Synthesis of Caged Nucleosides with Photoremovable Protecting Groups Linked to Intramolecular Antennae

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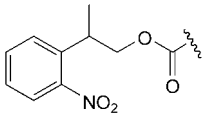
Based on the [2-(2-nitrophenyl)propoxy]carbonyl (nppoc) group, six new photolabile protecting groups (**2**, **8**, **9b**, **16b**, **25b**, and **26**), each covalently linked to a 9*H*-thioxanthen-9-one (Tx) unit functioning as an intramolecular triplet sensitizer, were synthesized. Linkers were introduced between the Me group or the aromatic ring of nppoc and the 2-position of Tx by means of classical organic synthesis combined with Pd catalyzed C–C coupling reactions. The new photolabile protecting groups to be used in light-directed synthesis of DNA chips were attached to the 5′-O-atom of thymidine *via* a carbonate linkage, giving rise to the caged nucleosides **7**, **11**, **13**, **19**, **20,** and **30**.

Introduction. – Light-directed, massive parallel combinatorial synthesis with photoremovable protecting groups allows the fabrication of high-density DNA chips [1][2], *i.e.*, arrays of up to 1 million spots of different oligonucleotides on an area of *ca.* 1 cm^2. Such high-density DNA chips represent highly effective diagnostic tools for a variety of genomic applications such as genotyping [3], gene-expression profiling [4], and sequencing by hybridization [5]. Several reviews on DNA chips and their application have been published [6–12].

The efficiency of the photolithographic technique for producing high-density DNA chips critically depends on the performance, *i.e.*, the light sensitivity and the uniformity of the photochemical cleavage reaction of the photolabile protecting groups blocking either the terminal 5′-OH or the 3′-OH group in the growing oligonucleotides. Among the photolabile protecting groups currently in use for photolithographic DNA-chip synthesis [13], the [2-(2-nitrophenyl)propoxy]carbonyl (nppoc) group (**1**) developed by *Pfleiderer* and co-workers is a prominent example [14][15]. It reacts in excellent yield and gives rise to a good quantum yield, the only draw-back for a higher light sensitivity being its low absorption coefficient in the near UV, where illumination is usually performed with the 366-nm Hg line. It has been shown that this problem can be overcome by triplet sensitization, *e.g.*, with 9*H*-thioxanthen-9-one ('thioxanthone'), which has a high absorption coefficient at 366 nm and, on diffusional encounters, transfers its triplet energy to the photoreactive nitrobenzyl chromophore [16]. In O_2-free solution, the rate of photodeprotection of nppoc-protected thymidine is enhanced by a factor of *ca.* ten, when thioxanthone is added as a sensitizer. However, since *intermolecular* energy transfer is rate-limited by diffusion, in the presence of O_2, the sensitizer is mostly quenched, and the enhancement of the photoreactivity is only weak or even absent. To avoid the diffusional step in energy transfer, we synthesized new

protecting groups that utilize the sensitization principle, but with *intramolecular* energy transfer from a covalently linked sensitizer group to the photoreactive chromophore.



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The structure of nppoc (**1**) allows the attachment of a thioxanthone (Tx) moiety to the aliphatic chain of the protecting group, or directly to the aromatic ring. In this paper we present strategies for the synthesis of several *intramolecularly* sensitized protecting groups, as well as the synthesis of 5′-*O*-caged thymidines derived from them. The photochemical and photophysical properties of these new protecting groups will be published elsewhere.

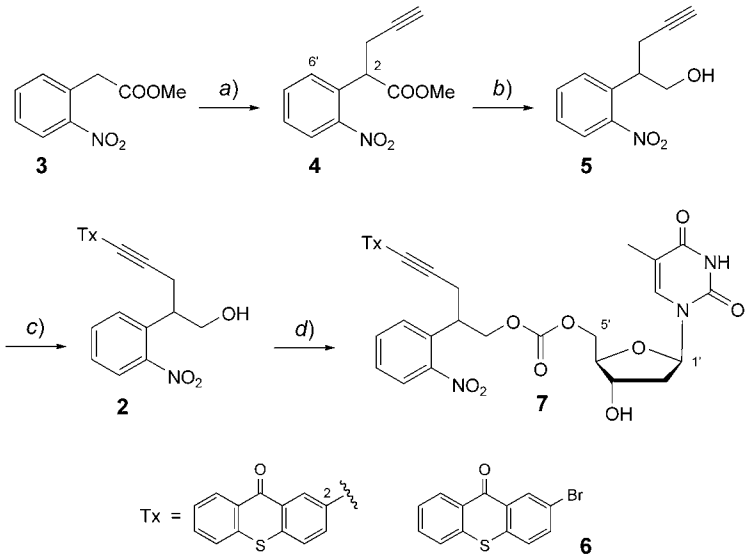
Results and Discussion. – 1. *Linkage of the Thioxanthone Moiety to the Aliphatic Chain of nppoc*. In linking the sensitizer to the photolabile protecting group, we tried to avoid adverse effects on the reactivity of the photoreactive group that might result from the structural change associated with the substitution of the linker. It has been established that the primary photoreaction of nppoc consists in an intramolecular H-atom transfer from the benzylic CH to the NO_2 group. Hence, the H-acceptor ability of the photo-excited NO_2 group and the H-donor ability of the benzylic CH group are relevant. Connecting the linker to the Me group of nppoc should neither have significant effect on the electronic system involved in the photoactive nπ*-state, nor should the extension of the side chain at the benzylic C-atom by another saturated C–C unit substantially reduce the H-donor activity of the benzylic C–H bond. Three C_3 linkages (propyne-1,3-diyl, propene-1,3-diyl, and propane-1,3-diyl) and one C_2 linkage (ethane-1,2-diyl) were realized in this work.

Our approach to the protecting group with a triple bond in the aliphatic C_3 linkage between the basic nppoc group **1** and the Tx residue is shown in *Scheme 1*. The synthesis of **2** started with the alkylation of methyl 2-nitrophenylacetate (**3**) with propargyl bromide in the presence of *t*-BuOK to give the pent-4-ynoate **4** in 48% yield. Reduction of **4** with $NaBH_4$ following the method of *Soai* and co-workers [17] proceeded smoothly, and allowed us to obtain the alcohol **5** in 78% yield. Coupling of **5** with 2-bromo-9*H*-thioxanthen-9-one (**6**) under classical *Sonogashira* conditions [18] provided the desired protecting group **2** in 31% yield.

The caged thymidine **7** was derived from **2** according to [14]. Compound **2** was treated with phosgene, and the resulting chloroformate was allowed to react with thymidine, which afforded the 5′-*O*-protected derivative **7**. The overall yield of the reaction was quite low (15%) due to some side reactions.

For the synthesis of the protecting groups **8** and **9b** with C=C and C–C bonds, respectively, in the C_3 linkage, we developed a synthetic strategy that allowed us to use the same precursor **10** for the synthesis of both compounds (Scheme 2). The key step to the protected thymidine **11**, bearing a C=C bond in the Tx-based linkage, was a *Heck* reaction of the allylic alcohol **10** with 2-iodo-9*H*-thioxanthen-9-one (**12**) [19][20]. For the analogue **13**, a hydroboration–*Suzuki* coupling sequence between the same

Scheme 1

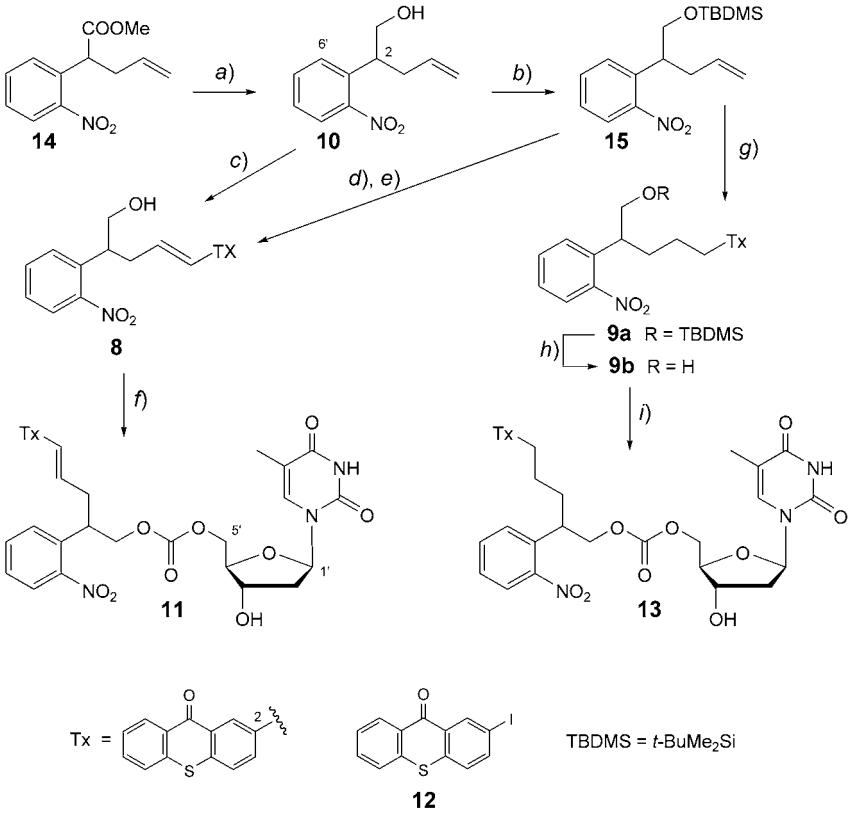


a) *t*-BuOK, $HC{\equiv}CCH_2Br$, THF; $-80° \rightarrow$ r.t., 12 h; 48%. *b*) $NaBH_4$, *t*-BuOH, MeOH, 80°, 4 h; 78%. *c*) 1. CuI, $[Pd(PPh_3)_4]$, Et_3N, THF; 2. **5**, r.t., 20 h; 31%. *d*) 1. 20% soln. of phosgene in toluene, THF, r.t., 14 h; 2. thymidine, pyridine, CH_2Cl_2, $-40° \rightarrow 0°$, 4 h, r.t. 48 h; 15%.

