Electronic supplementary information (ESI)

Diastereoselective synthesis of (*Z*)-fluoroalkene dipeptide isosteres utilizing chiral auxiliaries

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I. General information

I-I. General methods

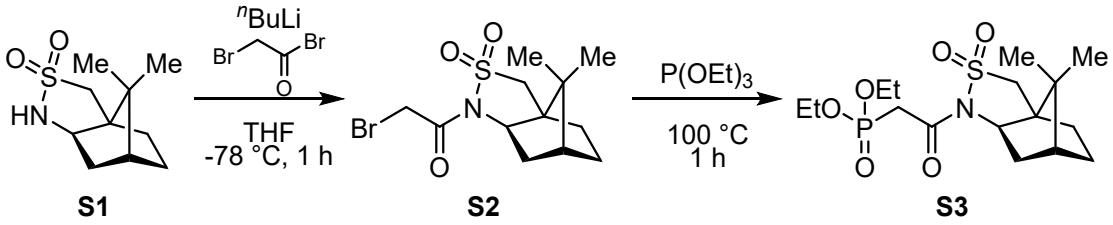
All reactions were performed using commercially supplied reagents and solvents in dried glassware under an atmosphere of nitrogen unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.). Flash column chromatography was carried out with ‘‘Biotage Isolera One’’ equipped with ‘‘Sfar Silica HC Duo Cartridge’’.

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of nitrogen or Ar, using commercially supplied solvents and reagents purchased from FUJIFILM Wako Pure Chemical Corporation, Kanto Chemical Co., Inc., Merck, Nacalai Tesque, Inc., Tokyo Chemical Industry Co., Ltd. (TCI), and Absolute Chiral without further purification unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.) or automatic silica gel flash column chromatography system (Isolera One (Biotage, Sweden) and Pure C-815 (Buchi, Switzerland)).

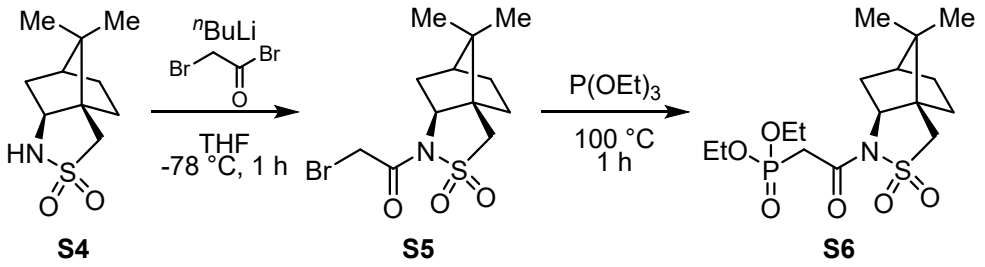
I-II. Characterization Data

^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were recorded using a Bruker AVANCE III 400 spectrometer, Bruker AVANCE 500 spectrometer (Bruker, USA), and JNM-ECA500 (JEOL, Japan). Coupling constants are reported in Hertz, and peak shifts are reported in d (ppm) relative to $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.16 ppm). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF focus in the positive and negative detection mode.

II. Experimental procedures

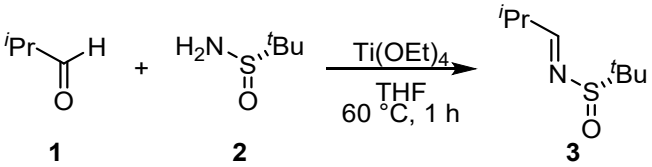


Diethyl (2-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-oxoethyl)phosphonate (**S3**): To a solution of (1*S*)-(−)-2,10-camphorsultam **S1** (4.31 g, 20.0 mmol) in THF (80.0 mL) was slowly added ^{n}BuLi (1.60 M, 15.0 mL, 24.0 mmol) at -78 °C under argon, and the mixture was stirred for 15 min. Bromoacetyl bromide (1.92 mL, 22.0 mmol) was added dropwise to the solution, the mixture was stirred for 1 h. The reaction mixture was quenched by the addition of silica gel (25.0 g), and the solvent was removed under reduced pressure. The mixture was eluted directly with Et_2O, and the solvent was removed under reduced pressure to obtain the bromoacetyl-(*S*)-camphor-10,2-sultam **S2**, which was used immediately in the next step without purification. A solution containing bromoacetyl-(*S*)-camphor-10,2-sultam **S2** in triethyl phosphite (6.86 mL, 40.0 mmol) was heated for 1 h under argon, and the triethyl phosphite was removed under reduced pressure. The crude product (still containing some triethyl phosphite) was purified using flash column chromatography over silica gel with ^{n}hexane/EtOAc (1:1) to obtain the title compound **S3** as a colorless oil (7.40 g, 18.8 mmol, 94% in 2 steps): $[\alpha]_D^{27}$ = -51.3 (c 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23-4.14 (m, 4H), 3.89 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.61-3.43 (m, 3H), 3.21 (dd, *J* = 22, 15 Hz,1H), 2.19-2.14 (m, 1H), 2.07 (dd, *J* = 14, 7.8 Hz, 1H), 1.96-1.86 (m, 3H), 1.44-1.31 (m, 8H), 1.18 (s, 3H), 0.971 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.8 (d, *J* = 7.1 Hz), 65.4, 63.0 (d, *J* = 6.2 Hz), 62.7 (d, *J* = 6.3 Hz), 53.0, 48.5, 48.0, 44.8, 38.3, 35.1 (d, *J* = 138 Hz), 32.9, 26.6, 20.9, 20.0, 16.5 (d, *J* = 6.3 Hz), 16.4 (d, *J* = 6.3 Hz); HRMS (ESI), *m/z* calcd for $C_{16}H_{28}NNaO_6PS$ $[M+H]^+$ 416.1267, found 416.1262.



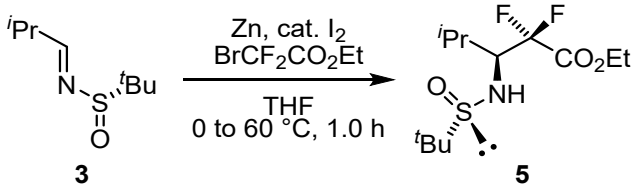
Diethyl (2-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-oxoethyl)phosphonate (**S6**): To a solution of (1*R*)-(+)-2,10-camphorsultam **S4**(4.32 g, 20.0 mmol) in THF (80.0 mL) was slowly added ^{n}BuLi (1.60 M, 15.0 mL, 24.0 mmol) at -78 °C under argon, and the mixture was stirred for 15 min. Bromoacetyl bromide (1.92 mL, 22.0 mmol) was added dropwise to the solution, the mixture was stirred for 1 h. The reaction mixture was quenched by the addition of silica gel (25.0 g), and the

solvent was removed under reduced pressure. The mixture was eluted directly with Et_2O, and the solvent was removed under reduced pressure to obtain the bromoacetyl-(*R*)-camphor-10,2-sultam **S5**, which was used immediately in the next step without purification. A solution containing bromoacetyl-(*S*)-camphor-10,2-sultam **S5** in triethyl phosphite (6.86 mL, 40.0 mmol) was heated for 1 h under argon, and the triethyl phosphite was removed under reduced pressure. The crude product (still containing some triethyl phosphite) was purified using flash column chromatography over silica gel with ^{n}hexane/EtOAc (1:1) to obtain the title compound **S6** as a colorless oil (7.78 g, 19.8 mmol, 99% in 2 steps): $[\alpha]_D^{27}$ = 36.1 (c 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20-4.08 (m, 4H), 3.87-3.84 (m, 1H), 3.53 (dd, *J* = 20, 15 Hz, 1H), 3.45 (dd, *J* = 29, 14 Hz, 2H), 3.17 (dd, *J* = 22, 15 Hz, 1H), 2.15-2.08 (m, 2H), 1.94-1.85 (m, 3H), 1.35-1.27 (m, 8H), 1.14 (s, 3H), 0.937 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.6 (d, *J* = 6.7 Hz), 65.3, 62.9 (d, *J* = 6.1 Hz), 62.8 (d, *J* = 6.2 Hz) , 53.0, 48.4, 47.9, 44.7, 38.3, 35.0 (d, *J* = 137 Hz), 32.8, 26.5, 20.8, 20.0, 16.4 (d, *J* = 3.5 Hz) 16.3 (d, *J* = 6.0 Hz); HRMS (ESI), *m/z* calcd for $C_{16}H_{29}NO_6PS$ $[M+H]^+$ 394.1448, found 394.1444.



1 **2** **3**

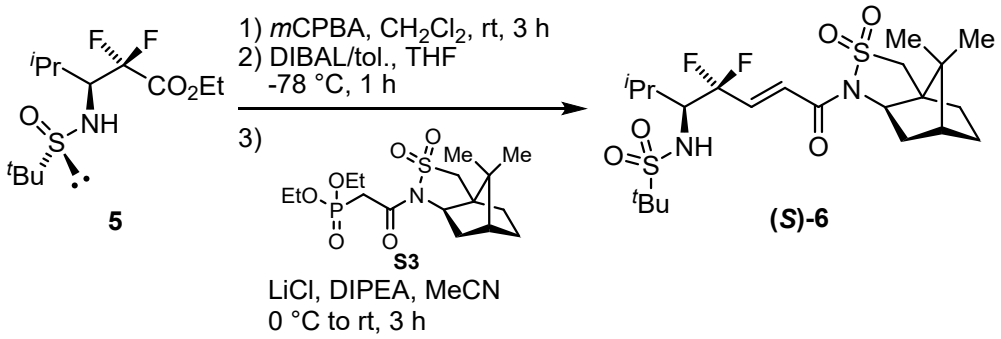
(*S*,*E*)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (**3**): To a solution of (*S*)-(-)-*tert*-butylsulfinamide **2** (1.21 g, 10.0 mmol) in THF (20.0mL) was added isobuthylaldehyde **1** (913 μL, 10.0 mmol) and $Ti(OEt)_4$ (3.15 mL, 15.0 mmol) under argon, and the reaction mixture was stirred at 60 °C for 1 h. After cooling to 0 °C, the reaction was quenched with crashed ice. The resulting suspension was filtrated through a plug of celite, and filter cake was washed with EtOAc. The mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel ^{n}hexane/EtOAc (9:1) to obtain the title compound **3** as a colorless oil (1.74g, 9.93 mmol, 99%): $[\alpha]_D^{22}$ = 48.2 (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 4.4 Hz, 1H), 2.75-2.69 (m, 1H), 1.19 (s, 9H), 1.18 (d, *J* = 2.6 Hz, 3H), 1.16 (d, *J* = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.7, 56.6, 35.0, 22.4 (3C), 19.1 (2C); HRMS (ESI), *m/z* calcd for $C_8H_{18}NOS$ $[M+H]^+$ 176.1104, found 176.1107.



3 **5**

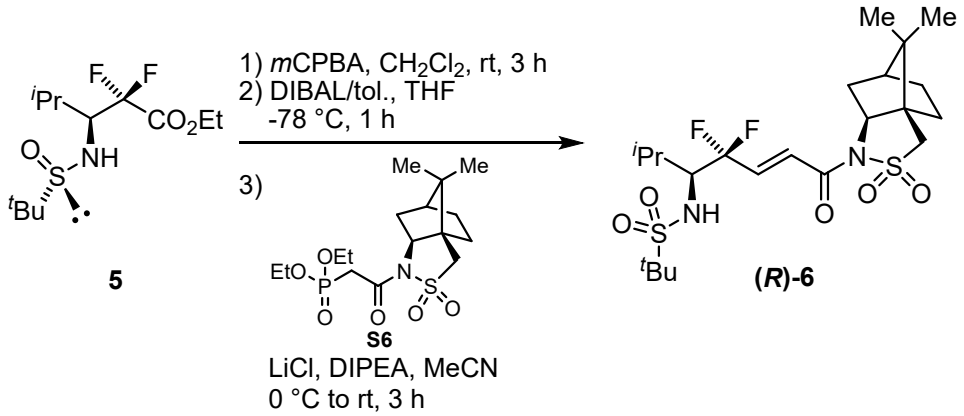
Ethyl (*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-2,2-difluoro-4-methylpentanoate (**5**): To a solution of zinc (1.96

g, 30.0 mmol) in THF (35.0 mL) was added iodine (634 mg, 2.50 mmol) and ethyl bromodifluoroacetate (2.56 mL, 20.0 mmol) under argon at 0 °C, and the reaction mixture was stirred at 60 °C for 30 min. After cooling to 0 °C, a solution of imine **3** (1.75 mg, 10.0 mmol) in THF (5.00 mL) under argon was added to the reaction mixture, and the mixture was stirred at 60 °C for 1 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel ^{n}hexane/EtOAc (3:1) to obtain the title compound **5** as a colorless oil (2.46 g, 8.21 mmol, 82%, >20:1 dr): $[\alpha]_D^{23}$ = 18.9 (c 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (q, *J* = 7.2 Hz, 2H), 3.80-3.72 (m, 1H), 3.59 (d, *J* = 9.9 Hz, 1H), 2.18 (dq, *J* = 9.1, 4.1 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.946 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.4 (t, *J* = 32 Hz), 115.3 (t, *J* = 257 Hz), 63.6, 62.8 (dt, *J* = 25, 22 Hz), 57.3, 27.9, 23.0 (3C), 21.1, 16.5, 14.0; HRMS (ESI), *m/z* calcd for $C_{12}H_{24}F_2NO_3S$ $[M+H]^+$ 300.1439, found 300.1438.



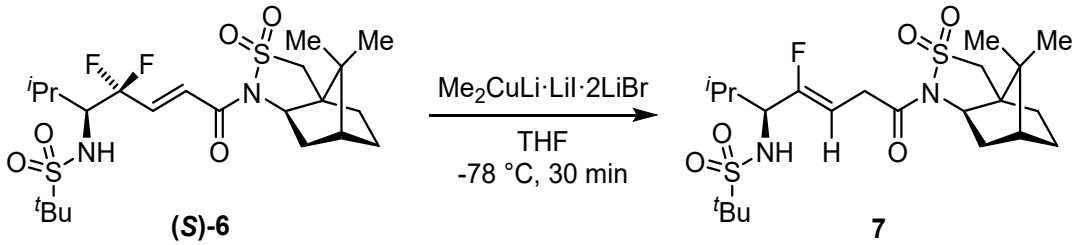
***N*-((*S*,*E*)-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4,4-difluoro-2-methyl-7-oxohept-5-en-3-yl)-2-methylpropane-2-sulfonamide** (**(*S*)-6**): To a solution of *N*-sulfinyl ethyl ester **5** (1.50 g, 5.00 mmol) in CH_2Cl_2 (15.0 mL) was added *m*CPBA (≤77% purity, 2.24 g, 10.0 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the *N*-sulfonyl ethyl ester, which was used immediately in next step without purification. To a solution of *N*-sulfonyl ethyl ester in THF (25.0 mL) was added dropwise a solution of DIBAL-H in toluene (1.00 M, 10.0 mL, 10.0 mmol) at -78 ºC under argon, and the mixture was stirred at -78 ºC for 1 h. The reaction was quenched by saturated aqueous Rochelle salt. The reaction mixture was extracted with diethyl ether and dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the aldehyde, which was used immediately in next step without purification. To a stirred solution of diethylphosphonylacetyl-(*S*)-camphor-10,2-sultam **S3** (2.36 g, 6.00 mmol) in MeCN (20.0 mL) was added LiCl (509 mg, 12.0 mmol) and DIPEA (1.05 mL, 6.00 mmol) at 0 ºC under argon. After stirred for 10 min, a solution of the aldehyde in MeCN (5.00 mL) under argon was added to the mixture, and the mixture was

stirred for 3 h at room temperature. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1) to obtain the title compound **(*S*)-6** as a semisolid (1.41 g, 2.76 mmol, 55 % in 3 steps, *E*/*Z* = >20:1): $[\alpha]_D^{23}$ = -41.6 (c 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 16 Hz, 1H), 6.85 (dt, *J* = 15, 9.5 Hz, 1H), 4.01 (d, *J* = 10 Hz, 1H), 3.96-3.93 (m, 1H), 3.84-3.77 (m, 1H), 3.55 (d, *J* = 14 Hz, 1H), 3.46 (d, *J* = 14 Hz, 1H), 3.12 (dd, *J* = 20, 14 Hz, 1H), 2.17-2.03 (m, 3H), 1.99-1.85 (m, 5H), 1.44 (s, 9H), 1.18 (s, 3H), 1.13-1.09 (m, 3H), 0.993 (s, 3H), 0.964-0.939 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.5, 137.7 (t, *J* = 27 Hz), 126.0 (t, *J* = 7.9 Hz), 120.0 (t, *J* = 246 Hz), 65.3, 62.8 (dd. *J* = 26, 23 Hz), 61.0, 54.2 (d, *J* = 254 Hz), 50.5, 48.5 (d, *J* = 115 Hz), 44.9, 38.4 (d, *J* = 271 Hz), 32.5 (d, *J* = 129 Hz), 28.0 (d, *J* = 254 Hz), 26.6, 24.6 (3C), 21.1 (d, *J* = 10 Hz), 20.6 (d, *J* = 8.3 Hz), 20.5 (d, *J* = 128 Hz), 17.0; HRMS (ESI), *m/z* calcd for $C_{22}H_{37}F_2N_2O_5S_2$ $[M+H]^+$ 511.2106, found 511.2104.

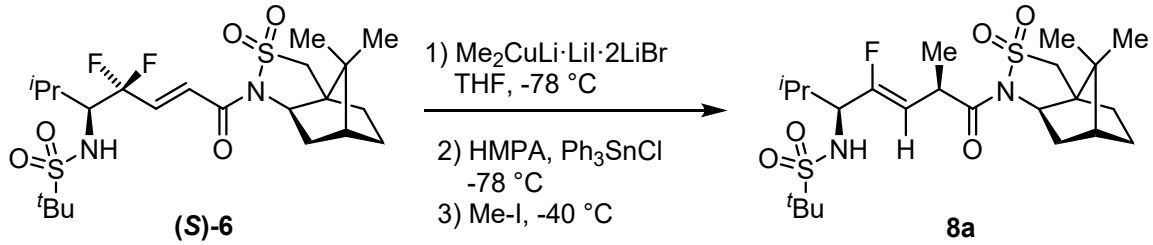


N*-((*S*,*E*)-7-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4,4-difluoro-2-methyl-7-oxohept-5-en-3-yl)-2-methylpropane-2-sulfonamide** ((R*)-6**): To a solution of *N*-sulfinyl ethyl ester **5** (2.47 g, 8.25 mmol) in CH_2Cl_2 (28.0 mL) was added *m*CPBA (≤77% purity, 2.77 g, 12.4 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the *N*-sulfonyl ethyl ester, which was used immediately in next step without purification. To a solution of *N*-sulfonyl ethyl ester in THF (33.0 mL) was added dropwise a solution of DIBAL-H in toluene (1.00 M, 16.5 mL, 16.5 mmol) at -78 ºC under argon, and the mixture was stirred at -78 ºC for 1 h. The reaction was quenched by saturated aqueous Rochelle salt. The reaction mixture was extracted with diethyl ether and dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the aldehyde, which was used immediately in next step without purification. To a stirred solution of diethylphosphonylacetyl-(*R*)-camphor-10,2-sultam **S6** (3.89 g, 9.90 mmol) in MeCN (28.0 mL) was added LiCl (839 mg, 19.8 mmol) and DIPEA (1.72 mL, 9.90 mmol) at 0 ºC under argon. After stirred for 10

min, a solution of the aldehyde in MeCN (5.00 mL) under argon was added to the mixture, and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **(*R*)-6** as a semisolid (2.07 g, 4.04 mmol, 49 % in 3 steps, *E*/*Z* = >20:1): $[\alpha]_D^{23}$ = 43.4 (c 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-7.01 (m, 1H), 6.91-6.81 (m, 1H), 3.97-3.93 (m, 2H), 3.86-3.76 (m, 1H), 3.56-3.40 (m, 3H), 3.15-3.07 (m, 1H), 2.16-2.07 (m, 3H), 1.96-1.84 (m, 5H), 1.43 (s, 9H), 1.16 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.962 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.5, 138.0 (t, *J* = 25 Hz), 125.8 (t, *J* = 8.4 Hz), 120.0 (t, *J* = 245 Hz), 65.3, 62.7 (t. *J* = 24 Hz), 61.0, 54.2 (d, *J* = 258 Hz), 50.5, 48.5 (d, *J* = 113 Hz), 44.8, 37.3 (d, *J* = 280 Hz), 32.5 (d, *J* = 129 Hz), 28.9, 26.8 (d, *J* =50 Hz), 24.6 (3C), 21.0 (d, *J* = 11 Hz), 20.8 (d, *J* = 48 Hz), 20.5 (d, *J* = 125 Hz), 17.0; HRMS (ESI), *m/z* calcd for $C_{22}H_{37}F_2N_2O_5S_2$ $[M+H]^+$ 511.2106, found 511.2108.

