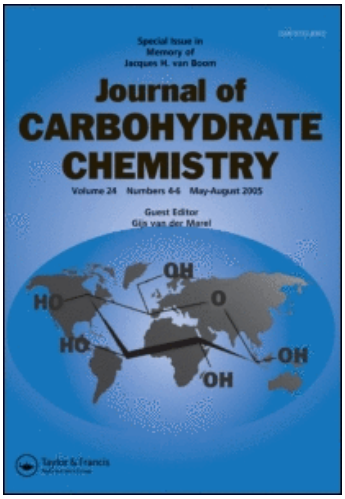

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A Highly Stereoselective Synthesis of *N*-Alkyl(2-deoxy-β-D-*arabino*-hexopyranosyl)amines Via 2-Deoxyglycosyl Phosphorodithioates as Glycosyl Donors

Maria Michalska[a]; Wieslawa Kudelska[a]; January Pluskowski[a]; Mariolo Nowińska[a]; Anna Juszczak[a]
[a] Laboratory of Organic Chemistry, Institute of Chemistry, Medical University, Lódź, Poland

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A HIGHLY STEREOSELECTIVE SYNTHESIS OF *N*-ALKYL(2-DEOXY-β-D-*ARABINO*-HEXOPYRANOSYL)AMINES VIA 2-DEOXYGLYCOSYL PHOSPHORODITHIOATES AS GLYCOSYL DONORS

Maria Michalska,* Wiesława Kudelska, January Pluskowski,
Mariolo Nowińska and Anna Juszczak

Laboratory of Organic Chemistry, Institute of Chemistry,
Medical University, Muszyńskiego 1, 90-151 Łódź, Poland

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ABSTRACT

This work demonstrates a new application of 2-deoxy-α-**D**-glycosyl phosphorodithioates **1** as glycosyl donors in the synthesis of *N*-alkyl-(2-deoxy-**D**-*arabino*-hexopyranosyl)amines **3**. The reaction of **1** with amines **2** proceeds with high β-stereoselectivity, at ambient temperature, in almost quantitative yield.

INTRODUCTION

The search for biologically active compounds related to nucleosides has resulted in an increase in the synthesis of various types of glycosylamines. Recently, synthetic efforts have concentrated on sugar-modified nucleosides that contain pento- or hexopyranosyl residues differing in substitution patterns.[1] In contrast to other types of glycosylamines, *N*-alkyl(2-deoxyhexopyranosyl)amines have received little attention. The only existing method, introduced by Van Doren *et al.*,[2] describes the reaction of unsubstituted 2-deoxysugars with long-chain aliphatic amines. The β-glycosylamines produced by this method are contaminated with 10-15% of the α-isomers. In this paper

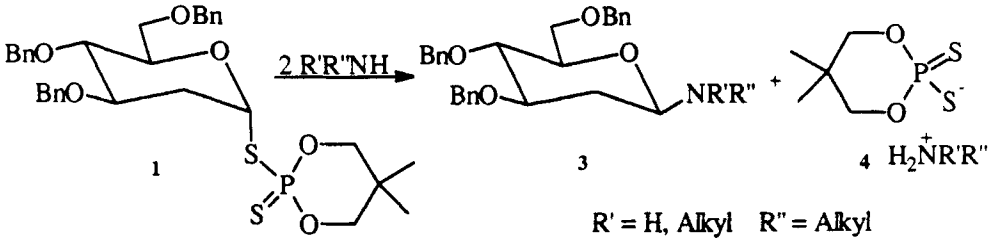
we describe an alternative, highly stereoselective synthesis of *N*-alkyl(2-deoxy-β-**D**-*arabino*-hexopyranosyl)amines.

RESULTS AND DISCUSSION

Our method utilizes *S*-(3',4',6'-tri-*O*-benzyl-2'-deoxy-α-**D**-*arabino*-hexopyranosyl)-5,5-dimethyl-1,3,2-dioxa-2-thiolo-2-phosphorinane (**1**) as a glycosyl donor[3] and a variety of primary and secondary aliphatic and alicyclic amines as glycosyl acceptors. (Scheme 1).

The glycosyl donor **1** was prepared by addition of 5,5-dimethyl-1,3,2-dioxa-2-thiolo-2-thioxo-phosphorinane[4] to 3,4,6-tri-*O*-benzyl-**D**-glucal[5] according to the procedure developed in our laboratory.[6a,b] In this case the addition is fully regio- and stereoselective and gives **1** as a stable, crystalline, odorless and easy-to-store reagent. The α-configuration of the dithiophosphate **1** was confirmed by ^{1}H NMR spectroscopy (See Experimental Section) and is in accord with the observed high positive specific rotation value characteristic of α-glycosides of the **D**-glucose series.

