In search of new antifungal agents. Synthesis of benzyl and thiophenyl 2-deoxy-6-*O*-diethylphosphonato-2-hydroxyimino-D-hexopyranosides

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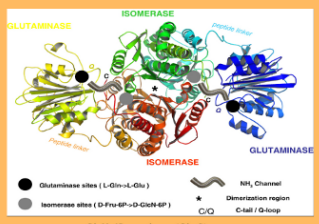
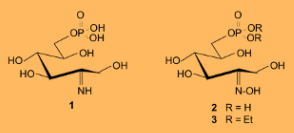


GlcN-6P synthase (GlmS)
[J. Mol. Biol. (2009) 385, 653–664]

Emerging challenge of systemic fungal infections, especially in immunocompromised patients, and a limited repertoire of effective antifungals stimulate a search for novel targets and drug candidates. Enzymes involved in biosynthesis of the fungal cell wall components are of a special interest in this respect. One of them is GlcN-6P synthase (GlmS), enzyme catalyzing the first committed step in chitin biosynthesis pathway, that is transformation of D-fructose-6-phosphate (Fru-6P) to D-glucosamine-6-phosphate (GlcN-6P). Another one is phosphomannose isomerase (PMI), that catalyses the reversible isomerization of D-mannose-6-phosphate (Man-6P) and D-fructose-6-phosphate (Fru-6P). PMI is reported to play a crucial role in the biosynthesis of many mannosylated structures, including the cell wall components of fungi. Both enzyms are proposed as the targets for antifungal chemotherapy and a search for their selective inhibitors has been continued. The reaction performed by GlmS is believed to proceed through the formation of intermediate **1**, a Schiff base created between the keto group of the sugar and the ammonia generated from the glutamine amide function Mechanism of the reaction catalyzed by PMI is similar to that catalyzed by GlmS.

Phosphomannose isomerase (PMI)
[J. Biol. Chem. (2004) Vol. 279, No. 2, p. 1491–1498]



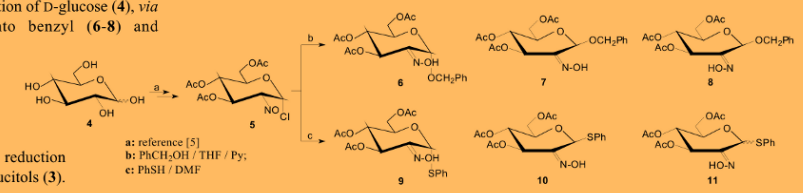
1 **2** R = H **3** R = Et

In the course of search of antifungal agents, we plan to synthesize 2-deoxy-2-hydroxyimino-6-*O*-phosphono-D-glucitol (**2**) and its diethyl ester (**3**), and test them as inhibitors of mentioned above enzymes and for antifungal activity. Ethyl residues are incorporated into **2** to increase a lipophilicity of the molecule, which is supposed to be advantageous for better penetration of the derivative through the cytoplasmic cell membrane. Probably, diethyl ester will be metabolized to **2** inside a cell.

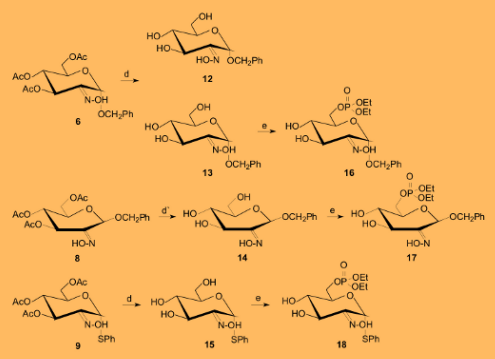
Here, the first steps of our synthesis are presented. This starts from the transformation of D-glucose (**4**), *via* 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride (**5**), into benzyl (**6-8**) and thiophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroxyimino-D-hexopyranosides (**9-11**).

Some of the obtained glycosides (**6**,**7**, **10**) were *O*-deacetylated (**12-15**) and then 6-*O*-phosphorylated with diethylchlorophosphate to provide benzyl and thiophenyl 2-deoxy-6-O-diethylphosphonato-2-hydroxyimino-D-hexopyranosides (**16-18**).

