CHAPTER II

EXPERIMENTS

2.1 Instruments and equipments

Melting points were determined with a Stuart Scientific Melting Point SMP1 (Bibby Sterlin Ltd., Staffordshire, UK). The FT-IR spectra were recorded on a Nicolet Fourier Transform Infrared Spectrophotometers: Impact 410 (Nicolet Instruments Technologies, Inc. WI, USA) or Perkin-Elmer FT-IR spectroscopy, spectrum RXI spectrometer (Perkin Elmer Instruments LLC, Shelton, USA). Solid samples were incorporated into a pellet of potassium bromide and liquid samples were dropped on potassium bromide crystal cell. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$), hexadeuterated dimethylsulfoxide (DMSO-*d6*), hexadeuterated acetone ($(CD_3)_2CO$) or tetradeuterated methanol (CD_3OD) using a Varian Mercury NMR Spectrometer (Varian Inc., CA, USA) or a Bruker Avance 400 spectrometer (Bruker Corporation, Germany) which operated at 400.00 MHz for ^{1}H and 100.00 MHz for ^{13}C nuclei. The mass spectra were recorded on Mass Spectrometer: Waters Micromass Quatto micro API ESCi (Waters, MA, USA). Samples were dissolved in solvent and directly injected (50 µL) into the Mass Spectrometer. Alternatively, mass spectrum of a high molecular weight sample was obtained from Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) mass spectrometer: Microflex mass spectrometer (Bruker Daltonik GmbH, Germany). The instrument was equipped with nitrogen laser to desorb and ionize the samples, which deposited on a stainless steel target. The sample was premixed with α-hydroxycyanocinnamic acid (CCA) matrix (10 mg/mL) solution in tetrahydrofuran.

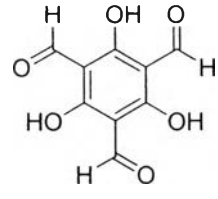
2.2 Chemicals

Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck Kieselgel 60 F254) (Merck KgaA, Darmstadt, Germany). Column chromatography was performed in silica gel (0.06-0.2 mm, 70-230 mesh ASTM), Merck Kieselgel 60 G (Merck KgaA, Darmstadt, Germany) and

Sephadex LH-20 (Sigma-Aldrich, Germany). All reagents used in synthesis were reagent or analytical grades and used as purchased except the solvents for column chromatography, which were distilled from commercial grade before use.

2.3 Experiments

2.3.1 Synthesis of 1,3,5-triformyl-2,4,6-trihydroxybenzene (51)



Method I: Duff Reaction

Hexamethylenetetramine (1.54 g, 11 mmol) and phloroglucinol dihydrate **(44)** (0.63 g, 5 mmol) were added into trifluoroacetic acid (12 mL) under nitrogen atmosphere. The solution was heated at 100 °C for 2.5 hours. Then 150 mL of 3 M HCl was added and the solution was heated at 100 °C for another hour. After cooling to room temperature, the solution was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Evaporation off the solvent then afforded white powder of the product (0.10 g, 10% yield).

Method II: Reimer-Tiemann reaction

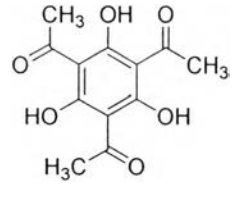
Powdered sodium hydroxide (2.88 g, 72.0 mmol) was added to a suspension of phloroglucinol dihydrate **(44)** (0.51 g, 4.0 mmol) in water (0.45 mL, 24.0 mmol) and chloroform (30 mL). The mixture was refluxed for 24 hours. Additional sodium hydroxide was added (0.24 g, 6.0 mmol) after an hour, sodium hydroxide was added again after another 1.5 hours (0.24 g, 6.0 mmol). The reaction was evaporated to remove chloroform and then diluted with water (30 mL). The aqueous layer was acidified to pH 1 with 10% HCl and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the desired product (0.46 g, 54% yield).

Method III:

A suspension of anhydrous phloroglucinol **(44)** (0.25 g, 2.0 mmol) in dry toluene (7 mL) was added tin(IV) chloride (0.07 mL, 0.6 mmol) and triethylamine (0.33 mL, 2.4 mmol). The mixture was stirred under nitrogen at 100 °C for 20 min at room temperature then paraformaldehyde (0.36 g, 12.0 mmol) was added. The resulting yellowish solution was heated at 100 °C for 8 hours. After cooling, the reaction mixture was poured into water (15 mL), acidified to pH 2 with 10% HCl and extracted with diethyl ether. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the desired product (0.12 g, 29% yield). m.p. 201-205 °C (lit.198-200 °C) [79]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 14.12 (s, 3H), 10.15 (s, 3H) (**Figure A.1**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.2, 173.7, 103.0 (**Figure A.2**); IR (KBr, cm^{-1}): 3354.38 (O-H st), 2921.71 (C-H st), 2844.05 (C-H st of aldehyde), 1649.58 (C=O st), 1590.42 (C=C st), 1253.90 (C-O st) (**Figure A.3**); $[MS]^+$: m/z = 209.02 (**Figure A.4**)

