Free-radical approach to the synthesis of fluorine-substituted cyclic compounds. Cyclization reactions of trifluoromethyl- and difluoromethylene-substituted carbon radicals

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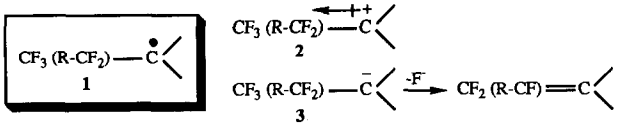
Abstract

Trifluoromethyl- or difluoromethylene-substituted alkyl radicals ($CF_3-\dot{C}-$ or $-CF_2-\dot{C}-$) and trifluoromethyl-substituted alkenyl radicals ($CF_3-\dot{C}=C-$) cyclize effectively intramolecularly to allow the synthesis of fluorine-substituted cyclic compounds. Radical reactions of thiocarbonylimidazolide derivatives (**7a,b**, **13a–d**, **14e,f**) gave CF_3-substituted cyclopentane derivatives (**22a**, **25a–d**) or cyclohexane derivatives (**22b**, **26e,f**) via 5- or 6-*exo* selective cyclization. CF_3-substituted cyclopentene derivatives (**27a,b**) or cyclohexene derivatives (**27c**) were also obtained from alkenyl iodides (**17a–c**) via radical cyclization. Cyclopentane derivatives (**29a–f**, **31**) containing the CF_2CO_2Et group were synthesized by Reformatsky reaction and radical cyclization.

Introduction

Fluorinated organic molecules are receiving increasing attention in view of their wide application in bio- and medicinal chemistry [1]. Hence, much effort has recently been paid to the development of synthetic reactions for trifluoromethyl- (CF_3-) and difluoromethylene- ($-CF_2-$) containing organic compounds. Carbon–carbon bond formation on the carbon atom β to the fluorine substituent(s), i.e. CF_3-C^* or $R-CF_2-C^*$ (**1**), is one of the fundamental reactions for the synthesis of such fluorine-containing compounds. However, reactions involving ionic intermediates suffer from major limitations (see Scheme 1) [2]. Generation of the carbocation **2** is very difficult because of the remarkable electron-withdrawing effect of the neighboring fluorine substituents. Reaction through the carbanion **3** competes with β-elimination of the fluoride anion. Thus, an efficient method for C–C bond formation on a CF_3- or $-CF_2$-substituted carbon atom is urgently required in organofluorine chemistry. In an attempt to partially solve this problem, we have studied reaction through the corresponding carbon radicals **1** which would be useful for C–C bond formation in intramolecular cyclization reactions [3, 4]. This paper describes the cyclization reactions of CF_3- or $-CF_2$-substituted alkyl radicals and CF_3-substituted alkenyl radicals for the synthesis of CF_3- or $-CF_2$-substituted cyclic compounds.



Scheme 1.

Preparation of substrates for radical cyclizations

For the generation of a CF_3-substituted alkyl radical ($CF_3-\dot{C}-$), radical deoxygenation [5] of an α-trifluoromethyl alcohol moiety [$CF_3-CH(OH)-$] through the thiocarbonylimidazolide was utilized. Thiocarbonylimidazolide derivatives of α-trifluoromethyl alcohols (**7a**, **7b**, **13**, **14**) containing a suitably placed acceptor double bond were prepared as substrates. Aldehyde **5** obtained from ethyl 1,1,1-trifluoroacetoacetate (**4**) was reacted with Grignard reagents, and then benzoylation followed by deprotection of the tetrahydropyranyl (THP) group provided **6a** or **6b**. On treatment with thiocarbonyldiimidazole [$S=C(Imd)_2$], **6a** or **6b** were converted to **7a** or **7b** in good yield [eqn. (1)]. Substrates **13** and **14** containing a substituted double bond were prepared from ethyl trifluoroacetate (**8**) [eqn. (2)]. Reaction of **8** with the lithium acetylide provided **9**, which was

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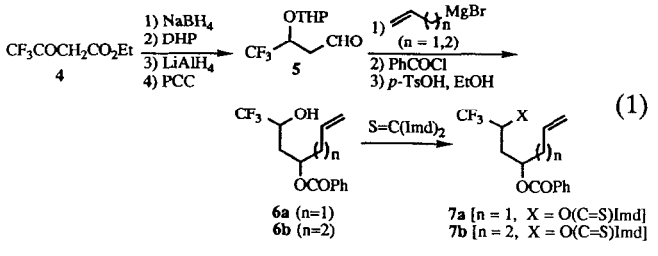
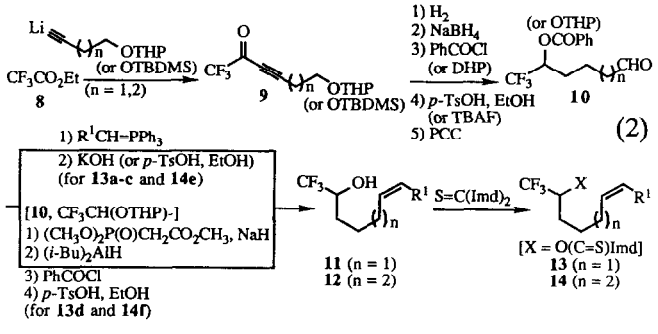
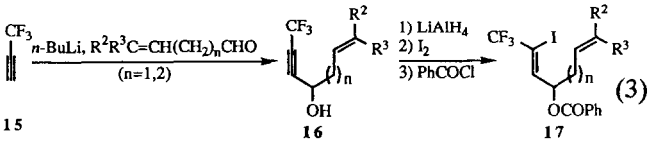
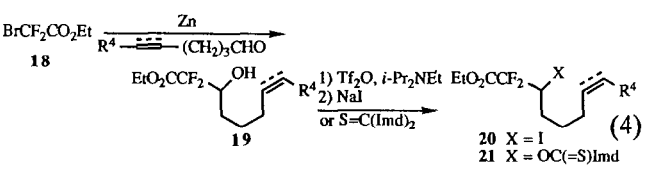
converted into aldehydes **10** by functional group transformations. Thiocarbonylimidazolides **13** and **14** were obtained by the introduction of an acceptor double bond using a Wittig-type reaction, deprotection and reaction with thiocarbonyldiimidazole through **11** and **12**, respectively. For the cyclization reaction of the CF_3-substituted alkenyl radical, CF_3-substituted alkenyl iodides **17** were prepared from 3,3,3-trifluoropropyne (**15**). CF_3-substituted propargyl alcohol derivatives **16** were obtained by the reaction of **15** with unsaturated aldehydes. Reduction of **16** with lithium aluminum hydride, followed by quenching with iodine [6] and benzoylation, gave **17** in good yields [eqn. (3)]. β-Hydroxy-α,α-difluoroesters **19** were used as substrates for the cyclization reactions of $-CF_2-$substituted alkyl radicals ($-CF_2-\dot{C}-$) owing to their ease of preparation via the Reformatsky reaction of unsaturated aldehydes with commercially available ethyl bromodifluoroacetate (**18**) [7]. Hydroxy esters **19** were converted to the iodides **20** through the triflate derivatives. For direct radical deoxygenation of the β-hydroxyl group, **19** was treated with thiocarbonyldiimidazole to obtain the thiocarbonylimidazolide **21** [eqn. (4)]. The structures of the substrates thus obtained were confirmed by ^1H and ^{19}F NMR spectroscopies, and the ratios of stereoisomers were determined by ^1H NMR spectroscopy or GLC analysis (see footnotes to Tables 1–3).









DHP = 3,4-Dihydro-2*H*-pyran, PCC = Pyridinium chlorochromate, *p*-TsOH=*p*-Toluenesulfonic acid, S=C(Imd)$_2$ = Thiocarbonyldiimidazole, TBDMS =*t*-Butyldimethylsilyl, TBAF = Tetrabutylammonium fluoride, Tf_2O = Trifluoromethanesulfonic anhydride

Cyclization reactions of trifluoromethyl- and difluoromethylene-substituted carbon radicals

