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Photochemical Cleavage of Benzylic C−O Bond Facilitated by an *Ortho* or *Meta* Amino Group

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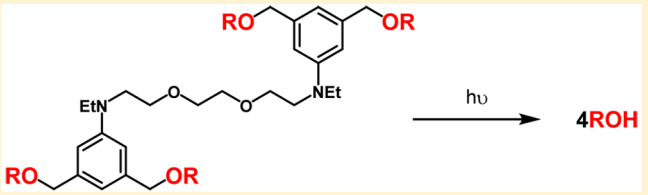
Supporting Information

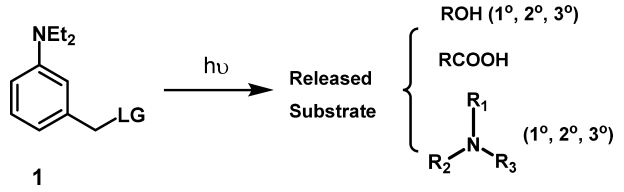
ABSTRACT: The excited state *meta* effect, also known as the *meta-ortho* effect, results from selective electron transmission from an electron-donating group to the *meta* and *ortho* sites on an aromatic ring in its first excited singlet state. This effect facilitates photochemical cleavage of benzylic C−O or C−N bond to release the corresponding alcohol, carboxylic acid, or amine when an electron-donating amino group is at the *meta* position, as demonstrated in our recent work of using a 3-diethylaminobenzyl (DEABn) group as an effective photolabile protecting group (PPG). Herein, we demonstrate that an *ortho* amino group can also facilitate benzylic C−O bond cleavage to release an alcohol or carboxylic acid. However, an amino group at the *meta* position results in a PPG with better overall chemical and photochemical properties.



INTRODUCTION

Photolabile protecting groups are valuable to a wide range of research areas owing to their chemical-reagent-free removal that can be achieved with high temporal and spatial precision. Their photochemistry and broad applications have been frequently reviewed.[1−8] Continuously increasing interests in PPG applications have attracted more efforts in developing new PPGs to complement the existing ones. Recently, our lab developed a number of structurally simple PPGs for protection of carbonyl, hydroxyl, diol, carboxyl, and amino functionalities.[8,9] These new PPGs are designed on the basis of the excited state *meta* effect, which is also known as the excited state *meta-ortho* effect. Zimmerman's MO computation revealed a selective transmission of electron density to the *meta* and *ortho* positions on an aromatic ring in the first excited singlet state.[10−13] As demonstrated in our PPGs, the *meta* effect facilitates photochemical cleavage of a benzylic C−O or C−N bond to release various functionalities. The particular *meta* amino group has been studied for its role in the *meta* effect[14−19] and has been utilized in PPG designs. Toscano et al. demonstrated release of diazeniumdiolates from 3-(dimethylamino)benzyl protection,[20] and Falvey et al. showed photochemical heterolysis of 3,5-bis(dimethylamino)benzyl ester to release carboxylic acids.[21] The most recent example is the 3-diethylaminobenzyl (DEABn) PPG, which can efficiently release hydroxyl, carboxyl, and amino functionalities (Scheme 1).[22−25] We notice that the DEABn PPG differs from the known 3,5-dimethoxy-benzyl (DMBn) PPG which was also based on the *meta* effect.[26] The latter is known for releasing only good leaving groups such as carboxylate, carbonate, and carbamate, while the DEABn PPG directly releases various alcohols and amines via effective cleavage of the benzylic C−O or C−N bond in the excited state (Scheme 1). We infer that similar benzylic bond cleavage can be facilitated by an *ortho* amino group, leading to new PPGs.

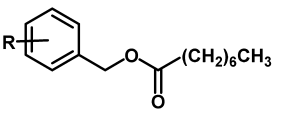
Scheme 1. DEABn PPG for Protection of Different Functionalities



RESULTS AND DISCUSSION

To examine feasibility of releasing substrates from the benzylic position *ortho* to an amino substituent, we planned to compare photolysis of benzyl esters **2**−**4** with a dimethylamino (DMA) group at the *ortho*, *meta*, and *para* positions, respectively (Figure 1). Unsubstituted and commercially available benzyl ester **5** was used as a control.

Esters **2**−**4** were easily synthesized (Scheme 2). Thus, reduction of commercially available methyl *N*,*N*-dimethylanthranilate **6** with $LiAlH_4$ led to 2-dimethylaminobenzyl alcohol **7**, which is also commercially available, in 91% yield. Its



2: R = *o*-Me_2N
3: R = *m*-Me_2N
4: R = *p*-Me_2N
5: R = H

Figure 1. Benzyl esters for photolysis.

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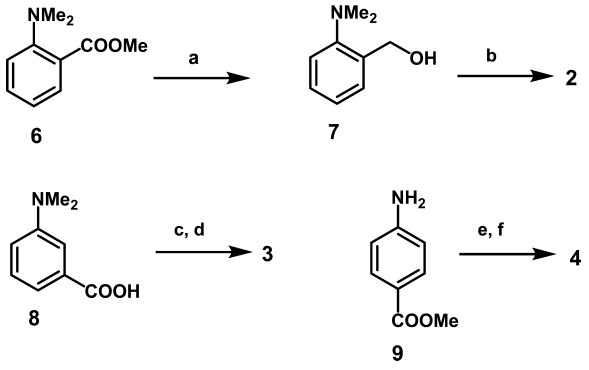
Scheme 2. Synthesis of Esters 2−4[a]



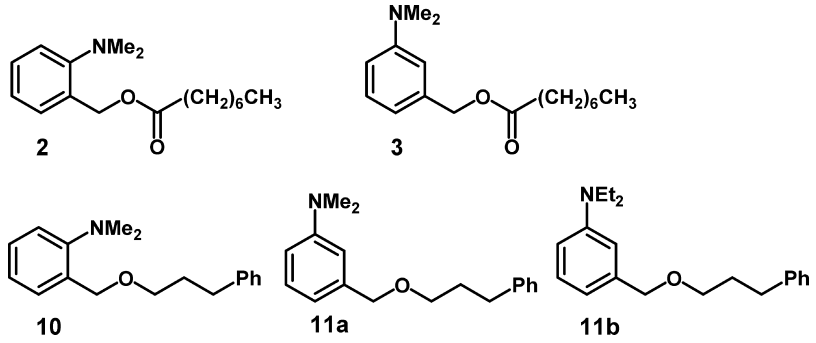
[a]Reagents and conditions: (a) $LiAlH_4$, THF, 0−50 °C, 93%; (b) octanoyl chloride, DMAP, Et_3N, DCM, 86%; (c) $LiAlH_4$, THF, rt, 97%; (d) octanoyl chloride, DMAP, Et_3N, DCM, 95%; (e) paraformaldehyde, $NaBH_3CN$, $LiAlH_4$, THF, 83%; (f) octanoyl chloride, DMAP, Et_3N, DCM.

reaction with octanoyl chloride provided ester **2** in 84% yield. Preparation of ester **3** and **4** was carried out in a similar manner from commercially available 3-dimethylaminobenzoic acid **8** and methyl 4-aminobenzoate **9**, respectively. However, para-substituted benzyl ester **4** was thermally unstable and decomposed during column chromatographic purification, while the esters **2** and **3** both remained stable at up to 80 °C for 30 min in MeCN:water (4:1) or methanol.