starting compounds was the main step. Precursor **10** was prepared in 93% yield by reduction of the ester **14** [21] with $NaBH_4$ in THF/MeOH [22] (initial attempts to use *t*-BuOH/MeOH, analogous to **4** → **5**, led to **10** in less then 20% yield). The *Heck* reaction [23][24] between **10** and **12** in the presence of a catalytic amount of $[Pd(OAc)_2]$, Bu_3P, and K_2CO_3 in DMF afforded the adduct **8** in 24% yield. Several attempts have been made at improving the yield of the *Heck* coupling reaction, but any variations in the catalytic system, solvents, and reaction time [23–25] did not increase the yield. The *Heck* coupling product **8** was also prepared from the silyl-protected alcohol **15**, made from **14**, employing the same conditions as for the unprotected form **10** [26][27]. Deblocking of the OH group of **15** with Bu_4NF in THF [26] gave the alcohol **8** in an overall yield of 42% from **10**. The caged thymidine **11** was finally derived from **8** by treatment with phosgene, and reaction of the chloroformate with thymidine (34% yield) [14].

For the synthesis of **13**, the silyl ether **15** was subjected to hydroboration with 9-BBN (= 9-borabicyclo[3.3.1]nonane), followed by *Suzuki* coupling [28][29] with 2-bromothioxanthone **6** in the presence of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($[Pd(dppf)Cl_2]$) and 3M aq. K_3PO_4 to afford the silyl-protected alcohol **9a**. Deprotection of the *t*-$BuMe_2Si$ group [26] led to the free alcohol **9b** in 47% yield (two steps). Treatment of **9b** with trichloromethyl chloroformate (diphosgene) in the presence of Et_3N [14][30][31], followed by reaction of the resulting chloroformate with thymidine, resulted in the formation of **13** in 58% yield.

Scheme 2

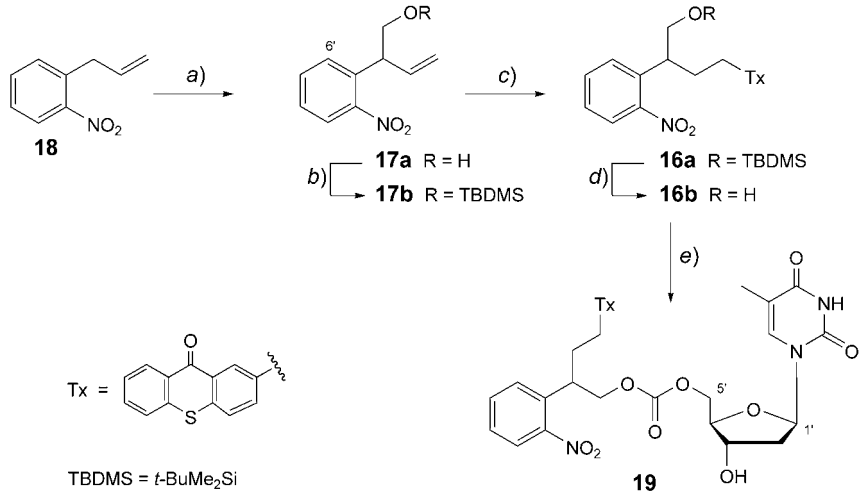


a) $NaBH_4$, THF, MeOH, r.t., 3 h; 81%. *b*) *t*-$BuMe_2SiCl$, imidazole, CH_2Cl_2, 0° → r.t., 12 h; 98%. *c*) **12**, $[Pd(OAc)_2]$, Bu_3P, K_2CO_3, DMF, 100°, 3 h; 24%. *d*) **12**, $[Pd(OAc)_2]$, Bu_3P, K_2CO_3, DMF, 100°, 3 h. *e*) Bu_4NF, THF, 0° → r.t., 18 h; 43% (2 steps). *f*) 1. 20% soln. of phosgene in toluene, THF, 0° → r.t., 12 h; 2. thymidine, pyridine, CH_2Cl_2, 0° → r.t., 12 h; 34%. *g*) 1. 9-BBN, THF, r.t., 3 h; 2. **12**, $[Pd(dppf)Cl_2]$, 3M aq. K_3PO_4, DMF, 100°, 2 h. *h*) Bu_4NF, THF, 0° → r.t., 17 h, 47% (2 steps). *i*) 1. Diphosgene, Et_3N, THF, 0° → r.t., 4 h, 2. thymidine, pyridine, CH_2Cl_2, 0°, 48 h; 58%.

For the synthesis of the protecting group **16b** with a saturated C_2 linkage, we followed the same synthetic strategy based on the hydroboration–*Suzuki* coupling tandem reaction, as used for the synthesis of **9b**. To follow this synthetic approach, the silyl-protected form **17b** of the alcohol **17a** was required as key intermediate. The synthesis of **16b** started from 1-allyl-2-nitro-benzene (**18**), which was prepared according to *Sapountzis* and *Knochel* [32]. Compound **18** was treated with paraformaldehyde in the presence of *t*-BuOK [30] to give the alcohol **17a** in 86% yield. Protection of the OH group with *t*-$BuMe_2SiCl$ [26][27] afforded the silyl ether **17b** quantitatively. The position of the olefinic C=C bond in compounds **17** was verified by ^{1}H-NMR analysis, and was in agreement with literature data [33].

Hydroboration of **17b** with 2 equiv. of 9-BBN proceeded smoothly [28][29]. The organoborane intermediate, when subjected to *Suzuki* coupling with **12**, afforded the

Scheme 3



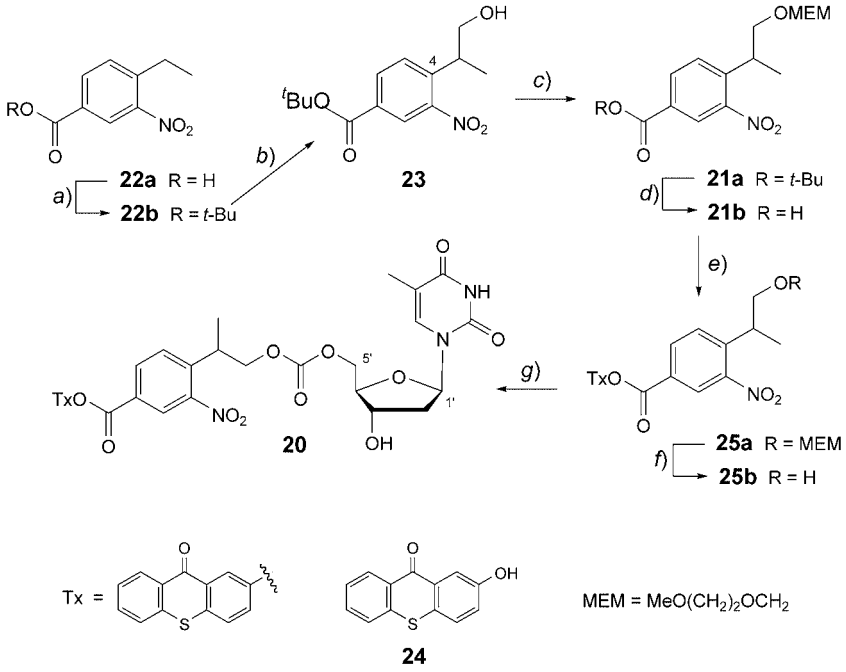
a) Paraformaldehyde, *t*-BuOK, DMSO, r.t., 2 h; 86%. *b*) *t*-BuMe$_2$SiCl, imidazole, CH_2Cl_2, 0° → r.t., 18 h; 100%. *c*) 1. 9-BBN, THF, r.t., 2 h, 2. **12**, [Pd(dppf)Cl_2], 3M aq. K_3PO_4, DMF, 100°, 2.5 h. *d*) Bu_4NF, THF, 0° → r.t.,18 h, 51%. *e*) 1. Diphosgene, Et_3N, THF, 0°, 2 h; 2. thymidine, pyridine, CH_2Cl_2, 0°, 20 h, 69%.

desired silyl-protected alcohol **16a**. The cleavage of the protecting group with Bu_4NF in THF led to the alcohol **16b** in two steps, in an overall yield of 51%. The caged thymidine **19** was finally derived from **16b** in 69% yield by the method described above for compound **13**.

