Stereoselective C-Glycosylation Reactions with Arylzinc Reagents

Sébastien Lemaire, Ioannis N. Houpis, Tingting Xiao, Juanjuan Li, Eric Digard, Charlotte Gozlan, Renmao Liu, Andrey Gavryushin, Coura Diène, Youchu Wang, Vittorio Farina and Paul Knochel*

General

Physical and spectral data were recorded on the following instrument; mp: BÜCHI B-545; optical rotation: Perkin Elmer Model 341; ^{1}HNMR and ^{13}CNMR: Bruker BioSpin GmbH; NOESY NMR: Bruker Avance 360 MHz, 400 MHz and 600 MHz; GC: Agilent Technologies 6890N; HPLC: SHIMADZU LC-2010A HT.

All commercial products are bought from Aldrich, Acros, AcroSeal, Merck, Maybridge, Fluka and Fisher.

General procedure for pivaloylation (method A)

In a 2 necked flask with overhead stirrer under inert atmosphere, a mixture of glucose (3 g, 18.3 mmol), pyridine (12 mL) and dichloromethane (24 mL) is stirred under reflux. Then, pivaloyl chloride (5 eq, 11.2 mL, 91 mmol) is added dropwise and the mixture is heated to reflux until complete conversion (monitored by GC, about 24 h). The mixture is concentrated under reduced pressure and the obtained residue was dissolved in dichloromethane (60 mL), washed with citric acid (60 mL). After phase separation, the aqueous layer is extracted with dichloromethane (60 mL). The combined organic layers are washed with water (60 mL) and brine (60 mL). The organic layer is then concentrated in rotavapor under reduced pressure.

General procedure for bromination (method B)

In a 50 mL Schlenk tube with magnetic stirrer, 1,2,3,4,6-penta-O-pivaloylpyranose (20 g, 33.33mmol) is diluted in dichloromethane (30 mL). Then, HBr 33% w/w in acetic acid (15 mL) is added dropwise and the mixture is mixed at room temperature. After complete conversion (monitored by GC, about 16 h), extra dichloromethane (70 mL) and water (100 mL) was added to the reaction mixture. After phase separation, the organic layer is washed with 100 mL saturated $NaHCO_3$ (1 M), 40 mL water and 40 mL brine. The organic layer is concentrated in rotavapor under reduced pressure.

Magnesate solution (method C)

In a 50 mL Schlenk tube, a solution of n-butyl lithium (42 mL, 100 mmol) in hexane or n-hexyl lithium (100mmol) in hexane was added dropwise over n-dibutylmagnesium in heptane (100 mL, 100 mmol) at 0 °C under Argon atmosphere. The mixture was stirred 15 hours and anhydrous n-butylether (14 mL, 177 mmol) was added. The solution was titrated with iodine extra pure in n-dibutylether (0.59 M).

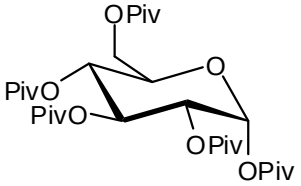
Zinc dibromide lithium bromide solution (method D)

In a 50 mL Schlenk tube with magnetic stirrer under inert atmosphere, solid $ZnBr_2$ (7.11 g, 31.6mmol) and lithium bromide solid (2.74 g, 31.6mmol) are heated to 250 °C for 15 min under vacuum. After cooling back to room temperature, anhydrous n-dibutylether (30 mL) is added under Argon atmosphere and stirred 4 hours at 50 °C.

General procedure for coupling reaction (method E)

In a 10 mL Schlenk tube under argon atmosphere at the appropriate temperature, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol) or butyl lithium in heptane (1.25 eq., 1.09 mmol) is added dropwise to a mixture of the aromatic compound (1.2 eq, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After complete halogen-metal exchange (monitored by GC or HPLC), a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol) is added dropwise. After 1 hour at room temperature, bromosugar (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 90-100°C until complete conversion (monitored by GC). After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is either purified by chromatography or crystallization.

1,2,3,4,6-Penta-O-pivaloyl-α-D-glucopyranose



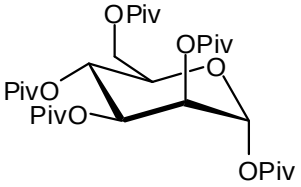
Chemical Formula: $C_{31}H_{52}O_{11}$
Exact Mass: 600.3510

This compound was prepared according to the general procedure **A** using α-D-Glucose (50 g, 278 mmol). The desired product was crystallized from methanol (5L/kg) in 74% yield as white powder (143 g, 238 mmol).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.32 (d, *J*=4Hz, 1H), 5.55 (t, J= 9.9Hz, 1H), 5.19 (t, *J*=9.9Hz, 1H), 5.12 (t, J=9.9Hz, 1H), 4.10 (m, 3H), 1.29 (s, 9H), 1.21 (s, 9H), 1.18 (s, 9H), 1.13 (s, 9H), 1.12 (s, 9H).

^{13}C NMR (90MHz, $CDCl_3$): δ 177.96, 177.07, 176.96, 176.42, 175.85, 88.64, 70.26, 69.62, 69.43, 67.39, 61.60, 39.16, 38.84, 38.76, 38.71, 27.16, 27.11, 27.05.

1,2,3,4,6-Penta-O-pivaloyl-α-D-mannopyranose



Chemical Formula: $C_{31}H_{52}O_{11}$
Exact Mass: 600.3510

This compound was prepared according the general procedure **A** starting from D-Mannose (25 g, 139 mmol). The crude mixture is purified by crystallization from methanol (70 mL) (18.16 g, 30 mmol, 22% yield).

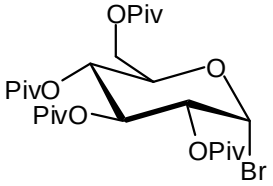
^{1}HNMR (400 MHz, $CDCl_3$): δ 6.02 (d, *J*=1.5Hz, 1H), 5.55 (t, *J*=10.2Hz, 1H), 5.35 (dd, *J*=10.2Hz and 3.2Hz, 1H), 5.28 (dd, J=3Hz & 1.5Hz, 1H), 4.16 (m, 2H), 1.28 (s, 9H), 1.27 (s, 9H), 1.22 (s, 9H), 1.17 (s, 9H), 1.13 (s, 9H).

^{13}CNMR (100MHz, $CDCl_3$): δ 177.96, 177.32, 176.74, 176.52, 175.47, 90.69, 71.15, 69.34, 68.17, 64.48, 61.66, 39.12, 38.89, 38.78, 27.04.

$[\alpha]_D^{25}$=+33 (w/w 1% in MeOH)

mp= 168.3°C.

1-bromo-2,3,4,6-tetra-O-pivaloyl-alpha-D-glucopyranose (3a)



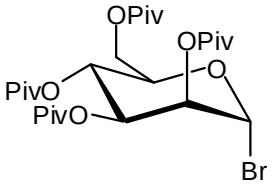
Chemical Formula: $C_{26}H_{43}BrO_9$
Exact Mass: 578.2090

This compound was prepared according the general procedure from **B** (300 g, 500 mmol). The crude mixture is purified by crystallization from isopropanol (1500 mL). White powder (259.9 g, 450 mmol, 90% yield).

^{1}HNMR (400 MHz, $CDCl_3$): δ 6.62 (d, *J*=4Hz, 1H), 5.64 (dd, *J*=9.5Hz and 9.5Hz, 1H), 5.22 (dd, *J*=9.9Hz and 9.9Hz, 1H), 4.83 (dd, J=9.9Hz and 4Hz, 1H), 4.32 (dt, J=9.7Hz and 2.6Hz, 1H), 4.18 (m, 2H), 1.23 (s, 9H), 1.20 (s, 9H), 1.18 (s, 9H), 1.14 (s, 9H).

^{13}CNMR (100MHz, $CDCl_3$): δ 177.90, 177.30, 176.74, 176.40, 86.88, 72.55, 70.87, 69.56, 66.54, 60.87, 38.89, 38.80, 38.74, 38.66, 27.08, 27.00.

1-bromo-2,3,4,6-tetra-O-pivaloyl-alpha-D-mannopyranose (8)



Chemical Formula: $C_{26}H_{43}BrO_9$
Exact Mass: 578.2090

This compound was prepared according the general procedure **B** (4.64 g, 7.72 mmol). The crude mixture is purified by reslurry in ethanol at 0°C (10 mL). White powder (1.87 g, 3.22 mmol, 42% yield).

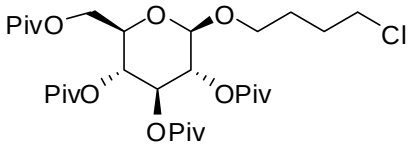
^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.02 (d, *J*=1.1Hz, 1H), 5.53 (t, *J*=10.2Hz, 1H), 5.33 (dd, *J*=10.6Hz and 3.3Hz, 1H), 5.47 (dd, J=3.3Hz and 1.5Hz, 1H), 4.26 (m, 2H), 4.17 (d, *J*=11.0Hz, 1H), 1.27 (s, 9H), 1.24 (s, 9H), 1.19 (s, 9H), 1.13 (s, 9H).

^{13}C NMR (90MHz, $CDCl_3$): δ = 178.31, 177.50, 177.07, 176.95, 92.94, 84.17, 73.62, 72.50, 70.23, 69.47, 69.35, 68.76, 65.56, 64.81, 62.31, 61.39, 39.38, 39.33, 39.29, 39.21, 27.57, 27.49.

$[\alpha]_D^{20}$=+98.6° (1 $g.L^{-1}$ in CH_2Cl_2).

mp= 108.2°C

(2R,3R,4S,5R,6R)-2-(4-chlorobutoxy)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (3c)



Chemical Formula: $C_{30}H_{51}ClO_{10}$
Exact Mass: 606.317

This product was obtained as side product when the reaction is performed in THF.

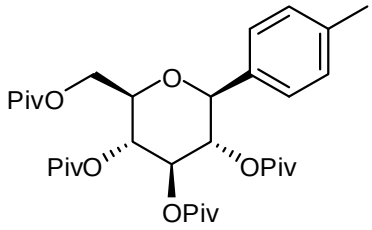
Selective preparation: In a 10 mL Schlenk tube under argon atmosphere at r.t, solid $ZnBr_2$ (1.72mmol, 387mg) is added in one portion to a solution bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous THF (0.86 mL). After 5h at 90 °C, the mixture is cooled to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL) and the water layer was extracted by AcOEt (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by chromatography on silica gel (hexane/ AcOEt 9/1) to afford the desired product as oil (260 mg, 0.43 mmol, 50%).

^{1}HNMR (400 MHz, $CDCl_3$): δ 5.30 (t, *J*=9.6Hz, 1H), 5.09 (t, *J*=10Hz, 1H), 5.00 (dd, *J*=8Hz and 9.6Hz, 1H), 4.49 (d, *J*=8Hz, 1H), 4.22 (d, *J*=12.4Hz, 1H), 4.04 (dd, *J*= 6Hz and 12.4Hz),3.86 (m, 1H), 3.71 (m, 1H), 3.05 (m, 2H), 3.40 (t, *J*=6.8Hz, 1H), 1.93-1.66 (m, 4H), 1.22 (s, 9H), 1.15 (s, 18H), 1.10 (s, 9H).

^{13}C NMR(100MHz, $CDCl_3$): *δ* 178.2, 177.3, 176.6, 101.1, 72.4, 72.3, 71.2, 68.8, 68.7, 68.2, 62.1, 44.8, 39.0, 38.9, 38.8, 33.5, 29.4, 29.2, 28.2, 27.3, 27.2, 27.0.

HRMS (ES^+) = [M+H] calc. 607.3244, found 607.3291.

(2R,3R,4R,5S,6S)-2-(pivaloyloxymethyl)-6-p-tolyltetrahydro-2H-pyran-3,4,5-triyltris(2,2-dimethylpro-panoate) (7a)

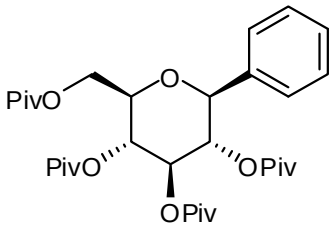


Chemical Formula: $C_{33}H_{50}O_9$
Exact Mass: 590.3455

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol, 0.610 mL) is added dropwise to a mixture of the *p*-iodotoluene (230mg, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After complete halogen-metal exchange (8h, monitored by GC or HPLC), a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 100 °C for 2h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by reverse phase (Kromasil C18) in ammonium carbonate 0.25% in water and acetonitrile (20/80 to 0/100) to afford the desired product as white powder (396 mg, 0.67 mmol, 78%).

^{1}HNMR (360 MHz, CDCl3): δ 7.22 (d, J=8.5Hz, 2H), 7.13 (d, J=8.1Hz, 2H), 5.43 (dd, J=9.5Hz and 9.2Hz, 1H), 5.30 (m, 2H), 4.38 (d, J=9.9Hz, 1H), 4.20 (dd, J=12.4Hz and 0.8Hz, 1H), 4.10 (dd, J=9.5Hz and 9.1Hz, 1H), 3.87 (m, 1H), 2.32 (s, 3H), 1.23 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.89 (s, 9H).
^{13}CNMR (90 MHz, CDCl3): δ 178.08, 177.32, 176.36, 176.03, 138.76, 133.18, 128.98, 127.73, 80.83, 76.51, 73.80, 72.12, 68.01, 61.90, 38.86, 38.75, 38.49, 27.19, 27.08, 26.92, 21.19.
$[\alpha]_D^{25}$=+4.3 (25 °C, 1 g.L^{-1} in MeOH).
mp= 128 °C.
HRMS (ES$^+$) = [M+H$^+$] calc. 591.3528, found 591.3543

(2S,3S,4R,5R,6R)-2-phenyl-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (7b)

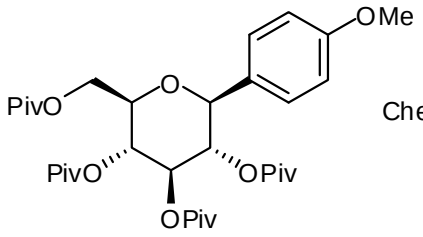


Chemical Formula: $C_{32}H_{48}O_9$
Exact Mass: 576.3298

In a 10 mL Schlenk tube under argon atmosphere at -20 °C, a solution of n-butyl lithium in heptane (1.25eq., 1.09 mmol, 0.403 mL) is added dropwise to a mixture of the iodobenzene (196mg, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 2h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 100 °C for 2h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by reverse phase (Kromasil C18) in ammonium carbonate 0.25% in water and acetonitrile (20/80 to 0/100) to afford the desired product pale white powder (347mg, 0.60 mmol, 70%).

^{1}HNMR (360 MHz, $CDCl_3$): 7.32 (m, 5H), 5.43 (t, J=9.2Hz, 1H), 5.33 (t, J=9.2Hz, 1H), 5.26 (t, J=9.2Hz, 1H), 4.41 (d, J=9.8Hz, 1H), 4.20 (d, J=12.4Hz, 1H), 4.12 (dd, J= 12Hz and 4HZ, 1H), 3.86 m, 1H), 1.22 (s, 9H),1.16 (s, 9H), 1.10 (s, 9H), 0.87 (s, 9H).
^{13}CHMR (90MHz, $CDCl_3$) : 178.01, 177.27, 176.31, 175.85, 136.16, 128.98, 128.31, 127.80, 80.95, 76.54, 73.71, 72.16, 67.44, 61.81, 38.83, 38.71, 38.61, 38.45, 27.15, 27.07, 26.88.
HRMS (ES^+) = [$M+H^+$] calc. 577.3371, found 577.3381.

(2S,3S,4R,5R,6R)-2-(4-methoxyphenyl)-6-(pivaloyloxymethyl)tetrahydro-*2H*-pyran-3,4,5-triyltris(2,2-dimethylpropanoate) (7c)

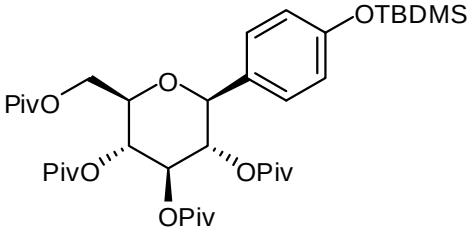


Chemical Formula: $C_{33}H_{50}O_{10}$
Exact Mass: 606.3404

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol, 0.610 mL) added dropwise to a mixture of p-iodoanisole (250mg, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 4.5h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hours at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 90 °C for 2h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is either purified by chromatography on silica gel (heptanes/AcOEt from 9/1 to 8/2) in 82% yield (427mg, 0.71mmol), or by crystallization from heptane (10mL) in 49% yield.

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.27 (d, *J*=8.5Hz, 2H), 6.85 (d, *J*=8.8Hz, 2H), 5.42 (dd, *J*=9.5Hz and 9.1Hz, 1H), 5.26 (m, 2H), 4.36 (d, *J*=9.9Hz, 1H), 4.15 (dd, *J*=12.5Hz and 1.8Hz, 1H), 4.12 (dd, *J*=12.5Hz and 4.1Hz, 1H), 3.86 (m, 1H), 3.79 (s, 3H), 1.23 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.90 (s, 9H).
^{13}CNMR (90 MHz, $CDCl_3$): δ 177.29, 176.34, 176.04, 160.03, 129.11, 128.32, 113.72, 80.58, 76.48, 73.76, 72.06, 67.98, 61.89, 55.25, 38.86, 38.74, 38.70, 38.50, 27.18, 27.10, 27.07, 26.91.
$[\alpha]_D^{25}$=+4.6° (1 g.L^{-1} in CH_2Cl_2).
mp= 173.1 °C
HRMS (ES^+) = [M+H$^+$] calc. 607.3477, found 607.3496.

(2S,3S,4R,5R,6R)-2-(4-(tert-butyldimethylsilyloxy)phenyl)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (7d)

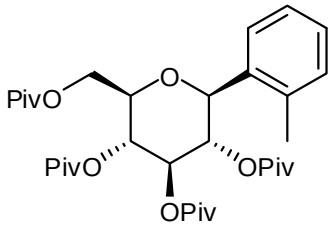


Chemical Formula: $C_{38}H_{62}O_{10}Si$
Exact Mass: 706.4112

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol, 0.610 mL) is added dropwise to a mixture of tert-butyl-(4-iodophenoxy)-dimethylsilane (306 mg, 0.91 mmol, 1.04 eq.) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 1.5 h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture was heated at 60 °C for 24h and the white powder was purified by reverse phase (Kromasil C18) in ammonium carbonate 0.5% in water and acetonitrile (20/80 to 0/100) to afford the desired product as white powder (303 mg, 0.43 mmol, 50% yield).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.21 (d, *J*=8.4Hz, 2H), 6.79 (d, *J*=8.1Hz, 2H), 5.41 (t, *J*=9.2Hz, 1H), 5.32 (t, *J*=9.9Hz, 1H), 5.23 (t, *J*=9.5Hz, 1H), 4.35 (d, *J*=9.9Hz, 1H), 4.19 (d, *J*=12.4Hz, 1H), 4.13 (dd, *J*=12.8Hz and 3.7Hz, 1H), 3.85 (d, *J*=9.9Hz, 1H), 1.23 (s, 9H), 1.17 (s, 9H), 1.11 (s, 9H), 0.96 (s, 9H), 0.90 (s, 9H).
^{13}C NMR (90MHz, $CDCl_3$): δ = 178.43, 177.68, 176.71, 176.36, 156.63, 129.41, 129.39, 120.43, 81.01, 76.83, 74.13, 72.53, 68.37, 62.21, 39.23, 39.11, 38.85, 27.44, 26.02, 18.58.
$[\alpha]_D^{20}$=+2.2° (1 g.L^{-1} in CH_2Cl_2)
HRMS (ES$^+$) = [M+H$^+$] calc. 707.4185, found 707.4222.

(2S,3S,4R,5R,6R)-2-(2-methylphenyl)-6-(pivaloyloxymethyl)tetrahydro-*2H*-pyran-3,4,5-triyltris (2,2-dimethylpropanoate) (7e)

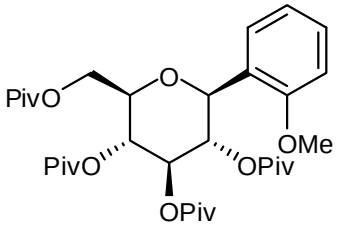


Chemical Formula: $C_{33}H_{50}O_9$
Exact Mass: 590.3455

In a 100 mL Schlenk tube under argon atmosphere at -10 °C, butyl lithium in heptane (1.25eq., 4.40mmol, 1.63 mL) is added dropwise to a mixture of 2-iodotoluene (0.921 g, 1.2 eq.) dissolved in anhydrous toluene (1.76 mL) and anhydrous n-dibutylether (1.06 mL). After 30 min., a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 2.32 mmol, 2,13 g) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 2.0 g, 3.52 mmol) dissolved in anhydrous toluene (3.52 mL) is added to the organozinc mixture. The mixture was directly transferred to a pre-heated oil bath at 110 °C for 24h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (20 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (20 mL). The combined organic layer are washed with water (20 mL), and then washed with a brine solution (20 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The black syrup was purified by reverse phase (Kromasil C18) in ammonium carbonate 0.5% in water and acetonitrile (20/80 to 0/100). The white powder **7e** was obtained (1.17 g, 1.99 mmol, 58%).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.30 (t, *J*=3.3Hz, 1H), 7.19 (m, 2H), 5.46 (m, 2H), 5.34 (t, *J*=9.2Hz, 2H), 4.70 (d, *J*=9.5Hz, 1H), 4.22 (dd, *J*=12.4Hz and 2.1Hz, 1H), 4.10 (dd, *J*=12.8Hz and 4Hz, 1H), 3.88 (dd, *J*=9.8Hz and 2.1Hz), 2.46 (s, 3H), 1.23 (s, 9H), 1.18 (s, 9H), 1.13 (s, 9H), 0.86 (s, 9H).
^{13}CNMR (90MHz, $CDCl_3$): δ = 178.06, 177.38, 176.37, 176.16, 136.81, 133.81, 130.63, 128.75, 127.84, 126.14, 77.93, 76.82, 74.01, 71.22, 67.99, 61.93, 27.21, 27.10, 26.78, 19.56.
$[\alpha]_D^{20}$=+6.1° (1 g.L^{-1} in CH_2Cl_2).
mp= 159.7 °C
HRMS (ES^+) = [M+H$^+$] calc. 591.3528, found 591.3554.

(2S,3S,4R,5R,6R)-2-(2-methoxyphenyl)-6-(pivaloyloxymethyl)tetrahydro-*2H*-pyran-3,4,5-triyltris (2,2-dimethylpropanoate) (7f)

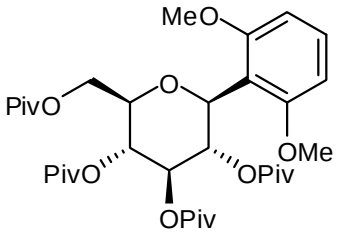


Chemical Formula: $C_{33}H_{50}O_{10}$
Exact Mass: 606.3404

In a 100 mL Schlenk tube under argon atmosphere at -10 °C, butyl lithium in heptane (1.25eq., 4.40mmol, 1.63 mL) is added dropwise to a mixture of o-iodoanisole (0.979 g, 1.2 eq.) dissolved in anhydrous toluene (1.76 mL) and anhydrous n-dibutylether (1.06 mL). After 30 min., a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 2.32 mmol, 2.13 g) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 2.0 g, 3.52 mmol) dissolved in anhydrous toluene (3.52 mL) is added to the organozinc mixture. The mixture was directly transferred to a pre-heated oil bath at 110 °C for 24h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (20 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (20 mL). The combined organic layer are washed with water (20 mL), and then washed with a brine solution (20 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The black syrup was purified by reverse phase (Kromasil C18) in ammonium carbonate 0.5% in water and acetonitrile (20/80 to 0/100). The white powder **7f** was obtained (1251mg, 2.06 mmol, 60%).

^{1}HNMR (360 MHz, $CDCl_3$): δ = 7.37 (d, *J*=7.6Hz, 1H), 7.26 (dd, *J*=9.5Hz and 1.5Hz, 1H), 6.96 (dd, *J*=7.7Hz and 7.7Hz, 1H), 6.83 (d, *J*=8.4Hz, 1H), 5.40 (m, 3H), 5.03 (d, *J*=8.8Hz, 1H), 4.22 (d, *J*=12.4Hz, 1H), 4.10 (dd, *J*=12.5Hz and 4Hz, 1H), 3.88 (dd, *J*=9.9Hz and 1.8Hz, 1H), 3.81 (s, 3H), 1.23 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.84 (s, 9H).
^{13}CNMR (90MHz, $CDCl_3$): δ = 177.73, 176.99, 175.86, 129.63, 128.33, 123.87, 120.43, 110.09, 73.68, 71.22, 67.69, 61.53, 54.99, 38.39, 26.84, 26.74, 26.31.
$[\alpha]_D^{20}$=+15.3° (1 g.L^{-1} in CH_2Cl_2).
mp= 144.7 °C
HRMS (ES^+) = [$M+H^+$] calc. 607.3477, found 607.3484.

(2S,3S,4R,5R,6R)-2-(2,6-dimethoxyphenyl)-6-(pivaloyloxymethyl)tetrahydro-*2H*-pyran-3,4,5-triyltris (2,2-dimethylpropanoate) (7g)

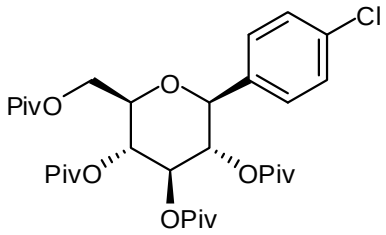


Chemical Formula: $C_{34}H_{52}O_{11}$
Exact Mass: 636.3510

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of s-BuLi (2.96 mL, 4.14 mmol, 1.62 mL) is added dropwise to a mixture of 1,3-dimethoxybenzene (0.54 mL, 4.14 mmol) dissolved in anhydrous toluene (1.76 mL) and anhydrous n-dibutylether (1.06 mL). After complete halogen-metal exchange (4h, monitored by GC or HPLC), a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise at 0 °C. After 30 min. at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 100 °C for 2 hours. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by chromatography on silica gel column heptanes/ethyl acetate (from 9/1 to 8/2) to afford the desired product as white powder. (470 mg, 0.74 mmol, 86% yield)

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.19 (dd, *J*=8.4Hz and 8.1Hz, 1H), 6.53 (d, *J*=8.1Hz, 1H), 6.45 (d, *J*=8.5Hz, 1H), 5.99 (dd, *J*=9.9Hz and 9.5Hz, 1H), 5.40 (dd, *J*=9.9Hz and 9.5Hz, 1H), 5.33 (dd, *J*=9.9Hz and 9.5Hz, 1H), 5.18 (d, *J*=10.3Hz, 1H), 4.20 (dd, *J*=12.5Hz and 1.8Hz, 1H), 4.14 (dd, *J*=12.5Hz and 3.3Hz, 1H), 3.87 (s, 3H), 3.82 (m, 1H), 3.77 (s, 3H), 1.24 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.82 (s, 9H).
^{13}CNMR (90 MHz, $CDCl_3$): δ 178.08, 177.43, 176.37, 160.37, 158.84, 130.43, 127.95, 114.38, 111.50, 105.16, 103.20, 76.53, 74.41, 71.90, 69.04, 67.88, 61.89, 56.00, 55.63, 38.87, 38.75, 38.41, 27.24, 27.12, 27.05, 26.69.
HRMS (ES^+) = [$M+H^+$] calc. 637.3582, found 637.3589.

(2S,3S,4R,5R,6R)-2-(4-chlorophenyl)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (7h)

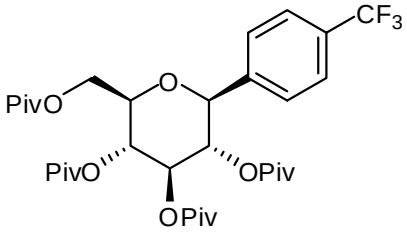


Chemical Formula: $C_{32}H_{47}ClO_9$
Exact Mass: 610.2909

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol, 0.610 mL) is added dropwise to a mixture of 1-chloro-4-iodobenzene (247mg, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 6h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 100 °C for 24h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by reverse phase (Kromasil C18) in ammonium carbonate 0.25% in water and acetonitrile (20/80 to 0/100) affords the desired product as white powder (304 mg, 0.50 mmol, 58%).

