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A Highly Diastereoselective Synthesis of *Trans*-3,4-(Difluoromethano)glutamic Acid

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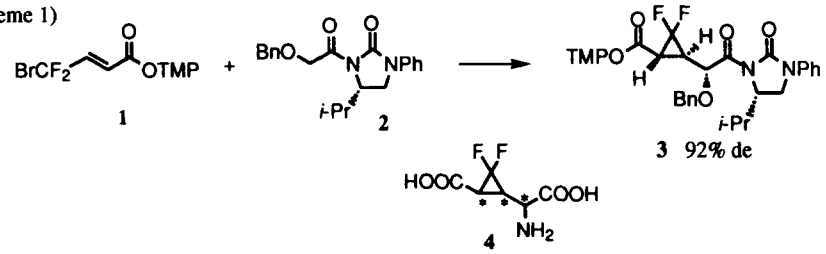
Abstract: Reaction of enantiomerically pure *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** with lithium enolate of *N*-diphenylmethylideneglycinate **6** in DMF proceeded in highly diastereoselective manner to give *trans*-disubstituted *gem*-difluorocyclopropane **7**, which was readily converted to the 3,4-(difluoro- methano)glutamic acid **4**.

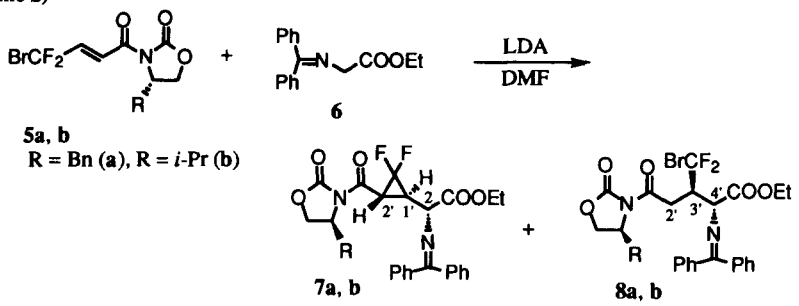
Introduction of cyclopropane moiety into biologically active substances has been recognized as one of the important chemical modifications owing to conformational rigidity and potential chemical reactivity brought about by this modification.[1-4] For example, conformationally restricted analogs of glutamic acid having the cyclopropane moiety were studied so as to elucidate the importance of conformations (extended and folded forms) for the receptor subtype specificity.[5] For such chemically modified substances, the introduction of fluorine atom(s) onto the cyclopropane ring would lead to interesting results in consideration of characteristic features of fluorinated compounds.[6] We have reported a regio- and stereoselective preparation of functionalized *gem*-difluorocyclopropanes through the sequential Michael addition of lithium enolate of ester or amide to 2,4,6-trimethylphenyl (TMP) 4-bromo-4,4-difluorocrotonate **1** followed by the triethylborane mediated intramolecular substitution reaction.[7] Furthermore, we have extended this reaction in asymmetric version using *N*-acylimidazolidinone derivative **2** as a Michael donor (Scheme 1).[8] For the synthesis of 3,4-(difluoromethano)glutamic acid **4**, attempts were made to conduct the reaction of **1** with several glycine derivatives having chiral auxiliary in ester part, but we could not obtain satisfactory results with respect to chemical yield and diastereoselectivity.

(Scheme 1)



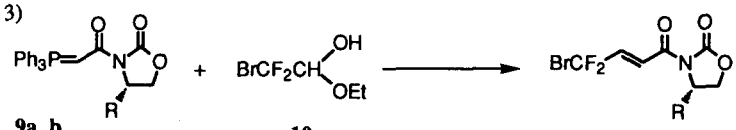
As an alternative approach, we introduced a chiral auxiliary into Michael acceptor. In this paper, we report that *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** serves as an efficient starting material for a highly diastereoselective preparation of *trans*-3,4-(difluoromethano)glutamic acid **4** through the reaction of **5** with *N*-(diphenylmethylidene)glycinate **6** (Scheme 2).

