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Orthogonal protection strategy for the synthesis of heparin and heparan sulfate oligosaccharides

Ph.D. theses

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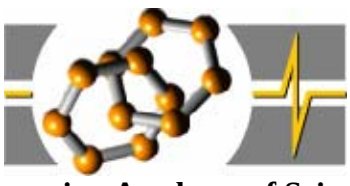

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Chemical Research Center, Institute of Biomolecular Chemistry

Department of Carbohydrate Chemistry

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1. INTRODUCTION

1.1. Synthesis of heparin oligosaccharides

The structurally related heparin (H) and heparan sulfate (HS), members of the glycosaminoglycan family of polysaccharides, are built up of alternating 1→4 linked D-glucosamine and hexuronic acid units.[1-3] Heparin and heparan sulfate interact with a large number of proteins of diverse biological functions.[1-3] Heparin-protein interactions modulate the biological activities of these proteins and affect a series of physiological processes. It is commonly assumed that specific oligosaccharide structures within the heterogeneous polysaccharide chains are responsible for the binding to individual proteins.

The homogeneous heparin oligosaccharides required for the study of heparin-protein interactions are available only by chemical syntheses. These syntheses present a series of difficulties compared to common oligosaccharide syntheses.

1.1.1. Synthesis strategies for heparin and heparan sulfate oligosaccharides

Most of the heparin and heparan sulfate syntheses[5-8] are followed by the first heroic total syntheses of an antithrombin III-binding pentasaccharide reported by *Sinaÿ*[4] in the mid-1980s. These highly target-oriented strategies afforded one target compound from one protected oligosaccharide.

Efficient chemical synthesis of a library of heparin oligosaccharides requires generation of a multitude of target compounds from common intermediates.

1.1.2. Synthesis strategies for Glc*p*A-Glc*p*N-Glc*p*A-Glc*p*NAc heparin and heparan sulfate oligosaccharides

Although the chemical syntheses of some HS oligosaccharides containing both *N*-acetylated and *N*-sulfated units have already been described,[9,10] this type of differentiation needed for target compound (*GlcpA-GlcpN-GlcpA-GlcpNAc)* still remains a challenge. The 4-OH group of *N*-acetyl-D-glucosamine is generally considered to have particularly low reactivity in glycosylations,[11] and the oxygen of the acetamido group may act as a competitive nucleophile, leading to the formation of unstable glycosyl imidate side-products.[12,13]

1.2. New methodologies for the synthesis of oligosaccharides

1.2.1. Reductive ring opening of 4,6-*O*-benzilidén acetals

The regioselective reductive ring opening of benzylidene acetals to 4-*O*-benzyl ethers is a frequently used reaction for the preparation of the monomer building blocks of heparin oligosaccharides. For the reductive cleavage of benzylidene acetals to 4-*O*-benzyl ethers $LiAlH_4$-$AlCl_3$,[14] BH_3NMe_3-$AlCl_3$,[15] Et_3SiH-$PhBCl_2$,[16] and BH_3.THF-Bu_2BOTf [17]/$Cu(OTf)_2$[18] are the most frequently used reagents. Most of these methods suffer from drawbacks, which limits their use in large-scale applications.

1.2.2. Development and introduction of new protecting groups

The chemistry of multifunctional organic compounds relies heavily on extensive use of protecting groups. Assisted cleavage is an often used concept for developing new protecting groups. A variety of protecting groups have been introduced recently based on this principle including, among the frequently used chloroacetyl and levulinoyl, the 4-azidobutyryl,[19] (2-(chloroacetoxyethyl)benzoyl,[20] 2-(azidomethyl)benzoyl,[21] 2-(allyloxy)phenylacetyl,[22] 2-(prenyloxymethyl)benzoyl[23] and 3-(2'-benzyloxyphenyl)-3,3-dimethylpropanoyl[24] groups.

