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A novel thiochromone-type photolabile protecting group for carbonyl compounds

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ABSTRACT

A novel photolabile protecting group, thiochromone *S*,*S*-dioxide, possessing the 1,2-diol group for protection of ketones and aldehydes is described. Photodeprotection of the successfully protected carbonyl derivatives proceeded smoothly under photoirradiation filtered through Pyrex glass (>280 nm) using an ultrahigh-pressure mercury lamp to recover the corresponding carbonyl compounds and the starting protecting group.

1. Introduction

Protecting groups are essential in organic synthesis, in order to achieve desired reactions by protecting reactive functional groups that are not desired in the reaction. However, most protected compounds are deprotected under acidic or basic conditions, or require a highly reactive reagent, which sometimes leads to an undesired reaction or decomposition of the substrates. In this context, much attention has been paid to photolabile protecting groups (PLPGs), which can be removed only by irradiation of light under neutral conditions without any additional reagents.[1] Thus, introducing PLPGs to substrates is a powerful method to perform desired reactions in organic synthesis. Moreover, since deprotection reactions of PLPGs proceed under irradiation with light, reaction scale can be reduced down to the nanoscale, so that the PLPGs can be applied in not only organic synthesis, but also in construction of DNA microarray,[2] or in caged compounds.[3] Especially, an application of PLPGs to caged compounds is now extensively studied in order to control biochemical reactions in a cell to investigate unknown biological phenomena or to remotely control cell functions, causing a demand for widely applicable and highly-efficient PLPGs.

Although a number of reports on PLPGs have already been published, relatively few PLPGs for ketones and aldehydes have been reported compared to those for alcohols, amines, carboxylic acid, and phosphates, even though there are many biological effectors, such as drugs possessing carbonyl moieties.[4] The first PLPG for carbonyl compounds was reported by Gravel et al., in which a diol derivative of a well-known PLPG *o*-nitrobenzyl group releases carbonyl compounds and α-hydroxyketone under photoirradiation.[4a] Dore et al. reported a diol coumarin derivative as a PLPG for ketones and aldehydes, which photodeprotects carbonyl compound and regenerate starting PLPG.[4b] They both modified a linker of typical PLPGs to diol and protected ketones and aldehydes as an acetal moiety.

Inspired by their molecular designs, we designed a novel thiochromone PLPG **1d** possessing diol group as a linker, of which derivatives **1a**–**c** were developed in our laboratory and applied to the protection and deprotection for alcohols, amines, carboxylic acids, and phosphates (Fig. 1).[5] Herein, we report how this design was realized, leading to the development of the novel PLPG **1d** possessing the diol group as linker to connect with ketones and aldehydes.

2. Results and discussion

PLPG **1d** was prepared from compound **2**, a common starting material for our PLPGs (Scheme 1).[5] Introduction of methoxy

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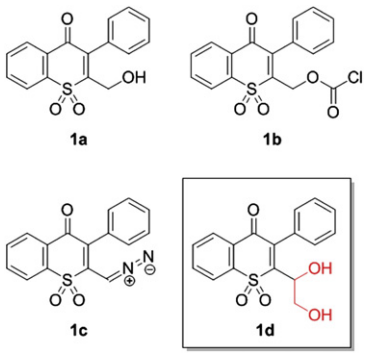
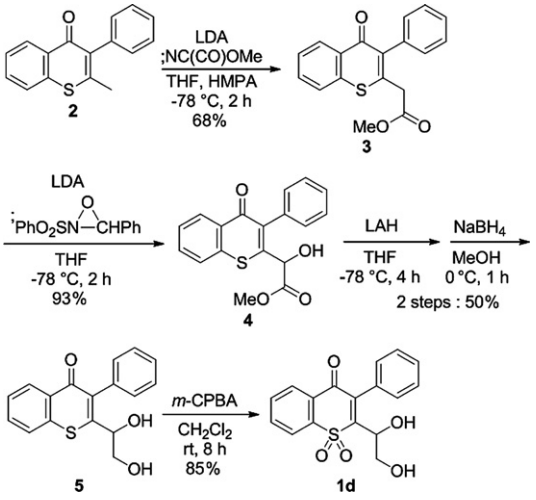


Fig. 1. Structures of new PLPGs.



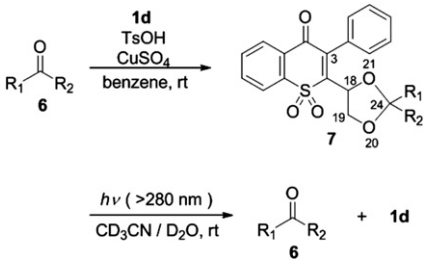
Scheme 1. Synthetic route for PLPG **1d**.

carbonyl moiety to **2** by LDA and methyl cyanoformate afforded methyl ester **3** in 68% yield. α-Hydroxylation of ester moiety in **3** using LDA and Davis reagent prepared by a previously reported procedure gave α-hydroxy methyl ester **4** in 93%.[6] Reduction of ester moiety in **4** to alcohol was achieved in two steps: LAH reduction to give aldehyde intermediate as a crude product, followed by sodium borohydride reduction to give desired diol product **5** in 50% yield. Direct reduction of **4** with LAH or DIBALH did not work well to give complex mixtures including the desired diol **5**. The final step was carried out by oxidation of the sulfur atom of **5** with *m*-CPBA to give target diol PLPG **1d** in 85%.

