Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis and biological profiling of tellimagrandin I and analogues reveals that the medium ring significantly contributes to ellagitannin biological activity

Shaojun Zheng, Luca Laraia, Cornelius J. O' Connor, David Sorrell, Yaw Sing Tan, Zhaochao Xu, Ashok Venkitaraman, Wenjun Wu, David R. Spring

Supporting Information

Biology

1 Materials and Methods

1.1 Cells

HeLa cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with fetal calf serum (FCS) without antibiotics, at 37 ºC in a 5% CO_2 humidified atmosphere.

1.2 Reagents

All compounds assayed were synthesized in our labs according to the procedures specified in *Chemistry* (*vide infra*). Resazurin and resofurin were purchased from Sigma Aldrich. BSA was purchased from Fluka. Hoechst was purchased from BD Pharmingen and used at 1:20,000. Anti cleaved PARP was purchased from BD Pharmingen and used at 1:800. AlexaFluor 546 Goat anti-mouse IgG was purchased from Molecular Probes and used at 1:500.

1.3 High Content Analysis (HCA)

HCA was performed using an Arrayscan II HCS reader and integrated software from Cellomics. HeLa cells were seeded in a NUNC clear flat bottomed 96-well plate at 5000/well in a total of 100 µL. They were incubated at 37 ºC overnight. Cells were then treated with compounds (25 µL) at a top concentration of 300 µM, diluting serially 1:2. Cells were then incubated at 37 ºC for 72 h. The medium was gently removed from all the wells and 100 µL cold methanol was added to each well. This was incubated at -20 ºC for 3 min, before the methanol was removed. The wells were washed for 3 x 5 min in 100 µL/well permeabilization buffer (PB, contains PBS + 0.1% Triton X-100). PB was removed and wells washed with 100 µL/well blocking buffer (BB, contains PBS + 1% BSA). BB was removed and 50 µL/well of primary antibody solution (anti c-PARP, 1:800) was added. Plates were incubated for 2 h at room temperature. The antibody was removed and wells washed with 2 x 100 µL/well BB. BB was removed and 50 µL/well of secondary antibody solution containing Hoechst (1:20,000) and AlexaFluor 546 Goat anti-mouse IgG (1:500) was added. Plates were incubated at RT for 1 h in the dark. Secondary antibody solution was removed and plates washed with 2 x 100 µL BB. The BB was then removed and 100 µL PBS/well were added. The plates were sealed with opaque film and images taken on a 20x 0.4 NA objective. Data was analysed on Cellomics Arrayscan software using the Target Activation v4 protocol. Critical output features are: ValidObjectCount and %Responder_AvgIntenCh2. IC_{50} and EC_{50} data was calculated using Prism (Graphpad).

1.4 Redox Assay

The assay was performed using a modified version of the protocol developed by Lor *et al.*[1] Ellagitannin derivatives were diluted in buffer A (50 mM HEPES, 50 mM NaCl, pH 7.5) in 1:2 from a

top concentration of 800 µM. Resazurin was made up in buffer A at a concentration of 10 µM, and DTT was added at a concentration of 100 µM. Then, 15 µL of the Ellagitannin compound solution was mixed with 15 µL of the Resazurin solution in a clear, flat bottomed Nunc 96-well plate (Corning). The wells were allowed to react for 60 min at RT after addition of the Resazurin/DTT solution and were then read on a PheraSTAR plate reader on the Cell Titre Blue setting.

1.5 Protein Precipitation Assay

This assay was performed using a modified version of the protocol from Kawamoto *et al.*[2] Compounds (1.3 µmoles, 14 mM) were made up in 88 µL of 0.2 M acetate buffer (pH 4.5) and mixed with a solution of BSA (625 µg, 9 nmol, 0.11 mM) in 88 µL of the buffer at RT. After shaking for 1 h, the resulting precipitates were separated by centrifugation (3000 rpm, 5 min) and washed with buffer (170 µL) followed by centrifugation (3000 rpm, 5 min). The precipitates obtained were dissolved by adding 250 µL of 2.0% aq. SDS solution containing 0.5 mg of catechol as internal standard and the resulting clear solution was analysed by HPLC. CC: column: Supelcosil cat. # 59194 (15 cm x 4.6 mm x 3.0 µm); eluent: 0.1% aq. TFA/0.1% TFA in MeCN (15% to 85%, 20 min); flow rate: 1 mL/min; detector: UV 220 nm. R_f (min) catechol (4.25), BSA (9.20).

1.6 Data Analysis

All data was analysed using Graphpad Prism (v5). IC_{50}s for cell viability were obtained by using the non-linear regression analysis with a 3 component model. EC_{50}s for the induction of apoptosis were calculated using the non-linear regression analysis, as for the redox activity. Errors are given to the nearest whole number.

Chemistry

2 General Experimental

Experimental techniques were performed using flame dried glassware apparatus unless otherwise indicated. Reactions were performed under nitrogen with dry, freshly distilled solvents. Dichloromethane, methanol and toluene were distilled over calcium hydride. Tetrahydrofuran and diethyl ether were distilled over a mixture of lithium aluminium hydride and calcium hydride in the presence of triphenyl methane. Petrol was distilled before use and refers to the fraction distilled between 30-40 ^{o}C. Anhydrous DMF was used as supplied by Fluka in sureseal bottles. All other reagents were purified in accordance with the instructions in 'Purification of Laboratory Chemicals' or used as obtained from commercial sources.

Room temperature (RT) refers to ambient temperature. Temperatures of 0 °C were maintained using an ice-water bath and temperatures of -78 °C were maintained using an acetone-cardice bath. Yields refer to chromatographically and spectroscopically pure compounds. All reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F_{254}. Visualization was by the quenching of UV fluorescence (ν_{max} = 254 nm) or by staining with either: ceric ammonium molybdate; potassium permanganate; or, Dragendorff's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3 M aq. AcOH). Retention factors (R_f) are quoted to 0.01. All flash column chromatography was performed using Merck 9385 Kieselgel 60 silica gel.

Full spectral data for all novel compounds are given below, all previously characterized compounds gave spectra consistent with the literature. Optical rotations were recorded on a Perkin Elmer 343 polarimeter. $[\alpha]_D^{28}$ values are reported in 10^{-1}deg.cm^2.g^{-1} at 589 nm, concentration (c) is given in g.(100 mL)$^{-1}$.

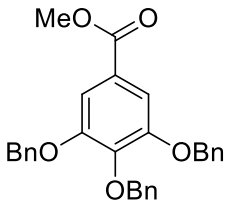
Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected. Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500 MHz spectrometers. Proton assignments are supported by ^{1}H-^{1}H correlation (COSY) spectra where necessary. Chemical shifts (δ_H) are quoted in ppm to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak (7.26 ppm for $CHCl_3$ of $CDCl_3$; 2.54 ppm for DMSO of d_6-DMSO; 3.31 ppm for CH_3 of CD_3OD; 2.09 ppm for CH_3 of C_3D_6O). Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz. Data are reported as follows: chemical shift; integration; multiplicity [app, apparent; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. app s, br d, dd, dt, ddd.)]; coupling constant(s); and, assignment. Carbon magnetic resonance spectra were recorded on Bruker 400 or 500 MHz spectrometers operating at 100 and 125 MHz respectively. Carbon spectra assignments are supported by DEPT editing and, where necessary, ^{13}C-^{1}H correlation (HMQC) spectra and ^{13}C-^{1}H long range correlation (HMBC) spectra. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.1 ppm (or 0.01 ppm where required), and are referenced to the deuterated solvent peak (77.00 ppm for $CDCl_3$; 40.45 ppm for d_6-DMSO, 50.41 for CD_3OD; 205.87 & 30.60 for C_3D_6O). Coupling constants (J) are

reported in Hertz (Hz) to the nearest 0.1 Hz. Data are reported as follows: chemical shift; multiplicity (singlet unless otherwise stated; d, doublet); coupling constant; and, assignment.

Infrared spectra were recorded on a Perkin Elmer 1 FT-IR Spectrometer fitted with an Attenuated Total Reflectance (ATR) sampling accessory as thin films or flattened solids. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectrometric (HRMS) analyses were measured on a Micromass QTOF or a Micromass LCT Premier spectrometer at the Department of Chemistry, University of Cambridge. Mass values are reported within the error limits of +\-5 ppm.

2.1 Synthesis of Coupling Precursors

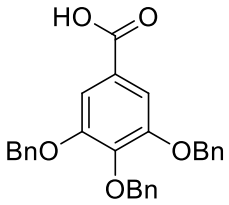
2.1.1 Methyl 3,4,5-tris(benzyloxy)benzoate



A mixture of methyl gallate (2.00 g, 10.84 mmol), benzyl bromide (4.28 mL, 36.00 mmol) and potassium carbonate (4.98 g, 36.00 mmol) in acetone (100 mL) was heated at reflux for 8 h. The reaction mixture was concentrated at reduced pressure and the resulting residue was partitioned between water (50 mL) and Et_2O (50 mL). The aqueous layer was extracted further with Et_2O (2 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was recrystallized (hexane) to give the title compound (3.10 g, 63%) as a white solid.

M.p. 98-99 °C (hexane), lit.[3] 98 °C; R_f 0.65 (SiO_2, EtOAc: Pet. ether, 1:1); ν_{max} (neat) 1715, 1214, 1107, 751, 740, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.52-7.38 (14H, m, Ar-H), 7.34-7.29 (3H, m, Ar-H), 5.20 (6H, s, CH_2), 3.95 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 167.0 (C), 153.0 (C), 142.9 (C), 137.9 (C), 137.1 (C), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 125.7 (C), 109.6 (CH), 75.6 (CH_2), 71.7 (CH_2), 52.6 (CH_3); HRMS found ESI $[M+H]^+$ 455.1877, $[C_{29}H_{27}O_5]^+$ requires 455.1858. The spectral data were consistent with literature values.[4]

2.1.2 3,4,5-tris(benzyloxy) benzoic acid

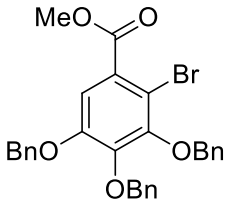


A mixture of methyl 3,4,5-tris(benzyloxy)benzoate (8.55 g, 18.80 mmol), potassium hydroxide (10.55 g, 188 mmol), MeOH (200 mL) and dioxane (200 mL) was heated at reflux for 30 min. The solvent was removed at reduced pressure, and the resulting residue was partitioned between water (150 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer was extracted further with EtOAc (2 x 100 mL). The combined organic layers were washed sequentially with dilute HCl (150 mL) and brine (200 mL), dried ($MgSO_4$) and concentrated at reduced pressure. The product was recrystallized (methanol) to give the title compound (7.67 g, 93%) as a white solid.

M.p. 195-197 °C (MeOH), lit.[5] 195-196 °C; ν_{max} (neat) 1682, 1593, 1427, 1332, 1125, 755, 728 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 7.47-7.46 (5H, m, Ar-H), 7.43-7.33 (9H, m, Ar-H), 7.31-7.28 (3H, m, Ar-H), 5.18 (4H, s, CH_2), 5.17(2H, s, CH_2); δ_C (100 MHz, d_6-DMSO) 167.7 (C), 152.9 (C), 141.9 (C), 138.3

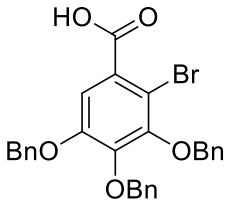
(C), 137.7 (C), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 126.9 (C), 109.1 (CH), 75.1 (CH_2), 71.1 (CH_2); HRMS found ESI $[M+Na]^+$ 463.1508, $[C_{28}H_{24}O_5Na]^+$ requires 463.1516.

2.1.3 Methyl 3,4,5-tris(benzyloxy)-2-bromobenzoate



A mixture of methyl 3,4,5-tris(benzyloxy)benzoate (6.16 g, 13.55 mmol) and *N*-bromosuccinimide (2.66 g, 14.95 mmol) in DMF (60 mL) was stirred at room temperature for 24 h. The solution was then diluted with water (100 mL) and extracted with Et_2O (200 mL). The organic layer was separated, washed with water (4 × 100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was recrystallized (hexane) to give the title compound (5.77 g, 80%) as white needles.
M.p. 91-93 °C (hexane), lit.[4] 91-93 °C; R_f 0.55 (SiO_2, EtOAc: Pet. ether, 1:6); ν_{max} (neat) 1729, 1332, 1094, 959, 736, 683 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 (2H, dd, J = 7.7, 1.7, Ar-H), 7.34-7.11 (14H, m, Ar-H), 4.99 (4H, s, CH_2), 4.93 (2H, s, CH_2), 3.81 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 166.0 (C), 151.4 (C), 150.5 (C), 145.4 (C), 136.3 (C), 136.2 (C), 135.6 (C), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.9 (CH), 127.3 (CH), 127.23 (CH), 127.21 (C), 126.5 (CH), 111.6 (C), 110.0 (CH), 75.3 (CH_2), 75.0 (CH_2), 70.8 (CH_2), 52.1 (CH_3); HRMS found ESI $[M+H]^+$ 533.0971, $[C_{29}H_{26}O_5Br]^+$ requires 533.0964.

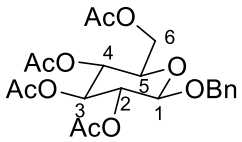
2.1.4 3,4,5-tris(benzyloxy)-2-bromobenzoic acid



A mixture of methyl 3,4,5-tris(benzyloxy)-2-bromobenzoate (10.03 g, 18.80 mmol), potassium hydroxide (10.55 g, 188 mmol), methanol (210 mL) and dioxane (210 mL) was heated at reflux for 30 min. The reaction was cooled to RT and concentrated. The resulting residue was partitioned between water (150 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer was extracted further with EtOAc (2 x 100 mL). The combined organic layers were washed sequentially with dilute HCl (100 mL) and brine (200 mL), dried (Na_2SO_4) and concentrated at reduced pressure. The product was recrystallized (methanol) to give the title compound (7.86 g, 81%) as a white solid.
M.p. 158-159 °C (methanol), lit.[4] 158-160 °C; ν_{max} (neat) 3036, 2945, 1697, 1370, 1325, 1096, 734, 683 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43-7.39 (3H, m, Ar-H), 7.33-7.26 (10H, m, Ar-H), 7.20-7.12 (3H, m, Ar-H), 5.02 (4H, s, CH_2), 4.93 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 171.0 (C), 151.6 (C), 151.1 (C), 146.8 (C), 138.6 (C), 136.5 (C), 135.8 (C), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.36 (CH), 128.31

(CH), 127.6 (CH), 125.5 (CH), 113.1 (CH), 111.7 (C), 75.8 (CH_2), 75.4 (CH_2), 71.2 (CH_2); HRMS found ESI $[M+H]^+$ 519.0819, $[C_{28}H_{24}O_5Br]^+$ requires 519.0807.

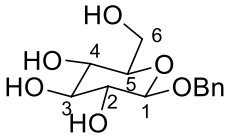
2.1.5 Benzyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside



To a solution of penta-*O*-acetyl glucose (3.90 g, 10.00 mmol) and benzyl alcohol (1.08 mL, 10.00 mmol) in anhydrous CH_2Cl_2 (20 mL) was added BF_3•Et_20 (1.25 mL, 10.00 mmol). The reaction mixture was stirred at RT for 24 h and diluted with 5% aq. $NaHCO_3$ (40 mL). The organic layer was separated, washed sequentially with aq. $NaHCO_3$ (20 mL) and water (30 mL), dried over Na_2SO_4, and concentrated. The crude product was recrystallized from EtOH to give the title compound (1.75 g, 49%) as a white solid.

M.p. 96-98 °C (EtOH), lit.[6] 96-97 °C; ν_{max} (neat) 1755, 1723, 1366, 1233, 1215, 731 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.28 (5H, m, Ar-H), 5.22-5.07 (3H, m, C[2]H, C[3]H & C[4]H), 4.92 (1H, d, J = 12.3, CH_2), 4.65 (1H, d, J = 12.3, CH_2), 4.57 (1H, d, J = 7.8, C[1]H), 4.30 (1H, dd, J = 12.3, 4.7, C[6]H), 4.19 (1H, dd, J = 12.3, 2.4, C[6]H), 3.72-3.67 (1H, m, C[5]H), 2.13 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.02 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 170.7 (C), 170.3 (C), 169.4 (C), 169.3 (C),136.6 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 99.2 (CH), 72.8 (CH),71.8 (CH_2), 71.2 (CH), 70.7 (CH_2), 68.4 (CH), 61.9(CH_2)，20.8 (CH_3)， 20.64 (CH_3)，20.61 (CH_3)，20.6 (CH_3); LRMS found ESI [M+Na] 461.2 requires 461.1.

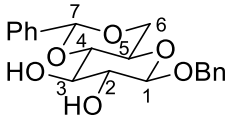
2.1.6 Benzyl β-D-Glucopyranoside



A mixture of benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (896 mg, 2.50 mmol), MeOH (16 mL), triethylamine (2 mL) and H_2O (2 mL) was stirred for 5 h. The reaction was concentrated *in vacuo* and the resulting residue was recrystallized from acetone to give the title compound (0.64 g, 95%) as a white solid.

M.p. 119-121 °C (acetone), lit.[7] 120-121 °C; ν_{max} (neat) 3382, 1048, 959, 734, 696 cm^{-1}; δH (400 MHz, CD_3OD) 7.33-7.17 (5H, m, Ar-H), 4.88 (1H, d, J = 11.8, CH_2), 4.57(1H, d, J = 11.8, CH_2), 4.25 (1H, d, J = 7.7 Hz, C[1]H), 3.80 (1H, dd, J = 11.9, 2.1, C[6]H), 3.59 (1H, dd, J = 11.9, 5.5, C[6]H), 3.25-3.13 (4H, m, C[2]H, C[3]H, C[4]H & C[5]H); δ_C (100 MHz, $CDCl_3$) 137.6 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 102.3 (CH), 76.6 (CH), 75.9 (CH), 73.7 (CH), 71.6 (CH), 69.7 (CH_2), 61.6 (CH_2); HRMS found ESI $[M+Na]^+$ 293.0994, $[C_{13}H_{18}O_6\ Na]^+$ requires 293.0996.

2.1.7 Benzyl 4,6-O-benzylidene-β-D-glucopyranoside (1)

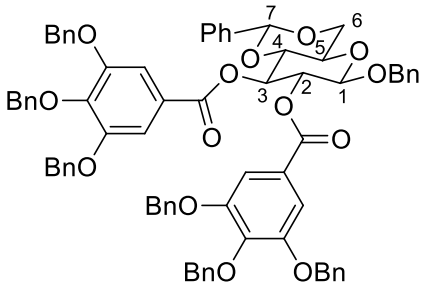


1

To a mixture of benzyl β-D-glucopyranoside (2.70 g, 10.00 mmol) and benzaldehyde dimethylacetal (1.80 mL, 12.00 mmol) in DMF (30 mL) at RT was added PTSA·H_2O (528 mg, 2.50 mmol). The reaction mixture was stirred for 5 min before heating to 80 °C and stirring for 2.5 h. The mixture was cooled to RT and subsequently concentrated at reduced pressure. The resulting residue was partitioned between CH_2Cl_2 (100 mL) and satd. Na_2CO_3 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated. Purification of the resulting residue by flash chromatography (EtOAc-Pet. ether, 1:1) provided the desired product (3.08 g, 86%) as a white solid.

M.p. 160-163 °C, lit.[8] 159-160 °C; R_f 0.30 (SiO_2, EtOAc: Pet. ether, 3:2); ν_{max} (neat) 3351, 1497, 1451, 1371, 1174, 1065, 737 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.54-7.50 (2H, m, Ar-H), 7.42-7.29 (8H, m, Ar-H), 5.57 (1H, s, C[7]H), 4.97 (1H, d, J = 11.5, CH_2), 4.67 (1H, d, J = 11.6, CH_2), 4.53 (1H, d, J = 7.8, C[1]H), 4.40 (1H, dd, J = 10.5, 4.9, C[4]H), 3.87-3.81 (2H, m, C[6]H and C[3]H), 3.63-3.58 (2H, m, C[6]H and C[2]H), 3.52-3.46 (1H, m, C[5]H); δ_C (125 MHz, $CDCl_3$) 136.9 (C), 136.7 (C), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.21 (CH), 128.20 (CH), 126.3 (CH), 102.1 (CH), 102.0 (CH), 80.6 (CH), 74.6 (CH), 73.1 (CH), 71.5 (CH_2), 68.7 (CH_2), 66.5 (CH); HRMS found ESI $[M+Na]^+$ 381.1307, $[C_{20}H_{22}O_6Na]^+$ requires 381.1309.

2.1.8 Benzyl 4,6-O-benzylidene-2,3-bis(3,4,5-tris-(benzyloxy)benzoyl)-8-D-glucopyranoside

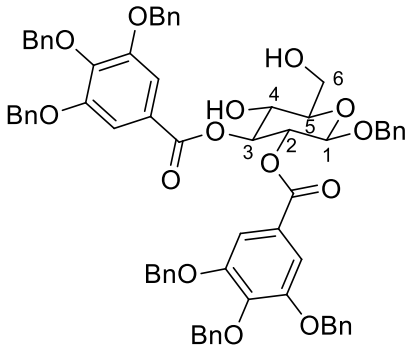


A mixture of tri-*O*-benzyl gallic acid (176 mg, 0.40 mmol), diol precursor (72 mg, 0.20 mmol), DCC (82.4 mg, 0.40 mmol), DMAP (6 mg, 0.05 mmol) and CH_2Cl_2 (15 mL) was stirred at room temperature for 18 h. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was triturated in cold Et_2O (30 mL) and filtered through Celite® (to remove the unwanted

urea byproduct). The filtrate was concentrated at reduced pressure and the crude product was purified by column chromatography (EtOAc-Toluene, 1:19) to give the title compound (200 mg, 83%) as a white solid.

