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# Multigram synthesis of an orthogonally protected pentasaccharide for use as glycan precursor in a *Shigella flexneri* 3a conjugate vaccine: application to a ready-for-conjugation decasaccharide

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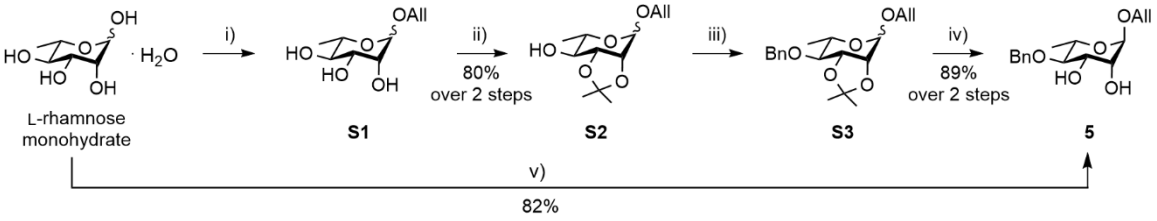
## Supplementary Information

**Content**

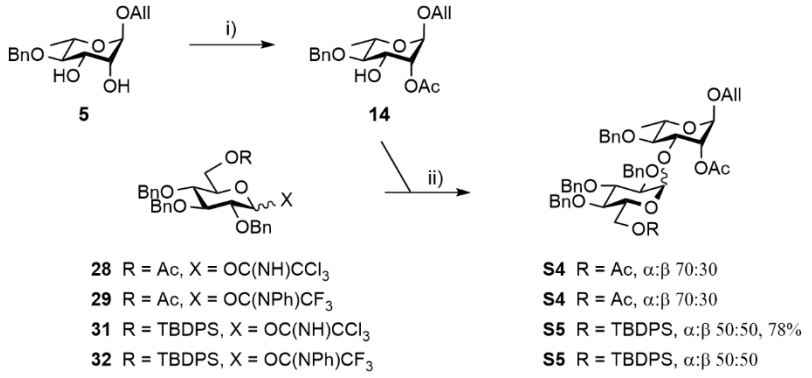
## I. Supplementary schemes

Scheme S1. Synthesis of diol **5** from L-rhamnose monohydrate




(i) AllOH, AcCl, reflux 2 h then 40 °C 20 h; (ii) 2,2-DMP, PTSA, Acetone, rt; (iii) BnBr, NaH, DMF, rt; (iv) 80% aq. AcOH, 60 °C; (v) *i.* AllOH, AcCl, 70 °C 2.5 h then 40 °C 15 h; *ii.* 2,2-DMP, PTSA, Acetone, rt; *iii.* BnBr, NaH, DMF, rt; *iv.* 80% aq. AcOH, 80 °C.

Scheme S2. Glycosylation of acceptor **14** from diol **5** with the 6-*O*-acetyl glucopyranosyl donors **28**[1] and **29** and 6-*O*-*tert*-butyldiphenylsilyl glucopyranosyl donors **31**[2] and **32**.




Conditions: Reactions were run on 70-80 mg of diol **5**, α:β ratio based on NMR data of the crude. (i) $MeC(OMe)_3$, $PTSA{\cdot}H_2O$, MeCN, rt then 80% aq. AcOH, 0 °C; (ii) Donor, 1.3 donor equiv., TMSOTf, toluene, -78 °C.

## II. Experimental procedures

### a. General methods

Anhydrous (Anhyd.) dichloromethane (DCM), toluene (Tol), tetrahydrofuran (THF), acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF) and 1,2-dichloroethane (1,2-DCE) were purchased over molecular sieves (MS) and used as received. Powdered 4 Å MS were activated before use by heating at 250 °C under vacuum. TLC was performed on precoated slides of silica gel 60 $F_{254}$ (Merck) using solvent mixtures of appropriately adjusted polarity. Detection was effected, when applicable, with UV light and/or by charring with orcinol (1 $g.L^{-1}$) in 10% aq. $H_2SO_4$. Preparative chromatography was performed manually by elution from columns of Silica

Gel 60 (particle size 40-63 µm) or using an automated system equipped with pre-packed columns. RP-HPLC purification was performed by elution from a Kromasil® 5 µm C18 100 Å 10x250 mm column, using a 0-20 % linear gradient over 20 min of MeCN in 0.08% aq. TFA at 5.5 mL/min flow rate and detecting at 215 nm. Analytical RP-HPLC was performed by elution from a Kromasil® 3.5 µm C18 100 Å 2x150 mm column, using a 0-20 % linear gradient over 20 min of MeCN in 0.08% aq. TFA at 0.4 mL/min flow rate and detecting at 215 nm. NMR spectra were recorded at 30 °C (400 MHz for $^{1}$H, 100 MHz for $^{13}$C). The external references were TMS (0.00 ppm for both $^{1}$H and $^{13}$C) for solutions in $CDCl_3$, HOD and DMSO for solutions in DMSO-*d6* (3.30 ppm for $^{1}$H and 39.5 ppm for $^{13}$C) and DSS (sodium 4,4-dimethyl-4-silapentane-1-sulfonate) for solutions in $D_2O$ (0.00 ppm for both $^{1}$H and $^{13}$C) respectively. Proton signal assignments were made by first-order analysis of the $^{1}$H, $^{13}$C, and DEPT spectra as well as by analysis of two-dimensional $^{1}$H–$^{1}$H (COSY) and $^{1}$H–$^{13}$C (HSQC) correlation maps. Of the two magnetically nonequivalent germinal protons at C-6, the one resonating at lower field is denoted H-6a and the one at higher field is denoted H-6b. Signal multiplicity is listed as s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, app: apparent. Sugar residues in oligosaccharides are serially lettered according to the lettering of the repeating unit of the SF3a O-Ag and are identified by a subscript in the listing of signal assignments. High resolution mass spectra (HRMS) were obtained in the positive ion mode using a Q-TOF mass spectrometer equipped with an electrospray ion source.

b. Monosaccharides B and C

**Allyl α-L-rhamnopyranoside (S1).**[3] Acetyl chloride (48.8 mL, 686 mmol, 2.5 equiv.) was added dropwise to allyl alcohol (623 mL) at 0 °C. The solution was stirred for 25 min, and then L-rhamnose monohydrate (50 g, 274 mmol, 1.0 equiv.) was added. The mixture was heated for 2 h at reflux then for 20 h at 40 °C. Follow up by TLC (DCM/MeOH, 80:20) indicated the total conversion of the starting hemiacetal into a less polar product. The bath temperature was cooled to 0 °C and the solution was neutralized by addition of solid $NaHCO_3$ (103 g). The suspension was filtered over a pad of Celite® and the mixture was concentrated under reduced pressure. The crude was used as such in the next step. Purification by flash column chromatography (DCM/MeOH, 95:5 to 90:10) afforded a pure analytical sample of the triol **S1** as a translucent oil. The latter had $R_f$ = 0.7 (DCM/MeOH, 80:20). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.90 (dddd, $J$ = 17.2, 10.4, 6.0, 5.2 Hz, 1H, C<u>H</u>=$CH_2$), 5.30 (ddd, $J$ = 17.2, 3.2, 1.3 Hz, 1H, CH=C<u>H</u>$_2$), 5.21

(ddd, $J$ = 10.4, 2.6, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 4.81 (d, $J$ = 1.2 Hz, 1H, H-1), 4.17 (ddt$_{app}$, $J$ = 12.9, 5.2, 1.3 Hz, 1H, C$\underline{H}_{2All}$), 4.03 (brs, 3H, O$\underline{H}$), 4.00 (ddt$_{app}$, $J$ = 12.9, 6.0, 1.3 Hz, 1H, C$\underline{H}_{2All}$), 3.98 (dd, $J$ = 3.2, 1.2 Hz, 1H, H-2), 3.82 (dd, $J$ = 9.3, 3.2 Hz, 1H, H-3), 3.71 (dq, $J$ = 9.3, 6.1 Hz, 1H, H-5), 3.48 (t$_{app}$, $J$ = 9.3 Hz, 1H, H-4), 1.34 (d, $J$ = 6.1 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 133.8 ($\underline{C}$H=CH$_2$), 117.4 (CH=$\underline{C}$H$_2$), 98.9 (C-1, $J_{C,H}$ = 169.8 Hz), 72.8 (C-4), 71.7 (C-3), 71.0 (C-2), 68.2 (C-5), 68.0 ($\underline{C}H_{2All}$), 17.6 (C-6). HRMS (ESI$^+$): *m/z* 227.0895 (calcd for $C_9H_{16}O_5Na$ [M+Na]$^+$: *m/z* 227.0890).

**Allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (S2).[3]** To a solution of crude triol **S1** (274 mmol) in acetone (290 mL) were successively added at rt 2,2-dimethoxypropane (2,2-DMP, 101 mL, 822 mmol, 3.0 equiv.) and PTSA·$H_2O$ (2.60 g, 13.7 mmol, 0.05 equiv.). The mixture was stirred for 3 h at rt. Follow up by TLC (DCM/MeOH, 90:10) indicated the total conversion of the starting material into a less polar product. The solution was neutralized by adding $Et_3N$ (4 mL) and solvents were evaporated under reduced pressure. The residue was dissolved in DCM and washed with $H_2O$ three times and then with brine. The organic layer was dried by passing through a phase separator filter and concentrated under reduced pressure. The residue was purified by flash column chromatography (Tol/EtOAc, 90:10 to 80:20) to give alcohol **S2** (53.7 g, 80% over 2 steps) as a yellow oil. The latter had $R_f$ = 0.6 (DCM/MeOH, 90:10). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.90 (dddd, $J$ = 17.0, 10.4, 5.9, 5.5 Hz, 1H, C$\underline{H}$=CH$_2$), 5.32 (dt$_{app}$, $J$ = 17.0, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 5.22 (dt$_{app}$, $J$ = 10.4, 1.3 Hz, 1H, CH=C$\underline{H}_2$), 5.01 (brs, 1H, H-1), 4.19 (ddt$_{app}$, $J$ = 12.8, 5.3, 1.4 Hz, 1H, C$\underline{H}_{2All}$), 4.17 (d$_{app}$, $J$ = 6.4 Hz, 1H, H-2), 4.10 (dd, $J$ = 7.2, 5.8 Hz, 1H, H-3), 4.02 (ddt$_{app}$, $J$ = 12.9, 5.1, 1.5 Hz, 1H, C$\underline{H}_{2All}$), 3.69 (dq, $J$ = 9.3, 6.3 Hz, 1H, H-5), 3.39 (dd, $J$ = 9.3, 7.2 Hz, 1H, H-4), 3.05 (brs, 1H, O$\underline{H}$), 1.53 (s, 3H, $CH_{3iPr}$), 1.36 (s, 3H, $CH_{3iPr}$), 1.31 (d, $J$ = 6.3 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 133.6 ($\underline{C}$H=CH$_2$), 117.7 (CH=$\underline{C}$H$_2$), 109.5 ($C_{iPr}$), 96.3 (C-1, $J_{C,H}$ = 169.5 Hz), 78.5 (C-3), 75.9 (C-2), 74.5 (C-4), 68.0 ($\underline{C}H_{2All}$), 65.9 (C-5), 27.9 ($\underline{C}H_{3iPr}$), 26.1 ($\underline{C}H_{3iPr}$), 17.4 (C-6). HRMS (ESI$^+$): *m/z* 267.1206 (calcd for $C_{12}H_{19}O_6Na$ [M+Na]$^+$: *m/z* 267.1208).

**Allyl 2,3-*O*-isopropylidene-4-*O*-benzyl-α-L-rhamnopyranoside (S3).[3]** To a cooled solution of alcohol **S2** (43.7 g, 179 mmol) in anhydrous DMF (300 mL) at 0 °C under an Ar atmosphere was added NaH (60% oil dispersion, 21.5 g, 537 mmol, 3.0 equiv.) portionwise. The mixture was stirred for 30 min at 0 °C. Benzyl bromide (42.6 mL, 358 mmol, 2.0 equiv.) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. Follow up by TLC (Tol/EtOAc, 80:20) indicated the total conversion of the starting material into a less polar product. The reaction was quenched at 0 °C by addition of MeOH. Solvents were eliminated under reduced

pressure. The residue was taken up in EtOAc and washed with aq. 10% HCl and brine. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude was used as such in the next step. Purification by flash column chromatography on silica gel (cHex/EtOAc, 100:0 to 95:5) afforded a pure analytical sample of allyl glycoside **S3** as a colorless oil. The latter had $R_f$ = 0.8 (cHex/EtOAc, 80:20). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41 – 7.35 (m, 5H, $H_{Ar}$), 5.92 (dddd, *J* = 17.3, 10.3, 6.2, 5.2 Hz, 1H, C<u>H</u>=$CH_2$), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H, CH=C<u>H</u>$_2$), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H, CH=C<u>H</u>$_2$), 5.03 ($s_{app}$, 1H, H-1), 4.93 (d, 1H, *J* = 11.6 Hz, $H_{Bn}$), 4.65 (d, 1H, *J* = 11.6 Hz, $H_{Bn}$), 4.59 ($s_{app}$, 1H, H-1), 4.30 ($t_{app}$, *J* = 7.0, 6.3 Hz, 1H, H-3), 4.19 (m, 1H, C<u>H</u>$_{2All}$), 4.19 (m, 1H, H-2), 4.02 ($ddt_{app}$, *J* = 12.8, 6.2, 1.3 Hz, 1H, C<u>H</u>$_{2All}$), 3.74 (dq, *J* = 9.9, 6.2 Hz, 1H, H-5), 3.24 (dd, *J* = 9.8, 7.1 Hz, 1H, H-4), 1.53 (s, 3H, C<u>H</u>$_{3iPr}$), 1.40 (s, 3H, C<u>H</u>$_{3iPr}$), 1.31 (d, *J* = 6.3 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.5 ($C_{Ar}$), 133.7 (<u>C</u>H=$CH_2$), 128.4 – 127.6 (5<u>C</u>$H_{Ar}$), 117.6 (CH=<u>C</u>$H_2$), 109.1 ($C_{iPr}$), 96.2 (C-1, $J_{C,H}$ = 169.4 Hz), 81.2 (C-4), 78.7 (C-3), 76.2 (C-2), 72.9 (<u>C</u>$H_{2Bn}$), 67.9 (<u>C</u>$H_{2All}$), 64.6 (C-5), 28.0 (<u>C</u>$H_{3iPr}$), 26.3 (<u>C</u>$H_{3iPr}$), 17.8 (C-6). HRMS ($ESI^+$): *m/z* 352.2124 (calcd for $C_{19}H_{26}O_5Na$ $[M+Na]^+$: *m/z* 352.2116).

**Allyl 4-*O*-benzyl-*α*-L-rhamnopyranoside (5).**[3] *Route 1.* The fully protected crude **S3** (179 mmol) was dissolved in 80% aq. AcOH (448 mL) and the solution was stirred for 3 h at 60 °C. Follow up by TLC (cHex/EtOAc, 70:30) indicated conversion of acetal **S3** into a more polar product. Solvents were removed under vacuum and traces of AcOH were eliminated by co-evaporation with toluene three times to give a white solid. Filtration over a pad of silica (cHex/EtOAc, 80:20) and crystallization of the material from hot diisopropyl ether gave diol **5** as a white solid. The mother liquor was purified by flash column chromatography on silica gel (Tol/EtOAc, 80:20 to 50:50) to afford in total 51.95 g of white solid (89% over 2 steps).

*Route 2.* Acetyl chloride (50 mL, 693 mmol, 2.5 equiv.) was added dropwise to allyl alcohol (610 mL) at 0 °C, the solution was stirred for 25 min, and L-rhamnose monohydrate (50 g, 277 mmol) was added. The mixture was heated for 2 h at 70 °C then for 15 h at 40 °C. Follow up by TLC (DCM/MeOH, 80:20) indicated the total conversion of the starting hemiacetal into a less polar product. The bath temperature was cooled to 0 °C and the solution was neutralized by addition of solid $NaHCO_3$ (103 g). The suspension was filtered over a pad of Celite® and solvents were evaporated and co-evaporated three times with toluene. The crude material was dissolved in acetone (300 mL), 2,2-DMP (100 mL, 810 mmol, 3.0 equiv.) and PTSA·$H_2O$ (3.04 g, 16 mmol, 0.05 equiv.) were successively added. After stirring at rt for 3 h, TLC (DCM/MeOH, 90:10) indicated the total conversion of the intermediate **S1** into a less polar

product. The solution was neutralized by adding $Et_3N$ (4 mL) and solvents were evaporated under reduced pressure. The residue was dissolved in DCM and washed with $H_2O$ three times and brine. The organic layer was dried by passing through a phase separator filter and concentrated to dryness. The crude **S2** was dissolved in DMF (800 mL) under an Ar atmosphere, the bath temperature was cooled to -5 °C and NaH (60% oil dispersion, 29.1 g, 730 mmol, 2.4 equiv.) was added portionwise to this suspension. The mixture was stirred at rt for 2 h under inert atmosphere and then benzyl bromide (65 mL, 330 mmol, 1.2 equiv.) was added dropwise while maintaining the bath temperature at -5 °C. After stirring the reaction mixture for 2 h at rt, a TLC control (cHex/EtOAc, 80:20) indicated the total conversion of the intermediate alcohol into a less polar product. The reaction was quenched at 0 °C by addition of MeOH (50 mL). Solvents were eliminated under reduced pressure and volatiles were co-evaporated with toluene. The residue was taken in EtOAc and washed with $H_2O$ three times and with brine. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated to dryness. The crude **S3** was dissolved in 80% aq. AcOH (500 mL) and the solution was stirred for 16 h at 80 °C. A TLC control (cHex/EtOAc, 50:50) indicated the total conversion of the intermediate **S3** into a more polar product. Solvents were removed under vacuum and traces of AcOH were eliminated by co-evaporation with toluene three times. The crude material was crystallized twice from *i*$Pr_2O$/petroleum ether (4:1, 300 mL) and the mother liquor was further purified by flash column chromatography on silica gel (CHex/EtOAc, 100:0 to 50:50) to give diol **5** (66.3 g, 82% over 4 steps) as a beige solid. The expected diol **5** had $R_f$ = 0.2 (CHex/EtOAc, 60:40). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41 – 7.31 (m, 5H, $H_{Ar}$), 5.90 (dddd, $J$ = 17.3, 10.5, 6.0, 5.1 Hz, 1H, C<u>H</u>=$CH_2$), 5.30 (dq, $J$ = 17.2, 1.7 Hz, 1H, CH=C<u>H</u>$_2$), 5.21 (dq, $J$ = 10.4, 1.4 Hz, 1H, CH=C$H_2$), 4.83 ($s_{app}$, 1H, H-1), 4.77 (s, 2H, $H_{Bn}$), 4.19 ($ddt_{app}$, $J$ = 13.0, 5.1, 1.6 Hz, 1H, C<u>H</u>$_{2All}$), 4.00 (ddt, $J$ = 13.0, 6.0, 1.4 Hz, 1H, C<u>H</u>$_{2All}$), 3.98 – 3.93 (m, 2H, H-2, H-3), 3.77 (dq, $J$ = 9.6, 6.3 Hz, 1H, H-5), 3.37 ($t_{app}$, $J$ = 9.2 Hz, 1H, H-4), 2.33 (d, $J$ = 3.4 Hz, 1H, OH-2), 2.30 (d, $J$ = 5.0 Hz, 1H, OH-3), 1.38 (d, $J$ = 6.3 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.3 ($C_{Ar}$), 133.8 (<u>C</u>H=$CH_2$), 128.6 – 128.0 (5<u>C</u>$H_{Ar}$), 117.3 (CH=<u>C</u>$H_2$), 98.5 (C-1, $J_{C,H}$ = 168.7 Hz), 81.8 (C-4), 75.1 (<u>C</u>$H_{2Bn}$), 71.5 (C-2), 71.2 (C-3), 67.9 (<u>C</u>$H_{2All}$), 67.3 (C-5), 18.0 (C-6). HRMS ($ESI^+$): *m/z* 317.1365 (calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: *m/z* 317.1355).

**Allyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (8).**[4] To a solution of alcohol **7** (22.7 g, 59.0 mmol) in DCM (210 mL) stirred at rt were successively added levulinic acid (13.7 g, 118 mmol, 2.0 equiv), DMAP (1.44 g, 11.8 mmol, 0.2 equiv) and EDC (23.2 mL, 106.2 mmol, 1.8 equiv) under an Ar atmosphere. The mixture was stirred at rt for 1.5 h. TLC

(Tol/EtOAc, 90:10) showed the complete disappearance of the starting **7** and the presence of a less polar product. The reaction mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ twice, 10% aq. NaOH twice and finally with brine. The organic layer was passed through a phase separator filter and concentrated under reduced pressure. Purification of the residue by flash column chromatography (cHex/EtOAc, 90:10 to 80:20) gave the known **8** (25.5 g, 90%) as a colourless syrup. The fully protected **8** had $R_f$ = 0.25 (Tol/EtOAc, 90:10). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 – 7.30 (m, 10H, $H_{Ar}$), 5.91 (m, 1H, C<u>H</u>=$CH_2$), 5.43 (m, 1H, H-2), 5.28 (m, $J$ = 15.8 Hz, 1H, CH=C<u>H</u>$_2$), 5.22 (m, $J$ = 10.4 Hz, 1H, CH=C<u>H</u>$_2$), 4.95 (d, $J$ = 10.8 Hz, 1H, $H_{Bn}$), 4.81 (d, $J$ = 1.5 Hz, 1H, H-1), 4.72 (d, $J$ = 11.2 Hz, 1H, $H_{Bn}$), 4.65 (d, $J$ = 10.8 Hz, 1H, $H_{Bn}$), 4.55 (d, $J$ = 11.2 Hz, 1H, $H_{Bn}$), 4.16 (m, 1H, C<u>H</u>$_{2All}$), 4.05 – 3.95 (m, 2H, C<u>H</u>$_{2All}$, H-3), 3.81 (m, 1H, H-5), 3.46 ($t_{app}$, $J$ = 9.4 Hz, 1H, H-4), 2.74 (m, 4H, C<u>H</u>$_{2Lev}$), 2.19 (s, 3H, C<u>H</u>$_{3Lev}$), 1.37 (d, $J$ = 6.2 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.6 (<u>C</u>O$_{Lev}$), 172.5 (<u>C</u>O$_{2Lev}$), 138.9 (<u>C</u>$_{Ar}$), 138.5 (<u>C</u>$_{Ar}$), 133.9 (<u>C</u>H=$CH_2$), 128.9 – 128.1 (10<u>C</u>H$_{Ar}$), 118.0 (CH=<u>C</u>H$_2$), 97.1 (C-1, $J_{C,H}$ = 169.8 Hz), 80.5 (C-4), 78.5 (C-3), 75.8 (<u>C</u>H$_{2Bn}$), 72.0 (<u>C</u>H$_{2Bn}$), 69.5 (C-2), 68.4 (<u>C</u>H$_{2All}$), 68.1 (C-5), 38.4 (<u>C</u>H$_{2Lev}$), 30.2 (<u>C</u>H$_{3Lev}$), 28.6 (CH$_{2Lev}$), 18.4 (C-6). HRMS (ESI$^+$): *m/z* 505.2201 (calcd for $C_{28}H_{34}O_7Na$ $[M+Na]^+$: *m/z* 505.2202).

**2-Oxopropyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (12a) and 3-Oxopropyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (12b).** To a solution of allyl glycoside **8** (60 mg, 0.12 mmol, 1.0 equiv.) in DMF/$H_2O$ (3:1, 2.0 mL) was added $PdCl_2$ (8.8 mg, 0.05 mmol, 0.4 equiv., 60% purity). After stirring at rt for 7 h, TLC (Tol/EtOAc, 80:20) revealed the absence of starting **8** and the presence of more polar products. The reaction mixture was diluted with sat. aq. $NH_4Cl$ and EtOAc. The two layers were separated. The aq. phase was extracted with EtOAc and the combined organic phases were extrated with sat. aq. $NaHCO_3$, water and brine. The organic phase was dried on $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (Tol/EtOAc, 100:0 to 80:20) led to a 4:1 mixture of the Wacker-type products **12a** and **12b** as a colourless oil (46 mg, 74%). The latter had $R_f$ = 0.4 (Tol/EtOAc, 70:30). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.79 (t, $J$ = 1.6 Hz, 0.2H, C<u>H</u>O$_b$), 7.40 – 7.29 (m, 10H, $H_{Ar}$), 5.47 (dd, $J$ = 3.4, 1.8 Hz, 0.8H, H-2$_a$), 5.34 (dd, $J$ = 3.4, 1.8 Hz, 0.2H, H-2$_b$), 4.94 (d, $J$ = 10.9 Hz, 0.8H, $H_{Bna}$), 4.92 (d, $J$ = 10.8 Hz, 0.2H, $H_{Bnb}$), 4.79 (d, $J$ = 1.8 Hz, 0.8H, H-1$_a$), 4.76 (d, $J$ = 1.8 Hz, 0.2H, H-1$_b$), 4.72 (d, $J$ = 11.2 Hz, 1H, $H_{Bn}$), 4.64 (d, $J$ = 10.9 Hz, 1H, $H_{Bn}$), 4.57 (d, $J$ = 11.2 Hz, 0.8H, $H_{Bna}$), 4.52 (d, $J$ = 11.2 Hz, 0.2H, $H_{Bnb}$), 4.17 (AB, $J$ = 17.0 Hz, 0.8H, OC<u>H</u>$_2$CO$_a$), 4.07 (AB, $J$ = 17.1 Hz, 0.8H, OC<u>H</u>$_2$CO$_a$), 3.98 (dd, $J$ = 9.3, 3.4 Hz, 0.8H, H-3$_a$), 3.88 (dd, $J$ = 9.3, 3.4 Hz, 0.2H, H-3$_b$), 3.76 (dq, $J$ = 9.9,

6.1 Hz, 1H, H-5), 3.45 (t, *J* = 9.4 Hz, 1H, H-4), 2.83 – 2.65 (m, 4H, C$\underline{H}_{2Lev}$), 2.19 (s, 3H, C$\underline{H}_{3Lev}$), 2.16 (s, 2.4H, COC$\underline{H}_{3a}$), 1.33 (d, *J* = 6.2 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.1 ($\underline{C}O_a$), 205.1 ($\underline{C}O_{Lev}$), 200.1 ($\underline{C}HO_b$), 172.0 ($\underline{C}O_{2Levb}$), 171.9 ($\underline{C}O_{2Leva}$), 138.4 ($\underline{C}_{Ar}$), 138.0 ($\underline{C}_{Ar}$), 128.4 – 127.7 (10$\underline{C}H_{Ar}$), 97.8 (C-1$_b$), 97.6 (C-1$_a$), 79.9 (C-4$_b$), 79.7 (C-4$_a$), 77.9 (C-3$_b$), 77.6 (C-3$_a$), 75.4 ($\underline{C}H_{2Bn}$), 72.0 (O$\underline{C}H_2CO_a$), 71.7 ($\underline{C}H_{2Bn}$), 69.0 (C-2$_b$), 68.9 (C-2$_a$), 68.3 (C-5$_a$), 67.9 (C-5$_b$), 43.4 ($\underline{C}H_{2Levb}$), 38.0 ($\underline{C}H_{2Leva}$), 29.8 ($\underline{C}H_{3Lev}$), 28.1 ($\underline{C}H_{2Lev}$), 26.4 (CO$\underline{C}H_{3a}$), 18.0 (C-6). HRMS (ESI$^+$): *m/z* 516.2595 (calcd for $C_{28}H_{38}NO_7$ $[M+NH_4]^+$: *m/z* 516.2598).

