Hydrolytic Stabilization of Protected *p*-Hydroxybenzyl Halides Designed as Latent Quinone Methide Precursors

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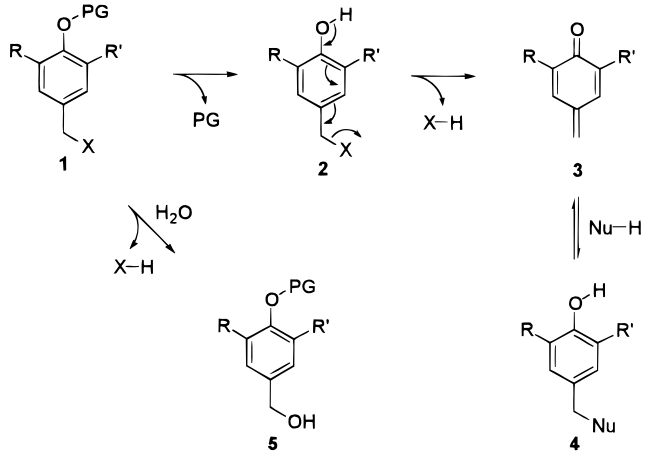
Received July 6, 1999

The hydrolysis rates of a series of protected *p*-hydroxybenzyl halides designed to generate a *p*-quinone methide through 1,6-elimination following photolytic deprotection have been investigated in order to optimize hydrolytic stability. A number of *p*-hydroxybenzyl halides containing an ether- or carbonate-linked photolabile hydroxy protecting group and a fluoride, chloride, or bromide benzylic leaving group have been synthesized. The hydrolysis rates of these derivatives in different water/acetonitrile mixtures and temperatures have been determined. The hydrolysis half-life of the benzyl bromide with the *p*-hydroxy protected as the carbonate-linked α-methylnitroveratryl (**18c)** is more than 750 times that of the ether-linked analogue (**16c**). These studies afford a Hammett σ_p^+ of +0.28 for the carbonate-linked derivatives compared to a σ_p^+ of −0.39 for the ether-linked derivatives. The theoretical hydrolysis half-life of the most stable benzyl fluoride in 100% water was sufficiently long so as to preclude extrapolation, while the chloride was approximately 50 h, and even the bromide was estimated to be nearly 5 h.

Introduction

The prolific role of reactive quinone methide intermediates in bioorganic and medicinal chemistry[1] warrants further optimization of their stability,[2] reactivity,[3] and chemoselectivity[4] for expanding applications.[5] A prevalent challenge in the application of quinone methides to bioalkylation processes is controlling the competitive hydrolysis of the reactive precursors.[6,7] In developing a research program applying quinone methides to drug delivery and biomolecular labeling,[8] we are studying various ways to control quinone methide formation for reactions in biological environments.[9] An initial objective in our investigations has been to develop a hydrolytically stable *p*-quinone methide precursor without altering the rate at which it will form the reactive quinone methide. These studies focus on optimizing the hydrolytic stability of protected *p*-hydroxy benzyl halides designed as photolabile quinone methide precursors.

Scheme 1



The most common method used to form *p*-quinone methides for bioalkylations is through 1,6-elimination of a *p*-hydroxybenzylic leaving group (**2** to **3**, Scheme 1).[6] For controlled formation of quinone methide **3**, we sought a protecting group that could be efficiently removed under relevant biological conditions. The reaction sequence would be initiated by removing the protecting group (PG) from the protected *p*-hydroxybenzyl halide **1** to form phenol **2** (Scheme 1). Subsequent 1,6-elimination of the leaving group (X) would produce quinone methide **3**. The ability to control quinone methide formation will enhance selectivity in alkylation of a target bionucleophile (Nu-H) leading to the desired alkylated product **4**.

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(4) (a) Ouyang, A.; Skibo, E. B. *J. Org. Chem.* **1998**, *63*, 1893. (b) Rokita, S. E.; Yang, J.; Pande, P.; Greenberg, W. A. *J. Org. Chem.* **1997**, *62*, 3010. (c) Mayalarp, S. P.; Hargreaves, R. H. J.; Butler, J.; O'Hare, C. C.; Hartley, J. A. *J. Med. Chem.* **1996**, *39*, 531.

(5) (a) Oded, R.; Vigalok, A.; Milstein, D. *J. Am. Chem. Soc.* **1998**, *120*, 7119. (b) Amouri, H.; Besace, Y.; Le Bras, J. *J. Am. Chem. Soc.* **1998**, *120*, 6171.

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10.1021/jo991085t CCC: $18.00
Published on Web 09/30/1999

However, the competitive pathway available to protected *p*-hydroxybenzyl halide **1** in aqueous systems is hydrolysis to form benzyl alcohol **5.** This commonly limits the efficiency of quinone methide precursors in biomolecular alkylation applications.[6,7] The rate of this competing hydrolysis pathway can be moderated by appropriate modification of the quinone methide precursor.[7]

Analysis of Hammett σ values reasonably predicts the effect of functional groups on hydrolytic stability in compounds containing benzylic leaving groups.[10] As the benzyl ring becomes more electron withdrawing, the rate of hydrolysis decreases. An analysis based on the application of Hammett σ constants leads to the conclusion that improved hydrolytic stability can be achieved when ring substituents have more positive σ values. However, improvement in hydrolytic stability of the protected *p*-hydroxybenzyl halide through increasing the electron deficiency of the phenyl ring with electron-withdrawing substituents also significantly decreases the rate of quinone methide formation. We have sought to balance these two factors in developing a versatile latent *p*-quinone methide precursor for bioalkylation.

Widlanski and co-workers have shown that the addition of a 3-nitro group (R = NO_2, R′ = H, Scheme 1) to a prostatic acid phosphatase mechanism-based inactivator related to **1** [where PG was a phosphate group (σ_p = 0.00)[11] and X was fluoride, chloride, or bromide] improved the hydrolytic stability of the protected *p*-hydroxybenzyl halide.[7a] The stabilizing effect of a 3-nitro group (σ_m = +0.71)[11] increased the hydrolysis half-life of the derivative having a fluoride leaving group (X = F, Scheme 1) from ~6 h to more than 1 month. This also allowed access to the benzylic bromide or chloride. As recognized by Widlanski and co-workers, the 3-nitro group would be expected to slow the rate of quinone methide formation.[7a] A direct application using a slight modification of the same mechanism-based inactivator to target a phosphotriesterase (where PG was a diethyl phosphate group and X was fluoride, chloride, or bromide) was accomplished by Raushel and co-workers.[3e] They also reported the inability of the fluoride and chloride derivatives to inactivate the phosphotriesterase.

