Supporting Information

Fast and Effective Preparation of Highly Cytotoxic Hybrid Molecules of Schweinfurthin E and OSW-1

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1. Supplementary Figures

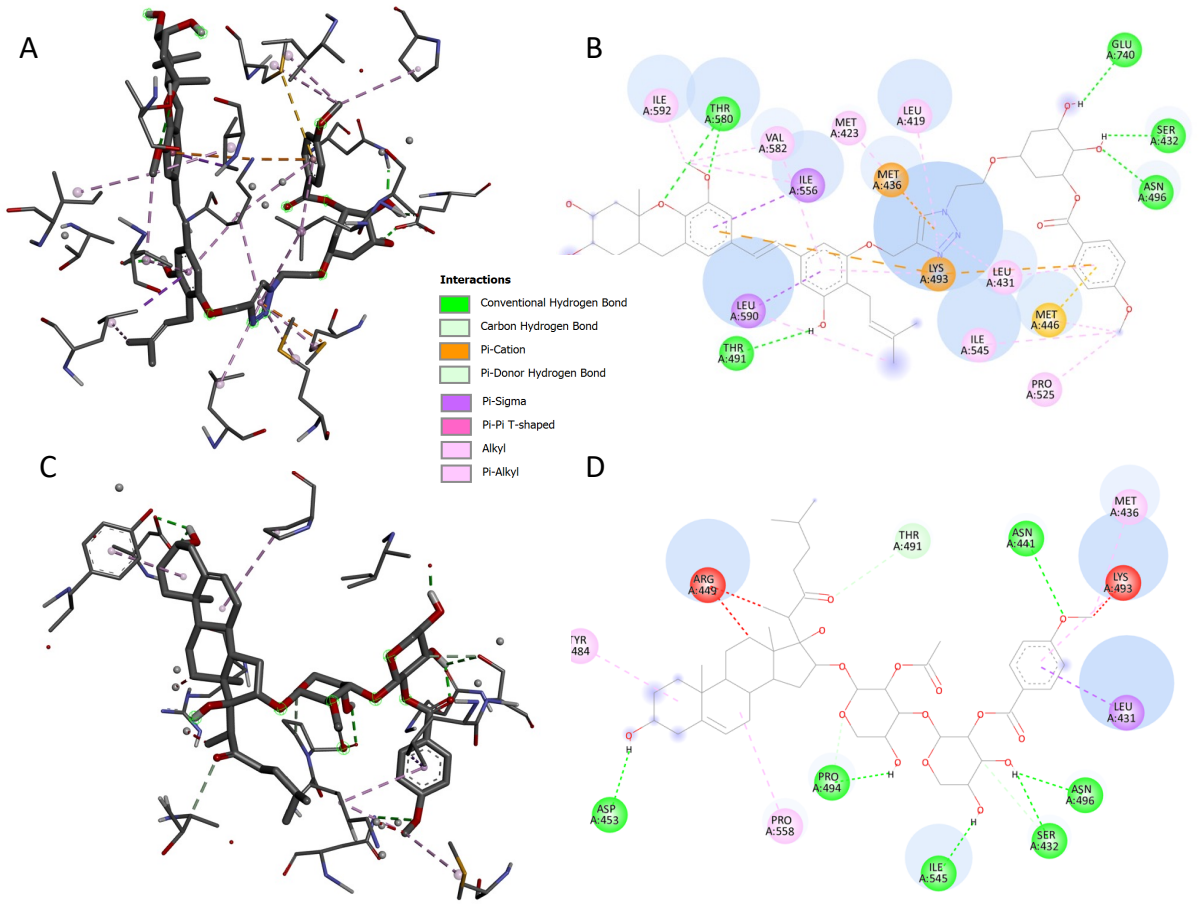


Fig.1S: 3D representation of hybrid **18** (**A**) and OSW-1 (**C**) and 2 D interaction map with the amino acids of the ORD domain of OSBP of hybrid **18** (**B**) and OSW1 (D), using BIOVIA Discovery Studio.

2. Experimental procedures

General

All reactions were performed in oven-dried round-bottomed flasks using anhydrous solvents and under an argon atmosphere unless otherwise stated. Anhydrous solvents (DMF, MeOH, MeCN, CH_2Cl_2, PhH) and reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} plates and

visualized under UV (254 nm) and/or by staining with $KMnO_4$ or vanillin. Silica gel SDS 60 ACC 35-70 mm was used for column chromatography. Preparative TLC was done using Merck 60 F_{254} 0.5 mm. NMR spectra were recorded with AM 300, AVANCE 300 and AVANCE 500 Brüker spectrometers. Chemical shifts are given in parts per million, referenced to the solvent peak of $CDCl_3$, defined at 77.23 ppm (^{13}C NMR) and 7.26 ppm (^{1}H NMR). Melting points (uncorrected) were determined with the aid of a Büchi B-540 apparatus. IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument with an FT-IR system. Optical rotations were measured on an Anton Paar MCP300 polarimeter using a cell of 1 dm-length path. All the reagent-grade chemicals obtained from commercial sources were used as received.

Plant Material. The green fruits of *M. tanarius* were collected in June 2014 at A Luoi, Thua Thien Hue Province, Vietnam, and authenticated by N.T. Cuong and D.D. Cuong. A voucher specimen (VN-2371) has been deposited at the Herbarium of the Institute of Ecology and Biological Resources of The Vietnam Academy of Science and Technology, Hanoi, Vietnam. ABS-CH Unique Identifier (UID): ABSCH-IRCC-VN-255602-1.

Extraction and Isolation. Isolation of SW-E **3** has already been described in a previous article.[1]

Synthesis

(2S,3R,4aR,9aR)-7-((E)-3-hydroxy-4-(3-methylbut-2-en-1-yl)-5-(prop-2-yn-1-yloxy)styryl)-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-2,3-diol **7**.

To a solution of SW-E **3** (400 mg, 0.81 mmol) in anhydrous DMF (20 mL) at 0 °C under argon was added K_2CO_3 (447 mg, 3.23 mmol, 4 equiv.). After 20 min, propargyl bromide (86 µL, 0.77 mmol, 0.95 equiv.) was added. The reaction mixture was stirred at r.t. for 24 h and an aqueous solution of NH_4Cl (20 mL) was added. The products were then extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by C18-reversed phase silica gel chromatography with H_2O/ACN from 8:2 to 0:10 to give compound **7**, obtained as a brown solid (138 mg, 0.26 mmol, 32 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.91 (d, J = 16.5 Hz, 1H), 6.85 (s, 1H) 6.83 (s, 1H), 6.82 (d, J = 16.5 Hz, 1H), , 6.69 (s, 1H), 6.67 (s, 1H), 5.22 (t, J = 7.0 Hz, 1H), 4.71 (s, 2H), 4.23 (d, J= 4.25 Hz, 1H), 3.87 (s, 3H), 3.40 (d, J = 7.0 Hz, 2H), 3.36 (d, J = 3.0 Hz, 1H), 2.82-2.71 (m, 2H), 2.51 (t, J = 2.1 Hz, 1H), 2.48 (dd, J = 14.3, 3.0 Hz, 1H), 2.00 (dd, J = 14.3, 3.0 Hz, 1H), 1.80 (s, 3H), 1.76 (dd, J = 12.4, 5.2 Hz, 1H), 1.72 (s, 3H), 1.43 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.1, 155.6, 149.0, 142.3, 136.9, 134.4, 128.8, 128.6, 126.0, 122.8, 121.7, 120.5, 115.3, 107.5, 107.1, 103.1, 78.8, 77.5, 76.6, 75.3, 70.8, 56.5, 56.0, 46.9, 43.3, 38.0, 28.9, 25.7, 23.0, 22.5, 21.5, 17.8, 15.9 ppm.

ESIHRMS: *m/z* calculated for $C_{33}H_{41}O_6^+$ $[M + H]^+$: 532.2898; found: 533.2903

[1] T. Péresse, G. Jézéquel, P. M. Allard, V. C. Pham, D. T. M. Huong, F. Blanchard, J. Bignon, H. Lévaique, J. L. Wolfender, M. Litaudon and F. Roussi, *J. Nat. Prod.* 2017, **80**, 2684.

IR (ν, cm^{-1}): 3441, 3284, 2927, 2120, 1702, 1660, 1586, 1493, 1463.

[α]$^{22}_{D}$ + 51.8 ° (*c* 0.5, $CHCl_3$).

Methyl-2-O-(4-methoxybenzoyl)-3,4-O-(di-levulinoyl)-β-D-xylopyranoside 10

To a round bottom flask under an inert atmosphere, commercially available methyl D-xylose (0.85g, 5.18 mmol, 1 equiv.) dissolved in dry pyridine (8 mL) and dry DCM (4 mL), was cooled to –45 °C with MeCN/dry ice bath. 4-methoxybenzoyl chloride (0.84 mL, 6.2 mmol, 1.2 equiv.) in dry DCM (4 mL) was added dropwise by syringe pump over 2 h while temperature was kept at –45 °C. After 3 h at –45 °C, the reaction was heated back slowly to r.t. After 2 days, the mixture was quenched with MeOH, concentrated, and co-evaporated with toluene. EtOAc (30 mL) and saturated K_2CO_3 solution (30 mL) were added to the mixture. After the phases' separation, the aqueous phase was extracted with EtOAc (30 mL), and the combined organic phases were washed with brine (50 mL). After being dried over Na_2SO_4 and concentrated, the crude residue was dissolved in dry DCM (30 mL). To this solution were then added successively levulinic acid (2.1 g, 18.13 mmol, 3.5 equiv.), EDC·HCl (3.5 g, 18.13 mmol, 3.5 equiv.) and DMAP (126 mg, 1.04 mmol, 0.2 eq.) at room temperature. After 2 h, the reaction mixture was diluted with DCM (30 mL) and subsequently washed with saturated $NaHCO_3$ solution (2 x 35mL), and brine (35 mL). After being dried over Na_2SO_4 and concentrated, the crude reaction mixture was purified by flash chromatography (SiO2, heptane/EtOAc : 7/3 to 5/5) to furnish the desired compound **10** as a colorless thick oil (1.56 g, 3.16 mmol, 63%).

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.93 (2H, d, J = 9.0 Hz, H_{Ar}), 6.89 (2H, d, J = 9Hz, H_{Ar}), 5.64 (1H, t, J = 10.0 Hz, H_3), 5.09-4.98 (2H, m, H_1 and H_4), 4.92 (1H, dd, J = 10.0, 3.5 Hz, H_2), 3.83 (3H, s, ArO*CH$_3$*), 3.79 (1H, dd, J= 11.0, 6.0 Hz, H_{5a}), 3.59 (1H, dd, J= 11.0, 10.5 Hz, H_{5b}), 3.35 (3H, s, O*CH$_3$*), 2.76-2.35 (8H, m, CH_{2Lev}), 2.15 (3H, s, CH_{3Lev}), 2.04 (3H, s, CH_{3Lev}).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.4 (CO), 205.9 (CO), 171.8 (CO), 171.7 (CO), 165.5 (CO), 163.8 (C_q), 132.1 (C_q), 121.6 (C_q), 113.8 (C_{Ar}), 97.1 (C_1), 71.6 (C_2), 69.5 (C_3), 69.2 (C_4), 58.2 (C_5), 55.5 (2xO*C*H$_3$), 37.8 (*C*H$_2$), 37.7 (*C*H$_2$), 29.7 (*C*H$_3$), 29.6 (*C*H$_3$), 28.1 (*C*H$_2$), 27.9 (*C*H$_2$).

ESIHRMS *m/z* calculated for $C_{24}H_{30}O_{11}Na$ 517.1686 $[M+Na]^+$, found 517.1685.

IR (ν, cm^{-1}): 2939, 1743, 1713, 1605, 1253, 1166, 1155, 1100, 1036.

[α]$^{22}_{D}$ + 121.9 (*c* 0.58, $CHCl_3$)

Bromide-2-O-(4-methoxybenzoyl)-3,4-O-(bis-levulinoyl)-β-D-xylopyranoside 9

To a solution of xyloside **10** (1.26 g, 2.55 mmol, 1 equiv.) in dry DCM (30 mL) under inert atmosphere was added freshly dried $ZnBr_2$ (0.573 g, 2.55 mmol, 1 equiv.) followed by the addition of TMSBr (1.1 mL, 7.65 mmol, 3 equiv.). After 12 hours of stirring at room temperature, the reaction mixture was diluted in DCM (20 mL) and a 1:1 solution of saturated $NaHCO_3$ and water (10 mL). After phase separation, the organic phase was washed with H_2O (20 ml), dried over Na_2SO_4 and concentrated under

reduced pressure to give the expected bromide **9** (1.3 g, 2.4 mmol, 94%), which was used as a glycoside donor without further purification.

^{1}H NMR ($CDCl_3$, 300MHz) : 7.95 (2H, d, J = 9.0 Hz, H_{Ar}), 6.91 (2H, d, J = 9.0 Hz, H_{Ar}), 6.67 (1H, d, J= 4.0 Hz, H_1), 5.73 (1H, t, J= 10.0 Hz, H_3), 5.12 (1H, ddd, J= 11.0, 10.0, 6.0 Hz, H_4), 4.95 (1H, dd, J = 10.0, 4.0 Hz, H_2), 4.05 (1H, dd, J=11.0, 6.0 Hz, H_{5a}) , 3.91 (1H, t, = 6Hz, H_{5b}), 3.85 (3H, s, O*CH₃*), 2.79-2.49 (8H, m, CH_2), 2.17 (3H, s, CH_3), 2.06 (3H, s, CH_3).

1-p-methoxyphenyl-(2,3,4-O-acetyl-β-L-arabinopyranoside) β-11

Following the protocol of Burns et al.,[2] α-D-xylose (1) (2.00 g, 13.32 mmol, 1 equiv.) and DMAP (0.17 g, 1.33 mmol, 0.1 equiv.) were added to a flask followed by CH_2Cl_2 (10 mL) and NEt_3 (15 mL,106.56 mmol, 8 equiv.). The white suspension was stirred at 25 °C and the flask was cooled to 0 °C and stirred for 10 min before dropwise addition of acetic anhydride (9 mL, 93.25 mmol). The white suspension was stirred at 0 °C for 2 h 30 min before being warmed to 25 °C for 2 h. The flask was then placed in an ice bath and quenched with chilled water (20 mL). The ice bath was removed after 20 min and the bi-phasic, yellow solution was then transferred to a 250 mL separatory funnel, washed with CH_2Cl_2 (3 x 20 mL). The combined organic layer was then washed with 1 M HCl (4 x 20 mL), chilled water (3 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL), and chilled water (2 x 20 mL). The CH_2Cl_2 layer was dried over Na_2SO_4, filtered through celite, and the solvent was removed under vacuum to yield a yellow glass (4.26 g, 100%), which was used in the next step without purification. To the residue in CH_2Cl_2 (20 mL) was added *p*-methoxyphenol (2.48 g, 20.1 mmol, 1.5 equiv.) and 4Å molecular sieves (4.3 g) and the mixture was stirred for 10 min at r.t before being cooled to 0 °C. $BF_3.OEt_2$ (9.9 mL, 40.16 mmol, 3 equiv.) was added dropwise and the reaction was allowed to warm back to r.t. After being stirred overnight, $BF_3.OEt_2$ (6.6 mL, 2 equiv.) was added and the solution was further stirred for 18 h. The reaction was diluted with CH_2Cl_2 (20 mL) and quenched saturated $NaHCO_3$ (60 mL). After filtration through celite, the solution was sequentially washed with saturated $NaHCO_3$ (30 mL), water (40 mL), and brine (40 mL). The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude reaction mixture was purified by flash chromatography (SiO2, heptane/EtOAc : 7/3 to 5/5) to furnish the desired compound **β-11** (1.84 g, 4.8 mmol, 36%) followed by **α-11** (2.2 g, 5.8 mmol, 43%). The experimental data agree with those reported in the literature.[3]

1-p-methoxyphenyl-(2-O-(4-methoxybenzoyl)-3,4-O-(bis-levulinoyl)-β-d-xylopyranosyl)-(1→3)-(2-O-acetyl- β-L-arabinopyranoside) 13a and 1-p-methoxyphenyl-(2-O-(4-methoxybenzoyl)-3,4-O-(bis-levulinoyl)-β-d-xylopyranosyl)-(1→4)-(2-O-acetyl-β- L-arabinopyranoside) 13b.

[2] Z. D. Herde, P. D. John, D. Alvarez-Fonseca, J. Satyavolu and C. T. Burns, *Carbohydr. Res.*, 2017, **443-444**, 1.
[3] B. Wang, Y. Zhang and X. He, *RSC Adv.*, 2023, **13**, 30985.

To a solution of 1-*p*-methoxyphenyl-(2,3,4-*O*-acetyl-β-L-arabinopyranoside) **β-11** (2.3 g, 6 mmol, 1 equiv.) in MeOH (20 mL) was added solid NaOMe (65 mg, 1.2 mmol, 0.2 equiv.). After being stirred for 2 h at room temperature, the mixture was neutralized with Dowex 50WX8, filtered and concentrated under reduced pressure to give the expected triol (1.5 g, 98%). To a solution of the triol (1.44 g, 5.62 mmol, 1 equiv.) in DCM (50 mL) was added 4Å MS (2 g) and 4-(trifluoromethyl)phenylboronic acid (1.07 g, 5.62 mmol, 1 equiv.). After 5 h, the resulting mixture was filtered in a pad of celite and concentrated *in vacuo*. The crude residue was then diluted in pyridine (15 mL) and AcCl (0.6 mL, 8.2 mmol, 1.5 equiv.) was then added at 0°C. The reaction mixture was allowed to return to r.t. and was stirred overnigt. After dilution with toluene (15 mL), the mixture was in a pad of celite and concentrated *in vacuo*. After 3 co-evaporations with toluene, the residue was diluted with Et_2O (30 mL), filtered and concentrated to afford **8** as a solid (2.5 g, 5.51 mmol, 98%). **^{1}H NMR** ($CDCl_3$, 300MHz) : 7.94 (2H, d, J = 8.0 Hz, H_{Ar}), 7.62 (2H, d, J = 7.0 Hz, H_{Ar}), 6.98 (2H, d, J = 9.0 Hz, H_{Ar}), 6.80 (2H, d, J = 9.0 Hz, H_{Ar}), 5.53 (1H, d, J= 4.0 Hz, H_1), 5.11 (1H, dd, J= 7.0, 4.0 Hz, H_2), 4.90 (1H, t, J= 7.0 Hz, H_3), 4.73 (1H, td, J= 7.0, 2.0 Hz, H_4), 4.20-4.06 (2H, m, H_5), 3.75 (3H, s, O*CH*$_3$), 2.16 (3H, s, CH_3).

To a solution of the boronic ester **8** (0.250 g, 0.55 mmol, 1 equiv.) in dry DCM (6 mL) is added 4Å MS (0.8 g). After stirring for 30 minutes, silver oxide (0.23 g, 0.99 mmol, 1.8 equiv.) and triethylamine (0.46 mL, 3.3 mmol, 6 equiv.) were added. A solution of xylopyranoside bromide **9** (0.54 g, 0.99 mmol, 1.8 equiv.) in DCM (2 mL) was then added portion-wise (8 x 0.25 mL every 45 minutes over 6 h). After the last addition, the reaction was further stirred for 1 h and was quenched with methanol, filtered on a pad of celite and concentrated *in vacuo*. Crude mixture was engaged on flash chromatography (SiO_2, toluene/acetone : 9/1 to 7/3) to obtain both (1→3) and (1→4) regioisomers **13a** (238 mg, 0.31 mmol, 57%) and **13b** (82 mg, 0.11 mmol, 19%) as an oil.

