The Azaquinone-Methide Elimination: Comparison Study of 1, 6- and 1, 4-Eliminations under Physiological Conditions

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Supporting Information

Experimental

General. All reactions requiring anhydrous conditions were performed under an Ar or N_2 atmosphere. Chemicals and solvents were either A.R. grade or purified by standard techniques. Thin layer chromatography (TLC): silica gel plates Merck 60 F_{254}; compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (20% wt. in ethanol), followed by heating. Flash chromatography (FC): silica gel Merck 60 (partical size 0.040-0.063 mm), eluent given in parentheses. ^{1}H NMR: Bruker AMX 200 or 400 instrument. The chemical shifts are expressed in δ relative to TMS (δ=0 ppm) and the coupling constants *J* in Hz. The spectra were recorded in $CDCl_3$, MeOD as a solvent at room temp. 400 Mesh copper grid SPI Supplies, West Chester, PA. All reagents, including salts and solvents, were purchased from Sigma-Aldrich.

Abbreviations. **AcOH**- Acetic acid, **ACN**- Acetonitrile, **DBTL**- Dibutyltin dilaurate**,** **DCM**- Dichloromethane, **DIPEA-** Diisopropylethyleneamine, **DMF**- Dimethyl formamide, **DMSO**- Dimethyl sulfoxide, **EDC**- *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride**,** **EtOAc**- Ethylacetate, **Et_3N-** Triethylamine, **Hex**-

Hexane, **MeOH**- Methanol, **PNA**- *p*-Nitroaniline, **PNPCl**- *p*-Nitrophenol chloroformate, **Py**- Pyridine, **TBAF**- Tetrabutylammonium fluorid, **TBDPSCl**- t-Butyldiphenylsillyl chloride, **TBSCl**- t-Butyldimethylsillyl chloride, **THF**- Tetrahydrofuran, **TMSE**- Trimethylsillyl ethanol.

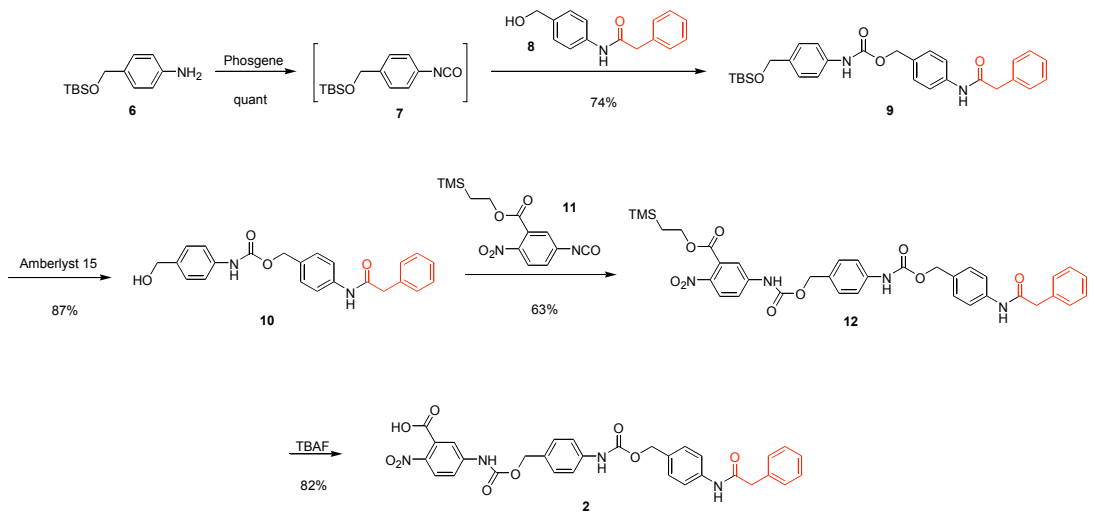

Figure 1. Chemical synthesis of compound **2**.

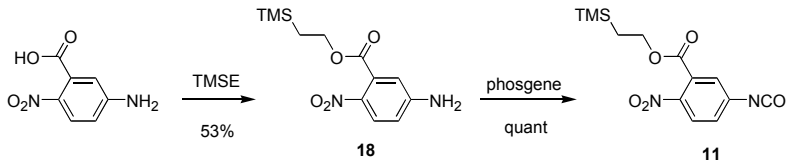

Figure 2. Chemical synthesis of compound **11**.

Compound 6

Compound **6** was synthesized according to the procedure described in *J. Med. Chem.* **2004,** *47 (2),* 303-324.

Compound 8

Compound **8** was synthesized according to the procedure described in *Bioorg. Med. Chem.* **2004,** *12,* 1859-1866.

Compound 9

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (4.96 mL, 9.57 mmol) was added. Then, a solution of compound **6** (227.15 mg, 0.95 mmol) in 2 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **8** (300 mg, 1.24 mmol) in 2.5 mL THF, followed by the addition of 20 µL DBTL, was added to the isocyanate residue. The reaction was stirred for 45 minutes and was monitored by TLC (EtOAc:Hex 1:2). Upon completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:2) to give compound **9** (357 mg, 74%) as a yellow solid. ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.44-7.25 (13H, m); 5.12 (2H, s); 4.68 (2H, s); 3.74 (2H, s); 0.92 (9H, s); 0.07 (6H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 168.91, 155.21, 138.70, 138.36, 137.55, 136.69, 131.61, 131.27, 130.42, 128.38, 127.71, 125.44, 122.43, 120.35, 66.61, 63.45, 46.73, 27.92, 19.84, -3.42. MS (FAB): *m/z*: 527.1 $[M+Na]^{+}$.