To compare photochemical properties of **2** and **3**, we irradiated 2-DMABn ester **2** and 3-DMABn ester **3** under the same conditions against unsubstituted benzyl ester **5** as the control. Compounds **2** and **3** have significantly different UV absorption profiles. Due to the steric interaction between the adjacent dimethylamino and methylene groups in **2**, conjugation of the dimethylamino group to the benzene ring cannot be achieved as completely as in **3**. As a consequence, the UV absorption of **2** does not have a distinct peak at ∼313 nm as in the 3-dialkylaminobenzyl counterparts; instead, the peak at 252 nm of the 2-DMABn group has a shoulder extending to ∼330 nm. Irradiation of these compounds was carried out with a 450W medium pressure mercury lamp equipped with a Pyrex filter sleeve (λ > 300 nm) without deaeration. For 10 min irradiation in CD_3CN/D_2O (4:1), **2** released the acid in 73% yield while **3** released the same acid in a lower yield of 55% (Table 1, entries 1 and 2). Irradiation for an additional 10 min increased the yield to 83% for **2** and 70% for **3**, respectively. The data showed that the 2-DMABn is more efficient than 3-DMABn in releasing acid in CD_3CN/D_2O. However, in CD_3OD, 2-DMABn becomes less efficient than 3-DMABn. Although irradiation for 10 min led to similar yields of releasing the acid from **2** (68%) and **3** (71%), 20 min irradiation led to a more drastic difference between **2** (75%) and **3** (94%). This solvent-dependent reactivity change is probably related to solvent effect on a proposed single electron transfer (SET) process (vide infra),[24] the resulting charge-transfer state, and subsequent decay pathways.[14,15] Control compound **5** was stable under the reaction conditions due to its lack of UV absorption at λ > 300 nm; it remained stable upon irradiation with a Vycor filter sleeve (λ > 220 nm).

Interestingly, with the 2-DMABn PPG, the efficiency of releasing alcohols is comparable with that of releasing acid in both CD_3CN/D_2O and CD_3OD (Table 1, entry 3), albeit alkoxide being a poorer leaving group compared with carboxylate. On the other hand, comparison between 2-DMABn (as in **10**) and 3-DMABn (as in **11a**) in releasing 3-phenyl-1-propanol showed that 3-DMABn is better than 2-DMABn. Within 10 min, the alcohol was released from **11a** in nearly quantitative yield in both CD_3CN/D_2O and CD_3OD (Table 1, entry 4), much higher than that of the corresponding 2-DMABn. We also compared the photoreaction of **11a** and **11b**[22] under the same conditions and confirmed that the DMABn (in **11a**) and DEABn PPG (in **11b**) have similar efficiency (Table 1, entries 4 and 5), showing that alkyl substitution on the aniline amino group did not alter the photoreaction outcomes. Ethers **10** and **11a** were prepared from the respective benzyl alcohols and 3-phenylpropyl

Table 1. Photochemical Release of Acid or Alcohol from Amino-Substituted Benzyl Group[a]



		releasing yield, 10 min		releasing yield, 20 min	
entry	compound	CH_3CN/D_2O (4:1) (%)	CD_3OD (%)	CH_3CN/D_2O (4:1) (%)	CD_3OD (%)
1	**2**	73	68	83	75
2	**3**	55	71	70	94
3	**10**	65	59	80	84
4	**11a**	95	93	95	96
5	**11b**	100	94	100	98

[a]A 5.0 mM solution in 5 mm NMR tubes was irradiated with a 450 W medium pressure mercury lamp equipped with a Pyrex filter sleeve (λ > 300 nm) without deaeration. The yields were determined by ^1H NMR analysis.

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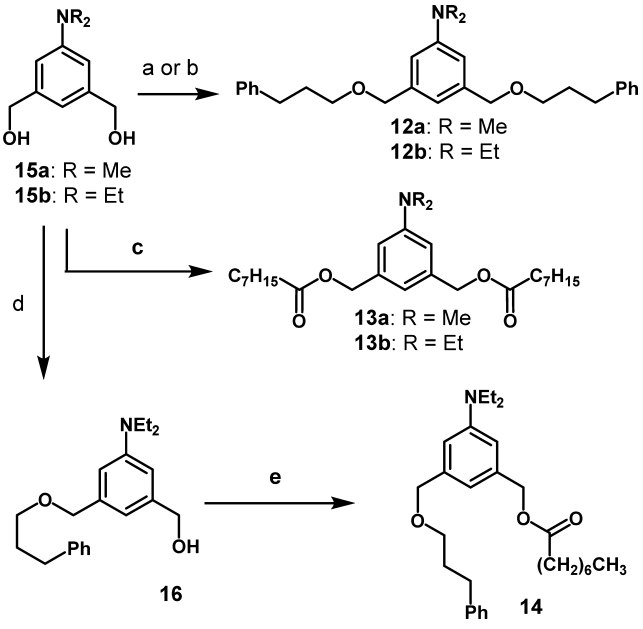
tosylate, while **11b** was prepared from 3-phenyl-1-propanol and the corresponding benzyl chloride in good yields.[22]

The data in Table 1 clearly showed that release of alcohol by 3-DMABn is more efficient than release of acid (Table 1, entries 2 and 4), which is consistent with our early observations with the 3-DEABn PPG.[22] We postulated that with the presence of the ester moiety, a SET process between the aromatic amino group and the ester functional group and the subsequent decay might serve as an internal filtering process, which reduces the efficiency of photochemical C−O bond cleavage. Similar SET from a *meta* amino group is known in literature.[14−17,19,21]

A relevant observation is that not only is an acid slower to be cleaved from the PPG than an alcohol, but also the presence of a benzyl ester moiety slows the release of alcohol, as demonstrated in the photoreactions of **12**−**14**. Because deprotection of DEABn does not destroy the working chromophore, we previously demonstrated that release of two alcohol substrates from one PPG chromophore could be achieved in high yield.[22] We thus synthesized diether **12**, diester **13**, and mixed ether and ester **14** to compare their efficiency in releasing the respective substrates. The synthesis was straightforward, starting from commercially available 5-dimethylamino-1,3-benzenedimethanol diol **15a** or **15b**,[22] as shown in Scheme 3.

