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
N₂ atmosphere. Chemicals and solvents were either A.R. grade or purified by standard
techniques. Thin layer chromatography (TLC): silica gel plates Merck 60 F₂₅₄;
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. ¹H 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 CDCl₃, 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- Diisopropylethylamine, DMF- Dimethyl
formamide, DMSO- Dimethyl sulfoxide, EDC- N-(3-Dimethylaminopropyl)-N'-
ethylicarbodiimide hydrochloride, EtOAc- Ethylacetate, Et₃N- Triethylamine, Hex-
Hexane, **MeOH**- Methanol, **PNA**- *p*-Nitroaniline, **PNPCI**- *p*-Nitrophenol chloroformate, **Py**- Pyridine, **TBAF**- Tetrabutylammonium fluorid, **TBDPSCI**- *t*-Butyldiphenylsilyl chloride, **TBSCI**- *t*-Butyldimethylsilyl chloride, **THF**- Tetrahydrofuran, **TMSE**- Trimethylsilyl ethanol.

![Chemical synthesis of compound 2.](image1)

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

![Chemical synthesis of compound 11.](image2)

**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): \(\delta = 7.57\) (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\(_3\)): \(\delta = 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 \(\mu\)L 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\(_3\)): \(\delta = 7.98\) (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\(_3\)): \(\delta = 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$_4$Cl. 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\(_3\)): \(\delta = 7.95\) (1H, d, \(J=10\) Hz); 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\(_3\)): \(\delta = 164.36, 151.55, 142.21, 132.27, 127.14, 114.11, 112.91, 64.81, 20.03, -5.36\). 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.

\[ \text{1H NMR (200MHz, CDCl}_3\text{): } \delta = 7.43-7.29 (10\text{H, m}); 7.07-6.96 (3\text{H, m}); 5.13 (2\text{H, s}); 4.70 (2\text{H, s}); 3.74 (2\text{H, s}); 0.87 (9\text{H, s}); 0.04 (6\text{H, s}). \]

\[ \text{13C NMR (100MHz, CDCl}_3\text{): } \delta = 169.11, 156.32, 139.49, 138.14, 137.56, 137.02, 131.61, 131.23, 130.42, 129.65, 129.14, 126.91, 126.11, 122.43, 121.39, 119.51, 66.43, 59.84, 46.73, 27.92, 20.21, -3.26. \]

\[ \text{MS (FAB): m/z: 527.1 [M+Na]}. \]

**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.

\[ \text{1H NMR (200MHz, MeOD): } \delta = 7.59-7.55 (3\text{H, m}); 7.39-7.25 (9\text{H, m}); 7.14-7.07 (1\text{H, m}); 5.13 (2\text{H, s}); 4.61 (2\text{H, s}); 3.68 (2\text{H, s}). \]

\[ \text{13C NMR (100MHz, CDCl}_3\text{): } \delta = 169.10, 157.02, 139.76, 138.14, 137.50, 137.00, 131.61, 131.23, 130.13, 129.65, 128.57, 126.91, 125.72, 120.11, 119.41, 119.24, 66.80, 60.12, 46.70. \]

\[ \text{MS (FAB): m/z: 391.2 [M+H]}. \]
**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$_3$): $\delta = 7.98$-$7.97$ (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$_3$): $\delta = 169.14$, 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): $\delta = 7.94$ (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): $\delta = 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 0º C. Imidazole (7.39 g, 108.56 mmol) and TBSCI (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 NH4Cl 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.

1H NMR (200MHz, CDCl3): δ = 7.35-7.15 (4H, m); 4.74 (4H, s); 0.94 (18H, s); 0.1 (12H, s). 13C NMR (100MHz, CDCl3): 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 5º 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 -20º 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 0º C and was stirred for additional 30 minutes. After completion, the reaction was diluted with EtOAc and was washed with NaHCO3 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.
\[ ^1 \text{H NMR (200MHz, CDCl}_3\text{)}: \delta = 8.10 (1H, d, \text{J}=8\text{Hz}); 7.87 (1H, s); 7.37 (1H, d, \text{J}=8\text{Hz}); 5.11 (2H, s); 4.82 (2H, s); 0.94 (18H, s); 0.13 (12H, s). \]

\[ ^{13} \text{C NMR (100MHz, CDCl}_3\text{)}: \delta = 144.64, 141.23, 125.41, 122.30, 118.23, 64.97, 61.39, 25.93, 18.36, -5.29. \text{ MS (FAB): } m/z: 411.2 [\text{M}]^+. \]

**Compound 21**

Compound 20 (3.52 g, 8.56 mmol) 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.