The reaction of the dithiophosphate **1** with primary and secondary amines **2a-2h** (Table I) proceeds smoothly when one molar equivalent of **1** is allowed to react with two molar equivalents of the acceptor **2** in acetonitrile or methylene chloride solution at 20 °C. The progress of the glycosylation process is conveniently monitored by ^{31}P NMR spectroscopy and TLC. The separation of the reaction products described in the experimental part is very straightforward, and the yields of the glycosylamines **3** thus obtained are quantitative according to ^{31}P and ^{13}C NMR spectroscopic analysis of the crude reaction mixtures. The time necessary to complete the glycosylation reaction



Scheme 1

Table I. Selected NMR and Physical Data for *N*-Alkyl(2-deoxy-β-D-*arabino*-hexopyranosyl)amines **3(a-h)**.

Glycosyl acceptors **2(a-h)**	β-Glycosyl amines **3(a-h)**	$\delta^{13}C$ C-1	C-2	C'-N	$\delta^{1}H$ H-1	($J_{1,2a}$; $J_{1,2e}$)	IR $\nu_{NH}cm^{-1}$
2a Cyclohexylamine	**3a**	83.61	37.92	52.40	4.15	(9.2; 1.0)	3240
2b Isobutylamine	**3b**	87.19	37.77	53.75	4.00	(10.0; 2.0)	3340
2c *n*-Butylamine	**3c**	86.67	37.70	45.39	3.95	(10.0; 2.0)	3260
2d Piperidine	**3d**	91.65	33.61	48.76	3.88	(9.5; 4.0)	-
2e Morpholine	**3e**	91.07	33.61	48.25	3.86	(10.0; 3.5)	-
2f Pyrrolidine	**3f**	87.94	36.20	47.33	4.00	(10.0; 3.0)	-
2g Benzylamine	**3g**	85.70	37.62	49.27	4.05	(10.0; 1.5)	3250
2h 1,6-Diaminohexane	**3h**	86.67	38.14	45.16	4.00	(10.0; 1.0)	3290-3350 broad band

depends on the amine used and the amine-glycosyl donor ratio. Reaction carried out with an excess of amine, under solvolytic conditions, is complete within 5-50 minutes. When glycosylation takes place in solution and stoichiometric amounts of reactants are employed, the time needed is considerably longer (up to 12 h). From a practical point of view, however, solvolytic conditions are restricted to the glycosylation of volatile amines.

The procedure leads with high stereoselectivity to β-glycosylamines **3**. The β-configuration of the *N*-alkyl(3,4,6-tri-*O*-benzyl-2-deoxy-**D**-*arabino*-hexopyranosyl)amines was assigned by chemical shift values and coupling constants corresponding to the anomeric proton (Table I). ^{13}C NMR spectra of the crude reaction mixtures confirmed that the β-glycosylamines **3** are formed stereoselectively.[8] The high degree of inversion at the anomeric center suggests an S_N2 mechanism for the above glycosylation process. A remarkable feature of the described procedure is that *S*-(2-deoxyglycosyl)-phosphorodithioates do not need activation by promoters in the reaction with aliphatic amines.

In conclusion, the present method affords a highly stereoselective procedure for the construction of β-*N*-glycosylic linkages in the 2-deoxyhexopyranose series. It also demonstrates the versatility of 2-deoxyglycosyl phosphorodithioates as glycosyl donors that can be applied to the synthesis of 2-deoxy-*O*-glycosides as well as 2-deoxyglycosyl amines.

EXPERIMENTAL

Melting points were determined with a Boetius PHKM 05 apparatus and are uncorrected. Optical rotations were determined in chloroform with a Polamat A polarimeter. IR spectra were obtained by using a Unicam SP-200 G Spectrophotometer. ^{31}P NMR spectra were measured in $CHCl_3$ with H_3PO_4 as external standard on a Bruker 360 instrument operating at 81.01 MHz. ^1H NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standard (with Bruker 300 MHz and Varian 60 MHz spectrometers). ^{13}C NMR spectra were determined on solutions in $CDCl_3$ with a Tesla BS 567A spectrometer operating at 25.2 MHz, Bruker 200 operating at 50.32 MHz and Bruker 360 operating at 90.55 MHz. Chemical shifts are given in parts per million; the coupling

constants are expressed as J values in units of Hz. Elemental Analyses were performed by the Micro-analytical Laboratory, Institute of Chemistry, Medical University, Łódź. TLC was performed on Merck silica gel plates $60F_{254}$ with benzene, acetone, chloroform 3:1:1 as the developing solvent. Detection was effected by exposure to iodine vapors. Amines were distilled from Na or CaH_2. Acetonitrile and dichloromethane were dried and redistilled.

