Pergamon

Tetrahedron, Vol. 53, No. 28, pp. 9497-9508, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00613-3

Preparation of Methylene-*gem*-difluorocyclopropanes and Its Reactivity as Michael Acceptor

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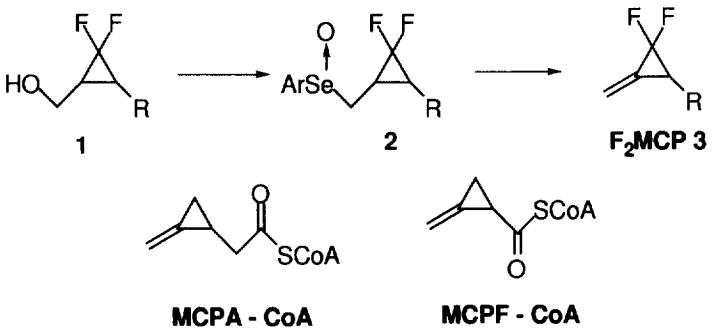
Abstract: Preparation of methylene-*gem*-difluorocyclopropanes **3** was achieved through the selenoxide elimination reaction derived from *gem*-difluorocyclopropylmethanols **1**, while this method can not be applied to non-fluorinated cyclopropylmethanols. The methylene-*gem*-difluorocyclopropane **3** showed a high reactivity as a Michael acceptor in the reaction with thiol or amine. © 1997 Elsevier Science Ltd.

INTRODUCTION

Methylenecyclopropane derivatives (MCPs) are well documented as useful intermediates in synthetic organic chemistry, particularly in thermal or transition-metal catalyzed cycloaddition reaction with unsaturated compounds giving rise to methylenated five-membered compounds.[1,2] In addition, interest in MCPs from biological perspective has emerged.[3] Methylenecyclopropane moiety is found in certain biologically active natural substances such as MCPA-CoA or MCPF-CoA which show highly inhibitory activities against the enzymes, general acyl-CoA dehydrogenase or enoyl-CoA hydratase (crotonase), responsible for β-oxidation pathway of fatty acid metabolism, while the mechanistic aspects of these inhibitory processes still remain unclear.[4,5] It would be expected that introduction of fluorine on the ring of such methylenecyclopropanes brings about little change with respect to the steric size of the molecules, but alters its chemical reactivities due to the strong electron-withdrawing nature of fluorine.[6] For example, due to electron-withdrawing nature of fluorine, exo-methylene moiety in methylene-*gem*-difluorocyclopropane (F_2MCP, **3**) would act as a reactive Michael acceptor or radical acceptor and this would lead to a molecular design of inhibitors of enzyme reactions.

Scheme 1



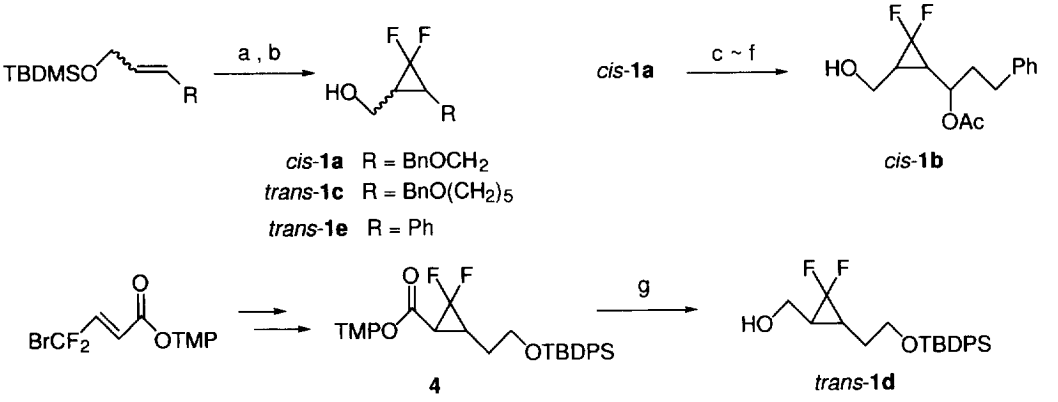
Furthermore, difluoro analog of MCPA-CoA or MCPF-CoA would be interesting as proves for mechanistic study of inhibitory processes related to the parent MCPA-CoA or MCPF-CoA.[7] For these purposes, an efficient method for the preparation of F_2MCP **3** having suitably functionalized substituent is needed.

Difluorocarbene addition to the C-C double bond in allenic compounds or their equivalents were reported in only limited cases such as allene itself [8] or perfluorinated allenic compounds.[9] It was also reported that difluorocarbene addition to the triple bond in propargylic ester provides the difluorocyclopropene derivative, which reacts with hydride reagent or methyl cuprate by S*N*2' mode to give the difluorocyclopropylidene compounds.[10] However, there is no report so far regarding the general methods for the preparation of 2,2-difluoro-3-substituted methylenecyclopropanes **3**.[11] In this paper, we report that F_2MCPs **3** can be prepared through elimination reaction of the selenoxide **2** derived from *gem*-difluorocyclopropylmethanols **1**, while this method cannot be applied to non-fluorinated cyclopropylmethanols due to the facile formation of cyclopropylmethyl cation from the intermediacy selenoxide. Furthermore, methylene-*gem*-difluoro-cyclopropane **3** was found to be a good Michael acceptor in the raction with thiol and amine.

