Selectin Antagonists:

Synthesis and Conformational Comparison

of *C*- and *O*-glycosidic Tetrasaccharide Mimetics

related to Sialyl Lewis^x.

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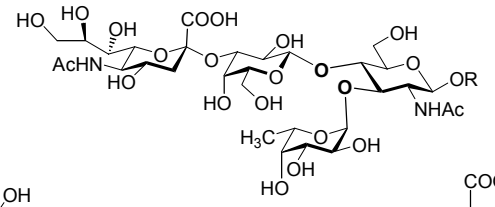
Declaration

I declare, that I wrote this thesis "*Selectin Antagonists: Synthesis and Conformational Comparison of C- and O-glycosidic Tetrasaccharide Mimetics related to Sialyl Lewis*^{x}" with the help indicated and only handed it in to the faculty of science of the University of Basel and to no other faculty and no other university.

Christian Müller, Basel, 06th of July 2004

Abstract

Numerous disease states can be traced back to an excessive or uncontrolled leukocyte accumulation to sites of inflammation or tissue injury. This recruitment of leukocytes, under normal conditions a vital defense mechanism against invading pathogens, is mediated by the interaction of the selectins with their physiological carbohydrate determinant sLe^x (**3**) as binding epitope of the natural selectin ligands. SLe^x (**3**) served as lead structure in the development of selectin antagonists, which have been considered as a promising therapeutic approach against these diseases. *C*-glycosidic structures play a prominent role in developing hydrolytically stable mimetics as well as in understanding conformational issues relevant for the binding process.



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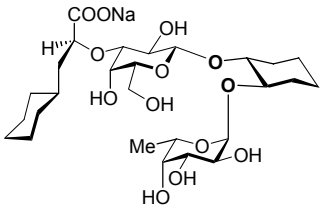

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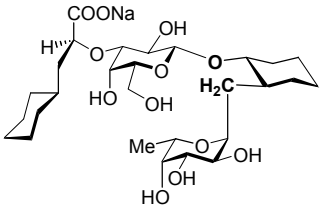

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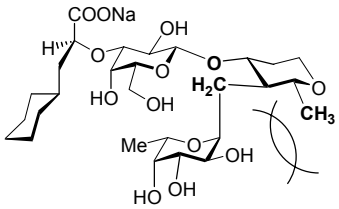


82

C-glycosidic sLe^x mimetics **81a** and **82** were designed to investigate the influence of the *exo*-anomeric effect on the conformational stability and the biological activity of these tetrasaccharide mimetics. Flexibility of target compound **81a** should be enhanced due to the lacking *exo*-anomeric effect around the *C*-glycosidic linkage. Implementation of steric constraints as the methyl group in compound **82** should proof the hypothesis, that the missing *exo*-anomeric effect can be compensated by steric factors. Furthermore, comparison of binding affinity should allow a quantification of the entropy contribution to the inhibitory potential caused by the *exo*-anomeric effect.

We successfully developed a synthesis for the target tetrasaccharide mimetics **81a** and **82** based on the Giese radical addition of an anomeric fucosyl radical to the electron deficient double bond of an enone system. Conformational investigation of the target molecules revealed the possibility to compensate for the loss of the *exo*-anomeric effect by the introduction of sterically demanding substituents next to the *C*-glycosidic linkage. The influence of the 20-30% larger distance of $H\text{-}5^{Fuc}$ and $H\text{-}2^{Gal}$ in compound **82** compared to *O*-glycosidic mimic **33** on biological activity has to be proven by current investigation.

Abbreviations

Ac	acetyl
AIBN	azoisobutyronitrile
Asn	asparagine
b.p.	boiling point
Bn	benzyl
BSA	bovine serum albumine
Bz	benzoyl
CD	circular dichroism
CRD	carbohydrate recognition domain
DMAP	2,5-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMTST	dimethy(methylthio)sulfonium triflate
dr	diastereomeric ratio
EGF	epidermal growth factor
eq.	equivalents
ESL-1	E-selectin ligand 1
Fuc	fucose
Gal	galactose
Glc*N*Ac	*N*-acetyl-glucosamine
GlyCAM-1	Glycosylation-dependent cell adhesion molecule 1
h	hour(s)
HEV	high endothelial venules
HOMO	highest occupied molecular orbital
HUVEC	human umbilical vein endothelial cells
ICAM-1	intercellular cell adhesion molecule 1
IL-1	interleukine-1
IR	infrared spectroscopy
kDa	kilo Dalton
LAD	leukocyte adhesion deficiency
LUMO	lowest unoccupied molecular orbital
MAb	monoclonal antibody
MadCAM-1	mucosal vascular addressin cell adhesion molecule 1
Man	mannose

MBP	mannose binding protein
Me	methyl
MeOH	methanol
min	minute(s)
MS	molecular sieves
mw	microwave
NaOMe	sodium methoxide
Neu*N*Ac	*N*-acetyl-neuraminic acid
NIS	*N*-iodo succinimide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
ORD	optical rotatory dispersion
PAGE	polyacryl gel electrophoresis
PDC	pyridinium chloro chromate
Ph	phenyl
Piv	pivaloyl
PMN	polymorphonuclear neutrophils
PSGL-1	P-selectin glycoprotein ligand 1
pyr	pyridine
Rf	retention factor
ROESY	nuclear overhauser enhancement spectroscopy in a rotating frame
satd.	saturated
SCR	short consensus repeats
Ser	serine
Sia	sialic acid
sLe^a	sialyl Lewis^a
sLe^x	sialyl Lewis^x
SOMO	single occupied molecular orbital
SPR	surface plasmon resonance
TBAF	*tert*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	friflate (triflouromethanesulfonate)
TfOH	trifluoromethanesulfonic acid
Thr	threonine
TLC	thin layer chromatography
TMS	trimethylsilyl
TNF	tumor necrosis factor
trNOE	transfer nuclear overhauser enhancement
VCAM	vascular cell adhesion molecule

Table of Contents

1. Introduction

The interaction of E-, P- and L-selectin, a family of cell-adhesion proteins, with their natural carbohydrate ligands, plays a crucial role in many physiological processes and disease states. Inflammation as a response of the organism to microbial pathogens or physical and chemical insults is an important defense mechanism. However, it can also lead to destructive effects, if the regulation of the complicated mechanism gets out of control or if the immune response towards microbial products or altered tissue components causes a permanent inflammatory response. This can lead to destruction of the tissue as it is the case in reperfusion injuries, asthma, allergies, rheumatoid arthritis etc.

A key event in inflammation is the extravasation of leukocytes from the blood stream through the vascular endothelium to sites of inflamed tissue. This process is controlled by numerous molecular interactions and is called the inflammatory cascade. In the early stage, the selectins initiate the tethering of leukocytes from the blood stream to the activated endothelial cell layer and their rolling along the endothelial surface by interaction with glycan structures presented by their natural ligands. Tethering and rolling is followed by integrin-mediated firm adhesion and final transendothelial migration.

The development of selectin antagonists applied in cases of excessive leukocyte extravasation leading to many disease states is a very attractive therapeutic target in pharmaceutical industry and academic research.

1.1. The selectins and their ligands

1.1.1. The selectin family

The lectins are carbohydrate-binding proteins with exception of carbohydrate-converting enzymes and are divided in four groups [1]:

- the C-type lectins, which incorporate one or more calcium ions in the binding site as requirement for binding activity,

- the S-lectins or galectins containing free thiol groups,
- the P-lectins for their ability to recognize phosphorylated mannose residues and
- other lectins not fitting in one of the above categories.

In the course of their molecular characterization, all three known selectins (E-, P- and L-selectin) have been identified as C-type lectins. In addition to the requirement of calcium ions for binding, they have a Carbohydrate Recognition Domain (CRD) of ~ 130 amino acids, five disulfide bridges and 18 conserved amino acid residues [2] in the CRD [3]. Other examples for C-type lectins are the asialo-glycoprotein receptor (AGPR) [4] and the mannose binding protein (MBP) [5,6].

The prefixes of the three selectins indicates the cell types were the molecules were first identified: E-selectin on activated endothelial cells, L-selectin on most types of leukocytes and P-selectin in storage granules of platelets. In addition, in case of an inflammatory stimulus, P-selectin is also exposed to the surface of endothelial cells from Waibel-Palade bodies.

L-selectin was first described in 1983 as a “lymphocyte homing” receptor which is blocked by the rat monoclonal antibody Mel 14. Mel 14 blocks the binding of lymphocytes to lymph node high endothelial venules (HEV) in lymph node tissue [7]. Later, it was also found on neutrophil granulocytes and monocytes and was shown to be generally involved in leukocyte entry into sites of inflamed tissue [8,9]. Weissman [10] and Lasky [11] reported concurrent work on the molecular characterization of L-selectin. It was isolated by immunoaffinity chromatography as a protein with a molecular mass of ~90’000. Cloning uncovered, that the protein is highly glycosylated and consists of 372 amino acids corresponding to a mass of 42 kDa.

In 1984, the groups of McEver [12] and Furie [13] independently discovered P-selectin by a monoclonal antibody approach as membrane glycoprotein antigen that is exposed on human blood platelets only after activation of these cells by thrombin or histamine. It was suggested, after analyzing the total extracts of resting platelets, that P-selectin is constitutively expressed in the membrane of α-granules of platelets [14,15]. Later, P-selectin was also found to be expressed constitutively in the membrane of Waibel-Palade bodies of human endothelial cells [16]. Cloning and PAGE analysis enabled the characterization of P-selectin as a C-type lectin with a molecular mass of 140’000 in the natural state. The mature protein contains 789 amino acids with a molecular mass of ~86 kDa [17,18].

E-selectin was discovered in the late 1980’s by Bevilacqua *et al.* [19,20] as antigen of two cell adhesion mouse monoclonal antibodies named H 18/7 and H 4/18. These mAbs

inhibited cell-cell adhesion in an assay [21] of polymorphonuclear neutrophils (PMN) or HL-60 cells to cytokine-activated human umbilical vein endothelial cells (HUVEC). Cloning and molecular characterization using a cDNA library [22,23] in 1989 revealed the C-type lectin nature of E-selectin. The mature protein consists of 589 amino acids and has a molecular weight of 64 kDa, the native protein has a molecular mass of 115'000. Investigation of a number of oligosaccharides for their ability to inhibit the adhesion of HL-60 cells to COS cells transformed with E-selectin led to the conclusion [23], that the adhesive function of E-selectin might rely on complex carbohydrate structures.

All three selectins contain five different protein domains [24] (see *figure* 1). The extracellular part contains the CRD, an *N*-terminal domain of ~ 120 –130 amino acids that shares some features of the lectin domain of C-type animal lectins [2]. It bears the carbohydrate binding site [25] conformationally stabilized by a calcium ion. There is more than 50% homology among the lectin domains of the selectins and about 30% homology between the lectin domain of E-selectin and the mannose binding protein (MBP) [6].

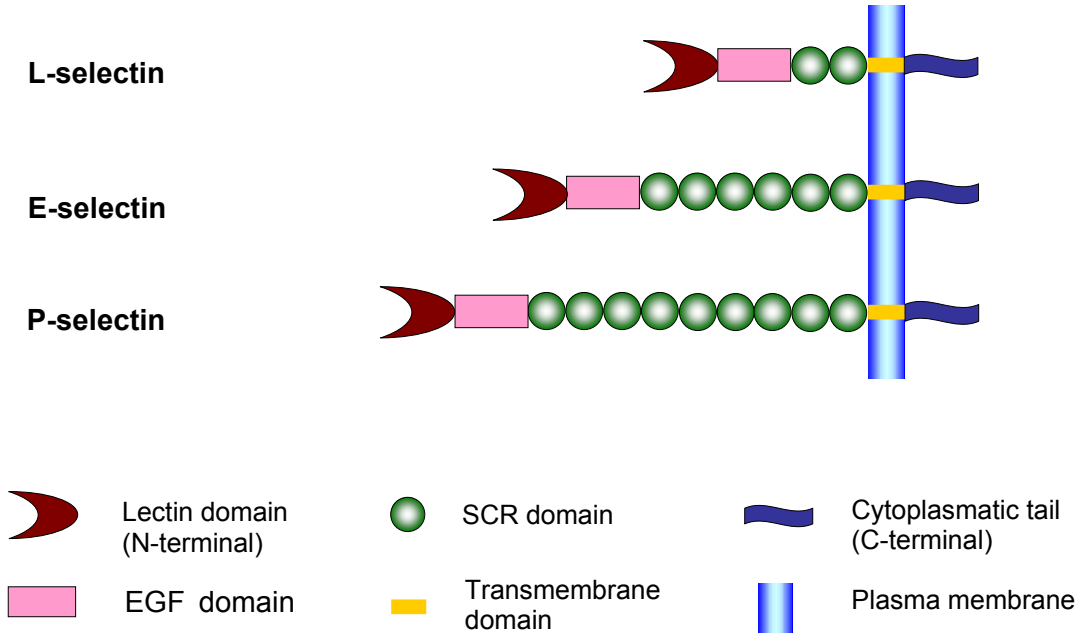


Figure 1: Domain organization of the selectin family.

The CRD is followed by a sequence of 35-40 amino acids, the so-called EGF-domain, resembling a sequence found in the epidermal growth factor. The EGF-domain contains six cysteins located at equivalent positions in the "EGF-repeats" of several proteins. Although

the binding site was identified on the CRD [25], the EGF-domain is required for binding the carbohydrate ligand. The EGF-domain is believed to contribute important impacts to the binding conformation of the CRD [26,27]. Between the EGF-domain and the transmembrane domain lies a variable number of short repetitive elements, each ~60 amino acids long, which resemble motives found in complement regulatory proteins, named “complement binding” (CB) elements or short consensus repeats (SCR). In human, E-selectin contains six, P-selectin contains nine, and L-selectin contains two SCR. Among other species, the number of SCR of E- and P-selectin varies form four to eight, whereas in L-selectin of mouse and rat the number of SCR is equal to that found in human. Truncating several of these elements in P-selectin was found to impair the efficiency of P-selectin to contribute to leukocyte rolling [28]. This findings led to the suggestion, that the CB-elements are responsible for keeping the CRD of P-selectin at a proper distance from the cell surface. The transmembrane domain is followed by a short C-terminal cytosolic tail of 17 amino acids in L-, and 32 and 34 amino acids in human E- and P-selectin, respectively. It is supposed to be involved in signal transduction [29].

1.1.2. The natural glycoprotein ligands of the selectins and their carbohydrate epitopes

Due to the nature of the selectins as carbohydrate binding proteins, their natural ligands are comprised of a scaffold protein or lipid carrier molecule which presents glycan structures as binding motifs. The debate over the physiological ligands for the three selectins is still ongoing, caused by the fact that selectin-binding can be transferred to usually physiologically irrelevant carrier proteins by modifying their glycosylation pattern [30]. Thus, Berg *et al.* [31,32] could demonstrate that sLe^x-substituted BSA shows selectin-binding affinity.

It is the current opinion that carbohydrates containing the trisaccharides $Lewis^x$ (**1**) and $Lewis^a$ (**2**) or their sialylated derivatives sialyl $Lewis^x$ (**3**) and sialyl $Lewis^a$ (**4**) are present in selectin-binding ligands (*figure* 2). In general, fucosylated and sialidated glycans such as sLe^x are required for function [31,33,34]. In some cases, additional sulfation is needed to obtain binding affinity.

Soluble recombinant forms of the selectins as well as selectin-IgG fusion proteins have been used as affinity probes to isolate and identify their natural glycoprotein ligands. Five glycoproteins have been identified so far as natural ligands for L-selectin: Gly-CAM-1 [35], CD34 [36], MAdCAM-1 [37,38], podocalyxin-like protein [39] and Spg200 [40]. All of them are expressed by HEV in lymph node tissue as L-selectin-binding glycoforms. Gly-CAM-1 and

CD34 are both sialomucins, which carry large clusters of sialic acid-rich *O*-linked carbohydrate side chains essential for L-selectin binding. Both proteins are also found in other tissue, however lacking the correct carbohydrate modifications. Gly-CAM-1 is a secretory protein, which is not found on the cell surface, but in cytoplasmic granula [41,42]. MAdCAM-1 is usually a ligand for the lymphocyte integrin $\alpha_4\beta_7$, but a subpopulation can also be recognized by L-selectin. It contains both a mucin- and an immunoglobulin-like domain.

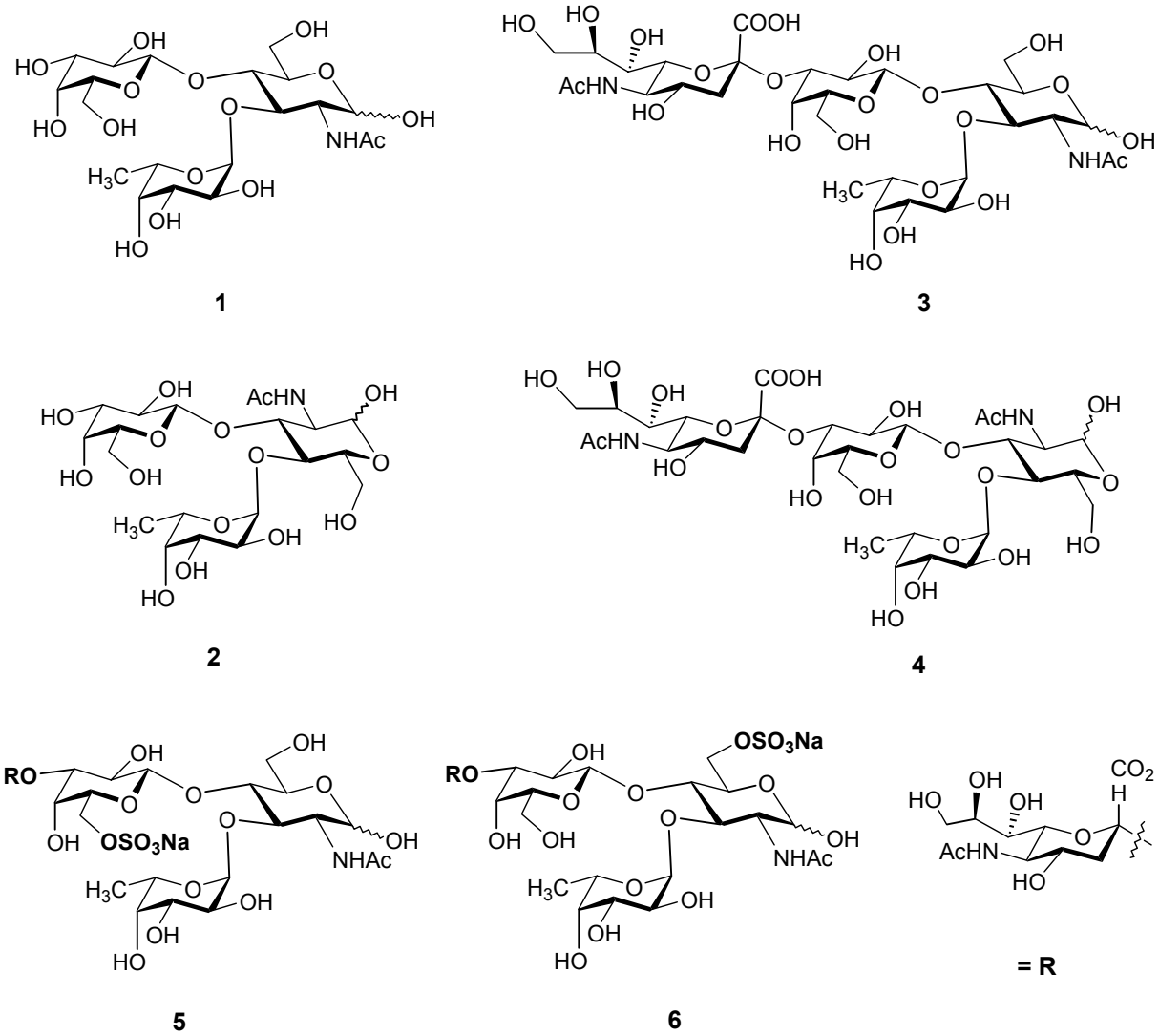


Figure 2: The lewis sugars Le^x (**1**) and Le^a (**2**), their sialidated derivatives sLe^x (**3**) and sLe^a (**4**) as well as the sulfated tetrasaccharides 6'-sulfo-sLe^x (**5**) and 6-sulfo-sLe^x (**6**). In sLe^x, the galactose is linked β-(1 → 4) (type 2) and the fucose α-(1 → 3) to the central Glc*N*Ac moiety. In sLe^a, the galactose is linked β-(1 → 3) (type 1) and the fucose α-(1 → 4) to the central Glc*N*Ac moiety.

The posttranslational modifications of Gly-CAM-1 have been intensively studied. Sulfation, fucosylation and sialidation was found to be essential for binding affinity [35,43,44]. Major capping structures of mouse Gly-CAM-1 were found to be 6'-sulfo sialyl Lewis^x (**5**) [45] and core-2 based 6-sulfo sialyl Lewis^x (**6**) (*figure* 2), which are incorporated in glycan motivs **7** and **8** shown in *figure* 3a and 3b. **6** was found to block binding of L-selectin-IgG to Gly-CAM-1 [46].

A 250kDa homodimeric protein linked by two disulfate bridges called PSGL-1 has been identified as natural occurring P-selectin ligand [47]. Similar to the ligands for L-selectin, PSGL-1 is a sialomucin with a high degree of *O*-linked glycan modifications. It requires sialidation and fucosylation for its binding affinity [48-52]. Detailed analysis of the carbohydrate side chains of PSGL-1 revealed a trifucosylated core-2 structure **9** with a terminal dimeric sLe^x (*figure* 3). As a special structural feature it was found, that PSGL-1 has to be sulfated at two of the three *N*-terminal tyrosine residues (Tyr^{46} and one of the two tyrosines Tyr^{48} or Tyr^{51}) for binding to P-selectin and probably also to L-selectin [53-56].

The structural requirements necessary for the binding to E-selectin are different to that elucidated for P- and L-selectin. In contrast to the ligands for L-selectin, ligands for E-selectin are not sulfated. A glycoprotein called ESL-1 was isolated on mouse myeloid cells and mouse neutrophils [57] and was characterized as 150kDa glycoprotein, which, in contrast to the sialomucin-type selectin ligands discussed above, requires *N*-linked glycans for binding to E-selectin and only binds to E-, but not to P-selectin [58]. Cloning revealed five putative *N*-glycosylation sites and 16 cysteine-rich repeats [59].

Three glycans were identified as physiologically relevant high-affinity ligands of E-selectin [60]. All three contain the sialyl di-Le^x structure on the β-D-Glc*N*Ac-(1→4)-α-D-Man-(1→3)-branch of tetraantennary *N*-glycans (see e.g. **10** in *figure* 3d). All glycans incorporate the trimannosyl chitobiosyl core typical of *N*-glycans. The specifity of these glycans as ligands of E-selectin was confirmed on an affinity column of recombinant, soluble E-selectin on agarose [61].

E-selectin also binds PSGL-1 [50,51,58,62-64]. However, tyrosine sulfation is not necessary for binding. [50,63]. Due to the fact, that L-selectin is consecutively expressed on leukocytes to fulfill its roll in permanent lymphocyte homing, its role in inflammation has to be controlled by the inducibility of its endothelial ligands. E-selectin is able to bind to carbohydrates present on L-selectin on human neutrophils, but not on lymphocytes [65,66]. *Figure* 4 [67] summarizes the appearance of the three selectins and their binding partners.

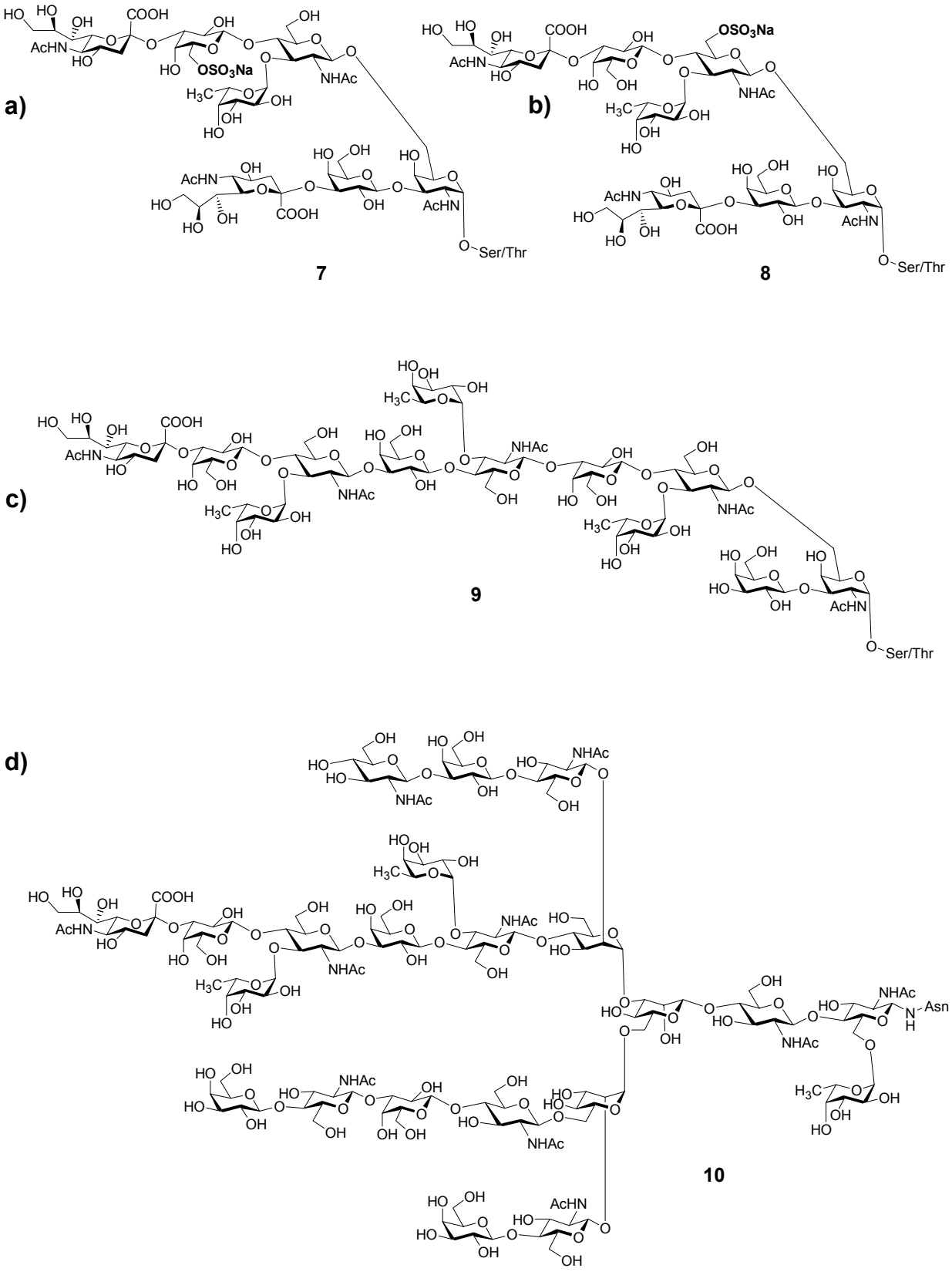


Figure 3: Carbohydrate epitopes of physiological selectin ligands: a) and b) *O*-linked high-affinity ligands **7** and **8** found on GlyCAM-1 being sulfated at the 6-position of Gal or Glc*N*Ac of sLe^x; c) *O*-linked high affinity glycan **9** found on PSGL-1; d) example for one of three isolated *N*-linked ESL-1 glycans, which all carry a differently substituted tetraantennary trimannosyl-core with one sialidated di-Le^x unit.

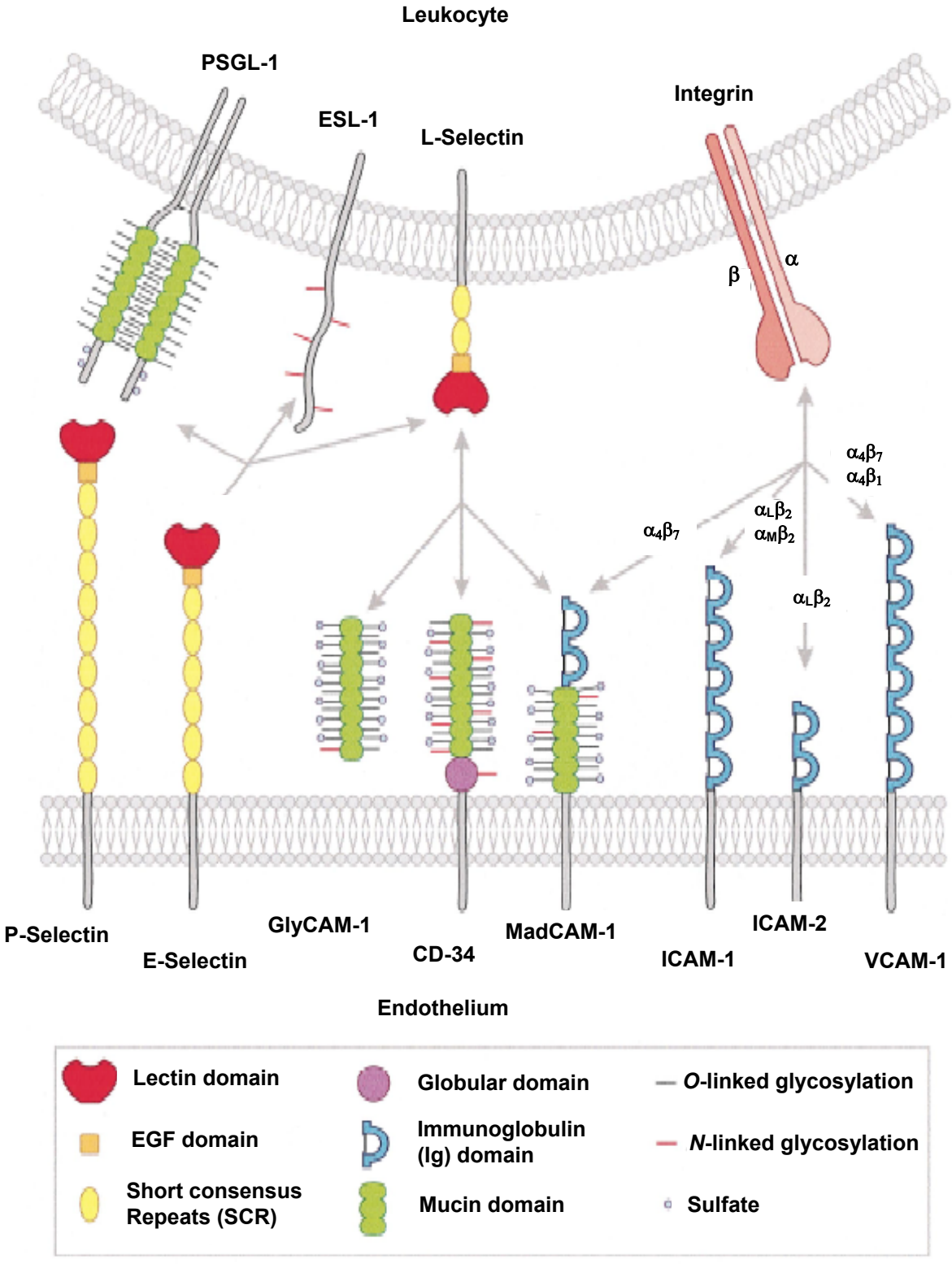


Figure 4: Selectins, integrins and their binding partners. The depicted selectin ligands are those, which have been identified by affinity isolation with the respective selectin as affinity probe. [67]

1.2. Significance of selectin-ligand interaction in pathophysiology

1.2.1. Biological background of selectin-carbohydrate interaction

The interaction of the selectins with their natural glycoprotein ligands plays a predominant role in cell-adhesion processes [9,68] during inflammation. Experimental observation of tethering, rolling and extravasation of leukocytes during acute inflammation have been reported since the 19th century [69-71]. The inflammatory cascade is initiated by a variety of inflammatory mediators such as chemokines or platelet activating factors [72,73] upon stimulation by invading pathogens or responding monocytes. These stimuli induce vascular endothelial cells to express E- and P-selectin. P-selectin, which is stored in α-granules of platelets and Waibel-Palade bodies of endothelial cells, can be rapidly presented to the cell surface within seconds to minutes upon fast stimulation of endocytosis by proinflammatory mediators such as thrombin or histamine [74,75]. Expression is maximal after 5-10 min after stimulation, and the protein is taken up from the endothelial surface after 30-60 min by endocytosis. Beside this fast exposure of P-selectin, a second regulatory mechanism similar to that found for E-selectin exists. TNF-α was found to stimulate the expression of P-selectin on the transcription level in mouse and bovine endothelial cells with similar kinetics found for that of E-selectin [76-78]. E-selectin in contrast to P-selectin is transcriptionally induced by TNF-α, IL-1 or lipopolysaccharide (LPS) [20,79]. Peak levels at the cell surface are reached within 3-4 h after stimulation [22] and basal levels can be found again after 16-24 h. The presentation of E- and P-selectin at the surface of endothelial cells and thus the interaction with ESL-1 and PSGL-1 present at the surface of leukocytes leads to tethering and rolling [80,81] of white blood cells along the vessel wall. L-selectin, which is constitutively expressed on leukocytes, contains carbohydrate structures that serve as ligands for E-selectin [66]. Interaction of L-selectin with PSGL-1 [82] leads to the tethering of leukocytes to leukocytes which are already adhering to the endothelium [83]. This mechanism expands the pool of leukocytes attracted to sites of inflamed tissue.

Cell activation causes rapid downregulation of L-selectin within minutes [84] by proteolytic activity cleaving L-selectin at an extracellular cleaving site [85]. This proteolytic cleavage occurs on neutrophils within 1-5 min and is speculated to facilitate detachment of leukocytes from endothelial cells prior to migration through the endothelial layer. Indeed, Walcheck *et al.* [86] showed in an elegant study, that neutrophils rolled at considerably lower velocity in the presence of a protease inhibitor, and that the neutrophil accumulation rate increased.

Shedding seems to be important to prevent too strong attachment of leukocytes via L-selectin.

Rolling of leukocytes enables further adhesion events [87,88] between chemokine-activated integrins on the leukocyte surface and endothelial integrin ligands ICAM-1 and VCAM-1, which are members of the immunoglobulin superfamily. This firm adhesion, which is another target of drug development [89-93], leads finally to the migration of leukocytes through the endothelial layer.

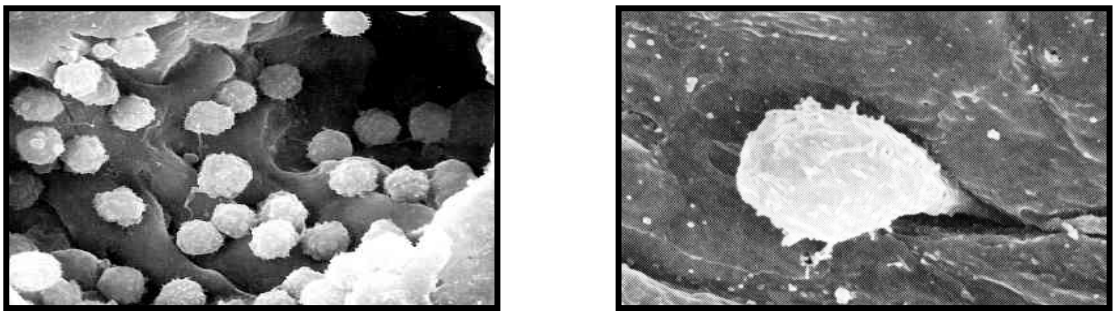


Figure 5: Photographs of leukocytes rolling along the vasculature (left) and a leukocyte in the state of migration through the endothelium (right).

The involvement of all three selectins in leukocyte rolling has been clearly established and confirmed by numerous investigations [94-97]. Experiments with gene-deficient mice (k.o. mice) delivered a large amount of knowledge about the physiological role of the selectins. Lymphocyte homing was significantly reduced in L-selectin k.o. mice [98,99]. L-selectin deficiency also affected the successful execution of an immune response [100-102]. P-selectin k.o. mice showed reduced neutrophil emigration into the inflamed peritoneum, especially 1-2 h after stimulus [103,104]. In contrast, E-selectin k.o. mice showed no abnormalities in inflammatory responses [105,106]. Severe defects were observed in E-selectin k.o. mice, whose P-selectin function was blocked by P-selectin antibodies [107]. E-/P-selectin k.o. mice showed an increased susceptibility to bacterial infections. Leukocyte rolling was significantly reduced and neutrophil emigration was completely absent within the first 4 h after stimulation [106,108].

In vitro flow chamber experiments established a two-step model for leukocyte adhesion [88] under flow *in vivo*, with the selectins mediating the tethering and rolling, and the integrins acting subsequently to arrest rolling leukocytes prior to transmigration. In the flow chamber experiments, an artificial lipid bilayer was intercalated with P-selectin, ICAM-1 or a mixture of both. Leukocyte rolling was observed in the flow chamber under physiologically relevant

shear stress using lipid bilayers containing only P-selectin. Instead, the velocity of free flowing leukocytes was not affected, if only ICAM-1 was incorporated. Neutrophils rolling on a bilayer containing P-selectin and ICAM-1 were brought to a halt by adding neutrophil integrin activators. Under static conditions however, leukocytes were found to attach to membranes containing fourfold lower concentrations of ICAM-1.

These data indicate that under physiological shear stress conditions, rolling mediated by the selectins is a prerequisite for the firm attachment of leukocytes enabled by integrin-ICAM-1 interaction and subsequent migration through the vascular endothelium.

1.2.2. Endothelial-leukocyte adhesion in human diseases

The selectins have been found to be involved in a number of acute and chronic diseases [109]. Ischemia-reperfusion injury is an important example of inflammatory conditions, in which selectin-ligand interactions play a role [110]. Typical of the condition is a rapid burst of oxygen-derived radicals that arise shortly after reperfusion of the ischemic tissue. As a consequence, P-selectin is transferred to the cell surface, resulting in strong accumulation of neutrophils. This accumulation in the damaged tissue induces vascular dysfunction and causes further injury to heart muscle cells. The prevention of reperfusion injury became, therefore, a highly desirable therapeutic goal in case of cardiac infarction, which is necessarily followed by reperfusion of the ischemic heart tissue. Antibodies against P-selectin significantly protected myocardial necrosis in a feline model [111] and administration of sLe^x-related oligosaccharides showed similar protective effects [112].

Eosinophil granulocytes, which are activated and recruited to extracellular sites by E-selectin together with the integrin receptors ICAM-1 and VCAM-1 [113], play a prominent role in allergic inflammation and asthma [114]. Groves *et al.* [115] found significant expression of E-selectin on vascular endothelium in cutaneous inflammatory disorders such as allergic contact dermatitis, atopic dermatitis and psoriasis as well as in skin infiltrates associated with benign, premalignant and malignant proliferation of keratinocytes.

Redl *et al.* [116] studied the expression of E-selectin under the conditions of septic vs. traumatic shock in baboons. Septic shock, which was induced with living *e. coli* bacteria, induced a widespread expression of E-selectin in capillaries, venules, small veins, arterioles and arteries. Expression was most pronounced on vessels of lung, liver and kidneys. By

contrast, animals with traumatic shock showed only minimal evidence of increased E-selectin expression.

In 1992, a rare genetic disorder called “type 2 leukocyte adhesion deficiency” (LAD-2) was discovered [117]. Patients suffering from this disease show mental retardation, short stature and recurrent bacterial infections accompanied by high leukocyte counts. Examination of the patient’s blood group phenotype revealed the presence of the Bombay (hh) blood group antigen [118]. This rare blood group results from failure to attach fucose in an α-(1→3)-fashion to form the blood group H determinant. LAD-2 patients were also negative for the secretor, Le^x and Le^a blood group antigens. Neutrophils from LAD-2 patients were found not to bind to HUVEC activated with interleukin-1β. These findings led to the assumption, that neutrophils of LAD-2 patients have an adhesion deficiency due to the lack of sLe^x epitopes and that LAD-2 underlies a general defect in fucose metabolism. Another human disease, LAD-1, is due to the lack of functional integrin β_2-chains (CD18), essential for neutrophil extravasation. Such patients suffer from life-threatening infections [119].

Increased expression of endothelial adhesion molecules has been observed at the rejection of human renal [120], cardiac [121,122] and liver transplants [123]. The enhanced expression results from several factors, including cytokines generated during the immune response to foreign antigens and the effects of ischemia-reperfusion injury. In monkeys, anti-ICAM-1 antibodies reduced lymphocyte infiltration and prolonged kidney allograft survival [124].

Recipients of bone marrow transplantation may develop “graft vs. host disease” (GvHD), a multiorgan disease caused by immune response of donor leukocytes against host tissue. GvHD-associated lesions showed increased E-selectin and VCAM-1 expression close to the sites of leukocyte infiltration [125,126]. In a mouse model, therapy with anti-ICAM-1 antibodies reduced the severity of the disease and prolonged the survival of mice receiving allogenic bone marrow [127].

Some of the carbohydrate epitopes serving as selectin ligand glycans have been identified as tumor-associated antigens [128,129]. Evidence has been found that profound changes in surface carbohydrate structures occur upon malignant transformation of cells [130]. Among others, Le^x, Le^a and their sialidated derivatives sLe^x and sLe^a are increasingly expressed during expression of cancer [131,132]. The significance of these surface glycan changes in conjunction with tumor progression and metastasis has been discussed in a recent review [133]. Several studies showed a significant correlation between sLe^a expression and a poor prognosis in a total of more than 500 patients with colon cancer in Japan [131].

1.3. Affinities and kinetics of selectin-ligand interactions

Capturing of leukocytes from the rapidly flowing blood stream is a special kind of cell-cell interaction requiring special forms of molecular mechanisms. Fast association (k_{on}) [88,134] and dissociation rate constants (k_{off}) together with special mechanical properties as tensile forces are supposed to be required to fulfill this purpose. The selectins seem to be ideally suited for this task, as they incorporate the above mentioned characteristics [88,135,136]. It was often argued that the affinity of the selectins to their ligands does not need to be high. Indeed, the selectins have been found to bind synthetic oligosaccharides like sLe^x and sLe^a with comparable low affinities (K_D ~ 0.1 – 5 mM) [9,46,137-139].

Table 1: Comparison of affinities and kinetics of selectin-ligand interactions measured by SPR [140].

Interaction	Species	Temp.	K_D	k_{on}	k_{off}	Refs.
		°C	µM	$M^{-1}\ s^{-1}$	s^{-1}	
E-selectin / ESL-1	Mouse	37	62	7.4×10^4	4.6	[140]
		25	56	4.8×10^4	2.7	[140]
L-selectin / GlyCAM-1	Mouse	25	108	$> 1 \times 10^5$	>10	[141]
P-selectin / PSGL-1	Human	25	0.32	4.4×10^6	1.4	[142]

In a recent study [140], binding affinities as well as kinetic and thermodynamic parameters of E-selectin binding to ESL-1 was determined using surface plasmon resonance (SPR). The data has been compared to those earlier obtained for the binding of PSGL-1 to P-selectin [142] and Gly-CAM-1 to L-selectin [141] (*table* 1).

The K_D of monomeric E-selectin binding to ESL-1 of 62 µM was found to be only slightly higher than that of L-selectin/Gly-CAM-1. However, P-selectin/PSGL-1-interaction has a much higher affinity (K_D = 0.32 µM), mainly due to a faster k_{on}. The k_{on} of E-selectin/ESL-1 lies within the range of reported values for protein-carbohydrate interactions [143] and is marginally slower than is typical for protein-protein interactions (10^5 to 10^6 $M^{-1}\ s^{-1}$) [144]. The fact, that k_{on} of P-selectin/PSGL-1 is nearly 2 orders of magnitude larger than the k_{on} measured for E-selectin/ESL-1 cannot be explained by greater conformational rearrangements, because k_{on} for E-selectin/ESL-1 is not unusually temperature-dependent

and because P-selectin itself undergoes substantial conformational changes upon binding to PSGL-1, as found by Camphausen *et al.* [145]. It is more likely, that favorable electrostatic interactions due to the sulfated tyrosines on PSGL-1 result in the faster k_{on}-values. The key observation in the thermodynamic investigations was, that there were no significant changes in affinity with temperature, implicating that binding is mostly driven by favorable entropic contributions with only small impact from enthalpic changes.

1.4. Structure-activity relationship of E-selectin binding to sLe^x

The development of low-molecular weight, high affinity sLe^x mimetics as E-selectin antagonists requires a profound understanding of the mechanisms of selectin-carbohydrate interactions on a molecular level. NMR-spectroscopic investigation, X-ray crystallography and molecular modeling as well as binding-affinity studies with modified sLe^x derivatives delivered detailed information about the structure-activity relationship, yet the picture drawn with the aid of these information changed slightly in the course of growing knowledge and some details are still controversially discussed.

1.4.1. Pharmacophores

All functional groups of sLe^x have been chemically modified in a systematic fashion to identify those groups being critical to maintain binding affinity. Those functional groups being significant for binding are called pharmacophores (*figure* 6).

- Gaeta *et al.* [146] and Hasegawa *et al.* [147] determined the role of the hydroxyl groups of fucose by replacing them with hydrogen. In analogy to the mannose binding protein MBP-A [6], fucose was correctly assumed to be responsible for calcium binding. Replacement of any hydroxyl group resulted in completely inactive deoxy-derivatives. Substitution of fucose by arabinose to elucidate the influence of the methyl group of fucose led to a five-fold less active compound [146]. There are, however, distinct differences between the three selectins. Thus, in case of P-selectin, only the 3-hydroxyl group was found to be critical for sLe^x binding.
- The role of the galactose hydroxyl groups was determined synthesizing deoxy- and fluoro-derivatives of sLe^x [148]. Reduced affinity could be observed on substituting the 4- and 6-hydroxyls implicating that those groups are important rather than crucial for binding. In contrast, derivatives modified at the 6-position of galactose were found to be

inactive (IC_{50} > 10 mM) [149], leading to the suggestion, that the 6-hydroxyl group is optimally suited for binding to E-selectin.

- The contribution of the functional groups of Neu*N*Ac (the glycerol side chain, the 4-hydroxyl group, the amide residue and the carboxylate) has also been examined in detail [147,150,151]. Modification of the glycerol side chain as well as removal of the amide group showed little to no effects. The carboxylate, however, was found to be highly significant for binding.

- The Glc*N*Ac moiety does not directly contribute to protein-ligand contacts, as several studies discussed [152-154]. It was rather suggested, that the Glc*N*Ac serves as a spacer unit to arrange the crucial functional groups at the fucose and galactose in the required spacial orientation.

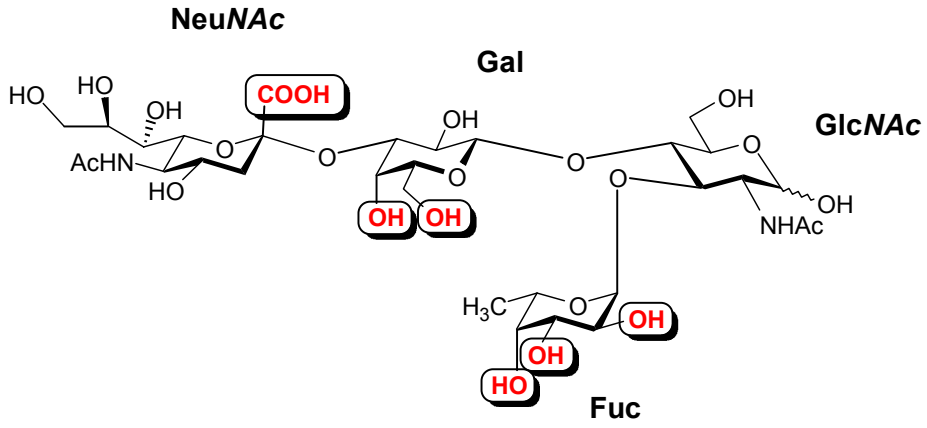


Figure 6: Structure/function map of sialyl Lewis^x. Pharmacophores for binding to E-selectin are highlighted.

1.4.2. Solution conformation vs. bioactive conformation

NMR studies with labeled and unlabeled compounds have been used in combination with molecular dynamics calculations to gain valuable information about conformational preferences of sialyl Lewis^x free in solution as well as bound to the receptor. Early work aimed at defining the solution conformation of sLe^x.

Bednarski *et al.* [155] and Ishikawa *et al.* [156,157] agreed in their findings of a single stable conformation of sLe^x in solution. ROESY and NOESY NMR-spectroscopy revealed significant interglycosidic nuclear Overhauser effects (nOe) between H-3 of Glc*N*Ac and H-1

of Fuc, H-4 of Glc*N*Ac and H-1 of Gal, H-2 of Gal and H-5 and $H_3C(6)$ of Fuc as well as between H-3 of Gal and H-3(ax) of Neu*N*Ac (*figure* 7). ROESY measurements in combination with MM2 calculations identified the interglycosidic dihedral angles Φ and Ψ [158] corresponding to the solution conformation as Neu*N*Ac(α2-3)Gal {163°, -61°}, Gal(β1-4)Glc*N*Ac {48°, 15°} and Fuc(α1-3)Glc*N*Ac {22°, 30°} (see *table* 2). In a subsequent study of the same group [156], four energy minima for the Neu*N*Ac-Gal linkage was found with the dihedral angles A, B, C and D being {163°, -57°}, {-170°, -8°}, {-79°, 7°} and {68°, -20°} (see *table* 2). Poppe [159] and Breg [160] found three different energy minima for the Neu*N*Ac-Gal linkage with angles of A = {-70°, 5°}, B = {-160°, -20°} and C = {-95°, -45°}. Studies by other groups [161,162] confirmed the high flexibility around the glycosidic bond between Neu*N*Ac and Gal.

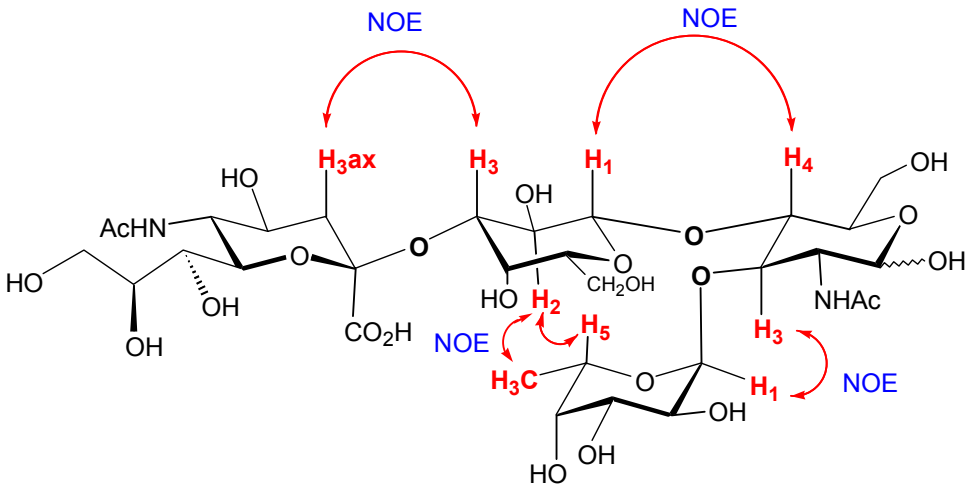
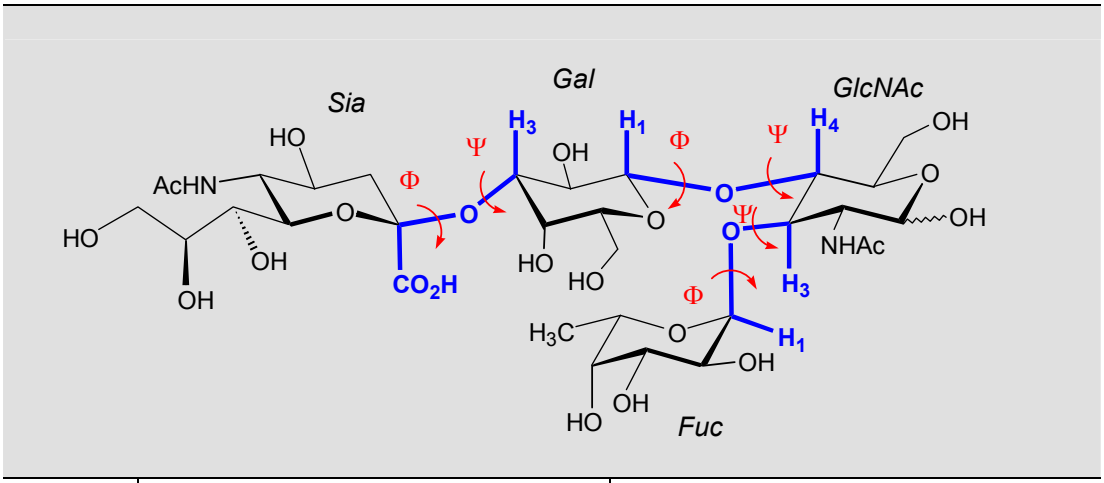


Figure 7: Nuclear Overhauser effects observed in the NMR-spectra of sLe^x in solution. The nOe between H-3ax^{Sia} and H-3^{Gal} is absent in the bioactive conformation [163].

The bioactive conformation of sLe^x (the conformation adopted while binding to E-selectin) was investigated by Peters *et al.* [163-165] and Cooke *et al.* [161] by transfer-NOE (trNOE) [166,167] spectroscopy. Peters and colleagues found significant changes in nOes in the free saccharide and the corresponding tr-nOes in the bound oligosaccharide. A prominent nOe between the H-3(ax) of Neu*N*Ac and H-3 of Gal in the free ligand was completely absent in the bound oligosaccharide. Instead, a tr-nOe was found between H-8 of Neu*N*Ac and H-3 of Gal. The interglycosidic dihedral angles were deduced from these data as Neu*N*Ac,Gal {-76° ± 10°, 6° ± 10°}, Gal,Glc*N*Ac {39° ± 10°, 12° ± 6°} and Fuc,Glc*N*Ac {38° ± 7°, 26° ± 6°} for the bioactive conformation (see *table* 2). This bound conformation refers to solution-conformer A of Breg concerning the Neu*N*Ac-Gal glycosidic bond. These findings imply a profound change in conformation around the Neu*N*Ac-Gal glycosidic bond switching from the free to

the bound state. The Le^x trisaccharide part of sLe^x, however, shows no conformational changes upon binding and seems to be rather rigid even in the free state. In contrast, Poppe and Breg argue that no conformational changes are needed upon binding of sLe^x to E-selectin, because the bioactive conformation adopts one of the most stable free conformations.

Table 2: Interglycosidic dihedral angles Φ and Ψ as determined for the solution conformation and the bioactive conformation of sLe^x .



		Ishikawa, solution conf. [156,157]				Peters, bioactive conf. [163,168]
Sia-Gal	Φ	163°	-170°	-79°	68°	-76° ± 10°
	Ψ	-61°	-8°	7°	-20°	6° ± 10°
Gal-Glc*N*Ac	Φ	48°				39° ± 10°
	Ψ	15°				12° ± 6°
Glc*N*Ac-Fuc	Φ	22°				38° ± 7°
	Ψ	30°				26° ± 6°

The bioactive conformation claimed by Peters *et al.* [163,168] is shown in *figure* 8. One decisive element of the bioactive conformation is the stacking of the fucose and galactose moiety above each other with the Glc*N*Ac unit acting as a spacer. This spacial arrangement

is stabilized by a hydrophobic interaction of the two touching monosaccharide faces as clarified by the loss of activity, if the methyl group of fucose is changed by substituents of different size or polarity. The carboxyl function of Neu*N*Ac is situated perpendicular to the Glc*N*Ac-plane. This conformation arranges all pharmacophores within a row along one side of the tetrasaccharide, pointing towards the reader in *figure* 8. This allows the pharmacophores to bind to a hydrophilic, relatively shallow cleft in the surface of E-selectin, which constitutes the binding site of the selectins together with the calcium-ion.

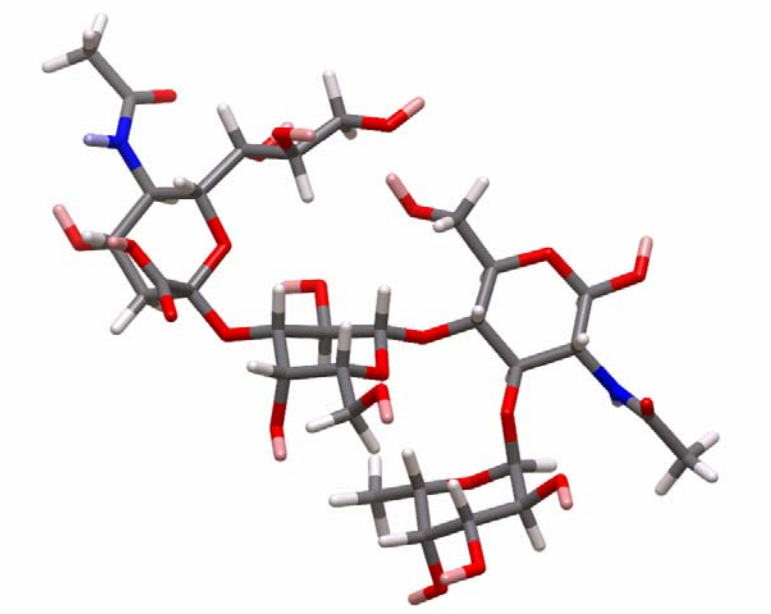


Figure 8: Conformation of sLe^x bound to E-selectin as determined by Peters *et al.* [163,168].

1.4.3. Hypothetical models for the binding mode of sLe^x/E-selectin

The effect of mutations in the lectin domain of a lectin/EGF construct of E-selectin on binding of anti-E-selectin mAbs as well as immobilized sLe^x-glycolipids was studied by Erbe *et al.* [25]. As a result of the mutagenesis studies, they claimed a relatively small, shallow patch of the lectin domain to be responsible for sLe^x binding, in which the amino acids Arg-97, Lys-111, Lys-113, Ser-47 and Tyr-48 are directly involved in the binding process. The group developed a three-dimensional model of the E-selectin CRD by superposition of the functional residues onto the crystal structure of MBP-A [5].

The crystal structure of MBP-A complexed with a mannose-containing oligosaccharide published by Drickamer *et al.* [6] was the first crystal structure of a saccharide bound to a C-type lectin domain and manifested a complexation of the calcium ion by the equatorial 3- and 4-hydroxyl groups of mannose. This crystal structure directly influenced all subsequent models developed to explain the molecular interaction of sLe^x with the CRD of E-selectin. The basis of all these following models was the superimposing of the fucose-hydroxyls 2 and 3 (both equatorially oriented) onto the 3- and 4-hydroxyls of mannose allowing the fucose to occupy the same space when binding to calcium. The third axial hydroxyl of each monosaccharide overlaid as well being able to interact with protein side chains. While this assumption was rational on the background of the data available by that time, it later turned out to be incorrect.

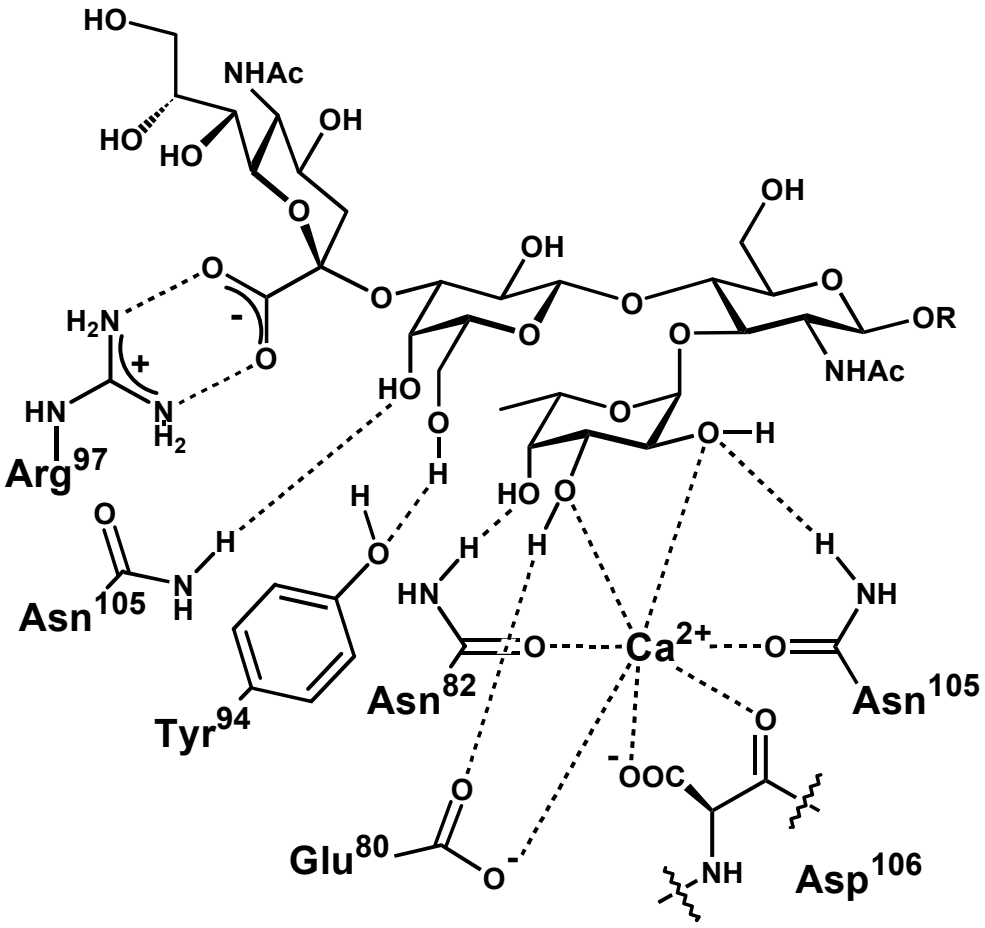


Figure 9: Binding mode of sLe^x binding to E-selectin as proposed by Ernst *et al.* [168] showing the contacts of the pharmacophores with the protein surface. As can be clearly seen, the Glc*N*Ac moiety is not involved in direct binding.

The first genuine insight into the binding site of E-selectin was provided by Graves *et al.* solving the x-ray crystal structure of the E-selectin CRD/EGF domains. Further details delivered the crystal structure of sLe^x bound to a selectin-like mutant of MBP-A [169], that confirmed the binding of the 2- and 3-hydroxyl groups of fucose to the calcium ion. It was, however, unexpected, that the carboxylate group of sialic acid did not interact with the protein, despite earlier findings that it is a pharmacophore for binding of sLe^x to E-selectin. Two theories were discussed: either sLe^x binds differently to E-selectin than to MBP triple mutant, or the importance of the sialic acid was not related to a direct binding to the protein.

Many different models for the binding mode of sLe^x/E-selectin has been developed over the years. All of them showed to be correct in some parts while showing some failures in other parts when compared to the crystal structure of sLe^x bound to E-selectin published in 2000 by Camphausen *et al.* [145].

Three models, which in fact are rather similar, will be discussed here in more detail. Kogan *et al.* [170] developed a model of sLe^x/E-selectin binding based on the bioactive conformation of sLe^x as proposed by Cooke [161], which was docked to E-selectin. Prior to energy minimization, the MBP-A structure was superimposed onto E-selectin to orientate the fucose unit of sLe^x identical to that of mannose binding to MBP-A. Protein-ligand contacts emerging from this model are listed in *table* 3. Ernst *et al.* [168] presented a binding mode (*figure* 9, *table* 3) based on docking of the bioactive conformation of sLe^x obtained from own NMR investigations into the crystal structure published by Graves.

Both models agree in the binding of the 2- and 3-hydroxyl groups of fucose to the calcium ion, the 6-OH of Gal binding to Tyr94 and the carboxylic acid maintaining contact to Arg97. Slight differences lie in coordination of the calcium ion by the protein residues, the contact of the 4-OH of Gal to Asn105 being not predicted by Kogan and the mode of binding of Asn82 to one of the three fucose hydroxyls.

The most direct insight into the possible binding mode of sLe^x/E-selectin was given by the crystal structure of sLe^x bound to E-selectin published by Camphausen *et al.* [145] (*figure* 10). The most striking difference to all other previous predictions suggests the fucose complexing the calcium ion with the 3- and 4- hydroxyl groups. The 2-hydroxyl group is indirectly binding to Asn83 and Glu107 via hydrogen bonds to an intercalated water molecule. Further, the 4-OH of Gal is binding to Glu92 instead of Asn105. The carboxylic acid is coordinating Tyr48 in addition to Arg97. Camphausen and colleagues did not discuss the conformation of sLe^x found in the crystal structure in detail. Thus, it is not obvious, whether sLe^x adopts the bioactive conformation observed in solution, or if crystal packing leads to slight changes in the conformation of sLe^x in the crystal.

Table 3: Contacts of sLe^x with E-selectin as defined in several models.

Residue	**Kogan** [170]	**Ernst** [168]	**Camphausen** [145]
Fuc O-2	**Ca^{2+}**	**Ca^{2+}**	H_2O – Glu 107
	Asn 105	Asn 105	H_2O – Asn 83
Fuc O-3	**Ca^{2+}**	**Ca^{2+}**	**Ca^{2+}**
	Glu 80	Glu 80	Asn 105
	Asn 82		H_2O – Asn 83
Fuc O-4		Asn 82	**Ca^{2+}**
			Glu 80
			Asn 82
Gal O-4		Asn 105	Glu 92
Gal O-6	Tyr 94	Tyr 94	Tyr 94
Neu*N*Ac COOH	Arg 97	Arg 97	Arg 97
			Tyr 48
Ca^{2+}	Glu80	Glu 80	Glu 80
	Asn 82	Asn 82	Asn 82
			Asn 83
	Asn 105	Asn 105	Asn 105
	Asp 106	Asp 106	Asp 106

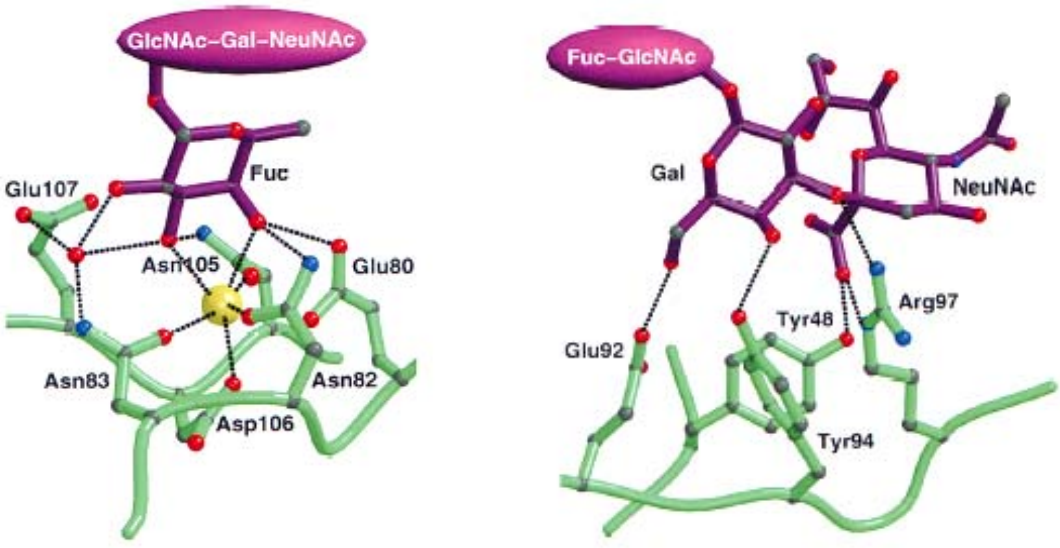


Figure 10: SLe^x bound to E-selectin as found from the crystal structure by Camphausen *et al.* Left: focus on fucose interactions; right: focus on Gal-Neu*N*Ac interactions [145].

1.5. Approaches towards the development of sLe^x mimetics as selectin-antagonists

After the demonstration that, under flow conditions, tethering and rolling of leukocytes initiated by selectin-carbohydrate ligand interaction is a necessary, preliminary event [88] prior to the firm adhesion of leukocytes mediated by the interaction of integrins with the immunoglobulins ICAM-1 and VCAM-1, a keen interest arose on developing inhibitors of selectin-ligand interactions as anti-inflammatory agents to cure diseases based on uncontrolled inflammatory reactions. The terminal carbohydrate epitope sialyl $Lewis^x$ served as lead in the drug development process to find antagonists fulfilling two main objects:

- modification of the lead structure towards molecules that overcome the pharmacokinetic (i.e. hydrolytical instability, fast renal excretion, and high polarity leading to low bioavailability) and pharmacodynamic disadvantages typical of carbohydrates, and
- simplification of the complex structure of sLe^x to small molecules that are easier to prepare, combined with an enhancement of the low binding affinity of the natural ligands.

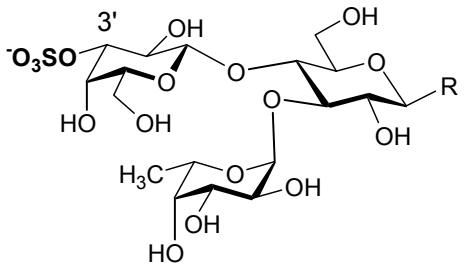
Approaches to this goal implied substitution of substructures by simplified linker groups while retaining the pharmacophores critical for binding. An important aspect in this respect is the annihilation of conformational preorganization of the pharmacophores, that is caused by the displacement of the relatively rigid $Lewis^x$ core structure with much more flexible linkers. As we will see later, high entropic costs have to be paid leading to decreased binding affinity.

In addition, approaches aiming at affinity enhancement by mimicking nature's use of polyvalency [171] or even more complex carbohydrate structures [172-175] compared to sLe^x itself have been reported. These approaches in part showed promising improvements, but the compounds developed are not feasible for oral drug formulations. Several reviews cover this field of research, that will not be taken into account here [171,176-183].

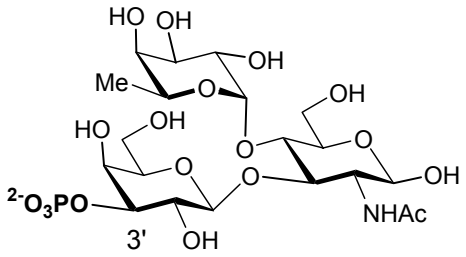
The following overview of contributions in the field of sLe^x mimetics will be sorted in a reductionist fashion starting with mimics in which only Neu*N*Ac has been replaced by anionic residues, then moving to those mimics in which two carbohydrates have been replaced (Neu*N*Ac and Glc*N*Ac, or Gal and Glc*N*Ac). Finally, mimics containing only one carbohydrate (Fuc, Gal, or Man) will be discussed. Within these categories, further strategies like addressing secondary binding sites for hydrophobic interactions or preorganization of pharmacophores in the bioactive conformation by rigidification will be incorporated.

