active Trifluoromethylated Epoxycarbamates

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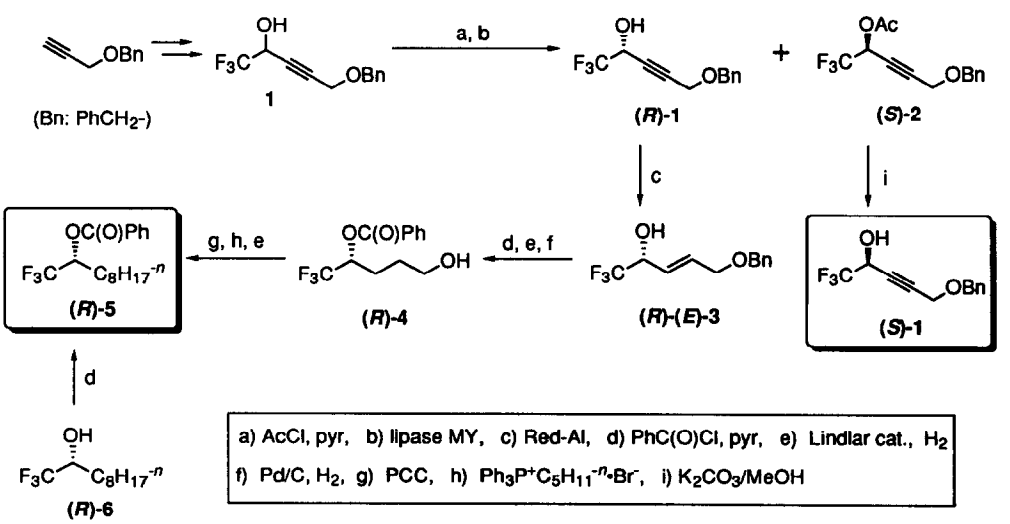
Abstract: Optically active trifluoromethylated propargylic alcohol was prepared by enzymatic asymmetric hydrolysis and was transformed into chiral aminoalcohol derivatives in a diastereospecific fashion, whose results were qualitatively supported by semiempirical molecular orbital calculations.

Optically active fluorine-containing compounds have been recently recognized as a quite important class of materials because of their interesting characteristics and potential applicability to biologically active materials[1] or optical devises such as ferroelectric liquid crystals.[2] We have focused our attention on the synthesis of functionalized chiral building blocks with a trifluoromethyl (CF_3) moiety for attaining the ready access to these types of molecules in a highly efficient manner. In this article, we would like to report the preparation of a novel optically active propargylic alcohol with this group and its derivatization into materials with three consecutive stereogenic centers controlled by the intramolecular asymmetric induction on the basis of the stereogenic carbon generated by the enzymatic resolution. This sequence was devised to obtain 6-deoxy-6,6,6-trifluorosugars[3] with an amino group in the ring systems,[4] which would be readily accessible from ***anti-anti*-9** by one carbon

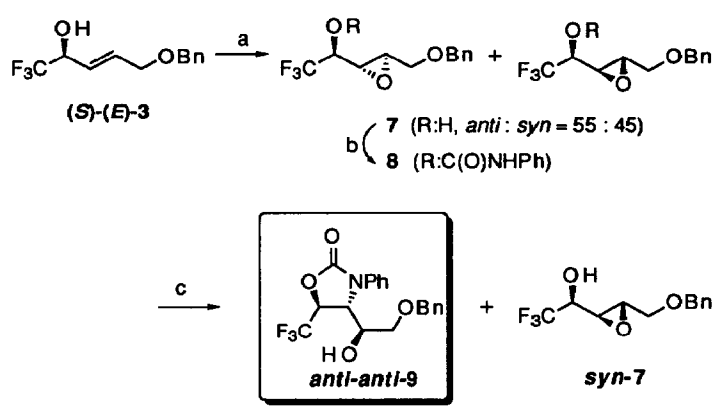
Scheme 1



homologation at the terminal carbon.