(Scheme 2)



The *N*-crotonoyloxazolidinones **5a,b** was obtained exclusively in *E* form by the Wittig reaction of the phosphoranes **9a,b** with bromodifluoroacetaldehyde hemiacetal **10**, prepared by DIBAL-H reduction of ethyl bromodifluoroacetate (Scheme 3).[7,9]

(Scheme 3)



For the synthesis of the (difluoromethano)glutamate derivative **7a**, reaction of **5a** with lithium enolate of ethyl *N*-(diphenylmethylidene)glycinate **6**[10] was conducted under several reaction conditions. Results are summarized in Table 1. In THF, reaction of **5a** with lithium enolate of **6** proceeded at low temperature (-78 °C) to give the 1,4-addition product **8a** in excellent yield with a high diastereoselectivity (entry 1), but no cyclopropane formation was observed by extending the reaction time at room temperature. Under similar reaction conditions for the synthesis of the difluorocyclopropane **3** from **1** and **2** as reported previously,[7,8] we obtained the desired cyclopropane **7a** in low yield (16%) along with **8a** as a major product (entry 2). When HMPA was added as co-solvent, chemical yield of **7a** increased to 43% and the diastereoselectivity of **7a** thus obained was found 71% de (entry 3). Finally, **7a** was obtained in highly diastereoselective manner when the reaction was carried out in DMF and no appreciable effect of triethylborane as an additive was observed (entries 4, 5). It is worth to note that the major isomers of both **7a** and **8a** thus obtained in each experiment were identical. The absolute stereochemistry of the cyclopropane **7a** was confirmed to be 2*R*,1'*R*,2'*R* as described later. Similar results (chemical yield, diastereoselectivity and the sense of asymmetric induction) were obtained in the reaction of **6** with **5b** instead of **5a**.

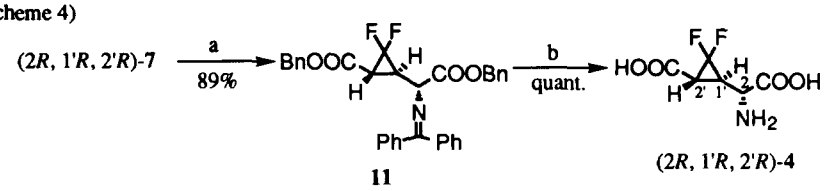
Table 1. Reactions of 5a with 6

entry	Solvent	Additive	Cyclopropane 7a Yield(%)[a] [% de][b]	1,4-Adduct 8a Yield(%)[a] [% de][b]
1	THF	—	0	93 [>95]
2	THF	Et_3B, DMI[c]	16 —[d]	84 —[d]
3	THF	HMPA[e]	43 [71]	48 [>95]
4	DMF	—	54 [>95]	16 [>95]
5	DMF	Et_3B[f]	47 [>95]	12 [>95]

a) Isolated yield. b) Determined by ^{19}F-NMR spectrum of reaction mixture. When a minor isomer could not be detected by ^{19}F-NMR, de was shown as >95%. c) DMI = 1,3-Dimethyl-2-imidazolidinone. d) Not determined. e) THF : HMPA = 10 : 1. f) 3 eq. Et_3B was added.

Conversion of (2*R*,1'*R*,2'*R*)-**7a** to the 3,4-(difluoromethano)glutamic acid **4** [2-(2'-carboxy-3',3'-difluoro)cyclopropylglycine] was readily achieved by titanium isopropoxide catalyzed ester exchange reaction with excess of benzyl alcohol[11] followed by hydrogenolysis, as shown in Scheme 4.

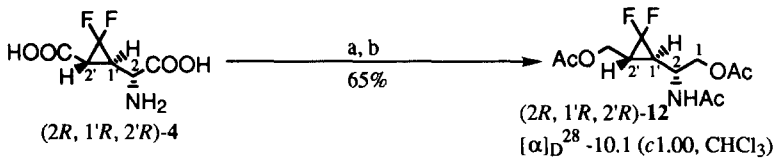
(Scheme 4)