2. *Linkage of the Thioxanthone Moiety to the Aromatic Ring of nppoc.* Two synthetic pathways were developed for new protecting groups with a Tx residue linked to the aromatic ring of **1**. In the first one, the protecting group was connected to the Tx moiety through an ester linkage (*Scheme 4*). In the second, Tx was directly attached to the aromatic ring of 1 (*Scheme 5*).

The synthesis of the 5′-*O*-caged thymidine **20**, with the ester linkage at the aromatic ring of the nppoc moiety, is outlined in *Scheme 4*. The nitrobenzoic acid **21a** was conveniently prepared from the known benzoic acid **22a** [34], which was converted to the *t*-Bu ester **22b** by DCC (= *N,N*-dicyclohexylcarbodiimide)-mediated esterification [35]. Treatment of **22b** with paraformaldehyde and *t*-BuOK afforded the alcohol **23**, which was converted to the 2-(methoxyethoxy)methyl (MEM) ether **21a** in 85% yield by treatment with MEMCl in the presence of *Hünig* base under standard conditions [36–38]. The *t*-Bu protecting group of **21a** was smoothly cleaved under basic conditions (NaH, DMF) [39], without formation of any side products, to yield the desired benzoic acid derivative **21b** in 94% yield. Attempts to remove the *t*-Bu group by the widely used acidolysis with anhydrous CF_3COOH (TFA) were unsuccessful because of partial or complete cleavage of the MEM ether, contrary to literature data [40]. Reaction between 2-hydroxythioxanthene-9*H*-one (**24**) [41] and **21b** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) and *N,N*-dimethylpyridin-4-amine (DMAP) [42–44] resulted in the formation of aromatic ester **25a**

Scheme 4

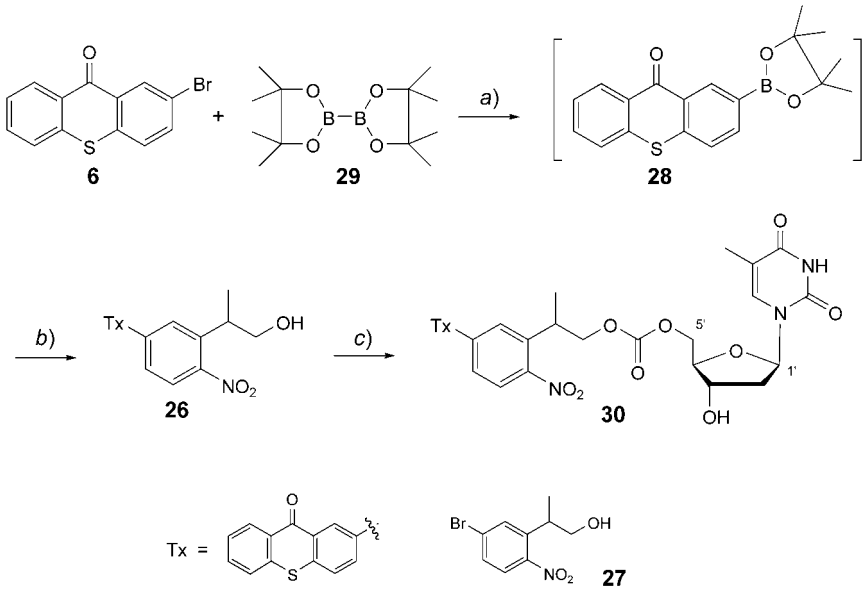


a) *t*-BuOH, DCC, DMAP, CH_2Cl_2, r.t., 3 h; 96%. *b*) Paraformaldehyde, *t*-BuOK, DMSO, r.t., 1 h; 100%. *c*) MEMCl, $Et(i\text{-}Pr)_2N$, CH_2Cl_2, r.t., 21 h; 85%. *d*) NaH, DMF, r.t., 1 h; 94%. *e*) **24**, EDCI, DMAP, CH_2Cl_2, r.t., 24 h; 64%. *f*) 3M aq. HCl, THF, 75°, 5 h; 66%. *g*) 1. Diphosgene, THF, 0° → r.t., 4 h; 2. thymidine, pyridine, CH_2Cl_2, 0°, 18 h; 58%.

in 64% yield. The MEM protecting group was removed with 3M aqueous HCl in THF under reflux [45][46] to yield the alcohol **25b**. Reaction with diphosgene, and reaction of the resulting chloroformate with thymidine, analogous to the method described above, proceeded in 58% yield.

The protective group **26**, bearing the Tx moiety directly linked to the aromatic ring of the nppoc chromophore, was synthesized by *Suzuki–Miyaura* reaction [47] between **6** and 2-(5-bromo-2-nitrophenyl)propan-1-ol (**27**), which was prepared according to [30]. Cross-coupling to **26** could be achieved by a one-pot procedure avoiding separation and purification of the intermediate **28**. First, the dioxaborolan **28** was prepared *in situ* from **6** in dioxane using $[Pd(dppf)_2]$ (3 mol-%) and AcOK (3 equiv.) in the presence of the bis(pinacolate)diborane **29**. Subsequent reaction of **28** with **27** in the presence of a new portion of $[Pd(dppf)_2]$ (3 mol%) and 3M aqueous K_3PO_4 (3 equiv.) led to the target compound **26** in 77% yield. By comparison, the traditional method involving isolation of **28** and reacting it, in a separate step, with **27** in THF led to **26** in only 39% overall yield. The caged thymidine **30** was finally derived from **26** in 59% yield by treatment with phosgene, followed by reaction of the resulting chloroformate with thymidine, as described above.

Scheme 5



a) AcOK, [Pd(dppf)$_2$], 1,4-dioxane, 70°, 16 h. *b*) **27**, [Pd(dppf)$_2$], 3M aq. K_3PO_4, 70°, 20 h, 77% (2 steps). *c*) 1. 20% soln. of phosgene in toluene, THF, r.t., 14 h; 2. thymidine, pyridine, $-40° \rightarrow 0°$ for 4 h, then r.t. for 48 h; 59%.

Conclusions. – We have developed synthetic methods for several new photolabile protecting groups wherein a thioxanthone moiety is covalently linked at different positions to the photolabile nppoc moiety **1**. In general, the methods are based on Pd-catalyzed cross-coupling reactions. To the best of our knowledge, these are the first such reactions with halogenated thioxanthones.

Experimental Part

All reactions with moisture-sensitive reagents were performed in dry, N_2-flushed glassware. THF was dried over Na/benzophenone. DMF was stored over 4-Å molecular sieves under N_2. Silica gel *60* (203–400 mesh; *Merck*) was used for flash chromatography (FC) and column chromatography (CC). Thin-layer chromatography (TLC) was performed on precoated silica gel *60* F_{254} plates (*Merck*), detection by UV light at 254 nm. Melting points (m.p.) were determined with a *Büchi B-545* apparatus in open glass capillaries; uncorrected. Elemental analyses were carried out by the Microanalytical Laboratory of the Department of Chemistry at the University of Konstanz.

Methyl 2-(2-Nitrophenyl)pent-4-ynoate (**4**). *t*-BuOK (1.85 g, 16.5 mmol) was added to a stirred soln. of **3** [48] (3.21 g, 16.4 mmol) and propargyl bromide (1.3 ml, 17.2 mmol) in THF (20 ml) at $-80°$. The cooling bath was removed, and stirring was continued for 12 h. After quenching with H_2O (30 ml), the mixture was extracted with Et_2O (3×30 ml), the combined org. phase was washed with H_2O (30 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (AcOEt/hexane $0:100 \rightarrow 25:75$) to give **4** (1.84 g, 48%). Orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (*dd*, $J = 8.2$, 1.4, H–C(3′)); 7.61 (*td*, $J = 7.6$, 1.2, H–C(5′)); 7.53 (*dd*, $J = 7.8$, 1.5, H–C(6′)); 7.46 (*td*, $J = 7.7$, 1.5, H–C(4′)); 4.45 (*dd*, $J = 8.3$, 6.4, H–C(2)); 3.69 (*s*, Me); 3.03 (*ddd*, $J = 17.0$, 6.2, 2.7, 1 H of CH_2); 2.85 (*ddd*, $J = 17.0$, 8.3, 2.7, 1 H of CH_2); 1.95 (*t*, $J = 2.5$, 1 H, ≡CH).

