CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Chemical Synthesis of Modified Hyaluronic Acid Disaccharides

Authors: Marco Mende, Martin Nieger, and Stefan Bräse

To be cited as: *Chem. Eur. J.* 10.1002/chem.201701238

Link to VoR: http://dx.doi.org/10.1002/chem.201701238

Supported by
ACES

WILEY-VCH

10.1002/chem.201701238

WILEY-VCH

Chemical Synthesis of Modified Hyaluronic Acid Disaccharides

Marco Mende,[a] Martin Nieger,[b] and Stefan Bräse*[a, c]

Abstract: Herein a chemical synthesis towards new modified hyaluronic acid oligomers for structure-related biological activity tests using only commercially available D-glucose and D-glucosamine hydrochloride is reported. The syntheses of various protected hyaluronic acid disaccharides bearing new functional groups at the C-6-position of the former β-D-glucuronic acid moiety are described. The orthogonal protecting group pattern creates a readily access to the appropriate higher oligomers. Also ^{1}H NMR studies of the new derivatives are displayed, showing the effect of the group replacement on the intramolecular electronic environment.

Introduction

Hyaluronic acid, first isolated from the vitreous humor of a cow,[1] is a linear polysaccharide and member of the glycosamino-glycans, which occurs ubiquitously in all vertebrates. Its molecular weight can reach values up to 10^7 Da. The polysaccharide itself consists of a disaccharide repeating unit composed of β-D-glucuronic acid (GlcA) and *N*-acetyl-β-D-glucosamine (GlcNAc) with the following structure motif: $[(\beta1\rightarrow4)\text{-GlcA-}(\beta1\rightarrow3)\text{-GlcNAc-}]_n$ (Figure 1).[2]

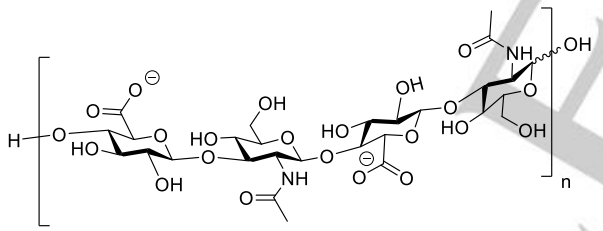


Figure 1. General chemical structure of a single native hyaluronic acid polymer chain in solution with its twisted backbone.[3]

Due to different types of hydrogen bonds, the polysaccharide is able to form very complex secondary and tertiary structures in solution.[4] This structural order in combination with the polyelectrolyte nature of hyaluronic acid polymers induce the unique viscoelastic properties[5] and the ability to absorb huge amounts of water.[6] The biosynthesis takes place at the inner side of the cell membrane operated by three membranous hyaluronic acid synthase enzymes (HAS1, HAS2 or HAS3). The polysaccharide is released into the extracellular matrix, where it represents one of its major components. The biosynthesis requires uridine diphosphate glucuronic acid (UDP-GlcA) and uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc).[7] Besides its moisturizing effects[5a] and lubrication of tissue in joints,[8] hyaluronic acid is also involved in essential biological processes like cell migration, proliferation, adhesion and recognition[9] as well as in tumor progression.[10]

There are two common cell surface receptors which interact with hyaluronic acid molecules. These are called CD44 and RHAMM (Receptor for Hyaluronic Acid Mediated-Motility).[11] The chain length of the polysaccharide plays a crucial role for the resulting effect, especially small hyaluronic acid oligomers, emerging due to hyaluronidase (HYAL) activity, possess an extraordinary high biological activity. For example high molecular weight hyaluronic acid molecules suppress angiogenesis, while small fragments stimulate the same process There are many more examples for such opposing impacts depending on the chain length.[12] Moreover, it is well known that small hyaluronic acid fragments are participating in inflammation procedures and tumor metastasis by interaction with the mentioned receptors.[13] This issue generates an attractive starting point for structural chemical modifications of hyaluronic acid molecules to investigate changes of the biological activities or the generation of new properties due to a change of the secondary-/tertiary structure and the polyelectrolyte behavior.

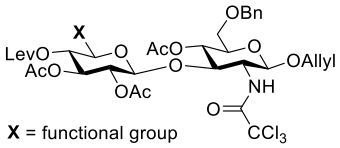
Many chemical syntheses towards native hyaluronic acid oligomers are known in literature. There are plenty of chemical preparations starting from unprotected monosaccharide building blocks,[14] semi-chemical methods using isolated precursors[15] and some solid-phase approaches.[16] Concerning modifications of sugar molecules, there are many reactions for various monosaccharides and also some other oligomers but referring to hyaluronic acid disaccharides and its higher oligomers there is a huge lack of procedures.

Based on the preliminary work by Virlouvet et al.[14e] we now report the syntheses of several protected hyaluronic acid disaccharides bearing new functional groups at the C-6-position of the former β-D-glucuronic acid moiety (Table 1). Applying our established orthogonal protecting group pattern, we also created a readily access towards higher hyaluronic acid oligomers with chemical modifications. Additionally the impact of the functional group variation on the intramolecular electronic environment is depicted through ^{1}H NMR studies.

[a] *M. Mende, Prof. Dr. S. Bräse*
Karlsruhe Institute of Technology, Institute of Organic Chemistry
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
phone: +49 721 608-42902, fax: +49 721 608-48581
e-mail: braese@kit.edu
[b] *Dr. M. Nieger*
Department of Chemistry
University of Helsinki, P. O. Box 55, 00014 University of Helsinki (Finland)
[c] *Prof. Dr. S. Bräse*
Karlsruhe Institute of Technology, Institute of Toxicology and Genetics
Hermann-von-Helmholtz-Platz 1
76344 Eggenstein-Leopoldshafen (Germany)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.2017xxxxx.

Table 1. Leitmotif of the hyaluronic acid disaccharide derivatives and naming.



X = functional group

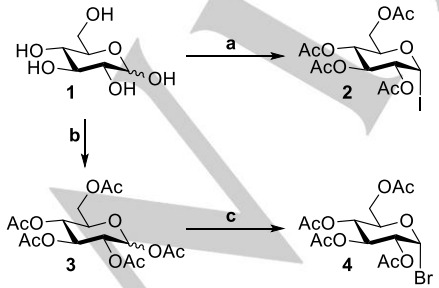
Suffix	**X**	Suffix	**X**	Suffix	**X**
a	CH_2H	g	CH_2SAc	m	CHNOH
b	CH_2N_3	h	CH_2F	n	COOH
c	CH_2OH	i	CH_2Cl	o	COOMe
d	CH_2OAc	j	CH_2Br	p	CN
e	CH_2OTs	k	CH_2I	q	Tetrazole
f	CH_2OPMB	l	CHO		

PMB = *p*-methoxybenzyl

Results and Discussion

Donor building block syntheses

For the syntheses of the new orthogonally protected, modified hyaluronic acid disaccharides **37a**–**37q** (Table 4) we prepared three new donor building blocks (**21f**, **22f**, **24**, Scheme 2), each of which showed its advantages and disadvantages during the reaction sequence and the subsequent glycosylation procedure. Commercially available D-glucose (**1**) was used as the starting compound for each reaction sequence. First of all, the peracetylated α-D-glucopyranosyl iodide (**2**) was prepared using a one-pot method reported by Valerio et al.[17] Also the peracetylated α-D-glucopyranosyl bromide (**4**) was provided applying a two-step procedure. In this approach the peracetylated D-glucose (**3**) was prepared in 95% yield as a 5:1 mixture of the anomers.[17] In the next step, the α-bromide **4** was obtained by general α-bromination of sugar molecules shown by Virlouvet et al. (Scheme 1).[14e]



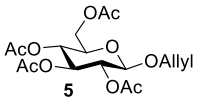
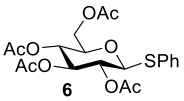
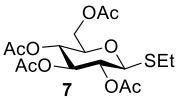
Scheme 1. Syntheses of α-glycosyl halides starting from commercially available D-glucose (**1**). **a** i. I_2, Ac_2O, r.t., 1 h; ii. I_2, Et_3SiH, CH_2Cl_2, 40 °C, 1 h; **b** I_2, Ac_2O, r.t., 1 h, 92%, α/β 5:1; **c** 33% HBr in AcOH, CH_2Cl_2, 0 °C → r.t., 16 h.

With these three building blocks in hand, studies were performed to figure out the most effective compound for the installation of new groups to the anomeric center with high stereoselectivity under various conditions. The results are depicted in Table 2.

For the preparation of the β-allyl protected glucose **5** three methods were tested, all of them using allyl alcohol as the nucleophile. The highest yield (64%) was achieved starting from α-bromide **4** using indium(III) chloride as activator,[14e] while under the same conditions the α-iodide **2** gave a yield of 22%. A direct glycosylation reaction of the peracetylated D-glucose (**3**) under $BF_3 \cdot OEt_2$ activation led to a yield of 4.8%, revealing that glucose derivatives compared to the appropriate mannosides are not suitable for such transformations.[18]

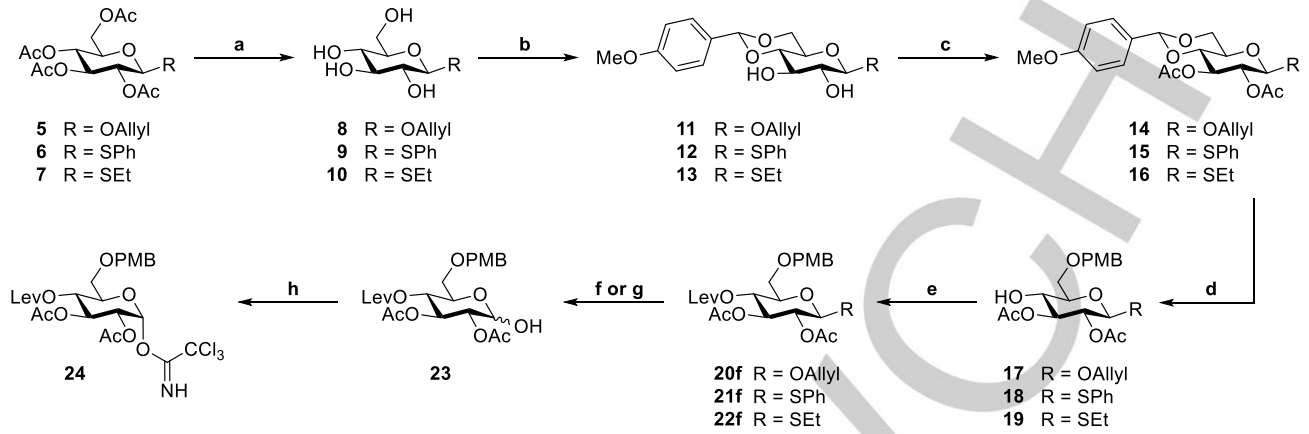
Thioethers are very convenient compounds for glycosylation strategies, because a thioether group connected to the anomeric center can serve both as a temporary protecting group and as an activatable group for glycosylations. Thus we synthesized the two β-thioethers **6** and **7** utilizing different conditions.

Table 2. Preparation of various β-donor building block precursors for the syntheses of hyaluronic acid derivatives.

Entry	Sub-strate	Conditions	Product	Yield[a] [%]
1 2	**4**[b] **2**[b]	AllylOH, $InCl_3$, 4 Å MS, CH_2Cl_2, r.t., 5 d	 **5**	64[c] 22[d]
3	**3**[b]	AllylOH, $BF_3 \cdot OEt_2$, 4 Å MS, CH_2Cl_2, 0 °C → r.t., 24 h	**5**	4.8
4	**4**[b]	PhSH, TBAHS, 1.5 M Na_2CO_3, EtOAc, r.t., 2 d	 **6**	86[c]
5	**3**[b]	PhSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C → r.t., 18 h	**6**	15
6 7	**2**[b] **4**[b]	Thiourea, EtI, NEt_3, MeCN, r.t., 17 h	 **7**	87[d] 57[c]
8	**4**[b]	EtSH, TBAHS, 1.5 M Na_2CO_3, EtOAc, r.t., 1 h	**7**	traces

[a] Isolated yield. [b] Crude starting material was used. [c] Yield over three steps. [d] Yield over two steps. MS = molecular sieves, TBAHS = tetrabutylammonium hydrogen sulfate.

10.1002/chem.201701238



Scheme 2. Syntheses of the three different orthogonal protected β-D-glucoside building blocks **21f**, **22f** and **24** for the preparation of modified hyaluronic acid derivatives. **a** 25% NH_3 aq., MeOH, r.t., 18 h, 99% **8**, 96% **9**, 94% **10**; **b** *p*-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, MeCN, 40 °C, 3 h, 62% **11**, 95% **12**, 71% **13**; **c** Ac_2O, DMAP, CH_2Cl_2, r.t., 1 h, 93% **14**, 99% **15**, 83% **16**; **d** $NaBH_3CN$, TFA, 4 Å MS, DMF, 0 °C → r.t., 3 d, 88% **17**, 57% **18**, 94% **19**; **e** levulinic acid, DIC, DMAP, CH_2Cl_2 0 °C → r.t., 15 h, 99% **20f**, 98% **21f**, 79% **22f**; **f** $Pd(OAc)_2$, NaOAc, AcOH, H_2O, r.t., 20 h, 70% (for R = OAllyl); **g** NBS, CH_2Cl_2, H_2O, r.t., 1.5 h (for R = SEt) or 15 h (for R = SPh); **h** Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 2 h, 57% (starting from R = OAllyl), 11% (over two steps, starting from R = SPh), 35% (over two steps, starting from R = SEt). PMB = *p*-methoxybenzyl, Lev = levulinoyl, *p*-TsOH = *p*-toluenesulfonic acid, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, MS = molecular sieves, DMF = *N*,*N*-dimethylformamide, DIC = *N*,*N'*-diisopropylcarbodiimide, NBS = *N*-bromosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

A very useful method for the preparation of phenyl thioether **6** in high stereoselectivity starting from α-bromide **4** was published by Desai et al. using basic conditions and phase-transfer catalysis.[19] An adoption of this reaction to the synthesis of ethyl thioether **7** led to traces of the desired product. The acidity of ethanethiol (pK_a = 10.54) compared to thiophenol (pK_a = 6.52) might not be high enough and additionally the solubility of both reagents in the depicted solvent system is too different.[20] With a moderate yield of 15% a direct glycosylation reaction of the peracetylated D-glucose (**3**) succeeded under $BF_3 \cdot OEt_2$ activation using thiophenol as the nucleophile. The highest yield (87%) for the preparation of ethyl thioether **7** with good stereoselectivity and purity was achieved using the two-step procedure by Valerio et al. utilizing α-iodide **2** as the starting material. Transferring this procedure to the α-bromide **4** the yield slightly decreased (57%) while the product still showed high stereoselectivity and extremely high purity.