RESULTS AND DISCUSSION

The starting alcohols **1** are easily obtainable by stereospecific *cis*-addition of difluorocarbene[12] to the corresponding *Z*- or *E*-allylic alcohols as shown in the preparation of **1a-1c** and **1e** (Scheme 2). Alternatively, *trans*-**1d** was prepared from the carboxylate **4** obtained by the regio- and stereo-selective synthesis of difluorocyclopropanecarboxylate using bromodifluoro-crotonate.[13]

Scheme 2

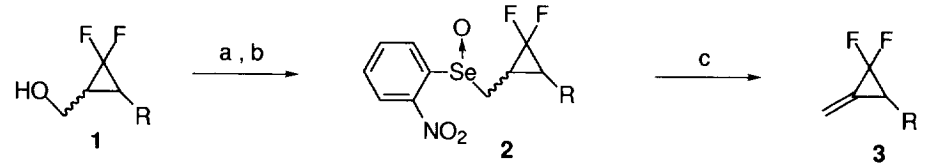


a) $ClCF_2COONa$, diglyme , 180 °C b) TBAF , THF c) Dess-Martin Oxi.
d) Ph−C≡C−Li , THF e) Ac_2O , Py f) H_2 , $Pd(OH)_2$ g) DIBAL-H , THF

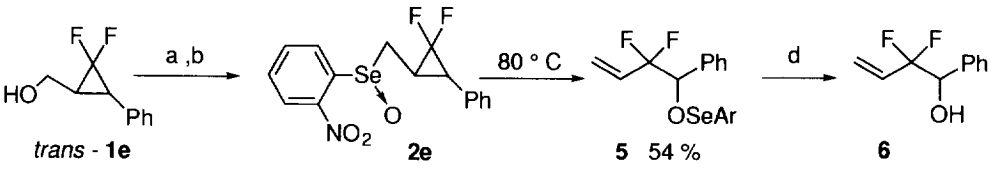
Olefination of **1** was found to be carried out by using selenoxide methodology.[14] Thus, replacement of the hydroxyl with 2-nitrophenylselenyl by treating the alcohol **1** with 2-nitrophenyl selenocyanate and tributyl-phosphine followed by oxidation with 30 % H_2O_2 gave the selenoxide **2**, which is stable enough to be isolated and purified by column chromatography on silica gel. With the substrates **2a-2d** having alkyl substituent on

the cyclopropane ring, selenoxide elimination reaction proceeded at 70-110 ℃ in toluene to give the desired F_2MCP **3** in reasonable yield (Scheme 3). For example, the selenoxide **2a** was obtained from **1a** in 93% yield as a mixture of diastereomers in a ratio of 2.8 : 1, then heating a toluene solution of **2a** at 80℃ for 48 h gave **3a** in 98% yield. In Scheme 3, the overall yields of **3a-3d** from **1a-1d** are shown. This method was found to have a limitation in the case of phenyl substituted cyclopropane **1e**; that is, when the corresponding selenoxide **2e** was heated at 80 °C, ring-opening rearrangement proceeded regioselectively, prior to elimination reaction, to form homoallylic selenate ester **5**, which was identified after conversion to the known alcohol **6**[15] by treating with $NaBH_4$.

Scheme 3

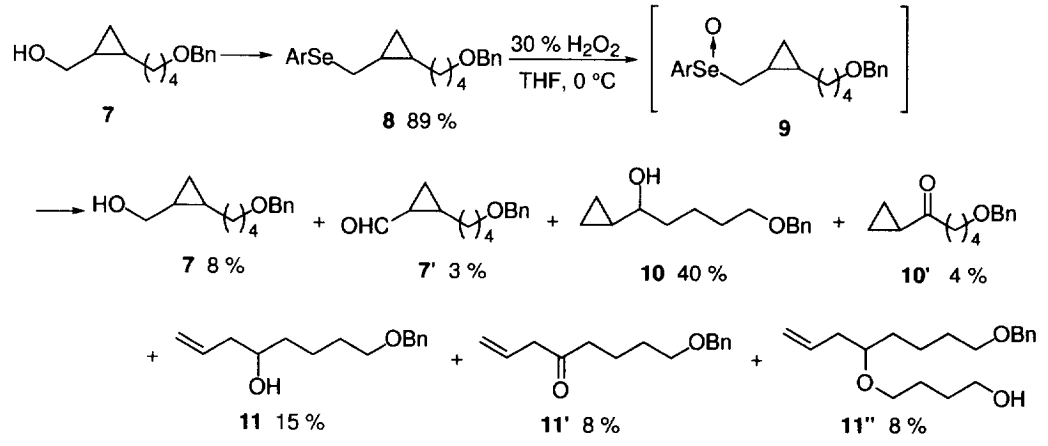


3a R = $BnOCH_2$ 91 %
3b R = $PhCH_2CH_2CH(OAc)$ 72 %
3c R = $BnO(CH_2)_5$ 51 %
3d R = $TBDPSOCH_2CH_2$ 40 %



a) 2-$NO_2C_6H_4SeCN$, Bu_3P, THF b) 30 % H_2O_2, THF c) 70 ~ 110 ° C , toluene d) $NaBH_4$

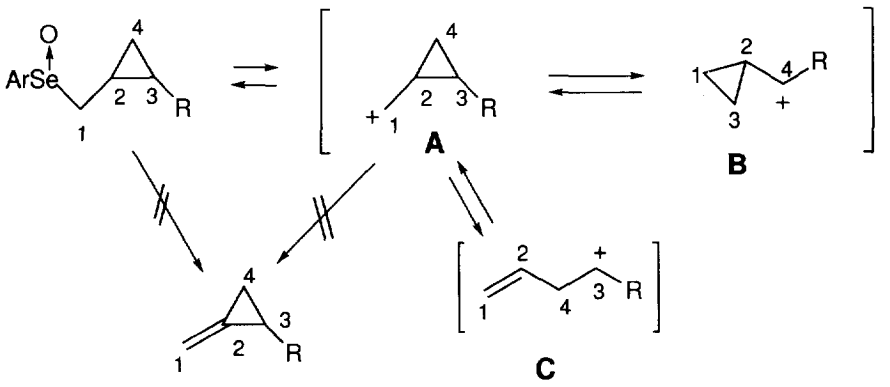
Scheme 4



It should be noted that methylenation of cyclopropylmethanols by selenoxide methodology is specific for the *gem*-difluoro compounds **1**, since solvolytic reaction takes place quite readily in the case of the cyclopropylmethylselenoxide without fluorine substituent. Thus, oxidation of the selenide **8**, isolated in 89 % yield from the *cis*-cyclopropylmethanol **7**, with 30 % H_2O_2 in THF at 0 °C for 12 h gave the several products as shown in Scheme 4. Similar products distribution was also found in the case of *trans* isomer of **7**. In both cases, the corresponding methylenecyclopropane was not detected.

