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Photolabile Protection of Alcohols, Phenols, and Carboxylic Acids with 3-Hydroxy-2-Naphthalenemethanol

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Irradiation of alcohols, phenols, and carboxylic acids "caged" with the (3-hydroxy-2-naphthalenyl)methyl group results in fast ($k_{release} \approx 10^5$ s^{-1}) release of the substrates with good quantum ($\Phi = 0.17-0.26$) and chemical (>90%) yields. The initial byproduct of the photoreaction, 2-naphthoquinone-3-methide, reacts rapidly with water ($k_{H_2O} = 144 \pm 11$ s^{-1}) to produce parent 3-hydroxy-2-naphthalenemethanol. The *o*-quinone methide intermediate can be also trapped by other nucleophiles or converted into a photostable Diels−Alder adduct with ethyl vinyl ether.

Introduction

Photolabile protecting groups (PPG), known as "cages" in biochemistry, allow for the spatial and temporal control of substrate release, as well as for "reagentless" deprotection.[1−3] PPGs have found numerous applications in biochemistry,[3] organic synthesis,[1,2,4] fabrication of high density probe arrays (aka biochips),[5] and time-resolved X-ray crystallography.[6] An ideal photolabile protecting group should be stable in the dark and should release the caged substrate in high quantum and chemical yields upon irradiation. In addition, a high rate of substrate release is crucial for kinetic and time-resolved studies, and substantial absorbance above 300 nm is beneficial for biochemical applications. For many common PPGs, the efficiency of uncaging depends on the basicity of the substrate, because the deprotection reaction proceeds via heterolysis of a C−O bond. Therefore, poor leaving groups such as alcohols represent an especially difficult target for photolabile protection. Several examples of successful release of alcohols and carbohydrates caged with *o*-nitrobenzyl-based PPGs have been reported.[2,7] However, substrate release can take minutes after irradiation, since this reaction proceeds via several slow dark steps.[8] Other common PPGs, such as 3′,5′-dimethoxybenzoin,[9] *p*-hydroxyphenacyl,[10] and a family of cages utilizing photochemical heterolysis of the C−O bond,[11] allow for the rapid release of a substrate but work well only with good leaving

(1) Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Synthesis*; Wiley: New York, 1991.

(2) (a) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441. (b) Bochet, C. G. *Chem. Soc., Perkin Trans. 1* **2002**, 125.

(3) (a) *Biological Applications of Photochemical Switches*; Morrison, H., Ed.; Wiley: New York, 1993. (b) *Dynamic Studies in Biology*; Goeldner, M., Givens, R., Eds.; Wiley: Weinheim, 2005. (c) Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4900.

(4) (a) Pillai, V. N. R. Photoremovable protecting groups in organic synthesis. *Synthesis* **1980**, *1*, 1. (b) Pillai, V. N. R. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1987; Vol. 9, pp 225−323.

(5) (a) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767. (b) Heller, M. J. *Ann. Rev. Biomed. Eng.* **2003**, *4*, 129. (c) Gao, X.; LeProust, E.; Zhang, H.; Srivannavit, O.; Gulari, E.; Yu, P.; Nishiguchi, C.; Xiang, Q.; Xiaochuan, Z. *Nucleic Acids Res.* **2001**, *29*, 4744. (d) Lipshutz, R. J.; Fodor, S. P. A.; Gingeras, T. R.; Lockhart, D. J. *Nat. Genet.* **1999**, *21*, 20. (e) Pirrung, M. C.; Fallon, L.; McGall, G. J. *J. Org. Chem.* **1998**, *63*, 241. (f) Kobayashi, Y.; Sakai, M.; Ueda, A.; Maruyama, K.; Saiki, T.; Suzuki, K. *Anal. Sci.* **2008**, *24*, 571.

(6) (a) Colletier, J. P.; Royant, A.; Specht, A.; Sanson, B.; Nachon, F.; Masson, P.; Zaccai, G.; Sussman, J. L.; Goeldner, M.; Silman, I.; Bourgeois, D.; Weik, M. *Acta Crystallogr. D* **2007**, *63*, 1115. (b) Bourgeois, D.; Royant, A. *Curr. Opin. Struct. Biol.* **2005**, *15*, 538. (c) Srajer, V.; Teng, T.-Y.; Ursby, T.; Pradervand, C.; Ren, Z.; Adachi, S.-I.; Schildkamp, W.; Bourgeois, D.; Wulff, M.; Moffat, K. *Science* **1996**, *274*, 1726. (d) Schlichting, I.; Almo, S. C.; Rapp, G.; Wilson, K.; Petratos, K.; Lentfer, A.; Wittinghofer, A.; Kabsch, W.; Pai, E. F.; Petsko, G. A.; Goody, R. S. *Nature* **1990**, *345*, 309.

(7) (a) Specht, A.; Goeldner, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2008. (b) Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2161. (c) Watanabe, S.; Sueyoshi, T.; Ichihara, M.; Uehara, C.; Iwamura, M. *Org. Lett.* **2001**, *3*, 255.

(8) (a) Corrie, J. E. T.; Barth, A.; Munasinghe, V. R. N.; Trentham, D. R.; Hutter, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 8546. (b) Il'ichev, Y. V.; Schworer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581.

(9) (a) Sheehan, J. C.; Wilson, R. M.; Oxford, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 7222. (b) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W., III; Xue, J.-y.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001.

