p-Hydroxyphenacyl photoremovable protecting groups — Robust photochemistry despite substituent diversity

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Abstract: A broadly based investigation of the effects of a diverse array of substituents on the photochemical rearrangement of *p*-hydroxyphenacyl esters has demonstrated that common substituents such as F, MeO, CN, CO_2R, $CONH_2$, and CH_3 have little effect on the rate and quantum efficiencies for the photo-Favorskii rearrangement and the release of the acid leaving group or on the lifetimes of the reactive triplet state. A decrease in the quantum yields across all substituents was observed for the release and rearrangement when the photolyses were carried out in buffered aqueous media at pHs that exceeded the ground-state pK_a of the chromophore where the conjugate base is the predominant form. Otherwise, substituents have only a very modest effect on the photoreaction of these robust chromophores.

Key words: substituent, pH, pK_a, solvent effects, photorelease.

Résumé : Une étude détaillée des effets de divers arrangements de substituants sur le réarrangement photochimique des esters de *p*-hydroxyphénacyle a démontré que les substituants communs, tel F, MeO, CN, CO_2R ou CH_3, n'ont que peu d'effet sur la vitesse et les efficacités quantiques du réarrangement de photo-Favorskii et sur la libération du groupe acide partant ou sur les temps de vies de l'état triplet réactif. On a observé que tous ces substituants provoquent des diminutions des rendements quantiques pour la libération et le réarrangement quand les réactions de photolyse sont effectuées dans un milieu aqueux tamponné à un pH supérieur à celui du pK_a de l'état fondamental du chromophore pour lequel la base conjuguée est la forme prédominante. Autrement, les substituants n'ont qu'un effet modeste sur la photoréaction de ces robustes chromophores.

Mots-clés : substituant, pH, pK_a, effets de solvant, libération photochimique.

[Traduit par la Rédaction]

Introduction

Among the known photoremovable protecting groups, *p*-hydroxyphenacyl (pHP, **1**, eq. [1]) has consistently provided very fast (within a few nanoseconds after excitation or even less) and efficient, high conversion release of substrates. Moreover, the photoproducts are transparent at irradiation wavelengths ≥280 nm, permitting essentially complete conversion. Since developing the pHP as a "caging group" a decade ago,[1] pHP derivatives have found several applications in neurobiology,[2] enzyme catalysis,[3] and chemistry[4–6] that have demonstrated the advantages of its rapid, efficient release properties. An intriguing aspect of pHP photochemistry is the rearrangement of the chromophore that accompanies the release of the substrate. Anderson and Reese,[7] who discovered the photorearrangement by photolysis of *p*-hydroxyphenacyl chloride, isolated ethyl *p*-hydroxyphenylacetate (HPAA), which they described as a "photo-Favorskii" rearrangement product and depicted the skeletal rearrangement as passing through a putative spirocyclohexa-2,5-dienylcyclopropyl-4,8-dione intermediate (**I_2**) (eq. [1]).

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Dedicated to Professor J. C. Scaiano, University of Ottawa, on the occasion of his 65th birthday. This article is part of a Special Issue dedicated to Professor J. C. Scaiano.

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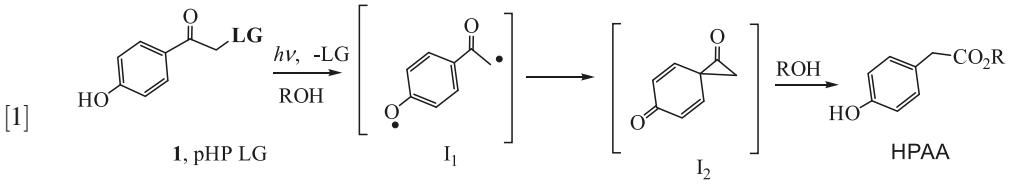

[1]

LG = leaving groups: including phosphates, carboxylates, thiols, imidazoles, phenols, and chloride.

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Our subsequent studies using a variety of leaving groups have affirmed that the major rearrangement pathway proceeds to the *p*-hydroxyphenylacetic acid as long as the reactions are carried out in aqueous or hydroxylic solvents.[8] Recent studies have been directed toward fine-tuning the requirements for the release and for the rearrangement of the pHP group, particularly, the effects of varying the leaving group (**LG**), the substituents on pHP, and the solvent.[8]

Details regarding the timing and multiplicity requirements of the bond-making and bond-breaking events in the photo-Favorskii rearrangement have been addressed in several mechanistic and theoretical investigations.[9–11] The release rates, as well as the product distribution, are sensitive to the presence of H_2O and other hydroxylic solvent combinations.[8–10] An adiabatic triplet sequence has been proposed[10,12] that involves both the deprotonation of the phenolic OH group and the heterolytic release of the leaving group[13] prior to formation of cyclopropanone $\mathbf{I_2}$ (eq. [1]). At least one additional intermediate, an oxyallyl–phenoxy triplet biradical ($\mathbf{I_1}$), has been proposed and evidence for $\mathbf{I_1}$ was recently reported.[9] Still, the molecular events including the multiplicities of the intermediates and the pathways that form $\mathbf{I_1}$ and $\mathbf{I_2}$ and their conversions to products are not fully established.

We report here the results of our investigations of the substituent effect on the photochemistry, multiplicity, quantum yield, reaction rate, and the effects of pK_a and pH. In addition, we have evaluated the substituent effect on the rearrangement including intermediates $\mathbf{I_1}$ and $\mathbf{I_2}$ suggested for the photo-Favorskii rearrangement. A series of substituted pHP esters (Fig. 1) were examined under a variety of conditions that included changes in solvent, pH, and ionic strength of the media. The mechanistic implications of these results provide a clearer understanding of this most interesting photorearrangement reaction.

Results and discussion

The array of substituted pHP derivatives was chosen to include both electron donor and acceptor functional groups (Fig. 1). Several of these compounds were also selected for future synthetic alterations or attachment sites for modifications desired for various applications of pHP photochemistry. There were a few instances where the γ-aminobutyric acid (GABA) leaving group was not easily installed, so the alternative acetate or diethyl phosphate leaving groups were inserted. These leaving groups are also well-documented in the literature of pHP photorelease chemistry and therefore can be related to the more numerous GABA representatives through comparisons of the known photochemistry of the parent, unsubstituted pHP acetate (**24**),[9,11] or diethyl phosphate (**27**).[1,2,10,11]

Synthesis of substituted pHP derivatives

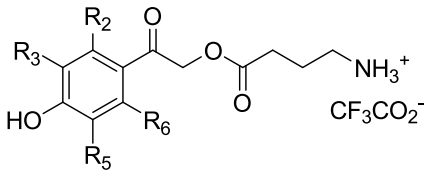
Schemes 1A and 1B describe the synthetic protocols employed for the substituted pHP esters in Fig. 1. The GABA leaving group was chosen to assure good aqueous solubility. GABA is particularly advantageous in this respect, and in our laboratories it has served as the standard leaving group for several previous studies of pHP release rates and efficiencies. In general, the synthetic strategies for substituted pHP chromophores vary according to the availability of the substituted phenol, *p*-hydroxybenzoic acid, or *p*-hydroxyacetophenone precursor. The *p*-hydroxyacetophenones, when available, are converted directly to the pHP GABA and other leaving-group analogs by any one of a number of convenient transformations that activate the α-methyl group, e.g., bromination to the α-bromomethyl ketone followed by S_N2 displacement with N-BOC protected GABA and then deprotection with TFA, e.g., **13**–**23** (Scheme 1B).

The syntheses of the GABA derivatives of pHP (**1**), 3-methoxy-pHP (**2**), and 3,5-dimethoxy-pHP (**3**) followed the published protocols developed earlier for glutamates.[2a,2b] The 3-carboxymethyl-pHP (**10**) and 3-carbamoyl-pHP (**11**) derivatives were derived by the same sequence from the commercially available methyl 5-acetylsalicylate. The 2- and 3-cyano and all of the fluoro ketones (**13d**–**23d**), were synthesized from the corresponding phenols by a sequence of bromination of the phenol (**13b**–**23b**), then benzyl protection (**13c**–**23c**), followed by acylation through Stille coupling with Pd(0) and 1-ethoxyvinyl stannane to furnish, in excellent yield, the substituted *p*-benzyloxyacetophenone. Debenzylation gave acetophenones **13d**–**23d**, which were then converted to the GABA esters **13**–**23**.

The synthesis of new acetate derivatives **25** and **26** stemmed from a protocol uniform to the GABA esters, but commencing with the *p*-hydroxyacetophenones available from the Stille coupling route mentioned above and using sodium acetate in lieu of GABA according to the method of Phillips.[10]

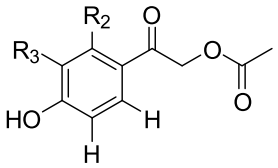
The synthesis of the new diethyl phosphates **30**–**32** constituted an altogether separate series of steps. For the electron-donating methoxy scaffolds **30a** and **31a**, Friedel–Crafts acylation of corresponding pivalate-protected phenols with chloroacetyl chloride, followed by chloro displacement with sodium bromide engendered α-bromo derivatives **30d**–**31d**. Facile diethyl phosphate substitution of the bromoketones

Fig. 1. Substituted *p*-hydroxyphenacyl (pHP) esters.



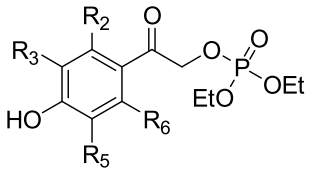
GABAs

1. R_2, R_3, R_5, R_6 = H
2. R_3 = OCH_3; R_2, R_5, R_6 = H
3. R_3, R_5 = OCH_3; R_2, R_6 = H
4. R_3 = OH; R_2, R_5, R_6 = H
5. R_2 = OH; R_3, R_5, R_6 = H
6. R_3 = CH_3; R_2, R_5, R_6 = H
7. R_2 = CH_3; R_3, R_5, R_6 = H
8. R_3, R_5 = CH_3; R_2, R_5 = H
9. R_3= CO_2H; R_2, R_5, R_6 = H
10. R_3 = CO_2CH_3; R_2, R_5, R_6 = H
11. R_3 = $CONH_2$; R_2, R_5, R_6 = H
12. R_3 = NO_2; R_2, R_5, R_6 = H
13. R_3 = CN; R_2, R_5, R_6 = H
14. R_3 = CF_3; R_2, R_5, R_6 = H
15. R_3 = OCF_3; R_2, R_5, R_6 = H
16. R_3 = F; R_2, R_5, R_6 = H
17. R_3 = H; R_2 = F; R_5, R_6 = H
18. R_2, R_3 = F; R_5, R_6 = H
19. R_3, R_5 = F; R_2, R_6 = H
20. R_2, R_5 = F; R_3, R_6 = H
21. R_3, R_5 = H; R_2, R_6 = F
22. R_2, R_3, R_6 = F; R_5 = H
23. R_2, R_3, R_5, R_6 = F



Acetates

24. R_2, R_3, R_5, R_6 = H
25. R_3 = CN, R_2 = H
26. R_2 = H, R_3 = CN



Diethyl phosphates

27. R_2, R_3, R_5, R_6 = H
28. R_2 = OCH_3; R_3, R_5, R_6 = H
29. R_2, R_5 = OCH_3; R_3, R_6 = H
30. R_3, R_5, R_6 = H; R_2 = OCH_3
31. R_3, R_5 = H; R_2, R_6 = OCH_3
32. R_3 = $COCH_3$; R_2, R_5, R_6 = H

was then mediated by Ag(I) followed by pivalate deprotection using ammonium acetate in aqueous methanol to furnish **30** and **31**.

An initial Fries rearrangement of acetyl-protected *p*-hydroxybenzoic acid **32b** provided the *o*-acetylated analog **32c**, whose carboxylic acid moiety was transformed into the α-diazo ketone through the acid chloride. After deacetylation with ammonium acetate in aqueous methanol, reaction with diethyl phosphoric acid gave **32**.

UV–vis spectral properties of substituted pHPs

The UV–vis spectral properties of **1–32** in H_2O and in aqueous buffer at pH 9 and the groundstate pK_as of the corresponding *p*-hydroxyacetophenones are given in Table 1. The pK_as range from 3.9 to >8.0, indicating that at physiological pH the chromophore will be a mixture of the conjugate base (phenoxide) and the neutral, un-ionized phenol. In most cases, the un-ionized form is prevalent at pH 5.0–7, whereas at pH 9, in all cases, the conjugate base prevails. It was anticipated that the photochemistry of the two forms might differ. In fact, the photochemistry will be shown to be sensitive to the solution pH as well as to the pK_a of the chromophore.

The UV–vis spectra of unsubstituted *p*-hydroxyacetophenone (pHA, **1d**) measured at neutral pH (phosphate buffer, pH 7) and in basic media (pH 8) typify the significant shifts in the absorption maxima upon ionization of these chromophores (Fig. 2).[4a] The spectrum of pHA displays a prominent π–π* absorption band with a maximum at 275 nm. In some solvents, a weak shoulder on the red edge of the π–π* band of the *p*-hydroxyketone (not shown) has been attributed to the carbonyl n–π* transition.[10c] The absorption band centered at 330 nm is assigned to the conjugate base π–π* transition. Based on the significant contributions of both chromophores in aqueous solutions between pH 5 and 8, it was necessary to study the photochemistry and physical properties of substituted pHP derivatives under buffered conditions to assure a constant ratio of the two forms of the