**3,4-Di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl trichloroacetimidate (13).**[4] *Route 2.* Hemiacetal **9** (17.3 g, 39.1 mmol) was dissolved in anhydrous 1,2-DCE (130 mL), placed under Ar, and the solution was cooled to 0 °C. Trichloroacetonitrile (19.6 mL, 195 mmol, 5.0 equiv.) and DBU (1.64 mL, 10.9 mmol, 0.28 equiv.) were added. The solution was stirred at 0 °C for 1 h. TLC (cHex/EtOAc, 70:30, + 0.5% $Et_3N$) showed the conversion of hemiacetal **9** into less polar products. The mixture was carefully concentrated to around 20 mL and directly purified by column chromatography on silica gel (cHex/EtOAc, 80:20, + 0.5% $Et_3N$) to give the known trichloroacetimidate **13** (19.8 g, 87%) as a yellow syrup. Donor **13** had $R_f$ = 0.65 (cHex/EtOAc, 70:30). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.68 (s, 1H, N$\underline{H}$), 7.37 – 7.28 (m, 10H, $H_{Ar}$), 6.20 (d, *J* = 1.9 Hz, 1H, H-1), 5.50 (m, 1H, H-2), 4.97 (d, *J* = 10.8 Hz, 1H, $H_{Bn}$), 4.74 (d, *J* = 11.3 Hz, 1H, $H_{Bn}$), 4.67 (d, *J* = 10.8 Hz, 1H, $H_{Bn}$), 4.58 (d, *J* = 11.3 Hz, 1H, $H_{Bn}$), 4.03 – 3.94 (m, 2H, H-3, H-5), 3.53 ($t_{app}$, *J* = 9.5 Hz, 1H, H-4), 2.78 (m, 4H, C$\underline{H}_{2Lev}$), 2.19 (s, 3H, C$\underline{H}_{3Lev}$), 1.37 (d, *J* = 6.2 Hz, 3H, H-6). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.4 ($\underline{C}O_{Lev}$), 172.2 ($\underline{C}O_{2Lev}$), 160.7 ($\underline{C}$=NH), 138.5 ($\underline{C}_{Ar}$), 138.0 ($\underline{C}_{Ar}$), 128.8 – 128.2 (10$\underline{C}H_{Ar}$), 95.5 (C-1, $J_{C,H}$ = 178.6 Hz), 91.3 ($\underline{C}Cl_3$), 79.7 (C-4), 77.6 (C-3), 76.0 ($\underline{C}H_{2Bn}$), 72.3 ($\underline{C}H_{2Bn}$), 71.1 (C-5), 68.2 (C-2), 38.4 ($\underline{C}H_{2Lev}$), 30.2 ($\underline{C}H_{3Lev}$), 28.5 ($\underline{C}H_{2Lev}$), 18.4 (C-6). HRMS (ESI$^+$): *m/z* 608.0986 (calcd for $C_{27}H_{30}NO_7Na$ $[M+Na]^+$: *m/z* 608.0986).

c. Disaccharides $B_{Ac}C$ and trisaccharide $B_{Ac}CD$

**Allyl (3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→3)-2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranoside (15).**[4, 5] To a solution of trichloroacetimidate **13** (43.5 g, 74 mmol, 1.2 equiv.) and freshly prepared acceptor **14** (20.7 g, 61.7 mmol, 1.0 equiv.) in toluene (617 mL) containing activated 4 Å MS (20.7 g) was slowly added TMSOTf (3.35 mL, 18.5

mmol, 0.3 equiv) dropwise at -78 °C. The reaction mixture was stirred for 2.5 h while slowly coming back to rt. TLC (Tol/EtOAc, 80:20) showed the absence of acceptor **14** and the presence of a major less polar product. $Et_3N$ (3 mL) was added, the mixture was filtered over a pad of Celite®. Solids were generously washed with DCM and the filtrate was concentrated to dryness. Filtration on silica gel of the residue (Tol/EtOAc, 100:0 to 85:15) gave a yellow oil with solids. Toluene (150 mL) was added and the mixture was left at 4 °C overnight. After filtration and concentration to dryness, the known disaccharide **15** was obtained as a yellow oil (43.7 g) containing traces of contaminants, albeit could be used as such in the next step. The coupling product had $R_f$ = 0.5 (Tol/EtOAc, 80:20). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 – 7.27 (m, 15H, $H_{Ar}$), 5.89 (m, 1H, C<u>H</u>=$CH_2$), 5.46 (m, 1H, H-$2_B$), 5.29 (m, $J$ = 17.2 Hz, 1H, CH=C<u>H</u>$_2$), 5.21 (m, $J$ = 10.4 Hz, 1H, CH=C<u>H</u>$_2$), 5.17 (m, 1H, H-$2_C$), 5.05 (d, $J$ = 1.5 Hz, 1H, H-$1_B$), 4.91 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.87 (d, $J$ = 10.9 Hz, 1H, $H_{Bn}$), 4.80 (d, $J$ = 1.5 Hz, 1H, H-$1_C$), 4.67 – 4.60 (m, 3H, $H_{Bn}$), 4.45 (d, $J$ = 11.3 Hz, 1H, $H_{Bn}$), 4.20 – 4.13 (m, 2H, H-$3_C$, C<u>H</u>$_{2All}$), 3.98 (m, 1H, C<u>H</u>$_{2All}$), 3.90 (dd, $J$ = 9.3, 3.3 Hz, 1H, H-$3_B$), 3.83 – 3.74 (m, 2H, H-$5_B$, H-$5_C$), 3.47 ($t_{app}$, $J$ = 9.5 Hz, 1H, H-$4_C$), 3.43 ($t_{app}$, $J$ = 9.4 Hz, 1H, H-$4_B$), 2.71 (m, 4H, C<u>H</u>$_{2Lev}$), 2.18 (s, 3H, C<u>H</u>$_{3Lev}$), 2.14 (s, 3H, OCOC<u>H</u>$_3$), 1.31 (m, 6H, H-$6_C$, H-$6_B$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.4 (<u>C</u>O$_{Lev}$), 172.2 (<u>C</u>O$_{2Lev}$), 170.6 (O<u>C</u>OCH$_3$), 138.9 – 138.4 (3<u>C</u>$_{Ar}$), 133.9 (<u>C</u>H=$CH_2$), 128.9 – 128.0 (15<u>CH</u>$_{Ar}$), 117.8 (CH=<u>C</u>H$_2$), 100.0 (C-$1_B$, $J_{C,H}$ = 169.5 Hz), 96.6 (C-$1_C$, $J_{C,H}$ = 170.0 Hz), 80.7 (C-$4_C$), 80.2 (C-$4_B$), 78.1 (C-$3_C$), 78.0 (C-$3_B$), 75.9 (<u>C</u>H$_{2Bn}$), 75.6 (<u>C</u>H$_{2Bn}$), 72.7 (C-$2_C$), 71.9 (<u>C</u>H$_{2Bn}$), 69.7 (C-$2_B$), 69.0 (C-$5_B$), 68.6 (<u>C</u>H$_{2All}$), 68.2 (C-$5_C$), 38.4 (<u>C</u>H$_{2Lev}$), 30.2 (<u>C</u>H$_{3Lev}$), 28.6 (<u>C</u>H$_{2Lev}$), 21.4 (OCO<u>C</u>H$_3$), 18.3 (2C, C-$6_B$, C-$6_C$). HRMS (ESI$^+$): *m/z* 783.3364 (calcd for $C_{43}H_{52}O_{12}Na$ [M+Na]$^+$: *m/z* 783.3356).

**(3,4-Di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→3)-2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranose (16).[5]** 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)-iridium hexafluorophosphate ([Ir(COD){$PCH_3(C_6H_5)_2$}$_2$]$^+PF_6^-$, 422 mg, 0.50 mmol, 0.02 equiv.) was dissolved in THF (10 mL) and the resulting red solution was degassed, then stirred under an hydrogen atmosphere, causing the colour to change to yellow. The solution was degassed again and a solution of allyl glycoside **15** (19 g, 25.0 mmol) in THF (123 mL) was added. The mixture was stirred overnight at rt. TLC (Tol/EtOAc, 80:20) showed the complete disappearance of the starting **15** and the presence of a less polar product. Iodine (12.7 g, 50.0 mmol, 2.0 equiv.) in THF/water (1:1, 32 mL) was added and the mixture was stirred for 1 h at rt. TLC (Tol/EtOAc, 80:20 and DCM/MeOH, 98:2) showed the conversion of the intermediate into more polar products. An additionnal amount of iodine (2.0 equiv.) in THF (16 mL) were added and the

mixture was stirred at rt for 30 minutes. Excess iodine was destroyed by adding a solution of freshly prepared 5% aq. $Na_2S_2O_3$. DCM was added and the organic phase was washed with brine three times, dried on $Na_2SO_4$, filtered, and concentrated to dryness. Purification of the crude by flash column chromatography on silica gel (cHex/EtOAc, 100:0 to 60:40) gave the known hemiacetal **16** (17.4 g, 90%) as a yellow syrup, which had $R_f$ = 0.15 (cHex/EtOAc, 60:40). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 – 7.28 (m, 15H, $H_{Ar}$), 5.41 (dd, *J* = 3.3, 1.9 Hz, 1H, H-$2_B$), 5.15 – 5.11 (m, 2H, H-$2_C$, H-$1_C$), 5.05 (d, *J* = 1.7 Hz, 1H, H-$1_B$), 4.92 (d, *J* = 11.0 Hz, 1H, $H_{Bn}$), 4.83 (d, *J* = 10.9 Hz, 1H, $H_{Bn}$), 4.66 (d, *J* = 11.1 Hz, 1H, $H_{Bn}$), 4.63 – 4.60 (m, 2H, $H_{Bn}$), 4.45 (d, *J* = 11.3 Hz, 1H, $H_{Bn}$), 4.20 (dd, *J* = 9.4, 3.0 Hz, 1H, H-$3_C$), 3.98 (dq, *J* = 9.5, 6.2 Hz, 1H, H-$5_C$), 3.89 (dd, *J* = 9.3, 3.3 Hz, 1H, H-$3_B$), 3.83 (dq, *J* = 9.3, 6.2 Hz, 1H, H-$5_B$), 3.47 ($t_{app}$, 1H, H-$4_C$), 3.43 ($t_{app}$, 1H, H-$4_B$), 2.70 (m, 4H, C$\underline{H}_{2Lev}$), 2.18 (s, 3H, C$\underline{H}_{3Lev}$), 2.14 (s, 3H, OCOC$\underline{H}_3$), 1.29 (d, *J* = 6.3 Hz, 3H, H-$6_B$), 1.30 (d, *J* = 6.2 Hz, 3H, H-$6_C$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.8 ($\underline{C}O_{Lev}$), 172.6 ($\underline{C}O_{2Lev}$), 171.6 (O$\underline{C}OCH_3$), 138.8 – 138.4 (3$\underline{C}_{Ar}$), 128.9 – 128.1 (15$\underline{C}H_{Ar}$), 99.9 (C-$1_B$, $J_{C,H}$ = 173.3 Hz), 92.0 (C-$1_C$, $J_{C,H}$ = 170.0 Hz), 80.7 (C-$4_C$), 80.2 (C-$4_B$), 78.0 (C-$3_B$), 77.7 (C-$3_C$), 75.8 ($\underline{C}H_{2Bn}$), 75.6 ($\underline{C}H_{2Bn}$), 73.2 (C-$2_C$), 72.0 ($\underline{C}H_{2Bn}$), 69.7 (C-$2_B$), 69.0 (C-$5_B$), 68.0 (C-$5_C$), 38.4 ($\underline{C}H_{2Lev}$), 30.2 ($\underline{C}H_{3Lev}$), 28.5 ($\underline{C}H_{2Lev}$), 21.5 (OCO$\underline{C}H_3$), 18.5 (C-$6_B$), 18.4 (C-$6_C$). HRMS (ESI$^+$) : *m/z* 743.3173 (calcd for $C_{40}H_{48}O_{12}Na$ $[M+Na]^+$: *m/z* 743.3043).

**(3,4-Di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→3)-2-*O*-acetyl-4-*O*-benzyl-α/β-L-rhamnopyranosyl trichloroacetimidate (17).**[5] *Route 3.* Hemiacetal **16** (8.7 g, 12.1 mmol) was dissolved in anhydrous 1,2-DCE (50 mL) under Ar, and cooled to 0 °C. Trichloroacetonitrile (6.1 mL, 60.7 mmol, 5.0 equiv.) and DBU (508 µL, 3.3 mmol, 0.28 equiv.) were added. The mixture was stirred at 0 °C for 10 min. TLC (cHex/EtOAc, 70:30, + 1% $Et_3N$) showed the complete disappearance of hemiacetal **16** and the presence of less polar products. The mixture was concentrated to a minimum of solvent and purified by column chromatography (cHex/EtOAc + 5% $Et_3N$, 70:30 to 50:50) on pre-neutralized silica gel to give the known donor **17** (8.7 g, 84%) as a yellow syrup.

*Route 4.* 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)-iridium hexafluorophosphate ($[Ir(COD)\{PCH_3(C_6H_5)_2\}_2]^+PF_6^-$, 630 mg, 0.74 mmol. 0.03 equiv.) was dissolved in THF (75 mL) and the resulting red solution was degassed repeatedly. Hydrogen was bubbled through the solution, causing the colour to change to yellow. The solution was again degassed and disaccharide **15** (18.8 g, 24.6 mmol) in anhydrous THF (125 mL) was added. The mixture was stirred for 2 h at rt. TLC (Tol/EtOAc, 80:20) showed the complete

disappearance of allyl glycoside **15** and the presence of a less polar product. The mixture was treated with iodine (25.0 g, 98.6 mmol, 4.0 equiv.) in THF/water (4:1, 165 mL), and stirred for 1 h at rt. TLC (cHex/EtOAc, 60:40) showed the conversion of the intermediate into more polar products. Excess iodine was destroyed by adding sat. aq. $Na_2S_2O_3$. DCM was added and the organic phase was washed with water and brine, dried on $Na_2SO_4$, filtered, and concentrated to dryness. Trichloroacetonitrile (11.8 mL, 118 mmol, 5.0 equiv.) and DBU (1.1 mL, 6.6 mmol, 0.28 equiv.) were added dropwise to the crude **16** in anhydrous 1,2-DCE (120 mL) under Ar, at 0 °C. After stirring at 0 °C for 3 h, TLC (cHex/EtOAc + 1% $Et_3N$, 80:20) showed the complete disappearance of hemiacetal **16** and the presence of less polar products. The solution was concentrated to a minimum of solvent under reduced pressure, and the residue was purified by chromatography on neutralized silica gel (cHex/EtOAc + 1% $Et_3N$, 100:0 to 80:20 to 40:60). Donor **17** (19.1 g, 89%) was isolated as an orange syrup along with recovered hemiacetal **16** (1.6 g, 9%). Donor **17** had $R_f$ = 0.6 (Tol/EtOAc, 80:20). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, N<u>H</u>), 7.42 – 7.29 (m, 15H, $H_{Ar}$), 6.22 (d, *J* = 1.9 Hz, 1H, H-$1_C$), 5.48 (dd, *J* = 3.3, 1.8 Hz, 1H, H-$2_B$), 5.31 (dd, *J* = 3.3, 2.1 Hz, 1H, H-$2_C$), 5.10 (d, *J* = 1.6 Hz, 1H, H-$1_B$), 4.92 (d, 1H, *J* = 11.0 Hz, $H_{Bn}$), 4.85 (d, 1H, *J* = 10.8 Hz, $H_{Bn}$), 4.68 – 4.62 (m, 3H, $H_{Bn}$), 4.51 (d, *J* = 11.3 Hz, 1H, $H_{Bn}$), 4.26 (dd, *J* = 9.5, 3.4 Hz, 1H, H-$3_C$), 3.96 (dq, *J* = 9.7, 6.2 Hz, 1H, H-$5_C$), 3.89 (dd, *J* = 9.3, 3.3 Hz, 1H, H-$3_B$), 3.82 (dq, 1H, *J* = 9.6, 6.2 Hz, 1H, H-$5_B$), 3.58 ($t_{app}$, *J* = 9.4 Hz, 1H, H-$4_C$), 3.44 ($t_{app}$, *J* = 9.5 Hz, 1H, H-$4_B$), 2.72 (m, 4H, $CH_{2Lev}$), 2.18 (s, 3H, $CH_{3Lev}$), 2.17 (s, 3H, OCOC<u>H</u>$_3$), 1.36 (d, *J* = 6.2 Hz, 3H, H-$6_C$), 1.29 (d, *J* = 6.2 Hz, 3H, H-$6_B$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.5 (<u>C</u>O$_{Lev}$), 172.3 (<u>C</u>O$_{2Lev}$), 170.3 (O<u>C</u>OCH$_3$), 160.5 (<u>C</u>=NH), 138.8 – 138.0 (3<u>C</u>$_{Ar}$), 129.2 – 127.9 (15<u>C</u>H$_{Ar}$), 99.9 (C-$1_B$, $J_{C,H}$ = 168.1 Hz), 94.5 (C-$1_C$, $J_{C,H}$ = 178.7 Hz), 91.2 (<u>C</u>Cl$_3$), 80.2 (C-$4_C$), 80.1 (C-$4_B$), 77.9 (C-$3_B$), 76.5 (C-$3_C$), 76.1 (<u>C</u>H$_{2Bn}$), 75.7 (<u>C</u>H$_{2Bn}$), 72.0 (<u>C</u>H$_{2Bn}$), 71.2 (C-$2_C$), 71.1 (C-$5_C$), 69.6 (C-$2_B$), 69.1 (C-$5_B$), 38.4 (<u>C</u>H$_{2Lev}$), 30.2 (<u>C</u>H$_{3Lev}$), 28.5 (<u>C</u>H$_{2Lev}$), 21.3 (OCO<u>C</u>H$_3$), 18.4 (C-$6_B$), 18.3 (C-$6_C$).

**Allyl (3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (2).**[6] A solution of donor **17** (45 g, 52.0 mmol, 1.15 equiv.) and the known acceptor[7] **18** (20.4 g, 45.2 mmol, 1.0 equiv.) in anhydrous DCM (520 mL) containing 4 Å MS (20.4 g) was stirred at rt under Ar for 30 min. The suspension was cooled at 0 °C and stirred for 15 min. TMSOTf (0.4 mL, 2.26 mmol, 0.05 equiv.) was added dropwise, very slowly. After stirring for 3 h, while slowly warming up to rt, TLC (Tol/EtOAc, 80:20) revealed the

disappearance of acceptor **18** and the presence of less polar products. The reaction mixture was neutralized with $Et_3N$. Solids were filtered over a pad of Celite® and washed generously with DCM. The filtrate was evaporated to dryness and the residue was crystallized from *i*$Pr_2O$ and a minimum amount of EtOAc to give the known crystalline **2** (39.3 g). The mother liquor was further purified by flash column chromatography (Tol/Acetone, 100:0 to 95:5) to give an additional amount of trisaccharide **2** as a white solid (44.5 g, 86%). The coupling product **2** had $R_f$ = 0.3 (Tol/Acetone, 19:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 – 7.24 (m, 20H, $H_{Ar}$), 7.09 (d, $J$ = 7.3 Hz, 1H, N<u>H</u>), 5.87 (m, 1H, C<u>H</u>=$CH_2$), 5.55 (s, 1H, $H_{Bzl}$), 5.39 (dd, $J$ = 3.1, 1.9 Hz, 1H, H-$2_B$), 5.32 – 5.21 (m, 2H, CH=C<u>$H_2$</u>), 5.16 (dd, $J$ = 3.3, 1.8 Hz, 1H, H-$2_C$), 5.09 (d, $J$ = 8.3 Hz, 1H, H-$1_D$), 5.00 (d, $J$ = 1.7 Hz, 1H, H-$1_B$), 4.89 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.83 (d, $J$ = 1.5 Hz, 1H, H-$1_C$), 4.72 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.63 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.57 (d, $J$ = 11.3 Hz, 1H, $H_{Bn}$), 4.53 ($t_{app}$, $J$ = 8.7 Hz, 1H, H-$3_D$), 4.47 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.41 (d, $J$ = 11.3 Hz, 1H, $H_{Bn}$), 4.41 – 4.33 (m, 2H, H-6$a_D$, C<u>$H_{2All}$</u>), 4.13 – 4.07 (m, 2H, H-$3_C$, C<u>$H_{2All}$</u>), 3.97 (dq, $J$ = 9.6, 6.2 Hz, 1H, H-$5_C$), 3.85 – 3.75 (m, 3H, H-$3_B$, H-$5_B$, H-6$b_D$), 3.61 – 3.58 (m, 2H, H-$4_D$, H-$5_D$), 3.45 (m, 1H, H-$2_D$), 3.39 ($t_{app}$, $J$ = 9.4 Hz, 1H, H-$4_B$), 3.31 ($t_{app}$, $J$ = 9.6 Hz, 1H, H-$4_C$), 2.73 – 2.63 (m, 4H, C<u>$H_{2Lev}$</u>), 2.17 (s, 3H, C<u>$H_{3Lev}$</u>), 2.04 (s, 3H, OCOC<u>$H_3$</u>), 1.27 (d, $J$ = 6.2 Hz, 3H, H-$6_B$), 0.76 (d, $J$ = 6.2 Hz, 3H, H-$6_C$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.4 (<u>C</u>$O_{Lev}$), 172.0 (<u>C</u>$O_{2Lev}$), 170.0 (O<u>C</u>O$CH_3$), 162.4 (<u>C</u>ONH), 138.7 – 137.1 (4<u>C</u>$_{Ar}$), 133.4 (<u>C</u>H=$CH_2$), 129.3 – 126.7 (20<u>C</u>$H_{Ar}$), 118.6 (CH=<u>C</u>$H_2$), 102.3 ($C_{Bzl}$), 99.5 (C-$1_B$, $J_{C,H}$ = 171.3 Hz), 98.4 (C-$1_D$, $J_{C,H}$ = 164.6 Hz), 97.7 (C-$1_C$, $J_{C,H}$ = 172.4 Hz), 92.3 (<u>C</u>$Cl_3$), 80.4 (2C, C-$4_B$, C-$4_D$), 80.0 (C-$4_C$), 77.8 (C-$3_B$), 77.4 (C-$3_C$), 75.3 <u>C</u>$H_{2Bn}$), 75.2 (<u>C</u>$H_{2Bn}$), 74.1 (C-$3_D$), 71.9 (C-$2_C$), 71.7 (<u>C</u>$H_{2Bn}$), 71.0 (C-$6_D$), 69.5 (C-$2_B$), 68.8 (C-$5_B$), 68.2 (C-$5_C$), 66.4 (C-$5_D$), 60.4 (C-$2_D$), 38.2 (<u>C</u>$H_{2Lev}$), 30.0 (<u>C</u>$H_{3Lev}$), 28.3 (<u>C</u>$H_{2Lev}$), 21.1 (OCO<u>C</u>$H_3$), 18.1 (C-$6_B$), 17.3 (C-$6_C$). HRMS ($ESI^+$): *m/z* 1176.3236 (calcd for $C_{58}H_{66}Cl_3NO_{17}Na$ $[M+Na]^+$: *m/z* 1176.3293).

d. Disaccharide EA and pentasaccharide $EAB_{Ac}CD$

**Allyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-α-L-rhamnopyranoside (24)[8] and Allyl (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-α-L-rhamnopyranoside (25).[8]** *Route 1 (11.5 g scale).* Trimethyl orthoacetate (9.45 mL, 74.2 mmol, 1.9 equiv.) and monohydrated PTSA (111 mg, 0.59 mmol, 0.015 equiv.) were added to diol **5** (11.5 g, 39.1 mmol, 1.0 equiv.) in anhydrous MeCN (26 mL) at rt. After stirring at rt for 2 h, 80% aq. AcOH (26 mL) was added at 0 °C and the mixture was stirred at this

temperature for 1 h. TLC (Tol/EtOAc, 70:30) showed total consumption of the intermediate orthoester. DCM was added along with water and the two layers were separated. The aq. phase was extracted repeatedly with DCM and the combined organic phases were washed successively with sat. aq. $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered and concentrated to dryness to give crude acceptor **14**. TfOH (3.45 mL, 39.1 mmol, 1.0 equiv.) was slowly added to a solution of the latter and trichloroacetimidate[9] **21** (30.8 g, 44.9 mmol, 1.15 equiv.) in DCM (450 mL) containing DMF (60.5 mL, 78.1 mmol, 20 equiv.) and activated 4 Å MS (5.1 g) at -78 °C. The suspension was stirred overnight while the temperature reached rt. TLC (Tol/EtOAc, 70:30) indicated the presence of a main less polar product together with some unreacted acceptor **14**. $Et_3N$ (5.45 mL) was added and after 1 h, the suspension was filtered over a pad of Celite®. Solids were washed thoroughly with DCM and the organic phase was washed with sat. aq. $NaHCO_3$, water and brine. The combined organic phases were concentrated to dryness and the crude was solubilized in DCM/MeOH (11:8, 560 mL). 25% Methanolic MeONa (13.4 mL, 58.6 mmol, 1.5 equiv.) was added and the solution was stirred overnight. Dowex $H^+$ resin was added to the solution under gentle stirring until neutralisation. Filtration, concentration of the filtrate to dryness, and purification of the crude by flash chromatography (Tol/EtOAc, 90:10) gave the glucosylated products **24** and **25** as a 95:5 α/β mixture (25.73 g, 81%), corresponding to the target **24** (77%) and the β anomer **25** (4%). The undesired disaccharide **25** had $R_f$ = 0.35 (cHex/EtOAc, 73:27). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 – 7.15 (m, 25H, $H_{Ar}$), 5.90 (m, 1H, C<u>H</u>=$CH_2$), 5.29 (dq, *J* = 17.3 Hz, 1.8 Hz, 1H, CH=C<u>H</u>$_2$), 5.20 (dq, *J* = 10.3 *J* = 1.5 Hz, 1H, CH=C<u>H</u>$_2$), 4.96 (d, *J* = 11.2 Hz, 1H, $H_{Bn}$), 4.90 (d, *J* = 11.1 Hz, 2H, 2$H_{Bn}$), 4.84 (bs, 1H, H-1$_A$), 4.84 (d, *J* = 10.9 Hz, 1H, $H_{Bn}$), 4.80 (d, *J* = 11.1 Hz, 1H, $H_{Bn}$), 4.72 (d, *J* = 7.5 Hz, 1H, H-1$_E$), 4.71 (d, *J* = 11.1 Hz, 1H, $H_{Bn}$), 4.62 – 4.52 (m, 4H, 4$H_{Bn}$), 4.17 (ddt, *J* = 12.9 Hz, 5.1 Hz, 1.5 Hz, 1H, C<u>H</u>$_{2All}$), 4.14 – 4.09 (m, 2H, H-3$_A$, H-2$_A$), 3.98 (ddt, *J* = 12.9 *J* = 6.0 Hz, 1.3 Hz, 1H, C<u>H</u>$_{2All}$), 3.80 (dq, *J* = 9.6 Hz, 6.2 Hz, 1H, H-5$_A$), 3.71 (dd, *J* = 10.6 Hz, 2.1 Hz, 1H, H-6a$_E$), 3.70 – 3.50 (m, 6H, H-3$_E$, H-4$_E$, H-4$_A$, H-6b$_E$, H-2$_E$, H-5$_E$), 3.21 (d, *J* = 2.8 Hz, 1H, OH-2$_A$), 1.33 (d, *J* = 6.2 Hz, 3H, H-6A). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.4 – 137.9 (5<u>C</u>$_{Ar}$), 133.9 (<u>C</u>H=CH), 128.4 – 127.5 (25<u>C</u>H$_{Ar}$), 117.3 (CH=<u>C</u>$H_2$), 102.6 (C-1$_E$, $J_{C,H}$ = 160.4 Hz), 98.3 (C-1$_A$, $J_{C,H}$ = 170.3 Hz), 84.8 (C-3$_E$), 82.1 (C-2$_E$), 80.9 (C-3$_A$), 80.0 (C-4$_A$), 77.7 (C-4$_E$), 75.6 (<u>C</u>H$_{2Bn}$), 75.0 (<u>C</u>H$_{2Bn}$), 75.0 (<u>C</u>H$_{2Bn}$), 74.7 (<u>C</u>H$_{2Bn}$), 74.5 (C-5$_E$), 76.6 (<u>C</u>H$_{2Bn}$), 70.0 (C-2$_A$), 68.9 (C-6$_E$), 67.8 (<u>C</u>H$_{2All}$), 67.5 (C-5$_A$), 17.9 (C-6$_A$). HRMS (ESI$^+$): *m/z* 834.4189 (calcd for $C_{50}H_{56}O_{10}NH_4$ [M+$NH_4$]$^+$: *m/z* 834.4212).

**Allyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (3).[4]** Levulinic acid (6.34 g, 54.6 mmol, 1.5 equiv), EDC (9.62 mL, 54.6 mmol, 1.5 equiv) and DMAP (0.22 g, 1.80 mmol, 0.05 equiv) were added to alcohol **23** (29.3 g, 35.9 mmol, 1.0 equiv.) in anhydrous DCM (130 mL) were added successively. The mixture was stirred at rt for 3.5 h, and more levulinic acid (4.17 g, 35.9 mmol, 1.0) and EDC (6.35 mL, 35.9 mmol, 1.0 equiv.) were added. After stirring overnight at rt, TLC (cHex/EtOAc, 70:30) showed the absence of the starting **24** and the presence of a less polar product. Volatiles were evaporated and the residue solubilized in EtOAc, was washed with 1 M aq. HCl, 10% aq. $CuSO_4$, water, sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $Na_2SO_4$, filtered, and the filtrate was concentrated to dryness. Purification by flash column chromatography on silica gel (CHex/EtOAc, 80:20 to 60:40) afforded the fully protected **3** (29.4 g, 90%), which had $R_f$ = 0.3 (cHex/EtOAc, 70:30). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 – 7.10 (m, 25H, $H_{Ar}$), 5.87 (m, 1H, C<u>H</u>=$CH_2$), 5.39 (m, 1H, H-$2_A$), 5.28 (m, $J_{trans}$ = 17.2 Hz, 1H, CH=C<u>H</u>$_2$), 5.19 (d, $J$ = 5.6 Hz, 1H, H-$1_E$), 5.28 (m, $J_{cis}$ = 10.3 Hz, 1H, CH=C<u>H</u>$_2$), 5.02 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.96 – 4.85 (m, 3H, $H_{Bn}$), 4.78 (d, $J$ = 1.8 Hz, 1H, H-$1_A$), 4.78 – 4.59 (m, 4H, $H_{Bn}$), 4.50 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.36 (d, $J$ = 12.0 Hz, 1H, $H_{Bn}$), 4.26 (dd, $J$ = 9.6, 3.2 Hz, 1H, H-$3_A$), 4.18 – 4.04 (m, 3H, <u>C</u>H$_{2All}$, H-$3_E$, H-$5_E$), 3.97 (m, 1H, <u>C</u>H$_{2All}$), 3.80 (m, 1H, H-$5_A$), 3.77 ($t_{app}$, $J$ = 9.2 Hz, 1H, H-$4_E$), 3.64 – 3.52 (m, 4H, H-$2_E$, H-$6a_E$, H-$4_A$, H-$6b_E$), 2.60 – 2.45 (m, 4H, C<u>H</u>$_{2Lev}$),2.09 (s, 3H, C<u>H</u>$_{3Lev}$), 1.40 (d, $J$ = 6.2 Hz, 3H, H-$6_A$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.5 (<u>C</u>O$_{Lev}$), 172.5 (<u>C</u>O$_{2Lev}$), 139.2 – 138.1 (5<u>C</u>$_{Ar}$), 134.0 (<u>C</u>H=$CH_2$), 129.0 – 127.8 (25<u>C</u>H$_{Ar}$), 117.8 (CH=<u>C</u>H$_2$), 97.0 (C-$1_E$, $J_{C,H}$ = 170.2 Hz), 93.3 (C-$1_A$, $J_{C,H}$ = 167.5 Hz), 82.5 (C-$3_E$), 80.3 (C-$4_A$), 80.0 (C-$2_E$), 78.3 (C-$4_E$), 76.5 – 72.8 (5<u>C</u>H$_{2Bn}$), 72.8 (C-$3_A$), 70.6 (C-$5_E$), 68.7 (C-$6_E$), 68.6 (C-$2_A$), 68.5 (<u>C</u>H$_{2All}$), 68.4 (C-$5_A$), 38.2 (<u>C</u>H$_{2Lev}$), 30.0 (<u>C</u>H$_{3Lev}$), 28.4 (<u>C</u>H$_{2Lev}$), 18.3 (C-$6_A$). HRMS (ESI$^+$): *m/z* 937.4109 (calcd for $C_{55}H_{62}O_{12}Na$ [M+Na]$^+$: *m/z* 937.4139).