The 1,3,5-trihydroxybenzaldehyde was synthesized by method II in which the refluxing time was only 8 hours. The monoformylated product was obtained as a white solid (0.14 g, 62% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 4H), 5.90 (s, 2H) (**Figure A.5**); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 191.5, 169.5, 169.2, 103.8, 94.1 (**Figure A.6**)

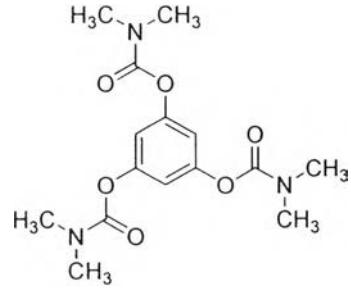
2.3.2 Synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene (53)



Phloroglucinol dihydrate **(44)** (5.01 g, 30.9 mmol) was dissolved in excess acetyl chloride (50 mL) and anhydrous $AlCl_3$ (20.47 g, 154.5 mmol) was then added. The reaction mixture was refluxed for an hour and then quenched with 10% HCl (10 mL) and water (150 mL). The mixture was filtered and the precipitate was collected. The crude product was recrystalized in ethanol to give colorless needle crystals (7.09 g, 91% yield). m.p. 149-151 °C (lit.149-151 °C) [81]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ

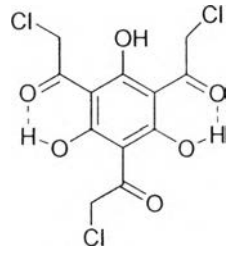
17.16 (s, 3H), 2.72 (s, 9H) (**Figure A.7**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.1, 175.9, 103.3, 33.0 (**Figure A.8**); IR (KBr, cm^{-1}): 3426.97 (O-H st), 1620.22 (C=O st), 1579.78 (C=C st), 1296.66 (C-O st) (**Figure A.9**); MS-H^+: m/z = 252.98 (**Figure A.10**)

2.3.3 Synthesis of 1,3,5-tris(*N*,*N*-dimethylcarbamoyl)benzene (57)



Phloroglucinol dihydrate **(44)** (0.35 g, 2.2 mmol) was dissolved in excess *N*,*N*-dimethyl carbamoyl chloride (8 mL) and then anhydrous $AlCl_3$ (1.43 g, 11.0 mmol) was added. The reaction mixture was refluxed for 1.5 hours and then quenched with 10% HCl (2 mL) and water (30 mL). After cooling to room temperature, the solution was extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Evaporation off the solvent then the product was obtained as yellow oil (0.51 g, 70% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 4.6 Hz, 3H), 2.88 (d, J = 5.9 Hz, 9H), 2.82 (d, J = 6.0 Hz, 9H) (**Figure A.11**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.9, 151.7, 112.1, 36.4, 36.2 (**Figure A.12**); MS-Na^+: m/z = 358.29 (**Figure A.13**)

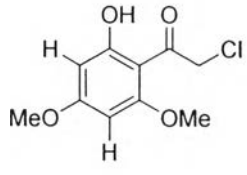
3.3.4 Synthesis of 1,3,5-tris(chloroacetyl)-2,4,6-trihydroxybenzene (60)



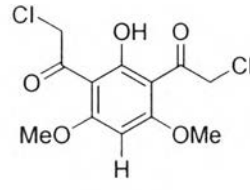
Phloroglucinol dihydrate **(44)** (0.34 g, 2.1 mmol) was dissolved in excess chloroacetyl chloride (7 mL) and then anhydrous $AlCl_3$ (1.45 g, 10.0 mmol) was added. The reaction mixture was refluxed for 1.5 hours and then quenched with 10%

HCl (2 mL) and water (30 mL). The mixture was filtered and the precipitate was collected. The crude product was recrystalized in ethanol to give colorless needle crystals (0.40 g, 54% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 16.47 (s, 2H), 4.96 (s, 6H) (**Figure A.14**)

3.3.5 Synthesis of 2-chloroacetyl-3,5-dimethoxyphenol (63) and 2,6-bis-(chloroacetyl)-3,5-dimethoxyphenol (64)



63



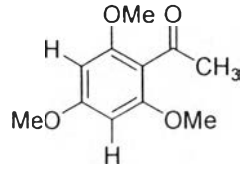
64

1,3,5-Trimethoxybenzene **(61)** (0.51 g, 3.0 mmol) was dissolved in excess chloroacetyl chloride (10 mL) and then anhydrous $AlCl_3$ (2.00 g, 15.0 mmol) was added. The reaction mixture was refluxed for 2.5 hours and then quenched with 10% HCl (2 mL) and water (30 mL). The mixture was filtered and the precipitate was collected. The crude product was purified by column chromatography (20:80 ethyl acetate/CH_2Cl_2) to give white powder products.

