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Diastereoselective free-radical synthesis of α-substituted C-glycosyl phosphonates, and their use as building blocks in the HWE-reaction

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Abstract

C-Glycosidic phosphonates were synthesized by the addition of pyranosidic and furanosidic glycosyl radicals to α-phosphonoacrylates which occurred with high diastereoselectivity towards the formation of α-C-glycosidic phosphonates. The products are useful substrates for the synthesis of complex higher-carbon sugars related to tunicamycin by Horner–Wadsworth–Emmons reactions.

Keywords: alkenylation; carbohydrate mimetics; coupling reactions; radical reactions.

The development of new methods for the preparation of C-glycosidic phosphonates is an attractive target in organic synthesis because such compounds offer a considerable potential for drug development. Phosphorylated sugars are key intermediates in the metabolism of monosaccharides as well as in the biosynthesis of complex oligosaccharides. Both the phosphonate and the C-glycoside partial structures are effective mimics for the corresponding moieties in naturally occurring sugar phosphates.[1] Because they confer stability to hydrolytic degradation, C-glycosidic phosphonate inhibitors are candidates for the modulation of biological signals, e.g., during cell–cell recognition in tumor development or inflammatory processes.[2] In view of the lack of broadly applicable synthetic approaches for this class of compounds, we have recently developed a new, free-radical approach to the synthesis of homologous C-ethylenephosphonate sugars **C** from simple acetobromosugars **A** and vinyl phosphonates **B** (R′=H) (Scheme 1). This highly stereoselective procedure leads to products with an α-configuration that predominates among naturally occurring compounds.[3]

Phosphonate esters are also useful building blocks in organic synthesis, e.g. for C=C bond formation from carbonyl precursors via the Horner–Wadsworth–Emmons (HWE) reaction,[4] for which α-phosphonoalkanoates are particularly attractive because they can be deprotonated easily under mildly

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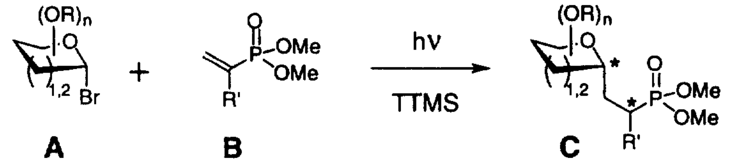


Scheme 1.

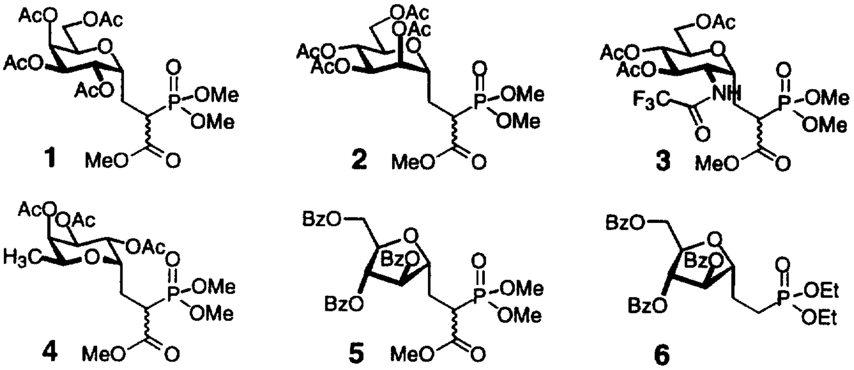


Figure 1. C-glycosidic phosphonates obtained by glycosyl radical addition to vinyl phosphonates

basic conditions. Here we apply our method for the stereoselective addition of glycosyl radicals to α-substituted vinyl phosphonates and demonstrate that the resulting functionalized C-glycosides are useful for the coupling to, e.g., glycosyl aldehydes along the HWE protocol.