**(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranose (33).[4]** 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)-iridium hexafluorophosphate (0.36 g, 0.42 mmol, 0.02 equiv.) was dissolved in THF (8.4 mL) and the resulting red solution was degassed repeatedly. Hydrogen was bubbled through the solution, causing the colour to change to yellow. The solution was then degassed again under Ar. A solution of disaccharide **3** (29.2 g, 21.0 mmol, 1.0 equiv.) in anhydrous THF (105 mL) was added. The solution was stirred at rt for 1 h, at which time TLC (Tol/EtOAc, 90:10) showed the complete disappearance of allyl glycoside **3** and the presence of a less polar product. Iodine (5.33 g, 42.0 mmol, 2.0 equiv.) in THF/water (4:1, 140 mL) was added, and the biphasic mixture

was stirred at rt for 3 h. TLC (cHex/EtOAc, 60:40) showed the conversion of the intermediate into more polar products. Excess iodine was destroyed by adding 10% aq. $NaHSO_3$. Volatiles were evaporated, EtOAc was added and the organic phase was washed with 10% aq. $NaHSO_3$, sat. aq. $NaHCO_3$ and brine, dried on $Na_2SO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography on silica gel (cHex/EtOAc, 60:40 to 40:60) afforded hemiacetal **33** (23.6 g, 85%) as a 85:15 α/β mix. Hemiacetal **33** had $R_f$ = 0.2 (DCM/MeOH, 98:2). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 – 7.14 (m, 25H, $H_{Ar}$), 5.43 (m, 1H, H-$2_A$), 5.25 (d, $J$ = 3.4 Hz, 1H, H-$1_E$), 5.15 (d, $J$ = 1.7 Hz, 1H, H-$1_A$), 5.07 – 4.87 (m, 3H, $H_{Bn}$), 4.80 (d, $J$ = 12.2 Hz, 1H, $H_{Bn}$), 4.74 – 4.59 (m, 3H, $H_{Bn}$), 4.52 (d, $J$ = 11.0 Hz, 1H, $H_{Bn}$), 4.46 – 4.36 (m, 2H, $H_{Bn}$), 4.34 (m, 1H, H-$3_A$), 4.20 – 4.10 (m, 2H, H-$3_E$, H-$5_E$), 4.05 (m, 1H, H-$5_A$), 3.78 – 3.73 (m, 2H, O<u>H</u>, H-$4_E$), 3.70 – 3.55 (m, 4H, H-$2_E$, H-$6a_E$, H-$4_A$, H-$6b_E$), 2.55 (m, 4H, C<u>H</u>$_{2Lev}$), 2.11 (s, 3H, C<u>H</u>$_{3Lev}$), 1.41 (d, $J$ = 6.2 Hz, 3H, H-$6_A$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.9 (<u>C</u>O$_{Lev}$), 172.6 (<u>C</u>O$_{2Lev}$), 139.2 – 138.9 (5<u>C</u>$_{Ar}$), 129.0 – 127.8 (25<u>C</u>H$_{Ar}$), 93.0 (C-$1_E$, $J_{C,H}$ = 169.0 Hz), 92.4 (C-$1_A$, $J_{C,H}$ = 170.7 Hz), 82.5 (C-$3_E$), 80.3 (C-$4_A$), 79.9 (C-$2_E$), 78.3 (C-$4_E$), 76.5 – 73.2 (5<u>C</u>H$_{2Bn}$), 72.3 (C-$3_A$), 70.5 (C-$5_E$), 69.0 (C-$2_A$), 68.7 (C-$6_E$), 68.3 (C-$5_A$), 38.3 (<u>C</u>H$_{2Lev}$), 30.1 (<u>C</u>H$_{3Lev}$), 28.6 (<u>C</u>H$_{2Lev}$), 18.5 (C-$6_A$). HRMS (ESI$^+$): *m/z* 897.3777 (calcd for $C_{52}H_{58}O_{12}Na$ [M+Na]$^+$: *m/z* 897.3826).

**(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl trichloroacetimidate (34).**[4] *Route 1.* Trichloroacetonitrile (5.40 mL, 53.8 mmol, 2.0 equiv.) and DBU (0.80 mL, 5.35 mmol, 0.2 equiv.) were added to hemiacetal **33** (23.4 g, 26.7 mmol, 1.0 equiv.) in DCM (67 mL) under Ar, at 0 °C. After stirring at 0 °C for 1 h, TLC (cHex/EtOAc, 70:30) showed conversion of the starting **33** into less polar products. The mixture was concentrated to one third of its volume and directly purified by flash column chromatography on silica gel (cHex/EtOAc, 100:0 to 60:40) to give the known trichloroacetimidate **34** (25.8 g, 93%).

*Route 2.* Levulinic acid (11.9 g, 103 mmol, 2.0 equiv.), EDC (19.1 g, 93 mmol, 1.8 equiv.) and DMAP (4.2 g, 21 mmol, 0.4 equiv.) were added to alcohol **24** (42 g, 51 mmol, 1.0 equiv.) in anhydrous DCM (250 mL). After stirring at rt for 2 days, TLC (Tol/EtOAc, 80:20) showed conversion of the starting alcohol **24** into a more polar product. The suspension was filtered over a pad of Celite®, and solids were washed thoroughly with DCM. The filtrate was washed with sat. aq. $NaHCO_3$, sat. aq. $CuSO_4$ twice, and brine. The organic layer was dried on $Na_2SO_4$, filtered, and concentrated to dryness. 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)-iridium hexafluorophosphate (1.29 g, 1.53 mmol, 0.03 equiv.) was dissolved in anhydrous THF

(38 mL) and the red solution was degassed repeatedly. Hydrogen was bubbled through the solution, causing the colour to change to yellow. The solution was degassed and the crude **3** (51 mmol, 1.0 equiv.) in anhydrous THF (255 mL) was added and the solution was stirred at rt for 3 h. TLC (Tol/EtOAc, 80:20) revealed the conversion of allyl glycoside **3** in a less polar product. Iodine (51.8 g, 204 mmol, 4.0 equiv.) in THF/water (4:1, 340 mL) was added and the biphasic mixture was stirred at rt for 2 h. TLC (Tol/EtOAc, 80:20) indicated the conversion of the intermediate into more polar products. Sat. aq. $Na_2S_2O_3$ was added and volatiles were evaporated. EtOAc was added to the residual aq. phase and the organic phase was washed with sat. aq. $NaHCO_3$ and brine, dried on $Na_2SO_4$, filtered, and concentrated to dryness. Trichloroacetonitrile (25.6 mL, 255 mmol, 5.0 equiv.) and DBU (2.2 mL, 14.3 mmol, 0.28 equiv.) were added dropwise to the crude hemiacetal **33** (51 mmol) in anhydrous 1,2-DCE (340 mL) under Ar, at 0 °C. After stirring at rt for 3 h, TLC (cHex/EtOAc, 70:30, + 1% $Et_3N$) showed the complete disappearance of hemiacetal **33** and the presence of less polar products. The mixture was concentrated to about one third of the original volume and purified by flash column chromatography on neutralized silica gel (cHex/EtOAc, 100:0 to 90:10 to 50:50, + 1% $Et_3N$) to give trichloroacetimidate **34** (35.0 g, 67% over 3 steps) as a brown oil along with the recovered hemiacetal **33** (13.6 g, 30%). The desired donor **34** had $R_f$ = 0.35 (CHex/EtOAc, 70:30). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.72 (s, 1H, N<u>H</u>), 7.42 – 7.14 (m, 25H, $H_{Ar}$), 6.24 (d, $J$ = 2.0 Hz, 1H, H-1$_A$), 5.61 (m, 1H, H-2$_A$), 5.27 (d, $J$ = 3.4 Hz, 1H, H-1$_E$), 5.05 – 4.99 (m, 2H, $H_{Bn}$), 4.92 – 4.88 (m, 2H, $H_{Bn}$), 4.80 (d, $J$ = 12.0 Hz, 1H, $H_{Bn}$), 4.74 – 4.53 (m, 4H, $H_{Bn}$), 4.42 (d, $J$ = 12.2 Hz, 1H, $H_{Bn}$), 4.34 (dd, $J$ = 9.7, 3.1 Hz, 1H, H-3$_A$), 4.16 – 4.06 (m, 2H, H-3$_E$, H-5$_E$), 4.02 (m, 1H, H-5$_A$), 3.79 ($t_{app}$, $J_{3,4}$ = 9.3 Hz, 1H, H-4$_E$), 3.71 – 3.62 (m, 3H, H-4$_A$, H-6a$_E$, H-2$_E$), 3.52 (m, 1H, H-6b$_E$), 2.59 (m, 4H, C<u>H</u>$_{2Lev}$), 2.11 (s, 3H, C<u>H</u>$_{3Lev}$), 1.45 (d, $J$ = 6.2 Hz, 3H, H-6$_A$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.3 (<u>C</u>O$_{Lev}$), 172.5 (<u>C</u>O$_{2Lev}$), 160.5 (<u>C</u>=NH), 139.1 – 137.9 (5<u>C</u>$_{Ar}$), 129.2 – 127.8 (25<u>C</u>H$_{Ar}$), 95.4 (C-1$_A$, $J_{C,H}$ = 178.9 Hz), 93.4 (C-1$_E$, $J_{C,H}$ = 168.3 Hz), 91.3 (<u>C</u>Cl$_3$), 82.4 (C-3$_E$), 79.8 (C-2$_E$), 79.5 (C-4$_A$), 78.2 (C-4$_E$), 76.8 – 73.2 (<u>C</u>H$_{2Bn}$), 72.5 (C-3$_A$), 71.4 (C-5$_A$), 70.8 (C-5$_E$), 68.4 (C-6$_E$), 66.9 (C-2$_A$), 38.2 (<u>C</u>H$_{2Lev}$), 30.0 (<u>C</u>H$_{3Lev}$), 28.4 (<u>C</u>H$_{2Lev}$), 18.4 (C-6$_A$). HRMS (ESI$^+$): *m/z* 897.3777 (calcd for $C_{54}H_{62}Cl_3N_2O_{13}Na$ $[M+NH_4]^+$: *m/z* 897.3826).

**Allyl (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (1).**[6] *Route 2*. Hydrazine hydrate (60% in water, 6.3

mL, 130 mmol, 5.0 equiv.) was added dropwise to a solution of the fully protected $B_{Ac}CD$ **2** (30.0 g, 26.0 mmol, 1.0 equiv.) in pyridine/AcOH (3:2, 550 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h. TLC (Tol/EtOAc, 80:20) showed the complete disappearance of the starting material and the presence of a more polar product. The reaction mixture was diluted with water and EtOAc. The two layers were separated, the aq. phase was extracted with EtOAc and the combined organic phases were washed with sat. aq. $NaHCO_3$, water and brine, dried over $Na_2SO_4$, filtered and evaporated to dryness. Filtration on a pad of silica (Tol/EtOAc, 80:20) afforded the desired compound as a white foam. Activated 4 Å MS (17.0 g) was added to the crude acceptor **36** (26.0 mmol, 1.0 equiv.) and donor **34** (27.5 g, 29.9 mmol, 1.15 equiv.) in anhydrous toluene (260 mL) and the suspension was stirred at rt, under Ar, for 30 min. TMSOTf (940 µL, 5.20 mmol, 0.2 equiv.) was added very slowly at rt. After stirring at rt for 1 h, TLC (Tol/Acetone, 80:20) showed the complete disappearance of acceptor **36** and the presence of less polar products. $Et_3N$ was added and after stirring for 10 min at rt, solids were filtered over a pad of Celite® and washed generously with DCM. Successive purifications by flash column chromatography on silica gel (Tol/EtOAc, 100:0 to 90:10 then Tol/EtOAc, 100:0 to 90:10) afforded the desired pentasaccharide **1** as a white foam (39.6 g, 80% over 2 steps) along with recovered starting material **36** (4.2 g, 15%) and contaminated Chapman-rearranged disaccharide (4.5 g, 15% from **34**). The fully protected target **1** had $R_f$ = 0.35 (Tol/EtOAc, 80:20). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50 – 7.10 (m, 45H, $H_{Ar}$), 5.95 – 5.85 (m, 1H, C$\underline{H}$=$CH_2$), 5.57 – 5.53 (m, 2H, $H_{Bzl}$, H-$2_A$), 5.34 – 5.22 (m, 3H, H-$1_E$, CH=C$\underline{H}_2$), 5.17 (m, 1H, H-$2_C$), 5.13 (d, $J$ = 8.2 Hz, 1H, H-$1_D$), 5.03 – 4.85 (m, 8H, H-$1_A$, H-$1_B$, H-$1_C$, 5$H_{Bn}$), 4.78 (d, $J$ = 13.1 Hz, 1H, $H_{Bn}$), 4.67 (d, $J$ = 13.1 Hz, 1H, $H_{Bn}$), 4.70 – 4.34 (m, 12H, H-$3_D$, H-6b$_D$, C$\underline{H}_{2All}$, 9$H_{Bn}$), 4.24 (dt, $J$ = 9.7, 2.6 Hz, 1H, H-$3_A$), 4.15 – 3.94 (m, 6H, H-$2_B$, H-$3_C$, H-$3_E$, H-$5_C$, H-$5_E$, C$\underline{H}_{2All}$), 3.87 – 3.77 (m, 4H, H-$3_B$, H-$4_E$, H-$5_A$, H-6a$_D$), 3.70 – 3.41 (m, 9H, H-$2_D$, H-$2_E$, H-$4_A$, H-$4_B$, H-$4_D$, H-$5_B$, H-$5_D$, H-6a$_E$, H-6b$_E$), 3.29 ($t_{app}$, $J$ = 9.5 Hz, 1H, H-$4_C$), 2.58 – 2.41 (m, 4H, C$\underline{H}_{2Lev}$), 2.08 (s, 3H, C$\underline{H}_{3Lev}$), 2.06 (s, 3H, OCOC$\underline{H}_3$), 1.28 (d, $J$ = 6.2 Hz, 3H, H-$6_A$), 1.25 (d, $J$ = 6.2 Hz, 3H, H-$6_B$), 0.74 (d, $J$ = 6.2 Hz, 3H, H-$6_C$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.2 ($\underline{C}O_{Lev}$), 171.8 ($\underline{C}O_{2Lev}$), 169.9 (O$\underline{C}OCH_3$), 162.3 ($\underline{C}ONH$), 138.9 – 137.1 (9$\underline{C}_{Ar}$), 133.4 ($\underline{C}H$=$CH_2$), 129.2 – 126.5 (45C$\underline{H}_{Ar}$), 118.4 (CH=$\underline{C}H_2$), 102.1 ($C_{Bzl}$), 101.2 (C-$1_B$, $J_{C,H}$ = 170.7 Hz), 99.1 (C-$1_A$, $J_{C,H}$ = 173.8 Hz), 98.3 (C-$1_D$, $J_{C,H}$ = 168.9 Hz), 97.5 (C-$1_C$, $J_{C,H}$ = 173.5 Hz), 92.9 (C-$1_E$, $J_{C,H}$ = 170.2 Hz), 92.3 ($\underline{C}Cl_3$), 82.2 (C-$3_E$), 80.4 (C-$4_D$), 80.3 (C-$4_B$), 80.0 (C-$4_C$), 79.9 (C-$4_A$), 79.5 (C-$2_E$), 79.4 (C-$3_B$), 78.5 (C-$3_C$), 77.9 (C-$4_E$), 76.4 ($\underline{C}H_{2Bn}$), 75.7 ($\underline{C}H_{2Bn}$), 75.4 ($\underline{C}H_{2Bn}$), 75.3 (C-$2_B$), 75.2 ($\underline{C}H_{2Bn}$), 75.1 ($\underline{C}H_{2Bn}$), 74.0 (C-$3_D$), 73.5 ($\underline{C}H_{2Bn}$), 72.9 ($\underline{C}H_{2Bn}$), 72.3 (C-$3_A$), 72.2 (2C, C-$2_C$, $\underline{C}H_{2Bn}$), 71.0 ($\underline{C}H_{2All}$), 70.4 (C-$5_E$), 69.1 (C-$5_B$), 68.8 (C-$6_D$), 68.7 (C-$5_A$), 68.4 (C-

$6_E$), 68.1 (2C, C-$2_A$, C-$5_C$), 66.3 (C-$5_D$), 60.4 (C-$2_D$), 38.0 ($\underline{C}H_{2Lev}$), 29.8 ($\underline{C}H_{3Lev}$), 28.8 ($\underline{C}H_{2Lev}$), 21.1 (OCO$\underline{C}H_3$), 18.0 (2C, C-$6_A$, C-$6_B$), 17.3 (C-$6_C$). HRMS ($ESI^+$): *m/z* 1934.6736 (calcd for $C_{105}H_{116}Cl_3NO_{26}Na$ $[M+Na]^+$: *m/z* 1934.6749).

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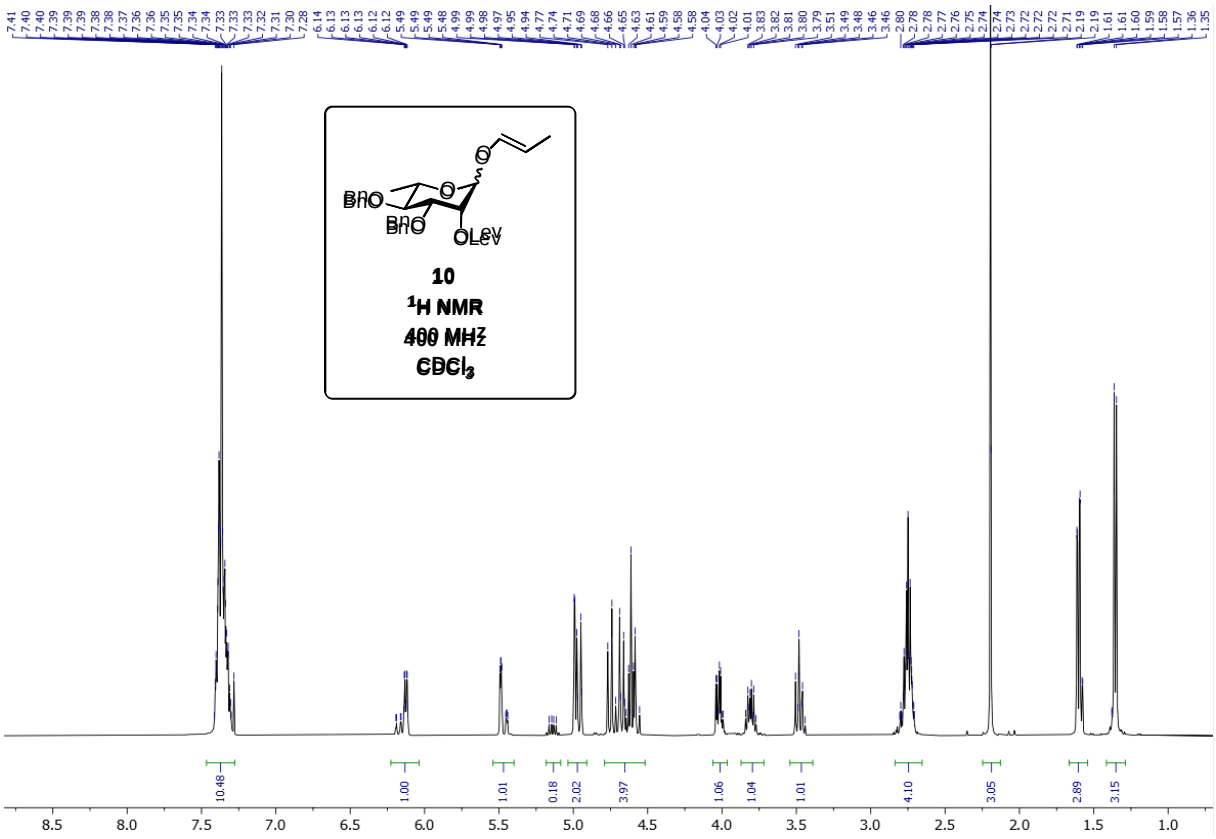
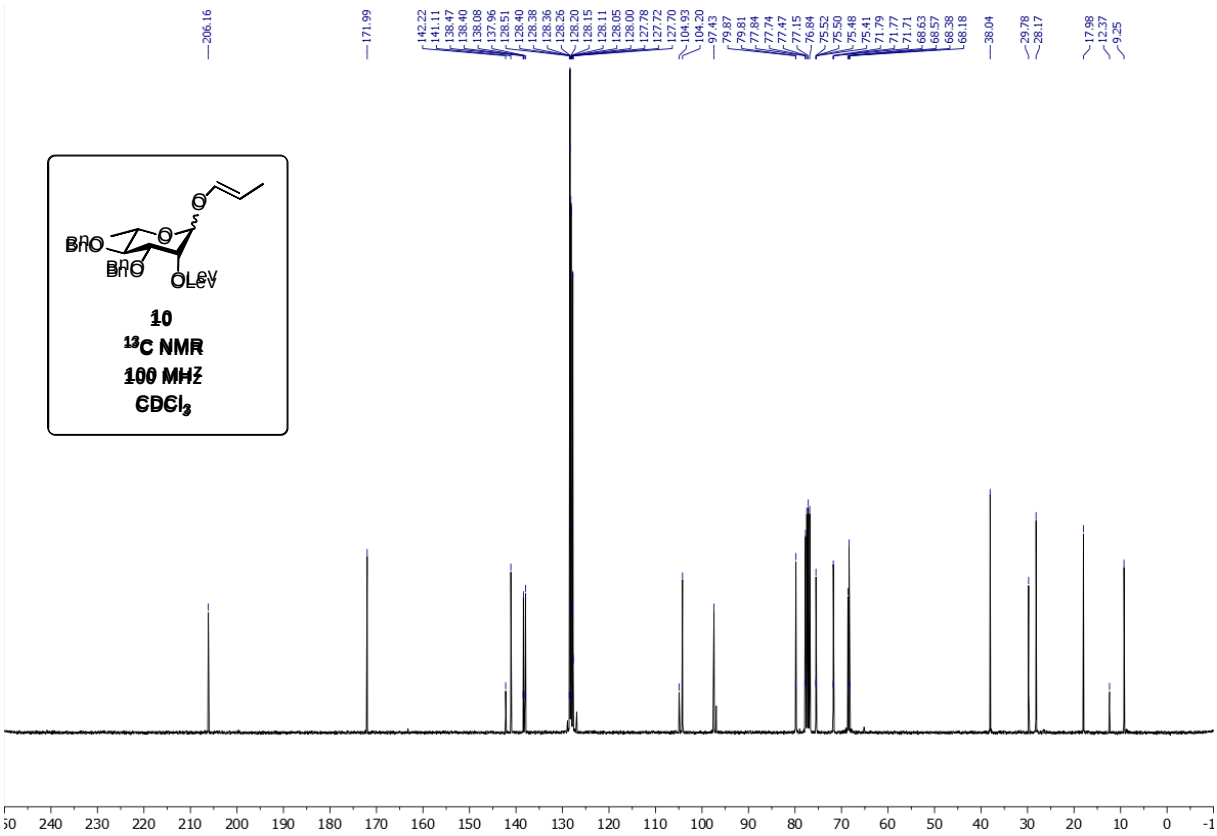
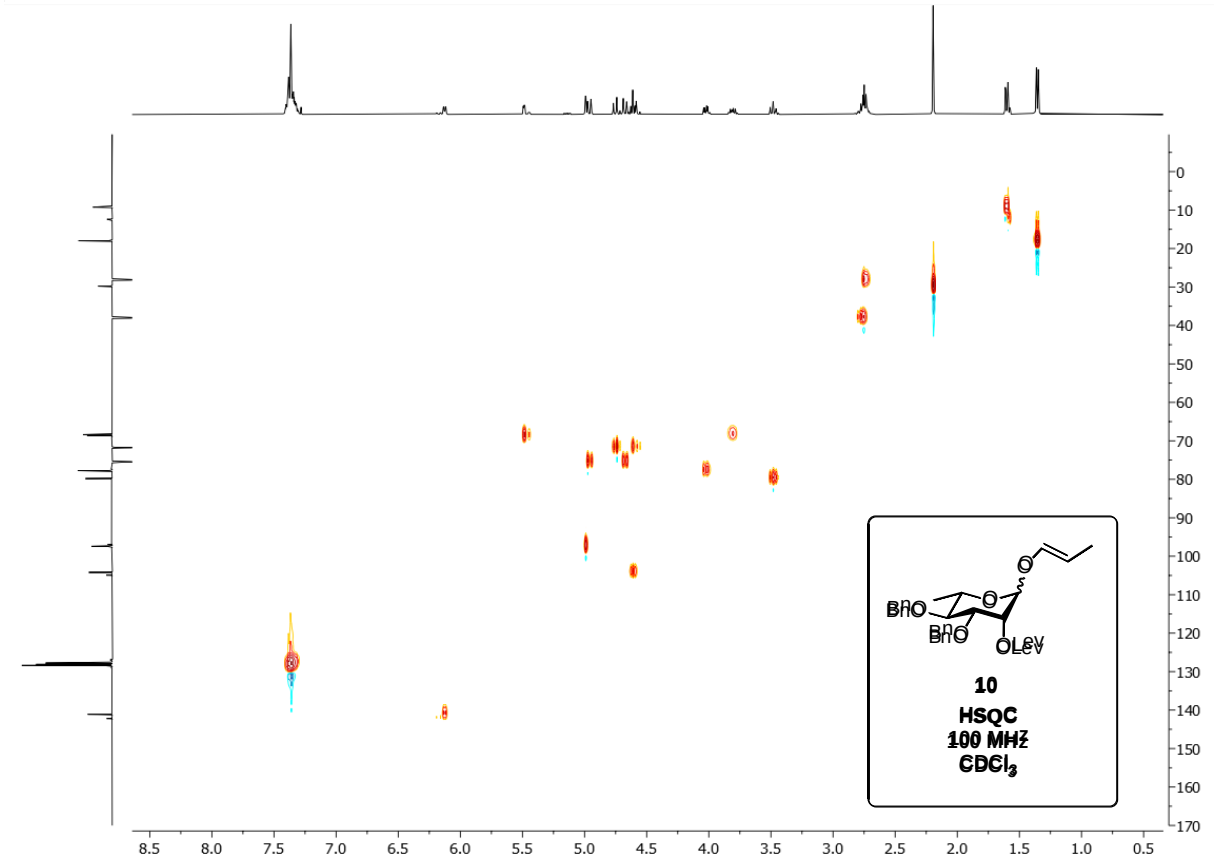
## IV. NMR spectra for compounds 10, 12a/12b, 27, 29, 30, 32, 35, 37, and 39-46

