Regioselective Silylation of Pyranosides Using a Boronic Acid / Lewis Base Co-Catalyst System

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Electronic Supplementary Information

General: Reactions were carried out without effort to exclude air or moisture, unless otherwise indicated. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was carried out using neutral silica gel (Silicycle).

Materials: HPLC grade acetonitrile was dried and purified using a solvent purification system equipped with columns of activated alumina, under argon (Innovative Technology, Inc.). Distilled water was obtained from an in-house supply. All other reagents and solvents were purchased from Sigma Aldrich, Caledon, Carbosynth or Alfa Aesar, and used without further purification.

Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD solutions using a Bruker Avance III 400 MHz or Varian Mercury 400 MHz spectrometer, referenced to residual protium in the solvent. Spectral features are tabulated in the following order: chemical shift (d, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet); number of protons; coupling constants (*J*, Hz); assignment. Assignments are based on analysis of coupling constants and COSY spectra. High-resolution mass spectra (HRMS) were obtained on a VS 70-250S (double focusing) mass spectrometer at 70 eV. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-reflection diamond / ZnSe ATR accessory, either in the solid state or as neat liquids, as indicated. Spectral features are tabulated as follows: wavenumber (cm^{-1}); intensity (s-strong, m-medium, w-weak, br-broad). Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected.

I. General Experimental Procedures

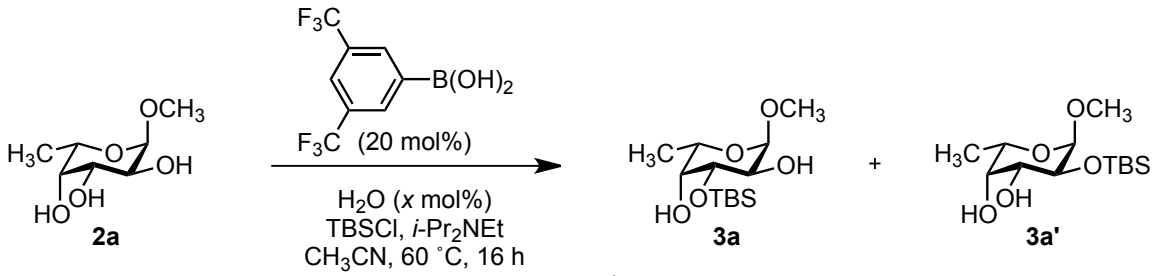
General Procedure A: Boronic Acid-Catalyzed Silylation of Carbohydrates in the Presence of a Lewis Base

Arylboronic acid (20 mol%), Lewis base (20 mol%), substrate (0.2 mmol) and *tert*-butyldimethylsilyl chloride (0.4 mmol) were transferred to a 2-dram vial containing a magnetic stir bar. Anhydrous acetonitrile (1 mL) was added to the vial, followed by *N*,*N*-diisopropylethylamine (0.4 mmol). The resulting mixture was stirred at 60 °C for 16 hours. The mixture was diluted with ethyl acetate (0.5 mL), and then concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography using ethyl acetate/pentane mixtures.

General Procedure B: Silylation of Carbohydrates in the Absence of Catalyst

Substrate (0.2 mmol) and *tert*-butyldimethylsilyl chloride (0.4 mmol) were transferred to a 2-dram vial containing a magnetic stir bar. Anhydrous acetonitrile (1 mL) was added to the vial, followed by *N*,*N*-diisopropylethylamine (0.4 mmol). The resulting mixture was stirred at 60 °C for 16 hours. The mixture was diluted with ethyl acetate (0.5 mL), and then concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography using ethyl acetate/pentane mixtures.

II. Effect of Water on the Regioselective Silylation Reaction



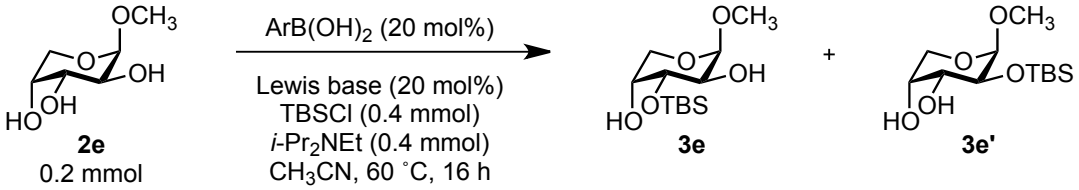
4 Å MS (100 mg)	NR
x = 0	62% (9.2 : 1)
x = 20	44% (5.0 : 1)
x = 40	27% (13.9 : 1)
x = 60	NR

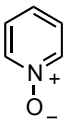
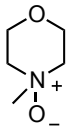
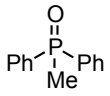
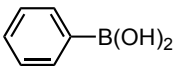
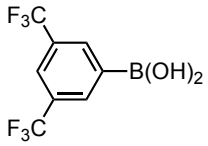
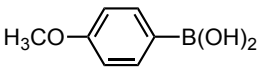
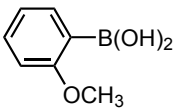
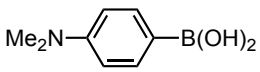
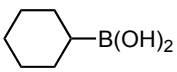
3,5-Bis(trifluoromethyl)phenylboronic acid (20 mol%), methyl α-L-fucopyranoside (0.2 mmol) and *tert*-butyldimethylsilyl chloride (0.24 mmol) were transferred to a 2-dram vial containing a magnetic stir bar. Anhydrous acetonitrile (1 mL) was added to the vial, followed by *N*,*N*-diisopropylethylamine (0.4 mmol) and water (*x* mol%). The resulting mixture was stirred at 60 °C for 16 hours. The mixture was diluted with ethyl acetate (0.5 mL), and then concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography using ethyl acetate/pentane mixtures.

As increasing amounts of water are added, the yield of the reaction decreases such that at 60 mol% of water, no reaction was observed.

III. Evaluation of Boronic Acids *vs.* Lewis Bases for Methyl β-D-arabinopyranoside

Following general procedure A, a variety of boronic acids and Lewis bases were tested for the regioselective silylation of methyl β-D-arabinopyranoside. From this screen, the optimal catalyst combination was 4-(dimethylamino)phenylboronic acid and pyridine *N*-oxide.



ArB(OH)$_2$	***n*-Bu$_3$P=O**	**Ph$_3$P=O**		**HMPA**			
	49% (>30 : 1)	47% (11.6 : 1)	49% (5.4 : 1)	45% (>30 : 1)	50% (15.5 : 1)	57% (4.8 : 1)	57% (8.1 : 1)
	45% (>30 : 1)	36% (>30 : 1)	50% (>30 : 1)	42% (>30 : 1)	42% (>30 : 1)	40% (12.9 : 1)	43% (>30 : 1)
	57% (>30 : 1)	47% (>30 : 1)	41% (8.3 : 1)	57% (26.2 : 1)	59% (>30 : 1)	43% (4.6 : 1)	45% (>30 : 1)
	57% (6.4 : 1)	55% (7.0 : 1)	48% (4.8 : 1)	63% (5.8 : 1)	63% (4.0 : 1)	55% (5.6 : 1)	55% (5.6 : 1)
	59% (>30 : 1)	63% (>30 : 1)	49% (11.3 : 1)	55% (>30 : 1)	**65% (>30 : 1)**	51% (6.5 : 1)	58% (>30 : 1)
	53% (5.9 : 1)	50% (6.1 : 1)	32% (4.0 : 1)	60% (6.9 : 1)	40% (3.8 : 1)	36% (4.6 : 1)	58% (10.7 : 1)