1.5.1. Three-sugar mimetics: deletion of sialic acid or Glc*N*Ac

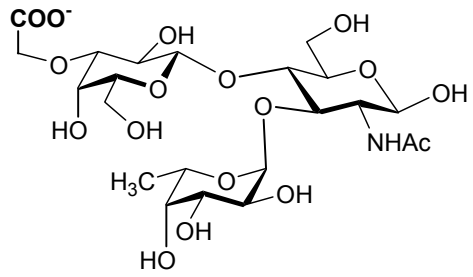
The carboxylic acid is the only pharmacophore contributed by the neuraminic acid part of sLe^x. In addition, neuraminic acid is the most expensive building block of sLe^x. Therefore, the replacement of Neu*N*Ac with a negatively charged group at the 3-position of galactose is a logical first step. Substitution of Neu*N*Ac by sulfate groups led to the known sulfo-Le^x and sulfo-Le^a natural ligands or related derivatives [147,184,185]. Also phosphate has been used as replacement for Neu*N*Ac. Hasegawa *et al.* [147] and Kondo *et al.* [186] as well as Kiessling *et al.* [187] prepared 3'-sulfate- and 3'-phosphate-bearing derivatives of Le^x and Le^a (*figure* 11).



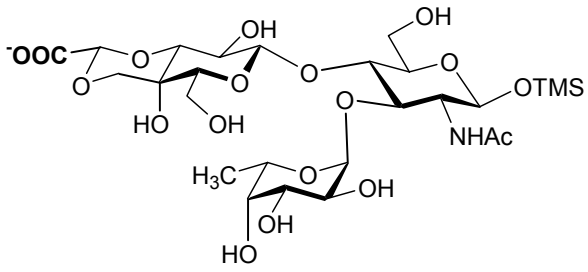
11: R = H; 0.28 mM [186]
12: R = $OCH_2CH(C_{14}H_{29})_2$; 0.33 mM



13: 100µM [187]
14: 3'-sulfo-Le^a; 140µM
15: 3'-sulfo-Le^x; 3mM



16: IC_{50} ~ IC_{50} (sLe^x) [188]



17: inactive up to 10 mM [189]

Figure 11: Mimics containing a negatively charged group replacing Neu*N*Ac. The carboxymethyl group is the most common substitution. Sulfate and phosphate have also been used. IC_{50} -values are given for E-selectin. IC_{50} (sLe^x) = 0.8 mM (E), 8.0 mM (P), 4.0 mM (L).

Affinities reported were similar to those of sLe^x [186]. 3'-phospho-Le^a (**13**) showed equal affinity to E-selectin as 3'-sulfo-Le^a (**14**) and both showed a 20-fold better affinity compared to 3'-sulfo-Le^x (**15**) [187]. The most common substitution used is CH_2COO^-. Compound **16** showed an affinity comparable to that of sLe^x towards E-selectin [188]. Duthaler *et al.* [189] fixed the freely rotatable carboxylic acid in a conformation opposite to the bioactive

conformation by embedding it into a cyclic six-membered acetal. Compound **17** turned out to be inactive. Other Neu*N*Ac replacements will be introduced in the next section when used in combination with Glc*N*Ac-substitutions.

Some work has been done on replacing only the Glc*N*Ac unit in sLe^x keeping the three other sugar units intact (*figure* 12). Since the Glc*N*Ac moiety contains no pharmacophores, it is most likely that it functions only as a spacer important for preorganizing the pharmacophores of fucose and galactose. Generating mimics as active or even more active as sLe^x by replacing Glc*N*Ac requires linker, that keep the core structure of sLe^x unchanged. Hanessian [190] reported on a mimic that replaced Glc*N*Ac by an indolizidinone type heterocycle (**18**, *figure* 12).

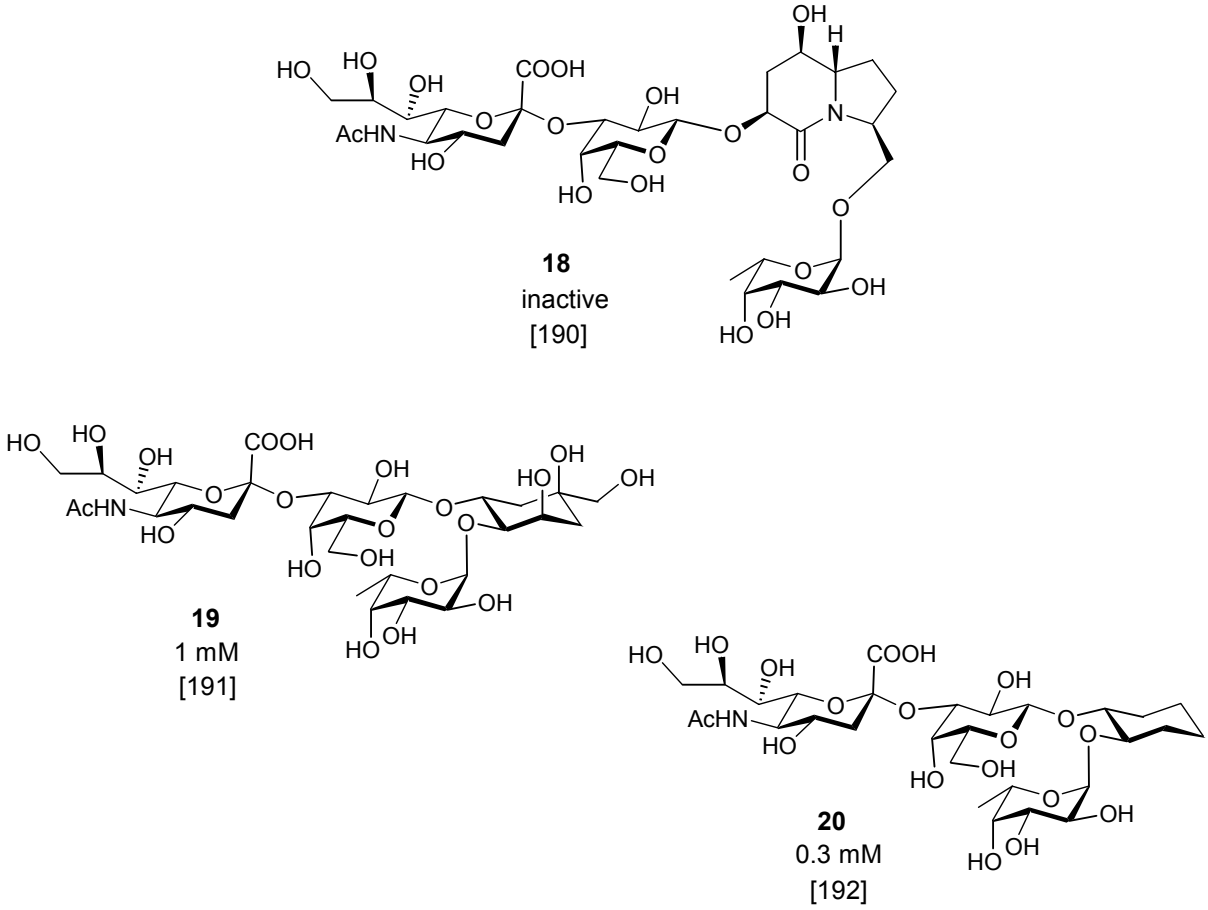


Figure 12: Mimics containing different Glc*N*Ac replacements. IC_{50}-values are given for E-selectin.

The compound showed no affinity in an E-selectin cell free assay. Substitution of Glc*N*Ac with quinic acid [191] produced mimic **19**, which was equally active as sLe^x. Töpfer used a *(1R,2R)*-cyclohexanediol ring to replace Glc*N*Ac and succeeded in obtaining the three-fold more active compound **20** compared to sLe^x [192].

1.5.2. Two-sugar mimetics (I): replacement of Neu*N*Ac and Glc*N*Ac

Several attempts have been reported to combine the effects of Neu*N*Ac- and Glc*N*Ac-replacement to develop even more potent selectin antagonists. Replacing Glc*N*Ac alone has shown to rarely improve binding affinity, yet leading to mimics to be prepared with less synthetic expenditure. A large variety of Glc*N*Ac substitutions has been tested in combination with glycolic acid or alkyl- and aryl lactic acid residues mimicking the sialic acid part (*figure* 13, *figure* 14).

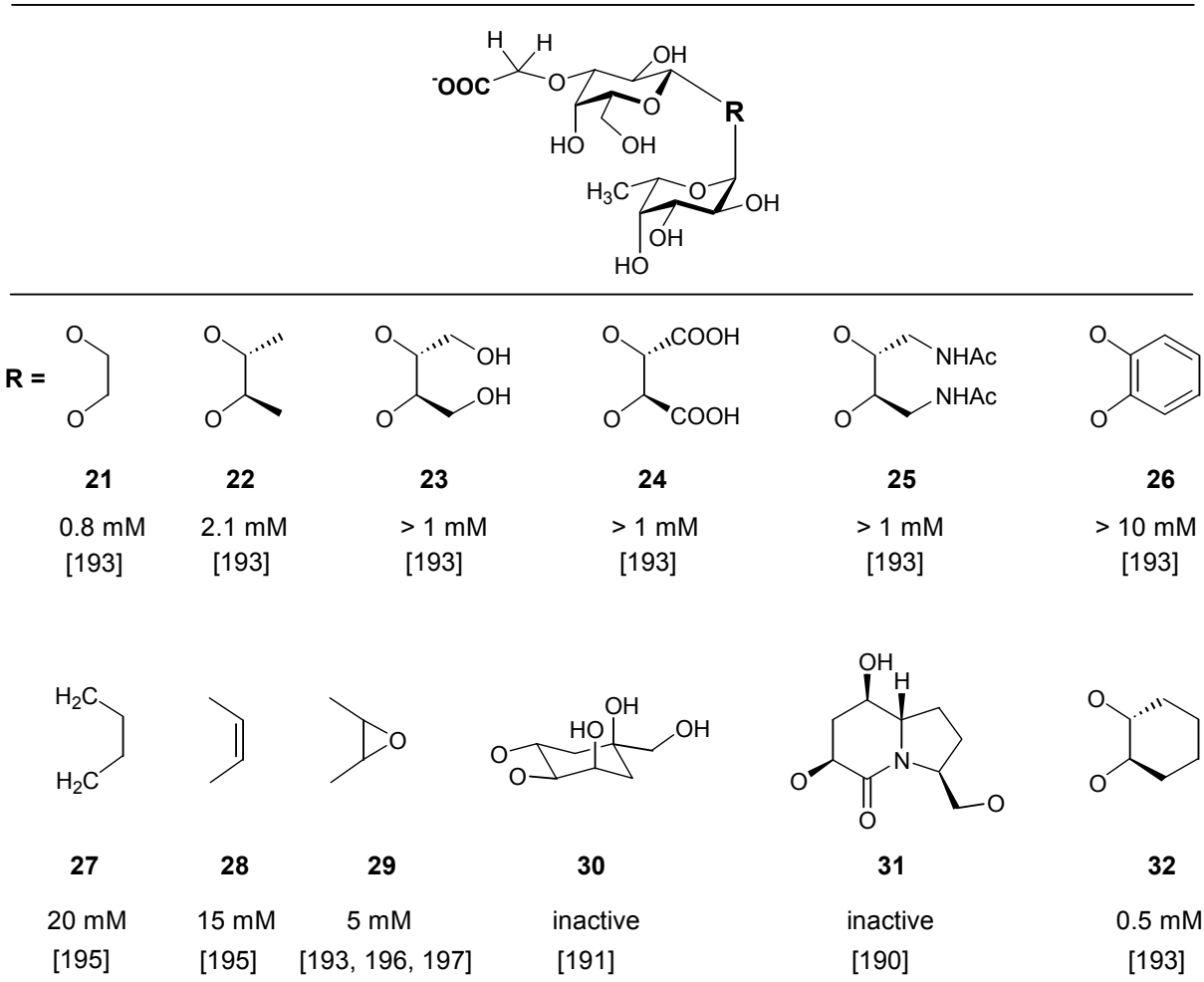


Figure 13: SLe^x mimics bearing a carboxymethyl group as sialic acid replacement and a variety of more or less flexible linker groups substituting the Glc*N*Ac unit. IC_{50} - values are given for binding to E-selectin.

Wong claimed [176], that *(1R,2R)*-cyclohexanediol seems to be energetically neutral in cases where the carboxymethyl group was used as Neu*N*Ac surrogate, leading to mimetic **32** (*figure* 13) [193] being as potent as sLe^x. Surprisingly, compound **21** [193-197], containing the much more flexible ethylenglycol linker, was almost as active as compound **32**.

The introduction of differently substituted, but still too flexible 1,2-diols as Glc*N*Ac replacement lead to compounds **22** to **25**, which all showed weaker affinity to E-selectin as sLe^x itself. Incorporation of a rigid *ortho*-substituted benzene ring as in compound **26** was even less successful. Also substitution of Glc*N*Ac by four-carbon-units as butane, a cis-olefin or an epoxide as in *C*-glycosidic mimetics **27**-**29** did not result in an improvement of binding affinity. Introduction of the previously mentioned quinic acid and indolizidinone templates in combination with the carboxymethyl group by Hanessian *et al.* [190,191] was rather fruitless and generated inactive mimics **30** and **31**.

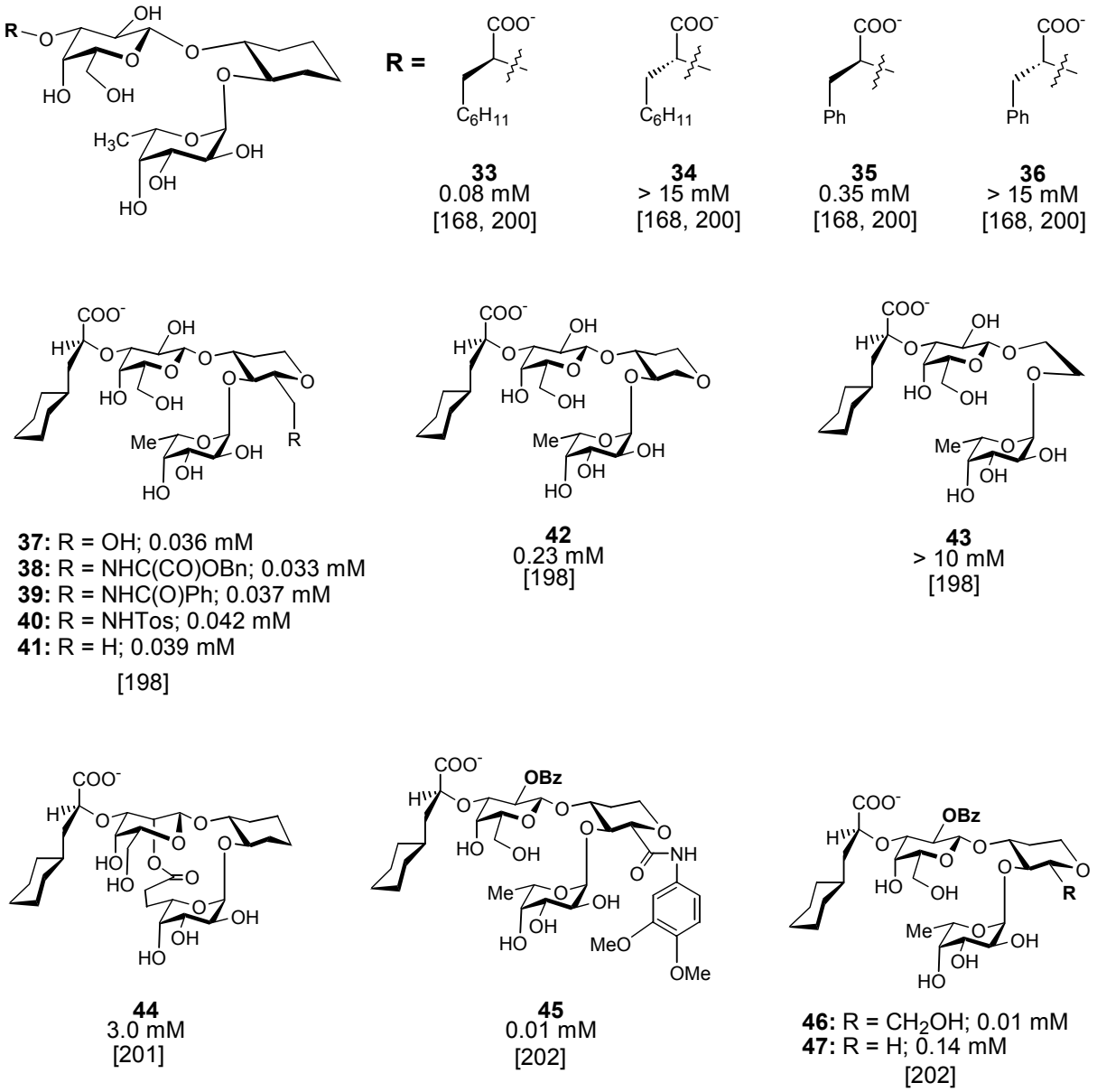


Figure 14: Mimics developed from Novartis AG, Basel. All mimics contain lactic acid derivatives replacing Neu*N*Ac. *(2S)*-lactic acid derivatives turned out to adopt very efficiently the bioactive conformation of the Neu*N*Ac part of sLe^x, thus leading to very potent E-selectin antagonists, whereas the diastereomeric *(2R)*-lactic acid derivatives showed inactive. IC_{50} - values were determined in a static cell free E-selectin competition binding assay.

Ernst *et al.* [198] investigated mimetics containing (*2S)*-cyclohexyl- or (*2S)*-phenyl-lactic acid residues as sialic acid replacement (*figure* 14). In their approach to develop preorganized mimics adopting the bioactive conformation of sLe^x by the aid of a molecular modeling tool [199,200], mimic **33** bearing a cyclohexanediol ring was 10-12 times more active than sLe^x, whereas mimic **43** containing only an ethylenglycol linker turned out to be inactive. The introduction of residues at the carbocycle in the position neighbored to the fucose linkage, that impose more steric constraints to the fucose moiety, led to even more active compounds **37**-**41**, being 25-fold more active than sLe^x. Using *(2R)*-alkyl- or aryl-substituted lactic acid derivatives (**34**, **36**) instead of the *(2S)*-substituted ones (**33**, **35**) as a sialic acid replacement extinguishes the activity of the mimics completely [168,200] (*figure* 14). Various modifications of the 6-position of Gal in mimic **33** carried out by the same group led to inactive compounds [149]. Rigidification of mimic **33** on linking the fucose and the galactose directly as done in macrocyclic mimic **44** did not improve binding affinity [201]. Mimic **44** turned out to be three times less active than sLe^x.

Further results have been published by Thoma *et al.* [202] (*figure* 14), indicating, that mimics **45**-**47** bearing a benzoyl group at the 2-position of the galactose due to incomplete deprotection were up to three times more active than the corresponding mimics with a free 2-OH group.

1.5.3. Two-sugar mimetics (II): replacement of the *N*-acetyl-lactosamine disaccharide

Another approach being explored is the replacement of the central *N*-acetyl-lactosamine part consisting of Gal and Glc*N*Ac. Using unfunctionalized mimics lacking hydroxyl groups imitating the 4- and 6-hydroxyls of galactose generally showed disappointing affinity. Another factor contributing to poor potency was the incorporation of too flexible alkyl chains burdened with extremely high entropic costs (*figure* 15).

Töpfer *et al.* [192] used propanediol-cyclohexane moieties (**48**-**50** in *figure* 15) to substitute the Glc*N*Ac-Gal part and found a drop in activity against E- and P-selectin. Rigid benzylmethoxy groups as in compounds **51** and **52** [203] resulted in 20-fold less active compounds compared to sLe^x. Spiroketal substitution (**53**) [204] led to even less potent inhibitors. Molecules **54** and **55** bearing very flexible alkyl chains turned out to be inactive [205]. Allanson and co-workers [206,207] introduced 6-membered chains as scaffolds ready to be functionalized with groups representing the pharmacophores of Gal (see **56** and **57** in *figure* 15). These mimics showed practically no affinity or were inactive in cell culture assays.

Finally, incorporation of the carboxymethyl group into a thiazine-derived spiro 1,1-galactosyl mannoside as in **58** [208] did not result in potent selectin inhibitors.

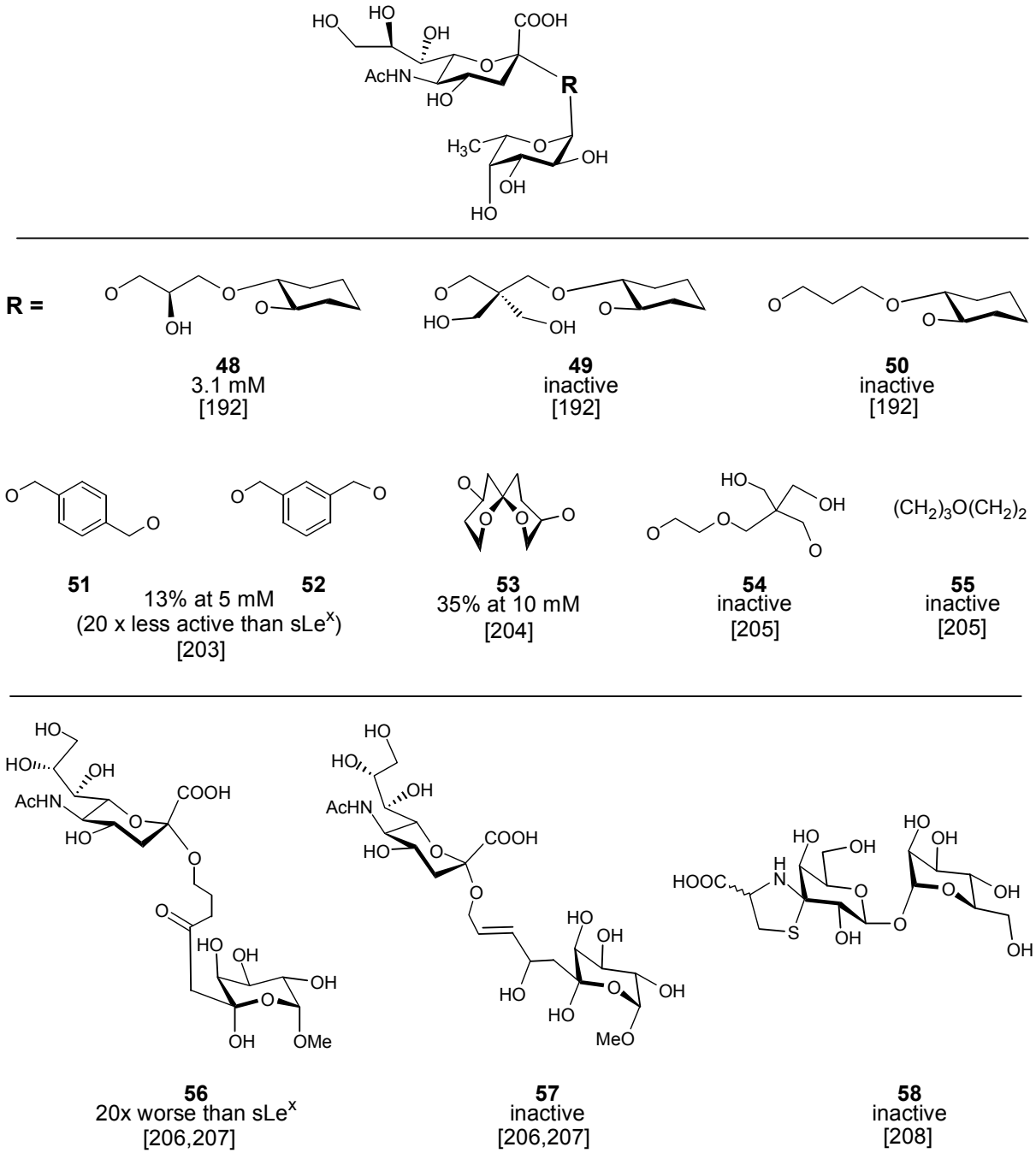


Figure 15: Mimics in which the central *N*-acetyl-lactosamin disaccharide part of sLe^x has been replaced by other units. In general, activity is lower as that of sLe^x itself. Reasons are entropic costs due to highly flexible spacer units or the lacking pharmacophores of galactose. IC_{50} - values for inhibition of E-selectin-sLe^x binding are given.

1.5.4. Mimetics containing one sugar: L-fucose-based inhibitors

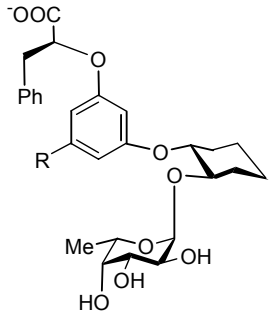
The L-fucose unit of sLe^x binds to the calcium atom in the CRD of the selectins and contains three of the six pharmacophores of sLe^x. The largest group of antagonists known to date consists of molecules containing only one sugar unit, namely fucose, which in some cases has been replaced by mannose or galactose.

Additional functional groups on the residues attached to the monosaccharide were installed to mimic the pharmacophores of the omitted sugar moieties Gal and Neu*N*Ac. Some approaches use substitutes that proofed suitable in former mimetics like the cyclohexyllactic acid residue to mimic Neu*N*Ac or the *trans*-cyclohexanediol unit to replace Glc*N*Ac. Most common linkers used were polyamides as in the glycopeptide libraries of Wong *et al.* [209-214] or polyaryl spacer as in the biphenyl-based glycoaromatics of Kogan *et al.* [215-217]. In addition, the two- and four-component Ugi-reaction has been used by Armstrong *et al.* [218] and Wong *et al.* [219].

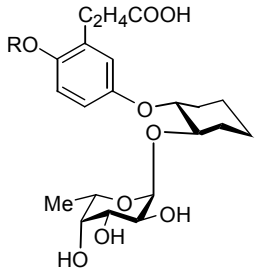
The groups of Ernst [220] and Liu [221] prepared fucose-based mimetics containing cyclohexanediol as Glc*N*Ac replacement and different disubstituted aryl groups to mimic Neu*N*Ac-Gal (**59**–**61** in *figure* 16). Ernst *et al.* [220] used their well fitting cyclohexyl- and phenyllactic acid unit as Neu*N*Ac substitute (**59a-d**, **61**). All molecules within these series were inactive, except the ones reported from Liu [221] containing a benzyl protected hydroxyl group rather than a free hydroxyl group (**60b**, **60d**).

Mimics containing malonic acid derivatives (**62**-**64**) [222] or piperidine carboxylic acid (**65**-**67**) [223] have also been reported. Malonic acid seems to suit better than piperidine carboxylic acid, however, none of these compounds showed better activity than sLe^x itself.

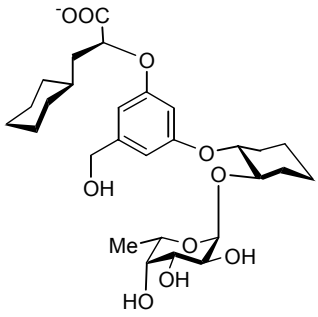
Kogan *et al.* [215,216] developed a library of overall 45 different glycoaromatics based on derivatized biphenyl residues linked to the anomeric position of mannose (**i** to **iii**, *figure* 17). With the exception of three compounds out of this library (**68**-**70**, *figure* 17), all of them were less active than sLe^x itself, probably due to the lacking hydroxyls of the galactose as well as conformational issues. Many compounds, however, showed increased activity against P-selectin. Nine molecules had activities 2- to 20-fold better than sLe^x. In addition, dimeric glycoaromatics have been studied by the same group [217] to mimic extended sialyl di-Lewis^x structures isolated from human neutrophils [60]. Dimer **70** was found to be 6-fold more active than sLe^x in antagonizing E-selectin binding to HL-60 cells. **70** is currently in phase II clinical trials by Texas Biotechnology [224] for the treatment of asthma, reperfusion injury and psoriasis.



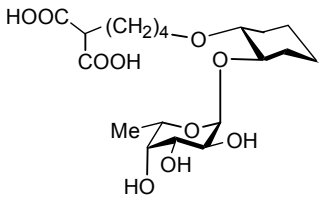
59a-d
R = H, Ph, *i*-Pr,
CO_2H, CH_2OH
inactive
[220]



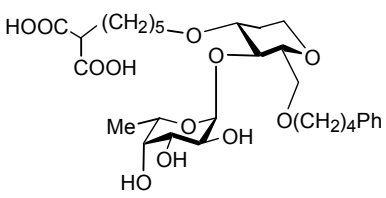
60a-d
R = H, (1R,2R) inactive
R = Bn, (1R,2R) 3.3 mM
R = H, (1R,2R) inactive
R = Bn, (1R,2R) 0.87 mM
[221]



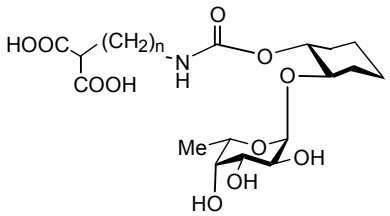
61
inactive
[220]



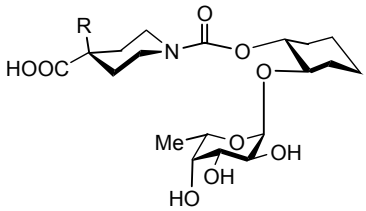
62
1.0 mM
[222]



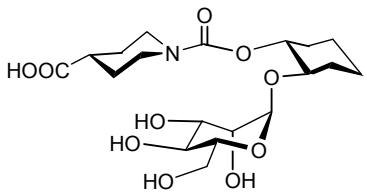
63
2.6 mM
[222]



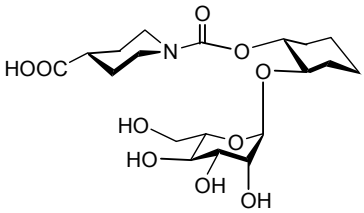
64
n = 1-8, all > 5 mM
[222]



65
R = H: > 5 mM,
R = COOH: 1.6 mM
[223]



66
inactive
[223]



67
5 mM
[223]

Figure 16: Fucose- and mannose-based sLe^x-mimics containing a cyclohexanediol spacer combined with a variety of linkers to attach the anionic endgroup. IC_{50} - values are given using E-selectin as receptor.

Large efforts have been invested to create a large library of fucose-, mannose-, or galactose-based glycopeptides by the group of Wong [209-214]. Two design elements have been chosen as variables: “turns” mimicking the Glc*N*Ac unit, and “hydroxyls” mimicking the galactose unit. *Figure* 18 gives an overview over the variations introduced and a selection of the most potent E-selectin inhibitors. Generally, activity improvement is much more distinct for P-selectin binding than for E-selectin, and rationalization of a structure-activity

relationship is very difficult due to substantial differences among the molecular structures showing activities ranging from “no activity” to low µM values. Nevertheless, this series of molecules contains some of the most active inhibitors known to date. A detailed discussion of these compounds can be found in a recent review [176].

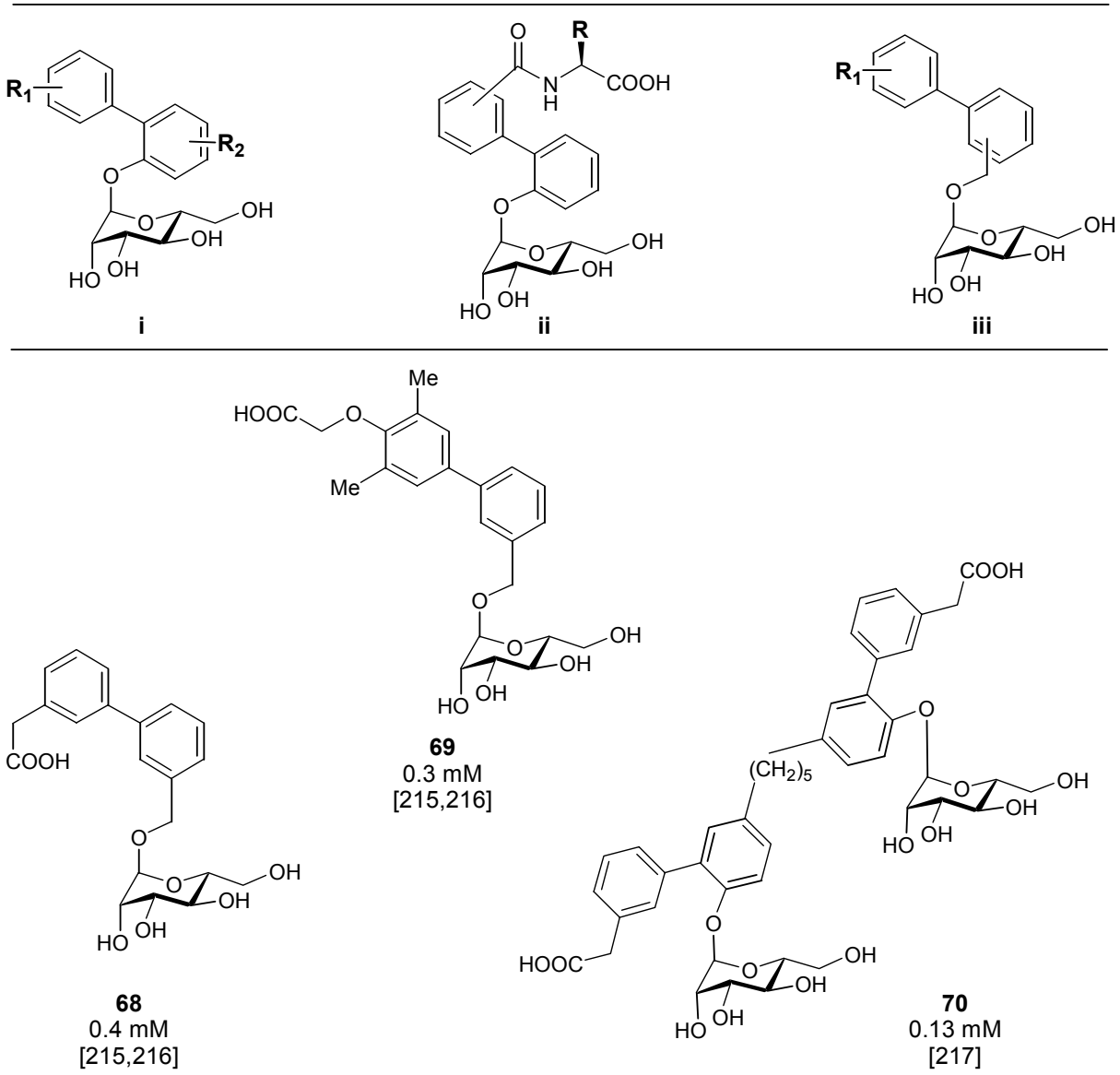


Figure 17: Biphenyl-based inhibitors investigated by Kogan and those showing improved binding activity to E-selectin compared to sLe^x.

Another approach using combinatorial synthesis of compound libraries has been realized by Armstrong *et al.* [218] and Wong *et al.* [219]. They used the two- and four-component Ugi-reaction condensating an aldehyde, a primary amine, an isonitrile and a carboxylic acid and thereby produced a variety of glycopeptide structures (*figure* 19).

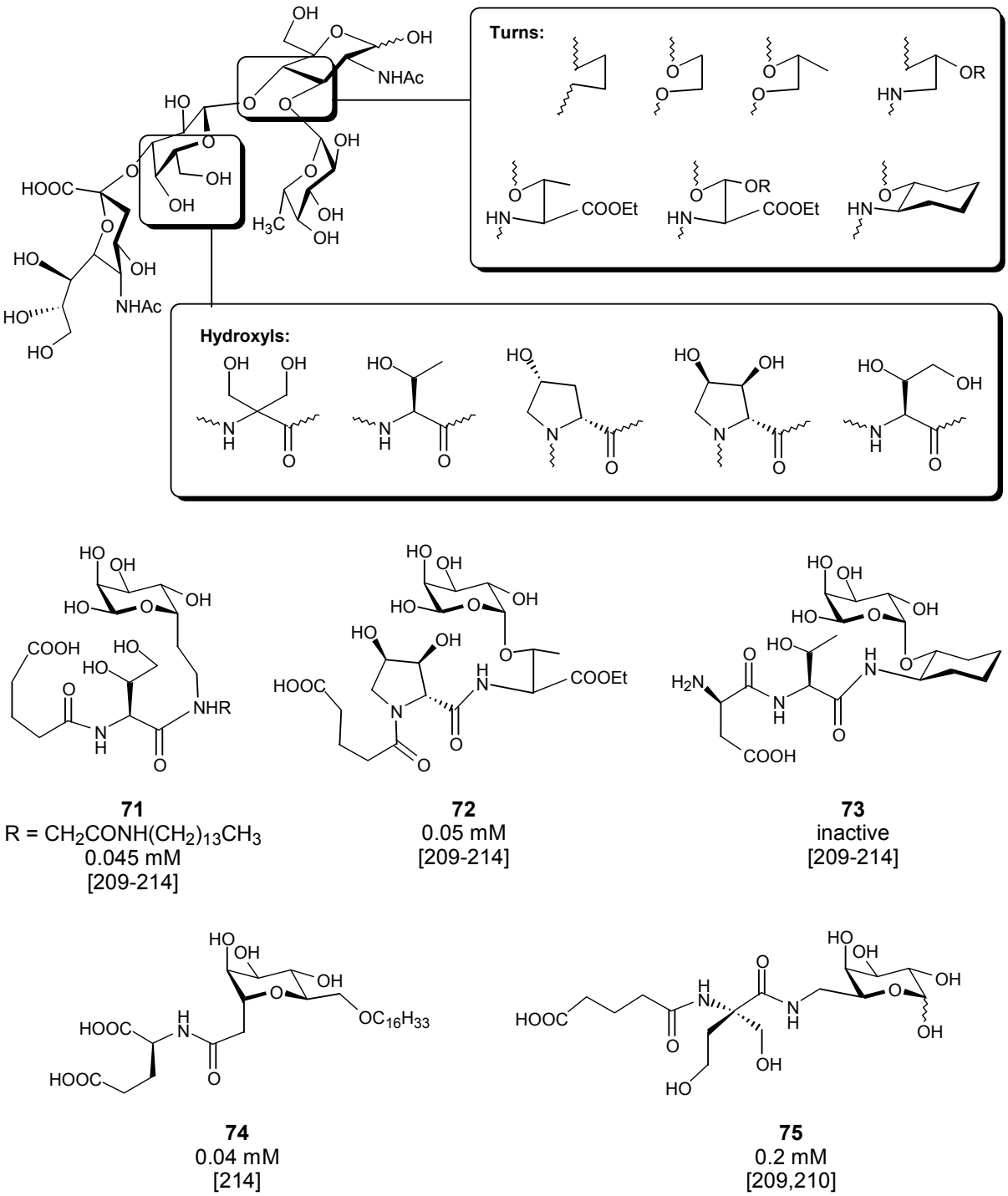
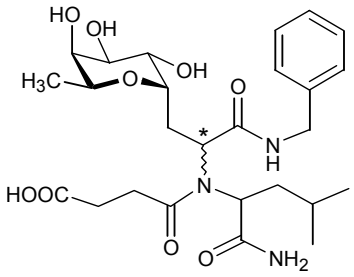


Figure 18: Construction principle and a selection of glycopeptides developed by Wong *et al.* IC_{50} - values are given for E-selectin.

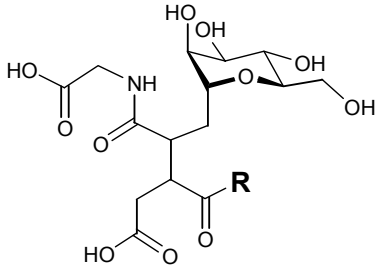
Armstrong [218] used a *C*-fucosidic aldehyde, six different amino acids or amines, two isonitriles and four different di-carboxylic acids as reactive pool to create mimetics of the type **76**. Unfortunately, no activities have been reported to date. Wong [219] produced a series of mannose-based inhibitors (**77**, **78**). Only two compounds being macrocyclic molecules

showed better activity than sLe^x towards E-selectin. Here again, activity upon P-selectin binding is much more enhanced compared to sLe^x than binding to E-selectin.



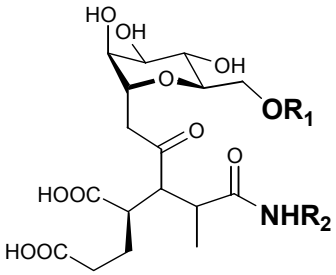
76

representative example



77

up to 52% inhibition (E-selectin) at 3 mM [219]



78

0.3 to >3 mM (E)
0.001 to 0.09 mM (P)
[219]

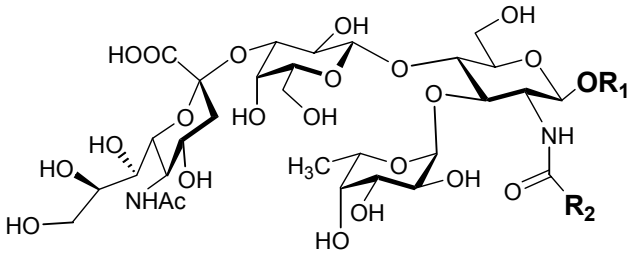
Figure 19: Mimetics synthesised by Armstrong (**76**) and Wong (**77-79**) using the four-component Ugi-reaction.

1.5.5. Groups addressing secondary binding sites

Many rational design approaches described aimed at the improvement of binding affinity by minimizing entropic costs. This was achieved by the development of inhibitors in which the pharmacophores were preorganized in the bioactive conformation of sLe^x, thus avoiding unfavorable conformational changes prior to docking to the binding site. Another possibility to improve affinity is the enhancement of the enthalpic contribution by additional protein-ligand contacts. It was suggested and later confirmed, that incorporation of lipophilic groups without changing the main interactions of the ligand's pharmacophores could lead to interaction with hydrophobic patches on the protein surface near the binding site.

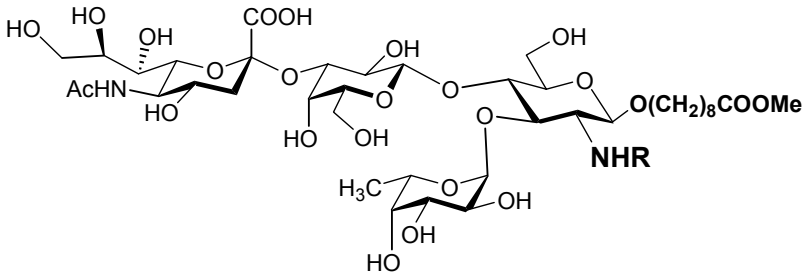
Hayashi [225] and DeFrees [226] published sLe^x derivatives functionalized with hydrophobic groups like alkyl chains or naphthoyl derivatives either at the reducing end or by variation of the *N*-acetyl group of Glc*N*Ac (*figure* 20). They found increased binding affinities of these compounds. Wong reported an improvement of activity by adding long alkoxy chains to the 6-OH of mannose in some of their glycopeptide inhibitors [209]. Compound **74** in *figure* 18 shows a three times stronger binding affinity to E-selectin compared to the same compound with a free 6-OH group at the mannose. Hasegawa *et al.* [227] performed molecular dynamics calculations that implied interactions of this groups with a hydrophobic cleft on the surface of the selectins. Ernst *et al.* [168] investigated the effect of aliphatic, aromatic and

heteroaromatic acyl substituents at the Glc*N*Ac-nitrogen and found a substantial improvement of binding affinity. The best antagonists showed an up to 60-fold increase compared to sLe^x. Aliphatic substitutions instead did not improve the affinity to E-selectin. Mimetic **80e** is one of the most potent inhibitors known to date.

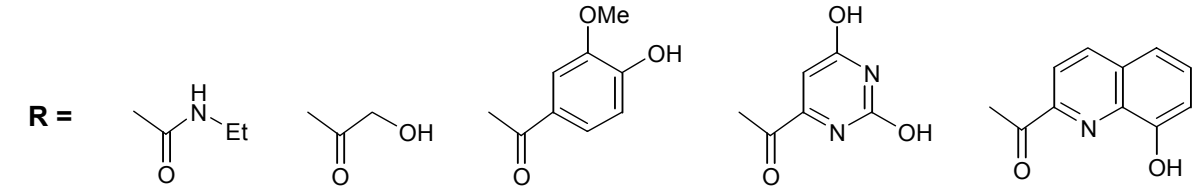


79a-e
[225,226]

R_1	R_2	IC_{50} (mM)
$C_{12}H_{25}$	C_4H_9	2.0
Et	C_4H_9	1.0
$C_{12}H_{25}$	Me	1.6
Et	Me	1.5
$C_{12}H_{25}$	naphth	0.1
Et	naphth	0.1



80a-e
[168]



R =					
rIC_{50} =	3.4	5.9	0.103	0.039	0.016

Figure 20: Derivatization of the reducing end and the glucosamine nitrogen with hydrophobic residues. IC_{50} - values are given for E-selectin. rIC_{50} = relative IC_{50} (standardized relative to sLe^x).

1.6. *C*-glycosidic compounds as E-selectin antagonists

Due to the acetal nature of the glycosidic linkages, carbohydrates and carbohydrate derivatives are prone to hydrolytic degradation by the acidic environment in the stomach and by glycosidase activities. Therefore, these compounds posses only limited suitability as orally formulated therapeutics. This draw-back has been addressed by the development of *C*-glycosidic carbohydrate mimics which are resistant to metabolic processes and show an improved chemical stability [228-231]. However, substitution of the anomeric oxygen by a methylene group leads to structural changes (C-O = 1.42 Å, C-C = 1.55 Å; C-O-C angle = 109°, C-C-C angle = 115°) [232] as well as to drastic changes of the stereoelectronic properties of the glycosidic linkage. In addition, the *exo*-anomeric effect [233-240], besides steric 1,3-diaxial interactions the most important factor influencing the conformational relationship of two monosaccharide moieties, is no longer effective in *C*-glycosides [241].

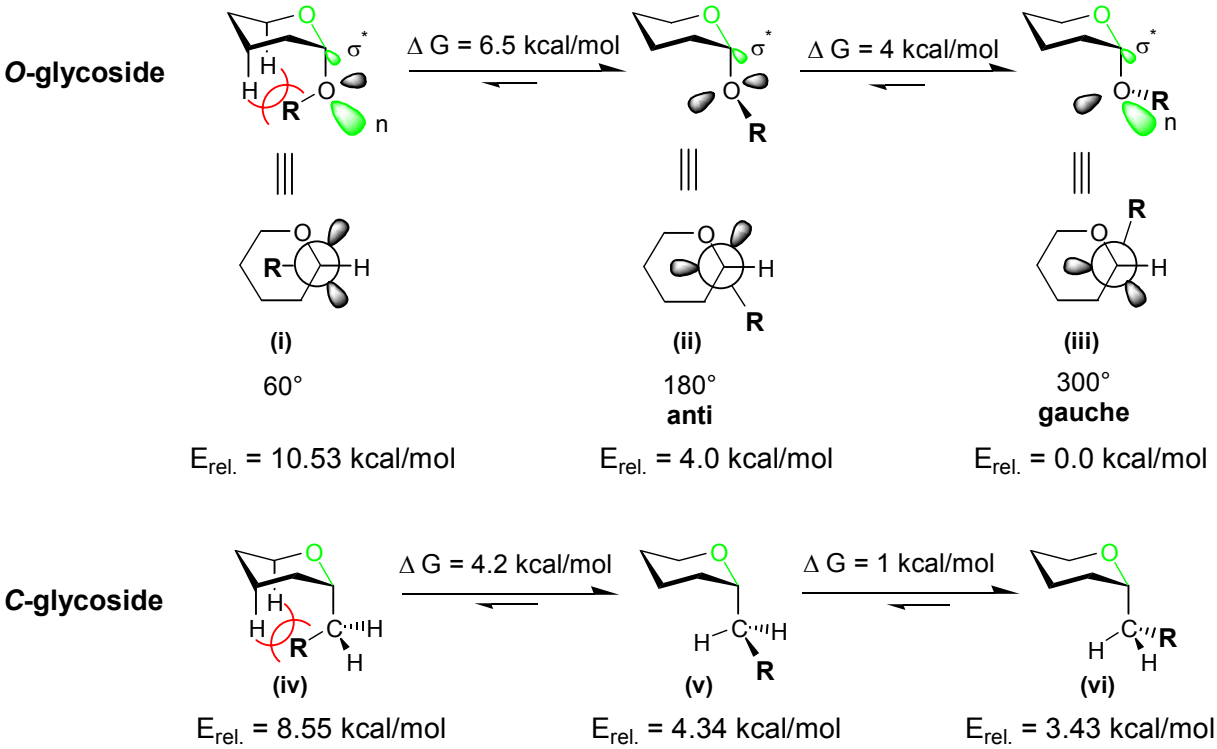


Figure 21: The *exo*-anomeric and steric effects as reason for the preference of glycosides to adopt the gauche conformation around the glycosidic bond and energetic consequences upon the change from *O*-glycosides to *C*-glycosides (*Ab Initio* calculations, Tvaroska, [242]).

It is based on a mesomeric n→σ* interaction between a lonepair of the anomeric oxygen and the antibonding σ*-orbital of the C_1-O bond (anomeric carbon – ring oxygen). This results in a stabilization of the gauche-conformation in respect to the aglyconic residue (structure **iii**, *figure* 21).

Ab initio calculations *in vacuo* estimated the contribution of the *exo*-anomeric effect to be between 1.5 and 4.0 kcal/mol [233-240,242]. For simple systems related to *C*-glycosides, the preference for the gauche conformation was calculated lying between 0.3 and 0.8 kcal/mol [232,238]. Jimenez-Barbero [243] determined the *exo*-anomeric effect in *O*-glycosides in water solution to be >2.3 kcal/mol for α-*O*-mannosides. The additional contribution of 1,3-diaxial type effects in the β-*O*-gluco- and β-*O*-galacto series bearing an equatorial *O*-2 substituent was determined to be about 1 kcal/mol.

Kolb *et al.* [244] calculated the rotational energy curves for both the *O*- and the *C*-fucosidic linkage of sLe^x using an MM2 force field (see *figure* 22). They found, that in both cases the absolute energy minimum is located at a torsion angle of 300°, corresponding to the *gauche*-conformation. In the *C*-glycosidic case, however, a second low energy minimum close to the anti-conformation (Φ = 210°) exists, which is about 1 kcal/M less in energy compared to the 210°-conformation of *O*-fucosidic sLe^x and only approximately 1.5 kcal/M higher in energy than the *gauche*-conformation. This second minimum is accessible by a low activation barrier. A considerable amount of the population should adopt this *"anti"*-like conformation. In addition, the conformational space between 0° and 120° is up to 6 kcal/M lower in energy containing a local energy minimum at about 90°. These figures indicate a higher flexibility of the *C*-fucosidic bond with a lower contribution of the *gauche*-conformation to the total population.

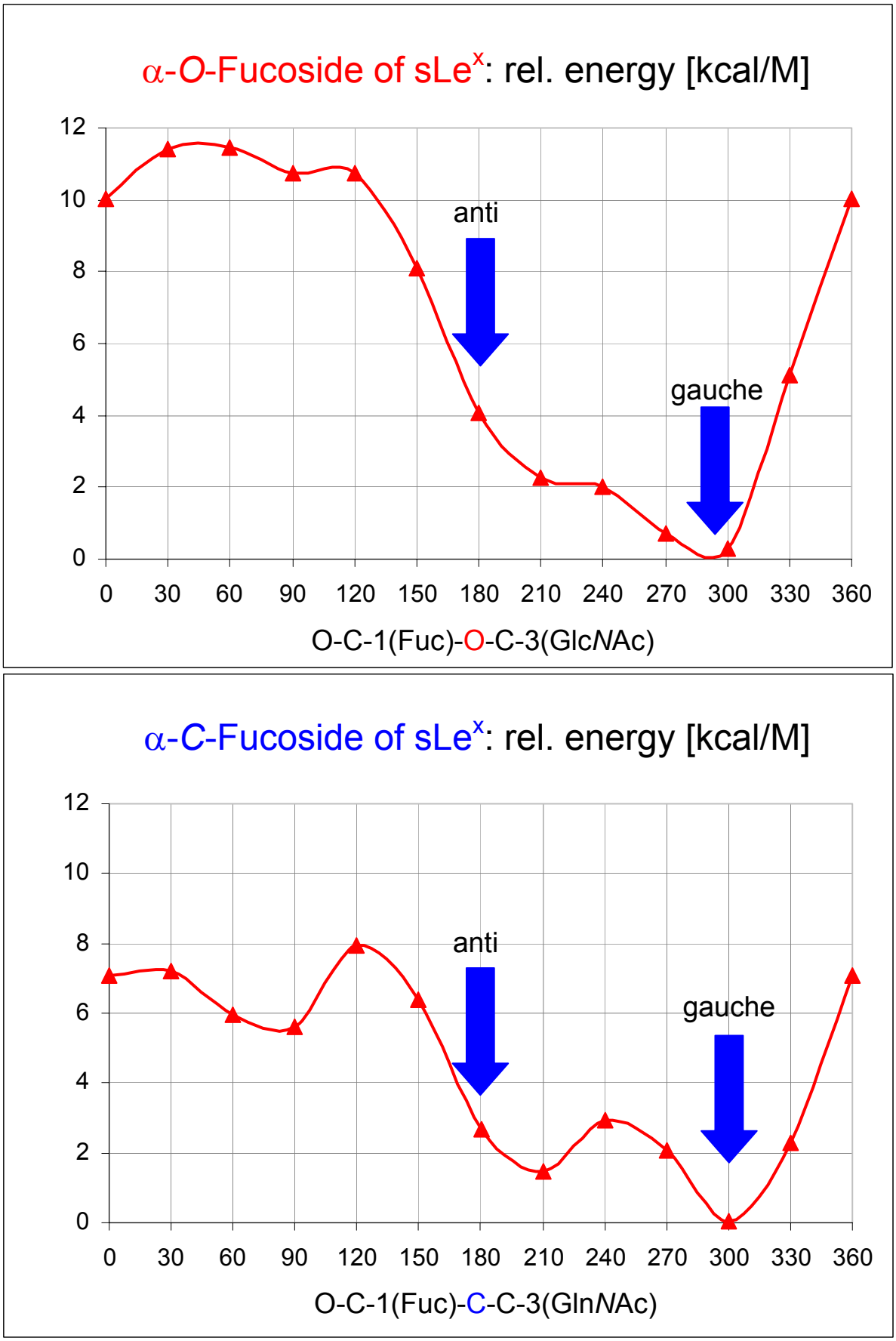


Figure 22: Rotational energy diagrams of the *O*-fucosidic (upper) and *C*-fucosidic (lower) linkage in sLe^x as calculated by Kolb *et al.* [244].

No clear agreement can be found in literature whether *C*-glycosides have similar conformational behavior as the parent *O*-glycosides or whether they show different conformational preferences. Kishi *et al.* [245-259] claimed, that the conformational behavior of *C*- and *O*-glycosides is very similar and that this similarity is a general phenomenon. He further proposed, based on semiquantitative NMR-analysis, that the preferred conformation of *C*- and *O*-glycosides can be predicted on the basis of

(1) the preference of the *O*- and *C*-glycosidic bond for those conformations which are in accordance with *exo*-anomeric effect and

(2) avoiding 1,3-diaxial-like interactions, which can be revealed by superposition of the conformers on a diamond lattice.

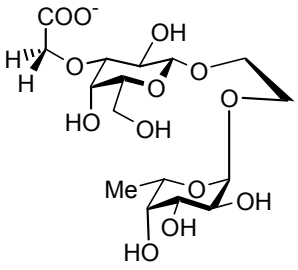
A further conclusion from their NMR-experiments with deoxy-derivatives was, that the preference of the gauche conformation around the glycosidic bond is so dominant, that structural deviations from the ideal staggered conformation to avoid 1,3-diaxial steric interactions occur by rotating primarily around the aglyconic bond rather than the glycosidic one. The *exo*-anomeric effect being the major factor why *O*-glycosides adopt their preferred conformation around the glycosidic bond was questioned.

In contrast to these findings, Jimenez-Barbero reported that the conformational behavior of *C*-disaccharides is clearly different to their *O*-glycosidic analogues. He used a combination of NMR spectroscopy (J and NOE data) and molecular mechanics (MM3, AMBER) and dynamics (MACROMODEL) calculations [243,260-266]. In agreement with the results from Kolb *et al.* [244], the *C*-glycosidic compounds possessed more minima on the potential energy surface than the corresponding *O*-glycosides, as found by MM3 calculations. The higher flexibility of the *C*-glycosides in general was shown by the fact, that *C*-glycosides populated a higher percentage of the total potential energy surface than the corresponding *O*-glycosides. In the β-gluco- and β-galacto cases, the most stable conformations adopt the same torsion angle Φ around the glycosidic bond, but differs in respect to the torsion angle Ψ around the aglyconic bond, indicating a higher flexibility around this bond. In some cases (α-manno and α-sia), even conformations around Φ, which are not in agreement with the *exo*-anomeric effect, were preferred by the *C*-glycosides, indicating that the *exo*-anomeric effect is indeed a key-factor determining the conformational behavior around Φ of *O*-glycosides.

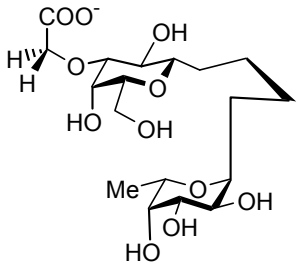
As far as the conformational similarities of *C*- and *O*-glycosides is concerned, Jimenez-Barbero showed, that in the case of *O*-glycosides, the global minimum is populated up to 97%, whereas the *C*-glycosidic counterpart possesses two or more almost equally populated minima with low energy barriers in between. The most populated global minimum is not the

same as in the *O*-glycosidic case, but occupies a conformation that is accessible also for the *O*-glycoside.

Numerous *C*-glycosidic analogues of sLe^x mimetics have been reported in literature (see compounds **27**-**29**, **55**, **71**, **74**, **76**-**78** in *chapter* 1.5 and references cited therein). However, only few examples allow a direct comparison with their *O*-glycosidic counterparts to derive the influence of the substitution of the anomeric oxygen by a methylene group on binding affinity. From the limited data available, Wong [176] suggested a 20-fold difference in affinity between *O*- and *C*-glycosides as can be seen in compounds **21** and **27** (see *figure* 23), but no generality has been established for this trend.



21
0.8 mM
[177]



27
20 mM
[179]

Figure 23: *O*- glycosidic mimic **21** and *C*-glycosidic mimic **27** allow a direct comparison of the binding affinities of *O*- and *C*-glycosides.

2. Thesis

The interest in *C*-glycosides is primarily based on their improved pharmacokinetic properties, e.g. their stability against acidic hydrolysis and metabolic degradation. However, the switch from *O*- to *C*-glycosidic bonds leads to a higher conformational flexibility due to a lack of stabilization by the *exo*-anomeric effect. This stereoelectronic effect strongly determines the preference of distinct conformations of *O*-glycosides. The missing *exo*-anomeric effect in *C*-glycosides leads to higher flexibility and therefore, as a consequence of increased entropic costs upon binding, to a reduction of affinity.

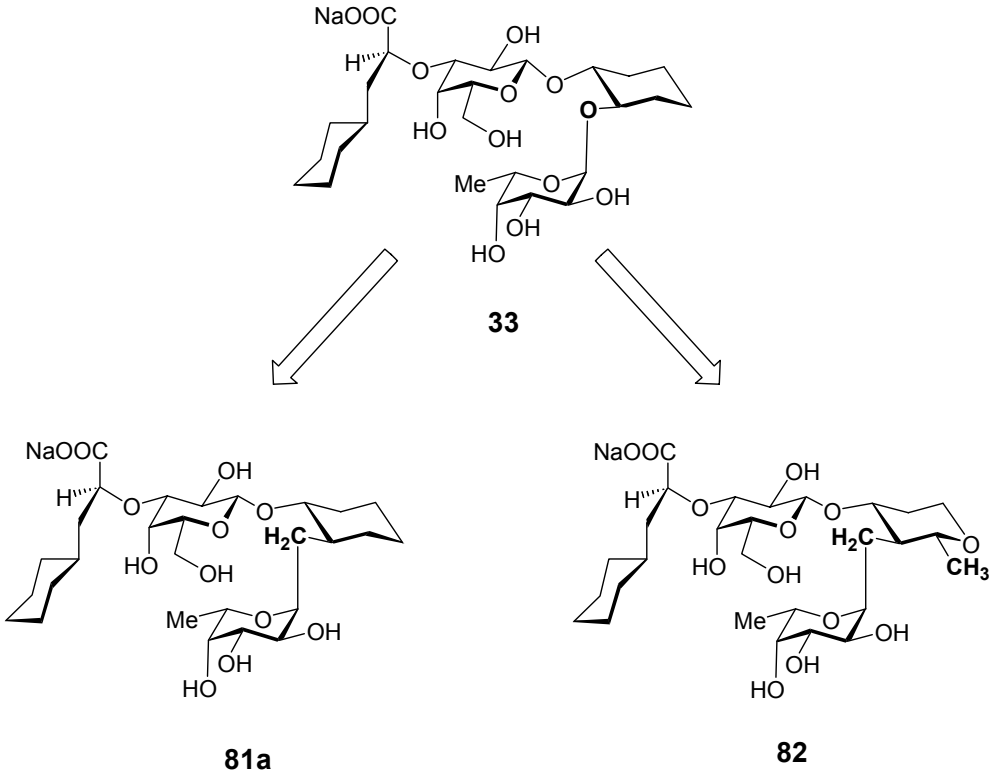


Figure 24: Parent *O*-glycosidic sLe^x-mimetic **33** and *C*-glycosidic target molecules **81a** and **82**.

The conformational stabilization by the *exo*-anomeric effect has been estimated by molecular modeling calculations [232-240]. However, the quantitative consequences for the binding affinity can hardly be predicted, since they depend on a series of molecular characteristics unique for each compound.

The *O*-glycosidic sLe^x-mimetic **33** turned out to be a potent E-selectin antagonist [168,198,199] with an IC_{50} of 80 µM (sLe^x: 1mM), binding 10 to 12 times stronger to E-selectin than sLe^x itself.

This Ph.D. thesis summarizes our approach towards the design and synthesis of *C*-glycosidic analogues **81a** and **82** of parent structure **33** (*figure* 24). In the target structures **81a** and **82** the *O*-fucosidic bond, highly sensitive towards hydrolysis in acidic environments, is replaced by the corresponding *C*-fucosidic bond. In compound **82** an additional equatorial substituent adjacent to the *C*-fucosidic linkage was introduced to compensate the missing *exo*-anomeric effect by steric constraints. The amount of compensation should be estimated by investigation and comparison of conformational preferences by NMR-spectroscopy.

Finally, a comparison of the binding affinities of compounds **33**, **81a** and **82** should allow a quantification of the entropy contribution to the inhibitory potential caused by the *exo*-anomeric effect.

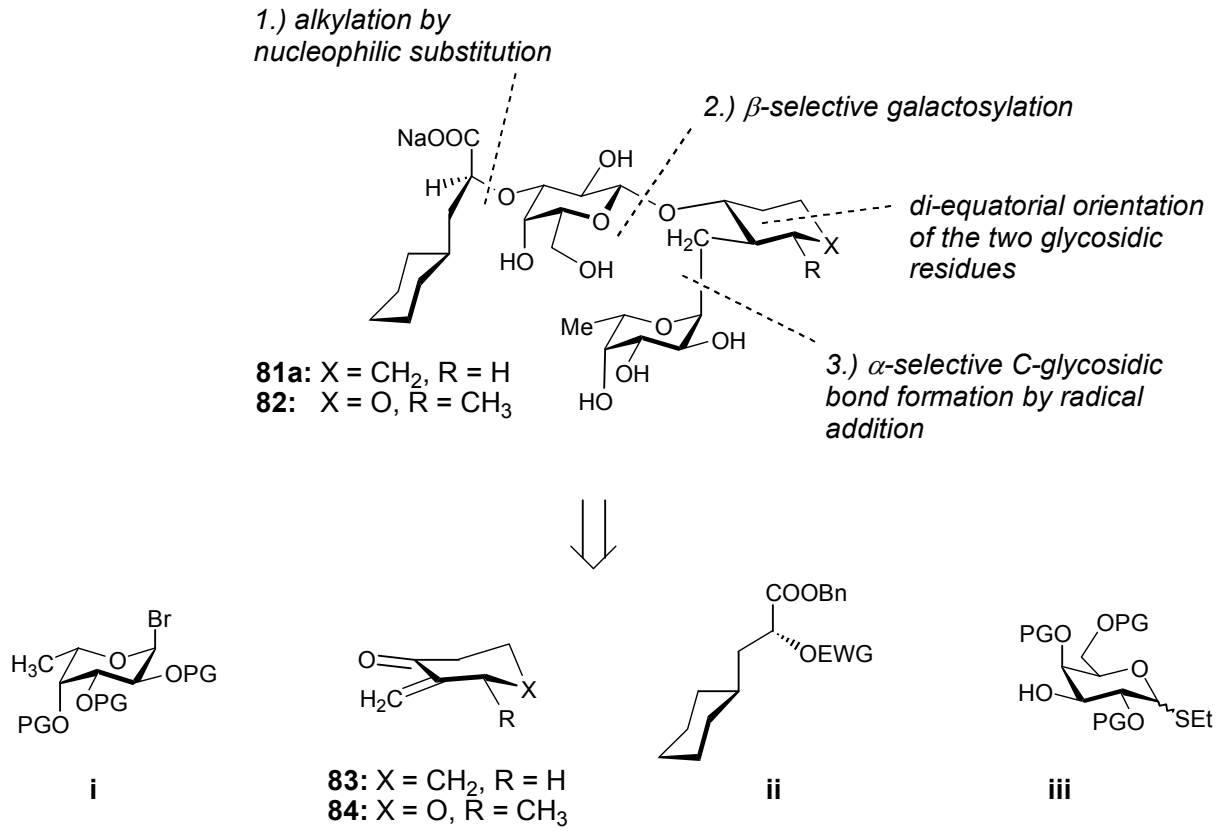
3. Results and Discussion

3.1. Retrosynthetic considerations and synthetic approach

The main objective of the project was the development of a synthetic route for the E-selectin antagonists **81a** and **82**, which contain a *C*-fucosidic bond in place of the *O*-fucosidic bond in the parent compound **33**. Since the synthetic strategy should be applicable to target molecules with structurally different Glc*N*Ac replacements, the concept should be flexible enough to cope with a variety of structural modifications.

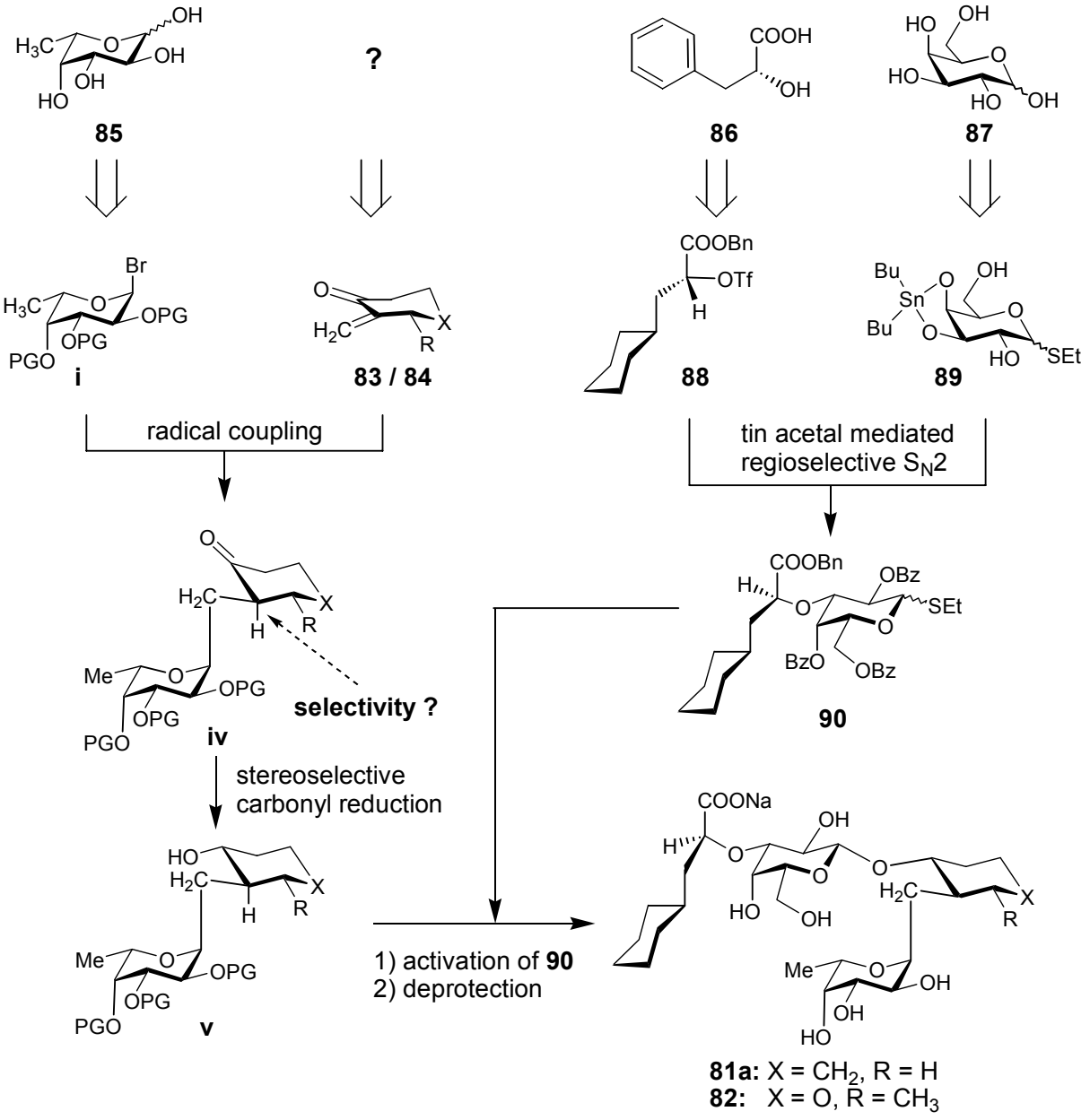
From a retrosynthetic point of view (see *scheme* 1) the key steps in the synthesis are:

1. Alkylation of the galactose moiety at the 3-position,
2. β-selective galactosylation of the Glc*N*Ac replacement and
3. α-selective *C*-glycosidic bond formation.



Scheme 1: Key steps and the key building blocks in the synthesis of the target molecules **81a** and **82** (PG = protecting group, EWG = electron withdrawing group).

Numerous methodologies have been described for the synthesis of *C*-glycosides [267,268], showing variable stereoselectivity at the anomeric center. We decided to apply the radical addition methodology [269-276], in which a radical generated from a glycosyl bromide precursor is added to an electron poor double bond. Giese *et al.* [275,277-282] have shown that this approach leads with good to excellent selectivity to the α-anomer. With fucosyl bromide **i** as radical donor and the methylene ketones **83** and **84** as radical acceptors, the strategic *C*-glycosidic bond can be obtained in both target molecules. Other key intermediates resulting from this retrosynthetic analysis are the cyclohexyllactic acid derivative **ii** containing a leaving group for nucleophilic substitution and the selectively protected galactosyl donor **iii** (*scheme* 1).



Scheme 2: Synthetic approach leading to the target molecules **81a** and **82**.

Our synthetic approach is outlined in *scheme* 2. It distinguishes itself by its high convergency and the possibility to introduce different Glc*N*Ac replacements making this strategy even interesting for a combinatorial approach.