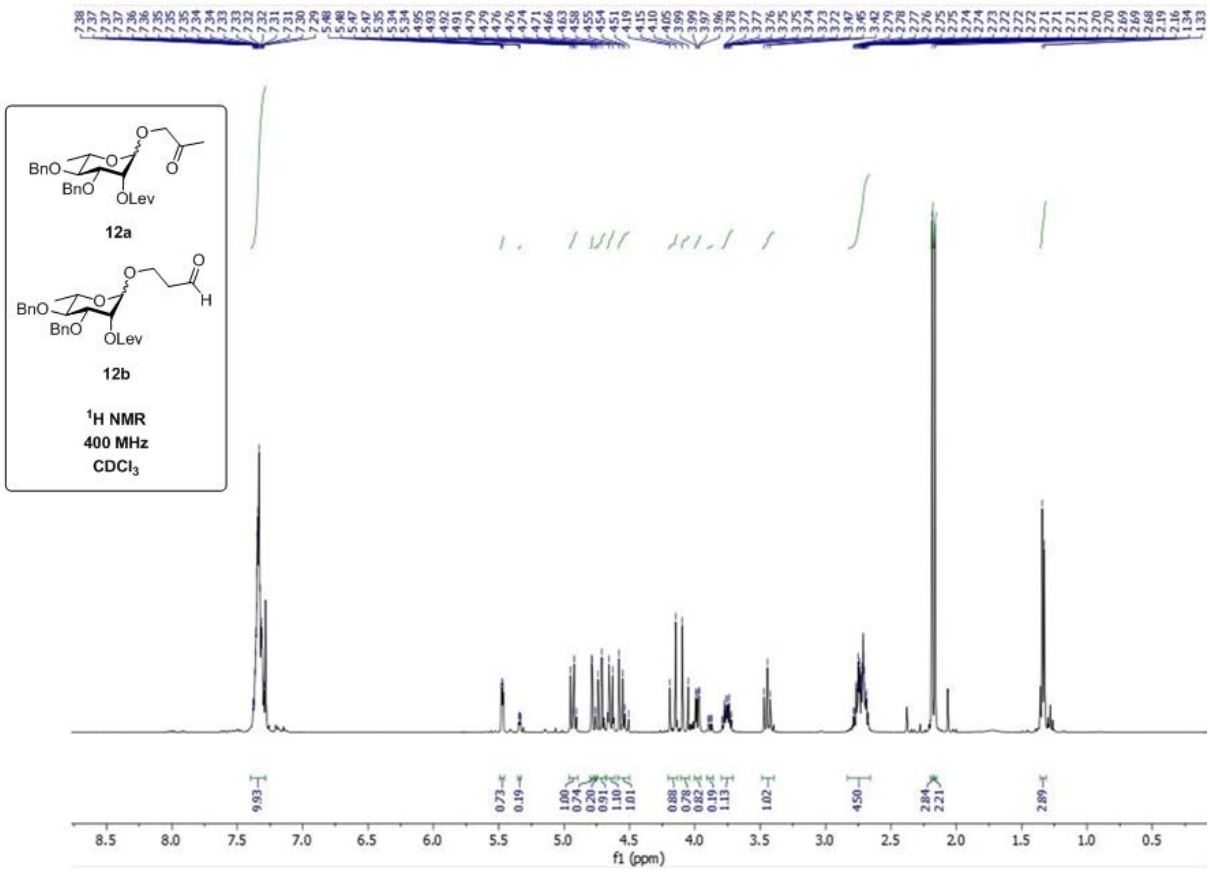
### Prop-1-enyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (10)

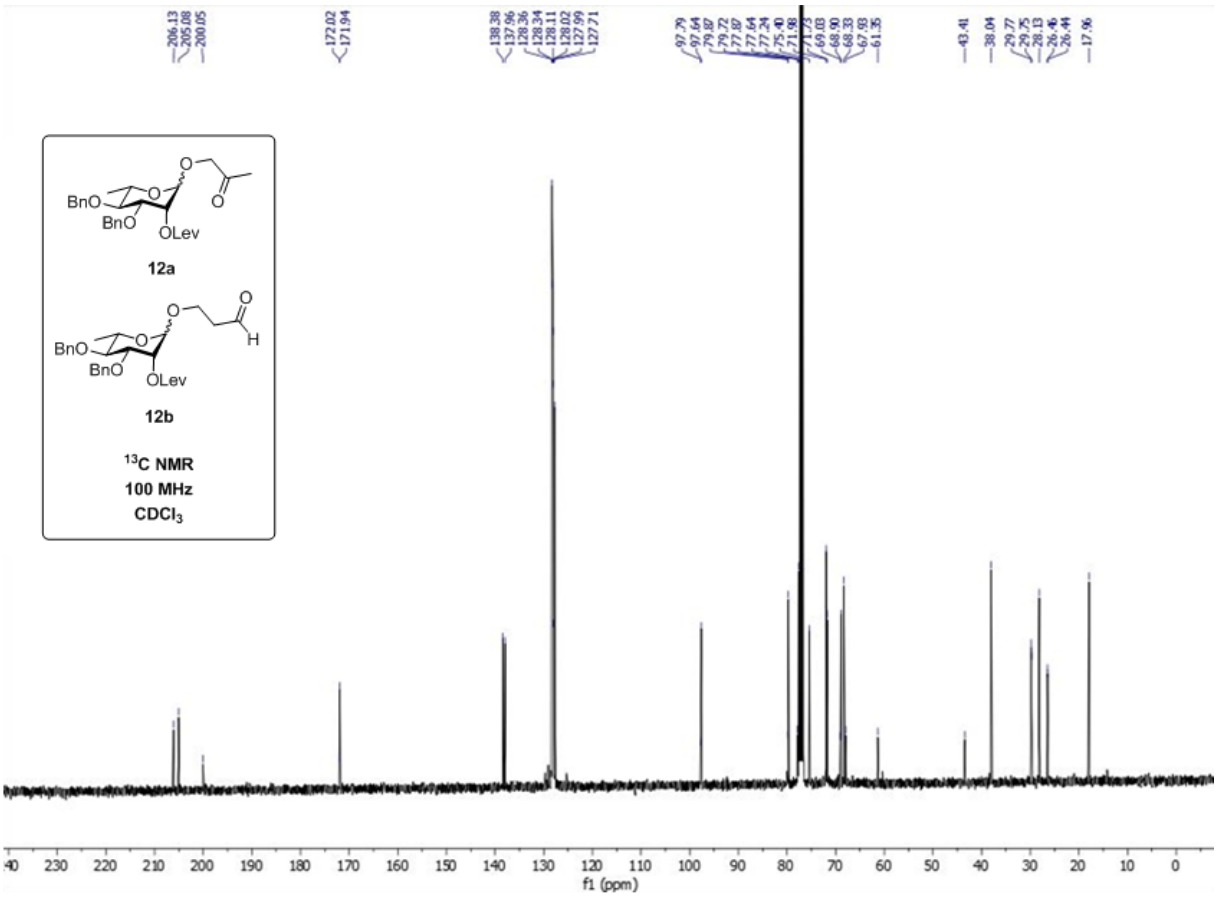


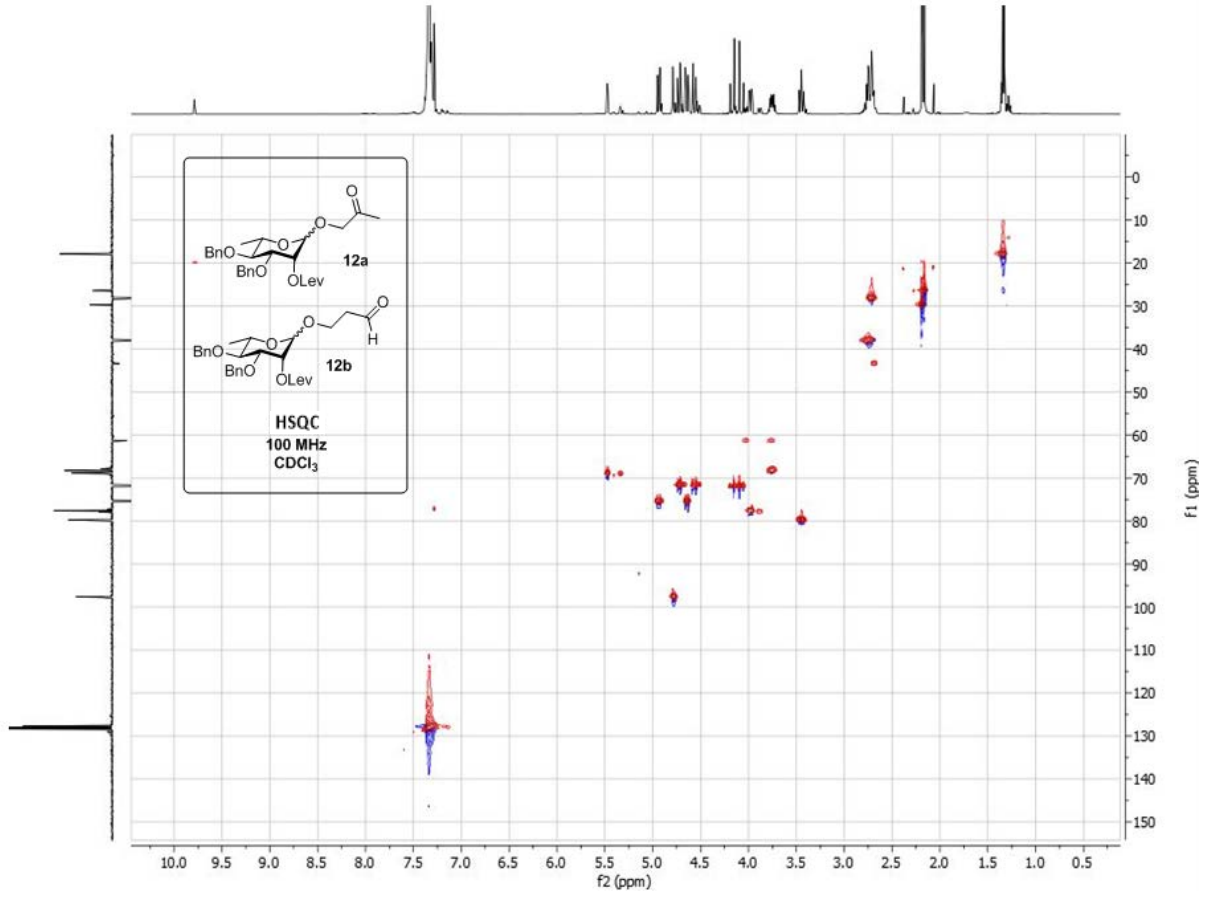

10
13C NMR
100 MHz
CDCl3


10
HSQC
100 MHz
CDCl3

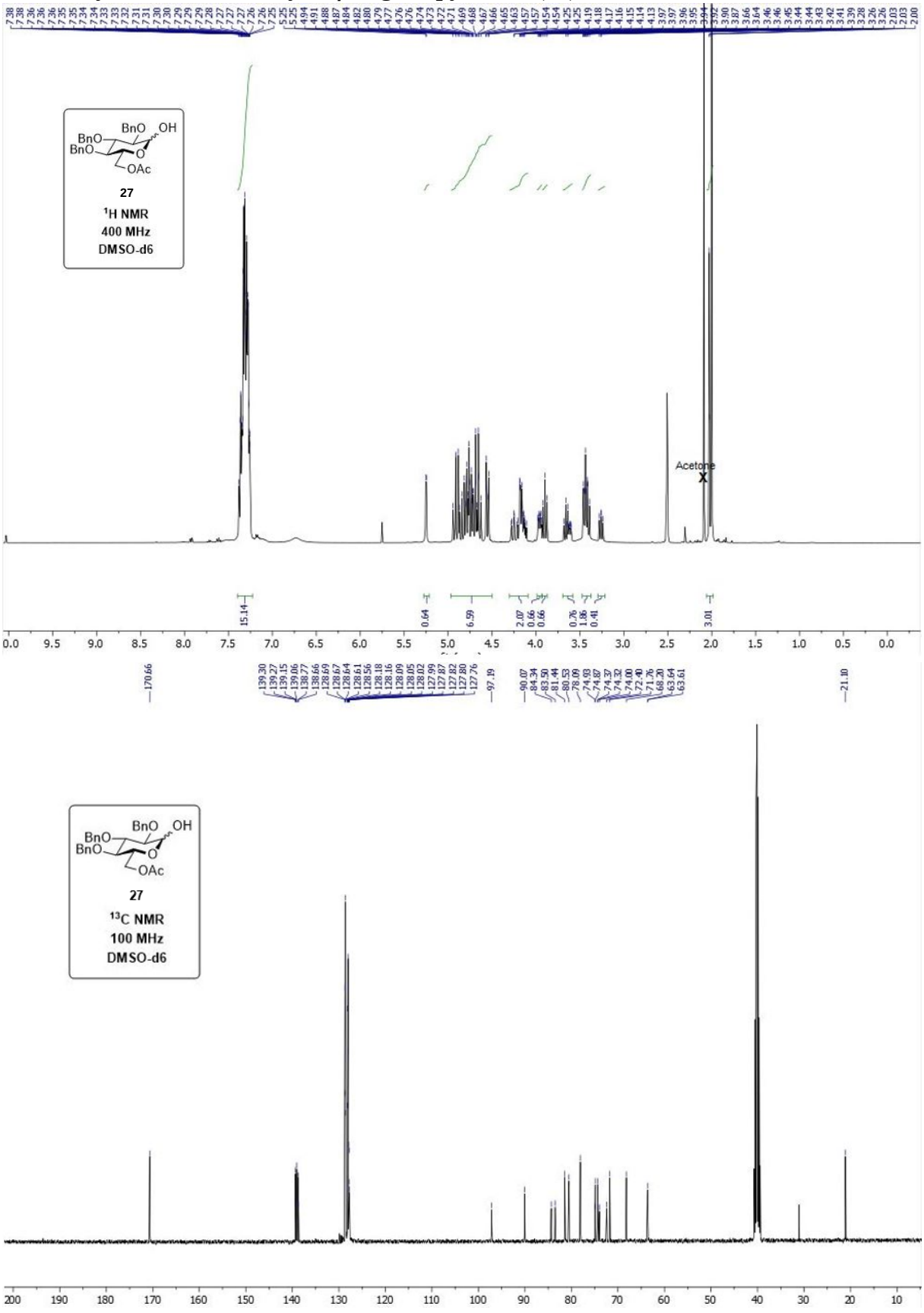
**2-Oxopropyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (12a) and 3-Oxopropyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (12b)**

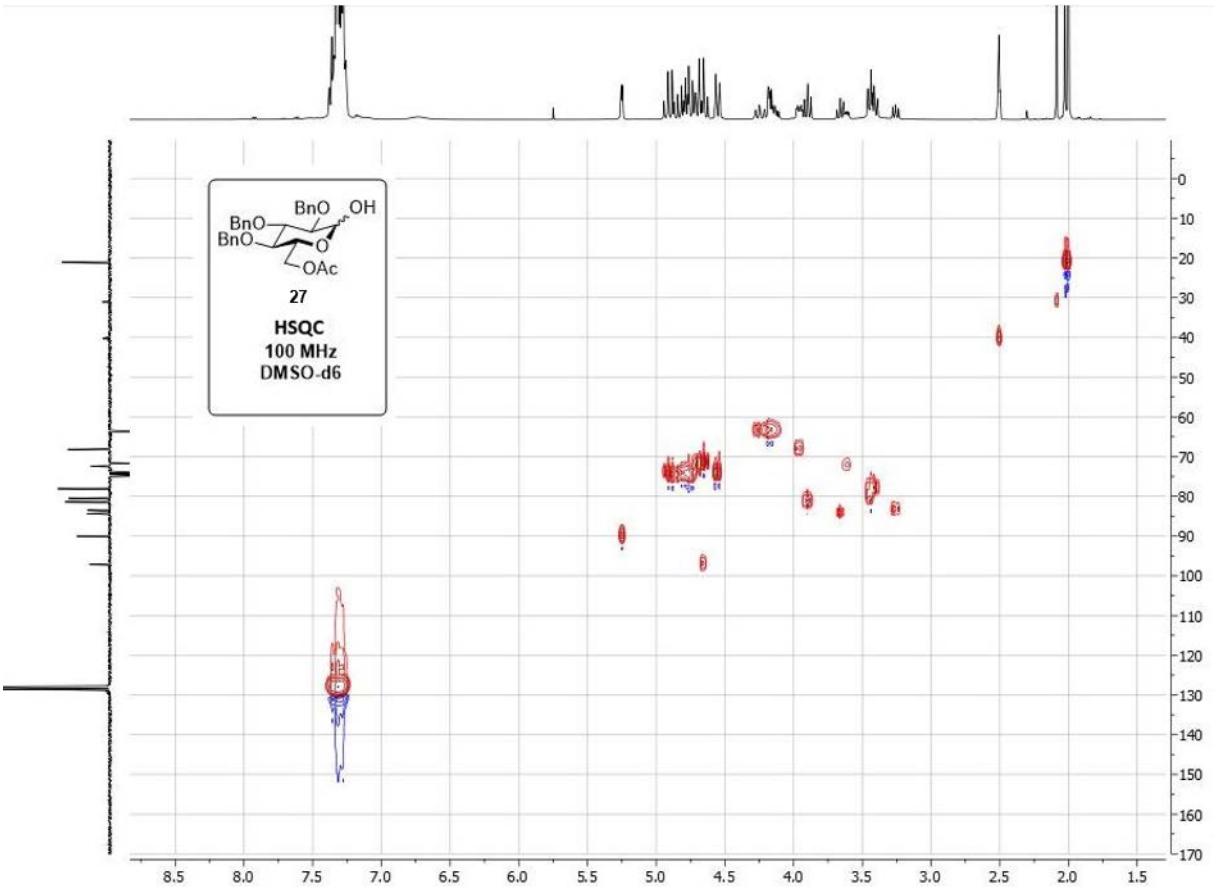



12a
12b
$^{13}$C NMR
100 MHz
CDCl$_3$
f1 (ppm)

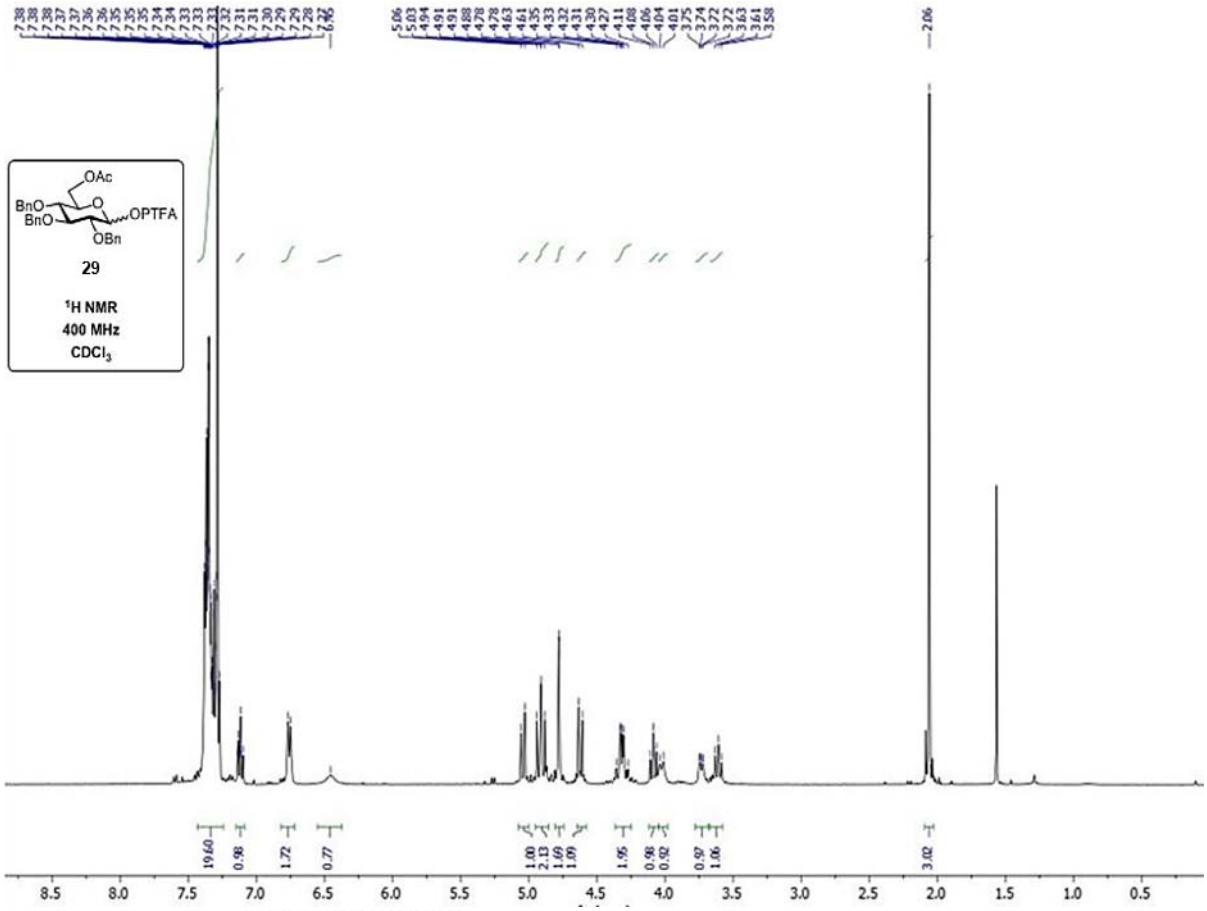

12a
12b
HSQC
100 MHz
CDCl$_3$
f2 (ppm)
f1 (ppm)

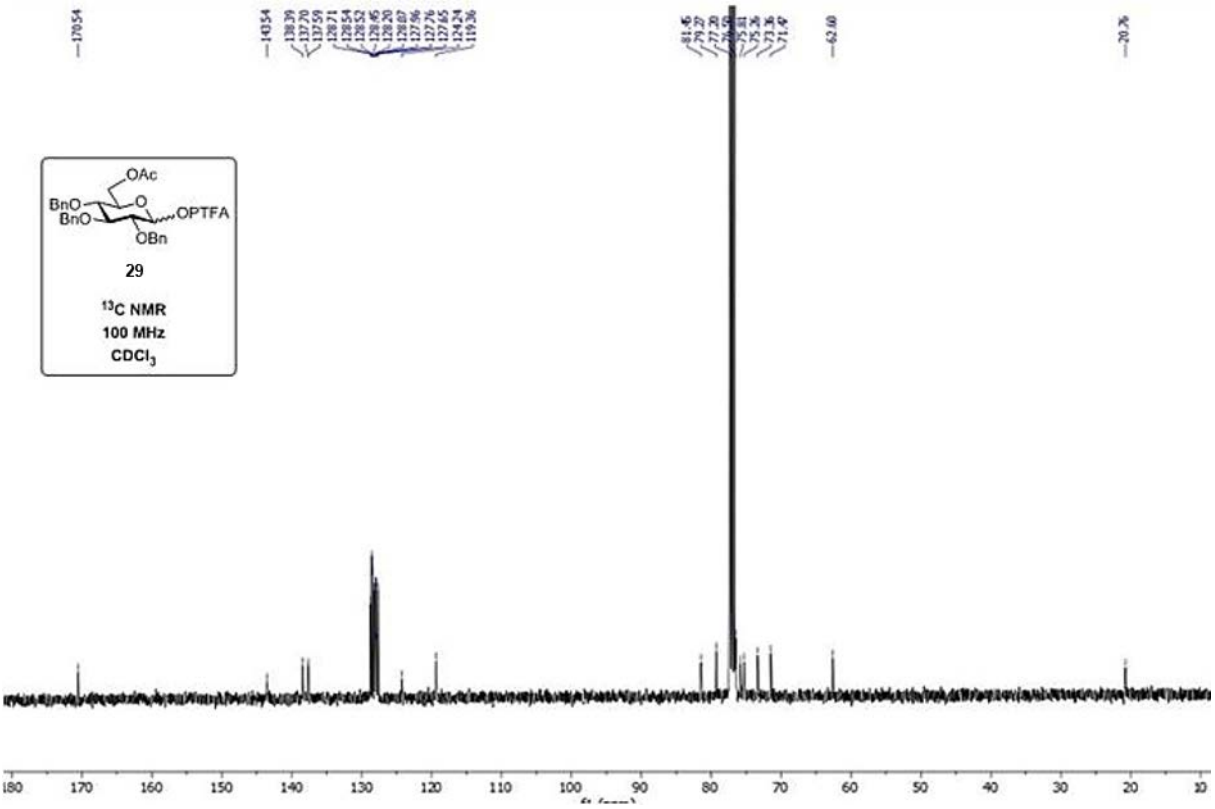
## 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranose (27)

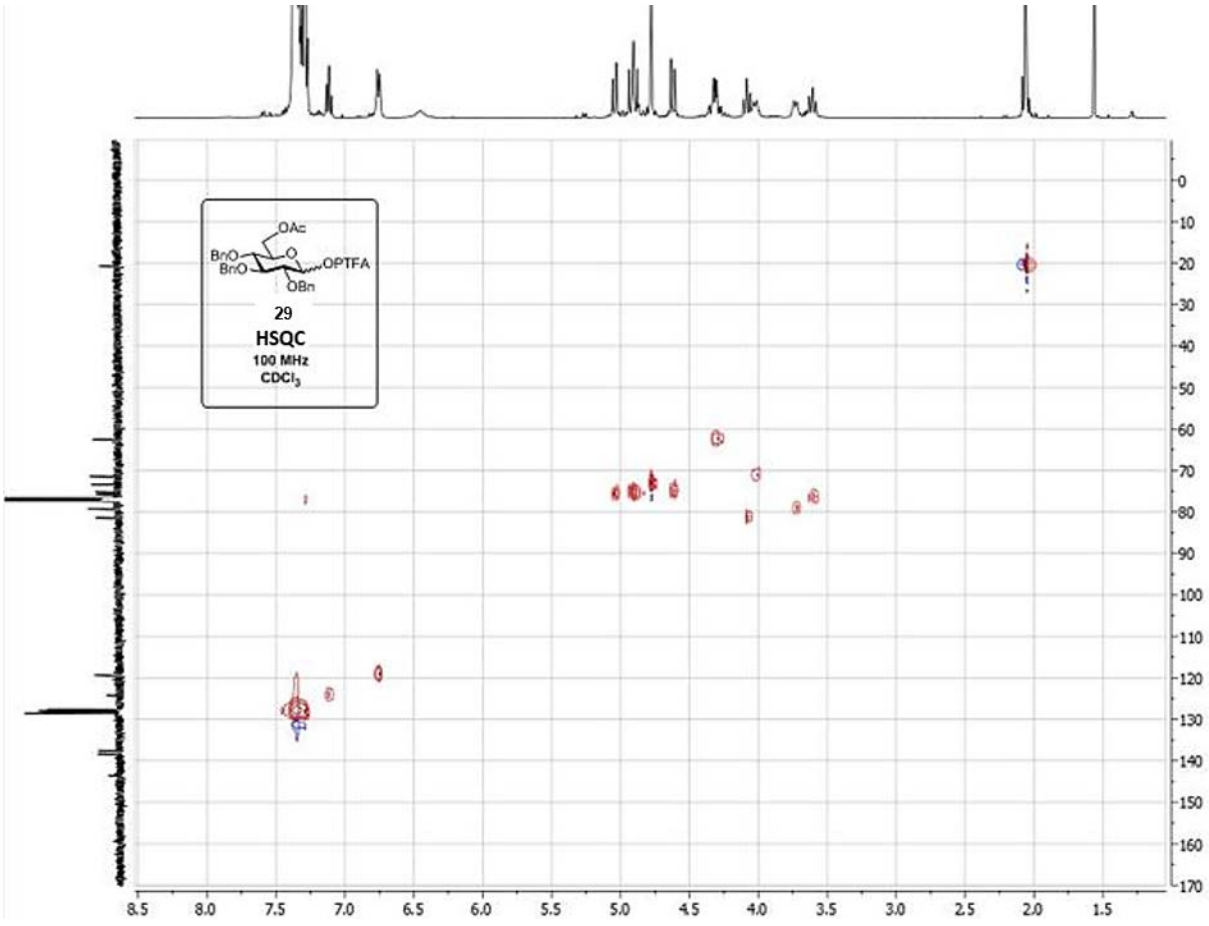



BnO
OH
BnO
O
OAc
27
HSQC
100 MHz
DMSO-d6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