For (1→3) regioisomer **13a.**

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.91 (2H, d, J = 9.0 Hz, H_{Ar}), 6.93-6.85 (m, 4H, H_{Ar}), 6.75 (2H, d, J = 9Hz, H_{Ar}), 5.47 (1H, d, J= 3.5 Hz, H_1), 5.35 (1H, t, J= 9.0 Hz, $H_{3'}$), 5.17 (1H, dd, J= 9.0, 7.0 Hz, $H_{2'}$), 5.13 (1H, dd, J= 10.0, 3.5 Hz, H_2), 5.02 (1H, td, J= 9.0, 5.0 Hz, $H_{4'}$), 4.85 (1H, d, J= 7.0 Hz, $H_{1'}$), 4.21 (1H, dd, J= 10.0, 3.5 Hz, H_3), 4.19-4.11 (2H, m, $H_{5'a}$ and H_4), 3.97-3.87 (1H, m, H_{5a}), 3.82 (3H, s, O*CH*$_3$), 3.79 (1H, dd, J= 12.5, 2.0 Hz, H_{5b}), 3.72 (3H, s, O*CH*$_3$), 3.44 (1H, dd, J=12.0, 9.0 Hz, $H_{5'b}$), 2.83-2.80 (1H, bs, OH), 2.76-2.35 (8H, m, CH_2), 2.15 (3H, s, CH_3), 2.04 (3H, s, CH_3), 1.60 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.4 (CO), 206.0 (CO), 171.8 (CO), 171.8 (CO), 171.7 (CO), 170.0 (CO), 164.6 (C_q), 163.8 (C_q), 155.2 (C_q), 150.6 (C_q), 132.0 (C_{Ar}), 121.5 (C_q), 117.9 (C_{Ar}), 114.6 (C_{Ar}), 113.8 (C_{Ar}), 101.9 ($C_{1'}$), 96.2 (C_1), 76.3 (C_3), 71.2 ($C_{3'}$), 70.7 ($C_{2'}$), 69.4 (C_2), 68.8 and 68.6 (C_4 and $C_{4'}$), 62.3 and 62.2 (C_5 and $C_{5'}$), 55.7 (O*C*H$_3$), 55.5 (O*C*H$_3$), 37.8 (*C*H$_2$), 29.7 (*C*H$_3$), 29.6 (*C*H$_3$), 27.9 (*C*H$_2$), 27.8 (*C*H$_2$), 20.2 (*C*H$_3$).

ESIHRMS *m/z* calculated for $C_{37}H_{44}O_{17}Na$ 783.2476 $[M+Na]^+$, found 783.2475.

IR (ν, cm^{-1}): 3512, 2924, 2853, 1740, 1716, 1605, 1507, 1253, 1058, 733.

$[\alpha]^{22}_D$ + 93.1 (*c* 0.48, $CHCl_3$)

For (1→4) regioisomer **13b.**

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.96 (2H, d, J = 9.0 Hz, H_{Ar}), 6.94 (2H, d, J = 9.0 Hz, H_{Ar}), 6.90 (2H, d, J = 9.0 Hz, H_{Ar}), 6.78 (2H, d, J = 9Hz, H_{Ar}), 5.53 (1H, d, J = 3.5 Hz, H_1), 5.31 (1H, t, J = 7.0 Hz, $H_{3'}$), 5.17 (1H, dd, J = 7.0, 5.0 Hz, $H_{2'}$), 5.04 (1H, dd, J = 10.5, 3.5 Hz, H_2), 5.02-4.94 (1H, m, $H_{4'}$), 4.88 (1H, d, J = 5.0 Hz, $H_{1'}$), 4.34 (1H, dd, J = 12.5, 4.5 Hz, $H_{5'a}$), 4.18-4.06 (1H, m, H_3), 4.02-3.87 (3H, m, H_4 and $H_{5a,b}$), 3.83 (3H, s, O*CH*$_3$),), 3.74 (3H, s, O*CH*$_3$), 3.55 (1H, dd, J = 12.5, 6.5 Hz, $H_{5'b}$), 2.93 (1H, bd, J = 10.5 Hz, OH), 2.78-2.43 (8H, m, CH_2), 2.13 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.03 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.6 (CO), 206.3 (CO), 171.9 (CO), 171.8 (CO), 170.7 (CO), 165.1 (C_q), 163.9 (C_q), 155.1 (C_q), 150.8 (C_q), 132.1 (C_{Ar}), 121.5 (C_q), 118.0 (C_{Ar}), 114.7 (C_{Ar}), 113.8 (C_{Ar}), 102.1 ($C_{1'}$), 96.3 (C_1), 79.9 (C_4), 71.4 (C_2), 70.3 ($C_{2'}$), 69.5 ($C_{3'}$), 68.8 ($C_{4'}$), 67.2 (C_3), 62.3 (C_5), 61.3 ($C_{5'}$), 55.7 (O*C*H$_3$), 55.5 (O*C*H$_3$), 38.1 (*C*H$_2$), 37.8 (*C*H$_2$), 29.7 (*C*H$_3$), 29.5 (*C*H$_3$), 28.1 (*C*H$_2$), 27.9 (*C*H$_2$), 20.9 (*C*H$_3$).

ESIHRMS *m/z* calculated for $C_{37}H_{44}O_{17}Na$ 783.2476 $[M+Na]^+$, found 783.2472.

IR (ν, cm^{-1}): 3516, 2929, 2852, 1741, 1719, 1609, 1504, 1251, 1059, 735.

$[\alpha]^{22}_D$ + 105.4 (*c* 0.33, $CHCl_3$)

1-O-acetate-(2-O-(4-methoxybenzoyl)-3,4-O-(bis-levulinoyl)-β-D-xylopyranosyl)-(1→3)-(2-O-acetyl-4-O-levulinoyl β-L-arabinopyranoside) 14

To a solution of **13a** (170 mg, 0.22 mmol, 1 equiv.) in DCM (1 mL) was added successively LevOH (36 mg, 0.31 mmol, 1.4 equiv.), DCC (69 mg, 0.33 mmol, 1.5 equiv.) and DMAP (5 mg, 0.045 mmol, 0.2 equiv.). After being stirred overnight at room temperature, the mixture was diluted with DCM (10 mL) and filtered in a pad of celite.The organic phase was washed with saturated $NaHCO_3$ solution (15 mL), dried over Na_2SO_4 and concentrated. To the crude residue in a 4:1 mixture of AcN/H_2O (3 mL) at 0°C, was added CAN (0.3 g, 0.56 mmol, 2.5 equiv. After 3 h at 0°C, brine (10 mL) and DCM were added. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude residue was then dissolved in pyridine (1 mL) and Ac_2O (0.5 mL) was added. After 1 night, the mixture was co-evaporated with toluene and the residue was purified by flash chromatography (SiO_2, heptane/EtOAc: 4/6 to 1/9) to furnish the desired compound **14** as a colorless thick oil (7:3 β/α mixture of anomers, 99 mg, 0.12 mmol, 56% over the 3 steps).

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.89-7.83 (2H, m, H_{Ar}), 6.93-6.85 (m, 4H, H_{Ar}), 6.87-6.81 (2H, m, H_{Ar}), 6.14 (1H, d, J = 3.5 Hz, $H_{1\beta}$), 5.51 (1H, d, J = 6.0 Hz, $H_{1\alpha}$), 5.27-4.19 (1.7H, m, $H_{4\beta}$ and $H_{3'\alpha,\beta}$), 5.15-5.10 (1H, m, $H_{2\beta}$ and $H_{4\alpha}$), 5.08-5.00 (1.3H, m, $H_{2\alpha}$ and $H_{2'\alpha,\beta}$), 4.99-4.92 (1H, m, $H_{4'\alpha,\beta}$), 4.74 (0.7H, d, J = 6.0 Hz, $H_{1'\beta}$), 4.71 (0.3H, d, J = 6.0 Hz, $H_{1'\alpha}$), 4.12-4.07 (1H, m, $H_{5'\alpha,\beta}$), 4.01 (0.7H, dd, J = 10.0, 3.5 Hz, $H_{3\beta}$), 3.96 (0.3H, dd, J = 12.5, 5.0 Hz, $H_{5\alpha}$), 3.89-3.83 (1H, m, $H_{3\alpha}$ and $H_{5\beta}$), 3.79 (3H, s, O*CH*$_3$), 3.74 (0.7H, dd, J = 12.5, 2.0 Hz, $H_{5\beta}$), 3.72 (3H, s, O*CH*$_3$), 3.58 (0.3H, td, J = 12.5, 2.0 Hz, $H_{5\alpha}$), 3.43-

3.36 (1H, m, $H_{5'\alpha,\beta}$), 2.78-2.31 (12H, m, CH_2), 2.15 (3H, s, CH_3), 2.15 (2.1H, s, CH_3), 2.09 (0.9H, s, CH_3), 2.03 (2.1H, s, CH_3), 2.00 (0.9H, s, CH_3), 1.99 (2.1H, s, CH_3), 1.91 (0.9H, s, CH_3), 1.76 (0.9H, s, CH_3), 1.63 (2.1H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.4 (CO), 206.3 (CO), 205.9 (CO), 172.1 (CO), 171.9 (CO), 171.7 (CO), 171.6 (CO), 169.5 (CO), 169.0 (CO), 168.9 (CO),164.4 (C_q), 163.8 (C_q), 132.0 (C_{Ar}), 131.9 (C_{Ar}), 121.6 (C_q), 113.8 101.7 ($C_{1'\beta}$), 101.5 ($C_{1'\alpha}$), 91.8 ($C_{1\beta}$), 90.3 ($C_{1\alpha}$), 75.9 ($C_{3\alpha}$), 72.8 ($C_{3\beta}$), 70.7, 70.6, 70.5, 70.4, 70. 2, 69.1, 68.9, 68.6, 68.3 ($C_{2'}$, $C_{3'}$, C_2, $C_{2'}$, C_4 and $C_{4'}$), 62.7 ($C_{5'}$), 62.0 ($C_{5\beta}$), 61.8 ($C_{5\alpha}$), 55.5 (O*C*H_3), 38.0 (*C*H_2), 37.9 (*C*H_2), 37.8 (*C*H_2), 37.7 (*C*H_2), 29.8 (*C*H_3), 29.7 (*C*H_3), 29.5 (*C*H_3), 28.3 (*C*H_2), 28.1 (*C*H_2), 27.9 (*C*H_2), 27.8 (*C*H_2), 20.9 (*C*H_3), 20.6 (*C*H_3), 20.4 (*C*H_3), 20.1 (*C*H_3).

ESIHRMS *m/z* calculated for $C_{37}H_{46}O_{19}Na$ 817.2531 $[M+Na]^+$, found 817.2571.

IR (ν, cm^{-1}): 2925, 1741, 1716, 1605, 1367, 1254, 1211, 1150, 1089, 1030.

1-azido-(2-O-(4-methoxybenzoyl)-3,4-O-(bis-levulinoyl)-β-d-xylopyranosyl)-(1→3)-(2-O-acetyl-4-O-levulinoyl β-L-arabinopyranoside) 6

To a solution of the disaccharide **14** (51 mg, 0.065 mmol, 1 equiv.) in dry DCM (0.5 mL) under inert atmosphere was added HBr (33% in AcOH, 0.12 mL) dropwide at 0°C. After 2 hours of stirring at 0°C, the reaction mixture was diluted hydrolyzed with ice (10 mL) and diluted with DCM. The organic phase was washed with saturated $NaHCO_3$ (2 x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the expected bromide which was used in the next step without further purification. To the crude bromide (53 mg, 0.065 mmol, 1 equiv.) in dry DMF (0.5 mL) under inert atmosphere was added NaN_3 (40 mg, 0.65 mmol, 10 equiv.). After 1 hours at r.t., H_2O (10 mL) and EtOAc (10 mL) were added. The organic phase was washed with H_2O (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, heptane/EtOAc: 3/7 to 2/8) to furnish the desired compound **6** as a colorless thick oil (21 mg, 0.027 mmol, 42% over the 2 steps).

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.92 (2H, d, *J* = 9.0 Hz, H_{Ar}), 6.89 (2H, d, *J* = 9.0 Hz, H_{Ar}), 5.26 (1H, t, *J* = 8.0 Hz, $H_{3'}$), 5.21-5.16 (1H, m, H_4), 5.08 (1H, dd, *J* = 8.5, 6.0 Hz, $H_{2'}$), 5.03-4.94 (2H, m, H_2 and $H_{4'}$), 4.72 (1H, d, *J* = 6.0 Hz, $H_{1'}$), 4.42 (1H, d, *J* = 7.0 Hz, H_1), 4.10 (1H, dd, *J* = 12.5, 4.5 Hz, $H_{5'a}$), 4.06 (1H, dd, *J* = 12.5, 4.0 Hz, H_{5a}), 3.86-3.79 (4H, m, O*CH$_3$* and H_3), 3.58 (1H, dd, *J* = 12.5, 1.5 Hz, H_{5b}), 3.42 (1H, dd, *J* = 12.5, 7.5 Hz, $H_{5'b}$), 2.83-2.36 (12H, m, CH_2), 2.19 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.06 (3H, s, CH_3), 1.8 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.3 (CO), 206.0 (CO), 171.9 (CO), 171.7 (CO), 171.6 (CO), 169.1 (CO), 164.4 (C_q), 163.7 (C_q), 132.0 (C_{Ar}), 121.6 (C_q), 113.7 (C_{Ar}), 101.3 ($C_{1'}$), 88.1 (C_1), 75.9 (C_3), 70.6 ($C_{3'}$), 70.2 ($C_{2'}$), 69.3, 69.1, 69.7 (C_4, C_2), $C_{4'}$), 64.4 (C_5), 61.9 ($C_{5'}$), 55.5 (O*C*H_3), 37.9 (*C*H_2), 37.8 (*C*H_2), 29.8 (*C*H_3), 29.7 (*C*H_3), 29.5 (*C*H_3), 28.2 (*C*H_2), 28.0 (*C*H_2), 27.8 (*C*H_2), 20.3 (*C*H_3).

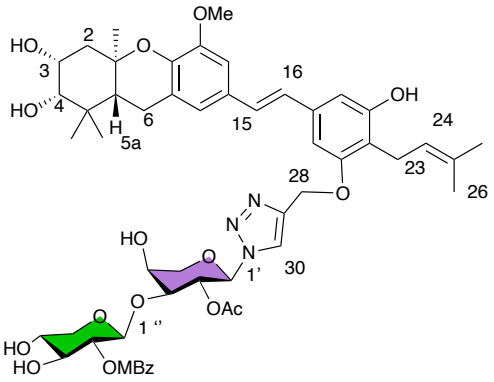
ESIHRMS *m/z* calculated for $C_{35}H_{43}N_3O_{17}Na$ 800.2490 $[M+Na]^+$, found 800.2489.

IR (ν, cm^{-1}): 2957, 2929, 2854, 2117, 1741, 1717, 1605, 1367, 1251, 1151, 1094, 1064, 1024, 733.

$[\alpha]^{22}_{D}$ – 4.1 (*c* 0.41, $CHCl_3$)

Glycosylated schweinfurthin 5

To a solution of the azide compound **6** (10 mg, 13.2 µmol, 1.1 equiv.) in 1/1/1 mixture of MeCN/*tert*-BuOH/H_2O (1.2 mL) at room temperature was added the propargyled Schweinfurthin E **7** (6.2 mg, 11.6 µmol, 1 equiv.) followed by $CuSO_4.5H_2O$ (7.5 mg, 30 µmol, 2.3 equiv.), sodium ascorbate (10.4 mg, 53 µmol, 4 equiv.), DABCO (3 mg, 26 µmol, 2 equiv.) and acetic acid (1.5 µL, 26 µmol, 2 equiv.). The reaction mixture was stirred at r.t. for 24 h and was treated with an aqueous solution of NH_4Cl (8 mL). The product was then extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The reaction mixture was then engaged without further purification in the next step. The crude residue was dissolved in a 1/1 mixture of DCM/MeOH (2mL), then hydrazine acetate (11 mg, 116 µmol, 10 equiv.) was added at rt and stirred for 1 h 30. The mixture was dissolved in HCl (0.5N, 1 mL) and extracted with *n*BuOH (3 x 10 mL). Collected organic fractions were dried on Na_2SO_4 and concentred *in vacuo. The c*rude mixture was then purified by by flash chromatography (C18, H_2O/AcN + 0.1% FA: 8/2 to 0/1) to furnish the desired compound **5** as yellow solid (3.7 mg, 36 µmol, 32% over the 2 steps). The compound was estimated to be 80% pure.



^{1}H NMR (MeOD, 500 MHz) :δ 8.15 (s, 1H, H_{30}), 7.94 (2H, d, J = 9.0 Hz, H_{Ar}), 7-03-6.82 (m, 6 H) 6.67 (s, 1H, H7), 6.61 (s, 1H), 5.71 (1H, d, J= 9.5 Hz, $H_{1'}$), 5.46 (1H, t, J= 9.5 Hz, $H_{2'}$), 5.24-5.11 (m, 3H, H_{24} and H_{28}), 4.94 (1H, dd, J= 8.5, 7.5 Hz, $H_{2''}$), 4.74 (1H, d, J= 7.5 Hz, $H_{1''}$), 4.24-4.20 (1H, m, $H_{4'}$), 4.18-4.14 (m, 1H, H_3), 4.11-4.05 (m, 2H, $H_{3'}$ and $H_{5'a}$), 4.01-3.95 (m, 1H, $H_{5''a}$), 3.91 (1H, d, J= 12.5 Hz, $H_{5'b}$), 3.85 (s, 3H, O*CH*$_3$), 3.83 (s, 3H, O*CH*$_3$), 3.67-3.62 (m, 2H, $H_{3''}$ and $H_{4''}$), 3.38-3.27 (m, 2H, H_4 and $H_{5''b}$), 3.50 (d, J = 7.0 Hz, 2H, H_{23}), 2.83-2.76 (m, 2H, H_6), 2.36 (dd, J = 14.0, 2.5 Hz, 1H, H_2), 1.94 (dd, J = 14.0, 3.0 Hz, 1H, H_2), 1.78-1.72 (m, 1H, H_{5a}), 1.62 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.25 (s, 3H, H13) 1.09 (3H, s, CH_3).

^{13}C NMR (MeOD, 100MHz): δ 170.3 (CO), 164.5 (CO), 157.2 (C_q), 150.4 (C_q), 147.8 (C_q), 143.5 (C_q), 141.9 (C_q), 138.0 (C_q), 133.3, 133.2, 131.5, 130.9, 129.2, 127.8, 124.5, 123.7, 123.6, 122.0, 118.4, 117.9, 114.9, 108.6, 104.2 ($C_{1''}$), 103.2, 88.4 ($C_{1'}$), 81.2, 79.0, 76.0, 75.4 (C2''), 71.9, 71.3, 71.0, 70.3, 70.2,

67.0, 62.8, 56.7 (O*C*H$_3$), 56.2 (O*C*H$_3$), 48.9 (C5a), 45.0 (C2), 31.1, 30.9, 29.6, 29.1, 24.2, 23.5, 22.2, 20.0, 18.1, 16.7.

ESIHRMS *m/z* calculated for $C_{53}H_{66}N_3O_{17}$ 1016.4392 $[M+H]^+$, found 1016.4397.

IR (ν, cm^{-1}): 3355, 2924, 2854, 1741, 1716, 1664, 1605, 1585, 1373, 1257, 1083.