The addition of nucleophilic glycosyl radicals to α,β-unsaturated carbonyl compounds in a free-radical chain reaction has been developed by Giese et al. as a practical method for the synthesis of C-glycosides.[5] While simple vinyl phosphonates proved less reactive than acrylates for the capture of glycosyl radicals,[3] phosphonoacrylates promised to be superior to both classes because of their strongly electrophilic nature.

Glycosyl radicals were generated from acylated halogenoses by irradiation in the presence of tris(trimethylsilyl)silane as a radical starter.[3] Trimethyl phosphonoacrylate was applied in stoichiometric quantities to restrict the formation of oligomeric adducts and to simplify purification.[3] Reactions were carried out on a 2.5–7.5 mmol scale, and products were isolated after complete conversion by flash chromatography in good to moderate yields. Presumably, some loss of material is due to the inevitable generation of TTMS-Br which may promote a partial ester cleavage.[6] Product composition was determined by high field NMR analysis of the crude reaction mixtures.

We have investigated acetate protected glycopyranosyl bromides of typical aldohexoses (**1**–**4**), including a deoxyaminosugar (**3**),[7] as well as a deoxysugar (**4**) (Fig. 1, Table 1). In each case, a typical high preference was found towards the axial pseudoanomeric C–C bond formation which can be explained by electronic interactions.[5] Owing to the prochiral nature of the acceptor, a second stereocenter adjacent to the ester functions is generated. Diastereoselectivity at this site is insignificant (dr ca. 1:1), however, this is likely to be because of the similar stereoelectronic properties of the phosphonate and carboxylate moieties of the alkene and because of the low steric influence of sugar substituents that are too remote at the transition state. These results are compatible to observations reported for the addition of glycosyl radicals to dehydroalanyl derivatives.[8]

Upon addition of the tribenzoylarabinofuranosyl radical, an exclusive formation of a *trans* configurated linkage resulted (**5**) which can be explained by the strong steric shielding effect of the 2-*O*-benzoyl group. In fact, when reacted with diethyl vinylphosphonate under similar conditions, adduct **6** formed with equally strong preference.[7] The latter phosphonate is a bioisosteric equivalent to β-furanoid fructose

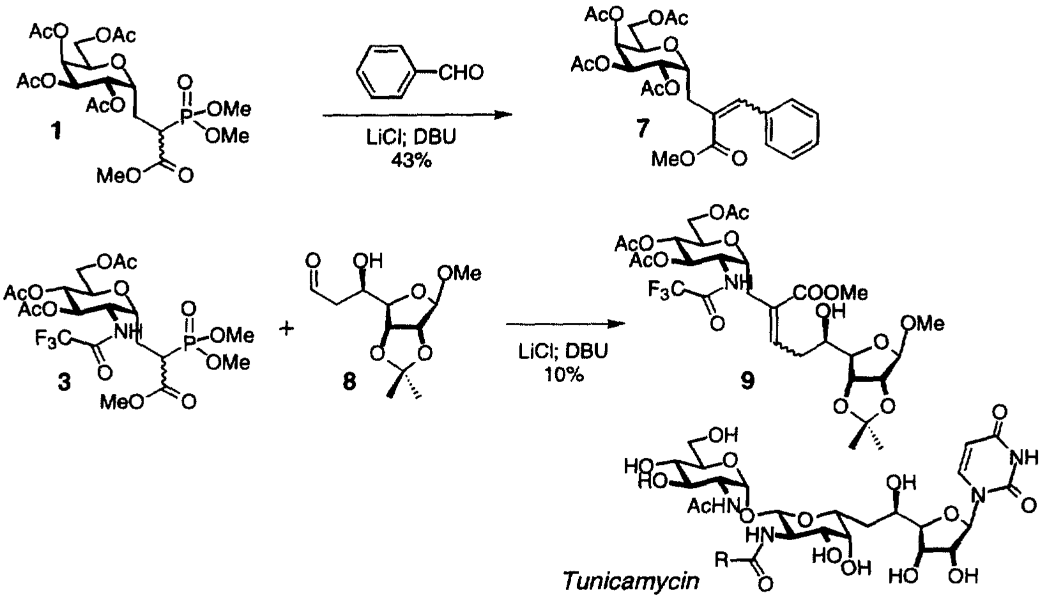
Table 1
Synthesis of C-glycosyl phosphonate esters[7]

