Published in "The Journal of Organic Chemistry 84(12): 7776–7785, 2019"
which should be cited to refer to this work.

Photochemical Amplifier Based on Self-Immolative Dendritic Spacers

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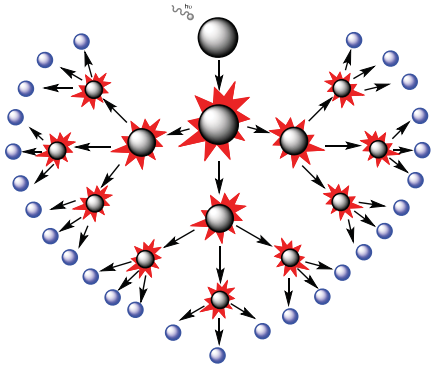
Supporting Information

ABSTRACT: A self-immolative dendritic structure was synthesized. It is based on phenol derivatives with three hydroxymethyl arms at both ortho and para positions of the core unit, potentially releasing up to 27 leaving groups in a third-generation dendrimer. The triggering event is the photolysis of a photosentive *ortho*-nitrobenzyl group. In doing so, we expected to transform a weak chemical or photochemical input into a large chemical output, which fulfills the definition of a molecular amplifier. Such dendrimers could find application as an indicator, a drug-delivery vector, or a solubilizing agent. The prepared dendrimer indeed released up to 27 leaving groups upon photolysis at 360 nm.



INTRODUCTION

Self-immolative spacers (linkers) are compounds capable of connecting two or more chemical entities together and be able to fragment upon triggering by a proper stimulus. This idea was introduced in 1981 for the first time,[1] and has since found multiple applications in sensors for chemicals or enzymes,[2,3] in prodrugs,[4] and for vector delivery.[5,6] Their inclusion in dendrimers offers powerful features, in particular, in the perspective of chemical amplification.[7] In order to be able to assemble different dendritic structures based on self-immolative spacers, the triggering function needs to be protected; its deprotection then initiates the fragmentation cascade. Various protecting groups have been used in the past for this purpose, such as an allyl group (cleaved by Pd^0/BH_4^-),[8,9] an *o*-nitrobenzyl group ($h\nu$),[10,11] a *p*-aminobenzyl group (Zn^0/AcOH),[12] a *t*-BOC group [(1) trifluoroacetyl (TFA); (2) tetraethylammonium], an aldol group (catalytic antibody 38C2, via a retro-aldol/retro-Michael reaction),[13] a phenylacetamide group (penicillin G amidase),[14] or a phenylboronic acid (H_2O_2).[15] In most of the cases, phenyl-type derivatives are used as a core, such as phenol, anilin or thiol, thanks to their capacity to eliminate leaving groups located at benzylic methylene groups in the ortho or para positions (Figure 1).[14,16−49]

In 2003, Shabat et al. reported the synthesis of self-immolative second and third-generation dendrimers based on carbamate linkages capable of releasing four (respectively eight) molecules (Figure 2) via a three-step process: (a) activation (b) cyclization and (c) elimination.[10] In 2004, McGrath and Szalai reported the synthesis of self-immolative dendrimers with benzyl ether linkages capable of releasing two (respectively four) (Figure 3) nitrophenol groups.[11]

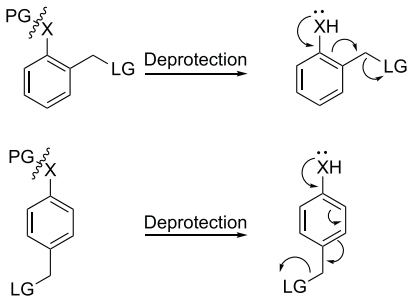


Figure 1. Self-immolative spacers based on lone pair activation (ortho or para). PG = protecting group; X = O, NH, or S; LG = leaving group.

These are only selected examples, but many other systems were developed because of these pioneering studies. In this work, in order to expand the existing arsenal of structures, we synthesized new dendritic structures capable of releasing more units, a prerequisite for a chemical amplifier. Our goal was to synthesize self-immolative dendritic structures based on phenol derivatives with three (instead of two) hydroxymethyl arms at both ortho and the para positions of the core unit (thus potentially releasing up to 27 leaving groups in a third-generation dendrimer instead of 8; Figure 4). In doing so, we expected to transform a weak chemical or photochemical input into a large chemical output in a similar approach as McGrath et al. Such dendrimers could find application as an indicator, a drug-delivery vector, or a solubilizing agent.

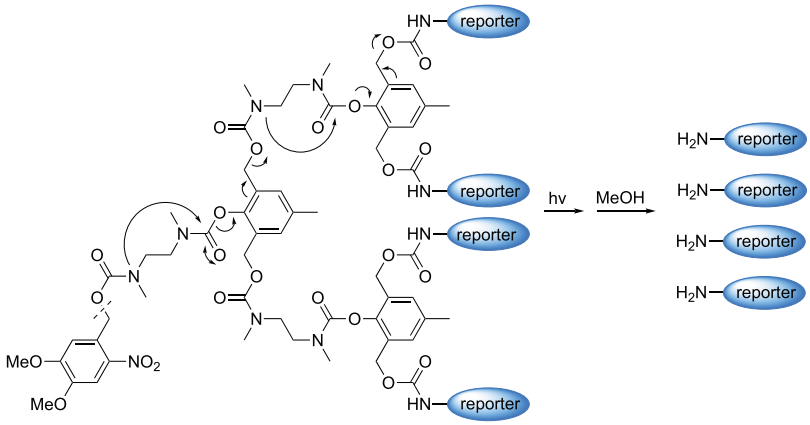


Figure 2. Second-generation self-immolative dendron releases four reporters after a UV light trigger.

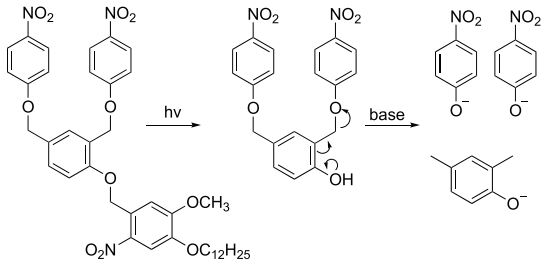


Figure 3. Activation of first-generation dendrimer releases two molecules of *p*-nitrophenol.

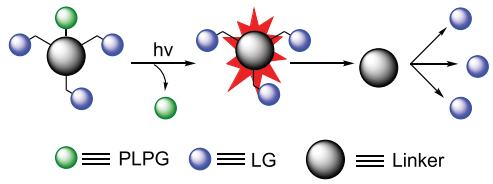


Figure 4. First generation: action mechanism.

Our dendritic structures are composed of three main components: (a) a photo labile protecting group: the well-established *ortho*-nitrobenzyl group, (b) a spacer/linker: phenol, which connects three entities and be able to fragment upon unmasking the phenolic position and (c) a leaving group: a nitrophenol moiety, turning yellow in basic medium, as a release indicator.

In order to better designate the dendrimers, we chose the following formalism: **1G**, **2G**, and **3G** which stands for first, second, and third generation, followed by the number and the acronym for the leaving groups. An example is shown in Figure 5:

1G3PNP—first generation, three *para*-nitrophenols.

2G9PNP—second generation, nine *para*-nitrophenols,

3G27PNP—third generation twenty-seven *para*-nitrophenol.

RESULTS AND DISCUSSION

Synthesis. We started the synthesis of the first-generation dendrimer with the inexpensive and commercially available phenol (Scheme 1), which was functionalized at both ortho and para positions using a known method to get the phenoxide **4**.[50] It was then chemoselectively protected by a photolabile-protecting group (*ortho*-nitrobenzyl bromide), and the hydroxymethyl groups were converted into the corresponding bromides using phosphorous tribromide. We obtained the first-generation precursor **6** (**1G3Br**) in 46% overall yield from phenol. As an example of the releasable group, we chose *para*-nitrophenol, which was introduced in basic medium in a 81% yield.