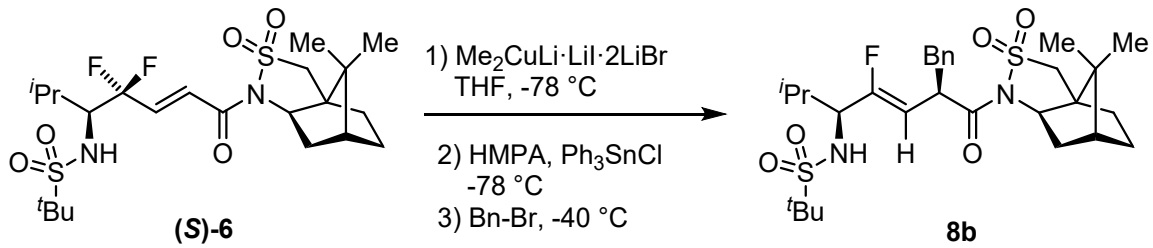


***N*-((*S*,*Z*)-7-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**7**): To a suspension of CuI (152 mg, 800 μmol) in THF (7.00 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.50 M, 1.07 mL, 1.60 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (102 mg, 200 μmol) in THF (1.00 mL) at -78 ºC. After stirred at -78 ºC for 30 min, the reaction was quenched by addition of a 3:2 saturated aqueous NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with diethyl ether, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **7** as colorless oil (74.3 mg, 151 μmol, 97%, *Z*/*E* = >20:1): $[\alpha]_D^{23}$ = -35.0 (c 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (dt, *J* = 36, 6.9 Hz, 1H), 3.78-3.61 (m, 3H), 3.54-3.39 (m, 3H), 3.10 (d, *J* = 4.0 Hz, 2H), 2.14-2.06 (m, 1H), 1.92-1.84 (m, 3H), 1.47-1.43 (m, 2H), 1.36 (s, 9H), 1.12 (s, 3H), 1.04-0.961 (m, 6H), 0.921 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.7, 159.0 (d, *J* = 261 Hz), 99.8 (d, *J* = 13 Hz), 77.4, 65.4, 63.0, 61.4 (d, *J* = 26 Hz), 60.0, 55.1, 53.0, 50.9, 50.5, 47.7 (d, *J* = 31 Hz), 44.8, 36.2, 32.9, 32.0, 26.7 (d, *J* = 38 Hz), 24.4 (d, *J* = 20 Hz), 20.6 (d, *J* = 4.4 Hz), 20.5 (d, *J* = 97 Hz), 19.2 (d, *J* = 38 Hz); HRMS (ESI), *m/z* calcd for $C_{22}H_{38}FN_2O_5S_2$ $[M+H]^+$ 493.2201, found 493.2196.



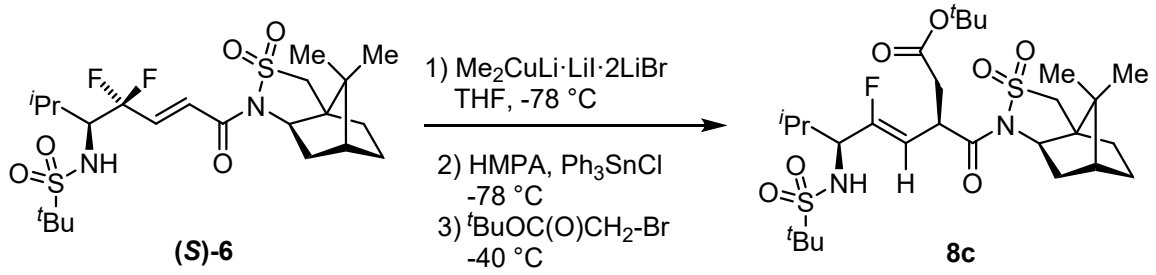
(*S*)-6 **8a**

***N*-((3*S*,6*R*,*Z*)-7-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2,6-dimethyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**8a**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (4100 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and methyl iodide (149 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **8a** (85.5 mg, 1.69 mmol, 56% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -46.8 (c 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 37, 8.8 Hz, 1H), 4.24 (d, *J* = 9.3 Hz, 2H), 4.20-4.16 (m, 1H), 3.88-3.85 (m, 1H), 3.72-3.61 (m, 1H), 3.47 (q, *J* = 14 Hz, 2H), 3.43-3.38 (m, 1H), 1.90-1.85 (m, 8H), 1.36 (s, 9 H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.942 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 156.9 (d, *J* = 261 Hz), 106.9 (d, *J* = 12 Hz), 65.0, 62.8, 61.4 (d, *J* = 26 Hz), 60.4, 59.8, 50.3, 48.1 (d, *J* = 68 Hz), 46.0 (d, *J* = 290 Hz), 44.7, 38.3, 36.1, 35.8 (d, *J* = 3.7 Hz), 32.3 (d, *J* = 96 Hz), 31.9, 26.6 (d, *J* = 38 Hz), 24.2, 20.6 (d, *J* = 35Hz), 20.2 (d, *J* = 65 Hz), 19.6, 19.2 (d, *J* = 26 Hz); HRMS (ESI), *m/z* calcd for $C_{23}H_{40}FN_2O_5S_2$ $[M+H]^+$ 507.2357, found 507.2353.



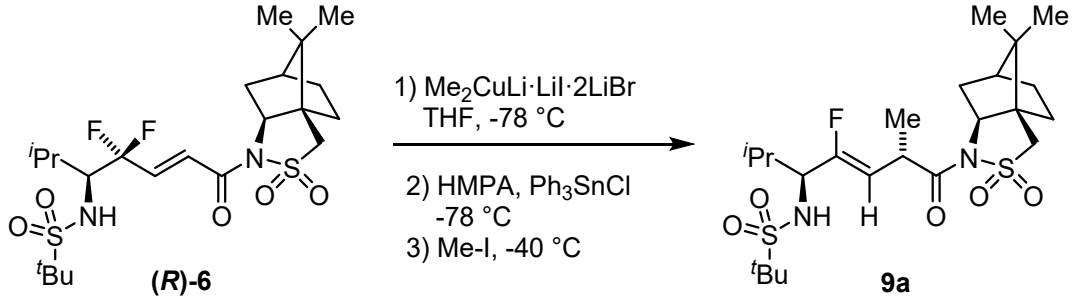
(*S*)-6 **8b**

***N*-((3*S*,6*R*,*Z*)-6-Benzyl-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**8b**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.0 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.0 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and benzyl bromide (285 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (4:1) to obtain the title compound **8b** (114 mg, 195 μmol, 65% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -38.8 (c 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.14 (m, 5H), 4.92 (dd, *J* = 36, 9.2 Hz, 1H), 4.54 (q, *J* = 8.1 Hz, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 1H), 3.70-3.62 (m, 1H), 3.45-3.36 (m, 2H), 3.15-3.08 (m, 2H), 2.81 (dd, *J* = 13, 7.3 Hz, 1H), 2.00-1.83 (m, 7H), 1.30 (s, 9H), 1.13 (s, 3H), 0.985 (d, *J* = 6.8 Hz, 3H), 0.945 (d, *J* = 6.8 Hz, 3H), 0.879 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.3, 157.9 (d, *J* = 262 Hz), 137.3, 129.5 (2C), 128.5 (2C),126.9, 105.6 (d, *J* = 12 Hz), 65.1, 63.0, 61.5 (d, *J* = 25 Hz), 61.4 (d, *J* = 394 Hz), 54.2 (d, *J* = 210 Hz), 49.4 (d, *J* = 272 Hz), 46.3 (d, *J* = 365 Hz), 46.2 (d, *J* = 369 Hz), 42.9, 39.3 (d, *J* = 249 Hz), 36.2, 32.9, 32.1 (d, *J* = 32 Hz), 26.9 (d, *J* = 49 Hz), 24.3 (3C), 20.6 (d, *J* = 3.2 Hz), 19.9 (d, *J* = 192 Hz), 19.5 (d, *J* = 93 Hz); HRMS (ESI), *m/z* calcd for $C_{29}H_{44}FN_2O_5S_2$ $[M+H]^+$ 583.2670, found 583.2672.



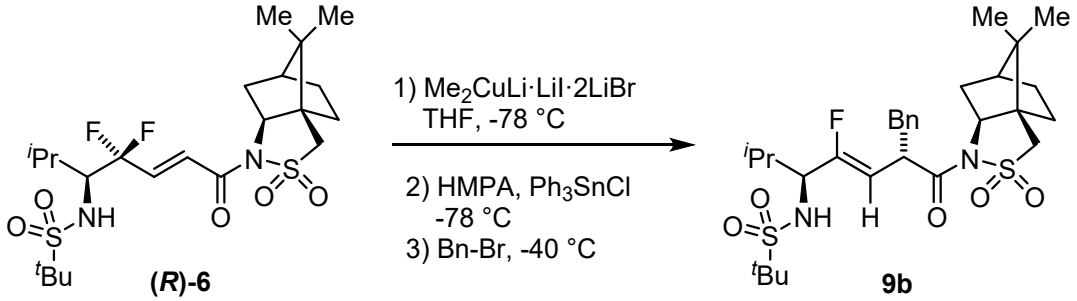
***tert*-Butyl (3*R*,6*S*,*Z*)-3-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidohexahydro-3*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)-6-((1,1-dimethylethyl)sulfonamido)-5-fluoro-7-methyloct-4-enoate** (**8c**): To a suspension of CuI (229 mg, 300 μmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin

chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and *tert*-butyl bromoacetate (352 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with *n*hexane/EtOAc (2:1) to obtain the title compound **8c** (91.0 mg, 150 μmol, 50% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -40.8 (c 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 36, 9.2 Hz, 1H), 4.41-4.35 (m, 1H), 4.14-4.11 (m 1H), 3.90-3.87 (m, 1H), 3.73-3.63 (m, 1H), 3.50-3.39 (m, 2H), 2.78 (dd, *J* = 16, 8.5 Hz, 1H), 2.52 (dd, *J* = 16, 5.4 Hz, 1H), 1.93-1.82 (m, 7H), 1.40 (s, 9H), 1.36 (s, 9H), 1.20 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.971 (d, *J* = 6.8 Hz, 3H), 0.952 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7 169.8, 158.2 (d, *J* = 263 Hz), 104.7 (d, *J* = 12 Hz), 81.2, 67.4, 65.3, 63.0, 61.4 (d, *J* = 26 Hz), 60.0, 55.1 53.1, 50.3 (d, *J* = 34 Hz), 48.3 (d, *J* = 73 Hz), 44.7, 38.5 (d, *J* = 102 Hz), 37.9 (d, *J* = 3.2 Hz), 35.2 (d, *J* = 191 Hz), 32.5 (d, *J* = 81 Hz), 28.1 (3C), 25.6 (d, *J* = 210 Hz), 24.3 (3C), 20.4 (d, *J* = 55 Hz), 19.1 (d, *J* = 22 Hz); HRMS (ESI), *m/z* calcd for $C_{28}H_{48}FN_2O_7S_2$ $[M+H]^+$ 607.2881, found 607.2880.

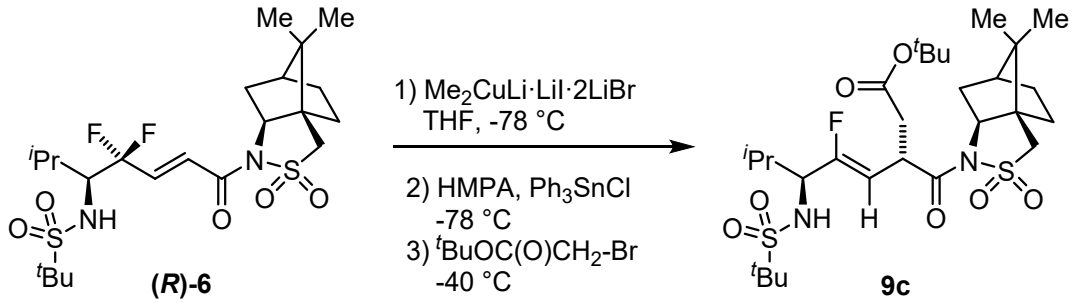


***N*-((3*S*,6*S*,*Z*)-7-((3a*R*,6*S*,7a*S*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2,6-dimethyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**9a**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and methyl iodide (149 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with *n*hexane/EtOAc (2:1) to obtain the title compound **9a** (88.2 mg,

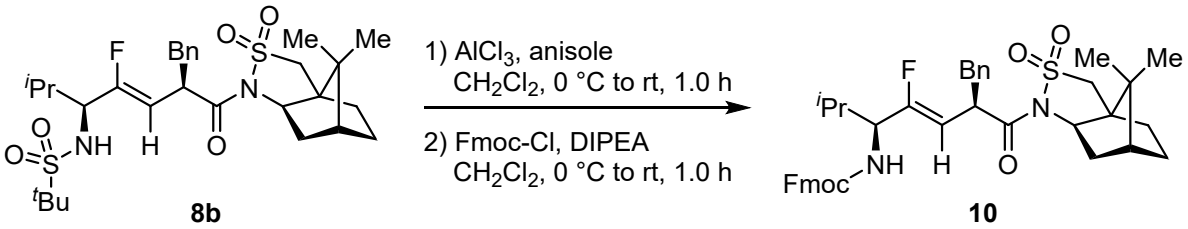
174 μmol, 58% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: [α] = 37.7 (c 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 37, 8.6 Hz, 1H), 4.22-4.15 (m, 1H), 4.12-4.11 (m, 2H), 3.87-3.84 (m, 1H), 3.76-3.66 (m, 1H), 3.53-3.39 (m, 3H), 1.93-1.85 (m, 8H), 1.35 (s, 9H), 1.15 (s, 3H), 1.12 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.970 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 157.2 (d, *J* = 261 Hz), 107.0 (d, *J* = 12 Hz), 65.1, 63.0, 61.2 (d, *J* = 27 Hz), 60.0, 54.2, 50.4, 48.6, 47.8 (d, *J* = 31 Hz), 46.6 (d, *J* = 366 Hz), 44.8, 38.4, 36.2, 32.9, 32.0, 26.9, 26.6, 24.3, 20.7 (d, *J* = 33 Hz), 20.3 (d, *J* = 65 Hz), 19.1 (d, *J* = 51 Hz); HRMS (ESI), *m/z* calcd for $C_{23}H_{40}FN_2O_5S_2$ $[M+H]^+$ 507.2357, found 507.2354.



***N*-((3*S*,6*S*,*Z*)-6-benzyl-7-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**9b**): To a suspension of CuI (229 mg, 1.2 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 2.40 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and benzyl bromide (285 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **9b** (115 mg, 198 μmol, 66% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: [α] = 28.6 (c 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 5H), 4.92 (dd, *J* = 36, 9.2 Hz, 1H), 4.54-4.48 (m, 1H), 3.77 (s, 1H), 3.71-3.61 (m, 1H), 3.42-3.39 (m, 2H), 3.18-3.10 (m, 2H), 2.76 (dd, *J* = 13, 8.1 Hz, 1H), 1.91-1.80 (m, 7H), 1.32 (s, 9H), 1.12 (s, 3H), 0.925-0.890 (m, 6H), 0.770-0.754 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.3, 158.0 (d, *J* = 263 Hz), 137.4, 129.5 (2C), 128.5 (2C), 126.9, 105.2 (d, *J* = 12 Hz), 65.1, 63.0, 61.5 (d, *J* = 301 Hz), 55.1, 53.1, 50.5, 48.1 (d, *J* = 60 Hz), 47.6, 44.7 (d, *J* = 17 Hz), 41.7 (d, *J* = 31 Hz), 40.3, 38.3, 36.2, 32.5 (d, *J* = 82 Hz), 32.0. 26.7 (d, *J* = 38 Hz), 24.5, 24.3, 20.3 (d, *J* = 70 Hz), 18.9 (d, *J* = 38 Hz); HRMS (ESI), *m/z* calcd for $C_{29}H_{43}FN_2NaO_5S_2$ $[M+Na]^+$ 605.2490, found 605.2493.

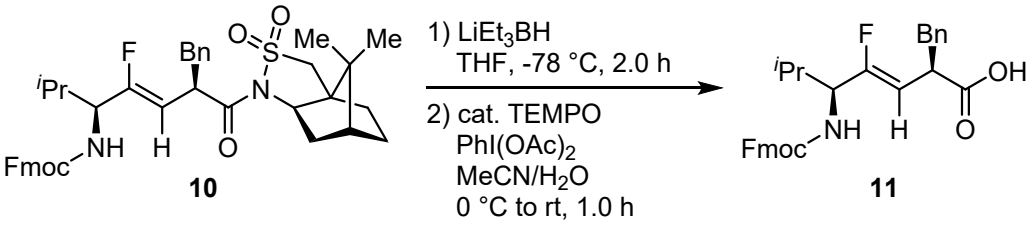


***tert*-Butyl (3*S*,6*S*,*Z*)-3-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-3*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)-6-((1,1-dimethylethyl)sulfonamido)-5-fluoro-7-methyloct-4-enoate** (**9c**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and *tert*-butyl bromoacetate (352 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **9c** (91.0 mg, 150 μmol, 50% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{27}$ = 30.5 (c 0.990, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (dd, *J* = 36, 9.1 Hz, 1H), 4.39-4.34 (m, 1H), 4.15-4.13 (m 1H), 3.90-3.86 (m, 1H), 3.75-3.65 (m, 1H), 3.50-3.39 (m, 2H), 2.79 (dd, *J* = 16, 7.9 Hz, 1H), 2.54 (dd, *J* = 16, 5.8 Hz, 1H), 2.03-1.86 (m, 7H), 1.40 (s, 9H), 1.35 (s, 9H), 1.19 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.971-0.955 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.6, 169.7, 158.2 (d, *J* = 263 Hz), 104.6 (d, *J* = 12 Hz), 81.3, 65.2, 61.2 (d, *J* = 27 Hz), 60.1, 55.1, 53.1, 47.9, 46.7 (d, *J* = 399 Hz), 38.6 (d, *J* = 133 Hz), 38.1, 37.1 (d, *J* = 174 Hz), 32.5 (d, *J* = 90 Hz), 28.1 (3C), 28.0, 26.6, 24.5, 24.3 (3C), 20.7, 20.4 (d, *J* = 63 Hz), 19.1 (d, *J* = 55 Hz); HRMS (ESI), *m/z* calcd for $C_{28}H_{47}FN_2NaO_7S_2$ $[M+Na]^+$ 629.2701, found 629.2706.



(9*H*-Fluoren-9-yl)methyl ((3*S*,6*R*,*Z*)-6-benzyl-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-

3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)carbamate (**10**): To a solution of the ester **8b** (117 mg, 200 μmol) in CH_2Cl_2 (2.00 mL) was added anisole (65.2 μL, 600 μmol) and $AlCl_3$ (99.9 mg, 750 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The reaction mixture was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification. To a solution of the amine in CH_2Cl_2 (2.00 mL) was added Fmoc-Cl (56.9 mg, 220 μmol) and DIPEA (40.1 μL, 230 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with *n*hexane/EtOAc (3:1 to 2:1) to obtain the title compound **10** as a white solid (119 mg, 174 μmol, 87%): $[\alpha]_D^{27}$ = -37.2 (c 1.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.23-7.07 (m, 5H), 5.00 (dd, *J* = 36, 9.3 Hz, 1H), 4.88 (d, *J* = 9.6 Hz, 1H), 4.55-4.35 (m, 3H), 4.23 (t, *J* = 6.8 Hz, 1H) 3.94 (dt, *J* = 24, 9.0 Hz, 1H), 3.78 (s, 1H), 3.42-3.35 (m, 2H), 3.14-3.07 (m, 1H), 2.77 (dd, *J* = 14, 7.5 Hz, 1H), 1.98-1.74 (m, 8H), 0.964 (dd, *J* = 20, 6.8 Hz, 6H), 0.879 (s, 3H), 0.735 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.3, 157.9 (d, *J* = 262 Hz), 155.8, 144.0, 141.4, 137.5, 129.6, 129.0 (d, *J* = 123 Hz), 128.3 (2C), 127.8, 127.2, 126.7, 125.2 (d, *J* = 8.6 Hz), 120.1 (2C), 105.6 (d, *J* = 13 Hz), 104.9 (d, *J* = 12 Hz), 66.0 (d, *J* = 221 Hz), 61.5 (d, *J* = 25 Hz), 61.4 (d, *J* = 394 Hz), 59.8, 58.4 (d, *J* = 26 Hz), 55.2, 53.1, 49.0 (d, *J* = 360 Hz), 48.3, 47.7, 47.4, 46.0 (d, *J* = 338 Hz), 41.8 (d, *J* = 336 Hz), 38.4, 36.2, 32.9, 32.0, 30.4, 26.5, 24.3, 20.3 (d, *J* = 89 Hz), 19.0 (d, *J* = 71 Hz); HRMS (ESI), *m/z* calcd for $C_{40}H_{46}FN_2O_5S$ $[M+H]^+$ 685.3106, found 685.3103.