(10) (a) Givens, R. S.; Park, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6259. (b) Givens, R. S.; Weber, J. F. W.; Conrad, P. G., II; Orosz, G.; Donahue, S. L.; Thayer, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 2687.

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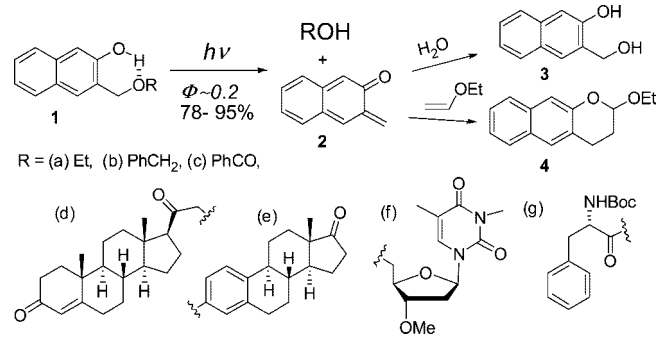
groups, making them unsuitable for the direct caging of alcohols.[12] The quantum and chemical yield of alcohol photorelease can be substantially improved by the introduction of a carbonate linker between the substrate and the cage.[13] In this case, however, the relatively slow dark decarboxylation of a mono carbonate becomes the rate-determining step of the alcohol release.[14] Photoremovable protecting groups based on photoinduced electron transfer often allow for the efficient deprotection of alcohols but require the addition of a sensitizer and/or an electron donor.[15] In our search for PPGs suitable for the direct caging of alcohols, we decided to explore the utility of photochemical dehydration of *o*-hydroxybenzyl alcohols.[16] Phenols and naphthols are known to be substantially more acidic in the excited state than in the ground state.[17] Their photoacidity allows for protonation of weakly basic sites in the molecule, a process that is known as excited-state intramolecular proton transfer (ESIPT).[18] ESIPT from phenols to oxygen,[19] nitrogen,[20] and even sp^2-hybridized carbon[21] is well documented. Zwitterionic species produced as a result of ESIPT are short-lived and rapidly undergo reverse proton transfer to regenerate starting material. However, ESIPT to the hydroxyl group in *o*-hydroxybenzyl alcohol or its derivatives is accompanied by C−O bond cleavage and the formation of an *o*-quinone methide.[16,22] *o*-Quinone methides are very reactive species and readily add nucleophiles or react with electron-rich alkenes to form Diels−Alder adducts.[16,23] The formation of an *o*-quinone methide is usually complete within a nanosecond laser pulse.[16] Since the *o*-hydroxybenzyl chromophore has little absorbance above 250 nm, we have focused our attention on its naphthalene analog (**3**).

Here we report that photolysis of (3-hydroxy-2-naphthalenyl)methyl-caged alcohols (**1a,b,d,g**), phenols (**1e**), and carboxylic acids (**1c,f**) results in efficient release of the substrates

SCHEME 1



(Scheme 1). 2-Naphthoquinone-3-methide (**2**) formed in this reaction undergoes rapid hydration to the parent diol **3** or is trapped as a Diels−Alder adduct with ethyl vinyl ether **4**.

Results and Discussion

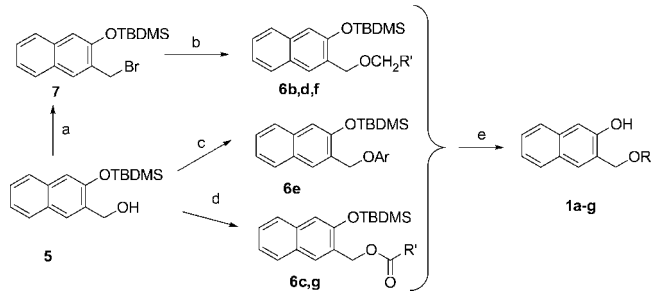
Synthesis of (3-Hydroxy-2-naphthalenyl)methyl-Caged Compounds. Simple esters and ethers of type **1** can be prepared by the direct reaction of an acid[24] or alcohol[24b] with 3-hydroxy-2-naphthalenemethanol (**3**). For caging of more complex substrates, where the use of large excesses of reagents becomes impractical, we have employed mono-TBDMS-protected diol **5** as a caging reagent (Scheme 2).

(3-Hydroxy-2-naphthalenyl)methyl carboxylates **6c,g** were prepared in a good yield by either the direct acylation of **5** with an acid chloride in the presence of pyridine (**6c**) or by a DCC/DMAP-promoted esterification of a free acid with **5** (**6g**). Aryl ether **6e** was synthesized by the coupling of estrone and **5** under modified Mitsunobu conditions. For the caging of alcohols, **5** was converted into bromide **7**, which was then reacted with target alcohols in the presence of silver triflate and di-(*tert*-butyl)pyridine to produce ethers **6b,d,f**. The conventional TBAF/THF treatment of **6b−f** resulted in clean deprotection to give caged compounds **1b−f** (Scheme 2).