In order to synthesize a second-generation core, we first let compounds **4** and **6** (**1G3Br**) react together, which were previously synthesized for the first-generation dendrimer. The formation of **2G9OH** was confirmed by mass spectrometry and NMR analysis, but solubility issues prevented its satisfactory purification. We thus decided to protect the hydroxybenzyl group of **7** with TBS-Cl to obtain silyl ether **8**, which was then further hydroxymethylated (Scheme 2).[50] Silylation of the remaining hydroxybenzyl groups was followed by reaction with tribromide **6**, leading to the silylated second-generation core **2G9OTBS**. After desilylation in acidic

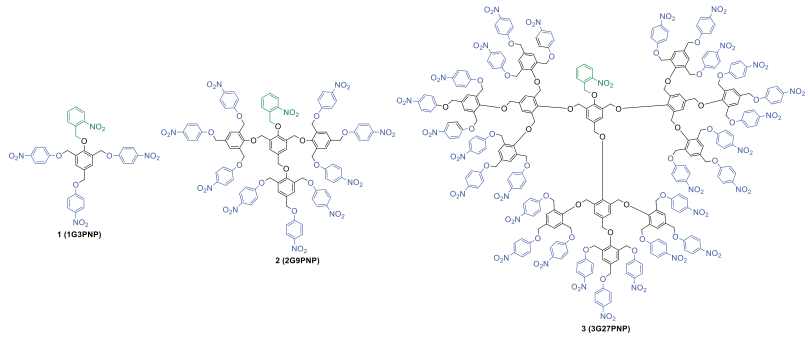
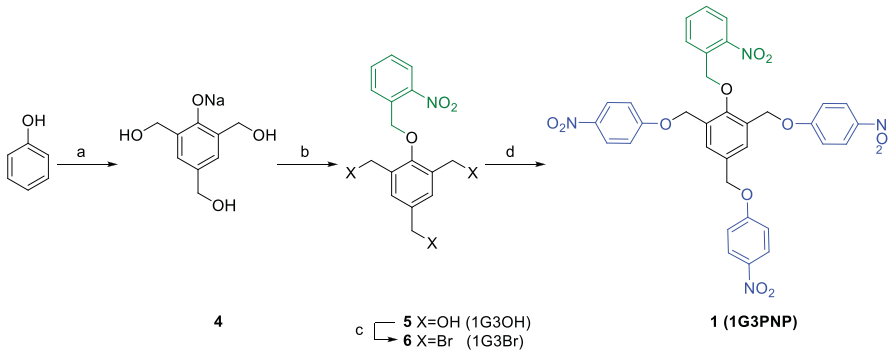


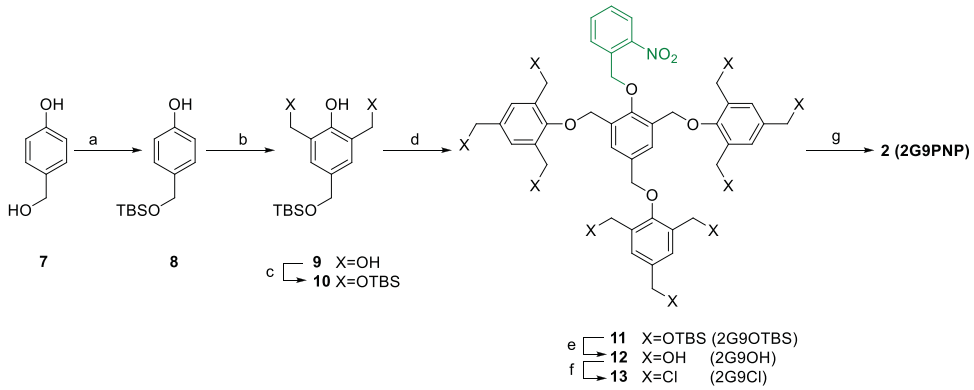
Figure 5. Targeted compounds.

Scheme 1. First-Generation Assembly (1G3PNP)[a]



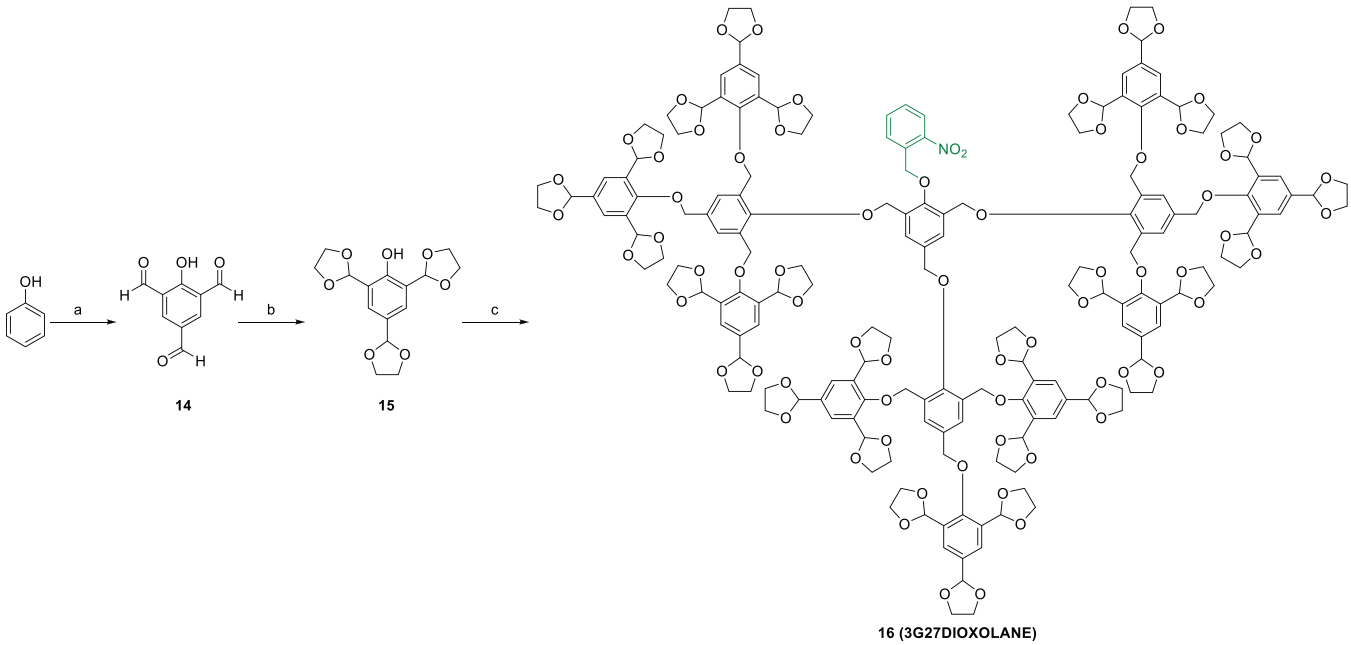
[a]Reagents and conditions: (a) formaldehyde, NaOH, H_2O, 2d, 86%. (b) *o*-Nitrobenzyl bromide, DMF, rt, 3 h, 68%. (c), PBr_3, ether, 0 °C → rt, o.n., 93%. (d) *p*-Nitrophenol, K_2CO_3, Me_2CO, reflux, 5 h, 81%.