The new PLPG was promising in protecting the carbonyl compounds and was further examined with various substrates. Protection reactions of the ketones **6a**–**e** and the aldehyde **6i**–**j** were straight forward, based on the reaction conditions reported by Wang et al.[4e] Treatment of carbonyl compounds **6** with 1.1 equiv of **1d** in the presence of 10 mol % of *p*-toluenesulfonic acid and 0.8 equiv of copper(II) sulfate in benzene at room temperature afforded the corresponding compounds **7** in high yield (Table 1, entries 1–5, 9, 10). However, protection reactions for ketones **6f**–**h** were not successful, supposedly due to their steric hindrance (entry 6).

Deprotection of all ketones and aldehydes proceeded smoothly under photoirradiation using a 500 W ultrahigh-pressure mercury lamp filtered through Pyrex glass (>280 nm) within 3 h (Table 1), except for aldehyde **6i** in which moderate photodecomposition of products was observed (entry 9). This decomposition would have happened because of the unstability of the aldehyde **6i** under photoreaction conditions.

Table 1
Protection and photodeprotection of carbonyl compounds **6**



Entry	Carbonyl compound **6**		Protection		Photodeprotection		
			Time (h)	Yield[a] (%)	Time (min)	Yield[b] (%)	
						6	**1d**
1	**a**		8	95	180	91	90
2	**b**		24	88	180	99	94
3	**c**		8	70	180	70	93
4	**d**		36	80	160	75	92
5	**e**		15	85[c]	60	89	89
6	**f**		55	20[c]	100	99	99
7	**g**		8	11[c]	120	99	89
8	**h**		44	N.R.	—	—	—
9	**i**		8	95[d]	120	58	59
10	**j**		52	64[c]	60	79	88

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Obtained as a diastereomeric mixture.
[d] Obtained as a single diastereomer whose stereochemistry is not determined.

Progress of photodeprotection of acetone protected compound **7a** was monitored by ^{1}H NMR spectra (Fig. 2). Before irradiation, three peaks at 4.8 ppm (H_a, dd, 1H), 4.3 ppm (H_b, dd, 1H) and 4.1 ppm (H_c, dd, 1H) derived from the linker methine and methylene of **7a** were observed. After 30 min irradiation, these peaks diminished and new peaks appeared instead. The peaks observed at 4.6 ppm ($H_{a'}$, dt, 1H), 3.9 ppm ($H_{b'}$, m, 1H), and 3.7 ppm ($H_{c'}$, m, 1H) correspond to the PLPG **1d**. The peak at 2.1 ppm corresponds to acetone. Further irradiation for 120 min made the peaks of the substrate disappeared, while the peaks of the PLPG **1d** and the acetone got stronger, proving that the photodeprotection of **7a** proceeds to release both acetone and PLPG **1d** quantitatively under photoirradiation.

The deprotection mechanism was initially studied with TD-DFT calculations (B3LYP/6–31+g(d)) of the acetone protected compound **7a**, of which HOMO and LUMO maps suggested a charge

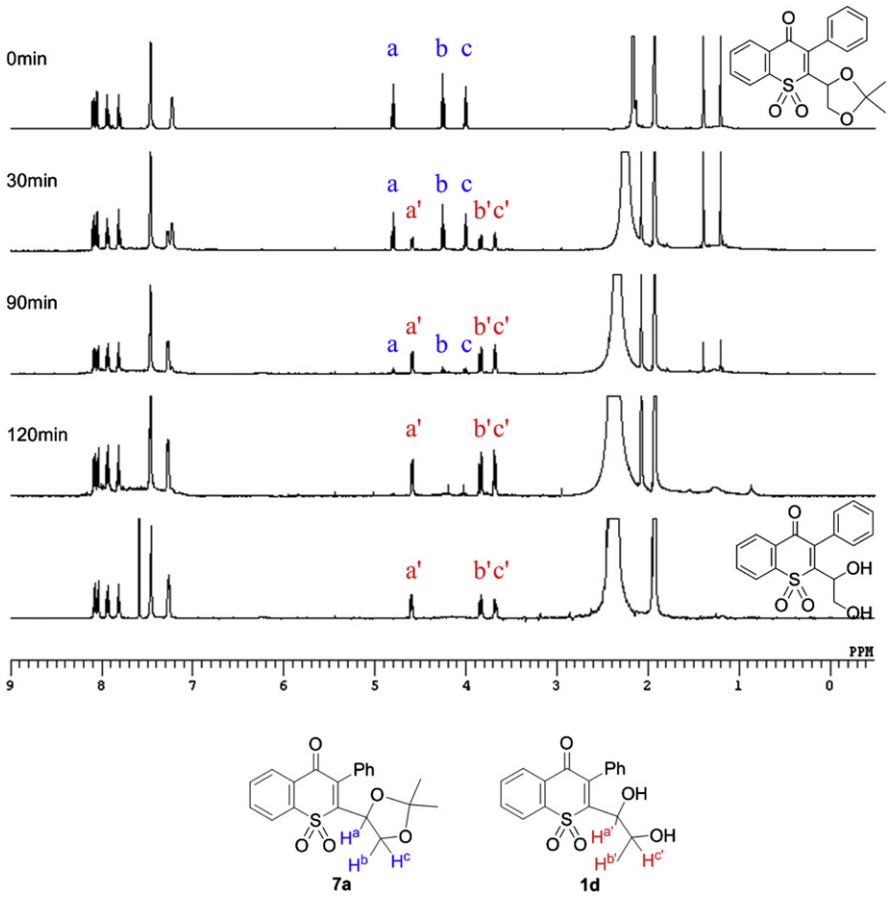
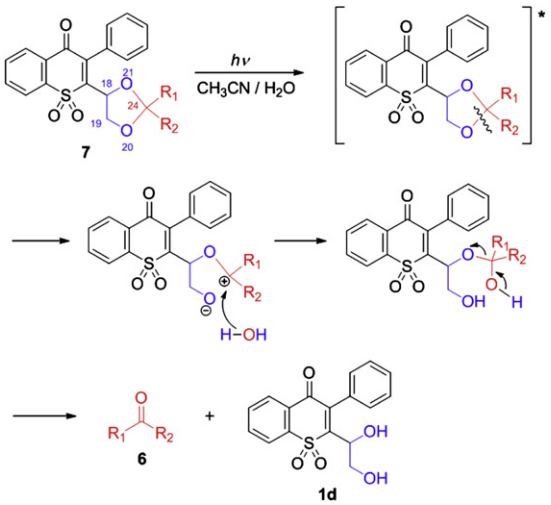