Radical reactions were carried out using tributyltin hydride (Bu_3SnH, 1.1 equiv.) and azobisisobutyronitrile (AIBN, catalytic amount) in benzene at reflux temperature for 2–4.5 h. The structures of the cyclized products were determined by ^1H and ^{19}F NMR spectroscopies, and by low-resolution and high-resolution mass spectrometry. The results of the cyclization reactions of CF_3-substituted alkyl radicals are shown in eqn. (5) and Table 1 [8, 9]*. Radical reaction of **7a** gave CF_3-substituted cyclopentane (**22a**) via 5-*exo* cyclization and cyclohexane (**23a**) via 6-*endo* cyclization in 77% yield in a ratio of 38:1. Regioisomers **22a** and **23a** were assigned by ^1H NMR spectra. Four sets of doublets (J = 6.3–7.3 Hz) at 1.15–1.24 ppm could be ascribed to the protons on the CH_3 group of the 5-*exo* cyclized products (**22a**). The ratio of the stereoisomers of **22a** was 3:1.9:1.3:1 (determined by GLC) and that of **23a** was 1.4:1. Reaction of **7b** gave the 6-*exo* cyclized product, the cyclohexane **22b**, the 7-*endo* cyclized product, the cycloheptane **23b** and the uncyclized reduction product **24b**. Compared to the good yield obtained in the radical cyclization of **7a**, cyclization of **7b** was accompanied by the formation of **24b** (35% yield), and the yield of the cyclized products (**22b** and **23b**) was reduced (45%) under the same reaction conditions ([Bu_3SnH] = 0.02 M). Reaction under conditions of high dilution ([Bu_3SnH] = 0.0023–0.004 M) improved the cyclization yield to 58–59% and reduced the formation of **24b**. Thus, lowering the concentration of the hydrogen donor (Bu_3SnH) was effective in the case of the slower cyclization via 6-*exo* (and 7-*endo*). The results of the reactions of **13** and **14** are shown in eqn. (6) and Table 2 [8, 9]. Radical cyclizations of **13a–d** to the substituted double bond regioselectively proceeded via the 5-*exo* form to give **25a–d** in good yield (66–83%). In these cases, no by-product was

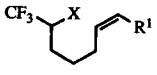
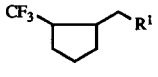
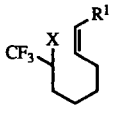
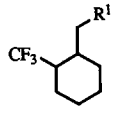
*The cyclized products were obtained as inseparable mixtures of stereoisomers in most cases. The stereochemistry of the products was not fully clarified since NMR spectroscopy was ineffective for the assignments.

TABLE 1. Radical cyclization reactions of **7a,b**

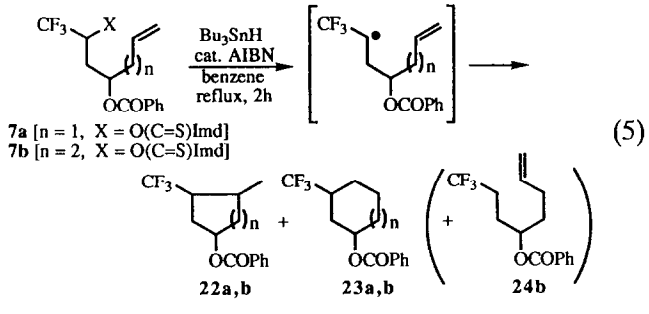
Substrate[a]	[Bu_3SnH] (M)	Yield of cyclized products [**22** (*exo*)/**23** (*endo*)] (%)	Yield of reduction product **24b** (%)
7a	0.02	77(**22a/23a** = 38:1)[b]	–
7b	0.02	45(**22b/23b** = ~ 9:1)[c]	35
7b	0.004	59(**22b/23b** = ~11:1)	14
7b	0.0023 (slow addn.)	58(**22b/23b** = ~ 7:1)	8

[a]A mixture of stereoisomers: **7a** (1.3:1 by GLC), **7b** (2.2:1 by GLC).
[b]A mixture of stereoisomers: **22a** (3:1.9:1.3:1 by GLC), **23a** (1.4:1).
[c]The ratio of **22b** to **23b** was determined by ^1H NMR spectroscopy. The ratios of stereoisomers of **22b** and **23b** were not determined.

TABLE 2. Radical cyclization reactions of **13** and **14**[a]

Substrate[b]		Product[c] (Yield, %)	
	**13a** (R^1 = n-C_9H_{19}) **13b** (R^1 = n-C_6H_{13}) **13c** (R^1 = Ph) **13d** (R^1 = $PhCO_2CH_2$)		**25a** (83) **25b** (66) **25c** (69) **25d** (81)
	**14e** (R^1 = Ph) **14f** (R^1 = $PhCO_2CH_2$)		**26e** (48)[d] **26f** (48)[e]

[a]Reactions were carried out in 0.015–0.085 M solutions except for the case of **14f**.
[b]A mixture of *E*- and *Z*-isomers.
[c]The ratios of stereoisomers were determined by GLC: **25a** (1:1), **25b** (1:1), **25c** (1.1:1), **25d** (1:1), **26e** (3:1), **26f** (1.4:1).
[d]The yield of uncyclized reduction product was 8%.
[e]High dilution method (0.002 M) by slow addition was employed. The yield of uncyclized reduction product was not determined.



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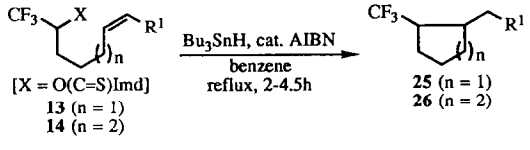
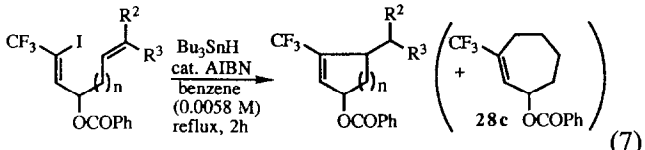


(6)

detected. CF_3-substituted cyclohexane (**26e,f**) were obtained in moderate yield via 6-*exo* cyclization of **14e,f**.

The cyclization reactions of CF_3-substituted alkenyl radicals ($CF_3-\dot{C}=C-$) were also successful [10]*. The CF_3-substituted alkenyl radicals generated from **17a–c** cyclized via an intramolecular double bond to give CF_3-substituted cycloalkenes on treatment with Bu_3SnH. Thus, reaction of **17a** proceeded selectively via the 5-*exo* form to give **27a** in 86% yield. The ^1H NMR signals of the olefinic ring-proton (6.27; 6.53–6.54; 6.54; 6.44 ppm) and methyl group (1.45; 1.20; 1.28; 1.40 ppm) suggest the cyclopentene structure for the four stereoisomers of **27a**, a suggestion which was also supported by GLC analysis. Similarly, **17b** gave **27b** selectively in high yield. In contrast, with **17b** the 6-*exo* cyclized product (**17c**) was obtained in lower yield (53%) and the 7-*endo* cyclized product (**27c**) was also isolated in 8% yield.



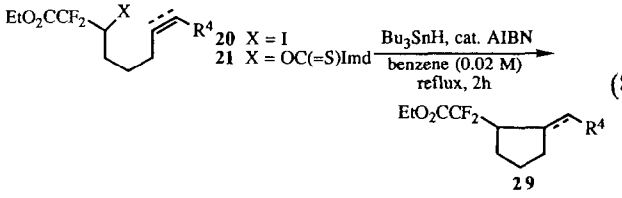
(7)

17a (n = 1, R^2=Ph, R^3=CH_3)[a] **27a** (86%, n = 1)[b]
17b (n = 1, R^2=H, R^3=$PhCH_2CH_2$)[a] **27b** (86%, n = 1)[b]
17c (n = 2, R^2=H, R^3= H) **27c** (53%, n = 2)[b] **28c** (8%)

[a] A mixture of stereoisomers: **17a** (7.5 : 1 by ^1H-NMR), **17b** (3.4 : 1 by GLC).
[b] A mixture of stereoisomers: **27a** (4.3 : 3 : 1.1 : 1 by GLC), **27b** (1.2 : 1), **27c** (1.7 : 1 by GLC).

*The aldol-type reaction of alkenyl-lithium [$CF_3-(Li^+)\ ^-C=CH_2$] was carried out at −100 °C due to its instability [11].

Next, the cyclization reactions of $-CF_2$-substituted alkyl radicals ($-CF_2-\dot{C}-$) were examined. The radical reactions of **20** and **21** with Bu_3SnH and AIBN as the catalyst under standard conditions gave cyclized products (**29a–f**) in moderate to good yield (40–83%). The results are summarized in Table 3. The structures of the cyclopentane derivatives **29** were clearly demonstrated by their ^1H NMR spectra which showed the conversion of the acceptor unsaturated bond ($-C\equiv C-R^4$) into $>C=CH-R^4$ by cyclization. Typically, **29a** exhibited signals at 0.99 (ddd) and 1.05 (d) ppm, ascribed to the methyl groups of stereoisomers. Thus, the intermediary CF_2-substituted alkyl radical cyclized to a double bond or triple bond via 5-*exo* on a selective basis. The iodides **20** showed higher yields of the cyclized product **29** than the corresponding thiocarbonylimidazolide **21**. The isolable by-product was the uncyclized reduction product in 3–12% yield. Iodine atom-transfer cyclization [12] was also carried out. Irradiation (100 W high-pressure mercury lamp through a Pyrex filter) of the iodide **20a** catalyzed with hexabutylditin ($Bu_3SnSnBu_3$, 0.1 equiv.) in benzene at room temperature for 2 h provided the cyclized iodide **31** in 59% yield. The ^1H NMR spectrum of **31** indicated two pairs of signals at 3.23 (major) and 3.43 (major), 3.12 (minor) and 3.59 (minor) ppm assigned to CH_2-I groups of stereoisomers, which clearly demonstrate that iodine atom-transfer occurred via cyclopentane ring formation. Iodine atom-transfer from the starting iodide **20a** to the intermediary cyclized radical **30** propagated the free-radical chain process. Thus, cyclopentane derivatives **29** and **31** containing the $-CF_2CO_2Et$ group were effectively synthesized by Reformatsky reaction and radical cyclization*.