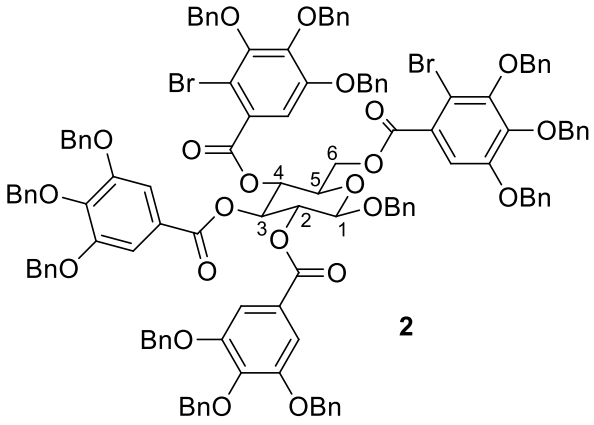
M.p. 173-175 °C, (lit.[7] 174.5-175.5); $[\alpha]_D^{28}$= +38 (c 0.17, $CHCl_3$), lit.[7] $[\alpha]_D^{25}$ = +37.4 (c 0.97, $CHCl_3$); R_f 0.60 (SiO_2, EtOAc-Toluene, 1:19); ν_{max} (neat) 1725, 1587, 1498, 1453, 1331, 1190, 1095, 734, 683 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38–7.01 (44H, m, Ar-H), 5.61 (1H, t, *J* = 9.6, [C3]H), 5.47–5.40 (2H, m, [C2]H & [C7]H), 5.06–4.87 (12H, m, CH_2), 4.81 (1H, d, *J* = 12.5, CH_2), 4.72 (1H, d, *J* = 7.8, [C1]H), 4.56 (1H, d, *J* = 12.5, CH_2), 4.38 (1H, dd, *J* = 10.5, 4.9, [C6]H), 3.90-3.76 (2H, m, [C4]H & [C6]H), 3.59 (1H, dt, *J* = 9.7, 4.9, [C5]H); δ_C (100 MHz, $CDCl_3$) 165.8 (C), 165.3 (C), 152.9 (C), 143.1 (C), 137.2 (C), 137.04 (C), 136.98 (C), 128.97 (C), 128.94 (CH), 128.86 (CH), 128.63 (CH), 128.47 (CH), 128.43 (C), 128.39 (C), 128.3 (C), 128.04 (C), 128.03 (C), 109.7 (CH), 102.0 (CH), 100.4 (CH), 79.3 (CH), 75.6 (CH_2), 73.0 (CH), 72.8 (CH), 71.6 (CH_2), 71.3 (CH_2), 69.1 (CH_2), 67.1 (CH); HRMS found ESI $[M+H_2O]^+$ 1220.4790, $[C_{76}H_{68}O_{15}]^+$ requires 1220.4787.

2.1.9 Benzyl 2,3-bis(3,4,5-tris(benzyloxy)benzoyl)-β-D-glucopyranoside



A solution of precursor (2.00 g, 1.66 mmol) and iodine (421 mg, 1.66 mmol) in dry CH_3OH (17 mL) and dry CH_2Cl_2 (17 mL) was heated at reflux under nitrogen for 40 h. The solution was cooled, diluted with EtOAc (50 mL), washed with satd. $Na_2S_2O_3$ (2 x 50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield 1.83 g (99%) of the title compound as a white solid foam.
M.p. 168-170 °C; $[\alpha]_D^{28}$= +70.0 (c 1.5, $CHCl_3$); R_f 0.50 (SiO_2, EtOAc: Pet. ether, 2:1); ν_{max} (neat) 3424, 1718, 1587, 1499, 1454, 1334, 1198, 1087, 730 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49-7.20 (39H, m, Ar-H), 5.56 (1H, t, *J* = 9.6, C[2]H), 5.30 (1H, t, *J* = 9.6, C[3]H), 5.14 (2H, d, *J* = 2.2, CH_2), 5.12 (6H, s, CH_2), 5.05-4.92 (5H, m, CH_2), 4.80 (1H, d, *J* = 8.0, C[1]H), 4.73 (1H, d, *J* = 12.5, CH_2), 4.08 (1H, dd, *J* = 11.9, 3.0, C[6]H), 4.09-3.94 (2H, m, C[4]H & C[6]H), 3.77 (1H, bs, OH), 3.63-3.59 (1H, m, C[5]H), 2.35 (1H, bs, OH); δ_C (100 MHz, $CDCl_3$) 167.6 (C), 165.0 (C), 152.6 (C), 152.6 (C), 143.0 (C), 142.9 (C), 137.38 (C), 137.36 (C), 136.8 (C), 136.53 (C), 136.51 (C), 128.6 (CH), 128.52 (CH), 128.48 (CH), 128.45 (CH), 128.4 (CH), 128.22 (CH), 128.20 (CH), 128.10 (CH), 128.06 (CH), 127.99 (CH), 127.96 (CH), 127.88 (CH), 127.64 (CH), 127.58 (CH), 124.3 (C), 123.7 (C), 109.36 (CH), 109.34 (CH), 99.5 (CH), 78.3 (CH), 76.8 (CH), 76.0 (CH_2), 75.2 (CH), 71.7 (CH_2), 71.22 (CH_2), 71.15 (CH_2), 71.0 (CH_2), 70.2 (CH), 62.4 (CH_2); HRMS found ESI $[M+Na]^+$ 1137.4065, $[C_{69}H_{62}O_{14}Na]^+$ requires 1137.4037.

2.1.10 Benzyl 4,6-*O*-bis(2-bromo-3,4,5-tris-(benzyloxy)benzoyl)-2,3-bis-(3,4,5-tris-(benzyloxy)benzoyl)-8-D-glucopyranoside (2)



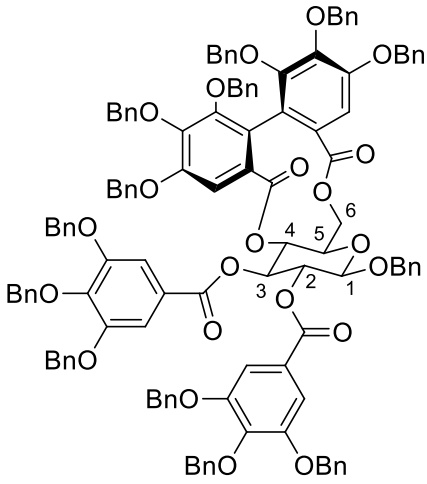
2

A mixture of benzoic acid precursor (213 mg, 0.41 mmol), diol (222 mg, 0.20 mmol), DCC (82 mg, 0.40 mmol), DMAP (6 mg, 0.05 mmol) and CH_2Cl_2 (15 mL) was stirred at room temperature for 18 h. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2-Hexane, 1:10) to give the title compound (301 mg, 71%) as a white solid.

M.p. 147-149 °C; $[\alpha]_D^{28}$ = +18.2 (c 10, $CHCl_3$); R_f 0.46 (SiO_2, CH_2Cl_2-Hexane, 1:10); ν_{max} (neat) 1728, 1329, 1188, 1097, 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53-7.19 (71H, m, Ar-H), 5.82 (1H, t, *J* = 9.5, C[3]H), 5.76 (1H, t, *J* = 9.5, C[4]H), 5.59 (1H, dd, *J* = 9.6, 8.0, C[2]H), 5.21-4.81 (28H, m, [C1]H & CH_2), 4.76 (1H, dd, *J* = 12.2, 3.0, [C6]H), 4.70 (1H, d, *J* = 12.5, CH_2), 4.59 (1H, dd, *J* = 12.2, 4.9, C[6]H), 4.18-4.11 (1H, m, C[5]H); δ_C (125 MHz, $CDCl_3$) 161.9 (C), 161.5 (C), 160.8 (C), 160.6 (C), 148.62 (C), 148.58 (C), 147.9 (C), 147.8 (C), 147.0 (C), 142.3 (C), 139.1 (C), 138.8 (C), 133.4, 132.6 (C), 132.5 (C), 132.4 (C), 124.7 (C), 124.6 (C), 124.5 (C), 124.43 (C), 124.37 (C), 124.3 (C), 123.6 (CH), 108.5 (CH), 107.7 (CH), 106.4 (CH), 105.4 (CH), 105.2 (CH), 99.4 (CH), 73.3 (CH_2), 73.1 (CH_2), 72.8 (CH_2), 71.8 (CH_2), 71.5 (CH_2), 71.2 (CH_2), 71.1 (CH_2), 69.5 (CH), 68.1 (CH), 67.8 (CH), 67.3 (CH_2), 67.2 (CH_2), 67.1 (CH_2), 66.7 (CH_2), 66.0 (CH), 59.8 (CH_2); HRMS found ESI $[M+Na]^+$ 2137.5152, $[C_{125}H_{104}O_{22}Br_2Na]^+$ requires 2137.5278.

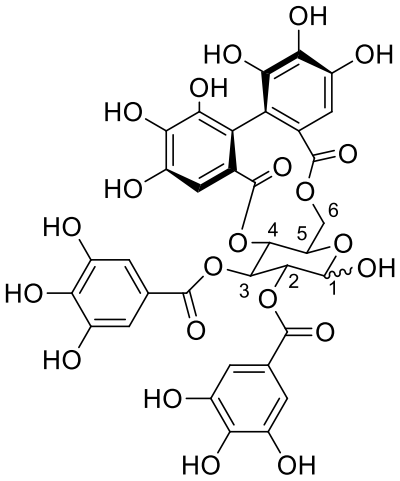
2.2 Coupling Reaction

2.2.1 Benzyl Ether-Protected Tellimagrandin I



A flame dried round bottom flask containing the bromide precursor (85 mg, 0.04 mmol) and THF (2 mL) under Argon was charged with Rieke Zinc (1 mL, 5 g/100 mL in THF) and the reaction mixture heated at 80 °C for 3 h. The suspension was allowed to settle and the resulting supernatant was transferred *via* cannula onto the copper (I) bromide dimethyl sulfide complex (8 mg, 0.04 mmol) contained in a second round bottom flask. The oxidant (24 mg, 0.08 mmol) and THF (2 mL) were then added and the solution stirred for 1 h at RT. The reaction mixture was filtered through a plug of silica, washed (EtOAc-hexane, 1:20), and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound (53 mg, 68%) as a brown solid.
M.p. 71-73 °C, $[\alpha]_D^{28}$ = +10 (c 0.18, $CHCl_3$); R_f 0.45 (SiO_2, EtOAc-hexane, 1:20); ν_{max} (neat) 1721, 1587, 1453, 1428, 1331, 1092, 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53-7.08 (62H, m, Ar-H), 7.06-6.81 (9H, m, Ar-H), 5.70-5.52 (2H, m, C[3]H & C[2]H), 5.49-5.35 (2H, m, C[6]H & C[4]H), 5.26-4.63 (27H, m, C[1]H, -CH_2), 4.16-4.07 (2H, m, C[6]H & C[5]H); δ_C (125 MHz, $CDCl_3$) 168.1 (C), 167.3 (C), 166.5 (C), 165.3 (C), 153.2 (C), 153.2 (C), 153.09 (C), 153.06 (C), 152.9 C), 152.8 (C), 145.2 (C), 145.0 (C), 143.5 (C), 143.3 (C), 138.2 (C), 138.1 (C), 137.9 (C), 137.1 (C), 137.0 (CH), 136.98 (CH), 136.93 (C), 129.2 (CH), 129.13 (CH), 129.09 (CH), 129.0 (CH), 128.97 (CH), 128.88 (CH), 128.86 (CH), 128.78 (CH), 128.75 (CH), 128.66 (CH), 128.63 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.15 (CH), 128.13 (CH), 127.9 (CH), 124.8 (C), 124.5 (C), 124.1 (C), 124.0 (C), 109.93 (C), 109.85 (C), 108.4 (CH), 108.3 (CH), 100.4 (CH), 76.04 (CH_2), 76.00 (CH_2), 75.7 (CH_2), 75.7 (CH_2), 75.6 (CH_2), 75.4 (CH_2), 74.1 (CH_2), 72.8 (CH), 72.3 (CH), 71.8 (CH_2), 71.7 (CH_2), 71.3 (CH_2), 71.0 (CH), 63.8 (CH_2); HRMS found ESI $[M+Na]^+$ 1979.6849, $[C_{125}H_{104}O_{22}Na]^+$ requires 1979.6911.

2.2.2 Tellimagrandin I (TI)



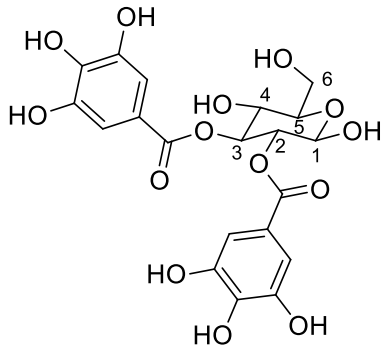
TI

A round bottom flask containing a solution of benzyl protected tellimagrandin I (40 mg, 0.02 mmol) in THF (10 mL) was charged with 10% Pd/C (25 mg, 10 wt. % loading). The system was purged several times with hydrogen and stirred under a balloon of hydrogen for 15 h. The reaction mixture was then filtered through Celite® and the filtrate concentrated at reduced pressure to give the tellimagrandin I (16 mg, 99%) as brown amorphous powder. The crude product was isolated in >95% purity as determined by ^{1}H NMR analysis. An analytically pure sample was prepared by purification of the crude product material using reverse phase column chromatography (stationary phase = KP-C18-HS, 60 Å, solution phase = MeOH-H_2O, 10:1).

M.p. 79-81°C; $[\alpha]_D^{28}$ = +139.8 (c 0.25, acetone), lit.[9] $[\alpha]_D^{28}$ = +140.7 (c 0.1, acetone); ν_{max} (neat) 3650-3000, 1705, 1614, 1446, 1318, 743 cm^{-1}; δ_H (500 MHz, C_3D_6O) 7.08 (2H, s, Ar-Hα), 7.07 (2H, s, Ar-Hβ), 7.00 (2H, s, Ar-H), 6.96 (2H, s, Ar-Hβ), 6.67 (1H, s, Ar -Hβ), 6.66 (1H, s, Ar-Hβ)), 6.48 (1H, s, Ar-Hα)), 6.45(1H, s, Ar-Hβ), 5.90 (1H, t, *J* = 10.0, C[3α]H), 5.64 (1H, t, *J* = 9.8, C[3β]H), 5.58 (1H, d, *J* = 3.7, C[1α]H), 5.35-5.23 (3H, m, C[1β]H, C[6α]H & C[6β]H), 5.16-5.09 (4H, m, C[4α]H, C[4β]H, C[2α]H & C[2β]H), 4.69 (1H, dd, *J* = 9.9, 6.7, C[5α]H), 4.29 (1H, dd, *J* = 9.7, 6.4, C[5β]H), 3.86 (1H, d, *J* = 13.2, C[6β]H), 3.80 (1H, d, *J* = 12.6, C[6α]H); δ_C (125 MHz, C_3D_6O) 168.1 (C), 168.0 (C), 167.6 (C), 166.4 (C), 166.2 (C), 166.0 (C), 165.5 (C), 145.9 (C), 145.8 (C), 145.61 (C), 145.58 (C), 145.2 (C), 144.3 (C), 138.7 (C), 136.2 (C), 126.7 (C), 126.1 (C), 120.9 (C), 120.8 (C), 115.6 (CH), 115.4 (CH), 109.98 (CH), 109.95 (CH), 108.13 (CH), 108.09 (CH), 107.8 (CH), 96.7 (CH), 91.2 (CH), 74.1 (CH), 73.5 (CH), 72.9 (CH), 72.0 (CH), 71.08 (CH), 71.05 (CH), 71.02 (CH), 67.3 (CH), 63.4 (CH_2); HRMS found ESI $[M+H]^+$ 787.1033, $[C_{34}H_{27}O_{22}]^+$ requires 787.0994.

2.3 Polyphenol Analogues

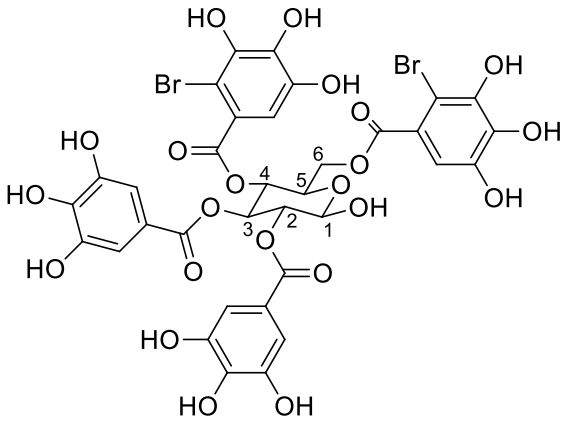
2.3.1 2,3-Digalloyl-D-glucose (3)



3

ν_{max} (neat) 3373, 1696, 1368, 1236 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.04 (2H, bs, OH), 7.00 (4H, s, Ar-H), 6.97 (1H, bs, OH), 5.72 (1H, t, J = 9.7), 5.43 (1H, d, J = 3.5), 5.38 (1H, t, J = 9.5), 5.06 (1H, dd, J = 9.8, 8.0), 4.97 (1H, dd, J = 10.2, 3.5), 4.02-3.96 (1H, m), 3.93-3.72 (6H, bs, OH); δ_C (125 MHz, CD_3OD) 168.3 (C), 167.9 (C), 167.7 (C), 167.4 (C), 146.3 (C), 140.0 (C), 139.8 (C), 121.5 (C), 121.2 (C), 121.1 (C), 120.8 (C), 110.4 (CH), 110.3 (CH), 96.4 (CH), 91.4 (CH), 78.2 (CH), 77.1 (CH), 74.8 (CH), 74.2 (CH), 73.7 (CH), 73.0 (CH), 69.93 (CH), 69.89 (CH), 62.4 (CH_2), 62.3 (CH_2); HRMS found ESI $[M+Na]^+$ 507.0724, $[C_{20}H_{20}O_{14}Na]^+$ requires 507.0745.

2.3.2 2,3-Digalloyl-4,5-di(bromo)galloyl-D-glucose (4)



4

ν_{max} (neat) 3313, 1738, 1365,1228, 1217, 1016 cm^{-1}; (mixture of anomers α:β-2:1) δ_H (500 MHz, CD_3OD) 7.13 (1H, Ar-H), 7.12 (1H, s, Ar-H), 7.01 (2H, s, Ar-H), 6.99 (2H, s, Ar-H), 6.97 (2H, s, Ar-H), 6.93 (2H, s, Ar-H), 6.82 (1H, s, Ar-H), 6.78 (1H, s, Ar-H), 6.00 (1H, t, J = 9.8), 5.74 (1H, t, J =

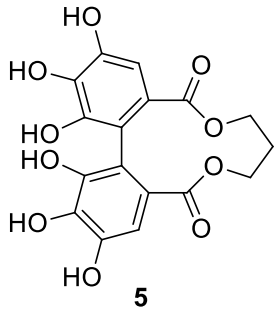
9.6) 5.64-5.56 (2H, m), 5.51 (1H, d, *J* = 3.5), 5.22 (1H, dd, *J* = 9.7, 8.0), 5.14 (1H, dd, *J* = 10.2, 3.5), 5.06 (1H, d, *J* = 8.0), 4.58-4.44 (5H, m), 4.23-4.19 (1H, m); δ_C (125 MHz,CD_3OD) 166.3 (C), 166.0 (C), 165.97 (C), 165.86 (C), 165.65 (C), 165.4 (C), 144.84 (C), 144.80 (C), 144.75 (C), 144.72 (C), 143.9 (C), 143.8 (C), 143.54 (C), 143.45 (C), 138.63 (C), 138.54 (C), 138.52 (C), 138.46 (C), 137.86 (C), 137.82 (C), 137.78 (C), 121.04 (C), 121.01 (C), 120.9 (C), 120.8 (C), 119.3 (CH), 119.26 (CH), 119.04 (CH), 118.96 (CH), 110.34 (C), 110.29 (C), 109.7 (C), 108.96 (CH), 108.93 (CH), 108.87 (CH), 108.82 (CH), 100.62 (CH), 100.58 (CH), 100.11 (CH), 100.03 (CH), 99.0 (CH), 89.9 (CH), 73.1 (CH), 72.8 (CH), 71.9 (CH), 71.6 (CH), 70.1 (CH), 69.2 (CH), 69.0 (CH_2), 66.8 (CH), 62.7 (CH_2); HRMS found ESI $[M+Na]^+$ 966.9216, $[C_{34}H_{26}O_{22}Br_2Na]^+$ requires 966.9175.

2.4 Medium Ring Analogue Synthesis

General Procedure for the Synthesis of Medium Ring Analogues, Procedure A:

A mixture of the diacid (176.0 mg, 0.20 mmol), the diol (0.20 mmol), DCC (41.2 mg, 0.20 mmol), DMAP (6.0 mg, 0.05 mmol) and CH_2Cl_2 (15.00 mL) was stirred at room temperature for 12 hr. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in ether (10.00 mL), filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was used in the next step without further purification. To a solution of the resulting compound in THF (10.00 mL) was added Pd/C (100.0 mg) and the reaction was placed under a hydrogen atmosphere. The reaction was stirred overnight and then filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was purified by HPLC to get the Medium Ring Analogue.

