# Supplementary Information

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1. General

NMR (\(^1\)H, \(^{13}\)C, and \(^{19}\)F) spectra were recorded with a Jeol JNMAL-400 or Jeol JNMECA-500 instruments (\(^1\)H, 500 or 400 MHz, \(^{13}\)C, 125 MHz, \(^{19}\)F, 470 MHz). Chemical shifts are reported relative to Me$_4$Si, except for fluorine-containing compounds where CFCl$_3$ was used as an internal standard. Mass spectra (MS) were taken in FAB mode with m-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd.) or neutral silica gel (Silica Gel 60N, Kanto Chemical Co., Inc.). Thin-layer chromatography (TLC) was performed on precoated silica gel plate F$_{254}$. THF was distilled from benzophenone ketyl.

2. Preparation of 5a

\[
\begin{align*}
\text{F}_2\text{BrC} & \quad \text{OH} \\
\text{CH}_2\text{Cl}_2 & \quad \text{TBDPSCI} \\
\text{imidazole} & \quad \text{S1} \\
\text{F}_2\text{BrC} & \quad \text{EtO} \\
\text{CH}_2\text{Cl}_2 & \quad \text{S2} \\
1) \text{DIBAL-H} & \quad \text{MeCN} \\
2) \text{Ph}_3\text{P}=\text{CHCO}_2\text{Me} & \quad \text{S3} \\
\text{OBz} & \quad \text{CH}_2\text{Cl}_2 \\
5a & \quad \text{CO}_2\text{Me}
\end{align*}
\]

4-Bromo-3-(tert-butylidiphenylsilyloxy)-4,4-difluoro-butyric acid ethyl ester (S2)

To a CH$_2$Cl$_2$ (27 mL) solution of S1 (4.56 g, 18.4 mmol) was added imidazole (2.13 g, 31.3 mmol) at 0 °C. After 20 min stirring of the resulting mixture, TBDPSCI (4.79 mL, 18.4 mmol) was dropwise added, then allowed to rt for 24 h. The mixture was partitioned between aq. saturated NaHCO$_3$ and CH$_2$Cl$_2$. Column chromatography on silica gel (hexane/Et$_2$O = 10/1) of the organic layer gave S2 (7.77 g, 87%) as an oil: \(^1\)H NMR (400 MHz, CDCl$_3$) \(\delta\) 1.06 (s, 9H), 1.12 (t, \(J = 7.2\) Hz, 3H), 2.67-2.76 (m, 2H), 3.83-3.90 (m, 2H), 4.35-4.41 (m, 1H), 7.25-7.48 (m, 6H), 7.61-7.63 (m, 2H), 6.69-7.75 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl$_3$) \(\delta\) 13.9, 19.4, 26.9, 38.9, 61.0, 74.2 (dd, \(J_{CF} = 28.6\) and 22.4 Hz), 124.5 (dd, \(J_{CF} = 312.3\) and 308.7 Hz), 127.5, 127.6, 129.8, 130.1, 131.5, 132.8, 135.8, 136.3, 169.1. HRFAB-MS (m/z) 485.0959 (M$^{+}$+H) calcd for C$_{22}$H$_{28}$BrF$_2$O$_3$Si (M$^{+}$+H) 485.0959.

6-Bromo-5-(tert-butylidiphenylsilyloxy)-6,6-difluoro-hex-2-enoic acid methyl ester (S3)

To a stirred solution CH$_2$Cl$_2$ (80 mL) of S2 (3.8 g, 7.83 mmol) was dropwise added DIBAL-H (1.0 mol/L in toluene, 15.7 mL, 15.7 mmol) over 3 min at −80 °C. The resulting mixture was stirred further 30 min at same temperature. To the mixture was added aq. saturated Rochelle salt (ca. 100 mL) then allowed to warm to rt. The mixture was filtrated through a celite pad, the filtrate was partitioned between brine and CH$_2$Cl$_2$. The resulting organic layer was dried by Na$_2$SO$_4$ then evaporated all of volatiles. The residue was treated with MeCN (150 mL) and Ph$_3$P=CHCO$_2$Me (7.85 g, 23.5 mmol). The mixture was stirred further 14 h at rt. The mixture was partitioned between brine and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 4.1) gave aclude alcohol. The residue was dissolved in CH$_2$Cl$_2$ (30 mL), then treated with i-Pr$_2$NEt.

Benzoic acid 1-(bromodifluoromethyl)-4-methoxycarbonyl-but-3-enyl ester (5a)

To a THF (30 mL) solution of S3 (1.39 g, 2.79 mmol) was added AcOH (176 μL, 3.07 mmol) and TBAF (1.0 mol/L solution in THF, 3.07 mL, 3.07 mmol). The resulting mixture was stirred for 20 h at rt. The mixture was partitioned between aq. saturated NaHCO$_3$ and CH$_2$Cl$_2$. After evaporation of all of volatiles, the residue was roughly purified by column chromatography on silica gel (hexane/AcOEt = 4.1) gave aclude alcohol. The residue was dissolved in CH$_2$Cl$_2$ (30 mL), then treated with i-Pr$_2$NEt.
(486 μL, 2.77 mmol), DMAP (342 mg, 2.79 mmol) and BzCl (392 μL, 3.35 mmol). The mixture was stirred for 20 h at rt. The resulting mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/Et₂O = 3/1) of the organic layer gave 5a (784 mg, 77%) as an oil: 1H NMR (400 MHz, CDCl₃) δ 2.77-2.86 (m, 1H), 2.88-2.95 (m, 1H), 3.69 (s, 3H), 5.67 (ddd, J = 16.8, 8.4 and 4.0 Hz, 1H), 5.97 (dt, J = 15.6 and 1.6 Hz, 1H), 6.89 (dt, J = 15.6 and 7.6 Hz, 1H), 7.47-7.51 (m, 2H), 7.60-7.65 (m, 1H), 8.07-8.09 (m, 2H); 13C NMR (500 MHz, CDCl₃) δ 32.4, 51.6, 74.0 (t, Jₐ₅C,F = 31.1 Hz), 121.0 (t, Jₐ₅C,F = 310.0 Hz), 125.1, 128.4, 128.6, 130.1, 133.9, 140.4, 164.6, 165.9. HRFAB-MS (m/z) 363.0073 (M⁺+H) calcd for C₁₄H₁₄BrF₂O₄ (M⁺+H) 363.0044.


3. Radical reaction of 5a: General procedure for the redical cyclization reaction

To a refluxing solution of 5 (337 mg, 0.93 mmol) in toluene (9 mL) was dropwise added a toluene (9 mL) solution of Bu₃SnH (500 μL, 1.86 mmol) and AIBN (31 mg, 0.19 mmol) over 4 h. The resulting mixture was stirred further 1 h at same temperature. After evaporation of all of volatiles, the residue was roughly purified by column chromatography on silica gel (hexane/Et₂O = 3/1). The crude mixture was further purified by preparative TLC (hexane/AcOEt = 8/1). This gave a mixture of 7a and trans-6a (102 mg, 39%, the ratio of 7a/trans-6a = 100:22, based on the integration of 1H NMR) and cis-6a (57 mg, 22%, as an oil).

Physical data for cis-6a: 1H NMR (400 MHz, CDCl₃) δ 1.67-1.75 (m, 1H), 2.55-2.79 (m, 3H), 2.87-2.99 (m, 1H), 3.71 (s, 1H), 5.35-5.44 (m, 1H), 7.44-7.48 (m, 2H), 7.57-7.61 (m, 1H), 8.04-8.08 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 26.5 (d, Jₐ₅C,F = 19.1 Hz), 31.8 (d, Jₐ₅C,F = 7.3 Hz), 36.5 (t, Jₐ₅C,F = 21.5 Hz), 51.9, 70.3 (dd, Jₐ₅C,F = 27.6 and 18.0 Hz), 119.5 (dd, Jₐ₅C,F = 298.0 and 278.9 Hz), 128.5, 128.9, 129.9, 133.5, 165.1, 171.3. HRFAB-MS (m/z) 285.0925 (M⁺+H) calcd for C₁₄H₁₅F₂O₄ (M⁺+H) 285.0938.

NOE experiments of cis-6a

Physical data for trans-6a: The physical data for trans-6a is illustrated at later stage.

Partial data for 7a: 1H NMR (400 MHz, CDCl₃) δ 2.72-2.84 (m, 2H), 3.78 (s, 3H), 5.33-5.43 (m, 1H), 5.95 (dd, Jₐ₅C,F = 57.6 and 54.4 Hz, J = 3.2 Hz, 1H), 5.99 (dt, J = 15.6 and 1.6 Hz, 1H), 6.94 (dt, J = 15.6 and 7.2 Hz, 1H), 7.45-7.49 (m, 2H), 7.58-7.63 (m, 1H), 8.04-8.09 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 30.2, 51.6, 70.4 (t, Jₐ₅C,F = 25.1 Hz), 113.4 (t, Jₐ₅C,F = 246.6 Hz), 124.8, 128.6, 128.8, 129.9, 133.7, 141.4, 165.3, 166.1. FAB-MS (m/z) 285 (M⁺+H).
4. Preparation of 5b

**Benzoic acid 1-(ethoxycarbonyl-difluoromethyl)-3-tributylstannyl-allyl ester (S5)**

To a THF (7 mL) suspension of activated Zn (1.38 g) was added TMSCl (190 μL, 1.38 mmol). The resulting mixture was stirred at 60 °C for 15 min, then cooled to rt. To the mixture was added THF (30 mL) and BrF₂CCO₂Et (2.72 mL, 21.2 mmol) then heated at 60 °C for 3 min. A vigorous reflux was observed during this period. The resulting Zn enolate solution was quickly transferred to a THF (30 mL) solution of S₄ (3.66 g, 10.6 mmol) at 0 °C, then the mixture was stirred at rt for 2 h. The mixture was partitioned between aq. saturated NaHCO₃ and AcOEt. Flash column chromatography on silica gel (hexane/Et₂O = 3/1) of the organic layer gave a crude alcohol (ca. 4.86 g). To a CH₂Cl₂ (50 mL) solution of above alcohol was added Et₃N (2.22 mL, 15.9 mmol) and BzCl (1.49 mL, 12.7 mmol) at 0 °C. After 25h stirring of the resulting mixture at rt, this was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/Et₂O = 11/1) of the organic layer gave S₅ (5.28 g, 86% for two steps) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 0.82-0.98 (m, 15H), 1.22-1.33 (m, 9H), 1.54-1.57 (m, 6H), 4.25-4.33 (m, 2H), 5.89-6.12 (m, 2H), 6.54-6.74 (m, 1H), 7.44-7.48 (m, 2H), 7.58-7.62 (m, 1H), 8.01-8.08 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 9.6, 13.6, 13.9, 27.2, 29.0, 63.1, 75.0 (dd, J_C,F = 29.8 and 25.0 Hz), 112.9 (dd, J_C,F = 256.3 and 252.8 Hz), 128.6, 129.1, 130.0, 133.5, 135.3, 140.3, 162.5 (t, J_C,F = 31.0 Hz), 164.5. HRFAB-MS (m/z) 575.2012 (M⁺+H) calcd for C₂₆H₄₁F₂O₄Sn (M⁺+H) 575.1995.