Fucosyl bromide **i** is available by standard bromination procedures [283-286] (see *chapter* 3.2.1). The synthetic strategy for the methylene ketones **83** and **84** is discussed in *chapter* 3.2.2 and 3.2.3. The *C*-fucosidic ketone **iv** obtained via radical addition (see *chapter* 3.2.4) will be converted to the equatorial alcohol **v** (see *chapter* 3.2.5), which in turn will be glycosylated with galactose donor **90** (see *chapter* 3.2.6) obtained via a tin acetal mediated [287-289] nucleophilic substitution of the triflate derivative **88** (see *chapter* 3.2.6). Since a thiogalactoside was successfully applied in the synthesis of the *O*-glycoside **33** [168,199], we planned to adopt this approach [290,291] for the synthesis of **81a** and **82**. The exclusive formation of the β-anomer is expected based on neighboring group participation by the benzoate at the 2-position of the galactose donor **90**. Finally, deprotection will lead to the target molecules **81a** and **82**.

The major drawback of our approach is the reported Diels-Alder dimerization of sterically unhindered methylene ketones of the type of **83** and **84** [292-295].

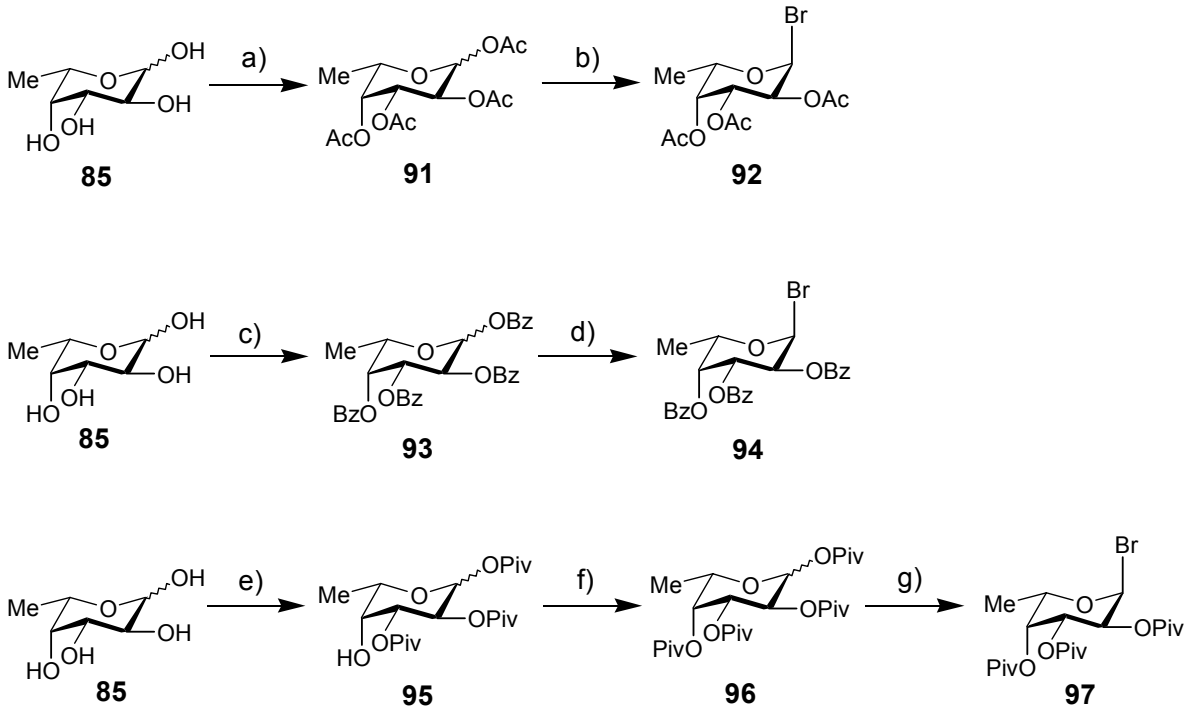
3.2. Synthesis of the *C*-fucosidic sLe^x-mimetics 81a and 82

3.2.1. Synthesis of fucosylbromides 92, 94 and 97

For the radical addition three differently protected fucosyl bromides were prepared. The acetate-protected fucoside **92** was obtained by standard procedures (*scheme* 3). To study the influence of different protective pattern on the selectivity of the radical addition step, the benzoate- and pivaloate-protected radical donors **94** and **97** were also synthesized (*scheme* 3).

According to standard procedures [283-286], fucose **85** was first converted to the tetraacylated fucosides **91**, **93** and **96**. Acylation with acetic anhydride or benzoylchloride at 0°C to rt yielded almost quantitatively the corresponding products **91** and **93**. With pivaloyl chloride, however, pivaloylation was incomplete even at elevated temperature (→ **95**). For a complete pivaloylation elevated temperature, DMAP activation and extended reaction time have to be applied (→ **96**) [285].

The peracylated fucosides **91**, **93** and **96** were then transformed into the corresponding fucosyl bromides **92**, **94** and **97** in good to excellent yields using HBr in acetic acid [285,296,297].



Scheme 3: Synthesis of the radical donor fucosyl bromides: a) Ac_2O, pyr, rt, 7h (95%); b) HBr/HOAc (33%), CH_2Cl_2, rt, 2h (86%); c) BzCl, pyr, 2h at 0°C + 1h at rt (96%); d) HBr/HOAc (33%), CH_2Cl_2, rt, 2h (97%); e) PivCl, pyr, 2h at 0°C + 16h at rt + 4 h at 50°C (59%); f) PivCl, cat. DMAP, pyr, 24h at 70°C + 48h at rt (95%); g) HBr/HOAc (33%), CH_2Cl_2, rt, 15h (100%).

3.2.2. Synthesis of α-methylene cyclohexanone (83)

Numerous preparative methods for the synthesis of α-methylene ketones have been reported over the last decades. Many approaches are based on a Mannich type condensation of an enolizable ketone with an aldehyde and an amine followed by thermal β-elimination of an ammonium salt [298-301]. Other examples use the desilylbromination of β-trimethylsilylketones [302] or the Aldol condensation of formaldehyde with ethyl oxalylketones followed by elimination under basic conditions [303]. Also Wittig approaches have been described [304,305]. All these methods, however, encounter only limited regioselectivity and low yields.

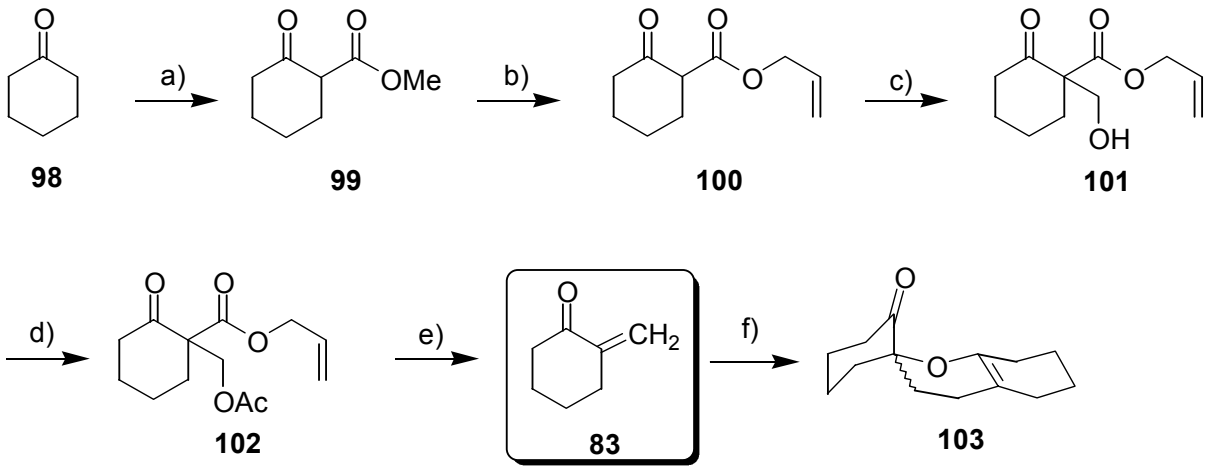
α-Methylene cyclohexanone (**83**) was first obtained, although mainly described as a dimer in 1920 by C. Mannich *et al.* [306] by thermal decomposition of the Mannich base 2-

piperidinomethyl-cyclohexanone hydrochloride. Some 20 years later, the same author described the synthesis of α-methylene cyclohexanone (**83**) and its dimerization behavior in more detail [293,307].

In our first attempt, we applied the procedure of Gras *et al.* [295] to achieve the α-methylene cyclohexanone (**83**) by the Aldol condensation of formaldehyde to cyclohexanone (**98**) promoted by *N*-methylanilinium trifluoracetate (TAMA). The desired methylene ketone could be detected in the reaction mixture by NMR, but could not be isolated due to dimerization during reaction and workup.

For a successful preparative approach, the synthesis and purification of methylene ketone **83** had to be carried out under mild conditions. Therefore, the method described by Tsuji *et al.* [308,309] was applied, which is based on a palladium-catalyzed decarboxylation-deacetoxylation of allyl α-acetoxymethyl-β-keto carboxylates (as e.g. **102**), and where the final olefination step proceeds under very mild conditions and a short reaction time.

The methylene ketone precursor allyl 1-acetoxymethyl-2-oxo-cyclohexanecarboxylate (**102**) [308,309] was obtained in four steps in high yields (*scheme* 4). In the first step, cyclohexanone (**98**) was carboxylated using dimethyl carbonate (→ **99**) followed by transesterification with allyl alcohol. The resulting allyl β-ketocarboxylate (**100**) was then hydroxymethylated by treatment with aqueous formaldehyde and $KHCO_3$ as a base to yield **101** in quantitative yield.



Scheme 4: Synthesis of α-methylene cyclohexanone (**83**): a) $(MeO)_2CO$, NaH, C_6H_6, 70°C, 4 h (82%); b) AllOH, AllONa, reflux, 48 h (73%); c) $KHCO_3$, H_2CO, THF/H_2O, rt, 7 h (100%); d) Ac_2O, pyr, rt, 4 h (88%); e) $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3, MeCN, rt, 20 min. (72%); f) Diels-Alder cyclization (see *table* 4).

After acetylation of the primary hydroxyl group (→ **102**), the palladium catalyzed decarboxylation-deacetoxylation step using tris(dibenzylideneacetone)-dipalladium in acetonitrile at 20-25°C yielded quantitatively the desired radical acceptor α-methylene cyclohexanone (**83**). As already described by Mannich [307], **83** can easily be identified by its characteristic odor. For a successful radical reaction it is very important to isolate the methylene ketone **83** in pure form. However, purification and handling of the pure methylene ketone **83** is complicated by its tendency to undergo dimerization by Diels-Alder cyclization.

Our investigation of the thermal stability of **83** revealed that dimerization cannot be suppressed during workup and is also the main side reaction during the subsequent radical reaction. Since only limited information on the stability of **83** are reported [294], a detailed study of its dimerization behavior was undertaken.

The Diels-Alder dimerization (→ **103**) under various conditions was analyzed by NMR-spectroscopy. For the Diels-Alder reaction the dimerization rate should be 2nd order in monomer concentration. For its determination, different fractions of **83** were investigated at different time points (see *table* 4). Entry 4 and 5 in *table* 4 clearly indicate that methylene ketone **83** cannot be produced and be stored over an extended period of time but rather has to be prepared immediately prior to use in the radical reaction.

Table 4: Investigation of dimerization behavior of α-methylene cyclohexanone (**83**). Monomer:dimer ratios were determined by comparison of the integral of one methylene proton of the monomer (5.14 ppm) with the integral of the axial $\underline{CH_2}$-C=O proton of the dimer (2.75 ppm) in the ^{1}H-NMR spectra.

entry	conditions	% monomer
1	crude product, without purification ($CDCl_3$)	100
2	pure product after distillation ($CDCl_3$)	69
3	entry 2 + 15 h at rt in $CDCl_3$	43
4	entry 2 + 2 d at rt without solvent	0
5	entry 2 + 12 h at -20°C without solvent	52
6	entry 2 + 1 h at 80°C in C_6D_6	46
7	entry 2 + 2 h at 80°C in C_6D_6	37
8	entry 2 + 3 h at 80°C in C_6D_6	27

Standard reagents for the subsequent radical addition reaction to olefins are AIBN (azobisisobutyronitrile) as initiator for the radical chain reaction and Bu_3SnH as hydrogen donor. Thermal decomposition of AIBN into the initial radicals, which have a half-life of about 1 hour, occurs at 80°C [269]. At this temperature, the half-life of α-methylene ketone (**83**) in deuterated benzene was determined to be approximately 3-4 hours (*entry* 6 to 8).

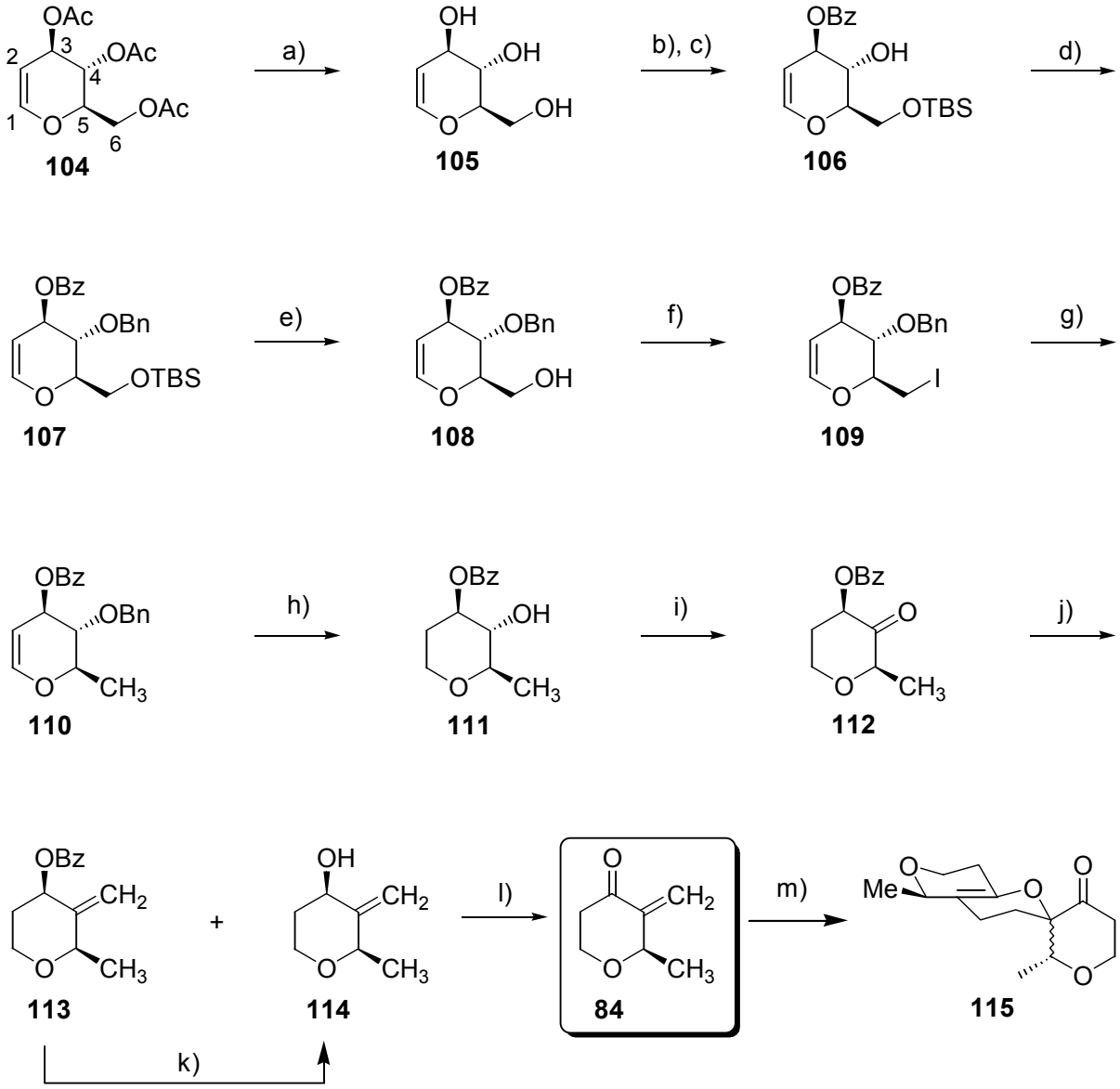
3.2.3. Synthesis of (*2R*)-2-methyl-3-methylene-tetrahydropyran-4-on (84)

For the synthesis of the tetrahydropyran derivative **84**, peracetylated *D*-glucal **104** was used as chiral starting material. It already contains the chiral center of the building block **84** and it is therefore not necessary to perform diastereoselective reaction steps.

The synthesis starting from the commercially available peracetylated *D*-glucal (**104**) involves the following transformations:

- orthogonal protection of the three hydroxyl groups of **105**,
- dehydroxylation of the C-6 primary alcohol to establish the methyl group,
- hydrogenation of the double bond,
- oxidation of the C-4 hydroxyl group and olefination of the resulting ketone and
- oxidation of the C-3 hydroxyl group into a ketone.

A first synthetic attempt is shown in *scheme* 5. The reaction protocol for the orthogonal protection [310] is based on the different reactivities of the three hydroxyl groups: The primary hydroxyl group at C-6 is the most reactive one followed by the allylic alcohol at C-3 and the least reactive secondary alcohol at C-4. TBDMS-, benzyl- and benzoyl-protecting groups were chosen due to their orthogonal stability towards cleaving conditions. After deacetylation of triacetylglucal (**104**), glucal **105** was instantly used without prior purification in the next step. Silylation and benzoylation were done in a one-pot reaction to yield **106** in 75% overall yield. A bulky silyl residue was chosen in order to support the reactivity difference by steric factors in favor of the primary alcohol. Additionally, low reaction temperatures were applied to improve selectivity. In both steps more than one equivalent of reagent was needed to completely consume the starting material. Consequently, undesired double-protection with TBDMSCl leading to the byproduct 4,6-bis(TBDMS)-glucal, could not be totally avoided. Benzyl ether formation of the secondary hydroxyl group in C-4 was achieved with benzyl bromide and NaH in DMF (→ **107**).



Scheme 5: Synthesis of the methyl substituted α-methylene ketone **84**; pathway (I): a) NaOMe, MeOH, rt, 2 h (quant.); b) TBSCl, pyr, CH_2Cl_2, 2 h at 0°C + 12 h at rt; c) BzCl, pyr, CH_2Cl_2, 14 h, rt (75% for two steps); d) BnBr, NaH, DMF, 2 h, rt (80 %); e) TBAF, THF, 1 h at 0°C + 2 h at rt (84%); f) I_2, PPh_3, imidazole, CH_2Cl_2, 10 h, rt (84%); g) Bu_3SnH, AIBN, C_6H_6, reflux, 20 h (52 %); h) $Pd(OH)_2$/C, 4 bar H_2, MeOH, 21 h, rt (97%); i) PDC, 3Å MS, CH_2Cl_2, 0°C to rt (93%); j) $MePPh_3Br$, BuLi, THF, 3 h at -40°C + 18 h at rt (60%); k) NaOMe, MeOH, rt, 17 h, (75%); l) PDC, 3 Å-MS, CH_2Cl_2, 0°C to rt, 16 h (90%); m) Diels-Alder dimerization (see *table* 5).

The silyl protection was removed using tetrabutylammonuimfluoride (TBAF) and the corresponding alcohol **108** iodinated by a procedure originally developed by Mukaiyama [311-314], in which the primary alcohol is activated by the oxophilic phosphonium salt $[PPh_3\text{-}I]^+ I^-$ generated from PPh_3 and I_2. $Ph_3P{=}O$ serves as leaving group to be displaced by the

nucleophilic iodide. 1-H-imidazole was used as a base to quench the emerging HI. This method allows the direct *in situ* conversion of the hydroxyl group into the iodide **109**. In the next step, the iodide **109** was reduced by radical dehalogenation using Bu_3SnH as hydrogen donor. The yield of **110** was rather low emerging from the difficulty of completely removing the phosphonium oxide, which interferes with the radical reaction.

Since hydrogenation of **110** under standard conditions (H_2, Pd/C, HOAc) was not successful, it was carried out in a Parr shaker using $Pd(OH)_2/C$ at 4 bar H_2. Oxidation of alcohol **111** with pyridinium dichromate (PDC) delivered ketone **112** in high yields. In order to convert the keto function into a methylene group we investigated two different methodologies: the Wittig olefination with $H_2C{=}PPh_3$ [315,316] and methenylation using the Tebbe methylene transfer reagent bis-(cyclopentadienyl)-μ-chloro-(dimethylaluminum)-μ-methylenetitanium [317,318].

Wittig olefinations with unstabilized phosphorous ylides often suffer from low yields and the strong basic reaction conditions leads to side reactions. Therefore, we suspected that the benzoyl protecting group in **112** could be partially cleaved. The Wittig ylide can be easily prepared by deprotonation of the inexpensive phosphonium bromide salt by n-BuLi.

The experiment showed indeed that the Wittig olefination of **112** to **113** proceeds with only moderate yields (60%), and 17% of the olefin undergoes benzoyl cleavage (→ **114**). Workup of the reaction and isolation of the product was complicated by the difficulty of removing the excessive phosphorous compounds from the crude reaction mixture.

Tebbe reactions often perform with better yields than Wittig olefinations. The Tebbe reagent converts esters to enolethers [319-321] which are easily hydrolysed to alcohols during workup. However, the Tebbe reagent is very expensive and extremely sensitive to moisture and oxygen, making the experimental effort very complicated.

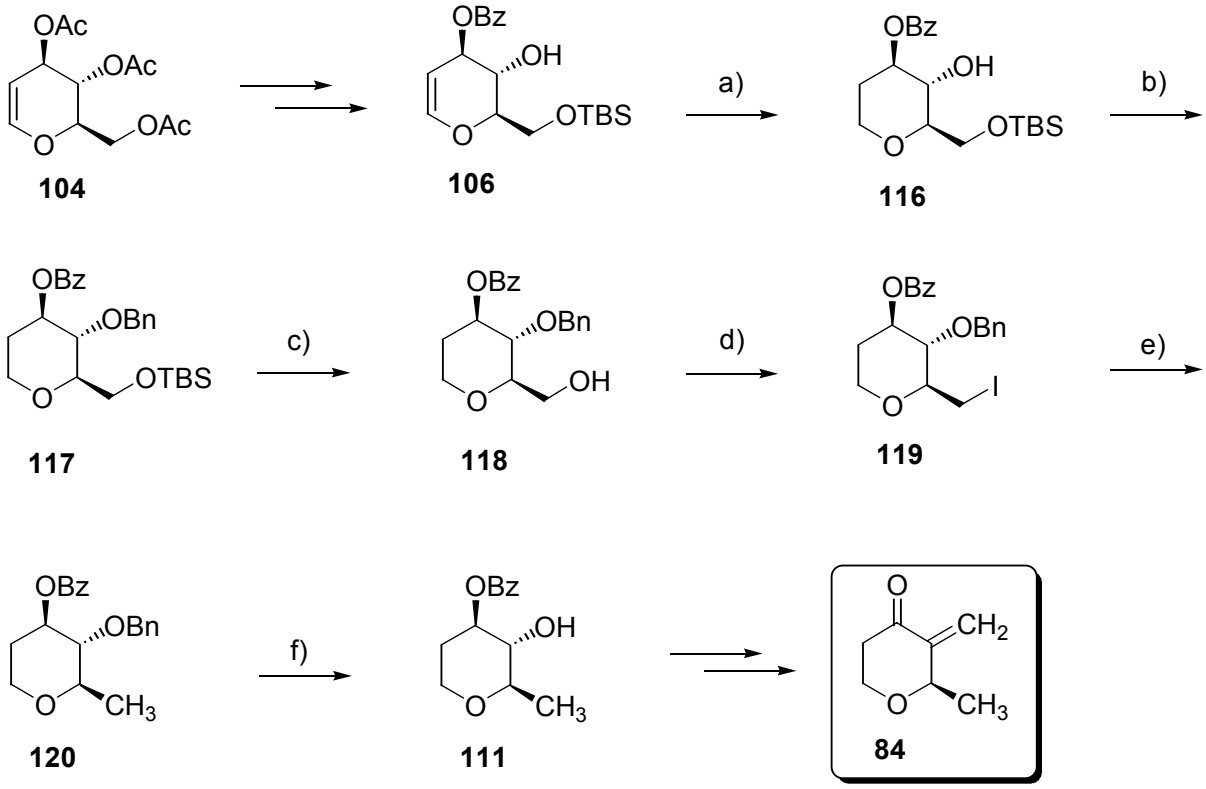
The alternative Tebbe-reaction performed similar concerning yields (60%). As in the Wittig reaction we found debenzoylated **114** as byproduct of the olefination. Isolation of the products from the aluminum- and titanium salts turned out to be as difficult as purification after the Wittig reaction.

Overall, both methods are equal in respect to the chemical yields. However, Wittig olefination is favored because of the high costs of the tebbe reagent.

After saponification of **113** to **114**, the oxidation of the hydroxyl group at C-3 was performed using PDC (→ **84**).

With this synthetic strategy building block (*2R*)-2-methyl-3-methylene-tetrahydropyran-4-on (**84**) was obtained in a 12-step synthesis and an overall yield of 8% (*scheme* 5).

In the second approach (*scheme* 6), the strategy was changed in two points. The double bond was hydrogenated right in the beginning of the synthesis and a different deiodination method was applied. **106** was obtained as already described in *scheme* 5. Now, the double bond was hydrogenated with quantitative yield to obtain **116**. Benzylation of **116** to **117** followed by cleavage of the silyl ether and iodination of the primary alcohol **118** yielded **119**.



Scheme 6: Synthesis of the methyl substituted α-methylene ketone **84**; pathway (II): a) Pd/C, 4 bar H_2, MeOH, 2 h, rt (quant.); b) BnBr, NaH, DMF, 6 h, rt (75 %); c) TBAF, THF, 1 h at 0°C + 4 h at rt (96%); d) I_2, PPh_3, imidazole, CH_2Cl_2, 17 h, rt (91%); e) Pd/C, NaOAc, 4 bar H_2, MeOH, 17 h rt, (95%); f) $Pd(OH)_2$/C, 4 bar H_2, MeOH, 21 h rt (97%).

The reduction of iodide **119** was accomplished by hydrogenation (H_2, Pd/C, NaOAc) [322,323] (→ **120**). By switching to this method, the yield of the reductive step could be improved from 52% to 95%. The following transformations (**120**→**111**→**84**) are identical to those used in the first strategy described in *scheme* 5.

In the second 13-step synthesis of (*2R*)-2-methyl-3-methylene-tetrahydropyran-4-on (**84**) the overall yield could be improved from 8% to 17%.

As for the α-methylene cyclohexanone (**83**), dimerization problems *(table* 5) forced us to freshly synthesize **84** prior to its use in the radical addition reaction. In the first approximation, half-life and dimerization rate for **83** and **84** are similar.

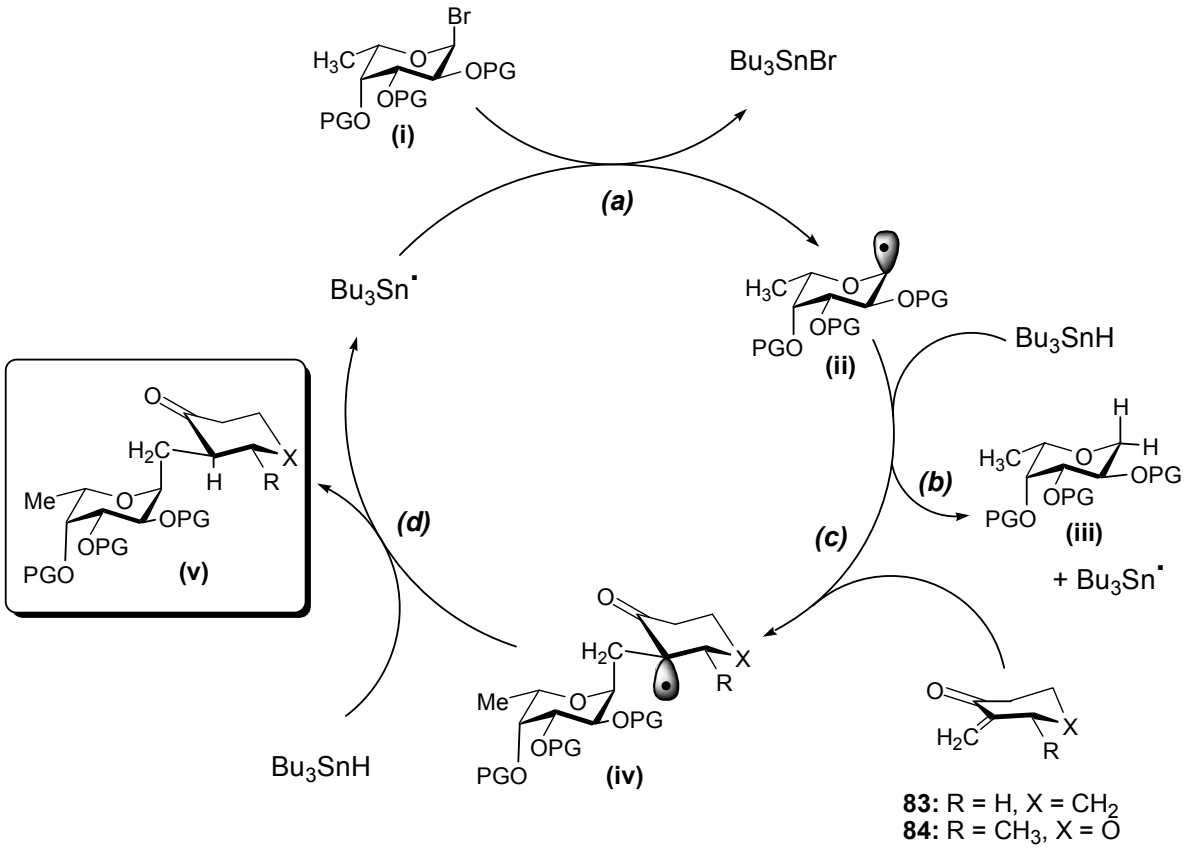
Table 5: Investigation of dimerization behavior of (*2R*)-2-methyl-3-methylene-tetra-hydropyran-4-on (**84**). Monomer:dimer ratios were determined by comparison of the integrals of one methylene proton (5.30 ppm) and the proton H-5 (q, 4.44 ppm) of the monomer with the integral of the proton H-5 of the dimer (q, 4.10 ppm) in the ^{1}H-NMR spectra.

entry	conditions	% mono
1	crude product without purification ($CDCl_3$)	100
2	purification and solvent evaporation at 0°C ($CDCl_3$)	59
3	entry 2 + 14 h at rt in $CDCl_3$	57
4	entry 2 + 26 h at rt in $CDCl_3$	55
5	entry 4 + 1.5 h at 40°C without solvent	27
6	entry 1 + 16 h at rt in C_6D_6	80
7	entry 1 + 24 h at rt in C_6D_6	72
8	entry 7 +1 h at 80°C in C_6D_6	50
9	entry 7 +2 h at 80°C in C_6D_6	40

3.2.4. Synthesis of the *C*-fucosidic ketones 122, 123 and 124 by radical addition

With the two α-methylene ketones **83** and **84** for the replacement of the Glc*N*Ac-moiety of sLe^x in hand, the addition of the radicals generated from the fucosyl bromides **92**, **94** and **97** to the olefins **83** and **84** could be investigated.

In order to reach high yields of *C*-fucoside **v** and to suppress the formation of deoxyfucose **iii**, the rates of the reactions **(c)** (**ii** → **iv**) and **(d)** (**iv** → **v**) in the radical propagation cycle (*scheme* 7) have to be higher than the rate of direct H-atom transfer **(b)** (**ii** → **iii**). The terminal hydrogen transfer **(d)** from Bu_3SnH to the *C*-fucosidic radical **iv** controls the radical cycle by regenerating the tin radical needed for the next cycle. Therefore, the concentration of the hydrogen donor can be seen as variable to influence product distribution.



Scheme 7: Propagation steps for the radical addition of the fucosyl bromide **i** to the methylene ketone **83 / 84**.

Another very important aspect of the reaction is the stereochemical outcome concerning both newly formed stereogenic centers, the anomeric center of the fucoside and the ring-carbon next to the carbonyl group.

The stereoselectivity of reactions at the anomeric center of carbohydrate radicals is mainly controlled by stereoelectronic and not by steric effects. The axial orientation of the radical-bearing anomeric orbital in $\mathbf{i_{ax}}$ is stabilized by mesomeric interaction of this radical-bearing orbital with the axial lonepair of the ring oxygen (n→SOMO interaction or anomeric effect) and is favored in the equilibrium shown in *figure* 25a. In a radical addition, the olefin is mainly attacked by $\mathbf{i_{ax}}$. In addition, the conformation of pyranosyl radicals is influenced by a second stereoelectronic effect, the so-called β-oxygen effect or quasi-homo-anomeric effect [324-326]. This effect is based on a mesomeric interaction of the radical-bearing orbital with the coperiplanar σ*-orbital of the β-C-O bond (see *figure* 25b). In analogy to the conformation preferred by the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical ($B_{2,5}$ conformation) [326], the 2,3,4-tri-*O*-acyl-L-fucopyranos-1-yl radical **ii** adopts a slightly twisted $B_{1,4}$-like conformation.

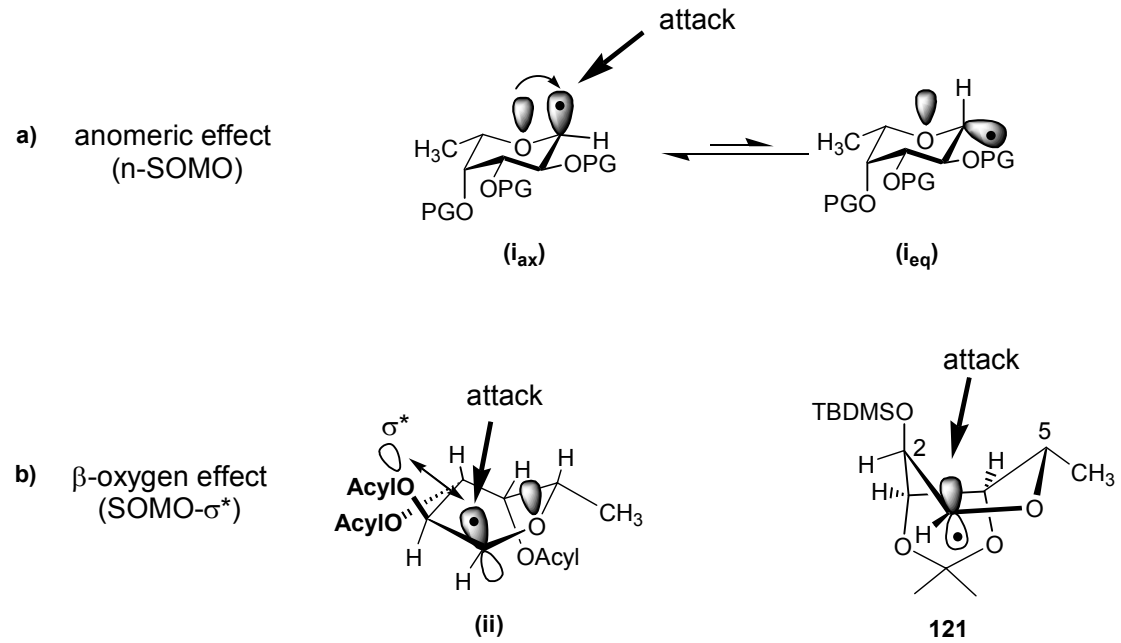


Figure 25: Stereoelectronic effects in pyranos-1-yl radicals.

In contrast, the 2-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-L-fucopyranos-1-yl radical **121** [327] (see *figure* 25b) was found to adopt a ^{2,5}B conformation [328], forced by the isopropylidene ring. As a consequence the β-oxygen effect is slightly weakened. The α-anomer, however, is still favored because of a pseudo-equatorial attack from the *exo*-face of the radical center.

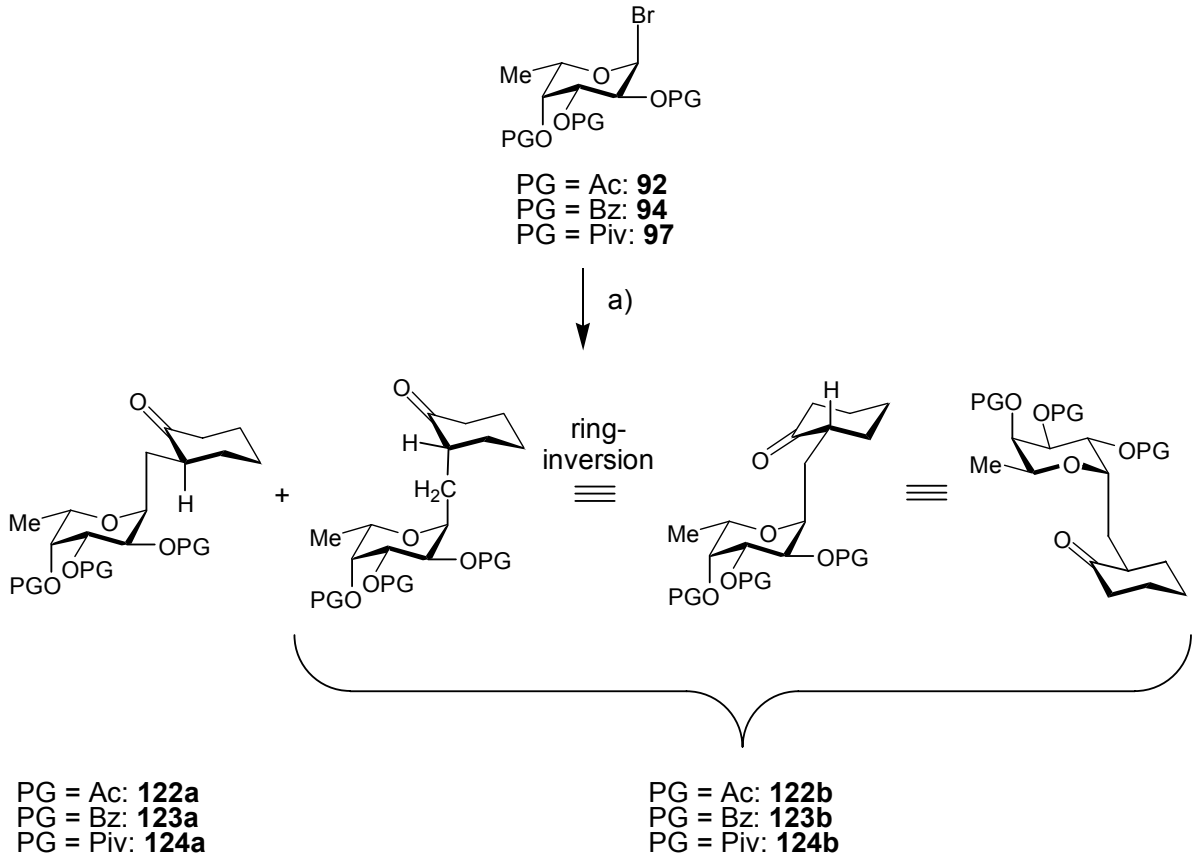
*Radical addition with 2-methylene cyclohexanone (**83**):*

The radical acceptor **83** suffers from dimerization (see *table* 4). Therefore, the crude product of **83** – obtained by filtration of the reaction mixture – was used in the subsequent reaction with bromide **92**. The radical reaction with crude **83** was performed in acetonitrile (applied for the formation of **83**) as well as in dimethoxyethane (used by Giese *at al.* [275]). Since this approach did not yield the desired *C*-fucoside **122**, we raised the hypothesis, that PPh_3/PPh_3O traps the intermediate radicals before the radical chain reaction is initiated. To verify this hypothesis, the methylene ketone **83** was purified prior to the radical reaction by distillation accepting partial dimerization to **103**.

Using an excess of the "purified" α-methylene cyclohexanone (**83**) and tri-*O*-acetylfucosylbromide (**92**) with Bu_3SnH and AIBN in dimethoxyethane at 80°C, the *C*-

fucoside **122** was finally obtained (*scheme* 8), although only with low yield (35%). In addition, a large amount of 1-deoxy-2,3,4-tri-*O*-acetylfucopyranose and 2-deoxy-1,3,4-tri-*O*-acetylfucopyranoside was formed, indicating, that the intermediate fucosyl radical is partly reduced before and after acyl migration. Probably the side products are formed due to the progressive dimerization of the olefin under reaction conditions. To optimize the formation of fucoside **122**, the hydrogen donor was slowly added with a syringe pump over a period of 12 h. The failure of this approach indicates, that the progressive dimerization of the olefin **83** causes the low overall yield. In addition, when benzene or toluene were used instead of dimethoxyethane, no positive influence on product distribution or yield of the *C*-fucoside **122** could be observed.

Yields of the analogous radical addition reactions with benzoyl- and pivaloyl-protected fucosylbromides **94** and **97** leading to the α-*C*-fucosides **123** and **124** were similar to those of the reaction with acetyl-protected fucosylbromide **92** (*scheme* 8, *table* 6).

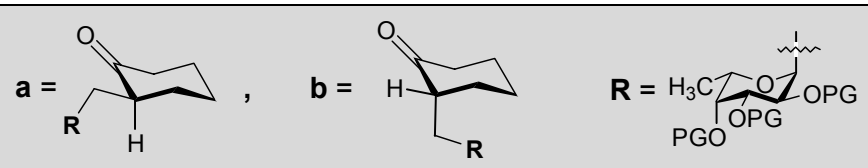


Scheme 8: Results for the radical addition of fucosyl bromides to α-methylene cyclohexanone; a) 2.5 eq. **83**, Bu_3SnH, AIBN, dimethoxyethane, 85°C, 15 - 18 h. Yields and selectivities are given in *table* 6.

As predicted based on stereoelectronic effects (see *figure* 25), exclusive formation of the α-*C*-fucosides was observed in all cases (*scheme* 8, *table* 6). Vicinal coupling constants between 5.3 and 5.8 Hz for the $J_{1,2}$ coupling of fucose are in good agreement with α-*C*-fucosides described in literature [329-331].

In contrast to the high stereoselectivity at the anomeric center, the hydrogen transfer to the *C*-fucosyl radical (see **iv** in *scheme* 7) was not stereoselective. In general, reactions of substituted and unsubstituted cyclohexyl radicals behave similar in stereochemistry as the reduction of related cyclohexanones [332]. There, the axial attack is thermodynamically favored, whereas kinetically favored equatorial attack suffers from steric 1,3 diaxial repulsion in the product. *Ortho*-substituted cyclic radicals are preferentially attacked *anti* to the substituents present in the ring system [333]. In special cases, this *anti*-rule can be outweighted by stereoelectronic effects (as discussed in *figure* 25) or by large exocyclic substituents next to the radical center leading to *syn* addition (see e.g. **126** in *scheme* 10).

Table 6: Yields and stereoselectivities obtained in the radical coupling with α-methylene cyclohexanone (**83**).



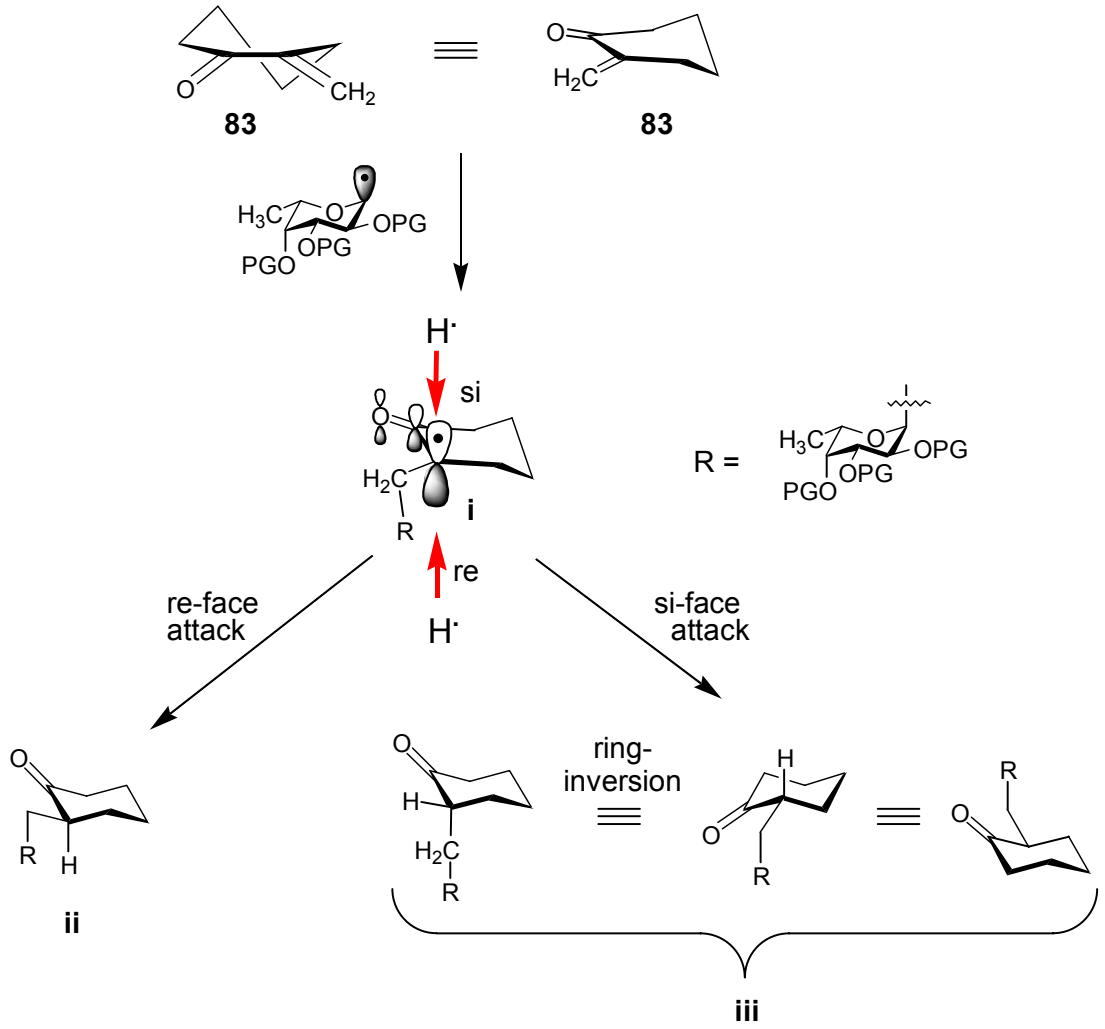
fucosylbromide		product ketones	diastereomeric ratio **a**:**b**	yield
PG = Ac	**92**	**122a** + **122b**	43 : 57	35 %
PG = Bz	**94**	**123a** + **123b**	35 : 65	26 %
PG = Piv	**97**	**124a** + **124b**	33 : 67	30 %

In the radical reactions with α-methylene cyclohexanone (**83**) only poor to moderate selectivities (between 57:43 and 67:33) was obtained at the carbon α to the carbonyl because of the absence of shielding and thus directing substituents (*table* 6). The *C*-fucosyl radical **i** (*scheme* 9) contains a planar sp^2-hybridized radical center, which is stabilized by mesomeric interaction with the π-orbital of the carbonyl group. Attack of the hydrogen radical from the re-face leads to the desired diastereomer **ii** with *S*-configuration at the carbon α to

the carbonyl, whereas by attack from the si-face, the undesired diastereomer **iii** with *R*-configuration is obtained (see *scheme* 9).

Comparing the results of the radical coupling reactions, a slight tendency depending on the protecting groups in favor of the diastereomers with *R*-configuration is observed (see *table* 6). The increasing steric demand of the fucosyl residue could be responsible for this trend.

The main problem we were facing at that point of the synthesis was the impossibility to assign the absolute configuration at the newly formed chiral center by NMR-spectroscopy. Consequently, we were not able to decide which of the two obtained diastereomers was the one mimicking sLe^x. The correlation shown in *scheme* 8 is based on the data obtained later from the x-ray analysis discussed in *chapter* 3.3.3. Due to this assignment problem we continued the synthesis with both diastereomers.

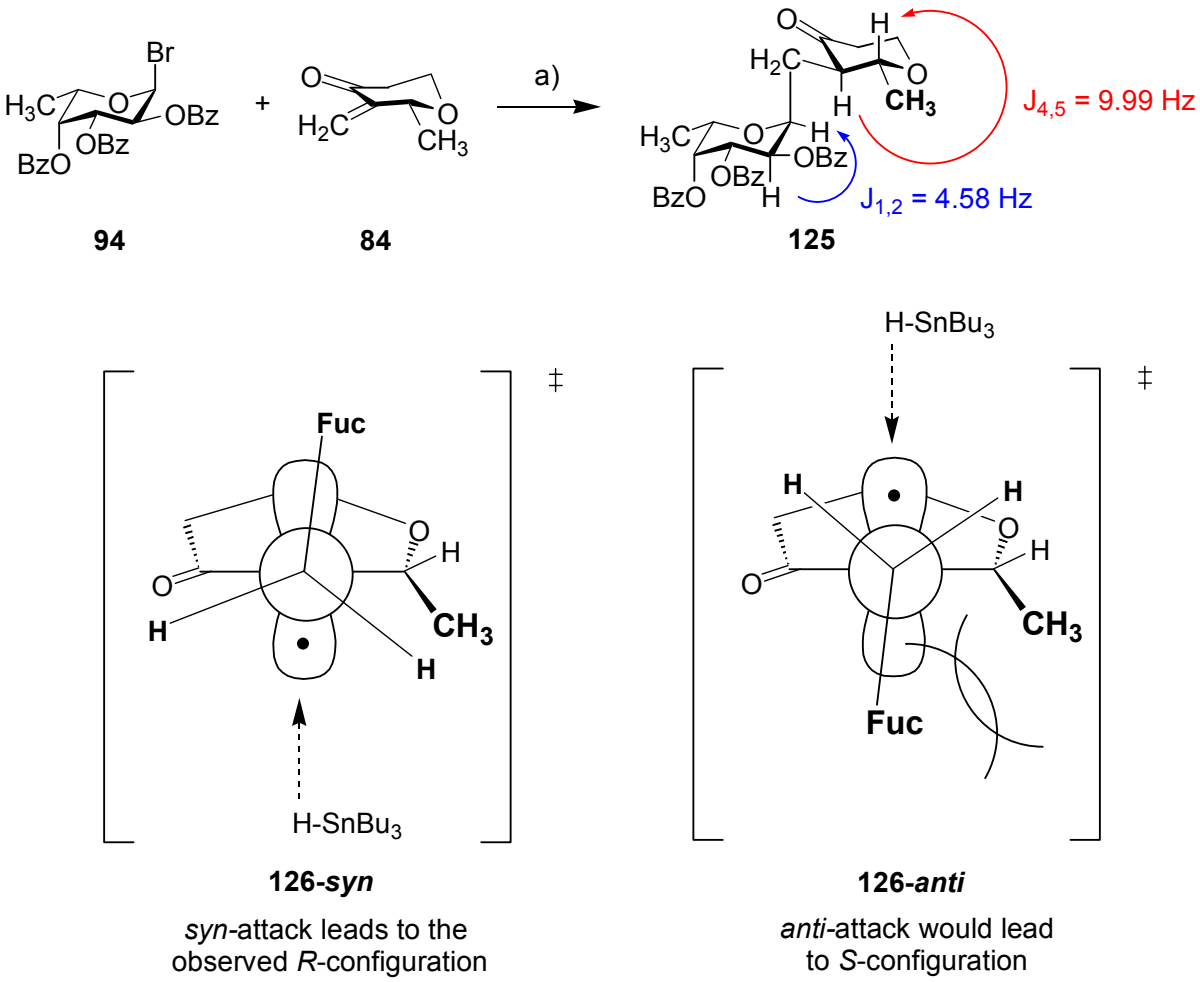


Scheme 9: Reaction mechanism of the radical addition leading to a diastereomeric mixture of desired (**ii**) and undesired (**iii**) *C*-fucosidic ketones.

*Radical addition with (2R)-2-methyl-3-methylene-tetrahydropyran-4-on (**84**):*

In contrast to the results of the radical reaction with α-methylene cyclohexanone (**83**), the reaction of 2,3,4-tri-*O*-benzoyl-fucosylbromide (**94**) with the methyl substituted methylene ketone (2*R*)-2-methyl-3-methylene-tetrahydropyran-4-on (**84**) performed with absolute stereocontrol at both newly formed stereocenters (*scheme* 10).

The single *C*-fucoside formed showed α-configuration at the anomeric center ($J_{1,2}$ = 4.58 Hz) and *R*-configuration at the chiral center next to the ketone function. This 2,3-*trans*-configuration can be proofed by the large coupling constant of 9.99 Hz for the two corresponding protons (*scheme* 10).



Scheme 10: Radical addition to the methyl substituted tetrahydropyrane methylene ketone **84**. The transition states **126-*syn*** and **126-*anti*** are shown in projection along the bond between the methylene bridge and the carbon radical in the pyrane ring. Steric hindrance between the fucose residue and the methyl group of the tetrahydropyrane ring makes transition state **126-*anti*** unfavorable. Hydrogen transfer occurs via **126-*syn*** leading to the observed product **125**. a) Bu_3SnH, AIBN, dimethoxyethane, 85°C, 18 h (11%).

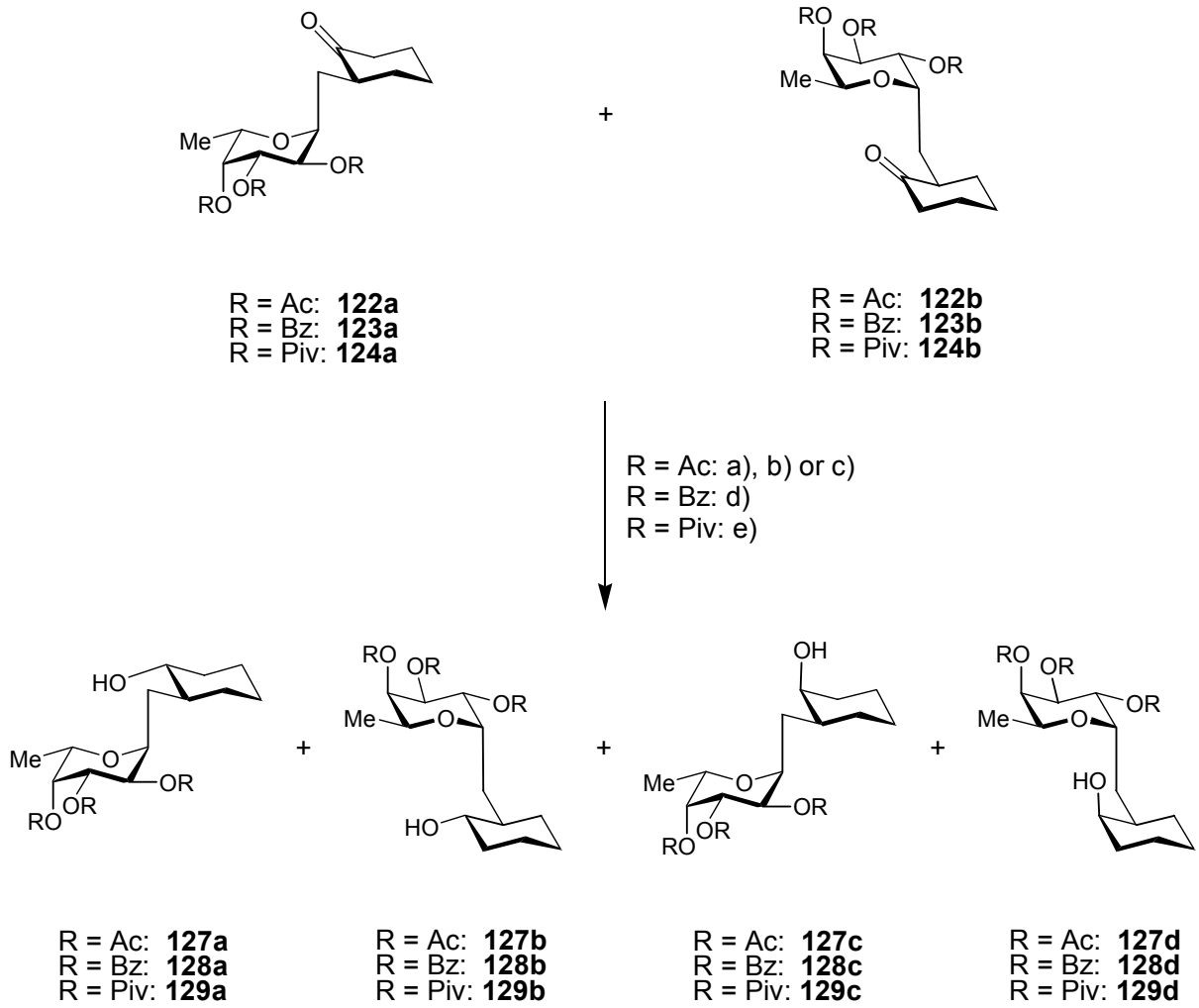
The 2,3-*trans*-configuration results from an attack of the hydrogen radical *syn* to the methyl group in **84** as shown in transition state **126-*syn*** in *scheme* 10. The orientation of the large fucose residue opposite to the methyl group avoids steric hindrance as in the transition state **126-*anti***. This stereochemical outcome is typical for cyclic radicals with large exocyclic substituents at the prochiral center.

3.2.5. Stereoselective reduction of the *C*-fucosidic ketones 122, 123 and 124

Following the synthetic strategy depicted in *scheme* 2, the *C*-fucosidic ketones **122**, **123** and **124** obtained from the radical reactions had to be transformed stereoselectively into the corresponding equatorial alcohols. Since the reduction of carbonyl compounds by complex metal hydride reducing agents is a well-elaborated transformation, a number of reagents have been developed for various substitution pattern.

4-*tert*-Butylcyclohexanone is reduced by small reducing agents like $NaBH_4$ or $LiAlH_4$ with selectivities of 7:3 and 9:1 respectively in favor of the thermodynamically more stable equatorial alcohol [334-337]. In contrast, when hydride reagents with bulky substituents like $K(i\text{-PrO})_3BH$, L-Selectride or $Li(Siamyl)_3BH$ were used, the axial alcohol was obtained. The reduction of 2-methylcyclohexanone should provide a suitable model system to predict the behavior of the *C*-fucosidic ketones **122**, **123** and **124** towards different reducing agents. 2-Methylcyclohexanone shows similar selectivities as 4-*tert*-butylcyclohexanone towards the above-mentioned reducing agents. However, opposite selectivity was obtained with $Li(t\text{-BuO})_3AlH$, which reduces 2-methylcyclohexanone with a selectivity of 73:27 in favor of the trans-alcohol [334]. To avoid undesired reduction of the acyl protecting groups present in our ketones **122**, **123** and **124** we were restricted to the use of chemoselective reducing agents like e.g. $NaBH_4$ or $Li(t\text{-BuO})_3AlH$.

In a first approach, we reduced the unseparable mixture of the two diastereomers **122a/b** containing acetate protecting groups with $NaBH_4$ in methanol. Surprisingly no selectivity was observed and a mixture of the four alcohols **127a-d** in a ratio of 1 : 1.3 : 1 : 1.3 was obtained (see *scheme* 11, *table* 7). Lowering the temperature to –20 °C did not show any effect on the stereochemical outcome. However, reduction of the diastereomeric mixture of **122a/b** with $Li(t\text{-BuO})_3AlH$ led to the expected selectivity in favor of the equatorial alcohol (4:1, *scheme* 11, *table* 7). In a control experiment with L-Selectride the predicted selectivity was confirmed: only the two axial alcohols **127c** and **127d** could be detected in the product mixture (*scheme* 11, *table* 7).



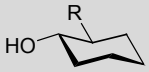
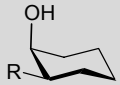
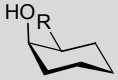
Scheme 11: Reduction of the *C*-fucosidic cyclohexanone derivatives; a) $NaBH_4$, MeOH, 1 h, -20°C (98%); b) Li(*t*-BuO)$_3$AlH, THF, 4 h at -5°C + 3 h at 0°C (quant.); c) L-Selectride, THF, 1.5 h, 0°C (92%); d) Li(*t*-BuO)$_3$AlH, THF, 5 h at 0°C (86%); e) Li(*t*-BuO)$_3$AlH, THF, 3 h at 0°C + 20 h at rt (81%); selectivities are given in *table* 5.

The reduction of the diastereomeric mixture of **122a/b** delivered in all three cases the corresponding alcohols in excellent to quantitative yields (see *scheme* 11). However, the R_f-values of the four alcohols were almost identical (R_f = 0.42 for the two axial alcohols **127c/d** and R_f = 0.38 for the two equatorial alcohols **127a/b**) and the isolation of the pure substances was not possible. However, relative yields and selectivities could be determined by partial chromatographic separation and comparison of the NMR-signals with those of the crude mixtures.

The equatorial and axial alcohols can be easily distinguished by the spin coupling pattern in the ^{1}H-NMR spectrum (*figure* 26). The values of the vicinal coupling constants depend on the

torsion angle between the two corresponding protons and can be calculated by the Karplus-equation [338]. The equatorial proton H_{eq}, which is geminal to the secondary hydroxyl group in the axial alcohol **i** has three small couplings resulting in a narrow multiplet, whereas the axial proton H_{ax} in the equatorial alcohol **ii** shows two large and one small coupling leading to a triplet-like coupling pattern (*figure* 26).

Table 7: Yields and stereoselectivities in the reduction of the *C*-fucosidic ketones **122a/b**, **123a/b** and **124a/b**.

starting material						yield
	R = CH_2-Fuc(**Ac**)$_3$, $NaBH_4$	**127a** 1	**127b** 1.3	**127c** 1	**127d** 1.3	98 %
122a/b	R = CH_2-Fuc(**Ac**)$_3$, Li(*t*-BuO)$_3$AlH	**127a** 4	**127b** 5.2	**127c** 1	**127d** 1.3	100 %
	R = CH_2-Fuc(**Ac**)$_3$, L-Selectride	**127a** 0	**127b** 0	**127c** 1	**127d** 1.3	92 %
123a/b	R = CH_2-Fuc(**Bz**)$_3$, Li(*t*-BuO)$_3$AlH	**128a** 3	**128b** 5.7	**128c** 1	**128d** 1.9	86 %
124a/b	R = CH_2-Fuc(**Piv**)$_3$,[a] Li(*t*-BuO)$_3$AlH	**129a** 2	**129b** 2	**129c** 1	**129d** 1	81 %

[a] diastereomeric mixture of ketones used in the reduction was in a ratio of 1 : 1

With Li(*t*-BuO)$_3$AlH as reducing agent showing the desired stereoselectivity in favor of the equatorial alcohol, the reduction of the benzoyl- and pivaloyl-protected ketones **123a/b** and **124a/b** was performed under the same conditions as previously described for ketone **122a/b**. As for **122a/b**, the diastereomeric mixtures had to be used due to separation problems. This leads to complex product mixtures which are difficult to analyze and separate.

Selectivities were lower as in the reduction of the acetate-protected ketones (see *table* 7). From the reduction of the benzoyl-protected ketones **123a/b**, the four corresponding alcohols **128a-d** were obtained in 86% yield in a 3 : 5.7 : 1 : 1.9 ratio, indicating a selectivity of 3 : 1 in favor of the equatorial alcohols **128a/b** (*scheme* 11, *table* 7). In case of the pivaloyl-protected

ketones **124a/b**, the observed selectivity was only 2 : 1. The four alcohols **129a-d** were isolated in a total yield of 81% (*scheme* 11, *table* 7).

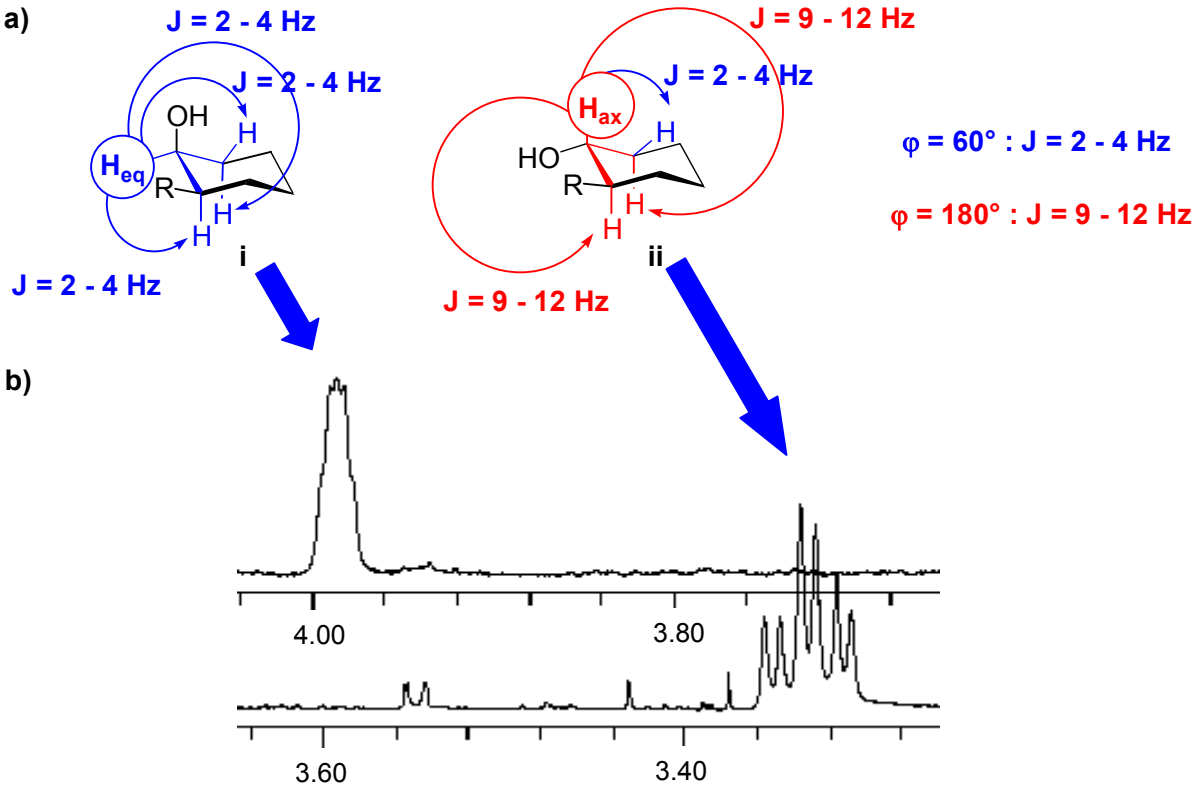


Figure 26: a) Predicted vicinal coupling constants for the axial and equatorial alcohols depending on torsion angles φ; b) observed coupling pattern of protons H_{eq} and H_{ax} in alcohols **i** and **ii**, respectively.

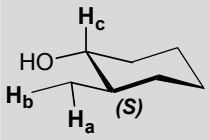
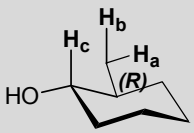
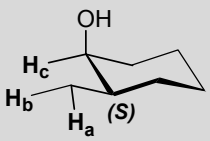
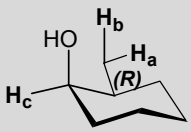
As observed in the radical addition, the selectivity of the reductions is influenced by steric parameters. A very bulky protecting group (Ac vs. Piv) lowers the predicted selectivity.

As previously described for the *C*-fucosidic ketones, it was not possible to determine the absolute configuration at the tertiary carbon center by NMR-analysis. The correct assignment of the absolute configuration as shown in *scheme* 8 and *scheme* 11 was obtained by X-ray (*chapter* 3.3).

The difficult separation of the diastereomeric alcohols could most efficiently be realized for the benzoate protected alcohols **128a-d**, which were therefore used for continuation of the synthesis.

The NMR-data of the twelve synthesized *C*-fucosidic alcohols show some interesting regularities, which are illustrated in *table* 8.

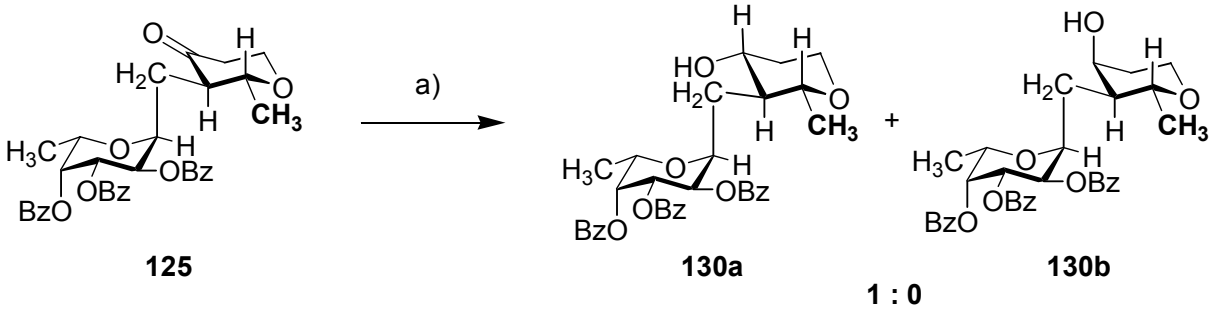
Table 8: Comparison of NMR-shifts of some selected protons of the *C*-fucosidic alcohols

	# (H)				
		127a	**127b**	**127c**	**127d**
R = Fuc(**Ac**)$_3$	H_a	1.14	**1.74**	1.39	**1.63**
	H_b	**2.16**		1.85	
	H_c	3.20	3.29	**3.88**	**3.94**
		128a	**128b**	**128c**	**128d**
R = Fuc(**Bz**)$_3$	H_a	1.25	**1.86**	1.49	**1.80**
	H_b	**2.44**		2.02	
	H_c	3.17	3.26	**3.88**	**3.92**
		129a	**129b**	**129c**	**129d**
R = Fuc(**Piv**)$_3$	H_a	1.16	**1.21**	1.37	**1.65**
	H_b	**2.28**		1.91	
	H_c	3.29	3.29	**3.87**	**3.93**

The methylene protons of the *C*-glycosidic linkage (H_a and H_b) show an identical chemical shift in the alcohols with the undesired *R*-configuration at the tertiary ring-carbon (**127b/128b/129b**, **127d/128d/129d**), whereas significantly different shifts for each methylene proton can be observed in the case of the alcohols with the desired *S*-configuration (**127a/128a/129a**, **127c/128c/129c**). Another regularity is the large shift difference of about 0.8 to 1.2 ppm between the two methylene protons in the diastereomers **127a/128a/129a** implicating a special magnetic influence of the surrounding due to conformational characteristics. Possibly one proton is unshielded by the oxygen of the hydroxyl group. As a third regularity, the proton H_c (being geminal to the secondary hydroxyl group) shows a significant downfield shift of about 0.6 ppm in the axial alcohols **127c/128c/129c** and **127d/128d/129d** compared to the equatorial alcohols **127a/128a/129a** and **127b/128b/129b**.