Scheme 3. Synthesis of Compounds 12−14 That Release Two Substrates from One Chromophore[a]



[a]Reagents and conditions: (a) NaH, $Ph(CH_2)_3OTs$, DMF, 0 °C to rt, 43% for **12a**; (b) $SOCl_2$, DCM, −10 °C to rt; $Ph(CH_2)_3OH$, NaH, Bu_4NBr, DMF, 0 °C to rt, 85% for **12b**; (c) octanoyl chloride, DMAP, Et_3N, DCM, 93% for **13a** and 95% for **13b**; (d) NaH, $Ph(CH_2)_3OTs$, DMF, rt to 50 °C, 37%; (e) octanoyl chloride, DMAP, Et_3N, DCM, 90%.

With 3-phenyl-1-propanol as the leaving alcohol substrate, irradiation of **12a** and **12b** ($\varepsilon_{313\ nm(MeCN)}$ = 3000 M^{-1} cm^{-1}, Φ = 0.20) in CD_3CN:D_2O (4:1) for 10 min resulted in releasing of the alcohol in a quantitative yield (Table 2, entries 1 and 2), consistent with our earlier results.[22] Irradiation of **13** under the same conditions led to slower release of the acid substrate

Table 2. Photoreaction of 12−14[a,b]

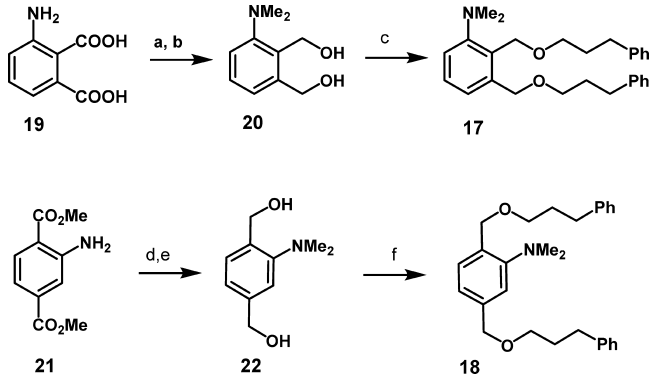
		releasing yield, 10 min		releasing yield, 20 min	
entry	compound	alcohol (%)	acid (%)	alcohol (%)	acid (%)
1	**12a**	100		100	
2	**12b**	100		100	
3	**13a**		27		49
4	**13b**		25		49
5	**14**	35	40	76	65

[a]A 5.0 mM solution (in CD_3CN:D_2O 4:1) in 5 mm NMR tubes was irradiated with a 450 W medium pressure mercury lamp equipped with a Pyrex filter sleeve (λ > 300 nm) without deaeration. The yields were determined by ^1H NMR analysis. [b]Yield = released substrate/total substrate expected to be released.

(Table 2, entries 3 and 4). On the basis of the results of **12** and **13**, we expected that irradiation of **14** would lead to sequential release of two different substrates from the same PPG, i.e., the alcohol would be released first, followed by the acid. However, under the same photoreaction conditions, compound **14** released the alcohol in only 35% yield after 10 min of irradiation and 76% yield after another 10 min of irradiation (Table 2, entry 5), much slower than **12**. It appeared that the presence of the benzylic ester moiety interfered with the release of the alcohol occurring at the other *meta* position. Presumably, the hypothesized SET process between the aromatic amino group and the ester functional group and the subsequent decay process might again serve as an internal filtering process to reduce the efficiency of photochemical C−O bond cleavage on the other side of the chromophore.

Encouraged by the highly efficient release of alcohols from structurally simple diether **12**, we went on to examine the feasibility of releasing alcohols from diethers **17** and **18** (Scheme 4). Diether **17** was synthesized from commercially

Scheme 4. Synthesis of Diethers 17 and 18[a]



[a]Reagents and conditions: (a) K_2CO_3, CH_3I, DMF, rt, 35%; (b) $LiAlH_4$, THF, 0 to 60 °C, 59%; (c) NaH, $Ph(CH_2)_3OTs$, DMF, 0 °C to rt, 77%; (d) K_2CO_3, CH_3I, DMF, 30 °C, 34%; (e) $LiAlH_4$, THF, 0 to 60 °C, 86%; (f) NaH, $Ph(CH_2)_3OTs$, DMF, 0 °C to rt, 83%.

available 3-aminophthalic acid **19** through diol intermediate **20**, and diether **18** was synthesized from commercially available dimethyl aminoterephthalate **21** through diol intermediate **22**, which is also commercially available.

Under the same irradiation conditions, **12a** released all the alcohols within 10 min, while **17** and **18** only released 27 and 29%, respectively (Table 3). At the end of 30 min of irradiation, there was only 58% of alcohol released from **17** and 54% from

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Table 3. Photoreaction of Diethers 12a, 17, and 18[a,b]

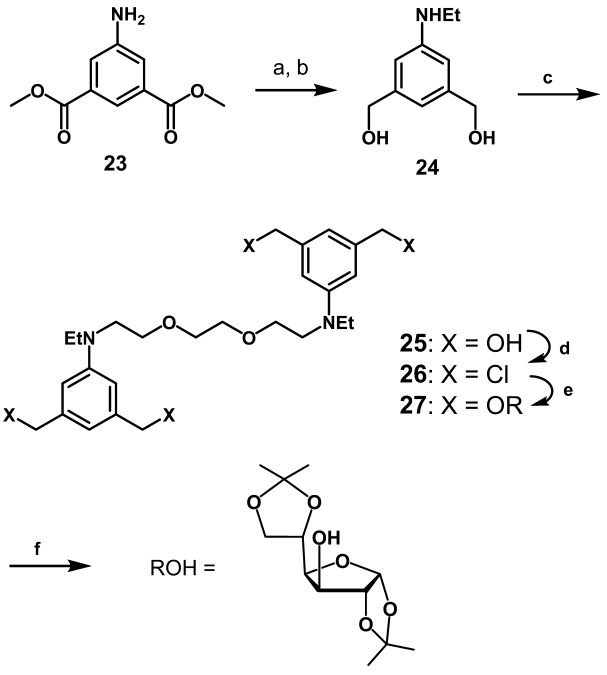
entry	compound	10 min (%)	20 min (%)	30 min (%)
1	**12a**	100	100	100
2	**17**	27	33	58
3	**18**	29	48	54

[a]A 5.0 mM solution (in CD_3CN:D_2O 4:1) in 5 mm NMR tubes was irradiated with a 450 W medium pressure mercury lamp equipped with a Pyrex filter sleeve (λ > 300 nm) without deaeration. The yields were determined by ^{1}H NMR analysis. [b]Yield = released substrate/total substrate expected to be released.