Compound **63** (R_f = 0.72) was obtained in 0.08 g, 12% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.33 (s, 1H), 6.11 (s, 1H), 5.94 (s, 1H), 4.81 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H) (**Figure A.15**)

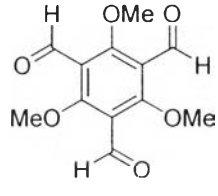
Compound **64** (R_f = 0.30) was obtained in 0.53 g, 57% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.64 (s, 1H), 5.98 (s, 1H), 4.64 (s, 4H), 3.95 (s, 6H) (**Figure A.16**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.4, 164.5, 164.3, 106.4, 86.5, 56.4, 50.8 (**Figure A.17**)

2.3.6 Synthesis of 2,4,6-trimethoxyacetophenone (65)



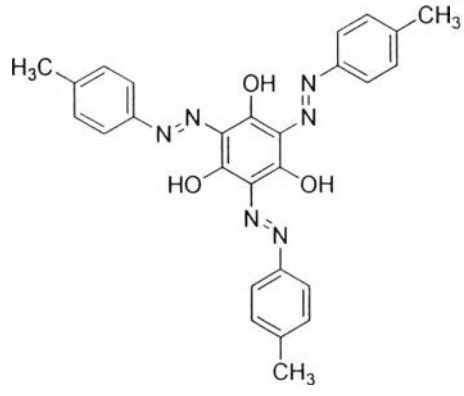
1,3,5-Trimethoxybenzene **(61)** (0.35 g, 2.1 mmol) was dissolved in excess acetyl chloride (8 mL) and then anhydrous $AlCl_3$ (0.96 g, 7.3 mmol) was added. The reaction mixture was refluxed for an hour and then quenched with 10% HCl (2 mL) and water (30 mL). The mixture was filtered and the precipitate was collected. The crude product was purified by column chromatography (70:30 hexane/ethyl acetate) to give a white powder product (0.20 g, 32% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 2H), 3.77 (s, 3H), 3.74 (s, 6H), 2.41 (s, 3H) (**Figure A.18**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.8, 162.3, 158.3, 113.5, 90.5, 55.8, 55.4, 32.5 (**Figure A.19**)

2.3.7 Synthesis of 1,3,5-triformyl-2,4,6-trimethoxybenzene (66)



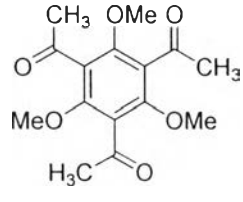
1,3,5-Triformyl-2,4,6-trihydroxybenzene **(51)** (0.20 g, 0.95 mmol) was dissolved in acetonitrile (20 mL) and stirred with K_2CO_3 (6.21 g, 14.3 mmol) at reflux temperature for an hour and then dimethyl sulfate (1.7 mL, 5.7 mmol) was added. Stirring was continued until no starting material was found by TLC monitoring (about 19 hours). After cooling, the reaction mixture was extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography (50:50 hexane/ethyl acetate) to give a white solid (0.14 g, 57% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 3H), 4.02 (s, 12H) (**Figure A.20**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 187.3, 169.9, 120.2, 65.7 (**Figure A.21**); MS-H^+: m/z = 253.08 (**Figure A.22**)

2.3.8 Synthesis of 1,3,5-tris-(*p*-tolyldiazo)-2,4,6-trihydroxybenzene (69)



p-Toluidine (0.54 g, 5.0 mmol) was dissolved in 1 M hydrochloric acid (12.5 mL, 12.5 mmol), cooled below 5 °C and sodium nitrite (0.41 g, 6.0 mmol) was added to give the solution of diazonium salt. The cooled solution of phloroglucinol dihydrate **(44)** (0.16 g, 1.0 mmol) in 1 M sodium hydroxide (6.0 mL, 6.0 mmol) was added dropwise into the prepared diazonium salt. The mixture turned into pale violet solution with large amount of crimson red precipitate formed during addition. It was then neutralized with 3 M sodium carbonate to pH between 9 and 10 and stirred for an hour at 0 °C. The product was filtered, washed with water and left dry for 1-2 days to give the scarlet red solid in quantitative yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 16.41 (s, 3H), 7.53 (d, J = 8.3 Hz, 6H), 7.25 (d, J = 8.3 Hz, 6H), 2.39 (s, 9H) (**Figure A.23**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.6, 139.1, 137.9, 130.5, 128.6, 117.7, 21.3 (**Figure A.24**)

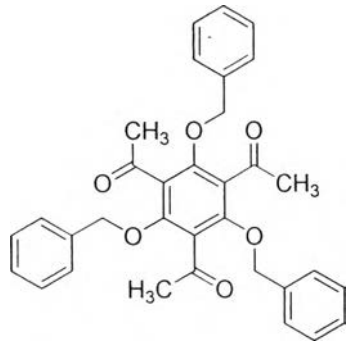
2.3.9 Synthesis of 1,3,5-triacetyl-2,4,6-trimethoxybenzene (70)