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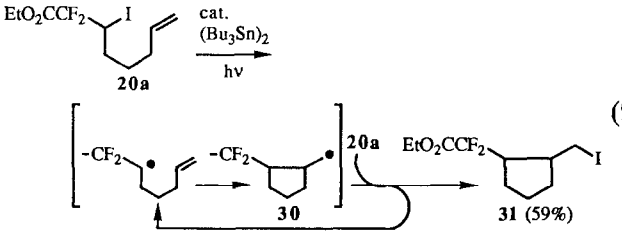
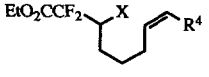
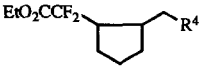
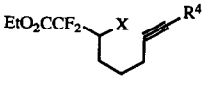
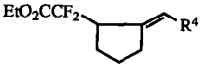


(9)

In summary, CF_3- or CF_2-substituted alkyl radicals and CF_3-substituted alkenyl radicals effectively promoted intramolecular C–C bond formation and processes have been developed to obtain fluorine-substituted cyclic compounds. The synthetic usefulness of an intermediary β-fluorine-substituted carbon radical is also advantageous since ordinary carbanion chemistry

*Reformatsky reaction of $BrCF_2CO_2Et$ followed by the removal of the β-hydroxy group of the product via reductive radical deoxygenation was utilized in the synthesis of the fluorine-containing steroid compound [13].

TABLE 3. Radical cyclization reactions of **20** and **21**

Substrate		Product[c] (Yield, %)	
	**20a** (R^4 = H)		**29a** (62)
	21a (R^4 = H)		**29a** (49)
	20b (R^4 = Ph)[a]		**29b** (82)
	21b (R^4 = Ph)[a]		**29b** (63)
	20c (R^4 = $CH_2OTBDPS$)[b]		**29c** (80)
	21c (R^4 = $CH_2OTBDPS$)[b]		**29c** (81)
20 X = I **21** X = OC(=S)Imd			
	20d (R^4 = Ph)		**29d** (83)
	21d (R^4 = Ph)		**29d** (72)
	**20e** (R^4 = TMS)		**29e** (64)
	21e (R^4 = TmS)		**29e** (55)
	20f (R^4 = $CH_2OTBDPS$)		**29f** (54)
	21f (R^4 = $CH_2OTBDPS$)		**29f** (40)

[a]A mixture of stereoisomers: **20b** (1:1), **21b** (2:1).

[b]Z-Isomer.

[c]The ratios of stereoisomers were determined by GLC except for the case of **29f/29a** (1.1:1 from **20a**, 1:1 from **21a**), **29b** (1.3:1 from **20b**, 1.1:1 from **21b**), **29c** (2.3:1 from **20c**, 2.2:1 from **21c**), **29d** (7.5:1 from **20d**, 1.9:1 from **21d**), **29e** (1:1 from **20e**, 1.2:1 from **21e**), **29f** (1.3:1 from **20f**, 1.3:1 from **21f**).

is ineffective in bringing about the C–C bond formation reaction at the carbon atom β to the fluorine substituent.

Experimental

^{1}H NMR spectra were measured on a Bruker AM400 (400 MHz) or Varian EM390L (90 MHz) spectrometer in $CDCl_3$, and chemical shifts are reported in parts per million (ppm) using $(CH_3)_4Si$ or $CHCl_3$ as internal standard. ^{19}F NMR spectra were measured on a Bruker AM400 (376 MHz) or Varian EM360L (56 MHz) spectrometer in $CDCl_3$, and chemical shifts are reported in ppm using benzotrifluoride as standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR-1710, Hitachi 260-30 or JASCO A-302 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 instrument. Gas chromatographic analysis (GLC) was performed on a Hitachi G-3000 gas chromatograph [FID, OV-1 (25 m)]. All air-sensitive reactions were carried out under an argon atmosphere. The letters (**l**, **m**, **n**, **o**) added to a compound number indicate the elution order of stereoisomers in column chromatography.

Preparation of substrates

Typical procedures for the preparation of compounds **7a**, **13a**, **17a**, **20a** and **21a** are given below.

Compound 7a

A solution of ethyl 1,1,1-trifluoroacetoacetate (**4**, 32.3 g, 175.6 mmol) in ether (30 ml) was added dropwise to a solution of sodium borohydride (3.9 g, 103.4 mmol) in ether (150 ml) at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was treated with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. Removal of the solvent gave $CF_3CH(OH)CH_2CO_2Et$ in quantitative yield.

A solution of $CF_3CH(OH)CH_2CO_2Et$ (32.6 g, 175.5 mmol), 3,4-dihydro-2*H*-pyran (48 ml, 526.9 mmol) and *p*-TsOH·H_2O (1.7 g, 8.9 mmol) was stirred for 8 h at room temperature. The reaction mixture was treated with aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave $CF_3CH(OTHP)CH_2CO_2Et$ (7.9 g, 17% yield).

A solution of $CF_3CH(OTHP)CH_2CO_2Et$ (2.9 g, 10.7 mmol) in ether (20 ml) was added dropwise to a suspension of lithium aluminum hydride (960 mg, 25.3 mmol) in ether (20 ml) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was treated with ethyl acetate to consume the excess lithium aluminum hydride and extracted with ether. The ether phase was washed with 5% HCl, aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. Removal of the solvent gave $CF_3CH(OTHP)CH_2CH_2OH$.

A solution of $CF_3CH(OTHP)CH_2CH_2OH$ in CH_2Cl_2 (15 ml) was added to a solution of pyridinium chlorochromate (3.4 g, 15.8 mmol) and CH_3CO_2Na (340 mg, 4.2 mmol) in CH_2Cl_2 (15 ml) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was subjected directly to column chromatography on silica gel to give compound **5** [870.5 mg, 36% yield (two steps)].

A solution of **5** (870.5 mg, 3.9 mmol) in ether (6 ml) was added dropwise to a solution of the Grignard reagent prepared from allyl bromide (0.67 ml, 7.7 mmol) and magnesium (188 mg, 7.7 mg atom) at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was treated with aq. NH_4Cl and extracted with ether. The ether phase was washed with aq. NaCl and dried over $MgSO_4$. Removal of the solvent gave $CF_3CH(OTHP)CH_2CH(OH)CH_2CH{=}CH_2$.

A solution of $CF_3CH(OTHP)CH_2CH(OH)CH_2$-$CH{=}CH_2$ and benzoyl chloride (0.55 ml, 4.7 mmol) in pyridine (10 ml) was stirred for 1.5 h at room temperature. The reaction mixture was treated with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. Purification by column chromatography on silica gel gave $CF_3CH(OTHP)CH_2CH(OCOPh)$-$CH_2CH{=}CH_2$ [1.0 g, 74% yield (two steps)].

A solution of $CF_3CH(OTHP)CH_2CH(OCOPh)$-$CH_2CH{=}CH_2$ (1.0 g, 2.7 mmol) and *p*-TsOH·H_2O (58.1 mg, 0.31 mmol) in ethanol (12 ml) was stirred for 15 h at room temperature. The reaction mixture was neutralized with aq. $NaHCO_3$ and extracted with ether. The ether phase was washed with aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave compound **6a** (734.2 mg, 93% yield).

A solution of **6a** (621.6 mg, 2.2 mmol) and thiocarbonyldiimidazole (751.8 mg, 4.2 mmol) in THF (15 ml) was stirred for 2 h at reflux temperature. After removal of the solvent, the residue was subjected to column chromatography on silica gel to give compound **7a** (780 mg, 91% yield, stereoisomeric mixture, 1.3:1 by GLC). ^{1}H NMR ($CDCl_3$) δ: 2.32–2.62 (4H, m, $2\times CH_2$); 5.13–5.40 (3H, m, $2\times$=CH and CH–O); 5.80 (1H, ddt, J=13.8, 10.1 and 6.9 Hz, CH=); 6.27–6.37 (1H, m, CH–CF_3); 6.97–6.99, 7.32–7.58, 7.87–7.96 and 8.19–8.24 (8H, each m, aromatic and imidazole ring) ppm. ^{19}F NMR ($CDCl_3$) δ: −13.8 (3F, d, J=6.6 Hz) ppm. MS (EI) *m/z*: 398 (M^+); 331; 276; 148; 105; 77.