Wakselman and co-workers used a coumarin derivative in their mechanism-based inactivator of α-chymotrypsin.[7b,12] In this protected *p*-hydroxybenzyl halide, the hydroxy functionality was protected as the lactone (an ester group has σ_p = +0.31 and σ_p^+ = −0.19).[11] This coumarin derivative showed sufficient hydrolytic stability to inactivate α-chymotrypsin, although the authors noted hydrolysis of the bromide derivative.[7b]

An alternative approach for reducing benzyl halide hydrolysis has been to incorporate a stabilizing substituent at the benzylic position. Withers and co-workers found the addition of a second fluoride at the benzylic position effective in reducing the hydrolytic susceptibility of a mechanism-based phosphatase inactivator related to **1** (R, R′ = H, Scheme 1), where PG was a phosphate and X was a fluoride.[7c] In studies with human prostatic acid phosphatase, the authors noted reduced hydrolysis from their benzylic difluorinated derivative compared with the monofluorinated derivative. However, they observed a reduced rate of quinone methide formation as well.[7c]

Having sought a mild method suitable for the generation of a quinone methide under biological conditions, we have pursued photolytic initiation[13] at >350 nm wavelengths.[14] The 2-nitrobenzyl and α-methylnitroveratryl protecting groups were chosen for phenolic protection of latent quinone methide precursors due to their rapid photolysis reaction rates.[15] Of these, the α-methylnitroveratryl protecting group is known to produce less reactive photolysis byproducts.[16] These photolabile protecting groups have seen widespread use in various bioorganic applications.[14,17]

We report the results of our investigations, which demonstrate the hydrolytic instability of protected *p*-hydroxybenzyl halides having an ether-linked protecting group (PG, Scheme 1) in conjunction with a bromide or chloride as the benzylic leaving group (X, Scheme 1). When the benzylic leaving group is a fluoride, the protected *p*-hydroxybenzyl halide is significantly more stable toward hydrolysis. The protected *p*-hydroxybenzyl halide having an electron-withdrawing carbonate-linked protecting group shows substantial hydrolytic stability. Importantly, the *p*-hydroxybenzyl halide protection modification reported here improves hydrolytic stability without modifying the rate at which the quinone methide will form or its ensuing electrophilic reactivity. This allows independent study of the reactivity of the quinone methide[8] for further developments in optimizing its use in bioalkylation processes.[18]

Results and Discussion

Synthesis of Protected *p*-Hydroxybenzyl Halides. Our investigations required the synthesis of a series of protected *p*-hydroxybenzyl halides with ether- and carbonate-linked photolabile protecting groups in conjunction with bromide, chloride, or fluoride leaving groups. This was accomplished as outlined in Table 1 (without optimization of yields). Commercially available 4-hydroxy-3,5-dimethylbenzaldehyde (**6**) was protected as the ether (**7**, **8**) or the carbonate (**9**, **10**) by using the corresponding benzyl bromide or chloroformate, respec-

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(11) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(12) Wakselman has recently reported the use of a related compound as a β-Lactamase inhibitor (see ref 3a).

(13) Wan and co-workers readily photogenerate quinone methides using laser flash photolysis at 266 nm (Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465.); however, this wavelength is not suitable for use in biological systems (see ref 14).

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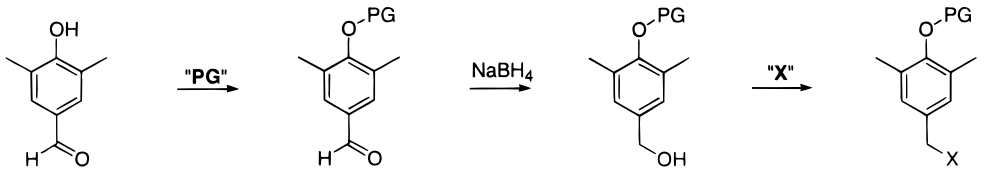
(17) (a) Kahl, J. D.; McMinn, D. L.; Greenberg, M. M. *J. Org. Chem.* **1998**, *63*, 4870. (b) Blawas, A. S.; Oliver, T. F.; Pirrung, M. C.; Reichert, W. M. *Langmuir* **1998**, *14*, 4243. (c) McGall, G. H.; Barone, A. D.; Diggelmann, M.; Fodor, S. P. A.; Gentalen E.; Ngo, N. *J. Am. Chem. Soc.* **1997**, *119*, 5081. (d) Pirrung, M. C. *Chem. Rev.* **1997**, *97*, 473. (e) Peng, L.; Wirz, J.; Goeldner, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 398. (f) Park, C.-H.; Givens, R. S. *J. Am. Chem. Soc.* **1997**, *119*, 2453. (g) Amit, B.; Hazum, E.; Fridkin, M.; Patchornik, A. *Int. J. Peptide Protein Res.* **1977**, *9*, 91.

(18) A complete account of the use of the quinone methide generated in these investigations in various alkylation processes will be reported in due course.

Table 1. Synthesis of Protected *p*-Hydroxybenzyl Halides



6 **7-10** **11-14** **15-18**

entry	aldehyde	PG[a]	protection method[b]	yield (%)	alcohol[c]	yield (%)	benzyl halide	X	halogenation method[d]	yield (%)
1	**7**	NBE	A	94	**11**	99	**15a**	F	E	79
2							**15b**	Cl	F	68
3							**15c**	Br	G	46
4	**8**	MVE	B	91	**12**	100	**16a**	F	E	59
5							**16b**	Cl	F	86
6							**16c**	Br	G	38
7	**9**	NBC	C	80	**13**	96	**17a**	F	E	48
8							**17b**	Cl	F	90
9							**17c**	Br	G	28
10	**10**	MVC	D	49	**14**	99	**18a**	F	E	63
11							**18b**	Cl	F	87
12							**18c**	Br	G	57

[a] NBE = 2-Nitrobenzyl ether; MVE = α-methylnitroveratryl ether; NBC = 2-nitrobenzyl carbonate; MVC = α-methylnitroveratryl carbonate. [b] Method A: **6**, 2-nitrobenzylbromide, K_2CO_3, DMF, rt, 3.5 h. Method B: **6**, α-methylnitroveratrylbromide, K_2CO_3, DMF, rt, 4.5 h. Method C: **6**, 2-nitrobenzylchloroformate, K_2CO_3, DMF, rt, 17 h. Method D: **6**, α-methylnitroveratryl alcohol, triphosgene, pyridine, CH_2Cl_2, −42 °C-rt, 16 h. [c] Sodium borohydride, ethanol, rt, 0.5 h. [d] Method E: DAST, CH_2Cl_2, 0 °C or room temperature, 1 h. Method F: triphosgene, pyridine, CH_2Cl_2, rt, 0.25−1 h. Method G: phosphorus tribromide, CH_2Cl_2, 0 °C or room temperature, 1−4.5 h.

tively (yields are shown in Table 1).[19] 2-Nitrobenzyl bromide is commercially available, while the α-methylnitroveratryl bromide is available in one step from the alcohol.[20] The necessary α-methylnitroveratryl alcohol was readily prepared by a two-step protocol.[21] The chloroformates required for carbonate formation are either derived from the corresponding alcohols[17c] or produced in situ during the protection step.[22] After appropriate protection of **6**, aldehydes **7**−**10** were then reduced to alcohols **11**−**14** with sodium borohydride.[23] The resulting alcohols were then transformed into the desired halides (**15**−**18**, Table 1). The fluorides **15a**−**18a** were prepared by treatment with DAST,[24] the chlorides **15b**−**18b** were readily prepared using triphosgene,[25] and the bromides **15c**−**18c** were generated using phosphorus tribromide.[20]

Hydrolysis of Protected *p*-Hydroxybenzyl Halides. The hydrolysis rates of the protected *p*-hydroxybenzyl halides (**15**−**18**) were determined by HPLC analysis in various water/acetonitrile mixtures at different temperatures. Reactions were conducted (in triplicate) by programmed addition of a 1 mM solution (50 μL) of the protected *p*-hydroxybenzyl halide in acetonitrile to 950 μL of the aqueous reaction medium (50 μM final concentration) using a temperature-controlled (±0.02 °C) automatic sample injector. All reactions were protected from light exposure. Aliquots were autoinjected at defined intervals onto a C-18 reversed-phase HPLC column. The first-order decay was followed by determining the change in the ratio of the areas of the hydrolysis product peak to the starting material peak at the λ_{max} using a photodiode array detector. All reactions were correlated with ^{1}H NMR experiments and independent HPLC analysis of authentic hydrolysis products. All experiments monitored by HPLC only showed peaks corresponding to starting benzyl halide and the corresponding benzyl alcohol hydrolysis product.

