Supplementary Information (SI) for Chemical Science.

Supporting Information

Electronegatively Substituted Adamantyl Units Accelerate Chemiexcitation of 1,2-Dioxetane Luminophores while Preserving Chemical Stability

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Contents

Experimental Section

Reagents

All reactions requiring anhydrous conditions were carried under an Argon atmosphere. Dry solvents over molecular sieves were purchased from Thermo Scientific. All other solvents were used as supplied (A.R grade). Water used was purified using a Millipore device. Commercially available materials were purchased from Sigma Aldrich or Aaron Chemicals and used without further purification unless stated otherwise.

Analytical Methods

^{1}H NMR, ^{13}C NMR and ^{31}P NMR were acquired on a Bruker Avance-400 spectrometer, chemical shifts are reported as parts per million (ppm) and measured relative to the solvent residual peak (^{1}H NMR: $CDCl_3$ = 7.26ppm, DMSO-d6 = 2.50ppm, MeOH-d4 = 3.31ppm, C_6D_6 = 7.16ppm. ^{13}C NMR: CDCl3 = 77.16ppm, DMSO-d6 = 39.52ppm, MeOH-d4 = 49.00, ppm C_6D_6 = 128.06ppm). NMR spectra of key compounds are attached. Mass spectrometry data was recorded on Waters Xebo SQD2 spectrometer using electrospray ionization (ESI) mode. Thin-layer chromatography (TLC) was performed using Merck 60 F254 silica gel plates. Flash chromatography was performed on SiliaFlash P60 silica unless noted otherwise. Analytical reverse-phase high-pressure liquid chromatography (RP-HPLC) was performed using Hitachi LaChrome *Elite* with a Thermo-Fischer Hypersil GOLD^{TM} 250x4.6 (mm) C18 column with HPLC grade acetonitrile (ACN) and H2O + 0.1% trifluoroacetic acid (TFA) as eluents (gradient is given in parentheses as ACN %). Irradiation reactions were performed using a 35W, 2700K LED lamp. Chemiluminescent measurements were recorded on Molecular Devices Spectramax iD3. Preperative RP-HPLC was conducted using ECOM LC preparative system with Phenomenex Luna 5µm C18(2) 100Å 250X21.2 mm column.

Abbreviations

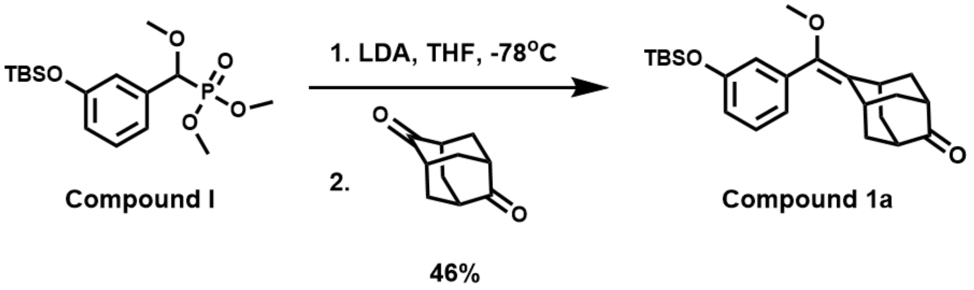
ACN – Acetonitrile, DCM – Dichloromethane, DMF – N,N'-Dimethylformamide, Et_3N – Triethylamine, EtOAc – Ethyl acetate, MeOH – Methanol, THF – Tetrahydrofuran, Hex – Hexanes, LDA – Lithium diisopropylamide, DBTL – Dibutyltin dilaurate, mCPBA – meta-chloroperoxybenzoic acid, sat. – saturated, Et_2O – Diethyl ether, TBAF – Tetrabutylammonium fluoride, NBS – N-bromosuccinimide, $BF_3{\cdot}Et_2O$ - Boron trifluoride diethyl etherate, CAM - Cerium ammonium molybdate, N/A – Not available, AcOH- Acetic acid, PBS – phosphate buffered saline.

Synthetic Procedures

Synthesis of Diox 1[1], β-gal-diox 1[2] was previously reported.

Lithium diisopropylamide (LDA) preparation general procedure:

To a heat gun-dried flask under argon was added dry THF and diisopropylamine (1.1eq), then, the solution was cooled to 0°C. n-butyllithium (^{n}BuLi) solution (2.5M in Hexanes, 1eq) was added dropwise using a syringe to obtain a light yellowish solution. After the addition, the solution was stirred for 1 minute and cooled to -78°C for the Horner-Wadsworth-Emmons reaction.



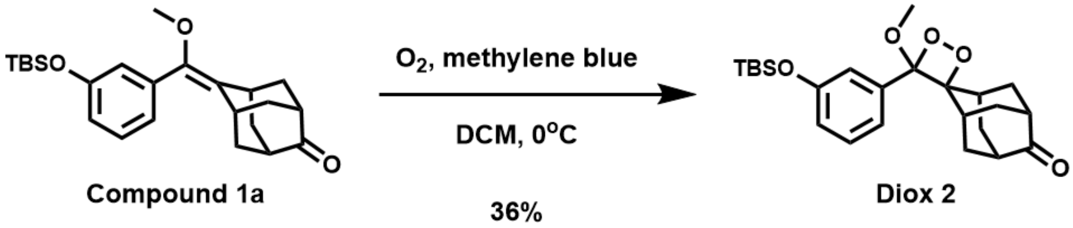
Compound 1a:

To a freshly prepared solution of LDA (1.66 mmol, 3eq) in THF (4 mL) under argon, a solution of phosphonate (Compound **I**)[2] (200mg, 0.55mmol in 2mL, 1eq) in dry THF is added dropwise at -78°C, the solution turns dark orange. Following 20 minutes of stirring, a solution of adamantane-2,6-dione (180mg, 1.1mmol in 2mL, 2eq) in dry THF is added all at once into the flask. The reaction is stirred for additional 20 minutes at -78°C and then allowed to reach room temperature. The reaction is quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography (20% EtOAc in Hex) afforded compound **1a** (100mg, 46%) as a yellowish oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.23 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.80 (s, 2H), 3.39 (s, 1H), 3.32 (s, 3H), 2.69 (s, 1H), 2.62 (s, 2H), 2.15 (s, 4H), 2.04 (q, J = 13.0 Hz, 5H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 217.8, 155.7, 145.4, 135.9, 129.4, 126.6, 122.7, 121.2, 120.1, 77.5, 77.2, 76.9, 57.6, 47.0, 40.7, 40.5, 31.4, 29.1, 25.8, 18.4, -4.3.

MS (ES+): m/z calc for $C_{24}H_{34}O_3Si$: 398.2; found: 399.6 $[M+H]^+$.



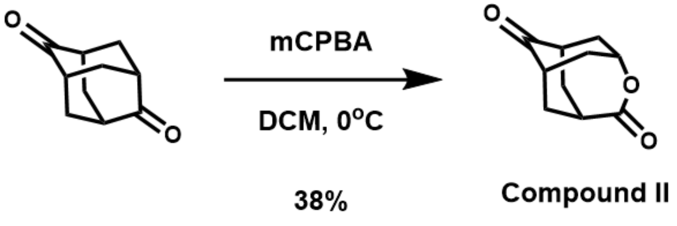
Diox 2:

Compound **1a** (31mg, 0.078mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light at 0°C. The reaction was monitored by RP-HPLC (70-100% gradient). Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **Diox 2** (12.1mg, 36%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.33 (t, *J* = 7.2 Hz, 2H), 6.92 (dd, *J* = 9.0, 2.3 Hz, 2H), 3.28 (s, 3H), 3.20 (s, 1H), 2.39 – 2.33 (m, 2H), 2.30 (s, 1H), 2.22 (dq, *J* = 13.4, 2.9 Hz, 1H), 2.16 – 2.01 (m, 3H), 1.85 (dq, *J* = 13.5, 2.9 Hz, 1H), 1.75 (dq, *J* = 13.4, 2.9 Hz, 1H), 1.50 (dq, *J* = 13.6, 2.7 Hz, 1H), 1.34 (dq, *J* = 13.7, 3.1 Hz, 1H), 0.99 (s, 9H), 0.20 (s, 6H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 216.6, 156.2, 135.6, 129.8, 121.9, 111.7, 93.3, 50.3, 44.5, 44.3, 36.2, 34.3, 33.9, 33.0, 32.6, 31.0, 25.8, 18.4, -4.2.

MS (ES+): m/z calc for $C_{24}H_{34}O_5Si$: 430.2; found: 494.6 $[M+ACN+Na]^+$.



Compound II:

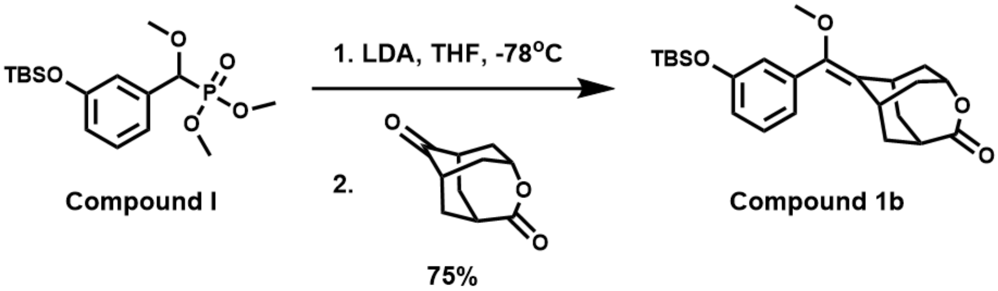
adamantane-2,6-dione (1g, 6.1mmol, 1eq) was dissolved in DCM (50mL), the solution was cooled to 0°C and mCPBA was added portion-wise. The reaction was stirred for 10 minutes and then allowed to warm to RT. The reaction was monitored by TLC, upon completion, sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ were added to the flask and the product was extracted with DCM.

The combined organic layers were washed by sat. NaCl and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (30% to 60% EtOAc in Hex) to afford **Compound II** (418mg, 38%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 4.55 (tt, *J* = 4.4, 2.2 Hz, 1H), 3.17 (tt, *J* = 5.9, 1.7 Hz, 1H), 2.68 (s, 2H), 2.48 – 2.31 (m, 5H), 2.30 – 2.27 (m, 1H), 2.20 (dddd, *J* = 13.3, 5.8, 2.9, 1.4 Hz, 2H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 215.2, 176.8, 71.1, 44.8, 40.0, 38.8, 33.9.

MS (ES+): m/z calc for $C_{10}H_{12}O_3$: 180.1 ; found: N/A.



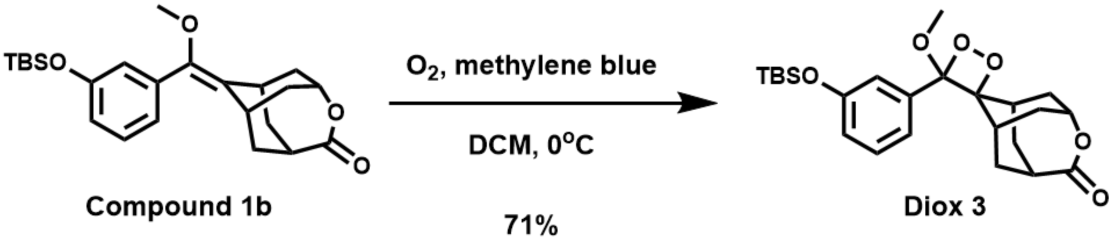
Compound 1b:

To a freshly prepared solution of LDA (1.66 mmol, 3eq) in THF (4 mL) under argon a solution of phosphonate (Compound **I**) (200mg, 0.55mmol in 2mL, 1eq) in dry THF is added dropwise at -78°C, the solution turns dark orange. Following 20 minutes of stirring, a solution of compound **II** (200mg, 1.1mmol in 2mL, 2eq) in dry THF is added all at once into the flask. The reaction is stirred for additional 20 minutes at -78°C and then allowed to reach room temperature. The reaction is quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography (20% to 40% EtOAc in Hex) afforded compound **1b** (172mg, 75%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.21 (t, J = 7.6 Hz, 1H), 6.82 (dd, J = 16.3, 7.8 Hz, 2H), 6.74 (s, 1H), 4.51 (s, 1H), 3.43 (s, 1H), 3.27 (s, 3H), 3.11 (s, 1H), 2.70 (s, 1H), 2.20 – 1.90 (m, 7H), 1.88 – 1.80 (m, 1H), 0.96 (s, 9H), 0.18 (s, 6H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 178.8, 155.7, 146.0, 135.5, 129.4, 123.9, 122.3, 120.9, 120.2, 73.4, 57.4, 41.4, 37.7, 37.4, 32.9, 32.6, 30.6, 28.1, 25.7, 18.3, -4.4.

MS (ES+): m/z calc for $C_{24}H_{34}O_4Si$: 414.2; found: 415.6 $[M+H]^+$.



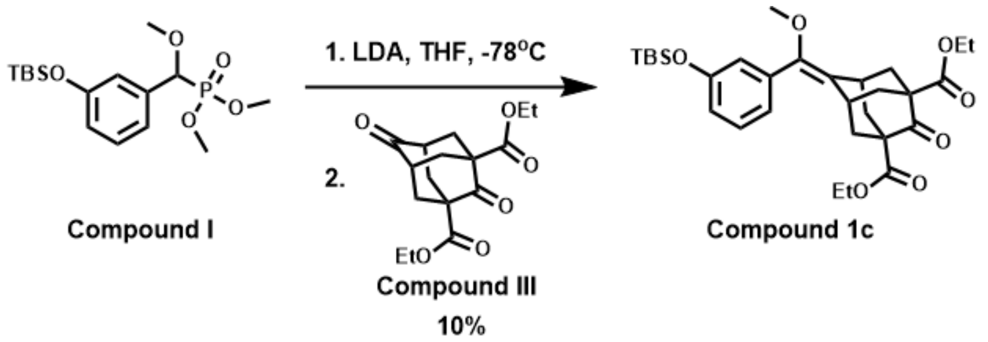
Diox 3:

Compound **1b** (20mg, 0.048mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light at 0°C. The reaction was monitored by RP-HPLC (90-100% gradient). Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **Diox 3** (15.3mg, 71%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.33 (m, 4H), 6.97 – 6.65 (m, 3H), 4.32 (dt, J = 4.5, 2.4 Hz, 1H), 4.19 (s, 1H), 3.26 (d, J = 1.5 Hz, 5H), 3.22 (s, 1H), 2.89 (t, J = 6.0 Hz, 1H), 3.30 – 3.24 (m, 6H), 2.81 – 2.74 (m, 1H), 2.41 (s, 2H), 2.26 (dtd, J = 15.4, 4.5, 2.1 Hz, 1H), 2.16 (dt, J = 5.6, 2.7 Hz, 1H), 2.12 (d, J = 4.9 Hz, 1H), 2.08 (d, J = 4.2 Hz, 1H), 2.02 (s, 1H), 1.96 – 1.89 (m, 3H), 1.85 – 1.76 (m, 2H), 1.71 – 1.65 (m, 1H), 1.59 (d, J = 15.6 Hz, 1H), 1.46 (d, J = 14.8 Hz, 1H), 1.29 – 1.20 (m, 1H), 1.15 – 1.07 (m, 1H), 0.99 (s, 15H), 0.20 (s, 10H). Mixture of diastereomers in a 1:0.7 ratio by integration. The aliphatic region between 2.30-1.06 ppm could not be properly assigned due to overlapping signals.

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 178.2, 177.9, 135.4, 130.1, 122.0, 111.6, 111.4, 92.9, 92.6, 71.6, 70.8, 50.4, 50.3, 39.3, 38.8, 34.4, 32.6, 31.8, 31.6, 30.8, 30.4, 30.2, 29.2, 27.3, 26.4, 25.8, 25.5, 18.4, -4.2.

MS (ES+): m/z calc for $C_{24}H_{34}O_6Si$: 446.2; found: 447.5 $[M+H]^+$.



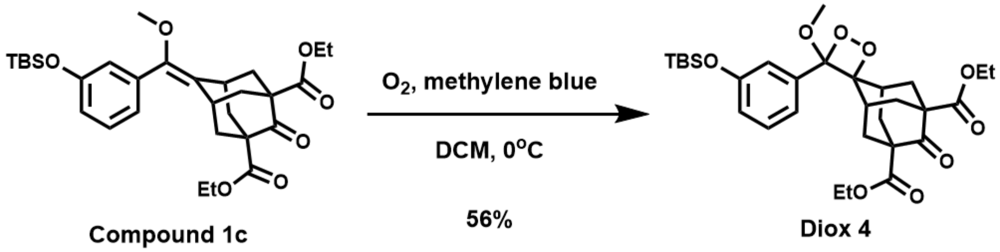
Compound 1c:

To a freshly prepared solution of LDA (1.66 mmol, 3eq) in THF (4 mL) under argon a solution of phosphonate (Compound **I**) (200mg, 0.55mmol in 2mL, 1eq) in dry THF is added dropwise at -78°C, the solution turns dark orange. Following 20 minutes of stirring, a solution of compound **III**[3] (254mg, 0.82mmol in 2mL, 1.5eq) in dry THF is added all at once into the flask. The reaction is stirred for additional 20 minutes at -78°C and then allowed to reach room temperature. The reaction is quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography (5% to 10% EtOAc in Hex) afforded compound **1c** (30mg, 10%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.27 – 7.20 (m, 1H), 6.86 (dd, *J* = 18.7, 7.7 Hz, 2H), 6.78 (s, 1H), 4.19 (q, 4H), 3.60 (s, 1H), 3.31 (s, 3H), 2.88 (s, 1H), 2.66 (d, *J* = 12.8 Hz, 2H), 2.52 (d, *J* = 12.6 Hz, 2H), 2.17 (d, *J* = 12.6 Hz, 2H), 2.08 (d, *J* = 12.5 Hz, 2H), 1.27 (t, *J* = 6.8 Hz, 6H), 0.99 (s, 9H), 0.20 (s, 6H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 206.2, 171.0, 155.9, 146.3, 135.4, 129.5, 123.1, 122.6, 121.1, 120.4, 61.3, 58.1, 57.6, 42.1, 41.9, 31.1, 29.8, 28.6, 25.8, 18.4, 14.3, -4.3.

MS (ES+): m/z calc for $C_{30}H_{42}O_7Si$: 542.3; found: 543.7 $[M+H]^+$.



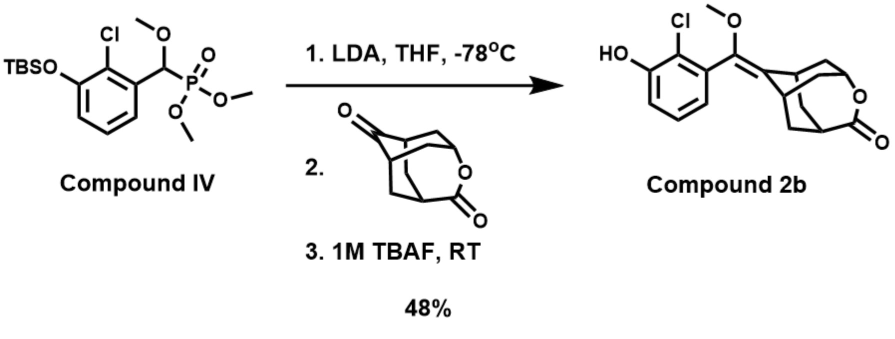
Diox 4:

Compound **1c** (14mg, 0.026mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light at 0°C. The reaction was monitored by RP-HPLC (70-100% gradient). Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **Diox 4** (8.3mg, 56%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.54 – 7.29 (m, 2H), 6.93 (dd, J = 8.7, 2.2 Hz, 2H), 4.24 – 4.09 (m, 4H), 3.39 (s, 1H), 3.27 (s, 3H), 2.57 (dt, J = 13.8, 3.3 Hz, 1H), 2.48 (s, 1H), 2.38 (dt, J = 13.9, 2.6 Hz, 1H), 2.27 – 2.17 (m, 3H), 2.14 (dt, J = 13.9, 3.0 Hz, 1H), 2.02 (d, J = 13.7 Hz, 1H), 1.81 (s, 1H), 1.42 (dt, J = 14.0, 2.5 Hz, 1H), 1.27 – 1.21 (m, 6H), 0.98 (s, 8H), 0.18 (s, 6H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 205.3, 170.3, 135.2, 130.2, 121.8, 111.3, 91.8, 61.5, 61.5, 56.0, 55.9, 50.4, 37.9, 36.1, 35.3, 34.6, 32.6, 31.1, 29.9, 25.8, 18.4, 14.2, 14.2, -4.3.

MS (ES+): m/z calc for $C_{30}H_{42}O_9Si$: 574.3; found: 575.6 $[M+H]^+$.



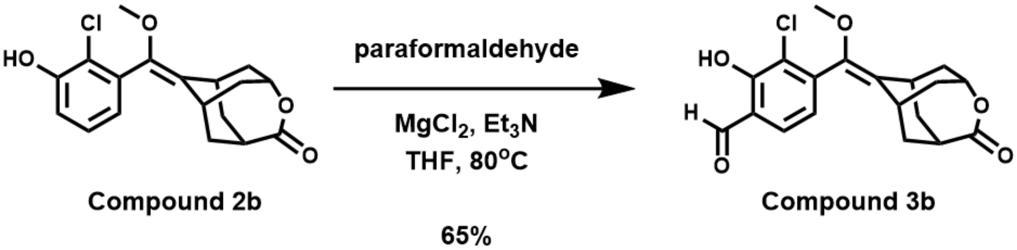
Compound 2b:

To a freshly prepared solution of LDA (1.53 mmol, 3eq) in THF (4 mL) under argon a solution of phosphonate (Compound **IV**)[4] (200mg, 0.51mmol in 2mL, 1eq) in dry THF is added dropwise at -78°C, the solution turns dark orange. Following 20 minutes of stirring, a solution of compound **II** (182mg, 1.0mmol in 2mL, 2eq) in dry THF is added all at once into the flask. The reaction is stirred for additional 20 minutes at -78°C and then allowed to reach room temperature. After completion of the reaction indicated by TLC, TBAF (0.56ml, 0.56mmol, 1M in THF) is added into the reaction flask. The reaction is further monitored by TLC, upon completion, the reaction is quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography (20% to 40% EtOAc in Hex) afforded compound **2b** (82mg, 48%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.19 (t, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 4.55 – 4.50 (m, 1H), 3.48 (s, 1H), 3.31 (s, 3H), 3.12 (s, 1H), 2.26 (s, 1H), 2.20 – 1.89 (m, 8H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 179.0, 179.0, 152.1, 142.3, 133.7, 127.8, 123.4, 123.3, 116.4, 73.5, 73.4, 56.6, 41.3, 37.7, 37.4, 37.3, 37.1, 32.8, 32.5, 32.4, 32.2, 31.0, 29.7, 27.6. (mixture of E/Z isomers)

MS (ES+): m/z calc for $C_{18}H_{19}ClO_4$: 334.1; found: 333.2 $[M-H]^-$.