2-(2-Nitrophenyl)pent-4-yn-1-ol (**5**). $NaBH_4$ (525 mg, 13.9 mmol) was added to a stirred soln. of **4** (1.84 g, 78.9 mmol) in *t*-BuOH (25 ml). The suspension was heated to 80°, MeOH (3.4 ml, 83.9 mmol) was added

dropwise over a period of 4 h, and heating was continued for 1 h. After cooling to r.t. and quenching with H_2O (30 ml), the product was extracted with Et_2O (3 × 30 ml), the combined org. phase was washed with sat. aq. NH_4Cl soln. (30 ml), dried ($MgSO_4$), and evaporated to give pure **5** (1.26 g, 78%). Viscous, red oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.80 (*d*, *J* = 7.6, H–C(3′)); 7.61–7.55 (*m*, 2 arom. H); 7.42–7.37 (*m*, arom. H); 4.03–3.95 (*m*, OCH_2); 3.63 (*quint.*, H–C(2)); 2.72 (*ddd*, *J* = 17.1, 6.8, 2.7, H_a–C(3)); 2.67 (*ddd*, *J* = 16.8, 7.0, 2.7, H_b–C(3)); 1.98 (*t*, *J* = 2.5, ≡CH).

*2-[5-Hydroxy-4-(2-nitrophenyl)pent-1-yn-1-yl]-9*H*-thioxanthen-9-one* (**2**). To a stirred soln. of **6** (735 mg, 2.52 mmol) [49] in anh. THF (20 ml), CuI (32 mg, 0.17 mmol), [$Pd(PPh_3)_4$] (48 mg, 0.042 mmol), and Et_3N (5 ml, 35.9 mmol) were added in this order. Then, a soln. of **5** (511 mg, 2.49 mmol) in anh. THF (5 ml) was added dropwise over a period of 2 h at r.t. The mixture was stirred overnight, and the solvent was evaporated. The residue was taken up in Et_2O (20 ml) and sat. aq. NH_4Cl soln. (20 ml), the org. phase was separated, and the aq. phase was re-extracted with Et_2O (2 × 10 ml). The combined org. phases were dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (AcOEt/hexane 0:100 → 35:65) afforded **2** (318 mg, 31%). Colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.59 (*dd*, *J* = 8.2, 1.4, H–C(8) (Tx)); 8.53 (*d*, *J* = 1.7, H–C(1) (Tx)); 7.83 (*d*, *J* = 8.8, arom. H); 7.65–7.39 (*m*, 8 arom. H); 4.10 (*dd*, *J* = 16.8, 6.1, 1 H of OCH_2); 4.06 (*dd*, *J* = 16.6, 6.4, 1 H of OCH_2); 3.75 (*quint.*, *J* = 6.8, benzylic CH); 3.00 (*dd*, *J* = 17.0, 6.6, 1 of CH_2); 2.91 (*dd*, *J* = 17.0, 6.9, 1 H of CH_2).

*5′-*O*-({[2-(2-Nitrophenyl)-5-(9-oxo-9*H*-thioxanthen-2-yl)pent-4-yn-1-yl]oxy}carbonyl)thymidine* (**7**). To a stirred soln. of **2** (318 mg, 0.765 mmol) in anh. THF (10 ml), a 20% soln. of phosgene in toluene (3 ml) was added, and the reaction mixture was stirred at r.t. for 14 h. The solvents were evaporated, and the chloroformate residue was dissolved in anh. CH_2Cl_2 (10 ml). In another flask, thymidine (200 mg, 0.83 mmol, dried for 5 h *in vacuo*) was dissolved in anh. pyridine (10 ml). The thymidine soln. was cooled to −40°, and the chloroformate soln. was added dropwise over 4 h with stirring. During the addition, the temp. was maintained between −30° to 0°. The mixture was allowed to warm to r.t., and stirring was continued for 2 d. Removal of the solvents, co-evaporation of the residue with toluene (3 × 5 ml), and FC (MeOH/CH_2Cl 0:100 → 5:95) gave **7** (81 mg, 15%). Colorless solid. M.p. 79–81°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.27 (*s*, NH); 8.45 (*dd*, *J* = 8.1, 1.2, H–C(8) (Tx)); 8.29 (*d*, *J* = 1.7, H–C(1) (Tx)); 7.91 (*d*, *J* = 8.1, arom. H); 7.88–7.72 (*m*, 5 arom. H); 7.64–7.52 (*m*, 3 arom. H); 7.40 (*dd*, *J* = 4.3, CH (T)); 6.16 (*td*, *J* = 6.9, 2.0, H–C(1′)); 5.40 (br. *s*, OH); 4.65–4.59 (*m*, 1 H of CH_2O); 4.54–4.48 (*m*, 1 H of CH_2O); 4.31–4.17 (*m*, CH_2(5′), H–C(3′)); 3.92–3.88 (*m*, H–C(4′)); 3.82 (*quint.*, *J* = 6.8, benzylic CH); 3.02 (*dd*, *J* = 17.3, 6.4, 1 H of CH_2–C≡); 2.93 (*dd*, *J* = 17.2, 7.9, 1 H of CH_2–C≡); 2.15–2.05 (*m*, CH_2(2′)); 1.72 (*d*, *J* = 3.2, Me). MALDI-MS (matrix: DHB): 683.2 (M^+, $C_{35}H_{29}N_3O_{10}S^+$).

2-(2-Nitrophenyl)pent-4-ene-1-ol (**10**). MeOH (20 ml) was added slowly within 3 h to a stirred suspension of **14** [21] (8.80 g, 37.4 mmol) and $NaBH_4$ (8.80 g, 232 mmol) in anh. THF (100 ml) under N_2 atmosphere at r.t. Stirring was continued overnight. H_2O (10 ml) was added, and, after 10 min of vigorous stirring, the solvents were evaporated. The residue was partitioned between CH_2Cl_2 (100 ml) and H_2O (100 ml), the org. layer was separated, the aq. layer was extracted with CH_2Cl_2 (3 × 30 ml), and the combined org. layers were washed with H_2O (100 ml), dried ($MgSO_4$), and concentrated. A yellow oil (7.2 g, 34.9 mmol, 93%) was obtained, which was used for the next step without further purification. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.74 (*dd*, *J* = 8.1, 1.2, H–C(3′)); 7.61–7.47 (*m*, H–C(5′), H–C(6′)); 7.36 (*td*, *J* = 7.0, 1.6, H–C(4′)); 5.69 (*ddt*, *J* = 17.1, 10.1, 7.1, H–C(4)); 5.05–4.94 (*m*, CH_2(5)); 3.93–3.78 (*m*, CH_2(1)); 3.49 (*quint.*, *J* = 6.7, H–C(2)); 2.62–2.36 (*m*, CH_2(3)); 1.67 (br. *s*, OH).

*5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-(2-nitrophenyl)pent-1-ene* (**15**)[1]). To an ice-cold soln. of **10** (7.2 g, 35 mmol) in anh. CH_2Cl_2 (150 ml), 1*H*-imidazole (3.0 g, 44 mmol) and *t*-$BuMe_2SiCl$ (5.9 g, 39 mmol) were added with stirring. The cooling bath was removed, and the mixture was stirred at r.t. for 12 h. The reaction was quenched with MeOH (20 ml), and after 10 min of stirring, sat. aq. $NaHCO_3$ soln. (100 ml) was added. The org. layer was separated, and the aq. phase was re-extracted with CH_2Cl_2 (3 × 30 ml). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (15 ml), dried ($MgSO_4$), and evaporated. The crude product was purified by FC (hexane/AcOEt 8:1) to give **15** (11.2 g, 90%). Light yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.72 (*dd*, *J* = 8.5, 1.8, H–C(3′)); 7.49–7.52 (*m*, H–C(5′), H–C(6′)); 7.26–7.35 (*m*, H–C(4′)); 5.70 (*ddt*, *J* = 17.1, 10.1, 7.1, H–C(2)); 5.05–4.92 (*m*, CH_2(1)); 3.83–3.72 (*m*, CH_2(5)); 3.49–3.38 (*m*, H–C(4)); 2.69–2.56 (*m*, H_a–C(3)); 2.49–2.36 (*m*, H_b–C(3)); 0.82 (*s*, *t*-Bu); −0.06 (*s*, Me); −0.09 (*s*, Me).

*2-[5-Hydroxy-4-(2-nitrophenyl)pent-1-enyl]-9*H*-thioxanthen-9-one* (**8**). *Method A.* To a stirred soln. of **10** (104 mg, 0.5 mmol) in anh., degassed DMF (5 ml), kept under N_2 atmosphere, K_2CO_3 (76 mg, 0.55 mmol),

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[1]) Systematic silane nomenclature was avoided for the sake of clarity.

