Tetrahedron Vol. 48, No. 41, pp. 8915-8926, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Cyclization Reactions of β,β-Difluoroalkyl Radicals (-CF_2-C•) for Synthesizing *gem*-Difluorocyclic Compounds

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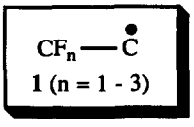
(*Received in Japan* 20 *July* 1992)

Key words: Radical cyclization; β,β-Difluoroalkyl radical; *gem*-Difluorocyclopentane; *gem*-Difluorocyclohexane; *gem*-Difluorotetrahydropyran

Abstract: Cyclization reactions of β,β-difluoroalkyl radicals were carried out. 5 or 6-Exo selective radical cyclizations gave gem-difluorocyclopentane or -cyclohexane derivatives in 53 - 96% yields. 2,5-Disubstituted-3,3-difluorotetrahydropyran derivatives were prepared in 36 - 82% yields with moderate trans-selectivity (2.0 : 1 - 3.1 : 1). 4,5-Disubstituted-3,3-difluorotetrahydropyran derivatives were obtained via radical deoxygenation in 60 - 74% yields. High stereo-selectivity of radical cyclization for the formation of gem-fluorotetrahydropyran rings was achieved by introducing the bulky TBDPS group onto the acceptor double bond.

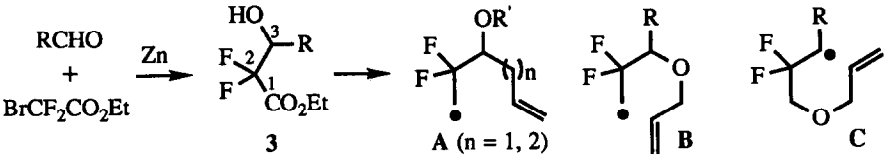
The importance of fluorine-substituted compounds in medicinal chemistry and material science has become increasingly evident in recent years.[1] However, methods for their preparation still remain a problem in many cases. For instance, the preparation of *gem*-difluorocyclic compounds through reactions of the corresponding carbonyl compounds with fluorinating reagents such as DAST (diethylaminosulfur trifluoride) has some limitations due to low yield and lack of functional group selectivity.[2] A new method for the preparation of *gem*-difluorocyclic compounds is thus highly desirable.[3] The free-radical mediated cyclization is particularly attractive as an efficient means for synthesizing cyclic compounds.[4] One synthetic advantage of free-radical reactions is that carbon radicals are not subject to β-elimination of functional groups (*e.g.* OR, NR_2) in contrast to carbanions.[4] In the course of our study on the synthetic applications of free-radical reactions to organofluorine chemistry,[5] interest was directed to β-fluorine-substituted alkyl radicals (**1**). The



1 (n = 1 - 3)

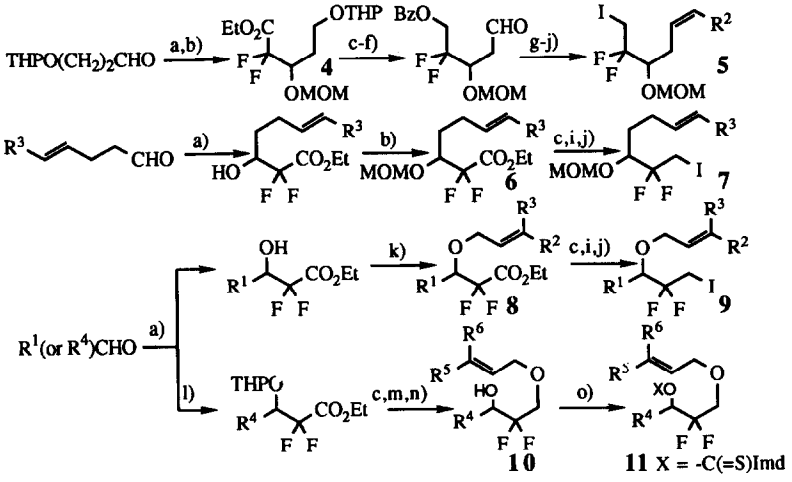
2 (n = 1 - 3)

synthetic use of β-fluorine-substituted carbanion (**2**) involves the problem of the β-elimination of the fluoride anion,[6] and thus the corresponding β-fluorine-substituted alkyl radicals (**1**) should serve as a useful reactive intermediate. We reported the preliminary results of the reaction of trifluoromethyl-substituted alkyl radical (**1**, n=3) in intramolecular C-C bond formation.[5c] As an extension of this work, we developed cyclization reactions through the β,β-difluoroalkyl radical (**1**, n=2) for the synthesis of various cyclic compounds each containing *gem*-fluorine-substituents. Preparation of *gem*-difluorocyclopentane and -tetrahydrofuran derivatives by cyclization of α,α-difluoromethyl radicals (-CF_2•) has recently been reported.[7] This paper describes an approach to the synthesis of *gem*-difluorocyclic compounds (cyclopentane, cyclohexane, and tetrahydropyran derivatives) involving cyclization reactions of β,β-difluoroalkyl radical (**1**).[8]



Scheme 1

β-Hydroxy-α,α-difluoroesters (**3**) were used to construct cyclization systems, in consideration of the ease of their preparation by the Reformatsky reaction of aldehydes with commercially available ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) [9] and since both C-1 and C-3 positions can serve as radical sites by the conventional method. Three cyclization pathways, shown by systems **A**, **B**, and **C**, are thus conceivable



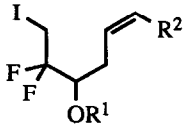
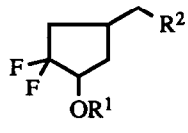
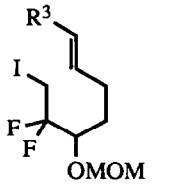
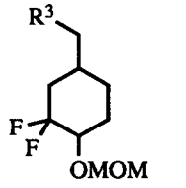
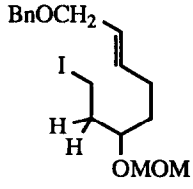
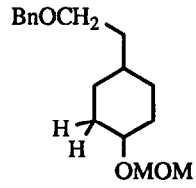
Reagents: a) $BrCF_2CO_2Et$ / Zn; b) MOMCl / NaH; c) $NaBH_4$; d) BzCl / Pyridine;
e) AcOH / THF / H_2O; f) PCC; g) $R^2CH{=}PPh_3$; h) KOH; i) $(CF_3SO_2)_2O$ / *i*-Pr_2NEt; j) NaI;
k) $R^2R^3C{=}CHCH_2Br$ / NaH; l) DHP / PPTS; m) $R^5R^6C{=}CHCH_2Br$ / NaH;
n) EtOH / *p*-TsOH; o) S=$CImd_2$.

Scheme 2

through the intermediary β,β-difluoroalkyl radical for the synthesis of *gem*-difluorocyclic compounds (Scheme 1). Preparation of substrates **5**, **7**, **9**, and **11** is shown in Scheme 2. The ester groups in **4**, **6**, and **8** were each converted to an iodomethyl group by reduction with sodium borohydride and subsequent iodination through the triflate derivative. Thiocarbonylimidazolide (**11**) was derived from **10** for the direct radical deoxygenation of β-hydroxy group.[10]

The radical cyclization of the system A was examined first (Table I). The cyclization of system A (n=1) was 5-exo selective and no by-product was produced. Radical reactions of **5a** with tributyltin hydride (Bu_3SnH) and a catalytic amount of azobisisobutyronitrile (AIBN) in benzene at reflux temperature for 3 hr gave *gem*-difluorocyclopentane derivatives (**12a**) in 96% yield. The radical cyclizations of **5b** - **5d** proceeded in 60 - 91% yields to give **12b** - **12d**. The cyclized products were obtained as a mixture of stereoisomers except in the case of **12d**. The 6-exo cyclization of the system A (n=2) proceeded selectively to give *gem*-

Table I. Radical Cyclization Reactions of **5**, **7**, and **14**[a]