**Benzoic acid 1-[2-(tert-butyldimethylsiloxy)-1,1-difluoroethyl]-3-iodoallyl ester (S6)**

To a MeOH (50 mL) solution of S₅ (5.11 g, 8.9 mmol) and AcOH (1.53 mL, 26.7 mmol) was portionwise added NaBH₄ (4.04 g, 106.8 mmol) at −40 °C. The resulting mixture was stirred at 0 °C for 1 h. The mixture was partitioned between aq. saturated NaHCO₃ and CHCl₃. After evaporation of all of volatiles of the organic layer, crude alcohol was obtained. To a CH₂Cl₂ (50 mL) solution of above alcohol was added DMAP (437 mg, 3.56 mmol), imidazole (727 mg, 10.68 mmol) and TBSCl (1.61 g, 10.68 mmol) at −40 °C. The resulting mixture was stirred at 0 °C for 13 h. The mixture was partitioned between aq. saturated NaHCO₃ and CHCl₃. After evaporation of all of volatiles of the organic layer, crude silyl ether was obtained. This was treated with THF (100 mL) and I₂ (4.52 g, 17.8 mmol). After 1 h stirring at rt of the resulting mixture, this was partitioned between aq. saturated Na₂S₂O₃, aq. saturated NaHCO₃ and AcOEt. Column chromatography on silica gel (hexane/Et₂O = 15/1) of the organic layer gave S₆ (2.83 g, 66% for three steps) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 3.80-3.93 (m, 2H), 5.83 (ddd, J = 14.8, 8.8 and 7.2 Hz, 1H), 6.69 (dd, J = 14.8 and 7.2 Hz, 1H), 6.78 (d, J = 14.8 Hz, 1H), 7.44-7.48 (m, 2H), 7.57-7.61 (m, 1H), 8.04-8.06 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.7, 18.1, 25.6, 62.4 (dd, J_C,F = 34.6 and 31.0 Hz), 72.6 (dd, J_C,F = 32.4 and 25.1 Hz), 84.9, 119.2 (dd, J_C,F = 251.3 and 247.8 Hz), 128.6, 129.1, 129.8, 133.6, 136.2, 164.4. HRFAB-MS (m/z) 483.0680 (M⁺+H) calcd for C₁₈H₂₆F₂O₃Si (M⁺+H) 483.0664.

**Benzoic acid 1-(1,1-difluoro-2-phenoxythiocarbonyloxyethyl)-3-methoxycarbonylallyl ester (5b)**

To a THF (100 mL) solution of S₆ (2.83 g, 66% for three steps) was added PdCl₂(MeCN)₂, i-Pr₂NEt (2.51 mmol, 2.51 mL) and CO (1.0 atm). After 1 h stirring of the resulting mixture, the mixture was partitioned between aq. saturated Na₂S₂O₃ and AcOEt. Column chromatography on silica gel (hexane/Et₂O = 15/1) of the organic layer gave S₇ (2.07 g, 36% for three steps) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 5.89 (ddd, J = 14.8, 8.8 and 7.2 Hz, 1H), 7.44-7.48 (m, 2H), 7.57-7.61 (m, 1H), 8.04-8.06 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 25.2, 72.6 (dd, J_C,F = 34.6 and 31.0 Hz), 72.6 (dd, J_C,F = 32.4 and 25.1 Hz), 84.9, 119.2 (dd, J_C,F = 251.3 and 247.8 Hz), 128.6, 129.1, 129.8, 133.6, 136.2, 164.4. HRFAB-MS (m/z) 575.0712 (M⁺+H) calcd for C₂₆H₄₁F₂O₃Sn (M⁺+H) 575.1995.

Electronic Supplementary Material (ESI) for Chemical Communications

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A mixture of \textbf{S6} (2.65 g, 5.52 mmol), \( \text{PdCl}_2(\text{MeCN})_2 \) (285 mg, 1.1 mmol) and \( i-\text{Pr}_2\text{NEt} \) (1.01 mL, 5.8 mmol) in MeOH (40 mL) was heated at 50 °C under positive pressure of CO (1 atm). After 1.5h heating of the resulting mixture, this was filtrated through a celite pad, then the filtrate was partitioned between aq. saturated NaHCO₃ and AcOEt. Evaporation of the organic layer gave a crude methyl acrylate (ca. 2.21 g). To a mixture of above acrylate and AcOH (379 μL, mmol) in THF (40 mL) was added Bu₄NF (1.0 mol/L in THF, 6.62 mL, 6.62 mmol). The resulting mixture was stirred at rt for 3.5h. This was partitioned between aq. saturated NaHCO₃ and AcOEt. Evaporation of the organic layer gave a crude alcohol. At this time, benzoyl migration was partially occurred to give an inseparable mixture (ca. 1:1). Therefore, this was used for next reaction without further purification. The mixture was dissolved in CH₂Cl₂ (40 mL), then treated with pyridine (893 μL, 11.04 mmol) and PhOC(S)Cl (764 μL, 5.52 mmol) at 0 °C. After 1.5 h stirring of the resulting mixture, this was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/AcOEt = 3/1) gave a mixture of thiocarbonate \textbf{5b} and \textbf{S7} (ca. 1:1 mixture, 760 mg, 32% for three steps). Preparative TLC (hexane/AcOEt = 17/1, 8 times evolution) gave a pure \textbf{5b} as an oil: \( ^1\text{H} \text{NMR} \) (400 MHz, CD₂Cl₂) δ 3.74 (s, 1H), 4.82-4.98 (m, 2H), 6.06-6.14 (m, 1H), 7.02 (dd, \( J = 15.6 \) and 1.6 Hz, 1H), 7.02 (dd, \( J = 15.6 \) and 5.6 Hz, 1H), 7.07-7.09 (m, 2H), 7.41-7.45 (m, 2H), 7.63-7.67 (m, 1H), 8.10-8.12 (m, 2H); \( ^{13}\text{C} \text{NMR} \) (125 MHz, CD₂Cl₂) δ 52.3, 69.9 (dd, \( J_{\text{C,F}} = 34.6 \) and 29.8 Hz), 70.9 (dd, \( J_{\text{C,F}} = 32.2 \) and 26.2 Hz), 118.5 (t, \( J_{\text{C,F}} = 248.0 \) Hz), 122.0, 126.7, 127.3, 128.8, 129.2, 130.1, 130.4, 134.5, 136.7, 153.9, 164.6, 165.6, 194.5. HRFAB-MS (\( m/z \)) 437.0861 (M++H) calcd for C₂₁H₁₉F₂O₆S (M++H) 437.0870.


5. Preparation of \textbf{5c}

\[ \begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{SePh} & \quad \text{SePh}
\end{align*} \]

\textbf{S8} \quad \text{BrCF₂COC₂Et} \quad \text{Zn/Cu couple} \quad \text{THF} \quad \text{MeNHOMe-HCl} \quad \text{BuLi} \quad \text{THF} \quad \text{O} \quad \text{Me} \quad \text{N} \quad \text{Me} \quad \text{MeO} \quad \text{Me}

\[ \begin{align*}
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{PhSe} & \quad \text{PhSe}
\end{align*} \]

\textbf{5c} \quad \text{BzCl, DMAP} \quad \text{i-Pr}_2\text{NEt} \quad \text{CH}_2\text{Cl}_2 \\

\text{O} \quad \text{O} \quad \text{F} \quad \text{F} \quad \text{O} \quad \text{SePh}

\text{2,2-Difluoro-3-hydroxy-4-phenylselenenyl-butyric acid ethyl ester (S9)}

To a stirring mixture of Cu(OAc)₂ (106 mg, 0.59 mmol) in AcOH (20 mL) was added activated Zn powder (1.9 g) at 110 °C. The resulting suspension was vigorously stirred further 3 min at same temperature. After decantation of most of AcOH, the crude Zn/Cu couple was sequentially washed by AcOH (20 mL) and Et₂O (20 mL). To a THF (70 mL) suspension of above wet Zn/Cu couple was carefully added ethyl bromodifluoroacetate (3.0 mL, 23.4 mmol) at 80 °C, then refluxed further 5 min. The resulting zinc enolate was cooled at 0 °C. To this, a THF (20 mL) solution of \textbf{S8} (2.9 g, 14.6 mmol) was dropwise added. The resulting mixture was stirred at rt further 1 h. After filtration of the mixture through a celite pad, the filtrate was partitioned between aq. saturated NaHCO₃ and AcOEt. Column chromatography on silica gel (hexane/Et₂O = 3/1) of the organic layer gave \textbf{S9} (2.98 g, 63%)
as an oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.34 (t, $J = 7.4$ Hz, 3H), 2.79 (br-s, 1H), 3.08 (dd, $J = 10.4$ and 3.0 Hz, 1H), 3.26 (dd, $J = 12.6$ and 3.0 Hz, 1H), 4.10-2.18 (m, 1H), 4.35 (q, $J = 7.4$ Hz, 2H), 7.29-7.31 (m, 3H), 7.53-7.56 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 13.7, 28.2, 63.3, 70.3 (dd, $J_{C,F} = 30.0$ and 25.2 Hz), 113.8 (dd, $J_{C,F} = 259.1$ and 254.3 Hz), 127.8, 128.2, 129.4, 133.2, 163.0 (t, $J_{C,F} = 32.2$ Hz). FAB-MS (m/z) 324 (M$^+$+H).

Found: C, 43.79; H, 4.24.

2,2-Difluoro-3-hydroxy-N-methoxy-N-methyl-4-phenylselenenyl butyramide (S10)
To a THF (150 mL) suspension of N,O-dimethylhydroxylamine hydrochloride (8.52 g, 81.4 mmol, previously dried by P$_2$O$_5$ under vacuum condition for 2 days) was dropwise added BuLi (2.69 mol/L in hexane, 65.0 mL, 174.7 mmol) at $-80$ °C. The resulting solution was allowed to rt for 5 min. To the mixture was added S9 (7.06 g, 21.8 mmol) in THF (50 mL) at $-80$ °C then rinsed by using further THF (20 mL). After 1 h stirring of the mixture, this was partitioned between aq. saturated NH$_4$Cl and AcOEt. Column chromatography on silica gel (hexane/ AcOEt = 1/1) of the organic layer gave S10 (5.24 g, 71%) as an oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.06-3.17 (m, 2H), 3.23-3.26 (m, 4H), 3.73 (s, 3H), 4.30-4.38 (m, 1H), 7.21-7.31 (m, 3H), 7.51-7.56 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 27.7, 33.1, 62.2, 71.2 (dd, $J_{C,F} = 28.6$ and 25.1 Hz), 115.3 (dd, $J_{C,F} = 263.3$ and 259.6 Hz), 127.5, 129.4, 131.1, 133.1, 163.0. HRFAB-MS (m/z) 340.0293 (M$^+$+H) calcd for C$_{12}$H$_{16}$F$_2$NO$_3$Se (M$^+$+H) 340.0263.