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.32 (d, J=8Hz, 2H), 7.28 (d, J=8Hz, 2H),5.43 (t, J=9.5Hz, 1H), 5.31 (t, J=9.5Hz, 1H), 5.22 (t, J=9.5Hz, 1H), 4.40 (d, J=9.5Hz, 1H),4.21 (dd, J=12.5Hz and 1.8Hz, 1H), 4.12 (dd, J=12.5Hz and 4.4Hz, 1H), 3.86 (m, 1H), 1.22 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H), 0.92(s, 3H).
^{13}CNMR (90 MHz, $CDCl_3$): δ 178.04, 177.28, 176.37, 176.02, 134.80, 129.13, 128.55, 80.16, 76.59, 73.56, 72.08, 67.92, 61.81, 38.87, 36.76, 38.71, 38.52, 27.71, 27.09, 26.96.
HRMS (ES^+) = [$M+H^+$] calc. 611.2981, found 611.2958

(2R,3R,4R,5S,6S)-2-(pivaloyloxymethyl)-6-(4-(trifluoromrthyl)phenyl)tetrahydro-*2H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (7i)

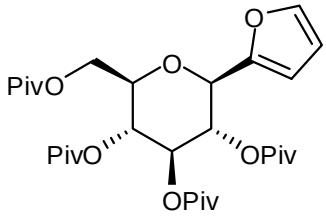


Chemical Formula: $C_{33}H_{47}F_3O_9$
Exact Mass: 644.3172

In a 10 mL Schlenk tube under argon atmosphere at -78 °C, butyl lithium in heptane (1.25eq., 1.09mmol, 0.404 mL) is added dropwise to a mixture of 1-iodo-4-(trifluoromethyl)benzene (0.979 g, 1.2 eq.) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). At the end of the addition, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at -78 °C, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture was directly transferred to a pre-heated oil bath at 110 °C for 24 hrs, After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The black syrup was purified by reverse phase (Kromasil C18) in ammonium carbonate 0.5% in water and acetonitrile (20/80 to 0/100). The white powder **7i** was obtained as brown powder. (111 mg, 0.17 mmol, 50% yield).

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.60 (d, *J*=8.06Hz, 2H), 7.47 (d, *J*=8.06Hz, 2H), 5.45 (t, *J*=9.60Hz, 1H), 5.32 (t, *J*=9.60Hz, 1H), 5.24 (t, *J*=9.69Hz, 1H), 4.48 (d, *J*=9.82Hz, 1H), 4.22 (dd, *J*=12.60Hz and 2.00Hz, 1H), 4.13 (dd, *J*=12.60Hz and 4.53Hz, 1H), 3.88 (m, 1H), 1.22 (s, 9H), 1.18 (s, 9H), 1.11 (s, 9H), 0.90 (s, 9H).
^{13}CNMR (100 MHz, $CDCl_3$): δ 178.01, 177.27, 176.37, 175.99, 140.22, 131.20, 128.19, 125.30, 123.84, 80.17, 76.74, 75.52, 72.09, 67.92, 61.78, 38.87, 38.77, 38.73, 38.52, 27.17, 27.09, 27.07, 26.92;
mp= 209.5 °C.
HRMS (ES^+) = [$M+H^+$] calc. 645.3245, found 645.3265.

(2R,3R,4S,5R,6R)-2-(furan-2-yl)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (7j)



Chemical Formula: $C_{30}H_{46}O_{10}$
Exact Mass: 566.3091

Hexyllithium (1 equiv., 10 mmol, C = 2.36M) was added to a solution of furan (10 mmol) in dibutyl ether (1 M) at 0 °C and warmed to RT for one hour. Iodolysis of an aliquot showed complete lithiation. $ZnBr_2$.LiBr (1.5 M in Bu_2O, 0.5 equiv) was then added at RT and stirred at that temperature for 30 min. A preheated solution of sugar **3a** in toluene (1 M) was then charged and the reaction mixture was heated to 90 °C for 12 hrs. Standard workup and purification by column chromatography led to the isolation of the desired furan-substituted sugar in 61% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.33 (d, *J* = 6.0Hz, 1 H), 6.33 (d, *J* = 6.0 Hz, 1 H), 6.26 (dd, *J* = 3.4, 1.9Hz, 1 H), 5.39 (t, *J* = 9.9Hz, 1 H), 5.33 (t, *J* = 9.3Hz, 1 H), 5.20 (t, *J* = 10.2Hz, 1 H), 4.49 (d, *J* = 9.9Hz, 1 H), 4.15 (dd, *J* = 12.4, 1.6Hz, 1 H), 4.06 (dd, *J* = 12.5, 4.7Hz, 1 H), 3.78 (ddd, *J* = 9.9, 4.7, 1.7Hz, 1 H), 1.15 (s, 9 H), 1.10 (s, 9 H), 1.06 (s, 9 H), 0.89 (s, 9 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 177.9, 177.2, 176.1, 149.1, 110.3, 109.8, 76.4, 73.6, 69.7, 67.7, 61.8, 38.8, 38.7, 38.7, 38.6, 27.1, 27.0, 27.0, 26.8.

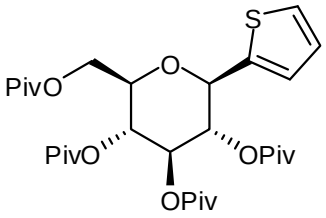
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2936, 2909, 1736, 1524, 1504, 1479, 1462, 1398, 1368, 1277, 1159, 1131, 1089, 1058, 1034, 936, 761

M.p.: 110.8-115.9 °C

Elemental Analysis. Calcd for $C_{30}H_{46}O_{10}$: C, 63.58; H, 8.18. Found: C, 63.24; H, 8.09.

$[\alpha]^{22}_D$ = + 0.81° (*c* 0.02, d6-acetone)

(2R,3R,4S,5R,6R)-2-(pivaloyloxymethyl)-6-(thiophene-2-yl)tetrahydro-*2H*-pyran-3,4,5-triyltris(2,2-di-methylpropanoate) (7k)

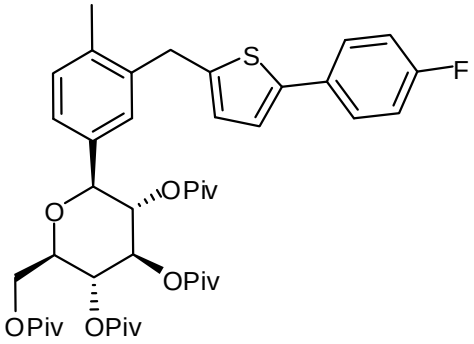


Chemical Formula: $C_{30}H_{46}O_9S$
Exact Mass: 582.2863

In a 10 mL Schlenk tube under argon atmosphere at -20 °C, butyl lithium in heptane (1.25eq., 1.09mmol, 0.403 mL) is added dropwise to a mixture of 2-iodothiophene (111 µL, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 1h at -20 °C, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar **3a** (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 100 °C for 2h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by chromatography on normal phase (Kromasil C18) in ammonium carbonate 0.5% in water and acetonitrile (20/80 to 0/100) to afford the desired product as white powder (300mg, 0.51 mmol, 60% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (dd, *J* = 5.1, 1.0Hz, 1 H), 7.05 (dd, *J* = 3.6, 1.2Hz, 1 H), 6.93 (dd, *J* = 4.9, 3.4Hz, 1 H), 5.41 (m, 1 H), 5.29 (m, 2 H), 5.33 (t, *J* = 9.7Hz, 1 H), 5.20 (t, *J* = 10.2Hz, 1 H), 4.49 (d, *J* = 9.7Hz, 1 H), 4.25 (dd, *J* = 12.4, 2.0Hz, 1 H), 4.09 (dd, *J* = 12.4, 4.4Hz, 1 H), 3.87 (ddd, *J* = 10.0, 4.4, 2.0Hz, 1 H), 1.22 (s, 9 H), 1.17 (s, 9 H), 1.12 (s, 9 H), 0.94 (s, 9 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 178.0, 177.3, 176.3, 176.1, 138.7, 126.9, 126.5, 126.3, 76.5, 76.2, 73.6, 72.4, 67.8, 61.8, 38.9, 38.8, 38.7, 38.6, 27.2, 27.1, 27.1, 26.9.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2871, 1734, 1478, 1461, 1396, 1367, 1275, 1158, 1095, 1032, 891, 724.
$[\alpha]_D^{25}$=+4.4° (1 $g.L^{-1}$ in CH_2Cl_2)
mp= 127.9 °C
HRMS (ES^+) = [$M+H^+$] calc. 583.2935, found 583.2946.

(2S,3S,4R,5R,6R)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (17)

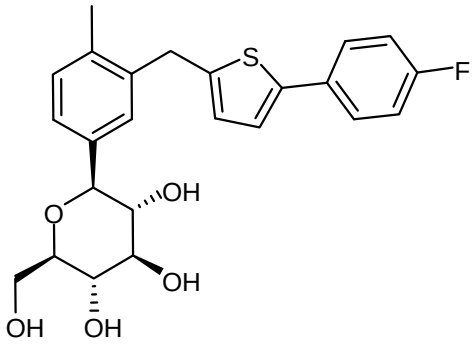


Chemical Formula: $C_{44}H_{57}FO_9S$
Exact Mass: 780.3707

In a Schlenk tube under inert atmosphere, 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (2.04g, 5mmol, 1.0eq) was dissolved in n-Bu_2O (1.5mL) / toluene (2.5mL). After cooling to -40 °C, *n*-BuLi (2.7M in hept., 5.25mmol, 1.05eq, 1.94 mL) was added dropwise to the reaction mixture. (Iodolysis of an aliquot showed complete lithiation.) Two hours later at -40 °C, $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.55 eq, 2.75 mmol, 2.52 g) was added dropwise and the reaction mixture was allowed to warm up to room temperature. Finally, compound **3a** (5mmol, 2.90 g, 1mol/L in toluene) was added to the heterogeneous mixture which was heated to 90 °C for 2 hours. After cooling to room temperature, the mixture was quenched with HCl aq. 1N (10mL). After phase separation, the organic layer was dried via a pre-packed column and evaporated under reduced pressure. The obtained crude mixture was purified by column chromatography on silicagel (heptanes/AcOEt from 9/1 to 8/2) to afford the desired product **17** (2.9g, 3.75mmol) in 75% yield.

^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.22-7.13 (m, 3H), 7.05-7.00(m, 3H), 6.60 (d, J=3.7Hz, 1H), 5.43(t, J=9.2Hz, 1H); 5.34 (t, J=9.5Hz, 1H); 5.32 (t, J=9.5Hz, 1H);4.38 (d, J=9.9Hz, 1H); 4.22 (dd, J= 2.2Hz & 12.8Hz, 1H); 4.15-4.03 (m, 3H); 3.87-3.83 (m, 1H), 2.28 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 0.88(s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 178.06, 177.32, 176.34, 175.96, 163.40, 160.68, 142.99, 141.43, 138.11, 137.42, 134.06, 130.49, 129.14, 127.11, 127.02, 125.93, 126.59, 122.62, 115.77, 115.53, 80.84, 76.52, 73.82, 71.97, 67.97, 61.84, 38.85, 38.75, 38.72, 38.46, 34.13, 27.20, 27.10, 26.93, 19.28.
$[\alpha]_D^{25}$=+18.8° (1 $g.L^{-1}$ in CH_2Cl_2)
mp : 142.5 °C
HRMS (ES^+) = [M+H^+] calc. 781.3780, found 781.3798.

Canaglifozin (2)



Chemical Formula: $C_{24}H_{25}FO_5S$
Exact Mass: 444.141

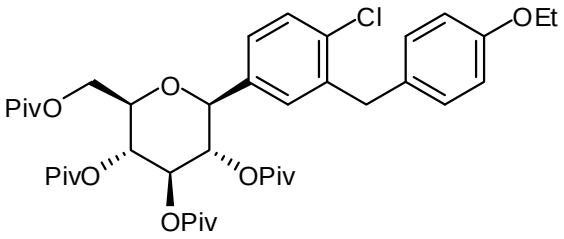
J. Med. Chem. **2010**, *53*, 6355

A reactor was charged with methanol (13mL) and (2S,3S,4R,5R,6R)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) **17** (5.08g, 6.50mmoles, 1eq.). $NaOCH_3$ 30w/w% in methanol (0.233g, 0.2eq.) was added and the resulting mixture was heated at reflux (65 °C) and stirred for 5 hours. The resulting mixture was heated to distill methanol (6.5mL) at 66 °C under atmospheric pressure. To the resulting residue was added methanol (6.5mL), and the mixture heated to distil methanol (6.5mL) at 66 °C under atmospheric pressure. Methanol (6.5mL) was added a second time, and the mixture heated to again distil methanol (6.5mL) at 66 °C under atmospheric pressure. he resulting mixture was then cooled to 60 °C. Acetic acid (78mg, 0.2eq.) and water (4.88mL) were added and the resulting mixture cooled to 26 °C, seeded with compound **2** (14.5mg, 0.005mol/mol) and stirred for 6h (min 4h). Water (3.9mL) was added over 2h and the resulting mixture stirred for at least 1h. The resulting suspension was then cooled to 20 °C (15-25 °C) and stirred for at least 5h, then filtered. The filtercake was washed with a mixture of water / methanol (1/1 v/v, 3.24mL), then dried under reduced pressure at 50 °C overnight to yield (2S,3R,4R,5S,6R)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol as a hemi-hydrate in 95% yield as off-white solid.

^{1}H-NMR (360 MHz, DMSO-d6 + D_2O): δ 7.61-7.57 (m, 2H); 7.27 (d, J=3.6Hz, 1H); 7.23-7.13 (m, 5H); 6.81 (d, J=3.7Hz, 1H); 4.15 (AB, J=16.1Hz, 1H); 4.10 (AB, J=16.1Hz, 1H); 3.99 (d, J=9.6Hz, 1H), 3.71 (dd, J=1.5Hz & 11.7Hz, 1H), 3.47(m, 1H); 3.32-3.16 (m, 4H); 2.27 (s, 3H).

^{13}C-NMR (90 MHz, DMSO-d6 + D_2O): δ 162.97, 160.27, 143.89, 140.49, 138.33, 137.68, 135.32, 130.76, 139.99, 127.24, 127.15, 126.65, 126.51, 123.63, 116.27, 116.03, 81.51, 81.27, 78.47, 74.78, 70.51,61.53, 33.69, 19.05.

(2S,3S,4R,5R,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (17)



Chemical Formula: $C_{41}H_{57}ClO_{10}$
Exact Mass: 744.3640

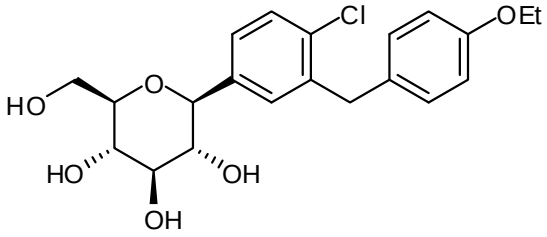
In a 50 mL Schlenk tube under argon atmosphere, a solution of lithium dibutyl hexyl magnesiate (0.4 eq, 1.44 mmol, 2.44 mL) is added dropwise to a mixture of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (1.2 eq, 4.14 mmol, 1.35 g) dissolved in anhydrous toluene (1.73 mL) and anhydrous n-dibutylether (1.04 mL) at 0 °C. After 48h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.6 eq, 2.24 mmol, 2.06 g) is added dropwise. After 1 hours, (2R,3R,4S,5R,6R)-2-bromo-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) **3a** (1 eq, 2000 mg, 3.44 mmol) dissolved in anhydrous toluene (3.44 mL) is added to the organozinc mixture. The mixture is heated to 100 °C until complete conversion (control by GC). After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). The two layers are separated. The aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by chromatography on silicagel (heptanes/AcOEt from 9/1 to 8/2) to yield the desired compound in 75% yield.

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.34 (d, *J*=8.1Hz, 1H), 7.17 (m, 2H), 7.05 (d, *J*=8.4Hz, 2H), 6.81 (d, *J*=8.4Hz, 2H), 5.39 (dd, *J*=9.5 Hz and 9.2Hz, 1H), 5.28 (m, 2H), 4.34 (d, *J*=9.9Hz, 1H), 4.19 (dd, *J*=12.5Hz and 1.5Hz, 1H), 4.04 (m, 5H), 3.82 (d, *J*=7.7Hz, 1H) 1.21 (s, 9H), 1.17 (s, 9H), 1.11 (s, 9H), 0.87 (s, 9H).

^{13}CNMR (90 MHz, $CDCl_3$): δ 157.31, 139.01, 137.04, 134.15, 131.14, 130.62, 129.72, 129.01, 128.20, 126.35, 125.28, 114.48, 81.08, 79.35, 77.93, 74.67, 69.88, 63.38, 61.80, 38.31, 29.69, 27.06, 14.80.

HRMS (ES^+) = [$M+H^+$] calc. 745.3713, found 745.3727.

Dapagliflozin (1)



Chemical Formula: $C_{21}H_{25}ClO_6$
Exact Mass: 408.134

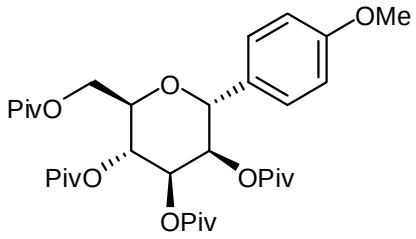
J. Med. Chem **2008**, *51*, 1145.

In a 25mL Schlenk tube under argon atmosphere, (2S,3S,4R,5R,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (1.00 equiv; 270.00 µmoles) was stirred in methanol 540.00 µL at room temperature Then a 30w% NaOMe in MeOH (50.09 µL) was added via syringe. After 5min., a heterogeneous mixture was formed. Then extra methanol (1.5mL) was added and the reaction mixture was warmed to 40 °C over week-end. After cooling to room temperature, an aqueous solution of ammonium chloride 1M (2mL) was added to the reaction mixture. After 15minutes stirring, the mixture was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate (10mL). The organic layer was washed with water. The organic layer was dried over drying cartridge and evaporated under reduced pressure to yield Dapagliflozin in 94% as clear yellow solid.

^{1}H NMR (360 MHz, MeOD): δ 7.35-7.28 (m, 3H); 7.09 (d, J=8.4Hz, 2H), 6.80 (d, J=8.8Hz, 2H), 4.09 (d, J=9.5Hz, 1H); 4.03-3.96 (m, 4H); 3.89-3.85 (m, 1H); 3.71-3.66 (m, 1H); 3.45-3.36 (m, 4H), 3.28-3.26 (m, 2H); 1.36 (t, J=6.9Hz, 3H).

^{13}CNMR (90 MHz, MeOD): δ 14.80, 38.31, 61.80, 63.38, 69.88, 74.67, 77.93, 79.35, 81.08, 114.48, 126.35, 128.20, 129.01, 129.72, 130.62, 131.14, 134.15, 137.04, 139.01, 157.31.

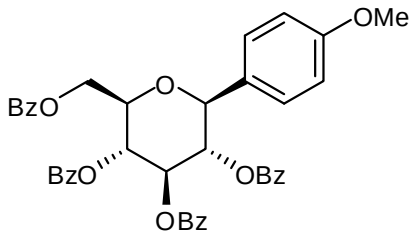
(2R,3R,4R,5R,6R)-2-(4-methoxyphenyl)-6-(pivaloyloxymethyl)tetrahydro-*2H*-pyran-3,4,5-triyltris(2,2-dimethylpropanoate) (9)



In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.36 mmol, 0.610 mL) added dropwise to a mixture of p-iodoanisole (250mg, 1.04 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 3.5h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol, 523 mg) is added dropwise. After 1 hour at room temperature, bromosugar (1 eq, 500 mg, 0.86 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 90 °C for 4h. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by reverse phase (Kromasil C18) with ammonium bicarbonate 0.25% in water and acetonitrile (20/80 to 0/100) to afford the desired product as white powder (320mg, 0.53 mmol, 61% yield).

^{1}HNMR (360 MHz, $CDCl_3$): δ 7.47 (d, *J*=8.7Hz, 2H), 6.96 (d, *J*=7Hz, 2H), 6.02 (dd, *J*=2.9Hz and 2.6Hz, 1H), 5.52 (dd, *J*=9.5Hz and 9.2Hz, 1H), 5.15 (dd, *J*=9.5Hz and 2.9Hz, 1H), 5.05 (d, *J*=2.5Hz, 1H), 4.28 (dd, *J*=12.5Hz and 5.5Hz, 1H), 4.14 (dd, *J*=12.3Hz and 2.0Hz, 1H), 3.83 (s, 3H), 3.76 (m,1H), 1.27 (s, 9H), 1.27 (s, 9H), 1.18 (s, 9H), 1.14 (s, 9H).
^{13}CNMR (90 MHz, $CDCl_3$): δ 178.57, 178.28, 177.80, 177.15, 159.94, 128.39, 127.79, 114.82, 76.35, 71.71, 70.86, 69.52, 66.40, 62.68, 55.71, 39.36, 39.34, 39.27, 39.22, 32.32, 30.13, 29.45, 27.64, 27.59, 27.56, 27.46, 23.12, 14.54.
$[\alpha]_D^{20}$=+38.2 (1 $g.L^{-1}$ in CH_2Cl_2).
mp= 118.8 °C
HRMS (ES^+) = [$M+H^+$] calc. 607.3477, found 607.3493.

(2R,3S,4R,5S,6S)-2-(benzoyloxymethyl)-6-(4-methoxyphenyl)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (10)

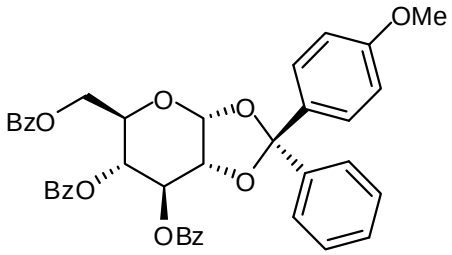


Chemical Formula: $C_{41}H_{34}O_{10}$
Exact Mass: 686.215

In a 10 mL Schlenk tube under argon atmosphere at 0 °C, a solution of lithium dibutyl hexyl magnesate (0.42 eq, 0.38 mmol, 0.644 mL) added dropwise to a mixture of p-iodoanisole (217mg, 0.91 mmol) dissolved in anhydrous toluene (0.43 mL) and anhydrous n-dibutylether (0.26 mL). After 4.5h, a solution of $ZnBr_2$.LiBr in dibutylether (34 w/w%, 0.66 eq, 0.57 mmol) is added dropwise. After 1 hours at room temperature, 1-bromo-2,3,4,6-tetra-O-benzoyl-alpha-D-glucopyranose (500 mg, 0.76 mmol) dissolved in anhydrous toluene (0.86 mL) is added to the organozinc mixture. The mixture is heated to 60 °C for 2 days. After cooling to room temperature, the reaction mixture is quenched with aqueous HCl 1M (10 mL). After phase separation, the aqueous layer is extracted with ethyl acetate (10 mL). The combined organic layer are washed with water (10 mL), and then washed with a brine solution (10 mL). The organic layer is dried through a pre-packed column and concentrated in rotavapor under reduced pressure. The obtained crude mixture is purified by chromatography on silica gel (heptanes/AcOEt from 9/1 to 8/2) to afford 10/11 in respectively 10% and 20%.

10 as white powder
^{1}HNMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J*=5.9Hz, 2H), 7.95 (d, *J*=8.0Hz, 2H), 7.82 (dd, *J*= 6.9Hz and 13.5Hz, 4H), 7.22-7.65 (m, 14H), 6.80 (d, *J*=8.8Hz, 2H), 6.01 (dd, *J*=10Hz and 9.5Hz, 1H), 5.84 (t, *J*=9.5Hz, 1H), 5.66 (dd, *J*=9.9Hz and 9.5Hz, 1H), 4.72 (d, *J*=9.9Hz , 1H), 4.66 (dd, *J*=12.1Hz and 2.9Hz, 1H), 4.51 (dd, *J*=12.5Hz and 4.8Hz, 1H), 4.28 (m, 1H), 2.82 (s, 3H).
^{13}CNMR (90 MHz, $CDCl_3$): δ 166.66, 166.39, 165.71, 165.11, 160.30, 133.98, 133.93, 133.88, 133.80, 133.55, 133.48, 130.58, 130.47, 130.40, 130.36, 130.27, 130.20, 130.14, 129.99, 129.58, 129.41, 129.37, 129.24, 128.93, 128.83, 128.78, 128.68, 113.90, 80.82, 76.84, 75.07, 73.68, 70.35, 63.87, 55.61, 30.15.
HRMS (ES^+) = [$M+H^+$] calc. 687.2225, found 687.2065.