3.2.6. Stereoselective reduction of the *C*-fucosidic ketone 125

The results obtained by using Li(*t*-BuO)$_3$AlH as reducing agent encouraged us to apply these conditions for the reduction of the *C*-fucosidic tetrahydropyranone intermediate **125** as well. This time the reduction proceeded stereospecifically. Only the axial attack of the hydride, which is leading to the equatorial alcohol **130a** (93% yield), could be observed (*scheme* 12). The methyl group next to the *C*-fucosidic side chain enhances the conformational stability of the cyclohexyl ring. Furthermore, the methyl group restricts the rotational flexibility of the fucosyl residue leading to a more efficient shielding of one face of the cyclohexanone ring. As in case of the derivatives **127**-**129**, the orientation of the hydroxyl group can be determined by the vicinal coupling constants in the ^{1}H-NMR spectrum: the coupling constants of the proton geminal to the hydroxyl group being 4.27, 9.75 and 10.64 Hz proof the equatorial orientation of the hydroxyl group.

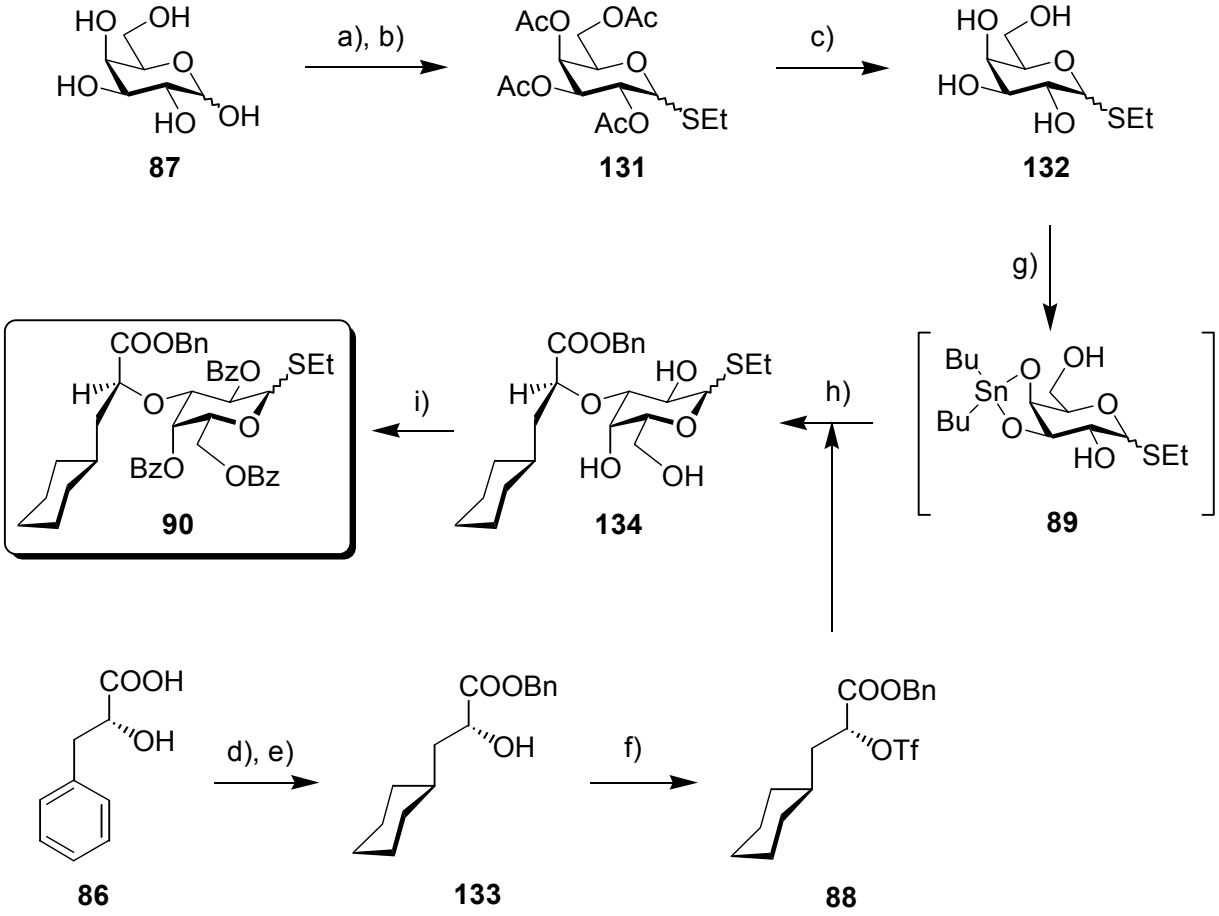


Scheme 12: Stereoselective reduction of the tetrahydropyranone intermediate **125**. Equatorial alcohol **130a** was formed exclusively. a) Li(*t*-BuO)$_3$AlH, THF, 20 h, 0°C to rt (93%).

The downfield-shift for one of the two methylene protons – as observed in the cyclohexanol-substituted *C*-fucosides – could not be confirmed in this case (δ = 1.61 and 1.96 ppm) indicating the influence of the methyl group on the conformational preference of alcohol **130a**.

3.2.7. Glycosylation of alcohols 128a, 128b and 130a with the galactose building block 90

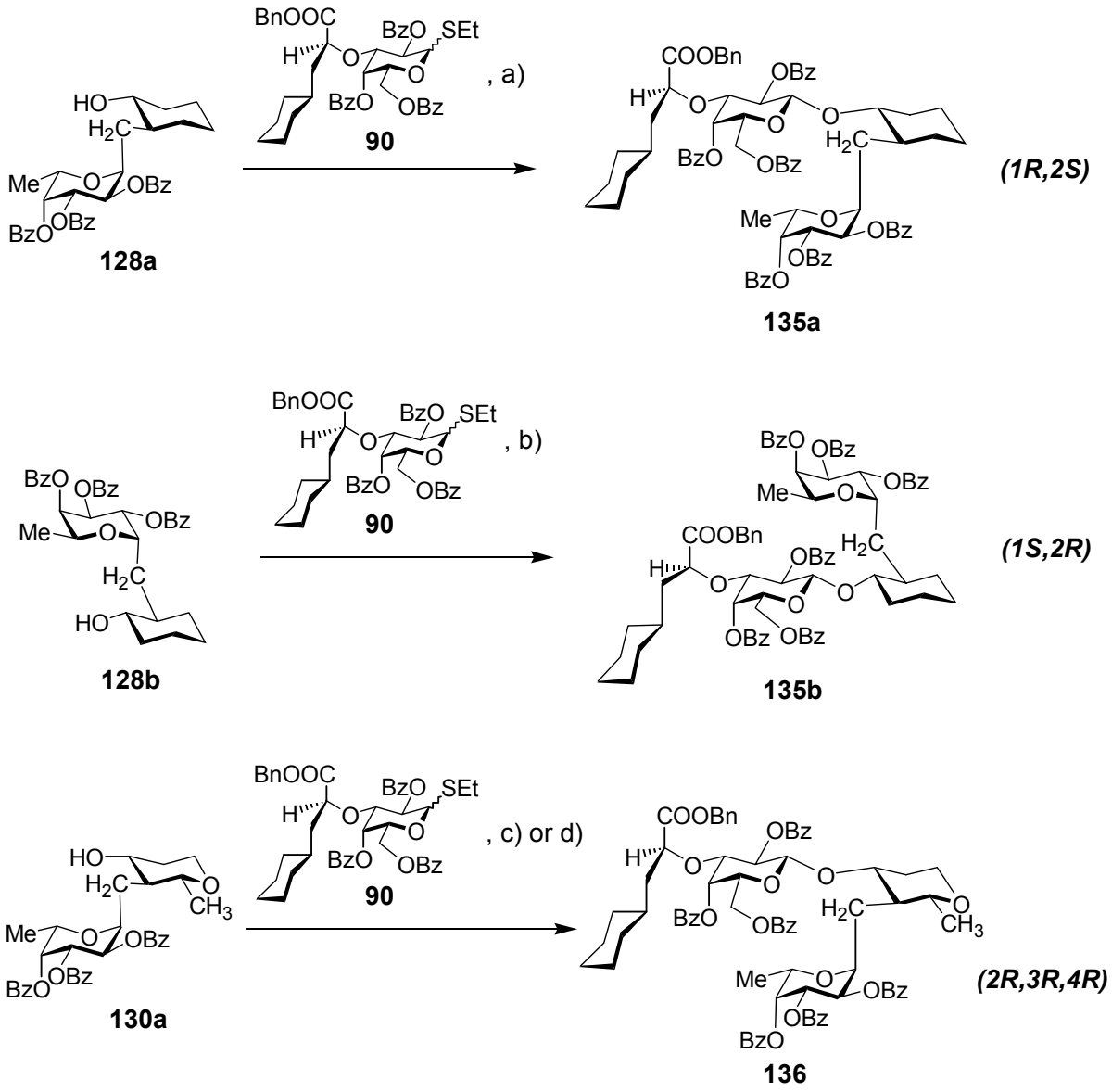
The next step in the synthesis of the sLe^x-mimetics **81a** and **82** incorporated the glycosylation of the *C*-fucosidic alcohols **128a**, **128b** and **130a** with the cyclohexyllactic acid-substituted galactosyl building block **90**.



Scheme 13: Synthesis of the galactose building block **90** containing a cyclohexyllactic acid residue: a) Ac_2O, pyr, rt, 12 h (90%); b) EtSH, $BF_3{\cdot}OEt_2$ (64%); c) NaOMe/MeOH, rt, 1h (98%); d) 5 bar H_2, 10% Pd/C, MeOH (98%); e) 1) Cs_2CO_3, MeOH, H_2O; 2) BnBr, DMF (92%); f) Tf_2O, pyr, CH_2Cl_2 (86%); g) Bu_2SnO, MeOH, reflux, 2 h; h) CsF, **88**, DME, rt, 2 h (67% over 2 steps); i) BzCl, pyr, DMAP, rt, 4 h (91%).

Derivatization of galactose (**87**) at position 3 to obtain the functionalized galactosyl building block **90** was done by a co-worker in our group [339] and is illustrated in *scheme* 13. **87** is transformed in three steps into ethyl thiogalactoside **132**. The alkylating agent benzyl-(*R)*-2-cyclohexyl-1-trifluoromethanesulfonyloxypropionate (**88**) was obtained from *R*-2-phenyllactic acid (**86**) [340,341]. The triflate serves as a leaving group rather than a protecting group for the following nucleophilic substitution with the unprotected thiogalactoside **132**.

Regioselectivity is achieved by increasing the nucleophilicity of the hydroxyl group at position three by formation of the tin-acetal intermediate **89** [287,289]. **134** could be obtained in 67% over 2 steps. Benzoylation of **134** delivers galactosyl donor **90** in 91% yield, which was used to glycosylate the *C*-fucosidic alcohols **128a**, **128b** and **130a** (see *scheme* 14). Both diastereomeric alcohols **128a** and **128b** were glycosylated due to the previously mentioned assignment problem (*chapter* 3.3).



Scheme 14: Glycosylation of the equatorial *C*-fucosidic alcohols with the thiogalactoside building block **90**. Absolute configuration of the chiral centers at the spacer rings are given. a) NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 4 h (82%); b) NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 4 h (90%); c) NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 6 h (69%); d) DMTST, CH_2Cl_2, -5°C, 24 h (80%).

A huge pool of glycosylation methodologies [342] has been developed over the last decades to find a method suitable for almost any problem in the synthesis of oligosaccharides and glycoconjugates [343]. However, still research is going on to find even milder, more selective and more generally useful glycosylation methods.

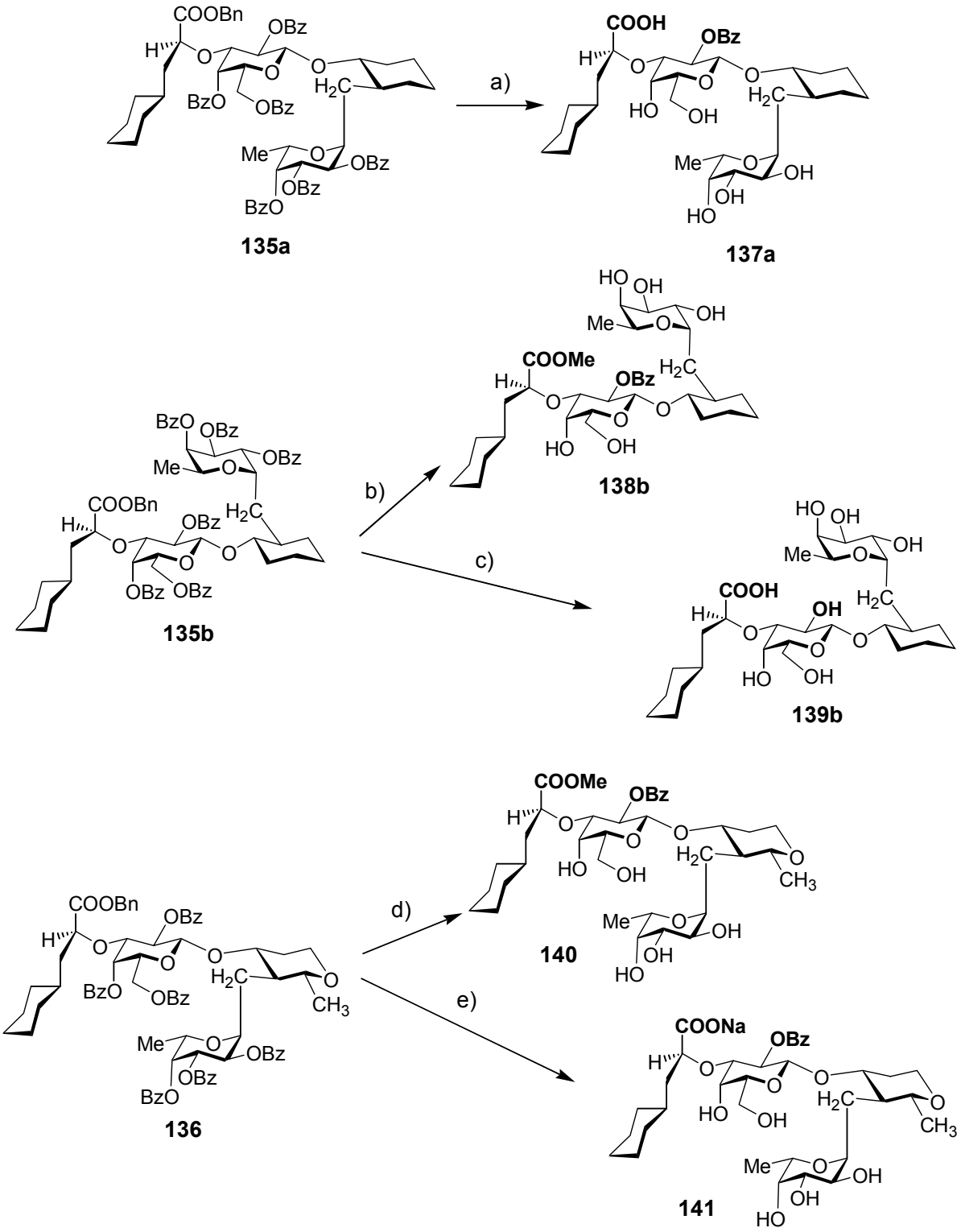
Glycosylations using thioglycosides [290,344] as glycosyl donors turned out to be a broadly applicable methodology. Thioglycosides can be used under mild reaction conditions and are more stable than glycosyl halides used in the Koenigs-Knorr-glycosylation [345-347] or trichloroacetimidates [348].

For the synthesis of all three tetrasaccharide mimetics **135a**, **135b** and **136** shown in *scheme* 14, *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH) was used as promoter. The mimetics **135a** and **135b** containing a cyclohexyl spacer was obtained in 90% and 82% yield respectively. Mimic **136** bearing the tetrahydropyran spacer was obtained in 69% yield using this method. Using dimethyl(methylthio)sulfonium triflate (DMTST) [349,350] as promoter the yield could be increased to 80% for mimic **136**. All three reactions showed excellent β-selectivity induced by neighboring group participation of the benzoyl protecting group at C-2 of the galactose moiety.

3.2.8. Deprotection of the tetrasaccharide-mimetics 135a, 135b and 136

The last steps in the synthesis of target molecules **81a**, **81b** and **82** incorporate the deprotection of the hydroxyl groups and saponification of the carboxylic ester of the complete tetrasaccharide mimics **135a**, **135b** and **136**. All hydroxyl groups of the mimics were protected by benzoyl esters making deprotection possible in a single reaction step under basic reaction conditions. The benzyl ester was expected to be cleaved under these conditions as well.

Treatment of derivatives **135a**, **135b** and **136** with a solution of sodium methoxide in methanol should deliver the unprotected target molecules **81a**, **81b** and **82**. However, in contrast to all other benzoyl groups, the benzoylate at C-2 of the galactose was inert under the conditions applied. Only the partially deprotected derivatives **137a**, **138b** and **140** could be isolated in high yields (*scheme* 15). The benzyl esters at the lactic acid moiety were trans-esterified to the methyl esters due to the large stochiometric excess of sodium methoxide used.

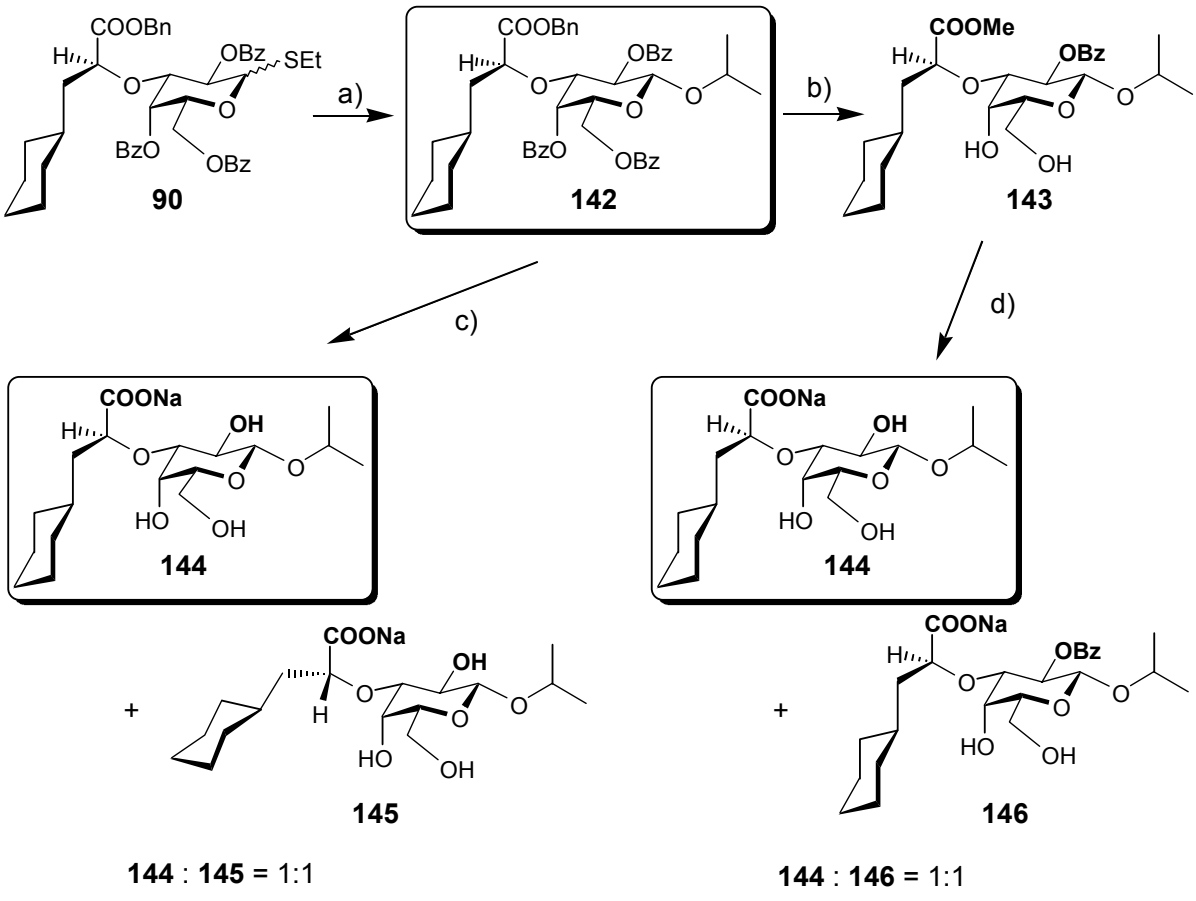


Scheme 15: Deprotection of the tetrasaccharide mimetics **135a**, **135b** and **136**. **135a** could not be completely deprotected under standard conditions. a) NaOMe/MeOH, rt, 1 h and then 40°C, 2 h (89%); b) NaOMe/MeOH, rt, 2 h (88%); c) NaOMe, MeOH, 55°C, 42 h (94%); d) NaOMe/MeOH, rt, 11 h (87%); e) 1) LiOH, dioxane/water (1:1), rt, 3 h; 2) HCl to pH 4; 3) Dowex 50 basic sodium ion exchange (60%).

By treatment of the 2-*O*-benzoyl-protected intermediates **137a**, **138b** and **140** with LiOH or NaOH in dioxane/water at room temperature the methyl ester was cleaved, but the benzoate at C-2 of galactose was not affected. Even extended reaction times in combination with elevated temperatures up to 55°C did not solve the problem. One exception was mimic **135b**, which could be deprotected to the target molecule **139b** after reaction at 55°C for 42 h (see *scheme* 15).

Model compound for the investigation of deprotection conditions

In order to determine whether the cyclic spacer, the fucose moiety or the cyclohexyllactic acid residue is responsible for the unusual stability of the benzoate at the 2-position, the isopropyl derivative **142** was synthesized in 98% yield (*scheme* 16) by reaction of thiogalactoside **90** with isopropanol and DMTST as promoter.



Scheme 16: Synthesis of the model compound **142** and results of the debenzoylation experiments. The concentration of the starting material in b) was 20 times higher than in d). a) ^{i}PrOH, DMTST, CH_2Cl_2, 3Å-MS, -5°C, 24 h (98%); b) NaOMe (0.02 mol/l, 0.5 equiv.), MeOH, rt, 20 h (85%); c) 1) NaOMe (0.03 mol/l, 3.0 equiv.), MeOH, microwave-radiation 40W, 70°C, 2 h and then without mw, rt, 20 h; 2) Dowex basic sodium ion exchange (94%); d) 1) NaOMe (0.04 mol/l, 20 equiv.), MeOH/toluene (1:1), rt, 26 h; 2) Dowex basic sodium ion exchange (99%).

Treatment of the isopropyl galactoside **142** with sodium methoxide led to the same results as observed in case of the tetrasaccharide mimetics: the 4- and 6-hydroxyl groups of the galactose were deprotected, whereas the benzoate at position 2 was not cleaved. The benzyl ester at the lactic acid residue was converted to the methyl ester. The 2-*O*-benzoylated methyl ester **143** could be isolated in 85% yield. These results clearly indicate, that the cyclohexyllactic acid residue is responsible for the unusual stability of the benzoyl ester, probably due to steric effects.

The derivatives **135a**, **135b**, **136** and **142** contain two hydrophobic substituents, the cyclohexyl ring of the lactic acid residue and the benzoyl group at C-2 of the galactose. In addition, they consist of a hydrophilic part contributed by the hydroxyl groups of fucose and galactose. These properties probably force the molecules, especially in polar solvents like methanol or water, to form aggregates which allow to burry the hydrophobic part in the inside and to orient the hydrophilic part towards the polar surrounding. As a consequence, it is no longer possible for the nucleophilic methoxide to reach the benzoyl ester group hidden inside the aggregate. This situation is comparable to the organization in micelles, where the lipophilic parts are hidden inside the aggregate and the hydrophilic parts are pointed to the water.

Two different strategies were investigated to cleave the stable benzoyl group and to check the proposed hypothesis. In the first approach the debenzoylation was investigated under microwave conditions. It has been shown for numerous reactions, that they proceed much faster when carried out under microwave conditions rather than under conventional reaction conditions [351-362]. We assumed, that microwave irradiation could probably break up the proposed aggregates. The second approach aimed at breaking up the aggregates by solvent interaction. Changing the polarity of the solvent by adding a lipophilic component should lead to a stronger interaction of the cyclohexyl- and phenyl-residues with the lipophilic component of the solvent mixture, thus weakening or even avoiding aggregation. Performing the reaction with lower educt-concentration but the same methoxide concentration should further decrease the tendency to form aggregates.

Stirring the model compound **142** in a solution of NaOMe/MeOH under microwave irradiation led to a 1:1 mixture of the totally unprotected isopropyl galactosides **144** and **145** (*scheme* 16). Based on the differences for the chemical shift for the α-proton of the lactic acid and the H-4 and H-5 of galactose (*figure* 27) we assumed that isomerization had taken place.

Treatment of **142** in a 1:1 mixture of methanol and toluene with a 20-fold dilution of the starting material in comparison to the former debenzoylation experiments led to 50% cleavage of the benzoyl group. 50% of the starting material could be recovered in form of the 2-*O*-benzoylated but saponificated lactic acid derivative **146** (*scheme* 16). Previous tests

showed, that sodium methoxide is soluble in methanol/toluene mixtures up to an amount of 50% toluene. Higher toluene ratios lead to a precipitation of the methoxide. These results support the proposed aggregation, that can be suppressed or at least weakened by using more lipophilic solvent mixtures.

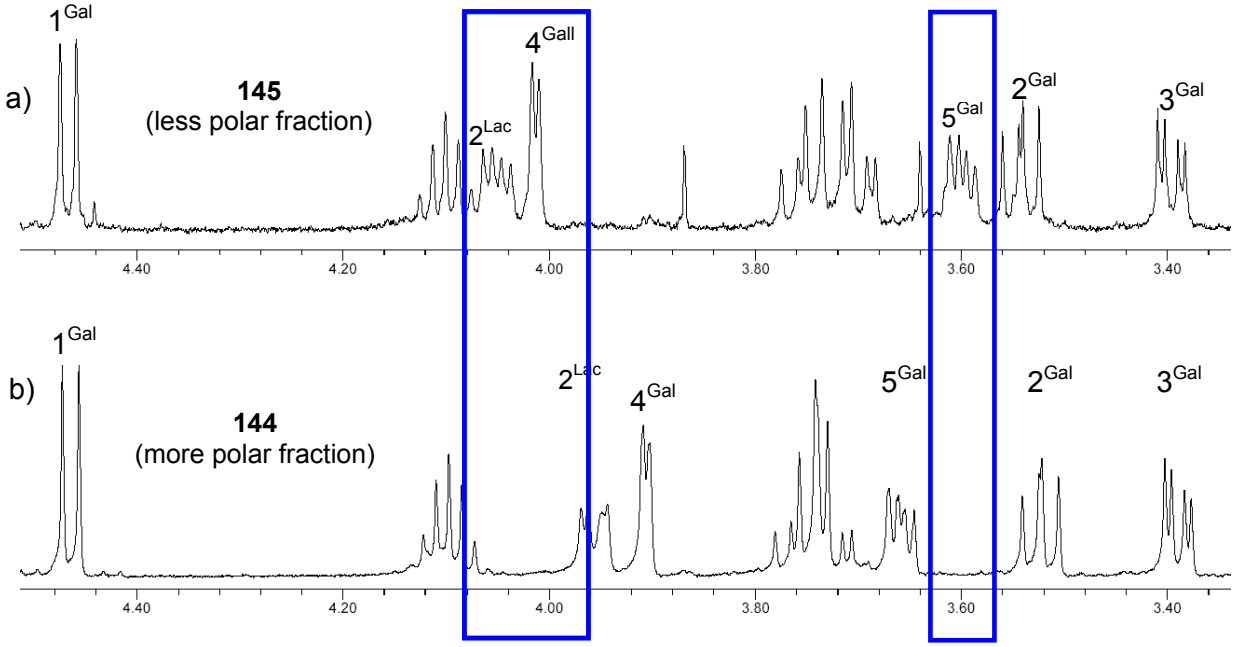
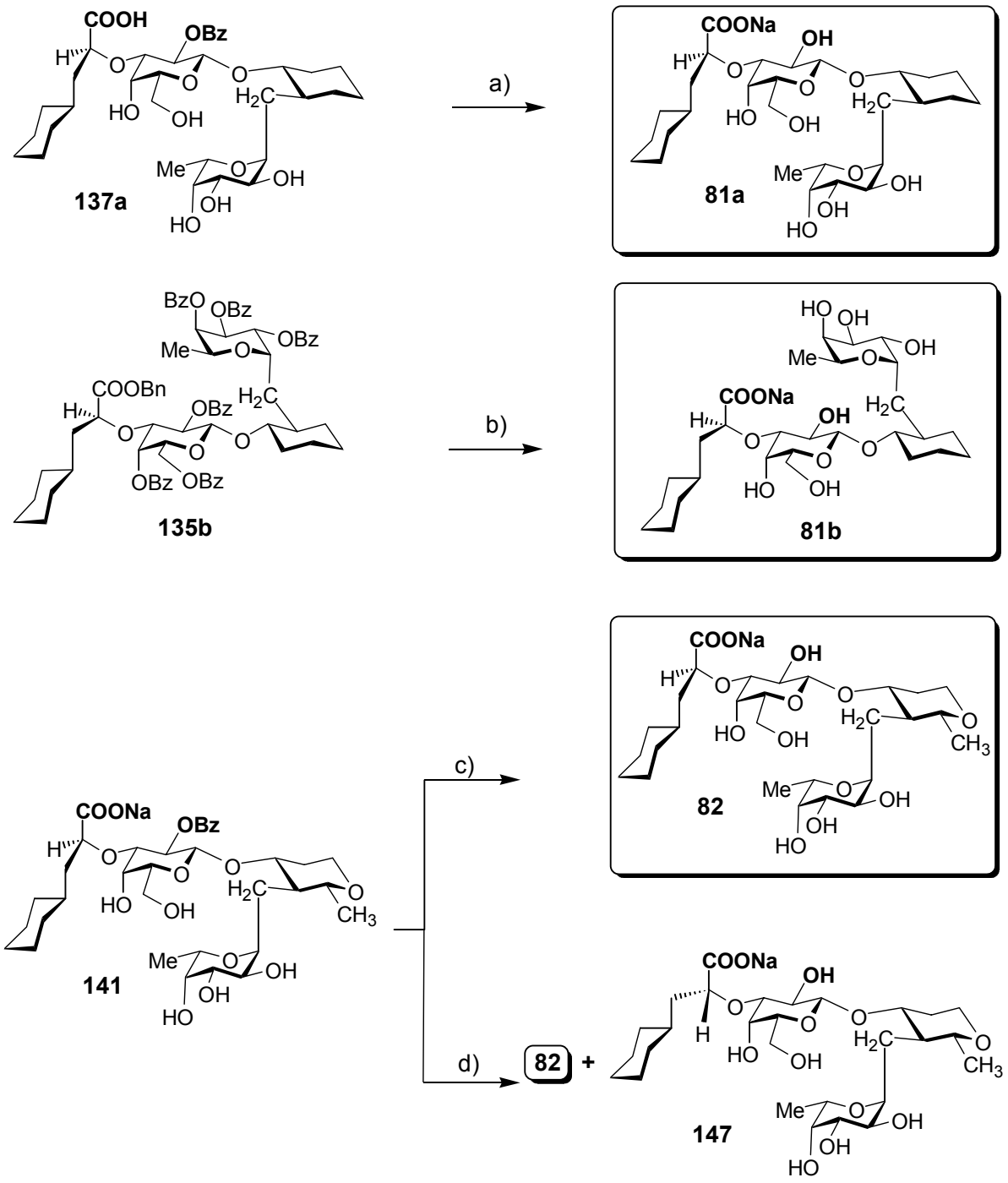


Figure 27: NMR-spectra of the two fractions of model compound **144/145** obtained from the debenzoylation under microwave conditions. a) less polar fraction (TLC: CH_2Cl_2/MeOH 2:1); b) more polar fraction (TLC: CH_2Cl_2/MeOH 2:1). Both spectra are calibrated to D_2O (4.79 ppm).

Application of the optimized deprotection protocol

The two above described methods were applied to the deprotected sLe^x mimetics **135b**, **137a** and **140**/**141**. Derivative **137a** could be successfully deprotected to yield 55% of the mimetic **81a** using microwave technology (*scheme* 17). The isomerized side product in analogy to **144**/**145** was not formed. Unfortunately cleavage of the benzoyl group using a less polar solvent mixture could not be investigated due to a lack of starting material.

When tetrahydropyran mimic **141** was treated with a solution of NaOMe/MeOH under microwave conditions, a 1:1 mixture of **82** and **147** was obtained in 89%. The two compounds showed very similar NMR-spectra (see *figure* 28) with the complete set of signals expected, as previously described for the model **141**. Obviously, in this case isomerization has taken place as well.



Scheme 17: Complete deprotection of the partially deprotected sLe^x-mimetics. a) NaOMe/MeOH, microwave radiation, 40 W, 70°C, 2 h and then 2 drops water, rt, 1 h (55%); b) 1) NaOMe/MeOH, 50°C, 40 h; 2) LiOH, dioxane/water (1:1), rt, 4 h; 3) Dowex 50 (70%); c) 1) NaOMe, MeOH/toluene (1:1), rt, 26 h; 2) Dowex 50 (80%); d) 1) NaOMe/MeOH, microwave radiation, 40 W, 70°C, 4 h and then without mw, rt, 15 h; 2) LiOH, dioxane/water (1:1), r.t., 4 h; 3) Dowex 50 (89%).

Treatment of the partially debenzoylated compound **141** with NaOMe in a 1:1 mixture of toluene and methanol led to a single product in 80% yield. The NMR signals were identical to those found for one of the two compounds obtained from the microwave cleavage, namely

the one with the lower R_f-value (**82**). As in the case of model compounds **144/145**, the signals of the protons H-5^{Gal}, H-4^{Gal} and the α-proton of the lactic acid show a shift difference of about 0.1 ppm, whereas the other signals possess almost identical shifts indicating an isomerization at the α-proton of the lactic acid (see *figure* 28).

Comparison of the NMR-spectra of the two fractions of the model compound **144** and **145** (*figure* 27) with the NMR-spectra of the two fractions **82** and **147** of the sLe^x-mimic (*figure* 28) shows for the more polar fraction on TLC a highfield shift of the signals H-2^{Lac} and H-4^{Gal}, whereas the signal H-5^{Gal} is shifted lowfield.

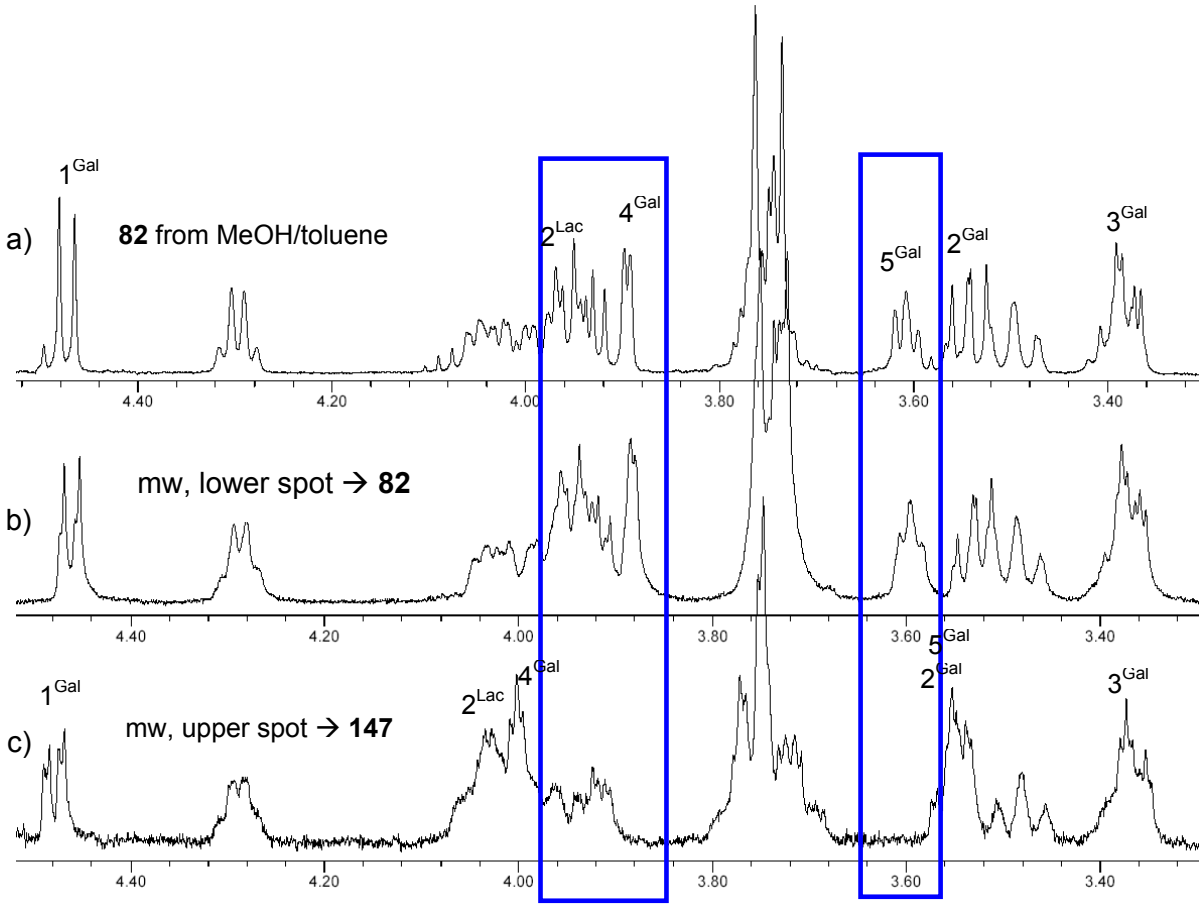


Figure 28: NMR-spectra of the two fractions of compound **82** and **147** obtained from the debenzoylation under microwave conditions in comparison to the spectrum of **82** obtained from the debenzoylation in toluene/methanol. a) product **82** from cleavage in toluene/methanol; b) microwave reaction: lower spot in reference to TLC; c) microwave reaction: upper spot in reference to TLC. All spectra are calibrated to D_2O (4.79 ppm).

3.3. Assignment of the absolute configuration of 81a and 81b

In the radical coupling reaction, which was used for the synthesis of the core of the sLe^x-mimic **81a**, a mixture of diastereomers was obtained. At no step during the synthesis it was possible to assign the absolute configuration based on NMR data. To solve this problem, X-ray (see *chapter* 3.3.3) and circular dichroism spectroscopy (see *chapter* 3.3.1 and 3.3.2) was applied. CD-spectroscopic investigation aimed at an indirect conformational assignment by comparison of the CD-data of the two *O*-glycosidic compounds **33** and **148** with the CD-data obtained for the *C*-glycosidic compounds **81a** and **81b** (see *figure* 29).

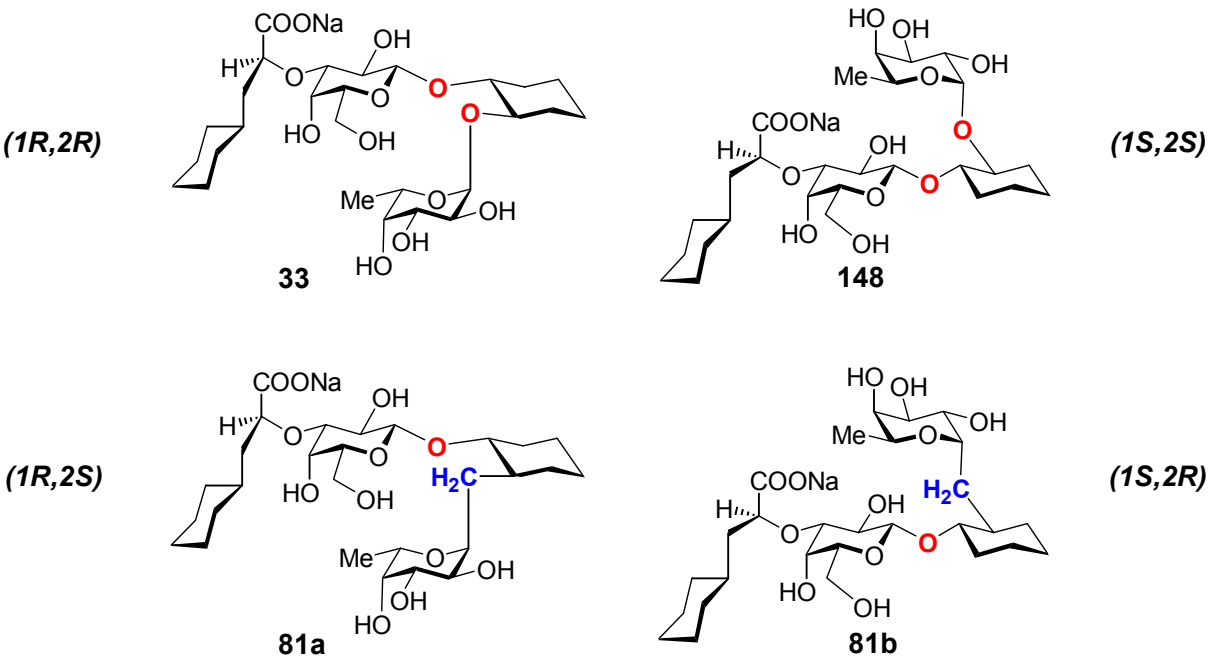
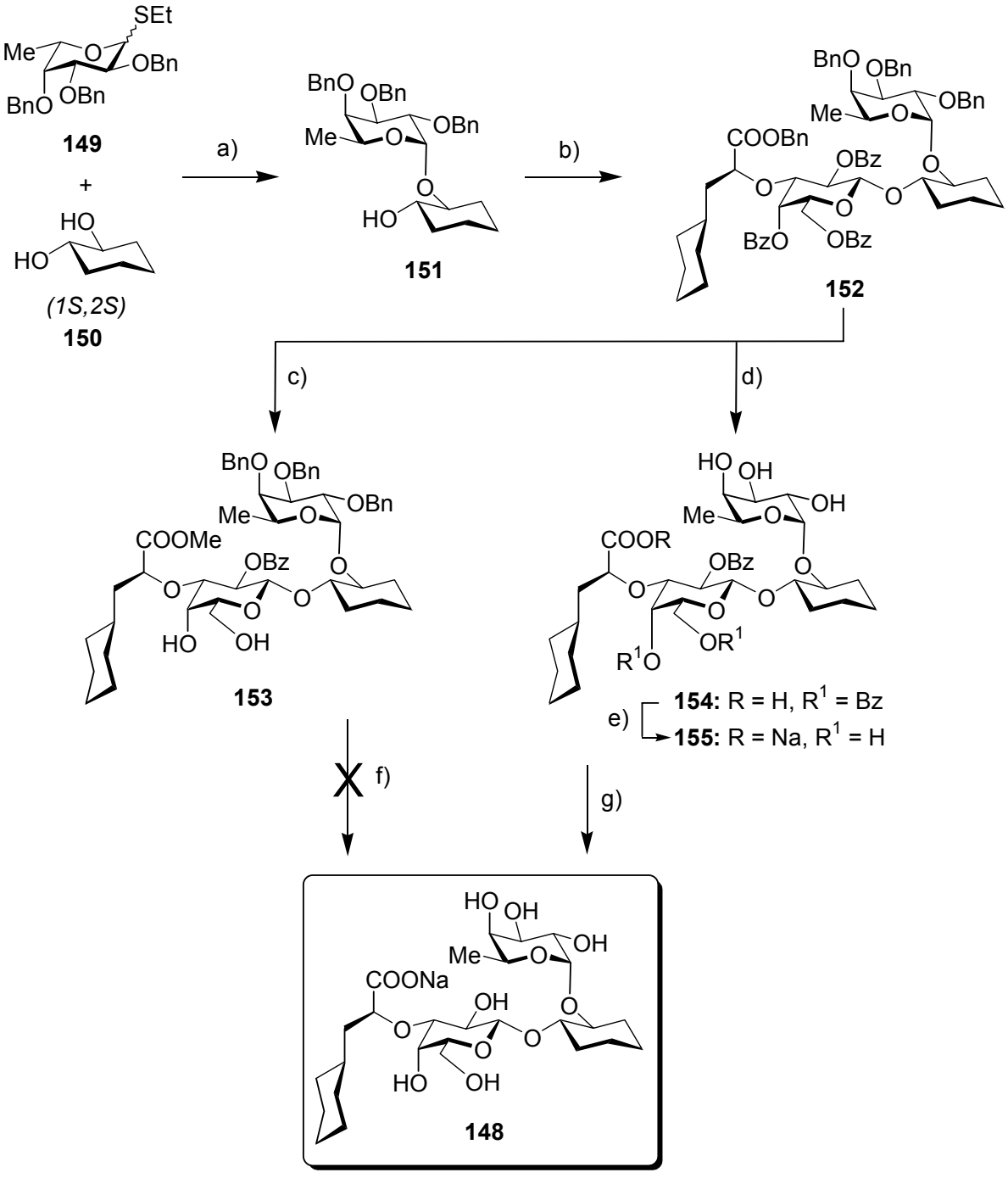


Figure 29: Correlation of the configuration of the two *C*-fucosidic derivatives **81a** and **81b** as well as the two *O*-fucosidic sLe^x derivatives **33** and **148**. Synthesis of compound **148** allowed us to compare structural information collected by NMR- and CD-spectroscopy.

3.3.1. Synthesis of the *(1S,2S)*-cyclohexanediol derivative 148

The fucosylation of *(1S,2S)*-cyclohexanediol (**150**) was performed by the *in-situ*-anomerization procedure [363,364]. In this reaction, the ethylthio fucoside **149** is transformed into the corresponding α-fucosylbromide by treatment with bromine at 0°C. In the presence of Et_4NBr, isomerization to the more reactive β-bromide occurs, which reacts with *(1S,2S)*-cyclohexanediol (**150**) in 74% yield. Galactosylation of **151** with ethylthio galactoside **90** was

performed using DMTST as promoter yielding **152** (92%). Thiogalactosylation with NIS/TfOH as promoter, as applied successfully in case of the *C*-fucosidic mimetics, failed due to cleavage of the *O*-fucosidic linkage under the acidic reaction conditions.



Scheme 18: Synthetic pathway leading to the *(1S,2S)*-cyclohexanediol derivative **148**. a) Br_2, NEt_4Br, CH_2Cl_2, 4Å MS, rt, 17 h (74%); b) **90**, DMTST, CH_2Cl_2, -2°C, 18 h (92%); c) NaOMe/MeOH, rt, 15 h (98%); d) 10% Pd/C, H_2, dioxane, rt, 24 h (94%); e) NaOMe/MeOH, rt, 20 h (92%); f) 1) NaOMe, toluene/MeOH, rt, 24 h; 2) 10% Pd/C, H_2, dioxane, rt; g) 1) NaOMe/MeOH, microwave radiation, 40 W, 70°C, 2 h; 2) Dowex 50 Na-form (71%).

The final deprotection steps (**152** → **148**, *scheme* 18) incorporated the basic cleavage of the benzoyl- and benzyl esters at the galactose and lactic acid units as well as hydrogenolysis of the benzyl ethers at the fucose. During the cleavage of the benzoyl esters at the galactose, the same problems arose as in case of the *C*-fucosidic mimetics **135** and **136**. The benzoyl group at C-2 of the galactose could not be cleaved using standard cleaving conditions (NaOMe/MeOH), neither at room temperature nor at elevated temperatures. Furthermore, it didn't matter whether the benzyl ethers at the fucose were present during the debenzoylation or whether they had been removed hydrogenolytical before the benzoyl cleavage (see *scheme* 18). In both cases, only the benzoyl groups at C-4 and C-6 of the galactose could be removed.

152 was converted into the debenzylated acid **154** in 94% yield using standard hydrogenation conditions (H_2, Pd/C, MeOH). After its partial debenzoylation (→ **155**) microwave conditions were successfully applied (→ **148**, 71%). In a second approach, **152** could not be debenzoylated completely in a mixture of toluene and methanol at low starting material concentration, as performed with model compound **143**. This indicates, that the lipophilic benzyl groups at the fucose even intensify the proposed tendency of lipophilic interaction in hydrophilic media.

3.3.2. Circular Dichroism Spectroscopy of the four sLe^x derivatives 33, 148, 81a and 81b

CD-spectroscopy became an important methodology in protein research [365-367] for the investigation of secondary structures of proteins in solution. In addition, it allows to determine the ratio of different secondary structural elements present in a protein. CD-spectroscopy is based on the principles of UV-spectroscopy, but uses circularly polarized instead of unpolarized light. The measured circular dichroism (ellipticity) is defined as the difference between the absorption of right circularly polarized and left circularly polarized light by an optically active molecule [368].

Differences in ellipticity of secondary structural elements of a protein emerge from slightly different torsion angles around the amide bonds in the polyamide backbone. This leads to different absorption behavior of the $n \rightarrow \pi^*$ transition of the amide bonds. These differences allow to distinguish e.g. β-sheets from α-helices by CD-spectroscopy (*figure* 30).

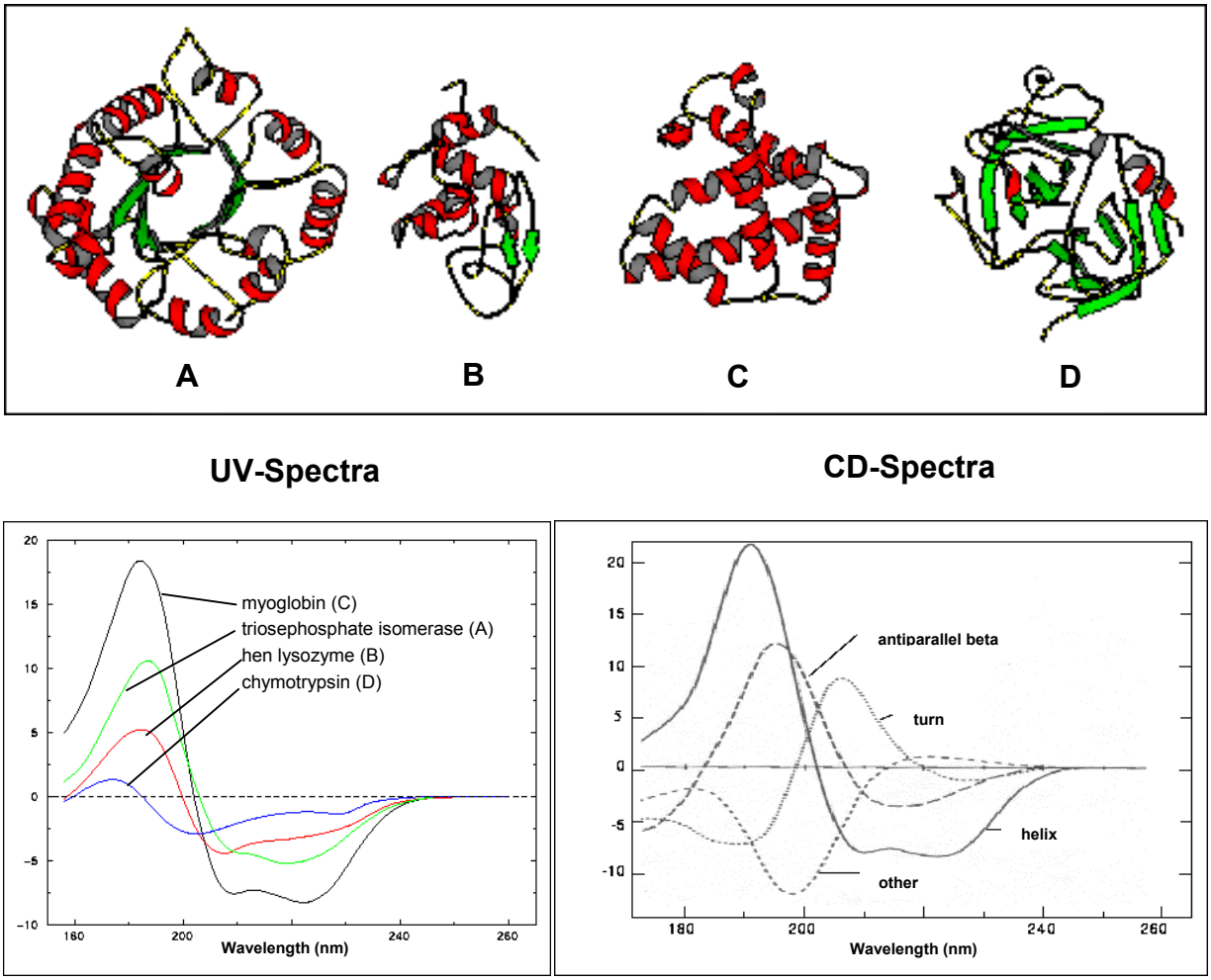


Figure 30: Example of proteins with different portions of secondary structural elements and the corresponding CD-spectra (lower right). In contrast to the CD-spectra, the UV-spectra (lower left) of the four proteins are very similar.

The CD of carbohydrates [369-371] is a challenging area of research. Data analysis is more complex for carbohydrates than for peptides and proteins, since they contain a large number of different chromophores that differ in distance and connectivity. They can be linear or branched and the monomers can occur in both isomeric forms, the common *D*-form and the less common *L*-form. Some chromophores like amides, acyl groups or carboxylic acids absorb in the detectable region observed for proteins and give rise to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Chromophores of unsubstituted carbohydrates like the ring oxygen, the glycosidic linkage and the hydroxyl groups make data acquisition even more difficult, since these chromophores absorb outside the range of commercially available instruments. They give rise to higher energy transitions like $n \rightarrow \sigma^*$ or $\sigma \rightarrow \sigma^*$ and therefore have an effect on the CD-pattern [372,373]. The transitions of the acetal oxygen for instance are centered at 175nm and 150nm. The latter transition can only be investigated using specialized techniques such as vacuum CD [374].

The fact that we were confronted with molecules of different chirality with a slightly helical conformation encouraged us to measure CD-spectra of the four mimetics **33**, **148**, **81a** and **81b** shown in *figure* 29. They all contain a carboxyl group of lactic acid and should therefore give rise to a $n \rightarrow \pi^*$ transition in the lower UV range.

Kenne *et al.* [375] compared the CD-spectra of 1-carboxyethyl substituted monosaccharides at different pH-values with the CD-spectra of *(R)*- and *(S)*-lactic acid. They reported, that the absolute configuration of the 1-carboxyethyl substituent can be assigned by comparison of the CD-spectra. *(S)*-1-carboxyethyl substituted glycosides showed a positive CD-band around 210 nm, whereas *(R)*-1-carboxyethyl substituted glycosides had a negative CD-band around 210 nm.

We collected the CD-spectra of the two derivatives **33** and **81b** at three different pH-values, but the pH-dependence of the intensities was much smaller than those reported by Kenne *et al.* [375]. In both cases, the intensity is about twice as strong at pH 2 compared to pH 4 and pH 7. The spectra at pH 4 and pH 7 are almost identical (λ_{max} = 205 nm). At pH 2, λ_{max} is shifted to 213 nm (*figure* 31). The CD-spectra of all four derivatives of interest (**33**, **148**, **81a** and **81b**) are shown in *figure* 32. The shift of λ_{max} upon switching from pH 2 to pH 7 can be observed for any of the four compounds. Except the differences in intensities, the CD-spectra of the four compounds are identical. The positive CD-bands are in accordance with the data published from Kenne *et al.* [375] and confirm the *(S)*-configuration at the chiral center of the cyclohexyllactic acid. As far as the configuration at the ring-carbon next to the *C*-glycosidic linkage is concerned, no clear correlation between the four investigated derivatives could be observed.

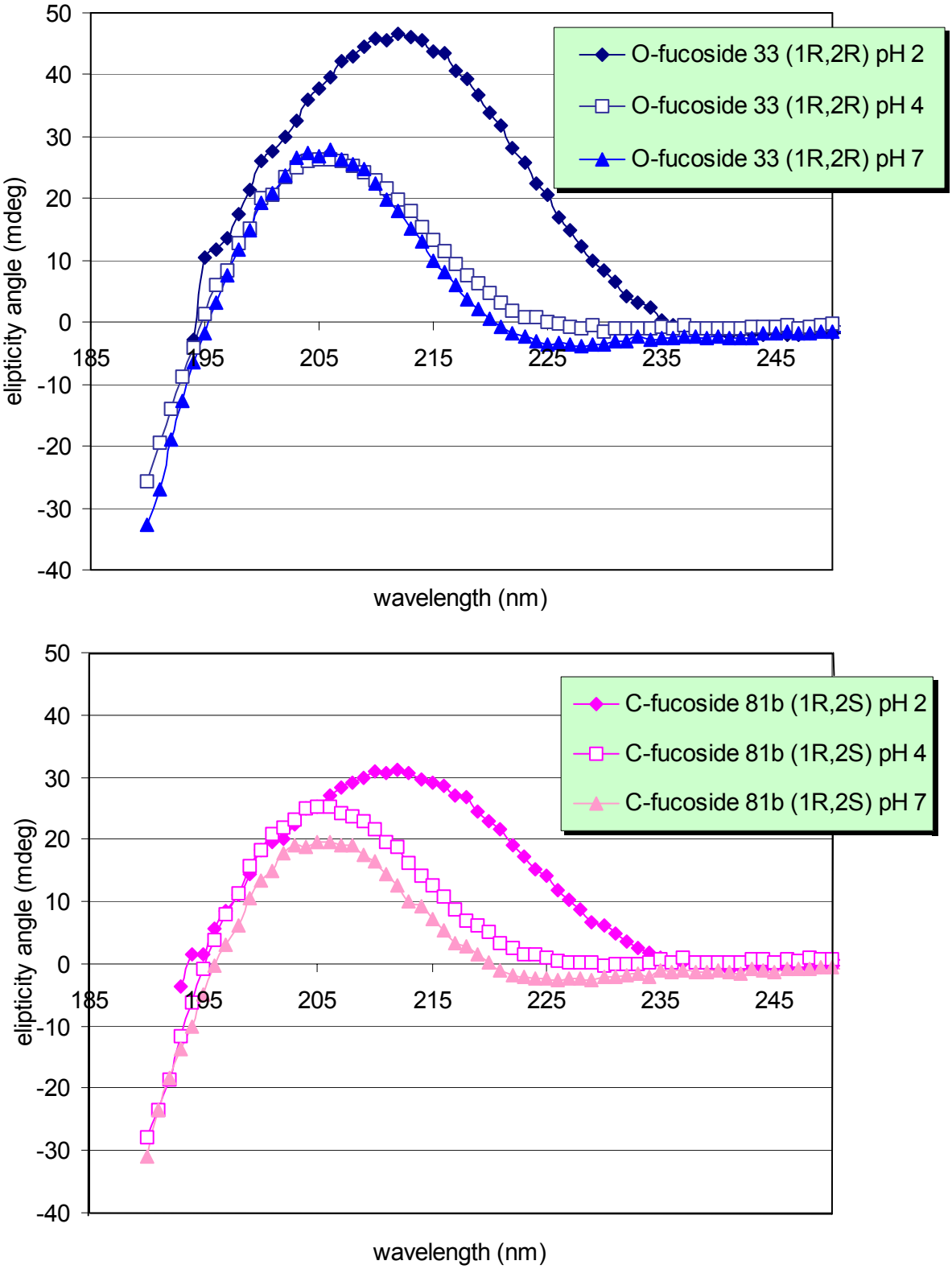


Figure 31: CD-spectra of the *O*-fucosidic mimic **33** and of the *C*-fucosidic mimic **81b** at three different pH-values. *O*-fucoside **33**: pH 7: 4.3 $\cdot 10^{-4}$ g/ml in H_2O; pH 4: 4.0 $\cdot 10^{-4}$ g/ml in diluted HOAc; pH 2: 4.5 $\cdot 10^{-4}$ g/ml in diluted HCl. *C*-fucoside **81b**: pH 7: 4.1 $\cdot 10^{-4}$ g/ml in H_2O; pH 4: 4.0 $\cdot 10^{-4}$ g/ml in diluted HOAc; pH 2: 3.5 $\cdot 10^{-4}$ g/ml in diluted HCl.

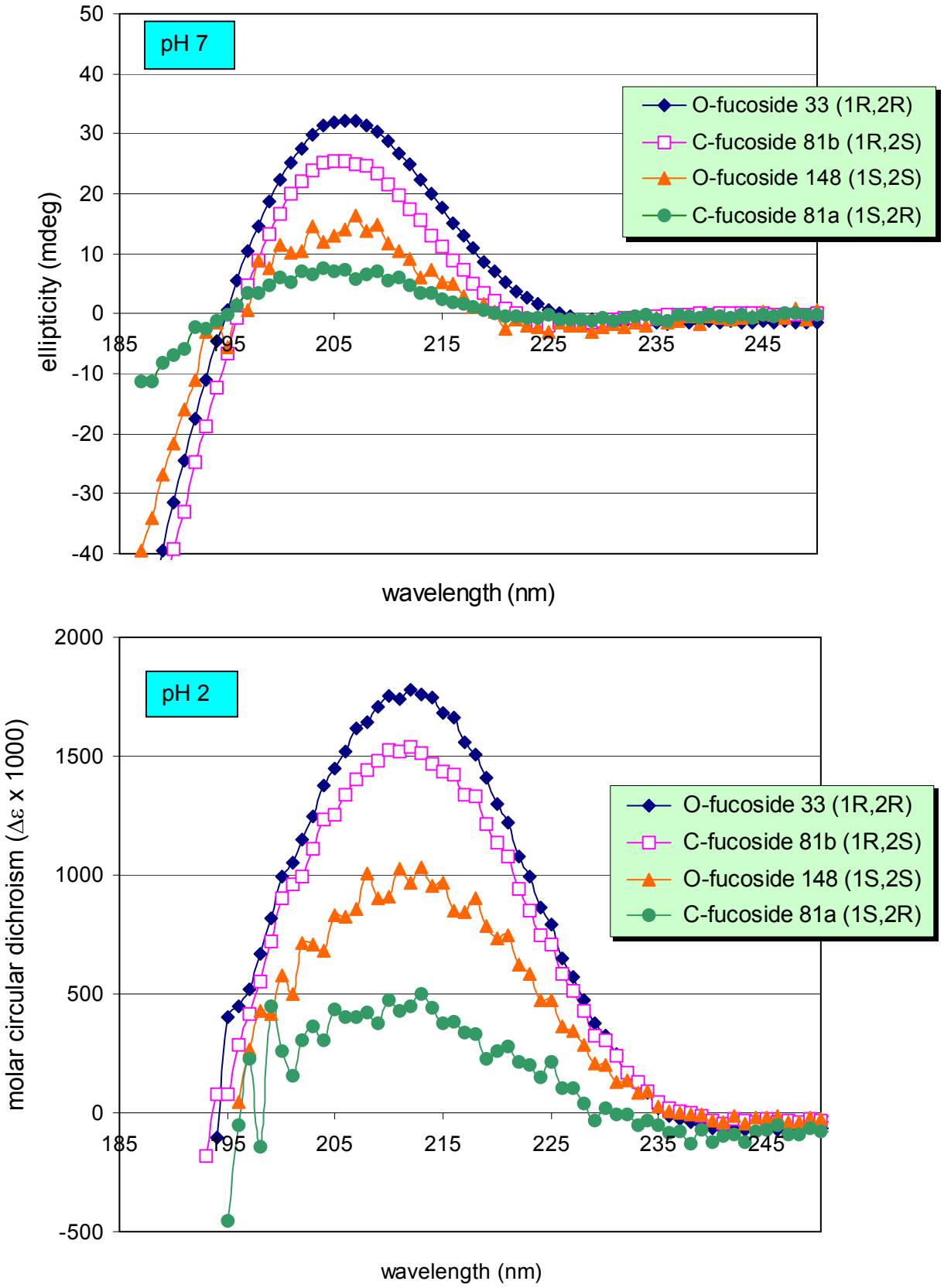


Figure 32: Comparison of the CD-spectra of the four tetrasaccharide mimetics **33**, **81a**, **81b** and **148** shown in *figure* 29. The upper graph shows the spectra of the four compounds at pH 7 in water, the lower graph shows the spectra of the four compounds at pH 2 in diluted HCl. In the upper graph, concentrations were adjusted in terms of maximal UV-absorption lying between 0.8 and 1.0.

3.3.3. X-ray crystal structure determination

In a second approach, the absolute configuration of the *C*-glycosidic mimetics **81a** and **81b** was determined by X-ray analysis. Crystal structures of oligosaccharides can hardly be found in literature due to the great difficulties to obtain crystals of appropriate regularity and size. In contrast to the crystal structure of Le^x [376,377], the crystal structure of sLe^x has not been published to date. However, the crystal structure of sLe^x co-crystallized with the natural receptor E-selectin was recently published by Camphausen [145].

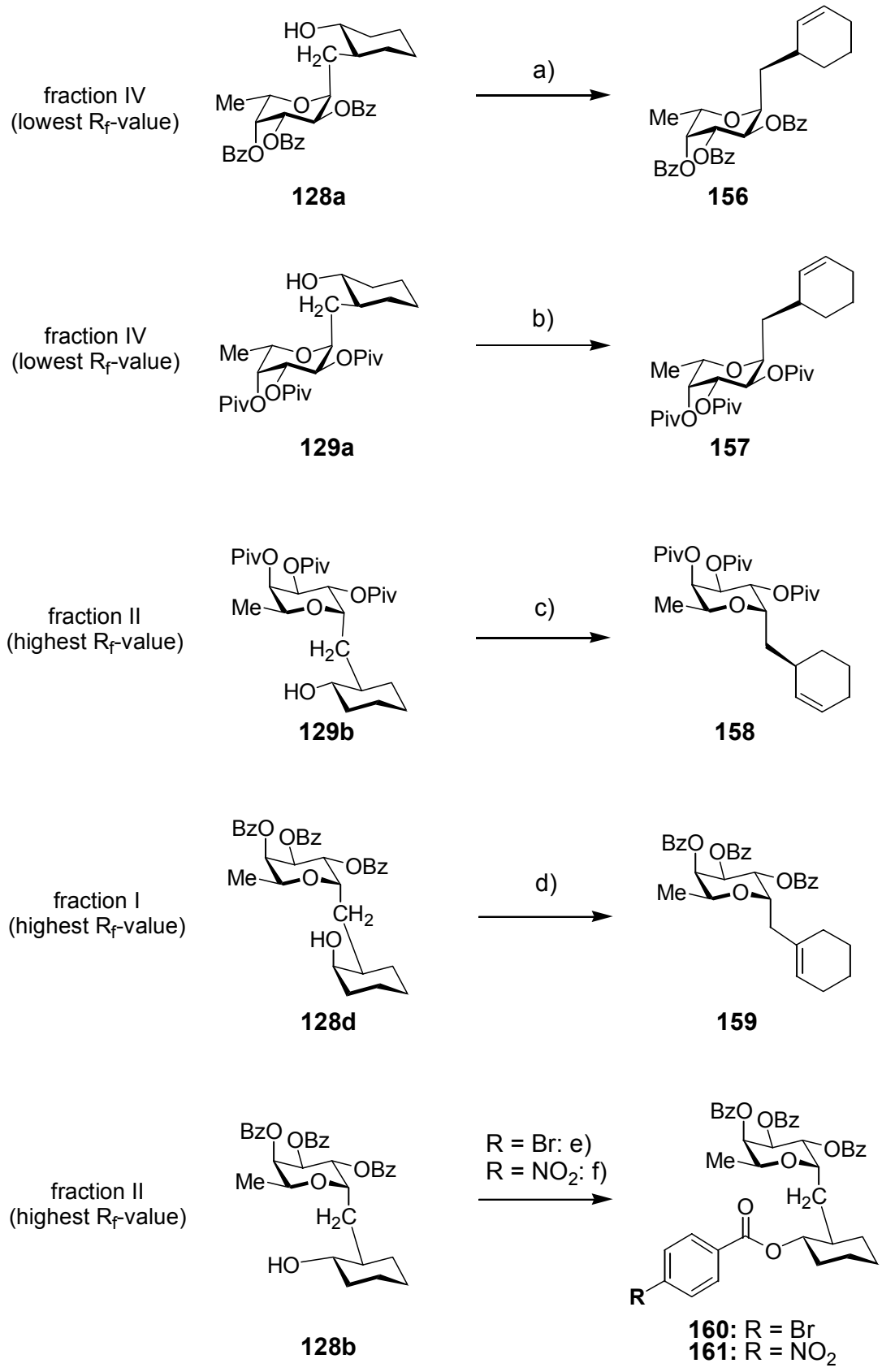
In order to determine the absolute configuration of the tertiary carbon center arising during the radical addition step, we decided to crystallize derivatized intermediates of the synthesis of **81a** and **81b**, which already contain the chiral center of interest (*scheme* 19).

The synthesis of triflate derivatives of the benzoate- and pivaloate-protected alcohols **128** and **129** as well as *p*-NO_2-benzoate- and *p*-Br-benzoate-protected derivatives of alcohol **128b** was planned. The synthesis of the triflate derivatives led to the elimination products **156**-**159**. Fortunately, the three equatorial triflates eliminated to olefins **156**, **157** and **158** without affecting the stereocenter, whereas the axially oriented triflate eliminated in an anti-elimination to **159** while destroying the chiral center of interest (see *scheme* 19).

We tried to crystallize the compounds shown in *scheme* 19 from different solvents and solvent mixtures. With di-isopropyl ether inhomogeneous crystals were obtained. We therefore chose solvents with different polarities as well as solvent mixtures, which lipophilicity rises during the evaporation of the more volatile polar component.

Each of the derivatives shown in *scheme* 19 as well as the two *C*-fucosidic alcohols **128b** and **128c** was dissolved for crystallization in one of the following solvents or solvent mixtures:

- ethyl acetate / heptane
- THF / hexane
- toluene / octane
- Bu_2O
- $^{i}Pr_2O$
- toluene
- $CHCl_3$
- ethyl acetate
- THF
- MeOH



Scheme 19: Derivatives of the *C*-fucosidic alcohols synthesized for crystallization experiments; a) Tf_2O, DMAP, CH_2Cl_2, pyr, 3 h, 0°C (41%); b) Tf_2O, CH_2Cl_2, pyr, 2 h, 0°C (67%) c) Tf_2O, CH_2Cl_2, pyr, 2 h, 0°C (83%) ; d) Tf_2O, DMAP, CH_2Cl_2, pyr, 3 h, 0°C (73%); e) *p*-Br-BzCl, pyr, 1/2 h, 0°C and 2 h rt (70%); f) *p*-NO_2-BzCl, pyr, 1/2 h, 0°C and 1 h rt (82%).

The substances **156**, **158** and **161** crystallized from THF, $CHCl_3$, ethyl acetate/heptane, $^{i}Pr_2O$ and methanol, but the crystals had not the necessary quality or size for an x-ray crystal structure determination with the exception of the crystals obtained of compound **158** from methanol. The size of the crystals was critical being only 0.05 mm in one dimension (*figure* 33).

