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Highly Diastereoselective Michael Addition to Optically Active Trifluoromethylated α,β-Unsaturated Sulfonamides Based on Their Hinge-Like Conformation

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Abstract: Conformational analysis of α,β-unsaturated sulfonamide based on *ab initio* calculation predicted a hinge-like molecular shape of ground state conformation. Referring to the result, three optically active trifluoromethylated sulfonamides **2a-c** were designed and prepared from optically active pyrrolidines **1a-c** as a chiral auxiliary. Michael additions to **2a-c** with acetophenone/LDA and dimethyl malonate/NaH gave the adducts with various diastereoselectivities. The most diastereoselective olefin **2c** with C_2-symmetric chiral auxiliary was utilized as Michael acceptor to give >98 % *de* in the reaction with several selected nucleophiles. Copyright © 1996 Elsevier Science Ltd

Recently, chirally trifluoromethylated compounds have been received much attention because these compounds are becoming a new important class of biologically active compounds[1] and functional materials such as ferroelectric liquid crystals.[2] For the asymmetric synthesis of trifluoromethylated compounds, asymmetric Michael additions to trifluoromethylated electron-deficient olefins have been becoming one of the useful synthetic procedures. There are several reports for these reactions using trifluoromethylated olefins as Michael acceptors, for example, 1-phenylsulfonyl-3,3,3-trifluoro-1-propene,[3] 3,3,3-trifluoro-1-propenyl phenyl sulfoxide,[4] ethyl 3-(trifluoromethyl)acrylate,[5] benzyl 2-(trifluoromethyl)propenate,[6] and 2-(trifluoromethyl)propenoic acid.[7]

In our continuing effort in the stereoselective synthesis of trifluoromethylated compounds, we have focused on the utilization of 3,3,3-trifluoro-1-propenylsulfonyl compounds.[8] As an example on the asymmetric Michael addition using sulfonyl compound, there was one report[3] on the addition to 1-phenylsulfonyl-3,3,3-trifluoro-1-propene with some chiral nucleophiles, however, the enantioselectivities were relatively low (7 – 43 % *ee*).[9] Concerning the asymmetric Michael addition utilizing sulfonyl functions, there seems no report of the reaction employing optically active trifluoromethylated α,β-unsaturated sulfonyl compounds as far as we know. Thus, we chose the trifluoromethylated chiral sulfonamides as stereoselective Michael acceptors since these compounds are readily available from various optically active pyrrolidine derivatives and the chiral auxiliaries may be recovered by desulfuryl synthetic operation.[10] In this paper, we report the synthesis of optically active β-trifluoromethylated α,β-unsaturated pyrrolidine sulfonamides **2a-c** and their asymmetric Michael additions with some selected nucleophiles (0 – >98 % *de*), and we also proposed a mechanism for the asymmetric induction by conformational analysis based on the theoretical calculation.

RESULTS AND DISCUSSION

Conformational Analysis of α,β-Unsaturated Sulfonamide and the Substrate Design. Since Michael addition where a C-C π-bond is converted into two σ-bonds is exothermic, the reaction occurs through a reactant-like transition state (Hamond's postulate).[11] Thus, in the asymmetric Michael addition, the π-facial selectivity would strongly depend on the ground state structure of the starting material. To clarify the ground state structure of unsaturated sulfonamide, we performed *ab initio* calculation of ethenesulfonamide as a model compound using RHF/3-21G*[12] basis set. In this calculation, the standard dihedral angle θ, defined by the four atoms C_2-C_1-S-N as shown in Figure 1, was varied in the fixed steps from -180 to 180° and other geometrical parameters were optimized at each point. Total energies of each optimized structures (**I** – **IV**) were obtained by single point calculations at the level of RHF/6-31G*. Relative energies were plotted along with θ in Figure 1. The energy minimum (**II** and **IV**) and maximum points (**I** and **III**) conformations are depicted in Figure 2.

From the calculation, two important conformational profiles are revealed: (1) The most stable conformer **II** (θ = 118°) has the p-orbitals of the C-C double bond nearly parallel with the center axis of SO_2 as shown by the Newman projection in Figure 3, **A**,[13,14] and this conformer is 1.9 kcal mol^{-1} more stable than the next stable conformer **IV** (θ = 0°). (2) In the conformer **II**, the nitrogen atom is almost planar (H-N-H bond angle: 119°) rather than tetrahedral structure, and the lone pair p-orbital also nearly parallels with the center axis of SO_2 (C_1-S-N-H angle: 87°) as shown in Figure 3, **B**. Consequently, the most stable conformer of α,β-unsaturated sulfonamide has a unique hinge-like shape (Figure 2, **II**), where the interactions of the p-orbitals (π-bond of C-C double bond and the lone pair orbital on the nitrogen) with the S=O three-centered 4-electron bonds[15] appear to be maximized.

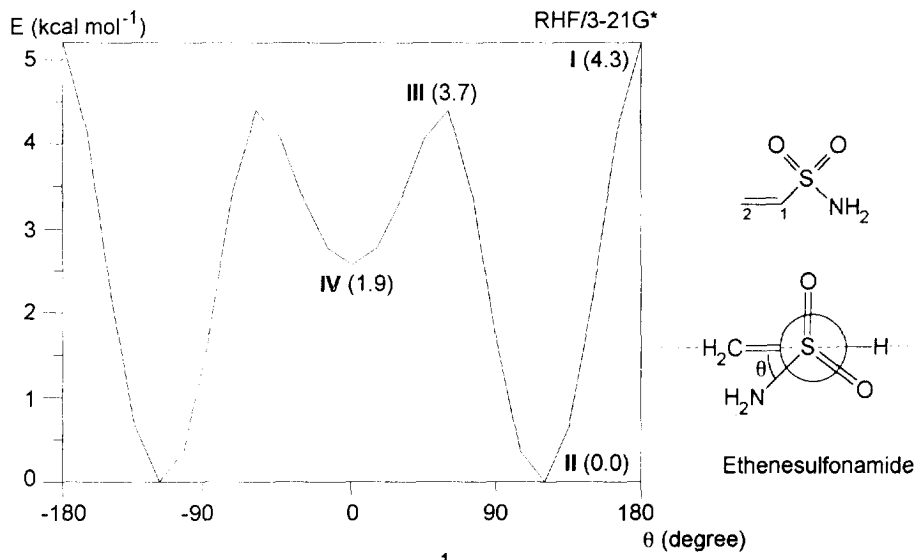


Figure 1. Plots of energies (kcal mol^{-1}) for ethenesulfonamide versus dihedral angle θ (degree). Relative energies of **I** - **IV** were calculated with RHF/6-31G*//RHF/3-21G*.

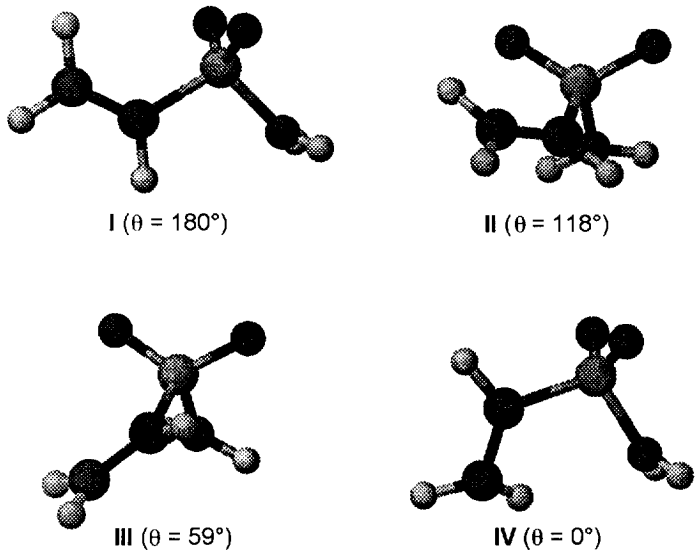


Figure 2. Optimized energy minimum (**II**, **IV**) and maximum (**I**, **III**) structures of ethenesulfonamide calculated with RHF/6-31G*//RHF/3-21G*.