To synthesize the desired orthogonal protected donor building blocks **21f**, **22f** and **24** a sequence of protection and deprotection steps based on our preliminary work[14e] was performed, starting from the β-allyl protected glucose **5** or alternatively from the β-thioether **6** or **7** (Scheme 2). The first five steps of the sequence were the same for each starting compound and were accomplished in good to excellent overall yields (36–50%). First of all the esters were cleaved using aqueous ammonia to yield the alcohols **8**, **9** and **10**. Then the hydroxy groups in C-4- and C-6-position were selectively protected as an acetal forming an energetic favorable 1,3-dioxane heterocycle through treatment with *p*-methoxybenzaldehyde dimethyl acetal under acid catalysis to provide the diols **11**,**12** and **13**. The two remaining hydroxy groups were protected with acetyl groups *via* an esterification reaction using acetic anhydride and DMAP (4-dimethylaminopyridine) as a catalyst. Regioselective reductive opening of the formed acetals **14**, **15** and **16** to the corresponding alcohols **17**, **18** and **19** was realized with sodium cyanoborohydride and TFA (trifluoroacetic acid) in dry DMF (*N*,*N*-dimethylformamide) to expose only the free hydroxy group in C-4-position and to create simultaneously the *p*-methoxybenzyl ether (PMB) in C-6-position. The last hydroxy group was then furnished with a levulinoyl protecting group *via* esterification reaction of levulinic acid applying Steglich conditions. Thus the preparations of the β-thioether donor building blocks **21f** and **22f** were finished. For the synthesis of the trichloroacetimidate building block **24** two more steps were required. The first step was the palladium(II)-induced cleavage of the allyl group on molecule **20f** followed by the base-catalyzed reaction of the hemiacetal **23** with trichloroacetonitrile to yield the final trichloroacetimidate building block **24**. Both steps were performed in moderate yields. It was also possible to generate the trichloroacetimidate building block **24** from the β-thioethers **21f** and **22f** in two-step procedures, but with lower yields.

With an overall yield of 42% phenyl thioether **21f** showed the most efficient reaction sequence, while ethyl thioether **22f** reached 36%, followed by the trichloroacetimidate **24** with 13% however including also two more reaction steps. Besides the two additional steps and the lowest overall yield, the large-scale synthesis of the trichloroacetimidate **24** also needed expensive palladium(II) acetate for the deprotection of the allyl protection group. One advantage of this approach is that strongly odorous sulfur compounds were not needed. Furthermore the donor building blocks **21f** and **24** have the advantage of being solid compounds which makes them easier to handle for the

subsequent reactions, compared to ethyl thioether **22f** which is a viscous oil.

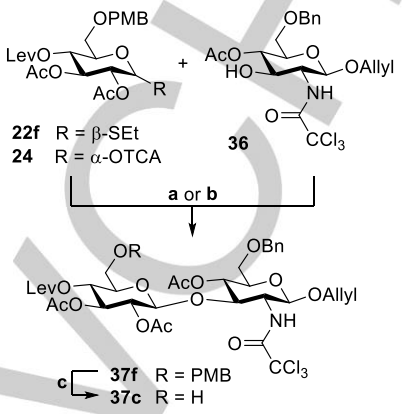
All three donor building blocks **21f**, **22f** and **24** bear an orthogonal protecting group pattern, necessary for the synthesis of our new hyaluronic acid derivatives. A selective access to the hydroxy groups in C-4- and C-6-position is required since the one in C-4-position is needed to build up the β(1→4)-glycosidic bond for the oligomer elongation steps and the one in C-6-position is required for the modification reactions. The remaining hydroxy groups were protected with acetyl groups.

Acceptor building block synthesis

Our selected acceptor building block **36** for the preparation of the modified hyaluronic acid disaccharides **37a–37q** was adopted from preliminary work of Virlouvet et al.[14e] This building block also possesses an orthogonal protecting group pattern necessary for the desired hyaluronic acid derivative reactions. The allyl protection group can be removed selectively by conversion with palladium(II) acetate also in the presence of the protecting groups at the donor building blocks. This is important, because the C-1'-position of the acceptor moiety in combination with the C-4-position of the donor building block moiety is needed to build up the β(1→4)-glycosidic bond for the oligomerization reactions. In addition the other protecting groups (acetyl, benzyl and trichloroacetamide) are very stable under many conditions and therefore eminently suitable for further transformations.

Glycosylation reactions

Utilizing the building blocks displayed in the upper sections, the synthesis of the fully protected disaccharide repeating unit **37f** with the essential orthogonal protecting group pattern as well as the selective deprotection step of the *p*-methoxybenzyl ether (PMB) group, revealing an access towards modification reactions, is shown in Scheme 3. The highest yield (79%) for the glycosylation reaction was achieved with the ethyl thioether donor building block **22f** using an assembly of *N*-iodosuccinimide (NIS) and silver(I) triflate as the activation reagent for the thioether. Connection of the phenyl thioether donor building block **21f** to the acceptor building block **36** was not successful under the same conditions. Furthermore, other common glycosylation procedures, especially concerning the toleration towards the used protecting groups, did not succeed. However, the glycosylation of the trichloroacetimidate **24** with our acceptor building block **36** applying trimethylsilyl triflate (TMSOTf) as an activator gave a moderate yield (32%). Both performed glycosylations provided the requested β(1→3)-glycosidic bond in a very high stereoselectivity triggered through the neighboring group effect of the acetyl group in C-2-position. The fully protected disaccharide repeating unit **37f** can be taken as a key intermediate towards its higher oligomers, because of the selective access to the hydroxy groups (C-4- and C-1'-position) required for the formation of the β(1→4)-glycosidic bonds. Selective oxidative removal of the *p*-methoxybenzyl ether (PMB) group succeeded in a good yield (72%) using ceric ammonium nitrate (CAN), providing disaccharide **37c** for subsequent modification reactions.[14e]

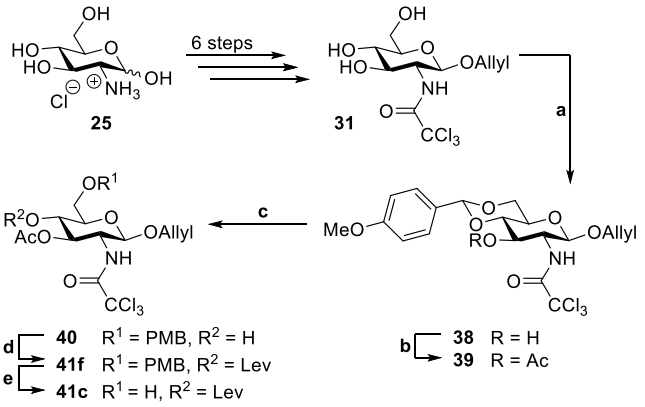


Scheme 3. Synthesis of the orthogonal protected disaccharide repeating unit **37c** for modification reactions and elongation steps. **a** NIS, AgOTf, 4 Å MS, CH_2Cl_2, –30 °C, 3 h, 79% (for R = β-SEt); **b** i. TMSOTf, 4 Å MS, CH_2Cl_2, 0 °C, 2 h; ii. NEt_3, 32% (for R = α-OTCA); **c** CAN, MeCN, H_2O, r.t., 1 h, 72%. TCA = trichloroacetimidate, PMB = *p*-methoxybenzyl, Lev = levulinoyl, Bn = benzyl, NIS = *N*-iodosuccinimide, TfO = triflate, MS = molecular sieves, TMS = trimethylsilyl, CAN = ceric ammonium nitrate.

Model system synthesis

For test reaction purposes we synthesized a monosaccharide model system, which bears all functional groups that are also located on the protected disaccharide **37c**, except for the benzyl group. Therefore, we wanted to explore the stability of our protecting group pattern during further modification reactions. For an exact identification of the new compounds we further aimed at the receipt of clear ^{1}H NMR spectra with a minimum amount of overlapping signals (like in the case of disaccharides).

The synthesis of our model system **41c**, which can be easily realized in excellent yields even on a multi-gram scale, is a combination of the syntheses of the acceptor and donor building block from the preliminary work of Virlouvet et al. starting from commercially available D-glucosamine hydrochloride (**25**) (Scheme 4).[14e] The first six steps for the preparation of triol **31** were synthesized according to literature.[14e] The next four steps are similar to the reaction sequence for the donor building blocks shown above, meaning selective acetal formation of the hydroxy groups in C-4- and C-6-position forming alcohol **38** followed by acetylation of the remaining hydroxy group in C-3-position leading to acetal **39**. Then regioselective reductive opening of the acetal protecting group to form alcohol **40** and esterification reaction of the last hydroxy group in C-4-position using levulinic acid to get the fully protected glucosamine **41f**. After deprotection of the *p*-methoxybenzyl ether (PMB) group using ceric ammonium nitrate (CAN), the free hydroxy group in C-6-position was exposed, providing the primary alcohol **41c** (Scheme 4) for subsequent modification reactions.



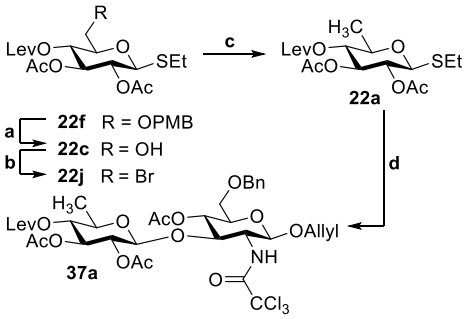
Scheme 4. Synthesis of the model system **41c** for modification reactions. **a** *p*-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, MeCN, 40 °C, 5 h, 82%; **b** Ac_2O, DMAP, CH_2Cl_2, r.t., 1.5 h, 95%; **c** $NaBH_3CN$, TFA, 4 Å MS, DMF, 0 °C → r.t., 5 d, 96%; **d** levulinic acid, DIC, DMAP, CH_2Cl_2 0 °C → r.t., 3 d, 98%; **e** CAN, MeCN, H_2O, r.t., 1 h, 95%. PMB = *p*-methoxybenzyl, Lev = levulinoyl, *p*-TsOH = *p*-toluenesulfonic acid, DMAP = 4-dimethylamino-pyridine, TFA = trifluoroacetic acid, MS = molecular sieves, DMF = *N*,*N*-di-methylformamide, DIC = *N*,*N'*-diisopropylcarbodiimide, CAN = ceric ammoni-um nitrate.

Modification reactions

Model system **41c** can be taken as a good surrogate for the disaccharide **37c**, because their protecting group patterns are similar. To verify the stability of the protecting groups, we performed all desired modification reactions primarily on our model system and then transferred them to the respective disaccharide. Table 3 shows the results of our studies.

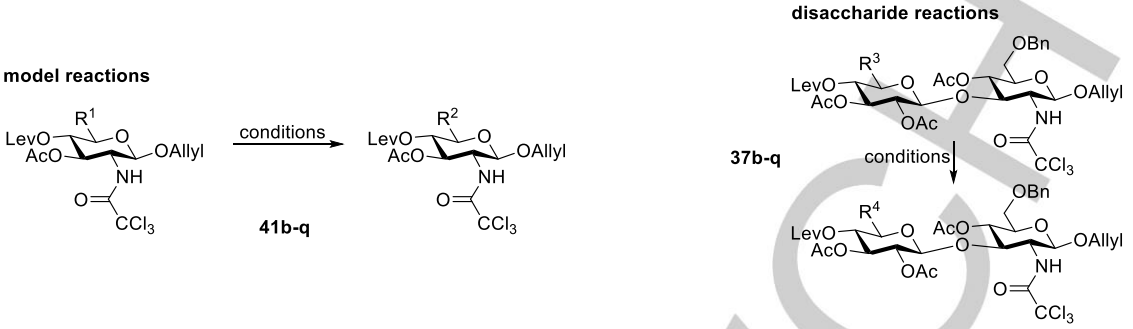
We were able to synthesize the four common halides (F, Cl, Br, I) (Entry 1–8) in good yields starting from the primary alcohol **41c** respectively **37c** *via* Appel reactions[21] or by nucleophilic substitutions. Due to an esterification reaction using acetic anhydride and catalytic amounts of DMAP (4-dimethylamino-pyridine) the acetylated compounds **41d** and **37d** were synthesized in very good yields, utilizing the primary alcohols **41c** and **37c** (Entry 9–10). An activation of the primary alcohol **41c** or **37c** through the installation of a tosyl group under basic conditions for subsequent modifications was also possible in good yields (Entry 11–12). The tosylates **41e** and **37e** were then converted successfully to the thioacetates **41g** and **37g** (Entry 25–26) and to the azides **41b** and **37b** (Entry 27–28) in very good yields by nucleophilic substitutions in a polar solvent at elevated temperature. A mild direct oxidation of the primary alcohol to the carboxylic acid **41n** or **37n** was also realized in very high yields using a hypervalent iodine reagent[22] (Entry 15–16). Furthermore, a stepwise oxidation first preparing the aldehyde **41l** or **37l** with Dess-Martin periodinane[23] (Entry 13–14) followed by a Pinnick Oxidation to the corresponding carboxylic acid **41n** or **37n** (Entry 17–18) was feasible.[24] Moreover, esterification reactions of the carboxylic acid **41n** or **37n** to the appropriate methyl glucuronates **41o** or **37o** were performed in very good yields by preparing first the acyl chlorides in situ followed by conversion with methanol as nucleophile (Entry 23–24). The acyl chlorides represent very interesting intermediates, as they generate a versatile access to a wide range of other adducts. Starting from the crude aldehydes **41l** and **37l** the oximes **41m** and **37m** were synthesized effectively as a mixture of their *trans*- and *cis*-isomers with a distinct excess of the *trans*-formation (Entry 19–20). Subsequent dehydration of these compounds using phosphoryl chloride led to the respective nitriles **41p** and **37p** in good yields (Entry 21–22). These nitriles were successfully converted to the tetrazoles **41q** and **37q** in good yields by 1,3-dipolar cycloaddition using TMS-azide as 1,3-dipole (Entry 29–30).

The already modified thioether donor building block **22a** was synthesized for the preparation of the 6-deoxy-disaccharide **37a** in very good yields over three steps starting from the ethyl thioether **22f**. The first step was the deprotection of the *p*-methoxybenzyl ether (PMB) group followed by bromination of the corresponding alcohol **22c** *via* Appel reaction[21] to the bromide **22j** and subsequent radical cleavage of the bromine atom leading to the 6-deoxy-β-D-glucose derivative **22a**. The glycosylation reaction of this donor building block **22a** with our acceptor building block **36** to 6-deoxy-disaccharide **37a** gave a yield of 33% (Scheme 5). In this case the modification reaction was done before the glycosylation, because of the radical cleavage of the bromine atom in the third step which could also demerge the chlorine atoms of the trichloroacetyl group on the D-glucosamine moiety.



Scheme 5. Synthesis of the protected hyaluronic acid disaccharide derivative **37a** bearing a methyl group at the C-5-position of the glucose moiety. **a** CAN, MeCN, H_2O, r.t., 2 h, 87%; **b** CBr_4, PPh_3, pyridine, 0 °C → r.t., 16 h, 83%; **c** Bu_3SnH, AIBN, toluene, 130 °C, 5 h, 78%; **d** **36**, NIS, TMSOTf, 4 Å MS, CH_2Cl_2, –30 °C, 1.5 h, 33%. Lev = levulinoyl, PMB = *p*-methoxybenzyl, Bn = benzyl, CAN = ceric ammonium nitrate, AIBN = azobisisobutyronitrile, NIS = *N*-iodosuccinimide, TfO = triflate, MS = molecular sieves, TMS = tri-methylsilyl.