The substrate for the enzymatic transformation was prepared by the reaction of the Grignard reagent from *O*-benzylated propargyl alcohol with ethyl trifluoroacetate, followed by the reduction with $NaBH_4$ and acetylation (Scheme 1). Treatment of the thus obtained racemic acetate **2** by lipase MY realized a good enzymatic resolution to furnish the optically active (*R*)-**1** in 88% ee at 27% conversion, while lipase P preferentially hydrolyzed the opposite enantiomer when the corresponding isobutyrate was employed as a substrate and (*S*)-**1** was obtained in 84% ee at 20% hydrolysis. Eventually, the former conditions allowed us to recover the unchanged acetate (*S*)-**2** in 97% ee at 67% conversion.[5] For determining the absolute configuration of this chiral trifluoromethylated propargylic alcohol, the hydrolyzed alcohol (*R*)-**1** was converted into benzoate (*R*)-**5**. Comparison of the specific rotation with the same compound independently derived from already known (*R*)-1,1,1-trifluorodecan-2-ol, (*R*)-**6**,[6] unambiguously verified the (*R*) configuration at the newly created stereogenic carbon atom in (+)-**1** (Scheme 1). For the transformation of (*R*)-(*E*)-**3** to (*R*)-**4**, we utilized two types of hydrogenation conditions. This is due to the fact that (*R*)-(*E*)-**3** after benzoylation and subsequent hydrogenation on Pd/C yielded 2-benzoyloxy-1,1,1-trifluoropentane, probably by removal of the benzyloxy group via the S_N2' like attack of H giving the terminal olefin followed by the hydrogenation at this site. Lindlar catalyst, on the other hand, effected only the desired hydrogenation at the olefin without any undesirable side reactions.

Scheme 2

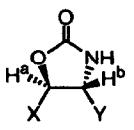


a) *m*CPBA, b) PhNCO, Et_3N, c) NaOMe

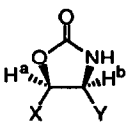
Conversion of enzymatically resolved (*S*)-**2** into the allylic alcohol (*S*)-(*E*)-**3** by the stereoselective reduction with Red-Al and *m*CPBA epoxidation furnished epoxyalcohols **7** in good chemical yield (83% yield from (*S*)-**1**) but in an almost nonselective manner (only in 10% de with *anti* isomer as the major product). Because this diastereomer mixture was found to be inseparable by silica gel column chromatography, it was employed, without further purification, for the investigation of the intramolecular cyclization via the corresponding phenyl carbamates **8**. This process was proved to be smoothly carried out in a stereospecific manner by the action of sodium methoxide in methanol at 0 °C to furnish the desired cyclic product ***anti-anti*-9** along with the recovery of hydrolyzed ***syn*-7** (Scheme 2). Instead of NaOMe, various type of bases such as NaH or Et_3N were used, but they gave only unsatisfactory results.

The stereochemistry of ***anti-anti*-9** was deduced from the ^1H NMR coupling constants of similar oxazolidinones. As shown in Figure 1, *anti* oxazolidinones were reported to possess the smaller vicinal coupling constants between ring protons H^a and H^b (3.5 to 5 Hz) than the corresponding *syn* isomer (7 to 9 Hz).[7] The same trend was also revealed by our MM2 calculation of the model compounds, ***anti-anti*-** and ***syn-anti*-10**,[8] with the expected coupling constants of 4.4 and 7.6 Hz, respectively. On the basis of these

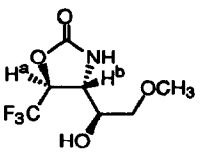
Figure 1



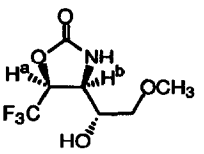
anti



syn



***anti-anti*-10**



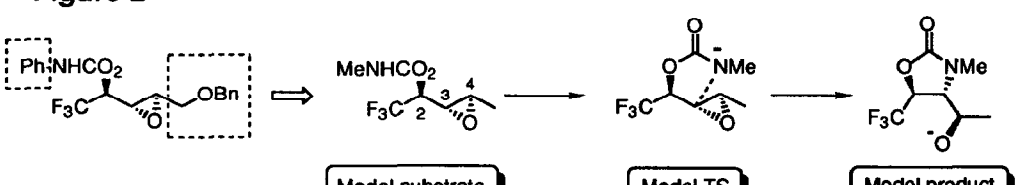
***syn-anti*-10**

X:$PhSCH_2$, Y:$R^{7a)}$	J = 4 to 5 Hz	J = 7 to 8 Hz	J = 4.4 Hz	J = 7.6 Hz
X:CF_3, Y:$CO_2Et^{7b)}$	J = 3.5 Hz	J = 9.1 Hz	Molecular Mechanics Calculation	

considerations, close analysis of the ^1H NMR spectrum of ***anti-anti*-9** demonstrated this vicinal coupling constant as 3.1 Hz, strongly suggesting its *anti* relative stereochemistry.