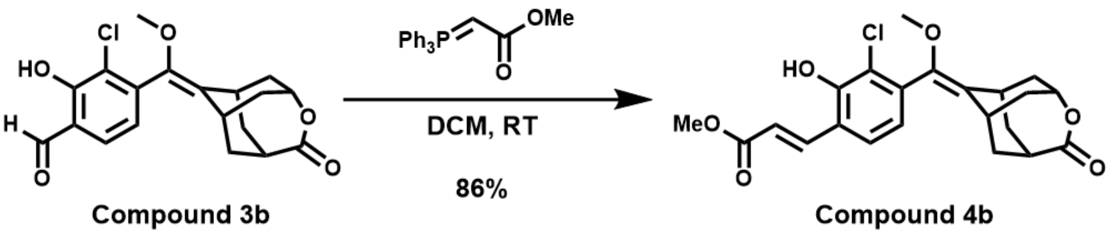
Compound 3b:

In a pressure flask, compound **2a** (82mg, 0.24mmol, 1eq) is dissolved in THF, Et_3N (0.3ml, 1.92mmol, 8eq) is added, followed by addition of paraformaldehyde (115mg, 3.84mmol, 16eq) and anhydrous $MgCl_2$ (91mg, 0.96mmol, 4eq). The pressure flask is immediately sealed and inserted into a pre-heated 80°C oil bath. The reaction turns bright yellow. After 4 hours, the reaction was cooled to RT, quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer is washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography (20% to 40% EtOAc in Hex) afforded compound **3b** (57mg, 65%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 9.92 (s, 1H), 7.54 (dd, *J* = 7.8, 2.9 Hz, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 4.61 – 4.48 (m, 1H), 3.48 (s, 1H), 3.34 (s, 3H), 3.14 – 3.08 (m, 1H), 2.23 – 2.08 (m, 5H), 2.03 – 1.89 (m, 4H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 195.8, 178.6, 178.5, 157.7, 141.9, 141.2, 131.4, 131.4, 125.6, 122.3, 122.2, 120.8, 73.2, 73.0, 57.0, 41.2, 41.1, 37.8, 37.4, 37.0, 37.0, 32.9, 32.5, 32.2, 32.0, 31.1, 29.7, 27.7. (mixture of E/Z isomers)

MS (ES+): m/z calc for $C_{19}H_{19}ClO_5$: 362.1; found: 361.1 $[M-H]^-$.



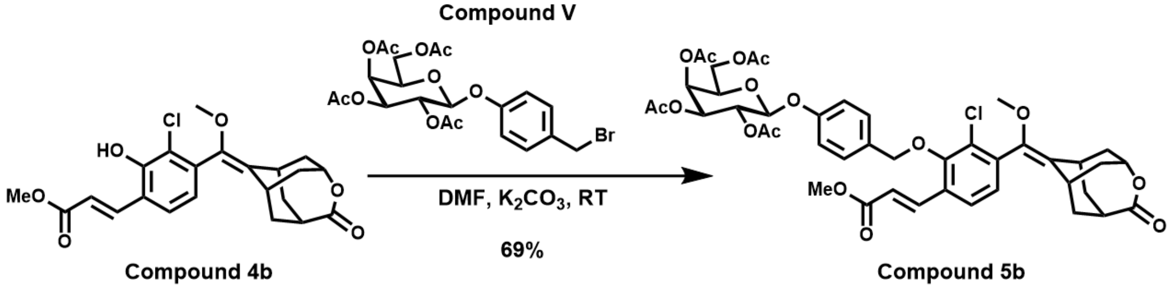
Compound 4b:

Compound **3b** (104mg, 0.29mmol, 1eq) is dissolved in DCM, followed by addition of Methyl-2-(triphenylphosphoranylidene)acetate (115mg, 0.34mmol, 1.2eq), the reaction changes color to yellow immediately (highly fluorescent under UV light). After 5 minutes of stirring, the reaction is quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layers are washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography (30% to 40% EtOAc in Hex) afforded compound **4b** (103mg, 86%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.93 (d, *J* = 16.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), 6.67 – 6.58 (m, 1H), 6.28 (s, 1H), 4.53 (s, 1H), 3.82 (s, 3H), 3.48 (s, 1H), 3.32 (d, *J* = 1.1 Hz, 3H), 3.13 (s, 1H), 2.29 (s, 1H), 2.19 – 1.89 (m, 12H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 178.8, 167.6, 150.8, 142.0, 138.8, 135.1, 127.3, 123.3, 123.0, 120.5, 116.0, 114.2, 73.3, 73.3, 57.0, 52.0, 41.3, 37.9, 37.5, 37.4, 37.2, 33.0, 32.6, 32.5, 32.4, 32.1, 31.8, 31.2, 29.8, 27.8, 22.8, 14.3.

MS (ES+): m/z calc for $C_{22}H_{23}ClO_6$: 418.1; found: 417.3 $[M-H]^-$.



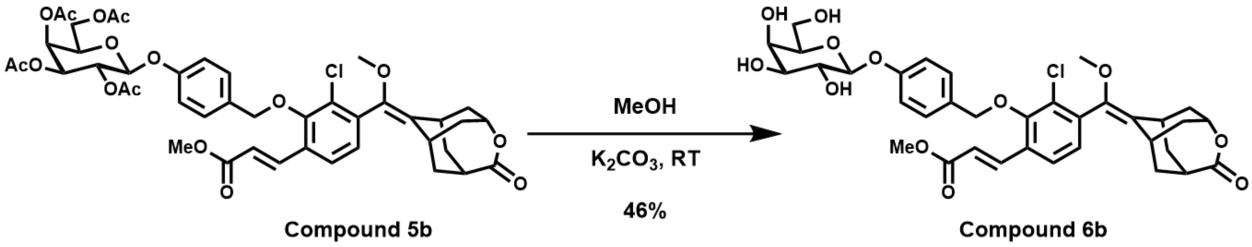
Compound 5b:

Compound **4b** (50mg, 0.2mmol, 1eq) is dissolved in dry DMF (2mL) followed by the addition of anhydrous K_2CO_3 (49mg, 0.36mmol, 3eq). The reaction is stirred for 5 min followed by the addition of compound **V**[2] (67mg, 0.086mmol, 1eq). Upon completion as indicated by TLC, the reaction is quenched with sat. NH_4Cl solution and sat. $Na_2S_2O_3$, extracted three times with EtOAc. The organic layers are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography (30% EtOAc in Hex) afforded compound **5b** (70mg, 69%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.92 (d, *J* = 16.2 Hz, 1H), 7.48 (dd, *J* = 7.9, 2.8 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 3.5 Hz, 2H), 6.47 (d, *J* = 16.2 Hz, 1H), 5.48 (dd, *J* = 11.3, 3.1 Hz, 2H), 5.15 – 5.10 (m, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 4.95 (s, 2H), 4.53 (s, 1H), 4.22 (dd, *J* = 7.0, 4.2 Hz, 1H), 4.16 (d, *J* = 4.1 Hz, 1H), 4.07 (t, *J* = 6.7 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 1H), 3.32 (s, 3H), 3.12 (s, 1H), 2.31 (td, *J* = 7.6, 2.6 Hz, 1H), 2.22 (d, *J* = 7.2 Hz, 1H), 2.19 (s, 3H), 2.16 – 2.10 (m, 2H), 2.07 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00 – 1.87 (m, 5H)

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 178.7, 178.6, 170.4, 170.3, 170.2, 169.4, 167.0, 157.3, 153.8, 141.8, 138.4, 136.6, 130.4, 127.4, 127.3, 125.6, 124.9, 120.6, 117.0, 99.7, 75.8, 73.3, 73.1, 71.1, 70.8, 68.6, 66.8, 62.1, 61.3, 56.8, 51.9, 41.2, 37.8, 37.4, 37.1, 32.9, 32.5, 32.2, 31.9, 27.7, 27.2, 25.6, 24.9, 22.7, 20.7, 20.7, 20.6, 14.1.

MS (ES+): m/z calc for $C_{43}H_{47}ClO_{16}$: 854.3; found: 878.0 $[M+Na]^+$.



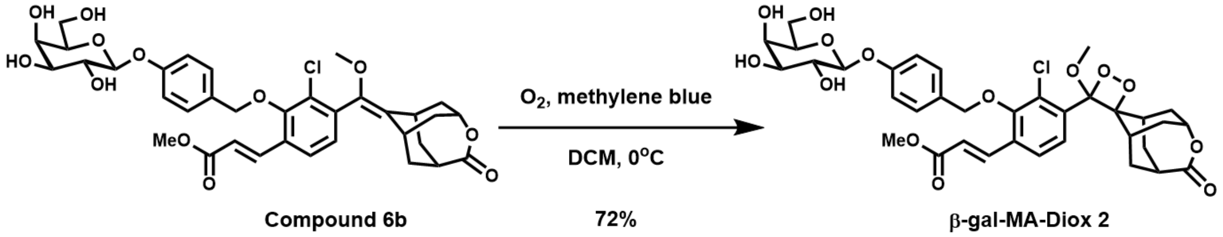
Compound 6b:

Compound **5b** (35mg, 0.041mmol, 1eq) was dissolved in MeOH (2mL) followed by the addition of few grains of anhydrous K_2CO_3. The reaction is monitored by RP-HPLC (30-100% ACN gradient). Upon completion, the reaction is quenched by sat. NH_4Cl solution and extracted 3 times with EtOAc. The organic extracts are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield compound **6b** (13mg, 46%) as a white solid. The crude product was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): 7.82 (d, *J* = 16.1 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.97 (d, *J* = 6.8 Hz, 2H), 6.41 (d, *J* = 16.1 Hz, 1H), 4.99 (d, *J* = 7.9 Hz, 1H), 4.88 (s, 2H), 4.51 (s, 1H), 4.14 (s, 1H), 4.00 (s, 1H), 3.86 (s, 2H), 3.77 (s, 3H), 3.64 (s, 2H), 3.44 (s, 1H), 3.29 (s, 3H), 3.08 (s, 1H), 2.15 (s, 1H), 2.10 – 1.84 (m, 9H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 179.7, 167.4, 157.5, 153.6, 141.9, 138.9, 136.7, 131.1, 130.7, 130.0, 127.3, 125.7, 124.8, 124.7, 120.4, 116.6, 101.0, 76.2, 74.4, 73.9, 73.4, 71.2, 69.5, 62.0, 56.9, 52.2, 41.3, 37.6, 37.4, 37.1, 32.5, 32.2, 31.2, 27.7.

MS (ES+): m/z calc for $C_{35}H_{39}ClO_{12}$: 686.2; found: 725.8 $[M+K]^+$.



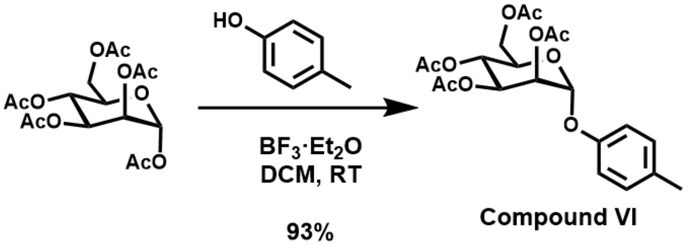
β-gal-MA-Diox 2:

Compound **6b** (13mg, 0.019mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light. The reaction was monitored by RP-HPLC (30-100% ACN gradient). – elution time: **β-gal-MA-Diox 2**: 11.0min. Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **β-gal-MA-Diox 2** (9.8mg, 72%) as a white solid.

^{1}**H-NMR** (400MHz, MeOD): 7.94 – 7.77 (m, 3H), 7.33 (dd, *J* = 8.9, 2.1 Hz, 2H), 7.09 (dt, *J* = 8.6, 2.5 Hz, 2H), 6.60 (dt, *J* = 16.2, 0.9 Hz, 1H), 4.99 – 4.94 (m, 2H), 4.34 (d, *J* = 8.8 Hz, 1H), 3.90 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.81 (d, *J* = 0.8 Hz, 3H), 3.80 – 3.76 (m, 3H), 3.77 – 3.74 (m, 1H), 3.70 (dddd, *J* = 8.0, 6.9, 4.9, 1.5 Hz, 1H), 3.59 (ddd, *J* = 9.8, 3.3, 2.1 Hz, 1H), 3.21 – 3.19 (m, 3H), 2.86 – 2.79 (m, 1H), 2.80 – 2.56 (m, 1H), 2.21 – 1.38 (m, 9H). Mixture of diastereomers.

^{13}**C-NMR** (101MHz, MeOD): δ(ppm) = 179.3, 179.1, 167.1, 158.3, 154.3, 138.0, 138.0, 134.2, 132.3, 130.6, 130.5, 129.5, 128.4, 127.5, 125.7, 121.0, 116.4, 116.3, 110.9, 101.5, 101.5, 93.1, 92.8, 76.0, 75.6, 73.4, 72.1, 71.4, 70.9, 68.8, 61.0, 51.1, 48.9, 48.8, 39.4, 38.7, 33.3, 32.2, 32.1, 32.0, 30.9, 30.4, 30.3, 30.2, 27.9, 26.7, 26.6, 25.6, 25.2. Mixture of diastereomers.

MS (ES+): m/z calc for $C_{35}H_{41}ClO_{12}$: 718.2; found: 719.7 [M+H]$^+$.



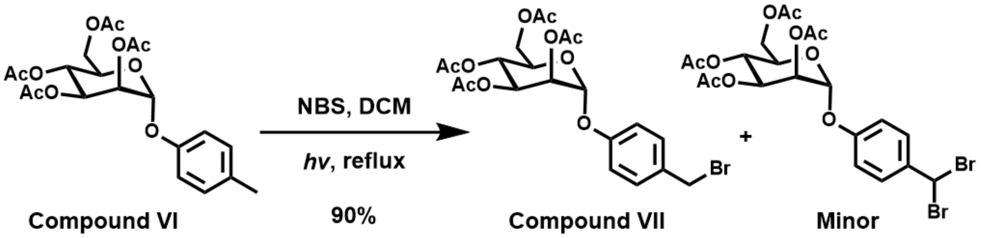
Compound VI:

α-d-mannose pentaacetate (500mg, 1.28mmol, 1eq) is dissolved in dry DCM (5mL) followed by the addition of $BF_3 \cdot Et_2O$ (0.49ml, 3.84mmol, 3eq). After stirring for a few minutes, para-cresol (277mg, 2.56, 2eq) is added and the reaction is stirred overnight. The starting material consumption is monitored by TLC using CAM stain, after completion, the reaction was slowly quenched with sat. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography afforded compound **VI** (561mg, 93%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.08 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.55 (dd, *J* = 10.0, 3.5 Hz, 1H), 5.47 (d, *J* = 1.7 Hz, 1H), 5.43 (dd, *J* = 3.5, 1.9 Hz, 1H), 5.35 (t, *J* = 10.0 Hz, 1H), 4.27 (dd, *J* = 12.0, 5.1 Hz, 1H), 4.15 – 4.03 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 2.04(s, 3H), 2.03 (d, *J* = 2.0 Hz, 6H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 170.7, 170.1, 170.0, 169.9, 153.6, 132.6, 130.1, 116.5, 96.1, 69.6, 69.1, 69.0, 66.1, 62.3, 21.0, 20.8, 20.8, 20.6.

MS (ES+): m/z calc for $C_{21}H_{26}O_{10}$: 438.2; found: 461.5 $[M+Na]^+$.



Compound VII:

Compound **VI** (100mg, 0.44mmol, 1eq) is dissolved in dry DCM (20mL) followed by the addition of NBS (78mg, 0.44mmol, 1eq). The reaction was heated to reflux and irradiated by a yellow lamp for 20 min. The reaction completion is monitored by RP-HPLC (30-100% ACN gradient) – elution times: Compound **VI –** 14.0min (273nm max); compound **VII** – 14.3min (239nm max); dibromo product – 11.2min (267nm max)**.** After consumption of the starting material, the solvent was evaporated to about 3mL and the mixture was directly loaded on a silica column, eluting starting with 20% DCM in Hex up to 100% DCM to afford compound **VII** and dibromo product mixture (108mg,compound **VII** : dibromo = 5:1, 90%) as a yellowish solid. The crude mixture was further reacted as obtained.

^{1}H-NMR (Major) (400MHz, $CDCl_3$): δ(ppm) = 7.33 (d, 2H), 7.05 (dt, *J* = 6.8, 2.4 Hz, 2H), 5.54 (dt, *J* = 10.0, 2.7 Hz, 2H), 5.43 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.36 (t, *J* = 10.0 Hz, 1H), 4.47 (s, 2H), 4.30 – 4.23 (m, 1H), 4.09 – 4.03 (m, 2H), 2.19 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H).

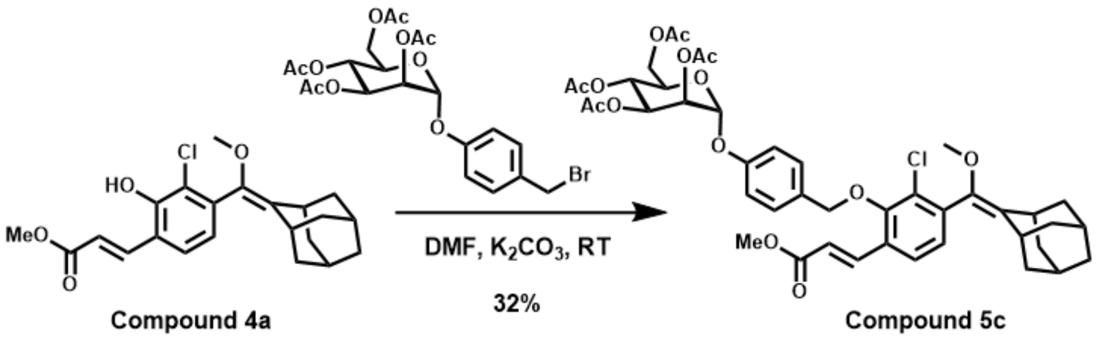
^{1}H-NMR (Minor) (400MHz, $CDCl_3$): δ(ppm) = 7.52 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 10.2 Hz, 2H), 6.63 (s, 1H), 5.54 (dt, *J* = 10.0, 2.7 Hz, 2H), 5.43 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.36 (t, *J* = 10.0 Hz, 1H), 4.30 – 4.23 (m, 1H), 4.09 – 4.03 (m, 2H), 2.19 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H).

(Aliphatic peaks of the mixture overlap)

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 170.6, 170.1, 169.8, 155.6, 132.6, 130.6, 128.2, 116.8, 116.4, 95.8, 77.5, 77.1, 76.8, 69.4, 68.9, 66.0, 62.2, 33.2, 29.8, 21.0, 20.8, 14.2.

MS (Major) (ES+): m/z calc for $C_{21}H_{25}{}^{81}BrO_{10}$: 518.1; found: 541.4 $[M+Na]^+$.

MS (Minor) (ES+): m/z calc for $C_{21}H_{24}{}^{81}Br_2O_{10}$: 596.0; found: 619.4 $[M+Na]^+$.



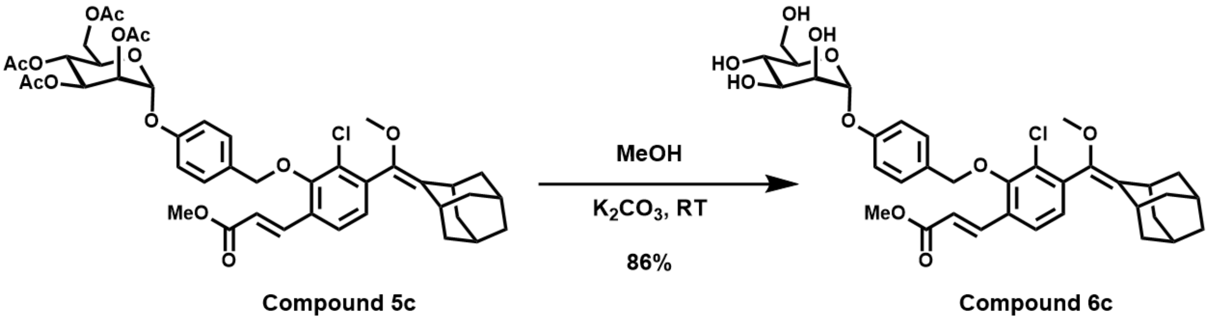
Compound 5c:

Compound **4a**[2] (40mg, 0.1mmol, 1.2eq) is dissolved in dry DMF (2mL) followed by the addition of anhydrous K_2CO_3 (28mg, 0.2mmol, 2eq). The reaction is stirred for 5 min followed by the addition of compound **VII** (45mg, 0.086mmol, 1eq). Upon completion as indicated by TLC, the reaction is quenched with sat. NH_4Cl solution and sat. $Na_2S_2O_3$, extracted three times with EtOAc. The organic layers are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography (30% EtOAc in Hex) afforded compound **5c** (26mg, 32%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.90 (d, *J* = 16.2 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 3H), 7.08 (dd, *J* = 10.5, 8.3 Hz, 3H), 6.43 (d, *J* = 16.2 Hz, 1H), 5.56 (dd, *J* = 10.0, 3.5 Hz, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 5.45 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.37 (t, *J* = 10.1 Hz, 1H), 4.94 (d, *J* = 4.8 Hz, 2H), 4.29 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.13 – 4.03 (m, 2H), 3.80 (s, 3H), 3.32 (s, 3H), 3.27 (s, 1H), 2.20 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96 – 1.65 (m, 13H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 170.7, 170.1, 169.9, 167.2, 155.9, 153.7, 139.5, 139.0, 138.3, 132.6, 130.8, 130.6, 129.9, 129.8, 127.9, 125.2, 120.0, 116.6, 95.9, 75.7, 69.5, 69.3, 69.0, 66.0, 62.2, 57.4, 51.9, 39.3, 39.1, 38.7, 37.2, 33.1, 29.8, 28.5, 28.3, 21.0, 20.8.

MS (ES+): m/z calc for $C_{43}H_{49}ClO_{14}$: 824.3; found: 847.9 $[M+Na]^+$.



