Some Substituted 9-Phenylxanthen-9-yl Protecting Groups

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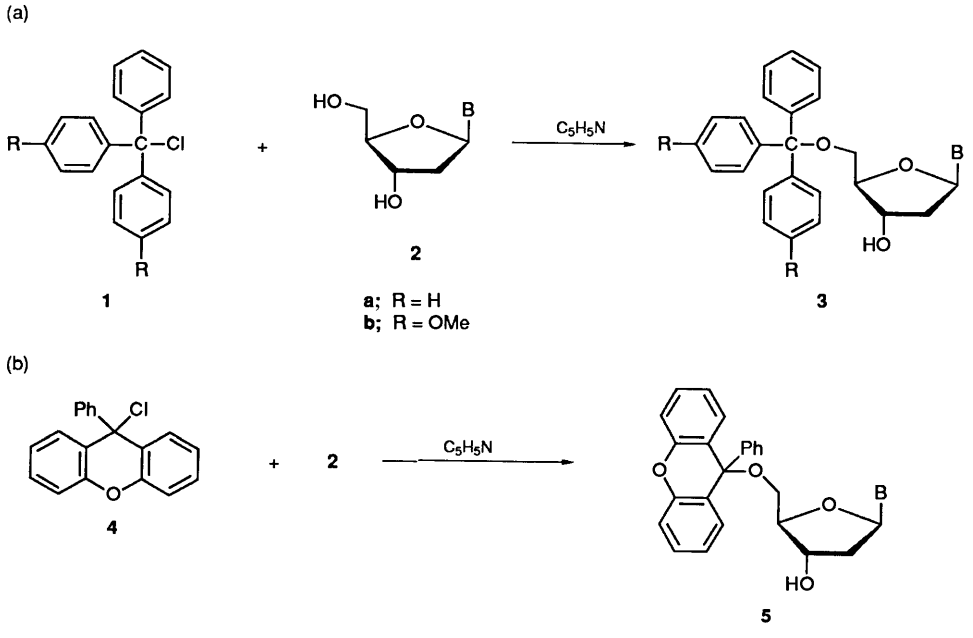
Xanthen-9-one **8** was converted into 9-(4-methoxyphenyl)-, 9-(4-methylphenyl)- and 9-[3-(trifluoromethyl)phenyl]-xanthen-9-ol (**10**; R^1 = OMe, R^2 = H, **10**; R^1 = Me, R^2 = H, and **10**; R^1 = H, R^2 = CF_3, respectively). The corresponding 5′-protected thymidine derivatives (**13**; R^1 = OMe, R^2 = H, **13**; R^1 = Me, R^2 = H and **13**; R^1 = H, R^2 = CF_3) were obtained in satisfactory yields from thymidine **12** and the appropriate 9-chloro compounds (**11**; R^1 = OMe, R^2 = H, **11**; R^1 = Me, R^2 = H and **11**; R^1 = H, R^2 = CF_3). In the same way, 2,7-dibromoxanthen-9-one **14** was converted into two 9-aryl-2,7-dibromoxanthen-9-ols (compounds **15a** and **15b**). Reaction between thymidine **12** and the corresponding 9-chlorocompounds gave the 5′-protected thymidine derivatives **16a** and **16b**, also in satisfactory yields. The rates of acid-catalysed cleavage of the above five 5′-protected thymidine derivatives (**13**; R^1 = OMe, R^2 = H, **13**; R^1 = Me, R^2 = H and **13**; R^1 = H, R^2 = CF_3), **16a** and **16b** were compared with those of 5′-*O*-(9-phenylxanthen-9-yl)thymidine **13**; R^1 = R^2 = H and 5′-*O*-(triphenylmethyl)thymidine **3a**; B = thymin-1-yl under the same conditions.

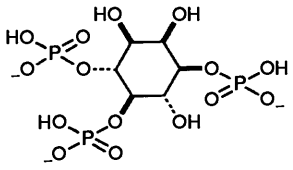
The triphenylmethyl (trityl) group (as in structure **3a**) has been used very widely[1,2] to protect hydroxy functions in sugar, nucleoside and steroid chemistry. Chloro(triphenyl)methane **1a** reacts with primary hydroxy functions in a highly selective manner,[3] and the resulting trityl ethers [*e.g.*, **3a**; see Scheme 1(a)] can be cleaved by acidic hydrolysis.[3] However, the hydrolytic conditions required for the removal of the trityl group are too drastic to allow it to be used effectively for the protection of the hydroxy functions of relatively acid-sensitive substrates such as 2′-deoxyribonucleosides **2**. For this reason, Khorana and co-workers[4] developed methoxy-substituted trityl protecting groups, and especially the 4,4′-dimethoxytrityl group (as in compound **3b**), which has subsequently been used very widely for the protection of hydroxy functions in oligo- and polydeoxyribonucleotide synthesis.[5]