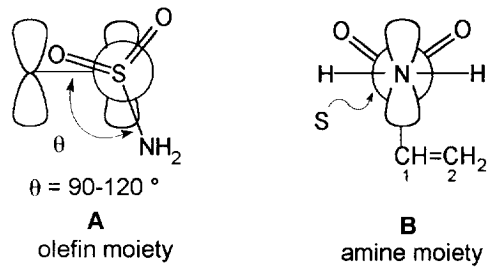
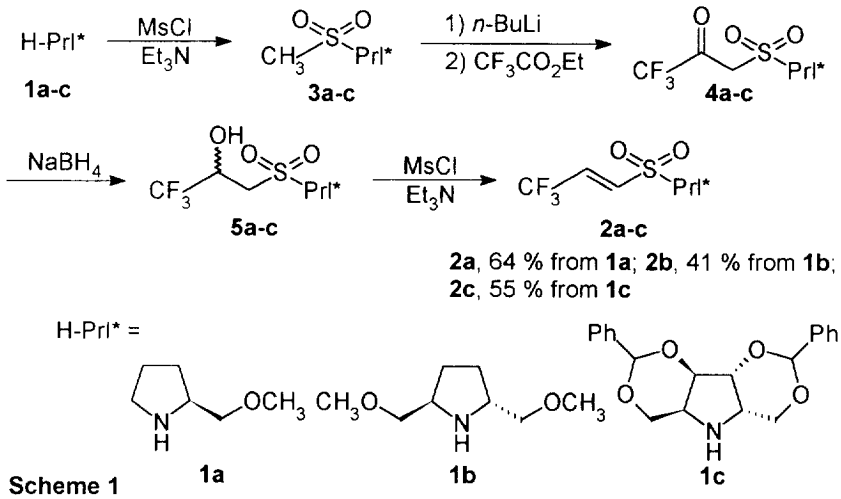


Figure 3. The most stable conformation of ethenesulfonamide.

Based on the above conformational features of ethenesulfonamide, we designed the chiral Michael acceptor as follows: (1) Vinyl group was replaced by a γ,γ,γ-trifluoropropenyl group to make the β-carbon prochiral. (2) NH_2 group was replaced by a chiral pyrrolidine to suppress the free rotation of the S-C bond by the steric interaction between the trifluoropropenyl group and substituent(s) on the pyrrolidine. Three kinds of chiral pyrrolidines (**1a-c**) were used for synthesis of the sulfonamides.

Preparation of Chiral Trifluoromethylated α,β-Unsaturated Sulfonamides 2a-c. Trifluoromethylated sulfonamides **2a-c** were prepared from (*2S*)-2-(methoxymethyl)pyrrolidine (**1a**), (*2R,5R*)-bis(methoxymethyl)-pyrrolidine (**1b**), and the tetrasubstituted C_2-symmetric pyrrolidine **1c** prepared from D-mannitol.[16,17] Olefins **2a-c** were synthesized as outlined in Scheme 1: Mesylation of **1a-c** with methanesulfonyl chloride and triethylamine at 0 °C gave the amides **3a-c**. The methyl groups of **3a-c** were deprotonated with *n*-BuLi and then

treated with ethyl trifluoroacetate to give the corresponding ketones **4a-c**. $NaBH_4$ reduction of **4a-c** to the alcohols **5a-c** and following treatment with methanesulfonyl chloride in the presence of an excess amount of triethylamine afforded the desired Michael acceptors **2a-c**, in good overall yields (64, 41, and 55 %, respectively, from **1a-c**).

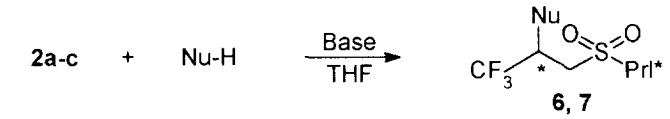


Scheme 1

Michael Addition to the Chiral Sulfonamides 2a-c. Since several attempts on the reactions of amides **2** with organometallic reagents such as alkyllithiums and alkylcuprates failed, we directed our attention to the reactions with metal enolates. In Table 1, results of the Michael additions to **2a-c** with acetophenone/LDA at -78 °C and dimethyl malonate/NaH at room temperature as nucleophilic reagents are summarized. Diastereoselectivity was determined by the ^1H NMR spectra of the crude product mixture. The obtained similar yields of adducts suggest similar reactivities of **2a-c**. In general, higher selectivity was observed in the reaction with acetophenone compared to the reaction with malonate for all amides. These results seem to be attributable to the lower reaction temperature for the former. The facial selectivity for monosubstituted pyrrolidine amide **2a** was poor, and no selectivity was observed at room temperature in the reaction with malonate (**6a**: 0 % *de*). On the other hand, C_2-symmetric pyrrolidine amide **2b** gave the adducts with moderate selectivities (**6b**: 30 % *de*, **7b**: 46 % *de*). Finally, tetrasubstituted bulky pyrrolidine amide **2c** afforded virtually single stereoisomers of the adducts **6c** and **7c** (>98 % *de*).

Michael reactions of the most diastereoselective sulfonamide **2c** were examined further with various enolate nucleophiles and the results are summarized in Table 2. The diastereoselectivities of products were high for all reactions (>98 %: no diastereomer was detected in the 500 MHz ^1H NMR spectra). Reaction with acetophenone/LDA at -78 °C followed by warming to 0 °C for 1.5 h afforded **7c** up to 85 % yield. Reaction with diethyl malonate/NaH gave the product **8** which was used for the stereochemical correlation of products (*vide infra*). Both acetate and acetamide afforded Michael adducts **9** and **10**, respectively, in good yields. The enolate

Table 1. Michael addition to **2a-c** with selected enolates.

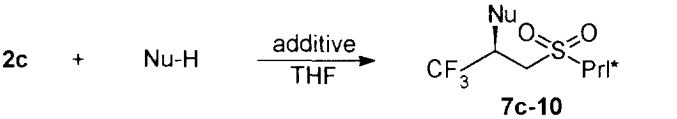


6, 7

Olefin	$Nu^{\ominus}$	Product	Yield (%)	*de* (%)[c]
2a	$^{\ominus}CH(CO_2CH_3)_2$	**6a**	89[a]	0
	$^{\ominus}CH_2COPh$	**7a**	36[b]	20
2b	$^{\ominus}CH(CO_2CH_3)_2$	**6b**	77[a]	30
	$^{\ominus}CH_2COPh$	**7b**	34[b]	46
2c	$^{\ominus}CH(CO_2CH_3)_2$	**6c**	72[a]	> 98[d]
	$^{\ominus}CH_2COPh$	**7c**	27[b]	> 98[d]

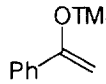
[a]In the case of reaction with dimethyl malonate, the reactions were carried out using NaH as a base at room temperature for 1 h. [b]In the case of reaction with acetophenone, the reactions were carried out using LDA as a base at -78 °C for 1 h. [c]Determined by ^{1}H NMR spectra. [d]No diastereomer peaks were detected in the ^{1}H NMR spectra.