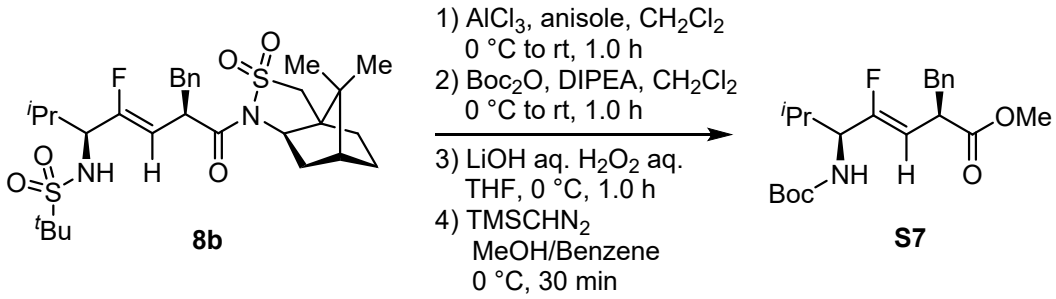


(2*R*,5*S*,*Z*)-5-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-benzyl-4-fluoro-6-methylhept-3-enoic acid (**11**): To a solution of **10** (171 mg, 250 μmol) in THF (2.50 mL) was added $LiEt_3BH$ in THF (1.00 M, 750 μL, 750 μmol) at -78 ºC under argon, and the mixture was stirred for 2.0 h at -78 ºC. The reaction was quenched with MeOH and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. The reaction mixture was concentration under reduced pressure to obtain the aldehyde, which was used immediately in the next step without purification. To solution of TEMPO (11.7 mg, 80 μmol) and $PhI(OAc)_2$ (11.7 mg, 80 μmol) in MeCN (1.00 mL) and H_2O (250 μL) was added the alcohol in MeCN (1.00 mL). After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was

concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (1:1) to obtain the title compound **11** as a white solid (23.3 mg, 47.5 μmol, 19%): $[\alpha]_D^{27}$ = -44.5 (c 1.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 5.0 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.20-7.10 (m, 5H), 4.89 (dd, *J* = 36, 9.8 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 4.52-4.49 (m, 2H), 4.40-4.36 (m, 1H), 4.22 (t, *J* = 6.8 Hz, 1H), 3.94 (dt, *J* = 22, 8.8 Hz, 1H), 3.77-3.70 (m, 1H), 3.12 (dd, *J* = 14, 6.3 Hz, 1H), 2.80 (dd, *J* = 13, 8.5 Hz, 1H), 1.85-1.78 (m, 1H), 0.857 (dd, *J* = 14, 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 178.0, 158.6 (d, *J* = 260 Hz), 155.8, 144.0 (2C), 141.5 (2C), 138.0, 129.2 (2C), 128.4 (2C), 127.9 (2C), 127.2 (2C), 126.7 (2C), 125.1, 120.2 (2C), 104.7 (d, *J* = 12 Hz), 67.0, 58.2 (d, *J* = 27 Hz), 47.4, 42.5, 38.5, 30.2, 19.4, 18.6; HRMS (ESI), *m/z* calcd for $C_{30}H_{31}FNO_4$ $[M+H]^+$ 488.2232, found 488.2229.

III. Determination of steric configuration

III-I. Derivation to the known compound: Boc-Val-ψ[(*Z*)-CF=CH]-Phe-OMe (S7)



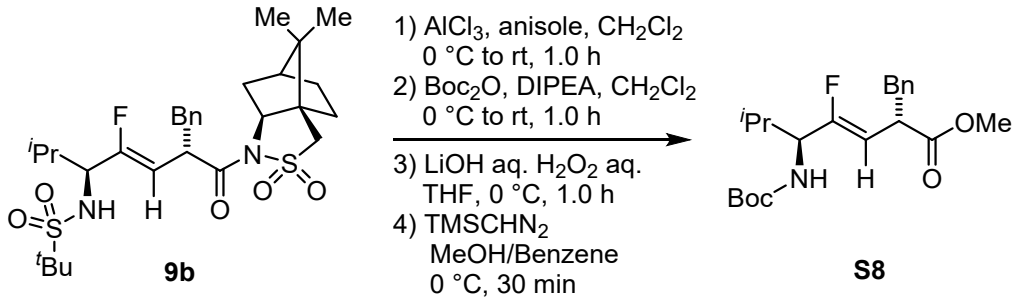
Methyl (2*R*,5*S*,*Z*)-2-benzyl-5-((*tert*-butoxycarbonyl)amino)-4-fluoro-6-methylhept-3-enoate (**S7**): To a solution of the ester **8b** (190 mg, 326 μmol) in CH_2Cl_2 (3.00 mL) was added anisole (53.1 μL, 489 μmol) and $AlCl_3$ (130 mg, 978 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification.

To a solution of the amine in CH_2Cl_2 (3.00 mL) was added Boc_2O (85.4 mg, 391 μmol) and DIPEA (85.2 μL, 489 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the protected amine, which was used immediately in the next step without purification.

To a solution of the protected amine in THF (3.00 mL) was added the aqueous H_2O_2 (166.5 μL, 1.63 mmol) and the aqueous LiOH (1.00 M, 652 μL, 652 μmol) at 0 °C, and the reaction mixture was stirred for 1.0 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The mixture was concentration under reduced pressure to obtain the carboxylic acid, which was used immediately in the next step without purification

To a solution of the carboxylic acid in toluene/MeOH (1:1, 6.00 mL) was added $TMSCHN_2$ in ^{n}hexane (0.6 M, 538 μL, 323 μmol) at 0 ºC under argon, and the mixture was stirred for 2 h at 0 ºC. The reaction mixture was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **S7** as a white solid (65.8 mg, 173 μmol, 53%): $[\alpha]_D^{20}$ = -75.2 (c 0.990, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.14 (m, 5H), 4.88 (dd, *J* = 36, 9.7 Hz, 1H), 4.59 (d, *J* = 9.4 Hz, 1H), 3.96-3.88 (m, 1H), 3.78-3.72 (m, 1H), 3.63 (s, 3H), 3.08 (dd, *J* = 14, 7.0 Hz, 3H), 2.81 (dd, *J* = 14, 7.9 Hz, 3H), 1.83-1.77 (m, 1H), 1.45 (s, 9H), 0.868 (d, *J* = 6.7 Hz, 1H), 0.833 (d, *J* = 6.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 158.8 (d, *J* = 260 Hz), 155.1, 138.2, 129.0 (2C), 128.3 (2C), 126.5, 104.5 (d, *J* = 13 Hz), 79.7, 57.3 (d, *J* = 27 Hz), 51.9, 42.5, 38.7, 30.1, 28.3 (3C), 19.2, 18.1; HRMS (ESI), *m/z* calcd for $C_{21}H_{31}FNO_4$ $[M+H]^+$ 380.2232, found 380.2330.

III-II. Derivation to the compound: Boc-Val-*ψ*[(*Z*)-CF=CH]-D-Phe-OMe (S8)



Methyl (2*S*,5*S*,*Z*)-2-benzyl-5-((*tert*-butoxycarbonyl)amino)-4-fluoro-6-methylhept-3-enoate (**S8**): To a solution of the ester **9b** (74.3 mg, 127 μmol) in CH_2Cl_2 (2.00 mL) was added anisole (20.7 μL, 191 μmol) and $AlCl_3$ (50.8 mg, 381 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification.

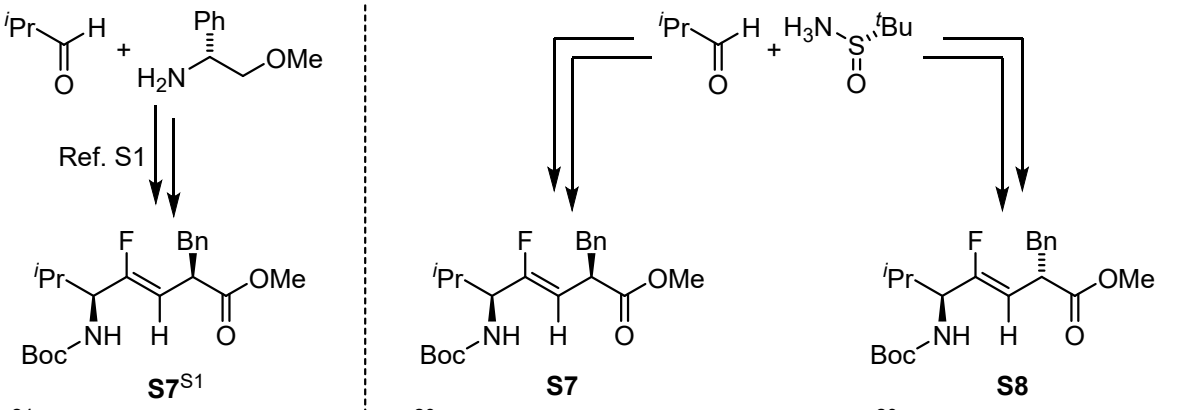
To a solution of the amine in CH_2Cl_2 (2.00 mL) was added Boc_2O (33.3 mg, 152 μmol) and DIPEA (33.2 μL, 191 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the protected amine, which was used immediately in the next step without purification.

To a solution of the protected amine in THF (2.00 mL) was added the aqueous H_2O_2 (64.9 μL, 640 μmol) and the aqueous LiOH (1.00 M, 254 μL, 254 μmol) at 0 °C, and the reaction mixture was stirred for 1.0 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The mixture was concentration under reduced pressure to obtain the carboxylic acid, which was used immediately in the next step without purification

To a solution of the carboxylic acid in toluene/MeOH (1:1, 3.00 mL) was added $TMSCHN_2$ in ^{n}hexane (0.6 M, 265 μL, 159 μmol) at 0 ºC under argon, and the mixture was stirred for 2 h at 0 ºC. The reaction mixture was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **S8** as a white solid (21.8 mg, 57.0 μmol, 45%): $[\alpha]_D^{20}$ = 17.8 (c 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.13 (m, 5H), 4.85 (dd, *J* = 36, 9.9 Hz, 1H), 4.65 (d, *J* = 9.4 Hz, 1H), 3.95-3.86 (m, 1H), 3.81-3.74 (m, 1H), 3.63 (s, 3H), 3.08 (dd, *J* = 14, 6.9 Hz, 1H), 2.81 (dd, *J* = 14, 8.1 Hz, 1H), 1.80-1.75 (m, 1H), 1.44 (s, 9H), 0.822 (d, *J* = 6.8 Hz, 3H), 0.733 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.4, 158.7 (d, *J* = 260 Hz), 155.1, 138.2, 129.0 (2C), 128.4 (2C), 126.5, 104.6 (d, *J* = 13 Hz), 79.7, 57.1 (d, *J* = 27 Hz), 51.9, 42.5, 38.7, 30.2, 28.3 (3C), 19.0, 18.0; HRMS (ESI), *m/z* calcd for $C_{21}H_{31}FNO_4$ $[M+H]^+$ 380.2232, found 380.2232.

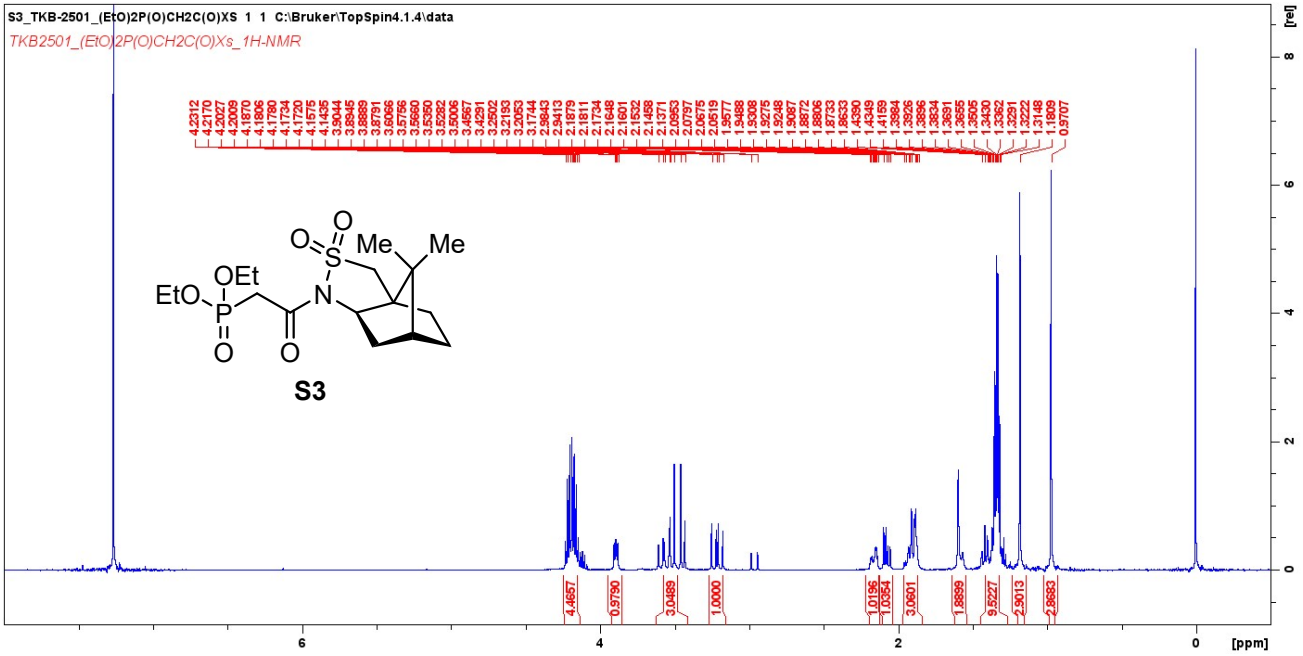
III-III. Comparison of Spectroscopic Methodology

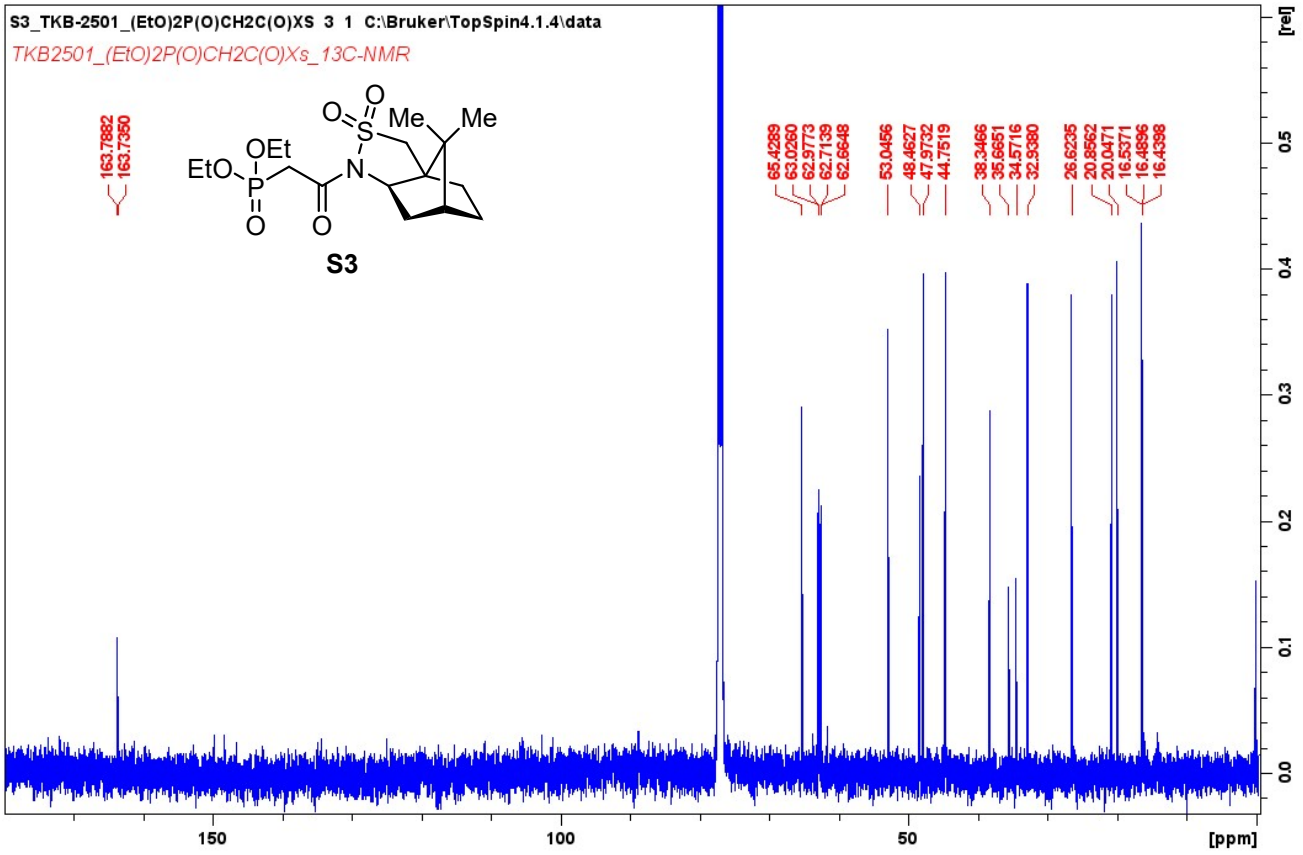
The spectroscopic data of compound **S7**, which was synthesized by the present method, were compatible with those of the previous research[S1] in analyses of ^{1}H NMR, ^{13}C NMR, and optical rotation. Furthermore, the optical rotation of the (L,L) isomer **S7** was negative, whereas that of the epimer, the (L,D) isomer **S8**, was positive.

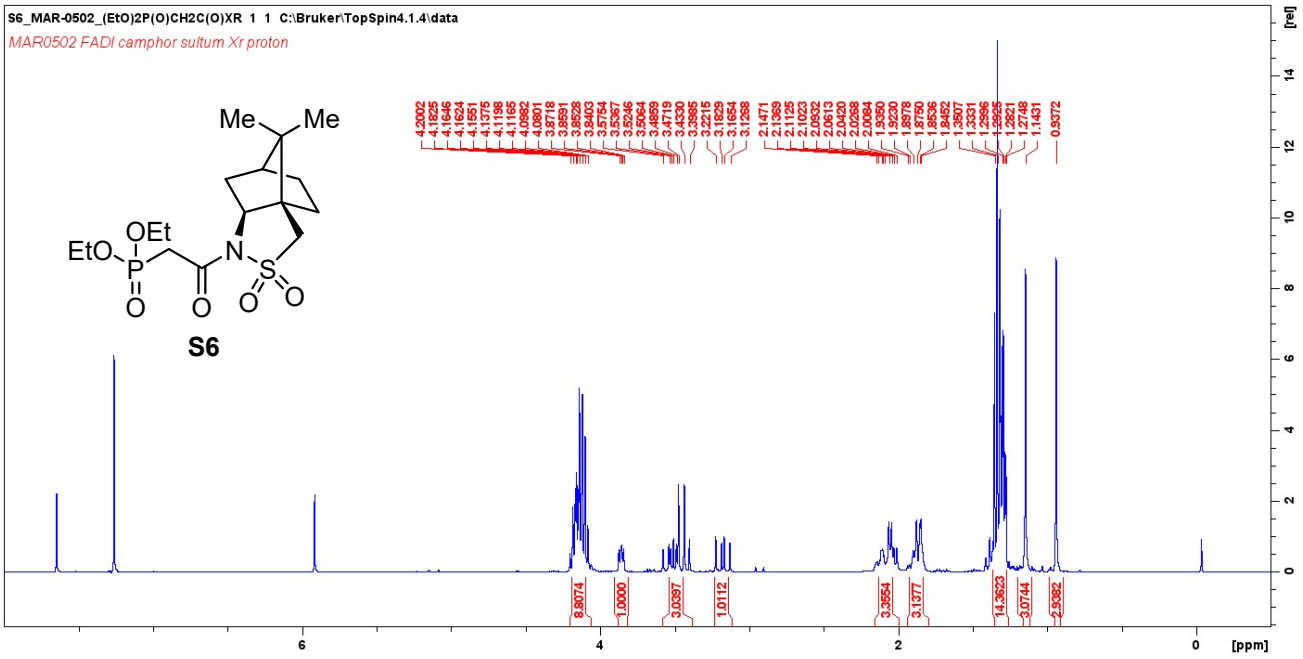


S1) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332-4346.