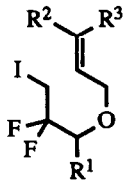
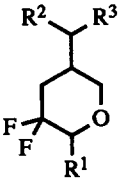
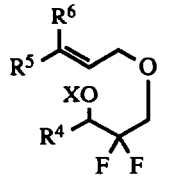
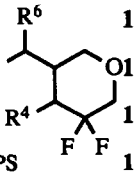
Substrate[b]		Product	(Yield, %)[c]
	**5a** R^1= MOM R^2= n-C_6H_{13}		**12a** (96)
	5b R^1= MOM R^2= Ph		**12b** (91)
	5c R^1= MOM R^2= $BzOCH_2$		**12c** (84)
	5d R^1= TBDMS R^2= $PhCH_2CH_2$		**12d** (60)
	**7e** R^3= Ph		**13e** (53)
	7f R^3= CO_2Et		**13f** (79)
	7g R^3= $BnOCH_2$		**13g** (64)[d]
	**14g**		**15g** (62)[d]

a) Reaction conditions: Bu_3SnH (1.2 - 1.8 eq., 0.02 - 0.05 mol dm^{-3}), AIBN (0.2 eq.), benzene, reflux, 3 hr. b) **5a,d** (Z-isomer), **5b** (E : Z = 1.6 : 1), **5c** and **7f,g** (E-isomer), **7e** (E : Z = 1.3 : 1). c) The cyclized products were obtained as a mixture of stereoisomers except for **12d** and **13e**. The stereochemistry was not fully clearified. **12a** (1.2 : 1 by ^{19}F-NMR), **12b** (1.9 : 1 by ^{19}F-NMR), **12c** (1.4 : 1 by ^{19}F-NMR), **13f** (2.4 : 1), **13g** (1.8 : 1), **15g** (1.2 : 1). d) The uncyclized reduction product was also obtained: $CH_3CF_2CH(OMOM)(CH_2)_2CH{=}CHCH_2OBn$ from **7g** (12% yield), $CH_3CH_2CH(OMOM)(CH_2)_2CH{=}CHCH_2OBn$ from **14g** (21% yield).

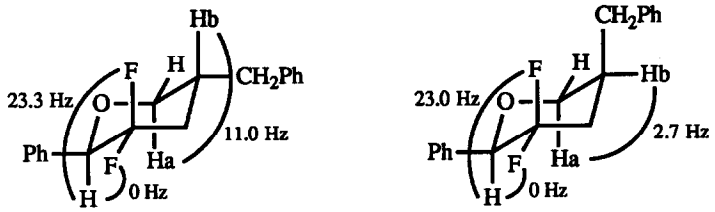
difluorocyclohexane derivatives. **13e** - **13g** were obtained from **7e** - **7g** in 53 - 79% yields. In the case of **7g**, the uncyclized reduction product was isolated (12% yield). To examine the effect of β-fluorine-substituents on radical cyclization, reaction of **14g** was carried out under the same conditions . Compared with the case of **7g**, the cyclization reactivities of **7g** and **14g** did not differ significantly [**13g** (64% yield), **15g** (62% yield)] except for the yield of a minor reduction product [footnote d) shown in Table I]. Neighboring fluorine-substituents at the carbon radical center thus do not exert marked effect *on the radical cyclization reactions.*

The cyclization of systems **B** and **C** was conducted for the synthesis of *gem*-difluorotetrahydropyran derivatives. The results of tin hydride promoted radical cyclizations of **9** and **11** are summarized in Table II. Reaction of **9a** gave 2,5-disubstituted-3,3-difluorotetrahydropyran derivative (**16a**) in 82% yield with a 2.9 : 1 stereoselectivity. The stereochemistry of *trans*- and *cis*-**16a** was assigned based on ^{1}H-NMR and ^{19}F-NMR; Ha showed characteristic coupling constants to Hb [trans diaxial (11.0 Hz) and cis (2.7 Hz)] for major (*trans*-) and minor (*cis*-) isomers, respectively (Scheme 3). **9b** - **9e** gave **16b** - **16e** in 36 - 78% yields with moderate

Table II. Radical Cyclization Reactions of **9** and **11**[a)]

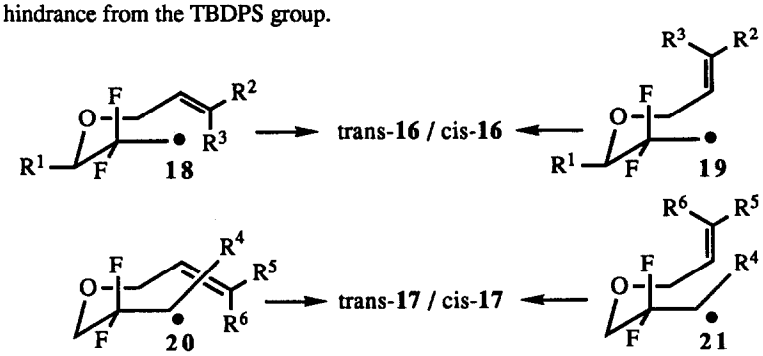
Substrate				Product (Yield, %)	Ratio of Stereoisomers (trans : cis)
	**9a** R^1= Ph	R^2= Ph	R^3= H	 **16a** (82)[b)]	2.9 : 1
	9b R^1= Ph	R^2= Me	R^3= Me	**16b** (60)[b)]	2.0 : 1
	9c R^1= Ph	R^2= H	R^3= $BnOCH_2$	**16c** (46)[b)]	2.1 : 1
	9c			**16c** (63)[c)]	2.4 : 1
	9d R^1= Ph	R^2= H	R^3= H	**16d** (36)[b,c)]	2.8 : 1
	9e R^1= *t*-Bu	R^2= Ph	R^3= H	**16e** (78)	3.1 : 1
	9f R^1= *t*-Bu	R^2= H	R^3= TBDPS	**16f** (43)	trans-only
 X = -C(=S)Imd	**11g** R^4= $PhCH_2CH_2$	R^5= Me	R^6= Me	**17g** (63)[b)]	1.2 : 1
	11h R^4= $PhCH_2CH_2$	R^5= Ph	R^6= H	**17h** (74)	1 : 1[d)]
	11i R^4= $PhCH_2CH_2$	R^5= H	R^6= $BnOCH_2$	 **17i** (65)[b)]	1.3 : 1
	11j R^4= Me	R^5= Ph	R^6= H	**17j** (61)[b)]	1 : 1.5
	11k R^4= Me	R^5= H	R^6= TBDPS	**17k** (70)[b)]	11.3 : 1
	11l R^4= $PhCH_2CH_2$	R^5= H	R^6= TBDPS	**17l** (60)[b)]	22.8 : 1

a) Reaction conditions: Bu_3SnH (1.3 eq., 0.02 mol dm^{-3}), AIBN (0.2 eq.), benzene, reflux, 3 hr. b) The uncyclized reduction product was also obtained: 11% yield from **9a**, 18% yield from **9b**, 32% yield from **9c** (0.02 mol dm^{-3} of Bu_3SnH), 3% yield from **9d**, 2% yield from **9f**, 19% yield from **11g**, 17% yield from **11i**, 7% yield from **11j**, 10% yield from **11k**, and 1% yield from **11l**. c) [Bu_3SnH] = 0.002 mol dm^{-3}. d) Approximately determined by GLC.



Scheme 3

stereoselectivity (trans : cis = 2.0 : 1 - 3.1 : 1). In the case of **9c**, a high dilution method with slow addition improved the cyclization yield of **16c** to 63% by suppressing the formation of the uncyclized reduction product. The radical cyclization of thiocarbonylimidazolide derivatives (**11g - 11j**) *via* deoxygenation gave *trans*- and *cis*-4,5-disubstituted-3,3-difluorotetrahydropyran derivatives (**17g - 17j**) unselectively (61 - 74% yields). For greater stereoselectivity of the cyclization of systems **B** and **C**, the bulky substituent was introduced onto the acceptor double bond. The effect of TBDPS group on the stereoselectivity of radical cyclization in the reaction of *the stabilized captodative radical* (-O-$\dot{C}$H-CO_2t-Bu) was recently reported.[11] As expected, the *cis*-TBDPS group (R^3 or R^6) dramatically enhanced the stereoselectivity of the radical cyclization of *the β,β-difluoroalkyl radical* (-CF_2-$\dot{C}$H-R, R = H or alkyl). **9f** gave *trans*-**16f** as the sole product, and **11k,l** gave *trans*-**17k,l** with 11.3 : 1 and 22.8 : 1 stereoselectivity, respectively. This stereoselectivity can be explained by considering the cyclization occurring through conformers **18** - **21** to the stereoisomers (Scheme 4). Cyclization process through conformer **18** to *trans*-**16** involving the radical acceptor at the equatorial position would appear to be more favorable. The *cis*-bulky substituent (R^3= TBDPS) in **9f** inhibited the cyclization from **19** to *cis*-**16f**. In **11k,l**, the TBDPS group (R^6) was importantly essential to *trans*-selective cyclization through conformer **20**. The cyclization of **21** (R^6= TBDPS) to *cis*-**17k,l** may occur with difficulty owing to steric hindrance from the TBDPS group.