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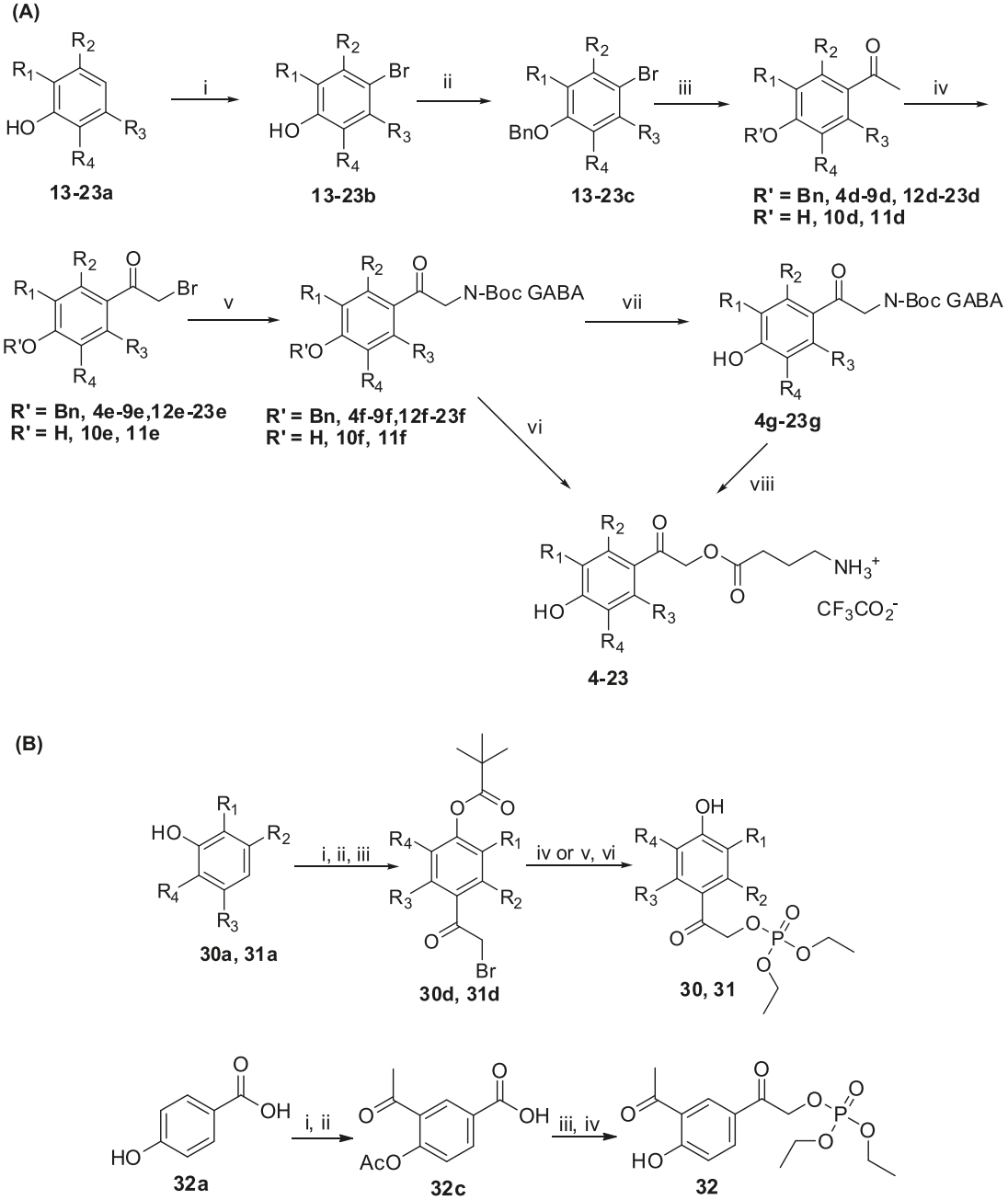
Scheme 1. (A) Synthetic strategy for γ-aminobutyric acid (GABA) derivatives **4**–**23.** Conditions: (i) Br_2, TFA, room temperature (rt) 90%–100%. (ii) BnBr, K_2CO_3, CH_3CN, rt, 85%–95%. (iii) $Pd(PPh_3)_4$, 1-ethoxyvinyltributyltin, $PhCH_3$, 100 °C, 70%–92%. (iv) (a) (R′ = Bn), phenyltrimethylammonium tribromide (PTAB), CH_3OH–CH_2Cl_2 (1:1) rt, 90%–98%; (b) (R′ = H), $CuBr_2$, $CHCl_3$–EtOAc (1:1), reflux, 70%–80%. (v) (a) (R′ = Bn), N-*t*-Boc GABA, K_2CO_3, CH_3CN, rt, 40%–95%; (b) (R′ = H), N-*t*-Boc GABA, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene–DMF (20:1), 7 °C to rt, 55%–60%. (vi) TFA, 24 h, rt, 50%–85%. (vii) Pd–H_2, EtOAc, rt, 95%–100%. (viii) TFA–CH_2Cl_2 (1:1), rt, 70%–100%. (B) Synthetic strategies for diethyl phosphate derivatives **30**–**32**. Conditions (top reaction): (i) $(CH_3)_3COCl$, Et_3N, 0 °C to rt, 100%. (ii) $ClCH_2COCl$, $AlCl_3$, 0 °C, 20%–50%. (iii) NaBr, acetone, reflux, 90%–98%. (iv for **30**) HO–P(O)$(OEt)_2$, Ag_2O, CH_3CN, 60 °C, 76%. (v for **31**) K^+ OP(O)$(OEt)_2$, dibenzo[18]crown-6, CH_3CN, reflux, for 20%. (vi) NH_4OAc, H_2O–MeOH, 1:4, 50 °C, 24 h, 90%–95%. Conditions (bottom reaction): (i) $AlCl_3$, $PhNO_2$, 150 °C, 98%. (ii) AcCl, TEA, CH_2Cl_2, rt, 70%. (iii) (a) $SOCl_2$; (b) CH_2N_2, Et_2O; (c) MeOH(aq), NH_4OAc, 50 °C, 21% overall. (iv) Diethyl phosphoric acid, benzene, 60 °C, 79%



chromophore. Studies were also conducted in unbuffered aqueous media for comparison.

Product studies

Two major photolysis products were obtained from each substituted pHP derivative: the leaving group, i.e., GABA, diethyl phosphate, or acetate, and the substituted *p*-hydroxyphenylacetic acid (pHPAA), which is the rearrangement product from the photo-Favorskii reaction (eq. [1]). A minor product, the substituted *p*-hydroxybenzyl alcohol, is formed

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Table 1. The pK_a and UV absorption maxima in H_2O and at pH 9 for substituted *p*-hydroxyphenacyl (pHP) γ-aminobutyric acid (GABA) derivatives arranged in order of ascending pK_a.

Derivatives	pK_a[a]	λ_{max} (nm) (log ε)[b]	λ_{max} (nm) (log ε) at pH 9[c]
23 (2,3,5,6-tetraF)	3.9	316 (3.95)	316 (4.10)
22 (2,3,5-triF)	4.5	324 (4.05)	323 (4.01)
12 (3-NO_2)	5.2	397 (3.20),[d] 334 (4.14)	399 (3.22), 335 (4.20)
13 (3-CN)	5.2	322 (3.46)[e]	321 (3.44)
19 (3,5-F)	5.3	331 (4.14)	330 (4.14)
14 (3-CF_3)	5.5	325 (4.22)[f]	328 (4.24)
20 (2,5-diF)	5.7	278 (3.26), 326 (3.92)	326 (4.12)
18 (2,3-diF)	5.9	272 (4.09), 328 (3.04)	323 (4.07)
11 (3-CO_2NH_2)	6.2	324 (4.15)	NA
15 (3-OCF_3)	6.5	273 (3.79), 328 (4.31)	329 (4.18)
16 (3-F)	6.7	274 (4.00), 335 (2.97)	351 (3.67), 328 (3.96)
21 (2,6-F)	6.8	274 (4.00)	313 (4.06)
17 (2-F)	7.2	271 (3.97)	328 (3.90), 319 (3.91)
10 (3-CO_2CH_3)	7.7	272 (4.09), 330 (3.94)	NA
3, **29** (3,5-OCH_3)	7.8	279, 300 (3.97), 355 (3.55)	357 (4.28)
5 (2-OH)	7.8	276 (3.85)	
2, **28** (3-OCH_3)	7.9	276 (3.93), 341 (3.58)	342 (4.27)
4 (3-OH)	7.9	309 (3.97), 279 (3.86)	
1, **24**, **27** (parent)	8.0	279 (4.09), 325 (3.40)	324 (4.33)
7 (2-CH_3)	8.0	287 (4.06)	343 (3.86), 328 (4.10)
6 (3-CH_3)	8.1	284 (3.84)	356 (3.75), 334 (3.97)
8 (3,5-CH_3)	8.2	304 (3.79), 287 (3.96)	362 (3.91), 348 (4.05)
26 (2-CN)	NA	275 (3.45), 305 (3.39)	
30 (2-OCH_3)	NA	278 (3.98), 307 (3.93)	
31 (2,6-OCH_3)	NA	283 (3.70)	
32 (3-$COCH_3$)	NA	274 (3.39), 319 (3.06)	
9 (3-CO_2H)	NA	280 (3.90), 310 (3.58)	

Note: NA, not available.

[a]The pK_a values of the corresponding *p*-hydroxyacetophenones were determined by spectrophotometric titration. Ionic strength was low (I < 0.05 mol/L) and not held constant. The ionization quotients pK_{ac} of the *p*-hydroxyacetophenone analogues of **1**–**3** and **9**–**11**, measured at constant ionic strength (I = 0.1 mol/L), were ~0.05 units lower.

[b]Water.

[c]*N*-(2-Hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES, 0.01 mol/L).

[d]The absorption maxima (λ_{max} (nm) (log ε) for **12** was also measured at pH 5 in 0.01 mol/L ammonium acetate: 256 (3.92).

[e]The absorption maxima (λ_{max}(nm) (log ε) for **13** was also measured at pH 5 in 0.01 mol/L ammonium acetate: 270 (sh).

[f]The absorption maxima (λ_{max}(nm) (log ε) for **14** was also measured at pH 5 in 0.01 mol/L ammonium acetate: 274 (4.14).

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in <5% yield and is derived by decarbonylation of the putative spirodienedione intermediate $\mathbf{I_2}$, followed by hydration of the resulting *p*-quinone methide.[9] All of the products were characterized by HRMS and by comparison of their ^{1}H and ^{13}C NMR spectral properties either with authentic samples or related products from our previous pHP studies.

Photolyses carried out in aprotic organic solvents generally produced reduction products such as the substituted pHA and other radical-derived products. These studies were not pursued further, and the products were not observed in the aqueous solution photolyzates.

Quantitative determination of the products was obtained by ^{1}H NMR or by LC–MS/MS. The ^{1}H NMR spectra of pHP caged GABAs in D_2O were cleanly transformed into spectra of the two major photoproducts accompanied by complete disappearance of pHP GABA. Product studies were routinely carried out to quantitative conversion.

Triplet-state pK_a, quantum yield, and Stern–Volmer studies

The pK_a of the excited triplet state of **1d** is strongly reduced by about 4.3 pK_a units relative to pHA's ground-state pK_a of 7.9.[8] Since proton transfer plays a significant role in the mechanism of the release of the leaving group,[4,8–13] changes in the pK_a of the chromophore will provide additional insight into the mechanistic features of the reaction. Currently, there remains a controversy over the timing and importance of the proton transfer to the solvent. One suggested pathway depicts proton transfer from the chromophore in concert with leaving group departure (vide infra).[10] For this scenario, the enhanced acidity of the pHP triplet would enhance the reactivity of the chromophore toward release and rearrangement. The second scenario suggests that the phenol group is merely a spectator and does not play a pivotal role in the release or rearrangement.[10,14] Therefore,

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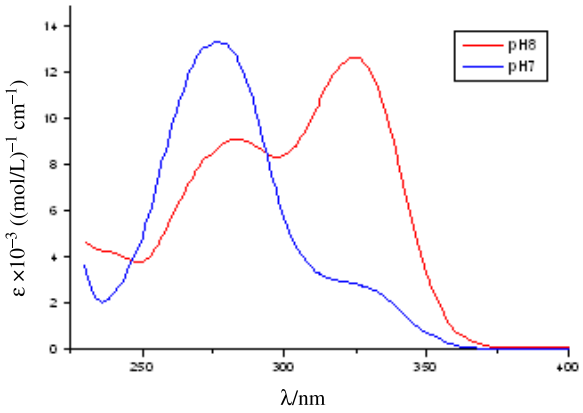
Fig. 2. UV spectral data for *p*-hydroxyacetophenone (**1d**). The absorption spectra are of a 0.13 mmol/L solution of **1d** in NaH_2PO_4 buffer (3% CH_3CN) at pH 7 and 8 showing the shift in absorption from the phenol to its conjugate base. (From Givens and Yousef 2005, in *Dynamic Studies in Biology: Phototriggers, Photoswitches, and Caged Biomolecules*, Chap. 1.3.2.2, p. 60, reproduced with permission, ©Wiley-VCH Verlag CmbH & Co. KGaA.)



a study of the effect of pK_a on the reaction efficiency and rate of release should be valuable.

The quantum yields for the disappearance of pHP esters and for the appearance of the two major products were determined by LC–MS/MS and ^{1}H NMR at low conversion (<5%) in unbuffered H_2O (Table 2) and in buffered solutions (Table 3) at acidic, neutral, and basic pH.

The quantum yields were first determined in unbuffered H_2O (Table 2). However, these must be considered less accurate because the pH changes during photolysis. The mildly acidic phenolic *p*-hydroxyphenacyl chromophore (pK_a ~ 4–8) is converted into a series of three new acids, a bifunctional *p*-hydroxyphenylacetic acid along with the leaving group, which, in several cases, is the strongest acid present, e.g., a phosphoric or sulfonic acid. The contributions of the three newly created acids decrease the pH. Since the photolysis solution for a particular chromophore is a delicate balance of the phenolic pHP ester and its conjugate base and since their ratio is dependent on the chromophore's pK_a, the changing pH of the media will affect that ratio and, therefore, the quantum yield. Furthermore, as reported earlier and amplified in this paper, the quantum yields are dramatically different for the un-ionized chromophore and its conjugate base. Taken together, the quantum yields in unbuffered media are a complex function of the pK_a, a changing pH, and the relative quantum yields. Nevertheless, the quantum yields reported in Table 2 may be considered as representative because they were derived by extrapolation to initial efficiencies at low conversions (<2%). However, they are not corrected for the relative concentrations of the un-ionized and conjugate base present.

Table 3 reveals that in buffered media the efficiencies for release decrease as the pH of the media increases for essentially every pHP ester. The decrease in efficiency is most pronounced as the increasing pH approaches the pK_a of the pHP ester, reaching its lowest when the chromophore is completely converted to its conjugate base, which is graphically depicted in Fig. 3. This normally resulted in a reduction of 60%–80% in the quantum yield.

Table 2. The effect of pK_a on the quantum yields for substituted *p*-hydroxyphenacyl (pHP) γ-aminobutyric acid (GABA) in unbuffered H_2O. Entries are arranged according to decreasing disappearance quantum yields.

		Quantum yield in H_2O		
Substituted pHP GABA	pK_a	Φ_{dis}[a]	Φ_{app}[b]	Φ_{app}[c]
13 (3-CN)[d]	5.2	0.42	0.35	0.39
17 (2-F)	7.2	0.28	0.27	0.26
18 (2,3-diF)	5.9	0.24	0.24	0.22
20 (2,5-diF)	5.7	0.22	0.21	0.20
1 (parent)	8.0	0.20	0.19	0.16
14 (3-CF_3)	5.5	0.17	0.16	0.14
21 (2,6-F)	6.8	0.16	0.16	0.15
16 (3-F)	6.7	0.16	0.15	0.15
8 (3,5-CH_3)	8.2	0.15	0.14	0.13
6 (3-CH_3)	8.1	0.15	0.14	0.13
23 (tetraF)	3.9	0.11	0.10	0.10
19 (3,5-F)	5.3	0.11	0.11	0.10
7 (2-CH_3)	8.0	0.11	0.10	0.10
15 (3-OCF_3)	6.5	0.09	0.09	0.07
22 (2,3,5-triF)	4.5	0.08	0.07	0.06
2 (3-OCH_3)	7.9	0.07	0.06	NA
3 (3,5-OCH_3)	7.8	0.03	0.03	NA

Note: NA, not available.All runs were low conversions to products (<2%). Standard deviations are <±0.02. 3-NO_2 (**12**), 3-OH (**4**), and 2-OH (**5**) did not react under these conditions and are omitted. Unbuffered 18 MΩ Ultrapure H_2O was used.

[a]Quantum yield for the disappearance of pHP GABA.
[b]Quantum yield for the appearance of GABA.
[c]Quantum yield for the appearance of rearranged acid.
[d]CH_3CN–H_2O (1:1).

The lower quantum yield may be attributable to several factors including a decrease in intersystem crossing (isc) efficiency (Φ_{ST}) or in the rate constant of release relative to that of competing nonproductive pathways. One of these may simply be deprotonation to the triplet conjugate base (**1**$^-$).[3] Results in Table 4 suggest, however, that the rates for intersystem crossing are essentially insensitive to substitution for the un-ionized esters. Less is known for the rates of isc for the conjugate bases.

Two substituents of interest are cyano and methoxy. The ortho (or 2) substituted derivatives were not amenable to our synthetic strategies and difficulty was encountered in the attempts to synthesize the GABA derivatives, especially in the Boc deprotection step. However, acetate and phosphate analogs were synthetically accessible and, therefore, their photochemistries were examined. Disappearance quantum yields were measured for 2- and 3-cyano pHP OAc and for the four variations of the methoxy pHP diethyl phosphates. These are given in Table 5 along with the parent pHP OAc and diethyl phosphates reported earlier for comparison.[1,9–11]

Clearly, the cyano-substituted acetates are less efficient than the parent, which was surprising, since the GABA analog of the 3-CN pHP GABA gave an enhanced efficiency for photodeprotection. It should be noted that poorer aqueous solubility of acetate and other carboxylic esters requires cosolvents such as acetonitrile or DMSO. There is mounting evidence that the concentration of the organic cosolvent re-

Table 3. Substituent effects on the quantum yields for γ-aminobutyric acid (GABA) release at 300 nm in buffered CH_3CN–H_2O. Entries are arranged according to decreasing disappearance quantum yields at pH 7.3.

