Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Glycosylation Intermediates Studied by Low Temperature ^{1}H- and ^{19}F-DOSY NMR: New Insight into the Activation of Trichloroacetimidates.

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Electronic Supplementary Information

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S1. Materials and methods

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl fluoride (98%) and α-D-glucose pentaacetate (98%) were obtained from Aladdin Reagent Company (Shanghai). N-(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide ($TMSNTf_2$, 95%) was purchased from Tokyo Chemical Industry Co., Ltd. 1,2,3,4,5,6,7,8-Octafluoro-9,10-bis[4-(trifluoromethyl)phenyl]anthracene (97%) was purchased from Sigma Aldrich. 1,3,5-Tris(trifluoromethyl)benzene (98%), trimethylsilyl trifluoromethanesulfonate (TMSOTf, 99%), boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$, 48% BF_3), methanol (99.5%), dichloromethane-d2 (CD_2Cl_2, 99.9 atom% D) were supplied by J&K Scientific Ltd. All chemicals were used without further purification.

2-O-benzyl-3,4,6-tri-O-acetyl α-D-glucopyranosyl trichloroacetimidate **1** was synthesized.[1]

^{1}H NMR (400 MHz, CD_2Cl_2) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.74 (s, 1 H, NH); 7.35-7.28 (m, 5 H, Ar); 6.50 (d, *J* = 3.7 Hz, 1 H, H-1); 5.45 (dd, *J* = 9.7, 10.0 Hz, 1 H, H-3); 5.05 (dd, *J* = 9.7, 10.0 Hz, 1 H, H-4); 4.68 (d, *J* = 12.1 Hz, 1 H, Bn); 4.60 (d, *J* = 12.1 Hz, 1 H, Bn); 4.22-4.15 (m, 2 H, H-5, H-6a); 4.08 (bd, *J* = 10.4 Hz, 1-H, H-6b); 3.80 (dd, *J* = 3.7, 9.7 Hz, 1 H, H-2); 2.02 (s, 3 H, Ac); 2.01 (s, 3 H, Ac); 1.99 (s, 3 H, Ac)

^{13}C NMR (100 MHz, CD_2Cl_2) δ 170.9 (Ac), 170.4 (Ac), 170.1 (Ac), 161.4 (C=N), 129.0, 128.6, 128.3, 126.7 (6 C, Ar), 93.9 (C-1), 76.5 (C-2), 73.5 (Bn), 71.9 (C-3), 70.6 (C-5), 68.5 (C-4), 62.1 (C-6), 21.2 (Ac), 21.0 (2xAc).

NMR spectra were acquired on a Bruker AV-III 400 MHz NMR spectrometer (9.39 T), using a 5 mm PABBO BB/19F-1H/D probe with z gradient coil producing a maximum gradient strength of 0.50 T m^{-1}. The "doped water ($GdCl_3$ in D_2O)" was used as a standard for the gradient strength calibration. The temperature was calibrated using the NMR temperature standards according to the manuals of Bruker (4% CH_3OH in CD_3OD for low temperature).

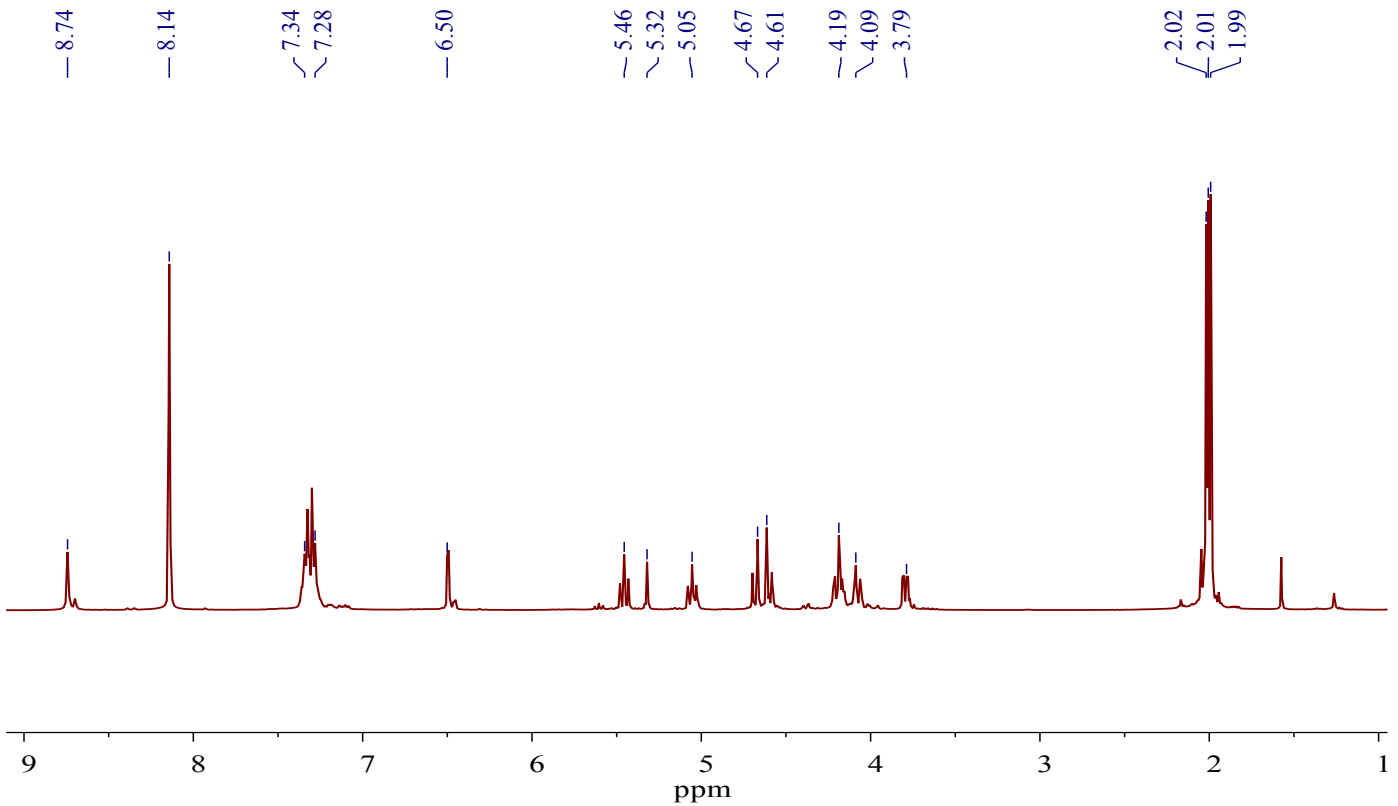
All used compounds have been measured in 0.04 M solutions of analyte and reference (in an equimolar ratio) in 400 μL CD_2Cl_2 for NMR measurement. ^{1}H NMR was obtained at frequencies of 400.13 MHz; ^{19}F NMR was obtained at frequencies of 376.47 MHz. Using the chemical shift of the CD_2Cl_2 as a reference for ^{1}H and ^{13}C NMR (at 5.32, 54 ppm). Using the chemical shift of 1,3,5-tris(trifluoromethyl)benzene signal (at -60.25 ppm) as the reference for ^{19}F NMR.[2]

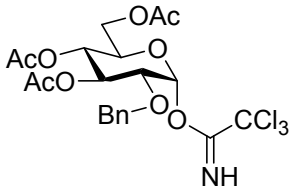
DOSY experiments were performed with the Bruker standard bipolar pulse longitudinal eddy current delay (ledbpgp2s) pulse sequence. All the DOSY measurements were performed at -55 °C without sample spinning. For each DOSY-NMR experiment, 16 BPPLED spectra with 32K date points were collected. The diffusion time (Δ) was 100 ms. The duration of the pulse field gradient (δ/2) was adjusted in a range of 600~2000 μs in order to obtain 2%~5% residual signal with the maximum gradient strength. The delay for gradient recovery was 0.2 ms and the eddy current delay was 5 ms. The gradient strength was incremented in 16 steps from 2% to 95% of its maximum value in a linear ramp. After Fourier transformation and baseline

correction, the diffusion dimension was processed using Bruker Topspin 3.1 software and the diffusion coefficients were calculated by Dynamics center 2.2.4. The diffusion coefficients of the compounds in CD_2Cl_2 were normalized to the 1,3,5-tris(trifluoromethyl)benzene signal with a fixed value of log $D_{ref,fix}$ = -9.1573.

S2. Spectra of donor 1 (2-O-benzyl-3,4,6-tri-O-acetyl α-D-glucopyranosyl trichloroacetimidate)

Figure S1. ^{1}H NMR spectrum of donor





^{1}H NMR (400 MHz, CD_2Cl_2) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.74 (s, 1 H, NH); 7.35-7.28 (m, 5H, Ar); 6.50 (d, *J* = 3.7 Hz, 1H, H-1); 5.45 (dd, *J* = 9.7, 10.0 Hz, 1H, H-3); 5.05 (dd, *J* = 9.7, 10.0 Hz, 1H, H-4); 4.68 (d, *J* = 12.1 Hz, 1H, Bn); 4.60 (d, *J* = 12.1 Hz, 1H, Bn); 4.22-4.15 (m, 2H, H-5, H-6a); 4.08 (bd, *J* = 10.4 Hz, 1H, H-6b); 3.80 (dd, *J* = 3.7, 9.7 Hz, 1H, H-2); 2.02 (s, 3H, Ac); 2.01 (s, 3 H, Ac); 1.99 (s, 3 H, Ac)

Figure S2. ^{13}C DEPT135 spectrum of donor **1**

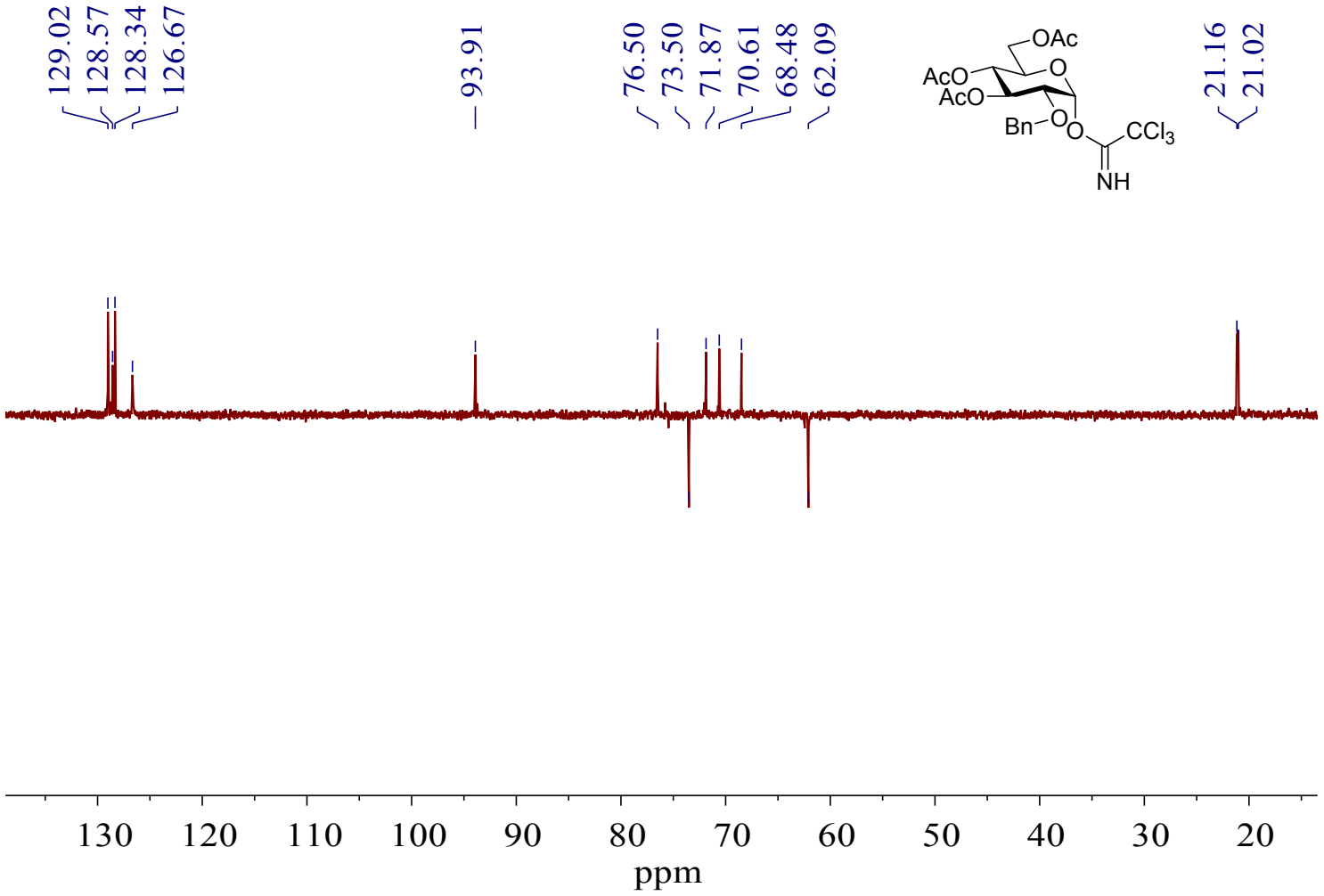
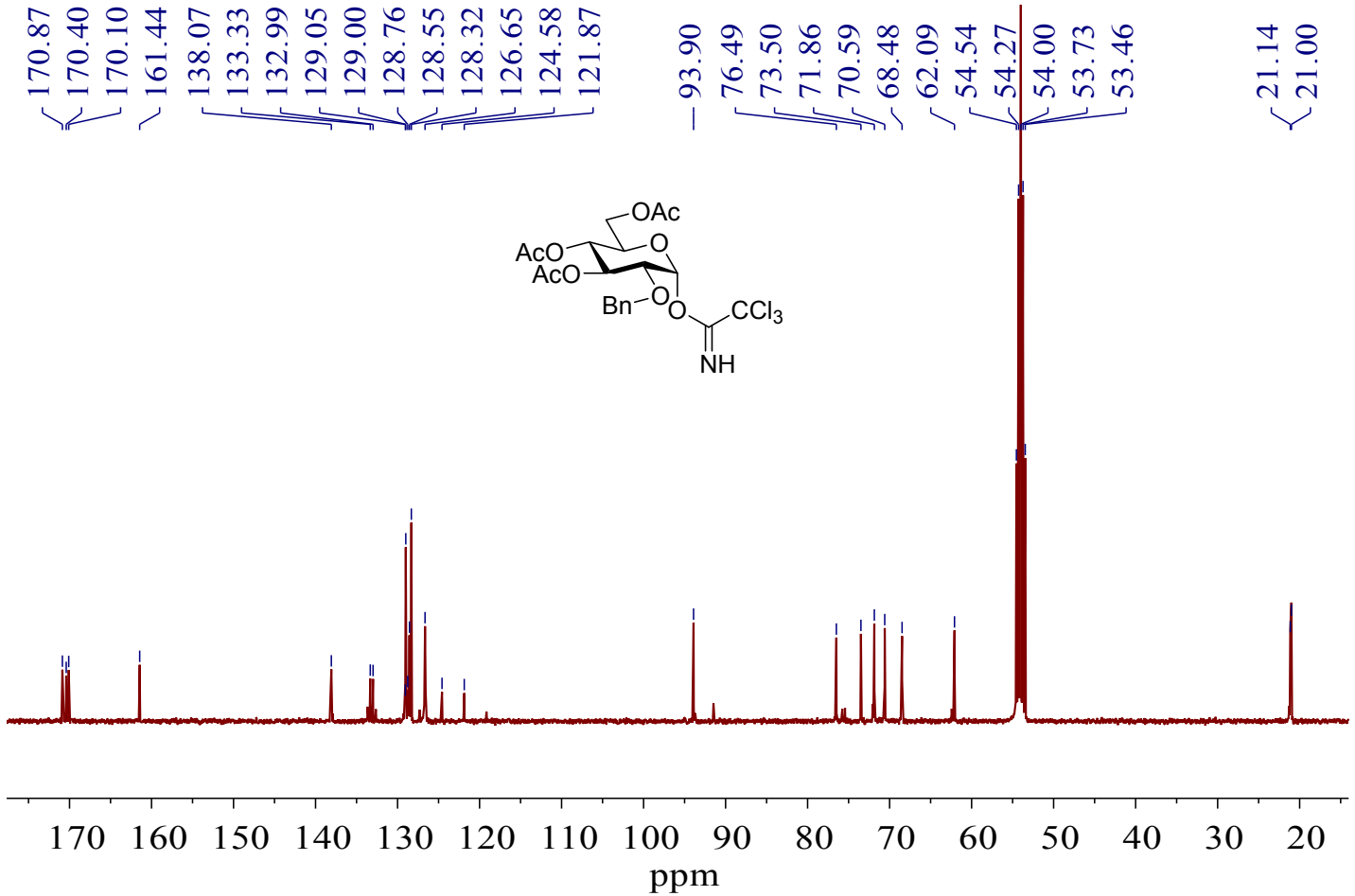


Figure S3. ^{13}C NMR spectrum of donor **1**



^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.9 (Ac), 170.4 (Ac), 170.1 (Ac), 161.4 (C=N), 129.0, 128.6, 128.3, 126.7 (6 C, Ar), 93.9 (C-1), 76.5 (C-2), 73.5 (Bn), 71.9 (C-3), 70.6 (C-5), 68.5 (C-4), 62.1 (C-6), 21.2 (Ac), 21.0 (2xAc).