a) BnOH, Ti(O*i*Pr)$_4$, 80°C b) H_2/Pd-C, EtOH

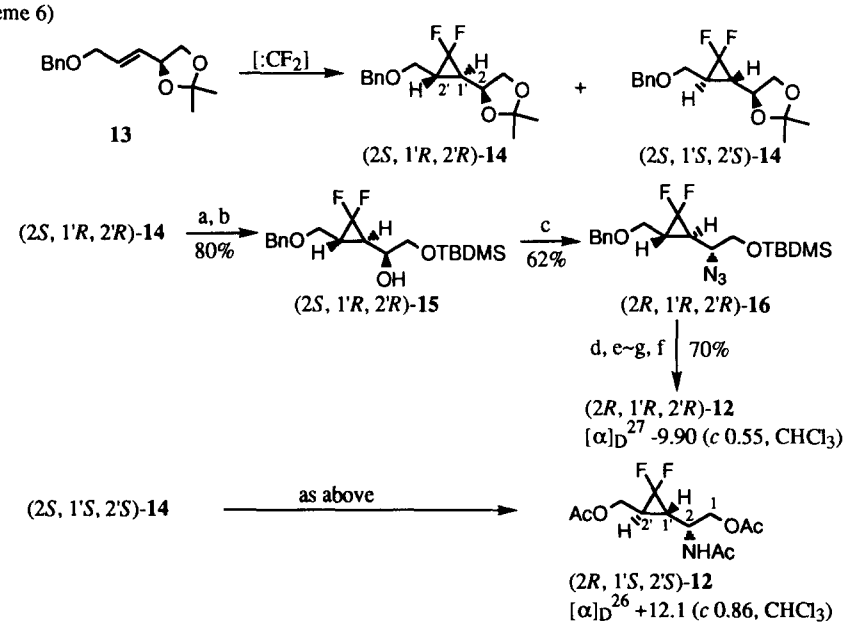
Determination of the stereochemistry of 3,4-(difluoromethano)glutamic acid **4** was carried out by comparison of $[\alpha]_D$ value, and ^{1}H-, ^{13}C- and ^{19}F-NMR spectra of the triacetyl derivative **12** formed from **4** with those data of the two authentic diastereomers prepared from the known precursors **14**.[8] Thus, borane reduction of **4** and subsequent reaction with Ac_2O in pyridine gave the triacetyl derivative **12** in 65% yield (Scheme 5). For the synthesis of authentic samples [(2*R*,1'*R*,2'*R*)- and (2*R*,1'*S*,2'*S*)-**12**], each diastereomer of the difluorocyclopropane **14**, which were prepared by difluorocarbene addition to the allylic alcohol derivative **13** and their stereochemistries were confirmed on the basis of X-ray crystallographic analysis[8] was

(Scheme 5)



a) BH_3•DMS, THF b) Ac_2O, pyridine

(Scheme 6)



a) 10% HCl, MeOH; b) TBDMS-Cl, imidazole, DMF; c) Ph_3P, DEAD, $(PhO)_2P(O)N_3$; d) TBAF, THF; e) H_2/Pd-C, AcOEt; f) Ac_2O, pyridine; g) H_2/Pd$(OH)_2$, AcOEt

used as a precursor (Scheme 6). Substitution of the secondary hydroxyl group of **15** by azide group with inversion by Mitsunobu reaction[12] followed by the ordinary reactions (desilylation, reduction of azide group, acetylation, debenzylation and acetylation) provided the corresponding triacetyl derivatives **12** having 2*R*,1'*R*,2'*R* and 2*R*,1'*S*,2'*S* configurations, respectively. Fortunately, physical data of (2*R*,1'*R*,2'*R*)-**12**, prepared from **13**, were identical with those of **12** derived from 3,4-(difluoromethano)glutamic acid **4**, thereby the absolute configuration of **4** was confirmed to be 2*R*,1'*R*,2'*R*.[13] This indicates that conjugate addition of lithium enolate of **6** proceeded in a manner of C(β)-*re*-face preference with respect to the Michael acceptor **5**, while the transition state of the conjugate addition was not clear because we could not determine the stereochemistry of the Michael donor, lithium enolate of **6** in DMF.

In summary, we have shown that *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** is an efficient starting material for the asymmetric preparation of functionalized *trans*-disubstituted *gem*-difluorocyclopropanes, including glutamic acid derivative **4**. We are currently carring out synthesis of other isomers of **4**.

EXPERIMENTAL

^{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 $CDCl_3$ or sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TSP) (0 ppm) in D_2O for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) in $CDCl_3$ or TSP (0 ppm) in D_2O 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 ppm using benzotrifluoride (0 ppm) 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. Specific rotations were recorded on a JASCO DIP spectrometer. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV detector.