**6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranosyl (*N*-phenyl)trifluoroacetimidate (29)**

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BnO
OPTFA
OBn
29
HSQC
100 MHz
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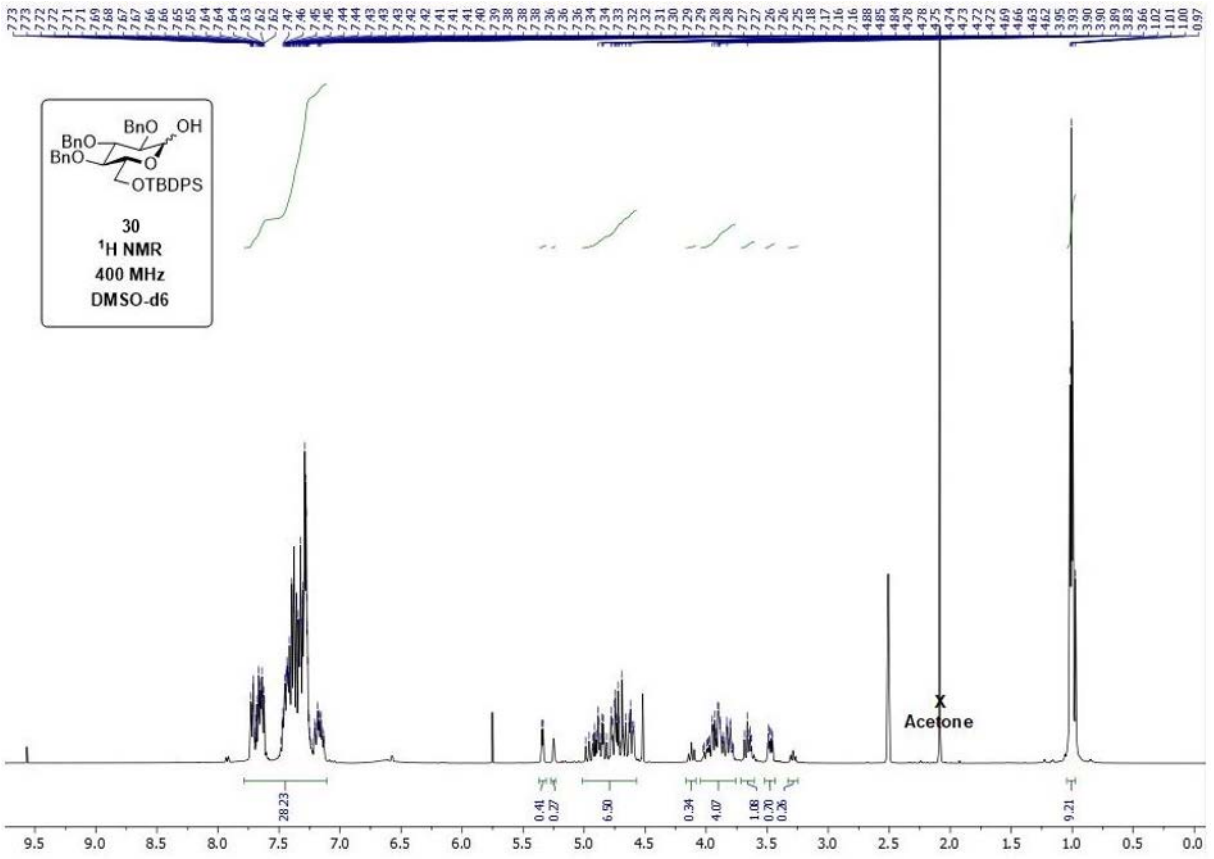
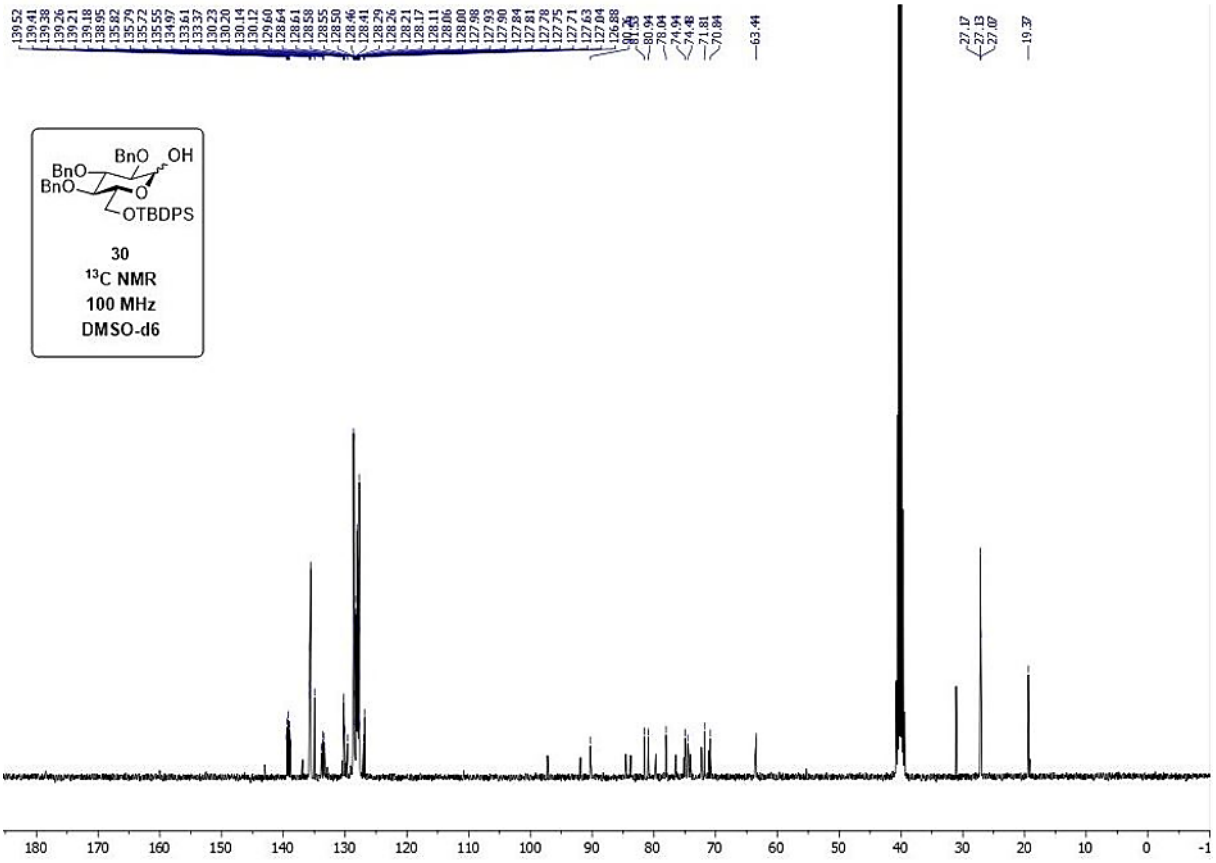
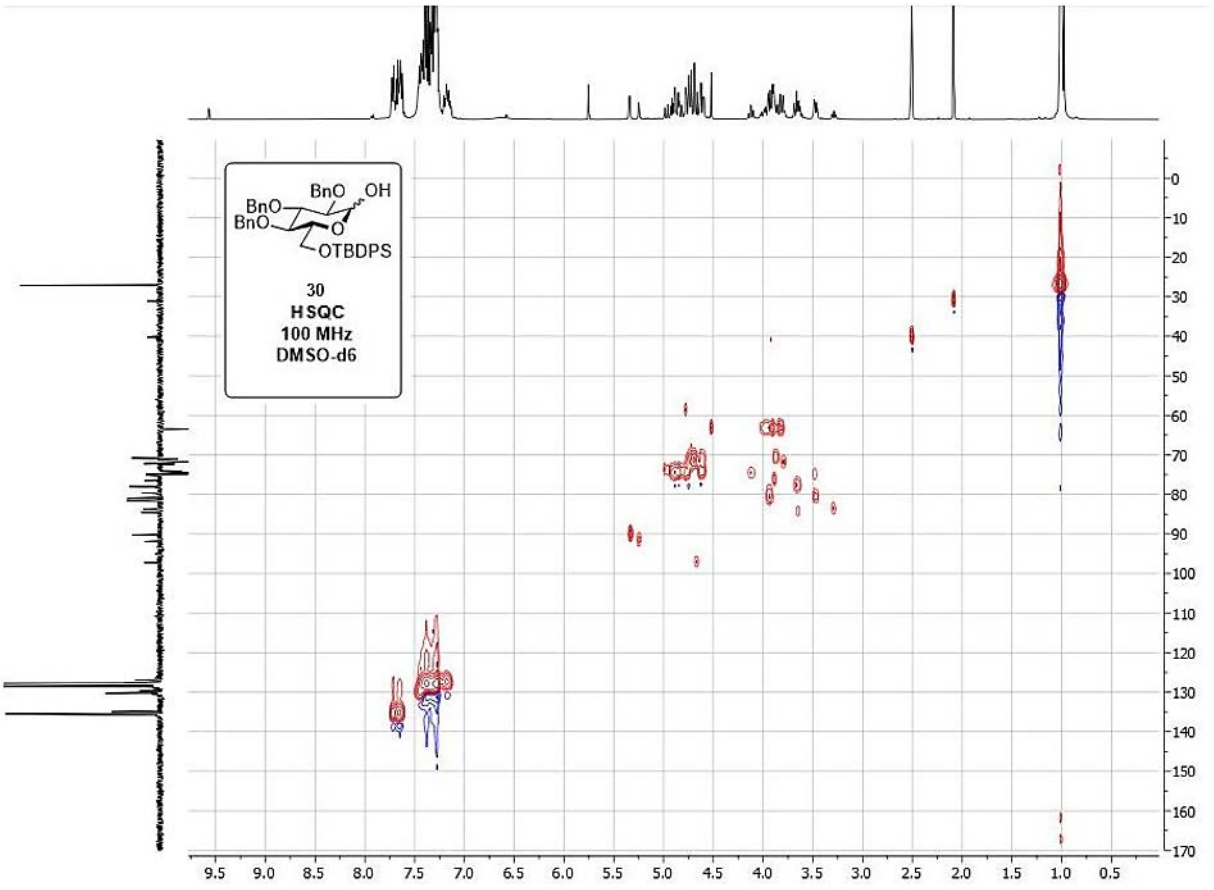
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

## 2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α/β-D-glucopyranose (30)




BnO
OH
BnO
O
OTBDPS
30
HSQC
100 MHz
DMSO-d6
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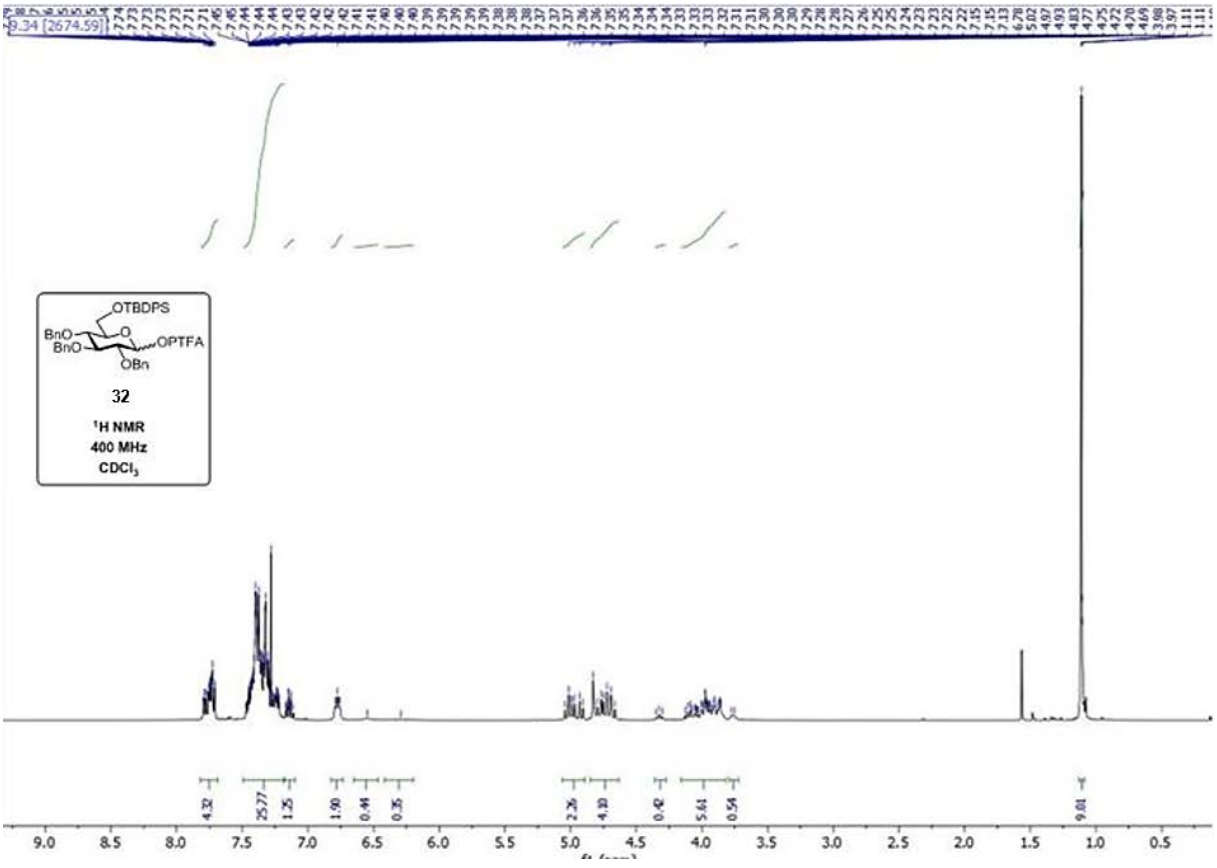
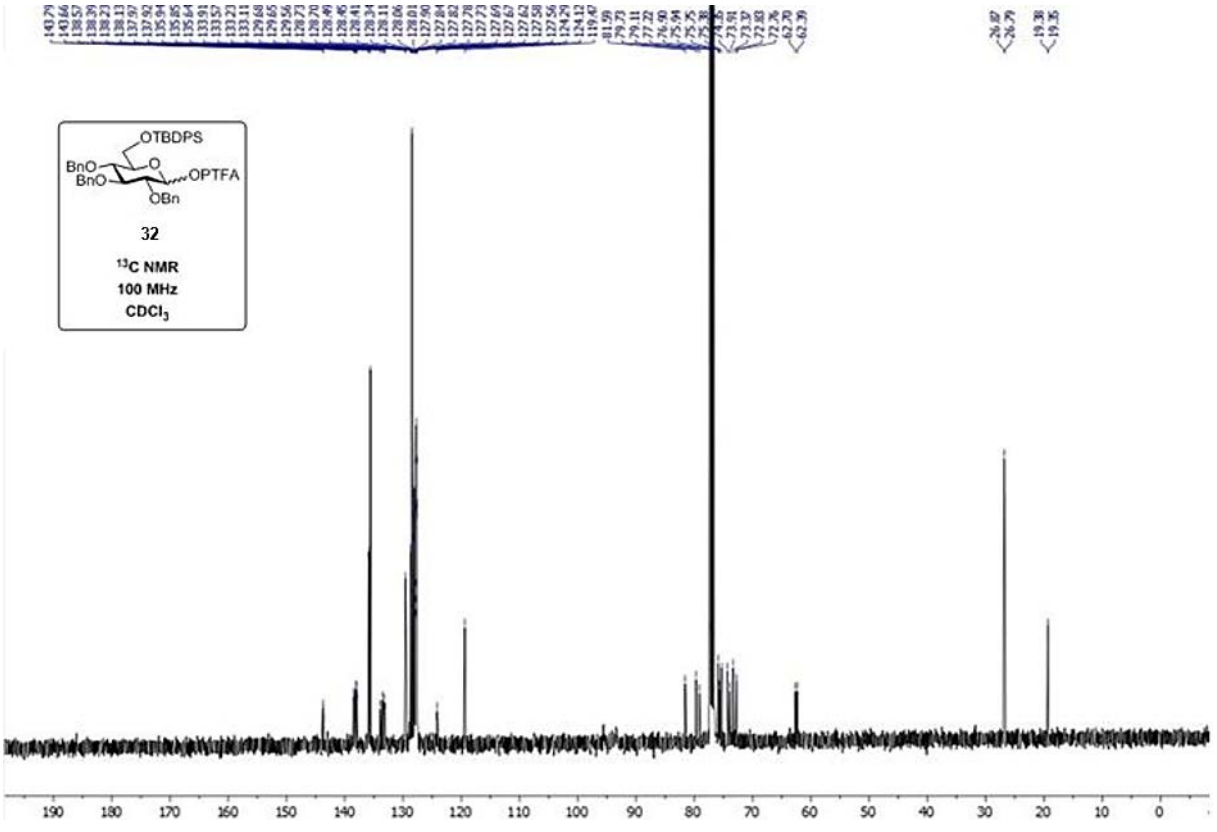
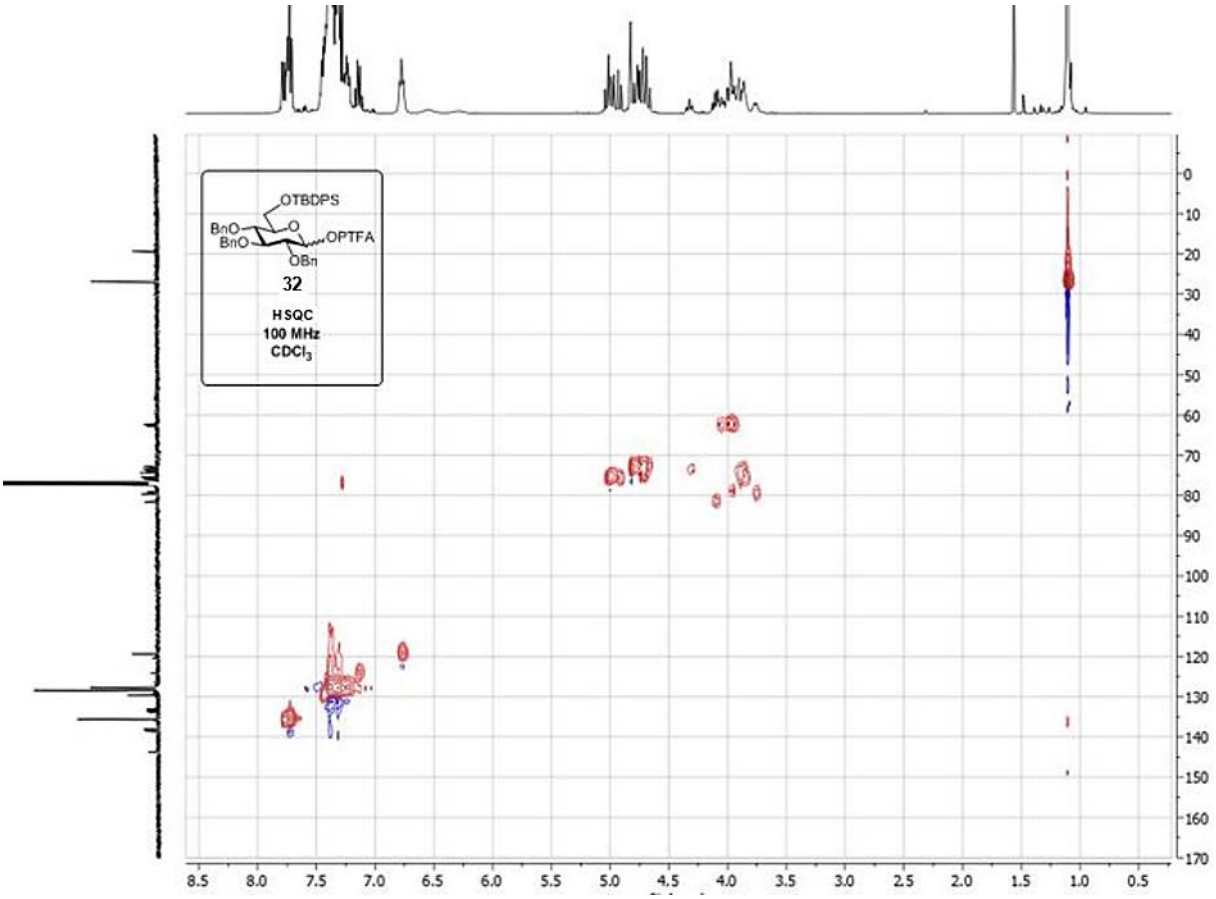
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170

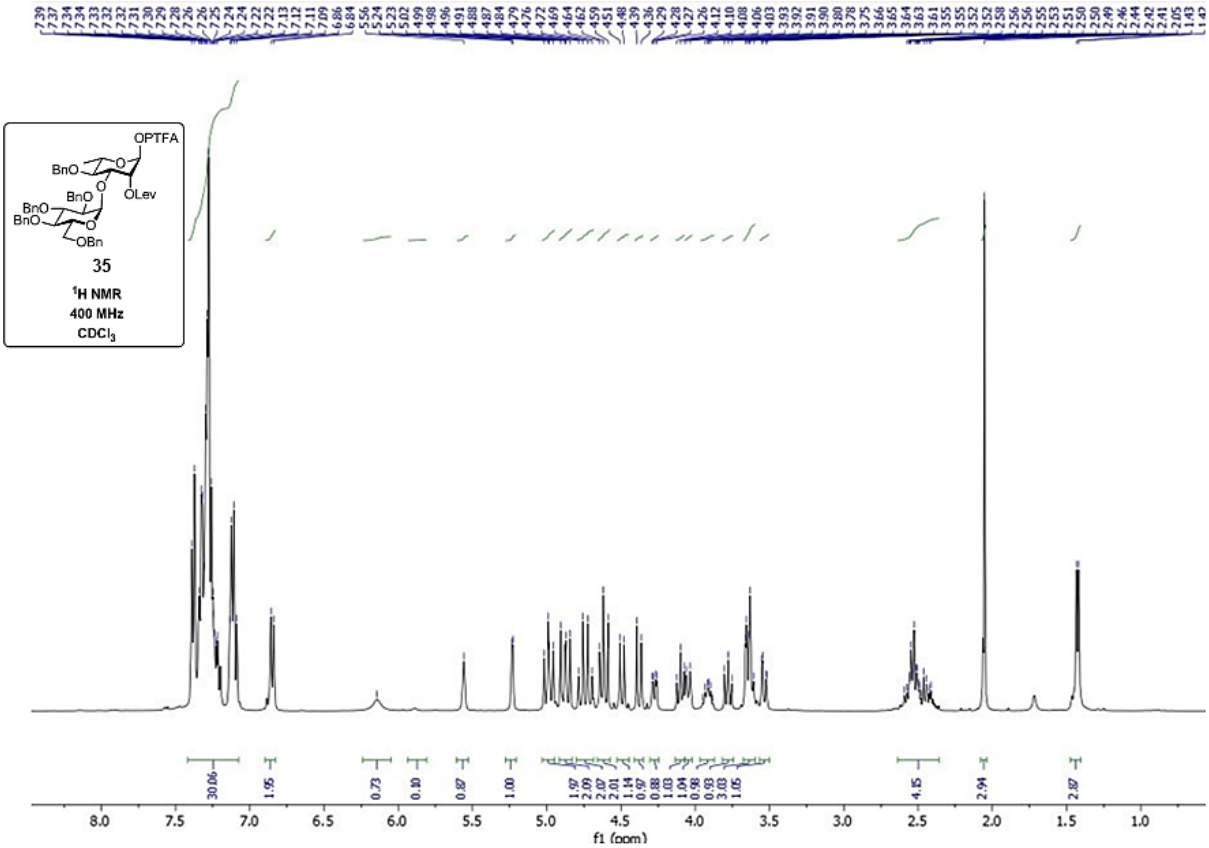
**2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α/β-D-glucopyranosyl (*N*-phenyl)trifluoroacetimidate (32)**

