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S-Pixyl Analogues as Photocleavable Protecting Groups for Nucleosides

Michael P. Coleman and Mary K. Boyd*

Department of Chemistry, Loyola University Chicago, Chicago, Illinois 60626

mboyd@luc.edu

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Several analogues of the 9-phenylthioxanthyl (S-pixyl) photocleavable protecting group have been synthesized, containing substituents on the 9-aryl ring and on the thioxanthyl backbone. Each analogue protected the 5′-hydroxy moiety of thymidine in good to excellent yield. The protected substrates were deprotected in 1:1 water:acetonitrile with irradiation at 300 nm, resulting in recovered thymidine in excellent yield, except for the nitro-substituted analogues which gave substantially lower yields. Substrates with 2,7-dibromo or 3-methoxy substitution on the thioxanthyl backbone were also deprotected efficiently with irradiation at 350 nm. Shorter irradiation times were observed in the less nucleophilic solvent mixture of 1:9 trifluoroethanol:acetonitrile, with no formation of secondary photooxidation products. Photodeprotection with high yields was also achieved in the absence of solvent, with no secondary photoproducts.

Introduction

The increasing demand for biologically significant, synthetically generated materials immobilized on solid surfaces is well-known. Advances in photolithography in conjunction with a combinatorial approach to organic synthesis on a surface have produced biopolymers in point-of-use devices with great precision and diversity.[1] Of particular interest is the technique of light-directed synthesis for the synthetic generation of high-density arrays of polynucleotide probes.[2] The synthetic approach uses nucleoside phosphoramidite monomers with nitrobenzyl oxycarbonyl or benzoin carbonate photocleavable protecting groups for the 5′-hydroxyl moiety to generate short oligomer probes on glass surfaces.[3] Although these protecting groups are effective, alternative chemistries are worthy of investigation in order to address synthetic limitations of the technologies which include a subquantitative stepwise yield that results in truncated probes and secondary photoproducts that can be damaging to the growing DNA strand.[1] Nitrobenzyl compounds modified by the inclusion of a pentadienyl group that traps the nitroso moiety were developed to address this difficulty.[4] Several photocleavable alcohol protecting groups that do not employ the *o*-nitrobenzyl moiety have also been reported.[5]

Our previous work demonstrated that 9-phenylxanthenol underwent photochemically induced proton transfer from the neutral aqueous solvent to an incipient hydroxide ion leaving group to generate the xanthyl cation upon steady-state irradiation.[6] We recently reported that primary alcohols protected by the 9-phenylxanthyl moiety as derivatized ethers underwent the same photochemically initiated carbon−oxygen bond cleavage to regenerate the substrate alcohol and 9-phenylxanthenol in good to excellent yield (Scheme 1).[7] The pixyl group was proven effective in the photodeprotection of a variety of primary alcohols, including thymidine, extending its utility to nucleosides. Our investigations then led us to consider the thioxanthyl analogue which contains sulfur as the heteroatom within the central xanthyl ring. 9-Phenylthioxanthenol similarly undergoes a photochem-

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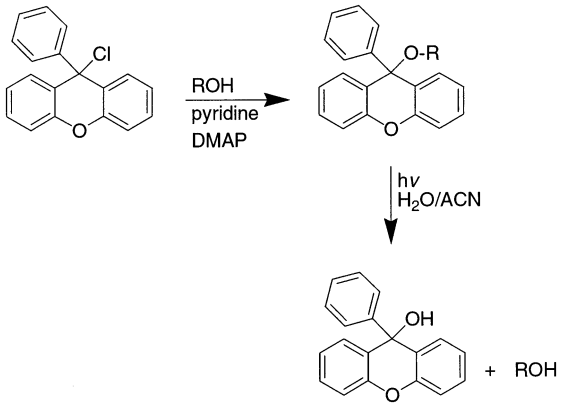
SCHEME 1



ically induced carbon−oxygen bond cleavage to generate the thioxanthyl cation.[8] The incorporation of sulfur offers the advantage of a significant bathochromic shift in the absorption spectrum, thus avoiding undesirable nucleoside photochemistry that occurs at lower wavelengths for irradiation.

Balgobin reported that the 9-phenylthioxanthyl (S-pixyl) group is an effective acid-labile protecting group for the 5′-hydroxyl moiety of nucleosides.[9] 9-Phenylthioxanthyl (S-pixyl) protected nucleosides underwent acid-catalyzed hydrolysis in 80% aqueous acetic acid in 90 s. In addition, the S-pixyl protecting group proved compatible with traditional phosphotriester oligonucleotide synthesis.

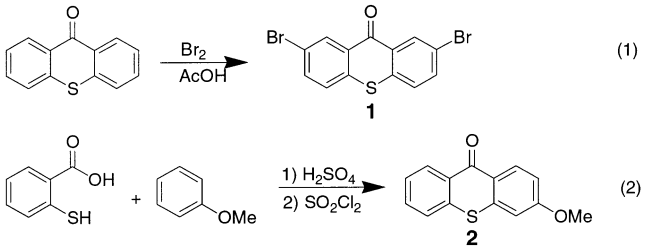
In a preliminary report, we demonstrated that primary alcohols protected by the S-pixyl moiety as derivatized ethers underwent the same photoinduced deprotection reaction as the pixyl-protected alcohols, but at a longer wavelength for irradiation and with significantly decreased irradiation times.[10] Further, the S-pixyl group proved effective toward the protection and photodeprotection at 300 nm of all four nucleoside building blocks. Additionally, use of S-pixyl proved compatible with the benzoyl and isobutyryl protecting groups for the exocyclic amino functions of adenosine and guanosine, respectively. We also showed that the preparative deprotection of S-pixyl protected nucleosides could be carried out in a Hanovia photochemical reactor using Pyrex filtered glassware in protic solvents.

However, upon extended irradiation in thoroughly degassed aqueous media beyond the time of optimum deprotection, a secondary photooxidative reaction resulted in the formation of thioxanthone, which appeared to damage the fidelity of substrate nucleosides upon prolonged exposure. Control experiments confirmed that irradiations of thioxanthone in the presence of equimolar amounts of nucleoside substrates prevented a quantitative recovery of the nucleoside after lengthy irradiation times. To pursue use of the thioxanthyl group as a viable protecting group for the 5′-hydroxyl moieties of nucleosides, analogues of S-pixyl are needed to determine whether the time for optimal deprotection can be decreased or whether the secondary photooxidation reaction can be prevented entirely. We also hoped that the S-pixyl analogues would address some additional considerations: to be effective as a photolabile group at wavelengths beyond 300 nm in order to avoid conditions that could be potentially damaging to oligonucleotides,[11] be less susceptible to secondary photochemistry after deprotection, to produce a photolabile protecting group that is nonsolvent dependent, and further, in the interests of photolithography, to produce a group that is effective in the solid-state.[1c]

We herein report the effect of substitution on the S-pixyl moiety on the efficiencies and time for deprotection of several 5′-hydroxyl protected thymidine derivatives. We also report on solvent effects for the most effective substituted S-pixyl analogues.

