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Bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol: a new and efficient photolabile protecting group for aldehydes and ketones

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Abstract—Synthesis of a new photolabile protecting group, bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol (**4**) from 4,5-dimethoxy-2-nitrobenzyl alcohol in three steps in good yields is described. The acetals and ketals of **4** are stable against acidic and basic reaction conditions and are cleaved smoothly on irradiation at 350 and 400 nm with regeneration of carbonyl compounds in high yields and efficiency.
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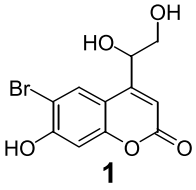
1. Introduction

The use of photolabile molecules as protecting groups has received considerable attention in recent years, as it offers a mild method to deprotect without the requirement of any reagent.[1] It also provides a greater specificity in the presence of other protecting groups and can be smoothly handled in variable acidic, basic and other very sensitive reaction conditions.[2] Although, many photo-removable protecting groups are known for carboxylic acids,[3] amines,[4] amides,[5] carbamates,[6] phenols,[7] alcohols[8] and phosphates,[9,10] surprisingly, less attention has been paid to develop photo-removable groups for aldehydes and ketones, though, they are most commonly used in organic synthesis.[1a] Earlier 6-bromo-4-(1,2-dihydroxyethyl)-7-hydroxy coumarin **1** (Bhc-diol),[11] 2-nitrophenyl ethylene glycol **2**[12] and bis(2-nitrophenyl)ethane diol **3**[13] were developed as photolabile protecting molecules for carbonyl compounds and found to have certain drawbacks.



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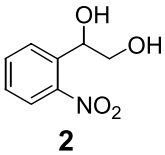

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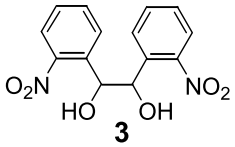

3

Bhc-diol is not a suitable substrate due to the more sensitive coumarin moiety and diol **2** takes several hours for photochemical deprotection under UV-light at longer wavelength (350 nm). We therefore, undertook the design of an efficient protecting group in terms of stability and ease of deprotection. We chose the 4,5-dimethoxy-2-nitrobenzyl group as it exhibited absorbance at longer wavelength than the 2-nitrobenzyl group. We describe herein, the synthesis of the new photolabile protecting group bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol **4** from 4,5-dimethoxy-2-nitrobenzyl alcohol in three steps in good yields. The acetals and ketals of **4** have been found to be stable under all normal reaction conditions and were efficiently deprotected at 350 and 400 nm with liberation of carbonyl compounds in high yields.

2. Results and discussion

4,5-Dimethoxy-2-nitrobenzyl alcohol (**5**),[17] was converted to 4,5-dimethoxy-2-nitro benzyl chloride (**6**) by reaction with PCl_5 and treated further, with KOH in DMSO–ethanol for 45 h to afford stilbene derivative **7** as pale yellow crystals. Stillbene **7** was dihydroxylated with a catalytic amount of OsO_4/NMO to obtain the diol **4** as a crystalline pale yellow solid, mp 154–157 °C (Scheme 1).

In order to study the efficiency of the new photosensitive protecting group, **4** was reacted with various aldehydes **8a–b** and ketones **8c–f** (entries i–vi, Table 1) by refluxing in benzene containing a catalytic amount of pyridinium *p*-toluenesulphonate (PPTS) to obtain the corresponding acetals **9a–b** and ketals **9c–f**, respectively, (Scheme 1). The products **9a–f** were purified by silica gel column chromatography and characterized by IR, NMR and mass spectra. It is worth mentioning the absence of double bond isomerization in enone substrates (entries iii, vi and viii).