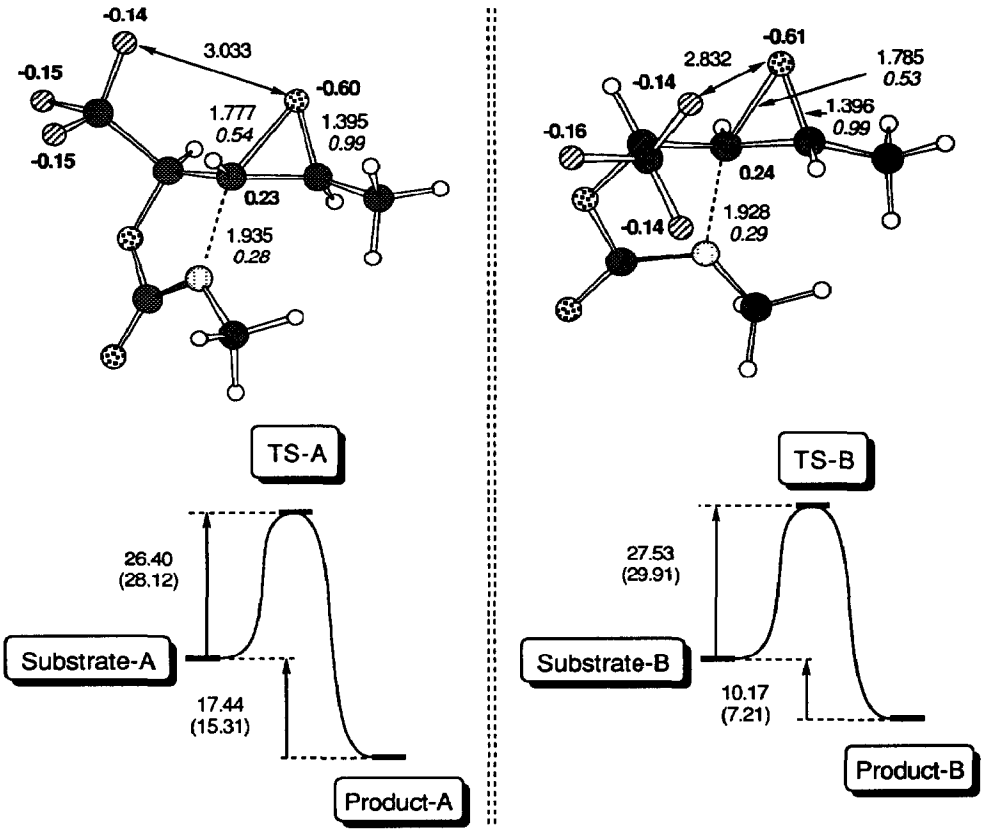
Then, for obtaining deeper mechanistic information on the present diastereospecific intramolecular cyclization, semiempirical MO calculations[9] of each transition states (TSs) were performed using model epoxycarbamates as described in Figure 2 with two methyl groups instead of (benzyloxy)methyl and phenyl groups for the convenience of the calculation. The significant changes of TS-A in Figure 3, for example, compared to the corresponding substrate (substrate-A) or product (product-A) were observed especially in C_3-O (1.777 Å; 1.438 Å in the substrate-A) and C_4-O (1.395 Å; 1.441 Å in the substrate-A and 1.326 Å in the product-A) bond lengths, and the partial charges at C_3 (0.23; -0.02 in the substrate-A and -0.19 in the product-A) and epoxy