Fig. 2. Process of photodeprotection monitored by ^{1}H NMR spectra.

transfer from acetal moiety to thiochromone framework through excitation, resulting in cleavage of a C–O bond of acetal moiety due to its low electron density (Fig. 3). Considering the selectivity of either of the four C–O bonds to be cleaved as the initiation of the photodeprotection, the cleavage of C24–O20 seems to be preferred due to a generation of stable tertiary carbocation and oxygen anion which is connected with the primary carbon being more stabilized compared to that connected with the secondary carbon (Scheme 2). After the cleavage of C24–O20 bond, nucleophilic addition of water the carbocation followed by the elimination of the ketone results in the recovery of corresponding ketone and PLPG **1d**. To experimentally determine, which C–O bond initially gets cleaved, we carried out the photodeprotection reaction using $H_2{}^{18}O$ (Fig. 4). If the oxygen on the ketone comes from the solvent, then the labeled ketone **6**-^{18}**O** will be formed and the PLPG **1d** won't be labeled, as we predicted above (Fig. 4a, route A). Alternatively, if unlabeled ketone **6** is observed while labeled PLPG **1d**-^{18}**O** is observed, then the source of the oxygen on the ketone would be from the acetal moiety (Fig. 4a, route B). Compound **7d** was chosen for the substrate due to its efficient photodeprotection and cyclopentanone's



Scheme 2. Possible photodeprotection mechanism.

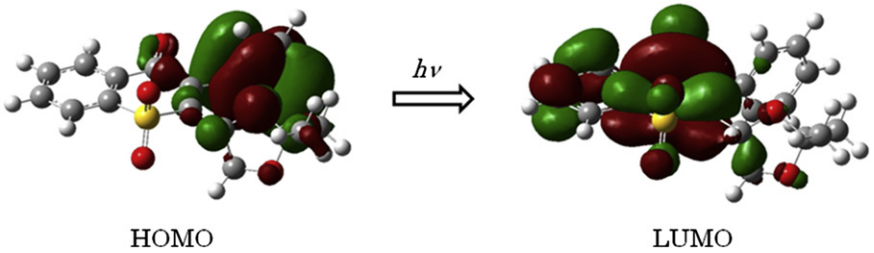


Fig. 3. HOMO and LUMO map of the acetone protected compound **7a**.

