Electronic Supplementary Information for

1-(*N*,*N*-Dialkylcarbamoyl)-1,1-difluoromethanesulfonyl ester as a stable and effective precursor for neopentyl labeling group with astatine-211

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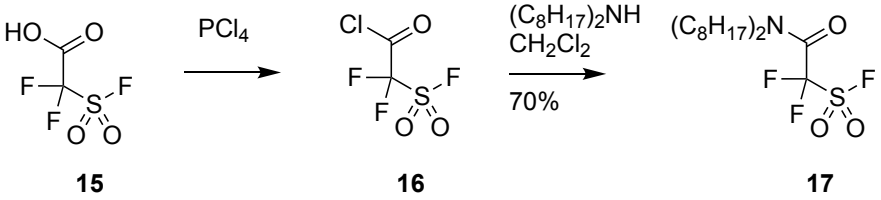
General Information

NMR spectra were recorded on a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F) and Bruker AVANCE III HD 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F) instrument in the indicated solvent. Chemical shifts are reported in units of parts per million (ppm) relative to the signal for internal tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. ^{1}H NMR spectral data are reported as follows: $CDCl_3$ (7.26 ppm). ^{13}C NMR spectral data are reported as follows: $CDCl_3$ (77.16 ppm). ^{19}F NMR spectral are reported as follows: $C_6H_5CF_3$ (-63.72 ppm) as an external standard. Multiplicities are reported by using the following abbreviations: s, singlet; br-s, broaded-singlet; d, doublet; br-d, broaded-doublet; dd, doublet of doublets; br-dd, broaded-doublet of doublets; t, triplet; dq, doublet of quartets; q, quartet, m, multiplet; and, J, coupling constants in Hertz.

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrophotometer or JASCO FT/IR-4200 spectrophotometer. Only the strongest and/or structurally important absorption is reported as the IR data in cm-1.

All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by p-anisaldehyde solution, ceric sulfate or ethanolic phosphomolybdic acid. Column chromatography separations were performed using silica gel (Merck silica gel 60, 0.063 – 0.200 mm).



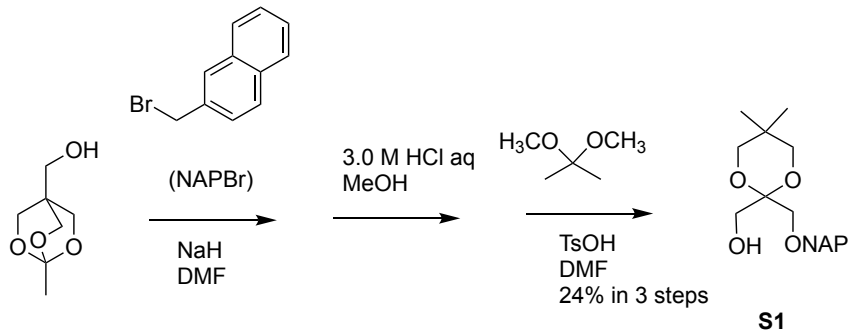
15 **16** **17**

Scheme S1. Synthesis of the sulfonyl fluoride **17**.

2-(Dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonyl fluoride (17)

According to the reported method for acid chloride **15**, 2,2-difluoro-2-(fluorosulfonyl)acetic acid (**14**) (1.2 mL, 11 mmol, 1.71 g/mL) was added cautiously to phosphorus pentachloride (2.6 g, 12 mmol) at 0°C under an Ar atmosphere. After being stirred at 25°C for 30min, the reaction mixture was warmed to 60°C. After being stirred at 60°C for 2h, the reaction mixture was distilled at 90°C to 110°C. Obtained **15** was dropped into a stirred solution of dioctylamine (7.0 mL, 22 mmol, 0.8 g/mL) in dry DCM (4 mL) at 0°C under Ar atmosphere. The carboxylic chloride **15** was washed by DCM (1mL) twice and added to the reaction mixture. After being stirred at 0°C for 10min, the reaction mixture was poured into water and DCM. The aqueous layer was extracted with DCM twice. The combined extract was washed with brine, dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel column with hexane:ethyl acetate (9:1) to **16** (4.5 g, 9.0 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34-3.40 (m, 4H), 1.55-1.62 (m, 4H), 1.28-1.30 (m, 20H), 0.86-0.91 (m, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 47.3, 47.2, 31.7, 29.1, 28.8, 26.8, 26.7, 26.5, 22.6, 14.0
^{19}F NMR (376 MHz, $CDCl_3$) δ 93.8, 37.2
FT-IR (neat) 2956, 2928, 2857, 1679, 1450, 1378, 1307, 1235, 1198, 1137, 1039, 799, 762, 724, 643, 607 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{18}H_{34}F_3NNaO_3S$ 424.21092 $[M+Na]^+$, found 424.21037



S1

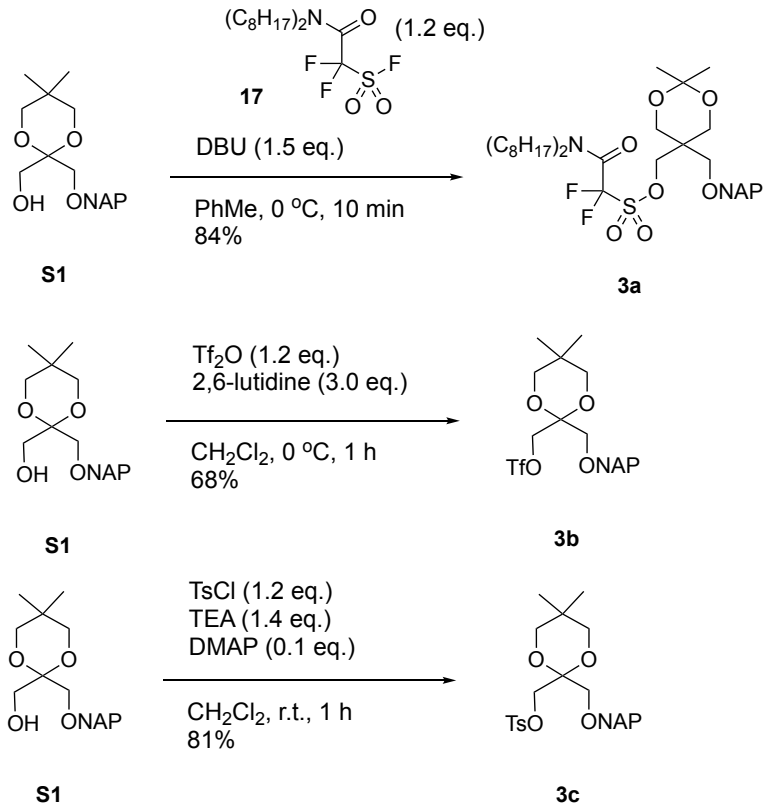
Scheme S2. Synthesis of the neopentyl alcohol **S1**

(2,2-Dimethyl-5-((naphthalene-2-ylmethoxy)methyl)-1,3-dioxane-5-yl)methanol (S1)

To a stirred solution of 60% sodium hydride (3.02 g, 74.9 mmol), washed three times with dry hexane, in DMF (16.5 mL) was added a solution of 4-(hydroxymethyl)-1-methyl-2,6,7-trioxabicyclo[2,2,2]-octane* (10.0 g, 62.4 mmol) in DMF (34.2 mL) at 0 ºC and the reaction mixture was stirred at room temperature for 1 h. Then a solution of 2-(bromomethyl)naphthalene (13.8 g, 62.4 mmol) in DMF (21 mL) was added to the reaction mixture at 0 ºC. After being stirred at room temperature for 3 h, EtOH and water were added to the stirred solution with cooling. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was used for the next reaction without further purification. To a stirred solution of the residue in MeOH (100 mL) was added 3.0 M HCl (10.0 mL) at room temperature. After being stirred at 40 °C for 14 h, the reaction mixture was evaporated *in vacuo*. To a stirred solution of the residue in DMF (27.2 mL) were added CSA (15.6 mg, 0.065mmol, 0.0012 eq.) and 2,2-dimethoxypropane (8.00 mL, 65.2 mmol, 1.20 eq.) at room temperature. After being stirred at 60 °C for 13 h, the reaction mixture was neutralized with NEt_3 and poured into H_2O. The aqueous layer was extracted with ethyl acetate twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with hexane:ethyl acetate (50:50) and recrystallized from hexane/EtOAc to give **S1** (4.70 g, 14.9 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.80 (m, 3H), 7.74 (s, 1Hc), 7.50-7.40 (m 3H), 4.68 (s, 2H), 3.75 (s, 2H), 3.74 (s, 2H), 3.69 (d, 2H, J = 5.8 Hz), 3.59 (s, 2H), 2.45 (t, 1H, J = 5.3 Hz), 1.41 (s, 3H), 1.39 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.3, 133.2, 128.5, 128.0, 127.8, 126.7, 126.3, 126.1, 125.6, 98.6, 74.0, 72.3, 65.1, 63.0, 39.1, 24.2, 23.5; FT-IR (neat) 3446, 2990, 2870, 1372, 1200, 1081, 1050, 827, 752, 420 (cm^{-1}), HRMS (ESI-TOF) calcd. For $C_{19}H_{24}NaO_4$ 339.15723 $[M+Na]^+$, found 339.15730

*T. Jeffrey Dunn, William L. Neumann, Milorad M. Rogic, and Steven R. Woulfe, *J. Org. Chem.* 1990, 55, 26, 6368–6373



Scheme S3. Synthesis of the sulfonyl esters **3a-c** from **S1**

(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl 2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate (3a)

To a stirred solution of **S1** (100 mg, 316 μmol) and **17** (152 mg, 379 μmol) in PhMe (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (71.5 μL, 474 μmol, 1.08 g/mL) at 0 °C under an Ar atmosphere. After being stirred at 0°C for 10 min, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by GPC to give **3a** (185 mg, 265 μmol, 84%) as colorless oil.

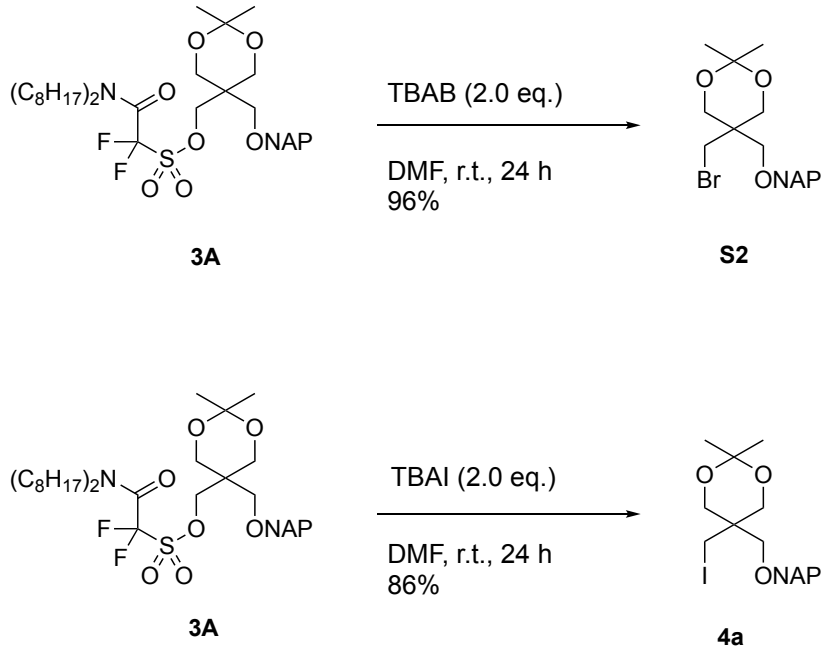
^{11}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.82 (m, 3H), 7.76 (s, 1H), 7.49-7.44 (m, 3H), 4.71 (s, 2H), 4.68 (s, 2H), 3.81 (d, 2H, J = 12.4 Hz), 3.76 (d, 2H, J = 12.4 Hz), 3.48 (s, 2H), 3.42-3.35 (m, 4H), 1.62-1.58 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H), 1.28 (br-s, 20H), 0.90-0.86 (m, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.8, 156.6, 135.4, 133.2, 133.0, 128.3, 127.9, 127.7, 126.4, 126.1, 125.9, 125.6, 118.4, 115.4, 112.4, 98.7, 75.1, 73.7, 68.6, 62.0, 48.2, 48.0, 39.1, 31.8, 31.7, 29.3, 29.2, 29.2, 26.8, 26.8, 26.6, 25.0, 22.6, 22.2, 14.1
^{19}F NMR (376 Hz, $CDCl_3$) δ -98.0
FT-IR (neat) 2927, 2857, 1676, 1456, 1395, 1200, 1163, 1089, 943, 828 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{37}H_{57}F_2NNaO_7S$ 720.37215 $[M+Na]^+$, found 720.37375

(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl trifluoromethanesulfonate (3b)

To a stirred solution of (2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methanol **(6)** (54.4 mg, 172 μmol, 1.0 eq.) and 2,6-lutidine (59.8 μL, 516 μmol, 0.925 g/mL, 3.0 eq.) was added trifluoromethanesulfonic anhydride (34.9 μL, 206 μmol, 1.670 g/mL 1.2 eq.) in CH_2Cl_2 (3 mL) at 0 ℃ under an Ar atmosphere. After being stirred at 0 ℃ for 1 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give (2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl trifluoromethanesulfonate (52.3 mg, 117 μmol, 68%) as colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.82 (m, 3H), 7.73 (s, 1H), 7.52-7.47 (m, 2H), 7.43-7.41 (m, 1H), 4.77 (s, 2H), 4.66 (s, 2H), 3.80 (d, 2H, *J* = 12.4 Hz), 3.72 (d, 2H, *J* = 12.4 Hz), 3.38 (s, 2H), 1.40 (s, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 133.2, 133.1, 128.4, 127.9, 127.8, 126.6, 126.1, 125.5, 120.3, 117.1, 98.9, 75.7, 73.8, 68.3, 12.0, 39.1, 26.3, 20.7
^{19}F NMR (376 Hz, $CDCl_3$) δ -74.2
FT-IR (neat) 3057, 2293, 2941, 2872, 1415, 1246, 1205, 1146, 1087, 942, 825, 617, 474 (cm^{-1})

2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl 4-methylbenzenesulfonate (3C)

To a stirred solution of **S1** (50.0 mg, 158 μmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (36.2 mg, 190 μmol, 1.2 eq.) in CH_2Cl_2 (3 mL) was added triethylamine (30.8 μL, 221 μmol, 0.726 g/mL, 1.4 eq.) and 4-dimethylaminopyridine (1.93 mg, 15.8 μmol) at 0 ℃ under an Ar atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give (2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl 4-methylbenzenesulfonate (60.2 mg, 128 μmol, 81%) as colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 5H), 7.76 (s, 1H), 7.66-7.46 (m, 2H), 7.35-7.33 (m, 1H), 7.26-7.24 (m, 2H), 4.56 (s, 2H), 4.17 (s, 2H), 3.74 (d, 2H, *J* = 12.0 Hz), 3.66 (d, 2H, *J* = 12.0 Hz), 3.40 (s, 2H), 2.33 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 135.4, 133.2, 133.0, 132.5, 129.8, 128.2, 128.0, 127.9, 127.7, 126.2, 126.2, 126.0, 125.4, 98.5, 73.5, 69.2, 68.8, 62.2, 38.6, 25.1, 22.0, 21.6
FT-IR (neat) 3055, 2991, 2938, 2870, 1599, 1455, 1361, 1189, 1087, 977, 816, 666, 556 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{26}H_{30}NaO_6S$ 493.16608 $[M+Na]^+$, found 493.16620



Scheme S4. Synthesis of neopentyl bromide **S**2 and iodide **4a** as authentic samples.