Keywords: Protecting groups; Cage compounds; Photolysis; Radical ions.
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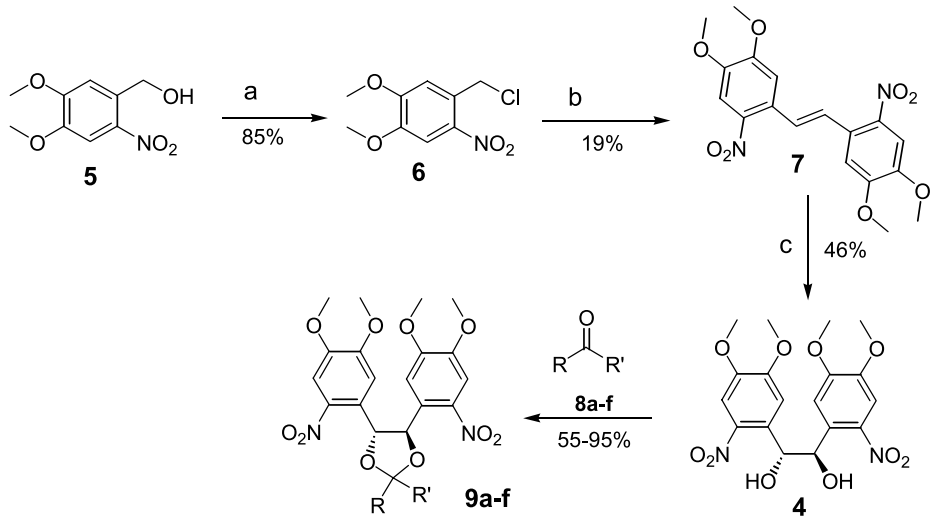


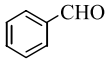
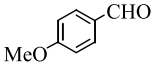
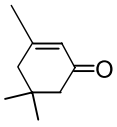
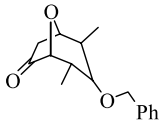
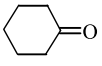
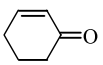
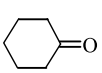
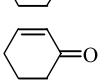
Scheme 1. (a) $PCl_5/CHCl_3$; (b) KOH/DMSO–ethanol; (c) OsO_4/NMO; (d) PPTS, benzene.

The use of 4 Å molecular sieves was essential to avoid deconjucation during the formation of the ketal.

The acetals **9a–b** and ketals **9c–f** were exposed to UV-light at 350 and 400 nm for 2–10 h to regenerate the carbonyl compounds **8a–f**, respectively, in good yields (Table 1). In a typical deprotection experiment 0.1 mmol solution of **9e** in acetonitrile in a Pyrex vessel was irradiated at 350 nm using Rayonet apparatus until TLC showed the disappearance of the starting material. Chromatography of the residue on silica gel afforded cyclohexanone **8e** in 92% yield. Examination of the UV–visible spectra revealed that dimethoxy diol **4** and its acetals **9a–b** and ketals **9c–f** showed very good absorbance at 400 nm (Fig. 1). Accordingly, on irradiation of **9e** at 400 nm for 10 h in a Pyrex vessel, 75% of cyclohexanone **8e** was regenerated (Table 1).

The stability of the compounds was tested in a broad variety of chemical conditions and for commonly used reagents to assess the general applicability of the new protecting group (Table 2). Here, it is worth mentioning that the acetals **9a–b** and ketals **9c–f** were found to be highly stable in acidic and basic reaction media. They did not show any significant decomposition in polar solvents such as DMSO and alcohols. We noticed that **9e** did not undergo reduction with $LiAlH_4$ (5 equiv) even after 48 h at rt in solvents such

Table 1. Protection and deprotection of aldehydes and ketones with diols **3** and **4**

Entry	Diol	Substrate (**8**)	Ketal	Yield (%)	Photolysis	
					350 nm	400 nm
i	**4**	(a) 	**9a**	77	80	58
ii	**4**	(b) 	**9b**	95	82	62
iii	**4**	(c) 	**9c**	55	68	—
iv	**4**	(d) 	**9d**	65	74	—
v	**4**	(e) 	**9e**	90	92	75
vi	**4**	(f) 	**9f**	73	81	—
vii	**3**	(e) 	**10a**	90	89	50
viii	**3**	(f) 	**10b**	80	78	—