Figure S4. COSY spectrum of donor **1**

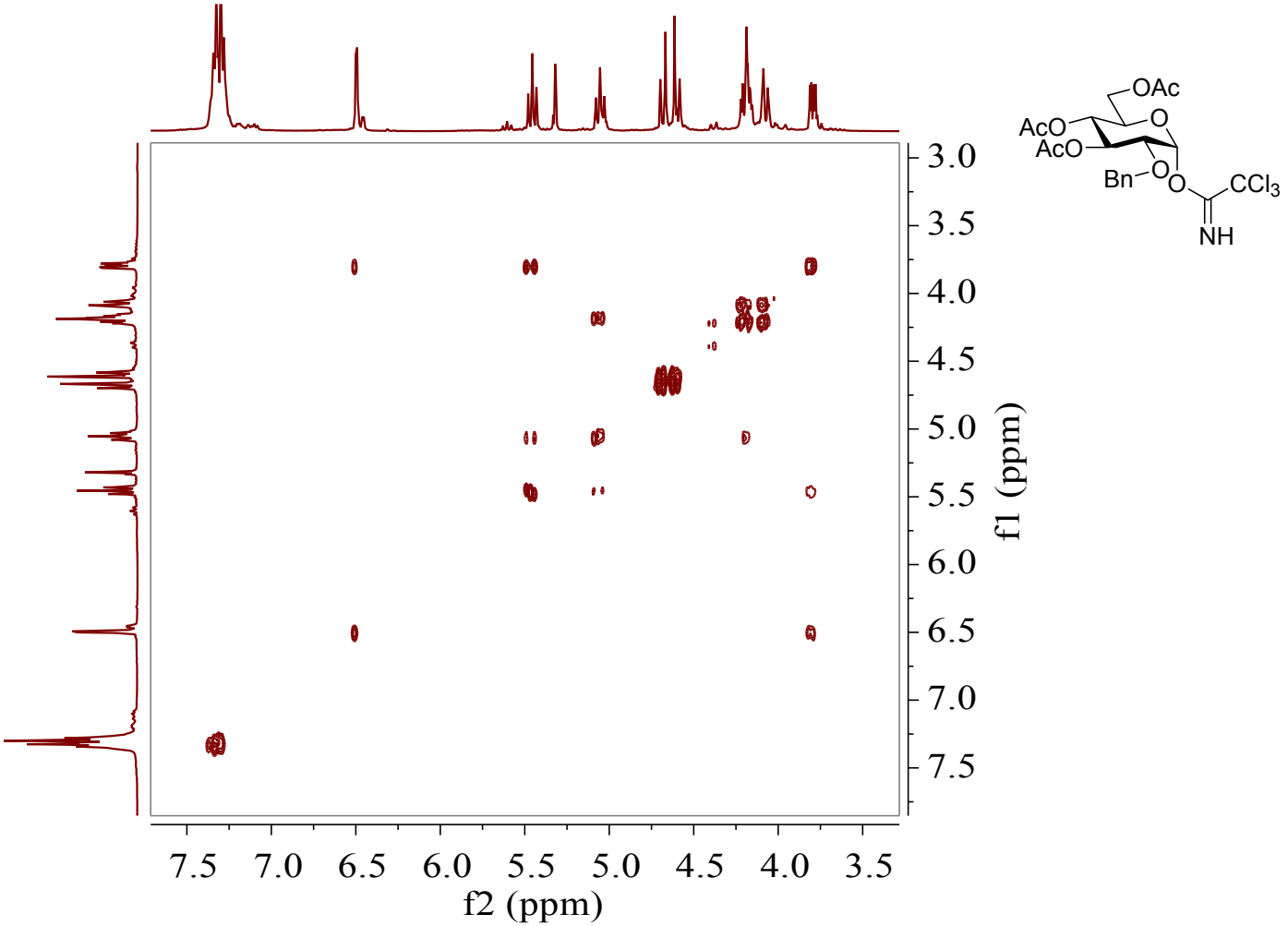
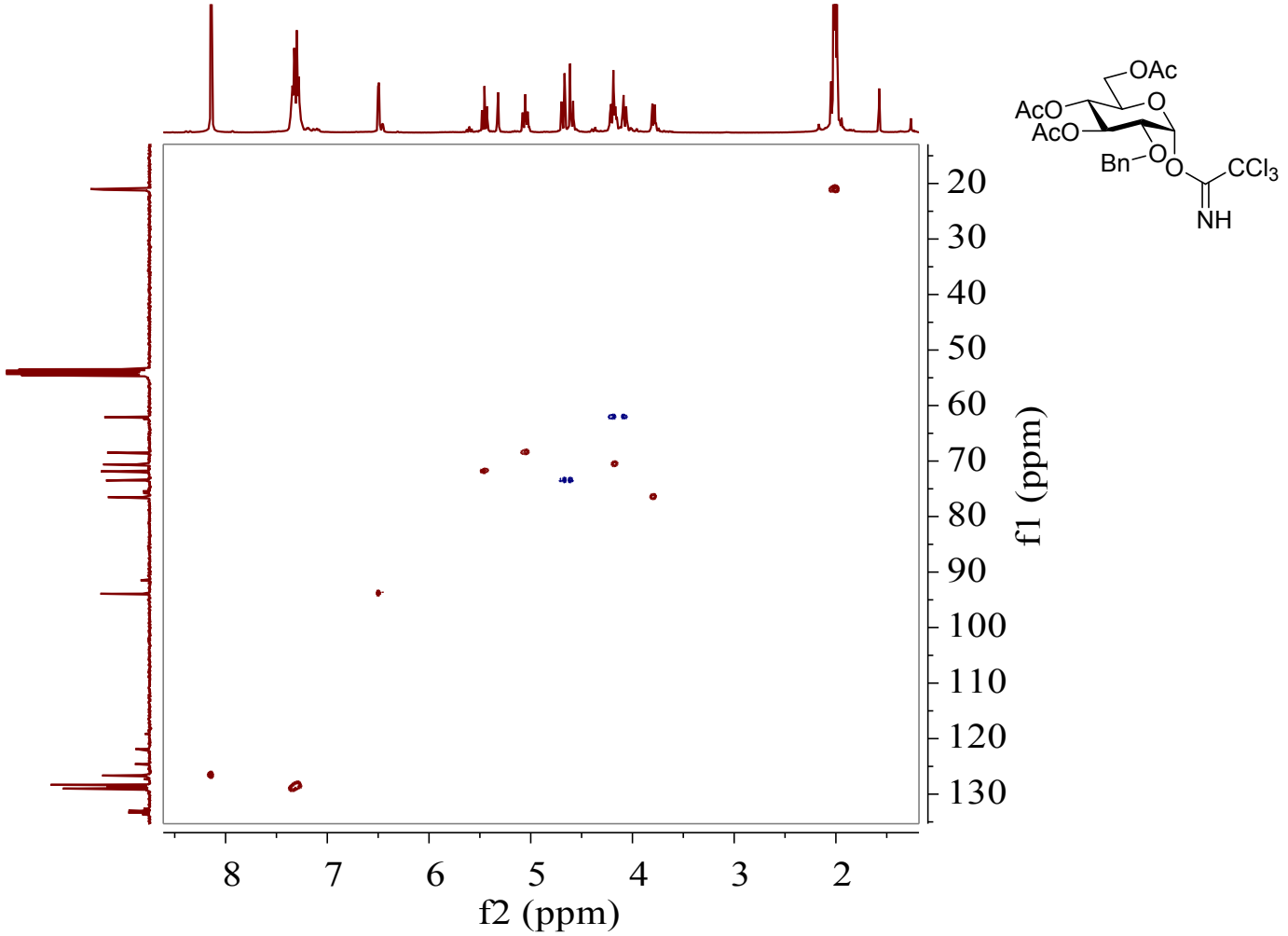


Figure S5. HSQC spectrum of donor **1**



S3. Decomposition studies of donor 1 with TMSOTf

Figure S6. ^{1}H NMR spectrum of glycosylation reactions catalyzed by TMSOTf at -55 °C

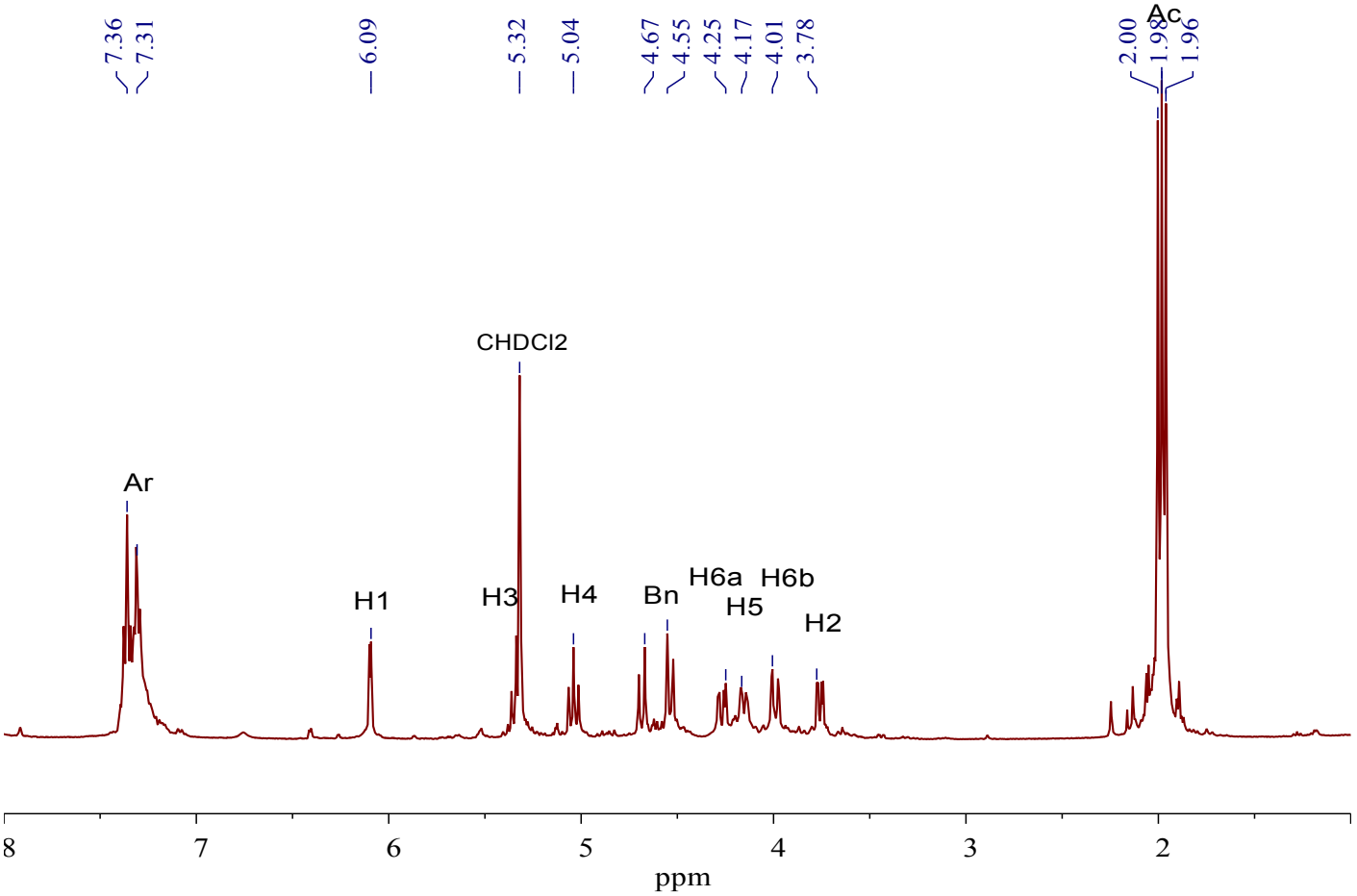


Figure S7. COSY spectrum of glycosylation reactions catalyzed by TMSOTf at -55 °C

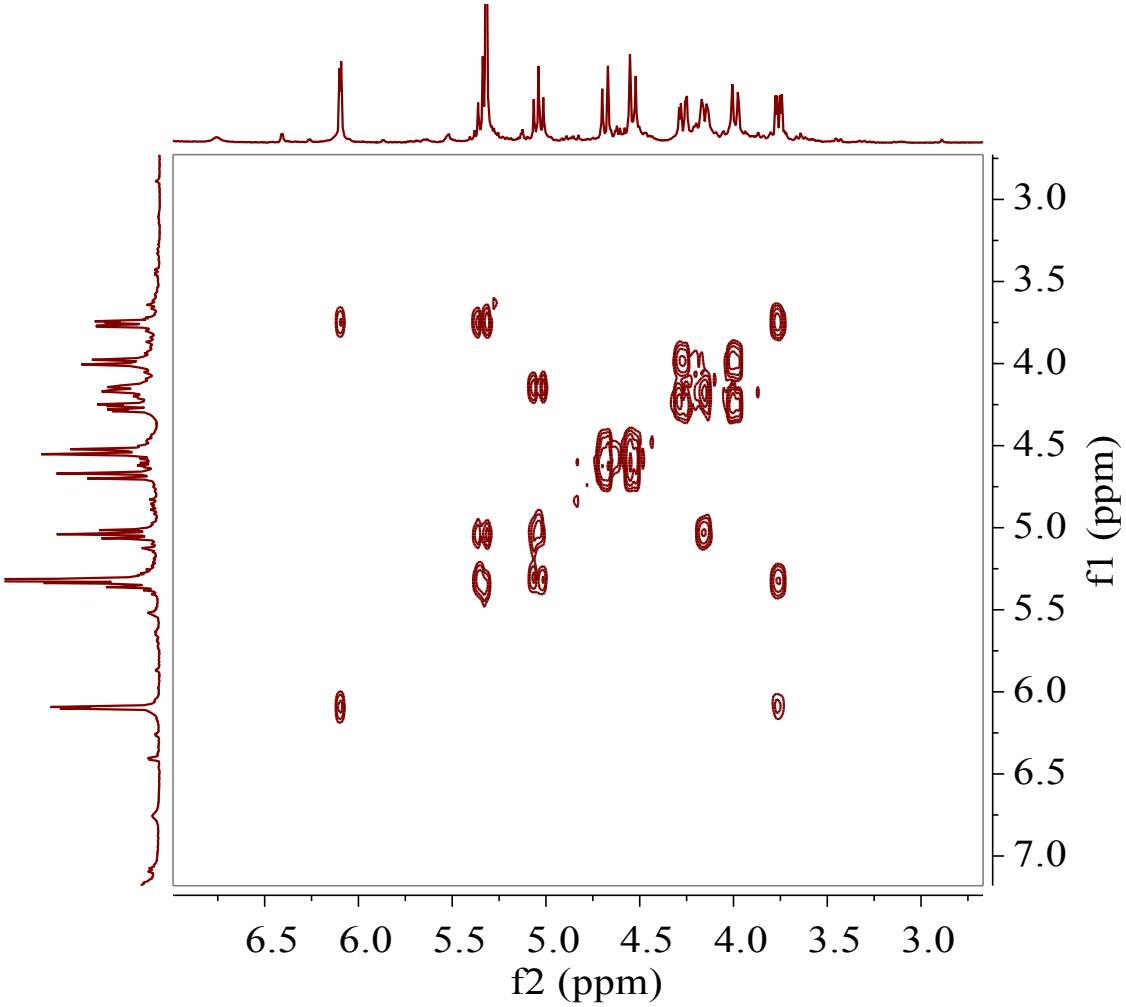


Figure S8. ^{13}C DEPT135 spectrum of glycosylation reactions catalyzed by TMSOTf at -55 °C

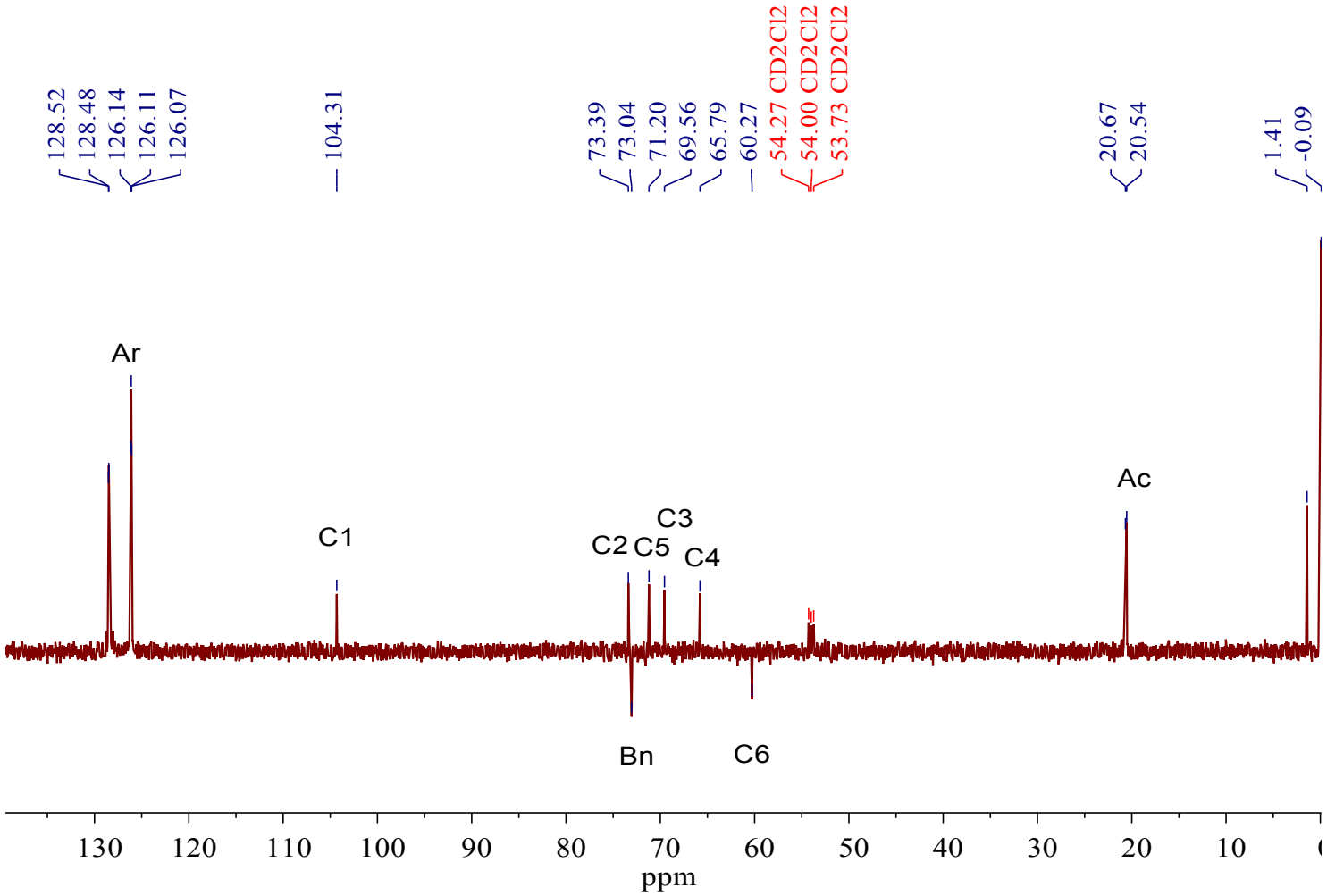


Figure S9. HSQC spectrum of glycosylation reactions catalyzed by TMSOTf at -55 °C

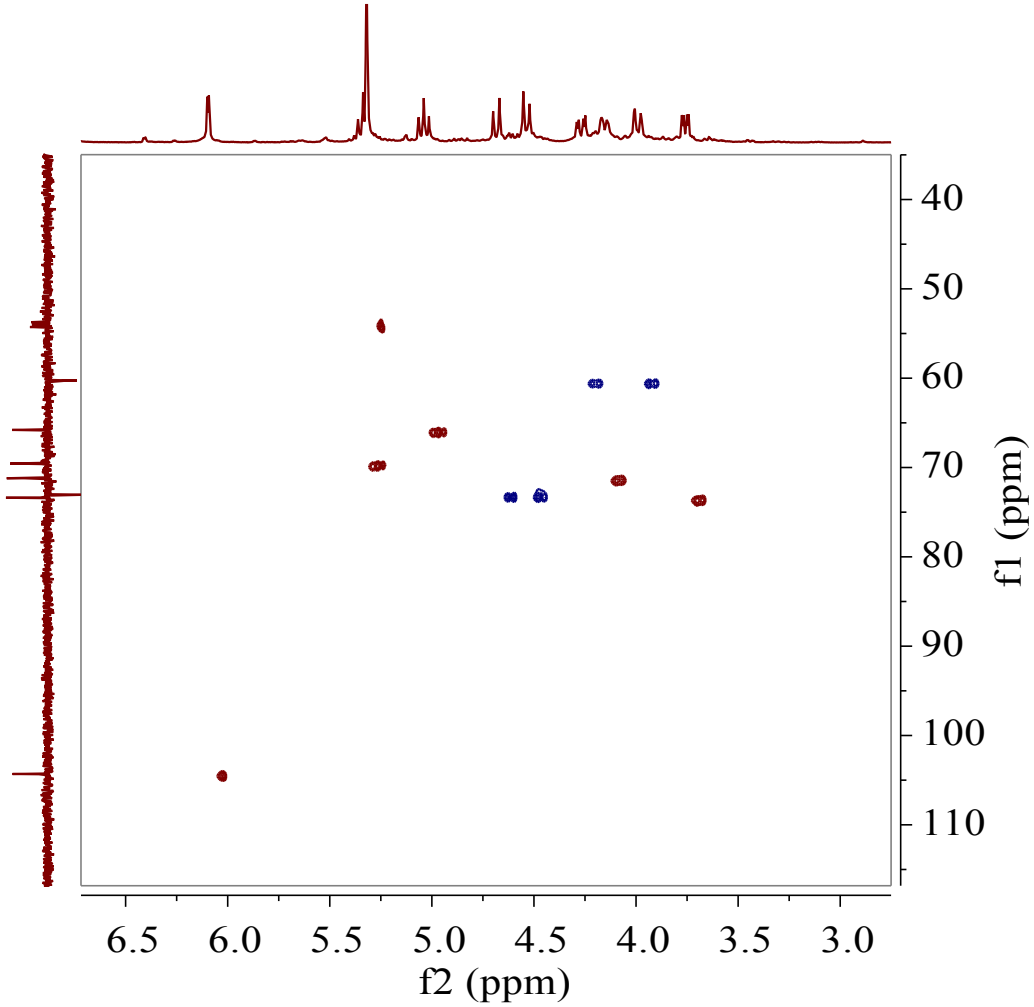


Figure S10. ^{13}C NMR spectrum of glycosylation reactions catalyzed by TMSOTf at -55 °C