A number of years ago, we introduced the 9-phenylxanthen-9-yl group[6] [as in structure **5**, Scheme 1(b)] especially for the protection of the 5′-hydroxy functions of 2′-deoxyribonucleosides. The 9-phenylxanthen-9-yl group undergoes hydrolytic cleavage in acetic acid–water (4:1 v/v) solution at room temperature at a rate[6] which is only marginally faster than the rate observed for the removal of the 4,4′-dimethoxytrityl group under the same conditions. Like chlorobis-(4-methoxyphenyl)-phenylmethane[4] **1b**, 9-chloro-9-phenylxanthene[7] **4** reacts fairly rapidly and regioselectively with base-protected 2′-deoxyribonucleosides **2** to give good yields[6] of the corresponding 5′-*O*-(9-phenylxanthen-9-yl) derivatives **5**. Apparently, unlike 4,4′-dimethoxytrityl derivatives[5] (such as compound **3b**), 9-phenylxanthen-9-yl derivatives (such as compound **5**) can almost invariably be induced to crystallize. Partly for this reason, in recent years we have used the 9-phenylxanthen-9-yl group very widely indeed for the protection of the 5′-hydroxy functions in the synthesis of oligodeoxyribo- and oligoribonucleotides both in solution[8] and on a solid support.[9]

In addition to exhibiting a strong tendency to crystallize, 9-phenylxanthen-9-yl derivatives are by design particularly acid sensitive.[6] In a recent study[10] directed towards the synthesis of 1D-*myo*-inositol 1,4,5-trisphosphate **6**, we initially considered



Scheme 1



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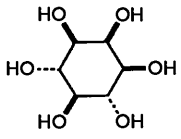

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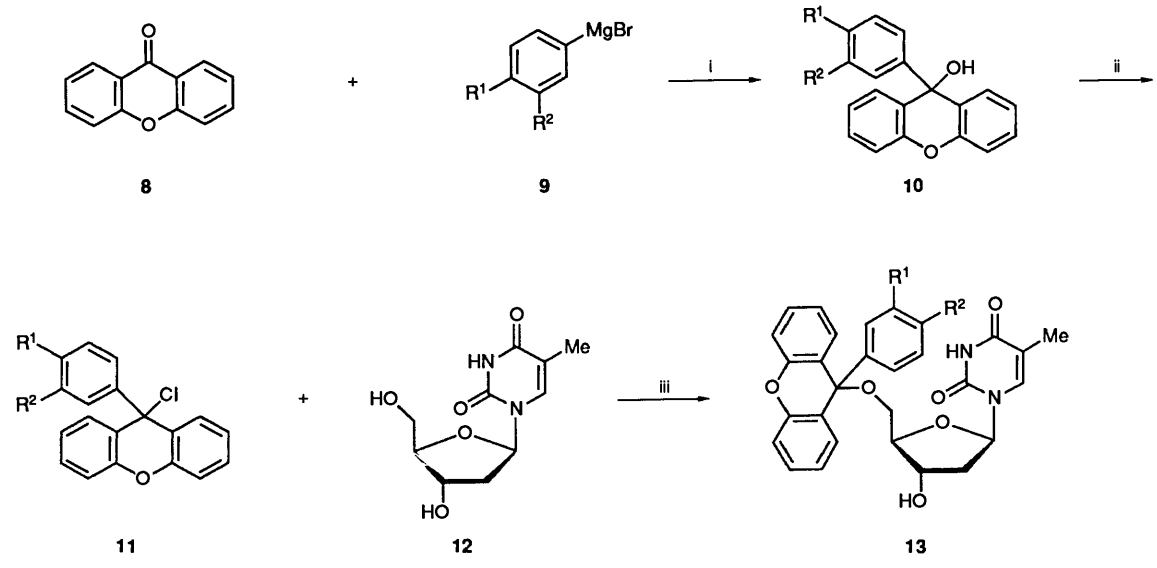
using the 9-phenylxanthen-9-yl protecting group in the hope that we should thereby be able to obtain easily crystallizable derivatives of *myo*-inisitol **7**. However, we soon found [11] that the latter protecting group was too acid sensitive to be useful for this particular purpose. We therefore set out to modify the 9-phenylxanthen-9-yl group in such a way as to make it more stable under acidic conditions. As *myo*-inositol **7** does not absorb in the unltraviolet, in order to facilitate TLC and LC analysis of protected intermediates, we decided that an additional requirement for the modified protecting group should be that it must has a strong chromophore. While the synthesis of 1D-*myo*-inositol 1,4,5-trisphosphate **6** was the driving force for the present study, we thought that it would be worthwhile to extend it in such a way as to obtain a clearer indication of the full potential of substituted 9-phenylxanthen-9-yl protecting groups. We have therefore modified the 9-phenylxanthen-9-yl group with the intention of making it both more sensitive and less sensitive to acid.

intended to be more acid labile than 9-phenylxanthen-9-yl, 9-(4-methoxyphenyl)xanthen-9-ol **10**; R^1 = OMe, R^2 = H had already been prepared [13] by treatment of xanthen-9-one **8** with 4-methoxyphenylmagnesium bromide **9**; R^1 = OMe, R^2 = H. As a second example, 9-(4-methylphenyl)xanthen-9-ol **10**; R^1 = Me, R^2 = H was prepared by allowing xanthen-9-one **8** to react with *p*-tolylmagnesium bromide **9**; R^1 = Me, R^2 = H, and was isolated as a crystalline solid in 79% yield.