Entry [a]	Configuration	Product	Yield (%) [b]	α/β Ratio [c]
1	*D-galacto*	**1**	80	98:2
2	*D-manno*	**2**	47	98:2
3	*D-gluco*	**3**	30	98:2
4	*L-fuco*	**4**	62	98:2
5	*D-fructo*	**5**	30	>99:1
6	*D-fructo*	**6**	27	>99:1

(a) All reactions were performed according to ref.[3] with complete conversion of the glycosyl bromide (24 h).
(b) Yields were determined after isolation by flash chromatography. (c) Determined by high field ^1H NMR analysis (assignments based on COSY spectra and $J_{4,5}$ coupling to pseudoanomeric α/β protons).

1-phosphate, except for a missing anomeric hydroxyl group, and is a source for potential inhibitors of enzymes from the glycolytic and pentose phosphate pathways, in particular of the phosphofructokinases.

Phosphonates **1** and **3** were chosen as substrates for the HWE reaction (Scheme 2). Due to the base instability of the acyl protecting groups, the ester enolate was generated using LiCl/DBU.[9] Condensation of **1** with benzaldehyde as a model acceptor provided the disubstituted acrylate **7** in 43% isolated yield (*E*:*Z* ratio ca. 1:1 by NMR analysis).[7]



Scheme 2.

For synthetic studies towards a hydrolytically stable analog of the dolichol-GlcNAc-transferase inhibitor *Tunicamycin*,[10] the β-hydroxyaldehyde **8** was synthesized in three steps from methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside via oxidation to the aldehyde,[11] Zn-mediated allyl addition (de >67%),[12] followed by ozonolysis in methanol (55% overall yield). From the HWE condensation of **3** and **8** in the presence of LiCl/DBU indeed the desired C-glycoside **9** (*E*:*Z* ratio ca. 1:1) was isolated,[7] albeit in only low yield (10%; unoptimized) which is probably due to the instability of **8** under basic conditions.

In conclusion, we have shown that the free-radical glycosylation is applicable to α-substituted vinyl phosphonates to generate functionalized C-glycosidic phosphonates with high pseudoanomeric selectivity. For C-glycofuranosyl phosphonates in particular, this technique provides a short and effective entry to potential inhibitors of carbohydrate metabolism. The α-phosphonoesters available from phosphonoacrylates are useful HWE components, which opens a rapid entry to highly functionalized C-glycosidic compounds containing two carbohydrate structural units.[13]