Photophysical and Photochemical Properties of (3-Hydroxy-2-naphthalenyl)methyl-Caged Compounds. The UV spectra of derivatives **1a−f** are similar to that of the parent 3-hydroxy-2-naphthalenemethanol (**3**, Figure 1). In aqueous acetonitrile, two major absorption bands are observed above 250 nm: at $\lambda_{max} = 276$ nm ($\log \varepsilon = 3.76$) and at $\lambda_{max} = 327$ nm ($\log \varepsilon = 3.38$). It is interesting to note that this chromophore also shows strong fluorescence ($\lambda_{em} = 360$, 423 nm, $\Phi_{Fl} = 0.230 \pm 0.002$). This property can be used to monitor the distribution of caged substrates in various media. The release of the substrate from compounds **1a−f** apparently proceeds via formation of the intermediate 3-methylene-2(3H)-naphthalenone (*o*-quinone methide **2**, Scheme 1). To test this mechanism, we have employed ethyl vinyl ether as a polar dienophile to trap **2** as a Diels−Alder adduct. Irradiation of a 1 mM solution of parent diol **3** in aqueous acetonitrile (1:1 v/v) in the presence of 10 mM ethyl vinyl ether results in the efficient formation of 2-ethoxy-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran **4** in 87% preparative and 96% analytical yield (by HPLC, Scheme 1). It is important to note that **4** is formed almost quantitatively despite a large excess of nucleophilic solvent (28 vs 0.01 M). Adduct

(11) (a) Chamberlin, J. W. *J. Org. Chem.* **1966**, *31*, 1658. (b) Schönleber, R. O.; Bendig, J.; Hagen, V.; Giese, B. *Bioorg. Med. Chem.* **2002**, *10*, 97. (c) Furuta, T.; Hirayama, Y.; Iwamura, M. *Org. Lett.* **2001**, *3*, 1809.
(12) (a) Misetic, A.; Boyd, M. K. *Tetrahedron Lett.* **1998**, *39*, 1653. (b) Coleman, M. P.; Boyd, M. K. *Tetrahedron Lett.* **1999**, *49*, 7911.
(13) (a) Loudwig, S.; Maurice, G. *Tetrahedron Lett.* **2001**, *45*, 7957. (b) Suzuki, A. Z.; Watanabe, T.; Kawamoto, M.; Nishiyama, K.; Yamashita, H.; Ishii, M.; Iwamura, M.; Furuta, T. *Org. Lett.* **2003**, *5*, 4867. (c) Pirrung, M. C.; Bradley, J.-C. *J. Org. Chem.* **1995**, *60*, 1116.
(14) (a) Papageorgiou, G.; Barth, A.; Corrie, J. E. T. *Photochem. Photobiol. Sci.* **2005**, *4*, 216. (b) Literak, J.; Wirz, J.; Klan, P. *Photochem. Photobiol. Sci.* **2005**, *4*, 43.
(15) (a) Banerjee, A.; Lee, K.; Falvey, D. E. *Tetrahedron* **1999**, *55*, 12699. (b) Jones, P. B.; Pollastri, M. P.; Porter, N. A. *J. Org. Chem.* **1996**, *61*, 9455. (c) Falvey, D. E.; Sundararajan, C. *Photochem. Photobiol. Sci.* **2004**, *3*, 831.
(16) (a) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369. (b) Wan, P.; Brousmiche, D. W.; Chen, C. Z.; Cole, J.; Lukeman, M.; Xu, M. *Pure Appl. Chem.* **2001**, *73*, 529. (c) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9854. (d) Leo, E. A.; Delgado, J.; Domingo, L. R.; Espinos, A.; Miranda, M. A.; Tormos, R. *J. Org. Chem.* **2003**, *68*, 9643.
(17) (a) Lahiri, S. C. *J. Sci. Ind. Res.* **1979**, *38*, 492. (b) Vander Donckt, E. *Prog. React. Kinet.* **1970**, *5*, 273. (c) Ireland, J. F.; Wyatt, P. A. H. *Adv. Phys. Org. Chem.* **1976**, *12*, 131. (d) Shizuka, H.; Tobita, S. *Mol. Supramol. Photochem.* **2006**, *14*, 37.
(18) Tolbert, L. M.; Solntsev, K. M. *Acc. Chem. Res.* **2002**, *35*, 19.
(19) (a) Cuma, M.; Scheiner, S.; Kar, T. *J. Am. Chem. Soc.* **1998**, *120*, 10497. (b) Brousmiche, D. W.; Xu, M.; Lukeman, M.; Wan, P. *J. Am. Chem. Soc.* **2003**, *125*, 12961.
(20) (a) Basaric, N.; Wan, P. *Photochem. Photobiol. Sci.* **2006**, 656. (b) Rios Vazquez, S.; Rios Rodriguez, M. C.; Mosquera, M.; Rodriguez-Prieto, F. *J. Phys. Chem. A* **2007**, *111*, 1814.
(21) (a) Lukeman, M.; Wan, P. *J. Am. Chem. Soc.* **2003**, *125*, 1164. (b) Basaric, N.; Wan, P. *J. Org. Chem.* **2006**, *71*, 2677.
(22) Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 1837.
(23) (a) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367. (b) Wang, H.; Wang, Y.; Han, K.-L.; Peng, X.-J. *J. Org. Chem.* **2005**, *70*, 4910. (c) Fischer, M.; Shi, Y.; Zhao, B.-p.; Snieckus, V.; Wan, P. *Can. J. Chem.* **1999**, *77*, 868.
(24) (a) Chen, C.-T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C.-H.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1188. (b) Ashram, M.; Miller, D. O.; Georghiou, P. E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1470.

SCHEME 2[a]



[a] Reagents and conditions: (a) CBr_4/Ph_3P or PBr_3; (b) DTBP, AgOTf, R′CH_2OH; (c) ADDP, Bu_3P, ArOH; (d) DMAP/DCC, R′CO_2H; (e) TBAF.

