A Novel Synthetic Approach to 2,2,2-Trifluoroethylidene Derivatives from Ketones

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An approach to 2,2,2-trifluoroethylidene derivatives from ketones was explored by employing the Corey–Winter's reductive elimination of 4-trifluoromethyl-1,3-dioxolane-2-thiones to 2,2,2-trifluoroethylidene derivatives as a key step. The 1,3-dioxolane-2-thione derivatives were readily prepared from ketones in five steps by sequential formation of *O*-silylated cyanohydrins, reduction, addition of trifluoromethyltrimethylsilane, desilylation, and formation of the 1,3-dioxolane-2-thione system.

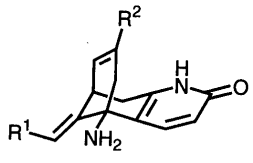
Key words 2,2,2-trifluoroethylidene derivative; ketone; Corey–Winter's reductive elimination; 4-trifluoromethyl-1,3-dioxolane-2-thione; *O*-silylated cyanohydrin; trifluoromethyltrimethylsilane

Biologically active compounds bearing a trifluoromethyl group have attracted much attention in the fields of medicinal and agricultural chemistry because they often exhibit unique biological properties.[3] In the course of our studies directed at improving the biological properties of huperzine A (**1**),[4] a potent acetylcholinesterase inhibitor, we designed and synthesized the novel trifluoromethyl-substituted analogues **2** and **3** (Fig. 1).[5] We have succeeded in constructing the 2,2,2-trifluoroethylidene moiety in **2** and **3** by employing Corey–Winter's reductive elimination of the 4-trifluoromethyl-1,3-dioxolane-2-thione system.[5]

Thus, as shown in Chart 1, treatment of the 4-trifluoromethyl-1,3-dioxolane-2-thione **7**, prepared from the known β-ketoester **4**[6] *via* the α-siloxy aldehyde **5** and the diol **6** in 7 steps,[5] under the conditions of the Corey–Winter's reductive elimination[7] was found to give the desired 2,2,2-trifluoroethylidene derivative **8** in an excellent yield. The elimination product **8** could be effectively transformed to **2** and **3**.[5] Since a ketone can be readily converted to the corresponding homologated α-siloxy aldehyde by sequential formation of the *O*-silylated cyanohydrin and reduction,[8] our synthetic route from **4** to **8** is anticipated to hold promise as a novel synthetic approach to the 2,2,2-trifluoroethylidene derivatives **10** from the corresponding ketones **9**.

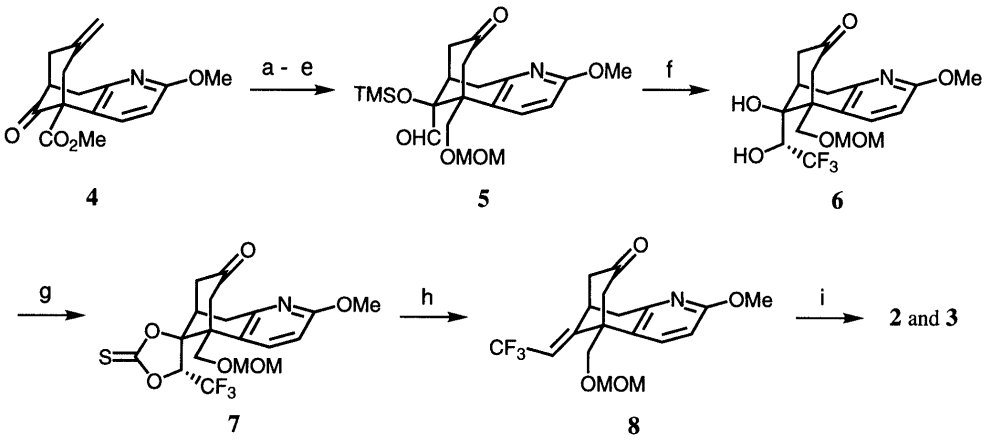
In order to explore this possibility, preparation of **10** from **9** bearing various fundamental structural arrays was studied. This paper describes a novel synthetic scheme to **10** from **9** which is highly reliable and general similarly to some existing methods.[9,10]

Thus, as shown in Chart 2, five sorts of ketones **9** were converted to the corresponding α-siloxy aldehydes **12** by treatment with trimethylsilyl cyanide (TMSCN) or *tert*-butyldimethylsilyl cyanide (TBDMSCN) in the presence



1 : $R^1 = R^2 = Me$ (huperzine A)
2 : $R^1 = CF_3$, $R^2 = Me$
3 : $R^1 = R^2 = CF_3$

Fig. 1



a) CH_2=CHMgBr, THF, -78 °C b) TMSOTf, 2,6-di-*t*-butylpyridine, CH_2Cl_2, rt, 51% (2 steps) c) DIBAL, CH_2Cl_2, -78 °C, 68% d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 81% e) O_3, 10% MeOH - CH_2Cl_2, -78 °C ; Me_2S, rt, 71% f) $TMSCF_3$ - TBAF (cat.), THF ; then TBAF (2.0eq), 81% g) Im_2CS, PhMe, reflux, 79% h) $(MeO)_3P$, 110°C, 92% i) See ref. 5 .
(For the abbreviations, see the manuscript and the experimental section.)