18. This reduced chemical efficiency of **17** and **18** can perhaps also be attributed to the reduced conjugation of the dimethylamino group with the benzene ring in **17** and **18** due to the steric interaction between the amino group and the *ortho* methylene group. The reduced conjugation affects not only release of alcohol from the *ortho* benzylic position as shown in **10** (Table 1, entry 3) but also cleavage of the *meta* benzylic C−O bond in **17** and **18**.

On the basis of these results as well as the fact that access to **12** is much easier than to **17** and **18**, we decided to continue the study of releasing multiple substrates from one molecule with the bifunctional PPG in **12**. We next examined the efficiency of releasing four alcohols from a single molecule. Synthesis of the PPG carrier started with commercially available dimethyl 5-aminoisophthalate **23** (Scheme 5). Its ethylation and subsequent reduction with LAH led to 5-(*N*-ethylamino)-1,3-benzenedimethanol **24**. Two **24** molecules were then joined together to provide the tetraol **25** in 75% yield. It was then converted to new PPG reagent **26** in 84% yield by treating with thionyl chloride. Reaction of the new PPG reagent with alcohol substrate, i.e., commercially available diacetone-D-glucose, loaded four monosaccharides to the photoresponsive carrier to provide **27** in 76% yield. Upon irradiation of a 5.0 mM solution of **27** ($\varepsilon_{317\ nm(MeCN)}$ = 4300 M^{-1} cm^{-1}, Φ = 0.09) in CH_3CN:H_2O (4:1), the monosaccharide was released completely within 20 min, and an isolated yield of 90% (obtained ROH/all expected ROH) was achieved, consistent with the yield determined by NMR.

Scheme 5. Photorelease of Multiple Substrates from One Chromophore[a]



[a]Reagents and conditions: (a) Na_2HPO_4, EtI, DMF, 60 °C, 44%; (b) $LiAlH_4$, THF, 0 to 60 °C, 82%; (c) K_2CO_3, $I(CH_2)_2O(CH_2)_2O(CH_2)_2I$, MeCN, 95 °C, 75%; (d) $SOCl_2$, MeCN, 0 °C to rt, 84%; (e) diacetone-D-glucose, NaH, Bu_4NBr, DMF, 0 °C to rt, 76%; (f) hν, MeCN/H_2O 4:1, 90% (released ROH/all ROH expected to be released).

In summary, we provided experimental evidence to show that an *ortho* amino group can indeed facilitate benzylic C−O bond cleavage to release alcohol and carboxyl acid. We compared the efficiency of cleaving benzylic C−O bond in 2-DMABn and 3-DMABn and concluded that the amino group at the *meta* position results in a PPG with better overall chemical and photochemical properties. We further demonstrated that by joining two PPGs as shown in Scheme 5, four alcohol substrates can be released from one molecule in high efficiency.

EXPERIMENTAL SECTION

General. Organic solutions were concentrated by rotary evaporation at ca. 12 Torr. Flash column chromatography was performed employing 230−400 mesh silica gel. Thin-layer chromatography was performed using glass plates precoated to a depth of 0.25 mm with 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). IR data are presented as frequency of absorption (cm^{-1}). ^{1}H NMR or ^{13}C NMR spectra were recorded on 300, 400, and 700 MHz NMR spectrometers; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. HRMS was conducted with ESI ionization method and with TOF mass analyzer.

Materials. Anhydrous solvents tetrahydrofuran (THF), dimethylformamide (DMF), and dichloromethane (DCM) were used without distillation. Solvents for workup and column chromatography such as petroleum ether (PE), ethyl acetate (EA), methanol (MeOH), triethylamine (TEA), and other chemicals were obtained from commercial vendors and used without further purification.

Synthesis of 2-(N,N-Dimethylamino)benzyl Octanoate ***2****.* To methyl 2-(dimethylamino) benzoate (3.580 g, 20.0 mmol) in THF (100.0 mL) was added $LiAlH_4$ (0.912 g, 24.0 mmol) at 0 °C under nitrogen atmosphere. The reaction was stirred at 50 °C for 3 h and was then quenched with H_2O and treated with 10% NaOH (aq) and water. The precipitate was removed through filtration, and the filtrate was concentrated under reduced pressure to give a yellow oil which was purified by column chromatography (PE:EA 3:1) to provide benzyl alcohol **7** (2.802 g, 93%, R_f = 0.15). To benzyl alcohol **7** (76.0 mg, 0.500 mmol), octanoyl chloride (0.082 mL, 0.480 mmol), and DMAP (1.0 mg, 0.005 mmol) in DCM (2.0 mL) was added triethylamine (0.174 mL, 1.250 mmol). The reaction mixture was stirred for 2 h and quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified with column chromatography (PE:EA 20:1, R_f = 0.8) to provide **3** (115.0 mg, 86%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (d, J = 7.6 Hz, 1 H), 7.28 (t, J = 7.7 Hz, 1 H), 7.12 (d, J = 7.7 Hz, 1 H), 7.06 (t, J = 7.7 Hz, 1 H), 5.25 (s, 2 H), 2.70 (s, 6 H), 2.37 (t, J = 7.7 Hz, 2 H), 1.66 (quint, J = 7.0 Hz, 2 H), 1.33−1.24 (m, 8 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.0, 153.0, 130.4, 129.6, 128.9, 123.1, 119.3, 62.5, 45.2, 34.5, 31.7, 29.1, 29.0, 25.0, 22.6, 14.1; IR (neat) 2927, 2857, 2830, 2785, 1734, 1494, 1454; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{17}H_{28}NO_2$ 278.2120; found 278.2126.

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Synthesis of 3-(N,N-Dimethylamino)benzyl Octanoate ***3***. To 3-(dimethylamino)benzoic acid (8.870 g, 54.0 mmol) in THF (150.0 mL) was added $LiAlH_4$ (4.104 g, 108.0 mmol) under N_2 at room temperature. The reaction mixture was stirred overnight and quenched with water (3.8 mL) followed by treatment with 10% NaOH aqueous solution. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The crude reaction product was purified by column chromatography (PE:EA 3:1, R_f = 0.20) to provide oil intermediate 3-(dimethylamino)benzyl alcohol (7.897 g, 97%). To the alcohol (100.0 mg, 0.662 mmol), octanoyl chloride (0.142 mL, 0.828 mmol), and DMAP (1.0 mg, 0.007 mmol) in DCM (5.0 mL) was added triethylamine TEA (0.184 mL, 1.665 mmol) at room temperature. After 5 h, the reaction was quenched with saturated $NaHCO_3$ (aq). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The reaction mixture was purified by column chromatography (PE:EA 95:5, R_f = 0.5) to provide **4** as a colorless oil (174.0 mg, 95%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24 (t, J = 8.0 Hz, 1 H), 6.71−6.69 (m, 3 H), 5.07 (s, 2 H), 2.95 (s, 6 H), 2.35 (t, J = 7.7 Hz, 2 H), 1.64 (quint, J = 7.4 Hz, 2 H), 1.30−1.25 (m, 8 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 150.7, 136.9, 129.3, 116.3, 112.4, 112.2, 40.6, 34.4, 31.7, 29.1, 29.0, 25.0, 22.6, 14.1; IR (neat) 2953, 2926, 2855, 2805, 1733, 1606, 1583, 1500, 1459, 1351; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{17}H_{28}NO_2$ 278.2120; found 278.2125.