1.3. Objectives of the dissertation

For the preparation of a heparin tetrasaccharide library based on orthogonal protecting group strategy we aimed to develop a new set of orthogonal protecting groups.

Our goal was also to synthesize the putative prion-associated heparan sulfate tetrasaccharide as target molecule using thioglycoside donors.

We have focused also on the development of a new chemo- and regioselective reductive ring opening method of benzylidene-type acetals affording the 4-*O*-benzyl and related ethers in excellent yields and regioselectivity.

Furthermore, we aimed to introduce a new hydroxyl protecting group, starting from the commercially available (2-nitrophenyl)acetic acid. We investigated the stability, selective removal and orthogonality of the new protecting group, as well as its behaviour in glycosylation reactions

2. EXPERIMENTAL METHODS

The macro- and micro methods of modern preparative organic chemistry were applied in the synthetic work. Thin layer chromatography was applied to monitor reactions. Crystallization, column chomatography and gel chromatography were used for the purification of the crude products. Modern spectroscopic methods (one- and two-dimensional nuclear magnetic resonance spectroscopy, mass spectroscopy) and classical methods (melting point determination, optical rotation determination, elemental analysis) were applied for the verification of the structures of the synthetized compounds.

3. RESULTS AND DISCUSSION

3.1. A new regio-and chemoselective ring opening method

We have studied the reductive ring cleavage using various borane complexes as hydride donors in combination with different Lewis acids to develop a new regio-and chemoselective ring opening method.

4,6-*O*-Benzylidene acetals of carbohydrates undergo reductive ring opening efficiently using BH_3·THF and a catalytic amount of TMSOTf affording the 4-*O*-benzyl ethers exclusively in high yields. A series of 4,6-*O*-benzylidene type acetals were reduced using BH_3·THF-TMSOTf in dry dichloromethane at room temperature (*Table 1.*) In all cases, the reactions afforded the 4-*O*-benzyl and related ethers in high yields. The results are summarized in *Table 1.*:

1. Our new method is compatible with most of the common protecting groups, such as benzyl (Bn) and *tert*-butyldimethylsilyl (TBDMS) ether (**9**), benzoyl (Bz), acetyl (Ac, **9**), *N*-benzyloxycarbonyl (**5**), (9-fluorenylmethoxy)carbonyl (Fmoc, **13**) and chloroacetyl (ClAc, **25**) groups. Furthermore, the reactions could also be performed in the presence of free hydroxyl (**7**, **17**), azido (**11**) and thioglycoside functions.

2. The regioselectivity was not influenced by the type of the ring annelation, both *trans*- and *cis*-annelated systems (**17**) gave the 4-*O*-benzyl ethers.

3. The results of the reductive cleavage of the D-mannose (**15)** and L-idose (**19)** acetals indicate that the regioselectivity is unaffected by the C-2 and C-5 configuration.

4. The reaction was also extended to the reductive cleavage of 4-methoxybenzylidene (**21**) and (1-naphthyl)methylene (**23**, **25**) acetals, affording essentially the same results.