Chart 1

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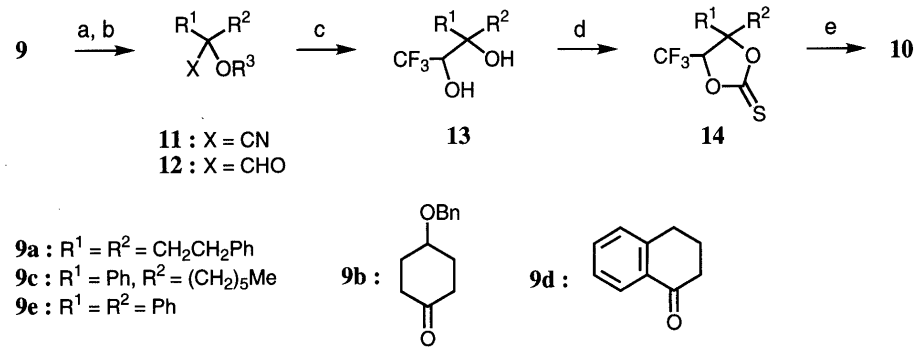

a) TMSCN (for **9a-d**) or TBDMSCN (for **9e**) -ZnI_2, rt, 1~2 h b) DIBAL, Et_2O, 0 °C, 30 ~ 40 min c) $TMSCF_3$ (1.1 eq)-TBAF (0.005 ~ 0.01 eq), THF, rt, 0.5 ~ 2 h ; then TBAF (2 eq), THF, rt, 10 min d) Im_2CS (1.1 eq), PhMe, 110 °C, 30 min e) $(MeO)_3P$, 130 °C, 13 h. (For the abbreviations, see the manuscript and the experimental section.)

Chart 2

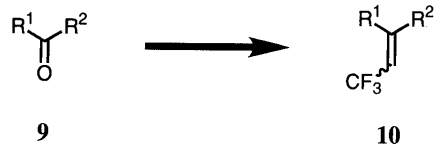

Fig. 2

of zinc iodide (ZnI_2) followed by reduction of the resulting *O*-silylated cyanohydrins **11** with diisobutylaluminum hydride (DIBAL).[8] Addition of trifluoromethyltrimethylsilane ($TMSCF_3$) to **12** in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF)[11] followed by desilylation with TBAF produced the α-trifluoromethyl-α,β-diols **13**. Treatment of **13** with 1,1′-thiocarbonyldiimidazole (Im_2CS) and Corey–Winter's reductive elimination[7] of the resulting 4-trifluoromethyl-1,3-dioxolane-2-thiones **14** with trimethyl phosphite [$(MeO)_3P$] cleanly furnished the desired **10**.

The results summarized in Table 1 deserve some comment. Thus, in the preparation of **10b**, a 4 : 1 mixture of the two stereoisomers was produced by the reaction of **9b** with TMSCN. This was subjected to further synthetic steps without separation, giving rise to a mixture of the major and the minor stereoisomers, **13Ab** and **13Bb**, at the stage of **13b**. These could be cleanly separated by column chromatography. Determination of the stereostructures of **13Ab** and **13Bb** was not attempted, since **14Ab** and **14Bb**, derived from **13Ab** and **13Bb**, respectively, converged to the same product **10b** in the reductive elimination. In the cases of **9c,d** where the R^1 and R^2 groups are different, mixtures of the major and the minor diastereomers, **13Ac, d** and **13Bc, d**, were produced by adding $TMSCF_3$ to **12c, d**. Separation of these diastereomers was achieved at the stage of **14c** and **13d** by column chromatography. Diastereomeric 4-trifluoromethyl-1,3-dioxolane-2-thiones **14Ac, d** and **14Bc, d** were subjected to the reductive elimination reaction to afford (*E*)- and (*Z*)-**10c, d** as the sole products, respectively. The configurations of (*E*)- and (*Z*)-**10c, d** were established by nuclear Overhauser effect (NOE) measurements in the ^{1}H-NMR spectra. Since the Corey–Winter's elimination reaction is well known to proceed with *cis*-stereospecificity,[7] the stereostructures of **13Ac, d**, **13Bc, d**, **14Ac, d**, and **14Bc, d** could be unambiguously assigned.

Table 1. Synthesis of 2,2,2-Trifluoroethylidene Derivatives (**10**) from Ketones (**9**)

	Yield (%)				
9	**11**	**12**	**13**	**14**	**10**
a	95	93	72	95	86
b	94[a]	50[a]	76 (**A**)[b]	100 (**A**)[b]	91
			11 (**B**)[b]	99 (**B**)[b]	80
c	89	85	95 (**A**+**B**)[c]	60 (**A**)[d]	92 (*E*)[e]
				37 (**B**)[d]	88 (*Z*)[e]
d	90	71	57 (**A**)[d]	84 (**A**)[d]	93 (*E*)[e]
			15 (**B**)[d]	88 (**B**)[d]	66 (*Z*)[e]
e	76	82	94	95	89

a) A 4 : 1 mixture of the two stereoisomers was obtained. This was directly subjected to the next step without separation. *b*) The stereostructure of this compound was not determined since **13Ab** and **13Bb** could be converged to the same **10** by way of **14Ab** and **14Bb**, respectively. *c*) A 2 : 1 mixture of the two diastereomers was produced. Attempted separation of this mixture met with failure. *d*) The stereostructure of this compound could be unambiguously assigned based on the configuration of **10** derived from this compound. *e*) The configuration of this compound was established by NOE measurement in the ^{1}H-NMR spectrum.

Thus, we have succeeded in developing a novel synthetic approach to **10** from **9**. Although six synthetic operations are required, this synthetic route may have potential as one of the most reliable and general methods to produce **10** from **9** due to its good overall yield, mild reaction conditions, and operational simplicity.

Experimental

All melting points were determined with a Yamato MP-21 micro melting point apparatus and are uncorrected. ^{1}H-NMR and ^{19}F-NMR spectra were measured with a Bruker AC-200 (200 MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (for protons) ($\delta=0$) and trichlorofluoromethane (for fluorine) ($\delta=0$) as internal standards. Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low- and high-resolution mass spectra (MS and HR-MS) were taken with a Hitachi RMU-6MG spectrometer and a Hitachi M-80A spectrometer, respectively. Routine

monitoring of reactions was carried out using Merck 60 F_{254} silica gel, glass-supported TLC plates. Flash column chromatography was performed on Silica gel 60 (Kanto Chemical Co.). The following abbreviations are used for solvents and reagents: diethyl ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), tetrahydrofuran (THF), toluene (PhMe), water (H_2O), ammonium chloride (NH_4Cl), sodium sulfate (Na_2SO_4), trimethyl phosphite [$(MeO)_3P$], and zinc iodide (ZnI_2).