Synthesis of 2-(N,N-Dimethylamino)benzyl 3-Phenyl-1-propyl Ether ***10***. To the solution of 7 (181.0 mg, 1.2 mmol) in DMF (2.0 mL) was added sodium hydride (60% dispersion in mineral oil, 120.0 mg, 3.0 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 20 min before 3-phenylpropyl 4-methylbenzenesulfonate (290.0 mg 1.0 mmol) was added. After 3 h at 40 °C, the reaction was quenched with saturated $NaHCO_3$ (aq) at 0 °C and extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (PE:EA 30:1, R_f = 0.6) to provide **10** (208.0 mg, 77%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.4, 1.2 Hz, 1 H), 7.29−7.25 (m, 2 H), 7.20−7.17 (m, 3 H), 7.08−7.05 (m, 2 H), 4.59 (s, 2 H), 3.54 (t, J = 6.3 Hz, 2 H), 2.73 (t, J = 7.7 Hz, 2 H), 2.70 (s, 6 H), 1.96 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 152.4, 142.1, 132.5, 129.4, 128.5, 128.3, 128.1, 125.6, 122.9, 118.6, 69.9, 68.8, 45.1, 32.5, 31.5; IR (neat) 2935, 2857, 2782, 1594, 1489, 1449; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{18}H_{24}NO$ 270.1858; found 270.1863.

Synthesis of 3-(N,N-Dimethylamino)benzyl 3-Phenyl-1-propyl Ether ***11a***. To the solution of 3-(*N*,*N*-dimethylamino)benzyl alcohol (38.0 mg, 0.250 mmol) in DMF (1.5 mL) was added sodium hydride (60% dispersion in mineral oil, 20.0 mg, 0.500 mmol) at room temperature. The reaction mixture was stirred for 90 min before 3-phenylpropyl 4-methylbenzenesulfonate (80.0 mg, 0.280 mmol) was added. After being stirred at 50 °C overnight, the reaction was quenched with saturated $NaHCO_3$ (aq) at 0 °C and extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (PE:EA 20:1, R_f = 0.4) to provide **11a** (51.0 mg, 76%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28−7.17 (m, 6 H), 6.74 (s, 1 H), 6.70 (d, J = 7.4 Hz, 1 H), 6.67 (d, J = 7.7 Hz, 1 H), 4.48 (s, 2 H), 3.49 (t, J = 6.3 Hz, 2 H), 2.95 (s, 6 H), 2.72 (t, J = 7.7 Hz, 2 H), 1.93 (quint, J = 7.7 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.8, 142.1, 139.4, 129.1, 128.5, 128.3, 125.8, 116.1, 111.9, 111.8, 73.4, 69.4, 40.7, 32.5, 31.5; IR (neat) 2932, 2853, 2799, 1603, 1496, 1350; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{18}H_{24}NO$ 270.1858; found 270.1866.

Synthesis of Diether ***12a***. To the solution of dimethyl 5-(*N*,*N*-dimethylamino)isophthalate (2.373 g, 10.0 mmol) in THF (100.0 mL) was added $LiAlH_4$ (0.912 g, 24.0 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was refluxed for 3 h and then quenched with H_2O (0.912 mL) and 10% NaOH aqueous (2 × 0.912 mL). The precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (DCM/MeOH 20:1, R_f = 0.2) to provide diol **15a** (1.445 g, 80%). To the solution of **15a** (13.0 mg, 0.072 mmol) in DMF (1.0 mL) was added sodium hydride (60% dispersion in mineral oil, 9.0 mg, 0.215 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature before 3-phenylpropyl 4-methylbenzenesulfonate (46.0 mg, 0.160 mmol) was added. After being stirred at room temperature overnight, the reaction was quenched with water 0 °C and concentrated under reduced pressure. The crude mixture was purified by column chromatography (PE:EA 20:1, R_f = 0.2) to provide **12a** (13.0 mg, 43%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27−7.26 (m, 4 H), 7.19−7.17 (m, 6 H), 6.68−6.67 (m, 3 H), 4.48 (s, 4 H), 3.49 (t, J = 6.3 Hz, 4 H), 2.96 (s, 6 H), 2.72 (t, J = 7.7 Hz, 4 H), 1.93 (quint, J = 6.7 Hz, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 151.0, 142.1, 139.5, 128.5, 128.3, 125.7, 115.5, 111.1, 73.3, 69.4, 40.7, 32.5, 31.5; IR (neat) 2929, 2854, 1600, 1487, 1449, 1361; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{28}H_{36}NO_2$ 418.2746; found 418.2740.

Synthesis of Diether ***12b***. To the solution of dimethyl 5-aminoisophthalate (5.0 g, 23.9 mmol) and Na_2HPO_4 (20.4 g, 143.4 mmol) in dry DMF (75.0 mL) was added iodoethane (7.68 mL, 95.6 mmol). The reaction mixture was stirred at 60 °C for 36 h and then diluted with 250 mL of water and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash column chromatography (PE:EA 9:1) to provide dimethyl 5-(*N*,*N*-diethylamino)- isophthalate (5.14 g, 81%) as a pale yellow solid. To the solution of dimethyl 5-(*N*,*N*-diethylamino)isophthalate (530.0 mg, 2.0 mmol) in THF was added $LiAlH_4$ (152.0 mg, 4.0 mmol) at −10 °C, and the mixture was warmed to room temperature and stirred overnight. The reaction was quenched by water (160 μL), 10% NaOH (aq, 320 μL), and then water (480 μL). The organic layer was concentrated and purified by flash column chromatography (DCM/MeOH 10:1) to provide **15b** (343.0 mg, 82%) as a pale yellow waxy solid. R_f = 0.50 (PE:EA 1:4). To a solution of **15b** (299.0 mg, 1.430 mmol) in DCM was added thionyl chloride (310 μL, 4.290 mmol) at −10 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for 4 h. The crude mixture was concentrated and purified by column chromatography (DCM) to the corresponding dichloride (320.0 mg, 91%) as a pale yellow solid. R_f = 0.50 (PE:EA 19:1). To the solution of 3-phenylpropan-1-ol (60.0 mg, 0.440 mmol) in DMF (1.5 mL) was added NaH (60% dispersion in mineral oil 53.0 mg, 1.32 mmol) at 0 °C under N_2 atmosphere. After being stirred at room temperature for 30 min, a solution of the dichloride (49.0 mg, 0.2 mmol) in DMF (0.5 mL) was added at 0 °C, followed by Bu_4NBr (32.0 mg, 0.1 mmol). After being stirred at room temperature overnight, the reaction was quenched with ice water. The organic solvent was evaporated, and the crude mixture was purified by column chromatography (PE:EA 40:1, R_f = 0.2) to provide **12b** (76.0 mg, 85%) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27−7.25 (m, 4 H), 7.18−7.16 (m, 6 H), 6.61 (s, 2 H), 6.59 (s, 1 H), 4.45 (s, 4 H), 3.49 (t, J = 6.4 Hz, 4 H), 3.36 (q, J = 7.1 Hz, 4 H), 2.71 (t, J = 7.7 Hz, 4 H), 1.93 (quint, J = 6.6 Hz, 4 H), 1.16 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.2, 142.1, 139.7, 128.51, 128.50, 128.46, 128.32, 128.28, 125.72, 125.71, 114.34, 114.30, 110.32, 110.28, 73.4, 69.4, 44.4, 32.5, 31.5, 12.7, 12.6; IR (neat) 2929, 2856, 1598, 1480, 1405; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{30}H_{40}NO_2$ 446.3059; found 446.3068.