(2S,3aR,5R,6S,7S,7aR)-5-(benzoyloxymethyl)-2-(4-methoxyphenyl)-2-phenyltetrahydro-3aH-[1,3] dioxolo[4,5-b]pyran-6,7-diyl dibenzoate (11)



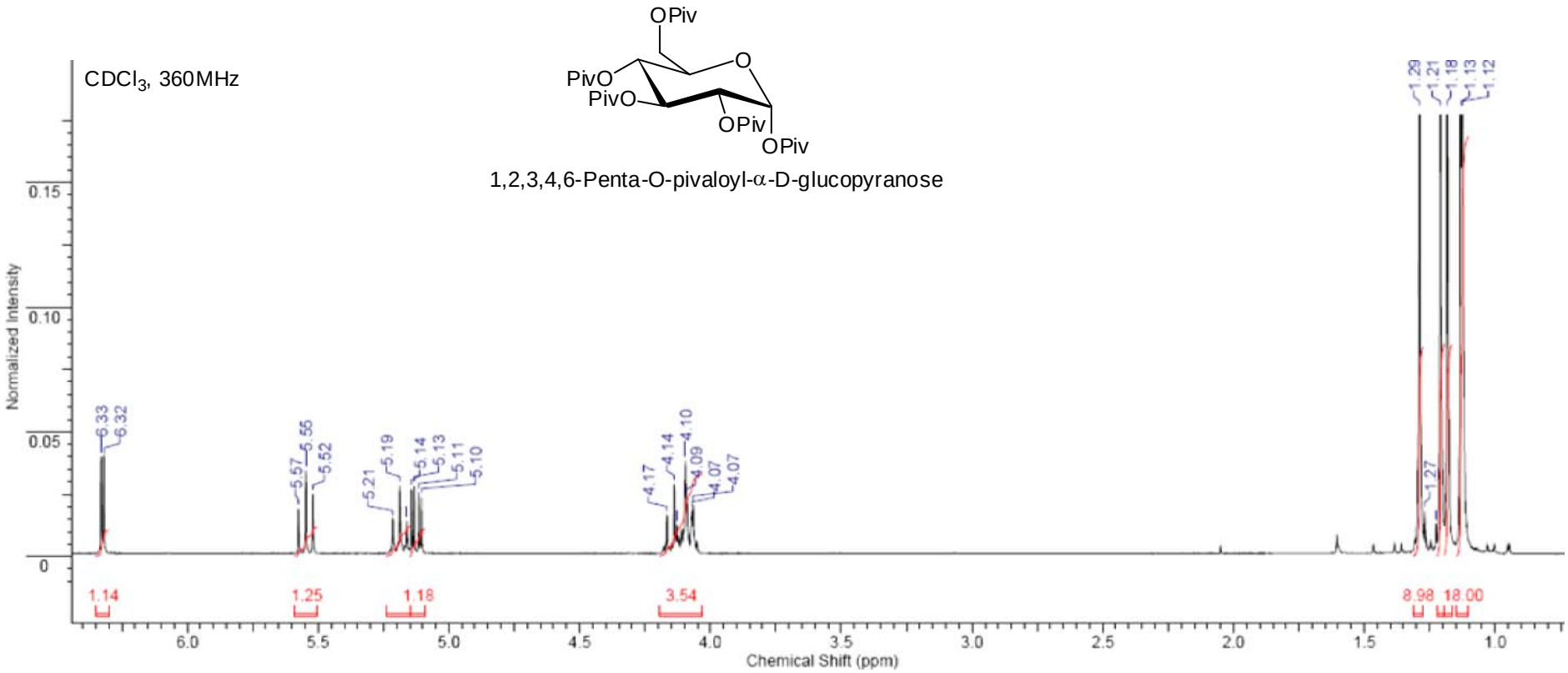
Chemical Formula: $C_{41}H_{34}O_{10}$
Exact Mass: 686.215

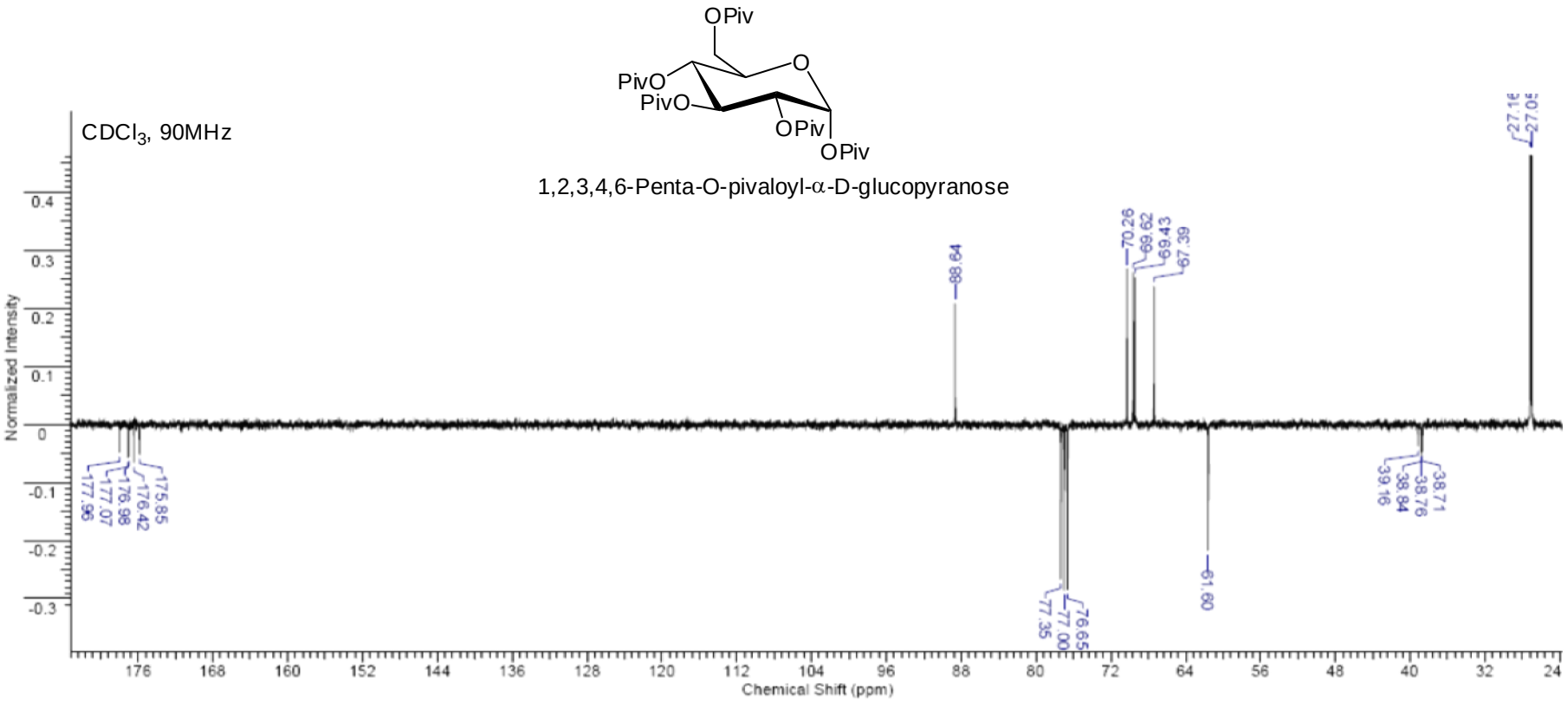
11 as white powder

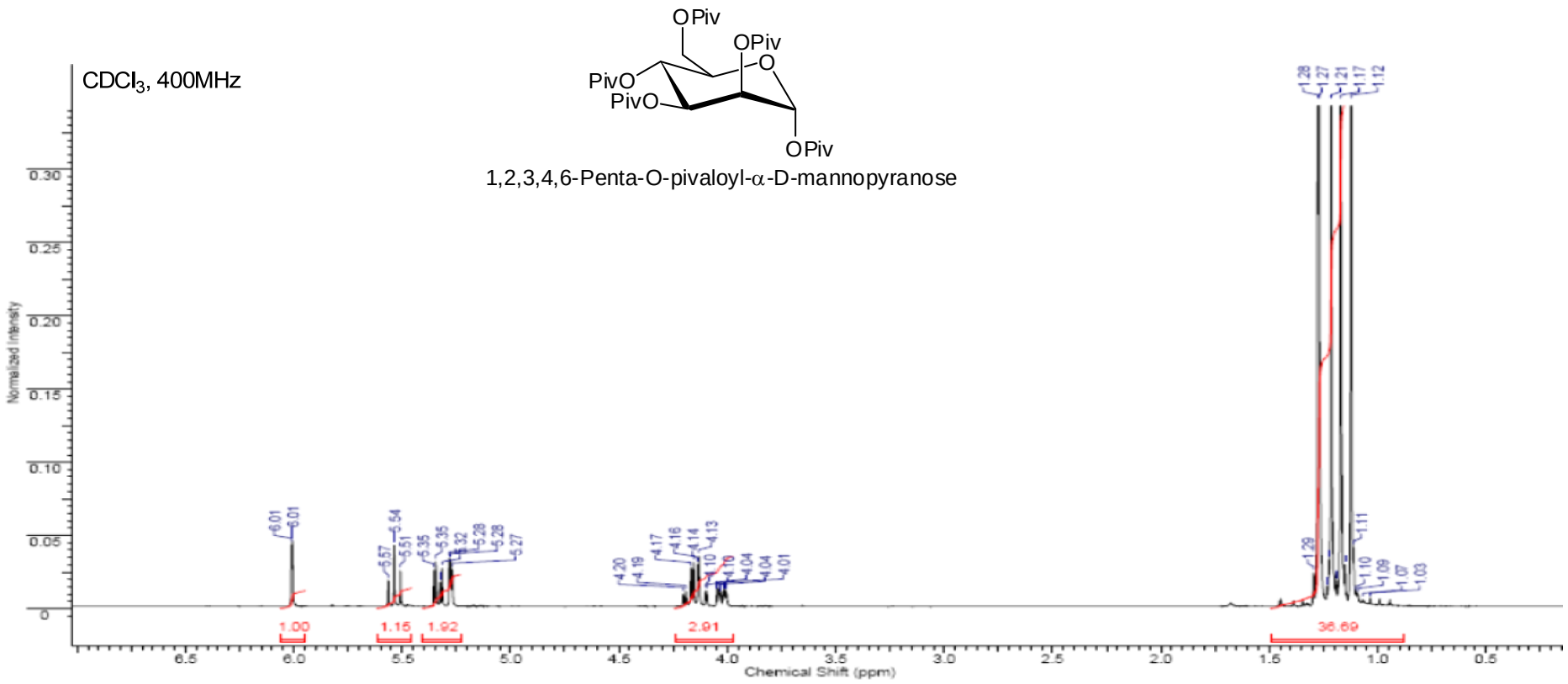
^{1}HNMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J*=7.3Hz, 4H), 7.93 (d, *J*=6.9Hz, 2H), 7.77 (d, *J*= 6.9Hz, 2H), 7.6 (m, 2H), 7.2-7.5 (m, 12H), 6.80 (d, *J*=8.8Hz, 2H), 5.89 (d, *J*=5.1Hz, 1H), 5.81 (d, *J*=2.2Hz, 1H), 5.51 (d, *J*=8.8Hz, 1H), 4.55 (d, *J*=9.2Hz , 1H), 4.35 (m, 3H), 3.77 (s, 3H).

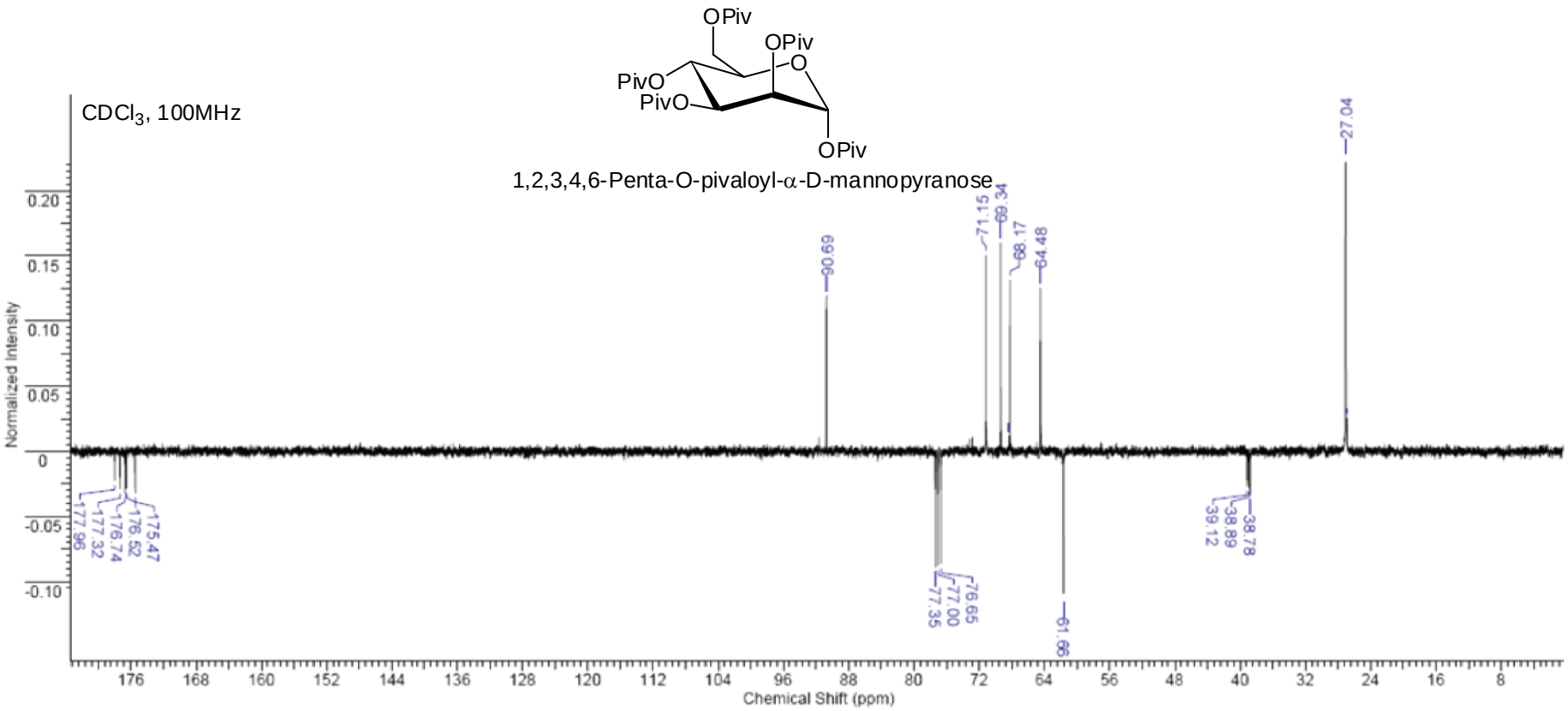
^{13}CNMR (150 MHz, $CDCl_3$): δ 166.04, 165.28, 164.60, 159.63, 141.01, 134.03, 133.66, 133.57, 133.50, 132.94, 130.15, 129.95, 129.80, 129.72, 129.69, 129.23, 128.97, 128.54, 128.49, 128.45, 128.40, 128.20, 120.16, 127.02, 125.56, 113.74, 110.56, 97.32, 72.02, 69.39, 68.78, 67.28, 64.12, 55.26.

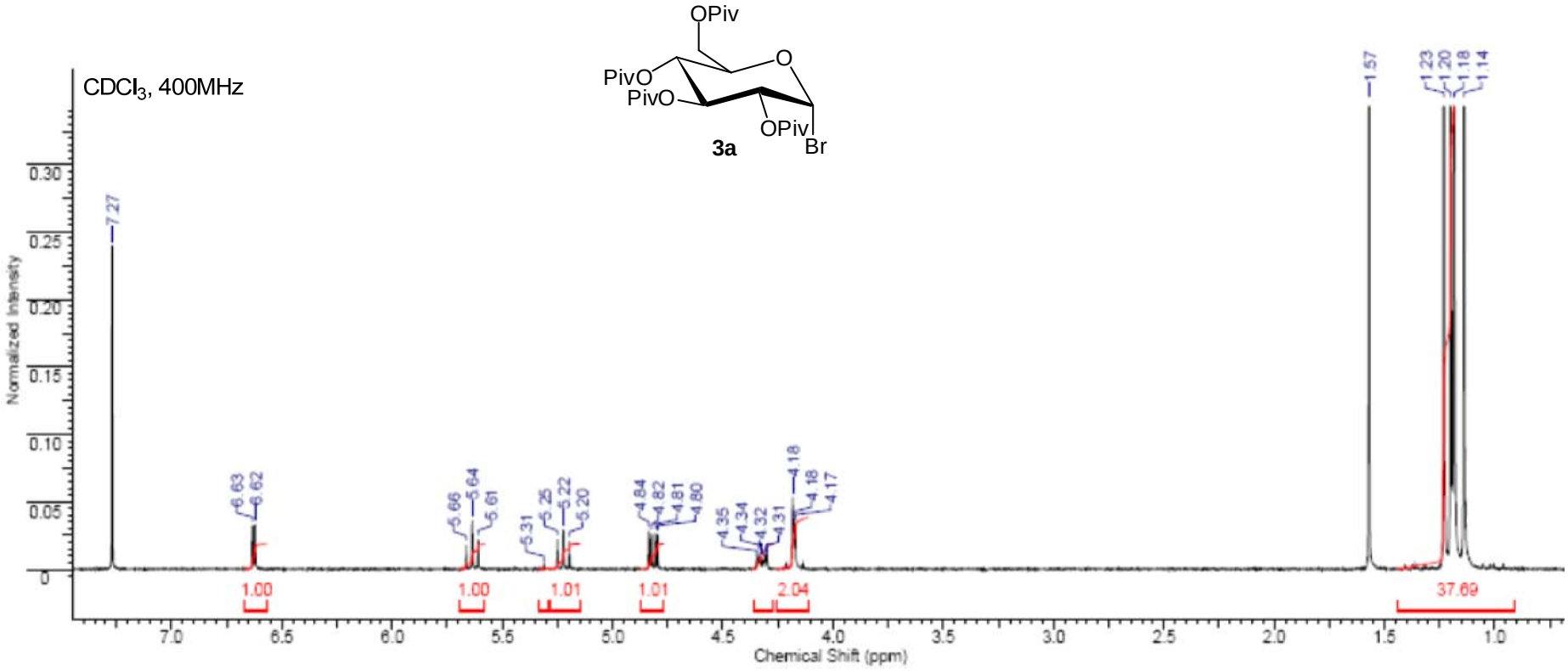
HRMS (ES^+) = [$M+H^+$] calc. 687.2225, found 687.2115.

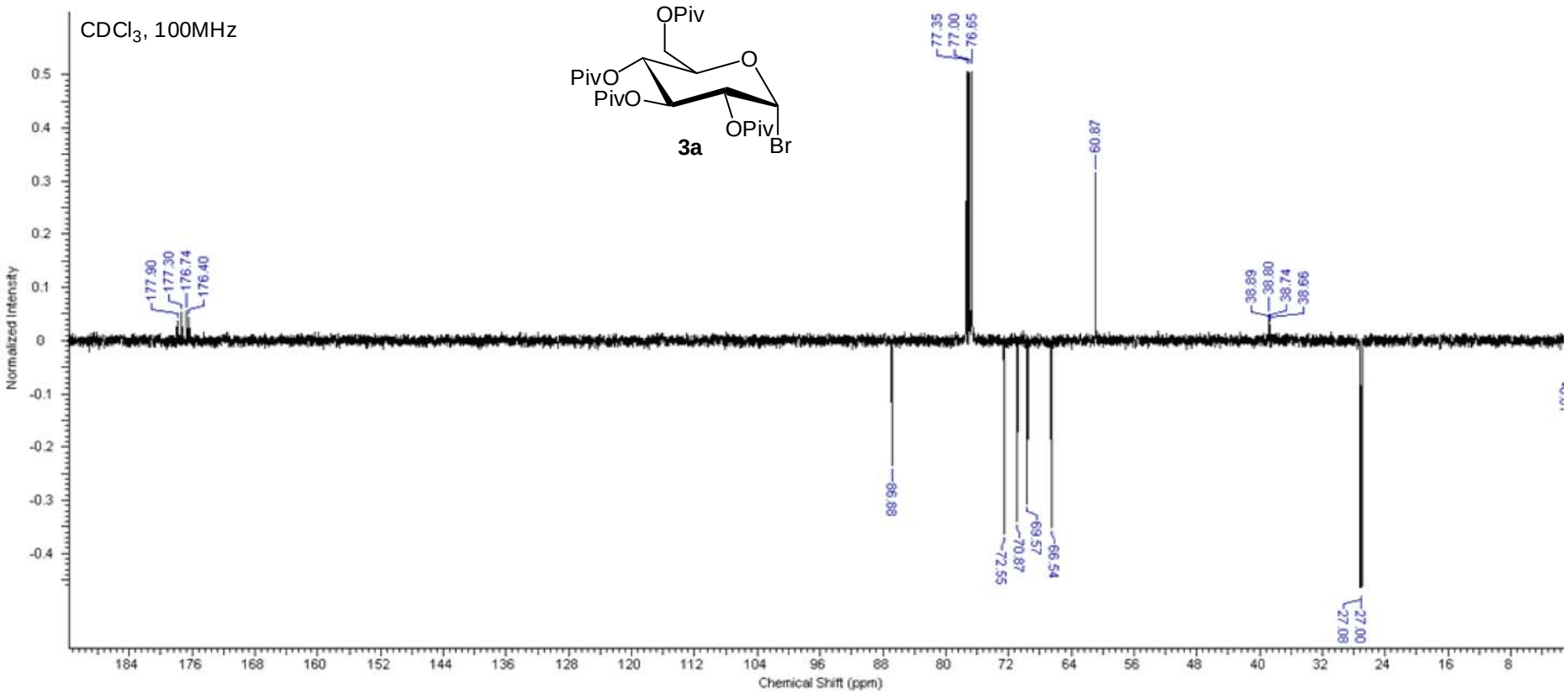

CDCl3, 360MHz
OPiv
PivO
PivO
O
OPiv
OPiv
1,2,3,4,6-Penta-O-pivaloyl-α-D-glucopyranose
Normalized Intensity
0.15
0.10
0.05
0
6.33
6.32
5.57
5.55
5.52
5.21
5.19
5.14
5.13
5.11
5.10
4.17
4.14
4.10
4.09
4.07
4.07
1.29
1.27
1.21
1.18
1.13
1.12
1.14
1.25
1.18
3.54
8.98
18.00
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

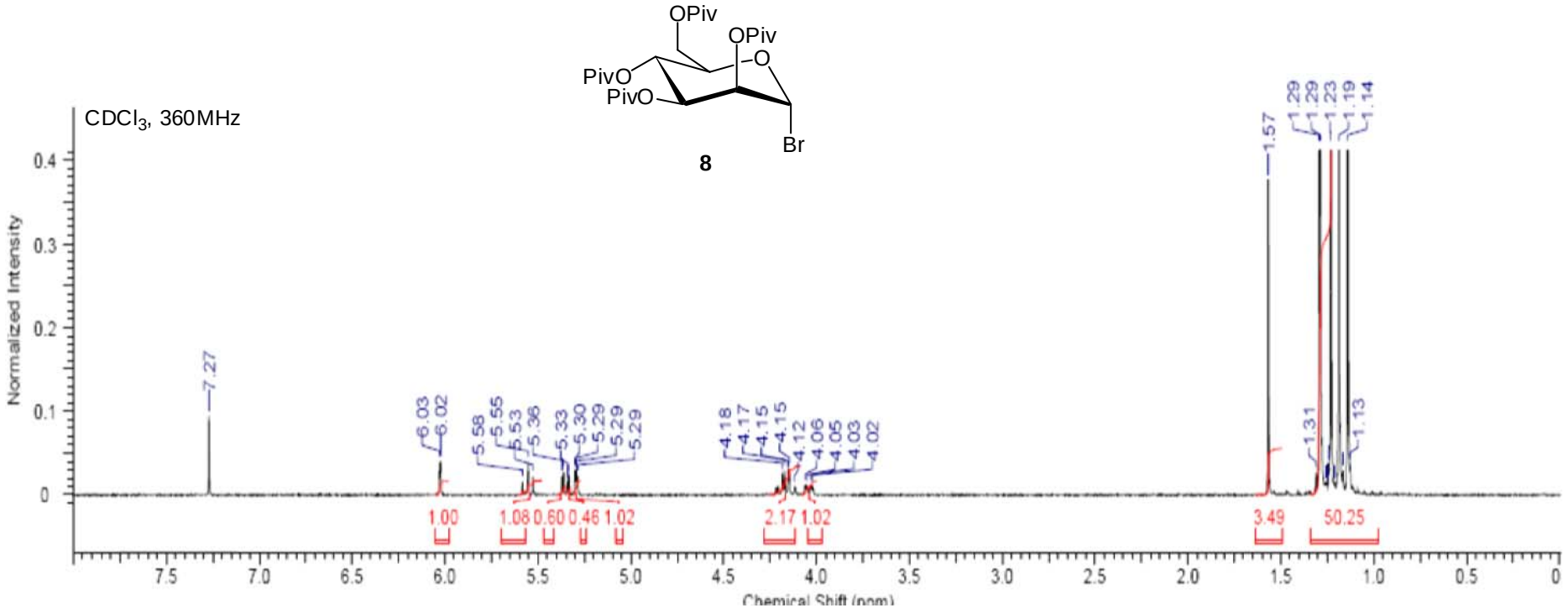

OPiv
PivO
PivO
O
OPiv
OPiv
CDCl3, 90MHz
1,2,3,4,6-Penta-O-pivaloyl-α-D-glucopyranose
Normalized Intensity
Chemical Shift (ppm)
88.64
70.26
69.62
69.43
67.39
61.60
77.35
77.00
76.65
39.16
38.84
38.76
38.71
177.96
177.07
176.98
176.42
175.85

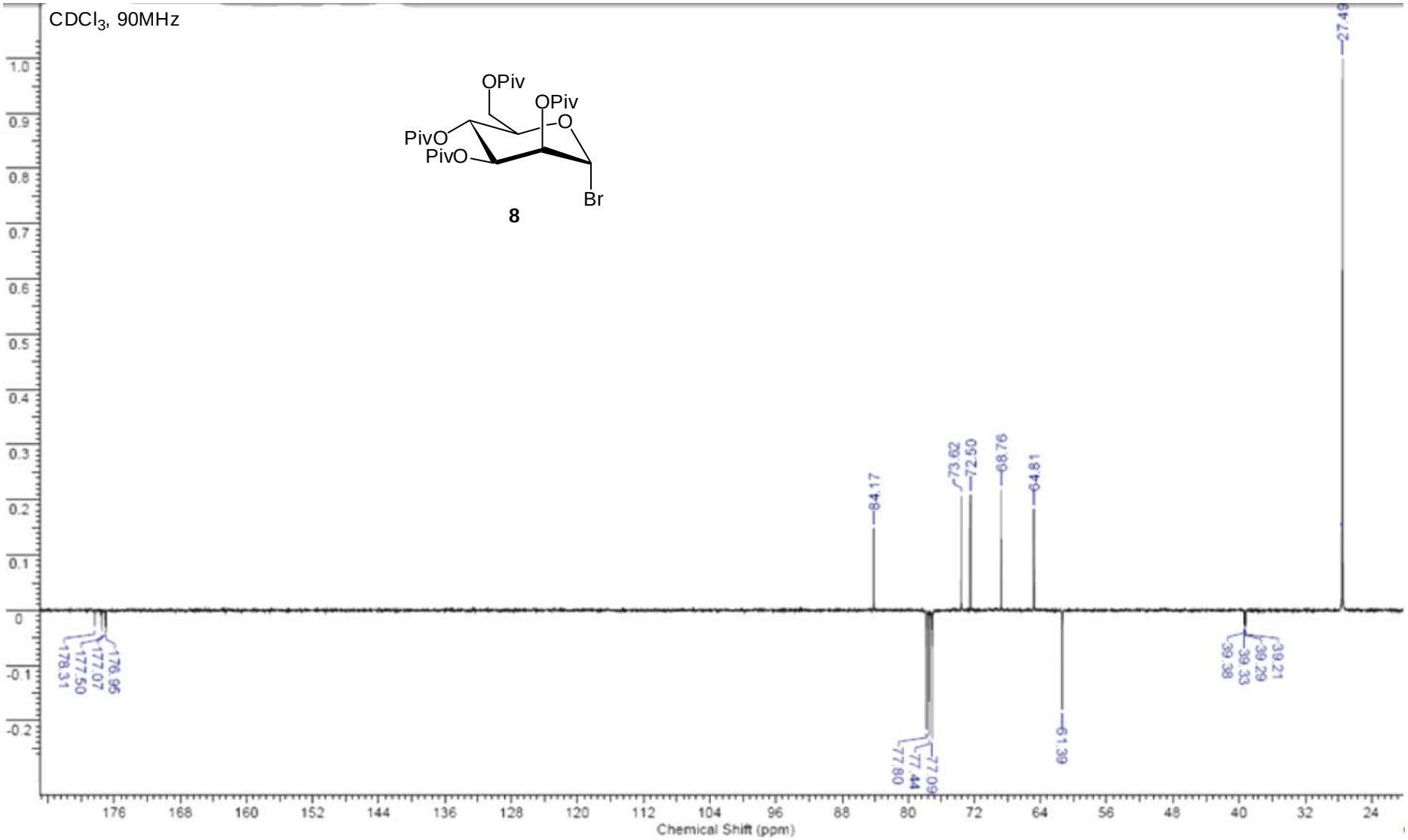

CDCl3, 400MHz
OPiv
OPiv
PivO
PivO
O
OPiv
1,2,3,4,6-Penta-O-pivaloyl-α-D-mannopyranose
Normalized Intensity
Chemical Shift (ppm)
1.00
1.15
1.92
2.91
36.69

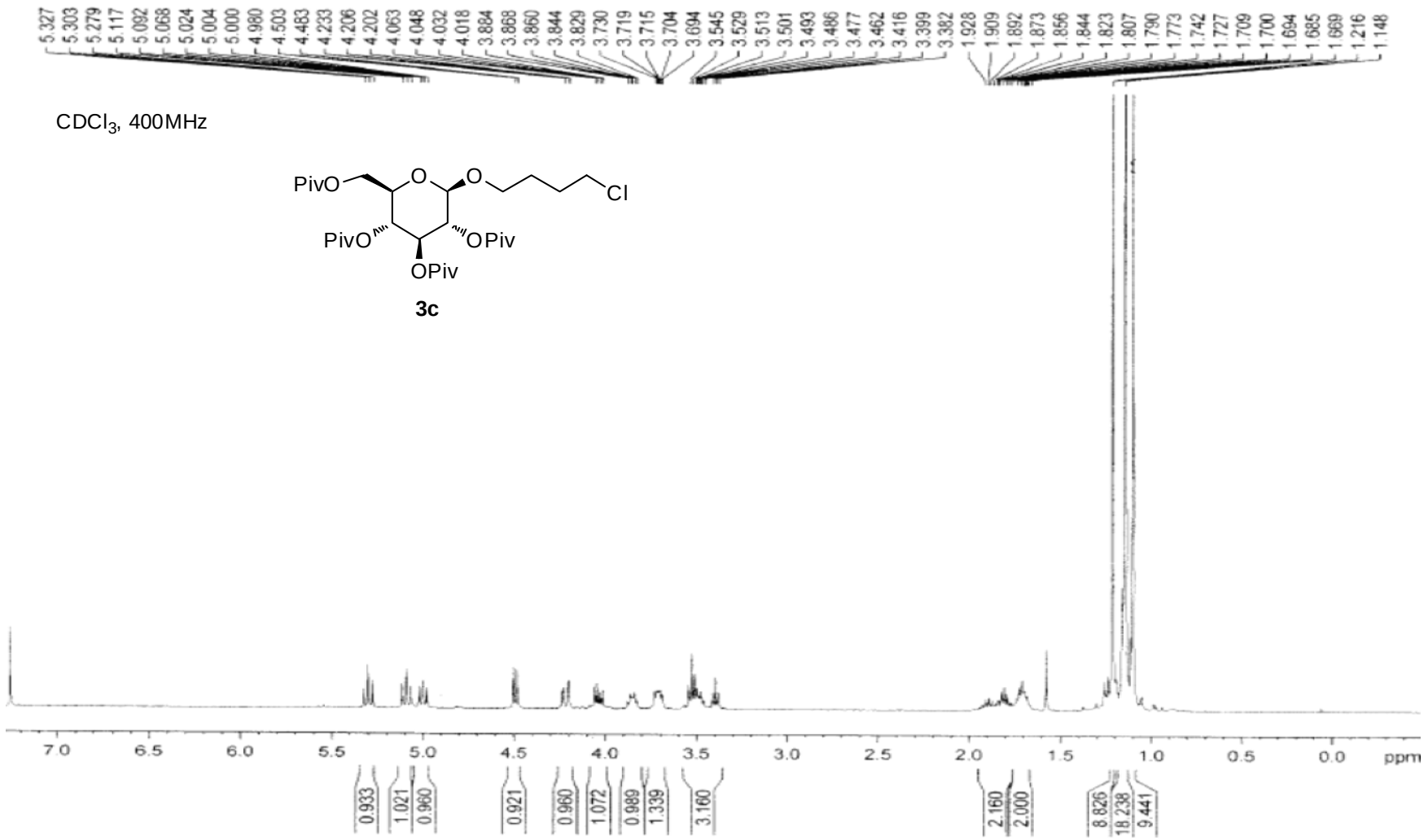

CDCl3, 100MHz
OPiv
OPiv
O
PivO
PivO
OPiv
1,2,3,4,6-Penta-O-pivaloyl-α-D-mannopyranose
Normalized Intensity
0.20
0.15
0.10
0.05
0
-0.05
-0.10
90.69
71.15
69.34
68.17
64.48
27.04
177.96
177.32
176.74
176.52
175.47
77.35
77.00
76.65
61.96
39.12
38.89
38.78
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)