(4*S*)-3-[(*E*)-4'-Bromo-4',4'-difluoro-2'-butenoyl]-4-benzyl-2-oxazolidinone (5a). Under Ar atmosphere, a solution of (4*S*)-*N*-bromoacetyl-4-benzyl-2-oxazolidinone (3.7 g, 12.4 mmol) and triphenylphosphine (3.6 g, 13.7 mmol) in CH_3CN (15 mL) was stirred for 2 days at 50 °C. To the reaction mixture was added 2*N* NaOH aq.(6.5 mL) and it was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to leave the crude phosphorane **9a**. A mixture of ethyl bromodifluoroacetate (1.7 mL, 13.7 mmol) and DIBAL-H (0.93 *M* in hexane, 14.7 mL, 13.7 mmol) in Et_2O (10 mL) was stirred for 20 min at -78 °C. To the reaction mixture was added MeOH (5 mL), then 5% HCl (10 mL) and the whole was stirred for 10 min at room temperature. The mixture was extracted with Et_2O and the organic layer was successively washed with sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ then concentrated under reduced pressure. A solution of the residue and the crude phosphorane **9a** described above in THF (35 mL) was stirred for 5 h at room temperature. Removal of solvent under reduced pressure to leave the residue, which was purified by silica gel column chromatography (hexane- AcOEt =10 : 1-5 : 1) to give **5a** (2.88 g, 65%). Colorless oil. $[\alpha]_D^{26.4}$ +59.2 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3064, 2923, 1786, 1691. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.81 (1 H, dd, *J* = 13.5, 9.6 Hz), 3.35 (1 H, dd, *J* = 13.5, 3.4 Hz), 4.15-4.35 (2 H, m), 4.75 (1 H, dddd, *J* = 9.6, 7.0, 3.4, 3.4 Hz), 7.14 (1 H, dt, *J* = 15.3, 10.2 Hz), 7.20-7.45 (5 H, m), 7.74 (1 H, dt, *J* = 15.3, 1.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 37.6, 55.3, 66.5, 115.4 (t, *J* = 301.5 Hz), 122.9 (t, *J* = 6.4 Hz), 127.5, 129.1, 129.4, 134.8, 139.1 (t, *J* = 25.8 Hz), 153.0, 162.6. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 13.4 (dd, *J* = 10.2, 1.6 Hz). MS (EI) m/z; 360, 358 (M^+), 230, 183, 91. Anal. Calcd for $C_{14}H_{12}BrF_2NO_3$: C, 46.69; H, 3.36; N, 3.89. Found: C, 47.05; H, 3.39; N, 3.91.

(4*S*)-3-[(*E*)-4'-Bromo-4',4'-difluoro-2'-butenoyl]-4-isopropyl-2-oxazolidinone (5b). In a similar procedure for the preparation of **5a**, **5b** was obtained in 56% yield. Colorless prisms. mp 59.5 - 62.5 °C. $[\alpha]_D^{22.4}$ +77.6 (*c* 1.00, $CHCl_3$). IR (KBr) ν, cm^{-1}; 1775, 1679, 1391, 1371, 1342, 1210. ^{1}H-NMR (300 MHz, $CDCl_3$) δ; 0.90 (3 H, d, *J* = 7.0 Hz), 0.95 (3 H, d, *J* = 7.0 Hz), 2.42 (1 H, dtt, *J* = 7.0, 6.9, 4.0 Hz), 4.27 (1 H, dd, *J* = 9.2, 3.3 Hz), 4.33 (1 H, dd, *J* = 9.2, 8.0 Hz), 4.50 (1 H, ddd, *J* = 8.1, 4.0,

3.5 Hz), 7.08 (1 H, dt, J = 15.4, 10.2 Hz), 7.75 (1 H, dt, J = 15.2, 1.7 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ; 14.6, 17.9, 28.3, 58.7, 63.7, 115.3 (t, J = 302.0 Hz), 122.9 (t, J = 6.7 Hz), 138.8 (t, J = 25.6 Hz), 153.5, 162.4. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 13.6 (dd, J = 10.3, 1.5 Hz). Anal. Calcd for $C_{10}H_{12}BrF_2NO_3$: C, 37.29; H, 3.75; N, 4.35. Found: C, 37.44; H, 3.91; N, 4.51.

