Synthesis of Glycosyl Phosphonates by Michael-Type Addition to 2-Nitroglycals

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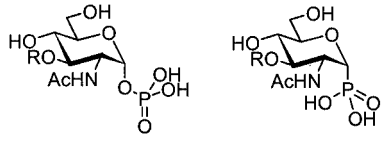
A new synthetic strategy, which allows to synthesize both α- and β-anomers of 2-acetylaminoglycosyl phosphonate or exclusively β-anomer is described. The present strategy is a successful Michael-type addition of dimethyl hydrogen phosphonate to 2-nitroglycals.

Introduction

During the last several years there has been considerable interest in the preparation and investigation of phosphonic acids and their derivatives that might be considered to be analogues of naturally occurring phosphates.[1] It is understood that the carbon−phosphorus bond is incapable of being hydrolyzed by the enzymes involved in phosphate cleavage. Thus, the use of phosphonic acids as analogues of natural phosphates represents a systematic approach to metabolic regulation, enhancement or inhibition studies.



R = myristoyl moiety

The outer surface of the outer membrane of *Escherichia coli* and other Gram-negative bacteria is made up primarily of lipid A, the hydrophobic anchor for lipopolysaccharides. Lipid A is essentially a β-(1′-6)-linked D-glucosamine disaccharide carrying phosphate residues at C-1 and C-4′, and several *N*- and *O*-bound long-chain acyl groups.[2] Lipid X (**I**), a monosaccharide isolated from *E. coli* mutants, is a biosynthetic precursor of Lipid A corresponding to the reducing end.[3] Although it was identified in 1984, the function of the phosphate group at C-1 is not fully understood. Therefore, synthesis of phosphonate analogues of type **II** might help to study the function of the phosphate group.

Vasella et al.[4−6] described the synthesis of such a type of nonisosteric glycosyl phosphonate analogues starting from 2-azido-2-deoxy sugars, employing the trichloroacetimidate method. In continuation of our work on Michael-type addition of various nucleophiles to 3,4,5-tri-*O*-benzyl-2-nitroglycals,[7−14] we now wish to report a convenient synthesis of such nonisosteric phosphonate analogues by Michael-type addition of dimethyl hydrogen phosphonate to 2-nitroglycals.

Results and Discussion

A straightforward way to synthesize the desired phosphonate analogues is Michael-type addition of $HPO(OMe)_2$ to 2-nitroglycals. The advantage of this method is mainly due to the easy preparation of the starting material in high yields and the convenient transformation of the nitro group into the corresponding amino group and hence, into an acylamino group. Treatment of 3,4,5-tri-*O*-benzyl-2-nitrogalactal with $HPO(OMe)_2$ in the presence of potassium *tert*-butoxide in toluene yielded the corresponding glycosyl phosphonates **2** and **3** in the ratio of 1:1.2 in 82% yield. Careful examination of the reaction revealed that the anomeric (α/β) ratio varies with time. A ratio of 1:1.2 for α/β was observed after 5 min at 0 °C, but after 2 h at the same reaction temperature only the β-product was observed in 60% yield, which indicates that the α-anomer was slowly transformed under basic reaction conditions into the thermodynamically more stable β-anomer presumably by ring opening to intermediate **A** followed by ring closure (Scheme 1).

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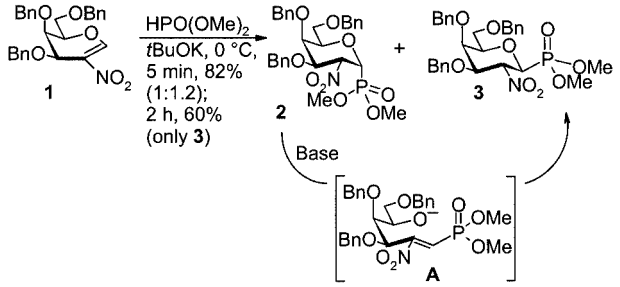
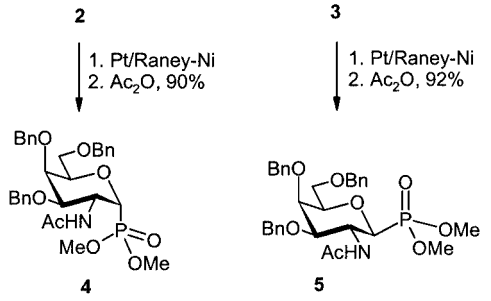


Scheme 1. Michael-type addition of $HPO(OMe)_2$ to 2-nitrogalactal **1**

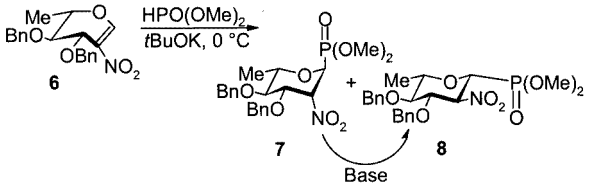
The anomeric configuration is evident from the ^1H and ^{13}C NMR spectroscopic data. In the ^1H NMR spectra, the signal of 1-H of **2** appears at $\delta = 4.7$ ppm ($^3J_{1,2} = 7.1$ Hz) and for **3** at $\delta = 4.19$ ppm ($^3J_{1,2} = 10.2$ Hz). In the ^{13}C NMR spectra, the C-1 signals for **2** and **3** appear at $\delta = 70.6$ and 73.5 ppm, respectively; the signal for the α-anomer **2** occurs at a higher field than that for the corresponding β-anomer **3**.