5-(bromomethyl)-2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxane (S2)

To a stirred solution of **3A** (7.5 mg, 11 μmol) in DMF (1.0 mL) was added tetrabutylammonium bromide (6.9 mg, 21 μmol, 2.0 eq.) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give **S2** (3.9 mg, 10 μmol, 96%) as colorless oil.

H NMR (400 MHz, $CDCl_3$) δ 7.85-7.82 (m, 3H), 7.77 (s, 1H), 7.49-7.44 (m, 3H), 4.69 (s, 2H), 3.83 (d, 2H, J = 12.0 Hz), 3.77 (2H, J = 12.0 Hz), 3.66 (s, 2H), 3.51 (s, 2H), 1.41 (s, 3H), 1.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.23, 133.0, 128.2, 127.9, 127.7, 126.4, 126.2, 125.9, 125.6, 98.6, 73.7, 69.9, 64.0, 38.5, 36.1, 24.4, 22.9

FT-IR (neat) 3054, 2991, 2924, 2864, 1371, 1101, 820 (cm^{-1})

HRMS (ESI-TOF) calcd. for $C_{19}H_{23}BrNaO_3$ 403.07078 $[M+Na]^+$, found 403.07134

5-(iodomethyl)-2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxane (4b)

To a stirred solution of **3A** (7.5 mg, 11 μmol) in DMF (1 mL) was added tetrabutylammonium iodide (7.1 mg, 21 μmol) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract

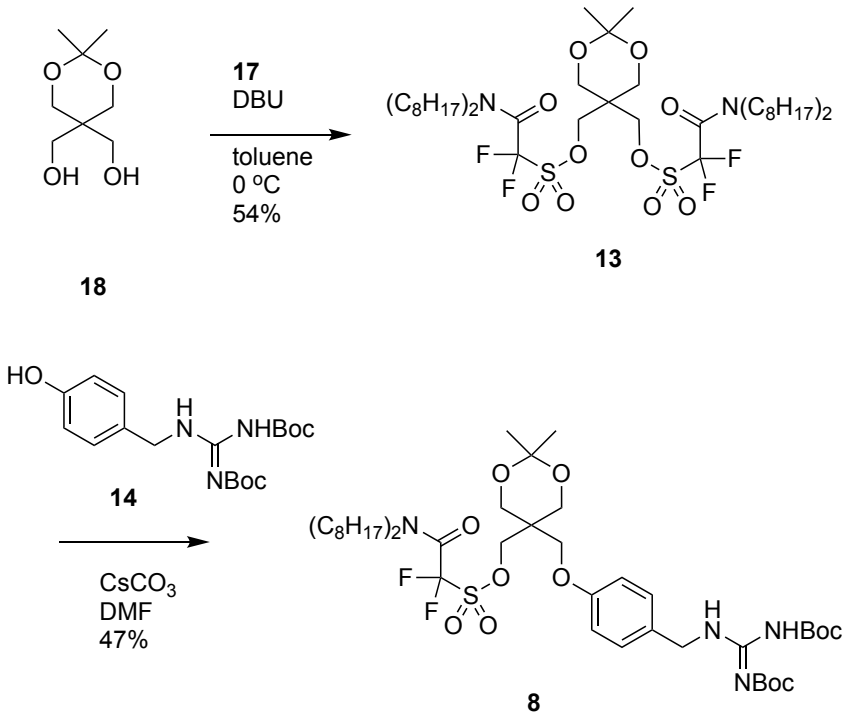
was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give **4b** (3.5 mg, 9.2 μmol, 86%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 3H), 7.77 (s, 1H), 7.49-7.45 (m, 3H), 4.69 (s, 2H), 3.82 (d, 2H, *J* = 12.0 Hz), 3.72 (d, 2H, *J* = 12.0 Hz), 3.50 (s, 2H), 3.42 (s, 2H), 1.41 (s, 3H), 1.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.4, 133.1, 128.3, 128.0, 127.9, 126.5, 126.3, 126.0, 125.8, 98.7, 73.8, 71.3, 65.0, 37.3, 23.8, 23.7, 11.7

FT-IR (neat) 3054, 2991, 2937, 2863, 1371, 1213, 1098, 818, 752 (cm^{-1})

HRMS (ESI-TOF) calcd. for $C_{19}H_{23}INaO_3$ 449.05896 $[M+Na]^+$, found 449.05975



Scheme S5. Synthesis of the sulfonyl ester 8 as a precursor for **17**.

(2,2-dimethyl-1,3-dioxane-5,5-diyl)bis(methylene) bis(2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate) (13)

To a stirred solution of (2,2-dimethyl-1,3-dioxane-5,5-diyl)dimethanol (**17**) (224 mg, 1.27 mmol) and **16** (1.07 g, 2.67 mmol) in toluene (5 mL) was added 1,8- diazabicyclo[5.4.0]undec-7-ene (422 μL, 2.80 mmol, 1.08 g/mL) at 0 °C under an Ar atmosphere. After being stirred at 0°C for 10 min, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by GPC to give **13** (641 mg, 682 μmol, 54%) as colorless oil.

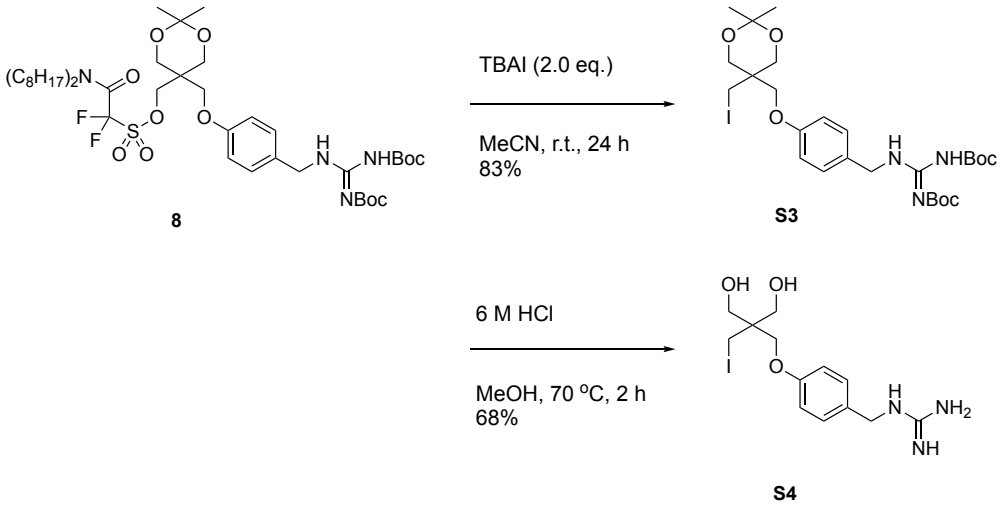
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 4H), 3.80 (s, 4H), 3.35-3.41 (m, 8H), 1.53-1.66 (m, 8H), 1.42 (s, 6H),

1.21-1.35 (m, 40H), 0.85-0.91 (m, 12H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 156.7, 156.4, 118.5, 115.5, 112.5, 99.2, 73.2, 60.9, 48.1, 48.1, 38.8, 31.8, 31.7, 29.2, 29.2, 29.1, 26.8, 26.8, 26.6, 23.4, 22.6, 14.1
^{19}F NMR (376 Hz, $CDCl_3$) δ -97.6
FT-IR (neat) (cm^{-1}) 2927, 2857, 1673, 1402, 1204, 945
HRMS (ESI-TOF) calcd. for $C_{44}H_{82}F_4N_2NaO_{10}S_2$ 961.52447 $[M+Na]^+$, found 961.52206

(5-((4-((2,3-bis(*tert*-butoxycarbonyl)guanidino)methyl)phenoxy)methyl)-2,2-dimethyl-1,3-dioxan-5-yl)methyl 2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate (8)

To a stirred solution of **13** (200 mg, 213 μmol) and *N*-(4-hydroxylbenzyl)-*N*',*N*''-Bis(tert-butoxycarbonyl) guanidine (**13**) (77.8 mg, 213 μmol) in DMF (5 mL) was added cesium carbonate (104 mg, 319 μmol) at 0 ℃ under an Ar atmosphere. After being stirred at 0℃ for 2 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give **8** (90.0 mg, 99.4 μmol, 47%) as colorless oil.

^{11}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br-s, 1H), 7.23 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.70 (s, 2H), 4.54 (d, 2H, *J* = 4.8 Hz), 3.98 (s, 2H), 3.91 (d, 2H, *J* = 12.4 Hz), 3.85 (d, 2H, *J* = 12.4 Hz), 3.37-3.31 (m, 4H), 1.63-1.44 (m, 28H), 1.27 (br-s, 20H), 0.88-0.85 (m, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 158.1, 157.1, 156.9, 156.6, 156.1, 153.3, 130.1, 129.4, 118.5, 115.5, 115.0, 112.53, 99.0, 83.3, 79.5, 74.9, 66.5, 61.8, 48.3, 48.2, 48.2, 44.7, 38.9, 31.9, 31.9, 29.4, 29.3, 29.3, 28.5, 28.2, 26.9, 26.9, 26.7, 24.1, 23.3, 22.8, 14.2
^{19}F NMR (376 Hz, $CDCl_3$) δ -97.9
FT-IR (neat) 3330, 2928, 2857, 1721, 1676, 1639, 1614, 1408, 1157, 1129, 947, 757 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{44}H_{74}F_2N_4NaO_{11}S$ 927.49405 $[M+Na]^+$, found 927.49404



Scheme S6. Synthesis of the neopentyl iodide **S4** as an authentic sample.

***N*-(4-(5-iodomethyl-2,2-dimethyl-1,3-dioxan-5-yl)methyloxy)phenyl)-*N*',*N*"-Bis(tert-butoxycarbonyl) guanidine (S3)**

To a stirred solution of **8** (70.0 mg, 155 μmol) in CH_3CN (1.0 mL) was added tetrabutylammonium iodide (TBAI) (57.1 mg, 77.3 μmol) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was poured into NH_4Cl aq. and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel with hexane/EtOAc (9:1) to give **S3** (40.5 mg, 63.9 μmol, 83%).

H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.50 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 2H, *J* = 8.8 Hz), 4.55 (d, 2H, *J* = 2.6 Hz), 4.00 (s, 2H), 3.89 (d, 2H, J = 12.0 Hz), 3.80 (d, 2H, *J* = 12.0 Hz), 3.41 (s, 2H), 1.52 (s, 9H), 1.47 (s, 9H), 1.45 (s, 3H), 1.43 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 158.2, 155.9, 153.2, 129.9, 129.3, 114.9, 98.8, 83.1, 79.4, 68.8, 64.8, 44.6, 36.8, 28.3, 28.1, 24.7, 22.4, 10.2
FT-IR (neat) 3331, 3132, 2979, 2929, 2870, 1720, 1638, 1615, 1327, 1248, 1157, 833, 757 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{26}H_{40}IN_3NaO_7$ 656.18086 $[M+Na]^+$, found 656.18038

1-(4-(3-hydroxy-2-(hydroxymethyl)-2-(iodomethyl)propoxy)benzyl)guanidine (S4)
To a stirred solution of **3S** (2.0 mg, 3.16 μmol) in 6 M HCl aq. (200 μL) and MeOH (200 μL) at 70 °C for 1 h. The mixture was concentrated in *vacuo*. The residue was purified by bond elute with water/MeOH (1:1) to give **S4** (0.72 mg, 1.8 μmol, 58%)

^1H NMR (400 MHz, CD_3OD) δ 7.26 (d, 2H, *J* = 8.4 Hz), 6.98 (d, 2H, J = 8.4 Hz), 4.32 (s, 2H), 3.92 (s, 2H), 3.66 (s, 4H), 3.41 (s, 2H)

^{13}C NMR (100 MHz, CD_3OD) δ 160.4, 158.5, 129.9, 129.7, 116.1, 68.9, 62.5, 45.6, 45.0, 10.1
FT-IR (neat) 3334, 2948, 1652, 1513, 1246, 1018 (cm^{-1})
HRMS (ESI-TOF) calcd. for $C_{13}H_{21}IN_3O_3$ 394.06276 $[M+H]^+$, found 394.06223

Radiochemistry

Production of ^{77}Br

Irradiations for production of ^{77}Br were performed using an AVF cyclotron installed at the Takasaki Ion Accelerators for Advanced Radiation Application (TIARA) of the National Institutes for Quantum Science and Technology (QST). Proton beams of 18.6 MeV irradiated a $Cu_2{}^{nat}Se$ (600 mg, 11-mm diameter) at 5 μA of beam current. ^{77}Br was then isolated using the dry distillation system reported previously[1]. The irradiated target was heated at 1120 °C under a continuous flow of argon gas (30 mL/min flow rate). ^{77}Br was trapped in H_2O. A CdZnTe detector (GR-1, Kromek, UK) was used to monitor radiation level of the H_2O trap. After the heating was stopped, the H_2O solution containing ^{77}Br was concentrated to 150–200 μL via evapolation. An aliquot of the H_2O solution containing ^{77}Br (100-500 kBq) was then provided to the radiolabeling studies. The radioactivity of [^{77}Br]bromide was determined using γ-ray spectroscopy with a high-purity germanium (HPGe) detector coupled with a multichannel analyzer (MCA7700; Seico EG&G).