(2*R*,1'*R*,2'*R*,4"*S*)-Ethyl *N*-diphenylmethylidene-2-[2'-{(4"-benzyl-2"-oxazolidinon-3"-yl)carbonyl}-3',3'-difluoro]cyclopropylglycinate (7a) and (4*S*,3'*R*,4'*R*)-3-[3'-bromo-difluoromethyl-4'-(diphenylmethylideneamino)-4'-ethoxycarbonyl]butanoyl-4-benzyl-2-oxazolidinone (8a). Experimental procedure corresponding to entry 4 in Table 1 is shown. Under Ar atmosphere, a mixture of the glycinate **6** (756 mg, 2.83 mmol) and LDA, formed from *N*,*N*-diisopropylamine (0.47 mL, 3.34 mmol) and *n*-butyllithium (1.65 *M* in hexane, 1.87 mL), in DMF (15 mL) was stirred for 15 min at -20 °C, and to this was added **5a** (926 mg, 2.57 mmol) in DMF (10 mL). After being stirred for 2 h at the same temperature and then quenched by addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=7:1) to give **7a** (758 mg, 54%) and **8a** (245 mg, 16%), respectively. **7a**; colorless oil. $[\alpha]_D^{26.0}$ +39.4 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3063, 1782, 1739, 1700, 701. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.30 (3 H, t, J = 7.1 Hz), 2.84 (1 H, dd, J = 13.5, 9.3 Hz), 3.25 (1 H, dd, J = 13.5, 3.2 Hz), 3.31 (1 H, m), 3.85 (1 H, dd, J = 14.1, 7.8 Hz), 4.13 (1 H, d, J = 8.1 Hz), 4.15-4.35 (4 H, m), 4.71 (1 H, m), 7.18-7.65 (15 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.0, 29.3 (dd, J = 11.0, 10.6 Hz), 30.9 (dd, J = 8.8, 7.8 Hz), 37.6, 55.4, 61.3, 61.8, 66.2, 111.7 (dd, J = 293.2, 290.2 Hz), 127.4, 127.7, 128.1, 128.7, 128.97, 129.02, 129.04, 129.4, 130.8, 134.8, 135.5, 139.0, 153.3, 164.5, 169.2, 172.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -71.6 (1 F, dd, J = 152.7, 13.9 Hz), -69.2 (1 F, dd, J = 152.7, 14.0 Hz). MS (EI) m/z; 546 (M^+), 473, 296, 182, 105. Anal. Calcd for $C_{31}H_{28}F_2N_2O_5$: C, 68.12; H, 5.16; N, 5.13. Found: C, 68.31; H, 5.16; N, 5.10. **8a**; colorless oil. $[\alpha]_D^{26.8}$ -3.78 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3062, 1782, 1740, 1703, 701. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.27 (3 H, t, J = 7.1 Hz), 2.76 (1 H, dd, J = 13.4, 9.6 Hz), 3.24 (1 H, dd, J = 18.1, 3.9 Hz), 3.29 (1 H, dd, J = 13.4, 3.2 Hz), 3.82 (1 H, dd, J = 8.4, 8.4 Hz), 4.01 (1 H, dd, J = 18.1, 7.8 Hz), 4.06 (1 H, dd, J = 9.0, 2.6 Hz), 4.16-4.21 (3 H, m), 4.53 (1 H, d, J = 4.1 Hz), 4.64 (1 H, m), 7.19-7.63 (15 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.0, 32.7, 37.7, 50.0 (dd, J = 19.6, 19.5 Hz), 55.3, 61.6, 63.6, 66.1, 124.4 (dd, J = 309.0, 308.6 Hz), 127.3, 127.7, 128.0, 128.5, 128.9, 129.0, 129.3, 130.7, 135.3, 135.7, 139.1, 153.3, 169.6, 170.0, 172.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 15.5 (1 F, dd, J = 161.0, 11.9 Hz), 16.0 (1 F, dd, J = 161.0, 11.4 Hz). MS (EI) m/z; 626 (M^+-1), 553, 497, 266, 193, 165. Anal. Calcd for $C_{31}H_{29}BrF_2N_2O_5$: C, 59.34; H, 4.66; N, 4.46. Found: C, 59.34; H, 4.71; N, 4.38.

(2*R*,1'*R*,2'*R*)-2-(2'-Carboxy-3',3'-difluoro)cyclopropylglycine (4). A mixture of benzyl alcohol (1 mL) and Ti(O*i*-Pr)$_4$ (154 mg, 0.54 mmol) was stirred for 30 min at room temperature under reduced pressure (4 mmHg). To the residue was added **7a** (100 mg, 0.18 mmol) and the mixture was stirred for 7 h at 70 °C. Purification of the mixture by silica gel column chromatography (hexane-AcOEt=10:1) gave the dibenzyl ester **11** (87 mg, 89%). Colorless oil. $[\alpha]_D^{25.6}$ -21.0 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.40 (1 H, dd, J = 11.4, 7.6 Hz), 3.09 (1 H, dddd, J = 12.3, 7.6, 7.4, 3.5 Hz), 4.18 (1 H, d, J = 7.2 Hz), 5.181 (1 H, d, J = 12.4 Hz), 5.184 (2 H, s), 5.18 (2 H, s), 5.23 (1 H, d, J = 12.4 Hz), 7.10-7.61 (20 H, m). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -70.7 (1 F, dd, J = 156.9, 12.5 Hz), -70.1 (1 F, ddd, J = 157.1, 11.8, 3.1 Hz). Under hydrogen atmosphere, a mixture of **11** (87 mg, 0.16 mmol) and 5% Pd-C in MeOH (1 mL) was stirred for 5 h at room temperature. After removal of catalyst by filtration, the filtrate was partitioned by hexane and water. The aqueous layer was concentrated under reduced pressure to leave solid mass, which was washed with Et_2O to give **4** (31 mg, quant.). Colorless prisms. 200 °C dec. $[\alpha]_D^{23.2}$ +39.4 (*c* 1.00, H_2O). IR (KBr) ν, cm^{-1}; 3106, 1621, 1530, 1476, 1393. ^{1}H-NMR (400 MHz, D_2O) δ; 4.16 (1 H, m), 4.25 (1 H, dd, J = 15.0, 7.8 Hz), 3.70 (1 H, d, J = 10.7 Hz). ^{13}C-NMR (100.6 MHz, D_2O) δ; 31.3 (dd, J = 11.6, 8.6 Hz), 34.1 (br), 54.2 (br), 113.7 (dd, J = 288.2, 286.1 Hz), 172.7, 173.7. ^{19}F-NMR

(376.5 MHz, D_2O) δ; -71.4 (1 F, dd, *J* = 157.6, 13.6 Hz), -69.0 (1 F, dd, *J* = 157.2, 14.8 Hz). MS(ESI) m/z; 195.9.