Scheme 4

In summary, a strategy was developed for the general synthesis of *gem*-difluorocyclic compounds [cyclopentanes (**12**), cyclohexanes (**13**), and tetrahydropyrans (**16** and **17**)] involving the cyclization of β,β-

difluoroalkyl radicals. The synthetic potential of β,β-difluoroalkyl radicals as a complement to synthetically inaccesible corresponding carbanions was also demonstrated.

Acknowledgement. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (No. 03857313).

EXPERIMENTAL

^{1}H-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer in $CDCl_3$, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ as an internal standard. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer in $CDCl_3$, and chemical shifts were reported in ppm using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or a VG Auto Spec.

Preparation of the substrates (5, 7, 9, and 11)

Typical procedure for the Reformatsky reaction of aldehydes with ethyl bromodifluoroacetate (Scheme 2): To a refluxing suspension of activated zinc dust (1.56g, 23.9 mg atom) in THF (20 ml) was added dropwise a solution of ethyl bromodifluoroacetate (3.86g, 19.0 mmol) and 3-(tetrahydropyranyloxy)propanal ($THPOCH_2CH_2CHO$, 3.0 g, 19.0 mmol) in THF (40 ml). After 2 hr the reaction mixture was cooled, quenched by the addition of NH_4Cl aq. and extracted with ether. The ether phase was washed with NaCl aq. and dried over $MgSO_4$. Purification by column chrmatography on silica gel gave β-hydroxy-α,α-difluoroester derivative [$THPOCH_2CH_2CH(OH)CF_2CO_2Et$, 2.43g] in 45% yields.

β-Hydroxy-α,α-difluoroester derivatives were converted into **5**, **7**, **9**, and **11** by the standard methods using reagents [a) - o)] shown in Scheme 2. The reaction conditions are given below: a) 1.1 eq. NaH, 1.3 eq. MOMCl, THF, r. temp., 2 hr, b) 6 eq. $NaBH_4$, MeOH, 0 °C, 30 min, c) 1.3 eq. BzCl, pyridine, 0 °C, 1 hr, e) AcOH : THF : H_2O = 4 : 2 : 7, 60 °C, 7 hr, f) 1.6 eq. PCC, 0.4 eq. AcONa, CH_2Cl_2, r. temp., 3 hr, g) 1.1 eq. $R^2CH{=}PPh_3$, Et_2O, r. temp., 2.5 hr, h) 1.5 *N* KOH in MeOH, r. temp., 2 hr, i) 1.5 eq. $(CF_3SO_2)_2O$, 2 eq. *i*-Pr_2NEt, CH_2Cl_2, -78 °C, 1 hr, j) 4 eq. NaI, acetone, r. temp., 15 hr, k) 1.2 eq. NaH, 1.1 eq. $R^2R^3C{=}CHCH_2Br$, THF, r. temp., 2 - 36 hr, l) 3 eq. DHP, cat. PPTS, CH_2Cl_2, r. temp., 4 hr, m) 1.2 eq. NaH, 1.1 eq. $R^5R^6C{=}CHCH_2Br$, THF, r. temp., 2 - 36 hr, n) cat. *p*-TsOH, EtOH, r. temp., 2 hr, o) 2 eq. $S{=}CImd_2$, THF, reflux, 3 hr.

Typical procedure for the radical cyclization

Under an argon atmosphere, a solution of **5a** (150 mg, 0.39 mmol), tributyltin hydride (Bu_3SnH, 0.16 ml, 0.60 mmol), and azobisisobutyronitrile (AIBN, 12.6 mg, 0.08 mmol) in benzene (20 ml) was refluxed for 3 hr. After removal of the solvent, the residue was dissolved in ether (3 ml) followed by the addition of 10% KF aq. (3 ml) with stirring. The precipitate was removed by filtration. The reaction mixture was extracted with ether, washed with NaCl aq., and dried over $MgSO_4$. Purification by column chromatography (and/or MPLC) on silica gel gave **12a** as a mixture of stereoisomers (97.1 mg, 96% yield, 1.2 : 1 by ^{19}F-NMR).

In the case of **9c**, the reaction under the high dilution conditions was carried out using syringe pump technique: A solution of Bu_3SnH (0.05 ml, 0.19 mmol) and AIBN (4.9 mg, 0.03 mmol) in benzene (18 ml) was added to a refluxing solution of **9c** (68.2 mg, 0.15 mmol) and AIBN (2.5 mg, 0.015 mmol) in benzene (75 ml) during 2.4 hr, and the reaction mixture was refluxed for 2 hr.

In the cases of **11g** - **11e**, work-up was carried out as follows: The reaction mixture was treated with NaCl aq. and extracted with ether. The ether phase was washed with NaCl aq. and dried over $MgSO_4$. Purification by column chromatography and/or MPLC on silica gel gave cyclized products.

1,1-Difluoro-4-heptyl-2-(methoxy)methoxycyclopentane (12a). ^{1}H-NMR δ: 0.86 - 0.92 (3H, m, CH_3), 1.25 - 1.43 (12H, m, CH_2×6), 1.58 - 2.00 (3H, m, CH_2 and CH), 2.19 - 2.41 (2H, m, CH_2), 3.39 (3H, bs, OCH_3), 3.95 - 4.10 (1H, m, CH-O), 4.67 and 4.76 (2H, AB, *J*=6.6 Hz, O-CH_2-O). ^{19}F-NMR δ: -35.11 (1F, d, *J*=232.3 Hz, for major isomer), -36.62 (1F, d, *J*=232.4 Hz, for minor isomer), -45.64 (1F, d, *J*=232.4 Hz, for minor isomer), -50.86 (1F, d, , *J*=232.3 Hz, for major isomer). IR (neat):

2959, 2928, 2856, 1731, 1466 cm^{-1}. EI-MS *m/z*: 200 (M^+-MOM-F). CI-MS *m/z*: 265 (M^++1). *Anal.* Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91. Found: C, 63.40; H, 9.98.

1,1-Difluoro-2-(methoxy)methoxy-4-(phenylmethyl)cyclopentane (12b). Reaction of **5b** (94.8 mg) gave **12b** as a mixture of stereoisomers (58.4 mg, 91% yield, 1.9 : 1 by ^{19}F-NMR). ^{1}H-NMR δ: 1.33 - 2.00 and 2.17 - 2.35 (4H, m, CH_2×2), 2.63 - 2.73 (3H, m, CH_2-Ph and CH), 3.38 and 3.40 (3H, each s, CH_3-O), 4.01 - 4.17 (1H, m, CH-O), 4.66 and 4.76 (2H, AB, *J*=6.8 Hz, O-CH_2-O for major isomer), 4.68 and 4.77 (2H, AB, *J*=6.8 Hz, O-CH_2-O for minor isomer), 7.15 - 7.34 (5H, m, aromatic). ^{19}F-NMR δ: -37.36 (1F, d, *J*=234.3 Hz, for major isomer), -39.35 (1F, d, *J*=233.3 Hz, for minor isomer), -48.68 (1F, d, *J*=233.3 Hz, for minor isomer), -53.45 (1F, d, *J*=234.3 Hz, for major isomer). IR (neat): 3087, 3064, 3029, 2936, 2855, 2827, 1729, 1604, 1497, 1454 cm^{-1}. EI-MS *m/z*: 256 (M^+), 224, 211, 193, 91. High-resolution MS *m/z*: Calcd for $C_{14}H_{18}F_2O_2$: 256.1273. Found: 256.1247.