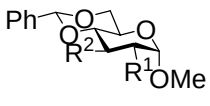
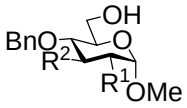
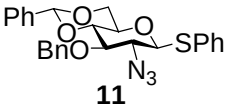
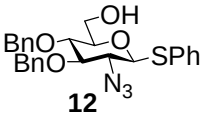
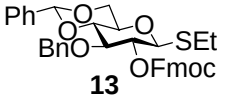
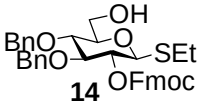
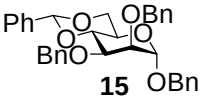
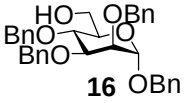
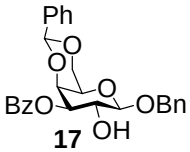
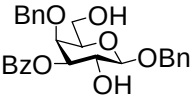
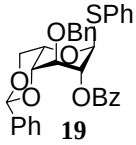
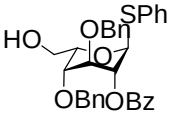
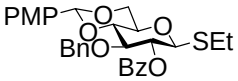
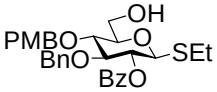
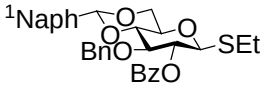
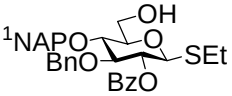
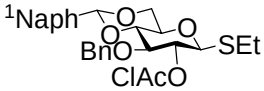
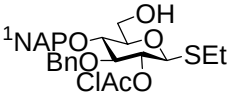
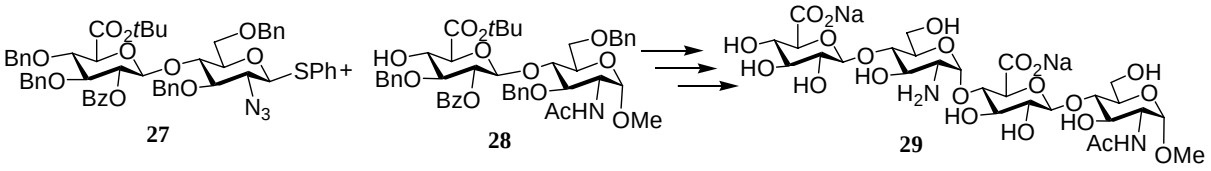
Entry	Benzylidene acetal	Product	Yield (%)
1			
a	**1** R_1 = OBn, R_2 = OBn	**2** R_1 = OBn, R_2 = OBn	96
b	**3** R_1 = OBz, R_2 = OBz	**4** R_1 = OBz, R_2 = OBz	87
c	**5** R_1 = $NHCO_2Bn$, R_2 = OBn	**6** R_1 = $NHCO_2Bn$, R_2 = OBn	99
d	**7** R_1 = OBn, R_2 = OH	**8** R_1 = OBn, R_2 = OH	72
e	**9** R_1 = OTBDMS, R_2 = OAc	**10** R_1 = OTBDMS, R_2 = OAc	95
2	 **11**	 **12**	95
3	 **13**	 **14**	89
4	 **15**	 **16**	91
5	 **17**	 **18**	88
6	 **19**	 **20**	95
7	 **21**	 **22**	76
8	 **23**	 **24**	90
9	 **25**	 **26**	84

Table 1. Reductive ring opening of benzylidene type acetals

Our new chemo- and regioselective ring-opening method has succesfully been applied in the monomer synthesis of the orthogonally protected heparin tetrasaccharides.

3.2. Synthesis of the prion-associated heparan sulfate tetrasaccharide

The synthesis of the methyl α-glycoside (**29**) of the putative prion-associated tetrasaccharide was accomplished in a highly stereoselective manner without masking the *N*-acetyl group at the reducing end (*Scheme 1.)*. Glycosylations which are considered problematic in the literature were successfully accomplished. Thus, high yielding glycosylation of the unreactive 4-OH group of an *N*-acetyl-D-glucosamine acceptor and α-selective glycosylation of the 4'-OH group of a β-D-Glc*p*A-(1→4)-D-Glc*p*NAc disaccharide building block were achieved by using thioglycoside glycosyl donors.