Acknowledgements

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7. NMR data of selected compounds: **3**: ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.89 (d, *J*=8.4 Hz, NH), 7.83 (d, *J*=8.7 Hz, NH), 5.18, 5.16 (2 t, *J*=6.7 Hz, 6-, 6′-H), 4.96, 4.92 (2 t, *J*=7.6 Hz, 7-, 7′-H), 4.42–4.29 (m, 8-, 8′-, 5-, 5′-H), 4.19 (m, 4-H), 4.12 (dd, *J*=3.7, 11.9 Hz, 9_a-, 9_a′-H), 4.10 (m, 4′-H), 3.99 (dd, *J*=3.7, 11.9 Hz, 9_b-, 9_b′-H), 3.84–3.76 (m, OCH_3), 3.28 (dddd, *J*=14.9, 9.4, 7.1, 2.0 Hz, 2′-H), 3.06 (ddd, *J*=23.8, 9.1, 3.4 Hz, 2-H), 2.46 (m, 3_a-H), 2.18 (m, 3_b-H, $3_{a,b}$′-H), 2.11, 2.08, 2.07, 2.06 (4 s, 9H, Ac). MS (EI; DEP) *m/z* (%): 580.1 (0.28) M^++H. **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–8.01 (m, 6H, H_{ar}), 7.63–7.29 (m, 9H, H_{ar}), 5.68 (dd, *J*=3.4, 2.2 Hz, 5-H), 5.48 (dd, *J*=3.4, 2.2 Hz, 4-H), 4.73 (dd, *J*=11.4, 6.0 Hz, 7-H_a), 4.68 (dd, *J*=11.4, 4.4 Hz, 7-H_b), 4.55 (ddd, *J*=4.7, 3.7, 3.4 Hz, 6-H), 4.36 (ddd, *J*=8.4, 5.0, 3.4 Hz, 3-H) 4.17–4.05 (m, 4H, OCH_2), 2.25–1.81 (m, 4H, 1-, 2-H), 1.31 (t, 6H, *J*=7.1 Hz, CH_3). MS (EI; DEP) *m/z* (%): 611.4 (0.01) M^++H. **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, $H'_{vinyl}(E)$), 7.44–7.22 (m, 5H, H_{ar}), 6.81 (s, H_{vinyl}), 5.45 (t, *J*=2.4 Hz, 7-H), 5.34 (t, *J*=3.4 Hz, 7′-H), 5.34 (dd, *J*=9.1; 5.4 Hz, 5-H), 5.25 (dd, *J*=9.4, 3.4 Hz, 6-H), 5.23 (dd, *J*=9.7, 5.0 Hz, 5′-H), 5.15 (dd, *J*=9.7, 3.4 Hz, 6′-H), 4.50 (ddd, *J*=9.7, 4.7, 4.4 Hz, 4-H), 4.43 (ddd, *J*=10.7, 4.7, 3.7 Hz, 4′-H), 4.21–3.92 (m, 8-, 8′-, 9-, 9′-H), 3.82, 3.62 (2 s, 2 OCH_3), 3.04 (dd, *J*=14.1, 10.4 Hz, 3_a′-H), 2.81 (dd, *J*=15.1, 10.8 Hz, 3_a-H), 2.73 (dd, *J*=14.1, 3.7 Hz, 3_b′-H) 2.66 (dd, *J*=15.1, 3.7 Hz, 3_b-H) 2.17, 2.12, 2.10, 2.08, 2.04, 2.01 (6 s, 12H, Ac). MS (FAB (+) DTE/DTT/Sul) *m/z* (%): 507.36 (12.84) M^++H.; **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J*=8.8 Hz, NH), 7.02 (d, *J*=8.7 Hz, NH), 6.72 (dd, 8.7, 6.7 Hz, 1′-H), 6.71 (dd, *J*=5.0, 2.4 Hz, 1-H), 5.05 (dd, *J*=6.7, 7.7 Hz, 12-H), 4.90 (t, *J*=6.0 Hz, 12′-H), 4.80, 4.79 (2 s, 1-, 1′-H), 4.78–4.64 (m, 13-, 13′-H), 4.48 (d, *J*=6.0 Hz, 2-H), 4.40 (d, *J*=5.7 Hz, 2′-H), 4.34–3.86 (m, 6H, 3-, 3′-, 4-, 4′-, 5-, 5′-, 10-, 10′-, 14-, 14′-, 15-, 15′-H), 3.58, 3.25, 3.16 (3 s, OCH_3), 2.62 (dd, *J*=14.0, 6.3 Hz, 9_a′-H), 2.52–2.20 (m, 3H, 3-, 3′-, 9_b-, 9_b′-H), 1.96, 1.92, 1.91, 1.90 (4 s, 9H, Ac), 1.32, 1.30, 1.18, 1.14 (4 s, OCH_3). MS (FAB (–) DTE/DTT/Sul) *m/z* (%): 698.81 (39.73) M^-.
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