Pergamon

Tetrahedron Letters 42 (2001) 1789–1791

TETRAHEDRON LETTERS

Xanthen-9-ylidene and 2,7-dimethylxanthen-9-ylidene protecting groups

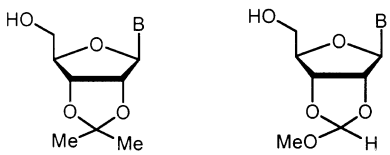
Colin B. Reese,* Quanlai Song and Hongbin Yan

Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK

Received 2 November 2000; accepted 21 December 2000

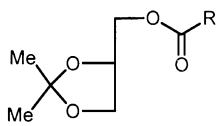
Abstract—The preparation of the 2′,3′-*O*-[di-(*p*-anisyl)methylene]uridine **10**, 2′,3′-*O*-(xanthen-9-ylidene)uridine **12a** and 2′,3′-*O*-(2,7-dimethylxanthen-9-ylidene)uridine **12b** is described. The rates of hydrolysis of these three compounds are compared with that of 2′,3′-*O*-isopropylideneuridine **6a** in trifluoroacetic acid–water–methanol (1:2:7 v/v) at 30°C.

In the 1960s, in connection with our earlier studies[1] on the solution phase synthesis of oligoribonucleotides, we required a protecting group for the 2′,3′-*cis*-diol system of a ribonucleoside that was considerably more acid-labile than the conventional isopropylidene group (as in **1**). Despite the fact that it was chiral, we decided to use the methoxymethylene group[2] (as in **2**), which is some two orders of magnitude more labile to acidic hydrolysis than the isopropylidene group. Much more recently, in connection with our work on the synthesis of phosphatidylinositol-3,4,5-trisphosphate [PtdIns(3,4,5)P_3],[3] we prepared[4] 1-*O*-stearoyl-*sn*-glycerol **4**; R = $C_{17}H_{35}$ from its 2,3-*O*-isopropylidene derivative **3**; R = $C_{17}H_{35}$. As the acidic conditions required for the removal of the isopropylidene group were relatively drastic,[4] it would have been desirable to have used a more acid-labile protecting group and thereby to have ensured that absolutely no concomitant acyl migration and hence racemisation could have occurred. In this, and no doubt in a number of other studies, a chiral protecting group such as methoxymethylene would have been unsuitable as its use would almost certainly have led to an undesirable mixture of diastereoisomers.

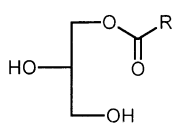


1

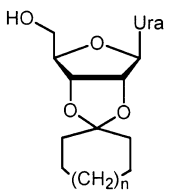
2



3 ; R = $C_{17}H_{35}$

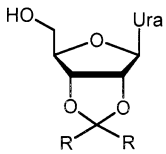


4 ; R = $C_{17}H_{35}$

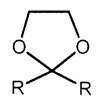


5 **a** ; n = 0
b ; n = 2
c ; n = 3

Ura = uracil-1-yl



6 **a** ; R = Me
b ; R = Et
c ; R = Pr^i

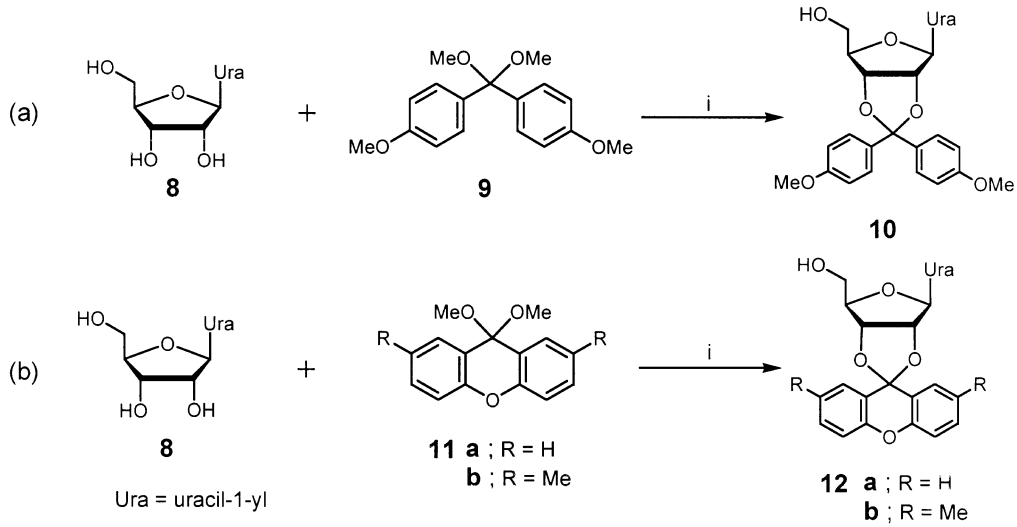


7 **a** ; R = Me
b ; R = Ph

Keywords: nucleosides; acetals; protecting groups.