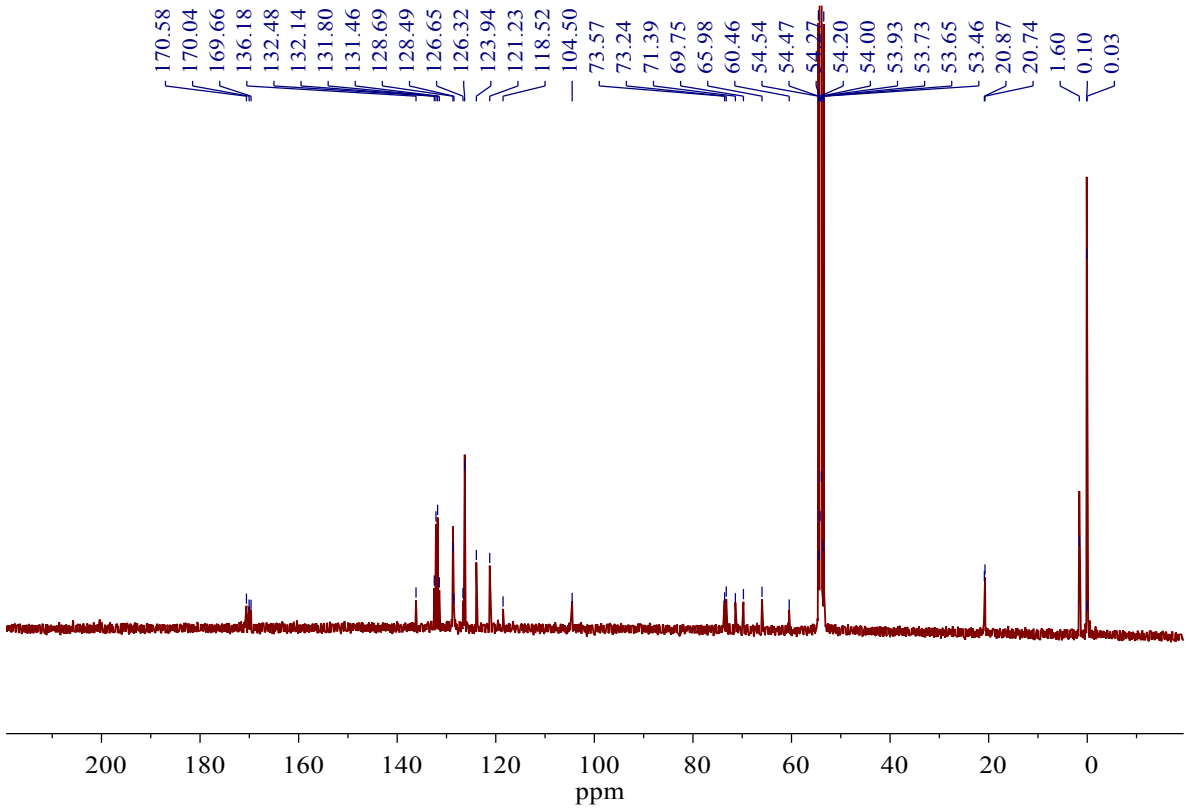


Figure S11. ^{1}H DOSY and ^{19}F DOSY spectra of glycosylation reactions catalyzed by TMSOTf at -55 °C

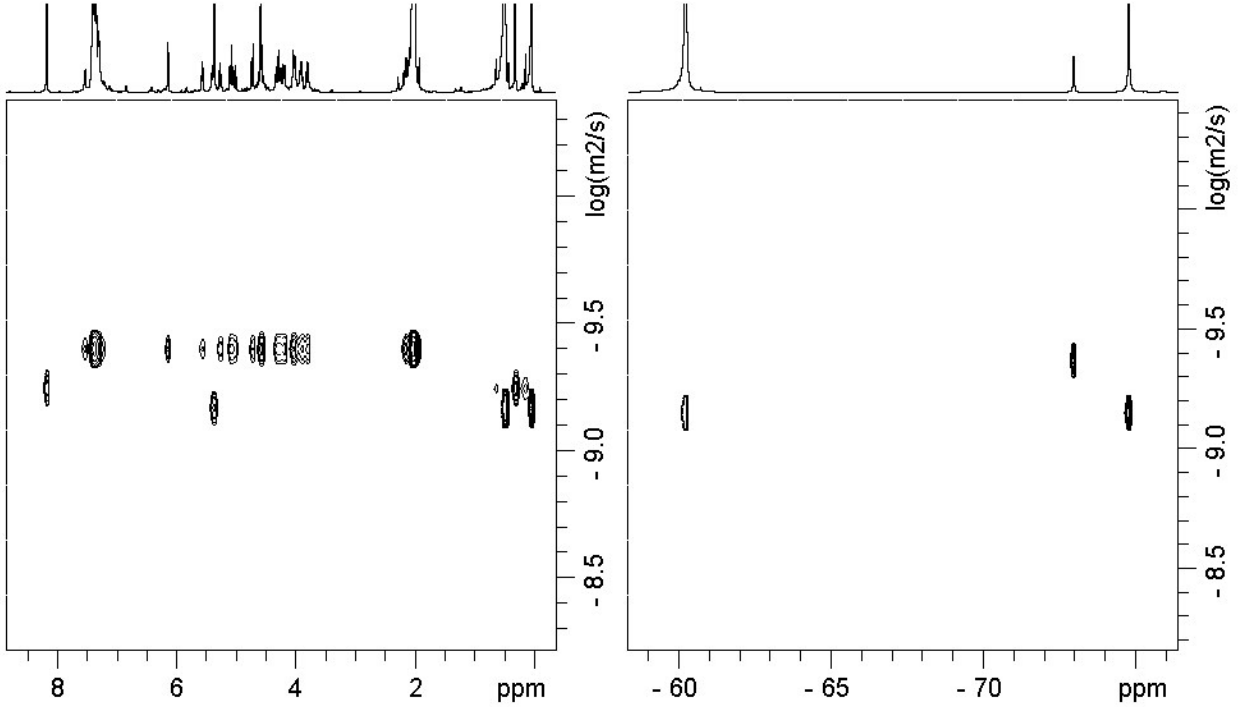
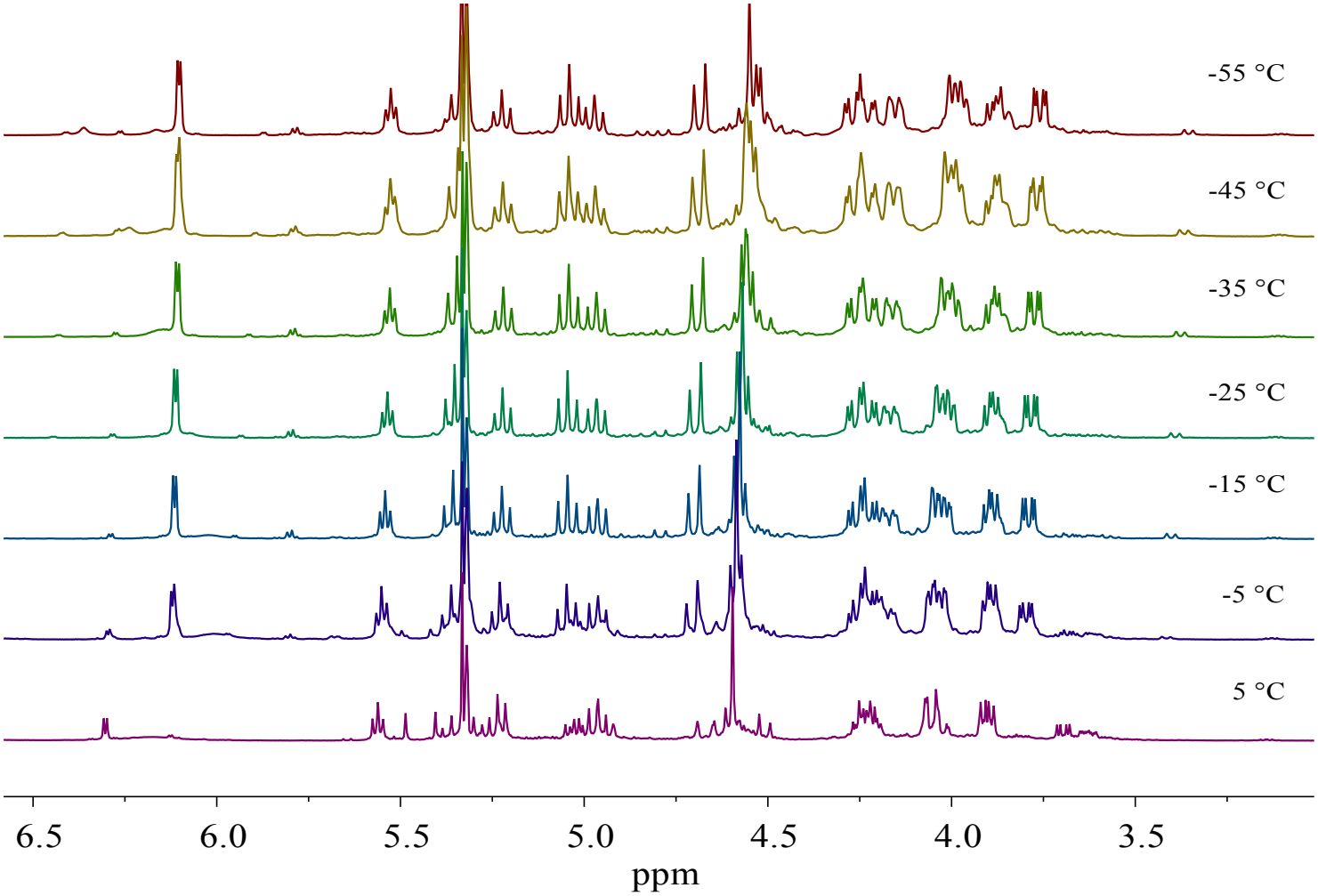


Figure S12. ^{1}H NMR spectra of glycosylation reactions catalyzed by TMSOTf from -55 °C to 5 °C



S4. Decomposition studies of donor with BF_3•OEt_2

Figure S13. ^{1}H NMR spectrum of glycosylation reactions catalyzed by BF_3·OEt_2 at -55 °C

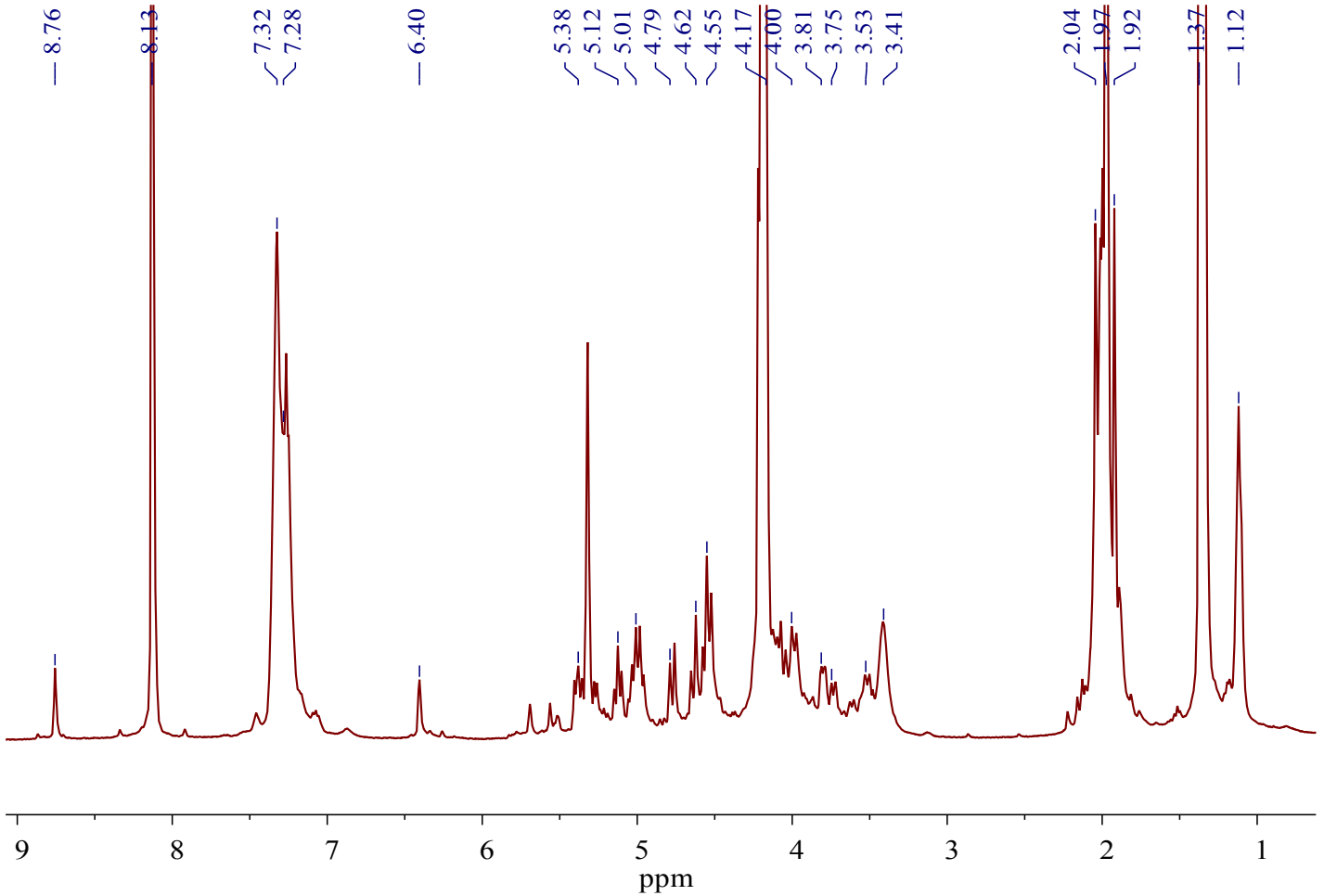


Figure S14. ^{19}F NMR spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -55 °C

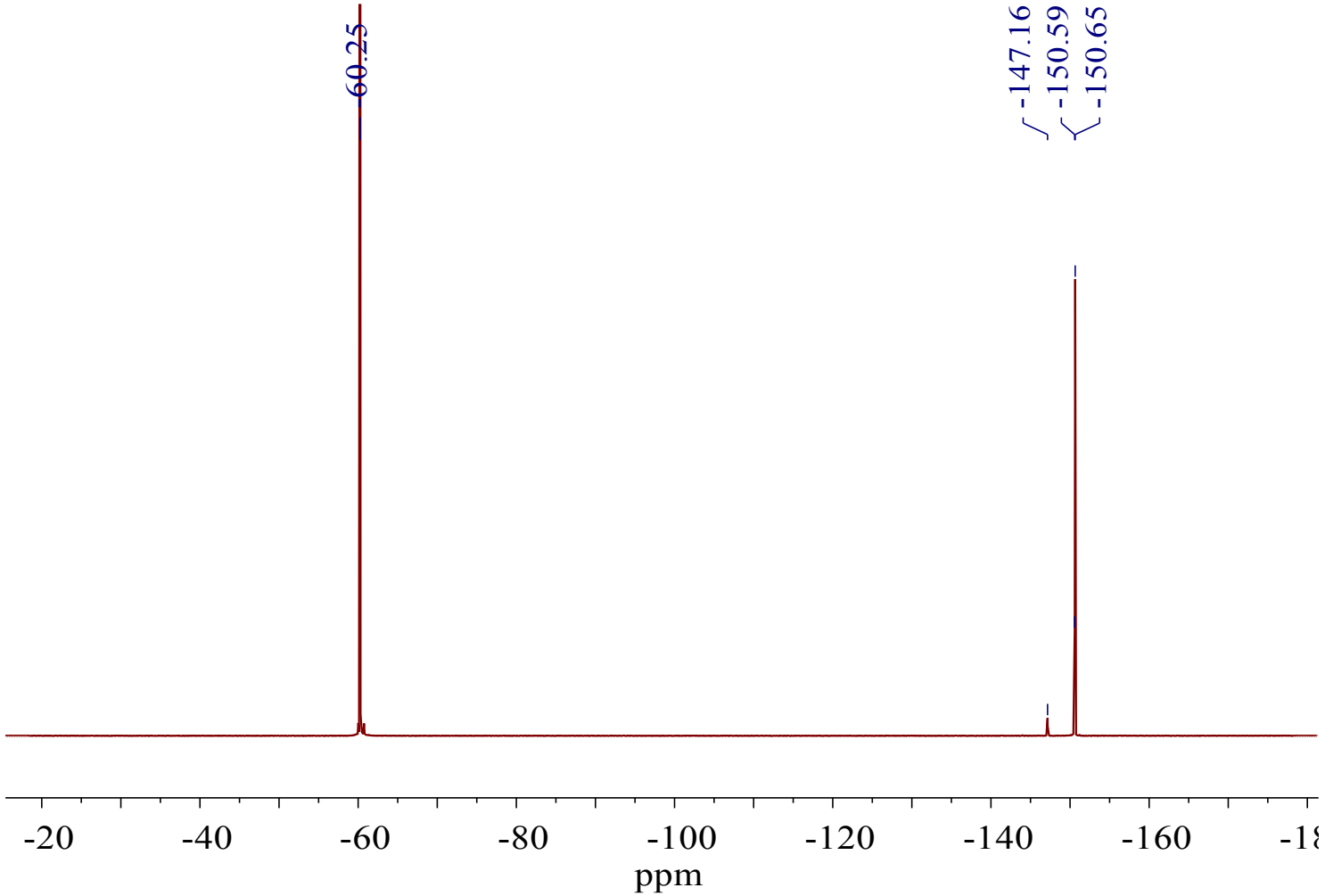


Figure S15. HSQC spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -55 °C

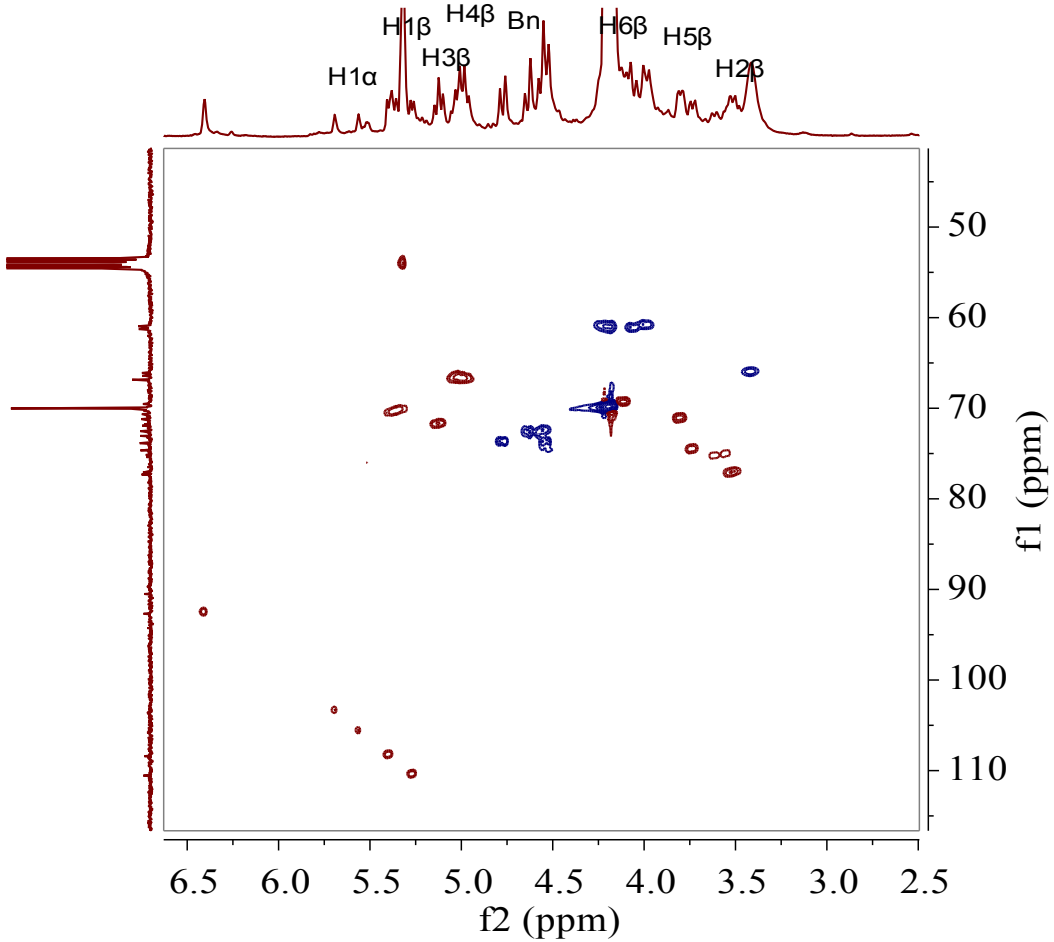


Figure S16. ^{13}C NMR spectrum of glycosylation reactions catalyzed by $BF_3 \cdot OEt_2$ at -55 °C