Compound 10

Compound **9** (156.5 mg, 0.31 mmol) was dissolved in 6 mL solution of DCM:MeOH, 1:1 and Amberlyst-15 was added. The reaction was stirred in room temperature for 1.5 hours and was monitored by TLC (EtOAc:Hex 1:1). Upon completion of the reaction, Amberlyst-15 was filtered out and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **10** (105.4 mg, 87%) as a white solid.

^{1}H NMR (200MHz, MeOD): δ = 7.57 (2H, d, J=8Hz); 7.42-7.23 (11H, m); 5.12 (2H, s); 4.53 (2H, s); 3.67 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 168.91, 154.67, 139.41, 138.36, 137.45, 137.05, 131.61, 131.20, 129.85, 128.36, 127.50, 125.31, 122.47, 120.35, 66.60, 63.02, 46.70. MS (FAB): *m/z*: 391.2 $[M+H]^+$.

Compound 12

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (3.9 mL, 7.68 mmol) was added. Then, a solution of compound **18** (211.5 mg, 0.75 mmol) in 2 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **10** (100 mg, 0.25 mmol) in 2 mL THF, followed by the addition of 20 µL DBTL, was added to the isocyanate residue. The reaction mixture was allowed to warm to 45° C and was stirred for 1 hour. The reaction was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **12** (112.3 mg, 64%) as a yellow solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.98 (1H, m); 7.64-7.59 (2H, m); 7.42-7.15 (12H, m); 6.82-6.77 (1H, m); 5.15 (2H, s); 5.11 (2H, s); 4.46-4.37 (2H, m); 3.74 (2H, s); 1.11-1.05 (2H, m); 0.05 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 169.10, 167.22, 154.63, 153.81, 143.16, 142.79, 141.51, 138.12, 137.56, 137.10, 135.05, 131.62, 130.42, 129.71, 129.03, 127.81, 125.13, 123.74, 123.46, 119.73, 118.21, 117.02, 67.10, 65.40, 63.55, 48.12, 20.77, -3.31. MS (FAB): *m/z*: 721.1 $[M+Na]^+$.

Compound 2

Compound **12** (112.3 mg, 0.16 mmol) was dissolved in THF (2.5 mL), and TBAF (0.24 mL, 1M in THF) was added. The reaction was stirred in room temperature for 3 hours and was monitored by TLC (EtOAc:MeOH:AcOH 97:2.5:0.5). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:MeOH:AcOH 97:2.5:0.5) to give compound **2 (**78.8 mg, 82%) as a yellow solid.

^{1}H NMR (400MHz, MeOD): δ = 7.96 (1H, d, J=8Hz); 7.79-7.70 (2H, m); 7.57 (2H, d, J=8Hz); 7.47 (2H, d, J=8Hz); 7.38-7.30 (8H, m); 7.25 (1H, m); 5.18 (2H, s); 5.15 (2H, s); 3.69 (2H, s). ^{13}C NMR (100MHz, MeOD): δ = 169.10, 166.12, 154.45, 153.14, 145.02, 143.70, 141.27, 138.16, 137.56, 137.08, 136.14, 134.95, 130.87, 130.41, 129.41, 128.42, 125.13, 123.72, 123.00, 119.51, 118.49, 117.64, 67.18, 65.41, 48.11. MS (FAB): *m/z*: 598.0 $[M]^{+}$.

Compound 18

Commercially available 5-amino-2-nitrobenzoic acid (800 mg, 4.39 mmol) was dissolved in ACN (8 mL) and the solution was cooled to 0° C. Then TMSE (1.03 mL, 7.02 mmol), EDC (1.38 g, 7.02 mmol) and pyridine (0.7 mL, 8.66 mmol) were added. The reaction mixture was stirred in room temperature for 18 hours and was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **18** (651.9 mg, 53%) as a yellow solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.95 (1H, d, J=10Hz); 6.67-6.61 (2H, m); 4.46 (2H, bs); 4.41 (2H, m); 1.11 (2H, m); 0.05 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 164.36, 151.55, 142.21, 132.27, 127.14, 114.11, 112.91, 64.81, 20.03, -5.36. MS (FAB): *m/z*: 305.0 $[M+Na]^+$.

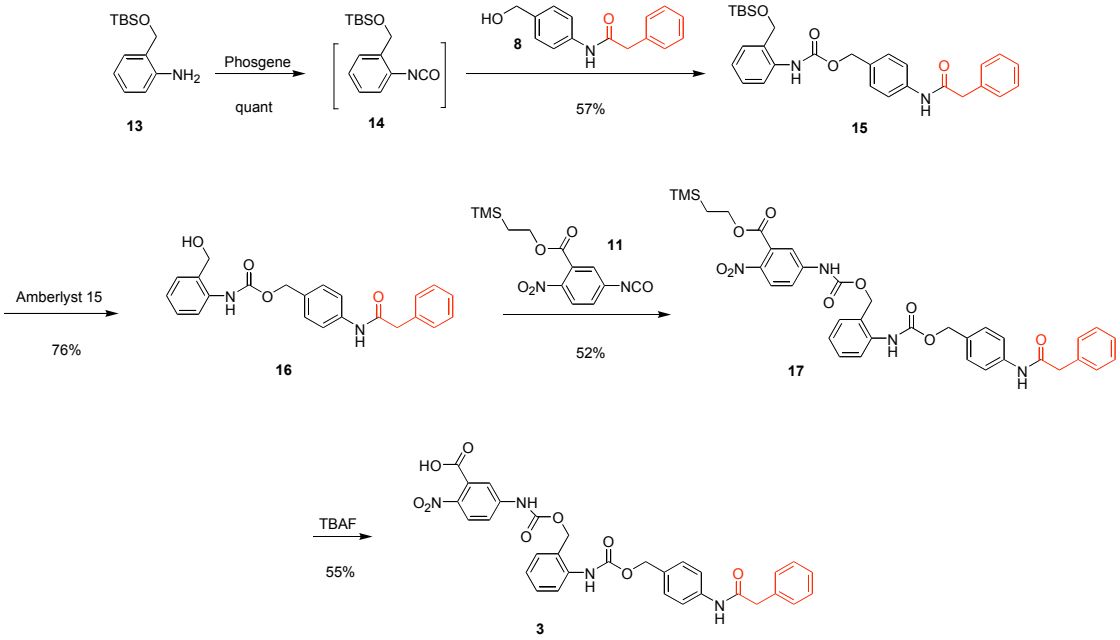

Figure 3. Chemical synthesis of compound **3**.