Compound 13a (n=*1*, $R'=n$-C_9H_{19})

A solution of n-BuLi (1.4 M, 75 ml, 101.9 mmol) in hexane was added dropwise to a solution of 1-tetrahydropyranyloxy-3-butyne (15.0 g, 97.2 mmol) in THF

(130 ml) over a period of 15 min at −78 °C. After being stirred for 1.5 h at −78 °C, a solution of ethyl trifluoroacetate (**8**, 20.5 g, 144.6 mmol) in THF (40 ml) was added and the whole was stirred for 1 h at the same temperature. The reaction mixture was treated with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give compound **9a** (14.4 g, 59% yield, b.p. 97–109 °C/7 mmHg), which was hydrogenated (5%Pd/C cat.) with an H_2 pressure of 5.7 kg cm^{-2} in THF for 4.5 h. After filtration through a short pad column (silica gel), the residue was distilled under reduced pressure to give $CF_3CO(CH_2)_4OTHP$ (10.7 g, 74% yield, b.p. 115–128 °C/7 mmHg). Reduction with sodium borohydride (quantitative yield), benzoylation (73% yield), deprotection of the THP group (90% yield) and oxidation with pyridinium chlorochromate (PCC) (59% yield) were carried out using the methods described above to give compound **10a**.

A solution of decyltriphenylphosphonium bromide (1.13 g, 2.3 mmol) in THF (5 ml) was added dropwise to a solution of lithium diisopropylamide (2.2 mmol) in THF (2.5 ml) at −78 °C. After being stirred for 1 h at −78 °C, a solution of **10a** (611.6 mg, 2.2 mmol) in THF (3 ml) was added and the whole was stirred for 15 min at −78 °C and then for 40 min at 0 °C. The reaction mixture was treated with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. Purification by column chromatography on silica gel gave $CF_3CH(OCOPh)(CH_2)_3CH{=}CH(CH_2)_8CH_3$ (578 mg, 65% yield).

A solution of this olefinic compound (569.1 mg, 1.4 mmol) and KOH (480 mg, 8.6 mmol) in methanol (8 ml) was stirred for 12 h at room temperature. The reaction mixture was acidified with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. Purification by column chromatography on silica gel gave compound **11a** ($R^1 = n\text{-}C_9H_{19}$, 418.8 mg, 99% yield).

Compound **11a** was allowed to react with thiocarbonyldiimidazole to give compound **13a** (281.0 mg, 97% yield, stereoisomeric mixture, 5:1 by GLC). ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz, CH_3); 1.18–1.38 (14H, m, $7\times CH_2$); 1.47–1.60 (2H, m, CH_2); 1.93–2.16 (6H, m, $3\times CH_2$); 5.30 (1H, dtt, J=10.8, 7.2 and 1.5 Hz, CH=); 5.43 (1H, dtt, J=10.8, 7.3 and 1.4 Hz, CH=); 6.09 (1H, m, CF_3–CH); 7.08, 7.63 and 8.35 (3H, each m, imidazole ring) ppm. ^{19}F NMR ($CDCl_3$) δ: −13.2 (3F, d, J=6.6 Hz) ppm. MS (EI) *m/z*: 404 (M^+); 371; 337; 68. MS (CI) *m/z*: 405 ($M^+ + 1$).

Compound 17a (n=*1*, R^2=*Ph*, R^3=CH_3)

A solution of n-BuLi (1.4 M, 3.2 ml, 4.5 mmol) in hexane was added dropwise to a solution of 3,3,3-trifluoropropyne (**15**, 3.8 ml, 40.4 mmol) in ether (24 ml) at −78 °C. After being stirred for 50 min at −78 °C, a solution of 4-phenyl-3-pentenal (676.8 mg, 4.2 mmol) in ether (8 ml) was added dropwise and the whole was stirred for 1.5 h at the same temperature. The reaction mixture was treated with aq. NH_4Cl. and extracted with ether. The ether phase was washed with saturated aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave compound **16a** (345.8 mg, 32% yield).

In accordance with the reported method [6], a solution of **16a** (345.8 mg, 1.4 mmol) in ether (4.5 ml) was added dropwise to a suspension of lithium aluminium hydride (107.8 mg, 2.8 mmol) in ether (10 ml) at 0 °C and the whole stirred for 30 min at room temperature. Ethyl acetate (1.2 ml) was added at 0 °C. After being stirred for 15 min, a solution of iodine (2.8 g, 11.1 mmol) in ether (7 ml) was added at −78 °C and the whole stirred for 15 min at the same temperature. The reaction mixture was treated with 5% aq. $Na_2S_2O_3$ and extracted with ether. The ether phase was washed with 5% aq. Na_2SO_3 and aq. NaCl, and dried over $MgSO_4$. Purification by column chromatography on silica gel gave the alkenyl iodide derivative (339.6 mg, 65% yield) which was converted to **17a** by benzoylation (421.6 mg, 98% yield, stereoisomeric mixture, 7.5: 1 by ^1H NMR spectroscopy) using the method described above. ^1H NMR ($CDCl_3$) δ: 2.05 (3H, br, CH_3 for major isomer); 2.09 (3H, br, CH_3 for minor isomer); 2.46–2.60 (2H, m, CH_2 for major isomer); 2.71–2.88 (2H, m, CH_2 for minor isomer); 5.54–5.61 (2H, m, CH−O and CH= for major isomer); 5.73–5.82 (2H, m, CH−O and CH= for minor isomer); 6.65 (1H, dd, J=7.7 and 1.2 Hz, CH= for major isomer); 6.83 (1H, dd, J=7.8 and 1.3 Hz, CH= for minor isomer); 7.10–7.67 and 7.98–8.08 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.5 (br) ppm. IR (neat) cm^{-1}: 3061; 3032; 2971; 2914; 2855; 1724; 1648; 1602; 1585. MS (EI) *m/z*: 364 ($M^+ - PhCO_2H$); 237; 205; 131.

Compounds 20a (R^4=*H*) *and 21a* (R^4=*H*)

In accordance with the reported method [7], a solution of ethyl bromodifluoroacetate (**18**, 2.49 g, 12.3 mmol) and 5-hexenal (1.0 g, 10.2 mmol) in THF (23 ml) was added dropwise to a suspension of activated zinc (804.3 mg, 12.3 mg atom) in THF (10 ml) at reflux temperature over a period of 5 min and the whole was stirred for 1.5 h at the same temperature. After cooling to 0 °C, the reaction mixture was treated with ether and aq. NH_4Cl with stirring. The precipitates were removed by filtration through Celite, and the ether phase was washed with aq. NaCl and dried over $MgSO_4$. Purification by

column chromatography on silica gel gave compound **19a** (1.53 g, 67% yield).

Trifluoromethanesulfonic anhydride (2.55 ml, 15.2 mmol) was added dropwise to a solution of **19a** (3.0 g, 13.7 mmol) and *N*-ethyl-*N*,*N*-diisopropylamine (5.3 ml, 30.4 mmol) at −78 °C. After being stirred for 4.5 h at the same temperature, the reaction mixture was treated with 5% HCl and extracted with ether. The ether phase was washed with aq. $NaHCO_3$ and aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave the triflate derivative (3.98 g, 82% yield).

A solution of the triflate derivative (798.7 mg, 2.3 mmol) in acetone (5 ml) was added to a suspension of sodium iodide (1.33 g, 8.9 mmol) in acetone (2.5 ml) and the whole stirred for 17 h at room temperature. The reaction mixture was treated with 5% aq. $Na_2S_2O_3$ and extracted with ether. The ether phase was washed with aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave compound **20a** (709.5 mg, 95% yield). Compound **19a** was converted to compound **21a** (89% yield) by the method described above. **20a**: ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.2 Hz, CH_3); 1.43–1.53 (1H, m, CH); 1.71–1.87 (3H, m, CH_2 and CH); 2.03–2.19 (2H, m, CH_2); 4.26–4.35 (1H, m, CH−I); 4.37 (2H, q, J=7.2 Hz, CH_2); 5.00 (1H, ddt, J=10.3, 1.8 and 1.1 Hz, CH=); 5.04 (1H, ddt, J=17.0, 1.8 and 1.7 Hz, CH=); 5.78 (1H, ddt, J=17.0, 10.3 and 6.7 Hz, CH=) ppm. ^{19}F NMR ($CDCl_3$) δ: −40.23 (1F, dd, J=252.1 and 12.3 Hz); −43.74 (1F, dd, J=252.1 and 14.9 Hz) ppm. IR (neat) (cm^{-1}): 2982; 2938; 1776; 1761. MS (EI) *m/z*: 332 (M^+); 205; 185; 157; 131; 111; 77. High-resolution MS: $C_{10}H_{15}F_2O_2I$, 332.0059. Calc., 332.0085. **21a**: ^{1}H NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.2 Hz, CH_3); 1.57 (2H, m, CH_2); 1.96 (2H, m, CH_2); 2.13 (2H, m, CH_2); 4.30 (2H, q, J=7.2 Hz, CH_2); 5.00 (1H, ddt, J=10.3, 1.7 and 1.6 Hz, CH=); 5.03 (1H, ddt, J=17.0, 1.6 and 1.6 Hz, CH=); 5.75 (1H, ddt, J=17.0, 10.3 and 6.7 Hz, CH=); 6.15 (1H, dddd, J=13.5, 7.9, 7.8 and 5.5 Hz, CH−O); 7.06, 7.61 and 8.32 (3H, each m, imidazole ring) ppm. ^{19}F NMR ($CDCl_3$) δ: −50.27 (1F, dd, J=267.0 and 7.9 Hz); −54.45 (1F, dd, J=267.0 and 13.5 Hz) ppm. IR (neat) (cm^{-1}): 3133; 2938; 1770; 1642. MS (EI) *m/z*: 332 (M^+); 300; 299; 265. High-resolution MS: $C_{14}H_{18}F_2N_2O_3$ (M^+ − S), 300.1255. Calc., 300.1284.