IV. ^{1}H NMR and ^{13}C NMR charts



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Me
OEt
EtO
P
N
S
O
O
O
O
O
S6
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4.1524
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4.1375
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2.0288
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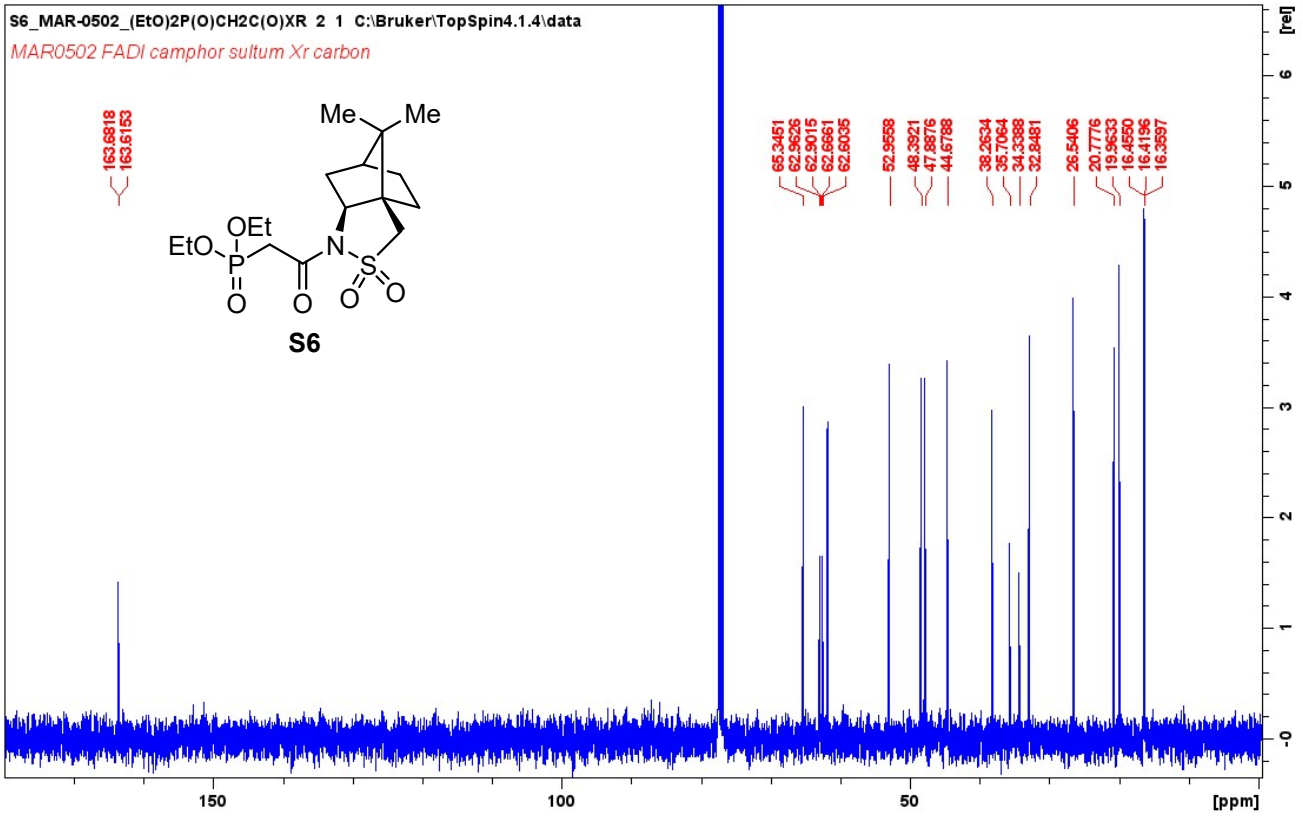
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Me
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EtO
P
N
S
O
O
O
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S6
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62.9015
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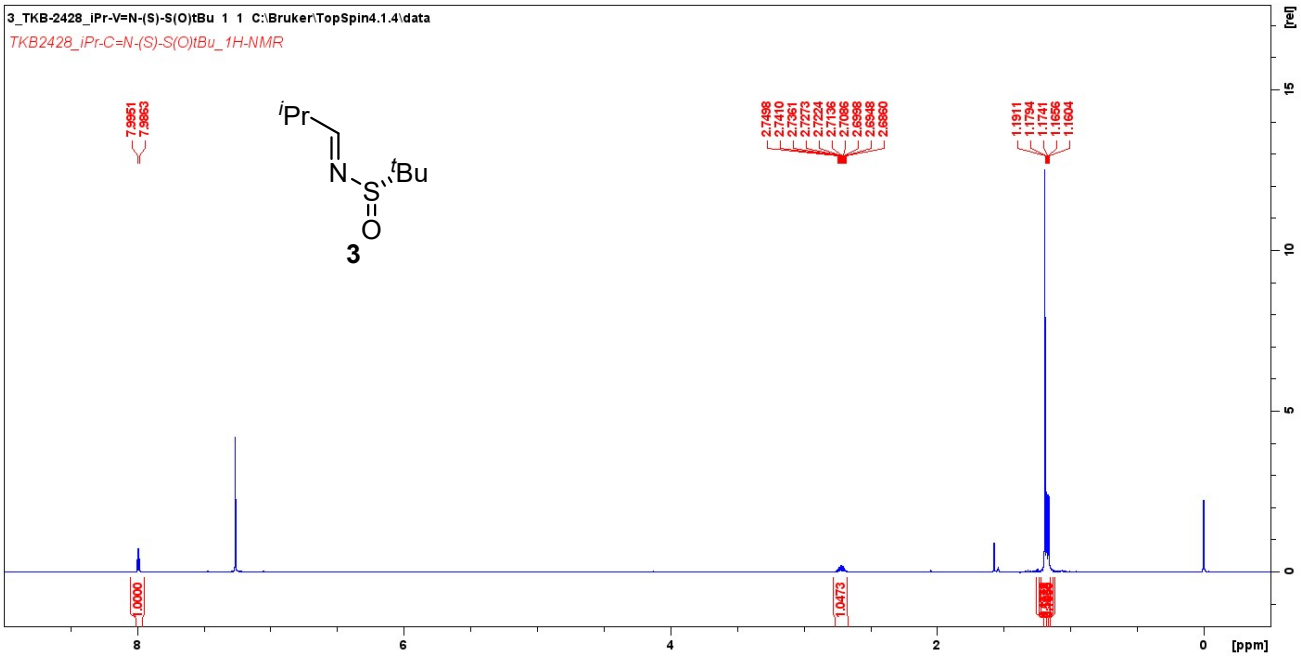
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2.7273
2.7224
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1.1794
1.1741
1.1656
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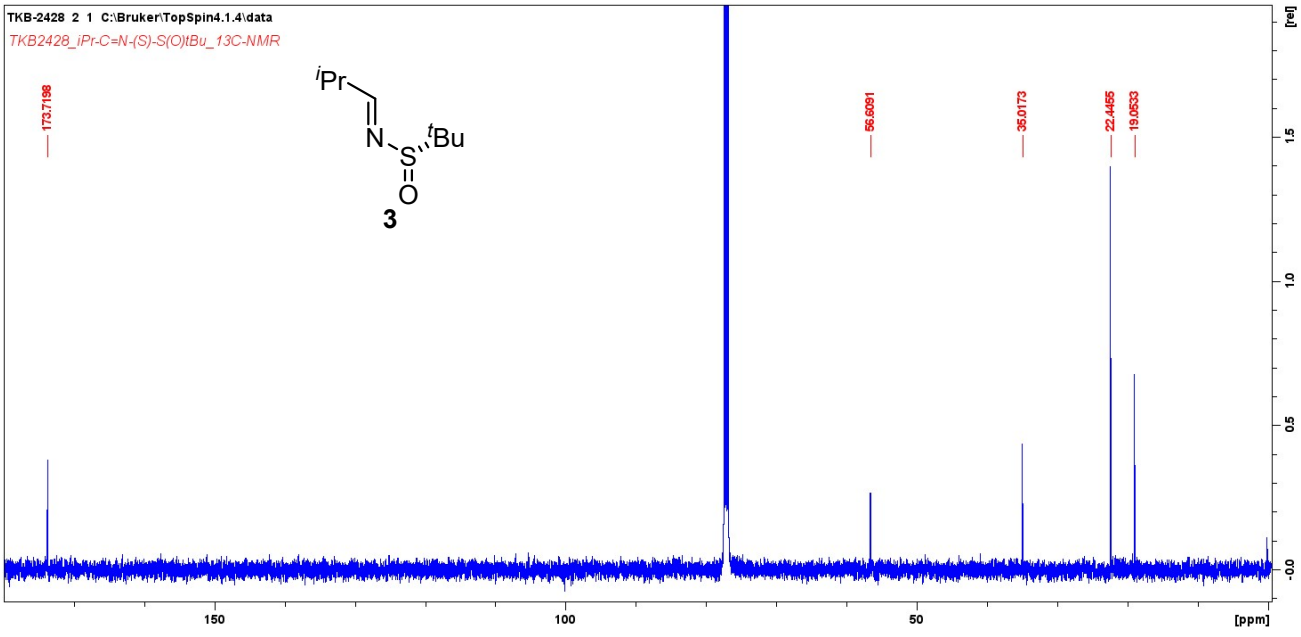