Removing of aglycone from **16**, **17** and **18**, respectively, followed by reduction will give us (2*Z*) and (2*E*) 2-deoxy-2-hydroxyimino-6-*O*-diethylphosphonato-D-glucitols (**3**).



a: reference [5]
b: $PhCH_2OH$ / THF / Py;
c: PhSH / DMF



d: CH_3ONa / CH_3OH; **d'**: K_2CO_3 / CH_3OH / H_2O; **e:** Cl-PO_3Et_2 / pyridine

Tabele 1
Characteristic and Malditof MS data for **6-18**.

No.	Configuration	Yield (%)	Form (mp [°C])	$[\alpha]_D^{20}$ (c, solvent)	M (g/mol)	MALDITOF MS
6	-(Z)-α-D-*arabino*-	26	syrup	+81.5 ° (c = 0.9, $CHCl_3$)	409	432 (M^+ + 23)
7	-(Z)-β-D-*arabino*-	9	syrup	———	409	432 (M^+ + 23)
8	-(E)-β-D-*arabino*-	14	syrup	-8.4 ° (c = 1, $CHCl_3$)	409	432 (M^+ + 23)
9	-(Z)-α-D-*arabino*-	43	syrup	———	411	412 (M^+ + 1)
10	-(Z)-β-D-*arabino*-	24	syrup	———	411	412 (M^+ + 1)
11	-(E)-α/β-D-*arabino*-	1	syrup	———	411	412 (M^+ + 1)
12	-(E)-α-D-*arabino*-	11	syrup	———	282	305 (M^+ + 23)
13	-(Z)-α-D-*arabino*-	43	solid (144 - 146)	+103.0 ° (c = 0.8, CH_3OH)	282	305 (M^+ + 23)
14	-(E)-β-D-*arabino*-	96	solid (146 – 147)	-23.0 ° (c = 0.8, CH_3OH)	282	305 (M^+ + 23)
15	-(Z)-α-D-*arabino*-	53	solid	———	285	———
16	-(Z)-α-D-*arabino*-	42	syrup	———	419	442 (M^+ + 23)
17	-(E)-β-D-*arabino*-	14	syrup	———	419	———
18	-(Z)-α-D-*arabino*-	8	syrup	———	421	———

Tabele 2
Chemical shifts (ppm) of the protons in the ^{1}H NMR spectra of **6-18**.