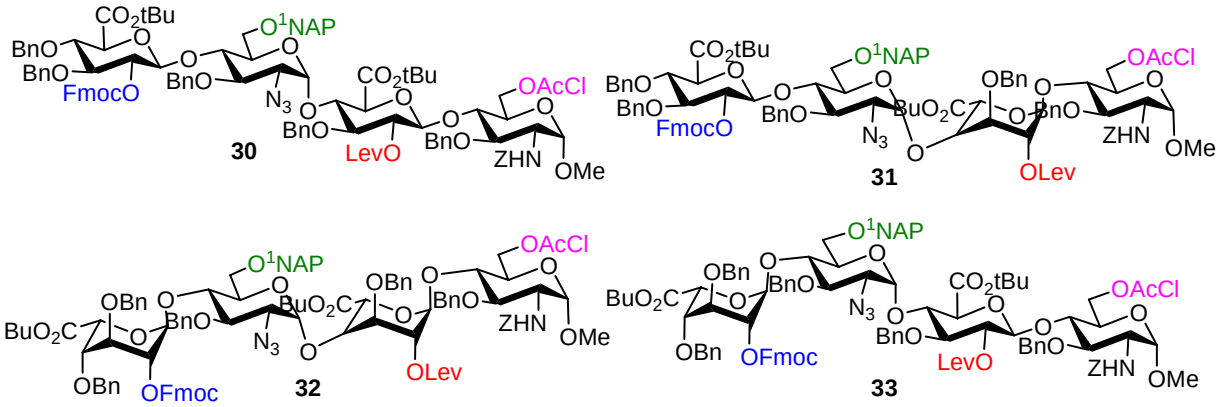
Scheme 1. Synthesis of the prion-associated heparan sulfate tetrasaccharide

3.3. Synthesis of heparin oligosaccharides by an orthogonal protecting group strategy

The structural heterogeneity of H/HS relies on the sulfation patterns of the polysaccharide chains, composed of two disaccharide repeating units. Our synthesis strategy is based on orthogonal protection in the positions which are optionally sulfated in the target compounds. The orthogonal protecting groups can be selectively cleaved in any sequence at any point in the synthesis without affecting the other functions present.

This approach allows the synthesis of multiple sulfated products from a common orthogonally protected precursor.

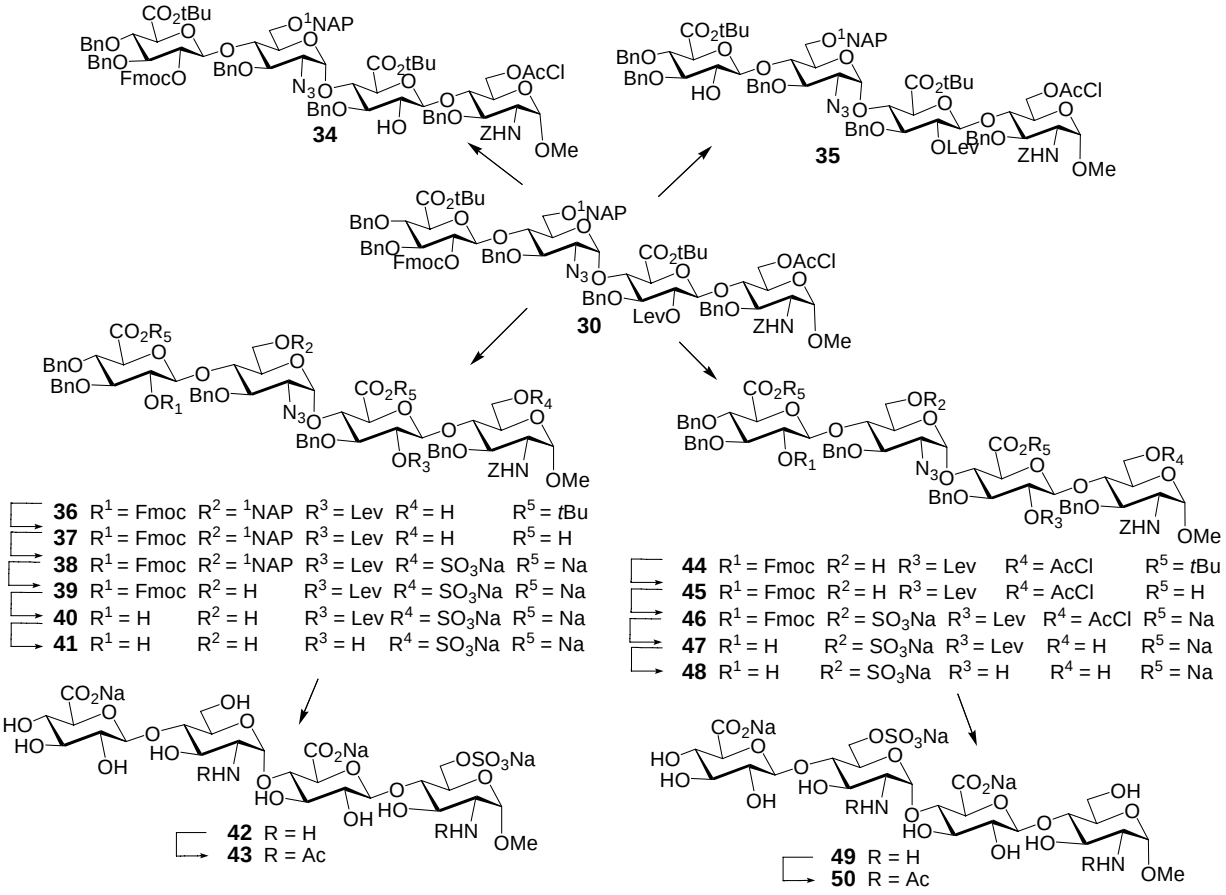
For the preparation of a heparin tetrasaccharide library a new set of orthogonal protecting groups including AcCl (chloroacetyl), Lev (levulinoyl), ^{1}NAP ((1-naphthyl)methyl) and Fmoc ((9-fluorenylmethoxy)carbonyl) groups has been developed. From the orthogonally protected tetrasaccharides (**30-33**) containing different carbohydrate backbones, 576 differently sulfated heparin derivatives can be synthesized (*Scheme 2*). The orthogonally protected tetrasaccharides (**30-33**) have been synthesized in good yield activating the disaccharide thioglycoside donors with different promoters (DMTST, Me_2S_2-Tf_2O).