The required 9-aryl-9-chloroxanthenes **11**; R^1 = H, R^2 = CF_3, **11**; R^1 = OMe, R^2 = H and **11**; R^1 = Me, R^2 = H were prepared by allowing the corresponding alcohols (**10**; R^1 = H, R^2 = CF_3, **10**; R^1 = OMe, R^2 = H and **10**; R^1 = Me, R^2 = H, respectively) to react with a large excess (*ca.* 9–10 mol equiv.) of acetyl chloride in anhydrous benzene solution at room temperature and then evaporating the products under reduced pressure; the crude chloro compounds thereby obtained were used without further purification. When thymidine **12** was allowed to react with these chloro compounds (**11**; R^1 = H, R^2 = CF_3, **11**; R^1 = OMe, R^2 = H and **11**; R^1 = Me, R^2 = H) in acetonitrile–pyridine solution at 0 °C to room temperature, the corresponding 5′-*O*-(9-arylxanthen-9-yl) derivatives (**13**; R^1 = H, R^2 = CF_3, **13**; R^1 = OMe, R^2 = H and **13**; R^1 = Me, R^2 = H, respectively) were obtained and isolated as crystalline solids in yields of between 70 and 75%.

An obvious alternative approach to making the 9-phenyl-



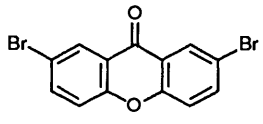
Scheme 2 *Reagents and conditions:* i, (a) Et_2O, reflux, (b) hydrochloric acid; ii, acetyl chloride, benzene, room temp.; iii, acetonitrile, pyridine, room temp

9-Arylxanthen-9-ols **10** may readily be prepared [7] (Scheme 2) by allowing xanthen-9-one **8** to react with appropriate Grignard reagents **9** in ethereal solution. If it is intended that the modified protecting group (as in structure **13**) should be more acid stable than 9-phenylxanthen-9-yl, it is necessary that R^1 or R^2 should be electron withdrawing. It seemed to us that CF_3 would be a suitable electron-withdrawing substituent for this purpose. Difficulties would clearly arise in attempting to prepare Grignard reagents from bromo derivatives of aromatic nitro compounds, nitriles, or esters. However, bromo derivatives of benzotrifluoride (α,α,α-trifluorotoluene) readily form Grignard reagents.[12] When xanthen-9-one **8** was treated with the Grignard reagent **9**; R^1 = H, R^2 = CF_3 derived [12] from 3-bromobenzotrifluoride, the corresponding alcohol **10**; R^1 = H, R^2 = CF_3 was obtained and isolated as a crystalline solid in 81% yield. With regard to modified protecting groups which are xanthen-9-yl group either more or less acid labile would be to introduce electron-donating or electron-withdrawing substituents directly into the xanthene moiety. Treatment of xanthen-9-one **8** with *ca.* 4 mol equiv. of bromine in acetic acid solution at 100 °C gave a mixture of products from which 2,7-dibromoxanthen-9-one [14] **14** was isolated by crystallization in 40% yield. When the latter compound was allowed to react with phenylmagnesium bromide and 3-(trifluoromethyl)phenylmagnesium bromide [12] (**9**; R^1 = H, R^2 = CF_3) in diethyl ether (see Scheme 2 and Experimental section), 2,7-dibromo-9-phenylxanthen-9-ol **15a** and 2,7-dibromo-9-[3-(trifluoromethyl)-phenyl]xanthen-9-ol **15b** were obtained and isolated as crystalline solids in 69 and 92% yields, respectively. These tertiary alcohols (**15a** and **15b**) were converted in the usual way (Scheme 2 and Experimental section) into the corresponding chloro compounds, which were then allowed to react with

Table 1 Half-times ($t_{\frac{1}{2}}$/min) of acid-promoted unblocking[a] of 5′-protected thymidine derivatives

Entry	Compound	$t_{\frac{1}{2}}$(min)
1	**13**; R^1 = OMe, R^2 = H	0.3
2	**13**; R^1 = Me, R^2 = H	0.55
3	**13**; R^1 = R^2 = H	1.37
4	**13**; R^1 = H, R^2 = CF_3	8.7
5	**16a**	244
6	**16b**	1560

[a] Unblocking was carried out (see Experimental section) by addition of 1.0 mol dm^{-3} solution of trifluoroacetic acid (TFA) (25 mm^3) in CH_2Cl_2–EtOH (95:5 v/v) to a 0.001 25 mol dm^{-3} solution (100 mm^3) in the same solvent at 22 °C.



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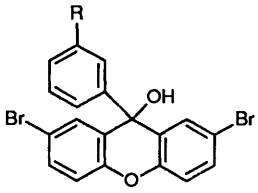
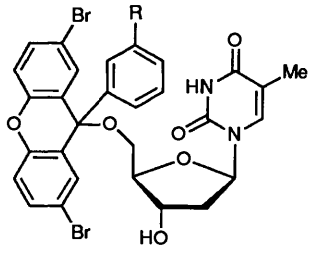


15 a; R = H
b; R = CF_3

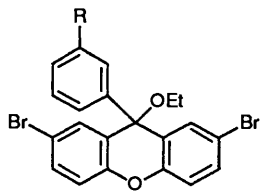


16 a; R = H
b; R = CF_3

thymidine **12** to give 5′-*O*-(2,7-dibromo-9-phenylxanthen-9-yl)thymidine **16a** and 5′-*O*-{2,7-dibromo-9-[3-(trifluoromethyl)-phenyl]xanthen-9-yl}thymidine **16b** as crystalline solids in 69 and 67% isolated yield, respectively.