4,4-Difluoro-5-hydroxy-6-phenylselenohex-2-enoic acid methyl ester (S11)
To a THF (90 mL) solution of S10 (3.75 g, 11.09 mmol) was dropwise added DIBAL-H (1.0 mol/L in toluene, 44.4 mL, 44.4 mmol) at $-80$ °C. After 15 min stirring of the resulting mixture, this was allowed to rt for 5 min. The mixture was partitioned between 0.5 N HCl and Ac OEt. The organic layer was filtrated through a celite pad then the filtrate was evaporated. This gave a crude aldehyde, which was used to the next step without further purification. An MeCN (90 mL) solution of the aldehyde was treated with Ph$_3$P=CHCO$_2$Me (11.1 g, 33.3 mmol). The resulting suspension was stirred at rt for 15 h. This was partitioned between brine and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 4/1) of the organic layer gave S11 (2.07 g, 56%) as an oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.78 (d, $J = 4.0$ Hz, 1H), 2.87 (dd, $J = 13.2$ and 10.4 Hz, 1H), 3.16 (dd, $J = 13.2$ and 2.4 Hz, 1H), 3.72 (s, 3H), 3.79-3.82 (m, 1H), 6.25-6.28 (m, 1H), 6.80-6.90 (m, 1H), 7.20-7.24 (m, 3H), 7.44-7.47 (m, 2H), 7.52-7.54 (m, 2H), 7.59-7.63 (m, 1H), 7.97-7.99 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 29.3, 52.2, 71.7 (t, $J_{C,F} = 30.6$ Hz), 118.8 (t, $J_{C,F} = 245.5$ Hz), 126.4 (t, $J_{C,F} = 8.4$ Hz), 127.9, 128.1, 129.4, 133.3, 136.6 (t, $J_{C,F} = 26.4$ Hz), 165.2. HRFAB-MS (m/z) 336.0089 (M$^+$+H) calcd for C$_{13}$H$_{14}$F$_2$O$_3$Se (M$^+$+H) 336.0076.

Benzoic acid 2,2-difluoro-4-methoxycarbonyl-1-phenylselenomethyl-but-3-enyl ester (5c)
To a CH$_2$Cl$_2$ (20 mL) solution of S11 (623 mg, 1.86 mmol) was added DMAP (228 mg, 1.86 mmol), i-Pr$_2$NEt (648 $\mu$L, 3.72 mmol) and BzCl (326 $\mu$L, 2.79 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 4 h. The mixture was partitioned between aq. saturated NaHCO$_3$ and CH$_2$Cl$_2$. Column chromatography on silica gel (hexane/CH$_2$Cl$_2$ = 9/1) of the organic layer gave 5c (639 mg, 78%) as an oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.20 (dd, $J = 13.6$ and 10.0 Hz, 1H), 3.33 (dd, $J = 13.6$ and 3.2 Hz, 1H), 3.78 (s, 3H), 5.63-5.68 (m, 1H), 6.36 (d, $J = 15.6$ Hz, 1H), 6.81-6.91 (m, 1H), 7.23-7.24 (m, 3H), 7.44-7.47 (m, 2H), 7.52-7.54 (m, 2H), 7.59-7.63 (m, 1H), 7.97-7.99 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 26.6, 52.2, 72.5 (t, $J_{C,F} = 29.8$ Hz), 117.9 (dd, $J_{C,F} = 245.6$ and 243.2 Hz), 126.9 (t, $J_{C,F} = 8.3$ Hz), 127.8, 128.6, 128.7, 129.2, 129.9, 133.5, 133.7, 136.0 (t, $J_{C,F} = 25.0$ Hz), 164.9, 164.9. HRFAB-MS (m/z) 440.0353 (M$^+$+H) calcd for C$_{20}$H$_{18}$F$_2$O$_4$Se (M$^+$+H) 440.0338.

6. Radical reaction of 5c

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{PhSe} \\
\text{F} & \quad \text{O} \\
\text{F} & \quad \text{MeO}_2\text{C} \\
\text{Bu}_3\text{SnH} & \quad \text{AIBN} \\
\text{toluene} & \quad \text{reflux}
\end{align*}
\]

\[
\begin{align*}
\text{cis-6a} & \quad \text{trans-6a} \\
\text{MeO}_2\text{C} & \quad \text{Me} \\
\text{F} & \quad \text{F} \\
\text{O} & \quad \text{OMe} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Compound 5c (220 mg, 0.5 mmol) was treated by the procedure described for the reaction of 5a. Column chromatography on silica gel (hexane/Et₂O = 9/1) gave an inseparable mixture of 7c and 8 (27 mg, 12% and 7% respectively, calculated by integration of 1H NMR) and a mixture of 6a (hexane/Et₂O = 5/1). This was purified by preparative TLC (hexane/AcOEt = 20/1, 7 times evolution). This gave cis-6a (60 mg, 48%, oil) and trans-6a (31 mg, 24%, oil) respectively.

**Physical data for trans-6a:**
- 1H NMR (400 MHz, CDCl₃) δ 2.05-2.14 (m, 1H), 2.19-2.29 (m, 1H), 2.46 (dd, J = 16.8 and 8.8 Hz, 1H), 2.65-2.72 (m, 1H), 3.65 (s, 3H), 5.40-5.48 (m, 1H), 7.34-7.41 (m, 2H), 7.51-7.55 (m, 1H), 8.00-8.02 (m, 2H);
- 13C NMR (125 MHz, CDCl₃) δ 26.0 (dd, Jₐₙ = 10.9 and 4.9 Hz), 33.0 (d, Jₐₙ = 22.8 Hz), 52.2, 72.2 (dd, Jₐₙ = 30.0 and 19.1 Hz), 119.2 (t, Jₐₙ = 289.6 Hz), 128.5, 129.0, 129.9, 133.4, 165.2, 171.3. HRFAB-MS (m/z) 285.0961 (M⁺+H) calcd for C₁₄H₁₅F₂O₄ (M⁺+H) 285.0938.

**Physical data for 7c and 8:**
- 1H NMR (400 MHz, CDCl₃) δ 1.38 (d, J = 6.4 Hz, 3H), 3.77 (s, 4.8H), 5.33-5.40 (m, 1H), 5.46 (dd, J = 3.2 and 1.2 Hz, 0.6H), 5.59 (d, J = 3.2 Hz, 0.6H), 6.28-6.38 (m, 1.6H), 6.79-6.91 (m, 1.6H), 7.37-7.49 (m, 3.2H), 7.56-7.63 (m, 1.6H), 8.00-8.07 (m, 3.2H);
- 13C NMR for 7c (125 MHz, CDCl₃) δ 13.7, 52.2, 70.4 (t, Jₐₙ = 31.0 Hz), 118.3 (t, Jₐₙ = 242.0 Hz), 126.7 (t, Jₐₙ = 8.4 Hz), 128.5, 129.8, 130.2, 133.6, 136.4 (t, Jₐₙ = 25.1 Hz), 165.1;
- 13C NMR for 8 (125 MHz, CDCl₃) δ 52.2, 107.2 (t, Jₐₙ = 3.6 Hz), 114.2 (t, 232.3 Hz), 126.3 (t, Jₐₙ = 8.3 Hz), 128.8, 129.2, 129.9, 134.0, 137.1 (t, Jₐₙ = 28.6 Hz), 146.3 (t, Jₐₙ = 29.8 Hz), 165.0. FAB-MS (m/z) 285 (M⁺+H) for 7c, 263 (M⁺+H-F) for 8.

7. Preparation of 5d

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{PhSe} \\
\text{F} & \quad \text{OH} \\
\text{MeO}_2\text{C} & \quad \text{PhSe}
\end{align*}
\]

\[
\begin{align*}
\text{TBSCI} & \quad \text{imidazole} \\
\text{DMF} & \quad \text{S11}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{PhSe} \\
\text{F} & \quad \text{OH} \\
\text{MeO}_2\text{C} & \quad \text{PhSe}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{PhSe} \\
\text{F} & \quad \text{OTBS} \\
\text{MeO}_2\text{C} & \quad \text{PhSe}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{O} & \quad \text{O}
\end{align*}
\]

5-(tert-Butyldimethylsiloxy)-4,4-difluoro-6-phenylseleno-hex-2-enoic acid methyl ester (5d)

To a DMF (6 mL) solution of S11 (373 mg, 1.11 mmol) was added imidazole (302 mg, 4.44 mmol) and TBSCI (335 mg, 2.22 mmol). The resulting solution was stirred at rt for 4 days. The mixture was partitioned between aq. saturated NaHCO₃ and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 11/1) of the organic layer gave 5d (260 mg, 52%) as an oil: 1H NMR (400 MHz,
CDCl₃ δ −0.06 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 2.71 (dd, J = 12.4 and 4.8 Hz, 1H), 2.98 (dt, J = 12.4 and 2.8 Hz, 1H), 3.66 (s, 3H), 3.94-4.01 (m, 1H), 6.17 (dq, J = 16.0 and 1.2 Hz, 1H), 6.75 (dd, J = 16.0, 14.8 and 9.6 Hz, 1H), 7.09-7.15 (m, 3H), 7.31-7.34 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −4.7, −4.4, 18.2, 25.8, 29.5 (d, J_C,F = 6.0 Hz), 52.2, 74.5 (dd, J_C,F = 32.2 and 27.4 Hz), 119.4 (t, J_C,F = 244.4 Hz), 126.3 (t, J_C,F = 7.2 Hz), 127.1, 129.2, 130.1, 132.4, 136.4 (t, J_C,F = 25.0 Hz), 165.3. HRFAB-MS (m/z) 451.0967 (M⁺+H) calcd for C₁₉H₂₉F₂O₃SiSe (M⁺+H) 451.1019.

8. Radical reaction of 5d

![Chemical structure of 5d](image1)

Compound 5d (2.17 g, 4.82 mmol) was treated by the procedure described for the reaction of 5a. Column chromatography on silica gel (hexane/Et₂O = 15/1) gave 6d (1.29 g, 91%, ca. 2:1 of inseparable mixture) as an oil:

Physical data for 6d: ¹H NMR (500 MHz, CDCl₃) δ 0.08 (s, 1.5H), 0.09 (s, 3H), 0.10 (s, 1.5H), 0.10 (s, 3H), 0.90 (s, 13.5H), 1.35-1.42 (m, 1H), 1.87-1.90 (m, 1H), 2.35-2.41 (m, 1.5H), 2.48-2.53 (m, 1H), 2.57-2.70 (m, 2.5H), 3.05-3.10 (m, 0.5H); ¹³C NMR (125 MHz, CDCl₃) of cis-6d: δ −5.2, −5.0, 18.1, 25.6, 29.6 (d, J_C,F = 22.8 Hz), 31.8 (d, J_C,F = 7.2 Hz), 35.0 (t, J_C,F = 22.7 Hz), 51.8, 70.4 (dd, J_C,F = 25.0 and 17.9 Hz), 121.2 (dd, J_C,F = 296.9 and 277.8 Hz), 171.8. ¹³C NMR (125 MHz, CDCl₃) of trans-6d: δ −5.2, −5.0, 18.1, 25.6, 29.0 (dd, J_C,F = 14.4 and 3.6 Hz), 33.5 (d, J_C,F = 3.6 Hz), 37.5 (t, J_C,F = 21.5 Hz), 51.8, 71.8 (dd, J_C,F = 27.4 and 19.1 Hz), 120.5 (dd, J_C,F = 290.9 and 286.2 Hz), 171.6. HRFAB-MS (m/z) 295.1537 (M⁺+H) calcd for C₁₃H₂₅F₂O₃Si (M⁺+H) 295.1541.