2.4.1 1,2,3,13,14,15-hexahydroxy-8,9-dihydro-5H-dibenzo[g,i][1,5]dioxacyclounDecine-5,11(7H)-dione (5)

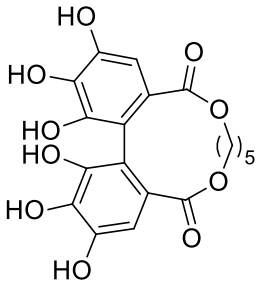


5

Prepared according to the previously reported literature procedure.[10]

ν_{max} (neat)/cm^{-1} 3119, 1686, 1614, 1514, 1398, 1340, 1247, 1188, 1041; δ_H (500 MHz, d_6-DMSO) 9.23 (1H, br s, OH), 8.70 (1H, br s, OH), 8.02 (1H, br s, OH), 7.01 (3H, br s, OH), 6.37 (2H, s, Ar-H), 4.57-4.40 (2H, m), 3.92-3.88 (2H, m), 1.97-1.92 (2H, m); HRMS found ESI $[M+H]^+$ 379.0658, $[C_{17}H_{15}O_{10}]^+$ requires 379.0665.

2.4.2 1,2,3,15,16,17-Hexahydroxy-8,9,10,11-tetrahydro-5H-dibenzo[i,k][1,7]dioxacyclotridecine-5,13(7H)-dione (6)

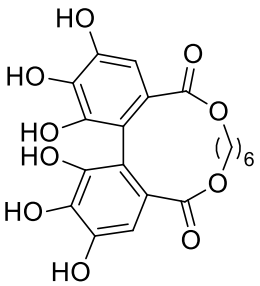


6

Prepared according the general procedure A using 1,5-Pentanediol (20.8 mg, 0.2 mmol). The desired product was isolated in 33% yield (26.6 mg), over 2 steps.

ν_{max} (neat) 3345, 1702, 1618, 1313, 1221, 1023 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.14 (2H, s, Ar-H), 3.96-3.86 (4H, m), 1.54-1.39 (4H, m), 1.24-1.13 (2H, m); δ_C (125 MHz, CD_3OD) 168.4 (C), 143.8 (C), 143.3 (C), 137.1 (C), 136.2 (C), 130.8 (C), 121.3 (C), 118.3 (C), 109.4 (CH), 61.3 (CH_2), 27.8 (CH_2), 21.8 (CH_2); HRMS found ESI $[M+Na]^+$ 429.0801, $[C_{19}H_{18}O_{10}Na]^+$ requires 429.0792.

2.4.3 1,2,3,16,17,18-Hexahydroxy-7,8,9,10,11,12-hexahydrodibenzo[c,e][1,8]dioxacyclotetradecine-5,14-dione (7)

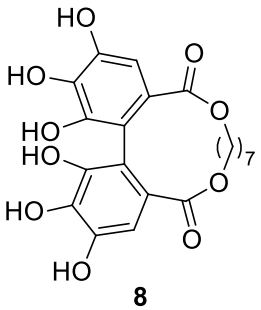


7

Prepared according the general procedure A using 1,6-Hexanediol (23.6 mg, 0.20 mmol). The desired product was isolated in 22% yield (18.1 mg), over 2 steps.

ν_{max} (neat) 3359, 1698, 1615, 1316, 1228, 1020 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.01 (2H, s, Ar-H), 4.47 (2H, dt, J = 11.4, 2.0), 3.83-3.80 (2H, m), 1.87-1.81 (2H, m), 1.58-1.40 (2H, m), 1.18-1.12 (2H, m); δ_C (125 MHz, CD_3OD) 168.7 (C), 145.2 (C), 145.0 (C), 138.4 (C), 123.0 (C), 119.3 (C), 110.6 (CH), 62.5 (CH_2), 28.6 (CH_2), 23.5 (CH_2); HRMS found ESI $[M+H]^+$ 421.1120, $[C_{20}H_{21}O_{10}]^+$ requires 421.1188.

2.4.4 1,2,3,17,18,19-Hexahydroxy-8,9,10,11,12,13-hexahydro-5H-dibenzo[c,e][1, 8]dioxacyclopentadecine-5,15(7H)-dione (8)

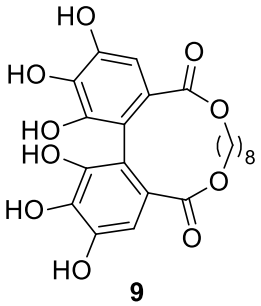


8

Prepared according the general procedure A using 1,7-Heptanediol (26.3 mg, 0.20 mmol), The desired product was isolated in 20% yield (17.5 mg), over 2 steps.

ν_{max} (neat)/cm^{-1} 3387, 1689, 1593, 1319, 1214, 1046; δ_H (500 MHz, CD_3OD) 7.15 (2H, s, Ar-H), 4.12-4.10 (2H, m), 3.95 (2H, t, J = 10.0), 1.47-1.33 (8H, m), 1.26-1.12 (2H, m); δ_C (125 MHz, CD_3OD) 168.7 (C), 145.2 (C), 145.0 (C), 138.4 (C), 123.0 (C), 119.3 (C), 110.6 (CH), 66.0 (CH_2), 28.6 (CH_2), 28.1 (CH_2) 26.1 (CH_2); HRMS found ESI $[M+H]^+$ 435.1277, $[C_{21}H_{23}O_{10}]^+$ requires 435.1286.

2.4.5 1,2,3,18,19,20-Hexahydroxy-7,8,9,10,11,12,13,14-octahydrodibenzo[c,e][1, 8]dioxacyclohexadecine-5,16-dione (9)

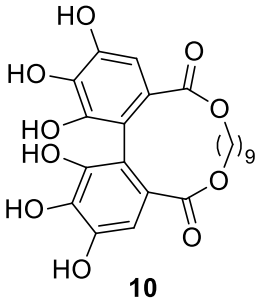


9

Prepared according the general procedure A using 1,7-Octanediol (29.2 mg, 0.20 mmol). The desired product was isolated in 17% yield (15 mg), over 2 steps.

ν_{max} (neat)/cm^{-1} 3316, 1738, 1617, 1365, 1228, 1040; δ_H (500 MHz, CD_3OD) 7.21 (2H, s, Ar-H), 4.07-4.00 (2H, m), 3.76-3.69 (2H, m), 1.89-1.86 (2H, m), 1.44-1.43 (4H， m), 1.30-1.23 (6H, m); δ_C (125 MHz, CD_3OD) 169.0 (C), 145.1 (C), 144.7 (C), 138.9 (C), 122.0 (C), 120.6 (C), 111.2 (CH), 65.0 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 26.5 (CH_2), 25.1 (CH_2); HRMS found ESI $[M+H]^+$ 449.1435, $[C_{22}H_{25}O_{10}]^+$ requires 449.1442.

2.4.6 1,2,3,19,20,21-Hexahydroxy-8,9,10,11,12,13,14,15-octahydro-5H-dibenzo[c,e][1,8]dioxacycloheptadecine-5,17(7H)-dione (10)

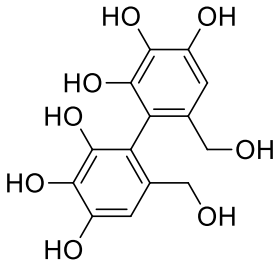


10

Prepared according the general procedure A using 1,7-Nonanediol (32.0 mg, 0.20 mmol). The desired product was isolated in 10% yield (10 mg), over 2 steps.

ν_{max} (neat) 3446, 1738, 1365, 1228, 1216 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.17 (2H, s, Ar-H), 4.01-3.95 (4H, m), 1.94-1.83 (2H, m), 1.67-154 (4H, m), 1.36-1.23 (8H, m); δ_C (125 MHz, CD_3OD) 169.5 (C), 145.07 (C), 144.7 (C), 138.7 (C), 122.2 (C), 120.4 (C), 110.8 (CH), 64.3 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 25.0 (CH_2); HRMS found ESI $[M+H]^+$ 463.1593, $[C_{23}H_{27}O_{10}]^+$ requires 463.1599.

2.4.7 6,6'-Bis(hydroxymethyl)-[1,1'-biphenyl]-2,2',3,3',4,4'-hexaol (11)



11

Di-*iso*-butylaluminum hydride (1.0 M solution in hexane, 1.00 mL, 1.00 mmol) was added to a solution of ester (200.0 mg, 0.20 mmol) in CH_2Cl_2 (3.50 mL) at 0 °C and stirred for 3 hours. The reaction was quenched by addition of saturated aqueous sodium potassium tartrate solution (5.0 mL) and allowed to warm to room temperature. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (5.0 mL). The combined organic extracts were washed with brine (15.0 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was used in the next step without further purification. To a solution of the resulting compround in THF (10.0 mL) was added Pd/C (100.0 mg) and the reaction was placed under a hydrogen atmosphere (balloon). The reaction was stirred overnight and then filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was purified by HPLC to obtain the diol as a white solid (76.8 mg, 38.4%)

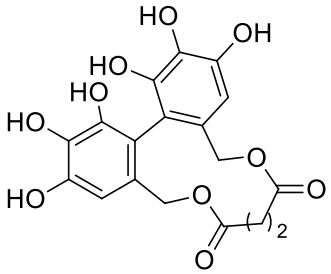
ν_{max} (neat) 3294, 1014 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.33 (2H, s, Ar-H), 5.41 (1H, s), 4.01 (1H, s), 1.76 (8H, m); δ_C (125 MHz, CD_3OD) 146.1 (C), 146.0 (C), 145.08 (C), 145.06 (C), 131.9 (C), 129.83 (C),

129.75 (C), 116.3 (C), 109.6 (CH), 19.44 (CH_2), 19.37 (CH_2) (isolated as a mixture of atropisomers); HRMS found ESI $[M+H]^+$ 311.0717, $[C_{14}H_{15}O_8]^+$ requires 311.0761.

General Procedure for the synthesis of medium ring analogues: Procedure B

A mixture of appropriate diol (127.0 mg, 0.15 mmol), the diacid (0.15 mmol), DCC (30.9 mg, 0.15 mmol), DMAP (6.0 mg, 0.05 mmol) and CH_2Cl_2 (10.0 mL) was stirred at room temperature for 12 hr. The resulting slurry was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in ether (10.0 mL), filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was used in the next step without further purification. To a solution of the resulting compound in THF (10.0 mL) was added Pd/C (80.0 mg) and the reaction was placed under a hydrogen atmosphere (balloon). The reaction was stirred overnight and then filtered through Celite® and the filtrate concentrated under reduced pressure. The crude product was purified by HPLC to get the deprotected medium ring analogue.

2.4.8 1,2,3,14,15,16-Hexahydroxy-8,9-dihydrodibenzo[h,j][1,6]dioxacyclododecine-7,10(5H,12H)-dione (12)

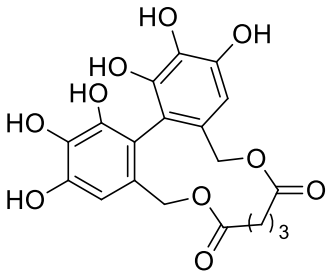


12

Prepared according to the general procedure B using succinic acid (17.7 mg, 0.15 mmol), to yield the product (17.1 mg, 13.5% over two steps) as an off-white solid.

ν_{max} (neat) 3256, 1721, 1345, 1032 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.53 (2H, s, Ar-H), 4.07-4.10 (4H, m), 2.51-2.41 (4H, m); δ_C (125 MHz, CD_3OD) 173.4 (C), 154.1 (C), 144.8 (C), 143.8 (C), 132.8 (C), 126.2 (C), 113.9 (CH), 107.8 (CH), 107.4 (CH), 64.4 (CH_2), 28.1 (CH_2); (isolated as a mixture of atropisomers); HRMS found ESI $[M+Na]^+$ 415.0636, $[C_{18}H_{16}O_{10}Na]^+$ requires 415.0685.

2.4.9 1,2,3,15,16,17-Hexahydroxy-9,10-dihydro-5H-dibenzo[i,k][1,7]dioxacyclotridecine-7,11(8H,13H)-dione (13)



13

Prepared according to the general procedure B using glutaric acid (19.8 mg, 0.15 mmol), to yield the product (27.1 mg, 21.3% over two steps) as an off-white solid.

ν_{max} (neat) 3304, 1707, 1335, 1025 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.55 (2H, s, Ar-H), 4.71-4.63 (4H, m), 2.51-2.36 (4H, m), 1.54-1.45 (2H,m); δ_C (125 MHz, CD_3OD) 173.1 (C), 154.1 (C), 144.7 (C), 143.9 (C), 143.6 (C), 134.7 (C), 133.0 (C), 132.5 (C), 126.6 (C), 126.1 (C), 113.3 (C), 107.9 (CH), 107.4 (CH), 64.6 (CH_2), 30.5 (CH_2), 20.2 (CH_2); (isolated as a mixture of atropisomers); HRMS found ESI $[M+Na]^+$ 429.0813, $[C_{19}H_{18}O_{10}Na]^+$ requires 429.0792.

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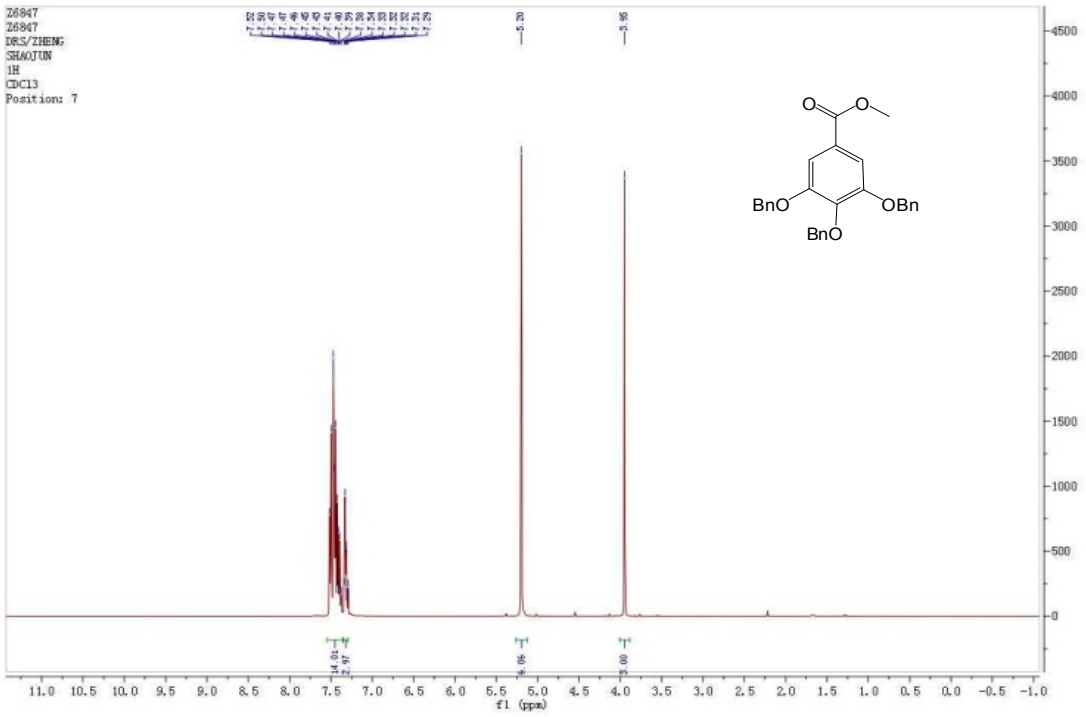
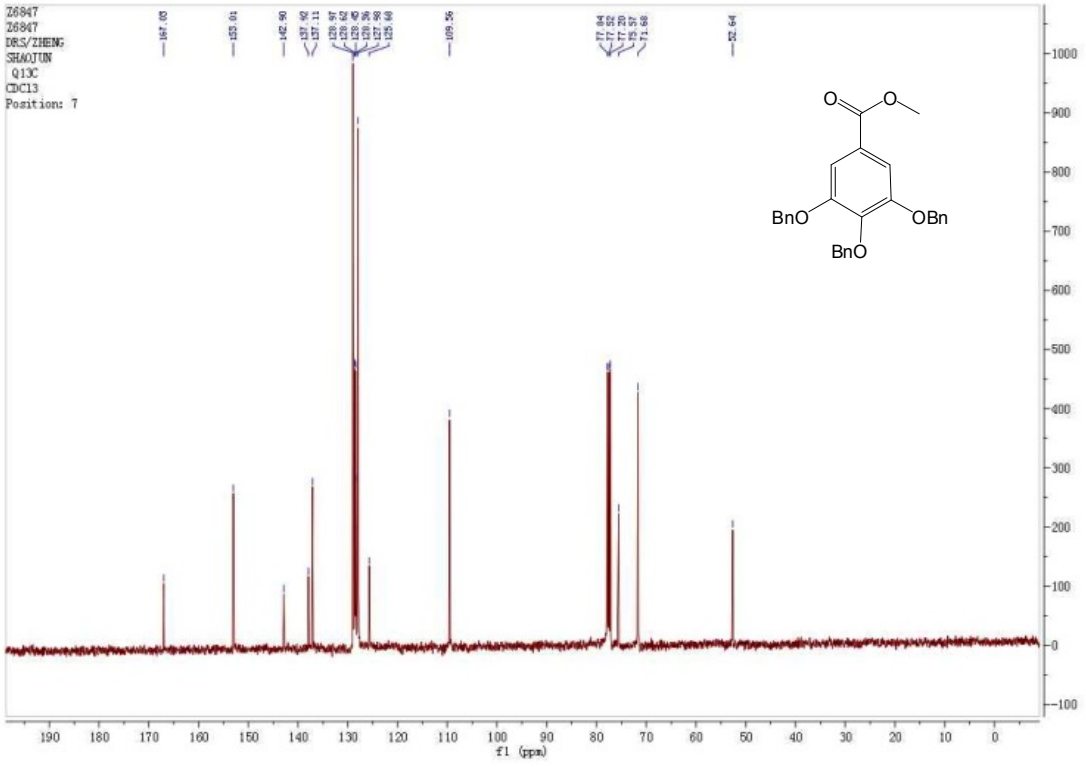
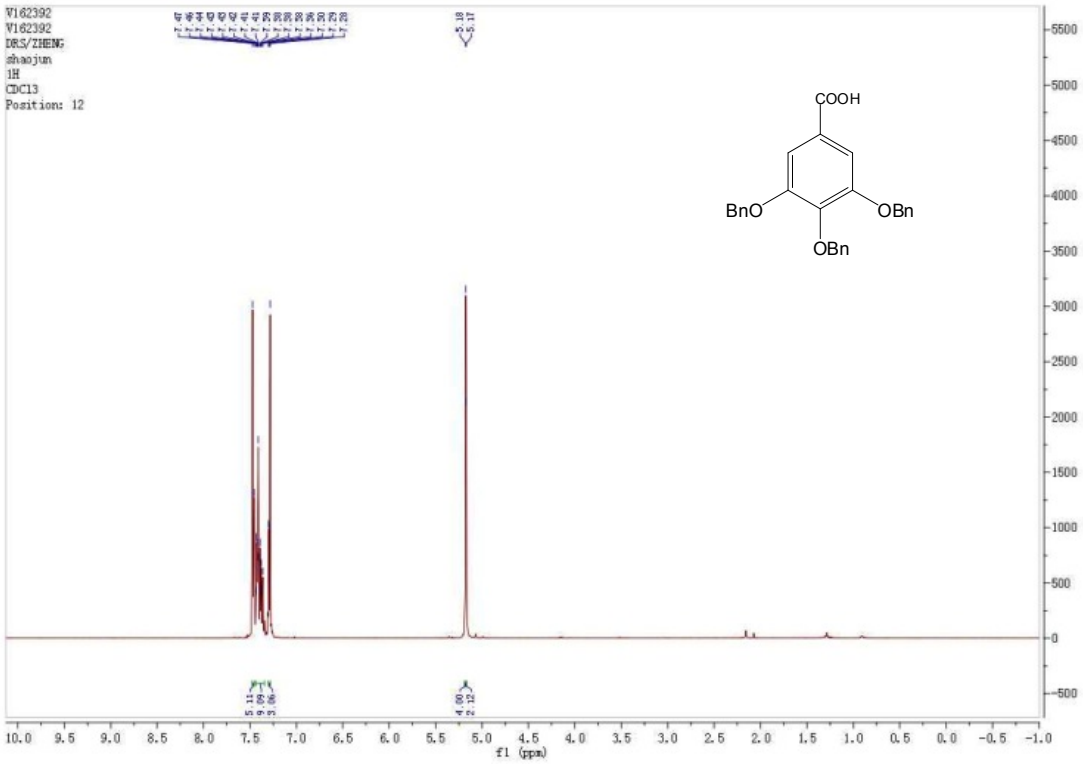
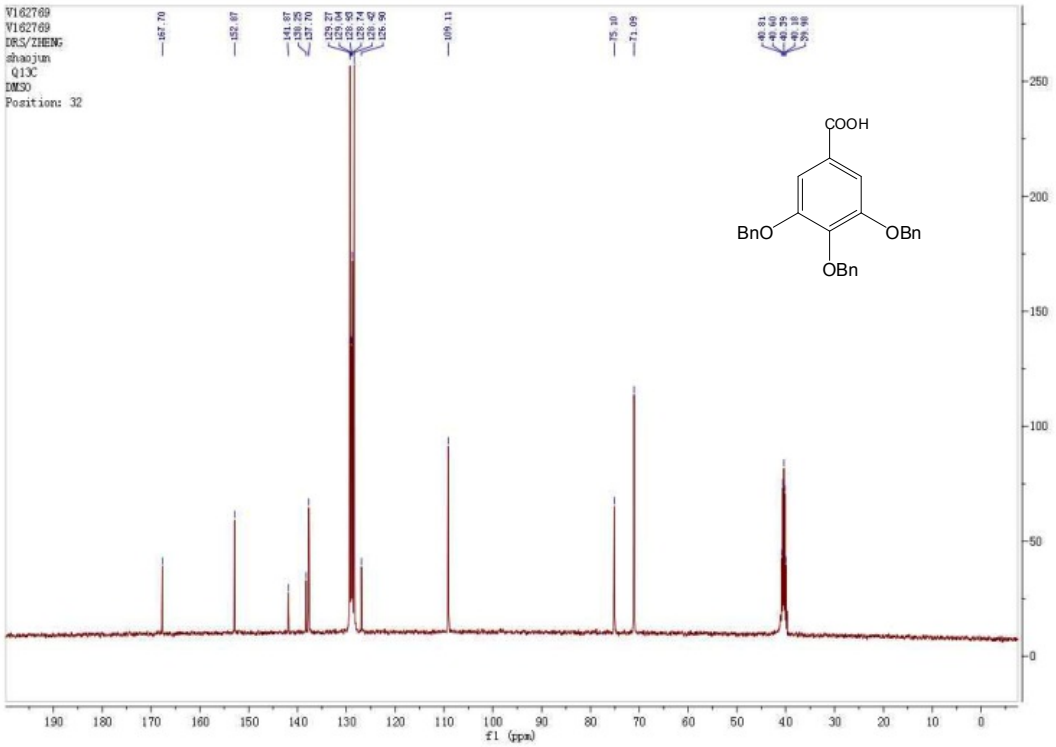
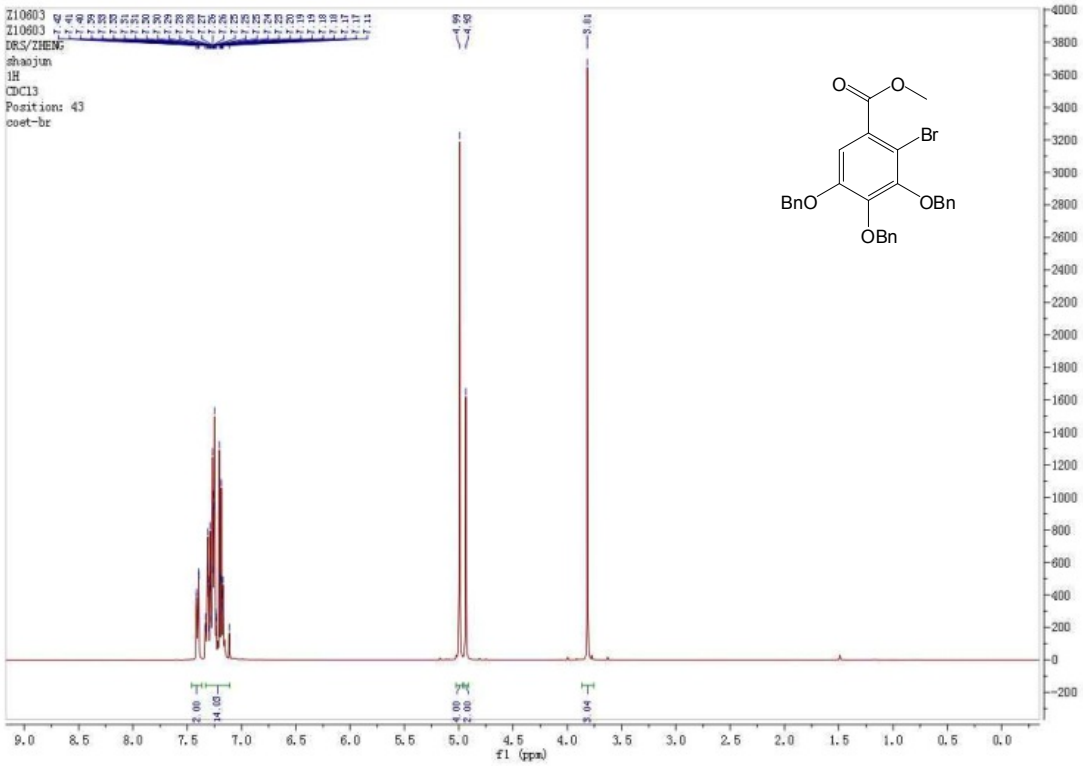
3 Spectra