		Quantum yield								
		pH 5.0[a,b]			pH 7.3[a,c]			pH 8.2[a,c]		
pHP GABA	pK_a	Φ_{dis}[d]	Φ_{app}[e]	Φ_{app}[f]	Φ_{dis}[d]	Φ_{app}[e]	Φ_{app}[f]	Φ_{dis}[d]	Φ_{app}[e]	Φ_{app}[f]
13 (3-CN)	5.2	0.21	0.13	0.19	0.33[g]	0.28[g]	0.28[g]	0.19[h]		
1 (Parent)	8.0	0.21	0.20	0.18	0.21	0.20	0.20	0.09	0.09	0.06
17 (2-F)	7.2	0.24	0.23	0.23	0.21	0.20	0.19	0.06	0.06	0.03
8 (3,5-CH_3)	8.2				0.17	0.17	0.15	0.11	0.11	0.09
6 (3-CH_3)	8.1				0.15	0.16	0.13	0.08	0.08	0.06
14 (3-CF_3)	5.5	0.24	0.23		0.12	0.11	0.10	0.08	0.08	
16 (3-F)	6.7	0.15	0.14	0.14	0.12	0.12	0.11	0.02	0.02	<0.01
18 (2,3-diF)	5.9	0.16	0.16	0.15	0.11	0.11	0.09	0.05	0.05	0.04
23 (tetraF)	3.9	0.08	0.07		0.10	0.10	0.08	0.09	0.09	
7 (2-CH_3)	8.0				0.10	0.09	0.08	0.07	0.07	0.06
21 (2,6-F)	6.8				0.10	0.09	0.08	0.04	0.04	0.02
20 (2,5-diF)	5.7	0.07	0.07		0.10	0.09	0.09	0.02	0.02	<0.01
22 (2,3,5-F)	4.5	0.07	0.06		0.06	0.06	0.04	0.02	0.02	<0.01
15 (3-OCF_3)	6.5	0.07	0.05		0.06	0.06	0.05	0.02	0.02	0.01
19 (3,5-F)	5.3	0.08	0.07	0.07	0.05	0.05	0.04	0.02	0.02	<0.01

[a]Standard deviations were <±0.02.
[b]Ammonium acetate (0.01 mol/L).
[c]*N*-(2-Hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES, 0.01 mol/L) and $LiClO_4$ (0.1 mol/L), pH 7.3.
[d]Quantum yield for the disappearance of *p*-hydroxyphenacyl (pHP) GABA.
[e]Quantum yield for the appearance of GABA.
[f]Quantum yield for the appearance of rearranged acid.
[g]Ammonium acetate (0.01 mol/L, pH 7).
[h]Ammonium acetate (0.01 mol/L, pH 9).

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duces quantum yields and rates of release.[9,11–13] This is not consistently the case, but may be a factor in the cyano acetate series.

Methoxy substitution, on the other hand, has little effect for the 3-MeO pHP phosphates but does enhance the reactivity of the 2-MeO pHP phosphates (**30** and **31**). These are among the most efficient photodeprotection efficiencies we have encountered in the phosphate series.[1,3c,4a,8,9,12] It was discovered, however, that these latter two derivatives were less soluble and less stable to aqueous hydrolysis.

Picosecond pump–probe spectroscopy on a cross section of the substituted pHP that included both electron-donating and -withdrawing derivatives and fluorinated examples showed little variation in the rate constants of triplet rise (k_1) and decay (k_2) (Table 4).

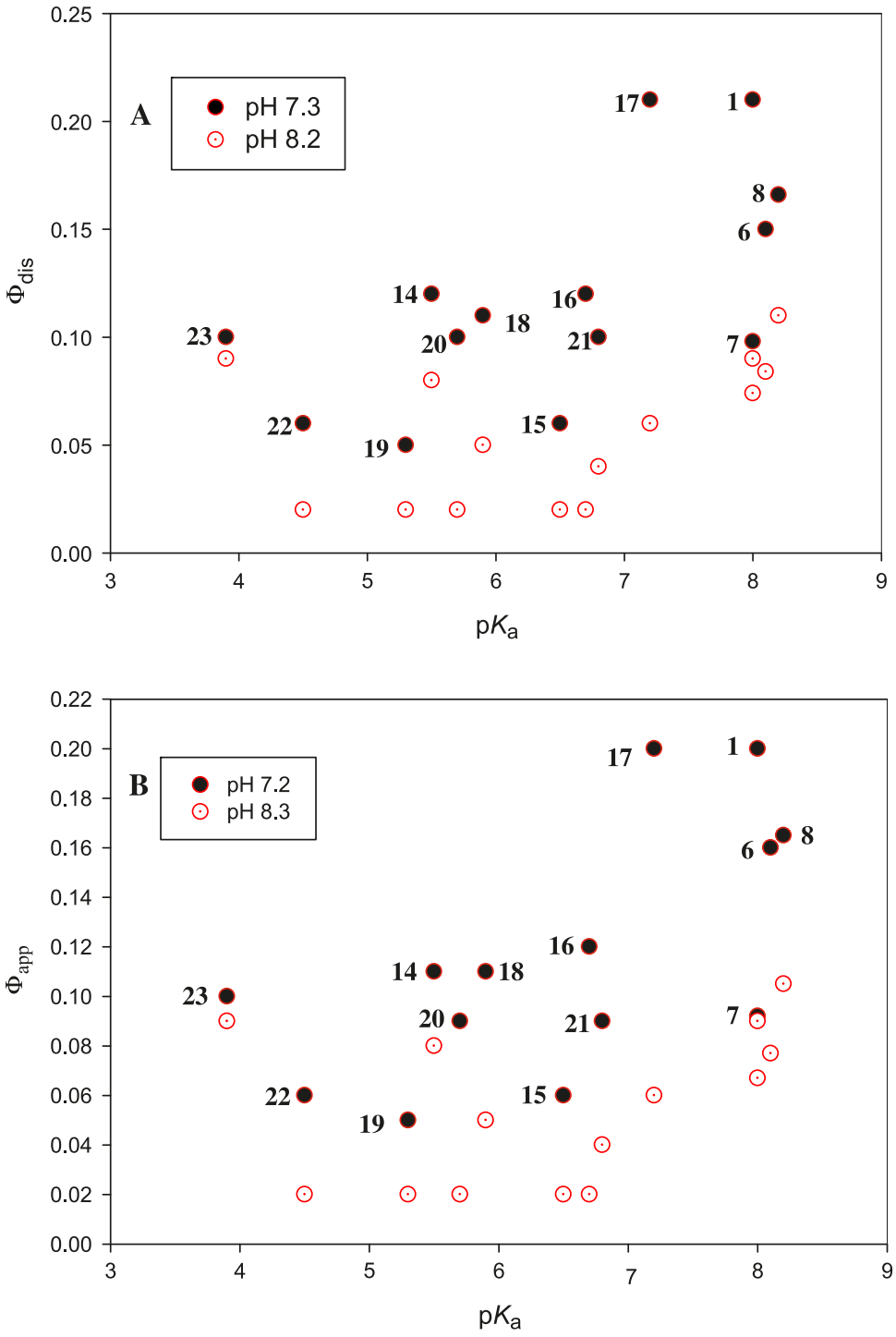
Scheme 2 summarizes a series of the parallel pathways available to the photoactivated pHP derivatives and their conjugate bases. The products are the same for both pathways, but the details concerning the excited states and the partitioning among their available decay and reaction pathways are different. We have a much less-detailed understanding of the mechanism for the reaction of the conjugate bases than the un-ionized pHP system. However, we have monitored the change in quantum yields at different pH and at a longer excitation wavelength (RPR 350 nm lamps). The values are uniformly much lower than those obtained for the un-ionized pHP analog using RPR 300 nm lamps. The conjugate bases display a weak fluorescence ($\Phi < 1 \times 10^{-4}$). Otherwise, the two forms show comparable rates of triplet formation and decay upon excitation at 350 nm. Thus, the low product quantum yields for the conjugate bases are most likely due to variations in the partitioning among the competing exit channels from the triplet excited states of the two chromophores.

Parallel studies on Stern–Volmer quenching of the ester disappearance and product appearance by sorbate for a few of the esters further indicated no significant differences in triplet lifetimes. This also suggests that there is little difference in the partitioning among the triplet decay pathways, but does not exclude the possibility of recombination of initially formed ion-triplet biradical pairs (See the Experimental section and Table 6 for details).

Heterolytic release of the leaving group generates an intermediate biradical–ion pair ([$\mathbf{I}_1{}^3$·**LG**]) raising the possibility of cage return, which might contribute to the differences in the photorelease quantum yields. Evidence for cage return was obtained by increasing the ionic strength of the aqueous solutions with $LiClO_4$, $NaClO_4$, $MgCl_2$, etc. With several derivatives, the quantum yields increased significantly, some by a factor of two or more, whereas others remained unchanged and, in a few cases, even decreased. The increased ionic strength had no effect on the LFP triplet decay rates.

Finally, the triplet energies of the pHP and its conjugate base may be a source of the differences in reactivity. The 71.6 kcal/mol (1 cal = 4.184 J) triplet energy of pHP is diminished to 61.2 kcal/mol for the conjugate base.[8] This ~10 kcal/mol decrease in energy may favor the barrierless or low-barrier processes over the more energy demanding

Fig. 3. Graphic representation of the effect of pK_a on the quantum yield of substituted *p*-hydroxyphenacyl (pHP) γ-aminobutyric acid (GABA) as a function of pH. Numerical identifications of the esters are placed adjacent to the pH 7.3 values. (A) Disappearance quantum yield of substituted pHP GABA as a function of its pK_a at pH 7.3 (●) and 8.2 (○). (B) Appearance quantum yields of GABA as a function of the pHP ester pK_a at pH 7.3 (●) and 8.2 (○). Data are from Table 3. The 3-CN derivative **13** is omitted because of a solvent change.



heterolytic release pathway of the photo-Favorskii rearrangement.

Pathways that may account for nonproductive decay of the triplet would include deprotonation to the conjugate base with subsequent rapid decay to its ground state[15] or proton tautomerization to **33**, the proton tautomer of pHP originally suggested by Wan and co-workers[11] (which was later shown to be a triplet[8]) that, following isc to the ground state, would rapidly tautomerize back to the pHP ester. Interestingly, there is a prominent, long-lived 340 nm transient that also is observed in the LFP spectra of most pHP derivatives. This band is appropriately positioned for assignment

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Table 4. Laser flash photolysis studies on selected derivatives in unbuffered H_2O.

	Rate constant	
pHP GABA	k_1 (10^{11} s^{-1})[a,b]	k_2 (10^9 s^{-1})[b]
1 (Parent)	4.4	3.0[c]
2 (3-OCH_3)	2.2	1.3
3 (3,5-OCH_3)	2.7	2.8[d]
10 (3-CO_2CH_3)	3.2	1.3
11 (3-$CONH_2$)	ND	2.2
9 (3-CO_2H)	2.1	1.0
20 (2,5-diF)	3.0	2.6
22 (2,3,5-triF)	3.9	0.90
23 (tetraF)	3.6	3.4[d]

Note: pHP, *p*-hydroxyphenacyl; GABA, γ-aminobutyric acid.

[a]Singlet $\lambda_{max} \sim 315$ nm.

[b]k_1 is the rate constant for triplet rise and k_2 is the rate constant for triplet decay.

[c]Near the tail end of the triplet decay, new absorption bands appeared at 320, 420, and 440 nm, which have been assigned to the oxyallyl–phenoxy biradical $\mathbf{I_1}$ and decayed with a rate constant of $k_{birad} \approx 1.30 \times 10^9$ s^{-1}.[9,15]

[d]Acetonitrile (5%) was added to the aqueous solvent to dissolve these esters.

Table 5. Quantum yields for cyano-pHP acetates and methoxy-pHP phosphates at λ = 300 nm.

Compound	Φ_{dis}[a]
pHP acetates[b]	
24 (Unsubstituted)	0.30
25 (3-CN)	0.17
26 (2-CN)	0.08
pHP diethyl phosphates[c]	
27 (Unsubstituted)	0.40
28 (3-OCH_3)	0.39
29 (3,5-OCH_3)	0.44[d]
30 (2-OCH_3)	0.59
31 (2,6-OCH_3)	0.69
32 (3-$COCH_3$)	0.03

Note: pHP, *p*-hydroxyphenacyl.

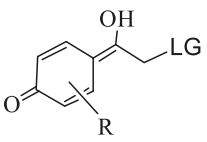
[a]Error limits for disappearance quantum yields (±0.03%).

[b]Analysis carried out in 20% aq CH_3CN or DMSO.

[c]Analysis carried out in 50% aq CH_3CN.

[d]$\Phi_{dis} = 0.13$ at $\lambda = 350$ nm.

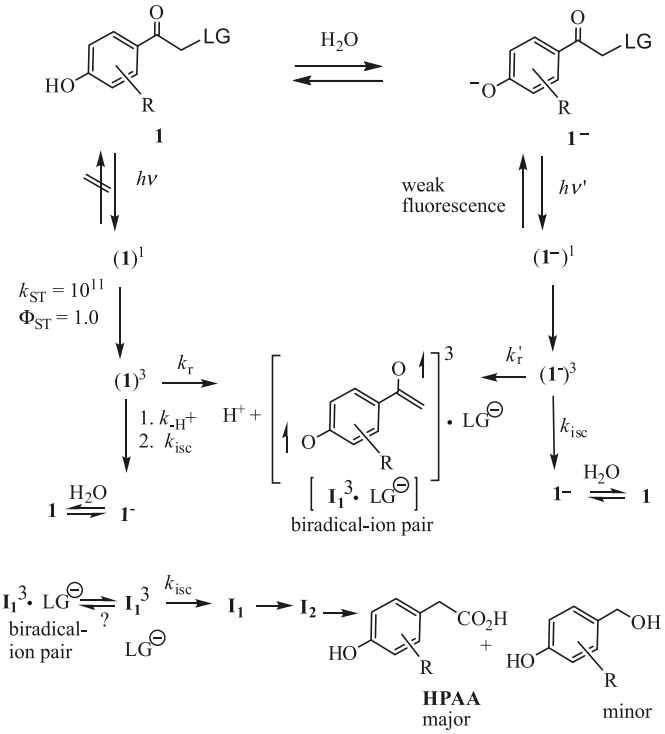
either to the ground-state conjugate base of the pHP group or to **33**.[11,14] As in the case of the conjugate base of pHP derivatives, the tautomer **33** is an unlikely candidate for room-temperature heterolysis.[9]



33

For the heterolytic pathway that proceeds on to the rearranged product, three scenarios have also been suggested.

Scheme 2. Parallel pathways for the photochemical and photophysical processes of *p*-hydroxyphenacyl (pHP) or its conjugate base.



Proton loss[14] or heterolysis could be the initial step or the two could occur in concert. Two such stepwise scenarios can be envisaged, differing by only the order of departure of two entities. Evidence that militates against proton loss preceding the departure of the leaving group comes from the poor efficiencies of the conjugate bases and from our earlier analysis of solvent kinetic isotope effects (SKIE). A "proton inventory" of the SKIE revealed that either two or three protons are "in flight" in the release process.[9,16] The partition functions are consistent with the phenolic proton and two solvent water protons associated with two carbonyls during the extrusion of $\mathbf{I_1}$.

The other stepwise construct would involve the departure of the leaving group before loss of the proton, thereby generating a triplet α-keto carbenium ion. This pathway is also unlikely based on the known photochemistry of released derivatives such as *p*-methoxyphenacyl analogs, which, even in hydroxylic solvents, do not efficiently follow a rearrangement pathway for the chromophore.[1b,17] This is in keeping with the requirement that the *para* hydroxyl function and a leaving group positioned α to the carbonyl be present on the phenacyl chromophore to ensure efficient photo-Favorskii rearrangement.

Taken together, these results are viewed as favoring the concomitant loss of the phenolic proton and the leaving group. Thus, the evidence is most consistent with the interpretation that a concerted proton and leaving group departure occurs with the resulting extrusion of a neutral triplet biradical $\mathbf{I_1}$. This process is not only a minimum energy pathway for heterolysis, but also conserves spin.[18] The oxyallyl–phenoxy triplet biradical $\mathbf{I_1}$ then relaxes to a singlet and closes to the spirobicyclohexadienedione $\mathbf{I_2}$. The fate of $\mathbf{I_2}$ as a groundstate intermediate mimics a typical Favorskii

Table 6. Stern–Volmer studies of *p*-hydroxyphenacyl (pHP) γ-aminobutyric acid (GABA) derivatives in unbuffered H_2O and in aqueous media at pH 7.3 buffer.