It can be seen from Table 1 (entries 1, 2 and 3) that the introduction of *p*-methoxy and *p*-methyl substituents into the 9-phenyl residue of the 9-phenylxanthen-9-yl protecting group makes it *more labile* to acid under the conditions examined by factors of *ca.* 4.5 and 2.5, respectively, and that the introduction of a *m*-trifluoromethyl substituent (entry 4) makes the protecting group *more stable* to acid by a factor of *ca.* 6.4. These effects are all relatively small and certainly the 9-[3-(trifluoromethyl)phenyl]xanthen-9-yl group (as in compound **13**; R^1 = H, R^2 = CF_3) is not stable enough to acidic hydrolysis to make it particularly suitable for the protection of the hydroxy functions of *myo*-inositol **7**. Much greater effects can clearly be obtained by xanthene substitution. Hence, the 2,7-dibromo-9-phenylxanthen-9-yl (as in structure **16a**) and 2,7-dibromo-9-[3-(trifluoromethyl)phenyl]xanthen-9-yl (as in structure **16b**) groups (entries 5 and 6) are, respectively, *ca.* 180- and 1140-times more stable to acid under the conditions examined than is the simple 9-phenylxanthen-9-yl protecting group. It is interesting to note that introduction of the 3-trifluoromethyl substituent has virtually the same stabilizing effect (of *ca.* 6.4) on both the 9-phenylxanthen-9-yl and 2,7-dibromo-9-phenylxanthen-9-yl protecting groups.

The acid stability of the trityl (as in compound **3a**) protecting group [estimated $t_{\frac{1}{2}}$ ~320 min, under the conditions examined (Table 1)] lies between the acid stabilities of the 2,7-dibromo-9-phenylxanthen-9-yl (as in compound **16a**) and 2,7-dibromo-9-[3-(trifluoromethyl)phenyl]xanthen-9-yl (as in compound **16b**) groups (entries 5 and 6). However, it is of considerable importance in the context of inositol and possibly also of carbohydrate chemistry in general, that the latter groups tend both to confer crystallinity and strong absorption in the UV on protected derivatives. With regard to the second point, the ethyl ethers **17a** and **17b** display absorption maxima at 253 and 255 nm, respectively, with very high extinction coefficients (2.5 and 2.4 × 10^4 dm^3 mol^{-1} cm^{-1}, respectively). In contrast, trityl ethyl ether **18** has absorption maxima at 253 and 258 nm with, as expected, low extinction coefficients (6.4 and 6.8 × 10^2 dm^3 mol^{-1} cm^{-1}, respectively).



17 a; R = H
b; R = CF_3

Ph_3C–OEt

18

Experimental

M.p.s were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 250 and 360 MHz, respectively, on Bruker WM 250 and AM 360 spectrometers; ^{13}C NMR spectra were measured at 62.9 and 90.6 MHz, respectively, on the same spectrometers. Tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [chloroform–hexane (3:7, v/v)], B [chloroform–methanol (9:1 v/v)] and C [chloroform–hexane (1:4 v/v)]. Merck silica gel H was used for short-column chromatography. Pyridine and acetonitrile were dried by heating, under reflux, over calcium hydride and were then distilled; diethyl ether was dried over sodium wire before distillation; benzene was dried by distillation with the forerun being discarded. All solvents were stored over 4 Å molecular sieves. Xanthen-9-one and 3-bromobenzotrifluoride were purchased from the Aldrich Chemical Co.

9-(4-*Methylphenyl*)*xanthen*-9-*ol* **10**; R^1 = Me, R^2 = H.—A solution of 4-bromotoluene (17.1 g, 12.3 cm^3, 0.10 mol) in dry diethyl ether (30 cm^3) was added dropwise during 1.5 h to magnesium turnings (2.43 g, 0.10 g-atom) containing a small crystal of iodine. The reaction was initiated by gentle heating and, after all the 4-bromotoluene had been added, the reactants were heated, under reflux, for a further 1 h. Solid xanthen-9-one **8** (9.81 g, 50 mmol) and more dry diethyl ether (50 cm^3) were then added and the reaction mixture was heated under reflux. After 3 h, the products were cooled and filtered off, and the residue was washed with diethyl ether. A solution of the residue in conc. hydrochloric acid (120 cm^3) was then added to a mixture of water (1000 cm^3) and ice (1000 g). The resulting precipitate was collected by filtration, washed with water, dried in a desiccator over KOH pellets, and then crystallized from cyclohexane to give the *title compound* (11.4 g, 79%) (Found: C, 83.3; H, 5.5. $C_{20}H_{16}O_2$ requires C, 83.3; H, 5.6%) as a buff-coloured crystalline solid, m.p. 141–142 °C; R_f 0.27 (system A); δ_C[$(CD_3)_2SO$] 20.40, 68.48, 115.69, 123.15, 125.44, 128.32, 128.56, 128.77, 135.21, 146.87 and 149.02.