4-Phenyl-2-(2-phenylethyl)-2-(trimethylsiloxy)butyronitrile (11a) Zinc iodide (12 mg, 38 μmol) was added to a mixture of **9a**[12] (515 mg, 2.2 mmol) and TMSCN (327 mg, 3.3 mmol) at room temperature. The mixture was stirred at the same temperature for 2 h, then excess TMSCN was removed *in vacuo*. The residue was purified by column chromatography on silica gel (C_6H_{14} : EtOAc = 50 : 1) to afford **11a** as a colorless oil (693 mg, 95%). IR (neat): 3040, 2970, 1610, 1500, 1460, 1260, 1120 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.32—7.19 (10H, m), 2.89—2.74 (4H, m), 2.14—2.06 (4H, m), 0.30 (9H, s). EI-MS *m/z*: 322 ($M-15^+$, 9), 247 (19), 105 (27), 91 (100), 73 (16). HR-MS *m/z*: Calcd for $C_{21}H_{27}NOSi-CH_3$($M-15^+$): 322.1625. Found: 322.1616.

4-Benzyloxy-1-cyano-1-(trimethylsiloxy)cyclohexane (11b) Treatment of **9b**[13] (295 mg, 1.5 mmol) in the same manner as described for **9a** gave **11b** as a colorless oil (412 mg, 94%) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (neat): 3080, 3040, 2960, 2870, 1500, 1450, 1370, 1255, 1125, 1090, 1070, 1030 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.36—7.30 (5H, m), 4.53 (0.4H, s), 4.51 (1.6H, s), 3.60—3.42 (1H, m), 2.22—1.68 (8H, m), 0.25 (9H, s). This ^{1}H-NMR spectrum showed that **11b** is a 4 : 1 mixture of the two stereoisomers. EI-MS *m/z*: 303 (M^+, 2), 288 ($M-15^+$, 2), 170 (22), 91 (100). HR-MS *m/z*: Calcd for $C_{17}H_{25}NO_2Si$ (M^+): 303.1653. Found: 303.1678.

2-Phenyl-2-(trimethylsiloxy)octanonitrile (11c) The same treatment of **9c** (0.81 g, 4.3 mmol) as described for **9a** gave **11c** as a colorless oil (1.09 g, 89%) after purification by column chromatography (C_6H_{14}). IR (neat): 2960, 2940, 2870, 1490, 1450, 1255, 1105 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.53—7.48 (2H, m), 7.41—7.35 (3H, m), 2.10—1.82 (2H, m), 1.55—1.20 (8H, m), 0.86 (3H, br t, J = 6.1 Hz), 0.13 (9H, s). EI-MS *m/z*: 289 (M^+, 3), 274 ($M-15^+$, 3), 204 (98), 105 (100), 75 (18). HR-MS *m/z*: Calcd for $C_{17}H_{27}NOSi$ (M^+): 289.1859. Found: 289.1834.

1-Cyano-1-(trimethylsiloxy)-1,2,3,4-tetrahydronaphthalene (11d)[14] Treatment of **9d** (292 mg, 2.0 mmol) in the same manner as described for **9a** gave **11d** as a colorless oil (442 mg, 90%) after purification by column chromatography (C_6H_{14} : EtOAc = 50 : 1). IR (neat): 3070, 3030, 2960, 2850, 1495, 1455, 1340, 1255, 1220, 1190, 1135, 1105, 1070, 1050, 1020 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.67—7.63 (1H, m), 7.29—7.24 (2H, m), 7.13—7.09 (1H, m), 2.83 (2H, t, J = 7.0 Hz), 2.40—1.88 (4H, m), 0.21 (9H, s). EI-MS *m/z*: 230 ($M-15^+$, 27), 203 (95), 155 (100), 129 (11), 75 (42). HR-MS *m/z*: Calcd for $C_{14}H_{19}NOSi-CH_3$ ($M-15^+$): 230.1000. Found: 230.1012.

2,2-Diphenyl-2-(*tert*-butyldimethylsiloxy)acetonitrile (11e) Similar treatment of **9e** (237 mg, 1.3 mmol) and TBDMSCN (221 mg, 1.6 mmol) to that described for **9a** gave **11e** as a colorless oil (319 mg, 76%) after purification by column chromatography (C_6H_{14}). IR (neat): 3080, 2960, 2940, 1490, 1475, 1450, 1260, 1200, 1120, 1100, 1070, 1010 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.56—7.48 (4H, m), 7.42—7.30 (6H, m), 0.98 (9H, s), 0.02 (6H, s). EI-MS *m/z*: 323 (M^+, 1), 308 ($M-15^+$, 3), 266 (100), 192 (13), 165 (18). HR-MS *m/z*: Calcd for $C_{20}H_{25}NOSi$ (M^+): 323.1704. Found: 323.1719.

4-Phenyl-2-(2-phenylethyl)-2-(trimethylsiloxy)butanal (12a) A solution of DIBAL (0.93 M solution in C_6H_{14}, 1.95 ml, 1.8 mmol) was added to a solution of **11a** (510 mg, 1.5 mmol) in Et_2O (8 ml) at 0 °C under an argon atmosphere. The mixture was stirred at the same temperature for 40 min, then poured into saturated NH_4Cl and extracted with EtOAc. The organic extracts were combined, washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (C_6H_{14} : EtOAc = 20 : 1) to afford **12a** as a colorless oil (478 mg, 93%). IR (neat): 3040, 2970, 1750, 1610, 1500, 1460, 1260, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.61 (1H, s, CHO), 7.31—7.16 (10H, m), 2.75—2.67 (2H, m), 2.59—2.51 (2H, m), 2.04—1.96 (4H, m), 0.25 (9H, s). EI-MS *m/z*: 325 ($M-15^+$, 3), 311 (100), 91 (69), 73 (32). HR-MS *m/z*: Calcd for $C_{21}H_{28}O_2Si-CH_3$ ($M-15^+$): 325.1622. Found: 325.1632.