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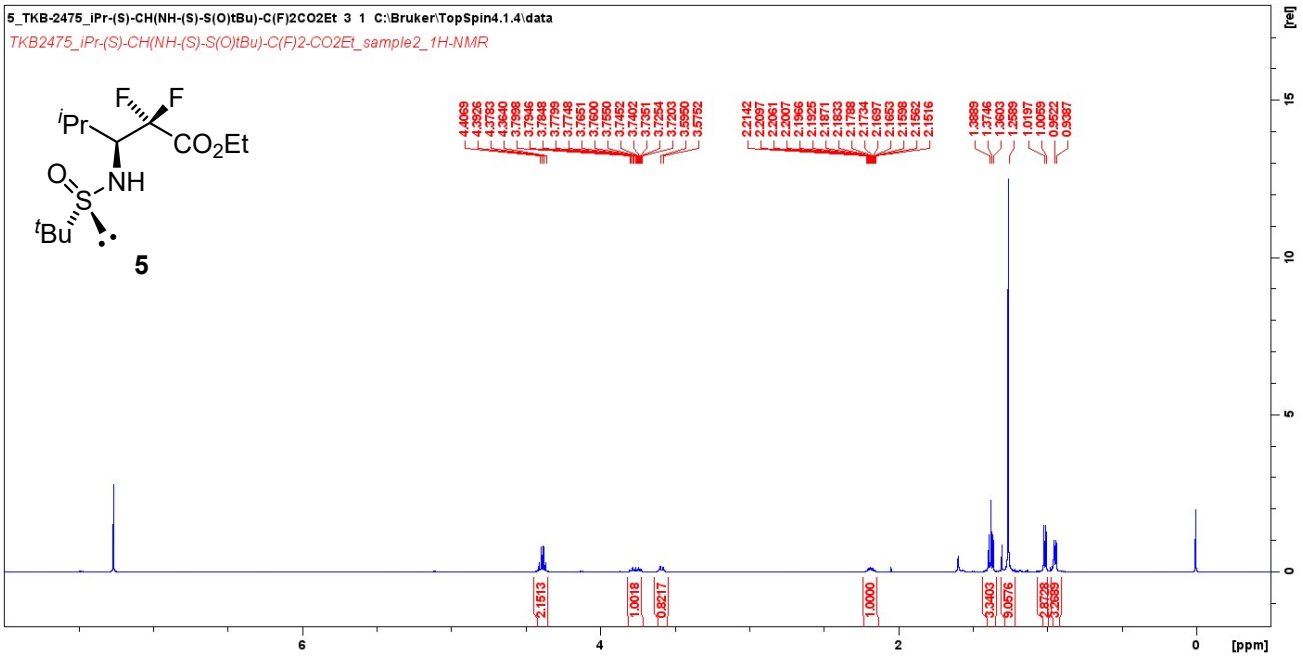
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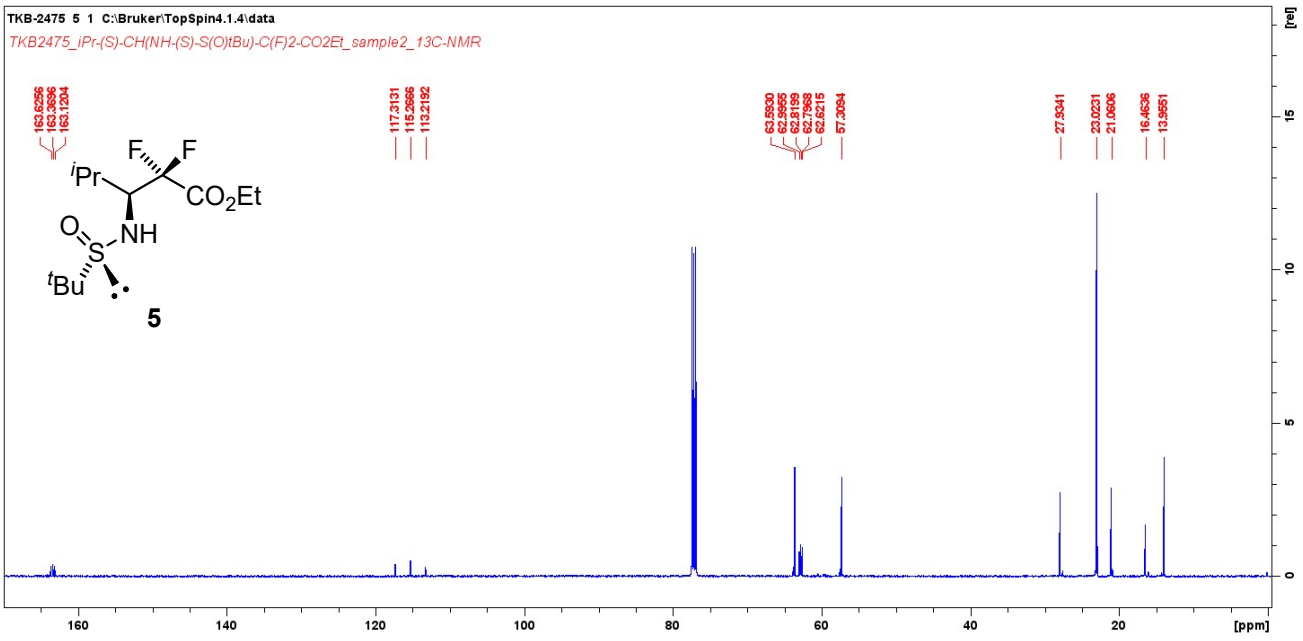
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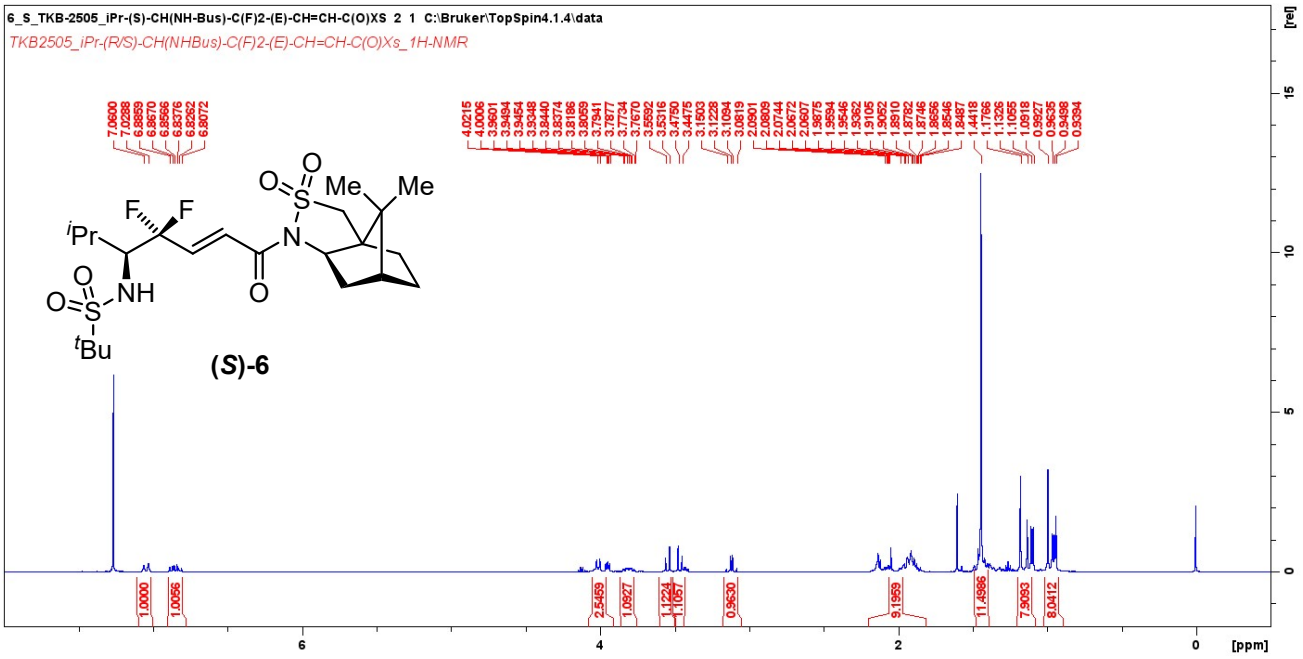
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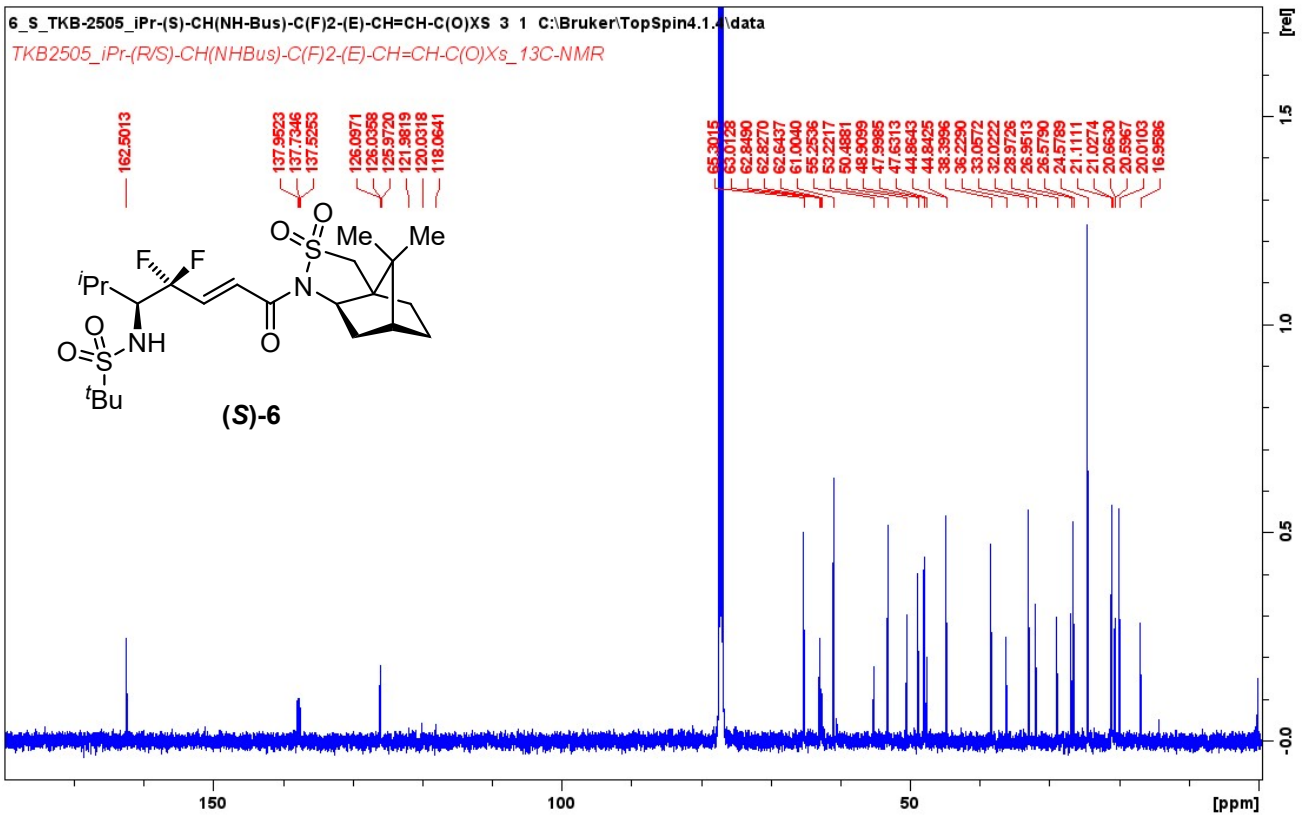
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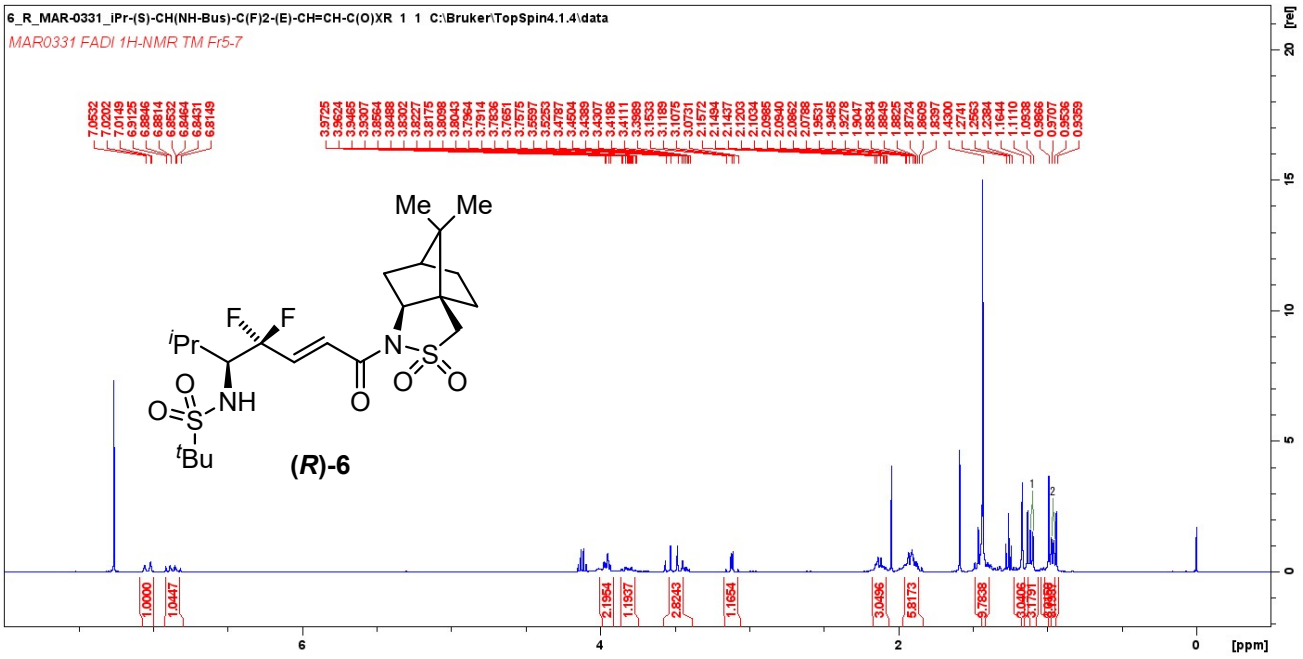
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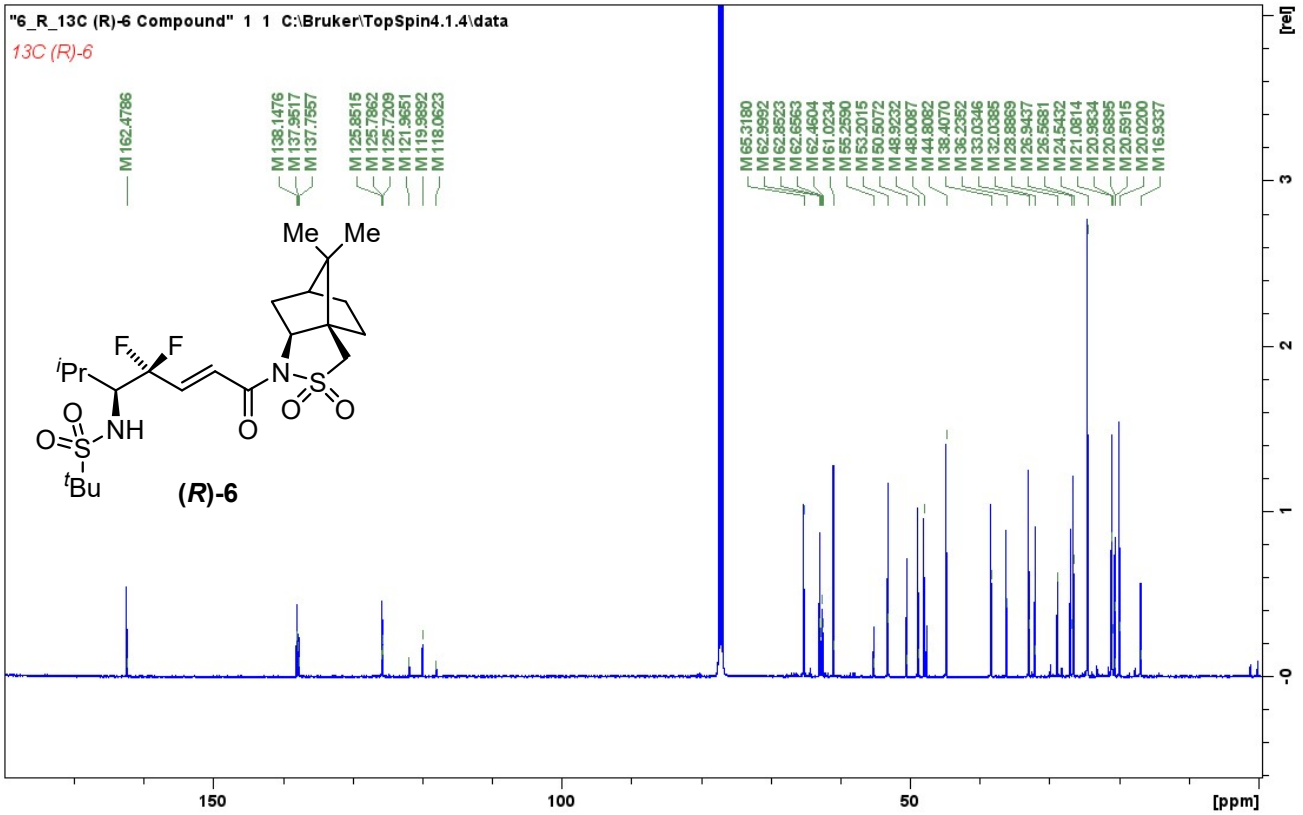
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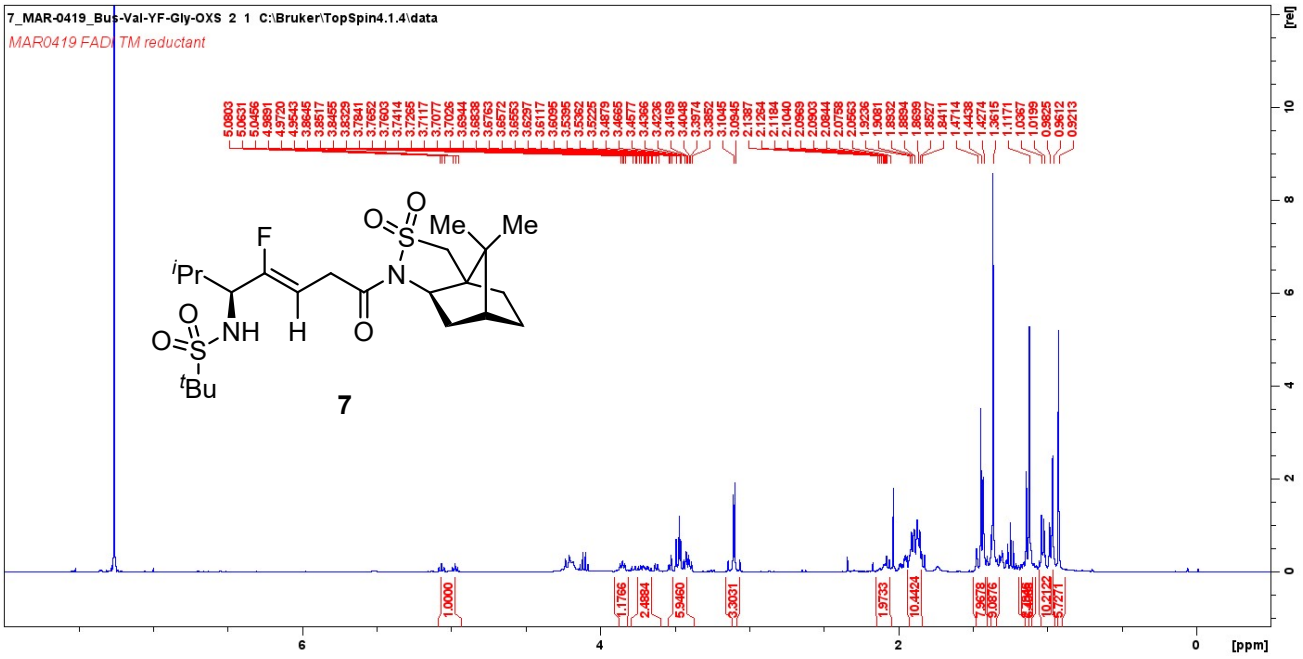
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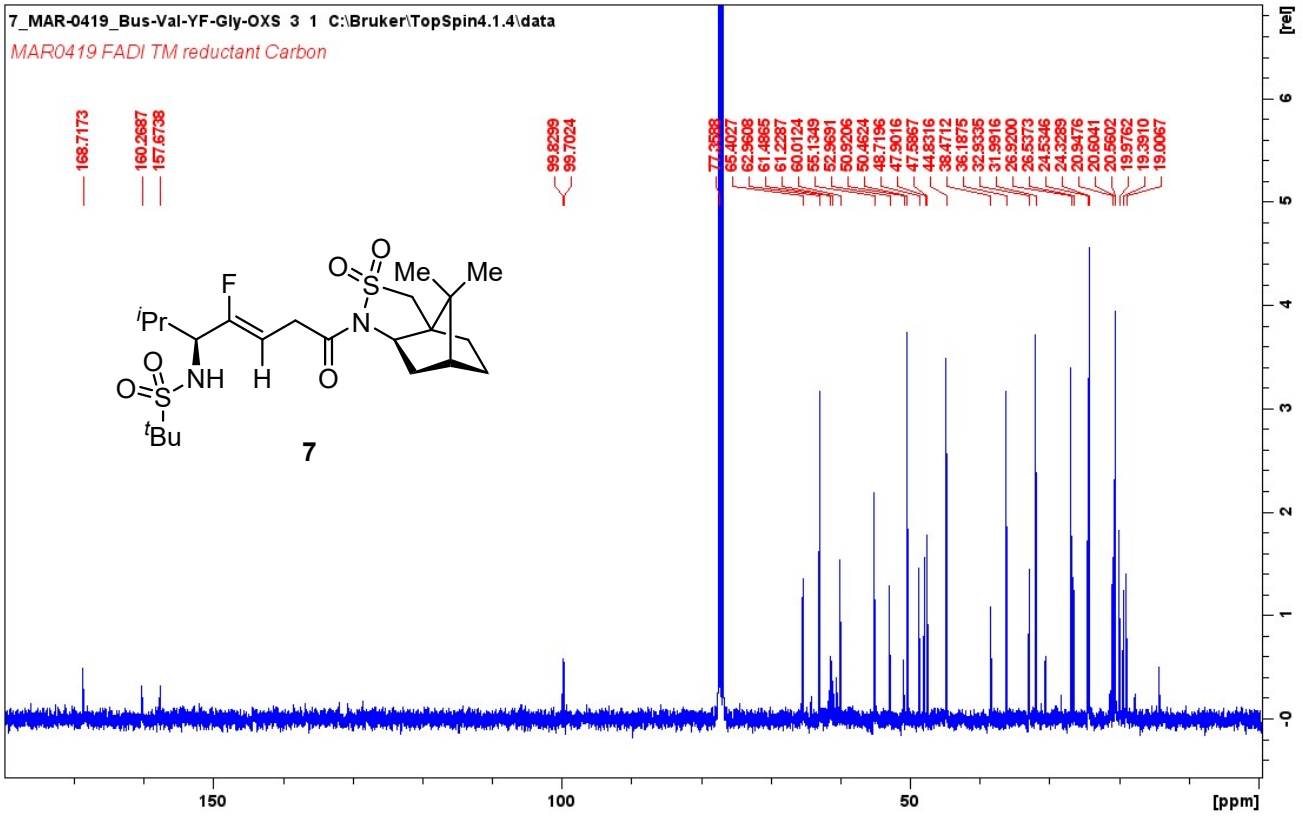
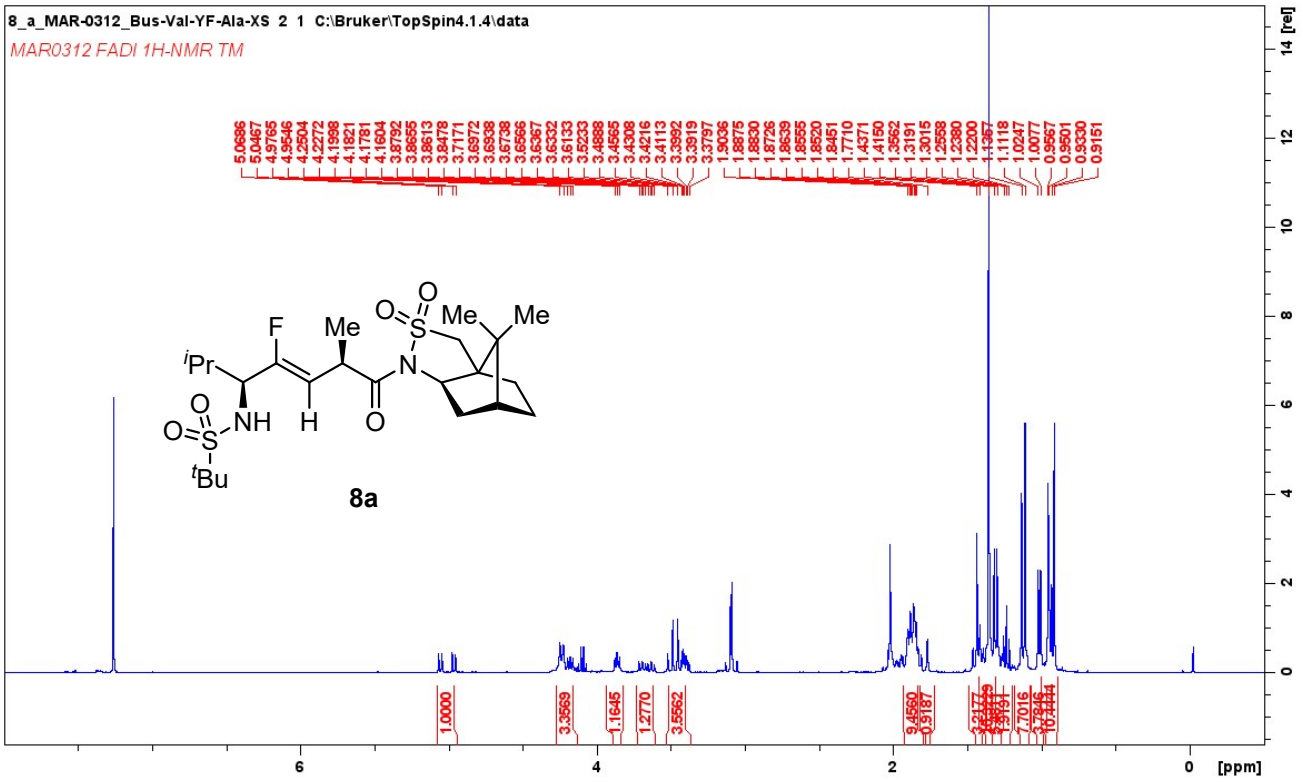
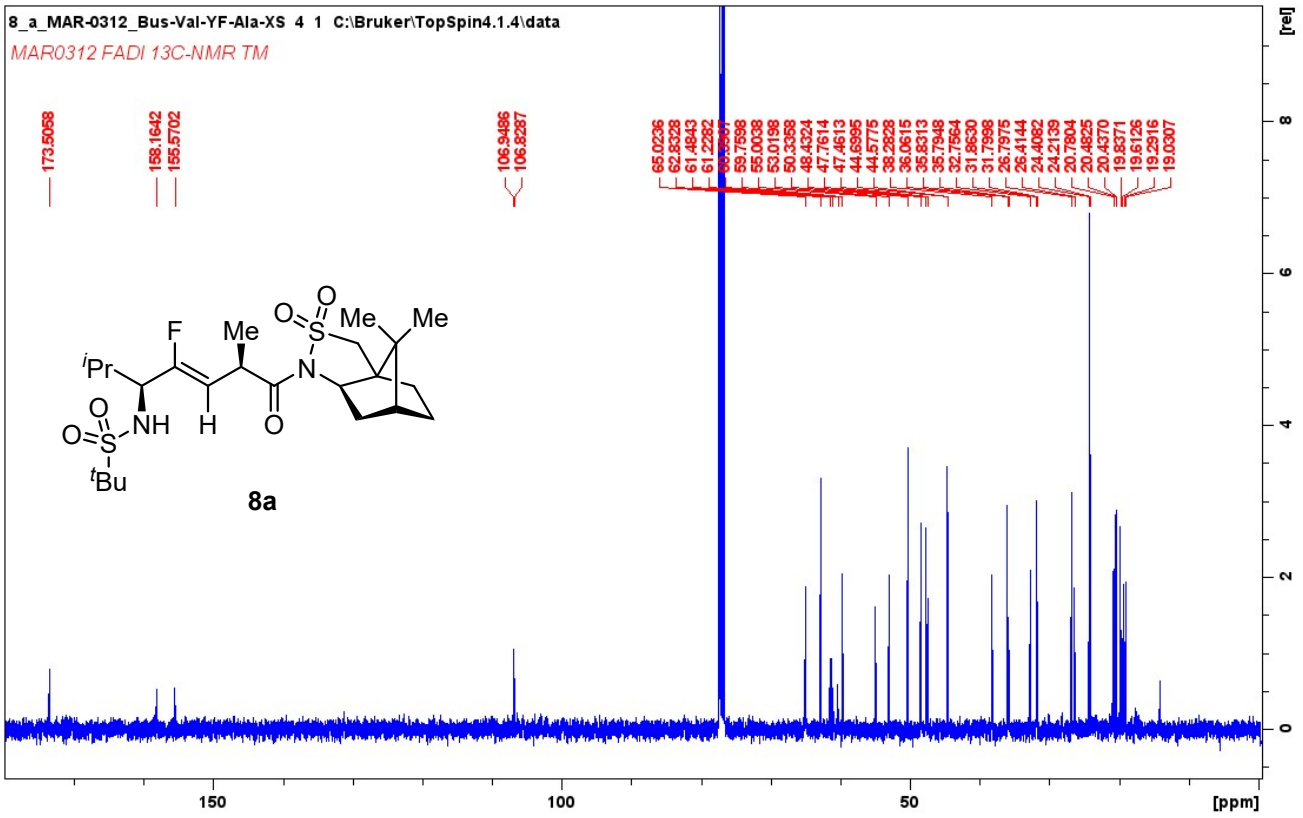
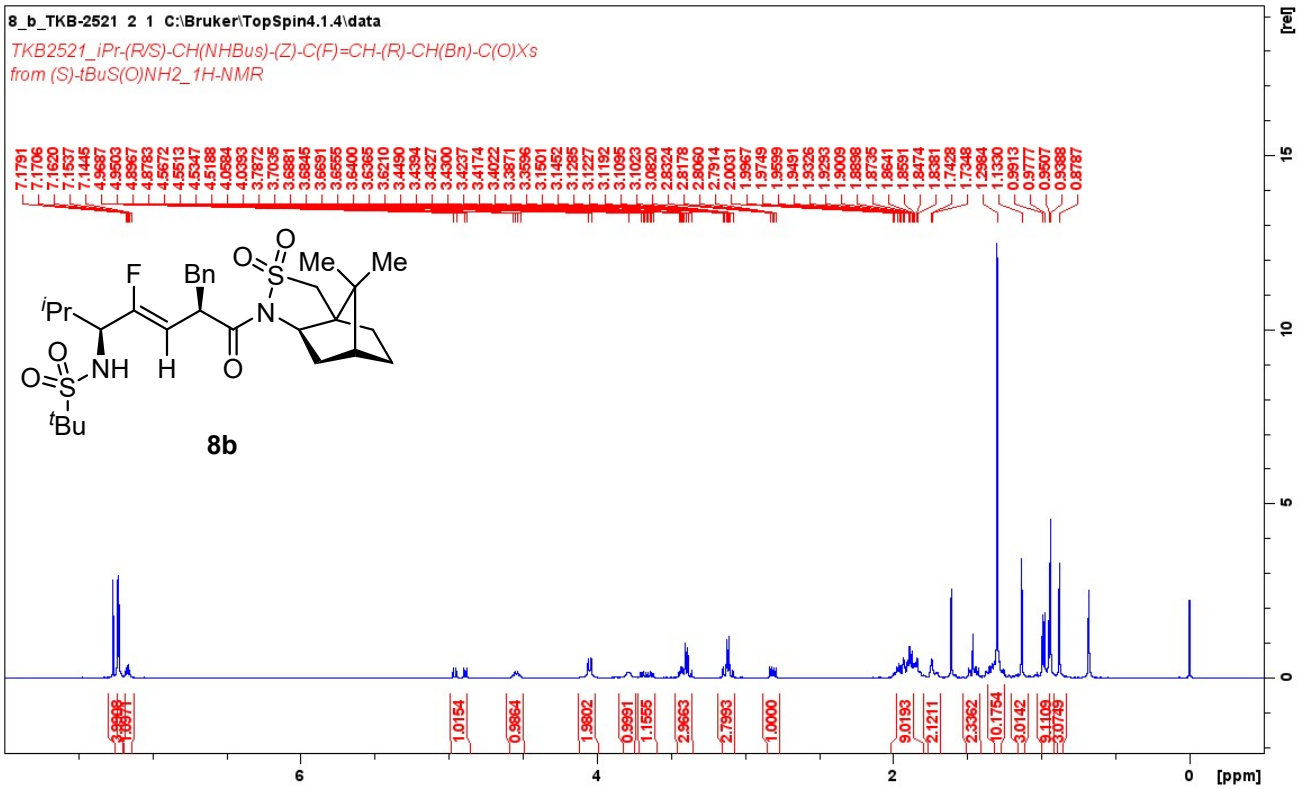
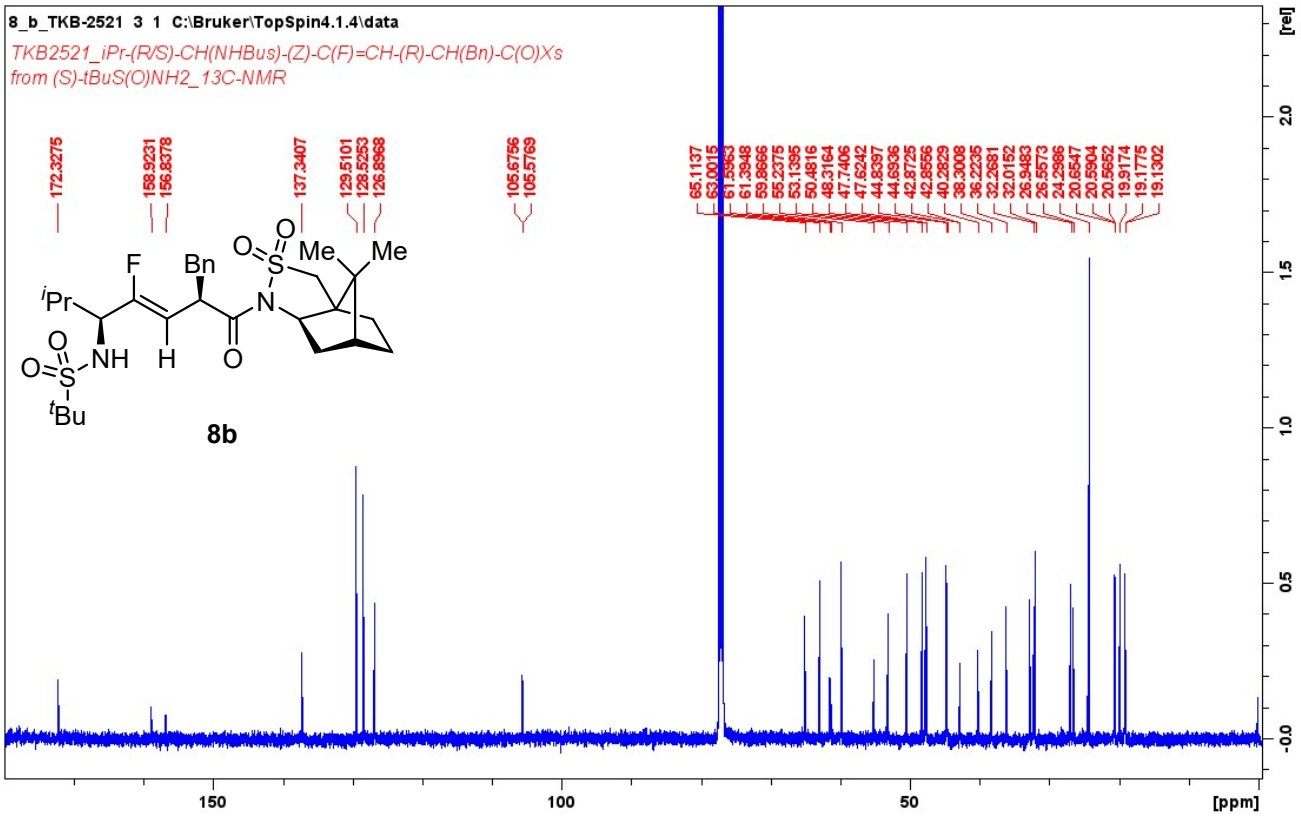
MAR0419 FADI TM reductant
7
[ppm]
[rel]