General procedure for radical cyclization

A solution of the thiocarbonylimidazolide, tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) in benzene was refluxed for 2 h. The reaction mixture was treated with aq. NaCl and extracted with ether. The ether phase was washed with aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave cyclized products.

In the cases of the iodides, work-up was carried out as follows. After removal of the solvent, the residue was dissolved in ether (5 ml) followed by the addition of 10% aq. KF (3 ml) with stirring. The precipitate was removed by filtration. The reaction mixture was extracted with ether, washed with aq. NaCl and dried over $MgSO_4$. Purification by column chromatography on silica gel gave the cyclized product.

In the cases of **7b** and **14f**, slow addition of Bu_3SnH for the high-dilution conditions was carried out using a syringe pump technique. Thus, a solution of Bu_3SnH in benzene (15 ml) was added to a refluxing solution of the substrate and AIBN in benzene over 2–4 h and the reaction mixture refluxed for 1 h.

1-Benzoyloxy-3-trifluoromethyl-4-methylcyclopentane (22a) and 1-benzoyloxy-3-trifluoromethylcyclohexane (23a)

Reaction of **7a** (510.2 mg) gave **22a–l** (16.5 mg, 5% yield), **22a–l,m** (132.8 mg, 38% yield, **l/m**=2.3:1 by GLC), **22a–m** (6.6 mg, 2% yield) **23a–l** (2.5 mg, 0.7%), **23a–m** (3.5 mg, 1% yield) and **22a–n,o** (104.6 mg, 30% yield, **n/o**=1.9:1 by GLC). **22a–l**: ^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, dq, J=7.3 and 2.0 Hz, CH_3); 1.88 (1H, ddd, J=14.3, 9.0 and 5.9 Hz, CH); 2.11 (1H, dd, J=14.3 and 7.3 Hz, CH); 2.17 (1H, ddt, J=15.0, 8.4 and 1.8 Hz, CH); 2.32 (1H, ddd, J=15.0, 8.4 and 6.3 Hz, CH); 2.62 (1H, tt, J=7.7 and 7.7 Hz, CH); 2.87 (1H, qtd, J=10.8, 8.4 and 8.4 Hz, CH−CF_3); 5.50 (1H, m, CH−O), 7.42–7.59 and 8.00–8.03 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −3.17 (d, J=10.8 Hz) ppm. IR (neat) (cm^{-1}): 3045; 2971; 1718; 1604. MS (EI) *m/z*: 272 (M^+); 167; 150; 123; 105; 77. High-resolution MS: $C_{14}H_{15}F_3O_2$, 272.1016. Calc., 272.1023. **22a–m**: ^{1}H NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.7 Hz, CH_3); 1.63 (1H, m, CH); 2.10–2.36 (3H, m, 3×CH); 2.41–2.55 (2H, m, 2×CH); 5.41 (1H, m, CH−O); 7.40–8.08 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −7.7 (d, J=8.5 Hz) ppm. MS (EI) *m/z*: 272 (M^+); 220; 205; 167; 150; 123; 105; 77. **22a–n,o**: ^{1}H NMR ($CDCl_3$)δ: 1.20 and 1.20 (3H, d and dq, J=6.3 Hz and J=7.20 and 2.0 Hz, respectively, CH_3); 1.63–1.74 (1H, m, CH); 2.03–2.11 (1H, m, CH); 2.16–2.71 (4H, m, 4×CH); 5.35–5.43 (1H, m, CH−O); 7.39–7.62 and 7.97–8.09 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.83 (d, J=9.4 Hz, for one isomer); −7.50 (d, J=7.5 Hz, for another isomer) ppm. IR (neat) (cm^{-1}): 3066; 2973; 1718; 1604. MS (EI) *m/z*: 272 (M^+); 182; 167; 150; 123; 105; 77. High-resolution MS: $C_{14}H_{15}F_3O_2$, 272.1045. Calc., 272.1023. **23a–l**: ^{1}H NMR ($CDCl_3$) δ: 1.49–1.85 (5H, m, 2×CH_2 and CH); 2.01–2.08 (2H, m, 2×CH); 2.20–2.26 (1H, m, CH); 2.45–2.57 (1H, m, CH); 5.46 (1H, m, CH−O); 7.41–7.63 and 7.99–8.10 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −11.17 (d, J=8.5 Hz) ppm. MS (EI) *m/z*: 272 (M^+); 220; 205; 167; 150; 123; 105; 77. **23a–m**: ^{1}H NMR

($CDCl_3$) δ: 1.19–1.71 (4H, m, $2\times CH_2$); 1.94–2.00 (2H, m, CH_2); 2.16–2.37 (3H, m, CH_2 and CH); 4.93–5.01 (1H, m, CH−O); 7.37–7.64 and 7.98–8.10 (5H, m, aromatic) ppm. ^{19}F NMR($CDCl_3$) δ: −11.00 (d, $J=8.5$ Hz) ppm. MS (EI) *m/z*: 272 (M^+); 220; 205; 167; 150; 123; 105; 77.

1-Benzoyloxy-3-trifluoromethyl-4-methylcyclohexane (22b), 1-benzoyloxy-3-trifluoromethylcycloheptane (23b) and 5-benzoyloxy-8,8,8-trifluoro-1-octene (24b)

Reaction of 7b (204.5 mg) gave **24b** (49.7 mg, 35% yield), **22b–l,m,n** and **23b–l,m** (51.8 mg, 37% yield, **22b–l,m,n/23b–l,m** = 9.8:1 by ^1H NMR spectroscopy), **23b–m** (1.2 mg, 1% yield), **22b–o** and **23b–m** (0.6 mg, 1% yield, **22b–o/23b–m** = 1.4:1 by GLC) and **22b–o** (10.8 mg, 8% yield). **22b–l,m,n** and **23b–l,m**: ^1H NMR ($CDCl_3$) δ: 1.09 and 1.13 (3H, each dq, $J=8.0$ and 1.6 Hz and $J=6.3$ and 1.7 Hz, CH_3 for **22b**); 1.22–2.79 (m); 4.93–5.01, 5.09–5.18 and 5.41 (1H, each m, CH−O); 7.39–7.62 and 7.98–8.10 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −5.50 (d, $J=7.5$ Hz); −5.83 (d, $J=6.6$ Hz); −6.50 (d, $J=10.3$ Hz); −10.67 and −10.67 (each d, $J=9.4$ Hz and $J=8.5$ Hz) ppm. IR (neat) (cm^{-1}) 3040; 2941; 1716; 1603. MS (EI) *m/z*: 286 (M^+); 205; 181; 164; 149; 123; 105; 77. **23b–m**: ^1H NMR ($CDCl_3$) δ: 1.46–1.91 (6H, m, $3\times CH_2$); 1.99–2.10 (3H, m, CH_2 and CH); 2.25–2.37 (2H, m, CH_2); 5.15 (1H, m, CH−O); 7.40–7.60 and 8.00–8.07 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −10.67 (d, $J=8.5$ Hz) ppm. **22b–o**: ^1H NMR ($CDCl_3$) δ: 1.08 (3H, dq, $J=7.1$ and 1.4 Hz, CH_3); 1.67–1.83 (4H, m, $2\times CH_2$); 1.95 (1H, m, CH); 2.16 (1H, m, CH); 2.28 (1H, m, CH), 2.33–2.45 (1H, m, CH); 4.92–5.00 (1H, m, CH–O); 7.40–7.60 and 8.00–8.08 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −6.50 (d, $J=9.4$ Hz) ppm. IR (neat) (cm^{-1}): 3045; 2937; 1718; 1604. MS (EI) *m/z*: 286 (M^+); 220; 205; 181; 164; 149; 123; 105; 77. High-resolution MS: $C_{15}H_{17}F_3O_2$, 286.1149. Calc. 286.1179. **24b**: ^1H NMR ($CDCl_3$) δ: 1.63–2.03 (4H, m, $2\times CH_2$); 2.10–2.56 (4H, m, $2\times CH_2$); 4.99 (1H, ddt, $J=10.3$, 1.7 and 1.4 Hz, CH=); 5.03 (1H, ddt, $J=17.1$, 1.7 and 1.0 Hz, CH=); 5.21 (1H, m, CH−O), 5.81 (1H, ddt, $J=17.1$, 10.3 and 6.6 Hz, CH=); 7.43–7.62 and 8.00–8.08 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −3.83 (t, $J=10.3$ Hz) ppm. IR (neat) (cm^{-1}): 3076; 2937; 1718; 1644. MS (EI) *m/z*: 286 (M^+); 205; 181; 164; 149; 123; 105; 77.