[α]$^{22}_D$ – 2.0 (*c* 0.15, MeOH)

1-azido-(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl 15

To the crude bromide **9** (100 mg, 0.184 mmol, 1 equiv.) in dry DMF (0.9 mL) under an inert atmosphere was added NaN_3 (120 mg, 1.84 mmol, 10 equiv.). After 4 hours at r.t., H_2O (10 mL) and EtOAc (10 mL) were added. The organic phase was washed with H_2O (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was then engaged without further purification in the next step. To the crude azido compound (43.5 mg, 0.086 mmol, 1 equiv.) in a 1/1 mixture of DCM/MeOH (1.8 mL) was added hydrazine acetate (79 mg, 0.86 mmol, 10 equiv.) and stirred for 18 h. The mixture was dissolved in HCl (0.5N, 10 mL) and extracted with EtOAc (3 x 10 mL). The collected organic fractions were washed with brine (10 mL), dried on Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash chromatography (SiO_2, heptane/EtOAc: 8/2 to 6/4) to furnish the desired compound **15** as a colorless thick oil (11 mg, 0.036 mmol, 42% over the 3 steps).

^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.98 (2H, d, *J* = 9.0 Hz, H_{Ar}), 6.90 (2H, d, *J* = 9.0 Hz, H_{Ar}), 4.87 (1H, t, *J* = 8.0 Hz, H_2), 4.70 (1H, d, *J* = 8.0 Hz, H_1), 4.13 (1H, dd, *J* = 12.0, 5.0 Hz, H_{5a}), 3.85 (3H, s, O*CH$_3$*), 3.85-3.76 (1H, m, H_4), 3.71 (1H, t, *J* = 8.0 Hz, H_3), 3.41 (1H, dd, *J* = 12.0, 10.0 Hz, $H_{5'b}$), 1.78-1.63 (2H, bs, OH).

^{13}C NMR ($CDCl_3$, 100MHz): δ 166.2 (CO), 164.7 (C_q), 132.1 (C_{Ar}), 121.4 (C_q), 113.9 (C_{Ar}), 88.7 (C_1), 75.6 (C_3), 73.7 (C_2), 70.0 (C_4), 67.0 (C_5), 55.5 (O*C*H$_3$).

ESIHRMS *m/z* calculated for $C_{13}H_{16}N_3O_6$ 310.1039 $[M+H]^+$, found 310.0999.

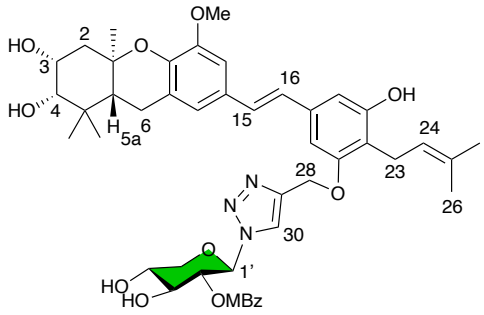
IR (ν, cm^{-1}): 3407, 2924, 2854, 2116, 1713, 1604, 1511, 1252, 1167, 1074, 1026, 766.

[α]$^{22}_D$ – 50.7 (*c* 0.41, $CHCl_3$)

Glycosylated schweinfurthin 16

To a solution of the azide compound **15**(5.9 mg, 19.2 µmol, 1.1 equiv.) in 1/1/1 mixture of MeCN/*tert*-BuOH/H_2O (1.2 mL) at room temperature was added the propargyled Schweinfurthin E **7** (9.3 mg, 17.5 µmol, 1 equiv.) followed by $CuSO_4.5H_2O$ (10 mg, 40 µmol, 2.3 equiv.), sodium ascorbate (13.8 mg, 70 µmol, 4 equiv.), DABCO (4 mg, 35 µmol, 2 equiv.) and acetic acid (2 µL, 35 µmol, 2 equiv.). The reaction mixture was stirred at r.t. for 24 h and was treated with an aqueous solution of NH_4Cl (8 mL). The product was then extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated *in vacuo.* The reaction mixture was then engaged without further purification in the next step. The crude residue was dissolved in a 1/1 mixture of DCM/MeOH (2mL),

then hydrazine acetate (11 mg, 116 µmol, 10 equiv.) was added at rt and stirred for 1 h 30. The mixture was dissolved in HCl (0.5N, 1 mL) and extracted with *n*BuOH (3 x 10 mL). Collected organic fractions were dried on Na_2SO_4 and concentred *in vacuo*. *The c*rude mixture was then purified by flash chromatography (C18, H_2O/AcN + 0.1% FA: 8/2 to 0/1) to furnish the desired compound **16** as an oil (3.3 mg, 4 µmol, 22%).



^{1}H NMR (CD_3CN, 500 MHz) :δ 8.03 (s, 1H, H_{30}), 7.81 (2H, d, J = 8.0 Hz, H_{Ar}), 7-03-6.85 (m, 6 H), 6.76 (s, 1H, H7), 6.60 (s, 1H), 5.89 (1H, d, J= 8.5 Hz, $H_{1'}$), 5.46 (1H, t, J= 8.5 Hz, $H_{2'}$), 5.17-5.05 (m, 3H, H_{24} and H_{28}), 4.11-4.04 (m, 2H, H_3 and $H_{5'a}$), 3.87-3.77 (m, 7H, $H_{3'}$ and 2*O*CH*$_3$*), 3.61-3.52 (m, 2H, $H_{3'}$ and $H_{5b'}$), 3.30-3.25 (m, 1H, H_4), 3.19 (d, J = 7.0 Hz, 2H, H_{23}), 3.05-2.96 (m, 2H, *OH), 2.80-2.70 (m, 2H, H_6), 2.26 (d, J = 14.0 Hz, 1H, H_2), 1.89 (d, J = 14.0 Hz, 1H, H_2), 1.77-1.70 (m, 1H, H_{5a}), 1.60 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.05 (s, 3H, CH_3) 1.02 (3H, s, CH_3).

^{13}C NMR (CD_3CN, 100MHz): δ 164.4 (CO), 156.4 (C_q), 145.4 (C_q), 138.0 (C_q), 137.8 (C_q), 132.6, 133.0, 131.6, 129.9, 129.3, 127.0, 124.3, 123.7, 123.4, 121.8, 114.9, 108.0, 107.8, 103.5, 87.5 ($C_{1'}$), 77.9 (C_4), 76.2 ($C_{3'}$), 73.9 ($C_{2'}$), 71.4 (C_3), 70.4 ($C_{4'}$), 69.5 ($C_{5'}$), 62.8 (C_{28}), 56.3 (O*C*H$_3$), 47.9 (C5a), 44.3 (C_2), 38.8, 30.3, 29.3, 27.9, 25.9, 23.7 (C_6), 23.1 (C_{23}), 22.1 (CH_3), 18.0 (CH_3), 16.6 (CH_3).

ESIHRMS *m/z* calculate for $C_{46}H_{56}N_3O_{12}$ 842.3864 $[M+H]^+$, found 842.3863.

IR (ν, cm^{-1}): 3360, 2957, 2921, 2852, 1716, 1661, 1633, 1463, 1378, 1258, 1066.

$[\alpha]^{22}_D$ + 12.0 (*c* 0.05, MeOH)

1-O-(azidoethanol)-(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl 17

To the crude bromide **9** (112 mg, 0.206 mmol, 1 equiv.) in dry DCM (2 mL) under an inert atmosphere was added azidoethanol (70 mg, 0.8 mmol, 4 equiv.) and 4 ÅMS (400 mg). After stirring for 45 min at r.t., AgOTf (106 mg, 0.41 mmol, 2 equiv.) was added at 0 °C and the reaction was stirred at r.t. for 2 h. The reaction was diluted with DCM (5 mL), $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The reaction mixture was then engaged without further purification in the next step. To the crude azido compound (113, 0.206 mmol, 1 equiv.) in a 1/1 mixture of DCM/MeOH (8 mL) was added hydrazine acetate (184 mg, 2 mmol, 10 equiv.) and stirred for 1 h. The mixture was dissolved in HCl (0.5N, 10 mL) and extracted with EtOAc (15 x 10 mL). The collected organic fractions were dried on Na_2SO_4, and concentrated *in vacuo*. The residue was purified

by flash chromatography (SiO_2, heptane/EtOAc: 2/8 to 0/1) to furnish the desired compound **17** as a colorless thick oil (38 mg, 0.1 mmol, 53% over the 2 steps).

^{1}H NMR ($CDCl_3$, 300MHz) :δ 7.95 (2H, d, J = 9.0 Hz, H_{Ar}), 6.88 (2H, d, J = 9.0 Hz, H_{Ar}), 4.92 (1H, t, J = 6.5 Hz, H_2), 4.61 (1H, d, J = 6.5 Hz, H_1), 4.04 (1H, dd, J = 12.0, 4.5 Hz, H_{5a}), 3.94 (1H, ddd, J = 9.5, 6.0, 4.0 Hz, CH_2), 3.82 (3H, s, O*CH₃*), 3.78-3.56 (3H, m, CH_2, H_3, H_4), 3.42-3.27 (3H, m, CH_2, H_{5b}).

^{13}C NMR ($CDCl_3$, 100MHz): δ 166.2 (CO), 163.8 (C_q), 132.0 (C_{Ar}), 121.7 (C_q), 113.7 (C_{Ar}), 100.8 (C_1), 74.3 (C_3), 73.4 (C_2), 69.9 (C_4), 67.8 (*C*H_2), 64.4 (C_5), 55.5 (O*C*H_3), 50.7 (*C*H_2).

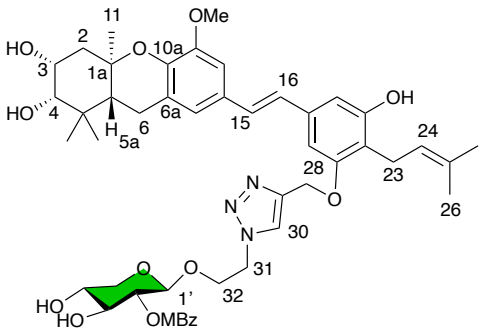
ESIHRMS *m/z* calculated for $C_{15}H_{19}N_3O_7Na$ 376.1121 $[M+Na]^+$, found 376.1130.

IR (ν, cm^{-1}): 3417, 2932, 2104, 1715, 1605, 1719, 1511, 1253, 1168, 1069, 1027.

$[\alpha]^{22}_D$ – 34.2 (*c* 0.5, $CHCl_3$)

Glycosylated schweinfurthin 18

To a solution of the azide compound **17** (5 mg, 13.8 µmol, 1.02 equiv.) in 1/1/1 mixture of MeCN/*tert*-BuOH/H_2O (1.2 mL) at room temperature was added the propargyled Schweinfurthin E **7** (5 mg, 13.8 µmol, 1 equiv.) followed by $CuSO_4.5H_2O$ (7.5 mg, 30 µmol, 2.3 equiv.), sodium ascorbate (10.4 mg, 53 µmol, 4 equiv.), DABCO (3 mg, 26 µmol, 2 equiv.) and acetic acid (1.5 µL, 26 µmol, 2 equiv.). After 24 h, 2 portions of **17** (2 mg, 5.6 µmol, 0.47 equiv.) were added 4 hours apart and left overnight. The mixture was treated with an aqueous solution of NH_4Cl (10 mL). The product was then extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The *c*rude mixture was then purified by by flash chromatography (C18, H_2O/AcN + 0.1% FA: 1/0 to 0/1) to furnish the desired compound **18** as an oil (5.7 mg, 6.4 µmol, 59%).



^{1}H NMR (CD_3CN, 500 MHz) :δ 7.92 (2H, d, J = 9.0 Hz, H_{Ar}), 7.61 (s, 1H, H_{30}), 7.06 (1H, d, J = 16.5 Hz, H_{15}), 7.02 (1H, d, J = 1.5 Hz, H_{Ar}), 6.97 (1H, d, J = 16.5 Hz, H_{16}), 6-92-6.88 (m, 2 H, H_{Ar}), 6.82 (s, 1H, H_{Ar}), 6.69 (s, 1H, H_{Ar}), 6.64 (s, 1H, H_{Ar}), 5.10 (1H, t, J = 7.5 Hz, H_{24}), 4.83 (1H, t, J = 8.5 Hz, $H_{2'}$), 4.73 (1H, d, J = 11.5 Hz, H_{28a}), 4.63 (1H, d, J = 11.5 Hz, H_{28b}), 4.54-4.40 (m, 3H, CH_{32} and $H_{1'}$), 4.14 (ddd, 1H, J = 3.5, 5.0, 9.0 Hz, CH_{31a}), 4.10-4.06 (m, 1H, H_3), 3.89 (dd, 1H, J = 5.0, 11.5 Hz, $H_{5'a}$), 3.85-3.79 (m, 4H, H_{31b} and O*CH₃*), 3.77 (s, 3H, O*CH₃*), 3.62-3.50 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.33 (d, J = 4.5 Hz, 1H, O*H*), 3.28 (dd, 1H, J = 7.5, 3.5 Hz, H_4), 3.27-3.19 (m, 3H, $H_{5'b}$ and H_{23}), 3.00 (d, J = 2.5 Hz, 1H, O*H*), 2.98 (d, J = 7.5 Hz, 1H, O*H*), 2.83-2.72 (m, 2H, H_6), 2.27 (dd, J = 3.0, 14.0 Hz, 1H, H_{2a}), 1.90 (dd,

J = 3.5, 14.0 Hz, 1H, H_{2b}), 1.74 ((dd, *J* = 6.0, 12.0 Hz, 1H, H_{5a}), 1.62 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.06 (s, 3H, CH_3) 1.03 (3H, s, CH_3).

^{13}C NMR (CD_3CN, 100MHz): δ 166.1 (CO), 164.7 (C_q), 158.4 (C_q), 156.4 (C_q), 150.2 (C_q), 144.4 (C_q), 143.5 (C_q), 139.9 (C_q), 132.6, 132.1 (Cq), 130.0 (Cq), 129.4 (C_{15}), 127.1 (C_{16}), 125.2, 124.4 (Cq), 123.8, 123.1 (Cq), 121.9, 114.9, 108.0, 107.7, 103.6, 102.2 ($C_{1'}$), 77.9 (C_4), 77.7 (C_{1a}), 75.7 ($C_{3'}$or $C_{4'}$), 74.7 ($C_{2'}$), 71.5 (C_3), 70.9 ($C_{3'}$or $C_{4'}$), 68.2 (C_{32}), 66.7 ($C_{5'}$), 62.8 (C_{28}), 56.4 (O*C*H_3), 56.3 (O*C*H_3), 50.9 (C_{31}), 47.9 (C5a), 44.4 (C_2), 38.9 (C5), 29.3, 25.9, 23.8 (C_6), 23.2 (C_{23}), 22.2 (CH_3), 18.0 (CH_3), 16.6 (CH_3).

ESIHRMS *m/z* calculate for $C_{48}H_{60}N_3O_{13}$ 886.4126 $[M+H]^+$, found 886.4122.

IR (ν, cm^{-1}): 3393, 2925, 2854, 1715, 1605, 1257, 1168, 1085.

$[\alpha]^{22}_D$ + 27.4 (*c* 0.38, MeOH)

Methyl-2-O-acetyl-3,4-O-(di-levulinoyl)-β-L-arabinopyranoside 20

To a solution of methyl-β-L-arabinopyranoside **19** (0.41 g, 2.5 mmol, 1 equiv.) in toluene (18 mL) was added was added phenylboronic acid (0.305 g, 2.5 mmol, 1 equiv.). After 18 h at 110 °C, the mixture was concentrated *in vacuo* and the crude residue was then diluted in pyridine (5 mL) and AcCl (0.27 mL, 3.75 mmol, 1.5 equiv.) was then added at 0°C. The reaction mixture was allowed to return to r.t. and was stirred overnigt. After dilution with toluene (15 mL), the mixture was filtered in a pad of celite and concentrated *in vacuo.* After 3 co-evaporations with toluene, the residue was diluted with DCM (10 mL) and pinacol (0.44 g, 3.75 mmol, 1.5 equiv.) was added. After 18 h at r.t., DCM was removed and the residue was dried under avccum. LevOH (1.16 g, 10 mmol, 4 equiv.), DCC (2 g, 10.25 mmol, 4.1 equiv.) and DMAP (60 mg, 0.5 mmol, 0.2 equiv.) and anhydrous DCM (15 mL) were successively added. After being stirred 7 h at room temperature, the mixture was diluted with DCM (20 mL) and filtered in a pad of celite. The organic phase was successively washed with saturated $NaHCO_3$ solution (25 mL) and brine (25 mL). Afer being dried over Na_2SO_4, the organic phase was, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, heptane/EtOAc: 6/4 to 3/7) to furnish the desired compound **21** (0.76 g, 1.9 mmol, 76% over the 4 steps).

^{1}H NMR ($CDCl_3$, 300MHz) :δ 5.39-5.31 (2H, m, H_3 and H_4), 5.21 (1H, dd, *J*= 3.5 and 10.0 Hz, H_2), 4.94 (1H, d, *J* = 3.5 Hz, H_1), 3.93 (1H, d, *J*= 13.0 Hz, H_{5a}), 3.67 (1H, dd, *J*= 13.0, 1.5 Hz, H_{5b}), 3.41 (3H, s, O*C*H_3), 2.87-2.41 (8H, m, CH_{2Lev}), 2.21 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.14 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 100MHz): δ 206.4 (CO), 206.3 (CO), 172.2 (CO), 171.9 (CO), 170.7 (CO), 97.9 (C_1), 69.6 (C_4 or C_3), 68.4 (C_2), 67.6 (C_4 or C_3), 60.4 (C_5), 55.8 (O*C*H_3), 38.0 (*C*H_2), 37.9 (*C*H_2), 30.0 (*C*H_3), 29.9 (*C*H_3), 28.3 (*C*H_2), 28.1 (*C*H_2), 21.0 (CH_3).

ESIHRMS *m/z* calculated for $C_{18}H_{26}O_{10}Na$ 425.1424 $[M+Na]^+$, found 425.1428.

IR (ν, cm^{-1}): 2924, 2853, 1737, 1716, 1369, 1230, 1166, 1151, 1135, 1065, 1004.

$[\alpha]^{22}_D$ + 132.5 (*c* 0.32, $CHCl_3$)

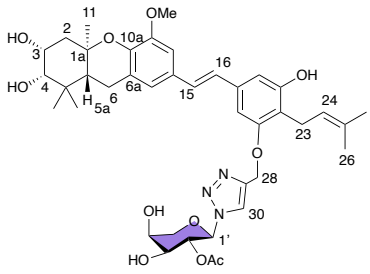
1-bromo-2-O-acetyl-3,4-O-(di-levulinoyl)-β-L-arabinopyranoside 21

To a solution of arabinoside **20** (0.177 g, 0.44 mmol, 1 equiv.) in dry DCM (5 mL) under inert atmosphere was added freshly dried $ZnBr_2$ (99 mg, 0.44 mmol, 1 equiv.) followed by the addition of TMSBr (0.18 mL, 1.32 mmol, 3 equiv.). After 12 hours of stirring at room temperature, the reaction mixture was diluted in DCM (20 mL) and a 1:1 solution of saturated $NaHCO_3$ and water (10 mL). After phase separation, the organic phase was washed with H_2O (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give the expected bromide **21** (0.198 g, 0.44 mmol, 100%), which was used without further purification.

^{1}H NMR ($CDCl_3$, 300MHz) :δ 6.69 (1H, d, J = 3.5 Hz, H_1), 5.44-5.39 (2H, m, H_3 and H_4), 5.13 (1H, dd, J= 3.5 and 10.0 Hz, H_2), 4.22 (1H, d, J= 13.5 Hz, H_{5a}), 3.95 (1H, dd, J= 13.5 Hz, H_{5b}), 2.86-2.47 (8H, m, CH_{2Lev}), 2.22 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.17 (3H, s, CH_3).