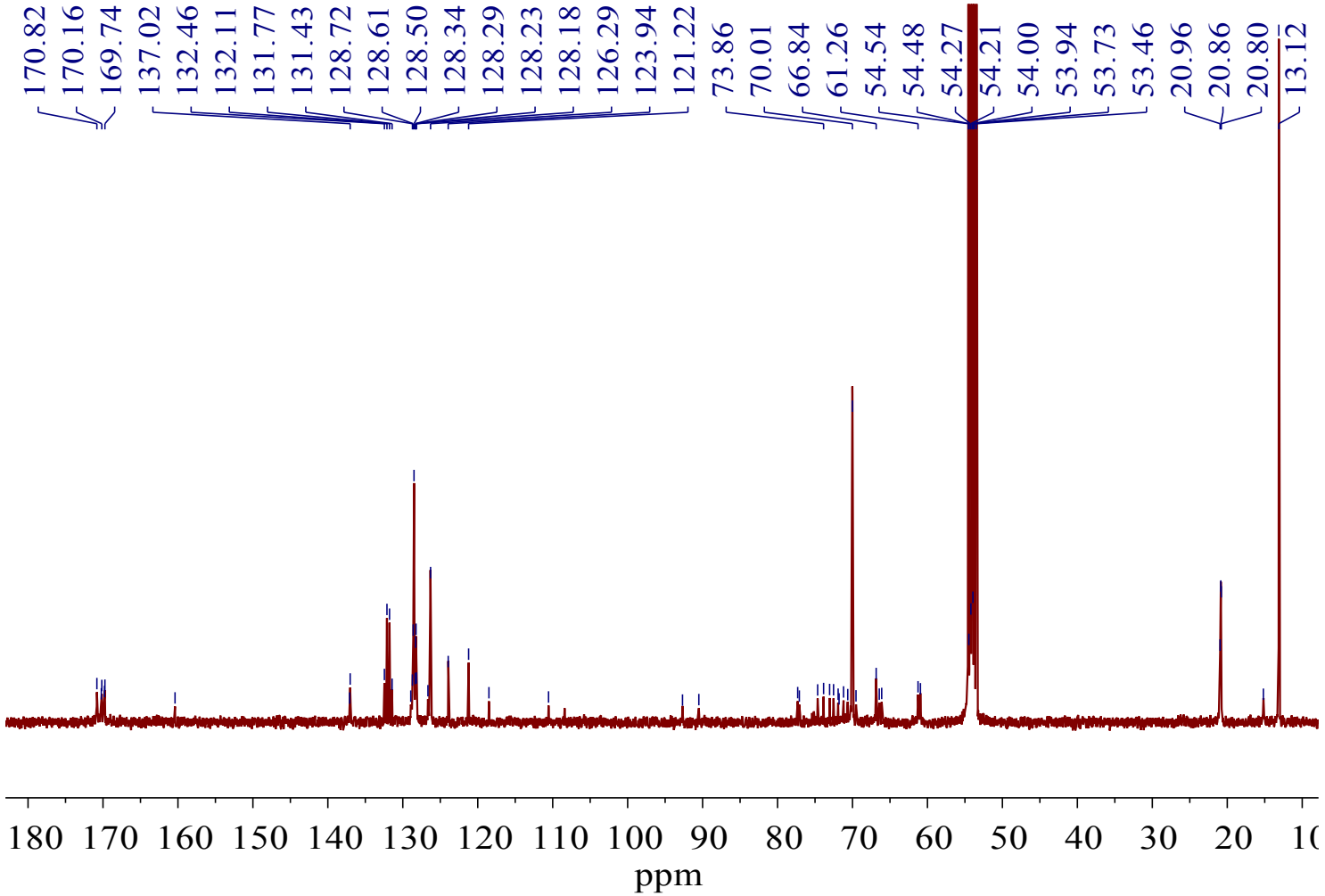


Figure S17. ^{11}B NMR spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -55 °C. Using the chemical shift of the $BF_3{\cdot}OEt_2$ as a reference (0 ppm). The peak at -1.21 ppm is characteristic for a B-O or B-N complex.

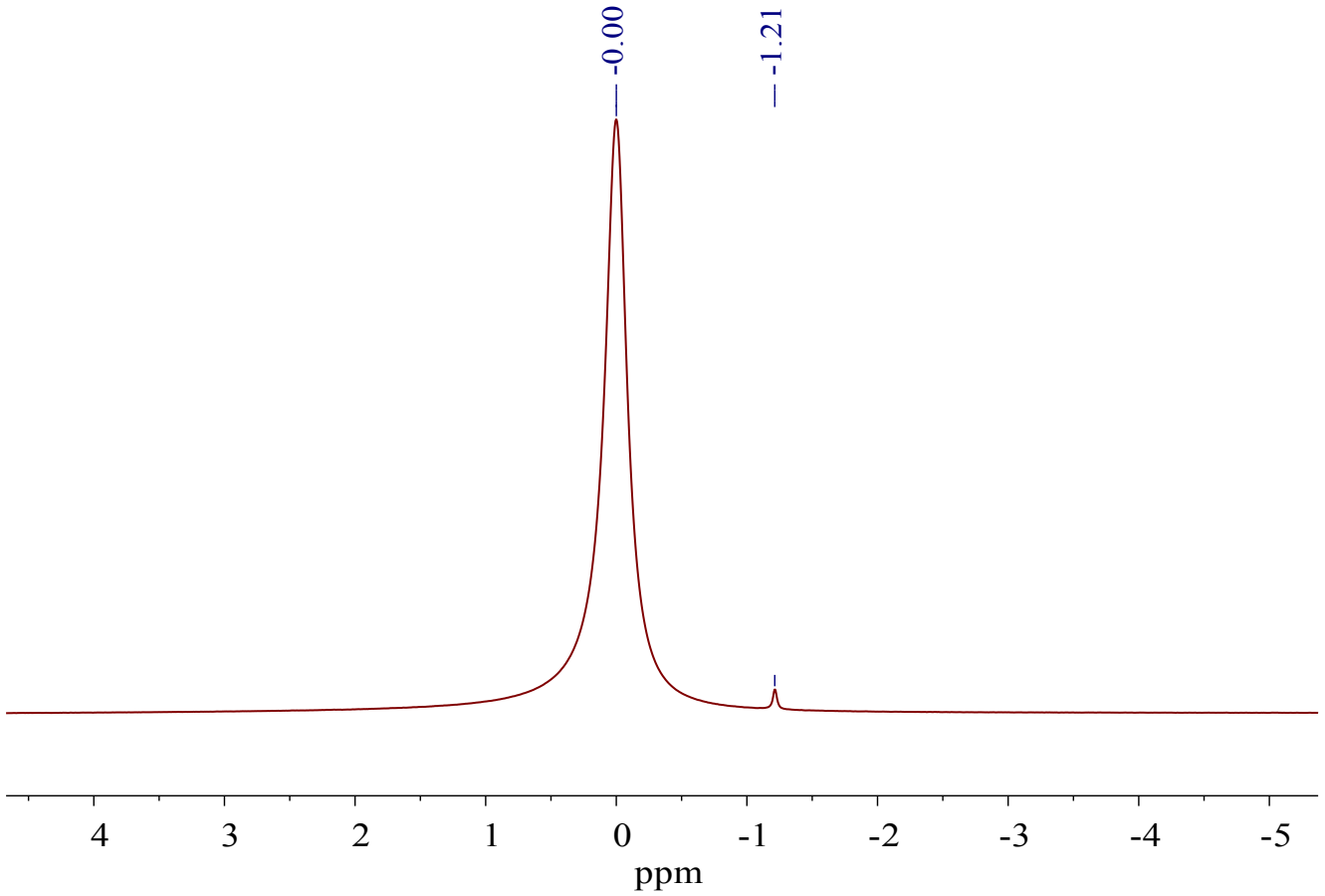


Figure S18. ^{1}H DOSY and ^{19}F DOSY spectra of glycosylation reactions catalyzed by $BF_3 \cdot OEt_2$ at -55 °C

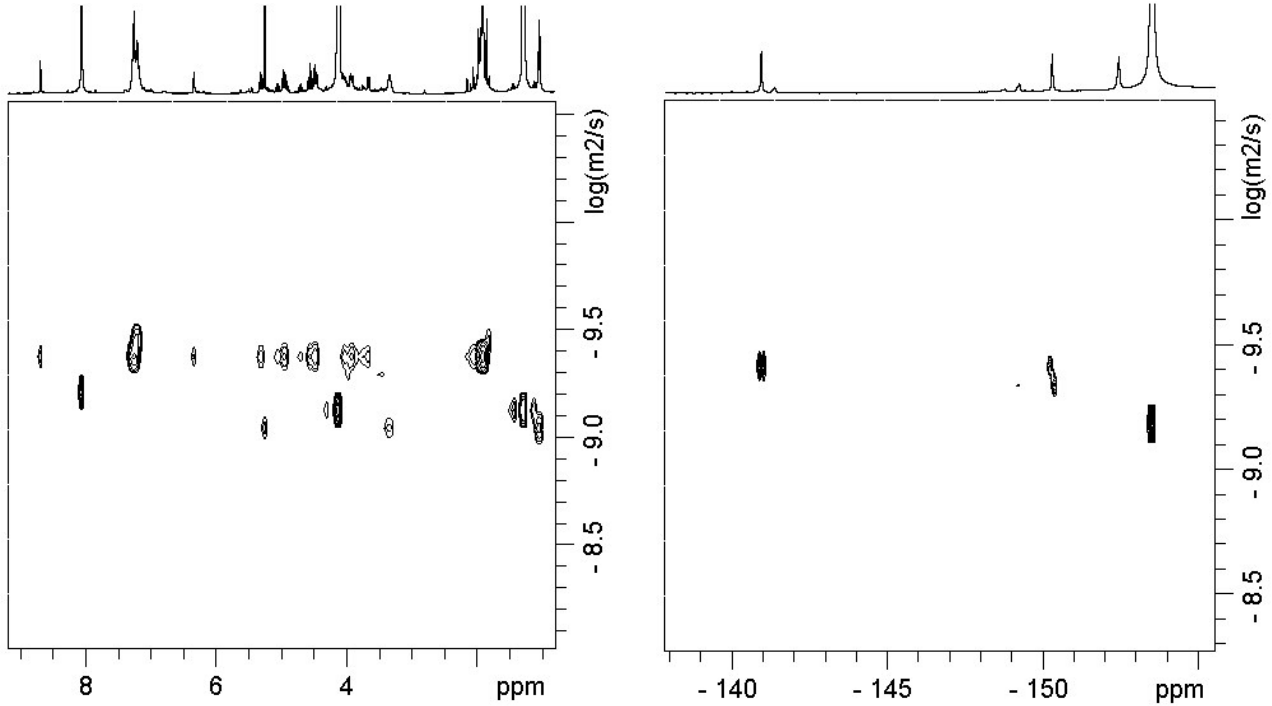


Figure S19. ^{1}H NMR spectra of glycosylation reactions catalyzed by $BF_3 \cdot OEt_2$ from -55 °C to -15 °C

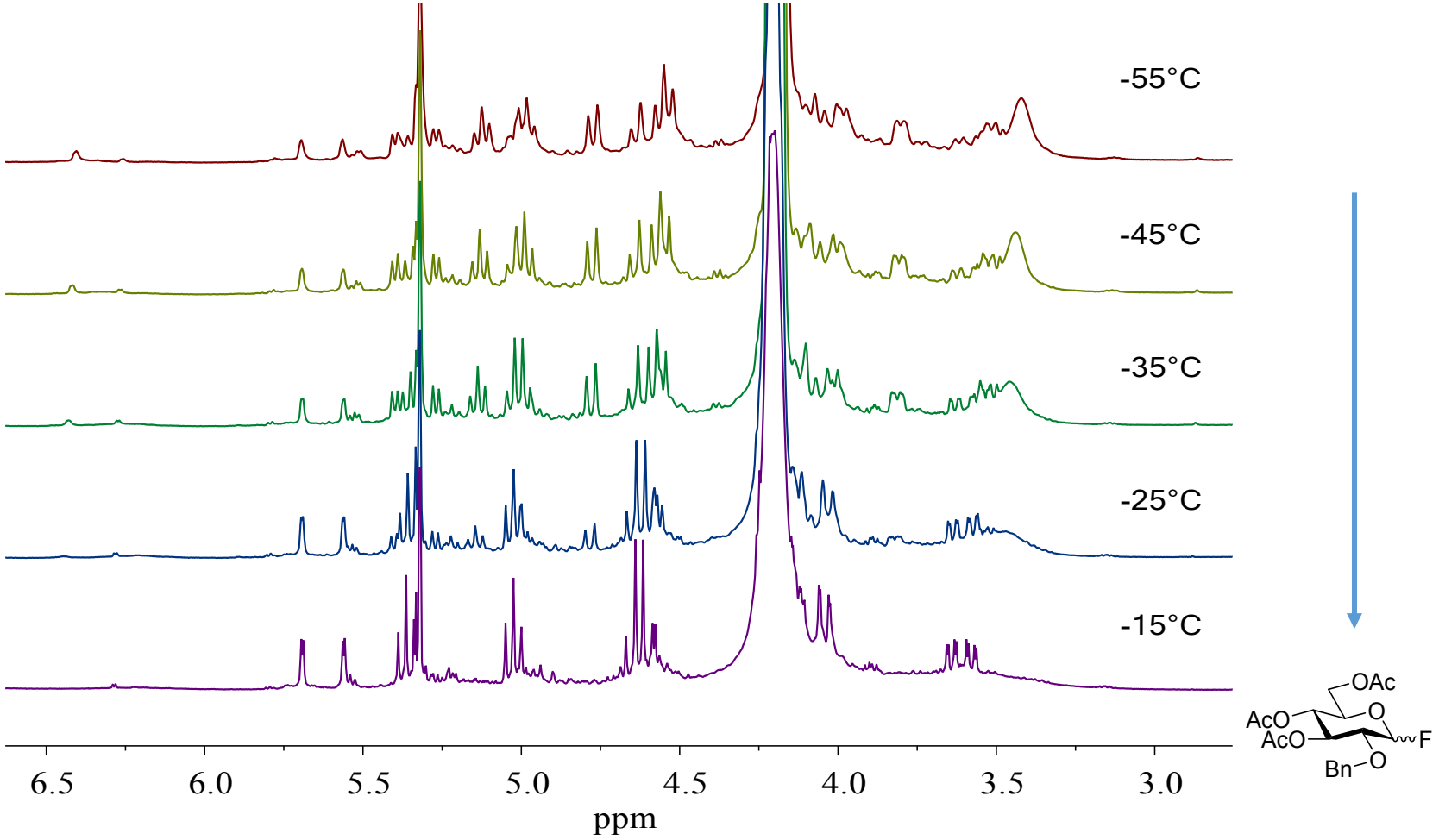


Figure S20. COSY spectrum of glycosylation reactions catalyzed by $BF_3 \cdot OEt_2$ at -15 °C

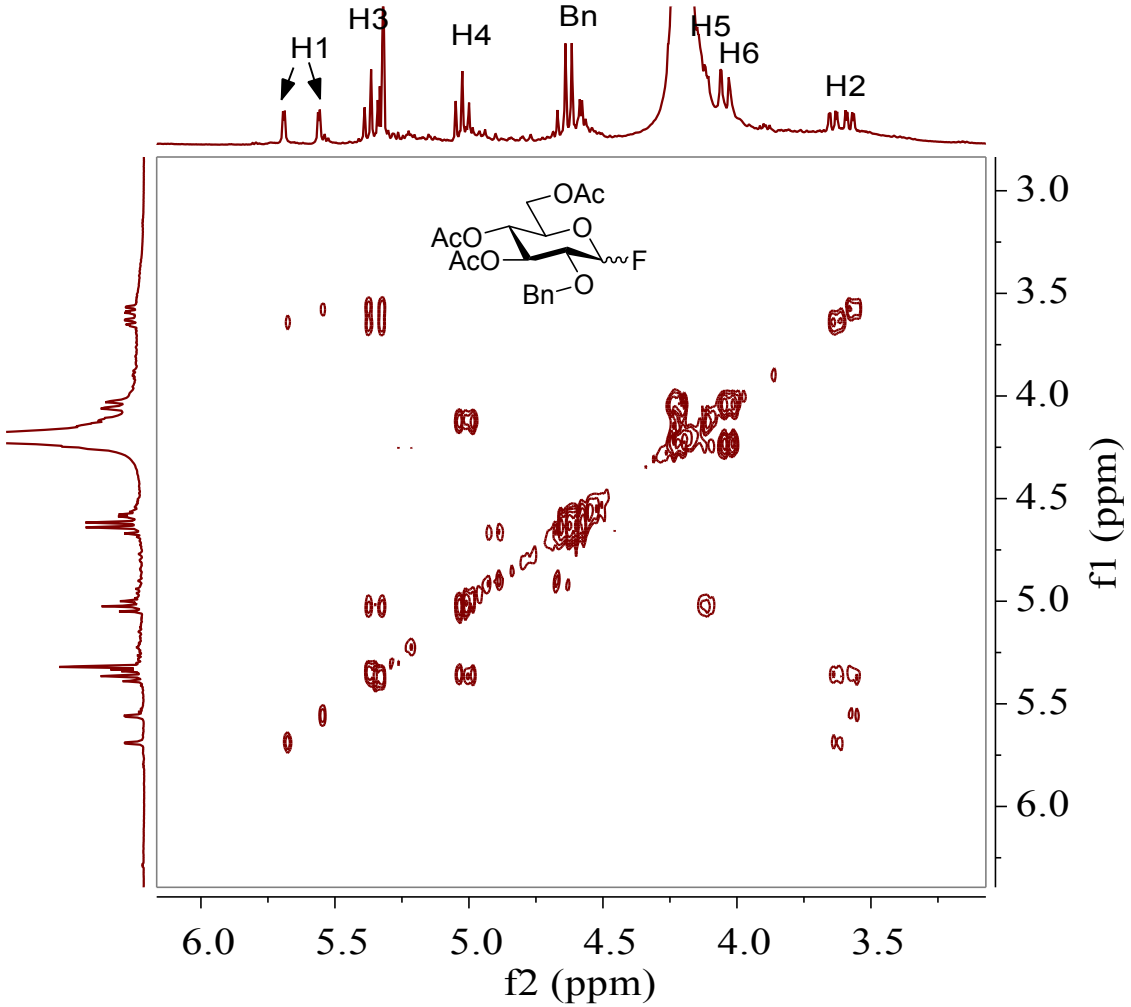


Figure S21. ^{13}C DEPT135 spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -15 °C