9-[3-(*Trifluoromethyl*)*phenyl*]*xanthen*-9-*ol* **10**; R^1 = H,

$R^2 = CF_3$.—3-(Trifluoromethyl)phenylmagnesium bromide was prepared as above from 3-bromobenzotrifluoride (67.5 g, 41.85 cm^3, 0.30 mol) and magnesium turnings (7.29 g, 0.30 g-atom) in dry diethyl ether (90 cm^3), and the product was allowed to react with xanthen-9-one **8** (29.43 g, 0.15 mol) in the presence of an additional quantity (150 cm^3) of dry diethyl ether according to the procedure described above in the preparation of 9-(4-methylphenyl)xanthen-9-ol. The products were worked up as above except that three times the quantities of conc. hydrochloric acid (*i.e.*, 360 cm^3), water (*i.e.*, 3000 cm^3) and ice (*i.e.*, 3000 g) were used. Recrystallization of the crude products from cyclohexane gave the *title compound* (41.69 g, 81%) (Found: C, 69.8; H, 3.8. $C_{20}H_{13}F_3O_2$ requires C, 70.2; H, 3.8%) as a buff-coloured crystalline solid, m.p. 134–135 °C; R_f 0.36 (system A); δ_C[$(CD_3)_2SO$] 68.53, 116.05, 121.11 (m), 123.29 (m), 123.57, 124.22 (q, *J* 272), 127.56, 128.74, 128.95, 129.23, 130.51, 149.13 and 150.96.

2,7-*Dibromoxanthen-9-one* **14**.—Xanthen-9-one **8** (50.0 g, 0.255 mol), bromine (165 g, 53.2 cm^3, 1.03 mol), iodine (0.5 g, 1.97 mmol) and glacial acetic acid (200 cm^3) were stirred and heated together at 100 °C for 24 h. The cooled products were filtered off, and the residue was retained. The filtrate was concentrated under reduced pressure to give a red-brown solid, which was combined with the residue and dissolved in dichloromethane (700 cm^3). The resulting solution was washed in succession with saturated aq. sodium hydrogen carbonate (500 cm^3), saturated aq. sodium thiosulphate (500 cm^3) and water (500 cm^3). Evaporation of the dried ($MgSO_4$) organic layer gave a solid, which was recrystallized twice from benzene to give 2,7-dibromoxanthen-9-one **14** (36.4 g, 40%) as needles, m.p. 203–204 °C (lit.,[14] 200 °C); R_f 0.45 (system A); $\delta_C(CDCl_3)$ 117.52, 120.07, 122.77, 129.32, 138.06, 154.80 and 174.77.

2,7-*Dibromo*-9-*phenylxanthen*-9-*ol* **15a**.—Phenylmagnesium bromide was prepared as above from bromobenzene (18.62 g, 12.5 cm^3, 0.118 mol) and magnesium turnings (2.91 g, 0.12 g-atom) in dry diethyl ether (87 cm^3) as above. 2,7-Dibromoxanthen-9-one **14** (21.0 g, 59.3 mmol) and dry diethyl ether (100 cm^3) were then added and the reactants were heated under gentle reflux. After 90 min, the cooled products were filtered off and the solid residue was added to stirred, conc. hydrochloric acid (120 cm^3). The resulting mixture was then added to a mixture of water (1000 cm^3) and ice (1000 g). The solid precipitate obtained was collected by filtration, dried in a desiccator over KOH pellets and recrystallized from cyclohexane to give the *title compound* (17.8 g, 69%) (Found: C, 52.6; H, 2.8; Br, 37.0. $C_{19}H_{12}Br_2O_2$ requires C, 52.8; H, 2.8; Br, 37.0%) as a buff-coloured crystalline solid, m.p. 149.5–150.5 °C; R_f 0.43 (system A); δ_C[$(CD_3)_2SO + CDCl_3$] 68.48, 114.99, 117.70, 125.20, 126.38, 127.64, 129.66, 130.93, 131.02 and 147.86.

2,7-*Dibromo*-9-[3-(*trifluoromethyl*)*phenyl*]*xanthen*-9-*ol* **15b**.— 3-(Trifluoromethyl)phenylmagnesium bromide was prepared as above from 3-bromobenzotrifluoride (21.62 g, 13.4 cm^3, 96 mmol) and magnesiun turnings (2.22 g, 91.3 g-atom) in dry diethyl ether (15 cm^3). More diethyl ether (250 cm^3), followed by 2,7-dibromoxanthen-9-one **14** (16.20 g, 45.8 mmol), were then added and the reactants were heated under gentle reflux. After 90 min, the cooled products were filtered off and dichloromethane (150 cm^3) followed by conc. hydrochloric acid (80 cm^3) were added to the stirred, solid residue. Water (400 cm^3) was then added to the clear, two-phase system. The organic layer was separated, washed successively with saturated aq. sodium hydrogen carbonate (2 × 150 cm^3), aq. sodium thiosulphate (100 cm^3) and brine (2 × 150 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was crystallized from cyclohexane to give the *title compound* (21.19 g, 92%) (Found: C, 47.7; H, 2.0. $C_{20}H_{11}Br_2F_3O_2$ requires C, 48.0; H, 2.2%); m.p. 127–128 °C; R_f 0.50 (system A); $\delta_C(CDCl_3)$ (*inter alia*) 69.71, 116.31, 118.59, 121.99, 124.34, 127.89, 128.96, 129.74, 131.31, 132.78, 147.83 and 148.22.

9-*Chloro*-9-(4-*methylphenyl*)*xanthene* **11**; R^1 = Me, R^2 = H.—9-(4-methylphenyl)xanthen-9-ol **10**; R^1 = Me, R^2 = H (8.12 g, 28.2 mmol) and acetyl chloride (18.8 cm^3, 0.264 mol) were stirred together in dry benzene (32 cm^3). After 16 h, the resulting solution was evaporated to dryness under reduced pressure and the residual orange solid (8.5 g) thus obtained, which was assumed to be crude 9-chloro-9-(4-methylphenyl)-xanthene, was used without further purification.