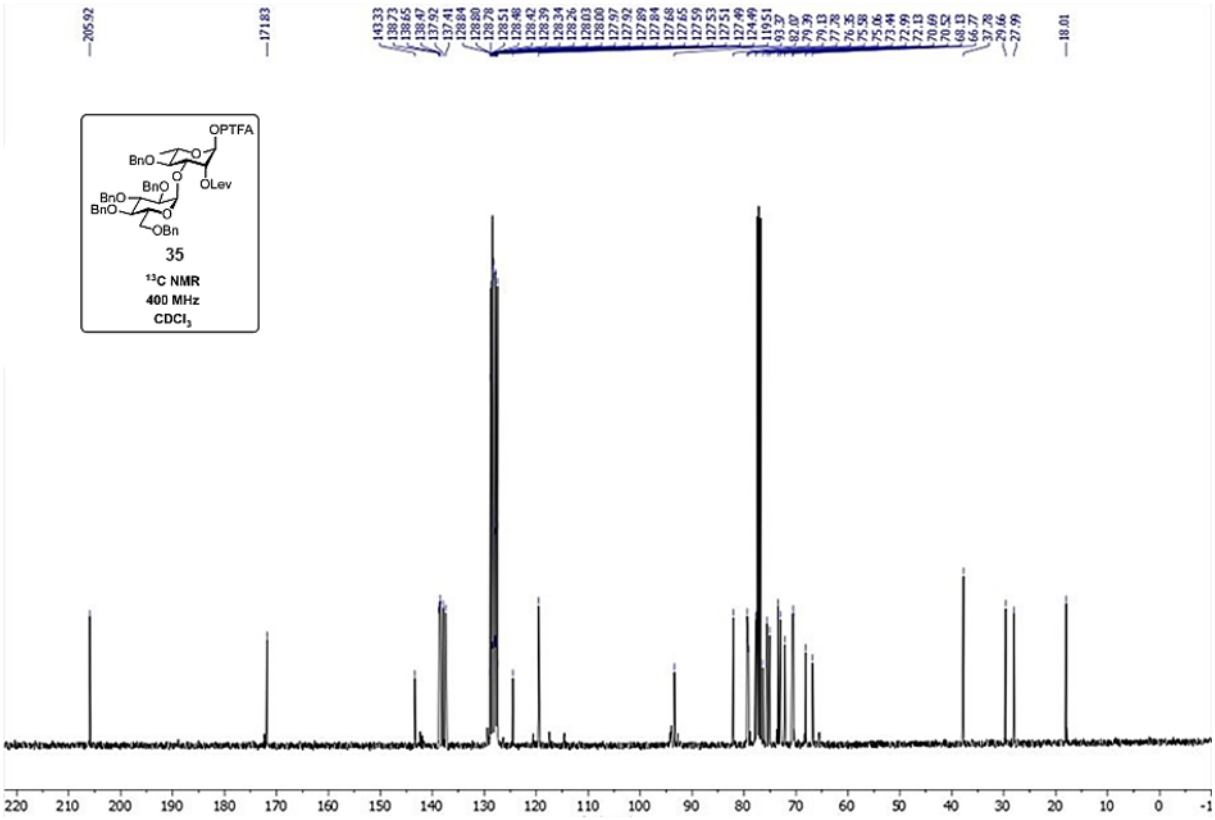





**(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl (*N*-phenyl)trifluoroacetimidate (35)**

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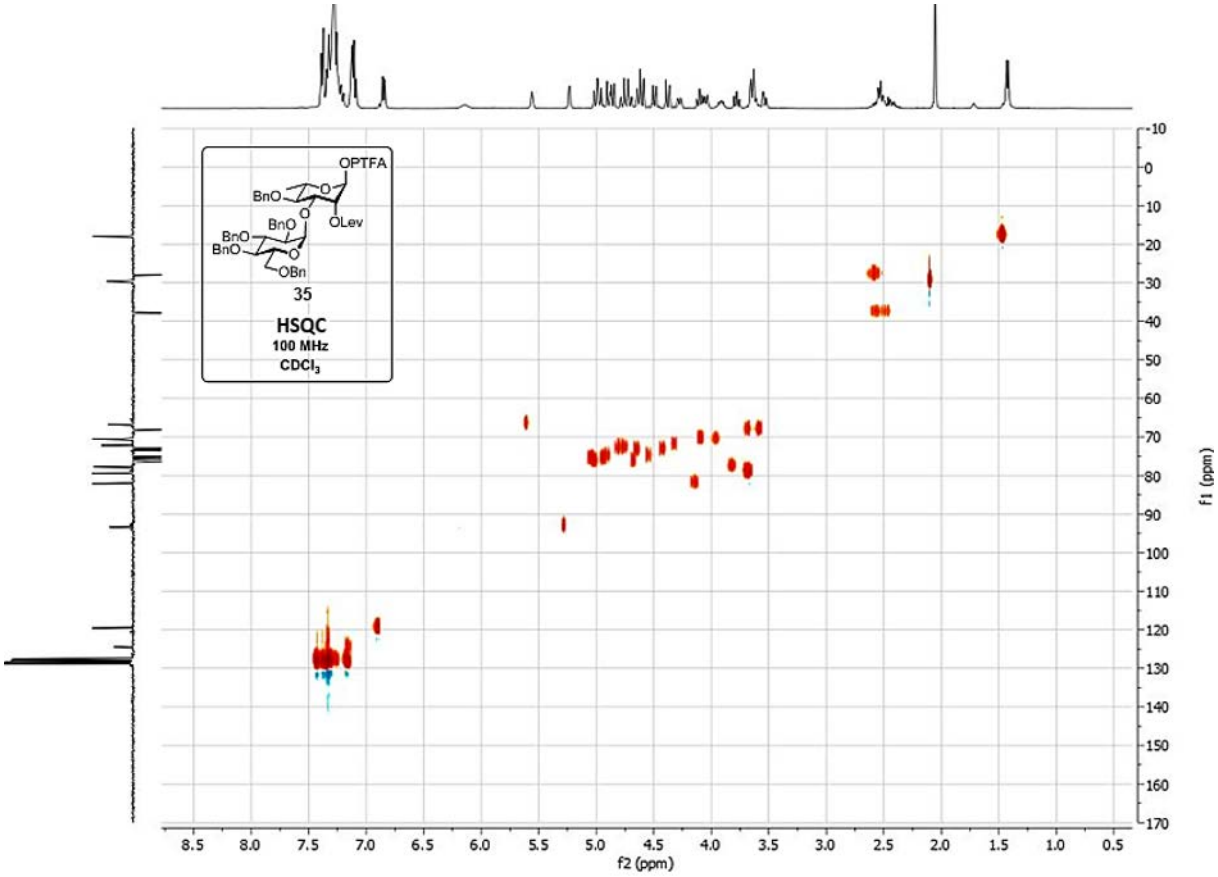
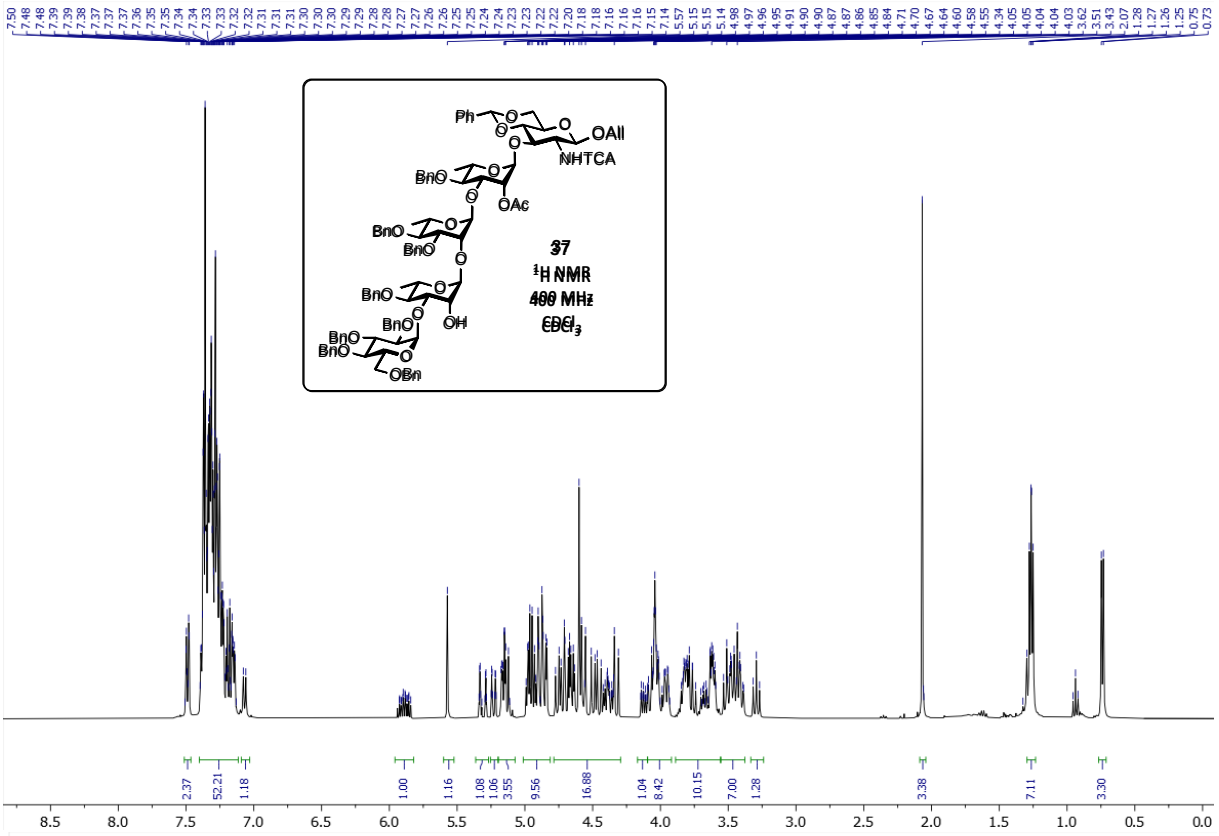
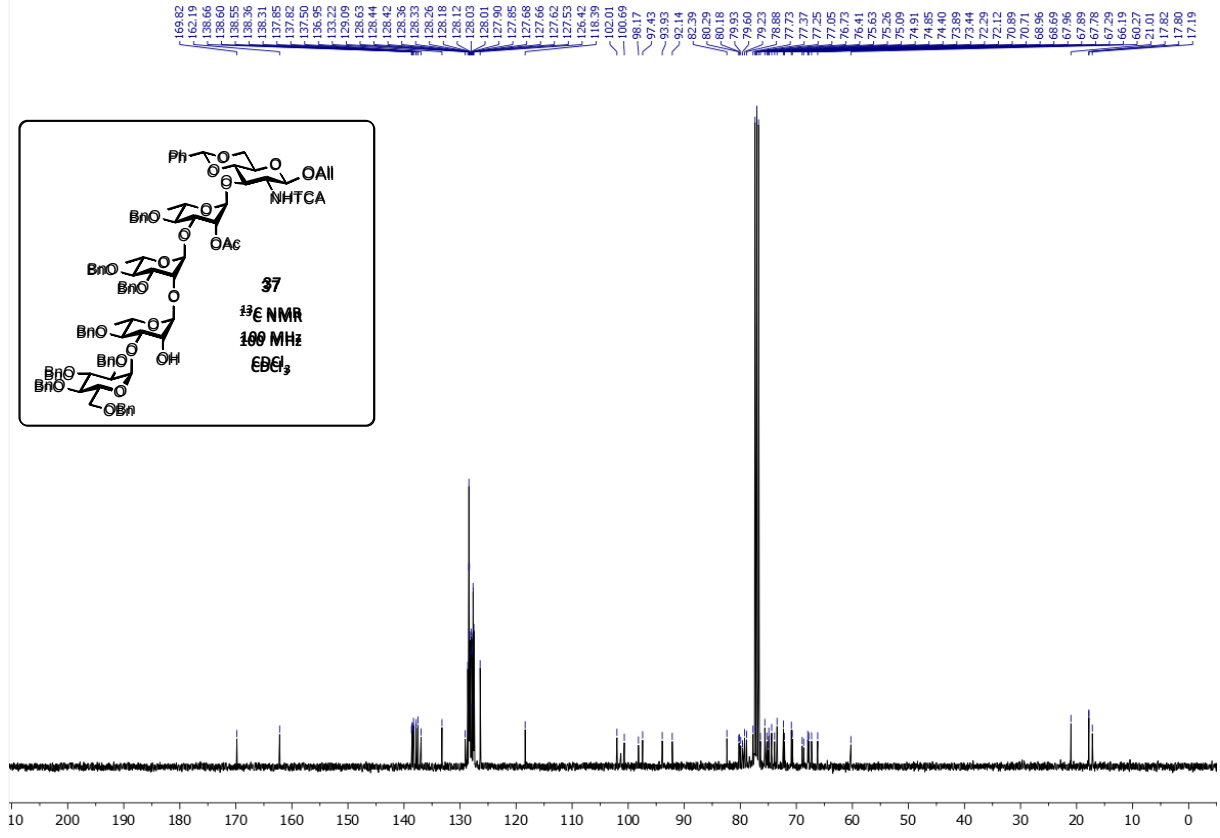
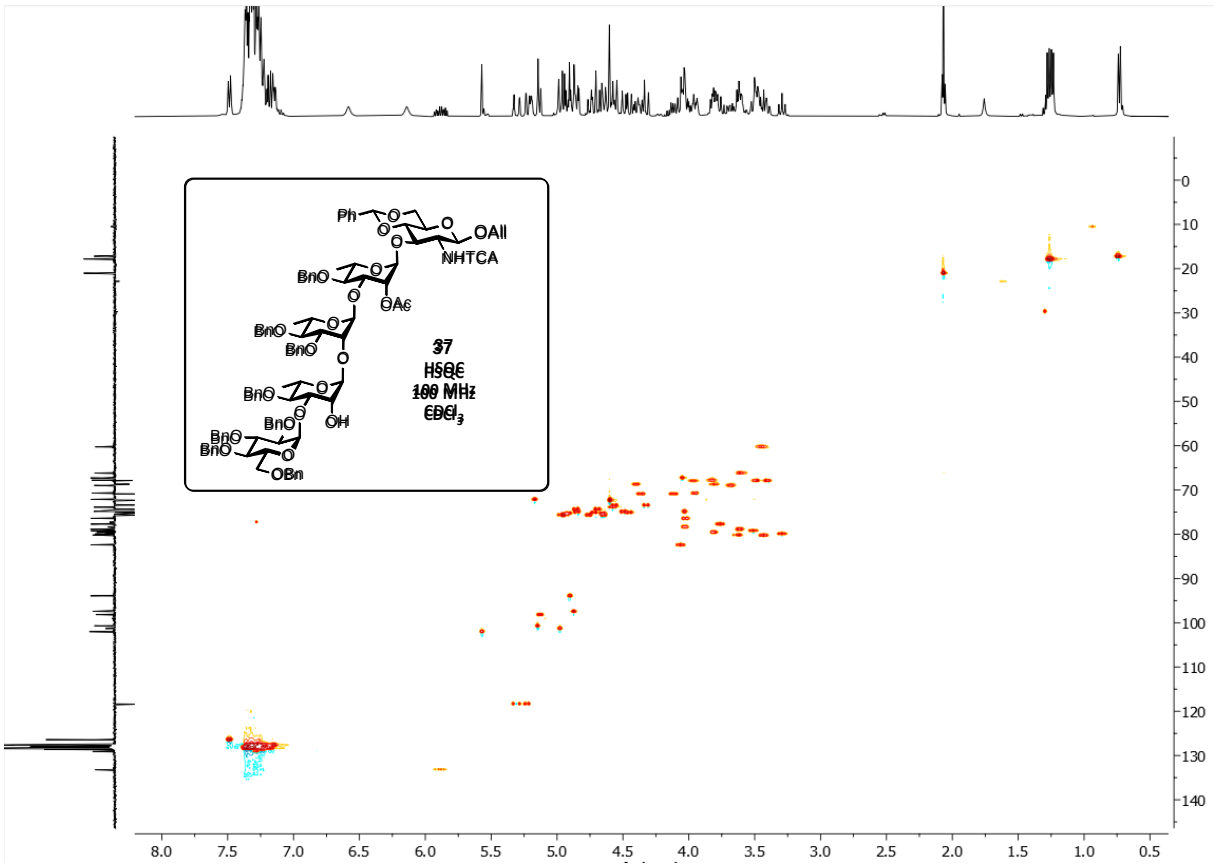
BnO
BnO
BnO
OLev
OBn
35
$^{13}$C NMR
400 MHz
CDCl$_3$


OPTFA
BnO
BnO
BnO
BnO
OLev
OBn
35
HSQC
100 MHz
CDCl$_3$
f2 (ppm)
f1 (ppm)

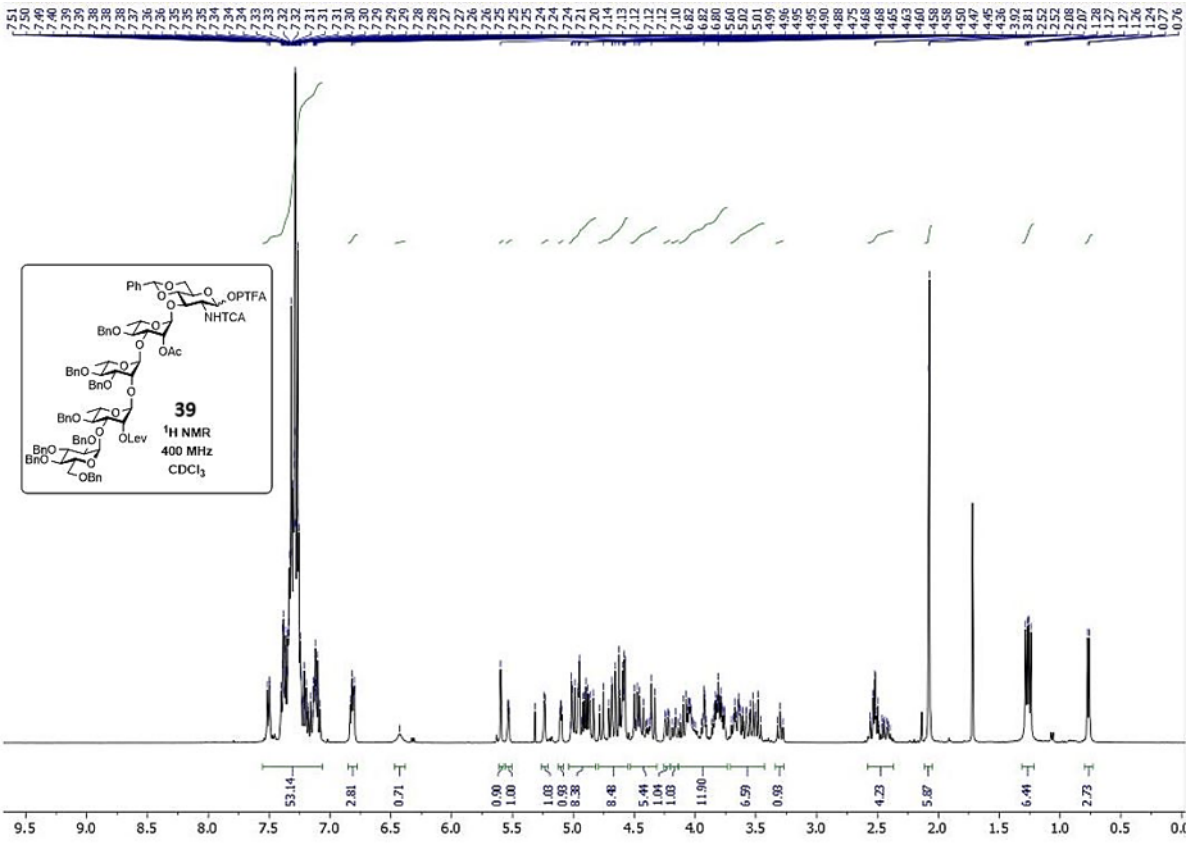
**Allyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (37)**

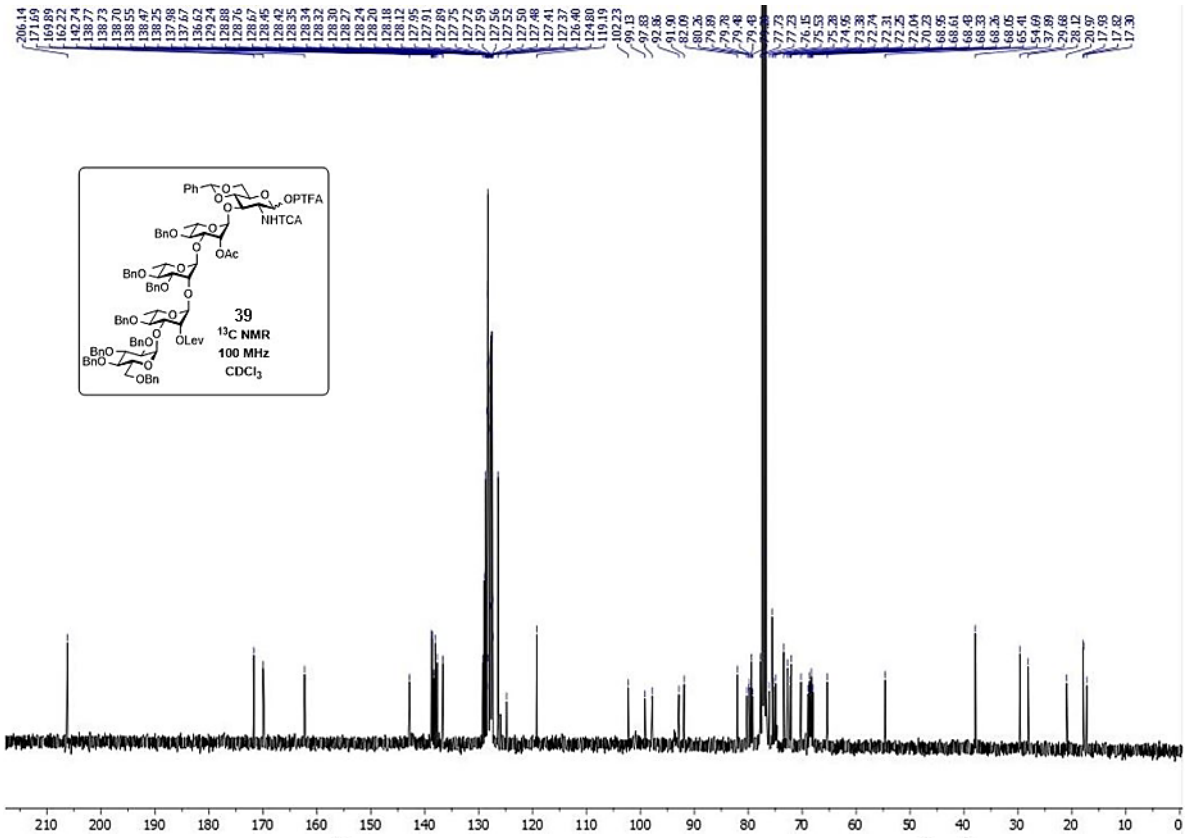


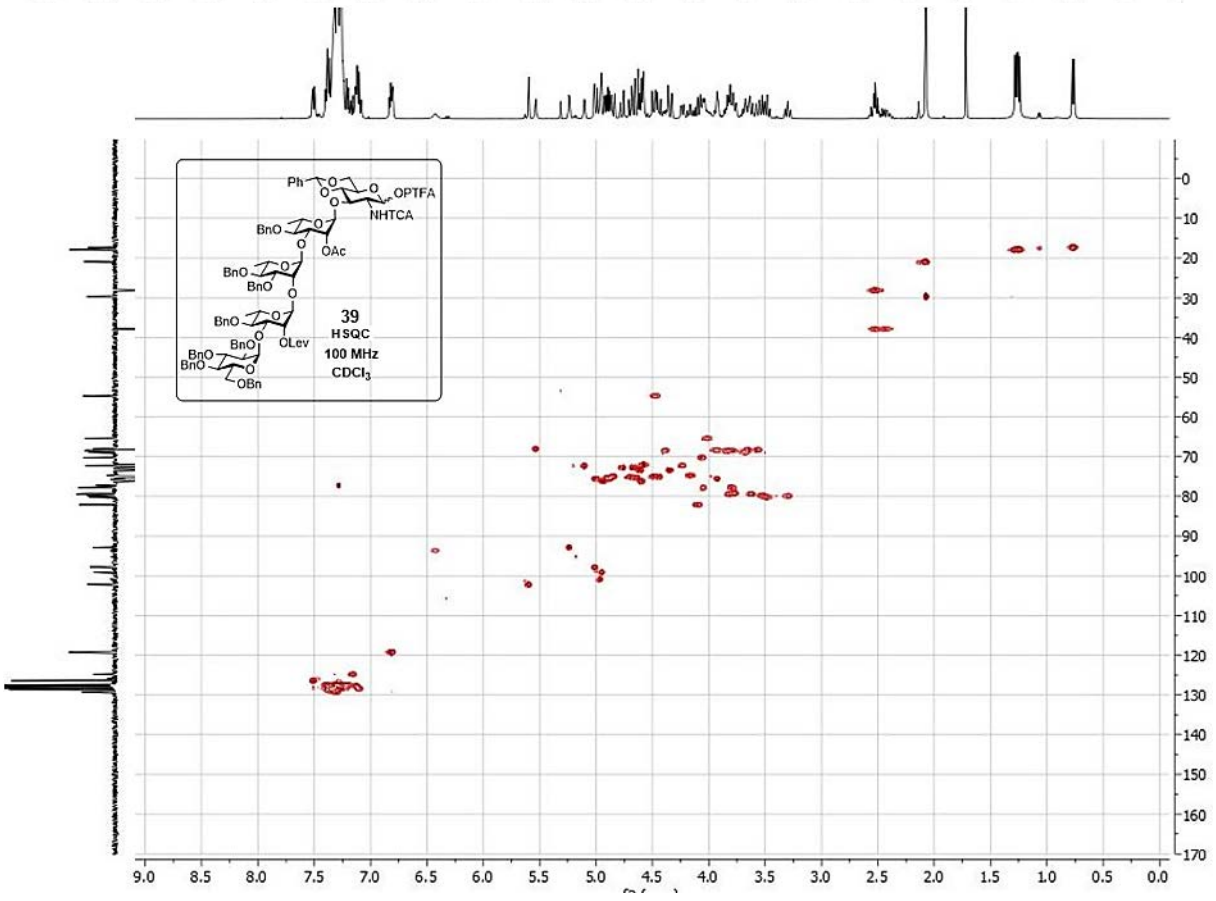




Ph
OAll
NHTCA
BnO
OAc
BnO
BnO
BnO
BnO
OH
BnO
BnO
OBn
37
HSQC
100 MHz
CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

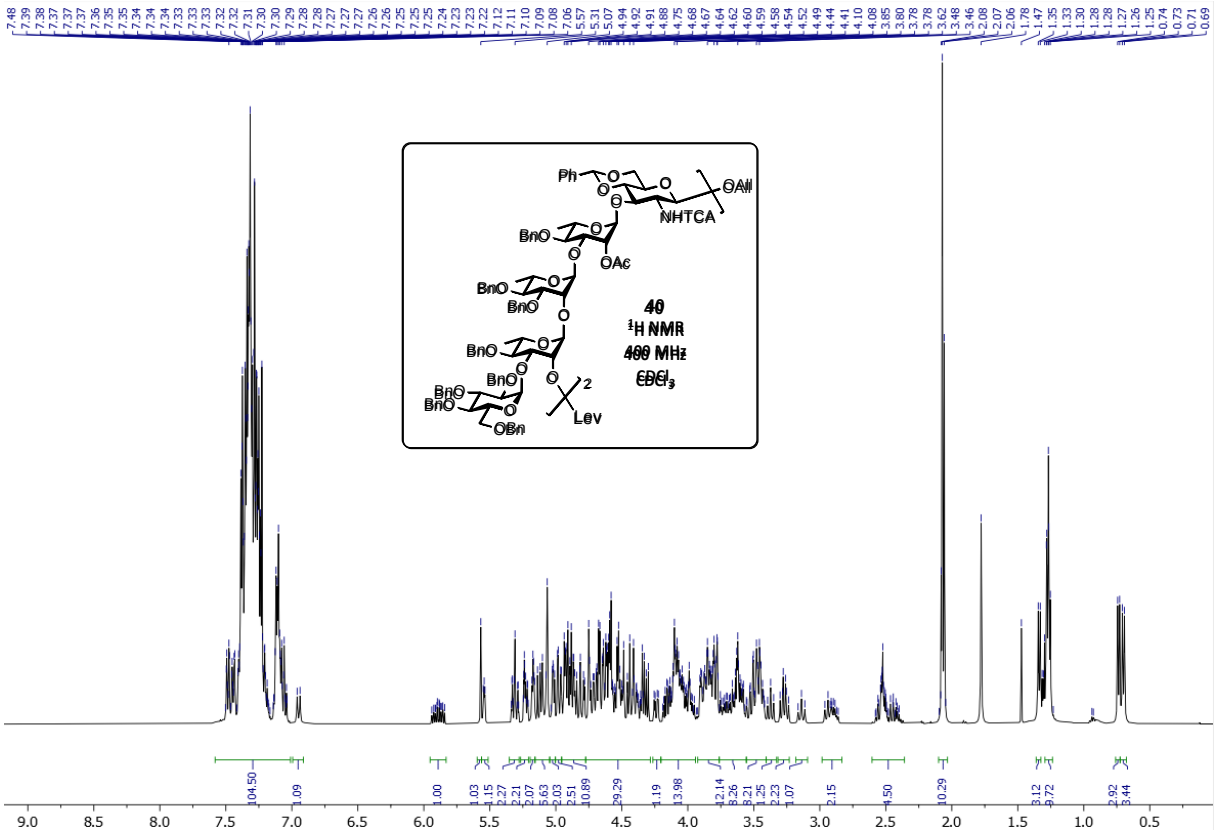
**(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-α/β-D-glucopyranosyl (*N*-phenyl)trifluoroacetimidate (39)**

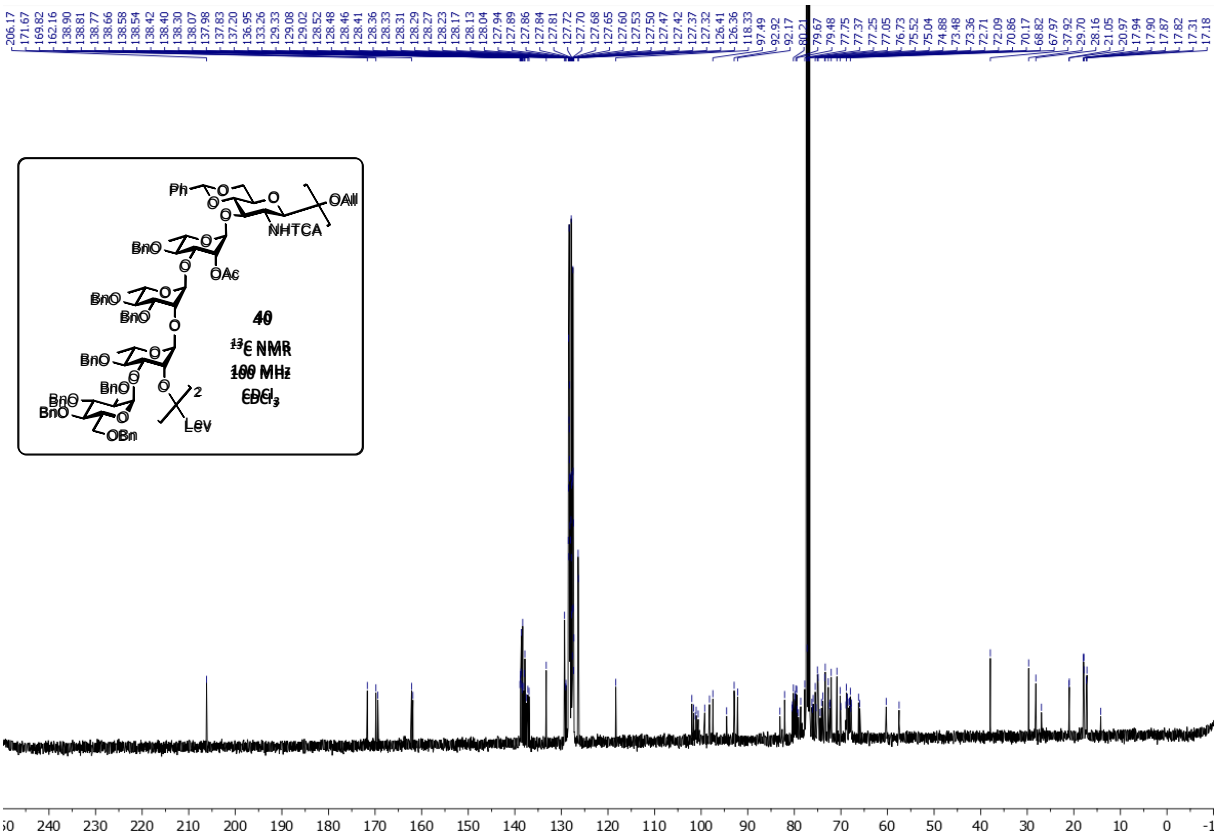


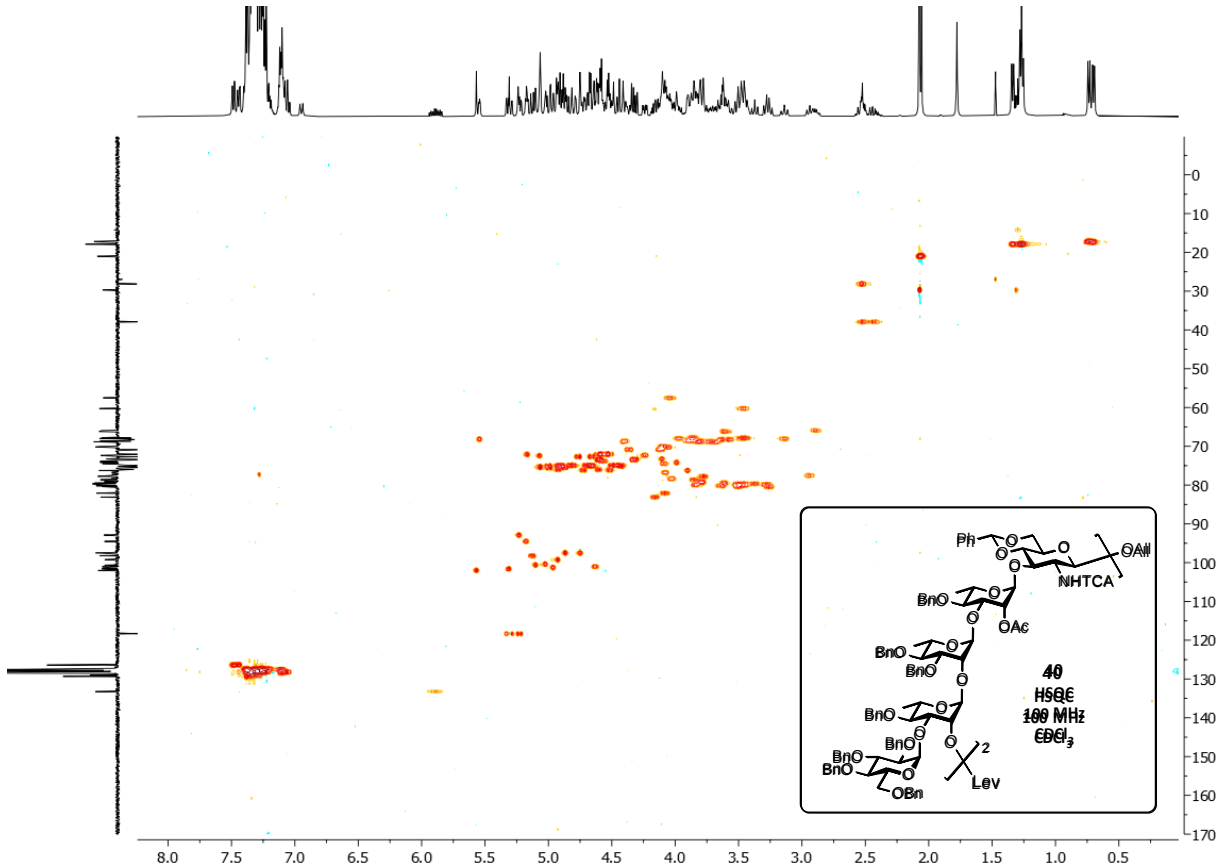

39
$^{13}$C NMR
100 MHz
CDCl$_3$


39
HSQC
100 MHz
CDCl$_3$

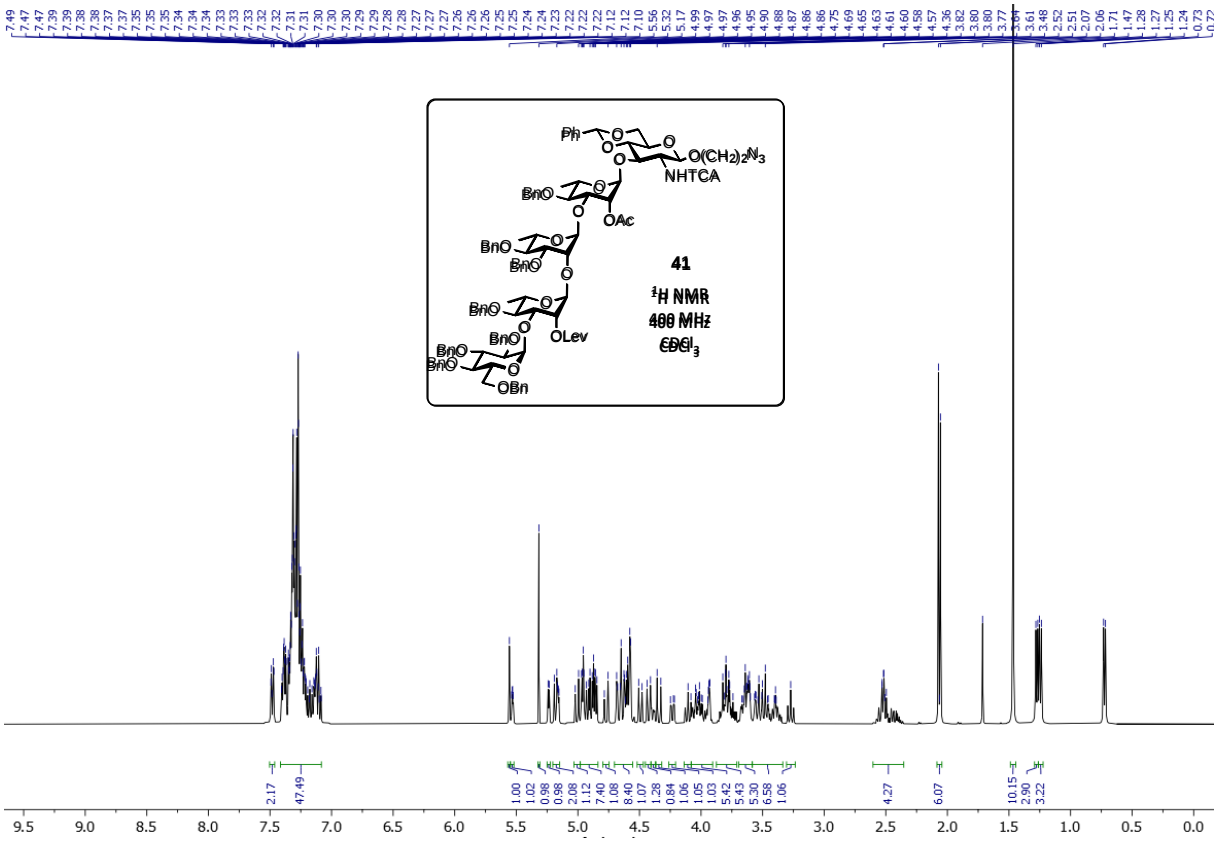
**Allyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (40)**