	Studies with water[a,b]		Studies with buffer at pH 7.3[b,c]	
Compound	K_{SV} ((mol/L)$^{-1}$)[d]	τ^3 (10^{-9}s)[e]	K_{SV} ((mol/L)$^{-1}$)[d]	τ^3 (10^{-9}s)[e]
13	299	40.5		
14	20.2	2.75	30.3	4.12
15	33.1	4.47	29.4	4.03
16	24.2	3.23	26.0	3.66
17	13.0	1.99	19.2	2.52
18	44.7	6.02	39.0	5.33
19	29.1	4.04	32.6	4.31
20	15.2	2.12	51.1	6.93
21	25.5	3.31	8.02	1.13
22	34.2	4.67	36.8	4.82
23	30.0	4.16	14.1	1.90

[a]Unbuffered 18 MΩ Ultrapure H_2O.
[b]Std. dev. <10%.
[c]*N*-(2-Hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES, 0.01 mol/L) and $LiClO_4$ (0.1 mol/L).
[d]Sorbic acid quencher, Stern–Volmer constant.
[e]Triplet lifetime.

rearrangement[19] by ring-opening hydrolysis via nucleophilic attack of solvent (water) to produce rearranged *p*-hydroxyphenylacetic acid. Decarbonylation, a minor pathway open to $\mathbf{I_2}$, yields *p*-quinone methide that hydrolyzes to *p*-hydroxybenzyl alcohol, the minor product.

The effect of structure on the photolytic reactivity of substituted pHP GABAs

There appears to be no correlation between the ground-state pK_as of the chromophores and their photochemical behavior in terms of their quantum yields or rate constants for release. The pK_a dictates the ratio of the un-ionized and conjugate base, and this ratio in turn affects the photochemical reactivity. Therefore, the photochemical and photophysical properties do not change with the introduction of most substituents. The most notable exceptions are the effect of 3-nitro and the 2- and 3-hydroxyl groups, which completely quench reactivity. Similarly unreactive were the 3-acetyl and any appended auxochromes that could quench such as naphthyl (not shown).

Conclusions

A unique rearrangement, the photo-Favorskii reaction, of pHP esters combines the accelerated release of substrate ligands with a hypsochromic shift of the pHP chromophore. The rearrangement occurs on the triplet manifold by a spin-conserved extrusion of the chromophore as a triplet biradical $\mathbf{I_1}$ followed by relaxation of the biradical and closure to yield $\mathbf{I_2}$, the "Favorskii" intermediate, merging the photochemical pathway with a ground-state Favorskii reaction.[19] With few exceptions, substituents on the chromophore do not influence the mechanics of the rearrangement sequence and cause only small variations in the quantum yields and reaction-rate constants. The release of substrate is consistently more efficient for the un-ionized chromophores. Substituents do influence the chromophore pK_a; electron-donating and -withdrawing groups both lower the pK_a and, therefore, favor the conjugate base at neutral pH. This causes lower quantum yields, since the conjugate base is much less efficient at releasing the leaving group.

4-Hydroxybenzyl alcohol, a ubiquitous minor product, serves as additional supporting evidence for the intermediacy of $\mathbf{I_2}$ through its formation by decarbonylation and hydrolysis.[9]

Finally, these results provide evidence that further modification of the chromophore is possible without decreasing its photoreactivity, enhancing the pHP physical and photochemical versatility. Carboxyl, carbonyl, ether, and amide functional groups can be introduced to enhance the solubility, binding, and other physical properties without fear of losing reactivity.

Current studies on this intriguing chromophore and on the mechanism of the unusual photochemical rearrangement are in progress.

Experimental

Methods

Melting points were conducted with open-ended capillary tubes using a noncalibrated Thomas–Hoover melting-point apparatus. Lyophilization was performed using a Labconco FreezeZone device set at –52 °C and 0.04 mbar (1 bar = 100 kPa). Solution pH values were determined using a Fisher Scientific pH 510 meter calibrated with certified Fisher buffer solutions of pH 4, 7, and 10. Products of all reactions were assessed for purity using the following instrumental techniques: For ^{1}H, ^{13}C, and ^{19}F NMR, Bruker DRX 400 and DRX 500 MHz spectrometers were utilized with trifluoroacetic acid as an internal standard (δ = –76.55 ppm). GC–MS analysis was done on an Agilent 6890N Network GC system equipped with a Quattro Micromass triple quadrupole electron impact mass spectrometer. Exact masses were performed on a Quattro Micromass triple quadrupole electrospray ionization mass spectrometer. UV–vis data were obtained on a Carey Bio100 instrument using 1.5 mL quartz cuvettes. Fluorescence data were acquired on a Carey Eclipse fluorescence spectrophotometer using a 10 mm

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quartz cell. IR data were obtained using a Shimadzu FT-IR 8400 S instrument with pressed potassium bromide (KBr) pellets or a prefabricated sodium chloride (NaCl) chloroform cell for solid-phase analysis and NaCl prefabricated plates for oil analysis. Ground-state pK_as were determined through sample titration with increasing amounts of 0.0461 mol/L NaOH (standardized with potassium hydrogen phthalate), correlating pH vs [OH^-] and ascertaining the half equivalence point as the pK_a. Product separation was achieved by flash chromatography using EM Science silica gel and gradient hexanes – ethyl acetate as eluting solvents. All reactions were run under ambient conditions unless otherwise stated. ^{1}H NMR spectroscopy was utilized to monitor the progress of the photolysis of all new pHP cages. In general, a 1–10 mmol/L sample of pHP-caged GABA was prepared in 2 mL D_2O and ~2 mL was placed in an NMR tube. This was positioned in a photoreactor equipped with two 15 W, 3000 Å Rayonet lamps and a merry-go-round. Irradiation for 30 min generally led to 100% conversion as judged by the absence of the ester proton signals. Photoproduct identification was achieved through the spiking the samples of the irradiated mixture with authentic samples of the resolved GABA. Quantitative photolysis conditions for determination of quantum yields and Stern–Volmer quenching constants (K_{SV}) were as follows: The lamp light output (in mEinsteins/min) was established using the potassium ferrioxalate method.[7] Milligram quantities of caged compounds and caffeine or acetamidophenol were weighed out on a Fisher brand microbalance and dissolved in 4 mL of 18 MΩ ultrapure water salt solutions of various concentrations, buffers with or without adjusted ionic strengths, or purified organic solvents were then added to a quartz tube and vortexed, resulting in a homogenous solution of the caged compound and internal standard. Concentrations of the caged compounds ranged from 1 to 9 mmol/L. These tubes were then placed in a carousel within a Rayonet photochemical reactor equipped with two 3000 Å, 15 W Rayonet photochemical reactor RPR3000 mercury lamps as light sources. One hundred microlitre samples were removed at 30 s intervals up to 5 min using a 250 μL Hamilton microsyringe and diluted to 1 mL with water using 1 mL volumetric flasks.

Quantum efficiency determinations

Quantitative analysis was achieved by HPLC–UV or HPLC–MS/MS. The LC–MS/MS instrument was a Waters 2695 Liquid Chromatographer equipped with a Quattro Micromass triple quadrupole electrospray ionization mass spectrometer, outfitted with an autosampler. UV–vis detection consisted of a Waters 2497 type with a dual wavelength detector set at 220 and 240 nm. The reservoirs used were as follows: (*i*) 99% water, 1% methanol, 10 mmol/L ammonium formate, and 0.06% formic acid; and (*ii*) 99% methanol, 1% water, 10 mmol/L ammonium formate, and 0.06% formic acid. The column was a reverse-phase (C18), 4 μm mesh Altech Altima, 50 mm in length. Injections of 100 μL were made with an automated sampler for each run for a total of three injections per vial. A mobile phase gradient was utilized to optimize compound separation. The flow rate was set at 300 μL/min. Data analysis was performed by Mass Lynx Ultima software and Microsoft Excel. Smoothing functions were used for peak analysis of the chromatographic peaks. Calibration curves to obtain *R* values from linear least-squares regression were determined at concentrations of the reactants and products in photolyses by systematic increases of pHP-caged GABA, free GABA, and *p*-hydroxyphenylacetic acid concentrations to determine correlations with internal standards caffeine or 4-acetamidophenol. The quantum efficiencies were then calculated from the ratio of the reactant or product concentrations to the photons absorbed using the actinometer values obtains as indicated above.

Lifetime and rate measurements

The Stern–Volmer quenching technique[20] effectively distinguished the triplet lifetimes of pHP derivatives, using potassium sorbate as the quencher. Concentrations of pHP GABA solutions ranged from 0.001 to 0.01 mol/L; these were diluted with sorbate solutions of increasing concentration (0–0.1 mol/L) and subsequently photolyzed under previously indicated conditions to ascertain the change in quantum efficiencies of GABA release. Φ_0/Φ vs [*Q*], and K_{SV} were determined. To establish the triplet lifetime (τ^3), the rate of quenching (k_q) was assumed to be commensurate with the rate of bimolecular diffusion in water ($k_{diff} \sim 7.2 \times 10^9$ s^{-1}). The results are shown in Table 6.

Femtosecond pump–probe spectroscopy

Femtosecond transient absorption was measured with the pump – supercontinuum probe technique using a Ti/Sa laser system (Clark MXR CPA-2001; 775 nm, pulse energy 0.9 mJ, full width at half maximum 150 fs, and operating frequency 426 Hz). Part of the beam was fed into a Clark MXR NOPA. The output at 532 nm was frequency-doubled by a β-barium borate (BBO) crystal to 266 nm and upon compression, elicited pump pulses with an energy of 1 μJ and <150 fs pulse width. A probe beam continuum was generated by focusing the 775 nm beam in front of a CaF_2 plate with a 2 mm path length that produced a supercontinuum probe beam spanning a wavelength range of 270–690 nm. The pump and probe beams were focused to a 0.2 mm spot on the sample that was flowing in an optical cell with a thickness of 0.4 mm. The probe beam and a reference signal (passing the solution beside the pump beam) were spectrally dispersed and registered with two photodiode arrays (512 pixels). Transient absorption spectra were calculated from the ratio of the two beams. The pump–probe cross-correlation was <100 fs over the entire spectrum. Measurements on short time scales (up to 50 ps) were corrected for chirp using a program (SPAN) kindly provided by Professor N. Ernsting, Institut für Chemie, Humboldt Universität zu Berlin, Germany. To improve the signal-to-noise ratio, the data were averaged over multiple pump–probe scans (3–6 scans with 400 shots per temporal point).

Materials

Unless indicated, starting materials were obtained from Sigma-Aldrich or Matrix Scientific. Before usage, solvents were purified via simple distillation employing phosphorus pentoxide, calcium hydride, or calcium chloride and stored in containers with microwave-activated 4 Å molecular sieves. Ultrapure (18 MΩ) water was used in all instances.

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Synthesis

pHP GABAs

4-(2-(4-Hydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (1)

The steps to synthesize **1** were described in the protocol by Givens et. al.[5]

4-(2-(4-Hydroxy-3-methoxyphenyl)-2-oxoethoxy)-4-oxobutan-1-amonium-2,2,2-trifluoroacetate (2)

The synthesis of **2** was accomplished by using the procedures of Givens et al.[5] and Conrad et al.[2] as reported for **1**. Under an inert atmosphere of argon, a flame-dried 100 mL round-bottom flask was charged with *N*-Boc-γ-aminobutyric acid (248 mg, 1.22 mmol), 2-bromo-1-(4-hydroxy-3-methoxyphenyl)ethanone (300 mg, 1.22 mmol), and acetonitrile (50 mL). Potassium carbonate (188 mg, 1.36 mmol) was added and the mixture was stirred at room temperature (rt) for 24 h. The solvent was removed under reduced pressure and the remaining residue was dissolved in ethyl acetate and washed with water (3 × 10 mL). The organic extract was dried with $MgSO_4$ and concentrated to afford a pink solid. The crude product was flash chromatographed on silica gel with 2:1, 1:1, and then 2:3 hexane – ethyl acetate. Collection of the appropriate fractions and removal of the solvent under reduced pressure provided 2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl-4-[(*tert*-butoxycarbonyl)amino]-butanoate as a light pink solid. Yield: 333 mg, 74%; mp 88–89 °C. The *t*-Boc group was removed by treating the 2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl-4-[(*tert*-butoxycarbonyl)amino]butanoate (281 mg, 0.76 mmol) with cold trifluoroacetic acid (TFA, 10 mL). The solution was stirred at 0 °C for 1 h. The excess TFA was removed under reduced pressure and the remaining residue was dissolved in water, and washed with ethyl acetate. The aqueous layer was collected and the water removed by lyophilization to give 4-(2-(4-hydroxy-3-methoxyphenyl)-2-oxoethoxy)-4-oxobutan-1-amonium-2,2,2-trifluoroacetate as a tan solid (**2**, 545 mg, 100% yield, mp 128–130 °C). IR (KBr, cm^{-1}): 3339, 3181, 3150, 2935, 2756, 2088, 1757, 1675, 1593, 1516, 1460, 1424, 1383, 1368, 1281, 1178, 1132, 1020. ^1H NMR (400 MHz, D_2O) δ: 1.94 (p, *J* = 7.3 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H), 3.79 (s, 3H), 5.37 (s, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 7.36 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H).

4-(2-(4-Hydroxy-3,5-dimethoxyphenyl)-2-oxoethoxy)-4-oxobutan-1-amonium-2,2,2-trifluoroacetate (3)

The synthesis of **3** was accomplished by using the procedure of Conrad et. al.[2] A solution of 2-bromo-1-(4-hydroxy-3-methoxyphenyl)ethanone[2] (600 mg, 2.18 mmol/L) was treated with 4-(*tert*-butoxycarbonylamino)butanoic acid (N-*t*-Boc-GABA; 443 mg, 2.18 mmol/L) in 10 mL of benzene at 7 °C to which was added 366 mg (2.41 mmol/L) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 10 mL of benzene. The mixture was allowed to reach rt and stirred overnight. The solvent was removed in vacuo and the crude product purified by silica gel chromatography (522 mg, 60% yield). The *t*-Boc protecting group was then removed by treatment with TFA (10 mL) at 0 °C for 4 h. The TFA was removed by rotary evaporation and the crude product was treated with H_2O–EA. The aqueous layer was collected and the water removed by lyophilization to give 4-(2-(4-hydroxy-3,5-dimethoxyphenyl)-2-oxoethoxy)-4-oxobutan-1-amonium-2,2,2-trifluoroacetate as a colorless oil (**3**, 100%). IR (film, cm^{-1}): 3388, 3179, 2943, 2847, 1737, 1693, 615, 1536, 1466, 1431, 1379, 1326, 1300, 1169, 1047. ^1H NMR (400 MHz, D_2O) δ: 1.94 (m, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H), 3.63 (s, 6H), 5.18 (s, 2H), 6.75 (s, 2H). FAB MS (free amine) *m*/*z*: 342 (M +1). HRMS calcd for $C_{15}H_{20}NO_8$ (M + H): 342.1189; found: 342.1193.

Representative description, with 16

1-(Benzyloxy)-4-bromo-2-fluorobenzene (16b)

The general method of Frechét and co-workers[21] was followed. A solution of 4-bromo-2-fluorophenol (**16a**, 3.83 g, 20.0 mmol), benzyl bromide (2.38 mL, 20.0 mmol), and potassium carbonate (6.91 g, 50.0 mmol) in CH_3CN (30 mL) was stirred at rt for 15 h. The solution was diluted with 50 mL CH_2Cl_2, washed with water (3 × 30 mL), dried (magnesium sulfate), and concentrated to give 5.24 g (93%) of 1-(benzyloxy)-4-bromo-2-fluorobenzene (**16b**) as a white precipitate; mp 65–67 °C. IR ($CHCl_3$, cm^{-1}): 3020, 2987, 2684, 2304, 1498, 1421, 1265, 1217, 1051, 896, 738, 695. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (m, 5H), 7.27 (dd, *J* = 6.4, *J* = 2.2 Hz, 1H), 7.26 (dt, *J* = 4.3, *J* = 2.0 Hz, 1H), 6.89 (t, *J* = 8.8 Hz, 1H), 5.13 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 154.23, 151.73, 146.06, 136.02, 128.88, 127.73, 120.14, 117.23, 115.86, 113.02, 71.90. ^{19}F NMR (376 MHz, $CDCl_3$ + 1 drop of CF_3CO_2H) δ (ppm): –130.78. HRMS (M+) calcd for $C_{13}H_{10}FBrO$: 279.9899; found: 279.9905.

