Pergamon

Tetrahedron Letters 40 (1999) 4247–4250

TETRAHEDRON
LETTERS

Synthesis of glycosyl phosphates from acetylated glycosyl nitrates

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Received 18 February 1999; accepted 6 April 1999

Abstract. Acetylated α-glycosyl nitrates were efficiently converted under mild conditions into protected β-glycosyl phosphates by treatment with cesium dibenzyl phosphate or into thermodynamically more stable α-glycosyl phosphate derivatives upon interaction with cesium diphenyl phosphate. These reactions were found to be applicable both to 2-azido-2,6-dideoxy- and 2-azido-2-deoxygalactopyranosyl nitrates as well as to 6-deoxygalactopyranosyl and galactopyranosyl derivatives.

Keywords: carbohydrates; phosphoric acid and compounds; nitric acid and compounds; cesium and compounds

Glycosyl phosphates serve as important intermediates in the synthesis of nucleoside and polyprenyl (glycosyl diphosphates) participating in enzymic synthesis of oligo- and polysaccharides (for reviews see Refs. [1-3]). Different approaches may be applied to the chemical synthesis of glycosyl phosphates (see Ref. [4] for a recent review). Here, we wish to report a useful addition to the existing methods, namely, that in many cases readily available acetylated glycosyl nitrates may be used for an efficient preparation of glycosyl phosphates.

In connection with our present studies on biosynthesis of capsular polysaccharides from *Staphylococcus aureus*, we were interested in the chemical synthesis of putative biosynthetic precursors for the type 5 and 8 polysaccharides. These polymers contain residues of both *N*-acetyl-D- and -L-fucosamine and, as was suggested some time ago [1], the activated forms of these monosaccharides would be derived from 2-acetamido-2,6-dideoxy-α-D- and -β-L-galactopyranosyl phosphates, respectively. To prepare these phosphates, we have chosen a strategy based on the use of the corresponding 2-azidoderivatives to allow incorporation of a radioactive label in the last step(s) of the synthesis through *N*-acetylation with radioactive acylation reagents.

The nitrate **1** easily obtainable through azidonitration of 3,4-di-*O*-acetyl-L-fucal [5] was used as a starting material in the L-series. We found that treatment of **1** with cesium dibenzyl phosphate (1.5 eq) under

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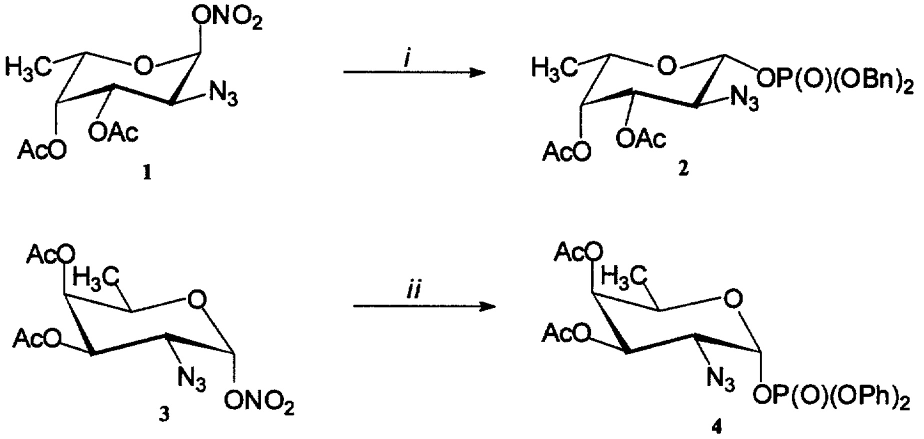
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00698-X

mild conditions (2 h, r. t., DMF) led to an efficient formation of the β-phosphate **2** in an isolated yield of 80% after flash chromatography on SiO_2 (Scheme 1). The product was shown to be identical with that prepared recently [6] from the initial azidonitration products through their conversion into the corresponding bromide and its interaction with dibenzyl phosphate/Ag_2CO_3.

Scheme 1



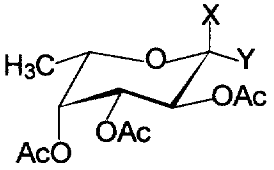
Reagents: *i* $CsOP(O)(OBn)_2$; *ii* $CsOP(O)(OPh)_2$

On the other side, when cesium diphenyl phosphate (1.5 eq) was used for the reaction with α-D-glycosyl nitrate **3** [7] (obtained in 65% yield through azidonitration of the D-fucal derivative), the α-diphenyl phosphate **4** [7] was isolated as a single product (78% after chromatography on SiO_2) after 5 h at r. t. In this case, the addition of 18-crown-6 was necessary to increase solubility of the reagent in DMF.

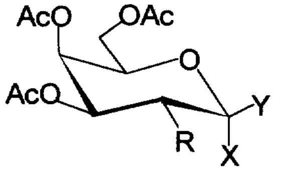
So it turns out that the use of cesium salts of phosphodiesters, readily available upon treatment of the corresponding acids with cesium carbonate in MeCN, results in efficient conversion of glycosyl nitrates into glycosyl phosphate derivatives of desired anomeric configuration. These reactions took place under mild conditions in homogeneous solution. The acceleration of S_N2 displacement reactions with cesium salts of weak acids is well known ("cesium effect" [8]) but was not used previously for phosphotriester synthesis.