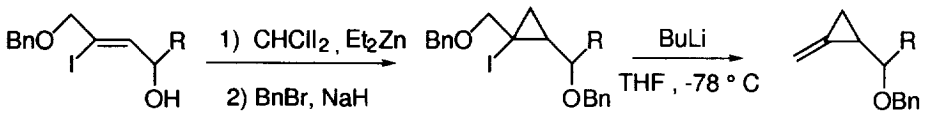
These results may indicate that the selenoxide **9** is so labile to form the cyclopropylcarbocation **A**, which further converts to skeletal-rearranged carbocation **B** and ring-cleaved homoallylic carbocation C (Scheme 5).[16] Each cation intermediate reacts with nucleophiles such as H_2O, H_2O_2 or THF existing in this reaction system to give the products isolated. Thus, the products having carbonyl group **7'**, **10'** and **11'** are possibly derived from reactions of the each carbocation with H_2O_2, and the product **11''** is formed from the reaction of C with THF. Contrary to the instability of the non-fluorinated selenoxide, the enhanced stability of the selenoxide by fluorine substituent on cyclopropane ring and successful elimination reaction leading to F_2MCP are possibly explained by considering the fluorine substituent effects as destabilization of β-carbocation[17] and enhancement of the acidity of hydrogen on β-carbon atom, in particular the vicinal hydrogen of selenoxyl group. In the case of phenyl substituted selenoxide **2e**, which provided ring-opened product **5**, a possible explanation for this result is that participation of phenyl group to stabilize the ring-opened cationic intermediate (type C, R=phenyl, *gem*-F_2 on carbon 4) would overcome the destabilization by fluorine substituent effect.

Scheme 5



For the synthesis of non-fluorinated methylenecyclopropane **14**,[11] Simmons-Smith reaction of iodoallylic alcohol **12**[18] followed by reductive elimination of **13** with buthyllithium was conducted to give **14** in good yield (Scheme 6). The Simmons-Smith reaction of the secodary alcohol **12b** proceeded in diastereoselective manner to give the cyclopropane **13b** as a single isomer, although its relative stereochemistry was not determined.

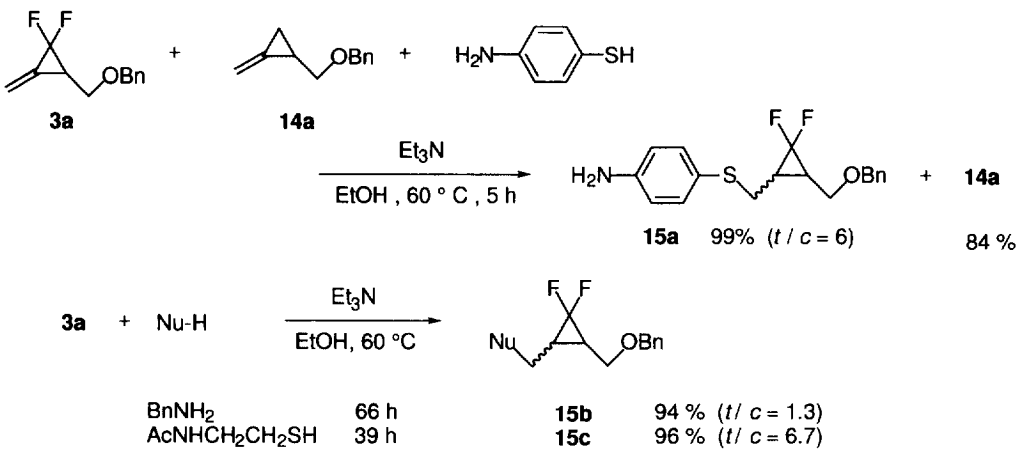
Scheme 6



12a R = H **13a** **14a** 87 %
12b R = $PhCH_2CH_2$ **13b** **14b** 80 %

It would be expected that fluorine substituent effect as strong electron-withdrawing nature and stabilization of β-carbanion brings about a high reactivity of F_2MCP **3** as a Michael acceptor. As expected, a competitive reaction of F_2MCP **3a** (1 eq) and MCP **14a** (1 eq) with 4-aminobenzenethiol (1 eq) in the presence of triethylamine in EtOH gave the Michael adduct **15a** derived from **3a** in quantitative yield, while **14a** was recovered. With other nucleophiles, benzylamine and 2-acetaminoethanethiol, F_2MCP **3a** reacted smoothly to provide the corresponding adducts, **15b** and **15c**, respectively (Scheme 7). These results may suggest that F_2MCP moiety would be useful for molecular design of irreversible inhibitors in certain enzyme reactions. Further study in line with this is currently carried out.

Scheme 7



In conclusion, F_2MCPs **3** can be prepared through elimination reaction of the selenoxide derived from *gem*-difluorocyclopropylmethanols **1**, while this method cannot be applied to non-fluorinated cyclopropylmethanols. Furthermore, due to fluorine substituent effect, F_2MCP shows a high reactivity as a Michael acceptor in the reaction with thiol and amine.

EXPERIMENTAL SECTION

^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million (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 VG Auto spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV detector.

***cis*-1-Benzyloxymethyl-2-hydroxymethyl-3,3-difluorocyclopropane 1a:** To a solution of (*Z*)-4-benzyloxy-2-butenyl *tert*-butyldimethylsilyl ether (1.72 g, 5.9 mmol) in diglyme (6 ml) heated at 180 ℃ was added a solution of sodium chlorodifluoroacetate (8.95 g, 59 mmol) in diglyme (20 ml) during 4 h and then the mixture was stirred for 3 h. After being cooled to ambient temperature, the reaction mixture was poured into water and extracted with hexane. The organic extracts were washed with water, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane-AcOEt, 10 : 1) to give the difluorocyclopropane (1.91 g, 95 %). Desilylation of the difluorocyclopropane (1.0 g, 2.93 mmol) with TBAF (1M THF solution, 3.5 ml) in THF (10 ml) at room temperature for 1 h gave **1a** (670 mg, quantitative). **1a**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 2.02-2.17 (2H, m), 2.50 (1H, brs), 3.61 (2H, m), 3.85 (2H, m), 4.54 (1H, d, *J*=11.6 Hz), 4.64 (1H, d, *J*=11.6 Hz), 7.33 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 25.0 (t, *J*=10.5 Hz), 28.5 (t, *J*=10.0 Hz), 55.7 (d, *J*=4.1 Hz), 62.7 (d, *J*=3.7 Hz), 73.4, 113.7 (dd, *J*=299.4, 284.3 Hz), 128.0, 128.3, 128.7, 136.7. ^{19}F-NMR ($CDCl_3$) δ; -60.1 (d, *J*=163.5 Hz), -85.7 (d, *J*=163.5 Hz). IR (cm^{-1}); 3387, 2887, 1479, 1073, 699. MS *m/z*; 229, 107, 91. Anal. Calcd for $C_{12}H_{14}F_2O_2$: C, 63.14; H, 6.18. Found: C, 63.04; H, 6.21.