1,3,5-Triacetyl-2,4,6-trihydroxybenzene **(53)** (5.99 g, 23.8 mmol) was dissolved in acetonitrile (250 mL) and stirred with K_2CO_3 (49.26 g, 357.0 mmol) at reflux temperature for an hour and then dimethyl sulfate (13.5 mL, 142.8 mmol) was added. Stirring was continued until no starting material was found by TLC monitoring

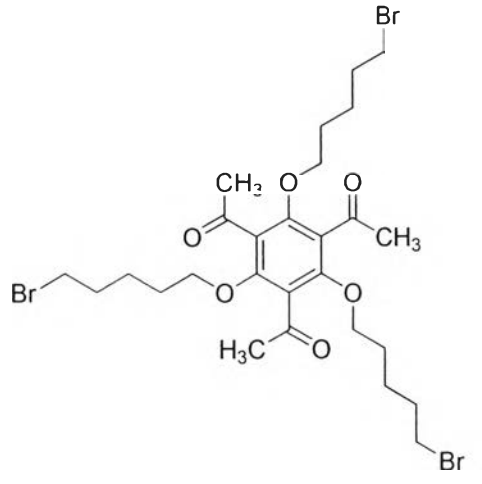
(about 13 hours). The reaction was then cooled down, the solvent was removed and then 150 mL of water was added. The product was precipitated and collected as a white powder (6.50 g, 93% yield). m.p. 124-126 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 9H), 2.54 (s, 9H) (**Figure A.25**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.8, 155.4, 127.3, 64.6, 32.6 (**Figure A.26**); IR (KBr, cm^{-1}): 2949.19 (C-H st), 1708.65 (C=O st), 1582.16 (C=C st), 1205 (C-O st) (**Figure A.27**); MS-H^+: m/z = 295.16 (**Figure A.28**)

2.3.10 Synthesis of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene (71)



1,3,5-Triacetyl-2,4,6-trihydroxybenzene **(53)** (0.54 g, 2.0 mmol) was dissolved in acetonitrile (20 mL) and stirred with K_2CO_3 (4.14 g, 30.0 mmol) at reflux temperature for an hour and then benzyl bromide (0.7 mL, 6.0 mmol) was added. Stirring was continued until no starting material was found by TLC monitoring (about 8 hours). The reaction was then cooled down, the solvent was evaporated and then 20 mL of water was added. The product was precipitated and collected in a white powder (0.23 g, 75% yield). m.p. 189-191 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 15H), 4.94 (s, 6H), 2.49 (s, 9H) (**Figure A.29**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.1, 153.9, 135.8, 129.1, 128.8, 128.8, 80.1, 32.8 (**Figure A.30**); IR (KBr, cm^{-1}): 3031.89 (=C-H st), 2920.00 (C-H st), 1698.92 (C=O st), 1572.43 (C=C st), 1197.84 and 1081.08 (C-O st) (**Figure A.31**); MS-H^+: m/z = 523.20 (**Figure A.32**)

2.3.11 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5'-bromopentyloxy)benzene (72)



1,3,5-Triacetyl-2,4,6-trihydroxybenzene **(53)** (5.01 g, 19.9 mmol) was dissolved in acetonitrile (200 mL) and stirred with K_2CO_3 (41.15 g, 298.2 mmol) at reflux temperature for an hour and then 1,5-dibromopentane (32.7 mL, 238.8 mmol) was added. After 2 days, the reaction was then cooled down, evaporized the solvent, added 100 mL of water, and then neutralized with 10% HCl. The solution was extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography (90:10 hexane/ethyl acetate) to give colorless oil product (10.7 g, 77% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (t, J = 6.4 Hz, 6H), 3.40 (t, J = 6.7 Hz, 6H), 1.93 – 1.79 (m, 6H), 1.71 – 1.57 (m, 6H), 1.55 – 1.40 (m, 6H) (**Figure A.33**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.0, 154.1, 127.8, 77.6, 33.7, 32.9, 32.4, 29.1, 24.5 (**Figure A.34**); IR (KBr, cm^{-1}): 2947.59 (C-H st), 1705.06 (C=O st), 1575.62 (C=C st), 1205-1085 (C-O st), 562.36 (C-Br st) (**Figure A.35**); MS^+: m/z = 699.30 (**Figure A.36**)

2.3.12 Synthesis of 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene (73) and 1-tribromoacetyl-3,5-diacetyl-2,4,6-trimethoxybenzene (74)