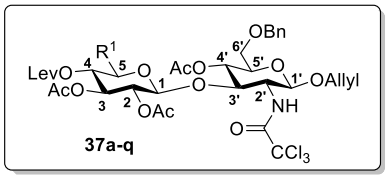
Table 3. Modification reactions of the synthesized model system and the appropriate protected hyaluronic acid disaccharide derivative.



Entry	Substrate		Conditions	Product		Yield[a] [%]
1	**41c**	$R^1 = CH_2OH$	DAST, CH_2Cl_2, r.t., 2 h	**41h**	$R^2 = CH_2F$	23
2	**37c**	$R^3 = CH_2OH$		**37h**	$R^4 = CH_2F$	59
3	**41c**	$R^1 = CH_2OH$	CCl_4, PPh_3, pyridine, r.t., 2 d	**41i**	$R^2 = CH_2Cl$	83
4	**37c**	$R^3 = CH_2OH$		**37i**	$R^4 = CH_2Cl$	65
5	**41c**	$R^1 = CH_2OH$	CBr_4, PPh_3, pyridine, 0 °C → r.t., 16 h	**41j**	$R^2 = CH_2Br$	67
6	**37c**	$R^3 = CH_2OH$		**37j**	$R^4 = CH_2Br$	68
7	**41c**	$R^1 = CH_2OH$	I_2, imidazole, PPh_3, toluene, r.t., 7 d	**41k**	$R^2 = CH_2I$	77
8	**37c**	$R^3 = CH_2OH$		**37k**	$R^4 = CH_2I$	60
9	**41c**	$R^1 = CH_2OH$	Ac_2O, DMAP, CH_2Cl_2, r.t., 2 h	**41d**	$R^2 = CH_2OAc$	92
10	**37c**	$R^3 = CH_2OH$		**37d**	$R^4 = CH_2OAc$	87
11	**41c**	$R^1 = CH_2OH$	TsCl, pyridine, r.t., 16 h	**41e**	$R^2 = CH_2OTs$	91
12	**37c**	$R^3 = CH_2OH$		**37e**	$R^4 = CH_2OTs$	56
13	**41c**	$R^1 = CH_2OH$	DMP, CH_2Cl_2, r.t., 1 h	**41l**	$R^2 = CHO$	not isolated[b]
14	**37c**	$R^3 = CH_2OH$		**37l**	$R^4 = CHO$	not isolated[b]
15	**41c**	$R^1 = CH_2OH$	BAIB, TEMPO, CH_2Cl_2, H_2O, r.t., 2.5 h	**41n**	$R^2 = COOH$	87
16	**37c**	$R^3 = CH_2OH$		**37n**	$R^4 = COOH$	83
17	**41l**	$R^1 = CHO$	$NaClO_2$, isoamylene, NaH_2PO_4, MeCN, H_2O, 10 °C → r.t., 17 h	**41n**	$R^2 = COOH$	73[c]
18	**37l**	$R^3 = CHO$		**37n**	$R^4 = COOH$	61[c]
19	**41l**	$R^1 = CHO$	$H_2NOH \cdot HCl$, Na_2CO_3, THF, H_2O, 0 °C → r.t., 2 h	**41m**	$R^2 = CHNOH$	43[c]
20	**37l**	$R^3 = CHO$		**37m**	$R^4 = CHNOH$	45[c]
21	**41m**	$R^1 = CHNOH$	$POCl_3$, MeCN, r.t. → 65 °C, 1.5 h	**41p**	$R^2 = CN$	63
22	**37m**	$R^3 = CHNOH$		**37p**	$R^4 = CN$	40
23	**41n**	$R^1 = COOH$	i. oxalyl chloride, DMF, CH_2Cl_2, 0 °C → r.t., 1 h; ii. MeOH, r.t., 2 h	**41o**	$R^2 = COOMe$	71
24	**37n**	$R^3 = COOH$		**37o**	$R^4 = COOMe$	80
25	**41e**	$R^1 = CH_2OTs$	KSAc, DMF, 80 °C, 2 h	**41g**	$R^2 = CH_2SAc$	94
26	**37e**	$R^3 = CH_2OTs$		**37g**	$R^4 = CH_2SAc$	84
27	**41e**	$R^1 = CH_2OTs$	NaN_3, DMF, 80 °C, 5 h	**41b**	$R^2 = CH_2N_3$	84
28	**37e**	$R^3 = CH_2OTs$		**37b**	$R^4 = CH_2N_3$	78
29	**41p**	$R^1 = CN$	$TMSN_3$, Bu_2SnO, toluene, 120 °C, 5 h	**41q**	R^2 = Tetrazole	55
30	**37p**	$R^3 = CN$		**37q**	R^4 = Tetrazole	47

[a] Isolated yield. [b] Further use without purification. [c] Yield over two steps. Lev = levulinoyl, Bn = benzyl, DMAP = 4-dimethylaminopyridine, TsO = tosylate, DAST = diethylaminosulfur trifluoride, BAIB = (diacetoxyiodo)benzene, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, DMP = Dess-Martin periodinane.

Table 4. Chemical shifts (in ppm) of the sugar scaffold protons and the amide proton related to the functional group at the C-6-position of the D-glucose moiety of the protected hyaluronic acid disaccharide derivative. The highlighted values in each column always represent the lowest and the highest chemical shift of the appropriate proton, representing the impact of the different functional groups on all the protons. 6-H protons are not shown.[a–b]



Entry	Disaccharide		NH	1-H	2-H	3-H	4-H	5-H	1'-H	2'-H	3'-H	4'-H	5'-H	6a'-H	6b'-H
1	**37a**	$R^1 = CH_3$	6.88	4.55	4.90	5.02	4.78	3.51	4.90	3.51	4.38	4.90	3.73	3.60	3.57
2	**37b**	$R^1 = CH_2N_3$	6.92	4.68	4.88	5.09	4.96	3.58	4.83	3.68	4.35	4.96	3.68	3.58	3.58
3	**37c**	$R^1 = CH_2OH$	7.00	4.64	4.91	5.14	4.91	3.48	4.77	3.73	4.37	4.92	3.80	3.65	3.58
4	**37d**	$R^1 = CH_2OAc$	7.04	4.63	4.91	5.09	5.03	3.63	4.97	3.50	4.46	4.97	3.68	3.58	3.54
5	**37e**	$R^1 = CH_2OTs$	7.01	4.61	4.84	5.03	4.92	3.67	4.76	3.67	4.33	4.92	3.68	3.57	3.54
6	**37f**	$R^1 = CH_2OPMB$	7.04	4.60	4.87	5.04	5.04	3.58	4.87	3.57	4.36	4.93	3.67	3.57	3.57
7	**37g**	$R^1 = CH_2SAc$	6.93	4.62	4.87	5.05	4.95	3.58	4.92	3.58	4.38	4.97	3.71	3.58	3.58
8	**37h**	$R^1 = CH_2F$	6.86	4.60	4.92	5.09	5.03	3.60	4.87	3.60	4.41	4.92	3.71	3.60	3.60
9	**37i**	$R^1 = CH_2Cl$	6.90	4.66	4.91	5.09	4.99	3.66	4.90	3.59	4.40	4.99	3.71	3.59	3.59
10	**37j**	$R^1 = CH_2Br$	6.92	4.68	4.91	5.09	4.95	3.64	4.90	3.64	4.40	4.99	3.70	3.58	3.58
11	**37k**	$R^1 = CH_2I$	6.94	4.67	4.88	5.08	4.88	3.46	4.88	3.70	4.39	5.02	3.70	3.59	3.59
12	**37m**	$R^1 = HCNOH$	6.95	4.64	4.94	5.12	5.05	4.02	4.84	3.58	4.36	4.94	3.68	3.58	3.58
13	**37n**	$R^1 = COOH$	7.34	4.75	4.92	5.15	5.15	4.01	4.82	3.77	4.39	4.97	3.68	3.59	3.53
14	**37o**	$R^1 = COOMe$	6.98	4.66	4.93	5.12	5.12	3.95	4.93	3.54	4.43	4.99	3.68	3.58	3.54
15	**37p**	$R^1 = CN$	6.86	4.57	4.95	5.03	5.28	4.29	4.86	3.49	4.49	4.97	3.69	3.58	3.55
16	**37q**	$R^1 = Tetrazole$	8.02	5.13	5.05	5.36	5.27	5.27	4.70	4.11	4.24	4.91	3.66	3.66	3.61

[a] All data were measured at 600 MHz in $CDCl_3$ as solvent using 7.26 ppm as the reference peak. [b] If the peaks of the depicted protons were located in multiplets, the center of this multiplet was chosen as the appropriate peak for the table. For the exact position of the multiplets see the experimental section.

NMR studies

To explore the impact of the new functional groups on the structure of our new disaccharide derivatives **37a**–**37q** we took a closer look on the chemical shifts of all the sugar scaffold protons and the amide proton to detect changes in the electronic environment of our molecules. Table 4 shows all the chemical shifts of these protons, except the protons at C-6-position of the β-D-glucose moiety, because their chemical shift should vary anyway due to the different groups connected to this position. The highlighted values always display the lowest and highest data.

Since the free carboxylic acid functionality is also located on the native hyaluronic acid disaccharide and an important part of the complex secondary-/tertiary structure, we took disaccharide **37n** as our reference for the comparison of the chemical shifts. The amide proton of the tetrazole functionalized disaccharide **37q** showed an extraordinary high chemical shift (8.02 ppm)

compared to the others, especially to the nitrile **37p** (6.85 ppm). This illustrates that there is an interaction between the amide proton and the functional group at the C-6-position of the β-D-glucose moiety even on a "disaccharide scale". But not only the amide proton was affected by the modifications, also other protons showed significant changes in their chemical shifts. For example the chemical shift of the proton at the anomeric center of the reducing end (1'H) reached values from 4.70 to 4.97 ppm. These changes shown in Table 4 reveal that the exchange reactions have a huge impact on the electronic environment. For the appropriate higher oligomers this modification could have interesting influences on the complex structure of hyaluronic acid oligomers and could lead to attractive compounds.

Conclusions

We successfully developed the syntheses of various new hyaluronic acid disaccharide derivatives bearing a distinct protecting group pattern for subsequent oligomerizations using only commercially available D-glucose (Glc) and *N*-acetyl-D-glucosamine (GlcNAc). Thereto, we designed a model system with similar protecting groups to verify their stability for our modification reactions. The approaches were performed on a multi-gram scale with good to excellent yields. Based on the reported ^{1}H NMR studies we found the electronic environment within the disaccharides to be affected in a strong way by the modifications, especially the amide proton, which is an important part of the complex structure of hyaluronic acid oligomers due to hydrogen bonding. With the used protecting group pattern subsequent elongation steps and also deprotection sequences should succeed in an easy way. On top of this, late stage modifications are conceivable.

Experimental Section

For information concerning the measurements and working techniques as well as the analytical data of all the other compounds please use our supporting information.

Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-6-O-p-methoxybenzyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (***37f***): *Method a*: Acceptor **36** (8.54 g, 17.2 mmol, 1.00 Equiv.) and donor **22f** (11.4 g, 21.6 mmol, 1.26 Equiv.) were dissolved in 340 mL of absolute dichloromethane under argon atmosphere and 4 Å molecular sieve powder (17.4 g) was added. The mixture was stirred for 1 h at room temperature and then cooled down to –30 °C. *N*-Iodosuccinimide (5.80 g, 25.8 mmol, 1.50 Equiv.) and silver trifluoromethanesulfonate (1.33 g, 5.16 mmol, 0.300 Equiv.) were added consecutively and the mixture was stirred for 3 h. The mixture was filtered through a pad of celite and the filtrate was washed with 5% aqueous $Na_2S_2O_3$-solution (200 mL), saturated aqueous $NaHCO_3$-solution (200 mL) and water (200 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37f** was obtained as a yellowish foam in 79% yield (15.0 g).

Method b: Acceptor **36** (79.2 mg, 160 µmol, 1.00 Equiv.) and donor **24** (120 mg, 191 µmol, 1.20 Equiv.) were dissolved in 10.0 mL of absolute dichloromethane under argon atmosphere and 4 Å molecular sieve powder (20 mg) was added. The mixture was stirred for 1 h at room temperature and then cooled down to 0 °C. Trimethylsilyl trifluoromethanesulfonate (7.44 µL, 9.19 mg, 41.1 µmol, 0.257 Equiv.) was added and the mixture was stirred for 2 h at 0 °C. Triethylamine (52.3 µL, 38.2 mg, 378 µmol, 2.36 Equiv.) was added and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37f** was obtained as a white foam in 32% yield (48.3 mg).

R_f = 0.33 (cyclohexane/EtOAc 1:1); m.p. 50–63 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38–7.25 (m, 5H, Ph), 7.25–7.20 (m, 2H, PMP) 7.04 (d, ^3J = 7.8 Hz, 1H, N*H*), 6.88–6.82 (m, 2H, PMP), 5.83 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.6 Hz, ^3J = 6.3 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.17 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.0 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.08–5.00 (m, 2H, 3-H, 4-H), 4.93 (t, ^3J = 9.2 Hz, 1H, 4'-H), 4.89–4.84 (m, 2H, 2-H, 1'-H), 4.60 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.54 (d, ^2J = 12.1 Hz, 1H, CH_aH_bPh), 4.52 (d, ^2J = 12.1 Hz, 1H, CH_aH_bPh), 4.39 (s, 2H, CH_2PMP), 4.36 (t, ^3J = 9.4 Hz, 1H, 3'-H), 4.32 (ddt, ^2J = 12.9 Hz, ^3J = 5.2 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 4.07 (ddt, ^2J = 12.9 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.78 (s, 3H, OCH_3), 3.68–3.65 (m, 1H, 5'-H), 3.63–3.51 (m, 5H, 5-H, 6a-H, 2'-H, 6'-H), 3.47 (dd, ^2J = 10.7 Hz, ^3J = 5.9 Hz, 1H, 6b-H), 2.66–2.61 (m, 2H, $CH_3COCH_2CH_2COO$), 2.38–2.34 (m, 2H, $CH_3COCH_2CH_2COO$), 2.12 (s, 3H, $CH_3COCH_2CH_2COO$), 2.01 (s, 3H CH_3COO), 1.97 (s, 3H, CH_3COO), 1.91 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.0 (C_q, $CH_3COCH_2CH_2COO$), 171.2 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 169.3 (C_q, CH_3COO), 161.7 (C_q, CCl_3CONH), 159.2 (C_q, $C_{Ar}OCH_3$), 137.7 (C_q, C_{Ar} (Ph)), 133.3 (+, CH_2CH=CH_2), 129.6 (C_q, C_{Ar} (PMP)), 129.6 (+, 2 × C_{Ar}H (PMP)), 128.3 (+, 2 × C_{Ar}H (Ph)), 127.8 (+, 2 × C_{Ar}H (Ph)), 127.7 (+, C_{Ar}H (Ph)), 118.1 (–, CH_2CH=CH_2), 113.7 (+, 2 × C_{Ar}H (PMP)), 99.3 (+, C-1), 98.0 (+, C-1'), 92.4 (C_q, CCl_3CONH), 76.1 (+, C-3'), 73.5 (–, CH_2Ph), 73.4 (+, C-5'), 73.1 (–, CH_2PMP), 73.0 (+, C-5), 72.8 (+, C-3), 71.3 (+, C-2), 70.2 (–, CH_2CH=CH_2), 69.2 (–, C-6'), 69.0 (+, C-4), 68.9 (+, C-4'), 68.4 (–, C-6), 58.0 (+, C-2'), 55.2 (+, OCH_3), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO), 20.5 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 2870, 1750, 1716, 1612, 1514, 1366, 1218 1150, 1049, 820, 756, 699, 673, 602, 488 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 958/960/962/964 (30/40/18/5) [*M*–H]$^+$, 923/925/927/929 (21/21/6/1), 865/867/869/871 (34/24/9/3), 440 (29), 435 (38), 405 (100); HRMS (FAB, 3-NBA): calcd for $C_{43}H_{53}O_{17}N^{35}Cl_3$ [*M*+H]$^+$: 960.2374; found: 960.2376.

Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (***37c***): PMB protected disaccharide **37f** (1.57 g, 1.63 mmol, 1.00 Equiv.) was dissolved in a mixture of 17.3 mL of acetonitrile and 2.47 mL of water. Ceric ammonium nitrate (1.79 g, 3.26 mmol, 2.00 Equiv.) was

added and the solution was stirred for 1 h at room temperature. The solution was diluted with dichloromethane (200 mL) and washed with water (100 mL). The aqueous layer was extracted with dichloromethane (3 × 100 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37c** was obtained as a white solid in 72% yield (991 mg).

R_f = 0.25 (cyclohexane/EtOAc 1:2); m.p. 75–91 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.37–7.23 (m, 5H, Ph), 7.00 (d, ^3J = 8.2 Hz, 1H, N*H*), 5.83 (dddd, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.2 Hz, ^3J = 5.1 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.6 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.14 (t, ^3J = 9.5 Hz, 1H, 3-H), 4.96–4.86 (m, 3H, 2-H, 4-H, 4'-H), 4.77 (d, ^3J = 7.6 Hz, 1H, 1'-H), 4.64 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.56 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.52 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.37 (t, ^3J = 9.1 Hz, 1H, 3'-H), 4.32 (ddt, ^2J = 13.0 Hz, ^3J = 5.1 Hz, ^4J = 1.4 Hz, 1H, CH_aH_bCH=CH_2), 4.05 (ddt, ^2J = 13.0 Hz, ^3J = 6.2 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.82–3.77 (m, 1H, 5'-H), 3.77–3.68 (m, 2H, 6a-H, 2'-H), 3.65 (dd, ^2J = 10.7 Hz, ^3J = 3.6 Hz, 1H, 6a'-H), 3.61–3.55 (m, 2H, 6b-H, 6b'-H), 3.51–3.45 (m, 1H, 5-H), 3.07 (s, 1H, 6-O*H*), 2.78–2.67 (m, 2H, $CH_3COCH_2CH_2COO$), 2.53–2.40 (m, 2H, $CH_3COCH_2CH_2COO$), 2.16 (s, 3H, $CH_3COCH_2CH_2COO$), 2.03 (s, 3H, CH_3COO), 2.02 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.4 (C_q, $CH_3COCH_2CH_2COO$), 172.1 (C_q, $CH_3COCH_2CH_2COO$), 170.4 (C_q, CH_3COO), 170.2 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 161.9 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, CH_2CH=CH_2), 128.3 (+, 2 × $C_{Ar}H$), 127.8 (+, 2 × $C_{Ar}H$), 127.7 (+, $C_{Ar}H$), 118.0 (–, CH_2CH=CH_2), 99.7 (+, C-1), 98.4 (+, C-1'), 92.4 (C_q, CCl_3CONH), 75.6 (+, C-3'), 74.5 (+, C-5), 73.5 (–, CH_2Ph), 72.8 (+, C-5'), 72.4 (+, C-3), 71.3 (+, C-2), 70.3 (+, C-4'), 70.0 (–, CH_2CH=CH_2), 69.1 (–, C-6'), 69.0 (+, C-4), 61.4 (–, C-6), 57.2 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.5 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 21.0 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 2872, 1751, 1714, 1529, 1366, 1216, 1151, 1036, 902, 821, 756, 698, 670, 603, 488 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 862/864/866/868 (53/54/22/2) [*M*+Na]$^+$, 838/840/842/844 (38/52/27/6) [*M*–H]$^+$, 782/784/786/788 (96/100/35/2) [*M*–OAllyl]$^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{45}O_{16}N^{35}Cl_3$ [*M*+H]$^+$: 840.1798; found: 840.1795.

*Allyl O-(2,3-di-O-acetyl-6-deoxy-6-fluoro-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloro-acetamido-β-D-glucopyranoside (**37h**)*: Alcohol **37c** (164 mg, 195 µmol,1.00 Equiv.) was dissolved in 10.0 mL of absolute dichloromethane under argon atmosphere and (diethylamino)sulfur trifluoride (49.5 µL, 60.3 mg, 374 µmol, 1.92 Equiv.) was added. The solution was stirred for 2 h at room temperature and washed with saturated aqueous $NaHCO_3$-solution (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37h** was obtained as a white solid in 59% yield (98.8 mg).

R_f = 0.63 (cyclohexane/EtOAc 1:2); m.p. 73–81 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35–7.26 (m, 5H, Ph), 6.86 (d, ^3J = 7.7 Hz, 1H, N*H*), 5.85 (dddd, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.6 Hz, ^3J = 6.2 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.3 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.19 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.0 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.09 (t, ^3J = 9.4 Hz, 1H, 3-H), 5.03 (t, ^3J = 9.7 Hz, 1H, 4-H), 4.95–4.88 (m, 2H, 2-H, 4'-H), 4.87 (d, ^3J = 8.0 Hz, 1H, 1'-H), 4.60 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.57–4.37 (m, 5H, 6-H, 3'-H, CH_2Ph), 4.34 (ddt, ^2J = 12.8 Hz, ^3J = 5.1 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 4.08 (ddt, ^2J = 12.7 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.73–3.69 (m, 1H, 5'-H), 3.67–3.53 (m, 4H, 5-H, 2'-H, 6'-H), 2.77–2.67 (m, 2H, $CH_3COCH_2CH_2COO$), 2.52–2.41 (m, 2H, $CH_3COCH_2CH_2COO$), 2.15 (s, 3H, $CH_3COCH_2CH_2COO$), 2.03 (s, 3H, CH_3COO), 2.00 (s, 3H, CH_3COO) 1.97 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.2 (C_q, $CH_3COCH_2CH_2COO$), 171.3 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 169.6 (C_q, CH_3COO), 169.1 (C_q, CH_3COO), 161.9 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, CH_2CH=CH_2), 128.3 (+, 2 × $C_{Ar}H$), 127.8 (+, 2 × $C_{Ar}H$), 127.7 (+, $C_{Ar}H$), 118.4 (–, CH_2CH=CH_2), 100.2 (+, C-1), 97.7 (+, C-1'), 92.3 (C_q, CCl_3CONH), 80.7 (–, d, $^1J_{C\text{-}F}$ = 175.8 Hz C-6), 76.6 (+, C-3'), 73.5 (–, CH_2Ph), 73.3 (+, C-5), 72.6 (+, d, $^2J_{C\text{-}F}$ = 18.9 Hz, C-5'), 72.5 (+, C-3), 71.1 (+, C-2), 70.2 (–, CH_2CH=CH_2), 69.3 (+, C-4'), 69.1 (–, C-6'), 67.6 (+, d, $^3J_{C\text{-}F}$ = 6.7 Hz, C-4), 58.5 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.6 (–, $CH_3COCH_2CH_2COO$), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; ^{19}F NMR: (376 MHz, $CDCl_3$, 25 °C): δ = –123.6 ppm; IR (ATR): $\tilde{\nu}$ = 3342, 2869, 1752, 1717, 1527, 1367, 1215, 1148, 1053, 1032, 912, 837, 821, 756, 698, 672, 603, 491, 390 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 840/842/844/846 (16/17/10/6) [*M*–H]$^+$, 784/786/788/790 (100/98/38/11) [*M*–OAllyl]$^+$, 663 (80), 634/636/638/640 (65/72/25/7) [*M*–OAllyl–OAc–Bn]$^+$, 506 (47); HRMS (FAB, 3-NBA): calcd for $C_{35}H_{42}O_{15}N^{35}Cl_3F$ [*M*–H]$^+$: 840.1599; found: 840.1602.

*Allyl O-(2,3-di-O-acetyl-6-chloro-6-deoxy-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37i**)*: Alcohol **37c** (110 mg, 131 µmol, 1.00 Equiv.) was dissolved in 5.00 mL of dry pyridine under argon atmosphere. Triphenylphosphane (77.2 mg, 294 µmol, 2.25 Equiv.) and tetrachloromethane (127 µL, 201 mg, 1.31 mmol, 10.0 Equiv.) were added consecutively. The solution was stirred for 2 d at room temperature. After that, 1.00 mL of methanol was added and the stirring was continued for further 30 min. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37i** was obtained as a white solid in 65% yield (73.0 mg).

R_f = 0.67 (cyclohexane/EtOAc 1:2); m.p. 65–85 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.26 (m, 5H, Ph), 6.91 (d, ^3J = 7.7 Hz, 1H, N*H*), 5.84 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.4 Hz, ^3J = 6.3 Hz, ^3J = 5.3 Hz, 1H, CH_2CH=CH_2), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.5 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.19 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.3 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.09 (t, ^3J = 9.4 Hz, 1H, 3-H), 5.03–4.96 (m, 2H, 4-H, 4'-H), 4.91 (dd, ^3J = 9.5 Hz, ^3J = 8.0 Hz, 1H, 2-H), 4.89 (d, ^3J = 7.9 Hz, 1H, 1'-H), 4.65 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.55 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.52 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.40 (t, ^3J = 9.3 Hz, 1H, 3'-H), 4.34 (ddt, ^2J = 12.8 Hz, ^3J = 5.2 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 4.07 (ddt, ^2J = 12.8 Hz, ^3J = 6.4 Hz, ^4J = 1.1 Hz, 1H,

$CH_aH_bCH=CH_2$), 3.74–3.63 (m, 3H, 5-H, 6a-H, 5'-H), 3.62–3.54 (m, 3H, 2'-H, 6'-H), 3.50 (dd, ^2J = 12.1 Hz, ^3J = 6.6 Hz, 1H, 6b-H), 2.76–2.69 (m, 2H, $CH_3COCH_2CH_2COO$), 2.53–2.40 (m, 2H, $CH_3COCH_2CH_2COO$), 2.16 (s, 3H, $CH_3COCH_2CH_2COO$), 2.03 (s, 3H, CH_3COO), 2.00 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.1 (C_q, $CH_3COCH_2CH_2COO$), 171.4 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 169.1 (C_q, CH_3COO), 161.8 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, $CH_2CH=CH_2$), 128.4 (+, 2 × $C_{Ar}H$), 127.9 (+, 2 × $C_{Ar}H$), 127.7 (+, $C_{Ar}H$), 118.3 (–, $CH_2CH=CH_2$), 99.7 (+, C-1), 97.7 (+, C-1'), 92.3 (C_q, CCl_3CONH), 76.5 (+, C-3'), 73.6 (–, CH_2Ph), 73.6 (+, CH), 73.4 (+, CH), 72.5 (+, C-3), 71.2 (+, C-2), 70.3 (–, $CH_2CH=CH_2$), 69.7 (+, C-4), 69.2 (–, C-6'), 68.9 (+, C-4'), 58.4 (+, C-2'), 43.0 (–, C-6), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 20.8 (+, CH_3COO), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 2922, 2854, 1752, 1716, 1526, 1367, 1216, 1148, 1049, 821, 756, 671, 603, 488 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 880/882/884/886 (11/17/9/2) $[M+Na]^+$, 856/858/860/862 (11/16/9/3) $[M–H]^+$, 800/802/804/806 (73/100/54/14) $[M–OAllyl]^+$, 650/652/654/656 (38/47/23/6) $[M–OAllyl–OAc–Bn]^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{44}O_{15}N^{35}Cl_4$ $[M+H]^+$: 858.1460; found: 858.1457.

*Allyl O-(2,3-di-O-acetyl-6-bromo-6-deoxy-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37j**)*: Alcohol **37c** (508 mg, 604 µmol, 1.00 Equiv.) was dissolved in 20.0 mL of dry pyridine under argon atmosphere and cooled down to 0 °C. Triphenylphosphane (317 mg, 1.21 mmol, 2.00 Equiv.) and tetrabromomethane (204 mg, 616 µmol, 1.02 Equiv.) were added consecutively. The solution was slowly warmed up to room temperature and stirred overnight (ca. 16 h). After that, 1.00 mL of methanol was added and the stirring was continued for further 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37j** was obtained as a white foam in 68% yield (370 mg).