\[ ^1 \text{H NMR (200MHz, CDCl}_3\text{)}: \delta = 7.02-6.99 (2H, m); 6.62 (1H, d, \text{J}=6\text{Hz}); 4.67 (2H, s); 4.61 (2H, s); 0.91 (18H, s); 0.06 (12H, s). \]

\[ ^{13} \text{C NMR (100MHz, CDCl}_3\text{)}: \delta = 144.93, 131.40, 128.51, 126.96, 121.31, 116.42, 64.02, 60.88, 27.79, 20.15, -3.26. \text{ MS (FAB): } m/z: 381.2 [\text{M}]^+. \]

**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): \(\delta = 7.12-7.05\) (2H, m); 6.76 (1H, d, J=8Hz); 4.51 (2H, s); 4.41 (2H, s). \(^{13}\)C NMR (100MHz, MeOD): \(\delta = 146.21, 139.29, 130.42, 126.92, 124.83, 116.11, 65.18, 62.05\). 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\(^\circ\) C. Imidazole (100.68 mg, 1.47 mmol) and TBDPSCl (382 \(\mu\)L, 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\(_3\)): \(\delta = 7.71-7.66\) (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\(_3\)): \(\delta = 146.11, 140.05, 134.61, 133.92, 128.51, 127.44, 125.12, 121.34, 115.67, 65.13, 59.11, 25.58, 18.38\). 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\(^\circ\) C. Imidazole (82.64 mg, 1.214 mmol) and TBSCI (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$_3$): $\delta = 7.68$-$7.63$ (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$_3$): $\delta = 144.12$, 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$_3$): $\delta = 7.66$-$7.61$ (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$_3$): $\delta = 170.96$, 156.20, 139.49, 138.00, 137.70, 137.21, 136.29, 135.30, 131.44, 131.19, 130.79, 129.65, 129.52,
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$_3$): $\delta$ = 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$_3$): $\delta$ = 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, 126.65, 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$_3$): $\delta = 8.15$ (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$_3$): $\delta = 171.14$, 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$_3$): $\delta = 8.15$ (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$_3$): $\delta = 171.01$, 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]$^+$. 

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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$_3$): $\delta$ = 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$_3$): $\delta$ = 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): $\delta$ = 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): $\delta$ = 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$_4$Cl. 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.
\[^1\text{H}\text{ NMR (200MHz, CDCl}_3\text{): } \delta = 7.71-7.66 \text{ (4H, m); 7.42-7.36 (6H, m); 7.27-7.19 (6H, m); 7.14 (1H, m); 6.83 (1H, m); 4.76 (2H, d, J=6Hz); 4.72 (2H, s); 1.09 (9H, s).}\]

\[^1\text{C} \text{ NMR (100MHz, CDCl}_3\text{): } \delta = 155.64, 152.12, 150.67, 136.00, 135.49, 133.40, 129.62, 129.51, 129.27, 127.63, 126.68, 125.48, 121.55, 120.48, 115.22, 64.48, 60.36, 26.77, 19.21. \text{MS (FAB): } m/z: 534.2 \text{ [M+Na]}^+.\]

**Compound 32**

Compound 31 (85 mg, 0.16 mmol) was dissolved in 3 mL toluene and DBTL was added (20 \(\mu\)L). 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.

\[^1\text{H} \text{ NMR (200MHz, CDCl}_3\text{): } \delta = 7.71-7.66 \text{ (4H, m); 7.46-7.34 (6H, m); 7.21 (1H, d, J=8Hz); 7.06 (1H, s); 6.79 (1H, d, J=8Hz); 5.31 (2H, s); 4.71 (2H, s); 1.10 (9H, s).}\]

\[^1\text{C} \text{ NMR (100MHz, CDCl}_3\text{): } \delta = 153.06, 144.82, 136.35, 135.46, 134.27, 133.27, 129.69, 127.65, 127.01, 126.45, 122.18, 68.69, 64.97, 26.76, 19.19. \text{MS (FAB): } m/z: 418.1 \text{ [M+H]}^+.\]
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$_3$): $\delta$ = 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$_3$): $\delta = 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$_3$): $\delta = 8.01$ (1H, m); 7.48-7.28 (12H, m); 7.04 (2H, m); 5.31-5.12 (6H, m); 4.89 (2H, m); 4.72 (2H, s); 3.72 (2H, s). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta = 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]$^+$.  

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**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$_3$SnH (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): $\delta =$ 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$_4$Cl. 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.

$^1$H NMR (200MHz, CDCl$_3$): $\delta =$ 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$_3$): $\delta =$ 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]$^+$. 