The hydrolysis rates of the protected *p*-hydroxybenzyl halides and the specific conditions under which they were determined are shown in Table 2. Two general trends are apparent: (i) the hydrolysis rates increase in the expected order fluoride < chloride < bromide and (ii) the ether-linked protected derivatives (**15**−**16**) hydrolyze significantly faster than the corresponding carbonate-linked derivatives (**17**−**18**). A change in the protecting group linker from ether to carbonate results in a marked decrease in the hydrolysis rate regardless of the specific protecting group or leaving group used. This is the anticipated result of the electron withdrawing capacity of the carbonate functional group compared to the electron-donating capacity of the ether functional group.

In the ether-linked protected compounds, a change in the protecting group from the 2-nitrobenzyl to the α-methylnitroveratryl group generally resulted in an approximate 2-fold increase in the hydrolysis rate of the protected *p*-hydroxybenzyl halide (see Table 2, Entries 1−6, **15a**−**c** vs **16a**−**c**). This may be explained by the electron donating ability of the α-methyl and the phenyl ring methoxy substituents (present only in the α-methylnitroveratryl protecting group) in competition with the electron withdrawing ability of the nitro substituent. Note that, in all of the hydrolysis reactions studied, the protecting group remained intact.

The carbonate protected precursors showed only minor correlation between hydrolysis rate and the 2-nitrobenzyl or α-methylnitroveratryl protecting group (see Table 2,

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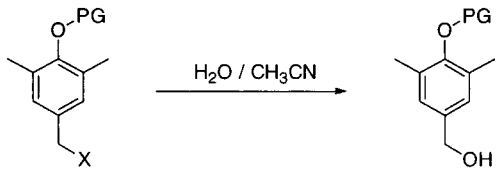
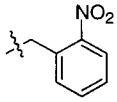
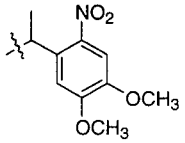
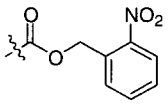
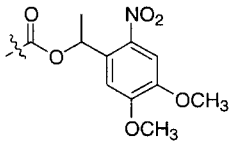
(20) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.
(21) (a) Nitration of commercially available 3,4-dimethoxyacetophenone following the procedure in ref 15c was accomplished in 63% yield. (b) Reduction of the nitro ketone following the procedure in ref 23 was accomplished in 77% yield after recrystallization from water/ethanol.
(22) Burk, R. M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395.
(23) Dai-Ho, G.; Moriano, P. S. *J. Org. Chem.* **1988**, *53*, 5113.
(24) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(25) Goren, Z.; Heeg, M. J.; Mobashery, S. *J. Org. Chem.* **1991**, *56*, 7186.

Table 2. Hydrolysis Rates (10^8k, s^{-1}) of Protected *p*-Hydroxybenzyl Halides in Different Water/Acetonitrile Mixtures and Temperatures



				water in acetonitrile (%, v/v)[a]				temperature (°C)[b]	
entry	PG	X	compound	20	40	50	60	37	55
1		F	**15a**	*c*	*c*	13	43	10	75
2		Cl	**15b**	338	3,220	7,910	24,800	5,990	48,800
3		Br	**15c**	5,470	34,200	80,800	215,000	70,300	374,000
4		F	**16a**	*c*	*d*	26	86	18	142
5		Cl	**16b**	787	6,180	14,300	41,300	10,400	85,900
6		Br	**16c**	10,200	49,400	127,000	292,000	120,000	616,000
7		F	**17a**	*c*	*c*	*c*	*c*	*c*	*c*
8		Cl	**17b**	*c*	*d*	17	41	25	159
9		Br	**17c**	78	250	491	913	522	3,500
10		F	**18a**	*c*	*c*	*c*	*c*	*c*	*c*
11		Cl	**18b**	*c*	*c*	18	37	20	191
12		Br	**18c**	81	245	467	836	504	3,160

[a] Measurements were made at 30 °C in a 50 μM solution. [b] Measurements were made in a 50 μM solution of 40% water in acetonitrile (v/v). [c] No evidence of hydrolysis was detected after 4−6 days. [d] Less than 3% hydrolysis was detected after 4 days.

entries 7−12, **17a**−**c** vs **18a**−**c**). On average, the rates of hydrolysis at 30 °C were approximately 6% faster for the 2-nitrobenzyl carbonate derivatives relative to their α-methylnitroveratryl carbonate analogues.

The hydrolysis rate of the protected *p*-hydroxybenzyl halide with different leaving groups followed the expected order bromide > chloride > fluoride regardless of protecting group and linking group combination (Table 2). The hydrolysis rate decreased by approximately 1 order of magnitude in going from bromide to chloride and by an additional 2 orders of magnitude in going from chloride to fluoride.

The hydrolysis rates obtained in 40% water/acetonitrile at 30, 37, and 55 °C (Table 2) allowed determination of the hydrolysis activation parameters. On the basis of an Arrhenius analysis of the data, the range of activation energies (18.9−21.8 kcal/mol) are in agreement with published values for hydrolysis of benzyl halides[26] as are the activation enthalpies (18.3−21.2 kcal/mol, 37 °C) and entropies (−9.5 to −19.5 cal/(deg mol), 37 °C).[26,27] One apparent trend was the increase in the Gibb's free energy of activation by approximately 3 kcal/mol in going from the ether-linked derivatives (Table 2, entries 1−6, **15**−**16**) to the carbonate-linked derivatives (Table 2, entries 7−12, **17**−**18**). This corresponds to the degree of the increased stability afforded by the electron-withdrawing carbonate linkage.

Table 3. Selected Half-Lives (h) of Protected *p*-Hydroxybenzyl Halides at 30 °C

	water in acetonitrile (%, v/v)	
compound	60	100[a]
15a	445	8.9[c]
15b	0.78	0.04
15c	0.089	0.007
16a	223	4.8[c]
16b	0.47	0.031
16c	0.066	0.006
17a	*b*	*d*
17b	471	29.4[c]
17c	21.1	3.9
18a	*b*	*d*
18b	520	50.2[c]
18c	23.0	4.6

[a] Extrapolated from experimentally determined data. [b] No evidence of hydrolysis was detected after 4−6 days. [c] Extrapolated from only two data points. [d] Not determined due to significant stability.

The hydrolysis half-lives of the protected *p*-hydroxybenzyl halides as determined at 30 °C in 60% water/acetonitrile (the highest water content experimentally determined) are shown in Table 3. A Grunwald−Winstein analysis allowed extrapolation of the hydrolysis rate to 100% water (vide infra). These theoretical half-lives at 100% water are also shown in Table 3. Note that compounds **17a** and **18a** showed no evidence of hydrolysis after 4−6 days[28] so their hydrolysis values were not

(26) Koshy, K. M.; Robertson, R. E.; Strachan, W. M. J. *Can. J. Chem.* **1973**, *51*, 2958.
(27) Hyne, J. B.; Wills, R.; Wonkka, R. E. *J. Am. Chem. Soc.* **1962**, *84*, 2914.

determined. Note also that the hydrolysis half-lives of compounds **15a**, **16a**, **17b**, and **18b** in 100% water were extrapolated from only two data points each due to their significant stability under the conditions studied. Two general trends are apparent from the half-lives. The hydrolysis rates were clearly relative to (i) the specific halide used at the benzylic position and (ii) the type of linker attaching the photolabile protecting group.

Consistent with the experimentally derived hydrolysis rate data, the extrapolated half-lives at 100% water show an approximate gain of 1 order of magnitude in going from bromide to chloride and an additional 2 orders of magnitude in going from chloride to fluoride (Table 3). Additionally, the extrapolated values for the hydrolysis half-lives of the carbonate protected chlorides are approximately 2−3 days and those of the carbonate-protected fluorides were not determined due to their tremendous stability under the conditions studied. These results indicate that the carbonate protected chlorides and fluorides should easily be satisfactory candidates for use in biologically relevant systems. Even the less stable carbonate-protected benzyl bromide derivatives **17c** and **18c** with estimated half-lives of nearly 5 h should be sufficiently stable for many applications.