Production of ^{211}At

Irradiations for production of ^{211}At were performed using an AVF cyclotron installed at QST or Fukushima Medical University. Helium beams of 28-29 MeV irradiated a Bi target. ^{211}At was then isolated using the dry distillation system reported previously[2]. The irradiated target was heated at 650 °C under a continuous flow of helium gas (30 mL/min flow rate). ^{211}At was trapped in a liquid nitrogen cryotrap and eluted with 500 μL of $CHCl_3$. An aliquot of the $CHCl_3$ solution containing of ^{211}At (100-500 kBq) was removed and then evaporated to dryness for provide to the radiolabeling studies. The radioactivity of ^{211}At was determined using γ-ray spectroscopy with the HPGe detector coupled with MCA.

^{125}I-iodination of neopentyl [^{125}I] iodide, [^{125}I]4b

A 0.05 M NaOH aqueous solution of ^{125}I (206 kBq, 10 μL) was added to a glass vial and then evaporated to dryness with gentle stream of N_2 gas. The vial was added anhydrous MeCN (100 μL) and then evaporated again to dryness with gentle stream of N_2 gas. The precursor **3a** (1.7 mg, 2.5 μmol) in anhydrous MeCN (35 μL) was added to the residue and then shaken at 70 °C for 10 min. After cooling to room temperature, an aliquot (5 μL) of the reactant was applied to TLC plate for radio-TLC analysis, and the rest of the reactant was provided to radio-HPLC analysis.

^{77}Br-bromination of neopentyl [^{77}Br] bromide, [^{77}Br]4c

After an aliquot of the H_2O solution containing ^{77}Br (100 kBq) was evaporated to dryness by gentle N_2 gas,

anhydrous MeCN (100 μL) was added to the residue and evaporated to dryness with gentle stream of N_2 gas again. To a residue containing ^{77}Br was added the precursor **3a** (1.7 mg, 2.5 μmol) in anhydrous MeCN (35 μL) and then shaken at 70 °C for 10 min. After cooling to room temperature, an aliquot (5 μL) of the reactant was applied to TLC plates for radio-TLC analysis, and the rest of the reactant was provided to radio-HPLC analysis.

^{211}At-astatination of neopentyl [^{211}At] astatide [^{211}At]4d

An aliquot of the $CHCl_3$ solution containing of ^{211}At (564 kBq) was added to a glass vial. In case of astatination in the presence of K_2CO_3, K_2CO_3 (4.2 mg, 30.7 μmol) in MeOH (750 μL) was added and then evaporated to dryness with gentle stream of N_2 gas. The vial was added anhydrous MeCN (100 μL) and then evaporated again to dryness with gentle stream of N_2 gas. The precursor **3a** (1.7 mg, 2.5 μmol) in anhydrous MeCN (35 μL) was added to the residue and then shaken at 70 °C for 10 min. After cooling to room temperature, an aliquot (5 μL) of the reactant was applied to TLC plates for radio-TLC analysis, and the rest of the reactant was provided to radio-HPLC analysis.

Synthesis of ^{211}At-NP-BG [^{211}At]6 and ^{125}I-NP-BG [^{125}I]7

A MeOH solution (350 μL) containing ^{211}At (564 kBq) or A 0.05M NaOH solution containing ^{125}I (250 kBq) was added to a glass vial. To the vial was added K_2CO_3 (0.5 mg, 3.6 μmol) in MeOH (90 μL) and then evaporated to dryness with gentle stream of N_2 gas. The vial was added anhydrous MeCN (100 μL) and then evaporated again to dryness with gentle stream of N_2 gas. The precursor **8** (0.5 mg, 0.55 μmol) in anhydrous MeCN (50 μL) was added to the residue and then shaken at 70 °C for 10 min. After cooling to room temperature, MeOH (20 μL) and 6.0 M HCl aqueous solution (80 μL) was added to the mixture and then shook at 70 °C for 30 min. After the mixture was neutralized with NaOH aqueous solution, [^{211}At]**6** or [^{125}I]**7** was purified using radio-HPLC. [^{211}At]**6**: RCY 31.9%, RCP >99.5%.; [^{125}I]**7**: RCY 31.9%, RCP >99.5%.

Radio-thin layer chromatography (radio-TLC)

Radiochemical conversion of [^{125}I]**4b**, [^{77}Br]**4c**, [^{211}At]**4d**, and [^{211}At]**19** were determined by radio-TLC. A reaction mixture diluted with H_2O was applied to a silica gel plate (TLC Silica gel 60 F254; Merck) and developed with hexane/ethyl acetate (4/1 or 2/1, v/v). The plate was dried and exposed to a BAS-III imaging plate (Fujifilm, Tokyo, Japan), and autoradiogram was obtained using a STORM 820 or Typhoon FLA 7000 (GE Healthcare, Buckinghamshire, UK). The data was analyzed using ImageQuant TL (GE Healthcare).

Radio high-performance liquid chromatography (radio-HPLC)

Radio-HPLC analysis was performed with SCL-10A VP (Shimadzu, Kyoto, Japan) system controller, LC-20AD (Shimadzu) pump, DGU-20A3 (Shimadzu) degassing unit, SIL-20AC (Shimadzu) autosampler, CTO-20AC (Shimadzu) column oven, FRC-10A (Shimadzu) fraction collector, SPD-20A (Shimadzu) UV detector, and GABI Star (Elysia-raytest GmbH, Straubenhardt, Germany) gamma-ray detector. Chromatography was performed under the following conditions: column, PEGASIL C8 SP100 (4.6 mm ID x 150 mm, 5 μm;

Senshu Scientific, Tokyo, Japan); mobile phase for [^{125}I]**4b**, [^{77}Br]**4c**, and [^{211}At]**4d**, MeCN/water (20/80 to 100/0 from 0 min to 20 min, 100/0 from 20 min to 30 min); mobile phase for [^{211}At]**6**, MeOH/water/formic acid (10/90/0.1 to 100/0/0.1 from 0 min to 5 min, 100/0/0.1 from 5 min to 20 min); flow rate, 1.0 mL/min; temperature, 30°C; UV wavelength, 220 nm; and gamma-ray energy, 20-800 keV.

Reference

1. S. Watanabe, A. Shimada, S. Watanabe, H. Hanaoka, N. S. Ishioka, Trans. Mat. Res. Soc. Japan., 2018, 43, 219-222.
2. Y. Ohshima, H. Sudo, S. Watanabe, K. Nagatsu, A.B. Tsuji, T. Sakashita, Y. M. Ito, K. Yoshinaga, T. Higashi, N.S. Ishioka, Eur. J. Nucl. Med. Mol. Imaging, 2018, 45, 999-1010.

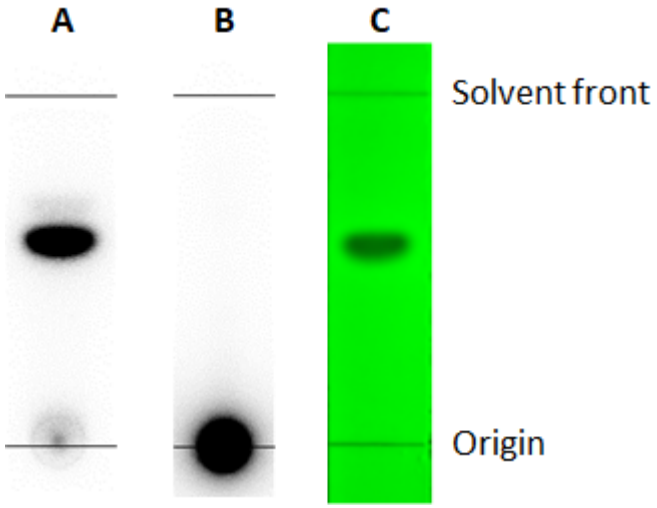


Figure S7. Radio-TLC of the mixture after [^{125}I]**4b** synthesis (**A**) and free [^{125}I] (**B**) and UV-TLC of **4a** (**C**). The R_f values of [^{125}I]**4b**, free [^{125}I], and **4a** were 0.53-0.63, 0, and 0.57, respectively, on TLC developed with hexane/ethyl acetate (4/1, v/v).

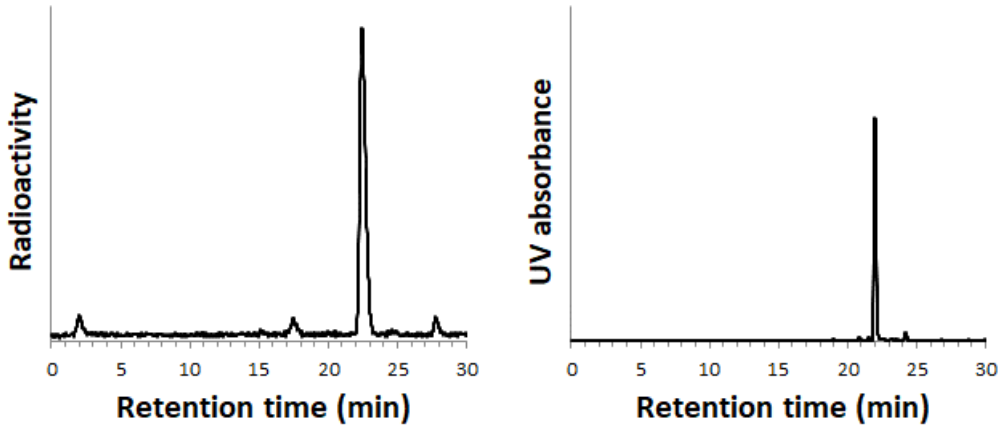


Figure S8. Radio-HPLC of the mixture after [^{125}I]**4b** synthesis (left) and UV-HPLC of **4a** (right). The retention time of [^{125}I]**4b** and **4a** was 22.5 min and 22.0 min, respectively.

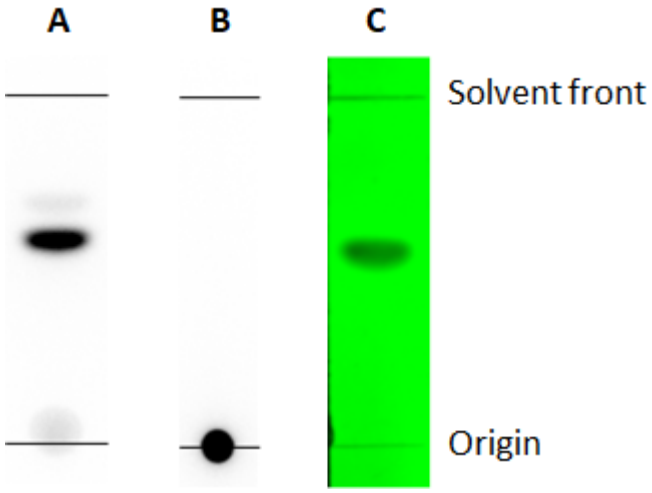


Figure S9. Radio-TLC of the mixture after [^{77}Br]**4c** synthesis (**A**) and free [^{77}Br] (**B**) and UV-TLC of **S2** (**C**). The R_f values of [^{77}Br]**4c,** free [^{77}Br], and **S2** were 0.55-0.61, 0, and 0.55, respectively, on TLC developed with hexane/ethyl acetate (4/1, v/v).

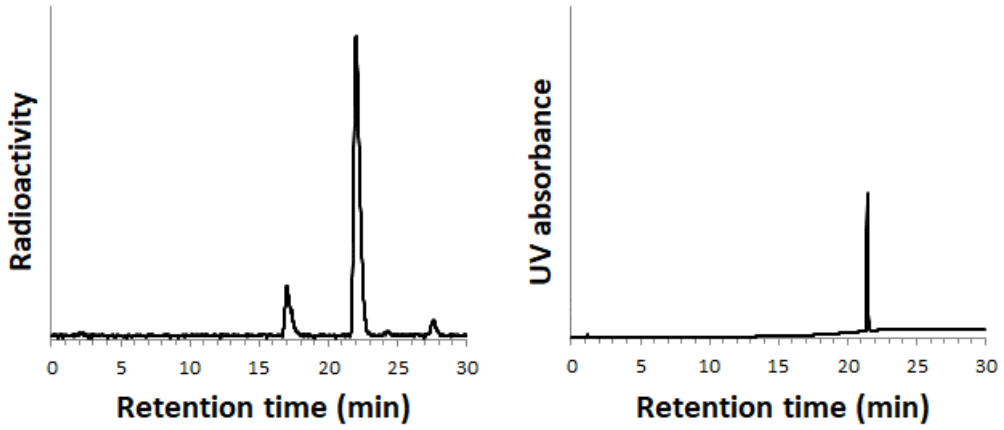


Figure S10. Radio-HPLC of the mixture after [^{77}Br]**4c** synthesis (left) and UV-HPLC of **S2** (right). The retention time of [^{77}Br]**4c** and **S2** was 22.0 min and 21.4 min.

