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Synthesis of naphthoxylosides on solid support

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Abstract—In order to investigate the selective antiproliferative effects shown by 2-(6-hydroxynaphthyl)-β-D-xylopyranoside, the 14 possible β-D-xylopyranosidic compounds were synthesized on solid support. An aminomethylated polystyrene resin was converted into an acid chloride resin and then esterified using dihydroxynaphthalene. The free hydroxy group was then xylosylated under $BF_3{\cdot}OEt_2$ mediated conditions. The xyloside was deprotected and simultaneously cleaved off the resin using NaOMe/MeOH. Final purification using reverse phase HPLC gave the pure xylosides in 6–42% yield with virtually no formation of α-xylosides.

Glycosaminoglycan (GAG) chains are anchored to core proteins to form proteoglycans, a class of extracellular macromolecules with functions ranging from specific cell–cell interactions to bulk construction material. The glycosidic linkage is formed between the unique xylose residue of the GAG chain and a serine of the core protein.[1]

It has been shown that xylosides carrying hydrophobic aglycons can enter cells and initiate GAG synthesis and thereby act as artificial chain initiators.[2] Different GAG chains are formed, dependent on the aglycon used.[3,4] 2-(6-Hydroxynaphthyl)-β-D-xylopyranoside (**5**), which can prime synthesis of both heparan sulfate (HS) and chondroitin sulfate (CS)/dermatan sulfate (DS), also inhibits growth of both normal and transformed cells. Transformed cells are preferentially inhibited, indicating selective antiproliferative properties of this class of compounds.[5] As part of our study to investigate the mechanism of the antiproliferative effect we decided to synthesize xylosides of the ten different dihydroxynaphthalenes and thereby generate a set of compounds with diversified properties (e.g. hydrophobicity, redox potential and pK_a) suitable for biological testing (cf. Fig. 1).

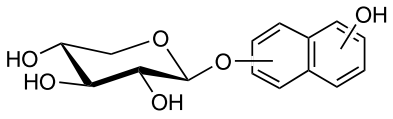

Figure 1. General structure of naphthoxylosides **1**–**10**.

The standard preparation of 2-(6-hydroxynaphthyl)-β-D-xylopyranoside (**5**) using monobenzoylated 2,6-dihydroxynaphthalene has several disadvantages.[5]

Monoprotection, i.e. acylation, of dihydroxynaphthalenes is usually low-yielding, giving the monoprotected compound together with starting material and diprotected compound. The yield of the monoprotected compounds ranges from 25 to 50%, depending on the dihydroxynaphthalene used. Selective deprotection of the diacylated product gives similar results.[6]

Instead we decided to perform the reactions on solid support, thus avoiding the problematic monoprotection. Monoethers of 1,5-dihydroxynaphthalene and 2,7-dihydroxynaphthalene have been synthesized using benzoic acid functionalized polystyrene resin with good results.[7] Initial attempts to use commercially available benzoic acid resin gave poor results. Instead we functionalized a commercially available aminomethylated polystyrene resin using succinic anhydride.[8] The carboxylic acid resin was then transformed into the corresponding acid chloride resin using oxalyl chloride.[9] The ten different dihydroxynaphthalenes were purchased or, in the case of 1,2-[10] and 1,8-dihydroxynaphthalene,[11,12] synthesized and then coupled to the resin using pyridine and a catalytic amount of dimethylaminopyridine (DMAP).

Keywords: xylosides; dihydroxynaphthalenes; antiproliferative; solid support.

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Anomerization to the more stable α-anomer is an often encountered problem in Lewis acid promoted glycosylation. In order to determine the rate of anomerization we monitored the $BF_3{\cdot}OEt_2$ mediated xylosylation reaction both in solution and on solid support (see experimental section for details). After 60 min the reaction in solution showed 9% α-xyloside compared with only trace amounts even after 300 min under similar reaction conditions on solid support.

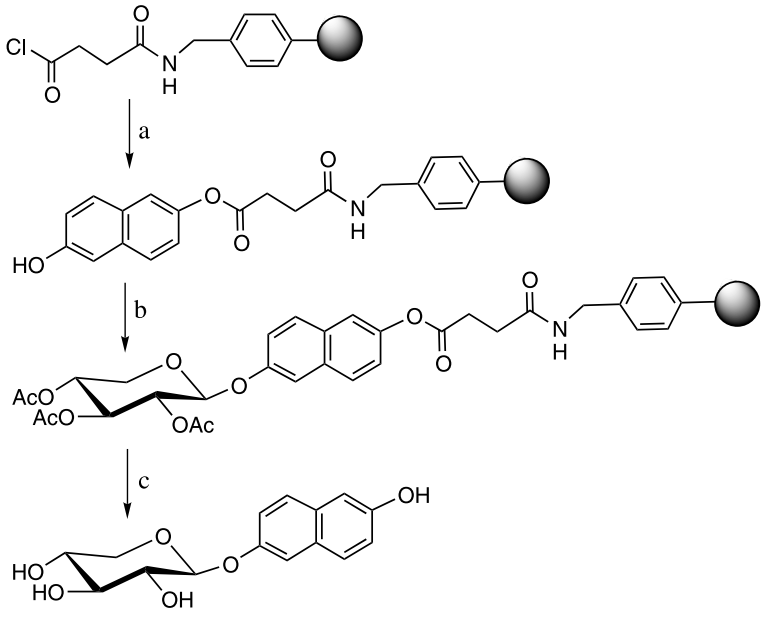
Xylosylation, using 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose under $BF_3{\cdot}OEt_2$ mediated conditions, followed by deprotection and simultaneous cleavage from the resin by standard deacylation (NaOMe–MeOH) gave naphthoxylosides **1**–**10** in good yields (cf. Scheme 1).