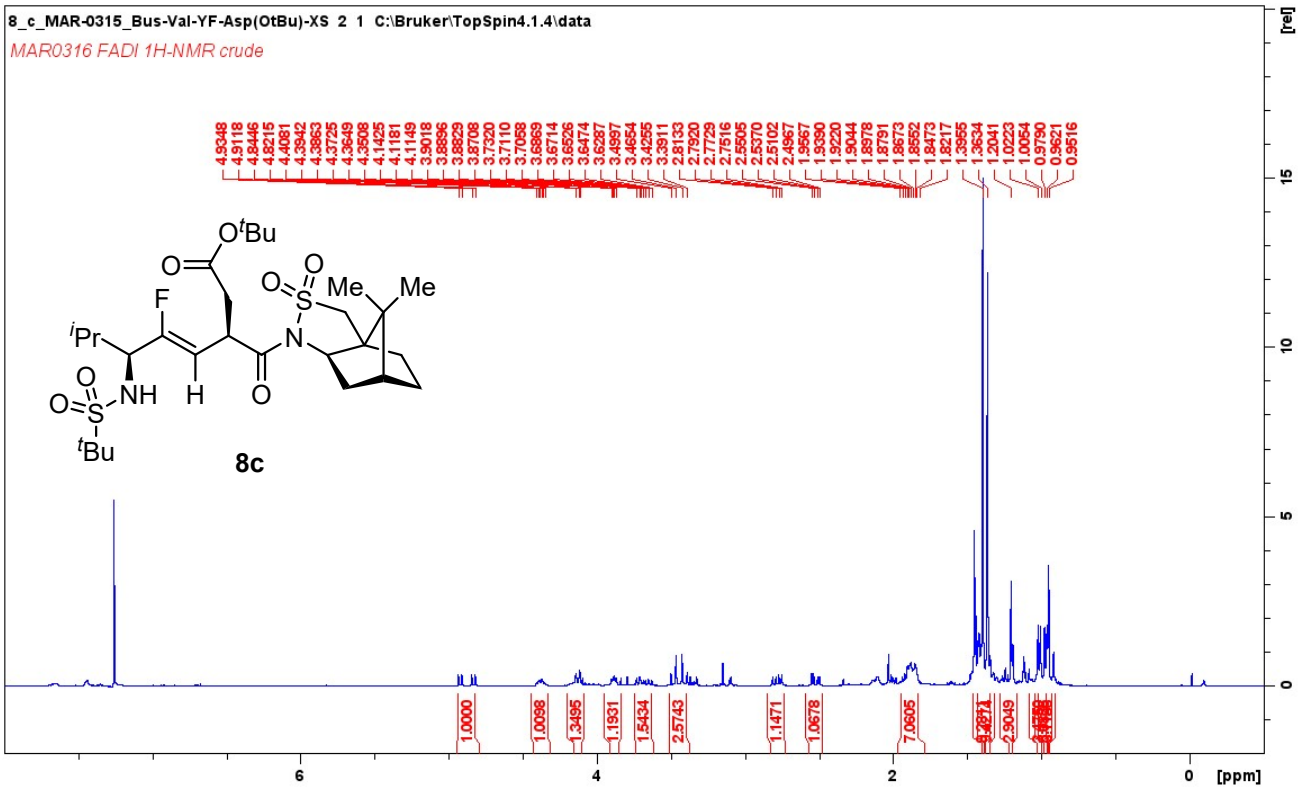

7_MAR-0419_Bus-Val-YF-Gly-OXS 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0419 FADI TM reductant Carbon
168.7173
160.2687
157.6738
99.8299
99.7024
7
[ppm]
[rel]

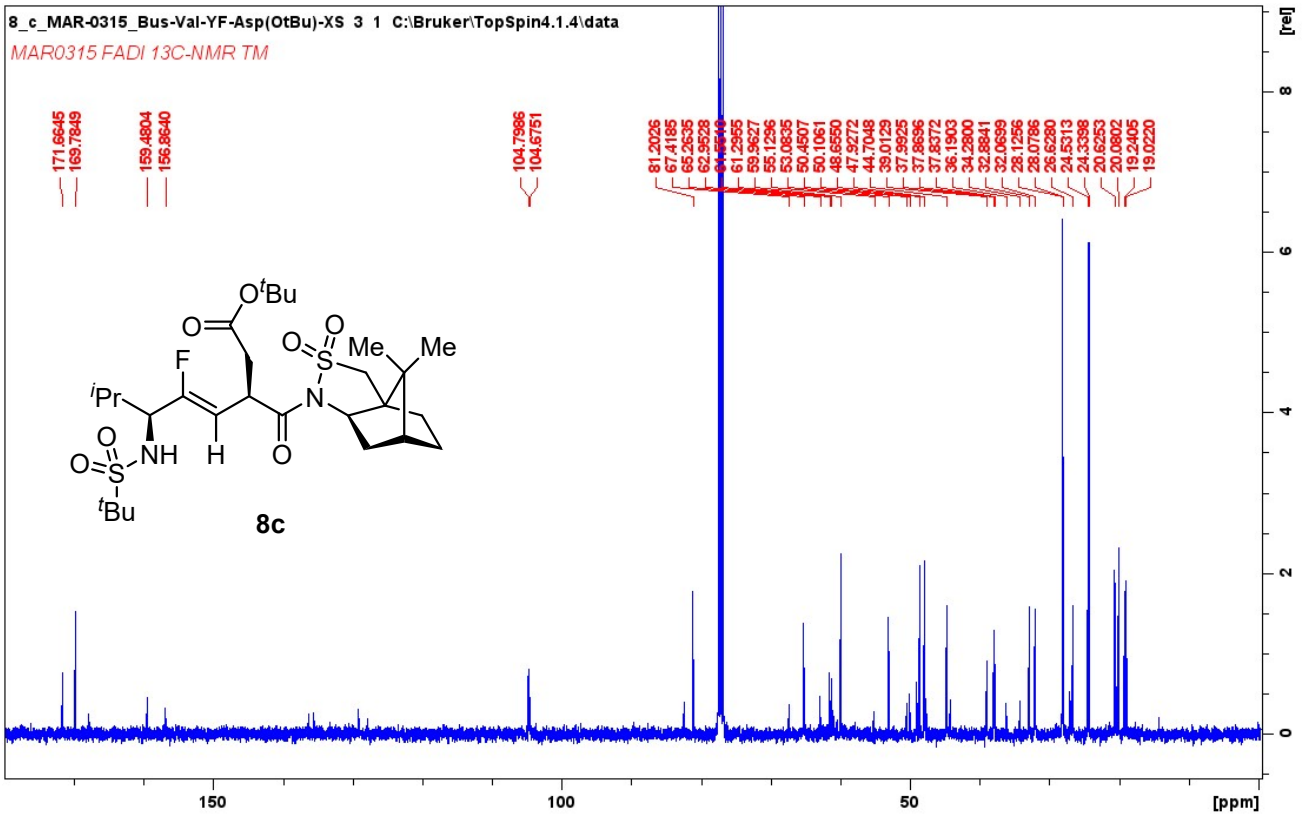

8_a_MAR-0312_Bus-Val-YF-Ala-XS 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0312 FADI 1H-NMR TM
8a
[ppm]

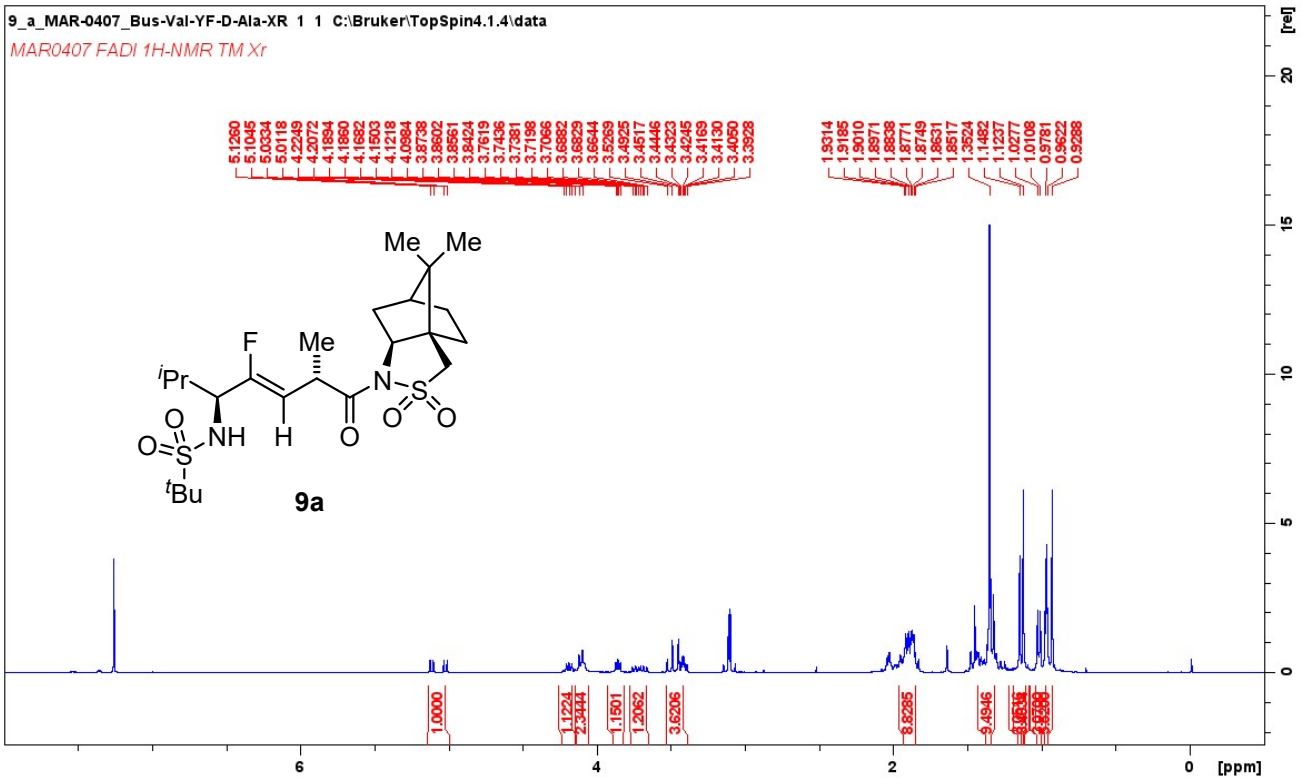

8_a_MAR-0312_Bus-Val-YF-Ala-XS 4 1 C:\Bruker\TopSpin4.1.4\data
MAR0312 FADI 13C-NMR TM
8a
[ppm]

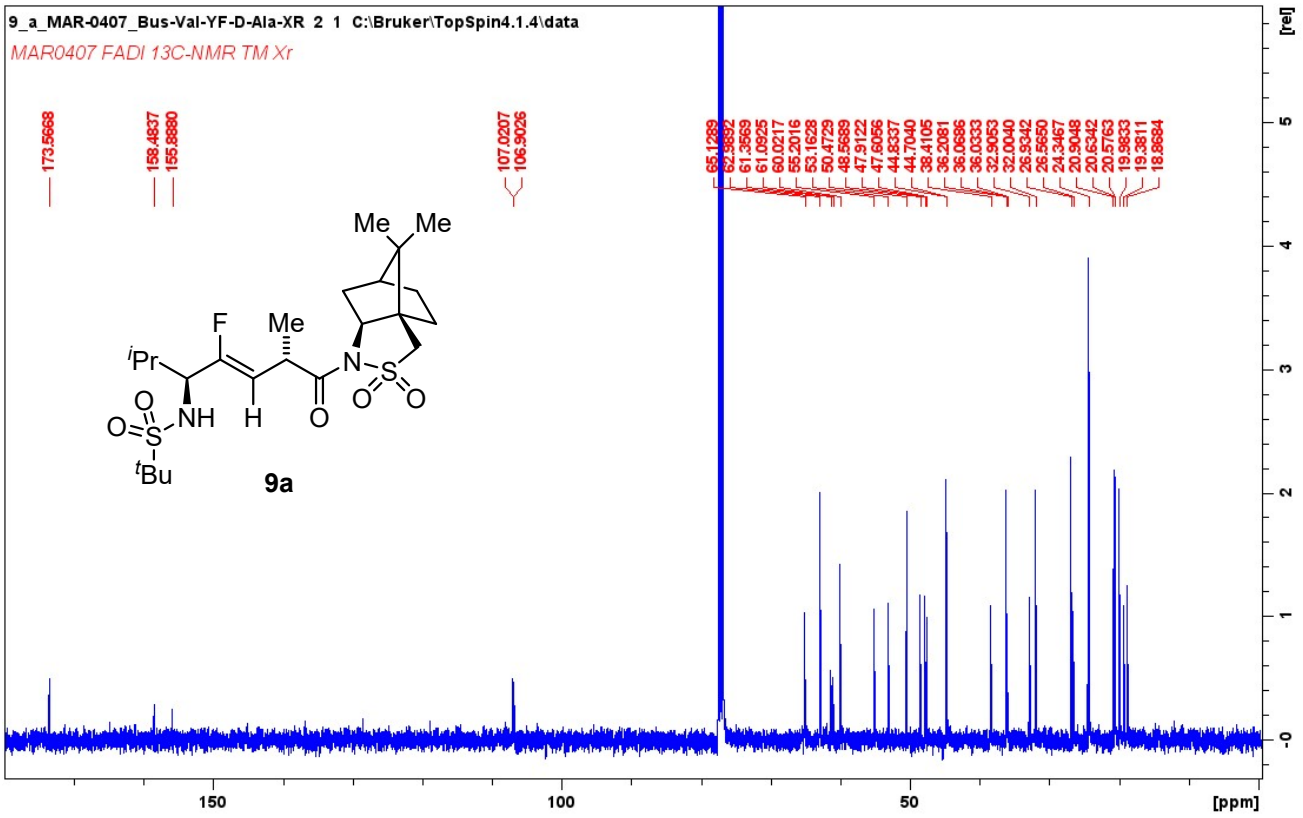

8_b_TKB-2521 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2521_iPr-(R/S)-CH(NHBus)-(Z)-C(F)=CH-(R)-CH(Bn)-C(O)Xs
from (S)-tBuS(O)NH2_1H-NMR
8b
[ppm]
[rel]

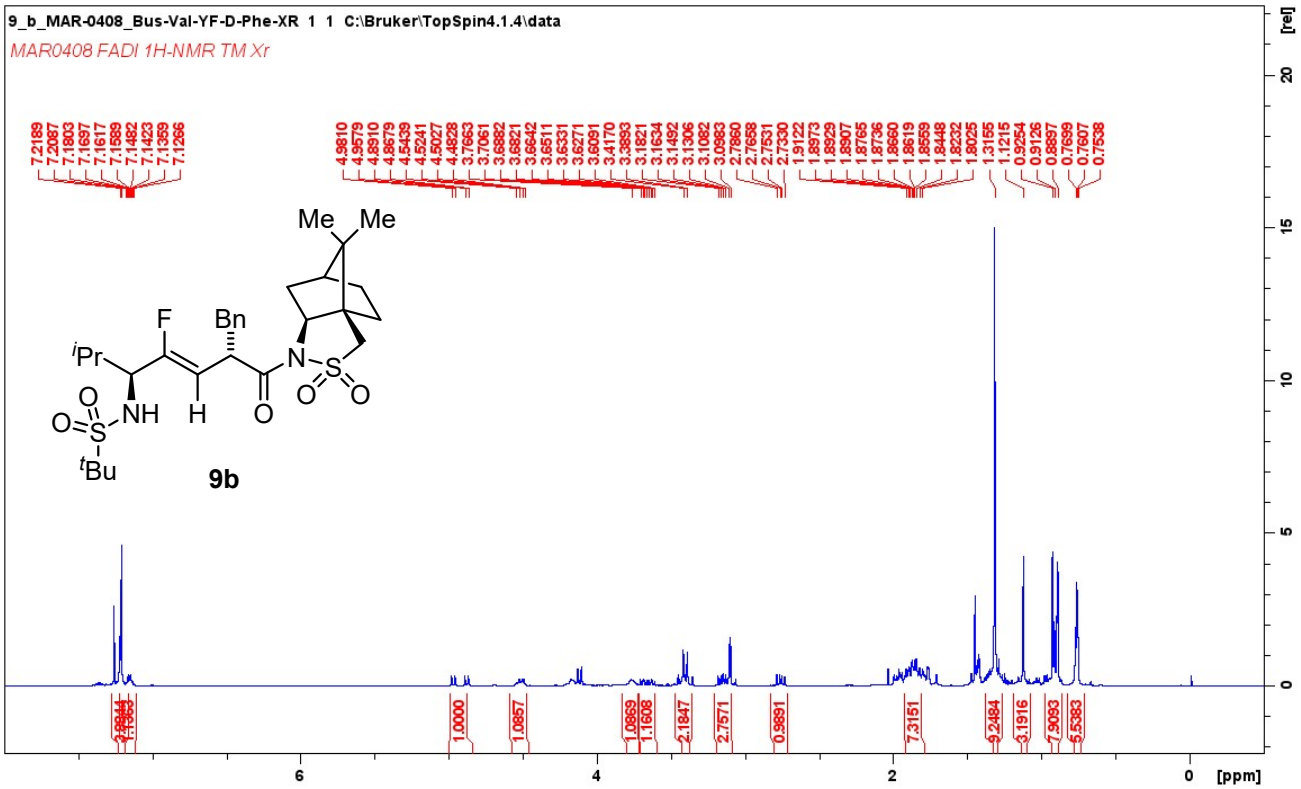

8_b_TKB-2521 3 1 C:\Bruker\TopSpin4.1.4\data
TKB2521_iPr-(R/S)-CH(NHBus)-(Z)-C(F)=CH-(R)-CH(Bn)-C(O)Xs
from (S)-tBuS(O)NH2_13C-NMR
8b
[ppm]
[rel]