9-*Chloro*-9-(4-*methoxyphenyl*)*xanthene* **11**; R^1 = OMe, R^2 = H.—This compound was similarly prepared[13] from 9-(4-methoxyphenyl)xanthen-9-ol **10**; R^1 = OMe, R^2 = H (8.69 g, 28.5 mmol) and acetyl chloride (18.8 cm^3, 0.264 mol) in dry benzene (33 cm^3), and was obtained as a crude, orange-coloured solid (9.15 g); it was used without further purification.

9-*Chloro*-9-[3-(*trifluoromethyl*)*phenyl*]*xanthene* **11**; R^1 = H, R^2 = CF_3.—This compound was similarly prepared from 9-[3-(trifluoromethyl)phenyl]xanthen-9-ol **10**; R^1 = H, R^2 = CF_3 (8.64 g, 25.2 mmol) and acetyl chloride (18.2 cm^3, 0.256 mol) in dry benzene (31 cm^3), and was obtained as a crude, yellow-orange-coloured solid (9.3 g); it was used without further purification.

2,7-*Dibromo*-9-*chloro*-9-*phenylxanthene*.—This compound was similarly prepared from 2,7-dibromo-9-phenylxanthen-9-ol **15a** (4.32 g, 10.0 mmol) and acetyl chloride (6.7 cm^3, 94 mmol) in dry benzene (11 cm^3), and was obtained as a crude, pale yellow-orange-coloured solid (4.5 g); it was used without further purification.

2,7-*Dibromo*-9-*chloro*-9-[3-(*trifluoromethyl*)*phenyl*]-*xanthene*.—This compound was similarly prepared from 2,7-dibromo-9-[3-(trifluoromethyl)phenyl]xanthen-9-ol **15b** (12.90 g, 25.8 mmol) and acetyl chloride (16.7 cm^3, 0.235 mol) in dry benzene (35 cm^3), and was obtained as a crude, pale yellow-coloured solid (13.4 g); it was used without further purification.

5′-O-[9-(4-*Methylphenyl*)*xanthen*-9-*yl*]*thymidine* **13**; R^1 = Me, R^2 = H.—A solution of 9-chloro-9-(4-methylphenyl)-xanthene **11**; R^1 = Me, R^2 = H (0.69 g, *ca.* 2.25 mmol) in dry acetonitrile (20 cm^3) was added dropwise during 1 h to a stirred solution of thymidine **12** (0.485 g, 2.0 mmol) in dry pyridine (20 cm^3) at 0 °C. After the reaction had been allowed to continue for a further 1 h at room temperature, the products were concentrated to small volume under reduced pressure and were then dissolved in chloroform (100 cm^3). The resulting solution was extracted with saturated aq. sodium hydrogen carbonate, and was then dried ($MgSO_4$), and evaporated under reduced pressure. The residual glass was fractionated by short-column chromatography on silica gel: the appropriate fractions, which were eluted with chloroform–ethanol (97:3 v/v), were combined, and evaporated under reduced pressure to give a solid. Crystallization of the latter material from ethyl acetate–hexane gave the *title compound* (0.77 g, 75%) (Found: C, 69.9; H, 5.4; N, 5.2. $C_{30}H_{28}N_2O_6$ requires C, 70.3; H, 5.5; N, 5.5%); m.p. 130 °C (decomp.); R_f 0.57 (system B); δ_H[$(CD_3)_2SO$] 1.46 (3 H, s), 2.05–2.35 (2 H, m), 2.22 (3 H, s), 3.04 (1 H, dd, *J* 4.0 and 10.5), 3.15 (1 H, m), 3.85 (1 H, m), 4.27 (1 H, m), 5.31 (1 H, m), 6.19 (1 H, t, *J* 6.8), 6.95–7.45 (12 H, m), 7.56 (1 H, m) and 11.35 (1 H, br).

5′-O-[9-(4-*Methoxyphenyl*)*xanthen*-9-*yl*]*thymidine* **13**; R^1 = OMe, R^2 = H.—A solution of 9-chloro-9-(4-methoxyphenyl)-xanthene **11**; R^1 = OMe, R^2 = H (0.89 g, *ca.* 2.75 mmol) in dry acetonitrile (10 cm^3) was added dropwise during 1.5 h to a stirred solution of thymidine **12** (0.485 g, 2.0 mmol) in dry pyridine (10 cm^3) at 0 °C. After the reaction had been allowed to continue for a further period of 2.5 h at room temperature the products were worked up and fractionated in the manner described above in the preparation of the corresponding 5′-*O*-[9-(4-methylphenyl)xanthen-9-yl] derivative **13**; R^1 = Me, R^2 = H. Crystallization of the purified product from ethyl acetate–hexane gave 5′-O-[9-(4-*methoxyphenyl*)*xanthen*-9-*yl*]*thymidine* **13**; R^1 = OMe, R^2 = H (0.75 g, 70%) (Found: C, 68.2; H, 5.5; N, 5.2. $C_{30}H_{28}N_2O_7$ requires C, 68.2; H, 5.3; N, 5.3%), m.p. 130 °C (decomp.); R_f 0.58 (system B); $\delta_H[(CD_3)_2SO]$ 1.47 (3 H, s), 2.1–2.3 (2 H, m), 3.10 (2 H, m), 3.69 (3 H, m), 3.85 (1 H, m), 4.28 (1 H, m), 5.31 (1 H, d, *J* 4.3), 6.20 (1 H, t, *J* 7.0), 6.85 (2 H, d, *J* 8.8), 6.95–7.45 (10 H, m), 7.56 (1 H, m) and 11.35 (1 H, s).