No.	H-1	H-3	H-4	H-5	H-6'	H-6	OAc	O-CH_2-Ph H-A	O-CH_2-Ph H-B	O-CH_2-Ph -C_6H_5	NOH	-CH_2CH_3 CH_2	-CH_2CH_3 CH_3	O-SPh -C_6H_5
6	6.09 (s) 1H	5.82 (d) 1H	5.21 (t) 1H	4.19 (ddd) 1H	4.02 (dd) 1H	4.29 (dd) 1H	2.09 (s) 3H 2.06 (s) 3H 2.04 (s) 3H	4.68 (d) 1H	4.75 (d) 1H	7.36 (m) 5H	8.22 (s) 1H	-	-	-
7	5.89 (s) 1H	5.54 (d) 1H	5.32 (t) 1H	4.04 (k) 1H	4.44 (d) 2H		2.07 (s) 3H 2.08 (s) 3H 2.09 (s) 3H	4.70 (d) 1H	4.91 (d) 1H	7.34 (m) 5H	*	-	-	-
8	5.23 (s) 1H	6.12 (d) 1H	5.68 (dd) 1H	3.97 (ddd) 1H	4.25 (dd) 1H	4.36 (dd) 1H	2.02 (s) H 2.05 (s) H	4.68 (d) 1H	4.92 (d) 1H	7.37 (m) 5H	7.51 (s) 1H	-	-	-
9	6.55 (s) 1H	5.54 (d) 1H	5.07 (t) 1H	4.63 (m) 1H	4.04 (dd) 1H	4.26 (dd) 1H	1.97 (s) 3H 2.07 (s) 3H 2.09 (s) 3H	-	-	-	12.11 (s) 1H	-	-	7.40 3H 7.58 2H
10	6.25 (s) 1H	5.33 (d) 1H	5.04 (dd) 1H	3.81 (m) 1H	4.29 (dd) 1H	4.34 (dd) 1H	2.02 (s) 3H 2.07 (s) 3H 2.09 (s) 3H	-	-	-	12.19 (s) 1H	-	-	7.10 1H 7.40 2H 7.50 2H
11α	6.38 (s) 1H	5.96 (d) 1H	4.98 (k) 1H	4.30 (m) 1H	4.20 (m) 1H	4.07 (m) 1H	~2.00 9H	-	-	-	12.00 (s) 1H	-	-	7.40 3H 7.55 2H
11β	5.96 (s) 1H	6.00 (d) 1H	5.23 (dd) 1H	4.05 (m) 1H	4.20 (m) 2H		~2.00 9H	-	-	-	11.92 (s) 1H	-	-	7.40 3H 7.55 2H
12	6.13 (s) 1H	5.01 (d) 1H	~3.72	~3.84	*	*	-	4.62 (d) 1H	4.74 (d) 1H	7.32 (m) 5H	-	-	-	-
13	6.08 (s) 1H	4.34 (d) 1H	3.41 (t) 1H	3.78 (ddd) 1H	3.84 (dd) 1H	3.70 (dd) 1H	-	4.61 (d) 1H	4.78 (d) 1H	7.34 (m) 5H	-	-	-	-
14	5.12 (s) 1H	4.55 (d) 1H	4.19 (dd) 1H	3.47 (m) 1H	3.85 (dd) 1H	3.73 (dd) 1H	-	4.61 (d) 1H	4.83 (d) 1H	7.32 (m) 5H	-	-	-	-
15	6.67 (s) 1H	4.32 (d) 1H	3.57 (t) 1H	4.25 (ddd)	3.92 (dd) 1H	3.86 (dd) 1H	-	-	-	-	-	-	-	7.39 3H 7.65 2H
16	6.07 (s) 1H	4.51 (d) 1H	3.66 (t) 1H	3.91 (m) 1H	4.16 1H	4.37 (ddd) 1H	-	4.61 (d) 1H	4.72 (d) 1H	7.30 (m) 5H	-	4.11 (m) 4H	1.31 (k) 6H	-
17	5.14 (s) 1H	4.64 (d) 1H	4.43 (dd) 1H	3.63 (m) 1H	4.22 (ddd) 1H	4.35 (ddd) 1H	-	4.57 (d) 1H	4.80 (d) 1H	7.26 (m) 5H	10.23 (s) 1H	4.09 (m) 4.02 (m) 4H	1.28 (dd) 3H 1.17 (dd) 3H	-
18	6.65 (s) 1H	4.45 (d) 1H	3.74 (dd) 1H	4.37 (dd) 1H	4.45 (m) 1H	4.28 (dd) 1H	-	-	-	-	-	4.08 (m) 4H	1.25 (k) 6H	7.53 1H 7.55 1H 7.28 3H

* not determined

Tabele 3
^{1}H-^{1}H and ^{1}H-^{31}P coupling constans (Hz) in the ^{1}H NMR spectra of **6-18**.

No.	$J_{5,4}$	$J_{4,3}$	$J_{3,2}$	$J_{5,6'}$	$J_{6,6'}$	$J_{6,6}$	$J_{CH_2CH_3}$	$J_{H,P}$	$J_{6',P}$
6	10.0	9.6	4.4	2.4	12.0	12.0	-	-	-
7	5.6	6.0	6.4		-	11.6	-	-	-
8	7.6	8.4	4.8	3.6	11.6	12.0	-	-	-
9	9.8	10.0	5.4	2.2	12.5	-	-	-	-
10	2.2	7.3	6.8	3.9	12.0	-	-	-	-
11α	4.4	8.3	*	*	*	-	-	-	-
11β	5.9	7.8	*	*	*	-	-	-	-
12	8.8	*	*	*	*	11.6	-	-	-
13	9.2	9.6	5.2	2.0	11.6	12.0	-	-	-
14	8.4	9.6	5.6	2.8	11.6	12.0	-	-	-
15	10.0	9.2	4.8	2.8	12.4	-	-	-	-
16	9.6	9.6	3.6	*	11.6	11.6	6.8	8.0	*
17	8.8	9.6	3.6	2.0	11.2	12.0	6.8	8.4	7.6
18	9.6	9.6	4.4	*	11.6	-	6.8	8.0	7.6

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