Six compounds were synthesized from the symmetric dihydroxynaphthalenes; 1 - (4 - hydroxynaphthyl) - β - D-xylopyranoside (**1**), 1-(5-hydroxynaphthyl)-β-D-xylopyranoside (**2**), 1 - (8 - hydroxynaphthyl) - β - D - xylopyranoside (**3**), 2 - (3 - hydroxynaphthyl) - β - D - xylopyranoside (**4**), 2 - (6 - hydroxynaphthyl) - β - D - xylopyranoside (**5**), and 2 - (7 - hydroxynaphthyl) - β - D - xylopyranoside (**6**). The eight xylosides formed from the four unsymmetric dihydroxynaphthalenes were easily separated on reverse phase HPLC; 1-(2-hydroxynaphthyl)-β-D-xylopyranoside (**7a**), 2-(1-hydroxynaphthyl)-β-D-xylopyranoside (**7b**), 1-(3-hydroxynaphthyl)-β-D-xylopyranoside (**8a**), 3-(1-hydroxynaphthyl)-β-D-xylopyranoside (**8b**), 1-(6-hydroxynaphthyl)-β-D-xylopyranoside (**9a**), 6-(1-hydroxynaphthyl)-β-D-xylopyranoside (**9b**), 1-(7-hydroxynaphthyl)-β-D-xylopyranoside (**10a**), 7-(1-hydroxynaphthyl)-β-D-xylopyranoside (**10b**).

Compound numbering and yields are given in Table 1. The identities of all new compounds were confirmed by HRMS and NMR analysis including COSY and long-range HETCOR. The chemical shifts, multiplicity and coupling constants for the anomeric and aromatic protons are given in Table 2.

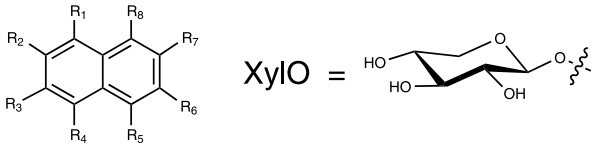
General procedure for synthesis of naphthoxylosides on solid support: Aminomethylated polystyrene resin (1.13 mmol/g, Novabiochem 01-64-0010) was converted into acid chloride resin by standard procedures.[8,9] The acid chloride resin (100 mg, theoretical loading 1.0 mmol/g) was swelled in CH_2Cl_2 and dihydroxynaphthalene (48 mg, 0.3 mmol) was added together with pyridine (0.2 mL) and DMAP (cat.). The mixture was shaken overnight at room temperature and the resin was then washed with CH_2Cl_2, MeOH, diethyl ether and dried in vacuum. The dry resin was swelled in CH_2Cl_2 and 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose (159 mg, 0.5 mmol) was added together with $BF_3{\cdot}OEt_2$ (0.037 mL, 0.3 mmol). The mixture was shaken at room temperature for 45 min and then washed with CH_2Cl_2. MeOH (1 mL), CH_2Cl_2 (1 mL) and NaOMe/MeOH (1 M, 0.5 mL) were added and the mixture was stirred for 1 h and then filtered and neutralized by addition of AcOH (1 mL). The filtrate was concentrated and then purified by reverse phase HPLC to give the pure naphthoxylosides.

Anomerization study: 6-Benzoyloxy-2-hydroxynaphthalene (26 mg, 0.1 mmol) and 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose (159 mg, 0.5 mmol) were dissolved in CH_2Cl_2 (2.5 mL) and $BF_3{\cdot}OEt_2$ (0.037 mL, 0.3 mmol) was added. Samples (0.050 mL) were taken at different



Scheme 1. Synthesis of 2-(6-hydroxynaphthyl)-β-D-xylopyranoside (**5**). (a) 2,6-Dihydroxynaphthalene, CH_2Cl_2, pyridine, DMAP, rt overnight. (b) 1,2,3,4-Tetra-*O*-acetyl-β-D-xylopyranose, CH_2Cl_2, $BF_3{\cdot}OEt_2$, rt 45 min. (c) CH_2Cl_2, MeOH, NaOMe/MeOH, rt 1 h.