1-(Benzyloxy)-3-fluorophenyl)ethanone (16c)

The general method of Kosugi et al.[22] was used. The experimental procedure is described with that for **23** (vide infra).[28] White precipitate; yield: 89%, mp 79–81 °C. IR ($CHCl_3$, cm^{-1}): 3053, 2987, 1679, 1610, 1514, 1498, 1421, 1265, 1217, 1052, 896, 738, 696. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (dd, *J* = 11.3, *J* = 2.4 Hz, 1H), 7.69 (dd, *J* = 9.0, *J* = 1.6 Hz, 1H) 7.44, (m, 5H), 7.04 (t, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 2.55, (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 196.05, 153.66, 151.16, 135.82, 130.92, 128.95, 127.57, 125.76, 116.36, 114.22, 71.25, 26.52. ^{19}F NMR (376 MHz, $CDCl_3$ + 1 drop of CF_3CO_2H) δ (ppm): –133.02. HRMS (M + H) calcd for $C_{15}H_{13}FO_2$: 245.0978; found: 245.0951.

1-(4-(Benzyloxy)-3-fluorophenyl)-2-bromoethanone (16d)

The method was adapted from Ohriand co-workers.[23] A 50 mL round-bottom flask was charged with **16c** (700 mg, 2.86 mmol) and phenyltrimethylammonium tribromide (PTAB) (1.07 g, 2.86 mmol). The mixture was subsequently dissolved by the addition of 40 mL of CH_2Cl_2–CH_3OH (1:1). The resultant solution was stirred at rt for 6 h, at which time full conversion was indicated by GC–MS. The solution was transferred to a separatory funnel, diluted with 50 mL of CH_2Cl_2, and washed profusely with water (3 × 50 mL). Excess solvent was removed under reduced pressure, affording an orange precipitate, 900 mg (2.58 mmol), ~95%.[24] IR ($CHCl_3$, cm^{-1}): 3055, 2988, 1679, 1615, 1511,

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1498, 1417, 1267, 1219, 1050, 891, 748, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (dd, *J* = 10.0, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 7.0, *J* = 2.8 Hz, 1H), 7.42 (m, 5H), 7.07 (t, *J* = 8.4 Hz, 1H), 5.24 (s, 2H), 4.37 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$ + 1 drop of CF_3CO_2H) δ (ppm): –133.12.

*2-(4-(Benzyloxy)-3-fluorophenyl)-2-oxoethyl-4-(*tert-*butoxycarbonylamino)butanoate (16e)*

The general method of Fujita and Hiyama[25] was utilized. A solution of 1-(4-(benzyloxy)-3-fluorophenyl)-2-bromoethanone (**16d**, 900 mg, 2.78 mmol), potassium carbonate (1.15 mg, 8.35 mmol), and 4-(*tert*-butoxycarbonylamino) butanoic acid (N-Boc–GABA, 678 mg, 3.33 mmol) in 50 mL of CH_3CN was stirred for 24 h at rt. The solution was washed with EtOAc, water, the aqueous phase discarded, and the resulting phase evaporated under reduced pressure. Flash column chromatography (hexanes–EtOAc, 5:1) afforded **16e** as a white precipitate. Yield: 1.10 g (89%); mp 97–99 °C. IR (KBr, cm^{-1}): 3300, 3100–2800, 1742, 1701, 1600, 1517, 1437, 1400 1309, 1200, 1165, 953, 750, 700, 668. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.80 (dd, *J* = 7.0, *J* = 2.4 Hz, 1H), 7.78 (dd, *J* = 7.0, *J* = 2.0 Hz, 1H), 7.47 (dd, *J* = 4.4, *J* = 1.8 Hz, 1H), 7.42 (m, 5H), 5.31 (s, 2H), 5.25 (s, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.76 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 190.67, 172.51, 155.60, 152.30, 150.80, 135.82, 128.39, 128.14, 127.68, 126.93, 125.60, 115.28, 114.82, 77.45, 70.36, 66.12, 39.64, 30.63, 28.22, 24.96. ^{19}F NMR (376 MHz, CD_3CN + 1 drop of CF_3CO_2H) δ (ppm): –133.44. HRMS (M + Na) calcd for $C_{24}H_{28}FNO_6Na$: 468.1798; found: 468.1796.

4-(2-(3-Fluoro-4-hydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (16)

The general method of Marsh and Goodman[26] was followed. To a flame-dried 50 mL round-bottom flask containing 2-(4-(benzyloxy)-3-fluorophenyl)-2-oxoethyl-4-(*tert*-butoxy-carbonylamino)-butanoate (**16e,** 850 mg, 1.91 mmol) was added 20 mL of freshly distilled TFA. Stirring continued for 24 h at rt under ambient conditions. The solution was evaporated under reduced pressure and washed with EtOAc–water. The water layer was then extracted, frozen, and then lyophilized, affording **16** as an adhesive precipitate. Yield: 550 mg (78%). IR (KBr, cm^{-1}): 3434, 3269, 3100–2800, 1741, 1693, 1610, 1553, 1420, 1201, 1050, 823, 759, 719. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.70 (d, *J* = 9.0 Hz, 2H), 7.12 (t, *J* = 9.9 Hz, 1H), 5.50 (s, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.05 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ (ppm): 190.05, 172.06, 161.60, 152.27, 151.07, 150.33, 126.03, 125.33, 117.30, 115.33, 65.95, 38.54, 30.02, 22.48. ^{19}F NMR (376 MHz, D_2O) δ (ppm): –133.58. HRMS (M+) calcd for $C_{12}H_{15}FNO_4$: 256.0985; found: 256.0977.

The synthetic protocol for generating compounds **14** and **15**[27] and **17**–**23**[28] has been previously published. The synthesis of **13** was analogous to that for **16** and, therefore, only the spectroscopic data for this is described.

1-Benzyloxy-4-bromo-2-cyanobenzene (13b)

White solid. Yield: 87%; mp 80–81 °C. IR (KBr, cm^{-1}): 3068, 3035, 2229, 1591, 1487, 1454, 1287, 1132, 1132, 1018, 813, 742, 696. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 5.22 (s, 2H), 7.14 (d, 1H), 7.45 (m, 5H), 7.73 (dd, 1H), 7.81 (d, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 71.9, 104.5, 112.5, 115.9, 116.2, 128.7, 129.4, 129.7, 136.7, 136.8, 138.4, 160.6. HRMS (M+) calcd for $C_{14}H_{10}BrNO$: 286.9946; found: 286.9937.

1-(4-Benzyloxy-3-cyanophenyl)ethanone (13c)

White solid. Yield: 90%; mp 120–123 °C. IR (KBr, cm^{-1}): 3068, 3033, 2229, 1681, 1602, 1500, 1419, 1355, 1275, 1137, 977, 817, 750, 630. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 2.53 (s, 3H), 5.31 (s, 2H), 7.26 (d, 1H), 7.44 (m, 5H), 8.17 (dd, 1H), 8.26 (d, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 25.45, 70.79. 101.53, 112.63, 115.27, 127.50, 128.19, 128.40, 130.15, 134.20, 134.50, 1335.27, 163.02, 194.85. HRMS (M + H) calcd for $C_{16}H_{13}NO_2$: 252.1024; found: 252.1022.

1-(4-Benzyloxy)-3-cyanophenyl)-2-bromoethanone (13d)

White solid. Yield: 91%; mp 94–96 °C. IR ($CDCl_3$, cm^{-1}): 688, 833, 1037, 1247, 1280, 1600, 1735, 2115, 2258, 3091. ^{1}H NMR (400 MHz CD_3CN) δ (ppm): 4.63 (s, 2H), 5.35 (s, 2H) 7.16 (d, 1H), 7.46 (m, 5H), 8.25 (dd, 1H), 8.32 (d, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 32.30, 71.30, 102.26, 113.31, 115.34, 117.36, 127.28, 127.88, 128.60, 128.78, 135.10, 135.46, 135.48, 163.87, 188.96. HRMS (M+) calcd for $C_{16}H_{13}BrNO_2$: 330.0130; found: 330.0140.

*2-(4-(Benzyloxy)-3-cyanophenyl-2-oxoethyl-4-(*tert-*butoxycarbonylamino)butanoate (13e)*

White solid. Yield: 81%; mp 119–120 °C. IR ($CHCl_3$, cm^{-1}): 3456, 2252, 1743, 1706, 1600, 1502, 1271, 1166. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 1.39 (s, 6H), 1.78 (t, 2H), 2.20 (m, 2H), 3.10 (t, 2H), 5.31 (s, 4H), 7.29 (d, 1H), 7.40 (m, 5H), 8.17 (dd, 1H), 8.25 (d, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 24.47, 25.46, 27.27, 30.34, 39.01, 65.62, 70.79, 70.93, 77.73, 101.89, 112.64, 112.97, 115.01, 117.00, 127.02, 127.53, 128.24, 133.88, 134.15, 135.13, 155.58, 163.57, 172.21, 189.92. HRMS (M + H) calcd for $C_{25}H_{29}N_2O_6$: 452.2026; found: 453.2021.

4-(2-(3-Cyano-4-hydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (13)

Waxy solid. Yield: 50%. IR (KBr, cm^{-1}): 3388, 2358, 2343, 2237, 1677 (broad), 1610, 1438, 1205, 1137, 842, 802, 723. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.94 (t, 2H), 2.59 (m, 2H), 3.08 (t, 2H), 5.39 (s, 2H), 7.05 (d, 1H), 8.01 (dd, 1H), 8.18 (d, 1H). ^{13}C NMR (100 MHz, D_2O) δ (ppm): 21.96, 29.43, 38.54, 66.59, 99.25, 112.76, 115.10, 117.42, 119.74, 134.87, 162.83, 172.45, 192.32. HRMS (M+) calcd for $C_{13}H_{15}N_2O_4$: 263.1032; found: 263.1023.

The synthetic course towards **4**–**9** and **12** followed the same protocol as for **13**–**23**, but commenced with the commercially available corresponding *p*-hydroxyacetophenones. Hence, only spectroscopic data for these are indicated.

1-(3,4-Bis(benzyloxy)phenyl)ethanone (4d)

White solid. Yield: 98%. *This compound is known.* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (dd, *J* = 8.8, *J* = 2.3 Hz, 1H), 7.40 (m, 11H), 6.94 (dd, *J* = 9.2, *J* = 2.0 Hz, 1H), 5.25 (s, 2H), 5.22 (s, 2H), 2.52 (s, 3H).

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1-(3,4-Bis(benzyloxy)phenyl)-2-bromoethanone (4e)

Oil. Yield: 96%[7]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (s, 1H), 7.41 (m, 11H), 6.96 (d, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 4.46 (s, 2H).

2-(3,4-Bis(benzyloxy)phenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (4f)

White precipitate. Yield: 90%; mp 112–114 °C. IR (KBr, cm^{-1}): 3310, 3100–2800, 1743, 1700, 1658, 1601, 1436, 1400, 1200, 1165, 955, 745, 742, 700, 697, 665, 651. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.62 (dd, J = 7.2, J = 2.4 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.38 (m, 10H), 7.19 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 5.40 (s, 2H), 5.27 (s, 2H), 5.21 (s, 2H), 2.97 (t, J = 6.8 Hz, 2H), 2.40 (t, J = 7.7 Hz, 2H), 1.70 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 197.09, 171.80, 155.60, 152.85, 147.98, 136.85, 128.41, 127.94, 127.58, 126.84, 122.64, 113.04, 112.51, 77.47, 70.00, 66.07, 39.61, 30.67, 28.22, 24.54. HRMS (M + H) calcd for $C_{31}H_{36}NO_7$: 534.2492; found: 534.2484.

2-(2,4-Dihydroxyphenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (4g)

An adapted method of Theodorakis and co-workers[29] was utilized. To a stoppered round-bottom flask containing a solution of **4f** (1.20 g, 2.24 mmol) and 120 mg of 10% *w*/*w* Pd/C in 25 mL of EtOAc was added H_2 via a needle from a reinforced balloon. The reaction was deemed complete after 4 h by the absence of the reagent band on TLC (hexanes–EtOAc, 1:1). Excess solvent was removed in vacuo to afford an adhesive precipitate. Yield: 98%. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.32 (d, J = 7.2 Hz, 2H), 6.93 (s, 1H), 6.89 (t, J = 6.9 Hz, 1H), 5.39 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.9 Hz, 2H), 1.68 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 197.34, 171.97, 155.66, 155.52, 136.92, 123.01, 113.09, 112.39, 77.55, 70.13, 39.56, 30.65, 28.19, 24.53.

4-(2-(3,4-Dihydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (4)

White precipitate. Yield: 92%; mp 56–58 °C. IR (KBr, cm^{-1}): 3432, 3274, 3100–2800, 1739, 1691, 1602, 1520, 1421, 1377, 1309, 1298, 1201, 1178, 1128, 1055, 1027, 1008, 823, 762, 717, 613. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.35 (s, 1H), 7.33 (s, 1H), 6.91 (d, J = 7.1 Hz, 1H), 5.36 (s, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 2.00 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ (ppm): 194.29, 174.13, 163.06, 150.88, 144.11, 125.88, 122.69, 119.74, 117.42, 115.10, 66.56, 38.30, 30.23, 21.95. HRMS (M+) calcd for $C_{12}H_{16}NO_5$: 254.1028; found: 254.1032.

1-(2,4-Bis(benzyloxy)phenyl)ethanone (5d)

White precipitate. Yield: 97%. *This compound is known.* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (t, J = 7.6, 1H), 7.39 (m, 11H), 6.64 (dd, J = 8.7, J = 2.3 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 2.57 (s, 3H).

1-(2,4-Bis(benzyloxy)phenyl)-2-bromoethanone (5e)

Waxy precipitate. Yield: 94%.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.35 (m, 10H), 6.60 (d, 2H), 5.12 (s, 2H), 5.09 (s, 2H), 4.51 (s, 2H).

2-(2,4-Bis(benzyloxy)phenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (5f)

Adhesive precipitate. Yield: 48%. IR (KBr, cm^{-1}): 3310, 3100–2800, 1743, 1700, 1658, 1601, 1436, 1400, 1200, 1165, 955, 745, 742, 700, 697, 665, 651. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.93 (t, J = 8.8 Hz, 1H), 7.43 (m, 10H), 7.14 (dd, J = 8.7, J = 2.2 Hz, 1H), 6.88 (t, J = 5.7 Hz, 1H), 6.62 (d, J = 4.7 Hz, 1H), 5.37 (s, 2H), 5.29 (s, 1H), 5.21 (s, 1H), 5.10 (s, 2H), 2.94 (t, J = 6.6 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.76 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 190.50, 172.15, 164.65, 159.78, 155.58, 135.99, 132.04, 128.35, 127.51, 118.10, 107.59, 103.90, 100.33, 77.43, 70.72, 69.19, 39.95, 30.68, 28.22, 24.88. HRMS (M + H) calcd for $C_{31}H_{36}NO_7$: 534.2492; found: 534.2504.

2-(2,4-Dihydroxyphenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (5g)

Adhesive precipitate. Yield: 97%. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 11.43, (s, 1H), 11.34 (s, 1H), 7.88 (s, 1H), 7.70 (d, 1H), 6.87 (t, 1H), 6.38 (d, 1H), 5.28 (s, 1H), 2.96 (t, 2H), 2.40 (t, 2H), 1.67 (m, 2H), 1.38 (s, 9H).

4-(2-(2,4-Dihydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (5)

White precipitate. Yield: 85%; mp 136–138 °C. IR (KBr, cm^{-1}): 3432, 3274, 3100–2800, 1739, 1691, 1602, 1520, 1421, 1377, 1309, 1298, 1201, 1178, 1128, 1055, 1027, 1008, 823, 762, 717, 613. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.97 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 7.6v, 1H), 5.48 (s, 1H), 5.43 (s, 1H), 3.14 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.0 Hz, 2H), 2.08 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ (ppm): 193.77, 174.15, 162.75, 151.02, 144.22, 125.92, 122.70, 119.65, 117.37, 115.58, 66.60, 38.51, 30.28, 22.00. HRMS (M+) calcd for $C_{12}H_{16}NO_5$: 254.1028; found: 254.1038.

