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Diastereoselective Synthesis of C–Glycosylphosphonates via Free-Radical Glycosylation

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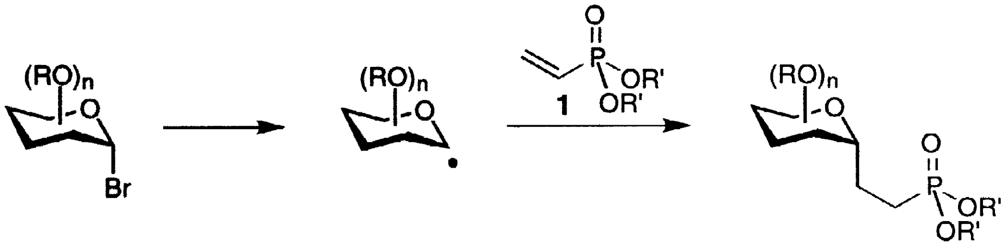
Abstract: A single step approach for the diastereoselective synthesis of C-glycosidic sugar phosphonates was developed by utilizing a free radical coupling to dialkyl vinylphosphonates to give the title compounds in moderate yield. The method is broadly applicable to sugars, deoxysugars, aminosugars, and oligosaccharides.

Anomeric sugar phosphates are ubiquitous intermediates and regulators of carbohydrate metabolism, and they serve a variety of important functions, e.g. in the activation of monosaccharide substrates as nucleotide sugars for the enzymatic synthesis of oligosaccharides and related glycoconjugates,[1] including those incorporating deoxy-, aminodeoxy- and other sugar derivatives.[2] Thus, the synthesis of C-glycosyl phosphonate analogs[3] as hydrolytically stable mimics of naturally occurring sugar phosphates is of great interest for the potential modulation of biological signals and metabolic activities, although there seems to be no rapid and broadly applicable method available yet for the stereoselective construction of this type of compounds. Particularly, the synthesis of aminodeoxysugar phosphonates has only very recently been achieved by a multi-step sequence which required introduction of the amino function *after* installation of the phosphono group.[4] Here we report on a new, free radical approach to the synthesis of related, homologous C-ethylenephosphonate sugars which starts from simple acetobromosugars and gives access to the naturally occurring α-configuration with high stereoselectivity.



The addition of glycosyl radicals to α,β-unsaturated carbonyl compounds has been developed by *Giese* et al. as a practical method for the synthesis of C-glycosides.[5] Although structurally related, vinyl phosphonates **1** have been largely neglected in carbohydrate chemistry, with few exceptions like in the *Michael* addition of nitrosugars[6] or for the radical promoted backbone extension of nucleosides.[7] We have found that indeed commercial vinylphosphonic acid dialkyl esters **1** can be utilized for the synthesis of C-ethylenephosphonate sugars by capture of nucleophilic glycosyl radicals in a radical chain reaction. Glycosyl radicals were conveniently gener-