1-Decyl-2-trifluoromethylcyclopentane (25a)

Reaction of **13a** (248.3 mg) gave **25a** (142.1 mg, 83% yield, stereoisomeric mixture, 1:1 by GLC). ^1H NMR ($CDCl_3$) δ: 0.89 (3H, t, $J=6.8$ Hz, CH_3); 1.17–1.93 (24H, m, $12\times CH_2$); 1.97–2.06 (1H, m, CH); 2.13–2.26 and 2.48–2.60 (1H, each m, CH) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.0 (d, $J=11.3$ Hz, for one isomer); −7.5 (d, $J=9.4$ Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 2960; 2940; 2860; 1465. MS (EI) *m/z*: 278 (M^+); 165; 151; 131; 117; 97; 85; 71. High-resolution MS: $C_{16}H_{29}F_3$, 278.2197. Calc., 278.2219.

2-Trifluoromethyl-1-heptylcyclopentane (25b)

Reaction of **13b** (231.1 mg) gave **25b** (98.8 mg, 66% yield, stereoisomeric mixture, 1:1 by GLC). ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=6.9$ Hz, CH_3); 1.17–1.94 (18H, m, $9\times CH_2$); 1.98–2.05 (1H, m, CH); 2.12–2.25 and 2.47–2.61 (1H, m, CH) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.2 (d, $J=11.3$ Hz, for one isomer); −7.5 (d, $J=9.4$ Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 2960; 2935; 2855; 1465. MS (EI) *m/z*: 236 (M^+); 193; 180; 165; 151; 131; 117; 57. High-resolution MS: $C_{13}H_{23}F_3$, 236.1772. Calc., 236.1750.

1-Benzyl-2-trifluoromethylcyclopentane (25c)

Reaction of **13c** (244.8 mg) gave **25c** (109.1 mg, 69% yield, stereoisomeric mixture, 1.1:1 by GLC). ^1H NMR ($CDCl_3$) δ: 1.25–2.01 (6H, m, $3\times CH_2$); 2.25–2.67 (3H, m, CH_2 and CH); 2.95–3.03 (1H, m, CH); 7.16–7.30 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.0 (d, $J=10.3$ Hz, for one isomer); −7.5 (d, $J=9.0$ Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 3040; 2975; 2880; 1455. MS (EI) *m/z*: 228 (M^+); 117; 92; 91. High-resolution MS: $C_{13}H_{15}F_3$, 228.1096. Calc., 228.1124.

1-(2-Benzoyloxy)ethyl-2-trifluoromethylcyclopentane (25d)

Reaction of **13d** (108.8 mg) gave **25d** (61.4 mg, 81% yield, stereoisomeric mixture, 1:1 by GLC). ^1H NMR ($CDCl_3$) δ: 1.23–2.72 (10H, m, $4\times CH_2$ and $2\times CH$); 4.31–4.43 (2H, m, CH_2−O); 7.43–7.58 and 8.02–8.06 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.2 (d, $J=11.3$ Hz, for one isomer); −7.5 (d, $J=9.4$ Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 2960; 1730; 1450. MS (EI) *m/z*: 286 (M^+); 220; 205; 164; 135; 123; 105; 77. High-resolution MS: $C_{15}H_{17}F_3O_2$, 286.1160. Calc., 286.1178.

1-Benzyl-2-trifluoromethylcyclohexane (26e)

Reaction of **14e** (210.3 mg) gave **26e** (65.9 mg, 48% yield, stereoisomeric mixture, 3:1 by GLC) and uncyclized reduction product (11.0 mg, 8%). **26e**: ^1H NMR ($CDCl_3$) δ: 0.86–2.04 (8H, m, $4\times CH_2$); 2.27–2.40 (2H, m, $2\times CH$); 2.66 and 2.82 (1H, each m, CH); 3.17 (1H, dd, $J=13.0$ and 4.0 Hz, CH); 7.13–7.30 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −3.83 (d, $J=8.5$ Hz, for one isomer); −4.50 (d, $J=10.3$ Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 3030; 2930; 2860; 1450. MS (EI) *m/z*: 242 (M^+); 131; 115; 77. High-resolution MS: $C_{14}H_{17}F_3$, 242.1302. Calc., 242.1281.

1-(2-Benzoyloxyethyl)-2-trifluoromethylcyclohexane (26f)

Reaction of **14f** (54.4 mg) gave **26f** (18.3 mg, 48% yield, stereoisomeric mixture, 1.4: 1 by GLC). ^{1}H NMR ($CDCl_3$) δ: 1.09–2.05 (11H, m, 5×CH_2 and CH); 2.15–2.31 (1H, m, CH); 4.29–4.42 (2H, m, CH_2O); 7.42–7.58 and 8.02–8.04 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −4.67 (d, J=8.5 Hz, for one stereoisomer); −5.0 (d, J=10.3 Hz, for another isomer) ppm. IR (CCl_4) (cm^{-1}): 3075; 2945; 2870; 1725; 1455. MS (EI) *m/z*: 300 (M^+); 279; 219; 178; 149; 123; 105; 77.

3-Benzoyloxy-1-trifluoromethyl-5-(1-phenylethyl)-1-cyclopentene (27a)

Reaction of **17a** (212.0 mg) gave **27a–l** (39.1 mg, 25% yield), **27a–l** and uncyclized reduction product (6.1 mg, 4% yield, **27a–l**/uncyclized reduction product = 1.4:1 by GLC), **27a–m** and unidentified product (4.0 mg, 2.5% yield, **27a–m**/unidentified product = 4.2:1 by GLC), **27a–m,n** (23.7 mg, 15% yield, **m/n** = 1:1.1 by GLC), **27a–n** (3.7 mg, 2% yield) and **27a–o** (61.7 mg, 39% yield). **27a–l**: ^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, d, J=7.2 Hz, CH_3); 2.02 (1H, ddd, J=13.8, 9.0 and 7.0 Hz, CH); 2.59 (1H, dd, J=13.8 and 7.3 Hz, CH); 3.23 (1H, qd, J=7.2 and 3.0 Hz, CH); 3.31 (1H, m, CH); 4.74–4.80 (1H, m, CH−O); 6.27 (1H, m, CH=); 7.19–7.56 and 7.90–7.97 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −0.1 (br) ppm. IR (neat) (cm^{-1}): 3089; 3064; 3033; 2968; 2938; 2880; 1718; 1664; 1603; 1585. MS (EI) *m/z*: 255 (M^+ − PhCO); 238; 226. **27a–m**: ^{1}H NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7.1 Hz, CH_3); 1.88 (1H, ddd, J=14.7, 9.2 and 5.3 Hz, CH); 2.46 (1H, ddd, J=14.7, 7.9 and 3.2 Hz, CH); 3.35 (1H, qd, J=7.1 and 3.3 Hz, CH); 3.55–3.57 (1H, m, CH); 5.96–6.01 (1H, m, CH−O); 6.53–6.54 (1H, m, CH=); 7.11–7.62 and 7.95–8.06 (10H, m, aromatic) ppm. **27a–n**: ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7.1 Hz, CH_3); 1.93 (1H, ddd, J=15.1, 3.6 and 3.6 Hz, CH); 2.33 (1H, ddd, J=15.1, 8.6 and 8.6 Hz, CH); 3.37–3.42 (2H, m, 2×CH); 5.83–5.87 (1H, m, CH−O); 6.54 (1H, m, CH=); 7.18–7.62 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −0.8 (br) ppm. **27a–o**: ^{1}H NMR ($CDCl_3$) δ: 1.40 (3H, d, J=6.7 Hz, CH_3); 1.89 (1H, ddd, J=15.0, 3.2 and 3.2 Hz, CH); 2.55 (1H, ddd, J=15.0, 8.5 and 8.5 Hz, CH); 3.23–3.31 (2H, m, 2×CH); 5.65–5.69 (1H, m, CH−O); 6.44 (1H, m, CH=); 7.07–7.75 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −1.33 (br) ppm. IR (neat) (cm^{-1}): 3063; 3032; 2968; 2938; 1717; 1603; 1496. MS (EI) *m/z*: 255 (M^+ − PhCO); 226; 205; 134; 106; 105. High-resolution MS: $C_{14}H_{14}F_3O$ (M^+ − PhCO), 255.0606. Calc., 255.0632.