4-[2-(Benzoyloxy)]ethyl-1,1-difluoro-2-(methoxy)methoxycyclopentane (12c). Reaction of **5c** (98.3 mg) gave **12c** as a mixture of stereoisomers (60.9 mg, 84% yield, 1.4 : 1 by ^{19}F-NMR). ^{1}H-NMR δ: 1.49 - 2.54 (7H, m, CH_2×3 and CH), 3.37 and 3.38 (3H, each s, CH_3-O), 4.00 - 4.13 (1H, m, CH-O), 4.33 (2H, *J*=6.5 Hz, CH_2-O for major isomer), 4.33 (2H, *J*=6.3 Hz, CH_2-O for minor isomer), 4.66 and 4.76 (2H, AB, *J*=6.6 Hz, O-CH_2-O for major isomer), 4.67 and 4.76 (2H, AB, *J*=6.7 Hz, O-CH_2-O for minor isomer), 7.43 - 7.59 and 8.02 - 8.04 (5H, m, aromatic). ^{19}F-NMR δ: -34.47 (1F, d, *J*=235.4 Hz, for major isomer), -37.13 (1F, d, *J*=233.8 Hz, for minor isomer), -46.13 (1F, d, *J*=233.8 Hz, for minor isomer), -51.15 (1F, d, *J*=235.4 Hz, for major isomer). IR (neat): 3064, 2956, 2900, 2827, 1720, 1603, 1583, 1453 cm^{-1}. EI-MS *m/z*: 314 (M^+), 283, 105. High-resolution MS *m/z*: Calcd for $C_{16}H_{20}F_2O_4$: 314.1330. Found: 314.1320.

2-(*tert*-Butyldimethylsilyl)oxy-1,1-Difluoro-4-benzylcyclopentane (12d). Reaction of **5d** (63.2 mg) gave **12d** as a single stereoisomer (27.9 mg, 60% yield). ^{1}H-NMR δ: 0.07 and 0.08 (6H, each s, CH_3-Si×2), 0.88 (9H, s, *t*-Bu), 1.35 - 1.68 (6H, m, CH_2×3), 1.78 - 1.88 (1H, m, CH), 2.21 - 2.39 (2H, m, CH_2), 2.60 (2H, t, *J*=7.6 Hz, CH_2Ph), 3.99 - 4.05 (1H, m, CH-OSi), 7.15 - 7.31 (5H, m, aromatic). ^{19}F-NMR δ: -35.83 (1F, d, *J*=229.4 Hz), -51.40 (1F, d, *J*=229.4 Hz). IR (neat): 3086, 3064, 3028, 2931, 2858, 1730, 1604 cm^{-1}. EI-MS *m/z*: 297 (M^+-*t*-Bu), 277, 205, 183, 143. CI-MS *m/z*: 355 (M^++1). *Anal.* Calcd for $C_{20}H_{32}F_2OSi$: C, 67.75; H, 9.10. Found: C, 67.88; H, 9.10.

1,1-Difluoro-2-(methoxy)methoxy-5-benzylcyclohexane (13e). Reaction of **7e** (114.3 mg) gave **13e** as a single stereoisomer (41.6 mg, 53% yield). ^{1}H-NMR δ: 1.33 - 1.97 (7H, m, CH_2×3 and CH), 2,58 (2H, m, CH_2Ph), 3.39 (3H, s, CH_3-O), 3.82 (1H, bs, CH-O), 4.68 (1H, d, *J*=6.7 Hz, O-CH-O), 4.73 (1H, d, *J*=6.7 Hz, O-CH-O), 7.13 - 7.31 (5H, m, aromatic). ^{19}F-NMR δ: -40.06 (1F, d, *J*=247.5 Hz), -41.89 (1F, dd, *J*=247.5, 33.9 Hz). IR (neat): 3028, 2931, 2857, 1496, 1455 cm^{-1}. EI-MS *m/z*: 270 (M^+), 238, 225, 207. High-resolution MS *m/z*: Calcd for $C_{15}H_{20}F_2O_2$: 270.1429. Found: 270.1421.

1,1-Difluoro-5-(carbethoxy)methyl-2-(methoxy)methoxycyclohexane (13f). Reaction of **7f** (80.1 mg) gave stereoisomers of **13f** (30.3 mg, 56% yield and 12.8 mg, 23% yield). Major stereoisomer: ^{1}H-NMR δ: 1.26 (3H, t, *J*=7.1 Hz, CH_3), 1.32 - 2.28 (9H, m, CH_2×4 and CH), 3.38 (3H, s, CH_3-O), 3.83 (1H, br, CH-O), 4.14 (2H, q, *J*=7.1 Hz, CH_2-OCO), 4.67 (1H, d, *J*=6.7 Hz, O-CH-O), 4.72 (1H, d, *J*=6.7 Hz, O-CH-O). ^{19}F-NMR δ: -40. 41 (1F, d, *J*=247.0 Hz), -42.22 (1F, dd, *J*=247.0 and 35.0 Hz). IR (neat): 2938, 1735 cm^{-1}. EI-MS *m/z*: 265 (M^+-1), 221, 191. CI-MS *m/z*: 267 (M^++1). High-resolution MS *m/z*: Calcd for $C_{12}H_{19}F_2O_4$ (M^+-1): 265.1251. Found: 265.1254. Minor stereoisomer: ^{1}H-NMR δ: 1.09 - 2.28 (7H, m, CH_2×3 and CH), 1.26 (3H, t, *J*=7.1 Hz, CH_3), 2.26 (2H, d, *J*=6.3 Hz, CH_2COO), 3.41 (3H, s, CH_3-O), 3.69 (1H, dddd, *J*=19.8, 11.5, 4.6, 4.5 Hz, CH-O), 4.14 (2H, q, *J*=7.1 Hz, CH_2-OCO), 4.72 (1H, d, *J*=6.8 Hz, O-CH-O), 4.78 (1H, d, *J*=6.8 Hz, O-CH-O). ^{19}F-NMR δ: -40.23 (1F, d, *J*=240.3 Hz), -55.14 (1F, d, *J*=240.3 Hz). IR (neat): 2943, 1734 cm^{-1}. EI-MS *m/z*: 266 (M^+), 265, 221. CI-MS *m/z*: 267 (M^++1). High-resolution MS *m/z*: Calcd for $C_{12}H_{20}F_2O_4$: 266.1330. Found: 266.1315.

1,1-Difluoro-5-(2-benzyloxy)ethyl-2-(methoxy)methoxycyclohexane (13g). Reaction of **7g** (79.1 mg) gave stereoisomers of **13g** (23.5 mg, 41% yield and 12.9 mg, 23% yield) and uncyclized reduction product (6.5 mg, 12% yield). Major stereoisomer: ^{1}H-NMR δ: 1.26 - 2.00 (9H, m, CH_2×4 and CH), 3.38 (3H, s, CH_3-O), 3.51 (2H, t, *J*=6.6 Hz, CH_2-O), 3.82 (1H, br, CH-O), 4.50 (2H, s, Ph-CH_2-O), 4.67 (1H, d, *J*=6.7 Hz, O-CH-O), 4.73 (1H, d, *J*=6.7 Hz, O-CH-O), 7.27 - 7.37 (5H, m, aromatic). ^{19}F-NMR δ: -39.94 (1F, d, *J*=250.6 Hz), -41.93 (1F, dd, *J*=250.6, 34.9 Hz). IR (neat): 3065, 3032, 2932, 2860, 1497, 1455 cm^{-1}. EI-MS *m/z*: 314 (M^+), 282, 269. High-resolution MS *m/z*: Calcd for $C_{17}H_{24}F_2O_3$: 314.1694. Found: 314.1666. Minor stereoisomer: ^{1}H-NMR δ: 1.00 - 2.27 (9H, m, CH_2×4 and CH), 3.41 (3H, s, CH_3-O), 3.49 (2H, t, *J*=6.4 Hz, CH_2-O), 3.68 (1H, m, CH-O), 4.49 (2H, s, Ph-CH_2-O), 4.73 (1H, d, *J*=6.8 Hz, O-CH-O), 4.78 (1H, d, *J*=6.8 Hz, O-CH-O), 7.27 - 7.37 (5H, m, aromatic). ^{19}F-NMR δ: -40.01 (1F, d, *J*=235.6 Hz), -55.41 (1F, d, *J*=235.6 Hz). IR (neat): 3066, 3032, 2931, 1497, 1455 cm^{-1}. EI-MS *m/z*: 314 (M^+), 282, 252. High-resolution MS *m/z*: Calcd for $C_{17}H_{24}F_2O_3$: 314.1694 Found: 314.1687.