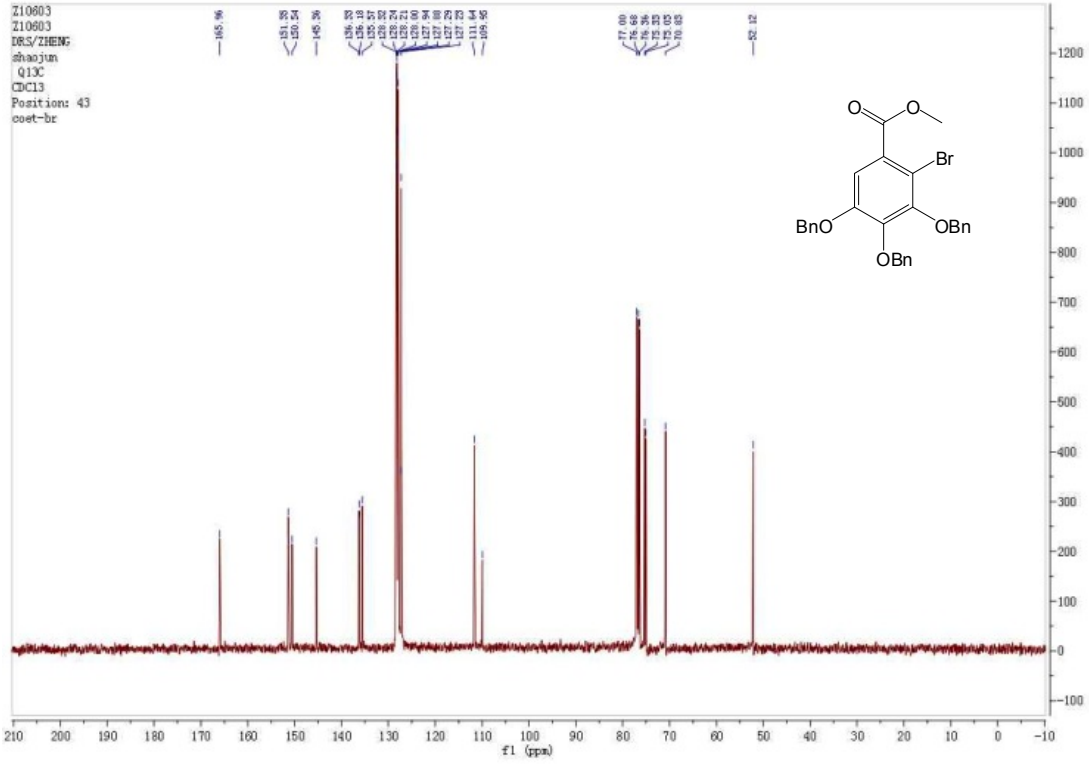


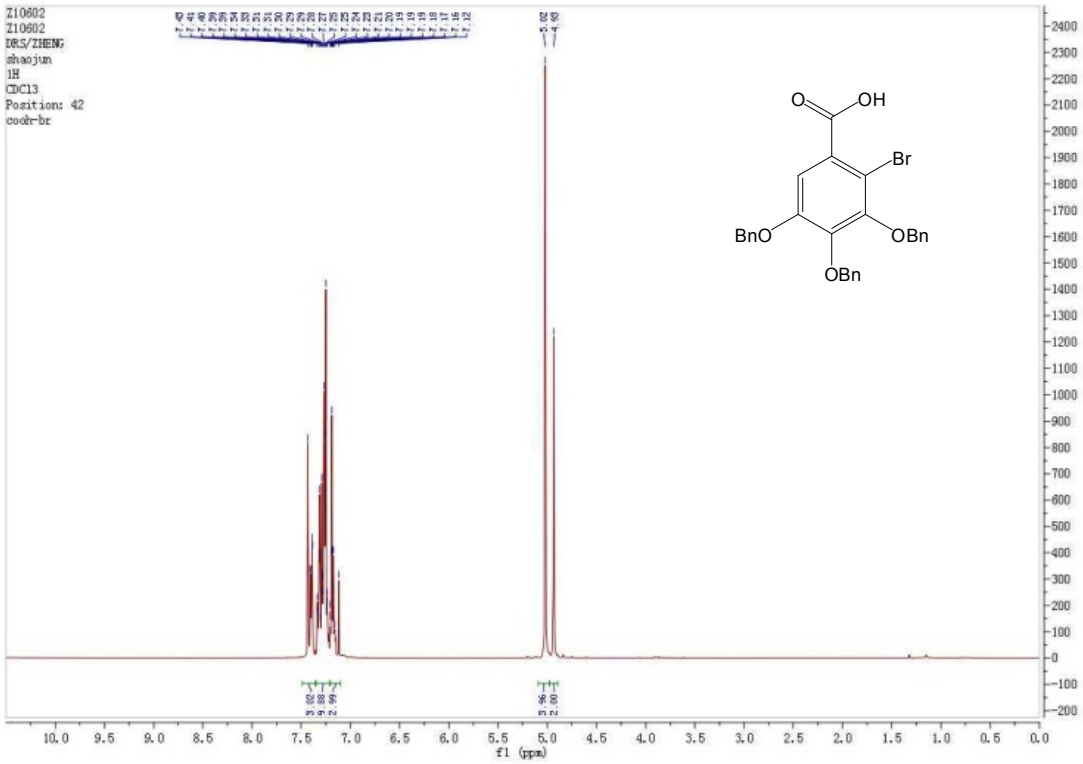


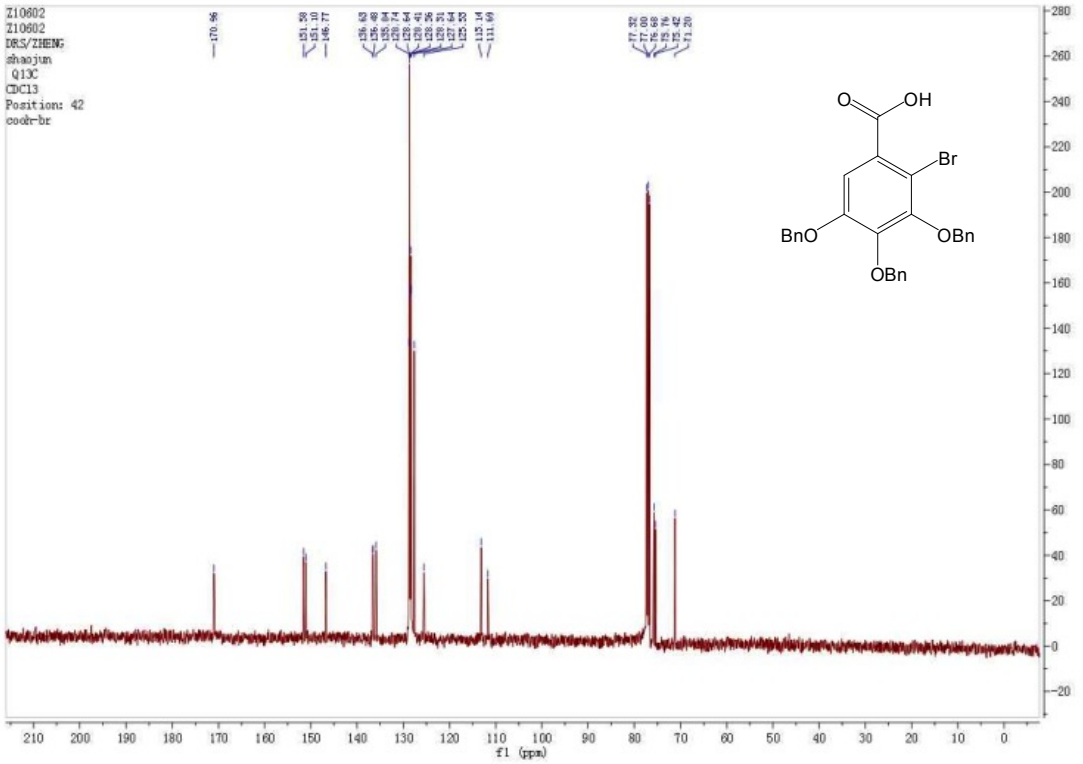


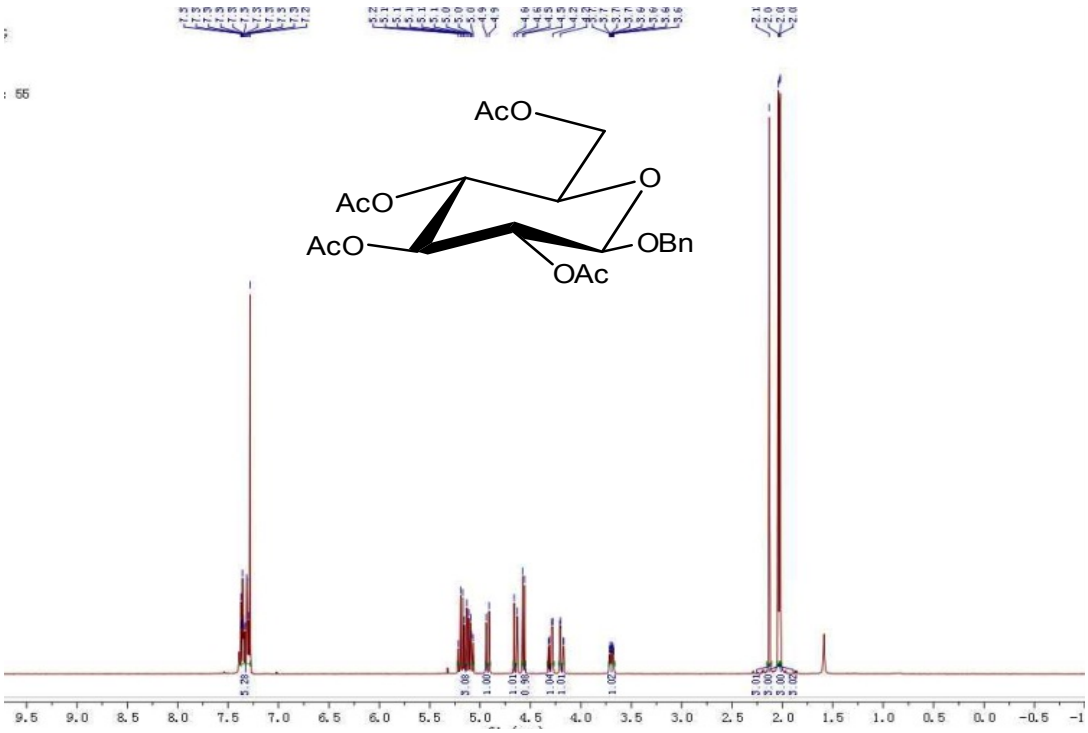








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AcO
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AcO
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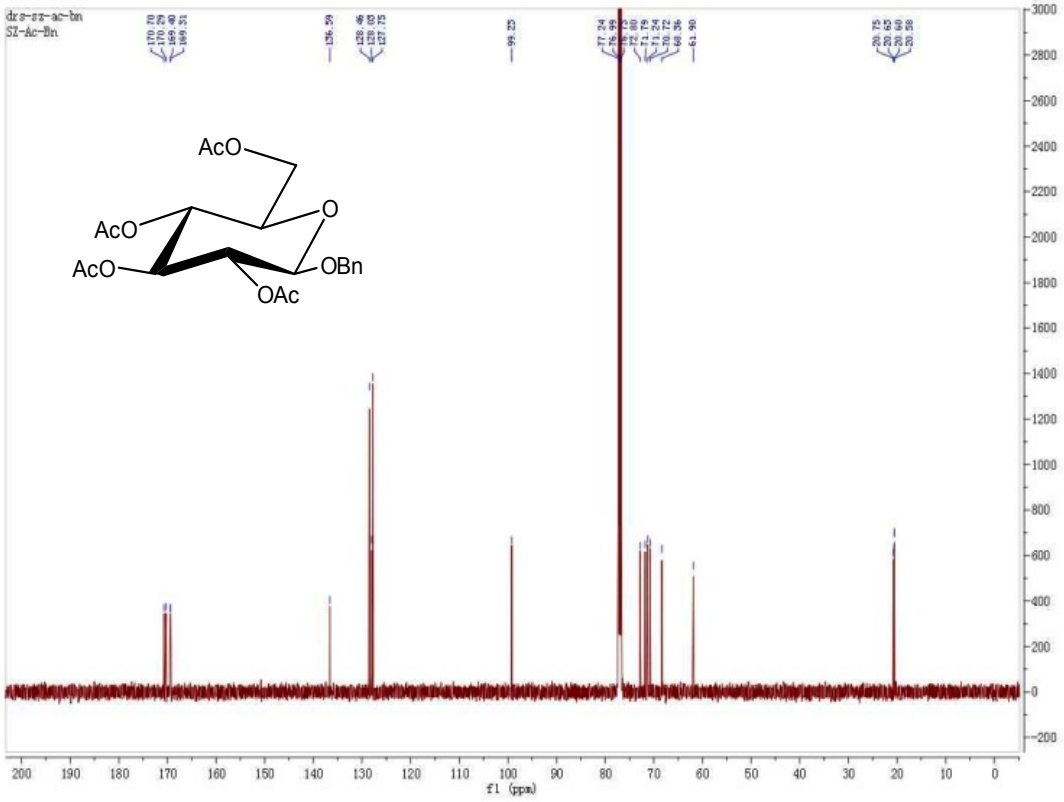
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AcO
OBn
AcO
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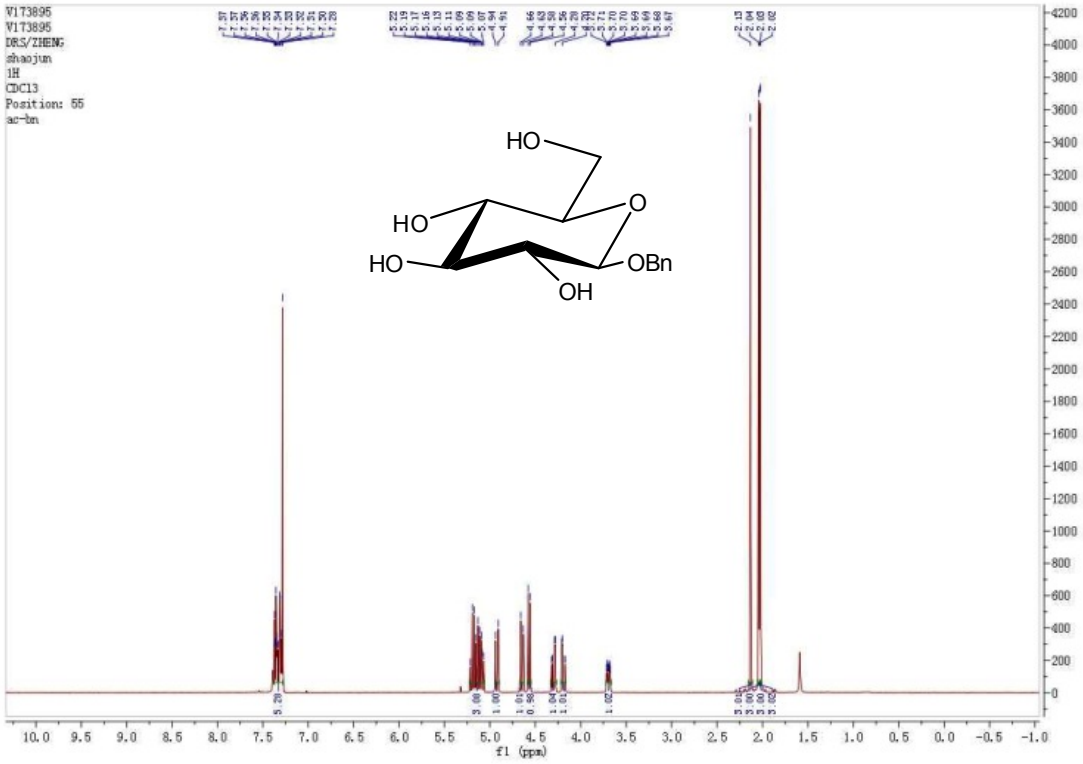
f1 (ppm)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V173895
DRS/ZHENG
shaojun
1H
CDCl3
Position: 55
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HO
HO
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OBn
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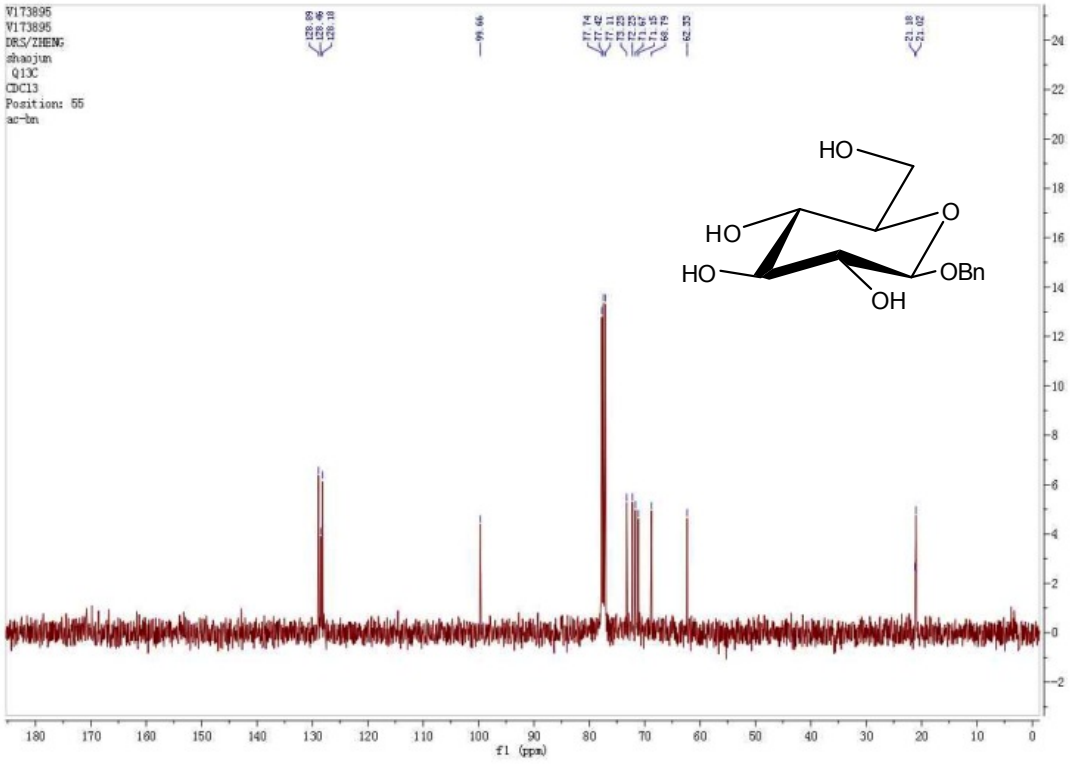
f1 (ppm)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V173895
DRS/ZHENG
shaojun
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CDCl3
Position: 55
ac-bn
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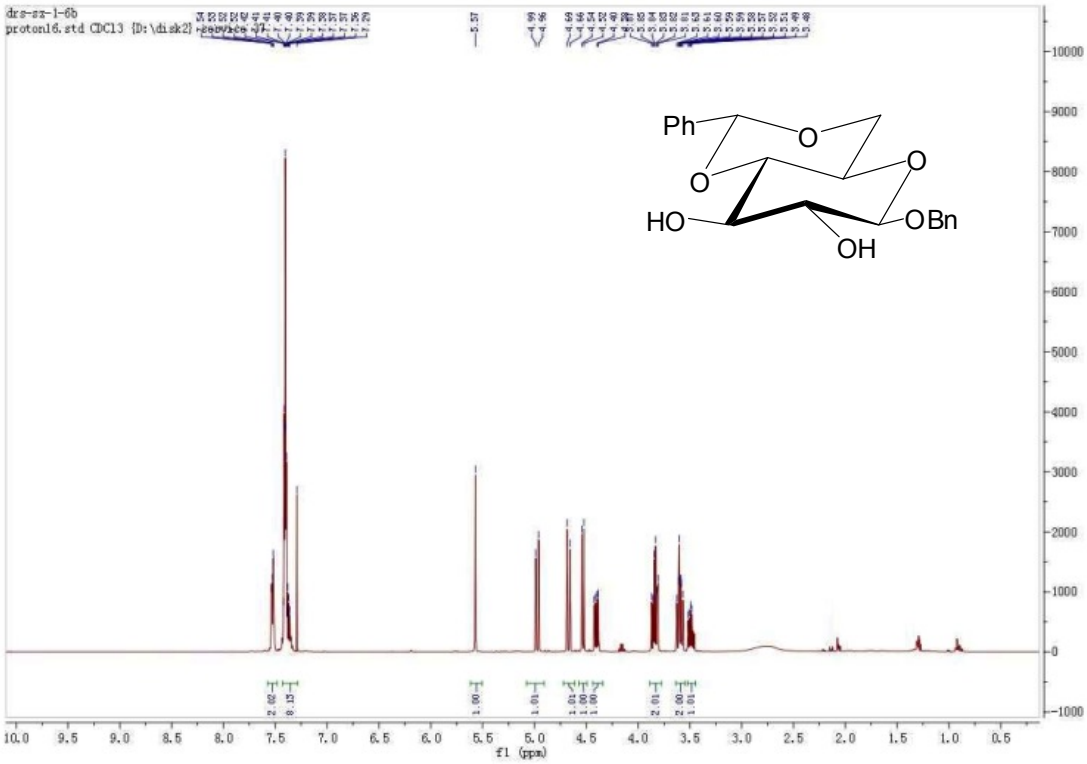
f1 (ppm)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HO