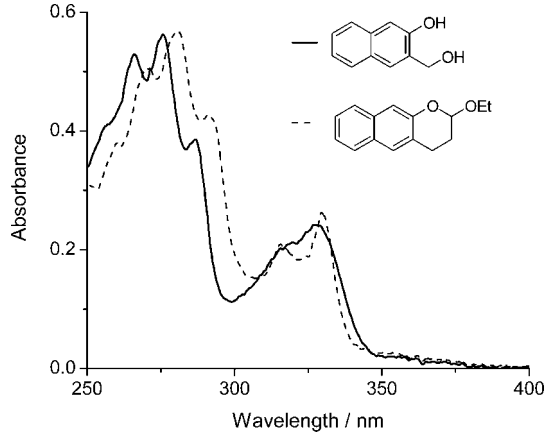


FIGURE 1. UV spectra of ca. 10^{-4} M solutions of 3-hydroxy-2-naphthalenemethanol (**3**, solid line) and adduct **5** (dashed line) in (1:1) acetonitrile−water.

4 (spectrum is shown in Figure 1) is photochemically stable and shows virtually no decomposition after prolonged exposure to UV light.

The rate of substrate release from caged compound **1a** has been studied using nanosecond kinetic spectroscopy. Laser flash photolysis of **1a** in aqueous solution allowed us to detect the rapid formation (k_{obs} = (8.03 ± 0.04) × 10^4 s^{-1}) and then somewhat slower decay (k_{obs}= 135 ± 7 s^{-1}) of an intermediate by the growth and decay of absorbance at 310 nm. While the first process is not affected by the presence of ethyl vinyl ether, the rate of the transient decay was linearly proportional to the concentration of the dienophile (k_{quench} = (4.07 ± 0.32) ×10^4 $M^{-1}s^{-1}$). This observation allowed us to identify this intermediate as *o*-quinone methide **2**. Since the release of a caged substrate happens before or simultaneously with the formation of **2**, we can set the lower limit for the rate of the uncaging reaction at 10^5 s^{-1}.

Substrate Release from 1a−f. (3-Hydroxy-2-naphthalenyl)-methyl-caged compounds **1a−f** are stable in the dark or under ambient light in the pure form, as well as in THF, aqueous acetonitrile, or methanol solutions. Compounds **1a−f** were irradiated at 254 and/or 300 nm using a Rayonet photoreactor in water-containing solvent mixtures. The presence of water was necessary to trap the *o*-quinone methide intermediate **2** formed upon deprotection (Scheme 1). The release of the substrates was followed by HPLC and quantum yields of uncaging were measured using chemical actinometry[25] (Table 1). Photolysis of (3-hydroxy-2-naphthalenyl)methyl-caged substrates **1a−f** results in efficient (Φ = 0.17−0.26) deprotection, releasing substrates in good to excellent chemical yields (Table 1). The quantum yield of the uncaging reaction decreases slightly at higher conversion (**1a**, Table 1). The quantum yield measurements were conducted using substrate solutions with high optical density (OD = 1.5−2) at the irradiation wavelength. During the course of the reaction, accumulation of the byproduct **3**, which has the same chromophore as the caged molecule, causes the so-called filtering effect and somewhat reduces the efficiency of photolysis. This effect becomes negligible at concentrations at or below 0.001 M.

TABLE 1. Yields and Quantum Efficiencies of Photochemical Release of Substrates from Caged Compounds 1a−g at Various Conversions

	Φ versus conversion (in parentheses)	yield in % (conversion)	yield in % with CH_2=$CHOEt$[a] (conversion)
1a	0.19 ± 0.03[b,c] (5%)	95 ± 5[b,c,f] (5%)	96 ± 1[b,d,g] (91%)
	0.173 ± 0.006[b,c] (11%)	95 ± 1[b,c,f] (11%)	
	0.17 ± 0.01[b,c] (17%)	91 ± 2[b,c,f] (17%)	
	0.17 ± 0.01[d,e] (10−17%)	76 ± 1[b,c,f] (60%)	
1b	0.24 ± 0.01[d,e] (20−80%)	97 ± 4[d,e] (100%)	
1c	0.26 ± 0.01[d,e] (10−80%)	96 ± 5[d,e] (100%)	
1d	0.24 ± 0.02[b,h] (9%)	91 ± 4[b,h] (29%)	91 ± 2[b,h] (100%)
		94 ± 1[b,h] (57%)	
		86 ± 3[b,h] (97%)	
1e	0.18 ± 0.02[b,h] (22%)	96 ± 3[b,h] (22%)	92 ± 1[b,h] (98%)
		98 ± 2[b,h] (46%)	
		89 ± 3[b,h] (96%)	
1f	0.24 ± 0.004[b,h] (14%)	95 ± 1[b,h] (33%)	95 ± 1[b,h] (98%)
		94 ± 2[b,h] (62%)	
		89 ± 3[b,h] (95%)	
1g		96 ± 4[e,i] (100)%	

[a] Approximately 0.03 M ethyl vinyl ether. [b] λ_{irr} = 254 nm. [c] Approximately 6 × 10^{-4} M in water. [d] In 40% CH_3CN_{aq}. [e] λ_{irr} = 300 nm. [f] Yield of **3**. [g] Yield of **4**. [h] In CH_3CN/THF/water (4:3:3) mixture. [i] 40% $MeOH_{aq}$.