(2*R*,1'*R*,2'*R*)-2-Acetylamino-2-(2'-acetoxymethyl-3',3'-difluoro)cyclopropylethyl acetate (12). Under Ar atmosphere, a mixture of **(2*R*,1'*R*,2'*R*)-4** (20 mg, 0.1 mmol) and BH_3•DMS (10 *M* in THF, 0.4 mmol) in THF (1 mL) was stirred for 6 h at room temperature. After addition of MeOH (1 mL), the reaction mixture was concentrated under reduced pressure (4 mmHg) overnight. The residue was treated with acetic anhydride (33 μL, 0.35 mmol) in pyridine (1 mL) for 5 h at 0 °C, and then the reaction mixture was concentrated under reduced pressure after addition of MeOH (1 mL). The residue was chromatographed on silica gel (hexane-AcOEt=1:1) to give **12** (19 mg, 65%). Colorless prisms. mp 132.5-135.5 °C. $[\alpha]_D^{27.6}$ -10.1 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3290, 1735, 1651, 1552. ^{1}H-NMR (300 MHz, $CDCl_3$) δ; 1.67 (1 H, dddd, *J* = 10.2, 10.2, 6.9, 4.3 Hz), 1.99 (3 H, s), 2.04 (1 H, m), 2.07 (3 H, s), 2.11 (3 H, s), 4.05 (1 H, dddd, *J* = 9.3, 9.3, 9.3, 4.1 Hz), 4.11 (2 H, d, *J* = 7.8 Hz), 4.13 (1 H, dd, *J* = 11.3, 4.6 Hz), 4.23 (1 H, dd, *J* = 11.3, 5.2 Hz), 5.79 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.7, 20.8, 23.2, 26.6 (dd, *J* = 10.8, 10.2 Hz), 29.5 (dd, *J* = 10.4, 9.6 Hz), 46.9, 60.7, 65.3, 113.2 (dd, *J* = 286.7, 286.7 Hz), 169.7, 170.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.8 (1 F, ddd, *J* = 163.8, 10.3, 2.3 Hz), -74.3 (1 F, ddd, *J* = 166.2, 10.6, 3.2 Hz). MS (EI) m/z; 294 (M^+), 178, 116, 84. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.69; H, 5.72; N, 4.78.

(2*S*,1'*R*,2'*R*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-hydroxyethyl *tert*-butyldimethylsilyl ether (15-Minor). **(2*S*,1'*R*,2'*R*)-14** (237 mg, 0.92 mmol) obtained as a minor isomer of difluorocarbene addition with **13**[8] was treated with 10% HCl in MeOH (2 mL) for 6 h at room temperature. After concentrated under reduced pressure, the residue was extracted with AcOEt by addition of sat. $NaHCO_3$ aq. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was treated with imidazole (138 mg, 2 mmol) and TBDMS-Cl (167 mg, 1.1 mmol) in DMF (2 mL) for 5 h at room temperature. After addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=15:1) to give **15-Minor** (273 mg, 79%). Colorless oil. $[\alpha]_D^{25.6}$ +15.5 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3454, 2954, 2930, 1114, 838. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.077 (6 H, s), 0.90 (9 H, s), 1.55 (1 H, m), 1.74 (1 H, dddd, *J* = 14.4, 7.3, 7.2, 7.1 Hz), 2.49 (1 H, d, *J* = 5.2 Hz), 3.51-3.56 (2 H, m), 3.61 (1 H, dd, *J* = 10.0, 6.0 Hz), 3.75 (1 H, dd, *J* = 10.0, 3.4 Hz), 4.48 (1 H, d, *J* = 12.0 Hz), 4.56 (1 H, d, *J* = 12.0 Hz), 7.29-7.37 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.51, 18.2, 25.7 (dd, *J* = 10.8, 10.8 Hz), 25.8, 28.9 (dd, *J* = 10.5, 10.4 Hz), 65.7, 65.87, 65.9, 69.7, 69.72, 72.5, 114.1 (dd, *J* = 286.2, 286.2 Hz), 127.5, 127.7, 128.4, 137.9. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.7 (1 F, dd, *J* = 163.1, 13.1 Hz), -74.9 (1 F, dd, *J* = 163.0, 13.1 Hz). MS (EI) m/z; 297, 193, 147, 91. Anal. Calcd for $C_{19}H_{30}F_2O_3Si$: C, 61.26; H, 8.12. Found: C, 61.27; H, 8.18.