Compound 13

Compound **13** was synthesized according to the procedure described in *Bioorg. Med. Chem.* **2005,** *13,* 3821-3839.

Compound 15

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (4.96 mL, 9.57 mmol) was added. Then, a solution of compound **13** (227.15 mg, 0.95 mmol) in 2 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was

removed under reduced pressure. A solution of compound **8** (300 mg, 1.24 mmol) in 2.5 mL THF, followed by the addition of 20 µL DBTL, was added to the isocyanate residue. The reaction was stirred for 2.5 hours and was monitored by TLC (EtOAc:Hex 1:2). Upon completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:2) to give compound **15** (270.9 mg, 57%) as a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.43-7.29 (10H, m); 7.07-6.96 (3H, m); 5.13 (2H, s); 4.70 (2H, s); 3.74 (2H, s); 0.87 (9H, s); 0.04 (6H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 169.11, 156.32, 139.49, 138.14, 137.56, 137.02, 131.61, 131.23, 130.42, 129.65, 129.14, 126.91, 126.11, 122.43, 121.39, 119.51, 66.43, 59.84, 46.73, 27.92, 20.21, -3.26. MS (FAB): *m/z*: 527.1 $[M+Na]^+$.

Compound 16

Compound **15** (270.9 mg, 0.53 mmol) was dissolved in 6 mL solution of DCM:MeOH 1:1 and Amberlyst-15 was added. The reaction was stirred in room temperature for 1.5 hours and was monitored by TLC (EtOAc:Hex 1:1). Upon completion of the reaction, Amberlyst-15 was filtered out and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **16** (157.5 mg, 76%) as a white solid.

^{1}H NMR (200MHz, MeOD): δ = 7.59-7.55 (3H, m); 7.39-7.25 (9H, m); 7.14-7.07 (1H, m); 5.13 (2H, s); 4.61 (2H, s); 3.68 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 169.10, 157.02, 139.76, 138.14, 137.50, 137.00, 131.61, 131.23, 130.13, 129.65, 128.57, 126.91, 125.72, 120.11, 119.41, 119.24, 66.80, 60.12, 46.70. MS (FAB): *m/z*: 391.2 $[M+H]^+$.

Compound 17

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (2.58 mL, 4.99 mmol) was added. Then, a solution of compound **18** (140.9 mg, 0.49 mmol) in 2 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **16** (65 mg, 0.16 mmol) in 2.5 mL THF, followed by the addition of 20 µL DBTL, was added to the isocyanate residue. The reaction mixture was allowed to warm to 45° C and was stirred for 18 hours. The reaction was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **17** (60.4 mg, 52%) as a yellow solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.98-7.97 (3H, m); 7.86-7.85 (1H, m); 7.61-7.59 (4H, m); 7.42-7.32 (6H, m); 7.14-7.13 (2H, m); 5.23 (2H, s); 5.15 (2H, s); 4.44-4.38 (2H, m); 3.79 (2H, s); 1.16-1.08 (2H, m); 0.05 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 169.14, 167.83, 155.97, 153.73, 143.16, 142.85, 142.25, 138.14, 137.55, 137.10, 131.59, 131.19, 130.42, 129.82, 129.63, 128.46, 128.31, 124.72, 121.63, 121.12, 119.81, 119.46, 118.73, 116.97, 67.10, 64.13, 63.54, 48.12, 18.81, -3.31. MS (FAB): *m/z*: 721.0 $[M+Na]^+$.

Compound 3

Compound **17** (45.8 mg, 65.5 µmol) was dissolved in THF (1.5 mL), and TBAF (98 µL, 1M in THF) was added. The reaction was stirred in room temperature for 2.5 hours and was monitored by TLC (EtOAc:MeOH:AcOH 97:2.5:0.5). Upon

completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:MeOH:AcOH 97:2.5:0.5) to give compound **3** (21.3 mg, 55%) as a yellow solid.

^{1}H NMR (200MHz, MeOD): δ = 7.94 (1H, d, J=8Hz); 7.70 (2H, m); 7.56-7.35 (5H, m); 7.37-7.20 (8H, m); 5.24 (2H, s); 5.13 (2H, s); 3.67 (2H, s). ^{13}C NMR (100MHz, MeOD): δ = 169.08, 166.41, 154.13, 153.71, 144.15, 143.16, 143.03, 139.10, 137.53, 137.10, 131.59, 130.87, 130.42, 130.17, 129.76, 129.60, 127.12, 125.92, 121.63, 120.74, 119.45, 118.71, 117.52, 116.83, 67.11, 64.16, 48.12. MS (FAB): *m/z*: 598.0 $[M]^{+}$.