The chemical yield of the uncaging reaction is also slightly reduced at higher conversions (**1d−f**, Table 1). This effect might be caused by the photochemical reactivity of the accumulating byproduct **3** via the regeneration of reactive *o*-quinone methide **2**. We decided to avoid the formation of **3** by trapping the initially formed **2** as the photostable Diels−Alder adduct **4** (vide supra). High conversion (98−100%) photolyses of caged compounds **1d−f** in aqueous acetonitrile in the presence of a 10-fold excess of ethyl vinyl ether produced 3−6% higher yield of the target substrates and quantitative amounts of adduct **4** (**1d−f**, Table 1).

Conclusions

A novel photolabile protecting group suitable for the direct caging of alcohols, as well as carboxylic acids and phenols, has been developed. (3-Hydroxy-2-naphthalenyl)methyl-caged

(25) Murov, S. L.; Carmichael, I.; Hug, G. L. In *Handbook of Photochemistry*; Marcel Dekker: New York, 1993; p 299.

compounds have a long shelf life in the solid state and in various solvents but efficiently ($\Phi \approx 0.2$) release substrates upon 254 or 300 nm irradiation in good chemical yield. The half-lifetime of substrate release is below 10 μs. The intermediate 2-naphthoquinone-3-methide (**2**) is rapidly deactivated by hydroxylic solvents or is trapped as a photostable Diels−Alder adduct with ethyl vinyl ether.

Experimental Section

3-Hydroxy-2-naphthalenemethanol (**3**) was prepared by the $LiAlH_4$ reduction of methyl 3-hydroxy-2-naphthoate.[26]

Ethyl (3-Hydroxy-2-naphthalenyl)methyl Ether (1a).[24b] Concentrated HCl (5 mL) was added to a solution of **3** (500 mg, 0.53 mmol) in 95% ethanol (20 mL), and the reaction mixture was stirred for 10 h at room temperature and then heated for 3 h at 70−75 °C. After cooling to room temperature, the reaction mixture was poured into crushed ice, and the precipitate was separated by filtration, washed with water until the washings were neutral, and dried under vacuum. The crude product was purified by column chromatography (25% dichloromethane in hexane) to give **1a** as a white solid (348 mg, 65%). Mp 80−82 °C (lit.[24b] 80−82 °C); ^{1}H NMR (400 MHz) 1.29 (t, J = 6.8 Hz, 3H), 3.64 (q, J = 6.8 Hz, 2H), 4.86 (s, 2H), 7.25 (s, 1H), 7.30 (m, 1H), 7.40 (m, 1H), 7.53 (s, 1H), 7.7 (m, 2H), 7.78 (s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) 15.3, 66.5, 72.2, 111.2, 123.8, 125.4, 126.60, 126.64, 127.77, 127.80, 127.84, 128.6; GC-MS *m*/*z* (%) 202 (17), 157 (8), 156 (35), 129 (13), 128 (100), 127 (12), 115 (9), 102 (6), 77 (6), 64 (6), 51 (5).

Benzyl (3-Hydroxy-2-naphthalenyl)methyl Ether (1b). Di(*tert*-butyl)pyridine (164 mg, 193 μL, 0.86 mmol) and silver triflate (162 mg, 0.63 mmol) were added to the solution of benzyl alcohol (52 mg, 50 μL, 0.48 mmol) in dichloromethane (0.65 mL). The reaction mixture was cooled to 0 °C, and a solution of **7** (200 mg, 0.53 mmol) in dichloromethane (0.45 mL) was added dropwise under vigorous stirring. The reaction mixture was stirred for 1 h, diluted with dichloromethane (50 mL), washed consecutively with 10% HCl, a saturated solution of sodium bicarbonate, and brine, and dried over sodium sulfate. Solvent was removed under reduced pressure and the residue was purified using short silica gel column (3% ethyl acetate in hexane) to give 148 mg of crude benzyl (3-*tert*-butyldimethylsilyloxy-2-naphthalenyl)methyl ether (**6b**).

Tetrabutylammonium fluoride (0.44 mL of a 1 M THF solution) was added dropwise to the solution of **6b** in THF (2 mL) at 0 °C, and the mixture was stirred for 5 min and then poured into 50 mL of brine. The reaction mixture was extracted with ethyl acetate; combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed under reduced pressure, and the residue was purified by chromatography (dichloromethane) to afford 51 mg (48%) of **1b** as colorless crystals. Mp 102−104 °C. ^{1}H NMR (300 MHz) 7.69 (m, 2H), 7.53 (m, 2H), 7.45−7.20 (m, 7H), 4.87 (s, 2H), 4.61 (2H); ^{13}C NMR (75 MHz) 154.1, 136.7, 134.8, 128.7, 128.3, 128.2, 128.1, 127.8, 127.5, 126.44, 126.35, 124.7, 123.6, 111.1, 72.4, 71.4; EIMS *m*/*z*: 264 (M+, 19), 172 (5), 168 (5), 156 (45), 141 (6), 128 (20), 127 (8), 115 (15), 91 (100), 77 (12), 71 (7). FW calcd for $C_{18}H_{16}O_2$ 264.1150, EI-HRMS found 264.1150.