5′-O-{9-[3-(*Trifluoromethyl*)*phenyl*]*xanthen*-9-*yl*}*thymidine* **13**; R^1 = H, R^2 = CF_3.—A solution of 9-chloro-9-[3-(trifluoromethyl)phenyl]xanthene **11**; R^1 = H, R^2 = CF_3 (0.89 g, *ca.* 2.4 mmol) in dry acetonitrile (20 cm^3) was added dropwise during 1 h to a stirred solution of thymidine **12** (0.485 g, 2.0 mmol) in dry pyridine (20 cm^3). After the reaction had been allowed to continue for a further 1 h, the products were worked up and fractionated in the manner described above in the preparation of the corresponding 5′-*O*-[9-(4-methylphenyl)xanthen-9-yl] derivative (**13**; R^1 = Me, R^2 = H). Crystallization of the purified product from ethyl acetate–hexane gave the *title compound* (0.82 g, 72%) (Found: C, 63.35; H, 4.3; N, 4.8. $C_{30}H_{25}F_3N_2O_6$ requires C, 63.6; H, 4.45; N, 4.9%), m.p. 199–200 °C; R_f 0.55 (system B); $\delta_H[(CD_3)_2SO]$ 1.48 (3 H, s), 2.20 (2 H, m), 3.09 (1 H, dd, *J* 4.3 and 10.3), 3.19 (1 H, dd, *J* 2.8 and 10.3), 3.89 (1 H, m), 4.26 (1 H, m), 5.34 (1 H, m), 6.19 (1 H, t, *J* 6.8), 7.1–7.65 (12 H, m), 7.74 (1 H, m) and 11.37 (1 H, br).

5′-O-(2,7-*Dibromo*-9-*phenylxanthen*-9-*yl*)*thymidine* **16a**.—A solution of 2,7-dibromo-9-chloro-9-phenylxanthene (1.08 g, 2.4 mmol) in dry pyridine (10 cm^3) was added dropwise during 30 min to a stirred solution of thymidine **12** (0.485 g, 2.0 mmol) in dry pyridine (10 cm^3). After the reaction had been allowed to continue for a further 2.5 h, the products were worked up and fractionated according to the procedure described above in the preparation of the corresponding 5′-*O*-[9-(4-methylphenyl)-xanthen-9-yl] derivative (**13**; R^1 = Me, R^2 = H). Crystallization of the purified product from ethyl acetate–hexane gave the *title compound* (0.912 g, 69%) (Found: C, 53.2; H, 3.8; N, 4.1; Br, 24.4. $C_{29}H_{24}Br_2N_2O_6$ requires C, 53.1; H, 3.7; N, 4.3; Br, 24.35%) as a crystalline solid, m.p. 233–236 °C; R_f 0.58 (system B): $\delta_H[(CD_3)_2SO]$ 1.45 (3 H, s), 2.1–2.45 (2 H, m), 3.19 (2 H, m), 3.85 (1 H, m), 4.39 (1 H, m), 5.39 (1 H, d, *J* 4.2), 6.23 (1 H, t, *J* 6.8), 7.15–7.65 (12 H, m) and 11.31 (1 H, br s).

5′-O-{2,7-*Dibromo*-9-[3-(*trifluoromethyl*)*phenyl*]*xanthen*-9-*yl*}*thymidine* **16b**.—A solution of 2,7-dibromo-9-chloro-9-[3-(trifluoromethyl)phenyl]xanthene (0.57 g, 1.10 mmol) in dry pyridine (10 cm^3) was added dropwise during 5 min to a stirred solution of thymidine **12** (0.485 g, 1.00 mmol) in dry pyridine (10 cm^3). After the reaction had been allowed to continue for a further 2 h, the products were worked up and fractionated according to the procedure described above in the preparation of the corresponding 5′-*O*-[9-(4-methylphenyl)xanthen-9-yl] derivative **13**; R^1 = Me, R^2 = H. Crystallization of the purified product from aq. ethanol gave the *title compound* (0.486 g, 67%) (Found: C, 49.55; H, 3.1; N, 3.8. $C_{30}H_{23}Br_2F_3N_2O_6$ requires C, 49.75; H, 3.2; N, 3.9%), m.p. 221–223 °C; R_f 0.59 (system B); $\delta_H[(CD_3)_2SO]$ 1.45 (3 H, s), 2.20 (2 H, m), 3.19 (1 H, dd, *J* 4.6 and 10.3), 3.26 (1 H, m), 3.88 (1 H, m), 4.35 (1 H, m), 5.40 (1 H, d, *J* 4.4), 6.22 (1 H, t, *J* 6.8), 7.19 (1 H, d, *J* 2.3), 7.25–7.45 (5 H, m), 7.5–7.7 (4 H, m), 7.78 (1 H, m) and 11.32 (1 H, br s).