(2*R*,1'*R*,2'*R*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-azidoethyl *tert*-butyldimethylsilyl ether (16-Minor). A mixture of **15-Minor** (222 mg, 0.6 mmol), triphenylphosphine (262 mg, 1.0 mmol), diphenylphosphoryl azide (0.19 mL, 0.9 mmol) and diethyl azodicarboxylate (0.14 mL, 0.9 mmol) in THF (4 mL) was stirred for 6 h at room temperature. After addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=20:1-10:1) to give **16-Minor** (243 mg, 98%). Colorless oil. $[\alpha]_D^{25.6}$ +37.1 (*c* 0.99, $CHCl_3$). IR (neat) ν, cm^{-1}; 2955, 2931, 1256, 1115, 839. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.10 (6 H, s), 0.92 (9 H, s), 1.63 (1 H, dddd, *J* = 11.8, 9.9, 7.1, 2.4 Hz), 1.93 (1 H, m), 3.18 (1 H, ddd, *J* = 9.3, 4.5, 4.4 Hz), 3.53 (1 H, dd, *J* = 10.8, 8.1 Hz), 3.66 (1 H, m), 3.73 (1 H, dd, *J* = 10.5, 5.9 Hz), 3.83 (1 H, dd, *J* = 10.5, 3.8 Hz), 4.53 (1 H, d, *J* = 12.0 Hz), 4.56 (1 H, d, *J* = 11.9 Hz), 7.28-7.36 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.64, -5.70, 18.2, 25.7, 26.4 (dd, *J* = 10.2, 10.2 Hz), 27.3 (dd, *J* =

10.2, 10.1 Hz), 60.6, 65.6, 66.0, 72.5, 113.5 (dd, J = 287.6, 287.4 Hz), 127.6, 127.7, 128.4, 137.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.5 (1 F, dd, J = 162.7, 11.6 Hz), -74.0 (1 F, dd, J = 162.9, 11.6 Hz). MS (EI) m/z; 267, 224, 148, 115, 91. Anal. Calcd for $C_{19}H_{29}F_2N_3O_2Si$: C, 57.41; H, 7.35; N, 10.57. Found: C, 57.67; H, 7.41; N, 10.21.

(2*R*,1'*R*,2'*R*)-2-Acetylamino-2-(2'-acetoxymethyl-3',3'-difluoro)cyclopropylethyl acetate (12-Minor). After deprotection of TBDMS group by treating **16-Minor** (37 mg, 0.064 mmol) with TBAF (1*M* in THF, 0.3 mL) in THF for 3 h at room temperature and subsequent purification by silica gel column chromatography (hexane-AcOEt=15:1-8:1), a mixture of the desilylated azide derivative (18 mg) and 5% Pd-C in AcOEt (1 mL) was stirred for 24 h under hydrogen atmosphere. Removal of the catalyst by filtration and evaporation of the filtrate gave the residue, which was treated with acetic anhydride in pyridine for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was hydrogenated over $Pd(OH)_2$ for 5 h at room temperature for debenzylation. The crude product was acetylated by repeating the similar procedure as above to give **12-Minor** (13 mg, 69%). Colorless prisms. mp 132.8-134.5 °C. $[\alpha]_D^{26.8}$ -9.90 (*c* 0.55, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3292, 1736, 1652, 1553. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.67 (1 H, dddd, J = 10.6, 10.5, 7.0, 4.0 Hz), 1.99 (3 H, s), 2.04 (1 H, m), 2.07 (3 H, s), 2.11 (3 H, s), 4.05 (1 H, dddd, J = 9.5, 9.5, 9.3, 4.6 Hz), 4.11 (2 H, d, J = 6.5 Hz), 4.13 (1 H, dd, J = 11.5, 4.6 Hz), 4.23 (1 H, dd, J = 11.3, 5.3 Hz), 5.79 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.67, 20.7, 23.1, 26.4 (dd, J = 9.9, 9.9 Hz), 29.4 (dd, J = 10.4, 10.1 Hz), 46.8, 60.7, 65.2, 113.2 (dd, J = 288.0, 287.7 Hz), 169.8, 170.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.8 (1 F, ddd, J = 165.3, 10.3, 2.2 Hz), -74.3 (1 F, ddd, J = 165.6, 10.5, 3.2 Hz). MS (EI) m/z; 294 (M^+), 178, 116, 84. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.16; H, 5.71; N, 4.78.