[$Pd(OAc)_2$] (12 mg, 0.05 mmol), Bu_3P (25 µl, 0.1 mmol), and **12** [19][20] (186 mg, 0.55 mmol) were rapidly added at r.t., and in the order mentioned. The flask was covered with Al foil, and the mixture was heated at 100° for 3 h. After cooling to r.t., brine (10 ml) and Et_2O (10 ml) were added under N_2 atmosphere. The org. phases were separated, the aq. phase was re-extracted with Et_2O (10 ml), the combined org. layer was dried ($MgSO_4$), and the solvent was evaporated. CC (AcOEt/hexane 10:90 → 60:40) followed by crystallization from hexane/Et_2O 1:1 afforded the desired coupling product **8** (50 mg, 24%).

Method B. To a stirred soln. of **15** (322 mg, 1.0 mmol) in anh. degassed DMF (10 ml), kept under N_2, K_2CO_3 (152 mg, 1.1 mmol), [$Pd(OAc)_2$] (23 mg, 0.1 mmol), Bu_3P (49.4 µl, 0.2 mmol), and **12** (372 mg, 1.1 mmol) were added rapidly at r.t., and in the order mentioned. The flask was covered with Al foil, and the mixture was heated at 100° for 3 h. After cooling to r.t., brine (10 ml) was added. The mixture was extracted with Et_2O (3 × 20 ml), the combined org. layer was washed with H_2O (2 × 20 ml), dried ($MgSO_4$), and evaporated. CC (AcOEt/hexane 10:90 → 25:75) gave the corresponding *silyl-protected* coupling product[2]) as an impure mixture. This crude product (532 mg) was dissolved in THF (10 ml) and treated at 0° with Bu_4NF (1M soln. in THF, 1.4 ml, 1.4 mmol). The mixture was then stirred at r.t. for 16 h, and extracted with CH_2Cl_2 (20 ml and 10 ml). The combined org. phase was washed with sat. aq. NH_4Cl soln. (20 ml), dried ($MgSO_4$), and evaporated. The crude product was purified as described in *Method A* to afford **8** (178 mg) in 43% overall yield.

Data of **8**. Yellow powder. M.p 132–133°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.45 (*dd*, *J* = 8.2, 1.2, H–C(8) (Tx)); 8.27 (*s*, H–C(1) (Tx)); 7.85–7.40 (*m*, 9 arom. H); 6.52 (*d*, *J* = 15.9, Tx–C*H*=); 6.33 (*dt*, *J* = 15.9, 7.0, CH_2C*H*=); 4.89 (*t*, *J* = 5.19, OH); 3.72–3.58 (*m*, OCH_2); 3.33 (*m*, benzylic CH, partly masked by water signal); 2.82–2.72 (*m*, 1 H of CH_2CH=); 2.63–2.54 (*m*, 1 H of CH_2CH=). Anal. calc. for $C_{24}H_{19}NO_4S$ (417.48): C 69.05, H 4.59, N 3.36; found: C 68.87, H 4.76, N 3.43.

Data of Silyl-Protected Intermediate[2]): ^{1}H-NMR (250 MHz, $CDCl_3$): 8.61 (*d*, *J* = 8.0, 1 H, H–C(8) (Tx)); 8.43 (*d*, *J* = 1.2, H–C(1) (Tx)); 7.72 (*dd*, *J* = 7.3, 1.2, H–C(3)); 7.43–7.67 (*m*, 7 arom. H); 7.29–7.40 (*m*, arom. H); 6.49 (*d*, *J* = 15.6, Tx–C*H*=); 6.26 (*dt*, *J* = 15.9, 6.7, CH_2C*H*=); 3.90–3.76 (*m*, OCH_2); 3.61–3.51 (*m*, benzylic CH); 2.93–2.79 (*m*, 1 H of CH_2CH=); 2.70–2.55 (*m*, 1 H of CH_2CH=); 0.84 (*s*, *t*-Bu); −0.04 (*s*, Me); −0.06 (*s*, Me).

*5′-*O*-({[2-(2-Nitrophenyl)-5-(9-oxo-9*H*-thioxanthen-2-yl)pent-4-en-1-yl]oxy}carbonyl)thymidine* (**11**). To a stirred soln. of **8** (67 mg, 0.16 mmol) in anh. THF (2 ml), a 20% soln. of phosgene in toluene (0.9 ml) was added dropwise *via* syringe under N_2 atmosphere at 0°. The cooling bath was removed, and the mixture was stirred for 12 h at r.t. Monitoring by TLC indicated complete consumption of the starting material and the formation of the corresponding chloroformate (R_f 0.60 (CH_2Cl_2)). The solvent was evaporated, the residue was co-evaporated with anh. CH_2Cl_2 (3 × 2 ml), and the chloroformate intermediate was dissolved in anh. CH_2Cl_2 (1 ml). In a separate flask, thymidine (39 mg, 0.16 mmol) was first co-evaporated with anh. pyridine (2 × 1 ml), and then dissolved in anh. pyridine (1 ml). To the stirred thymidine soln., the chloroformate soln. was added dropwise *via* syringe under N_2 at 0°. The mixture was stirred at this temp. for 2 h, then an additional 2 h at r.t., and was finally kept for 12 h at 10°. The solvent was evaporated, the oily residue was dissolved in CH_2Cl_2 (15 ml), and washed with 0.1M aq. HCl soln. (3 × 10 ml). The combined aq. layer was re-extracted with CH_2Cl_2 (2 × 5 ml). The combined org. phase was dried ($MgSO_4$), and the solvent was evaporated. Purification by CC (MeOH/CH_2Cl_2 0:100 → 4:96) followed by crystallization from Et_2O afforded **11** (41 mg, 34%). Yellow powder. M.p. 152–154°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.24 (br. *s*, NH); 8.44 (*d*, *J* = 8.1, H–C(8) (Tx)); 8.27 (br. *s*, H–C(1) (Tx)); 7.82–7.73 (*m*, 5 arom. H); 7.69 (*t*, *J* = 7.0, arom. H); 7.57 (*t*, *J* = 8.1, arom. H); 7.47 (*t*, *J* = 8.1, arom. H); 7.37 (*dd*, *J* = 3.8, 0.9, CH (T)); 6.52 (*d*, *J* = 16.2, Tx–C*H*=); 6.30 (*dt*, *J* = 16.2, 6.7, CH_2C*H*=); 6.19–6.12 (*m*, H–C(1′)); 5.38 (*d*, *J* = 4.4, 3′-OH); 4.53–4.35 (*m*, CHCH_2O); 4.26–4.15 (*m*, H–C(3′), CH_2(5′)); 3.91–3.84 (*m*, H–C(4′)); 3.65 (*quint.*, *J* = 6.7, benzylic CH); 2.80–2.60 (*m*, CH_2CH=); 2.13–2.05 (*m*, CH_2(2′)); 1.69 (*d*, *J* = 4.6, Me). Anal. calc. for $C_{35}H_{31}N_3O_{10}S \cdot 0.5\ H_2O$ (694.71): C 59.74, H 4.73, N 5.97; found: C 59.92, H 4.78, N 6.05.

*2-[5-Hydroxy-4-(2-nitrophenyl)pentyl]-9*H*-thioxanthen-9-one* (**9b**). 9-Borabicyclo[3.3.1]nonane (9-BBN; 0.5M in THF, 60 ml, 30 mmol) was added dropwise to a stirred soln. of **15** (6.7 g, 20.8 mmol) in anh. THF (15 ml) over a period of 1 h under N_2 atmosphere. The mixture was stirred for 4 h. In a separate flask, a cat. amount of [$Pd(dppf)Cl_2$] (0.50 g, 0.68 mmol, 3 mol-%), aq. K_3PO_4 (3M soln., 8 ml, 24 mmol), and degassed DMF (60 ml) were mixed in this order under N_2 atmosphere. After 15 min, compound **6** (6.3 g, 21.6 mmol) was added with vigorous stirring, followed by dropwise addition of the above borane *via* syringe. The flask was covered with Al foil, and the mixture was stirred at 80° for 4 h. After cooling to r.t., the mixture was taken up in Et_2O (150 ml) and brine (100 ml). The aq. layer was re-extracted with Et_2O (3 × 30 ml), and the combined org. phase was

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[2]) 2-[5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-(2-nitrophenyl)pent-1-enyl]-9*H*-thioxanthen-9-one.

washed with sat. aq. $NaHCO_3$ soln. (50 ml), dried ($MgSO_4$), and evaporated. The crude product was subjected to FC (AcOEt/hexane 3.5:96.5 → 8:92) to afford the silyl-protected product **9a**[3]) (contaminated with borate), which was used without further purification. Crude **9a** (7.72 g, 14.5 mmol) was dissolved in THF (120 ml) and treated with $Bu_4NF \cdot 3\ H_2O$ (6.3 g, 20 mmol) under stirring at 0°. The cooling bath was removed, and the mixture was stirred for 15 h at r.t., diluted with Et_2O (100 ml), and washed with sat. aq. NH_4Cl soln. (50 ml). The combined aq. layer was re-extracted with Et_2O (20 ml). The combined org. phase was dried ($MgSO_4$) and evaporated. Purification by CC (AcOEt/hexane 5:95 → 50:50) and crystallization from hexane afforded **9b** (4.07 g, 47% based on **15**).