Table 2. Michael addition to **2c** with various enolates.



7c-10

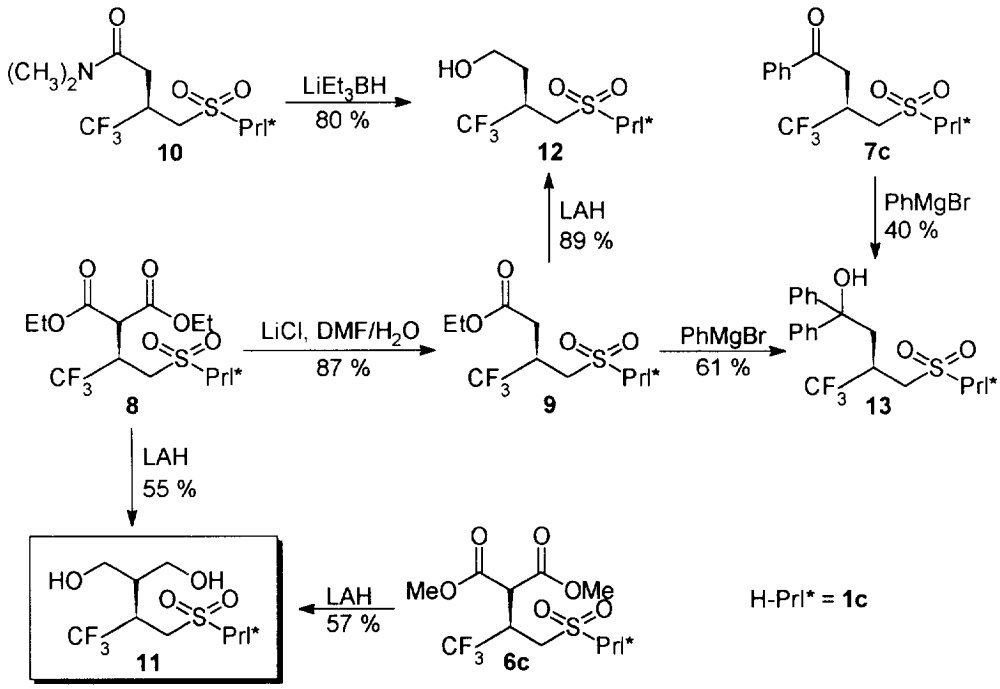
H-Prl* = **1c**

Nu-H/Base	Reaction conditions	Product	Yield (%)[a]
CH_3COPh/LDA	-78 °C, 1 h, then 0 °C, 1.5 h	**7c**	85
$CH_2(CO_2Et)_2$/NaH	-78 °C, 1.5 h	**8**	78
CH_3CO_2Et/LDA	-78 °C, 1.5 h	**9**	91
$CH_3CON(CH_3)_2$/LDA	0 °C, 1.5 h	**10**	95
 /TBAF	r.t., 1.5 h	**7c**	37

[a]Adducts were obtained with high diastereoselectivities (>98 % *de*). Practically, no diastereomer peaks were detected in the ^{1}H NMR spectra.

generated from trimethylsilyloxystyrene/TBAF gave also the adduct **7c** in a modest yield but with high diastereoselectivity, even at room temperature.

The configurational correlation between the adducts **6c**, **7c**, **8-10** was confirmed by chemical transformations as illustrated in Scheme 2. Both malonates **6c** and **8** were reduced with $LiAlH_4$ to afford the same diol **11**. Diethyl malonate derivative **8** was also decarboxylated to ethyl monoester **9**. $LiEt_3BH$ reduction of **10** and $LiAlH_4$ reduction of **9** gave the same alcohol **12**. Finally, Grignard reaction of **9** and **7c** with PhMgBr led to the same carbinol **13**. Absolute configuration at the carbon attached to trifluoromethyl group was determined by X-ray crystallographic analysis of the crystallized diol **11** as *R*-configuration (Figure 4). Thus, the configurations of **6c**, **7c**, **8-10** were determined as *R*.



Scheme 2

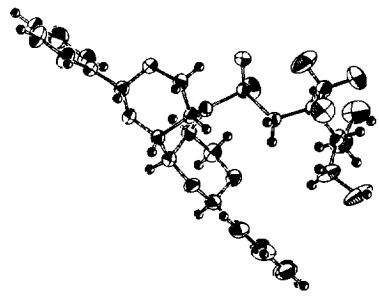


Figure 4. ORTEP drawing of the crystal structure of **11**.

Stable Conformations of Sulfonylpyrrolidines and the Diastereoselectivity. The X-ray structure of **11** revealed that the nitrogen in sulfonamide was almost planar and that the lone pair p-orbital was oriented toward the direction bisecting O-S-O plane in compatible with the *ab initio* calculation (*cf.* Figure 3, **B**), and hence, α,β -unsaturated sulfonamide is assumed to take the hinge-like conformation as predicted by calculation. Thus, one side of the olefin **2c** is sterically blocked by the bulky amide moiety for the nucleophilic attack.

If the consideration of the stable conformation of ethenesulfonamide is applied to sulfonamide **2a**, four possible conformers **A-D** can be expected (Figure 5). In contrast, for the C_2-symmetric amides **2b** and **2c**, conformers **A** and **C**, and **B** and **D** are the same ones because of molecular symmetry. Among these conformers **A-D**, conformer **B** for **2a** is apparently less stable due to the steric interaction between $CHCF_3$ moiety of the olefin and R^2 substituent (= methoxymethyl) on the pyrrolidine. Similarly, **B** (= **D**) are the less stable conformers than **A** (= **C**) for **2b** and **2c**. Particularly, for the more crowded **2c**, the ground state conformation would be almost **A** (= **C**) only. In the case of **2a**, the relative populations of **A-D** would be expected to be **C≅D>A>B**. Because **C** and **D** will be attacked by nucleophiles from the opposite sides, very scant or no diastereoselectivity would be expected in the reaction of **2a** as in fact observed (Table 1). In order to control the conformation of α,β-unsaturated sulfonamides as conformer **A**, at least two same substituents on α,α' positions of the pyrrolidine with the same configuration (C_2-symmetry) are required as **2b** and **2c**. However, bis(methoxymethyl) substitution insufficiently controlled the conformation, and as the results, only modest diastereoselectivity was found in the Michael reaction of **2b**. Complete conformational control of unsaturated sulfonamide was successful in **2c** having tetrasubstituted bulky pyrrolidine, and the virtually single products were obtained in the Michael addition to **2c**. The all Michael adducts **6c**, **7c**, **8-10** had the *R* configuration at the CCF_3 carbon, and this is consistent with the above mentioned conformational analysis which predicts the attack of nucleophiles from *Re* face of the olefin to yield *R*-configuration products.

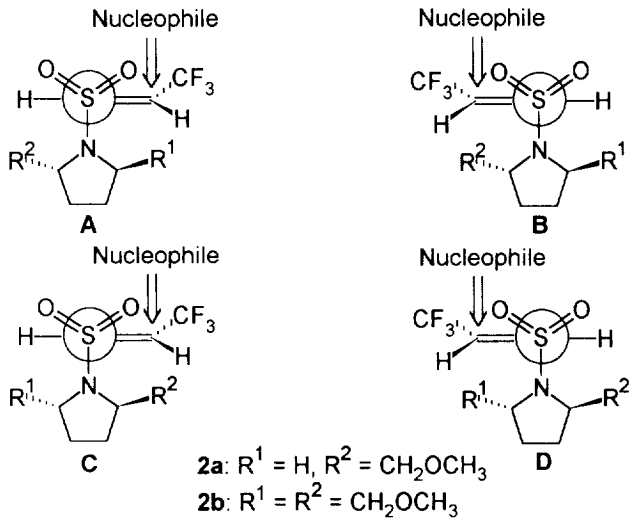


Figure 5. Four possible conformers of **2a** and **2b**.