(2*S*,1'*S*,2'*S*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-hydroxyethyl *tert*-butyldimethylsilyl ether (15-Major). Colorless oil. $[\alpha]_D^{28.4}$ -10.6 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3424, 2954, 2931, 1255. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.092 (6 H, s), 0.91 (9 H, s), 1.52 (1 H, ddd, J = 15.6, 7.5, 7.5 Hz), 1.97 (1 H, ddd, J = 14.9, 14.4, 7.3 Hz), 2.35-2.60 (1 H, br), 3.52 (2 H, m), 3.57 (1 H, dd, J = 9.8, 6.3 Hz), 3.68 (1 H, dddd, J = 10.9, 6.5, 2.1, 2.1 Hz), 3.73 (1 H, dd, J = 9.8, 3.3 Hz), 4.53 (1 H, d, J = 11.9 Hz), 4.60 (1 H, d, J = 11.9 Hz), 7.26-7.35 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.45, 18.3, 25.8, 26.7 (dd, J = 10.3, 10.0 Hz), 29.0 (dd, J = 9.6, 9.5 Hz), 65.9, 66.6, 69.4, 72.4, 113.9 (dd, J = 287.0, 287.0 Hz), 127.7, 128.4, 137.9. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.0 (dd, J = 7.6, 7.2 Hz). MS (EI) m/z; 297, 193, 147, 91. Anal. Calcd for $C_{19}H_{30}F_2O_3Si$: C, 61.26; H, 8.12. Found: C, 61.33; H, 8.18.

(2*R*,1'*S*,2'*S*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-azidoethyl *tert*-butyldimethylsilyl ether (16-Major). Colorless oil. $[\alpha]_D^{26.8}$ -3.03 (*c* 0.99, $CHCl_3$). IR (neat) ν, cm^{-1}; 2931, 2109, 1255, 1115, 839. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.085 (6 H, s), 0.91 (9 H, s), 1.63 (1 H, ddd, J = 13.0, 10.1, 7.0 Hz), 1.78 (1 H, dddd, J = 13.7, 7.1, 7.1, 7.1 Hz), 3.21 (1 H, dddd, J = 10.0, 6.1, 3.7, 1.4 Hz), 3.56 (2 H, d, J = 7.0 Hz), 3.71 (1 H, dd, J = 10.6, 6.1 Hz), 3.81 (1 H, dd, J = 10.6, 3.7 Hz), 4.49 (1 H, d, J = 12.0 Hz), 4.65 (1 H, d, J = 12.0 Hz), 7.26-7.37 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.62, 18.2, 25.7, 26.8 (dd, J = 11.0, 10.8 Hz), 27.3 (dd, J = 10.7, 10.6 Hz), 61.3, 65.0, 65.6, 65.63, 72.7, 113.5 (dd, J = 287.1, 287.0 Hz), 127.5, 127.7, 128.4, 137.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.5 (1 F, dd, J = 163.3, 13.0 Hz), -74.2 (1 F, dd, J = 163.3, 13.5 Hz). MS (EI) m/z; 310, 267, 195, 115, 91. Anal. Calcd for $C_{19}H_{29}F_2N_3O_2Si$: C, 57.41; H, 7.35; N, 10.57. Found: C, 57.30; H, 7.43; N, 10.44.

(2*R*,1'*S*,2'*S*)-2-Acetylamino-2-(2'-acetoxymethyl-3',3'-difluoro)cyclopropylethyl acetate (12-Major). Colorless prisms. mp 99.2-100.5 °C. $[\alpha]_D^{25.6}$ +12.1 (*c* 0.86, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3313, 1738, 1655, 1540. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.71 (1 H, m), 1.81 (1 H, ddd, J = 19.9, 7.4, 7.2 Hz), 1.97 (3 H, s), 2.03 (3 H, s), 2.07 (3 H, s), 4.06-4.20 (5 H, m), 6.13 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.6, 23.1, 25.6 (dd, J = 10.8, 10.7 Hz), 28.0 (dd, J = 10.4, 10.2 Hz), 46.3,

60.06, 60.1, 64.8, 113.2 (dd, J = 287.1, 287.1 Hz), 169.5, 170.67, 170.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.3 (1 F, dd, J = 165.1, 12.9 Hz), -74.5 (1 F, dd, J = 165.2, 12.9 Hz). MS (EI) m/z; 294 (M^+), 252, 234. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.69; H, 5.95; N, 4.67.

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