IV. Characterization Data

Methyl 3-*O*-(*tert*-butyldimethylsilyl)-*α*-L-fucopyranoside (3a). Synthesized according to general procedure A, from methyl *α*-L-fucopyranoside **2a** using 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and tri-*n*-butylphosphine oxide (20 mol%), >99% yield, white solid. **^{1}H NMR (400 MHz, CD_3OD):** *δ* 4.62 (d, *J* = 3.9 Hz, 1H, *H*-1), 3.92–3.84 (m, 2H, *H*-5 and *H*-3), 3.72 (dd, *J* = 9.8, 3.9 Hz, 1H, *H*-2), 3.61 (dd, *J* = 3.4, 1.4 Hz, 1H, *H*-4), 3.37 (s, 3H, OCH_3), 1.22 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 0.94 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.13 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$). **^{13}C NMR (100 MHz, CD_3OD):** *δ* 101.9, 74.3, 73.5, 69.9, 67.1, 55.6, 26.5, 19.2, 16.7, -4.2, -4.6. **R_f:** 0.3 (ethyl acetate/pentane 25:75). **IR (Powder, cm^{-1}):** 3471 (br), 2929 (m), 2895 (w), 1463 (w), 1359 (w), 1248 (m), 1086 (s), 1054 (s), 1000 (m), 924 (m), 836 (s), 782 (s), 678 (m). **HRMS (DART, m/z):** Calculated for $C_{13}H_{32}NO_5Si$ $((M+NH_4)^+)$: 310.2050; Found: 310.2057.

Methyl 2-*O*-(*tert*-butyldimethylsilyl)-*α*-L-fucopyranoside (3a'). Synthesized according to general procedure B, from methyl *α*-L-fucopyranoside **2a**, <3% yield, viscous colourless oil. **^{1}H NMR (400 MHz, CD_3OD):** *δ* 4.57 (d, *J* = 3.8 Hz, 1H, *H*-1), 3.93–3.87 (m, 2H, *H*-5 and *H*-2), 3.71 (dd, *J* = 9.8, 3.5 Hz, 1H, *H*-3), 3.65 (dd, *J* = 3.5, 1.3 Hz, 1H, *H*-4), 3.36 (s, 3H, OCH_3), 1.21 (d, *J* = 6.6 Hz, 1H, $CHCH_3$), 0.92 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.12 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.12 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$). **R_f:** 0.2 (ethyl acetate/pentane 25:75).

Methyl 3-*O*-(triethylsilyl)-*α*-L-fucopyranoside (3b). Synthesized according to general procedure A, from methyl *α*-L-fucopyranoside **2a**, 62% yield, viscous colourless oil. **^{1}H NMR (400 MHz, CD_3OD):** *δ* 4.62 (d, *J* = 3.9 Hz, 2H, *H*-1), 3.89 (qd, *J* = 6.7, 1.2 Hz, 1H, *H*-5), 3.84 (dd, *J* = 9.8, 3.5 Hz, 1H, *H*-3), 3.72 (dd, *J* = 9.8, 3.9 Hz, 1H, *H*-2), 3.59 (dd, *J* = 3.5, 1.2 Hz, 1H, *H*-4), 3.37 (s, 3H, OCH_3), 1.22 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 1.00 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.69 (q, *J* = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$). **^{13}C NMR (100 MHz, CD_3OD):** *δ* 101.8, 74.4, 73.3, 69.8, 67.1, 55.6, 16.7, 7.2, 5.8. **R_f:** 0.25 (ethyl acetate/pentane 25:75). **IR (Neat, cm^{-1}):** 3244 (br), 2934 (m), 2909 (m), 1458 (w), 1361 (w), 1132 (m), 1079 (s), 1037 (s), 959 (s), 916 (m), 809 (m), 725 (s). **HRMS (DART, m/z):** Calculated for $C_{13}H_{32}NO_5Si$ $((M+NH_4)^+)$: 310.2050; Found: 310.2056.

Methyl 2-*O*-(triethylsilyl)-*α*-L-fucopyranoside (3b'). Isolated from same reaction mixture as **3b**, 5% yield, viscous colourless oil. **^{1}H NMR (400 MHz, CD_3OD):** *δ* 4.57 (d, *J* = 3.8 Hz, 1H, *H*-1), 3.93–3.87 (m, 2H, *H*-5 and *H*-2), 3.71 (dd, *J* = 9.8, 3.5 Hz, 1H, *H*-3), 3.65 (dd, *J* = 3.5, 1.3 Hz, 1H, *H*-4), 3.36 (s, 3H, OCH_3), 1.21 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 1.00 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.67 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$). **R_f:** 0.15 (ethyl acetate/pentane 25:75).

Methyl 3-*O*-(*tert*-butyldiphenylsilyl)-*α*-L-fucopyranoside (3c). Synthesized according to general procedure A, from methyl *α*-L-fucopyranoside **2a** and *tert*-butyldiphenylsilyl chloride using 4-(dimethylamino)phenylboronic acid (20 mol%) and tri-*n*-butylphosphine oxide (20 mol%), 75% yield, viscous colourless oil. Spectral data were in agreement with literature values.[1] **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 7.76–7.68 (m, 4H, Ar*H*), 7.47–7.37 (m, 6H, Ar*H*), 4.68 (d, *J* = 3.8 Hz, 1H, *H*-1), 3.92–3.82 (m, 2H, *H*-2 and *H*-3), 3.68 (q, *J* = 6.7 Hz, 1H, *H*-5), 3.44–3.43 (m, 1H, *H*-4), 3.29 (s, 3H, OCH_3), 2.55 (br s, 1H, C_4-O*H*), 1.54 (d, *J* = 9.3 Hz, 1H, C_2-O*H*), 1.22 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 1.11 (s, 9H, $Si(C(CH_3)_3)Ph_2$). **R_f:** 0.45 (ethyl acetate/pentane 25:75).

Methyl 3-*O*-(*tert*-butyldimethylsilyl)-*α*-L-rhamnopyranoside (3d). Synthesized according to general procedure A, from methyl *α*-L-rhamnopyranoside **2d** using 3,5-bis(trifluoromethyl)phenylboronic acid (20 mol%) and tri-*n*-butylphosphine oxide (20 mol%), >99% yield, viscous colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 4.68 (d, *J* = 1.3 Hz, 1H, *H*-1), 3.81–3.77 (m, 2H, *H*-3 and *H*-2), 3.67–3.60 (m, 1H, *H*-5), 3.46 (dd, *J* = 9.0, 9.0 Hz, 1H, *H*-4), 3.35 (s, 3H, OCH_3), 2.51 (br s, 1H, C_2-O*H*), 1.96 (br s, 1H, C_4-O*H*), 1.31 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 0.91 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.13 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 101.1, 73.3, 73.2, 71.5, 67.3, 54.8, 25.7, 18.0, 17.6, -4.6, -4.6. **R_f:** 0.3 (ethyl acetate/pentane 20:80). **IR (Neat, cm^{-1}):** 3465 (br), 2929 (m), 2957 (w), 1523 (w), 1464 (m), 1253 (m), 1108 (s), 1054 (s), 973 (m), 836 (s), 779 (s), 675 (m). **HRMS (DART, m/z):** Calculated for $C_{13}H_{32}NO_5Si$ ($(M+NH_4)^+$): 310.2050; Found: 310.2041.