4-Benzyloxy-1-formyl-1-(trimethylsiloxy)cyclohexane (12b) Treatment of **11b** (a 4 : 1 mixture of the two stereoisomers) (476 mg, 1.6 mmol) in the same manner as described for **11a** gave **12b** as a colorless oil (239 mg, 50%) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (neat): 3080, 3040, 2960, 2870, 1740, 1675, 1500, 1455, 1370, 1250, 1090, 1070, 1030 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.54 (0.8H, s, CHO), 9.50 (0.2H, s, CHO), 7.36—7.27 (5H, m), 4.56 (1.6H, s), 4.51 (0.4H, s), 3.68—3.42 (1H, m), 2.09—1.65 (8H, m), 0.16 (9H, s). This ^{1}H-NMR spectrum showed that **12b** is a 4 : 1 mixture of the two stereoisomers. EI-MS *m/z*: 277 ($M-29^+$, 82), 169 (92), 91 (100). HR-MS *m/z*: Calcd for $C_{17}H_{26}O_3Si-CHO$ ($M-29^+$): 277.1623. Found: 277.1631.

2-Phenyl-2-(trimethylsiloxy)octanal (12c) The same treatment of **11c** (1.09 g, 3.8 mmol) as described for **11a** gave **12c** as a colorless oil (0.93 g, 85%) after purification by column chromatography (C_6H_{14}). IR (neat): 2960, 2940, 2860, 1740, 1450, 1255, 1160, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.54 (1H, s, CHO), 7.39—7.27 (5H, m), 2.25—2.08 (1H, m), 1.98—1.82 (1H, m), 1.38—1.00 (8H, m), 0.84 (3H, t, J = 6.1 Hz), 0.19 (9H, s). EI-MS *m/z*: 277 ($M-15^+$, 6), 263 (77), 120 (74), 105 (100), 75 (42). HR-MS *m/z*: Calcd for $C_{17}H_{28}O_2Si-CH_3$ ($M-15^+$): 277.1623. Found: 277.1639.

1-Formyl-1-(trimethylsiloxy)-1,2,3,4-tetrahydronaphthalene (12d) Treatment of **11d** (1.07 g, 4.4 mmol) in the same manner as described for **11a** gave **12d** as a colorless oil (0.77 g, 71%) after purification by column chromatography (C_6H_{14} : EtOAc = 50 : 1). IR (neat): 2960, 1740, 1490, 1450, 1250, 1140, 1100, 1060, 1040 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.55 (1H, s, CHO), 7.37—7.21 (4H, m), 2.85—2.73 (2H, m), 2.33—2.22 (1H, m), 2.01—1.89 (3H, m), 0.07 (9H, s). EI-MS *m/z*: 233 ($M-15^+$, 10), 219 (100), 73 (55). HR-MS *m/z*: Calcd for $C_{14}H_{20}O_2Si-CH_3$ ($M-15^+$): 233.0997. Found: 233.0997.

2,2-Diphenyl-2-(*tert*-butyldimethylsiloxy)acetaldehyde (12e) Treatment of **11e** (69 mg, 0.21 mmol) in a similar manner to that described for **11a** gave **12e** as a colorless oil (57 mg, 82%) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (neat): 3080, 2960, 2940, 2860, 1740, 1495, 1475, 1450, 1260, 1200, 1140, 1100, 1075 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.70 (1H, s, CHO), 7.34 (10H, s), 0.95 (9H, s), −0.18 (6H, s). EI-MS *m/z*: 311 ($M-15^+$, 4), 297 (100), 269 (80), 239 (12), 165 (19), 73 (47).

1,1,1-Trifluoro-5-phenyl-3-(2-phenylethyl)pentane-2,3-diol (13a) A solution of TBAF (1.0 M solution in THF, 10 μl, 10 μmol) was added to a solution of **12a** (394 mg, 1.2 mmol) and $TMSCF_3$, (200 μl, 1.3 mmol) in THF (3 ml) at 0 °C. The mixture was stirred at room temperature for 2 h, then a solution of TBAF (1.0 M solution in THF, 2.4 ml, 2.4 mmol) was added to the reaction mixture at room temperature. The whole was stirred for 10 min, then poured into water and extracted with EtOAc. The organic extracts were combined, washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The residue was purified by column chromatography (C_6H_{14} : EtOAc = 4 : 1) to give **13a** as a colorless solid (282 mg, 72%). Recrystallization from C_6H_{14}–EtOAc gave an analytical sample of **13a** as colorless needles, mp 117—118 °C. IR (KBr): 3400, 2970, 1610, 1500, 1460, 1400, 1280, 1150 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.33—7.19 (10H, m), 4.01 (1H, quint, J = 7.6 Hz), 3.04 (1H, d, J = 7.8 Hz, OH), 2.82—2.69 (4H, m), 2.15—1.93 (5H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.5 (d, J = 6.7 Hz). EI-MS *m/z*: 320 ($M-18^+$, 14), 239 (14), 117 (23), 105 (15), 91 (100). *Anal.* Calcd for $C_{19}H_{21}F_3O_2$: C, 67.44; H, 6.26. Found: C, 67.69; H, 6.49.