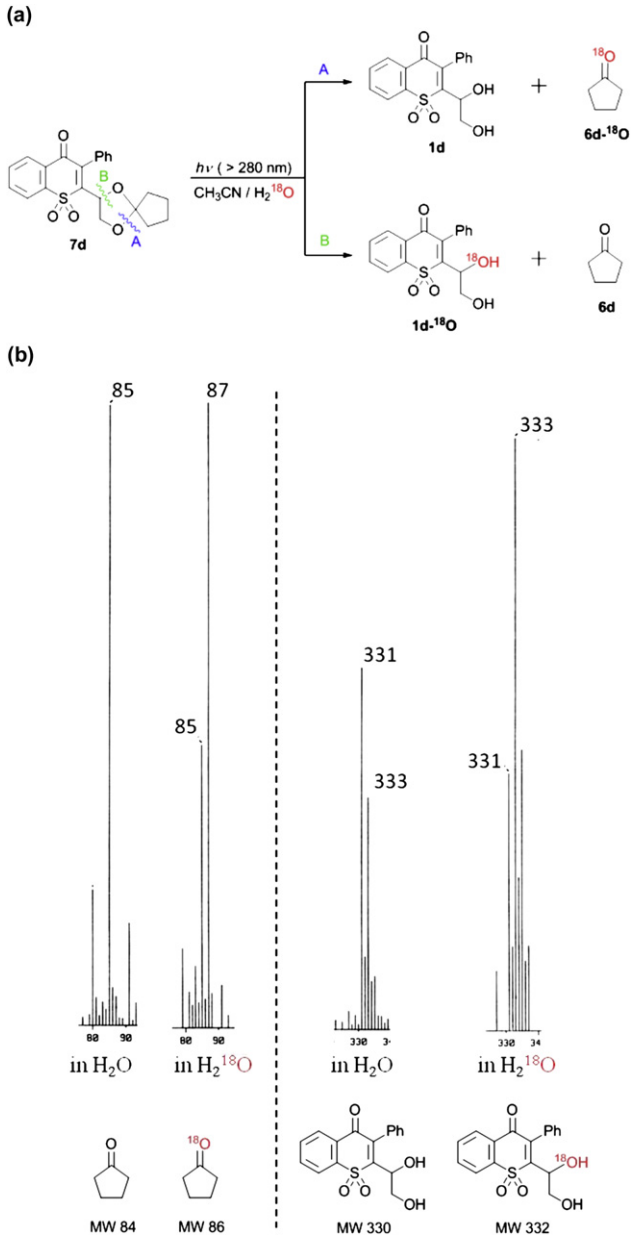


Fig. 4. (a) ^{18}O labeling experiment. (b) MS (CI) spectra of the reaction solution of the labeled and unlabeled experiment of **7d**.

low volatility. A solution of **7d** in either H_2O or $H_2{}^{18}O$ (97% label) was exposed to >280 nm light until **7d** was totally consumed. Then the reaction solution was analyzed by MS (CI) (Fig. 4b). For the reaction in H_2O, mass spectral analysis of the peak on the chromatogram corresponding to cyclopentanone gave exclusively *m*/*z* 85 ($[M+H]^+$). But the one corresponding to PLPG **7d** gave 331 ($[M+H]^+$) with its unusually high isotope ion peak 333 ($[M+2+H]^+$). The reaction in $H_2{}^{18}O$ gave strong *m*/*z* 87 and 333, both as labeled peaks. A comparison of the MS data of the labeled and unlabeled reactions revealed that 64% of the label was incorporated into the cyclopentanone **6d** and 17% of that into the PLPG **1d**. These results did not let us determine, which specific C–O bond was to be cleaved since both the ketone and the PLPG were labeled. However, much higher labeling ratio in ketone **6d**-^{18}**O** (64%) compared to the PLPG **1d**-^{18}**O** (17%) suggest that the way of cleavage of a C–O bond are likely to occur as a simple hydrolysis of an acetal compared to the photolytic cleavage of C18–O21 leading to **1d**-^{18}**O**. To confirm the reproducibility, another labeling experiment was conducted with compound **7j** and the result showed that 56% of the label was incorporated into the benzaldehyde **6j** and 39% of that into the PLPG **1d** (see the Supplementary data for MS spectra). The similar tendency of labeling ratio, higher ratio for carbonyl compounds, was observed and further supported our proposed mechanism. This result is interesting because the proposed intermediate of C–O cleaved diol–protected aldehydes and ketones reported by Dore et al., is different from ours, although the structure of their compound and ours resembles each others in some points.[4b]

3. Conclusion

A novel PLPG for carbonyl compounds has been developed. Protection for carbonyl compounds proceeded successfully, except for the bulky ones. Photodeprotection of all carbonyl compounds proceeded smoothly to regenerate corresponding carbonyl compounds and starting PLPG **1d** in moderate to high yield. The photodeprotection mechanism was discussed along with the molecular orbital map obtained from TD-DFT calculation, supporting the hypothesis that the C–O cleavage is caused by a charge transfer from HOMO to LUMO making the C–O electron density small easily to be cleaved. Although the ^{18}O labeling experiment conducted for further investigation didn't give clear results, it generally supported our proposed mechanism. Interestingly, our proposed intermediate in the photodeprotection reaction was much different from those reported by Dore et al., and this would give a mechanistic insight into the photolysis of acetal structure.

4. Experimental section

4.1. General experimental procedures

Air and/or moisture sensitive reactions were carried out under a nitrogen atmosphere with commercially available anhydrous solvents. All reagents and solvents were commercially purchased and further purified according to the standard methods, if necessary. The progress of reactions was monitored by silica gel TLC plates (mesh size 60 Å, MERCK). Products were purified by flash column chromatography on 40–63 μm silica gel 60 (MERCK). ^1H NMR were recorded on JEOL JNM-ECP 500 (500 MHz). Chemical shifts are reported in parts per million relative to TMS (0 ppm) as an internal standard, or the peak of chloroform-*d* (7.26 ppm). Data is reported as follows: chemical shift, integration, coupling constants (hertz), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet). ^{13}C NMR were recorded on a JEOL JNM-ECP 500 instrument (125 MHz). Chemical shifts are reported in ppm relative to TMS (0 ppm) as an internal standard, or the middle peak of chloroform-*d* (77.0 ppm). Melting points were determined on a Yanaco MP-500D and uncorrected. IR spectra were recorded on a Jasco FT/IR-4200 spectrometer. MS and HRMS were measured on a JEOL JMS-700 spectrometer using EI, CI, ESI or FAB. UV/vis spectra were measured in a quartz cell (10 mm thickness) on a JASCO V-630 spectrometer. DFT calculations were done using the Gaussian 03 program.[7]