Methyl 3-*O*-(*tert*-butyldimethylsilyl)-*β*-D-arabinopyranoside (3e). Synthesized according to general procedure A, from methyl *β*-D-arabinopyranoside **2e** using 4-(dimethylamino)phenylboronic acid (20 mol%) and pyridine *N*-oxide (40 mol%), 84% yield, viscous yellow oil. Spectral data were consistent with literature values.[2] **^{1}H NMR (400 MHz, CD_3OD):** *δ* 4.66 (d, *J* = 3.5 Hz, 1H, *H*-1), 3.88 (dd, *J* = 9.0, 3.4 Hz, 1H, *H*-3), 3.82 (dd, *J* = 3.2, 1.8 Hz, 1H, *H*-4), 3.77–3.72 (m, 2H, *H*-5a and *H*-2), 3.58 (dd, *J* = 12.2, 2.9 Hz, 1H, *H*-5b), 3.39 (s, 3H, OCH_3), 0.94 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.13 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$). **^{13}C NMR (100 MHz, CD_3OD):** *δ* 102.2, 72.8, 71.0, 70.4, 63.6, 55.9, 26.5, 19.2, -4.3, -4.6. **R_f:** 0.25 (ethyl acetate/pentane 45:55).

[1] M. S. Arias-Pérez, M. S. López, M. J. Santos, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1549.
[2] M.-K. Chung, G. Orlova, J. D. Goddard, M. Schlaf, R. Harris, T. J. Beveridge, G. White, F. R. Hallett, *J. Am. Chem. Soc.*, 2002, **124**, 10508.

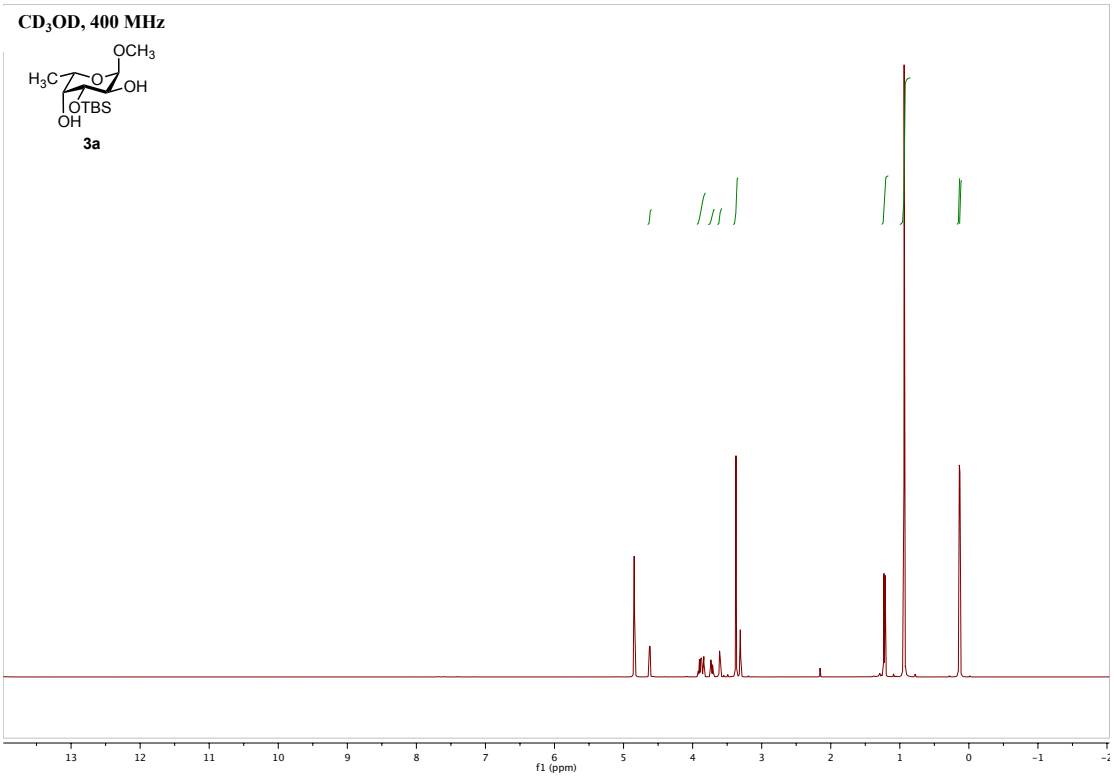
Methyl 2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-arabinopyranoside (3e'). Synthesized according to general procedure B, from methyl *β*-D-arabinopyranoside **2e**, 13% yield, isolated as a 1.7:1 3-OTBS : 2-OTBS mixture, viscous yellow oil. Spectral data were consistent with literature values.[2] **^{1}H NMR (400 MHz, CD_3OD):** δ 4.61 (d, J = 3.5 Hz, 1H, *H*-1), 3.90 (dd, J = 9.0, 3.5 Hz, 1H, *H*-2), 3.86 (dd, J = 3.0, 2.9 Hz, 1H, *H*-4), 3.79–3.71 (m, 2H, *H*-5a and *H*-3), 3.56 (dd, J = 12.1, 3.0 Hz, 1H, *H*-5b), 3.38 (s, 3H, OCH_3), 0.92 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.11 (s, 6H, $Si(C(CH_3)_3)(CH_3)_2$). **R_f:** 0.4 (ethyl acetate/pentane 45:55).

Methyl 3,6-di-*O*-(*tert*-butyldimethylsilyl)-*α*-D-galactopyranoside (3f). Synthesized according to general procedure A, from methyl *α*-D-galactopyranoside **2f** and *tert*-butyldimethylsilyl chloride (5 equiv.) and *N*,*N*-diisopropylethylamine (5 equiv.), 82% yield, white solid. Spectral data were consistent with literature values.[2] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.68 (d, J = 3.8 Hz, 1H, *H*-1), 3.86–3.71 (m, 6H, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6a and *H*-6b), 3.39 (s, 3H, OCH_3), 0.94 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.91 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.09 (s, 6H, $Si(C(CH_3)_3)(CH_3)_2$). **^{13}C NMR (100 MHz, CD_3OD):** δ 101.8, 73.5, 72.0, 71.2, 70.2, 63.5, 55.6, 26.5, 26.3, 19.2, 19.1, -4.2, -4.6, -5.2, -5.3. **R_f:** 0.25 (ethyl acetate/pentane 15:85).

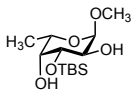
Methyl 3,6-di-*O*-(*tert*-butyldimethylsilyl)-*α*-D-mannopyranoside (3g). Synthesized according to general procedure A, from methyl *α*-D-mannopyranoside **2g**, TBSCl (1.0 mmol) and *i*-Pr_2NEt (1.0 mmol), using 3,5-bis(trifluoromethyl)-phenylboronic acid (20 mol%) and tri-*n*-butylphosphine oxide (20 mol%), 86% yield, white solid. Spectral data were in agreement with literature values.[3] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.72 (d, J = 1.5 Hz, 1H, *H*-1), 3.87 (dd, J = 5.5, 1.4 Hz, 2H, *H*-6a and *H*-6b), 3.84 (dd, J = 8.9, 3.6 Hz, 1H, *H*-3), 3.76–3.74 (m, 1H, *H*-2), 3.70 (ddd, J = 9.4, 8.9, 1.9 Hz, 1H, *H*-4), 3.56 (ddd, J = 9.4, 5.5, 5.5 Hz, 1H, *H*-5), 3.36 (s, 3H, OCH_3), 2.70 (d, J = 1.9 Hz, 1H, C_4-O*H*), 2.57 (br s, 1H, C_2-O*H*), 0.91 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.90 (s, 9H, $Si(C(CH_3)_3)(CH_3)_2$), 0.15 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.14 (s, 3H, $Si(C(CH_3)_3)(CH_3)_2$), 0.09 (s, 6H, $Si(C(CH_3)_3)(CH_3)_2$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 100.1, 73.1, 71.1, 70.6, 70.4, 64.9, 54.8, 25.9, 25.8, 18.3, 18.1, -4.5, -4.8, -5.4, -5.5. **R_f:** 0.4 (ethyl acetate/pentane 10:90).