4-Benzyloxy-1-(2,2,2-trifluoro-1-hydroxyethyl)cyclohexanol (13Ab, 13Bb) Treatment of **12b** (a 4 : 1 mixture of the two stereoisomers) (239 mg, 0.78 mmol) in the same manner as described for **12a** gave a mixture of **13Ab** and **13Bb** after concentration *in vacuo*. Separation of this mixture by column chromatography (C_6H_{14} : EtOAc = 10 : 1) afforded the major product **13Ab** as colorless needles (180 mg, 76%), mp 103—104 °C (recrystallized from C_6H_{14}) and **13Bb** as colorless needles (25 mg, 11%), mp 96—97 °C (recrystallized from C_6H_{14}). **13Ab**: IR (KBr): 3460, 3400, 2950, 1370, 1280, 1170, 1120, 1100, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.36—7.29 (5H, m), 4.57 (2H, s), 3.67 (1H, quint, J = 8.1 Hz), 3.45—3.30 (1H, m), 3.08 (1H, d, J = 8.1 Hz, OH), 2.00—1.40 (9H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.9 (d, J = 6.8 Hz). EI-MS *m/z*: 286 ($M-18^+$, 1), 107 (28), 91 (100). *Anal.* Calcd for $C_{15}H_{19}F_3O_3$: C, 59.20; H, 6.29. Found: C, 59.30; H, 6.39. **13Bb**: IR (KBr): 3400, 2950, 2900, 1400, 1380, 1280, 1170, 1140, 1100 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.35—7.27 (5H, m), 4.51 (2H, s), 3.74 (1H, quint, J = 8.1 Hz), 3.66 (1H, br s), 3.04 (1H, d, J = 8.5 Hz, OH), 2.09—1.90 (1H, m), 1.90—1.60 (8H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.8 (d, J = 7.1 Hz). EI-MS *m/z*: 213 (8), 104 (10), 91 (100). CI-MS *m/z*: 305 (MH^+). *Anal.* Calcd for $C_{15}H_{19}F_3O_3$: C, 59.20; H, 6.29. Found: C, 59.41; H, 6.39.

(2*R,3*S**)- and (2*R**,3*R**)-1,1,1-Trifluoro-3-phenylnonane-2,3-diol (13Ac, 13Bc)** The same treatment of **12c** (291 mg, 1.0 mmol) as described for **12a** gave a mixture of **13Ac** and **13Bc** as a colorless solid (275 mg, 95%) after purification by column chromatography (C_6H_{14}: EtOAc = 5 : 1). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.41—7.28 (5H, m), 4.12 (1H, quint, J = 7.1 Hz), 2.98 (0.33H, d, J = 7.5 Hz, OH), 2.80 (0.67H, d, J = 7.5 Hz, OH), 2.39 (0.67H, s, OH), 2.37 (0.33H, s, OH), 2.28—1.85 (2H, m), 1.29—1.19 (7H, m), 0.95—0.80 (1H, m), 0.82 (3H, t, J = 6.2 Hz). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.0 (2F, d, J = 6.9 Hz), −71.1 (1F, d, J = 7.1 Hz). The ratio of **13Ac** and **13Bc** was estimated as 2 : 1 based on these ^{1}H-NMR and ^{19}F-NMR spectra. EI-MS m/z: 272 ($M-18^+$, 1), 205 (14), 191 (100), 105 (32), 91 (20), 77 (29). HR-MS m/z: Calcd for $C_{15}H_{21}F_3O_2$–H_2O ($M-18^+$): 272.1387. Found: 272.1371. The stereostructures of **13Ac** and **13Bc** were determined based on the formation ratio of (*E*)- and (*Z*)-**10c** derived from this sample by way of **14Ac** and **14Bc**.

(1*R,1′*S**)- and (1*R**,1′*R**)-1-(2,2,2-Trifluoro-1-hydroxyethyl)-1,2,3,4-tetrahydro-1-naphthol (13Ad, 13Bd)** Treatment of **12d** (400 mg, 1.6 mmol) in the same manner as described for **12a** gave a mixture of **13Ad** and **13Bd** after concentration *in vacuo*. Separation of this mixture by column chromatography (C_6H_{14} : EtOAc = 4 : 1) afforded the major product **13Ad** as colorless needles (227 mg, 57%), mp 123—124 °C (recrystallized from C_6H_{14}–EtOAc) and the minor product **13Bd** as a colorless oil (61 mg, 15%). **13Ad**: IR (KBr): 3530, 3400, 3300, 1265, 1190, 1165, 1140, 1100, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.60—7.50 (1H, m), 7.28—7.20 (2H, m), 7.18—7.10 (1H, m), 4.38 (1H, dq, J = 6.7, 6.3 Hz), 3.30 (1H, d, J = 6.3 Hz, OH), 2.92—2.70 (2H, m), 2.44 (1H, s, OH), 2.30—2.15 (1H, m), 2.10—2.03 (1H, m), 1.99—1.82 (2H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.0 (d, J = 6.7 Hz). EI-MS m/z: 228 ($M-18^+$, 100), 211 (10), 147 (54). *Anal.* Calcd for $C_{12}H_{13}F_3O_2$: C, 58.56; H, 5.32. Found: C, 58.51; H, 5.29. **13Bd**: IR (neat): 3450, 2950, 1390, 1340, 1280, 1170, 1080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.65—7.55 (1H, m), 7.30—7.20 (2H, m), 7.20—7.10 (1H, m), 4.37 (1H, dq, J = 7.0, 5.8 Hz), 2.80 (2H, t, J = 6.3 Hz), 2.42 (1H, d, J = 5.8 Hz, OH), 2.42—2.30 (1H, m), 2.22 (1H, s, OH), 2.02—1.82 (3H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −71.3 (d, J = 7.0 Hz). EI-MS m/z: 228 ($M-18^+$, 3), 211 (2), 147 (100), 129 (27), 118 (12), 115 (11), 91 (36). HR-MS m/z: Calcd for $C_{12}H_{13}F_3O_2$–H_2O ($M-18^+$): 228.0761. Found: 228.0764. The stereostructures of **13Ad** and **13Bd** were assigned based on those of (*E*)- and (*Z*)-**10d** derived from these samples by way of **14Ad** and **14Bd**, respectively.