NOE experiments of 6d: The NOE experiments were carried out as a mixture of two diastereomers.

![Diagram showing NOE experiments](image2)

9. Preparation of 5e

![Chemical structure of S9 and S12](image3)

3,3-Difluoro-1-phenylselenopent-4-en-2-ol (S12)

To a THF (30 mL) solution of S9 (1.25 g, 3.7 mmol) was dropwise added DIBAL-H (1.0 mol/L in toluene, 14.8 mL, 14.8 mmol) at −80 °C. The resulting mixture was allowed to rt for 5 min. This was partitioned between 0.5 N HCl and AcOEt. The organic layer was dried by Na₂SO₄, then through a celite pad. Evaporation of the filtrate gave a crude aldehyde (ca. 1.12 g). This was used for the next step without further purification. To a THF (20 mL) suspension of Ph₃PCH₃Br (4.64 g, 13.0 mmol) was dropwise added t-BuOK (1.0 mol/L in THF, 11.1 mL, 11.1 mmol) at 0 °C. The resulting yellowish
suspension was stirred at rt for 1 h. To the mixture was added above aldehyde in THF (20 mL) at −80 °C. The mixture was stirred further 1 h at rt. The mixture was partitioned between aq. saturated NH₄Cl and AcOEt. Column chromatography on silica gel (hexane/Et₂O = 4/1) gave S12 (757 mg, 74%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 2.67 (d, J = 4.0 Hz, 1H), 2.95 (dd, J = 13.2 and 10.4 Hz, 1H), 3.23 (dd, J = 13.2 and 2.8 Hz, 1H), 3.83-3.92 (m, 1H), 5.56 (d, J = 10.8 Hz, 1H), 5.70-5.75 (m, 1H), 5.94-6.07 (m, 1H), 7.27-7.31 (m, 3H), 7.52-7.56 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 29.4, 71.9 (t, J_C,F = 29.9 Hz), 119.3 (t, J_C,F = 245.4 Hz), 121.5 (t, J_C,F = 9.5 Hz), 127.7, 128.5, 129.4, 129.6 (t, J_C,F = 26.4 Hz), 133.2. HRFAB-MS (m/z) 278.0015 (M⁺+H) calcd for C₁₁H₁₂F₂OSe (M⁺+H) 278.0021.

**Benzoic acid 2,2-difluoro-1-phenylselenomethyl-but-3-enyl ester (5e)**

To a CH₂Cl₂ (25 mL) solution of S12 (680 mg, 2.45 mmol) was treated with BzCl (374 μL, 3.2 mmol), DMAP (601 mg, 4.9 mmol) and i-Pr₂NEt (854 μL, 4.0 mmol). The resulting solution was stirred at 0 °C for 3 h. The mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/AcOEt = 9/1) gave 5e (874 mg, 94%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 3.20 (dd, J = 13.6 and 10.4 Hz, 1H), 3.32 (dd, J = 13.6 and 2.8 Hz, 1H), 5.51 (dd, J = 11.2 and 0.4 Hz, 1H), 5.56-5.64 (m, 1H), 5.69-5.74 (m, 1H), 5.85-5.98 (m, 1H), 7.20-7.22 (m, 3H), 7.40-7.44 (m, 2H), 7.49-7.59 (m, 3H), 7.95-7.97 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 25.7 (t, J_C,F = 35.9 Hz), 72.8 (dd, J_C,F = 33.5 and 30.0 Hz), 118.3 (dd, J_C,F = 247.8 and 244.1 Hz), 122.1 (t, J_C,F = 9.6 Hz), 127.6, 128.4, 129.0, 129.1, 129.2, 129.5 (t, J_C,F = 25.1 Hz), 129.9, 133.4, 133.6, 165.1. HRFAB-MS (m/z) 382.0287 (M⁺+H) calcd for C₁₈H₁₆F₂O₂Se (M⁺+H) 382.0284.

10. Radical reaction of 5e

![Reactions diagram](image)

Compound 5e (529 mg, 1.39 mmol) was treated by the procedure described for the reaction of 5a. Column chromatography on silica gel (hexane/Et₂O = 20/1) gave 7e (227 mg, 72%) as an oil.

**Physical data for 7e** ¹H NMR (400 MHz, CDCl₃) δ 1.44 (d, J = 6.4 Hz, 3H), 5.36-5.44 (m, 1H), 5.56 (d, J = 11.2 Hz, 1H), 5.77 (dt, J = 17.2 and 2.4 Hz, 1H), 5.93-6.06 (m, 1H), 7.44-7.48 (m, 2H), 7.57-7.61 (m, 1H), 8.03-8.06 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.7, 70.6 (t, J_C,F = 31.1 Hz), 118.7 (dd, J_C,F = 245.3 and 242.9 Hz), 121.6 (t, J_C,F = 9.6 Hz), 128.4, 129.0, 129.1, 129.2, 129.5 (t, J_C,F = 25.1 Hz), 129.9, 133.4, 133.6, 165.1. HRFAB-MS (m/z) 226.0827 (M⁺+H) calcd for C₁₂H₁₂F₂O₂ (M⁺+H) 226.0805.

11. Preparation of 5f

![Reaction diagram](image)

3-Hydroxy-N-methoxy-N-methyl-4-(phenylseleno)butyramide (S13)

To a THF (25 mL) solution of diisopropylamine (2.11 mL, 15.1 mmol) was dropwise added BuLi (2.66 mol/L in hexane, 5.7 mL, 15.1 mmol) at −80 °C. The resulting mixture was further stirred for 10 min at same temperature then 10 min at rt. To the mixture was dropwise added AcOEt (1.48 mL, 15.1 mmol) at −80 °C then stirred further 1 h at same temperature. To the resulting lithium enolate solution was
dropwise added S8 (1.5 g, 7.53 mmol) in THF (20 mL) over 3 min. The mixture was stirred at −80 °C for 30 min. The suspension was partitioned between aq. saturated NH4Cl and AcOEt. Evaporation of the organic layer gave a crude ester (ca. 2.12 g) which was used for next step without further purification. To a stirred suspension of N,O-dimethylhydroxylamine hydrochloride (2.13 g, 21.8 mmol) in THF (40 mL) was dropwise added BuLi (2.66 mol/L in hexane, 16.4 mL, 43.7 mmol) at −40 °C. The mixture was stirred at rt for 10 min. To the resulting lithium amide solution was added above ester in THF (15 mL) at −40 °C then stirred for 1 h at same temperature. The mixture was partitioned between aq. saturated NH4Cl and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 1/4) gave S13 (1.29 g, 57% for two steps) as an oil: 1H NMR (400 MHz, CDCl3) δ 2.61-2.67 (m, 1H), 2.81-2.84 (m, 1H), 3.08 (dd, J = 12.8 and 6.4 Hz, 1H), 3.13 (dd, J = 12.8 and 6.4 Hz, 1H), 3.17 (s, 3H), 3.65 (s, 3H), 3.97 (br-d, 1H), 4.19-4.21 (m, 1H), 7.24-7.29 (m, 3H), 7.52-7.55 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 31.7, 34.1, 37.1, 61.1, 67.4, 126.9, 129.0, 129.7, 132.5, 172.9. HRFAB-MS (m/z) 304.0438 (M++H) calcd for C12H18NO3Se (M++H) 304.0452.

5-Hydroxy-6-(phenylseleno)-hex-2-enoic acid methyl ester (S14)
To a CH2Cl2 (30 mL) solution of S13 (1.27 g, 4.2 mmol) was dropwise added DIBAL-H (0.99 mol/L in toluene, 9.3 mL, 9.2 mmol) at −80 °C. After 30 min stirring at same temperature, further DIBAL-H (4.23 mL, 4.2 mmol) then stirred for 1 h. The mixture was partitioned between aq. saturated NH4Cl and CH2Cl2. Evaporation of the organic layer gave a crude aldehyde. This was dissolved in MeCN (40 mL) then treated with Ph3P=CHCO2Me (3.09 g, 9.24 mmol). The resulting suspension was stirred at rt for 24h. After evaporation of all of volatiles, the residue was purified by column chromatography on silica gel (hexane/Et2O = 2/1). This gave S14 (507 mg, 40% for two steps) as an oil: 1H NMR (400 MHz, CDCl3) δ 2.40-2.53 (m, 3H), 2.91 (dd, J = 13.2 and 8.8 Hz, 1H), 3.12 (dd, J = 13.2 and 4.0 Hz, 1H), 3.72 (s, 3H), 3.78-3.84 (m, 1H), 5.88 (dt, J = 15.6 and 1.2 Hz, 1H), 6.94 (dt, J = 15.6 and 7.5 Hz, 1H), 7.27-7.30 (m, 3H), 7.51-7.56 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 36.5, 39.0, 51.5, 68.6, 123.7, 127.6, 128.7, 129.3, 133.3, 144.5, 166.6. HRFAB-MS (m/z) 300.0288 (M++H) calcd for C13H16O3Se (M++H) 300.0265.

Benzoic acid 4-methoxycarbonyl-1-(phenylselenomethyl)-but-3-enyl ester (5f)
To a mixture of S14 (500 mg, 1.67 mmol), DMAP (410 mg, 3.34 mmol) and i-Pr2NEt (580 μL, 3.34 mmol) in CH2Cl2 (17 mL) was added BzCl (254 μL, 2.17 mmol) at 0 °C. After 30 min stirring of the resulting mixture at rt, this was partitioned between aq. saturated NaHCO3 and CH2Cl2. Column chromatography on silica gel (hexane/Et2O = 3/1) gave 5f (575 mg, 85%) as a solid: 1H NMR (400 MHz, CDCl3) δ 2.73-2.83 (m, 1H), 3.15 (dd, J = 12.8 and 6.4 Hz, 1H), 3.27 (dd, J = 12.8 and 6.0 Hz, 1H), 3.71 (s, 3H), 5.31-5.38 (m, 1H), 5.89 (dd, J = 15.6 and 0.8 Hz, 1H), 6.92 (dt, J = 15.6 and 7.2 Hz, 1H), 7.20-7.26 (m, 3H), 7.39-7.45 (m, 1H), 7.53-7.57 (m, 3H), 7.92-7.94 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 30.6, 36.1, 51.5, 72.4, 124.4, 127.4, 128.3, 129.2, 129.7, 132.5, 133.1, 145.0, 165.7, 166.4. HRFAB-MS (m/z) 404.0514 (M++H) calcd for C20H20O4Se (M++H) 404.0527.