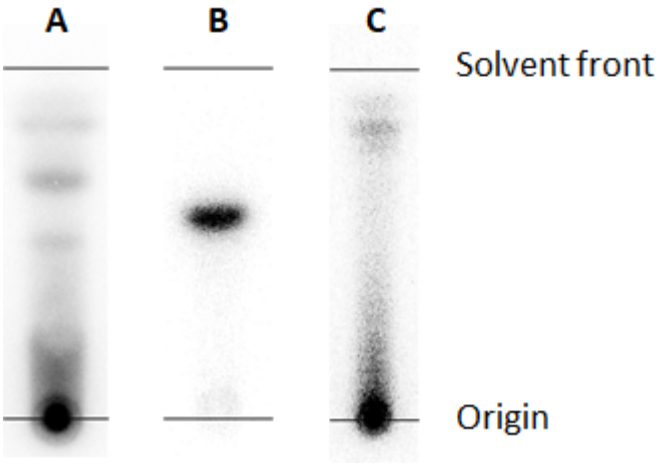


Figure S11. Radio-TLC of the mixtures after [^{211}At]**4d** synthesis in the absence and presence of K_2CO_3 (**A** and **B**) and free [^{211}At] (**C**). The R_f value of [^{211}At]**4d** was 0.53-0.61 on TLC developed with hexane/ethyl acetate (4/1, v/v).

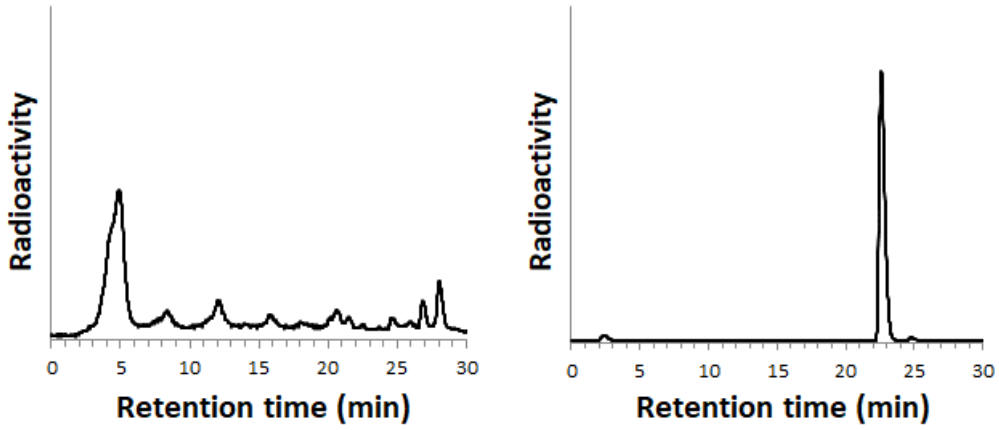


Figure S12. Radio-HPLC of the mixture after [^{211}At]**4d** synthesis in the absence and presence of K_2CO_3 (left and right). The retention time of [^{211}At]**4d** was 22.6 min.

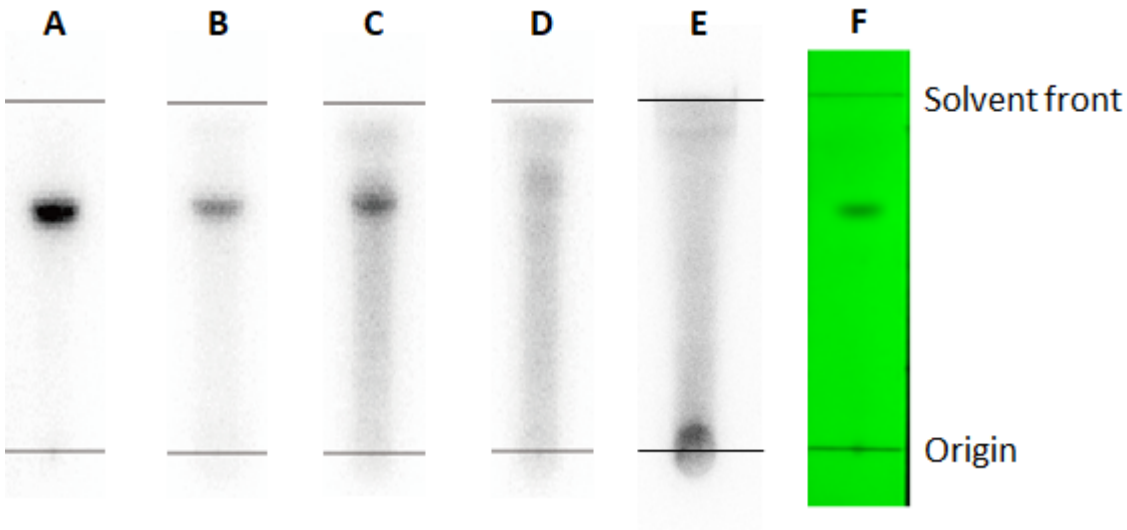


Figure S13. Radio-TLC of the mixtures after [^{211}At]**19** synthesis (**A**-**D**) and free [^{211}At] (**E**) and UV-TLC of **S3** (**F**). **A** and **B** were synthesized in the presence of K_2CO_3 at 70 °C and room temperature, respectively. **C** and **D** were synthesized in the absence of K_2CO_3 at 70 °C and room temperature, respectively. The R_f value of **19** and **S3** was 0.63-0.71 and 0.67, respectively, on TLC developed with hexane/ethyl acetate (2/1, v/v).

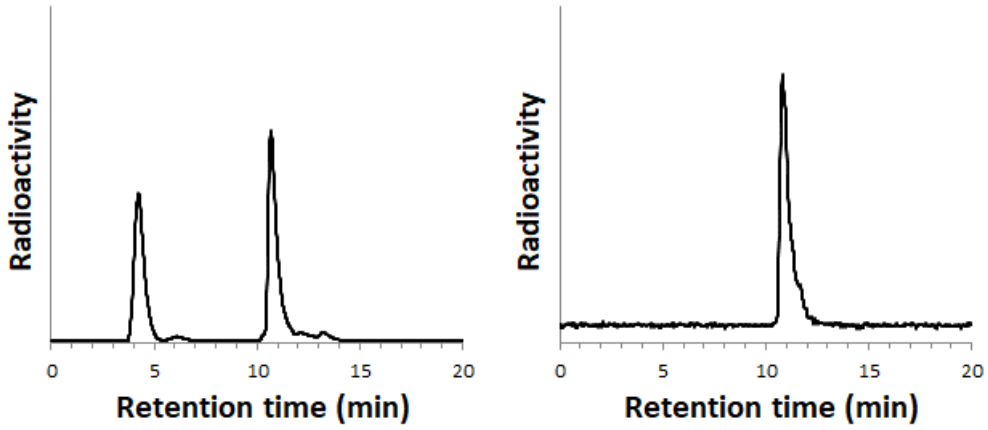


Figure S14. Radio-HPLC of [^{211}At]**6** after synthesis and purification (left and right). The retention time of [^{211}At]**6** was 10.8 min.

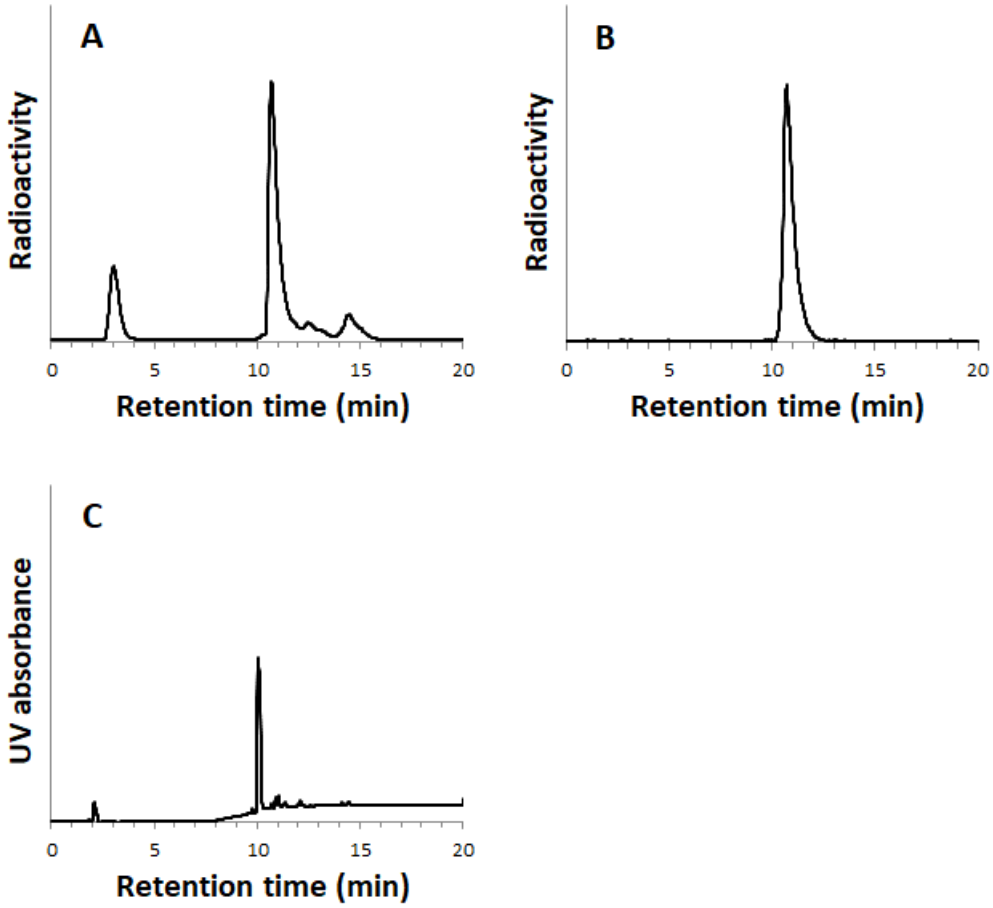
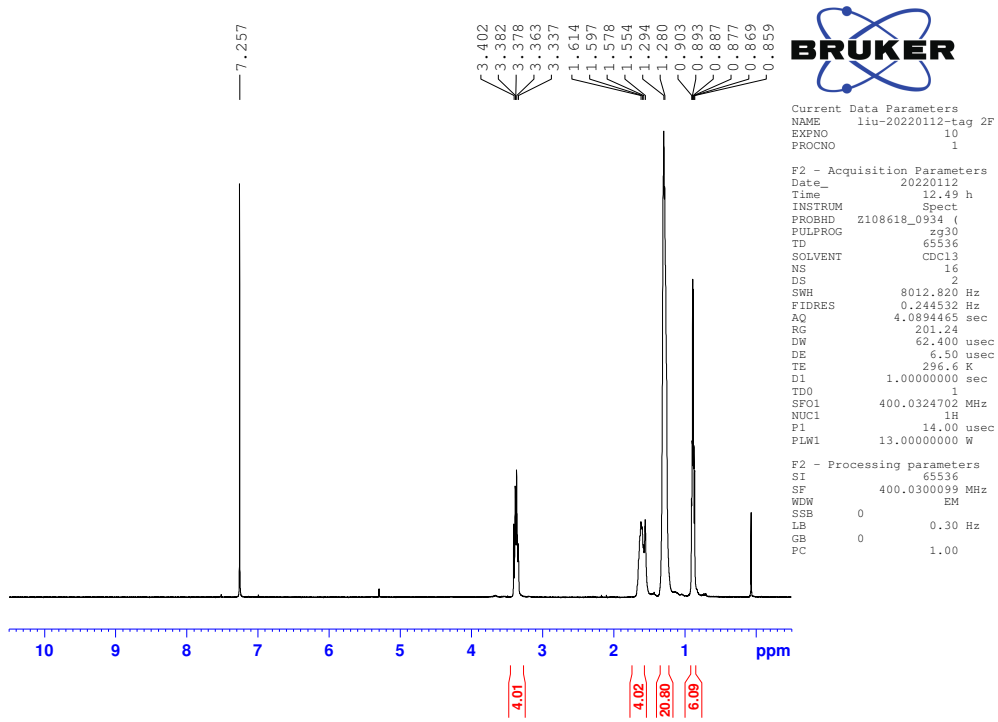
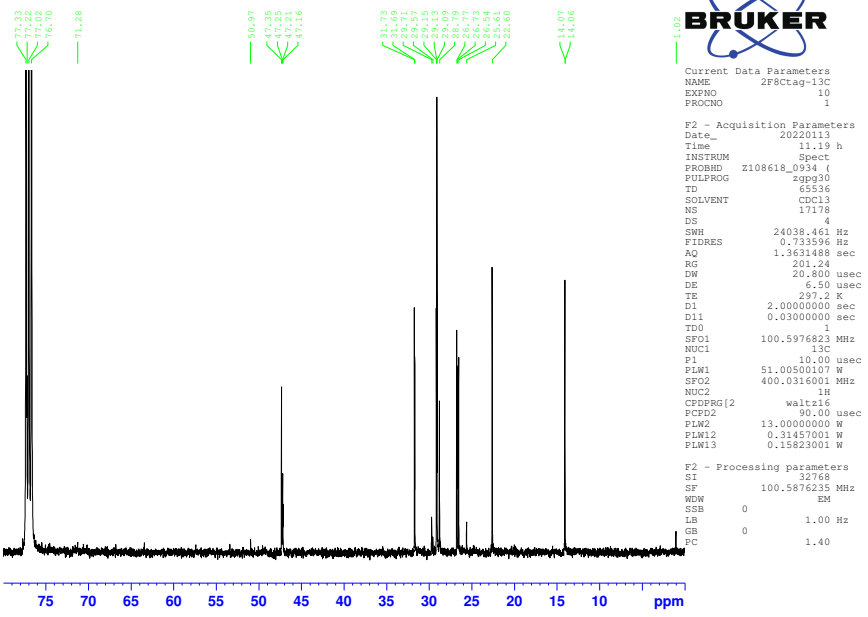


Figure S15. Radio-HPLC of [^{125}I]**7** after synthesis and purification (**A** and **B**) and UV-HPLC of **S4** (**C**). The retention time of [^{125}I]**7** and **S4** was 10.8 min and 10.1 min, respectively.