Scheme 2. Second-Generation Assembly (2G9PNP)[a]



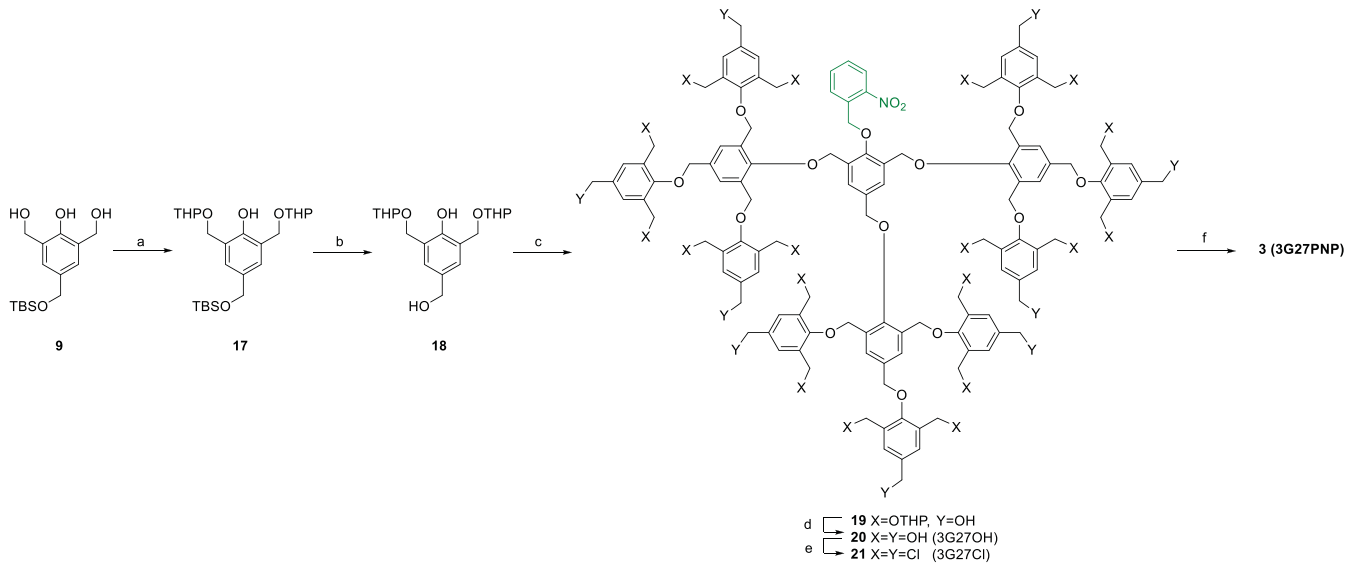
[a]Reagents and conditions: (a) TBS-Cl, imidazole, DMF, 0 °C → rt, 2 h, 89%. (b) Formaldehyde, NaOH, H_2O, 50 °C, 3 h, 42%. (c) TBS-Cl, imidazole, DMF, 0 °C → rt, o.n., 67%. (d) **6**, K_2CO_3, rt to 50 °C, 24 h, 54%. (e) TMS-Cl, MeOH, rt, o.n., 90%, (f) $SOCl_2$, DCM/DMF (10/1), reflux, o.n., 84%. (g) *p*-Nitrophenol, K_2CO_3, KI, Me_2CO, reflux, o.n., 78%.

Scheme 3. First Attempt for a Third Generation[a]



[a]Reagents and condition: (a) TFA, hexamethylenetetramine, 20 h, 125 °C, 3 h, 150 °C, 0.5 h, 100 °C, 65%. (b) PPTS, ethylene glycol, benzene, reflux, 24 h, 75%. (c) **13**, KI, Me_2CO, 55 °C, 23 h, 58%.

Scheme 4. Third-Generation Assembly (3G27PNP)[a]



[a]Reagents and conditions: (a) DHP, PPTS, DCM, rt, o.n., 94%. (b) TBAF, THF, rt, o.n., 84%. (c) **13**, K_2CO_3, KI, acetone, rt → 55 °C, 23 h, 37%. (d) TMS-Cl, MeOH, rt, o.n., 78%. (e) $SOCl_2$, DCM/DMF (10/1), reflux, 4.5 h, 58%. (f) *p*-Nitrophenol, K_2CO_3, KI, Me_2CO, 55 °C, 48 h, 86%.

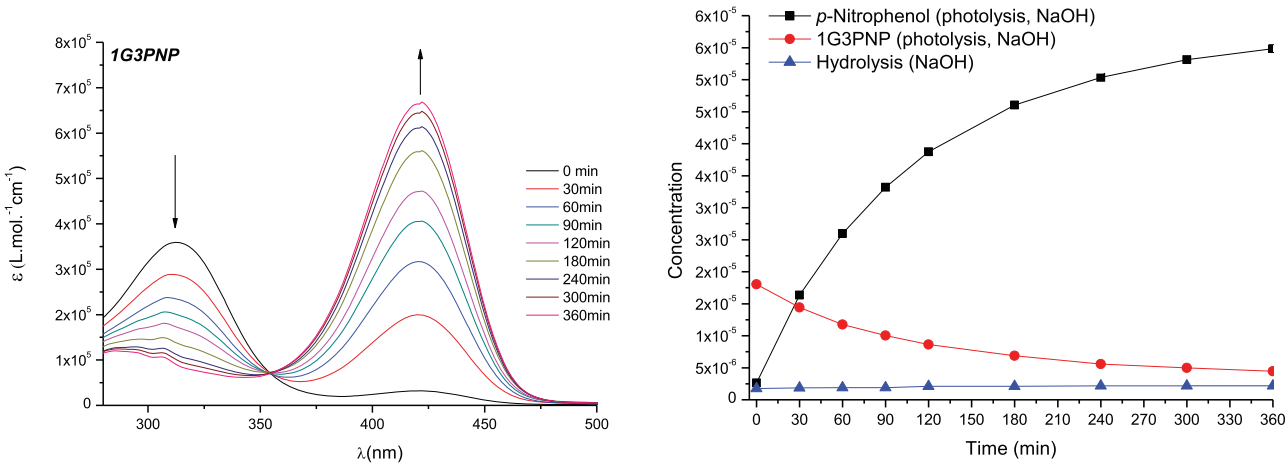


Figure 6. Activation and cascade release of the *p*-nitrophenoxide from **1G3PNP** (1.8×10^{-5} M), as a function of irradiation time at 360 nm in NaOH 1.9×10^{-3} M in DMF/H_2O (9:1 v/v).

medium (TMSCl in methanol),[51] **2G9OH** was isolated in high purity. Like above, we chose to decorate the dendrimer termini with a *p*-nitrophenol group in order to facilitate later release kinetic analysis. This was achieved by a potassium iodide-assisted substitution in refluxing acetone, and **2** was obtained in a 78% yield. Alternatively, we also obtained **2G9OH** by coupling **17** with **6**, followed by the same acidic hydrolysis in a slightly improved overall yield.

We then first attempted to access a third-generation dendrimer from trialdehyde **14**, which was prepared by formylation of phenol (Scheme 3). Its reaction with chloride **13** failed, probably because of the presence of three electron-withdrawing groups; we thus masked the aldehydes as dioxolanes (**15**). Its reaction with nonachloride **13** smoothly led to dendrimer **16** (**3G27dioxolane**) in a decent yield and high purity. However, later deprotection of the ketals proved very sluggish in all the conditions we tested. We thus turned to a slightly modified route.

Our first attempt to have more labile-protecting groups involved the triply silylated intermediate **10**, but the reaction with the nonachloride **13** was incomplete, most probably because of the severe steric hindrance of the reagent. On the other hand, protection as a tetrahydropyranyl derivative proved successful, and **9** was converted into **21** in five steps (Scheme 4). Final substitution of the 27 chlorides of **21** with a *p*-nitrophenyl group led to dendrimer **3** (**3G27PNP**).

Properties. All three dendrimers were also characterized by DOSY-NMR, with approximate radii for **1**, **2**, and **3** of 6.14, 11.49, and 18.34 Å, respectively.