5-(2-Benzyloxy)ethyl-1-(methoxy)methoxycyclohexane (15g). Reaction of **14g** (119.7 mg) gave stereoisomers of **15g** (27.8 mg, 34% yield and 23.4 mg, 28% yield) and uncyclized reduction product (16.9 mg, 21% yield). Major stereoisomer: ^{1}H-NMR δ: 0.89 - 1.83 (11H, m, CH_2×5 and CH), 3.37 (3H, s, CH_3-O), 3.51 (2H, t, *J*=6.5 Hz, CH_2-O), 3.78 (1H, m, CH-O), 4.50 (2H, s, Ph-CH_2-O), 4.66 (2H, s, O-CH_2-O), 7.26 - 7.37 (5H, m, aromatic). IR (neat): 3064, 3030, 2927, 2855, 1496, 1453 cm^{-1}. EI-MS *m/z*: 246 (M^+-CH_3OH), 233. *Anal.* Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.21; H, 9.38. Minor stereoisomer. ^{1}H-NMR δ: 0.89 - 2.03 (11H, m, CH_2×5 and CH), 3.36 (3H, s, CH_3-O), 3.41 - 3.50 (1H, m, CH-O), 3.49 (2H, t, *J*=6.6 Hz, CH_2-O), 4.49 (2H, s, Ph-CH_2-O), 4.68 (2H, s, O-CH_2-O), 7.24 - 7.38 (5H, m, aromatic). IR (neat): 3064, 3030, 2929, 2857, 1496, 1452 cm^{-1}. EI-MS *m/z*: 278 (M^+), 246, 233. *Anal.* Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 72.96; H, 9.37.

3,3-Difluoro-2-phenyl-5-benzyltetrahydropyran (16a). Reaction of **9a** (120.9 mg) gave *trans*-**16a** (48.5 mg, 58% yield), a mixture of *cis*- and *trans*-**16a** (20.1 mg, 24% yield, 7.5 : 1 by ^{1}H-NMR) and uncyclized reduction product (9 mg, 11% yield). *Trans*-**16a**: mp 66°C (recrystallized from hexane). ^{1}H-NMR δ: 1.70 (1H, dddd, *J*=33.5, 13.0, 13.0, 4.7 Hz, CH), 2.29 - 2.38 (1H, m, CH), 2.42 - 2.55 (1H, m, CH), 2.54 (1H, dd, *J*=13.2, 7.3 Hz, CH-Ph), 2.65 (1H, dd, *J*=13.2, 6.6 Hz, CH-Ph), 3.35 (1H, dd, *J*=11.0, 11.0 Hz, CH-O), 4.12 (1H, m, CH-O), 4.38 (1H, d, *J*=23.3 Hz, Ph-CH-O), 7.16 - 7.43 (10H, m, aromatic). ^{19}F-NMR δ: -40.17 (1F, d, *J*=246.4 Hz), -53.24 (1F, dddd, *J*=246.4, 33.5, 23.3, 10.5 Hz). IR (neat): 3064, 3030, 2957, 2927, 1605, 1496, 1455 cm^{-1}. EI-MS *m/z*: 288 (M^+), 268. *Anal.* Calcd for $C_{18}H_{18}F_2O$: C, 74.98; H, 6.29. Found: C, 74.96; H, 6.28. *Cis*-**16a**: mp 91°C (recrystallized from hexane). ^{1}H-NMR δ: 2.05 - 2.30 (3H, m, CH_2 and CH), 2.92 - 3.04 (2H, m, CH_2-Ph), 3.73 (1H, dd, *J*=12.0, 2.7 Hz, CH-O), 4.00 (1H, d, *J*=12.0 Hz, CH-O), 4.48 (1H, d, *J*=23.0 Hz, Ph-CH-O), 7.16 - 7.50 (5H, m, aromatic). ^{19}F-NMR δ: -35.34 (1F, d, *J*=249.0 Hz), -44.68 (1F, dddd, *J*=249.0, 34.5, 23.0, 12.0 Hz). IR (neat): 3064, 3030, 2960, 2929, 2858, 1604, 1497, 1455 cm^{-1}. EI-MS *m/z*: 288 (M^+), 268. *Anal.* Calcd for $C_{18}H_{18}F_2O$: C, 74.98; H, 6.29. Found: C, 74.89; H, 6.32.

3,3-Difluoro-2-phenyl-5-*iso*-propyltetrahydropyran (16b). Reaction of **9b** (111.5 mg) gave *trans*-**16b** (28.9 mg, 40% yield), *cis*-**16b** (14.7 mg, 20% yield) and uncyclized reduction product (12.8 mg, 18% yield). *Trans*-**16b**: ^{1}H-NMR δ: 0.96 (3H, d, *J*=6.8 Hz, CH_3), 0.97 (3H, d, *J*=6.8 Hz, CH_3), 1.55 (1H, m, CH), 1.70 (1H, dddd, *J*=33.7, 13.1, 13.1, 5.1 Hz, CH), 1.95 (1H, m, CH), 2.40 (1H, m, CH), 3.35 (1H, dd, *J*=11.4, 11.4 Hz, CH-O), 4.21 (1H, d, *J*=11,4 Hz, CH-O), 4.35 (1H, d, *J*=23.4 Hz, Ph-CH-O), 7.32 - 7.44 (5H, m, aromatic). ^{19}F-NMR δ: -39.58 (1F, dd, *J*=245.0, 3.3 Hz), -52.85 (1F, dddd, *J*=245.0, 33.7, 23.4, 11.0 Hz). IR (neat): 3067, 3036, 2964, 2932, 2874, 1499, 1455 cm^{-1}. EI-MS *m/z*: 240 (M^+), 197, 119. High-resolution MS *m/z*: Calcd for $C_{14}H_{18}F_2O$: 240.1326. Found: 240.1296. *Cis*-**16b**: ^{1}H-NMR δ: 1.00 (3H, d, *J*=6.6 Hz, CH_3), 1.01 (3H, d, *J*=6.6 Hz, CH_3), 2.00 - 2.17 (3H, m, CH_2 and CH), 2.44 (1H, m, CH), 3.67 (1H, dd, *J*=12.0, 3.1 Hz, CH-O), 4.12 (1H, ddd, *J*=12.0, 5.0, 2.5 Hz,

CH-O), 4.51 (1H, dd, *J*=20.8, 3.3 Hz, Ph-CH-O), 7.31 - 7.45 (5H, m, aromatic). ^{19}F-NMR δ: -34.90 (1F, d, *J*=247.0 Hz), -46.15 (1F, dddd, *J*=247.0, 32.0, 20.8, 10.7 Hz). IR (neat): 3035, 2966, 2932, 2872, 1498, 1455, 1440 cm^{-1}. EI-MS *m/z*: 240 (M^+), 197, 119. High-resolution MS *m/z*: Calcd for $C_{14}H_{18}F_2O$: 240.1326. Found: 240.1303.