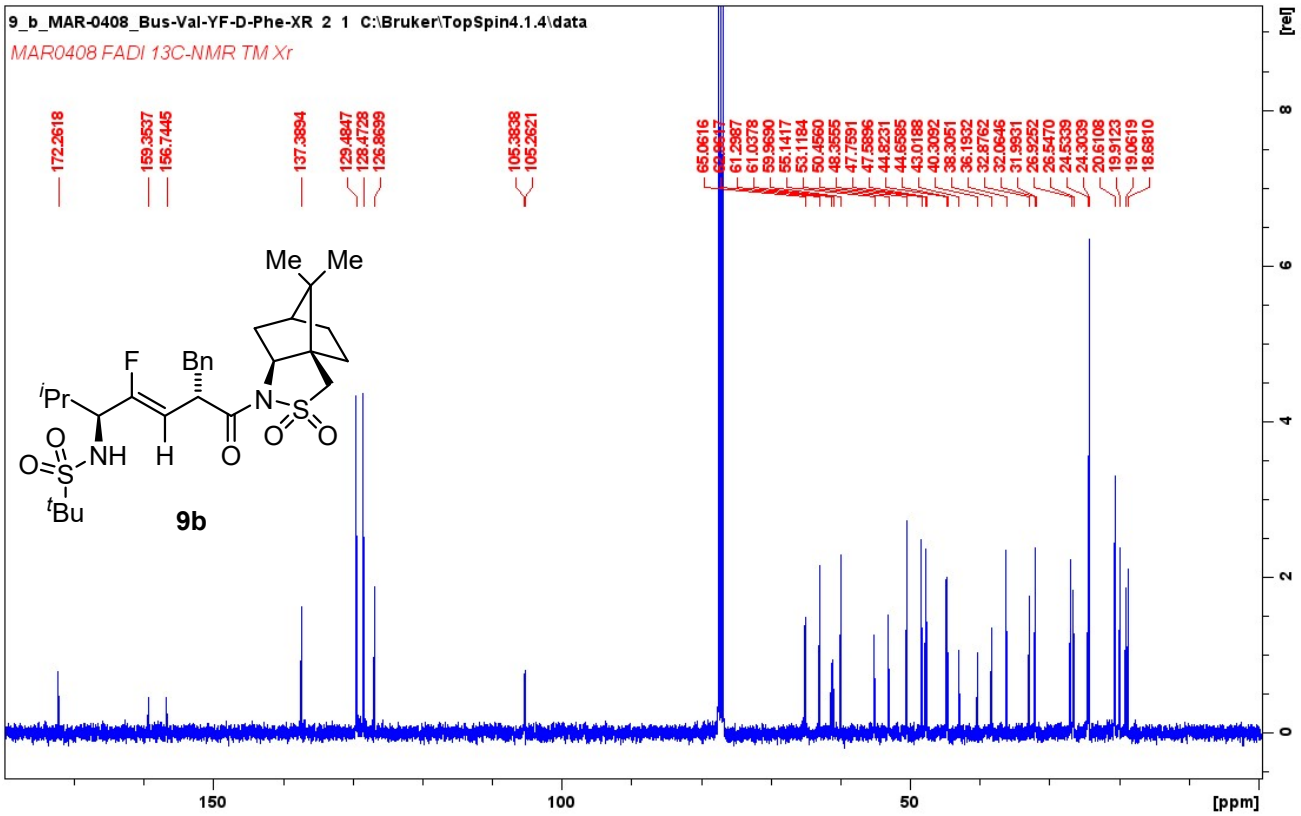

8_c_MAR-0315_Bus-Val-YF-Asp(OtBu)-XS 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0316 FADI 1H-NMR crude
8c
[ppm]
[rel]

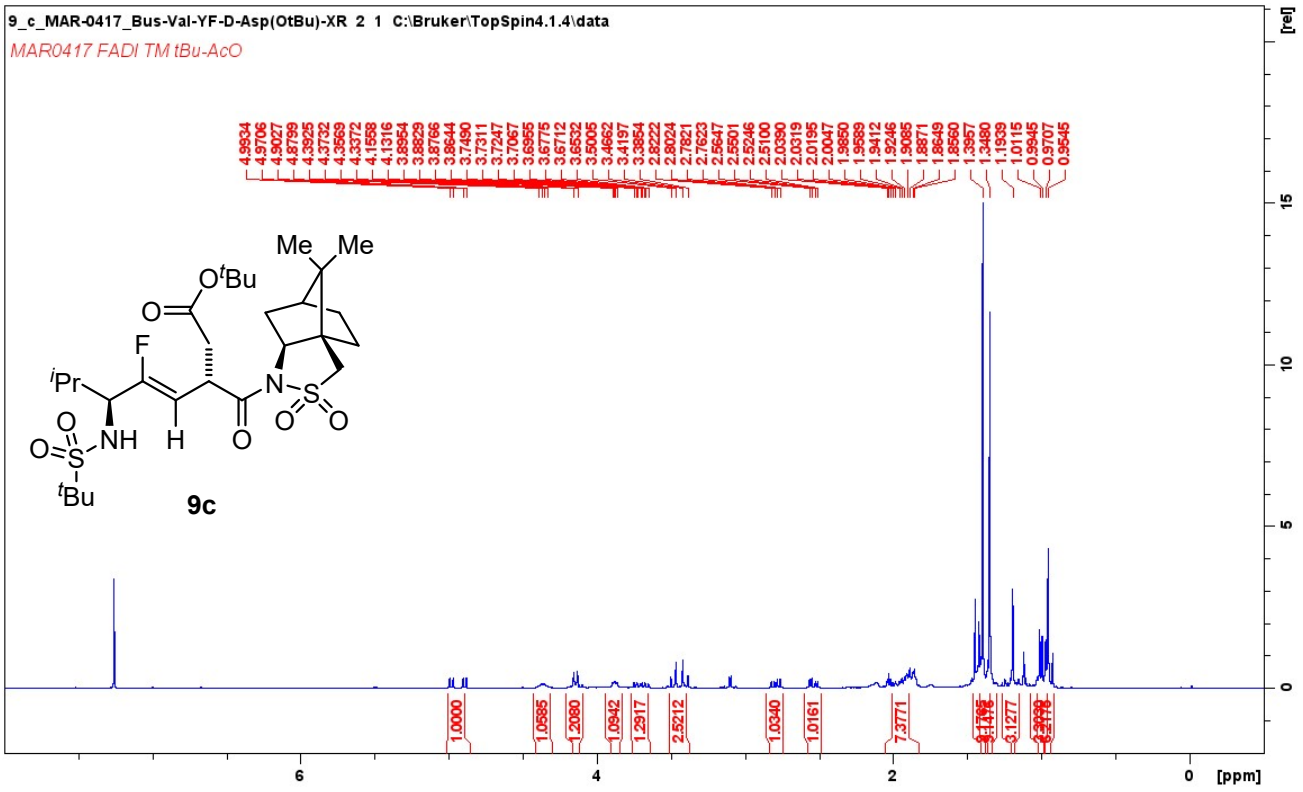

8_c_MAR-0315_Bus-Val-YF-Asp(OtBu)-XS 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0315 FADI 13C-NMR TM
8c
[ppm]
[rel]

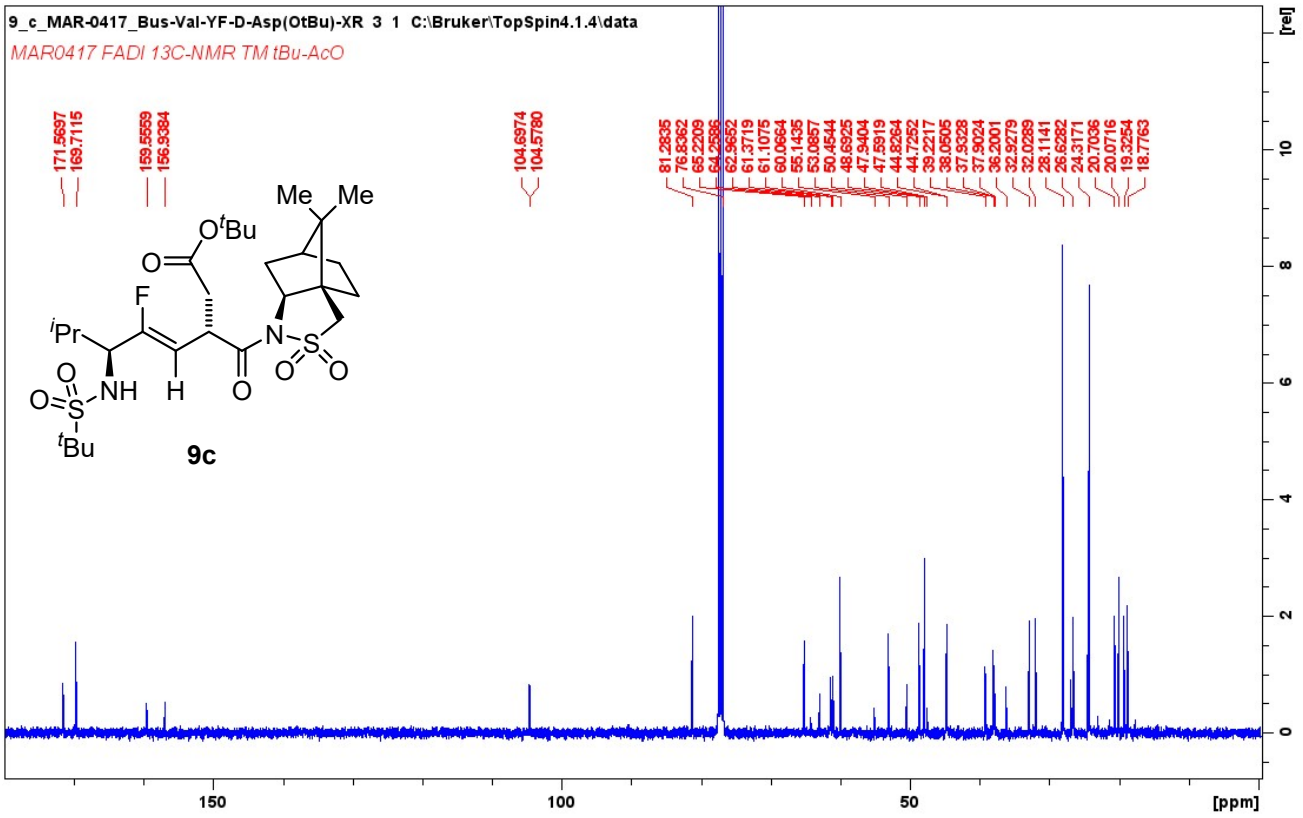

9_a_MAR-0407_Bus-Val-YF-D-Ala-XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0407 FADI 1H-NMR TM Xr
9a
[ppm]
[rel]

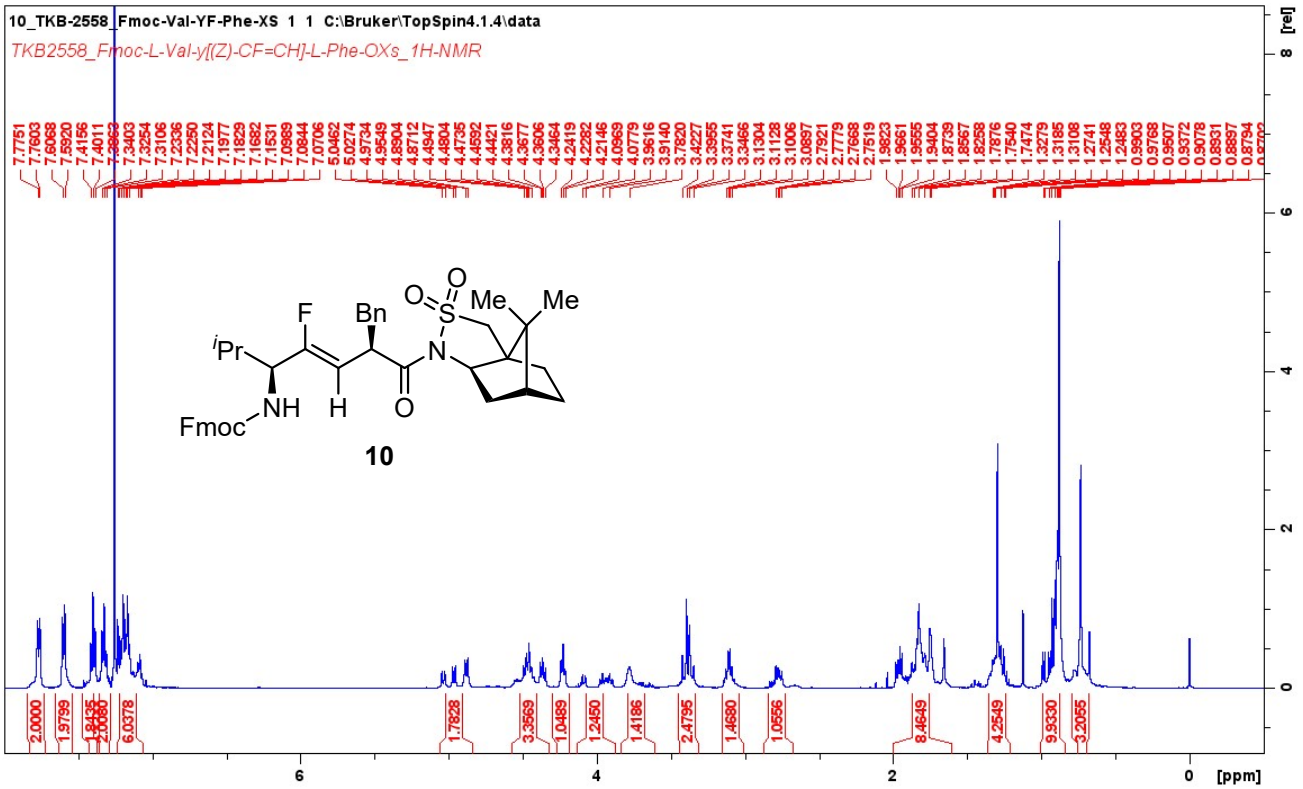

9_a_MAR-0407_Bus-Val-YF-D-Ala-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0407 FADI 13C-NMR TM Xr
9a
[ppm]
[rel]

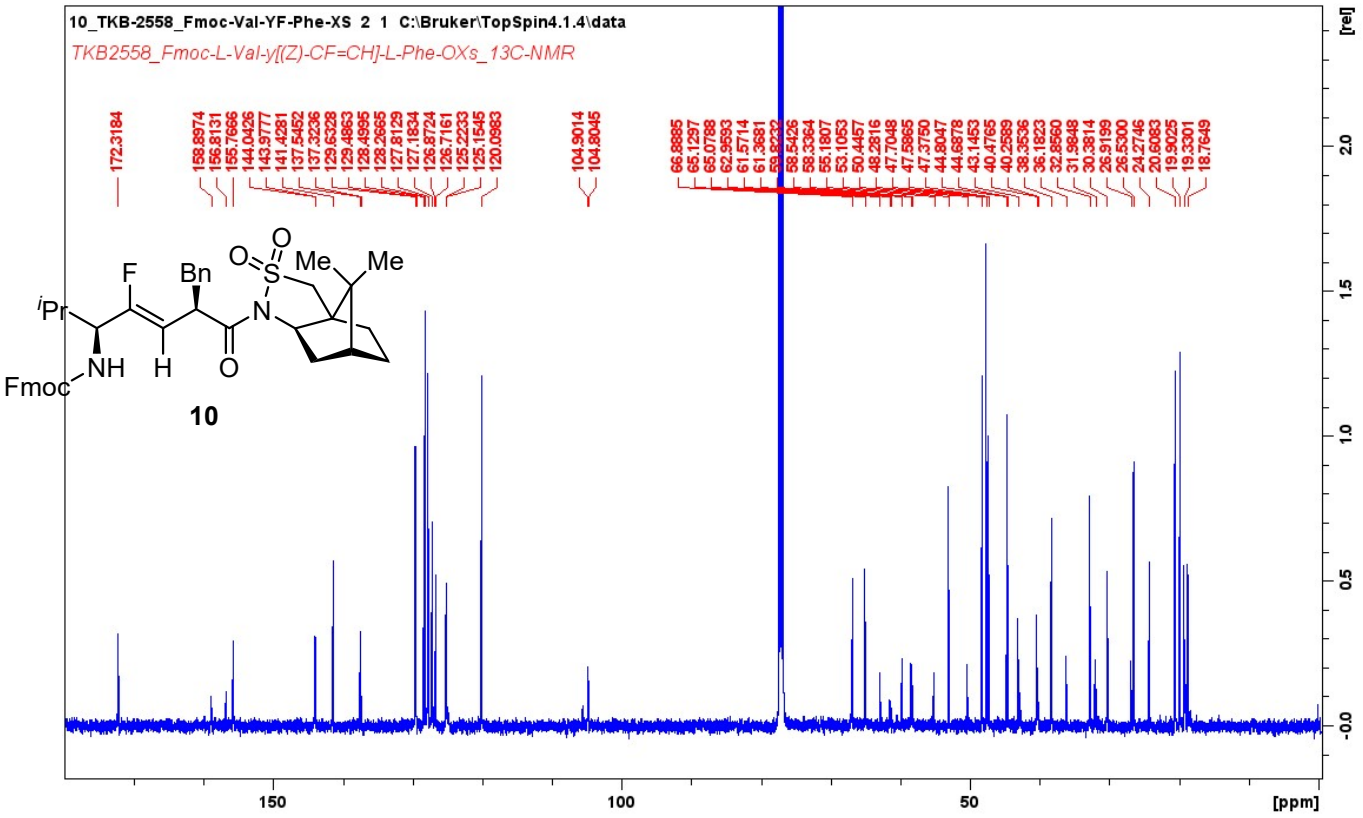

9_b_MAR-0408_Bus-Val-YF-D-Phe-XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0408 FADI 1H-NMR TM Xr
9b
[ppm]
[rel]