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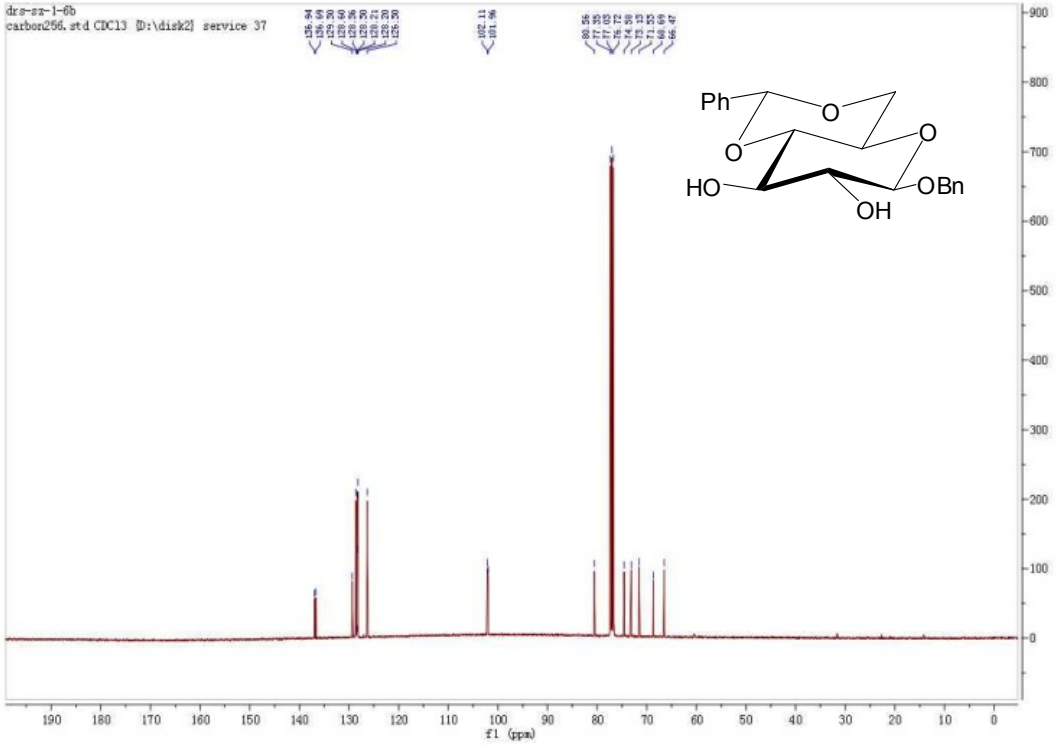
f1 (ppm)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HO
OBn
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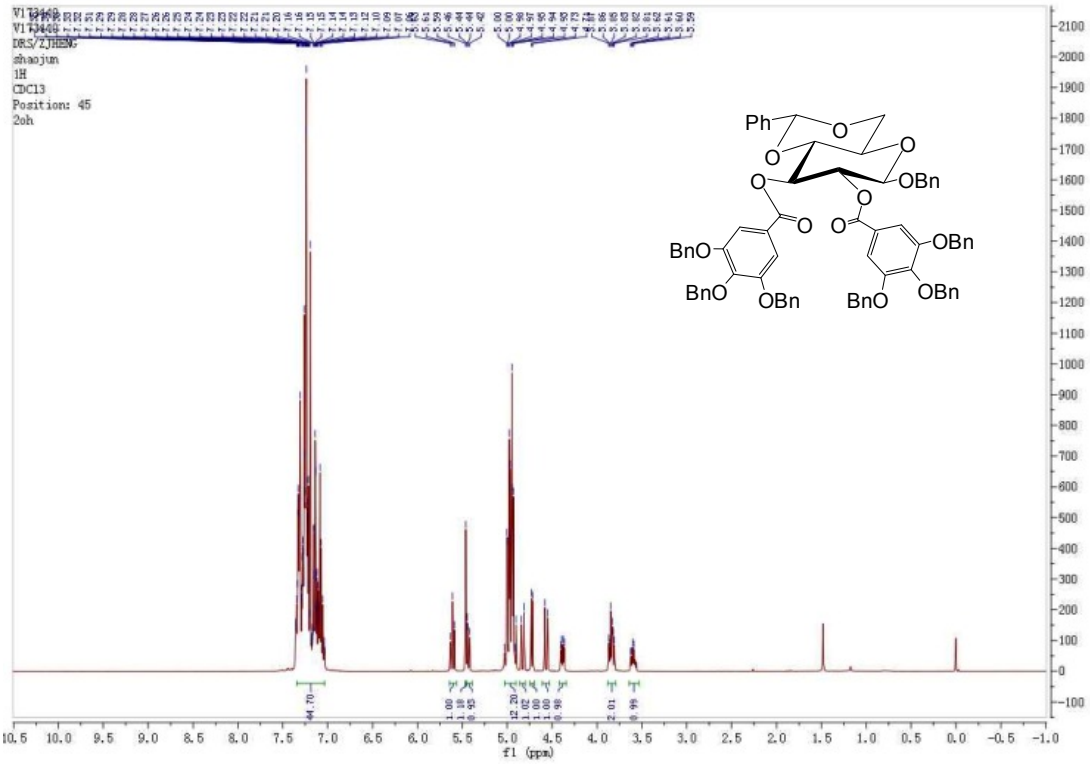
f1 (ppm)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V173440
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1H
CDCl3
Position: 45
2oh
Ph
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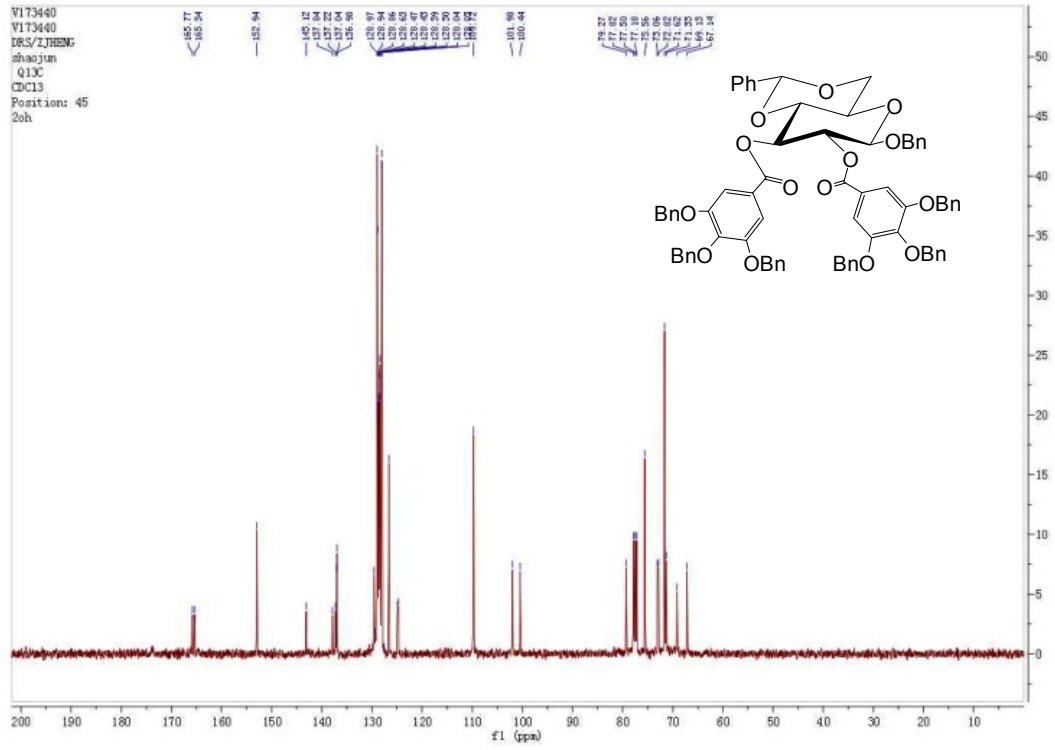
OBn
BnO
f1 (ppm)


V173440
V173440
DRS/ZJHENG
shaojun
Q13C
CDCl3
Position: 45
2oh
Ph
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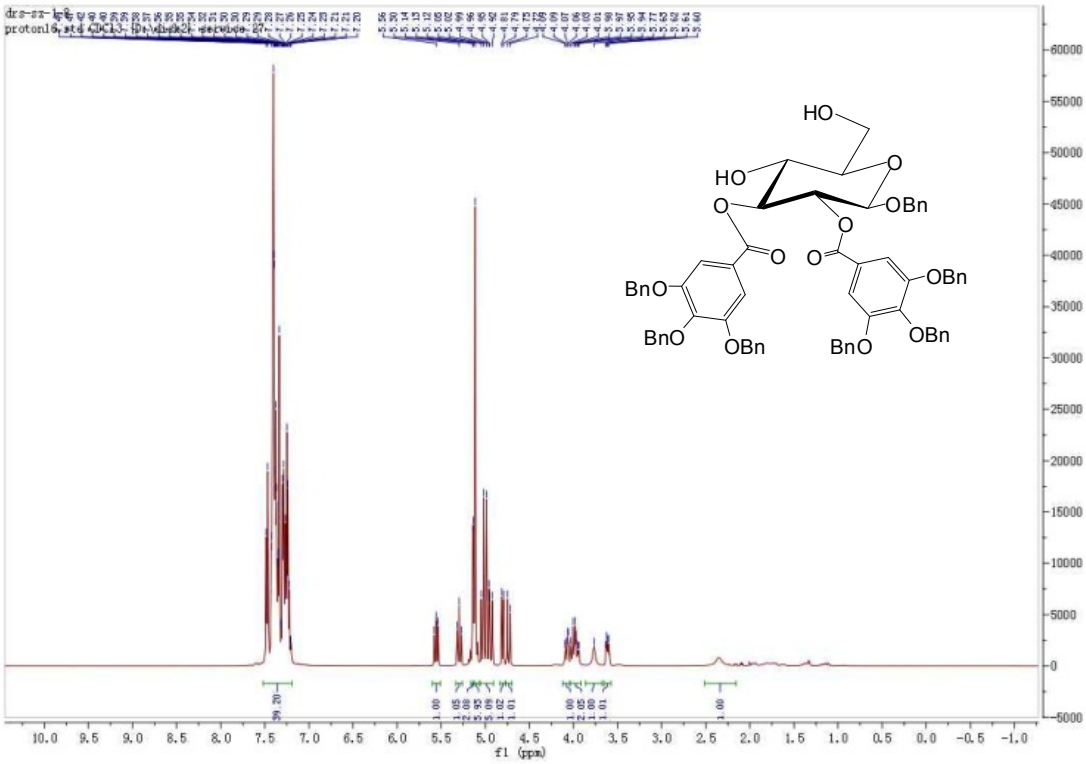
OBn
BnO
f1 (ppm)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BnO
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OBn
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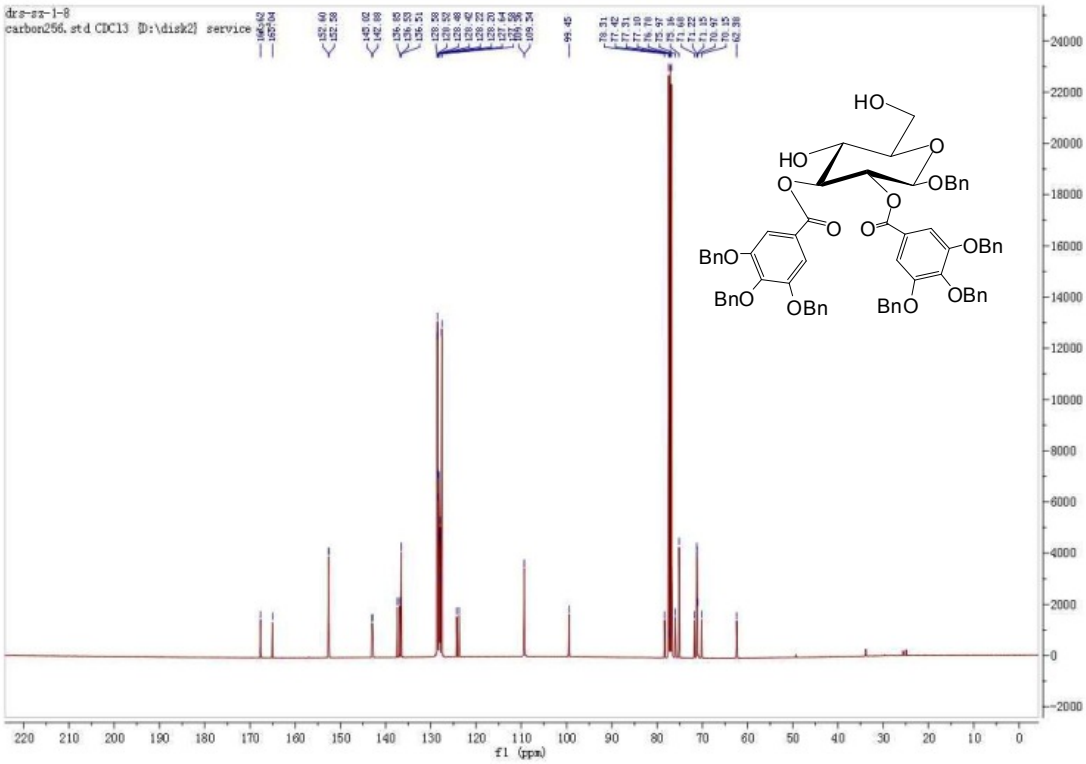
OBn
f1 (ppm)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BnO
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OBn
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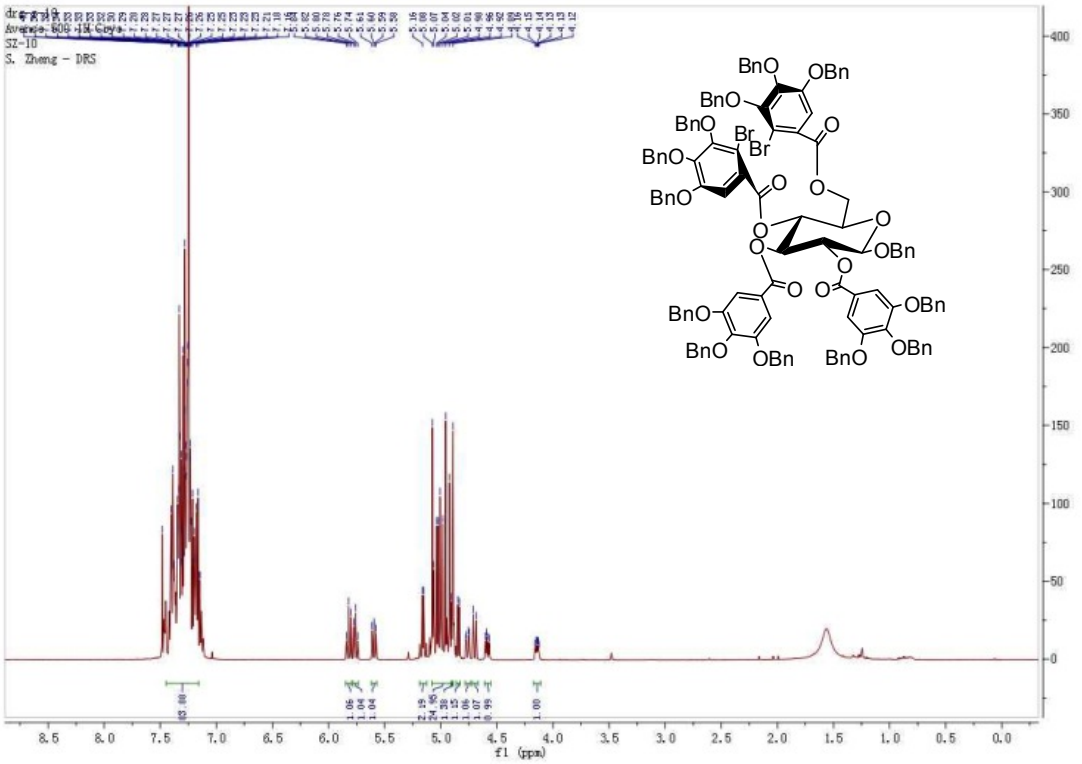
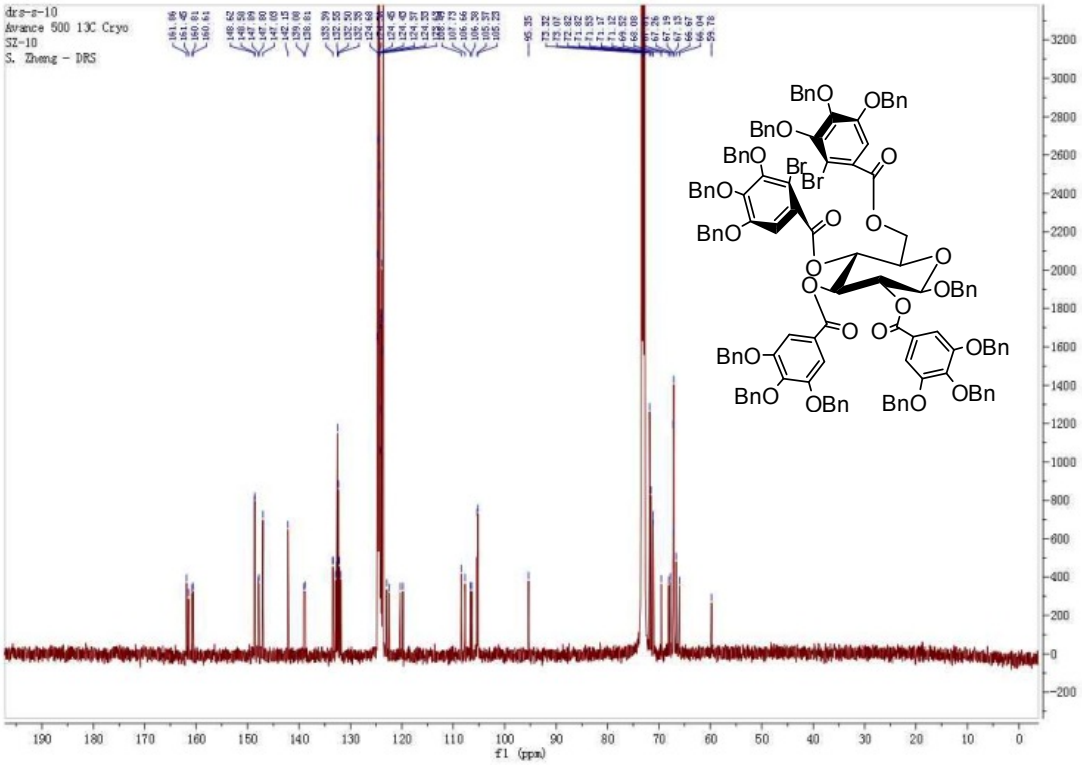
OBn
f1 (ppm)