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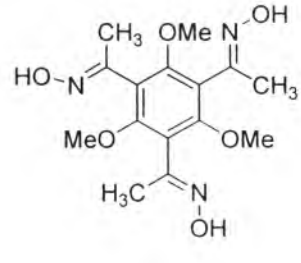
1,3,5-Triacetyl-2,4,6-trimethoxybenzene **(70)** (0.23 g, 0.8 mmol) was dissolved in CH_2Cl_2 (5 mL). NBS (0.45 g, 2.5 mmol) and anhydrous $AlCl_3$ (0.003 g, 0.02 mmol) were added and stirred the mixture at room temperature under nitrogen atmosphere. After 5 days, the reaction mixture was filtered to remove excess NBS and $AlCl_3$ from the reaction and then removed the solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/ethyl acetate) to give product **73** as yellow oil (0.05 g, 17 % yield). R_f = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 6H), 3.75 (s, 9H) (**Figure A.37**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.7, 157.7, 122.9, 77.3, 77.01, 76.7, 64.97, 36.3 (**Figure A.38**); IR (KBr, cm^{-1}): 2955 (C-H st), 1708 (C=O st), 1562 (C=C st), 1457 and 1391 (C-H bend), 1198 and 1118 (C-O st), 590 (C-Br st) (**Figure A.39**); MS-H^+: m/z = 531.13 (**Figure A.40**)

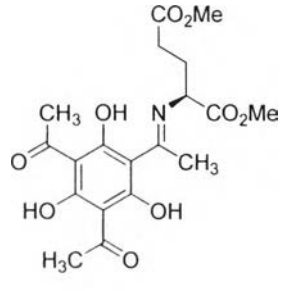
Compound **74** was also obtained as the yellow oil major product (0.12 g, 40% yield). R_f = 0.45; ^{1}H- NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.73 (s, 3H) 3.63 (s, 3H), 2.42 (s, 6H) (**Figure A.41**); MS-H^+: m/z = 530.93 (**Figure A.42**)

2.3.13 Synthesis of 1,3,5-tris(*N*-hydroxyimino)ethyl)-2,4,6-trimethoxybenzene (75)

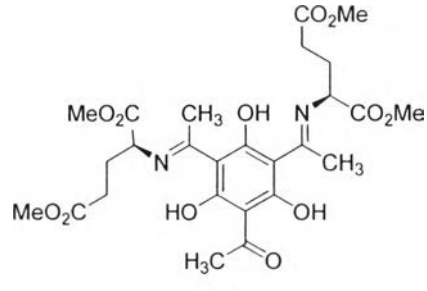


Hydroxylamine hydrochloride (0.47 g, 6.8 mmol) solution (2 mL) was cooled in an ice-bath. 3 mL of sodium hydroxide (0.45 g, 11.3 mmol) solution was added dropwise followed by 1,3,5-triacetyl-2,4,6-trimethoxybenzene **(53)** (0.28 g, 1.1 mmol) solution in ethanol (20 mL). The reaction mixture was stirred at reflux temperature until no starting material was found by TLC monitoring (about 2 hours). The reaction was then cooled down, acidified with 10% HCl to pH 1 and extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography (50:50 hexane/ethyl acetate) to give a white powder product (0.20 g, 53% yield). m.p. 211-215 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 3H), 3.60 (s, 9H), 2.03 (s, 9H) (**Figure A.43**); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 156.9, 149.6, 122.6, 62.2, 16.2 (**Figure A.44**); IR (KBr, cm^{-1}): 3425.46 (O-H st), 3103.32 (=C-H st), 1628.78 (C=C and C=N st) (**Figure A.45**); MS-Na$^+$: m/z = 362.00, 2MS-Na$^+$: m/z = 701.17 (**Figure A.46**)

2.3.14 Synthesis of mono-imine 83 and bis-imine 84



83



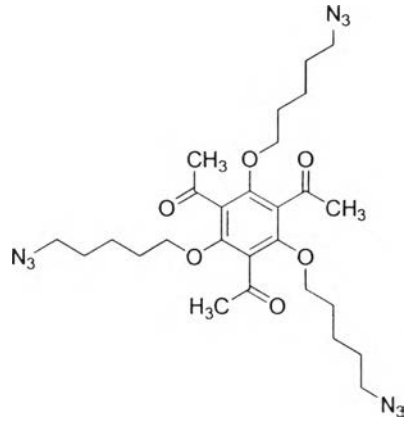
84

1,3,5-Triacetyl-2,4,6-trihydroxybenzene **(53)** (0.25 g, 0.99 mmol) was dissolved in toluene (30 mL) and then L-glutamate dimethyl ester (0.85 g, 4.0 mmol) and triethylamine (0.55 mL, 4.0 mmol) were added. The reaction was stirred and refluxed with Dean-Stark apparatus until no starting material was found by TLC monitoring (about 4.5 hours). The reaction was then cooled down, filtered out of solid and evaporated the solvent. The concentrated crude product was purified by column chromatography (70:30 hexane/ethyl acetate) to give product **83** as a white powder (0.10 g, 24% yield). R_f = 0.28; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 18.07(s, 1H), 18.05 (s, 1H), 16.44 (s, br, 1H), 4.70 (q, J = 6.5 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 2.65 (s,

3H), 2.60 (s, 3H), 2.53 (s, 3H), 2.52 (t, J = 7.1 Hz, 2H), 2.36 (ddd, J = 16.8, 12.0, 4.8 Hz, 1H), 2.27 (dt, J = 14.3, 7.1 Hz, 1H) (**Figure A.55**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.4, 203.1, 182.6, 178.9, 178.3, 175.9, 172.5, 170.0, 107.1, 101.7, 101.5, 56.0, 53.3, 52.1, 32.0, 31.8, 29.5, 27.8, 20.1 (**Figure A.56**)