CDCl3, 400MHz
OPiv
PivO
PivO
O
OPiv
Br
3a
Normalized Intensity
Chemical Shift (ppm)
7.27
6.63
6.62
5.66
5.64
5.61
5.31
5.25
5.22
5.20
4.84
4.82
4.81
4.80
4.35
4.34
4.32
4.31
4.18
4.18
4.17
1.57
1.23
1.20
1.18
1.14
1.00
1.00
1.01
1.01
2.04
37.69


CDCl3, 100MHz
OPiv
PivO
PivO
O
OPiv
Br
3a
77.35
77.00
76.65
60.87
38.69
38.80
38.74
38.66
177.90
177.30
176.74
176.40
88.88
72.55
70.87
69.57
66.54
27.00
27.08
Normalized Intensity
Chemical Shift (ppm)

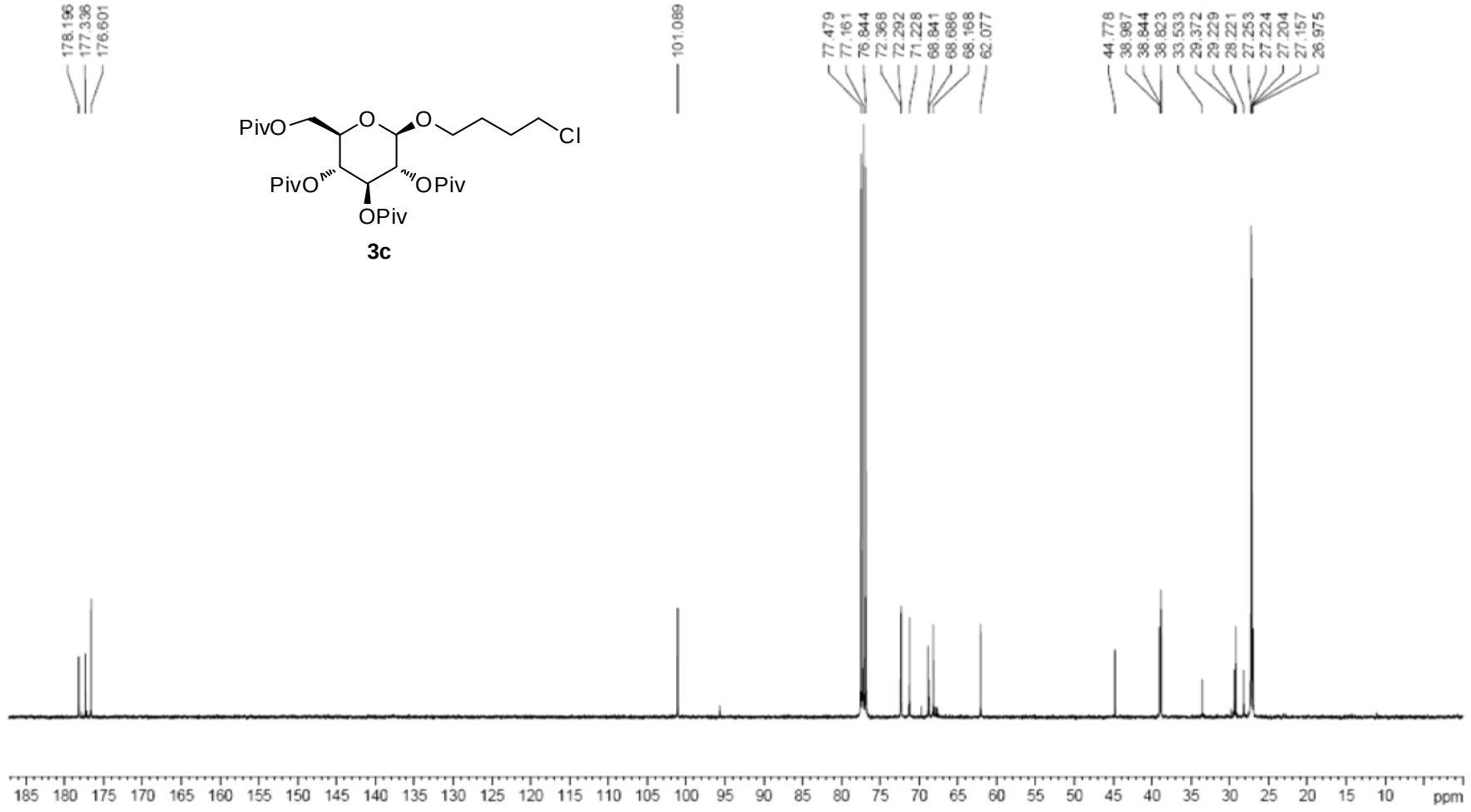

OPiv
OPiv
O
PivO
PivO
Br
8
CDCl3, 360MHz
Normalized Intensity
0.4
0.3
0.2
0.1
0
7.27
6.03
6.02
5.58
5.55
5.53
5.36
5.33
5.30
5.29
5.29
5.29
4.18
4.17
4.15
4.15
4.12
4.06
4.05
4.03
4.02
1.57
1.31
1.29
1.29
1.23
1.19
1.14
1.13
1.00
1.08
0.60
0.46
1.02
2.17
1.02
3.49
50.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CDCl3, 90MHz
OPiv
OPiv
O
PivO
PivO
Br
8
27.48
84.17
73.62
72.50
68.76
64.81
61.39
39.38
39.33
39.29
39.21
178.31
177.50
177.07
176.96
77.80
77.44
77.09
Chemical Shift (ppm)

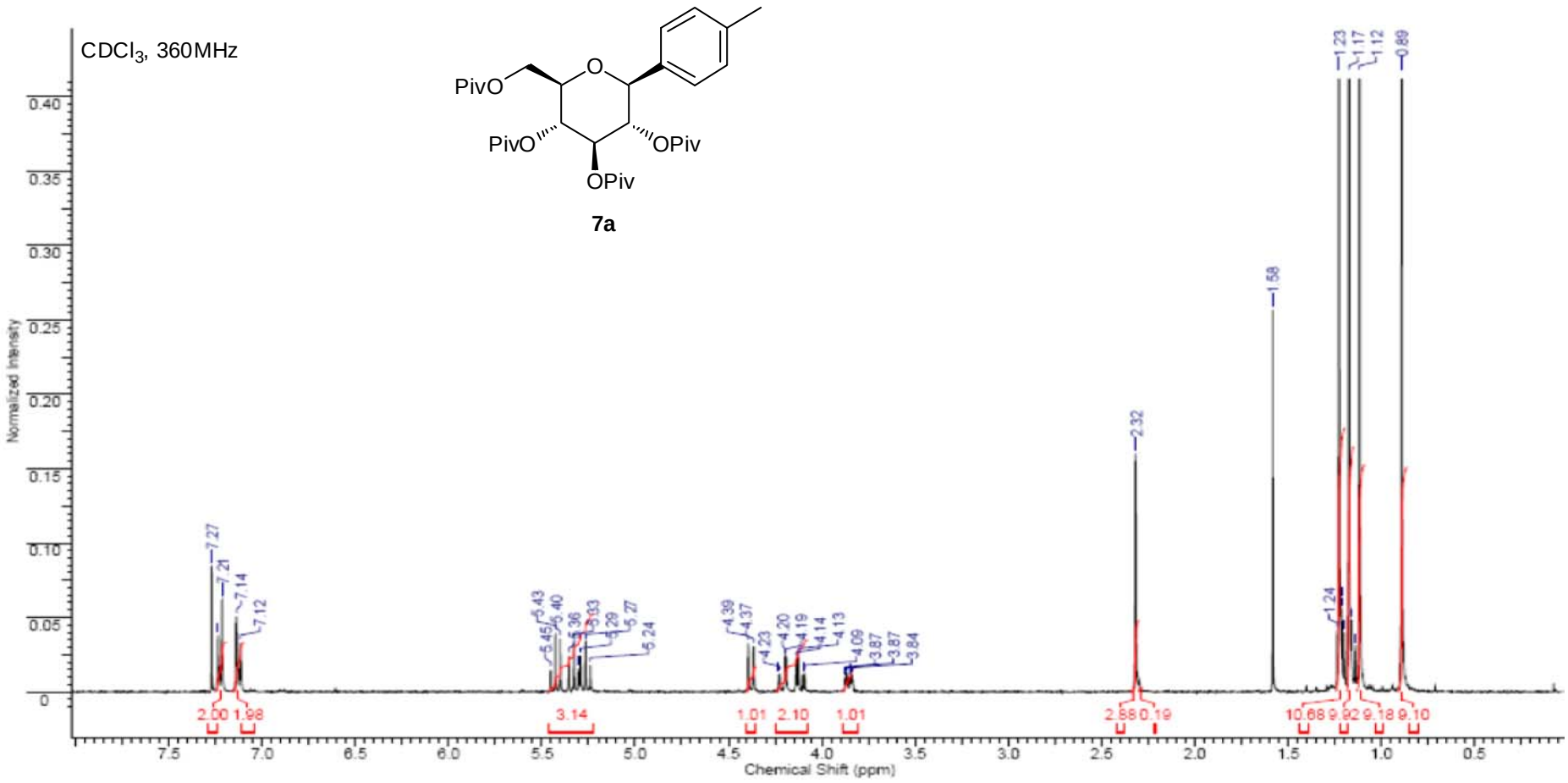

5.327
5.303
5.279
5.117
5.092
5.068
5.024
5.004
5.000
4.980
4.503
4.483
4.233
4.206
4.202
4.063
4.048
4.032
4.018
3.884
3.868
3.860
3.844
3.829
3.730
3.719
3.715
3.704
3.694
3.545
3.529
3.513
3.501
3.493
3.486
3.477
3.462
3.416
3.399
3.382
1.928
1.909
1.892
1.873
1.856
1.844
1.823
1.807
1.790
1.773
1.742
1.727
1.709
1.700
1.694
1.685
1.669
1.216
1.148
CDCl3, 400MHz
PivO
O
O
Cl
PivO
OPiv
OPiv
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.933
1.021
0.960
0.921
0.960
1.072
0.989
1.339
3.160
2.160
2.000
8.826
18.238
9.441

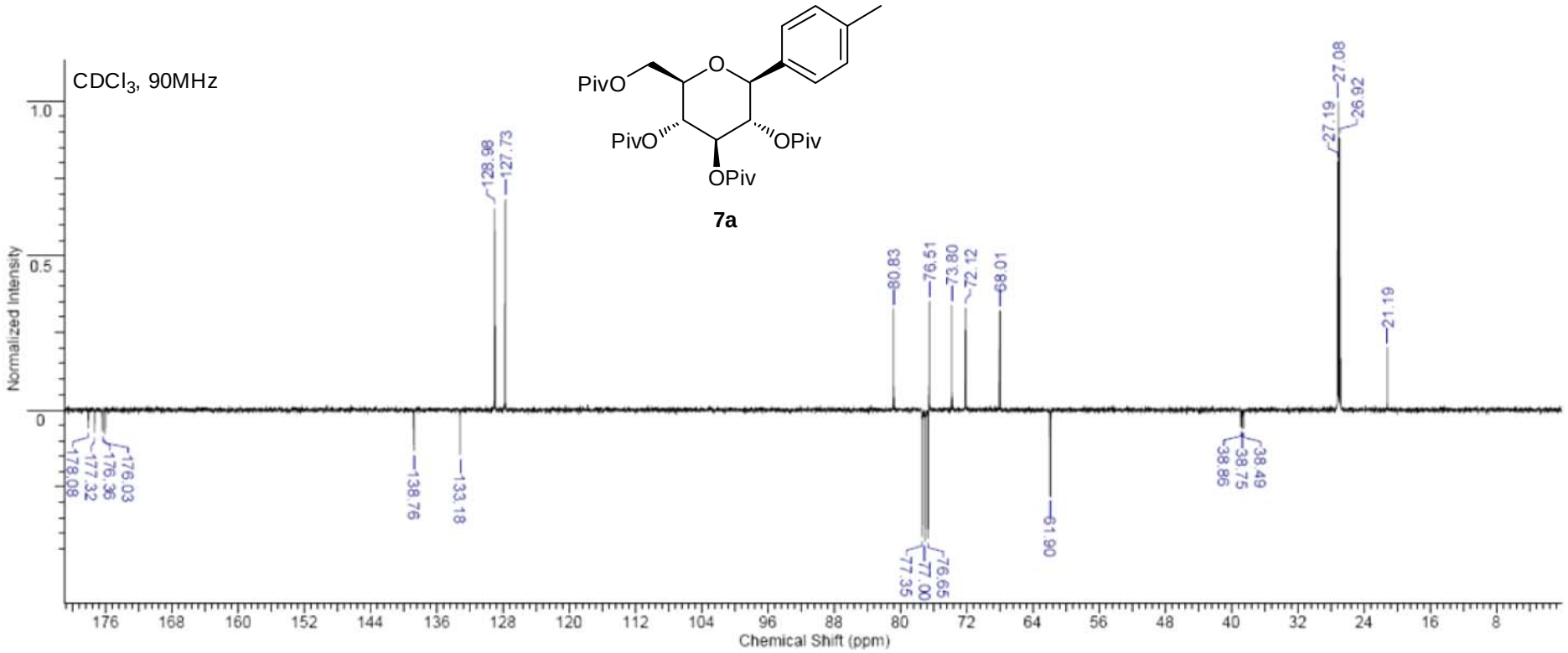
3c

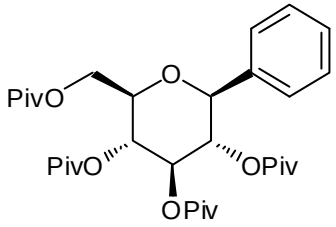
$CDCl_3$, 100MHz



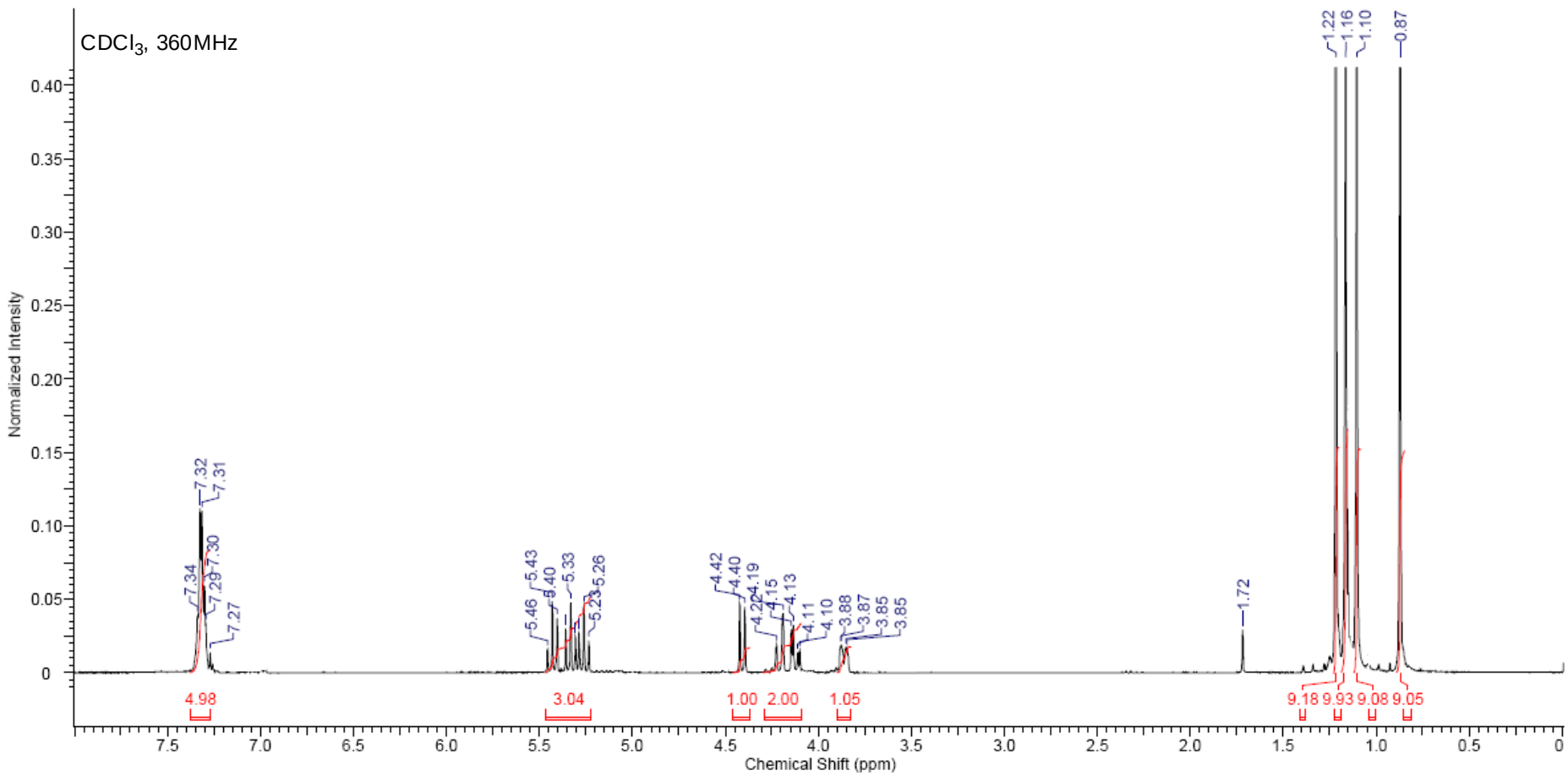
3c

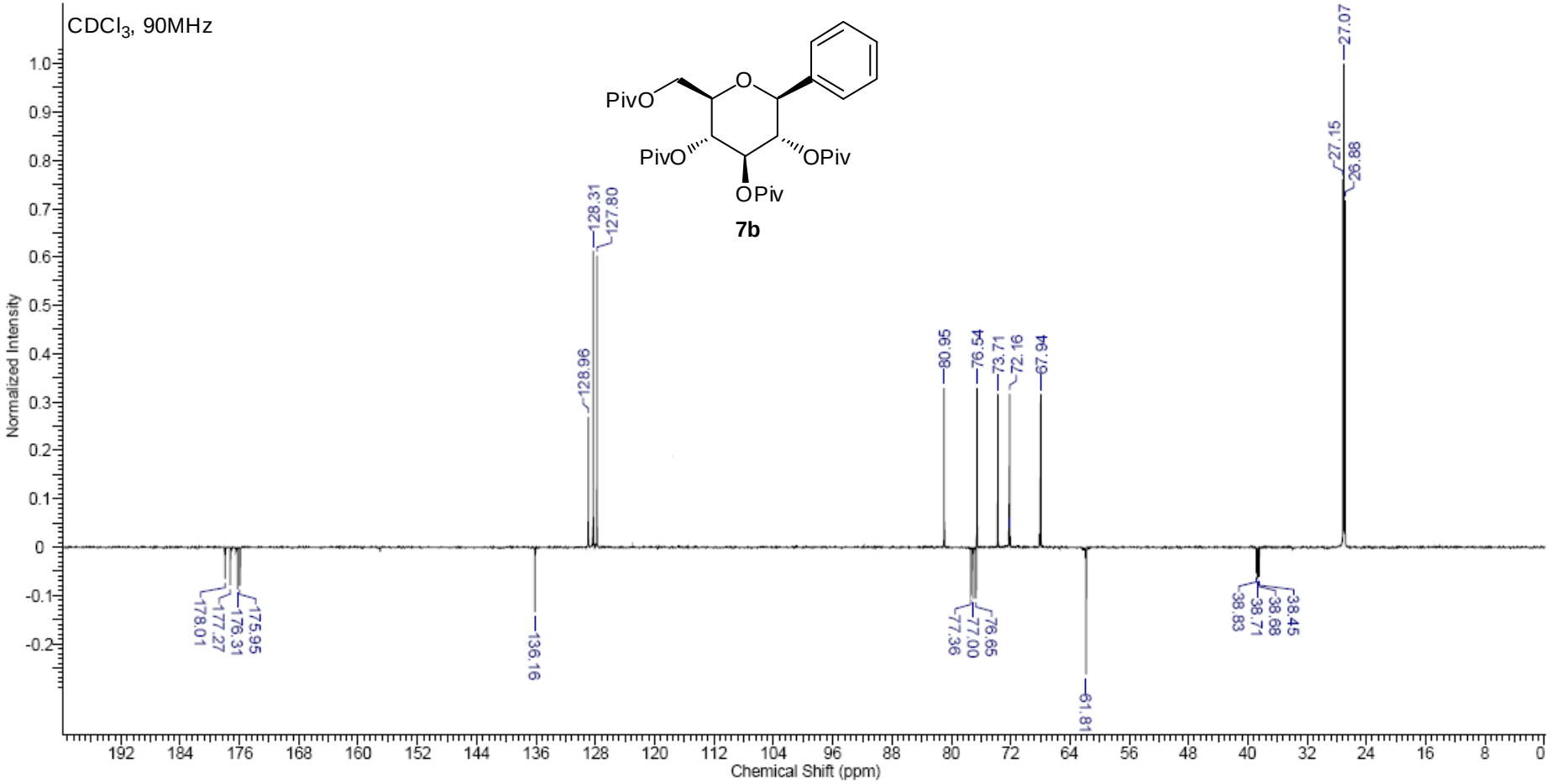

CDCl3, 360MHz
PivO
O
PivO
OPiv
OPiv
7a
Normalized Intensity
Chemical Shift (ppm)
7.27
7.21
7.14
7.12
5.43
5.40
5.36
5.33
5.29
5.27
5.24
4.39
4.37
4.23
4.20
4.19
4.14
4.13
4.09
3.87
3.87
3.84
2.32
1.58
1.24
1.23
1.17
1.12
0.89
2.00
1.98
3.14
1.01
2.10
1.01
2.88
0.19
10.68
9.92
9.18
9.10

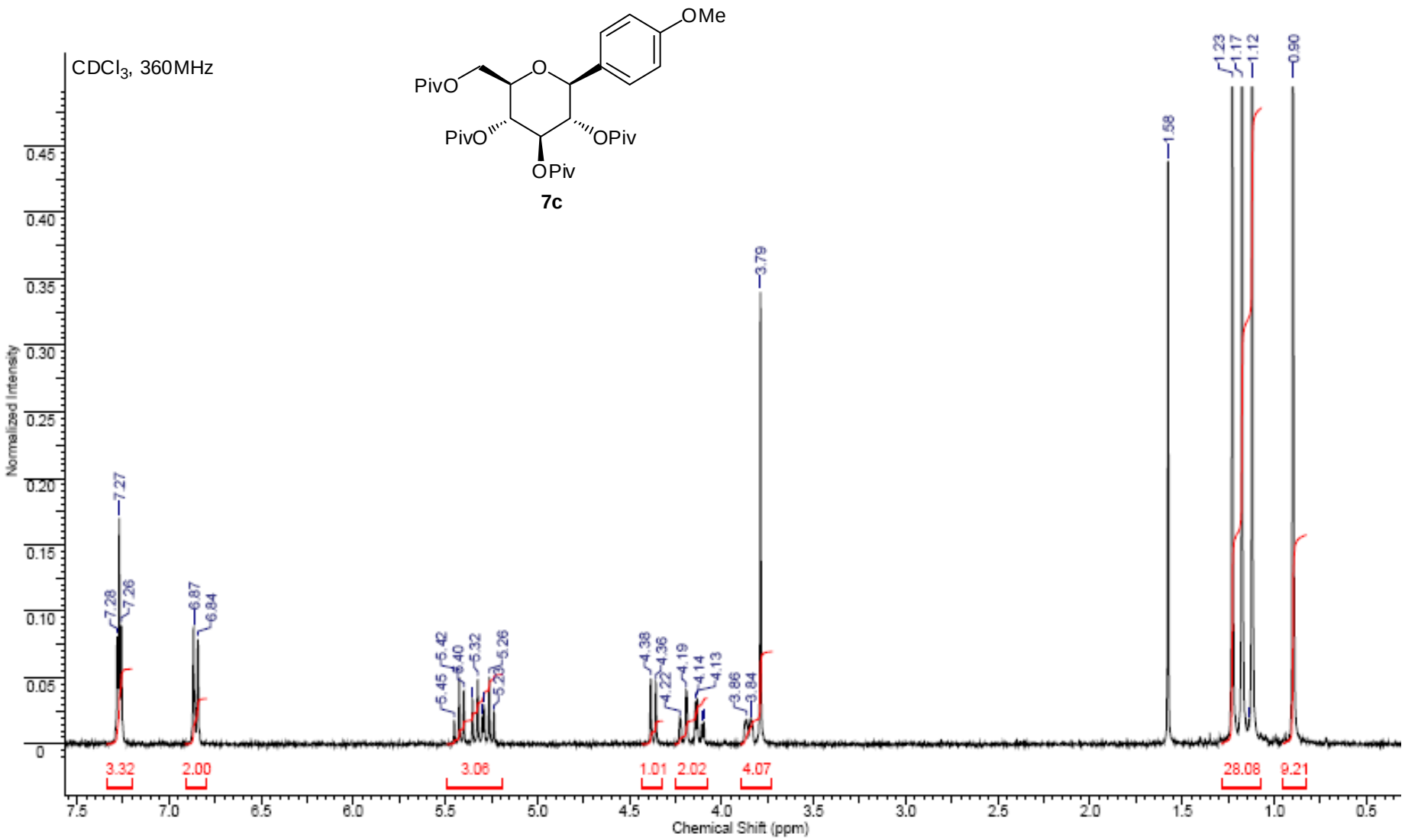

CDCl3, 90MHz
PivO
PivO
OPiv
OPiv
O
7a
Normalized Intensity
1.0
0.5
0
128.98
127.73
80.83
76.51
73.80
72.12
68.01
27.19
27.08
26.92
21.19
178.08
177.32
176.36
176.03
138.76
133.18
77.35
77.00
76.65
61.90
38.86
38.75
38.49
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