1-(4-(Benzyloxy)-3-methyl-phenyl)ethanone (6d)

White precipitate. Yield: 95%. *This compound is known.* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (s 1H), 7.80 (s, 1H), 7.40 (m, 5H), 6.90 (d, J = 8.8 Hz, 1H), 5.17 (s, 2H), 2.56 (s, 3H), 2.33 (s, 3H).

1-(4-(Benzyloxy)-3-methylphenyl)-2-bromoethanone (6e)

Oil. Yield: 97%.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (d, 2H), 7.40 (m, 5H), 6.88 (d, J = 8.8 Hz, 1H), 5.19 (s, 2H), 4.33 (s, 2H), 2.33 (s, 3H).

2-(4-(Benzyloxy)-3-methylphenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (6f)

White precipitate. Yield: 94%; mp 105–106 °C. IR (KBr, cm^{-1}): 3307, 3100–2800, 1742, 1701, 1659, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.82 (d, J = 9.1 Hz, 2H), 7.40 (m, 5H), 7.14 (d, J = 8.1 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 5.39 (s, 2H), 5.25 (s, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H), 2.24 (s, 3H), 1.70 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 191.14, 172.20, 161.40, 155.60, 136.67, 131.00, 130.10, 129.26, 128.50, 127.34, 126.45, 125.07, 111.62, 77.45, 69.55, 66.03, 39.33, 30.68, 28.18, 24.98, 16.04. HRMS (M + Na) calcd for $C_{25}H_{31}NO_6Na$: 464.2049; found: 464.2017.

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2-(4-Hydroxy-3-methylphenyl)-2-oxoethyl-4-(tert-butoxycarbonylamino)butanoate (6g)

Adhesive precipitate. Yield: 98%. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 10.76 (s, 1H), 7.86 (d, J = 9.2 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 6.89 (t, 1H), 5.38 (s, 2H) 2.96 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 7.8 Hz, 2H), 2.24 (s, 3H), 1.70 (m, 2H), 1.38 (s, 9H).

4-(2-(4-Hydroxy-3-methylphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (6)

White precipitate. Yield: 89%; mp 118–120 °C. IR (KBr, cm^{-1}): 3432, 3274, 3100–2800, 1739, 1691, 1602, 1520, 1421, 1377, 1309, 1298, 1201, 1178, 1128, 1055, 1027, 1008, 823, 762, 717, 613. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.86 (s, 3H), 7.72 (d, J = 6.2 Hz, 1H), 7.67 (dd, J = 9.0, J = 1.8 Hz, 1H), 5.39 (s, 1H), 2.88 (t, J = 7.0 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.87 (m, 2H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 190.67, 171.72, 160.98, 158.27, 130.76, 127.76, 125.10, 120.30, 117.94, 114.76, 66.11, 38.09, 30.15, 22.10, 15.80. HRMS (M+) calcd for $C_{13}H_{18}NO_4$: 252.1230; found: 252.1212.

1-(4-(Benzyloxy)2-methylphenyl)ethanone (7d)

White precipitate. Yield: 93%. *This compound is known.* GC–MS (EI): One peak; retention time, 8.24 min (initial temp 50 °C, ramp 25 °C/min until 300 °C). MS *m*/*z*: 240.0.

1-(4-(Benzyloxy)-2-methylphenyl)-2-bromoethanone (7e)

White precipitate. Yield: 92%. *This compound is known.* GC–MS (EI): One peak; retention time, 9.77 min (initial temp 50 °C, ramp 25 °C/min until 300 °C). MS *m*/*z*: 317.9, 319.9.

2-(4-(Benzyloxy)-2-methylphenyl)-2-oxoethyl-4-(tert-butoxycarbonylamino)butanoate (7f)

Adhesive precipitate.Yield: 91%. IR (KBr, cm^{-1}): 3307, 3100–2800, 1742, 1701, 1659, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.86 (d, J = 9.1 Hz, 1H), 7.47–7.40 (m, 5H), 6.97 (t, J = 6.5 Hz, 2H), 6.87 (t, J = 7.4 Hz, 1H), 5.28 (s, 2H), 5.19 (s, 2H), 2.97 (t, J = 6.7 Hz, 2H), 2.42 (m, 5H), 1.68 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 193.63, 172.21, 161.05, 155.60, 141.48, 136.40, 132.04, 128.47, 127.42, 125.06, 118.30, 111.85, 107.74, 77.45, 69.30, 67.05, 38.83, 30.68, 28.22, 24.54, 21.11. HRMS (M + Na) calcd for $C_{25}H_{31}NO_6Na$: 464.2049; found: 464.2040.

2-(4-Hydroxy-2-methylphenyl)-2-oxoethyl-4-(tert-butoxycarbonylamino)butanoate (7g)

Adhesive precipitate. Yield: 98%. IR (KBr, cm^{-1}): 3460, 3300, 3100–2800, 1740, 1699, 1662, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 10.30 (d, 1H), 7.78 (d, J = 9.1 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.71 (t, J = 6.3 Hz, 1H), 5.26 (s, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.41 (m, 5H), 1.69 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 192.91, 172.21, 160.96, 155.60, 141.83, 131.87, 125.29, 118.74, 112.51, 77.45, 66.86, 38.97, 30.46, 28.22, 24.95, 21.68. HRMS (M + Na) calcd for $C_{18}H_{25}NO_6Na$: 374.1580; found: 374.1577.

4-(2-(4-Hydroxy-2-methylphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (7)

White precipitate. Yield: 95%; mp 110–112 °C. IR (KBr, cm^{-1}): 3460, 3300, 3100–2800, 1740, 1699, 1662, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.86 (s, 3H), 7.80 (d, J = 9.0 Hz, 1H), 6.74 (t, J = 6.2 Hz, 1H), 5.28 (s, 2H), 2.96 (t, J = 6.7 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H), 1.87 (m, 2H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 192.71, 171.72, 161.19, 158.64, 141.88, 131.90, 124.55, 118.81, 117.56, 112.58, 67.02, 37.84, 30.14, 22.54, 20.34. HRMS (M+) calcd for $C_{13}H_{18}NO_4$: 252.1236; found: 252.1227.

1-(4-(Benzyloxy)-3,5-dimethylphenyl)ethanone (8d)

Oil. Yield: 95%. *This compound is known.* GC–MS (EI): One peak; retention time, 8.38 min (initial temp 50 °C, ramp 25 °C/min until 300 °C). MS *m*/*z*: 254.0.

1-(4-(Benzyloxy)-3,5-dimethylphenyl)-2-bromoethanone (8e)

White precipitate. Yield: 95%. *This compound is known.* GC–MS (EI): One peak; retention time, 9.87 min (initial temp 50 °C, ramp 25 °C/min until 300 °C). MS *m*/*z*: 331.9, 333.9.

2-(4-(Benzyloxy)-3,5-dimethylphenyl)-2-oxoethyl-4-(tert-butoxycarbonylamino)butanoate (8f)

Adhesive precipitate. Yield: 96%. IR (KBr cm^{-1}): 3307, 3100–2800, 1742, 1701, 1659, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 7.70 (d, J = 8.6 Hz, 1H), 7.50–7.40 (m, 5H), 6.89 (t, J = 7.2 Hz, 1H), 5.42 (s, 2H), 4.88 (s, 2H), 2.97 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 7.8 Hz, 2H), 2.29 (s, 6H), 1.68 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 191.84, 172.19, 160.04, 155.60, 137.06, 131.49, 129.59, 128.68, 128.36, 128.13, 127.85, 77.45, 73.52, 66.20, 38.97, 30.50, 28.18, 24.97, 16.20. HRMS (M + Na) calcd for $C_{26}H_{33}NO_6Na$: 478.2206; found: 478.2191; (M + H) calcd for $C_{26}H_{34}NO_6$: 456.2386; found: 456.2388.

2-(4-Hydroxy-3,5-dimethylphenyl)-2-oxoethyl-4-(tert-butoxycarbonylamino)butanoate (8g)

Adhesive precipitate. Yield: 99%. IR (KBr, cm^{-1}): 3548, 3301, 3100–2800, 1739, 1702, 1661, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 9.40 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 5.36 (s, 2H), 2.98 (t, J = 7.0 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.20 (s, 6H), 1.92 (m, 2H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 190.91, 172.20, 159.67, 155.59, 128.60, 125.25, 123.74, 77.44, 65.91, 38.96, 30.90, 28.18, 24.98, 16.52. HRMS (M + Na) calcd for $C_{19}H_{27}NO_6Na$: 388.1736; found: 388.1735.

4-(2-(4-Hydroxy-3,5-dimethylphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (8)

White precipitate. Yield: 92%; mp 125–127 °C. IR (KBr, cm^{-1}): 3550, 3301, 3100–2800, 1739, 1702, 1661, 1606, 1437, 1407, 1209, 1167, 955, 743, 700, 667. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 9.36 (s, 1H), 7.86 (s, 3H), 7.62 (d, J = 8.6 Hz, 2H), 5.36 (s, 2H), 2.98 (t, J = 7.0 Hz, 2H), 2.43 (m, 5H), 2.22 (s, 6H), 1.69 (m, 2H), 1.37

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(s, 9H). ^{13}C NMR (125 MHz, d_6-DMSO) δ (ppm): 189.74, 170.61, 157.71, 156.71, 127.72, 124.97, 123.15, 116.95, 65.02, 37.10, 28.88, 21.48, 15.55. HRMS (M+) calcd for $C_{14}H_{20}NO_4$: 266.1392; found: 266.1389.

Benzyl 5-acetyl-2-(benzyloxy)benzoate (9d)

White precipitate. Yield: 93%; mp 98–100 °C. IR (KBr, cm^{-1}): 3325, 3100–2800, 1726, 1697, 1676, 1598, 1500, 1452, 1370, 1269, 1230, 1176, 1060, 1030, 1008, 821, 757, 721, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.46 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 9.0, J = 2.4 Hz, 1H), 7.44–7.33 (m, 10H), 7.09 (d, J = 8.8 Hz, 2H), 5.38 (s, 2H), 5.25 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 195.42, 165.04, 160.91, 135.11, 134.24, 133.04, 130.28, 129.16, 128.22, 127.81, 119.35, 117.36, 112.49, 70.08, 68.86, 25.74. HRMS (M + Na) calcd for $C_{23}H_{20}O_4Na$: 383.1259; found: 383.1262.

Benzyl 2-(benzyloxy)-5-(2-bromoacetyl)benzoate (9e)

Oil. Yield: 95%. IR (KBr, cm^{-1}): 3325, 3100–2800, 1726, 1697, 1676, 1598, 1500, 1452, 1370, 1269, 1230, 1176, 1060, 1030, 1008, 821, 757, 721, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.50 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 9.0, J = 2.4 Hz, 1H), 7.44–7.33 (m, 10H), 7.10 (d, J = 8.9 Hz, 2H), 5.38 (s, 2H), 5.25 (s, 2H), 4.41 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 189.39, 165.32, 162.18, 135.68, 135.48, 134.52, 133.49, 128.74, 128.26, 127.11, 126.47, 120.87, 113.44, 70.86, 67.21, 30.48. HRMS (M + Na) calcd for $C_{23}H_{19}BrO_4Na$: 461.0365; found: 461.0372.

Benzyl-2-(benzyloxy)-5-(2-(4-(*tert*-butoxycarbonylamino)butanoyloxy)acetyl)benzoate (9f)

White precipitate. Yield: 75%; mp 75–77 °C. IR (KBr, cm^{-1}): 3271, 3100–2800, 1733, 1701, 1697, 1600, 1577, 1500, 1454, 1415, 1365, 1269, 1251, 1215, 1166, 1056, 1028, 1008, 919, 875, 821, 758, 700. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 8.26 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 9.0, J = 2.3 Hz, 1H), 7.44–7.33 (m, 11H), 6.89 (t, J = 5.5 Hz, 2H), 5.45 (s, 2H), 5.33 (s, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.68 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 190.85, 172.13, 165.28, 161.01, 155.90, 135.82, 133.51, 130.81, 128.42, 128.04, 127.89, 127.33, 126.27, 113.95, 77.78, 70.10, 64.96, 59.73, 39.30, 30.64, 28.22, 25.24. HRMS (M + Na) calcd for $C_{32}H_{35}NO_8Na$: 584.2260; found: 584.2239.

5-(2-(4-(*tert*-Butoxycarbonylamino)butanoyloxy)acetyl)-2-hydroxybenzoic acid (9g)

Adhesive precipitate. Yield: 96%. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm): 8.37 (d, J = 2.4 Hz, 1H), 8.08 (dd, J = 9.2, J = 2.3 Hz, 1H), 7.10 (d, J = 8.9 Hz, 2H) 6.90 (t, J = 5.5 Hz, 2H), 5.43 (s, 2H), 2.98 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.68 (m, 2H), 1.36 (s, 9H).

4-(2-(3-Carboxy-4-hydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (9)

Adhesive precipitate. Yield: 94%. IR (KBr, cm^{-1}): 3440, 3274, 3100–2800, 1733, 1741, 1692, 1649, 1631, 1596, 1500, 1450, 1416, 1299, 1201, 1184, 1124, 1053, 1006, 823, 800, 760, 707, 680. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 8.36 (s, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 8.1 Hz), 5.46 (s, 2H), 3.12 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.06 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ (ppm): 193.77, 174.11, 171.62, 165.14, 163.06, 134.87, 131.89, 119.72, 117.89, 115.09, 113.41, 66.60, 38.55, 30.45, 21.97. HRMS (M+) calcd for $C_{13}H_{16}NO_6$: 282.0978; found: 282.0967.

1-(4-(Benzyloxy)-3-nitrophenyl)ethanone (12d)

White precipitate. Yield; 96%. *This compound is known.* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (dd, J = 9.2, J = 2.4 Hz, 1H), 8.14 (dd, J = 9.2, J = 1.8 Hz, 1H), 7.42 (m, 6H), 5.34 (s, 2H), 2.60 (s, 2H).

1-(4-(Benzyloxy)-3-nitrophenyl)-2-bromoethanone (12e)

Oil. Yield: 97%.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.34 (s, 1H), 8.00 (d, 1H), 7.28 (m, 6H), 5.20 (s, 2H), 4.23 (s, 2H).

2-(4-(Benzyloxy)-3-nitrophenyl)-2-oxoethyl-4-(*tert*-butoxycarbonylamino)butanoate (12f)

White precipitate. Yield: 67%; mp 144–146 °C. IR (KBr, cm^{-1}): 3310, 3100–2800, 1740, 1700, 1655, 1603, 1433, 1400, 1204, 1170, 955, 745, 697, 665. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 8.37 (dd, J = 7.2, J = 2.6 Hz, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.43 (m, 6H), 6.85 (t, J = 7.2 Hz, 1H), 5.34 (s, 2H), 3.09 (t, J = 6.8 Hz, 2H), 2.46 (t, J = 7.6 Hz, 2H), 1.77 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, CD_3CN) δ (ppm): 195.22, 173.42, 160.65, 158.77, 139.23, 136.54, 135.40, 133.98, 131.78, 128.36, 125.89, 119.24, 116.82, 66.72, 38.44, 30.51, 29.11, 21.88. HRMS (M + Na) calcd for $C_{24}H_{28}N_2O_8Na$: 495.1743; found: 495.1755

4-(2-(4-Hydroxy-3-nitrophenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (12)

White precipitate. Yield: 78%; mp 76–78 °C. IR (KBr, cm^{-1}): 3441, 3265, 3100–2800, 1740, 1690, 1605, 1520, 1430, 1377, 1309, 1252, 1225, 1199, 1166, 1055, 820, 760. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 8.72 (d, J = 2.2 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 5.56 (s, 2H), 3.14 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 9.2 Hz, 2H), 2.08 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ (ppm): 193.16, 174.10, 163.13, 157.81, 135.75, 134.33, 126.61, 120.50, 117.44, 115.12, 66.69, 38.54, 30.23, 21.96. HRMS (M+) calcd for $C_{12}H_{15}N_2O_6$: 283.0925; found: 283.0914.

