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2,5-Dihydroxybenzyl and (1,4-Dihydroxy-2-naphthyl)methyl, Novel Reductively Armed Photocages for the Hydroxyl Moiety

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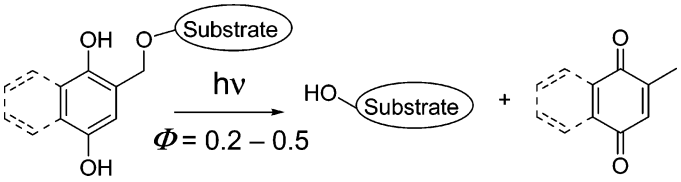

Irradiation of alcohols, phenols, and carboxylic acids "caged" with the 2,5-dihydroxybenzyl group or its naphthalene analogue results in the efficient release of the substrate. The initial byproduct of the photoreaction, 4-hydroxyquinone-2-methide, undergoes rapid tautomerization into methyl *p*-quinone. The UV spectrum of the latter is different from that of the caging chromophore, thus permitting selective irradiation of the starting material in the presence of photochemical products. These photoremovable protecting groups can be armed in situ by the reduction of photochemically inert *p*-quinone precursors.

Introduction

Photolabile protecting groups (PPG), known as "cages" in biochemistry, allow for the spatial and temporal control of substrate release, as well as "reagentless" deprotection.[1−3] PPGs have found numerous applications in biochemistry,[3] organic synthesis,[1,2] fabrication of high-density probe arrays (aka biochips),[4] and time-resolved X-ray crystallography.[5] To exploit benefits of photochemical deprotection, the caging group should comply with the following requirements: high quantum and chemical yields, as well as a fast rate of substrate release; substantial absorbance above 300 nm; and good dark stability. Byproducts of the uncaging reaction should ideally be transparent at the wavelength of irradiation and possess low reactivity.

Among common functional groups, alcohols are one of the most difficult functionalities to cage. Several examples of successful release of alcohols and carbohydrates caged with *o*-nitrobenzyl-based PPGs have been reported.[2,6] However, substrate release can take minutes after irradiation since this reaction proceeds via several slow dark steps.[7] Other common PPGs, such as 3′,5′-dimethoxybenzoin,[8] *p*-hydroxyphenacyl,[9] and a family of cages utilizing photochemical heterolysis of the C−O bond,[10] allow for the rapid release of a substrate but work well only with good leaving groups and are rarely suitable for the direct caging of alcohols.[11] The quantum and chemical

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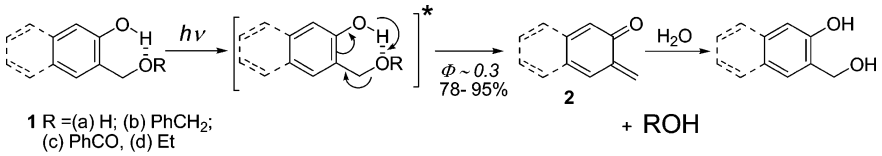
SCHEME 1



1 R =(a) H; (b) $PhCH_2$; (c) PhCO, (d) Et

2

yield of alcohol photorelease can be improved substantially by the introduction of a carbonate linker between the substrate and the cage.[12] In this case, however, the relatively slow dark decarboxylation of a monocarbonate becomes the rate-determining step of the alcohol release.[13] 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.[14]

Our group is interested in developing new PPGs based on the photochemistry of *o*-hydroxybenzyl ethers and esters. *o*-Hydroxybenzyl alcohol and its derivatives lose water upon irradiation, generating reactive *o*-quinone methides.[15] The formation of the *o*-quinone methide is usually complete within the nanosecond laser pulse. It apparently proceeds via the excited-state proton transfer, accompanied by a concerted C−O bond cleavage (Scheme 1). Recently, we have shown that ethers and esters of (3-hydroxymethyl)naphthalen-2-ol (**1**) efficiently release the corresponding hydroxy compounds upon irradiation (Scheme 1).[16] (3-Hydroxymethyl)naphthalen-2-ol was chosen over *o*-hydroxybenzyl alcohol because it allows for the use of longer irradiation wavelengths for deprotection.