We monitored the disassembly of the dendritic structures by UV−vis spectroscopy. All measurements were performed under basic medium in order to shift the absorbance of the *p*-nitrophenol (315 nm) as a *p*-nitrophenoxide (422 nm). Thus, a solution of sodium hydroxide was added in a concentration so as to deprotonate all possible phenol derivatives generated during the photolysis. However, under these conditions, spontaneous hydrolysis was observed for the

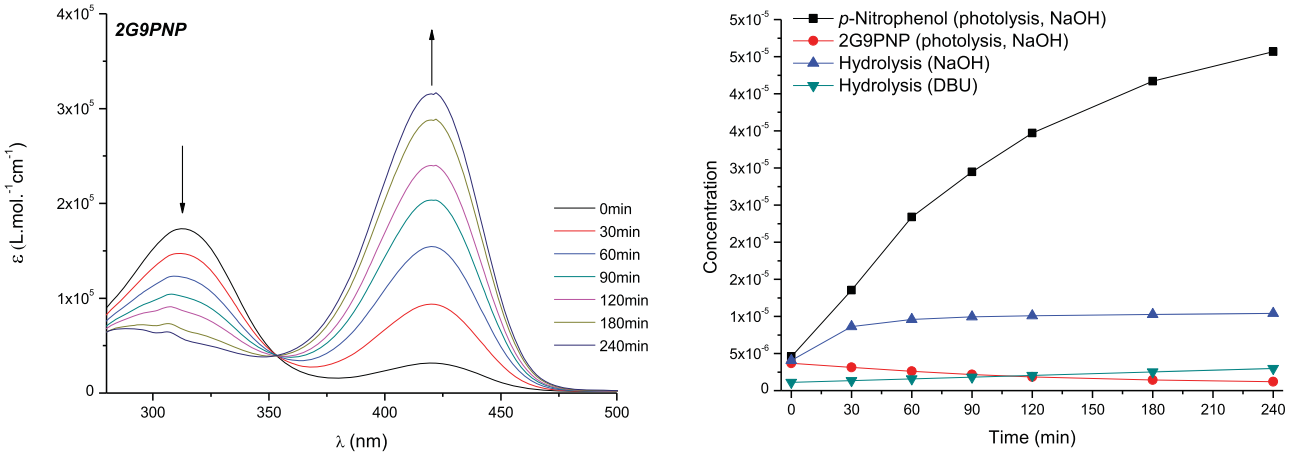


Figure 7. Activation and cascade release of the *p*-nitrophenoxide from **2G9PNP** (3.7×10^{-6} M), as a function of irradiation time at 360 nm in NaOH 3×10^{-3} M in DMF/H_2O (9:1 v/v).

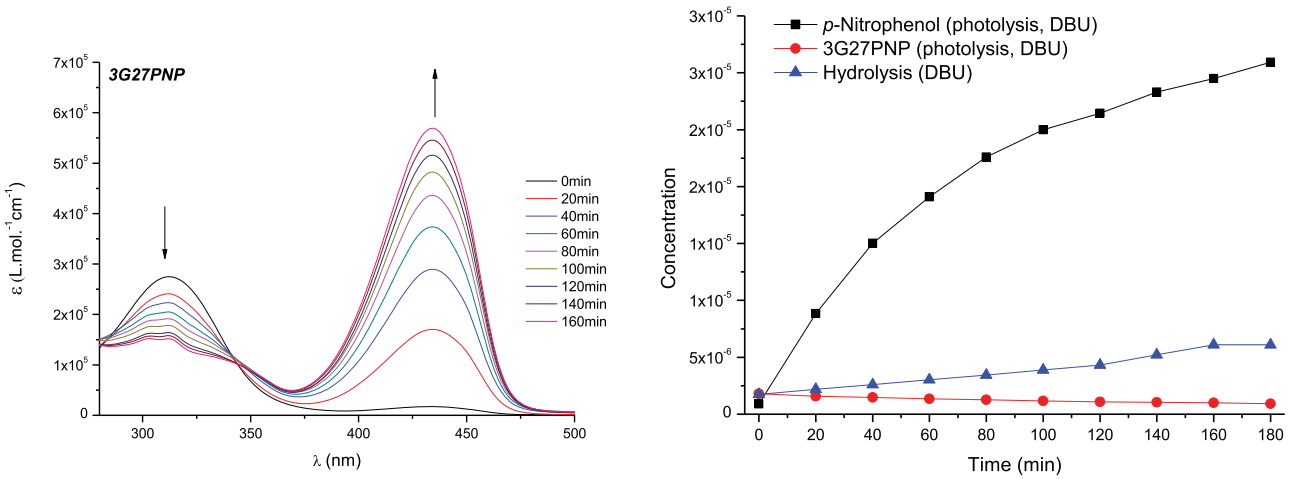


Figure 8. Activation and cascade release of the *p*-nitrophenoxide from **3G27PNP** (1.6×10^{-6} M), as a function of irradiation time at 360 nm in DBU 4×10^{-3} M in DMF/H_2O (9:1 v/v).

second- and third-generation dendrimers (12% of *p*-nitrophenol was detected after 160 min of reaction time of **3** in the same conditions but without irradiation). In neutral medium, no hydrolysis was detected. Attempts to use any weaker base, like potassium carbonate or trisodium phosphate failed, presumably because of solubility issue. The use of a nonnucleophilic base (DBU) did not completely prevent hydrolysis, but it was slower than that with sodium hydroxide. The latter base was preferable for studying the third-generation dendrimer, as its faster dissolution allowed a faster measurement. The extinction coefficient of the *p*-nitrophenoxide was always measured right before testing the disassembly of our dendritic structures using the same solvent, which allowed us to quantify the amount of the nitrophenol liberated during photolysis.

First Generation. A solution of known concentration of **1G3PNP** placed in a quartz cuvette was irradiated with a 360 nm light. After each irradiation, the UV–vis absorbance was measured until no change was observed. Knowing the extinction coefficient of *p*-nitrophenoxide alone, we could estimate the amount of *p*-nitrophenol released as about 98% (Figure 6) in 360 min. In basic medium, the chemical release of *p*-nitrophenol is faster than the photon flux, thus, the kinetics reflects the photon absorption (zero order at low conversion, then undefined, as many absorbing species coexist).

Second Generation. By using the same procedure as mentioned above, we observed a slightly lower efficiency, about 86% (Figure 7), in 240 min.

Third Generation. The photolysis of the third generation was less straightforward than the lower homolog, as spontaneous hydrolysis made the measurement complex. Using sodium hydroxide, we estimated the release at around 60%, while using DBU, the hydrolysis is a bit slower and the release of the nitrophenol amounted to 75% (Figure 8) in 160 min.

CONCLUSIONS

In conclusion, we have successfully synthesized first-, second-, and third-generation of a dendrimer capable of releasing up to twenty-seven end groups, which is the highest number to date. Their capability of releasing three, nine, and twenty-seven nitrophenol moieties, respectively, were demonstrated with an efficiency of 75–98%.

EXPERIMENTAL PART

Unless otherwise indicated, all reagents were obtained from commercial suppliers (Fluka, Aldrich, Acros, TCI, Roth) and were

used without further purification. Deuterated solvents were obtained from Cambridge Isotope Laboratory. Analytical thin-layer chromatography was performed on Kieselgel F-254 precoated aluminum sheet TLC plates from Merck. Visualization was performed with a 254 nm UV lamp and/or a $KMnO_4$ solution. Flash column chromatography was carried out using Brunschwig silica gel (SiO_2, 60 Å, 32−63 mesh) or reverse-phase silica gel (C18, 30 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-DRX-300 spectrometers. All NMR spectra were recorded in $CDCl_3$, CD_3CN, Acetone-d_6, MeOD, D_2O, and DMSO-d_6. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Coupling constant (J) is reported in Hz. Splitting patterns are designated as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), bs (broad singlet), and m (multiplet). Mass spectra were recorded on Matrix-assisted laser desorption and ionization MALDI (Bruker UltrafleXtreme MALDI-TOF), and electrospray ionization (ESI-ITMS) mass spectra Bruker-Ion Trap MS esquire HCT mass spectrometer. A Bruker Tensor 27 spectrometer equipped with a golden gate was used to record infrared spectra. Melting points were measured by using Doric-Trendicator 400A Type K/°C.