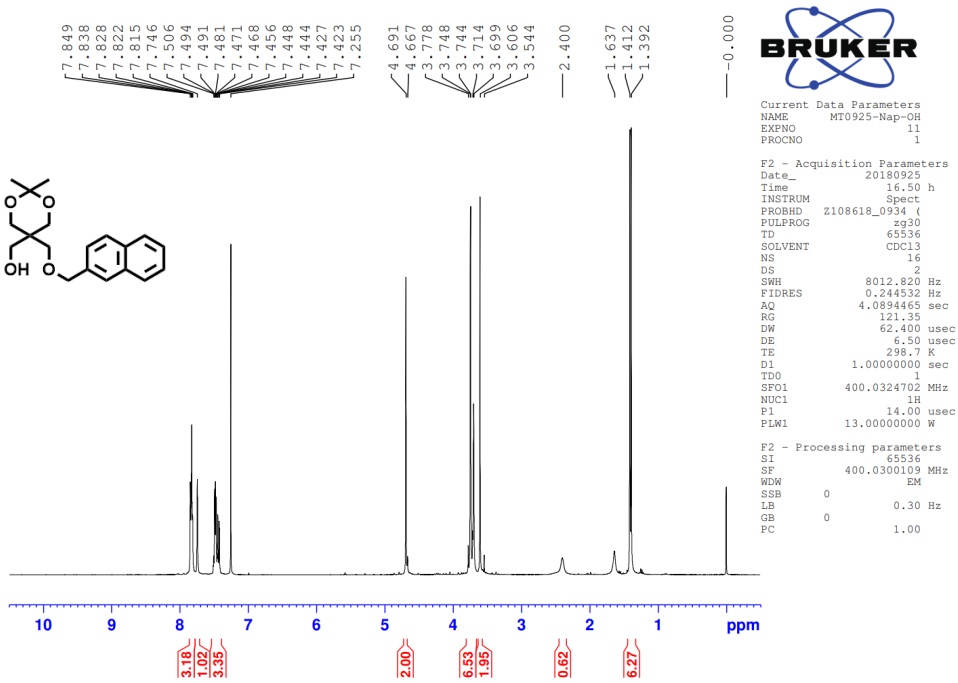
NMR Spectra

2-(Dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonyl fluoride (16)





(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methanol (S1)



BRUKER

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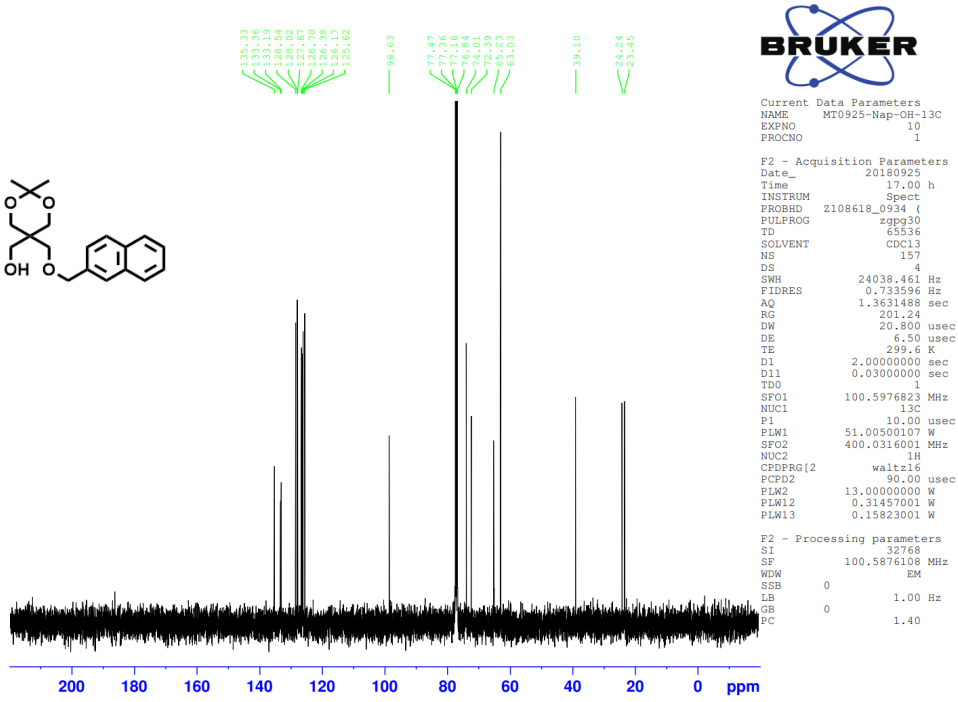

BRUKER

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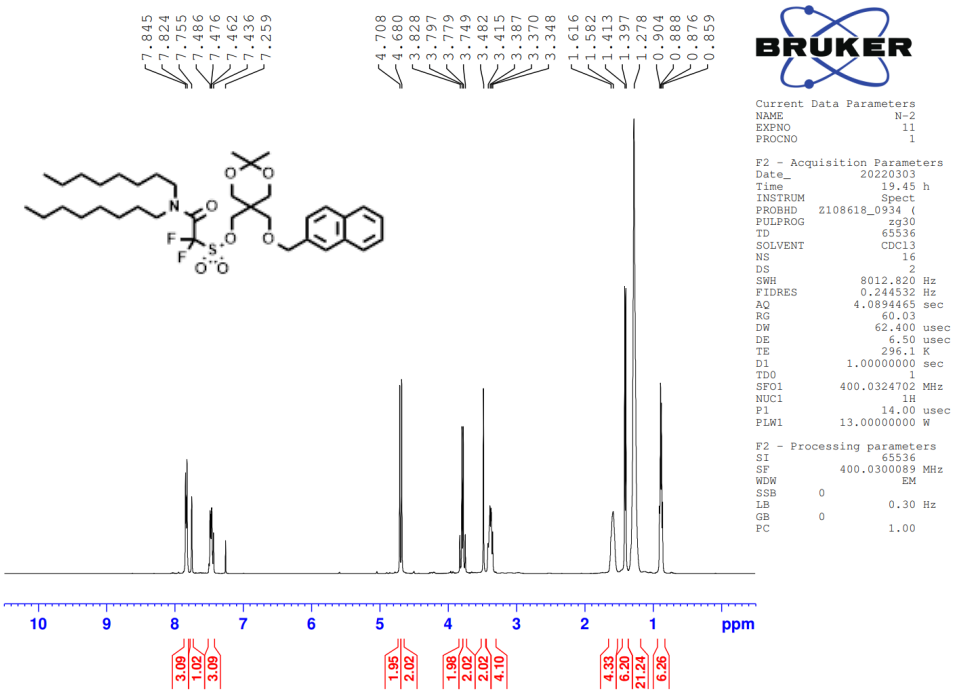
(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl 2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate (3a)

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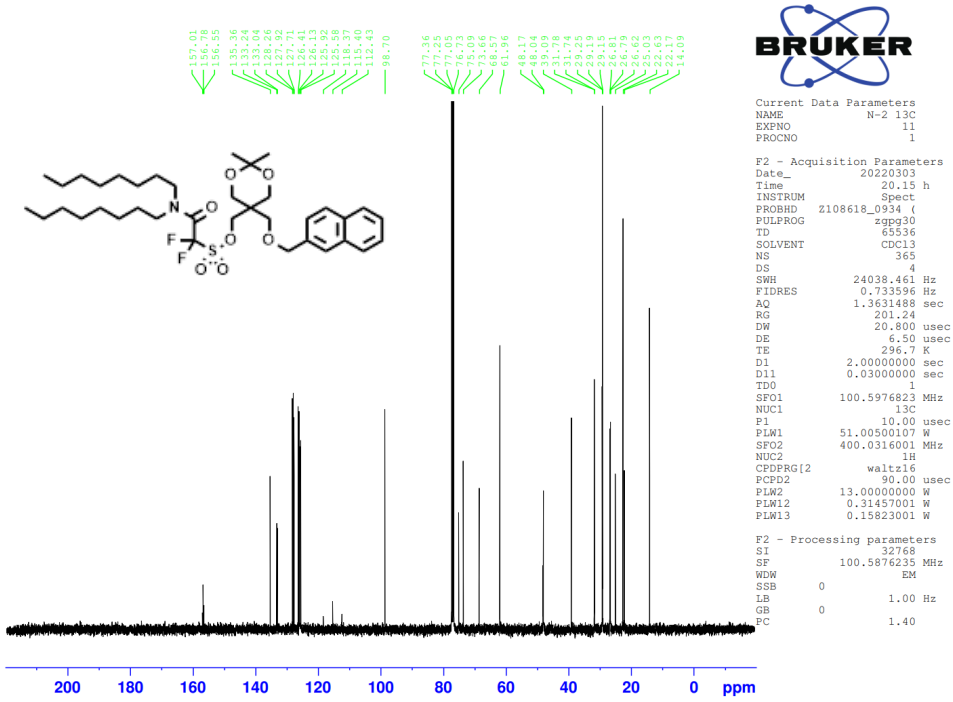


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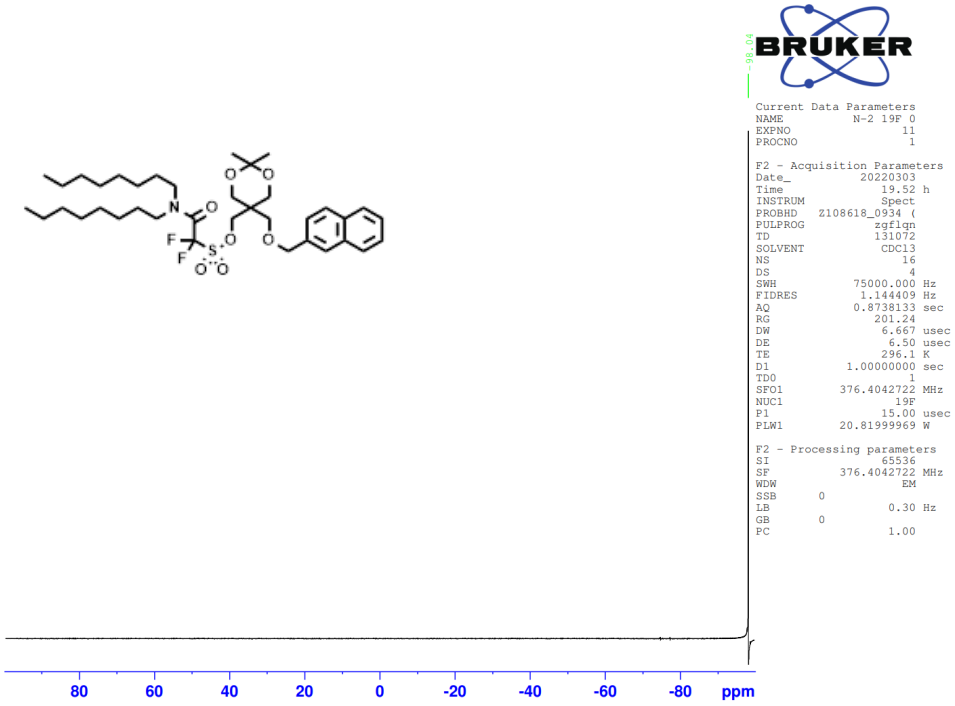
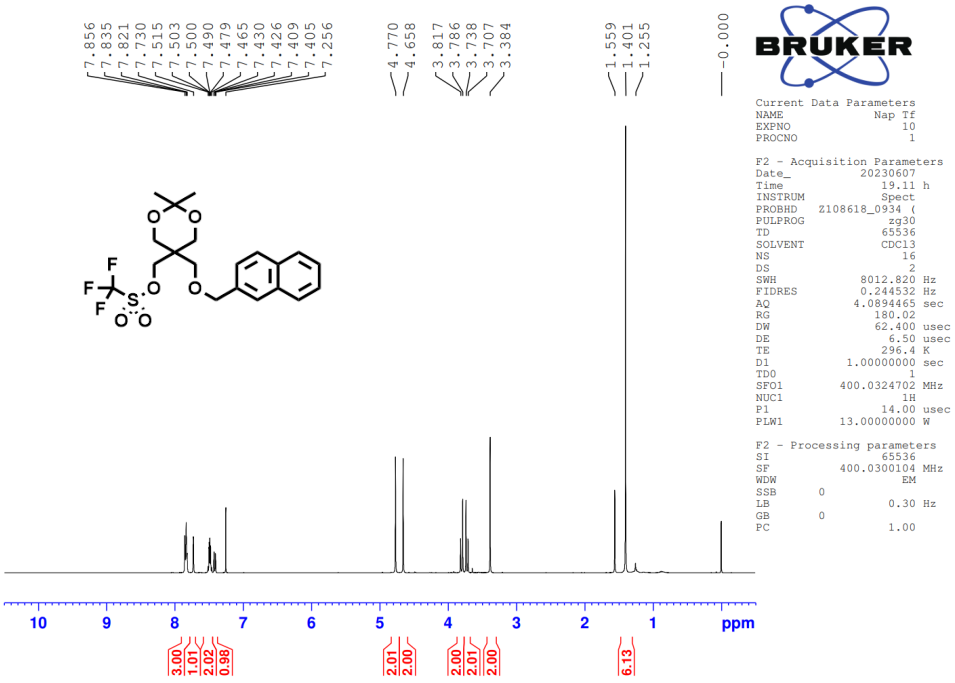
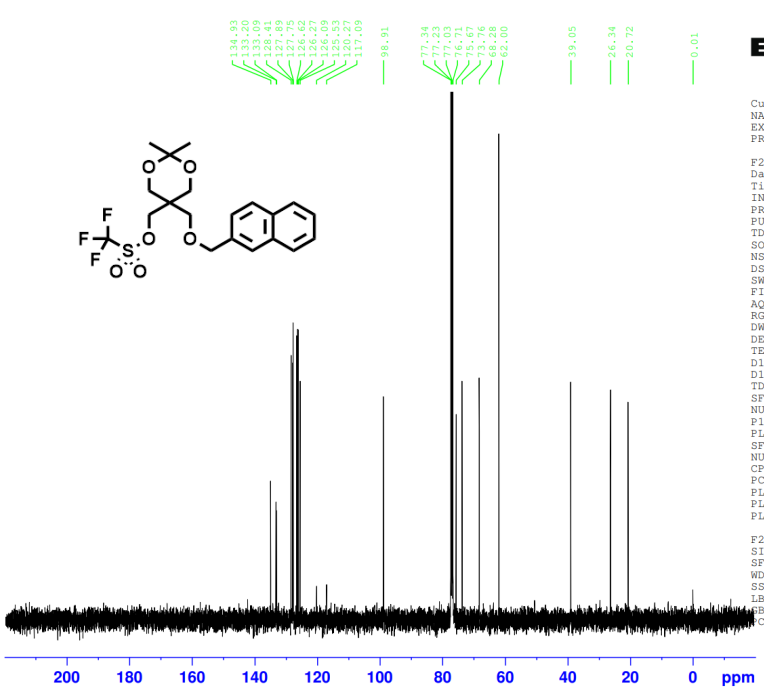