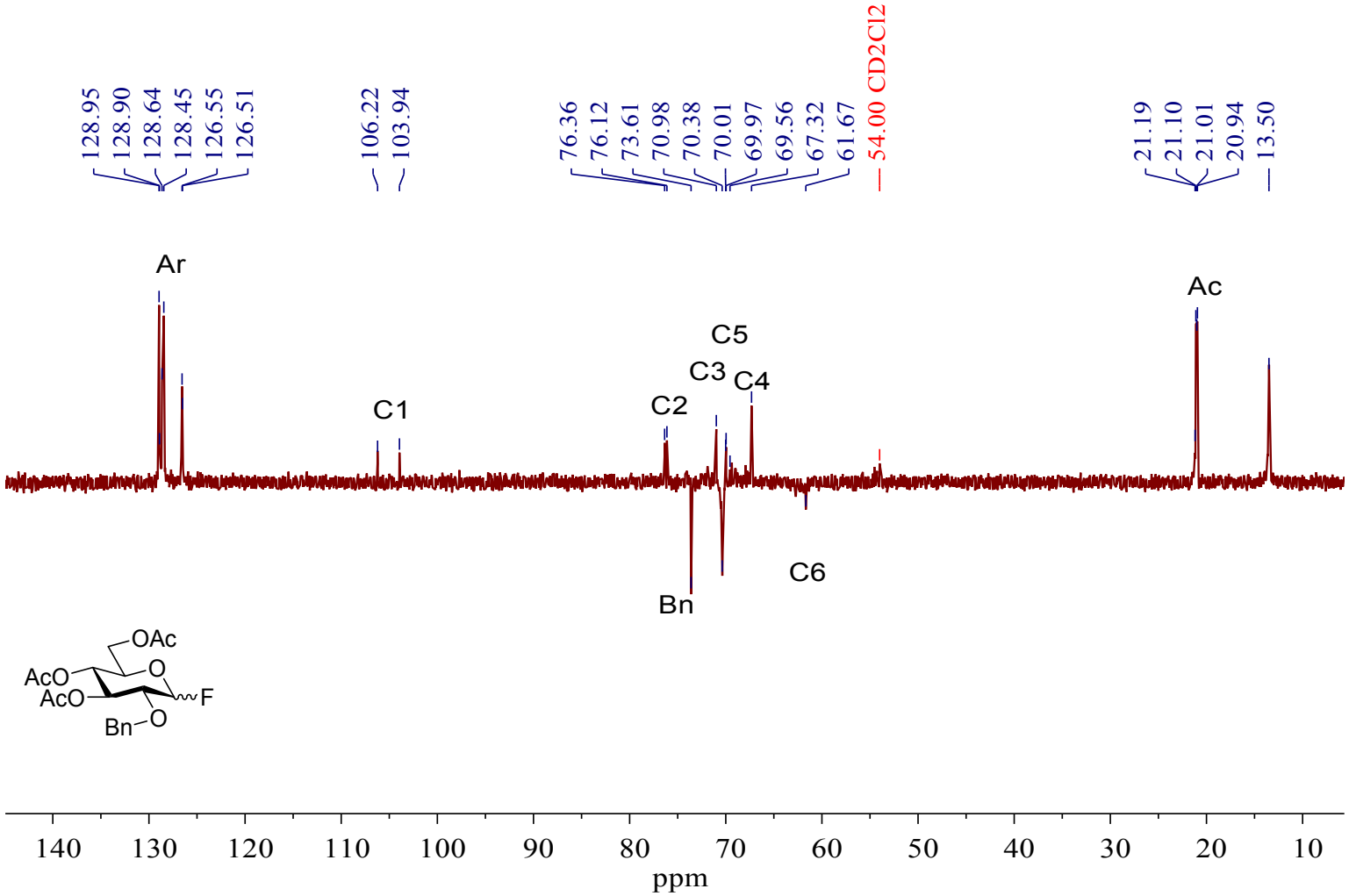


Figure S22. HSQC spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -15 °C

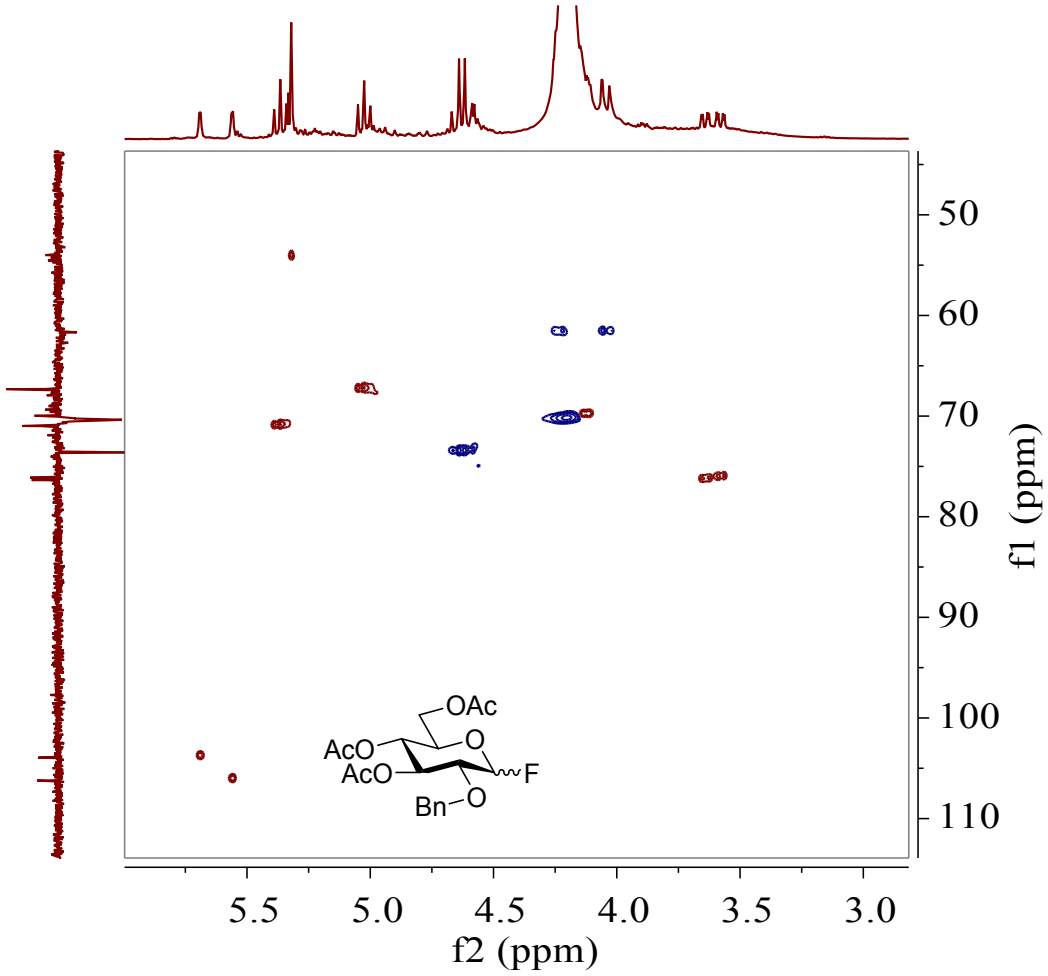


Figure S23. ^{19}F NMR spectrum of glycosylation reactions catalyzed by $BF_3{\cdot}OEt_2$ at -15 °C

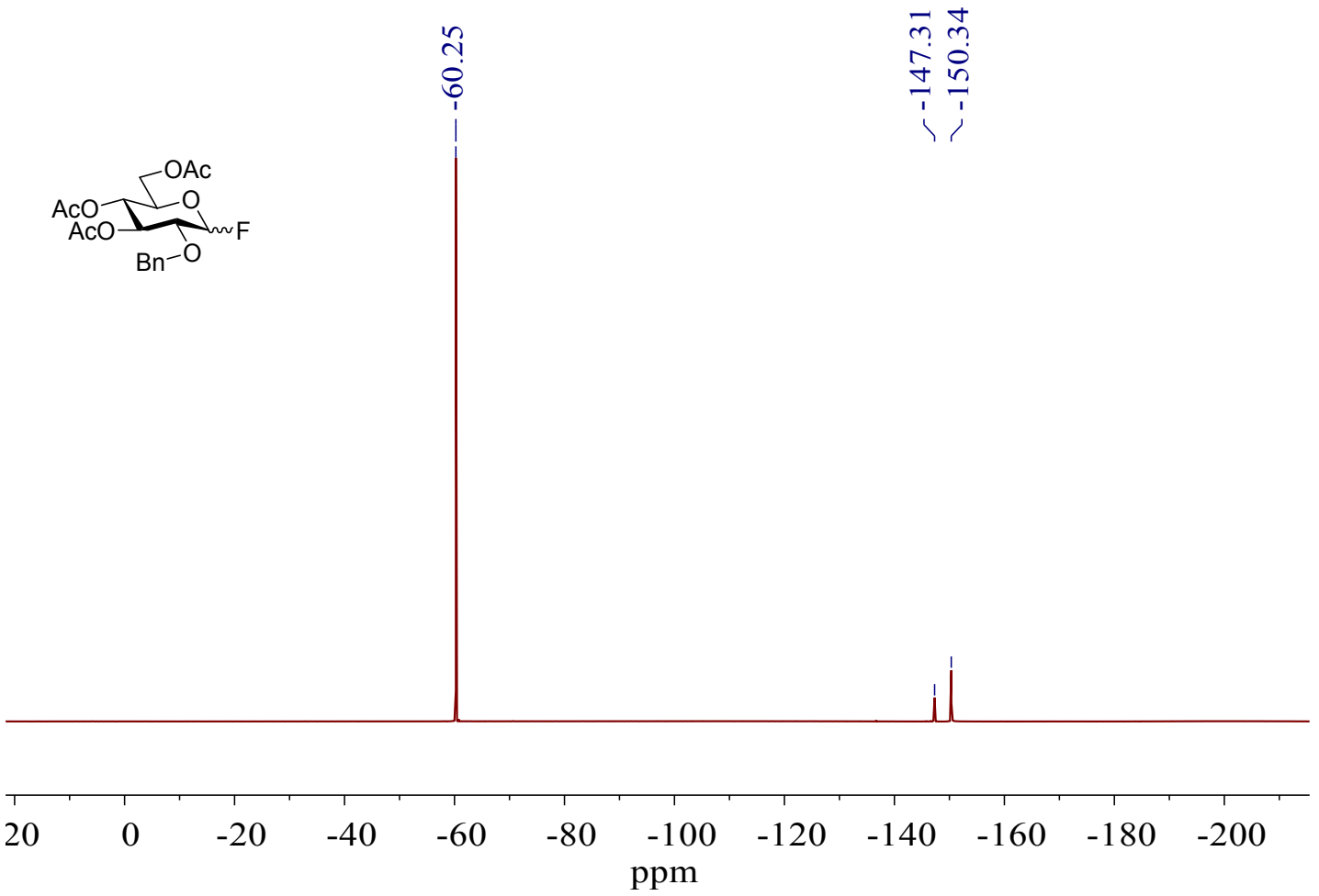
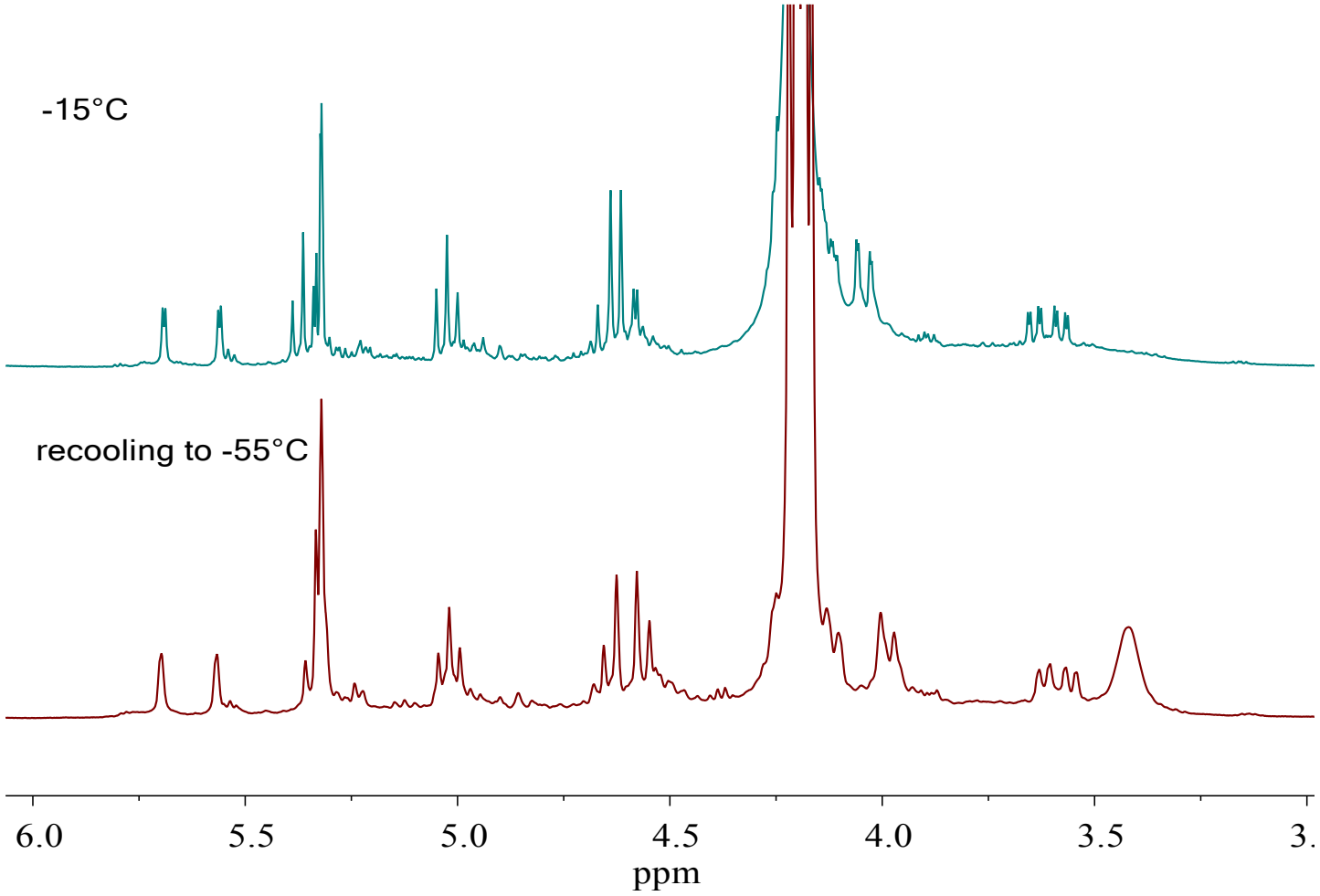


Figure S24. ^{1}H NMR spectra of glycosylation reactions catalyzed by $BF_3 \cdot OEt_2$ at -15 °C and recooling to -55 °C