Data of **9a**. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.62 (*dd*, *J* = 7.9, 1.2, H–C(8) (Tx)); 8.38 (*d*, *J* = 1.8, H–C(1) (Tx)); 7.68 (*dd*, *J* = 7.9, 1.2, H–C(3′)); 7.62–7.39 (*m*, 7 arom. H); 7.31 (*td*, *J* = 7.9, 1.5, H–C(4′)); 3.70 (*d*, *J* = 5.8, CH_2O); 3.42–3.31 (*m*, CH); 2.77–2.69 (*m*, Tx–CH_2); 1.34–1.75 (*m*, $(CH_2)C_2$); 0.77 (*s*, *t*-Bu); −0.10 (*s*, Me); −0.11 (*s*, Me).

Data of **9b**[3]). Light yellow solid. M.p. 115–117°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.46 (*dd*, *J* = 8.2, 1.0, H–C(8) (Tx)); 8.22 (*d*, *J* = 1.5, H–C(1) (Tx)); 7.86–7.66 (*m*, 8 arom. H); 7.42 (*td*, *J* = 7.9, 1.5, H–C(4′)); 4.77 (*t*, *J* = 5.2, OH); 3.60–3.45 (*m*, CH_2O); 3.17–3.07 (*m*, CH); 2.70 (*t*, *J* = 7.0, Tx–CH_2); 1.40–1.70 (*m*, $(CH_2)_2$). Anal. calc. for $C_{24}H_{21}NO_4S$ (419.49): C 68.72, H 5.05, N 3.36; found: C 68.64, H 5.11, N 3.40.

*5′-O-({[2-(2-Nitrophenyl)-5-(9-oxo-9*H*-thioxanthen-2-yl)pentyl]oxy}carbonyl)thymidine* (**13**). To an ice-cold soln. of trichloromethyl chloroformate (171 µl, 1.41 mmol) in anh. THF (5 ml) was added dropwise a soln. of **9b** (443 mg, 1.06 mmol) and Et_3N (148 µl, 1.06 mmol) in anh. THF (5 ml). The mixture was stirred for 2 h at 0°, and then for 2 h at r.t., until TLC monitoring indicated complete consumption of **9b** and formation of the chloroformate (R_f 0.51 (CH_2Cl_2)). The solid was filtered off and washed with anh. THF. The solvent was evaporated, and the residue was dissolved in anh. CH_2Cl_2 (5 ml). In a separate flask, thymidine (257 mg, 1.06 mmol) was first co-evaporated with anh. pyridine (4 × 5 ml), and then dissolved in anh. pyridine (5 ml). To the stirred thymidine soln., the above chloroformate soln. was added *via* syringe at 0°, and the mixture was kept at this temp. for 2 d. The solvents were evaporated, the residue was co-evaporated with EtOH (4 × 5 ml), then with CH_2Cl_2 (3 × 5 ml). The crude product was purified by FC (MeOH/CH_2Cl_2 0.5:95.5 → 5:95) and crystallized from EtO_2 to give **13** (422 mg, 58%). Light yellow powder. M.p. 100–102°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 11.29 (br. *s*, NH); 8.45 (*dd*, *J* = 8.2, 1.2, H–C(8) (Tx)); 8.22 (*d*, *J* = 1.8, H–C(1) (Tx)); 7.85–7.47 (*m*, 9 arom. H); 7.37 (*dd*, *J* = 4.8, 0.9, CH (T)); 6.15 (*t*, *J* = 7.0, H–C(1′)); 5.41 (*d*, *J* = 4.3, 3′-OH); 4.38–4.12 (*m*, CH_2O, CH_2(5′), H–C(3′)); 3.87 (*m*, H–C(4′)); 3.43–3.37 (*m*, CH); 2.73–2.65 (*m*, Tx–CH_2); 2.12–2.04 (*m*, CH_2(2′)), 1.85–1.69 (*m*, CH_2); 1.69 (*d*, *J* = 2.7, Me); 1.61–1.37 (*m*, CH_2). Anal. calc. for $C_{35}H_{33}N_3O_{10}S \cdot 0.5\ H_2O$ (696.72): C 60.33, H 4.91, N 6.03; found: C 60.40, H 5.07, N 5.93.

2-(2-Nitrophenyl)but-3-en-1-ol (**17a**). To a stirred soln. of **18** [32] (462 mg, 2.83 mmol) in anh. DMSO (2 ml), paraformaldehyde (128 mg 4.25 mmol) was added, and the suspension was treated with *t*-BuOK (13 mg, 0.11 mmol). The mixture was stirred at r.t. for 2 h, and then poured into brine (40 ml). The product was extracted with AcOEt (3 × 20 ml), the combined org. phase was washed with brine (20 ml), H_2O (2 × 30 ml), dried ($MgSO_4$), and evaporated. Purification by FC (AcOEt/hexane 20:80 → 40:60) afforded **17a** (472 mg, 86%). Light yellowish oil. ^{1}H-NMR (250 MHz, (D_6)DMSO): 7.82 (*dd*, *J* = 8.2, 1.2, H–C(3′)); 7.66 (*td*, *J* = 7.0, 1.2, H–C(5′)); 7.59 (*dd*, *J* = 7.8, 1.5, H–C(6′)); 7.46 (*td*, *J* = 8.2, 1.8, H–C(4′)); 6.02 (*ddd*, *J* = 17.4, 10.4, 7.0, H–C(3)); 5.12 (*dt*, *J* = 10.4, 1.2, H_a–C(4)); 5.02 (*dt*, *J* = 17.4, 1.2, H_b–C(4)); 4.87 (br., OH); 3.94–3.83 (*m*, CH); 3.76–3.60 (*m*, OCH_2). Anal. calc. for $C_{10}H_{11}NO_3$ (193.20): C 62.17, H 5.74, N 7.25; found: C 61.72, H 5.90, N 7.26.

*4-[[(*tert*-Butyl)(dimethyl)silyl]oxy]-3-(2-nitrophenyl)but-1-ene* (**17b**). Prepared from **17a** (410 mg, 2.12 mmol), imidazole (361 mg, 5.30 mmol) and *t*-$BuMe_2SiCl$ (639 mg, 4.24 mmol), as described for **15**, followed by FC (hexane/AcOEt 12:1): 651 mg (quant.). Light yellowish oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.75 (*dd*, *J* = 8.6, 1.2, H–C(3′)); 7.58–7.45 (*m*, H–C(5′), H–C(6′)); 7.34 (*td*, *J* = 8.9, 2.1, H–C(4′)); 6.05 (*ddd*, *J* = 17.2, 10.7, 6.7, CH=); 5.19 (*dt*, *J* = 11.0, 1.2, 1 H of CH_2=); 5.14 (*dt*, *J* = 17.4, 1.2, 1 H of CH_2=); 4.16 (*dd*, *J* = 6.7, 6.7, CH); 3.91 (*dd*, *J* = 9.8, 5.8, 1 H of CH_2OSi); 3.85 (*dd*, *J* = 9.8, 6.7, 1 H of CH_2OSi); 0.73 (*s*, *t*-Bu); −0.06 (*s*, Me); −0.07 (*s*, Me). The product was used without further purification.

*2-[4-Hydroxy-3-(2-nitrophenyl)butyl]-9*H*-thioxanthen-9-one* (**16b**). Prepared from **17b** (421 mg, 1.37 mmol), 9-BBN (0.5M soln. in THF, 5.5 ml, 2.74 mmol), **12** (435 mg, 1.29 mmol), [Pd(dppf)Cl_2] (47 mg, 0.065 mmol), and aq. 3M K_3PO_4 soln. (0.86 ml, 2.58 mmol), as described for **9b**. The silyl-protected intermediate **16a** was purified by FC (AcOEt/hexane 3.5:96.5 → 30:70), and the *t*-$BuMe_2Si$ group was cleaved with Bu_4NF

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[3]) 2-[5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-(2-nitrophenyl)pentyl]-9*H*-thioxanthen-9-one.

(1M soln. in THF, 1.8 ml, 1.8 mmol) in THF (10 ml), as described above. Purification by CC (AcOEt/hexane 15:85 → 50:50) and crystallization from hexane afforded **16b** (266 mg, 51% from **12**).