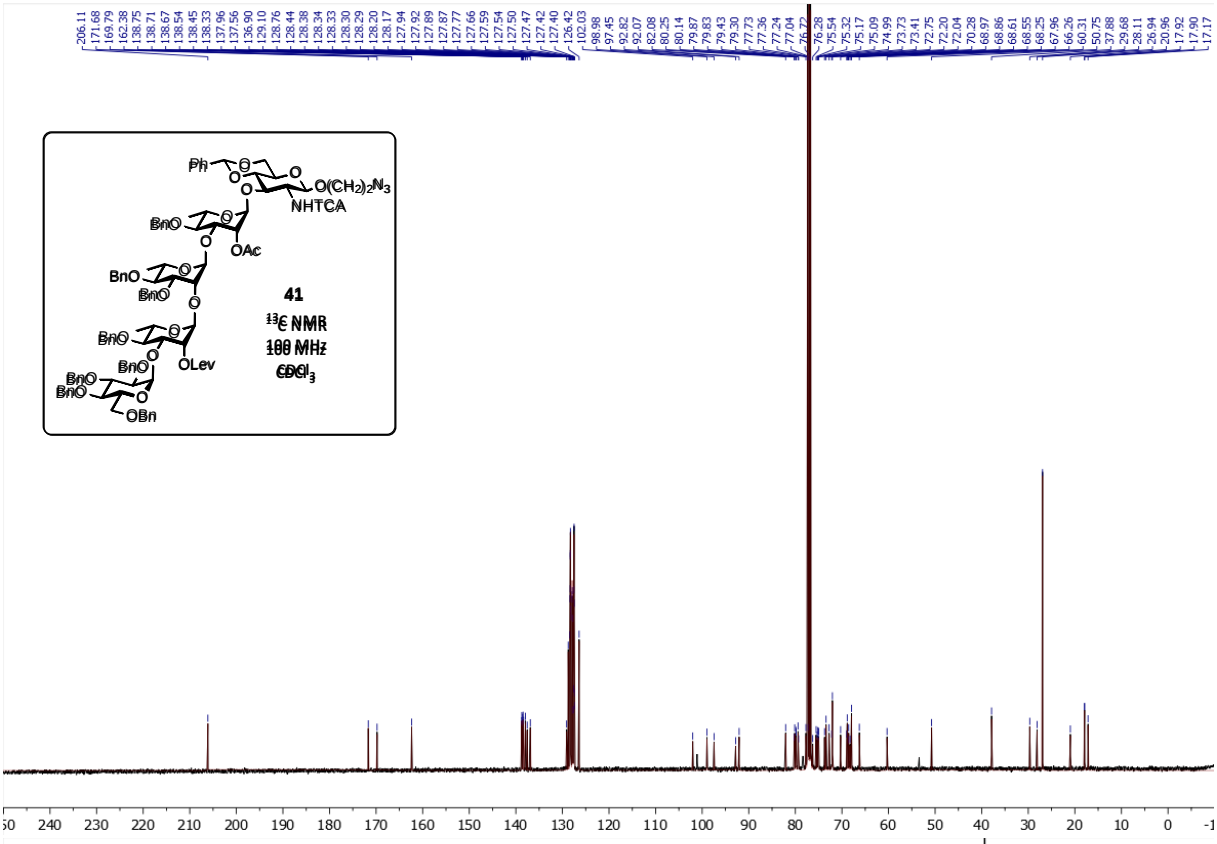


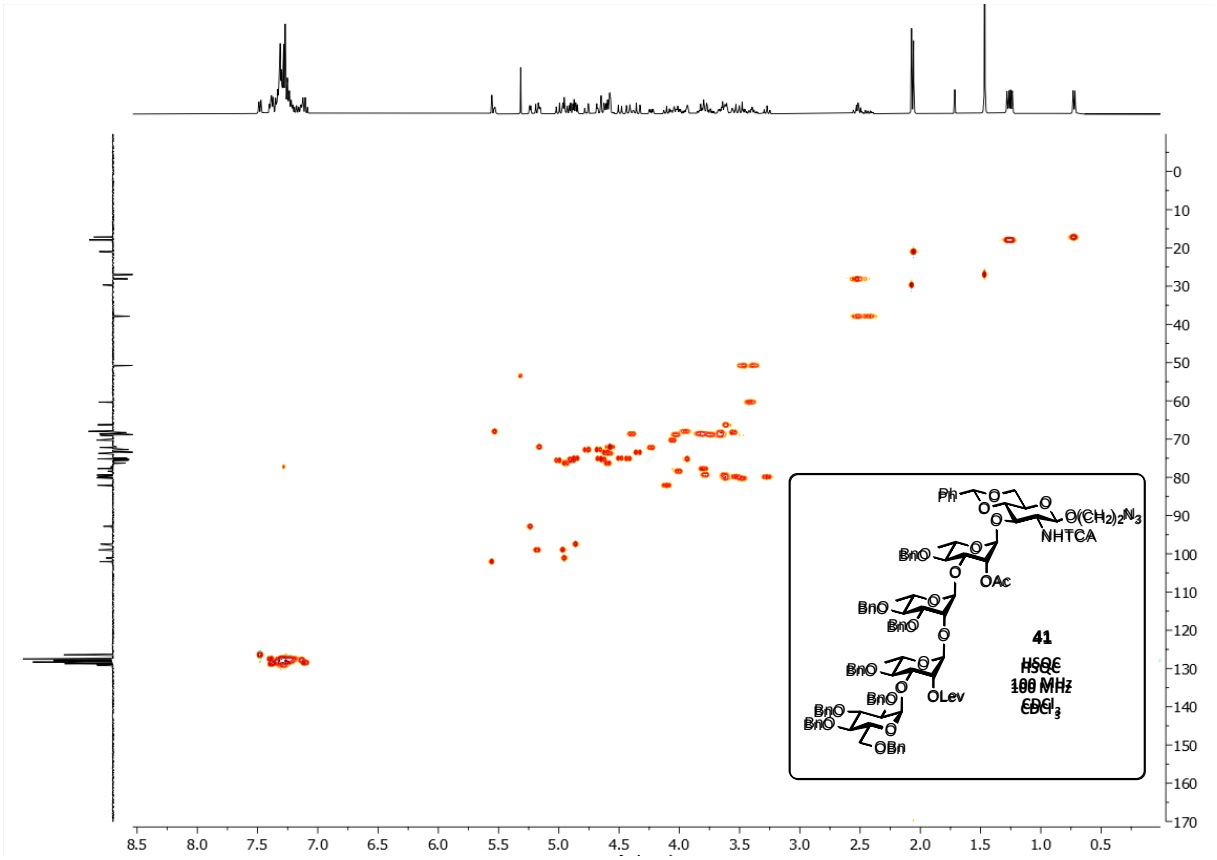

40
$^{13}$C NMR
100 MHz
$CDCl_3$


40
HSQC
100 MHz
$CDCl_3$

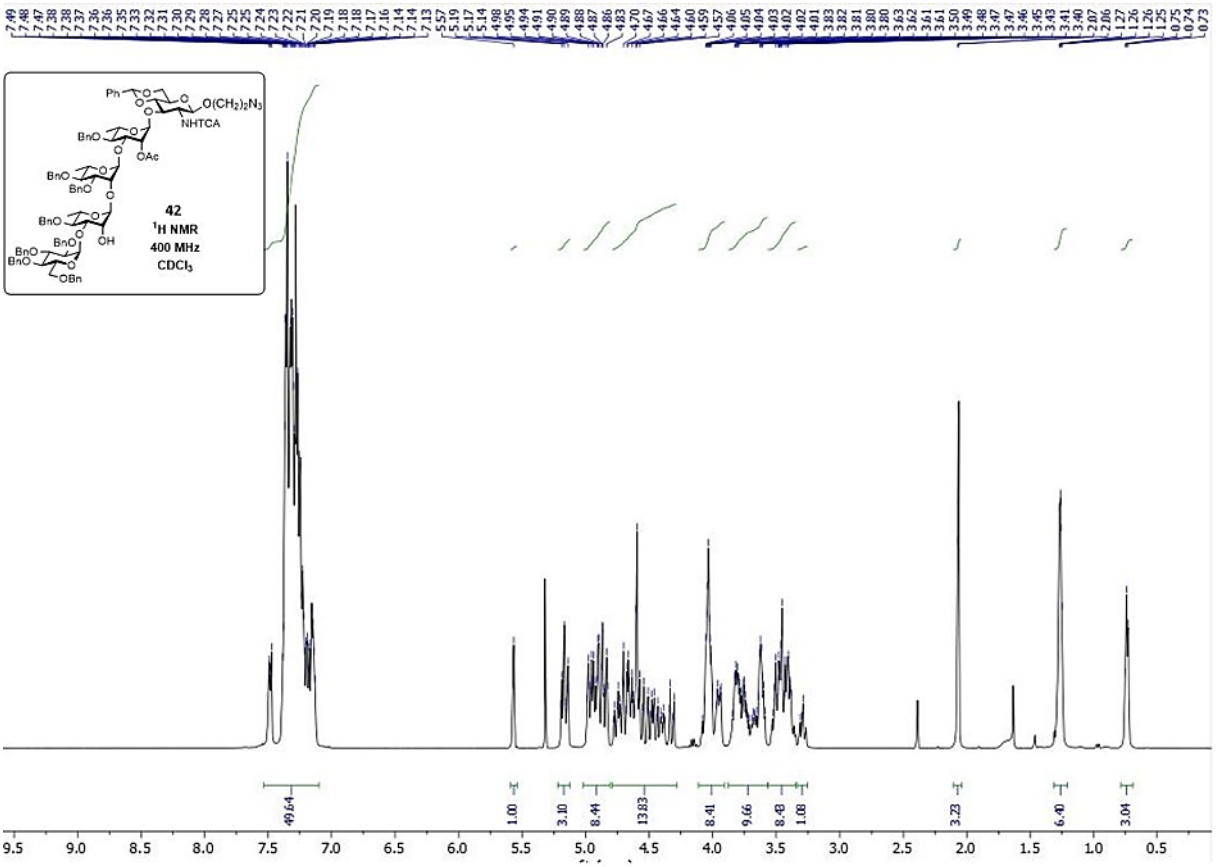
**2-Azidoethyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (41)**

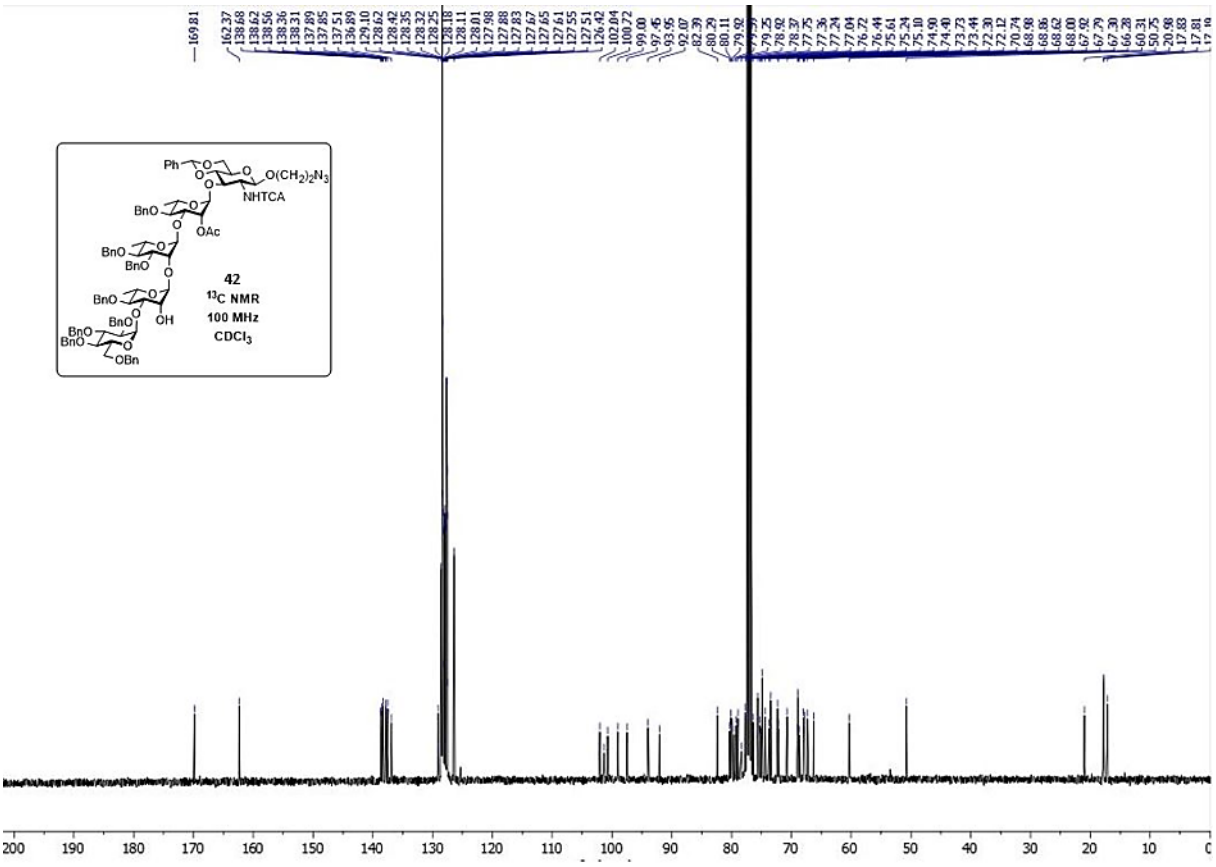


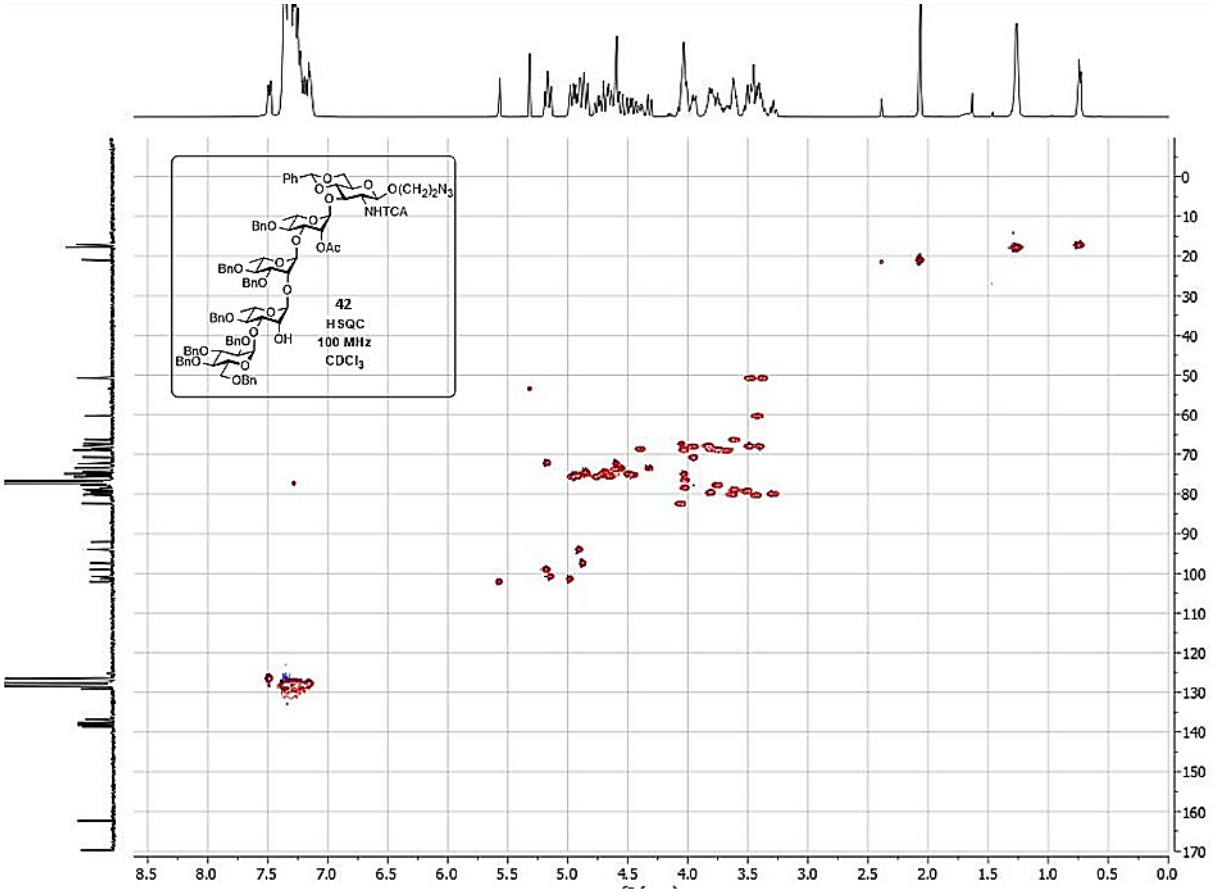

41
$^{13}$C NMR
100 MHz
$CDCl_3$


41
HSQC
100 MHz
$CDCl_3$

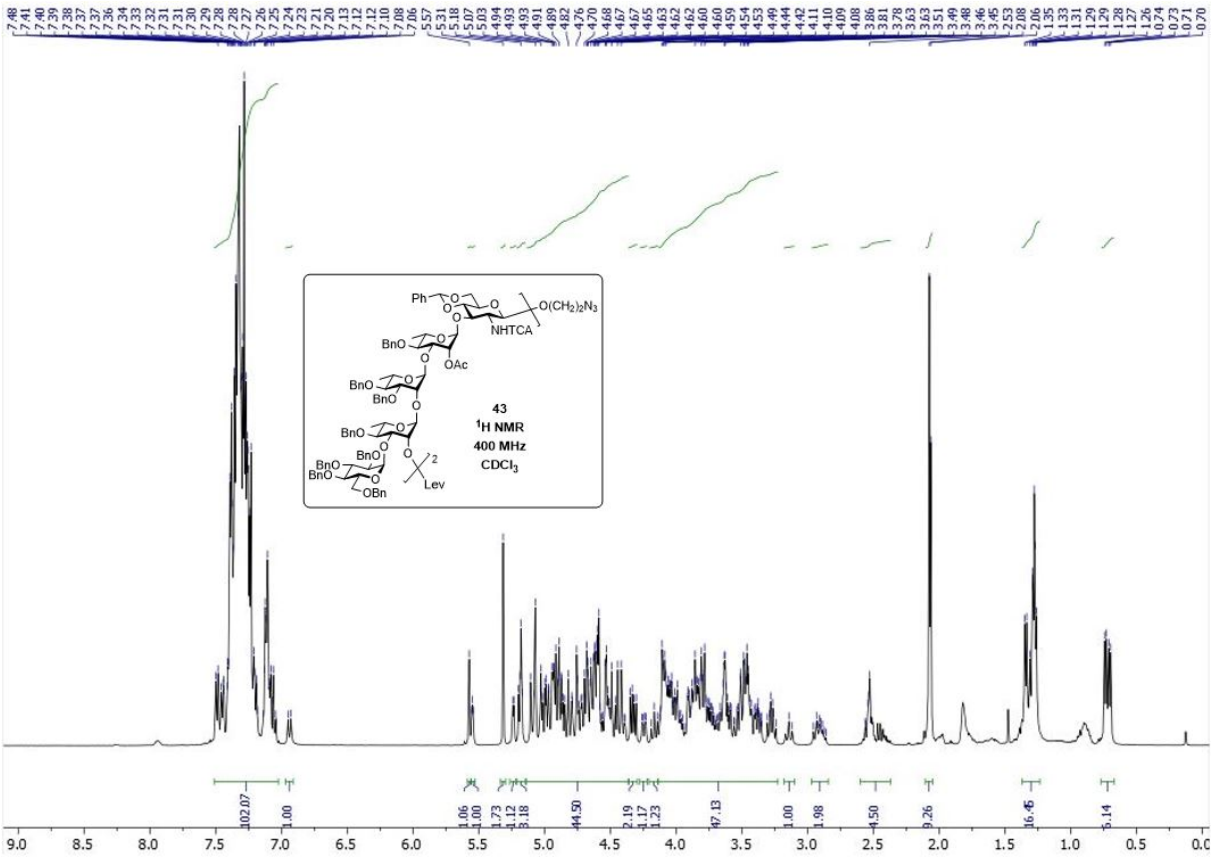
**2-Azidoethyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (42)**