[3] A. Pastore, M. Adinolfi, A. Iadonisi, S. Valerio, *Carbohydr. Res.*, 2010, **345**, 1316.

Section V: ^{1}H, COSY and ^{13}C NMR Spectra.
See Section IV for experimental details and assignments of spectra.

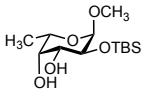


CD_3OD, 100 MHz

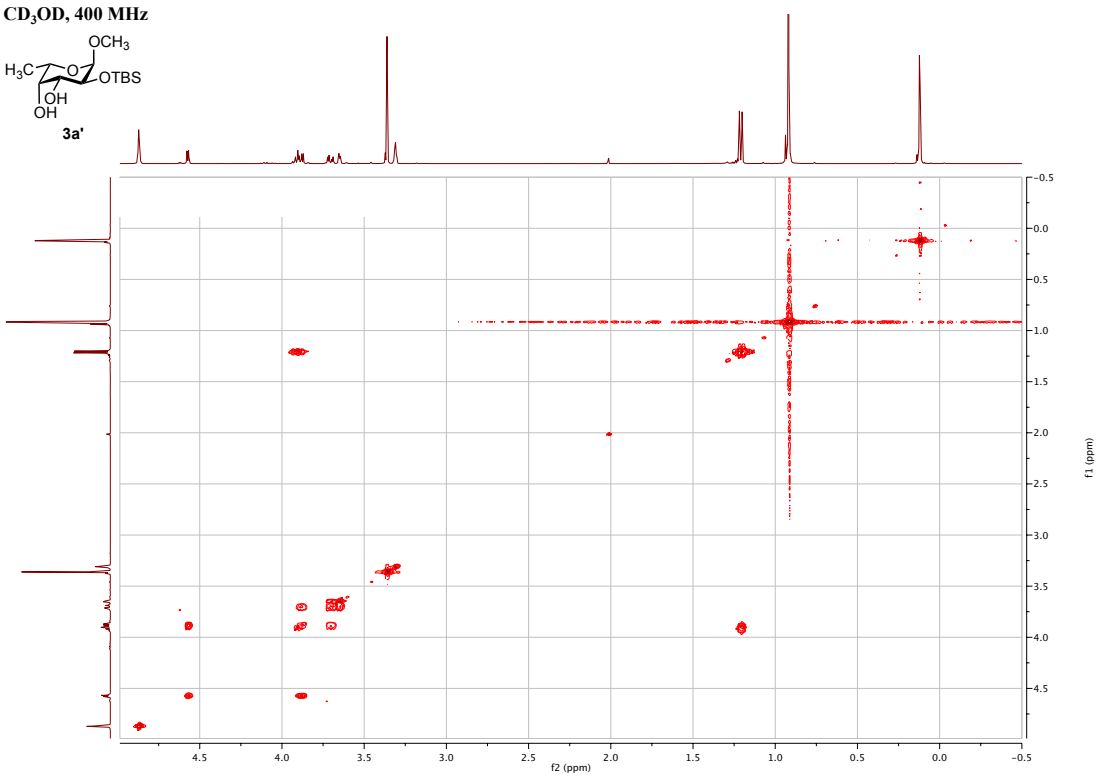


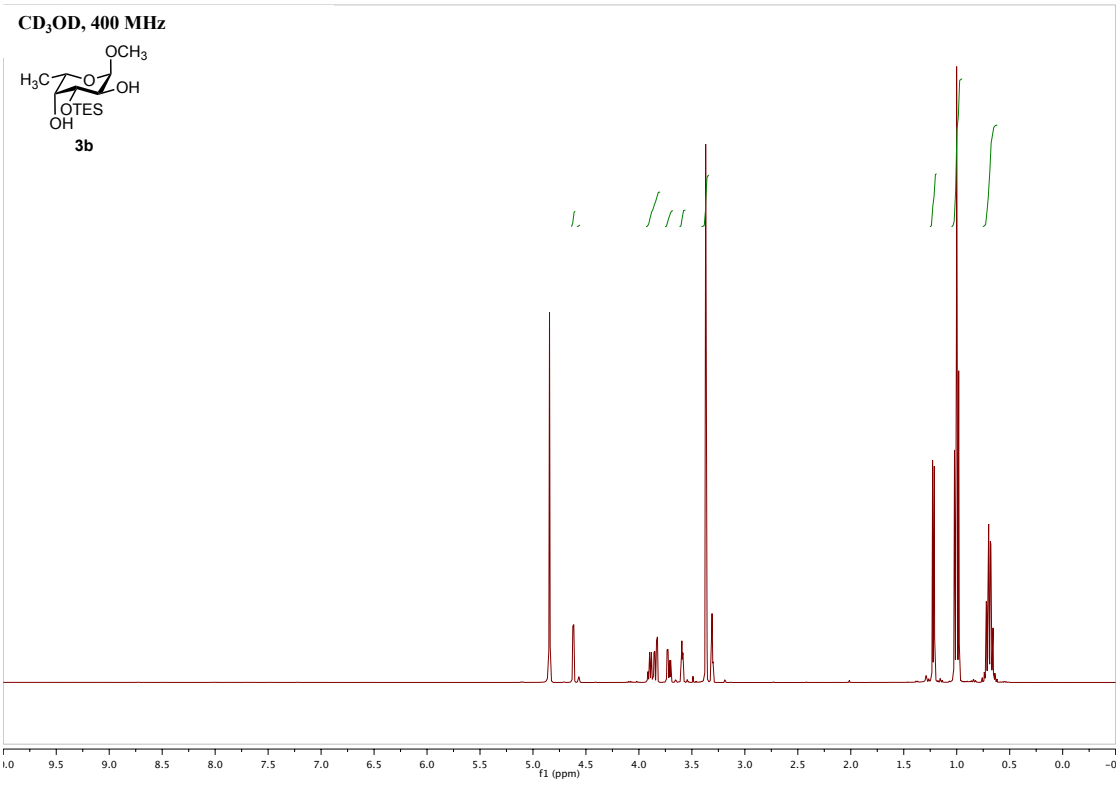
3a

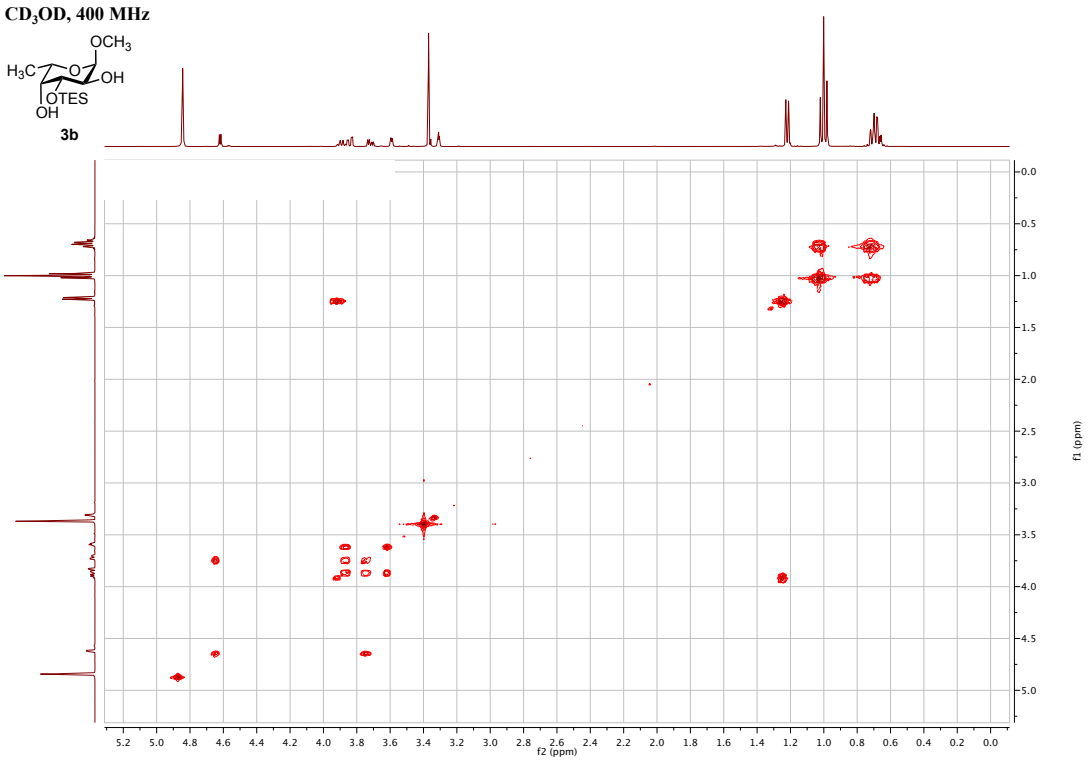
CD_3OD, 400 MHz

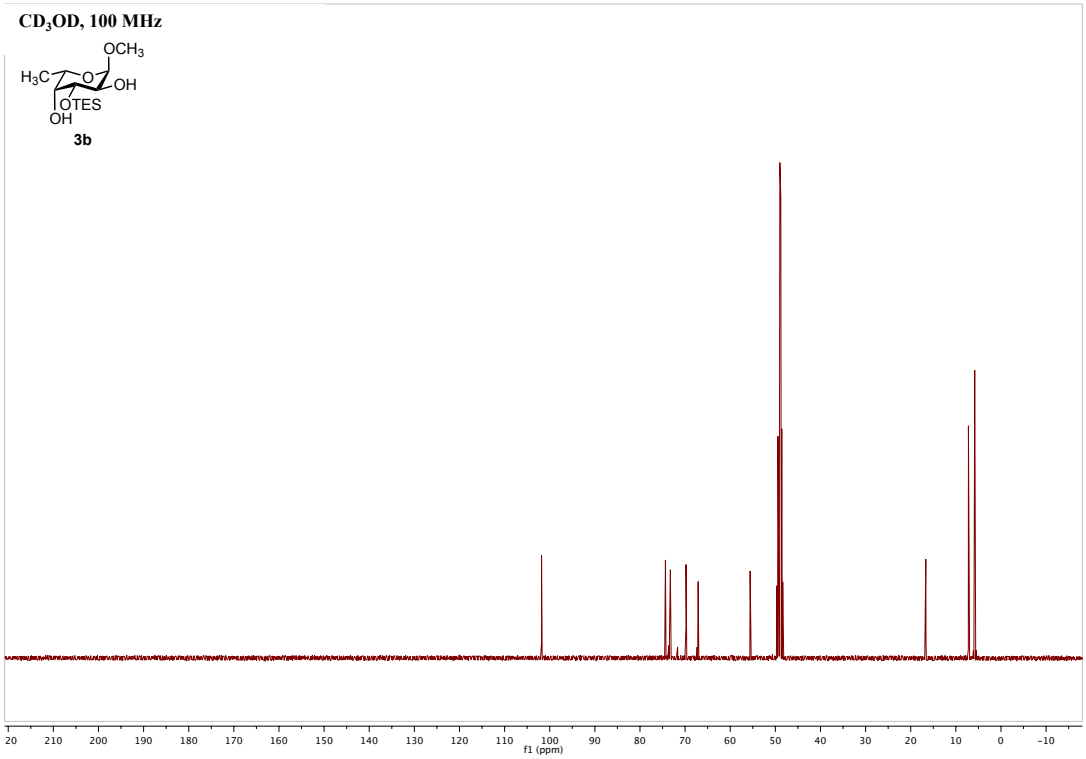


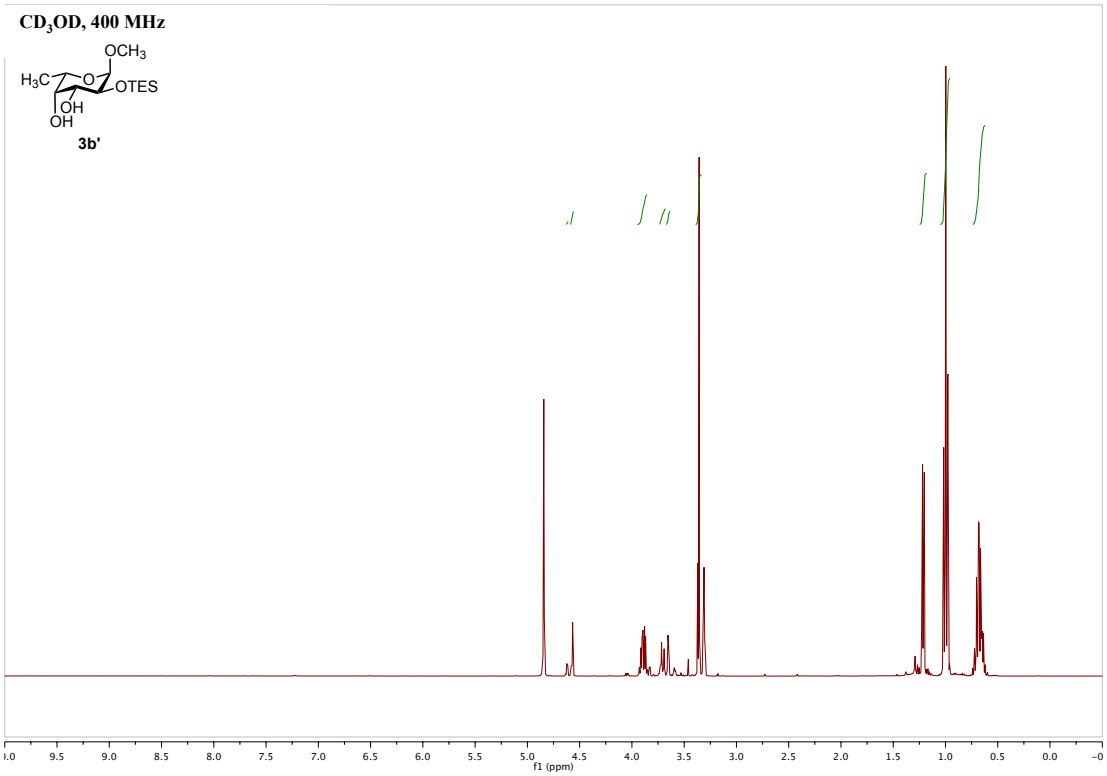
3a'