Synthesis of Diester ***13a***. To the solution of **15a** (80.0 mg, 0.442 mmol), octanoyl chloride (0.189 mL, 1.105 mmol), and DMAP (0.6 mg, 0.004 mmol) in DCM (5.0 mL) was added triethylamine (0.246 mL, 1.768 mmol) at room temperature. The reaction was stirred overnight and quenched with saturated $NaHCO_3$ (aq). The layer of DCM was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (PE:EA 19:1, R_f = 0.2) to provide **13a** (179.0 mg, 93%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.69 (s, 1 H), 6.65 (s, 2 H), 5.06 (s, 4 H), 2.96 (s, 6 H), 2.35 (t, J = 7.7 Hz, 4 H), 1.65 (quint, J = 7.1 Hz, 4 H), 1.32−1.25 (m, 16 H), 0.87 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 150.8, 137.3, 115.9, 111.9, 66.4, 40.5, 34.4, 31.7, 29.1, 29.0, 25.0, 22.6, 14.1; IR (neat) 2954, 2926, 2855, 1733, 1604, 1491, 1459; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{26}H_{44}NO_4$ 434.3270; found 434.3264.

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*Synthesis of Diester **13b**.* To the solution of **15b** (100.0 mg, 0.478 mmol), octanoyl chloride (0.204 mL, 1.196 mmol), and DMAP (0.5 mg, 0.005 mmol) in DCM (5.0 mL) was added triethylamine (0.266 mL, 1.912 mmol) at room temperature. After being stirred overnight, the reaction was quenched with saturated $NaHCO_3$ (aq). The layer of DCM was washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (PE:EA 19:1, R_f = 0.6) to provide **13b** (209.0 mg, 95%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.60 (s, 1 H), 6.58 (s, 2 H), 5.04 (s, 4 H), 3.35 (q, J = 7.0 Hz, 4 H), 2.35 (t, J = 7.7 Hz, 4 H), 1.64 (quint, J = 7.0 Hz, 4 H), 1.31−1.25 (m, 16 H), 1.16 (t, J = 7.0 Hz, 6 H), 0.87 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 148.1, 137.4, 114.8, 111.1, 66.6, 44.4, 34.4, 31.7, 29.1, 29.0, 25.0, 22.6, 14.1, 12.5; IR (neat) 2956, 2926, 2856, 1733, 1603, 1487, 1466; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{28}H_{48}NO_4$ 462.3583; found 462.3577.

*Synthesis of Intermediate **16** and **14**.* To a solution of **15b** (105.0 mg 0.5 mmol) in DMF (3.0 mL) was added NaH (60% dispersion in mineral oil 40.0 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred for 30 min, and 3-phenylpropyl 4-methylbenzenesulfonate (29.0 mg 0.1 mmol) in DMF (1.0 mL) was added at room temperature. After being stirred at 50 °C overnight, the reaction was quenched with water at 0 °C and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (PE:EA 5:1, R_f = 0.3) to provide **16** (12.0 mg, 37%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2 H), 7.19−7.17 (m, 3 H), 6.62−6.61 (m, 3 H), 4.62 (s, 2 H), 4.45 (s, 2 H), 3.49 (t, J = 6.4 Hz, 2 H), 3.36 (q, J = 7.0 Hz, 4 H), 2.72 (t, J = 7.7 Hz, 2 H), 1.94 (quint, J = 6.4 Hz, 2 H), 1.16 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.3, 142.2, 142.1, 140.0, 128.5, 128.3, 125.7, 113.4, 110.3, 109.6, 73.4, 69.5, 66.1, 44.4, 32.4, 31.4, 12.6; IR (neat) 3401, 2967, 2926, 2861, 1598, 1471, 1403, 1354, 1289; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{21}H_{30}NO_2$ 328.2277; found 328.2277.

To a solution of **16** (33.0 mg, 0.10 mmol), octanoyl chloride (0.018 mL, 0.105 mmol), and DMAP (0.6 mg, 0.005 mmol) in DCM (1.0 mL) was added triethylamine (0.028 mL, 0.20 mmol) at room temperature. After being stirred for 3 h, the reaction was quenched with water. The layer of DCM was washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (PE:EA 20:1, R_f = 0.3) to provide **14** (41.0 mg, 90%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2 H), 7.19−7.17 (m, 3 H), 6.63 (s, 1 H), 6.60 (s, 1 H), 6.56 (s, 1 H), 5.05 (s, 2 H), 4.45 (s, 2 H), 3.49 (t, J = 6.3 Hz, 2 H), 3.36 (q, J = 7.0 Hz, 4 H), 2.72 (t, J = 7.7 Hz, 2 H), 2.34 (t, J = 7.6 Hz, 2 H), 1.93 (quint, J = 7.0 Hz, 2 H), 1.64 (quint, J = 7.0 Hz, 2 H), 1.31−1.24 (m, 8 H), 1.17 (t, J = 7.0 Hz, 6 H), 0.85 (t, J = 6,8 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 148.1, 142.0, 139.9, 137.1, 128.5, 128.3, 125.7, 114.5, 110.62, 110.57, 73.2, 69.4, 66.7, 44.3, 34.4, 32.4, 31.6, 31.5, 29.1, 28.9, 25.0, 22.6, 14.1, 12.6; IR (neat) 2926, 2856, 1734, 1601, 1457, 1408, 1375; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{29}H_{44}NO_3$ 454.3321; found 454.3321.