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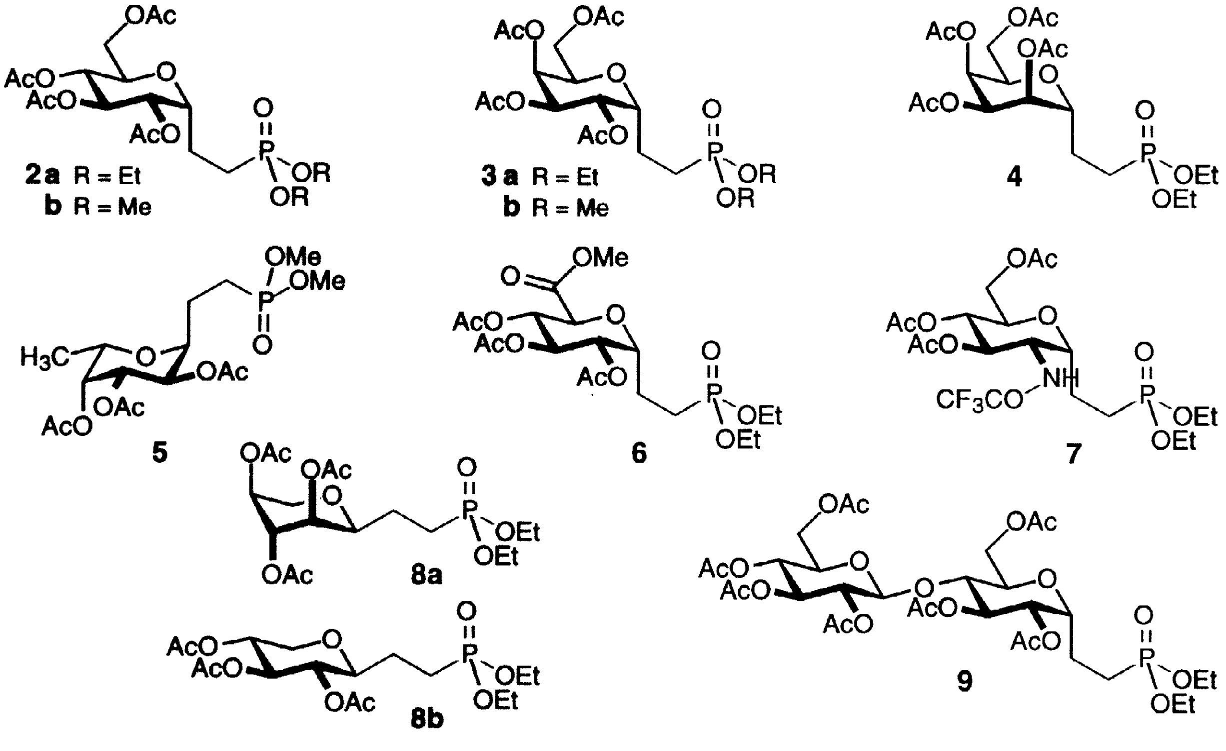
ated from the acetobromosugars in dry ether using light (method A, C) or AIBN (method B) as initiator. After the addition, product radicals were intercepted in the presence of a chain sustaining hydrogen donor such as tributyltin hydride (method A, B) or tris(trimethylsilyl)silane (method C). All reactions were carried out on a 2.5 to 25 mmol scale, and products were isolated after complete conversion in moderate yields by flash chromatography. Product composition was determined by high field NMR analysis of the crude reaction mixtures. In order to demonstrate the scope of the method, we have investigated acetate protected glycopyranosyl bromides of aldopentoses **8** and aldohexoses **2** – **4**, deoxysugars **5**, glycuronic acid esters **6**, deoxyaminosugars **7** and disaccharides **9** (Scheme 1, Table 1).[8]



Scheme 1. Sugar phosphonates obtained by glycosyl radical addition to vinylphosphonates **1**

Besides the desired product formation, the main competing reaction was immediate reduction of the glycosyl radicals by the hydrides under all conditions tested (generation of the corresponding anhydroalditols). Interestingly, it was found that sequential additions to **1** could take place before the reductive step, with formation of noticable quantities of bisphosphonic C-glycosides;[8] also, a small percentage of organometal radical addition to **1** was detectable.[9] Selectivity could not be improved by lowering the temperature (Table 1, entry 8). Within experimental error, the choice of initiator is not crucial. Not only for the lower costs, the organotin mediated route is the most effective (method A, B). Because of the higher reduction potential of the tin hydride, the use of a large excess of **1** is recommended. When using the less toxic tris(trimethylsilyl)silane as a radical source having a lower reduction potential,[10] the concentration of **1** can be reduced (method C). Particularly in case of the methyl ester of **1**, however, the accompanying generation of TTMS-Br causes lower yields due to the promotion of a partial ester cleavage in the products (Table 1, entry 5).[11]