Results and Discussion

Synthesis of Substituted Thioxanthone and 9-Arylthioxanthenol Derivatives. The effect of substitution on both the 9-aryl ring and on the thioxanthyl backbone was investigated. Two backbone-substituted thioxanthone derivatives were prepared. Bromination of thioxanthone in bromine/acetic acid at 100 °C yielded 2,7-dibromothioxanthone **1**, after quenching with bisulfite and recrystallization from toluene (eq 1).[12] Friedel-Crafts acylation of thiosalicylic acid and anisole with sulfuric acid and sulfonyl chloride generated 3-methoxythioxanthone **2**, after recrystallization from toluene (eq 2).



Several aryl halide derivatives were reacted with crushed magnesium turnings in THF to generate Grignard reagents. These arylmagnesium halides were then reacted with thioxanthone or substituted thioxanthones **1** and **2**, followed by weak acid hydrolysis with aqueous ammonium chloride, to generate the 9-arylthioxanthyl derivatives **3a**−**l** in good to excellent yield (Scheme 2).

Compounds **3c** and **3e** required the entrainment method for formation of the Grignard reagent by slowly titrating ethylene dibromide into the reaction mixture containing the aryl halide and magnesium in THF, followed by the addition of thioxanthone.[13] Compounds **3g** and **3d** were then nitrated in acetic anhydride with 10 mol equiv of nitrated silica gel,[14] followed by an aqueous basic workup to generate 9-(3-methyl-4-nitrophenyl)thioxanthenol **4a** and 9-(4-methyl-3-nitrophenyl)-thioxanthenol **4b**, after column chromatography (eq 3).

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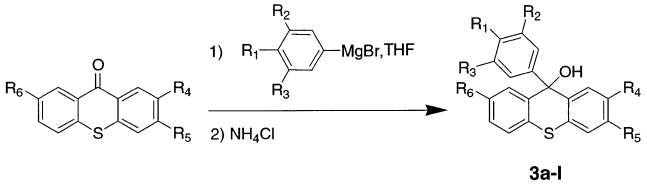
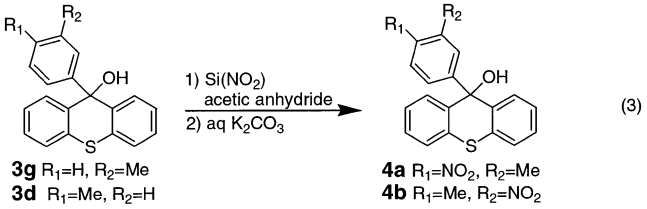
SCHEME 2



Compound	R_1	R_2	R_3	R_4	R_5	R_6
3a	-	-	-	-	-	-
3b	MeO	-	-	-	-	-
3c	-	MeO	MeO	-	-	-
3d	Me	-	-	-	-	-
3e	MeO	MeO	-	-	-	-
3f	F	-	-	-	-	-
3g	-	Me	-	-	-	-
3h	-	-	-	Cl	-	-
3i	-	MeO	-	-	-	-
3j	-	-	-	-	MeO	-
3k	-	-	-	Br	-	Br
3l	MeO	-	-	-	MeO	-

An entry of a hyphen indicates hydrogen is present

Alcohols **3a**−**l** and **4a**,**b** were purified by recrystallization or silica gel chromatography to obtain white solids and were characterized by ^{1}H and ^{13}C NMR spectroscopy and HRMS exact mass measurement.



(3)

Synthesis of Substituted 5′-S-Pixyl-Protected 2′-Deoxythymidine Ethers. Thymidine was chosen as the nucleoside substrate for studies of protection and photodeprotection in order to test substituent effects of S-pixyl analogues. Thymidine is well-behaved in photodeprotection studies, and its behavior with the pixyl and S-pixyl protecting groups are well-characterized.[7,10] Compounds **3a**−**l** and **4a**,**b** were chlorinated with trimethylsilyl chloride with a DMSO catalyst[15] in methylene chloride, followed by solvent removal to generate the activated protecting reagent. These activated groups were then introduced to substrate thymidine in pyridine/DMAP[16] to yield the derivatized 5′-*O*-[S-pixyl]-2′-deoxythymidine nucleosides **5a**−**m** (Scheme 3). Note that substrate letters for compounds **3** and **5** do not necessarily correspond since the entire set of derivatized thymidines was not made. Protected nucleosides **5a**−**m** were purified by silica gel chromatography to give off-white solids in good to excellent yield (Table 1). Compounds **5a**−**m** were characterized by UV/vis, ^{1}H and ^{13}C NMR spectroscopy, and HRMS exact mass measurement.

Photodeprotection Efficiencies. Solutions of 4.5−5.0 × 10^{-4} M were prepared of compounds **5a**−**m** in 50:50 (v:v) water/acetonitrile in quartz photolysis tubes, the highest percentage of water that solubility would allow. Lower percentages of water resulted in increased formation of the secondary photoproduct thioxanthone for some substrates. Reaction mixtures were thoroughly degassed with argon for 15 min in a quartz photolysis tube prior to irradiation. The irradiations were conducted using 16

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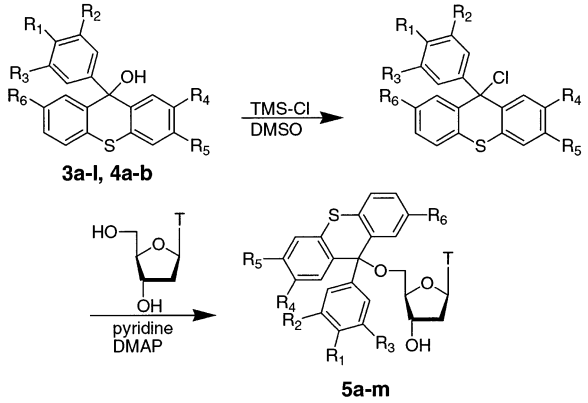
SCHEME 3



lamps of 300 nm in a Rayonet photolysis reactor. For each derivative, several irradiations were conducted at irradiation times ranging from 30 s to 60 min in order to optimize yield. The temperature was held between 10 and 15 °C throughout each experiment. All reactions were monitored with HPLC. Parallel "dark" reactions were run against each block of reactions to ensure no thermal reaction.

Yields for the protection, molar absorptivity at 300 nm (ϵ_{300}), photolytic half-life or time for 50% recovery of thymidine ($t_{1/2}$), and optimal deprotection yield were recorded (Table 1). Several analogues showed improved performance relative to the parent compound, unsubstituted S-pixyl protected thymidine **5a**. With the exception of the nitro analogues **5g** and **5m**, all substrates showed decreased $t_{1/2}$ values, and each gave deprotection yields of 90% or greater. S-Pixyl analogues containing electron-donating methoxy substituents in the thioxanthyl backbone or 9-aryl ring *para* to the 9-position, i.e., substrates **5b**, **5d**, **5e**, and **5j**, were most effective in producing a photosolvolytic reaction in the shortest amount of time. This result closely parallels the findings of trityl derivatives when they were being developed for acid-labile nucleoside protection.[17] These analogues also produced clean chromatograms that contained no oxidized thioxanthyl photoproducts, in comparison to **5a** which produced significant amounts of thioxanthone upon irradiation. Substrate **5i**, with a *m*-methoxy substituent on the 9-aryl ring, also gave an excellent yield with a short irradiation time with no thioxanthone produced. However, substrate **5l** which contains a *p*-methoxy group on the 9-aryl ring as well as a methoxy substituent on the thioxanthyl backbone was not stable under the aqueous reaction conditions, as it underwent a thermal deprotection reaction in the aqueous acetonitrile solvent.