(3-*tert*-Butyldimethylsilyloxy-2-naphthalenyl)methyl Benzoate (6c). Benzoyl chloride (60 μL, 49 mg, 0.35 mmol) was added to the solution of **5** (100 mg, 0.35 mmol) in dry pyridine (0.7 mL), and the mixture was was stirred at room temperature for 2 h and poured into 50 mL of a saturated solution of sodium bicarbonate. The resulting suspension was extracted with ethyl acetate; combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed under vacuum, and the residue was purified by chromatography (20% of ethyl acetate in hexanes) to afford 120 mg (90%) of **6c** as a yellowish oil. ^{1}H NMR (300 MHz) 8.13 (m, 2H), 7.91 (s, 1H), 7.79 (d, J = 8.67 Hz, 1H), 7.71 (d, J = 7.56 Hz, 1H), 7.57 (m, 1H), 7.50−7.40 (m, 3H), 7.35 (m, 1H), 7.21 (s, 1H), 5.57 (s, 2H), 1.07 (s, 9H), 0.36 (s, 6H); ^{13}C NMR (75 MHz) 166.5, 152.0, 134.4, 132.9, 130.4, 126.7, 129.3, 128.8, 128.3, 128.2, 127.8, 126.4, 126.3, 124.0, 113.3, 63.0, 25.8, 18.3, −4.2; MS *m*/*z*: 394 (M+ 2, 2), 392 (M+, 5), 337 (8), 336 (23), 335 (100), 255 (5), 230 (12), 229 (16), 216 (5), 215 (58), 200 (10), 199 (42), 185 (19), 179 (56), 155 (9), 153 (10), 142 (16), 139 (17), 128 (42). FW calcd for $C_{18}H_{28}O_3Si$ 392.1808, EI-HRMS found 392.1808.

(3-Hydroxy-2-naphthalenyl)methyl Benzoate (1c). Tetrabutylammonium fluoride (0.33 mL of 1 M THF solution) was added dropwise to the solution of **6c** (120 mg, 0.31 mmol) in dry THF (2 mL) at 0 °C, and the mixture was stirred for 5 min and then poured into 50 mL of brine. The reaction mixture was extracted with ethyl acetate; combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and passed through a short silica gel column to afford 75 mg (87%) of **1c** as a colorless oil. ^{1}H NMR (300 MHz) 8.08 (m, 2H), 7.90 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.57 (m, 1H), 7.50−7.38 (m, 3H), 7.36−7.28 (m, 2H), 5.56 (s, 2H). ^{13}C NMR (300 MHz) 168.4, 152.8, 135.4, 133.6, 132.0, 130.0, 129.4, 128.6, 128.5, 127.8, 127.0, 126.3, 124.1, 123.9, 112.2, 63.8; MS *m*/*z* 265 (11), 264 (44), 171 (5), 168 (7), 158 (13), 157 (23), 156 (97), 139 (5), 129 (20), 128 (92), 127 (17), 115 (23), 105 (6), 102 (5), 92 (10), 91 (100). FW calcd for $C_{18}H_{14}O_3$ 278.0943, EI-HRMS found 278.0939.

21-((3-Hydroxy-2-naphthalenyl)methyloxy)progesterone (1d). 2,6-Di-*tert*-butylpyridine (80 μL) and silver triflate (64 mg) were added to a solution of 21-hydroxyprogesterone (40 mg, 0.12 mmol) in 1 mL of dichloromethane. The resulting suspension was cooled to 0 °C, and **7** (80 mg, 0.23 mmol) in 0.5 mL of dichloromethane was added. The reaction mixture was stirred at room temperature for 2 h and diluted with dichloromethane, and solids were removed by filtration. The filtrate was filtered through a short silica gel column, and solvent was removed under vacuum. TBAF (0.5 mL 1 M in THF) was added to the solution of crude 21-((3-*tert*-butyldimethylsilyloxy-2-naphthalenyl)methyloxy)progesterone (**6d**) in 1 mL of dry THF. The mixture was stirred for 15 min at 0 °C, poured into 50 mL of brine solution, and extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography (30% ethyl acetate in hexanes) to yield 20 mg (34%) of **1d** as a colorless oil. ^{1}H NMR (400 MHz) 8.71 (s, 1H), 7.72 (m, 2H), 7.60 (m, 1H), 7.45 (m, 1H), 7.29 (m, 2H), 5.74 (s, 1H), 4.69 (m, 2H), 4.26 (m, 2H), 2.62−2.12 (m, 6H), 2.10−0.53 (m, 17H), 0.73 (s, 2H), 2.89 (m, 2H), 2.6−1.8 (m, 8H), 1.72−1.30 (m, 6H), 0.9 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) 13.6, 17.3, 21.0, 23.0, 24.5, 31.9, 32.7, 33.9, 35.5, 35.7, 38.5, 38.6, 44.8, 53.5, 56.2, 59.0, 72.1, 70.6, 111.4, 123.4, 124.0, 124.5, 126.3, 126.5, 127.6, 128.0, 128.9, 135.4, 154.3, 170.6, 199.3, 210.2; MS (DIP) *m*/*z* 486 (17), 300 (6), 299 (19), 272 (5), 271 (15), 253 (19), 172 (9), 159 (5), 158 (19), 157 (100), 156 (38), 129 (15), 128 (37), 105 (10), 91 (17), 79 (12), 77 (10), 55 (24); FW calcd for $C_{32}H_{38}O_4$ 486.2770, EI-HRMS found 486.2774.