In conclusion, in the Michael additions to optically active trifluoromethylated α,β-unsaturated sulfonamides **2a-c**, the Michael adducts of **2c** bearing chiral C_2-symmetric bulky amine **1c** were obtained with highest diastereoselectivities (>98 %) in high yields. Synthetic application of these adducts and further work on expanding the scope of this methodology are being studied in our laboratory.

EXPERIMENTAL

Melting points were determined by a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Varian GEMINI-200 spectrometer at 200 and at 50 MHz, respectively, for samples in $CDCl_3$ solution with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained with a Hitachi FT-NMR R-90F spectrometer at 85 MHz for samples in $CDCl_3$ solutions with $CFCl_3$ as an internal standard. Mass spectra were recorded on a JEOL JMS-AX 505 HA mass spectrometer at 70 eV. Flash chromatography was performed with a silica gel column (Fuji-Davison BW-300). Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel $60F_{254}$. Microanalyses were performed with a Perkin-Elmer 2400S CHN elemental analyzer.

(*E*)-(2*S*)-1-(3,3,3-Trifluoro-1-propenylsulfonyl)-2-(methoxymethyl)pyrrolidine (2a).

To a solution of (2*S*)-(methoxymethyl)pyrrolidine (**1a**) (500 mg, 4.34 mmol) and triethylamine (527 mg, 5.21 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C was added methanesulfonyl chloride (597 mg, 5.21 mmol) under nitrogen atmosphere. After being stirred for 1 h at 0 °C, the solution was poured into 1 M aqueous K_3PO_4 solution (20 mL) and extracted with chloroform (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **3a** as a yellow oil (804 mg, R_f 0.33, CH_2Cl_2; IR 1130 and 1331 cm^{-1}). Without purification, to a solution of the amide **3a** (804 mg) in dry THF (10 mL) at -78 °C, *n*-BuLi (1.6 M hexane solution, 4.04 mL, 6.51 mmol) was added under nitrogen atmosphere in 15 min. The solution was stirred for 15 min at -78 °C and then for additional 1 h at 0 °C. To the resulting solution was added ethyl trifluoroacetate (1.04 mL, 8.68 mmol) during 15 min at -78 °C. After being stirred overnight at room temperature, the solution was poured into saturated aqueous NaCl solution (30 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the ketone **4a** (1.39 g; R_f 0.33, 1 : 1 hexane : EtOAc; IR 1715 cm^{-1}). Without purification, $NaBH_4$ (250 mg, 6.51 mmol) was added to a solution of **4a** (1.39 g) in MeOH (7 mL). After being stirred overnight at room temperature, the solution was poured into saturated aqueous NaCl solution (30 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the alcohol **5a** (1.10 g; R_f 0.17, 1 : 1 hexane : EtOAc; IR 3447 cm^{-1}). Without purification, methanesulfonyl chloride (624 mg, 5.45 mmol) was added to a solution of **5a** (1.10 g) and triethylamine (1.52 mL, 10.89 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under nitrogen atmosphere. After being stirred for 1 h at 0 °C, the solution was poured into 1 M aqueous K_3PO_4 solution (15 mL) and extracted with $CHCl_3$ (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : EtOAc) to give **2a** as a yellow oil (763 mg, 64 % from **1a**): R_f 0.53 (1 : 1 hexane : EtOAc); $[\alpha]_D^{25}$ -23.8° (*c* 2.1, $CHCl_3$); IR (neat) 1358, 1300, 1132 cm^{-1}; ^1H NMR δ 1.84-2.08 (4 H, m), 3.32-3.41 (2 H, m), 3.36 (1 H, dd, J = 9.7, 2.3 Hz), 3.36 (3 H, s), 3.47 (1 H, dd, J = 9.7, 4.4 Hz), 3.83-3.94 (1 H, m), 6.63 (1 H, dq, J = 15.4, 6.1 Hz),

6.93 (1 H, dq, J = 15.4, 1.6 Hz); ^{13}C NMR δ 24.6, 29.1, 49.0, 59.1, 59.5, 74.6, 121.8 (q, J = 270 Hz), 128.5 (q, J = 36 Hz), 134.9 (q, J = 6 Hz); ^{19}F NMR δ -65.2 (d, J = 6 Hz); MS (CI) *m/z* 274 (M + H^+). Anal. Calcd for $C_9H_{14}F_3NO_3S$: C, 39.56; H, 5.16; N, 5.13. Found: C, 39.89; H,5.28 ; N, 4.90.

(*E*)-(2*R*,5*R*)-1-(3,3,3-Trifluoro-1-propenylsulfonyl)-2,5-bis(methoxymethyl)pyrrolidine (2b).

Olefin **2b** was synthesized as similar as **2a** from pyrrolidine (**1b**) (500 mg, 3.14 mmol) as a colorless solid (405 mg, 41 % from **1b**) after chromatography (silica gel, 2 : 1 hexane : EtOAc): R_f 0.41 (2 : 1 hexane : EtOAc); $[\alpha]_D^{25}$ 22.2° (*c* 1.5, $CHCl_3$); mp 64-67 °C; IR (KBr) 1354, 1196, 1159 cm^{-1}; ^{1}H NMR δ 1.81-2.00 (2 H, m), 2.05-2.30 (2 H, m), 3.33 (6 H, s), 3.45 (2 H, dd, J = 9.9, 3.2 Hz), 3.56 (2 H, dd, J = 9.9, 5.5 Hz), 3.83-3.91 (2 H, m), 6.63 (1 H, dq, J = 15.2, 6.1 Hz), 6.95 (1 H, dq, J = 15.2, 1.8 Hz); ^{13}C NMR δ 28.3, 59.00, 60.5, 73.9, 122.1 (q, J = 270 Hz), 126.6 (q, J = 35 Hz), 137.6 (q, J = 6 Hz); ^{19}F NMR δ -65.2 (d, J = 6 Hz); MS (CI) *m/z* 318 (M + H^+). Anal. Calcd for $C_{11}H_{18}F_3NO_4S$: C, 41.64; H, 5.72; N, 4.41. Found: C, 41.82; H, 5.76; N, 4.13.

(*E*)-(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-(3,3,3-Trifluoro-1-propenylsulfonyl)-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (2c).