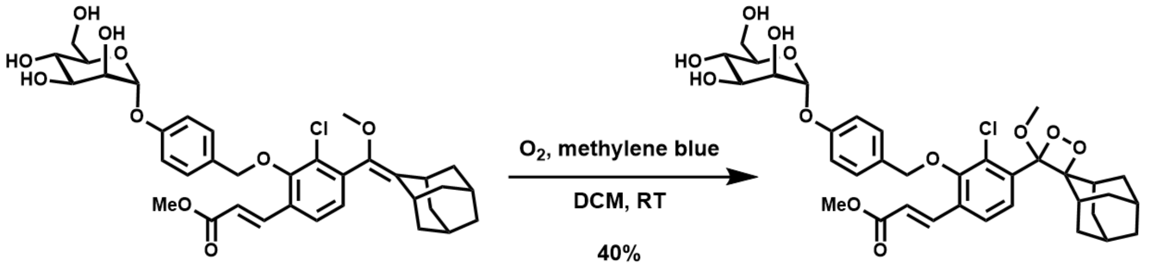
Compound 6c:

Compound **5c** (26mg, 0.032mmol, 1.2eq) was dissolved in MeOH (2mL) followed by the addition of few grains of anhydrous K_2CO_3. The reaction is monitored by RP-HPLC (50-100% ACN gradient) – elution times: compound **5c**: 21.5min, compound **6c**: 14.3min. Upon completion, the reaction is quenched by sat. NH_4Cl solution and extracted 3 times with EtOAc. The organic extracts are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield compound **6c** (18mg, 86%) as a white solid. The crude product was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): 7.84 (d, *J* = 16.2 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.05 (dd, *J* = 8.3, 3.0 Hz, 3H), 6.37 (d, *J* = 16.2 Hz, 1H), 5.63 (s, 1H), 4.91 (d, *J* = 2.7 Hz, 2H), 4.25 – 4.15 (m, 3H), 4.00 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 1H), 3.69 – 3.65 (m, 1H), 3.30 (s, 3H), 3.26 (s, 1H), 2.06 (s, 1H), 1.93 – 1.66 (m, 12H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 167.4, 156.4, 153.7, 139.5, 139.1, 138.3, 132.5, 130.8, 130.1, 130.0, 129.9, 127.9, 125.1, 119.7, 116.5, 98.3, 75.9, 73.1, 71.6, 71.0, 66.3, 61.0, 60.6, 57.4, 52.0, 39.2, 38.8, 37.2, 33.1, 32.1, 31.8, 29.8, 28.5, 22.8.

MS (ES+): m/z calc for $C_{35}H_{41}ClO_{10}$: 656.2; found: 679.7 $[M+Na]^+$.



Compound 6c

α-man-MA-Diox 1

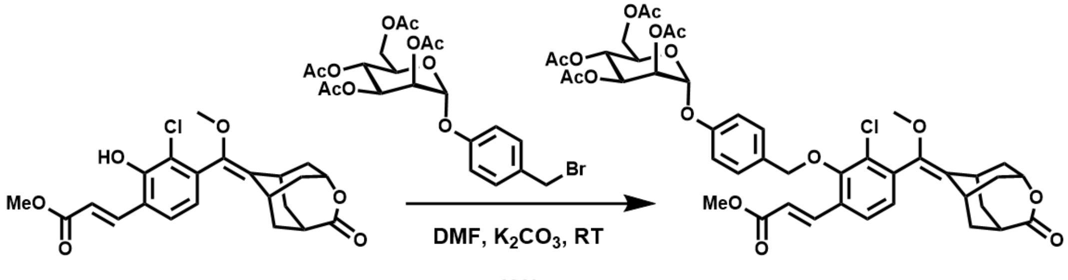
α-man-MA-Diox 1:

Compound **6c** (18mg, 0.027mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light. The reaction was monitored by RP-HPLC (50-100% ACN gradient). – elution times: compound **6c**: 14.3min, **α-man-MA-Diox 1**: 12.4min. Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **α-man-MA-Diox 1** (7.5mg, 40%) as a white solid.

^{1}H-NMR (400MHz, MeOD): 7.88 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.31 (dd, *J* = 8.7, 2.7 Hz, 2H), 7.10 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.51 (dd, *J* = 16.2, 0.9 Hz, 1H), 5.51 – 5.44 (m, 1H), 4.93 (d, *J* = 2.5 Hz, 2H), 4.00 (dd, *J* = 3.0, 1.9 Hz, 1H), 3.90 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.68 (m, 3H), 3.59 (ddd, *J* = 9.8, 4.9, 2.7 Hz, 1H), 3.19 (d, *J* = 1.3 Hz, 3H), 2.97 (s, 1H), 2.39 (d, *J* = 12.7 Hz, 1H), 1.98 (s, 1H), 1.75 (ddd, *J* = 49.4, 26.4, 13.5 Hz, 8H), 1.51 (d, *J* = 12.4 Hz, 1H), 1.39 (s, 2H).

^{13}C-NMR (101MHz, MeOD): δ(ppm) = 168.5, 158.4, 155.4, 139.5, 136.5, 133.3, 132.0, 130.9, 130.0, 126.5, 121.7, 117.7, 112.9, 100.2, 97.2, 93.5, 77.1, 75.4, 72.4, 72.0, 68.3, 62.6, 52.4, 50.0, 37.6, 35.1, 34.9, 33.6, 33.2, 32.9, 32.7, 27.7, 27.3.

MS (ES+): m/z calc for $C_{35}H_{41}ClO_{12}$: 688.2; found: 801.8 $[M+TFA-H]^-$.



Compound 4b

Compound 5d

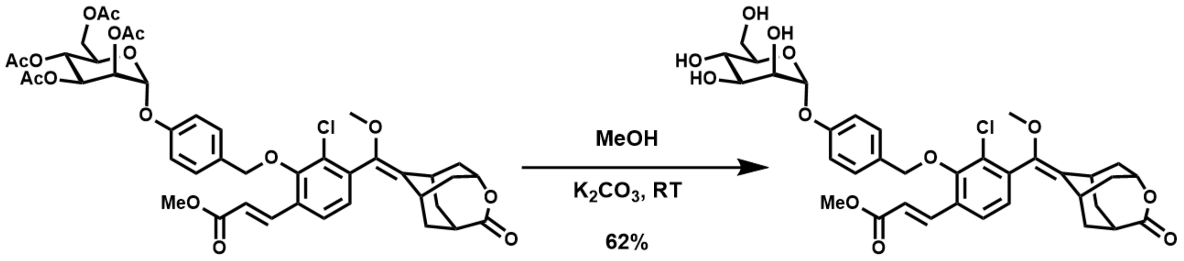
Compound 5d:

Compound **4b** (18mg, 0.043mmol, 1eq) is dissolved in dry DMF (2mL) followed by the addition of anhydrous K_2CO_3 (28mg, 0.2mmol, 2eq). The reaction is stirred for 5 min followed by the addition of compound **VII** (27mg, 0.052mmol, 1.2eq). Upon completion as indicated by TLC, the reaction is quenched with sat. NH_4Cl solution and sat. $Na_2S_2O_3$, extracted three times with EtOAc. The organic layers are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, purification of the crude product by column chromatography (50% to 70% EtOAc in Hex) afforded compound **5d** (18mg, 49%) as a white solid.

^{1}**H-NMR** (400MHz, $CDCl_3$): δ(ppm) = 7.89 (d, *J* = 16.2 Hz, 1H), 7.47 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.06 (ddd, *J* = 8.2, 5.3, 2.9 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 5.58 – 5.55 (m, 1H), 5.55 – 5.53 (m, 1H), 5.45 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 4.94 (s, 2H), 4.53 (s, 1H), 4.29 (dd, *J* = 12.3, 5.1 Hz, 1H), 4.12 – 4.04 (m, 2H), 3.82 (s, 3H), 3.51 – 3.48 (m, 1H), 3.32 (s, 3H), 3.12 (s, 1H), 2.24 (s, 1H), 2.20 (s, 3H), 2.17 – 2.13 (m, 1H), 2.11 – 2.06 (m, 2H), 2.05 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H), 2.01 – 1.86 (m, 5H).

^{13}**C-NMR** (101MHz, $CDCl_3$): δ(ppm) = 178.8, 170.7, 170.1, 169.9, 167.0, 156.0, 153.9, 141.9, 138.6, 136.7, 130.6, 127.5, 127.4, 125.7, 124.9, 124.2, 123.6, 120.7, 116.7, 116.0, 114.2, 99.8, 95.9, 75.9, 73.4, 73.3, 69.5, 69.4, 69.0, 66.0, 62.2, 60.6, 56.9, 52.0, 41.4, 37.9, 37.5, 37.2, 34.0, 33.0, 32.6, 32.3, 32.1, 31.8, 31.3, 29.8, 29.5, 29.3, 29.1, 27.8, 22.8, 21.0, 20.8, 14.3.

MS (ES+): m/z calc for $C_{43}H_{44}ClO_{16}$: 854.3; found: 855.9 $[M+H]^+$.



Compound 5d Compound 6d

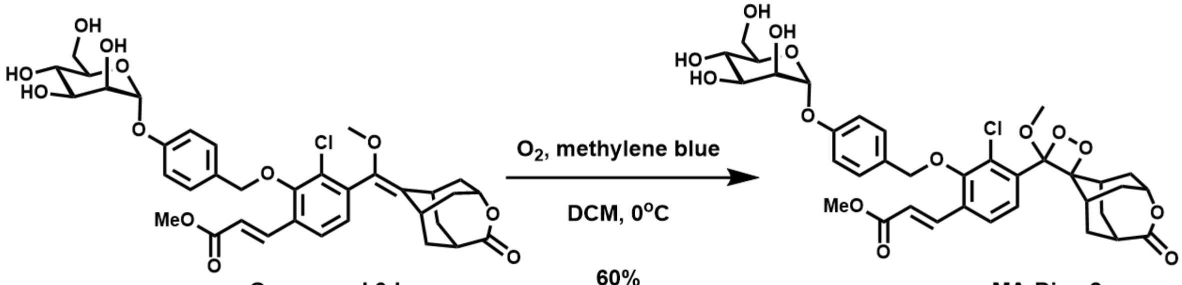
Compound 6d:

Compound **5d** (18mg, 0.021mmol) was dissolved in MeOH (2mL) followed by the addition of few grains of anhydrous K_2CO_3. The reaction is monitored by RP-HPLC (50-100% and 30-100% ACN gradient) – elution times: compound **5d**: 12.4min, compound **6d**: 10.5min respectively. Upon completion, the reaction is quenched by sat. NH_4Cl solution and extracted 3 times with EtOAc. The organic extracts are combined, washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield compound **6d** (9mg, 62%) as a white solid. The crude product was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): 7.89 (d, *J* = 16.2 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 6.7 Hz, 2H), 7.05 (dt, *J* = 8.6, 4.1 Hz, 3H), 6.45 (d, *J* = 16.2 Hz, 1H), 5.62 (s, 1H), 5.03 – 4.97 (m, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.53 (s, 1H), 4.21 (s, 3H), 4.01 (d, *J* = 10.9 Hz, 1H), 3.81 (s, 3H), 3.75 (d, *J* = 11.1 Hz, 1H), 3.66 (s, 1H), 3.48 (s, 1H), 3.32 (s, 3H), 3.14 – 3.08 (m, 1H), 2.25 – 2.21 (m, 1H), 2.19 (s, 1H), 2.12 – 2.07 (m, 2H), 2.02 – 1.85 (m, 5H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 179.3, 167.1, 156.6, 153.7, 141.9, 138.7, 136.7, 130.9, 130.7, 129.9, 129.7, 127.3, 125.7, 124.8, 124.6, 120.5, 116.5, 98.3, 76.2, 73.6, 73.5, 73.2, 71.5, 70.9, 66.3, 61.0, 56.9, 52.1, 41.3, 37.8, 37.5, 37.2, 32.9, 32.5, 32.3, 32.1, 31.2, 29.8, 29.5, 27.8, 22.8, 14.3.

MS (ES+): m/z calc for $C_{35}H_{39}ClO_{12}$: 686.2; found: 725.7 $[M+K]^+$.



Compound 6d

α-man-MA-Diox 2

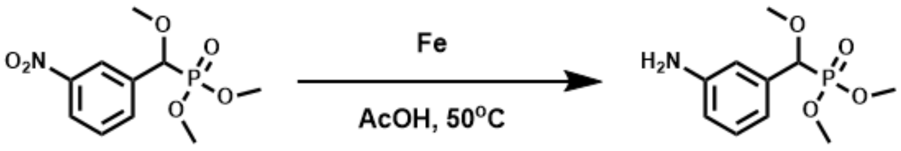
α-man-MA-Diox 2:

Compound **6d** (18mg, 0.027mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light. The reaction was monitored by RP-HPLC (30-100% ACN gradient). – elution times: compound **6d**: 10.5min, **α-man-MA-Diox 2**: 11.2min. Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **α-man-MA-Diox 2** (5.6mg, 60%) as a white solid.

^{1}H-NMR (400MHz, MeOD): 7.90 (d, *J* = 8.4 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.55 (dd, *J* = 16.2, 2.6 Hz, 1H), 5.47 (d, *J* = 1.9 Hz, 1H), 4.95 (s, 2H), 4.36 – 4.31 (m, 1H), 4.00 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.89 (dt, *J* = 9.4, 2.6 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.67 (m, 3H), 3.57 (dq, *J* = 6.8, 2.4, 1.9 Hz, 1H), 3.20 (dd, *J* = 3.3, 1.2 Hz, 4H), 2.83 – 2.79 (m, 1H), 2.23 – 2.14 (m, 2H), 2.10 (d, *J* = 16.1 Hz, 1H), 2.02 – 1.40 (m, 6H).

^{13}C-NMR (101MHz, MeOD): δ(ppm) = 179.1, 167.0, 157.1, 137.9, 134.2, 132.5, 130.7, 129.4, 128.4, 127.4, 125.7, 120.8, 116.3, 98.8, 93.1, 76.0, 74.0, 72.1, 71.4, 71.0, 70.6, 66.9, 61.3, 51.0, 48.8, 39.4, 38.7, 33.3, 32.2, 32.1, 30.9, 30.4, 30.3, 30.2, 27.9, 26.6, 25.6, 25.2.

MS (ES+): m/z calc for $C_{35}H_{41}ClO_{12}$: 718.2; found: 831.8 $[M+TFA-H]^-$.



Compound VIII 68% Compound IX

Compound IX:

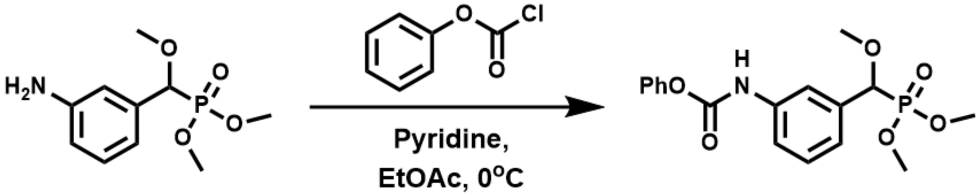
Compound **VIII**[5] (500mg, 1.8mmol, 1eq) was dissolved in AcOH (4mL), followed by addition of iron powder (500mg, 9.1mmol, 5eq). The reaction was heated to 50°C using an oil bath and monitored by TLC, the reaction turns into a grey thick suspension. After completion, the reaction was cooled to RT, quenched with 1M NaOH and diluted with $CHCl_3$, a brown precipitate forms. The mixture was filtered through celite and extracted with $CHCl_3$. The combined organic layers are washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded compound **IX** (305mg, 68%) as an off-white solid. The crude product was used without further purification.

^{1}H-NMR (400MHz, C_6D_6): δ(ppm) = 6.99 (t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 6.28 (d, *J* = 7.9 Hz, 1H), 4.35 (d, *J* = 15.4 Hz, 1H), 3.45 (d, *J* = 10.5 Hz, 3H), 3.31 (d, *J* = 10.4 Hz, 3H), 3.06 (s, 3H).

^{13}C-NMR (101MHz, C_6D_6): δ(ppm) = 147.5, 135.9, 129.1, 118.1, 118.0, 114.9, 114.9, 114.7, 114.7, 81.7, 80.0, 57.9, 57.8, 53.1, 53.1, 52.8, 52.7.

^{31}P-NMR (162MHz, C_6D_6): δ(ppm) = 21.7.

MS (ES+): m/z calc for $C_{10}H_{16}NO_4P$: 245.1; found: 268.2 $[M+Na]^+$.



Compound IX Compound X

70%

Compound X:

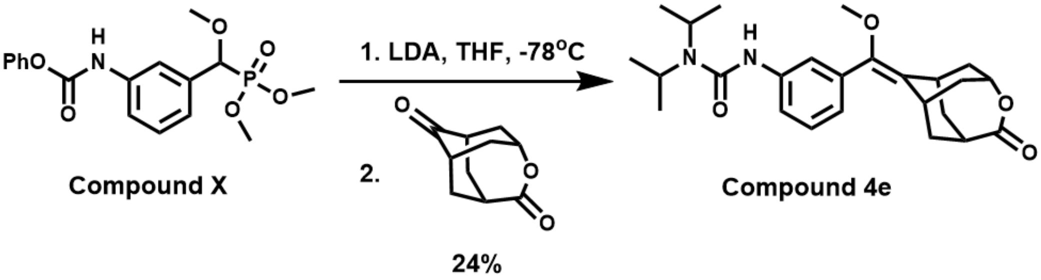
Compound **IX** (305mg, 1.24mmol, 1eq) was dissolved in EtOAc (5mL), followed by addition of pyridine (0.2mL, 2.48mmol, 2eq). The reaction was cooled to 0°C using an ice bath, phenyl chloroformate (0.234Ml, 1.86mmol, 1.5eq) was slowly added to the solution, a white precipitate forms. The reaction was quenched with 1M HCl and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. The crude product was purified on a short silica column to afford compound **X** (317mg, 70%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.57 – 7.49 (m, 2H), 7.43 – 7.32 (m, 4H), 7.26 – 7.21 (m, 1H), 7.20 – 7.15 (m, 3H), 4.54 (d, *J* = 15.7 Hz, 1H), 3.74 (d, *J* = 10.5 Hz, 3H), 3.69 (d, *J* = 10.5 Hz, 3H), 3.39 (s, 3H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 151.8, 150.7, 138.1, 135.4, 129.6, 125.9, 123.5, 121.8, 119.2, 118.4, 81.0, 79.4, 59.0, 58.8, 54.1, 54.0, 53.9, 53.8.

^{31}P-NMR (162MHz, $CDCl_3$): δ(ppm) = 21.0.

MS (ES+): m/z calc for $C_{17}H_{20}NO_6P$: 365.1; found: 388.4 $[M+Na]^+$.



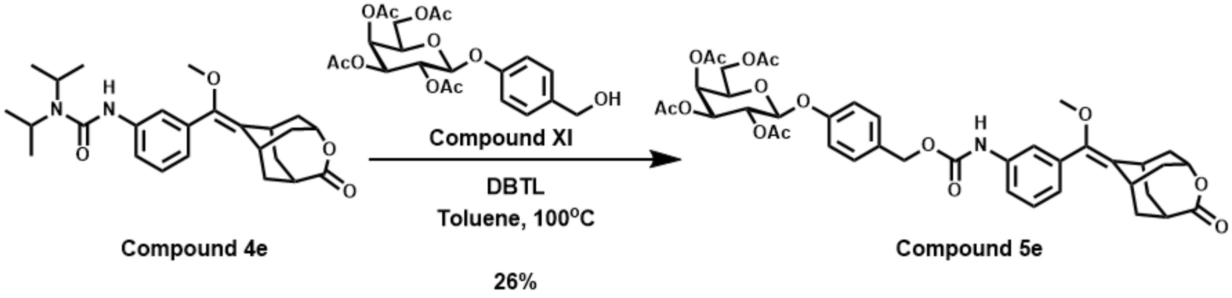
Compound 4e:

To a freshly prepared solution of LDA (0.82 mmol, 4eq) in THF (2 mL) under argon a solution of phosphonate **X** (75mg, 0.20mmol in 1mL, 1eq) in dry THF was added dropwise at -78°C, the solution turns orange. Following 20 minutes of stirring, a solution of compound **II** (74mg, 0.41mmol in 2mL, 2eq) in dry THF is added all at once into the flask. The reaction is stirred for additional 20 minutes at -78°C and then allowed to reach room temperature. After completion of the reaction indicated by TLC, the reaction is quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography (30% to 40% EtOAc in Hex) afforded the urea derivative, compound **4e** (21mg, 24%) as a yellowish oil.

^{1}H-NMR (400MHz, C_6D_6): δ(ppm) = 7.91 (s, 1H), 7.25 – 7.21 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.12 (s, 1H), 4.01 (s, 1H), 3.52 (hept, *J* = 6.9 Hz, 2H), 3.22 (s, 1H), 3.16 – 3.12 (m, 3H), 3.01 (t, *J* = 5.5 Hz, 1H), 2.68 (s, 1H), 1.74 (dd, *J* = 13.6, 5.6 Hz, 2H), 1.63 – 1.61 (m, 2H), 1.57 – 1.51 (m, 2H), 1.33 – 1.28 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 12H).

^{13}C-NMR (101MHz, C_6D_6): δ(ppm) = 177.0, 153.9, 146.1, 140.6, 135.3, 128.7, 124.9, 123.0, 120.5, 118.9, 72.4, 57.1, 45.6, 41.8, 37.7, 37.4, 32.7, 32.5, 30.8, 30.0, 28.2, 21.1.

MS (ES+): m/z calc for $C_{25}H_{34}N_2O_4$: 426.3; found: 427.6 $[M+H]^+$.



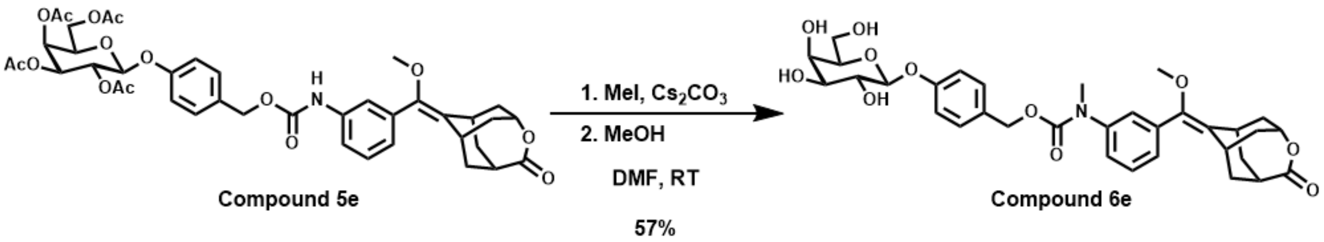
Compound 5e:

Compound **4e** (65mg, 0.15mmol, 1eq) and compound **XI**[5] (54mg, 0.12mmol, 0.8eq) were dissolved in toluene (2mL) and then, DBTL (0.017mL, 0.3mmol, 2eq) was added to the solution. The reaction flask was heated to 100°C using an oil bath and the reaction was monitored by TLC. Upon completion, the solution was cooled to RT and directly loaded on a silica column. Purification of the crude product by column chromatography (40% to 60% EtOAc in Hex) afforded compound **5e** (32mg, 26%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.41 (s, 1H), 7.38 – 7.33 (m, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.03 – 6.96 (m, 3H), 6.74 (s, 1H), 5.52 – 5.44 (m, 2H), 5.15 (s, 2H), 5.11 (dd, *J* = 10.4, 3.4 Hz, 1H), 5.04 (d, *J* = 7.9 Hz, 1H), 4.57 – 4.49 (m, 1H), 4.25 – 4.04 (m, 3H), 3.45 (s, 1H), 3.29 (s, 3H), 3.13 (t, *J* = 5.8 Hz, 1H), 2.74 (s, 1H), 2.23 – 2.20 (m, 1H), 2.18 (s, 3H), 2.14 – 2.08 (m, 2H), 2.06 (d, 6H), 2.01 (s, 3H), 1.99 – 1.83 (m, 5H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 178.9, 170.5, 170.4, 170.3, 169.5, 157.1, 153.3, 145.9, 138.0, 135.3, 130.2, 129.2, 124.8, 124.4, 119.4, 118.5, 117.2, 99.7, 73.5, 71.2, 70.9, 68.7, 67.0, 66.7, 61.4, 57.7, 41.4, 37.8, 37.5, 33.0, 32.7, 30.7, 29.8, 28.2, 20.9, 20.8, 20.7.