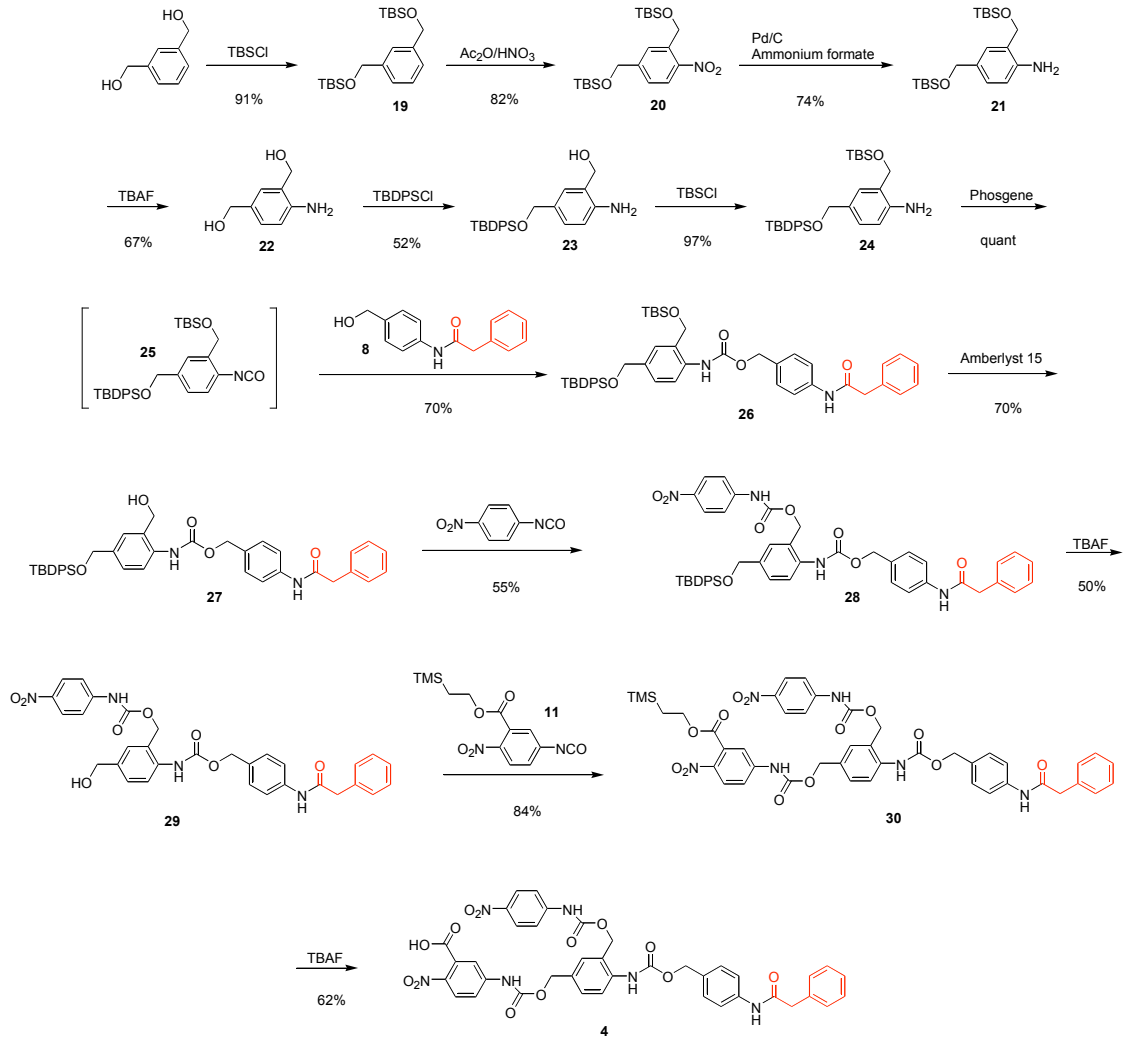

Figure 4. Chemical synthesis of dendritic molecule **4**.

Compound 19

Commercially available 1,3-dimethanolbenzene (5 g, 36.18 mmol) was dissolved in DMF (9 mL) and cooled to 0° C. Imidazole (7.39 g, 108.56 mmol) and TBSCl (16.36 g, 108.56 mmol) were added. The reaction was allowed to warm to room temperature and was stirred for additional 2 hours. The reaction was monitored by TLC (EtOAc:Hex 1:9). Upon completion of the reaction, the reaction was diluted with diethyl ether and washed with NH_4Cl solution. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:9) to give compound **19** (12 g, 91%) as a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.35-7.15 (4H, m); 4.74 (4H, s); 0.94 (18H, s); 0.1 (12H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 143.27, 127.22, 125.12, 124.34, 67.00, 27.94, 20.39, -3.28. MS (FAB): *m/z*: 365.1 $[M-H]^-$.

Compound 20

Acetic anhydride (20 mL) was cooled to 5° C and nitric acid (1.9 mL, 71%) was added dropwise. After the addition was completed, the mixture was stirred for 15 minutes at room temperature and then cooled to -20° C. A solution of compound **19** (4 g, 10.92 mmol) in 7 mL acetic anhydride was added dropwise. The reaction mixture was allowed to warm to 0° C and was stirred for additional 30 minutes. After completion, the reaction was diluted with EtOAc and was washed with $NaHCO_3$ solution followed by brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc:Hex 5:95) to give compound **20** (3.68 g, 82%) in the form of a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.10 (1H, d, J=8Hz); 7.87 (1H, s); 7.37 (1H, d, J=8Hz); 5.11 (2H, s); 4.82 (2H, s); 0.94 (18H, s); 0.13 (12H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 144.64, 141.23, 125.41, 122.30, 118.23, 64.97, 61.39, 25.93, 18.36, -5.29. MS (FAB): *m/z*: 411.2 $[M]^+$.