*Synthesis of Diether **17** and Intermediate **20**.* To a stirred solution of 3-aminophthalic acid (1.0 g, 5.5 mmol) and potassium carbonate (5.320 g, 38.6 mmol) in DMF (20.0 mL) was added methyl iodide (10.940 g, 77.1 mmol). The reaction mixture was stirred at room temperature for 24 h and then diluted with H_2O (100 mL) and extracted with EA (50 mL × 3). The combined organic layers were washed with H_2O (50 mL × 3), dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (PE:EA 15:1) to provide corresponding dimethyl 3-(*N*,*N*-dimethylamino)phthalate (0.460 g, 35%). R_f = 0.6 (PE:EA 3:1). To a suspension of $LiAlH_4$ (0.170 g, 4.2 mmol) in THF (15.0 mL) at 0 °C was added dimethyl 3-(*N*,*N*-dimethylamino)phthalate (0.350 g, 1.4 mmol) dissolved in THF (4.0 mL). After being refluxed at 60 °C overnight, the reaction was quenched with sequential addition of H_2O (0.170 mL), 10% NaOH aqueous solution (2 × 0.170 mL), and H_2O (3 × 0.170 mL) and stirred for 15 min. The resulting white precipitate was filtered off, and the filtrate was concentrated, diluted with H_2O (100 mL), and extracted with EA (50 mL × 3). The combined organic layers were washed with H_2O (50 mL × 3), dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (PE:EA 1:1, R_f = 0.4) to provide **20** (0.158 g, 59%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.25 (t, J = 8.3 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 7.08 (d, J = 7.4 Hz, 1 H), 4.91 (s, 2 H), 4.68 (s, 2 H), 2.74 (s, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.3, 140.2, 134.0, 128.4, 124.8, 119.8, 64.3, 59.3, 45.3; IR (neat) 2939, 2866, 2830, 2785, 1584, 1468, 1455, 1312; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$ 182.1181; found 182.1185.

To a solution of **20** (22.0 mg, 0.484 mmol) in DMF (1.0 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 19.0 mg 0.121 mmol). After being stirred for 30 min at room temperature, 3-phenylpropyl 4-methylbenzenesulfonate (105.0 mg 0.363 mmol) was added. The reaction was then stirred at room temperature overnight and quenched with water at 0 °C. The crude product was purified by column chromatography (DCM:MeOH 100:1, R_f = 0.5) to provide **17** (39.0 mg, 77%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27−7.26 (m, 5 H), 7.20−7.17 (m, 7 H), 7.04 (d, J = 7.7 Hz, 1 H), 4.67 (s, 2 H), 4.66 (s, 2 H), 3.54 (t, J = 6.2 Hz, 4 H), 2.73−2.68 (m, 10 H), 1.96−1.91 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.8, 142.1, 140.0, 130.0, 128.7, 128.51, 128.48, 128.37, 128.34, 128.32, 125.77, 125.75, 123.4, 118.3, 70.5, 70.1, 69.9, 65.4, 45.7, 32.6, 32.5, 31.50, 31.47; IR (neat) 2933, 2857, 2783, 1590, 1460, 1357, 1311; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{28}H_{36}NO_2$ 418.2746; found 418.2746.

*Synthesis of Diether **18**.* To the solution of dimethyl aminoterephthalate (0.500 g, 2.392 mmol) and potassium carbonate (1.320 g, 9.570 mmol) in DMF (8.0 mL) was added methyl iodide (1.893 g, 14.340 mmol) under N_2 atmosphere. After being stirred at 30 °C for 7 days, the reaction mixture was diluted with 150.0 mL of H_2O and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with H_2O (50 mL × 3), brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (PE:EA 10:1, R_f = 0.4) to provide intermediate dimethyl (*N*,*N*-dimethylamino)terephthalate (0.194 g, 34%). To a suspension of $LiAlH_4$ (63.0 mg, 1.671 mmol) in THF (10.0 mL) at 0 °C was added dimethyl (*N*,*N*-dimethylamino) terephthalate (132.0 mg, 0.557 mmol) in THF (3.0 mL). After being refluxed overnight, the reaction mixture was quenched by the sequential dropwise addition of H_2O (0.1 mL), 10% NaOH aqueous solution (2 × 0.1 mL), and H_2O (3 × 0.1 mL). The resulting white precipitate was filtered off, and the filtrate was concentrated, diluted with H_2O (50 mL), and extracted with EA (50 mL × 3). The combined organic layers were washed with H_2O (50 mL × 3), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (PE:EA 3:2, R_f = 0.3) to provide **22** (86.0 mg, 86%). To a solution of **22** (21.0 mg, 0.113 mmol) in DMF (1.0 mL) was added sodium hydride (60% dispersion in mineral oil, 18.0 mg 0.452 mmol) at 0 °C. After being stirred for 30 min at room temperature, 3-phenylpropyl 4-methylbenzenesulfonate (98.0 mg 0.339 mmol) was added at 0 °C. The reaction was stirred at room temperature overnight and quenched with water at 0 °C. The crude product was purified by column chromatography (DCM, R_f = 0.2) to **18** (39.0 mg, 83%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43 (d, J = 7.7 Hz, 1 H), 7.28−7.26 (m, 4 H), 7.20−7.18 (m, 6 H), 7.07 (s, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 4.57 (s, 2 H), 4.48 (s, 2 H), 3.54 (t, J = 6.3 Hz, 2 H), 3.49 (t, J = 6.3 Hz, 2 H), 2.80−2.71 (m, 10 H), 1.94 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 152.5, 142.1, 142.0, 138.5, 131.6, 129.5, 128.5, 128.3, 125.75, 125.72, 122.1, 117.9, 72.9, 69.8, 69.4, 68.7, 45.0, 32.5, 32.4, 31.5, 31.4; IR (neat) 2933, 2854, 2783, 1603, 1494, 1452; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{28}H_{36}NO_2$ 418.2746; found 418.2746.

*Synthesis of Tetraol **25**.* To the solution of dimethyl 5-aminoisophthalate (1.000 g, 4.780 mmol) and Na_2HPO_4 (1.350 g, 9.560 mmol) in dry DMF (50.0 mL) was added iodoethane (0.198 mL, 4.780 mmol). The reaction mixture was stirred at 60 °C for 72 h, and then diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash column chromatography (PE:EA 5:1) to provide dimethyl 5-(*N*-ethylamino)-

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isophthalate (0.500 g, 44%) as a pale yellow solid. To a solution of dimethyl 5-(*N*-ethylamino)isophthalate (1.329 g, 5.600 mmol) in THF (50.0 mL) was added $LiAlH_4$ (638.0 mg, 16.8 mmol) at 0 °C. After being refluxed for 3 h, the reaction was quenched with sequential addition of H_2O (0.638 mL), 10% NaOH aqueous (2 × 0.638 mL), and H_2O (3 × 0.638 mL). The precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH 10:1, R_f = 0.20) to provide intermediate 5-(*N*-ethylamino)-1,3-benzenedimethanol **24** (831.0 mg, 82%) as a yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.62 (s, 4 H), 6.49 (s, 2 H), 4.54 (s, 4 H), 3.14 (q, J = 7.0 Hz, 4 H), 1.24 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.9, 142.5, 114.4, 110.6, 65.3, 38.6, 14.8; IR (neat) 3279, 3184, 2968, 2899, 2837, 1605, 1524, 1457, 1366, 1336, 1296; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$ 182.1181; found 182.1189.