MS (ES+): m/z calc for $C_{40}H_{45}NO_{15}$: 779.3; found: 802.9 $[M+Na]^+$.



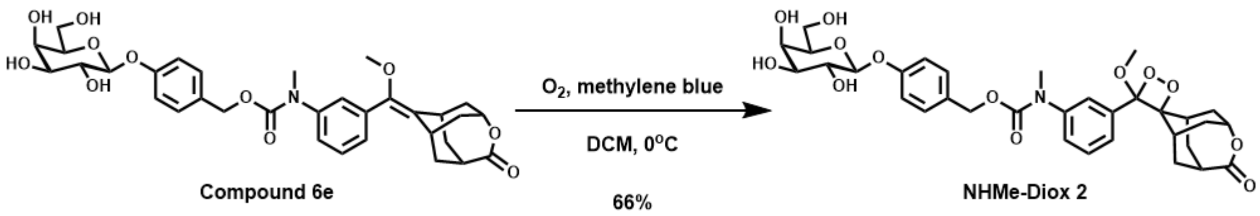
Compound 6e:

Compound **5e** (35mg, 0.043mmol, 1eq) was dissolved in DMF (1.5mL) and Cs_2CO_3 (85mg, 0.26mmol, 6eq) was added to the solution. After stirring for 5 minutes, iodomethane (0.027mL, 0.43mmol, 10eq) was added to the suspension. After reaction completion indicated by TLC, the excess iodomethane was evaporated in vacuo and MeOH was added to the suspension and stirred at RT. After reaction completion as indicated by RP-HPLC, the reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with sat. NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded compound **6e** (10mg, 57% - two steps, white solid) that was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.34 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.05 (m, 5H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.02 (s, 2H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.47 (s, 1H), 3.95 (s, 1H), 3.78 (t, *J* = 13.9 Hz, 3H), 3.72 – 3.56 (m, 2H), 3.37 (s, 1H), 3.30 (s, 3H), 3.24 (s, 3H), 3.04 (s, 1H), 2.56 (s, 1H), 2.16 – 2.07 (m, 1H), 2.01 (d, *J* = 15.2 Hz, 2H), 1.84 (s, 3H), 1.72 – 1.59 (m, 2H).

^{13}C-NMR (101MHz, $CDCl_3$): δ(ppm) = 179.7, 157.3, 155.5, 145.6, 143.3, 134.8, 130.7, 129.7, 129.1, 126.7, 125.0, 116.9, 101.3, 74.7, 73.8, 73.5, 71.2, 68.9, 67.3, 61.4, 57.8, 41.3, 37.9, 37.5, 37.3, 32.5, 32.1, 31.8, 30.5, 29.8, 29.5, 28.1, 22.8.

MS (ES+): m/z calc for $C_{33}H_{39}NO_{11}$: 625.3; found: 648.7 $[M+Na]^+$.



NHMe-Diox 2

Compound **6e** (10mg, 0.027mmol) was dissolved in DCM (10mL), a catalytic amount of methylene blue (<1mg) was added to the solution. Oxygen was bubbled through the solution while irradiating with a yellow light for a duration of 12min. The reaction was monitored by

RP-HPLC (30-100% ACN gradient) – elution times: compound **6e**: 8.0 min, **NHMe-Diox 2**: 8.8min. Upon completion, the solvent was evaporated under reduced pressure at 20°C. The crude product was purified by preparative RP-HPLC. The acetonitrile was evaporated under reduced pressure at 20°C following a freeze drying to afford **NHMe-Diox 2** (5.6mg, 66%) as a fluffy white solid.

^{1}H-NMR (400MHz, MeOD): 7.53 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.08 – 7.05 (m, 3H), 5.07 (d, *J* = 7.9 Hz, 2H), 4.30 (s, 1H), 3.89 (d, *J* = 3.3 Hz, 1H), 3.80 – 3.77 (m, 1H), 3.75 (d, *J* = 3.9 Hz, 2H), 3.70 – 3.67 (m, 1H), 3.58 (ddd, *J* = 9.7, 4.4, 2.7 Hz, 2H), 3.32 (s, 3H), 3.19 (s, 3H), 3.14 (s, 1H), 2.78 (t, *J* = 5.8 Hz, 1H), 2.65 (s, 1H), 2.20 (s, 2H), 2.11 – 2.05 (m, 2H), 1.97 – 1.87 (m, 3H), 1.76 (d, *J* = 14.5 Hz, 1H).

^{13}C-NMR (101MHz, MeOD): δ(ppm) = 179.5, 179.2, 158.0, 155.9, 143.8, 135.0, 130.2, 129.3, 127.0, 116.5, 111.1, 101.7, 92.5, 75.7, 73.6, 72.1, 71.4, 71.0, 69.0, 67.2, 61.1, 49.2, 39.4, 38.8, 36.8, 33.8, 31.9, 31.0, 30.5, 30.4, 28.7, 26.7, 25.8, 25.2.

(Mixture of diastereomers as indicated by the carbonyl peaks)

MS (ES+): m/z calc for $C_{33}H_{39}NO_{13}$: 657.2; found: 770.8 [M+TFA-H]

Experimental Protocols:

TBS-Kinetics evaluations in DMSO:

Chemiluminescent kinetic profiles were recorded using Spectramax iD3 equipped with an injector cartridge. Solutions of dioxetanes in ACN were diluted to a concentration of 100nM, the injector was washed with ACN and primed with the working solution. 10μL of the working solution was injected to a 96-well white Corning™ plate (each well containing 89μL DMSO, 1μL TBAF (10mM), 10μL probe (10nM)). Measurements were recorded as triplicates at room temperature with 100ms shutter speed of the detector. Luminometer

Visual demonstration and image analysis:

Light emission was recorded using an iPhone XS with ProCamera software. To a vial containing 1 mL of DMSO was added 20 μL of TBAF (1M in THF) and stirred for a few seconds, then 50 μL of Diox 1-4 were added, and the light emission was recorded for 2 minutes in total.

Camera settings: 120fps, 1/120 shutter speed, ISO 50.

The videos were analyzed using ImageJ software to extract mean grey area information to plot as normalized intensity plots for the video graphs.

Data acquisition and processing:

All chemiluminescent data were recorded on Spectramax iD3 luminometer, and the signal is obtained as relative luminescence units vs. time. All data was processed using Origin 2024 software. Kinetic plots are plotted as relative luminescence units (RLU) vs. time. Total light emission (TLE) is obtained by integrating the luminescence intensity over time. The background signal is defined as the signal in the absence of the enzyme, following initial signal burn-off.

Signal-to-noise (S/N) graphs are obtained by plotting the integrated intensity (TLE) divided by the integrated background signal vs. time.

Detector shutter speed (integration time) was set to 100 msec in all measurements.

Chemiluminescence measurements of the enzymatic probes with β-galactosidase or α-mannosidase:

Working solutions of MA-diox and NHMe-diox probes were prepared by diluting a 10mM stock solution in ACN/DMSO to a concentration of 100μM using ACN. Enzyme stock solution of 80u/mL was diluted with PBS to a concentration of 20u/mL, 10u/mL, 0.1u/mL or 0.01u/mL. The measurement was conducted using a 96-well white Corning™ plate – to each well was added 80μL of PBS 7.4 and 10μL of probe working solution. The measurement was started and background burn-off was monitored, after reaching a steady state, 10μL of the enzyme solution was added and the measurement was started again (final concentration of probe: 10μM. final concentration of enzyme: 2u/mL, 1u/mL, 0.01u/mL, 0.001u/mL.)

Stability assays in PBS pH 7.4

100μM solution of the probes β-gal-MA-Diox 1 and 2 were prepared in PBS 7.4 with 10% ACN and incubated at 37°C. 50μL of each solution were injected into the HPLC every 24h. Decomposition percentage was determined from integration of the dioxetane peak compared to the decomposition products at 280nM.

Biological evaluation of β-gal activity in bacteria

Test strain: *Escherichia coli* ATCC 8739

Culture: Tube with 2mL nutrient broth and 1mM IPTG, inoculated with approx. 100cfu/mL, incubated for 24h at 37°C in dry block heater.

Probes β-gal-MA-Diox 1 and 2 were diluted (1:20) with PBS 7.4 and incubated for 1h at 37°C for background burn-off.

PBS with cell lysis agents were added to transparent polypropylene tubes , 1mL total liquid volume, *E. coli* culture added (10μL) and mixed by vortexing at room temperature (21°C). Working solutions of the probes were added and chemiluminescence measurement was recorded using a bench top luminometer BLT1, NEMIS Technologies AG. Final probe concentration was 20μM, 1% DMSO as co-solvent.

Biological evaluation of α-man activity in bacteria

Test strain: *Enterococcus thailandicus* NEMIS 502

Culture: Shake flask with 50mL broth (Nutrient Broth + 1mM Methyl-alpha-D-mannopyranoside + 150mM K/Na phosphate buffer pH 7.1 + 0.5g/L MgSO4 $7 \cdot H_2O$), inoculated with approx. 10cfu/mL from BHI broth pre-culture, flask incubated for 24h at 37°C and 150 rpm.

Probes α-man-MA-Diox 1 and 2 were diluted (1:20) with PBS 7.4 and incubated for 1h at 37°C for background burn-off.

0.79mL culture sample added to transparent polypropylene tube, 10µL of lysis agent added (N,N-Dimethyldodecylammonium N-oxide, final concentration 70µg/mL), 0.2mL dioxetane working solution added, mixed by shaking, assay performed at 37°C, using a bench top luminometer BLT1, NEMIS Technologies AG. Final probe concentration was 20µM, 1% DMSO as co-solvent.

Supplementary figures

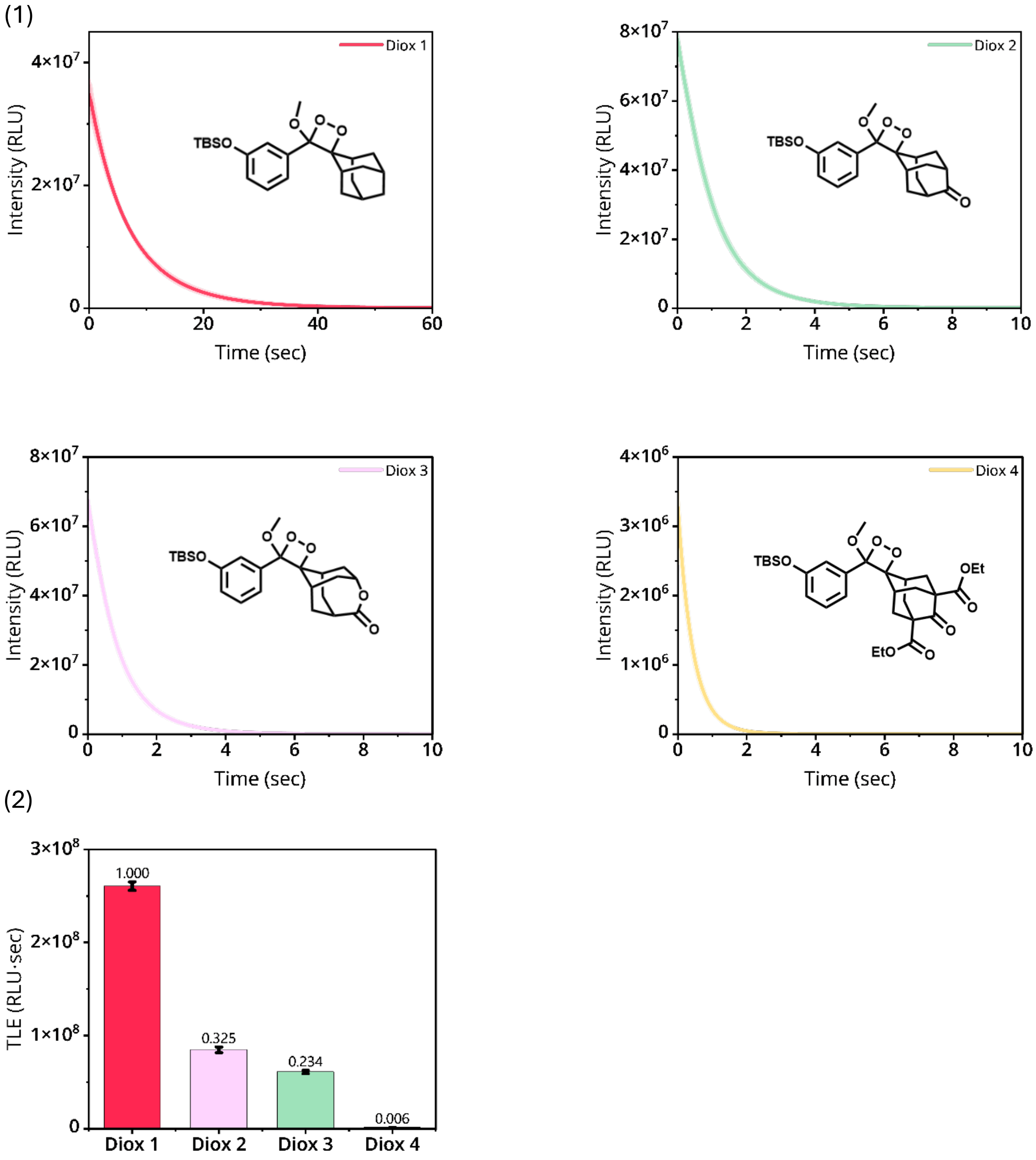


Figure S1: (1) Chemiluminescent activation of Diox 1-4 [10nM] in DMSO in the presence of TBAF [10mM]. (2) Total light emission of Diox 1-4 [10nM] in DMSO in the presence of TBAF [10mM] with relative TLE compared to Diox 1 above bars.

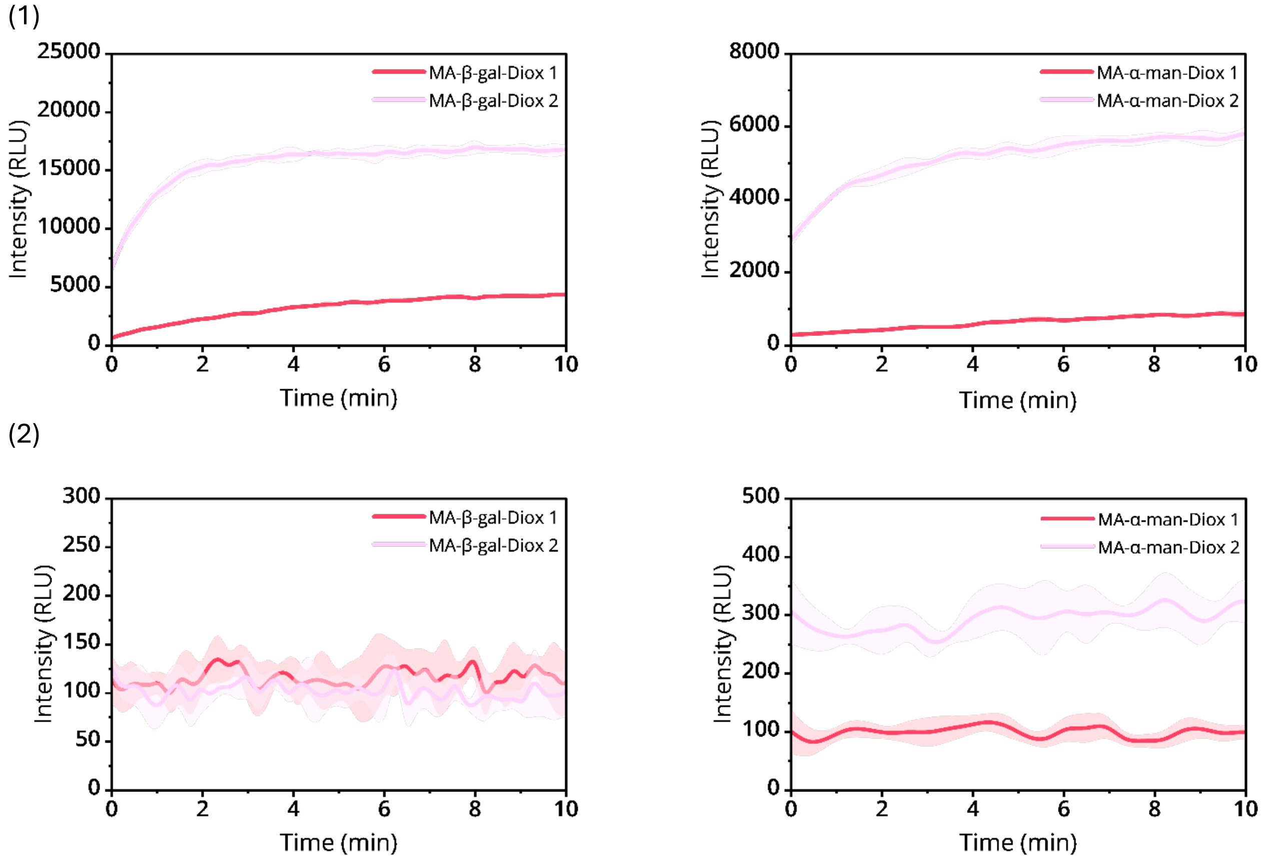


Figure S2: Chemiluminescent activation of (1) β-gal-MA-Diox 1, 2 and α-man-MA-Diox 1, 2 [10mM] in PBS 7.4 in the presence of β-galactosidase and α-mannosidase respectively [0.001u/mL]. (2) Kinetic profiles of β-gal-MA-Diox 1, 2 and α-man-MA-Diox 1, 2 [10mM] in PBS 7.4 in the absence of β-galactosidase and α-mannosidase.

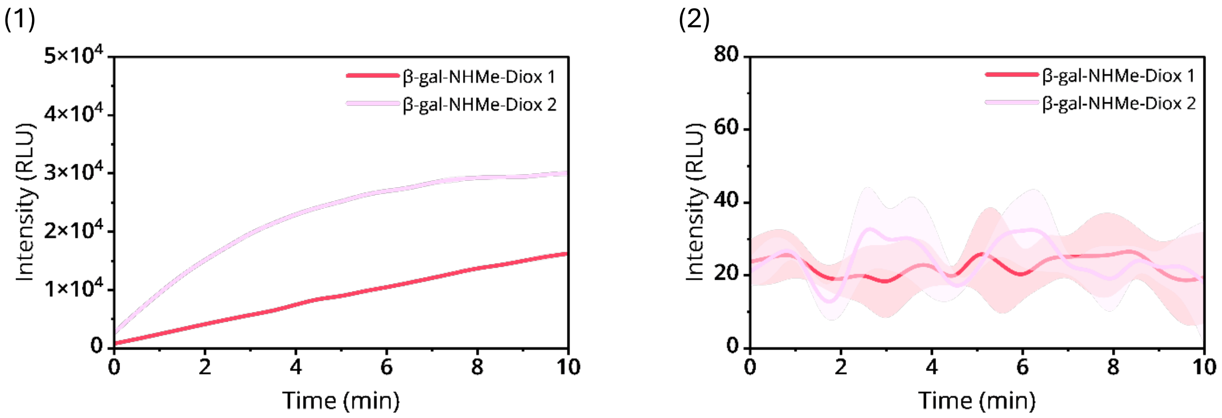


Figure S3: (1) Chemiluminescent activation of β-gal-NHMe-Diox 1 and 2 [10mM] in PBS 7.4 in the presence of β-galactosidase [0.01u/mL]. (2) Background kinetic profiles of β-gal-NHMe-Diox 1 and 2 [10mM] in PBS 7.4 in the absence of β-galactosidase.