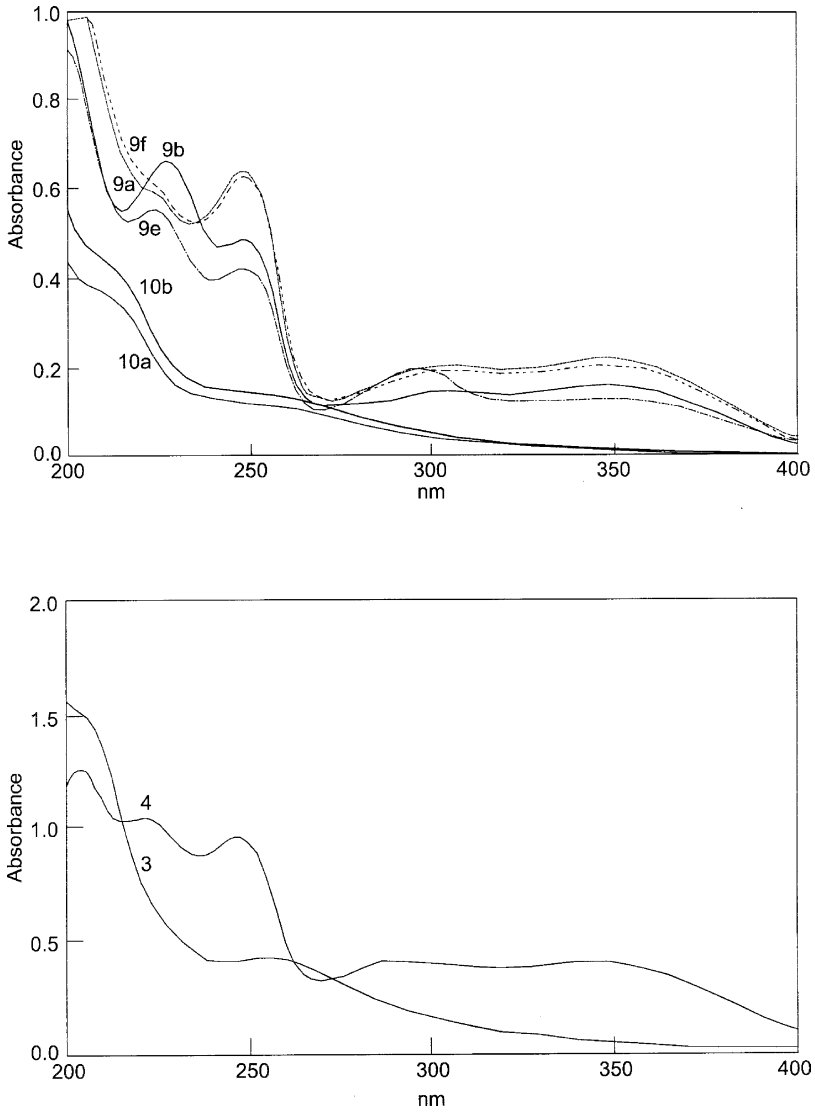