1c ($[\alpha]_D^{25}$ 6.3° (*c* 1.6, $CHCl_3$); lit.[10] $[\alpha]_D^{25}$ 7.7 (*c* 1.4, $CHCl_3$)) was prepared according to literature method. Olefin **2c** was synthesized as similar as **2a** from **1c** (901 mg, 2.65 mmol) as a colorless solid (670 mg, 55 % from **1c**) after chromatography (silica gel, 2 : 1 hexane : EtOAc): R_f 0.35 (2 : 1 hexane : EtOAc); $[\alpha]_D^{20}$ 20.0° (*c* 1.5, $CHCl_3$); mp 167-170 °C; IR (KBr) 1331, 1146, 1125 cm^{-1}; ^{1}H NMR δ 3.83-3.94 (2 H, m), 4.12 (2 H, dd, J = 13.6, 2.2 Hz), 4.48 (2 H, d, J = 2.4 Hz), 5.19 (2 H, dd, J = 13.6, 0.8 Hz), 5.56 (2 H, s), 6.61 (1 H, dq, J = 15.2, 6.2 Hz), 7.36-7.46 (11 H, m); ^{13}C NMR δ 58.1, 66.6, 78.3, 100.3, 121.7 (q, J = 271 Hz), 128.6 (q, J = 36 Hz), 126.3, 128.8, 129.8, 136.6 (q, J = 6 Hz), 137.3; ^{19}F NMR δ -65.0 (d, J = 6 Hz); MS (CI) *m/z* 498 (M + H^+). Anal. Calcd for $C_{23}H_{22}F_3NO_6S$: C, 55.53; H, 4.46; N, 2.82. Found: C, 55.39; H, 4.55; N, 2.79.

General Procedure for Michael Addition of 2a-c with Dimethyl Malonate.

To a solution of dimethyl malonate (52 mg, 0.39 mmol) in dry THF (1 mL) at 0 °C was added NaH (60 % oil dispersion, 16 mg, 0.39 mmol) under nitrogen atmosphere. The solution was stirred for 10 min at room temperature and then a solution of olefin **2a-c** (0.30 mmol) in dry THF (1 mL) was added. After being stirred for 1 h at room temperature, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : EtOAc). The results are listed in Table 1.

50 : 50 Diastereomeric mixture of (2*S*)-1-[3,3-bis(methoxycarbonyl)-2-(trifluoromethyl)propylsulfonyl]-2-(methoxymethyl)pyrrolidine (6a).

This was obtained from **2a** (82 mg, 0.30 mmol) as a colorless oil (121 mg, 89 %): R_f 0.55 (2 : 1 hexane : EtOAc); IR (neat) 1748, 1155, 1117 cm^{-1}; ^{1}H NMR δ 1.83-2.04 (4 H, m), 3.29-3.55 (5 H, m), 3.37 (1.5 H, s), 3.37 (1.5 H, s), 3.61-3.88 (3 H, m), 3.79 (3 H, s), 3.81 (3 H, s), 4.02 (0.5 H, d, J = 3.6 Hz), 4.08 (0.5 H, d, J = 3.6 Hz); ^{13}C NMR δ 24.9 (combined peak), 28.9, 28.9, 39.6 (q, J = 29 Hz), 39.8 (q, J = 29 Hz), 46.2, 46.3, 48.9, 49.2, 53.2, 53.4, 58.9, 59.0, 59.0, 59.3, 74.9, 75.0, 125.9 (q, J = 281 Hz), 126.0 (q, J = 280 Hz), 167.2

(combined peak), 129.1 167.5, 167.5; ^{19}F NMR δ -69.1 (d, J = 7 Hz), -69.5 (d, J = 10 Hz); MS (CI) *m/z* 406 (M + H^+). Anal. Calcd for $C_{14}H_{22}F_3NO_7S$: C, 41.48; H, 5.47; N, 3.46. Found: C, 41.46; H, 5.40; N, 3.22.

65 : 35 Diastereomeric mixture of (2*R*,5*R*)-1-[3,3-bis(methoxycarbonyl)-2-(trifluoromethyl)-propylsulfonyl]-2,5-bis(methoxymethyl)pyrrolidine (6b).

This was obtained from **2b** (93 mg, 0.30 mmol) as a colorless oil (104 mg, 77 %): R_f 0.43 (2 : 1 hexane : EtOAc); IR (neat) 1740, 1154, 1113 cm^{-1}; ^{1}H NMR δ 1.80-1.99 (2 H, m), 2.06-2.23 (2 H, m), 3.18-3.46 (2 H, m), 3.34 (2.1 H, s), 3.36 (3.9 H, s), 3.47 (0.7 H, dd, J = 9.9, 3.4 Hz), 3.48 (1.3 H, dd, J = 9.9, 3.4 Hz), 3.57 (0.7 H, dd, J = 9.9, 5.6 Hz), 3.58 (1.3 H, dd, J = 9.9, 5.6 Hz), 3.68-3.74 (1 H, m), 3.76 (3.9 H, s), 3.81 (2.1 H), 3.86-3.94 (2 H, m), 4.02 (0.35 H, d, J = 4.0 Hz), 4.08 (0.65 H, d, J = 3.6 Hz); ^{13}C NMR δ 28.0 (combined peak), 39.6 (q, J = 29 Hz), 40.0 (q, J = 29 Hz), 48.0, 48.9, 53.1, 53.4, 59.0 (combined peak), 60.2, 60.5, 73.9, 74.0, 126.0 (q, J = 280 Hz) (combined peak), 167.3, 167.4; ^{19}F NMR δ -69.2 (d, J = 8 Hz, major), -69.4 (d, J = 10 Hz, minor); MS (CI) *m/z* 450 (M + H^+). Anal. Calcd for $C_{16}H_{26}F_3NO_8S$: C, 42.76; H, 5.83; N, 3.12. Found: C, 42.62; H, 5.90; N, 3.19.

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[3,3-Bis(methoxycarbonyl)-2-(trifluoromethyl)propylsulfonyl]-4,4a,5a,6,9*a*,9-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (6c).

This was obtained from **2c** (149 mg, 0.30 mmol) as a colorless oil (147 mg, 72 %): R_f 0.30 (2 : 1 hexane : EtOAc); $[\alpha]_D^{26}$ 50.5° (*c* 1.0, $CHCl_3$); IR (neat) 1746, 1150, 1121 cm^{-1}; ^{1}H NMR δ 3.48 (1 H, dd, J = 14.8, 4.4 Hz), 3.64 (3 H, s), 3.71 (3 H, s), 3.72-3.86 (1 H, m), 3.85-4.00 (2 H, m), 4.07 (2 H, dd, J = 13.6, 2.2 Hz), 4.10 (1 H, d, J = 6.0 Hz), 4.,33 (1 H, dd, J = 14.8, 7.2 Hz), 4.44 (2 H, d, J = 2.2 Hz), 5.18 (2 H, d, J = 13.6 Hz), 5.53 (2 H, s), 7.35-7.48 (10 H, m); ^{13}C NMR δ 40.0 (q, J = 29 Hz), 47.42, 49.2, 53.0, 53.2, 57.9, 65.9-67.0 (m), 78.2, 100.3, 123.1, 125.9 (q, J = 280 Hz), 126.5, 128.7, 129.7, 137.5, 167.0, 167.3; ^{19}F NMR δ -68.6 (d, J = 7 Hz); MS (CI) *m/z* 630 (M + H^+). Anal. Calcd for $C_{28}H_{30}F_3NO_{10}S$: C, 53.42; H, 4.80; N, 2.22. Found: C, 53.39; H, 4.76; N, 2.24.

General Procedure for Michael Addition of 2a-c with Acetophenone.

To a solution of LDA, prepared from *n*-BuLi (1.6 M hexane solution, 0.68 mL, 1.10 mmol) and diisopropylamine (0.14 mL, 1.00 mmol) in dry THF (3 mL) at -78 °C, acetophenone (90 mg, 0.75 mmol) was added under nitrogen atmosphere at -78 °C during 5 min. The solution was stirred for 1 h at -78 °C and then a solution of olefin **2a-c** (0.50 mmol) in THF (1 mL) was added. After being stirred for 1 h at -78 °C, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : EtOAc). The results are listed in Table 1.