Figure 2



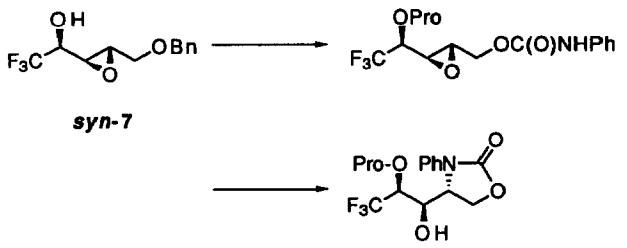
oxygen (-0.60; -0.29 in the substrate-A and -0.74 in the product-A). One might be able to recognize easily TS-A and B as the transition state on the basis of these specific values as well as bond orders of C_3-O (0.54 and 0.53) and C_3-N (0.28 and 0.29). From the energetic point of view, TS-A, the cyclization reaction model for the *anti* isomer, was calculated to be 26.40 kcal/mol higher in energy than the corresponding most stable substrate conformer, while 27.53 kcal/mol heat of formation difference was obtained for TS-B leading to 2,3-*syn* oxazolidinone. Consideration of the free energy difference ($\Delta\Delta G^{\neq}$) of these two TSs also led to the same conclusion that the *anti* isomer would more readily cyclize than the corresponding *syn* counterpart due to their activation energy difference of 1.79 kcal/mol. Thus, MOPAC calculations, at least in a qualitative fashion, expect that the route via TS-A should be more favorable path than the other on the basis of the both energetic explanations. The most important factor responsible for such energy differences between two stereoisomers would mainly stem from the O···F distances: in TS-A, epoxy oxygen and the nearest fluorine atom were separated by 3.03 Å, while they were 0.2 Å closer in TS-B. Sum of the van der Waals radii of both elements (F: 1.35 Å, O: 1.40 Å) led to the understanding that O···F distance in TS-B was only 3% longer, causing the severer steric as well as electronic repulsion because of their electronegative nature.

Figure 3 Calculated Transition States and Energy Profiles for the Both Diastereomers



Bond lengths (Å) were shown with partial charges (bold) and bond orders (italic) for the both diastereomers. Heat of formation difference (ΔH; kcal/mol) was described in the enrgy diagram with free energy difference (ΔG; kcal/mol) in the parenthesis.

As was described above, we have succeeded in preparing optically active trifluoromethylated oxazolidinone, ***anti-anti*-9**, possessing three consecutive stereogenic centers, as an important intermediate for 6-deoxy-6,6,6-trifluorinated aminosugars. Its diastereomer would be also accessible by the same route employing the corresponding epoxycarbamate from (*Z*) allylic alcohol, **(*Z*)-3**, whose TS calculations assumed that the similar diastereospecific intramolecular cyclizations would afford ***anti-syn*-9** because of the larger energy difference of two TSs' ($\Delta\Delta H^{\neq}$= 3.86 kcal/mol and $\Delta\Delta G^{\neq}$= 4.97 kcal/mol). Moreover, unreacted ***syn*-7** might be able to be utilized for the alternative ring formation after protection of the hydroxyl group, followed by the removal of the terminal benzyl moiety and carbamate formation, furnishing the regioisomeric 3-aminosugars. Investigation of more effective resolution systems as well as the utilization of trifluorinated chiral materials to access various types of 4- or 3-amino-6-deoxy-6,6,6-trifluorosugars is in progress in our laboratory and the detailed results will be published in the future.



syn-7

Pro: An appropriate protective group

Experimental

^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 200 MHz (Varian XL Gemini-200 spectrometer), ^{13}C NMR spectra were taken at 50 MHz (Varian XL Gemini-200 spectrometer), and ^{19}F NMR spectra were observed at 56.5 MHz (Hitachi R-24F spectrometer). All spectra were recorded in $CDCl_3$ unless otherwise noted, and the chemical shifts were reported in parts per million (δ ppm) relative to tetramethylsilane (Me_4Si, δ 0.00 ppm for ^{1}H and ^{13}C NMR) and trichlorofluoromethane ($CFCl_3$, δ 0.00 ppm for ^{19}F NMR). Coupling constants were reported in hertz (Hz). Infrared spectra (IR) were recorded on a JASCO A-102 infrared spectrometer and were reported in wave number (cm^{-1}). Optical rotations were observed on a JASCO DIP-140 spectrometer. All melting points are uncorrected. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl, and methylene dichloride was distilled from calcium hydride prior to use. Methanol and ethanol were distilled from magnesium methoxide and ethoxide, respectively.