(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl trifluoromethanesulfonate (3b)





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RG                201.24
DW                20.800 usec
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TD0                   1
SFO1          100.5976823 MHz
NUC1                 13C
P1                10.00 usec
PLW1          51.00500107 W
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PLW2          13.00000000 W
PLW12          0.31457001 W
PLW13          0.15823001 W

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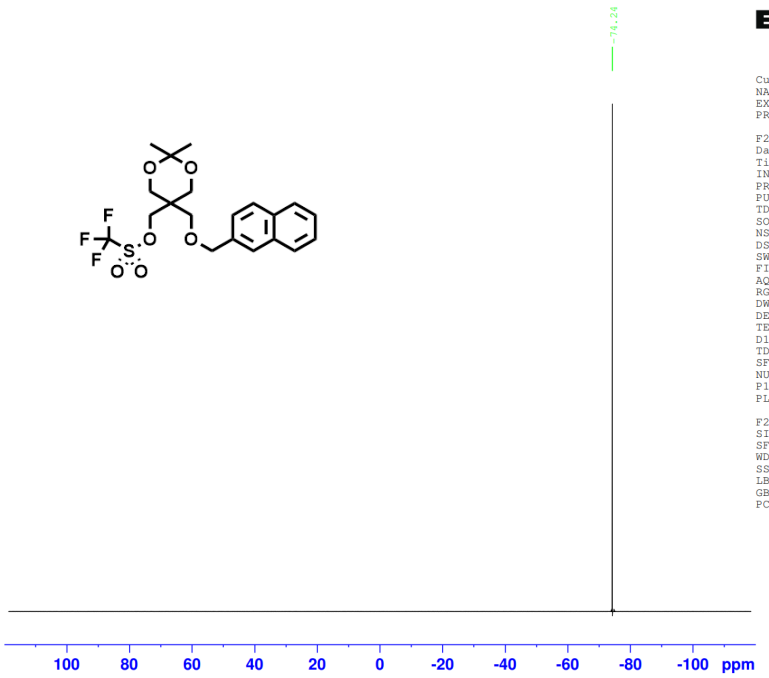

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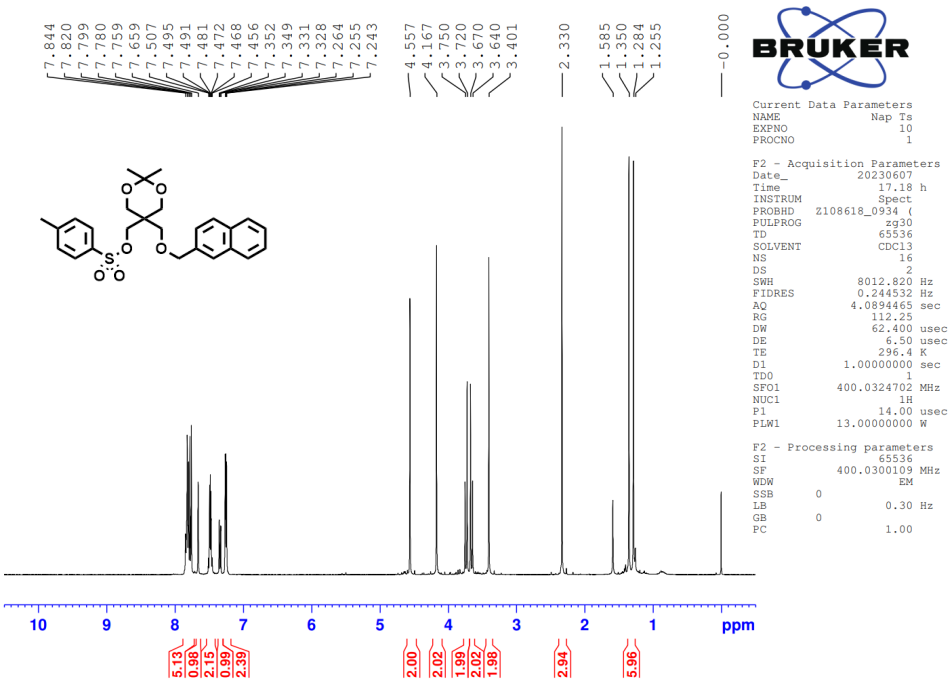
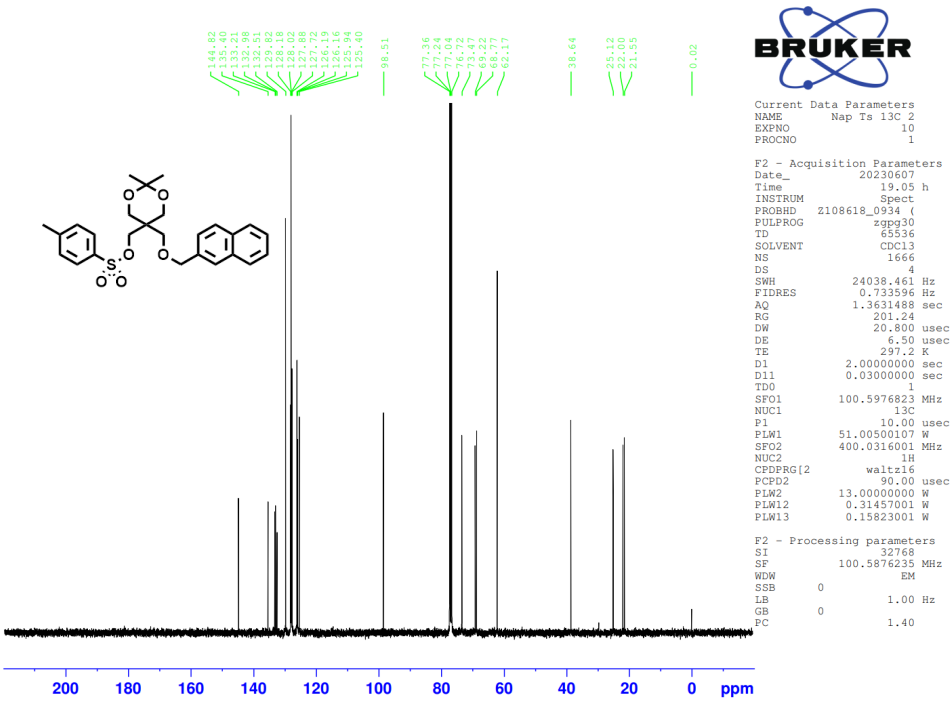
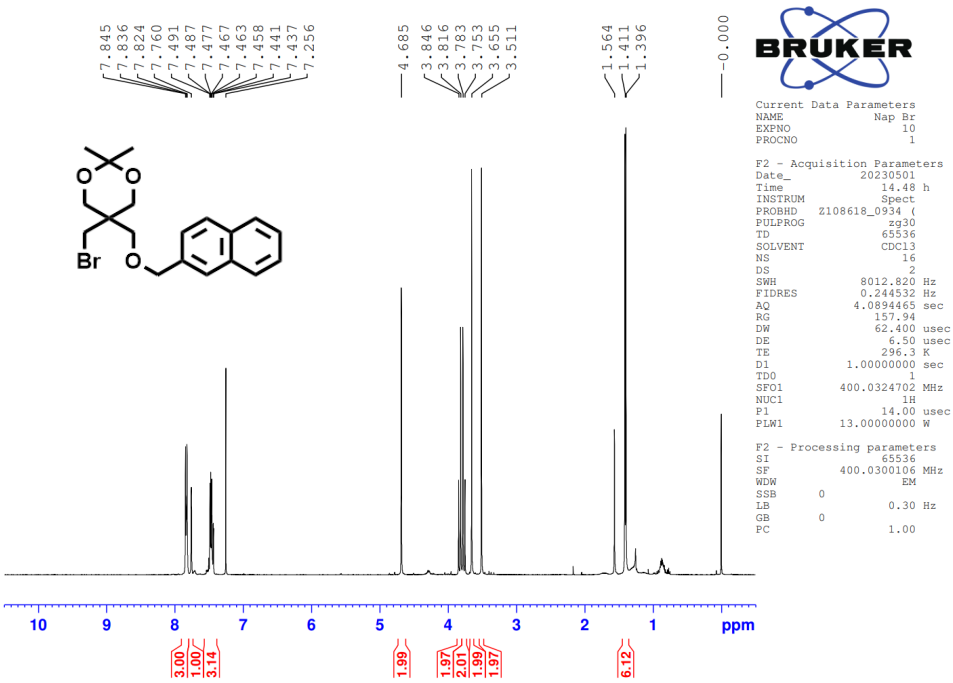
```

(2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxan-5-yl)methyl 4-methylbenzenesulfonate (3c)





5-(bromomethyl)-2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxane (S2)

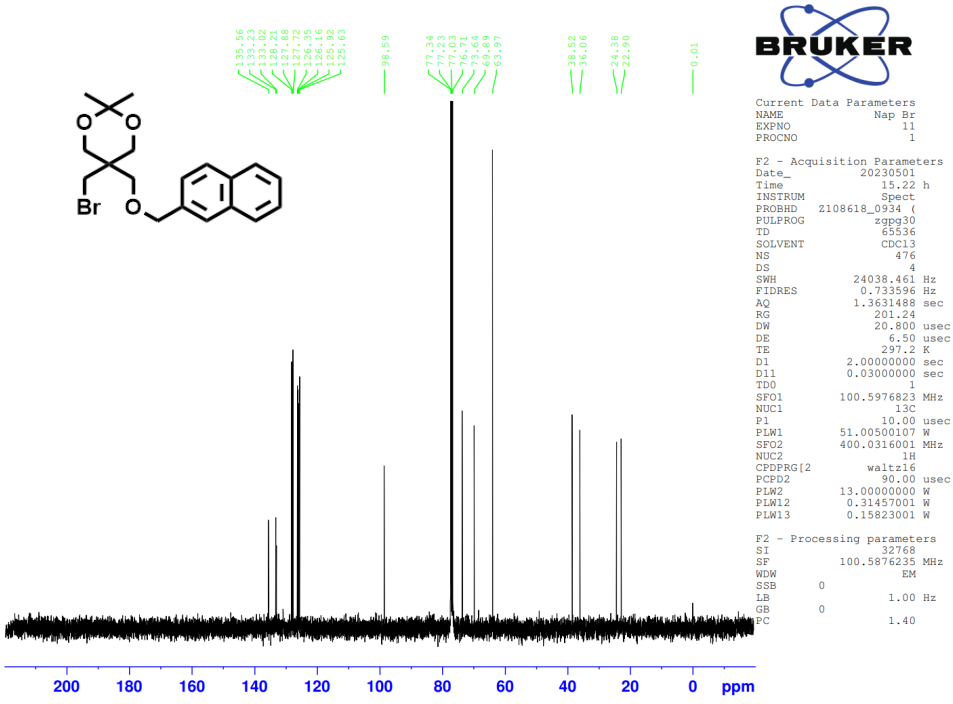


BRUKER

```
Current Data Parameters
NAME                  Nap Br
EXPNO                     10
PROCNO                     1

F2 - Acquisition Parameters
Date_              20230501
Time                  14.48 h
INSTRUM                Spect
PROBHD    Z108618_0934 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES             0.244532 Hz
AQ                 4.0894465 sec
RG                    157.94
DW                    62.400 usec
DE                     6.50 usec
TE                   296.3 K
D1                 1.00000000 sec
TD0                        1
SFO1             400.0324702 MHz
NUC1                      1H
P1                    14.00 usec
PLW1              13.00000000 W

F2 - Processing parameters
SI                    65536
SF               400.0300106 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