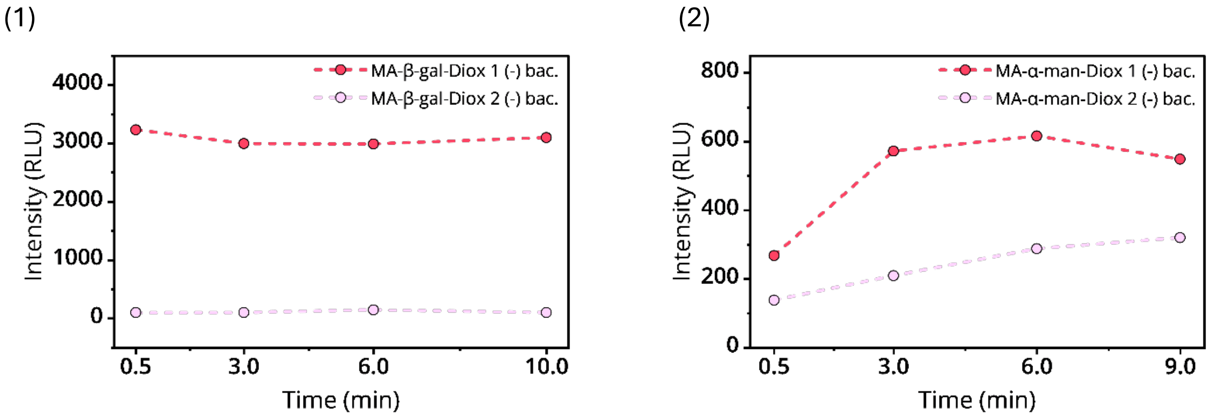
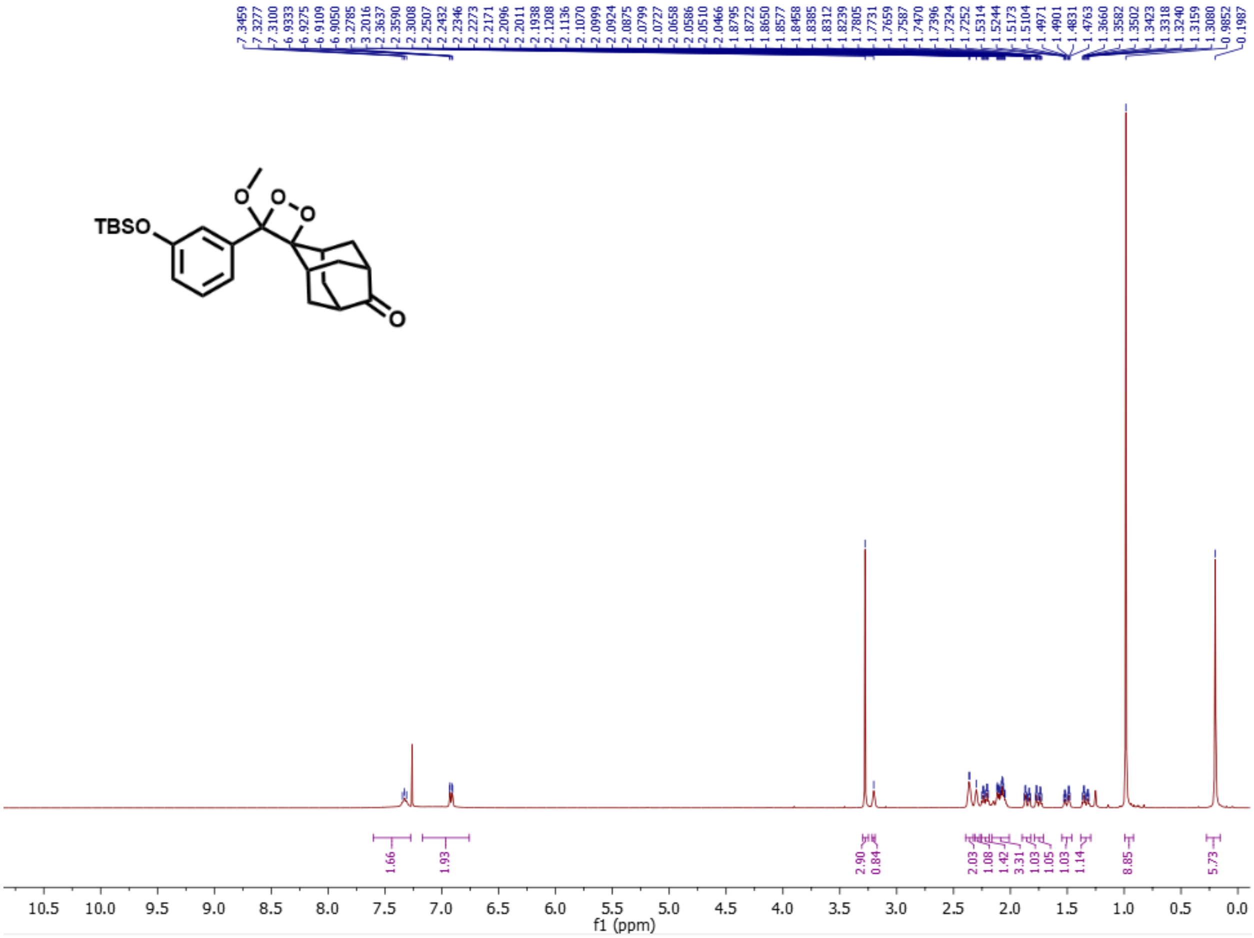


Figure S4: (1) Background kinetic profiles of β-gal-MA-Diox 1, 2 [20mM] in sterile nutrient broth in the absence of *E. coli*. (2) Background kinetic profiles of α-man-MA-Diox 1, 2 [20mM] in sterile nutrient broth in the absence of *E. thailandicus*.

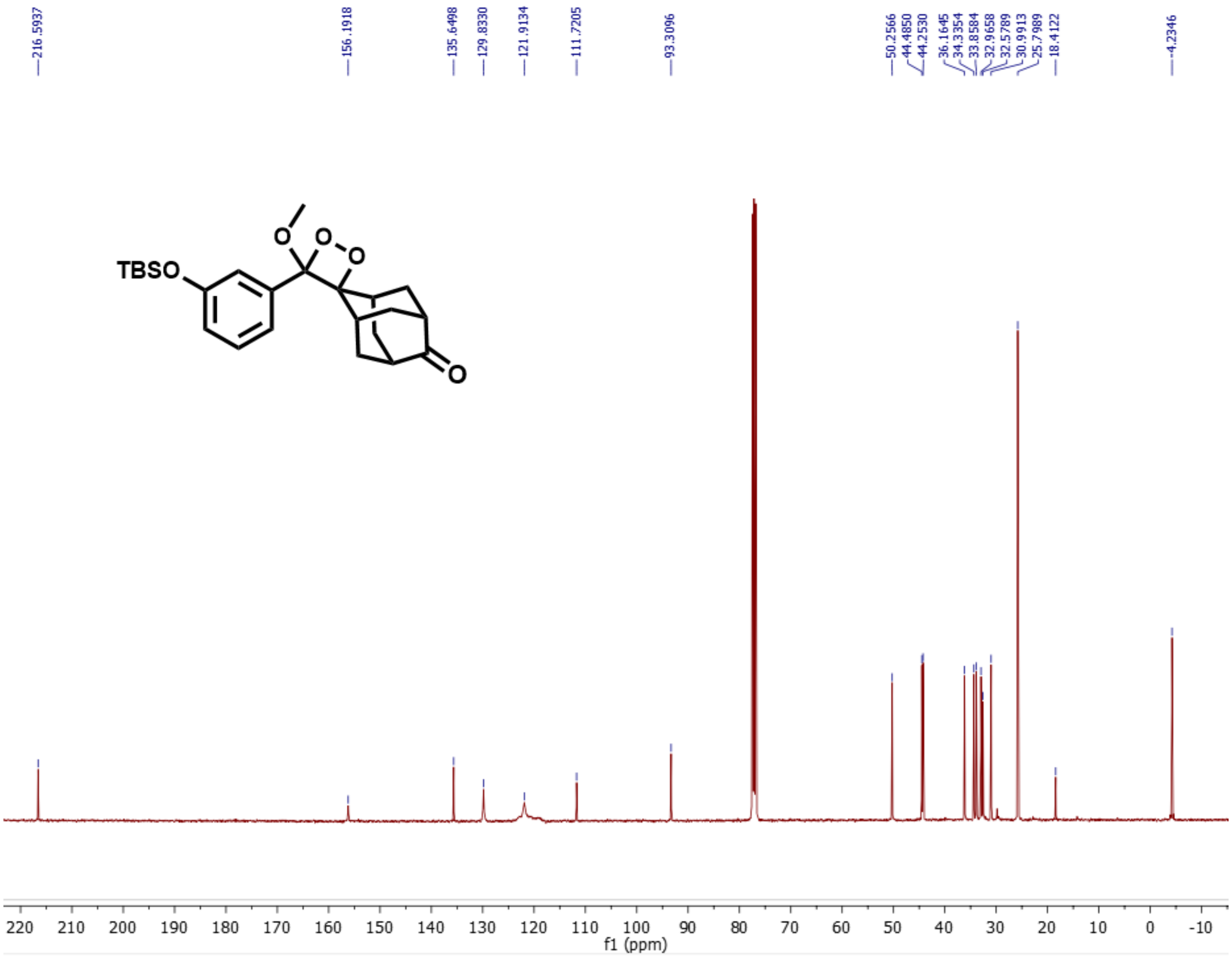
NMR, MS and HPLC Spectra of Key Compounds

Diox 2:

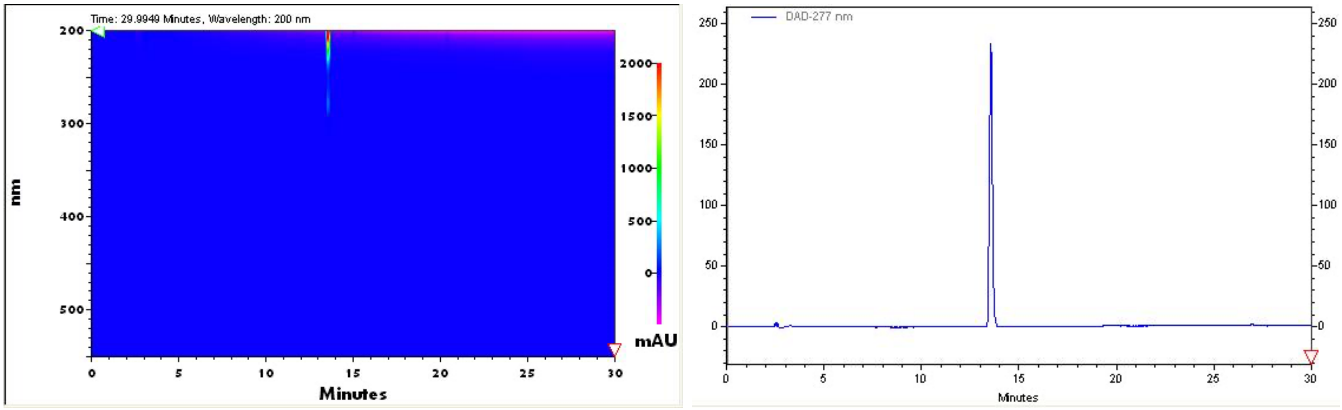
^{1}H-NMR



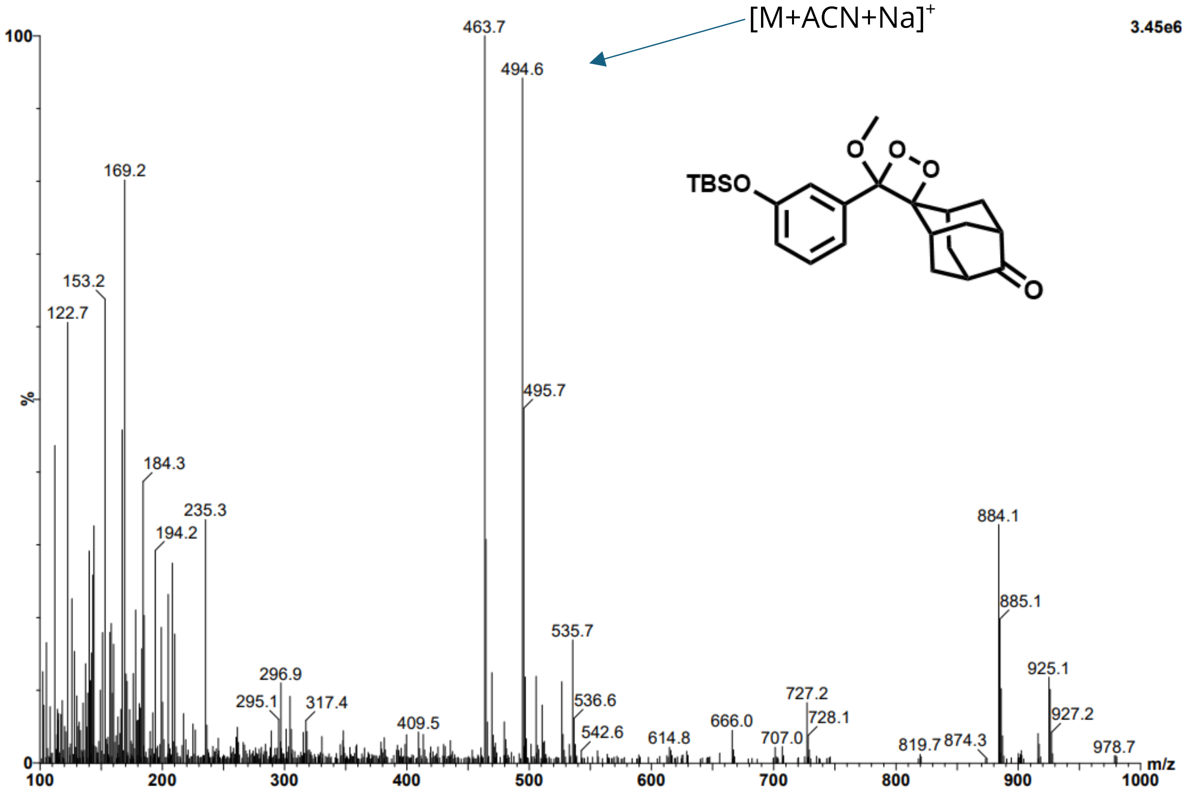
^{13}C-NMR



HPLC (70-100% ACN gradient)

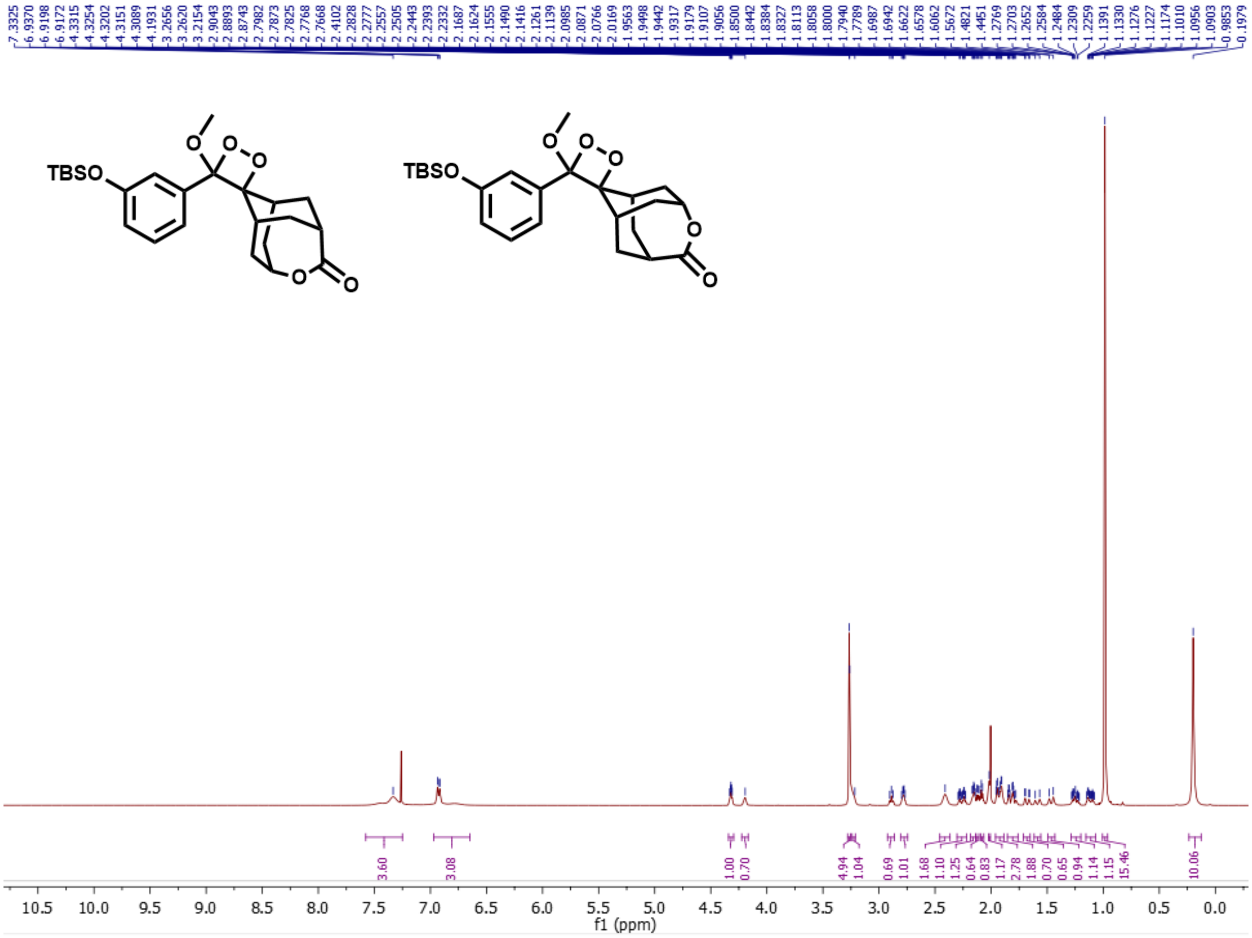


MS


[M+ACN+Na]+
3.45e6
100
%
0
463.7
494.6
495.7
169.2
153.2
122.7
184.3
235.3
194.2
296.9
295.1
317.4
409.5
535.7
536.6
542.6
614.8
666.0
727.2
728.1
707.0
819.7
874.3
884.1
885.1
925.1
927.2
978.7
100
200
300
400
500
600
700
800
900
1000
m/z
TBSO
O
O
O
O

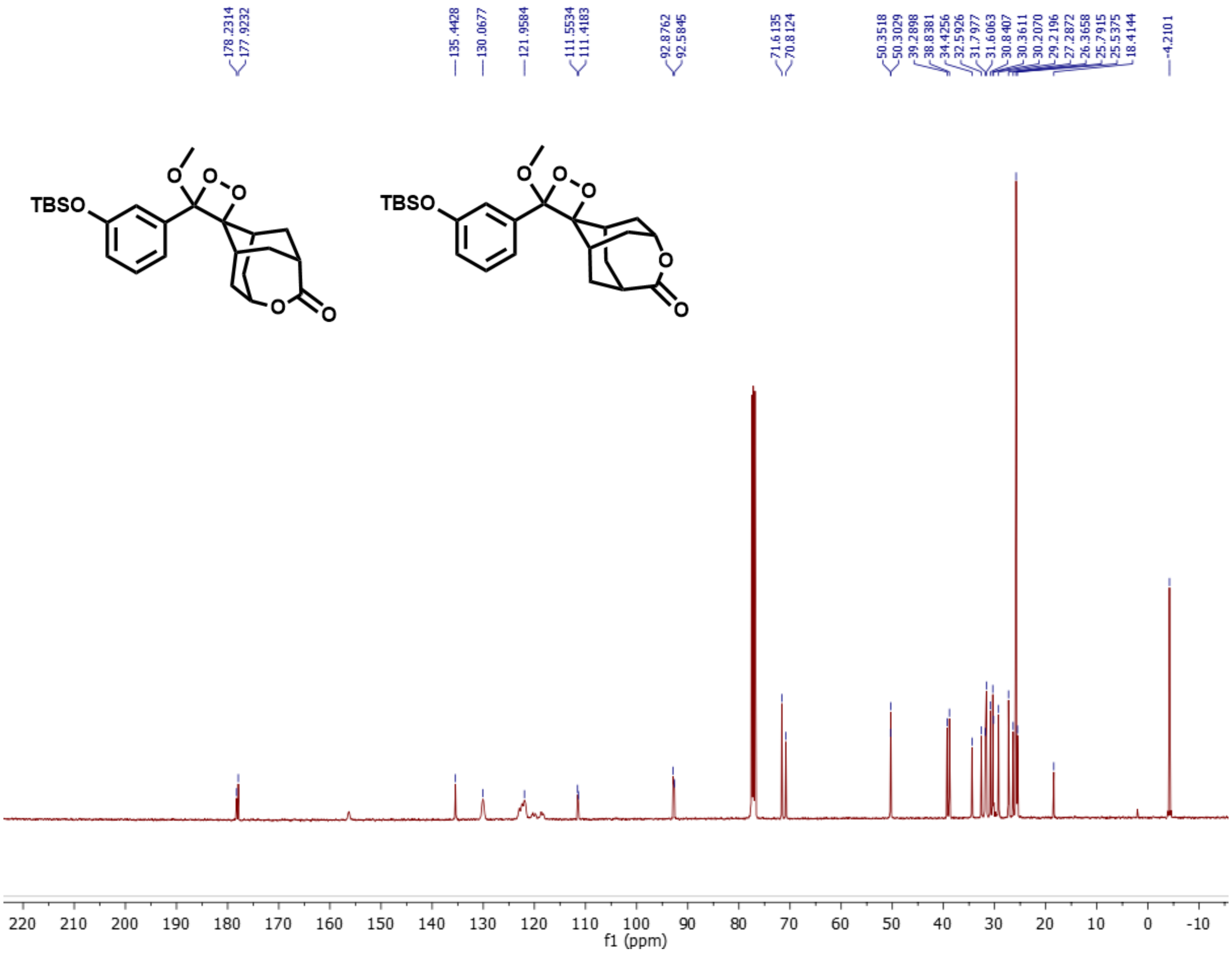
Diox 3:

^{1}H-NMR

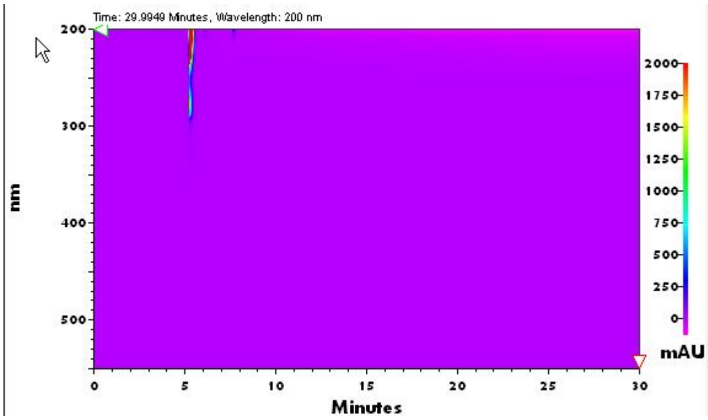


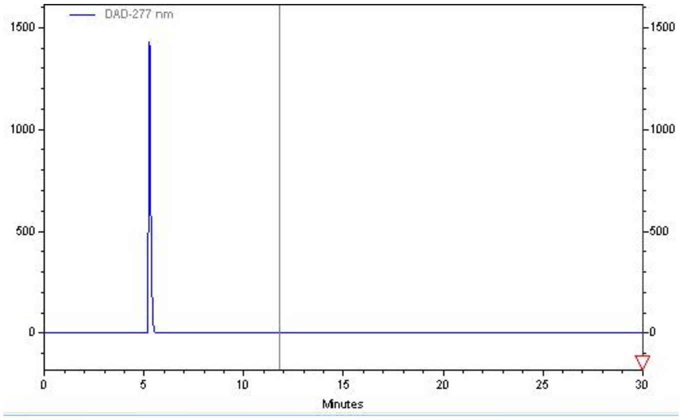
7.3325
6.9370
6.9198
6.9172
4.3315
4.3254
4.3202
4.3151
4.3089
4.1931
3.2656
3.2620
3.2154
2.9043
2.8893
2.8743
2.7982
2.7873
2.7825
2.7768
2.7668
2.4102
2.2828
2.2777
2.2557
2.2505
2.2443
2.2393
2.2332
2.1687
2.1624
2.1555
2.1490
2.1416
2.1261
2.1139
2.0985
2.0871
2.0766
2.0169
1.9563
1.9498
1.9442
1.9317
1.9179
1.9107
1.9056
1.8500
1.8442
1.8384
1.8327
1.8113
1.8058
1.8000
1.7940
1.7789
1.6987
1.6942
1.6622
1.6578
1.6062
1.5672
1.4821
1.4451
1.2769
1.2703
1.2652
1.2584
1.2484
1.2309
1.2259
1.1391
1.1330
1.1276
1.1227
1.1174
1.1010
1.0956
1.0903
0.9853
0.1979
TBSO
O
O
O
O
O
TBSO
O
O
O
O
O
3.60
3.08
1.00
0.70
4.94
1.04
0.69
1.01
1.68
1.10
1.25
0.64
0.83
1.17
2.78
1.88
0.70
0.65
0.94
1.14
1.15
15.46
10.06
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