Glycosylated schweinfurthin 22

To the crude bromide **21** (84 mg, 0.187 mmol, 1 equiv.) in dry DMSO (1 mL) under inert atmosphere was added NaN_3 (14.5 mg, 0.224 mmol, 1.2 equiv.). After 10 min, 0.2 mL of the solution (0.037 mmol, 2 equiv.) were added to the propargyled Schweinfurthin E **7** (10 mg, 18.9 µmol, 1 equiv.) followed by $CuSO_4.5H_2O$ (0.5 M in water, 0.2 mL, 0.1 mmol, 5.3 equiv.), sodium ascorbate (1M in water, 0.1 mL, 0.1 mmol, 5.3 equiv.). After 18 h, the mixture was filtered and diluted with EtOAc (10 mL) and H_2O (10 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated *in vacuo*. To the crude mixture a 1/1 mixture of DCM/MeOH (0.5 mL) was added hydrazine acetate (10 mg, 0.1 mmol, 5.3 equiv.) and stirred for 2 h at r.t. The mixture was dissolved in HCl (0.5N, 10 mL) and extracted with EtOAc (3 x 10 mL). The collected organic fractions were dried on Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (C18, H_2O/AcN + 0.1% FA: 1/0 to 0/1) to furnish the desired compound **23** as an oil (2.5 mg, 3.3 µmol, 18%).



^{1}H NMR (MeOD, 500 MHz) :δ 8.23 (s, 1H, H_{30}), 6.99-6.94 (2H, m, H_{Ar}), 6.92-6.84 (2H, m, H_{Ar}), 6.72 (s, 1H, H_{Ar}), 6.63 (s, 1H, H_{Ar}), 5.75 (d, 1H, J= 9.5 Hz, $H_{1'}$), 5.49 (1H, t, J= 9.5 Hz, $H_{2'}$), 5.23-5.15 (3H, m, H_{24} and H_{28}), 4.17-4.13 (m, 1H, H_3), 4.09 (dd, 1H, J= 2.0, 12.5 Hz, $H_{5'a}$), 4.02-3.99 (m, 1H, $H_{4'}$), 3.97-3.91 (m, 2H, $H_{3'}$ and $H_{5'a}$), 3.85 (s, 3H, OCH_3), 3.33-3.27 (m, 3H, H_4 and H_{23}), 2.81-2.74 (m, 2H, H_6), 2.36 (dd, J = 3.0, 14.0 Hz, 1H, H_{2a}), 1.94 (dd, J = 3.5, 14.0 Hz, 1H, H_{2b}), 1.85 (s, 3H, CH_3), 1.79-

1.70 (m, 1H, H_{5a}), 1.66 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.11 (s, 3H, CH_3) 1.09 (3H, s, CH_3).

^{13}C NMR (MeOD, 100MHz): δ 171.1 (CO), 165.0 (C_q), 158.3 (C_q), 157.7 (C_q), 149.9 (C_q), 146.6 (C_q), 143.6 (C_q), 138.0 (C_q), 130.9, 129.2, 127.7, 124.5, 123.8, 122.0, 108.6, 107.7, 103.4, 88.4 ($C_{1'}$), 78.9 (C_4), 78.2 (C_{1a}), 73.0 ($C_{3'}$ or $C_{2'}$), 72.7 ($C_{3'}$ or $C_{2'}$), 71.9 (C_3), 71.0 ($C_{5'}$), 70.3 ($C_{4'}$), 63.0 (C_{28}), 56.7 (O*C*H$_3$), 49.3 (C_{5a}), 45.0 (C_2), 39.3 (C_5), 29.6 (CH_3), 26.1 (CH_3), 24.2 (C_6), 23.5 (C_{23}), 22.1 (CH_3), 20.5 (CH_3), 18.1 (CH_3), 16.7 (CH_3).

ESIHRMS *m/z* calculate for $C_{40}H_{52}N_3O_{11}$ 750.3596 $[M+H]^+$, found 750.3602.

IR (ν, cm^{-1}): 3513, 2924, 2853, 1740, 1717, 1605, 1507, 1253, 1058, 733.

$[\alpha]^{22}_D$ + 10.5 (*c* 0.2, MeOH)

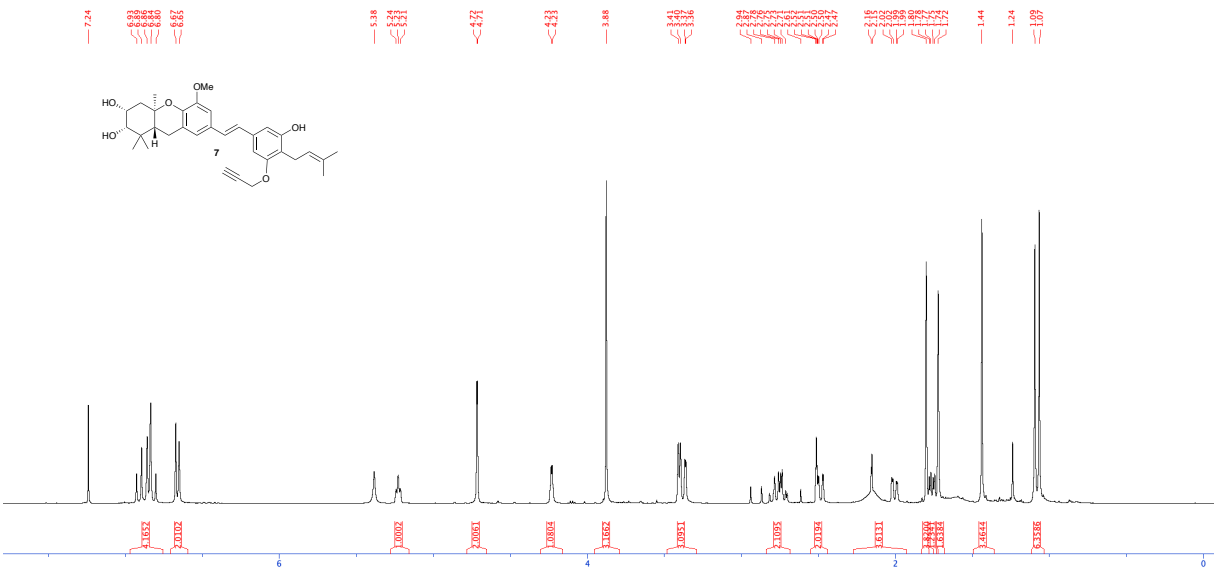
Cell culture and proliferation assay. Human U-87MG glioblastoma cells were obtained from the American Type Culture Collection (Rockville, MD, USA) and were grown in DMEM supplemented with 10% FCS and 1% glutamine at 37 °C in a humidified atmosphere containing 5% CO_2. Cells were seeded at 3000 cells/well density into white wall 96-well plates and then treated on the following day with the drugs. After 72 h treatment, cell viability was measured using CellTiter-Glo Luminescent Cell Viability Assay (Promega) and the luminescence was detected in a FLUOstar Omega microplate reader (BMG Labtech). The viability values of DMSO-treated cells were considered as 100%, then surviving curves and IC_{50} values were determined using GraphPad Prism 7.0 software.

Docking simulations. The 3D crystal structure of OSBP ORD was downloaded from the Protein Data Bank (PDB ID: 7v62[1]) and saved in pdb format. It was composed of four monomers complexed with cholesterol, citric acid, 2,3-dihydroxy-1,4-dithiobutane, DMSO and water. The file was first pre-processed with AutoDockTools. Three out of four monomers were discarded as well as water and complexed compounds. In the monomeric structure of chain A, missing atoms, polar hydrogen atoms and Gasteiger charges were added. The docking area was selected and the grid was saved as a txt file. Finally, the protein was split in two moieties (as pdbqt files), a flexible one containing 26 amino acids corresponding to those of the binding site (LEU16, MET20, LEU28, MET33, PHE37, MET43, ARG46, LEU47, ASP50, SER80, TYR81, THR84, ARG87, THR88, SER89, LYS90, PRO91, ILE142, LEU151, ILE153, PRO155, LYS174, THR177, VAL179, LEU187, ILE189) and a rigid one corresponding to the rest of the ORD domain. All the ligand were drawn on Avogadro, the energy of their 3D structure was minimized with ORCA, using Hartree–Fock method, and the STO-3G basis set. Xyz ligand files were then prepared in OpenBabel GUI, and saved as a pdbqt file. Ligands were

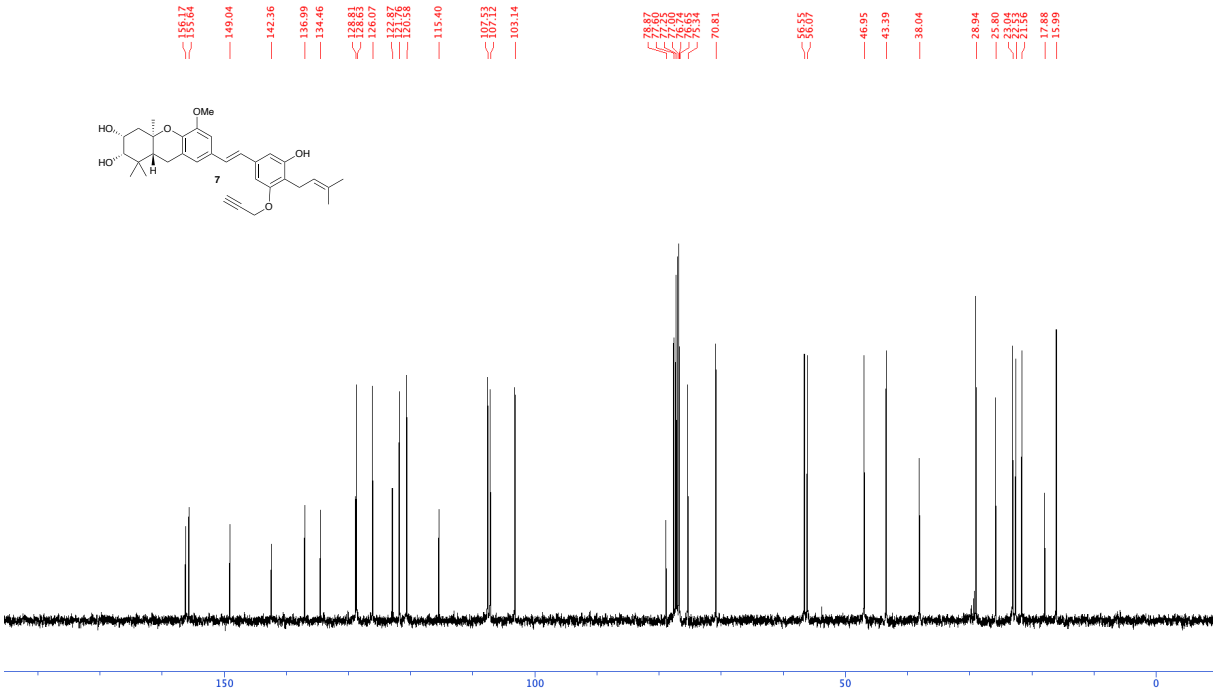
docked within the flexible moiety of the protein (one grid box). The exhaustiveness was set to 20, the number of conformations generated for each ligand was set to 50, and the energy range to 4. Docking simulations were run with AutoDock Vina v1.1.2 on a Dell Precision 7760. The docked conformations of each compound were ranked into clusters based on the binding energy and the ten most favorable binding conformations with the lowest free energies were selected and visually analyzed. For each molecule, we determined the best docking pose by examining the lowest energy poses. A Python script (Result_Treatment.py) was developed in order to extract each model, and generate the protein with flexible residues included for each model. The protein-ligand 3D visualization was processed using PyMOL software. The 2D visualization of the interaction between the hybrids and the amino-acid residues of the ORD domain of OSBP was performed using BIOVIA Discovery Studio (Dassault System).