5-(2-Benzyloxyethyl)-3,3-difluoro-2-phenyltetrahydropyran (16c). Reaction {[Bu_3SnH] = 0.02 mol dm^{-3}} of **9c** (134.8 mg) gave *trans*-**16c** (30.8 mg, 31% yield), *cis*-**16c** (14.8 mg, 15% yield) and uncyclized reduction product (31 mg, 32% yield). Reaction {[Bu_3SnH] = 0.002 mol dm^{-3}} of **9c** (68.2 mg) gave *trans*-**16c** (22.2 mg, 45% yield) and *cis*-**16c** (9.1 mg, 18% yield). *Trans*-**16c**: ^{1}H-NMR δ: 1.50 - 1.76 (3H, m, CH_2 and CH), 2.32 - 2.45 (2H, m, CH_2), 3.30 (1H, dd, *J*=11.3, 11.3 Hz, CH), 3.50 - 3.58 (2H, m, CH_2-O), 4.18 (1H, m, CH-O), 4.37 (1H, d, *J*=23.3 Hz, CH-Ph), 4.52 (2H, d, *J*=0.96 Hz, Ph-CH_2-O), 7.27 - 7.44 (10H, m, aromatic). ^{19}F-NMR δ: -40.05 (1F, d, *J*=246.0 Hz), -53.40 (1F, dddd, *J*=246.0, 33.5, 23.3, 10.6 Hz). IR (neat): 3065, 3033, 2928, 2858, 1606, 1548, 1497, 1455 cm^{-1}. EI-MS *m/z*: 332 (M^+), 221. High-resolution MS *m/z*: Calcd for $C_{20}H_{22}F_2O_2$: 332.1588. Found: 332.1590. *Cis*-**16c**: ^{1}H-NMR δ: 1.89 - 2.34 (5H, m, CH_2×2 and CH), 3.60 (2H, t, *J*=6.0 Hz, CH_2-O), 3.74 (1H, dd, *J*=11.9, 2.5 Hz, CH-O), 4.00 (1H, dq, *J*=11.9, 2.5 Hz, CH-O), 4.45 (1H, d, *J*=23.0 Hz, CH-Ph), 4.52 (2H, s, CH_2-Ph), 7.27 - 7.44 (10H, m, aromatic). ^{19}F-NMR δ: -35.49 (1F, d, *J*=247.0 Hz), -45.91 (1F, dddd, *J*=247.0, 34.2, 23.0, 11.0 Hz). IR (neat): 3065, 3033, 2958, 2927, 1606, 1587, 1497, 1455 cm^{-1}. MS *m/z*: 332 (M^+), 241, 221. High-resolution MS *m/z*: Calcd for $C_{20}H_{22}F_2O_2$: 332.1588. Found: 332.1592.

3,3-Difluoro-2-phenyl-5-methyltetrahydropyran (16d). Reaction of **9d** (51.1 mg) gave *trans*-**16d** (8.5 mg, 27% yield) and *cis*-**16d** (3 mg, 9% yield) and uncyclized reduction product (1 mg, 3% yield). *Trans*-**16d**: ^{1}H-NMR δ: 0.96 (3H, d, *J*=6.6 Hz, CH_3), 1.65 (1H, dddd, *J*=34.0, 12.9, 12.9, 4.8 Hz, CH), 2.21 - 2.41 (2H, m, CH×2), 3.23 (1H, dd, *J*=11.3, 11.3 Hz, CH-O), 4.08 (1H, m, CH-O), 4.37 (1H, d, *J*=23.4 Hz, Ph-CH-O), 7.32 - 7.45 (5H, m, aromatic). ^{19}F-NMR δ: -40.33 (1F, d, *J*=246.4 Hz), -53.59 (1F, dddd, *J*=246.4, 34.0, 23.4, 10.7 Hz). IR (neat): 3066, 3036, 2959, 2934, 2879, 2855, 1498, 1456 cm^{-1}. EI-MS *m/z*: 212 (M^+), 192, 105. *Cis*-**16d**: ^{1}H-NMR δ: 1.26 (3H, dd, *J*=7.2, 2.4 Hz, CH_3), 2.13 - 2.27 (3H, m, CH_2 and CH), 3.77 (1H, dd, *J*=11.6, 2.6 Hz, CH-O), 3.87 (1H, dq, *J*=11.6, 2.4 Hz, CH-O), 4.45 (1H, dd, *J*=20.5, 1.9 Hz, Ph-CH-O), 7.32 - 7.47 (5H, m, aromatic). ^{19}F-NMR δ: -34.75 (d, *J*=247.3 Hz), -44.57 (d, *J*=247.3 Hz). IR (neat): 3067, 3035, 2965, 2933, 2858, 1499, 1456 cm^{-1}. EI-MS *m/z*: 212 (M^+), 192, 157.

2-*tert*-Butyl-3,3-difluoro-5-benzyltetrahydropyran (16e). Reaction of **9e** (117.2 mg) gave *trans*-**16e** (22.9 mg, 29% yield), *cis*-**16e** (13 mg, 16% yield) and a mixture of *trans*- and *cis*-**16e** (25.7 mg, 33% yield, 11.4 : 1 by ^{1}H-NMR) *Trans*-**16e**: ^{1}H-NMR δ: 1.03 (9H, s, *t*-Bu), 1.49 (1H, dddd, *J*=33.4, 13.1, 13.1, 5.6 Hz, CH), 2.15 (1H, m, CH), 2.29 (1H, m, CH), 2.46 (1H, dd, *J*=13.6, 7.2 Hz, CH-Ph), 2.53 (1H, dd, *J*=13.6, 7.4 Hz, CH-Ph), 2.94 (1H, d, *J*=27.1 Hz, CH-O), 3.09 (1H, dd, *J*=11.3, 11.2 Hz, CH-O), 3.96 (1H, dddd, *J*=11.2, 3.6, 3.6 Hz, CH-O), 7.11 - 7.31 (5H, m, aromatic). ^{19}F-NMR δ: -34.38 (1F, d, *J*=242.0 Hz), -51.74 (1F, dddd, *J*=242.0, 33.4, 27.1, 12.2 Hz). IR (neat): 3029, 2960, 2926, 1605, 1497, 1483, 1456 cm^{-1}. EI-MS *m/z*: 268 (M^+), 212, 192, 177. High-resolution MS *m/z*: Calcd for $C_{16}H_{22}F_2O$: 268.1639. Found: 268.1664. *Cis*-**16e**: ^{1}H-NMR δ: 1.10 (9H, s, *t*-Bu), 1.91 (1H, dddd, *J*=33.2, 14.6, 8.6, 5.7 Hz, CH), 2.03 - 2.13 (2H, m, CH×2), 2.79 - 2.91 (2H, m, CH_2-Ph), 3.02 (1H, dd, *J*=27.8, 1.4 Hz, CH-O), 3.50 (1H, dd, *J*=11.6, 2.9 Hz, CH-O), 3.86 (1H, dd, *J*=11.6, 2.0 Hz, CH-O), 7.19 - 7.32 (5H, m, aromatic). ^{19}F-NMR δ: -28.77 (1F, d, *J*=243.1 Hz), -44.21 (1F, ddd, *J*=243.1, 33.2, 27.8 Hz). IR (neat): 3028, 2960, 2915, 1497, 1484, 1456 cm^{-1}. EI-MS *m/z*: 268 (M^+), 212, 192, 177. High-resolution MS *m/z*: Calcd for $C_{16}H_{22}F_2O$: 268.1639. Found: 268.1662.

2-*tert*-Butyl-3,3-difluoro-5-(*tert*-butyldiphenylsilyl)methyltetrahydropyran (16f). Reaction of **9f** (69.2 mg) gave *trans*-**16f** (23.4 mg, 43% yield) and uncyclized reduction product (1.3 mg, 2% yield). *Trans*-**16f**: mp 123 - 123.5°C (recrystallized from hexane). ^{1}H-NMR δ: 0.88 - 1.07 (2H, m, CH_2-

Si), 0.95 and 1.02 (18H, each s, *t*-Bu×2), 1.26 (1H, dddd, *J*=33.5, 13.5, 13.5, 5.6 Hz, CH), 1.76 - 1.85 (1H, m, CH), 2.06 - 2.09 (1H, m, CH), 2.82 (1H, d, *J*=27.0 Hz, CH-O), 2.90 (1H, dd, *J*=11.1, 11.1 Hz, CH-O), 3.72 (1H, m, CH-O), 7.35 - 7.44 and 7.59 - 7.62 (10H, m, aromatic). ^{19}F-NMR δ: -34.39 (1F, d, *J*=240.7 Hz), -52.52 (1F, dddd, *J*=240.7, 33.5, 27.0, 12.3 Hz). IR (neat): 3072, 3051, 2960, 2859, 1483, 1471, 1428 cm^{-1}. EI-MS *m/z*: 373 (M^+-*t*-Bu), 201. *Anal.* Calcd for $C_{26}H_{36}F_2OSi$: C, 72.51; H, 8.43. Found: C, 72.53; H, 8.46.