2,7-*Dibromo*-9-*ethoxy*-9-*phenylxanthene* **17a**.—TFA (0.40 cm^3, 5.2 mmol) was added to a stirred solution of 2,7-dibromo-9-phenylxanthen-9-ol **15a** (0.433 g, 1.0 mmol) in chloroform–ethanol [(9:1 v/v); 10 cm^3]. After 1 h, triethylamine (0.5 cm^3, 3.6 mmol) was added and the products were extracted with saturated aq. sodium hydrogen carbonate (3 × 10 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the solid residue obtained was crystallized from absolute ethanol to give the *title compound* (0.343 g, 74%) (Found: C, 54.6; H, 3.4. $C_{21}H_{16}Br_2O_2$ requires C, 54.8; H, 3.5%) as needles, m.p. 134–135 °C; R_f 0.51 (system C); λ_{max}(95% EtOH)/nm 253 (ε 25 300), 292 (2900) and 302 (4100); λ_{min}/ nm 240 (14 800), 280 (1800) and 296 (2500); $\delta_C(CDCl_3)$ 15.34, 59.26, 74.91, 115.98, 118.21, 125.54, 126.10, 127.00, 128.12, 131.69, 132.19, 148.09 and 149.87.

2,7-*Dibromo*-9-*ethoxy*-9-[3-(*trifluoromethyl*)*phenyl*]-*xanthene* **17b**.—This compound was prepared from 2,7-dibromo-9-[3-(trifluoromethyl)phenyl]xanthen-9-ol **15b** (0.50 g, 1.0 mmol) according to the procedure described above in the preparation of 2,7-dibromo-9-ethoxy-9-phenylxanthene **17a**. The *title compound* (0.361 g, 68%) (Found: C, 49.8; H, 2.7. $C_{22}H_{15}Br_2F_3O_2$ requires C, 50.0; H, 2.9%) was obtained as crystals; m.p. 134–135 °C; R_f 0.58 (system C); λ_{max}(95% EtOH)/nm 255 (ε 24 300), 292 (3050) and 302 (4100); λ_{min}/nm 239 (9800), 282 (2000) and 296 (2700); $\delta_C(CDCl_3)$ (*inter alia*) 15.27, 59.41, 74.62, 116.20, 118.47, 122.24 (m), 124.08 (m), 124.68, 128.71, 130.21, 131.50, 132.64, 149.02 and 149.85.

Determination of the Rates of Acid-promoted Unblocking of 5′-Protected Thymidine Derivatives.—A 1.0 mol dm^{-3} solution of TFA (0.025 cm^3) in dichloromethane–ethanol (95:5 v/v) was added, with thorough mixing, to a 1.25 × 10^{-3} mol dm^{-3} solution of substrate in the same solvent mixture (0.10 cm^3), maintained at 22 °C. After an appropriate interval of time, 1.4 mol dm^{-3} triethylamine [in dichloromethane–ethanol (95:5 v/v); 0.15 cm^3, 0.21 mmol] was added. The composition of the products, consisting of thymidine, remaining substrate, and the corresponding 9-aryl-9-ethoxyxanthene, was determined by liquid chromatography on a Jones APEX C_{18} 5μ column which was eluted with methanol–water mixtures. At least six measurements after different intervals of time were made for each substrate and the half-lives for deprotection with 0.2 mol dm^{-3} TFA in dichloromethane–ethanol (95:5 v/v) were obtained by plotting $\log_{10}$ of the percentage of substrate remaining against time. Straight-line plots were obtained. The half-times ($t_{\frac{1}{2}}$) of unblocking are indicated in Table 1.

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References

1 C. B. Reese in *Protective Groups in Organic Chemistry*, ed. J. F. W. McOmie, Plenum, London and New York, 1973, p. 100 *et seq.*
2 T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1981, p. 34 *et seq.*
3 B. Helferich, *Adv. Carbohydr. Chem.*, 1948, **3**, 79.
4 M. Smith, D. H. Rammler, I. H. Goldberg and H. G. Khorana, *J. Am. Chem. Soc.*, 1962, **84**, 430; H. Schaller, G. Weimann, B. Lerch and H. G. Khorana, *J. Am. Chem. Soc.*, 1963, **85**, 3821.3

5 *Oligonucleotide Synthesis. A Practical Approach*, ed. M. J. Gait, IRL Press, Oxford, 1984.
6 J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1978, 640.
7 M. Gomberg and L. H. Cone, *Justus Liebig's Ann. Chem.*, 1909, **370**, 142.
8 B. Chaudhuri, C. B. Reese and K. Weclawek, *Tetrahedron Lett.*, 1984, **25**, 4037.
9 T. S. Rao, C. B. Reese, H. T. Serafinowska, H. Takaku and G. Zappia, *Tetrahedron Lett.*, 1987, **28**, 4897.
10 C. B. Reese and J. G. Ward, *Tetrahedron Lett.*, 1987, **28**, 2309.
11 C. B. Reese and J. G. Ward, unpublished observations.
12 G. B. Bachman and L. L. Lewis, *J. Am. Chem. Soc.*, 1947, **69**, 2022.
13 M. Kwiatkowski and J. Chattopadhyaya, *Acta Chem. Scand., Ser. B*, 1984, **38**, 657.
14 S. Char, *J. Chem. Soc.*, 1916, **109**, 744.

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