Hammett Analysis of Protecting Group Linker. The calculated Hammett σ_p^+ value for the carbonate group from our studies is +0.28[29] based on a ρ value of −4.54.[30] While ρ values are reaction and solvent dependent, the ρ value we selected gave reasonable calculated values for our σ_p^+ constants and is in the range generally given for the solvolysis of benzyl chlorides.[10,30,31] Using the same ρ value, we calculated a σ_p^+ value of −0.39 for the benzyl ether group.[32] This results in $\Delta\sigma_p^+ = 0.67$, which is an approximate 3 orders of magnitude increase in stabilization in going from the ether-linked to the carbonate-linked photolabile protected *p*-hydroxybenzyl halides.[33]

Grunwald−Winstein Plot of Selected Protected *p*-Hydroxybenzyl Halides. The Grunwald−Winstein plot of those protected *p*-hydroxybenzyl halide with sufficient hydrolysis rates to give four data points for extrapolation to 100% water is shown in Figure 1. The data show a good linear correlation ($r > 0.99$) between the log of the hydrolysis rate and the solvent polarity. The slopes of the lines demonstrate a moderate to high dependence of the hydrolysis rate on solvent polarity as expected for a benzyl halide solvolysis reaction.[34] The average slope (0.78) of the ether-linked derivatives (**15b**−**c** and **16b**−**c**, Figure 1) is approximately 0.29 units higher than the average slope (0.49) of the carbonate-linked derivatives (**17c**, **18c**, Figure 1). The smaller slope for the carbonate protected precursor is characteristic of the decreased ability of the carbonate group to stabilize a positive charge. This indicates a shift toward less positive charge buildup in the transition state.[36]

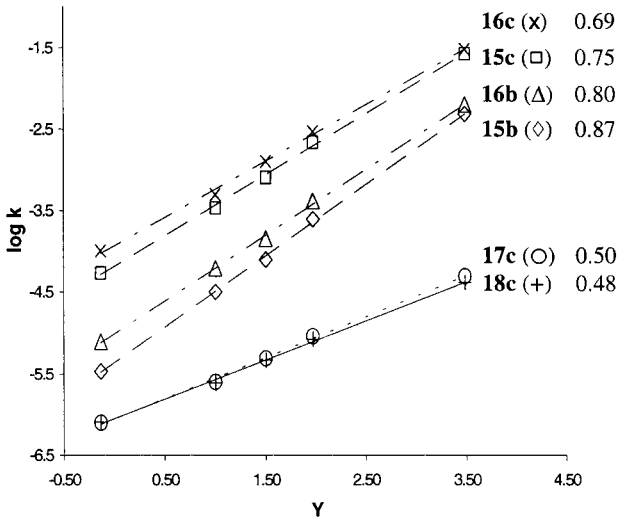


Figure 1. Correlation of the log of the rate constants for hydrolysis relative to the *Y* values of the solvent ($r > 0.99$ in all cases). *Y* values correspond to the respective acetonitrile/water mixtures.[35] The log *k* value at $Y = 3.49$ (100% H_2O) is based on extrapolation of the experimentally determined hydrolysis rates.

Conclusions

We have directly compared a series of protected *p*-hydroxybenzyl halide latent quinone methide precursors whose hydroxy functionality was protected with either a carbonate-linked or an ether-linked photolabile protecting group. The protected *p*-hydroxybenzyl halides having a carbonate-linked protecting group clearly demonstrated enhanced hydrolytic stability over the corresponding ether-linked derivatives. Of the compounds investigated, we found the α-methylnitroveratryl carbonate protected *p*-hydroxybenzyl halide having a fluoride leaving group to be indeterminately stable toward hydrolysis under the conditions studied. The most stable protected *p*-hydroxybenzyl chloride has an estimated half-life in 100% water of over 50 h. Even the most hydrolysis prone carbonate-linked derivative, the benzyl bromide, is anticipated to have a half-life of nearly 5 h in 100% water. This systematic analysis will allow the rational design of quinone methide precursors anticipated to be useful in a variety of bioalkylation processes.[18]

Experimental Section

General Methods. All nonaqueous reactions, except for sodium borohydride reductions, were conducted under an inert nitrogen atmosphere. Unless specified otherwise, solvents and reagents are commercially available chemicals and were used as received. Tetrahydrofuran (THF), diethyl ether, and methylene chloride were purified using the Solv-Tek ST-002 solvent purification system.[37] Dimethylformamide (DMF) was stirred with barium oxide for 14 h and distilled under reduced pressure from magnesium sulfate. HPLC acetonitrile was used as received. HPLC water was purified using a Millipore Milli-Q

(28) Note also that, even at 55 °C, compounds **17a** and **18a** showed no evidence of hydrolysis after 4−6 days (Table 2).

(29) The value was calculated from the 100% water extrapolated rate using the formula $\sigma = \log(k/k_0)/-4.54$ and was adjusted for the presence of the two *m*-methyl groups by subtracting −0.13 (see ref 31). The value $k_0 = 2.44 \times 10^{-5}$ (30 °C, 100% H_2O) is taken from: Robertson, R. E.; Scott, J. M. W. *J. Chem. Soc.* **1961**, 1596.

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(33) Rearrangement of the formula $\sigma = \log(k/k_0)/-4.54$ leads to $k/k_0 = 10^{-4.54\sigma} = 10^{(-4.54)(0.67)} = 10^{-3}$.

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RG ultrapure water purification system.[38] External bath temperatures were used to record all reaction temperatures. Aqueous workup (solvent (number of extractions × volume used for each extraction), drying agent) refers to the extraction of the aqueous phase with the indicated volume of organic solvent for the indicated number of times followed by drying of the combined organic phases with the indicated drying reagent and filtration to remove the drying agent. Concentration in vacuo refers to removal of solvent via distillation using Buchi rotary evaporator at water aspirator pressure and/or residual solvent removal at high vacuum. Melting points are uncorrected. Unless otherwise noted, all ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 and 67.9 MHz, respectively. Chemical shifts are reported as δ values in ppm relative to TMS.

Measurement of Hydrolysis Rates. Each of the substrates was monitored by HPLC for hydrolytic stability in 20−60% (v/v) water/acetonitrile mixtures at 30 °C and in a 40% (v/v) water/acetonitrile mixture at 37 or 55 °C. Reactions were conducted in triplicate by programmed addition of 50 μL of a 1 mM acetonitrile solution of the substrate at the specified temperature to 950 μL of the acetonitrile/water reaction mixture at the same temperature to form a solution whose final concentration was 50 μM. All solutions were maintained at the specified temperature (±0.02 °C) through circulation of water from a constant temperature water bath. An autoinjector was used to inject 25 μL aliquots of the reaction mixture at predetermined intervals onto a Varian Res-Elut column (5 μm, C18, 90A, 4.6 mm × 150 mm) eluting with 75% acetonitrile/water (v/v). The resulting chromatograms taken at the λ_{max} using a photodiode array detector were analyzed to determine the percent of the starting material remaining. No peaks other than starting benzyl halide and the hydrolysis product were present in the chromatograms. The hydrolysis products were identified through comparison of retention times and UV spectra of authentic compounds. For each experiment, the respective value of *k* for hydrolysis was estimated by linear regression from the slope of the plot of the natural logarithm of the percent starting material remaining versus time. The reported value of *k* for hydrolysis is the average of three determinations (average deviation ±2%).