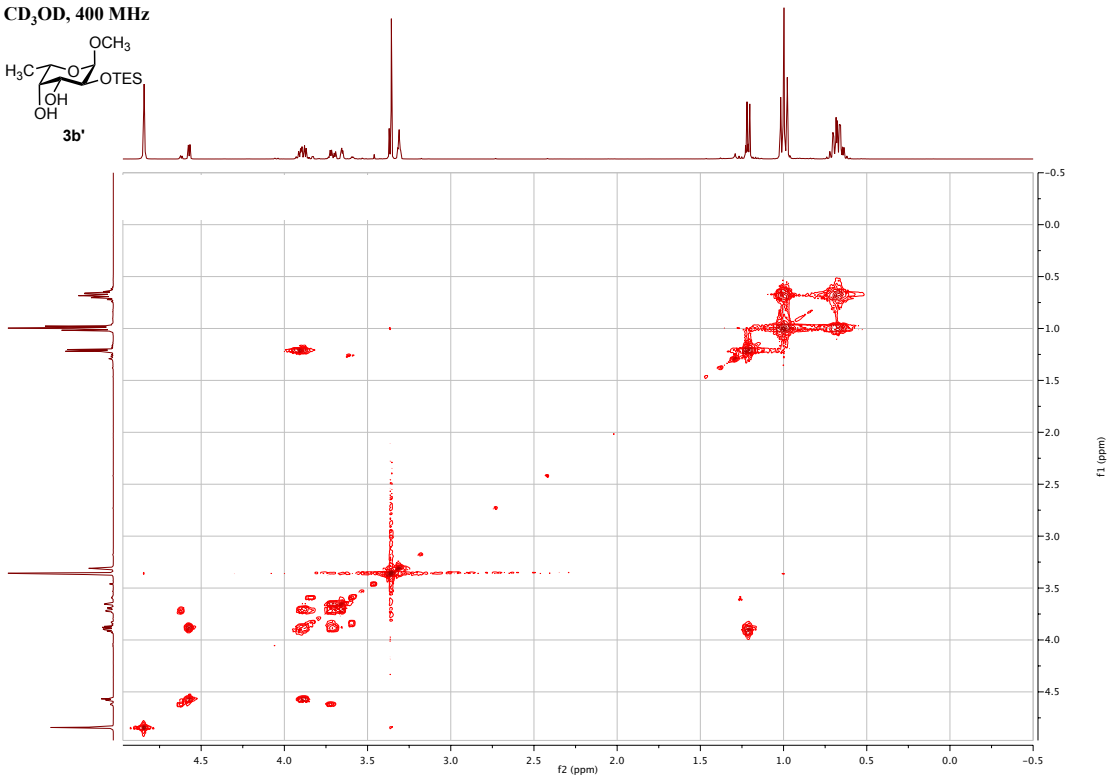


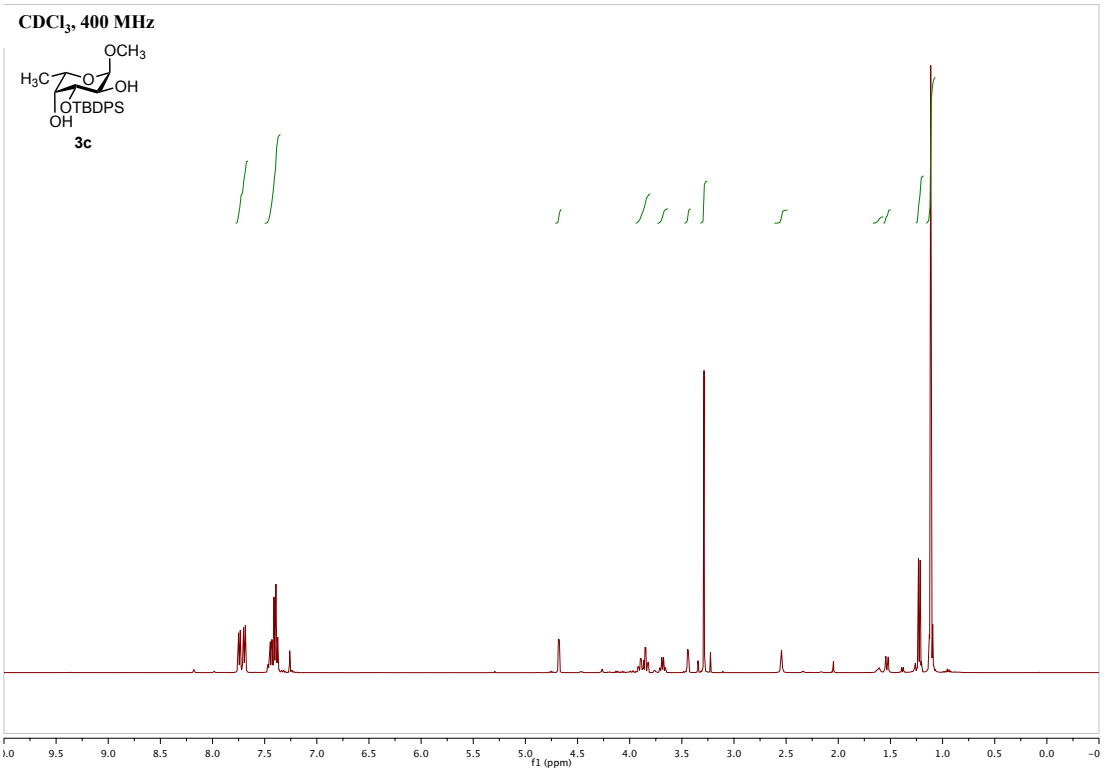


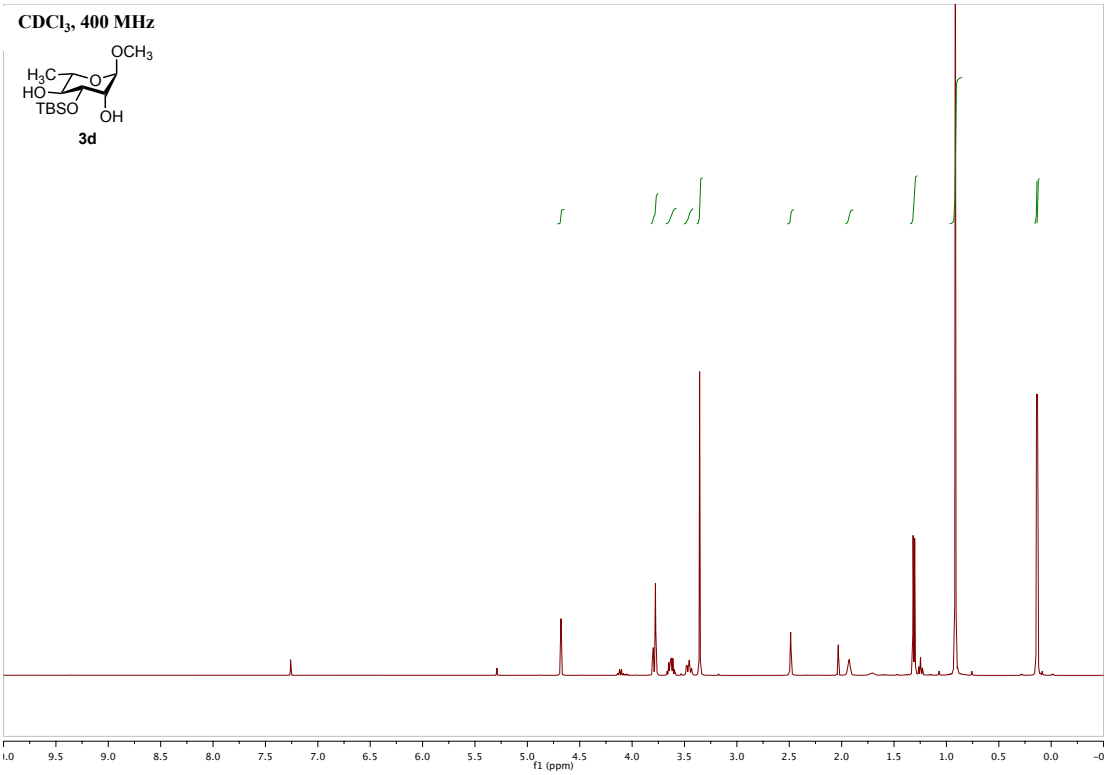


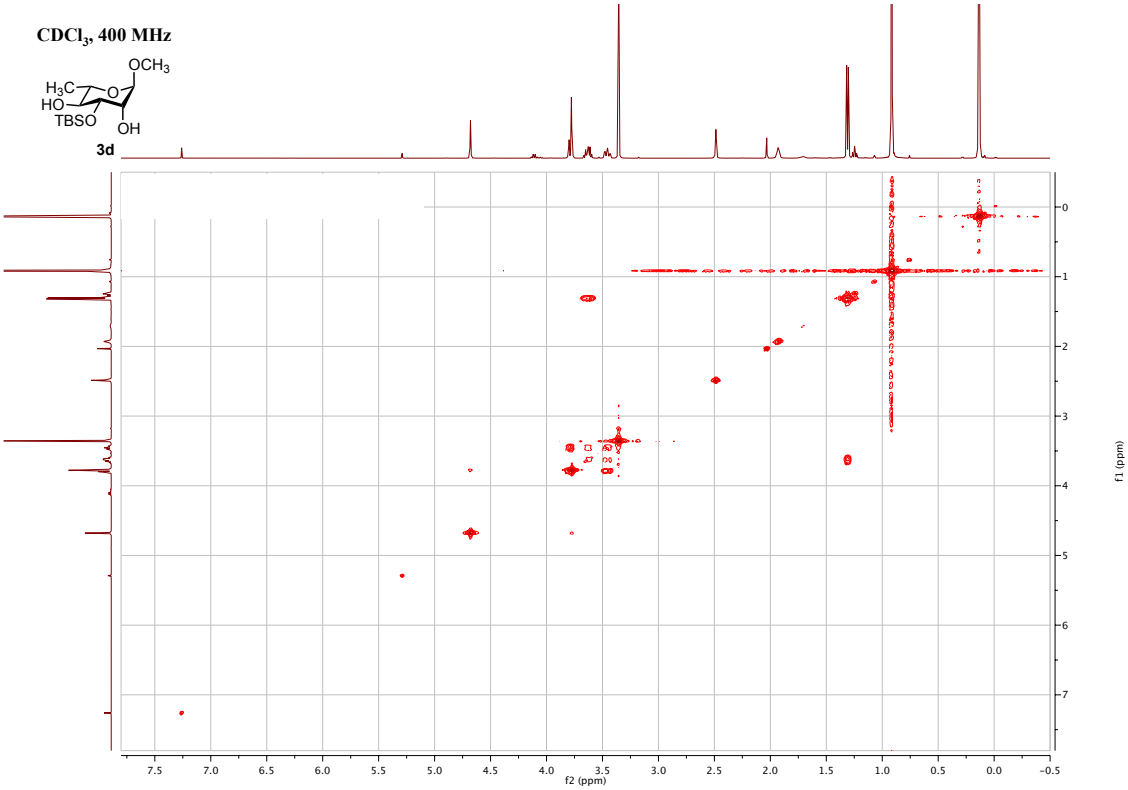




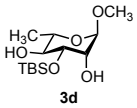






