Preparation of some new anomeric carbohydrate difluoromethylene-phosphonates *via* phosphonyl radical addition to *gem*-difluoroenol ethers

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Generation of a phosphonyl radical either from diethyl phosphite, or diethyl (phenylselenyl)phosphonate in conjunction with tributylstannane, in the presence of a carbohydrate *gem*-difluoroenol ether provides a new route to anomeric difluoromethylenephosphonates; in the course of these reactions, some unusual stereochemical effects are observed.

There is currently considerable interest in difluoromethylene-phosphonates (CF_2-phosphonates) as hydrolytically stable analogues of phosphate esters.[1,2] Although the concept of difluoromethylene phosphonates as isopolar and isosteric analogues of phosphate esters has been much argued,[3–5] this replacement has provided several natural product analogues with significant biological activity.[6–8] The preparation of these compounds invariably involves introduction of the difluoromethylenephosphonate moiety by formation of a carbon–carbon bond and has been achieved by acylation[9] or alkylation[2] using ionic displacement of halides or triflates and diethyl (lithiodifluoromethyl)phosphonate, or the congeneric cadmium,[6,10] zinc[7,11,12] or cerium[13,14] reagents. The free radical addition of iododifluoromethylphosphonate across alkenes, catalysed by copper,[15] palladium[16] or a cobaloxime(III)/Zn bimetal redox system[17] has also been reported. An alternative to these methods is the direct transformation of benzylic α-oxophosphonates to their corresponding benzylic α,α-difluorophosphonates using diethylaminosulfur trifluoride (DAST).[18] As a part of our programme designed to explore the reactivity of carbohydrate *gem*-difluoroenol ethers, we have previously shown that the addition of sulfur- and carbon-centred radicals opens up a variety of general routes to *gem*-difluoromethylene-linked glycoside analogues (CF_2 glycosides).[19,20] We were therefore particularly intrigued by the possibility that the classical light- or peroxide-initiated[21] free radical chain addition of dialkyl phosphites to unsaturated systems could be applied in this instance and hence lead, *via* regiospecific phosphorus–carbon bond formation at the difluoromethylene terminus, to hitherto unknown anomeric difluoromethylene phosphonates.

The results for a series of carbohydrate *gem*-difluoroenol ethers (**1a–6a**) are shown in Table 1, (method A) and the obtention of the adducts (**1b–6b**) confirmed the viability of this approach. These reactions were carried out by slow addition of a solution of di-*tert*-butyl peroxide in octane to a refluxing solution of diethyl phosphite and the *gem*-difluoroenol ether in the same solvent. Yields however were disappointly low, presumably because of the relatively harsh reaction conditions and the possibility of competition[22] between the desired addition and benzylic hydrogen atom abstraction from certain substrates (entries 5 and 6). Clearly, both of these problems stem from the energetically difficult chain propagation step which requires abstraction of a hydrogen atom from diethyl phosphite. We therefore reasoned, as shown in Scheme 1, that the selection of readily prepared diethyl (phenylselenyl)-phosphonate[23] **7**, in conjunction with tributylstannane could obviate this problematical step, albeit through the incorporation of an additional propagation step into the chain sequence. Thus,