As shown in Table 1, the reactions may be successfully applied to other glycosyl nitrates. In the case of the α-L-fucopyranosyl derivative **5a**, prepared by treatment of tetra-*O*-acetyl-L-fucopyranose with 100% HNO_3 (DCM, 5 h, 0 °C), the formation of the β-phosphate **5b** in reaction with cesium dibenzyl phosphate occurred under conditions quite similar to those used for the preparation of **1**, whereas transformation of acetylated α-D-galactopyranosyl nitrate **6a** and 2-azido-2-deoxy-α-D-galactopyranosyl nitrate **7a** required slightly more prolonged duration of the process.

Table 1. Conversion of glycosyl nitrates into glycosyl phosphates.



5a-c



6a-c R=OAc; **7a-d** R=N_3

a X= ONO_2, Y= H; **b** X= H, Y= $OP(O)(OBn)_2$; **c** X= $OP(O)(OPh)_2$, Y= H; **d** X= H, Y= $OP(O)(OPh)_2$

Glycosyl nitrate	Reagents[#] and conditions	Glycosyl phosphate	Yield, %
5a [9]	*i*, DMF, 3 h, r. t.	**5b** [6]	64
	ii, 18-crown-6, DMF, 12 h, r. t.	**5c** [10]	60
6a [11]	*i*, DMF, 12 h, r. t.	**6b** [12]	75
	ii, 18-crown-6, DMF, 12 h, 50 °C	**6c** [10b]	60
7a [13]	*i*, DMF, 12 h, r. t.	**7b** [9]	89
	ii, 18-crown-6, DMF, 2 h, 50 °C	**7c** + **7d**, (1:1) [14]	72
	ii, 18-crown-6, DMF, 2 h, 50 °C, followed by 12 h, 37 °C	**7c** + **7d**, (4:1)	63

[#] For *i* and *ii* see a legend to Scheme 1.

With cesium diphenyl phosphate as a reagent, the difference in reactivity of the glycosyl nitrates seems more significant. Formation of the α-phosphate **5c** from **5a** required longer reaction time than conversion of **3** into **4**. Reactions with **6a** and **7a** occurred at elevated temperature. In the latter case, the β-diphenyl phosphate **7d** seems to be formed initially and then further converted into thermodynamically more stable **7c**.

In conclusion, new reactions for the synthesis of protected glycosyl phosphates from glycosyl nitrate derivatives were demonstrated on several examples of monosaccharides. These reactions seem to be quite useful preparatively and may be of interest for mechanistic studies of the glycosyl phosphate formation. Apparently, cesium salts of phosphodiesters may serve as efficient reagents for other nucleophilic displacement reactions. Particularly, we were able to demonstrate an efficient formation of **5b** (82%) after reaction of cesium dibenzyl phosphate with tri-*O*-acetyl-α-L-fucopyranosyl bromide under similar conditions (DMF, 1 h, r. t.).

Acknowledgements. The authors thank Mr. Valentin P. Ananikov for recording the NMR spectra. This work was supported by the Wellcome Trust Foundation (Grant 049419/Z/96/Z) and Russian Foundation for Basic Research (Project 96-03-32473).

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7. Selected data for **3**: m.p. 118-119 °C, IR: ν_{max} 2115 (N_3), 1665 cm^{-1} (ONO_2), $[\alpha]^{28}_D$ +129.6° (c 1.0, $CHCl_3$). For **4**: m.p. 92-93 °C, IR: ν_{max} 2115 cm^{-1} (N_3), $[\alpha]^{24}_D$ +71.3° (c 1.0, $CHCl_3$), NMR ^1H (C_6D_6): δ 6.1 (dd, $J_{1,2}$ = 3.1 Hz $J_{1,P}$ = 6.2 Hz, 1H, H-1), 3.62 (ddd, $J_{2,P}$ = 3.1 Hz, $J_{2,3}$ =11.1 Hz, 1H, H-2), 0.78 (d, $J_{5,6}$ = 6.6 Hz, 3H, H-6); ^{13}C ($CDCl_3$): 97.2 (d, $J_{1,P}$ = 5.5 Hz, C-1), 57.4 (d, $J_{2,P}$ =8.7 Hz, C-2), 15.6 (CH_3); ^{31}P ($CDCl_3$): –12.66.
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9. Selected data for new compounds: **5a**, m.p. 79-80 °C, IR: ν_{max} 1650 cm^{-1} (ONO_2), $[\alpha]^{29}_D$ –142.3° (c 1.5, $CHCl_3$), NMR ^1H ($CDCl_3$): δ 6.43 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-1), 1.18 (d, $J_{5,6}$ = 6.6 Hz, 3H, H-6); ^{13}C ($CDCl_3$): 96.4 (C-1), 70.2 (C-5), 67.9 (C-3), 67.4 (C-4), 65.6 (C-2), 15.8 (C-6); **7b**, $[\alpha]^{29}_D$ –3.86° (c 1.5, $CHCl_3$), NMR ^1H ($CDCl_3$): δ 3.83 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.7 Hz, 1H, H-2); ^{13}C ($CDCl_3$): 97.5 (d, $J_{1,P}$ = 4,8 Hz), 60.8(d, $J_{2,P}$ = 6,8 Hz); ^{31}P ($CDCl_3$): –2.12.
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14. ^1H NMR in $CDCl_3$ indicated the isolated product to be a mixture of α- and β-anomers: **7c**, δ 6.02 (dd, $J_{1,2}$ =3.6 Hz, $J_{1,P}$ = 6.2 Hz, H-1), 4.86 (dd, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.4 Hz, H-3); **7d**, δ 5.30 (dd, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ =3.2 Hz, H-3), 5.23 (t, $J_{1,2}$ = $J_{1,P}$ = 7.6 Hz, H-1).