SZ-10
S. Zheng - DRS
f1 (ppm)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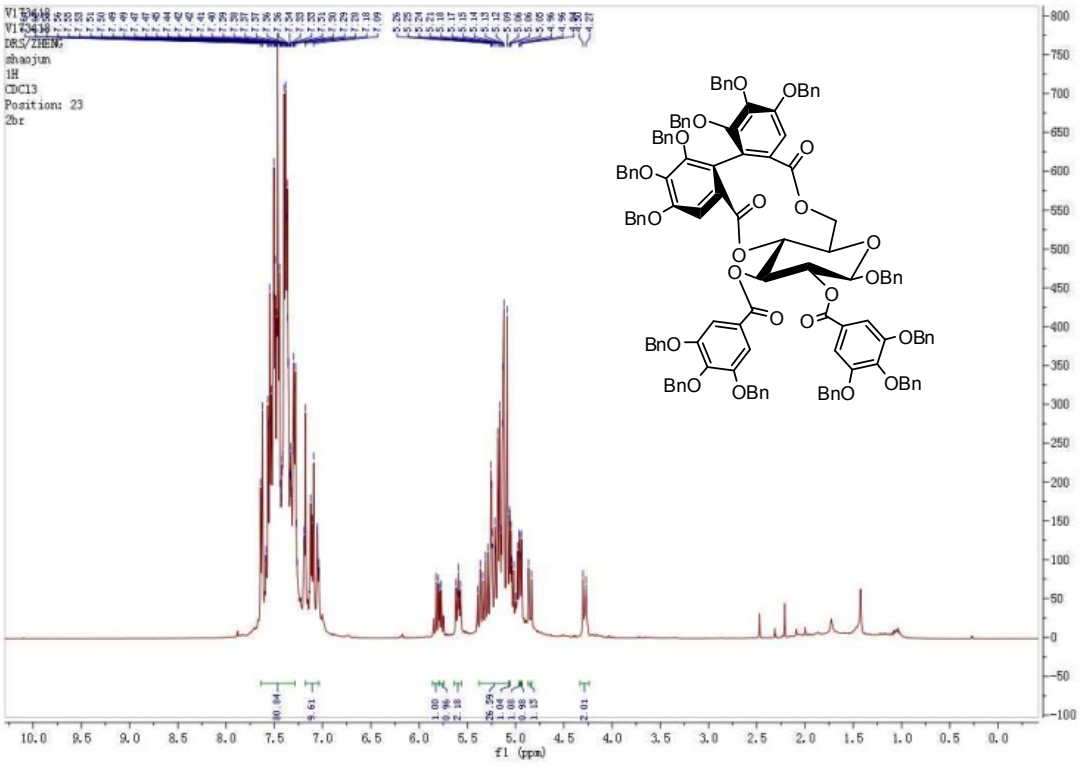
S. Zheng - DRS
f1 (ppm)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CDCl3
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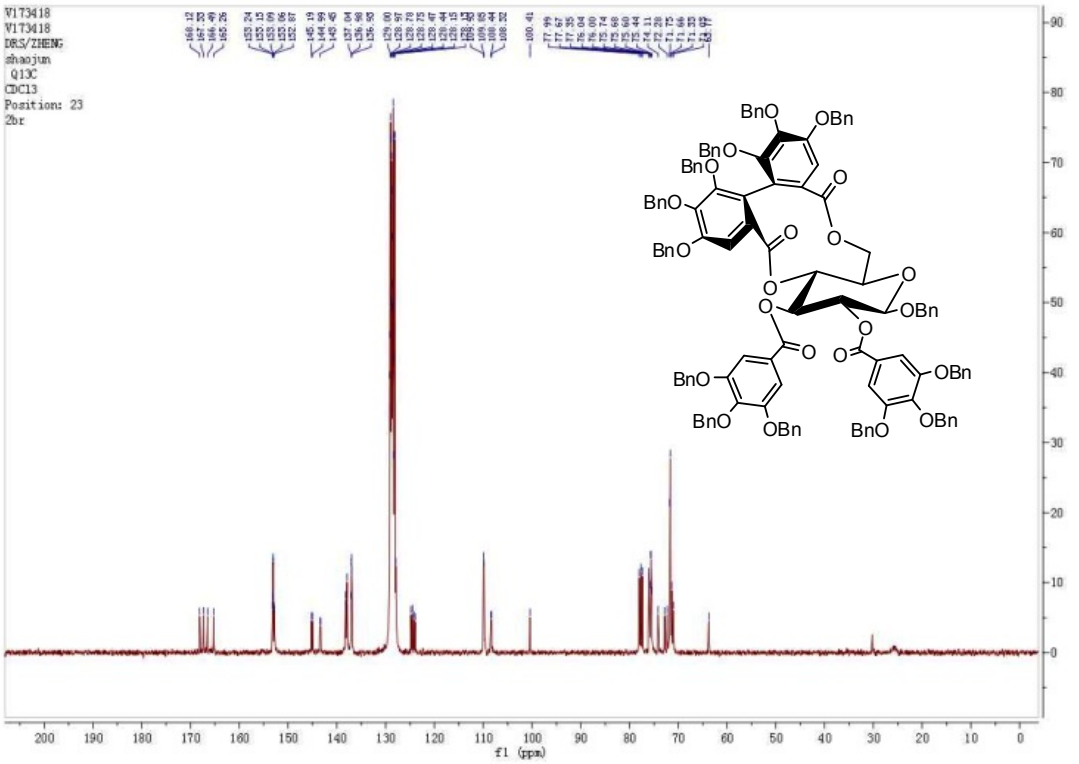
OBn
f1 (ppm)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V173418
DRS/ZHENG
shaojun
Q13C
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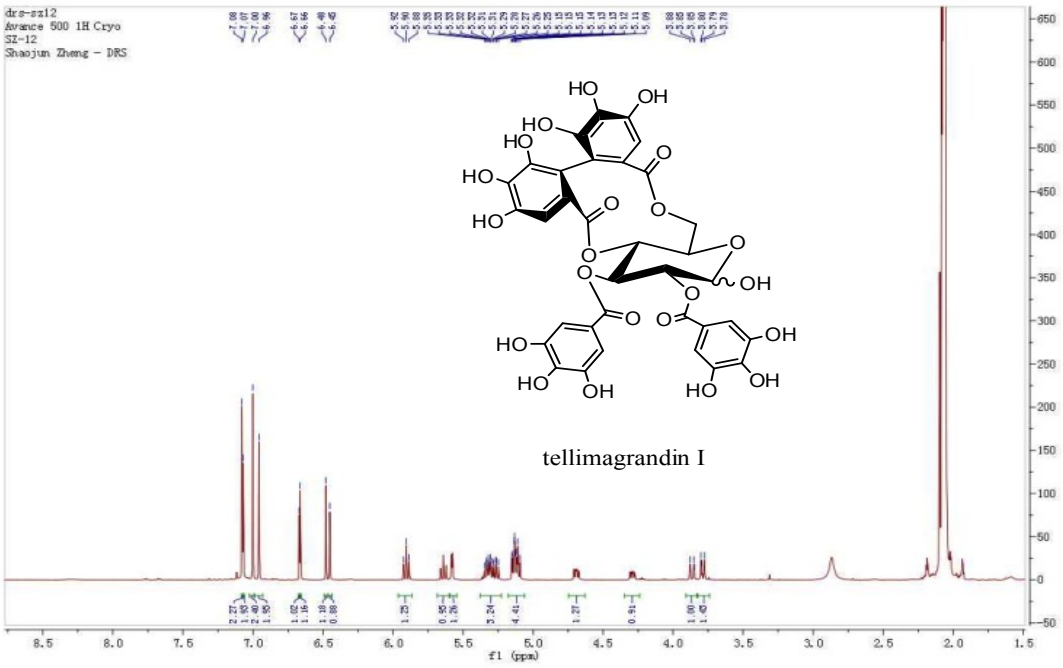
BnO
OBn
f1 (ppm)



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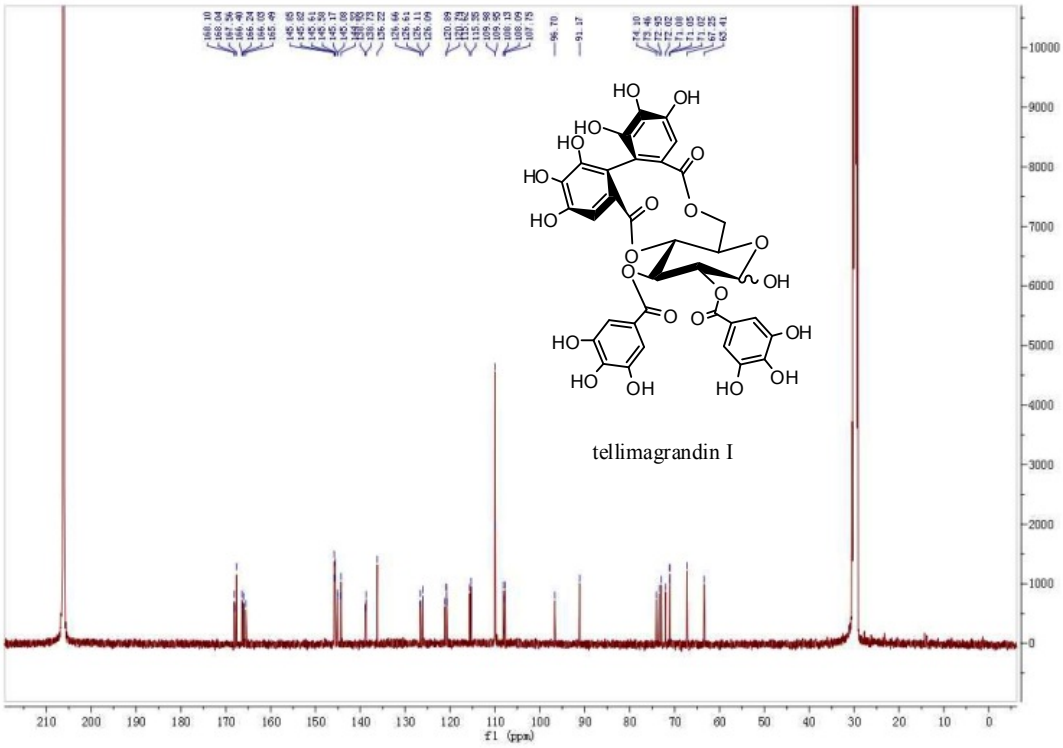

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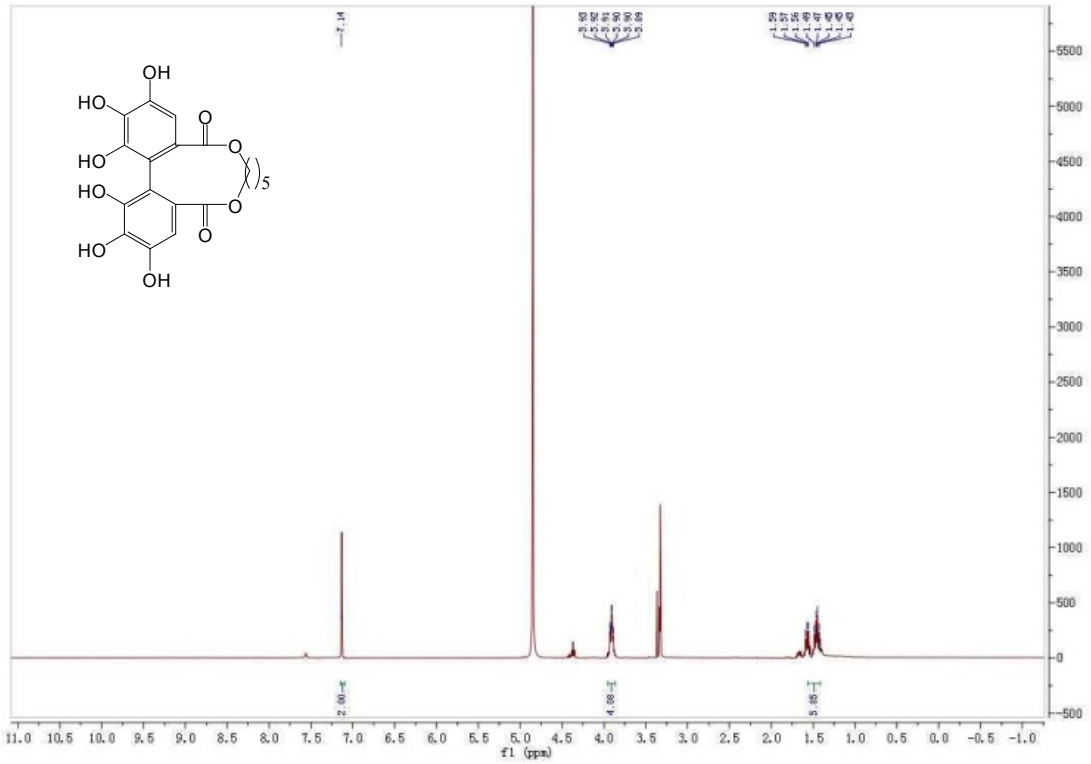
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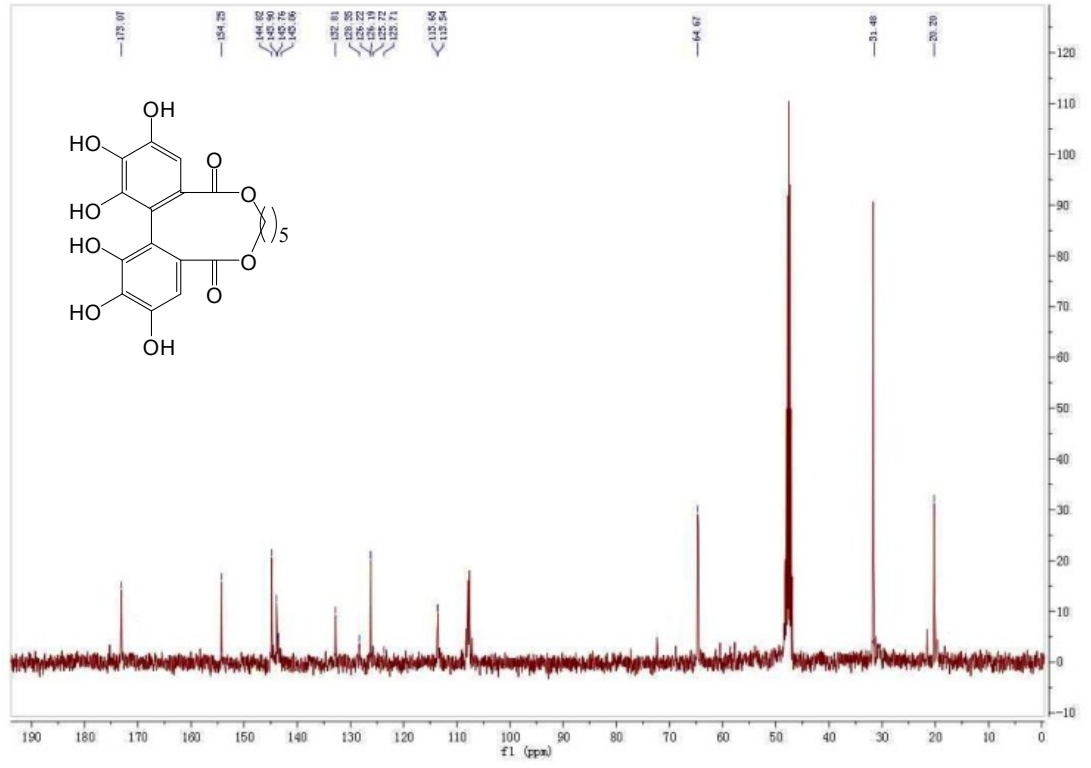
O
O
5
f1 (ppm)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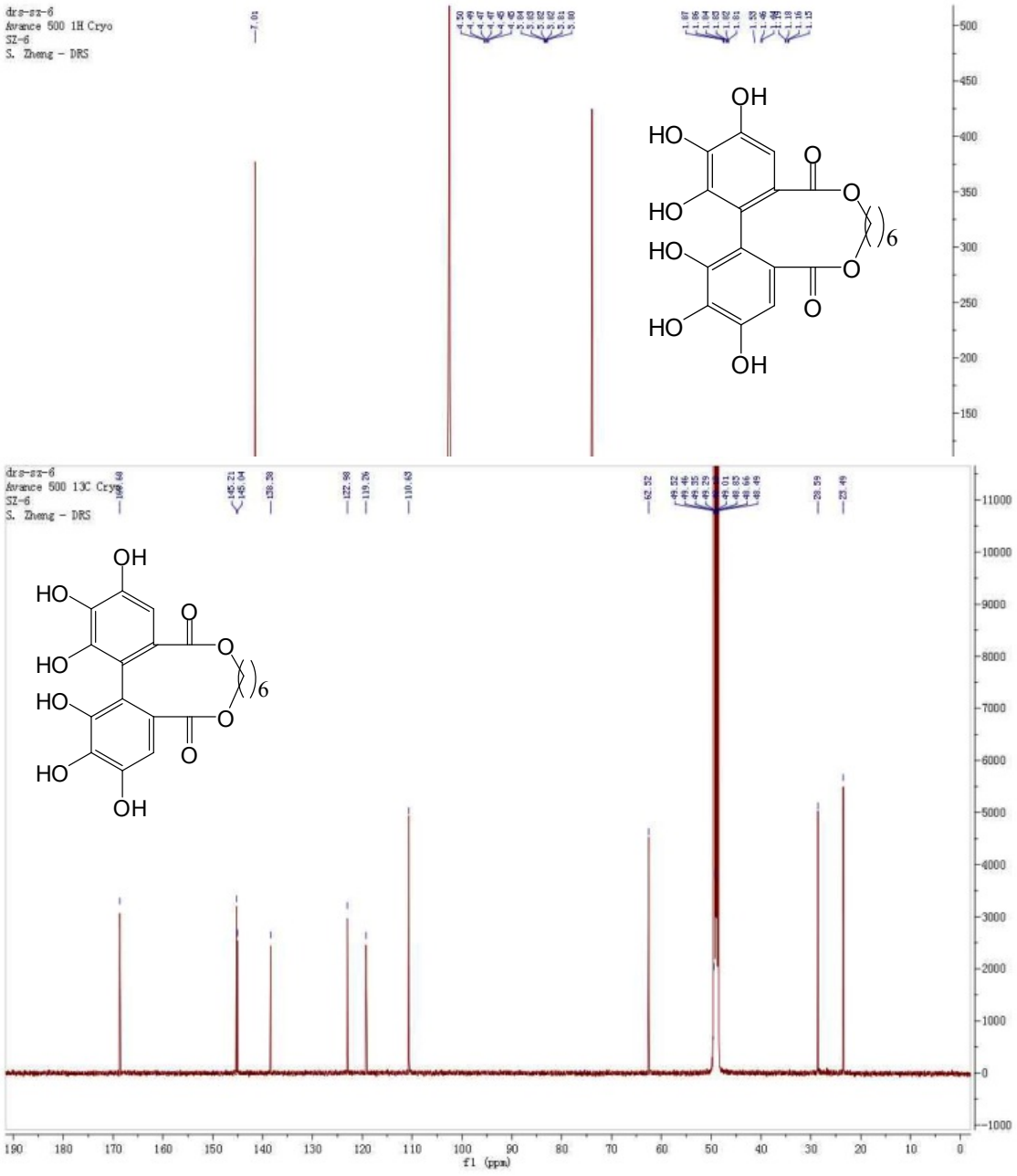
f1 (ppm)