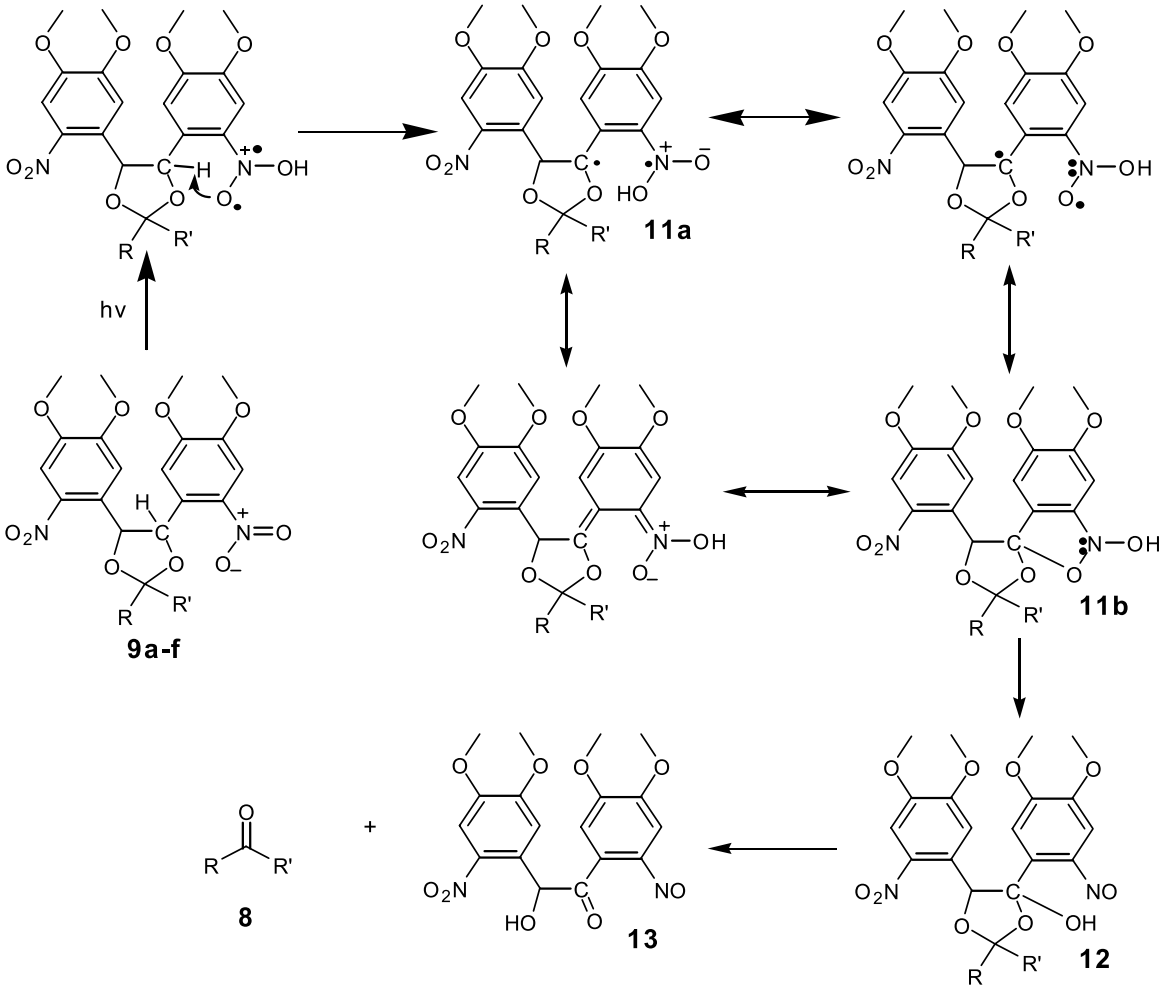