Table 1. Numbering and yields[a] for compounds **1**–**10b**



Cmpd	R1	R2	R3	R4	R5	R6	R7	R8	Yield (%)[a]	HRMS[c]
1	XylO	H	H	OH	H	H	H	H	16	291.0885
2	XylO	H	H	H	OH	H	H	H	27	291.0864
3	XylO	H	H	H	H	H	H	OH	7	291.0876
4	H	XylO	OH	H	H	H	H	H	42	291.0866
5	H	XylO	H	H	H	OH	H	H	28	291.0887
6	H	XylO	H	H	H	H	OH	H	21	291.0897
7a	XylO	OH	H	H	H	H	H	H	6[b]	291.0876
7b	OH	XylO	H	H	H	H	H	H	10[b]	291.0871
8a	XylO	H	OH	H	H	H	H	H	16[b]	291.0889
8b	OH	H	XylO	H	H	H	H	H	9[b]	291.0904
9a	XylO	H	H	H	H	OH	H	H	14[b]	291.0855
9b	OH	H	H	H	H	XylO	H	H	16[b]	291.0866
10a	XylO	H	H	H	H	H	OH	H	14[b]	291.0890
10b	OH	H	H	H	H	H	XylO	H	15[b]	291.0866

[a] The yields are calculated from the loading of the aminomethylated resin.
[b] Maximum yield is 50%.
[c] Calculated for $C_{15}H_{15}O_6$ (M–H): 291.0869.

Table 2. Selected ^{1}H NMR-data (CD_3OD) δ (ppm)[a,b]

Cmpd	H-1	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′	H-7′	H-8′
1	4.85 d, 7.5	–	7.00 d, 8.2	6.70 d, 8.2	–	8.10–8.15 m	7.40–7.46 m	7.40–7.46 m	8.27–8.33 m
2	5.03 d, 7.5	–	7.11 dd, 7.7, 0.8	7.31 dd, 8.4, 7.7	7.86 dt, 8.3, 0.9	–	6.82 dd, 7.5, 1.0	7.25 dd, 8.5, 7.5	7.83 dt, 8.4, 0.9
3	5.27 d, 5.8	–	7.18 dd, 7.7, 1.1	7.33 t, 8.0	7.50 dd, 8.3, 1.1	7.30–7.35 m	7.30–7.35 m	6.80 dd, 5.0, 3.4	–
4	4.96 d, 7.4	7.43 s	–	–	7.17 s	7.60 d, 7.6	7.20–7.30 m	7.20–7.30 m	7.67 d, 7.5
5	4.94 d, 7.2	7.33 d, 2.3	–	7.19 dd, 8.9, 2.5	7.57 d, 9.1	7.02–7.07 m	–	7.02–7.07 m	7.62 d, 9.0
6	5.00 d, 7.2	7.21 d, 2.3	–	7.05 dd, 8.9, 2.5	7.66 d, 8.3	7.64 d, 8.3	6.94 dd, 8.8, 2.4	–	7.02 d, 2.5
7a	4.62 d, 7.9	–	–	7.14 d, 8.8	7.58 d, 8.7	7.73 d, 8.3	7.34 ddd, 8.0, 6.8, 1.1	7.41 ddd, 8.0, 6.8, 1.1	8.29 d, 7.4
7b	4.71 d, 7.6	–	–	7.30–7.45 m	7.30–7.45 m	7.74 d, 8.0	7.30–7.45 m	7.30–7.45 m	8.15 d, 8.1
8a	5.00 d, 7.5	–	6.76 d, 2.1	–	6.80 d, 1.8	7.56 d, 8.1	7.35 ddd, 8.1, 6.8, 1.2	7.22 ddd, 8.3, 6.8, 1.2	8.20 d, 8.4
8b	4.98 d, 7.3	–	6.65 d, 2.2	–	6.92 d, 2.2	7.66 d, 8.3	7.39 ddd, 8.2, 6.9, 1.4	7.27 ddd, 8.2, 6.9, 1.2	8.07 d, 8.4
9a	5.02 d, 7.5	–	6.91 dd, 7.1, 1.4	7.25–7.30 m	7.25–7.30 m	7.00–7.05 m	–	7.00–7.05 m	8.22 d, 9.0
9b	5.01 d, 7.2	–	6.65–6.71 m	7.20–7.25 m	7.20–7.25 m	7.32 d, 2.4	–	7.18 dd, 9.2, 2.6	8.10 d, 9.2
10a	5.03 d, 7.5	–	7.42 d, 8.2	7.16 t, 7.8	7.04–7.08 m	7.67 d, 8.8	7.04–7.08 m	–	7.59 d, 2.5
10b	5.00 d, 7.1	–	6.79 dd, 7.5, 0.9	7.15 t, 7.5	7.27 d, 8.3	7.70 d, 8.9	7.23 dd, 8.9, 2.5	–	7.73 d, 2.5

[a] The anomeric proton together with the aromatic protons are reported for each compound.
[b] Given as chemical shift (ppm), multiplicity and coupling constants (Hz).

times (15, 30, 45, 60, 90, 180 and 300 min), NaOMe/MeOH (0.5 M, 0.20 mL) was added and the mixture was stirred for 15 min and then neutralized with AcOH (0.10 mL). The samples were analyzed by reverse phase HPLC. Samples were also taken from xylosylation of resin-bound 2,6-dihydroxynaphthalene (prepared using the general procedure) and treated in the same way.

Acknowledgements

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