Compound 21

Compound **20** (3.52 g, 8.56mmol) was dissolved in a 50:50 THF/MeOH solution. A catalytic amount of palladium and ammonium formate (869 mg, 13.78 mmol) were added. The reaction was stirred in room temperature for 2.5 hours, and was monitored by TLC (EtOAc:Hex 5:95). Upon completion of the reaction, salts were filtered out in sinter glass and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and was washed with brine. The organic layer was dried over magnesium sulfate, and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 5:95) to give compound **21** (2.41 g, 74%) as a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.02-6.99 (2H, m); 6.62 (1H, d, J=6Hz); 4.67 (2H, s); 4.61 (2H, s); 0.91 (18H, s); 0.06 (12H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 144.93, 131.40, 128.51, 126.96, 121.31, 116.42, 64.02, 60.88, 27.79, 20.15, -3.26. MS (FAB): *m/z*: 381.2 $[M]^+$.

Compound 22

Compound **21** (1.5 g, 3.92 mmol) was dissolved in THF (5 mL), and TBAF (11 mL, 1M in THF) was added. The reaction was stirred in room temperature for 2 hours and was monitored by TLC (MeOH:EtOAc 2:98). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by

using column chromatography on silica gel (MeOH:EtOAc 2:98) to give compound **22** (362 mg, 67%) as a white solid.

^{1}H NMR (200MHz, MeOD): δ = 7.12-7.05 (2H, m); 6.76 (1H, d, J=8Hz); 4.51 (2H, s); 4.41 (2H, s). ^{13}C NMR (100MHz, MeOD): δ = 146.21, 139.29, 130.42, 126.92, 124.83, 116.11, 65.18, 62.05. MS (FAB): *m/z*: 153.1 $[M]^{+}$.

Compound 23

Compound **22** (204.1 mg, 1.47 mmol) was dissolved in 1.5 mL DMF and cooled to 0° C. Imidazole (100.68 mg, 1.47 mmol) and TBDPSCl (382 μL, 1.47 mmol) were added. The reaction was allowed to warm to room temperature and was stirred for 1 hour. The reaction was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **23** (287.7 mg, 52%) as a colorless oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.71-7.66 (4H, m); 7.41-7.33 (6H, m); 7.08 (1H, d, J=8Hz); 6.97 (1H, s); 6.66 (1H, d, J=8Hz); 4.62 (4H, s); 1.10 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 146.11, 140.05, 134.61, 133.92, 128.51, 127.44, 125.12, 121.34, 115.67, 65.13, 59.11, 25.58, 18.38. MS (FAB): *m/z*: 391.1 $[M]^{+}$.

Compound 24

Compound **23** (228.7 mg, 0.607 mmol) was dissolved in 1.5 mL DMF and cooled to 0° C. Imidazole (82.64 mg, 1.214 mmol) and TBSCl (183 mg, 1.214 mmol) were added. The reaction was allowed to warm to room temperature and was stirred for additional 2 hours. The reaction was monitored by TLC (EtOAc:Hex 3:97). Upon completion of the reaction, the solvent was removed under reduced pressure and the

crude product was purified by using column chromatography on silica gel (EtOAc:Hex 3:97) to give compound **24** (300 mg, 97%) as a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.68-7.63 (4H, m); 7.39-7.32 (6H, m); 6.95 (2H, m); 6.59 (1H, d, J=8Hz); 4.63 (2H, s); 4.61 (2H, s); 4.12 (2H, bs); 1.03 (9H, s); 0.86 (9H, s); 0.04 (6H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 144.12, 135.24, 133.65, 132.07, 129.55, 128.52, 128.10, 126.14, 121.29, 115.90, 64.10, 60.88, 28.44, 27.75, 20.14, 19.41, -3.25. MS (FAB): *m/z*: 505.2 $[M]^+$.

Compound 26

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (3.43 mL, 6.62 mmol) was added. Then, a solution of compound **24** (325.2 mg, 0.66 mmol) in 2 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **8** (207.63 mg, 0.86 mmol) in 2.5 mL THF, followed by the addition of 20 μL DBTL, was added to the isocyanate residue. The reaction was stirred for 1 hour and was monitored by TLC (EtOAc:Hex 1:3). Upon completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:3) to give compound **26** (346.2 mg, 70%) as a yellow oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.66-7.61 (4H, m); 7.40-7.28 (15H, m); 7.22 (1H, m); 6.99 (2H, m); 5.10 (2H, s); 4.65 (2H, s); 4.64 (2H, s); 3.71 (2H, s); 1.03 (9H, s); 0.83 (9H, s); 0.02 (6H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 170.96, 156.20, 139.49, 138.00, 137.70, 137.21, 136.29, 135.30, 131.44, 131.19, 130.79, 129.65, 129.52,

128.12, 128.10, 126.69, 126.01, 121.59, 119.20, 66.70, 64.87, 61.12, 46.79, 27.92, 26.11, 20.21, 19.20, -3.42. MS (ESI): *m/z*: 773.2 $[M+H]^+$.

Compound 27

Compound **26** (346.2 mg, 0.44 mmol) was dissolved in 6 mL solution of DCM:MeOH, 1:1 and Amberlyst-15 was added. The reaction was stirred in room temperature for 45 minutes and was monitored by TLC (EtOAc:Hex 1:2). Upon completion of the reaction, Amberlyst-15 was filtered out and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:2) to give compound **27** (203.6 mg, 70%) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.65-7.61 (4H, m); 7.39-7.28 (15H, m); 7.23 (1H, m); 7.06 (2H, m); 5.10 (2H, s); 4.66 (2H, s); 4.61 (2H, s); 3.71 (2H, s); 1.04 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 170.86, 155.88, 141.36, 138.34, 137.81, 137.13, 137.01, 135.28, 135.21, 130.24, 129.92, 129.36, 128.61, 127.63, 126.45, 126.12, 124.73, 124.41, 121.73, 119.62, 66.18, 63.60, 60.05, 46.90, 26.98, 19.13. MS (ESI): *m/z*: 659.1 $[M+H]^+$.