***cis*-1-(1-Acetoxy-3-phenyl)propyl-2-hydroxymethyl-3,3-difluorocyclopropane 1b:** Reaction of **1a** (1.84g, 8.1 mmol) with Dess-Martin periodinane[19] (4.44 g) in CH_2Cl_2 (40 ml) at 0 ℃ for 2 h gave the crude aldehyde after extractive workup (CH_2Cl_2) followed by concentration. To a solution of lithium phenylacetylide prepared from phenylacetylene (0.76 ml, 8.0 mmol) and butyllithium (1.6 M hexane solution, 4.9 ml) in Et_2O (30 ml) at -78 ℃, was added the aldehyde and the mixture was stirred for 8 h at the same temperature. After usual workup, a mixture of diastereomeric alcohols was separated by silica gel column (hexane-AcOEt, 10 : 1) to give less polar alcohol (936 mg, 38 %) and more polar alcohol (763 mg, 31 %). After treating the less polar alcohol (750 mg, 2.29 mmol) with acetic anhydride (0.5 ml) in pyridine (5 ml) for 5 h and then concentration under reduced pressure, the residue dissolved in AcOEt was hydrogenated with $Pd(OH)_2$ under hydrogen atmosphere for 12 h. The reaction mixture was purified by silica gel column (hexane-AcOEt, 10 : 1) to give the acetate **1b** (647 mg, 94 %). **1b**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.83-2.18 (4H, m), 2.07 (3H, s), 2.68 (2H, m), 3.73 (1H, dd, *J*=12.8, 8.96 Hz), 3.88 (1H, dd, *J*=12.8, 6.01 Hz), 4.96 (1H, m), 7.24 (5H, m). ^{19}F-NMR ($CDCl_3$) δ; -62.3 (dt, *J*=162.5, 13.0 Hz), -89.5 (d, *J*=162.5 Hz). IR (cm^{-1}); 3380, 2887, 1745, 1073, 699. MS *m/z*; 272, 212, 91.

***trans*-1-(5-Benzyloxypentyl)-2-hydroxymethyl-3,3-difluorocyclopropane 1c:** This compound

was prepared in a similar manner to that for **1a**. **1c**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.29-1.66 (10H, m), 3.47 (2H, t, *J*=6.47 Hz), 3.69 (2H, m), 4.50 (2H, s), 7.32 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 25.6, 26.2, 26.8 (t, *J*=10.2 Hz), 28.6, 29.5, 30.3 (t, *J*=9.9 Hz), 59.6, 70.3, 72.9, 115.7 (t, *J*=287.4 Hz), 127.6, 127.7, 128.4, 138.6. ^{19}F-NMR ($CDCl_3$) δ; -75.8 (dd, *J*=158.9, 13.9 Hz), -76.4 (dd, *J*=158.9, 12.4 Hz). IR (cm^{-1}); 3386, 2936, 1102, 1040, 699. MS *m/z*; 284, 265, 107, 91. Anal. Calcd for $C_{16}H_{22}F_2O_2$: C, 67.59; H, 7.80. Found: C, 67.45; H, 7.76.

***trans*-1-(2-*tert*-Butyldiphenylsilyloxy)ethyl-2-hydroxymethyl-3,3-difluorocyclopropane 1d**: After a mixture of the difluorocyclopropylcarboxylate **4** (251 mg, 0.48 mmol) and DIBAL-H (1M hexane solution, 1.2 ml) in Et_2O (10 ml) was stirred for 1 h at -78 ℃, the reaction was quenched by addition of water and the precipitates were filtered off through Celite pad. The filtrate was purified by column chromatography on silica gel (hexane-AcOEt; 10:1) to give **1d** (179 mg, 95 %). colorless oil: ^{1}H-NMR ($CDCl_3$) δ; 1.06 (9H, s), 1.57 (4H, m), 1.80-1.85 (1H, m), 3.70 (4H, m), 7.37-7.67 (10H, m). ^{19}F-NMR ($CDCl_3$) δ; -75.55 (dd, *J*=160.2, 12.3 Hz), -76.23 (dd, *J*=160.2, 12.8 Hz). IR (cm^{-1}); 3353, 3072, 2932, 1474. MS *m/z*; 313, 269, 231, 201.