R_f = 0.69 (cyclohexane/EtOAc 1:2); m.p. 77–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.25 (m, 5H, Ph), 6.97 (d, ^3J = 7.8 Hz, 1H, NH), 5.83 (dddd, $^3J_{trans}$ = 15.7 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.2 Hz, ^3J = 5.3 Hz, 1H, $CH_2CH=CH_2$), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.5 Hz, 1H, $CH_2CH=CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.1 Hz, 1H, $CH_2CH=CH_{cis}H_{trans}$), 5.08 (t, ^3J = 9.5 Hz, 1H, 3-H), 4.99 (t, ^3J = 9.1 Hz, 1H, 4'-H), 4.94 (t, ^3J = 9.6 Hz, 1H, 4-H), 4.91 (dd, ^3J = 9.6 Hz, ^3J = 8.1 Hz, 1H, 2-H), 4.88 (d, ^3J = 7.9 Hz, 1H, 1'-H), 4.66 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.55 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.51 (d, ^2J = 11.9 Hz, 1H, CH_aH_bPh), 4.38 (t, ^3J = 9.4 Hz, 1H, 3'-H), 4.33 (ddt, ^2J = 12.9 Hz, ^3J = 5.1 Hz, ^4J = 1.4 Hz, 1H, $CH_aH_bCH=CH_2$), 4.07 (ddt, ^2J = 12.9 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, $CH_aH_bCH=CH_2$), 3.68 (ddd, ^3J = 9.8 Hz, ^3J = 6.5 Hz, ^3J = 3.8 Hz, 1H, 5'-H), 3.66–3.61 (m, 2H, 5-H, 2'-H), 3.60–3.53 (m, 3H, 6a-H, 6'-H), 3.30 (dd, ^2J = 11.5 Hz, ^3J = 7.4 Hz, 1H, 6b-H), 2.78–2.67 (m, 2H, $CH_3COCH_2CH_2COO$), 2.52–2.40 (m, 2H, $CH_3COCH_2CH_2COO$), 2.15 (s, 3H, $CH_3COCH_2CH_2COO$), 2.02 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.2 (C_q, $CH_3COCH_2CH_2COO$), 171.4 (C_q, $CH_3COCH_2CH_2COO$), 170.2 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 169.2 (C_q, CH_3COO), 161.8 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, $CH_2CH=CH_2$), 128.3 (+, 2 × $C_{Ar}H$), 127.9 (+, 2 × $C_{Ar}H$), 127.7 (+, $C_{Ar}H$), 118.2 (–, $CH_2CH=CH_2$), 99.5 (+, C-1), 97.8 (+, C-1'), 92.3 (C_q, CCl_3CONH), 76.4 (+, C-3'), 73.5 (–, CH_2Ph), 73.4 (+, CH), 73.4 (+, CH), 72.3 (+, C-3), 71.1 (+, C-2), 70.7 (+, C-4), 70.2 (–, $CH_2CH=CH_2$), 69.1 (–, C-6'), 68.8 (+, C-4'), 58.1 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 30.6 (–, C-6), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 20.9 (+, CH_3COO), 20.6 (+, CH_3COO), 20.5 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3341, 2869, 1751, 1716, 1526, 1422, 1367, 1215, 1147, 1049, 902, 821, 756, 698, 672, 602, 540, 484 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 924/926/928/930 $[M+Na]^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{44}O_{15}N^{79}Br^{35}Cl_3$ $[M+H]^+$: 902.0954; found: 902.0954.

*Allyl O-(2,3-di-O-acetyl-6-deoxy-6-iodo-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37k**)*: Alcohol **37c** (209 mg, 248 µmol, 1.00 Equiv.) was dissolved in 24.0 mL of absolute toluene under argon atmosphere and triphenylphosphane (104 mg, 397 µmol, 1.60 Equiv.), imidazole (53.5 g, 786 µmol, 3.17 Equiv.) and iodine (126 mg, 497 µmol, 2.00 Equiv.) were added consecutively. The mixture was stirred for 7 d at room temperature After that, the mixture was diluted with ethyl acetate (50 mL) and all the solids were filtered off. The filtrate was washed with saturated aqueous $Na_2S_2O_3$-solution (50 mL) and saturated aqueous $NaHCO_3$-solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37k** was obtained as a white solid in 60% yield (142 mg).

R_f = 0.44 (cyclohexane/EtOAc 1:1); m.p. 60–75 °C (decomposition); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.37–7.26 (m, 5H, Ph), 6.94 (d, ^3J = 7.9 Hz, 1H, NH), 5.84 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.3 Hz, ^3J = 5.3 Hz, 1H, $CH_2CH=CH_2$), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, $CH_2CH=CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.2 Hz, 1H, $CH_2CH=CH_{cis}H_{trans}$), 5.08 (t, ^3J = 9.5 Hz, 1H, 3-H), 5.02 (t ^3J = 9.0 Hz, 1H, 4'-H), 4.92–4.83 (m, 3H, 2-H, 4-H, 1'-H), 4.67 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.56 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.52 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.39 (t, ^3J = 9.2 Hz, 1H, 3'-H), 4.34 (ddt, ^2J = 12.9 Hz, ^3J = 5.1 Hz, ^4J = 1.3 Hz, 1H, $CH_aH_bCH=CH_2$), 4.07 (ddt, ^2J = 12.9 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, $CH_aH_bCH=CH_2$), 3.73–3.66 (m, 2H, 2'-H, 5'-H), 3.62–3.56 (m, 2H, 6'-H), 3.49–3.43 (m, 1H, 5-H), 3.39 (dd, ^2J = 11.1 Hz, ^3J = 2.4 Hz, 1H, 6a-H), 3.05 (dd, ^2J = 11.1 Hz, ^3J = 8.6 Hz, 1H, 6b-H), 2.78–2.68 (m, 2H, $CH_3COCH_2CH_2COO$), 2.49 (ddd, ^2J = 17.2 Hz, ^3J = 7.3 Hz, ^3J = 5.2 Hz, 1H, $CH_3COCH_2CH_aH_bCOO$), 2.44 (ddd, ^2J = 17.3 Hz, ^3J = 6.6 Hz, ^3J = 5.4 Hz, 1H, $CH_3COCH_2CH_aH_bCOO$), 2.16 (s, 3H, $CH_3COCH_2CH_2COO$), 2.03 (s, 3H, CH_3COO), 2.02 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.1 (C_q, $CH_3COCH_2CH_2COO$), 171.5 (C_q, $CH_3COCH_2CH_2COO$), 170.2 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 169.2 (C_q, CH_3COO), 161.7 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, $CH_2CH=CH_2$), 128.4 (+, 2 × $C_{Ar}H$), 127.9 (+, 2 × $C_{Ar}H$), 127.7 (+, $C_{Ar}H$), 118.2 (–, $CH_2CH=CH_2$), 99.4 (+, C-1), 97.8 (+, C-1'), 92.4 (C_q, CCl_3CONH), 76.2 (+, C-3'), 73.8 (+, C-5), 73.6 (–, CH_2Ph), 73.8 (+, C-5'), 72.1 (+, C-3), 72.0 (+, C-2), 71.4 (+, C-4), 70.2 (–, $CH_2CH=CH_2$), 69.2 (–, C-6'), 68.7 (+, C-4'), 58.0 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 21.6 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO), 2.89 (–, C-6) ppm; IR (ATR): $\tilde{\nu}$ = 3345, 2920, 1751, 1717,

1526, 1420, 1367, 1217, 1146, 1048, 903, 820, 756, 698, 670, 601, 481, 436, 397 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 972/974/976/978 $[M+Na]^+$.

*Allyl O-(2,3,6-tri-O-acetyl-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37d**)*: Alcohol **37c** (136 mg, 162 µmol, 1.00 Equiv.) was dissolved in 10.0 mL of absolute dichloromethane under argon atmosphere and acetic anhydride (21.6 µL, 23.1 mg, 226 µmol, 1.40 Equiv.) and DMAP (3.96 mg, 32.4 µmol, 0.200 Equiv.) were added consecutively. The solution was stirred for 1.5 h at room temperature. The solution was washed with saturated aqueous NaHCO3-solution (30 mL). The organic layer was separated and dried over Na2SO4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37d** was obtained as a white solid in 87% yield (124 mg).

R_f = 0.44 (cyclohexane/EtOAc 2:3); m.p. 56–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.26 (m, 5H, Ph), 7.04 (d, ^3J = 7.4 Hz, 1H, N*H*), 5.83 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.2 Hz, ^3J = 5.7 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.0 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.09 (t, ^3J = 9.4 Hz, 1H, 3-H), 5.03 (t, ^3J = 9.6 Hz, 1H, 4-H), 5.00–4.94 (m, 2H, 1'-H, 4'-H), 4.91 (dd, ^3J = 9.3 Hz, ^3J = 8.1 Hz, 1H, 2-H), 4.63 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.55 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.51 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.46 (t, ^3J = 9.6 Hz, 1H, 3'-H), 4.33 (ddt, ^2J = 12.7 Hz, ^3J = 5.3 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 4.22 (dd, ^2J = 12.4 Hz, ^3J = 5.3 Hz, 1H, 6a-H), 4.12 (dd, ^2J = 12.4 Hz, ^3J = 2.0 Hz, 1H, 6b-H), 4.07 (ddt, ^2J = 12.7 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.70–3.61 (m, 2H, 5-H, 5'-H), 3.58 (dd, ^2J = 10.8 Hz, ^3J = 3.1 Hz, 1H, 6a'-H), 3.54 (dd, ^2J = 10.8 Hz, ^3J = 5.5 Hz, 1H, 6b'-H), 3.50 (dt, ^3J = 10.1 Hz, ^3J = 7.8 Hz, 1H, 2'-H), 2.73 (ddd, ^2J = 18.5 Hz, ^3J = 7.1 Hz, ^3J = 5.7 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.66 (ddd, ^2J = 18.6 Hz, ^3J = 6.7 Hz, ^3J = 5.3 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.51–2.40 (m, 2H, $CH_3COCH_2CH_2COO$), 2.14 (s, 3H, $CH_3COCH_2CH_2COO$), 2.06 (s, 3H, CH_3COO), 2.02 (s, 3H, CH_3COO), 2.00 (s, 3H, CH_3COO), 1.93 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 205.9 (C_q, $CH_3COCH_2CH_2COO$), 171.3 (C_q, $CH_3COCH_2CH_2COO$), 170.5 (C_q, CH_3COO), 170.3 (C_q, CH_3COO), 169.4 (C_q, CH_3COO), 169.1 (C_q, CH_3COO), 161.9 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, CH_2CH=CH_2), 128.4 (+, 2 × C_{Ar}H), 127.9 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.4 (–, CH_2CH=CH_2), 99.3 (+, C-1), 97.6 (+, C-1'), 92.3 (C_q, CCl_3CONH), 76.1 (+, C-3'), 73.6 (–, CH_2Ph), 73.3 (+, C-5'), 72.5 (+, C-3), 71.9 (+, C-5), 71.2 (+, C-2), 70.4 (–, CH_2CH=CH_2), 69.1 (–, C-6'), 68.8 (+, C-4'), 68.1 (+, C-4), 61.9 (–, C-6), 58.5 (+, C-2'), 37.6 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3334, 2924, 1746, 1716, 1526, 1365, 1216, 1146, 1034, 901, 837, 821, 756, 699, 675, 601, 489, 429, 381 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 904/906/908/910 $[M+Na]^+$.

*Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-6-O-tosyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37e**)*: Alcohol **37c** (218 mg, 259 µmol, 1.00 Equiv.) was dissolved in 10.0 mL of dry pyridine under argon atmosphere and cooled down to 0 °C. *p*-Toluenesulfonyl chloride (74.1 mg, 389 µmol, 1.50 Equiv.) was added. The solution was stirred overnight (ca. 16 h) at room temperature. The solvent was removed under reduced pressure and the crude product was dissolved in 70 mL of dichloromethane and washed with saturated aqueous $NaHCO_3$-solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:2) as eluent. The product **37e** was obtained as a white solid in 56% yield (144 mg).

R_f = 0.66 (cyclohexane/EtOAc 1:2); m.p. 71–78 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.80–7.72 (m, 2H, Ts), 7.38–7.26 (m, 7H, Ph, Ts), 7.01 (d, ^3J = 8.2 Hz, 1H, N*H*), 5.83 (dddd, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.7 Hz, ^3J = 6.1 Hz, ^3J = 5.5 Hz, 1H, CH_2CH=CH_2), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.3 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.17 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.0 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.03 (t, ^3J = 9.5 Hz, 1H, 3-H), 4.95–4.88 (m, 2H, 4-H, 4'-H), 4.84 (dd, ^3J = 9.4 Hz, ^3J = 8.1 Hz, 1H, 2-H), 4.76 (d, ^3J = 8.0 Hz, 1H, 1'-H), 4.61 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.54 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.51 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.36–4.30 (m, 2H, 3'-H, CH_aH_bCH=CH_2), 4.17 (dd, ^2J = 11.2 Hz, ^3J = 2.0 Hz, 1H, 6a-H), 4.11 (dd, ^2J = 11.2 Hz, ^3J = 5.7 Hz, 1H, 6b-H), 4.06 (ddt, ^2J = 12.9 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.72–3.62 (m, 3H, 5-H, 2'-H, 5'-H), 3.57 (dd, ^2J = 10.9 Hz, ^3J = 3.1 Hz, 1H, 6a'-H), 3.54 (dd, ^2J = 10.9 Hz, ^3J = 5.7 Hz, 1H, 6b'-H), 2.73 (ddd, ^2J = 18.5 Hz, ^3J = 7.1 Hz, ^3J = 5.6 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.66 (ddd, ^2J = 18.5 Hz, ^3J = 7.1 Hz, ^3J = 6.9 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.44 (s, 3H, ArCH_3), 2.45–2.34 (m, 2H, $CH_3COCH_2CH_2COO$), 2.14 (s, 3H $CH_3COCH_2CH_2COO$), 2.01 (s, 3H, CH_3COO), 1.97 (s, 3H, CH_3COO), 1.87 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.0 (C_q, $CH_3COCH_2CH_2COO$), 171.2 (C_q, $CH_3COCH_2CH_2COO$), 170.2 (C_q, CH_3COO), 169.5 (C_q, CH_3COO), 169.2 (C_q, CH_3COO), 161.8 (C_q, CCl_3CONH), 145.3 (C_q, $C_{Ar}SO_3$), 137.7 (C_q, C_{Ar} (Ph)), 133.2 (+, CH_2CH=CH_2), 132.5 (C_q, $C_{Ar}CH_3$), 129.9 (+, 2 × C_{Ar}H (Ts)), 128.3 (+, 2 × C_{Ar}H (Ph)), 128.0 (+, 2 × C_{Ar}H (Ts)), 127.8 (+, 2 × C_{Ar}H (Ph)), 127.7 (+, C_{Ar}H (Ph)), 118.1 (–, CH_2CH=CH_2), 99.8 (+, C-1), 98.1 (+, C-1'), 92.4 (C_q, CCl_3CONH), 76.2 (+, C-3'), 73.5 (–, CH_2Ph), 73.4 (+, C-5'), 72.3 (+, C-3), 71.7 (+, C-5), 71.0 (+, C-2), 70.1 (–, CH_2CH=CH_2), 69.2 (–, C-6'), 69.0 (+, C-4'), 68.2 (+, C-4), 67.0 (–, C-6), 57.9 (+, C-2'), 37.6 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.6 (–, $CH_3COCH_2CH_2COO$), 21.7 (+, ArCH_3), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO), 20.5 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3347, 2871, 1753, 1717, 1597, 1526, 1365, 1216, 1190, 1175, 1146, 1053, 993, 940, 819, 757, 698, 669, 602, 552, 491, 395 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 992/994/996/998 (10/11/5/1) $[M–H]^+$, 936/938/940/942 (100/95/56/9) $[M–OAllyl]^+$; HRMS (FAB, 3-NBA): calcd for $C_{42}H_{49}O_{18}N^{35}Cl_3{}^{32}S$ $[M–H]^+$: 992.1730; found: 992.1731.

*Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-β-D-gluco-hexodialdo-1,5-pyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37l**)*: Alcohol **37c** (484 mg, 575 µmol, 1.00 Equiv.) was dissolved in 25 mL of dichloromethane and Dess-Martin-periodinane (488 mg, 1.15 mmol, 2.00 Equiv.) was added. The mixture was stirred for 3 h at room temperature, diluted with dichloromethane (20 mL) and then filtered through a pad of celite. The filtrate was washed with 5% aqueous

$Na_2S_2O_3$-solution (100 mL), saturated aqueous $NaHCO_3$-solution (100 mL) and water (100 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product of **37l** was used for the subsequent reactions without further purifications.

Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-β-D-glucopyranuronosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (***37n***): *Method a*: Alcohol **37c** (130 mg, 155 µmol, 1.00 Equiv.) was dissolved in 15.0 mL of a mixture of dichloromethane/water (2:1). (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (5.09 mg, 32.6 µmol, 0.210 Equiv.) and (diacetoxyiodo)benzene (124 mg, 386 µmol, 2.50 Equiv.) were added and the solution was stirred for 5 h at room temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$-solution (10 mL) and washed with saturated aqueous NaCl-solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of ethyl acetate combined with 6% glacial acetic acid as eluent. The product **37n** was obtained as a white solid in 83% yield (109 mg).

Method b: Aldehyde **37l** (crude product) (1.44 g, 1.72 mmol, 1.00 Equiv.) was dissolved in 80.0 mL of a mixture of acetonitrile/water (5:2) and NaH_2PO_4 (55.1 mg, 459 µmol, 0.267 Equiv.) and 2-methyl-2-butene (250 µL, 169 mg, 2.41 mmol, 1.40 Equiv.) were added consecutively. The mixture was cooled down to 0 °C and a solution of $NaClO_2$ (217 mg, 2.41 mmol, 1.40 Equiv.) dissolved in 1.92 mL of water was added dropwise. The solution was slowly warmed up to room temperature and stirred overnight (ca. 18 h). Afterwards, it was extracted with dichloromethane (2 × 70 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of ethyl acetate combined with 6% glacial acetic acid as eluent. The product **37n** was obtained as white solid in 61% yield (893 mg) over two steps.

R_f = 0.28 (EtOAc + 6% glacial acetic acid); m.p. 84–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.46 (d, ^3J = 8.2 Hz, 1H, N*H*), 7.35–7.22 (m, 5H, Ph), 6.05 (s, 1H, COO*H*), 5.83 (dddd, $^3J_{trans}$ = 16.7 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.1 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.21–5.09 (m, 3H, 3-H, 4-H, CH_2CH=$CH_{cis}H_{trans}$), 4.97 (t, ^3J = 9.2 Hz, 1H, 4'-H), 4.92 (t, ^3J = 8.5 Hz, 1H, 2-H), 4.79 (d, ^3J = 8.0 Hz, 1H, 1'-H), 4.75 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.55 (d, ^2J = 12.1 Hz, 1H, CH_aH_bPh), 4.50 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.39 (t, ^3J = 9.5 Hz, 1H, 3'-H), 4.32 (ddt, ^2J = 13.0 Hz, ^3J = 5.1 Hz, ^4J = 1.4 Hz, 1H, CH_aH_bCH=CH_2), 4.05 (ddt, ^2J = 13.0 Hz, ^3J = 6.2 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 4.01 (d, ^3J = 9.5 Hz, 1H, 5-H), 3.81–3.73 (m, 1H, 2'-H), 3.71–3.64 (m, 1H, 5'-H), 3.59 (dd, ^2J = 10.8 Hz, ^3J = 2.8 Hz, 1H, 6a'-H), 3.54 (dd, ^2J = 10.8 Hz, ^3J = 5.4 Hz, 1H, 6b'-H), 2.73–2.67 (m, 2H, $CH_3COCH_2CH_2COO$), 2.52–2.44 (m, 2H, $CH_3COCH_2CH_2COO$), 2.14 (s, 3H, $CH_3COCH_2CH_2COO$), 2.05 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 207.4 (C_q, $CH_3COCH_2CH_2COO$), 171.4 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 170.3 (C_q, CH_3COO), 169.6 (C_q, CH_3COO), 168.8 (C_q, COOH), 161.9 (C_q, CCl_3CONH), 137.6 (C_q, C_{Ar}), 133.3 (+, CH_2CH=CH_2), 128.4 (+, 2 × C_{Ar}H), 127.9 (+, 2 × C_{Ar}H), 127.8 (+, C_{Ar}H), 118.0 (–, CH_2CH=CH_2), 99.6 (+, C-1), 98.5 (+, C-1'), 92.5 (C_q, CCl_3CONH), 76.8 (+, C-3'), 73.5 (–, CH_2Ph), 73.1 (+, C-5'), 72.1 (+, CH), 72.0 (+, CH), 70.8 (+, C-2), 70.1 (–, CH_2CH=CH_2), 69.3 (+, C-4), 69.1 (+, C-4'), 69.0 (–, C-6'), 57.7 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 29.7 (+, $CH_3COCH_2CH_2COO$), 27.8 (–, $CH_3COCH_2CH_2COO$), 20.8 (+, CH_3COO), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 2941, 1750, 1717, 1523, 1367, 1216, 1147, 1042, 821, 756, 698, 671, 602, 490 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 876/878/880 (95/100/44) $[M+Na]^+$, 852/854/856/858 (20/28/17/2) $[M–H]^+$, 796/798/800/802 (67/71/28/4) $[M–OAllyl]^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{43}O_{17}N^{35}Cl_3$ $[M+H]^+$: 854.1591; found: 854.1593.

Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-β-D-gluco-hexodialdo-1,5-pyranosyl oxime)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (***37m***): Aldehyde **37l** (crude product) (1.21 g, 1.44 mmol, 1.00 Equiv.) was dissolved in 100 mL of tetrahydrofuran and a solution of hydroxylamine hydrochloride (100 mg, 1.44 mmol, 1.00 Equiv.) dissolved in 2.90 mL of water was added dropwise. The mixture was cooled down to 0 °C and a solution of sodium carbonate (183 mg, 1.73 mmol, 1.20 Equiv.) dissolved in 1.73 mL of water was added dropwise. The solution was slowly warmed up to room temperature and stirred for 3 h. The mixture was diluted with water (100 mL) and then extracted with ethyl acetate (3 × 150 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (2:3) as eluent. The product **37m** was obtained as a white solid in 45% yield (550 mg) as a 33:1 mixture of the *trans*/cis-isomers.

R_f = 0.31 (cyclohexane/EtOAc 2:3); m.p. 85–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) *data for the trans-isomer*: δ = 8.32 (s, 1H, O*H*), 7.36–7.23 (m, 6H, Ph, *H*C=N), 7.05 (d, ^3J = 8.0 Hz, 1H, N*H*), 5.83 (dddd, $^3J_{trans}$ = 16.7 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.1 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.12 (t, ^3J = 9.5 Hz, 1H, 3-H), 5.05 (t, ^3J = 9.6 Hz, 1H 4-H), 4.93 (dd, ^3J = 9.2 Hz, ^3J = 8.2 Hz, 1H, 2-H), 4.92 (t, ^3J = 9.1 Hz, 1H, 4'-H), 4.79 (d, ^3J = 8.0 Hz, 1H, 1'-H), 4.66 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.55 (d, ^2J = 12.1 Hz, 1H, CH_aH_bPh), 4.51 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.37–4.29 (m, 2H, 3'-H, CH_aH_bCH=CH_2), 4.06 (ddt, ^2J = 12.8 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 4.02 (dd, ^3J = 9.7 Hz, ^3J = 6.7 Hz, 1H, 5-H), 3.71–3.63 (m, 2H, 2'-H, 5'-H), 3.58 (dd, ^2J = 10.9 Hz, ^3J = 3.1 Hz, 1H, 6a'-H), 3.54 (dd, ^2J = 10.9 Hz, ^3J = 5.7 Hz, 1H, 6b'-H), 2.74–2.62 (m, 2H, $CH_3COCH_2CH_2COO$), 2.52–2.39 (m, 2H, $CH_3COCH_2CH_2COO$), 2.15 (s, 3H, $CH_3COCH_2CH_2COO$), 2.04 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO), 1.92 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS) *data for the trans-isomer*: δ = 206.8 (C_q, $CH_3COCH_2CH_2COO$), 171.4 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 169.4 (C_q, CH_3COO), 169.3 (C_q, CH_3COO), 161.9 (C_q, CCl_3CONH), 146.2 (+, H*C*=N), 137.7 (C_q, C_{Ar}), 133.2 (+, CH_2CH=CH_2), 128.4 (+, 2 × C_{Ar}H), 127.9 (+, 2 × C_{Ar}H), 127.8 (+, C_{Ar}H), 118.3 (–, CH_2CH=CH_2), 100.3 (+, C-1), 98.0 (+, C-1'), 92.4 (C_q, CCl_3CONH), 77.1 (+, C-3'), 73.6 (–, CH_2Ph), 73.3 (+, C-5'), 72.0 (+, C-3), 71.8 (+, C-5), 71.1 (+, C-2), 70.2 (–, CH_2CH=CH_2), 69.6 (+, C-4), 69.5 (+, C-4'), 69.2 (–, C-6'), 58.1 (+, C-2'), 37.6 (–, $CH_3COCH_2CH_2COO$), 29.8 (+, $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 21.0 (+, CH_3COO), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3336, 2866,

1750, 1716, 1526, 1367, 1215, 1145, 1032, 955, 820, 739, 698, 601, 490, 403 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 853/855/857/859 (25/28/11/3) $[M+H]^+$, 795/797/799/801 (50/55/20/5) $[M–OAllyl]^+$; 663 (100), 647 (51), 578 (32); HRMS (FAB, 3-NBA): calcd for $C_{35}H_{44}O_{16}N_2{}^{35}Cl_3$ $[M+H]^+$: 853.1751; found: 853.1752.

*Allyl O-(2,3-di-O-acetyl-4-O-levulinoyl-β-D-glucopyranosyluronononitrile)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37p**)*: Oxime **37m** (308 mg, 361 µmol, 1.00 Equiv.) was dissolved in 20.0 mL of dry acetonitrile and phosphoryl chloride (32.9 µL, 55.3 mg, 361 µmol, 1.00 Equiv.) was added at room temperature. The solution was stirred for 5 min, heated up to 65 °C and then stirred for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$-solution and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37p** was obtained as a light brownish solid in 40% yield (122 mg).

R_f = 0.42 (cyclohexane/EtOAc 1:1); m.p. 74–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.24 (m, 5H, Ph), 7.08 (d, ^3J = 7.7 Hz, 1H, N*H*), 5.82 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.3 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.27 (t, ^3J = 9.6 Hz, 1H, 4-H), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.0 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.03 (t, ^3J = 9.3 Hz, 1H, 3-H), 4.97–4.91 (m, 2H, 2-H, 4'-H), 4.80 (d, ^3J = 8.1 Hz, 1H, 1'-H), 4.59 (d, ^3J = 7.7 Hz, 1H, 1-H), 4.54 (d, ^2J = 12.1 Hz, 1H, CH_aH_bPh), 4.50 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.45 (t, ^3J = 9.4 Hz, 1H, 3'-H), 4.35–4.30 (m, 2H, 5-H, CH_aH_bCH=CH_2), 4.06 (ddt, ^2J = 12.8 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.70–3.65 (m, 1H, 5'-H), 3.59–3.51 (m, 3H, 2'-H, 6'-H), 2.81 (ddd, ^2J = 18.5 Hz, ^3J = 8.3 Hz, ^3J = 5.2 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.66 (ddd, ^2J = 18.5 Hz, ^3J = 6.3 Hz, ^3J = 5.1 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.59–2.45 (m, 2H, $CH_3COCH_2CH_2COO$), 2.14 (s, 3H, $CH_3COCH_2CH_2COO$), 2.03 (s, 3H, CH_3COO), 2.03 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 205.9 (C_q, $CH_3COCH_2CH_2COO$), 170.7 (C_q, $CH_3COCH_2CH_2COO$), 170.1 (C_q, CH_3COO), 169.6 (C_q, CH_3COO), 168.9 (C_q, CH_3COO), 162.1 (C_q, CCl_3CONH), 137.6 (C_q, C_{Ar}), 133.1 (+, CH_2CH=CH_2), 128.3 (+, 2 × C_{Ar}H), 127.8 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.4 (–, CH_2CH=CH_2), 114.1 (C_q, C≡N), 100.9 (+, C-1), 97.6 (+, C-1'), 92.2 (C_q, CCl_3CONH), 77.8 (+, C-3'), 73.5 (–, CH_2Ph), 73.2 (+, C-5'), 70.9 (+, C-3), 70.2 (–, CH_2CH=CH_2), 70.2 (+, C-4'), 69.3 (+, C-2), 68.9 (–, C-6'), 68.7 (+, C-4), 62.7 (+, C-5), 58.3 (+, C-2'), 37.5 (–, $CH_3COCH_2CH_2COO$), 29.5 (+, $CH_3COCH_2CH_2COO$), 27.5 (–, $CH_3COCH_2CH_2COO$), 21.0 (+, CH_3COO), 20.5 (+, CH_3COO), 20.4 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3335, 2922, 1753, 1716, 1524, 1368, 1210, 1140, 1053, 894, 838, 821, 735, 698, 676, 601, 490, 431, 409, 381 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 857/859/861/863 $[M+Na]^+$.