The procedures for constructing **10** and **11** were the same as those described by Conrad et. al.;[2a,2c] therefore, only spectral data for these are indicated.

5-Bromoacetyl-2-hydroxybenzoic acid methyl ester (10b)

White solid. Yield: 73%; mp 91–92 °C. IR ($CHCl_3$, cm^{-1}): 3030, 3010, 2957, 1675, 1589, 1491, 1444, 1355, 1309, 1089, 965. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.01 (s, 3 H), 4.41 (s, 2 H), 7.05 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 8.8 Hz, 2.2, 1H), 8.50 (d, J = 2.2 Hz, 1H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ (ppm): 30.4, 52.8, 112.3, 118.4, 125.6, 132.2, 133.1, 136.0, 165.8, 169.9, 189.3. HRMS (M + H) calcd for $C_{10}H_{10}BrO_4$: 272.9762; found: 272.9759.

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5-[4-*tert*-Butoxycarbonylaminobutyryloxy)acetyl]-2-hydroxybenzoic acid methyl ester (10c)

White solid. Yield: 46%; mp 113–114 °C. IR ($CHCl_3$, cm^{-1}): 3447, 3023, 2981, 2953, 1745, 1695, 1681, 1588, 1504, 1444, 1368, 1163, 1089, 962. ^1H (400 MHz, $CDCl_3$) δ (ppm): 1.44 (s, 9 H), 1.91 (q, J = 7.0 Hz, 2 H), 2.54 (t, J = 7.3 Hz, 2 H), 3.23 (q, J = 6.4 Hz, 2 H), 4.00 (s, 3 H), 5.32 (s, 2 H), 7.07 (d, J = 8.8 Hz, 1 H), 8.04 (dd, J = 8.8 Hz, 2.2, 1 H), 8.44 (d, J = 2.2 Hz, 1 H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ (ppm), 25.5, 28.6, 31.3, 53.0, 65.8, 112.5, 118.7, 126.0, 131.0, 135.1, 166.0, 170.0, 172.9, 190.2. HRMS (M + H) calcd for $C_{19}H_{26}NO_8$: 396.1650; found: 396.1648.

4-(2-(4-Hydroxy-3-(methoxycarbonyl)phenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (10)

Clear oil. Yield: 100%. IR (CH_2Cl_2, cm^{-1}) 3695, 3440, 3040, 2967, 1739, 1648, 1601, 1526, 1492, 1454, 1359, 1228, 1203, 773, 671. ^1H NMR (400 MHz, D_2O) δ (ppm): 2.04 (q, J = 7.0 Hz, 2H), 2.70 (t, J = 7.1 Hz, 2H), 3.10 (t, J = 7.3 Hz, 2H), 3.96 (s, 3H), 5.47 (s, 2H), 7.03 (d, J = 8.73 Hz, 1H), 8.02 (dd, J = 8.8 Hz, 2.2, 1H), 8.36 (d, J = 8.8 Hz, 2.2, 1H). ^{13}C NMR (74.5 MHz, D_2O) δ (ppm): 22.1, 30.4, 38.7, 53.0, 66.5, 112.7, 117.8, 125.1, 131.3, 134.9, 164.3, 169.4, 174.0, 193.2. HRMS (M+) calcd for $C_{14}H_{18}NO_6$: 296.1134; found: 296.1132.

5-Bromoacetyl-2-hydroxybenzamide (11b)

White solid. Yield: 29%; mp 185 °C (dec.). IR (film, cm^{-1}): 3417, 3364, 3305, 3280, 1671, 1650, 1625, 1587, 1487, 1427, 1363, 1286, 1228, 837, 592. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.72 (s, 2 H), 7.03 (d, J = 8.2 Hz, 1H), 7.45 (bs, 1H), 8.12 (dd, J = 8.8 Hz, 2.20, 1H), 8.38 (bs, 1H), 8.56, (d, J = 2.0 Hz, 1H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ (ppm): 32.7, 114.6, 119.2, 126.2, 130.5, 135.8, 167.9, 173.4, 190.2. HRMS (M + H) calcd for $C_9H_9BrNO_3$ (M + H): 257.9766; found: 257.9783.

4-*tert*-Butoxycarbonylaminobutyric acid 2-(3-carbamoyl-4-hydroxyphenyl)-2-oxoethyl ester (11c)

White solid. Yield: 59%; mp 138–139 °C. IR ($CHCl_3$, cm^{-1}): 3535, 3462, 3414, 3028, 2975, 2931, 1750, 1699, 1663, 1611, 1508, 1417, 1368, 1166. ^1H NMR (400 MHz, acetone-d_6) δ (ppm): 1.4 (s, 9H), 1.85 (q, J = 7.2 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 3.17 (q, J = 6.6 Hz, 2H), 5.42 (s, 2H), 6.05 (bs, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.55 (bs, 1H), 8.07 (dd, J = 8.7, 1.7 Hz, 1H), 8.37 (bs, 1H), 8.51 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75.4 MHz, acetone-d_6) δ (ppm): 26.3, 28.7, 31.7, 40.4, 66.7, 78.6, 114.5, 119.2, 126.2, 129.4, 134.6, 156.8, 167.7, 173.2, 173.4, 191.2. HRMS (M + H) calcd for $C_{18}H_{25}N_2O_7$: 381.1662; found: 381.1645.

4-(2-(3-Carbamoyl-4-hydroxyphenyl)-2-oxoethoxy)-4-oxobutan-1-aminium-2,2,2-trifluoroacetate (11)

Clear oil. Yield: 100%. IR ($CHCl_3$, cm^{-1}): 3415, 3219, 1728, 1692, 1665, 1629, 1497, 1432, 1377, 1238, 1200, 1144. ^1H NMR (400 MHz, D_2O) δ (ppm): 1.92 (q, J = 7.16 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 3.00 (q, J = 6.6 Hz, 2H), 5.40 (s, 2H), 6.94 (d, J = 8.7 Hz, 1H), 7.90 (dd, J = 8.72, 1.72 Hz, 1 H), 8.32 (d, J = 1.88 Hz, 1 H). ^{13}C NMR (75.4 MHz, D_2O) δ (ppm): 22.4, 30.6, 38.9, 66.9, 115.6, 118.2, 125.2, 130.4, 134.1, 163.2, 171.1, 174.4, 193.7. HRMS (M + H) calcd for $C_{13}H_{17}N_2O_5$: 281.1137; found: 281.1114.

The same protocol used for **13**–**23** was utilized for the synthesis of **24** and **25** up to the formation of benzyl-protected α-bromoacetophenones **13**–**23a**.

2-(4-Hydroxyphenyl)-2-oxoethyl acetate (24)

The sequence towards the synthesis of **24** conformed to that of Wan and co-workers.[30]

2-(Acetyloxy)-1-[3-cyano-4-(phenylmethoxy)phenyl]ethanone (26f)

A solution of NaOAc (175 mg, 2.13 mmol) and **25e** (470 mg, 1.42 mmol) in acetone was stirred overnight. The resulting solution was evaporated to dryness, 15 mL of water was added, and the mixture was extracted with ethyl acetate (3× 15 mL). The ethyl acetate layer was dried with anhyd $MgSO_4$. The solvent was removed and the resulting solid was further purified by column chromatography (hexanes – ethyl acetate, 1:1) to give 2-(acetyloxy)-1-[3-cyano-4-(phenylmethoxy)phenyl]ethanone (**25f**) as a white solid (250 mg, 57%); mp 122–124 °C. IR (KBr, cm^{-1}): 2225, 1735, 1701, 1595, 1321, 1222, 1078, 989, 761. ^1H NMR (400 MHz, CD_3Cl) δ (ppm): 2.20 (s, 3H), 5.17 (s, 2H), 5.27 (s, 2H), 7.21 (m, 1H), 7.37 (m, 6H), 7.87 (d, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 19.3, 65.8, 70.3, 112.2, 118.0, 118.2, 122.2, 127.4, 127.6, 128.1, 128.3, 128.4, 128.4, 131.5, 135.5, 161.7, 169.9, 190.0. HRMS (M + Na) calcd for $C_{18}H_{15}NO_4Na$: 332.0899; found: 332.0901.

2-(3-Cyano-4-hydroxyphenyl)-2-oxoethyl acetate (26)

An adapted method from the synthesis of **4g** was employed. White solid. Yield: 80%; mp 158–160 °C. IR (KBr cm^{-1}): 3203, 2227, 1741, 1672, 1604, 1560, 1321, 1220, 1122, 1074, 896, 837, 740. ^1H NMR (400 MHz $(CD_3)_2CO$) δ (ppm): 2.13 (s, 3H), 5.37 (s, 2H), 7.23 (m, 1H), 7.25 (s, 1H), 8.10 (d, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): 19.5, 65.9, 113.0, 117.2, 118.1, 122.5, 128.0, 132.1, 161.5, 169.6, 189.6. HRMS (M + Na) calcd for $C_{11}H_9NO_4Na$: 242.0429; found: 242.0417.

2-(Acetyloxy)-1-[2-cyano-4-(phenylmethoxy)phenyl]ethanone (25f)

The same procedure used for **26f** was followed. White solid. Yield: 90%; mp 92–94 °C. IR (KBr, cm^{-1}): 2231, 1741, 1691, 1604, 1377, 1284, 1224, 1085, 823, 738. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H), 5.24 (s, 2H), 5.30 (s, 2H), 7.08 (d, 2H), 8.05 (m, 5H), 8.16 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.6, 65.6, 71.2, 113.2, 115.1, 127.0, 127.4, 128.7, 128.9, 134.1, 134.2, 134.6, 163.8, 170.4, 189.3. HRMS (M + Na) calcd for $C_{17}H_{16}NO_4Na$: 332.0899; found: 332.0916.

2-(2-Cyano-4-hydroxyphenyl)-2-oxoethyl acetate (25)

White solid. Yield: 90%; mp 185–186 °C. IR (KBr, cm^{-1}): 3150, 2237, 1739, 1666, 1585, 1508, 1421, 1379, 1240, 1124, 1083, 941, 835. ^1H NMR (400 MHz $(CD_3)_2CO$) δ (ppm): 2.14 (s, 3H), 5.42 (s, 2H), 7.19 (d, 1H) 8.12 (dd, 1H), 8.29 (d, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): 19.5, 65.8, 100.0, 115.3, 116.8, 129.9, 133.8,

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134.0, 163.1, 169.6, 189.7. HRMS (M + H) calcd for $C_{11}H_8NO_4$: 218.0453: found: 218.

pHP Diethyl phosphates

Diethyl (2-(4-hydroxyphenyl)-2-oxoethyl) phosphate (27)

The synthesis of **27** was achieved using the protocol of Givens and Park.[1]

Diethyl (2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl) phosphate (28)

The synthesis of **28** was achieved using the same protocol used for **27**.[1]

Diethyl (2-(4-hydroxy-3,5-dimethoxyphenyl)-2-oxoethyl) phosphate (29)

The procedure for synthesizing **29** has been previously published.[25]

3-Methoxyphenyl pivalate (30b)

The general method of Gorobets et al.[31] was followed with modifications. To a cooled (0 °C), stirred solution of 3-methoxyphenol (**30a**, 2.0 g, 16.1 mmol) in dry CH_2Cl_2 (10 mL), freshly distilled triethyl amine (3.350 mL, 24.2 mmol) and catalytic amount of 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added under Ar. After 10 min, pivaloyl chloride (2.98 mL, 24.2 mmol) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir for 30 min at 0 °C, brought to rt, and then stirred overnight. At that point, water (10 mL) and ethyl acetate (30 mL) were added to the reaction mixture and the organic phase was washed sequentially with 10% HCl (3 × 25 mL), water (2 × 25 mL), saturated $NaHCO_3$ solution (3 × 25 mL) and brine (2 × 25 mL. The organic phase was separated, dried over anhyd $MgSO_4$, filtered, and the supernatant concentrated under reduced pressure to produce 3-methoxyphenyl pivalate (**30b**) as thick yellow oil (3.335 g, 100%). IR (Teflon film, cm^{-1}) 2972–2837, 1753, 1606, 1593, 1490, 1140, 1115, 1043, 766. ^1H NMR (500 MHz, CD_3COCD_3) δ (ppm): 7.31–7.28 (1H, t, J = 8.1 Hz), 6.82–6.82 (1H, d, J = 2.3 Hz), 6.81–6.80 (1H, d, J = 2.4 Hz), 6.69–6.66 (1H, m), 3.79 (3H, s), 1.33 (9H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 177.8, 161.6, 153.4, 130.6, 114.7, 112.1, 108.7, 55.8, 39.6, 27.4. HRMS (M + H) calcd for $C_{12}H_{17}O_3$: 209.1178; found: 209.1182. The ^1H NMR data were similar to the literature values.[32]

4-(2-Chloroacetyl)-3-methoxyphenyl pivalate (30c)

The general method of Gonzalez-Gomez et al.[33] was followed with modifications. To a cooled (0 °C) stirred solution of $AlCl_3$ (4.73 g, 35.4 mmol) in chloroacetyl chloride (10 mL) under Ar was added 3-methoxyphenyl pivalate (**30b**, 3.355 g, 16.1 mmol). The reaction mixture was allowed to stir for 3 h at 0 °C under Ar. Then, water (20 mL) was added cautiously to quench the reaction and the resulting solution was extracted to EtOAc (4 × 25 mL). The organic phase was washed sequentially with saturated $NaHCO_3$ solution (3 × 25 mL) and brine (2 × 25 mL). The organic phase was separated, dried over anhyd $MgSO_4$, filtered, and the supernatant concentrated under reduced pressure to afford the crude product that was chromatographed on silica gel (EtOAc–hexanes–CH_2Cl_2, 1:2:2) to give 4-(2-chloroacetyl)-3-methoxyphenyl pivalate (**30c**) as green-white crystalline solid (2.32 g, 50%), mp 58–61 °C. IR (KBr, cm^{-1}): 2980–2854, 1757, 1686, 1606, 1420, 1271, 1186, 1117, 897, 791. ^1H NMR (500 MHz, CD_3COCD_3) δ (ppm): 7.85–7.84 (1H, d, J = 8.6 Hz), 7.01–7.00 (1H, d, J = 2.0 Hz), 6.86–6.83 (1H, d, J = 8.6 Hz), 4.90 (2H, s), 4.01 (3H, s), 1.34 (9H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 190.4, 176.7, 161.3, 157.6, 132.6, 123.4, 115.4, 107.2, 56.8, 51.8, 39.8, 27.3. HRMS (M + H) calcd for $C_{14}H_{18}O_4Cl$: 285.0894; found: 285.0912.