5-Benzyloxy-1,1,1-trifluoro-3-pentyn-2-ol (1). To a solution of EtMgBr, prepared from 2.29 g of Mg (120 mmol) and 7.46 mL of EtBr (120 mmol) in 120 mL of freshly distilled THF, was added 14.62 g of 1-benzyloxy-2-propyne (100 mmol) in 20 mL of THF at room temperature under argon atmosphere, and the mixture was further stirred for 1 h at 40 °C. Then, the whole was added dropwise to a solution of ethyl trifluoroacetate (21.31 g, 150 mmol) in 100 mL of THF at -78 °C. After 1.5 h at that temperature, the reaction mixture was stirred for additional 1.5 h at 0 °C. Then the whole was quenched with saturated NH_4Cl aq, extracted with ether, washed with saturated NaCl aq, and dried over anhydrous $MgSO_4$. Evaporation of the volatiles afforded crude materials, whose ethanol (50 mL) solution was added to 1.451 g of $NaBH_4$ (38.4 mmol) in ethanol (50 mL) at 0 °C. After stirring overnight at room temperature, the reaction mixture was quenched with saturated NH_4Cl aq. Evaporation of the solvent gave the crude oil and the usual workup afforded the crude product, which was chromatographed on silica gel (hexane:AcOEt = 2:1) to furnish the desired alcohol (20.51 g, 84.0 mmol) in 84% total yield. ^{1}H NMR (with a few drops of D_2O) δ 4.21 (2 H, d, J = 1.67 Hz), 4.60 (2 H, s), 4.68 (1 H, dq, J = 1.73, 5.90 Hz), 7.36 (5 H, s). ^{13}C NMR (with a few drops of D_2O) δ 56.66, 61.98 (q, J = 36.4 Hz), 71.79, 78.73 (q, J = 2.4 Hz), 83.59, 122.8 (q, J = 283 Hz), 128.3, 128.4, 128.6, 136.7. ^{19}F NMR (with a few drops of D_2O) δ -77.8 (d, J = 5.7 Hz). IR (neat) ν 3400, 3100, 2900 cm^{-1}.

5-Benzyloxy-2-acetoxy-1,1,1-trifluoro-3-pentyne (2). To a solution of alcohol **1** (20.51 g, 84.0 mmol) in 170 mL of CH_2Cl_2 was added pyridine (7.97 g, 100.8 mmol, 1.2 equiv) and acetyl chloride (7.91 g,

100.8 mmol, 1.2 equiv) at 0 °C under nitrogen. After being stirred overnight, the mixture was quenched with 1 *N* HCl and the usual workup afforded the crude product, which was purified by silica gel column chromatography (hexane:AcOEt = 3:1) to yield the desired acetate (22.36 g, 78.1 mmol) in 93% yield. ^{1}H NMR δ 2.16 (3 H, s), 4.20 (2 H, d, *J* = 1.67 Hz), 4.57 (2 H, s), 5.91 (1 H, dq, *J* = 1.73, 5.87 Hz), 7.33 (5 H, s). ^{13}C NMR δ 20.35, 57.04, 61.55 (q, *J* = 37.5 Hz), 72.08, 75.83 (q, *J* = 2.3 Hz), 83.59, 122.2 (q, *J* = 281 Hz), 128.5, 128.6, 129.0, 137.4, 168.9. ^{19}F NMR δ -75.2 (d, *J* = 6.2 Hz). IR (neat) ν 3050, 2950, 2850, 1760, 1500 cm^{-1}. HRMS for $C_{14}H_{13}F_3O_3$ M$^+$ 286.0817, found 286.0815.

Enzymatic hydrolysis. To a suspension of lipase MY (1.3 g, 3.9x10^4 units, *Candida rugosa*, Meito Sangyo Co., Ltd.) in distilled water (70 mL) was added **2** (2.06 g, 7.20 mmol) at 40-41 °C and the whole was stirred for 10 h at that temperature with titrating with 1 *N* NaOH aq to check the reaction as well as to keep the pH of the solution at about 7. Then, the flocculant (10 mL of 200 ppm aqueous solution prepared from P-713, Daiichi Kogyo Seiyaku) was added to the reaction mixture, which was stirred for 1 h. After filtration through Celite, the whole was treated as usual to afford the mixture of hydrolyzed alcohol and recovered substrate, which was separated by column chromatography on silica gel (hexane:AcOEt = 3:1) to furnish optically active (***R***)**-1** (1.052 g, 4.31 mmol, 60% yield) and (***S***)**-2** (0.607 g, 2.12 mmol, 29% yield). Their physical data were identical to those of the racemic compounds except for the specific rotation. (***S***)**-2** ($[\alpha]_D^{17}$ +89.47 (*c* 1.12, $CHCl_3$) in 97% ee) afforded the corresponding (***S***)**-1** ($[\alpha]_D^{20}$ -4.27 (*c* 1.30, $CHCl_3$)) by the usual chemical hydrolysis by K_2CO_3 in MeOH at room temperature (96% yield).