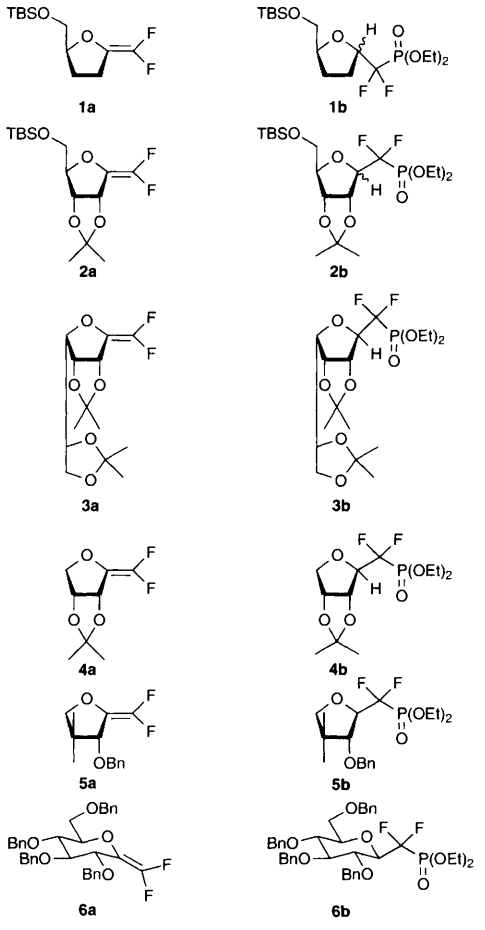


Table 1 Reaction substrates, products and yields

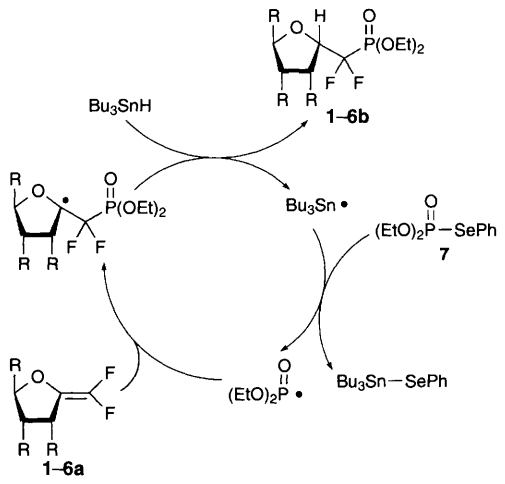
		Phosphonates (yield[a], ratio)	
Entry	Substrate	Method A[b]	Method B[c]
1	**1a**	**1b** (5%, α:β, 4:6)	**1b** (52%, α:β, 45:55)
2	**2a**	**2b** (47%, α:β, 0:1)	**2b** (73%, α:β, 1:6)[d]
3	**3a**	**3b** (23%)	**3b** (29%)
4	**4a**	**4b** (8%)	**4b** (36%)
5	**5a**	[e]	**5b** (28%)
6	**6a**	[e]	**6b** (14%)

[a] Yields of isolated product. In all cases, the diastereoisomers were separated by column chromatography or HPLC. [b] Reaction of **1a–6a** (1 equiv.) and diethyl phosphite (3 equiv.) in refluxing octane in the presence of di-*tert*-butyl peroxide (0.5 equiv.). [c] Reaction of **1a–6a** (1 equiv.) and **7** (3 equiv.) in refluxing benzene with tributyltin hydride (4 equiv.) and AIBN (0.5 equiv.). [d] Reaction in refluxing octane and with di-*tert*-butyl peroxide (0.5 equiv.) as initiator. [e] No addition products observed.

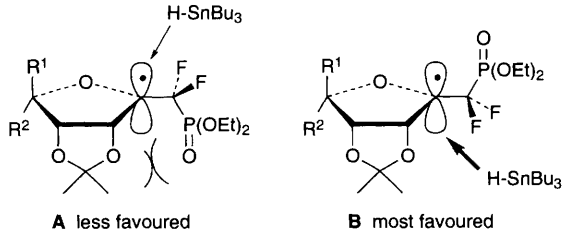
it was anticipated that the bimolecular homolytic substitution reaction of **7** with the tributylstannyl radical should be especially favoured by virtue of the formation of the strong tin–selenium bond as a driving force. Addition of the resultant phosphonyl radical to the double bond could then be followed by hydrogen atom capture from the stannane with concomitant liberation of the chain carrier. To the best of our knowledge, free radical chain reactions involving diethyl (phenylselenyl)phosphonate **7** have not been reported.

In the event, reactions were carried out by slow addition of a solution of tributyltin hydride containing AIBN as initiator in benzene to a refluxing solution of the carbohydrate *gem*-difluoroenol ether (**1a–6a**) and diethyl (phenylselenyl)phosphonate **7** in benzene to afford the corresponding difluoromethylene phosphonate **1b–6b**, in yields which proved to be higher than those found in the reaction with diethyl phosphite (Table 1, method B). In particular, the mild conditions of this procedure led to a dramatic increase of the yield for volatile compounds and those substrates sensitive to hydrogen abstraction (entries 4, 5 and 6).

The stereochemical features of this reaction proved to be particularly fascinating inasmuch as they ran entirely contrary to our initial expectations. Thus, in general terms for the furanoside derivatives, the β-stereochemistry of the major isomer at the anomeric centre was apparently indicative of hydrogen atom capture from the more hindered face of the molecule. This situation was especially highlighted by the excellent selectivity observed for the classical case of 2,3-isopropylidene derivatives **3b** and **4b** where the observed result was not only in direct opposition to that which is generally predicted[24,25] for such V-shaped molecules, but also in contrast to our own observations on the addition of smaller carbon- and sulfur-centred radicals[19,20] to such *gem*-difluoroenol ethers. Further examination of the results reveals that the absence of a functional group at position 2 leads to an essentially equimolar mixture of both possible anomeric derivatives (entry 1), while the introduction of a 4β-substituent as in entries 1 and 2 appears to diminish the inherent preference for formation of the β-substituted anomeric derivative (compare entries 2 and 3). Within the pyranose series however, the stereochemical outcome is consistent with operation of the 'radical anomeric effect',[25] (entry 6).