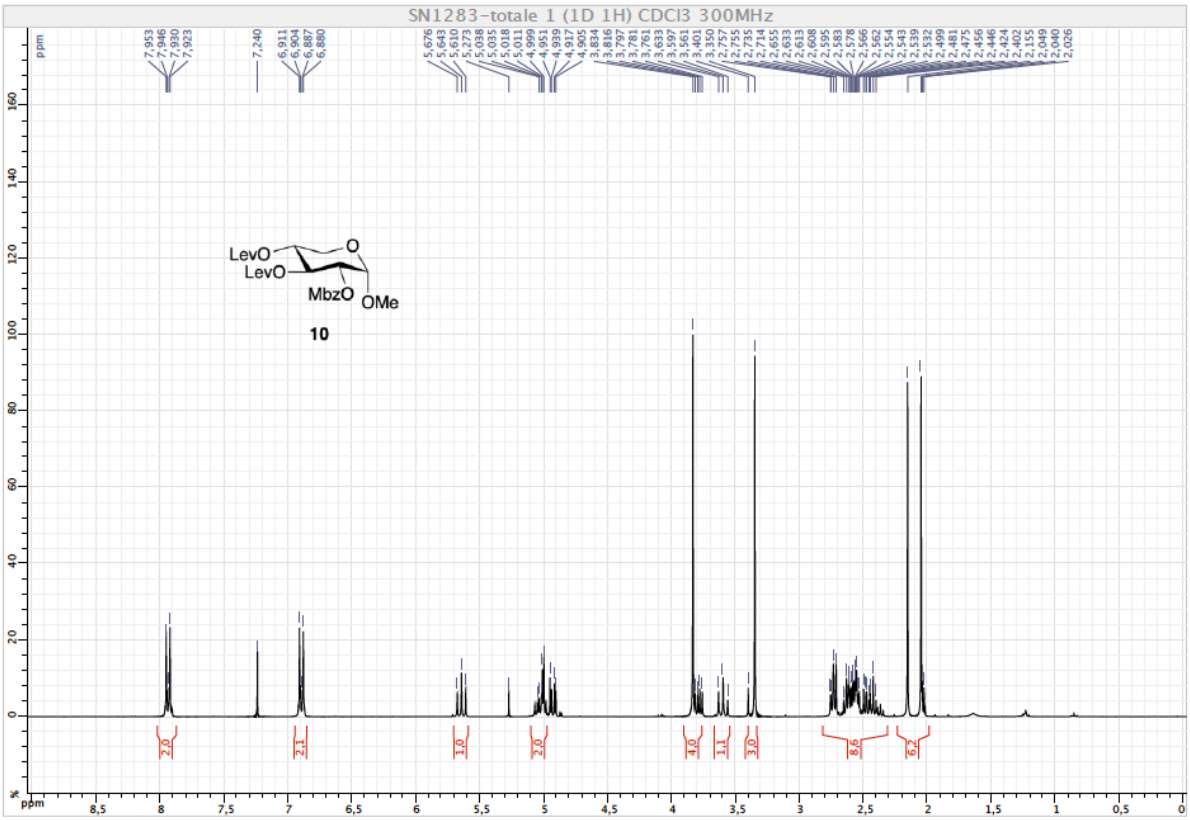
NMR spectra

^{1}H NMR (500 MHz, CDCl3) of **7**



^{13}C (125 MHz, CD_3Cl) of **7**

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MbzO
OMe
10


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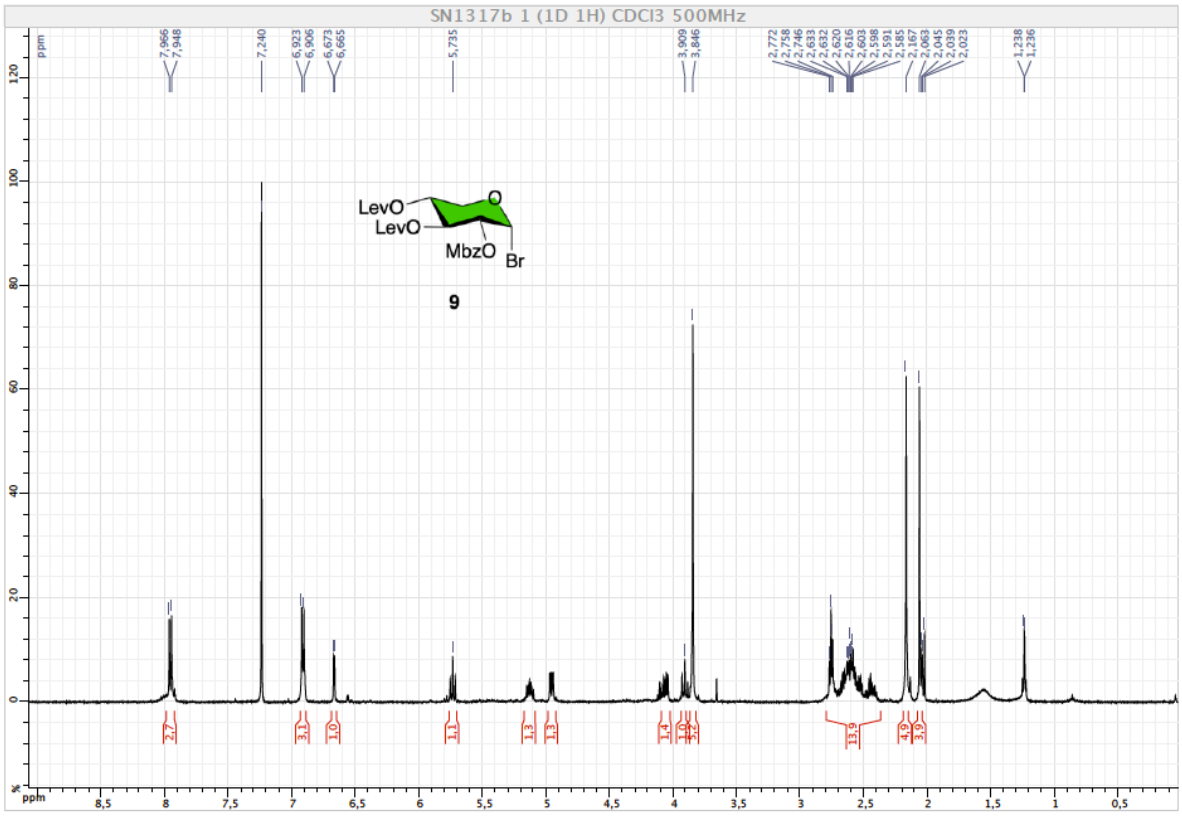
LevO
MbzO
OMe
10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LevO
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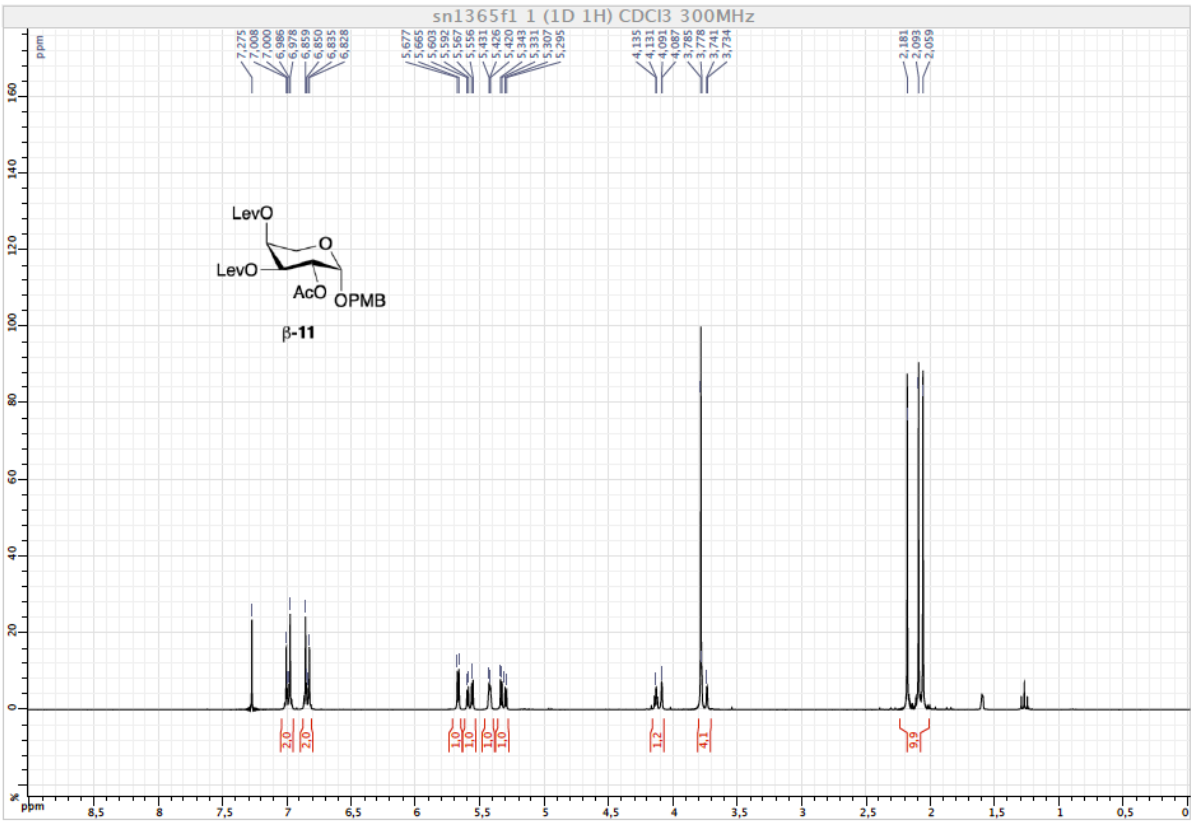
O
Br
9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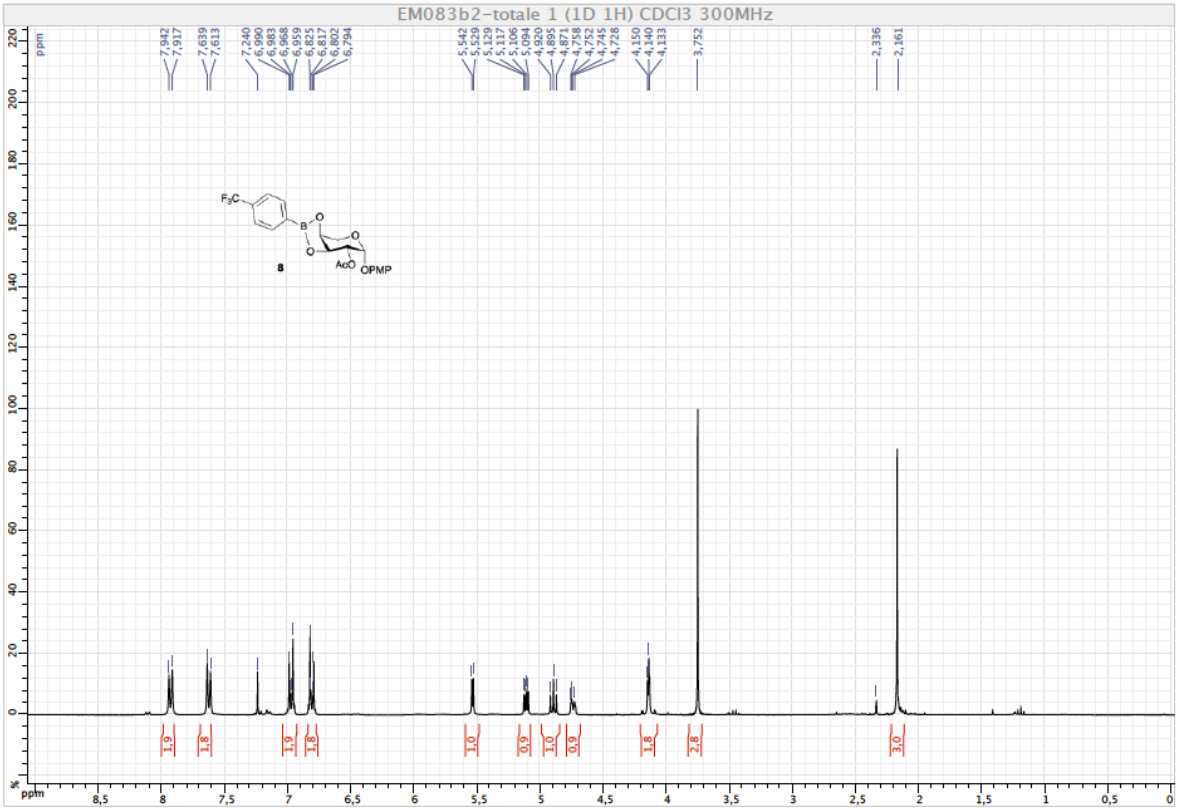
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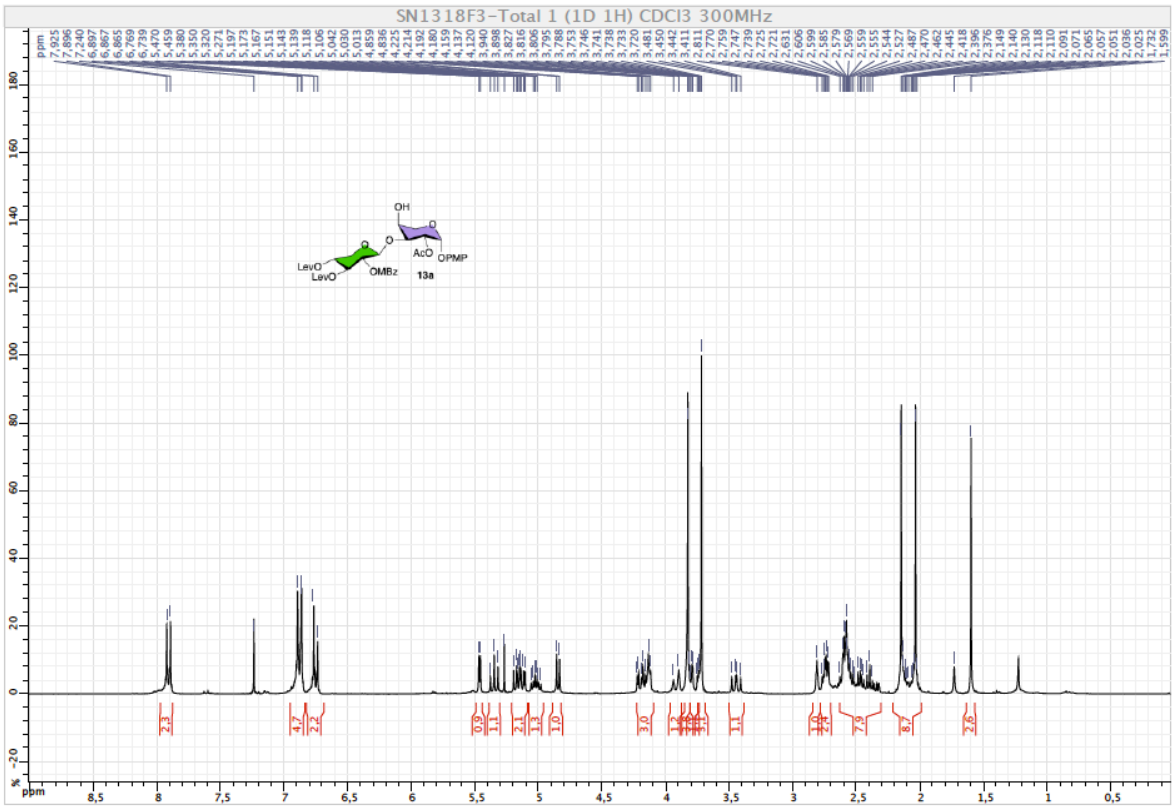
8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LevO