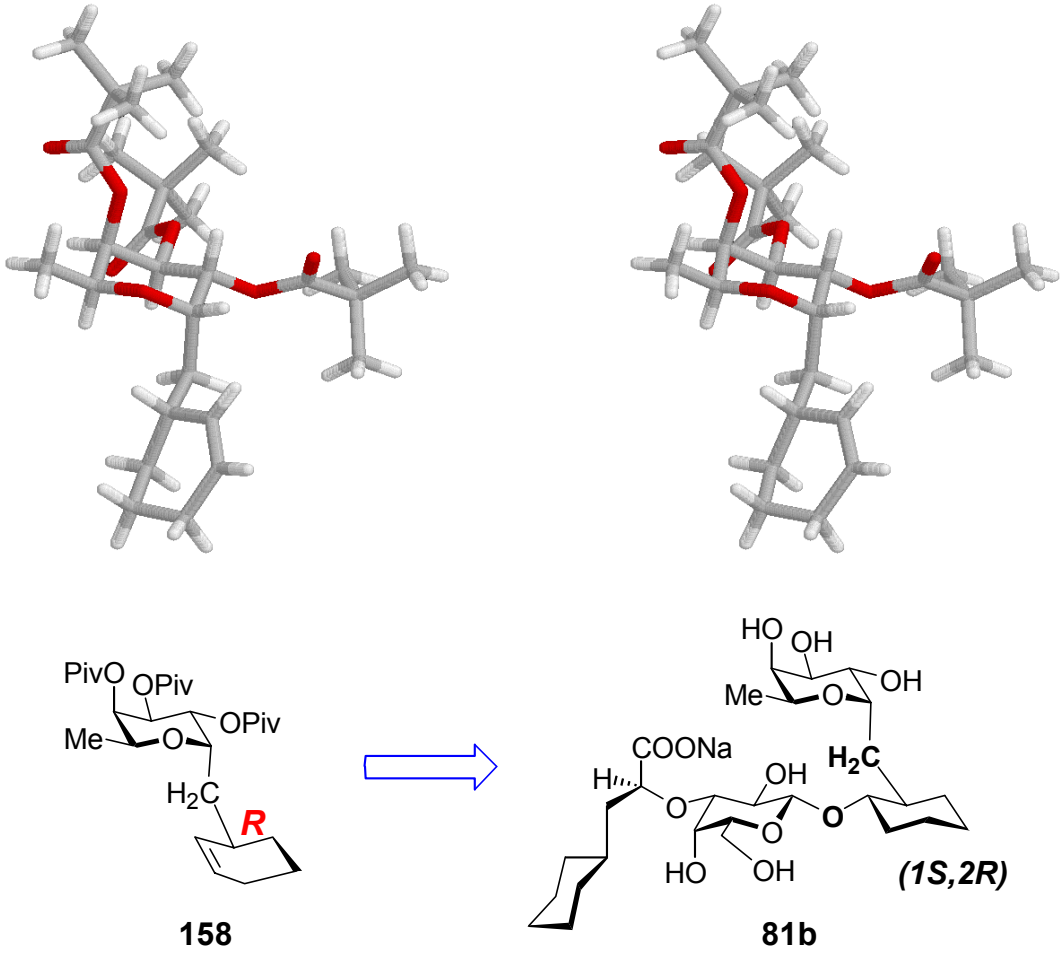


Figure 33: Stereoview of the crystal structure of compound **158**. The absolute configuration of the tertiary cyclohexenyl carbon near the methylene bridge can be assigned as *R*. α-configuration at the anomeric center is also confirmed by the crystal structure.

In contrast to the atoms in the two ring systems, the pivaloyl residues on the fucose showed large thermal motion within the crystal. Nevertheless, the configuration at the critical stereo center could be clearly assigned as *R*. This means that compound **158** with the higher R_f-value has the undesired configuration. As a consequence, the second fraction of the two equatorial alcohols (**157**, lower R_f-value) bears the correct *S*-configuration. Assuming that by

changing the protecting groups, the relative polarity among the four alcohols and thus the order on the TLC should remain unchanged, the configuration of the benzoyl-protected *C*-fucosidic alcohols was assigned in analogy to those of the pivaloyl-protected ones. Consequently the benzoyl-protected alcohol **128a** possessing the lower R_f-value should bear the desired *S*-configuration, whereas alcohol **128b** with the higher R_f-value should posses *R*-configuration. This TLC-based correlation is clearly confirmed by the NMR-data shown in *table* 8 in *chapter* 3.2.5.

3.4. Investigation of conformational preferences

The rigid conformation of the Lewis^x core of sLe^x in solution as well as the characteristic stacking of the galactose and fucose unit are reflected by the nuclear Overhauser effect (nOe) between the protons H-2 at galactose and H-5 and CH_3 of fucose [156,157,159,161,164,378]. This same solution conformation is adopted in mimetics, in which the glucosamine unit has been replaced by simpler cyclohexanediol spacers, as demonstrated by Ernst *et al.* [198,378] (see also *chapter* 1.4.2).

The same group demonstrated, that nOe intensities and chemical shift differences of the proton H-5^{Fuc} correlate with the biological activity [198]. It increases with decreasing distance between fucose and galactose, caused by the introduction of steric constraints by equatorial substituents next to the fucosidic linkage.

In case of the *C*-glycoside **81a**, more flexibility around the *C*-fucosidic bond is expected due to the lack of the stabilizing *exo*-anomeric effect. This should also lead to a reduced biological activity. To compensate for the lacking *exo*-anomeric effect, steric factors can be introduced. The following discussion shows, that our hypothesis proofed well-founded.

To compare the core conformation of the synthesized mimetics with that of mimic **33**, 2-dimensional ROESY experiments were performed with compounds **81b**, **82**, **147** and **148**. Unfortunately, not enough material of compound **81a** was available for these experiments. Experimental details are given in *chapter* 5.

The ROESY spectra of both compounds **82** and **147** show a clear nOe between the H-2^{Gal} and the H-5^{Fuc} as well as between the H-2^{Gal} and the $CH_3{}^{Fuc}$, indicating a close proximity between the galactose and the fucose unit (*figure* 34). In the ROESY spectra of compounds **81b** and **148**, no nOe crosspeaks between the fucose- and galactose protons could be found (*figure* 35). The different linkage of the fucose and galactose to the spacer cyclohexane ring leads to a completely changed core conformation compared to **33** or sialyl Lewis^x.

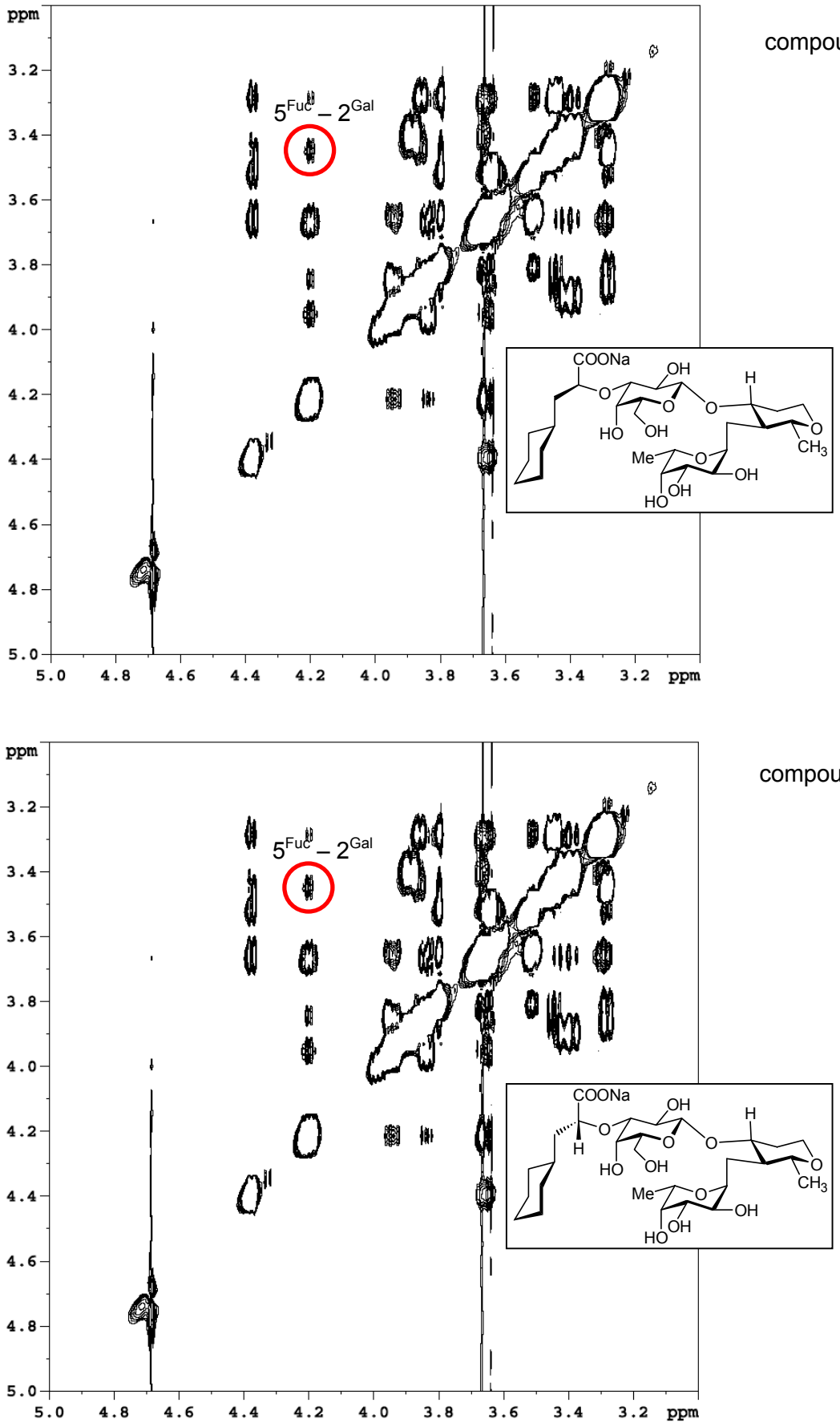


Figure 34: Section of the 2D-ROESY spectra of compounds **82** and **147**. The ROE's of H-5^{Fuc} and H-2^{Gal} are encircled.

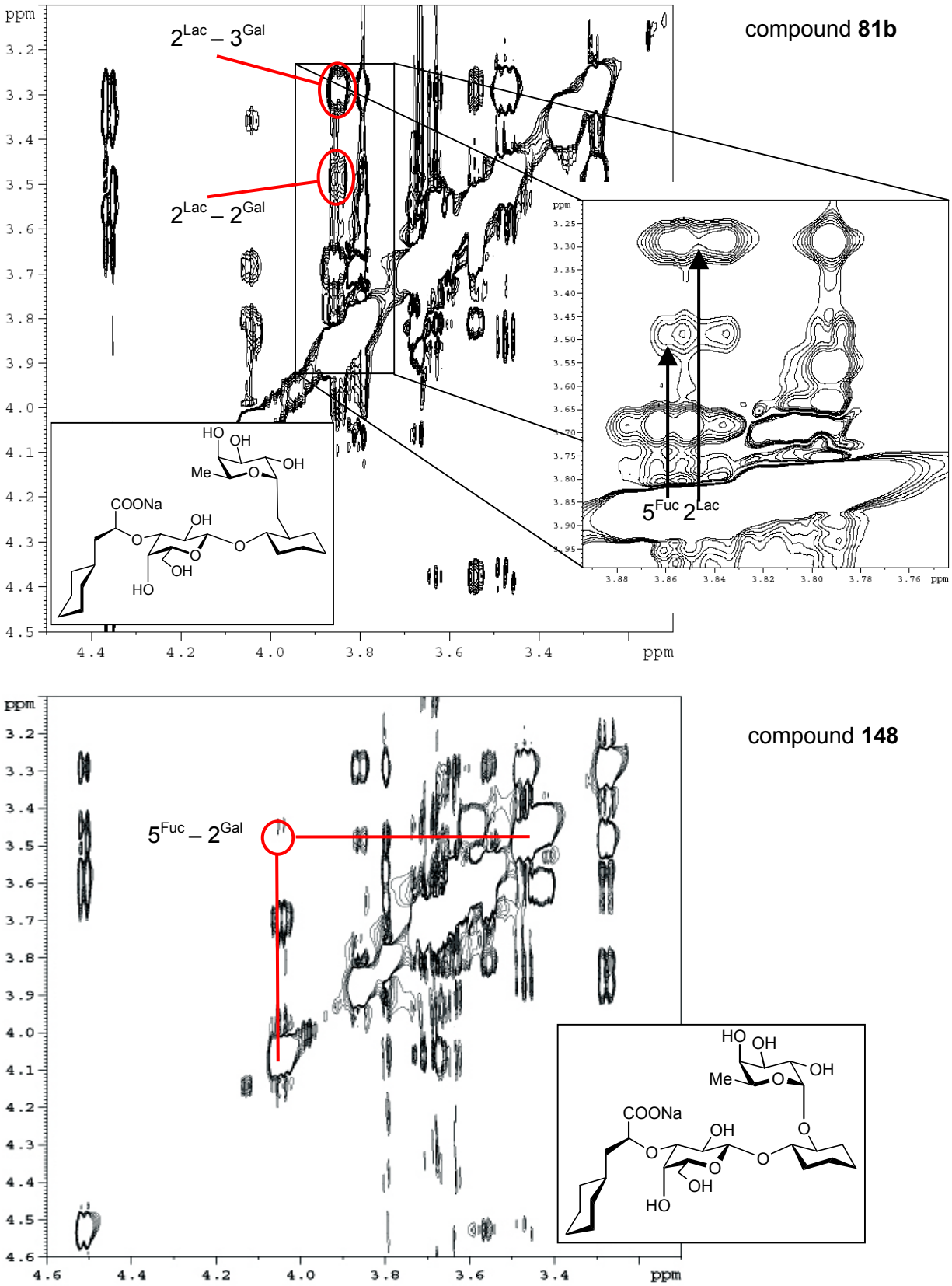


Figure 35: Section of the 2D-ROESY spectra of compounds **81b** and **148**. The chemical shifts of H-5^{Fuc} and H-2^{Lac} of compound **81b** are that similar, that the lacking ROE between H-5^{Fuc} and H-2^{Gal} can only be seen by zooming very close into the region of interest.

To quantitatively compare the intensities of the nOe signals as indicator of the proximity of the fucose and the galactose unit, we performed selective excitation ROESY spectra [379] for compounds **33** and **82**. The source of the magnetization in each experiment was proton H-5^{Fuc}. Each 1-dimensional experiment was performed with different spin-lock times.

The intensity of the positive signals grows with increasing mixing time and indicates the relative spacial proximity of a particular proton to that of the source proton (*figure* 36).

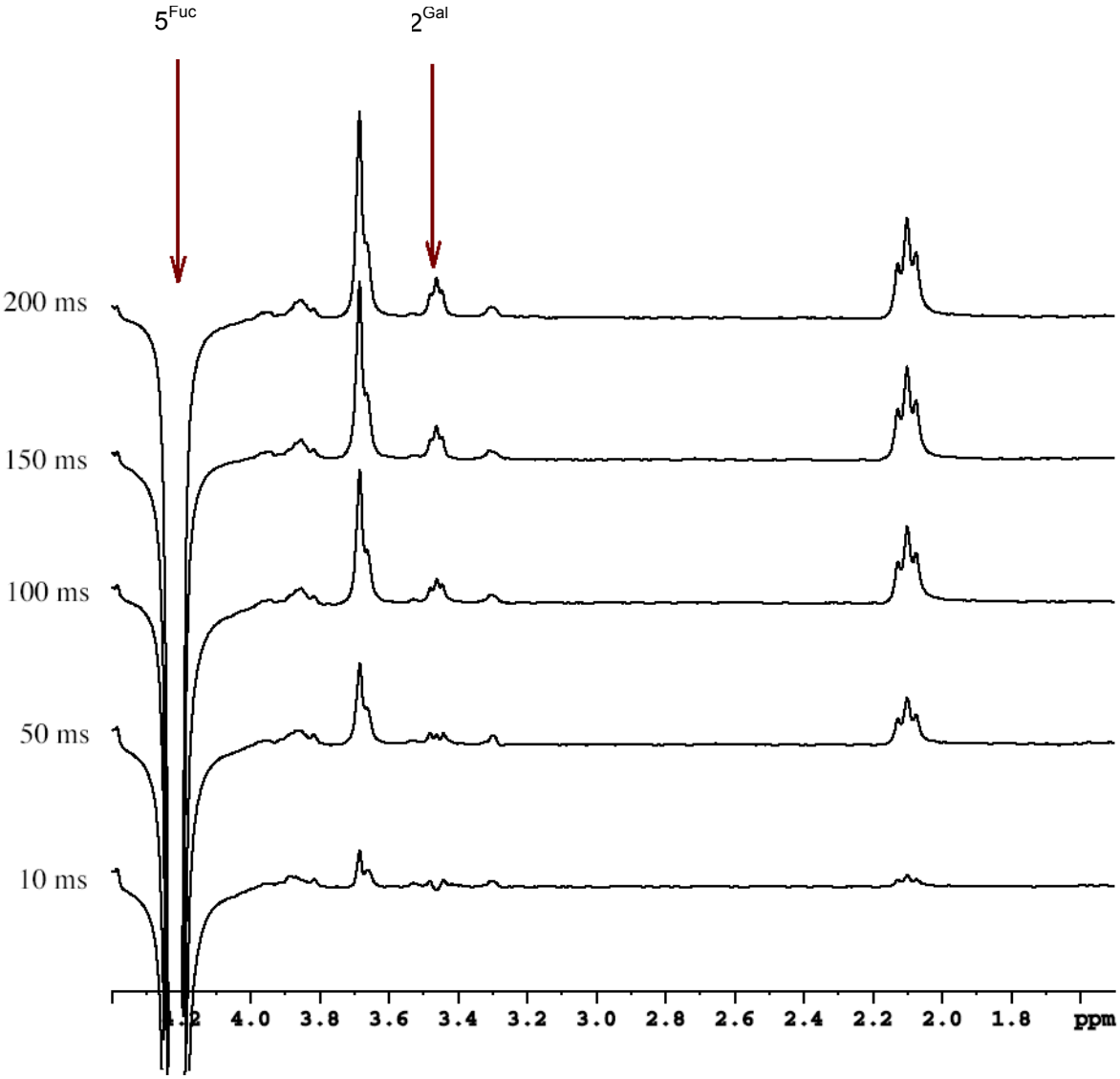


Figure 36: Selective excitation ROESY spectra for compound **82**. The time scale contains the different mixing times needed to obtain the ROE build-up rates.

The nOe's of the H-2^{Gal} proton (int_{cross}) were normalized to the intensity of the diagonal peak of H-5^{Fuc} (large negative signal, int_{diag}). Plotting these normalized intensities against the mixing time results in a straight line for each compound (*figure* 37). After equation (3), the

slopes of these build-up curves deliver the crossrelaxation rates σ [380] or the rates for the rotating frame nuclear Overhauser effect (ROE), which can be used to calculate relative distances of pairs of protons after equation (1) [381] and (2) [380].

$$\frac{Int_{cross}}{Int_{diag}} = \frac{\sinh(ROE \cdot t_{mix}) \cdot e^{(-r_{auto} \cdot t_{mix})}}{\cosh(ROE \cdot t_{mix}) \cdot e^{(-r_{auto} \cdot t_{mix})}} = \tanh(ROE \cdot t_{mix}) \qquad (1)$$

$$\sqrt[6]{\frac{ROE_1}{ROE_2}} = \frac{d_2}{d_1} \qquad (2)$$

Int_{cross} = intensity of the ROE crosspeak

Int_{diag} = intensity of the ROE diagonal peak

t_{mix} = mixing time

r_{auto} = auto-relaxation time

d_i = distance of two protons in compound i

In the linear approximation, the tanh(x) is a straight line for small x, which is true for the range of mixing times used in these experiments. This simplification results in equation (3).

$$\frac{Int_{cross}}{Int_{diag}} \approx ROE \cdot t_{mix} \quad \Rightarrow \quad S = \frac{\partial\left(\frac{Int_{cross}}{Int_{diag}}\right)}{\partial t_{mix}} = ROE \qquad (3)$$

Linear regression of the normalized ROE intensities delivers a slope of -0.093 (±0.013) for compound **33** and a slope of -0.024 (±0.0012) for compound **82** (*figure* 37). Combination of equation (2) and (3) results in equation (4), which delivers the relative distances of H-5^{Fuc} to H-2^{Gal} for both compounds:

$$\boxed{\frac{d_{82}}{d_{33}} = \sqrt[6]{\frac{S_{33}}{S_{82}}} = \frac{-0.093\ (\pm 0.013)}{-0.024\ (\pm 0.001)} = 1.25 \pm 0.04} \qquad (4)$$

These numbers indicate, that the two protons H-5^{Fuc} and H-2^{Gal} are 25(±4)% closer to each other in compound **33** than in compound **82**. Based on the determined distance of 3.5 Å for H-2^{Gal} and H-5^{Fuc} in compound **33** [378], the distance in compound **82** should be 4.2 – 4.5 Å. These results demonstrate the possibility to partly compensate the loss of the *exo*-anomeric effect by steric factors.

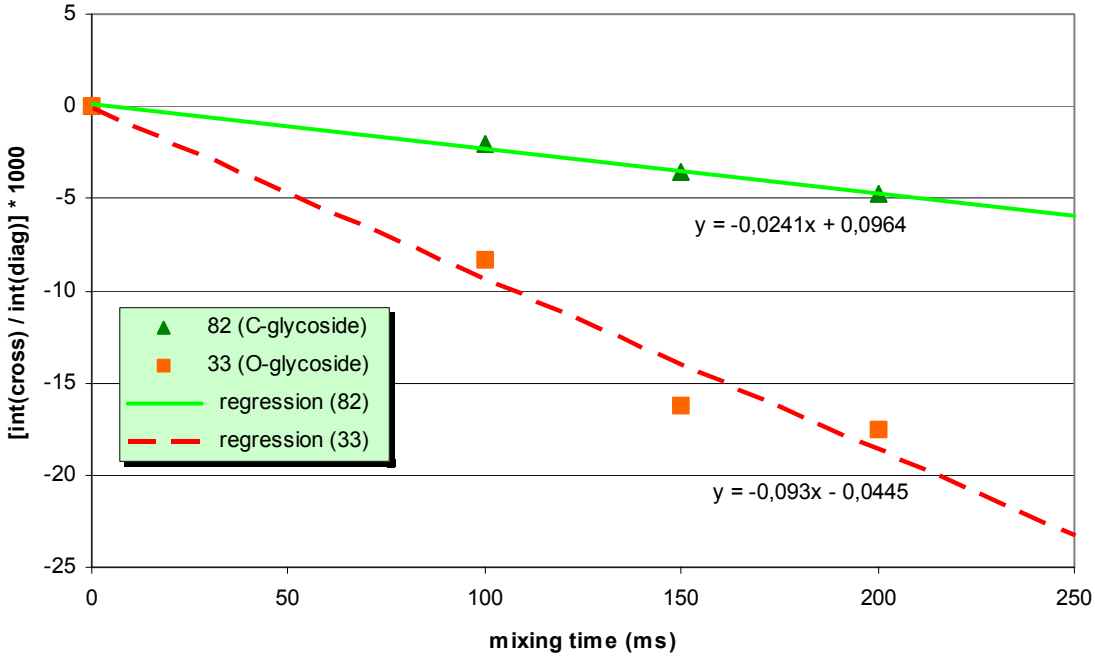
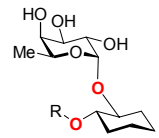
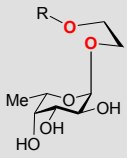
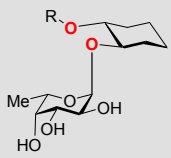
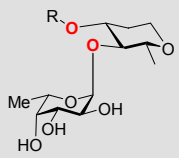
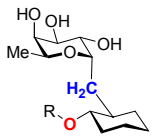
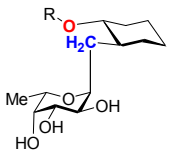
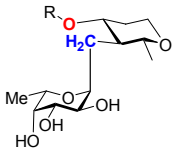
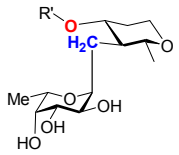


Figure 37: ROE build-up curves for compounds **33** and **82** arising from the selective excitation ROESY spectra.

Surprisingly, the postulated downfield shift [198] for proton H-5^{Fuc} as from δ = 4.12 ppm in compound **43** to δ = 4.77 ppm in compound **41** could not be observed in compound **82**. Proton H-5^{Fuc} of compound **82** shows only a small absolute downfield shift to δ = 4.29 ppm. However, compared to compound **81a** with a chemical shift of δ = 3.82 ppm for H-5^{Fuc}, the chemical shift difference of Δδ = 0.47 ppm in the row of the *C*-glycosidic compounds is comparable to Δδ = 0.65 ppm between **41** and **43**. Compared to the chemical shift of compounds **41** (δ = 4.77) and **33** (δ = 4.60), the downfield shift in the *C*-glycosidic row is even more distinct (*table* 9). The observed trend in both classes of compounds is also confirmed by the chemical shifts of H-5^{Fuc} of **148** (δ = 4.12 ppm) and of **81b** (δ = 3.80 ppm), which didn't show any nOe's between H-5^{Fuc} or $CH_3{}^{Fuc}$ and H-2^{Gal} and therefore lack a close proximity of the fucose and galactose unit.

The strong highfield shift of proton H-5^{Fuc} of compound **81a** in comparison to **82** and **33** is an indication of the expected flexibility and low bioactivity of this compound.

Table 9: Comparison of the chemical shifts of the proton H-5^{Fuc} in key tetrasaccharide mimics. Literature-known compounds [198] are highlighted in gray, compounds synthesized in the course of this thesis are not highlighted.

compound				
number	**148**	**43**	**33**	**41**
δ (H-5^{Fuc})	4.12	4.12	4.60	4.77
compound				
number	**81b**	**81a**	**82**	**147**
δ (H-5^{Fuc})	3.80	3.82	4.29	4.29

4. Summary and Conclusion

4.1. General background

The recruitment of leukocytes from the blood flow to sites of inflammation or tissue injury is initiated by their rolling and their subsequent firm attachment on the activated endothelial cell layer [9,68-71,382,383]. Rolling as the first event of a multi-step process called the inflammatory cascade was found to be a prerequisite for firm attachment and final endothelial transmigration to take place. Capturing and rolling is mediated by the interaction of the selectins, a family of three related cell-adhesion molecules, with their natural glycoprotein ligands [94-97]. All three selectins recognize a common, terminal carbohydrate epitope, the tetrasaccharide sialyl Lewis^x (sLe^x) **3** [31-34].

Excessive leukocyte accumulation is related to many acute and chronic diseases [109-127] as ischemia reperfusion injury, asthma, rheumatoid arthritis, psoriasis or septic shock. Furthermore, a contribution of selectin-carbohydrate interaction to cancer metastasis [128-131] could be shown. The blocking of the selectin-ligand interaction by potent sLe^x mimetics was proposed to be a highly promising therapeutic target to overcome these diseases.

C-glycosidic structures play a prominent role in developing hydrolytically stable mimetics [228-231] as well as in understanding conformational issues relevant for the binding process.

4.2. Aim of the thesis

Within this thesis we describe the successful development of a synthesis of the two *C*-glycosidic sLe^x mimetics **81a** and **82**, which are conformationally less stable than the corresponding *O*-glycosides due to the missing *exo*-anomeric effect. The hypothesis was raised, that the implementation of steric constraints as realized in mimic **82** can be used to compensate for the higher flexibility around the *C*-glycosidic bond in **81a**. Furthermore, comparison of binding affinity should allow a quantification of the entropy contribution to the inhibitory potential caused by the *exo*-anomeric effect.

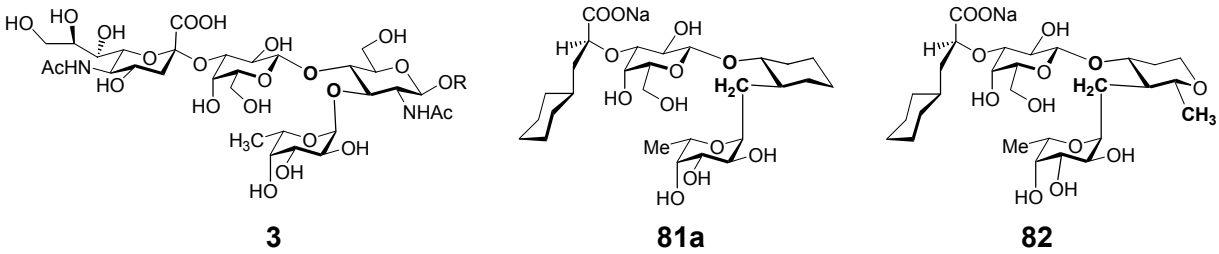


Figure 38: SLe^x and the target molecules **81a** and **82**.

4.3. Synthetic strategy

The synthetic pathways for **81a** and **82** are based on the radical addition of an anomeric glycosyl radical to an activated olefin developed by Giese *et al.* [271,272,275]. This key step was expected to establish the *C*-glycosidic bond α-selectively. By selective reduction of the cyclohexanones, β-selective galactosylation of the *C*-fucosidic equatorial alcohols and derivatization of the galactose at position 3, the target molecules are obtained (see *figure* 39).

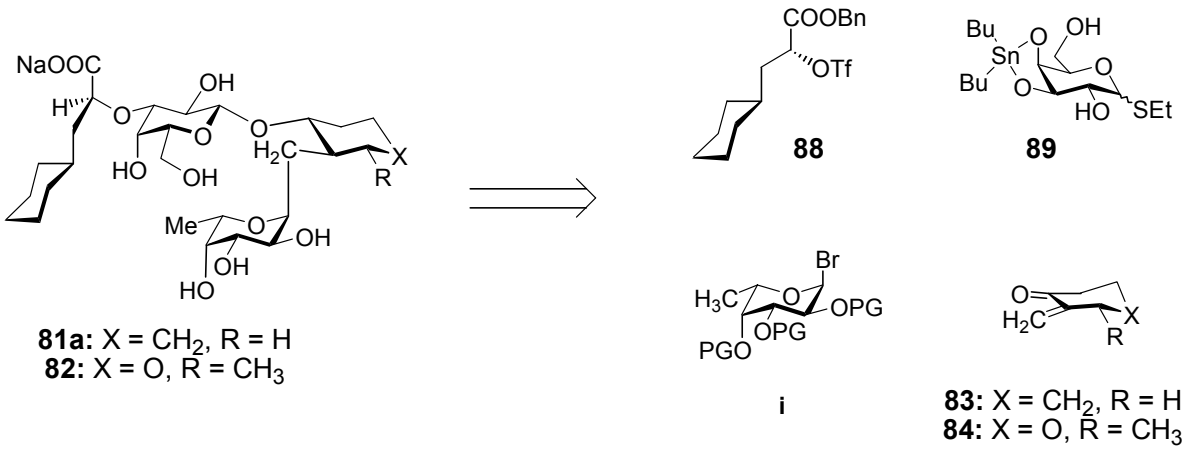


Figure 39: Retrosynthetic cleavage leading to the key building blocks for the synthesis of the two target tetrasaccharide mimetics **81a** and **82**.

4.4. Summary of Results

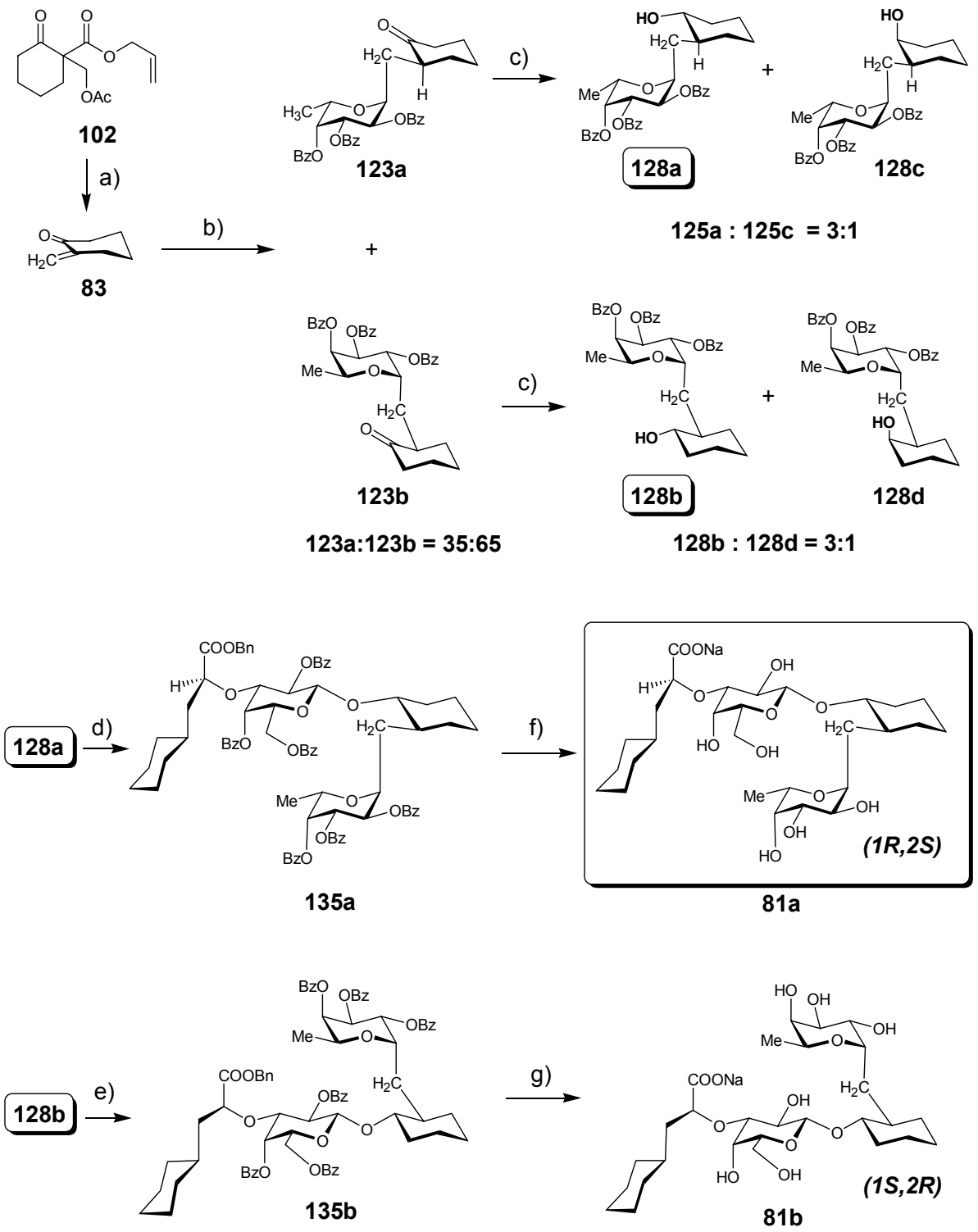
4.4.1. Synthesis of the tetrasaccharide mimetic 81a and its diastereomer 81b

α-Methylene cyclohexanone (**83**) used as radical acceptor was synthesized in a 5-step reaction sequence with an overall yield of 38% as described by Tsuji *et al.* [308,309] (see *chapter* 3.2.2). Compound **83** turned out to be highly susceptible to Diels-Alder dimerization. Temperature- and time-dependent stability of the methylene ketone **83** was investigated by NMR (see *table* 4, *chapter* 3.2.2). Half-life at a concentration of 15 mg/ml and 80°C was determined to be approximately 3-4 hours.

The radical addition developed by Giese *et al.* [271,272,275] was performed under different reaction conditions. In addition, the influence of the protecting groups on yields and stereoselectivities was investigated (see *chapter* 3.2.4). In all cases, exclusive α-selectivity at the anomeric center of fucose was observed. In contrast, the selectivity at the chiral center formed during the hydrogen atom transfer was rather low (dr = 57:43 to 67:33). As expected, the yields of the radical reaction were rather poor (26 to 35%) due to the concurrent dimerization of the radical acceptor **83**.

Because the absolute configuration of the diastereomers **123a** and **123b** could not be assigned at that point, the synthesis was continued with both diastereomers. The assignment problem could be solved later by an X-ray analysis (see below).

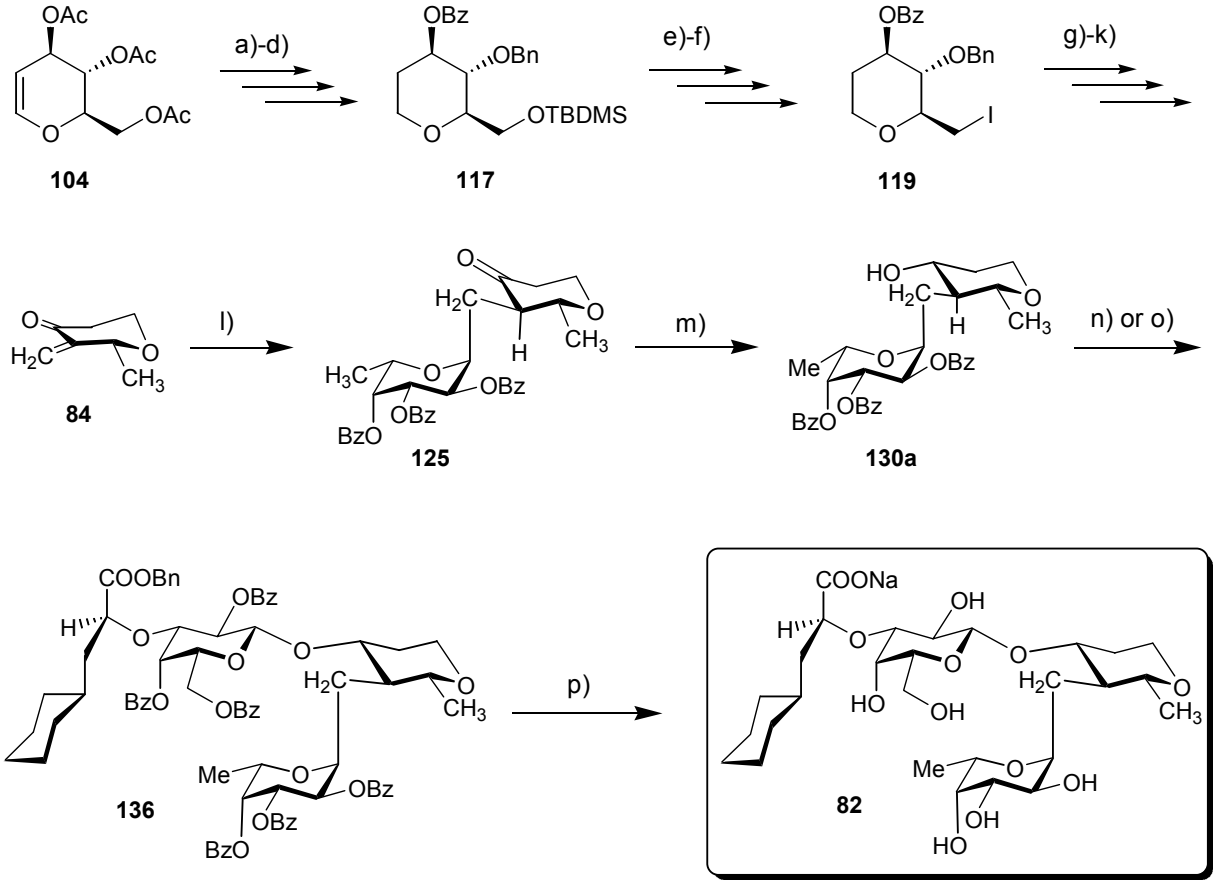
With different reducing agents as well as protecting groups, the subsequent reduction of the *C*-fucosidic ketones **122a/b**, **123a/b** and **124a/b** was optimized (see *chapter* 3.2.5). Glycosylation of the equatorial alcohols **128a** and **128b** with the galactose building block **90** led with excellent yields to the exclusive formation of the β-anomers (see *scheme* 20 and *chapter* 3.2.7). Finally, deprotection of the hydroxyl groups and the carboxylic acid led to the target molecule **81a** and its diastereomer **81b**.



Scheme 20: a) $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3, MeCN, rt, 20 min. (72%); b) **94,** Bu_3SnH, AIBN, dimethoxyethane, 85°C, 15 - 18 h (26%); c) Li(*t*-BuO)$_3$AlH, THF, 5 h at 0°C (86%); d) **90**, NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 4 h (90%); e) **90**, NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 4 h (82%); f) 1) NaOMe/MeOH, rt, 1 h and then 40°C, 2 h; 2) NaOMe/MeOH, microwave radiation, 40 W, 70°C, 2 h and then 2 drops water, rt, 1 h; 3) H^+/H_2O; 4) LiOH, dioxane/water (1:1), rt, 4 h; 5) Dowex 50 (55%); g) 1) NaOMe/MeOH, 50°C, 40 h; 2) H^+/H_2O; 3) LiOH, dioxane/water (1:1), rt, 4 h; 4) Dowex 50 (70%).

4.4.2. Synthesis of the methyl substituted tetrasaccharide mimic *82*

The radical acceptor methylene ketone **84** leading to the sLe^x mimic **82** was synthesized in a 13-step reaction sequence with an overall yield of 17% using D-glucal as chiral starting material (see *scheme* 21 and *chapter* 3.2.3).



Scheme 21: a)-k): see chapter 3.2.3 (overall: 17%); l) **94**, Bu_3SnH, AIBN, dimethoxyethane, 85°C, 18 h (11%); m) Li(*t*-BuO)$_3$AlH, THF, 20 h, 0°C to rt (93%); n) **90**, NIS, 4Å-MS, TfOH, CH_2Cl_2, -20°C, 6 h (69%); o) **90**, DMTST, CH_2Cl_2, -5°C, 24 h (80%); p) 1) NaOMe, MeOH/toluene (1:1), rt, 26 h; 2) H^+/H_2O; 3) Dowex 50 (80%).

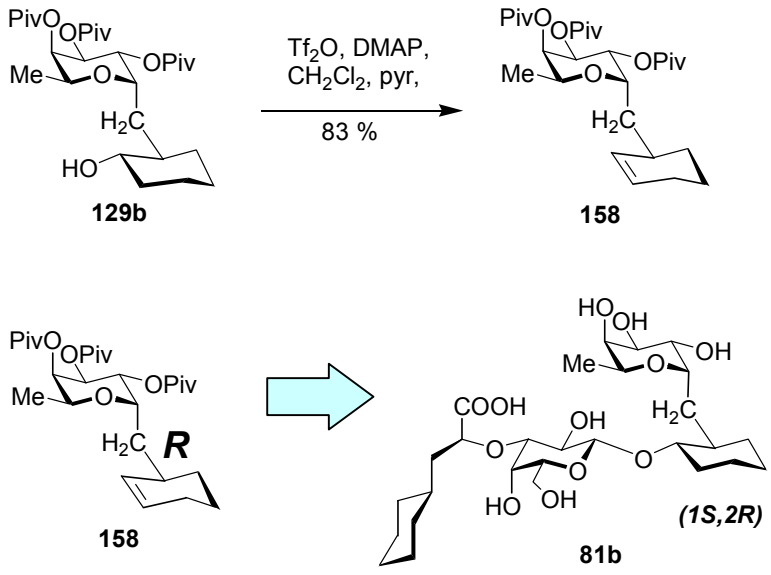
As during the synthesis of α-methylene cyclohexanone (**83**), a strong tendency of the methylene ketone **84** to undergo dimerization was observed. In the radical addition, exclusive stereoselectivity on both newly formed chiral centers was observed (see *chapter* 3.2.4). The subsequent reduction of the cyclic ketone **125** could be performed stereoselectively in favor of the desired equatorial alcohol **130a** (see *scheme* 21 and *chapter* 3.2.6). Glycosylation of

the equatorial alcohols with the galactose building block **90** gave **136** with high yield and exclusive β-selectivity (see *chapter* 3.2.7). Deprotection of tetrasaccharide mimetic **136** using the optimized deprotection protocol described in *chapter* 3.2.8 yielded the sLe^x mimetic **82**.

4.4.3. Determination of the absolute configuration of mimics *81a* and *81b*

In order to solve the assignment of the absolute configuration of **81a** and **81b**, two different approaches were undertaken. First, circular dichroism spectroscopy was applied to indirectly assign the configuration relative to the two well-assigned *O*-glycosidic parent structures **33** and **148**. The *O*-glycosidic mimetic **148** was synthesized in an overall yield of 45% (see *chapter* 3.3.1). CD-measurements of the four compounds **33**, **148**, **81a** and **81b** showed no significant differences that could help to assign the absolute configuration (see *chapter* 3.3.2).

In a second approach, derivatized intermediates of the synthesis were crystallized (see *chapter* 3.3.3). Crystals of compound **158** obtained from methanol were used to perform an X-ray analysis (*scheme* 22, *figure* 39).



Scheme 22: Derivatization of compound **129b** and assignment of the absolute configuration of molecule **81b** with the aid of the crystal structure determination of derivative **158**.

Correct assignment of the absolute configuration of both tetrasaccharide mimics was possible by a correlation of the TLC-R_f values of the crystallized compound with those of the intermediate *C*-fucosidic alcohols. This correlation could be confirmed by a comparison of the NMR data (see *table* 8, *chapter* 3.2.5).

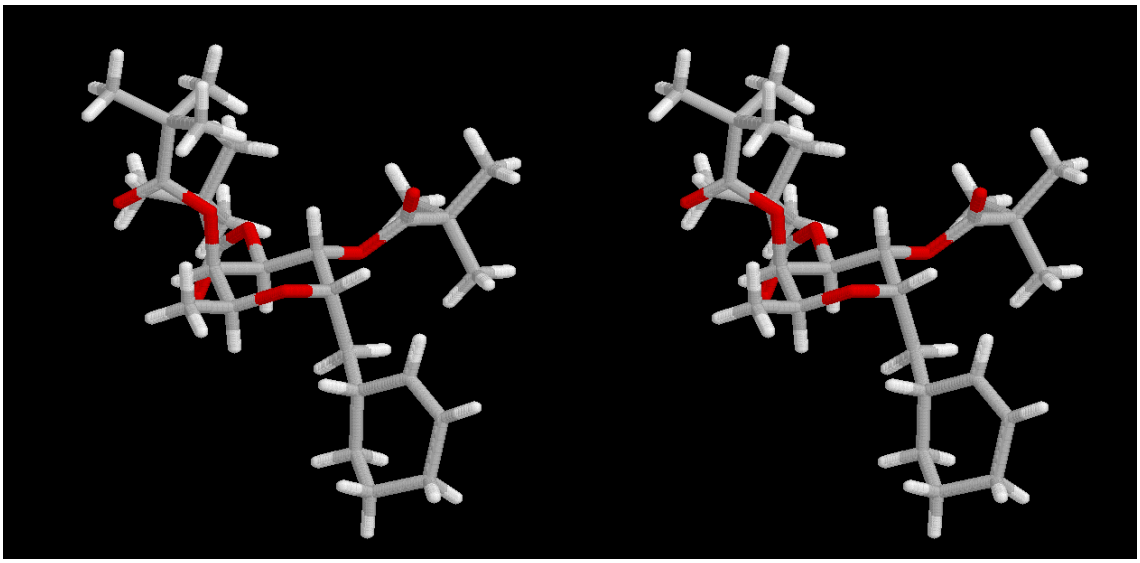


Figure 40: Stereoview of the crystal structure of **158**

4.4.4. Investigation of conformational preferences in solution

2D-ROESY experiments revealed nOe's between the protons H-5 and H-6 of fucose and the proton H-2 of galactose in compound **82**, which implicate the conformational similarity to the bioactive conformation of sLe^x (see *chapter* 3.4). The tetrasaccharide mimics **81b** and **148** bearing a different configuration at the cyclohexane spacer were lacking these nOe's. Quantitative comparison of the intensities of nOe's of **82** and **33** disclosed a 20-30% larger distance of $H\text{-}5^{Fuc}$ and $H\text{-}2^{Gal}$ in compound **82** than in compound **33**.

Another indicator for the spacial proximity of fucose and galactose, as found by Ernst *et al.* [198] for a series of *O*-glycosidic mimetics, could be confirmed in terms of a downfield chemical shift of $H\text{-}5^{Fuc}$ in compound **82** compared to compounds **81a**, **81b** and **148** (see *table* 9, *chapter* 3.4).

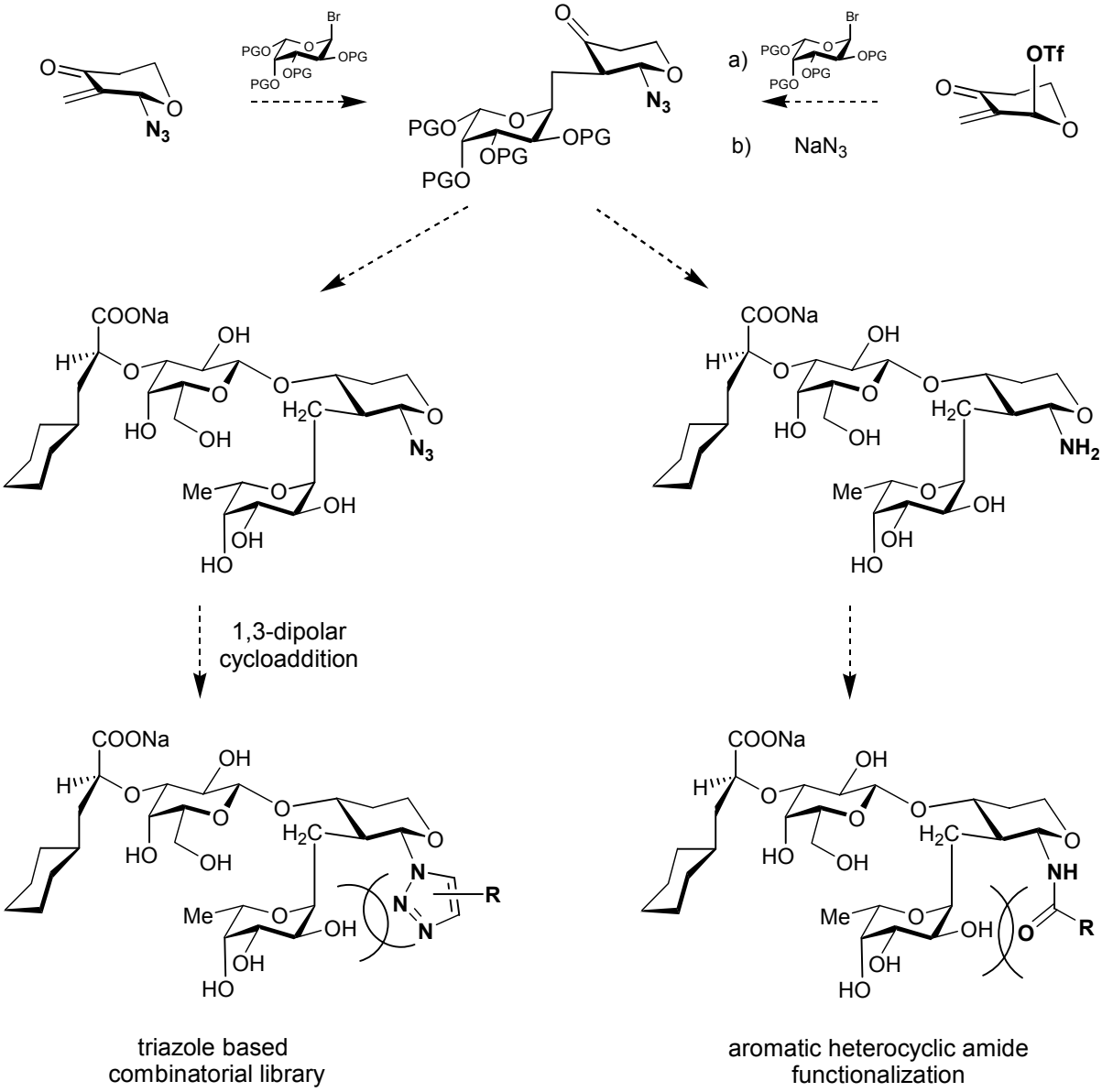
4.5. Conclusion and outlook

We successfully developed a synthesis for the target tetrasaccharide mimetics **81a** and **82**. The Giese radical addition reaction turned out to be a versatile method for the establishment of the *C*-fucosidic linkage in an α-selective manner. The main draw-back of our approach, however, is the tendency of the radical acceptors to dimerize in a Diels Alder cyclization reaction. By optimization of the workup and purification procedure of the methylene ketones, dimerization prior to the radical coupling itself can possibly be restricted. Concurrent dimerization under the high reaction temperatures needed for radical chain initiation can't be avoided.

The results of the debenzoylation experiments led to the conclusion, that problems can be avoided by modifying the reaction sequence: the lactic acid moiety is introduced after galactosylation of the *C*-fucosidic alcohols.

Conformational investigation of the target molecules revealed the possibility to partially compensate the loss of the *exo*-anomeric effect by the introduction of sterically demanding substituents next to the *C*-glycosidic linkage. The measured distance of H-5^{Fuc} and H-2^{Gal} in mimic **82** indicates that the sterical demand of the methyl group next to the *C*-glycosidic linkage is not sufficient to force the fucose unit into the bioactive conformation. The introduction of even bulkier substituents at the spacer unit should therefore be investigated. To what extent the larger distance of H-5^{Fuc} and H-2^{Gal} in compound **82** has an effect on, and whether the observed downfield shift of H-5^{Fuc} is in line with biological activity as shown by Ernst *et al.* [198] for *O*-glycosidic antagonists, has to be proven.

Investigation of compounds **79a-e** and **80a-e** (see *chapter* 1.5.5) support the approach to introduce hydrophobic residues at the 2-position of Glc*N*Ac of sLe^x to address a second binding site on the E-selectin surface. Our methodology opens the possibility to introduce spacer units functionalized with an azide group at the position next to the *C*-glycosidic linkage. This azide group can be used to build up a combinatorial triazole library containing a vide variety of differently modified triazole derivatives via 1,3-dipolar cycloaddition reactions (see *scheme* 23). In addition, this azide group can be converted into the amine in order to introduce hydrophobic residues like aromatic heterocycles via an amide bond.



Scheme 23: Functionalization of *C*-glycosidic sLe^x-mimetics containing an azide group with hydrophobic residues to address secondary binding sites of E-selectin.

5. Experimental Section

5.1. General methods

Nuclear magnetic resonance:

Nuclear magnetic resonance spectroscopy was performed on a *Bruker Avance 500 Ultra Shield spectrometer* at 500 MHz (^{1}H NMR) or 125 MHz (^{13}C NMR). Chemical shifts are given in ppm and were assigned in relation to the solvent signals [384] on the δ-scale or to tetramethylsilane (0 ppm) as internal standard.

^{1}H: 7.26 ppm ($CDCl_3$), 7.16 ppm (C_6D_6), 3.31 ppm (CD_3OD), 4.79 ppm (D_2O);

^{13}C: 77.16 ppm ($CDCl_3$), 128.06 ppm (C_6D_6), 49.00 ppm (CD_3OD).

Coupling constants J are given in Hertz (Hz). Multiplicities were specified as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), dq (double quartet), m (multiplet). Interpretation of the spectra was done according to 1st order [385].

For assignment of resonance signals to the appropriate nuclei the following abbreviations have been used: Fuc (fucose), Gal (galactose), Lac (lactic acid), Pyr (tetrahydropyran), Cyc (cyclohexane). In cases where the numbering of nuclei does not accord to the numbering in IUPAC nomenclature, the differences are illustrated in a formula scheme of the corresponding substance.

Two-dimensional ROESY experiments:

Spin-lock duration for ROESY was 200 ms. 128 increments were recorded in the indirect dimension, and 512 points were used for its Fourier transform (e.g. “zero-filling” by a factor of 3). In the direct dimension (e.g. normal 1D spectrum) 4k points were acquired and 4k used for the Fourier transformation of this dimension. Water suppression was achieved with presaturation during the interscan delay. The sweep-width was optimized by shifting the central frequency from H_2O (for presaturation) to 0 ppm during the 200 ms ROESY spin-lock

(to minimize TOCSY artifacts) and to 3 ppm (center of spectrum) during acquisition of the FID. As no signals were observed to the left of the H_2O, this frequency changing allowed smaller spectral-width in both dimensions, allowing for better resolution for a given number of increments in the indirect dimension (e.g. 128 t_1 increments between 0-6 ppm, instead of 256 if the FID was recorded centered on the H_2O frequency).

Selective ROESY spectra

A selective pulse was applied to the proton H-5^{Fuc}. Each 1-dimensional experiment was performed using a different mixing time (spin-lock). The intensity of the positive signals indicates the relative special proximity of a particular proton to that of the source proton (H-5^{Fuc}). The selective pulse was shaped in the form of an E-BURP-1 [386], to achieve better selectivity.

The frequency was changed during the experiment as

- f1 : start on H_2O for presaturation
- f2 : change to H-5^{Fuc} for selective excitation
- f3: change to 0 ppm during ROESY spin-lock (reduces TOCSY-artifacts)
- f1 : change back to H_2O for next scan (of 400 total)

Infrared spectroscopy:

IR spectra were recorded on a *Perkin Elmer Spectrum One FT-IR* spectrometer as KBr pellets or films. Most characteristic absorption bands of the spectrum were given in cm^{-1} and specified as vs (very strong), s (strong), m (medium), w (weak), b (broad).

Optical rotation:

Optical rotation was measured on a *Perkin Elmer 241* polarimeter either in chloroform or in methanol. The optical rotation for the Na-D-line (589 nm) can be extrapolated from the lines of a mercury lamp (546 nm and 579 nm) using the Drude equation [387]:

$$[\alpha]_D^T = \frac{[\alpha]_{579}^T \cdot 3.199}{4.199 - \frac{[\alpha]_{579}^T}{[\alpha]_{546}^T}} \quad \text{with} \quad [\alpha]_\lambda^T = \frac{\alpha \cdot 100}{c \cdot d}$$

α = measured rotation

c = concentration in g/100 ml

d = cell length in dm

T = temperature in °C

λ = wavelength in nm

Microanalysis:

Microanalysis was performed at the Institute of Organic Chemistry at the University of Basel, Switzerland.

Mass spectroscopy:

Mass spectra were recorded on an *Agilent 1100 Series LC/MSD* spectrometer in API-ES ionization mode or on a *Bruker Daltonics Esquire 3000 plus* ESI mass spectrometer at Gilson AG, Basel, Switzerland.

Circular dichroism spectroscopy:

CD spectra were measured using an *Aviv 62A DS* CD-spectrometer. The concentrations of the solutions were adapted in a way that the UV absorption A at λ_{max} lay in the range from 1.0 to 0.8.

The following solvents have been used: pH = 7: H_2O (dest.), pH = 4: HOAc, pH = 2: aqueous HCl.

Molar circular dichroism $\Delta\varepsilon$ has been calculated with the following equation [375]:

$$\Delta\varepsilon = \frac{\Theta}{\ell \cdot c} \cdot \frac{M}{33000}$$

$\Delta\varepsilon$ = molar circular dichroism

Θ = ellipticity angle [mdeg]

ℓ = cell length in dm; here: 0.1 dm

c = concentration in g/ml

M = molar mass

In cases where the concentrations were very similar, ellipticity angles as values produced by the CD-spectrometer were given instead of the molar CD-values due to equal molecular masses of the compounds.

Crystallization experiments:

Crystallization experiments were carried out by dissolving mg-samples of the compounds in 2.5 ml flasks from Infochroma AG, Zug, Switzerland and sealing the flasks with a plastic-cap penetrated with a metal syringe-canule. Storing the flasks at room temperature, the solvent was able to evaporate slowly thus steadily increasing the concentration and/or the polarity of the solvent mixtures towards the polarity of the less volatile component.

X-ray crystal structure determination:

The crystal structure was solved at Hoffmann-La Roche, Pharmaceutical Division, Pharma Research 65/308, Basel, CH. The diffraction pattern was measured on an IPDS (Image Plate Diffraction System) diffractometer from STOE, Darmstadt, Germany using Mo-radiation with a wavelength of 0.71073 Å. Structure refinement was performed using the ShelX [388] software (G.Sheldrick, Göttingen, Germany).

Thin layer chromatography:

TLC was performed using silica gel 60 coated glass plates containing fluorescence indicator from Merck KGaA, Darmstadt, Germany using either UV light (254 nm) or Mostain solution [1 g $Cer(SO_4)_2$, 50 g $(NH_4)_6(Mo_7O_{24}) \cdot 4\ H_2O$ dissolved in 1000 ml of 10% H_2SO_4] followed by heating to 140°C for 5 minutes to visibilize the substances.

Chromatography:

Column chromatography was performed using silica gel *C-560 D* (40-63 µm) from Uetikon AG, Switzerland. Reversed-phase column chromatography was carried out using *LiChroprep RP-18* (40-63 µm) from Merck KGaA, Darmstadt, Germany.

Microwave reactions:

Microwave reactions were performed in a *CEM Discover* microwave apparatus.

Hydrogenations:

Hydrogenation reactions were performed in a shaking apparatus of Parr Instruments Company, Moline, Illinois, USA in 250 ml or 500 ml bottles under a H_2 pressure of 4 to 5 bar.

Solvents:

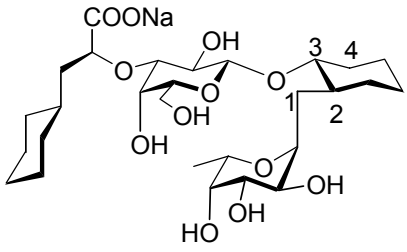
Solvents were purchased from Fluka and dried prior to use. Unpolar solvents (CH_2Cl_2, toluene, petroleum ether, hexane) were dried by filtration over basic aluminum oxide (Fluka). THF and methanol were dried by distillation from sodium. Pyridine was dried by distillation from CaH_2.

Numbering of experiments:

For every experiment, volume and page of the lab journal as well as the number of the batch are given (e.g. “I-112, cm024” means: volume I, page 112, batch cm024).

5.2. Experiments

Sodium (*2S*)-3-cyclohexyl-2-*O*-{1-*O*-[(*1S,2R*)-2-(α-L-fucopyranosyl-methyl)-cyclohexyl]-β-D-galactopyranos-3-yl}propanoate (81a) (II-155, cm213):



A solution of **135a** (20.0 mg, 15.2 µmol) in methanol (2 ml) and NaOMe/MeOH (1 M, 100 µl) was stirred in a microwave oven at 70°C for 2 h. After adding 2 drops of water, the reaction mixture was stirred for 1 h at room temperature. The solution was neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite and concentrated. The obtained oil was purified by silica gel chromatography (CH_2Cl_2/MeOH/H_2O 10:4:0.8), passed over Dowex 50x8 resin (Na^+ form) and chromatographed on a P2 gel column to yield **81a** (5.00 mg, 8.40 µmol, 55%).

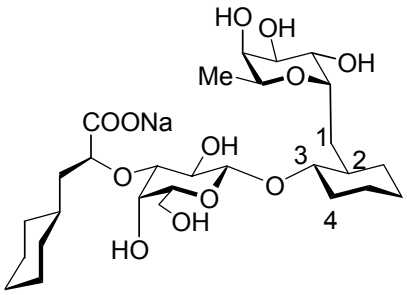
R_f = 0.17 (CH_2Cl_2/MeOH/H_2O 10:4:0.8);

^{1}H NMR (500 MHz, D_2O): δ 0.74-1.95 (m, 20 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.03 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.03 (m, 1 H, H-1$_a$^{Cyc}), 1.40 (m, 1 H, H-3$_a$^{Lac}), 1.47 (m, 1 H, H-3$_b$^{Lac}), 2.25 (m, 1 H, H-1$_b$^{Cyc}), 3.24 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Gal}), 3.35 (ddd, ^3J = 4.7 Hz, 9.1 Hz, 9.2 Hz, H-3^{Cyc}), 3.40 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.5 Hz, 1 H, H-2^{Gal}), 3.49 (m, 1 H, H-5^{Gal}), 3.57-3.62 (m, 3 H, H-4^{Fuc}, H-6$_{a+b}$^{Gal}), 3.72 (dd, $^3J_{2,3}$ = 10.4 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 3.76 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 0.6 Hz, 1 H, H-4^{Gal}), 3.78-3.83 (m, 3 H, H-2^{Fuc}, H-5^{Fuc}, H-2^{Lac}), 3.99 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.1 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.6 Hz, $^3J_{1,2}$ = 5.6 Hz, 1 H, H-1^{Fuc}), 4.33 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 16.2 (C-6^{Fuc}), 24.6-41.3 (13 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}, C-3^{Lac}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 72.5 (C-6^{Gal}), 70.0 (C-4^{Gal}), 67.2 (C-5^{Fuc}), 68.5 (C-2^{Fuc}), 70.3 (C-3^{Fuc}), 70.5 (C-2^{Gal}), 73.0 (C-1^{Fuc}), 74.6 (C-5^{Gal}), 79.7 (C-2^{Lac}), 82.0 (C-3^{Cyc}), 83.7 (C-3^{Gal}), 100.8 (C-1^{Gal}), 183.1 (COONa);

MS (-40.0 eV, ES): calculated for $C_{28}H_{48}O_{12}$ [M^- - Na]: 575.67; found: 575.44.

Sodium (*2S*)-3-cyclohexyl-2-*O*-{1-*O*-[(*1S,2R*)-2-(α-L-fucopyranosyl-methyl)-cyclohexyl]-β-D-galacto-pyranos-3-yl}propanoate (81b) (II-30, cm084):



To a solution of **135b** (62.0 mg, 0.048 mmol) in methanol (5 ml), NaOMe/MeOH (1 M, 100 µl) was added and the reaction mixture was stirred at 50°C for 40 h. The solution was neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite and concentrated. The residue (20.7 mg) and 10 equiv. of LiOH x H_2O (15.0 mg) in dioxane/water (1:1, 5 ml) were stirred at room temperature for 4 h. After acidification with 7% aqueous HCl, evaporation of the solvent and purification by silica gel chromatography (CH_2Cl_2/MeOH/H_2O 10:4:0.8), the product was passed over Dowex 50x8 resin (Na^+ form) followed by a P2 gel column to yield **81b** (20.0 mg, 0.033 mmol, 70%).

R_f = 0.27 (CH_2Cl_2/MeOH/H_2O 10:4:0.8);

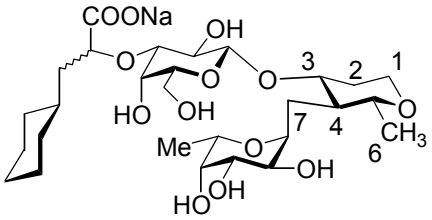
$[\alpha]_D^{22}$ = -40.6 (c = 0.95, CH_3OH);

^{1}H NMR (500 MHz, D_2O): δ 0.78-1.80 (m, 18 H, H-2^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.04 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.18 (m, 1 H, H-4$_a$^{Cyc}), 1.35 (m, 1 H, H-1$_a$^{Cyc}), 1.38 (m, 1 H, H-3$_a$^{Lac}), 1.40 (m, 1 H, H-4$_b$^{Cyc}), 1.54 (m, 1 H, H-3$_b$^{Lac}), 1.98 (m, 2 H, H-1$_b$^{Cyc}, H-2^{Cyc}), 3.24 (dd, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Gal}), 3.30 (dt, ^3J = 3.9 Hz, 9.2 Hz, 9.2 Hz, H-3^{Cyc}), 3.43 (dd, $^3J_{1,2}$ = 8.1 Hz, $^3J_{2,3}$ = 9.5 Hz, 1 H, H-2^{Gal}), 3.55 (m, 1 H, H-5^{Gal}), 3.58-3.65 (m, 4 H, H-3^{Fuc}, H-4^{Fuc}, H-6$_{a+b}$^{Gal}), 3.76 (m, 1 H, H-4^{Gal}), 3.78 (m, 2 H, H-2^{Fuc}, H-2^{Lac}), 3.80 (dq, $^3J_{4,5}$ = 1.3 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.01 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.5 Hz, $^3J_{1,1b\text{-}Cyc}$ = 9.3 Hz, $^3J_{1,2}$ = 5.2 Hz, 1 H, H-1^{Fuc}), 4.30 (d, $^3J_{1,2}$ = 8.1 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 15.7 (C-6^{Fuc}), 24.2, 24.8, 26.8, 27.0, 27.3, 31.1, 31.9, 32.8, 33.2, 34.4, 42.0 (11 C, C-1^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 33.0 (C-2^{Cyc}), 33.5 (C-6^{Cyc}), 33.8 (C-3^{Lac}), 61.5 (C-6^{Gal}), 66.0 (C-4^{Gal}), 67.6 (C-5^{Fuc}), 68.6 (C-2^{Fuc}), 70.6 (C-2^{Gal}), 70.8 (C-3^{Fuc}), 72.4 (C-4^{Fuc}), 74.8 (C-5^{Gal}), 76.3 (C-1^{Fuc}), 79.4 (C-2^{Lac}), 83.4 (C-3^{Gal}), 85.6 (C-3^{Cyc}), 103.8 (C-1^{Gal}) , 183.5 (COONa);

MS (2.02 eV, ES): calcd for $C_{28}H_{48}NaO_{12}$ [M^+ + H]: 599.67; found: 599.56.

Sodium (*2S*)-3-cyclohexyl-2-*O*-{1-*O*-[(*2R,3R,4R*)-4-hydroxy-2-methyl-3-(α-L-fucopyranosyl-methyl)-tetrahydropyran-4-yl]-β-D-galactopyranos-3-yl} propanoate (82) and



sodium (*2R*)-3-cyclohexyl-2-*O*-{1-*O*-[(*2R,3R,4R*)-4-hydroxy-2-methyl-3-(α-L-fucopyranosyl-methyl)-tetrahydropyran-4-yl]-β-D-galacto-pyranos-3-yl} propanoate (147):

Method A (microwave oven) (II-241, cm295/296)**:** Under argon, **141** (9.00 mg, 12.7 µmol) was dissolved in methanol (4 ml) in a microwave tube and a solution of NaOMe in MeOH (1 M, 150 µl) was added. The solution was then radiated in the microwave oven at 70°C for 4 h

and stirred without radiation at room temperature for 15 h. The reaction was neutralized with amberlyste ion-exchange resin (H^+ form), filtered, concentrated and dissolved in a mixture of dioxane and water (1:1, 2 ml). After adding LiOH (10.0 mg, 0.400 mmol), the reaction mixture was stirred for 3 h at room temperature, acidified to pH 4-5 with diluted acetic acid, passed over Dowex 50x8 ion-exchange resin (Na^+ form), purified by RP-18 reversed-phase silica gel chromatography (gradient MeOH/H_2O 0:1 → 1:0) and P2 column chromatography to yield a 1:1 mixture of the two diastereomers **82** (F II, R_f = 0.12) and **147** (F I, R_f = 0.24) (7.00 mg, 11.4 µmol, 89%).

Method B (toluene/methanol) (II-246, cm301)**:** Under an atmosphere of argon, **141** (6.00 mg, 8.00 µmol) was dissolved in toluene/methanol (10 ml, 1:1) and a solution of NaOMe in MeOH (1M, 600 µl) was added. After stirring at room temperature for 26 h, the reaction was neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, concentrated and passed over Dowex 50x8 ion-exchange resin (Na^+ form). Purification by RP-18 reversed-phase silica gel chromatography (gradient MeOH/H_2O 0:1 → 1:0) and P2 column chromatography yielded **82** (R_f = 0.12) (4.00 mg, 6.40 µmol, 80%).