S5. Decomposition studies of donor with $TMSNTf_2$

Figure S25. ^1H NMR spectra of $TMSNTf_2$ in CD_2Cl_2 at -55 °C

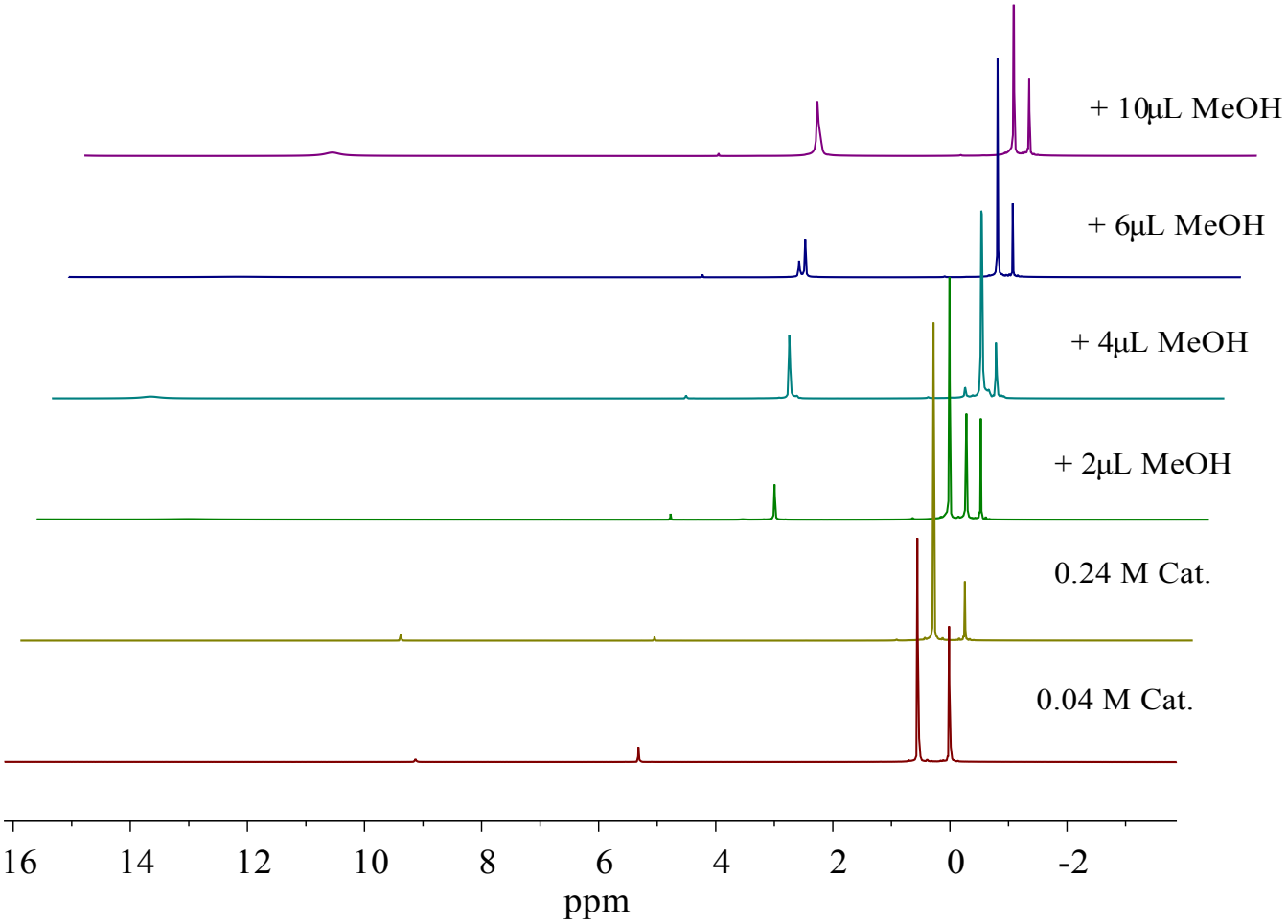


Figure S26. ^{19}F NMR spectra of $TMSNTf_2$ in CD_2Cl_2 at -55 °C

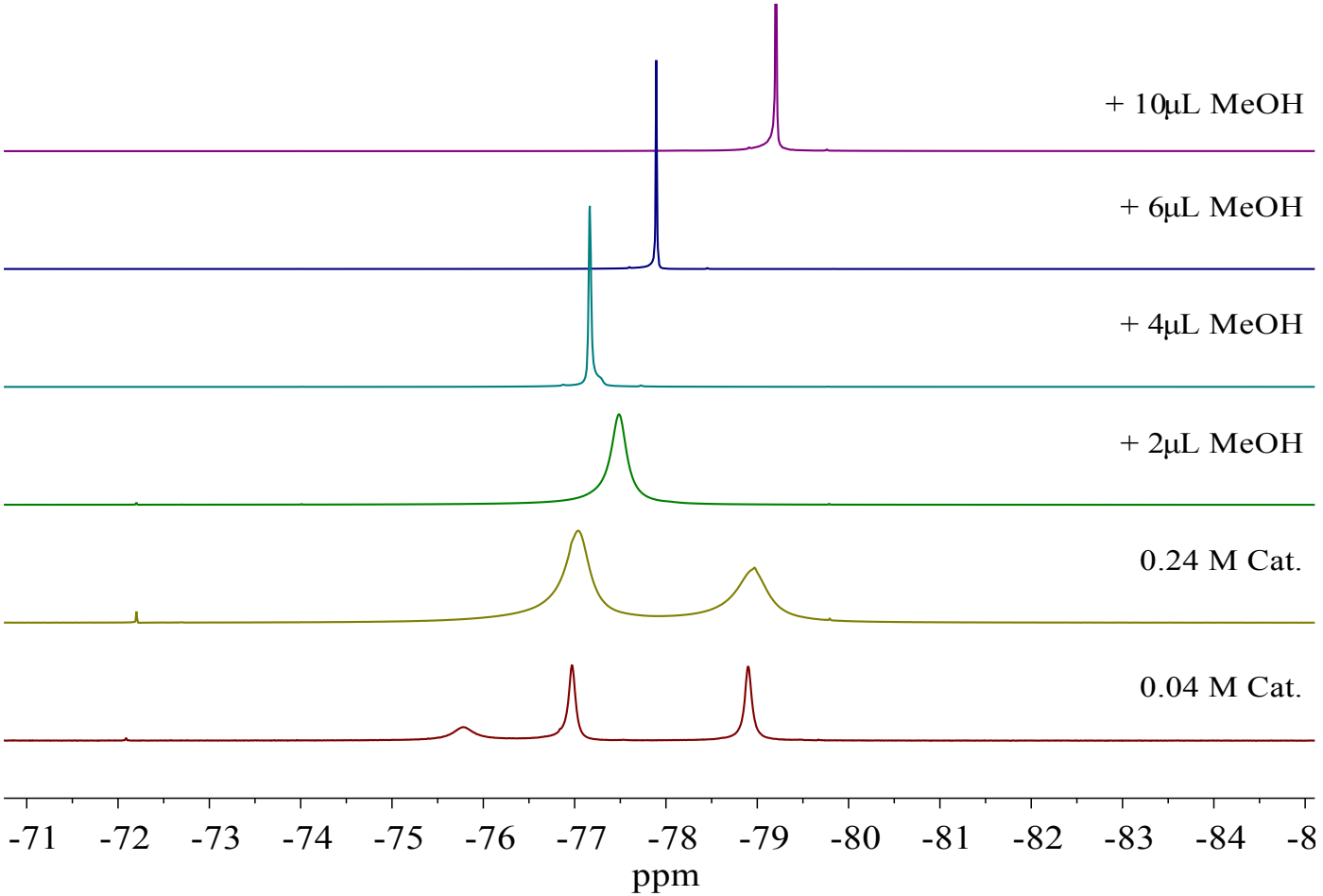


Figure S27. ^{1}H NMR spectra of glycosylation reactions catalyzed by $TMSNTf_2$ from 0 min to 30 min at -55 °C

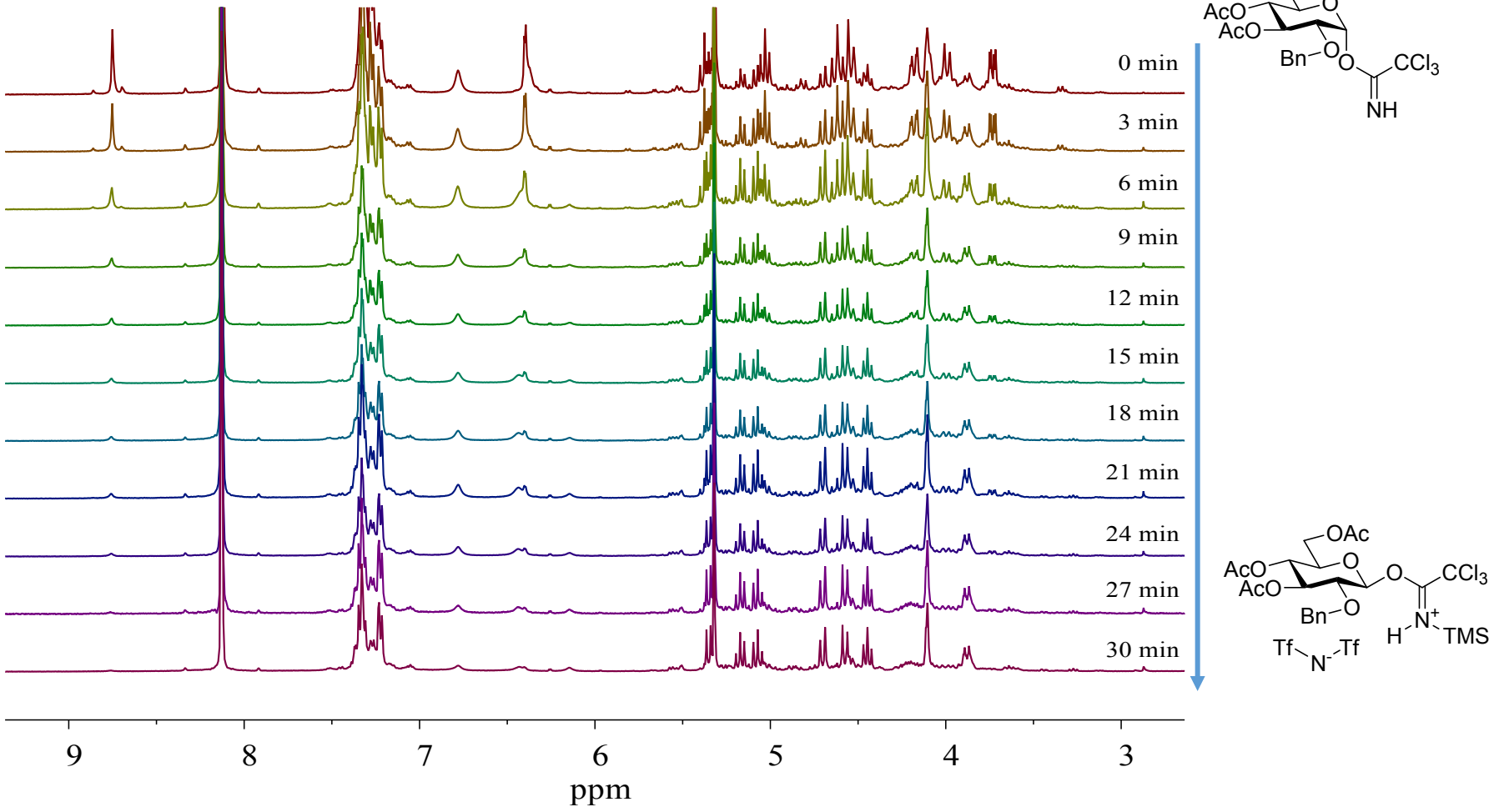
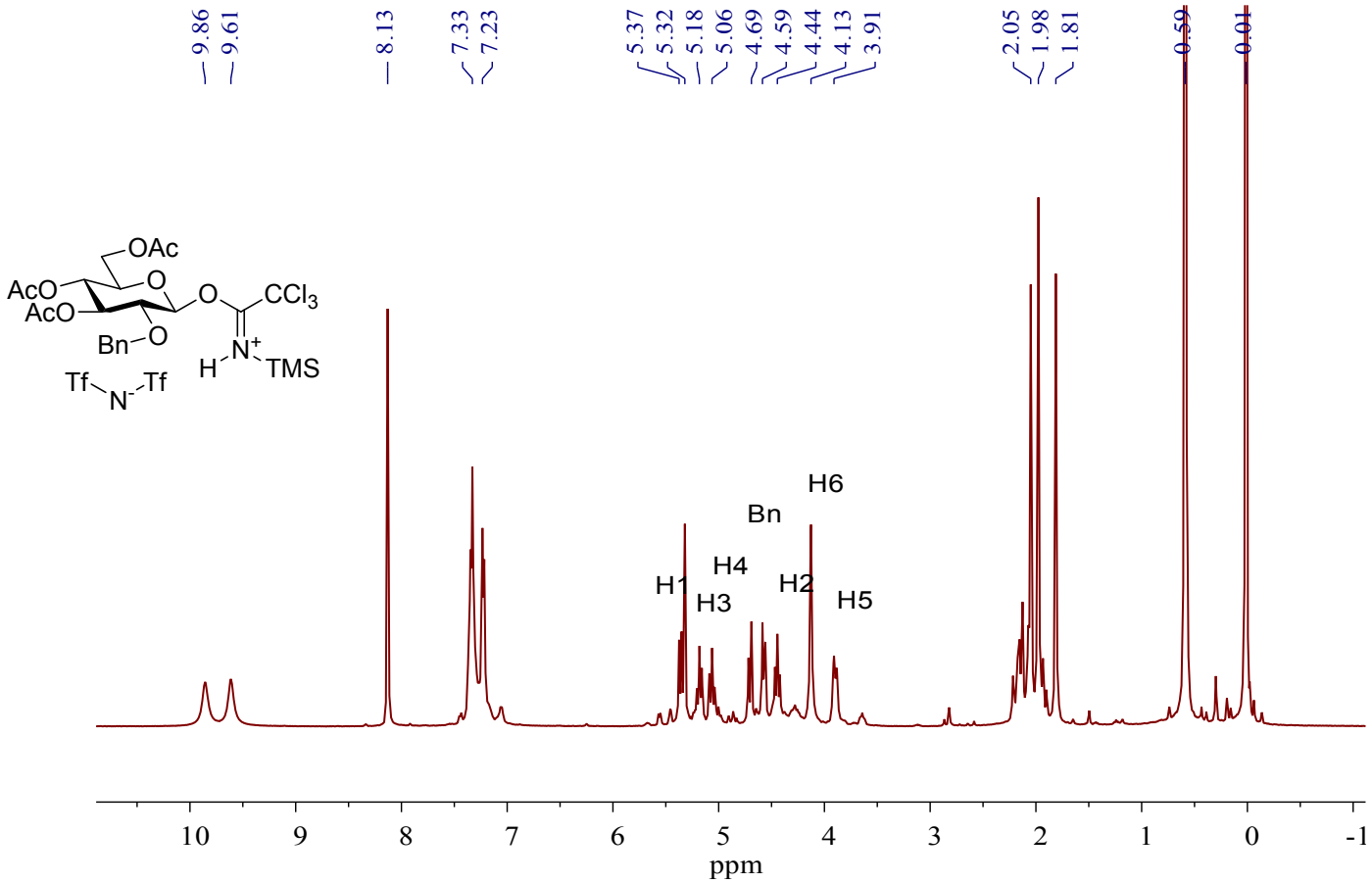


Figure S28. ^{1}H NMR spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C



^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.36-7.19 (m, 5 H, Ph), 5.35 (d, *J* = 9.4 Hz, 1H, H-1), 5.17 (t, *J* = 9.4 Hz, 1H, H-3), 5.06 (t, *J* = 9.9 Hz, 1H, H-4), 4.69 (d, *J* = 11.2 Hz, 1H, Bn), 4.56 (d, *J* = 11.1 Hz, 1H, Bn), 4.43 (t, *J* ~ 9.4 Hz, 1H), 4.09 (bs, 2H, H-6), 3.88 (bd, ; J ~ 9.9 Hz, 1H, H-5), 2.01 (bs, 3H, Ac), 1.96 (bs, 3H, Ac), 1.80 (bs, 3H), 0.58 (bs, ~3H. TMS)

Figure S29. COSY spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C

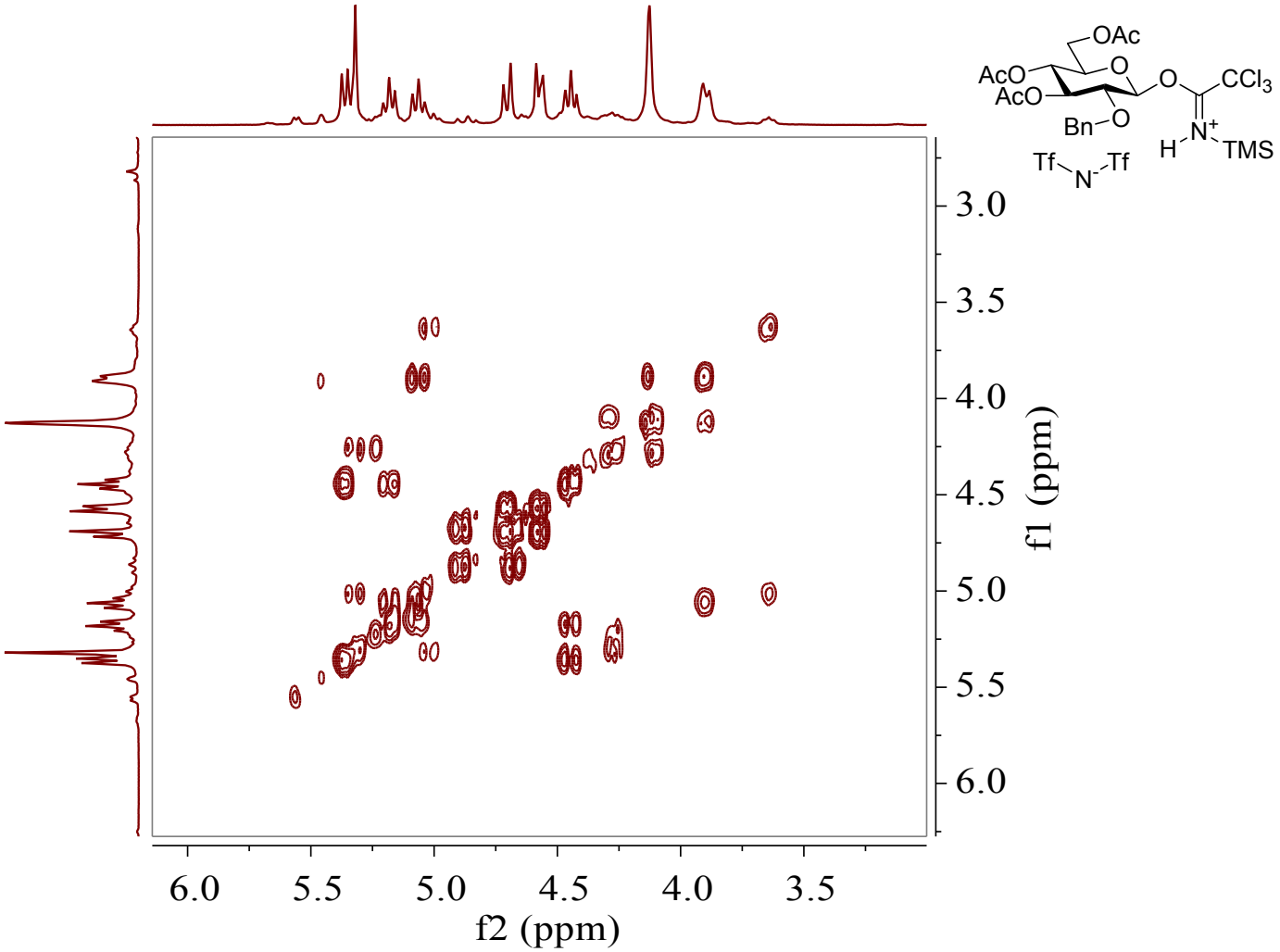
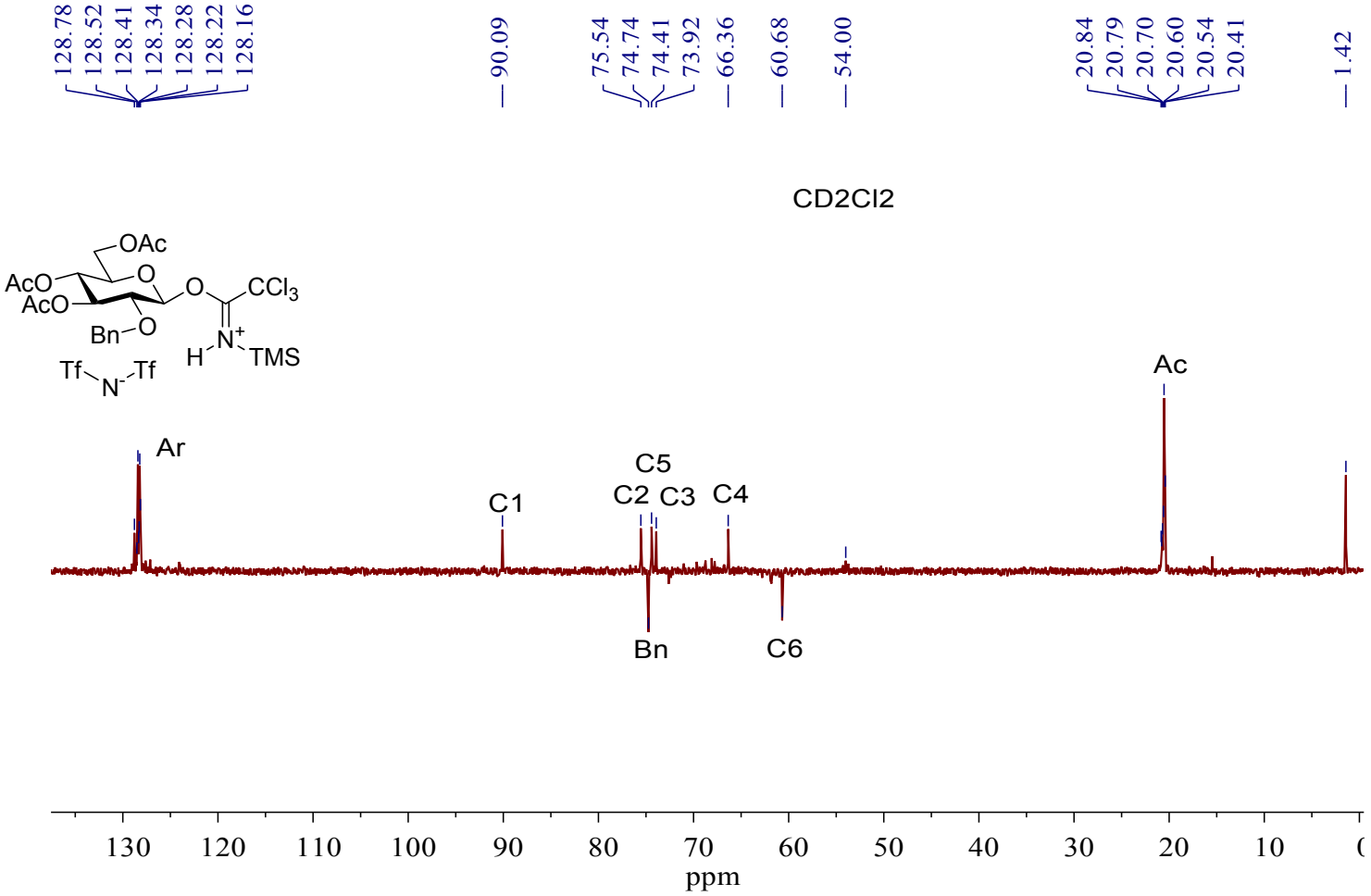