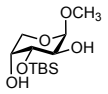


$CDCl_3$, 100 MHz

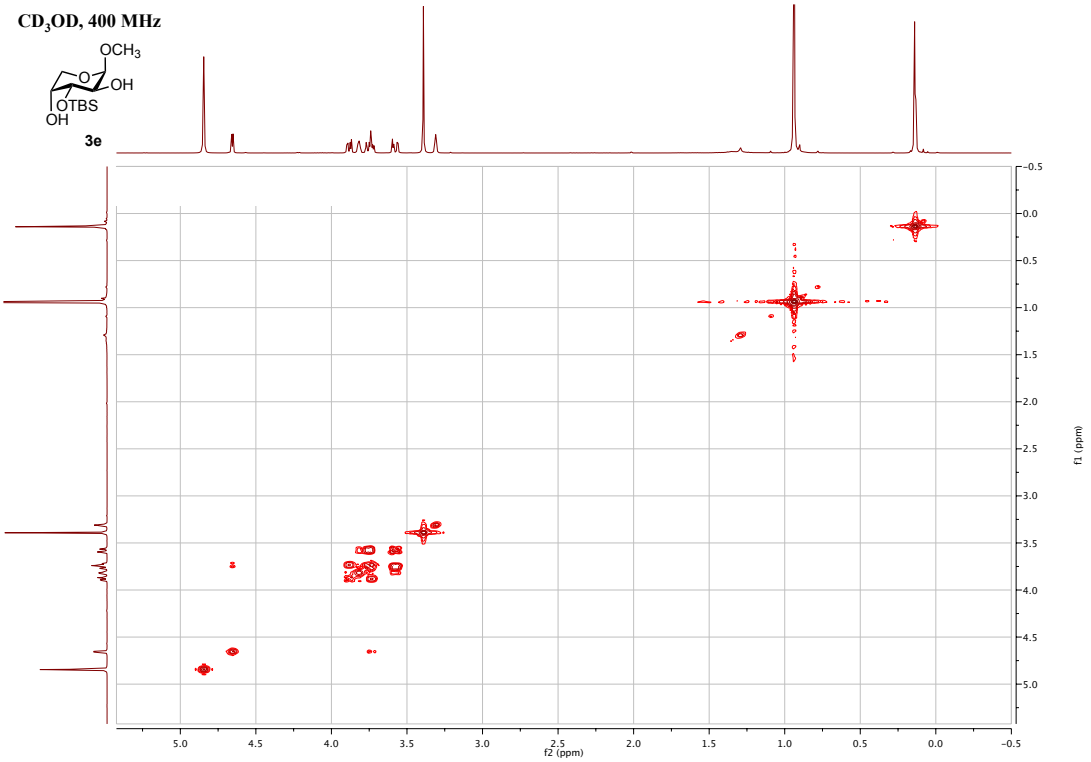


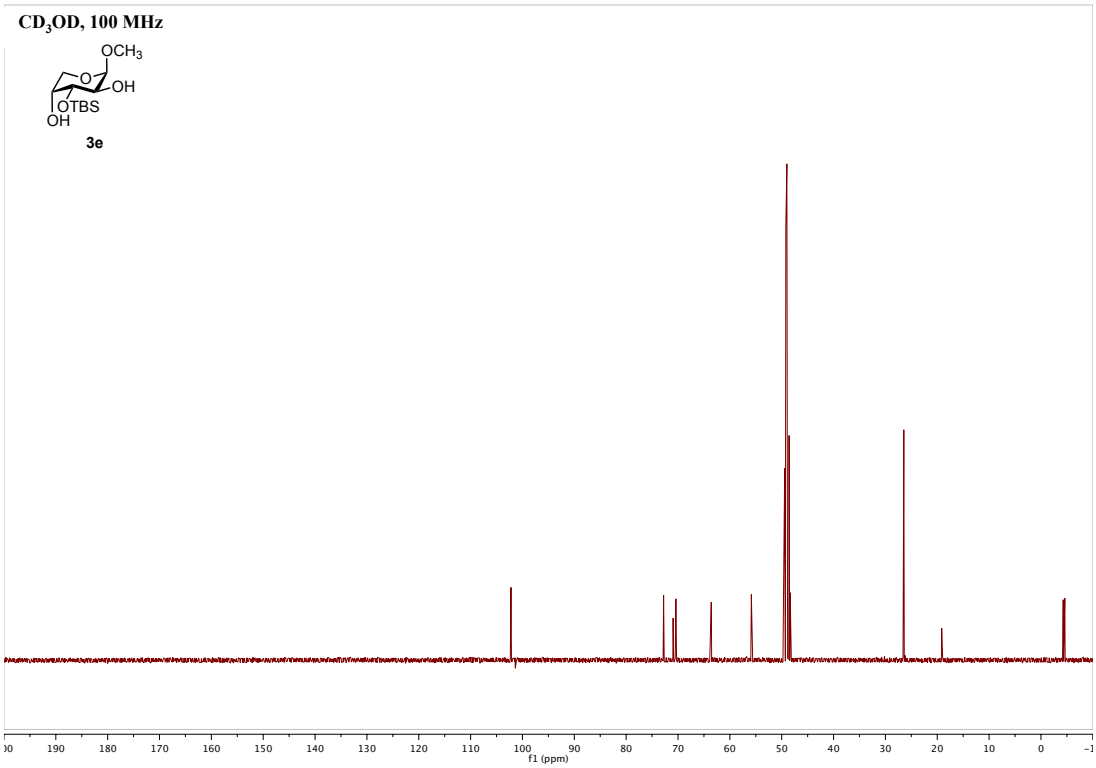
3d

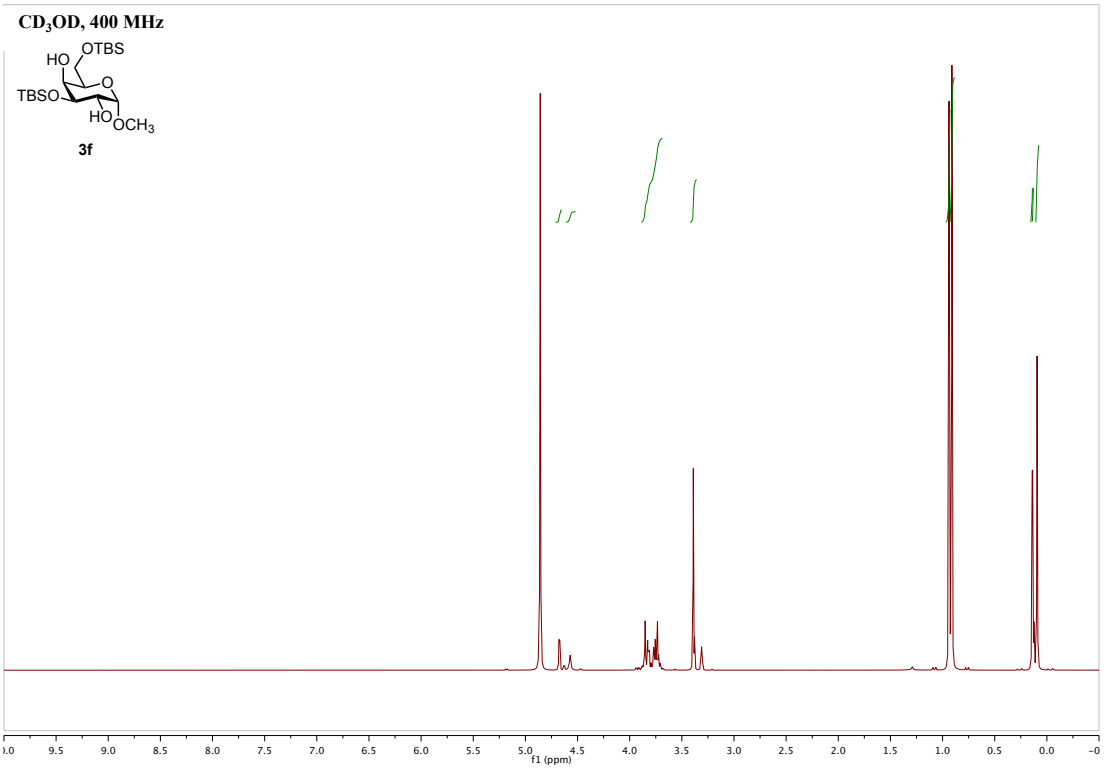