147 (F I):

R_f = 0.24 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.82-1.80 (m, 11 H, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.17 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.22 (d, $^3J_{5,6}$ = 5.9 Hz, 3 H, H-6^{Pyr}), 1.37 (m, 1 H, H-4^{Pyr}), 1.40 (m, 1 H, H-7$_a^{Pyr}$), 1.52 (m, 1 H, H-3$_a^{Lac}$), 1.58 (m, 1 H, H-2$_a^{Pyr}$), 1.63 (m, 1 H, H-3$_b^{Lac}$), 2.10 (m, 1 H, H-2$_b^{Pyr}$), 2.19 (m, 1 H, H-7$_b^{Pyr}$), 3.37 (m, 2 H, H-3^{Gal}, H-5^{Pyr}), 3.48 (ddd, J = 1.9 Hz, 11.6 Hz, 12.3 Hz, 1 H, H-1$_a^{Pyr}$), 3.55 (m, 2 H, H-2^{Gal}, H-5^{Gal}), 3.71 (m, 2 H, H-6$_{a+b}^{Gal}$), 3.75 (m, 1 H, H-4^{Fuc}), 3.76 (m, 2 H, H-3^{Fuc}, H-3^{Pyr}), 3.92 (dd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{2,3}$ = 10.1 Hz, 1 H, H-2^{Fuc}), 3.96 (m, 1 H, H-1$_b^{Pyr}$), 4.03 (m, 3 H, H-4^{Gal}, H-2^{Lac}, H-1^{Fuc}), 4.29 (dq, $^3J_{4,5}$ = 0.6 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.48 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 16.4 (C-6^{Fuc}), 19.1 (C-6^{Pyr}), 22.7 (C-7^{Pyr}), 26.9, 27.2, 27.8, 33.4, 34.0, 34.9 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 31.5 (C-2^{Pyr}), 33.8 (C-3^{Lac}), 44.5 (C-4^{Pyr}), 61.9 (C-6^{Gal}), 65.7 (C-1^{Pyr}), 66.4 (C-4^{Gal}), 67.1 (C-5^{Fuc}), 68.3 (C-2^{Fuc}), 69.7 (C-2^{Gal}), 70.0 (C-3^{Fuc}), 72.4 (C-4^{Fuc}), 75.2 (C-5^{Gal}), 75.4 (C-1^{Fuc}), 76.9 (C-3^{Pyr}), 78.3 (C-2^{Lac}), 78.5 (C-5^{Pyr}), 81.6 (C-3^{Gal}), 100.0 (C-1^{Gal}) , 182.8 (COONa);

MS (API-ES, neg. mode):calcd for $C_{28}H_{27}O_{13}$ [M - Na^+]: 591.66; found: 591.30.

82 (F II):

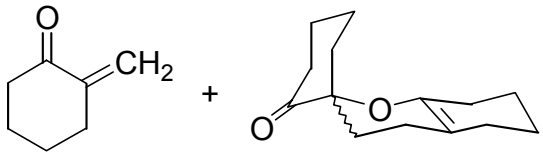
R_f = 0.12 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.82-1.80 (m, 11 H, H-4^{Lac}, H-$5_{a+b}{}^{Lac}$, H-$6_{a+b}{}^{Lac}$, H-$7_{a+b}{}^{Lac}$, H-$8_{a+b}{}^{Lac}$, H-$9_{a+b}{}^{Lac}$), 1.15 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.22 (d, $^3J_{5,6}$ = 5.9 Hz, 3 H, H-6^{Pyr}), 1.37 (m, 1 H, H-4^{Pyr}), 1.40 (m, 1 H, H-$7_a{}^{Pyr}$), 1.52 (m, 1 H, H-$3_a{}^{Lac}$), 1.58 (m, 1 H, H-$2_a{}^{Pyr}$), 1.63 (m, 1 H, H-$3_b{}^{Lac}$), 2.09 (m, 1 H, H-$2_b{}^{Pyr}$), 2.17 (m, 1 H, H-$7_b{}^{Pyr}$), 3.37 (m, 2 H, H-3^{Gal}, H-5^{Pyr}), 3.48 (ddd, J = 1.9 Hz, 11.6 Hz, 12.3 Hz, 1 H, H-$1_a{}^{Pyr}$), 3.53 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.4 Hz, 1 H, H-2^{Gal}), 3.60 (m, 1 H, H-5^{Gal}), 3.72 (m, 3 H, H-$6_{a+b}{}^{Gal}$, H-3^{Pyr}), 3.75 (m, 2 H, H-3^{Fuc}, H-4^{Fuc}), 3.88 (m, 1 H, H-4^{Gal}), 3.95 (m, 2 H, H-2^{Fuc}, H-2^{Lac}), 3.99 (m, 1 H, H-$1_b{}^{Pyr}$), 4.02 (ddd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{1,7a}$ = 2.8 Hz, $^3J_{1,7b}$ = 11.9 Hz, 1 H, H-1^{Fuc}), 4.29 (dq, $^3J_{4,5}$ = 0.6 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.46 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 16.4 (C-6^{Fuc}), 19.1 (C-6^{Pyr}), 21.8 (C-7^{Pyr}), 26.3, 27.5, 27.8, 33.6, 34.2, 34.4 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 31.5 (C-2^{Pyr}), 33.3 (C-3^{Lac}), 44.6 (C-4^{Pyr}), 61.5 (C-6^{Gal}), 65.9 (C-1^{Pyr}), 66.1 (C-4^{Gal}), 66.8 (C-5^{Fuc}), 68.4 (C-2^{Fuc}), 69.8 (C-3^{Fuc}), 70.2 (C-2^{Gal}), 72.7 (C-4^{Fuc}), 74.8 (C-5^{Gal}), 75.6 (C-1^{Fuc}), 77.2 (C-3^{Pyr}), 78.6 (C-5^{Pyr}), 79.2 (C-2^{Lac}), 83.6 (C-3^{Gal}), 100.3 (C-1^{Gal}) , 182.9 (COONa);

MS (API-ES, neg. mode):calcd for $C_{28}H_{27}O_{13}$ [M - Na^+]: 591.66; found: 591.30.

α-Methylene cyclohexanone (83) and **Diels-Alder adduct (103)** [308] (I-100, cm017):



Under argon, **102** (254 mg, 1.00 mmol) and PPh_3 (52.0 mg, 0.200 mmol) were dissolved in acetonitrile (20 ml). $Pd_2(dba)_3{\cdot}CHCl_3$ (50.0 mg, 0.050 mmol) was added and the reaction mixture was stirred for 20 min at room temperature. The dark yellow solution was filtered through a short silica gel column and the solvent was evaporated at room temperature. The remaining colorless oil was distilled (Kugelrohr) under vacuum at 100-120 °C and used instantly for the radical coupling reaction.

83:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69-1.78 (m, 2 H, CH_2), 1.83-1.91 (m, 2 H, CH_2), 2.30-2.48 (m, 2 H, CH_2), 2.52-2.57 (m, 2 H, CH_2-CO), 5.14 (d, ^2J = 1.9 Hz, 1 H, CH_2-H_a), 5.83 (d, ^2J = 1.9 Hz, 1 H, CH_2-H_b);

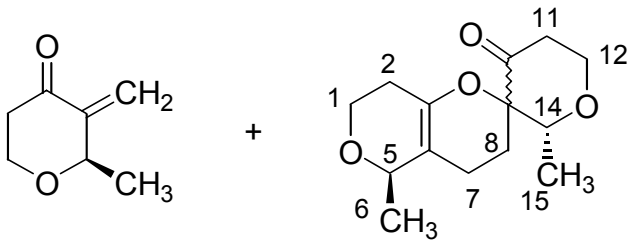
^{13}C NMR (125 MHz, $CDCl_3$): δ 23.6, 24.8, 33.7 (3 CH_2), 41.3 ($\underline{C}H_2$-CO), 119.2 (C=$\underline{C}H_2$), 146.0 ($\underline{C}$=CH_2), 202.4 (CO).

103:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40-2.06 (m, 17 H), 2.13 (m, 1 H, CH_2-H_a), 2.26 (m, 1 H, CH_2-CO-H_a), 2.75 (m, 1 H, CH_2-CO-H_b);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 23.2, 23.3, 23.5, 27.9, 28.2, 28.8, 29.3, 39.2 (9 CH_2), 40.0 ($\underline{C}H_2$-CO), 80.0 ($C_{quart.}$), 105.3 ($\underline{C}$=C-O), 145.1 (C=$\underline{C}$-O), 212.5 (CO).

(*2R*)-2-Methyl-3-methylene-tetrahydropyran-4-on (84) and **dimer 115** (II-189, cm246):



Under an atmosphere of argon, **114** (60.0 mg, 0.470 mmol) was dissolved in CH_2Cl_2 (10 ml) containing 3Å molecular sieves. After 15 min, PDC (50.0 mg, 0.130 mmol) was added and the mixture was stirred for 16 h at room temperature. The reaction was stopped by filtration through celite and **84** (54.0 mg, 0.420 mmol, 90%) was isolated by evaporation of the solvent and instantly used in the subsequent radical reaction without further purification. Upon longer storage of the product solution, dimer **115** is formed.

84:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, CH_3), 2.52 (ddd, $^3J_{1ax,2eq}$ = 3.4 Hz, $^3J_{1eq,2eq}$ = 2.2 Hz, $^2J_{2ax,2eq}$ = 17.6 Hz, 1 H, H-2_{eq}), 2.69 (ddd, $^3J_{1ax,2ax}$ = 11.3 Hz, $^3J_{1eq,2ax}$ = 7.2

Hz, $^{2}J_{2ax,2eq}$ = 17.6 Hz, 1 H, H-2_{ax}), 3.86 (ddd, $^{2}J_{1ax,1eq}$ = 11.9 Hz, $^{3}J_{1ax,2eq}$ = 3.4 Hz, $^{3}J_{1ax,2ax}$ = 11.3 Hz, 1 H, H-1_{ax}), 4.20 (ddd, $^{2}J_{1ax,1eq}$ = 11.9 Hz, $^{3}J_{1eq,2eq}$ = 2.2 Hz, $^{3}J_{1eq,2ax}$ = 7.2 Hz, 1 H, H-1_{eq}), 4.44 (q, $^{3}J_{5,6}$ = 6.3 Hz, H-5), 5.30 (d, ^{2}J = 2.2 Hz, 1 H, CH_2-H_a), 6.12 (d, ^{2}J = 2.2 Hz, 1 H, CH_2-H_b);

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0 (C-6), 39.1 (C-2), 63.0 (C-1), 73.9 (C-5), 119.2 (C=$\underline{C}H_2$), 145.8 (C-4), 195.9 (C-3);

^{1}H NMR (500 MHz, C_6D_6): δ 1.15 (d, $^{3}J_{5,6}$ = 6.3 Hz, 3 H, CH_3), 2.04 (ddd, $^{3}J_{1ax,2eq}$ = 3.4 Hz, $^{3}J_{1eq,2eq}$ = 2.2 Hz, $^{2}J_{2ax,2eq}$ = 17.6 Hz, 1 H, H-2_{eq}), 2.26 (ddd, $^{3}J_{1ax,2ax}$ = 11.3 Hz, $^{3}J_{1eq,2ax}$ = 7.2 Hz, $^{2}J_{2ax,2eq}$ = 17.6 Hz, 1 H, H-2_{ax}), 3.19 (ddd, $^{2}J_{1ax,1eq}$ = 11.9 Hz, $^{3}J_{1ax,2eq}$ = 3.4 Hz, $^{3}J_{1ax,2ax}$ = 11.3 Hz, 1 H, H-1_{ax}), 3.63 (ddd, $^{2}J_{1ax,1eq}$ = 11.9 Hz, $^{3}J_{1eq,2eq}$ = 2.2 Hz, $^{3}J_{1eq,2ax}$ = 7.2 Hz, 1 H, H-1_{eq}), 3.94 (q, $^{3}J_{5,6}$ = 6.3 Hz, H-5), 4.78 (d, ^{2}J = 1.8 Hz, 1 H, CH_2-H_a), 6.01 (d, ^{2}J = 1.8 Hz, 1 H, CH_2-H_b);

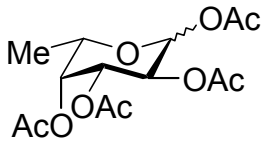
^{13}C NMR (125 MHz, C_6D_6): δ 18.6 (C-6), 38.8 (C-2), 62.5 (C-1), 73.5 (C-5), 117.7 (C=$\underline{C}H_2$), 148.8 (C-4), 193.9 (C-3).

115:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (d, J = 6.5 Hz, 3 H, H-6), 1.28 (d, J = 6.3 Hz, 3 H, H-15), 1.59 (m, 1 H, H-8_a), 1.94 (m, 1 H, H-8_b), 2.00 (m, 1 H, H-7_a), 2.14 (m, 1 H, H-2_a), 2.22 (ddd, J = 2.0 Hz, 5.2 Hz, 13.3 Hz, 1 H, H-7_b), 2.27 (m, 1 H, H-2_b), 2.45 (ddd, J = 2.3 Hz, 3.4 Hz, 13.7 Hz, 1 H, H-11_a), 2.84 (ddd, J = 7.2 Hz, 11.4 Hz, 13.7 Hz, 1 H, H-11_b), 3.71 (q, J = 6.3 Hz, 1 H, H-14), 3.73 (ddd, J = 7.9 Hz, 8.1 Hz, 11.3 Hz, 1 H, H-12_a), 3.76 (ddd, J = 4.6 Hz, 7.9 Hz, 11.2 Hz, 1 H, H-1_a), 3.97 (ddd, J = 4.4 Hz, 5.6 Hz, 11.2 Hz, 1 H, H-1_b), 4.10 (q, J = 6.5 Hz, 1H, H-5), 4.18 (m, 1 H, H-12_b);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (C-15), 17.5 (C-8), 19.6 (C-6), 22.4 (C-7), 29.7 (C-2), 40.1 (C-11), 62.2 (C-1), 66.9 (C-12), 71.2 (C-5), 79.7 (C-14), 83.7 (C-9), 106.5 (C-4), 143.9 (C-3), 205.1 (C-10).

1,2,3,4-Tetra-*O*-acetyl-L-fucopyranoside (91) (l-123, cm032):



A solution of L-fucose (1.00 g, 6.10 mmol) in dry pyridine (10 ml) and acetic anhydride (5 ml) was stirred at room temperature for 7 h. After dilution with ethyl acetate (100 ml), the mixture was washed with water (50 ml), 10% HCl (2 x 50 ml) and satd. aqueous $NaHCO_3$ (50 ml). Evaporation of the solvent and chromatography on silica gel (petroleum ether/ethyl acetate 3:1) yielded **91** (1.92 g, 5.8 mmol, 95 %, α:β = 5:1).

R_f = 0.65 (petroleum ether/ethyl acetate 1:1);

91-α:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6), 2.01, 2.02, 2.14, 2.17 (4 s, 12 H, 4 CH_3CO), 4.27 (dq, $^3J_{4,5}$ = 0.7 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5), 5.34 (m, 3 H, H-2, H-3, H-4), 6.35 (d, $^3J_{1,2}$ = 2.8 Hz, H-1);

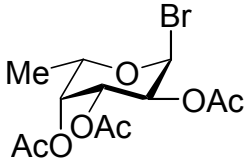
^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6), 20.9, 21.0, 21.2, 21.4 (4 CH_3), 66.8 (C-3), 67.6 (C-5), 68.2 (C-4), 70.9 (C-2), 90.3 (C-1), 169.5, 169.8, 170.4, 170.9 (4 COO);

91-β:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{5,6}$ = 6.7 Hz, 3 H, H-6), 1.98, 2.04, 2.12, 2.19 (4 s, 12 H, 4 CH_3CO), 3.95 (dq, $^3J_{4,5}$ = 1.1 Hz, $^3J_{5,6}$ = 6.7 Hz, 1 H, H-5), 5.34 (m, 3 H, H-2, H-3, H-4), 5.64 (d, $^3J_{1,2}$ = 8.4 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5 (C-6), 21.0, 21.1, 21.3, 21.4 (4 CH_3), 68.3 (C-3), 70.3 (C-5), 70.6 (C-4), 71.6 (C-2), 92.5 (C-1), 169.8, 170.3, 170.6, 170.9 (4 COO).

2,3,4-Tri-*O*-acetyl-α-L-fucopyranosylbromide (92) (l-127, cm036):



To a solution of **91** (720 mg, 2.20 mmol) in CH_2Cl_2 (10 ml), HBr/HOAc (33%, 4 ml) in CH_2Cl_2 (4 ml) was added dropwise at 0°C. The mixture

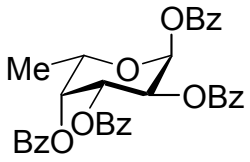
was stirred for 15 min at 0°C and further 2 h at room temperature. Dilution with CH_2Cl_2 (50 ml) followed by washing of the organic layer with water (50 ml) and satd. aqueous $KHCO_3$ (2 x 50 ml) gave, after drying with Na_2SO_4 and evaporation of the solvent, 0.830 g crude product. Column chromatography (petroleum ether/ethyl acetate 3:1) yielded α-L-fucosylbromide (**92**) (760 mg, 1.86 mmol, 86%).

R_f = 0.45 (petroleum ether / ethyl acetate 3:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, H-6), 2.03, 2.10, 2.18 (3 s, 9 H, 3 CH_3CO), 4.40 (dq, $^3J_{4,5}$ = 1.4 Hz, $^3J_{5,6}$ = 6.5 Hz, 1 H, H-5), 5.02 (dd, $^3J_{1,2}$ = 4.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1 H, H-2), 5.36 (dd, $^3J_{3,4}$ = 3.2 Hz, $^3J_{4,5}$ = 1.4 Hz, 1 H, H-4), 5.41 (dd, $^3J_{2,3}$ = 10.4 Hz, $^3J_{3,4}$ = 3.2 Hz, 1 H, H-3), 6.69 (d, $^3J_{1,2}$ = 4.0 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6 (C-6), 20.4, 20.6, 20.7 (3 CH_3), 67.8, 68.7, 69.6, 69.9 (C-2, C-3, C-4, C-5), 89.4 (C-1), 169.7, 169.9, 170.3 (3 CO).

1,2,3,4-Tetra-*O*-benzoyl-α-L-fucopyranoside (93) (II-48, cm101):



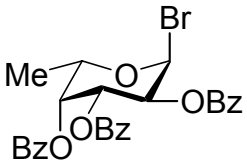
L-fucose (1.60 g, 9.76 mmol) was dissolved in pyridine (25 ml) under argon and cooled to 0°C. Benzoylchloride (6.88 g, 5.70 ml, 49.0 mmol) was added dropwise and the reaction mixture was stirred for 3 h at 0°C and for 1 h at room temperature. Dilution with ethyl acetate (100 ml), washing of the organic phase with satd. aqueous $NaHCO_3$ (3 x 100 ml), 10% HCl (3 x 100 ml) and sat. $CuSO_4$ (3 x 50 ml), drying with Na_2SO_4, filtration and evaporation of the solvent gave a yellow foam. Purification by silica gel chromatography (petroleum ether/ethyl acetate 6:1) and recrystallization from hot ethanol yielded **93** (5.43 g, 9.36 mmol, 96 %).

R_f = 0.35 (petroleum ether/ethyl acetate 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, CH_3), 4.64 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.5 Hz, 1 H, H-5), 5.90 (dd, $^3J_{3,4}$ = 3.0 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4), 6.00 (dd, $^3J_{1,2}$ = 3.6 Hz,

$^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 6.07 (dd, $^3J_{2,3}$ = 10.7 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, H-3), 6.88 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, H-1), 7.20-8.20 (m, 20 H, 4 C_6H_5).

2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosylbromide (94) (II-13, cm068):



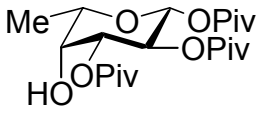
Under argon, **93** (3.82 g, 6.58 mmol) was dissolved in CH_2Cl_2 (15 ml) and cooled to 0°C. HBr/HOAc (7 ml, 35.0 mmol) was added dropwise over a period of 15 min. The ice bath was removed and the reaction mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (100 ml) and washed with water (60 ml) and satd. aqueous $NaHCO_3$ (60 ml). After drying of the organic layer with Na_2SO_4, filtration and evaporation of the solvent, **94** (3.46 g, 6.41 mmol, 97.5 %) was obtained.

R_f = 0.76 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6), 4.68 (dq, $^3J_{4,5}$ = 2.0 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5), 5.62 (dd, $^3J_{1,2}$ = 3.7 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 5.84 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 2.0 Hz, 1 H, H-4), 6.01 (dd, $^3J_{2,3}$ = 10.1 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3), 6.94 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, H-1), 7.16-8.23 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2 (C-6), 69.0 (C-2), 69.6 (C-3), 70.8 (C-5), 71.2 (C-4), 89.8 (C-1), 128.2, 128.9, 129.0, 130.1, 130.3, 130.4, 131.3, 131.7, 132.1, 133.7, 134.0, 134.1 (18 C, 3 C_6H_5), 164.8, 165.3, 165.6 (3 CO).

1,2,3-Tri-*O*-pivaloyl-β-L-fucopyranoside (95) (II-51, cm104):



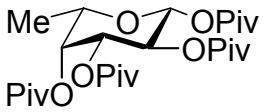
To a solution of L-fucose (500 mg, 3.05 mmol) in pyridine (10 ml), pivaloylchloride (1.84 g, 1.88 ml, 15.2 mmol) was added dropwise at 0°C. After stirring at 0°C for 2 h, at room temperature for 16 h and at 50°C for 4 h, the reaction was diluted with CH_2Cl_2 (50 ml). Washing of the organic layer with sat. aqueous $NaHCO_3$ (3 x 50 ml), 10% HCl (3 x 50 ml) and sat. aqueous $CuSO_4$ (2 x 50 ml), drying with Na_2SO_4, filtration and evaporation of the solvent lead to the crude product, which was purified

by silica gel chromatography (petroleum ether/ethyl acetate 4:1) to yield **95** (750 mg, 1.80 mmol, 59%).

R_f = 0.29 (petroleum ether/ethyl acetate 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06, 1.12, 1.14 (3 s, 27 H, 3 CMe_3), 1.28 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6), 3.79 (dq, $^3J_{4,5}$ = 1.0 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5), 3.82 (dd, $^3J_{3,4}$ = 3.2 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, H-4), 4.92 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.34 (dd, $^3J_{1,2}$ = 8.1 Hz, $^3J_{2,3}$ = 10.3 Hz, 1 H, H-2), 5.58 (d, $^3J_{1,2}$ = 8.1 Hz, 1 H, H-1).

1,2,3,4-Tetra-*O*-pivaloyl-β-L-fucopyranoside (96) (II-52, cm105):



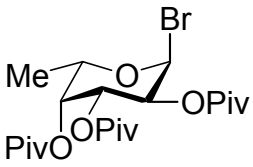
95 (700 mg, 1.68 mmol) and DMAP (82.0 mg, 0.670 mmol) were dissolved in pyridine (8 ml). At room temperature pivaloylchloride (608 mg, 620 µl, 5.04 mmol) was added slowly and the reaction was stirred at 70 °C for 24 h and at room temperature for 48 h. Completion of the reaction was monitored by TLC. Work-up was performed as in the previous reaction (→ **95**). Crystallization of the crude product from hot ethanol yielded crystalline **96** (801 mg, 1.60 mmol, 95 %).

R_f = 0.60 (petroleum ether/ethyl acetate 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12, 1.13 (2 s, 18 H, 2 CMe_3), 1.18 (d, $^3J_{5,6}$ = 6.0 Hz, 3 H, CH_3), 1.21, 1.30 (2 s, 18 H, 2 CMe_3), 3.95 (dq, $^3J_{4,5}$ = 0.6 Hz, $^3J_{5,6}$ = 6.0 Hz, 1 H, H-5), 5.14 (dd, $^3J_{2,3}$ = 10.4 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, H-3), 5.26 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{4,5}$ = 0.6 Hz, 1 H, H-4), 5.35 (dd, $^3J_{1,2}$ = 8.2 Hz, $^3J_{2,3}$ = 10.4 Hz, 1 H, H-2), 5.79 (d, $^3J_{1,2}$ = 8.2 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6), 27.3, 27.4, 27.5, 27.6 (12 C, 4 C$\underline{Me}_3$), 39.1, 39.2, 39.3, 39.5 (4 $\underline{C}Me_3$), 68.1 (C-3), 70.1 (C-5), 70.7 (C-4), 71.8 (C-2), 92.6 (C-1), 176.9, 177.2, 177.6, 177.8 (4 COO).

2,3,4-Tri-*O*-pivaloyl-α-L-fucopyranosylbromide (97) (II-53, cm106):

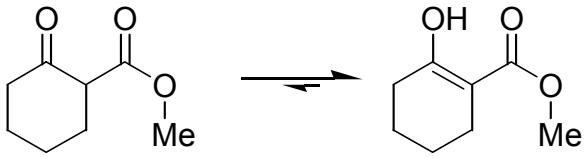


To a solution of **96** (430 mg, 0.870 mmol) in CH_2Cl_2, HBr/HOAc (33%, 1.00 ml) in CH_2Cl_2 (2 ml) was added slowly at 0°C. After stirring at room temperature for 15 h, the mixture was diluted with CH_2Cl_2 (50 ml) followed by washing with water (50 ml) and satd. aqueous $NaHCO_3$ (2 x 50 ml). Evaporation of the solvent delivered **97** (417 mg, 0.870 mmol, 100%), which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (s, 9 H, CMe_3), 1.12 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6), 1.13, 1.21 (2 s, 18 H, 2 CMe_3), 4.36 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5), 4.95 (dd, $^3J_{1,2}$ = 3.7 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 5.31 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4), 5.43 (dd, $^3J_{2,3}$ = 10.7 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3), 6.62 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8 (C-6), 27.1, 27.2, 27.6, 28.2 (4 C$\underline{Me}_3$), 39.0, 39.2, 39.3, 39.7 (4 $\underline{C}Me_3$), 67.7 (C-3), 70.4 (C-5), 70.8 (C-4), 71.5 (C-2), 89.2 (C-1), 175.3, 176.2, 177.5, 177.9 (4 COO).

Methyl 2-oxo-cyclohexanecarboxylate (99) [389] (I-112, cm024):



In a three-necked flask equipped with stirrer, dropping funnel and reflux condenser, NaH (34.9 g, 0.768 mol, 55% suspension in oil) was washed with benzene (3 X 20 ml) under argon. Dimethylcarbonate (71.0 g, 0.537 mol) and benzene (300 ml) were added and the suspension was heated to reflux. Cyclohexanone (25.9 g, 0.264 mol) in benzene (50 ml) was added slowly within 2 h. Stirring was continued until gas evolution ceased. After cooling to room temperature glacial acetic acid (60 ml) was added and the reaction mixture was poured onto ice. The aqueous layer was extracted with benzene (3 x 50 ml). The combined organic layers were washed with brine and dried with Na_2SO_4. Benzene was evaporated under reduced pressure and the remaining oil distilled under reduced pressure (bp: 70-72°C, 1 mbar) yielding **99** (38.4 g, 0.246 mol, 82%) as a colorless oil.

R_f = 0.63 (petroleum ether/ethyl acetate 5:1);

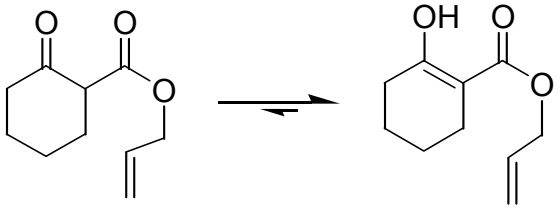
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 2.20 (m, 2 H, CH_2), 2.25 (m, 2 H, $COCH_2$), 3.73 (s, 3 H, OMe), 12.14 (s, 1 H, enol-OH);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 22.7, 22.8 (3 CH_2), 29.4 ($\underline{C}H_2C(OH)=C$), 57.5 (OCH_3), 97.9 ($C(OH)=\underline{C}R_2$), 172.4 (COO), 206.5 (CO).

elemental analysis calcd (%) for $C_8H_{12}O_3$ (156.18): C 61.52, H 7.74, O 30.73;
found: C 61.50, H 7.70, O 30.39.

Allyl 2-oxo-cyclohexanecarboxylate (100)

[390] (I-115, cm026):



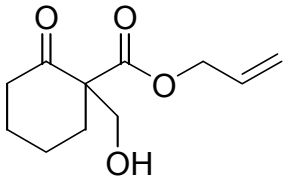
A solution of sodium (15.0 mg, 0.023 mmol) and methyl cyclohexanone-2-carboxylate (**99**) (15.6 g, 0.100 mol) in benzene (10 ml) and allyl alcohol (150 ml) was refluxed for 48 h with continuous removal of methanol. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (200 ml), washed with brine (2 x 20 ml) and dried with Na_2SO_4. Removal of the solvent followed by distillation under reduced pressure (bp: 90°C at 0.04 mbar) afforded the allyl ester **100** (13.3 g, 72.9 mmol, 73%).

R_f = 0.68 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 2.26 (m, 4 H, 2 CH_2), 4.65, 4.66 (m, 2 H, $COOC\underline{H}_2$), 5.24 (dd, J = 10.4 Hz, 1.3 Hz, 1 H, $CH=C\underline{H}_2$-H_a), 5.34 (dd, J = 17.3 Hz, 1.3 Hz, 1 H, $CH=C\underline{H}_2$-H_b), 5.94 (m 1 H, $C\underline{H}=CH_2$), 12.14 (s, 1 H, enol-OH);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 22.4, 22.5 (3 CH_2), 29.2 ($\underline{C}H_2C(OH)=C$), 64.7 ($COO\underline{C}H_2$), 97.6 ($C(OH)=\underline{C}R_2$), 117.8 ($CH=\underline{C}H_2$), 132.3 ($\underline{C}H=CH_2$), 172.3 (COO), 208.5 (CO).

Allyl 1-hydroxymethyl-2-oxo-cyclohexanecarboxylate (101) [308] (I-118, cm029):



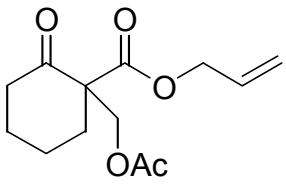
100 (31.0 g, 0.170 mol) was dissolved in a mixture of THF (125 ml), water (90 ml) and allyl alcohol (125 ml). $KHCO_3$ (20.0 g, 0.200 mol) and formaldehyde (36% in water, 16.7 ml, 0.200 mol) were added with stirring at room temperature. After 5 h, a further portion of formalin (5 ml) was added. After 2 h, the mixture was diluted with CH_2Cl_2 (200 ml). Washing with saturated NH_4Cl solution, drying with Na_2SO_4 and removal of the solvent under reduced pressure yielded **101** (36.1 g, 0.170 mol, 100 %), which was used in the next step without further purification.

R_f = 0.12 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60, 2.02, 2.33, 2.44, 2.62 (m, 8 H, 4 CH_2), 3.69, 3.81 (AB, ^2J = 11.4 Hz, 2 H, C$\underline{H_2}$OH), 4.65, 4.66 (m, 2 H, COOC$\underline{H_2}$), 5.23 (dd, J = 10.4 Hz, 1.3 Hz, 1 H, CH=C$\underline{H_2}$-H_a), 5.31 (dd, J = 17.0 Hz, 1.3 Hz, 1 H, CH=C$\underline{H_2}$-H_b), 5.88 (m, 1 H, C$\underline{H}$=CH_2);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 26.7, 32.6, 40.8 (4 CH_2), 62.4 ($C_{quart.}$), 65.9 (COO$\underline{C}H_2$), 66.1 (CH_2OH), 118.8 (CH=$\underline{C}H_2$), 131.3 ($\underline{C}$H=CH_2), 170.0 (COO), 210.4 (CO).

Allyl 1-acetoxymethyl-2-oxo-cyclohexanecarboxylate (102) [308] (I-119, cm030):



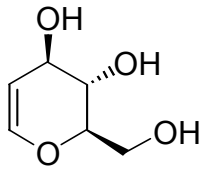
A solution of **101** (36.1 g, 170 mmol) and acetic anhydride (37.0 ml, 360 mmol) in pyridine (100 ml) was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (150 ml) and washed with 1N HCl (3 x 100 ml) followed by satd. $NaHCO_3$ solution (4 x 100 ml). The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate 5:1) to yield **102** (36.0 g, 150 mmol, 88%).

R_f = 0.25 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.78 (m, 4 H, 2 CH_2), 2.00-2.52 (m, 4 H, 2 CH_2), 1.98 (s, 3 H, CH_3), 4.21, 4.46 (AB, ^{2}J = 11.0 Hz, 2 H, C$\underline{H_2}$OH), 4.61, 4.62 (m, 2 H, COOC$\underline{H_2}$), 5.22 (dd, J = 10.4 Hz, 1.3 Hz, 1 H, CH=C$\underline{H_2}$-H_a), 5.29 (dd, J = 17.0 Hz, 1.3 Hz, 1 H, CH=C$\underline{H_2}$-H_b), 5.85 (m, 1 H, C$\underline{H}$=CH_2);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1 (CH_3), 22.3, 27.5, 33.9, 41.3 (4 CH_2), 60.9 ($C_{quart.}$), 66.0 (COO$\underline{C}H_2$), 66.6 (CH_2-OH), 119.5 (CH=$\underline{C}H_2$), 131.6 ($\underline{C}$H=CH_2), 169.8 ($\underline{C}OCH_3$), 170.8 (COO), 205.9 (CO).

1,5-Anhydro-2-deoxy-D-*arabino*-hex-1-enitol (105) (II-95, cm148):

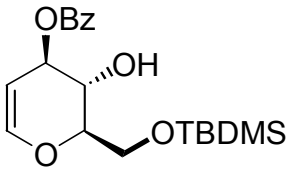


3,4,5-tri-*O*-acetyl-D-glucal (10.0 g, 36.7 mmol) was dissolved in methanol (60 ml). After adding NaOMe/MeOH (1 ml, 1 M), the reaction mixture was stirred at room temperature for 2 h and then neutralized with amberlyste ion-exchange resin (H^+ form). Filtration through celite, evaporation of the solvent and drying under vacuum yielded **105** (5.40 g, 36.7 mmol, 100%), which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63 (dd, $^3J_{3,4}$ = 7.1 Hz, $^3J_{4,5}$ = 9.7 Hz, 1 H, H-4), 3.76 (ddd, $^3J_{4,5}$ = 9.7 Hz, $^3J_{5,6a}$ = 4.9 Hz, $^3J_{5,6b}$ = 2.7 Hz, 1 H, H-5), 3.83 (dd, $^3J_{5,6a}$ = 4.9 Hz, $^3J_{6a,6b}$ = 12.1 Hz, 1 H, H-6_a), 3.90 (dd, $^3J_{5,6b}$ = 2.7 Hz, $^3J_{6a,6b}$ = 12.1 Hz, 1 H, H-6_b), 4.17 (dd, $^3J_{2,3}$ = 2.2 Hz, $^3J_{3,4}$ = 7.1 Hz, 1 H, H-3), 4.70 (dd, $^3J_{1,2}$ = 6.0 Hz, $^3J_{2,3}$ = 2.2 Hz, 1 H, H-2), 6.34 (dd, $^3J_{1,2}$ = 6.0 Hz, $^4J_{1,3}$ = 1.6 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 62.8 (C-6), 71.0 (C-4), 71.4 (C-3), 79.0 (C-5), 104.8 (C-2), 145.5 (C-1).

1,5-Anhydro-3-*O*-benzoyl-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-D-*arabino*-hex-1-enitol (106) (II-128, cm184):



105 (5.40 g, 37.0 mmol) was dissolved in a mixture of pyridine (75 ml) and CH_2Cl_2 (15 ml) and cooled to 0°C. TBDMSCl (6.13 g, 40.7 mmol) in CH_2Cl_2 (30 ml) was added dropwise over a period of 2 h. The reaction mixture was stirred for 2 h at 0°C and 12 h at room temperature. Since the starting material had not

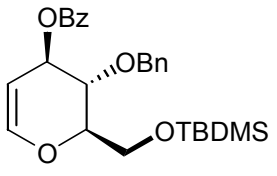
been used completely in the reaction, an additional portion of TBDMSCl (1.67 g, 11.1 mmol) in CH_2Cl_2 (10 ml) was added at 0°C. After stirring for 1 h at 0°C and 12 h at room temperature, the mixture was cooled to 0°C again and benzoylchloride (4.30 ml, 37.0 mmol) in CH_2Cl_2 (15 ml) was added dropwise. The ice cooling was removed and the reaction mixture stirred overnight. The reaction was then diluted with CH_2Cl_2 (250 ml), washed with 5% aqueous HCl (3 x 100 ml), and with satd. aqueous $NaHCO_3$ (3 x 200 ml). The organic layer was dried with Na_2SO_4 and evaporated. The crude material was purified on a silica gel column (petroleum ether/ethyl acetate 9:1) and **106** was obtained as a slightly yellow oil (10.1 g, 27.9 mmol, 75%).

R_f = 0.32 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 6 H, 2 Si-CH_3), 0.81 (s, 9 H, Si-C$\underline{Me}_3$), 3.43 (s, 1 H, OH), 3.81-3.94 (m, 3 H, H-5, H-6_{a+b}), 4.03 (dd, $^3J_{3,4}$ = 6.6 Hz, $^3J_{4,5}$ = 6.7 Hz, 1 H, H-4), 4.72 (dd, $^3J_{1,2}$ = 6.0 Hz, $^3J_{2,3}$ = 2.5 Hz, 1 H, H-2), 5.44 (dd, $^3J_{2,3}$ = 2.5 Hz, $^3J_{3,4}$ = 6.7 Hz, 1 H, H-3), 6.38 (d, $^3J_{1,2}$ = 6.0 Hz, 1 H, H-1), 7.25-7.98 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.9 (2 C, 2 Si-CH_3), 18.8 (Si-$\underline{C}Me_3$), 26.2 (3 C, Si-C$\underline{Me}_3$), 63.2 (C-6), 68.8 (C-4), 74.0 (C-3), 78.2 (C-5), 99.2 (C-2), 128.7, 130.2, 130.3, 133.6 (6 C, C_6H_5), 146.6 (C-1), 167.9 (CO).

1,5-Anhydro-3-*O*-benzoyl-4-*O*-benzyl-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-D-*arabino*-hex-1-enitol (107) (II-185, cm242):



NaH (3.04 g, 69.6 mmol, 55% suspension in oil) was washed with hexane (3 x 10 ml) under argon and was suspended in DMF (100 ml). Benzylbromide (9.14 ml, 75.4 mmol) was added. **106** (21.1 g, 58.8 mmol) was dissolved in DMF (100 ml) and added dropwise to the NaH suspension within 45 min. The mixture was stirred until TLC control showed complete consumption of the starting material (2 h). The reaction was quenched with MeOH (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was dried with Na_2SO_4, evaporated and purified on a silica gel column (petroleum ether/ethyl acetate 7:1) to obtain **107** (21.1 g, 46.4 mmol, 80%).

R_f = 0.58 (petroleum ether/ethyl acetate 6:1);

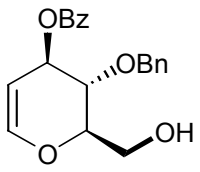
$[\alpha]_D^{21}$ = -106.0 (c = 1.85, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02, 0.03 (2 s, 6 H, 2 Si-CH_3), 0.82 (s, 9 H, Si-C$\underline{Me}_3$), 3.85-4.02 (m, 4 H, H-4, H-5, H-6_{a+b}), 4.67, 4.71 (AB, $^2J_{A,B}$ = 11.4 Hz, 2 H, C$\underline{H}_2$-Ph), 4.79 (dd, $^3J_{1,2}$ = 6.0 Hz, $^3J_{2,3}$ = 3.1 Hz, 1 H, H-2), 5.58 (m, 1 H, H-3), 6.39 (d, $^3J_{1,2}$ = 6.0 Hz, 1 H, H-1), 7.06-7.98 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.9, -4.8 (2 C, 2 Si-CH_3), 18.8 (Si-$\underline{C}Me_3$), 26.2 (3 C, Si-C$\underline{Me}_3$), 61.6 (C-6), 71.0 (C-3), 73.2 ($\underline{C}H_2$-Ph), 73.9 (C-4), 78.3 (C-5), 99.0 (C-2), 128.1, 128.3, 128.7, 128.8, 130.0, 130.5, 133.4, 138.3 (12 C, 2 C_6H_5), 146.4 (C-1), 166.5 (CO).

elemental analysis calcd (%) for $C_{26}H_{34}O_5Si$ (454.64): C 68.69, H 7.54, O 17.60;
found: C 68.43, H 7.56.

1,5-Anhydro-3-*O*-benzoyl-4-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (108) (II-187, cm244):



To a solution of **107** (200 mg, 0.440 mmol) in THF (5 ml) TBAF (1 M in THF, 830 µl) was added dropwise under vigorous stirring at 0°C under argon. The mixture was then stirred 1 h at 0°C and 2 h at room temperature, diluted with CH_2Cl_2 (20 ml), washed with satd. aqueous $NaHCO_3$ (50 ml), dried with Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography (petroleum ether/ethyl acetate 3:1) yielded **108** (127 mg, 0.370 mmol, 84%).

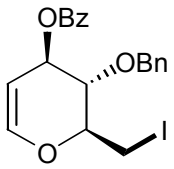
R_f = 0.17 (petroleum ether/ethyl acetate 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (s, 1 H, OH), 3.93 (dd, $^3J_{5,6a}$ = 2.8 Hz, $^2J_{6a,6b}$ = 11.9 Hz, 1 H, H-6_a), 3.97 (dd, $^3J_{5,6b}$ = 3.7 Hz, $^2J_{6a,6b}$ = 11.9 Hz, 1 H, H-6_b), 4.06 (m, 2 H, H-4, H-5), 4.72,

4.78 (AB, $^2J_{A,B}$ = 11.3 Hz, 2 H, C$\underline{H}_2$-Ph), 4.89 (dd, $^3J_{1,2}$ = 5.9 Hz, $^3J_{2,3}$ = 2.8 Hz, 1 H, H-2), 5.73 (m, 1 H, H-3), 6.46 (d, $^3J_{1,2}$ = 5.9 Hz, 1 H, H-1), 7.22-8.01 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 61.7 (C-6), 72.3 (C-3), 73.6 (C-4), 74.1 ($\underline{C}H_2$-Ph), 78.3 (C-5), 100.2 (C-2), 128.3, 128.4, 128.9, 129.0, 130.0, 130.4, 133.6, 138.0 (12 C, 2 C_6H_5), 146.0 (C-1), 166.5 (CO).

1,5-Anhydro-3-*O*-benzoyl-4-*O*-benzyl-2,6-dideoxy-6-iodo-D-*arabino*-hex-1-enitol (109) (II-191, cm248):



Imidazole (3.28 g, 48.2 mmol), PPh_3 (11.1 g, 42.8 mmol) and **108** (8.70 g, 25.6 mmol) were dissolved in CH_2Cl_2 (250 ml) under argon and cooled to 0°C. Iodine (9.78 g, 38.5 mmol) was added and the reaction mixture was stirred for 30 min at 0°C and 10 h at room temperature. Diluting with CH_2Cl_2 (250 ml), washing with satd. aqueous $NaHCO_3$ (200 ml), drying with Na_2SO_4, evaporation of the solvent under reduced pressure and silica gel column chromatography (petroleum ether/ethyl acetate 7:1) yielded **109** (9.66 g, 21.5 mmol, 84 %).

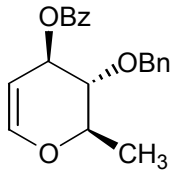
R_f = 0.66 (petroleum ether/ethyl acetate 4:1);

$[\alpha]_D^{21}$ = -41.8 (c = 1.03, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.57 (dd, $^3J_{5,6a}$ = 4.7 Hz, $^2J_{6a,6b}$ = 10.7 Hz, 1 H, H-6_a), 3.61 (dd, $^3J_{5,6b}$ = 4.7 Hz, $^2J_{6a,6b}$ = 10.7 Hz, 1 H, H-6_b), 3.85 (dt, $^3J_{4,5}$ = 7.5 Hz, $^3J_{5,6a}$ = 4.7 Hz, $^3J_{5,6b}$ = 4.7 Hz, 1 H, H-5), 4.07 (dd, $^3J_{3,4}$ = 5.6 Hz, $^3J_{4,5}$ = 7.5 Hz, 1 H, H-4), 4.77, 4.83 (AB, $^2J_{A,B}$ = 11.0 Hz, 2 H, C$\underline{H}_2$-Ph), 4.95 (dd, $^3J_{1,2}$ = 5.9 Hz, $^3J_{2,3}$ = 2.8 Hz, 1 H, H-2), 5.71 (dd, $^3J_{2,3}$ = 2.8 Hz, $^3J_{3,4}$ = 5.6 Hz, 1 H, H-3), 6.49 (d, $^3J_{1,2}$ = 5.9 Hz, 1 H, H-1), 7.30-8.05 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 5.89 (C-6), 71.3 (C-3), 74.3 ($\underline{C}H_2$-Ph), 75.9 (C-5), 76.5 (C-4), 100.0 (C-2), 128.5, 128.6, 128.9, 130.6, 131.9, 132.7, 133.0, 137.8 (12 C, 2 C_6H_5), 145.8 (C-1), 166.4 (CO).

1,5-Anhydro-3-*O*-benzoyl-4-*O*-benzyl-2,6-dideoxy-D-*arabino*-hex-1-enitol (110) (II-106, cm160):



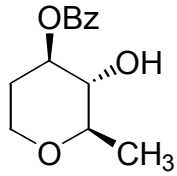
To a solution of **109** (400 mg, 0.890 mmol) in benzene (25 ml), AIBN (15.0 mg, 0.090 mmol) and Bu_3SnH (388 mg, 353 µl, 1.33 mmol) were added and the reaction was stirred under reflux for 20 h. Benzene was removed under reduced pressure, the remaining oil dissolved in acetonitrile and washed with hexane (3 x 20 ml). After concentration of the acetonitrile layer, purification by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) yielded **110** (150 mg, 0.460 mmol, 52%).

R_f = 0.37 (petroleum ether/ethyl acetate 8:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, CH_3), 3.71 (dd, $^3J_{3,4}$ = 5.6 Hz, $^3J_{4,5}$ = 7.8 Hz, 1 H, H-4), 4.15 (dq, $^3J_{4,5}$ = 7.8 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5), 4.70, 4.79 (AB, $^2J_{A,B}$ = 11.3 Hz, 2 H, C$\underline{H}_2$-Ph), 4.89 (dd, $^3J_{1,2}$ = 5.9 Hz, $^3J_{2,3}$ = 3.1 Hz, 1 H, H-2), 5.66 (dd, $^3J_{2,3}$ = 3.1 Hz, $^3J_{3,4}$ = 5.6 Hz, 1 H, H-3), 6.45 (d, $^3J_{1,2}$ = 5.9 Hz, 1 H, H-1), 7.28-8.03 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2 (C-6), 71.0 (C-3), 73.5 ($\underline{C}H_2$-Ph), 73.8 (C-5), 78.0 (C-4), 99.0 (C-2), 127.8, 128.1, 128.4, 128.5, 129.6, 130.2, 133.1, 137.8 (12 C, 2 C_6H_5), 146.0 (C-1), 166.1 (CO).

1,5-Anhydro-3-*O*-benzyl-2,6-dideoxy-D-*arabino*-hexitol (111) (II-176, cm233):



Under argon, **120** (3.25 mg, 9.96 mmol) was dissolved in methanol (12 ml). $Pd(OH)_2$/C (200 mg, 0.290 mmol) was added and the suspension was hydrogenated (4 bar H_2) at room temperature for 21 h. The reaction mixture was filtered through celite and evaporated. Purification of the crude product by silica gel column chromatography yielded **111** (2.26 g, 9.56 mmol, 97 %).

R_f = 0.55 (petroleum ether/ethyl acetate 2:1);

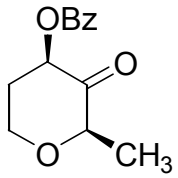
$[\alpha]_D^{21}$ = -16.6 (c = 1.00, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, $^3J_{5,6}$ = 5.9 Hz, 3 H, CH_3), 1.83 (dddd, $^3J_{1ax,2ax}$ = 11.6 Hz, $^3J_{1eq,2ax}$ = 5.0 Hz, $^2J_{2ax,2eq}$ = 12.8 Hz, $^3J_{2ax,3}$ = 11.3 Hz, 1 H, H-2_{ax}), 2.13 (dddd, $^3J_{1ax,2eq}$ = 2.0 Hz, $^3J_{1eq,2eq}$ = 1.6 Hz, $^2J_{2eq,2ax}$ = 12.8 Hz, $^3J_{2eq,3}$ = 5.2 Hz, 1 H, H-2_{eq}), 2.99 (s, 1H, OH), 3.32 (dq, $^3J_{4,5}$ = 8.9 Hz, $^3J_{5,6}$ = 5.9 Hz, 1 H, H-5), 3.37 (dd, $^3J_{3,4}$ = 8.7 Hz, $^3J_{4,5}$ = 8.9 Hz, 1 H, H-4), 3.51 (ddd, $^2J_{1ax,1eq}$ = 11.8 Hz, $^3J_{1ax,2ax}$ = 11.6 Hz, $^3J_{1ax,2eq}$ = 2.0 Hz, 1 H, H-1_{ax}), 3.94 (ddd, $^2J_{1eq,1ax}$ = 11.8 Hz, $^3J_{1eq,2eq}$ = 1.6 Hz, $^3J_{1eq,2ax}$ = 5.0 Hz, 1 H, H-1_{eq}), 5.00 (ddd, $^3J_{2ax,3}$ = 11.3 Hz, $^3J_{2eq,3}$ = 5.2 Hz, $^3J_{3,4}$ = 8.7 Hz, 1 H, H-3), 7.27-8.06 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.5 (C-6), 31.7 (C-2), 65.5 (C-1), 75.7 (C-3), 76.7 (C-4), 77.7 (C-5), 128.8, 130.1, 130.2, 133.6 (6 C, C_6H_5), 167.4 (CO);

elemental analysis calcd (%) for $C_{13}H_{16}O_4$ (236.27): C 66.09, H 6.83, O 27.09;
found: C 66.10, H 6.72, O 27.18.

1,5-Anhydro-3-*O*-benzyl-2,6-dideoxy-D-*threo*-hex-4-ulose



(112) (II-180, cm237):

Under argon, **111** (140 mg, 0.590 mmol) was dissolved in CH_2Cl_2 (5 ml) containing 3Å molecular sieves and cooled to 0°C. After 5 min, glacial acetic acid (1 drop) was added and the mixture was stirred for further 10 min before PDC (240 mg, 0.640 mmol) was added. After stirring for 15 min at 0°C and 8 h at room temperature, the reaction was stopped by filtration through celite and washing with satd. aqueous $CuSO_4$ (50 ml) and satd. aqueous NaCl (20 ml). Drying of the organic layer with Na_2SO_4, filtration, evaporation of the solvents and purification by silica gel chromatography (petroleum ether/ethyl acetate 3:1) yielded **112** (130 mg, 0.550 mmol, 93%).

R_f = 0.61 (petroleum ether/ethyl acetate 2:1);

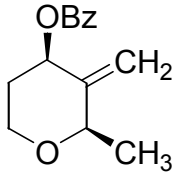
$[\alpha]_D^{21}$ = +34.7 (c = 1.01, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, CH_3), 2.42 (dddd, $^3J_{1ax,2ax}$ = 12.3 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, $^2J_{2ax,2eq}$ = 12.7 Hz, $^3J_{2ax,3}$ = 12.5 Hz, 1 H, H-2_{ax}), 2.53 (dddd, $^3J_{1ax,2eq}$ = 2.0 Hz, $^3J_{1eq,2eq}$ = 1.7 Hz, $^2J_{2eq,2ax}$ = 12.7 Hz, $^3J_{2eq,3}$ = 7.0 Hz, 1 H, H-2_{eq}), 3.97 (ddd, $^2J_{1ax,1eq}$ = 12.1 Hz, $^3J_{1ax,2ax}$ = 12.3 Hz, $^3J_{1ax,2eq}$ = 2.0 Hz, 1 H, H-1_{ax}), 4.08 (q, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5), 4.18 (ddd, $^2J_{1eq,1ax}$ = 12.1 Hz, $^3J_{1eq,2eq}$ = 1.7 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, 1 H, H-1_{eq}), 5.64 (dd, $^3J_{2ax,3}$ = 12.5 Hz, $^3J_{2eq,3}$ = 7.0 Hz, 1 H, H-3), 7.43-8.13 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (C-6), 35.4 (C-2), 65.6 (C-1), 74.7 (C-3), 79.1 (C-5), 128.8, 130.3, 130.4, 133.7 (6 C, C_6H_5), 165.8 (COO), 200.9 (CO);

elemental analysis calcd (%) for $C_{13}H_{14}O_4$ (234.25): C 66.66, H 6.02, O 27.32;
found: C 66.49, H 6.07, O 27.44.

1,5-Anhydro-3-*O*-benzyl-4-methylene-2,4,6-trideoxy-D-*threo*-hexitol (113) (II-183, cm240):



Under argon, $MePPh_3Br$ (911 mg, 2.55 mmol) was suspended in THF (5 ml) and cooled to -40 °C. *n*-BuLi (1.6 M in hexane, 1.60 ml, 2.55 mmol) was added dropwise by a syringe and the reaction was stirred for 2 h at -40 °C. A solution of **112** (200 mg, 0.850 mmol) in THF (5 ml) was added carefully. The mixture was stirred for 1 h at –40 °C and 18 h at –5°C, quenched with satd. aqueous NH_4Cl (50 ml), extracted with CH_2Cl_2 (2 x 100 ml), dried with Na_2SO_4, filtered and concentrated. Purification on a silica gel column (petroleum ether/ethyl acetate 2:1) yielded **113** (100 mg, 0.430 mmol, 50%) as well as **114** (11.0 mg, 0.090 mmol, 10%).

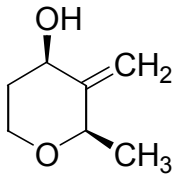
R_f = 0.77 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, CH_3), 1.94 (dddd, $^3J_{1ax,2ax}$ = 12.2 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, $^2J_{2ax,2eq}$ = 12.2 Hz, $^3J_{2ax,3}$ = 11.3 Hz, 1 H, H-2_{ax}), 2.19 (dddd, $^3J_{1ax,2eq}$ = 2.0 Hz, $^3J_{1eq,2eq}$ = 2.0 Hz, $^2J_{2eq,2ax}$ = 12.2 Hz, $^3J_{2eq,3}$ = 5.3 Hz, 1 H, H-2_{eq}), 3.76 (ddd, $^2J_{1ax,1eq}$ = 11.8 Hz, $^3J_{1ax,2ax}$ = 12.2 Hz, $^3J_{1ax,2eq}$ = 2.0 Hz, 1 H, H-1_{ax}), 3.98 (q, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5), 4.10 (ddd, $^2J_{1eq,1ax}$ = 11.8 Hz, $^3J_{1eq,2eq}$ = 2.0 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, 1 H, H-1_{eq}), 5.01 (d, ^2J = 1.9

Hz, 1 H, CH_2-H_a), 5.10 (d, ^2J = 1.9 Hz, 1 H, CH_2-H_b), 5.63 (dd, $^3J_{2ax,3}$ = 11.3 Hz, $^3J_{2eq,3}$ = 5.3 Hz, 1 H, H-3), 7.26-8.16 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8 (C-6), 34.9 (C-2), 65.6 (C-1), 72.7 (C-3), 74.4 (C-5), 105.9 (C=$\underline{C}H_2$), 128.8, 130.0, 130.1, 133.6 (6 C, C_6H_5), 146.3 (C-4), 165.9 (COO).

1,5-Anhydro-4-methylene-2,4,6-trideoxy-D-*threo*-hexitol (114):



Method A (II-194, cm250)**:** Under an atmosphere of argon, **113** (79.0 mg, 0.340 mmol) was dissolved in MeOH (5 ml) and NaOMe/MeOH (1 M, 100 µl), was added at room temperature. The mixture was stirred for 19 h, neutralized with amberlyste ion-exchange resin (H^+ form), filtered and evaporated under reduced pressure. Purification by silica gel chromatography yielded **114** (32.0 mg, 0.260 mmol, 75%).

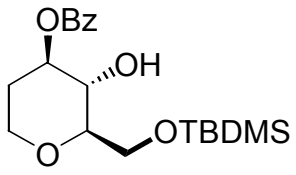
Method B (II-196, cm252)**:** Under an atmosphere of argon, **112** (200 mg, 0.850 mmol) was dissolved in THF (10 ml) and cooled to –40°C. Tebbe reagent (0.5 M in THF, 5 ml, 2.55 mmol) was added dropwise by a syringe. The reaction mixture was then stirred for 2 h at –40 °C and 3 h at –5 °C. Remaining Tebbe reagent was quenched at 0°C with satd. aqueous NH_4Cl (100 ml) and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). After drying with Na_2SO_4, filtration and evaporation of the solvent, purification of the crude product by silica gel column chromatography (petroleum ether/ethyl acetate 2:1) yielded **114** (61.0 mg, 0.510 mmol, 60%).

R_f = 0.15 (petroleum ether/ethyl acetate 2:1);

^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, CH_3), 1.66 (dddd, $^3J_{1ax,2ax}$ = 12.0 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, $^2J_{2ax,2eq}$ = 12.2 Hz, $^3J_{2ax,3}$ = 11.3 Hz, 1 H, H-2_{ax}), 2.07 (dddd, $^3J_{1ax,2eq}$ = 2.2 Hz, $^3J_{1eq,2eq}$ = 1.7 Hz, $^2J_{2eq,2ax}$ = 12.2 Hz, $^3J_{2eq,3}$ = 5.3 Hz, 1 H, H-2_{eq}), 3.63 (ddd, $^2J_{1ax,1eq}$ = 11.7 Hz, $^3J_{1ax,2ax}$ = 12.0 Hz, $^3J_{1ax,2eq}$ = 2.2 Hz, 1 H, H-1_{ax}), 3.83 (q, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5), 4.01 (ddd, $^2J_{1eq,1ax}$ = 11.7 Hz, $^3J_{1eq,2eq}$ = 1.7 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, 1 H, H-1_{eq}), 4.23 (dd, $^3J_{2ax,3}$ = 11.3 Hz, $^3J_{2eq,3}$ = 5.2 Hz, 1 H, H-3), 4.98 (d, ^2J = 1.8 Hz, 1 H, CH_2-H_a), 5.16 (d, ^2J = 1.8 Hz, 1 H, CH_2-H_b);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8 (C-6), 38.2 (C-2), 66.0 (C-1), 70.9 (C-3), 74.2 (C-5), 104.6 (C=$\underline{C}H_2$), 151.3 (C-4).

1,5-Anhydro-3-*O*-benzyl-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-D-*arabino*-hexitol (116) (II-130, cm186):



To a solution of **106** (4.73 g, 13.0 mmol) in methanol (10 ml), Pd/C (1.00 g, 0.940 mmol) was added under an atmosphere of argon. The reaction mixture was shaken in a hydrogenation apparatus under an atmosphere of H_2 (4 bar) for 2 h. After filtration through celite and evaporation of the solvent the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate 5:1). **116** was isolated as colorless oil (4.76 g, 13.0 mmol, 100%).

R_f = 0.27 (petroleum ether/ethyl acetate 5:1);

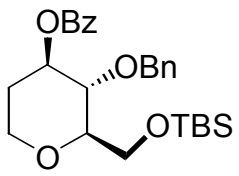
$[\alpha]_D^{21}$ = -33.4 (c = 1.04, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10, 0.11 (2 s, 6 H, 2 Si-CH_3), 0.91 (s, 9 H, Si-C$\underline{Me}_3$), 1.82 (dddd, $^3J_{1ax,2ax}$ = 12.6 Hz, $^3J_{1eq,2ax}$ = 5.0 Hz, $^2J_{2ax,2eq}$ = 12.9 Hz, $^3J_{2ax,3}$ = 11.3 Hz, 1 H, H-2_{ax}), 2.16 (dddd, $^3J_{1ax,2eq}$ = 1.8 Hz, $^3J_{1eq,2eq}$ = 1.5 Hz, $^2J_{2ax,2eq}$ = 12.9 Hz, $^3J_{2eq,3}$ = 5.0 Hz, 1 H, H-2_{eq}), 3.34 (ddd, $^3J_{4,5}$ = 9.1 Hz, $^3J_{5,6a}$ = 5.9 Hz, $^3J_{5,6b}$ = 4.4 Hz, 1 H, H-5), 3.56 (ddd, $^2J_{1ax,1eq}$ = 11.9 Hz, $^3J_{1ax,2ax}$ = 12.6 Hz, $^3J_{1ax,2eq}$ = 1.8 Hz, 1 H, H-1_{ax}), 3.79 (dd, $^3J_{3,4}$ = 8.8 Hz, $^3J_{4,5}$ = 9.1 Hz, 1 H, H-4), 3.84 (dd, $^3J_{5,6a}$ = 5.9 Hz, $^2J_{6a,6b}$ = 10.4 Hz, 1 H, H-6_a), 3.97 (dd, $^3J_{5,6b}$ = 4.4 Hz, $^2J_{6a,6b}$ = 10.4 Hz, 1 H, H-6_b), 4.00 (ddd, $^2J_{1eq,1ax}$ = 11.9 Hz, $^3J_{1eq,2ax}$ = 5.0 Hz, $^3J_{1eq,2eq}$ = 1.5 Hz, 1 H, H-1_{eq}), 5.11 (ddd, $^3J_{2ax,3}$ = 11.3 Hz, $^3J_{2eq,3}$ = 5.0 Hz, $^3J_{3,4}$ = 8.8 Hz, 1 H, H-3), 7.45-8.09 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4 (2 C, 2 Si-$\underline{C}H_3$), 18.3 (Si-$\underline{C}Me_3$), 25.9 (3 C, Si-C$\underline{Me}_3$), 30.9 (C-2), 65.2 (C-6), 65.3 (C-1), 72.6 (C-4), 75.9 (C-3), 78.9 (C-5), 128.4, 129.8, 130.1, 133.1 (6 C, C_6H_5), 166.7 (CO).

elemental analysis calcd (%) for $C_{19}H_{30}O_5Si$ (366.53): C 62.26, H 8.25, O 21.83;
found: C 62.34, H 8.32.

1,5-Anhydro-3-*O*-benzyl-4-*O*-benzoyl-2-deoxy-6-*O*-*tert*-butyldimethylsilyl-D-*arabino*-hexitol (117) (II-158, cm216):



NaH (1.60 g, 32.8 mmol, 55% suspension in oil) was washed with hexane (3 x 10 ml) under argon and then suspended in DMF (170 ml). At room temperature benzylbromide (4.20 ml, 34.4 mmol) and **116** (9.50 g, 25.9 mmol) were dissolved in DMF (120 ml) and added dropwise to the NaH suspension within 45 min. The mixture was stirred until TLC control showed complete consumption of the starting material (6 h). The reaction was quenched with satd. aqueous NH_4Cl (50 ml) and extracted with CH_2Cl_2 (150 ml). The organic layer was dried with Na_2SO_4, evaporated and purified on a silica gel column (petroleum ether/ethyl acetate 7:1) to obtain **117** (8.75 g, 19.2 mmol, 75%).

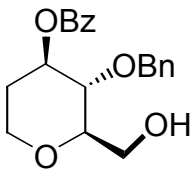
R_f = 0.51 (petroleum ether/ethyl acetate 4:1);

$[\alpha]_D^{21}$ = - 38.7 (c = 1.45, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.16, 0.17 (2 s, 6 H, 2 Si-CH_3), 1.01 (s, 9 H, Si-C$\underline{Me}_3$), 1.84 (dddd, $^3J_{1ax,2ax}$ = 12.6 Hz, $^3J_{1eq,2ax}$ = 4.7 Hz, $^2J_{2ax,2eq}$ = 12.9 Hz, $^3J_{2ax,3}$ = 11.3 Hz, 1H, H-2_{ax}), 2.27 (dddd, $^3J_{1ax,2eq}$ = 2.2 Hz, $^3J_{1eq,2eq}$ = 1.5 Hz, $^2J_{2ax,2eq}$ = 12.9 Hz, $^3J_{2eq,3}$ = 5.0 Hz, 1H, H-2_{eq}), 3.37 (ddd, $^3J_{4,5}$ = 9.4 Hz, $^3J_{5,6a}$ = 1.8 Hz, $^3J_{5,6b}$ = 3.7 Hz, 1 H, H-5), 3.57 (ddd, $^2J_{1ax,1eq}$ = 11.6 Hz, $^3J_{1ax,2ax}$ = 12.6 Hz, $^3J_{1ax,2eq}$ = 2.2 Hz, 1 H, H-1_{ax}), 3.81 (dd, $^3J_{3,4}$ = 9.1 Hz, $^3J_{4,5}$ = 9.4 Hz, 1 H, H-4), 3.96 (ddd, $^3J_{5,6a}$ = 1.8 Hz, $^3J_{5,6b}$ = 3.7 Hz, $^2J_{6a,6b}$ = 11.3 Hz, 2 H, H-6_{a+b}), 4.05 (ddd, $^2J_{1eq,1ax}$ = 11.6 Hz, $^3J_{1eq,2ax}$ = 4.7 Hz, $^3J_{1eq,2eq}$ = 1.5 Hz, 1 H, H-1_{eq}), 4.74, 4.80 (AB, $^2J_{A,B}$ = 12.0 Hz, 2 H, C$\underline{H}_2$-Ph), 5.30 (ddd, $^3J_{2ax,3}$ = 11.3 Hz, $^3J_{2eq,3}$ = 5.0 Hz, $^3J_{3,4}$ = 9.1 Hz, 1 H, H-3), 7.22-8.14 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6 (2 C, 2 Si-CH_3), 18.9 (Si-$\underline{C}Me_3$), 26.6 (3 C, Si-C$\underline{Me}_3$), 32.1 (C-2), 63.2 (C-6), 65.8 (C-1), 75.4 ($\underline{C}H_2$-Ph), 76.5 (C-3), 77.7 (C-4), 81.7 (C-5), 128.1, 128.3, 128.8, 130.0, 130.1, 133.4, 138.6, 139.0 (12 C, 2 C_6H_5), 166.3 (CO).

1,5-Anhydro-3-*O*-benzyl-4-*O*-benzoyl-2-deoxy-D-*arabino*-hexitol (118)
(II-164, cm220):



A solution of **117** (8.31 g, 18.2 mmol) in THF (100 ml) was cooled to 0°C. After 15 min, TBAF (27.3 ml, 1 M in THF) was added dropwise. The mixture was stirred for 1 h at 0°C and 4 h at room temperature. Diluting with CH_2Cl_2 (300 ml), washing with satd. aqueous $NaHCO_3$ (3 x 100 ml), drying with Na_2SO_4, evaporation and silica gel chromatography (petroleum ether/ethyl acetate 2:1) yielded **118** (5.97 g, 17.5 mmol, 96%).

R_f = 0.21 (petroleum ether/ethyl acetate 2:1);

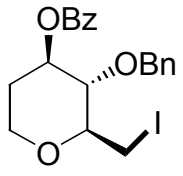
$[\alpha]_D^{21}$ = - 56.0 (c = 1.01, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 (dddd, $^3J_{1ax,2ax}$ = 12.4 Hz, $^3J_{1eq,2ax}$ = 4.5 Hz, $^2J_{2ax,2eq}$ = 12.6 Hz, $^3J_{2ax,3}$ = 11.7 Hz, 1 H, H-2_{ax}), 2.25 (dddd, $^3J_{1ax,2eq}$ = 2.4 Hz, $^3J_{1eq,2eq}$ = 1.9 Hz, $^2J_{2ax,2eq}$ = 12.6 Hz, $^3J_{2eq,3}$ = 4.7 Hz, 1 H, H-2_{eq}), 3.38 (ddd, $^3J_{4,5}$ = 9.4 Hz, $^3J_{5,6a}$ = 3.1 Hz, $^3J_{5,6b}$ = 1.7 Hz, 1 H, H-5), 3.57 (ddd, $^2J_{1ax,1eq}$ = 11.6 Hz, $^3J_{1ax,2ax}$ = 12.4 Hz, $^3J_{1ax,2eq}$ = 2.4 Hz, 1 H, H-1_{ax}), 3.73 (dd, $^3J_{3,4}$ = 9.2 Hz, $^3J_{4,5}$ = 9.4 Hz, 1 H, H-4), 3.77 (dd, $^3J_{5,6a}$ = 3.1 Hz, $^2J_{6a,6b}$ = 11.6 Hz, 1 H, H-6_a), 3.89 (dd, $^3J_{5,6b}$ = 1.7 Hz, $^2J_{6a,6b}$ = 11.6 Hz, 1 H, H-6_b), 3.99 (ddd, $^2J_{1eq,1ax}$ = 11.6 Hz, $^3J_{1eq,2ax}$ = 12.6 Hz, $^3J_{1eq,2eq}$ = 2.2 Hz, 1 H, H-1_{eq}), 4.66, 4.76 (AB, $^2J_{A,B}$ = 12.0 Hz, 2 H, C$\underline{H}_2$-Ph), 5.27 (ddd, $^3J_{2ax,3}$ = 11.7 Hz, $^3J_{2eq,3}$ = 4.7 Hz, $^3J_{3,4}$ = 9.2 Hz, 1 H, H-3), 7.20-8.09 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 31.9 (C-2), 62.6 (C-6), 65.7 (C-1), 75.4 ($\underline{C}H_2$-Ph), 76.4 (C-3), 77.0 (C-4), 80.1 (C-5), 128.4, 128.5, 128.8, 128.9, 130.0, 130.5, 133.5, 138.2 (12 C, 2 C_6H_5), 166.2 (CO);

elemental analysis calcd (%) for $C_{20}H_{22}O_5$ (342.39): C 70.16, H 6.48, O 23.36;
found: C 70.22, H 6.71, O 23.07.

1,5-Anhydro-3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-6-iodo-D-*arabino*-hexitol (119) (II-169, cm226):



Imidazole (400 mg, 5.84 mmol), PPh_3 (1.55 g, 5.84 mmol) and **118** (1.00 g, 2.92 mmol) were dissolved in CH_2Cl_2 (50 ml) under argon. Iodine (1.50 g, 5.84 mmol) was added and the reaction mixture was stirred for 17 h at room temperature. Diluting with CH_2Cl_2 (50 ml), washing with satd. aqueous $Na_2S_2O_3$ (100 ml) and satd. aqueous $NaHCO_3$ (100 ml), drying with Na_2SO_4, evaporation of the solvent under reduced pressure and silica gel column chromatography (petroleum ether/ethyl acetate 7:1) yielded **119** (1.20 g, 2.65 mmol, 91 %).