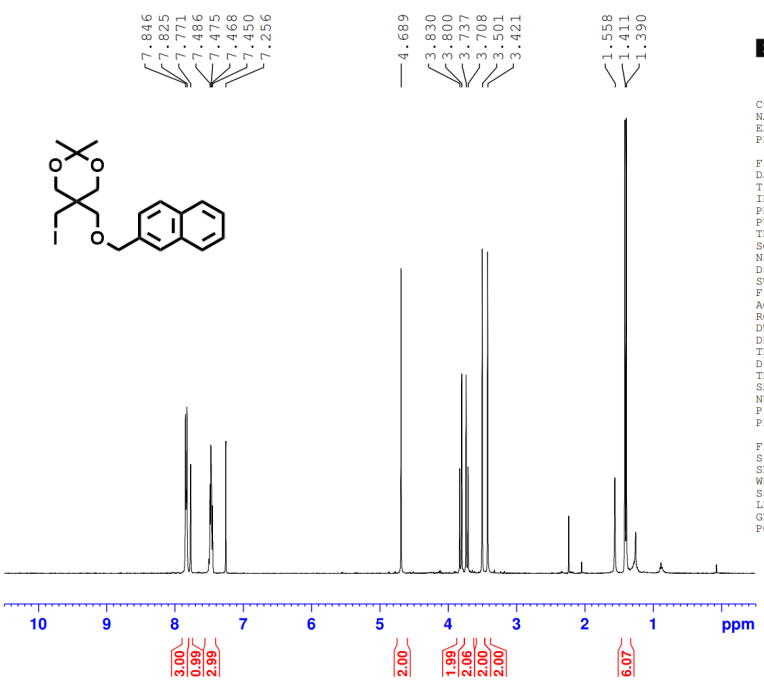
BRUKER

```
Current Data Parameters
NAME                  Nap Br
EXPNO                     11
PROCNO                     1

F2 - Acquisition Parameters
Date_              20230501
Time                  15.22 h
INSTRUM                Spect
PROBHD    Z108618_0934 (
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      476
DS                        4
SWH               24038.461 Hz
FIDRES             0.733596 Hz
AQ                 1.3631488 sec
RG                    201.24
DW                    20.800 usec
DE                     6.50 usec
TE                   297.2 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1
SFO1             100.5976823 MHz
NUC1                      13C
P1                    10.00 usec
PLW1              51.00500107 W
SFO2             400.0316001 MHz
NUC2                      1H
CPDPRG[2              waltz16
PCPD2                 90.00 usec
PLW2              13.00000000 W
PLW12              0.31457001 W
PLW13              0.15823001 W

F2 - Processing parameters
SI                    32768
SF               100.5876235 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

5-(iodomethyl)-2,2-dimethyl-5-((naphthalen-2-ylmethoxy)methyl)-1,3-dioxane (4a)

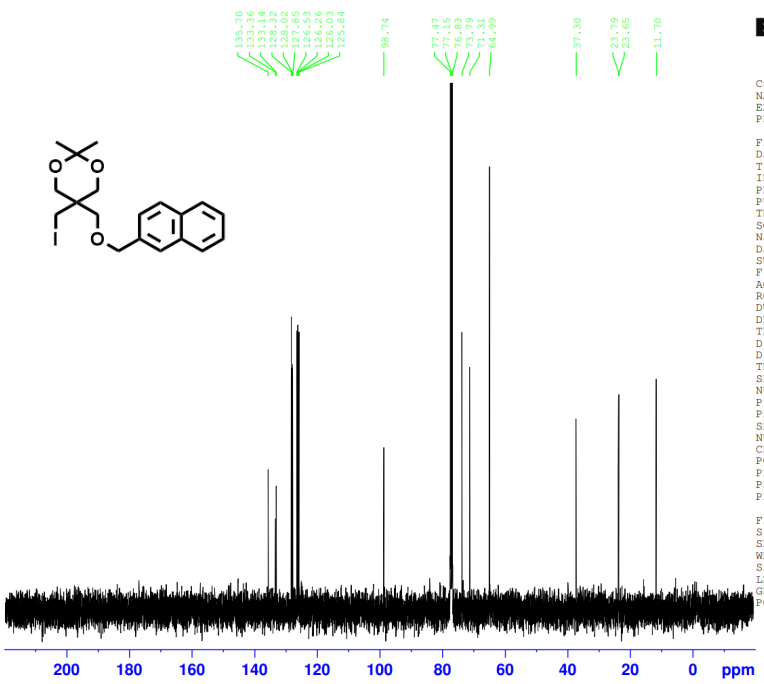


BRUKER

```
Current Data Parameters
NAME                  nap I
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_              20220322
Time                 17.17 h
INSTRUM                Spect
PROBHD    Z108618_0934 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES             0.244532 Hz
AQ                 4.0894465 sec
RG                    180.02
DW                    62.400 usec
DE                     6.50 usec
TE                    296.2 K
D1                 1.00000000 sec
TD0                       1
SFO1              400.0324702 MHz
NUC1                      1H
P1                    14.00 usec
PLW1              13.00000000 W

F2 - Processing parameters
SI                    65536
SF                400.0300102 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```



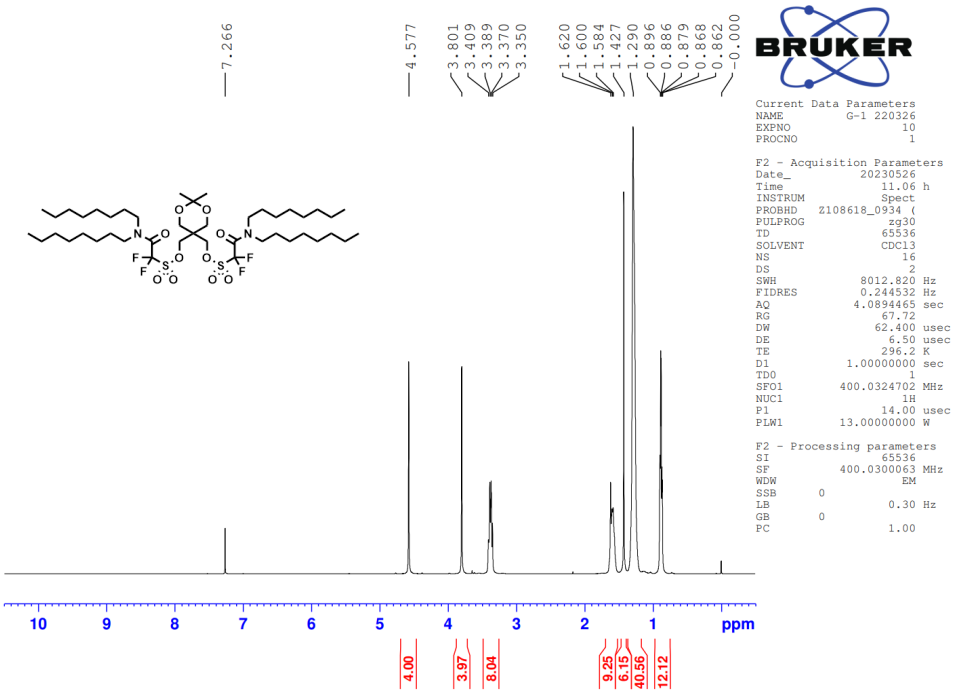
BRUKER

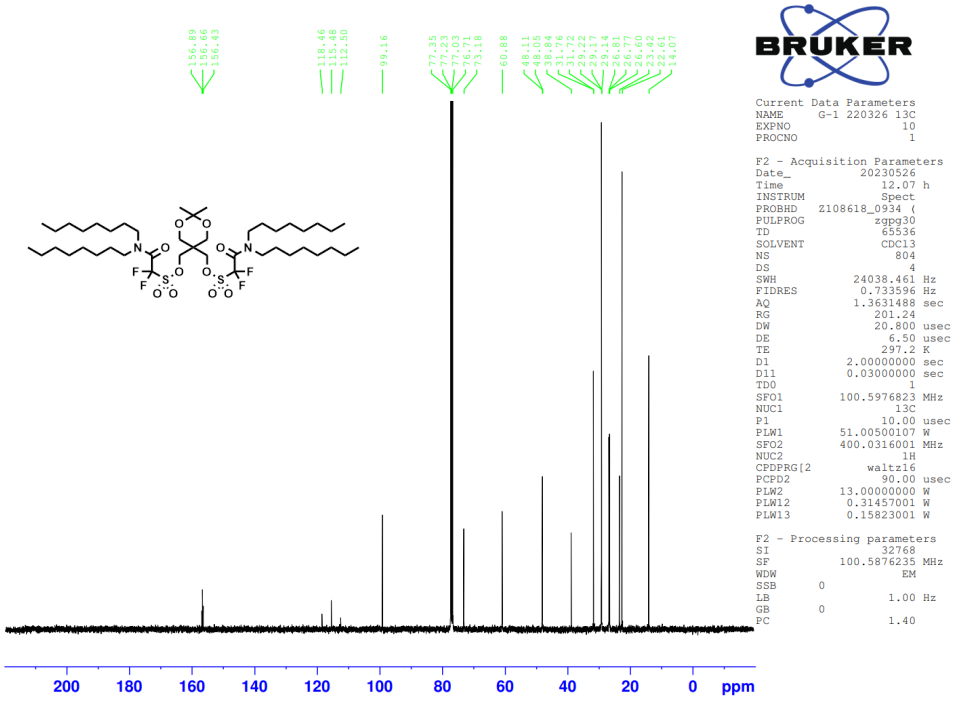
```
Current Data Parameters
NAME              nap I 13C
EXPNO                    10
PROCNO                    1

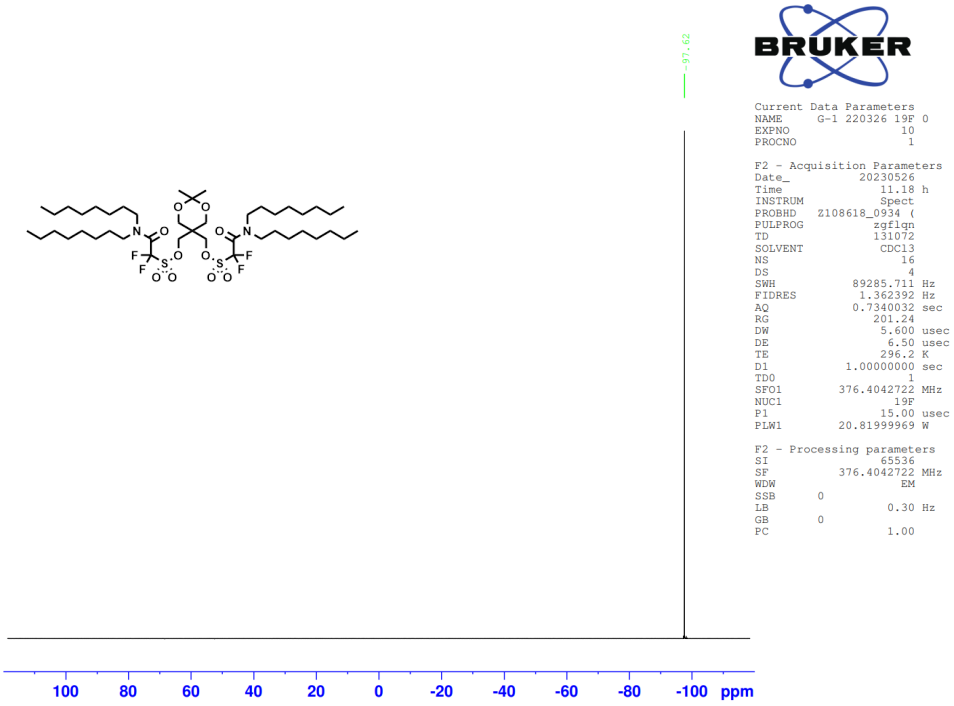
F2 - Acquisition Parameters
Date_              20220322
Time                 17.33 h
INSTRUM                Spect
PROBHD    Z108618_0934 (
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      270
DS                        4
SWH               24038.461 Hz
FIDRES             0.733596 Hz
AQ                 1.3631488 sec
RG                    201.24
DW                    20.800 usec
DE                     6.50 usec
TE                    296.9 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                       1
SFO1              100.5976823 MHz
NUC1                     13C
P1                    10.00 usec
PLW1              51.00500107 W
SFO2              400.0316001 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2              13.00000000 W
PLW12              0.31457001 W
PLW13              0.15823001 W

F2 - Processing parameters
SI                    32768
SF                100.5876110 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

(2,2-dimethyl-1,3-dioxane-5,5-diyl)bis(methylene) bis(2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate) (13)







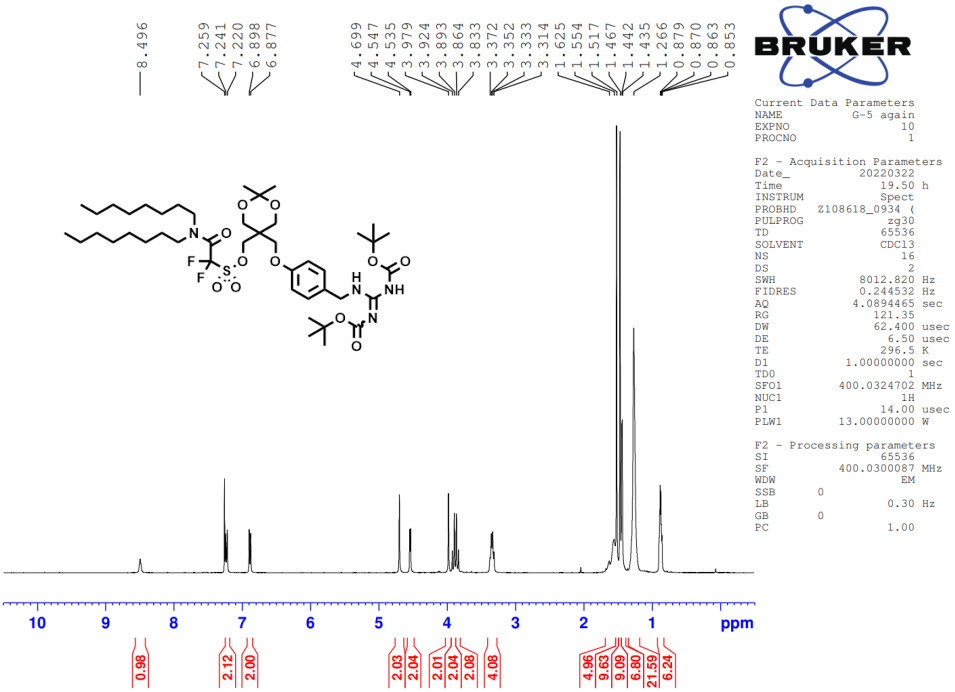
BRUKER

```
Current Data Parameters
NAME      G-1 220326 19F 0
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230526
Time              11.18 h
INSTRUM             Spect
PROBHD   Z108618_0934 (
PULPROG           zgflqn
TD                131072
SOLVENT             CDCl3
NS                    16
DS                     4
SWH           89285.711 Hz
FIDRES         1.362392 Hz
AQ             0.7340032 sec
RG                201.24
DW                 5.600 usec
DE                 6.50 usec
TE                296.2 K
D1             1.00000000 sec
TD0                    1
SFO1         376.4042722 MHz
NUC1                 19F
P1                15.00 usec
PLW1         20.81999969 W

F2 - Processing parameters
SI                 65536
SF           376.4042722 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

(5-((4-((2,3-bis(tert-butoxycarbonyl)guanidino)methyl)phenoxy)methyl)-2,2-dimethyl-1,3-dioxan-5-yl)methyl 2-(dioctylamino)-1,1-difluoro-2-oxoethane-1-sulfonate (8)