Meta substitution is well-known to promote benzylic heterolytic carbon−oxygen bond cleavage, so the enhanced photoreactivity of **5i** compared to **5a** was not surprising. Unexpectedly, substrate **5c**, with methoxy substitution at both *meta* positions on the 9-aryl ring gave considerably longer $t_{1/2}$ values compared to other analogues. *m*- and *p*-Methoxy substitution on the 9-aryl ring in substrate **5e**, and *p*-methoxy substitution in substrate **5b** was reasonably effective. *m*-Methoxy substitution on the thioxanthyl backbone, substrate **5j**, was the most effective in producing an S-pixyl analogue with

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TABLE 1. Protection and Deprotection Yields for Irradiation at 300 nm of S-Pixyl Analogues

compound	R_1	R_2	R_3	R_4	R_5	R_6	% protection	ϵ_{300}	$t_{1/2}$ (min)	% deprotection[a]
5a	H	H	H	H	H	H	89	4560	10.1	97
5b	MeO	H	H	H	H	H	82	3839	4.8	93
5c	H	MeO	MeO	H	H	H	93	4849	7.3	92
5d	Me	H	H	H	H	H	90	4005	4.3	95
5e	MeO	MeO	H	H	H	H	87	4259	5.2	94
5f	F	H	H	H	H	H	52	3079	9.3	90
5g	NO_2	Me	H	H	H	H	79	9007	70	72
5h	H	H	H	Cl	H	H	63	7805	4.2	92
5i	H	MeO	H	H	H	H	83	4690	4.4	91
5j	H	H	H	H	MeO	H	89	4619	3.6	97
5k	H	H	H	Br	H	Br	84	6876	6.6	94
5l	MeO	H	H	H	MeO	H	64	8592	50	78
5m	Me	NO_2	H	H	H	H	72	6617	N/A[b]	—[b]

[a] % Deprotection based on recovery of thymidine in 50:50 (v:v) water/acetonitrile with irradiation at 300 nm. Substrate concentration for irradiations was $4.5-5.0 \times 10^{-4}$ M. [b] Comprehensive data for compound **5l** was problematic in that it was unstable for extended lengths of time in aqueous media.

TABLE 2. Deprotection Yields for Irradiation at 350 nm of S-Pixyl Analogues

compd	R_1	R_2	R_3	R_4	R_5	R_6	ϵ_{320}	ϵ_{350}	$t_{1/2}$ (min)	% deprotection[a]
5g	NO_2	Me	H	H	H	H	N/A	1856	120	75
5j	H	H	H	H	MeO	H	2758	240	7.3	99
5k	H	H	H	Br	H	Br	3748	51	11.2	97

[a] % Deprotection based on recovery of thymidine in 50:50 (v:v) water/acetonitrile with irradiation at 350 nm. Substrate concentration for irradiation was $4.5-5.0 \times 10^{-4}$ M.

enhanced photodeprotection performance. This is presumably due to more effective conjugation to the 9-carbon compared to substitution on the 9-aryl ring which is twisted out of planarity with the thioxanthyl backbone.

The nitrated substrates, **5g** and **5m**, performed poorly. Nitro substitution was investigated due to large changes in the long wavelength absorption of the derivatives. *o*-Nitrotoluyl moieties are also the basis for the nitrobenzyl oxycarbonyl protecting groups,[3] and we wished to compare the same compound structures. Despite the strong molar absorptivity of these compounds, **5g** and **5m** required extensive irradiation times and gave disappointing yields. UV/vis spectra of the reaction mixtures following prolonged irradiation display a strong absorption band characteristic of a stable aryl nitroso moiety, the predominant product after α-hydrogen abstraction from an excited-state nitro group and subsequent rearrangement to a possible nitroso benzyl alcohol.

Several analogues were selected that exhibited potential to undergo photodeprotection with irradiation at 350 nm. This longer wavelength irradiation is crucial for the development of viable photodeprotecting groups for nucleosides. The criteria for choosing a good analogue target for longer wavelength irradiation included a short time for deprotection and a reasonable molar absorptivity above 300 nm. Substrate **5g** was also selected, despite a long $t_{1/2}$ value, due to its high molar absorptivity at 350 nm. Solutions of substrates **5g**, **5j**, and **5k** were irradiated in a Rayonet photochemical reactor using 16 lamps at 350 nm and analyzed via HPLC. Molar absorptivities at 320 and 350 nm, the ϵ_{320} and ϵ_{350} values respectively, photolytic half-life $t_{1/2}$, and optimal deprotection yields were recorded (Table 2). The parent unsubstituted S-pixyl moiety **5a** was ineffective as a photolabile protecting group with irradiation at 350 nm due to minimal absorption at that wavelength. Nitro-substituted substrate **5g** gave poor results at this irradiation wavelength also, requiring extended irradiation times and giving disappointing yields. However, substrates **5j** and **5k** show excellent deprotection yields. The $t_{1/2}$ values for deprotection at 350 nm are longer than for irradiation at 300 nm, 7.3 min compared to 3.6 min for **5g**, but are still reasonable for synthetic applications. Compounds **5j** and **5k** are both substituted directly on the thioxanthyl backbone which has the largest effect on extending the absorption wavelength. These findings suggest the effective use of 9-arylthioxanthyl moieties as photocleavable protecting groups in the synthesis of short oligonucleotides.

Solvent Effects on Photodeprotection Yields. The 5′-(α-methyl-2-nitropiperonyl)oxycarbonyl or MeNPOC photocleavable protecting group has been used in the light-directed synthesis of oligonucleotides. Deprotection yields with the MeNPOC group exhibited a moderate dependence on solvent polarity, with the shortest irradiation times obtained in nonpolar solvents or the absence of solvent.[2d] We investigated the effect of solvent on the photodeprotection of 9-arylthioxanthyl protected thymidine substrates. Protic solvents react with cations in the order methanol > water ≫ 2,2,2-trifluoroethanol since solvents of poorer nucleophilicity are less effective in quenching a ground or excited-state carbocation.[18] To investigate the effects of solvent on the photodeprotection, compounds **5a** and **5j** were irradiated under identical solution-phase conditions as described above, with the exception that each reaction was carried out in a variety of solvent conditions: 50/50 v:v methanol−acetonitrile, 10/90 v:v 2,2,2-trifluoroethanol−acetonitrile, and 50/50 v:v water−acetonitrile as a control. Compound **5j** was selected for this study since it was the S-pixyl analogue with the best photodeprotection yields, short irradiation times and no photooxidation products.