R_f = 0.75 (petroleum ether/ethyl acetate 2:1);

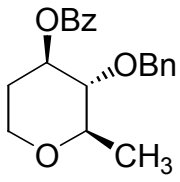
$[\alpha]_D^{21}$ = -2.76 (c = 2.3, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (dddd, $^3J_{1ax,2ax}$ = 12.4 Hz, $^3J_{1eq,2ax}$ = 4.5 Hz, $^2J_{2ax,2eq}$ = 12.6 Hz, $^3J_{2ax,3}$ = 11.7 Hz, 1 H, H-2_{ax}), 2.27 (dddd, $^3J_{1eq,2eq}$ = 1.4 Hz, $^3J_{1ax,2eq}$ = 2.3 Hz, $^2J_{2eq,2ax}$ = 12.6 Hz, $^3J_{2eq,3}$ = 5.1 Hz, 1 H, H-2_{eq}), 3.03 (m, 1 H, H-5), 3.53 (m, 2 H, H-6_{a+b}), 3.63 (ddd, $^2J_{1ax,1eq}$ = 11.4 Hz, $^3J_{1ax,2ax}$ = 12.4 Hz, $^3J_{1ax,2eq}$ = 2.3 Hz, 1 H, H-1_{ax}), 3.65 (dd, $^3J_{3,4}$ = 8.9 Hz, $^3J_{4,5}$ = 8.6 Hz, 1 H, H-4), 4.06 (ddd, $^2J_{1eq,1ax}$ = 11.4 Hz, $^3J_{1eq,2eq}$ = 1.4 Hz, $^3J_{1eq,2ax}$ = 4.5 Hz, 1 H, H-1_{eq}), 4.74, 4.82 (AB, $^2J_{A,B}$ = 10.7 Hz, 2 H, C$\underline{H}_2$-Ph), 5.30 (ddd, $^3J_{2ax,3}$ = 11.7 Hz, $^3J_{2eq,3}$ = 5.1 Hz, $^3J_{3,4}$ = 8.9 Hz, 1 H, H-3), 7.18-8.06 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 9.0 (C-6), 31.9 (C-2), 60.8 (C-1), 75.8 (C-3), 76.0 ($\underline{C}H_2$-Ph), 77.7 (C-5), 81.1 (C-4), 128.4, 128.5, 128.7, 128.8, 128.9, 130.0, 133.6, 138.0 (12 C, 2 C_6H_5), 166.1 (CO);

elemental analysis calcd (%) for $C_{20}H_{21}IO_4$ (452.29): C 53.11, H 4.68, O 14.15;
found: C 53.16, H 4.70.

1,5-Anhydro-3-*O*-benzyl-4-*O*-benzoyl-2,6-dideoxy-D-*arabino*-hexitol (120) (II-172, cm229):



Under argon, **119** (3.40 g, 7.50 mmol) was dissolved in methanol (10 ml). Pd/C (200 mg, 0.190 mmol) and NaOAc (2.00 g, 24.4 mmol) were added and the suspension was hydrogenated (4 bar H_2) at room temperature for 17 h. The reaction mixture was filtered through celite and the solvent was evaporated. Purification of the crude product by silica gel column chromatography yielded **120** (2.33 g, 7.12 mmol, 95 %).

R_f = 0.65 (petroleum ether/ethyl acetate 2:1);

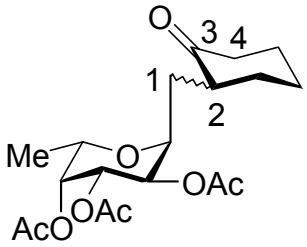
$[\alpha]_D^{21}$ = -78.6 (c = 1.05, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, $^3J_{5,6}$ = 6.1 Hz, 3 H, CH_3), 1.80 (dddd, $^3J_{1ax,2ax}$ = 11.7 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, $^2J_{2ax,2eq}$ = 12.6 Hz, $^3J_{2ax,3}$ = 11.4 Hz, 1 H, H-2_{ax}), 2.23 (dddd, $^3J_{1ax,2eq}$ = 2.0 Hz, $^3J_{1eq,2eq}$ = 1.4 Hz, $^2J_{2eq,2ax}$ = 12.6 Hz, $^3J_{2eq,3}$ = 5.2 Hz, 1 H, H-2_{eq}), 3.33 (dd, $^3J_{3,4}$ = 9.0 Hz, $^3J_{4,5}$ = 9.1 Hz, 1 H, H-4), 3.42 (dq, $^3J_{4,5}$ = 9.1 Hz, $^3J_{5,6}$ = 6.1 Hz, 1 H, H-5), 3.52 (ddd, $^2J_{1ax,1eq}$ = 11.8 Hz, $^3J_{1ax,2ax}$ = 11.7 Hz, $^3J_{1ax,2eq}$ = 2.0 Hz, 1 H, H-1_{ax}), 3.93 (ddd, $^2J_{1eq,1ax}$ = 11.8 Hz, $^3J_{1eq,2eq}$ = 1.4 Hz, $^3J_{1eq,2ax}$ = 4.9 Hz, 1 H, H-1_{eq}), 4.65, 4.76 (AB, $^2J_{A,B}$ = 10.9 Hz, 2 H, C$\underline{H}_2$-Ph), 5.22 (ddd, $^3J_{2ax,3}$ = 11.4 Hz, $^3J_{2eq,3}$ = 5.2 Hz, $^3J_{3,4}$ = 9.0 Hz, 1 H, H-3), 7.17-8.09 (m, 10 H, 2 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0 (C-6), 32.2 (C-2), 65.5 (C-1), 75.5 (C-3), 76.3 ($\underline{C}H_2$-Ph), 77.4 (C-5), 83.0 (C-4), 128.0, 128.1, 128.7, 128.8, 130.0, 130.6, 133.4, 138.3 (12 C, 2 C_6H_5), 166.2 (CO);

elemental analysis calcd (%) for $C_{20}H_{22}O_4$ (326.39): C 73.60, H 6.79, O 19.61;
found: C 73.44, H 6.83, O 19.73.

(2*S*)-2-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanone (122a) and **(2*R*)-2-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanone (122b)** (l-136, cm042):



92 (700 mg, 1.98 mmol) was dissolved in dimethoxyethane (20 ml) under argon. **83** [freshly prepared from **102** (2.00 g, 8.00 mmol) as described previously] was instantly added to the bromide solution. After adding azobisisobutyronitrile (60.0 mg, 0.370 mmol) the reaction mixture was heated to 85°C and tributyltin hydride (900 µl, 3.40 mmol) was added dropwise over a period of 1 h. Stirring was continued for 15 h at 85°C. The solvent was evaporated and the crude mixture dissolved in acetonitrile (100 ml). Remaining tin hydride was extracted with hexane (3 x 50 ml) and the acetonitrile layer evaporated. The remaining oil (1.31 g) was purified by silica gel chromatography (petroleum ether/ethyl acetate 2:1) to yield an unseparable mixture of diastereomers **122a** and **122b** in a ratio of 1:1.3 as determined by ^{1}H NMR (270 mg, 0.702 mmol, 35%) as well as 2,3,4-tri-*O*-acetyl-1-deoxy-L-fucopyranose (**162**) (180 mg, 0.660 mmol, 33%) and 1,3,4-tri-*O*-acetyl-2-deoxy-L-fucopyranoside (**163**) (90.0 mg, 0.320 mmol, 16%).

122a:

R_f = 0.18 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.48 (m, 1 H, H-1$_a$^{Cyc}), 2.04 (m, 1 H, H-1$_b$^{Cyc}), 2.00, 2.06, 2.17 (3 s, 9 H, 3 CH_3CO), 1.30-2.40 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 3.90 (dq, $^3J_{4,5}$ = 1.8 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.18 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 11.2 Hz, $^3J_{1,1b\text{-}Cyc}$ = 2.3 Hz, $^3J_{1,2}$ = 5.6 Hz, 1 H, H-1^{Fuc}), 5.23 (dd, $^3J_{2,3}$ = 10.0 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 5.24 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4^{Fuc}), 5.31 (dd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{2,3}$ = 10.0 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.9 (C-6^{Fuc}), 20.6, 20.7, 20.8 (3 $\underline{C}H_3CO$), 23.9, 27.8, 28.2, 35.4, 42.1 (5 C, C-1^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 46.7 (C-2^{Cyc}), 65.4 (C-5^{Fuc}), 68.1 (C-2^{Fuc}), 70.1 (C-3^{Fuc}), 70.8 (C-1^{Fuc}), 70.9 (C-4^{Fuc}), 170.0, 170.5, 171.1 (3 COO), 212.3 (C-3^{Cyc}).

122b:

R_f = 0.18 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.25 (m, 1 H, H-1$_a$^{Cyc}), 2.43 (m, 1 H, H-1$_b$^{Cyc}), 2.02, 2.05, 2.15 (3 s, 9 H, 3 CH_3CO), 1.30-2.40 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 3.95 (dq, $^3J_{4,5}$ = 1.8 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.27 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 11.2 Hz, $^3J_{1,1b\text{-}Cyc}$ = 2.3 Hz, $^3J_{1,2}$ = 5.6 Hz, 1 H, H-1^{Fuc}), 5.18 (dd, $^3J_{2,3}$ = 10.0 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 5.24 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4^{Fuc}), 5.31 (dd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{2,3}$ = 10.0 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (C-6^{Fuc}), 20.7, 20.8, 20.9 (3 $\underline{C}H_3CO$), 25.5, 28.2, 33.2, 35.4, 42.3 (5 C, C-1^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 47.0 (C-2^{Cyc}), 65.6 (C-5^{Fuc}), 67.9 (C-2^{Fuc}), 68.3 (C-3^{Fuc}), 71.3 (C-1^{Fuc}), 72.6 (C-4^{Fuc}), 169.9, 170.2, 170.5 (3 COO), 212.1 (C-3^{Cyc}).

162:

R_f = 0.29 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6), 2.01, 2.13, 2.18 (3 s, 9 H, 3 CH_3CO), 3.27 (dd, $^2J_{1ax,1eq}$ = 10.7 Hz, $^3J_{1ax,2}$ = 10.2 Hz, 1 H, H-1$_{ax}$), 3.73 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5), 4.14 (dd, $^2J_{1ax,1eq}$ = 10.7 Hz, $^3J_{1eq,2}$ = 5.7 Hz, 1 H, H-1$_{eq}$), 5.03 (dd, $^3J_{2,3}$ = 10.1 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3), 5.22 (ddd, $^3J_{1ax,2}$ = 10.2 Hz, $^3J_{1eq,2}$ = 5.7 Hz, $^3J_{2,3}$ = 10.1 Hz, 1 H, H-2), 5.29 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4 (C-6), 20.7, 20.8, 21.1 (3 $\underline{C}H_3CO$), 66.2 (C-1),66.5 (C-2), 70.8 (C-4), 72.0 (C-3), 73.4 (C-5), 170.0, 170.3, 170.6 (3 COO).

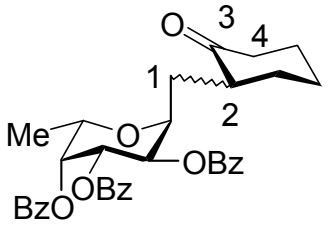
163:

R_f = 0.29 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6), 1.85 (ddd, $^3J_{1,2eq}$ = 1.4 Hz, $^2J_{2ax,2eq}$ = 13.1 Hz, $^3J_{2eq,3}$ = 4.7 Hz, 1 H, H-2$_{eq}$), 2.01, 2.12, 2.16 (3 s, 9 H, 3 CH_3CO), 2.16 (ddd, $^3J_{1,2ax}$ = 4.0 Hz, $^2J_{2ax,2eq}$ = 13.1 Hz, $^3J_{2ax,3}$ = 12.4 Hz, 1 H, H-2$_{ax}$), 4.18 (dq, $^3J_{4,5}$ = 1.7 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5), 5.22 (dd, $^3J_{3,4}$ = 2.4 Hz, $^3J_{4,5}$ = 1.7 Hz, 1 H, H-4), 5.30 (ddd, $^3J_{2ax,3}$ = 12.4 Hz, $^3J_{2eq,3}$ = 4.7 Hz, $^3J_{3,4}$ = 2.4 Hz, 1 H, H-3), 6.29 (dd, $^3J_{1,2ax}$ = 1.4 Hz, $^3J_{1,2eq}$ = 4.0 Hz, 1 H, H-1);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6), 20.6, 20.7, 20.8 (3 $\underline{C}H_3CO$), 28.7 (C-2), 66.5 (C-3), 67.3 (C-5), 70.8 (C-4), 91.9 (C-1), 169.3, 170.0, 170.6 (3 COO).

(*2S*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanone (123a) and **(*2R*)-2-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanone (123b)** (II-14, cm069):



94 (1.00 g, 1.84 mmol) was dissolved in dimethoxyethane (20 ml) under argon. **83** [freshly prepared from **102** (2.00 g, 8.00 mmol) as described previously] was instantly added to the bromide solution. After adding azobisisobutyronitrile (60 mg, 0.370 mmol) the reaction mixture was heated to 85°C and tributyltin hydride (900 µl, 3.40 mmol) was added dropwise over a period of 4 h. Stirring was continued for 15 h at 85°C. The solvent was evaporated and the crude mixture dissolved in acetonitrile (100 ml). Remaining tin hydride was extracted with hexane (3 x 50 ml) and the acetonitrile layer evaporated. The remaining oil was purified by silica gel chromatography (petroleum ether/ethyl acetate 6:1) to yield an unseparable mixture of diastereomers **123a** and **123b** in a ratio of 1 : 1.9 as determined by ^{1}H NMR (290 mg, 0.508 mmol, 26%) as well as 2,3,4-tri-*O*-benzoyl-1-deoxy-L-fucopyranose (**164**) (246 mg, 0.530 mmol, 27%) and 1,3,4-tri-*O*-benzoyl-2-deoxy-L-fucopyranoside (**165**) (160 mg, 0.350 mmol, 17%).

123a:

R_f = 0.55 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.20-2.50 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 1.40 (m, 1 H, H-1$_a^{Cyc}$), 2.72 (ddd, J = 12.6 Hz, 12.5 Hz, 3.3 Hz, 1 H, H-1$_b^{Cyc}$), 4.28 (dq, $^3J_{4,5}$ = 1.8 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.46 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 12.5 Hz, $^3J_{1,1b\text{-}Cyc}$ = 3.5 Hz, $^3J_{1,2}$ = 4.7 Hz, 1 H, H-1^{Fuc}), 5.72 (m, 1 H, H-4^{Fuc}), 5.84 (m, 2 H, H-2^{Fuc}, H-3^{Fuc}), 7.21-8.16 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4 (C-6^{Fuc}), 24.8, 27.7, 32.2, 34.5, 41.9 (5 C, C-1^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 46.9 (C-2^{Cyc}), 65.8 (C-5^{Fuc}), 66.4 (C-2^{Fuc}), 70.2 (C-1^{Fuc}), 71.3 (C-3^{Fuc}), 71.5 (C-4^{Fuc}), 128.2, 128.3, 128.4, 128.5, 129.2, 129.4, 129.6, 129.9, 130.4, 133.1, 133.3, 133.4 (18 C, 3 C_6H_5), 165.6, 165.7, 165.9 (3 COO), 212.3 (C-3^{Cyc});

MS (2.02 eV, ES): calcd for $C_{34}H_{34}O_8$ [M^+ + H]: 571.24; found: 571.43.

123b:

R_f = 0.55 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.20-2.60 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.73 (m, 1 H, H-1$_a$^{Cyc}), 2.25 (m, 1 H, H-1$_b$^{Cyc}), 4.28 (dq, $^3J_{4,5}$ = 2.0 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.62 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 11.3 Hz, $^3J_{1,1b\text{-}Cyc}$ = 2.5 Hz, $^3J_{1,2}$ = 5.3 Hz, 1 H, H-1^{Fuc}), 5.72 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 2.0 Hz, 1 H, H-4^{Fuc}), 5.75 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 5.84 (m, 1 H, H-2^{Fuc}), 7.21-8.16 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2 (C-6^{Fuc}), 25.2, 28.1, 32.2, 35.3, 41.2 (5 C, C-1^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 47.0 (C-2^{Cyc}), 65.9 (C-5^{Fuc}), 66.3 (C-2^{Fuc}), 69.1 (C-1^{Fuc}), 71.4 (C-3^{Fuc}), 71.7 (C-4^{Fuc}), 128.2, 128.3, 128.5, 129.1, 129.2, 129.4, 129.7, 129.9, 130.4, 133.2, 133.3, 133.4 (18 C, 3 C_6H_5), 165.6, 165.7, 165.9 (3 COO), 211.9 (C-3^{Cyc});

164:

R_f = 0.65 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6), 3.57 (dd, $^2J_{1ax,1eq}$ = 11.0 Hz, $^3J_{1ax,2}$ = 10.1 Hz, 1 H, H-1$_{ax}$), 3.98 (dd, $^3J_{4,5}$ = 0.9 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5), 4.44 (dd, $^2J_{1ax,1eq}$ = 11.0 Hz, $^3J_{1eq,2}$ = 5.4 Hz, 1 H, H-1$_{eq}$), 5.65 (dd, $^3J_{2,3}$ = 10.1 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3), 5.72 (ddd, $^3J_{1ax,2}$ = 10.1 Hz, $^3J_{1eq,2}$ = 5.4 Hz, $^3J_{2,3}$ = 10.1 Hz, 1 H, H-2), 5.76 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 0.9 Hz, 1 H, H-4), 7.25-8.24 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2 (C-6), 67.4 (C-1), 67.7 (C-2), 71.6 (C-3), 72.6 (C-4), 74.0 (C-5), 128.2, 128.4, 128.6, 129.1, 129.2, 129.4, 129.6, 129.7, 129.9, 133.2, 133.3, 133.4 (18 C, 3 C_6H_5), 165.7, 165.9, 166.0 (3 COO).

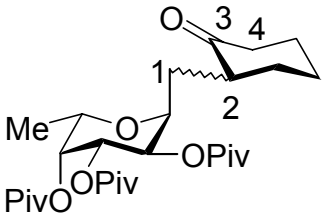
165:

R_f = 0.74 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6), 2.33 (ddd, $^3J_{1,2eq}$ = 1.3 Hz, $^3J_{2ax,2eq}$ = 13.2 Hz, $^3J_{2eq,3}$ = 5.0 Hz, 1 H, H-2_{eq}), 2.56 (ddd, $^3J_{1,2ax}$ = 3.5 Hz, $^3J_{2ax,2eq}$ = 13.2 Hz, $^3J_{2ax,3}$ = 12.9 Hz, 1 H, H-2_{ax}), 4.49 (dq, $^3J_{4,5}$ = 0.5 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5), 5.70 (dd, $^3J_{3,4}$ = 2.8 Hz, $^3J_{4,5}$ = 0.5 Hz, 1 H, H-4), 5.81 (ddd, $^3J_{2ax,3}$ = 12.9 Hz, $^3J_{2eq,3}$ = 5.0 Hz, $^3J_{3,4}$ = 2.8 Hz, 1 H, H-3), 6.71 (dd, $^3J_{1,2eq}$ = 1.3 Hz, $^3J_{1,2ax}$ = 3.5 Hz, 1 H, H-1), 7.34-8.22 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.8 (C-6), 29.4 (C-2), 67.3 (C-4), 68.0 (C-5), 69.9 (C-3), 92.5 (C-1), 128.3, 128.5, 128.6, 129.5, 129.6, 129.6, 129.8, 129.9, 130.1, 133.2, 133.4, 133.5 (18 C, 3 C_6H_5), 164.8, 165.6, 165.9 (3 COO).

(*2S*)-2-(2,3,4-Tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanone (124a) and **(*2R*)-2-(2,3,4-tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanone (124b)** (II-56, cm108):



97 (400 mg, 0.830 mmol) was dissolved in dimethoxyethane (20 ml) under argon. **83** [freshly prepared from **102** (2 g, 8 mmol) as described previously] was instantly added to the bromide solution. After adding azobisisobutyronitrile (60.0 mg, 0.370 mmol) the reaction mixture was heated to 85°C and tributyltin hydride (900 µl, 3.40 mmol) was added dropwise over a period of 4 h. Stirring was continued for 17 h at 85°C and 1 h at room temperature. The solvent was evaporated and the crude mixture dissolved in acetonitrile (100 ml). Remaining tin hydride was extracted with hexane (3 x 50 ml) and the acetonitrile layer evaporated. The remaining oil was purified by chromatography to yield the diastereomers **124a** (43.0 mg, 0.084 mmol, 10%) and **124b** (85.0 mg, 0.166 mmol, 20%) as well as 2,3,4-tri-*O*-pivaloyl-1-deoxy-L-fucopyranose (**166**) (105 mg, 0.260 mmol, 31%).

124a:

R_f = 0.29 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.16, 1.18, 1.29 (3 s, 27 H, 3 CMe_3), 1.20 (m, 1 H, H-1_a^{Cyc}), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-6_{a+b}^{Cyc}, H-7_{a+b}^{Cyc}), 2.51 (ddd, J = 4.3 Hz, 12.8 Hz, 15.3 Hz, 1 H, H-1_b^{Cyc}), 4.00 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.23 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.7 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.5 Hz, $^3J_{1,2}$ = 5.7 Hz, 1 H, H-

1^{Fuc}), 5.26 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4^{Fuc}), 5.30 (dd, $^3J_{2,3}$ = 10.8 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 5.35 (dd, $^3J_{1,2}$ = 5.7 Hz, $^3J_{2,3}$ = 10.8 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0 (C-6^{Fuc}), 26.5, 26.8, 27.1, (3 C$\underline{Me}_3$), 23.7, 26.1, 32.4, 34.6, 41.3, 46.7 (6 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 38.6, 39.4, 39.7 (3 $\underline{C}Me_3$), 66.3 (C-5^{Fuc}), 69.5 (C-2^{Fuc}), 69.9 (C-3^{Fuc}), 70.0(C-4^{Fuc}), 70.2 (C-1^{Fuc}), 176.3, 176.8, 177.4, (3 COO), 211.7 (C-3^{Cyc}).

124b:

R_f = 0.35 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, H-6^{Fuc}), 1.16, 1.22, 1.27 (3 s, 27 H, 3 CMe_3), 1.50 (m, 1 H, H-$1_a{}^{Cyc}$), 2.05 (m, 1 H, H-$1_b{}^{Cyc}$), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-$4_{a+b}{}^{Cyc}$, H-$5_{a+b}{}^{Cyc}$, H-$6_{a+b}{}^{Cyc}$, H-$7_{a+b}{}^{Cyc}$), 3.96 (dq, $^3J_{4,5}$ = 1.5 Hz, $^3J_{5,6}$ = 6.5 Hz, 1 H, H-5^{Fuc}), 4.25 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 11.9 Hz, $^3J_{1,1b\text{-}Cyc}$ = 2.4 Hz, $^3J_{1,2}$ = 5.8 Hz, 1 H, H-1^{Fuc}), 5.22 (dd, $^3J_{2,3}$ =10.2 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, H-3^{Fuc}), 5.25 (dd, $^3J_{3,4}$= 3.3 Hz, $^3J_{4,5}$ = 1.5 Hz, 1 H, H-4^{Fuc}), 5.36 (dd, $^3J_{1,2}$ = 5.8 Hz, $^3J_{2,3}$ = 10.2 Hz, 1 H, H-2^{Fuc});

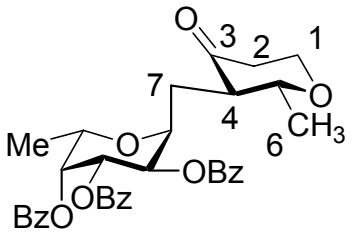
^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6^{Fuc}), 27.2, 27.5, 27.7 (3 C$\underline{Me}_3$), 24.3, 27.6, 33.9, 35.5, 40.9, 47.1 (6 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 39.3, 39.6, 39.8 (3 $\underline{C}Me_3$), 67.1 (C-5^{Fuc}), 67.5 (C-2^{Fuc}), 67.8 (C-3^{Fuc}), 70.2 (C-4^{Fuc}), 72.9 (C-1^{Fuc}), 175.3, 175.8, 176.4, (3 COO), 212.6 (C-3^{Cyc}).

166:

R_f = 0.54 (petroleum ether/ethyl acetate 5:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18, 1.19, 1.31 (3 s, 27 H, 3 CMe_3), 1.18 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6), 3.30 (dd, $^2J_{1ax,1eq}$ = 11.7 Hz, $^3J_{1ax,2}$ = 11.2 Hz, 1 H, H-1_{ax}), 3.74 (dq, $^3J_{4,5}$ = 1.0 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5), 4.11 (dd, $^2J_{1ax,1eq}$ = 11.7 Hz, $^3J_{1eq,2}$ = 4.6 Hz, 1 H, H-1_{eq}), 5.09 (dd, $^3J_{2,3}$ = 10.4 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3), 5.20 (dd, $^3J_{1ax,2}$ = 11.2 Hz, $^3J_{1eq,2}$ = 4.6 Hz, $^3J_{2,3}$ = 10.4 Hz,1 H, H-2), 5.31 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, H-4).

(*2R,3R*)-2-Methyl-3-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-tetrahydropyran-4-on (125) (II-207, cm263):



To a solution of 2,3,4-tri-*O*-benzoyl-α-L-fucopyranosylbromide (**94**) (270 mg, 0.468 mmol) and freshly prepared **84** (50.0 mg, 0.396 mmol) in dimethoxyethane (10 ml), AIBN (8.00 mg, 0.040 mmol) was added and the solution was heated to 85°C. Bu_3SnH (80.0 mg, 55.0 µl, 0.280 mmol) was added. After stirring for 2 h, another portion of Bu_3SnH (80.0 mg, 55.0 µl, 0.280 mmol) was added and the reaction mixture was stirred at 85°C for 18 h. The solvent was then evaporated, the crude reaction mixture dissolved in acetonitrile (50 ml) and washed with n-hexane (3 x 20 ml). Evaporation of the acetonitrile lead to a crude oil, which was purified by silica gel chromatography (petroleum ether/ethyl acetate 2:1) to yield **125** (25.0 mg, 0.042 mmol, 11%) together with 2,3,4-tri-*O*-benzoyl-1-deoxy-α-L-fucopyranose **164** and 1,3,4-tri-*O*-benzoyl-2-deoxy-α-L-fucopyranoside **165** (177 mg, 0.384 mmol, 82%).

R_f = 0.32 (petroleum ether/ethyl acetate 2:1);

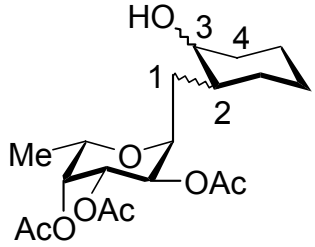
$[\alpha]_D^{22}$ = -162.8 (c = 1.25, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.19 (d, $^3J_{5,6}$ = 6.0 Hz, 3 H, H-6^{Pyr}), 1.33 (ddd, ^3J = 2.9 Hz, 4.6 Hz, 15.7 Hz, 1 H, H-7$_a^{Pyr}$), 2.34 (m, 2 H, H-2$_a^{Pyr}$, H-4^{Pyr}), 2.62 (ddd, $^3J_{1ax,2b}$ = 12.5 Hz, $^3J_{1eq,2b}$ = 7.1 Hz, $^2J_{2a,2b}$ = 14.2 Hz, 1 H, H-2$_b^{Pyr}$), 2.72 (ddd, ^3J = 3.9 Hz, 11.9 Hz, 15.7 Hz, 1 H, H-7$_b^{Pyr}$), 3.44 (dq, $^3J_{4,5}$ = 9.9 Hz, $^3J_{5,6}$ = 6.0 Hz, 1 H, H-5^{Pyr}), 3.61 (ddd, $^2J_{1ax,1eq}$ = 11.4 Hz, $^3J_{1ax,2a}$ = 2.5 Hz, $^3J_{1ax,2b}$ = 12.5 Hz, 1 H, H-1$_{ax}^{Pyr}$), 4.18 (ddd, $^2J_{1eq,1ax}$ = 11.4 Hz, $^3J_{1eq,2a}$ = 1.6 Hz, $^3J_{1eq,2b}$ = 7.1 Hz, 1 H, H-1$_{eq}^{Pyr}$), 4.32 (dq, $^3J_{4,5}$ = 1.6 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.47 (ddd, $^3J_{1,2}$ = 5.5 Hz, $^3J_{1,7a}$ = 2.9 Hz, $^3J_{1,7b}$ = 11.9 Hz, 1 H, H-1^{Fuc}), 5.65 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{4,5}$ = 1.6 Hz, 1 H, H-4^{Fuc}), 5.71 (dd, $^3J_{1,2}$ = 5.5 Hz, $^3J_{2,3}$ = 10.2 Hz, 1 H, H-2^{Fuc}), 5.76 (dd, $^3J_{2,3}$ = 10.2 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, H- 3^{Fuc}), 7.18-8.04 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.7 (C-6^{Fuc}), 19.9 (C-7^{Pyr}), 20.8 (C-6^{Pyr}), 42.7 (C-2^{Pyr}), 55.4 (C-4^{Pyr}), 66.6 (C-5^{Fuc}), 67.2 (C-1^{Pyr}), 69.4 (C-3^{Fuc}), 70.0 (C-2^{Fuc}), 72.1 (C-4^{Fuc}), 73.3 (C-1^{Fuc}), 79.4 (C-5^{Pyr}), 128.7, 128.8, 128.9, 129.5, 129.6, 129.8, 130.1, 130.2, 130.3, 133.6, 133.8, 133.9 (18 C, 3 C_6H_5), 166.1, 166.2, 166.3 (3 COO), 207.7 (C-3^{Pyr});

elemental analysis calcd (%) for $C_{34}H_{34}O_9$ (586.65): C 69.61, H 5.84, O 24.55;
found: C 69.31, H 6.16, O 24.53.

(*1R,2S*)-2-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanol (127a),
(*1S,2R*)-2-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanol (127b),
(*1S,2S*)-2-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanol (127c) and
(*1R,2R*)-2-(2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-methyl)-cyclohexanol (127d):



Reduction with $NaBH_4$ in MeOH (II-147, cm052):

An unseparable mixture of the ketone diastereomers **122a** and **122b** (100 mg, 0.260 mmol) was dissolved in methanol (5 ml) under argon and cooled to –20°C. $NaBH_4$ (7.00 mg, 0.170 mmol) was added and the reaction mixture was stirred at –20°C for 1 h. Quenching of the remaining reducing agent with 5% aqueous HCl (10 ml), extraction of the organic layer with CH_2Cl_2 (3 x 20 ml), drying with Na_2SO_4 and evaporation of the solvents lead to a crude mixture (110 mg) of the four alcohols **127a**, **127b**, **127c** and **127d** in a ratio of 1 : 1.3 : 1 : 1.3 as determined by ^{1}H NMR-spectroscopy. Purification of the crude mixture by silica gel chromatography (petroleum ether/ethyl acetate 2:1) yielded **127a** (23.0 mg, 0.060 mmol, 21%), **127b** (31.0 mg, 0.080 mmol, 28%), **127c** (23.0 mg, 0.060 mmol, 21%) and **127d** (31.0 mg, 0.080 mmol, 28%).

Reduction with Li(^{t}BuO)$_3$AlH in THF (II-10, cm065):

An unseparable mixture of the ketone diastereomers **122a** and **122b** (50.0 mg, 0.130 mmol) was dissolved in THF (3 ml) under argon and cooled to -5°C. Li[(^{t}BuO)$_3$AlH] (49.0 mg, 0.195 mmol) was added and the reaction mixture was stirred at –5°C for 4 h and at 0°C for 3 h. Quenching of the remaining reducing agent with 5% aqueous HCl (10 ml), extraction of the organic layer with CH_2Cl_2 (3 x 20 ml), drying with Na_2SO_4 and evaporation of the solvent lead to a crude mixture (60 mg) of the four alcohols **127a**, **127b**, **127c** and **127d** in a ratio of 4 : 5.2 : 1 : 1.3 as determined by ^{1}H NMR-spectroscopy. Purification of the crude mixture by silica gel chromatography (petroleum ether/ethyl acetate 2:1) yielded **127a** (17.0 mg, 0.044 mmol, 35%), **127b** (23.0 mg, 0.059 mmol, 45%), **127c** (4.00 mg, 0.01 mmol, 9%) and **127d** (6.00 mg, 0.016 mmol, 11%).

Reduction with L-Selectride in THF (II-8, cm063):

An unseparable mixture of the ketone diastereomers **122a** and **122b** (20.0 mg, 0.052 mmol) was dissolved in THF (3 ml) under argon and cooled to 0°C. L-selectride (1.0 M in THF, 57.0 µl, 0.057 mmol) was added slowly by a syringe and the reaction mixture was stirred at 0°C for 1.5 h. Quenching of the remaining reducing agent with water (10 ml), extraction of the organic layer with CH_2Cl_2 (3 x 20 ml), drying with Na_2SO_4 and evaporation of the solvent lead to a crude mixture (27 mg) of the two axial alcohols **127c** and **127d** in a ratio of 1:1.3 as determined by ^{1}H NMR spectroscopy. Purification of the crude mixture by silica gel chromatography (petroleum ether/ethyl acetate 2:1) yielded **127c** (8.00 mg, 0.021 mmol, 40%) and **127d** (10.0 mg, 0.027 mmol, 52%).

127a:

R_f = 0.38 (petroleum ether/ethyl acetate 1:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (m, 1 H, H-1_a^{Cyc}), 1.15 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-6_{a+b}^{Cyc}, H-7_{a+b}^{Cyc}), 2.02, 2.08, 2.14 (3 s, 9 H, 3 CH_3), 2.16 (m, 1 H, H-1_b^{Cyc}), 3.20 (ddd, $^3J_{2,3}$ = 9.8 Hz, $^3J_{3,4a}$ = 4.3 Hz, $^3J_{3,4b}$ = 10.2 Hz, 1 H, H-3^{Cyc}), 4.06 (dq, $^3J_{4,5}$ = 1.7 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.35 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.7 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.2 Hz, $^3J_{1,2}$ = 5.5 Hz, 1 H, H-1^{Fuc}), 5.17 (dd, $^3J_{2,3}$ = 8.6 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3^{Fuc}), 5.26 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 1.7 Hz, 1 H, H-4^{Fuc}), 5.30 (dd, $^3J_{1,2}$ = 5.5 Hz, $^3J_{2,3}$ = 8.6 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.5 (C-6^{Fuc}), 21.0, 21.2, 21.5 (3 $\underline{C}H_3CO$), 25.8 (C-1^{Cyc}), 26.0, 28.6, 29.4, 33.2, 35.4 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 66.1 (C-5^{Fuc}), 68.7 (C-3^{Fuc}), 68.9 (C-2^{Fuc}), 70.8 (C-1^{Fuc}), 71.0 (C-4^{Fuc}), 75.0 (C-3^{Cyc}), 168.0, 169.3, 170.0 (3 COO).

127b:

R_f = 0.38 (petroleum ether/ethyl acetate 1:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-6_{a+b}^{Cyc}, H-7_{a+b}^{Cyc}), 1.74 (m, 2 H, H-1_{a+b}^{Cyc}), 2.00, 2.09, 2.16 (3 s, 9 H, 3 CH_3), 3.29 (ddd, $^3J_{2,3}$ = 9.8 Hz, $^3J_{3,4a}$ = 3.9 Hz, $^3J_{3,4b}$ = 10.3 Hz, 1 H, H-3^{Cyc}), 4.06 (dq, $^3J_{4,5}$ =

1.6 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.45 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 4.7 Hz, $^3J_{1,1b\text{-}Cyc}$ = 8.2 Hz, $^3J_{1,2}$ = 5.1 Hz, 1 H, H-1^{Fuc}), 5.17 (dd, $^3J_{2,3}$ = 8.4 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 5.26 (m, 2 H, H-2^{Fuc}, H-4^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4 (C-6^{Fuc}), 21.0, 21.2, 21.5 (3 CH_3), 31.2 (C-1^{Cyc}), 27.8, 29.0, 31.7, 33.2, 35.4 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 66.1 (C-5^{Fuc}), 68.7 (C-3^{Fuc}), 68.9 (C-2^{Fuc}), 71.0 (C-4^{Fuc}), 71.9 (C-1^{Fuc}), 75.0 (C-3^{Cyc}), 168.0, 169.2, 170.2 (3 COO).

127c:

R_f = 0.42 (petroleum ether/ethyl acetate 1:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.39 (m, 1 H, H-1$_a$^{Cyc}), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.85 (m, 1 H, H-1$_b$^{Cyc}), 1.98, 2.05, 2.12 (3 s, 9 H, 3 CH_3), 3.88 (ddd, $^3J_{2,3}$ = 2.3 Hz, $^3J_{3,4a}$ = 4.3 Hz, $^3J_{3,4b}$ = 3.8 Hz, 1 H, H-3^{Cyc}), 4.06 (dq, $^3J_{4,5}$ = 1.6 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.28 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.1 Hz, $^3J_{1,1b\text{-}Cyc}$ = 11.8 Hz, $^3J_{1,2}$ = 5.5 Hz, 1 H, H-1^{Fuc}), 5.17 (dd, $^3J_{2,3}$ = 8.4 Hz, $^3J_{3,4}$ = 3.2 Hz, 1 H, H-3^{Fuc}), 5.26 (dd, $^3J_{3,4}$ = 3.2 Hz, $^3J_{4,5}$ = 1.6 Hz,1 H, H-4^{Fuc}), 5.27 (dd, $^3J_{1,2}$ = 5.5 Hz, $^3J_{2,3}$ = 8.4 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8 (C-6^{Fuc}), 20.4 (C-1^{Cyc}), 21.0, 21.2, 21.5 (3 CH_3), 23.6, 26.9, 27.4, 29.8, 33.1 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 66.1 (C-5^{Fuc}), 68.3 (C-3^{Cyc}), 68.7 (C-3^{Fuc}), 68.9 (C-2^{Fuc}), 71.0 (C-4^{Fuc}), 71.6 (C-1^{Fuc}), 168.3, 169.1, 169.7 (3 COO).

127d:

R_f = 0.42 (petroleum ether/ethyl acetate 1:1);

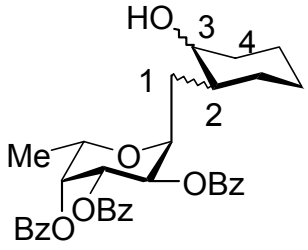
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.61-2.53 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.63 (m, 2 H, H-1$_{a+b}$^{Cyc}), 2.01, 2.06, 2.10 (3 s, 9 H, 3 CH_3), 3.94 (ddd, ^3J = 1.5 Hz, 2.7 Hz, 3.9 Hz, 1 H, H-3^{Cyc}), 3.98 (dq, $^3J_{4.5}$ = 1.9 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.40 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 4.8 Hz, $^3J_{1,1b\text{-}Cyc}$ = 7.9 Hz, $^3J_{1,2}$ = 4.9 Hz, 1 H, H-1^{Fuc}), 5.17 (dd, $^3J_{2,3}$ = 8.5 Hz, $^3J_{3,4}$ = 3.3 Hz, 1 H, H-3^{Fuc}), 5.26 (dd, $^3J_{3,4}$ = 3.3 Hz, $^3J_{4,5}$ = 1.9 Hz,1 H, H-4^{Fuc}), 5.28 (dd, $^3J_{1,2}$ = 4.9 Hz, $^3J_{2,3}$ = 8.5 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6 (C-6^{Fuc}), 21.0, 21.2, 21.5 (3 CH_3), 25.4 (C-1^{Cyc}), 26.7, 27.5, 30.1, 31.8, 33.2 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 65.8 (C-5^{Fuc}), 67.7 (C-3^{Cyc}), 68.7 (C-3^{Fuc}), 68.9 (C-2^{Fuc}), 70.6 (C-1^{Fuc}), 71.0 (C-4^{Fuc}), 168.4, 168.9, 169.9 (3 COO).

(*1R,2S*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanol (128a),

(*1S,2R*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanol (128b),

(*1S,2S*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanol (128c) and



(*1R,2R*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexanol (128d) (II-57, cm109)**:**

To a solution of the diastereomeric mixture of **123a** and **123b** (570 mg, 1.00 mmol) in THF (30 ml), Li[(^{t}BuO)$_3$AlH] (393 mg, 1.50 mmol) was added at 0°C and the suspension was stirred at 0°C for 5 h. Quenching of the remaining reducing agent with water (50 ml), extraction of the organic layer with CH_2Cl_2 (3 x 50 ml), drying with Na_2SO_4, evaporation of the solvent and purification of the crude mixture by silica gel chromatography (petroleum ether/ethyl acetate 5:1) yielded **128a** (130 mg, 0.230 mmol, 23%), **128b** (243 mg, 0.420 mmol, 42%), **128c** (41.0 mg, 0.070 mmol, 7%) and **128d** (80.0 mg, 0.140 mmol, 14%) in an overall yield of 86%.

128a:

R_f = 0.42 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, H-6^{Fuc}), 1.28-2.04 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.25 (m, 1 H, H-1$_a$^{Cyc}), 2.44 (m, 1 H, H-1$_b$^{Cyc}), 3.17 (dt, ^3J = 9.6 Hz, 9.6 Hz, 3.7 Hz, 1 H, H-3^{Cyc}), 4.29 (dq, $^3J_{4,5}$ = 1.8 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.59 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.0 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.5 Hz, $^3J_{1,2}$ = 5.0 Hz, 1 H, H-1^{Fuc}), 5.66 (m, 1H, H-4^{Fuc}), 5,75 (m, 2 H, H-2^{Fuc}, H-3^{Fuc}), 7.18-8.02 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6^{Fuc}), 25.0, 26.3, 29.4, 32.6, 36.8 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 32.2 (C-1^{Cyc}), 67.0 (C-5^{Fuc}), 70.5 (C-2^{Fuc}), 70.6 (C-3^{Fuc}), 71.0 (C-1^{Fuc}), 71.7 (C-4^{Fuc}), 75.3 (C-3^{Cyc}), 128.8, 128.9, 130.0, 130.2, 130.4, 130.8, 132.3, 132.5, 132.6, 133.7, 133.9, 134.0 (18 C, 3 C_6H_5), 164.7, 165.3, 166.6 (3 COO).

elemental analysis calcd (%) for $C_{34}H_{36}O_8$ (572.65): C 71.31, H 6.34, O 22.35;
found: C 70.90, H 6.365, O 22.74.

128b:

R_f = 0.50 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.21-1.80 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.86 (m, 2 H, H-1$_{a+b}$^{Cyc}), 3.26 (ddd, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4a}$ = 9.5 Hz, $^3J_{3,4b}$ = 4.3 Hz, 1 H, H-3^{Cyc}), 4.26 (dq, $^3J_{4,5}$ = 1.7 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.70 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.5 Hz, $^3J_{1,1b\text{-}Cyc}$ = 8.5 Hz, $^3J_{1,2}$ = 4.7 Hz, 1 H, H-1^{Fuc}), 5.65 (dd, $^3J_{3,4}$ = 3.0 Hz, $^3J_{4,5}$ = 1.7 Hz, 1 H, H-4^{Fuc}), 5,70 (dd, $^3J_{2,3}$ = 7.9 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, H-3^{Fuc}), 5.70 (m, 1 H, H-2^{Fuc}), 7.18-8.02 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.0 (C-6^{Fuc}), 25.0, 26.3, 29.4, 32.6, 36.8 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 37.0 (C-1^{Cyc}), 67.1 (C-5^{Fuc}), 70.7 (C-2^{Fuc}), 70.8 (C-3^{Fuc}), 71.8 (C-4^{Fuc}), 72.0 (C-1^{Fuc}), 75.0 (C-3^{Cyc}), 128.2, 128.4, 128.8, 129.1, 129.2, 129.4, 129.5, 129.7, 129.9, 133.2, 133.4, 133.7 (18 C, 3 C_6H_5), 166.1, 166.8, 167.4 (3 CO);

128c:

R_f = 0.50 (petroleum ether/ethyl acetate 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.21-.80 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}),1.49 (m, 1 H, H-1$_a$^{Cyc}), 2.02 (m, 1 H, H-1$_b$^{Cyc}), 3.88 (ddd, ^3J = 5.3 Hz, 4.7 Hz, 2.8 Hz, 1 H, H-3^{Cyc}), 4.27 (dq, $^3J_{5,4}$ = 1.8 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.52 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.5 Hz, $^3J_{1,1b\text{-}Cyc}$ = 11.6 Hz, $^3J_{1,2}$ = 4.7 Hz, 1 H, H-1^{Fuc}), 5.70 (m, 3 H, H-2^{Fuc}, H-3^{Fuc}, H-4^{Fuc}), 7.18-8.02 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6^{Fuc}), 25.2, 26.6, 29.7, 32.2, 35.4 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 30.6 (C-1^{Cyc}), 68.4 (C-5^{Fuc}), 69.8 (C-3^{Cyc}), 70.4 (C-2^{Fuc}), 71.8 (C-1^{Fuc}), 72.4 (C-4^{Fuc}), 75.3 (C-3^{Cyc}), 128.6, 128.8, 130.2, 130.3, 130.4, 131.6, 132.0, 132.4, 132.6, 133.5, 133.7, 134.6 (18 C, 3 C_6H_5), 165.3, 165.5, 166.2 (3 COO).

128d:

R_f = 0.58 (petroleum ether/ethyl acetate 2:1);

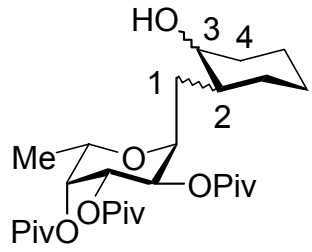
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, H-6^{Fuc}), 1.25-1.78 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.80 (m, 2 H, H-1$_{a+b}$^{Cyc}), 3.92 (ddd, ^3J = 1.1 Hz, 2.3 Hz, 2.9 Hz, 1 H, H-3^{Cyc}), 4.18 (dq, $^3J_{4,5}$ = 1.3 Hz, $^3J_{5,6}$ = 6.5 Hz, 1 H, H-5^{Fuc}), 4.61 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.9 Hz, $^3J_{1,1b\text{-}Cyc}$ = 10.8 Hz, $^3J_{1,2}$ = 5.1 Hz, 1 H, H-1^{Fuc}), 5.64 (dd, $^3J_{3,4}$ = 3.2 Hz, $^3J_{4,5}$ = 1.3 Hz, 1 H, H-4^{Fuc}), 5.74 (dd, $^3J_{2,3}$ = 9.1 Hz, $^3J_{3,4}$ = 3.2 Hz, 1 H, H-3^{Fuc}), 5.74 (m, 1 H, H-2^{Fuc}), 7.18-8.02 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.8 (C-6^{Fuc}), 25.0, 26.3, 29.4, 32.6, 36.8 (5C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 32.8 (C-1^{Cyc}), 66.9 (C-5^{Fuc}), 68.6 (C-3^{Cyc}), 70.1 (C-2^{Fuc}), 70.3 (C-3^{Fuc}), 71.2 (C-1^{Fuc}), 71.5 (C-4^{Fuc}), 128.0, 128.4, 128.6, 129.1, 129.3, 129.4, 129.6, 129.8, 129.9, 132.7, 133.1, 133.4 (18 C, 3 C_6H_5), 165.6, 165.8, 166.3 (3 COO).

(*1R,2S*)-2-(2,3,4-Tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanol (129a),

(*1S,2R*)-2-(2,3,4-Tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanol (129b),

(*1S,2S*)-2-(2,3,4-Tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanol (129c), and



(*1R,2R*)-2-(2,3,4-tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexanol (129d) (II-58, cm110)**:**

A diastereomeric (1:1)-mixture of **124a** and **124b** (200 mg, 0.390 mmol), was dissolved in THF (10 ml) and cooled to 0°C. After addition of Li[(^{t}BuO)$_3$AlH] (231 mg, 0.910 mmol) the reaction was stirred for 3 h at 0°C and 20 h at room temperature. Quenching of the remaining reducing agent with water (50 ml), extraction of the organic layer with CH_2Cl_2 (3 x 50 ml), drying with Na_2SO_4, evaporation of the solvent and purification of the crude mixture (**129a** : **129b** : **129c** : **129d** = 1.4 : 1.4 : 0.7 : 0.8 as determined by ^{1}H NMR spectroscopy) by silica gel chromatography (toluene/ethyl acetate 6:1) yielded **129a** (60.0 mg, 0.120 mmol, 37%), **129b** (47.0 mg, 0.090 mmol, 29%), **129c** (13.0 mg, 0.025 mmol, 9%) and **129d** (40.0 mg, 0.080 mmol, 25 %) in an overall yield of 81%.

129a:

R_f = 0.24 (petroleum ether/ethyl acetate 3:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, $^3J_{5,6}$ = 6.2 Hz, 3 H, H-6^{Fuc}), 1.14, 1.18, 1.28 (3 s, 27 H, 3 CMe_3), 1.16 (m, 1 H, H-1$_a$^{Cyc}), 1.20-1.81 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 2.28 (m, 1 H, H-1$_b$^{Cyc}), 3.20 (ddd, $^3J_{2,3}$ = 7.0 Hz, $^3J_{3,4a}$ = 7.0 Hz, $^3J_{3,4b}$ = 4.4 Hz, 1 H, H-3^{Cyc}), 4.12 (dq, $^3J_{4,5}$ = 1.3 Hz, $^3J_{5,6}$ = 6.2 Hz, 1 H, H-5^{Fuc}), 4.33 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.2 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.2 Hz, $^3J_{1,2}$ = 5.5 Hz, 1 H, H-1^{Fuc}), 5.26 (m, 2 H, H-3^{Fuc}, H-4^{Fuc}), 5.31 (m, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2 (C-6^{Fuc}), 22.3, 24.6, 28.1, 31.4, 35.8 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.4, 27.6, 27.9 (3 C$\underline{Me}_3$), 34.8 (C-1^{Cyc}), 38.2, 39.6, 42.3 (3 $\underline{C}Me_3$), 66.2 (C-5^{Fuc}), 68.6 (C-2^{Fuc}), 69.4 (C-3^{Fuc}), 71.0 (C-4^{Fuc}), 71.6 (C-1^{Fuc}), 73.6 (C-3^{Cyc}), 177.4, 177.6, 177.9 (3 COO).

129b:

R_f = 0.31 (petroleum ether/ethyl acetate 3:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.14, 1.20, 1.29 (3 s, 27 H, 3 CMe_3), 1.21 (m, 2 H, H-1$_{a+b}$^{Cyc}), 1.22-1.74 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}$^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 3.29 (ddd, $^3J_{2,3}$ = 8.1 Hz, $^3J_{3,4a}$ = 8.2 Hz, $^3J_{3,4b}$ = 3.8 Hz, 1 H, H-3^{Cyc}), 4.09 (dq, $^3J_{4,5}$ = 1.6 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.44 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.6 Hz, $^3J_{1,1b\text{-}Cyc}$ = 8.1 Hz, $^3J_{1,2}$ = 5.3 Hz, 1 H, H-1^{Fuc}), 5.20 (m, 1 H, H-3^{Fuc}), 5.23 (m, 1 H, H-4^{Fuc}), 5.26 (m, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2 (C-6^{Fuc}), 24.6, 25.9, 27.5, 31.9, 36.2 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.2, 27.5, 28.1 (3 C$\underline{Me}_3$), 28.5 (C-1^{Cyc}), 39.2, 39.4, 43.5 (3 $\underline{C}Me_3$), 65.8 (C-5^{Fuc}), 67.6 (C-2^{Fuc}), 68.2 (C-3^{Fuc}), 71.2 (C-4^{Fuc}), 73.4 (C-1^{Fuc}), 74.8 (C-3^{Cyc}), 177.1, 177.4, 177.8 (3 COO).

129c:

R_f = 0.27 (petroleum ether/ethyl acetate 3:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.15, 1.19, 1.29 (3 s, 27 H, 3 CMe_3), 1.26-1.76 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 1.37 (m, 1 H, H-1$_a^{Cyc}$), 1.91 (m, 1 H, H-1$_b^{Cyc}$), 3.87 (ddd, ^3J = 2.1 Hz, 4.3 Hz, 5.4 Hz, 1 H, H-3^{Cyc}), 4.09 (dq, $^3J_{4,5}$ = 1.9 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.27 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 2.3 Hz, $^3J_{1,1b\text{-}Cyc}$ = 11.6 Hz, $^3J_{1,2}$ = 4.9 Hz, 1 H, H-1^{Fuc}), 5.20 (dd, $^3J_{2,3}$ = 10.1 Hz, $^3J_{3,4}$ = 2.8 Hz, 1 H, H-3^{Fuc}), 5.24 (dd, $^3J_{3,4}$ = 2.8 Hz, $^3J_{4,5}$ = 1.9 Hz, 1 H, H-4^{Fuc}), 5.29 (dd, $^3J_{1,2}$ = 4.9 Hz, $^3J_{2,3}$ = 10.1 Hz, 1 H, H-2^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6^{Fuc}), 25.2, 26.0, 27.4, 32.2, 37.6 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.1, 27.5, 27.9 (3 C$\underline{Me}_3$), 36.3 (C-1^{Cyc}), 38.7, 39.3, 43.1 (3 $\underline{C}Me_3$), 66.0 (C-5^{Fuc}), 68.6 (C-2^{Fuc}), 69.2 (C-3^{Fuc}), 70.9 (C-3^{Cyc}), 72.4 (2 C, C-4^{Fuc}, C-1^{Fuc}), 177.2, 177.4, 177.7 (3 COO).

129d:

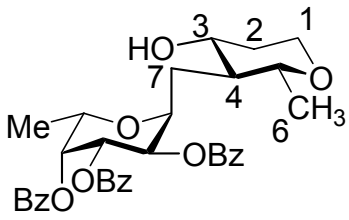
R_f = 0.39 (petroleum ether/ethyl acetate 3:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.14, 1.18, 1.28 (3 s, 27 H, 3 CMe_3), 1.26-1.76 (m, 9 H, H-2^{Cyc}, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 1.65 (m, 2 H, H-1$_{a+b}^{Cyc}$), 3.93 (ddd, ^3J = 1.6 Hz, 3.3 Hz, 4.4 Hz, 1 H, H-3^{Cyc}), 4.01 (dq, $^3J_{4,5}$ = 1.3 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.39 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.9 Hz, $^3J_{1,1b\text{-}Cyc}$ = 8.9 Hz, $^3J_{1,2}$ = 6.1 Hz, 1 H, H-1^{Fuc}), 5.25 (d, $^3J_{3,4}$ = 3.3 Hz, $^3J_{4,5}$ = 1.3 Hz, 1 H, H-4^{Fuc}), 5.30 (m, 2 H, H-2^{Fuc}, H-3^{Fuc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6^{Fuc}), 20.2, 25.5, 26.8, 27.4, 29.7 (5 C, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.1, 27.3, 27.6 (3 C$\underline{Me}_3$), 33.3 (C-1^{Cyc}), 38.5, 38.7, 39.2 (3 $\underline{C}Me_3$),

66.3 (C-5^{Fuc}), 68.7 (C-3^{Cyc}), 69.4 (C-2^{Fuc}), 69.8 (C-3^{Fuc}), 71.5 (C-4^{Fuc}), 72.0 (C-1^{Fuc}), 177.2, 177.5, 177.6 (3 COO).

(*2R,3R,4R*)-4-Hydroxy-2-methyl-3-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-tetrahydropyran (130a) (II-227, cm281):



A solution of **125** (41.0 mg, 0.068 mmol) in THF (10 ml) was cooled to 0°C, Li[(^{t}BuO)$_3$AlH] (52.0 mg, 0.204 mmol) was added and the mixture was stirred for 20 h, being allowed to warm to room temperature. The reaction was then quenched at 0°C with satd. aqueous NH_4Cl (50 ml), extracted with CH_2Cl_2 (100 ml), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (petroleum ether/ethyl acetate 2:1) yielded **130a** (37.0 mg, 0.063 mmol, 93%).

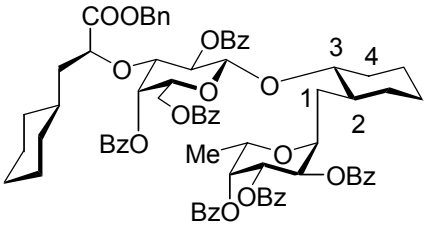
R_f = 0.28 (petroleum ether/ethyl acetate 1:1);

$[\alpha]_D^{22}$ = -142.8 (c = 0.5, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (d, $^3J_{5,6}$ = 6.1 Hz, 3 H, H-6^{Pyr}), 1.28 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.28 (m, 1 H, H-4^{Pyr}), 1.57 (m, 1 H, H-2$_a$^{Pyr}), 1.61 (m, 1 H, H-7$_a$^{Pyr}), 1.86 (m, 1 H, H-2$_b$^{Pyr}), 1.96 (m, 1 H, H-7$_b$^{Pyr}), 3.09 (dq, $^3J_{4,5}$ = 9.6 Hz, $^3J_{5,6}$ = 6.1 Hz, 1 H, H-5^{Pyr}), 3.34 (ddd, $^2J_{1ax,1eq}$ = 11.7 Hz, $^3J_{1ax,2eq}$ = 1.8 Hz, $^3J_{1ax,2ax}$ = 11.4 Hz, 1 H, H-1$_{ax}$^{Pyr}), 3.40 (ddd, ^3J = 4.2 Hz, 9.7 Hz, 10.6 Hz, 1 H, H-3^{Pyr}), 3.88 (ddd, ^3J = 2.0 Hz, 4.8 Hz,11.7 Hz, 1 H, H-1$_{eq}$^{Pyr}), 4.47 (dq, $^3J_{4,5}$ = 2.0 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.57 (ddd, $^3J_{1,2}$ = 4.5 Hz, $^3J_{1,7a}$ = 2.1 Hz, $^3J_{1,7b}$ = 11.4 Hz, 1 H, H-1^{Fuc}), 5.68 (m, 3 H, H-2^{Fuc}, H-3^{Fuc}, H-4^{Fuc}), 7.18-8.05 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6^{Fuc}), 20.2 (C-6^{Pyr}), 26.8 (C-7^{Pyr}), 34.4 (C-2^{Pyr}), 48.3 (C-4^{Pyr}), 65.9 (C-1^{Pyr}), 68.0 (C-5^{Fuc}), 69.9 (2 C, C-2^{Fuc}, C-3^{Fuc}), 72.0 (C-4^{Fuc}), 71.3 (C-1^{Fuc}), 71.4 (C-3^{Pyr}), 76.0 (C-5^{Pyr}), 127.4, 127.6, 128.0, 128.3, 128.7, 128.8, 129.8, 130.3, 130.6, 132.3, 132.4, 132.5 (18 C, 3 C_6H_5), 164.6, 164.7, 164.8 (3 COO).

Benzyl (*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-[(*1R,2S*)-2-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexyl]-β-D-galactopyranos-3-yl}propanoate (135a) (II-86, cm138):



A solution of **128a** (50.0 mg, 0.087 mmol), benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-β-D-thio-galactopyranos-3-yl] propanoate (**90**) (102 mg, 0.131 mmol) and 3Å molecular sieves (0.5g) in CH_2Cl_2 (10 ml) was cooled to -20°C. After stirring for 30 min at –20°C, NIS (59.0 mg, 0.262 mmol) was added and stirring was continued for 30 min. Trifluoromethanesulfonic acid (70 µl) was added and the dark-purple solution was stirred at –20°C for 4 h. Filtration of molecular sieves, washing of the organic layer with satd. aqueous $Na_2S_2O_3$ (50 ml) and satd. aqueous $NaHCO_3$ (50 ml), drying with Na_2SO_4, evaporation of the solvent and purification of the crude product mixture by silica gel chromatography (toluene/ethyl acetate 25:1) yielded **135a** (92.0 mg, 0.071 mmol, 82%).

R_f = 0.58 (toluene/ethyl acetate 5:1);

$[\alpha]_D^{21}$ = -50.9 (c = 0.55, $CHCl_3$);

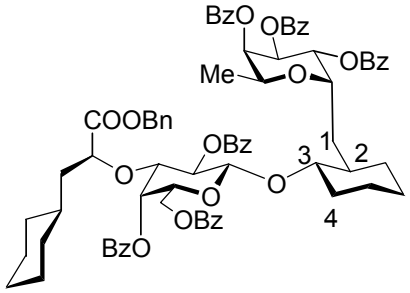
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.42-1.96 (m, 20 H, H-2^{Cyc}, H-$4_{a+b}{}^{Cyc}$, H-$5_{a+b}{}^{Cyc}$, H-$6_{a+b}{}^{Cyc}$, H-$7_{a+b}{}^{Cyc}$, H-4^{Lac}, H-$5_{a+b}{}^{Lac}$, H-$6_{a+b}{}^{Lac}$, H-$7_{a+b}{}^{Lac}$, H-$8_{a+b}{}^{Lac}$, H-$9_{a+b}{}^{Lac}$), 1.08 (m, 1 H, H-$1_a{}^{Cyc}$), 1.18 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.26 (m, 1 H, H-$3_a{}^{Lac}$), 1.34 (m, 1 H, H-$3_b{}^{Lac}$), 2.84 (m, 1 H, H-$1_b{}^{Cyc}$), 3.31 (ddd, $^3J_{2,3}$ = 9.8 Hz, $^3J_{3,4a}$ = 4.2 Hz, $^3J_{3,4b}$ = 9.8 Hz, 1 H, H-3^{Cyc}), 3.90 (dd, $^3J_{2,3}$ = 9.8 Hz, $^3J_{3,4}$ = 3.6 Hz, 1 H, H-3^{Gal}), 3.98 (ddd, $^3J_{4,5}$ = 1.1 Hz, $^3J_{5,6a}$ = 6.6 Hz, $^3J_{5,6b}$ = 6.8 Hz, 1 H, H-5^{Gal}), 4.18 (dd, $^3J_{2,3a}$ = 4.4 Hz, $^3J_{2,3b}$ = 7.8 Hz, 1 H, H-2^{Lac}), 4.31 (dq, $^3J_{4,5}$ = 0.8 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 4.56 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 3.4 Hz, $^3J_{1,1b\text{-}Cyc}$ = 12.9 Hz, $^3J_{1,2}$ = 5.9 Hz, 1 H, H-1^{Fuc}), 4.60 (m, 1 H, H-$6_a{}^{Gal}$), 4.65 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, H-1^{Gal}), 4.67 (m, 1 H, H-$6_b{}^{Gal}$), 5.10, 5.13 (AB, $^2J_{A,B}$ = 12.8 Hz, 2 H, C$\underline{H}_2$-Ph), 5.66 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.8 Hz, 1 H, H-2^{Gal}), 5.73 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 0.8 Hz, 1 H, H-4^{Fuc}), 5.78 (dd, $^3J_{1,2}$ = 5.9 Hz, $^3J_{2,3}$ = 10.5 Hz, 1 H, H-2^{Fuc}), 5.95 (dd, $^3J_{2,3}$ = 10.5 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 5.97 (dd, $^3J_{3,4}$ = 3.6 Hz, $^3J_{4,5}$ = 1.1 Hz, 1 H, H-4^{Gal}), 7.22-8.20 (m, 35 H, 7 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6^{Fuc}), 24.3, 24.9, 25.5, 25.8, 26.1, 29.7, 30.3, 30.8, 32.7, 33.3, 33.4, 37.9, 40.5 (13 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}, C-3^{Lac}, C-4^{Lac},

C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 62.7 (C-6^{Gal}), 65.5 (C-5^{Fuc}), 66.6 (CH_2-Ph), 69.0 (C-3^{Fuc}), 69.8 (C-4^{Gal}), 69.4 (C-2^{Fuc}), 70.4 (C-1^{Fuc}), 71.9 (C-5^{Gal}), 72.6 (C-2^{Gal}), 72.7 (C-4^{Fuc}), 77.2 (C-3^{Gal}), 78.3 (C-2^{Lac}), 79.9 (C-3^{Cyc}), 98.5 (C-1^{Gal}), 128.0, 128.2, 128.3, 128.5, 128.6, 128.6, 128.9, 129.3, 129.4, 129.4, 129.6, 129.7, 129.9, 130.1, 130.1, 130.2, 130.5, 130.6, 130.7, 130.8, 130.9, 132.7, 133.1, 133.2, 133.4, 133.8, 134.4, 135.6 (42 C, 7 C_6H_5), 164.8, 165.1, 165.8, 165.9, 166.0, 166.1, 172.5 (7 COO).

elemental analysis calcd (%) for $C_{77}H_{78}O_{18}$ (1291.47): C 71.61, H 6.09, O 22.30;
found: C 71.29, H 6.12, O 22.59.

Benzyl (*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-[(*1S,2R*)-2-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexyl]-β-D-galactopyranos-3-yl} propanoate (135b) (II-67, cm119):



A solution of **128b** (100 mg, 0.175 mmol), benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-β-D-thio-galactopyranos-3-yl] propanoate (**90**) (205 mg, 0.262 mmol) and activated 3Å molecular sieves (1g) in CH_2Cl_2 (20 ml) was cooled to -20°C. After stirring for 30 min at -20°C, NIS (78.0 mg, 0.345 mmol) was added and stirring was continued for 30 min. Trifluoromethanesulfonic acid (70.0 µl) was added and the dark-purple solution was stirred at -20°C for 4 h. Filtration of molecular sieves, washing of the organic layer with satd. aqueous $Na_2S_2O_3$ (50 ml) and satd. aqueous $NaHCO_3$ (50 ml), drying with Na_2SO_4, evaporation of the solvent under reduced pressure and purification of the crude product mixture by silica gel chromatography (toluene/ethyl acetate 25:1) yielded **135b** (170 mg, 0.132 mmol, 80%).

R_f = 0.65 (toluene/ethyl acetate 5:1);

$[\alpha]_D^{21}$ = -33.0 (c = 0.25, $CHCl_3$);

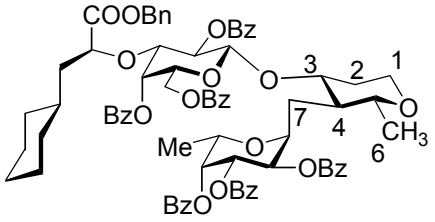
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.50-1.80 (m, 17 H, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.02 (d, $^3J_{5,6}$ = 6.8 Hz, 3 H, H-6^{Fuc}), 1.16 (m, 1

H, H-1_a^{Cyc}), 1.32 (m, 2 H, H-3_a^{Lac}, H-4_a^{Cyc}), 1.39 (m, 1 H, H-3_b^{Lac}), 1.48 (m, 1 H, H-2^{Cyc}), 1.92 (m, 1 H, H-4_b^{Cyc}), 2.26 (m, 1 H, H-1_b^{Cyc}), 3.22 (ddd, $^3J_{2,3}$ = 8.5 Hz, $^3J_{3,4a}$ = 3.5 Hz, $^3J_{3,4b}$ = 8.5 Hz, 1 H, H-3^{Cyc}), 3.49 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.8 Hz, 1 H, H-5^{Fuc}), 3.90 (dd, $^3J_{2,3}$ = 8.9 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3^{Gal}), 3.92 (dd, $^3J_{4,5}$ = 0.8 Hz, $^3J_{5,6}$ = 7.3 Hz, 1 H, H-5^{Gal}), 4.16 (dd, $^3J_{2,3a}$ = 4.5 Hz, $^3J_{2,3b}$ = 7.7 Hz, 1 H, H-2^{Lac}), 4.31 (m, 1 H, H-1^{Fuc}), 4.42 (m, 2 H, H-6_{a+b}^{Gal}), 4.62 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal}), 5.10, 5.12 (AB, $^2J_{A,B}$ = 12.6 Hz, 2 H, C$\underline{H}_2$-Ph), 5.52 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 1.7 Hz, 1 H, H-4^{Fuc}), 5.58 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3^{Fuc}), 5.63 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 8.9 Hz, 1 H, H-2^{Gal}), 5.77 (dd, $^3J_{1,2}$ = 5.7 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Fuc}), 5.84 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 0.7 Hz, 1 H, H-4^{Gal}), 7.22-8.20 (m, 35 H, 7 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.9 (C-6^{Fuc}), 24.3, 24.5, 26.4, 26.5, 26.7, 29.7, 30.1, 32.5, 33.0, 33.7, 34.8, 40.8, 41.0 (13 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}, C-3^{Lac}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 63.3 (C-6^{Gal}), 66.4 (C-5^{Fuc}), 66.6 ($\underline{C}H_2$-Ph), 69.4 (C-2^{Fuc}), 70.0 (C-3^{Fuc}), 70.2 (C-4^{Gal}), 71.5 (C-4^{Fuc}), 71.8 (C-1^{Fuc}), 72.3 (C-5^{Gal}), 73.7 (C-2^{Gal}), 78.2 (C-3^{Gal}), 78.8 (C-2^{Lac}), 84.3 (C-3^{Cyc}), 101.0 (C-1^{Gal}), 128.5, 128.6, 128.7, 128.8, 129.1, 129.2, 129.2, 130.1, 130,2, 130.3, 130.4, 130.5, 130.7, 130.7, 130.8, 130.9, 131.1, 131.2, 131.2, 131.3, 131.3, 133.2, 133.3, 133.4, 133.4, 133.5, 133.7, 133.8 (42 C, 7 C_6H_5), 164.5, 165.2, 166.0, 166.1, 166.8, 167.2, 173.2 (7 COO);

elemental analysis calcd (%) for $C_{77}H_{78}O_{18}$ (1291.47): C 71.61, H 6.09, O 22.30;
found: C 71.27, H 6.05, O 22.68.

Benzyl (*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-[(*2R,3R,4R*)-4-hydroxy-2-methyl-3-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-tetrahydropyran-4-yl]-β-D-galactopyranos-3-yl} propanoate (136):



Method A (II-230, cm284)**: 130a** (20.0 mg, 0.034 mmol) and benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-β-D-thio-galactopyranos-3-yl] propanoate (**90**) (80.0 mg, 0.102 mmol) were dissolved in CH_2Cl_2 (10ml) containing 3Å MS and cooled to –20°C. After 30 min, NIS (24.0 mg, 0.102 mmol) was added and the mixture was stirred for further 30 min. TfOH (15.0 µl) was added and the reaction was stirred for 6 h at –20°C. The dark-red suspension was then filtered through celite, diluted with CH_2Cl_2 (50 ml), washed with satd. aqueous

$Na_2S_2O_3$ (50 ml) and satd. aqueous $NaHCO_3$ (2 x 50 ml), dried with Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (petroleum ether/ethyl acetate 3:1) yielded **136** (31.0 mg, 0.023 mmol, 69%).

Method B (II-216, cm270)**: 130a** (10.0 mg, 0.017 mmol) and benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-β-D-thio-galactopyranos-3-yl] propanoate (**90**) (40.0 mg, 0.034 mmol) were dissolved in CH_2Cl_2 (10ml) containing 3Å MS and cooled to –5°C. After 30 min of stirring, DMTST (20.0 mg, 0.068 mmol) was added and the reaction was stirred for 24 h at –5°C. The mixture was then filtered through celite, washed with satd. aqueous $NaHCO_3$ (2 x 50 ml), dried with Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (petroleum ether/ethyl acetate 3:1) yielded **136** (18.0 mg, 0.014 mmol, 80%).