* Corresponding author. Tel.: +44(0)20 7848 2260; fax: +44(0)20 7848 1771; e-mail: colin.reese@kcl.ac.uk

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02359-5



Scheme 1. *Reagents and conditions*: i. (±)-camphor-10-sulfonic acid, MeCN, room temp., 2–4 h.

We therefore set out to identify an achiral protecting group that was at least one order of magnitude more acid-labile than the isopropylidene group. Acetal groups derived from certain alicyclic ketones have been reported[5] to be more acid-labile than the isopropylidene group. For example, 2′,3′-*O*-cyclopentylidene-, -cycloheptylidene- and -cyclooctylidene-uridines (**5a**, **5b** and **5c**, respectively) undergo acid-catalysed hydrolysis, in 0.01 mol dm^{-3} hydrochloric acid at 26°C, ca. 5, 7 and 8 times more rapidly[5] than 2′,3′-*O*-isopropylideneuridine **6a**. On the other hand, acetal groups derived from higher molecular weight aliphatic ketones are generally less susceptible to acidic hydrolysis than corresponding isopropylidene derivatives. For example, 2′,3′-*O*-(pent-3-ylidene)-[5] and 2′,3′-*O*-(2,4-dimethylpent-3-ylidene)-[6] uridine (**6b** and **6c**, respectively), have been found to be 2 and 7 times **more stable** to acidic hydrolysis than 2′,3′-*O*-isopropylideneuridine **6a**. The same is apparently generally true of acetal groups derived from aromatic ketones. Thus, 2,2-diphenyl-1,3-dioxalane **7b** is ca. 20 times more stable to acidic hydrolysis[7] than the corresponding 2,2-dimethyl derivative **7a**. However, acetal protecting groups derived from aromatic ketones have a distinct advantage over those derived from alicylic or aliphatic ketones in that their stabilities can easily be adjusted by the introduction of appropriate substituents.

As in the case of substituted trityl protecting groups,[8] *para*-methoxy substituents would be expected to facilitate the acid-catalysed hydrolysis of 2,2-diphenyl-1,3-dioxalane **7b** and its derivatives. A similar comparison can be made between 9-phenylxanthen-9-yl[9] and xanthen-9-ylidene (as in **12a**; Scheme 1b) protecting groups. The preparation of 2′,3′-*O*-[di-(*p*-anisyl)methylene]uridine **10** was undertaken first. This compound was readily prepared (Scheme 1a) by reacting uridine **8** with di-(*p*-anisyl)-dimethoxymethane[10] **9** in the presence of a catalytic quantity of camphor-10-sulfonic acid in acetonitrile solution; it was isolated as a colourless crystalline solid[11] in 95% yield. Under the same conditions, uridine **8** reacted with 9,9-dimethoxyxanthene[12] **11a** (Scheme 1b) to give its 2′,3′-*O*-(xanthen-9-ylidene) derivative **12a**, which was isolated as a colourless crystalline solid[14] in 88% yield. Similarly, 2′,3′-*O*-(2,7-dimethylxanthen-9-ylidene)-uridine **12b** (Scheme 1b) was prepared from uridine **8** and 9,9-dimethoxy-2,7-dimethylxanthene[15] **11b** and was isolated as a colourless crystalline solid[18] in 70% yield.

Hydrolysis studies[19] were carried out on compounds **6a**, **10**, **12a** and **12b** under the conditions indicated in Table 1 (footnote a). In each case, pseudo first order kinetics was observed and good straight lines were obtained by plotting $\log_{10}$ (% remaining substrate) against time. It can be seen from Table 1 that all of the new protecting groups (entries 2–4) are more acid-labile than the isopropylidene group (entry 1). It is particularly noteworthy that the 2,7-dimethylxanthen-9-ylidene group meets our original lability criterion in that compound **12b** (entry 4) undergoes hydrolysis at a rate just over 20 times faster than that of 2′,3′-*O*-isopropylideneuridine **6a** in trifluoroacetic acid–water–methanol (1:2:7 v/v) at 30°C. Clearly, by an appropriate choice of substituents an even more labile xanthen-9-ylidene protecting group could be designed. The main limiting factor would be

