Carbohydrate Analogues

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Carbohydrate-2-deoxy-2-phosphonates: Simple Synthesis and Horner–Emmons Reaction**

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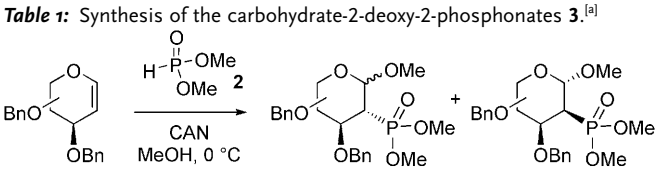
Glycosyl phosphates play an important role in the biosynthesis of oligosaccharides.[1] Therefore, there is ongoing interest in hydrolytically stable analogues that can be used as enzyme inhibitors.[2] Phosphonates that are linked by a methylene group to the 1- or 5-position of carbohydrates have turned out to be especially promising candidates.[2b,d,3] Phosphorus has also been introduced at the 2-position of carbohydrates by using 2,3-anhydrosaccharides as substrates, and the resulting phosphines have found application as enantiomerically pure ligands.[4] However, only less common altrose derivatives are available by using this strategy, as ring-opening of the intermediates always affords 2,3-diaxial products.

The chemistry of phosphorus-containing carbohydrates was described in several publications in the 1970s by Paulsen and co-workers, who investigated the introduction of phosphonates at the 2-position of pyranoses.[5] Furthermore, the great importance and current relevance of such compounds was demonstrated in a study reported in 2008 by Leonelli et al.[6] However, all previous syntheses required many steps and afforded products with additional functional groups. Carbohydrates in which only the oxygen atom at the 2-position has been substituted with a phosphonate group were hitherto unknown, although they best resemble naturally occurring saccharides. Herein we describe a simple and general synthesis of such analogues and their subsequent Horner–Emmons reaction with benzaldehyde.

For many years, during the course of our investigations on transition-metal-mediated radical reactions,[7] we have been interested in the addition of CH-acidic compounds to glycals.[8] Cerium (IV) ammonium nitrate (CAN) has proven to be the reagent of choice for radical generation and offers ready one-step access to C2-branched carbohydrates in good yields and high stereoselectivities. We recently extended the synthetic potential of our methodology through transformations of the side chain.[9] Surprisingly, despite the pioneering azidonitration of carbohydrates by Lemieux and Ratcliffe,[10] the addition of heteroatom radicals to glycals did not attract any further attention. Furthermore, the generation of phosphinyl radicals in the presence of CAN and their reaction with alkenes was hitherto unknown, although the corresponding formation of C–N, C–S, C–Se, and C–halogen bonds is well-established.[11]

We therefore investigated the transformation of dimethyl phosphite (**2**) with CAN and the *O*-benzyl-protected glycals **1**,[12] which are suitable precursors for radical C–C bond formation[9] and contain base-stable protecting groups (Table 1). Indeed, the reaction proceeded smoothly in methanol at 0 °C to afford carbohydrate-2-deoxy-2-phosphonates **3** in high yields in only one step. Complete conversion required 10 equivalents of the phosphite. However, **2** is one of the cheapest phosphorus reagents available and can be removed readily with a Kugelrohr apparatus after the reaction. All products were characterized unequivocally on the basis of the coupling constants in their ^{1}H NMR spectra and were isolated by column chromatography in analytically pure form (see the Supporting Information).

Table 1: Synthesis of the carbohydrate-2-deoxy-2-phosphonates **3**.[a]



Glycal	β-*anti*-**3** (yield [%])[b]	α-*anti*-**3** (yield [%])[b]	*syn*-**3** (yield [%])[b]
glucal (**1a**)	β-*gluco*-**3a** (64)	α-*gluco*-**3a** (8)	α-*manno*-**3a** (11)
galactal (**1b**)	β-*galacto*-**3b** (67)	α-*galacto*-**3b** (7)	α-*talo*-**3b** (9)
xylal (**1c**)	β-*xylo*-**3c** (61)	α-*xylo*-**3c** (8)	α-*lyxo*-**3c** (13)
arabinal (**1d**)[c]	α-*arabino*-**3d** (43)[c]	β-*arabino*-**3d** (32)[c]	β-*ribo*-**3d** (<5)[c]
maltal (**1e**)	β-*malto*-**3e** (53)	α-*malto*-**3e** (9)	α-*epi-malto*-**3e** (12)
lactal (**1f**)	β-*lacto*-**3f** (51)	α-*lacto*-**3f** (11)	α-*epi-lacto*-**3f** (14)

[a] For reaction conditions, see the Experimental Section. [b] Yield of the analytically pure product (isolated by column chromatography). [c] Opposite configurations at C2 and C3. Bn = benzyl.