Data of **16a**. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.62 (*d*, *J* = 8.0, H–C(8) (Tx)); 8.36 (*d*, *J* = 1.5, H–C(1) (Tx)); 7.72 (*d*, *J* = 7.9, H–C(3′)); 7.66–7.31 (*m*, 8 arom. H); 3.78 (*d*, *J* = 5.5, CH_2O); 3.45–3.36 (*m*, CH); 2.81–2.59 (*m*, CH_2); 2.34–2.03 (*m*, CH_2); 0.81 (*s*, *t*-Bu); −0.07 (*s*, Me); −0.08 (*s*, Me).

Data of **16b**. Colorless solid. M.p. 100–112°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.46 (*dd*, *J* = 8.2, 1.5, H–C(8) (Tx)); 8.20 (*d*, *J* = 1.5, H–C(1) (Tx)); 7.88–7.40 (*m*, 9 arom. H); 4.84 (*t*, *J* = 5.19, OH); 3.66–3.54 (*m*, CH_2O); 3.22–3.10 (*m*, benzylic CH); 2.76–2.54 (*m*, CH_2); 2.28–1.90 (*m*, CH_2CH). Anal. calc. for $C_{23}H_{19}NO_4S$ (405.47): C 68.13, H 4.72, N 3.45; found: C 68.16, H 4.67, N 3.51.

*5′-*O*-({[2-(2-Nitrophenyl)-4-(9-oxo-9*H*-thioxanthen-2-yl)butyl]oxy}carbonyl)thymidine* (**19**). Prepared as described for **13**, from **16b** (100 mg, 0.27 mmol), trichloromethyl chloroformate (43.4 µl, 0.36 mmol), and Et_3N (38 µl, 0.27 mmol) in anh. THF (4 ml), followed by reaction of the resulting chloroformate with thymidine (65 mg, 0.27 mmol) in anh. pyridine/CH_2Cl_2 1:1 (3 ml). Purification by FC (MeOH/CH_2Cl_2 0:100 → 4:96) followed by crystallization from Et_2O: 126 mg (69%) of **16b**. Colorless powder. M.p. 110–112°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 11.30 (br. *s*, NH); 8.46 (*d*, *J* = 7.9, H–C(8) (Tx)); 8.18 (*d*, *J* = 1.8, H–C(1) (Tx)); 7.87–7.45 (*m*, 9 arom. H); 7.38 (*d*, *J* = 6.10, CH (T)); 6.16 (*t*, *J* = 6.10, H–C(1′)); 5.43 (*d*, *J* = 4.3, 3′-OH); 4.54–4.11 (*m*, H–C(3′), CH_2(5′), CH_2); 3.92–3.84 (*m*, H–C(4′)); 3.56–3.40 (*m*, benzylic CH); 2.80–2.53 (*m*, CH_2); 2.25–1.99 (*m*, CH_2(2′), CH_2); 1.68 (*d*, *J* = 4.8, Me). Anal. calc. for $C_{34}H_{31}N_3O_{10}S$ (673.69): C 60.62, H 4.64, N 6.24; found: C 60.23, H 4.60, N 6.30.

tert-*Butyl 4-Ethyl-3-nitrobenzoate* (**22b**). A stirred soln. of **22a** [34] (4.5 g, 23.1 mmol), DMAP (342 mg, 2.3 mmol), and *t*-BuOH (2.6 g, 35.1 mmol) in anh. CH_2Cl_2 (70 ml) was treated with DCC (5.23 g, 25.4 mmol) at 0°. After 5 min of stirring at 0°, the cooling bath was removed, and the mixture was stirred at r.t. for 3 h. The precipitate was suction-filtered, washed with CH_2Cl_2, and evaporated. To the oily residue containing a precipitate, hexane (90 ml) was added. This mixture was passed through a short plug of SiO_2 (7 g) to remove insoluble dicyclohexylurea, and the pad was washed with hexane/AcOEt 50:1 (50 ml). The org. soln. was washed with 1M aq. HCl soln. (2 × 50 ml), 5% aq. K_2CO_3 soln. (50 ml), and dried ($MgSO_4$). Removal of the solvent afforded pure **22b** (5.57 g, 96%). Light yellowish oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.43 (*d*, *J* = 1.8, H–C(2)); 8.11 (*dd*, *J* = 8.2, 1.8, H–C(6)); 7.42 (*d*, *J* = 7.9, H–C(5)); 2.95 (*q*, *J* = 7.3, CH_2); 1.60 (*s*, *t*-Bu); 1.29 (*t*, *J* = 7.3, Me).

tert-*Butyl 4-(2-Hydroxy-1-methylethyl)-3-nitrobenzoate* (**23**). Prepared as described for **17a**, starting from **22b** (4.24 g, 16.87 mmol), paraformaldehyde (763 mg, 25.41 mmol), and *t*-BuOK (70 mg, 0.62 mmol). Purification by FC (AcOEt/hexane 10:90 → 35:65) gave **23** (4.75g, 100%). Yellow oil. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.19 (*d*, *J* = 1.8, H–C(2)); 8.09 (*dd*, *J* = 8.2, 1.5, H–C(6)); 7.75 (*d*, *J* = 8.2, H–C(5)); 4.79 (*t*, *J* = 5.2, OH); 3.55–3.49 (*m*, CH_2); 3.27 (*q*, *J* = 6.7, benzylic CH); 1.55 (*s*, *t*-Bu); 1.24 (*d*, *J* = 7.0, Me).

tert-*Butyl 4-{2-[(2-Methoxyethoxy)methoxy]-1-methylethyl}-3-nitrobenzoate* (**21a**). To a stirred soln. of **23** (4.75g, 16.88 mmol) in anh. CH_2Cl_2 (15 ml) was added Et(i-Pr)$_2$N (5.6 ml, 32.07 mmol), followed by a soln. of $MeO(CH_2)_2OCH_2Cl$ (MEMCl; 2.9 ml, 25.32 mmol) in anh. CH_2Cl_2 (10 ml). After 4 h of stirring at r.t., a new portion of MEMCl (0.5 ml, 3.0 mmol) was added, and stirring was continued for 17 h. The mixture was diluted with CH_2Cl_2 (60 ml) and washed with 0.1M aq. HCl soln. (2 × 30 ml), sat. aq. $NaCO_3$ soln. (30 ml), and H_2O (30 ml). The org. layer was separated, dried ($MgSO_4$), and evaporated. The crude product was purified by FC (AcOEt/hexane 10:90 → 35:65) to give **21a** (5.31g, 85%). Yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.29 (*d*, *J* = 1.8, H–C(2)); 8.13 (*dd*, *J* = 8.2, 1.8, H–C(6)); 7.56 (*d*, *J* = 8.2, H–C(5)); 4.66–4.58 (*m*, OCH_2O); 3.71–3.46 (*m*, benzylic CH, CHCH_2O, 2 OCH_2); 3.37 (*s*, MeO); 1.60 (*s*, *t*-Bu); 1.34 (*d*, *J* = 6.74, Me). Anal. calc. for $C_{18}H_{27}NO_7$ (369.41): C 58.52, H 7.37, N 3.79; found: C 58.32, H 7.40, N 3.98.

4-{2-[(2-Methoxyethoxy)methoxy]-1-methylethyl}-3-nitrobenzoic Acid (**21b**). To a stirred suspension of NaH (60% dispersion in mineral oil; 2.24 g, 56 mmol) in anh. DMF (15 ml), a soln. of **21a** (2.59 g, 7.00 mmol) in DMF (10 ml) was added. The mixture was stirred for 1 h, and then carefully poured into H_2O (160 ml). The aq. soln. was acidified with 3M HCl to pH 4–5, and extracted with Et_2O (2 × 70 ml). The combined org. layer was washed with H_2O (4 × 70 ml), dried ($MgSO_4$), and evaporated. The crude product was purified by FC (AcOEt/hexane 25:75 → 50:50) to afford **21b** (2.05 g, 94%). Yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.45 (*d*, *J* = 1.8, H–C(2)); 8.23 (*dd*, *J* = 8.2, 1.8, H–C(6)); 7.64 (*d*, *J* = 8.2, H–C(5)); 4.68–4.60 (*m*, OCH_2O); 3.74–3.50 (*m*, benzylic CH, CHCH_2O, 2 OCH_2); 3.38 (*s*, MeO); 1.37 (*d*, *J* = 6.7, Me). Anal. calc. for $C_{14}H_{19}NO_7$ (313.30): C 53.67, H 6.11, N 4.47; found: C 53.55, H 6.26, N 4.61.

*9-Oxo-9*H*-thioxanthen-2-yl 4-{2-[(2-Methoxyethoxy)methoxy]-1-methylethyl}-3-nitrobenzoate* (**25a**). To a stirred soln. of **21b** (300 mg, 0.96 mmol) in anh. DMF (9 ml), DMAP (98 mg, 0.79 mmol), **24** (240 mg, 1.05 mmol) [41], and EDCI (368 mg, 1.92 mmol) were added in this order. The mixture was stirred for 24 h at r.t.