Sodium 2,4,6-Tris(hydroxymethyl)phenolate (4). It was prepared according to a literature procedure,[50] using 5.25 g (55.9 mmol) of phenol. **4** (9.945 g) was obtained (48.2 mmol, 86%).

1G3OH (5). A solution of sodium 2,4,6-tris(hydroxymethyl)-phenolate **4** (0.54 g, 2.65 mmol) and 2-nitrobenzyl bromide (0.44 g, 2.04 mmol) in dimethylformamide (DMF) (5.10 mL) was stirred at room temperature for 3 h. The reaction mixture was quenched with water and extracted four times with ethyl acetate, washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated until the desired compound started to precipitate and then was poured into a beaker containing ether. The white precipitate formed was filtered after 20 min to give **5** (**1G3OH**) (0.444 g, 1.390 mmol, 68%) as a white solid. ^{1}H NMR (300 MHz, CD_3CN): δ 8.11 (ddd, J = 1.05, 8.05, 11.35 Hz, 2H), 7.82 (td, J = 1.28, 7.61 Hz, 1H), 7.55−7.63 (m, 1H), 7.36 (s, 2H), 5.30 (s, 2H), 4.59 (s, 4H), 4.57 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ 154.1, 148.1, 139.5, 135.8, 135.2, 135.0, 129.8, 129.6, 127.9, 125.7, 73.6, 64.5, 62.4, 60.1. FT-IR (golden gate, 600−4000 cm^{-1}) 2923, 2851, 1611, 1590, 1520, 1336, 1207, 1005. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{16}H_{17}NO_6Na$, 342.0948; found, 342.0942. mp (122.0−122.8 °C).

1G3Br (6). Tribromophosphine (20.43 mL, 217 mmol) was added dropwise to a cooled (ice bath) solution of (2-((2-nitrobenzyl)oxy)-benzene-1,3,5-triyl)trimethanol **5** (11.57 g, 36.20 mmol) in ether (600 mL). The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with ether and slowly quenched with cold water. The phases were separated and extracted two more times with ether, washed with water and brine, and dried over magnesium sulfate. The crude product was purified by flash chromatography using pentane/ethyl acetate (9/1−7/3, v/v) to give the desired product (**1G3Br**) as a white to green-like solid (17.2 g, 33.9 mmol, 93%). ^{1}H NMR (400 MHz, CD_3CN): δ 8.17 (ddd, J = 1.04, 3.73, 8.07 Hz, 2H), 7.86 (td, J = 1.22, 7.64 Hz, 1H), 7.60−7.66 (m, 1H), 7.55 (s, 2H), 5.52 (s, 2H), 4.58 (s, 4H), 4.57 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.0, 146.7, 135.3, 134.2, 133.4, 132.8, 132.7, 128.7, 128.3, 125.1, 72.7, 31.8, 29.7, 26.9. MALDI-TOF m/z: (M + Na$^+$) calcd for $C_{16}H_{14}Br_3NO_3Na$, 529.8396; found, 529.8397. FT-IR (golden gate, 600−4000 cm^{-1}) 1524, 1466, 1377, 1237, 1211, 988, 857. mp (97.9−98.6 °C).

1G3PNP (1). Following a similar procedure,[11] a mixture of 1,3,5-tris(bromomethyl)-2-((2-nitrobenzyl)oxy)benzene **6** (0.21 g, 0.42 mmol), p-nitrophenol (0.355 g, 2.55 mmol), and K_2CO_3 (1.05 g, 7.65 mmol) in acetone (10.63 mL) was refluxed for 5 h. The reaction mixture was quenched with water/methanol (1/1 v/v), the solid formed was filtered and washed with water and then with methanol to get the desired compound **2** (**1G3PNP**) as a green-like solid (0.235 g, 0.344 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14−8.27 (m, 6H), 8.03 (dd, J = 1.24, 8.21 Hz, 1H), 7.86 (d, J = 6.97 Hz, 1H), 7.65 (s, 2H), 7.56 (td, J = 1.28, 7.61 Hz, 1H), 7.37−7.46 (m, 1H), 7.01−7.09 (m, 2H), 6.92−7.01 (m, 4H), 5.45 (s, 2H), 5.20 (s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 163.2, 163.0, 155.9, 146.6, 141.9, 133.9, 132.9, 130.4, 130.1, 128.8, 128.0, 126.0, 125.0, 114.8, 114.5, 74.2, 69.7, 65.8, 31.9, 29.7. MALDI-TOF m/z: (M + Na$^+$) calcd for $C_{34}H_{26}N_4O_{12}Na$, 705.1439; found, 705.1446. FT-IR (golden gate, 600−4000 cm^{-1}) 1609, 1592, 1509, 1336, 1262, 1174, 1110, 1068, 1012, 844, 751, 731, 681, 665. mp (176−178 °C).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenol (8). It was prepared according to a literature procedure,[26] using 2.0 g (15.79 mmol) of 4-(hydroxymethyl)phenol. **8** (3.35 g) was obtained (14.05 mmol, 89%).

(5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-hydroxy-1,3-phenylene)dimethanol (9). A solution of sodium hydroxide (0.80 g, 20.22 mmol) in water (12.64 mL) was added to phenol **8** (3.01 g, 12.64 mmol), followed by formaldehyde (37 wt % in water) (3.76 mL, 50.6 mmol). The reaction mixture was stirred for 3 h at 50 °C, and then was quenched with NH_4Cl sol. and extracted four times with ethyl acetate, washed with water and brine, and dried over sodium sulfate. The crude product was purified by flash chromatography using pentane/ethyl acetate (8/2 v/v) to give the desired product **9** as a white solid with a yield of (1.58 g, 5.30 mmol, 42%). ^{1}H NMR (300 MHz, CD_3CN): δ 7.05 (s, 2H), 4.68 (s, 4H), 4.62 (s, 2H), 0.90−0.94 (m, 9H), 0.07−0.11 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ 153.9, 133.4, 127.6, 126.3, 65.7, 62.4, 26.4, 19.1, −4.9. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{15}H_{26}O_4SiNa$, 321.1492; found, 321.1490. FT-IR (golden gate, 600−4000 cm^{-1}) 3403, 3270, 2953, 2929, 2856, 1484, 1469, 1361, 1253, 1209, 1091, 1063, 833, 772, 678. mp (95.5−96.0 °C).

2,4,6-Tris(((*tert*-butyldimethylsilyl)oxy)methyl)phenol (10). It was prepared according to a literature procedure,[26] using 0.5 g of **9** (1.675 mmol). **10** (0.59 g) was obtained (1.12 mmol, 67%).