^{13}C-NMR

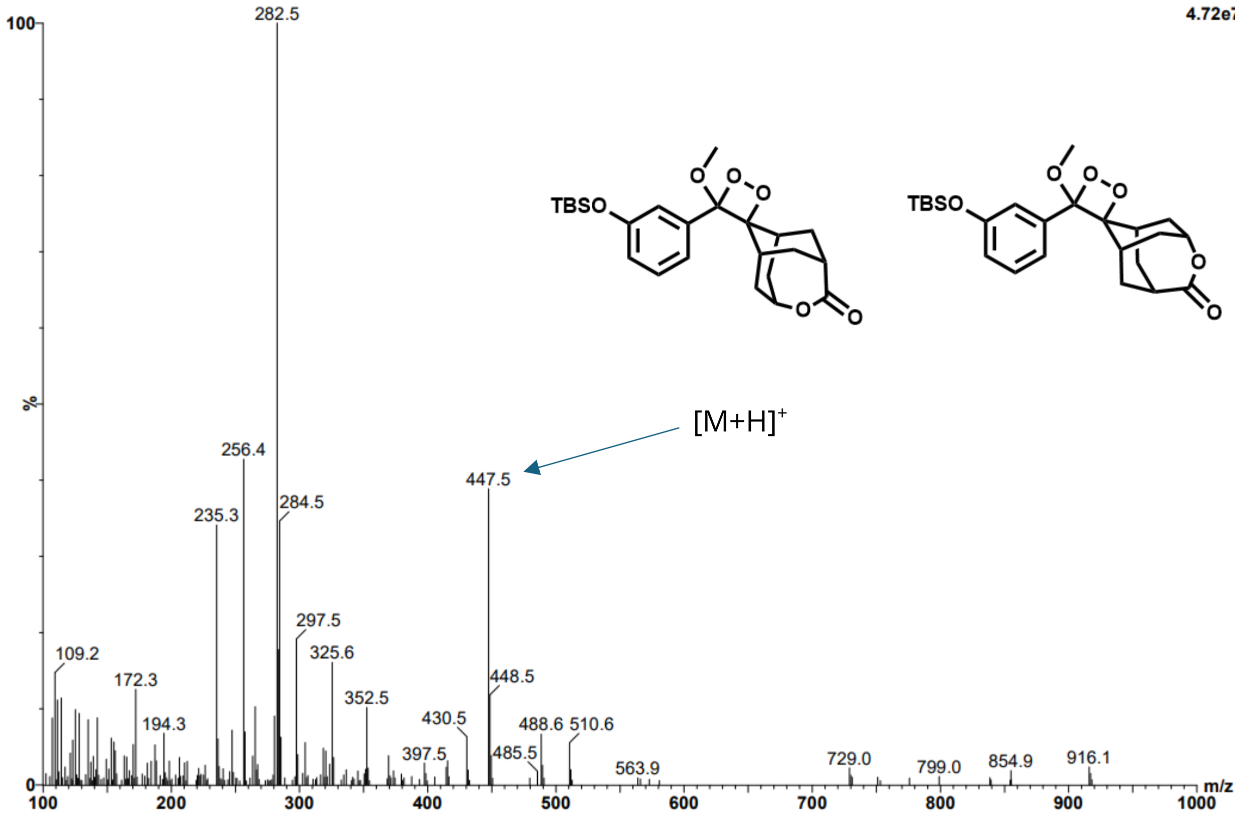


HPLC (90-100% ACN gradient)



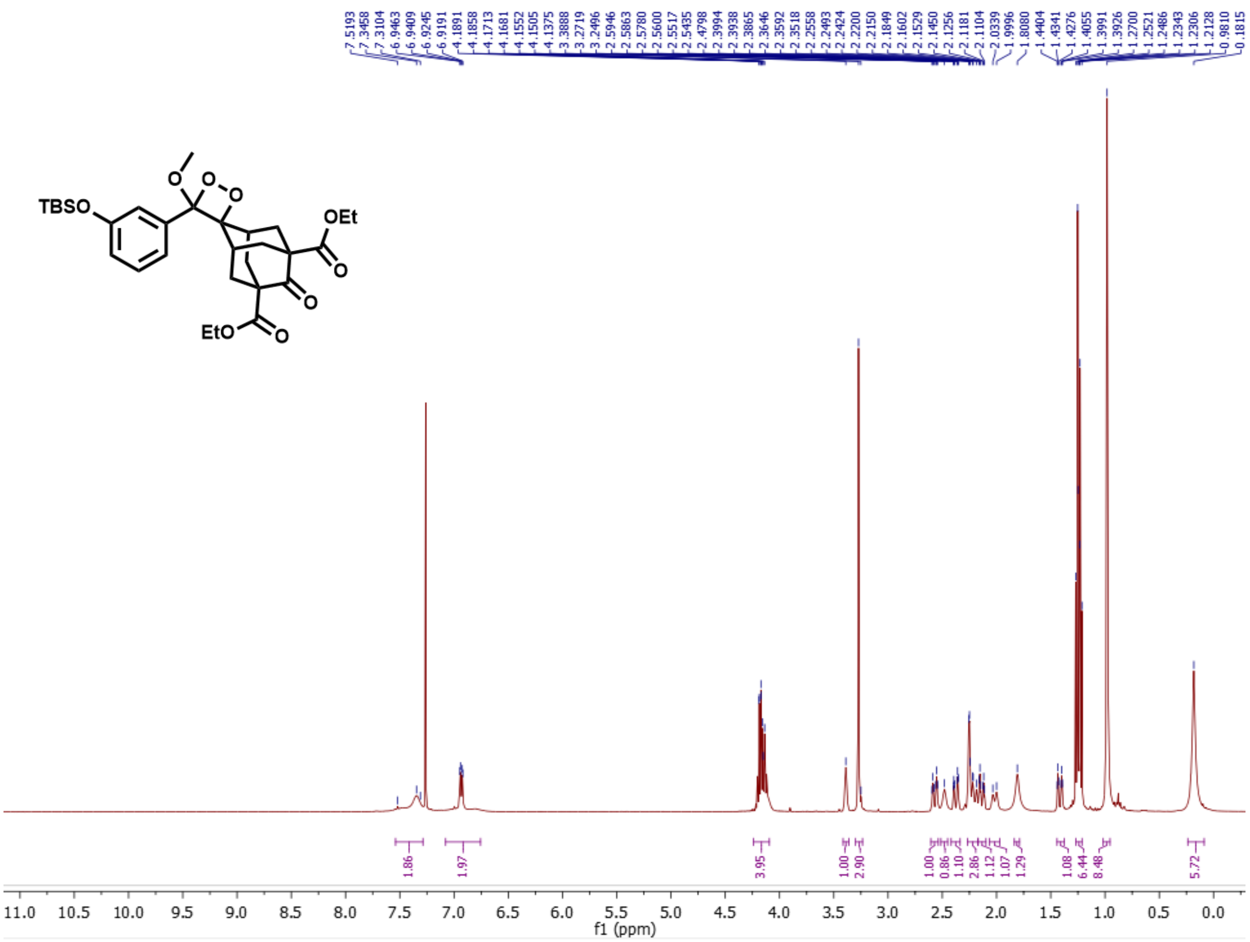


MS

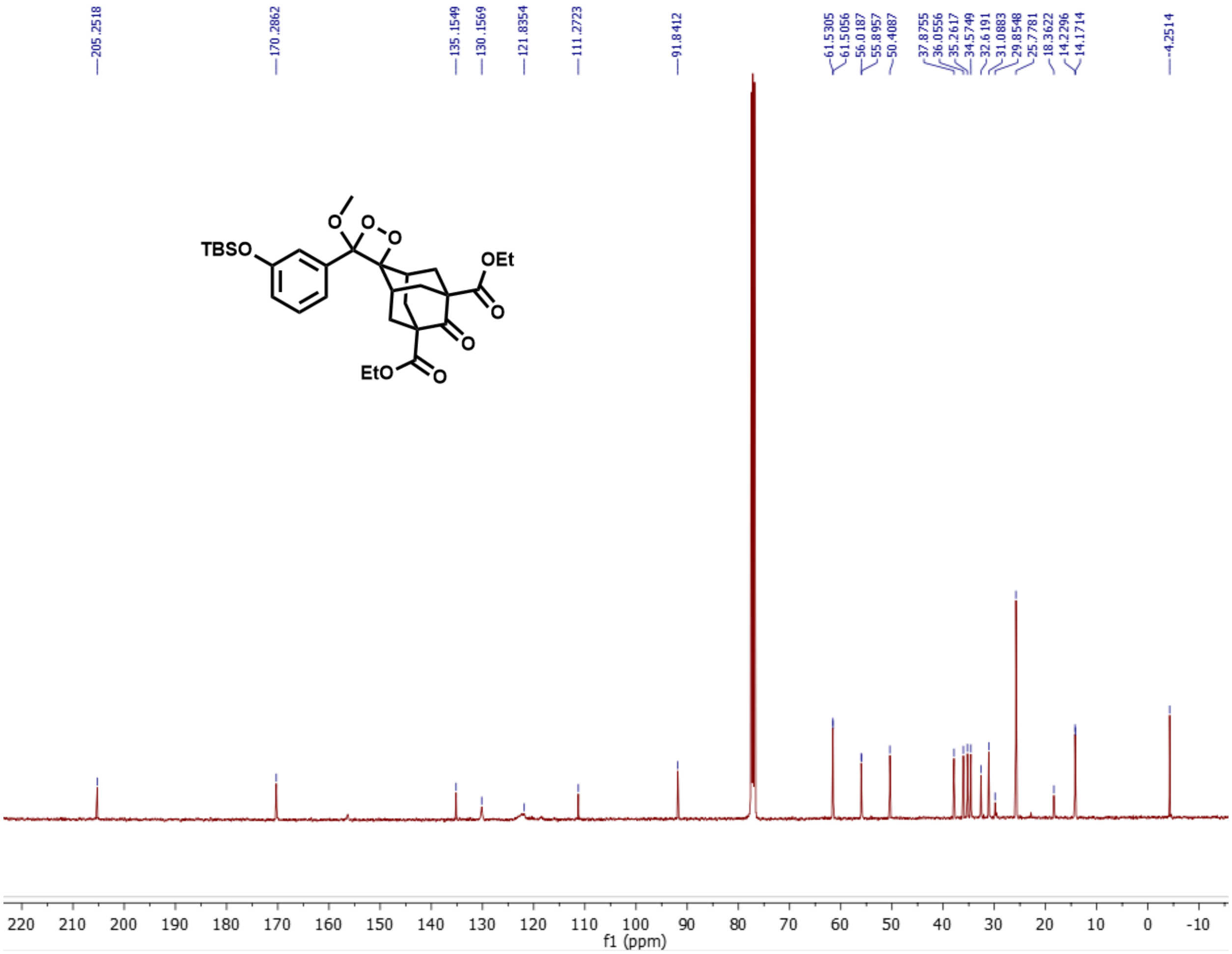

100
%
0
282.5
4.72e7
256.4
235.3
284.5
447.5
[M+H]$^+$
297.5
325.6
109.2
172.3
194.3
352.5
430.5
448.5
488.6
510.6
397.5
485.5
563.9
729.0
799.0
854.9
916.1
TBSO
TBSO
O
O
O
O
100
200
300
400
500
600
700
800
900
1000
m/z

Diox 4:

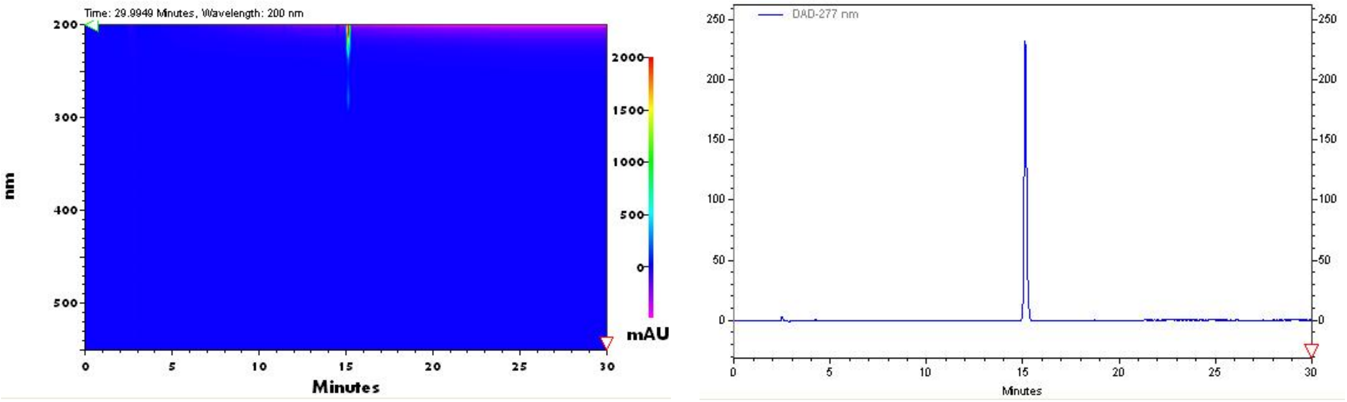
^{1}H-NMR


TBSO
O
O
O
OEt
O
O
EtO
O
7.5193
7.3458
7.3104
6.9463
6.9409
6.9245
6.9191
4.1891
4.1858
4.1713
4.1681
4.1552
4.1505
4.1375
3.3888
3.2719
3.2496
2.5946
2.5863
2.5780
2.5600
2.5517
2.5435
2.4798
2.3994
2.3938
2.3865
2.3646
2.3592
2.3518
2.2558
2.2493
2.2424
2.2200
2.2150
2.1849
2.1602
2.1529
2.1450
2.1256
2.1181
2.1104
2.0339
1.9996
1.8080
1.4404
1.4341
1.4276
1.4055
1.3991
1.3926
1.2700
1.2521
1.2486
1.2343
1.2306
1.2128
0.9810
0.1815
1.86
1.97
3.95
1.00
2.90
1.00
0.86
1.10
2.86
1.12
1.07
1.29
1.08
6.44
8.48
5.72
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

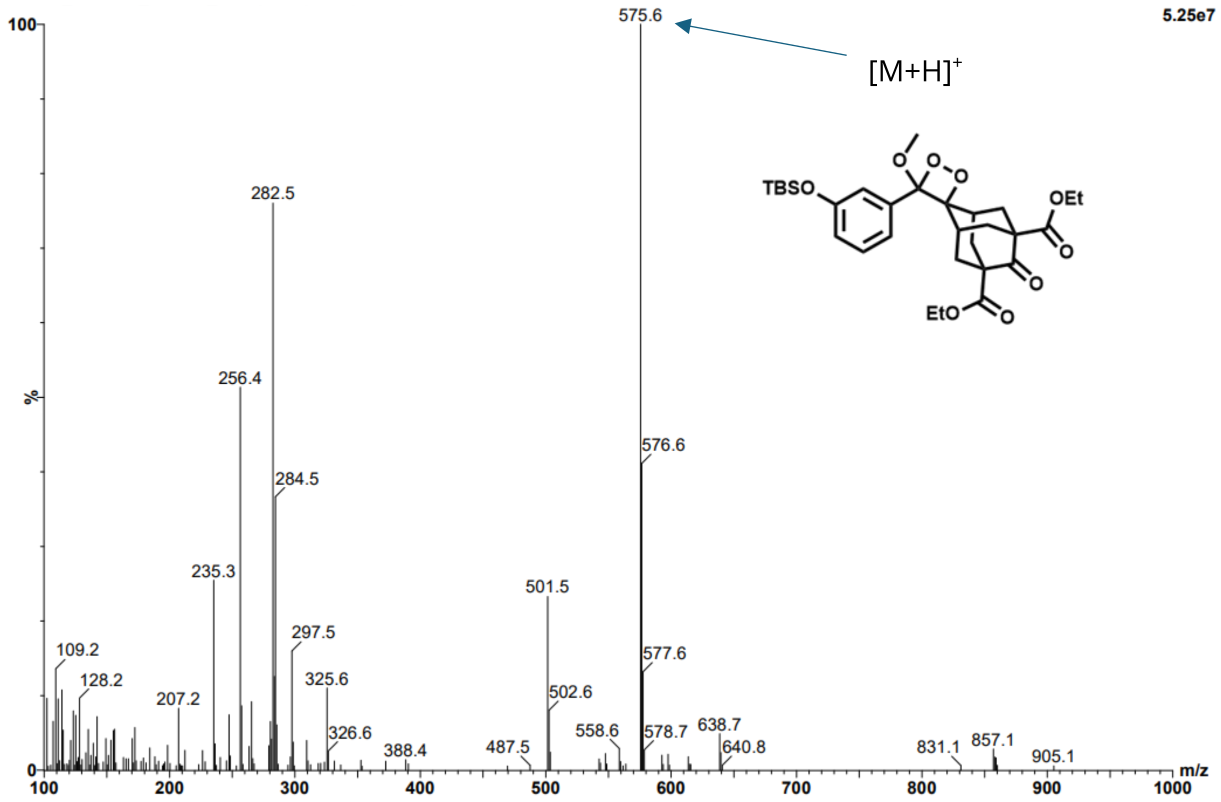
^{13}C-NMR



HPLC (70-100% ACN gradient)



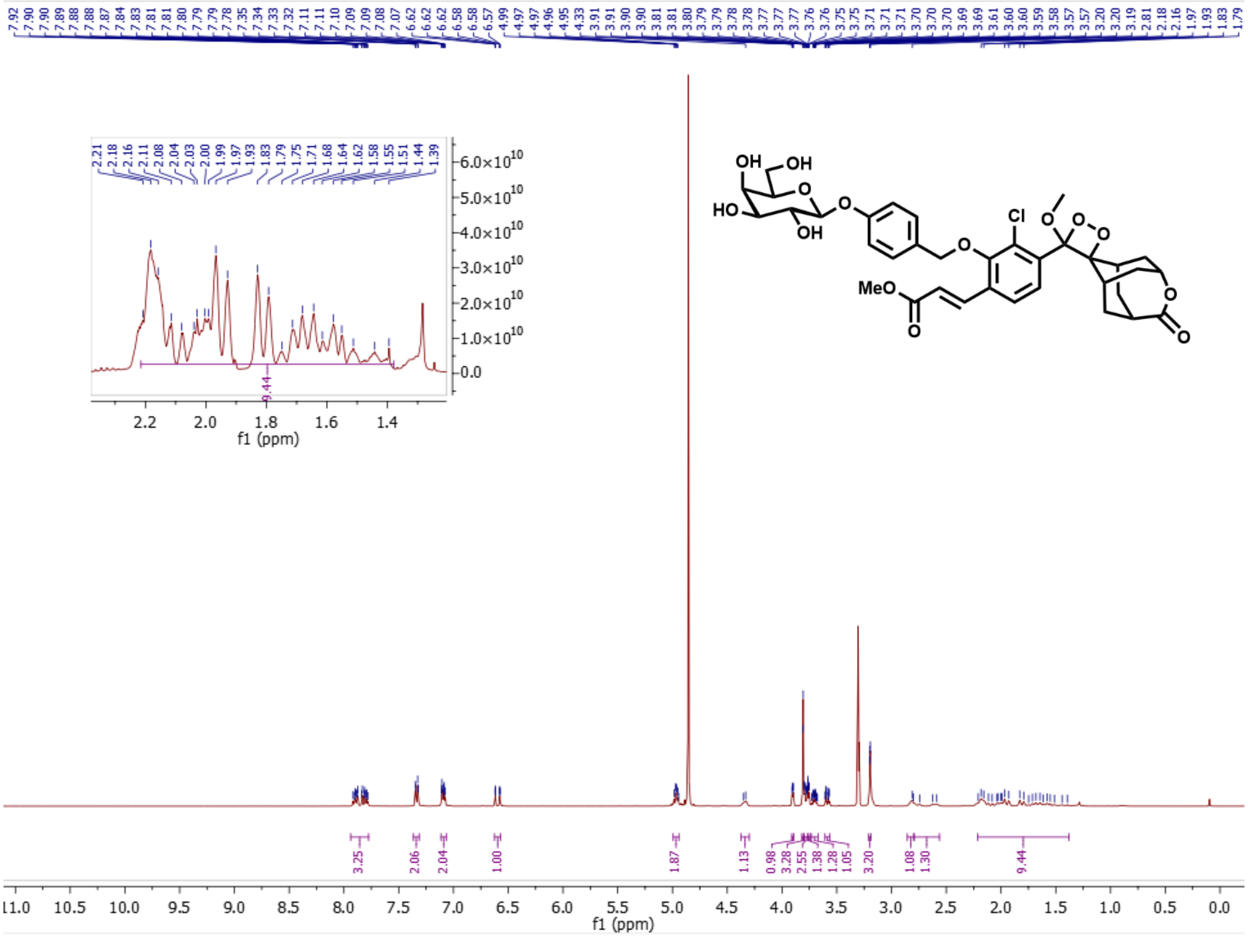
MS



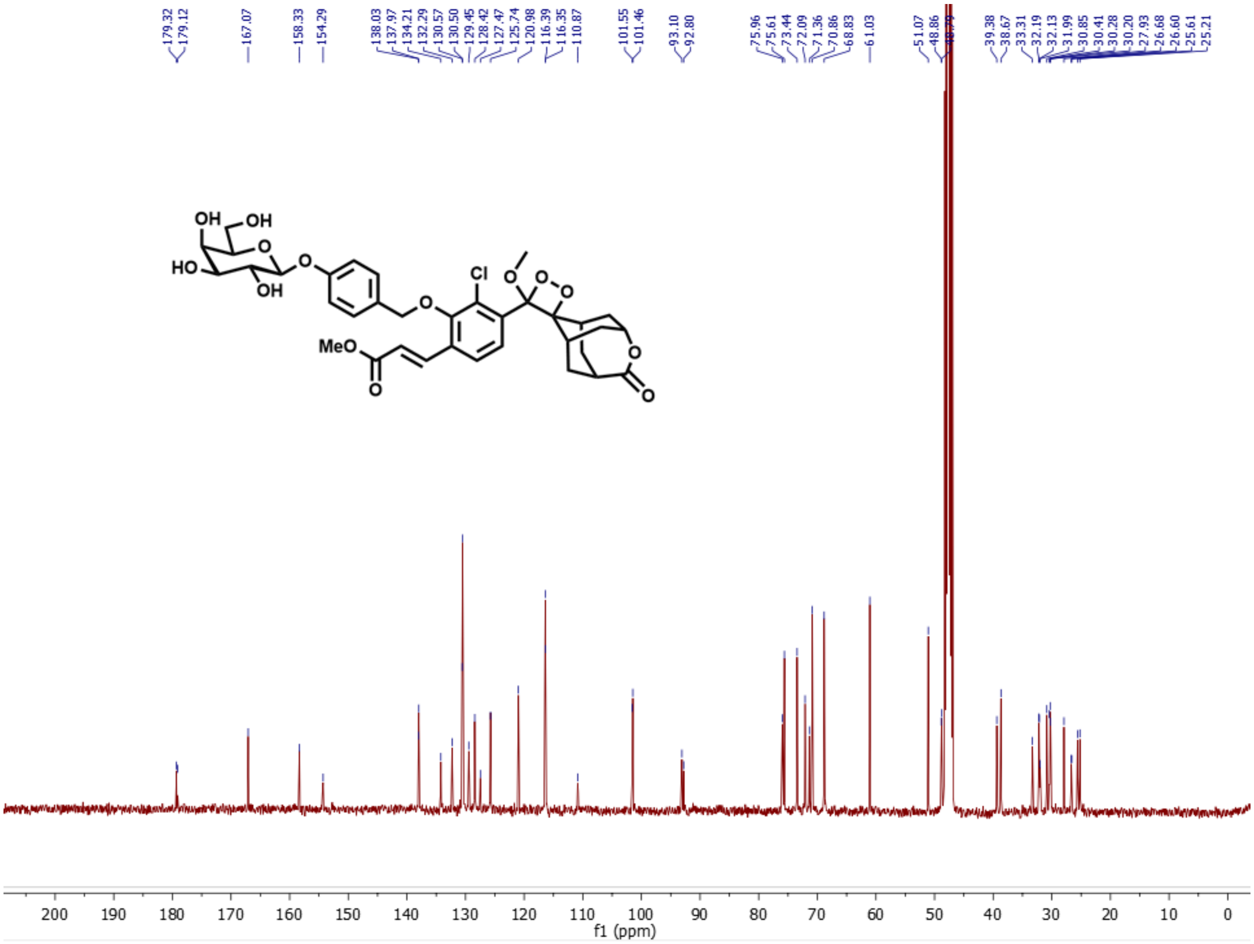
575.6
[M+H]$^+$
5.25e7
100
%
0
282.5
256.4
284.5
235.3
501.5
576.6
297.5
109.2
128.2
207.2
325.6
326.6
388.4
487.5
502.6
558.6
577.6
578.7
638.7
640.8
831.1
857.1
905.1
100
200
300
400
500
600
700
800
900
1000
m/z
TBSO
O
O
O
OEt
O
O
EtO
O