60 : 40 Diastereomeric mixture of (2*S*)-1-[4-oxo-4-phenyl-2-(trifluoromethyl)propylsulfonyl]-2-(methoxymethyl)pyrrolidine (7a).

This was obtained from **2a** (137 mg, 0.50 mmol) as a yellow oil (70 mg, 36 %): R_f 0.45 (1 : 1 hexane : EtOAc); IR (neat) 1688, 1339, 1148 cm^{-1}; ^{1}H NMR δ 1.78-2.12 (4 H, m), 3.22 (0.6 H, dd, J = 14.3, 10.7 Hz), 3.31-3.65 (7.4 H, m), 3.36 (1.8 H, s), 3.37 (1.2 H, s), 3.68-3.91 (1 H, m), 4.02-4.19 (1 H, m), 7.23-7.65 (3 H, m), 7.94-8.01 (2 H, m); ^{13}C NMR δ 24.9, 25.1, 28.9, 29.0, 34.9 (q, J = 28 Hz), 35.2 (q, J = 28 Hz), 36.3, 36.5, 48.5, 49.0, 49.4, 49.7, 59.0, 59.1, 59.1, 59.5, 74.8, 75.3, 127.1 (q, J = 279 Hz), 128.5 (combined peak), 129.1

(combined peak), 132.6 (q, J = 269 Hz), 133.9, (combined peak), 136.6, (combined peak), 195.7, 196.0; ^{19}F NMR -71.8 (d, J = 15 Hz, minor), -71.9 (d, J = 15 Hz, major); MS (CI) m/z 394 (M + H$^+$). Anal. Calcd for $C_{17}H_{22}F_3NO_4S$: C, 51.90; H, 5.64; N, 3.56. Found: C, 51.59; H, 5.84; N, 3.34.

73 : 27 Diastereomeric mixture of (2*R*,5*R*)-1-[4-oxo-4-phenyl-2-(trifluoromethyl)propylsulfonyl]-2,5-bis(methoxymethyl)pyrrolidine (7b).

This was obtained from **2b** (156 mg, 0.50 mmol) as a yellow oil (53 mg, 34 %): R_f 0.30 (2 : 1 hexane : EtOAc); IR (neat) 1692, 1340, 1153 cm^{-1}; ^{1}H NMR δ 1.80-2.00 (2 H, m), 2.05-2.26 (2 H, m), 3.33 (4.4 H, s), 3.34 (1.6 H, s), 3.16-3.39 (2 H, m), 3.39-4.01 (2 H, m), 3.43-3.78 (7 H, m), 7.44-7.64 (3 H, m), 7.96-8.03 (2 H, m); ^{13}C NMR δ 27.9, 28.0, 35.2 (q, J = 28 Hz), 35.5 (q, J = 28 Hz), 36.1, 36.4, 49.7, 50.6, 59.0 (combined peak), 127.1 (q, J = 280 Hz), 127.3 (q, J = 262 Hz), 128.5 (combined peak), 129.1 (combined peak), 133.9 (combined peak), 136.7 (combined peak), 195.8, 196.0; ^{19}F NMR δ -71.7 (d, J = 10 Hz), Minor peak was not separable.; MS (CI) m/z 438 (M + H$^+$). Anal. Calcd for $C_{19}H_{26}F_3NO_5S$: C, 52.16; H, 5.99; N, 3.20. Found: C, 52.39; H, 6.13; N, 3.00.

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[4-Oxo-4-phenyl-2-(trifluoromethyl)propylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (7c).

This was obtained from **2c** (249 mg, 0.50 mmol) as a colorless solid (84 mg, 27 %): R_f 0.21 (2 : 1 hexane : Et_2O); $[\alpha]_D^{23}$ 68.6° (c 1.6, $CHCl_3$); mp 70-71 °C; IR (KBr) 1692, 1148, 1117 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.34 (1 H, dd, J = 7.3, 2.8 Hz), 3.51 (1 H, dd, J = 5.6, 1.0 Hz), 3.66 (1 H, dd, J = 7.3, 1.6 Hz), 3.77 (1 H, dd, J = 5.6, 4.4 Hz), 3.81-3.91 (1 H, m), 3.95-4.10 (2 H, m), 4.06-4.17 (2 H, m), 4.45-4.53 (2 H, m), 5.08-5.22 (2 H, m), 5.57 (2 H, s), 7.36-7.98 (15 H, m); ^{13}C NMR δ 35.1 (q, J = 28 Hz), 36.3, 49.6, 58.0, 65.1-68.0 (m), 77.6-78.7 (m), 100.2, 126.3, 127.1 (q, J = 266 Hz), 128.5, 128.7, 129.0, 129.6, 133.8, 136.5, 137.5, 195.7; ^{19}F NMR δ -71.7 (d, J = 7 Hz); MS (CI) m/z 618 (M + H$^+$). Anal. Calcd for $C_{31}H_{30}F_3NO_7S$: C, 60.28; H, 4.90; N, 2.27. Found: C, 60.25; H, 5.02; N, 2.18.

The same Michael reaction of **2c** (249 mg, 0.50 mmol) at 0 °C for 1.5 h after 1 h at -78 °C gave **7c** in a better yield (262 mg, 85 %) (Table 2).

7c was also prepared from **2c** and 1-trimethylsilyloxystyrene. To a solution of **2c** (50 mg, 0.10 mmol) and tetrabutylammonium fluoride (35 mg, 0.25 mmol) in dry THF (1.5 mL) was added a solution of 1-trimethylsilyloxystyrene (29 mg, 0.15 mmol) in dry THF (1 mL) under nitrogen atmosphere. After being stirred overnight at room temperature, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (1 : 1 hexane : Et_2O) to give **7c** (23 mg, 37 %) (Table 2).

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[3,3-Bis(ethoxycarbonyl)-2-(trifluoromethyl)propylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (8).

To a solution of diethyl malonate (120 mg, 0.75 mmol) in dry THF (5 mL) at 0 °C was added NaH (60 % oil dispersion, 30 mg, 0.75 mmol) under nitrogen atmosphere. The solution was stirred for 10 min at room temperature and then a solution of **2c** (249 mg, 0.50 mmol) in dry THF (2.5 mL) was added. After being stirred for 1 h at room temperature, the solution was poured into saturated aqueous NaCl solution (20 mL) and

extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (3 : 1 hexane : EtOAc) to give **8** as a colorless solid (255 mg, 78 %): R_f 0.18 (1 : 1 hexane : Et_2O); $[\alpha]_D^{26}$ 49.4° (*c* 1.3, $CHCl_3$); mp 49-51 °C; IR (KBr) 1738, 1150, 1119 cm^{-1}; ^1H NMR δ 1.18 (3 H, t, *J* = 6.9 Hz), 1.24 (3 H, t, *J* = 7.2 Hz), 3.52 (1 H, dd, *J* = 14.9, 4.6 Hz), 3.71-3.90 (1 H, m), 3.92-4.02 (2 H, m), 4.03-4.29 (5 H, m), 4.13 (2 H, dd, *J* = 13.8, 2.1 Hz), 4.31 (1 H, dd, *J* = 14.9, 6.6 Hz), 4.46 (2 H, d, *J* = 2.1 Hz), 5.20 (2 H, d, *J* = 13.8 Hz), 5.54 (2 H, s), 7.36-7.48 (10 H, m); ^{13}C NMR δ 13.7, 13.9, 40.0 (q, *J* = 29 Hz), 47.8, 49.6, 57.9, 62.2, 62.6, 66.0-67.1 (m), 78.3, 100.4, 126.0 (q, *J* = 281 Hz), 126.5, 128.7, 129.7, 137.6, 166.7, 167.0; ^{19}F NMR δ -72.2 (d, *J* = 8 Hz); MS (CI) *m/z* 658 ($M + H^+$). Anal. Calcd for $C_{30}H_{34}F_3NO_{10}S$: C, 54.79; H, 5.21; N, 2.13. Found: C, 54.53; H, 5.25; N, 2.20.