2G9OTBS (11). A solution of 1,3,5-tris(bromomethyl)-2-((2-nitrobenzyl)oxy)benzene **6** (0.65 g, 1.28 mmol)), phenol **10** (2.53 g, 4.80 mmol), and K_2CO_3 (2.65 g, 19.19 mmol), in MeCN (22.97 mL) was stirred at 50 °C for 24 h. The reaction mixture was quenched with water and extracted three times with ether washed with water and brine, and dried over magnesium sulfate. The crude product was purified by flash chromatography using pentane/ether (98/2 v/v) to give the desired product (**2G9TBS**) (0.340 g, 0.184 mmol, 54%) as a colorless gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (dd, J = 1.19, 8.25 Hz, 1H), 7.95 (d, J = 6.97 Hz, 1H), 7.80 (s, 2H), 7.67 (td, J = 1.24, 7.63 Hz, 1H), 7.42−7.51 (m, 1H), 7.40 (s, 2H), 7.34 (s, 4H), 5.28 (s, 2H), 4.98 (s, 4H), 4.94 (s, 2H), 4.85 (s, 4H), 4.75 (s, 2H), 4.71 (s, 12H), 0.96 (s, 9H), 0.93−0.95 (m, 19H), 0.90−0.92 (m, 18H), 0.85−0.88 (m, 36H), 0.12−0.14 (m, 6H), 0.09−0.12 (m, 13H), 0.06−0.08 (m, 12H), −0.02−0.01 (m, 24H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 152.9, 152.1, 145.9, 137.3, 134.9, 134.4, 134.0, 133.9, 133.8, 131.7, 128.1, 127.9, 127.5, 124.9, 124.9, 124.7, 75.4, 72.7, 70.7, 65.0, 64.9, 60.4, 60.3, 26.0, 26.0, 25.9, 18.4, 18.4, 18.3, −5.2, −5.3. MALDI-TOF m/z: (M + Na$^+$) calcd for $C_{97}H_{173}NO_{15}Si_9Na$, 1868.0654; found, 1868.0643. FT-IR (golden gate, 600−4000 cm^{-1}) 2953, 2983, 2856, 1530, 1471, 1360, 1253, 1107, 832, 773.

2G9OH (12). TMS-Cl (0.05 mL, 0.388 mmol) was added dropwise at rt to a solution of **11** (0.47 g, 0.25 mmol), in dry MeOH (5.18 mL). The reaction was stirred for 2 h. After completion, the desired product was precipitated as a pure compound by pouring the reaction mixture into a beaker containing ether. The solid was filtered off and washed with ether to afford the desired compound (**2G9OH**) as a white solid with a yield of (0.190 g, 0.232 mmol, 90%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.11−8.16 (m, 1H), 8.04 (d, J = 7.34 Hz, 1H), 7.73−7.81 (m, 3H), 7.56 (t, J = 7.66 Hz, 1H), 7.43 (s, 2H), 7.37 (s, 4H), 5.43 (s, 2H), 5.06 (s, 4H), 5.01 (s, 2H), 4.71 (s, 4H), 4.61 (s, 2H), 4.58 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 170.3, 153.2, 152.0, 151.9, 146.1, 137.9, 134.7, 134.6, 134.5, 134.4, 133.4, 131.3, 128.7, 127.9, 125.5, 125.4, 124.7, 75.0, 72.9, 70.4, 62.9, 62.9, 59.8, 58.1, 58.0, 20.8, 14.1. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{43}H_{47}NO_{15}Na$, 840.2837; found, 840.2832. FT-IR (golden gate, 600−4000 cm^{-1}) 3298, 2872, 1534, 1461, 1367, 1342, 1202, 1141, 1068, 1049, 1012, 975, 893, 862, 823. mp (207.2−209 °C).

2G9Cl (13). Thionyl chloride (1.08 mL, 14.67 mmol), was added dropwise at rt to a solution of alcohol **12** (0.40 g, 0.48 mmol), in dichloromethane (DCM)/DMF (10 mL (10/1 v/v) and the reaction was heated to reflux for 16 h. After completion, the reaction was quenched with saturated $NaHCO_3$ solution, and extracted three times with DCM washed with water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure until a small amount was left and then was poured into a beaker containing pentane. After cooling with an ice bath, the desired compound **3** (**2G9Cl**) precipitated as a white solid with a yield of (0.405 g, 0.412 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (dd, J = 1.10, 8.25 Hz, 1H), 8.15 (d, J = 7.79 Hz, 1H), 7.98 (s, 2H), 7.77 (td, J = 1.10, 7.61 Hz, 1H), 7.49−7.57 (m, 3H), 7.44 (s, 4H), 5.47 (s, 2H), 5.26 (s, 4H), 5.24 (br s, 2H), 4.73 (s, 4H), 4.60 (br s, 2H), 4.59 (s, 8H), 4.56 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.1, 155.1, 154.5, 145.9, 134.6, 134.5, 134.3, 134.0, 133.6, 132.1, 132.0, 132.0, 131.9, 131.0, 129.9, 128.3, 127.6, 124.9, 76.4, 73.6, 73.6, 72.0, 72.0, 45.0, 45.0, 40.6, 40.5. MALDI-TOF m/z: (M + Na) calcd for $C_{43}H_{38}C_{l9}NO_6Na$, 1005.9729; found, 1005.9749. FT-IR (golden gate, 600−4000 cm^{-1}) 1528, 1475, 1367, 1342, 1265, 1211, 1131, 992, 968, 888, 789, 727, 678. mp (99−102 °C).

2G9PNP (2). A solution of **13** (84 mg, 0.06 mmol), *p*-nitrophenol (127 mg, 0.910 mmol), potassium iodide (10.20 mg, 0.06 mmol), and K_2CO_3 (377 mg, 2.73 mmol) in acetone (5 mL), was stirred under reflux overnight. The reaction mixture was diluted with acetone and filtered, the filtrate was concentrated until a small amount of the solvent was left and poured into a beaker containing water/methanol (1/1 v/v). The solid formed was filtered and washed with methanol to get the desired compound **2** (**2G9PNP**) as a light green solid (91 mg, 0.048 mmol, 78%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.15−8.24 (m, 6H), 7.97−8.12 (m, 13H), 7.85 (dd, J = 0.79, 7.76 Hz, 1H), 7.78 (s, 2H), 7.68−7.73 (m, 1H), 7.67 (s, 4H), 7.52 (s, 3H), 7.12−7.26 (m, 10H), 7.03 (d, J = 9.29 Hz, 1H), 6.92−7.00 (m, 7H), 5.35 (s, 2H), 5.29 (s, 4H), 5.27 (s, 4H), 5.24 (s, 2H), 5.12 (s, 8H), 5.09 (s, 4H), 4.93 (s, 2H). ^{13}C{^{1}H} NMR (400 MHz, acetone-d_6): δ 164.8, 164.7, 164.6, 164.4, 157.2, 157.1, 154.8, 147.2, 142.7, 142.6, 142.6, 142.5, 135.3, 135.0, 134.4, 134.1, 134.0, 132.4, 131.9, 131.5, 131.1, 131.0, 130.5, 129.6, 128.5, 126.7, 126.7, 126.6, 126.6, 125.7, 116.1, 116.1, 115.8, 115.7, 77.9, 73.9, 73.3, 70.7, 70.7, 67.1, 66.9. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{97}H_{74}N_{10}O_{33}Na$, 1929.4311; found, 1929.4297. FT-IR (golden gate, 600−4000 cm^{-1}) 1589, 1508, 1495, 1331, 1247, 1172, 1109, 996, 863, 843, 751. mp (96−98 °C).

2-Hydroxy-1,3,5-benzenetricarbaldehyde (14). This procedure was adapted from a similar transformation.[52] Trifluoroacetic acid (57.2 mL) was added slowly while cooling (ice bath) to a solid mixture of phenol (5.00 g, 53.10 mmol), and hexamethylenetetramine (16.39 g, 117.00 mmol. Caution: exothermic reaction). The reaction mixture was heated to 125 °C for 20 h, at which point the temperature was raised to 150 °C and stirred for another 3 h. After cooling to 100 °C, the reaction mixture was treated with 50 mL 3N HCl and stirred for another 30 min. The reaction mixture was allowed to cool overnight to room temperature. The brown solid formed was filtered off and washed with water and dried under high vacuum to give the desired compound **14** as a brown solid with a yield of (6.20 g, 34.8 mmol, 65%). ^{1}H NMR (300 MHz, acetone-d_6): δ 10.38 (s, 2H), 10.08 (s, 1H), 8.63 (s, 2H).