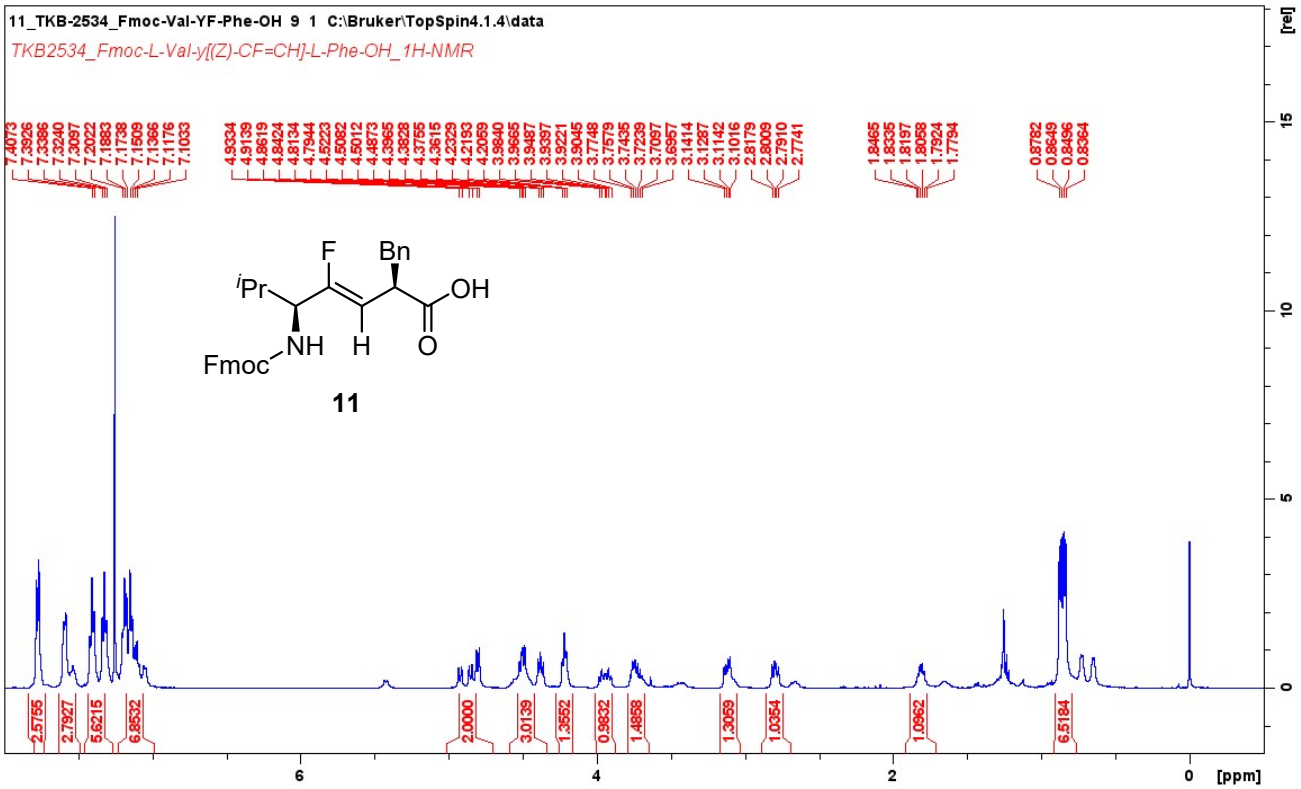

9_b_MAR-0408_Bus-Val-YF-D-Phe-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0408 FADI 13C-NMR TM Xr
9b
[ppm]
[rel]

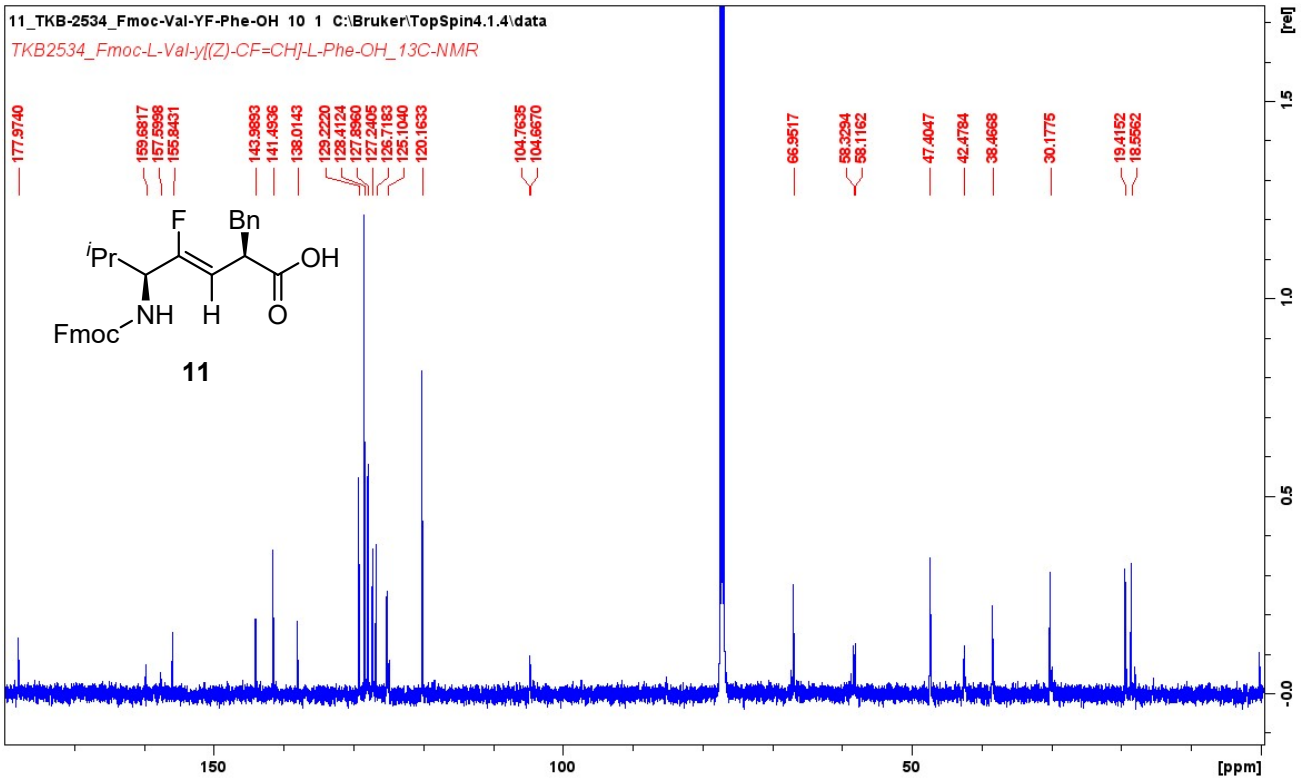

9_c_MAR-0417_Bus-Val-YF-D-Asp(OtBu)-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0417 FADI TM tBu-AcO
9c
[ppm]
[rel]

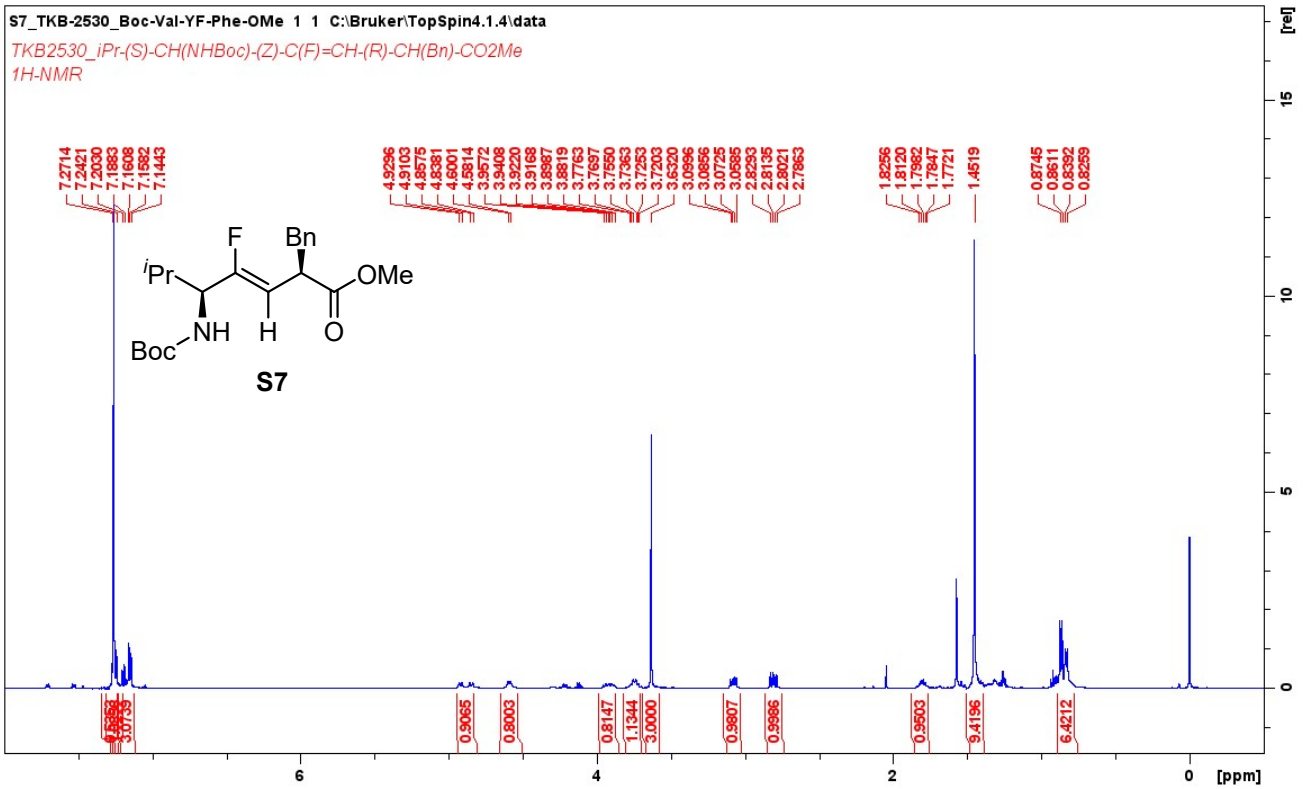

9_c_MAR-0417_Bus-Val-YF-D-Asp(OtBu)-XR 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0417 FADI 13C-NMR TM tBu-AcO
9c
[ppm]
[rel]

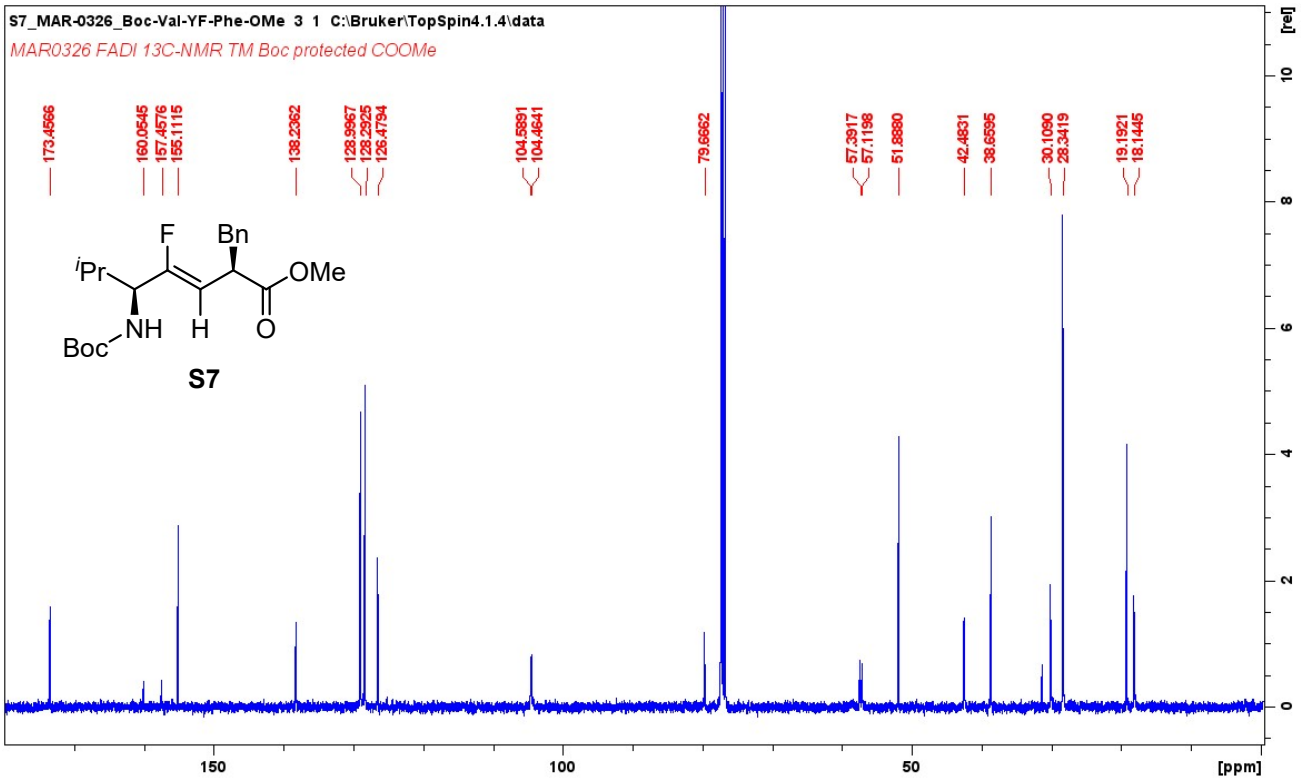

10_TKB-2558_Fmoc-Val-YF-Phe-XS 1 1 C:\Bruker\TopSpin4.1.4\data
TKB2558_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OXs_1H-NMR
F
Bn
O
S
Me
Me
N
iPr
NH
H
O
Fmoc
10
[ppm]
[rel]

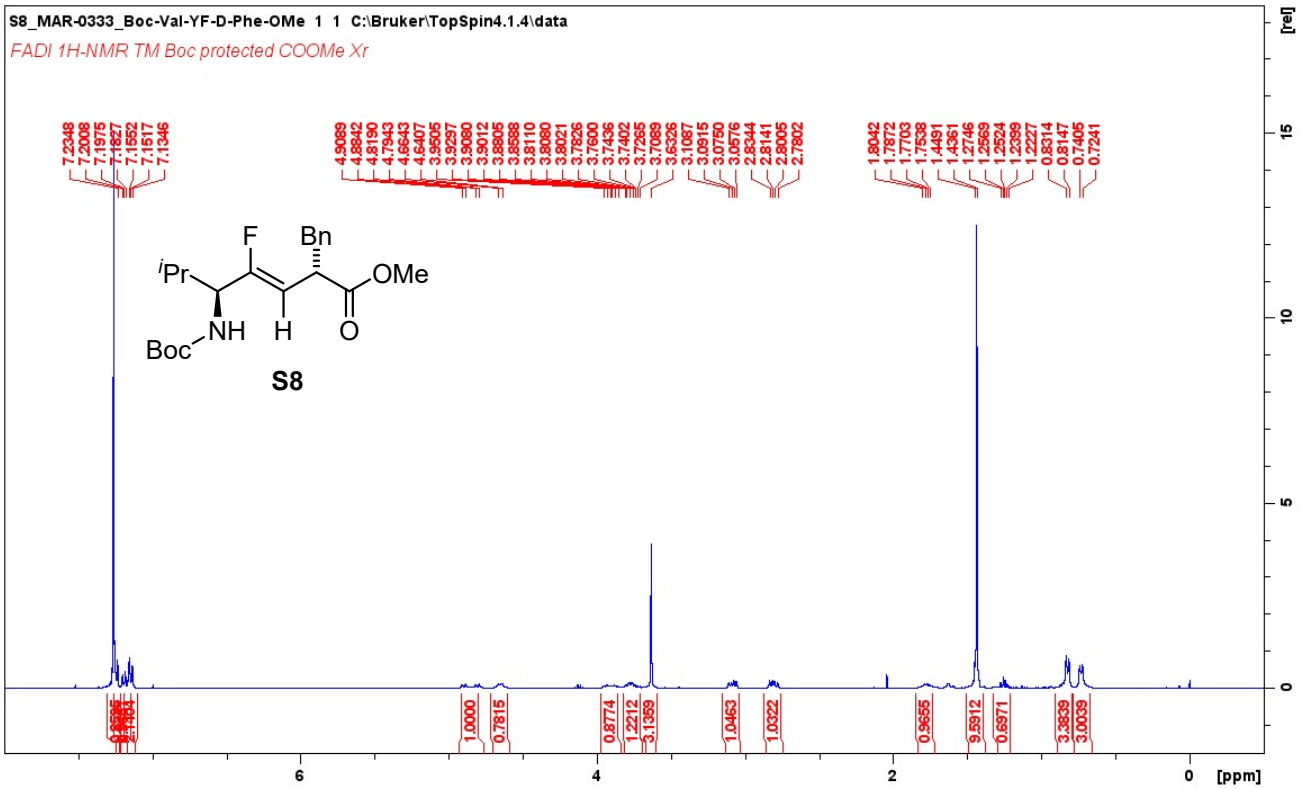

10_TKB-2558_Fmoc-Val-YF-Phe-XS 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2558_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OXs_13C-NMR
F
Bn
O
S
Me
Me
N
iPr
NH
H
O
Fmoc
10
[ppm]
[rel]

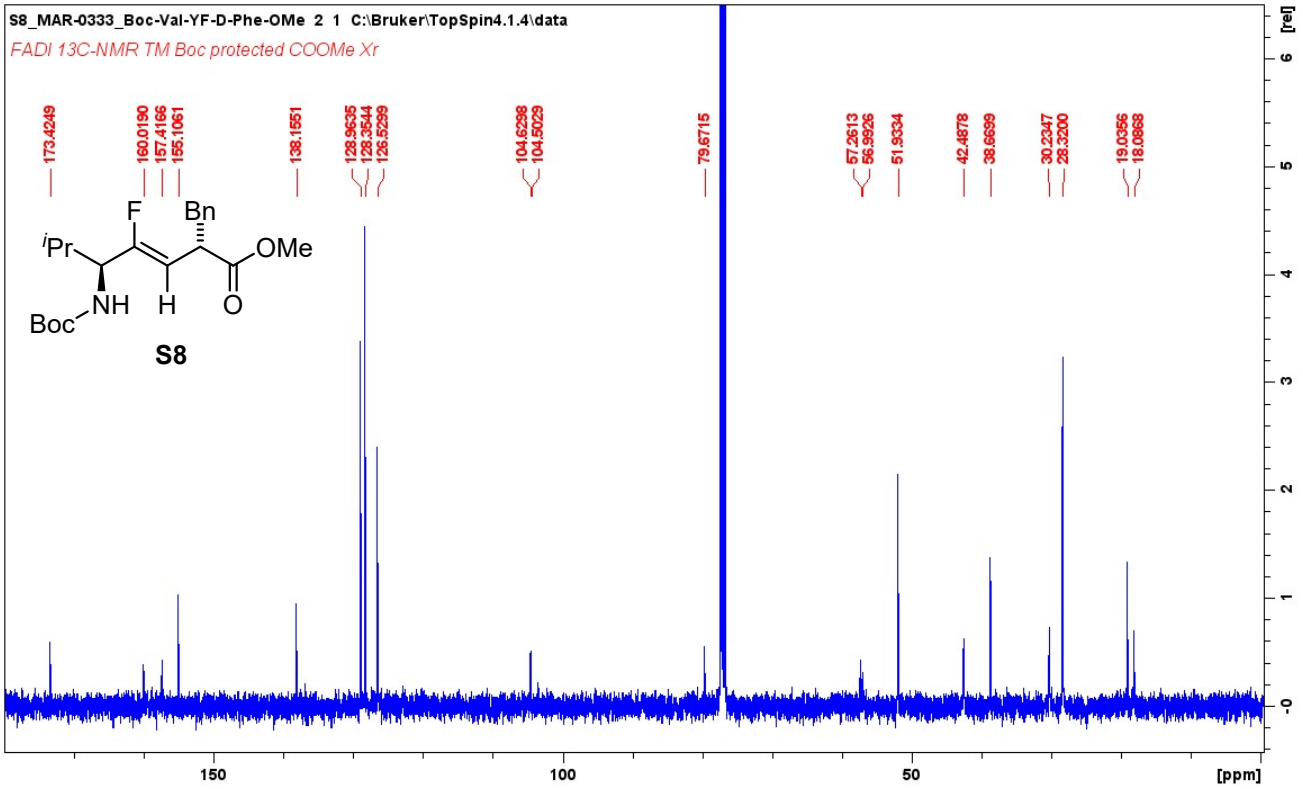

11_TKB-2534_Fmoc-Val-YF-Phe-OH 9 1 C:\Bruker\TopSpin4.1.4\data
TKB2534_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OH_1H-NMR
F
Bn
iPr
OH
NH
H
O
Fmoc
11
[ppm]
[rel]


11_TKB-2534_Fmoc-Val-YF-Phe-OH 10 1 C:\Bruker\TopSpin4.1.4\data
TKB2534_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OH_13C-NMR
F
Bn
iPr
OH
NH
H
O
Fmoc
11
[ppm]
[rel]


S7_TKB-2530_Boc-Val-YF-Phe-OMe 1 1 C:\Bruker\TopSpin4.1.4\data
TKB2530_iPr-(S)-CH(NHBoc)-(Z)-C(F)=CH-(R)-CH(Bn)-CO2Me
1H-NMR
F
Bn
iPr
OMe
NH
H
O
Boc
S7
[ppm]
[rel]


S7_MAR-0326_Boc-Val-YF-Phe-OMe 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0326 FADI 13C-NMR TM Boc protected COOMe
F
Bn
iPr
OMe
NH
H
O
Boc
S7
[ppm]
[rel]


S8_MAR-0333_Boc-Val-YF-D-Phe-OMe 1 1 C:\Bruker\TopSpin4.1.4\data
FADI 1H-NMR TM Boc protected COOMe Xr
F
Bn
iPr
OMe
NH
H
O
Boc
S8
[ppm]
[rel]


S8_MAR-0333_Boc-Val-YF-D-Phe-OMe 2 1 C:\Bruker\TopSpin4.1.4\data
FADI 13C-NMR TM Boc protected COOMe Xr
F
Bn
iPr
OMe
NH
H
O
Boc
S8
[ppm]
[rel]