The time for 50% conversion ($t_{1/2}$) and overall deprotection efficiency were recorded in each solvent (Table

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TABLE 3. Deprotection Yields and $t_{1/2}$ Values in Competitive Solvents

compound	MeOH[a]	H_2O[b]	CF_3CH_2OH[c]
5a ($t_{1/2}$, % yield)	21.1, 91	10.1, 97	6.7, 94
5j ($t_{1/2}$, % yield)	17.5, 95	3.6, 97	2.0, 95

[a] 50% (v:v) in acetonitrile. [b] 50% (v:v) in acteonitrile. [c] 10% (v:v) in acetonitrile. All photolysis reactions were done at concentrations ranging from $4-5.3 \times 10^{-4}$ M using 16 300 nm lamps. Reactions were quantitated by HPLC based on the recovery of substrate thymidine, $t_{1/2}$ values are in minutes and % yields are based on best overall percent recoveries.

3). Shorter irradiation times for substrate **5j** compared to **5a** were observed in each solvent. In addition, the $t_{1/2}$ data for **5a** and **5j** show a significant solvent effect. The $t_{1/2}$ values decrease in the order methanol > water > trifluoroethanol. The trend in the data can be evaluated in terms of solvent parameters, although caution should taken since solvent mixtures were used (50:50 methanol: acetonitrile, 50:50 water:acetonitrile and 10:90 trifluoroethanol:acetonitrile), and solvent parameters are not available for those solvent compositions. Instead we considered the trend in the $t_{1/2}$ values using solvent parameters for pure methanol, water and trifluoroethanol. Only limited data are available for acetonitrile so we could not attempt to account for the percent acetonitrile in the solvent mixtures. As the $t_{1/2}$ values decrease, the solvent nucleophilicity (N_T and N'_{OTs}) decreases,[19] while solvent acidity and hydrogen bond donating ability (α) increase.[20,21] Solvent polarity ($E_T(30)$) and solvent ionizing ability (Y and Y_{OTs}) did not follow an increasing or decreasing trend for these solvents.[22] These interesting trends will be explored in future work.

The trifluoroethanol−acetonitrile solvent mixture offered a benefit in addition to lower $t_{1/2}$ values. The thioxanthyl cation produced in the photodeprotection reaction was highly stable in this solvent mixture, and allowed the extent of deprotection to be estimated spectroscopically, with observation of the 9-phenylthioxanthyl cation at 394 nm and the 3-methoxy-9-phenylthioxanthyl cation at 397 nm. In addition, this solvent also decreased the amount of thioxanthone produced from irradiation of **5a** to negligible amounts. No thioxanthone was produced from **5j** in any solvent. The use of methanol/acetonitrile also resulted in minimal thioxanthone formation from **5a** compared to irradiation in water/acetonitrile. Substrates **5a** and **5j** were also irradiated in anhydrous acetonitrile, which resulted in no deprotection after 60 min irradiation time.

Irradiation in the Absence of Solvent. Effective solid-state deprotection has significant advantages in photolithographic techniques.[1c] Solutions (3 mL, 6.64 M) of compounds **5g**, **5j**, and **5k** in 5% water/acetonitrile were coated onto glass microscope slides of 2 × 4 cm to produce a thin film of approximately 2.5 mmol/cm^2, which was calculated based on the volume and concentration of the solution applied to the surface of known area. After complete evaporation of solvent, the plates were placed into an airtight Pyrex vessel and filled with argon. Irradiations were carried out from 20 to 90min at 300 nm, after which the plates were washed with 10 mL of 50/50 water/acetonitrile and the washings analyzed by HPLC. Three key points were monitored: the recovery of thymidine over time as determined by HPLC analysis, a clean reaction that would not produce excessive byproducts, and the absence of any T−T dithymidine lesions that are known to occur upon exposure to irradiations below 280 nm.[8] Of the three investigated, only 5′-*O*-[3-methoxy-9-phenylthioxanthyl]-2′-deoxythymidine **5j** proved effective in photodeprotection under these conditions, which produced an optimal deprotection yield of 93% with no observation of secondary photoproducts. We note, however, the addition of a protic solvent (water or methanol) was necessary after irradiation in order to recover the substrate nucleoside. Compounds **5g** and **5k** needed prolonged irradiation times and produced complex product mixtures.

Conclusion

Several 9-arylthioxanthyl derivatives have been proven effective in the photodeprotection of the 5′ hydroxyl functionality of thymidine under a variety of conditions. Relative to the unsubstituted parent derivative (S-pixyl), electron-donating methoxy and methyl substituents in the position para to the 9-carbon on either the 9-aryl ring or thioxanthyl backbone were most effective in achieving near quantitative deprotection in the shortest amount of time while producing the least amount of byproducts. Further, irradiations in 10% 2,2,2-trifluoroethanol produced a highly stabilized carbocation, negligible byproducts, and decreased the irradiation times relative to other solvents. The derivatives were also stable thermally under this solvent condition. The use of a methoxy substituent within the xanthyl backbone (i.e., compound **5j**) combined with a protic, nonnucleophilic solvent system thus produced the most effective reaction reported herein.

Although no correlation between molar absorptivity and an overall effectiveness as a photocleavable protecting group was clearly observed among the derivatives, the incorporation of substituents on the thioxanthyl ring produced the greatest increase in molar absorptivity and was directly related to a decreased time for irradiation. The results reported herein now permit the use of 9-arylthioxanthyl moieties to be used as photocleavable protecting groups in the synthesis of short oligonucleotides with conventional solid-phase protocols.

Experimental Section

General Methods. NMR spectra were obtained at 300 Hz and 400 Hz for ^{1}H, and 75 Hz and 91 Hz for ^{13}C. ^{1}H NMR signals are reported in parts per million (δ) from TMS as an internal standard. ^{13}C NMR chemical shifts (δ) were reported in reference to the 77.23 ppm peak for $CDCl_3$, 39.45 ppm peak for DMSO, and 23.21 peak for acetone, respectively. HPLC analyses were conducted using a Zorbax column (XDB C18, 5 μm, 4.6 X 150 mm), with detection at 254 nm and a xanthene internal standard, with 0.2% TFA (buffered to pH5.6)/ACN gradient, 0.75 mL/min. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR00954). Melting points are uncorrected. All photochemical reactions were

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conducted in a Rayonet RPR-100 reactor using 16 300 nm or 350 nm mercury lamps. Reaction mixtures were in quartz tubes, degassed with argon, and inserted into a rotating carousel. The reactor was air cooled with fans in a cold room at 5 °C. Solid-state photolysis was conducted in a specially prepared, Pyrex filtered vessel that held six 1.5 × 4 cm microscope slides in a carousel. Pyridine, acetonitrile and methylene chloride were distilled from calcium chloride. Methanol was stored over molecular sieves. THF was distilled from sodium−benzophenone ketyl. NMR grade 2,2,2-trifluoroethanol was purchased from a commercial source and used without further purification.