(*S*)-(*E*)-5-Benzyloxy-1,1,1-trifluoro-3-penten-2-ol ((*S*)-(*E*)-3). To a solution containing Red-Al (14.1 mL, 48.0 mmol; 3.4 mol/L in toluene) and 80 mL of freshly distilled ether was added (***S***)**-1** (9.77 g, 40.0 mmol) in 20 mL of ether at -20 °C under nitrogen and the whole was stirred for 1 h, followed by another 1 h at 0 °C. After the addition of 2 *N* NaOH (100 mL), usual workup and purification by chromatography (hexane:AcOEt = 2:1) afforded (***S***)-(***E***)**-3** (8.89 g, 36.1 mmol, 91% yield). $[\alpha]_D^{20}$ -8.85 (*c* 1.25, MeOH). ^{1}H NMR (with a few drop of D_2O) δ 4.08 (2 H, ddd, *J* = 1.16, 1.49, 5.12 Hz), 4.45 (1 H, m), 4.54 (2 H, s), 5.82 (1 H, ddt, *J* = 1.67, 6.02, 15.63 Hz), 6.10 (1 H, ddt, *J* = 1.27, 5.05, 15.62 Hz), 7.34 (5 H, s). ^{13}C NMR δ 69.26, 70.85 (q, *J* = 32.2 Hz), 72.58, 78.73 (q, *J* = 2.4 Hz), 83.59, 124.1, 124.2 (q, *J* = 282 Hz), 127.8, 128.5, 133.7, 137.7. ^{19}F NMR δ -77.3 (d, *J* = 6.6 Hz). IR (neat) ν 3400, 3050, 2880, 980 cm^{-1}. HRMS for $C_{12}H_{13}F_3O_2$ M$^+$ 246.0868, found 246.0881.

5-Benzyloxy-3,4-epoxy-1,1,1-trifluoropentan-2-ol (7). To an *m*CPBA (15.53 g, 90.0 mmol; 2.0 equiv) solution in freshly distilled $CHCl_3$ (100 mL) was added ((***S***)-(***E***)**-3**) (10.82 g, 44.0 mmol) at 0 °C and the whole was stirred for 1 day at ambient temperature. After quenching the reaction mixture with saturated aqueous solution of Na_2SO_3, the usual workup procedure gave the crude material, which was further purified by silica gel chromatography (hexane:AcOEt = 2:1) to afford 10.96 g (41.8 mmol) of the inseparable diastereomer mixture of the desired epoxide in 95% yield (*anti*:*syn* = 55:45). IR (neat) ν 3400, 3100, 2900, 1280 cm^{-1}. HRMS for $C_{12}H_{13}F_3O_3$ M$^+$ 262.0817, found 262.0804. ***Syn* form** ^{1}H NMR δ 2.80 (1 H, d, *J* = 8.14 Hz), 3.26 (2 H, m), 3.58 (1 H, dd, *J* = 4.86, 11.82 Hz), 3.80 (1 H, dd, *J* = 2.81, 11.76 Hz), 4.02 (1 H, m), 4.58 (2 H, s), 7.35 (5 H, s). ^{13}C NMR δ 51.74 (q, *J* = 2.4 Hz), 53.01, 67.88 (q, *J* = 31.4 Hz), 68.44, 73.54, 124.0 (q, *J* = 283 Hz), 127.8, 127.9, 128.5, 137.4. ^{19}F NMR δ -73.6 (d, *J* = 6.2 Hz). ***Anti***

form ^{1}H NMR δ 3.14 (1 H, d, *J* = 3.80 Hz), 3.26 (2 H, m), 3.53 (1 H, dd, *J* = 5.26, 11.69 Hz), 3.76 (1 H, t, *J* = 2.40 Hz), 4.02 (1 H, m), 4.58 (2 H, s), 7.35 (5 H, s). ^{13}C NMR δ 51.87 (q, *J* = 2.6 Hz), 53.12, 67.88 (q, *J* = 31.4 Hz), 68.57, 73.41, 124.8 (q, *J* = 283 Hz), 128.0, 128.0, 128.6, 137.4. ^{19}F NMR δ -74.4 (d, *J* = 6.9 Hz).