Synthesis of 2-*S*-(3',4',6'-tri-*O*-benzyl-2'-deoxy-α-D-*arabino*-hexo-pyranosyl)-5,5-dimethyl-1,3,2-dioxa-2-thiolo-2-thioxophosphorinane (1). 3,4,6-Tri-*O*-benzyl-D-glucal (0.416; 1 mmol) and 5,5-dimethyl-1,3,2-dioxa-2-thiolo-2-thioxophosphorinane (0.198 g; 1 mmol) were dissolved in dry benzene (5 mL) and allowed to react at 20 °C until TLC showed no starting sugar component. The reaction mixture was washed with water (2 x 3 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The syrupy residue was triturated with diethyl ether to give colorless crystals of **1**, mp 96-98 °C, 0.5 g, 81.4%. The crude product was purified by crystallization (EtOH): mp 99.5-100.5 °C; $[\alpha]_{578}^{20}$ = +156.5 (*c*, 1.4); ^{31}P NMR δ 83.79. ^{1}H δ 6.07 ($J_{1,2a}$ = 4.5 Hz, $J_{1,2e}$ = 1.5 Hz and $J_{1,P}$ = 11.0 Hz, H-1'), 2.52-2.45 (H-2'e), 2.22-2.11 (H-2'a), 1.20, 0.80 (2 x CH_3); ^{13}C NMR δ 78.53 (C-1'), 37.17, 37.47 (J = 7.5 Hz, C-2'), 32.32, 32.10 (J = 5.6 Hz, C-5) 22.09 (CH_3,a), 20.75 (CH_3,e), 128.33-127.65 (C_6H_5).

Anal. Calcd for $C_{32}H_{39}O_6PS_2$: C, 62.52; H, 6.39; P, 5.03; S, 10.43. Found: C, 62.72; H, 6.41; P, 5.11; S, 10.64.

General procedure for glycosylation

Procedure A. A solution of the dithiophosphate **1** (1 mmol) and amine **2a-2h** (2 mmol) in dry CH_3CN (5 mL) or CH_2Cl_2 (5 mL) was kept at room temperature in a moisture-free atmosphere until TLC and ^{31}P NMR analysis showed complete conversion of **1**. The solvent was evaporated *in vacuo* (below 30 °C) and the syrupy residue was triturated with cold diethyl ether (20 mL). The salt **4** was filtered off and the filtrate washed twice with cold water, dried ($MgSO_4$) and concentrated *in vacuo*.

Procedure B. The dithiophosphate **1** (1 mmol) was dissolved in dry amine **2a-2g** (3 mL) with cooling. The mixture was stirred at 20 °C until TLC and ^{31}P NMR analysis showed complete conversion of **1**. The excess of amine was evaporated *in vacuo* and the residue containing the glycosyl amine **3** and the salt **4** was worked up as in procedure A.

***N*-Cyclohexyl(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)amine (3a).** Prepared by procedure B, time: 50 min, yield, 63.8% as colourless crystals, mp 43-45 °C (ethyl acetate - *n*-hexane, 2:8); $[\alpha]_{578}^{20}$ + 0.72 (*c* 1.3).

Anal. Calcd for $C_{33}H_{41}O_4N$: C, 76.86; H, 8.01; N, 2.71. Found: C, 76.64; H, 8.27; N, 2.28.

***N*-Isobutyl(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)amine (3b).** Prepared by procedure B, time: 40 min, yield, 72.6% as a homogeneous syrup; $[\alpha]_{578}^{20}$ + 9.03 (*c*, 1.6).

Anal. Calcd for $C_{31}H_{39}O_4N$: H, 8.03; N, 2.86. Found: C, 75.75; H, 8.22; N, 2.76.

***N*-Butyl(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)amine (3c).** Prepared by procedure B, time: 30 min, yield, 64.0% as a homogeneous syrup; $[\alpha]_{578}^{20}$ + 8.33 (*c*, 1.7).

Anal. Calcd for $C_{31}H_{39}O_4N$: C, 76.04; H, 8.03; N, 2.86. Found: C, 75.91; H, 8.33; N, 2.76.

***N*-(2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)piperidine (3d).** Prepared by procedure B, time: 20 min, yield, 51.6% as colourless crystals, mp 71-72 °C (ethyl acetate - *n*-hexane, 2:8); $[\alpha]_{578}^{20}$ + 15.7 (*c*, 2.1).