2,4,6-Tri(1,3-dioxolan-2-yl)phenol (15). A solution of PPTS (1.00 g, 3.99 mmol), 2-hydroxybenzene-1,3,5-tricarbaldehyde **14** (1.00 g, 5.61 mmol), and ethylene glycol (3.78 mL, 67.4 mmol) in benzene (112 mL) was refluxed for 24 h with a Dean−Stark apparatus. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted two times with benzene washed with water and brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave the desired compound **15** as a yellow solid (1.30 g, 4.21 mmol, 75%) which was launched in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.50 (s, 2H), 6.07 (s, 2H), 5.75 (s, 1H), 3.95−4.18 (m, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.5, 129.1, 126.7, 123.2, 103.3, 101.6, 65.1, 64.9. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{15}H_{18}O_7Na$, 333.0944; found, 333.0937. FT-IR (golden gate, 600−4000 cm^{-1}) 32867, 2971, 2877, 1632, 1477, 1462, 1401, 1362, 1266, 1247, 1223, 1164, 1106, 1082, 1006, 949, 882. mp (81−84 °C).

3G27DIOXOLANE (16). A solution of 2,4,6-tri(1,3-dioxolan-2-yl)phenol **15** (0.189 g, 0.610 mmol), **13** (**2G9Cl**) (0.04 g, 0.041 mmol), K_2CO_3 (0.169 g, 1.220 mmol), and potassium iodide (0.061 g, 0.366 mmol) in acetone (4.07 mL) was stirred at 55 °C overnight. The reaction mixture was quenched with water and extracted four times with ethyl acetate washed with water and brine, and dried over magnesium sulfate. The crude product was purified by flash chromatography using ethyl acetate/acetone (EtOAc 100% then 30% acetone) to give the desired product **16** (**3G27dioxolane**) as a white solid (0.081 g, 0.023 mmol, 58%). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.96 (s, 2H), 7.94 (s, 2H), 7.82 (s, 5H), 7.76 (s, 2H), 7.72 (s, 4H), 7.68 (s, 5H), 7.64 (s, 9H), 7.12−7.21 (m, 1H), 7.03−7.12 (m, 1H), 6.21 (s, 2H), 6.14 (s, 4H), 6.10 (s, 4H), 5.95 (s, 8H), 5.77 (s, 1H), 5.75 (s, 2H), 5.72 (s, 4H), 5.69 (s, 2H), 5.32 (s, 4H), 5.24 (br s, 6H), 5.15−5.21 (m, 10H), 5.13 (s, 6H), 3.63−4.24 (m, 108H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6): δ 171.0, 158.1, 158.0, 157.9, 155.3, 155.2, 154.7, 146.7, 135.6, 135.5, 135.4, 134.8, 134.7, 134.6, 134.3, 132.9, 132.9, 132.9, 132.8, 132.4, 132.3, 130.2, 130.0, 129.4, 129.0, 128.4, 127.9, 127.8, 127.8, 127.7, 125.3, 104.0, 103.9, 103.9, 103.8, 99.8, 99.7, 99.6, 79.2, 79.1, 76.9, 74.4, 74.3, 74.0, 72.7, 66.2, 66.1, 66.0, 66.0, 66.0, 60.6, 20.9, 14.6. MALDI-TOF m/z: (M + Na$^+$) calcd for $C_{178}H_{191}NO_{69}Na$, 3470.1393; found, 3471.1424. MALDI-TOF m/z: (M + Ag$^+$) calcd for $C_{178}H_{191}NO_{69}Ag$, 3554.0547; found, 3556.05. FT-IR (golden gate, 400−4000 cm^{-1}) 2955, 2887, 1733, 1615, 1526, 1473, 1361, 1232, 1113, 1007, 967, 943, 890, 730, 661. mp (119.8−122.2 °C).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,6-bis(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (17). Pyridin-1-ium 4-methylbenzenesulfonate (0.044 g, 0.176 mmol) was added to a cooled (ice bath) solution of (5-(((*tert*-butyldimethylsilyl)oxy)-methyl)-2-hydroxy-1,3-phenylene)dimethanol **9** (1.052 g, 3.52 mmol), and 3,4-dihydro-2*H*-pyran (0.696 mL, 7.40 mmol) in DCM (22 mL) and stirred under the same condition (ice bath) for 10 min. The ice bath was removed and stirring at rt was continued for 22 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted three times with DCM washed with water and brine, and dried over sodium sulfate. Purification by flash chromatography using pentane/ethyl acetate (8.5/1.5 v/v) gave the desired compound as a colorless liquid (1.56 g, 3.31 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.16 (s, 2H), 4.90 (d, J = 2.93 Hz, 1H), 4.86 (d, J = 2.93 Hz, 1H), 4.75 (dt, J = 2.41, 4.46 Hz, 2H), 4.67 (d, J = 1.83 Hz, 1H), 4.65 (s, 2H), 4.64 (d, J = 1.83 Hz, 1H), 3.96 (ddd, J = 3.12, 7.55, 11.10 Hz, 2H), 3.54−3.63 (m, 2H), 1.72−1.98 (m, 4H), 1.48−1.71 (m, 10H), 0.93−0.95 (m, 9H), 0.05−0.16 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 152.95, 132.42, 126.97, 123.78, 98.27, 98.23, 65.95, 64.70, 62.71, 60.37, 30.52, 25.99, 25.31, 21.03, 19.56, 18.44, 14.19, −5.18. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{25}H_{42}O_6SiNa$, 489.2642; found, 489.2615. FT-IR (golden gate, 400−4000 cm^{-1}) 3394, 2937, 2855, 1740, 1612, 1463, 1360, 1253, 1201, 1121, 1074, 1023, 901, 835, 775, 667.

4-(Hydroxymethyl)-2,6-bis(((tetrahydro-2*H*-pyran-2-yl)oxy)-methyl)phenol (18). TBAF (33.5 mL, 33.5 mmol) was added to a cooled (ice bath) solution of **17** (4.428 g, 22.34 mmol). The ice bath was removed and the temperature was allowed to raise to rt and stirring was continued for 18.5 h. After completion, the reaction mixture was quenched with water and extracted three times with ethyl acetate washed with water and brine, and dried over sodium sulfate. The crude product was purified by flash chromatography using pentane/ethyl acetate (7/3 v/v) to give the desired compound **18** as a slightly yellow gel (6.62 g, 18.78 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.22 (s, 2H), 4.91 (d, J = 3.12 Hz, 1H), 4.87 (d, J = 3.12 Hz, 1H), 4.70−4.80 (m, 2H), 4.66 (d, J = 2.02 Hz, 1H), 4.62 (d, J = 2.11 Hz, 1H), 4.60 (br s, 2H), 3.88−4.04 (m, 2H), 3.51−3.66 (m, 2H), 1.71−2.01 (m, 4H), 1.45−1.71 (m, 8H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.6, 132.0, 128.2, 124.2, 98.5, 98.4, 65.8, 65.1, 62.8, 30.5, 25.3, 19.6. HRMS (ESI-ITMS) m/z: (M + Na$^+$) calcd for $C_{19}H_{28}O_6Na$, 375.1778; found, 375.1771. FT-IR (golden

gate, 400−4000 cm^{-1}) 3389, 2941, 2869, 1737, 1612, 1485, 1455, 1373, 1350, 1260, 1227, 1201, 1118, 1073, 1020, 900, 869, 812.