Scheme 2. The orthogonally protected heparin tetrasaccharide units

The orthogonality of the new set of protecting groups has been proved on tetrasaccharide level. Starting from the orthogonally protected tetrasaccharide (**30**), first selective removal of the chloroacetyl group followed by *O*-sulfation, deprotection, and selective *N*-acetylation afforded the first target compound (**43)** (*Scheme 3.*).

Alternatively, selective removal of the (1-naphthyl)methyl group first, followed by the same sequence of steps afforded the second monosulfated derivative (**50)** (*Scheme 3.*).



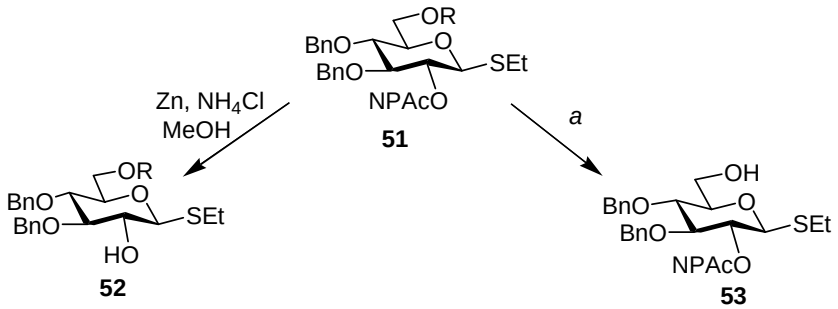
Scheme 3. Synthesis of heparin tetrasaccharides by the orthogonal protecting group strategy

3.4. Introduction of a new protecting group

Besides heparin oligosaccharide synthesis, we have introduced the (2-nitrophenyl)acetyl (NPAc) group, as a new hydroxyl protecting group which can be selectively removed in the presence of most of the common protective groups, and was found to be stable under a series of common carbohydrate transformations. Introduction of the (2-nitrophenyl) acetyl group was accomplished by various methods, all starting from the commercially available (2-nitrophenyl)acetic acid.