3,3,3-Trifluoro-1,1-diphenylpropane-1,2-diol (13e) Similar treatment of **12e** (50.5 mg, 0.16 mmol) to that described for **12a** gave **13e** as colorless needles (41.0 mg, 94%), mp 118—119 °C (recrystallized from C_6H_{14}) after purification by column chromatography (C_6H_{14} : EtOAc = 3 : 1). IR (KBr): 3600, 3450, 1450, 1375, 1340, 1260, 1195, 1120, 1055 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.55—7.25 (10H, m), 4.97 (1H, dq, J = 7.0, 6.9 Hz), 3.02 (1H, d, J = 7.0 Hz, OH), 3.00 (1H, s, OH). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −70.7 (d, J = 7.1 Hz). EI-MS m/z: 264 ($M-18^+$, 1), 183 (81), 105 (100), 77 (62). *Anal.* Calcd for $C_{15}H_{13}F_3O_2$: C, 63.83; H, 4.64. Found: C, 64.03; H, 4.61.

4-Trifluoromethyl-5,5-bis(2-phenylethyl)-1,3-dioxolane-2-thione (14a) A solution of **13a** (119 mg, 0.35 mmol) and Im_2CS (75 mg, 0.42 mmol) in PhMe (2.0 ml) was heated at 110 °C for 30 min. After concentration *in vacuo*, the residue was purified by column chromatography (C_6H_{14} : EtOAc = 5 : 1) to afford **14a** (127 mg, 95%) as a colorless solid. Recrystallization from C_6H_{14} gave an analytical sample of **14a** as colorless prisms, mp 87—88 °C. IR (KBr): 3040, 2970, 1610, 1500, 1460, 1400, 1320, 1280, 1190, 1150, 1130, 1040 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.37—7.18 (10H, m), 4.79 (1H, q, J = 6.6 Hz), 2.94—2.68 (4H, m), 2.38—2.18 (4H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.6 (d, J = 6.5 Hz). EI-MS m/z: 380 (M^+, 12), 211 (17), 91 (100). *Anal.* Calcd for $C_{20}H_{19}F_3O_2S$: C, 63.14; H, 5.03. Found: C, 62.88; H, 4.94.

4-Benzyloxy-5′-trifluoromethylcyclohexanespiro-4′-(1′,3′-dioxolane)-2′-thione (14Ab, 14Bb) Treatment of **13Ab** (105 mg, 0.35 mmol) and **13Bb** (3.1 mg, 10 μmol) in the same manner as described for **13a** gave **14Ab** as colorless prisms (119 mg, 100%), mp 117—118 °C (recrystallized fom C_6H_{14}–EtOAc) and **14Bb** as a colorless oil (3.5 mg, 99%), respectively, after purification by column chromatography (C_6H_{14} : EtOAc = 5 : 1 for **14Ab** and C_6H_{14} : EtOAc = 6 : 1 for **14Bb**). **14Ab**: IR (KBr): 2980, 2890, 1500, 1460, 1390, 1355, 1310, 1280, 1240, 1210, 1135, 1090, 1030 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.28 (5H, m), 4.62 (1H, q, J = 6.6 Hz), 4.57 (2H, s), 3.51—3.40 (1H, m), 2.30—2.13 (2H, m), 2.12—1.92 (2H, m), 1.90—1.64 (4H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −73.6 (s). EI-MS m/z: 346 (M^+, 1), 269 (4), 162 (7), 107 (14), 91 (100). *Anal.* Calcd for $C_{16}H_{17}F_3O_3S$: C, 55.48; H, 4.95. Found: C, 55.75; H, 4.85. **14Bb**: IR (KBr): 2950, 2890, 1500, 1460, 1390, 1355, 1310, 1280, 1240, 1200, 1140, 1120, 1070, 1030 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.28 (5H, m), 4.59 (1H, q, J = 6.6 Hz), 4.52 (2H, s), 3.80—3.73 (1H, m), 2.30—1.80 (8H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −73.4 (d, J = 7.0 Hz). EI-MS m/z: 346 (M^+, 2), 161 (3), 107 (3), 91 (100). HR-MS m/z Calcd for $C_{16}H_{17}F_3O_3S$ (M^+) : 346.0850. Found: 346.0868.

(4*R,5*S**)- and (4*R**,5*R**)-4-Trifluoromethyl-5-hexyl-5-phenyl-1,3-dioxolane-2-thione (14Ac, 14Bc)** The same treatment of a 2 : 1 mixture of **13Ac** and **13Bc** (212 mg, 0.73 mmol) as described for **13a** gave **14Ac** (146 mg, 60%) and **14Bc** (88 mg, 37%), each as a colorless oil, after purification by column chromatography (C_6H_{14} : EtOAc = 100 : 1). **14Ac**: IR (neat): 3080, 3040, 2960, 2940, 2870, 1500, 1470, 1455, 1380, 1320, 1280, 1200, 1150, 1120, 1050 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.50—7.39 (3H, m), 7.32—7.29 (2H, m), 4.97 (1H, q, J = 6.7 Hz), 2.33—2.09 (2H, m), 1.50—1.13 (7H, m), 1.00—0.85 (1H, m), 0.83 (3H, t, J = 6.6 Hz). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.9 (d, J = 6.6 Hz). EI-MS m/z: 332 (M^+, 15), 271 (12), 262 (22), 254 (81), 247 (100), 231 (10), 218 (29), 215 (21), 211 (52), 197 (44), 186 (38), 173 (19), 159 (26), 129 (19), 117 (47). HR-MS m/z: Calcd for $C_{16}H_{19}F_3O_2S$: 332.1057. Found 332.1071. **14Bc**: IR (neat): 3080, 3040, 2960, 2940, 2870, 1500, 1455, 1380, 1310, 1195, 1160, 1130, 1090, 1035 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.46—7.32 (5H, m), 4.91 (1H, q, J = 6.2 Hz), 2.33—2.15 (2H, m), 1.54—1.12 (8H, m), 0.85 (3H, t, J = 6.6 Hz). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −73.2 (d, J = 7.2 Hz). EI-MS m/z: 332 (M^+, 13), 271 (15), 262 (20), 254 (71), 247 (100), 231 (14), 218 (24), 215 (23), 211 (48), 197 (42), 186 (30), 173 (16), 159 (28), 117 (40), 104 (25), 91 (61). HR-MS m/z: Calcd for $C_{16}H_{19}F_3O_2S$: 332.1057. Found 332.1074. The stereostructures of **14Ac** and **14Bc** were determined based on those of (*E*)- and (*Z*)-**11c** derived from these samples.