2,7-Dibromothioxanthen-9-one (1).[12] Bromine (10 mL) was added dropwise over 20 min to a solution of thioxanthone (5.0 g, 0.024 mol) in acetic acid (45 mL). The solution was stirred continuously and heated at reflux temperature for 20 h, after which half of the solvent volume was removed by distillation. The reaction mixture was then allowed to cool and poured over crushed ice. The resulting yellow precipitate was collected by filtration and washed with saturated sodium bicarbonate, a 20% aqueous solution of sodium bisulfite, and finally with water. The solid was then dried under vacuum and recrystallized twice from toluene to afford 4.8 g (54%) of compound **1** as a bright yellow solid. mp 263−266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d), 7.78 (2H, d), 8.76 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.86, 127.47, 127.85, 130.32, 132.80, 135.81, 177.84. Exact mass (EI, M^+) Calcd for $C_{13}H_6Br_2OS$ 367.8506, found 367.8508.

3-Methoxythioxanthen-9-one (2). To concentrated sulfuric acid (30 mL) was added sulfonyl chloride dropwise (2.4 mL) until the effervescence of hydrogen gas ceased. Thiosalicylic acid (4.0 g, 0.027 mol) was added slowly over 10 min to generate a deep red solution. Anisole (8.5 g, 0.079 mol) was then added dropwise to the initially orange solution slowly over a 30 min period. The reaction mixture was heated to 60 °C and allowed to stir for 3 h. The reaction mixture was then cooled to room temperature and poured over ice. The resulting orange precipitate was filtered and washed with water. The solid was then collected and repeatedly washed with saturated sodium bicarbonate and filtered in order to remove a major byproduct, dithiosalicylic acid. The final solid was then rinsed with water and then cold methanol and finally dried under vacuum to afford 2.91 g (44%) of compound **2** as a pale yellow solid. mp 115−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s), 7.26 (1H, m), 7.48−7.59 (4H, m), 8.08 (1H, d), 8.63 (1H, dd); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.91, 110.60, 122.93, 126.17, 126.27, 127.23, 128.51, 129.03, 130.07, 130.47, 132.20, 137.70, 158.61, 179.85. Exact mass (EI, M^+) Calcd for $C_{14}H_{10}O_2S$ 242.0402, found 242.0389.

Synthesis of Substituted 9-Arylthioxanthyl-9-ols. Appropriate aryl bromides or chlorides (0.0534 mol) were added dropwise over 30 min to refluxing THF containing Mg turnings (0.0521 mol) before ethylene dibromide (1.68 mmol, 50 μL) was added all at once. The solution was allowed to stir at reflux temperature until all the Mg was consumed, at which point a solution of thioxanthone (0.0241 mol) in THF was added dropwise over 15min. Every 45 min aliquots of the reaction mixture were taken and added to a vial containing THF and aqueous NH_4Cl. The organic layer was then separated and subjected to TLC (10% hexane in methylene chloride) and then stained with 15% sulfuric acid, which produced a deep red, purple, or violet spot as an indication of product formation. After 3 h the reaction mixture was allowed to cool, and 50 mL of saturated aqueous ammonium chloride was added and allowed to stir for 30 min or until any Mg salts were digested. The mixture was then poured into a separatory funnel, extracted three times with 50 mL of methylene chloride each. The combined organic layers were then washed with 150 mL of water and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give a brown oil. The crude product was then purified by flash chromatography (10% hexane in methylene chloride) on silica gel and/or recrystallized from toluene to give the target compound. Special considerations are listed as indicated.

9-Phenylthioxanthenol (3a). White powder (85%) mp 115−116 °C (lit. 103−107 °C);[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (1H, s, D_2O ex.), 6.96−7.41 (11H, m), 8.00 (2H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.15, 126.43, 126.63, 126.87, 127.24, 127.71, 128.01, 131.59, 139.98, 143.27, 198.08. Exact mass (EI, M^+) Calcd for $C_{19}H_{14}OS$ 290.0765, found 290.0762.

9-(4-Methoxyphenyl)thioxanthenol (3b). White powder (76%) mp 105−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (1H, br, D_2O ex.), 3.51 (3H, s), 6.75 (4H, dd), 7.19−7.53 (6H, m), 7.97 (2H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.23, 112.43, 125.73, 126.07, 126.58, 127.91, 127.47, 128.04, 131.81, 135.71, 140.02, 158.43. Exact mass (EI, M^+) Calcd for $C_{20}H_{16}O_2S$ 320.0871, found 320.0870.

9-(3,5-Dimethoxyphenyl)thioxanthenol (3c). Following the entrainment method,[13] 1 mol equiv of ethylene dibromide was titrated into the THF solution containing the aryl halide and magnesium metal over 36 h. The red brown solution was then allowed to stir at reflux temperature for an additional 24 h at which time the reaction was executed in the usual manner. Off-white powder (27%) mp 120−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (1H, s, D_2O ex.), 3.61 (6H, s), 6.18 (2H, d), 6.24 (1H, t), 7.21−7.63 (6H, m), 7.94 (2H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.49, 99.44, 105.93, 125.83, 126.48, 126.51, 126.63, 127.39, 129.89, 131.45, 132.28. Exact mass (EI, M^+) Calcd for $C_{21}H_{18}O_3S$ 350.0977, found 350.0981.

9-(4-Methylphenyl)thioxanthenol (3d). White powder (81%) mp 164−166 °C (lit. 161−163 °C);[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.79 (1H, s, D_2O ex.), 6.81 (4H, q), 7.23−7.49 (6H, m), 8.01 (2H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.25, 126.20, 126.67, 126.86, 127.12, 127.42, 128.98, 131.77, 137.76, 140.35, 140.68. Exact mass (EI, M^+) Calcd for $C_{20}H_{16}OS$ 304.0922, found 304.0928.

9-(3,4-Dimethoxyphenyl)thioxanthenol (3e). Following the entrainment method,[13] 1 mol equiv of ethylene dibromide (6.05 g, 0.0331mol) was titrated into the THF solution containing the aryl halide and magnesium metal over 10 h. The brown solution was then allowed to stir at reflux temperature for an additional 2 h at which time the reaction was executed in the usual manner. Off-white powder (51%) mp 119−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (1H, s, D_2O ex.), 3.57 (3H, s), 3.69 (3H, s), 6.39 (1H, d), 6.57 (2H, d), 7.16−7.43 (6H, m), 7.91 (2H, d); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.61, 55.85, 109.94, 110.20, 110.82, 111.12, 119.07, 125.81, 126.31, 126.63, 127.09, 131.32, 135.73, 139.98, 148.21. Exact mass (EI, M^+) Calcd for $C_{21}H_{18}O_3S$ 350.0977, found 350.0967.

9-(4-Fluorophenyl)thioxanthenol (3f). White powder (79%); mp 134−135 °C (lit. 140−142 °C);[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (1H,s), 6.70−7.39 (10H, m), 7.92 (2H,d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.01, 115.05, 115.26, 126.29, 126.92, 127.01, 127.79, 129.15, 129.23, 131.76, 140.12, 161.85, 163.59. Exact mass (EI, M^+) Calcd for $C_{19}H_{13}FOS$ 308.0671, found 308.0672.