12. Radical reaction of 5f

Bu2SnH AlBN
toluene reflux

\[
\begin{align*}
\text{MeO}_2\text{C} &- \text{PhSe}^- & \text{OBz} \\
\text{Bu}_2\text{SnH} & \text{AlBN} & \text{toluene reflux} \\
\text{MeO}_2\text{C} & - \text{Me} & \text{OBz}
\end{align*}
\]

Compound 5f (403 mg, 1.0 mmol) was treated by the procedure described for the reaction of 5a. Column chromatography on silica gel (hexane/Et2O = 3/1) gave 7f and 6f [206 mg, 83%, ca. 1:0.20:0.16 (7f, 61%, 6f, 22% respectively), calculated by integration of 1H NMR] as an inseparable mixture.
Physical data for a mixture of 7f and 6f: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.39 (d, $J$ = 6.4 Hz, 3H), 1.88-1.92 (m, 0.47H), 2.26-2.82 (m, 3.6H), 3.67 (s, 0.6H), 3.68 (s, 0.3H), 3.72 (s, 3H), 5.08-5.15 (m, 0.2H), 5.24-5.35 (m, 1.16H), 5.94 (d, $J$ = 15.6 Hz, 1H), 6.98 (dt, $J$ = 15.6 and 7.2 Hz, 1H), 7.42-7.46 (m, 2.86H), 7.54-7.58 (m, 1.6H), 8.02-8.06 (m, 2.84H); $^{13}$C NMR for 7f (125 MHz, CDCl$_3$) $\delta$ 19.7, 38.5, 51.5, 69.7, 123.9, 128.3, 129.5, 130.3, 132.9, 143.7, 165.6, 166.5. Partial $^{13}$C NMR for 6f (125 MHz, CDCl$_3$) $\delta$ 23.8, 25.6, 34.7, 36.3, 39.9, 40.8, 66.0, 68.8, 172.6, 172.8. FAB-MS ($m/z$) 249 (M$^+$H).

13. Preparation of radical precursor 13

3-Benzylolxy-2-phenylselenenylpropionaldehyde (10)

To a THF (160 mL) solution of 9 (13.66 g, 52.9 mmol) was dropwise added Li-HMDS (1.0 mol/L in THF, 58.2 mL, 58.2 mmol) at $-80^\circ$C over 10 min. The resulting mixture was stirred further 30 min at same temperature. To this was sequentially added freshly distilled BOMCl (8.35 mL, 60.84 mmol) and HMPA (18.4 mL, 105.8 mmol). The mixture was slowly warmed to $-55^\circ$C then stirred further 20 h at same temperature. The mixture was partitioned between aq. saturated NaHCO$_3$ and AcOEt then dried by Na$_2$SO$_4$. After evaporation of all of volatiles of the organic layer, the residue was roughly purified by column chromatography on neutral silica gel (hexane/Et$_2$O = 6/4). This gave crude benzyl ether (14.08 g) as an oil. This benzyl ether was used for the next step without further purification. To a THF (90 mL) solution of above residue was dropwise added DIBAL-H (1.0 mol/L in toluene, 63.5 mL, 63.5 mmol) at $-80^\circ$C. Then the mixture was treated with aq. saturated Rochelle salt (ca. 100 mL) and stirred at rt for 1 h. The resulting mixture was partitioned between brine and Et$_2$O. Column chromatography on neutral silica gel (hexane/Et$_2$O = 3/1) of the organic layer gave an unstable aldehyde 10 (7.9 g, 47% for two steps) as a yellowish oil: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 3.81-3.89 (m, 3H), 4.53 (s, 2H), 7.28-7.55 (m, 10H), 9.49 (d, $J$ = 3.2 Hz, 1H); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) $\delta$ 51.4, 67.5, 73.7, 126.0, 128.1, 128.7, 129.3, 129.7 (2C), 136.3, 138.2, 192.9. HRFAB-MS ($m/z$) 321.0384 (M$^+$H) calcd for C$_{16}$H$_{17}$O$_2$Se (M$^+$H) 321.0394.

5-Benzylolxy-3-(tert-butyldimethylsilanyloxy)-2,2-difluoro-4-phenylselenenyl-pentanoic acid ethyl ester (11)

To a THF (10 mL) suspension of activated zinc (2.52 g) was added TMSCl (342 $\mu$L, 2.7 mmol). The resulting mixture was heated at 60 $^\circ$C. After 15 min stirring of the resulting mixture, THF (50 mL) and BrF$_2$CO$_2$Et (4.93 mL, 38.5 mmol) were sequentially added, then heated at 60$^\circ$C for 5 min. The resulting THF solution which include zinc enolate was quickly transferred via cannula to a THF (50 mL) solution of 10 (6.14 g, 19.23 mmol) which was cooled at 0 $^\circ$C. The resulting mixture was stirred at rt for 2 h. The mixture was partitioned between 0.5 N HCl and AcOEt. Column chromatography (hexane/AcOEt = 3:1) of the organic layer gave a crude alcohol (7.29 g) as an oil. This
was used for the next step without further purification. The crude alcohol was dissolved in DMF (70 mL). This was treated with 2,6-lutidine (7.25 mL, 65.6 mmol) and TBSOTf (7.53 mL, 32.8 mmol). The resulting mixture was stirred at rt for 4 days. This was partitioned between aq. saturated NaHCO₃ and AcOEt, then 0.5 N HCl and AcOEt. Column chromatography on neutral silica gel (hexane/AcOEt = 11/1) of the organic layer gave 11 (8.23 g, 77% for two steps) as a diastereomixture (ca. 5:1). Analytical samples were prepared by preparative TLC (hexane/AcOEt = 40/1, 4 times evolution). This gave major-11 (slow moving) and minor-11 (fast moving) each as an oil.

**Physical data for major-11:** ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 1.25 (dt, J = 7.6 and 0.4 Hz, 3H), 3.63-3.70 (m, 2H), 3.95 (dd, J = 9.6 and 6.8 Hz, 1H), 4.19 (q, 7.6 Hz, 2H), 4.47-4.60 (m, 3H), 7.23-7.35 (m, 8H), 7.54-7.57 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.3, −4.7, 13.8, 18.4, 25.7, 45.6, 63.0, 70.3, 71.6 (t, Jₐₖₛ = 29.9 Hz), 72.3, 77.2, 114.2 (t, Jₐₖₛ = 256.1 Hz), 127.6, 127.7, 127.8, 128.4, 129.1, 134.1, 137.7, 163.3 (t, Jₐₖₛ = 32.3 Hz); ¹⁹F NMR (470 MHz, CDCl₃) δ −111.5 (m). HRFAB-MS (m/z) 558.1531 (M⁺+H) calcd for C₂₆H₃₆F₂O₄SiSe (M⁺+H) 558.1516.

**Physical data for minor-11:** ¹H NMR (400 MHz, CDCl₃) δ 0.08 (s, 3H), 0.15 (s, 3H), 0.93 (s, 9H), 1.31 (t, J = 7.6 Hz, 3H), 3.49-3.56 (m, 2H), 3.77 (t, J = 10.0 Hz, 1H), 4.22-4.40 (m, 3H), 4.49 (d, J = 12.0 Hz, 1H), 4.56 (t, J = 9.2 Hz, 1H), 7.22-7.36 (m, 8H), 7.53-7.57 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.3, −4.7, 13.8, 18.4, 25.7, 45.6, 63.0, 70.3, 71.6 (t, Jₐₖₛ = 29.9 Hz), 72.3, 77.2, 114.2 (t, Jₐₖₛ = 256.1 Hz), 127.6, 127.7, 127.8, 128.4, 129.1, 134.2, 137.7, 163.3 (t, Jₐₖₛ = 32.4 Hz); ¹⁹F NMR (470 MHz, CDCl₃) δ −111.1 (d, J = 263.4 Hz), −114.8 (d, J = 263.4 Hz). HRFAB-MS (m/z) 558.1531 (M⁺+H) calcd for C₂₆H₃₆F₂O₄SiSe (M⁺+H) 558.1516.

5-Benzylx-o-(tert-butyldimethylsilyloxy)-2,2-difluoro-4-phenylselenenyl-pentanoic acid methyl amide (12) To a THF (80 mL) suspension of N, O-dimethylhydroxylamine hydrochloride (4.05 g, 41.57 mmol, previously dried by P₂O₅ under vacuum condition for 2 days) was added a THF (50 mL) solution of 11 (7.73 g, 13.86 mmol, ca. 5:1 mixture of two stereoisomers) via cannula. The mixture was stirred at same temperature for 24 h. Then the mixture was partitioned between aq. saturated NH₄Cl and AcOEt. Column chromatography on neutral silica gel (hexane/Et₂O = 11/1) of the organic layer gave 11 (7.0 g, 12.2 mmol, ca. 5:1 mixture of two stereoisomers) as a 5:1 mixture of two stereoisomers). Analytical samples were prepared by preparative TLC (hexane/AcOEt = 8/1, five times evolution). This gave major-12 (slow moving) and minor-12 (fast moving) each as an oil.

**Physical data for major-12:** ¹H NMR (400 MHz, CDCl₃) δ −0.08 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 2.98 (s, 3H), 3.39 (s, 3H), 3.52-3.59 (m, 2H), 3.88-3.89 (m, 1H), 4.36 (d, J = 15.2 Hz, 1H), 4.43 (d, J = 15.2 Hz, 1H), 4.56-4.63 (m, 1H), 7.10-7.29 (m, 8H), 7.44-7.46 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.0, −4.3, 18.4, 25.8, 33.1, 45.5, 61.7, 68.9, 72.9, 74.1 (t, Jₐₖₛ = 22.7 Hz), 116.3 (t, Jₐₖₛ = 256.4 Hz), 127.4, 127.6, 127.8, 128.2, 129.1, 129.6, 134.8, 138.2, 162.9 (t, Jₐₖₛ = 28.6 Hz); ¹⁹F NMR (470 MHz, CDCl₃) δ −108.4 (d, J = 254.3 Hz), −114.1 (d, J = 254.3 Hz). HRFAB-MS (m/z) 574.1683 (M⁺+H) calcd for C₂₆H₃₆F₂O₄SiSe (M⁺+H) 574.1703.

**Physical data for minor-12:** ¹H NMR (400 MHz, CDCl₃) δ −0.04 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 3.09 (br-s, 3H), 3.42-3.45 (m, 2H), 3.61 (s, 3H), 3.68-3.73 (m, 1H), 4.24 (d, J = 12.0 Hz, 1H), 3.70 (d, J = 12.0 Hz, 1H) 4.74 (dd, J = 15.2 and 9.6 Hz, 1H), 7.12-7.25 (m, 8H), 7.48-7.50 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.2, −4.6, 18.4, 28.8, 33.4, 45.5, 61.8, 70.5, 70.5 (t, Jₐₖₛ = 28.6 Hz), 72.2, 116.3 (t, Jₐₖₛ = 254.0 Hz), 127.4, 127.5, 127.6, 127.7, 128.2, 129.0, 134.5, 138.9, 162.9 (t, Jₐₖₛ = 28.6 Hz); ¹⁹F NMR (470 MHz, CDCl₃) δ −110.6 (d, J = 254.3 Hz), −114.4 (d, J = 254.3 Hz). HRFAB-MS (m/z) 574.1683 (M⁺+H) calcd for C₂₆H₃₆F₂O₄SiSe (M⁺+H) 574.1703.