Anal. Calcd for $C_{32}H_{39}O_4N$: C, 76.61; H, 7.84. Found: C, 76.56; H, 8.07.

***N*-(2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)morpholine (3e).** Prepared by procedure B, time: 20 min, yield, 66.8% as colourless crystals mp 90-92 °C (ethyl acetate - *n*-hexane 2:8); $[\alpha]_{578}^{20}$ + 5.9 (*c*, 2.2).

Anal. Calcd for $C_{31}H_{37}O_5N$: C, 73.93; H, 7.40; N, 2.78. Found: C, 73.64; H, 7.52; N, 2.71.

***N*-(2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)pyrrolidine (3f).** Prepared by procedure A, time: 10 h or by procedure B, time 5 min, yield, 64.0% as a homogeneous syrup; $[\alpha]_{578}^{20}$ + 6.8 (*c*, 1.6).

Anal. Calcd for $C_{31}H_{37}O_4N$: C, 76.36; H, 7.65; N, 2.87. Found: C, 76.40; H, 7.41; N, 2.67.

***N*-Benzyl(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)amine (3g).** Prepared by procedure B, time: 40 min, yield 93.0% as a homogeneous syrup; $[\alpha]_{578}^{20}$ - 2.4 (*c*, 1.2).

Anal. Calcd for $C_{34}H_{37}O_4N$: C, 77.98; H, 7.12; N, 2.67. Found: C, 77.46; H, 7.28; N, 2.71.

***N*-6'-Aminohexyl(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosyl)-1'-amine (3h).** Prepared by procedure A, time: 7 h or by procedure B, time 90 min, yield, 66.0% as a homogeneous syrup; $[\alpha]_{578}^{20}$ + 8.1 (*c*, 2.7).

Anal. Calcd for $C_{33}H_{44}O_4N_2$: C, 74.40; H, 8.33; N, 5.26. Found: C, 73.94; H, 8.01; N, 5.03.

^1H and ^{13}C NMR data for compounds **3a-3h** are given in Table I.

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REFERENCES

1. a) L. M. Lerner, B. Sheid, E. J. Gaetjens, *J. Med. Chem.*, **30**, 1521 (1987); b) E. De Clercq, *Nucleosides Nucleotides*, **10,** 167 (1991); c) P. Herdewijn, A. Van Aerschot, J. Balzarini, E. De Clercq, *Nucleosides Nucleotides*, **10**, 199 (1991); d) D. Komiotis, S. Delatre, L. Holt, A.P. Ollapally, J. Balzarini, E. De Clercq, M. Iigo, *Nucleosides Nucleotides*, **10**, 431 (1991); e) K. Augustyns, A. Van Aerschot, P. Herdewijn, *Nucleosides Nucleotides*, **10,** 587 (1991); f) A. Van Aerschot, L. Kerremans, J. Balzarini, E. De Clercq, P. Herdewijn, *Nucleosides Nucleotides*, **10**, 589 (1991); g) P. Herdewijn, A. Van Aerschot, R. Busson, P. Claes, E. De Clercq, *Nucleosides Nucleotides,* **10**, 1525 (1991).

2. H. A. Van Doren, R. Van der Geest, C. de Ruijter, *Lig. Cryst.* **8**, 109-121 (1990).

3. It is noteworthy that *O,O*-dimethyl-*S*-(2-deoxyglycosyl)phosphorodithioates that have been introduced by us previously as efficient stereoselective glycosylating reagents for alcohols and phenols[7a-c] were not suitable for the synthesis of 2-deoxyglycosylamines due to side reactions such as dealkylation of the phosphate residue by amines.

4. R. S. Edmundson, *Tetrahedron*, **21**, 2378 (1965).

5. M. Chmielewski, I. Fokt, J. Grodner, G. Grynkiewicz, W. Szeja, *J. Carbohyr. Chem.*, **8**, 735 (1989).

6. a) J. Borowiecka, M. Michalska, *Carbohydr. Res.*, **68**, C8 (1979); b) J. Borowiecka, P. Lipka, M. Michalska, *Tetrahedron*, **44**, 2067 (1988).

7. a) J. Borowiecka, M. Michalska, *J. Carbohydr. Chem.*, **2**, 99 (1983); b) H. Bielawska, M. Michalska, *J. Carbohydr. Chem.*, **5**, 445 (1986); c) H. Bielawska, M. Michalska, *J. Carbohydr. Chem.*, **10**, 107 (1991).

8. ^{13}C NMR spectra indicated trace amounts of the α-anomers.