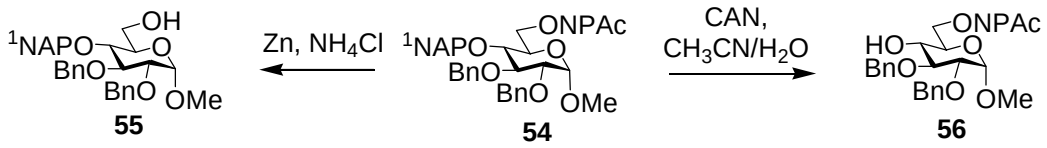
Selective removal of the NPAc group with Zn and NH_4Cl in methanol was accomplished in the presence of the most common protecting groups. In all cases, the reactions afforded the corresponding hydroxy products in high yields. The reaction is compatible with most of the common protecting groups, such as benzyl, 4-methoxybenzyl, allyl, 1-naphthylmethyl (^{1}NAP), and *tert*-butyldimethylsilyl (TBDMS) ethers; benzylidene and isopropylidene acetals, and acyl groups, including acetyl, benzoyl, levulinoyl (Lev), (9-fluorenylmethoxy)carbonyl (Fmoc), and benzyloxycarbonyl groups. Furthermore, the reactions could be performed on both *O*- and *S*-glycosides, and, importantly, the azido group also remained intact.

The orthogonality of the (2-nitrophenyl)acetyl group against some common protecting groups was tested (*Table 2.*). The NPAc group was found to be orthogonal with the commonly used TBDMS, Lev, Fmoc, and partly benzoyl groups. Furthermore, the (2-nitrophenyl)acetyl group was also found to be orthogonal with the 1-naphthylmethyl (^{1}NAP) group (Scheme 3).



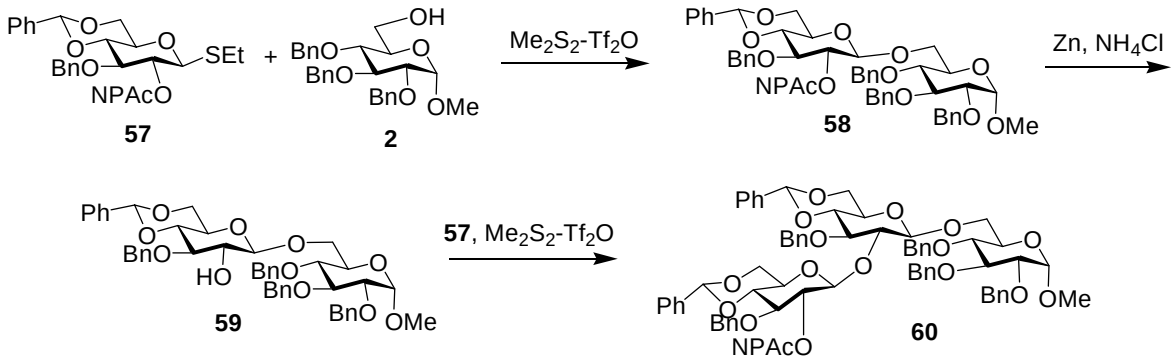
Substrate	Product	Yield (%)	*a*	Yield of **53** (%)
51a R= TBDMS	**52a** R= TBDMS	81	Bu_4NF	78
51b R = Fmoc	**52b** R = Fmoc	73	Et_3N	81
51c R = Lev	**52c** R = Lev	63	H_2NNH_2	87
51d R = Bz	**52d** R = Bz	91	NaOMe	78

Table 2. Orthogonality of the NPAc group with common protecting groups



Scheme 4. Orthogonality of the NPAc and [1]NAP groups

The (2-nitrophenyl)acetyl group is an effective participating neighboring group leading to the exclusive formation of 1,2-*trans* glycosides in glycosylations, therefore it is anticipated to become a valuable tool in oligosaccharide synhesis.