Scheme 1



Scheme 2

A possible explanation for these stereoselective trends may arise through hyperconjugative delocalisation of the unpaired electron into the σ^*_{C-P} orbital which requires the eclipsed conformations shown in Scheme 2, and indeed such conformational preferences of β-phosphorus-substituted radicals have been observed by EPR spectroscopy.[26–28] Of the two possible intermediates **A** or **B**, steric factors would favour **B** in which the phosphorus substituent effectively impedes hydrogen atom abstraction from the top (β) face. Although the corresponding β-phenylthiyl-substituted radicals probably exhibit the same preference for an eclipsed conformation,[29] steric interactions with the two-coordinate sulfur group will differ appreciably from those involving the four-coordinate phosphonyl substituent. In the case of the *tert*-butylsilyl (TBS)-protected ribose derivative **1b**, the bulky protecting group would tend to destabilise intermediate **B** and therefore allow some of the radicals to exist in the less favoured conformation **A**.

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References

1 J. Matulic-Adamic, P. Maeberli and N. Usman, *J. Org. Chem.*, 1995, **60**, 2563.
2 D. B. Berkowitz, M. Eggen, Q. Shen and D. Sloss, *J. Org. Chem.*, 1993, **58**, 6174.
3 G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1119.
4 G. R. J. Thatcher and A. S. Campbell, *J. Org. Chem.*, 1993, **58**, 2272.
5 J. Nieschalk and D. O'Hagan, *J. Chem. Soc., Chem. Commun.*, 1995, 719.
6 R. D. Chambers, R. Jaouhari and D. O'Hagan, *Tetrahedron*, 1989, **45**, 5101.
7 G. M. Blackburn, D. L. Jakeman, A. J. Ivory and M. P. Williamson, *Bioorg. and Med. Chem. Lett.*, 1994, **4**, 2573.
8 T. R. Burke Jr., M. S. Smyth, A. Otaka, M. Nomizu, P. P. Roller, G. Wolf, R. Care and S. E. Shoelson, *Biochem.*, 1994, **33**, 6490.
9 S. F. Martin, D. W. Dean and A. S. Wagman, *Tetrahedron Lett.*, 1992, **33**, 1839.
10 D. J. Burton, S. Shin-Ya and R. Takei, *J. Fluorine Chem.*, 1981, **18**, 197.
11 D. J. Burton and L. G. Sprague, *J. Org. Chem.*, 1989, **54**, 613.
12 D. J. Burton and L. G. Sprague, *J. Org. Chem.*, 1988, **53**, 1523.
13 T. P. Lequeux and J. M. Percy, *Synlett*, 1995, 361.
14 T. P. Lequeux and J. M. Percy, *J. Chem. Soc., Chem. Commun.*, 1995, 2111.
15 Z.-Y. Yang and D. J. Burton, *Tetrahedron Lett.*, 1992, **32**, 1019.
16 Z.-Y. Yang and D. J. Burton, *J. Org. Chem.*, 1992, **57**, 4676.
17 C.-M. Hu and J. Chen, *J. Chem. Soc., Perkin Trans. 1*, 1993, 327.
18 M. S. Smyth and T. R. Burke Jr., *Tetrahedron Lett.*, 1994, **35**, 551.
19 W. B. Motherwell, M. J. Tozer and B. C. Ross, *Synlett*, 1989, 68.
20 T. F. Herpin, W. B. Motherwell and M. J. Tozer, *Tetrahedron: Asymmetry*, 1994, **5**, 2269.
21 G. Sosnovsky, in *Free Radical Reactions in Preparative Organic Chemistry*, McMillan, New York, 1964.
22 J. F. Harris and J. F. Stacey, *Org. React.*, 1963, **13**, 150.
23 N. Petragnani, V. G. Toscano and M. de Moura Campos, *Chem. Ber.*, 1968, **101**, 3070.
24 D. H. R. Barton, S. D. Gero, B. Quiclet-Sire and M. Samadi, *Tetrahedron: Asymmetry*, 1994, **5**, 2123.
25 B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 969.
26 A. G. Davies, D. Griller and B. P. Roberts, *J. Am. Chem. Soc.*, 1972, **94**, 1782.
27 I. G. Neil and B. P. Robters, *J. Organomet. Chem.*, 1975, **102**, C17.
28 B. P. Roberts and K. Singh, *J. Organomet. Chem.*, 1978, **159**, 31.
29 See, for example: P. J. Krusic and J. K. Kochi, *J. Am. Chem. Soc.*, 1971, **93**, 846.

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