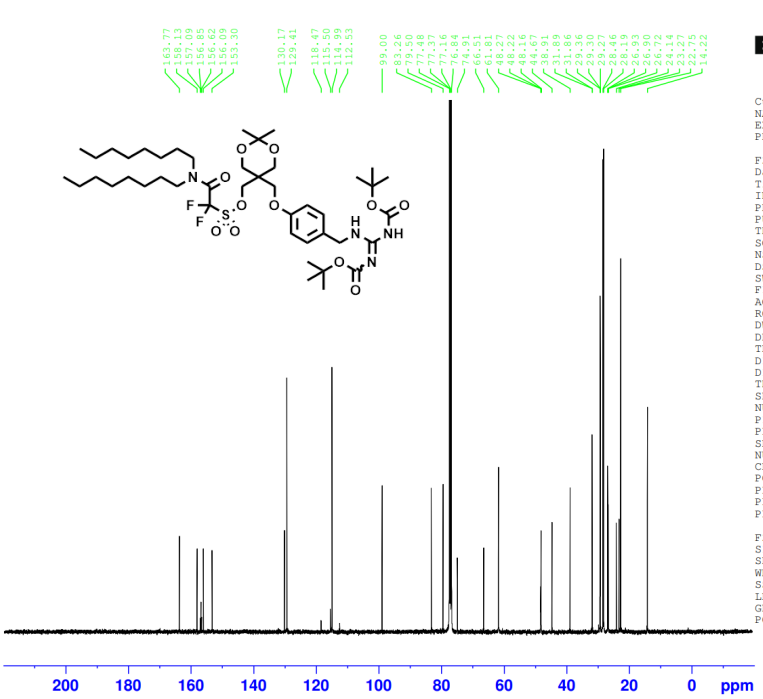


BRUKER

```
Current Data Parameters
NAME          G-5 again
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220322
Time              19.50 h
INSTRUM             Spect
PROBHD   Z108618_0934 (
PULPROG             zg30
TD                 65536
SOLVENT             CDCl3
NS                    16
DS                     2
SWH            8012.820 Hz
FIDRES         0.244532 Hz
AQ             4.0894465 sec
RG                121.35
DW                62.400 usec
DE                 6.50 usec
TE                296.5 K
D1             1.00000000 sec
TD0                    1
SFO1         400.0324702 MHz
NUC1                   1H
P1                14.00 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.0300087 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

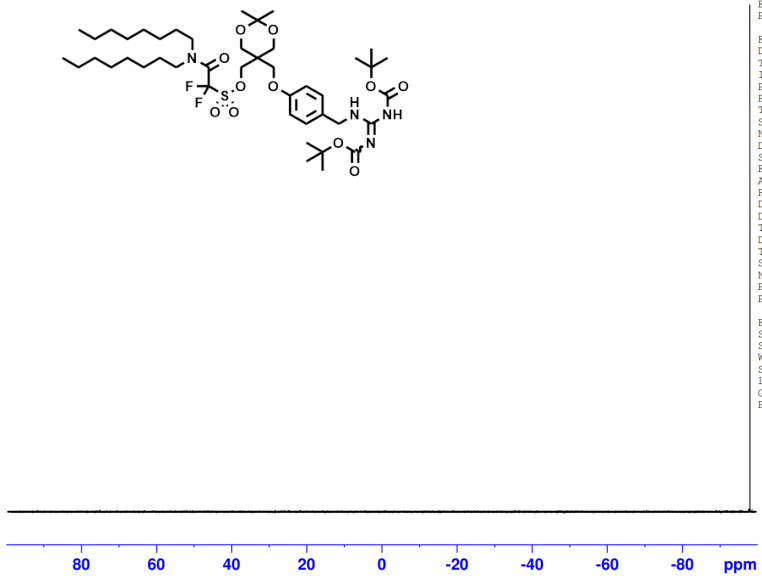


BRUKER

```
Current Data Parameters
NAME       G-5 again 13C
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220323
Time              11.31 h
INSTRUM             Spect
PROBHD    Z108618_0934 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                16384
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ            1.3631488 sec
RG               201.24
DW               20.800 usec
DE                6.50 usec
TE               297.4 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1
SFO1         100.5976823 MHz
NUC1                 13C
P1                10.00 usec
PLW1         51.00500107 W
SFO2         400.0316001 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         13.00000000 W
PLW12         0.31457001 W
PLW13         0.15823001 W

F2 - Processing parameters
SI                32768
SF           100.5876096 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



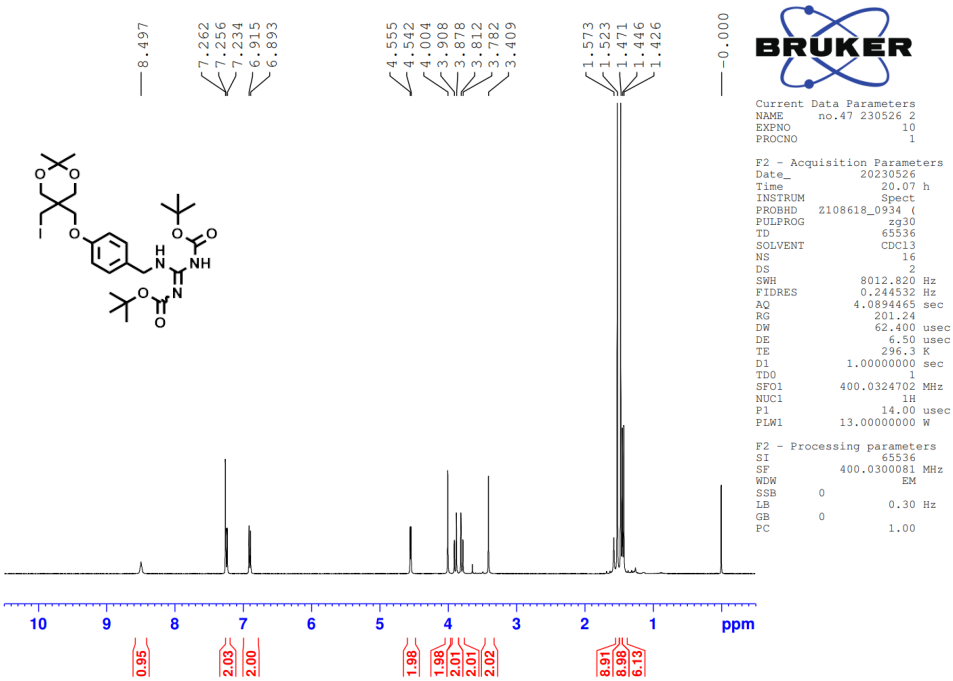
BRUKER

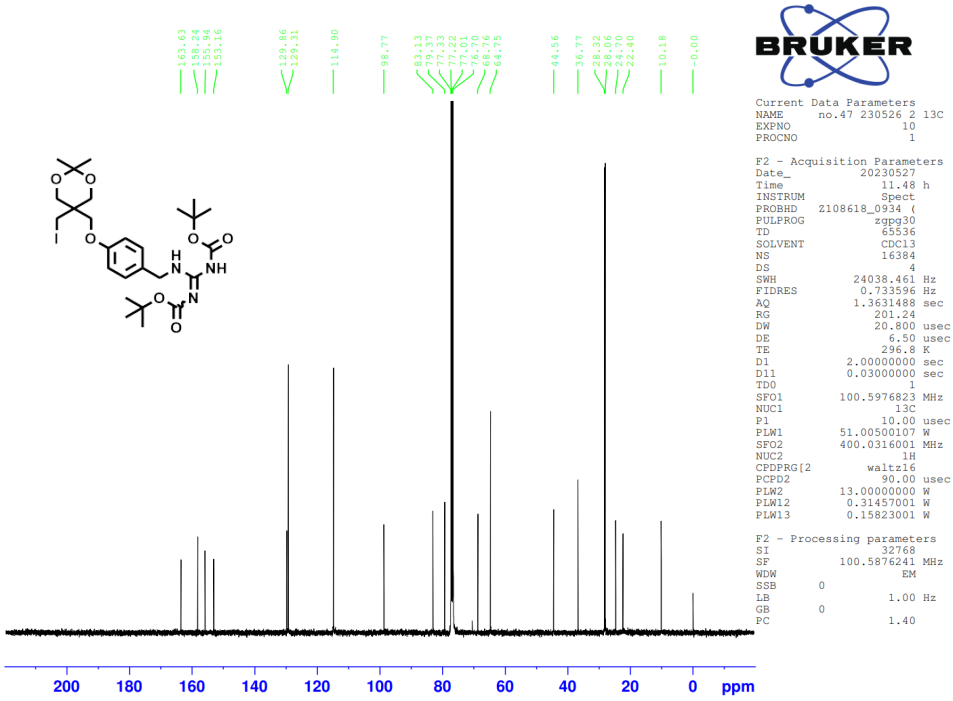
```
Current Data Parameters
NAME       G-5 again 19F 0
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220322
Time              19.53 h
INSTRUM             Spect
PROBHD    Z108618_0934 (
PULPROG          zgflqn
TD               131072
SOLVENT           CDCl3
NS                   16
DS                    4
SWH           75000.000 Hz
FIDRES         1.144409 Hz
AQ            0.8738133 sec
RG               201.24
DW                6.667 usec
DE                6.50 usec
TE               296.6 K
D1           1.00000000 sec
TD0                   1
SFO1         376.4042722 MHz
NUC1                 19F
P1               15.00 usec
PLW1         20.81999969 W

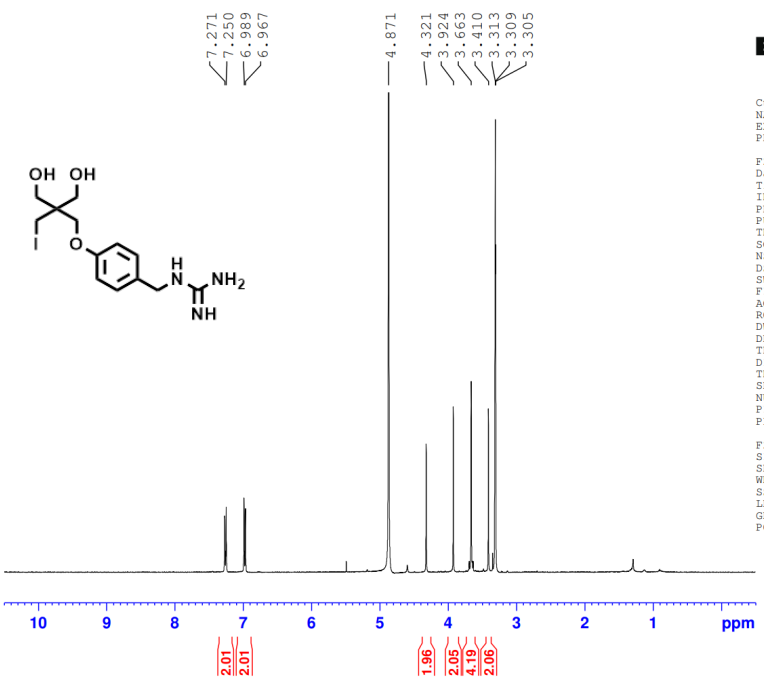
F2 - Processing parameters
SI                65536
SF           376.4042722 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

***N*-(4-(5-iodomethyl-2,2-dimethyl-1,3-dioxan-5-yl)methyloxy)phenyl)-*N*',*N*"-Bis(tert-butoxycarbonyl) guanidine (S3)**





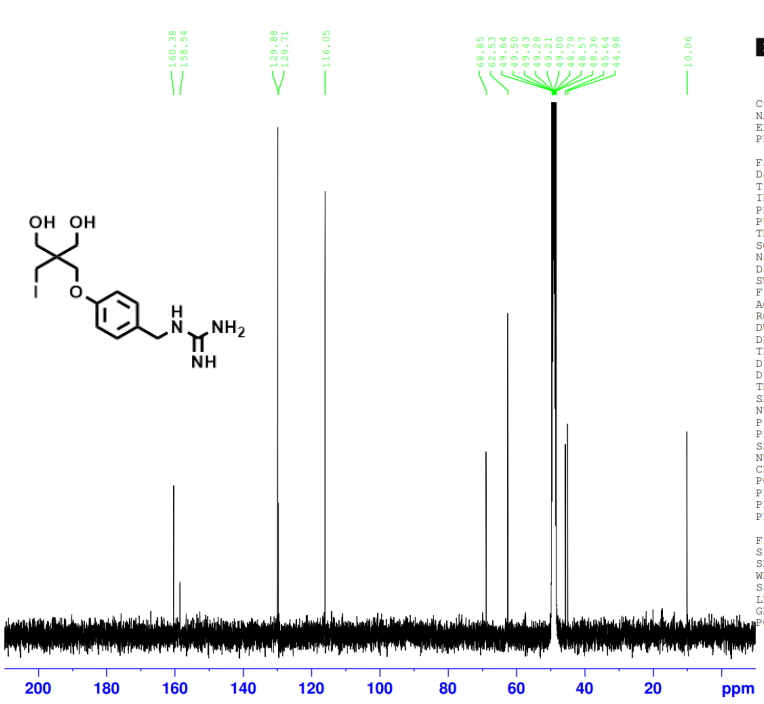
1-(4-(3-hydroxy-2-(hydroxymethyl)-2-(iodomethyl)propoxy)benzyl)guanidine (S4)



Current Data Parameters
NAME no.50 230529
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230529
Time 13.37 h
INSTRUM Spect
PROBHD Z108618_0934 (
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 201.24
DW 62.400 usec
DE 6.50 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
SFO1 400.0324702 MHz
NUC1 1H
P1 14.00 usec
PLW1 13.00000000 W

F2 - Processing parameters
SI 65536
SF 400.0300078 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME no.50 230529 3 13C
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230530
Time 11.02 h
INSTRUM Spect
PROBHD Z108618_0934 (
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 15931
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 201.24
DW 20.800 usec
DE 6.50 usec
TE 297.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.5976823 MHz
NUC1 13C
P1 10.00 usec
PLW1 51.00500107 W
SFO2 400.0316001 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 13.00000000 W
PLW12 0.31457001 W
PLW13 0.15823001 W

F2 - Processing parameters
SI 32768
SF 100.5876235 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40