9-(3-Methylphenyl)thioxanthenol (3g). Off-white solid (88%); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.79 (1H, s), 6.7−7.42 (10H, m), 7.98 (2H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.79, 77.23, 124.23, 126.36, 126.67, 126.84, 127.44, 127.75 128.08, 128.81, 131.74, 137.91, 140.23, 143.55. Exact mass (EI, M^+) Calcd for $C_{20}H_{16}OS$ 304.0922, found 304.0910.

2-Chloro-9-phenylthioxanthenol (3h). After formation of the Grignard reagent, the solution was added dropwise via Ar partial pressure through a glass cannula tube into a solution of 2-chlorothioxanthone in THF over a 30 min period. White powder (83%); mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (1H, s, D_2O ex.), 6.95 (2H, m), 7.16−7.43 (10H, m), 8.02 (2H, q); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.98, 126.30, 126.55, 126.95, 126.98, 127.08, 127.61, 127.74, 128.08, 128.29, 128.43,

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130.44, 131.56, 132.95, 139.65, 142.13, 142.88. Exact mass (EI, M^+) Calcd for $C_{19}H_{13}ClOS$ 324.0376, found 324.0373.

9-(3-Methoxyphenyl)thioxanthenol (3i). White powder (70%); mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (1H, br, D_2O ex.), 3.65 (3H, s), 6.56 (2H, m), 6.69 (1H, m), 7.05−7.43 (10H, m), 7.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.24, 77.23, 112.79, 113.55, 119.57, 126.40, 126.67, 126.78, 127.52, 129.22, 131.69, 139.99, 145.43, 159.42. Exact mass (EI, M^+) Calcd for $C_{20}H_{16}O_2S$ 320.0871, found 320.0867.

3-Methoxy-9-phenylthioxanthenol (3j). White powder (49%); mp 117−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (1H, s, D_2O ex.), 3.80 (3H, s), 6.82 (1H, q), 6.96 (2H, m), 7.13−7.40 (5H, m), 7.61 (2H, d), 8.00 (2H, q); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.79, 77.50, 111.86, 113.89, 123.06, 126.13, 126.58, 127.02, 127.24, 127.50, 128.01, 128.11, 128.32, 132.64, 140.22, 141.98, 143.00, 159.22. Exact mass (EI, M^+) Calcd for $C_{20}H_{16}O_2S$ 320.0871, found 320.0864.

2,7-Dibromo-9-phenylthioxanthenol (3k). After formation of the Grignard reagent, the solution was added dropwise via Ar partial pressure through a glass cannula tube into a solution of 2,7-dibromothioxanthone (**1**) in THF over a 30 min period. Off-white powder (66%); mp 244−245 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (1H, s), 6.96 (2H, m), 7.18 (2h, m), 7.42−7.55 (5H, m), 8.28 (2H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.06, 121.21, 127.80, 128.64, 128.90, 129.16, 130.50, 131.30, 131.41, 143.61. Exact mass (EI, M^+) Calcd for $C_{19}H_{12}Br_2OS$ 445.8976, found 445.8971.

3-Methoxy-9-(4-methoxyphenyl)thioxanthenol (3l). Off-white powder (59%); mp 99−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (1H, s, D_2O ex.), 3.67 (3H, s), 3.77 (3H, s), 6.64−6.84 (4H, m), 7.23−7.41 (3H, m), 7.63 (2H, d), 8.01 (2H, q); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.30, 55.71, 68.98, 111.74, 113.53, 113.68, 122.99, 125.94, 126.50, 126.94, 127.33, 127.94, 128.60, 132.53, 135.31, 140.47, 142.26, 159.13, 159.18. Exact mass (EI, M^+) Calcd for $C_{21}H_{18}O_3S$ 350.0977, found 350.0972.

9-(3-Nitro-4-methylphenyl)thioxanthenol (4a). 9-(4-Methylphenyl)thioxanthenol (**3d**) (3.22 g, 0.0106 mol) was azeotroped into 30 mL of acetic anhydride over 1 h. After the compound was completely dissolved, 4.05 g of nitrated silica gel[14] was added slowly over 20 min while shaking the mixture. Once all the nitrated silica gel was added, the solution was allowed to heat near reflux temperature without stirring. After 3 h the solution was allowed to cool, the silica gel was removed by filtration and the solution was poured into a separatory funnel, followed by the addition of 100 mL of water and 100 mL of methylene chloride. After separation of the organic layer, the aqueous layer was extracted with an additional 100 mL of methylene chloride. The two organic layers were combined, and the solution was added to 75 mL of saturated aqueous K_2CO_3 and vigorously stirred for 1 h in order to deprotect any 9-thioxanthyl carbonate ester that may have formed. The solution was then poured back into a separatory funnel, washed an additional time with 75 mL of saturated aqueous K_2CO_3, and then finally with two 50 mL portions of distilled water. The organic layer was then evaporated to dryness under reduced pressure to yield bright yellow crystals. The crude product was then purified by preparative TLC (silica, 30/70 ethyl acetate/methylene chloride) to give a pale yellow solid (2.56 g, 69%). mp 181−183 °C; FTIR cm^{-1} 1580, 1375; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.45 (3H, s), 3.04 (1H, s, D_2O ex.), 7.10 (2H, m), 7.28−7.43 (6H, m), 7.67 (1H, s), 7.95 (2H, q); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.25, 76.17, 123.11, 126.22, 126.89, 127.09, 128.08, 131.30, 131.44, 132.56, 133.00, 139.08, 143.24, 149.02. Exact mass (EI, M^+) Calcd for $C_{20}H_{15}NO_3S$ 349.0773, found 349.0773.

9-(3-Methyl-4-nitrophenyl)thioxanthenol (4b). 9-(3-Methylphenyl)thioxanthenol (**3g**) was subjected to the same conditions as in **4a** followed by column chromatography to yield an off-white solid (75%); mp 172−174 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.41 (3H, s), 2.87 (1H, br), 6.96−7.04 (2H, m), 7.27−7.41 (6H, m), 7.69 (1H, d), 7.89 (2H, q); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.96, 76.14, 124.64, 125.37, 126.37, 126.56, 126.75, 127.00, 128.08, 131.00, 131.11, 133.60, 138.86, 148.17, 149.13. Exact mass (EI, M^+) Calcd for $C_{20}H_{15}NO_3S$ 349.0773, found 349.0771.

Synthesis of 5′-*O*-[9-Phenylthioxanthyl]-2′-deoxythymidine Ethers. Trimethyl silyl chloride (TMS-Cl) (6 mL) was added dropwise over 10 min to the appropriate 9-arylthioxanthen-9-ol (1.480 mmol) dissolved in 10 mL of methylene chloride and 200 μL of dimethyl sulfoxide. After 12 h the solvent was removed under reduced pressure to generate the appropriate 9-chloro-9-arylthioxanthene[15] in nearly quantitative yields that were then used in situ without further purification. The red, purple, or violet solid was then dissolved in 7 mL of pyridine and added dropwise to thymidine (1.345 mmol) and DMAP (0.041 mmol) in 10 mL of pyridine. TLC on a silica plate indicated that the reaction was complete within 7−12 h. The reaction was quenched with 10 mL of 25% aqueous Na_2CO_3, extracted three times with 30 mL of methylene chloride and dried over magnesium sulfate. Evaporation of the organic layer gave a faintly colored glassy oil that was coevaporated with 20 mL of toluene to produce a foam. The foam was then dissolved in methylene chloride and subjected to silica gel chromatography using methylene chloride/2-propanol or methylene chloride/acetone eluents. Sorbents for chromatography were previously treated with a 1% TEA/methylene chloride solution and allowed to stand for 30 min. The solution was washed from the silica, rinsed with methylene chloride and then allowed to air-dry for 4 h. All compounds were isolated as off-white powders.