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[3-Ethoxycarbonyl-2-(trifluoromethyl)propylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (9).

To a solution of LDA prepared from *n*-BuLi (1.6 M hexane solution, 0.37 mL, 0.60 mmol) and diisopropylamine (60 mg, 0.59 mmol) in dry THF (3 mL) at -78 °C, ethyl acetate (40 mg, 0.45 mmol) was added during 5 min at -78 °C under nitrogen atmosphere. The solution was stirred for 1 h at -78 °C and then a solution of olefin **2c** (149 mg, 0.50 mmol) in dry THF (1.5 mL) was added. After being stirred for 1 h at -78 °C, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (1 : 2 hexane : Et_2O) to give **9** as a colorless oil (159 mg, 91 %): R_f 0.39 (1 : 2 hexane : Et_2O); $[\alpha]_D^{21}$ 59.5° (*c* 0.9, $CHCl_3$); IR (neat) 1738, 1148, 1117 cm^{-1}; ^1H NMR δ 1.25 (3 H, t, *J* = 7.1 Hz), 2.67 (1 H, dd, *J* = 17.2, 8.0 Hz), 3.01 (1 H, dd, *J* = 17.2, 3.8 Hz), 3.35 (1 H, dd, *J* = 13.6, 2.4 Hz), 3.36-3.54 (1 H, m), 3.79 (1 H, dd, *J* = 13.6, 10.4 Hz), 3.92-4.04 (2 H, m), 4.10 (2 H, dd, *J* = 13.6, 2.2 Hz), 4.17 (2 H, q, *J* = 7.1 Hz), 4.48 (2 H, d, *J* = 2.2 Hz), 5.17 (2 H, d, *J* = 13.6 Hz), 5.56 (2 H, s), 7.36-7.47 (10 H, m); ^{13}C NMR δ 14.1, 32.6, 36.8 (q, *J* = 28 Hz), 49.0, 58.1, 61.4, 64.8-68.2 (m), 77.5-79.2 (m), 126.3, 126.7 (q, *J* = 280 Hz), 128.8, 129.8, 137.4, 170.4; ^{19}F NMR δ -72.2 (d, *J* = 8 Hz); MS (CI) *m/z* 586 ($M + H^+$). Anal. Calcd for $C_{27}H_{30}F_3NO_8S$: C, 55.38; H, 5.16; N, 2.39. Found: C, 55.30; H, 5.41; N, 2.22.

9 was also prepared from **8** by decarboxylation. The solution of **8** (40 mg, 0.06 mmol), LiCl (3 mg, 0.06 mmol) and H_2O (0.2 mL) in DMF (1 mL) was heated at 130 °C for 14 h in a sealed tube under argon atmosphere. The resulting solution was poured into saturated aqueous NaCl solution (10 mL) and extracted with Et_2O (5 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (3 : 1 hexane : AcOEt) to give **9** (31 mg, 87 %).

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[3-(*N*,*N*-Dimethylaminocarbonyl)-2-(trifluoromethyl)propylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (10).

To a solution of LDA prepared from *n*-BuLi (1.6 M hexane solution, 0.25 mL, 0.40 mmol) and diisopropylamine (39 mg, 0.39 mmol) in dry THF (2.0 mL) at -78 °C, *N*,*N*-dimethylacetamide (26 mg, 0.30 mmol) was added under nitrogen atmosphere. The solution was stirred for 1 h at -78 °C and then a solution of olefin **2c** (100 mg, 0.20 mmol) in dry THF (0.5 mL) was added. After being stirred for 1 h at -78 °C, the solution was poured into saturated aqueous NaCl solution (10 mL) and extracted with Et_2O (5 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (1 : 3 hexane : AcOEt) to give **10** as a colorless solid (111 mg, 95 %): R_f 0.47 (1 : 3 hexane :

EtOAc); $[\alpha]_D^{27}$ 42.7° (*c* 1.2, $CHCl_3$); mp 61-62 °C; IR (KBr) 1651, 1150, 1115 cm^{-1}; ^1H NMR δ 2.62 (1 H, dd, *J* = 17.0, 6.0 Hz), 2.96 (3 H, s), 2.99 (3 H, s), 3.49-3.84 (4 H, m), 4.01-4.17 (4 H, m), 4.46 (2 H, d, *J* = 2.2 Hz), 5.14 (2 H, dd, *J* = 13.0 Hz), 5.55 (2 H, s), 7.34-7.48 (10 H, m); ^{13}C NMR δ 30.8, 35.9, 36.5 (q, *J* = 28 Hz), 37.2, 50.1, 58.1, 62.3-65.8 (m), 78.2, 100.3, 126.4, 127.0 (q, *J* = 279 Hz), 128.7, 129.7, 137.5, 169.2; ^{19}F NMR δ -71.7 (d, *J* = 7 Hz); MS (CI) *m/z* 585 ($M + H^+$). Anal. Calcd for $C_{27}H_{31}F_3N_2O_7S$: C, 55.47; H, 5.34; N, 4.79. Found: C, 55.44; H, 5.47; N, 4.69.

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[4-Hydroxy-3-(hydroxymethyl)-2-(trifluoromethyl)butylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (11).

To a solution of $LiAlH_4$ (9 mg, 0.25 mmol) in dry THF (2 mL) at 0 °C was added a solution of **8** (67 mg, 0.10 mmol) in dry THF (1 mL) under nitrogen atmosphere. After 1 h under reflux, 2 N aqueous NaOH solution (0.3 mL) was added to the solution. After stirring for 1 h at room temperature, resulted precipitates were filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (Et_2O) to give **11** as a colorless solid (32 mg, 55 %): R_f 0.22 (Et_2O); $[\alpha]_D^{24}$ 67.4° (*c* 1.3, $CHCl_3$); mp 70-71 °C; IR (KBr) 3403, 1117, 1086 cm^{-1}; ^1H NMR δ 1.75-2.71 (2 H, br s), 2.23-2.37 (1 H, m), 3.10-3.27 (1 H, m), 3.28 (1 H, dd, *J* = 14.8, 3.6 Hz), 3.65 (2 H, d, *J* = 6.0 Hz), 3.76 (2 H, d, *J* = 6.0 Hz), 3.85-4.04 (2 H, m), 4.03 (1 H, dd, *J* = 14.8, 7.0 Hz), 4.13 (2 H, dd, *J* = 13.6, 2.1 Hz), 4.49 (2 H, d, *J* = 2.1 Hz), 5.16 (2 H, d, *J* = 13.6 Hz), 5.57 (2 H, s), 7.36-7.48 (10 H, m); ^{13}C NMR δ 38.2 (q, *J* = 27 Hz), 42.0, 47.3, 58.1, 62.1, 62.3, 66.3-67.0 (m), 78.3, 100.2, 126.3, 127.4 (q, *J* = 280 Hz), 128.8, 129.8, 137.4; ^{19}F NMR δ -67.5 (d, *J* = 10 Hz); MS (CI) *m/z* 574 ($M + H^+$). Anal. Calcd for $C_{26}H_{30}F_3NO_8S$: C, 54.44; H, 5.27; N, 2.44. Found: C, 54.45; H, 5.33; N, 2.37.