3-Benzoyloxy-1-trifluoromethyl-5-(3-phenylpropyl)-1-cyclopentene (27b)

Reaction of **17b** (251.6 mg) gave **27b–l** (73.3 mg, 39% yield) and **27b–m** (88.2 mg, 47% yield). **27b–l**: ^{1}H NMR ($CDCl_3$) δ: 1.34–1.44 (1H, m, CH); 1.57–1.76 (2H, m, CH_2); 1.80–1.88 (1H, m, CH); 2.21–2.34 (2H, m, CH_2); 2.58–2.72 (2H, m, CH_2); 3.20 (1H, br, CH); 5.96 (1H, m, CH−O); 6.44 (1H, m, CH=); 7.18–7.59 and 8.01–8.04 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −1.33 (br) ppm. IR (neat) (cm^{-1}): 3065; 3028; 2943; 1717; 1603; 1585; 1541. MS (EI) *m/z*: 374 (M^+); 252; 205. High-resolution MS: $C_{22}H_{21}F_3O_2$, 374.1464. Calc., 374.1492. **27b–m**: ^{1}H NMR ($CDCl_3$) δ: 1.44–1.53 (1H, m, CH); 1.62–1.91 (4H, m, 2×CH_2); 2.57–2.79 (3H, m, CH_2 and CH); 2.97 (1H, br, CH); 5.87 (1H, m, CH−O); 6.44 (1H, m, CH=), 7.16–7.59 and 7.96–7.99 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −1.0 (br) ppm. IR (neat) (cm^{-1}): 3064; 3029; 2942; 2863; 1717; 1603; 1497. High-resolution MS: $C_{22}H_{21}F_3O_2$, 374.1473. Calc., 374.1492.

3-Benzoyloxy-1-trifluoromethyl-6-methyl-1-cyclohexene (27c) and 3-benzoyloxy-1-trifluoromethyl-1-cycloheptene (28c)

Reaction of **17c** (166.9 mg) gave **27c–l,m** (57.9 mg, 50% yield, **l/m** = 1:1.9 by GLC), **27c–m** and **28c** (8.9 mg, 8% yield, **27c–m/28c** = 1:2.1 by GLC) and **28c** (3.1 mg, 3% yield). **27c–l,m**: ^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, dd, J=7.0 and 1.0 Hz, CH_3 for one stereoisomer); 1.24 (3H, dd, J=7.0 and 0.9 Hz, CH_3 for another isomer); 1.48–2.20 (4H, m, 2×CH_2); 2.51–2.62 (1H, m, CH); 5.57–5.61 (1H, m, CH−O); 6.40–6.41 (1H, m; CH=); 7.40–7.61 and 8.00–8.09 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −3.0 (br) ppm. IR (neat) (cm^{-1}): 3066; 2944; 2870; 1719; 1603; 1586; 1493; 1453. MS (EI) *m/z*: 284 (M^+); 269; 179; 163. High-resolution MS: $C_{15}H_{15}F_3O_2$, 284.1028. Calc., 284.1023. **28c**: ^{1}H NMR ($CDCl_3$) δ: 1.80–2.55 (8H, m, 4×CH_2); 5.75 (1H, m, CH−O); 6.48 (1H, m, CH=); 7.41–7.62 and 8.01–8.10 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −7.7 (br) ppm.

1-(Ethoxycarbonyl)difluoromethyl-2-methylcyclopentane (29a)

Reaction of **20a** (383.4 mg) gave **29a–l,m** (106.3 mg, 45% yield, **l/m** = 1.4:1 by GLC), **29a–l,m** and uncyclized reduction product (URP) (40.1 mg, 17% yield, **29a–l,m**/URP = 27.6:1 by GLC, **l/m** = 2.1:1 by GLC), **29a–m** and URP (9.4 mg, 4% yield, **29a–m**/URP = 1:6.8 by GLC) and URP (5.0 mg, 2% yield). Reaction of **21a** (296.2 mg) gave **29a–l,m** (72.1 mg, 39% yield, **l/m** = 1.4:1 by ^{1}H NMR spectroscopy), **29a–l,m** and URP (19.4 mg, 11% yield, **29a–l,m**/URP = 21.1: by GLC, **l/m** = 4.3:1 by GLC) and URP (3.8 mg, 2% yield). **29a–l,m**: ^{1}H NMR ($CDCl_3$) δ: 0.99 (3H, ddd, J=7.2,

2.1 and 2.1 Hz, CH_3 for one isomer); 1.05 (3H, d, J=6.5 Hz, CH_3 for another isomer); 1.35 (3H, t, J=7.1 Hz, CH_3 for one stereoisomer); 1.35 (3H, t, J=7.1 Hz, CH_3 for another stereoisomer); 1.19–2.66 (8H, m, 3×CH_2 and 2×CH); 4.32 (2H, q, J=7.1 Hz, CH_2–O) ppm. ^{19}F NMR ($CDCl_3$) δ: −42.66 (1F, dd, J=260.5 and 17.6 Hz, for one isomer); −46.37 (1F, dd, J=260.5 and 18.3 Hz, for one isomer); −47.48 (1F, dd, J=254.1 and 14.5 Hz, for another isomer); −48.86 (1F, dd, J=254.1 and 17.5 Hz, for another isomer) ppm. IR (neat) (cm^{-1}): 2959; 2927; 2857; 1732. MS (EI) *m/z*: 206 (M^+); 186; 133; 124; 113. High-resolution MS: $C_{10}H_{16}F_2O_2$, 206.1112. Calc., 206.1116.

2-Benzyl-1-[(ethoxycarbonyl)difluoromethyl]-cyclopentane (29b)

Reaction of **20b** (286.8 mg) gave **29b** (163.1 mg, 82% yield, stereoisomeric mixture, 1.3:1 by GLC). Reaction of **21b** (295.0 mg) gave **29b** (127.7 mg, 63% yield, stereoisomeric mixture, 1.1:1 by GLC). ^{1}H NMR ($CDCl_3$) δ: 1.35 and 1.38 (3H, each t, each J=7.1 Hz, CH_3); 1.42–1.94 (6H, m, 3×CH_2); 2.33–2.84 (3H, m, 3×CH); 2.91 (0.5H, brd, J=9.2 Hz, CH); 3.02 (0.5H, d, J=10.9 Hz, CH); 4.30 (2H, qd, J=7.1 and 5.6 Hz, CH_2–O for one isomer); 4.35 (2H, q, J=7.1 Hz, CH_2–O for another isomer); 7.10–7.31 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −43.05 (1F, dd, J=261.0 and 18.2 Hz, for one isomer); −44.04 (1F, dd, J=261.0 and 18.0 Hz, for one isomer); −46.6 (1F, dd, J=254.5 and 15.2 Hz, for another isomer); −48.59 (1F, dd, J=254.5 and 17.2 Hz, for another isomer) ppm. IR (neat) (cm^{-1}): 3029; 2962; 2877; 1767; 1604. MS (EI) *m/z*: 282 (M^+); 191; 163; 143; 117; 91. High-resolution MS: $C_{16}H_{20}F_2O_2$, 282.1450. Calc., 282.1430.

2-[(2-t-Butyldiphenylsilyloxy)ethyl]-1-[(ethoxycarbonyl)difluoromethyl]cyclopentane (29c)

Reaction of **20c** (296.4 mg) gave **29c** (188.1 mg, 80% yield, stereoisomeric mixture, 2.3:1 by GLC) and uncyclized reduction product (6.3 mg, 3% yield). Reaction of **21c** (299.1 mg) gave **29c** (191.8 mg, 81% yield, stereoisomeric mixture, 2.2:1 by GLC) and uncyclized reduction product (6.7 mg, 3% yield). **29c**: ^{1}H NMR ($CDCl_3$) δ: 1.05 [9H, s, $(CH_3)_3C$]; 1.32 and 1.34 (3H, each t, each J=7.1 Hz, CH_3); 1.18–1.90 and 2.18–2.37 (10H, each m, 4×CH_2 and 2×CH); 3.60–3.74 (2H, m, CH_2–O); 4.29 and 4.30 (2H, each q, each J=7.1 Hz, CH_2–O); 7.33–7.45 and 7.62–7.70 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −43.77 (2F, dd, J=43.8 and 19.4 Hz, for one isomer); −46.07 (1F, dd, J=255.5 and 14.1 Hz, for another isomer); −49.53 (1F, dd, J=255.5 and 18.4 Hz, for another isomer) ppm. IR (neat) (cm^{-1}): 3072; 2958; 2859; 1768; 1590. MS (EI) *m/z*: 417 ($M^+ - Bu^t$); 231; 201. MS (CI) *m/z*: 475 ($M^+ + 1$).