4.2. Experimental procedures and characterization data for the synthesis of PLPG 1d

*4.2.1. Methyl 2-(4-oxo-3-phenyl-4H-thiochromen-2-yl) acetate (**3**).* To a solution of lithium *N*,*N*-diisopropylamide in THF (1.0 ml), prepared from 1.6 M *n*-BuLi in hexane (0.65 ml, 1.0 mmol) and *N*,*N*-diisopropylamine (0.14 ml, 1.0 mmol), 2-methyl-3-phenyl-4*H*-thiochromen-4-one **2**[5] (126 mg, 0.50 mmol) in HMPA (1.0 ml) was added at −78 °C. After stirring at −78 °C for 5 min, a mixture of

methyl cyanoformate (44 μl, 0.55 mmol) and THF (0.5 ml) was added. After stirring at −78 °C for 30 min, the reaction was quenched with satd NH_4Cl aq, and the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc=3:1) to give **3** (107 mg, 0.34 mmol, 68%) as colorless solid. Mp: 131.5–132.8 °C. IR (neat): 1739, 1618, 1592, 1438, 1343, 1197, 1172, 1084, 985, 961 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.51 (d, *J*=9.5 Hz, 1H), 7.65–7.59 (m, 2H), 7.55–7.52 (m, 1H), 7.46–7.43 (m, 2H), 7.40–7.37 (m, 1H), 7.20 (d, *J*=7.0 Hz, 2H), 3.67 (s, 3H), 3.56 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.44, 169.12, 142.64, 138.31, 136.40, 135.33, 131.50, 131.03, 129.64, 129.48, 128.59, 128.06, 127.66, 125.86, 52.55, 40.87. HRMS (EI) calcd for $C_{18}H_{14}O_3S$: 310.0664; found 310.0675.

*4.2.2. Methyl 2-hydroxy-2-(4-oxo-3-phenyl-4H-thiochromen-2-yl) acetate (**4**).* To a solution of lithium *N*,*N*-diisopropylamide in THF (1.0 ml), prepared from 1.6 M *n*-BuLi in hexane (0.33 ml, 0.50 mmol) and *N*,*N*-diisopropylamine (73 μl, 0.50 mmol), methyl 2-(4-oxo-3-phenyl-4*H*-thiochromen-2-yl)acetate **3** (81 mg, 0.26 mmol) in THF (1.0 ml) was added at −78 °C. After stirring at −78 °C for 10 min, 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (138 mg, 0.53 mmol) in THF (1.0 ml) was added. After stirring at −78 °C for 1.5 h, the reaction was quenched with satd NH_4Cl aq and the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. The residue was purified by flash chromatography (hexane/CH_2Cl_2/EtOAc=6:3:1) to give **4** (79 mg, 0.24 mmol, 93%) as colorless solid. Mp: 197.3–199.2 °C. IR (neat): 3350, 1746, 1619, 1584, 1437, 1213, 1083 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.49 (d, *J*=8.0 Hz, 1H), 7.63–7.61 (m, 2H), 7.55–7.52 (m, 1H), 7.47–7.44 (m, 2H), 7.42–7.39 (m, 1H), 7.30 (br, 2H), 5.24 (d, *J*=3.5 Hz, 1H), 3.80 (s, 3H), 3.64 (d, *J*=3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.70, 171.85, 147.74, 137.85, 136.02, 135.02, 131.66, 130.89, 129.36, 128.12, 127.66, 126.57, 71.47, 53.76. HRMS (EI) calcd for $C_{18}H_{14}O_4S$: 326.0613; found 326.0619.

*4.2.3. 2-(1,2-Dihydroxyethyl)-3-phenyl-4H-thiochromen-4-one (**5**).* To a solution of $LiAlH_4$ (23.2 mg, 0.90 mmol) in THF (5.0 ml), methyl 2-hydroxy-2-(4-oxo-3-phenyl-4*H*-thiochromen-2-yl)acetate **4** (200 mg, 0.61 mmol) in THF (8.0 ml) was added at −78 °C. After stirring at −78 °C for 4 h, the reaction was quenched with 1 N HCl aq and the reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. To the obtained residue dissolved in MeOH (1.0 ml), $NaBH_4$ (24 mg, 0.63 mmol) was added at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with satd NH_4Cl aq and the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc=5:3) to give **5** (91 mg, 0.31 mmol, 50% within two steps) as colorless solid. Mp: 128.0–128.8 °C. IR (neat): 3346, 2927, 1727, 1581, 1437, 1340, 1263, 1072 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.48 (d, *J*=8.0 Hz, 1H), 7.68–7.61 (m, 2H), 7.53 (dd, *J*=8.0, 8.0 Hz, 1H), 7.47–7.44 (m, 2H), 7.41–7.38 (m, 1H), 7.19 (br, 2H), 4.90–4.87 (m, 1H), 3.73–3.63 (m, 2H), 2.96 (d, *J*=3.0 Hz, 1H), 1.92 (dd, *J*=6.0, 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.72, 154.33, 137.25, 135.50, 135.11, 131.47, 130.71, 129.00, 128.78, 127.98, 127.65, 126.71, 72.45, 65.72. HRMS (EI) calcd for $C_{17}H_{14}O_3S$: 298.0664; found 298.0669.