5-Benzyloxy-3,4-epoxy-2-phenylcarbamoyloxy-1,1,1-trifluoropentane (8). To a solution of epoxy alcohol **7** (5.26 g, 20.1 mmol) in freshly distilled CH_2Cl_2 (30 mL) was added phenylisocyanate (2.4 mL, 22.1 mmol; 1.1 equiv), followed by triethylamine (3.6 mL, 26.1 mmol) at 0 °C under nitrogen and the whole was stirred for 1 h at ambient temperature. After being quenched the reaction with 1 *N* HCl, the usual workup procedure gave the crude material, which was further purified by silica gel chromatography (hexane:AcOEt = 3:1) to afford the inseparable diastereomer mixture of the desired carbamate in 90% yield (6.90 g, 18.1 mmol, *anti*:*syn* = 55:45). IR (neat) ν 3300, 3050, 3000, 2850, 1720, 1600, 1540 cm^{-1}. HRMS for $C_{19}H_{18}F_3O_4N$ M$^+$ 381.1188, found 381.1215. ***Syn* form** ^{1}H NMR δ 2.80 (1 H, d, *J* = 8.14 Hz), 3.2-3.4 (2 H, m), 3.54 (1 H, dd, *J* = 3.46, 11.85 Hz), 3.79 (1 H, dd, *J* = 2.69, 11.83 Hz), 4.56 (2 H, s), 5.28 (1 H, m), 6.8-7.4 (11 H, m). ^{13}C NMR δ 50.20 (q, *J* = 2.3 Hz), 53.21, 68.34, 69.88 (q, *J* = 31.4 Hz), 73.38, 123.1 (q, *J* = 282 Hz), 124.3, 127.7, 127.9, 127.9, 128.5, 129.2, 136.7 (q, *J* = 3.4 Hz), 150.7. ^{19}F NMR δ -72.8 (d, *J* = 6.2 Hz). ***Anti* form** ^{1}H NMR δ 3.2-3.4 (2 H, m), 3.57 (1 H, dd, *J* = 3.35, 11.89 Hz), 3.82 (1 H, dd, *J* = 2.57, 11.91 Hz), 4.57 (2 H, s), 5.28 (1 H, m), 6.8-7.4 (11 H, m). ^{13}C NMR δ 51.02 (q, *J* = 2.5 Hz), 54.01, 68.10, 69.02 (q, *J* = 32.4 Hz), 73.38, 118.9, 122.8 (q, *J* = 282 Hz), 127.7, 127.9, 127.9, 128.5, 129.2, 137.5 (q, *J* = 2.4 Hz), 150.9. ^{19}F NMR δ -72.4 (d, *J* = 6.2 Hz).

Intramolecular cyclization of 9. To a solution of **8** (13.200 g, 34.6 mmol) in distilled MeOH (60 mL) was added sodium methoxide (1.869 g, 34.6 mmol) at 0 °C and the whole was stirred for 3 h at that temperature. After quenched the reaction with 1 *N* HCl, the usual workup procedure gave the crude material, which was further purified by silica gel chromatography (hexane:AcOEt = 2:1) to afford the cyclized oxazolidinone, ***anti-anti*-9**, and the unreacted epoxy alcohol, ***syn*-7** in 92% total yield. ***Anti-anti*-9** $[\alpha]_D^{16}$ -17.20 (*c* 0.68, $CHCl_3$). ^{1}H NMR δ 2.78 (1 H, d, *J* = 5.21 Hz), 3.39 (1 H, dd, *J* = 5.36, 9.92 Hz), 3.47 (1 H, dd, *J* = 5.34, 9.85 Hz), 3.99 (1 H, dq, *J* = 2.97, 5.25 Hz), 4.42 (2 H, s), 4.51 (1 H, t, *J* = **3.07** Hz), 5.04 (1 H, dq, *J* = **3.10**, 6.36 Hz), 7.2-7.4 (11 H, m). ^{13}C NMR δ 59.45, 67.75, 70.05, 70.63 (q, *J* = 34.6 Hz), 74.30, 123.6 (q, *J* = 281 Hz), 123.7, 127.1, 128.4, 128.7, 129.1, 130.0, 135.8, 137.3, 154.4. ^{19}F NMR δ -75.4 (d, *J* = 6.2 Hz). IR (neat) ν 3450, 3100, 3050, 2875, 1765, 1600, 1505 cm^{-1}. HRMS for $C_{19}H_{18}F_3O_4N$ M$^+$ 381.1188, found 381.1197. *Syn*-**7** $[\alpha]_D^{17}$ -27.38 (*c* 1.58, $CHCl_3$). mp. 51.5-53.0 °C. Other physical properties were consistent with those described above.