***O*-(3-Hydroxy-2-naphthalenyl)methyl)estrone (1e).** 1,1′-(Azodicarbonyl)dipiperidine (225 mg, 0.89 mmol) was added to a solution of 0.23 mL of tributylphosphine in dry toluene (6 mL) at 0 °C and stirred for 1 h. A solution of estrone (165 mg, 0.61 mmol) and **5** (390 mg, 1.35 mmol) in 1:1 toluene and THF was added dropwise to the reaction mixture over 15 min at 0 °C, and the mixture was stirred for 1 h, kept at −15 °C for 48 h, poured into 40 mL of pentane, and stirred for 1 h at 0 °C. Solids were removed by filtration, and solvents were removed under reduced pressure. Crude *O*-(3-*tert*-butyldimethylsiloxy-2-naphthalenyl)methyl)estrone (**6e**) was redissolved in ethyl acetate and passed through a short silica gel column, the solvent was removed by evaporation, and

(26) Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819.

the residue was taken up in dry THF (2 mL). TBAF (0.5 mL of THF 1 M) was added to the solution of **6e**, stirred for 5 min, and poured into 30 mL of brine. The reaction mixture was extracted by ethyl acetate; the combined organic layers were washed with brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. Crude **1e** was purified by chromatography (25% of ethyl acetate in hexanes) to yield 145 mg (50%) of **7** as a pale yellow oil. ^{1}H NMR (400 MHz) 7.74−7.77 (m, 3H), 7.70 (d, 8.4 Hz), 7.45 (m, 1H), 7.35 (m, 1H), 7.28 (s, 1H), 7.23 (d, 8.4 Hz), 6.86 (dd, 8.8 Hz, 2.8 Hz, 1H), 6.81 (d, 2.8 Hz, 1H), 6.6 (s, 1H), 5.38 (s, 2H), 2.89 (m, 2H), 2.6−1.8 (m, 8H), 1.72−1.30 (m, 6H), 0.9 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 13.8, 21.5, 25.4, 26.4, 29.6, 31.5, 35.9, 38.2, 43.9, 48.0, 50.4, 68.6, 110.9, 112.6, 115.3, 124.7, 124.8, 126.5, 126.8, 126.8, 127.9, 128.4, 128.8, 133.3, 134.6, 138.0, 153.0, 155.9, 220.1; DIP-MS *m*/*z* 426 (M, 47), 283(8), 261 (4), 157 (100), 144 (7), 128 (29), 115 (4), 97 (4), 77 (4), 45 (4); HRMS: 426.2195; FW calcd for $C_{29}H_{30}O_3$ 426.2195, EI-HRMS found 426.2195.

5′-*O*-(3-Hydroxy-2-naphthalenyl)methyl-3′-*O*-3-dimethylthymidine (1f). 2,6-Di-*tert*-butylpyridine (200 μL, 0.89 mmol) and silver triflate (150 mg, 0.58 mmol) were added to the solution of 3′-*O*-3-dimethylthymidine (**8**, 110 mg, 0.41 mmol) in dichloromethane (2 mL) and cooled to 0 °C, and **7** (230 mg, 0.66 mmol) in dichloromethane (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and diluted with dichloromethane (20 mL), and the solids were removed by filtration. The filtrate was passed through a short silica gel column, and the solvent was removed under reduced pressure to produce 150 mg of crude 5′-*O*-(3-*tert*-butyldimethylsiloxy-2-naphthalenyl)methyl-3′-*O*-3-dimethylthymidine (**6f**). DIP-MS *m*/*z*: 540 (5), 501 (3), 483 (8), 353 (13), 311 (20), 296 (5), 281 (8), 271 (15), 255 (5), 229 (16), 215 (51), 199 (8), 185 (5), 176 (11), 156 (5), 141 (21), 131 (20), 111 (9), 81 (100), 57 (29), 55 (31), 45 (21).

TBAF (0.3 mL of 1 M THF, 0.3 mmol) was added to the solution of crude **6f** in THF (2 mL) at 0 °C. The reaction mixture was stirred for 10 min, poured into 30 mL of brine, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (50% of ethyl acetate in hexanes) to give 103 mg (60%) of **1f** as a colorless oil. ^{1}H NMR (400 MHz) 7.68−7.74 (m, 2H), 7.62 (s, 1H), 7.42−7.46 (m, 2H), 7.31−7.37 (m, 2H), 7.24 (s, 1H), 7.03 (s, 1H), 6.29−6.32 (m, 1H), 4.87−97 (m, 2H) 4.15−4.18 (m, 1H), 4.0−4.04 (m, 1H), 3.88−3.91 (m, 1H), 3.78−3.81 (m, 1H), 3.35 (s, 1H), 3.32 (s, 1H), 2.41−2.47 (m, 1H), 2.05−2.12 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 13.3, 28.1, 37.4, 57.4, 70.8, 72.5, 80.8, 83.2, 86.1, 110.5, 111.2, 124.1, 124.8, 126.5, 127.0, 127.8, 128.4, 128.6, 133.7, 135.0, 151.3, 153.5, 163.9; DIP-MS *m*/*z*: 426 (4), 296 (4), 254 (27), 236 (14), 172 (5), 157 (100), 128 (59), 81 (95), 71 (12), 57 (5), 45 (5); HRMS 426.1295; FW calcd for $C_{23}H_{26}$ N_2O_6 426.1791, EI-HRMS found 426.1785.