4,5-Dimethoxy-2-nitroacetophenone. A solution of 3,4-dimethoxyacetophenone (10.0 g, 55.5 mmol) in acetic anhydride (30 mL) at room temperature was added slowly over 30 min to a stirring mixture of concentrated nitric acid (200 mL) and acetic anhydride (10 mL) at 0 °C (ice/water). This mixture was allowed to warm slowly to room temperature with stirring for 4 h. The reaction mixture was poured into water (1.5 L), diluted to 2.0 L total volume, and cooled to 4 °C. The precipitate was collected, washed with water, and dried (high vacuum) to afford the known compound[39] as a yellow solid (7.83 g, 63% yield): mp 129−133 °C (lit.[39] mp 130−132 °C); ^{1}H NMR δ 7.60 (s, 1H), 6.74 (s, 1H), 3.97 (s, 6H), 2.49 (s, 3H).

4,5-Dimethoxy-α-methyl-2-nitrobenzyl Alcohol. Sodium borohydride (0.34 g, 8.8 mmol) was added to a stirring suspension of 2-nitro-4,5-dimethoxyacetophenone (2.0 g, 8.8 mmol) in ethanol (100 mL, 0.1 M) at room temperature. After 19 h, the reaction mixture was poured into 5% acetic acid (100 mL). The mixture was diluted with water to 500 mL total volume, and yellow crystals formed after a few minutes of stirring. The crystals were collected by vacuum filtration and oven dried at 80 °C for 3 h to afford the known compound[40] as bright yellow crystals (1.6 g, 77% yield): mp 125−126 °C; IR (KBr) 3291, 3209, 1508, 1270, 1096; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.40 (s, 1H), 7.20 (s, 1H), 5.36 (q, J = 6.2 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 1.34 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 154.6, 148.2, 139.9, 138.7, 109.1, 108.1, 65.5, 56.6, 56.5, 24.7.

4,5-Dimethoxy-α-methyl-2-nitrobenzyl Bromide. Phosphorus tribromide (46 μL, 0.48 mmol) was added to a solution of α-methyl-2-nitro-4,5-dimethoxybenzyl alcohol (0.30 g, 1.3 mmol) in CH_2Cl_2 (15 mL, 0.1 M) at 0 °C and stirred for 2.5 h. The reaction mixture was diluted with Et_2O (50 mL), washed with 5% $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was purified by flash chromatography on silica gel (20 g, 2:1 hexanes/CH_2Cl_2) to afford the known compound[40] as a yellow oil (0.33 g, 85% yield): ^{1}H NMR δ 7.33 (s, 1H), 7.16 (s, 1H), 5.89 (q, J = 6.7 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 1.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 153.3, 148.4, 139.6, 132.4, 111.0, 107.4, 56.5, 56.4, 43.4, 27.5; MS (EI) *m*/*z* 291 (4.0, M^+, ^{81}Br), 289 (3.7, M^+, ^{79}Br), 210 (100).

2-Nitrobenzylchloroformate. A phosgene solution (20% w/v in toluene, 8.00 mL, 16.3 mmol) was added to a solution of 2-nitrobenzyl alcohol in THF at room temperature and stirred for 21 h. Excess phosgene was removed by water aspirator through an aqueous NaOH solution. The remaining toluene was removed by concentration in vacuo to afford the known compound[15b,41] as a brown oil (1.40 g, 99% yield): ^{1}H NMR δ 8.17 (d, J = 8.2 Hz, 1H), 7.75−7.53 (m, 3H), 5.73 (s, 2H); ^{13}C NMR δ 150.5, 147.2, 134.3, 129.8, 129.7, 129.1, 125.5, 69.6.

4-(2′-Nitrobenzyloxy)-3,5-dimethylbenzaldehyde (7). DMF (20 mL) at room temperature was added to a stirring mixture of 4-hydroxy-3,5-dimethylbenzaldehyde (0.50 g, 3.3 mmol), potassium carbonate (0.92 g, 6.6 mmol), and 2-nitrobenzyl bromide (0.72 g, 3.3 mmol), and stirring was continued for 3.5 h at room temperature. The reaction was diluted with 5% $NaHCO_3$ (200 mL), and aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo afforded **7** (0.89 g, 94% yield) as a cream-colored solid: mp 116−118 °C; IR (KBr) 1693, 1598, 1518, 1479 cm^{-1}; ^{1}H NMR δ 9.85 (s, 1H), 8.14 (d, J = 7.5 Hz, 1H), 8.11 (app d, J = 6.5 Hz, 1H), 7.74 (app t, J = 7.7 Hz, 1H), 7.55 (s, 2H), 7.49 (t, J = 7.5 Hz, 1H), 5.24 (s, 2H), 2.29 (s, 6H); ^{13}C NMR δ 191.6, 160.7, 146.5, 134.3, 134.0, 132.8, 132.2, 130.9, 128.5, 128.3, 125.0, 70.2, 16.5.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxy)-3,5-dimethylbenzaldehyde (8). A solution of α-methyl-2-nitro-4,5-dimethoxybenzyl bromide (0.47 g, 1.2 mmol) in DMF (2 mL) at room temperature was added to a stirring suspension of 4-hydroxy-3,5-dimethylbenzaldehyde (0.18 g, 1.2 mmol) and potassium carbonate (0.33 g, 2.4 mmol) in DMF (10 mL) at room temperature, and stirring was continued for 4.5 h. The reaction mixture was then poured into 5% $NaHCO_3$ (200 mL). Aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo yielded a brown oil that was purified by flash chromatography on silica gel (15 g, 5:1 hexanes/ethyl acetate) to afford **8** (0.39 g, 91% yield) as a yellow oil: IR (film) 1692, 1517, 1274, 1019 cm^{-1}; ^{1}H NMR δ 9.81 (s, 1H), 7.57 (s, 1H), 7.49 (s, 3H), 5.83 (q, J = 6.2 Hz, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 2.22 (s, 6H), 1.56 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 191.5, 160.5, 153.8, 148.1, 139.0, 134.5, 131.7, 132.1, 131.1, 109.0, 107.5, 76.6, 56.5, 56.4, 23.5, 17.6.

4-(2-Nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzaldehyde (9). 2-Nitrobenzylchloroformate (0.52 mL, 3.3 mmol) was added to a stirring mixture of 4-hydroxy-3,5-dimethylbenzaldehyde (0.50 g, 3.3 mmol) and potassium carbonate (0.92 mg, 6.7 mmol) in DMF (20 mL) at room temperature. After being stirred for 17 h, the reaction mixture was quenched by pouring into 5% $NaHCO_3$ (200 mL). Aqueous workup (Et_2O (3 × 35 mL), $MgSO_4$) and concentration in vacuo afforded an off-yellow solid that was purified by flash chromatography on silica gel (50 g, 4:1 CH_2Cl_2/hexanes) to afford **9** (0.88 mg, 80% yield) as a light yellow solid: mp 105−107 °C; IR (KBr) 1750, 1695, 1596, 1526, 1468 cm^{-1}; ^{1}H NMR δ 8.08 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 3.9 Hz, 2H), 7.53 (s, 2H), 7.50−7.45 (m, 1H), 5.66 (s, 2H), 2.22 (s, 6H); ^{13}C NMR δ 191.4, 152.7, 151.9, 147.4, 134.4, 134.1, 131.6, 131.0, 130.4, 129.5, 129.0, 125.4, 67.3, 16.1.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzaldehyde (10). Triphosgene (0.22

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g, 0.70 mmol) in CH_2Cl_2 (10 mL) at room temperature was added to a solution of α-methyl-2-nitro-4,5-dimethoxybenzyl alcohol (0.50 g, 2.2 mmol) and pyridine (0.53 mL, 6.6 mmol) in CH_2Cl_2 (20 mL) at −42 °C (CH_3CN/CO_2). After 2 h, 4-hydroxy-3,5-dimethylbenzaldehyde (0.33 g, 2.2 mmol) and pyridine (0.53 mL, 6.6 mmol) in CH_2Cl_2 (10 mL) at room temperature were added, and the mixture was allowed to slowly warm to room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride (80 mL), and aqueous workup (CH_2Cl_2 (2 × 40 mL), $MgSO_4$) followed by concentration in vacuo afforded a brown solid that was recrystallized (EtOH) to afford **10** (0.43 g, 49% yield) as a cream-colored solid: mp 128−129 °C; IR (KBr) 1749, 1700, 1583, 1521, 1457 cm^{-1}; ^1H NMR δ 9.88 (s, 1H), 7.59 (s, 1H), 7.55 (s, 2H), 7.11 (s, 1H), 6.47 (q, J = 6.4 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 2.18 (s, 6H), 1.76 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 191.4, 153.8, 152.7, 151.2, 148.4, 140.1, 134.3, 132.0, 131.5, 130.4, 107.8, 107.5, 73.6, 56.6, 56.5, 22.0, 16.2.