β-gal-MA-Diox 2:

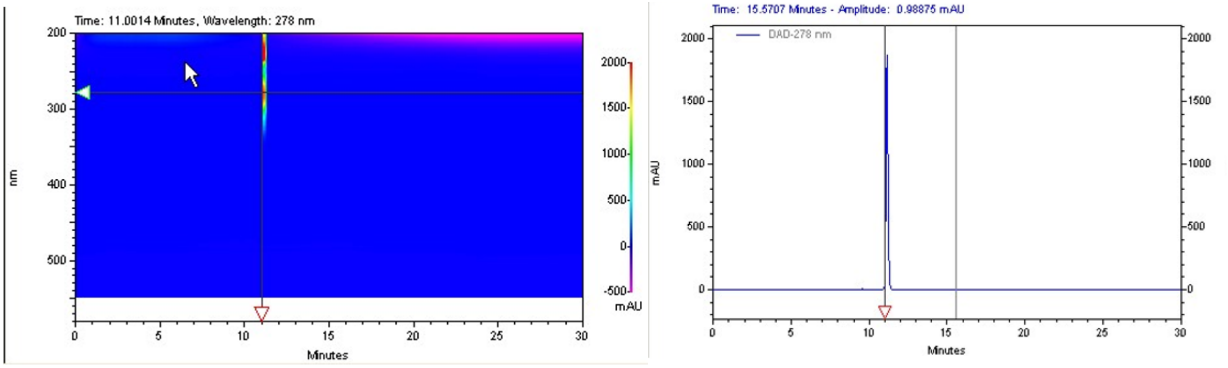
^{1}H-NMR



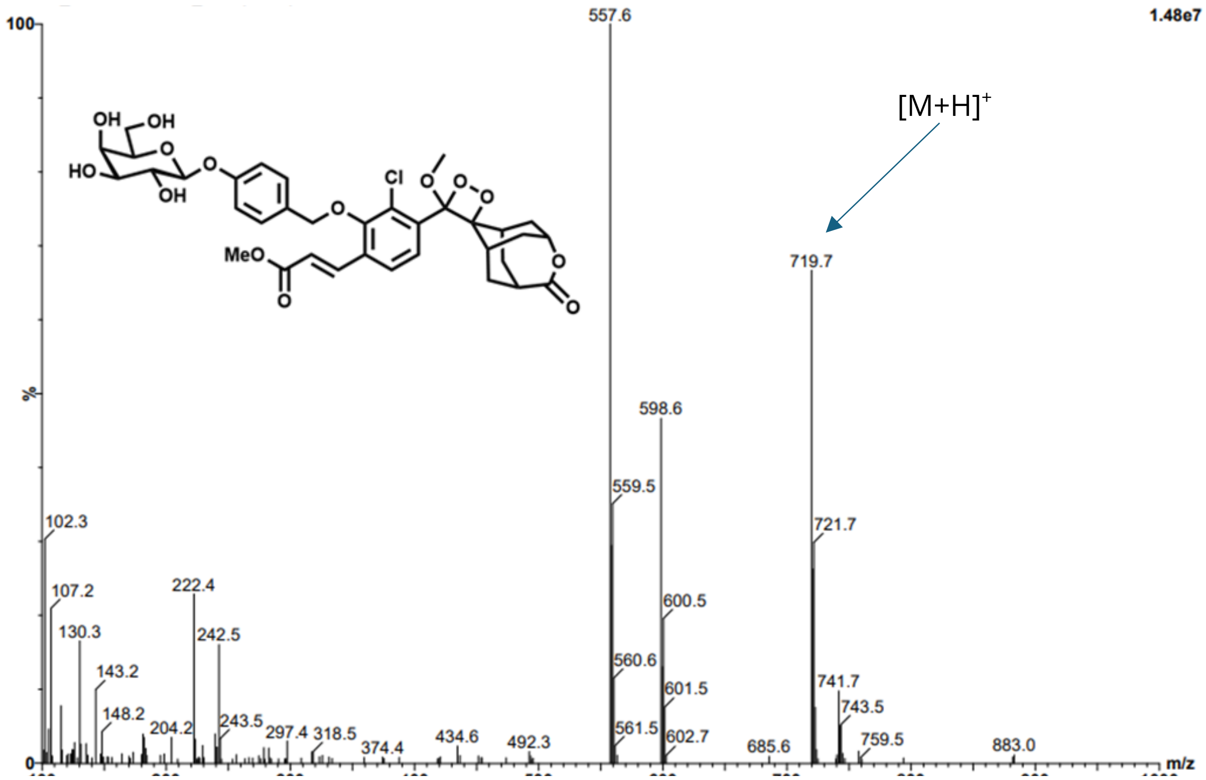
^{13}C-NMR



HPLC (30-100% ACN gradient)



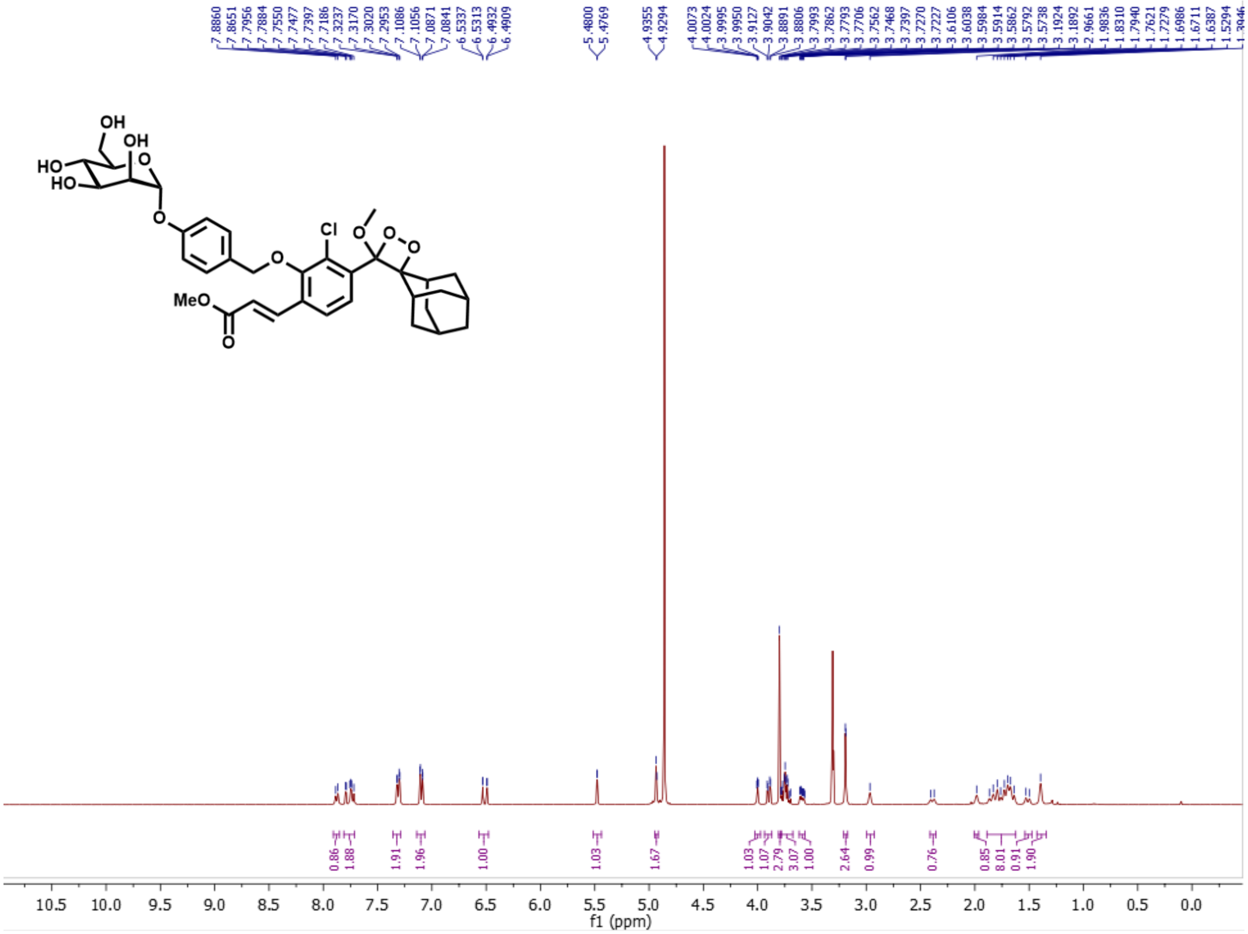
MS


100
%
0
1.48e7
m/z
557.6
719.7
598.6
559.5
102.3
721.7
107.2
222.4
600.5
130.3
242.5
560.6
143.2
601.5
741.7
743.5
148.2
204.2
243.5
297.4
318.5
374.4
434.6
492.3
561.5
602.7
685.6
759.5
883.0
OH
OH
HO
OH
O
O
O
Cl
O
O
O
MeO
O
O
O

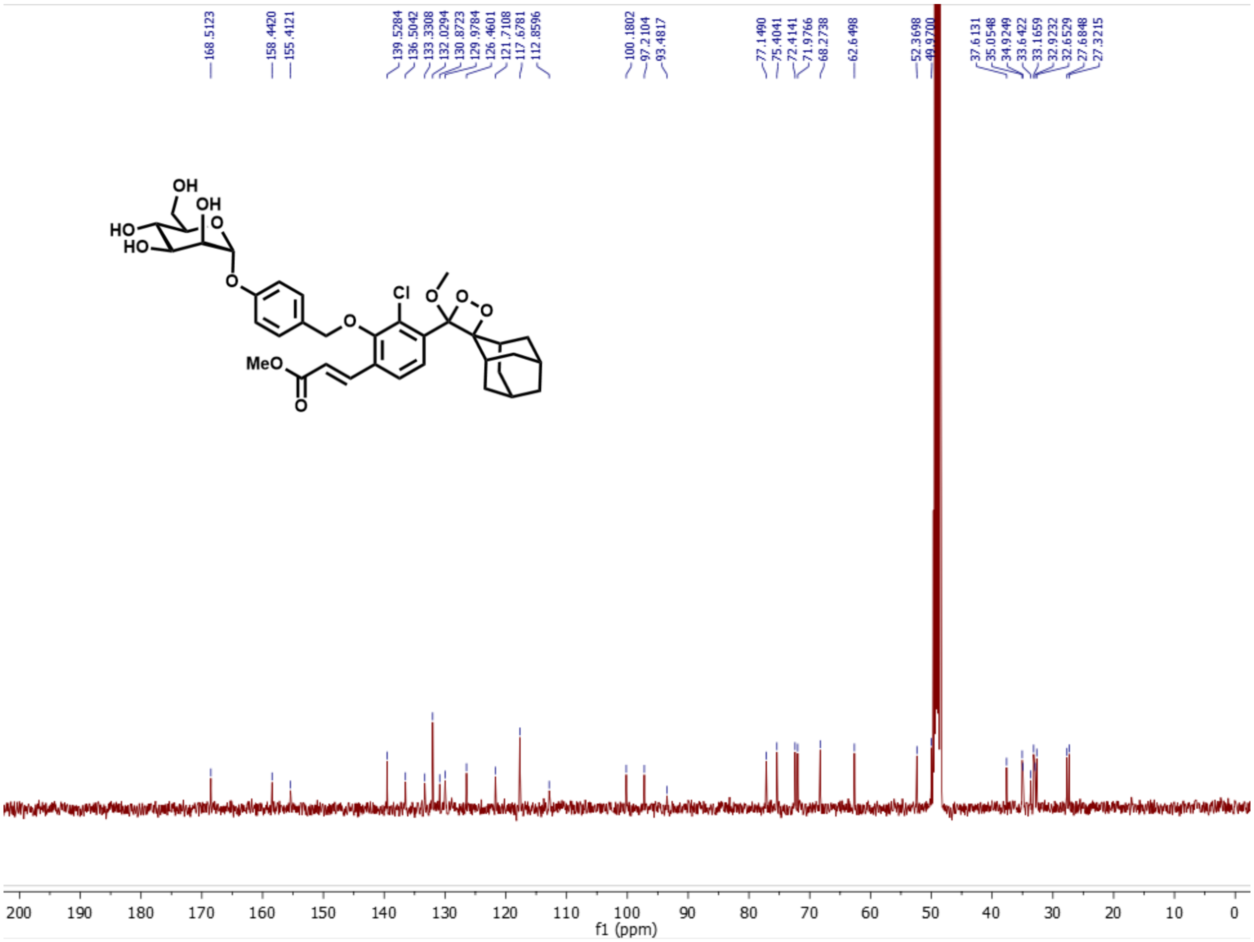
[M+H]$^+$

α-man-MA-Diox 1:

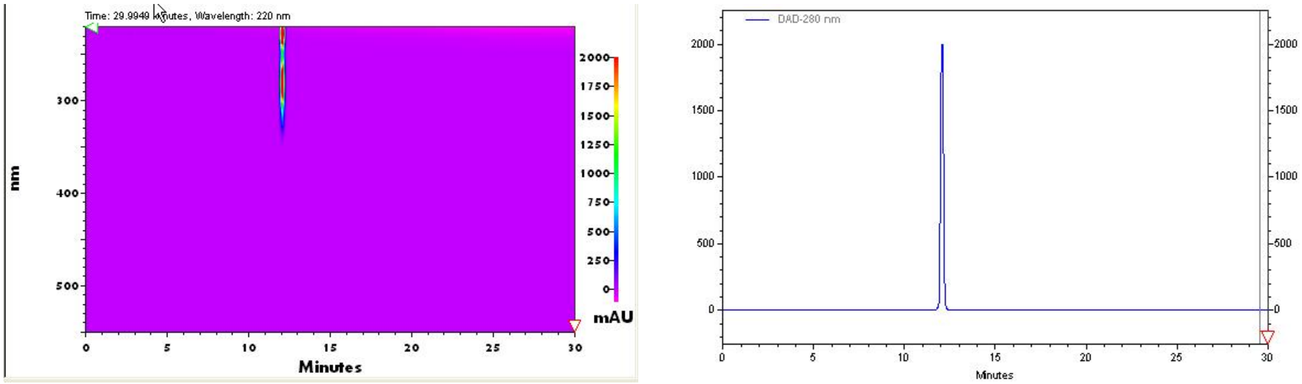
^{1}H-NMR



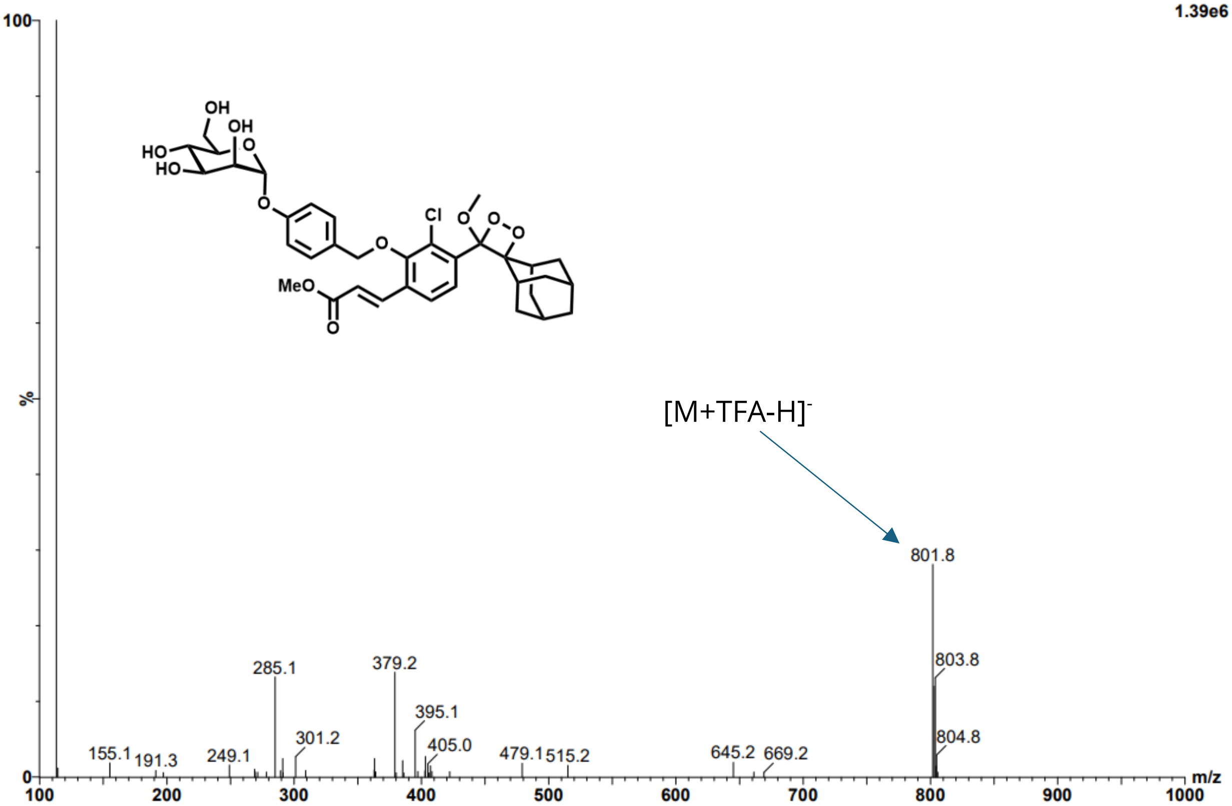
^{13}C-NMR



HPLC (50-100% ACN gradient)