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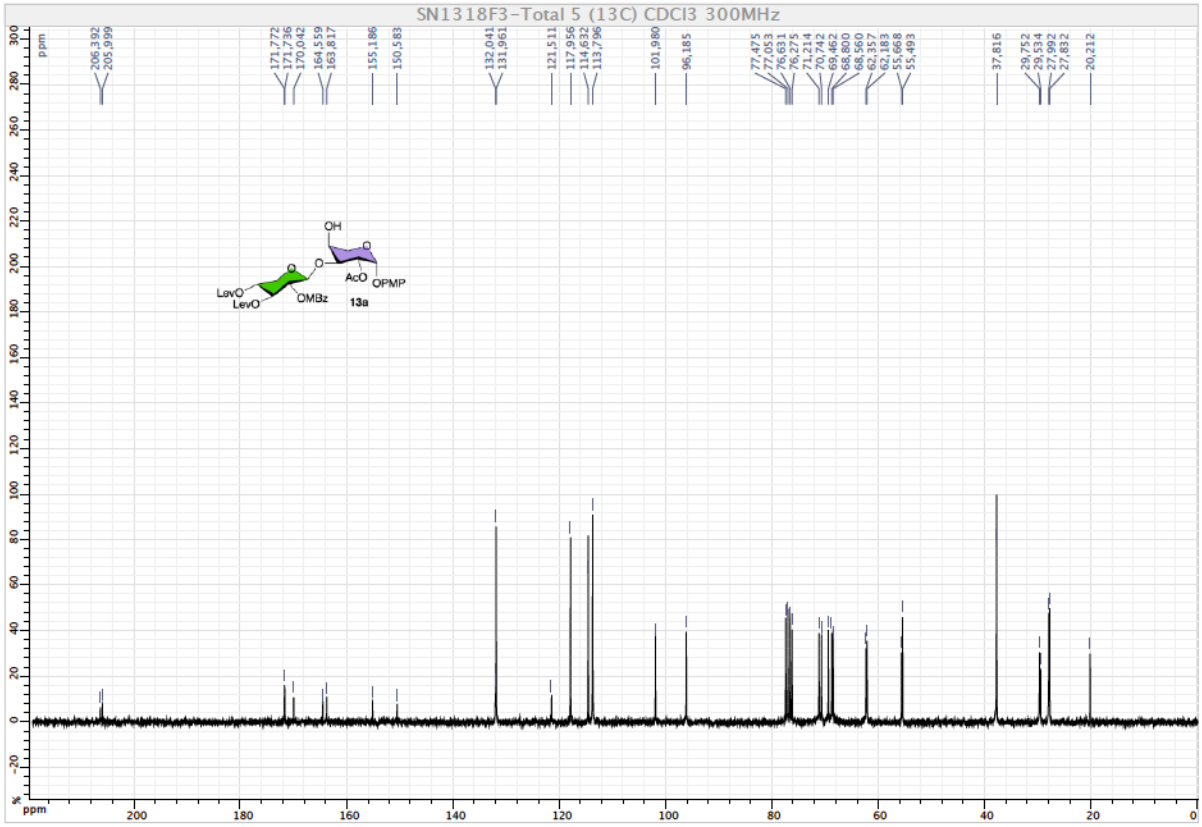
13a
ppm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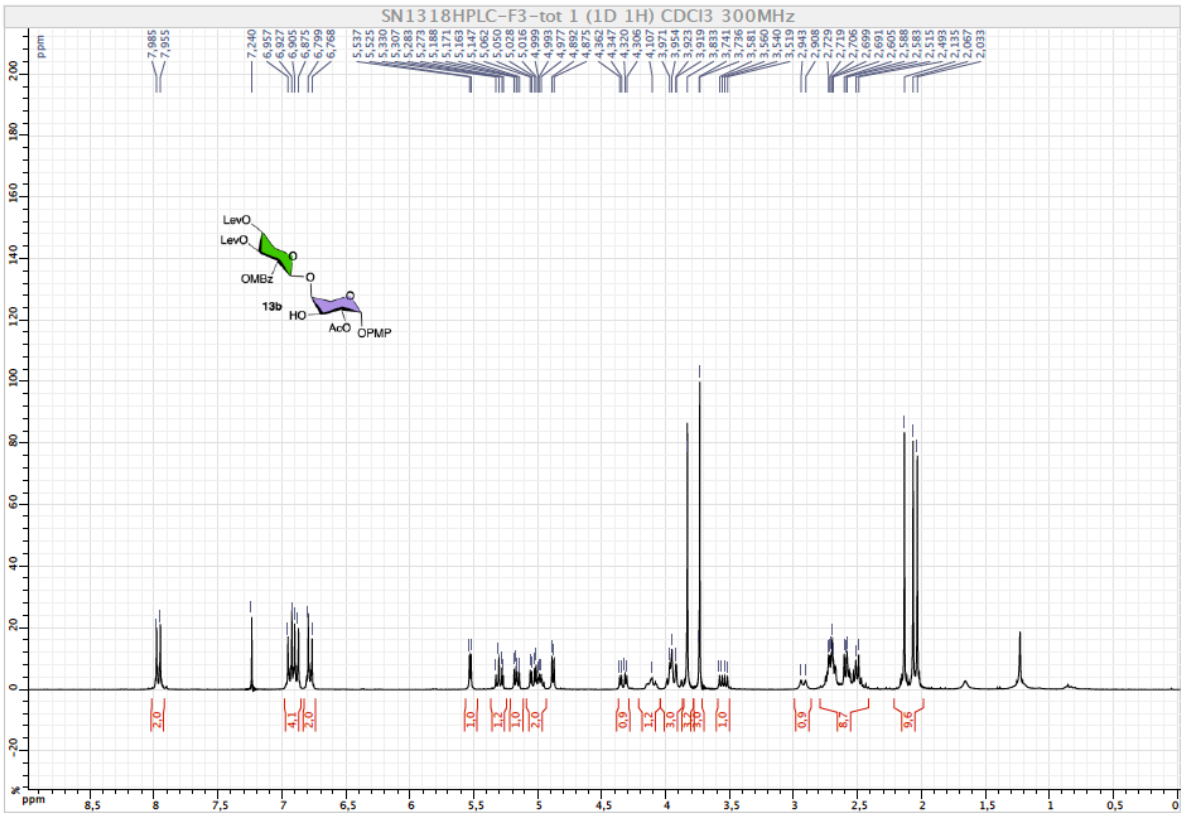
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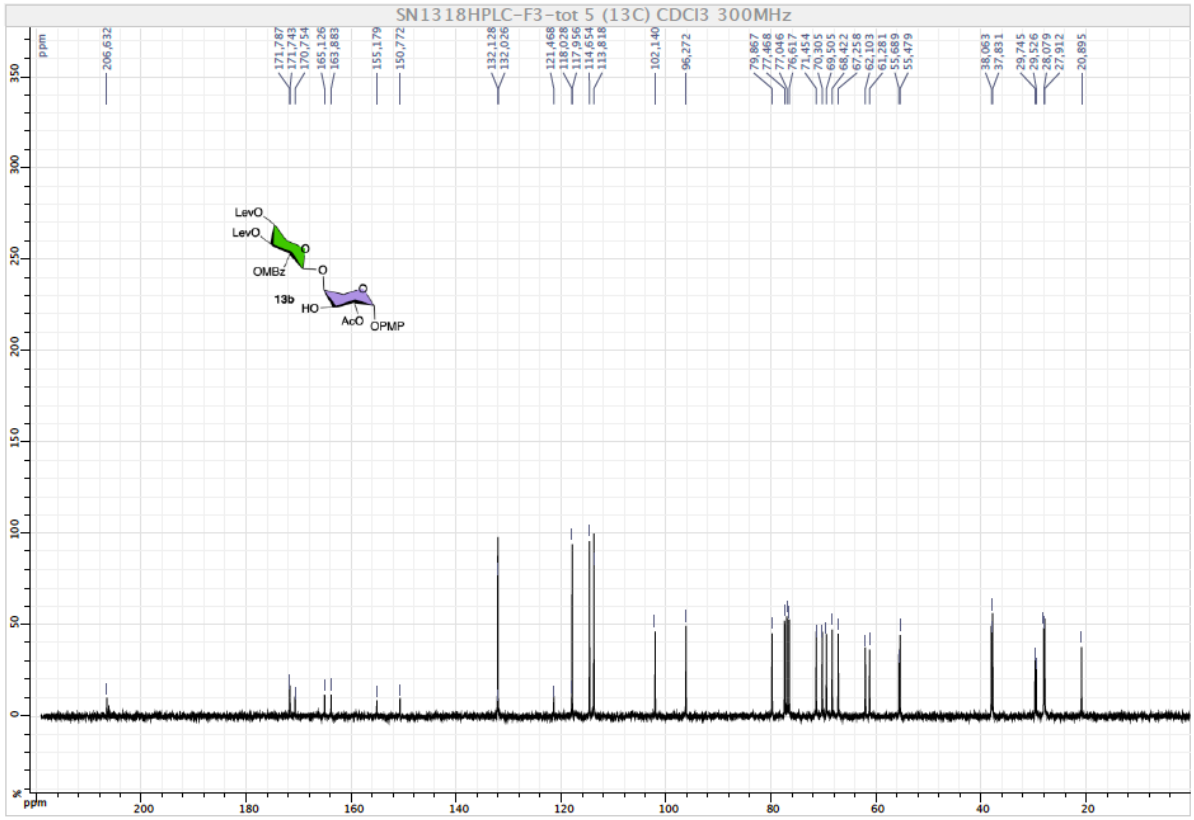
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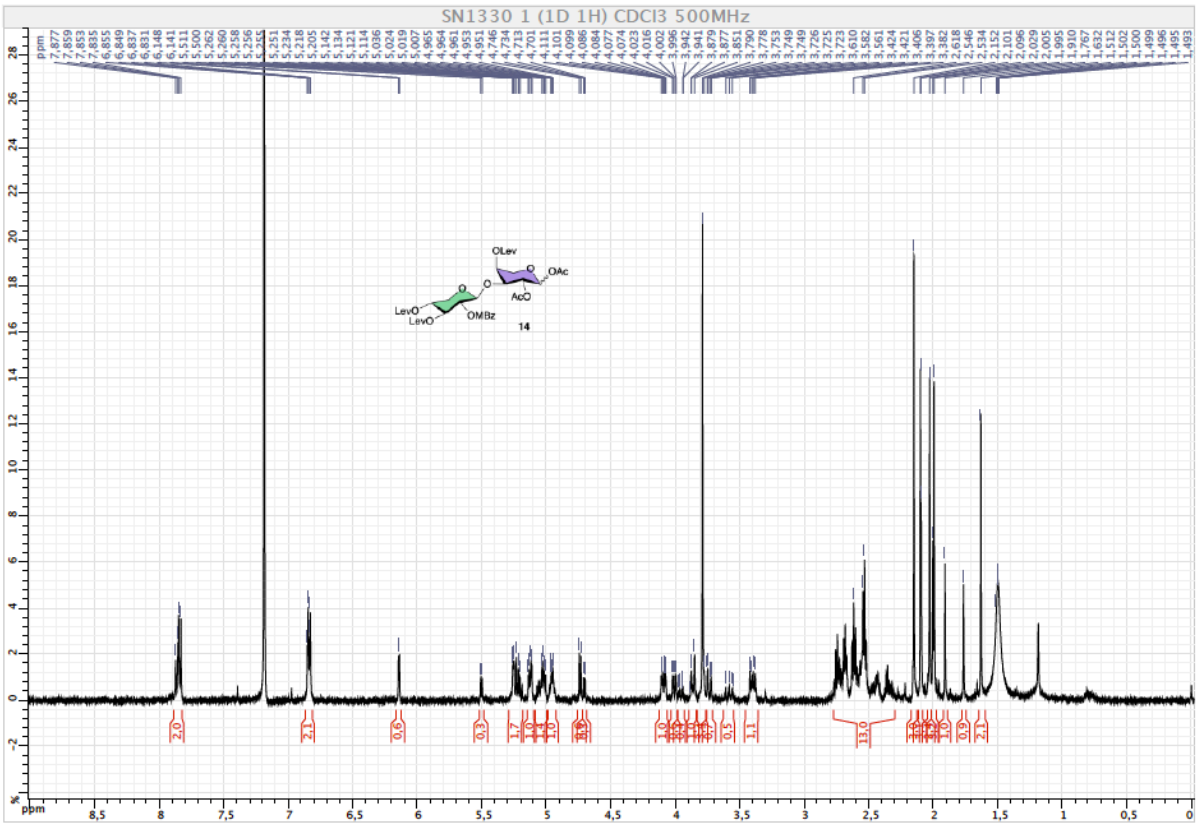
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OAc
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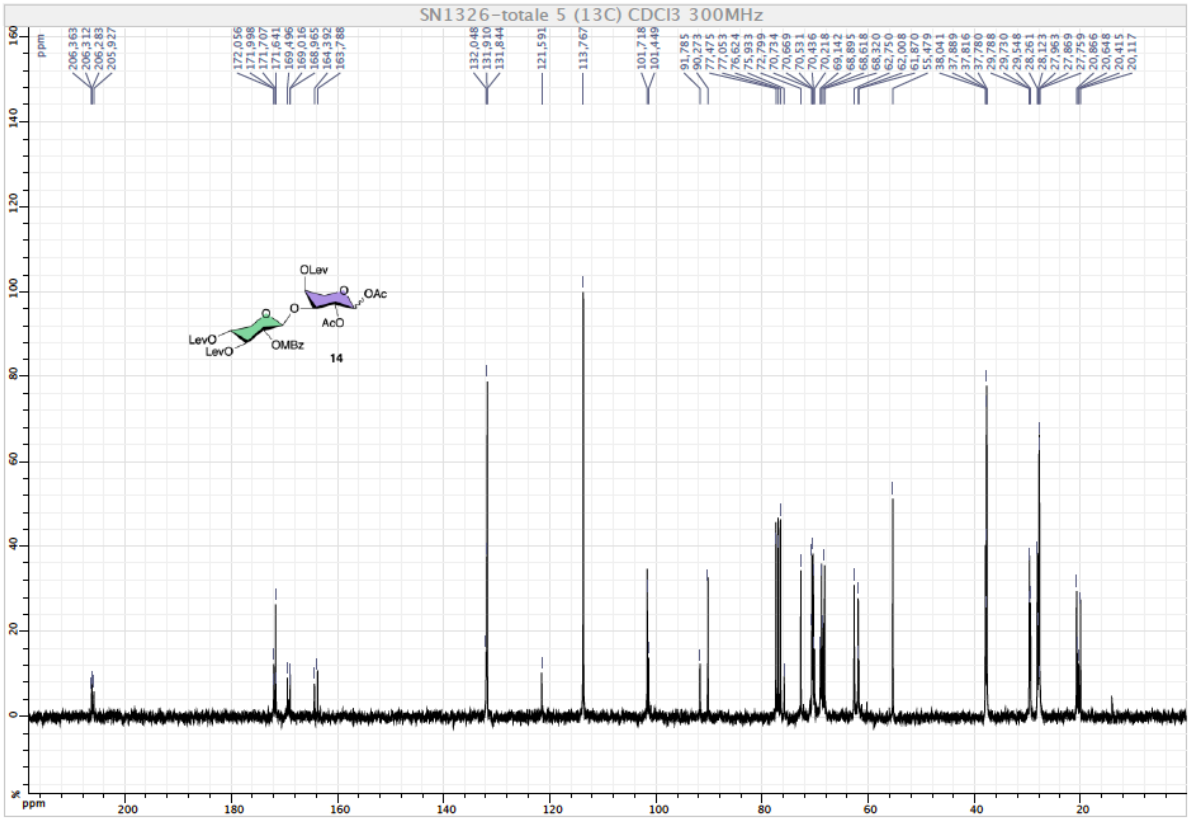
LevO
LevO
OMBz
14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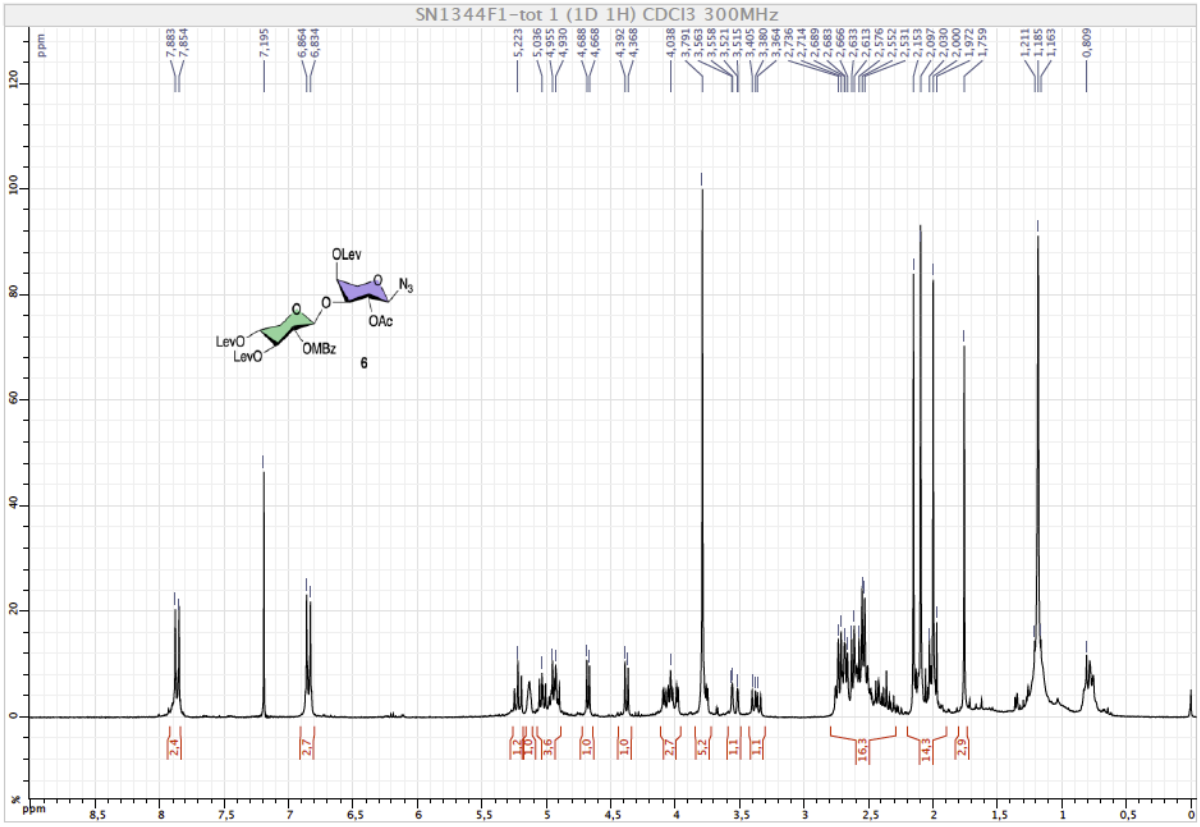
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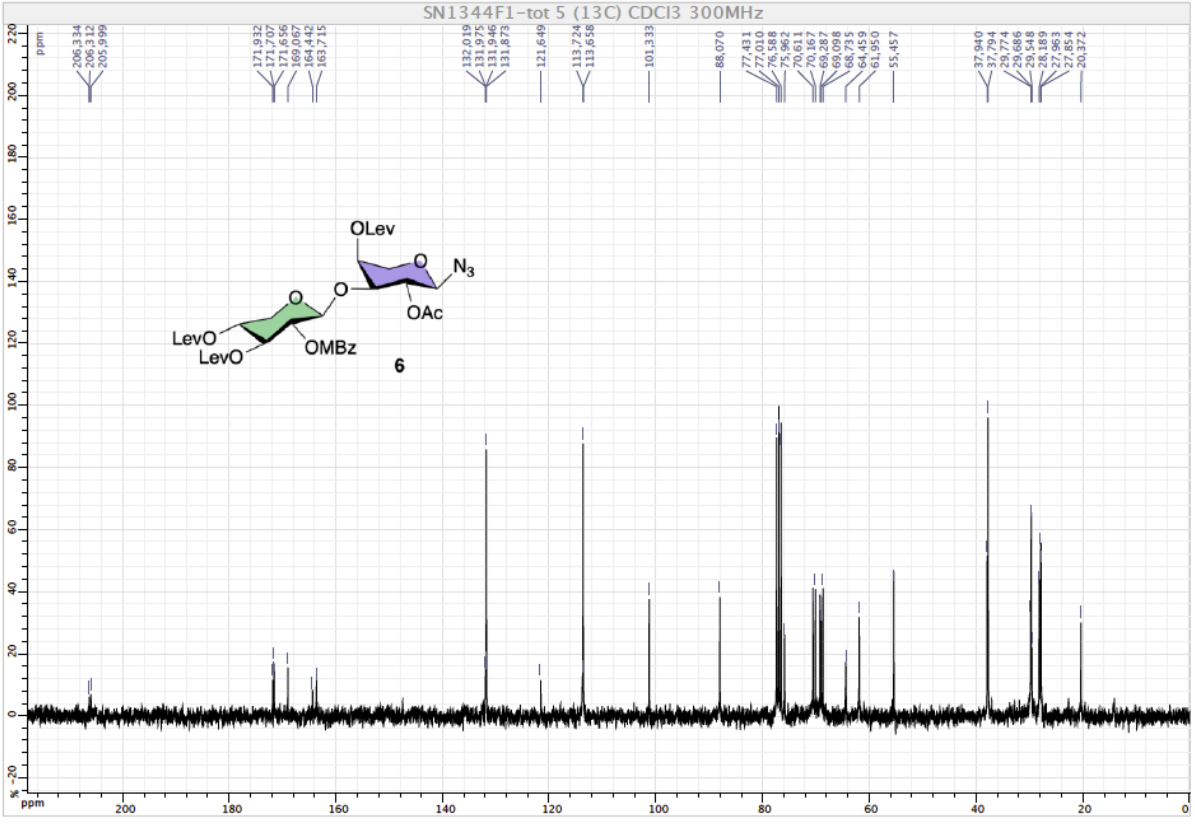