4-(2′-Nitrobenzyloxy)-3,5-dimethylbenzyl Alcohol (11). EtOH (17 mL) was added to a mixture of sodium borohydride (66 mg, 1.7 mmol) and **7** (0.50 g, 1.7 mmol) at room temperature and allowed to sit for 2 h. The reaction mixture was poured into 5% $NaHCO_3$ (150 mL). Aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo afforded **11** (0.50 mg, 99% yield) as an off-white solid: mp 94−95 °C; IR (KBr) 3287, 1609, 1521, 1482 cm^{-1}; ^1H NMR δ 8.18 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.04 (s, 2H), 5.21 (s, 2H), 4.57 (s, 2H), 2.26 (s, 6H); ^{13}C NMR δ 154.9, 146.6, 136.9, 134.8, 134.2, 131.1, 128.4, 128.2, 127.9, 124.9, 70.1, 64.9, 16.4; MS (EI) m/z 287 (5.6, M^+), 152 (7.1), 136 (100). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.02; H, 5.62; N, 4.81.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxy)-3,5-dimethylbenzyl Alcohol (12). Sodium borohydride (35 mg, 0.90 mmol) was added to a stirring solution of **8** (0.33 g, 0.90 mmol) in EtOH (7 mL) at room temperature and allowed to stir for 3 h. The reaction mixture was poured into 5% $NaHCO_3$ (150 mL). Aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo afforded **12** (0.33 g, 100% yield) as a yellow oil: IR (film) 3529, 3404, 1518, 1021 cm^{-1}; ^1H NMR δ 7.59 (s, 1H), 7.55 (s, 1H), 7.00 (s, 2H), 5.73 (q, J = 6.2 Hz, 1H), 4.56 (s, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 2.18 (s, 6H), 1.56 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 154.6, 153.8, 147.9, 139.0, 136.1, 135.4, 131.0, 128.1, 109.2, 107.5, 76.2, 65.1, 56.5, 56.4, 23.4, 17.6; MS (EI) m/z 361 (0.2, M^+), 210 (4.9), 149 (78.7).

4-(2′-Nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Alcohol (13). EtOH (15 mL) was added at room temperature to a mixture of **9** (0.50 g, 1.5 mmol) and sodium borohydride (57 mg, 1.5 mmol) and allowed to stir for 1 h. The reaction mixture was poured into 5% $NaHCO_3$ (200 mL). Aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo afforded a yellow oil that, after addition and removal of hexane, afforded **13** (0.48 g, 96% yield) as an off-white solid: mp 80−82 °C; IR (KBr) 3297, 1754, 1611, 1574, 1530, 1487 cm^{-1}; ^1H NMR δ 8.15 (d, J = 7.9 Hz, 1H), 7.72−7.69 (m, 2H), 7.55−7.49 (m, 1H), 7.04 (s, 2H), 5.69 (s, 2H), 4.56 (s, 2H), 2.19 (s, 6H); ^{13}C NMR δ 152.7, 147.7, 147.3, 138.9, 134.1, 131.6, 130.3, 129.3, 128.8, 127.5, 125.4, 66.9, 64.7, 16.1; MS (EI) m/z 331 (1.0, M^+), 151 (4.6), 136 (7.8). Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.84; H, 4.98; N, 4.09.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Alcohol (14). EtOH (12 mL) was added at room temperature to a stirring mixture of sodium borohydride (47 mg, 1.2 mmol) and **10** (0.50 g, 1.2 mmol) and allowed to stir for 1.5 h. The reaction mixture was poured into 5% $NaHCO_3$ (100 mL). Aqueous workup (CH_2Cl_2 (3 × 50 mL), $MgSO_4$) followed by concentration in vacuo afforded **14** (0.50 mg, 99% yield) as a cream-colored solid: mp 151−152 °C; IR (KBr) 3371, 3308, 1748, 1582, 1520, 1459 cm^{-1}; ^1H NMR δ 7.52 (s, 1H), 7.06 (s, 1H), 6.92 (s, 2H), 6.39 (q, J = 6.4 Hz, 1H), 4.45 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.03 (s, 6H), 1.68 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 153.7, 151.7, 148.1, 147.4, 139.8, 138.7, 132.3, 129.9, 127.2, 107.6, 107.4, 73.0, 64.4, 56.4, 56.3, 21.9, 16.0; MS (EI) m/z 405 (0.3, M^+), 210 (0.81), 152 (12.6), 151 (3.9). Anal. Calcd for $C_{20}H_{23}NO_8$: C, 59.25; H, 5.72; N, 3.46. Found: C, 58.81; H, 5.67; N, 3.44.

4-(2′-Nitrobenzyloxy)-3,5-dimethylbenzyl Fluoride (15a). DAST (70 μL, 0.53 mmol) was added to a stirring solution of **11** (0.10 g, 0.35 mmol) in CH_2Cl_2 (15 mL) at 0 °C (ice/water). After 1 h, the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). Aqueous workup (CH_2Cl_2 (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a yellow oil. This was purified by flash chromatography on silica gel (5 g, 1:1 CH_2Cl_2/hexanes) to afford **15a** (79 mg, 79% yield) as a white solid: mp 96−99 °C; IR (KBr) 1610, 1523, 1480 cm^{-1}; ^1H NMR δ 8.21−8.16 (m, 2H), 7.76 (app t, J = 7.4 Hz, 1H), 7.51 (app t, J = 8.2 Hz, 1H), 7.09 (s, 2H), 5.29 (d, J_{C-F} = 48.3 Hz, 2H), 5.23 (s, 2H), 2.28 (s, 6H); ^{13}C NMR δ 155.9, 146.6, 134.7, 134.2, 132.2 (d, J_{C-F} = 17.1 Hz), 131.4, 128.4, 128.2, 124.9, 128.8 (d, J_{C-F} = 5.2 Hz), 84.5 (d, J_{C-F} = 165.1 Hz), 70.1, 16.4; MS (EI) m/z 289 (8.5, M^+), 153 (25.6), 136 (45.6). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; F, 6.57; N, 4.84. Found: C, 66.57; H, 5.43; F, 6.37; N, 4.81.

4-(2′-Nitrobenzyloxy)-3,5-dimethylbenzyl Chloride (15b). Pyridine (79 μL, 0.97 mmol) was added to a stirring mixture of **11** (0.11 g, 0.39 mmol) and triphosgene (46 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 15 min, the reaction mixture was concentrated in vacuo. Flash chromatography on silica gel (20 g, 5:1 hexanes/ethyl acetate) afforded **15b** (81 mg, 68% yield) as a white solid: mp 102−106 °C; IR (KBr) 1521 cm^{-1}; ^1H NMR δ 8.18 (d, J = 7.4 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.76 (app t, J = 7.4 Hz, 1H), 7.51 (app t, J = 8.2 Hz, 1H), 7.09 (s, 2H), 5.23 (s, 2H), 4.52 (s, 2H), 2.27 (s, 6H); ^{13}C NMR δ 155.6, 146.6, 134.7, 134.2, 133.5, 131.5, 129.5, 128.4, 128.2, 124.9, 70.1, 46.2, 16.4; MS (EI) m/z 307 (0.9, M^+, ^{37}Cl), 305 (2.8, M^+, ^{35}Cl), 171 (1.7), 169 (7.4), 136 (100). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.24; H, 5.41; N, 4.40.