From a mechanistic point of view, the reaction evidently proceeds via phosphonyl radicals generated from dimethyl phosphite and CAN. Orbital control is responsible for the highly regioselective attack at the 2-position of the glycal, and the methyl glycosides are formed by oxidation of the anomeric center to a cation and subsequent trapping by the solvent methanol. Importantly, addition reactions of dialkyl phosphites to glycals under acidic conditions proceed exclu-

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sively at the 1-position with an allylic shift;[13] thus, it is clear that the present reaction in the presence of CAN indeed occurs through a radical mechanism.

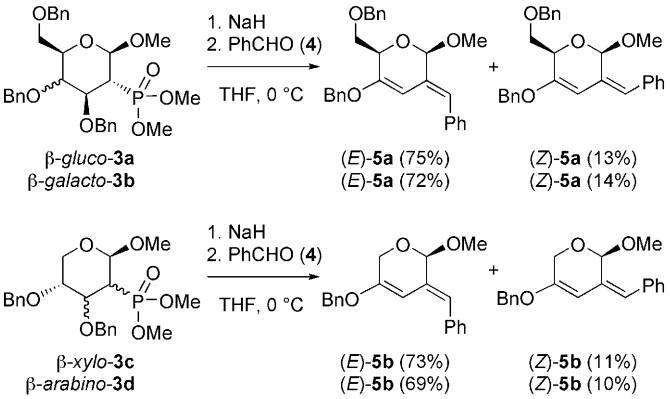
The stereoselectivities of the reactions are interesting, since two new stereogenic centers are formed in one step. In all examples, the phosphonyl radical attacked the double bond of the glycal **1** preferentially *anti* to the 3-*O*-benzyl group (Table 1). This preference can be rationalized on the basis of steric interactions. Carbohydrate-2-deoxy-2-phosphonates *syn*-**3**, obtained as by-products, were separated readily by column chromatography. Overall, the stereoselectivities of the radical reactions with dimethyl phosphite (**2**) are somewhat lower than those observed in the addition of malonates;[9b] however, they are in accordance with transformations with nitromethane,[9c,d] probably owing to the similar steric demand of the radical precursors.

In contrast to the *anti*/*syn* selectivities, the formation of anomeric methyl glycosides was initially surprising (Table 1). No α-*gluco* or α-*galacto* isomers were observed during the addition of malonates or nitromethane.[9] This difference can be rationalized by a weaker neighboring-group participation of the phosphonate substituent, which can not stabilize and shield the anomeric cation in a four-membered ring as effectively as an ester or a nitro group in a five-membered ring. Despite the product mixtures, all reactions afforded one main product, and the isomers could be separated by column chromatography and isolated in analytically pure form (see the Supporting Information).

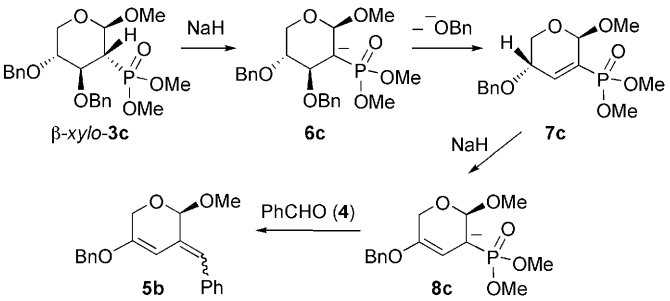
Subsequently, we investigated the Horner–Emmons reaction of the isolated main products β-*anti* **3** and selected benzaldehyde (**4**), which is very reactive in such C–C bond formations, as the carbonyl compound.[14] Despite the CH acidity of the 2-position, the reaction conditions had to be optimized carefully, as bases that were too strong led to decomposition products as a result of the lability of the carbohydrate. On the other hand, no conversion was observed with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which has been applied in Horner–Emmons reactions of carbohydrate phosphonates previously.[15]

The best conditions found for the deprotonation of the carbohydrate-2-deoxy-2-phosphonates **3a–d** were treatment with sodium hydride at 0 °C, which afforded two compounds **5** in good yields (Scheme 1). Interestingly, irrespective of the configuration of the starting material (*gluco*/*galacto* or *xylo*/*arabino*), product **5a** or **5b**, respectively, was obtained. This result is in accordance with the degradation of several stereogenic centers during the Horner–Emmons reaction. We established unequivocally by two-dimensional NMR spectroscopy that the products **5** had a 3,6-dihydro-2*H*-pyran structure with a 3-benzylidene group. *E*/*Z* isomers were separated by column chromatography and isolated in high yields in analytically pure form, and the configuration at the double bond was determined by NOE measurements (see the Supporting Information).