*4.2.4. 2-(1,2-Dihydroxyethyl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**1d**).* 2-(1,2-Dihydroxyethyl)-3-phenyl-4*H*-thiochromen-4-one **5** (298 mg, 1.0 mmol) and *m*-CPBA (70% assay) (516 mg, 2.1 mmol) were added to CH_2Cl_2 (2.0 ml) at room temperature. After stirring at room temperature for 8 h, the reaction was quenched with satd $Na_2S_2O_3$ aq and the reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc=1:1) to give **1d** (280 mg, 0.85 mmol, 85%) as colorless solid. Mp: 68.1–69.9 °C. IR (neat): 3502, 3369, 1662, 1306, 1155, 1049 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.17 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.91 (dd, *J*=8.0, 8.0 Hz, 1H), 7.80 (dd, *J*=8.0, 8.0 Hz, 1H), 7.49–7.47 (m, 3H), 7.29–7.27 (m, 2H), 4.79 (dt, *J*=9.0, 7.0 Hz, 1H), 4.11–4.06 (m, 1H), 4.02–3.97 (m, 1H), 3.22 (d, *J*=9.0 Hz, 1H), 2.48 (dd, *J*=7.5, 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.63, 148.66, 143.92, 140.61, 134.69, 133.47, 131.15, 129.53, 129.04, 128.92, 128.61, 122.83, 72.58, 64.46. HRMS (FAB) calcd for $C_{17}H_{14}O_3S$ $(M+Na)^+$: 298.0664; found 298.0669.

4.3. General procedure for the synthesis of acetal derivatives 7

To a solution of 2-(1,2-dihydroxyethyl)-3-phenyl-4*H*-thiochromen-4-one 1,1-dioxide **1d** (0.070 mmol) in benzene (3 ml), TsOH (1.2 mg, 0.0070 mmol), $CuSO_4$ (8.9 mg, 0.056 mmol), and carbonyl compound (0.077 mmol) were added at room temperature and stirred until **1d** was totally consumed. The reaction was quenched with satd $NaHCO_3$ aq and the reaction mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered through filter paper, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc=2:1) to give acetal **7**.

*4.3.1. 2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7a**).* Yellow oil. IR (neat): 2253, 1665, 1317, 1154, 912 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.13 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.88 (dd, *J*=8.0, 8.0 Hz, 1H), 7.74 (dd, *J*=8.0, 8.0 Hz, 1H), 7.49–7.47 (m, 3H), 7.17 (br, 2H), 4.84 (dd, *J*=8.5, 7.0 Hz, 1H), 4.37 (dd, *J*=8.5, 8.5 Hz, 1H), 4.08 (dd, *J*=8.5, 7.0 Hz, 1H), 1.53 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.28, 152.59, 136.99, 135.70, 135.18, 131.32, 130.96, 129.09, 128.75, 128.09, 127.55, 126.77, 111.19, 75.73, 70.53, 25.69, 25.29. HRMS (FAB) calcd for $C_{20}H_{18}O_5S$ $(M+Na)^+$: 393.0773; found 393.0773.

*4.3.2. 2-(2,2-Diethyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7b**).* Yellow oil. IR (neat): 2253, 1666, 1317, 1157, 911 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.13 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.87 (dd, *J*=8.0 Hz, 1H), 7.74 (dd, *J*=8.0 Hz, 1H), 7.48–7.47 (m, 3H), 7.19 (br, 2H), 4.76 (dd, *J*=8.5, 8.5 Hz, 1H), 4.40 (dd, *J*=8.5, 8.5 Hz, 1H), 4.05 (dd, *J*=8.5, 8.5 Hz, 1H), 1.82 (q, *J*=8.0 Hz, 2H), 1.58 (q, *J*=8.0 Hz, 2H), 0.99 (t, *J*=8.0 Hz, 3H), 0.78 (t, *J*=8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.31, 147.36, 143.26, 142.26, 134.73, 132.89, 131.71, 129.42, 128.64, 128.58, 128.51, 122.94, 115.85, 74.93, 69.06, 29.01, 28.43, 8.44, 7.77. HRMS (EI) calcd for $C_{22}H_{22}O_5S$: 398.1188; found 398.1184.

*4.3.3. 3-Phenyl-2-(1,4-dioxaspiro[4.5]decan-2-yl)-4H-thiochromen-4-one 1,1-dioxide (**7c**).* Yellow oil. IR (neat): 2253, 1666, 1317, 1160, 905 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.12 (d, *J*=8.0 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (dd, *J*=8.0, 8.0 Hz, 1H), 7.73 (dd, *J*=8.0, 8.0 Hz, 1H), 7.47–7.47 (m, 3H), 7.18 (br, 2H), 4.84 (dd, *J*=8.0, 8.0 Hz, 1H), 4.36 (dd, *J*=8.0, 8.0 Hz, 1H), 4.08 (dd, *J*=8.0, 8.0 Hz, 1H), 1.82–1.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.31, 148.13, 142.65, 142.25, 134.70, 132.85, 131.74, 129.33, 128.66, 128.58, 128.49, 122.91, 112.65, 74.09, 69.24, 34.98, 34.90, 24.95, 23.78. HRMS (FAB) calcd for $C_{23}H_{22}O_5S$ $(M+Na)^+$: 433.1086; found 433.1085.

*4.3.4. 3-Phenyl-2-(1,4-dioxaspiro[4.4]nonan-2-yl)-4H-thiochromen-4-one 1,1-dioxide (**7d**).* Yellow oil. IR (neat): 1666, 1315, 1156 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, δ): 8.12 (d, *J*=8.0 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (dd, *J*=8.0, 8.0 Hz, 1H), 7.73 (dd, *J*=8.0, 8.0 Hz,

1H), 7.48–7.47 (m, 3H), 7.17 (br, 2H), 4.81 (dd, *J*=8.0 Hz, 1H), 4.31 (dd, *J*=8.0, 8.0 Hz, 1H), 4.04 (dd, *J*=8.0, 8.0 Hz, 1H), 2.04–1.98 (m, 1H), 1.92–1.87 (m, 1H), 1.77–1.62 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.31, 148.46, 142.54, 142.12, 134.71, 132.90, 131.71, 129.33, 128.69, 128.59, 128.52, 122.93, 121.73, 74.02, 69.58, 36.18, 35.87, 23.46, 23.44. HRMS (EI) calcd for $C_{22}H_{20}O_5S$: 396.1031; found 396.1031.