drs-sz-6
Avance 500 1H Cryo
SZ-6
S. Zheng - DRS
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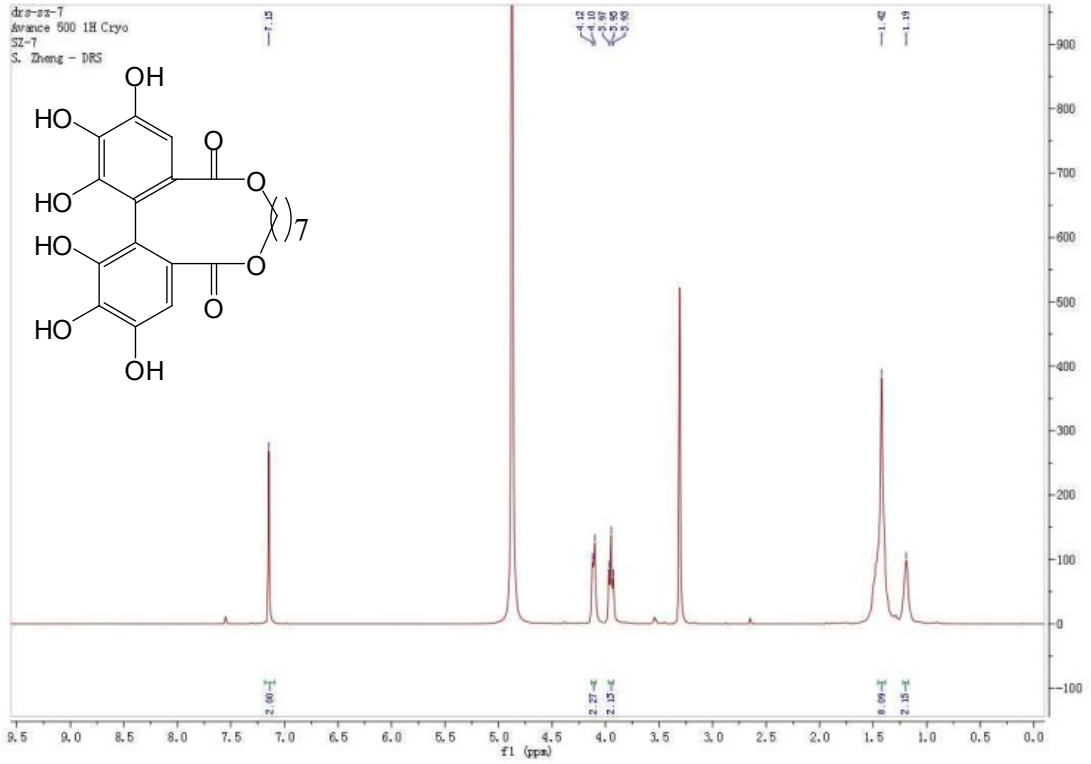
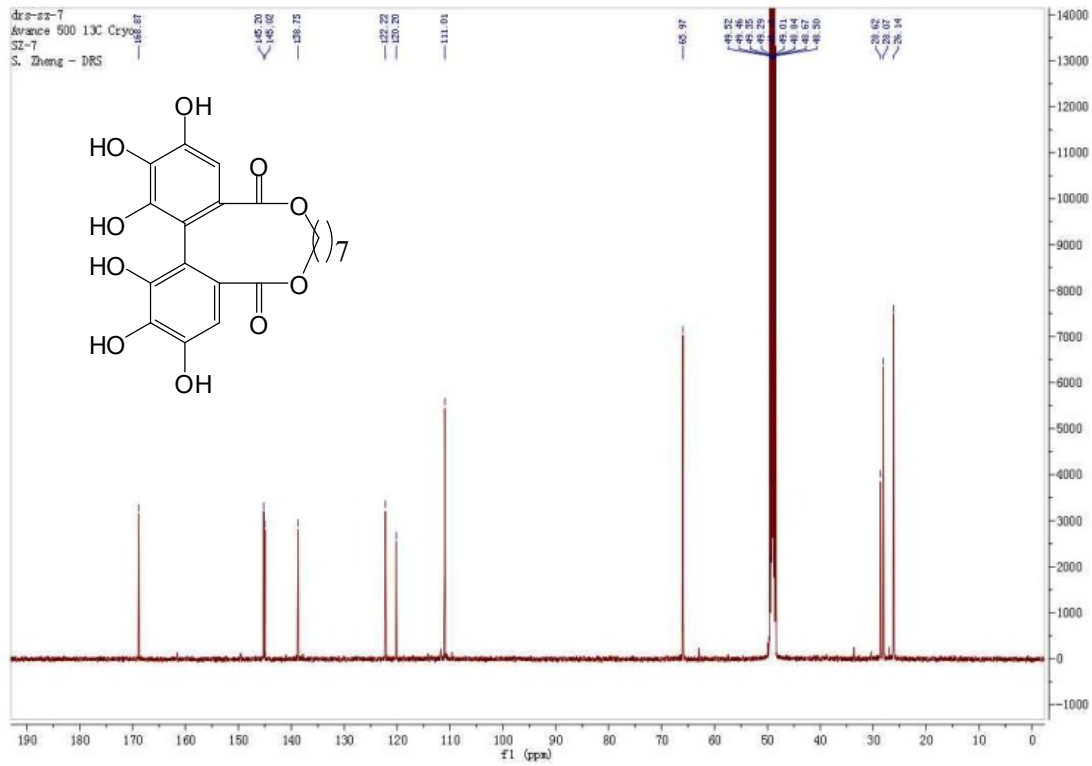
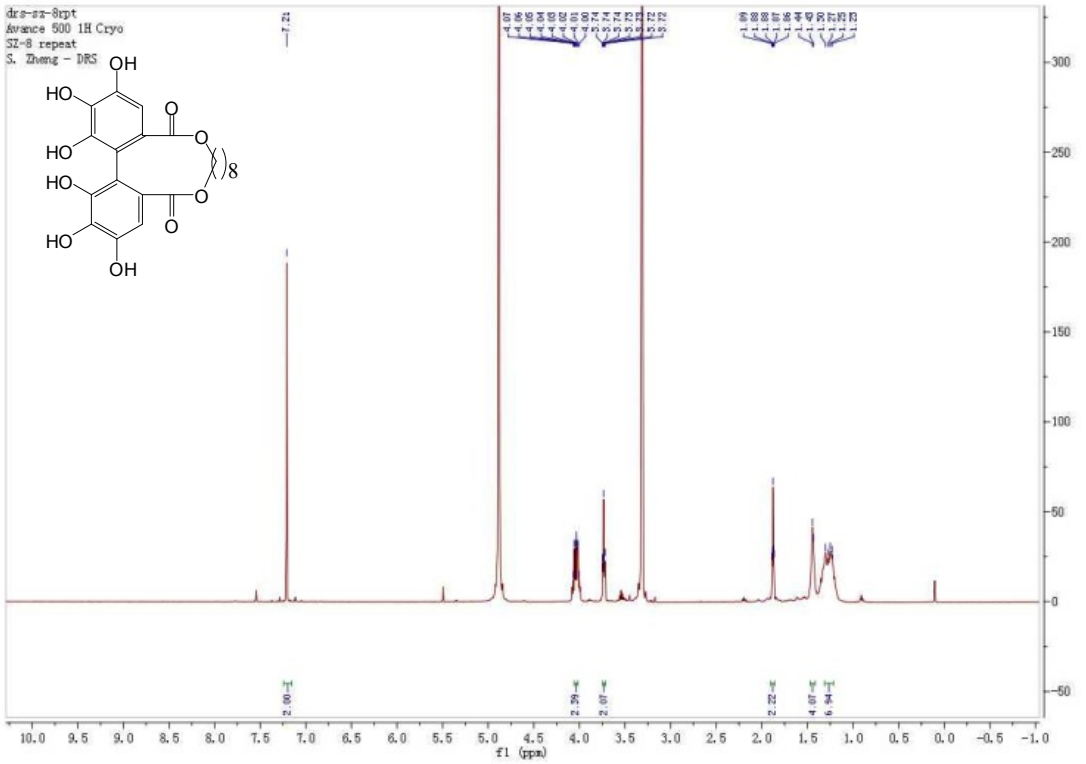
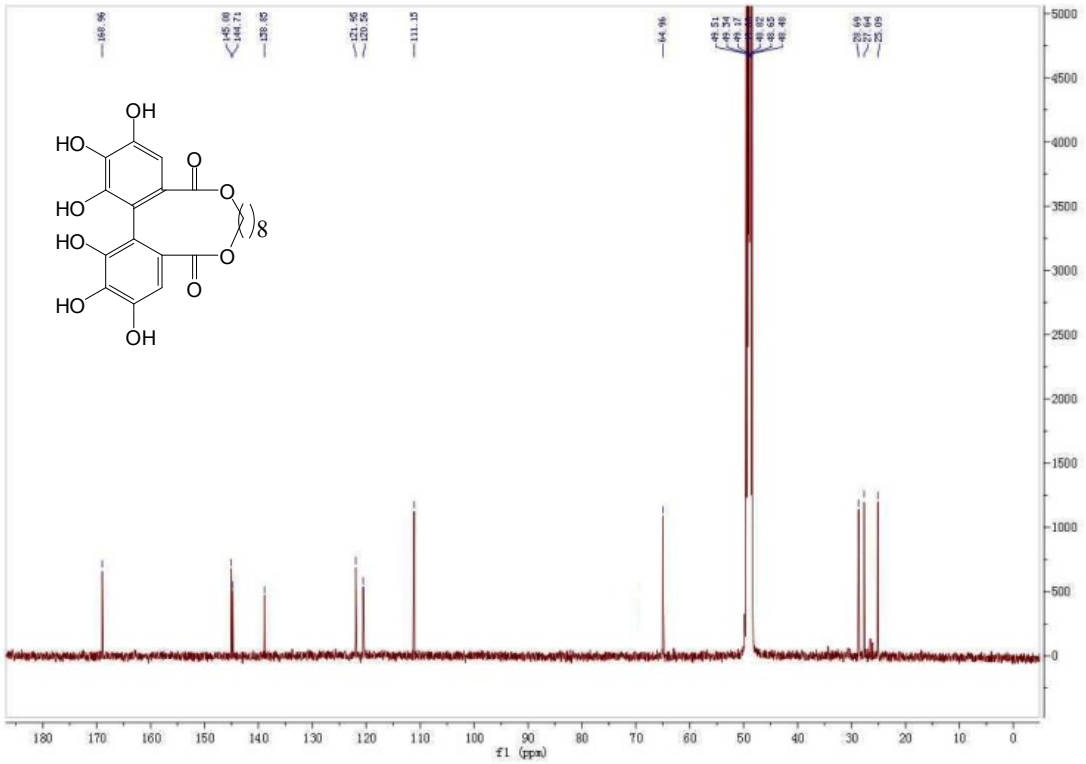
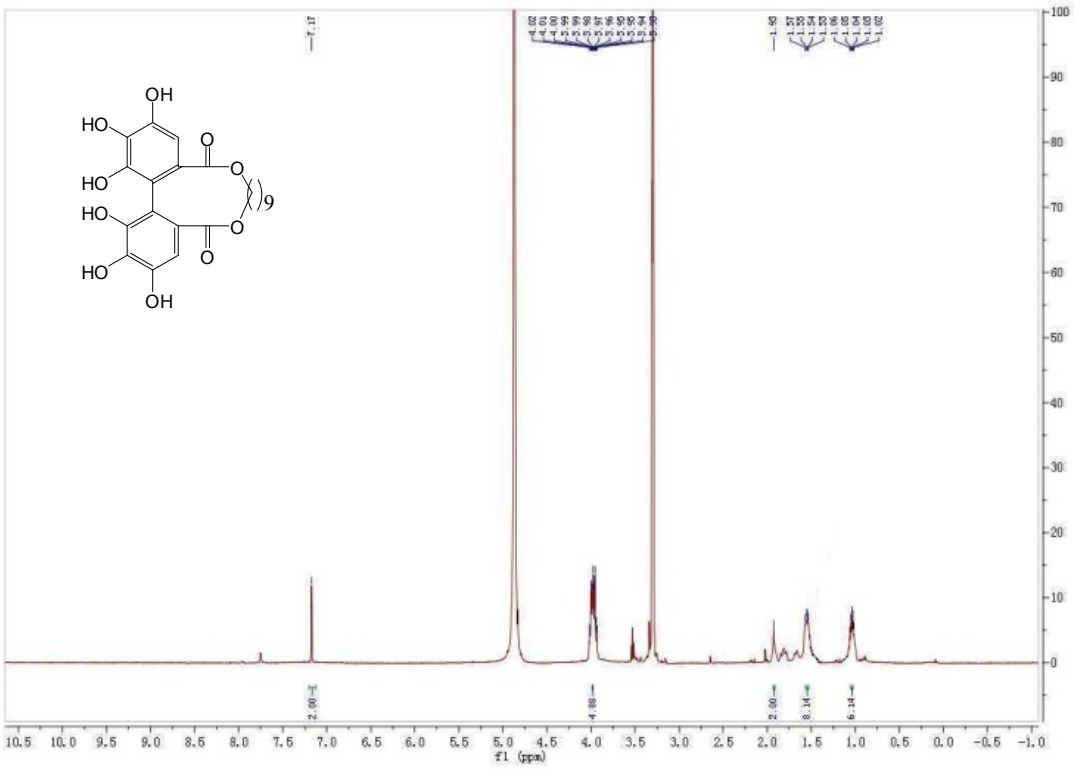
SZ-6
S. Zheng - DRS
f1 (ppm)

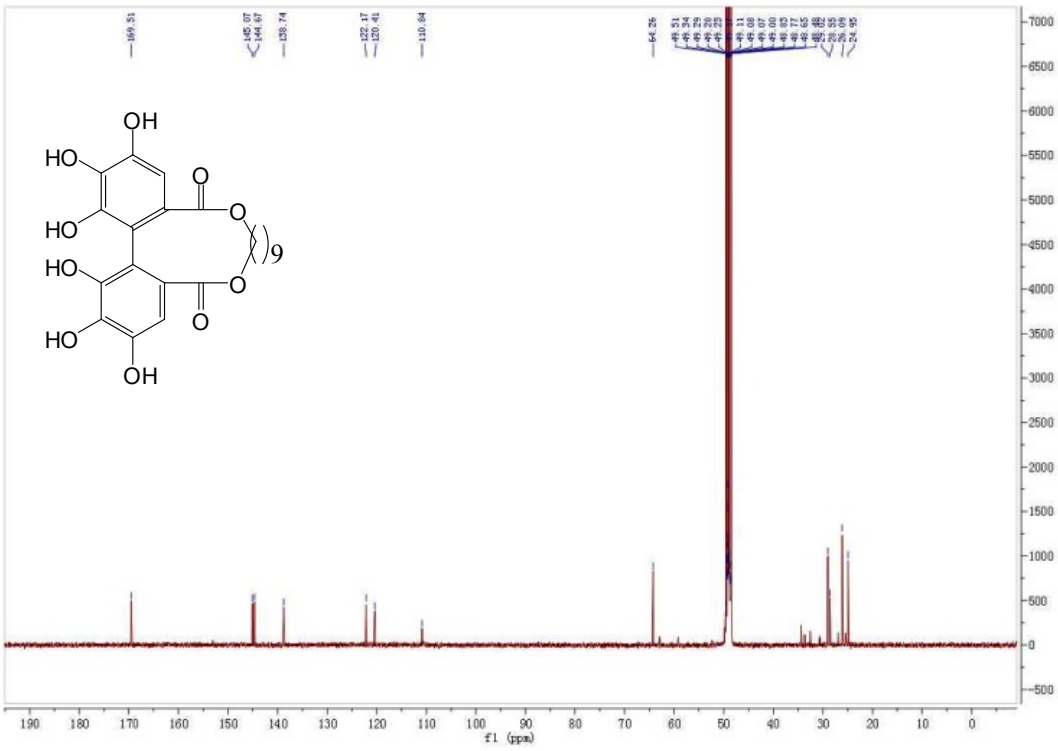


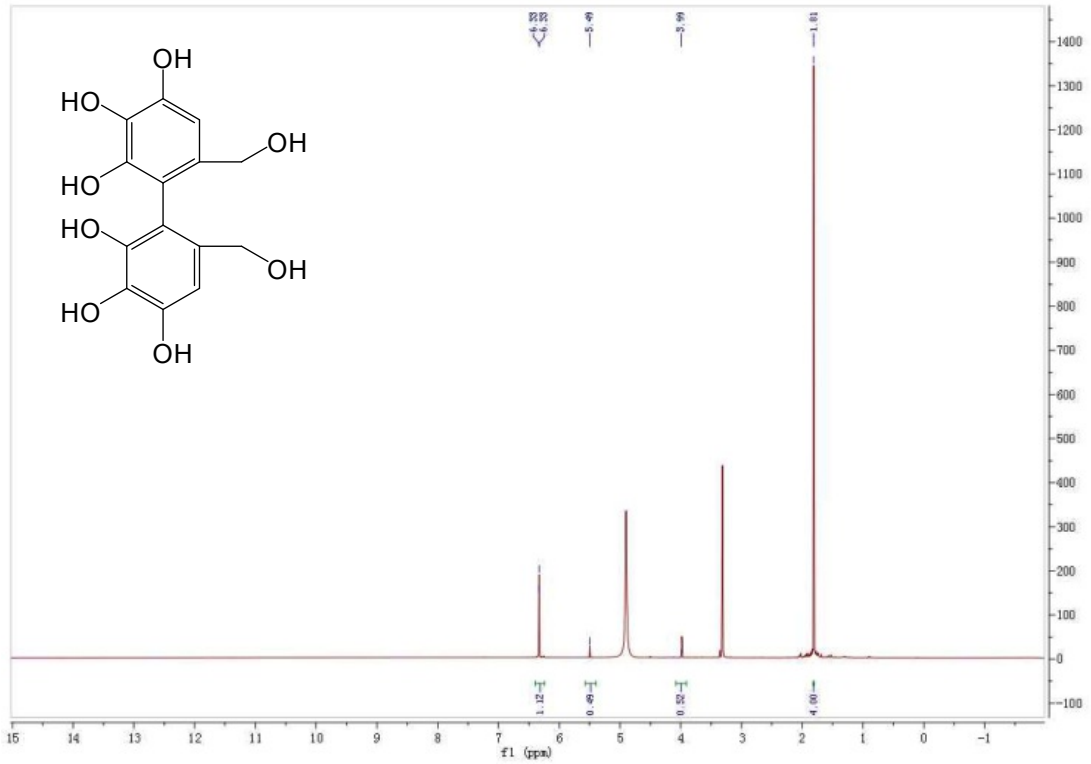


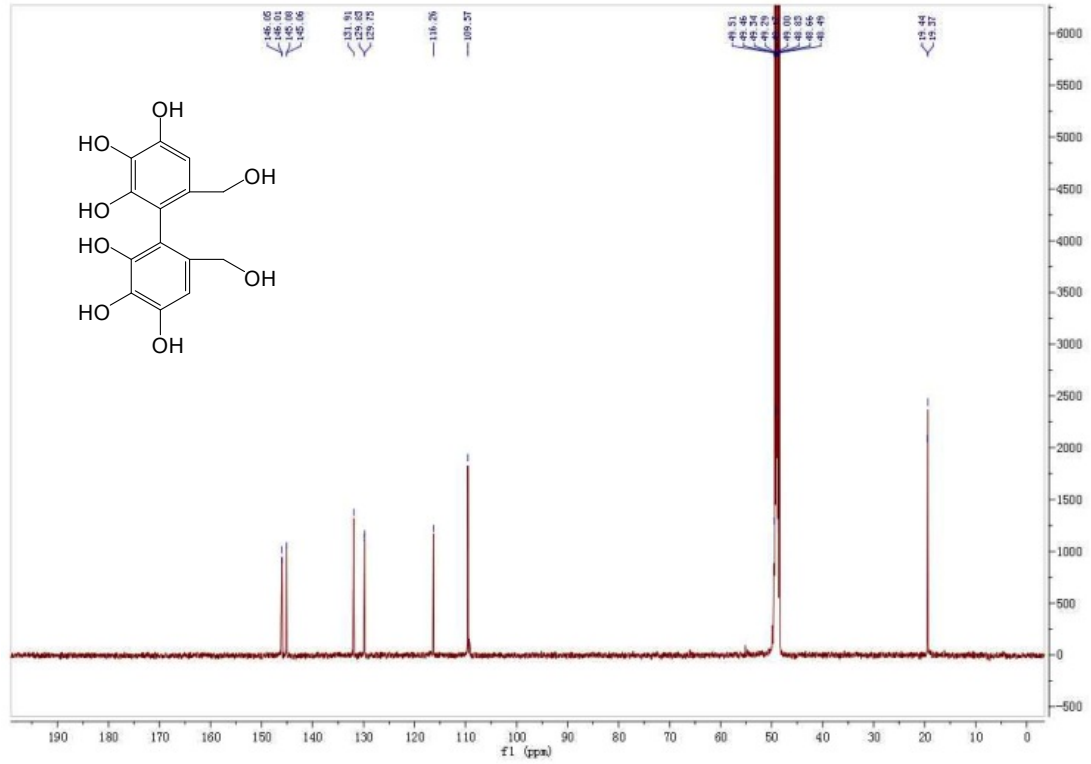

drs-sz-8rpt
Avance 500 1H Cryo
SZ-8 repeat
S. Zheng - DRS
OH
HO
HO
HO
HO
OH
O
O
O
O
O
8
f1 (ppm)