3,3-Difluoro-4-(2-phenylethyl)-5-*iso*-propyltetrahydropyran (17g). Reaction of **11g** (126.6 mg) gave *trans*-**17g** (28.1 mg, 35% yield), *cis*-**17g** (24.2 mg, 28% yield) and uncyclized reduction product (16.2 mg, 19% yield). *Trans*-**17g**: ^{1}H-NMR δ: 0.75 (3H, d, *J*=7.0 Hz, CH_3), 0.99 (3H, d, *J*=7.0 Hz, CH_3), 1.71 - 2.05 (5H, m, CH_2 and CH×3), 2.71 - 2.86 (2H, m, CH_2-Ph), 3.27 (1H, dd, *J*=11.0, 11.0 Hz, CH-O), 3.38 (1H, dd, *J*=29.0, 11.0 Hz, CH-O), 3.85 - 3.95 (2H, m, CH-O), 7.17 - 7.31 (5H, m, aromatic). ^{19}F-NMR δ: -44.08 (1F, d, *J*=248.0 Hz), -52.07 (1F, dddd, *J*=248.0, 29.0, 24.3, 11.0 Hz). IR (neat): 3063, 3028, 2964, 2875, 1604, 1497, 1461 cm^{-1}. EI-MS *m/z*: 268 (M^+). High-resolution MS *m/z*: Calcd for $C_{16}H_{22}F_2O$: 268.1639. Found: 268.1658. *Cis*-**17g**: ^{1}H-NMR δ: 0.84 (3H, d, *J*=6.5 Hz, CH_3), 0.94 (3H, d, *J*=6.5 Hz, CH_3), 1.50 - 1.79 (4H, m, CH_2 and CH×2), 2.28 - 2.32 (1H, m, CH), 2.64 (1H, ddd, *J*=14.0, 8.0, 8.0 Hz, CH-Ph), 2.89 (1H, ddd, *J*=14.0, 6.7, 6.7 Hz, CH-Ph), 3.22 (1H, dd, *J*=11.4, 11.4 Hz, CH-O), 3.67 (1H, dd, *J*=29.9, 12.3 Hz, CH-O), 3.75 (1H, dd, *J*=12.3, 11.7, Hz, CH-O), 3.81 (1H, ddd, *J*=11.4, 3.3, 3.3 Hz, CH-O), 7.18 - 7.32 (5H, m, aromatic). ^{19}F-NMR δ: -37.70 (1F, dddd, *J*=248.0, 29.9, 11.7, 11.7 Hz), -49.19 (1F, dd, *J*=248.0, 3.4 Hz). IR (neat): 3064, 3028, 2965, 2873, 1605, 1497, 1456 cm^{-1}. EI-MS *m/z*: 268 (M^+), 205. High-resolution MS *m/z*: Calcd for $C_{16}H_{22}F_2O$: 268.1639. Found: 268.1651.

3,3-Difluoro-4-(2-phenylethyl)-5-benzyltetrahydropyran (17h). Reaction of **11h** (131.2 mg) gave **17h** as a mixture of stereoisomers (69.2 mg, 74% yield, *ca.* 1 : 1 by ^{1}H-NMR). ^{1}H-NMR δ: 1.72 - 2.31 (4H, m, CH_2 and CH×2), 2.69 - 3.01 (4H, m, CH_2-Ph×2), 3.15 (1H, dd, *J*=10.2, 10.0 Hz, CH-O for one isomer), 3.25 (1H, dd, *J*=11.8, 1.8 Hz, CH-O for another isomer), 3.38 - 3.49 (1H, m, CH-O), 3.69 - 3.74 (1H, m, CH-O), 3.87 (1H, ddd, *J*=11.9, 10.4, 6.1 Hz, CH-O for one isomer), 3.96 (1H, ddd, *J*=11.9, 11.9, 3.7 Hz, CH-O for another isomer), 7.09 - 7.34 (10H, m, aromatic). ^{19}F-NMR δ: -43.6 (1F, d, *J*=251.6 Hz, for one isomer), -43.9 (1F, d, *J*=247.6 Hz, for another isomer), -47.3 (1F, dddd, *J*=247.6, 27.7, 27.7, 11.9 Hz, for another isomer), -51.8 (1F, dddd, *J*=251.6, 24.4, 24.4, 10.4 Hz, for one isomer). IR (neat): 3027, 2924, 2859, 1603, 1496, 1455 cm^{-1}. EI-MS *m/z*: 316 (M^+), 212, 91. *Anal.* Calcd for $C_{20}H_{22}F_2O$: C, 75.92; H, 7.01. Found: C, 75.90; H, 7.00.

5-(2-Benzyloxyethyl)-3,3-difluoro-4-(phenylethyl)tetrahydropyran (17i). Reaction of **11i** (71.8 mg) gave *trans*-**17i** (20.1 mg, 37% yield), *cis*-**17i** (15.1 mg, 28% yield) and uncyclized reduction product (9.3 mg, 17% yield). *Trans*-**17i**: ^{1}H-NMR δ: 1.40 (1H, m, CH), 1.63 - 2.08 (5H, m, CH_2 and CH×3), 2.71 (1H, ddd, *J*=13.8, 10.3, 6.4 Hz, CH-Ph), 2.84 (1H, ddd, *J*=13.8, 10.7, 5.5 Hz, CH-Ph), 3.17 (1H, dd, *J*=10.5, 10.5 Hz, CH-O), 3.40 (1H, ddd, *J*=28.0, 12.1, 1.2 Hz, CH-O), 3.43 (2H, t, *J*=6.3 Hz, CH_2-O), 3.88 (1H, ddd, *J*=12.1, 11.1, 5.2 Hz, CH-O), 3.97 (1H, dt, *J*=10.5, 3.3 Hz, CH-O), 4.45 and 4.48 (2H, AB, *J*=12.0 Hz, Ph-CH_2-O), 7.18 - 7.37 (10H, m, aromatic). ^{19}F-NMR δ: -43.89 (1F, d, *J*=250.0 Hz), -52.55 (1F, dddd, *J*=250.0, 28.0, 25.5, 11.1 Hz). IR (neat): 3087, 3063, 3029, 2922, 2861, 1604, 1497, 1455 cm^{-1}. EI-MS *m/z*: 360 (M^+), 269. High-resolution MS *m/z*: Calcd for $C_{22}H_{26}F_2O_2$: 360.1901. Found: 360.1910. *Cis*-**17i**: ^{1}H-NMR δ: 1.73 - 1.82 (3H, m, CH_2 and CH), 1.97 - 2.13 (3H, m, CH_2 and CH), 2.60 - 2.79 (2H, m, CH_2-Ph), 3.38 (1H, ddd, *J*=11.6, 3.0, 3.0 Hz, CH-O), 3.43 - 3.57 (3H, m, CH_2-O and CH-O), 3.85 (1H, d, *J*=11.6 Hz, CH-O), 3.87 (1H, ddd, *J*=11.8, 11.8, 5.2 Hz, CH-O), 4.48 and 4.53 (2H, AB, *J*=12.0 Hz, Ph-CH_2-O), 7.17 - 7.36 (10H, m, aromatic). ^{19}F-NMR δ: -43.92 (1F, d, *J*=247.0 Hz), -48.55 (1F, dddd, *J*=247.0. 26.0. 26.0, 11.8 Hz). IR (neat): 3028, 2954, 2858, 1604, 1497, 1455 cm^{-1}. EI-MS *m/z*: 360 (M^+), 269. High-resolution MS *m/z*: Calcd for $C_{22}H_{26}F_2O_2$: 360.1901. Found: 360.1915.