*4.3.5. 2-(2-Methyl-2-propyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7e**).* A 1:1 diastereomeric mixture of **7e** was obtained, which was not separated by column chromatography and characterized as a mixture. Yellow oil. IR (neat): 1664, 1314, 1157 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.13 (d, *J*=7.5 Hz, 1H), 8.17–8.08 (m, 1H), 7.88 (dd, *J*=7.5, 7.5 Hz, 1H), 7.74 (dd, *J*=7.5, 7.5 Hz, 1H), 7.48–7.47 (m, 3H), 7.18 (br, 2H), 4.83 (dd, *J*=8.5, 8.5 Hz, 0.5H), 4.77 (dd, *J*=8.5, 8.5 Hz, 0.5H), 4.40 (dd, *J*=8.5, 8.5 Hz, 0.5H), 4.33 (dd, *J*=8.5, 8.5 Hz, 0.5H), 4.06 (ddd, *J*=8.5, 8.5, 8.5 Hz, 1H), 1.79–1.73 (m, 1H), 1.56–1.52 (m, 1H), 1.47 (s, 1.5H), 1.33–1.28 (m, 1H), 1.25 (s, 1.5H), 0.96 (dd, *J*=7.5, 7.5 Hz, 1.5H), 0.93–0.88 (m, 1H), 0.85 (dd, *J*=7.5, 7.5 Hz, 1.5H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.34, 147.77, 147.69, 142.98, 142.81, 142.26, 142.14, 134.74, 132.92, 132.88, 131.72, 131.66, 129.41, 129.39, 128.68, 128.61, 128.60, 128.56, 128.53, 128.52, 122.97, 122.95, 113.65, 113.52, 74.73, 74.27, 69.42, 69.19, 41.34, 41.02, 23.55, 23.03, 17.67, 17.20, 14.38, 14.14. Four ^{13}C NMR peaks are missing apart from equivalent peaks probably due the overlap of the peaks of each diastereomers. HRMS (EI) calcd for $C_{22}H_{22}O_5S$: 398.1188; found 398.1190.

*4.3.6. 2-(2-Decyl-2-methyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7f**).* A 1:1 diastereomeric mixture of **7f** was obtained, which was not separated by column chromatography and characterized as a mixture. Yellow oil. IR (neat): 1665, 1314, 1158 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.12 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.87 (dd, *J*=8.0 Hz, 1H), 7.74 (dd, *J*=8.0 Hz, 1H), 7.48–7.47 (m, 3H), 7.19 (br, 2H), 4.83 (dd, *J*=8.0, 6.5 Hz, 0.5H), 4.76 (dd, *J*=8.0, 6.5 Hz, 0.5H), 4.40 (dd, *J*=8.0, 8.0 Hz, 0.5H), 4.33 (dd, *J*=8.0, 8.0 Hz, 0.5H), 4.06 (ddd, *J*=8.0, 6.5, 6.5, 1H), 1.79–1.74 (m, 1H), 1.56–1.53 (m, 1H), 1.47 (s, 1.5H), 1.44–1.39 (m, 1H), 1.30–1.20 (m, 16.5H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.34, 178.32, 147.76, 147.72, 143.07, 142.78, 142.26, 142.13, 134.73, 134.70, 132.92, 132.86, 131.74, 131.67, 129.39, 129.38, 128.64, 128.60, 128.58, 128.55, 128.50, 122.98, 122.95, 113.71, 113.67, 74.70, 74.22, 69.41, 69.10, 39.20, 38.85, 31.92, 31.89, 29.84, 29.67, 29.63, 29.59, 29.58, 29.55, 29.51, 29.35, 29.29, 24.38, 23.89, 23.59, 22.98, 22.69, 22.67, 14.12, 14.11. Four ^{13}C NMR peaks are missing apart from equivalent peaks probably due to overlaps of the peaks of each diastereomers. HRMS (EI) calcd for $C_{29}H_{36}O_5S$: 496.2283; found 496.2283.

*4.3.7. 2-(2-Methyl-2-phenyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7g**).* A 17:3 diastereomeric mixture of **7g** was obtained, which was not separated by column chromatography and characterized as a mixture. Yellow oil. IR (neat): 2922, 1664, 1442, 1313, 1202, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.03 (dd, *J*=8.0, 1.5 Hz, 0.15H), 7.90 (dt, *J*=7.5, 1.0 Hz, 0.85H), 7.84 (dt, *J*=7.5, 1.5 Hz, 0.15H), 7.76 (dt, *J*=7.5, 1.0 Hz, 0.85H), 7.72 (dt, *J*=7.5, 1.0 Hz, 0.15H), 7.59–7.57 (m, 0.3H), 7.48–7.36 (m, 5H), 7.31–7.24 (m, 2.7H), 7.17 (br, 2H), 4.97 (dd, *J*=9.0, 6.0 Hz, 0.15H), 4.78 (dd, *J*=8.5, 6.0 Hz, 0.85H), 4.47 (dd, *J*=8.5, 6.0 Hz, 0.85H), 4.29 (dd, *J*=9.0, 6.0 Hz, 0.15H), 4.12 (dd, *J*=9.0, 6.0 Hz, 0.15H), 3.90 (t, *J*=8.5 Hz, 0.85H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.59, 178.30, 148.70, 146.67, 142.59, 142.12, 142.06, 141.87, 134.75, 134.70, 133.00, 132.87, 131.54, 131.47, 129.33, 128.81, 128.75, 128.70, 128.64, 128.61, 128.56, 128.54, 128.49, 128.43, 128.30, 128.09, 127.96, 127.87, 125.30, 125.06, 123.03, 123.00, 111.89, 111.63, 75.05, 73.67, 69.69, 27.88, 27.20. Three ^{13}C NMR peaks are missing apart from equivalent peaks probably due to overlaps of the peaks of each diastereomers. HRMS (ESI) calcd for $C_{25}H_{20}NaO_5S$: 455.09291; found 455.09249.