*Allyl ((5R) 2,3-O-acetyl-4-O-levulinoyl-5-C-(2H-tetrazol-5-yl)-β-D-xylopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosid (**37q**)*: Nitrile **37p** (97.3 mg, 116 µmol, 1.00 Äquiv.) was dissolved in 10.0 mL of absolute toluene under argon atmosphere and trimethylsilyl azide (45.9 µL, 40.2 mg, 349 µmol, 3.00 Äquiv.) and dibutyltin(IV) oxide (5.78 mg, 23.2 µmol, 0.200 Äquiv.) were added consecutively. The mixture was heated up to 120 °C and stirred for 5 h. After that, the mixture was cooled down to room temperature, diluted with ethyl acetate (50 mL) and washed with an aqueous 0.1 M HCl-solution (30 mL). The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by preparative HPLC (5–95% acetonitrile + 0.1% TFA in 30 min, 25 °C, t_{Ret} = 27.5 min). After lyophilization the product **37q** was obtained as a white solid in 47% yield (48.2 mg).

m.p. 100–110 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.02 (sbr, 1H, N*H*), 7.34–7.26 (m, 5H, Ph), 5.86 (dddd, $^3J_{trans}$ = 16.7 Hz, $^3J_{cis}$ = 10.7 Hz, ^3J = 5.9 Hz, ^3J = 5.3 Hz, 1H, CH_2CH=CH_2), 5.36 (t, ^3J = 9.3 Hz, 1H, 3-H), 5.30–5.23 (m, 3H, CH_2CH=$CH_{cis}H_{trans}$, 4-H, 5-H), 5.19 (dq, $^3J_{cis}$ = 10.5 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.13 (d, ^3J = 7.9 Hz, 1H, 1-H), 5.05 (t, ^3J = 8.6 Hz, 1H, 2-H), 4.91 (t, ^3J = 6.8 Hz, 1H, 4'-H), 4.70 (d, ^3J = 7.6 Hz, 1H, 1'-H), 4.56 (d, ^2J = 11.9 Hz, 1H, CH_aH_bPh), 4.50 (d, ^2J = 11.9 Hz, 1H, CH_aH_bPh), 4.34 (ddt, ^2J = 13.0 Hz, ^3J = 5.0 Hz, ^4J = 1.4 Hz, 1H, CH_aH_bCH=CH_2), 4.24 (t, ^3J = 8.8 Hz, 1H, 3'-H), 4.15–4.06 (m, 2H, CH_aH_bCH=CH_2, 2'-H), 3.68–3.58 (m, 3H, 5'-H, 6'-H), 2.76 (ddd, ^2J = 18.5 Hz, ^3J = 8.8 Hz, ^3J = 4.5 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.64 (ddd, ^2J = 18.5 Hz, ^3J = 6.1 Hz, ^3J = 4.8 Hz 1H, $CH_3COCH_aH_bCH_2COO$), 2.55 (ddd, ^2J = 16.9 Hz, ^3J = 8.7 Hz, ^3J = 4.3 Hz, 1H, $CH_3COCH_2CH_aH_bCOO$), 2.41 (ddd, ^2J = 17.2 Hz, ^3J = 6.1 Hz, ^3J = 4.8 Hz, 1H, $CH_3COCH_2CH_aH_bCOO$), 2.13 (s, 3H, $CH_3COCH_2CH_2COO$), 2.12 (s, 3H, CH_3COO), 2.06 (s, 3H, CH_3COO), 1.88 (s, 3H, CH_3COO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.5 (C_q, $CH_3COCH_2CH_2COO$), 171.2 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 170.1 (C_q, CH_3COO), 170.1 (C_q, CH_3COO), 162.3 (C_q, CCl_3CONH), 162.3 (C_q, tetrazole), 137.4 (C_q, C_{Ar}), 133.1 (+, CH_2CH=CH_2), 128.5 (+, 2 × C_{Ar}H), 128.0 (+, 2 × C_{Ar}H), 128.0 (+, C_{Ar}H), 118.0 (–, CH_2CH=CH_2), 100.4 (+, C-1), 99.2 (+, C-1'), 92.6 (C_q, CCl_3CONH), 77.0 (+, C-3'), 73.7 (–, CH_2Ph), 72.7 (+, C-5'), 71.2 (+, C-3), 70.7 (+, C-2), 70.7 (+, C-4'), 70.3 (+, C-4), 70.2 (–, CH_2CH=CH_2), 68.8 (–, C-6'), 67.3 (+, C-5), 56.3 (+, C-2'), 37.6 (–, $CH_3COCH_2CH_2COO$), 29.5 (+ $CH_3COCH_2CH_2COO$), 27.7 (–, $CH_3COCH_2CH_2COO$), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO), 20.5 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 2870, 1753, 1718, 1526, 1368, 1214, 1146, 1040, 912, 822, 756, 698, 673, 603, 489, 398 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 900/902/904/906 (91/100/40/7) $[M+Na]^+$, 878/880/882/884 (38/40/17/5) $[M+H]^+$, 820/822/824/826 (20/21/9/6) $[M–OAllyl]^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{43}O_{15}N_5{}^{35}Cl_3$ $[M+H]^+$: 878.1816; found: 878.1815; Analytical HPLC (5–95% acetonitrile + 0.1% TFA in 20 min, detection at 218 nm): t_{Ret} = 15.1 min; IR (ATR): $\tilde{\nu}$ = 2870, 1753, 1718, 1526, 1368, 1214, 1146, 1040, 912, 822, 756, 698, 673, 603, 489, 398 cm^{-1}; MS (FAB, 3-NBA): m/z (%): 900/902/904/906 (91/100/40/7) $[M+Na]^+$, 878/880/882/884 (38/40/17/5) $[M+H]^+$, 820/822/824/826 (20/21/9/6) $[M–OAllyl]^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{43}O_{15}N_5{}^{35}Cl_3$ $[M+H]^+$: 878.1816; found: 878.1815; Analytical HPLC (5–95% acetonitrile + 0.1% TFA in 20 min, detection at 218 nm): t_{Ret} = 15.1 min; elemental analysis calcd (%) for $C_{35}H_{42}O_{15}N_5Cl_3$: C 47.82, H 4.82, N 7.97; found C 46.38, H 4.68, N 7.55.

*Allyl O-(methyl 2,3-di-O-acetyl-4-O-levulinoyl-β-D-glucopyranosyluronate)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37o**)*: Carboxylic acid **37n** (79.9 mg, 93.4 µmol, 1.00 Equiv.) was dissolved in 10.0 mL of absolute dichloromethane under argon atmosphere and cooled down to 0 °C. Oxalyl chloride (12.2 µL,

17.8 mg, 140 µmol, 1.50 Equiv.) and *N*,*N*-dimethylformamide (12.9 µL, 10.2 mg, 140 µmol, 1.50 Equiv.) were added consecutively. The solution was stirred for 1 h at 0 °C and then 1 h at room temperature. Afterwards, 500 µL of dry methanol were added and the solution was stirred for further 1 h. The mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous $NaHCO_3$-solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (2:3) as eluent. The product **37o** was obtained as a white solid in 80% yield (65.3 mg).

R_f = 0.41 (cyclohexane/EtOAc 2:3); m.p. 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35–7.25 (m, 5H, Ph), 7.06 (d, ^3J = 7.6 Hz, 1H, N*H*), 5.83 (dddd, $^3J_{trans}$ = 16.7 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.1 Hz, ^3J = 5.4 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.17 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.14–5.09 (m, 2H, 3-H, 4-H), 4.97 (t, ^3J = 9.3 Hz, 1H, 4'-H), 4.94–4.89 (m, 1H, 2-H), 4.89 (d, ^3J = 8.1 Hz, 1H, 1'-H), 4.66 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.54 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.50 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.41 (t, ^3J = 9.5 Hz, 1H, 3'-H), 4.32 (ddt, ^2J = 12.8 Hz, ^3J = 5.2 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 4.06 (ddt, ^2J = 12.8 Hz, ^3J = 6.4 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 3.95 (m, 1H, 5-H), 3.71 (s, 3H, OCH_3), 3.69–3.64 (m, 1H, 5'-H), 3.60–3.50 (m, 3H, 2'-H, 6'-H), 2.71–2.65 (m, 2H, $CH_3COCH_2CH_2COO$), 2.46 (t, ^3J = 6.2 Hz, 2H, $CH_3COCH_2CH_2COO$), 2.14 (s, 3H, $CH_3COCH_2CH_2COO$), 2.02 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 205.8 (C_q, $CH_3COCH_2CH_2COO$), 171.1 (C_q, $CH_3COCH_2CH_2COO$), 170.1 (C_q, CH_3COO), 169.7 (C_q, CH_3COO), 169.1 (C_q, CH_3COO), 166.9 (C_q, $COOCH_3$), 161.9 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.2 (+, CH_2CH=CH_2), 128.3 (+, 2 × C_{Ar}H), 127.8 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.2 (–, CH_2CH=CH_2), 99.5 (+, C-1), 97.8 (+, C-1'), 92.3 (C_q, CCl_3CONH), 76.4 (+, C-3'), 73.5 (–, CH_2Ph), 73.4 (+, C-5'), 72.2 (+, C-5), 71.9 (+, C-3), 70.9 (+, C-2), 70.3 (–, CH_2CH=CH_2), 69.3 (+, C-4), 69.0 (–, C-6'), 68.7 (+, C-4'), 58.5 (+, C-2'), 52.8 (+, $COOCH_3$), 37.5 (–, $CH_3COCH_2CH_2COO$), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.6 (–, $CH_3COCH_2CH_2COO$), 20.6 (+, CH_3COO), 20.6 (+, CH_3COO), 20.5 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3344, 2924, 1753, 1714, 1522, 1434, 1366, 1262, 1216, 1133, 1092, 1049, 1018, 979, 942, 919, 887, 819, 757, 735, 693, 665, 639, 498, 444, 393 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 890/892/894/896 [*M*+Na]$^+$.

*Allyl O-(2,3-di-O-acetyl-6-acetyl-6-deoxy-4-O-levulinoyl-6-thio-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37g**)*: Tosylate **37e** (80.0 mg, 80.4 µmol, 1.00 Equiv.) was dissolved in 5.00 mL of dry *N*,*N*-dimethylformamide and potassium thioacetate (27.5 mg, 241 µmol, 3.00 Equiv.) was added. The solution was heated up to 80 °C and stirred for 2 h. After that, the solution was diluted with water (50 mL) and ethyl acetate (100 mL). The mixture was washed with saturated aqueous $NaHCO_3$-solution (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37g** was obtained as a white foam in 84% yield (60.7 mg).

R_f = 0.26 (cyclohexane/EtOAc 1:1); m.p. 64–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.26 (m, 5H, Ph), 6.94 (d, ^3J = 7.7 Hz, 1H, N*H*), 5.84 (dddd, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.3 Hz, ^3J = 6.3 Hz, ^3J = 5.3 Hz, 1H, CH_2CH=CH_2), 5.27 (dq, $^3J_{trans}$ = 17.3 Hz, ^2J and ^4J = 1.5 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.19 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.05 (t, ^3J = 9.5 Hz, 1H, 3-H), 4.99–4.93 (m, 2H, 4-H, 4'-H), 4.91 (d, ^3J = 7.8 Hz, 1H, 1'-H), 4.87 (dd, ^3J = 9.6 Hz, ^3J = 8.0 Hz, 1H, 2-H), 4.60 (d, ^3J = 8.0 Hz, 1H, 1-H), 4.56 (d, ^2J = 12.0 Hz, 1H, CH_aH_bPh), 4.52 (d, ^2J = 11.9 Hz, 1H, CH_aH_bPh), 4.37 (t, ^3J = 9.3 Hz, 1H, 3'-H), 4.33 (ddt, ^2J = 12.8 Hz, ^3J = 5.3 Hz, ^4J = 1.3 Hz, 1H, CH_aH_bCH=CH_2), 4.07 (ddt, ^2J = 12.8 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, CH_aH_bCH=CH_2), 3.70 (ddd, ^3J = 9.1 Hz, ^3J = 5.4 Hz, ^3J = 3.6 Hz, 1H, 5'-H), 3.62–3.51 (m, 4H, 5-H, 2'-H, 6'-H), 3.25 (dd, ^2J = 14.4 Hz, ^3J = 2.8 Hz, 1H, 6a-H), 2.96 (dd, ^2J = 14.4 Hz, ^3J = 7.4 Hz, 1H, 6b-H), 2.78 (dt, ^2J = 18.5 Hz, ^3J = 6.6 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.69 (dt, ^2J = 18.5 Hz, ^3J = 6.0 Hz, 1H, $CH_3COCH_aH_bCH_2COO$), 2.54 (t, ^3J = 6.3 Hz, 2H, $CH_3COCH_2CH_2COO$), 2.35 (s, 3H, CH_3COS), 2.16 (s, 3H, $CH_3COCH_2CH_2COO$), 2.01 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO), 1.97 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 206.0 (C_q, $CH_3COCH_2CH_2COO$), 194.7 (C_q, CH_3COS), 171.5 (C_q, $CH_3COCH_2CH_2COO$), 170.3 (C_q, CH_3COO), 169.3 (C_q, CH_3COO), 169.1 (C_q, CH_3COO), 161.8 (C_q, CCl_3CONH), 137.7 (C_q, C_{Ar}), 133.3 (+, CH_2CH=CH_2), 128.4 (+, 2 × C_{Ar}H), 127.9 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.0 (–, CH_2CH=CH_2), 99.4 (+, C-1), 97.7 (+, C-1'), 92.3 (C_q, CCl_3CONH), 75.8 (+, C-3'), 73.6 (–, CH_2Ph), 73.4 (+, C-5'), 73.3 (+, C-5), 72.4 (+, C-3), 71.3 (+, C-2), 70.5 (+, C-4'), 70.3 (–, CH_2CH=CH_2), 69.3 (–, C-6'), 68.9 (+, C-4), 58.3 (+, C-2'), 37.7 (–, $CH_3COCH_2CH_2COO$), 30.5 (+ CH_3COS), 29.9 (–, C-6), 29.6 (+, $CH_3COCH_2CH_2COO$), 27.8 (–, $CH_3COCH_2CH_2COO$), 20.9 (+, CH_3COO), 20.7 (+, CH_3COO), 20.6 (+, CH_3COO) ppm; IR (ATR): $\tilde{\nu}$ = 3349, 2927, 1752, 1718, 1527, 1366, 1216 1147, 1051, 909, 838, 821, 734, 698, 674, 622, 488, 403 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 920/922/924/926 [*M*+Na]$^+$.

*Allyl O-(2,3-di-O-acetyl-6-azido-6-deoxy-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37b**)*: Tosylate **37e** (80.0 mg, 80.4 µmol, 1.00 Equiv.) was dissolved in 5.00 mL of dry *N*,*N*-dimethylformamide and sodium azide (6.53 mg, 100 µmol, 1.25 Equiv.) was added. The solution was heated up to 80 °C and was stirred for 4 h. The solution was cooled down to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was washed with water (50 mL) and saturated aqueous NaCl-solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37b** was obtained as a white foam in 78% yield (54.6 mg).