6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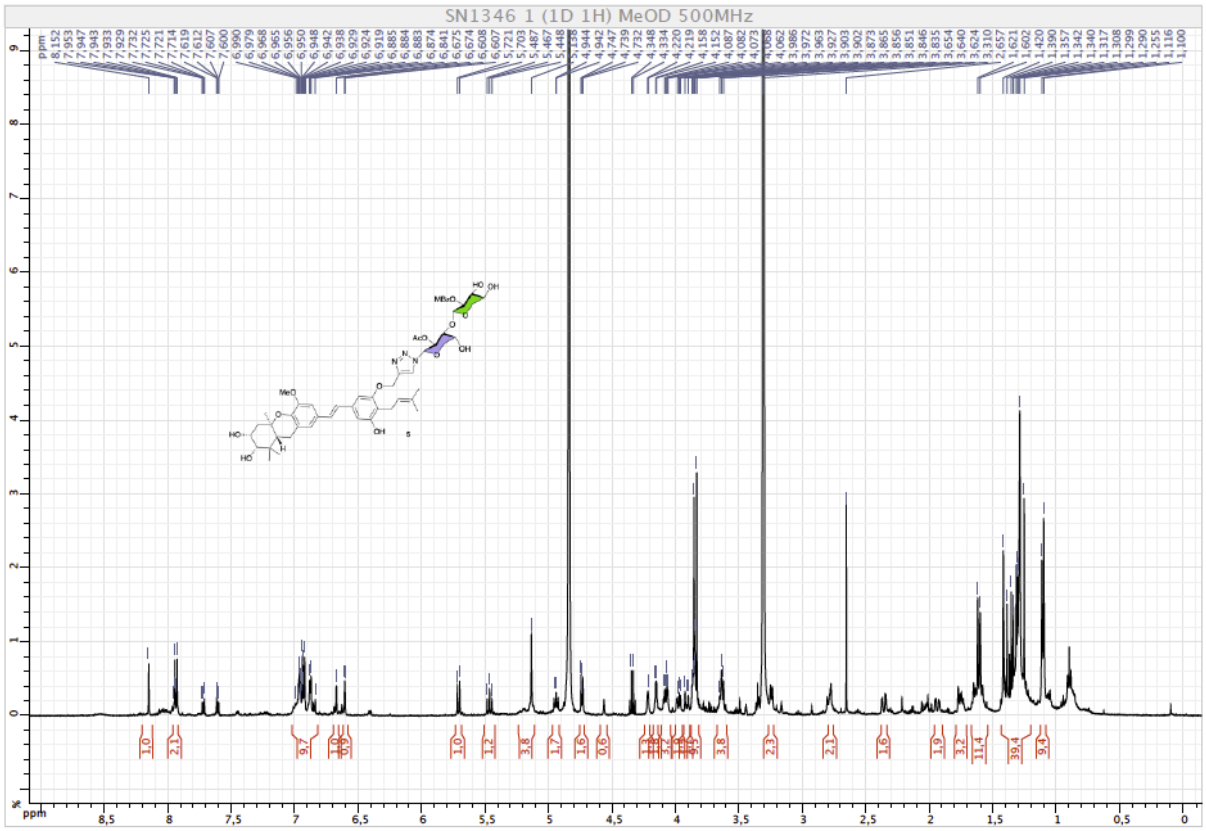
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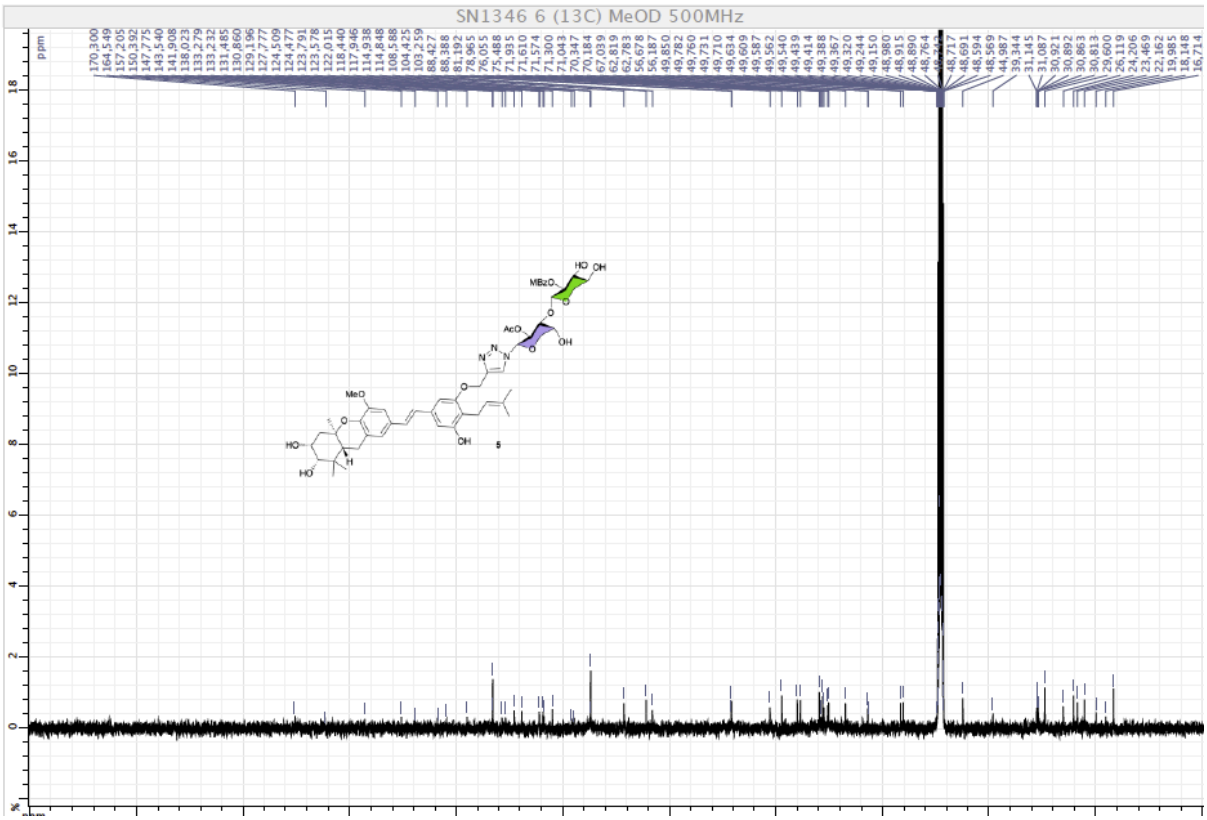
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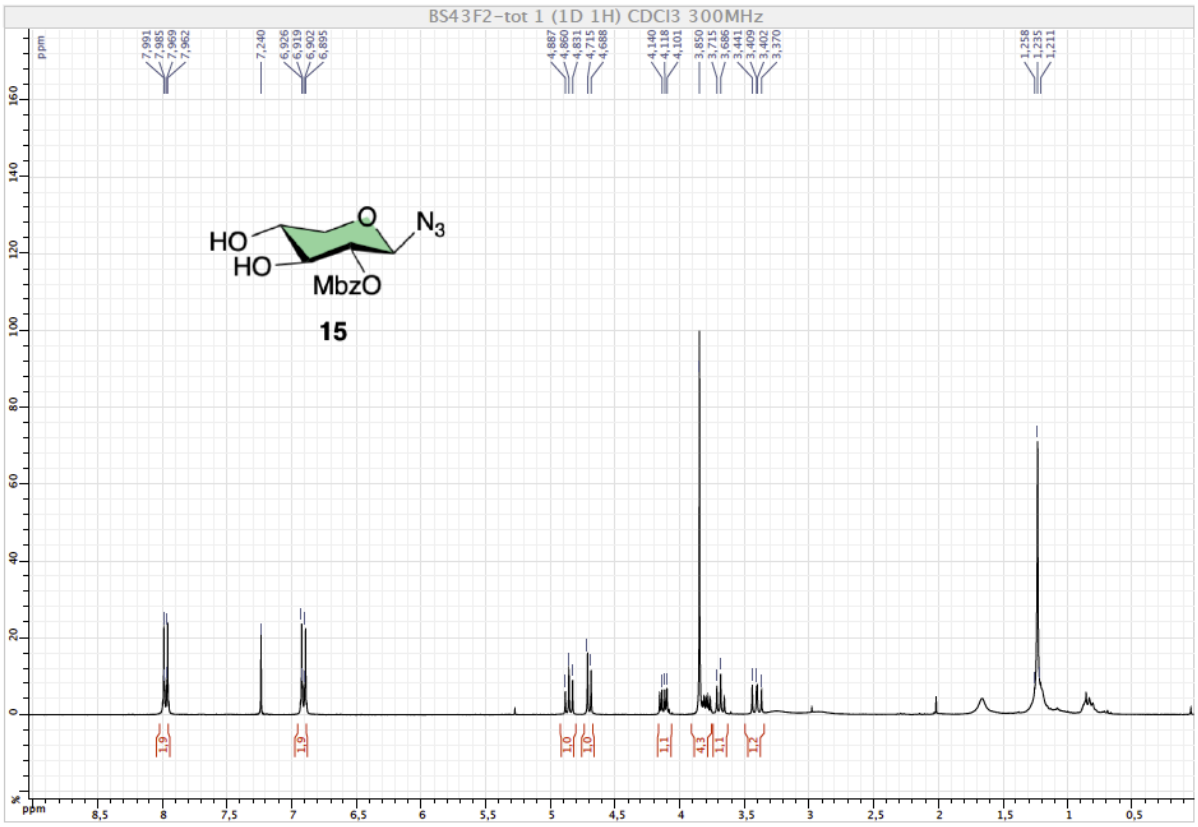
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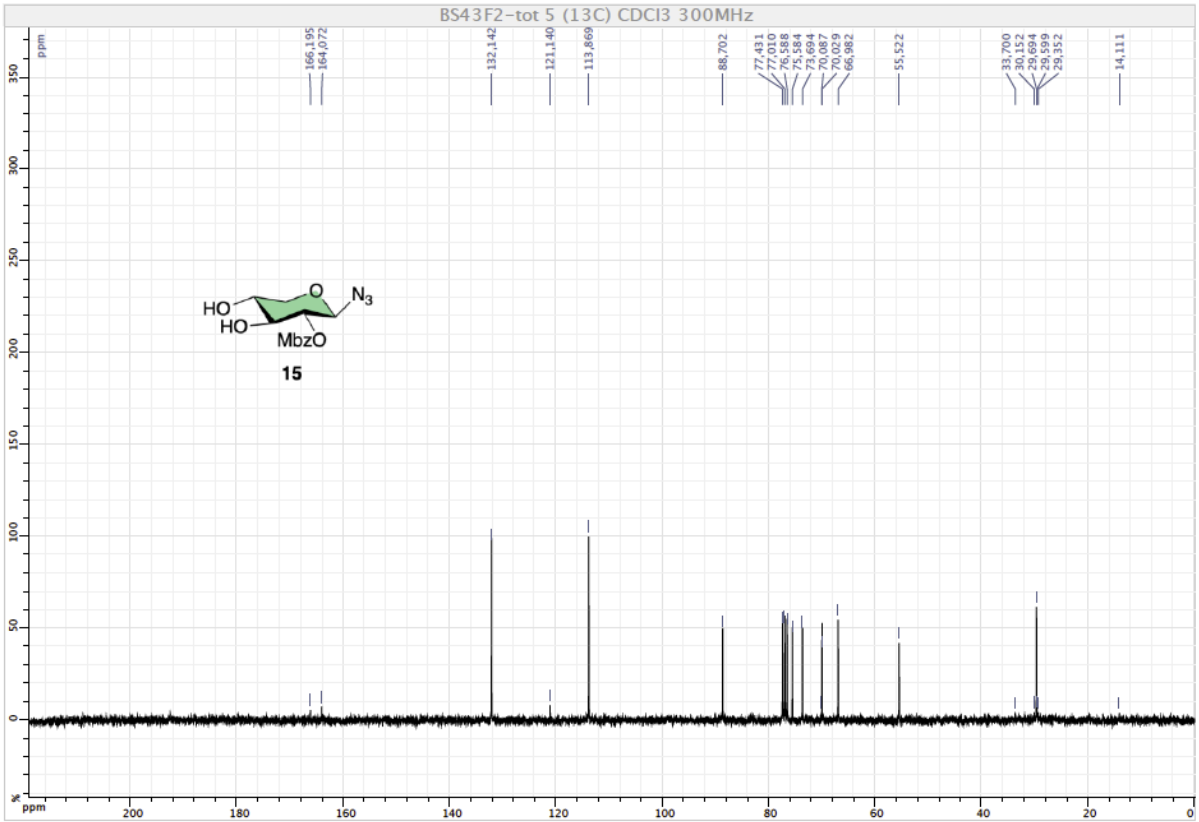
15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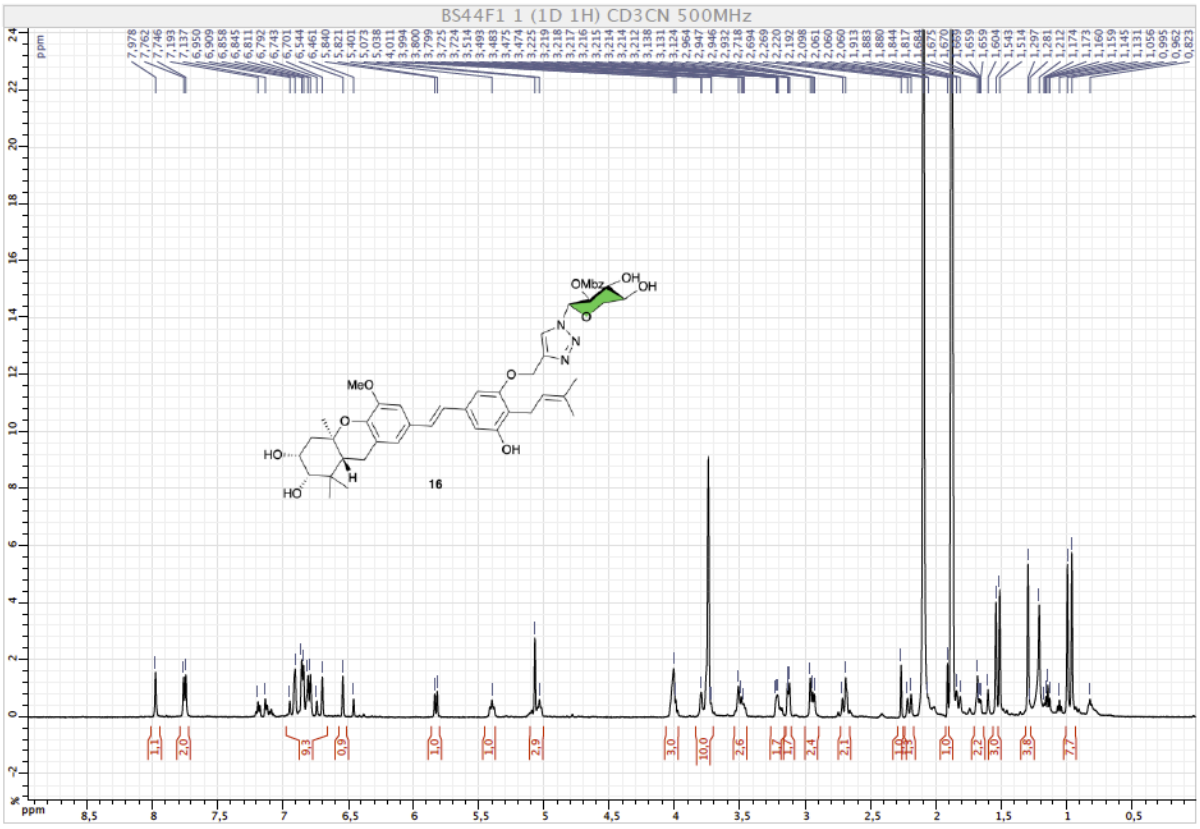
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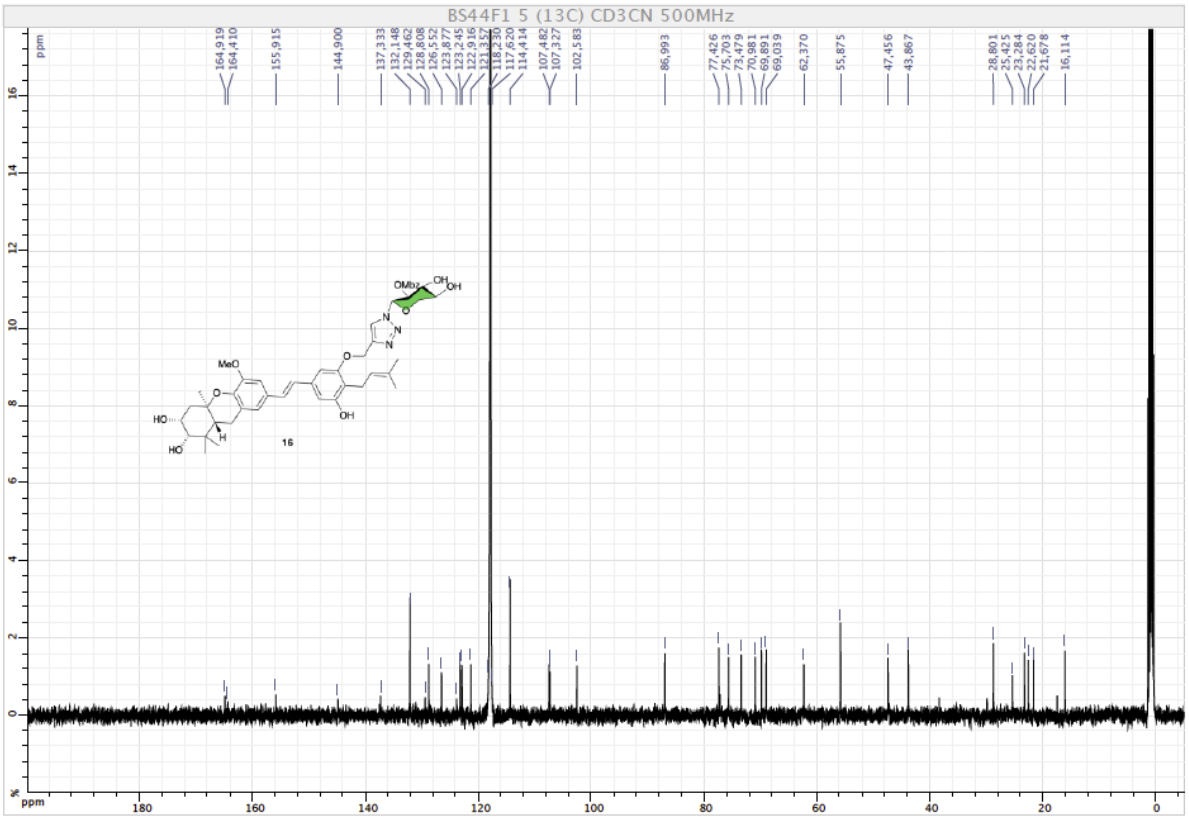
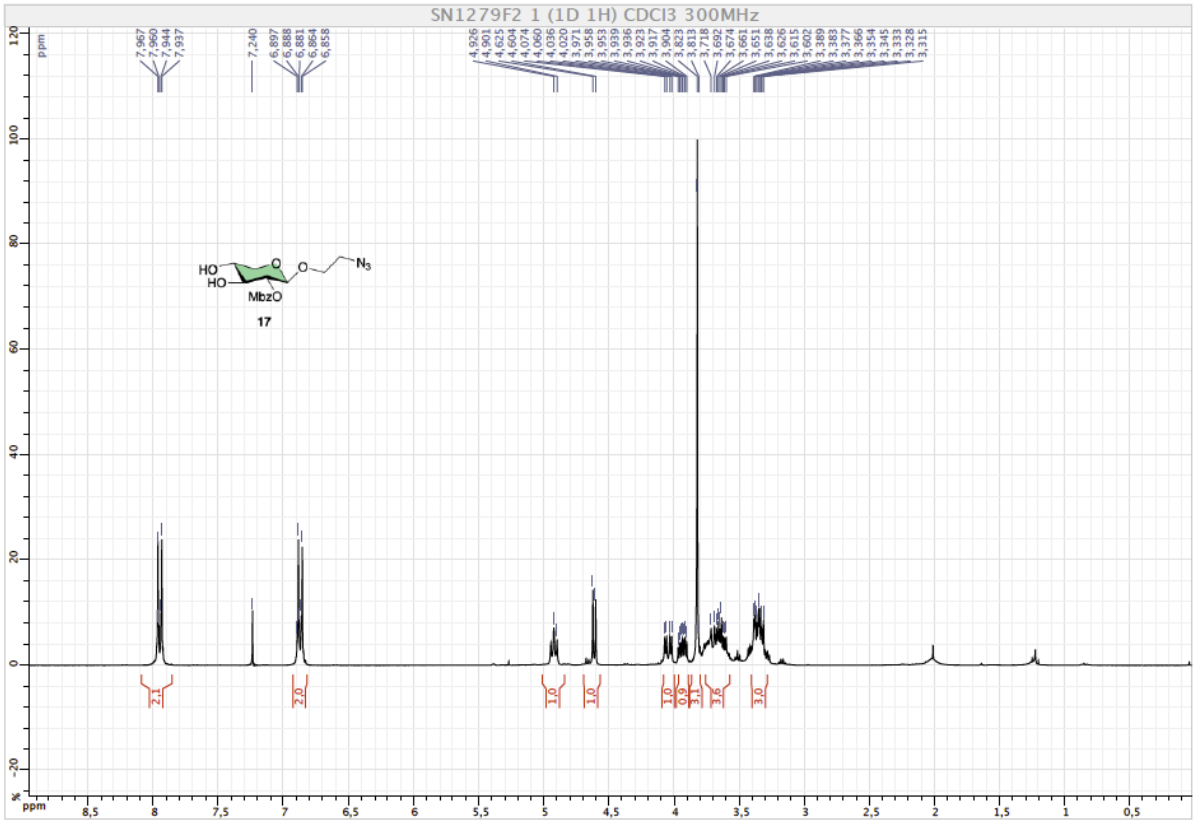
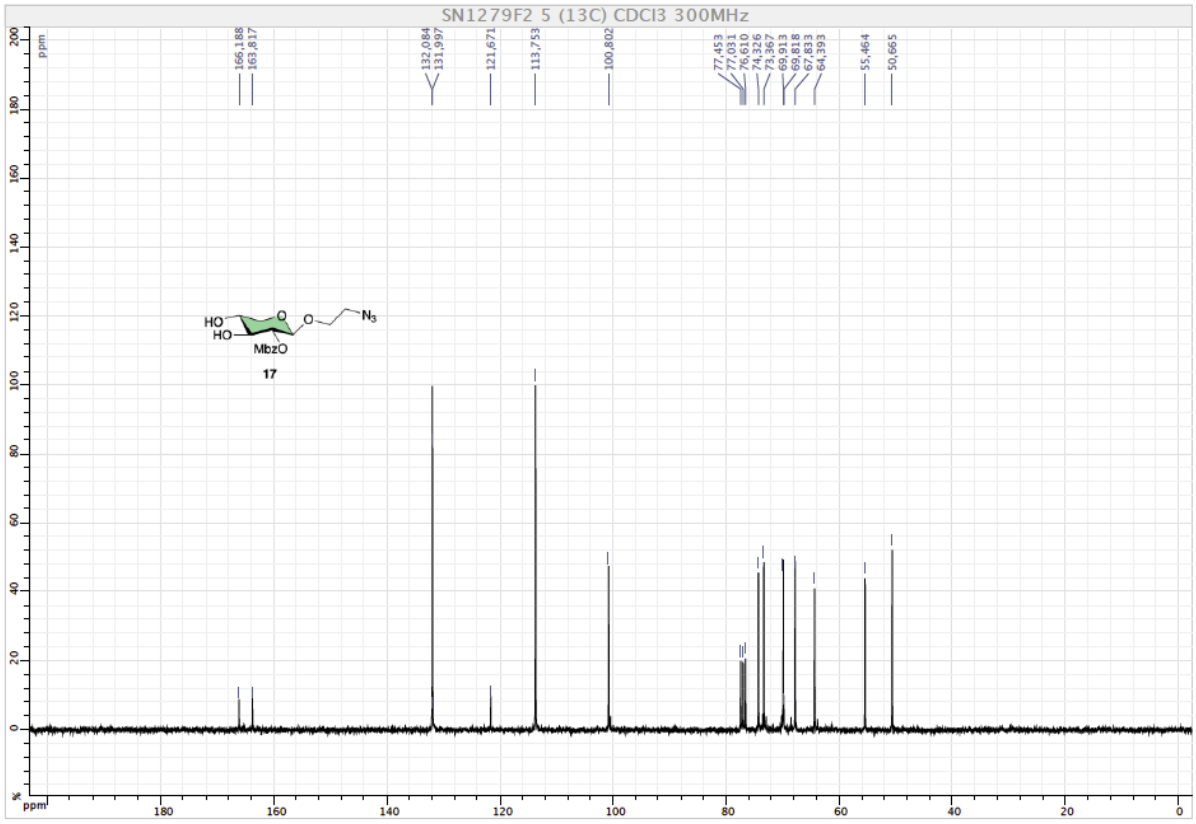
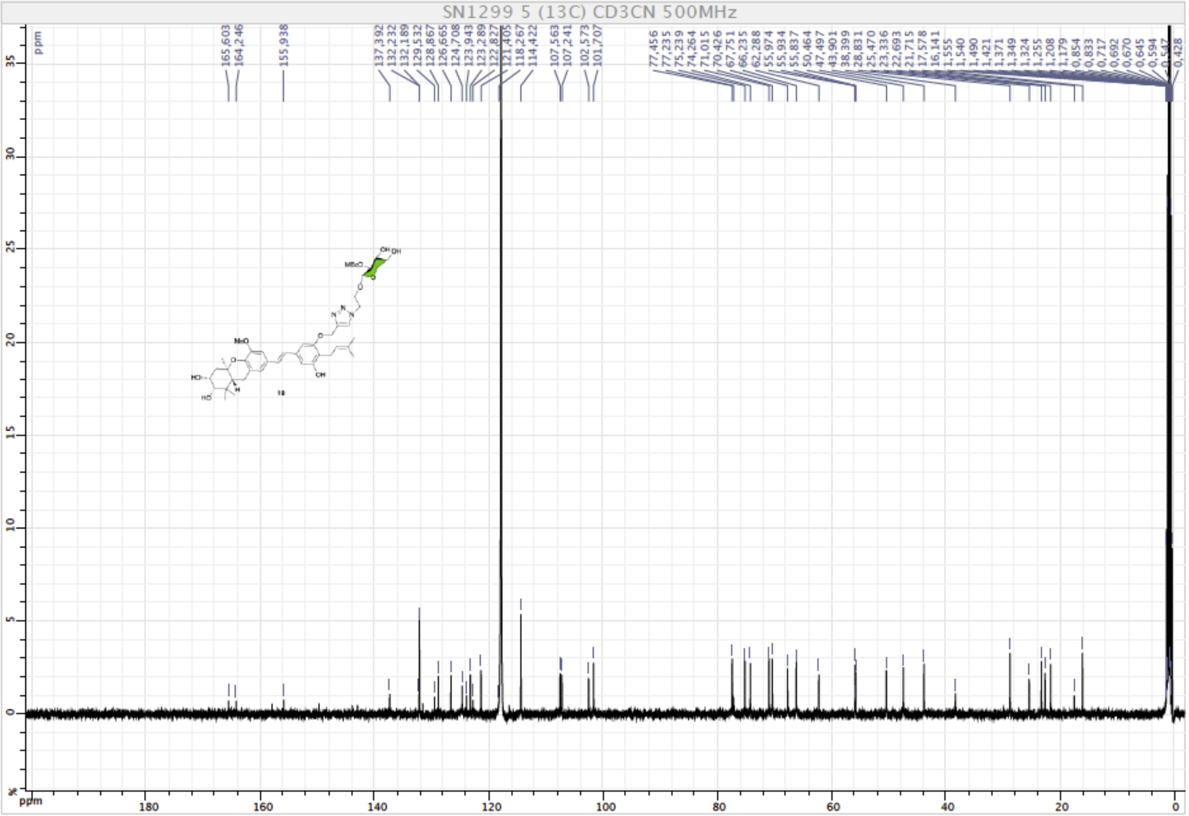
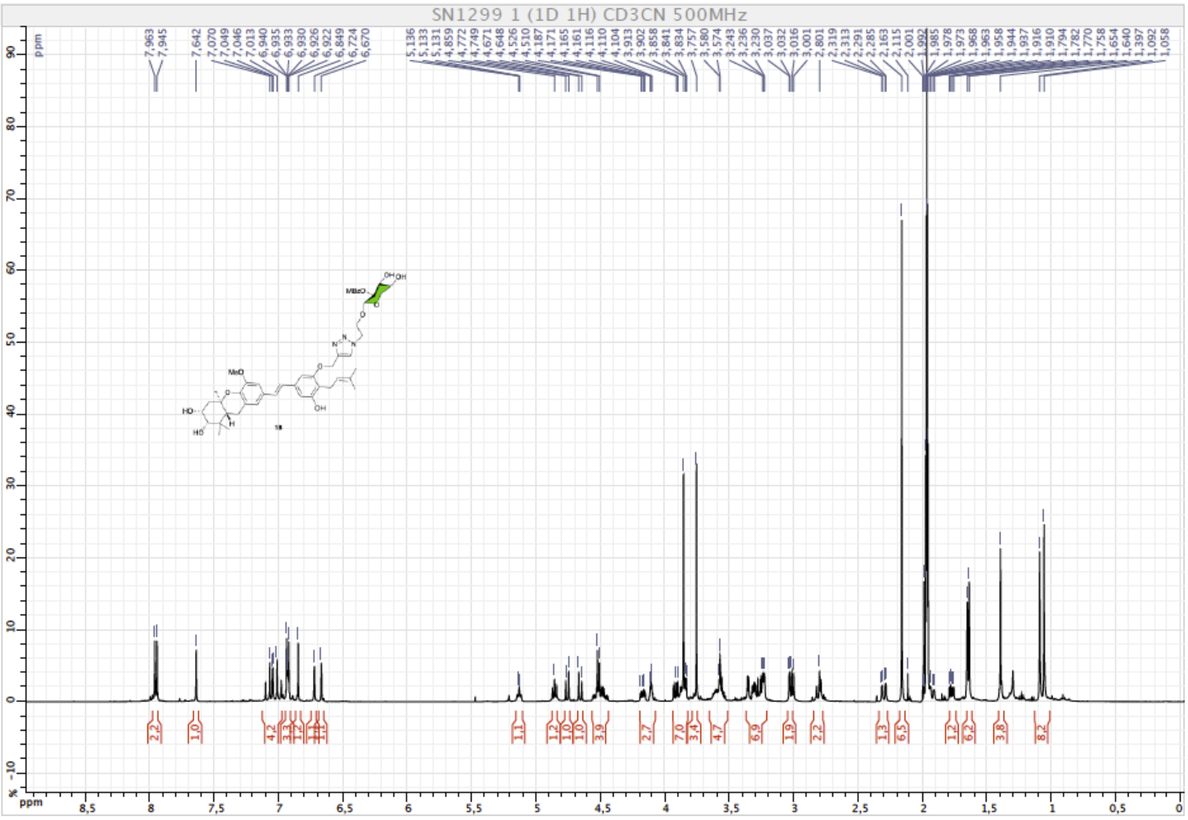
ppm
16