In aqueous solvents, intermediate *o*-quinone methide **2** rapidly adds water to form the parent diol **1a**. The transient **2** has a microsecond life time in wholly aqueous solution.[15] This cage is well-suited for the time-resolved release of hydroxyl compounds in aqueous media. Under steady-state irradiation, however, accumulation of (3-hydroxymethyl)naphthalen-2-ol (**1a**), which has the same chromophore as the caged compound, causes the filtering effect and reduces yields of deprotection.

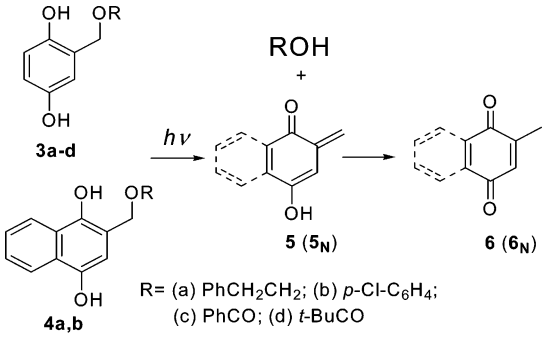
To alleviate this problem, we have designed a new PPG, 2,5-dihydroxybenzyl (**3**, Scheme 2). The 4-hydroxy-1-quinone-2-methide intermediate **5**, formed upon deprotection of the substrate, undergoes rapid tautomerization to stable 2-methyl-1,4-benzoquinone (**6**). The UV spectrum of the latter is significantly different from that of **3**, allowing for selective irradiation of the caged compound even at higher substrate concentrations (Figure 1). The photochemical properties of the naphthalene analogue of **3** have been also explored (**4**, Scheme 2).

Results and Discussion

2,5-Dihydroxybenzyl-caged 2-phenylethanol (**3a**), as well as benzoic (**3c**) and pivalic (**3d**) acids, was prepared by the reduction of corresponding quinones **7a**,**c**,**d** with sodium dithionite in a biphasic chloroform−water system (Scheme 3).

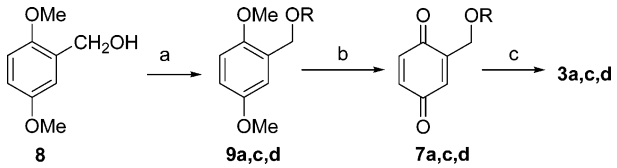
Direct acylation of the starting 2,5-dimethoxybenzyl alcohol (**8**), which was prepared from commercially available 2,5-dimethoxybenzaldehyde,[17] afforded esters **9c**,**d** in good yield. For the synthesis of ether **9a**, alcohol **8** was first converted into

SCHEME 2



3a-d **5 (5_N)** **6 (6_N)** **4a,b**

SCHEME 3 [a]



8 **9a,c,d** **7a,c,d**

[a] Reagents and conditions: (a) R = $PhCH_2CH_2$: (i) HBr (aq) 91%; (ii) $PhCH_2CH_2OH$, NaH, THF 85%; R = PhCO: PhCOCl, CH_2Cl_2, pyridine 81%; R = *t*-BuCO: *t*-BuCOCl, CH_2Cl_2, pyridine 84%; (b) CAN, CH_3CN, 71−87%; (c) $Na_2S_2O_4$, $H_2O/CHCl_3$ 90−99%.