Figure S30. ^{13}C DEPT135 spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C



^{13}C NMR (100 MHz, Methylene Chloride-d_2) δ 90.1 (C1), 75.5(C2), 74.7(Bn), 74.4(C5), 73.9(C3), 66.4(C4), 60.7(C6)

Figure S31. HSQC spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C

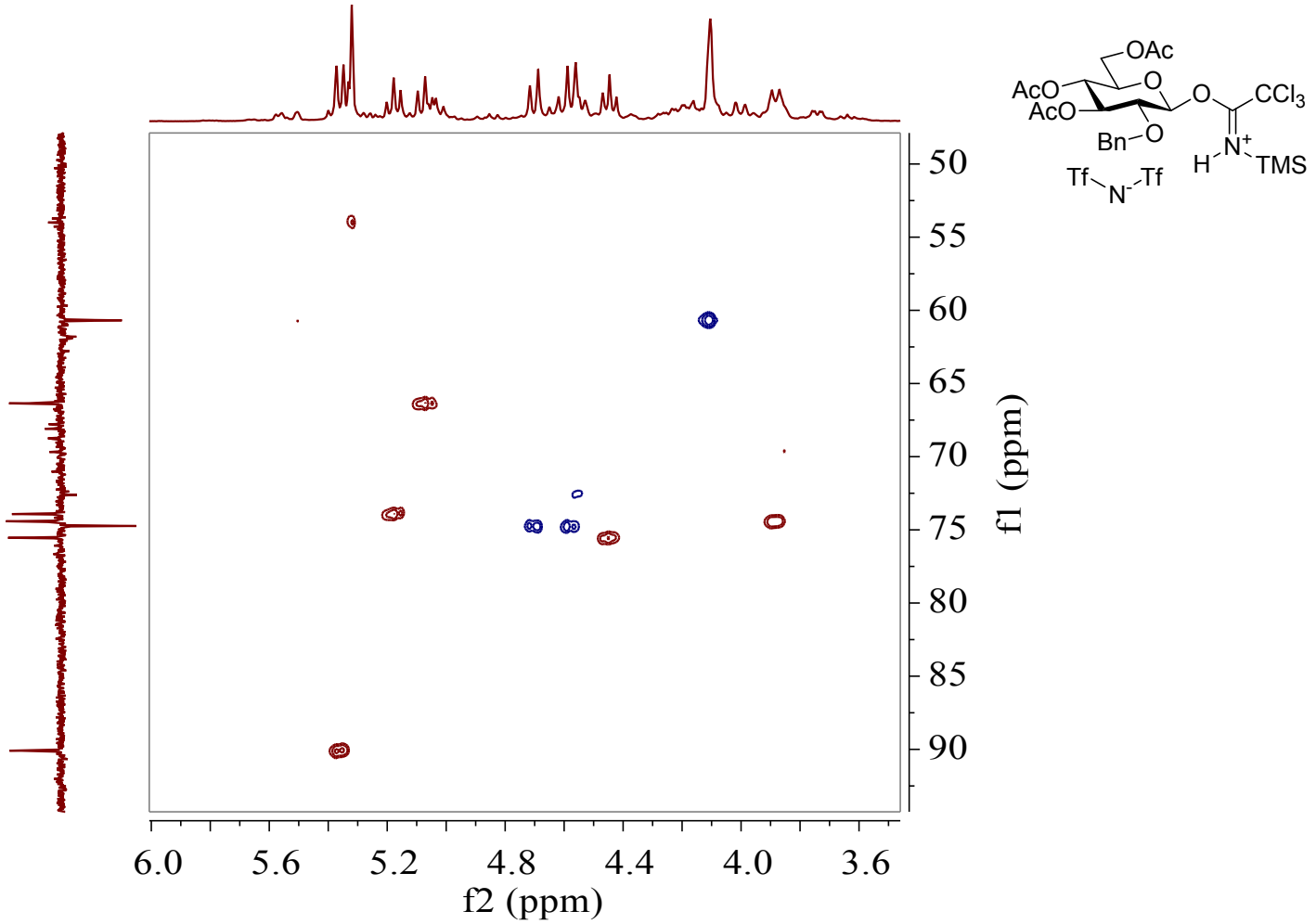


Figure S32. ^{19}F NMR spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C

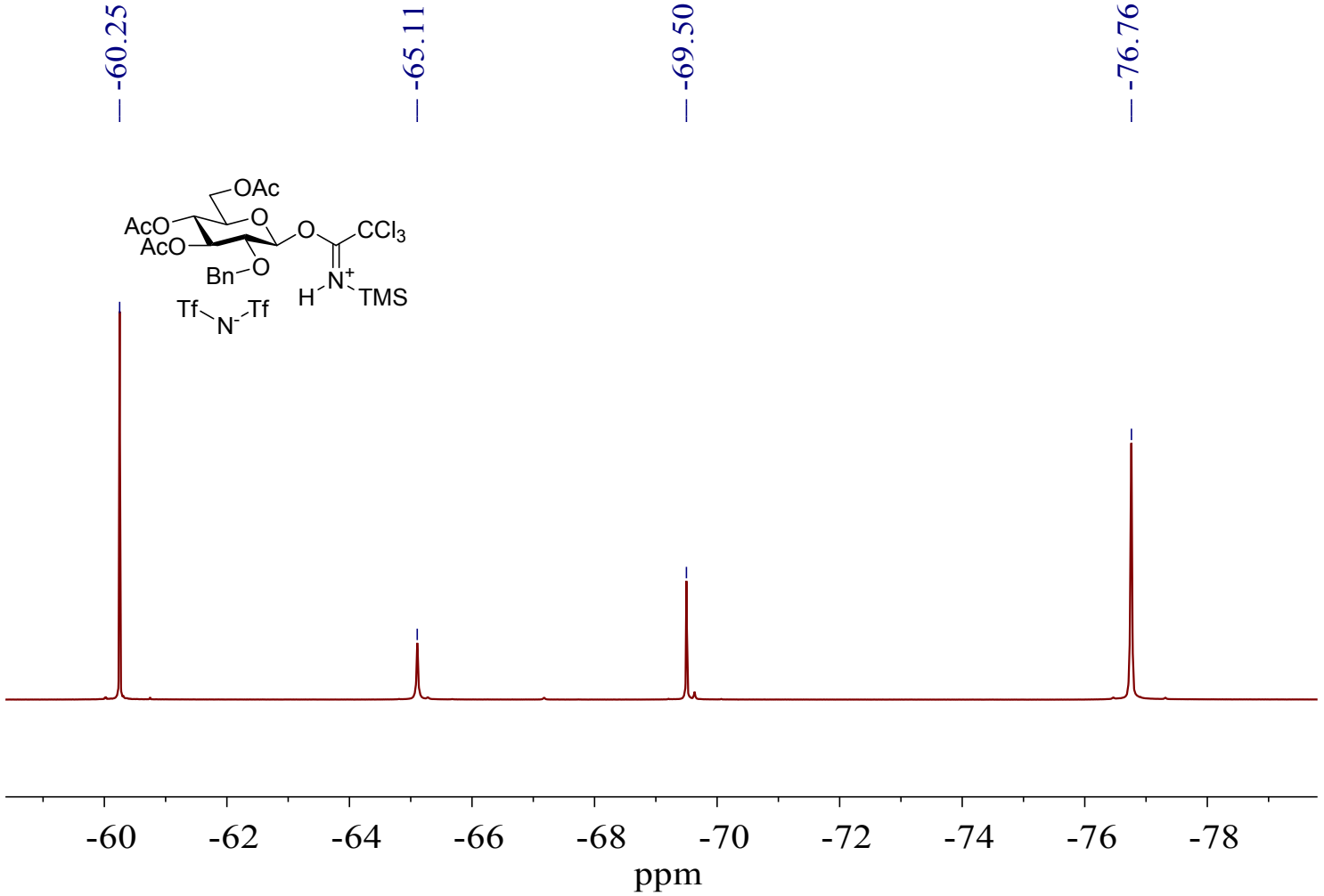
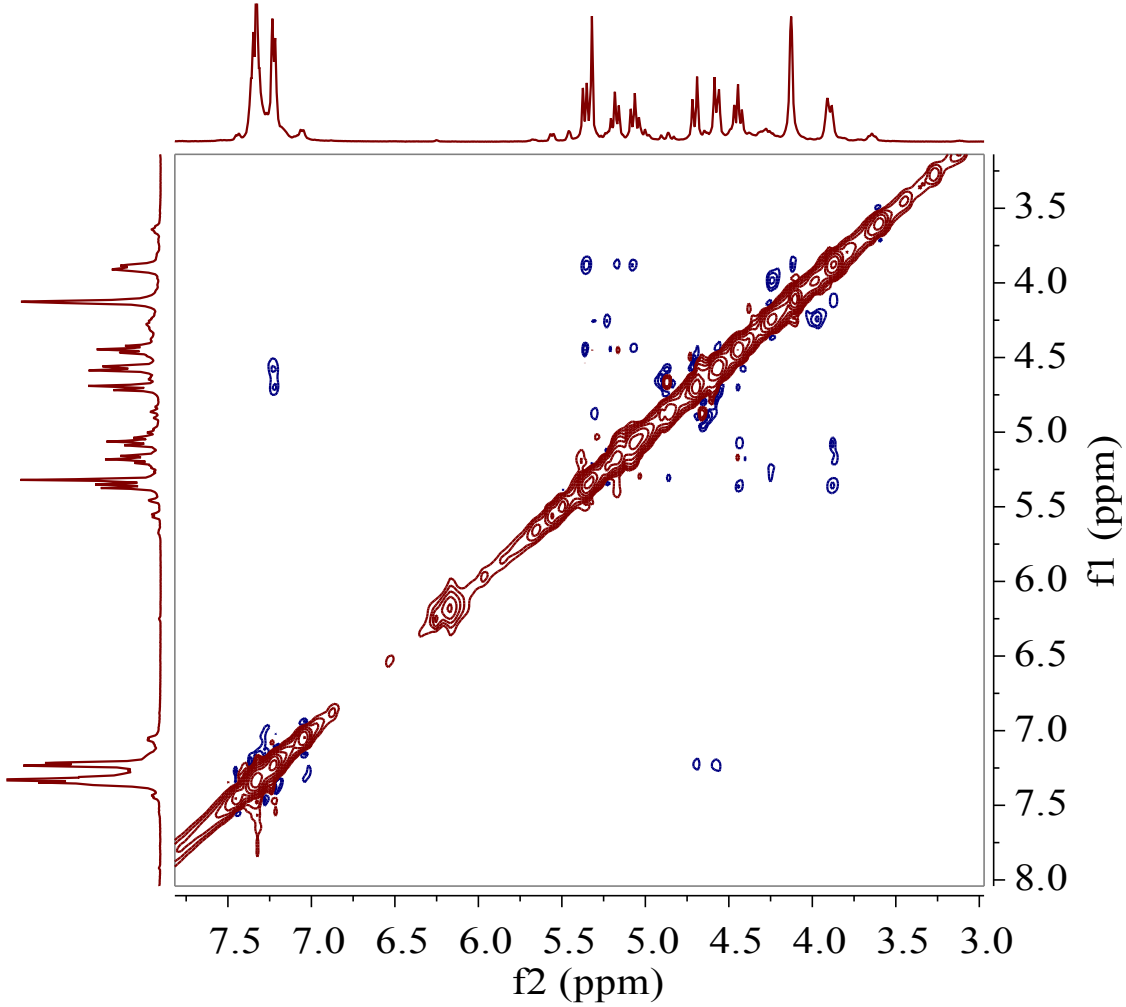


Figure S33. NOESY spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -55 °C



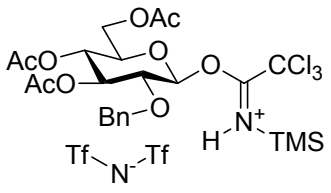


Figure S34. ^{1}H DOSY and ^{19}F DOSY spectra of glycosylation reactions catalyzed by $TMSNTf_2$

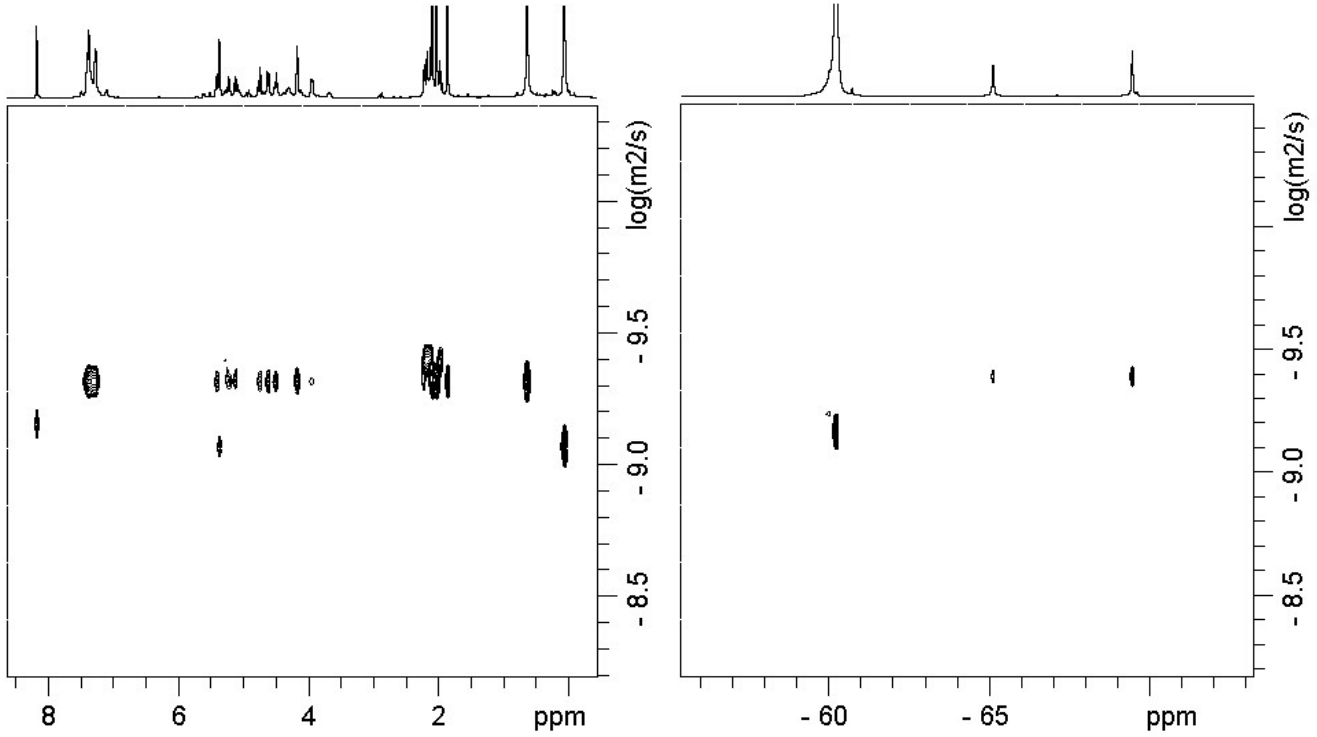


Figure S35. ^{19}F NMR spectra of glycosylation reactions catalyzed by $TMSNTf_2$ from -55 °C to 15 °C