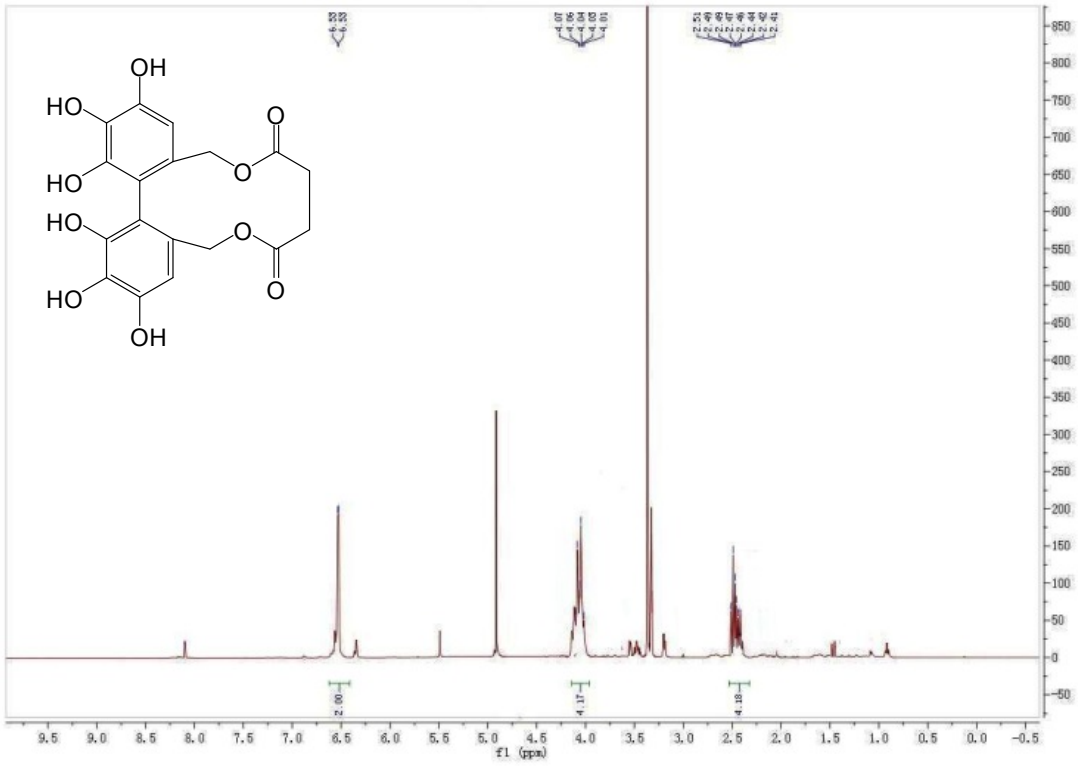

OH
HO
HO
HO
HO
OH
O
O
O
O
O
8
f1 (ppm)

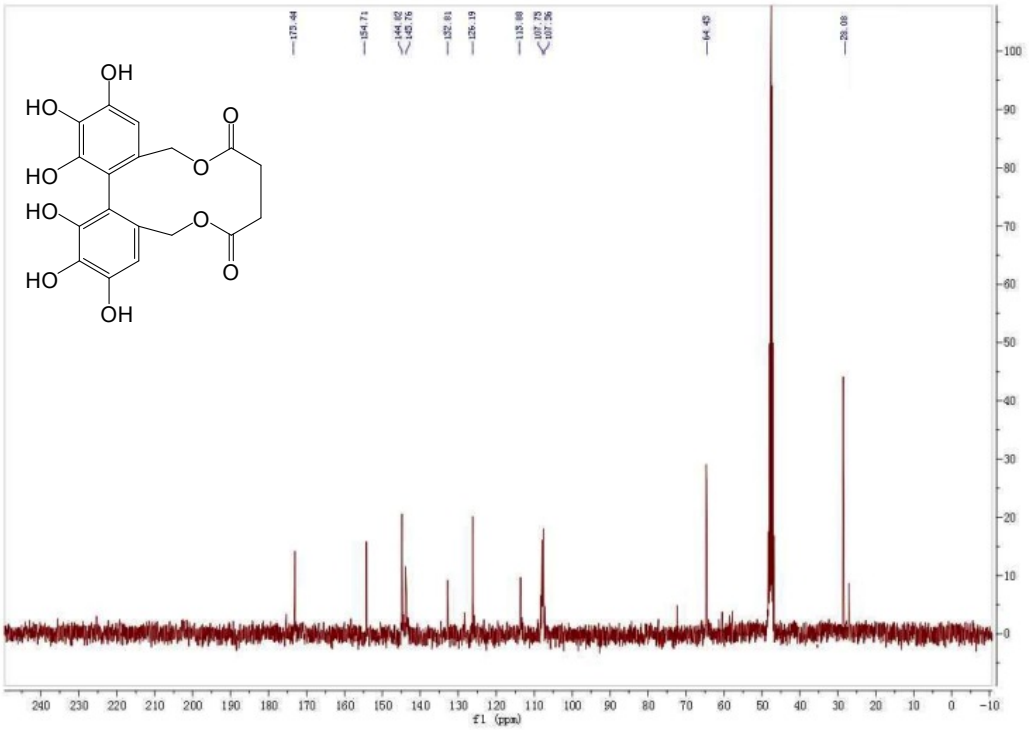

OH
HO
HO
HO
HO
OH
O
O
O
O
9
f1 (ppm)

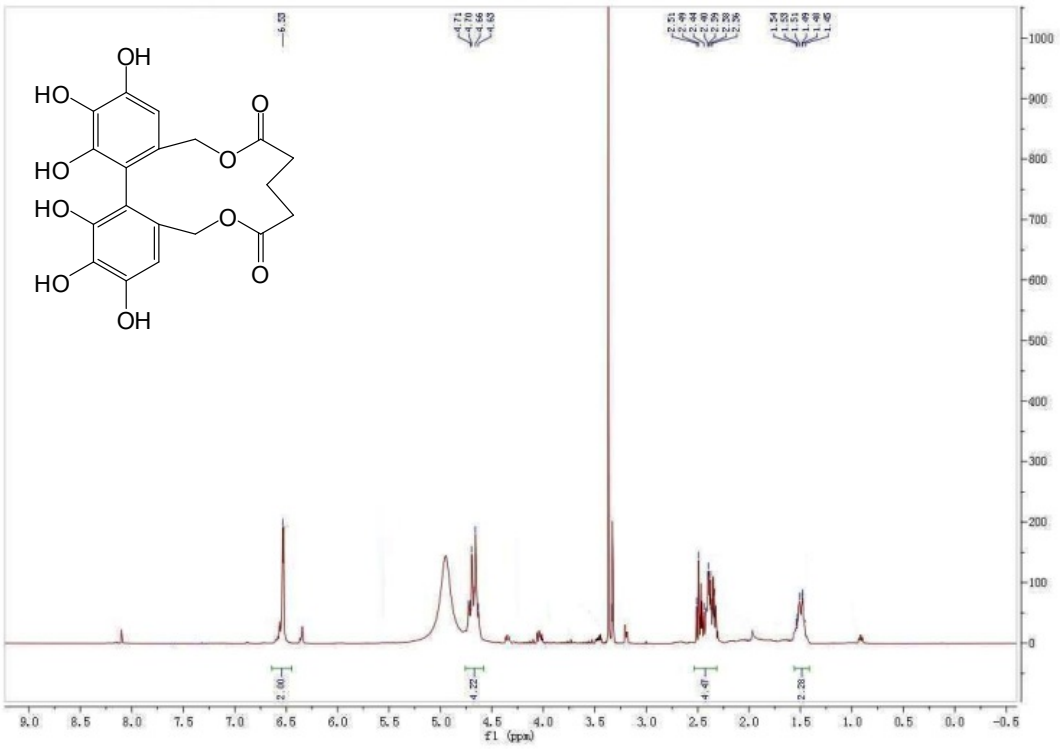

OH
HO
HO
HO
HO
OH
O
O
O
O
9
f1 (ppm)

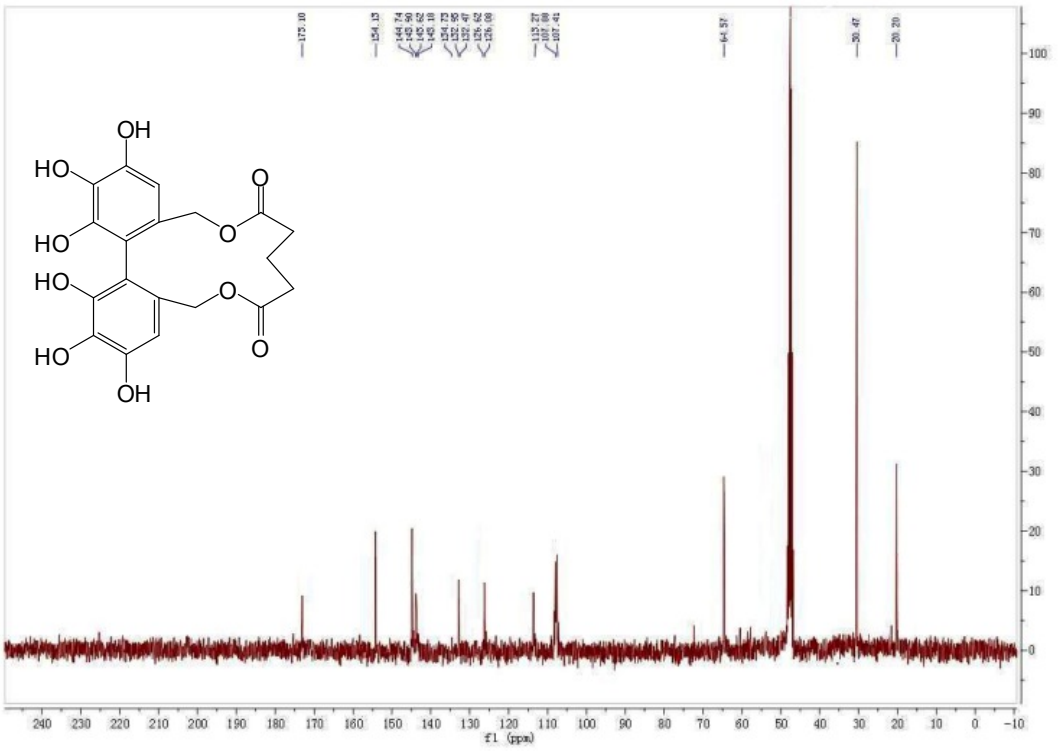


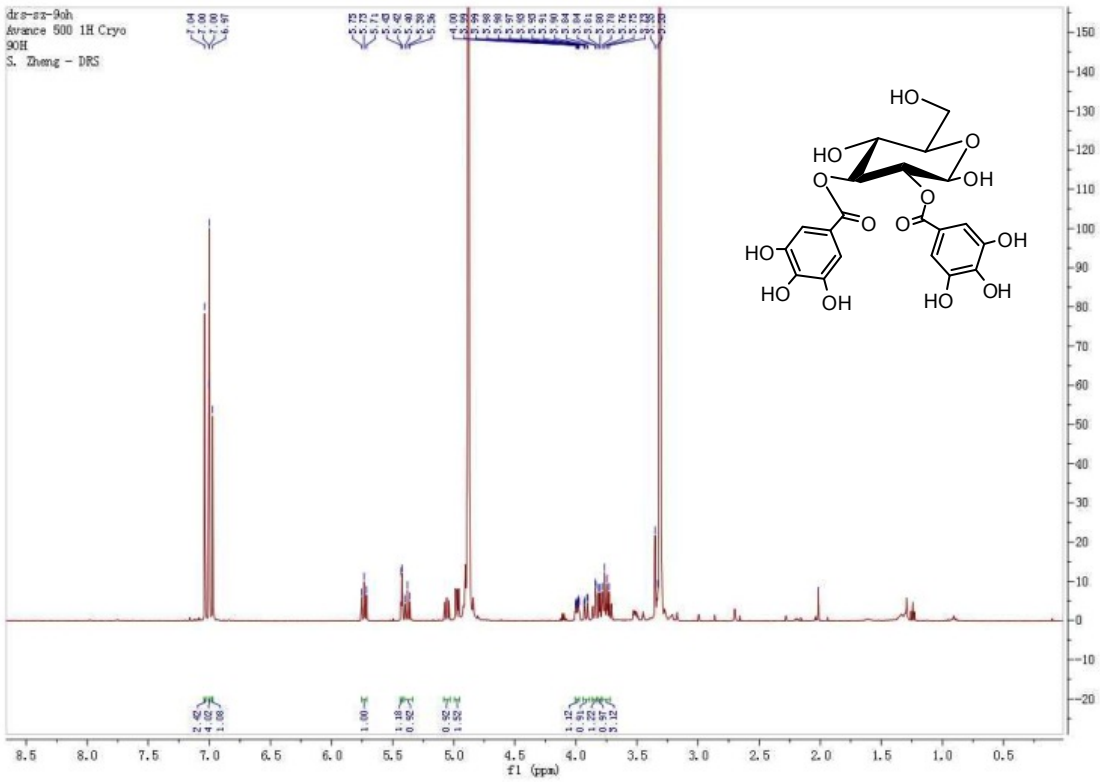


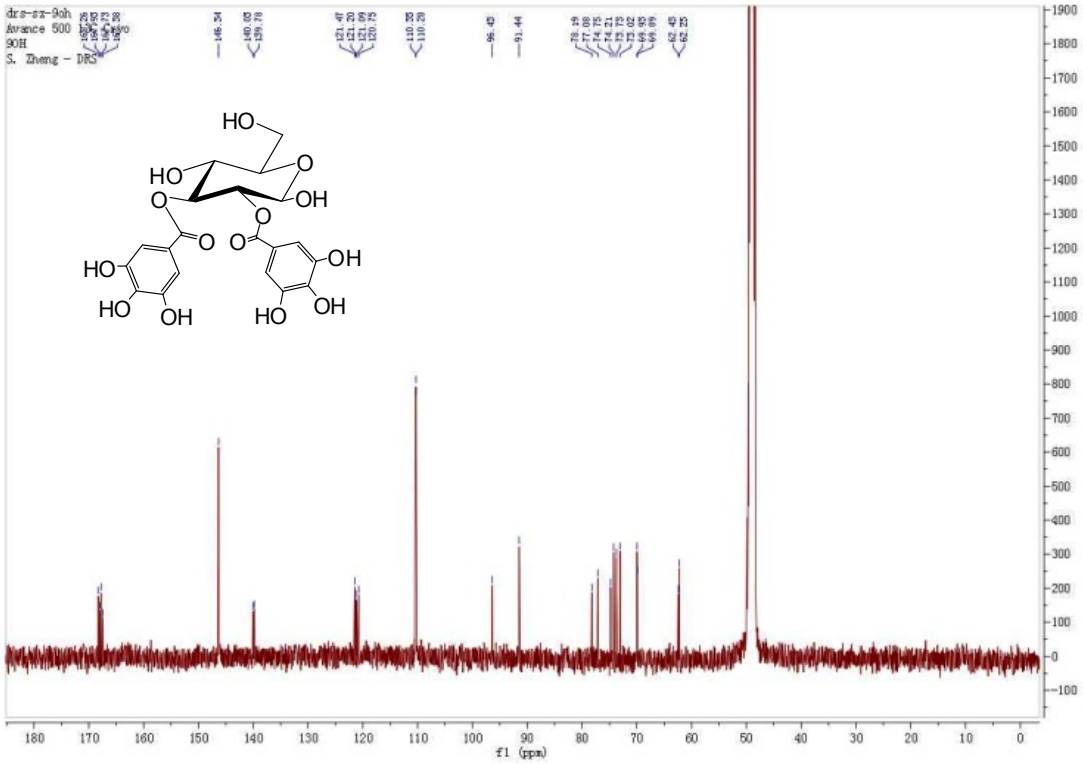


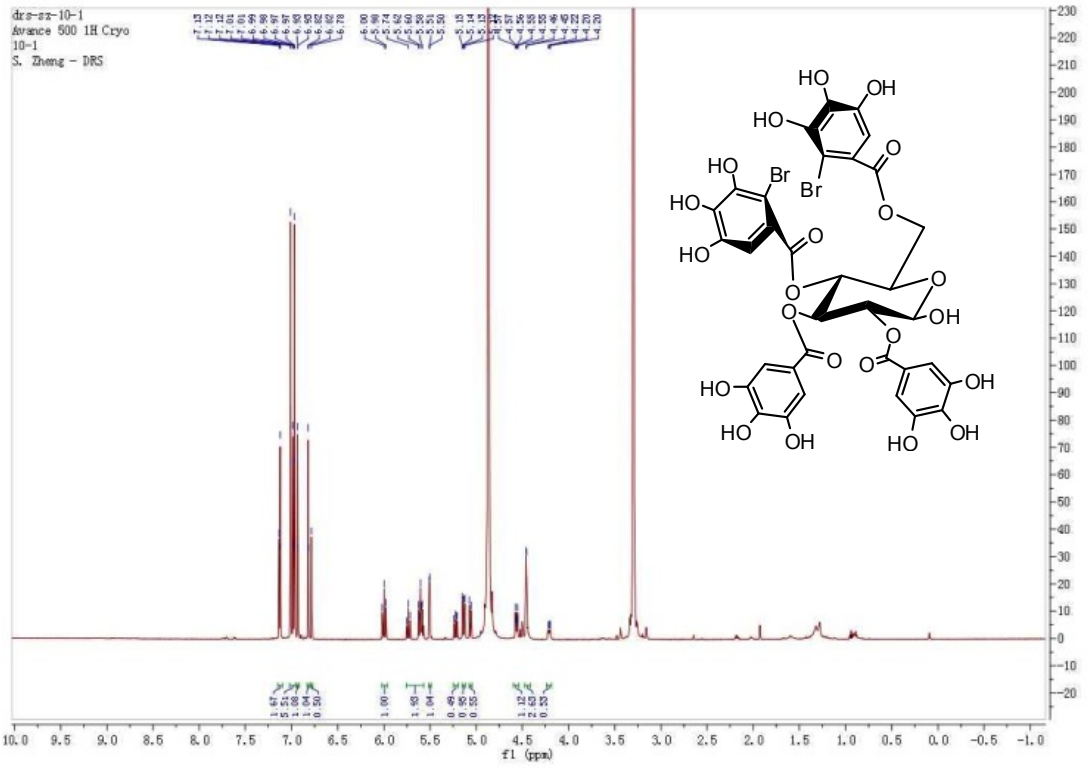


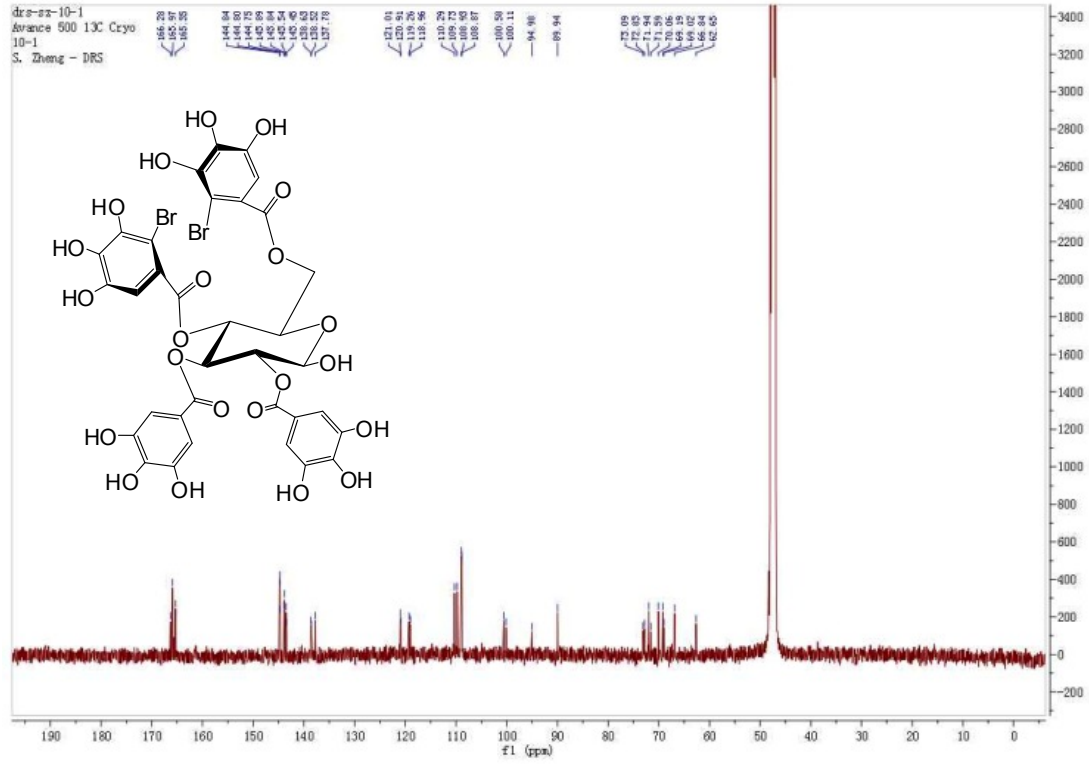





drs-sz-9oh
Avance 500 1H Cryo
90H
S. Zheng - DRS
f1 (ppm)


drs-sz-9oh
Avance 500
90H
S. Zheng - DRS
f1 (ppm)


dzs-zz-10-1
Avance 500 1H Cryo
10-1
S. Zheng - DRS
f1 (ppm)


dzs-zz-10-1
Avance 500 13C Cryo
10-1
S. Zheng - DRS
f1 (ppm)

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