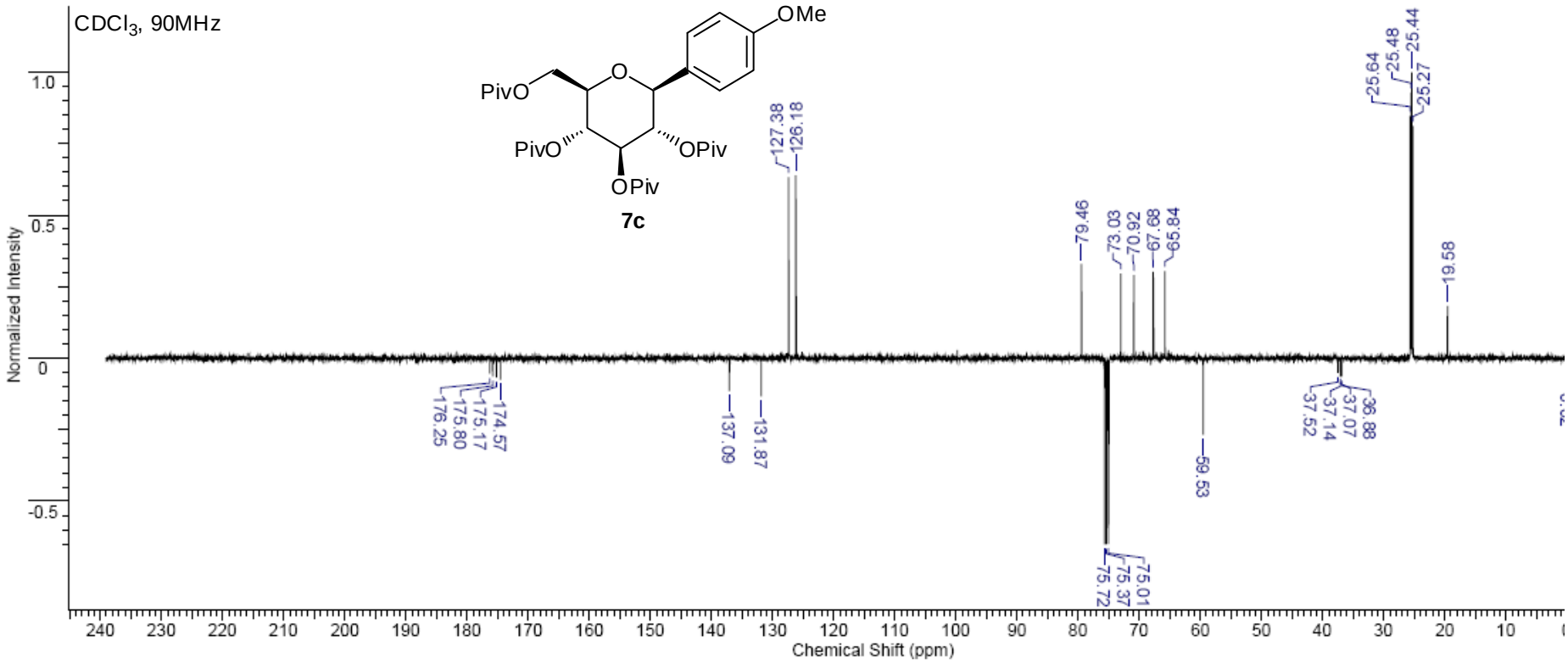


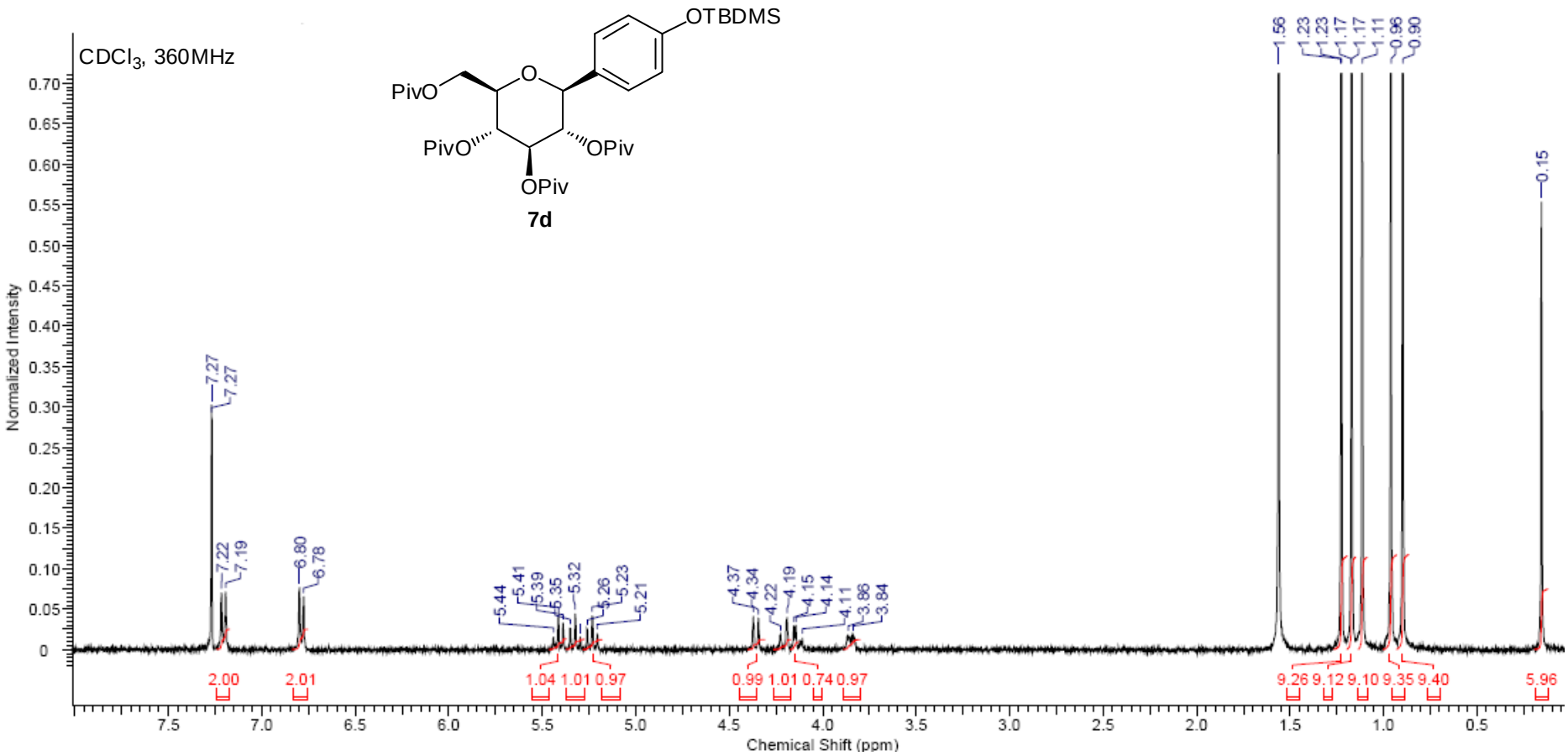
7b

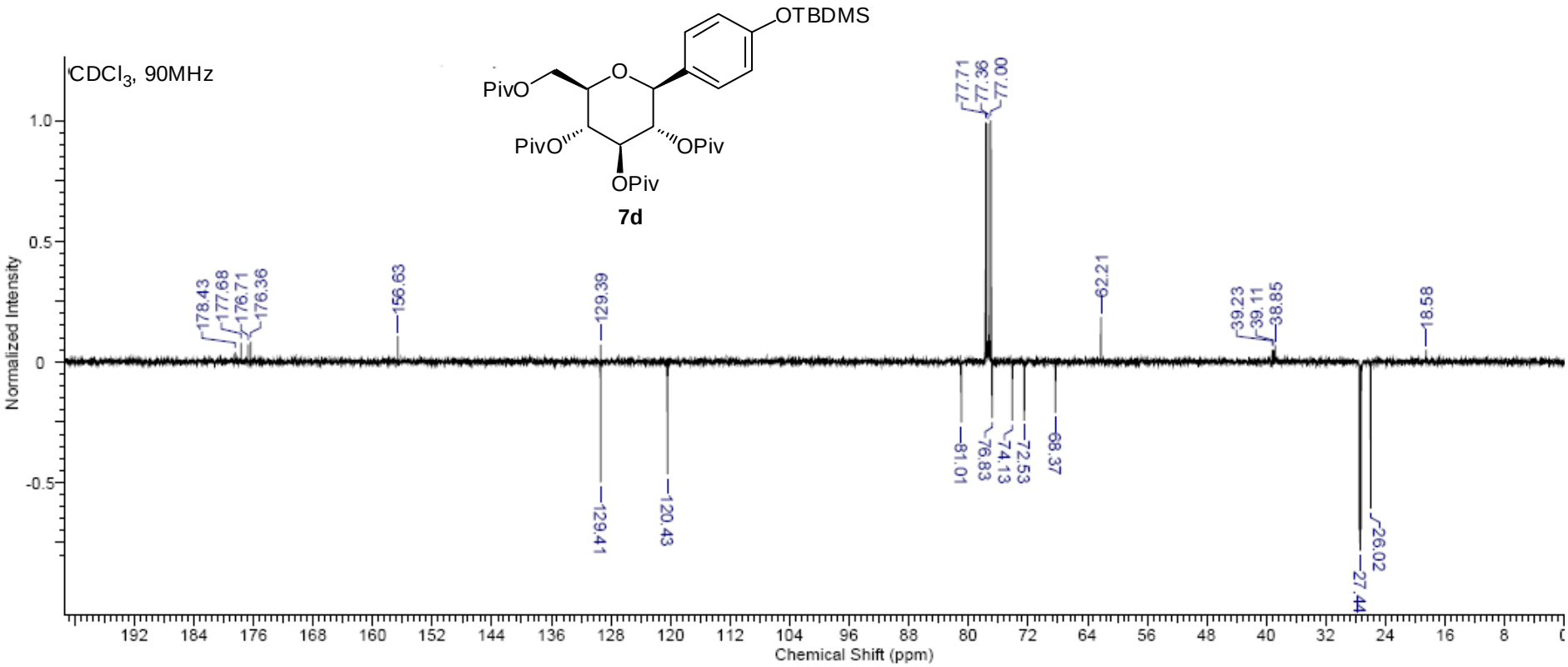

CDCl3, 360MHz
Normalized Intensity
Chemical Shift (ppm)
7.34
7.32
7.31
7.30
7.29
7.27
5.46
5.43
5.40
5.33
5.26
5.23
4.42
4.40
4.22
4.19
4.15
4.13
4.11
4.10
3.88
3.87
3.85
3.85
1.72
1.22
1.16
1.10
0.87
4.98
3.04
1.00
2.00
1.05
9.18
9.93
9.08
9.05

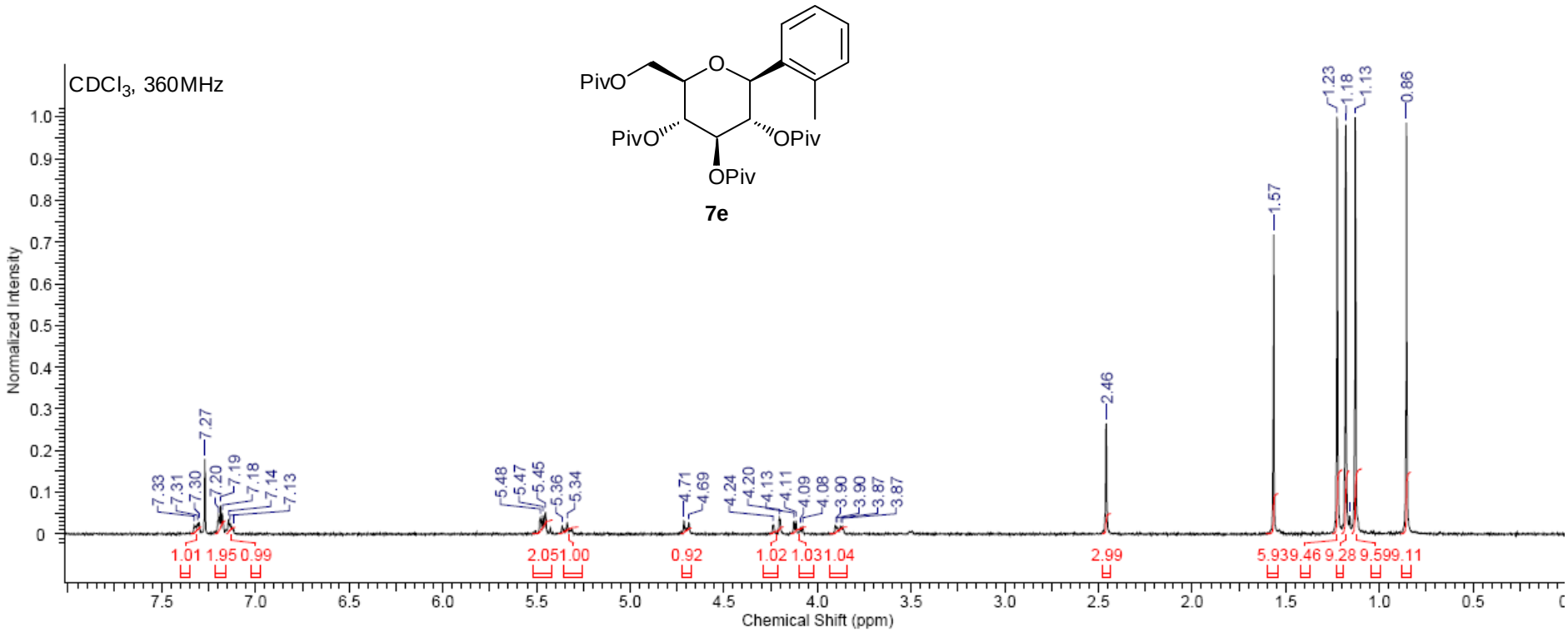

CDCl3, 90MHz
PivO
O
PivO
OPiv
OPiv
7b
Normalized Intensity
Chemical Shift (ppm)
178.01
177.27
176.31
175.95
136.16
128.96
128.31
127.80
80.95
77.36
77.00
76.65
76.54
73.71
72.16
67.94
61.81
38.83
38.71
38.68
38.45
27.15
26.88
27.07

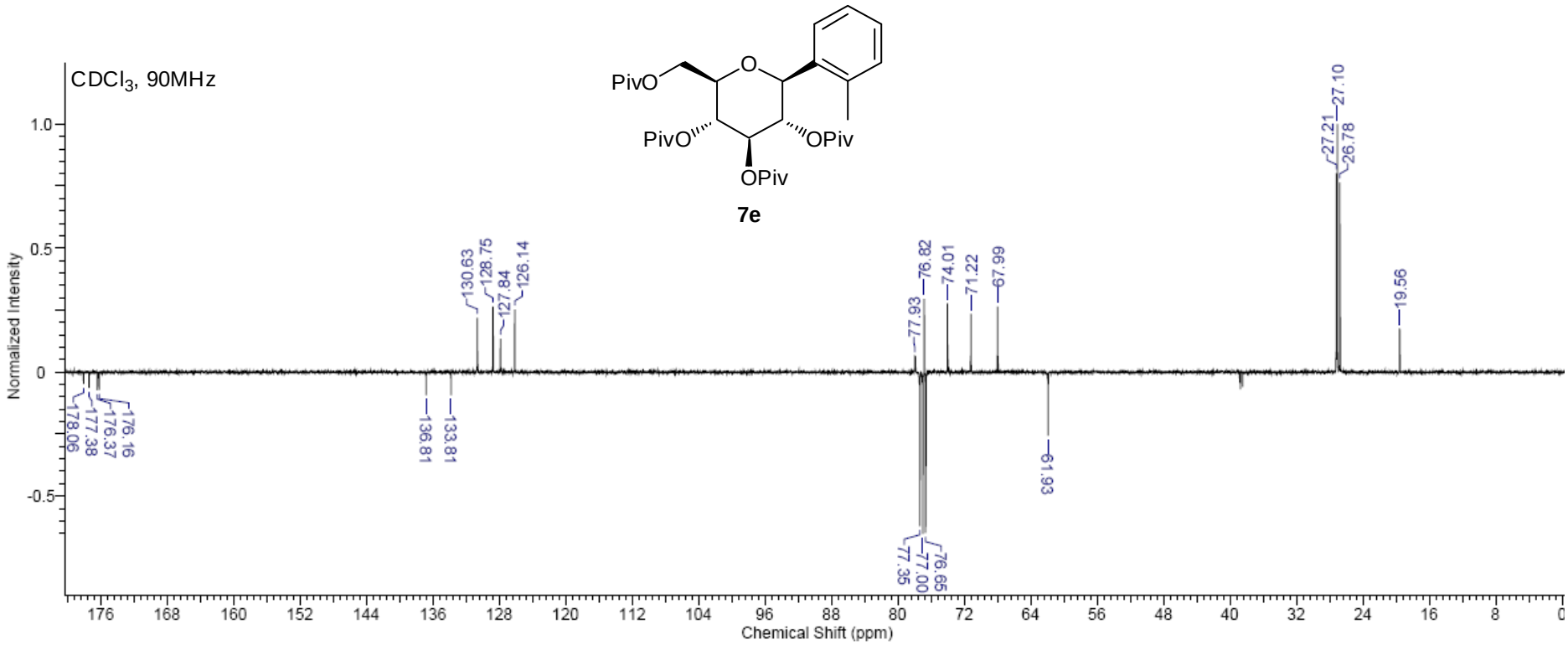

CDCl3, 360MHz
OMe
PivO
O
PivO
OPiv
OPiv
7c
Normalized Intensity
Chemical Shift (ppm)
7.28
7.27
7.26
6.87
6.84
6.45
6.42
6.40
6.32
5.26
4.38
4.36
4.22
4.19
4.14
4.13
3.86
3.84
3.79
1.58
1.23
1.17
1.12
0.90
3.32
2.00
3.06
1.01
2.02
4.07
28.08
9.21

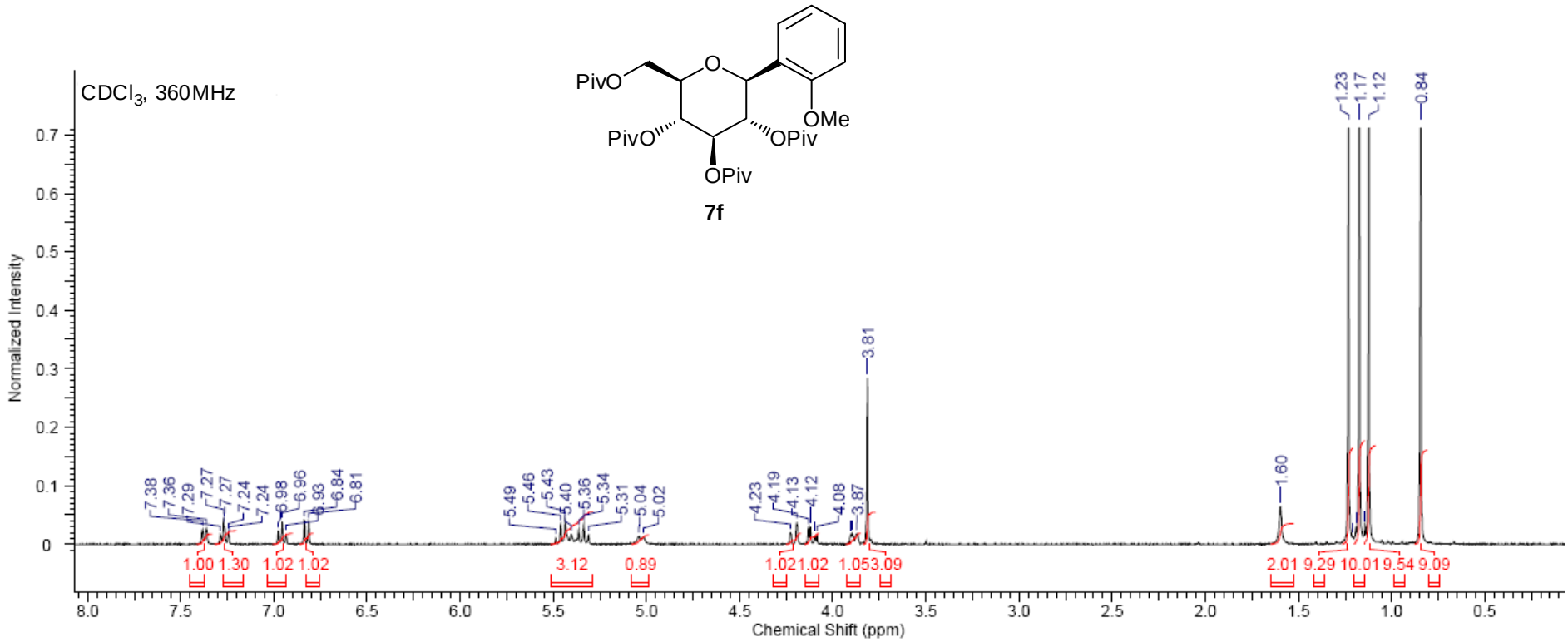

CDCl3, 90MHz
OMe
PivO
O
PivO
OPiv
OPiv
7c
Normalized Intensity
1.0
0.5
0
-0.5
127.38
126.18
79.46
73.03
70.92
67.68
65.84
25.64
25.48
25.44
25.27
19.58
176.25
175.80
175.17
174.57
137.09
131.87
75.72
75.37
75.01
59.53
37.52
37.14
37.07
36.88
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
Chemical Shift (ppm)

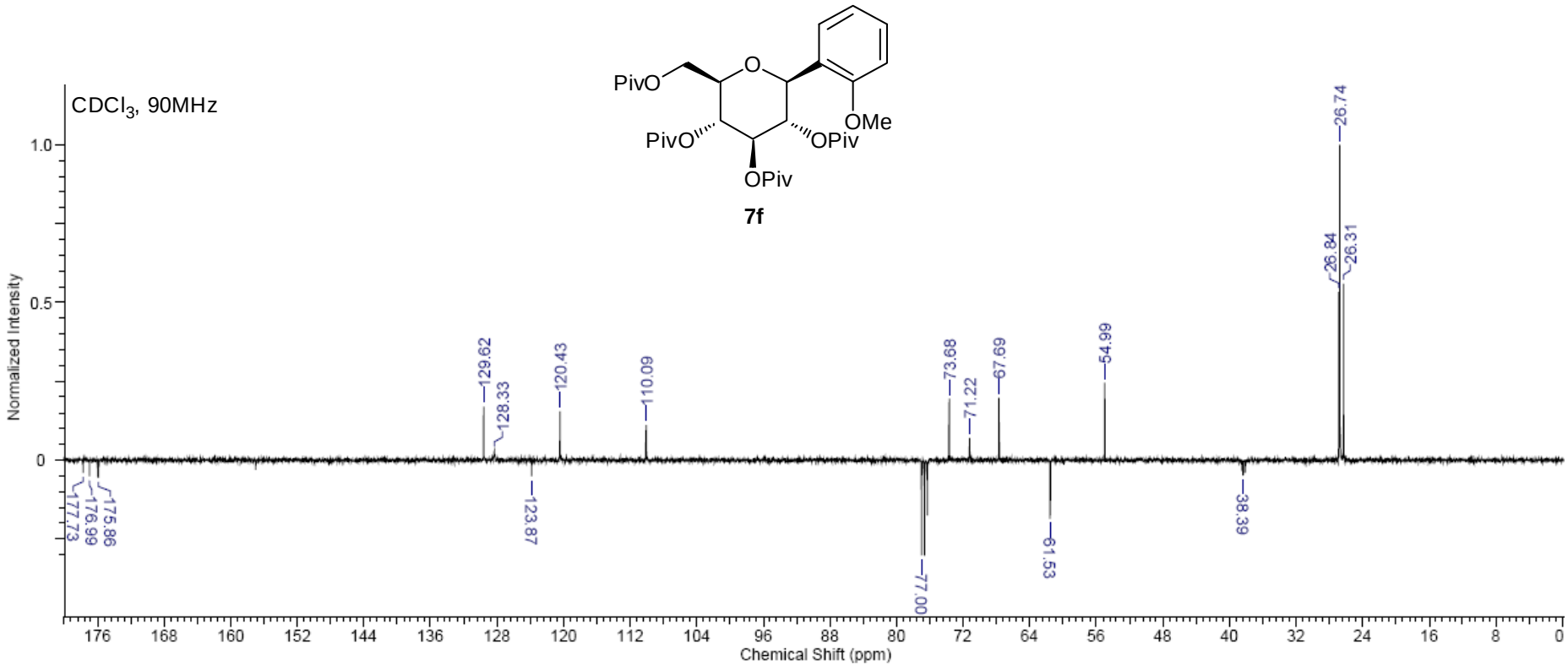

CDCl3, 360MHz
OTBDMS
PivO
O
PivO
OPiv
OPiv
7d
Normalized Intensity
Chemical Shift (ppm)
7.27
7.27
7.22
7.19
6.80
6.78
5.44
5.41
5.39
5.35
5.32
5.26
5.23
5.21
4.37
4.34
4.22
4.19
4.15
4.14
4.11
3.86
3.84
1.56
1.23
1.23
1.17
1.17
1.11
0.96
0.90
0.15
2.00
2.01
1.04
1.01
0.97
0.99
1.01
0.74
0.97
9.26
9.12
9.10
9.35
9.40
5.96

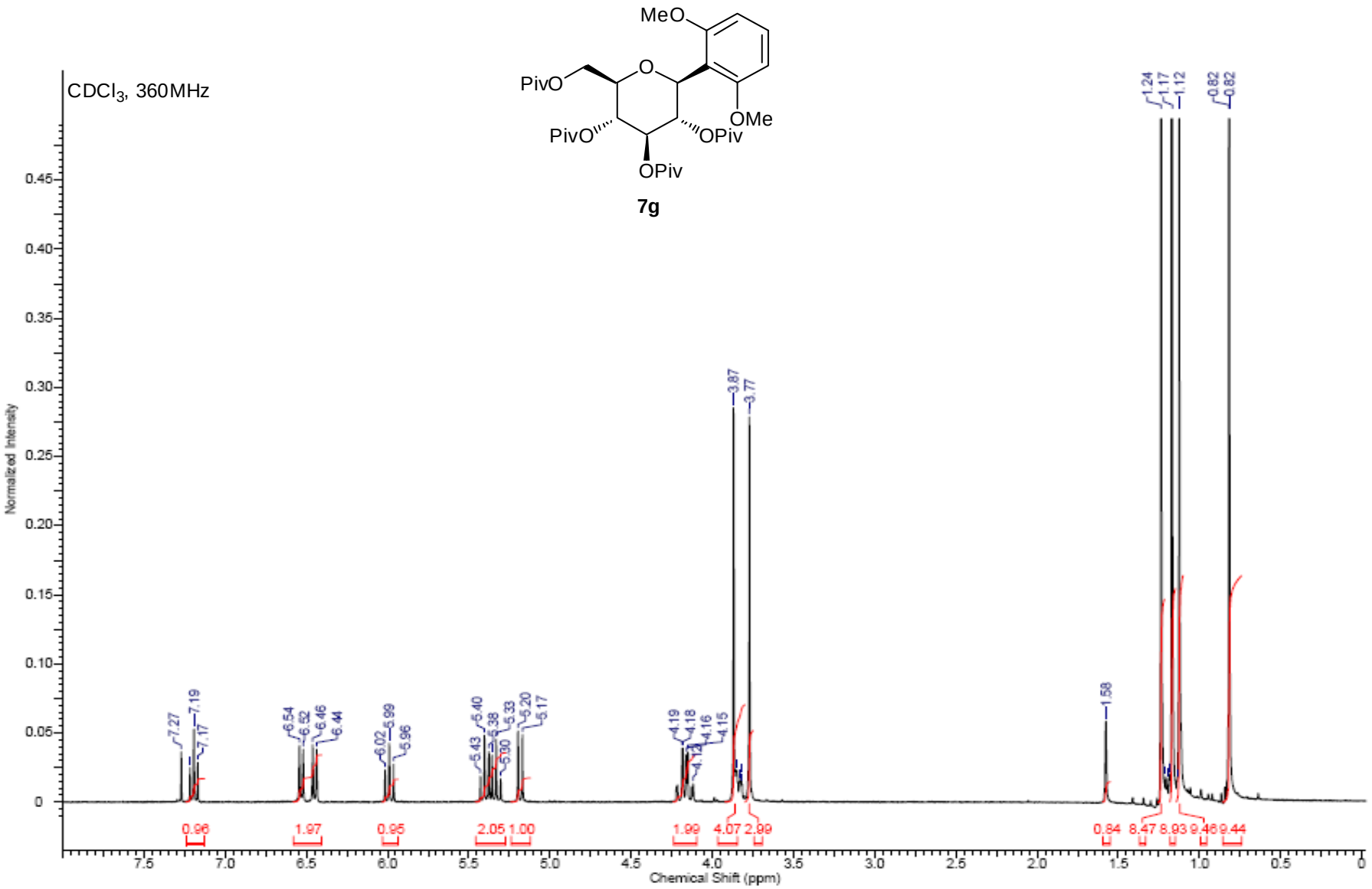

CDCl3, 90MHz
OTBDMS
PivO
O
PivO
OPiv
OPiv
7d
Normalized Intensity
1.0
0.5
0
-0.5
178.43
177.68
176.71
176.36
156.63
129.39
129.41
120.43
77.71
77.36
77.00
81.01
76.83
74.13
72.53
68.37
62.21
39.23
39.11
38.85
18.58
27.44
26.02
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