2-Benzyloxymethyl-3,3-difluoro-1-methylenecyclopropane 3a: After a mixture of **1a** (300 mg, 1.3 mmol), 2-nitrophenyl selenocyanate (357 mg, 1.6 mmol) and Bu_3P (0.4 ml, 1.6 mmol) in THF (3 ml) was stirred for 2 h at room temperature, the mixture was concentrated in vacuo. The residue was chromatographed on silica gel column (hexane-AcOEt, 10 : 1) to give the crude selenide (513 mg, 93 %) as pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ; 2.04 (2H, m), 3.00 (2H, m), 3.70 (2H, m), 4.51 (1H, d, *J*=11.8 Hz), 4.60 (1H, d, *J*=11.8 Hz), 7.33 (6H, m), 7.48 (1H, dd, *J*=8.05, 1.32 Hz), 7.53 (1H, ddd, *J*=8.24, 7.04, 1.32 Hz), 8.31 (1H, dd, *J*=8.24, 1.32 Hz). ^{19}F-NMR ($CDCl_3$) δ; -61.7 (dt, *J*=160.5, 11.8 Hz), -88.3 (d, *J*=160.5 Hz). MS *m/z*; 413, 322, 292, 202. The selenide (978 mg, 2.4 mmol) was treated with 30 % H_2O_2 (1.6 ml) in THF (10 ml) for 2 h at 0 °C. The reaction mixture was extracted with ether after addition of water. The organic extracts were dried over $MgSO_4$, then purified by silica gel column to give the selenoxide **2a** (998 mg, 98 %) as a diastereomeric mixture in a ratio of 2.8 : 1. ^{19}F-NMR ($CDCl_3$) δ; -62.0 (dt, *J*=159.4, 9.8 Hz), -86.9 (d, *J*=159.4 Hz) for major isomer of **2a**, -61.8 (dt, *J*=160.5, 12.3 Hz), -86.2 (d, *J*=160.5 Hz) for minor isomer of **2a**. MS *m/z*; 219, 202, 186, 160. A solution of **2a** (329 mg, 0.77 mmol) in toluene (5 ml) was heated at 80 ° C for 48 h and then evaporeted in vacuo. The residue was purified by silica gel column (hexane-AcOEt, 50 : 1) to give **3a** (154 mg, 91 % from **1a**). **3a**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 2.48-2.51 (1H, m), 3.56 (1H, ddd, *J*=11.9, 8.39, 1.99 Hz), 3.67 (1H, dddd, *J*=11.9, 6.35, 3.49, 1.43 Hz), 4.52 (1H, d, *J*=11.9 Hz), 4.59 (1H, d, *J*=11.9 Hz), 5.74 (1H, dd, *J*=4.36, 2.40 Hz), 6.03 (1H, ddd, *J*=3.38, 1.69, 1.20 Hz), 7.34 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 29.4 (t, *J*=12.3 Hz), 65.7, 72.7, 107.1 (t, *J*=291.7 Hz), 112.9, 127.7, 127.8, 128.5, 129.8 (t, *J*=7.0 Hz), 138.0. ^{19}F-NMR ($CDCl_3$) δ; -65.2 (dd, *J*=178.7, 11.4 Hz), -77.9 (d, *J*=178.7 Hz). IR (cm^{-1}); 2867, 1758, 1225, 1079, 739, 699. MS *m/z*; 210, 160, 129, 103, 91. Anal. Calcd for $C_{12}H_{12}F_2O$: C, 68.56; H, 5.75. Found: C, 68.54; H, 5.85.

2-(1-Acetoxy-3-phenyl)propyl-3,3-difluoro-1-methylenecyclopropane 3b: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.96-2.16 (2H, m), 2.06 (3H, s), 2.42 (1H, m), 2.69 (2H, m), 4.90 (1H, dd, *J*=14.5, 7.46 Hz), 5.71 (1H, dd, *J*=4.15, 2.22 Hz), 6.04 (1H, d, *J*=3.34 Hz), 7.24 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 20.8, 31.2, 32.6 (t, *J*=12.1 Hz), 36.2, 70.5, 106.4 (t, *J*=292.6 Hz), 113.1, 126.0, 128.2, 128.4, 129.2 (t, *J*=6.5

Hz), 140.8, 169.9. ^{19}F-NMR ($CDCl_3$) δ; -63.3 (dd, *J*=178.2, 10.7 Hz), -75.0 (d, *J*=178.2 Hz). IR (cm^{-1}); 3029, 1742, 1186, 700. MS *m/z*; 266, 206, 178, 155, 115, 91. Anal. Calcd for $C_{15}H_{16}F_2O_2$: C, 67.66; H, 6.06. Found: C, 67.45; H, 6.11.

2-(5-Benzyloxy)pentyl-3,3-difluoro-1-methylenecyclopropane 3c: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.43-1.68 (8H, m), 2.11 (1H, m), 3.49 (2H, t, *J*=6.51 Hz), 4.52 (2H, s), 5.63 (1H, dd, *J*=4.57, 2.45 Hz), 5.95 (1H, d, *J*=1.66 Hz), 7.32 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 25.7, 26.0, 28.5, 29.3 (t, *J*=11.8 Hz), 29.6, 70.2, 72.9, 108.1 (t, *J*=292.3 Hz), 110.8, 127.5, 127.6, 128.3, 133.2 (t, *J*=6.9 Hz), 138.7. ^{19}F-NMR ($CDCl_3$) δ; -65.2 (dd, *J*=176.0, 11.9 Hz), -79.8 (d, *J*=176.0 Hz). IR (cm^{-1}); 2935, 1752, 1256, 1106, 736. MS *m/z*; 267, 247, 175, 159, 91.

2-(2-*tert*-Butyldiphenylsilyloxy)ethyl-3,3-difluoro-1-methylenecyclopropane 3d: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.07 (9H, s), 1.70 (1H, m), 1.87 (1H, m), 2.35 (1H, m), 3.75 (2H, m), 5.55 (1H, dd, *J*=4.5, 2.5 Hz), 5.93 (1H, t, *J*=1.6 Hz), 7.37-7.69 (10H, m). ^{19}F-NMR ($CDCl_3$) δ; -65.12 (dd, *J*=176.1, 11.1 Hz), -79.12 (ddd, *J*=176.1, 2.5, 1.6 Hz). IR (cm^{-1}); 3072, 2932, 1753, 1473. MS *m/z*; 372, 315, 269, 231, 201. HRMS *m/z*; Calcd for $C_{18}H_{17}F_2OSi$: 315.1017. Found: 315.1022.