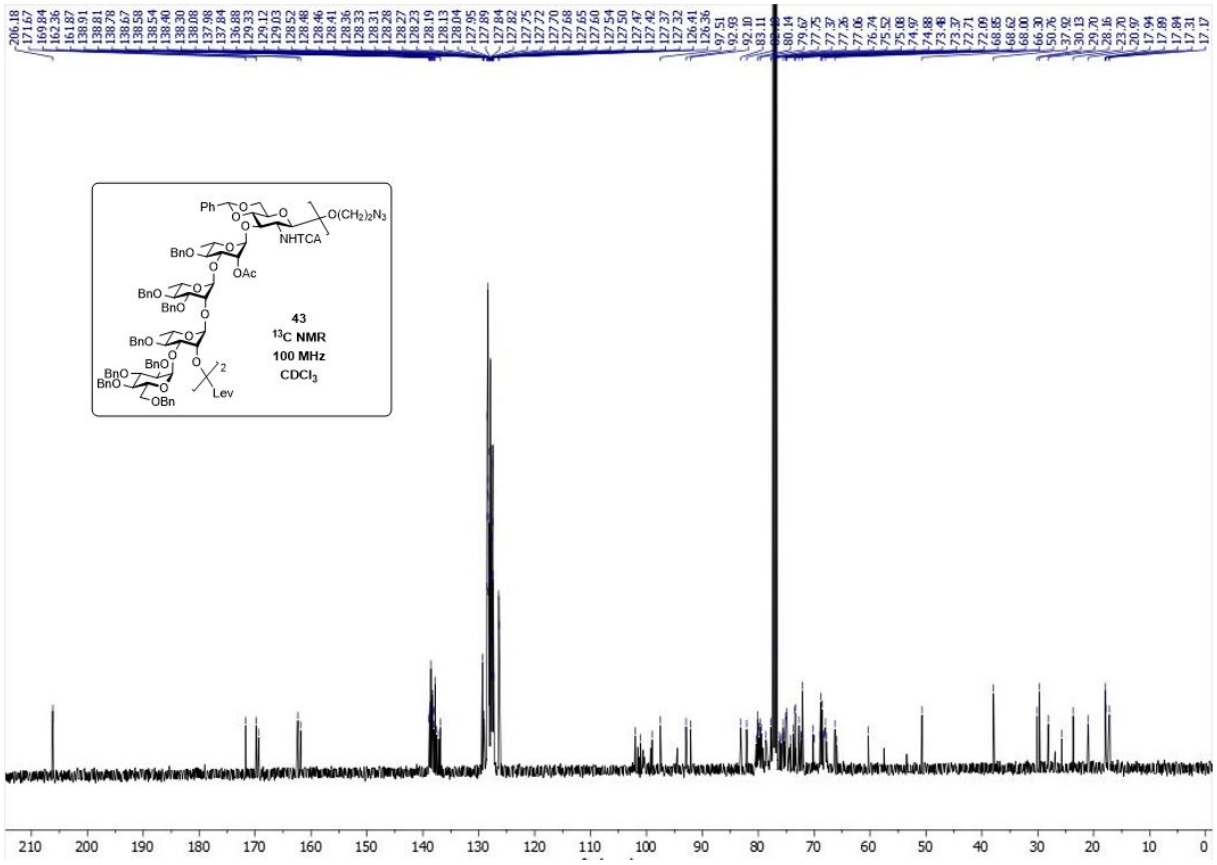


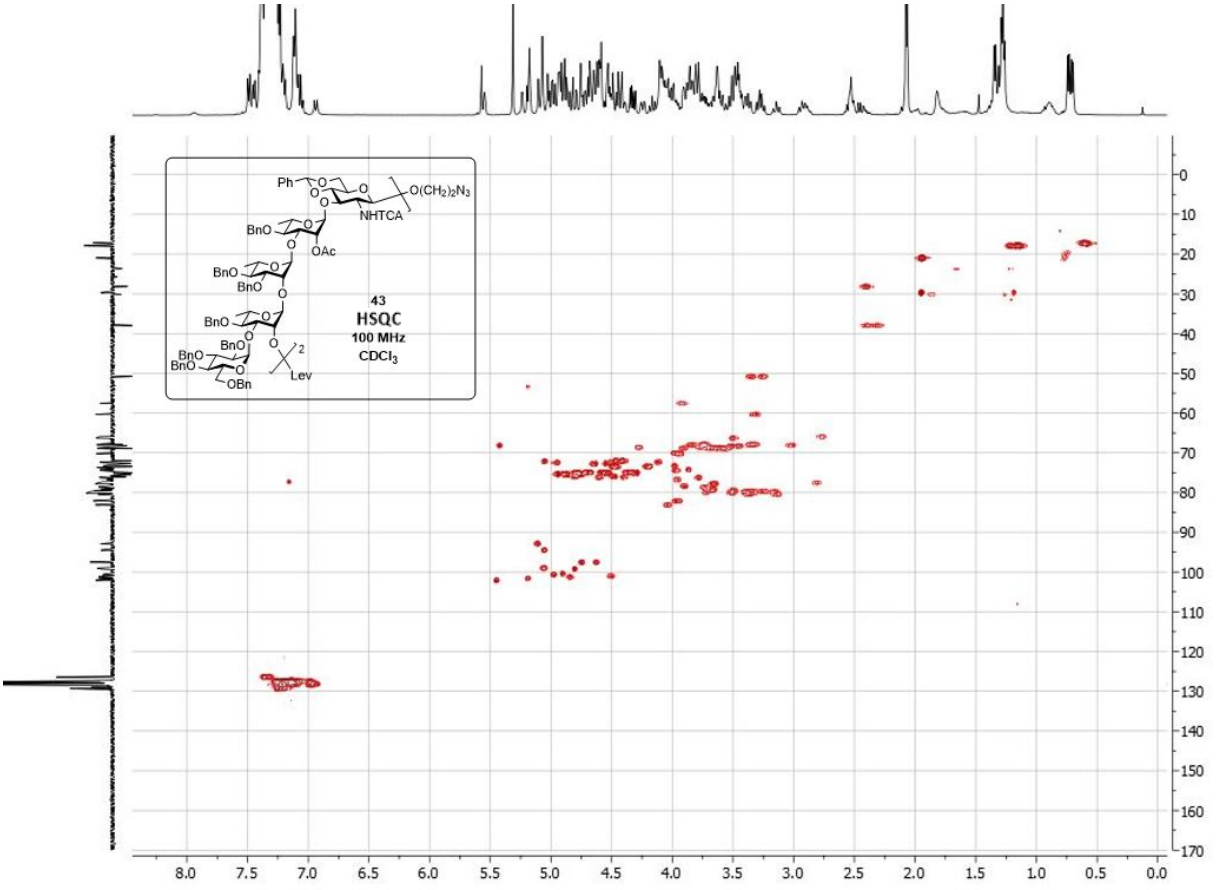

42
$^{13}$C NMR
100 MHz
$CDCl_3$


42
HSQC
100 MHz
$CDCl_3$

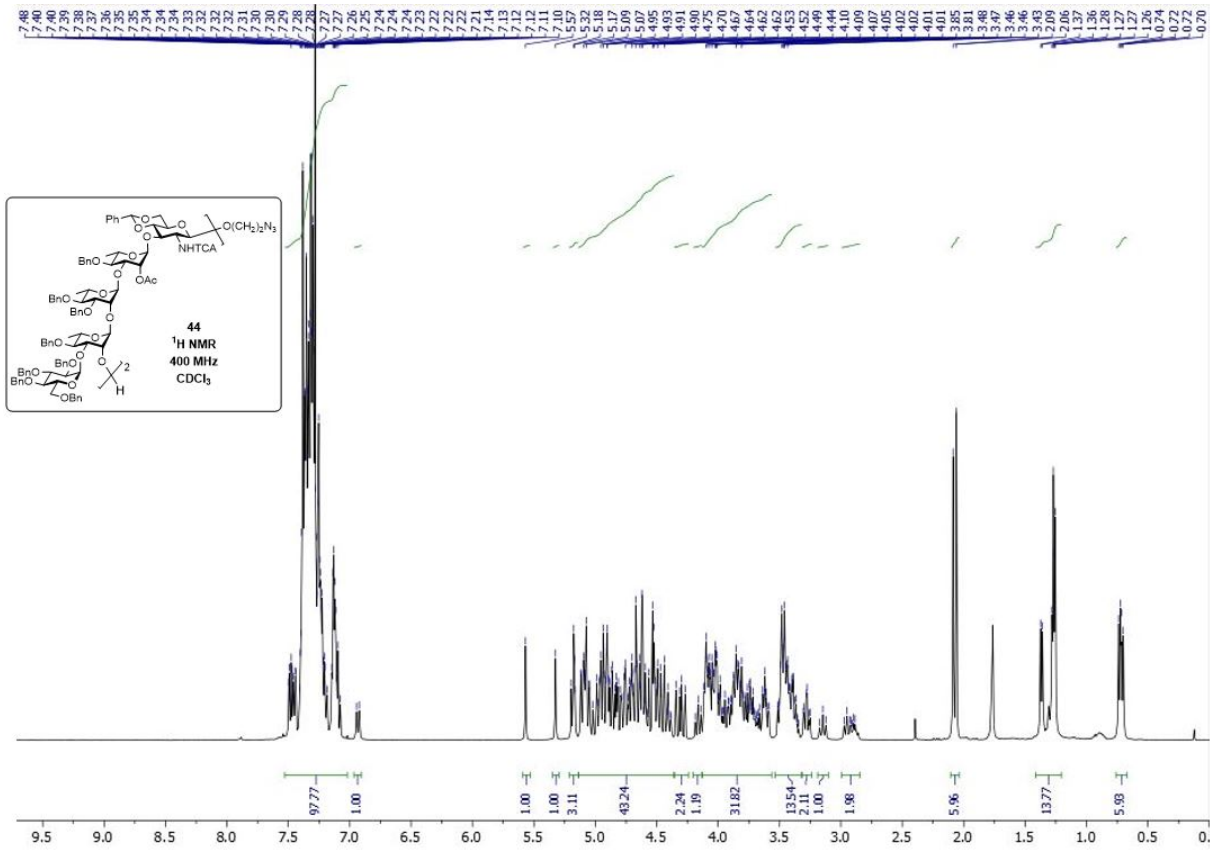
**Azidoethyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-2-*O*-levulinoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (43)**

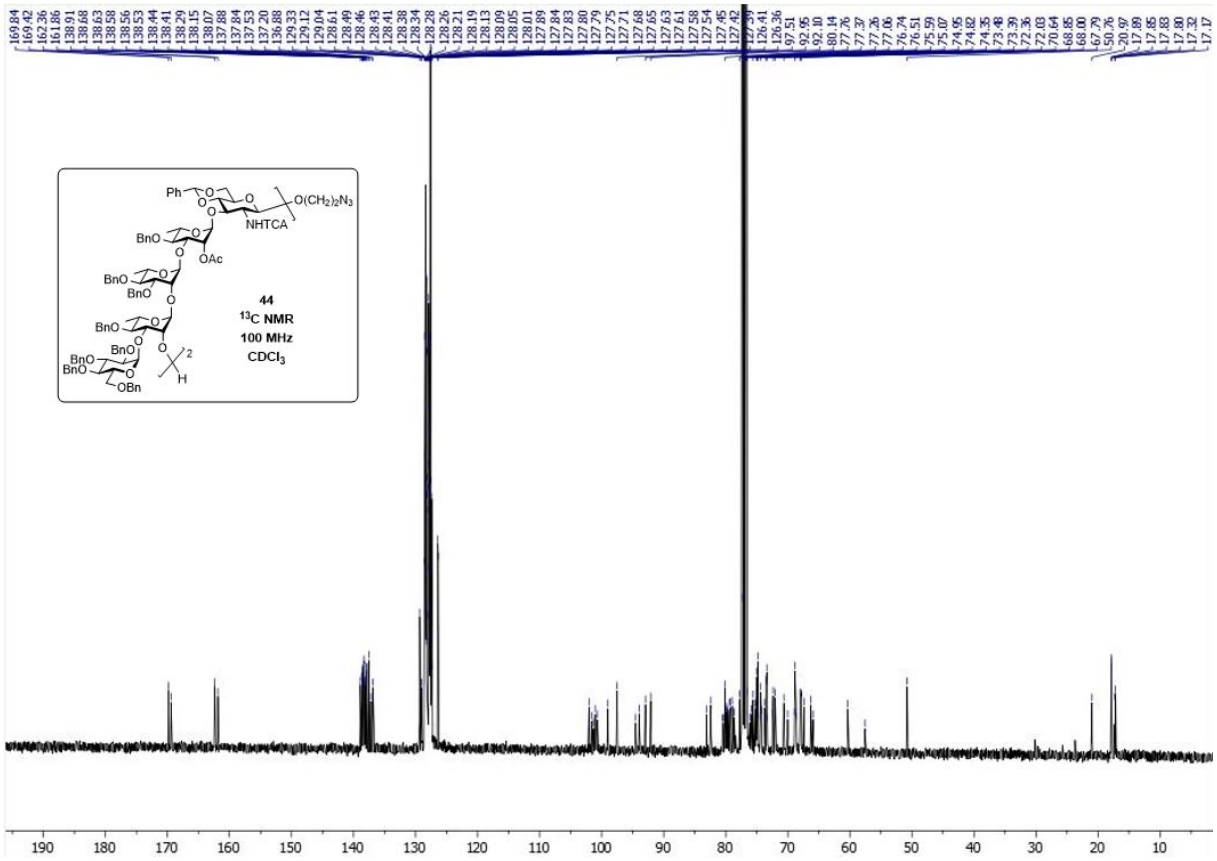


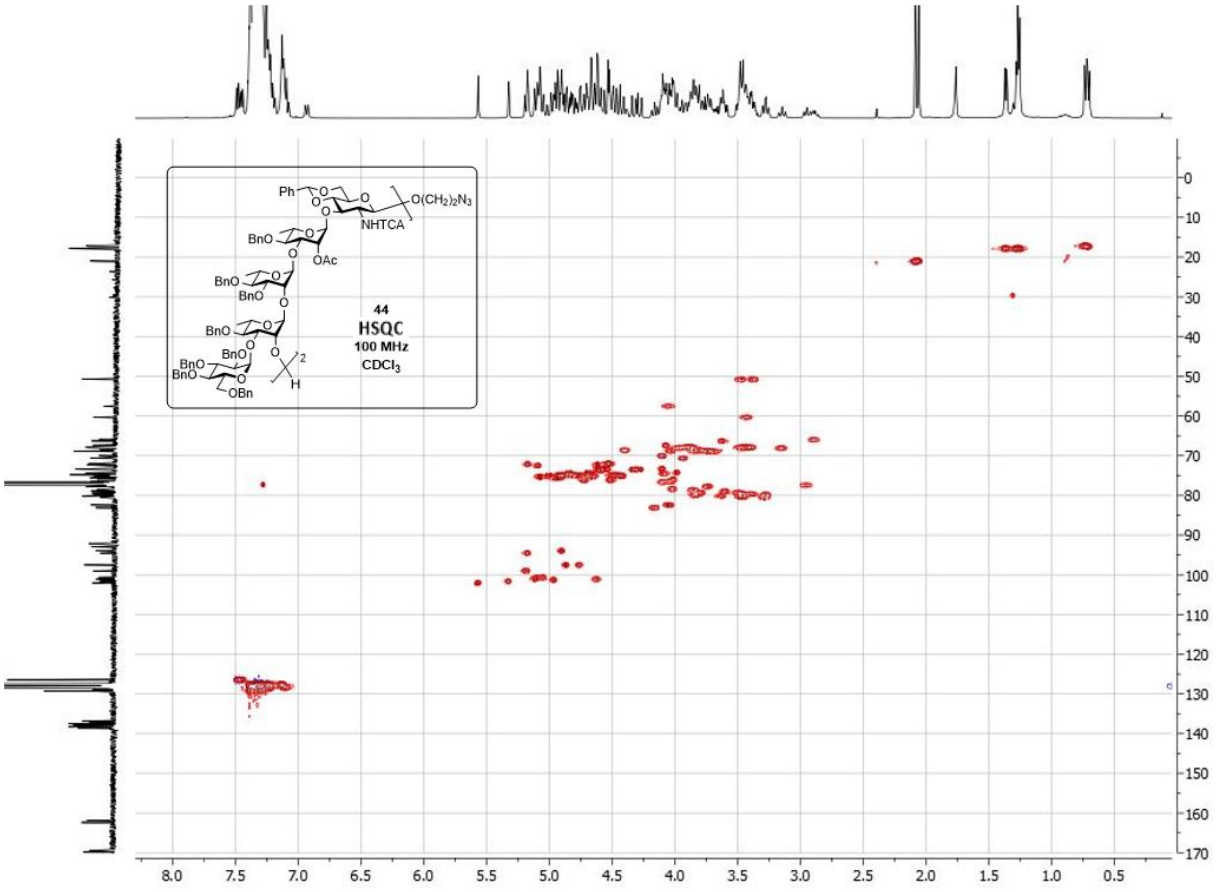

43
$^{13}$C NMR
100 MHz
CDCl$_3$


43
HSQC
100 MHz
CDCl$_3$

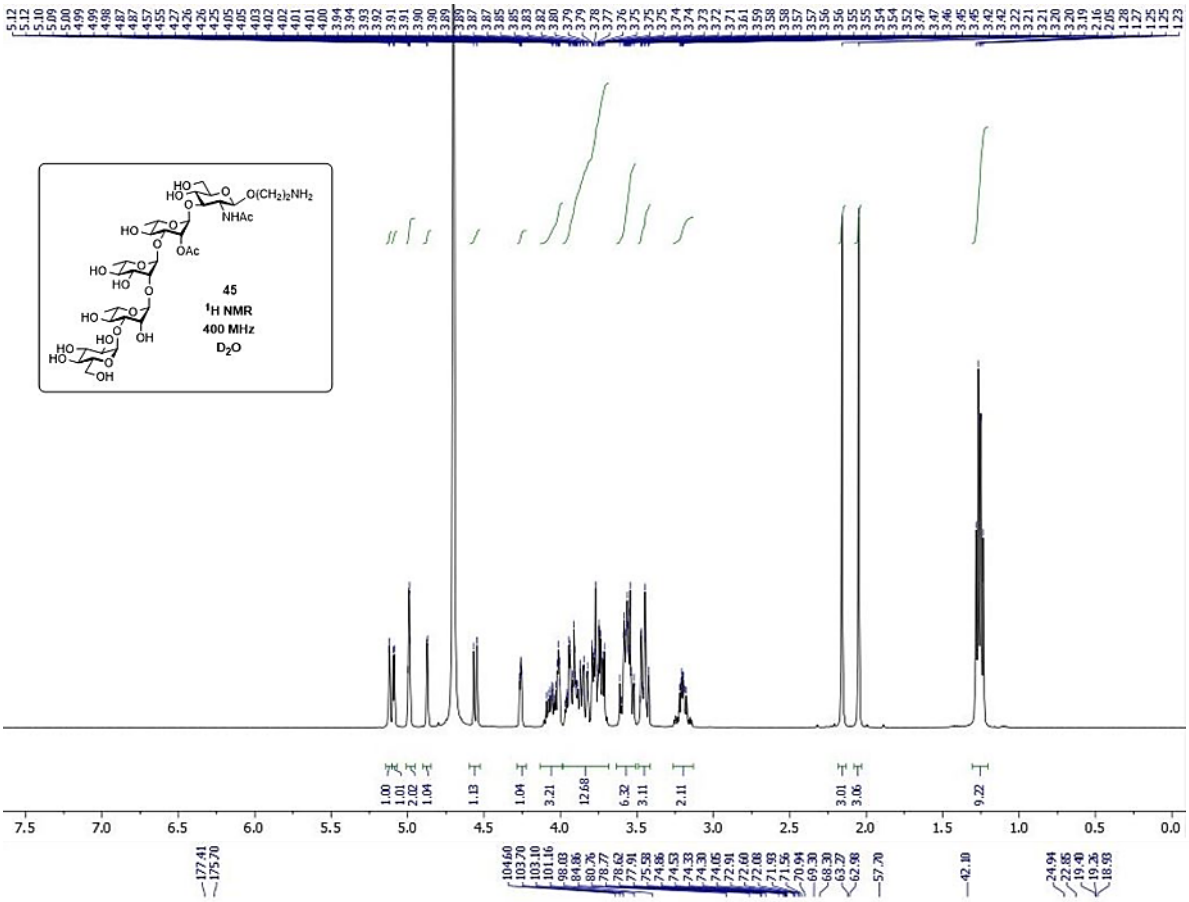
**Azidoethyl (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-(2-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (44)**

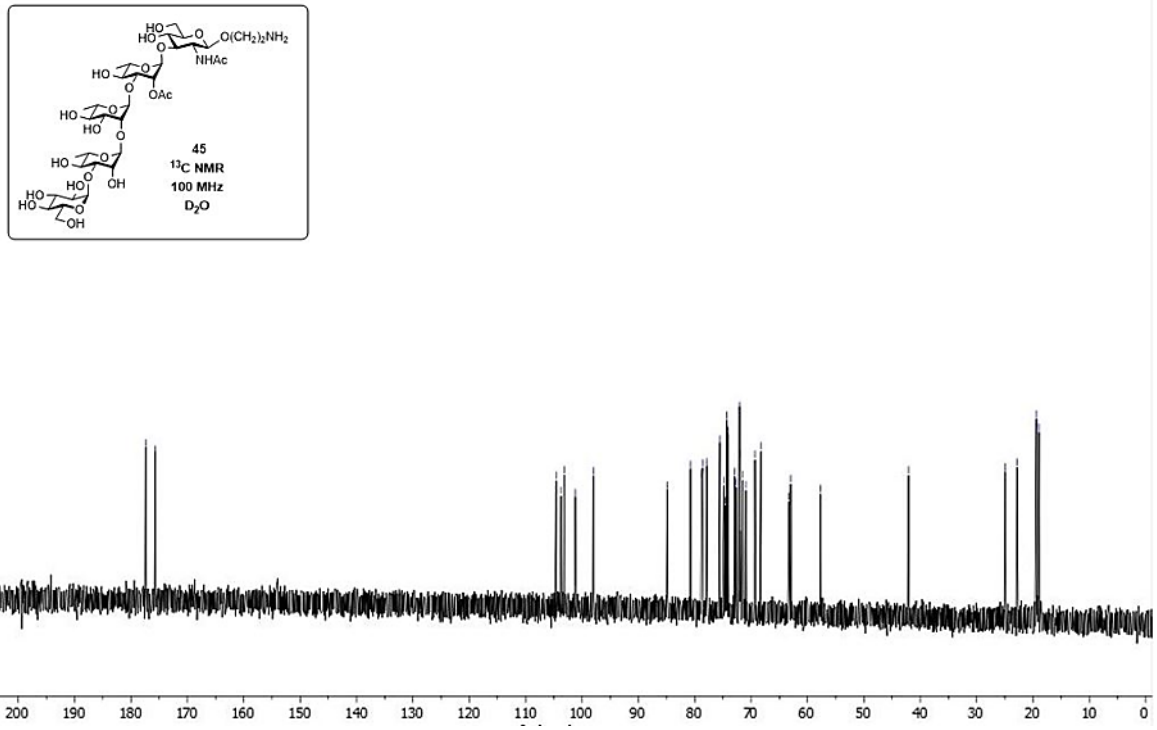


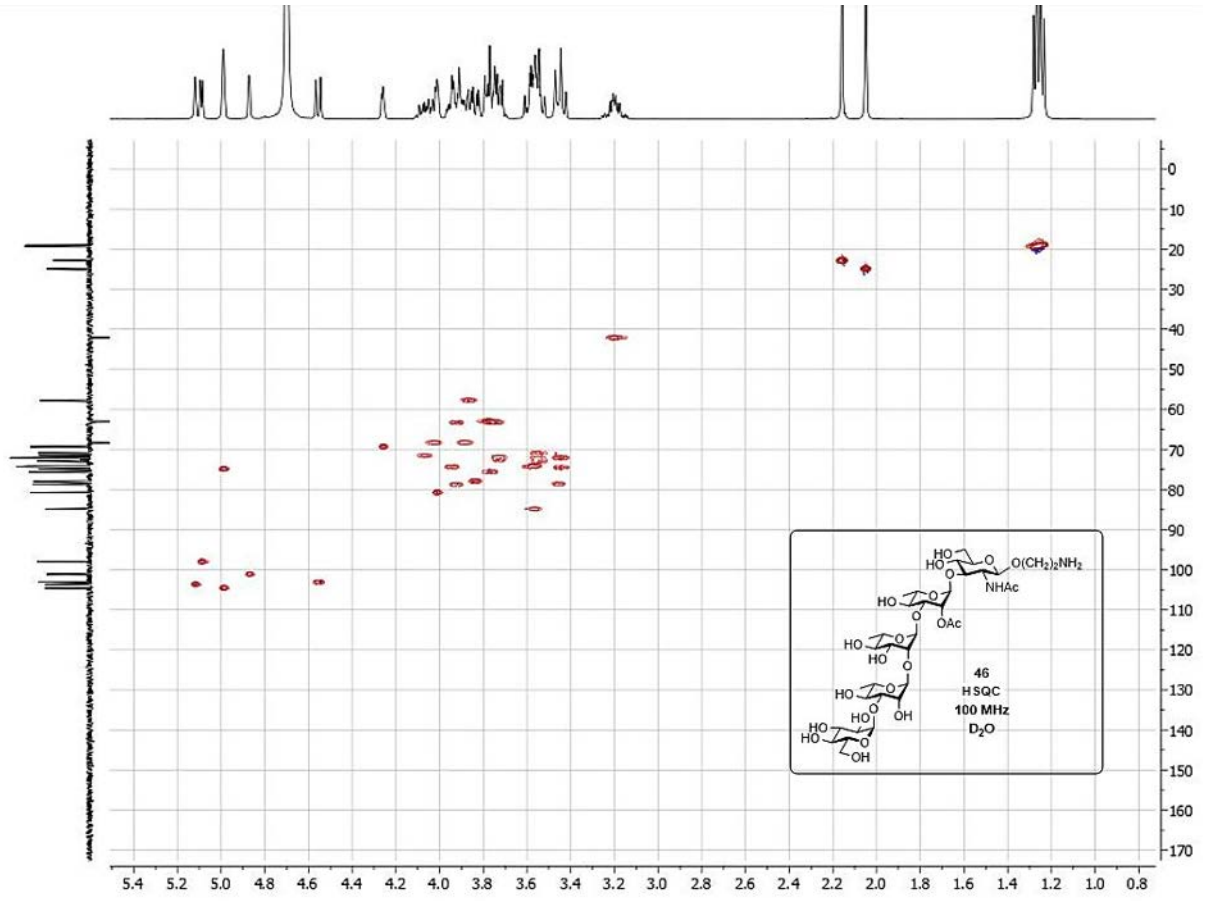

44
$^{13}$C NMR
100 MHz
CDCl$_3$


44
HSQC
100 MHz
CDCl$_3$

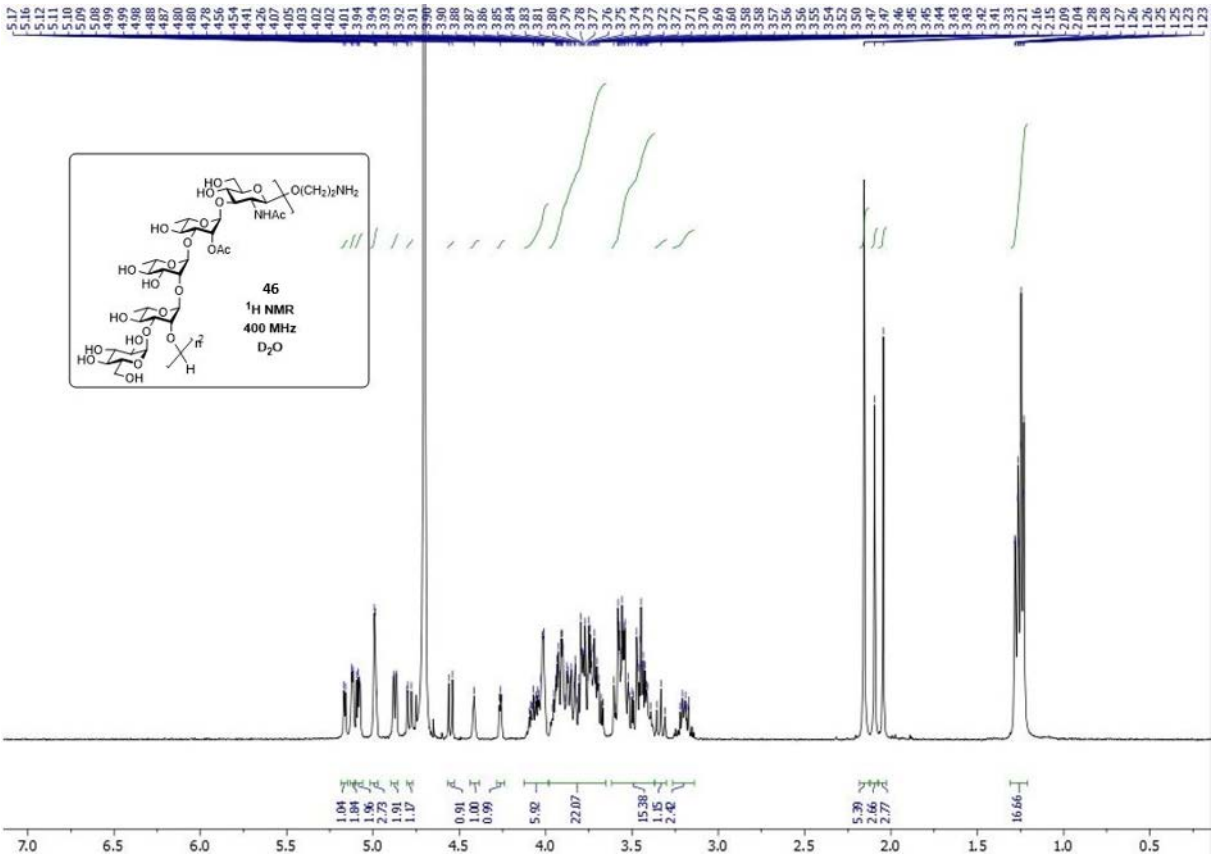
**2-Aminoethyl α-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-(2-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (45)**

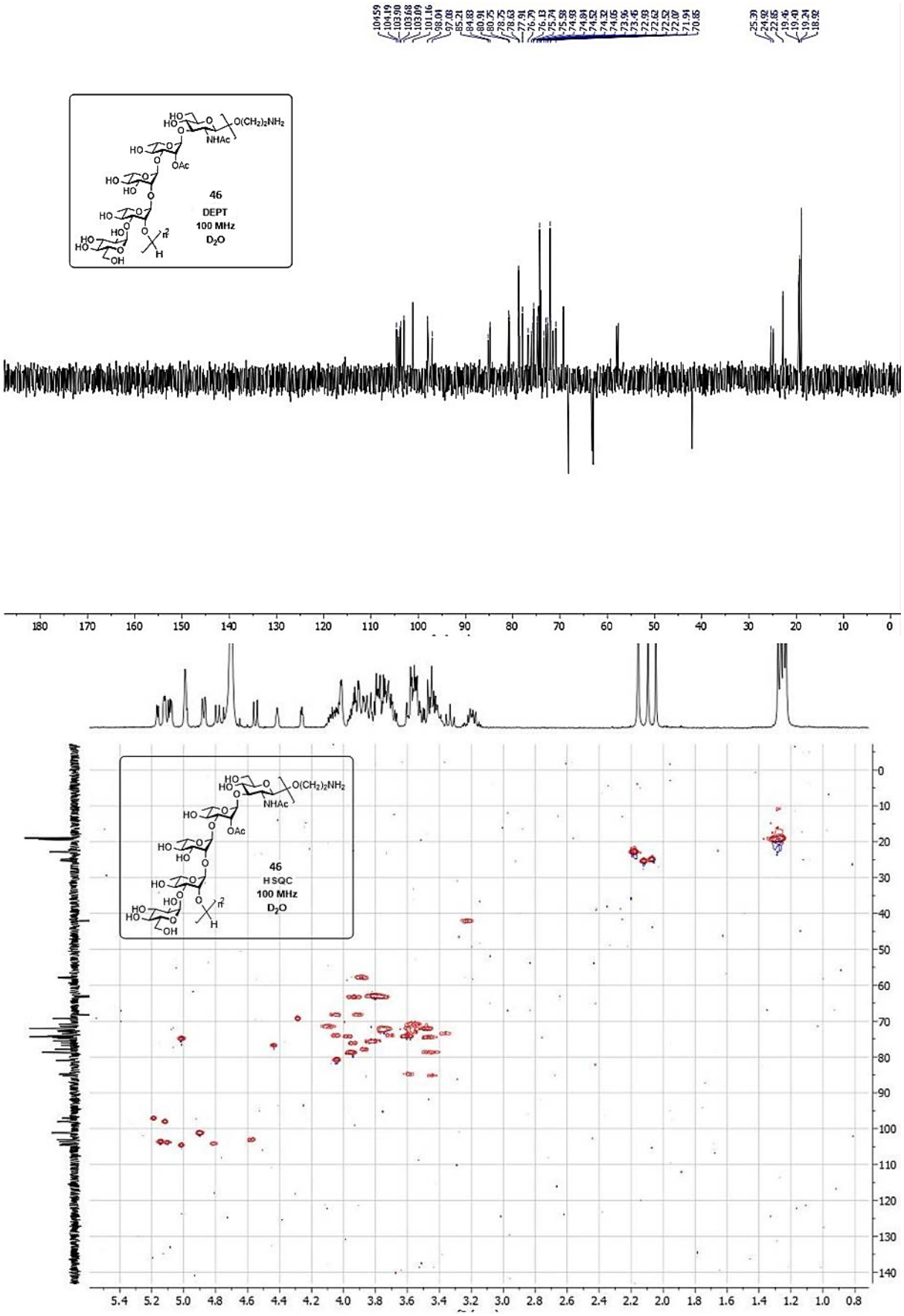



46
HSQC
100 MHz
D2O

**2-Aminoethyl α-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-(2-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-[α-D-glucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-(2-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-[α-D-glucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-(2-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside (46)**




46
DEPT
100 MHz
D2O
46
HSQC
100 MHz
D2O