*4.3.8. 2-(2-Heptyl-1,3-dioxolan-4-yl)-3-phenyl-4H-thiochromen-4-one 1,1-dioxide (**7i**).* A single isomer whose stereochemistry is not determined. Yellow oil. IR (neat): 2891, 1663, 1315, 1162 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.13 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.87 (dd, *J*=8.0, 8.0 Hz, 1H), 7.74 (dd, *J*=8.0, 8.0 Hz, 1H), 7.48–7.46 (m, 3H), 7.17 (br, 2H), 4.89–4.85 (m, 2H), 4.33 (dd, *J*=7.5, 7.5 Hz, 1H), 3.98 (dd, *J*=7.5, 7.5 Hz, 1H), 1.74 (m, 2H), 1.44–1.38 (m, 2H), 1.32–1.26 (m, 8H), 0.88 (t, *J*=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.40, 148.58, 142.36, 142.05, 134.72, 132.92, 131.72, 129.32, 128.73, 128.68, 128.62, 128.48, 122.98, 106.97, 74.25, 70.04, 33.04, 31.74, 29.37, 29.13, 24.25, 22.62, 14.09. HRMS (EI) calcd for $C_{25}H_{28}O_5S$: 440.1657; found 440.1657.

*4.3.9. 3-Phenyl-2-(2-phenyl-1,3-dioxolan-4-yl)-4H-thiochromen-4-one 1,1-dioxide (**7j**).* A 3:1 diastereomeric mixture of **7j** was obtained, which was not separated by column chromatography and characterized as a mixture. Yellow oil. IR (neat): 1664, 1310, 1158, 1088, 1070, 912 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 8.19–8.11 (m, 2H), 7.94–7.87 (m, 1H), 7.78–7.74 (m, 1H), 7.67–7.64 (m, 0.5H), 7.51–7.48 (m, 3H), 7.43–7.40 (m, 2.25H), 7.36–7.37 (m, 2.25H), 7.20 (br, 2H), 6.04 (s, 0.75H), 5.70 (s, 0.25H), 5.05 (dd, *J*=8.5, 6.5 Hz, 0.75H), 5.01 (dd, *J*=8.5, 6.5 Hz, 0.25H), 4.58 (t, *J*=7.5 Hz, 0.25H), 4.41 (t, *J*=8.5 Hz, 0.75H), 4.34 (dd, *J*=8.5, 6.5 Hz, 0.75H), 4.13 (t, *J*=7.5 Hz, 0.25H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 69.93, 71.40, 74.39, 75.13, 105.89, 105.96, 122.94, 123.00, 126.78, 127.59, 218.30, 128.37, 128.55, 128.64, 218.68, 128.70, 128.74, 128.77, 129.50, 129.54, 129.62, 129.82, 131.48, 131.51, 132.98, 133.07, 134.75, 134.78, 135.21, 136.20, 141.80, 142.10, 142.54, 143.00, 147.40, 149.38, 178.24, 178.38. Two ^{13}C NMR peaks are missing apart from equivalent peaks probably due to overlaps of the peaks of each diastereomers. HRMS (ESI) calcd for $C_{24}H_{18}NaO_5S$: 441.07726; found 441.07706.

4.4. General procedure for photodeprotection reaction

Irradiation reactions were carried out using an ultra-high pressure mercury lamp (SX–UI–500H, USHIO) as a light source. A CH_3CN (1.0 vol % H_2O, 1.0×10^{-2} M) solution of acetal **7** in an NMR tube was irradiated through Pyrex filter until **7** was totally consumed. The yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trioxane as an internal standard.

4.5. ^{18}O labeling experiment

As a control, a 1.0×10^{-2} M solution of **7d** or **7j** in CH_3CN/H_2O (99/1 v/v) was irradiated at >280 nm from an ultra-high pressure mercury lamp until **7d** or **7j** was totally consumed. For experiment of **7d**, the reaction solution was directly analyzed by MS (CI). For experiment of **7j**, aldehyde **6j**, and PLPG **1d** were isolated from the reaction solution and then analyzed by MS (CI), respectively. Next, a 1.0×10^{-2} M solution of **7d** or **7j** in $CH_3CN/H_2{}^{18}O$ (99/1 v/v) was irradiated. Analysis of each resulting reaction solution was done as above. The values of label incorporation into the products were calculated from the comparison of the height of $[M+H]^+$ peak and $[M+2+H]^+$ peak of each labeled and unlabeled products.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.022.

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