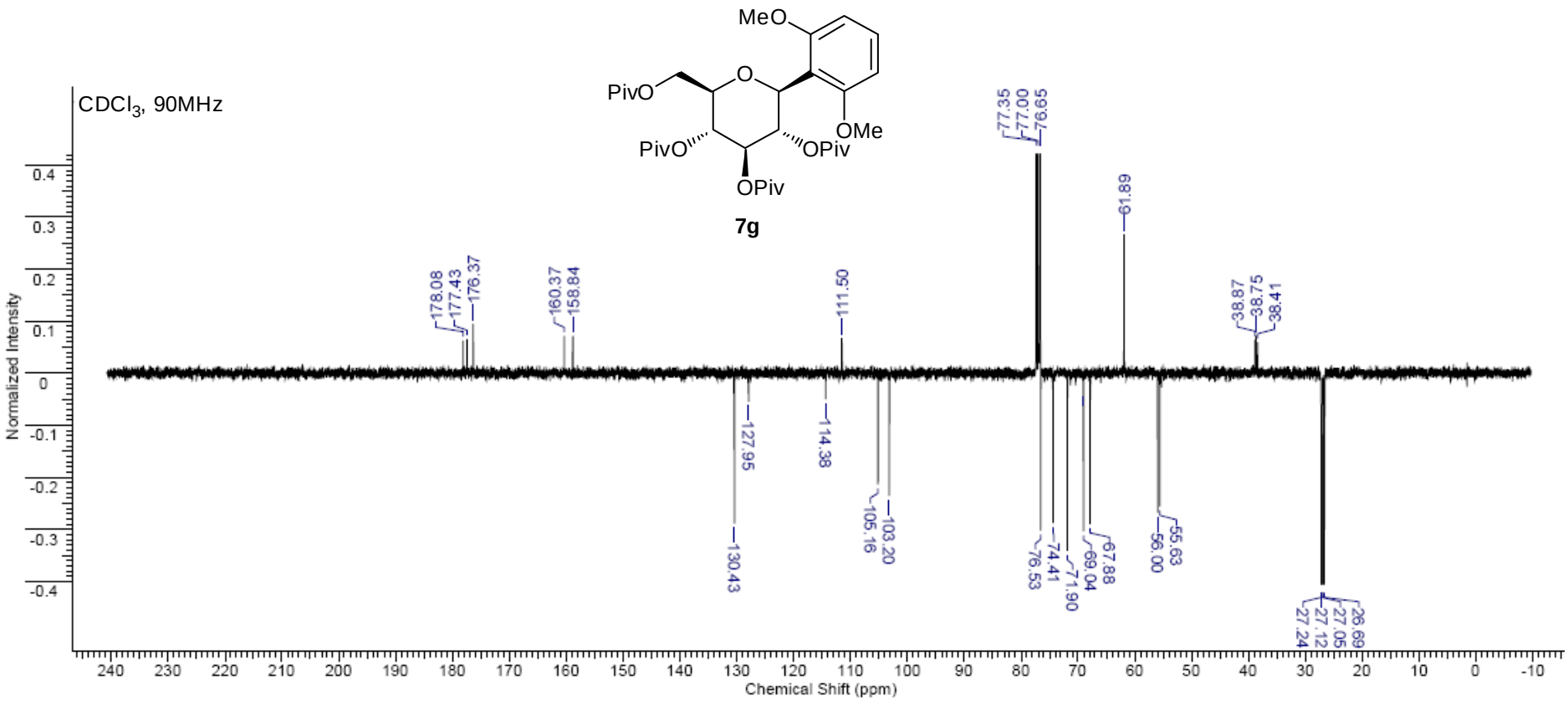

CDCl3, 360MHz
PivO
PivO
OPiv
OPiv
7e
Normalized Intensity
Chemical Shift (ppm)
7.33
7.31
7.30
7.27
7.20
7.19
7.18
7.14
7.13
5.48
5.47
5.45
5.36
5.34
4.71
4.69
4.24
4.20
4.13
4.11
4.09
4.08
3.90
3.90
3.87
3.87
2.46
1.57
1.23
1.18
1.13
0.86
1.01 1.95 0.99
2.05 1.00
0.92
1.02 1.03 1.04
2.99
5.93 9.46 9.28 9.59 9.11

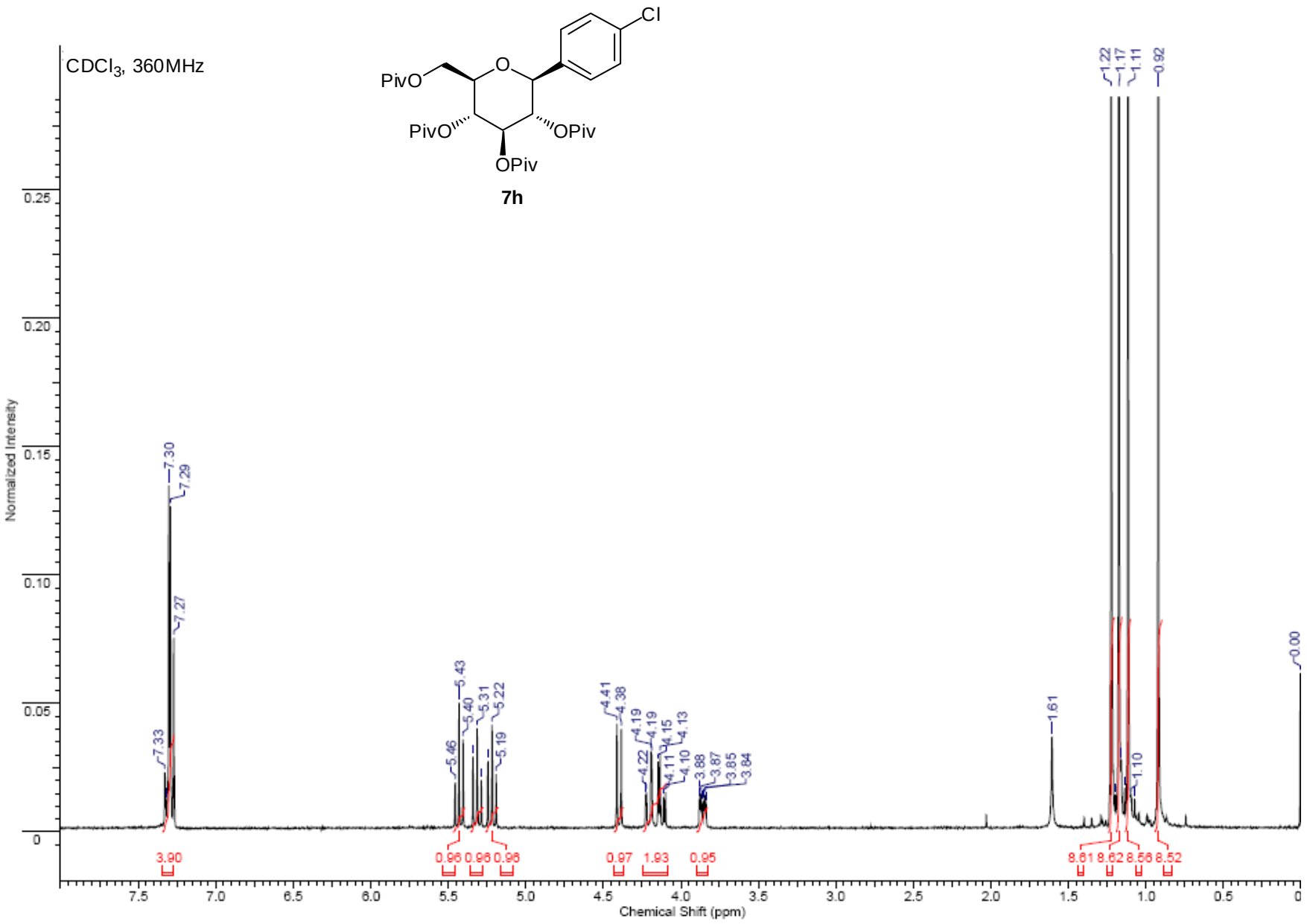

CDCl3, 90MHz
PivO
PivO
OPiv
OPiv
7e
Normalized Intensity
Chemical Shift (ppm)
178.06
177.38
176.37
176.16
136.81
133.81
130.63
128.75
127.84
126.14
77.93
76.82
74.01
71.22
67.99
61.93
27.21
27.10
26.78
19.56

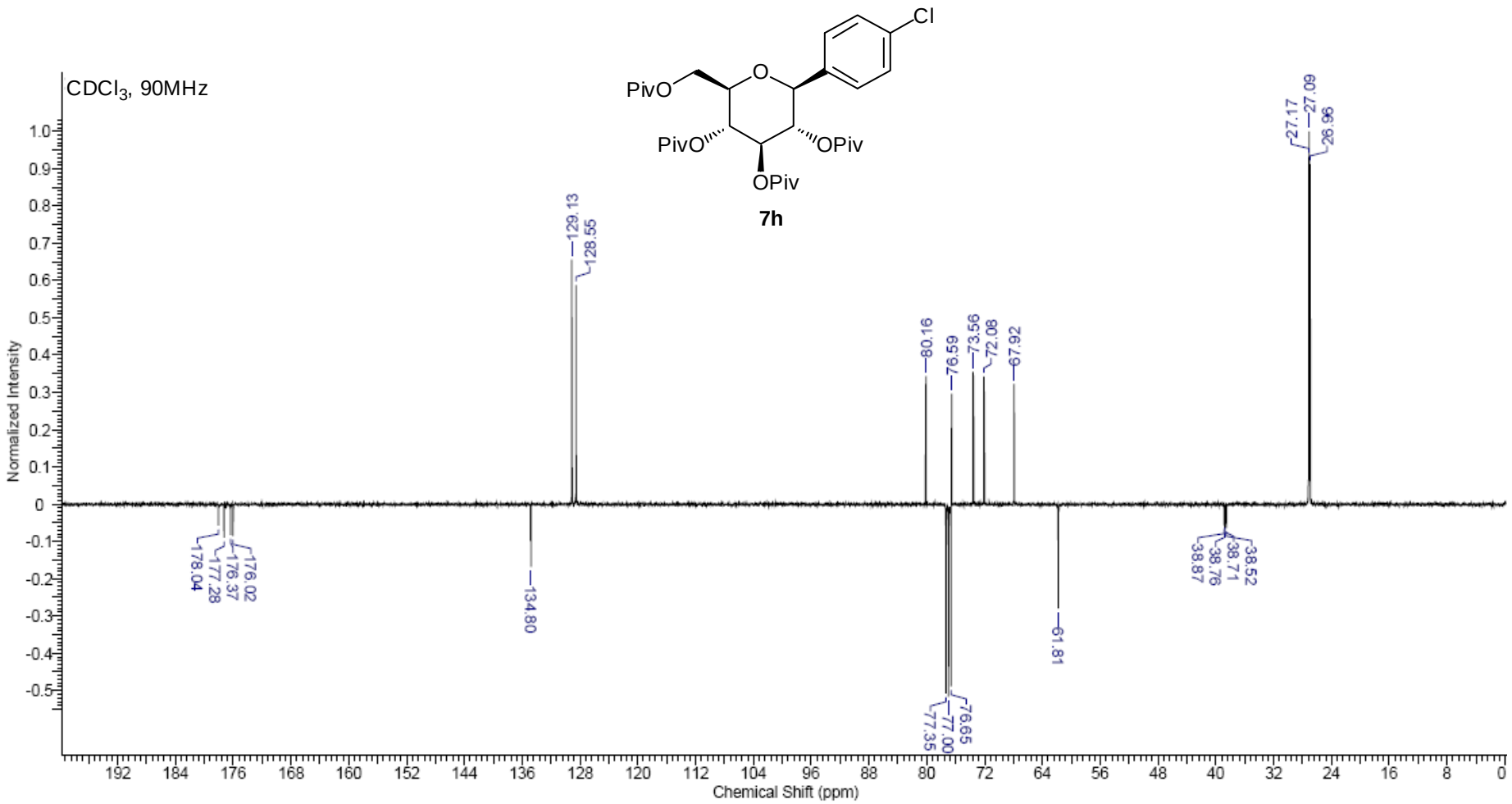

CDCl3, 360MHz
PivO
O
OMe
PivO
OPiv
OPiv
7f
Normalized Intensity
Chemical Shift (ppm)
7.38
7.36
7.29
7.27
7.27
7.24
7.24
6.98
6.96
6.93
6.84
6.81
5.49
5.46
5.43
5.40
5.36
5.34
5.31
5.04
5.02
4.23
4.19
4.13
4.12
4.08
3.87
3.81
1.60
1.23
1.17
1.12
0.84
1.00 1.30 1.02 1.02
3.12
0.89
1.02 1.02 1.05 3.09
2.01 9.29 10.01 9.54 9.09


CDCl3, 90MHz
PivO
O
OMe
PivO
OPiv
OPiv
7f
Normalized Intensity
1.0
0.5
0
129.62
128.33
120.43
110.09
73.68
71.22
67.69
54.99
26.74
26.84
26.31
177.73
176.99
175.86
123.87
77.00
61.53
38.39
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

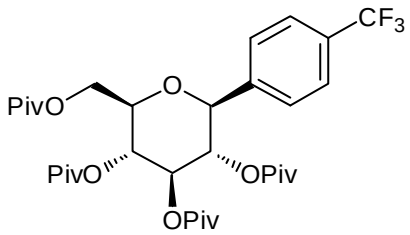

CDCl3, 360MHz
MeO
PivO
O
OMe
PivO
OPiv
OPiv
7g
Normalized Intensity
Chemical Shift (ppm)
0.96
1.97
0.95
2.05
1.00
1.99
4.07
2.99
0.84
8.47
8.93
9.46
9.44


CDCl3, 90MHz
MeO
PivO
O
OMe
PivO
OPiv
OPiv
7g
Normalized Intensity
Chemical Shift (ppm)
178.08
177.43
176.37
160.37
158.84
127.95
130.43
114.38
111.50
105.16
103.20
77.35
77.00
76.65
76.53
74.41
71.90
69.04
67.88
61.89
56.00
55.63
38.87
38.75
38.41
27.24
27.12
27.05
26.69

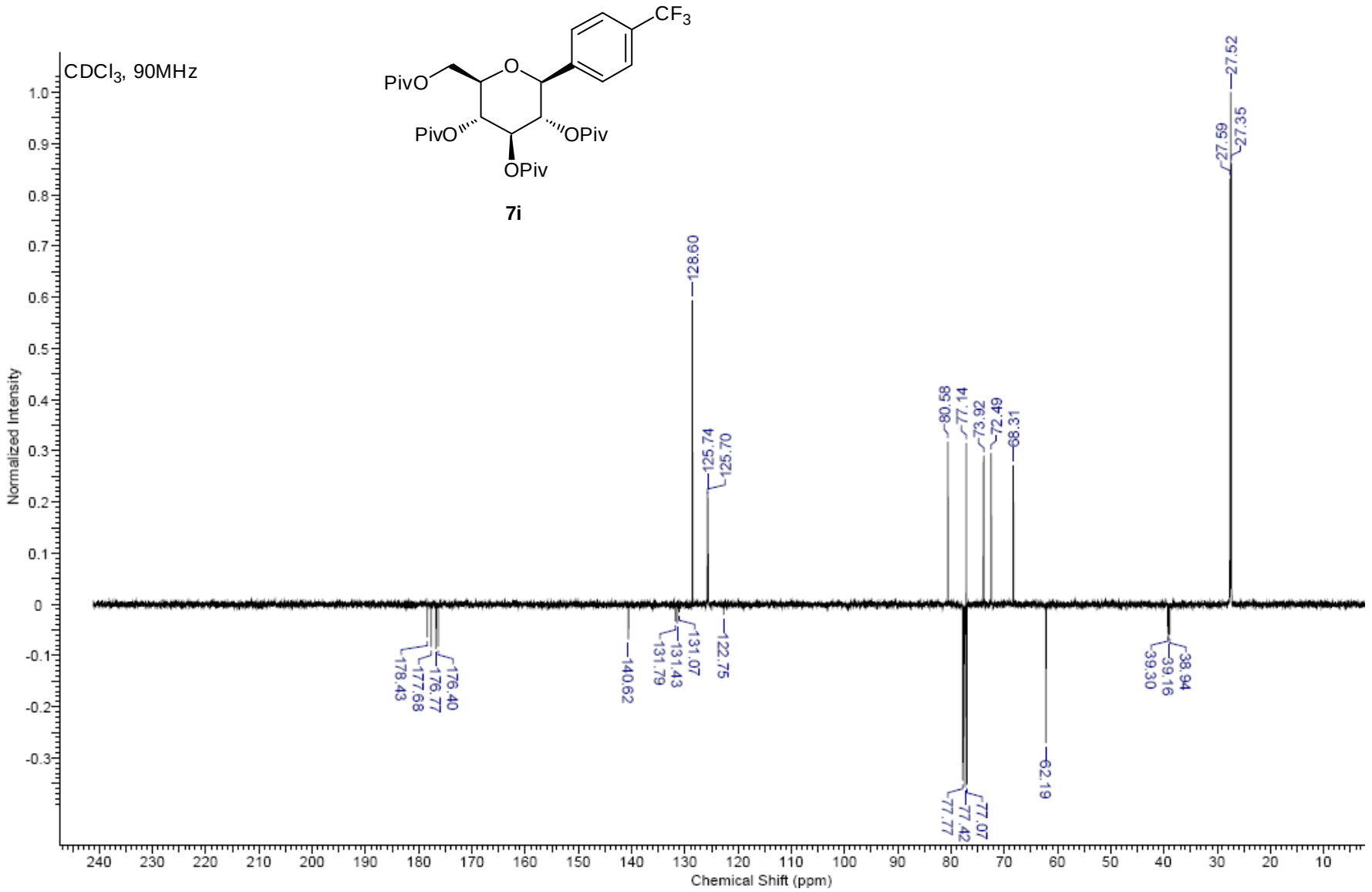

CDCl3, 360MHz
PivO
PivO
OPiv
OPiv
O
Cl
7h
Normalized Intensity
Chemical Shift (ppm)
7.33
7.30
7.29
7.27
5.46
5.43
5.40
5.31
5.22
5.19
4.41
4.38
4.22
4.19
4.19
4.15
4.13
4.11
4.10
3.88
3.87
3.85
3.84
1.61
1.22
1.17
1.11
1.10
0.92
0.00
3.90
0.96
0.96
0.96
0.97
1.93
0.95
8.61
8.62
8.56
8.52


CDCl3, 90MHz
Cl
PivO
O
PivO
OPiv
OPiv
7h
Normalized Intensity
Chemical Shift (ppm)
178.04
177.28
176.37
176.02
134.80
129.13
128.55
80.16
76.59
73.56
72.08
67.92
77.35
77.00
76.65
61.81
38.87
38.76
38.71
38.52
27.17
27.09
26.96

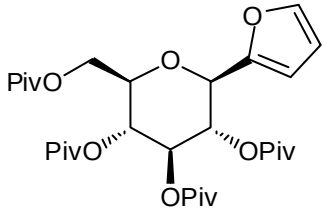
$CDCl_3$, 360MHz



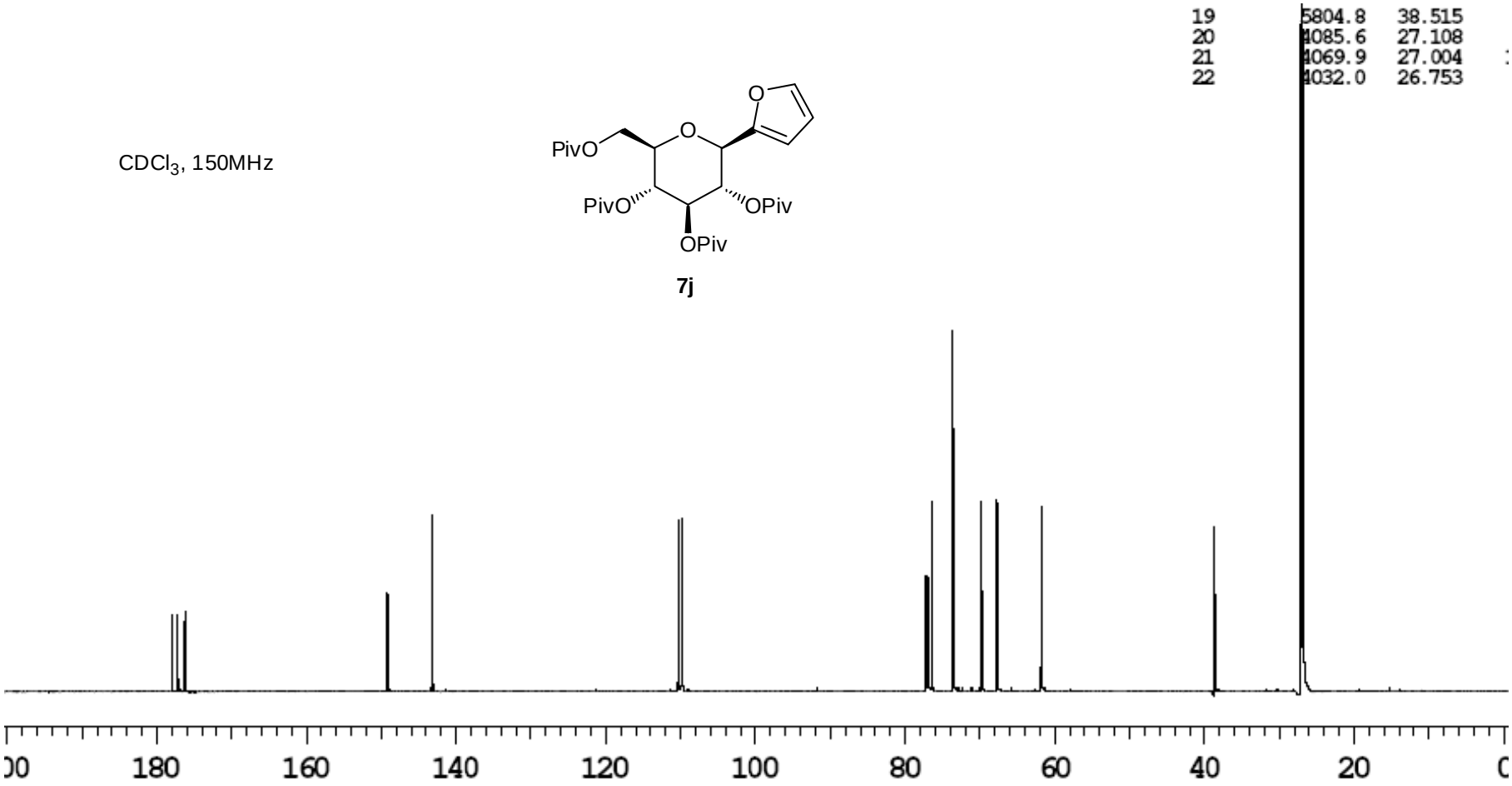
7i

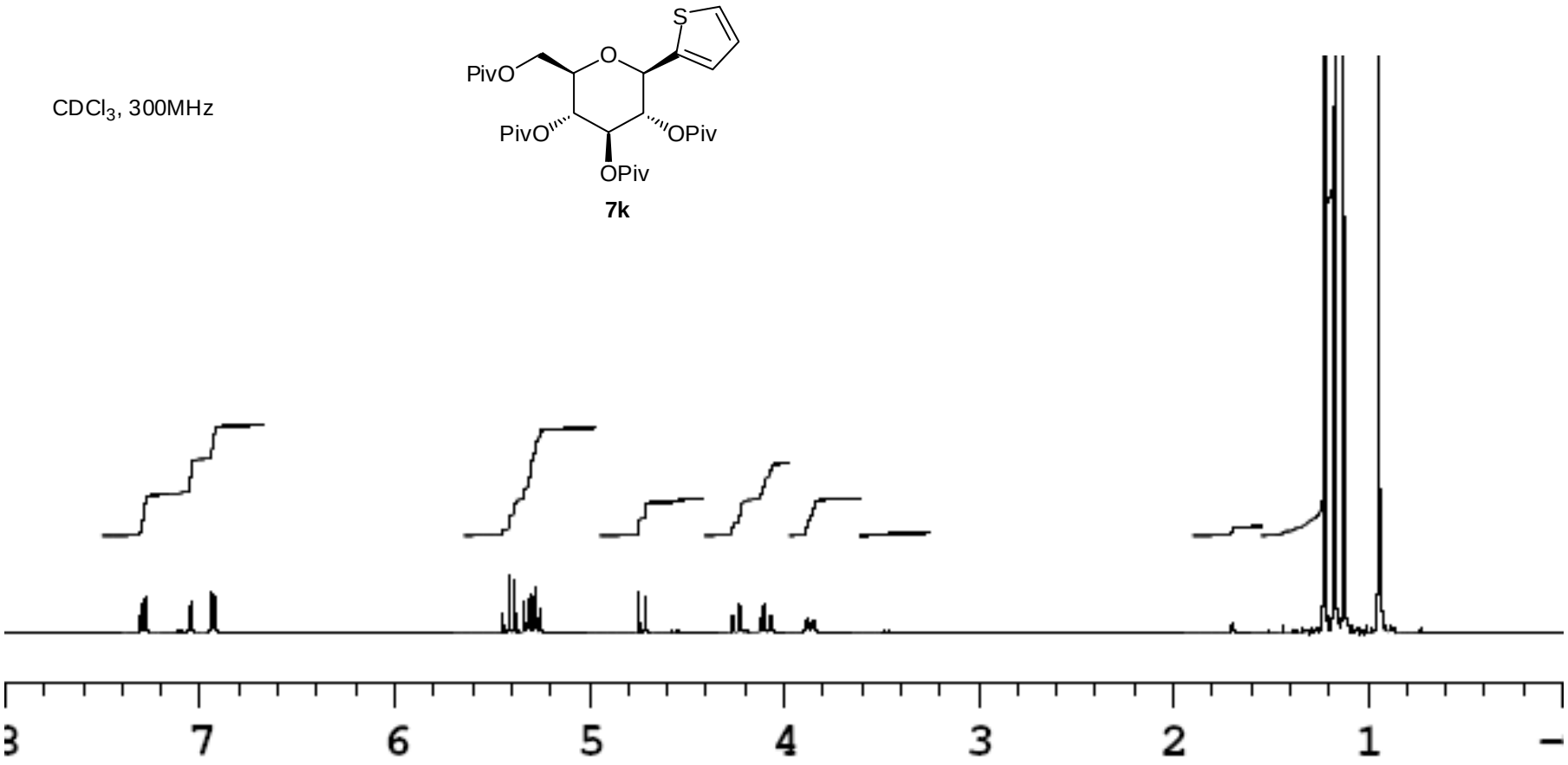

CDCl3, 90MHz
PivO
PivO
OPiv
OPiv
O
CF3
7i
Normalized Intensity
Chemical Shift (ppm)
128.60
125.74
125.70
80.58
77.14
73.92
72.49
68.31
27.52
27.59
27.35
178.43
177.68
176.77
176.40
140.62
131.79
131.43
131.07
122.75
77.77
77.42
77.07
62.19
39.30
39.16
38.94