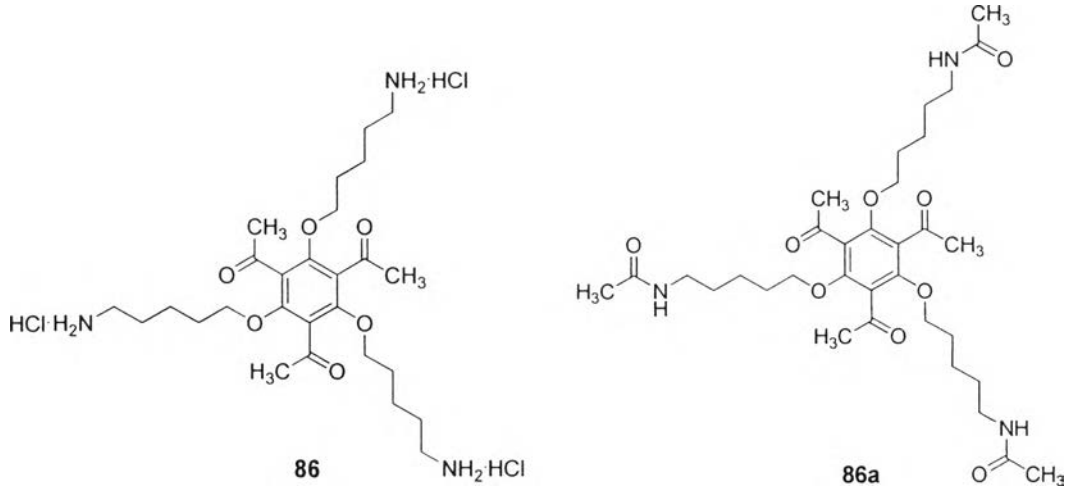
Compound **84** was obtained as a yellow solid (0.11 g, 19% yield). R_f = 0.24; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 3.78 (m, 1H), 2.67 (s, 3H), 2.57 (m, 6H), 2.49 (t, J = 7.2 Hz, 2H), 2.32 (m, 1H), 2.24 (m, 1H) (**Figure A.57**).

2.3.15 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5'-azidopentyloxy)benzene (85)



1,3,5-Triacetyl-2,4,6-tris(5'-bromopentyloxy)benzene (**72**) (3.69 g, 5.3 mmol) was dissolved in acetone (24 mL) and then freshly prepared solution of sodium azide (1.37 g, 21.1 mmol) in water (6 mL) was added. The reaction mixture was stirred at reflux temperature until no starting material was found by TLC monitoring (about 8 hours). The reaction was then cooled down and extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography (CH_2Cl_2) to give the yellow oil product (2.82 g, 85% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (t, J = 6.4 Hz, 6H), 3.27 (t, J = 6.8 Hz, 6H), 2.52 (s, 1H), 1.87 – 1.47 (m, 12H), 1.43 (dt, J = 12.6, 6.8 Hz, 6H) (**Figure A.58**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.1, 154.2, 127.8, 77.6, 51.4, 32.8, 29.5, 28.6, 23.0 (**Figure A.59**); MS-Na^+: m/z = 608.70 (**Figure A.60**)

2.3.16 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5'-aminopentyloxy)benzene trihydrochloride (86) and its *N*-acetylated derivatives (86a)

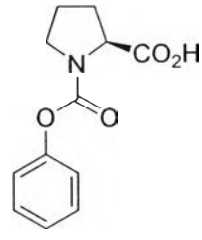


To the solution of 1,3,5-triacetyl-2,4,6-tris(5'-azidopentyloxy)benzene **(85)** (0.3 g, 0.5 mmol) and ammonium chloride (0.23 g, 3.6 mmol) in ethanol (3 mL) and water (10 mL), zinc powder (0.14 g, 2.0 mmol) were added. The mixture was stirred vigorously at reflux temperature until no starting material was found by TLC monitoring (about 15 min). Ethyl acetate (15 mL) and 30% aqueous ammonia (5 mL) were added. The mixture was filtered, and the filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent, the concentrated crude product was converted into hydrochloride salt by adding methanol (5 mL) and 10% HCl (1 mL). The reaction was stirred for 3 hours. The salt product **86** was purified by column chromatography using Sephadex LH-20 as the absorbent and methanol as the eluent. The product was obtained as yellow oil (0.23 g, 90% yield), and was acetylated into compound **86a** for characterization as follows:

Compound **86** (0.18 g, 0.35 mmol) was treated with acetic anhydride (1 mL), DMAP (39 mg, 0.35 mmol) and pyridine (2 mL). The reaction mixture was stirred at room temperature overnight. It was quenched with water (10 mL) and then extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (80:20 ethyl acetate/methanol). The product **86a** was obtained as a white solid (0.15 g, 69% yield). ^{1}H-NMR (400 MHz, Acetone-d_6) δ 7.06 (s, 1H), 3.84 (t, J = 6.4 Hz, 6H), 3.16 (q, J = 6.5 Hz, 6H),