4-(2′-Nitrobenzyloxy)-3,5-dimethylbenzyl Bromide (15c). Phosphorus tribromide (33 μL, 0.35 mmol) was added to a stirring solution of **11** (0.10 g, 0.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C (ice/water). After being stirred for 4.5 h, the reaction mixture was poured into an equal volume mixture of saturated NaCl and saturated $NaHCO_3$ (10 mL). Aqueous workup (CH_2Cl_2 (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a white solid. This was purified by flash column chromatography on silica gel (5 g, 1:1 CH_2Cl_2/hexanes) to afford **15c** (56 mg, 46% yield) as an off-white solid: mp 120−121 °C; IR (KBr) 1525, 1480 cm^{-1}; ^1H NMR δ 8.17 (app d, J = 8.1 Hz), 7.75 (app t, J = 7.8 Hz), 7.50 (app t, J = 7.8 Hz), 7.08 (s, 2H), 5.21 (s, 2H), 4.43 (s, 2H), 2.25 (s, 6H); ^{13}C NMR δ 155.6, 146.6, 134.7, 134.2, 133.8, 131.6, 129.8, 128.3, 128.2, 124.9, 70.1, 33.6, 16.4; MS (EI) m/z 351 (1.9, M^+, ^{81}Br), 349 (1.9, M^+, ^{79}Br), 215 (1.0), 213 (1.0), 136 (100). Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; Br, 22.82; N, 4.00. Found: C, 55.13; H, 4.59; Br, 22.76; N, 3.85.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxy)-3,5-dimethylbenzyl Fluoride (16a). DAST (55 μL, 0.42 mmol) was added to a stirring solution of **12** (0.10 g, 0.28 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 1 h, the reaction mixture was poured into saturated $NaHCO_3$ (5 mL). Aqueous workup (CH_2Cl_2 (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a yellow oil. This was purified by flash chromatography on silica gel (5 g, 1:1 CH_2Cl_2/hexanes) to afford **16a** (59 mg, 59% yield) as a yellow oil: IR (film) 1517, 1273, 1019 cm^{-1}; ^1H NMR 7.60 (s, 1H), 7.03 (s, 2H), δ 7.55 (s, 1H), 5.76 (q, J = 6.2 Hz, 1H), 5.24 (d, J_{C-F} = 48.2 Hz, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 2.20 (s, 6H), 1.57 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 155.6 (d, J_{C-F} = 3.6 Hz), 153.8, 147.9, 139.0, 135.3, 131.4 (d, J_{C-F} = 17.1 Hz), 131.2, 129.0 (d, J_{C-F} = 5.2 Hz), 109.2, 107.5, 84.5 (d, J_{C-F} = 164.9 Hz), 76.3, 56.5, 56.4, 22.7, 17.6; MS (EI) m/z 363 (0.6, M^+), 210 (53.3), 153 (6.0). Anal. Calcd for $C_{19}H_{22}FNO_5$: C, 62.80; H, 6.10; N, 3.85. Found: C, 63.25; H, 6.09; N, 3.90.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxy)-3,5-dimethylbenzyl Chloride (16b). Pyridine (15 μL, 0.19 mmol) was added to a stirring mixture of **12** (27 mg, 0.070 mmol) and triphosgene (27 mg, 0.090 mmol) in CH_2Cl_2 (3 mL) at room temperature. After 1 h, the reaction mixture was filtered

through a layer of silica gel (5 g, 3 cm), washed with CH_2Cl_2 (25 mL), and concentrated in vacuo to afford pure **16b** (24 mg, 86% yield) as a yellow oil: IR (film) 1580, 1273, 874 cm^{-1}; ^1H NMR δ 7.60 (s, 1H), 7.54 (s, 1H), 7.03 (s, 2H), 5.74 (q, $J = 6.2$ Hz, 1H), 4.49 (s, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 2.18 (s, 6H), 1.57 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR δ 155.3, 153.8, 147.9, 139.0, 135.3, 132.7, 131.3, 129.6, 109.1, 107.5, 76.2, 56.5, 56.4, 46.2, 23.5, 17.6; MS (EI) *m/z* 210 (5.5), 171 (0.2), 169 (0.6). Anal. Calcd for $C_{19}H_{22}ClNO_5$: C, 60.08; H, 5.84; Cl, 9.33; N, 3.69. Found: C, 60.14; H, 5.85; Cl, 9.39; N, 3.66.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxy)-3,5-dimethylbenzyl Bromide (16c). Phosphorus tribromide (25 μL, 0.28 mmol) was added to a stirring solution of **12** (0.10 g, 0.28 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 2 h, the reaction mixture was poured into saturated $NaHCO_3$ (5 mL). Aqueous workup (CH_2Cl_2 (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a yellow oil that was purified by flash column chromatography on silica gel (5 g, 1:1 CH_2Cl_2/hexanes) to afford **16c** (45 mg, 38% yield) as a yellow oil: IR (film) 1518, 1020 cm^{-1}; ^1H NMR δ 7.60 (s, 1H), 7.53 (s, 1H), 7.03 (s, 2H), 5.74 (q, $J = 6.2$ Hz, 1H), 4.41 (s, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 2.17 (s, 6H), 1.56 (d, $J = 6.2$ Hz, 3H);^{13}C NMR δ 155.3, 153.8, 148.0, 139.0, 135.2, 133.0, 131.3, 130.0, 109.2, 107.6, 76.6, 56.5, 56.4, 33.6, 23.5, 17.5; MS (EI) *m/z* 425 (0.5, M^+, ^{91}Br), 423 (0.5, M^+, ^{79}Br), 215 (0.5), 213 (0.6), 210 (100). Anal. Calcd for $C_{19}H_{22}BrNO_5$: C, 53.79; H, 5.23; N, 3.30. Found: C, 53.78; H, 5.20; N, 3.35.

4-(2′-Nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Fluoride (17a). DAST (90 μL, 0.68 mmol) was added at room temperature to stirring solution of **13** (0.15 g, 0.45 mmol) in Et_2O (15 mL) at 0 °C (ice/water). After 0.5 h, the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). Aqueous workup (Et_2O (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded an oil that was purified by flash chromatography on silica gel (5 g, 2:1 hexanes/CH_2Cl_2) to afford **17a** (72 mg, 48% yield), which, after addition of acetonitrile, became a yellow-white solid: mp 86−89 °C; IR (KBr) 1754, 1611, 1579, 1526, 1564 cm^{-1}; ^1H NMR δ 8.17 (d, $J = 7.9$ Hz, 1H), 7.72−7.70 (m, 2H), 7.57−7.50 (m, 1H), 7.08 (s, 2H), 5.70 (s, 2H), 5.29 (d, $J_{C-F} = 47.8$, 2H), 2.22 (s, 6H); ^{13}C NMR δ 152.5, 148.5 (d, $J_{C-F} = 3.6$ Hz), 147.4, 134.3 (d, $J_{C-F} = 17.7$ Hz), 134.1, 131.5, 130.6 (d, $J_{C-F} = 1.0$ Hz), 129.3, 128.8, 128.1 (d, $J_{C-F} = 5.7$ Hz), 125.4, 84.1 (d, $J_{C-F} = 166.6$ Hz), 67.0, 16.1; MS (EI) *m/z* 333 (0.2, M^+), 153 (17.2), 136 (100). Anal. Calcd for $C_{17}H_{16}FNO_5$: C, 61.26; H, 4.84; F, 5.70; N, 4.20. Found: C, 61.14; H, 4.72; F, 5.67; N, 4.08.