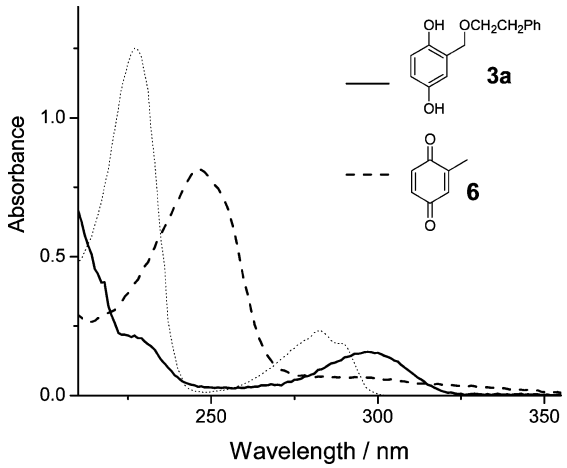


FIGURE 1. UV spectra of ca. 5×10^{-5} M methanol solutions of caged 2-phenylethanol **3a** (solid line), methylbenzoquinone (**6**, dashed line), and *p*-chlorophenol (dotted line).

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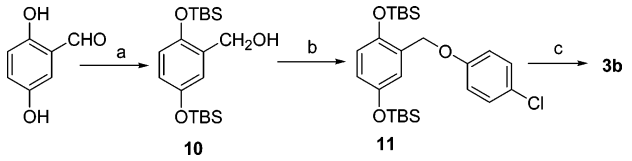
2,5-dimethoxybenzyl bromide, which was then reacted with sodium 2-phenylethoxide in THF. 2,5-Dimethoxybenzyl derivatives **9a**,**c**,**d** were converted into the corresponding quinones **7a**,**c**,**d** by oxidation with cerium ammonium nitrate (CAN).[18]

p-Chlorophenol was caged using a different approach: bis-TBDMS-protected 2,5-dihydroxybenzyl alcohol (**10**) was prepared by TBDMS protection and subsequent sodium borohydride reduction of 2,5-dihydroxybenzaldehyde (Scheme 4). Alcohol **10** was coupled with *p*-chlorophenol under modified Mitsunobu conditions.[19] TBAF-promoted deprotection of the resulting hydroquinone (**11**) produced 2-(4-chlorophenoxymethyl)-1,4-benzohydroquinone (**3b**) in a good yield.

SCHEME 4 [a]



[a] Reagents and conditions: (a) (i) TBDMSCl, imidazole, DMF; (ii) $NaBH_4$, MeOH 79%; (b) *p*-ClC_6H_4OH, ADDP, *n*-Bu_3P, benzene 98%; (c) TBAF, THF 88%.

2,5-Dihydroxybenzyl-caged compounds **3a**−**d** are stable in the dark in neat form, as well as in acetonitrile−water or methanol solutions. UV spectra of these compounds exhibit a characteristic band of the 2,5-dihydroxybenzyl group at λ_{max} = 297 nm. The expected product of the uncaging reaction, methyl *p*-benzoquinone (**6**), on other hand, has little absorption at this wavelength (Figure 1).

Irradiation of ca. 0.001 M solutions of compounds **3a**−**d** in various solvents using 300 nm light resulted in the rapid bleaching of 297 nm band and the formation of a new band at 246 nm, which corresponds to methyl *p*-benzoquinone (**6**, Figure 2). The release of substrates was monitored by HPLC or GC, while the quantum yields of uncaging were calculated using chemical actinometry[20] (Table 1).

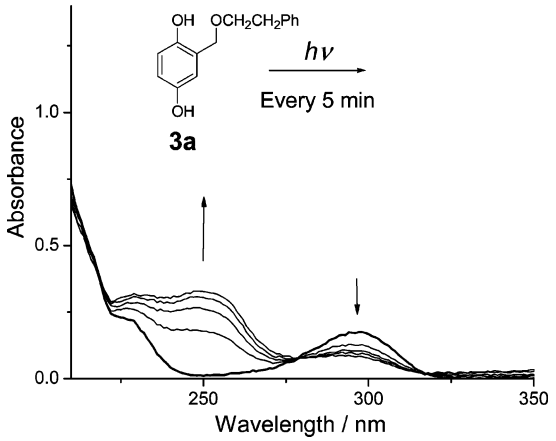


FIGURE 2. Photolysis of 5×10^{-5} M methanol solutions of **3a**.