(4′*R,5′*S**)- and (4′*R**,5′*R**)-5′-Trifluoromethyl-1,2,3,4-tetrahydronaphthalenespiro-4′-(1′,3′-dioxolane)-2′-thione (14Ad, 14Bd)** Treatment of **13Ad** (68 mg, 0.28 mmol) and **13Bd** (60 mg, 0.24 mmol) in the same manner as described for **13a** gave **14Ad** (67 mg, 84%), mp 115—116 °C (recrystallized from C_6H_{14}) and **14Bd** (62 mg, 88%) mp 144—145 °C (recrystallized from C_6H_{14}), each as colorless needles, respectively, after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1 for **14Ad** and **14Bd**). **14Ad**: IR (KBr): 2950, 1500, 1460, 1405, 1350, 1310, 1280, 1205, 1180, 1160, 1080, 1030 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.42—7.30 (3H, m), 7.28—7.20 (1H, m), 5.28 (1H, q, J = 6.6 Hz), 2.90—2.72 (2H, m), 2.59—2.47 (1H, m), 2.38—2.19 (1H, m), 2.13—1.99 (2H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.7 (d, J = 6.6 Hz). EI-MS m/z: 288 (M^+, 46), 227 (30), 211 (14), 200 (34), 162 (14), 141 (31), 129 (100), 115 (58), 91 (30). *Anal.* Calcd for $C_{13}H_{11}F_3O_2S$: C, 54.16; H, 3.85. Found: C, 54.29; H, 3.65. **14Bd**: IR (KBr): 2960, 1415, 1350, 1335, 1290, 1240, 1225, 1190, 1150, 1085, 1040 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.47—7.41 (1H, m), 7.38—7.25 (2H, m), 7.22—7.14 (1H, m), 4.93 (1H, q, J = 6.5 Hz), 2.94—2.88 (2H, m), 2.32—2.24 (2H, m), 2.24—2.10 (1H, m), 2.00—1.80 (1H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.6 (d, J = 6.3 Hz). EI-MS m/z: 288 (M^+, 100), 227 (43), 211 (27), 200 (53), 162 (17), 141 (27), 129 (95), 115 (51), 91 (25). *Anal.* Calcd for $C_{13}H_{11}F_3O_2S$: C, 54.16; H, 3.85. Found: C, 54.33; H, 3.67. The stereostructures of **14Ad** and **14Bd** were assigned based on those of (*E*)- and (*Z*)-**10d** derived from these samples.

4-Trifluoromethyl-5,5-diphenyl-1,3-dioxolane-2-thione (14e) Treatment of **13e** (20.0 mg, 71 μmol) in a similar manner to that described for **13a** gave **14e** as colorless prisms (21.9 mg, 95%), mp 131—132 °C (recrystallized from C_6H_{14}) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (KBr): 3010, 1500, 1460, 1395, 1330, 1280, 1240, 1200, 1160, 1150, 1115, 1095, 1040 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.47 (5H, m), 7.39—7.29 (5H, m), 5.71 (1H, q, J = 6.3 Hz). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −72.3 (d, J = 6.8 Hz). EI-MS m/z: 324 (M^+, 16), 263 (38), 195 (24), 178 (14), 165 (100), 152 (14), 105 (16), 77 (19). *Anal.* Calcd for $C_{16}H_{11}F_3O_2S$: C, 59.25; H, 3.42. Found: C, 59.16; H, 3.28.

1,1,1-Trifluoro-5-phenyl-3-(2-phenylethyl)-2-pentene (10a) A solution of **14a** (57 mg, 0.15 mmol) in $(MeO)_3P$ (0.5 ml) was heated at 130 °C for 13 h. Excess $(MeO)_3P$ was removed *in vacuo*, and the residue was purified by column chromatography (C_6H_{14}) to afford **10a** (39 mg, 86%) as a colorless oil. IR (neat): 3040, 2950, 1670, 1500, 1460, 1280, 1120 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.32—7.15 (10H, m), 5.46 (1H, q, J = 8.6 Hz), 2.79—2.74 (4H, m), 2.59—2.54 (2H, m), 2.45—2.40 (2H, m).

^{19}F-NMR (188 MHz, $CDCl_3$) δ: −57.4 (d, J=7.7 Hz). EI-MS m/z: 304 (M^+, 9), 213 (3), 181 (3), 138 (3), 91 (100). HR-MS m/z: Calcd for $C_{19}H_{19}F_3$ (M^+): 304.1438. Found: 304.1464.