Figure 1. UV–visible spectra of diols **3**, **4**; acetals **9a**, **9b** and ketals **9e**, **9f**, **10a** and **10b**.

Table 2. Stability of ketal **8c** in acidic, basic, oxidation and reduction conditions

S. No	Solvent	Reagent	Reaction conditions[a]		Ketal **8c**[b] (%)	Cyclohexanone
			Temp (°C)	Time (h)		
a	THF	aq HCl (5%)	rt	48	100	0
b	THF	aq H_2SO_4 (10%)	rt	78	99	Trace
c	Dioxane	2 N NaOH	rt	24	100	0
d	Dioxane	2 N NaOH	Reflux	24	89	8
e	THF	NaH	rt	24	98	Trace
f	DMSO	NaH	rt	24	95	Trace
g	DMSO	NaH	100	10	65	Trace
h	CH_3CN	NaH	rt	20	100	0
i	Ether	NaH	rt	24	100	0
j	Ether	$LiAlH_4$	rt	48	98	Trace
k	THF	$LiAlH_4$	rt	48	96	Trace
l	DME	NaH	rt	24	100	0
m	*t*-Butanol	Potassium *t*-butoxide	rt	24	80	Trace
n	Methanol	NaBH4	rt	24	100	0
o	CH_3CN	DDQ	rt	18	85	Trace
p	THF	TBAF	rt	20	95	Trace
q	CH_3CN	CAN	rt	24	85	Trace
r	TFA	TFA	rt	1	58	40
s	Methanol	$NaBH_4 + CeCl_3 \cdot 7H_2O$	rt	24	98	Trace
t	Methanol	Pd/C, H_2	rt	24	0	0

[a] 0.04 mmol of ketal in appropriate solvent was stirred with 5 equiv of reagent in the dark.
[b] Yields are determined by ^{1}H NMR analysis of crude reaction mixture after workup.



Scheme 2. Proposed mechanism for the photodeprotection of ketal **9a–f**.

as ethyl ether and THF (entries j and k, Table 2). Hydrogenation of **9e** with $Pd/C/H_2$ resulted in the formation of the corresponding aniline and deprotection of acetal was not observed. Under aqueous acidic conditions, ketal **9e** showed high stability, whereas in neat TFA at rt, the respective carbonyl compound was isolated in 1 h (entry r, Table 2).

Although, the exact mechanism of the photochemical deprotection is not yet fully understood, it is probably analogous to that described for uncaging of caged calcium,[14] caged neurotransmitters[15] caged peptides[16] and protected diols[12] (Scheme 2). The key step involves intramolecular abstraction of benzylic hydrogen in a singlet or a triplet state to give **11a** or **11b**, its rearrangement to hemiacetal **12** and collapse of the latter afford the free carbonyl compound **8** and nitroso compound **13**. The sensitivity of **13** to irradiated light prevented its isolation and it could not therefore, be characterized.

In conclusion, we have synthesized a new photolabile protecting group bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol **4** for aldehydes and ketones and demonstrated the stability of its ketals in various reaction conditions. The ketals were efficiently deprotected both at 350 and 400 nm to regenerate carbonyl compounds in good yields.

3. Experimental

3.1. General

Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV-light at 254 and 365 nm, iodine and heating plates after dipping in 2% phosphomolybdic acid in 15% aq H_2SO_4 solution. Column chromatography was carried out using silica gel 60–120 mesh purchased from ACME Chemical Company, Bombay. All solvents used were purified and dried according to the standard procedures. IR spectra were recorded on Perkin-Elmer 683 or 1310 FT-IR spectrometer with KBr pellets. NMR spectra were recorded on Varian Unity-400 MHz and BRUKER AMX 300 MHz spectrometers using tetramethylsilane as an internal standard. ^{13}C NMR was recorded on Varian Unity 100 MHz using $CDCl_3$ as internal standard. Mass spectra were recorded on a VG Micromass 7070H and Finnigan Mat 1020B mass spectrometers operating at 70 eV. UV-spectra were recorded on a Perkin-Elmer UV/Vis spectrophotometer. Benzaldehyde, *p*-methoxybenzaldehyde, cyclohexanone, 2-cyclohexenone, 3,5,5-trimethyl-2-cyclohexenone were purchased from SD-Fine chemicals,

Bombay. Bis(2-nitrophenyl)ethanediol **3** and its cyclohexanone ketal **10a** and cyclohexanone ketal **10b** were synthesized according to the literature procedure.[13]