5′-*O*-[9-Phenylthioxanthyl]-2′-deoxythymidine (5a). (79%) mp (dec) 137−145 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 3H); 2.35 (m, 2H); 3.24 (dd, 2H); 3.95 (d, 1H); 4.41 (br, 1H),); 5.40 (t, 1H); 6.23 (t, 1H); 7.20−7.77 (m, 13H); 8.28 (s, 1H); 11.40 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.90, 62.24, 70.46, 79.92, 82.0, 82.8, 109.98, 124.8, 125.5, 126.7, 127.0, 128.9, 128.2, 128.82, 129.1, 129.3, 130.0, 133.8, 133.9, 136.1, 148.1, 150.5, 163.9; Exact mass (EI, M^+) Calcd for $C_{29}H_{26}N_2O_5S$ 514.1565, found 514.1562.

5′-*O*-[9-(4-Methoxyphenyl)thioxanthyl]-2′-deoxythymidine (5b). (82%) mp (dec) 149−150 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.4 (s, 3H); 2.22 (m, 2H); 3.25 (q, 2H); 3.62 (s, 3H); 4.40 (m, 1H, D_2O ex.); 4.95 (d, 1H); 5.39 (d, 1H); 6.23 (t, 1H); 6.80 (d, 2H); 7.18 (d, 1H); 7.20−7.68 (m, 8H); 11.25 (s, 1H, D_2O ex.).^{13}C NMR (75 MHz, DMSO-d_6) δ 12.9, 55.0, 62.0, 70.1, 79.9, 83.8, 85.5, 109.8, 113.7, 125.4, 126.25, 126.6, 127.7, 128.0, 128.7, 128.9, 129.3, 130.1, 134.2, 134.5, 135.7, 140.0, 150.1, 158.0, 163.8. Exact mass (FAB, M + Na^+) Calcd for $C_{30}H_{28}N_2O_6SNa$ 567.1566, found 567.1564.

5′-*O*-[9-(3,5-Dimethoxyphenyl)thioxanthyl]-2′-deoxythymidine (5c). (93%) mp (dec) 169−172 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (s, 3H); 2.25 (m, 2H); 3.20−3.33 (m, 2H); 3.63 (s, 3H); 3.95 (d, 1H); 4.39 (br, 1H, D_2O ex.); 5.40 (m, 1H); 6.25 (t, 1H); 6.34 (s, 1H); 6.40 (d, 2H); 7.22−7.62 (m, 9H); 11.35 (s, 1H, D_2O ex.). ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.30, 59.8, 63.88, 70.38, 79.24, 83.58, 85.06, 97.28, 103.44, 109.94, 125.11, 125.19, 126.38, 127.76, 127.98, 128.63, 128.71, 128.98, 129.63, 133.29, 133.44, 135.26, 150.11, 159.99, 163.38. Exact mass (FAB, M + Na^+) Calcd. for $C_{31}H_{30}N_2O_7SNa$ 597.1671, found 597.1648.

5′-*O*-[9-(4-Methylphenyl)thioxanthyl]-2′-deoxythymidine (5d). (90%) mp (dec) 165−167 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 3H); 2.15 (m, 2H); 3.35 (m, 2H); 3.95 (dd, 1H); 4.35 (m, 1H); 6.25 (t, 1H); 7.0−7.65 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.0, 20.5, 64.05, 70.5, 79.5, 84.0, 85.5, 109.5, 124.9, 125.3, 125.4, 126.5, 127.8, 128.0, 128.7, 128.8, 129.0, 129.3, 130.0, 133.9, 134.2, 135.3, 136.1, 145.0, 151.0, 164.5. Exact mass (FAB, M + Na^+) Calcd for $C_{30}H_{28}N_2O_5SNa$ 551.1617, found 551.1641.

5′-*O*-[9-(3,4-Dimethoxyphenyl)thioxanthyl]-2′-deoxythymidine (5e). (87%) mp (dec) 160−161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (s, 3H); 2.24 (m, 2H); 3.59 (s, 3H); 3.66 (s, 3H); 3.96 (dd, 1H); 4.23 (m, 2H); 5.40 (d, 1H); 6.25 (t, 1H); 6.56−7.66 (m, 12H); 11.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-

d_6) δ 11.53, 54.88, 55.27, 55.47, 64.19, 70.77, 79.67, 83.82, 85.40, 108.97, 109.59, 111.54, 117.95, 125.44, 125.89, 126.30, 126.55, 126.59, 127.06, 127.79, 128.07, 128.65, 128.86, 129.30, 130.12, 134.10, 134.36, 135.60, 140.10, 147.76, 148.24, 150.35, 163.60. Exact mass (FAB, M + Na^+) Calcd for $C_{31}H_{30}N_2O_7$SNa 597.1671. Found 597.1668.

5′-*O*-[9-(4-Fluorophenyl)thioxanthyl]-2′-deoxythymidine (5f). (52%) mp (dec) 154−156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 3H); 2.22 (m, 2H); 3.26 (m, 2H); 3.95 (m, 1H); 4.38 (m, 1H); 6.24 (t, 1H); 7.08−7.62 (m, 13H); 11.35 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.4, 64.18, 70.46, 79.40, 83.71, 85.11, 109.54, 114.92, 115.13, 125.47, 125.52, 126.72, 126.93, 127.02, 128.02, 128.25, 128.79, 128.89, 129.31, 129.95, 133.64, 133.80, 135.68, 144.18, 150.34, 159.62, 162.05, 163.58. Exact mass (FAB, M + Na^+) Calcd for $C_{29}H_{25}FN_2O_5$SNa 555.1366, found 555.1375.

5′-*O*-[9-(3-Methyl-4-nitrophenyl)thioxanthyl]-2′-deoxythymidine (5g). (79%) mp (dec) 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H); 2.18 (s, 2H); 2.49 (s, 3H); 3.22 (br, 1H, D_2O ex.); 3.36 (m, 2H); 4.13 (q, 1H); 4.43 (d, 1H); 6.37 (t, 1H); 7.10−7.45 (m, 11H), 7.85 (d, 1H), 9.60 (br, 1H, D_2O ex.); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.88, 20.01, 64.39, 70.34, 79.12, 83.84, 84.97, 109.50, 123.95, 124.84, 125.49, 125.63, 126.83, 126.89, 128.36, 128.44, 128.60, 129.22, 129.28, 129.41, 129.81, 132.51, 132.58, 132.96, 135.71, 147.38, 150.35, 153.17, 163.62. Exact mass (FAB, M + Na^+) Calcd for $C_{30}H_{27}N_3O_7$SNa 596.1467, found 596.1469.