Table 1. Acidic hydrolysis of 2′,3′-protected uridine derivatives[a]

Entry	Substrate	Half-time ($t_{1/2}$) min
1	2′,3′-*O*-Isopropylideneuridine **6a**	178
2	2′,3′-*O*-[Di-(*p*-anisyl)methylene]uridine **10**	56.7
3	2′,3′-*O*(Xanthen-9-ylidene)uridine **12a**	31.7
4	2′,3′-*O*-(2,7-Dimethylxanthen-9-ylidene)-uridine **12b**	8.6

[a] Hydrolysis studies were carried out in trifluoroacetic acid–water–methanol (1:2:7 v/v) solution at 30(±0.1)°C.

the ready availability of the corresponding xanthen-9-ones. Finally, from an analytical point of view, xanthen-9-ylidene groups have an advantage over the isopropylidene group in that they absorb in the ultraviolet. This may not be of importance in nucleoside and nucleotide chemistry but it might very well prove to be so in lipid and carbohydrate chemistry.

Acknowledgements

We thank Scotia Pharmaceuticals Ltd. for financial support. We should also like to thank Mr. A. Miah for his help.

References

1. Griffin, B. E.; Reese, C. B. *Tetrahedron Lett.* **1964**, 2925–2931.
2. Jarman, M.; Reese, C. B. *Chem. Ind.* **1963**, 1493–1494.
3. Gaffney, P. R. J.; Reese, C. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3171–3176.
4. Gaffney, P. R. J.; Reese, C. B. *Tetrahedron Lett.* **1997**, *38*, 2539–2542.
5. Hampton, A.; Fratantoni, J. C.; Carroll, P. M.; Wang, S. *J. Am. Chem. Soc.* **1965**, *87*, 5481–5487.
6. Jarman, M. Ph.D. Thesis, Cambridge University, 1965; p. 87.
7. Fife, T. H.; Hagopian, L. *J. Org. Chem.* **1966**, *31*, 1772–1775.
8. Schaller, H.; Weimann, G.; Lerch, B.; Khorana, H. G. *J. Am. Chem. Soc.* **1963**, *85*, 3821–3827.
9. Chattopadhyaya, J. B.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1978**, 639–640.
10. Thurkauf, A.; Jacobson, A. E.; Rice, K. C. *Synthesis* **1988**, 233–234.
11. Found: C, 61.1; H, 5.2; N, 5.65. $C_{24}H_{24}N_2O_8 \cdot 0.2H_2O$ requires: C, 61.06; H, 5.21, N, 5.93%; mp 112–114°C; δ_H [$(CD_3)_2SO$] 3.59 (2H, m), 3.74 (3H, s), 3.76 (3H, s), 4.26 (1H, m), 4.70 (1H, dd, *J* 3.2 and 6.6), 4.90 (1H, dd, *J* 2.6 and 6.6), 5.10 (1H, t, *J* 5.4), 5.63 (1H, d, *J* 8.0), 6.00 (1H, d, *J* 2.6), 6.93 (4H, m), 7.33 (4H, m), 7.82 (1H, d, *J* 8.1), 11.39 (1H, br s); δ_C [$(CD_3)_2SO$] 55.14, 61.38, 81.61, 84.17, 86.30, 91.41, 101.75, 113.36, 113.64, 127.63, 127.65, 133.36, 142.33, 150.36, 159.16, 159.30, 163.21.
12. Xanthen-9-one (19.62 g, 0.10 mol) and thionyl chloride (40 ml) were heated, under reflux, for 4 h. The products were evaporated under reduced pressure. A solution of the residual 9,9-dichloroxanthene[13] in tetrahydrofuran (100 ml) was added dropwise, in an atmosphere of nitrogen, to a stirred solution of methanolic sodium methoxide (ca. 4.3 mol dm^{-3}, 76.3 ml, ca. 0.33 mol) at 0°C. The stirred reactants were then allowed to warm up to room temperature. After a further period of 1 h, the products were concentrated under reduced pressure and the residue was partitioned between dichloromethane (100 ml) and saturated aqueous sodium hydrogen carbonate (3×100 ml). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure to give 9,9-dimethoxyxanthene (22.9 g, 94.5%) (found in material recrystallised from absolute ethanol: C, 74.2; H, 5.6. $C_{15}H_{14}O_3$ requires: C, 74.36; H, 5.28%); mp 59–61°C; δ_H [$CDCl_3$] 2.94 (6H, s), 7.23 (4H, m), 7.42 (2H, m), 7.74 (2H, m); δ_C [$CDCl_3$] 51.81, 96.60, 116.51, 118.77, 123.38, 127.36, 130.20, 153.23.
13. Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692–703.
14. Found: C, 61.3; H, 4.2; N, 6.4. $C_{22}H_{18}N_2O_7 \cdot 0.5\ H_2O$ requires: C, 61.31; H, 4.44; N, 6.50%; mp 152–153°C; δ_H[$(CD_3)_2SO$] 3.68 (2H, m), 4.40 (1H, m), 5.22 (2H, m), 5.48 (1H, dd, *J* 2.5 and 6.4), 5.70 (1H, d, *J* 8.0), 6.14 (1H, d, *J* 2.5), 7.35 (4H, m), 7.55 (2H, m), 7.75 (1H, dd, *J* 1.2 and 7.8), 7.92 (2H, m), 11.48 (1H, br s); δ_C [$(CD_3)_2SO$] 61.38, 82.54, 85.44, 86.40, 91.40, 101.73, 105.12, 116.55, 116.83, 121.10, 122.68, 123.66, 123.90, 125.52, 126.43, 130.43, 130.97, 142.06, 150.28, 150.49, 151.71, 163.30.
15. 9,9-Dimethoxy-2,7-dimethylxanthene **11b** was prepared from 2,7-dimethylxanthen-9-one[16] by the procedure used above in the conversion of xanthen-9-one into 9,9-dimethoxyxanthene **11a**; it was obtained as a pale yellow solid, mp 81–82.5°C in 91% yield (found, in material recrystallised from absolute ethanol: C, 75.5; H, 6.7. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%); δ_H [$CDCl_3$] 2.40 (6H, s), 2.92 (6H, s), 7.08 (2H, d, *J* 8.3), 7.21 (2H, d, *J* 8.3), 7.50 (2H, s); δ_C [$CDCl_3$] 20.91, 51.84, 96.94, 116.19, 118.16, 126.98, 131.09, 132.64, 151.45.
16. 2,7-Dimethylxanthen-9-one may readily be prepared in good yield from commercially available di-(*p*-tolyl) ether by Schönberg and Asker's procedure.[17]
17. Schönberg, A.; Asker, W. *J. Chem. Soc.* **1946**, 609–610.
18. Found: C, 63.9; H, 4.8; N, 6.1. $C_{24}H_{22}N_2O_7$ requires: C, 64.00; H, 4.92, N, 6.22%; mp 153–155°C; δ_H [$(CD_3)_2SO$] 2.39 (3H, s), 2.40 (3H, s), 3.67 (2H, m), 4.36 (1H, m), 5.15 (1H, dd, *J* 2.8 and 6.4), 5.22 (1H, t, *J* 5.3), 5.45 (1H, dd, *J* 2.9 and 6.3), 5.70 (1H, dd, *J* 1.9 and 8.0), 6.16 (1H, d, *J* 2.7), 7.22 (2H, m), 7.32 (2H, m), 7.49 (1H, s), 7.68 (1H, s), 7.90 (1H, d, *J* 8.0), 11.47 (1H, br s); δ_C [$(CD_3)_2SO$] 20.53, 61.32, 82.28, 85.26, 86.05, 90.96, 101.75, 105.38, 116.27, 116.54, 120.67, 122.29, 125.21, 126.10, 130.97, 131.54, 132.57, 132.69, 141.83, 148.43, 149.88, 150.52, 163.24.
19. A stock solution of an internal standard (3′-*O*-benzoylthymidine, 0.050 g) in methanol (35 ml), water (10 ml) and trifluoroacetic acid (5 ml) was prepared. Substrates (ca. 0.001 g) were dissolved in preheated (to 30°C) stock solution (1.0 ml) and the resulting solutions were maintained at 30 (±0.1)°C in a Digi-block heating apparatus. After appropriate intervals of time, aliquots (20 μl) were removed, quenched with 0.1 mol dm^{-3} triethylammonium acetate buffer (pH 7.0, 40 μl) and methanol (40 μl), and analysed by HPLC (25 cm×4.6 mm Hypersil ODS 5 μ column). The HPLC column was eluted with acetonitrile–0.1 mol dm^{-3} triethylammonium acetate buffer (pH 7.0) mixtures.