Compound 28

Commercially available PNA isocyanate (60.91 mg, 0.37 mmol) was dissolved in THF (2.5 mL). Compound **27** (203.6 mg, 0.31 mmol) and DBTL (20 μL) were added. The reaction was allowed to warm to 45° C and was stirred for 1 hour. The reaction was monitored by TLC (EtOAc:Hex 1:1). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by

using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **28** (139.3 mg, 55%) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.15 (2H, d, J=10Hz); 7.69-7.64 (4H, m); 7.43 (2H, d, J=10Hz); 7.42-7.31 (16H, m); 7.07 (2H, m); 5.18 (2H, s); 5.15 (2H, s); 4.72 (2H, s); 3.75 (2H, s); 1.08 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 171.14, 156.94, 153.10, 143.45, 142.87, 139.91, 139.21, 138.52, 138.14, 137.03, 136.12, 136.01, 132.39, 131.12, 131.10, 130.03, 129.61, 129.43, 128.72, 127.47, 126.63, 126.44, 125.03, 122.12, 119.87, 69.43, 67.14, 61.32, 47.34, 26.38, 20.01. MS (ESI): *m/z*: 823.2 $[M+H]^+$.

Compound 29

Compound **28** (139.3 mg, 0.17 mmol) was dissolved in THF (2 mL), and TBAF (220 μL, 1M in THF) was added. The reaction was stirred in room temperature for 45 minutes and was monitored by TLC (EtOAc:Hex 3:1). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 3:1) to give compound **29** (49.3 mg, 50%) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.15 (2H, d, J=10Hz); 7.48 (2H, d, J=10Hz); 7.36-7.28 (10H, m); 7.05 (2H, m); 5.17 (2H, s); 5.12 (2H, s); 4.70 (2H, s); 3.72 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 171.01, 156.11, 153.15, 143.31, 143.12, 139.71, 137.83, 137.72, 137.14, 136.63, 133.45, 131.91, 131.21, 131.01, 128.49, 128.17, 127.63, 125.92, 125.03, 122.35, 119.13, 68.11, 67.42, 60.52, 47.02. MS (FAB): *m/z*: 607.1 $[M+Na]^+$.

Compound 30

Toluene (3 mL) was heated to reflux (110° C) and a solution of 20% phosgene in toluene (3.18 mL, 1.65 mmol) was added. Then, a solution of compound **18** (46.54 mg, 0.16 mmol) in 1 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **29** (32.6 mg, 55 μmol) in 2 mL THF, followed by the addition of 10 μL DBTL, was added to the isocyanate residue. The reaction mixture was allowed to warm to 45° C and was stirred for 18 hours. The reaction was monitored by TLC (EtOAc:Hex 2:1). The solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 2:1) to give compound **30** (41 mg, 84%) as a yellow solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.15 (2H, d, J=10Hz); 7.95 (1H, d, J=10Hz); 7.60-7.31 (16H, m); 5.17-5.13 (6H, m); 4.49-4.38 (2H, m); 3.82 (2H, s); 1.12-1.10 (2H, m); 0.06 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 172.31, 164.31, 156.17, 153.73, 143.48, 143.22, 142.83, 141.93, 139.42, 138.03, 138.01, 137.91, 137.12, 133.31, 132.01, 131.49, 131.21, 128.71, 128.47, 128.31, 128.12, 125.03, 121.11, 120.34, 119.81, 118.21, 117.82, 117.02, 68.32, 67.12, 64.01, 64.72, 48.21, 20.01, -3.30. MS (ESI): *m/z*: 893.3 $[M+H]^{+}$.

Compound 4

Compound **30** (41 mg, 45.9 μmol) was dissolved in THF (1.5 mL), and TBAF (68 μL, 1M in THF) was added. The reaction was stirred in room temperature for 45 minutes and was monitored by TLC (EtOAc:MeOH:AcOH 94:5:1). Upon completion

of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:MeOH:AcOH 94:5:1) to give compound **4 (**22.5 mg, 62%) as a white solid. ^{1}H NMR (200MHz, MeOD): δ = 8.12 (2H, d, J=8Hz); 7.93 (1H, d, J=10Hz); 7.70-7.52 (8H, m); 7.37-7.31 (8H, m); 5.24-5.21 (6H, m); 3.67 (2H, s). ^{13}C NMR (100MHz, MeOD): δ = 171.85, 166.47, 155.23, 151.44, 142.28, 141.58, 141.02, 140.53, 139.41, 138.33, 138.09, 137.46, 136.43, 133.12, 132.57, 131.66, 130.40, 128.11, 127.69, 127.11, 126.89, 125.42, 121.01, 120.97, 118.71, 118.22, 117.04, 116.76, 67.41, 66.74, 63.81, 48.97. MS (ESI): *m/z*: 791.1 $[M-H]^-$.

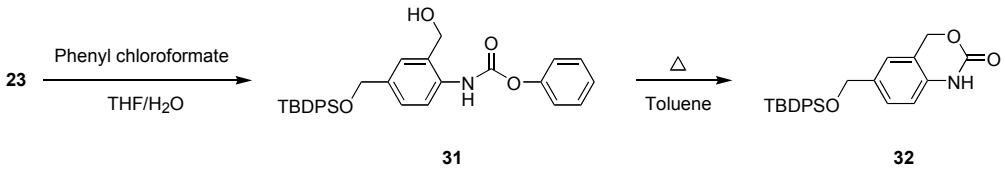

Figure 5. Chemical synthesis of carbamate **32** which, indicates the regioselective protection of compound **22**.