R_f = 0.45 (cyclohexane/EtOAc 1:1); m.p. 72–82 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.25 (m, 5H, Ph), 6.93 (d, ^3J = 8.0 Hz, 1H, N*H*), 5.84 (dddd, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.2 Hz, ^3J = 5.3 Hz, 1H, CH_2CH=CH_2), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.4 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.2 Hz, 1H, CH_2CH=$CH_{cis}H_{trans}$), 5.09 (t, ^3J = 9.5 Hz, 1H, 3-H), 5.00–4.91 (m, 2H, 4-H, 4'-H), 4.88 (dd, ^3J = 9.4 Hz, ^3J = 8.0 Hz, 1H, 2-H), 4.82 (d, ^3J = 7.5 Hz, 1H, 1'-H), 4.67 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.55 (d, ^2J =

12.0 Hz, 1H, CH_aH$_b$Ph), 4.51 (d, ^2J = 12.0 Hz, 1H, CH$_a$$H_b$Ph), 4.37–4.29 (m, 2H, 3'-H, CH_aH$_b$CH=CH$_2$), 4.05 (ddt, ^2J = 12.8 Hz, ^3J = 6.3 Hz, ^4J = 1.2 Hz, 1H, CH$_a$$H_b$CH=CH$_2$), 3.72–3.63 (m, 2H, 2'-H, 5'-H), 3.63–3.52 (m, 3H, 5-H, 6'-H), 3.39 (d, ^3J = 4.7 Hz, 2H, 6-H), 2.80–2.65 (m, 2H, CH$_3$COCH_2CH$_2$COO), 2.52–2.37 (m, 2H, CH$_3$COCH$_2$CH_2COO), 2.15 (s, 3H, CH_3COCH$_2$CH$_2$COO), 2.03 (s, 3H, CH_3COO), 2.00 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO) ppm; ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C, TMS): δ = 206.2 (C$_q$, CH$_3$*C*OCH$_2$CH$_2$COO), 171.5 (C$_q$, CH$_3$COCH$_2$CH$_2$*C*OO), 170.2 (C$_q$, CH$_3$*C*OO), 169.3 (C$_q$, CH$_3$*C*OO), 169.2 (C$_q$, CH$_3$*C*OO), 161.7 (C$_q$, CCl$_3$*C*ONH), 137.8 (C$_q$, C_{Ar}), 133.2 (+, CH$_2$*C*H=CH$_2$), 128.3 (+, 2 × C_{Ar}H), 127.8 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.2 (–, CH$_2$CH=*C*H$_2$), 99.5 (+, C-1), 97.8 (+, C-1'), 92.4 (C$_q$, *C*Cl$_3$CONH), 75.6 (+, C-3'), 73.5 (–, *C*H$_2$Ph), 73.4 (+, C-5'), 73.2 (+, C-5), 72.4 (+, C-3), 71.2 (+, C-2), 70.1 (–, *C*H$_2$CH=CH$_2$), 69.4 (+, C-4), 69.2 (–, C-6'), 69.0 (+, C-4'), 57.6 (+, C-2'), 50.8 (–, C-6), 37.7 (–, CH$_3$COCH$_2$CH$_2$COO), 29.6 (+, *C*H$_3$COCH$_2$CH$_2$COO), 27.7 (–, CH$_3$COCH$_2$*C*H$_2$COO), 20.9 (+, *C*H$_3$COO), 20.6 (+, *C*H$_3$COO), 20.6 (+, *C*H$_3$COO) ppm; IR (ATR): $\tilde{\nu}$ = 3345, 2923, 2103, 1751, 1716, 1526, 1366, 1215, 1147, 1050, 900, 821, 756, 698, 671, 602, 488, 389 cm^{-1}; MS (MALDI, matrix: DHB/CHCA 1:1): *m/z*: 887/889/891/893 [*M*+Na]$^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{44}O_{15}N_4{}^{35}Cl_3$ [*M*+H]$^+$: 865.1863; found: 865.1867.

*Allyl O-(2,3-di-O-acetyl-6-deoxy-4-O-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**37a**)*: Acceptor **36** (737 mg, 1.48 mmol, 1.00 Equiv.) and donor **22a** (730 mg, 1.87 mmol, 1.26 Equiv.) were dissolved in 10.0 mL of absolute dichloromethane under argon atmosphere and 4 Å molecular sieve powder (215 mg) was added. The mixture was stirred for 1 h at room temperature and then cooled down to –30 °C. *N*-Iodosuccinimide (501 mg, 2.23 mmol, 1.50 Equiv.) and trimethylsilyl trifluoromethanesulfonate (20.0 µL, 24.6 mg, 111 µmol, 0.0747 Equiv.) were added consecutively and the mixture was stirred for 1.5 h. The mixture was filtered through a pad of celite and the filtrate was washed with 5% aqueous $Na_2S_2O_3$-solution (50 mL), saturated aqueous $NaHCO_3$-solution (50 mL) and water (50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate (1:1) as eluent. The product **37a** was obtained as a yellowish foam in 33% yield (407 mg).

R_f = 0.33 (cyclohexane/EtOAc 1:1); m.p. 74–87 °C; ^{1}H NMR (600 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.36–7.25 (m, 5H, Ph), 6.88 (d, ^3J = 7.6 Hz, 1H, N*H*), 5.85 (dddd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.2 Hz, ^3J = 5.2 Hz, 1H, CH$_2$C*H*=CH$_2$), 5.26 (dq, $^3J_{trans}$ = 17.2 Hz, ^2J and ^4J = 1.3 Hz, 1H, CH$_2$CH=CH$_{cis}$*H*$_{trans}$), 5.19 (dq, $^3J_{cis}$ = 10.4 Hz, ^2J and ^4J = 1.3 Hz, 1H, CH$_2$CH=C*H*$_{cis}$H$_{trans}$), 5.02 (t, ^3J = 9.5 Hz, 1H, 3-H), 4.94–4.85 (m, 3H, 2-H, 1'-H, 4'-H), 4.78 (t, ^3J = 9.6 Hz, 1H, 4-H), 4.55 (d, ^2J = 12.1 Hz, 1H, CH_aH$_b$Ph), 4.55 (d, ^3J = 7.9 Hz, 1H, 1-H), 4.53 (d, ^2J = 12.1 Hz, 1H, CH$_a$$H_b$Ph), 4.38 (t, ^3J = 9.2 Hz, 1H, 3'-H), 4.33 (ddt, ^2J = 12.8 Hz, ^3J = 5.3 Hz, ^4J = 1.3 Hz, 1H, CH_aH$_b$CH=CH$_2$), 4.08 (ddt, ^2J = 12.8 Hz, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 1H, CH$_a$$H_b$CH=CH$_2$), 3.74–3.70 (m, 1H, 5'-H), 3.60 (dd, ^2J = 10.8 Hz, ^3J = 3.1 Hz, 1H, 6a'-H), 3.57 (dd, ^2J = 10.8 Hz, ^3J = 5.6 Hz, 1H, 6b'-H), 3.56–3.45 (m, 2H, 5-H, 2'-H), 2.75–2.66 (m, 2H, CH$_3$COCH_2CH$_2$COO), 2.54–2.42 (m, 2H, CH$_3$COCH$_2$CH_2COO), 2.15 (s, 3H, CH_3COCH$_2$CH$_2$COO), 2.02 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO), 1.96 (s, 3H, CH_3COO), 1.22 (d, ^3J = 6.1 Hz, 3H, 6-H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C, TMS): δ = 206.2 (C$_q$, CH$_3$*C*OCH$_2$CH$_2$COO), 171.5 (C$_q$, CH$_3$COCH$_2$CH$_2$*C*OO), 170.4 (C$_q$, CH$_3$*C*OO), 169.4 (C$_q$, CH$_3$*C*OO), 169.3 (C$_q$, CH$_3$*C*OO), 161.8 (C$_q$, CCl$_3$*C*ONH), 137.6 (C$_q$, C_{Ar}), 133.2 (+, CH$_2$*C*H=CH$_2$), 128.3 (+, 2 × C_{Ar}H), 127.8 (+, 2 × C_{Ar}H), 127.7 (+, C_{Ar}H), 118.4 (–, CH$_2$CH=*C*H$_2$), 100.0 (+, C-1), 97.6 (+, C-1'), 92.2 (C$_q$, *C*Cl$_3$CONH), 76.2 (+, C-3'), 73.5 (–, *C*H$_2$Ph), 73.2 (+, C-5'), 73.1 (+, C-4), 72.6 (+, C-3), 71.5 (+, C-2), 70.2 (–, *C*H$_2$CH=CH$_2$), 70.0 (+, C-5), 69.4 (+, C-4'), 69.0 (–, C-6'), 58.4 (+, C-2'), 37.6 (–, CH$_3$COCH_2CH$_2$COO), 29.6 (+, *C*H$_3$COCH$_2$CH$_2$COO), 27.7 (–, CH$_3$COCH$_2$CH$_2$COO), 21.0 (+, *C*H$_3$COO), 20.7 (+, *C*H$_3$COO), 20.6 (+, *C*H$_3$COO), 17.4 (+, C-6) ppm; IR (ATR): $\tilde{\nu}$ = 2872, 1750, 1715, 1528, 1367, 1217, 1149, 1055, 916, 821, 756, 698, 672, 603, 489 cm^{-1}; MS (FAB, 3-NBA): *m/z* (%): 822/824/826/828 (30/32/20/8 [*M*–H]$^+$, 766/768/770/772 (100/99/42/8) [*M*–OAllyl]$^+$; HRMS (FAB, 3-NBA): calcd for $C_{35}H_{43}O_{15}N^{35}Cl_3$ [*M*–H]$^+$: 822.1693; found: 822.1694.

CCDC 1534116 (**6**), 1534118 (**7**), 1534119 (**13**), 1534117 (**15**), 1534120 (**16**), 1534121 (**27**), 1534122 (**29**), 1534123 (**30**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We gratefully acknowledge the Baden-Württemberg Stiftung and the DFG (SFB 1176) for the financial support of this work. We also thank Benjamin E. Görling for his previous work on this field

Keywords: Hyaluronic acid • Synthesis • Oligosaccharides • Derivatization • Glycosides

[1] K. Meyer, J. W. Palmer, *J. Biol. Chem.* **1934**, *107*, 629-634.

[2] a) J. R. E. Fraser, T. C. Laurent, U. B. G. Laurent, *J. Intern. Med.* **1997**, *242*, 27-33; b) M. Mende, C. Bednarek, M. Wawryszyn, P. Sauter, M. B. Biskup, U. Schepers, S. Bräse, *Chem. Rev.* **2016**, *116*, 8193-8255.

[3] J. E. Scott, F. Heatley, W. E. Hull, *Biochem. J.* **1984**, *220*, 197-205.

[4] J. E. Scott, C. Cummings, A. Brass, Y. Chen, *Biochem. J.* **1991**, *274*, 699-705.

[5] a) T. C. Laurent, U. B. Laurent, J. R. Fraser, *Ann. Rheum. Dis.* **1995**, *54*, 429-432; b) H. Fam, J. Bryant, M. Kontopoulou, *Biorheology* **2007**, *44*, 59-74.

[6] H. J. Granger, G. A. Laine, G. E. Barnes, R. E. Lewis, in *Edema, Vol. 8* (Eds.: N. C. Staub, A. E. Taylor), Raven Press, New York, **1984**, pp. 189-228.

[7] N. Itano, K. Kimata, *IUBMB Life* **2002**, *54*, 195-199.

[8] T. C. Laurent, U. B. G. Laurent, J. R. E. Fraser, *Immunol. Cell Biol.* **1996**, *74*, A1-A7.

[9] T. C. Laurent, J. R. Fraser, *FASEB J.* **1992**, *6*, 2397-2404.

[10] a) C. B. Knudson, W. Knudson, *FASEB J.* **1993**, *7*, 1233-1241; b) C. Zeng, B. P. Toole, S. D. Kinney, J.-w. Kuo, I. Stamenkovic, *Int. J. Cancer* **1998**, *77*, 396-401.

[11] B. Yang, B. L. Yang, R. C. Savani, E. A. Turley, *EMBO J.* **1994**, *13*, 286-296.

[12] R. Stern, A. A. Asari, K. N. Sugahara, *Eur. J. Cell Biol.* **2006**, *85*, 699-715.

[13] a) C. L. Hall, B. Yang, X. Yang, S. Zhang, M. Turley, S. Samuel, L. A. Lange, C. Wang, G. D. Curpen, R. C. Savani, A. H. Greenberg, E. A. Turley, *Cell* **1995**, *82*, 19-28; b) W. Y. J. Chen, G. Abatangelo, *Wound Repair. Regen.* **1999**, *7*, 79-89; c) E. Puré, C. A. Cuff, *Trends Mol. Med.* **2001**, *7*, 213-221; d) T. Murai, H. Kawashima, *Biochem. Biophys. Res. Commun.* **2008**, *376*, 620-624.

[14] a) J. Dinkelaar, J. D. Codée, L. J. van den Bos, H. S. Overkleeft, G. A. van der Marel, *J. Org. Chem.* **2007**, *72*, 5737-5742; b) L. Huang, X. Huang, *Chem. Eur. J.* **2007**, *13*, 529-540; c) J. Dinkelaar, H. Gold, H. S. Overkleeft, J. D. Codée, G. A. van der Marel, *J. Org. Chem.* **2009**, *74*, 4208-4216; d) X. Lu, M. N. Kamat, L. Huang, X. Huang, *J. Org. Chem.* **2009**, *74*, 7608-7617; e) M. Virlouvet, M. Gartner, K. Koroniak, J. P. Sleeman, S. Bräse, *Adv. Synth. Catal.* **2010**, *352*, 2657-2662; f) H. Gold, S. Munneke, J. Dinkelaar, H. S. Overkleeft, J. M. Aerts, J. D. Codée, G. A. van der Marel, *Carbohydr. Res.* **2011**, *346*, 1467-1478; g) G. Gu, P. J. P. Adabala, M. G. Szczepina, S. Borrelli, B. M. Pinto, *J. Org. Chem.* **2013**, *78*, 8004-8019; h) S. Rigol, L. Xia, A. Giannis, *Bioorg. Med. Chem.* **2013**, *21*, 733-741; i) G. Macchione, J. L. de Paz, P. M. Nieto, *Carbohydr. Res.* **2014**, *394*, 17-25.

[15] a) C. Lopin, J. C. Jacquinet, *Angew. Chem. Int. Ed.* **2006**, *45*, 2574-2578; b) A. Ferrer Lopez, J. C. Jacquinet, C. Lopin- Bon, *Eur. J. Org. Chem.* **2013**, *2013*, 6934-6947.

[16] a) M. T. Walvoort, A. G. Volbeda, N. R. Reintjens, H. van den Elst, O. J. Plante, H. S. Overkleeft, G. A. van der Marel, J. D. Codée, *Org. Lett.* **2012**, *14*, 3776-3779; b) A. R. de Jong, A. G. Volbeda, B. Hagen, H. van den Elst, H. S. Overkleeft, G. A. van der Marel, J. D. Codée, *Eur. J. Org. Chem.* **2013**, *2013*, 6644-6655.

[17] S. Valerio, A. Iadonisi, M. Adinolfi, A. Ravidà, *J. Org. Chem.* **2007**, *72*, 6097-6106.

[18] M. Poláková, M. U. Roslund, F. S. Ekholm, T. Saloranta, R. Leino, *Eur. J. Org. Chem.* **2009**, *2009*, 870-888.

[19] R. N. Desai, L. F. Blackwell, *Synlett* **2003**, *2003*, 1981-1984.

[20] G. Barlin, D. Perrin, *Q. Rev. Chem. Soc.* **1966**, *20*, 75-101.

[21] R. Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801-811.

[22] Z. Guan, L.-H. Zhang, P. Sinaÿ, Y. Zhang, *J. Org. Chem.* **2012**, *77*, 8888-8895.

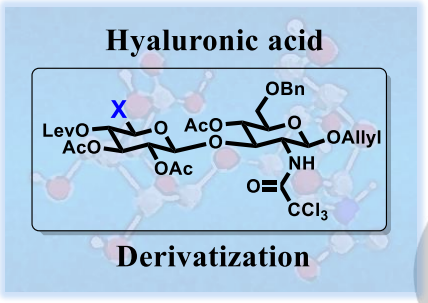
[23] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

[24] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.

10.1002/chem.201701238

FULL PAPER

Various novel hyaluronic acid disaccharide derivatives with a distinct protecting group pattern providing an easy access to higher oligomers were synthesized. ^{1}H NMR studies showed essential changes in the electronic environment within the molecules, especially in the hydrogen bonding amide proton, which could result in new properties or biological activities concerning the appropriate higher oligomers.



*M. Mende, M. Nieger, S. Bräse**

Page No. – Page No.

Chemical Synthesis Towards Modified Hyaluronic Acid Disaccharides