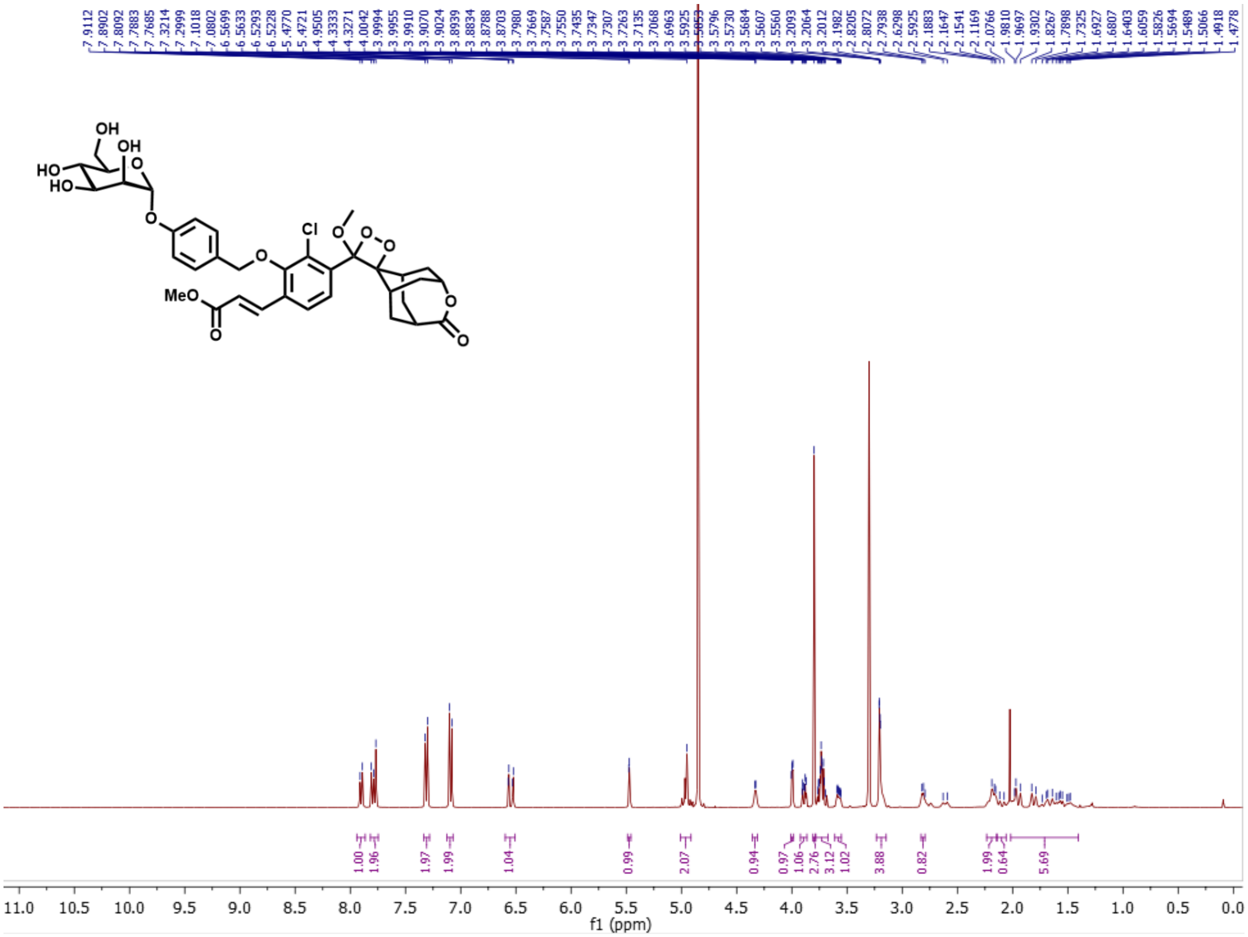


MS

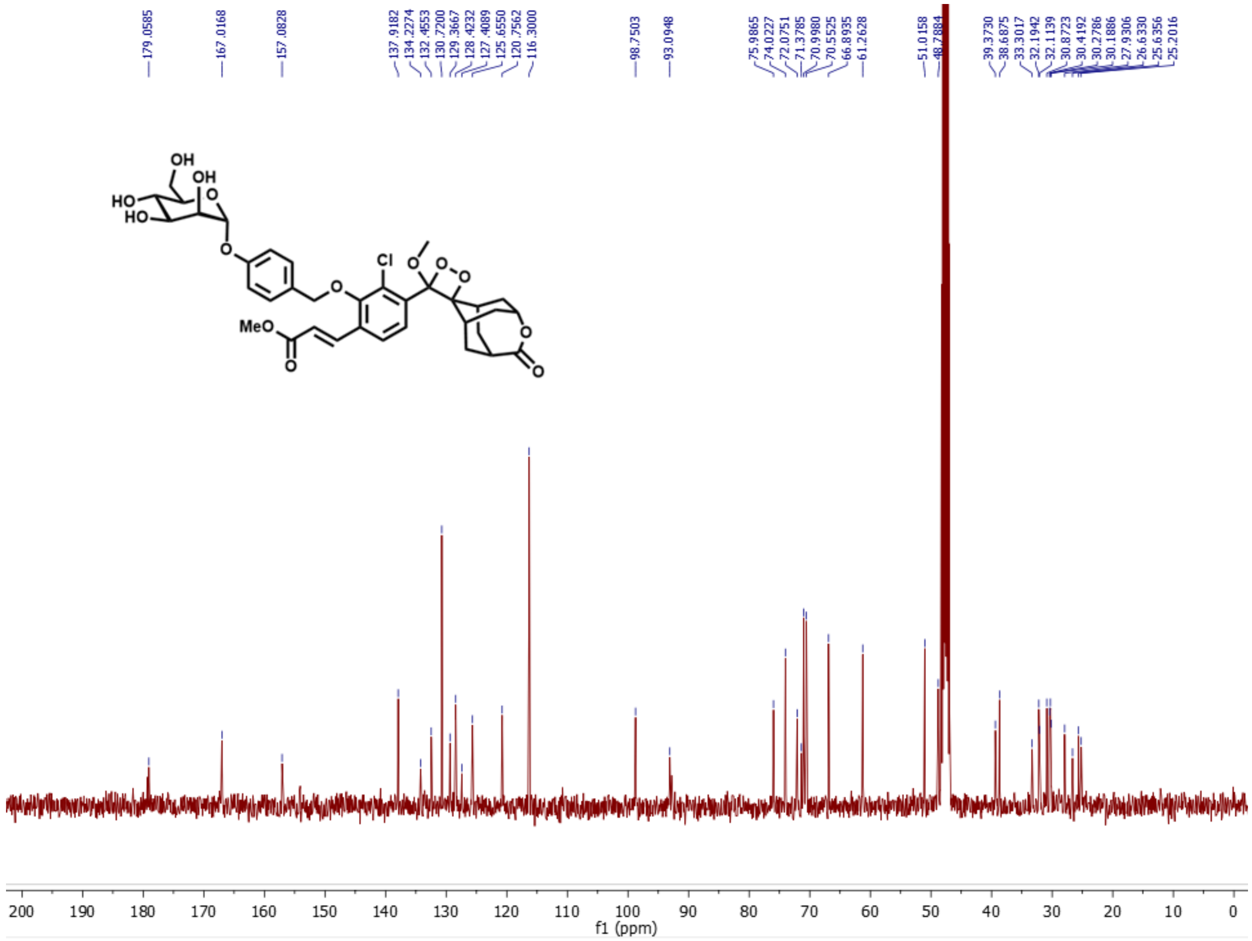

1.39e6
100
%
0
OH
OH
O
HO
HO
O
O
Cl
O
O
O
MeO
O
[M+TFA-H]-
801.8
803.8
804.8
285.1
379.2
395.1
301.2
405.0
155.1
191.3
249.1
479.1
515.2
645.2
669.2
100
200
300
400
500
600
700
800
900
1000
m/z

α-man-MA-Diox 2:

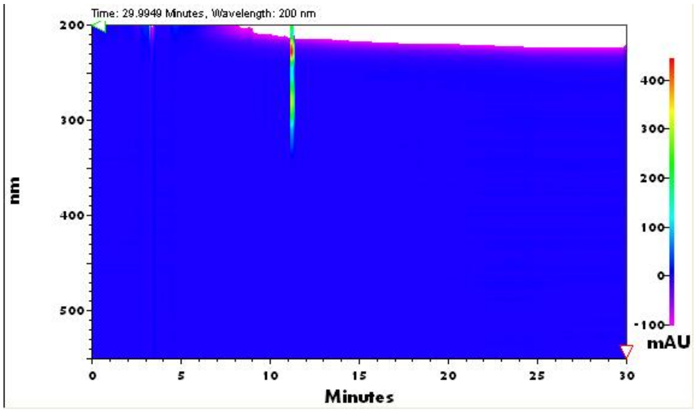
^{1}H-NMR

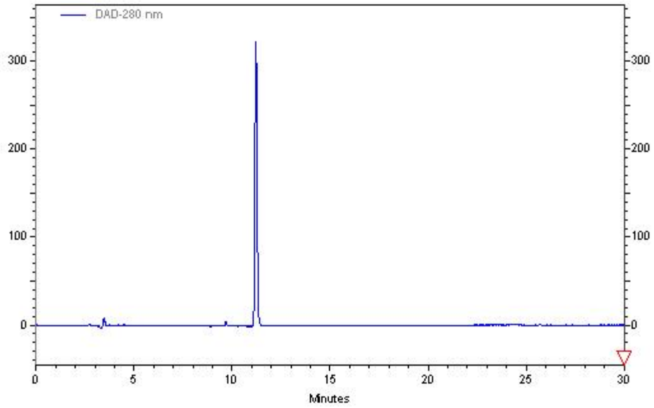


^{13}C-NMR

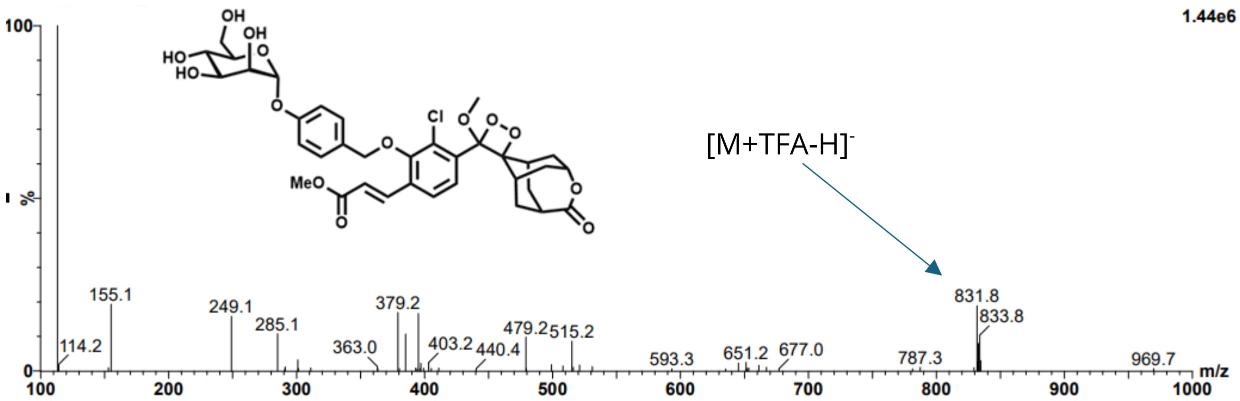


HPLC (30-100% ACN gradient)



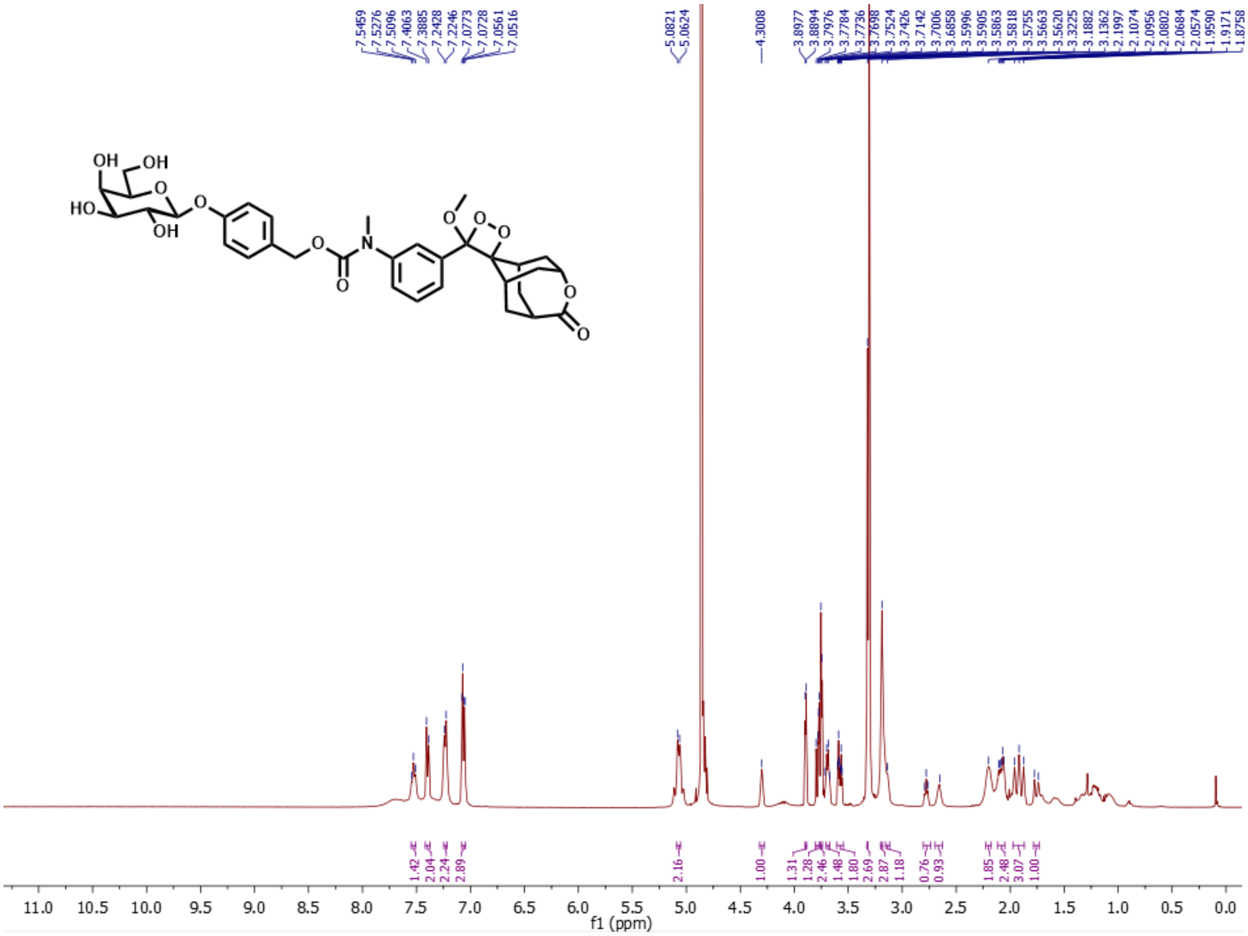


MS

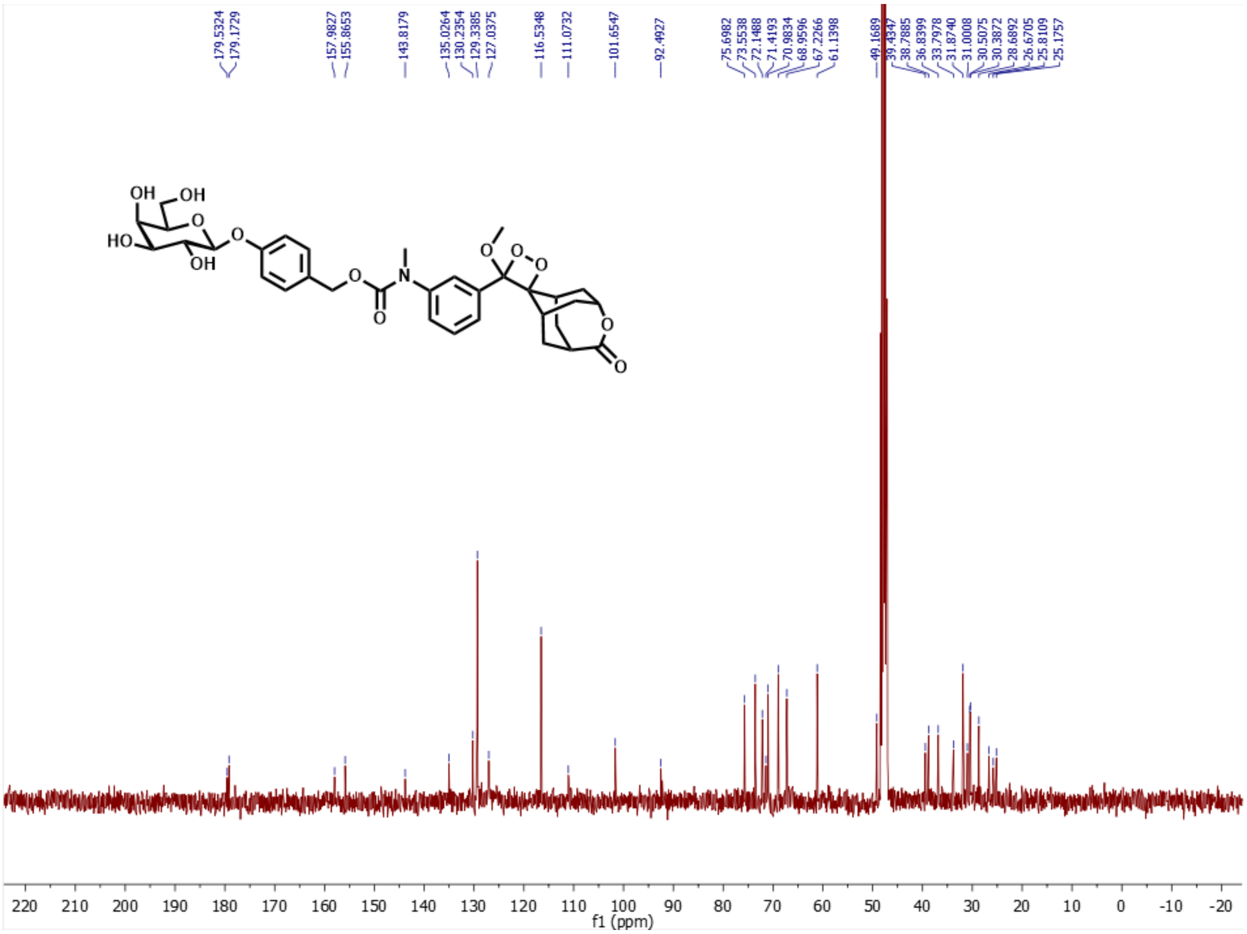

1.44e6
100
%
0
OH
OH
HO
HO
O
O
Cl
O
O
O
MeO
O
O
O
O
[M+TFA-H]-
155.1
114.2
249.1
285.1
363.0
379.2
403.2
440.4
479.2
515.2
593.3
651.2
677.0
787.3
831.8
833.8
969.7
m/z
100
200
300
400
500
600
700
800
900
1000

NHMe-Diox 2:

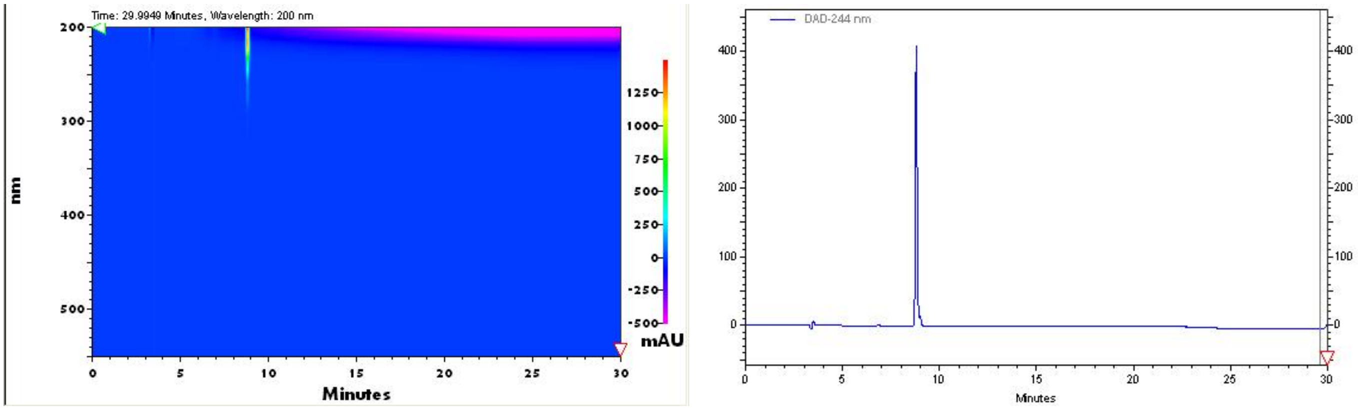
^{1}H-NMR



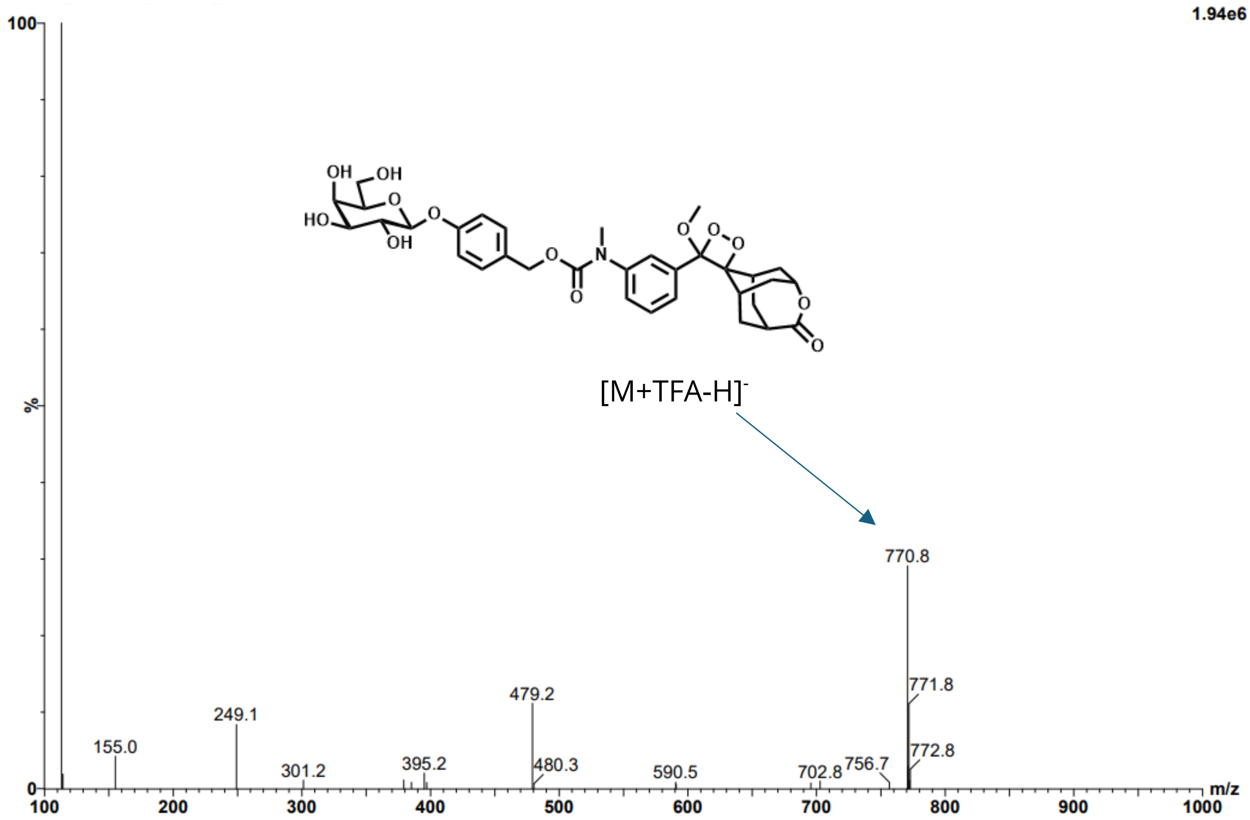
^{13}C-NMR



HPLC (30-100% ACN gradient)



MS


1.94e6
100
%
0
OH
OH
O
HO
OH
O
O
O
N
O
O
O-O
O
O
[M+TFA-H]-
770.8
771.8
772.8
756.7
702.8
590.5
480.3
479.2
395.2
301.2
249.1
155.0
100
200
300
400
500
600
700
800
900
1000
m/z

References

[1] S. Hisamatsu, S. Suzuki, S. Kohmoto, K. Kishikawa, Y. Yamamoto, R. Motokawa, T. Yaita, *Tetrahedron* 2017, ***73***, 3993-3998.

[2] O. Green, T. Eilon, N. Hananya, S. Gutkin, C. R. Bauer, D. Shabat, *ACS Cent. Sci.* 2017, ***3***, 349-358.

[3] H. Stetter, H.G. Thomas, *Angew. Chem. Int. Ed. Engl*., 1967, **6**, 554-555

[4] N. Hananya, A. E. Boock, C. R. Bauer, R. Satchi-Fainaro, D. Shabat, *J. Am. Chem. Soc.* 2016, ***138***, 13438-13446.

[5] M. David, T. Leirikh, N. Naama, T. Kopp, D. Shabat, *Angew. Chem. Int. Ed.*. 2025, **64**, e202515674.