3.1.1. 4,5-Dimethoxy-2-nitrobenzyl chloride 6. 4,5-Dimethoxy-2-nitrobenzyl alcohol **5** (3.0 g, 14.0 mmol) in chloroform (80 ml) was treated with PCl_5 (3.2 g, 15.4 mmol) at rt for 30 min. The reaction was quenched with addition of water (80 ml), organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure to give a solid residue, which was passed over silica gel column (eluted with ethyl acetate/hexane 1:9) to isolate the titled compound **6** (2.72 g, 85%) as a pale yellow solid, mp 65–66 °C. IR (ν_{max}, cm^{-1}) 3030, 2985, 1425, 1505, 1425, 1285, 1100, 675. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 4.04 (s, 3H), 5.00 (s, 2H), 7.14 (s, 1H), 7.55 (s, 1H). MS (*m/z*, %) 231 (M+, 10), 183 (100), 153 (8), 79 (28). Analysis found: C, 46.84; H, 4.44; Cl, 15.22; N, 6.12. Calcd for $C_9H_{10}ClNO_4$: C, 46.67; H, 4.35; Cl, 15.35; N, 6.05.

3.1.2. *trans*-2,2′-Dinitro-3,3′,4,4′-tetramethoxystilbene 7. To a solution of 4,5-dimethoxy-2-nitrobenzyl chloride **6** (2.0 g, 8.6 mmol) in DMSO (1 ml) and ethanol (3 ml) was added KOH (1.54 g, 26.8 mmol) in ethanol (14 ml) dropwise slowly and stirred for 45 h at rt. The solid precipitate was filtered and washed with ethanol (10 ml) and redissolved in hot ethyl acetate. The insoluble portion was filtered and filtrate was cooled to give the title compound **7** (0.300 g, 19%) as yellow solid, mp 245–248 °C. IR (ν_{max}, cm^{-1}) 2950, 1650, 1500, 1250, 1200, 820, 740. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.95 (s, 6H), 4.60 (s, 6H), 7.14 (s, 2H), 7.59 (s, 2H), 7.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.5, 148.8, 145.2, 128.8, 128.1, 110.0, 107.9, 56.4. MS (EI, *m/z*, %): 390 (M+, 28), 358 (10), 211 (18), 194 (18), 179 (24), 164 (70), 152 (38), 136 (100), 125 (14), 108 (24), 79 (20). Analysis found: C, 55.12; H, 4.58; N, 7.19. Calcd for $C_{18}H_{18}N_2O_8$: C, 55.39; H, 4.65; N, 7.18.

3.1.3. Bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol 4. To a mixture of *trans*-2,2′dinitro-3,3′,4,4′-tetramethoxystilbene **7** (150 mg, 0.38 mmol) in dichloromethane (4 ml) and water (1 ml) and *N*-methyl morpholine oxide (NMO) (50 mg, 0.5 mmol) in water (0.5 ml), OsO_4 (0.1 ml, 0.02 mmol, 4% in water) was added. The reaction mixture was vigorously stirred at rt. After 48 h, reaction mixture was quenched with $Na_2S_2O_4$ (0.45 g in 4.5 ml water) and stirred for an additional 24 h. The dichloromethane layer was separated and the aqueous phase was extracted with ethyl acetate (2×5 ml). The combined organic layers were dried over sodium sulfate and evaporated under vacuum. The residue obtained was chromatographed over silica gel (eluted with hexane/ethyl acetate, 1:1) to isolate diol **4** (50 mg, 46%) as a pale yellow solid, mp 154–157 °C. IR (ν_{max}, cm^{-1}): 3320, 2985, 2895, 1420, 1340, 1280, 100, 1080, 810, 780. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.99 (s, 6H), 4.00 (s, 6H), 5.69 (s, 2H), 7.19 (s, 2H), 7.31 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 148.7, 141.3, 129.8, 111.4, 108.4, 72.3 and 56.4. MS (ESI−ve, $CHCl_3$): 459 (M+Cl−), 884 (2M+Cl−). Analysis found: C, 50.88; H, 4.62; N, 6.71. Calcd for $C_{18}H_{20}N_2O_{10}$: C, 50.95; H, 4.75; N, 6.60.