4-(2′-Nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Chloride (17b). Pyridine (34 μL, 0.42 mmol) was added to a stirring solution of **13** (56 mg, 0.17 mmol) and triphosgene (60 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) at room temperature. After 45 min, the reaction mixture was filtered through a layer of silica gel (5 g, 3 cm), washed with CH_2Cl_2 (20 mL), and concentrated in vacuo to afford pure **17b** (53 mg, 90% yield) as a clear oil that became an off-white solid on addition of hexane: mp 66−68 °C; IR (neat) 1757, 1538, 1264 cm^{-1}; ^1H NMR δ 8.16 (d, $J = 7.9$ Hz, 1H), 7.72−7.69 (m, 2H), 7.56−7.50 (m, 1H), 7.09 (s, 2H), 5.70 (s, 2H), 4.50 (s, 2H), 2.20 (s, 6H); ^{13}C NMR δ 152.7, 147.7, 147.3, 138.9, 134.1, 131.6, 130.3, 129.3, 128.8, 127.5, 125.4, 66.9, 64.7, 16.1; MS (EI) *m/z* 351 (0.08, M^+, ^{37}Cl), 349 (0.22, M^+, ^{35}Cl), 171 (2.64), 169 (9.70), 136 (100). Anal. Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; Cl, 10.14; N, 4.00. Found: C, 58.57; H, 4.59; Cl, 9.97; N, 3.79.

4-(2′-Nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Bromide (17c). Phosphorus tribromide (43 μL, 0.45 mmol) at room temperature was added to a stirring solution of **13** (0.15 g, 0.45 mmol) in Et_2O (15 mL) at 0 °C (ice/water). After being stirred for 1 h, the reaction mixture was poured into saturated $NaHCO_3$ (10 mL). Aqueous workup (Et_2O (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a bright yellow oil that was purified by flash column chromatography on silica gel (5 g, 2:1 hexanes/CH_2Cl_2) to afford **17c** (49 mg, 28% yield) as an off-white solid: mp 72−74 °C; IR (KBr) 1756, 1540, 1426 cm^{-1}; ^1H NMR δ 8.17 (d, $J = 8.2$ Hz), 7.72−7.65 (m, 2H), 7.58−7.47 (m, 1H), 7.09 (s, 2H), 5.70 (s, 2H), 4.41 (s, 2H), 2.19 (s, 6H); ^{13}C NMR δ 152.5, 148.2, 135.8, 134.1, 131.5, 130.8, 129.6, 129.3, 128.8, 125.4, 67.0, 32.9, 16.1; MS (EI) *m/z* 395 (6.9, M^+, ^{81}Br), 393 (5.7, M^+, ^{79}Br), 215 (4.9), 213 (5.6), 135 (100). Anal. Calcd for $C_{17}H_{16}BrNO_5$: C, 51.79; H, 4.09; N, 3.55. Found: C, 52.19; H, 4.30; N, 3.57.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Fluoride (18a). DAST (50 μL, 0.37 mmol) at room temperature was added to a stirring solution of **14** (0.10 g, 0.25 mmol) in CH_2Cl_2 (10 mL) at 0 °C (ice/watwer). After 0.75 h, the reaction mixture was poured into saturated $NaHCO_3$ (5 mL). Aqueous workup (CH_2Cl_2 (2 × 5 mL), $MgSO_4$) followed by concentration in vacuo yielded a yellow oil that was purified by flash chromatography on silica gel (5 g, 1:1 CH_2Cl_2/hexanes) to afford **18a** (63 mg, 63% yield) as a white solid: mp 132−134 °C; ^1H NMR δ 7.59 (s, 1H), 7.10 (s, 1H), 7.03 (s, 2H), 6.46 (q, $J = 6.4$ Hz, 1H), 5.24 (d, $J_{C-F} = 47.7$ Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.12 (s, 6H), 1.75 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR δ 153.8, 151.7, 148.5 (d, $J_{C-F} = 3.1$ Hz), 148.3, 140.0, 134.2 (d, $J_{C-F} = 17.7$ Hz), 132.4, 130.4, 128.1 (d, $J_{C-F} = 5.7$ Hz), 107.8, 107.5, 84.1 (d, $J_{C-F} = 166.1$ Hz), 73.2, 56.5, 56.4, 22.1, 16.1; MS (EI) *m/z* 407 (4.5, M^+), 210 (100), 153 (7.0). Anal. Calcd for $C_{20}H_{22}FNO_7$: C, 58.96; H, 5.44; F, 4.66; N, 3.44. Found: C, 58.86; H, 5.39; F, 4.85; N, 3.28.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Chloride (18b). Pyridine (50 μL, 0.62 mmol) was added to a stirring mixture of **14** (0.10 g, 0.25 mmol) and triphosgene (95 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 15 min, the reaction mixture was concentrated in vacuo. Flash chromatography (8 g, 1:1 CH_2Cl_2/hexanes) afforded **18b** (91 mg, 87% yield) as an off-white solid: mp 124−126 °C; IR (KBr) 1749, 1582, 1525, 1455 cm^{-1}; ^1H NMR δ 7.59 (s, 1H), 7.11 (s, 1H), 7.05 (s, 2H), 6.46 (q, $J = 6.4$ Hz, 1H), 4.47 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 2.11 (s, 6H), 1.75 (d, $J = 6.4$ Hz, 3H);^{13}C NMR δ 153.9, 151.7, 148.4, 148.2, 140.1, 135.4, 132.3, 130.5, 129.1, 107.9, 107.6, 73.2, 56.5, 56.4, 45.6, 22.1, 16.1; MS (EI) *m/z* 425 (0.05, M^+, ^{37}Cl), 423 (0.14, M^+, ^{35}Cl), 210 (11.14), 171 (0.13), 169 (0.53). Anal. Calcd for $C_{20}H_{22}ClNO_7$: C, 56.68; H, 5.23; Cl, 8.36; N, 3.30. Found: C, 56.95; H, 5.26; Cl, 8.23; N, 3.13.

4-(4′,5′-Dimethoxy-α′-methyl-2′-nitrobenzyloxycarbonyloxy)-3,5-dimethylbenzyl Bromide (18c). Phosphorus tribromide (8.0 μL, 0.090 mmol) at room temperature was added to a stirring solution of **14** (0.10 g, 0.30 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C (ice/water). After being allowed to warm to room temperature and stir for 1 h, the reaction mixture was washed through a layer of silica gel (5 g, CH_2Cl_2). Concentration in vacuo afforded **18c** (66 mg, 57% yield) as a yellow solid: mp 133−134 °C; IR (KBr) 1752, 1582, 1522, 1453 cm^{-1}; ^1H NMR δ 7.59 (s, 1H), 7.10 (s, 1H), 7.04 (s, 2H), 6.45 (q, $J = 6.4$ Hz, 1H), 4.37 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 2.09 (s, 6H), 1.74 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR δ 153.8, 151.7, 148.3, 148.2, 140.1, 135.7, 132.3, 130.6, 129.5, 107.8, 107.6, 73.2, 56.6, 56.5, 32.9, 22.1, 16.1; MS (EI) *m/z* 469 (0.06, M^+, ^{81}Br), 467 (0.04, M^+, ^{79}Br) 215 (0.15), 213 (0.11), 210 (2.49). Anal. Calcd for $C_{20}H_{22}BrNO_7$: C, 51.30; H, 4.74; N, 2.99. Found: C, 51.95; H, 4.80; N, 2.69.

Acknowledgment. This work was supported by the National Science Foundation (EHR-9108762 and CHE-9734187) and the Arkansas Science and Technology Authority (98-B-03).

JO991085T