Reaction of the selenide 8 with 30 % H_2O_2: A mixture of the selenide **8** (454 mg, 1.09 mmol) and 30 % H_2O_2 (1 ml) in THF (10 ml) was stirred for 12 h at 0 ℃. The reaction mixture was extracted with ether after addition of water. The organic layer was successively washed with $Na_2S_2O_3$ aq. and water, dried over $MgSO_4$ and then concentrated. The residue was purified by MPLC (hexane - AcOEt, 4 : 1 ~ 1 : 1) to give the products shown in Scheme 4. Physical data of each product are as follows. **10**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.23 (2H, dddt, *J* = 18.7, 9.26, 4.68, 3.64 Hz), 0.50 (2H, dddt, *J* = 17.2, 8.45, 4.57, 3.67 Hz), 0.89 (1H, ddt, *J* = 16.4, 8.25, 4.91 Hz), 1.56 (7H, m), 2.87 (1H, dt, *J* = 8.25, 5.98 Hz), 3.49 (2H, t, *J* = 6.47 Hz), 4.51(2H, s), 7.30 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 2.4, 2.6, 17.8, 22.3, 29.7, 36.9, 70.2, 72.8, 76.5, 127.4, 127.5, 128.2, 138.5. IR (cm^{-1}); 3433. MS *m/z*; 235, 233, 218, 199, 125, 91. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.5. **10'**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.85 (2 H, ddt, *J* = 7.23, 4.21, 3.26 Hz), 1.00 (2 H, m), 1.66 (4 H, m), 1.90 (1 H, tt, *J* = 7.83, 4.59 Hz), 2.57 (2 H, t, *J* = 7.06 Hz), 3.48 (2 H, t, *J* = 6.15 Hz), 4.50 (2 H, s), 7.23 (5 H, m). ^{13}C-NMR ($CDCl_3$) δ; 10.5, 20.3, 20.8, 29.2, 43.1, 70.0, 72.9, 127.5, 127.6, 128.3, 138.6, 210.8. IR (cm^{-1}); 1707. MS *m/z*; 233, 191, 125, 98. **11**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.40-1.71 (7 H, m), 2.14 (1 H, dt, *J* = 13.7, 7.65 Hz), 2.30 (1 H, dddt, *J* = 13.7, 6.71, 4.29, 1.28 Hz), 3.48 (2 H, t, *J* = 6.41 Hz), 3.65 (1 H, m), 4.51 (2 H, s), 5.13 (1 H, dm, *J* = 9.65 Hz), 5.15 (1 H, dm, *J* = 17.5 Hz), 5.83 (1 H, dddd, *J* = 17.5, 9.65, 7.83, 6.58 Hz), 7.31 (5 H, m). ^{13}C-NMR ($CDCl_3$) δ; 22.3, 29.6, 36.5, 41.9, 70.2, 70.5, 72.8, 117.8, 127.4, 127.6, 128.3, 134.8, 138.5. IR (cm^{-1}); 3424. MS *m/z*; 235, 233, 217, 165, 127, 102. **11'**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.65 (4 H, m), 2.47 (2 H, t, *J* = 7.04 Hz), 3.15 (2 H, dt, *J* = 7.02, 1.25 Hz), 3.47 (2 H, t, *J* = 6.10 Hz), 4.49 (2 H, s), 5.13 (1 H, dm, *J* = 17.2 Hz), 5.17 (1 H, dm, *J* = 10.2 Hz), 5.91 (1 H, ddt, *J* = 17.2, 10.2, 7.01 Hz), 7.31 (5 H, m). ^{13}C-NMR ($CDCl_3$) δ; 20.4, 29.1, 41.9, 47.7, 69.9, 72.9, 118.6, 127.5, 127.6, 128.3, 130.6, 138.5, 208.5. IR (cm^{-1}); 1715. MS *m/z*; 233, 217, 191, 125, 101. **11''**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.46 (4 H, m), 1.63 (6 H, m), 2.26 (2 H, t, *J* = 6.84 Hz), 2.45 (1 H, brs), 3.31 (1 H, t, *J* = 11.8, 5.85 Hz), 3.48 (4 H, m), 3.63 (2 H, m), 4.50 (2 H, s), 5.05 (1 H, dm, *J* = 10.2 Hz), 5.08 (1 H, dm, *J* = 17.3 Hz), 5.80 (1 H, ddt, *J* = 17.3, 10.2, 7.00 Hz), 7.31 (5 H, m). ^{13}C-NMR ($CDCl_3$) δ; 22.1, 27.1, 29.8, 30.3, 38.2, 62.7,

68.9, 70.3, 72.9, 79.2, 116.9, 127.5, 128.3, 134.8, 138.6. MS *m/z*; 308, 307, 265, 237, 217.

***cis*-1-Iodo-1,2-bis(benzyloxymethyl)cyclopropane 13a**: Treatment of 4-benzyloxy-3-iodo-2-propen-1-ol (2.5 g, 8.3 mmol) with chloroiodomethane (3.64 ml, 50 mmol) and diethylzinc (1 M in hexane, 50 ml) in 1,2-dichloroethane (25 ml) for 1 h at 0 ℃ followed by usual workup gave the crude product, which was purified by column chromatography on silica gel (hexane-AcOEt, 10 : 1) to give the iodocyclopropyl carbinol (1.65 g, 63 %) as colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.76 (1H, m), 0.92 (1H, t, *J*=6.56 Hz), 1.18 (1H, dd, *J*=9.65, 6.37 Hz), 1.87 (1H, brs), 3.46 (1H, d, *J*=10.8 Hz), 3.55 (1H, m), 3.60 (1H, d, *J*=10.8 Hz), 3.97 (1H, m), 4.60 (2H, s), 7.32 (5H, m). IR (cm^{-1}); 3405. MS *m/z*; 318, 107. Treatment of the iodocyclopropyl carbinol (1.80 g, 5.7 mmol) with NaH (60 % in oil; 7.4 mmol) and benzylbromide (0.82 ml, 6.8 mmol) in THF (15 ml) and DMF (10 ml) for 6 h at room temperature followed by purification by column chromatography on silica gel (hexane-AcOEt, 20 : 1) gave the benzyl ether **13a** (2.17 g, 93 %). **13a**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.79 (1H, m), 0.91 (1H, t, *J*=6.4 Hz), 1.22 (1H, dd, *J*=9.6, 6.4 Hz), 3.50 (1H, d, *J*=10.8 Hz), 3.59 (1H, t, *J*=10.3 Hz), 3.60 (1H, d, *J*=10.8 Hz), 3.69 (1H, dd, *J*=10.3, 5.9 Hz), 4.57 (1H, d, *J*=11.8Hz), 4.57 (1H, d, *J*=12.1 Hz), 4.61 (1H, d, *J*=11.8Hz), 4.63 (1H, d, *J*=12.1 Hz), 7.33 (10H, m). IR (cm^{-1}); 2857, 1454, 1099, 697. MS *m/z*; 408, 316, 107, 91. Anal. Calcd for $C_{19}H_{21}IO_2$: C, 55.90; H, 5.18. Found: C, 56.06; H, 5.25.