Photodeprotection of 2,5-dihydroxybenzyl-caged substrates is quite efficient ($\Phi_{300\ nm}$ = 0.2−0.5), with the exception of benzoic acid. We believe that relatively low quantum and chemical yields of substrate release from **3c** can be explained by energy transfer from the caging chromophore to the benzoate moiety. Pivalic acid, for which such process is not viable, was deprotected quantitatively. Yield of *p*-chlorophenol at complete consumption of **3b** was in the range of 50−60%, and HPLC analysis of the reaction mixture indicated the presence of numerous minor byproducts. This can be explained by secondary photochemical decomposition of the phenol since its longer wavelength band (λ_{max} = 290 nm, dotted line in Figure 1) overlaps with emission of the source. In fact, the yield of *p*-chlorophenol at 40% conversion of **4b** was above 80% (Table 1).

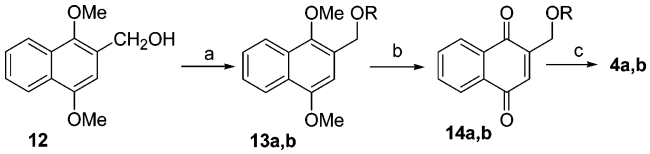
TABLE 1. Photochemical Release of Substrates from Caged Compounds 3a−d and 4a,b

	solvent	$\lambda_{irradiation}$ (nm)	Φ (%)	yield of the substrate (%)	yield of quinone **6** or $\mathbf{6_N}$ (%)
3a	MeOH	300	19	79	28
	$MeCN/H_2O$[a]	300	30	80	traces
3b	MeOH	300	31	49	14
	$MeOH/H_2O$[a]	300	50	58 (84)[b]	26
3c	MeOH	300	6	59	21
	$MeCN/H_2O$[a]	300	11	55	traces
3d	H_2O	300	31	quantitative	traces
4a	MeOH	300	31	99	43
	MeOH	350	29	94	35
	$MeCN/H_2O$[a]	300	20	87	traces
	$MeCN/H_2O$[a]	350	25	70	traces
4b	MeOH	350	7	85	traces

[a] 1/1 ratio. [b] 40% conversion.

In an attempt to shift the absorbance of the caging chromophore to longer wavelengths, we have explored photochemical properties of the naphthalene analogue of 2,5-dihydroxybenzyl cage. Preparation of (1,4-dihydroxy-2-naphthyl)methyl-caged 2-phenylethanol (**4a**) and *p*-chlorophenol (**4b**) was similar to the synthesis of **3a** (Scheme 5).

SCHEME 5 [a]



[a] Reagents and conditions: (a) (i) CBr_4, PPh_3, CH_3CN; (ii) R = $PhCH_2CH_2$: BuLi, 2-phenylethanol, THF 63%; or R = *p*-ClC_6H_4: Na_2CO_3, *p*-chlorophenol, THF 92%; (b) CAN, CH_3CN, 87−92%; (c) $Na_2S_2O_4$, H_2O/$CHCl_3$ 90−92%.

1,4-Dimethoxy-2-naphthylmethanol (**12**), which was prepared from 1,4-dihydroxy-2-naphthoic acid,[21] was treated with carbon tetrabromide in the presence of triphenylphosphine to give 2-bromomethyl-1,4-dimethoxynaphthalene. Reaction of the latter with 2-phenylethoxide or *p*-chlorophenolate in THF produced ethers **13a** or **13b**, respectively. Quinones **14a**,**b** were obtained by oxidative deprotection of the methoxy groups in **13a**,**b** and then reduced to target hydroquinones **4a**,**b** with sodium dithionite (Scheme 5).