Compound 31

Compound **23** (98.7 mg, 0.26 mmol) was dissolved in THF (2 mL) and a solution of saturated $NaHCO_3$ in water (2 mL) was added. Then, phenyl chloroformate (32.9 µL, 0.26 mmol) was slowly added dropwise. The reaction mixture was stirred for 15 minutes and was monitored by TLC (EtOAc:Hex = 1:3). Upon completion of the reaction, the THF was removed under reduced pressure. The crude product was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex = 1:3) to give compound **31** (86 mg, 65%) as a colorless oil.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.71-7.66 (4H, m); 7.42-7.36 (6H, m); 7.27-7.19 (6H, m); 7.14 (1H, m); 6.83 (1H, m); 4.76 (2H, d, J=6Hz); 4.72 (2H, s); 1.09 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 155.64, 152.12, 150.67, 136.00, 135.49, 133.40, 129.62, 129.51, 129.27, 127.63, 126.68, 125.48, 121.55, 120.48, 115.22, 64.48, 60.36, 26.77, 19.21. MS (FAB): *m/z*: 534.2 $[M+Na]^+$.

Compound 32

Compound **31** (85 mg, 0.16 mmol) was dissolved in 3 mL toluene and DBTL was added (20 μL). The reaction was stirred for 15 minutes in reflux and was monitored by TLC (EtOAc:Hex 1:3). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:3) to give compound **32** (67.9 mg, 98%) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 7.71-7.66 (4H, m); 7.46-7.34 (6H, m); 7.21 (1H, d, J=8Hz); 7.06 (1H, s); 6.79 (1H, d, J=8Hz); 5.31 (2H, s); 4.71 (2H, s); 1.10 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 153.06, 144.82, 136.35, 135.46, 134.27, 133.27, 129.69, 127.65, 127.01, 126.45, 122.18, 68.69, 64.97, 26.76, 19.19. MS (FAB): *m/z*: 418.1 $[M+H]^+$.

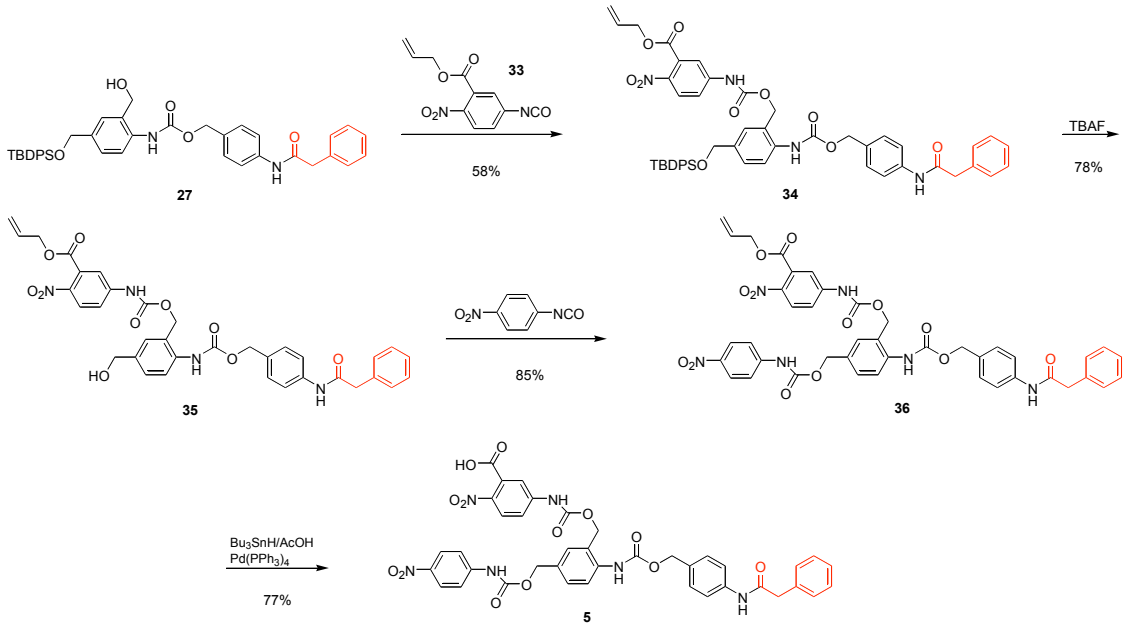

Figure 6. Chemical synthesis of dendritic molecule **5**.

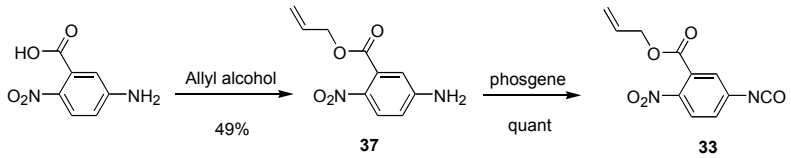

Figure 7. Chemical synthesis of compound **33**.

Compound 34

Toluene (3 mL) was heated to reflux (110 °C) and a solution of 20% phosgene in toluene (1.26 mL, 2.43 mmol) was added. Then, a solution of compound **37** (53.99 mg, 0.24 mmol) in 1 mL toluene was slowly added dropwise with an injector. The reaction was stirred for 30 minutes in reflux and was monitored by ^{1}H NMR (200MHz, $CDCl_3$). After the isocyanate derivative was observed, the solvent was removed under reduced pressure. A solution of compound **27** (53.5 mg, 81.27 µmol) in 2 mL THF, followed by the addition of 10 µL DBTL, was added to the isocyanate residue. The reaction mixture was allowed to warm to 45 °C and was stirred for 18 hours. The reaction was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was purified by using column

chromatography on silica gel (EtOAc:Hex 1:1) to give compound **34** (42.6 mg, 58%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.01 (1H, m); 7.65 (4H, m); 7.43-7.31 (18H, m); 7.03 (2H, m); 5.88-5.80 (1H, m); 5.30-5.12 (6H, m); 4.83 (2H, m); 4.70 (2H, s); 3.72 (2H, s); 1.08 (9H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 170.35, 163.71, 156.82, 153.08, 143.72, 139.21, 139.01, 138.47, 137.41, 137.27, 136.33, 136.14, 132.37, 131.46, 131.20, 130.72, 130.11, 129.50, 129.43, 128.70, 128.21, 127.62, 127.12, 126.43, 124.81, 122.12, 120.05, 118.50, 113.01, 69.41, 66.97, 66.80, 61.15, 48.02, 26.10, 19.87. MS (ESI): *m/z*: 907.2 $[M+H]^+$.