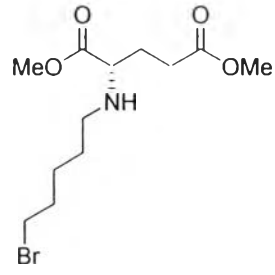
2.51 (s, 9H), 1.84 (s, 9H), 1.78 – 1.52 (m, 6H), 1.43 (m, J = 22.7, 14.7, 7.5 Hz, 12H) (**Figure A.61**); ^{13}C-NMR (100 MHz, Acetone-d_6) δ 201.0, 169.8, 154.8, 128.3, 77.9, 39.6, 32.9, 30.27, 30.1, 23.8, 22.9 (**Figure A.62**); MS-Na^+ (MALDI-TOF, CCA matrix): m/z = 656.31 (**Figure A.63**)

2.3.17 Synthesis of *N*-(phenyloxycarbonyl)-L-proline (87)



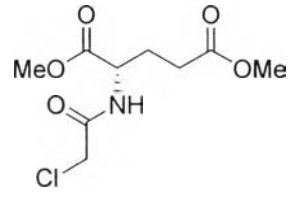
To solution of L-proline (0.46 g, 4.0 mmol) in water (10 mL) was added lithium chloride (0.94 g, 22.2 mmol) and aluminum oxide (0.12 g, 1.3 mmol). The mixture was cooled below -10 °C in an ice-salt bath. The pH value of the suspension mixture was adjusted to 10 using 3.2 M LiOH. Phenyl chloroformate (0.55 mL, 4.4 mmol), precooled to -20 °C, was added. Additional 3.2 M LiOH was added slowly to maintain the pH of the mixture between 9.8 and 10.0. The temperature was kept less than -5 °C. After 3 hours of adding LiOH solution into the stirred reaction, the white suspension was filtered and then washed with water. The combined aqueous phase was washed twice with diethyl ether. After acidified to pH 2 with concentrated H_2SO_4, the organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The product was obtained as colorless oil (0.55 g, 58% yield). ^{1}H-NMR (400 MHz, Acetone-d_6) δ 7.37 (t, J = 7.1 Hz, 2H), 7.19 (t, J = 7.1 Hz, 2H), 7.13 (d, J = 7.8 Hz, 1H), 4.57 (d, J = 8.6 Hz, 1H), 4.49 (dd, J = 67.2, 8.6 Hz, 1H), 3.82 – 3.45 (m, 2H), 2.51 – 2.24 (m, 1H), 2.24 – 1.76 (m, 3H) (**Figure A.64**); ^{13}C-NMR (100 MHz, Acetone-d_6) δ 174.4, 173.9, 152.6, 130.0, 126.0, 122.6, 60.0, 47.9, 31.6, 30.6 (**Figure A.65**)

2.3.18 Synthesis of *N*-(5'-bromopentyl)-L-glutamate dimethyl ester (90)



L-Glutamate dimethyl ester hydrochloride (1.5 g, 7.1 mmol) was dissolved in acetonitrile (30 mL) and stirred with K_2CO_3 (6.6 g, 27.7 mmol) at reflux temperature for an hour and then 1,5-dibromopentane (4.6 mL, 33.6 mmol) was added. After 3 days, the reaction was then cooled down, evaporated the solvent and then water (30 mL) was added. The solution was extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/ethyl acetate) to give the colorless oil product (1.47 g, 79% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.63 (s, 3H), 3.14 (dd, J = 8.4, 7.0 Hz, 1H), 2.64–2.55 (m, 2H), 2.41–2.34 (m, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.18 – 1.82 (m, 2H), 1.82 – 1.25 (m, 6H) (**Figure A.66**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8, 172.2, 67.1, 51.6, 51.1, 50.7, 30.7, 26.4, 24.6, 24.1 (**Figure A.67**)

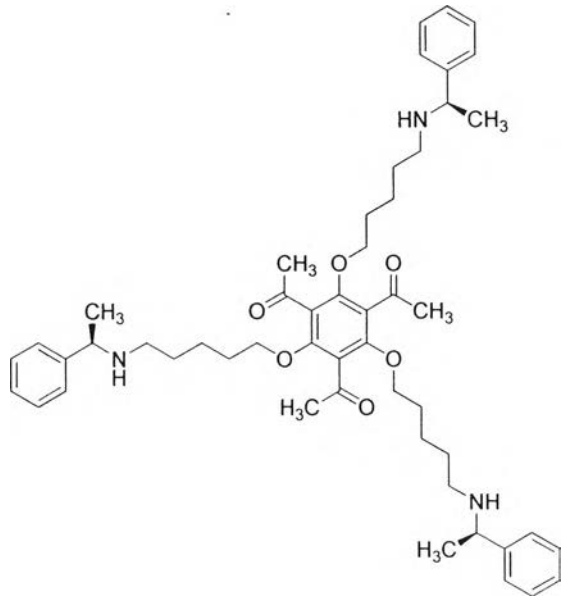
2.3.19 Synthesis of *N*- chloroacetyl-L-glutamate dimethyl ester (91)