***N*-BOC-L-Phenylalanine (3-*tert*-Butyldimethylsilyloxy-2-naphthalenyl)methyl Ester (6g).** DMAP (14 mg, 0.11 mmol) and DCC (480 mg, 2.33 mmol) were added to a solution of *N*-BOC-L-phenylalanine (265 mg, 1 mmol) and **5** (334 mg, 1.21 mmol) in dichloromethane (7 mL), and the reaction mixture was stirred overnight at room temperature Solids were removed by filtration, the organic layer was washed with brine and dried over sodium sulfate, and solvent was removed under vacuum. The residue was purified by chromatography (10% ethyl acetate in hexanes) to afford 524 mg (98%) **6g** as a colorless oil. ^{1}H NMR (300 MHz) 7.74 (m, 2H), 7.67 (d, J = 7.7 Hz, 1H), 7.43 (m, 1H), 7.34 (m, 1H), 7.22−6.95 (m, 6H), 5.34 (s, 2H), 5.01 (d, J = 8.3 Hz, 1H), 4. 66 (dt, J = 8.3 Hz, 6.0 Hz, 5.8 Hz, 1H), 3.1 (m, 2H), 1.41 (s, 9H), 1.05 (s, 9H), 0.33 (s, 6H); ^{13}C NMR (75 MHz) 171.7, 155.0, 151.8, 135.9, 134.5, 129.9, 129.3, 128.7, 128.4, 127.8, 127.3, 126.9, 126.6, 126.5, 124.0, 113.2, 69.1, 63.1, 54.5, 38.4, 28.3, 25.7, 18.3, −4.17, −4.21; EI-MS *m*/*z* 422 (15), 404 (10), 378 (29), 350 (20), 333 (10), 332 (31), 271 (11), 246 (12), 232 (18), 231 (79), 229 (13), 220(20), 216 (20), 215 (100), 214 (17), 213 (21), 201 (13), 200 (10), 199 (39), 185 (16), 164 (13), 158 (25), 157 (38), 146 (15), 141 (38), 129 (14), 128 (53), 120 (80), 115 (10), 100 (20); FW calcd for $C_{31}H_{41}NO_5Si$ 535.2754, EI-HRMS found 535.2762.

***N*-BOC-L-Phenylalanine (3-Hydroxy-2-naphthalenyl)methyl Ester (1g).** TBAF (1 mL of 1 M THF solution, 1 mmol) was added dropwise to a solution of **6g** (426 mg, 0.98 mmol) in dry THF (4 mL). The reaction mixture was stirred at room temperature for 10 min, poured into saturated NH_4Cl solution, and extracted with ethyl acetate. Combined extracts were washed with brine and dried over sodium sulfate. The solvent was removed, and the residue was purified using a short layer of silica gel (methylene chloride) to give 404 mg (98%) of **1g** as a yellowish oil. ^{1}H NMR (300 MHz) 7.70 (m, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.41 (m, 1H), 7.31 (m, 1H), 7.23 (s,1H), 7.19−6.89 (m, 5H), 5.34 (dd, J = 33.7, 12.4 Hz, 2H), 5.07 (d, J = 7.9 Hz, 1H), 4.66 (m, 1H), 3.05 (d, J = 5.64 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz) 173.0, 155.3, 152.7, 135.4, 135.1, 131.2, 129.2, 128.4, 127.8, 127.0, 126.8, 123.73, 123.69, 111.2, 80.4, 63.8, 54.5, 38.1, 28.2, 24.6; EI-MS *m*/*z* 395 (5), 351 (6), 264 (5), 263 (19), 178 (10), 158 (18), 157 (100), 156 (10), 129 (10), 128 (18), 127 (5), 107 (22); FW calcd for $C_{25}H_{27}NO_5$ 421.1889, EI-HRMS found 421.1888.

2-Ethoxy-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran (4). A solution of **3** (50 mg, 0.29 mmol) and ethyl vinyl ether (2.8 mL, 29 mmol) in acetonitrile−water (1:1, 290 mL) was irradiated at 254 nm in mini-Rayonet photoreactor for 1.5 h. The photolysate was extracted with ethyl acetate and dried over sodium sulfate, and solvents were removed under vacuum. The residue was purified by chromathography (20% ethyl acetate in hexane) to give 57 mg (87%) of **4** as a colorless oil. ^{1}H NMR (400 MHz) 7.69 (m, 2H), 7.55 (s, 1H), 7.69 (d, 8.3 Hz, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.23 (s, 1H), 5.38 (t, 2.8 Hz, 1H), 3.89 (m, 1H), 3.64 (m, 1H), 3.21 (m, 1H), 2.87 (m, 1H), 2.15 (m, 2H), 1.10 (t, 7.0 Hz, 3H); ^{13}C NMR (100 MHz) 16.0, 20.5, 27.5, 64.0, 98.0, 112.1, 123.8, 124.9, 125.6, 126.6, 127.3, 127.79, 127.83, 129.2, 133.7, 152.0; EI-MS *m*/*z* 229(18), 228(100), 183 (20), 182 (39), 181 (33), 154 (11), 153 (11), 152 (11), 128 (36), 115 (12), 102 (5), 89 (4); FW calcd for $C_{15}H_{16}O_2$ 228.1150, EI-HRMS found 228.1147.

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Supporting Information Available: General experimental methods, detailed preparative procedures for caging reagents **5** and **7**, as well as 3′-*O*-3-dimethylthymidine (**8**); copies of ^{1}H and ^{13}C NMR spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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