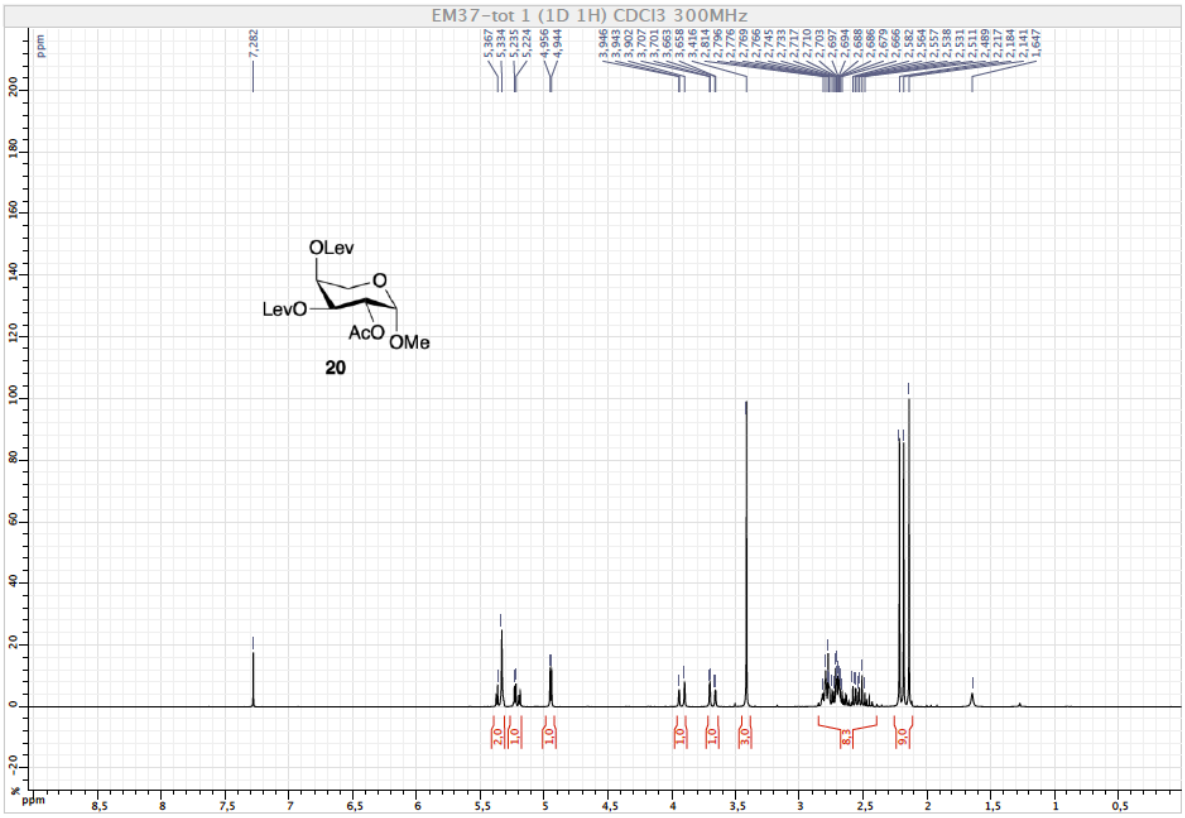

BS44F1 5 (13C) CD3CN 500MHz
ppm
16

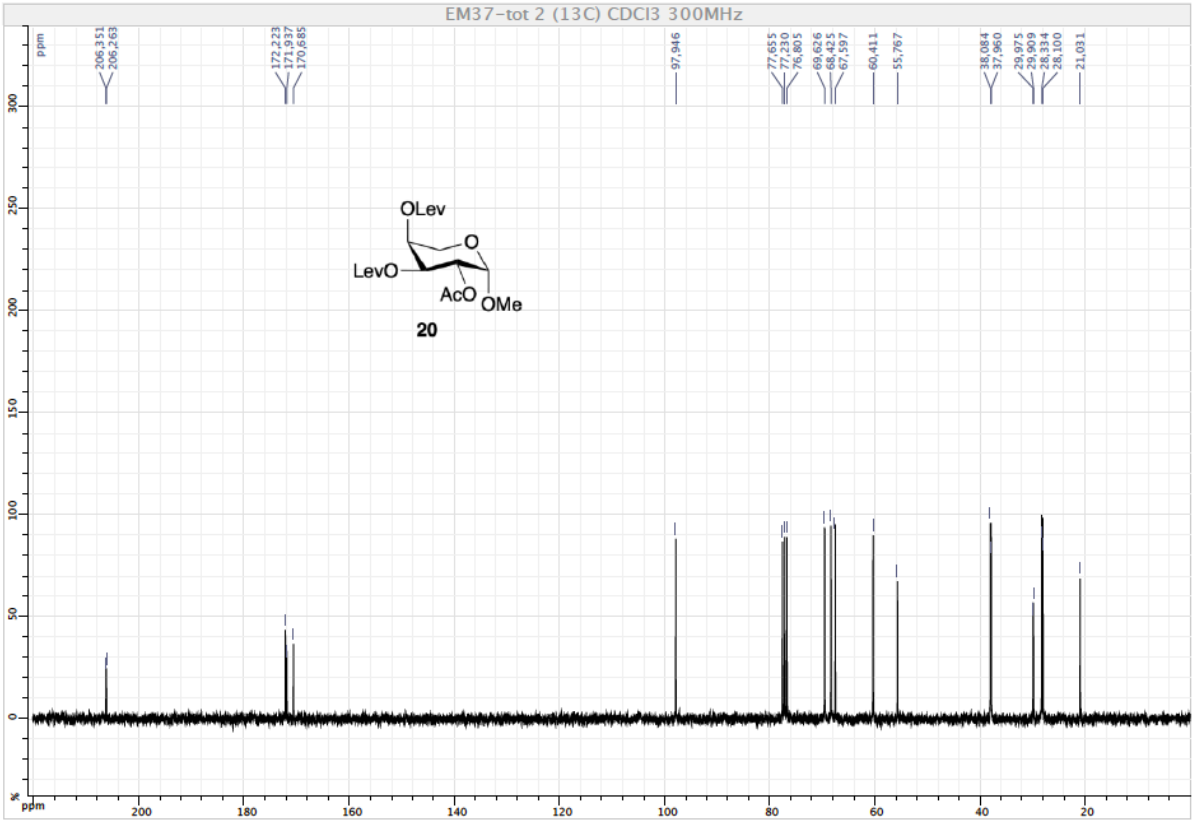

SN1279F2 1 (1D 1H) CDCl3 300MHz
ppm
7,967
7,960
7,944
7,937
7,240
6,897
6,888
6,881
6,864
6,858
4,906
4,901
4,625
4,604
4,074
4,060
4,036
4,020
3,971
3,958
3,953
3,939
3,936
3,933
3,917
3,904
3,823
3,813
3,718
3,692
3,674
3,661
3,651
3,638
3,626
3,615
3,602
3,389
3,383
3,377
3,366
3,354
3,345
3,333
3,328
3,315
HO
HO
O
O
N3
MbzO
17
2,1
2,0
1,0
1,0
1,0
0,9
3,1
3,6
3,0

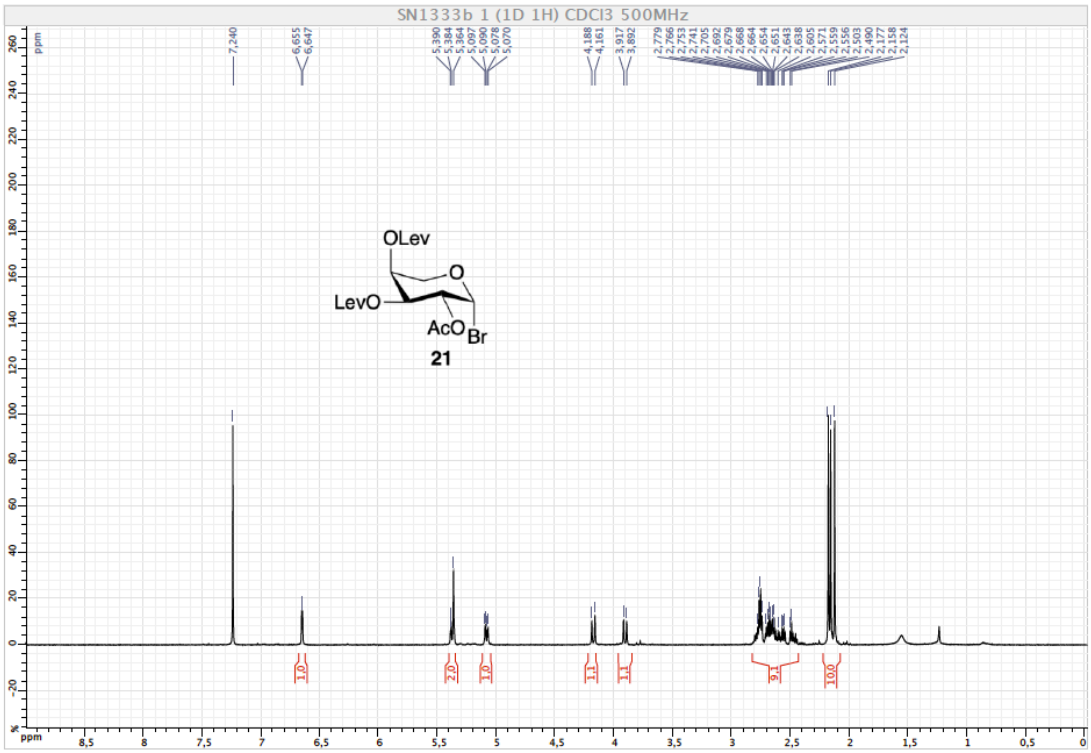

SN1279F2 5 (13C) CDCl3 300MHz
ppm
166,188
165,817
132,084
131,997
121,671
113,753
100,802
77,453
77,031
76,610
74,326
73,367
69,913
69,818
67,833
64,393
55,464
50,665
HO
HO
O
O
N3
MbzO
17

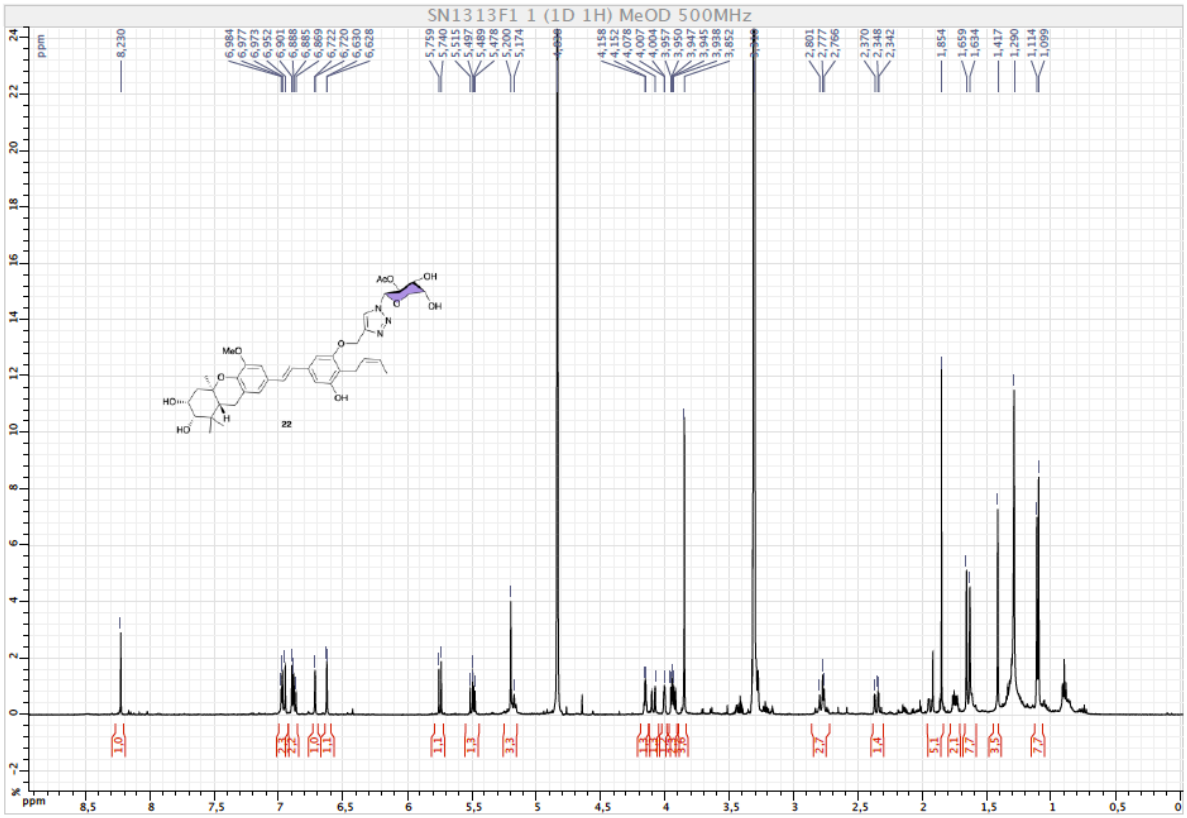

SN1299 5 (13C) CD3CN 500MHz

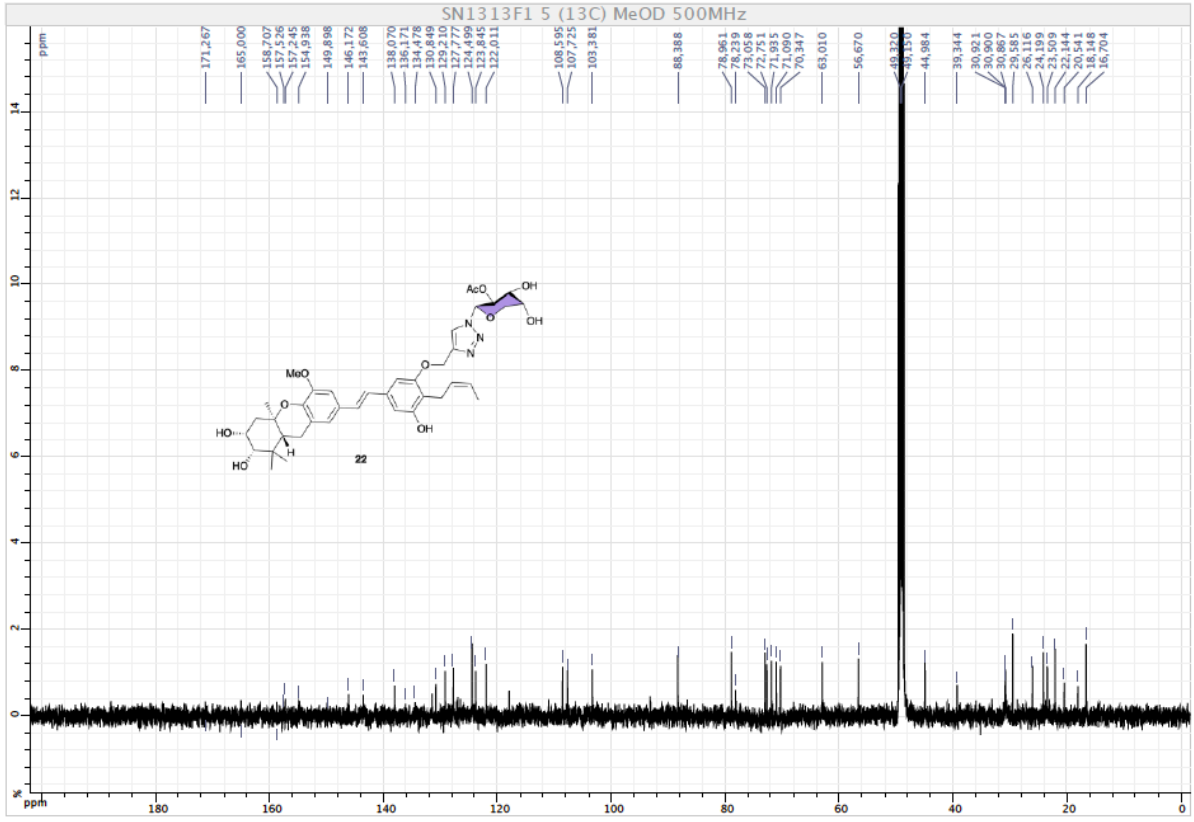

SN1299 1 (1D 1H) CD3CN 500MHz


EM37-tot 1 (1D 1H) CDCl3 300MHz
OLev
O
LevO
AcO
OMe
20


EM37-tot 2 (13C) CDCl3 300MHz
OLev
O
LevO
AcO
OMe
20


SN1333b 1 (1D 1H) CDCl3 500MHz
OLev
O
LevO
AcO
Br
21


SN1313F1 1 (1D 1H) MeOD 500MHz
ppm
8,230
6,984
6,977
6,973
6,952
6,901
6,888
6,885
6,659
6,722
6,720
6,630
6,628
5,759
5,740
5,515
5,497
5,489
5,478
5,200
5,174
4,158
4,152
4,078
4,007
4,004
3,957
3,950
3,947
3,945
3,938
3,852
2,801
2,777
2,766
2,370
2,348
2,342
1,854
1,659
1,634
1,417
1,290
1,114
1,099
1,0
2,2
1,0
1,1
1,1
1,3
3,3
2,7
1,4
3,1
2,1
7,7
3,5
7,7
22


SN1313F1 5 (13C) MeOD 500MHz
ppm
171,267
165,000
158,707
157,526
157,245
154,938
149,898
146,172
143,608
138,070
136,171
134,478
130,449
129,210
127,777
124,499
123,845
122,011
105,595
107,725
103,381
88,388
78,961
78,239
73,058
72,751
71,935
71,090
70,347
63,010
56,670
49,320
49,150
44,984
39,344
30,921
30,900
30,867
29,585
26,116
24,199
23,509
22,144
20,541
18,148
16,704
22