Scheme 5. The NPAc as a participating neighboring group in glycosylations.

4. POSSIBLE UTILIZATION OF THE RESULTS

Our new reductive ring opening method should have utility in the preparation of complex carbohydrates, as the conversions are highly chemo- and regioselective and afford the 4-*O*-ethers in excellent yield. The extension of the method to *4*-methoxybenzylidene and (1-naphtyl)methylene acetals give us also the possibility to introduce a temporary protecting group at position O-4.

The development of a new set of orthogonal protecting groups (Fmoc-[1]NAP-Lev-ClAc) result in more efficient oligosaccharide synthesis.

Due to its advantegous properties, such as ease of introduction, selective removal, orthogonality with a series of common protecting groups, and being an effective participating neighboring group, the (2-nitrophenyl)acetyl group is anticipated to become a valuable tool for the protection of hydroxyl groups.

5. THESES

1. We have developed a new chemo- and regioselective ring opening method of 4,6-*O*-benzylidene-hexopyranosides to the corresponding 4-*O*-benzyl ethers using BH_3·THF and a catalytic amount of TMSOTf. Other benzylidene-type acetals, such as (1-naphthyl)methylene and 4-methoxybenzylidene acetals can also be cleaved with the same reagent. The conversions are highly regio- and chemoselective and afford the benzyl type ethers in excellent yields. It has also succesfully been applied in the monomer synthesis of the orthogonally protected heparin tetrasaccharides [1 and 4].

2. A new set of orthogonal protecting groups including chloroacetyl (AcCl), levulinoyl (Lev), (1-naphtyl)methyl (^{1}NAP) and 9-fluorenyl)methoxycarbonyl (Fmoc) protecting groups has been developed.
Four orthogonally protected tetrasaccharides containing different carbohydrate backbones, from which 576 differently sulfated heparin derivatives can be synthesized, have been prepared in good yield based on our new orthogonal protecting group strategy. The orthogonality of the new set of protecting groups has been proved on tetrasaccharide level.
Two monosulfated heparin tetrasaccharides have been synthesized from the orthogonally protected one.

The syntheses also demonstrates that the preparation of multiple heparin oligosaccharides is more efficient and less time consuming by our orthogonal protection strategy, than synthesizing these oligosaccharides one-by-one.

3. The synthesis of the methyl α-glycoside of the putative prion-associated tetrasaccharide was accomplished in a highly stereoselective manner without masking the *N*-acetyl group at the reducing end. Glycosylations which are considered problematic in the literature were successfully accomplished [3].

4. We have introduced the (2-nitrophenyl)acetyl group as a new, selectively removable hydroxyl protecting group. Selective removal of the NPAc group with Zn-NH_4Cl can be accomplished in the presence of the most common carbohydrate protecting groups. The NPAc group is orthogonal with TBDMS, Fmoc, Lev, NAP, and MBn protecting groups [2].

The (2-nitrophenyl)acetyl group is an effective participating neighboring group, which leads to the selective formation of 1,2-*trans* glycosides in glycosylations [2].

6. LIST OF PUBLICATIONS

Publications on the subject of the thesis:

[1] Katalin Daragics, Péter Fügedi: Regio- and chemoselective reductive cleavage of 4,6-*O*-benzylidene-type acetals of hexopyranosides using BH_3·THF-TMSOTf, *Tetrahedron Lett.* **2009**, 50, 2914-2916.
IF: 2,538 (2008); I: 4.

[2] Katalin Daragics, Péter Fügedi: (2-Nitrophenyl)acetyl: A New, Selectively Removable Hydroxyl Protecting Group; *Organic Letters*, **2010**, 12, 2076-2079.
IF: 5,128 (2008); I: 1.