DMF was removed by co-evaporation with toluene, the oily residue was dissolved in CH_2Cl_2 (20 ml), and washed with sat. aq. NH_4Cl soln. (2 × 15 ml), 5% aq. K_2CO_3 soln. (15 ml), and brine (2 × 15 ml). The org. phase was separated, dried ($MgSO_4$), and evaporated. Purification by FC (AcOEt/hexane 10:90 → 50:50) afforded **25a** (321 mg, 64%). Yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.63 (*dd*, *J* = 8.2, 1.5, H–C(8) (Tx)); 8.58 (*d*, *J* = 1.8, H–C(2)); 8.45 (*d*, *J* = 2.4, H–C(1) (Tx)); 8.37 (*dd*, *J* = 8.2, 1.8, H–C(6)); 7.73–7.49 (*m*, 6 arom. H); 4.69–4.63 (*m*, OCH_2O); 3.77–3.49 (*m*, benzylic CH, $CHCH_2O$, 2 OCH_2); 3.39 (*s*, MeO); 1.40 (*d*, *J* = 6.7, Me). Anal. calc. for $C_{27}H_{25}NO_8S$ (523.56): C 61.94, H 4.81, N 2.68; found: C 61.92, H 4.78, N, 2.70.

*9-Oxo-9*H*-thioxanthen-2-yl 4-(2-Hydroxy-1-methylethyl)-3-nitrobenzoate* (**25b**). To a stirred soln. of **25a** (389 mg, 0.74 mmol) in THF (10 ml) was slowly added a 3M aq. HCl soln. (10 ml) at 0°. The mixture was gently refluxed for 5 h, cooled to r.t., and poured into chilled sat. aq. $NaHCO_3$ soln. (50 ml). After gas evolution had ceased, the mixture was extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (2 × 20 ml), dried ($MgSO_4$), and evaporated. Purification by FC (AcOEt/hexane 20:80 → 60:40) and crystallization from Et_2O yielded **25b** (212 mg, 66%). Yellow crystals. M.p. 189–190°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.50–8.45 (*m*, 2 arom. H); 8.40–8.34 (*m*, 2 arom. H); 8.02 (*d*, *J* = 8.6, arom. H); 7.93–7.77 (*m*, 4 arom. H); 7.62 (*td*, *J* = 8.2, 1.2, arom. H); 4.89 (*t*, *J* = 5.2, OH); 3.63–3.55 (*m*, CH_2O); 3.35–3.26 (*m*, benzylic CH, partly masked by water signal); 1.29 (*d*, *J* = 7.0, Me). Anal. calc. for $C_{23}H_{17}NO_6S$ (435.45): C 63.44, H 3.94, N 3.22; found: C 63.30, H 3.93, N 3.25.

*5′-*O*-{[2-(2-Nitro-4-{[(9-oxo-9*H*-thioxanthen-2-yl)oxy]carbonyl}phenyl)propoxy]carbonyl}thymidine* (**20**). Prepared as described for **13**, but starting from **25b** (130 mg, 0.30 mmol), by phosgenation with trichloromethyl chloroformate (43 µl, 0.40 mmol) in the presence of Et_3N (42 µl, 0.30 mmol) in anh. THF (4 ml), and subsequent reaction of the chloroformate with thymidine (73 mg, 0.30 mmol) in anh. pyridine/CH_2Cl_2 1 : 1 (4 ml). Purification by FC (MeOH/CH_2Cl_2 0:100 → 5:95) followed by crystallization from Et_2O afforded **20** (123 mg, 58%). Light yellow solid. M.p. 162–164°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 11.33 (*s*, NH); 8.58–8.37 (*m*, 3 arom. H); 8.06–7.77 (*m*, 5 arom. H); 7.62 (*td*, *J* = 8.2, 1.2, arom. H); 7.42–7.40 (*m*, CH (T)); 6.17 (*t*, *J* = 7.3, H–C(1′)); 5.45 (*d*, *J* = 4.3, 3′-OH); 4.55–4.15 (*m*, CH_2O, H–C(3′), CH_2(5′)); 3.91–3.85 (*m*, H–C(4′)); 3.66–3.57 (*m*, benzylic CH); 2.14–2.06 (*m*, CH_2(2′)); 1.73 (*s*, Me (T)); 1.33 (*d*, *J* = 7.0, Me). Anal. calc. for $C_{34}H_{29}N_3O_{12}S \cdot 0.5\ H_2O$ (712.67): C 57.30, H 4.24, N 5.90; found: C 57.43, H 4.24, N 6.16.

*2-[3-(2-Hydroxy-1-methylethyl)-4-nitrophenyl]-9*H*-thioxanthene-9-one* (**26**). A mixture of **6** (1.0 g, 3.44 mmol), commercially available bis(pinacolate)diborane **29** (1.05 g, 4.13 mmol), and AcOK (1.35 g, 13.76 mmol) in 1,4-dioxane (50 ml) was degassed by gentle bubbling N_2 through the stirred mixture for 30 min. Then, [Pd(dppf)Cl_2] (3 mol-%, 76 mg, 0.103 mmol) was added. The mixture was stirred at 65–70° for 16 h under N_2 atmosphere, and then cooled to r.t. A degassed soln. of **27** [30] (1.07 g, 4.13 mmol) in 1,4-dioxane (6 ml) was added, followed by [Pd(dppf)Cl_2] (3 mol-%, 76 mg, 0.103 mmol) and aq. 3M K_3PO_4 soln. (2.13 ml, 12.39 mmol), and in the order mentioned. The mixture was heated and stirred at 80° for 7 h under N_2 atmosphere. After cooling to r.t., the inorganic precipitate was filtered off, washed with CH_2Cl_2 and H_2O, and the filtrate was concentrated to 5–7 ml. EtOH (15 ml) and H_2O (15 ml) were added to the residue, and the suspension was sonicated for 5 min. The precipitate was suction-filtered, washed with 50% aq. EtOH, suspended in EtOH/Et_2O 1:1 (25 ml), and sonicated for 5 min. Filtration and washing with EtOH/Et_2O 1 : 1 afforded **26** (1.04 g, 77%). Yellow powder. M.p. 174–176°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.74 (*d*, *J* = 1.9, H–C(1) (Tx)); 8.50 (*dd*, *J* = 8.1, 1.0, H–C(8) (Tx)); 8.19 (*dd*, *J* = 8.5, 2.2, arom. H); 8.03–7.80 (*m*, 6 arom. H); 7.62 (*td*, *J* = 8.1, 1.2, H–C(7) (Tx)); 4.81 (*t*, *J* = 5.4, OH); 3.70–3.60 (*m*, CH_2); 3.37–3.29 (*m*, benzylic CH, partly masked by water signal); 1.33 (*d*, Me). Anal. calc. for $C_{22}H_{17}NO_4S$ (391.44): C 67.50, H 4.38, N 3.58; found: C 66.67, H 5.03, N 3.65.

*5′-*O*-{[2-(2-Nitro-5-{[(9-oxo-9*H*-thioxanthen-2-yl)oxy]carbonyl}phenyl)propoxy]carbonyl}thymidine* (**30**). Prepared as described for **11**, starting from **26** (480 mg, 1.23 mmol), treated with a 20% soln. of phosgene in toluene (4 ml), followed by reaction of the resulting chloroformate with thymidine (388 mg, 1.60 mmol) in anh. pyridine/CH_2Cl_2 1:1 (30 ml). The reaction was carried out at −44° → r.t. for 20 h. Purification by FC (MeOH/CH_2Cl_2 0:100 → 3:97) yielded **30** (478 mg, 59%). Yellow powder. M.p. 228–230°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.27 (*s*, NH); 8.78 (*d*, *J* = 2.0, H–C(1) (Tx)); 8.51 (*d*, *J* = 8.0, H–C(8) (Tx)); 8.20 (*dd*, *J* = 8.3, 1.8, arom. H); 8.08–7.80 (*m*, 6 arom. H); 7.63 (*t*, *J* = 7.5, H–C(7) (Tx)); 7.37 (*s*, CH (T)); 6.14 (*t*, *J* = 6.8, H–C(1′)); 5.38 (br. *s*, OH); 4.51–4.41 (*m*, CH_2O); 4.26–4.15 (*m*, H–C(3′), CH_2(5′)); 3.91–3.86 (*m*, H–C(4′)); 3.64 (*q*, *J* = 6.7, benzylic CH); 2.17–2.03 (*m*, CH_2(2′)); 1.68 (*s*, Me (T)); 1.39 (*d*, *J* = 6.8, CH–*Me*). Anal. calc. for $C_{33}H_{29}N_3O_{10}S$ (659.66): C 60.08, H 4.43, N 6.37; found: C 58.00, H 4.41, N 6.38.

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