The absorbance of the (1,4-dihydroxy-2-naphthyl)methyl chromophore extends up to 400 nm, allowing for the use of longer wavelengths for uncaging than in the case of the 2,5-dihydroxybenzyl chromophore (Figure 3). Irradiation of **4a** at either 300 or 350 nm results in bleaching of the starting material

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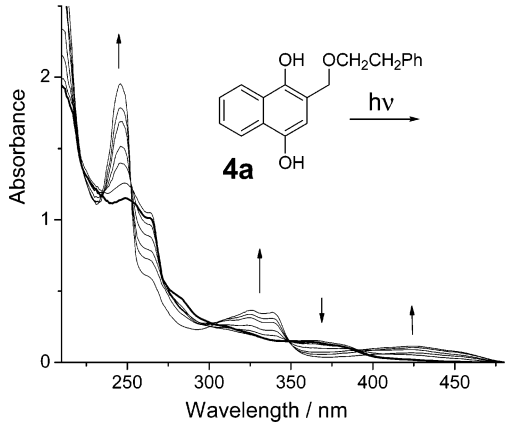

FIGURE 3. UV spectra of 5×10^{-5} M methanol solutions of **4a** recorded after 0, 1, 3, 5, 7, 10, and 15 min of irradiation.

(Figure 3) and efficient deprotection of the substrate (Table 1). In aqueous acetonitrile, release of 2-phenylethanol is almost quantitative, while yields are slightly lower in methanol. Photolysis of (1,4-dihydroxy-2-naphthyl)methyl-caged *p*-chlorophenol **4b** at 350 nm regenerated the substrate in 85% yield at full conversion. This result supports the suggestion that poor yield of *p*-chlorophenol in high conversion photolysis of **3b** is due to secondary photochemical transformations of the substrate (Table 1).

Overall, irradiation of (1,4-dihydroxy-2-naphthyl)methyl-caged substrates produces somewhat higher yields of substrate release than 2,5-dihydroxybenzyl-protected hydroxy compounds (Table 1). However, the former are less stable and undergo slow decomposition in aqueous solutions and in the solid state under ambient conditions. We are currently exploring analogues of **4a** with various substituents on the naphthalene ring in an attempt to enhance the stability of (1,4-dihydroxy-2-naphthyl)-methyl-caged compounds.

Naphthoquinone precursors **14a**,**b**, on the other hand, are perfectly stable in solution and in the solid state. The photochemical stability of quinones **7a**,**c**,**d** and **14a**,**b** is also noteworthy. Irradiation of these compounds at 300 or 350 nm for the period of time required for the complete consumption of **3a**,**c**,**d** and **4a**,**b** does not result in any detectable decomposition of quinones or release of the caged substrates. Since quinones **7a**,**c**,**d** and **14a**,**b** are quantitatively reduced to target hydroquinones **3a**,**c**,**d** and **4a**,**b** under very mild conditions, stable protecting groups in **7** and **14** can be "armed" in situ by using a suitable reducing agent.

The release of hydroxy compounds from caged precursors **3a**−**d** and **4a**,**b** is accompanied by pronounced bleaching, but expected 2-methyl benzoquinone (**6**) is formed in surprisingly low yield (Table 1). To test whether **6** undergoes subsequent photoconversion under steady-state irradiation, we have conducted preparative photolyses of **3a** under various conditions. Irradiation of **3a** in the flow photoreactor[22] allowed us to achieve complete conversion of the starting material but limit exposure of the photoproducts. Only methyl *p*-quinone (**6**) and 2,5-dihydroxybenzyl methyl ether **15**, along with 2-phenylethanol, were isolated from the photolysate. Ether **15** is apparently formed by a competitive nucleophilic addition of methanol to the transient quinone methide **5** (Scheme 6).

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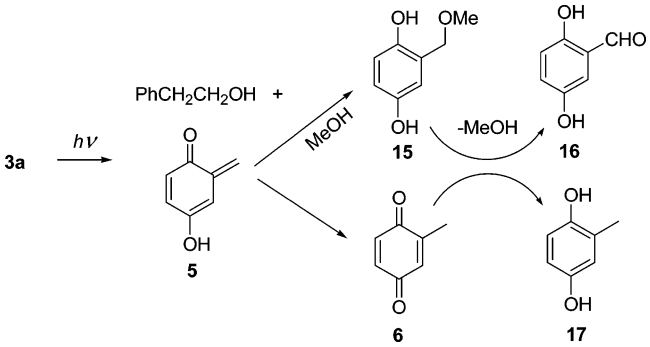
SCHEME 6