[3] Katalin Daragics, Péter Fügedi: Synthesis of a putative heparan sulfate tetrasaccharide antigen involved in prion diseases; *Tetrahedron*, submitted
IF: 2,897 (2008)

[4] Katalin Daragics, Péter Fügedi: A new regio- and chemoselective reductive cleavage of cyclic acetals, *Per. Pol. Chem. Eng.* **2007**, 51/2, 81-82.

Oral presentations on the subject of the thesis:

1. Daragics Katalin, Fügedi Péter: Új kemo-és régioszelektív módszer 4,6-O-benzilidén típusú acetálok reduktív gyűrűnyitására, *VIII. Doctoral Chemical School, Tahitótfalu, May 5-6, 2005.*

2. Katalin Daragics, Péter Fügedi: A new regio- and chemoselective reductive cleavage of cyclic acetals using BH_3.THF and TMSOTf, *2nd Austrian-Hungarian Carbohydrate Conference, Somogyaszaló, May 24-26, 2005.*

3. Daragics Katalin, Fügedi Péter: Új kemo-és regioszelektív módszer szénhidrátok 4,6-O-benzilidén típusú acetáljainak reduktív gyűrűnyitására, *II. Conference of PhD students, BME, Budapest, Febr. 7, 2006.*

4. Daragics Katalin, Fügedi Péter: Prion fehérjék kötődéséért felelős heparin tetraszacharid szintézise, *9. Doctoral Chemical School, Tahitótfalu, April 24-25, 2006.*

5. Katalin Daragics, Péter Fügedi: Synthesis of a prion-associated heparan-sulfate tetrasaccharide, *Annual Meeting of the Committee of Carbohydrate Chemistry, Mátrafüred, May 31-June 2, 2006.*

6. Daragics Katalin, Fügedi Péter: Prion fehérjék kötődéséért felelős heparin tetraszacharid szintézise és szerkezetvizsgálata, *MTA Kémiai Kutatóközpont, Szerves Kémiai Szeminárium, Budapest, Nov. 20, 2006.*

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12. Katalin Daragics, Péter Fügedi: Synthesis of a putative heparin tetrasaccharide antigen involved in prion diseases, *V. International Congress of Young Chemists, Jurata, Poland, October 10-15, 2007,* Abstract T16;

13. Katalin Daragics, Péter Fügedi: Synthesis of Heparin Tetrasaccharides Based on Orthogonal Protecting Group Strategy, *24th International Carbohydrate Symposium, Oslo, July 27-August 1, Norway, 2008,* Abstract A-0036;

Poster presentations on the subject of the thesis:

1. Katalin Daragics, Péter Fügedi: A new regio- and chemoselective reductive cleavage of cyclic acetals using BH_3·THF and TMSOTf, *13th European Carbohydrate Symposium*; *Bratislava, Slovakia, August 21-26, 2005,* Abstract P20;

2. Katalin Daragics, Péter Fügedi: A new regio-and chemoselective reductive ring opening of cyclic acetals, *9th European Training Course on Carbohydrates, Wageningen, The Netherlands, June 6-9, 2006.*

3. Katalin Daragics, Péter Fügedi: Synthesis of a putative prion-associated heparane sulfate tetrasaccharide, *14th European Carbohydrate Symposium, Lübeck, Germany, September 2-7, 2007,* Abstract PO-050;

4. Katalin Daragics, Péter Fügedi: A new regio- and chemoselective reductive cleavage of cyclic acetals, *V. International Congress of Young Chemists, Jurata, Poland, October 10 -15, 2007,* Abstract P05;

5. Péter Fügedi, Katalin Daragics: 2-Nitrophenylacetyl: A New Selectively Removable Protective Group, *24th International Carbohydrate Symposium, Oslo, Norway, July 27-August 1, 2008,* Abstract A-P100;

6. Katalin Daragics, Péter Fügedi: Synthesis of Heparin Tetrasaccharides Based on Orthogonal Protecting Group Strategy, *4th Central European Conference, Chemistry towards Biology, Dobogókő, Hungary, September 8-11,* 2008.

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