***cis*-1-Benzyloxymethyl-1-iodo-2-(1-benzyloxy-3-phenyl)propylcyclopropane 13b**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.54 (1 H, dt, *J* = 9.16, 7.04 Hz), 1.15 (1 H, t, *J* = 6.67 Hz), 1.38 (1 H, dd, *J* = 9.3, 6.20 Hz), 2.01 (1 H, ddt, *J* = 18.6, 8.63, 5.15 Hz), 2.15 (1 H, ddt, *J* = 17.0, 9.94, 3.40 Hz), 2.78 (1 H, ddd, *J* = 13.7, 10.2, 6.6 Hz), 2.95 (1 H, ddd, *J* = 13.9, 10.4, 4.97 Hz), 3.20 (1 H, dt, *J* = 8.62, 3.11 Hz), 3.43 (1 H, d, *J* = 10.6 Hz), 3.52 (1 H, d, *J* = 10.6 Hz), 4.51 (1 H, d, *J* = 11.4 Hz), 4.54 (1 H, d, *J* = 12.1 Hz), 4.60 (1 H, d, *J* = 12.1 Hz), 4.73 (1 H, d, *J* = 11.4 Hz), 7.27 (15 H, m). IR (cm^{-1}); 1360, 1204, 1098, 1029. MS *m/z*; 384, 91. Anal. Calcd for $C_{27}H_{29}IO_2$: C, 63.29; H, 5.70. Found: C, 63.70; H, 5.90.

2-Benzyloxymethyl-1-methylenecyclopropane 14a: A mixture of the iodocyclopropane **13a** (2.17 g, 5.3 mmol) and butyllithium (1.6 M hexane solution, 5.4 ml) in THF was stirred at -78 ℃ for 1 h. After usual workup, the crude mixture was purified by silica gel column chromatography (hexane-AcOEt, 20 : 1) to give **14a** (838 mg, 87 %) as colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 0.97 (1H, m), 1.36 (1H, ttd, *J*=9.0, 1.9, 0.46 Hz), 1.81 (1H, m), 3.32 (1H, dd, *J*=10.3, 7.8 Hz), 3.53 (1H, dd, *J*=10.3, 6.2 Hz), 4.53 (1H, d, *J*=12.0 Hz), 4.58 (1H, d, *J*=12.0 Hz), 5.42 (1H, m), 5.47 (1H, m), 7.32 (5H, m). ^{13}C-NMR ($CDCl_3$) δ; 9.3, 16.2, 73.1, 73.4, 104.8, 128.2, 128.3, 129.0, 133.8, 139.1. IR (cm^{-1}); 3031, 2855, 1028, 737, 698. MS *m/z*; 174, 160, 129, 107, 91. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.35; H, 8.19.

2-(1-Benzyloxy-3-phenyl)propyl-1-methylenecyclopropane 14b: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.08 (1 H, m), 1.43 (1 H, tt, *J* = 8.79, 1.89 Hz), 1.65 (1 H, m), 1.98 (2 H, m), 2.70 (1 H, dt, *J* = 10.11, 6.42 Hz), 2.87 (1 H, dt, *J* = 10.22, 5.16 Hz), 2.96 (1 H, dt, *J* = 8.09, 4.10 Hz), 4.56 (1 H, d, *J* = 11.81 Hz), 4.80 (1 H, d, *J* = 11.81 Hz), 5.43 (2 H, m), 7.28 (10 H, m). ^{13}C-NMR ($CDCl_3$) δ;9.8, 19.8, 31.8, 37.2, 70.9, 80.7, 104.4, 125.7, 127.4, 127.6, 128.3, 128.4, 132.0, 139.0, 142.4. IR (cm^{-1}); 3027, 1496, 1454, 1088. MS *m/z*; 277, 220, 205, 155,120, 105, 91. Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H,7.97. Found: C, 85.79; H, 8.05.