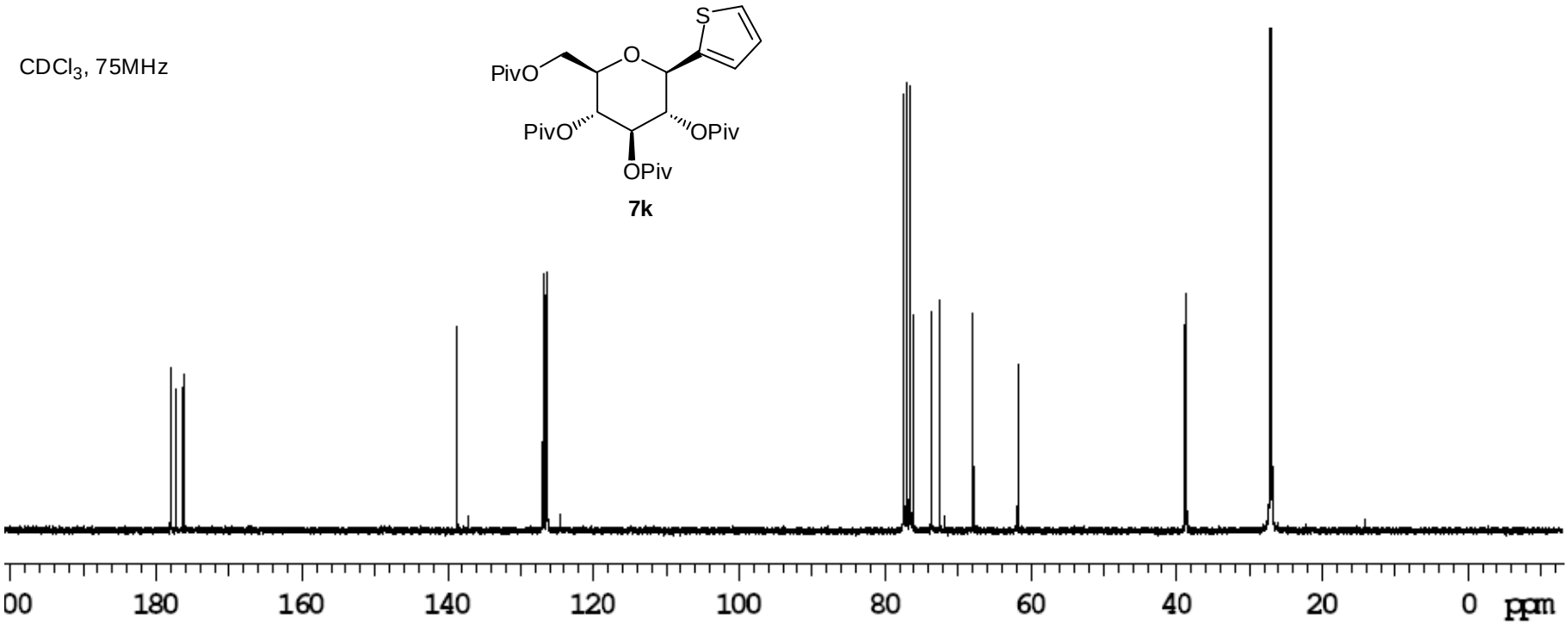
$CDCl_3$, 600MHz

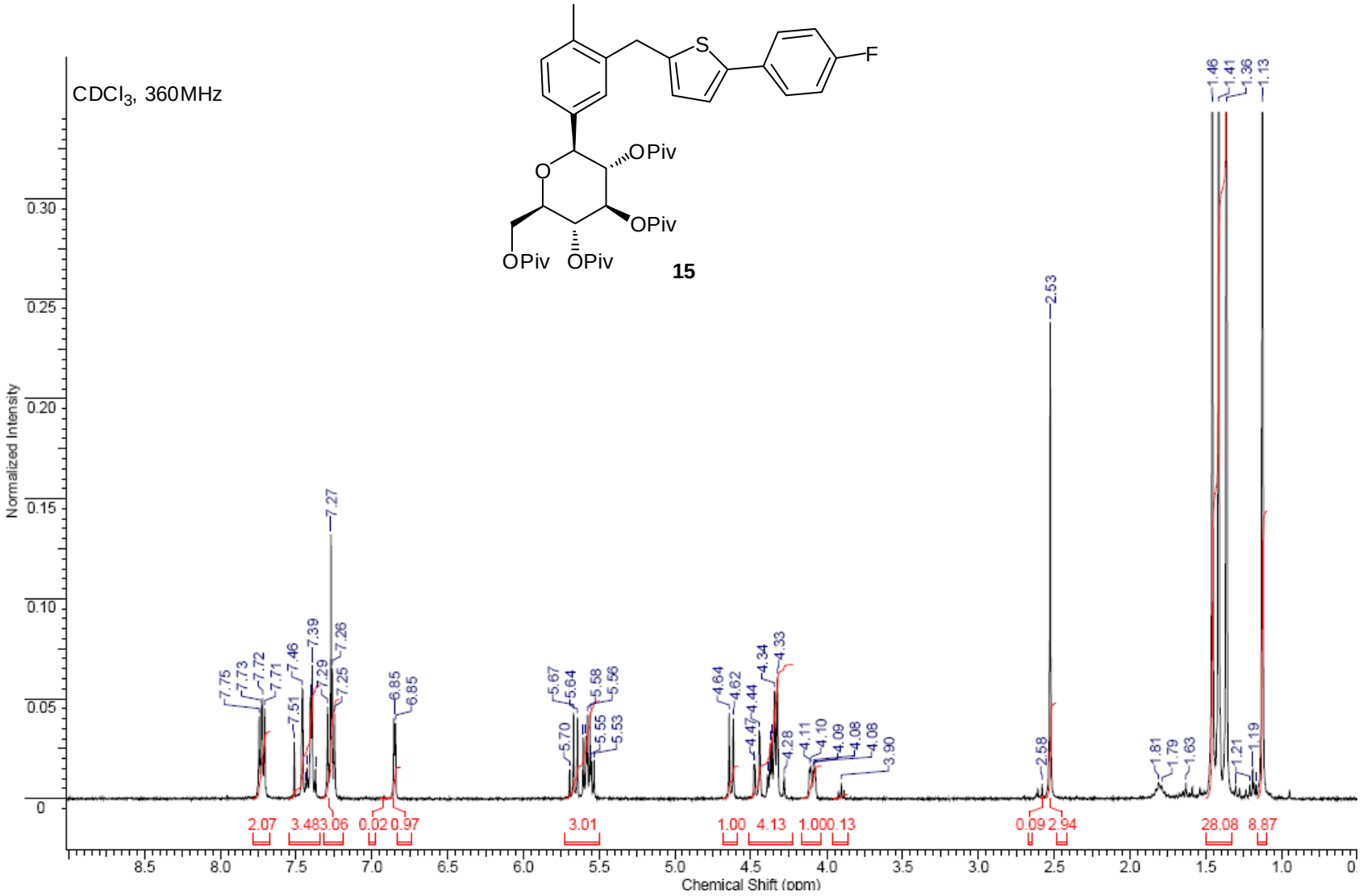


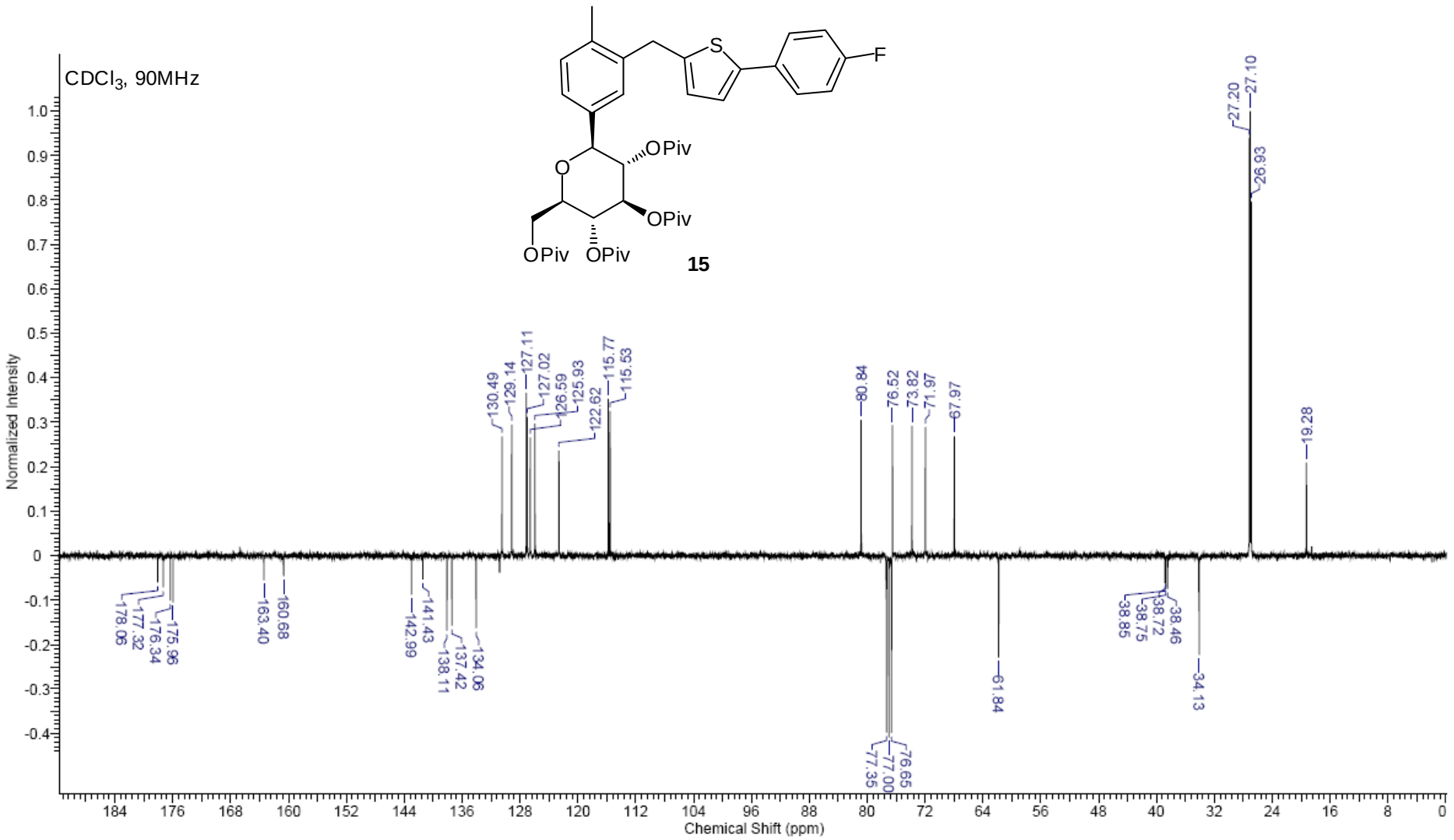
7j

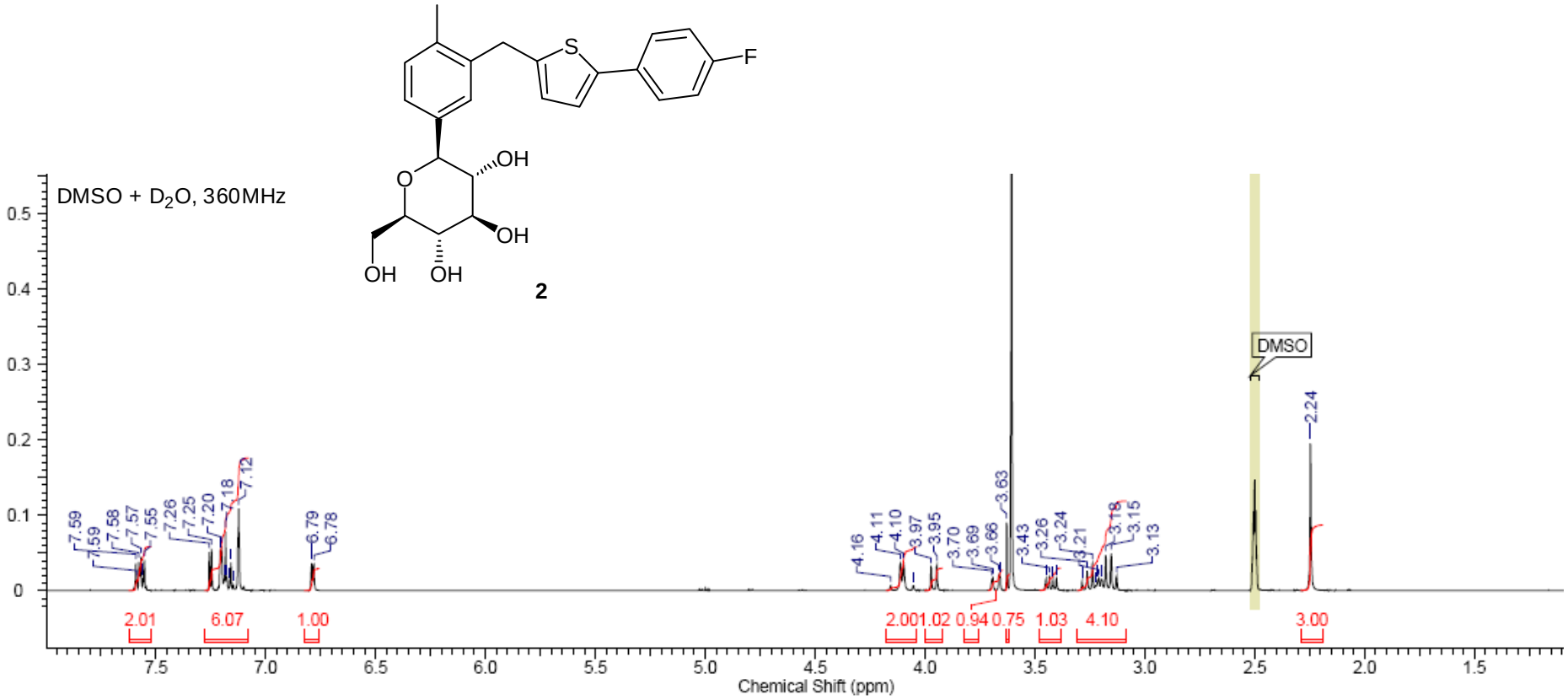

19 5804.8 38.515
20 4085.6 27.108
21 4069.9 27.004
22 4032.0 26.753
CDCl3, 150MHz
PivO
O
O
PivO
OPiv
OPiv
7j
180
160
140
120
100
80
60
40
20

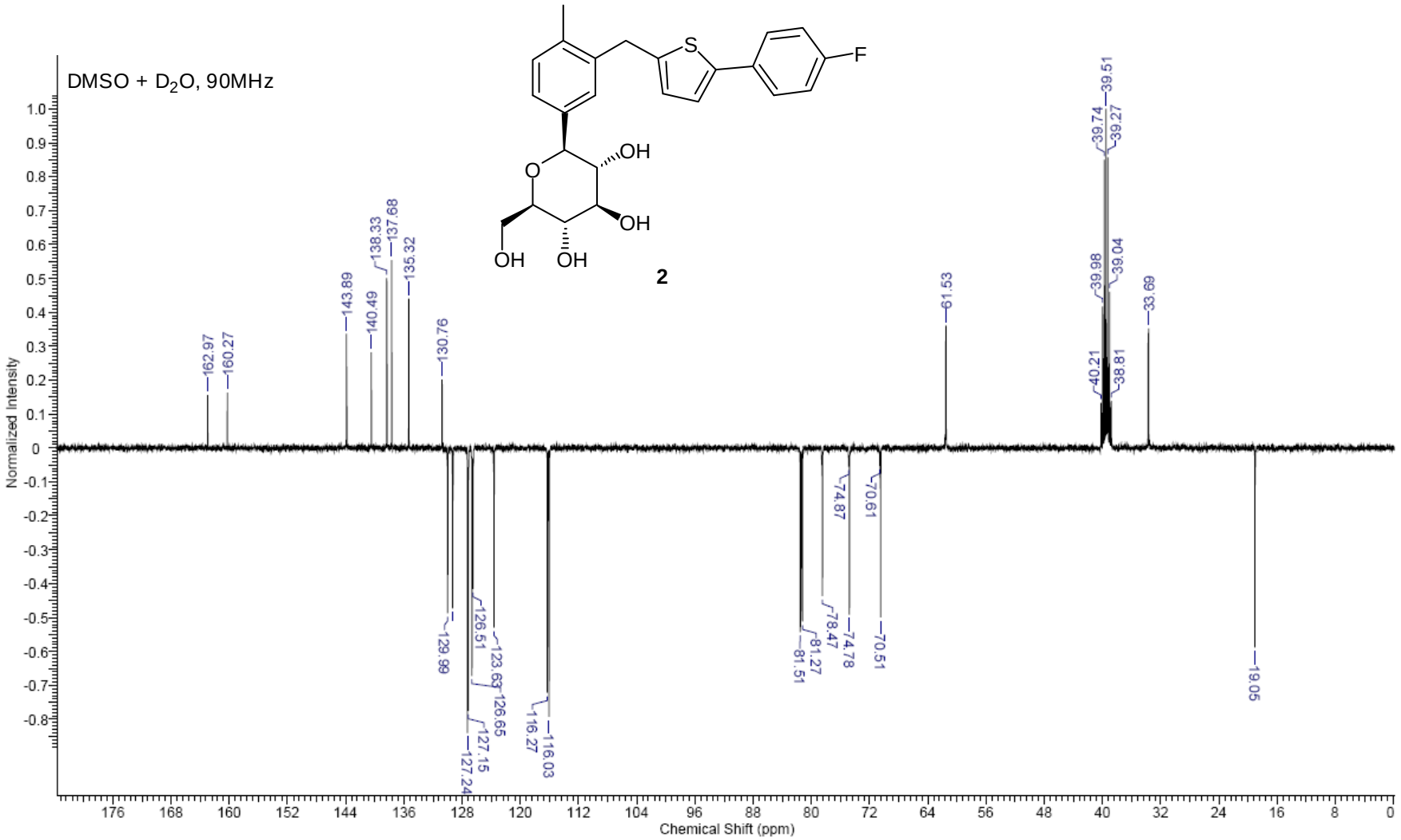

CDCl3, 300MHz
S
O
PivO
PivO
OPiv
OPiv
7k
7
6
5
4
3
2
1

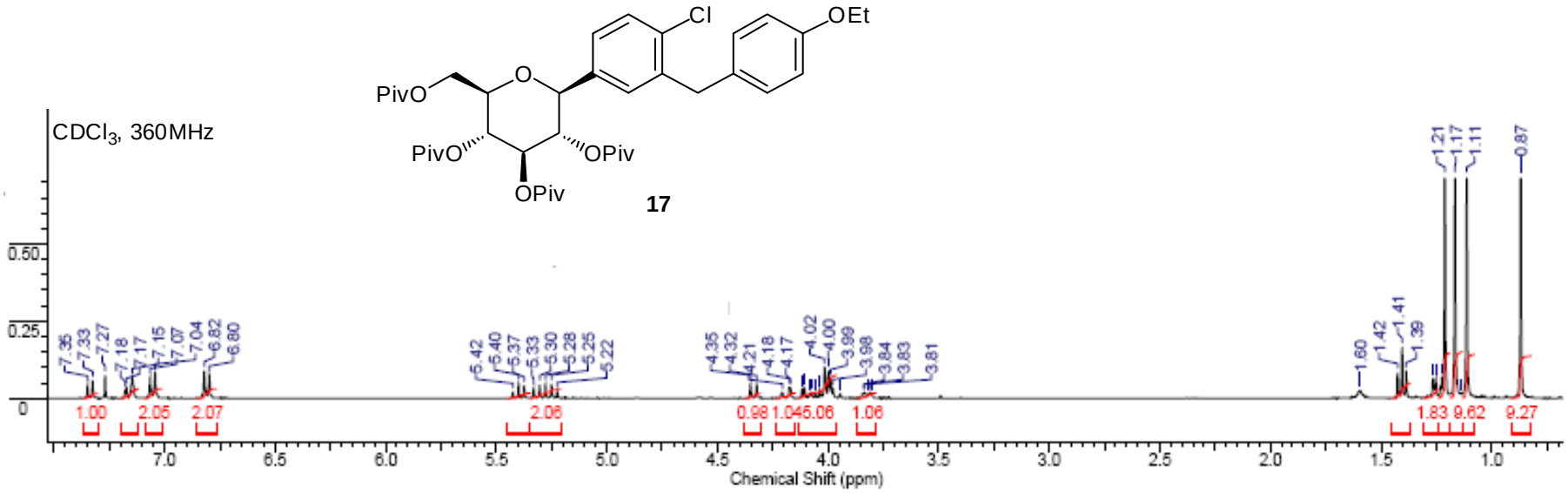

CDCl3, 75MHz
S
O
PivO
PivO
OPiv
OPiv
7k
00
180
160
140
120
100
80
60
40
20
0
ppm

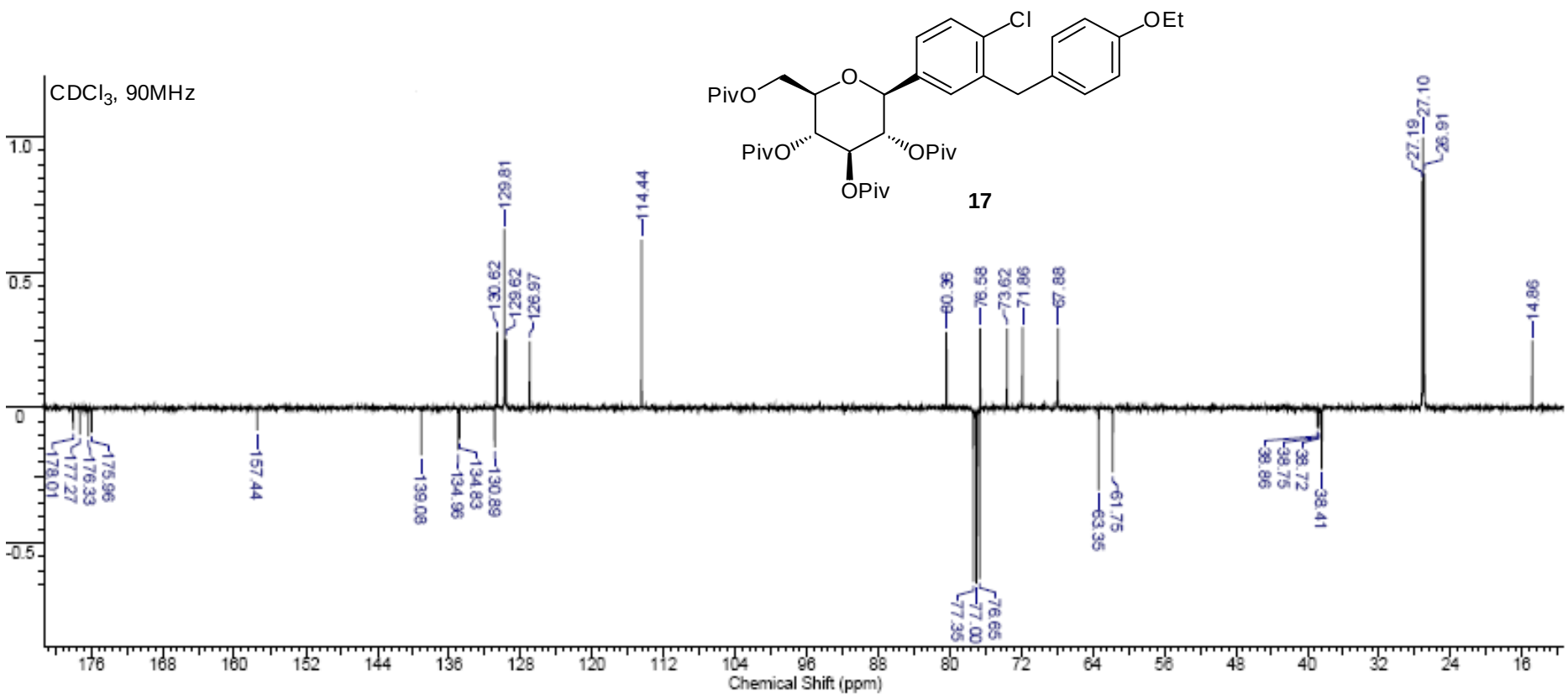

CDCl3, 360MHz
OPiv
OPiv
OPiv
OPiv
O
S
F
15
Normalized Intensity
Chemical Shift (ppm)

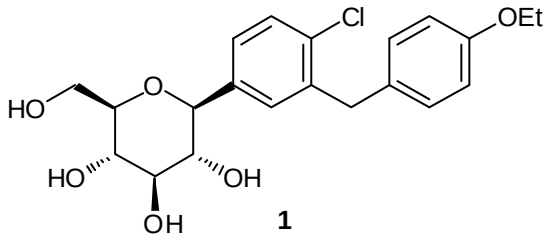

CDCl3, 90MHz
S
F
O
OPiv
OPiv
OPiv
OPiv
15
Normalized Intensity
Chemical Shift (ppm)
27.20
27.10
26.93
19.28
80.84
76.52
73.82
71.97
61.84
34.13
38.46
38.72
38.75
38.85
130.49
129.14
127.11
127.02
126.59
125.93
122.62
115.77
115.53
178.06
177.32
176.34
175.96
163.40
160.68
142.99
141.43
138.11
137.42
134.06
77.35
77.00
76.65


DMSO + D2O, 360MHz
S
F
O
OH
OH
OH
OH
2
DMSO
7.59
7.59
7.58
7.57
7.55
7.26
7.25
7.20
7.18
7.12
6.79
6.78
4.16
4.11
4.10
3.97
3.95
3.70
3.69
3.66
3.63
3.43
3.26
3.24
3.21
3.18
3.15
3.13
2.24
2.01
6.07
1.00
2.00
1.02
0.94
0.75
1.03
4.10
3.00
Chemical Shift (ppm)

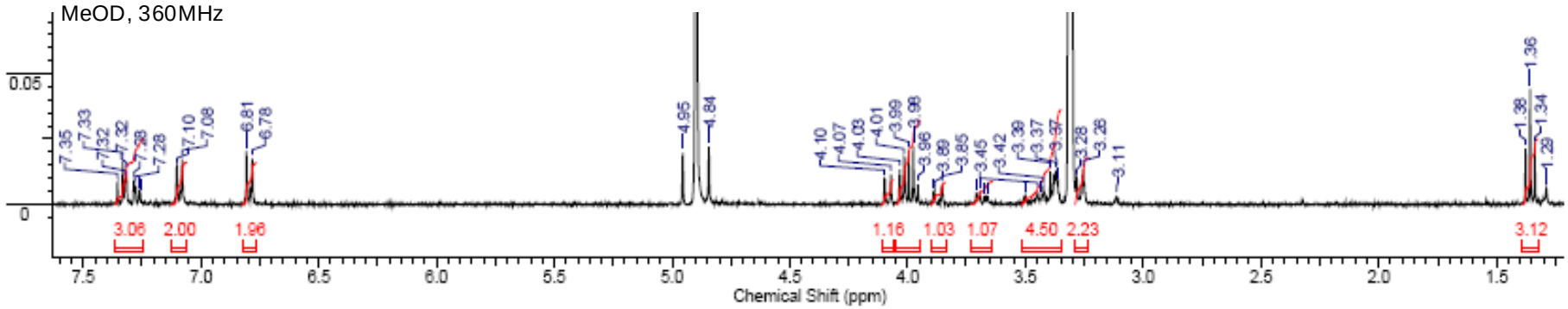

DMSO + D2O, 90MHz
S
F
O
OH
OH
OH
OH
2
Normalized Intensity
Chemical Shift (ppm)
162.97
160.27
143.89
140.49
138.33
137.68
135.32
130.76
129.99
126.51
123.63
126.65
127.15
127.24
116.27
116.03
81.51
81.27
78.47
74.87
74.78
70.61
70.51
61.53
40.21
39.98
39.74
39.51
39.27
39.04
38.81
33.69
19.05