7-Benzylx-o-(tert-butyldimethylsilyloxy)-4,4-difluoro-6-phenylselenenyl-hept-2-enoic acid methyl ester (13) To a stirred solution of 12 (7.0 g, 12.2 mmol, ca. 5:1 mixture of two stereoisomers) in THF (100 mL) was dropwise added Dibal-H (1.0 mol/L in toluene, 36.7 mL, 36.7 mmol) at −80 °C.
The resulting mixture was stirred for 15 min at rt. The mixture was partitioned between 0.5 N HCl and AcOEt. The organic layer was dried by Na₂SO₄, then filtrated through a celite pad. The filtrate was evaporated. The crude aldehyde was dissolved in MeCN (100 mL), then treated with Ph₃P=CHCO₂Me (12.26 g, 36.7 mmol). The resulting mixture was stirred at rt for 14 h. This was partitioned between brine and AcOEt. Column chromatography on silica gel (hexane/Et₂O = 4/1) of the organic layer gave 13 (6.45 g, 93% for two steps as a diastereomixture, major-(E)-13:(Z)-13:minor-(E)-13 = 1.0:0.14:0.22 calculated by integration of ¹H NMR). Analytical samples were prepared by preparative TLC (hexane/AcOEt = 50/1, seven times evolution). This gave major-(E)-13, (Z)-13 and minor-(E)-13 respectively each as an oil.

Physical data for major-(E)-13: ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 3.59-3.67 (m, 2H), 3.75 (s, 3H), 3.89 (dd, J = 10.0 and 5.6 Hz, 1H), 4.34 (dd, J = 12.8, 7.2 and 1.6 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 6.23 (dt, J = 16.0 and 1.6 Hz, 1H), 6.89 (dd, J = 16.0, 13.6 and 11.2 Hz, 1H), 7.24-7.34 (m, 8H), 7.52-7.54 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −4.8, −4.7, 18.3, 25.8, 45.4 (d, J_{C,F} = 3.6 Hz), 52.1, 69.2, 73.0, 76.4 (t, J_{C,F} = 29.8 Hz), 119.3 (t, J_{C,F} = 245.6 Hz), 125.6 (t, J_{C,F} = 8.4 Hz), 127.6, 127.6, 127.7, 128.3, 129.2, 129.7, 134.2, 137.3 (t, J_{C,F} = 25.1 Hz), 137.9, 165.3; ¹⁹F NMR (470 MHz, CDCl₃) δ −101.3 (d, J = 254.3 Hz), −107.4 (d, J = 254.3 Hz). HRFAB-MS (m/z) 570.1523 (M⁺+H) calcd for C₂₇H₃₆F₂O₄SiSe (M⁺+H) 570.1516.

Physical data for (Z)-13: ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 3.62-3.72 (m, 2H), 3.66 (s, 3H), 4.02 (dd, J = 10.0 and 6.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.66-4.72 (m, 1H), 5.97 (d, J = 12.4 Hz, 1H), 6.02 (dt, J = 24.8 and 12.4 Hz, 1H), 7.23-7.32 (m, 8H), 7.53-7.56 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −4.7, −4.6, 18.4, 25.9, 46.4, 52.0, 69.2, 73.0, 76.4 (t, J_{C,F} = 247.8 Hz), 127.5, 127.6, 127.8, 128.3, 129.1, 130.0, 133.7 (t, J_{C,F} = 27.5 Hz), 134.1, 138.1, 165.0; ¹⁹F NMR (470 MHz, CDCl₃) δ −100.5 (d, J = 245.2 Hz), −101.7 (dd, J = 245.2 and 18.2 Hz). HRFAB-MS (m/z) 570.1485 (M⁺+H) calcd for C₂₇H₃₆F₂O₄SiSe (M⁺+H) 570.1516.

Physical data for minor-(E)-13: ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 3.35-3.38 (m, 1H), 3.62 (dd, J = 10.0 and 1.6 Hz, 1H), 3.76-3.81 (m, 1H), 3.78 (s, 3H), 4.42 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.56 (dd, J = 12.4 and 4.4 Hz, 1H), 6.26 (dt, J = 16.0 and 1.6 Hz, 1H), 7.16-7.35 (m, 9H), 7.39-7.41 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ −5.3, −4.5, 18.3, 25.8, 29.7, 45.9 (d, J_{C,F} = 6.0 Hz), 52.0, 70.6, 72.5, 73.0 (dd, J_{C,F} = 34.6 and 28.6 Hz), 119.6 (t, J_{C,F} = 243.2 Hz), 124.1 (t, J_{C,F} = 8.3 Hz), 127.4, 127.8, 128.8, 128.4, 129.1, 129.7, 133.4, 137.4 (t, J_{C,F} = 23.9 Hz), 137.6, 165.6; ¹⁹F NMR (470 MHz, CDCl₃) δ −99.4 (d, J = 254.3 Hz), −108.8 (d, J = 254.3 Hz). HRFAB-MS (m/z) 570.1568 (M⁺+H) calcd for C₂₇H₃₆F₂O₄SiSe (M⁺+H) 570.1516.

14-1. Radical cyclization of 13: Transformation to [4-Benzoyloxymethyl-3-(tert-butyldimethylsiloxy)-2,2-difluorocyclobutyl]-acetic acid methyl ester (14) (Table 2, entry 5)

To a benzene (230 mL) solution of 13 (6.52 g, 11.45 mmol, 1.0:0.14:0.22 of diastereomeric mixture) and freshly opened Et3B (1.0 mol/L in THF, 5.73 mL, 5.73 mmol) was dropwise added Bu3SnH (6.16 mL, 22.9 mmol) over 24 h using motor driven syringe at rt. When half volume of Bu3SnH was transferred to the reaction mixture (ca. 12 h), further Et3B (5.73 mL, 5.73 mmol) was added then continued to stir further 12 h at rt. After evaporation of all of volatiles, the residue was purified by column chromatography on silica gel (hexane/Et2O = 4/1). This gave 14 (3.71 g, 78%, oil) as a diastereomeric mixture (trans, trans-14/trans, cis-14 = ca. 2.6:1 based on the integration of 1H NMR):

**1H NMR (500 MHz, CDCl3)**

\[ \delta_{0.06} (s, 1.16H), 0.07 (s, 3H), 0.08 (s, 1.16H), 0.09 (s, 3H), 0.88 (s, 3.47H), 0.89 (s, 9H), 1.86-1.90 (m, 1H), 2.39-2.49 (m, 0.39H), 2.48-2.70 (m, 3.77H), 3.13-3.21 (m, 0.39H), 3.53-3.62 (m, 2.77H), 3.63 (s, 1.16H), 3.64 (s, 3H), 4.22-4.28 (m, 1H), 4.31-4.36 (m, 0.39H), 4.43 (d, \text{J} = 12.1 \text{ Hz}, 0.39H), 4.48 (d, \text{J} = 12.1 \text{ Hz}, 0.39H), 4.51 (d, \text{J} = 12.0 \text{ Hz}, 1H), 4.54 (d, \text{J} = 12.0 \text{ Hz}, 1H), 7.27-7.36 (m, 6.95H);**

**13C NMR (125 MHz, CDCl3)**

\[ \delta_{-5.2}, -5.1, 18.1, 25.6, 31.4 (d, \text{J}_{C,F} = 15.5 \text{ Hz}), 39.0 (d, \text{J}_{C,F} = 21.5 \text{ Hz}), 51.6, 66.9 (d, \text{J}_{C,F} = 2.4 \text{ Hz}), 71.8 (dd, \text{J}_{C,F} = 29.39 \text{ and } 282.0 \text{ Hz}), 73.3, 119.9 (dd, \text{J}_{C,F} = 297.5 \text{ and } 177.1 \text{ Hz}), 127.5, 127.6, 128.4, 138.1, 171.8.\]

**13C NMR (125 MHz, CDCl3)**

\[ \delta_{-5.5}, -5.1, 18.2, 25.6, 29.6, 39.0 (d, \text{J}_{C,F} = 15.5 \text{ Hz}), 39.2 (t, \text{J}_{C,F} = 21.5 \text{ Hz}), 51.6, 66.9 (d, \text{J}_{C,F} = 2.4 \text{ Hz}), 72.8 (dd, \text{J}_{C,F} = 26.4 \text{ and } 20.4 \text{ Hz}), 73.3, 120.0 (dd, \text{J}_{C,F} = 293.9 \text{ and } 282.0 \text{ Hz}), 127.2, 127.8, 128.3, 137.8, 172.1;**

**19F NMR (470 MHz, CDCl3)**

\[ \delta_{-103.7} (d, \text{J} = 199.8 \text{ Hz}), -117.4 (d, \text{J} = 199.8 \text{ Hz}).\]

HRFAB-MS (m/z) 415.2130 (M++H) calcd for C21H33F2O4Si (M++H) 415.2116.

**NOE experiments of 14:** The NOE experiments were carried out as a mixture of two diastereomers.

14-2. Radical reaction of major-(E)-13

Compound major-(E)-13 (219 mg, 0.38 mmol) was treated with a same procedure described for 13. This gave a mixture of 14 (112 mg, 71%, trans-14/cis-14 = ca. 2.6:1 based on the integration of 1H NMR).

14-3. Radical reaction of (Z)-13

Compound (Z)-13 (106 mg, 0.19 mmol) was treated with a same procedure described for 13. This gave a mixture of 14 (49 mg, 64%, trans,trans-14/trans, cis-14 = ca. 1:1 based on the integration of 1H NMR).
1. Synthesis of 4

15. Synthesis of 4

3-Benzylxomethyl-2-tert-butyldimethylsiloxy-1,1-difluoro-4-(phenylseleno)ethylcyclobutane (15)

To a stirred solution of 14 [3.5 g, 8.44 mmol, diasteromeric mixture (ca. 2.6:1)] in CH2Cl2 (85 mL) was dropwise added DIBAL-H (1.0 mol/L in toluene, 33.8 mL, 33.8 mmol) at −80 °C. The resulting mixture was stirred further 20 min at rt. The mixture was partitioned between 0.5 N HCl and CH2Cl2. Evaporation of all of volatiles of the organic layer gave a crude alcohol (ca. 3.3 g). This was used for next step without further purification. To a THF (85 mL) solution of above alcohol was added PhSeCN (2.07 mL, 16.9 mmol) and Bu3P (4.22 mL, 16.9 mmol) at 0 °C. The resulting mixture was further stirred for 16 h at same temperature. This was partitioned between aq. saturated NaHCO3 and AcOEt. Column chromatography on neutral silica gel (hexane/Et2O = 7/1) of the organic layer gave a mixture of 15 (4.32 g, 97% for two steps, ca. 3:1 of diastereomeric mixture). Analytical samples were prepared by preparative TLC (hexane/ACOEt = 50/1, four times evolution). This gave major-15 (fast moving) and minor-15 (slow moving) respectively each as an oil.