3G18OTHP9OH (19). A solution of **13** (0.701 g, 0.712 mmol), **18** (3.76 g, 10.68 mmol), potassium iodide (1.06 g, 6.41 mmol), and potassium carbonate (3.94 g, 28.5 mmol) in acetone (23.74 mL) was heated to 55 °C for 23 h. The reaction was quenched with water and extracted three times with ethyl acetate washed with water and brine, and dried over sodium sulfate. The crude product was purified by flash chromatography using ethyl acetate/methanol (100% to 90/10 v/v) to give the desired compound with a yield of (1.00 g, 0.264 mmol, 37%), ^{1}H NMR (300 MHz, acetone-d_6): δ 7.11−8.06 (m, 30H), 4.12−5.46 (m, 106H), 3.56−3.97 (m, 18H), 3.19−3.55 (m, 18H), 1.23−1.93 (m, 110H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6): δ 155.7, 155.6, 155.3, 155.0, 154.9, 154.5, 154.1, 146.5, 139.2, 139.2, 139.1, 135.9, 135.3, 135.2, 135.1, 134.7, 132.7, 132.6, 132.6, 132.5, 132.4, 129.7, 129.4, 129.2, 128.8, 128.6, 128.0, 127.8, 125.4, 98.8, 98.6, 98.5, 77.3, 72.5, 72.3, 72.2, 64.9, 64.8, 64.7, 64.7, 64.6, 64.5, 64.4, 62.5, 62.4, 62.3, 31.5, 31.4, 31.3, 31.3, 26.4, 26.3, 26.3, 21.0, 20.2, 20.1, 20.1. MALDI-TOF m/z: (M + Na^+) calcd for $C_{214}H_{281}NO_{60}Na$, 3849.8927; found, 3849.89. FT-IR (golden gate, 400−4000 cm^{-1}) 3438, 2939, 2868, 1527, 1463, 1347, 1201, 1117, 1019, 902, 869, 813, 729.

3G27OH (20). To a solution of **19** (0.60 g, 0.12 mmol), in MeOH (20 mL) at room temperature was added TMS-Cl (0.08 mL, 0.0.619 mmol), and the reaction was stirred at room temperature overnight. After completion, the reaction mixture was concentrated under reduced pressure and then was precipitated by pouring into a beaker containing ether, the solid was filtered off and washed with ether to afford the desired compound (**3G27OH**) as a white solid (0.22 g, 0.096 mmol), with a yield of 78%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.01−7.94 (m, 30H), 4.74−5.31 (m, 52H), 4.26−4.73 (m, 54H) ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 153.6, 153.3, 152.0, 151.9, 151.8, 151.8, 145.4, 137.9, 137.8, 137.7, 134.7, 134.7, 134.5, 134.4, 133.9, 133.8, 133.8, 132.9, 131.3, 131.1, 130.8, 128.3, 128.0, 125.6, 125.4, 75.2, 75.0, 70.4, 70.2, 65.0, 62.9, 62.9, 58.2, 58.0, 15.2. MALDI-TOF m/z: (M + Na^+) calcd for $C_{124}H_{137}NO_{42}Na$, 2335.8541; found, 2335.8485. FT-IR (golden gate, 400−4000 cm^{-1}) 3312, 2934, 2880, 1525, 1459, 1361, 1298, 1200, 1142, 1066, 1020, 982, 885.

3G27Cl (21). Thionyl chloride (1.136 mL, 15.42 mmol) was added slowly at rt to a solution of **20** (0.223 g, 0.096 mmol) in DCM/DMF [22 mL, (10/1 v/v)], and refluxed for 4.5 h. The reaction was quenched with cold water and extracted three times with DCM washed with water and brine, dried over sodium sulfate. The crude product was purified by flash chromatography using pentane/ethyl acetate (1/1 v/v) to get the desired compound as white solid with a yield of (0.158 g, 0.056 mmol, 58%). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.35−8.14 (m, 30H), 4.98−5.48 (m, 26H), 4.45−4.97 (m, 54H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6): δ 156.2, 156.1, 156.1, 156.0, 154.6, 146.9, 136.0, 135.9, 135.8, 135.2, 135.0, 134.7, 134.6, 134.4, 133.4, 133.4, 133.3, 133.2, 133.1, 132.2, 132.1, 131.0, 130.8, 129.8, 129.2, 128.4, 125.5, 77.6, 77.4, 77.3, 74.0, 73.2, 73.1, 45.9, 41.8, 41.6, 41.6, 23.0, 14.4. MALDI-TOF m/z: (M + Na^+) calcd for $C_{124}H_{110}Cl_{27}NO_{15}Na$, 2832.9214; found, 2834.1. FT-IR (golden gate, 600−4000 cm^{-1}) 2925, 2856, 2361, 1733, 1610, 1525, 1467, 1370, 1265, 1211, 1133, 1040, 968, 905, 729, 677. mp (63−69 °C).

3G27PNP (3). A solution of **21** (**3G27Cl**) (0.1 g, 0.031 mmol), *p*-nitrophenol (0.495 g, 3.56 mmol), potassium iodide (0.159 g, 0.960 mmol), and K_2CO_3 (0.983 g, 7.11 mmol) in acetone (15 mL) was heated at 55 °C for 65 h. The reaction mixture was then diluted with acetone and filtered off. The filtrate was concentrated under vacuum until small amount of solvent was left, and then was poured into a beaker containing water where an immediate light green solid was formed which was then filtered off and washed with water and methanol to get the desired compound (**3G27PNP**) as a light green solid with a yield of (0.171 g, 0.032 mmol, 86%). ^{1}H NMR (400 MHz, acetone-d_6): δ 6.66−8.33 (m, 138H), 4.60−5.49 (m, 80H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 163.4, 163.4, 163.2, 163.1, 163.0, 162.7, 162.6, 155.4, 155.2, 154.9, 154.6, 153.0, 152.1, 141.0, 140.9, 140.9, 140.7, 140.6, 140.5, 133.7, 133.3, 132.6, 132.3, 131.0, 130.7, 130.5, 129.5, 129.2, 128.7, 127.5, 125.8, 125.6, 125.5, 125.2, 119.3, 115.3, 115.0, 114.9, 114.8, 114.3, 76.1, 71.5, 69.3, 65.5, 65.2. MALDI-TOF m/z: (M + Na^+) calcd for $C_{286}H_{218}N_{28}O_{96}Na$, 5605.3030; found, 5605.36. FT-IR (golden gate, 600−4000 cm^{-1}) 1591, 1510, 1496, 1399, 1371, 1340, 1298, 1252, 1173, 1111, 1006, 982, 832, 752, 703. mp (116−120 °C).

Disassembly Monitored by UV−Vis. A solution of **1** (**1G3PNP**) (1.8 × 10^{-5} M, 5.4 × 10^{-8} mol) in basic medium (DMF/NaOH sol. 1.9 × 10^{-3} M, 9/1 v/v) at rt was irradiated in a LUMOS 43A photoreactor equipped with light-emitting diode (LED) at 360 nm for a specific time and monitored by UV−vis. Up to 98% of the *p*-nitrophenoxide released was observed based on its absorbance at λ = 422 nm, after 360 min.

A solution of **2** (**2G9PNP**) (3.67 × 10^{-6} M, 1.10 × 10^{-8} mol) in basic medium (DMF/NaOH sol. 2.99 × 10^{-3} M, 9/1 v/v) at rt was irradiated in a LUMOS 43A photoreactor equipped with LED at 360 nm for a specific time and monitored by UV−vis. Up to 86% of the *p*-nitrophenoxide released was observed based on its absorbance at λ = 422 nm, after 240 min.

A solution (3 mL) of **3** (**3G27PNP**) (1.8 × 10^{-6} M, 5.4 × 10^{-9} mol) in (0.004 M) DBU in DMF at rt was irradiated in a LUMOS 43A photoreactor equipped with LED at 360 nm for a precise time and monitored by UV−vis. Up to 75% *p*-nitrophenoxide released was observed based on its absorbance at λ = 434 nm, after 160 min.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available.

Copies of spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The support of the Swiss National Science Foundation (grant 200020-165856) is gratefully acknowledged.

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