By employing different weak bases and lowering the reaction temperature, the same result was obtained. Reduction of the nitro group in compounds **2** and **3** with the use of platinized Raney nickel in ethanol yielded the corresponding amines, which were acetylated to give the known compounds **4** and **5** in 90 and 92% yield, respectively,[4] as shown in Scheme 2. The spectroscopic data are identical to literature values.[4]



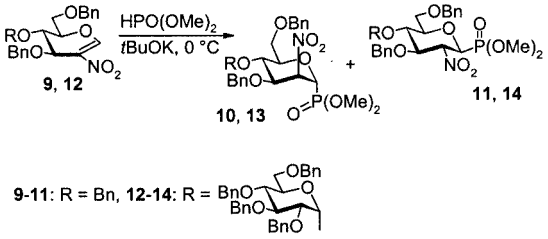
Scheme 2. Conversion of 2-nitrogalactosyl phosphonate to 2-(acetylamino)galactosyl phosphonate

Reaction of 2-nitrorhamnal **6** with $HPO(OMe)_2$ at 0 °C yielded the corresponding glycosyl phosphonates **7** and **8** in 5 min and with a ratio of 1:1.2 (α/β) in 80% yield. After 2 h, only product **8** was isolated in 55% yield (Scheme 3 and Table 1).



Scheme 3. Michael-type addition of $HPO(OMe)_2$ to 2-nitrorhamnal **6**

On the other hand, reaction of 2-nitroglucal **9** with $HPO(OMe)_2$ at 0 °C for 5 min yielded mannose-configured α-anomer **10** and glucose-configured β-anomer **11** in a ratio of 1:1.2 in 81% yield (Scheme 4 and Table 1). A prolonged reaction time yielded only the β-anomer **11** in 80% yield, as was the case for the galactal derivative. The structures of **10** and **11** were deduced from their ^1H and ^{13}C NMR spectroscopic data. In the ^1H NMR spectra of compound **10**, the signal for 1-H appears at $\delta = 4.63$ ($^3J_{1,2} = 2.6$ Hz) and in the spectra of **11** at $\delta = 4.18$ ppm ($^3J_{1,2} = 9.1$ Hz), whereas the signal for 3-H for **10** appears at $\delta = 4.31$ ppm ($^3J_{3,4} = 8.3$, $^3J_{3,2} = 5.1$ Hz) and that for **11** at $\delta = 4.22$ ppm ($^3J_{3,4} = {}^3J_{3,2} = 9.1$ Hz). Likewise, reaction of 2-nitromaltal **12** also yielded the same result. After 5 min at 0 °C, the products obtained were **13** and **14** in a ratio of 1:1.5, and after 2 h, only β-*gluco*-configured **14** was found. All compounds were characterized by spectral and analytical means.



Scheme 4. Michael-type addition of $HPO(OMe)_2$ to 2-nitroglucals **9** and **12**

Conclusion

In conclusion, an efficient and very simple method for the synthesis of various glycosyl phosphonates by Michael-type addition of $HPO(OMe)_2$ to 2-nitroglycals in high yields is described. Applications of this methodology to synthesize various phosphonate analogues of glycosyl con-

Table 1. Results obtained with 2-nitroglycals **6**, **9**, and **12**

Starting compound	Reaction time	Products	Yield [%]	Reaction time	Yield [%]
6	5 min	**7** + **8**	81 (1:1.2)	2 h	55 (only **8**)
9	5 min	**10** + **11**	80 (1:1.2)	2 h	80 (only **11**)
12	5 min	**13** + **14**	80 (1:1.5)	2 h	80 (only **14**)

jugates and glycopeptides are under progress in our laboratory.

Experimental Section

General Remarks: Solvents were purified according to standard procedures. NMR spectroscopic measurements were performed at 22 °C with a Bruker DRX600 instrument. TMS or the resonance of the deuterated solvent was used as internal standard. $CDCl_3$ (δ = 7.24 ppm) was used as external standard. MALDI mass spectra were recorded with a Kratos Kompact Maldi 1 instrument, and 2,5-dihydroxybenzoic acid (DHB) or 6-aza-2-thiothymine (ATT) were used as matrices. Optical rotations were measured with a Perkin−Elmer polarimeter 241/MS in a 1-dm cell at 22 °C. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plastic plates or Merck amino phase glass plates. Compounds were visualized by treatment with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL). Flash chromatography was performed on J. T. Baker silica gel 60 (0.040−0.063 mm) at a pressure of 0.3 bar.

General Experimental Procedure for the Synthesis of 2, 3, 7, 8, 10, 11, 13 and 14: To a stirred solution of the 2-nitroglycal (1 mmol) and $HPO(OMe)_2$ (1.1 mmol) in dry toluene at 0 °C was added potassium *tert*-butoxide (1 mmol), and the resulting solution was stirred for 5 min. The solvent was then evaporated under reduced pressure, followed by extraction of the residue with ethyl acetate, washing of the combined extracts with dild. HCl, water, brine, and drying with anhydrous $MgSO_4$. After filtration, evaporation of the solvent gave the corresponding glycosyl phosphonates; provided are isolated yields.

General Experimental Procedure for the Synthesis of 4 and 5: To a stirred solution of freshly prepared Pt/Raney nickel (1 g) in ethanol was added the phosphonate **2** or **3**, and the mixture stirred under hydrogen overnight. Filtration of the catalyst and evaporation of the solvent yielded the corresponding amines, which were dissolved in acetic anhydride (5 mL) and stirred overnight at room temperature. Evaporation of the acetic anhydride, followed by flash column purification afforded the 2-acetylamino-2-deoxygalactosyl phosphonates **4** and **5**.

Supporting Information: Data for **2**, **3**, **7**, **8**, **10**, **11**, **13** and **14**.

Acknowledgments

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