Compound 35

Compound **34** (41.4 mg, 45.6 μmol) was dissolved in THF (1 mL), and TBAF (59.3 μL, 1M in THF) was added. The reaction was stirred in room temperature for 1 hour and was monitored by TLC (EtOAc:Hex 2:1). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 2:1) to give compound **35** (23.7 mg, 78%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.01 (1H, m); 7.48-7.28 (12H, m); 7.04 (2H, m); 5.88-5.82 (1H, m); 5.31-5.12 (6H, m); 4.89 (2H, m); 4.72 (2H, s); 3.72 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 169.21, 163.98, 154.11, 153.12, 142.73, 139.72, 139.01, 138.42, 137.83, 137.57, 132.36, 131.31, 131.04, 130.39, 130.02, 129.67, 129.01, 128.52, 127.63, 126.13, 124.56, 122.10, 120.41, 118.37, 115.24, 69.40, 66.87, 66.25, 59.83, 48.12. MS (FAB): *m/z*: 691.1 $[M+Na]^+$.

Compound 36

Commercially available PNA isocyanate (5.79 mg, 35.2 μmol) was dissolved in THF (1.5 mL). Compound **35** (11.8 mg, 17.6 μmol) and DBTL (5 μL) were added. The reaction was allowed to warm to 45° C and was stirred for 18 hour. The reaction was monitored by TLC (EtOAc:Hex 2:1). The solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **36** (12.4 mg, 85%) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$): δ = 8.15 (2H, d, J=8Hz); 7.89-7.73 (3H, m); 7.56-7.52 (5H, m); 7.38-7.27 (5H, m); 7.22-7.00 (4H, m); 5.89-5.74 (1H, m); 5.32-5.12 (2H, m); 5.02 (6H, m); 4.89 (2H, m); 3.72 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 171.42, 164.12, 156.42, 153.70, 143.72, 143.12, 142.63, 139.46, 139.40, 138.19, 138.12, 138.02, 135.14, 133.30, 131.87, 131.62, 131.18, 131.02, 130.41, 128.31, 127.92, 127.62, 127.21, 125.21, 124.19, 121.40, 120.35, 118.52, 117.82, 115.21, 67.81, 66.91, 66.84, 63.47, 48.71. MS (ESI): *m/z*: 833.3 $[M+H]^+$.

Compound 5

Compound **36** (10 mg, 12 μmol) was dissolved in THF (1 mL). Then acetic acid (3.43 μL, 60 μmol), Bu_3SnH (19.36 μL, 72 μmol) and a catalytic amount of $Pd(PPh_3)_4$ were added. The reaction mixture was stirred for 15 minutes and was monitored by TLC (EtOAc:MeOH:AcOH 94:5:1). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by using column chromatography on silica gel (EtOAc:MeOH:AcOH 94:5:1) to give compound **5** (7.3 mg, 77%) as a white solid.

^{1}H NMR (400MHz, MeOD): δ = 8.12 (2H, d, J=8Hz); 7.92 (1H, d, J=10Hz); 7.71-7.52 (8H, m); 7.37-7.31 (8H, m); 5.24-5.21 (6H, m); 3.66 (2H, s). ^{13}C NMR

(100MHz, MeOD): δ = 171.69, 166.47, 155.20, 151.44, 142.28, 141.58, 140.98, 140.53, 139.41, 138.21, 138.09, 137.46, 136.43, 132.86, 132.57, 131.66, 130.40, 128.10, 127.69, 127.11, 126.80, 125.42, 121.12, 120.97, 118.71, 118.22, 117.04, 116.76, 67.40, 66.74, 63.81, 48.57. MS (ESI): *m/z*: 791.1 $[M-H]^-$.

Compound 37

Commercially available 5-amino-2-nitrobenzoic acid (500 mg, 2.74 mmol) was dissolved in ACN (5 mL) and the solution was cooled to 0 °C. Then allyl alcohol (0.29 mL, 4.39 mmol) was added followed by EDC (842 mg, 4.39 mmol) and pyridine (0.44 mL, 5.49 mmol). The reaction mixture was stirred in room temperature for 18 hours and was monitored by TLC (EtOAc:Hex 1:1). The solvent was removed under reduced pressure and the crude product was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel (EtOAc:Hex 1:1) to give compound **37** (298.3 mg, 49%) as a yellow oil.

^1H NMR (200MHz, $CDCl_3$): δ = 7.96 (1H, d, J=10Hz); 6.69-6.63 (2H, m); 6.02-5.93 (1H, m); 5.43-5.26 (2H, m); 4.81 (2H, d, J=8Hz); 4.46 (2H, bs). ^{13}C NMR (100MHz, $CDCl_3$): δ = 164.21, 151.77, 143.02, 131.26, 127.21, 125.12, 119.23, 114.24, 112.93, 66.94. MS (FAB): *m/z*: 245.1 $[M+Na]^+$.