11 (75 mg, 57 %) was also prepared similarly from $LiAlH_4$ (22 mg, 0.58 mmol) in dry THF (3 mL), **6c** (147 mg, 0.23 mmol) in dry THF (1.5 mL), and 2 N aqueous NaOH solution (0.6 mL) as above.

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[4-Hydroxy-2-(trifluoromethyl)butylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (12).

To a solution of $LiAlH_4$ (15 mg, 0.40 mmol) in dry THF (3 mL) at 0 °C was added a solution of **9** (254 mg, 0.43 mmol) in dry THF (2 mL) under nitrogen atmosphere. After heating for 1 h under reflux, 2 N aqueous NaOH solution (0.4 mL) was added to the solution. After stirring for 1 h at room temperature, resulted precipitates were filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (1 : 2 hexane : EtOAc) to give **12** as a colorless solid (201 mg, 89 %): R_f 0.37 (1 : 2 hexane : EtOAc); $[\alpha]_D^{24}$ 74.5° (*c* 1.4, $CHCl_3$); mp 42-44 °C; IR (KBr) 3538, 1148, 1117 cm^{-1}; ^1H NMR δ 1.78-2.13 (4 H, m), 2.95-3.12 (1 H, m), 3.35 (1 H, dd, *J* = 14.5, 3.0 Hz), 3.64-3.84 (1 H, br s), 3.75 (1 H, dd, *J* = 14.5, 8.8 Hz), 3.86-4.02 (2 H, m), 4.12 (2 H, dd, *J* = 13.5, 2.2 Hz), 4.48 (2 H, d, *J* = 2.2 Hz), 5.17 (2 H, d, *J* = 13.5 Hz), 5.56 (2 H, s), 7.35-7.47 (10 H, m); ^{13}C NMR δ 30.9, 36.3 (q, *J* = 27 Hz), 49.4, 58.1, 59.1, 66.2-67.3 (m), 78.4, 100.2, 126.3, 127.5 (q, *J* = 279 Hz), 128.8, 129.8, 137.4; ^{19}F NMR δ -71.5 (d, *J* = 10 Hz); MS (CI) *m/z* 544 ($M + H^+$). Anal. Calcd for $C_{25}H_{28}F_3NO_7S$: C, 55.24; H, 5.19; N, 2.58. Found: C, 55.16; H, 5.30; N, 2.55.

12 was also prepared from **10** by reduction. To a solution of $LiEt_3BH$ (1.0 M THF solution, 1.14 mL, 1.14 mmol) was added a solution of **10** (167 mg, 0.29 mmol) in dry THF (1 mL) at 0 °C under nitrogen atmosphere. After being stirred for 1 h, H_2O (2 mL) and 30 % aqueous H_2O_2 solution (1 mL) was added to the

solution. After being stirred for 1 h at 60 °C, powdered solid K_2CO_3 was added to the solution until the solution was saturated. The resulting solution was extracted with Et_2O (5 mL × 3) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : EtOAc) to give **12** as a colorless solid (120 mg, 80 %).

(2*R*,4a*S*,5a*S*,8*R*,9a*R*)-1-[4-Hydroxy-4,4-diphenyl-2-(trifluoromethyl)butylsulfonyl]-4,4a,5a,6,9a,9b-hexahydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4',5'-*d*]pyrrole (13).

To a solution of PhMgBr prepared from bromobenzene (590 mg, 3.76 mmol) and magnesium (turnings, 101 mg, 4.14 mmol) in dry Et_2O (3 mL) was added a solution of **9** (220 mg, 0.38 mmol) in dry Et_2O (1.5 mL) at 0 °C under nitrogen atmosphere. After being stirred overnight at room temperature, the solution was poured into saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (3 : 1 hexane : EtOAc) to give **13** as a colorless solid (159 mg, 61 %): R_f 0.32 (3 : 1 hexane : EtOAc); $[\alpha]_D^{23}$ 68.6° (*c* 1.6, $CHCl_3$); mp 89-90 °C; IR (KBr) 3524, 1148, 1117 cm^{-1}; ^1H NMR δ 2.54 (1 H, dd, *J* = 15.0, 8.0 Hz), 2.85 (1 H, dd, *J* = 15.0, 2.4 Hz), 2.83-3.08 (1 H, m), 3.48 (1 H, dd, *J* = 15.0, 5.0 Hz), 3.598 (1 H, s), 3.88-4.01 (2 H, m), 4.00-4.16 (1 H, m), 4.08 (2 H, dd, *J* = 13.6, 2.2 Hz), 4.45 (2 H, d, *J* = 2.2 Hz), 5.16 (2 H, d, *J* = 13.6 Hz), 5.55 (2 H, s), 7.21-7.49 (20 H, m), ^{13}C NMR δ 25.5, 36.0 (q, *J* = 28 Hz), 39.8, 50.8, 58.0, 66.2-66.9 (m), 78.3, 100.2, 126.1, 126.1, 126.3, 126.4, 127.4 (q, *J* = 279 Hz), 127.5, 128.7, 128.8 (2C), 128.9, 129.8, 137.5, 144.7, 148.0; ^{19}F NMR δ -71.4 (d, *J* = 10 Hz); MS (CI) *m/z* 696 ($M + H^+$). Anal. Calcd for $C_{37}H_{36}F_3NO_7S$: C, 63.87; H, 5.22; N, 2.01. Found: C, 63.78; H, 5.54; N, 2.12.

13 was similarly prepared from **7c**. To a solution of PhMgBr prepared from bromobenzene (345 mg, 2.20 mmol) and magnesium (turnings, 58 mg, 2.40 mmol) in dry Et_2O (2 mL) was added a solution of **7c** (161 mg, 0.26 mmol) in dry Et_2O (0.5 mL) at 0 °C in 15 min under nitrogen atmosphere. After being stirred overnight at room temperature, the solution was poured into saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (3 : 1 hexane : EtOAc) to give **13** (72 mg, 40 %).

X-Ray Structure Determination of 11.

Colorless crystals of **11** were obtained by layering a concentrated solution of **11** in chloroform with ethanol. One of the crystals having approximate dimensions of 0.8, 0.5, 0.3 mm was mounted on a glass capillary. All measurements were made on a Rigaku diffractometer (AFC5R) with Mo Kα radiation. Cell constants and an orientation matrix for data collection were obtained from least squares refinement using the setting angles of 25 reflections in the range $41.6 < \theta < 46.4$ corresponding to a monoclinic cell with dimensions a = 10.835 (1) Å, b = 9.793 (1) Å, c = 12.690 (1) Å, β = 103.548 (7)°. For Z = 2 and FW = 573.58, the calculated density is 1.455 g/cm^3. Based on the systematic absences, the space group was determined to be $P2_1$. The data were collected at 23 °C using the ω – 2θ scan technique to a maximum 2θ value of 55.0°. A total of 3337 reflections was collected. The unique set contains only 3176 reflections (R_{int} = 0.012). The standards were measured after every 150 reflections. No crystal decay was noticed. No absorption correction was made.

The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The final least-squares refinement gave R = 0.034, Rw = 0.042, and GoF = 1.69. The weighting scheme was based on

counting statistics and included a factor (p = 0.03) to downright the intense reflections. The maximum and minimum peaks on the final difference Fourier map corresponding to 0.18 and -0.17 e/a^3, respectively.

All calculations were performed using the TEXSAN^{TM} crystallographic software package of Molecular Structure Corporation (1985).

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