The high preference for α-anomer formation parallels investigations with the corresponding carbonyl acceptors.[5,12] This has been rationalized by a conformational control due to favorable interactions of the SOMO of the anomeric radical center with the LUMO of the adjacent axial ester C–O bond, effectively directing the radical attack.[13] It is interesting to note that this selectivity parallels that observed for the addition of nitroglycosyl anions to **1** (and thus furnishes the complementary, *inversely* configurated C-glycosides upon radical denitration).[6] In case of the chromatographically separable pentopyranosyl derivatives **8a/8b**, the slight opposite preference to the β-anomeric product may be explained by a higher conformational fexibility of the glycosyl radical and an onset of thermodynamic control.[13]

Table 1. Synthesis of C-Glycosyl Phosphonate Esters[a]

Entry	Method[8]	Product	Configuration	Yield (%)[b]	α/β Ratio[c]
1	A	**2a**	D-*gluco*	28	91: 9
2	C	**2a**	D-*gluco*	44	91: 9
3	A	**2b**	D-*gluco*	47	91: 9
4	B	**2b**	D-*gluco*	47	93: 7
5	C	**2b**	D-*gluco*	17	93: 7
6	A	**3a**	D-*galacto*	31	>98: 2
7	A	**3b**	D-*galacto*	27	>98: 2
8	A[d]	**3b**	D-*galacto*	22	>98: 2
9	B	**3b**	D-*galacto*	20	>98: 2
10	A	**4**	D-*manno*	38	>98: 2
11	A	**5**	L-*fuco*	40	>98: 2
12	A	**6**	D-*gluco*	26	88:12
13	A	**7**	D-*gluco*	44	>98: 2
14	A	**8**	D-*xylo*	25	44:66
15	A[e]	**9**	D-*gluco*	32	85:15

(a) All reactions were performed according to protocols A, B or C[8] until complete conversion of the glycosyl bromide (24 h). (b) Yield after isolation by flash chromatography. (c) Determined by high field ^1H NMR analysis (assignments based on COSY spectra and $J_{3,4}$ coupling to α/β "anomeric" protons). (d) T = –25°C. (e) CH_2Cl_2 as solvent.

Liberation of the free phosphonic acids for biological assays was achieved by removing the acetyl groups using catalytic sodium methoxide in methanol prior to saponification of the phosphonate ester groups using TMSBr[11] or TMSI followed by hydrolysis.

In summary we have shown that the radical promoted C-C bond formation between glycosyl radicals and vinylphosphonate esters offers a practical way for the synthesis of various C-glycopyranosyl phosphonates that are CH_2-extended analogues of natural sugar phosphates. An extension of this method to the synthesis of bioisosteric C-glycofuranosyl phosphonates is under current investigation.

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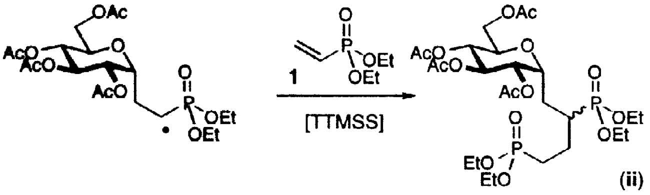
8. *Typical procedures:*

(Method A) A mixture of 2.32 g (5.0 mmol) of tri-*O*-acetyl-2-deoxy-2-trifluoracetamido-D-glucopyranosyl bromide, 6.0 mL (38.5 mmol) of **1** (R=Et), and 1.6 mL (6.0 mmol) of Bu_3SnH in 15 mL of dry Et_2O was irradiated under Ar to reflux using 5 halogen lamps (5 x 50 W). After 24 h the solution was concd, and excessive **1** was recovered by vacuum distillation (0.5 mbar, 50°C). Flash chromatography of the residue (EtOAc) yielded pure **7** as a white solid (1.21 g, 44 %; mp 124°C).