(*R*)-4-Benzoyloxy-5,5,5-trifluoropentanol ((*R*)-4). To a suspension of Lindlar catalyst (200 mg) in freshly distilled hexane (10 mL) and ether (1 mL) was added **(*R*)-3** (2.32 g, 9.42 mmol; 40% ee) at room temperature under hydrogen, and the whole was stirred overnight. After filtration followed by evaporation, the obtained oily material in 15 mL of freshly distilled CH_2Cl_2 was reacted with pyridine (0.83 mL, 10.3 mmol) and benzoyl chloride (1.20 mL, 10.3 mmol) overnight at room temperature. Usual workup gave crude material, which was dissolved in methanol (30 mL) containing 10% Pd/C (300 mg) and stirring was continued overnight at room temperature under hydrogen. Filtration and evaporation gave crude oil, which was purified by column

chromatography (hexane:AcOEt = 2:1) to afford 1.95 g (7.70 mmol) of **(*R*)-4** in 82% overall yield. $[\alpha]_D^{16}$ +17.68 (*c* 1.12, MeOH). ^{1}H NMR δ 1.50-2.23 (5 H, m), 3.67 (2 H, t, *J* = 6.00 Hz), 5.63 (1 H, tq, *J* = 1.53, 6.32 Hz), 7.5-8.2 (5 H, m). ^{19}F NMR δ -78.0 (d, *J* = 6.6 Hz). IR (neat) ν 3350, 2900, 2850, 1720, 1590 cm^{-1}.

(*R*)-2-Benzyloxy-1,1,1-trifluorodecane ((*R*)-5). To a suspension of PCC (3.32 g, 15.40 mmol) in freshly distilled CH_2Cl_2 (120 mL) was added 1.95 g (7.70 mmol) of **(*R*)-4** at room temperature, and the whole was stirred for 4 h at that temperature. Addition of ether and filtration, evaporation of the solvent afforded the crude aldehyde, which was added, at 0 °C, to the solution containing $Ph_3PC_5H_{10}$ (from 2.37 g (5.73 mmol) of $Ph_3P^+C_5H_{11}{\cdot}Br^-$ and 3.58 mL of *n*-BuLi (1.6 M; 5.73 mmol)) in 45 mL of freshly distilled ether, and the whole was stirred for 0.5 h at that temperature. Usual workup gave the crude olefin as *E, Z* mixture, which was subjected to the hydrogenation conditions as described above. Removal of the catalyst and the solvent, followed by column chromatography (hexane:AcOEt = 4:1) furnished the desired benzoate **(*R*)-5** (0.73 g, 2.31 mmol) in 30% overall yield. $[\alpha]_D^{16}$ +18.44 (*c* 0.84, MeOH; 38% ee determined by its MTPA ester analysis). ^{1}H NMR δ 0.72-1.95 (17 H, m), 5.57 (1 H, tq, *J* = 6.65, 6.83 Hz), 7.4-8.2 (5 H, m). ^{19}F NMR δ -75.1 (d, *J* = 6.8 Hz). IR (neat) ν 2900, 2840, 1720, 1590 cm^{-1}. The benzoylation reaction of **(*R*)-6** (80% ee) provided **(*R*)-5** in 90% yield, whose specific rotation was measured as $[\alpha]_D^{16}$ +40.76 (*c* 0.89, MeOH).

References and Notes

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9) On the basis of the mechanistic consideration, these two diastereomers, ***anti-anti*-** and ***syn-anti*-10**, were employed for the estimation of coupling constants out of four possible isomers.
10) Calculations were performed by MOPAC v 6.10 (PM 3) implemented in CAChe Worksystem (SONY/ Tektronix Corporation). The obtained conformers were verified as the real TSs not only by their force calculation giving only one imaginary frequencies, but also by the intrinsic reaction coordinate calculation affording the corresponding substrates and products.

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