**Physical data for major-15:** 1H NMR (400 MHz, CDCl3) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.79-1.89 (m, 2H), 1.97-2.06 (m, 1H), 2.31-2.39 (m, 1H), 2.84 (ddd, J = 12.0, 8.8 and 6.4 Hz, 1H), 2.94 (ddd, J = 12.0, 9.2 and 6.4 Hz, 1H), 3.52 (d, J = 4.4 Hz, 2H), 4.12-4.18 (m, 1H), 4.49-4.51 (m, 2H), 7.23-7.36 (m, 8H), 7.45-7.48 (m, 2H); 13C NMR (125 MHz, CDCl3) δ −5.2, −5.0, 18.1, 25.0, 25.6, 27.3 (d, JCF = 4.8 Hz), 41.2, (t, JCF = 20.3 Hz), 42.6 (d, JCF = 23.4 Hz), 68.5, 71.6 (dd, JCF = 23.8 and 17.9 Hz), 73.1, 120.7 (dd, JCF = 293.3 and 274.2 Hz), 126.9, 127.6, 127.7, 128.4, 129.0, 129.8, 132.6, 138.0; 19F NMR (470 MHz, CDCl3) δ −90.0 (d, J = 199.8 Hz), −137.2 (d, J = 199.8 Hz). HRFAB-MS (m/z) 527.1700 (M+H) calcd for C26H37F2O2SiSe (M+H) 527.1696.

**Physical data for minor-15:** 1H NMR (400 MHz, CDCl3) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.79-1.96 (m, 2H), 2.34-2.43 (m, 1H), 2.75-2.80 (m, 1H), 2.85 (dd, J = 12.0, 10.0 and 6.4 Hz, 1H), 2.94 (dd, J = 12.0, 10.4 and 5.2 Hz, 1H), 3.48 (t, J = 10.0 Hz, 1H), 3.53 (dd, J = 10.0 and 4.8 Hz, 1H), 4.13-4.20 (m, 1H), 4.43 (t, J = 12.4 Hz, 2H), 7.23-7.34 (m, 8H), 7.46-7.48 (m, 2H); 13C NMR (125 MHz, CDCl3) δ −5.2, −5.0, 18.1, 25.0, 25.6, 29.7, 39.3 (d, JCF = 17.9 Hz), 43.0 (t, JCF = 20.3 Hz), 67.3 (d, JCF = 3.6 Hz), 73.2, 73.6 (dd, JCF = 27.4 and 20.3 Hz), 120.6 (dd, JCF = 293.3 and 281.4 Hz), 126.8, 127.7, 127.8, 128.4, 129.0, 129.9, 132.5, 137.8; 19F NMR (470 MHz, CDCl3) δ −104.6 (d, J = 199.8 Hz), −115.2 (d, J = 199.8 Hz). HRFAB-MS (m/z) 527.1700 (M+H) calcd for C26H37F2O2SiSe (M+H) 527.1696.
3-Benzoyloxymethyl-2-tert-butyldimethylsiloxy-1,1-difluoro-4-vinylcyclobutane (16)

To a CH₂Cl₂ (80 mL) solution of 15 (4.2 g, 7.99 mmol, ca. 2.6:1 of diastereomeric mixture) was treated with m-CPBA (70%, 1.99 g, 8.07 mmol) at 0 °C. The resulting mixture was stirred for 10 min at same temperature, then added Et₃N (5.58 mL, 40 mmol). The mixture was refluxed for 20 h. The mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/ Et₂O = 60/1) of the organic layer gave an inseparable mixture of 16 (2.52 g, 86% for two steps, 2.6:1) as oil. Analytical sample was prepared by preparative TLC (hexane/AcOEt = 40/1, ca. 2:1 mixture): ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, 4.5H), 0.10 (s, 4.5H), 0.90 (s, 13.5H), 2.02-2.09 (m, 1H), 2.45-2.49 (m, 0.5H), 2.79-2.88 (m, 1H), 3.30-3.34 (m, 0.5H), 3.49-3.62 (m, 3H), 4.23-4.30 (m, 1H), 4.47-4.55 (m, 3H), 5.15-5.21 (m, 3H), 5.75 (dt, J = 16.4 and 9.6 Hz, 0.5H), 5.84 (ddd, J = 17.2, 10.4 and 7.6 Hz, 1H), 7.27-7.37 (m, 7.5H); ¹³C NMR for major-16 (125 MHz, CDCl₃) δ −5.2, −5.0, 18.1, 25.6, 42.4 (d, J_C,F = 23.9 Hz), 44.4 (dd, J_C,F = 22.7 and 19.1 Hz), 67.0 (d, J_C,F = 2.4 Hz), 71.4 (dd, J_C,F = 23.9 and 17.9 Hz), 73.0, 118.9, 120.1 (dd, J_C,F = 296.3 and 274.8 Hz), 127.5, 127.6, 128.4, 130.7 (d, J_C,F = 199.8 Hz), 104.6 (d, J = 190.7 Hz), 130.8 (d, J = 190.7 Hz); ¹³C NMR for minor-16 (125 MHz, CDCl₃) δ −5.2, −5.0, 18.1, 25.6, 40.7 (d, J_C,F = 19.9 Hz), 48.0 (t, J_C,F = 21.5Hz), 67.4 (d, J_C,F = 3.6 Hz), 73.1, 73.6 (dd, J_C,F = 26.2 and 19.1 Hz), 119.7 (dd, J_C,F = 294.5 and 281.4 Hz), 120.2, 127.6, 127.8, 128.3, 130.0 (t, J_C,F = 3.6 Hz), 138.1; ¹⁹F NMR for minor-16 (470 MHz, CDCl₃) δ −100.2 (d, J = 199.8 Hz), −118.0 (d, J = 199.8 Hz). HRFAB-MS (m/z) 369.2086 (M⁺+H) calcd for C₂₀H₂₅F₂O₃Si (M⁺+H) 369.2061.

3,4-Bis-benzyloxymethyl-2,2-difluorocyclobutanol (17)

To a mixture of 16 (2.7 g, 7.35 mmol, ca. 2.6:1 of diastereomeric mixture), NaIO₄ (12.56 g, 58.8 mmol) and 2,6-lutidine (1.63 mL, 14.7 mmol) in 1,4-dioxane/H₂O (3/1, 200 mL) was added OsO₄ (0.16 mol/L in THF, 16.2 mL, 16.2 mmol). After 14 h stirring of the resulting mixture at rt, the mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/Et₂O = 60/1) of the organic layer gave an inseparable mixture of 17 (2.52 g, 86% for two steps, 2.6:1 of diastereomeric mixture), NaIO₄ (12.56 g, 58.8 mmol) and 2,6-lutidine (1.63 mL, 14.7 mmol) in 1,4-dioxane/H₂O (3/1, 200 mL) was added OsO₄ (0.16 mol/L in H₂O, 938 µL, 0.15 mmol). The resulting suspension was stirred at rt for 7 h. After filtration of the mixture through a celite pad, the filtrate was evaporated below 30 °C until half volume of the volatiles were removed. To the residue was added MeOH (100 mL) and NaBH₄ (2.78 g, 73.5 mmol) at 0 °C. The mixture was stirred further 30 min at same temperature, then added acetone (3 mL). The mixture was filtered through a celite pad, then the filtrate was evaporated. The residue was partitioned between 1 N HCl and CH₂Cl₂. Flash column chromatography on silica gel (hexane/AcOEt = 1/1) of the organic layer gave crude alcohol (ca. 2.25 g). This was used for next step without further purification. To an anhydrous THF (30 mL) solution of above alcohol was added NaH (60%, 294 mg, 7.35 mmol) at 0 °C. After 20 min stirring of the resulting mixture, this was treated with BnBr (1.05 mL, 8.82 mmol) and Bu₄NI (2.71 g, 7.35 mmol). The mixture was stirred further 6 h at rt. Then, this was partitioned between aq. saturated NH₄Cl and AcOEt. After evaporation of all of volatiles of the organic layer, this was dissolved in THF (50 mL), then added AcOH (1.26 mL, 22.05 mmol) and Bu₄NF (1.0 mol/L in THF, 16.2 mL, 16.2 mmol). After 14 h stirring of the resulting mixture at rt, the mixture was partitioned between aq. saturated NaHCO₃ and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 1/1) of the organic layer gave an inseparable mixture of 17 (1.66 g, 65% for four steps, ca. 3.0:1) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 1.86-1.93 (m, 1H), 2.05 (br-s, 1.3H), 2.39-2.42 (m, 0.3H), 2.56-2.68 (m, 1H), 2.90-2.92 (m, 0.3H), 3.55 (dd, J = 9.6 and 4.8 Hz, 1H), 3.59-3.64 (m, 2.6H), 3.67-3.77 (m, 1.6H), 4.20-4.27 (m, 1H), 4.34-4.41 (m, 0.3H), 4.43-4.57 (m, 5.2H), 7.28-7.37 (m, 1.3H); ¹³C NMR for major-17 (125 MHz, CDCl₃) δ 40.7 (d, J_C,F = 20.3 Hz), 41.9 (t, J_C,F = 20.3 Hz), 66.0 (d, J_C,F = 6.0 Hz), 68.6 (d, J_C,F = 2.4 Hz), 72.3 (dd, J_C,F = 25.0 and 19.1 Hz), 73.0, 73.1, 119.9 (dd, J_C,F = 295.7 and 271.9 Hz), 127.5, 127.6, 127.7, 127.8, 128.4, 128.4, 137.3, 138.0; ¹⁹F NMR for major-17 (470 MHz, CDCl₃) δ −92.7 (d, J = 199.8 Hz), −91.4 (d, J = 199.8 Hz), −136.0 (d, J = 190.7 Hz); ¹³C NMR for minor-17 (125 MHz, CDCl₃) δ −39.9 (d, J_C,F = 17.9 Hz), 43.1 (t, J_C,F = 20.3 Hz), 64.8, 67.6 (d, J_C,F = 3.6 Hz), 73.2, 73.3, 74.3 (dd, J_C,F = 25.1 and 19.1 Hz), 120.1 (dd, J_C,F = 287.4 and 270.7 Hz), 127.6, 127.7, 127.8, 128.4, 128.5, 137.8, 137.9; ¹⁹F NMR for minor-17 (470 MHz, CDCl₃) δ −104.6 (d, J = 199.8 Hz), −120.1 (d, J = 199.8 Hz). HRFAB-MS (m/z) 349.1613 (M⁺+H) calcd for C₂₀H₂₃F₂O₃ (M⁺+H) 349.1615.
To a CH₂Cl₂ (20 mL) solution of 17 (700 mg, 2.01 mmol, ca. 3:1) was added Dess-Martin periodinane (1.45 g, 3.42 mmol). The resulting mixture was stirred for 1 h at rt. To the mixture was added brine (50 mL) then stirred further 20 min. The mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. Evaporation of all of volatiles of the organic layer gave a crude aldehyde (ca. 950 mg). The aldehyde was dissolved in pyridine (30 mL). The pyridine solution was treated with HONH₂·HCl (1.4 g, 20.1 mmol). The resulting mixture was stirred for 3 days at rt. The resulting mixture was partitioned between NaHCO₃ and CH₂Cl₂. Flush column chromatography on silica gel (hexane/AcOEt = 1/1) gave a crude oxime (589 mg). This was well dried under vacuum condition by using P₂O₅ for 20 h. This was used for next reaction without further purification. To a THF (20 mL) solution of above oxime was dropwise added LiAlH₄ (1.0 mol/L in THF, 4.02 mL, 4.02 mmol) at −40 ℃. After 30 min stirring of the resulting mixture, this was stirred further 2 h at rt. The mixture was carefully treated with H₂O (6 mL), aq. 15% NaOH (6 mL) and H₂O (6 mL) sequentially. After filtration of the mixture through a celite pad, the filtrate was partitioned between brine and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 1/3) of the organic layer gave 18 (220 mg, 32% for three steps) as an oil: 1H NMR (400 MHz, CDCl₃) δ 1.55 (br-s, 2H), 1.62-1.69 (m, 1H), 2.62-2.75 (m, 1H), 3.49 (dt, J = 11.6 and 8.4 Hz, 1H), 3.56 (dd, J = 9.8 and 4.8 Hz, 1H), 3.60 (dd, J = 9.8 and 4.8 Hz, 1H), 3.63-3.67 (m, 2H), 4.49 (d, J = 12.0 Hz, 1H), 4.53 (s, 2H), 4.54 (d, J = 12.0 Hz, 1H), 7.26-7.35 (m, 10J); 13C NMR (125 MHz, CDCl₃) δ 40.1 (d, J_C,F = 20.4 Hz), 43.4 (t, J_C,F = 20.4 Hz), 56.5 (t, J_C,F = 22.8 Hz), 66.3 (d, J_C,F = 7.3 Hz), 69.0 (d, J_C,F = 2.4 Hz), 73.0, 73.1, 120.8 (dd, J_C,F = 300.4 and 271.6 Hz), 127.5, 127.6, 127.6, 128.3, 128.4, 138.1, 138.2; 19F NMR (470 MHz, CDCl₃) δ −91.8 (d, J = 190.7 Hz), −136.7 (dd, J = 190.7 and 18.2 Hz). HRFAB-MS (m/z) 348.1786 (M++H) calcd for C₂₀H₂₄F₂NO₂ (M++H) 348.1775.