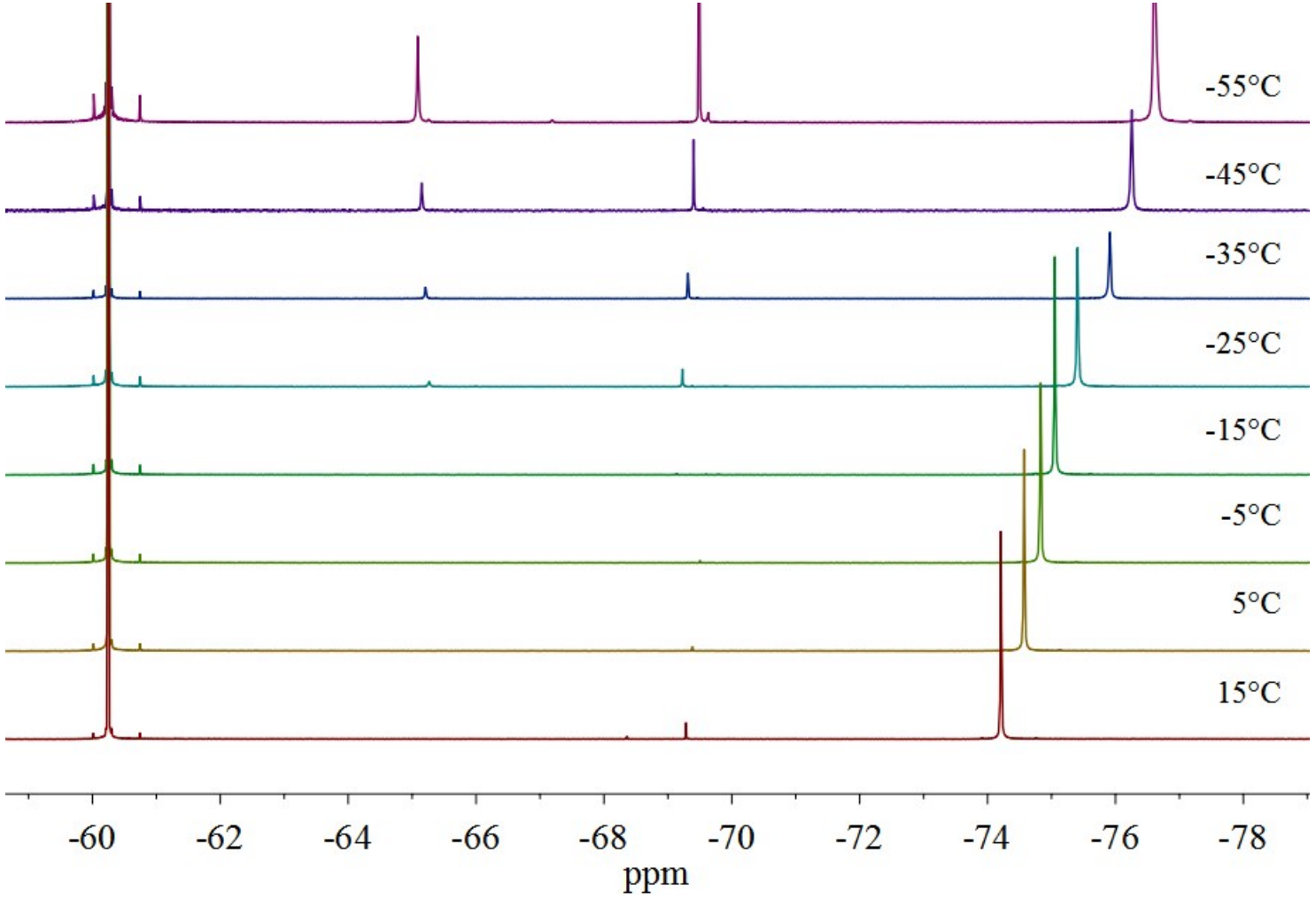


Figure S36. COSY spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -5 °C

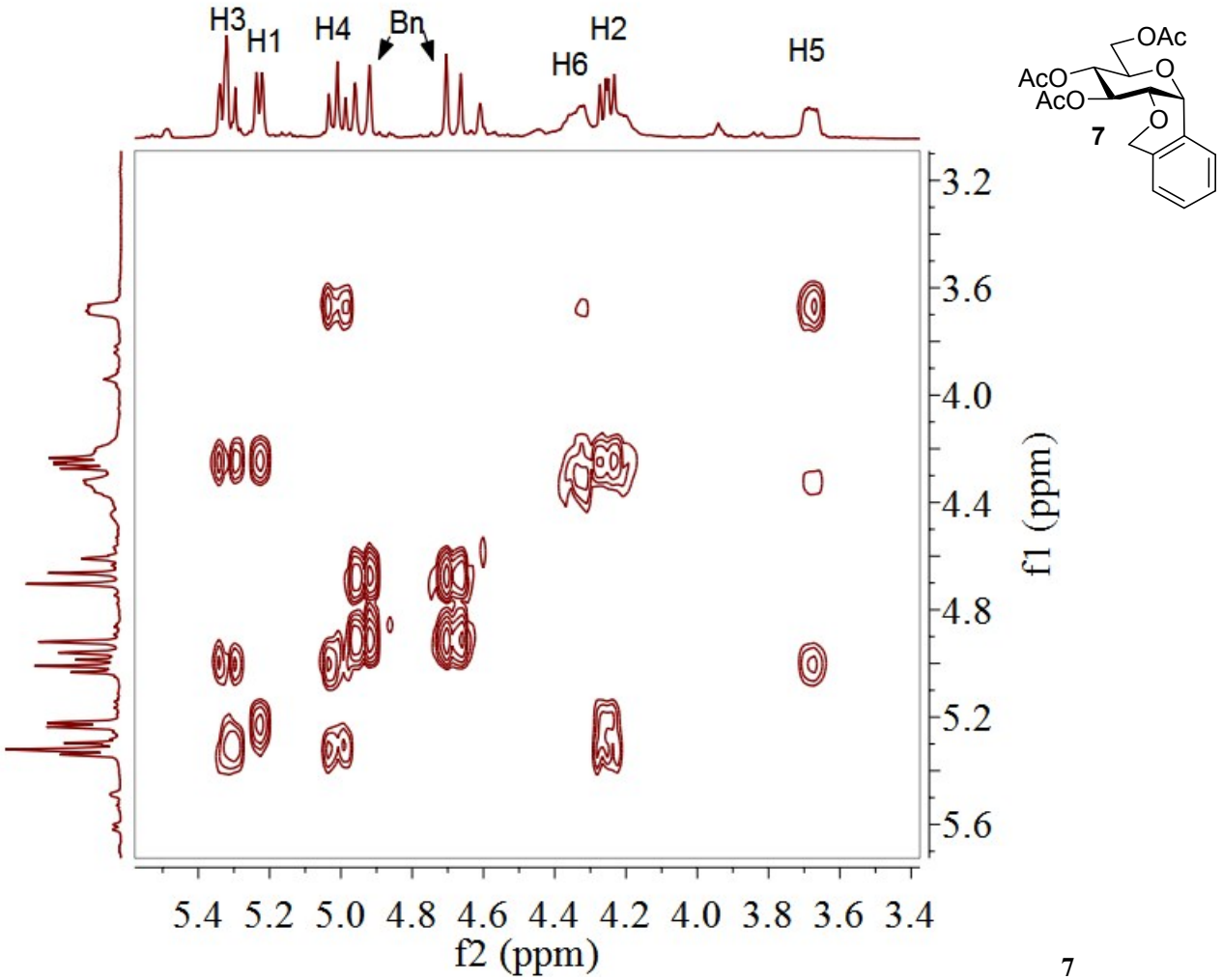


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Figure S37. ^{13}C NMR spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -5 °C

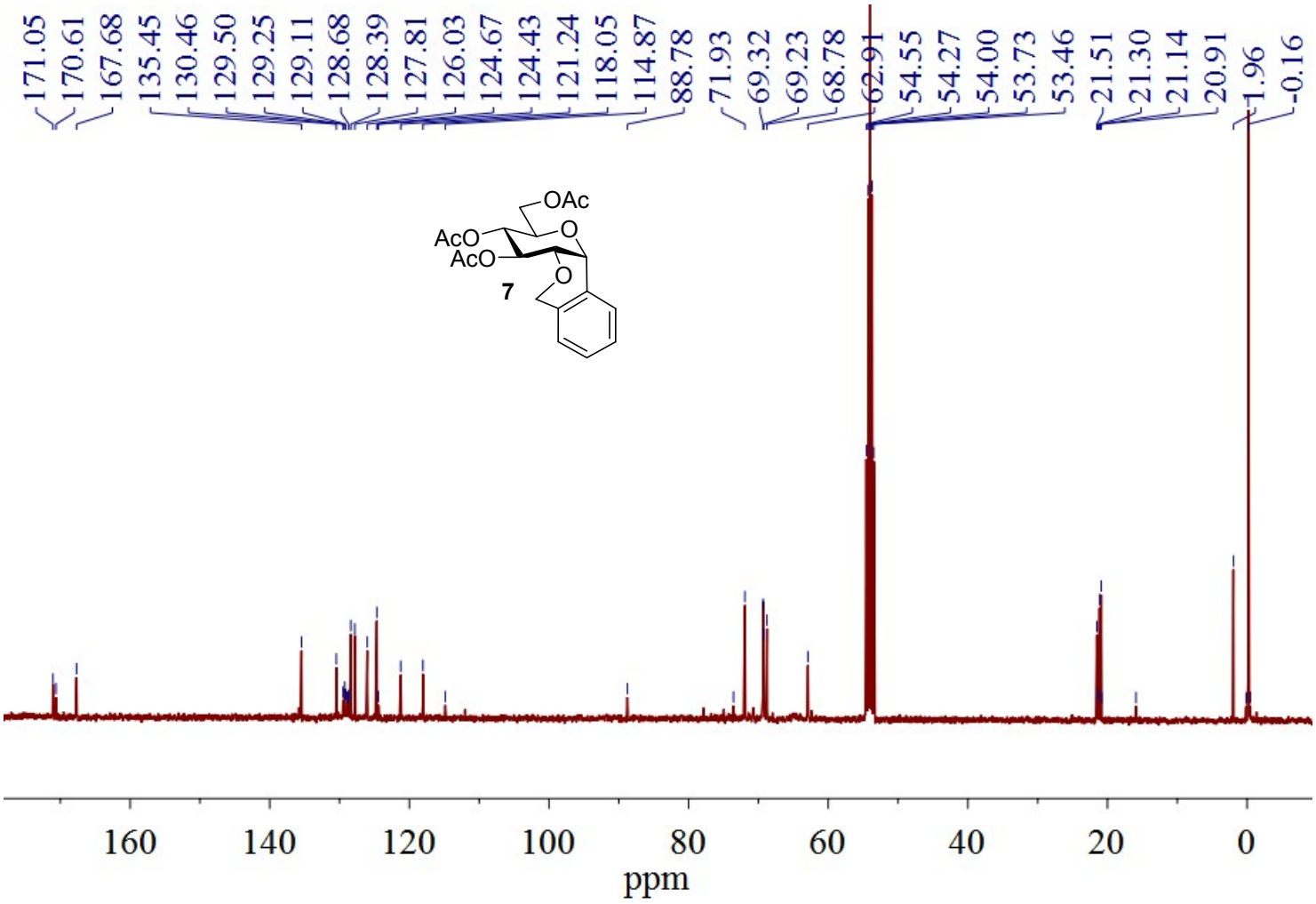
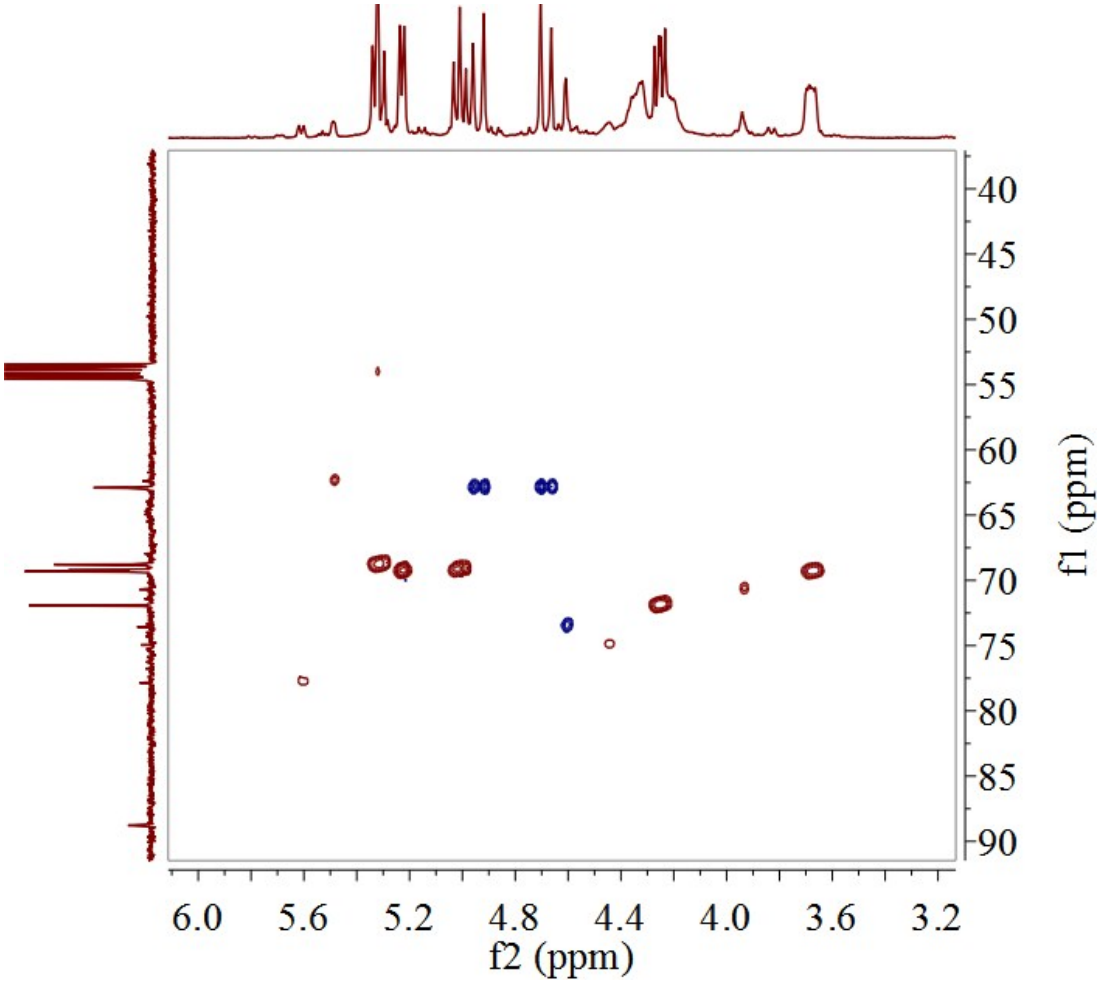
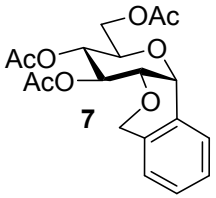


Figure S38. HSQC spectrum of glycosylation reactions catalyzed by $TMSNTf_2$ at -5 °C

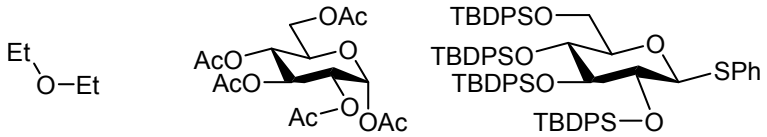




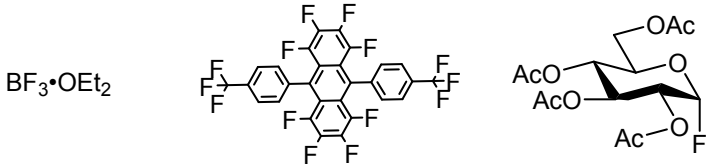
HRMS: Calculated for $C_{19}H_{22}O_8Na$: 401.1253 found: 401.1253

6. Molecular Weight Determination of the intermediates via DOSY by using External Calibration Curves

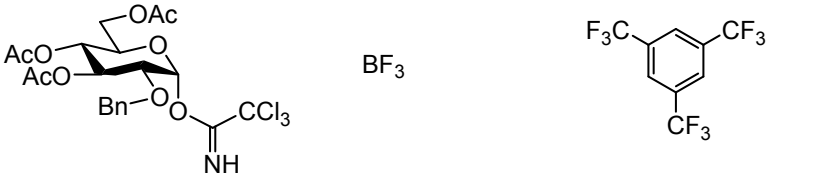
Figure S39. Overview of the used compounds (S1-S8) for calibration curves and the internal reference.



S1: MW=74.07 S4: MW=390.34 S7: MW=1225.94



S2:MW=141.93 S5: MW=610.34 S8: MW=350.29



S3: MW=540.78 S6: MW=67.81 Internal ref.: MW=282.11

Table S1. The compounds for calibration curves by ^{1}H DOSY NMR and their normalized diffusion coefficients log $D_{x,norm}$

Analyte	log *MW*	log D_{ref}	log D_x	log $D_{x,norm}$	error
S1	1.8699	-9.0580	-9.0269	-9.1225	1.37E-02
S2	2.1521	-9.0580	-9.0872	-9.1829	1.87E-02
S3	2.5914	-9.1073	-9.2343	-9.2806	2.23E-02
S4	2.7330	-9.1284	-9.2790	-9.3043	2.26E-02
S5	2.7856	-9.2823	-9.4510	-9.3223	1.74E-02
S7	3.0885	-9.2328	-9.4685	-9.3893	3.25E-02

log $D_{x,norm}$ = log $D_{ref,\ fix}$ - log D_{ref} + log D_x; the 1,3,5-tris(trifluoromethyl)benzene was used as the internal reference with log $D_{ref,fix}$ = -9.1573. All compounds have been measured in 0.04 M solutions of analyte and 1,3,5-tris(trifluoromethyl)benzene in an equimolar ratio.

Table S2. The compounds for calibration curves by ^{19}F DOSY NMR and their normalized diffusion coefficients log $D_{x,norm}$,

Analyte	log *MW*	log D_{ref}	log D_x	log $D_{x,norm}$	error
S6	1.8313	-9.1878	-9.1296	-9.0955	7.17E-03
S2	2.1521	-9.1878	-9.2161	-9.1820	1.78E-02
S8	2.5444	-9.1643	-9.2725	-9.2618	2.58E-02
S5	2.7856	-9.3170	-9.5072	-9.3439	1.26E-02

log $D_{x,norm}$ = log $D_{ref,\ fix}$ - log D_{ref} + log D_x; the 1,3,5-tris(trifluoromethyl)benzene was used as the internal reference with log $D_{ref,fix}$ = -9.1573. All compounds have been measured in 0.04 M solutions of analyte and 1,3,5-tris(trifluoromethyl)benzene in an equimolar ratio.

Figure S40. log *D* versus log *MW* in CD_2Cl_2 by ^1H DOSY NMR. All compounds were normalized to log $D_{ref.fix}$ = -9.1537.

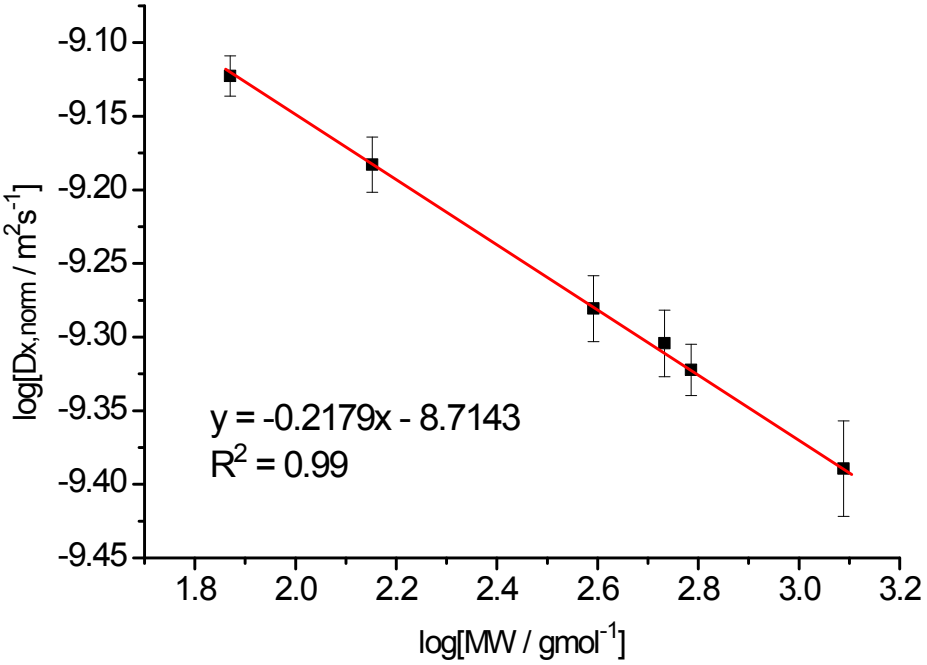
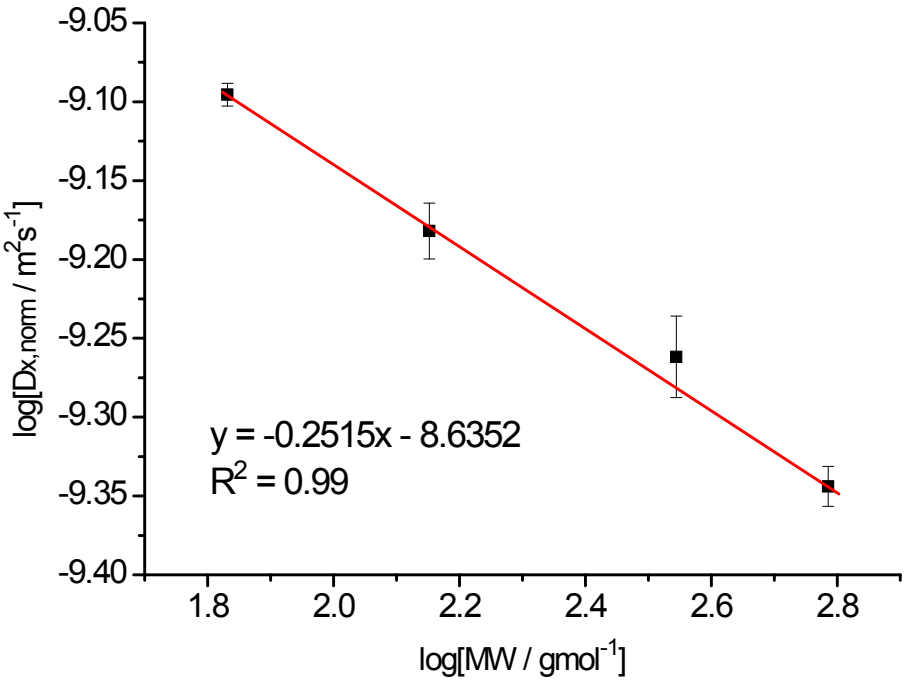


Figure S41. log *D* versus log *MW* in CD_2Cl_2 by ^{19}F DOSY NMR. All compounds were normalized to log $D_{ref.fix}$ = -9.1537.



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[2] D. Naumann, J. Kischkewitz, *J. Fluorine Chem.* **1990**, *47*, 283-299