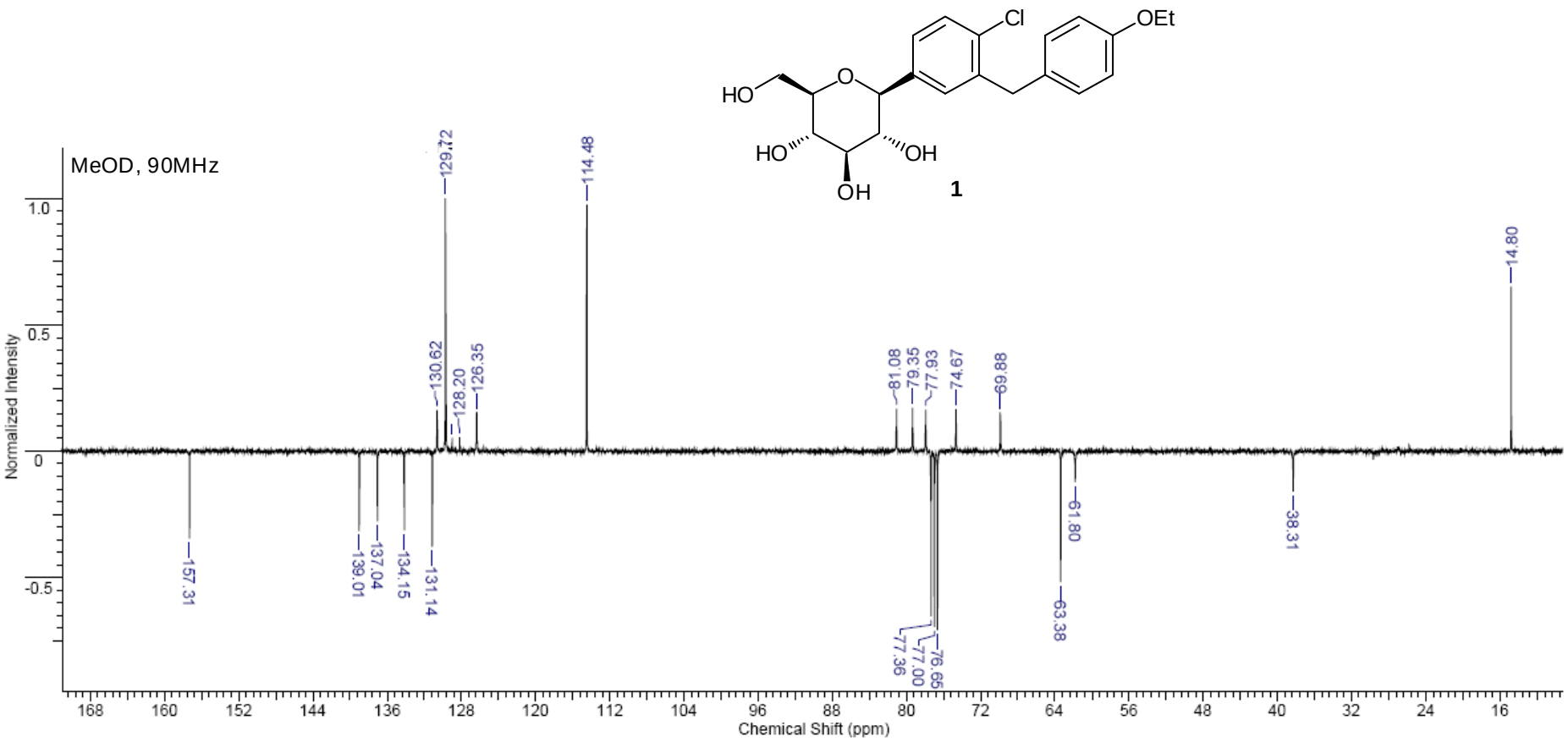

CDCl3, 360MHz
Cl
OEt
O
PivO
PivO
OPiv
OPiv
17
0.50
0.25
0
7.35
7.33
7.27
7.18
7.17
7.15
7.07
7.04
6.82
6.80
6.42
5.40
5.37
5.33
5.30
5.28
5.25
5.22
4.35
4.32
4.21
4.18
4.17
4.02
4.00
3.99
3.98
3.84
3.83
3.81
1.60
1.42
1.41
1.39
1.21
1.17
1.11
0.87
1.00
2.05
2.07
2.06
0.98
1.04
5.06
1.06
1.83
9.62
9.27
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

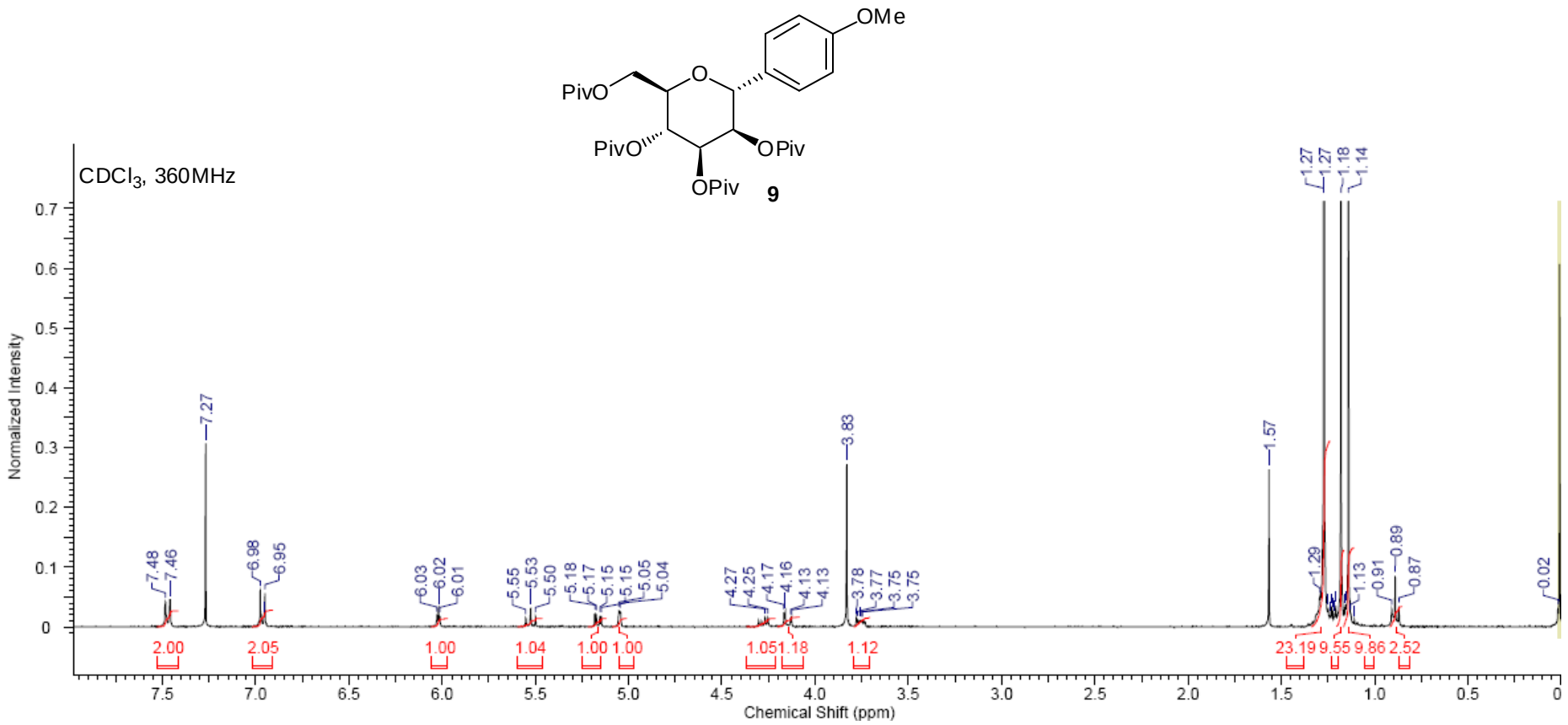

CDCl3, 90MHz
Cl
OEt
PivO
O
PivO
OPiv
OPiv
17
1.0
0.5
0
-0.5
129.81
130.62
129.62
126.97
114.44
80.36
76.58
73.62
71.86
67.88
27.19
27.10
26.91
14.86
178.01
177.27
176.33
175.96
157.44
139.08
134.96
134.83
130.89
77.35
77.00
76.65
63.35
61.75
38.86
38.75
38.72
38.41
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

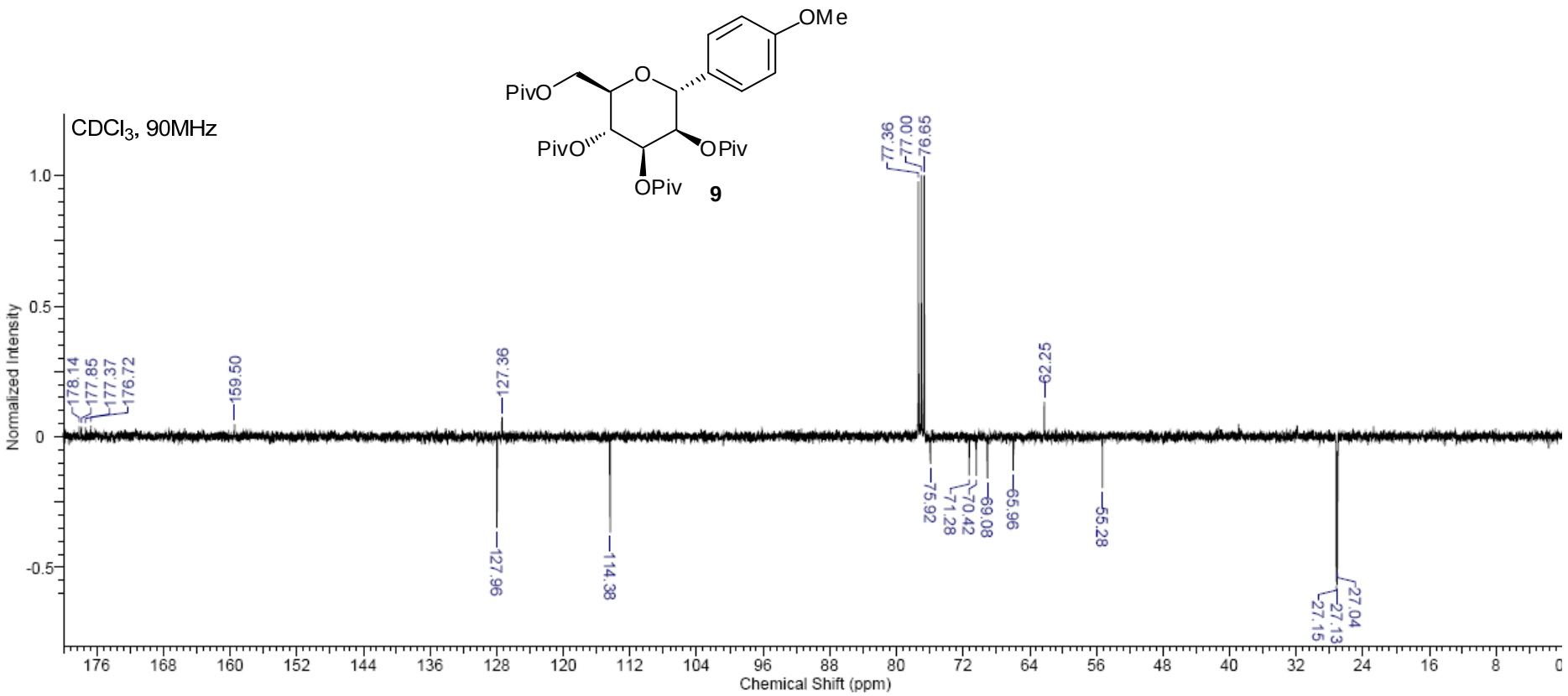

Cl
OEt
O
HO
HO
OH
OH

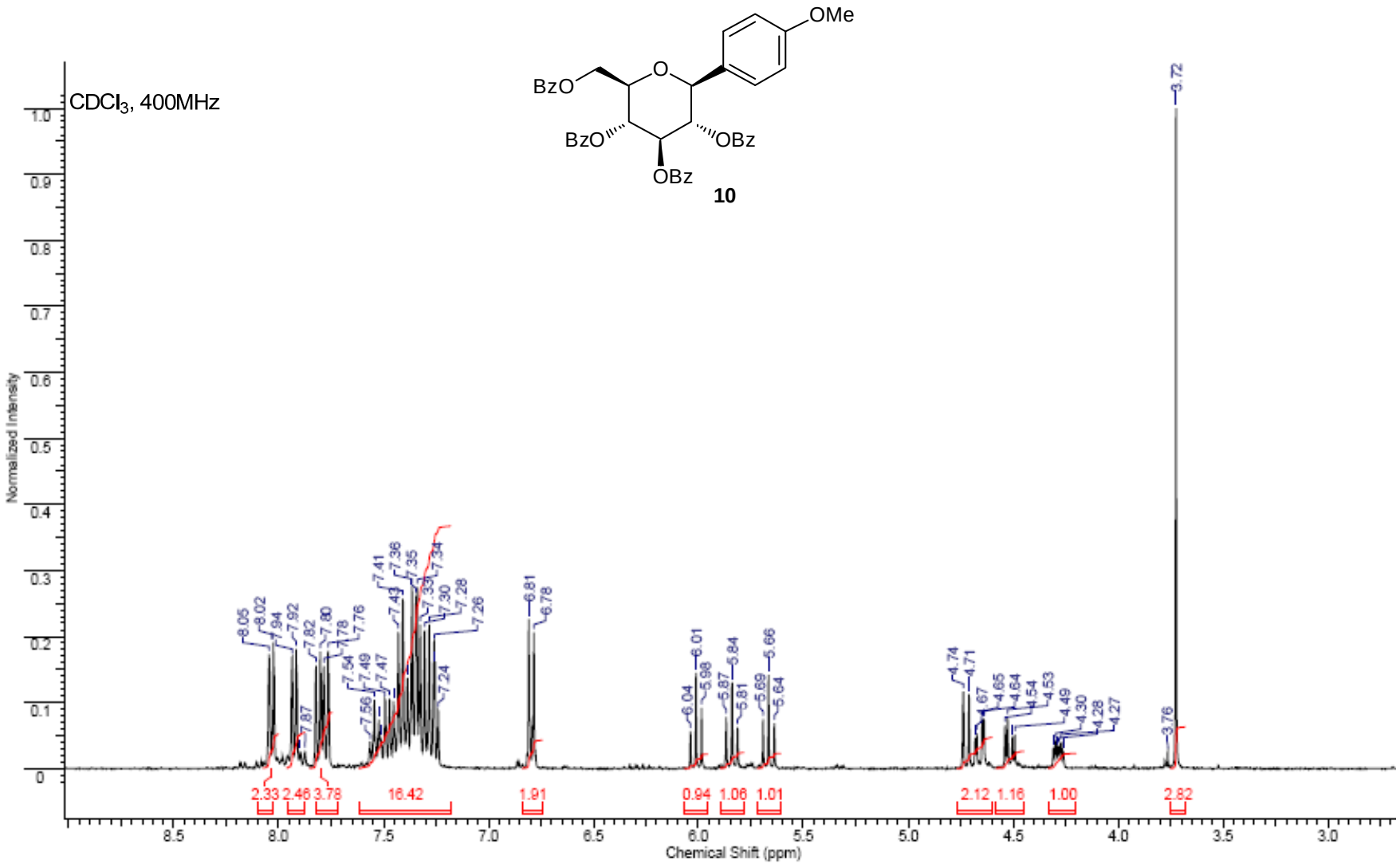
1

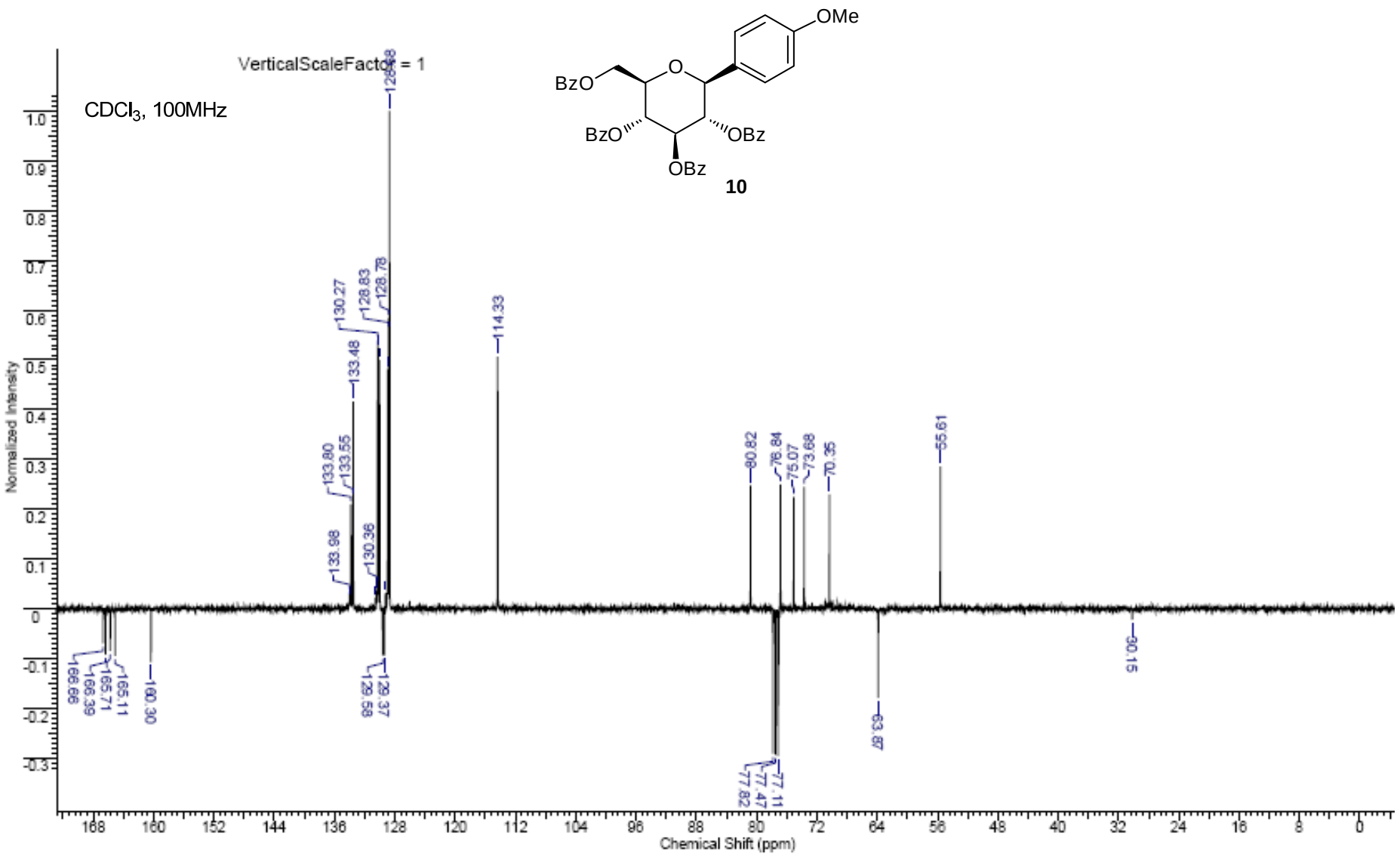

MeOD, 360MHz
0.05
0
7.35
7.33
7.32
7.32
7.28
7.10
7.08
6.81
6.78
4.95
4.84
4.10
4.07
4.03
4.01
3.99
3.98
3.96
3.89
3.85
3.45
3.42
3.39
3.37
3.28
3.26
3.11
1.38
1.36
1.34
1.29
3.06
2.00
1.96
1.16
1.03
1.07
4.50
2.23
3.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

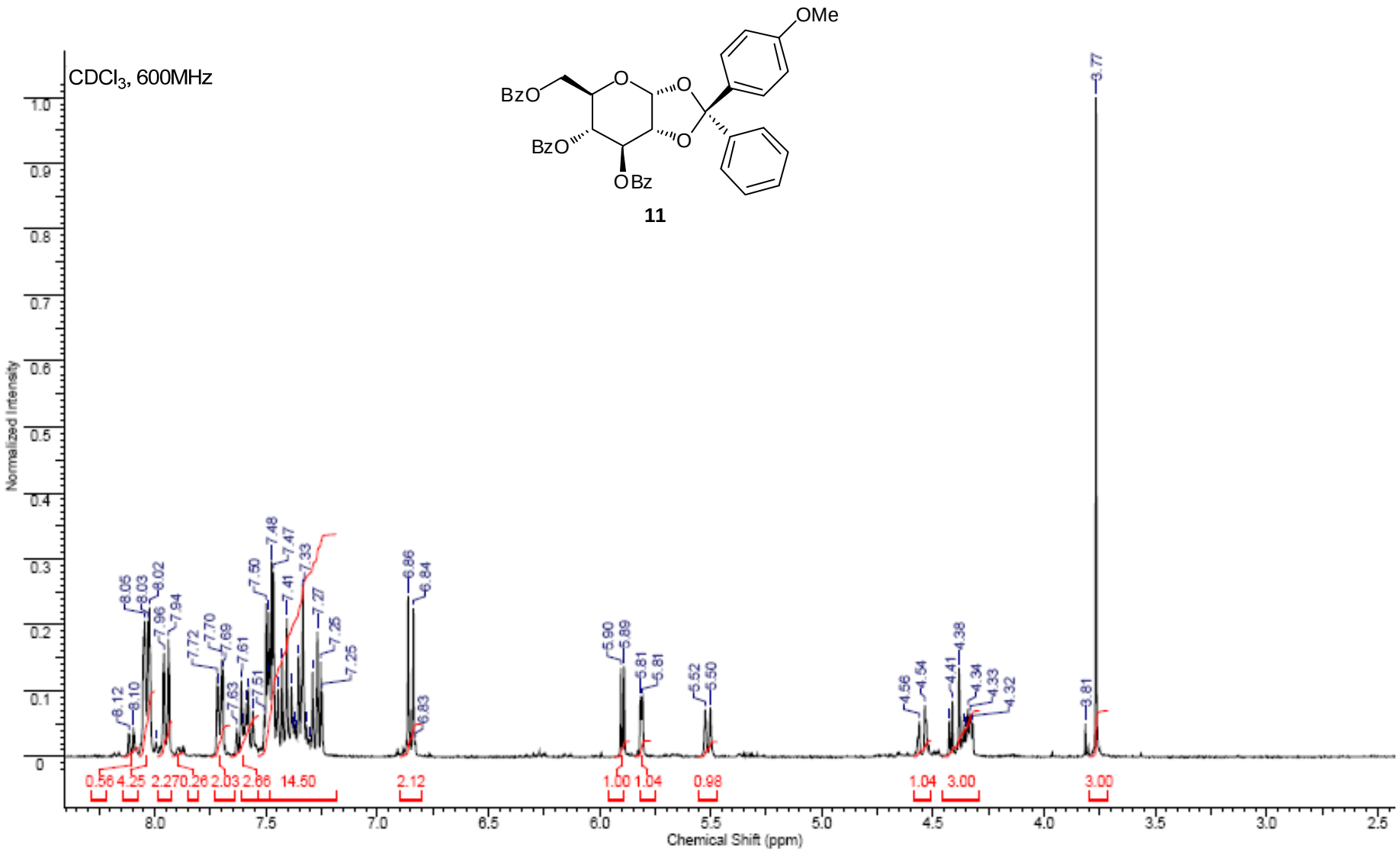

MeOD, 90MHz
Cl
OEt
HO
O
HO
OH
OH
1
129.72
114.48
130.62
128.20
126.35
81.08
79.35
77.93
74.67
69.88
14.80
157.31
139.01
137.04
134.15
131.14
77.36
77.00
76.65
63.38
61.80
38.31
Normalized Intensity
1.0
0.5
0
-0.5
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

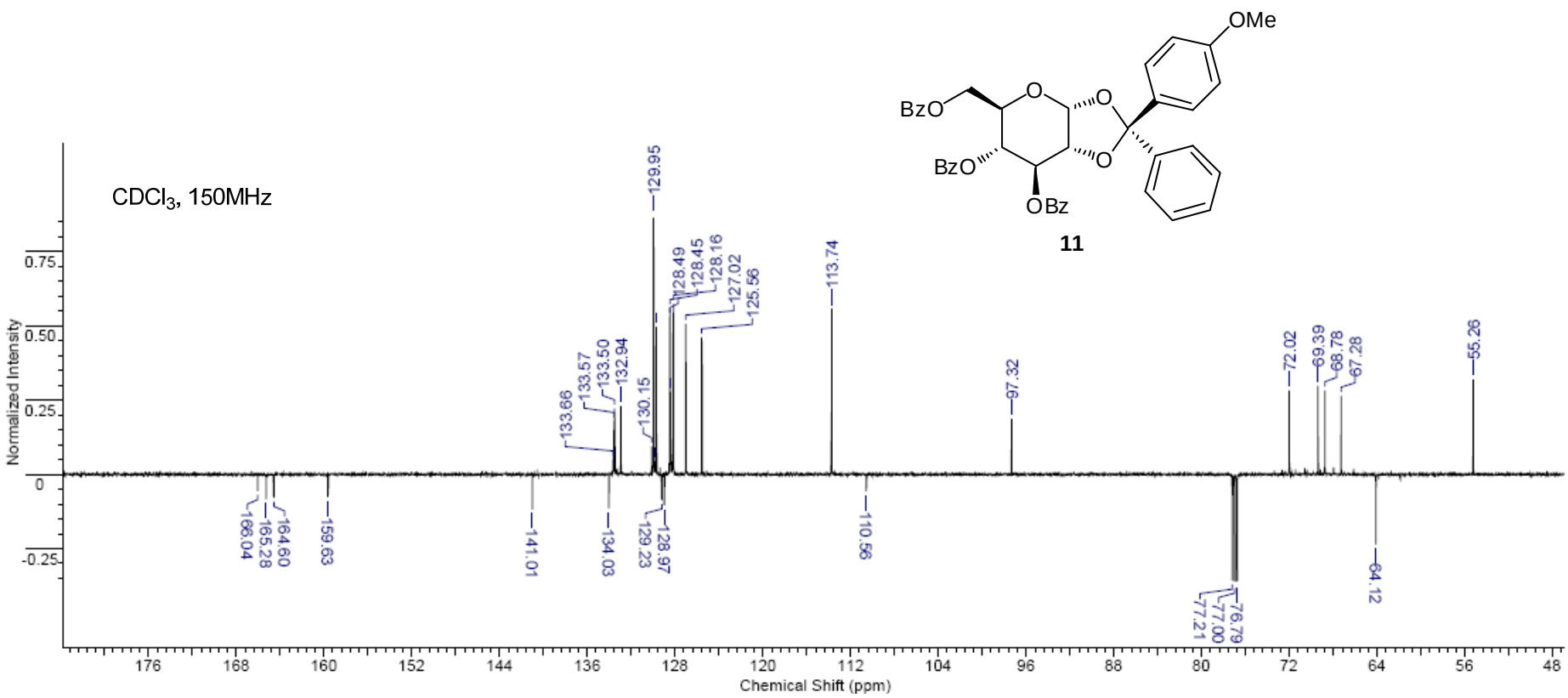

OMe
PivO
O
PivO
OPiv
OPiv
9
CDCl3, 360MHz
Normalized Intensity
Chemical Shift (ppm)
7.48
7.46
7.27
6.98
6.95
6.03
6.02
6.01
5.55
5.53
5.50
5.18
5.17
5.15
5.15
5.05
5.04
4.27
4.25
4.17
4.16
4.13
4.13
3.83
3.78
3.77
3.75
3.75
1.57
1.27
1.27
1.18
1.14
1.29
1.13
0.91
0.89
0.87
0.02
2.00
2.05
1.00
1.04
1.00
1.00
1.05
1.18
1.12
23.19
9.55
9.86
2.52


CDCl3, 90MHz
OMe
PivO
O
PivO
OPiv
OPiv
9
Normalized Intensity
1.0
0.5
0
-0.5
178.14
177.85
177.37
176.72
159.50
127.36
127.96
114.38
77.36
77.00
76.65
75.92
71.28
70.42
69.08
65.96
62.25
55.28
27.04
27.13
27.15
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


CDCl3, 400MHz
OMe
BzO
O
BzO
OBz
OBz
10
Normalized Intensity
Chemical Shift (ppm)
8.05
8.02
7.94
7.92
7.87
7.82
7.80
7.78
7.76
7.56
7.54
7.49
7.47
7.43
7.41
7.36
7.35
7.34
7.33
7.30
7.28
7.26
7.24
6.81
6.78
6.04
6.01
5.98
5.87
5.84
5.81
5.69
5.66
5.64
4.74
4.71
4.67
4.65
4.64
4.54
4.53
4.49
4.30
4.28
4.27
3.76
3.72
2.33
2.46
3.78
16.42
1.91
0.94
1.06
1.01
2.12
1.16
1.00
2.82


VerticalScaleFactor = 1
CDCl3, 100MHz
OMe
BzO
O
BzO
OBz
OBz
10
Normalized Intensity
Chemical Shift (ppm)
166.66
166.39
165.71
165.11
160.30
133.80
133.55
133.48
133.08
130.36
130.27
129.58
129.37
128.83
128.78
114.33
80.82
77.82
77.47
77.11
76.84
75.07
73.68
70.35
63.87
55.61
30.15


CDCl3, 600MHz
OMe
BzO
BzO
OBz
O
O
O
O
11
Normalized Intensity
Chemical Shift (ppm)
8.12
8.10
8.05
8.03
8.02
7.96
7.94
7.72
7.70
7.69
7.63
7.61
7.51
7.50
7.48
7.47
7.41
7.33
7.27
7.25
7.25
6.86
6.84
6.83
5.90
5.89
5.81
5.81
5.52
5.50
4.56
4.54
4.41
4.38
4.34
4.33
4.32
3.81
3.77
0.56
4.25
2.27
0.26
2.03
2.86
14.50
2.12
1.00
1.04
0.98
1.04
3.00
3.00


CDCl3, 150MHz
OMe
BzO
BzO
O
O
O
OBz
11
Normalized Intensity
0.75
0.50
0.25
0
-0.25
129.95
128.49
128.45
128.16
127.02
125.56
133.66
133.57
133.50
132.94
130.15
113.74
97.32
72.02
69.39
68.78
67.28
55.26
166.04
165.28
164.60
159.63
141.01
134.03
129.23
128.67
110.56
77.21
77.00
76.79
64.12
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
Chemical Shift (ppm)