5-(*N*-Ethylamino)-1,3-benzenedimethanol **24** (565.0 mg, 3.122 mmol) was mixed with 1,2-bis(2-iodoethoxy)ethane (565.0 mg 1.527 mmol) and K_2CO_3 (1.400 g 10.200 mmol) in CH_3CN (2.0 mL) in a sealed vial. The reaction was heated at 95 °C for 72 h; then, K_2CO_3 was filtered off, and the filtrate was concentrated. The obtained crude product was purified by column chromatography (DCM:MeOH 30:1, R_f = 0.2) to provide **25** (545.0 mg, 75%) as a white solid. ^{1}H NMR (700 MHz, MeOD-*d*4) δ 6.66 (s, 4 H), 6.62 (s, 2 H), 4.54 (s, 8 H), 3.66 (t, J = 6.2 Hz, 4 H), 3.63 (s, 4 H), 3.51 (t, J = 6.2 Hz, 4 H), 3.45 (q, J = 7.0 Hz, 4 H), 1.16 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (176 MHz, MeOD-*d*4) δ 148.1, 142.2, 113.0, 109.4, 70.4, 68.7, 64.4, 49.7, 45.1, 11.1; IR (neat) 3297, 2975, 2857, 1595, 1472, 1404, 1358, 1279; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{26}H_{41}N_2O_6$ 477.2965; found 477.2964.

Synthesis of Tetrachloride ***26***. To a solution of **25** (540.0 mg, 1.133 mmol) in CH_3CN (20.0 mL) was added $SOCl_2$ (166 μL, 2.278 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature and quenched by saturated $NaHCO_3$ (aq) at 0 °C. After removal of CH_3CN, DCM was added to extract the product. The organic layer was washed with brine, dried over $NaSO_4$, concentrated, and purified by column chromatography (PE:EA 5:1, R_f = 0.40) to **26** (525.0 mg, 84%) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.68 (s, 1 H), 6.64 (s, 2 H), 4.01 (s, 4 H), 3.64−3.62 (m, 4 H), 3.51 (t, J = 6.4 Hz, 2 H), 3.41 (q, J = 7.1, 2 H), 1.16 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.4, 139.0, 115.9, 111.7, 70.8, 68.9, 50.0, 46.7, 45.4, 12.1; IR (neat) 2965, 2913, 2874, 1598, 1447, 1359; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{26}H_{37}Cl_4N_2O_2$ 549.1609; found 549.1609.

Synthesis of ***27***. To the solution of the commercially available diacetone-D-glucose (57.0 mg 0.220 mmol) in DMF (0.5 mL) was added sodium hydride (60% dispersion in mineral oil, 18.0 mg, 0.440 mmol) at 0 °C under N_2 atmosphere. After the suspension was stirred at room temperature for 30 min, compound **26** (28.0 mg, 0.050 mmol) in DMF (0.5 mL) was added, followed by Bu_4NBr (6.0 mg, 0.020 mmol). The reaction mixture was stirred for 22 h at room temperature and quenched with water at 0 °C. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by preparative TLC plate (DCM:MeOH 10:1, R_f = 0.6) to provide **27** (55.0 mg 76%) as a white foam. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.58 (s, 2 H), 6.57 (s, 4 H), 5.89 (d, J = 3.5 Hz, 4 H), 4.60−4.56 (m, 12 H), 4.38−4.35 (q, J = 6.0, 4 H), 4.16 (dd, J = 7.5, 3.0 Hz, 4 H), 4.10 (t, J = 7.4 Hz, 4 H), 4.05−4.00 (m, 8 H), 1.49 (s, 12 H), 1.43 (s, 12 H), 1.36 (s, 12 H), 1.31 (s, 12 H), 1.15 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.1, 139.0, 114,2, 111.8, 110.2, 108.9, 105.3, 82.6, 81.7, 81.2, 72.8, 72.7, 70.7, 68.9, 67.2, 50.0, 45.5, 29.7, 26.9, 26.8, 26.3, 25.5, 12.1; IR (neat) 2980, 2930, 1731, 1600, 1472, 1372; HRMS (ESI-TOF) m/e: $[M + H]^+$ calcd for $C_{74}H_{113}N_2O_{26}$ 1445.7528; found 1445.7513.

Photoreaction in NMR Tube in Deuterated Solvent. To a 5 mm NMR tube was added a stock solution of the substrate (0.5 mL, 5.0 mM) in MeOD or CD_3CN:D_2O (4:1) with a microsyringe. The NMR tube was sealed with PTFE tape, bound to the immersion well condenser of the photoreactor, and irradiated for the indicated time. The conversion and yield of reaction was calculated based on ^{1}H NMR integration of the products.

Larger Scale Photoreaction in NMR Tube in Nondeuterated Solvent. To 5 mm NMR tubes was added solution of the substrate (0.5 mL, 5.0 mM) in CH_3CN:H_2O (4:1). The NMR tubes were sealed with PTFE tape, bound to the immersion well condenser of the photoreactor, and irradiated for 20 min. The reaction solutions in all NMR tubes were combined in a flask and concentrated. The crude product was purified by column chromatography.

Photoreaction of ***27***. To 5 mm NMR tubes was added solution of **27** (0.5 mL × 14, 5.0 mM) in CH_3CN:H_2O (4:1). The NMR tubes were sealed with PTFE tape, bound to the immersion well condenser of the photoreactor, and irradiated for 20 min. The reaction solutions in all NMR tubes were then combined and concentrated, and the reaction yield was estimated to be quantitative by ^{1}H NMR. The crude product was purified by column chromatography (DCM:MeOH 60:1, R_f = 0.15) to provide the released diacetone-D-glucose (33 mg) in 90% yield.

Quantum Yield Determination. A 5.0 mM solution of the sample and a 5.0 mM solution of DEABn-protected 3-phenyl-1-propanol (with known quantum yield of 0.26) in NMR tubes were irradiated side-by-side under the same conditions. The yields of the photoreactions were determined by ^{1}H NMR analysis, and the quantum yield of the new reaction was calculated based on the measured chemical yields of the two reactions, the known quantum yield of the reference reaction, and the PPG chromophore UV absorption profiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00927.

^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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