3,3-Difluoro-4-metyl-5-benzyltetrahydropyran (17j). Reaction of **11j** (101.5 mg) gave *trans*-**17j** (16.3 mg, 24% yield), *cis*-**17j** (25 mg, 37% yield) and uncyclized reduction product (0.5 mg, 7% yield). *Trans*-**17j**: ^{1}H-NMR δ: 1.23 (3H, d, J=6.7 Hz, CH_3), 1.79 (1H, ddqd, J=26.2, 10.9, 6.7, 5.8 Hz, CH), 2.00 (1H, m, CH), 2.27 (1H, dd, J=14.0, 10.0 Hz, CH-Ph), 2.98 (1H, dd, J=14.0, 4.0 Hz, CH-Ph), 3.1 (1H, dd, J=11.7, 11.5 Hz, CH-O), 3.38 (1H, dd, J=30.2, 12.1 Hz, CH-O), 3.74 (1H, ddd, J=11.7, 3.3, 3.3 Hz, CH-O), 3.91 (1H, ddd, J=12.1, 11.4, 1.9 Hz, CH-O), 7.12 - 7.31 (5H, m, aromatic). ^{19}F-NMR δ: -49.11 (d, J=247.4 Hz), -56.44 Hz (1F, dddd, J=247.4, 30.2, 26.2, 11.4 Hz). IR (neat): 3064, 3028, 2980, 2946, 2920, 2860, 1605, 1497, 1456 cm^{-1}. EI-MS *m/z*: 226 (M^+), 117, 92. *Anal.* Calcd for $C_{13}H_{16}F_2O$: C, 69.00; H, 7.13. Found: C, 68.91; H, 7.15. *Cis*-**17j**: ^{1}H-NMR δ: 1.16 (3H, d, J=7.0 Hz, CH_3), 2.20 - 2.34 (2H, m, CH×2), 2.58 - 2.68 (2H, m, CH_2-Ph), 3.44 (1H, d, J=11.8 Hz, CH-O), 3.53 - 3.62 (2H, m, CH-O×2), 3.79 (1H, ddd, J=16.9, 12.3, 6.0 Hz, CH-O), 7.16 - 7.32 (5H, m, aromatic). ^{19}F-NMR δ: -43.28 (1F, d, J=246.6 Hz), -49.48 (1F, J=246.6, 15.6, 15.6, 5.5 Hz). IR (neat): 3086, 3064, 3028, 2978, 2922, 1604, 1497, 1456 cm^{-1}. EI-MS *m/z*: 226 (M^+), 117, 91. *Anal.* Calcd for $C_{13}H_{16}F_2O$: C, 69.00; H, 7.13. Found: C, 68.87; H, 7.15.

5-(tert-Butyldiphenylsilyl)methyl-3,3-difluoro-4-methyltetrahydropyran (17k). Reaction of **11k** (63 mg) gave *trans*-**17k** (30.5 mg, 64% yield), *cis*-**17k** (2.7 mg, 5.7% yield) and uncyclized reduction product (4.8 mg, 10% yield). *Trans*-**17k**: ^{1}H-NMR δ: 0.73 (1H, dd, J=15.3, 11.1 Hz, CH-Si), 1.03 (9H, s, *t*-Bu), 1.14 (3H, d, J=6.6 Hz, CH_3), 1.51 (1H, dd, J=15.3, 2.5 Hz, CH-Si), 1.64 (1H, m, CH), 1.74 - 1.82 (1H, m, CH), 2.73 (1H, dd, J=12.0, 12.0 Hz, CH-O), 3.26 (1H, dd, J=30.5, 12.0 Hz, CH-O), 3.36 (1H, ddd, J=12.0, 3.4, 3.4 Hz, CH-O), 3.78 (1H, dd, J=12.0, 11.5 Hz, CH-O), 7.34 - 7.66 (10H, m, aromatic). ^{19}F-NMR δ: -48.22 (1F, d, J=248.0 Hz), -56.58 (1F, d, J=248.0 Hz). IR (neat): 3016, 2929, 2858, 1589, 1488, 1462 cm^{-1}. EI-MS *m/z*: 331 (M^+-*t*-Bu), 311. High-resolution MS *m/z*: Calcd for $C_{19}H_{21}F_2OSi$ (M^+-*t*-Bu): 331.1330. Found: 331.1338. *Cis*-**17k**: ^{1}H-NMR δ: 1.01 (3H, d, J=7.1 Hz, CH_3), 1.03 (9H, s, *t*-Bu), 1.13 (2H, m, CH_2-Si), 1.97 (1H, m, CH), 2.10 (1H, m, CH), 3.08 (1H, ddd, J=11.9, 3.5, 2.0 Hz, CH-O), 3.18 (1H, ddd, J=11.9, 7.3, 1.7 Hz, CH-O), 3.42 (1H, ddd, J=13.0, 13.0, 7.0 Hz, CH-O), 3.63 (1H, ddd, J=18.9, 13.0, 5.3 Hz, CH-O), 7.34 - 7.64 (10H, m, aromatic). ^{19}F-NMR δ: -42.56 (1F, d, J=248.0 Hz), -48.81 (1F, d, J=248.0 Hz). IR (neat): 3072, 2961, 2930, 2858, 1472, 1428 cm^{-1}. EI-MS *m/z*: 331 (M^+-*t*-Bu). High-resolution MS *m/z*: Calcd for $C_{19}H_{21}F_2OSi$ (M^+-*t*-Bu): 331.1330. Found: 331.1330.

5-(tert-Butyldiphenylsilyl)methyl-3,3-difluoro-4-(2-phenylethyl)tetrahydropyran (17l)]. Reaction of **11l** (90.4 mg) gave *trans*-**17l** (41 mg, 57% yield), *cis*-**17l** (1.8 mg, 2.5% yield) and uncyclized reduction product (0.9 mg, 1% yield). *Trans*-**17l**: ^{1}H-NMR δ: 0.74 (1H, dd, J=15.3, 11.0 Hz, CH-Si), 1.02 (9H, s, *t*-Bu), 1.42 (1H, dd, J=15.3, 2.7 Hz, CH-Si), 1.60 (1H, dddd, J=23.8, 13.7, 7.3, 3.3 Hz, CH), 1.73 - 1.85 (2H, m, CH×2), 2.00 (1H, dddd, J=15.0, 10.0, 7.3, 5.4 Hz, CH), 2.66 (1H, ddd, J=13.7, 10.0, 6.9 Hz, CH-Ph), 2.76 (1H, dd, J=11.5, 10.6 Hz, CH-O), 2.76 - 2.84 (1H, m, CH-Ph), 3.29 (1H, dd, J=27.5, 11.5 Hz, CH-O), 3.41 (1H, ddd, J=11.5, 3.4, 2.7 Hz, CH-O), 3.74 (1H, ddd, J=11.5, 11.5, 4.9 Hz, CH-O), 7.19 - 7.63 (15H, m, aromatic). ^{19}F-NMR δ: -43.61 (1F, d, J=247.0 Hz), -52.12 (1F, d, J=247.0 Hz). IR (neat): 3071, 3026, 2930, 2858, 1604, 1496, 1471, 1456 cm^{-1}. EI-MS *m/z*: 421 (M^+-*t*-Bu), 201. *Anal.* Calcd for $C_{30}H_{36}F_2OSi$: C, 75.27; H, 7.58. Found: C, 75.18; H, 7.56. *Cis*-**17l**: ^{1}H-NMR δ: 1.04 (9H, s, *t*-Bu), 1.10 (2H, d, J=15.4 Hz, CH_2-Si), 1.38 - 1.45 (1H, m, CH), 1.78 - 1.85 (3H, m, CH×3), 2.01 - 2.08 (1H, m, CH), 2.37 - 2.44 and 2.49 - 2.56 (2H, m, CH_2), 2.99 (1H, d, J=11.9 Hz, CH-O), 3.30 (1H, ddd, J=26.6, 12.2, 3.1 Hz, CH-O), 3.44 (1H, d, J=11.6 Hz, CH-O), 3.85 (1H, ddd, J=12.2, 10.8, 6.0 Hz, CH-O), 7.05 - 7.70 (15H, m, aromatic). ^{19}F-NMR δ: -42.64 (1F, d, J=249.4 Hz), -47.38 (1F, d, J=249.4 Hz). IR (neat): 3071, 3027, 2931, 2858, 1604, 1497, 1463 cm^{-1}. EI-MS *m/z*: 421 (M^+-*t*-Bu), 201.

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