1-Benzyloxy-4-(2,2,2-trifluoroethylidene)cyclohexane (10b) Treatment of **14Ab** (48 mg, 0.14 mmol) and **14Bb** (17.4 mg, 50 μmol) in the same manner as described for **14a** gave the same product (**10b**) as a colorless oil (34 mg, 91% from **14Ab**, and 10.9 mg, 80% from **14Bb**) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (neat): 2950, 2860, 1675, 1455, 1380, 1360, 1270, 1100 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.36—7.30 (5H, m), 5.43 (1H, q, J=8.2 Hz), 4.56 (2H, s), 3.69—3.58 (1H, m), 2.70—2.55 (1H, m), 2.50—2.20 (2H, m), 2.19—2.03 (1H, m), 1.97—1.70 (4H, m). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −57.0 (d, J=8.9 Hz). EI-MS m/z: 270 (M^+, 1), 252 (1), 162 (1), 143 (1), 107 (13), 91 (100). HR-MS m/z: Calcd for $C_{15}H_{17}F_3O$ (M^+): 270.1230. Found: 270.1251.

(*E*)- and (*Z*)-1,1,1-Trifluoro-3-phenyl-2-nonene [(*E*)- and (*Z*)-10c] The same treatment of **14Ac** (92 mg, 0.30 mmol) and **14Bc** (65 mg, 0.20 mmol) as described for **14a** gave (*E*)-**10c** (65 mg, 92%) and (*Z*)-**10c** (44 mg, 88%), each as a colorless oil, respectively, after purification by column chromatography (C_6H_{14} : EtOAc = 20 : 1). (*E*)-**10c**: IR (neat): 2940, 2870, 1655, 1360, 1270, 1140, 1120 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.36 (5H, m), 5.73 (1H, q, J=8.7 Hz), 2.75—2.60 (2H, m), 1.45—1.15 (8H, m), 0.84 (3H, t, J=6.9 Hz). No NOE was observed between the signals at 5.73 and 2.75—2.60 ppm. ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −57.1 (d, J=10.0 Hz). EI-MS m/z: 256 (M^+, 3), 186 (100), 115 (11), 103 (10). HR-MS m/z: Calcd for $C_{15}H_{19}F_3$ (M^+): 256.1438. Found: 256.1451. (*Z*)-**10c**: IR (KBr): 2940, 2870, 1675, 1385, 1285, 1230, 1140, 1120 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.29 (3H, m), 7.18—7.13 (2H, m), 5.65 (1H, tq, J=8.1, 1.3 Hz), 2.42—2.32 (2H, m), 1.39—1.20 (8H, m), 0.88 (3H, t, J=6.8 Hz). 4% NOE was observed for the signals at 2.42—2.32 ppm when the signals at 5.65 ppm were irradiated. ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −56.5 (d, J=7.3 Hz). EI-MS m/z: 256 (M^+, 2), 186 (100), 115 (12), 103 (11). HR-MS m/z: Calcd for $C_{15}H_{19}F_3$ (M^+): 256.1438. Found: 256.1411. Based on the NOE measurements, the stereostructures of (*E*)- and (*Z*)-**10c** were definitely established.

(*E*)- and (*Z*)-1-(2,2,2-Trifluoroethylidene)-1,2,3,4-tetrahydronaphthalene [(*E*)- and (*Z*)-10d] The same treatment of **14Ad** (42 mg, 0.14 mg) and **14Bd** (29 mg, 0.10 mmol) as described for **14a** gave (*E*)-**10d** (28 mg, 93%) and (*Z*)-**10d** (14 mg, 66%), each as a colorless oil, respectively, after purification by column chromatography [C_6H_{14} : EtOAc = 10 : 1 for (*E*)-**10d** and C_6H_{14} for (*Z*)-**10d**]. (*E*)-**10d**: IR (neat): 2950, 1650, 1370, 1330, 1280, 1265, 1140, 1115 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.56 (1H, d, J=7.6 Hz), 7.29—7.26 (1H, m), 7.22—7.18 (1H, m), 7.15 (1H, d, J=7.5 Hz), 6.06 (1H, tq, J=8.8, 1.6 Hz), 2.84 (2H, t, J=6.2 Hz), 2.78—2.74 (2H, m), 1.90 (2H, quint, J=6.3 Hz). An 8% NOE was observed for the signals at 6.06 ppm when the signals at 7.56 ppm were irradiated. ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −56.7 (d, J=9.4 Hz). EI-MS m/z: 212 (M^+, 100), 197 (12), 177 (17), 143 (48), 129 (60), 115 (51), 91 (20). HR-MS m/z: Calcd for $C_{12}H_{11}F_3$ (M^+): 212.0812. Found: 212.0786. (*Z*)-**10d**: IR (neat): 2950, 1650, 1390, 1280, 1220, 1140, 1115 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.54 (1H, d, J=7.7 Hz), 7.29—7.13 (3H, m), 5.49 (1H, tq, J=9.3, 1.5 Hz), 2.85 (2H, t, J=6.7 Hz), 2.53—2.45 (2H, m), 2.02—1.91 (2H, m). No NOE was observed between the signals at 7.54 and 5.49 ppm. ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −56.1 (d, J=9.7 Hz). EI-MS m/z: 212 (M^+, 100), 197 (10), 177 (11), 143 (32), 129 (34), 115 (23), 91 (10). HR-MS m/z: Calcd for $C_{12}H_{11}F_3$ (M^+): 212.0812. Found: 212.0804.

3,3,3-Trifluoro-1,1-diphenylpropene (10e) Treatment of **14e** (22 mg, 68 μmol) in a similar manner to that described for **14a** gave **10e** as a colorless oil (15 mg, 89%) after purification by column chromatography (C_6H_{14} : EtOAc = 10 : 1). IR (neat): 3070, 2940, 1640, 1370, 1270, 1230 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.41—7.30 (6H, m), 7.29—7.20 (4H, m), 6.13 (1H, q, J=8.3 Hz). ^{19}F-NMR (188 MHz, $CDCl_3$) δ: −56.2 (d, J=10.3 Hz). EI-MS m/z: 248 (M^+, 100), 247 (10), 227 (16), 179 (64), 165 (52), 151 (12), 89 (10). HR-MS m/z: Calcd for $C_{15}H_{11}F_3$ (M^+): 248.0812. Found: 248.0801.

References and Notes

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