5′-*O*-[2-Chloro-9-phenylthioxanthyl]-2′-deoxythymidine (5h). Isolated as a mixture of isomers (63%). mp (dec) 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, 3H); 2.38 (m, 2H); 3.10 (m, 2H); 3.37 (m, 2H); 4.09 (s, 1H); 4.57 (s, 1H), 6.40 (q, 1H); 7.13−7.53 (m, 13H); 9.35 (d, 1H). ^{13}C NMR (100 MHz, $CDCL_3$) δ 12.27, 40.95, 40.99, 64.33, 64.36, 72.46, 72.54, 80.87, 80.90, 85.19, 85.24, 86.03, 86.13, 111.54, 111.63, 125.70, 125.75, 125.80, 126.79, 126.89, 126.99, 127.63, 127.68, 128.19, 128.30, 128.36, 128.52, 128.56, 128.59, 129.26, 129.38, 129.62, 129.75, 129.88, 130.79, 132.18, 132.29, 133.57, 133.87, 135.73, 135.81, 135.96, 136.46, 146.97, 147.29, 150.78, 164.13. Exact mass (FAB, M + Na^+) Calcd for $C_{29}H_{25}ClN_2O_5$SNa 571.107, found 571.109.

5′-*O*-[9-(3-Methoxyphenyl)thioxanthyl]-2′-deoxythymidine (5i). (83%) mp (dec) 138−141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (s, 3H); 2.25 (m, 2H); 3.23 (m, 2H); 3.63 (s, 3H); 3.91 (s, 1H); 4.38 (s, 1H); 5.39 (s, 1H); 6.24 (t, 1H); 6.76 (q, 2H); 6.85 (s, 1H); 7.14−7.61 (m, 10H), 11.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.63, 54.91, 64.64, 70.64, 79.52, 83.76, 85.24, 109.63, 111.32, 117.41, 125.36, 125.42, 126.61, 127.96, 128.18, 128.91, 129.00, 129.26, 129.45, 129.92, 133.64, 133.80, 135.55, 150.27, 150.35, 158.96, 163.61. Exact mass (FAB, M + Na^+) Calcd for $C_{30}H_{28}N_2O_6$SNa 567.1566, found 567.1564.

5′-*O*-[3-Methoxy-9-phenylthioxanthyl]-2′-deoxythymidine (5j). Isolated as a mixture of isomers (89%) mp (dec) 171−173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50 (d, 3H); 2.37 (m, 2H); 2.96 (br, 1H); 3.32−3.59 (m, 2H); 3.65 (d, 3H); 4.07 (q, 1H); 4.63 (m, 1H), 6.43 (dt, 1H); 6.80−6.90 (m, 1H); 7.01−7.65 (m, 12H); 9.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.13, 41.04, 41.07, 55.41, 55.54, 63.89, 64.07, 72.45, 72.61, 81.37, 81.39, 84.92, 85.05, 86.16, 86.21, 111.50, 111.60, 114.36, 114.60, 115.53, 121.45, 122.50, 125.77, 125.85, 125.89, 126.96, 126.38, 126.43, 126.78, 126.82, 127.45, 127.48, 127.87, 128.09, 128.43, 128.49, 129.03, 129.73, 131.24, 131.86, 134.22, 135.44, 135.76, 136.00, 147.13, 150.68, 158.51, 158.73, 163.96, 164.00. Exact mass (FAB, M + Na^+) Calcd for $C_{30}H_{28}N_2O_6$SNa 567.1566, found 567.1574.

5′-*O*-[2,7-Dibromo-9-phenylthioxanthyl]-2′-deoxythymidine (5k). (84%) mp (dec) 180−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (s, 3H); 2.23 (m, 2H, J = 6.59); 3.28−3.42 (t, 1H); 3.93 (t, 1H); 4.44 (q, 1H); 5.46 (d, 1H); 6.28 (t, J = 6.59, 1H); 7.22−7.71 (m, 12H); 11.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.74, 64.53, 69.97, 70.07, 79.26, 83.26, 84.64, 109.91, 119.52, 124.61, 126.28, 127.59, 127.63, 127.69, 128.36, 128.43, 128.69, 129.02, 131.09, 131.22, 131.28, 135.73, 135.80, 135.90, 147.05, 150.38, 150.46, 163.55. Exact mass (FAB, M + Na^+) Calcd for $C_{29}H_{24}$Br(81)N_2O_5SNa 694.965, found 694.964.

5′-*O*-[3-Methoxy-9-(4-methoxyphenyl)thioxanthyl]-2′-deoxythymidine (5l). Isolated as a mixture of isomers (84%). mp (dec) 163−164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34−1.43 (d, 3H); 2.09 (s, 3H); 2.19−2.42 (m, 2H); 3.29−3.52 (m, 2H); 3.67 (s, 3H); 3.99 (m, 1H, D_2O ex.); 4.41−4.58 (dq, 2H); 6.31 (dt, 1H); 6.82−7.74 (m, 10H); 8.06 (d, 2H); 11.25 (d, 1H, D_2O ex.). ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.49, 11.60, 54.80, 55.00, 55.03, 63.57, 64.47, 70.45, 70.48, 79.96, 80.01, 83.56, 83.68, 85.23, 109.70, 109.75, 112.88, 113.08, 113.51, 113.63, 114.73, 115.38, 120.38, 121.24, 124.99, 125.59, 125.91, 126.33, 126.45, 126.68, 126.73, 127.59, 127.82, 128.22, 128.26, 128.53, 129.73, 130.54, 131.54, 133.15, 134.30, 135.68, 135.76, 135.83, 136.18, 138.94, 150.40, 158.10, 158.13, 158.19, 158.24, 163.57, 163.63, 167.63. Exact mass (FAB, M + Na^+) Calcd for $C_{31}H_{30}N_2O_7$SNa 597.1671, found 597.1683.

5′-*O*-[9-(3-Nitro-4-methylphenyl)thioxanthyl]-2′-deoxythymidine (5m). (64%) mp (dec) 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H); 2.21 (m, 2H); 2.43 (s, 3H); 2.51 (br, 1H); 3.24 (m, 2H); 3.96 (q, 1H); 4.30 (m, 1H); 5.39 (d, 1H, D_2O ex.); 6.21 (t, 1H); 7.21−7.55 (m, 11H); 7.89 (d, 1H); 11.36 (s, 1H, D_2O ex.). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.61, 21.13, 40.92, 64.54, 72.42, 80.26, 85.90, 111.37, 124.19, 125.02, 125.76, 125.81, 126.77, 126.87, 128.57, 128.68, 129.81, 129.88, 129.99, 130.82, 131.01, 132.63, 132.93, 133.96, 135.53, 147.87, 150.67, 153.47, 164.03. Exact mass (FAB, M + Li^+) Calcd for $C_{30}H_{27}N_3O_7$SLi 580.173, found 580.173.

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Supporting Information Available: ^{13}C NMR spectra of **1**, **2**, **3b**−**c**, **3e**, **3g**−**l**, **4a**−**b**, **5a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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