In a sharp contrast with a previous experiment, the reaction mixture did not contain compounds **6** or **15** after 1 h of steady-state irradiation of a methanol solution of **3a** with 450 W medium-pressure Hg lamp. 2,5-Dihydroxybenzaldehyde (**16**) and methyl-*p*-hydroquinone (**17**) were only isolated byproducts. These observations suggest that quinone **6** oxidizes methyl benzyl ether **15** to aldehyde **16** in a photochemically driven redox reaction. Quinone **6** is observed by HPLC in low conversion photolysis of **3a** in aqueous acetonitrile. However, only **16** and **17** were isolated after complete uncaging of the substrate. The faster consumption of benzoquinone (**6**) in aqueous solutions is apparently due to the fact that 2,5-dihydroxybenzyl alcohol (**3**, R = H), which is expected to be produced in the presence of water, undergoes much faster oxidation than methyl ether **15**. In fact, direct irradiation of methanol solution of **6** and 2,5-dihydroxybenzyl alcohol at 300 nm results in the formation of **16** and **17**.

Conclusions

Two novel photolabile protecting groups, 2,5-dihydroxybenzyl and (1,4-dihydroxynaphthyl)methyl, were tested for caging of various hydroxy groups. 2,5-Dihydroxybenzyl and (1,4-dihydroxynaphthyl)methyl-caged aliphatic acids, phenols, and alcohol derivatives efficiently release the substrate upon irradiation at 300 or 350 nm in a good to excellent yield. Photodeprotection is accompanied by substantial bleaching, allowing for the use of a higher substrate concentration. Alcohols can be directly caged with these PPGs without the necessity of a carbonate linker. This enhances the hydrolytic stability of caged alcohols and makes fast ($\tau < 1$ μs) release of the substrates possible. Quinone precursors of 2,5-dihydroxybenzyl and (1,4-dihydroxynaphth-2-yl)methyl cages are photochemically inert but can be quantitatively converted into photoreactive form using mild reducing agents. Our current work is focused on the mechanism and dynamics of the photorelease and on the tuning of photochemical properties of this novel class of protecting groups.

Experimental Section

General Procedure for the Conversion of Dimethoxyarenes into Quinones. 2-(Phenethyloxymethyl)-1,4-benzoquinone (7a): An aqueous solution of cerium ammonium nitrate (2.74 g, 5 mmol) was added to a solution of **9a** (231 mg, 0.77 mmol) in acetonitrile (25 mL) and stirred at room temperature for 30 min. The reaction mixture was extracted with ether; the combined organic layers were washed with brine and dried over Na_2SO_4, and solvents were removed in vacuo. Chromatographic purification (hexane/ether = 4:1) gave 148 mg (0.61 mmol, 79%) of quinone **7a** as a bright

yellow oil; **7c** yellow oil, 71%; **7d** yellow oil, 73%; **14a** yellow crystals, 87%; **14b** yellow crystals, 92%.

General Procedure for the Reduction of Quinones to Hydroquinones. 2-Phenethyloxymethylbenzene-1,4-diol (3a): A solution of sodium dithionite (870 mg, 5 mmol) in 25 mL of water was added to a solution of **7a** (128 mg, 0.53 mmol) in 25 mL of chloroform. The mixture was vigorously stirred until the complete disappearance of yellow color. One hundred milliliters of 10% aqueous ammonium chloride was added to the reaction mixture, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with 10% aqueous ammonium chloride (2 × 50 mL) and dried over Na_2SO_4, and solvents were removed in vacuo. Column chromatography (hexane/ether = 1:1) gave 128 mg (0.53 mmol, 99%) of **3a** as white solid; **3c** colorless oil, 99%; **3d** colorless oil, 97%; **4a** air-sensitive white solid, 90%; **4a** air-sensitive white solid, 92%.

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Supporting Information Available: Preparative procedures, analytical data, and ^1H 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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