1-Benzylidene-2-[(ethoxycarbonyl)difluoromethyl]-cyclopentane (29d)

Reaction of **20d** (328.0 mg) gave **29d–l,m** (188.7 mg, 83% yield, **l/m**=7.5:1 by GLC). Reaction of **21d** (280.4 mg) gave **29d–l** (9.5 mg, 5% yield), **29d–l,m** (115.5 mg, 59% yield, **l/m**=2.4:1 by GLC) and **29d–m** (14.8 mg, 8% yield). **29d–l**: ^{1}H NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz, CH_3); 1.59–1.69 (1H, m, CH); 1.91–1.99 (3H, m, CH_2 and CH); 2.51–2.69 (2H, m, CH_2); 3.34–3.46 (1H, m, CH); 4.33 (2H, q, J=7.2 Hz, CH_2–O); 6.51 (1H, br, CH=); 7.17–7.36 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −45.52 (2F, d, J=16.6 Hz) ppm. IR (neat) (cm^{-1}): 3080; 3020; 2964; 1771. MS (EI) *m/z*: 280 (M^+); 260; 240; 157; 129; 115; 91. High-resolution MS: $C_{16}H_{18}F_2O_2$, 280.1256. Calc., 280.1273. **29d–m**: ^{1}H NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz, CH_3); 1.62–1.73 (1H, m, CH); 1.84–2.07 (3H, m, CH_2 and CH); 2.41–2.48 (1H, m, CH); 2.62–2.71 (1H, m, CH); 3.79–3.89 (1H, m, CH); 3.90 (1H, dq, J=10.8 and 7.1 Hz, CH–O); 4.08 (1H, dq, J=10.8 and 7.1 Hz, CH–O); 6.61 (1H, br, CH=); 7.16–7.40 (5H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −45.52 (1F, dd, J=253.0 and 13.4 Hz); −47.61 (1F, dd, J=253.0 and 19.5 Hz) ppm. IR (neat) (cm^{-1}): 3040; 3020; 2965; 1770. MS (EI) *m/z*: 280 (M^+); 260; 240; 157; 129; 115; 91. High-resolution MS: $C_{16}H_{18}F_2O_2$, 280.1262. Calc., 280.1273.

2-(Ethoxycarbonyl)difluoromethyl-1-(trimethylsilylmethylene)cyclopentane (29e)

Reaction of **20e** (306.6 mg) gave **29e–l** (17.5 mg, 8% yield), **29e–l,m** (117.7 mg, 56% yield, **l/m**=1.4:1 by GLC) and uncyclized reduction product (21.6 mg, 10% yield). Reaction of **21e** (300.0 mg) gave **29e–l** (12.5 mg, 6% yield), **29e–l,m** (99.8 mg, 49% yield, **l/m**=1.7:1 by GLC) and uncyclized reduction product (16.0 mg, 8% yield). **29e–l**: ^{1}H NMR ($CDCl_3$) δ: 0.09 [9H, s, $(CH_3)_3Si$]; 1.35 (3H, t, J=7.1 Hz, CH_3); 1.56–1.66 (1H, m, CH); 1.82–1.94 (3H, m, CH_2 and CH); 2.27–2.43 (2H, m, CH_2); 3.18 (1H, m, CH); 4.30 (2H, q, J=7.1 Hz, CH_2–O); 5.54 (1H, br, CH=) ppm. ^{19}F NMR ($CDCl_3$) δ: −43.77 (1F, dd, J=256.7 and 15.7 Hz); −46.99 (1F, dd, J=256.7 and 16.7 Hz) ppm. IR (neat) (cm^{-1}): 2959; 1772; 1760; 1623. MS (EI) *m/z*: 276 (M^+); 261; 213; 155; 139; 103; 77. **29e–l,m**: ^{1}H NMR ($CDCl_3$) δ: 0.09 [9H, s, $(CH_3)_3Si$ for one isomer]; 0.12 [9H, d, J=0.9 Hz, $(CH_3)_3Si$ for another isomer]; 1.35 (3H, t, J=7.1 Hz, CH_3 for one isomer); 1.36 (3H, t, J=7.1 Hz, CH_3 for another isomer); 1.56–1.66 (1H, m, CH); 1.76–1.94 (3H, m, CH_2 and CH); 2.26–2.43 and 2.50–2.58 (2H, m, CH_2); 3.12–3.33 (1H, m, CH); 4.30 (2H, q, J=7.1 Hz, CH_2–O for one isomer); 4.33 (2H, q, J=7.1 Hz, CH_2–O for another isomer); 5.54 (1H, br, CH= for one isomer); 5.68 (1H, br, CH= for another isomer) ppm. ^{19}F NMR ($CDCl_3$) δ: −36.91 (1F, dd, J=254.0 and 4.8 Hz, for one isomer); −43.77 (1F, d, J=256.7

Hz, for another isomer); −46.99 (1F, dd, J=256.7 and 16.7 Hz, for another isomer); −53.71 (1F, dd, J=254.0 and 28.3 Hz, for one isomer) ppm. IR (neat) (cm^{-1}): 2958; 1771; 1628; 1451. MS (EI) *m/z*: 276 (M^+); 261; 233; 213; 185; 169; 155; 139; 103.

1-2-(t-Butyldiphenylsilyloxy)ethylidene-2-[(ethoxycarbonyl)difluoromethyl]cyclopentane (29f)

Reaction of **20f** (307.9 mg) gave **29f–l** (74.6 mg, 31% yield), **29f–m** (56.0 mg, 23% yield) and uncyclized reduction product (28.7 mg, 12% yield). Reaction of **21f** (315.9 mg) gave **29f–l** (56.0 mg, 23% yield), **29f–m** (43.6 mg, 17% yield) and uncyclized reduction product (8.4 mg, 3% yield). **29f–l**: ^{1}H NMR ($CDCl_3$) δ: 1.04 [9H, s, $(CH_3)_3C$]; 1.33 (3H, t, J=7.1 Hz, CH_3); 1.46–1.54 (1H, m, CH); 1.72–1.86 (3H, m, CH_2 and CH); 1.93–2.12 (2H, m, CH_2); 3.2 (1H, ddt, J=17.7, 15.8 and 7.4 Hz, CH); 4.16–4.25 (2H, m, CH_2−O); 4.31 (2H, q, J=7.1 Hz, CH_2−O); 5.66 (1H, br, CH=); 7.34–7.46 and 7.64–7.72 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −45.62 (1F, dd, J=256.1 and 15.8 Hz); −46.78 (1F, dd, J=256.1 and 17.7 Hz) ppm. IR (neat) (cm^{-1}): 3072; 2961; 2933; 2858; 1771. MS (EI) *m/z*: 415 ($M^+ - Bu^t$); 231; 199; 143. High-resolution MS: $C_{23}H_{25}F_2O_3Si$ ($M^+ - Bu^t$), 415.1531. Calc., 415.1539. **29f–m**: ^{1}H NMR ($CDCl_3$) δ: 1.05 [9H, s, $(CH_3)_3C$]; 1.24 (3H, t, J=7.2 Hz, CH_3); 1.70–1.76 (4H, m, 2×CH_2); 2.27 (2H, m, CH_2); 2.75–2.86 (1H, m, CH); 4.09–4.25 (4H, m, 2×CH_2−O); 5.75 (1H, m, CH=); 7.33–7.46 and 7.64–7.73 (10H, m, aromatic) ppm. ^{19}F NMR ($CDCl_3$) δ: −40.87 (1F, dd, J=253.0 and 10.6 Hz); −50.13 (1F, dd, J=253.0 and 22.5 Hz) ppm. IR (neat) (cm^{-1}): 3072; 2961; 2933; 1769; 1590. High-resolution MS: $C_{23}H_{25}F_2O_3Si$ ($M^+ - Bu^t$), 415.1549. Calc., 415.1539.

1-(Ethoxycarbonyl)difluoromethyl-2-(iodomethyl)-cyclopentane (31)

A solution of **20a** (98.4 mg) and $Bu_3SnSnBu_3$ (18.2 mg) in benzene (3 ml) was stirred for 2 h at room temperature with irradiation via a 100 W high-pressure mercury lamp through a pyrex filter. The reaction mixture was subjected directly to column chromatography to give **31** (58.0 mg, 59% yield, stereoisomeric mixture, 1.5: 1 by ^{1}H NMR spectroscopy). ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.2 Hz, CH_3 for minor isomer); 1.37 (3H, t, J=7.2 Hz, CH_3 for major isomer); 1.45–2.76 (8H, m, 3×CH_2 and 2×CH); 3.12 (1H, dd, J=10.0 and 9.9 Hz, CH−I for minor isomer); 3.23 (1H, dd, J=9.9 and 7.4 Hz, CH−I for major isomer); 3.43 (1H, dd, J=9.9 and 3.9 Hz, CH−I for major isomer); 3.59 (1H, brd, J=10.0 Hz, CH−I for minor isomer); 4.34 (2H, q, J=7.1 Hz, CH_2−O) ppm. ^{19}F NMR ($CDCl_3$) δ: −43.0 to −48.7 (m) ppm. IR (neat) (cm^{-1}): 2964; 2877; 1766. MS (EI) *m/z*: 205 ($M^+ - I$); 185; 157. MS (CI) *m/z*: 333 ($M^+ + 1$).

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