3.2. General procedure for preparation of acetals 9a–b and ketals 9c–f

A solution of bis(4,5-dimethoxy-2-nitrophenyl)ethylene glycol **4** (1.0 mmol), carbonyl compounds **8a–f** (1.0 mmol), pyridinium *p*-toluenesulfonate (0.1 mmol) in dry benzene (10 ml) was taken in a flask equipped with Dean-Stark water separator (protected from day light) and was heated to reflux. Progress of the reaction was monitored by TLC After completion of reaction, benzene was evaporated under vacuum to obtain residue, which was dissolved in ethyl acetate (10 ml). The organic phase was washed with saturated $NaHCO_3$, brine, dried over sodium sulfate, filtered and evaporated to obtain a residue, which was purified by silica gel column chromatography (eluted with hexane:ethyl acetate) to isolate the acetals and ketals as crystalline solids.

3.2.1. Benzaldehyde acetal 9a. Yield: 77%, pale yellow solid, mp 117 °C. IR (ν_{max}, cm^{-1}): 2923, 2852, 1582, 1516, 1459, 1269, 1064, 869, 752. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.70 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.98 (s, 3H), 5.90 (d, J=5 Hz, 1H), 6.00 (d, J=5 Hz, 1H), 6.39 (s, 1H), 7.10 (s, 1H), 7.35 (s, 1H), 7.44 (m, 3H), 7.51 (s, 1H), 7.54 (s, 1H), 7.60 (d, J=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7, 153.5, 148.7, 148.6, 141.3, 140.6, 137.7, 129.5, 128.6, 110.1, 109.4, 108.3, 107.7, 104.5, 81.0, 80.5, 56.5, 56.4, 56.3, 56.1. MS (ESI−ve, $CHCl_3$): 547 (M+ Cl−), 1059 (2M+Cl−). Analysis found: C, 58.32; H, 4.68; N, 5.48. Calcd for $C_{25}H_{24}N_2O_{10}$: C, 58.59; H, 4.72; N, 5.47.

3.2.2. *p*-Anisaldehyde acetal 9b. Yield: 95%; yellow solid, mp 167 °C. IR (ν_{max}, cm^{-1}): 2933, 2880, 1600, 1520, 1456, 1380, 1200, 1140, 1115, 799. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.09 (s, 3H), 5.90 (d, J=7.8 Hz, 1H), 5.98 (d, J=7.8 Hz, 1H), 6.30 (s, 1H), 6.98 (d, J=10.5 Hz, 2H), 7.18 (s, 1H), 7.35 (s, 1H), 7.52–7.54 (d, J=10.5 Hz, 2H; s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 153.6, 153.4, 148.5, 148.4, 141.0, 140.5, 129.5, 129.4, 128.9, 127.7, 114.0, 109.9, 109.2, 108.1, 107.5, 104.5, 80.8, 80.4, 56.4, 56.2, 56.1, 55.3. MS (ESI−ve, $CHCl_3$): 577 (M+Cl−), 1119 (2M+Cl−). Analysis found: C, 57.78; H, 4.78; N, 5.12. Calcd for $C_{26}H_{26}N_2O_{11}$: C, 57.56; H, 4.83; N, 5.16.

3.2.3. 3,5,5-Trimethyl-2-cyclohexenone ketal 9c. Yield: 55%; yellow solid, mp 152–155 °C. IR (ν_{max}, cm^{-1}): 2925, 2858, 2359, 1667, 1585, 1458, 1274, 1171, 1080, 798, 760. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.09 (s, 6H), 1.29 (s, 3H), 1.80 (s, 2H), 2.00 (s, 2H), 3.91 (s, 6H), 4.09 (s, 6H), 5.51–5.60 (m, 3H), 7.32 (s, 1H), 7.34 (s, 1H), 7.38 (s, 2H). MS (ESI−ve, $CHCl_3$): 579 (M+C1−), 1123 (2M+C1−). Analysis found: C, 59.68; H, 5.88; N, 5.12. Calcd for $C_{27}H_{32}N_2O_{10}$: C, 59.55; H, 5.92; N, 5.14.