CD_3OD, 400 MHz

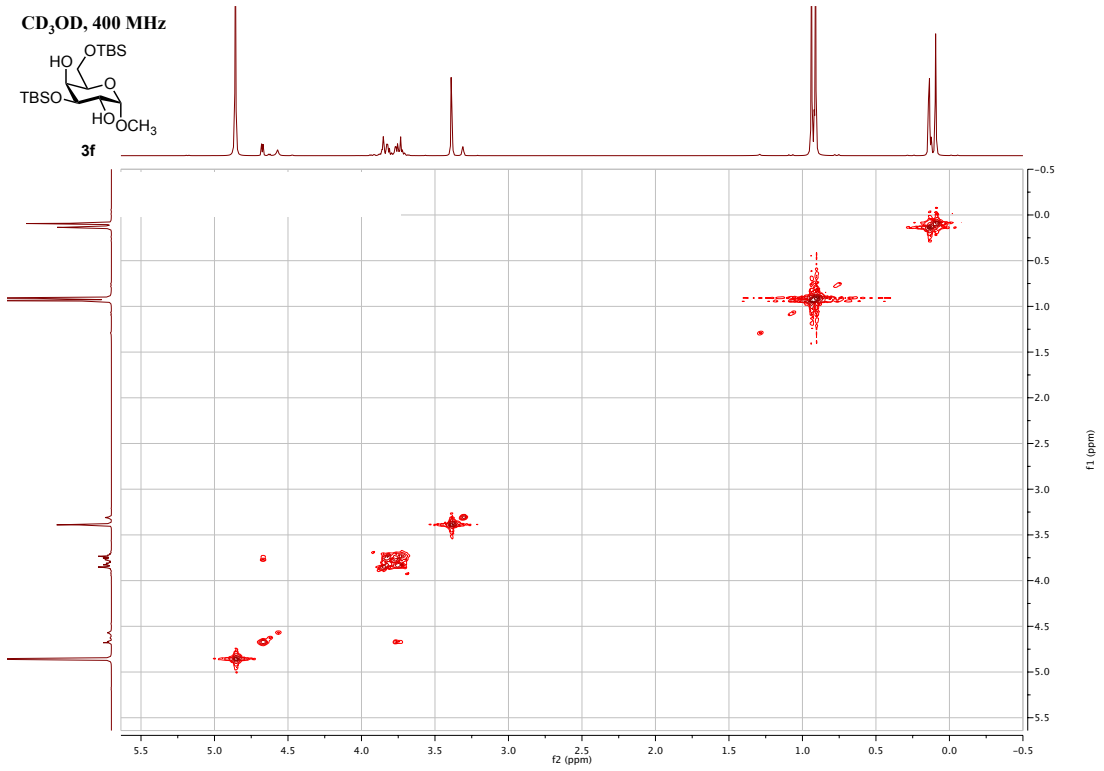


3e

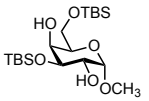






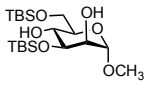


CD_3OD, 100 MHz



3f

$CDCl_3$, 400 MHz



3g