(Method B) A mixture of 4.11 g (10.0 mmol) of tetra-*O*-acetyl-D-galactopyranosyl bromide, 12.0 mL (86.0 mmol) of **1** (R=Me), 3.2 mL (12.0 mmol) Bu_3SnH and 500 mg of AIBN in 15 mL of dry Et_2O was refluxed for 5 h. After addition of another portion of AIBN, reflux was contd for 5 h. Work-up gave **3b** as a colorless syrup (0.98 g, 20%).

(Method C) A mixture of 2.06 g (5.0 mmol) of tetra-*O*-acetyl-D-glucopyranosyl bromide, 2.0 mL (6.5 mmol) of TTMSS, and 1.6 mL (10.3 mmol) of **1** (R=Et) in 15 mL of dry Et_2O was irradiated to reflux for 20 h, then worked up. Chromatography provided **2a** as a colorless syrup (1.10 g, 44%), and further elution (EtOAc/EtOH 10:1) gave bisphosphonates **ii** (230 mg, 7%).



2a: ^1H (500 MHz, $CDCl_3$): δ 5.31(t, 1H, *J* 9.5 Hz, H5), 5.10 (dd, 1H, *J* 5.7, 9.5 Hz, H4), 4.98 (t, 1H, *J* 9.5 Hz, H6), 4.24 (dd, 1H, *J* 5.5, 11.9 Hz, H8a), 4.10-4.17 (m, 6H, H3, H8b, OCH_2), 3.81 (m, 1H, H7), 2.03, 2.05, 2.07, 2.09 (4 s, 12H, OAc), 1.60-1.92 (m, 4H, H1, H2), 1.34 (dt, 6H, $OCH_2C\mathit{H}_3$); *m/z* = 497.2 (M+H).

3b: ^1H (500 MHz, $CDCl_3$): δ 5.42 (t, 1H, *J* 2.8 Hz, H6), 5.30 (dd, 1H, *J* 5.2, 9.4 Hz, H4), 5.20 (dd, 1H, *J* 3.3, 9.4 Hz, H5), 4.23 (dd, 1H, *J* 7.5, 11.5 Hz, H8a), 4.19 (m, 1H, H3), 4.07 (dd, 1H, *J* 5.1, 11.5 Hz, H8b), 4.01 (ddd, 1H, J 2.4, 5.2, 7.5 Hz, H7), 3.77 (d, 6H, *J* 10.7 Hz, OMe), 2.03, 2.06, 2.09, 2.13 (4 s, 12H, OAc), 1.65-2.00 (m, 4H, H1, H2); *m/z* = 469.2 (M+H).

7: ^1H (500 MHz, $CDCl_3$): δ 8.60 (m, 1H, NH), 5.26 (t, 1H, *J* 7.6 Hz, H5), 4.96 (t, 1H, *J* 7.6 Hz, H6), 4.42-4.37 (m, 2H, H8a, H4), 4.14 (m 2H, H3, H8b), 4.02-4.08 (m, 4H, OCH_2), 3.96 (m, 1H, H7), 2.03, 2.06, 2.10 (3 s, 9H, OAc), 1.60-2.02 (m, 4H, H1, H2), 1.34, 1.30 (2t, 6H, $OCH_2C\mathit{H}_3$); *m/z* = 550.2 (M+H).

ii: ^1H (300 MHz, $CDCl_3$): δ 5.32, 5.25 (2t, 1H, H7), 5.13, 5.06 (2dd, 1H, H6), 5.00, 4.97 (2t, 1H, H8), 4.46, 4.24 (2m, 1H, H5), 4.04-4.28 (m, 10H, H10, OCH_2), 3.85 (m, 1H, H9), 2.00-2.10 (8s, 12H, OAc), 1.50-2.00 (m, 7H, H1-H4), 1.29-1.39 (m, 12 H, $CH_2C\mathit{H}_3$); FAB-MS *m/z* = 667.1 (M+Li).

9. Under these reaction conditions no rearrangement to 2-deoxysugars[5] was observed.

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