3.2.4. Ketal 9d. Yield: 65%, 61–64 °C. IR (ν_{max}, cm^{-1}): 2924, 2855, 2360, 1514, 1458, 1266, 1215, 1083, 868, 802. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (d, J=6.8 Hz, 3H), 1.08 (d, J=6.8 Hz, 3H), 2.20–2.40 (m, 3H), 2.75 (m, 1H), 3.58 (t, J=3.4 Hz, 1H), 3.65 (d, J=3.6 Hz, 1H), 4.31 (m, 1H), 3.71 (s, 3H), 3.96 (s, 3H), 4.10 (s, 3H), 4.55 (ABq, J= 10.8 Hz, 2H), 5.82 (d, J=8.7 Hz, 1H), 6.01 (d, J=8.7 Hz,

1H), 7.12–7.62 (m, 9H). Analysis found: C, 61.51; H, 5.78; N, 4.26. Calcd for $C_{24}H_{28}N_2O_{10}$: C, 61.25; H, 5.75; N, 4.20.

3.2.5. Cyclohexanone ketal 9e. Yield: 90%; pale yellow solid, mp 197–200 °C. IR (ν_{max}, cm^{-1}): 2930, 1520, 1350, 1290, 1210, 1130, 1090, 790. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50 (m, 2H), 1.75 (m, 4H), 1.92 (m, 4H), 3.90 (s, 6H), 4.02 (s, 6H), 5.60 (s, 2H), 7.39 (s, 2H), 7.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.5, 148.5, 141.3, 127.8, 109.8, 107.6, 79.3, 56.3, 56.2, 36.8, 25.5, 23.7. MS (ESI− ve, $CHCl_3$): 539 (M+Cl−), 1043 (2M+Cl−). Analysis found: C, 57.39; H, 5.58; N, 5.62. Calcd for $C_{24}H_{28}N_2O_{10}$: C, 57.14; H, 5.59; N, 5.55.

3.2.6. Cyclohexenone ketal 9f. Yield: 73%; yellow solid, mp 140–142 °C. IR (ν_{max}, cm^{-1}): 2924, 2855, 1584, 1515, 1464, 1386, 1332, 1216, 1117, 1071, 1026, 873. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.90 (m, 2H), 2.19 (m, 4H), 3.90 (s, 6H), 4.08 (s, 6H), 5.61 (d, J=7.5 Hz, 1H), 5.72 (d, J=7.5 Hz, 1H), 5.89 (d, J=9.3 Hz, 1H), 6.11 (d, J=9.2 Hz, 1H), 7.39 (s, 2H), 7.40 (s, 2H). MS (ESI− ve, $CHCl_3$): 537 (M+Cl−), 1040 (2M+Cl−). Analysis found: C, 57.56; H, 5.08; N, 5.11. Calcd for $C_{24}H_{26}N_2O_{10}$: C, 57.37; H, 5.22; N, 5.01.

3.3. General procedure for photolytic deprotection of acetals and ketals 9a–f

A solution of acetals **9a**–**b** or ketals **9c**–**f** (0.1 mmol) in acetonitrile (10 ml) in a Pyrex vessel was degassed by bubbling dry nitrogen gas and irradiated at 350 and 450 nm separately with stirring in Rayonet apparatus equipped with monochromatic lamps. Progress of deprotection was monitored by thin layer chromatography (hexane/ethyl acetate 4:1). Samples were drawn intermittently and yields were determined by GC and proton NMR spectroscopy (Table 1). The reddish brown solution so obtained was evaporated to a residue and purified by flash column chromatography over silica gel to recover carbonyl compounds **8a**–**e**. The irradiation at 400 nm was carried out for 10 h and analogously analyzed by thin layer chromatography and NMR spectroscopy. The carbonyl compounds **8a**–**f** recovered were characterized by comparison with the authentic samples.

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