L-Glutamate dimethyl ester hydrochloride (0.5 g, 2.4 mmol) was dissolved in dichloromethane (16 mL) and triethylamine (0.82 mL, 4.0 mmol) was added. The reaction was stirred and cooled in an ice-bath for 15 min and then chloroacetyl chloride (0.25 mL, 2.8 mmol) was added. The mixture was stirred at room temperature for an hour and then quenched with 10% HCl (2 mL) and water (20 mL). The reaction was extracted with dichloromethane. The organic layers were separated,

combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The desired product was obtained as colorless oil (0.59 g, 91% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 4.58 (td, J = 7.9, 5.2 Hz, 1H), 4.02 (s, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 2.48 – 2.10 (m, 2H), 2.01 (td, J = 14.4, 7.7 Hz, 3H) (**Figure A.68**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.1, 171.6, 166.3, 52.8, 52.0, 51.9, 42.4, 29.9, 27.0 (**Figure A.69**)

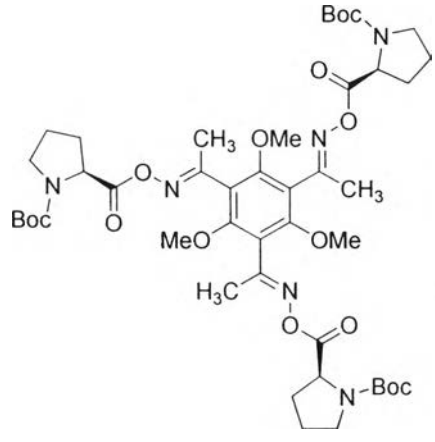
2.3.20 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5'-((*R*)-1-phenylethylamino)pentyl-oxy)benzene (94)



1,3,5-Triacetyl-2,4,6-tris(5'-bromopentyloxy)benzene **(72)** (0.51 g, 0.7 mmol) was dissolved in acetonitrile (25 mL) and stirred with K_2CO_3 (0.5 g, 3.5 mmol) at reflux temperature for an hour and then (*R*)-(+)-phenylethylamine (0.3 mL, 2.4 mmol) was added. The reaction mixture was stirred at reflux temperature until no starting material was found by TLC monitoring (about 13 hours). The reaction was then cooled down and extracted with ethyl acetate. The organic layers were separated, combined, dried over anhydrous Na_2SO_4 and evaporated the solvent. The concentrated crude product was purified by column chromatography using Sephadex LH-20 as adsorbent (80:20 methanol/water) to give the yellow oil product (0.26 g, 44% yield). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.72 – 7.26 (m, 15H), 4.41 (q, J = 6.5 Hz, 3H), 3.83 (t, J = 5.4 Hz, 6H), 2.96 (dd, J = 16.5, 11.1 Hz, 3H), 2.76 (dd, J = 16.5, 11.1 Hz, 3H), 2.50 (s, br. 9H), 1.91 – 1.43 (m, 8H), 1.71 (d, J = 6.5 Hz, 9H), 1.43 – 1.14

(m, 6H) (**Figure A.70**); ^{13}C-NMR (100 MHz, CD_3OD) δ 202.6, 155.4, 137.9, 130.7, 130.5, 130.0, 128.7, 78.2, 59.7, 46.9, 33.0, 30.3, 26.9, 23.9, 19.8 (**Figure A.71**)

2.3.21 Synthesis of tris-oxime 100



1,3,5-Tris(*N*-hydroxyimino)ethyl)-2,4,6-trimethoxybenzene **(75)** (0.34 g, 1.0 mmol) was dissolved in dried tetrahydrofuran (5 mL) and then Boc-L-Pro-OSu (1.00 g, 3.2 mmol) and pyridine (0.3 mL, 3.7 mmol) were added. The mixture was stirred at room temperature under nitrogen atmosphere until no starting material was found by TLC monitoring (about 45 hours). The solvent was evaporated and the resulting concentrated crude product was purified by column chromatography (50:50 hexane/ethyl acetate) to obtain colorless oil product (0.26 g, 28% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.53 (m, 1H), 4.40 (m, 2H), 3.79 (s, 3H), 3.73 (s, 6H), 3.68 – 3.35 (m, 6H), 2.40 – 1.82 (m, 12H), 2.26 (s, 6H), 2.17 (s, 6H), 1.45 (s, 9H), 1.41 (s, 18H) (**Figure A.72**); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 161.8, 158.3, 157.0, 154.5, 153.8, 152.0, 121.32, 80.4, 80.1, 64.1, 63.9, 63.4, 58.6, 58.1, 46.7, 46.5, 31.1, 30.2, 28.5, 28.4, 24.5, 23.9, 18.4, 16.1 (**Figure A.73**)