NOE experiments of 18

(±)-3,4-3,4-Bis(hydroxymethyl)-1,1-difluorocyclobut-r-2-ylamine (4)
To a CH₂Cl₂ (2.7 mL) solution of β-methoxy-α-metacrylic acid 6 (208 mg, 1.79 mmol) was added oxalyl chloride (172 μL, 1.97 mmol) and DMF (one drop) at rt. The resulting mixture was stirred for 40 min at same temperature. After evaporation of all of volatiles, the residue was dissolved in dry benzene (3.5 mL) then added a benzene (3.5 mL) suspension of silver cyanate (295 mg, 1.97 mmol). The mixture was refluxed for 30 min, then cooled to rt. The resulting supernatant solution include isocyanate (19) was slowly transferred over 1.5 min via cannula to a THF (9.3 mL) solution of 18 (207 mg, 0.596 mmol) at −40 ℃. The resulting mixture was stirred for 40 min at same temperature. After warming to rt of the mixture, this was stirred further 2 h at rt. The residue was roughly purified by flush column chromatography on silica gel (hexane/AcOEt = 1/3). This gave a crude adduct, which was used for next reaction without further purification. The above residue was dissolved in EtOH (10 mL), 1,4-dioxane (10 mL) and 29% NH₄OH (20 mL). The resulting solution was heated at 110 ℃ in a shield tube for 15 h. After evaporation of all of volatiles, the residue was dissolved in MeOH (20 mL). This was treated with 20 wt % of Pd(OH)₂ (200 mg) under positive pressure of H₂ (1 atm) at rt for 4 h. After filtration through a celite pad, the filtrate was purified by preparative TLC (CHCl₃/acetone = 1/1). This gave 4 (93 mg, 56% for three steps). This was recrystallized from MeOH/1,2-dichloroethane. Mp = 235-237 ℃; ¹H NMR (500 MHz, CD₃OD) δ 1.90 (s, 3H), 2.60-2.63 (m, 1H), 2.65-2.75 (m, 1H), 3.67;
(dd, J = 11.5 and 4.6 Hz, 1H), 3.71 (dd, J = 11.5 and 4.6 Hz, 1H), 3.76 (dd, J = 11.5 and 5.7 Hz, 1H), 3.85 (dd, J = 11.5 and 8.0 Hz, 1H), 5.10-5.16 (m, 1H), 7.52 (s, 1H); $^{13}$C NMR (125 MHz, CD$_2$OD) δ 12.8, 37.6 (d, $J_{CF}$ = 16.7 Hz), 46.4 (t, $J_{CF}$ = 19.1 Hz), 58.0 (dd, $J_{CF}$ = 25.0 and 17.9 Hz), 59.0 (d, $J_{CF}$ = 7.2 Hz), 61.9, 111.8, 121.9 (dd, $J_{CF}$ = 295.7 and 271.8 Hz), 140.1 (d, $J_{CF}$ = 2.4 Hz), 153.4, 166.7; $^{19}$F NMR (470 MHz, CD$_2$OD) δ −86.4 (d, J = 196.2 Hz), −132.7 (d, J = 196.2 Hz). FAB-MS (m/z) 277 (M$^+$+H) Anal. Calcd for C$_{11}$H$_{14}$F$_2$ N$_2$O$_4$: C, 47.83; H, 5.11; N, 10.14. Found: C, 47.48; H, 5.06; N, 10.02.

NOE experiments of 4


16. Table SI-1. SOMO and LUMO values of model radical intermediates 5c’-5f’

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$^a$Calculations were carried out by using UB3LYP/6-31G.
$^b$Calculations were carried out by using UB3LYP/6-31G ※.
**OTBDPS**

F<sub>2</sub>BrC

EtO

S<sub>2</sub>

**1H NMR (400 MHz, CDCl<sub>3</sub>)**

**13C NMR (125 MHz, CDCl<sub>3</sub>)**

---

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1H NMR (400 MHz, CDCl₃)

13C NMR (MHz, CDCl₃)

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$^1\text{H NMR (400 MHz, CDCl}_3)$

$^{13}\text{C NMR (125 MHz, CDCl}_3)$
$^1$H NMR (400 MHz, CDCl$_3$)

$^{31}$C NMR (125 MHz, CDCl$_3$)

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$^{1}H$ NMR (400 MHz, CD$_2$Cl$_2$)

$^{13}C$ NMR (125 MHz, CD$_2$Cl$_2$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)

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$^1$H NMR (400 MHz, CDCl₃)

$^{13}$C NMR (125 MHz, CDCl₃)
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**1H NMR (400 MHz, CDCl₃)**

![1H NMR spectrum](image1)

**13C NMR (125 MHz, CDCl₃)**

![13C NMR spectrum](image2)
trans-6a

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
6d (2:1 mixture)

$^1$H NMR (500 MHz, CDCl$_3$)

6d (2:1 mixture)

$^{13}$C NMR (125 MHz, CDCl$_3$)
**1H NMR (400 MHz, CDCl₃)**

**13C NMR (125 MHz, CDCl₃)**

--- PREPARING PARAMETERS ---

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$\text{PhSe}^5 \text{e}$

$\text{F} \text{F} \text{OBz}$

$^1\text{H NMR (400 MHz, CDCl}_3)$
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)

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S13

$^1\text{H}$ NMR (400 MHz, CDCl$_3$)

$^{13}\text{C}$ NMR (125 MHz, CDCl$_3$)
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**Acquisition Parameters**

- **File Name**: S00A2521_01A.D
- **Sample ID**: S00A2521_01A
- **Sample Name**: S00A2521_01A
- **Mass**: 125 MHz
- **Chemical Shift (ppm)**: 22.66
- **Resolution (Hz)**: 10.000
- **Signal**: 10000
- **Instrument**: JEOL
- **Software**: ACDLABS

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**1H NMR (400 MHz, CDCl3)**

- **Chemical Structure**: MeO₂C-CH₂-CH₂-Me
- **Assignments**:
  - 6f: MeO₂C
  - 7f: MeO₂C

---

**13C NMR (125 MHz, CDCl3)**

- **Chemical Structure**: MeO₂C-CH₂-CH₂-Me
- **Assignments**:
  - 6f: MeO₂C
  - 7f: MeO₂C

---

**Additional Notes**

- **Additional Information**: Provided for detailed analysis.
- **Synthetic Details**: Further information available in the full manuscript.

---

This page contains diagrams and spectra for compounds 6f and 7f, highlighting their 1H and 13C NMR characteristics in CDCl₃. The spectra indicate the presence of MeO₂C and Me groups, with specific shifts and multiplicities.
**1H NMR (400 MHz, CD$_2$Cl$_2$)**

**13C NMR (125 MHz, CD$_2$Cl$_2$)**

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1H NMR (400 MHz, CDCl₃)

13C NMR (125 MHz, CDCl₃)
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**1H NMR (400 MHz, CDCl₃)**

**13C NMR (125 MHz, CDCl₃)**
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**minor-12**

1H NMR (400 MHz, CDCl3)

13C NMR (125 MHz, CDCl3)

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$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
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**1H NMR (400 MHz, CDCl₃)**

**13C NMR (125 MHz, CDCl₃)**
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**ACQUISITION PARAMETERS**

- **1H NMR (500 MHz, CDCl3)**
  - Spectrum Type: 1H_Spectra
  - Sample ID: 2097
  - Dilution: 1x
  - Spin Rate: 20 KHz
  - Field Strength: 14.1 T (100.6 MHz)
  - **Resonance Frequencies:**
    - Hr: 1.00, 1.50 (OCH3), 2.00 (NH), 4.00 (CH2), 5.00 ppm
  - **Other Parameters:**
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    - V2: 0.00, 0.10 (OCH3), 0.20 (NH), 0.30 (CH2), 0.40 ppm

- **13C NMR (125 MHz, CDCl3)**
  - Spectrum Type: 13C_Spectra
  - Sample ID: 2097
  - Dilution: 1x
  - Field Strength: 14.1 T (100.6 MHz)
  - **Resonance Frequencies:**
    - C1: 20.00 (CH2), 40.00 ppm
  - **Other Parameters:**
    - V1: 0.00, 0.10 (CH2), 0.20 (CH2), 0.30 (CH2), 0.40 ppm
    - V2: 0.00, 0.10 (CH2), 0.20 (CH2), 0.30 (CH2), 0.40 ppm
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--- ACQUISITION PARAMETERS ---
Derived from: ESI-XXE13-152-2-0.2
File Name: ESI-XXE13-152-2-0.2
Version: 1.0
Date: 2012
Contact: ESI
Creation Date: 2012-11-24
Revision Date: 2012-11-24

--- 1H NMR (400 MHz, CDCl₃) ---

--- 13C NMR (125 MHz, CDCl₃) ---

X: parts per Million: 13C
16 (ca. 2:1 mixture)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
**17 (ca. 3:1 mixture)**

**$^{13}$C NMR (125 MHz, CDCl$_3$)**

**$^1$H NMR (400 MHz, CDCl$_3$)**
**1H NMR (400 MHz, CDCl₃)**

![1H NMR Spectrum](image1)

**13C NMR (125 MHz, CDCl₃)**

![13C NMR Spectrum](image2)
$\text{NH}$

$\text{N}$

$\text{O}$

$\text{Me}$

$\text{F}$

$\text{HO}$

$\text{OH}$

$4$

$\text{1H NMR (500 MHz, CD$_3$OD)}$

$\text{13C NMR (125 MHz, CD$_3$OD)}$

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