4-(2-Diethoxyphosphoryloxyacetyl)-3-methoxyphenyl pivalate (30e)

The general methods of Finkelstein[34] and Yoh et al.[35] were utilized with modifications. A 50 mL round-bottom flask was charged with 4-(2-chloroacetyl)-3-methoxyphenyl pivalate (**30c**, 500 mg, 1.8 mmol) and NaBr (1.08 g, 10.5 mmol). Acetone (20 mL) was added and the resulting mixture was refluxed at 60 °C for 24 h. The reaction mixture was then concentrated and the resulting residue was suspended in ethyl acetate (20 mL) and washed sequentially with brine (2 × 20 mL) and water (20 mL). The ethyl acetate layer was separated, dried over anhyd $MgSO_4$, filtered, and the supernatant concentrated under reduced pressure to afford 4-(2-bromoacetyl)-3-methoxyphenyl pivalate (**30d**) as a white solid (95% conversion to the α-bromo ketone analog according to ^1H NMR). This compound was used directly in the next step without purification. To a stirred solution of 4-(2-bromoacetyl)-3-methoxyphenyl pivalate (**30d**, 548 mg, 1.66 mmol) in CH_3CN (10 mL), diethyl phosphoric acid (641 mg, 4.16 mmol) and Ag_2O (772 mg, 3.33 mmol) were added. The resulting mixture was stirred at 60 °C and the progress of the reaction was monitored by TLC. After 16 h, the black-colored suspension was filtered through a plug of Celite, the filtrate concentrated, and EtOAc (20 mL) was added. The organic layer was washed sequentially with saturated $NaHCO_3$ (40 mL) and water (20 mL) and dried over anhyd $MgSO_4$. The solvent was evaporated to afford the crude product as a yellow-brown liquid that was chromatographed on silica gel using a gradient solvent system (EtOAc–hexanes (1:2), EtOAc–hexanes (1:1), EtOAc–hexanes (2:1), EtOAc–hexanes (3:1), EtOAc–MeOH (19:1)) to produce the 4-(2-(diethoxyphosphoryloxy)acetyl)-2-methoxyphenyl pivalate (**30e**) as a yellow-brown solid (468 mg, 76%), mp 80–84 °C. IR (KBr, cm^{-1}): 2982–2852 (br), 1747, 1686, 1605, 1261, 1124, 1028, 854, 798. ^1H NMR (500 MHz, CD_3COCD_3) δ (ppm): 7.93–7.91 (1H, d, J = 8.6 Hz), 7.01 (1H, d, J = 2.0 Hz), 6.86–6.84 (1H, d, J = 8.5 Hz), 5.18–5.16 (2H, d, J = 10.8 Hz), 4.18–4.12 (4H, m), 4.00 (3H, s), 1.34 (9H, s), 1.32–1.29 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 193.0, 192.9, 176.7, 161.7, 157.7, 132.4, 122.8, 115.4, 107.1, 73.0, 64.4, 64.3, 56.8, 39.8, 27.3, 16.5. ^{31}P NMR (162 MHz, CD_3COCD_3) δ (ppm): –0.24. HRMS (M + H) calcd for $C_{19}H_{26}O_8PNa$: 425.1341; found: 425.1323.

Diethyl (2-(4-hydroxy-2-methoxyphenyl)-2-oxoethyl) phosphate (30)

NH_4OAc (1.435 g, 18.61 mmol) was added to a stirred solution of 4-(2-(diethoxyphosphoryloxy)acetyl)-2-methoxyphenyl pivalate (**30e**, 468 mg, 1.16 mmol) in aq MeOH

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(H_2O–MeOH, 1:4, 20 mL). The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 36 h, the reaction mixture was concentrated and the residue was extracted with EtOAc (5 × 10 mL). Combined organic layers were dried over anhyd $MgSO_4$ and the solvent was evaporated to afford diethyl 2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl phosphate (**30**) as a dark yellow solid that was further purified on silica gel using a gradient solvent system (EtOAc–hexanes (3:1), EtOAc–MeOH (19:1)) to isolate the pure compound as a white crystalline solid (340 mg, 92%), mp 95–98 °C. IR (KBr, cm^{-1}): 3134, 1672, 1602, 1473, 1383, 1337, 1231, 1032, 984, 849. ^{1}H NMR (400 MHz, CD_3COCD_3) δ (ppm): 9.40 (1H, s) 7.83–7.81 (2H, d, J = 8.8 Hz), 6.56 (2H, m), 5.12–5.09 (2H, d, J = 11.2 Hz), 4.20–4.13 (4H, m), 3.94 (3H, s), 1.33–1.29 (6H, m). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 191.5, 164.97, 162.9, 133.4, 117.3, 109.4, 99.7, 73.1, 73.0, 64.4, 56.1, 16.5. ^{31}P NMR (162 MHz, CD_3COCD_3) δ (ppm): –0.37. HRMS (M – H) calcd for $C_{13}H_{18}O_7P$: 317.0790; found: 317.0795.

The same protocol was used for the synthesis of **31b** and **31d** except for the final step for **31** and only spectral data are conveyed for these derivatives.

3,5-Dimethoxyphenyl pivalate (31b)

Oil. Yield: 100%. IR (Teflon film, cm^{-1}): 2968–2839, 1751, 1618, 1475, 1130, 1063, 895, 835, 681. ^{1}H NMR (500 MHz, CD_3COCD_3) δ (ppm): 6.38–6.37 (1H, t, J = 2.3 Hz), 6.29 (1H, s), 6.28 (1H, s), 3.77 (6H, s), 1.32 (9H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 176.9, 162.2, 154.0, 101.8, 98.4, 55.9, 39.6, 27.4. HRMS (M + Na) calcd for $C_{13}H_{18}O_4Na$: 261.1103; found: 261.1100.

4-(2-Bromoacetyl)-3,5-dimethoxyphenyl pivalate (31d)

White solid. Yield: 20%; mp 125–128 °C. IR (KBr, cm^{-1}): 3018–2841, 1749, 1732, 1597, 1464, 1412, 1221, 1128, 997, 892. ^{1}H NMR (500 MHz, CD_3COCD_3) δ (ppm): 6.53 (2H, s), 4.59 (2H, s), 3.81 (6H, s), 1.33 (9H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 193.9, 176.8, 158.9, 155.6, 114.9, 99.7, 56.8, 51.0, 39.7, 27.4. HRMS (M + Na) calcd for $C_{15}H_{19}O_5BrNa$: 381.0314; found: 381.0312.

Diethyl (2-(4-hydroxy-2,6-dimethoxyphenyl)-2-oxoethyl) phosphate (31)

The general methods of Knopik et al.[36] and Das et al.[37] were followed with some modifications. The potassium salt of diethyl phosphoric acid (535 mg, 2.78 mmol) and dibenzo-[18]-crown-6 (50 mg, 0.14 mmol) were added to a stirred solution of 4-(2-bromoacetyl)-3,5-dimethoxyphenyl pivalate (**31d**, 500 mg, 1.40 mmol) in CH_3CN (10 mL). The resulting mixture was stirred at 80 °C and the progress of the reaction was monitored by TLC. After 16 h, the reaction mixture was concentrated and EtOAc (20 mL) was added. The organic layer was washed sequentially with saturated $NaHCO_3$ (40 mL) and water (20 mL) and dried over anhyd $MgSO_4$. The solvent was evaporated to afford the crude product as a yellow-white solid that was chromatographed on silica gel using a gradient solvent system (EtOAc–hexanes (1:2), EtOAc–hexanes (1:1), EtOAc–hexanes (2:1), EtOAc–hexanes (3:1), EtOAc–MeOH (19:1)) to isolate the crude diethyl 2-(4-hydroxy-2,6-dimethoxyphenyl)-2-oxoethyl phosphate as a dark yellow thick oil. Several attempts were made to purify the product on silica gel, but they were unsuccessful. Therefore, the crude product was used in the deprotection step without further purification. NH_4OAc (456 mg, 5.92 mmol) was added to a stirred solution of the crude phosphate from the previous step (160 mg) in aq MeOH (H_2O–MeOH, 1:4, 10 mL). The resulting mixture was warmed at 50 °C and the progress of the reaction monitored by TLC. After 36 h, the reaction mixture was concentrated and the residue was extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over anhyd $MgSO_4$, and the solvent was evaporated to afford diethyl 2-(4-hydroxy-2,6-dimethoxyphenyl)-2-oxoethyl phosphate (**31**) as a yellow-brown thick oil that was further purified by preparative TLC (hexanes–isopropanol–chloroform, 1:1:11) to produce the pure product as a thick yellow oil (10 mg, overall 2%). UV–vis [H_2O–CH_3CN (1:1)] λ_{max} (ε $(mol/L)^{-1}$ cm^{-1}): 283 (5013). IR (Teflon film, cm^{-1}): 2959–2852, 1738, 1593, 1462, 1342, 1261, 1211, 1153, 1028, 800. ^{1}H NMR (400 MHz, CD_3COCD_3) δ (ppm): 9.04 (1H, s), 6.18 (1H, s), 4.81–4.79 (2H, d, J = 9.3 Hz), 4.13–4.05 (2H, m), 3.75 (3H, s), 1.30–1.27 (6H, m). ^{13}C NMR (125 MHz, CD_3COCD_3) δ ppm 196, 162.4, 160.2, 108.8, 92.9, 72.2, 64.4, 56.2, 16.5. ^{31}P NMR (162 MHz, CD_3COCD_3) δ (ppm): –0.75. MS (ESI (–)) m/z calcd for $(C_{14}H_{21}O_8P–H)^-$: 347.0896; found: 347.0887.

3-Acetyl-4-hydroxybenzoic acid (32b)

The general method of Nagano and Matsumura[38] was followed with modifications. Aluminum chloride (2.96 g, 22.2 mmol) was added into a flame-dried three-neck round-bottom flask containing a solution of 4-hydroxybenzoic acid (**32a**; 1.0 g, 5.55 mmol) in nitrobenzene (10 mL) under Ar. The reaction mixture was kept stirring vigorously at 150 °C for 14 h in the three-neck flask fitted with a $CaCl_2$ tube. On cooling, some crushed ice and 10% HCl (50 mL) were added to the flask, and the separated nitrobenzene was removed by distillation. The aqueous phase was extracted with EtOAc (3 × 25 mL) and washed with saturated $NaHCO_3$ solution (3 × 25 mL). The alkaline aqueous phase was acidified with 10% HCl and extracted again with EtOAc (3 × 25 mL). The combined later organic layers were dried over anhyd $MgSO_4$, filtered, and the supernatant concentrated under reduced pressure to afford 3-acetyl-4-hydroxybenzoic acid (**32b**) as a pink colored solid (980 mg, 98%), mp 227–230 °C. IR (KBr, cm^{-1}): 3433, 1684, 1643, 1610, 1578, 1420, 1325, 1296, 1215, 1122, 943, 825, 771. ^{1}H NMR (400 MHz, CD_3COCD_3) δ (ppm): 12.71 (1H, s), 8.56 (1H, s), 8.17–8.15 (1H, d, J = 8.0 Hz), 7.05–7.03 (1H, d, J = 8.0 Hz), 2.77 (3H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 166.7, 166.6, 138.1, 134.6, 122.4, 120.2, 119.1, 119.0, 27.0. HRMS (M – H) calcd for $C_9H_7O_4$: 179.0344; found: 179.0323

4-Acetoxy-3-acetylbenzoic acid (32c)

Triethyl amine (1.465 mL, 10.55 mmol) followed by acetyl chloride dropwise (564 μL, 7.91 mmol) was added to a stirred solution of **32b** (950 mg, 5.27 mmol) in dry CH_2Cl_2 (15 mL) under Ar. The reaction mixture was allowed to stir for 45 min at rt. At that point, ethyl acetate (40 mL) was added to the reaction mixture, and the organic phase was

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washed with 10% HCl (3 × 25 mL) followed by saturated $NaHCO_3$ solution (3 × 25 mL). The aqueous fractions from the $NaHCO_3$ extraction were combined, acidified with 10% HCl, and extracted into EtOAc (3 × 25 mL). The EtOAc fractions were combined, dried over anhyd $MgSO_4$, filtered, and the supernatant concentrated under reduced pressure to afford the 4-acetoxy-3-acetylbenzoic acid (**32c**) as a pink solid (820 mg, 70%), mp 125–145 °C (dec.). IR (KBr, cm^{-1}) 3078–2552 (br), 1767, 1689, 1647, 1429, 1296, 1192, 918, 735; ^1H NMR (400 MHz, CD_3COCD_3) δ (ppm): 10.44 (1H, s), 8.48 (1H, d, *J* = 1.8 Hz), 8.23–8.21 (1H, d, *J* = 8.4 Hz), 7.35–7.33 (1H, d, *J* = 8.4 Hz), 2.60 (3H, s), 2.33 (3H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 197.3, 169.4, 166.4, 153.5, 138.1, 135.1, 132.3, 129.3, 125.4, 119.1, 27.0, 21.2. HRMS (M – H) calcd for $C_{11}H_9O_5$: 221.0450; found: 221.0440.

1-(3-Acetyl-4-hydroxyphenyl)-2-diazoethanone (32d)

A flame-dried 50 mL round-bottom flask was charged with **32c** (830 mg, 3.74 mmol) and freshly distilled $SOCl_2$ (20 mL) was added under Ar. The resulting mixture was refluxed at 80 °C for 8 h and concentrated under reduced pressure to afford 4-acetoxy-3-acetylbenzoyl chloride as colorless oil. This acid chloride was used in next step without further purification. To a solution of KOH (3.0 g, 53.5 mmol) in 2-methoxyethanol (17 mL) and water (5 mL), diazold (5.0 g, 23.3 mmol) in diethyl ether (75 mL) was added carefully. The resulting mixture was gently heated to reflux temperatures (40–45 °C). The ether layer was distilled into the collection flask in an ice bath at 0 °C. The ether distillate was sequentially dried over KOH pellets for 1 h at 0 °C and with Na pieces for 1 h at 0 °C. Then a solution of acid chloride (899 mg, 3.74 mmol) in dry ether (10 mL) was added dropwise to the distillate (diazomethane) with vigorous stirring at –5 °C. The reaction mixture was allowed to come to 0 °C and stirred overnight. The solvent was evaporated, and the yellowish orange thick oil was used in the deptrotection step without purification. To a stirred solution of crude 2-acetyl-4-(2-diazoacetyl)phenyl acetate (340 mg, 1.38 mmol) in aq MeOH (H_2O–MeOH, 1:4, 20 mL), NH_4OAc (852 mg, 11.05 mmol) was added. The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated and the residue was extracted with acetone (5 × 10 mL). The combined organic layers were dried over anhyd $MgSO_4$ and the solvent was evaporated to afford 1-(3-acetyl-4-hydroxyphenyl)-2-diazoethanone (**32d**) as a yellowish brown oil that was further purified on silica gel (hexanes–EtOAc, 1:1) to generate the pure compound as a yellow oil (254 mg, 21% overall yield). IR (Teflon film, cm^{-1}): 3364, 2112, 1761, 1690, 1614, 1418, 1362, 1196, 1150, 1011, 914, 847, 733. ^1H NMR (400 MHz, CD_3COCD_3) δ (ppm): 12.68 (1H, s), 8.40 (1H, d, *J* = 2.2 Hz), 8.04–8.01 (1H, d, *J* = 8.8 Hz), 7.03–7.01 (1H, d, *J* = 8.8 Hz), 6.69 (1H, s), 2.76 (3H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 197.5, 185.0, 169.5, 153.2, 135.3, 132.2, 129.6, 125.4, 54.9, 21.2. HRMS (M – H) calcd for $C_{10}H_7N_2O_3$: 203.0457; found: 203.0452.

2-(3-Acetyl-4-hydroxyphenyl)-2-oxoethyl diethyl phosphate (32)

To a stirred solution of **32d** (240 mg, 1.18 mmol) in benzene (10 mL), diethyl phosphoric acid (362 mg, 2.35 mmol) in benzene (5 mL) was added dropwise. The resulting mixture was stirred at 60 °C and the progress of the reaction was monitored by the TLC. After 24 h, EtOAc (20 mL) was added to the reaction mixture. The organic layer was washed sequentially with saturated $NaHCO_3$ (40 mL) and water (20 mL) and then dried over anhyd $MgSO_4$. The solvent was evaporated to afford the crude product as a brownish yellow oil that was chromatographed on silica gel (with a gradient solvent system: EtOAc–hexanes (1:2), EtOAc–hexanes (1:1), EtOAc–hexanes (2:1), EtOAc–hexanes (3:1)) to produce 2-(3-acetyl-4-hydroxyphenyl)-2-oxoethyl diethyl phosphate (**32**) as a thick brown oil (306 mg, 79% yield). IR (Teflon film, cm^{-1}): 3443, 2985–2872, 1703, 1643, 1597, 1369, 1265, 1209, 1153, 1030, 820. ^1H NMR (400 MHz, CD_3COCD_3) δ (ppm): 12.81 (1H, s), 8.59–8.58 (1H, d, *J* = 2.2 Hz), 8.17–8.14 (1H, d, *J* = 8.8 Hz), 7.08–7.06 (1H, d, *J* = 8.8 Hz), 5.42–5.39 (2H, d, *J* = 10.6 Hz), 4.18–4.13 (4H, m), 2.79 (3H, s), 1.33–1.30 (6H, m). ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm): 191.6, 167.2, 136.5, 133.3, 126.8, 120.2, 119.4, 119.3, 69.5, 64.6, 27.2, 16.5, 16.4. ^{31}P NMR (162 MHz, CD_3COCD_3) δ (ppm): –0.14. HRMS (M – H) calcd for $C_{14}H_{18}O_7P$: 329.0790; found: 329.0772.

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