We explain the surprising formation of the C–C coupling products **5** by the mechanism depicted for *xylo*-**3c** in Scheme 2. In the initial step, the anion **6c** is generated by deprotonation. As a result of steric hindrance, **6c** eliminates the *O*-benzyl group in the 3-position faster than it reacts with



Scheme 1. Horner–Emmons reactions of the carbohydrate-2-deoxy-2-phosphonates **3** (see the Experimental Section).



Scheme 2. Proposed mechanism of the elimination during the Horner–Emmons reaction (shown for *xylo*-**3c**).

benzaldehyde. This cleavage of a neighboring protecting group is in accordance with transformations of carbanions at an anomeric center.[16] Because of the vinylogous phosphonate, the resulting unsaturated carbohydrate **7c** has an acidic hydrogen atom in the 4-position; deprotonation generates the intermediate **8c**. Only now does the Horner–Emmons reaction with benzaldehyde (**4**) occur to afford the final product **5b**. The preferential formation of the *E*-configured double bond can be rationalized on the basis of steric interactions with the methoxy group and supports the postulated elimination of the 3-*O*-benzyl substituent prior to the C–C coupling step.

To suppress fragmentation reactions during the Horner–Emmons reaction, the *O*-benzyl protecting groups were removed from β-*gluco*-**3a** by catalytic hydrogenation,[17] and the free carbohydrate-2-deoxy-2-phosphonate was isolated in 87% yield in analytically pure form (see the Supporting Information). However, even the deprotonation of this substrate with sodium hydride resulted only in decomposition products. This decomposition can be explained by the required excess of base and poor solubility of the tetraanion in organic solvents. All the same, this deprotection gave a water-soluble carbohydrate–phosphorus analogue: an important compound for future biological studies.

In summary, we generated phosphonyl radicals with cerium(IV) ammonium nitrate and succeeded in their addition to glycals for the first time. Thus, carbohydrate-2-deoxy-2-phosphonates became available in only one step in good

yields and stereoselectivities. Hexoses, pentoses, and disaccharides could be used in this procedure, and all products were isolated in analytically pure form. An interesting fragmentation took place during the Horner–Emmons reaction with benzaldehyde, which afforded multiply unsaturated products by a mechanism involving consecutive deprotonation–elimination steps. The conjugated π systems obtained should be suitable for further transformations and have promising photophysical properties. Since glycals can be synthesized on a multigram scale or are even commercially available, and dimethyl phosphite is one of the cheapest phosphorus reagents, relatively large amounts of the carbohydrate–phosphorus derivatives are accessible. The biological activity of these carbohydrate analogues will be investigated in future studies.

Experimental Section

General procedure for the synthesis of **3**: A solution of **1** (1.0 mmol) and dimethyl phosphite (**2**; 1.1 g, 10.0 mmol) in methanol (5 mL) was cooled to 0 °C under an argon atmosphere, and a solution of cerium(IV) ammonium nitrate (2.2 g, 4.0 mmol) in methanol (15 mL) was added dropwise until conversion was complete (TLC, approximately 4 h). The reaction mixture was stirred for a further 30 min at 0 °C, and then an ice-cold dilute solution of sodium hydrogen sulfite (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the excess of dimethyl phosphite was removed at 0.01 mbar and 120 °C with a Kugelrohr apparatus. The crude product **3** was purified by column chromatography on silica gel (cyclohexane/ethyl acetate/methanol 4:2:1).

General procedure for the Horner–Emmons reactions**:** A solution of **3** (1.0 mmol) in anhydrous THF (5 mL) was cooled to 0 °C under an argon atmosphere. Sodium hydride (70 mg, 3.0 mmol) was added at this temperature, and stirring was continued for 10 min. A solution of benzaldehyde **4** (320 mg, 3.0 mmol) in anhydrous THF (5 mL) was then added dropwise until conversion was complete (TLC, 1 h). The reaction mixture was stirred for a further 30 min at 0 °C and then quenched with a dilute solution of ammonium chloride (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product **5** was purified by column chromatography (cyclohexane/ethyl acetate 8:1). All compounds **3** and **5** were isolated in analytically pure form and characterized completely (see the Supporting Information).

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