1-(4-Aminophenylthio)methyl-2-benzyloxymethyl-3,3-difluorocyclopropane 15a: After a mixture of **3a** (50 mg, 0.24 mmol), **14a** (41 mg, 0.24 mmol), 4-aminobenzenethiol (30 mg, 0.24 mmol) and Et_3N (0.24 mmol) in EtOH was stirred for 5 h at 60 °C, the reaction mixture was purified by silica gel column chromatography (hexane-AcOEt, 50 : 1 ~ 1 : 1) to give recovered **14a** (35 mg, 84 %) and the adduct **15a** (79 mg, 99 %) as a *cis/trans* mixture in a ratio of 1 : 6. ***trans*-15a:** yellow oil. ^{1}H-NMR ($CDCl_3$) δ; 1.58 (2H, m), 2.77 (1H, ddd, *J*=13.7, 7.7, 2.7 Hz), 2.95 (1H, dd, *J*=13.7, 7.17 Hz), 3.43 (1H, ddd, *J*=10.8, 8.0, 1.9 Hz), 3.58 (1H, ddd, *J*=10.8, 6.5, 4.3 Hz), 3.73 (2H, brs), 4.47 (1H, d, *J*=12.0 Hz), 4.55 (1H, d, *J*=12.0 Hz), 6.59 (2H, dt, *J*=8.6, 2.4 Hz), 7.32 (7H, m). ^{13}C-NMR ($CDCl_3$) δ; 26.8 (t, *J*=10.5 Hz), 28.5 (t, *J*=10.3 Hz), 33.5 (d, *J*=3.3 Hz), 66.2 (d, *J*=4.5 Hz), 72.6, 114.6 (dd, *J*=290, 287 Hz), 115.6, 121.6, 127.6, 127.7, 128.5, 135.2, 138.0, 146.6. ^{19}F-NMR ($CDCl_3$) δ; -74.6 (dd, *J*=160, 13.6 Hz), -75.6 (dd, *J*=160, 13.6 Hz). IR (cm^{-1}); 3370, 2866, 1622, 1598, 1496, 1092, 825, 699. MS *m/z*; 335, 220, 205, 145, 105, 91. Anal. Calcd for $C_{18}H_{19}F_2NOS$: C, 64.45; H, 5.17; N, 4.18. Found: C, 64.58; H, 5.94; N, 4.10. ***cis*-15a:** colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.81-1.98 (2H, m), 2.76 (1H, dd, *J*=13.8, 8.10 Hz), 2.87 (1H, ddd, *J*=13.8, 6.30, 3.90 Hz), 3.55 (2H, dm, *J*= 7.24 Hz), 3.73 (2H, br), 4.49 (1H, d, *J*=12.0 Hz), 4.53 (1H, d, *J*=12 Hz), 6.62 (2H, d, *J*=8.54 Hz), 7.25-7.37 (7H, m). ^{13}C-NMR ($CDCl_3$) δ; 25.3 (dd, *J*=5.2, 10.6 Hz), 25.5 (dd, *J*=4.9, 10.4 Hz), 29.7 (d, *J*=3.7 Hz), 72.9 (d, *J*=4.7 Hz), 113.5 (dd, *J*=283.5, 292.4 Hz), 115.5, 121.4, 127.7, 127.8, 128.4, 135.1, 137.7, 146.6. ^{19}F-NMR ($CDCl_3$) δ; -62.2 (dt, *J*=160.3, 13 Hz), -88.5 (d, *J*=160.3 Hz). IR (cm^{-1}); 3374, 2924, 1717, 1599, 1496, 1270, 791, 714. MS *m/z*; 335, 227, 124, 91. Anal. Found: C, 64.57; H, 5.97; N, 4.10.

1-(*N*-Benzylaminomethyl)-2-benzyloxymethyl-3,3-difluorocyclopropane 15b: This compound was obtained as a *trans/cis* mixture in a ratio of 1.3 : 1 determined by ^{1}H-NMR. Separation of the stereoisomers was carried out by MPLC (hexane-AcOEt, 2 : 1). ***trans*-15b**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.55 (1H, br), 1.60-1.72 (2H, m), 2.82 (2H, m), 3.59 (2H, d, *J*=6.47 Hz), 3.81 (1H, d, *J*=13.2 Hz), 3.86 (1H, d, *J*=13.2 Hz), 4.53 (1H, d, *J*=11.9 Hz), 4.59 (1H, d, *J*=11.9 Hz), 7.33 (10H, m). ^{13}C-NMR ($CDCl_3$) δ; 27.1 (t, *J*=10.9 Hz), 27.3 (t, *J*=11.0 Hz), 46.0 (d, *J*=3.18 Hz), 53.4, 66.3 (d, *J*=4.16 Hz), 72.7, 114.8 (t, *J*=286.0 Hz), 127.1, 127.7, 127.8, 128.1, 128.5, 138.5, 138.1, 140.1. ^{19}F-NMR ($CDCl_3$) δ; -74.66 (dd, *J*=161.1, 13.6 Hz), -76.02 (dd, *J*=161.1, 12.8 Hz). IR (cm^{-1}); 3330, 3029, 2860, 1261, 1026, 739, 699. MS *m/z*; 318, 317, 316, 226, 210, 106, 91. Anal. Calcd for $C_{19}H_{21}F_2NO$: C, 71.90; H, 6.67; N, 4.41. Found: C, 71.77; H, 6.68; N, 4.35. ***cis*-15b**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.74 (1H, *br*), 1.97 (2H, m), 2.80 (2H, m), 3.54 (1H, m), 3.68 (1H, m), 3.73 (1H, d, *J*=13.2 Hz), 3.81 (1H, d, *J*=13.2 Hz), 4.45 (1H, d, *J*=11.8 Hz), 4.52 (1H, d, *J*=11.8), 7.29 (10H, m). ^{13}C-NMR ($CDCl_3$) δ; 24.8 (t, *J*=10.3 Hz), 25.9 (t, *J*=10.2 Hz), 42.0 (d, *J*=3.86 Hz), 53.7, 62.9 (d, *J*=3.78 Hz), 73.1, 114.1 (dd, *J*=290.2, 283.6 Hz), 127.1, 127.9, 128.0, 128.2, 128.6, 128.7, 137.7, 140.0. ^{19}F-NMR ($CDCl_3$) δ; -61.2 (dt, *J*=162.0 Hz), -87.6 (d, *J*=162.0 Hz). IR (cm^{-1}); 3314, 2863, 1076, 738, 699. MS *m/z*; 317, 226, 206, 132, 106, 91.

1-(2-Acetoaminoethylthiomethyl)-2-benzyloxymethyl-3,3-difluorocyclopropane 15c: This compound was obtained as a *trans/cis* mixture in a ratio of 5 : 1 determined by ^{1}H-NMR. colorless oil. ^{1}H-NMR ($CDCl_3$) δ; 1.65 (2H, m), 1.95 (2.5H, s), 1.96 (0.5 H, s), 2.60-2.77 (4H, m), 3.37-3.47 (2H, m), 3.53-3.64 (2H, m), 4.47 and 4.55 (total 0.3H, both d, *J*=11.8 Hz), 4.50 and 4.57 (total 1.7H, both d, *J*=11.9 Hz), 5.88 (1H, brs), 7.33 (5H, m). ^{19}F-NMR ($CDCl_3$) δ; -74.2 (dd, *J*=158.9, 12.8 Hz), -75.1 (dd, *J*=158.9, 13.1 Hz) for ***trans*-15c**, -62.1 (dt, *J*=159.4, 12.8 Hz), -87.1 (d, *J*=159.4 Hz) for ***cis*-15c**. IR (cm^{-1});

MS *m/z*; 330, 221, 201, 162.

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(*Received in Japan* 23 *April* 1997; *accepted* 22 *May* 1997)