R_f = 0.27 (petroleum ether/ethyl acetate 2:1);

$[\alpha]_D^{22}$ = -53.4 (c = 0.5, $CHCl_3$);

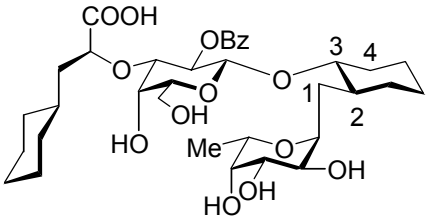
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.38-1.24 (m, 11 H, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.03 (m, 1 H, H-7$_a$^{Pyr}), 1.06 (d, $^3J_{5,6}$ = 6.1 Hz, 3 H, H-6^{Pyr}), 1.24 (m, 2 H, H-2$_a$^{Pyr}, H-3$_a$^{Lac}), 1.32 (m, 1 H, H-3$_b$^{Lac}), 1.34 (d, $^3J_{5,6}$ = 5.9 Hz, 3 H, H-6^{Fuc}), 1.44 (m, 1 H, H-4^{Pyr}), 1.68 (m, 1 H, H-2$_b$^{Pyr}), 2.56 (ddd, $^3J_{1,7b}$ = 3.4 Hz, $^3J_{4,7b}$ = 11.5 Hz, $^2J_{7a,7b}$ = 13.8 Hz, 1 H, H-7$_b$^{Pyr}), 2.78 (dq, $^3J_{4,5}$ = 9.7 Hz, $^3J_{5,6}$ = 6.1 Hz, 1 H, H-5^{Pyr}), 3.12 (ddd, $^3J_{1ax,1eq}$ = 11.6 Hz, $^3J_{1ax,2eq}$ = 2.1 Hz, $^3J_{1ax,2ax}$ = 12.0 Hz, 1 H, H-1$_{ax}$^{Pyr}), 3.25 (ddd, ^3J = 4.8 Hz, 9.8 Hz, 10.7 Hz, 1 H, H-3^{Pyr}), 3.72 (ddd, ^3J = 1.8 Hz, 4.8 Hz, 11,6 Hz, 1 H, H-1$_{eq}$^{Pyr}), 3.84 (dd, $^3J_{2,3}$ = 9.9 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Gal}), 3.98 (ddd, $^3J_{4,5}$ = 1.6 Hz, $^3J_{5,6a}$ = 5.8 Hz, $^3J_{5,6b}$ = 7.4 Hz, 1 H, H-5^{Gal}), 4.11 (dd, ^3J = 4.5, 7.9 Hz, 1 H, H-2^{Lac}), 4.53 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal}), 4.56 (ddd, $^3J_{1,2}$ = 5.9 Hz, $^3J_{1,7a\text{-}Pyr}$ = 13.8 Hz, $^3J_{1,7b\text{-}Pyr}$ = 3.4 Hz, 1 H, H-1^{Fuc}), 4.65 (m, 2 H, H-6$_a$^{Gal}, H-5^{Fuc}), 4.87 (dd, $^3J_{5,6b}$ = 7.4 Hz, $^3J_{6a,6b}$ = 11.6 Hz, 1 H, H-6$_b$^{Gal}), 5.01, 5.09 (AB, $^2J_{A,B}$ = 12.0 Hz, C$\underline{H}_2$-Ph), 5.55 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.9 Hz, 1 H, H-2^{Gal}), 5.65 (m, 2 H, H-2^{Fuc}, H-4^{Fuc}), 5.92 (m, 2 H, H-3^{Fuc}, H-4^{Gal}), 7.03-8.14 (m, 35 H, 7 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0 (C-6^{Fuc}), 20.2 (C-6^{Pyr}), 24.0 (C-7^{Pyr}), 25.9, 26.1, 26.6, 30.1, 32.3, 33.7 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}) 33.0 (C-2^{Pyr}), 40.8 (C-3^{Lac}), 43.1 (C-4^{Pyr}), 63.1 (C-6^{Gal}), 65.8 (C-1^{Pyr}), 67.0 (C-5^{Fuc}), 67.2 ($\underline{C}H_2$-Ph), 69.1 (C-3^{Fuc}), 70.1 (C-

4^{Gal}), 71.1 (C-2^{Fuc}), 72.6 (C-1^{Fuc}), 72.8 (C-5^{Gal}), 72.9 (C-2^{Gal}), 73.4 (C-4^{Fuc}), 78.0 (C-3^{Gal}), 78.7 (C-2^{Lac}), 78.8 (C-5^{Pyr}), 80.2 (C-3^{Pyr}), 100.0 (C-1^{Gal}), 128.3, 128.4, 128.5, 128.6, 128.6, 128.9, 129.3, 129.4, 129.4, 129.6, 129.7, 129.9, 130.1, 130.1, 130.2, 130.5, 130.6, 130.7, 130.8, 130.9, 132.7, 133.1, 133.2, 133.4, 133.8, 134.4, 135.6, 135.9 (42 C, 7 C_6H_5), 165.2, 165.5, 165.8, 166.3, 166.4, 166.6, 172.9 (7 COO).

elemental analysis calcd (%) for $C_{77}H_{78}O_{19}$ (1307.44): C 70.74, H 6.01, O 23.25;
found: C 70.79, H 6.28, O 22.95.

Methyl (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*1R,2S*)-2-(*α*-L-fucopyranosyl-methyl)-cyclohexyl]-*β*-D-galactopyranos-3-yl} propanoate (137a) (II-136, cm192):

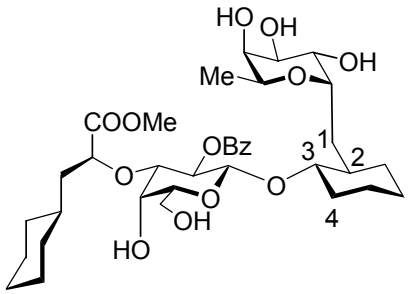


To a solution of **135a** (64.0 mg, 0.049 mmol) in MeOH (5 ml), NaOMe/MeOH (1M, 100 µl) was added and the reaction was stirred at room temperature for 1 h and at 40°C for 2 h. The mixture was then neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, concentrated and the remaining crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 3:1) to yield **137a** (30.0 mg, 0.044 mmol, 89%).

R_f = 0.16 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.60-1.90 (m, 17 H, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 0.98 (m, 1 H, H-2^{Cyc}), 1.27 (d, $^3J_{5,6}$ = 6.1 Hz, 1 H, H-6^{Fuc}), 1.34 (m,1 H, H-3$_a^{Lac}$), 1.46 (m, 2 H, H-1$_a^{Cyc}$, H-4$_a^{Cyc}$), 1.55 (m, 1 H, H-3$_b^{Lac}$), 1.91 (m, 1 H, H-4$_b^{Cyc}$), 2.26 (m, 1 H, H-1$_b^{Cyc}$), 3.34 (ddd, ^3J = 4.2 Hz, ^3J = 8.5 Hz, ^3J = 8.6 Hz, 1 H, H-3^{Cyc}), 3.53 (dd, $^3J_{2,3}$ = 9.6 Hz, $^3J_{3,4}$ = 4.8 Hz, 1 H, H-3^{Gal}), 3.59 (m, 1 H, H-5^{Gal}), 3.82 (dd, $^3J_{3,4}$ = 2.1 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, H-4^{Fuc}), 3.86 (m, 2 H, H-3^{Fuc}, H-4^{Gal}), 3.89 (dq, $^3J_{4,5}$ = 1.0 Hz, $^3J_{5,6}$ = 6.1 Hz, 1 H, H-5^{Fuc}), 3.97 (m, 2 H, H-2^{Lac}, H-6$_a^{Gal}$), 4.04 (m, 2 H, H-2^{Fuc}, H-6$_b^{Gal}$), 4.21 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 10.6 Hz, $^3J_{1,1b\text{-}Cyc}$ = 2.1 Hz, $^3J_{1,2}$ = 5.3 Hz, 1 H, H-1^{Fuc}), 4.61 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, H-1^{Gal}), 5.44 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.6 Hz, 1 H, H-2^{Gal}), 7.40-8.12 (m, 5 H, C_6H_5);

Methyl (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*1S,2R*)-2-(α-L-fucopyranosyl-methyl)-cyclohexyl]-β-D-galactopyranos-3-yl} propanoate (138b) (II-25, cm079)**:**

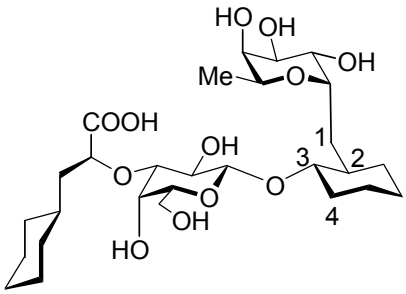


Under argon, **135b** (155 mg, 0.120 mmol) was dissolved in methanol (5 ml). A solution of NaOMe in MeOH (0.1 M, 5 ml) was added and the reaction mixture was stirred at room temperature for 2 h. After neutralization with amberlyste ion-exchange resin (H^+ form), the suspension was filtered through celite, concentrated and the remaining crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 6:1) to yield **138b** (73.0 mg, 0.105 mmol, 88%).

R_f = 0.71 (CH_2Cl_2/MeOH 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.52-1.95 (m, 20 H, H-2^{Cyc}, H-$4_{a+b}{}^{Cyc}$, H-$5_{a+b}{}^{Cyc}$, H-$6_{a+b}{}^{Cyc}$, H-$7_{a+b}{}^{Cyc}$, H-4^{Lac}, H-$5_{a+b}{}^{Lac}$, H-$6_{a+b}{}^{Lac}$, H-$7_{a+b}{}^{Lac}$, H-$8_{a+b}{}^{Lac}$, H-$9_{a+b}{}^{Lac}$), 1.05 (m, 1 H, H-$1_a{}^{Cyc}$), 1.13 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.32 (m, 1 H, H-$3_a{}^{Lac}$), 1.56 (m, 1 H, H-$3_b{}^{Lac}$), 2.19 (m, 1 H, H-$1_b{}^{Cyc}$), 3.39 (m, 2 H, H-5^{Fuc}, H-3^{Cyc}), 3.55 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{3,4}$ = 2.5 Hz, 1 H, H-3^{Gal}), 3.62 (m, 2 H, H-3^{Fuc}, H-5^{Gal}), 3.66 (dd, 1 H, H-4^{Fuc}), 3.74 (s, 3 H, OMe), 3.80 (dd, $^3J_{1,2}$ = 3.7 Hz, $^3J_{2,3}$ = 11.3 Hz, 1 H, H-2^{Fuc}), 3.91 (m, 1 H, H-4^{Gal}), 3.95-4.05 (m, 4 H, H-1^{Fuc}, H-2^{Lac}, H-$6_{a+b}{}^{Gal}$), 4.70 (d, $^3J_{1,2}$ = 8.5 Hz, 1 H, H-1^{Gal}), 5.51 (dd, $^3J_{1,2}$ = 8.5 Hz, $^3J_{2,3}$ = 9.4 Hz, 1 H, H-2^{Gal}), 7.47, 7.59, 8.08 (m, 5 H, C_6H_5).

(*2S*)-3-cyclohexyl-2-*O*-{1-*O*-[(*1S,2R*)-2-(α-L-fuco-pyranosyl-methyl)-cyclohexyl]-β-D-galactopyranos-3-yl} propanoic acid (139b) (II-68, cm120):



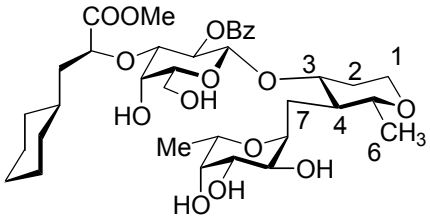
Under argon, **135b** (140 mg, 0.110 mmol) was dissolved in methanol (5 ml) and a solution of NaOMe in MeOH (23.0 mg Na dissolved in 5 ml MeOH) was added. The mixture was then stirred at 55°C for 42 h, neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, concentrated and the remaining crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH/H_2O 10:4:0.8) to yield **139b** (60.0 mg, 0.104 mmol, 94%).

R_f = 0.27 (CH_2Cl_2/MeOH/H_2O 10:4:0.8);

^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD): δ 0.90-2.17 (m, 20 H, H-2^{Cyc}, H-$4_{a+b}{}^{Cyc}$, H-$5_{a+b}{}^{Cyc}$, H-$6_{a+b}{}^{Cyc}$, H-$7_{a+b}{}^{Cyc}$, H-4^{Lac}, H-$5_{a+b}{}^{Lac}$, H-$6_{a+b}{}^{Lac}$, H-$7_{a+b}{}^{Lac}$, H-$8_{a+b}{}^{Lac}$, H-$9_{a+b}{}^{Lac}$), 1.24 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.38 (m, 1 H, H-$1_a{}^{Cyc}$), 1.66 (m, 1 H, H-$3_a{}^{Lac}$), 1.69 (m, 1 H, H-$3_b{}^{Lac}$), 2.17 (m, 1 H, H-$1_b{}^{Cyc}$), 3.24 (dd, $^3J_{2,3}$ = 9.2 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Gal}), 3.29 (ddd, ^3J = 3.7 Hz, 10.0 Hz, 10.1 Hz, H-3^{Cyc}), 3.47 (m, 1 H, H-5^{Gal}), 3.67 (m, 2 H, H-2^{Gal}, H-3^{Fuc}), 3.71 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.8 Hz, 1 H, H-4^{Fuc}), 3.75 (m, 2 H, H-$6_{a+b}{}^{Gal}$), 3.85 (dq, $^3J_{4,5}$ = 1.8 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 3.85 (dd, $^3J_{1,2}$ = 5.3 Hz, $^3J_{2,3}$ = 9.2 Hz, 1 H, H-2^{Fuc}), 3.93 (m, 2 H, H-2^{Lac}, H-4^{Gal}), 4.16 (ddd, $^3J_{1,1a\text{-}Cyc}$ = 4.0 Hz, $^3J_{1,1b\text{-}Cyc}$ = 9.1 Hz, $^3J_{1,2}$ = 5.3 Hz, 1 H, H-1^{Fuc}), 4.30 (d, $^3J_{1,2}$ = 7.5 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD): δ 16.2 (C-6^{Fuc}), 25.1, 25.9, 26.7, 27.1, 28.4, 32.7, 34.0, 34.3, 34.6, 42.1, 42.4 (12 C, C-1^{Cyc}, C-2^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 26.5 (C-3^{Lac}), 61.8 (C-6^{Gal}), 66.6 (C-4^{Gal}), 68.1 (C-5^{Fuc}), 69.7 (C-2^{Fuc}), 71.2 (C-3^{Fuc}), 71.3 (C-2^{Gal}), 71.8 (C-4^{Fuc}), 74.7 (C-5^{Gal}), 75.2 (C-1^{Fuc}), 78.4 (C-2^{Lac}), 84.5 (C-3^{Gal}), 86.5 (C-3^{Cyc}), 105.0 (C-1^{Gal}) , 183.7 (COONa).

Methyl (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*2R,3R,4R*)-4-hydroxy-2-methyl-3-(α-L-fuco-pyranosyl)-methyl-tetrahydropyran-4-yl]-β-D-galacto-pyranos-3-yl} propanoate (140) (II-234, cm288):



To a solution of **136** (35.0 mg, 0.027 mmol) in methanol (5 ml), NaOMe/MeOH (1 M, 100µl) was added and the reaction was stirred for 11 h at room temperature. The mixture was then neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite and concentrated. Purification by silica gel chromatography (CH_2Cl_2/MeOH 5:1) yielded **140** (16.5 mg, 0.023 mmol, 87%).

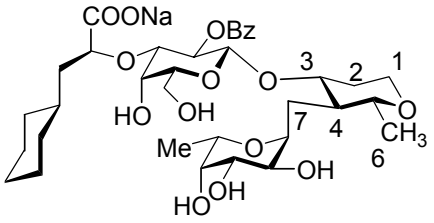
R_f = 0.43 (CH_2Cl_2/MeOH 4:1);

$[\alpha]_D^{22}$ = -57.2 (c = 0.9, MeOH);

^{1}H NMR (500 MHz, CD_3OD): δ 0.60-1.61 (m, 11 H, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.15 (m, 1 H, H-2$_{ax}$^{Pyr}), 1.20 (d, $^{3}J_{5,6}$ = 5.9 Hz, 3 H, H-6^{Pyr}), 1.27 (d, $^{3}J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.31 (m, 1 H, H-4^{Pyr}), 1.36 (m, 2 H, H-3$_{a}$^{Lac}, H-7$_{a}$^{Pyr}), 1.53 (m, 1 H, H-3$_{b}$^{Lac}), 1.95 (m, 1 H, H-2$_{eq}$^{Pyr}), 2.24 (ddd, J = 11.9 Hz, 12.2 Hz, 3.0 Hz, 1 H, H-7$_{b}$^{Pyr}), 3.19 (dq, $^{3}J_{4,5}$ = 9.7 Hz, $^{3}J_{5,6}$ = 5.9 Hz, 1 H, H-5^{Pyr}), 3.38 (ddd, J = 12.6 Hz, 12.3 Hz, 1.5 Hz, 1 H, H-1$_{ax}$^{Pyr}), 3.56 (ddd, J = 10.7 Hz, 10.4 Hz, 4.4 Hz, 1 H, H-3^{Pyr}), 3.62 (ddd, $^{3}J_{4,5}$ = 2.5 Hz, $^{3}J_{5,6a}$ = 6.6 Hz, $^{3}J_{5,6b}$ = 6.0 Hz, 1 H, H-5^{Gal}), 3.72 (m, 2 H, H-3^{Gal}, H-3^{Fuc}), 3.76 (s, 3 H, OMe), 3.77 (m, 1 H, H-4^{Fuc}), 3.81 (m, 3 H, H-6$_{a+b}$^{Gal}, H-1$_{eq}$^{Pyr}), 3.95 (m, 2 H, H-1^{Fuc}, H-2^{Fuc}), 4.02 (dd, $^{3}J_{3,4}$ = 1.8 Hz, $^{3}J_{4,5}$ = 2.5 Hz, 1 H, H-4^{Gal}), 4.17 (dd, $^{3}J_{2,3a}$ = 3.1 Hz, $^{3}J_{2,3b}$ = 9.7 Hz, 1 H, H-2^{Lac}), 4.31 (dq, $^{3}J_{4,5}$ = 1.5 Hz, $^{3}J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.73 (d, $^{3}J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal}), 5.47 (dd, $^{3}J_{1,2}$ = 7.8 Hz, $^{3}J_{2,3}$ = 6.6 Hz, 1 H, H-2^{Gal}), 7.52-8.11 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, CD_3OD): δ 17.3 (C-6^{Fuc}), 20.7 (C-6^{Pyr}), 24.3 (C-7^{Pyr}), 24.9, 26.9, 27.2, 27.6, 31.1, 33.6 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 34.0 (C-2^{Pyr}), 42.9 (C-3^{Lac}), 45.8 (C-4^{Pyr}), 53.2 (OCH_3), 62.9 (C-6^{Gal}), 66.8 (C-1^{Pyr}), 68.6 (C-4^{Gal}), 68.7 (C-5^{Fuc}), 70.5 (C-2^{Fuc}), 72.3 (C-3^{Fuc}), 73.6 (C-2^{Gal}), 73.8 (C-4^{Fuc}), 76.2 (C-1^{Fuc}), 76.4 (C-5^{Gal}), 78.7 (C-2^{Lac}), 79.9 (C-3^{Pyr}), 80.0 (C-5^{Pyr}), 83.5 (C-3^{Gal}), 100.6 (C-1^{Gal}), 131.3, 131.9, 132.3, 133.6, 135.0 (6 C, C_6H_5).

Sodium (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*2R,3R,4R*)-4-hydroxy-2-methyl-3-(α-L-fuco-pyranosyl-methyl)-tetrahydropyran-4-yl]-β-D-galacto-pyranos-3-yl} propanoate (141) (II-240, cm294):



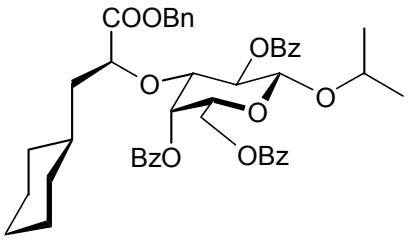
To a solution of **140** (5.00 mg, 7.03 µmol) in a mixture of dioxane and water (1:1, 4 ml), LiOH (16.0 mg, 0.700 mmol) was added and the reaction was stirred at room temperature for 3 h. The mixture was then acidified to pH 4 (diluted HCl), freeze-dried, passed over Dowex 50x8 ion-exchange resin (Na^+ form), purified by RP-18 reversed-phase silica gel column chromatography (gradient MeOH/H_2O 0:1 → 1:0) and P2 column chromatography to yield **141** (3.00 mg, 4.17 µmol, 60 %).

R_f = 0.24 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.51-1.63 (m, 11 H, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.17 (m, 1 H, H-2$_a$^{Pyr}), 1.18 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Pyr}), 1.23 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.29 (m, 1 H, H-4^{Pyr}), 1.37 (m, 1 H, H-7$_a$^{Pyr}), 1.41 (m, 1 H, H-3$_a$^{Lac}), 1.50 (ddd, J = 9.7 Hz, 6.6 Hz, 3.4 Hz, 1 H, H-3$_b$^{Lac}), 1.97 (m, 1 H, H-2$_b$^{Pyr}), 2.22 (ddd, J = 15.1 Hz, 12.9 Hz, 1.5 Hz, H-7$_b$^{Pyr}), 3.19 (dq, $^3J_{5,6}$ = 6.3 Hz, $^3J_{5,4}$ = 9.4 Hz, 1 H, H-5^{Pyr}), 3.39 (ddd, J = 12.9 Hz, 11.6 Hz, 1.5 Hz, 1 H, H-1$_a$^{Pyr}), 3.57 (ddd, J = 11.3 Hz, 10.4 Hz, 4.4 Hz, 1 H, H-3^{Pyr}), 3.61 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 2.5 Hz, 1 H, H-3^{Gal}), 3.63 (ddd, J = 0.6 Hz, 5.3 Hz, 5.9 Hz, 1 H, H-5^{Gal}), 3.72 (m, 1 H, H-3^{Fuc}), 3.75 (m, 1 H, H-4^{Fuc}), 3.77-3.85 (m, 3 H, H-1b^{Pyr}, H-6$_{a+b}$^{Gal}), 3.79 (m, 1 H, H-2^{Lac}), 3.92 (dd, $^3J_{1,2}$ = 5.3 Hz, $^3J_{2,3}$ = 9.8 Hz,1 H, H-2^{Fuc}), 3.94 (m, 1 H, H-1^{Fuc}), 3.98 (m, 1 H, H-4^{Gal}), 4.27 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.73 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal}), 5.36 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Gal}), 7.50-8.10 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, D_2O): δ 16.1 (C-6^{Fuc}), 19.1 (C-6^{Pyr}), 22.7 (C-7^{Pyr}), 26.9, 27.2, 27.8, 33.4, 34.0, 34.9 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 32.5 (C-2^{Pyr}), 42.6 (C-3^{Lac}), 61.9 (C-6^{Gal}), 65.4 (C-1^{Pyr}), 66.8 (C-4^{Gal}), 67.3 (C-5^{Fuc}), 68.9 (C-2^{Fuc}), 70.0 (C-3^{Fuc}), 72.0 (C-2^{Gal}), 72.3 (C-4^{Fuc}), 74.6 (C-1^{Fuc}), 74.9 (C-5^{Gal}), 78.1 (C-3^{Pyr}), 78.7 (C-5^{Pyr}), 79.5 (C-2^{Lac}), 82.6 (C-3^{Gal}), 99.2 (C-1^{Gal}), 128.4, 129.8, 133.0, 134.7 (6 C, C_6H_5) , 183.1 (COONa).

Benzyl (*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-isopropyl-*β*-D-galactopyranos-3-yl} propanoate (142) (II-161, cm217):



Under argon, benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-*β*-D-thio-galactopyranos-3-yl] propanoate (**90**) (300 mg, 0.380 mmol) was dissolved in CH_2Cl_2 (10 ml) containing freshly activated 3Å molecular sieves (600 mg) and cooled to -5°C. After stirring for 1 h at –5°C, isopropanol (90.0 µl, 0.770 mmol) was added and stirring was continued for an additional hour, before DMTST (200 mg, 0.510 mmol) was added. The reaction mixture was then stirred for 24 h at –5°C, molecular sieves were filtered off, the reaction was quenched with satd. aqueous $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were dried with Na_2SO_4, filtered, evaporated and dried under high vacuum. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 6:1) to yield **142** (292 mg, 0.370 mmol, 98%).

R_f = 0.41 (petroleum ether/ethyl acetate 3:1);

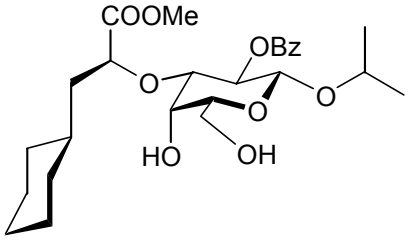
$[\alpha]_D^{22}$ = +17.7 (c = 1.03, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.49-1.29 (m, 11 H, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.38 (m, 2 H, H-3$_{a+b}$^{Lac}), 1.00 (d, $^3J_{1,Me-1}$ = 6.1 Hz, 3 H, CH<u>Me</u>$_2$), 1.18 (d, $^3J_{1,Me-2}$ = 6.2 Hz, 3 H, CH<u>Me</u>$_2$), 3.87 (dq, $^3J_{1,Me-1}$ = 6.1 Hz, $^3J_{1,Me-2}$ = 6.2 Hz, 1 H, C<u>H</u>Me$_2$), 3.91 (dd, $^3J_{2,3}$ = 9.9 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Gal}), 3.98 (ddd, $^3J_{4,5}$= 0.5 Hz, $^3J_{5,6a}$ = 5.3 Hz, $^3J_{5,6b}$ = 7.4 Hz, 1 H, H-5^{Gal}), 4.18 (dd, $^3J_{2,3a}$ = 4.5 Hz, $^3J_{2,3b}$ = 8.2 Hz, 1 H, H-2^{Lac}), 4.43 (dd, $^3J_{5,6a}$ = 5.3 Hz, $^2J_{6a,6b}$ = 11.5 Hz, 1 H, H-6$_a$^{Gal}), 4.48 (dd $^3J_{5,6b}$ = 7.4 Hz, $^2J_{6a,6b}$ = 11.5 Hz, 1 H, H-6$_b$^{Gal}), 4.60 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, H-1^{Gal}), 5.04, 5.16 (AB, $^2J_{A,B}$ = 12.1 Hz, 2 H, C<u>H</u>$_2$-Ph), 5.59 (dd, $^3J_{1,2}$= 7.9 Hz, $^3J_{2,3}$= 9.9 Hz, 1 H, H-2^{Gal}), 5.91 (dd, $^3J_{3,4}$= 3.4 Hz, $^3J_{4,5}$= 0.5 Hz, 1 H, H-4^{Gal}), 7.20-8.20 (m, 20 H, 4 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 23.2 (4 C, 2 CH<u>Me</u>$_2$), 25.5, 25.8, 26.1, 32.6, 33.3, 33.4, 40.4 (7 C, C-3^{Lac}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 62.9 (C-6^{Gal}), 66.6 (<u>C</u>H$_2$-Ph), 69.9 (C-4^{Gal}), 71.7 (C-5^{Gal}), 72.9 (C-2^{Gal}), 73.3 (<u>C</u>HMe$_2$), 77.4 (C-3^{Gal}), 78.0 (C-2^{Lac}), 100.6 (C-1^{Gal}), 128.3, 128.4, 128.4, 128.5, 128.6, 128.7, 128.9, 129.6, 129.7, 129.7, 129.8, 129.9, 130.2, 133.1, 133.2, 135.5 (24 C, 4 C_6H_5), 164.9, 165.9, 166.1, 172.5 (4 COO);

elemental analysis calcd (%) for $C_{46}H_{50}O_{11}$ (778.89): C 70.94, H 6.47, O 22.59;
found: C 70.71, H 6.54, O 22.75.

Methyl (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-isopropyl-*β*-D-galactopyranos-3-yl} propanoate



(143) (II-162, cm218):

Under argon, **142** (150 mg, 0.190 mmol) was dissolved in methanol (5 ml) and a freshly prepared solution of NaOMe/MeOH (1 M, 100 µl) was added slowly. The reaction mixture was stirred for 20 h at room temperature. The mixture was then neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, evaporated and dried at high vacuum. The crude product was

purified by silica gel chromatography (toluene/ethyl acetate 5:1) to yield **143** (80.0 mg, 0.160 mmol, 85%).

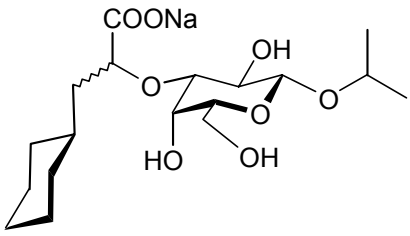
R_f = 0.55 (CH_2Cl_2/MeOH 6:1);

$[\alpha]_D^{22}$ = -22.3 (c = 1.03, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.60-1.60 (m, 11 H, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.01 (d, $^3J_{1,Me-1}$ = 6.1 Hz, 3 H, CH<u>Me</u>$_2$), 1.18 (d, $^3J_{1,Me-2}$ = 6.3 Hz, 3 H, CH<u>Me</u>$_2$), 1.50 (m, 1 H, H-3$_a^{Lac}$), 1.60 (m, 1 H, H-3$_b^{Lac}$), 3.58 (ddd, $^3J_{4,5}$ = 1.0 Hz, $^3J_{5,6a}$ = 5.6 Hz, $^3J_{5,6b}$ = 11.4 Hz, 1H, H-5^{Gal}), 3.60 (dd, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, H-3^{Gal}), 3.76 (s, 3 H, OMe), 3.84 (ddd, $^3J_{5,6a}$ = 5.6 Hz, $^3J_{5,6b}$ = 11.4 Hz, $^2J_{6a,6b}$ = 14.0 Hz, 2 H, H-6$_{a+b}^{Gal}$), 3.96 (dq, $^3J_{1,Me-1}$ = 6.1 Hz, $^3J_{1,Me-2}$ = 6.3 Hz, 1 H, C<u>H</u>Me$_2$), 3.98 (dd, $^3J_{3,4}$ = 3.0 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, H-4^{Gal}), 4.06 (dd, $^3J_{2,3a}$ = 3.0 Hz, $^3J_{2,3b}$ = 12.7 Hz, 1 H, H-2^{Lac}), 4.62 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, H-1^{Gal}), 5.42 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 9.5 Hz, 1 H, H-2^{Gal}), 7.3-8.05 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 23.8 (4 C, 2 CH<u>Me</u>$_2$), 26.2, 26.4, 27.0, 32.9, 33.8, 34.6 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 42.2 (C-3^{Lac}), 53.2 (OMe), 62.0 (C-6^{Gal}), 67.7 (C-4^{Gal}), 72.8 (C-2^{Gal}), 73.3 (<u>C</u>HMe$_2$), 75.6 (C-5^{Gal}), 78.1 (C-2^{Lac}), 83.0 (C-3^{Lac}), 101.0 (C-1^{Gal}), 129.1, 129.4, 129.7, 129.8, 130.6, 130.9, 131.2, 134.2 (12 C, 2 C_6H_5), 166.7, 176.7 (2 COO).

Sodium (*2S*)-3-cyclohexyl-2-*O*-{1-*O*-isopropyl-*β*-D-galactopyranos-3-yl} propanoic acid (144) and **Sodium (*2R*)-3-cyclohexyl-2-*O*-{1-*O*-isopropyl-*β*-D-galactopyranos-3-yl} propanoic acid (145)**:



Method A (microwave oven) (II-237, cm297)**:** Under argon, **142** (25.0 mg, 0.032 mmol) was dissolved in methanol (3 ml) in a microwave tube and a solution of NaOMe/MeOH (1 M, 100 µl) was added. The solution was radiated in a microwave oven at 70°C for 2 h and stirred without radiation at room temperature for 20 h. The reaction was then neutralized with

amberlyste ion-exchange resin (H^+ form), filtered, concentrated and dissolved again in a mixture of dioxane and water (1:1, 2 ml). After adding LiOH (10.0 mg, 0.396 mmol), the reaction mixture was stirred for 3 h at room temperature, acidified to pH 4-5 with diluted acetic acid, passed over Dowex 50x8 ion-exchange resin (Na^+ form), purified by RP-18 reversed-phase silica gel column chromatography (gradient MeOH/H_2O 0:1 → 1:0) and P2 column chromatography to yield a 1:1 mixture of the two diastereomers **144** and **145** (12.0 mg, 0.030 mmol, 94%).

Method B (toluene/methanol) (II-244, cm299)**:** Under argon, **143** (20.0 mg, 0.040 mmol) was dissolved in toluene/methanol (1:1, 20 ml) and a freshly prepared solution of NaOMe in MeOH (1 M, 750 µl) was added. The reaction was stirred for 26 h at room temperature, neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, evaporated and dried under high vacuum. The crude mixture was purified by RP-18 reversed-phase silica gel column chromatography (gradient MeOH/H_2O 1:1 → 1:0) and passed over a basic Na-ionexchange column to yield **144** (8.00 mg, 0.020 mmol, 51%). Starting material **143** (10.0 mg, 0.019 mmol, 49%) could be recovered.

145 (F I):

R_f = 0.48 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.88-1.81 (m, 11 H, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.19 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me</u>$_2$), 1.22 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me</u>$_2$), 1.54 (m, 2 H, H-3$_{a+b}^{Lac}$), 3.40 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Gal}), 3.54 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Gal}), 3.60 (m, 1 H, H-5^{Gal}), 3.72 (m, 2 H, H-6$_{a+b}^{Gal}$), 3.41 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 0.9 Hz, 1 H, H-4^{Gal}), 4.05 (dd, J = 4.4 Hz, 8.8 Hz, 1 H, H-2^{Lac}), 4.10 (m, 1 H, C<u>H</u>Me$_2$), 4.47 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 21.4, 22.8 (4 C, 2 CH<u>Me</u>$_2$), 26.3, 26.5, 26.9, 30.4, 32.5, 33.3, 41.0 (7 C, C-3^{Lac}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 61.1 (C-6^{Gal}), 66.4 (C-4^{Gal}), 69.8 (C-2^{Gal}), 73.1 (<u>C</u>HMe$_2$), 75.6 (C-5^{Gal}), 78.5 (C-2^{Lac}), 81.4 (C-3^{Gal}), 101.6 (C-1^{Gal});

^{1}H NMR (500 MHz, CD_3OD): δ 0.78-1.91 (m, 11 H, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.18 (d, ^3J = 6.0 Hz, 3 H, CH<u>Me</u>$_2$), 1.22 (d, ^3J = 6.0 Hz, 3 H, CH<u>Me</u>$_2$), 1.56

(m, 1 H, H-3_a^{Lac}), 1.64 (m, 1 H, H-3_b^{Lac}), 3.19 (dd, $^3J_{2,3}$ = 9.2 Hz, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3^{Gal}), 3.48 (ddd, $^3J_{4,5}$ = 1.5 Hz, $^3J_{5,6a}$ = 4.9 Hz, $^3J_{5,6b}$ = 4.6 Hz, 1 H, H-5^{Gal}), 3.58 (dd, $^3J_{1,2}$ = 7.4 Hz, $^3J_{2,3}$ = 9.2 Hz, 1 H, H-2^{Gal}), 3.75 (m, 2 H, H-6_{a+b}^{Gal}), 3.87 (dd, J = 3.7 Hz, 9.7 Hz, 1 H, H-2^{Lac}), 3.89 (dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{4,5}$ = 1.5 Hz, 1 H, H-4^{Gal}), 4.04 (m, 1 H, C<u>H</u>Me_2), (d, $^3J_{1,2}$ = 7.4 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, CD_3OD): δ 21.6, 23.2 (4 C, 2 CH<u>Me_2</u>), 62.1 (C-6^{Gal}), 67.2 (C-4^{Gal}), 70.9 (C-2^{Gal}), 72.0 (<u>C</u>HMe_2), 75.5 (C-5^{Gal}), 80.3 (C-2^{Lac}), 85.1 (C-3^{Gal}), 102.6 (C-1^{Gal}), 182.9 (COONa).

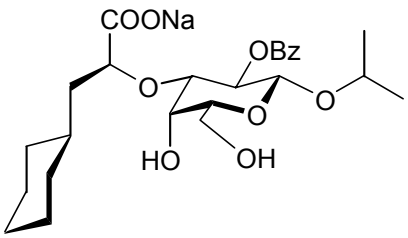
144 (F II):

R_f = 0.45 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.88-1.79 (m, 11 H, H-4^{Lac}, H-5_{a+b}^{Lac}, H-6_{a+b}^{Lac}, H-7_{a+b}^{Lac}, H-8_{a+b}^{Lac}, H-9_{a+b}^{Lac}), 1.19 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me_2</u>), 1.22 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me_2</u>), 1.54 (m, 1 H, H-3_a^{Lac}), 1.59 (m, 1 H, H-3_b^{Lac}), 3.39 (dd, $^3J_{2,3}$ = 9.4 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Gal}), 3.52 (dd, $^3J_{1,2}$ = 8.2 Hz, $^3J_{2,3}$ = 9.4 Hz, 1 H, H-2^{Gal}), 3.65 (m, 1 H, H-5^{Gal}), 3.72 (m, 2 H, H-6_{a+b}^{Gal}), 3.41 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4.5}$ = 0.7 Hz, 1 H, H-4^{Gal}), 3.90 (dd, J = 3.4 Hz, 10.0 Hz, 1 H, H-2^{Lac}), 3.95 (m, 1 H, C<u>H</u>Me_2), 4.46 (d, $^3J_{1,2}$ = 8.2 Hz, 1 H, H-1^{Gal});

^{13}C NMR (125 MHz, D_2O): δ 21.2, 22.6 (4 C, 2 CH<u>Me_2</u>), 26.1, 26.3, 26.5, 30.6, 32.2, 33.6, 41.6 (7 C, C-3^{Lac}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 41.6 (C-3^{Lac}), 61.0 (C-6^{Gal}), 66.4 (C-4^{Gal}), 70.2 (C-2^{Gal}), 73.6 (<u>C</u>HMe_2), 75.1 (C-5^{Gal}), 79.4 (C-2^{Lac}), 83.6 (C-3^{Gal}), 101.3 (C-1^{Gal}) , 183.1 (COONa).

Sodium (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzyl-1-*O*-isopropyl-*β*-D-galactopyranos-3-yl} propanoate



(146) (II-244, cm299):

Under argon, **143** (20 mg, 0.04 mmol) was dissolved in toluene/methanol (1:1, 20 ml) and a freshly prepared solution of NaOMe in MeOH (1 M, 750 µl) was added. The reaction was stirred for 26 h at

room temperature, neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, evaporated and dried under high vacuum. The crude mixture was purified by RP-18 reversed-phase silica gel column chromatography (gradient MeOH/H_2O 1:1 → 1:0) and passed over Dowex 50x8 ion-exchange resin (Na^+ form) to yield **146** (10.0 mg, 0.019 mmol, 49%) together with **144** (8.00 mg, 0.021 mmol, 51%).

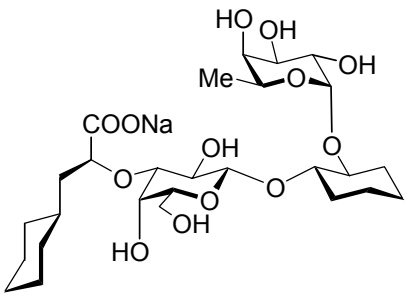
146:

R_f = 0.67 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, CD_3OD): δ 0.51-1.66 (m, 11 H, H-4^{Lac}, H-5$_{a+b}$^{Lac}, H-6$_{a+b}$^{Lac}, H-7$_{a+b}$^{Lac}, H-8$_{a+b}$^{Lac}, H-9$_{a+b}$^{Lac}), 1.01 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me</u>$_2$), 1.15 (d, ^3J = 5.9 Hz, 3 H, CH<u>Me</u>$_2$), 1.42 (m, 1 H, H-3$_a$^{Lac}), 1.49 (m, 1 H, H-3$_b$^{Lac}), 3.64 (m, 2 H, H-5^{Gal}, H-3^{Gal}), 3.78 (m, 2 H, H-6$_{a+b}$^{Gal}), 3.79 (dd, $^3J_{2,3a}$ = 6.6 Hz, $^3J_{2,3b}$ = 2.5 Hz, 1 H, H-2^{Lac}), 3.98 (m, 1 H, C<u>H</u>Me$_2$), 4.02 (dd, $^3J_{3,4}$ = 4.1 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-4^{Gal}), 4.71 (d, $^3J_{1,2}$ = 7.8 Hz, 1 H, H-1^{Gal}), 5.34 (dd, $^3J_{1,2}$ = 7.8 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Gal}), 7.49-8.10 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, CD_3OD): δ 21.9, 23.4 (4 C, 2 CH<u>Me</u>$_2$), 27.0, 27.3, 27.8, 33.5, 33.9, 35.8 (6 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 43.9 (C-3^{Lac}), 61.9 (C-6^{Gal}), 67.3 (C-4^{Gal}), 72.0 (C-2^{Gal}), 72.8 (<u>C</u>HMe$_2$), 75.2 (C-5^{Gal}), 80.3 (C-2^{Lac}), 83.1 (C-3^{Gal}), 100.8 (C-1^{Gal}), 129.2, 130.4, 131.1, 133.9 (6 C, C_6H_5), 166.8, 183.0 (2 COO).

Sodium (*2S*)-3-cyclohexyl-2-*O*-{1-*O*-[(*1S,2S*)-2-*O*-(α-L-fucopyranosyl)cyclohexyl]-β-D-galactopyranos-3-yl}propanoate (148) (II-236, cm290):



A solution of **154** (30.0 mg, 33.8 µmol) in methanol (3 ml) and NaOMe/MeOH (1 M, 100 µl) was stirred in a microwave oven at 70°C for 2 h. The solution was neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite and concentrated. The obtained syrup was purified by RP-18 reversed-phase silica gel chromatography (gradient MeOH/H_2O 0:1 → 1:0), passed over Dowex 50x8 ion-exchange resin (Na^+ form) and chromatographed on a P2 gel column to yield **148** (16.0 mg, 26.6 µmol, 71%).

R_f = 0.23 (CH_2Cl_2/MeOH/H_2O 10:4:0.8);

$[\alpha]_D^{21}$ = -57.4 (c = 0.75, MeOH);

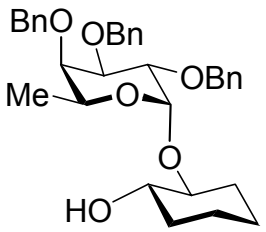
^{1}H NMR (500 MHz, D_2O): δ 0.82-2.10 (m, 15 H, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-4^{Lac}, H-5_{a+b}^{Lac}, H-6_{a+b}^{Lac}, H-7_{a+b}^{Lac}, H-8_{a+b}^{Lac}, H-9_{a+b}^{Lac}), 1.16 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.32 (m, 1 H, H-3_a^{Cyc}), 1.36 (m, 1 H, H-6_a^{Cyc}), 1.50 (m, 1 H, H-3_a^{Lac}), 1.56 (m, 1 H, H-3_b^{Lac}), 1.96 (m, 1 H, H-6_b^{Cyc}), 2.09 (m, 1 H, H-3_b^{Cyc}), 3.35 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Gal}), 3.49 (m, 1 H, H-1^{Cyc}), 3.54 (dd, $^3J_{1,2}$ = 8.2 Hz, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2^{Gal}), 3.61 (m, 1 H, H-5^{Gal}), 3.66 (m, 1 H, H-2^{Cyc}), 3.69-3.78 (m, 4 H, H-6_{a+b}^{Gal}, H-2^{Fuc}, H-4^{Fuc}), 3.80 (dd, $^3J_{2,3}$ = 10.7 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 3.87 (dd, $^3J_{3,4}$ = 3.1 Hz $^3J_{4,5}$ = 0.6 Hz, 1 H, H-4^{Gal}), 3.98 (dd, ^3J = 3.7, 8.8 Hz, 1 H, H-2^{Lac}), 4.12 (dq, $^3J_{4,5}$ = 0.9 Hz, $^3J_{5,6}$ = 6.6 Hz, 1 H, H-5^{Fuc}), 4.59 (d, $^3J_{1,2}$ = 8.2 Hz, 1 H, H-1^{Gal}), 5.14 (d, $^3J_{1,2}$ = 4.1 Hz, 1 H, H-1^{Fuc});

^{1}H NMR (500 MHz, CD_3OD): δ 0.76-1.80 (m, 15 H, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-4^{Lac}, H-5_{a+b}^{Lac}, H-6_{a+b}^{Lac}, H-7_{a+b}^{Lac}, H-8_{a+b}^{Lac}, H-9_{a+b}^{Lac}), 1.08 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.16 (m, 1 H, H-3_a^{Cyc}), 1.19 (m, 1 H, H-6_a^{Cyc}), 1.47 (m, 1 H, H-3_a^{Lac}), 1.56 (m, 1 H, H-3_b^{Lac}), 1.92 (m, 1 H, H-6_b^{Cyc}), 2.06 (m, 1 H, H-3_b^{Cyc}), 3.18 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 2.8 Hz, 1 H, H-3^{Gal}), 3.36 (ddd, J = 5.0 Hz, 8.8 Hz, 10.4 Hz, 1 H, H-1^{Cyc}), 3.40 (m, 1 H, H-5^{Gal}), 3.48 (ddd, J = 5.0 Hz, 9.1 Hz, 10.4 Hz, 1 H, H-2^{Cyc}), 3.55 (m, 2 H, H-2^{Gal}, H-4^{Fuc}), 3.62 (m, 2 H, H-6_{a+b}^{Gal}), 3.65 (m, 1 H, H-3^{Fuc}), 3.68 (dd, $^3J_{1,2}$ = 3.7 Hz, $^3J_{2,3}$ = 10.4 Hz, 1 H, H-2^{Fuc}), 3.82 (m, 1 H, H-4^{Gal}), 3.83 (dd, ^3J = 4.7 Hz, 9.4 Hz, 1 H, H-2^{Lac}), 3.94 (dq, $^3J_{5,6}$ = 6.6 Hz, $^3J_{4,5}$ = 1.2 Hz, 1 H, H-5^{Fuc}), 4.53 (d, $^3J_{1,2}$ = 8.1 Hz, 1H, H-1^{Gal}), 5.02 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, H-1^{Fuc});

^{13}C NMR (125 MHz, CD_3OD): δ 16.9 (C-6^{Fuc}), 25.5, 25.7, 27.7, 27.9, 28.2, 30.9, 31.1, 34.0, 34.2 (9 C, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 33.5 (C-3^{Cyc}), 43.2 (C-3^{Lac}), 63.0 (C-6^{Gal}), 67.9 (C-5^{Fuc}), 68.2 (C-4^{Gal}), 70.7 (C-3^{Fuc}), 71.9 (C-2^{Gal}), 72.4 (C-4^{Fuc}), 74.0 (C-5^{Gal}), 81.3 (C-2^{Lac}), 83.8 (C-1^{Cyc}), 84.2 (C-2^{Cyc}), 85.4 (C-3^{Gal}), 102.3 (C-1^{Fuc}), 105.7 (C-1^{Gal}) , 183.5 (COONa);

MS (40.0 eV, ES): calcd for $C_{27}H_{46}NaO_{13}$ [M^+ + H]: 601.64; found: 601.24.

2,3,4-Tri-*O*-benzyl-1-*O*-[(*1S,2S*)-cyclohexanol-2-yl]-α-L-fucopyranoside (151) (II-134, cm190):



2,3,4-tri-*O*-benzyl-1-*S*-ethyl-L-thio-fucopyranoside (617 mg, 1.29 mmol) was dissolved in CH_2Cl_2 (5 ml) and cooled to 0°C. After adding bromine (232 mg, 28.6 µl, 1.46 mmol) with a syringe at 0°C, the orange solution was stirred at room temperature for 30 min. Remaining bromine was quenched with cyclohexene. (*1S,2S*)-cyclohexanediol (100 mg, 0.860 mmol), NEt_4Br (361 mg, 1.72 mmol) and 4Å molecular sieves (500 mg) were stirred at room temperature for 1 h. The freshly prepared 2,3,4-tri-O-benzylfucosylbromide (**94**) was added and the mixture was stirred at room temperature. TLC control (petroleum ether/ethyl acetate 2:1) showed complete consumption of the diol after 17 h. The crude mixture was diluted with CH_2Cl_2 (50 ml), filtered through celite, washed with satd. aqueous $NaHCO_3$ (2 x 20 ml), dried with Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (petroleum ether/ethyl acetate 4:1) yielded **151** (360 mg, 0.680 mmol, 74%).

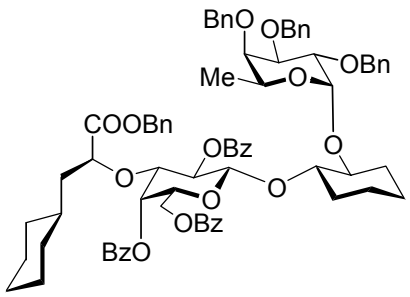
R_f = 0.61 (petroleum ether/ethyl acetate 2:1);

$[\alpha]_D^{22}$ = -48.4 (c = 1.75, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.10-1.95 (m, 8 H, H-$3_{a+b}{}^{Cyc}$, H-$4_{a+b}{}^{Cyc}$, H-$5_{a+b}{}^{Cyc}$, H-$6_{a+b}{}^{Cyc}$), 3.12 (ddd, ^3J = 3.9 Hz, 8.6 Hz, 9.9 Hz, 1 H, H-1^{Cyc}), 3.35 (ddd, ^3J = 3.9 Hz, 8.6 Hz, 10.6 Hz, 1 H, H-2^{Cyc}), 3.60 (dd, $^3J_{3,4}$ = 2.6 Hz, $^3J_{4,5}$ = 0.5 Hz, 1 H, H-4^{Fuc}), 3.89 (dd, $^3J_{2,3}$ = 9.6 Hz, $^3J_{3,4}$ = 2.6 Hz, 1 H, H-3^{Fuc}), 3.92 (dd, $^3J_{4,5}$ = 0.5 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 3.97 (dd, $^3J_{1,2}$ = 3.5 Hz, $^3J_{2,3}$ = 9.6 Hz, 1 H, H-2^{Fuc}), 4.54-4.86 (m, 6 H, 3 C$\underline{H}_2$-Ph), 4.86 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1^{Fuc}), 7.10-7.30 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.1 (C-6^{Fuc}), 24.3, 24.9, 32.2, 32.4 (4 C, C-3^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}), 67.0 (C-5^{Fuc}), 73.0, 74.0, 74.9 (3 $\underline{C}H_2$-Ph), 75.2 (C-1^{Cyc}), 76.7 (C-2^{Fuc}), 77.9 (C-4^{Fuc}), 80.4 (C-3^{Fuc}), 87.5 (C-2^{Cyc}), 101.4 (C-1^{Fuc}), 127.8, 127.9, 128.0, 128.3, 128.6, 128.7, 128.8, 128.9, 128.9, 138.4, 138.9, 139.0 (18 C, 3 C_6H_5).

Benzyl (*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-[(*1S,2S*)-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)cyclohexyl]-β-D-galactopyranos-3-yl} propanoate (152) (II-144, cm200):



151 (92.0 mg, 0.170 mmol) and benzyl (*2S*)-3-cyclohexyl-2-*O*-[1-*S*-ethyl-2,4,6-tri-*O*-benzoyl-β-D-thio-galactopyranos-3-yl] propanoate (**90**) (203 mg, 0.260 mmol) were dissolved in CH_2Cl_2 (15 ml) containing 3Å molecular sieves and stirred at -2°C for 1 h. DMTST (90.0 mg, 0.346 mmol) was added and the reaction mixture was stirred at -2°C for 18 h. The mixture was diluted with CH_2Cl_2 (50 ml), filtered through celite, washed with satd. aqueous $NaHCO_3$ (20 ml), dried with Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (petroleum ether/ethyl acetate 5:1) yielded **152** (200 mg, 0.160 mmol, 92%).

R_f = 0.45 (petroleum ether/ethyl acetate 3:1);

$[\alpha]_D^{21}$ = -7.11 (c = 0.58, $CHCl_3$);

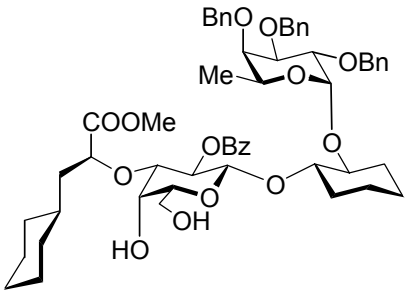
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.44-1.64 (m, 15 H, H-4_{a+b}^{Cyc}, H-5_{a+b}^{Cyc}, H-4^{Lac}, H-5_{a+b}^{Lac}, H-6_{a+b}^{Lac}, H-7_{a+b}^{Lac}, H-8_{a+b}^{Lac}, H-9_{a+b}^{Lac}), 1.02 (d, $^3J_{5,6}$ = 6.1 Hz, 3 H, H-6^{Fuc}), 1.22 (m, 1 H, H-6_a^{Cyc}), 1.27 (m, 1 H, H-3_a^{Lac}), 1.36 (m, 1 H, H-3_b^{Lac}), 1.54 (m, 1 H, H-3_a^{Cyc}), 1.65 (m, 1 H, H-6_b^{Cyc}), 1.87 (m, 1 H, H-3_b^{Cyc}), 3.45 (ddd, ^3J = 3.9 Hz, 5.8 Hz, 5.9 Hz, 1 H, H-1^{Cyc}), 3.59 (dd, $^3J_{3,4}$ = 1.8 Hz, $^3J_{4,5}$ = 0.3 Hz, 1 H, H-4^{Fuc}), 3.68 (dd, $^3J_{2,3}$ = 10.1 Hz, $^3J_{3,4}$ = 3.6 Hz, 1 H, H-3^{Gal}), 3.74 (ddd, ^3J = 3.6 Hz, 6.5 Hz, 6.6 Hz, 1 H, H-2^{Cyc}), 3.80 (m, 2 H, H-5^{Gal}, H-5^{Fuc}), 3.89 (m, 2 H, H-2^{Fuc}, H-3^{Fuc}), 4.08 (dd, $^3J_{2,3a}$ = 4.3 Hz, $^3J_{2,3b}$ = 7.6 Hz, 1 H, H-2^{Lac}), 4.37 (dd, $^3J_{5,6a}$ = 6.1 Hz, $^2J_{6a,6b}$ = 10.8 Hz, 1 H, H-6_a^{Gal}), 4.46 (dd, $^3J_{5,6b}$ = 7.2 Hz, $^2J_{6a,6b}$ = 10.8 Hz, 1 H, H-6_b^{Gal}), 4.58-5.11 (m, 8 H, 4 C$\underline{H}_2$-Ph), 4.82 (d, $^3J_{1,2}$ = 4.4 Hz, 1 H, H-1^{Fuc}), 4.86 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, H-1^{Gal}), 5.57 (dd, $^3J_{1,2}$ = 7.9 Hz, $^3J_{2,3}$ = 10.1 Hz, 1 H, H-2^{Gal}), 5.80 (dd, $^3J_{3,4}$ = 3.6 Hz, $^3J_{4,5}$ = 0.8 Hz, 1 H, H-4^{Gal}), 7.21-8.16 (m, 35 H, 7 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6^{Fuc}), 21.8, 21.9, 22.3, 25.5, 25.8, 26.1, 29.4, 29.7, 32.7, 33.4 (10 C, C-3^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 40.4 (C-3^{Lac}), 62.8 (C-6^{Gal}), 66.4 (C-5^{Gal}), 66.5 ($\underline{C}H_2$-Ph), 70.0 (C-4^{Gal}), 71.5 (C-5^{Fuc}), 72.7, 72.9, (2 $\underline{C}H_2$-Ph), 73.1 (C-2^{Gal}), 74.7 ($\underline{C}H_2$-Ph), 76.0 (C-2^{Fuc}), 77.0 (C-1^{Cyc}), 77.2 (C-2^{Cyc}), 77.4

(C-3^{Gal}), 77.6 (C-4^{Fuc}), 78.2 (C-2^{Lac}), 79.6 (C-3^{Fuc}), 97.7 (C-1^{Fuc}), 100.3 (C-1^{Gal}), 127.3, 127.4, 127.4, 127.5, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 128.8, 128.9, 130.2, 130.4, 130.6, 133.1, 133.2, 133.3, 135.5, 135.6, 138.7, 138.8, 138.9 (42 C, 7 C_6H_5), 165.0, 165.2, 165.3, 165.9, 165.9, 166.0, 172.4 (7 COO);

elemental analysis calcd (%) for $C_{76}H_{82}O_{16}$ (1251.49): C 72.94, H 6.60, O 20.46;
found: C 72.85, H 6.54, O 20.61.

Methyl (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*1S,2S*)-2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-cyclohexyl]-β-D-galactopyranos-3-yl} propanoate (153) (II-239, cm293):



To a solution of **152** (40.0 mg, 0.032 mmol) in methanol (5 ml), NaOMe/MeOH (1 M, 100 µl) was added and the mixture was stirred for 15 h at room temperature. After neutralization with amberlyste ion-exchange resin (H^+ form), filtration, evaporation of solvents and purification by silica gel chromatography (CH_2Cl_2/MeOH 30:1), **153** (22.0 mg, 0.031 mmol, 98%) was isolated.

R_f = 0.49 (CH_2Cl_2/MeOH 10:1);

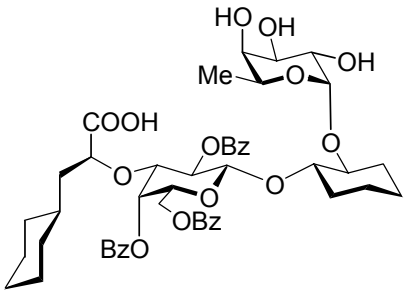
$[\alpha]_D^{21}$ = -24.3 (c = 1.2, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.40-1.60 (m, 15 H, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.04 (d, $^3J_{5,6}$ = 6.4 Hz, 3 H, H-6^{Fuc}), 1.23 (m, 1 H, H-6$_a^{Cyc}$), 1.33 (m, 1 H, H-3$_a^{Lac}$), 1.52 (m, 2 H, H-3$_{a+b}^{Lac}$), 1.59 (m, 1 H, H-6$_b^{Cyc}$), 1.84 (m, 1 H, H-3$_b^{Cyc}$), 3.19 (dd, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, H-3^{Gal}), 3.42 (m, 1 H, H-5^{Gal}), 3.50 (m, 1 H, H-1^{Cyc}), 3.64 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 0.7 Hz, 1 H, H-4^{Fuc}), 3.69 (dd, $^3J_{3,4}$ = 3.0 Hz, $^3J_{4,5}$ = 0.9 Hz, 1 H, H-4^{Gal}), 3.73 (s, 3 H, OMe), 3.78 (m, 3 H, H-2^{Cyc}, H-2^{Lac}, H-6$_a^{Gal}$), 3.87 (dq, $^3J_{4,5}$ = 0.7 Hz, $^3J_{5,6}$ = 6.4 Hz, 1 H, H-5^{Fuc}), 3.95 (dd, $^3J_{2,3}$ = 10.2 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 4.00 (m, 1 H, H-6$_b^{Gal}$), 4.01 (dd, $^3J_{1,2}$ = 3.0 Hz, $^2J_{2,3}$ = 10.2 Hz, 1 H, H-2^{Fuc}), 4.60-4.98 (m, 6 H, 3 C$\underline{H}_2$-

Ph), 4.89 (d, $^3J_{1,2}$ = 7.6 Hz, 1 H, H-1^{Gal}), 4.97 (d, $^3J_{1,2}$ = 3.0 Hz, 1 H, H-1^{Fuc}), 5.43 (dd, $^3J_{1,2}$ = 7.6 Hz, $^3J_{2,3}$ = 9.5 Hz, 1 H, H-2^{Gal}), 7.21-8.02 (m, 20 H, 4 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.9 (C-6^{Fuc}), 22.2 (C-6^{Cyc}), 25.6, 25.7, 26.5, 29.8, 29.9, 32.5, 33.1, 34.0 (8 C, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}, C-4^{Cyc}, C-5^{Cyc}), 32.4 (C-3^{Cyc}), 41.7 (C-3^{Lac}), 52.8 (OCH_3), 62.9 (C-6^{Gal}), 66.9 (C-5^{Fuc}), 67.7 (C-4^{Fuc}), 71.9 (C-2^{Gal}), 73.2, 73.6, 74.3 (3 $\underline{C}H_2$-Ph), 75.1 (C-5^{Gal}), 76.8 (C-2^{Fuc}), 77.4 (C-2^{Cyc}), 77.7 (C-1^{Cyc}), 78.0 (C-2^{Lac}), 79.9 (C-3^{Fuc}), 82.7 (C-3^{Gal}), 98.2 (C-1^{Fuc}), 100.4 (C-1^{Gal}), 127.8, 127.9, 127.9, 128.5, 128.6, 128.7, 128.7, 128.8, 129.0, 130.0, 130.5, 130.7, 133.4, 139.1, 139.2, 139.6 (24 C, 4 C_6H_5), 165.5, 175.9 (2 COO).

(*2S*)-3-cyclohexyl-2-*O*-{2,4,6-tri-*O*-benzoyl-1-*O*-[(*1S,2S*)-2-*O*-(α-L-fucopyranosyl)cyclohexyl]-β-D-galactopyranos-3-yl} propanoic acid (154) (II-153, cm209):



A solution of **152** (130 mg, 0.104 mmol) and Pd/C (100 mg, 0.080 mmol) in dioxane (5 ml) was shaken for 24 h under an atmosphere of 4 bar H_2 in a hydrogenation apparatus. After filtration through celite, evaporation of the solvent and purification by silica gel chromatography (CH_2Cl_2/MeOH 8:1), **154** was isolated (87.0 mg, 0.098 mmol, 94%).

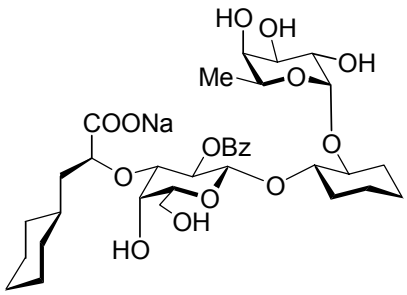
R_f = 0.24 (CH_2Cl_2/MeOH 6:1);

$[\alpha]_D^{21}$ = -23.8 (c = 1.07, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.36-2.01 (m, 19 H, H-3$_{a+b}^{Cyc}$, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.14 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.28 (m, 2 H, H-3$_{a+b}^{Lac}$), 3.40 (m, 1 H, H-1^{Cyc}), 3.61-3.79 (m, 4 H, H-2^{Cyc}, H-2^{Fuc}, H-3^{Fuc}, H-4^{Fuc}), 3.84 (dq, $^3J_{5,6}$ = 6.6 Hz, $^3J_{4,5}$ = 1.4 Hz, 1 H, H-5^{Fuc}), 4.03 (dd, $^3J_{2,3}$ = 8.5 Hz, $^3J_{3,4}$ = 2.8 Hz, 1 H, H-3^{Gal}), 4.22 (m, 2 H, H-2^{Lac}, H-5^{Gal}), 4.46 (dd, $^3J_{5,6a}$ = 5.6 Hz, $^2J_{6a,6b}$ = 11.3 Hz, 1 H, H-6$_a^{Gal}$), 4.60 (dd, $^3J_{5,6b}$ = 7.2 Hz, $^2J_{6a,6b}$ = 11.3 Hz, 1 H, H-6$_b^{Gal}$), 4.88 (d, $^3J_{1,2}$ = 3.4 Hz, 1 H, H-1^{Fuc}), 5.17 (d, $^3J_{1,2}$ = 7.5 Hz, 1 H, H-1^{Gal}), 5.53 (dd, $^3J_{1,2}$ = 7.5 Hz, $^3J_{2,3}$ = 8.5 Hz, 1 H, H-2^{Gal}), 5.82 (dd, $^3J_{3,4}$ = 2.8 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, H-4^{Gal}), 7.40-8.20 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.0 (C-6^{Fuc}), 23.6, 23.7, 25.5, 25.7, 25.9, 26.0, 31.4, 32.1, 32.9, 33.2 (10 C, C-3^{Cyc}, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-4^{Lac}, C-5^{Lac}, C-6^{Lac}, C-7^{Lac}, C-8^{Lac}, C-9^{Lac}), 40.6 (C-3^{Lac}), 62.2 (C-4^{Fuc}), 62.5 (C-6^{Gal}), 66.2 (C-3^{Fuc}), 67.1 (C-5^{Fuc}), 69.4 (C-2^{Fuc}), 70.1 (C-4^{Gal}), 70.2 (C-5^{Gal}), 73.1 (C-2^{Gal}), 84.9 (C-1^{Cyc}), 78.0 (C-2^{Cyc}), 79.9 (C-2^{Lac}), 83.0 (C-3^{Gal}), 99.8 (C-1^{Fuc}), 100.1 (C-1^{Gal}), 128.5, 128.9, 130.1, 130.3, 130.5, 130.7, 130.9, 131.2, 131.5, 133.2, 133.6, 133.9 (18 C, 3 C_6H_5), 165.8, 166.2, 167.9 (3 COO).

Sodium (*2S*)-3-cyclohexyl-2-*O*-{2-*O*-benzoyl-1-*O*-[(*1S,2S*)-2-*O*-(α-L-fucopyranosyl)cyclohexyl]-β-D-galactopyranos-3-yl} propanoate (155) (II-247, cm302):



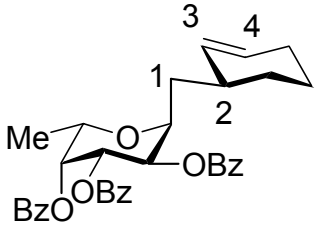
To a solution of **152** (10.0 mg, 0.008 mmol) in toluene/methanol (1:1, 20 ml) NaOMe/MeOH (1 M, 750 µl) was added and the reaction was stirred at room temperature for 24 h. The mixture was neutralized with amberlyste ion-exchange resin (H^+ form), filtered through celite, concentrated and dissolved again in dioxane/methanol (1:1, 5 ml). After addition of $Pd(OH)_2/C$ (10 mg), the mixture was hydrogenated (5 bar H_2) for 19 h at room temperature, filtered through celite, concentrated and passed over Dowex 50x8 ion-exchange resin (Na^+ form). Purification of the isolated crude product by RP-18 reversed-phase column chromatography (gradient MeOH/H_2O 0:1 → 1:0) and P2-gel column chromatography yielded **155** (4.00 mg, 0.006 mmol, 76%).

R_f = 0.14 (CH_2Cl_2/MeOH 2:1);

^{1}H NMR (500 MHz, D_2O): δ 0.38-1.47 (m, 15 H, H-4$_{a+b}^{Cyc}$, H-5$_{a+b}^{Cyc}$, H-4^{Lac}, H-5$_{a+b}^{Lac}$, H-6$_{a+b}^{Lac}$, H-7$_{a+b}^{Lac}$, H-8$_{a+b}^{Lac}$, H-9$_{a+b}^{Lac}$), 1.02 (d, $^3J_{5,6}$ = 6.6 Hz, 3 H, H-6^{Fuc}), 1.15 (m, 1 H, H-6$_a^{Cyc}$), 1.30 (m, 1 H, H-3$_a^{Lac}$), 1.35 (m, 1 H, H-3$_b^{Lac}$), 1.42 (m, 1 H, H-3$_a^{Cyc}$), 1.57 (m, 1 H, H-6$_b^{Cyc}$), 1.89 (m, 1 H, H-3$_b^{Cyc}$), 3.45 (m, 1 H, H-1^{Cyc}), 3.57 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 1.1 Hz, 1 H, H-4^{Fuc}), 3.58 (dd, $^3J_{1,2}$ = 3.1 Hz, $^3J_{2,3}$ = 10.0 Hz, 1 H, H-2^{Fuc}), 3.67 (dd, $^3J_{2,3}$ = 10.0 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 3.76 (m, 4 H, H-3^{Gal}, H-5^{Gal}, H-6$_{a+b}^{Gal}$), 3.81 (m, 2 H, H-2^{Cyc}, H-5^{Fuc}), 3.87 (dd, J = 2.5 Hz, 9.4 Hz, 1 H, H-2^{Lac}), 3.98 (dd, $^3J_{3,4}$ = 2.5 Hz, $^3J_{4,5}$ = 0.6 Hz, 1 H, H-4^{Gal}), 4.81 (d, $^3J_{1,2}$ = 3.1 Hz, 1 H, H-1^{Fuc}), 5.02 (d, $^3J_{1,2}$ = 8.1 Hz, 1 H, H-1^{Gal}), 5.21 (dd, $^3J_{1,2}$ = 8.1 Hz, $^3J_{2,3}$ = 8.8 Hz, 1 H, H-2^{Gal}), 7.56-8.13 (m, 5 H, C_6H_5);

^{13}C NMR (125 MHz, D_2O): δ 15.0 (C-6^{Fuc}), 61.2 (C-6^{Gal}), 66.6 (C-4^{Gal}), 66.8 (C-5^{Fuc}), 68.7 (C-2^{Fuc}), 70.0 (C-3^{Fuc}), 71.8 (C-4^{Fuc}), 72.7 (C-2^{Gal}), 75.2 (C-5^{Gal}), 78.3 (C-1^{Cyc}), 79.3 (C-2^{Cyc}), 81.2 (C-3^{Gal}), 98.7 (C-1^{Fuc}), 99.9 (C-1^{Gal}), 129.4, 130.7, 131.3, 134.7 (6 C, C_6H_5), 165.3 (COO).

(*3S*)-3-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexene (156) (II-83, cm135):



Under argon, **128a** (140 mg, 0.266 mmol) and DMAP (20.0 mg, 0.160 mmol) were dissolved in a mixture of pyridine and CH_2Cl_2 (10 ml, 1:1) and cooled to 0°C. Triflic acid anhydride (90.0 µl, 154 mg, 0.570 mmol) was added slowly with a syringe and the reaction was stirred for 3 h at 0°C. The mixture was then poured onto ice water, extracted with CH_2Cl_2 (50 ml), washed with 7% aqueous HCl (2 x 50 ml) and satd. aqueous $NaHCO_3$ (2 x 50 ml), dried with Na_2SO_4, filtered, concentrated and dried under high vacuum. Purification by silica gel chromatography (toluene/ethyl acetate 30:1) yielded **156** (73.0 mg, 0.131 mmol, 54%).

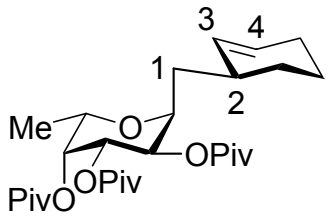
R_f = 0.15 (petroleum ether/ethyl acetate 10:1);

$[\alpha]_D^{21}$ = -162.9 (c = 0.80, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.45-2.33 (m, 7 H, H-2^{Cyc}, H-5$_{a+b}$^{Cyc}, H-6$_{a+b}$^{Cyc}, H-7$_{a+b}$^{Cyc}), 1.44 (ddd, J = 3.1 Hz, 10.4 Hz, 14.8 Hz, 1 H, H-1$_a$^{Cyc}), 2.13 (ddd, J = 4.0 Hz, 11.9 Hz, 14.8 Hz, 1 H, H-1$_b$^{Cyc}), 4.25 (dq, $^3J_{4,5}$ = 1.5 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.67 (ddd, J = 3.1 Hz, 5.6 Hz, 11.9 Hz, 1 H, H-1^{Fuc}), 5.60 (dd, J = 1.8 Hz, 10.0 Hz, 1 H, H-3^{Cyc}), 5.73 (m, 1 H, H-4^{Cyc}), 5.74 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 1.5 Hz, 1 H, H-4^{Fuc}), 5.80 (dd, $^3J_{2,3}$ = 10.0 Hz, $^3J_{3,4}$ = 3.1 Hz, 1 H, H-3^{Fuc}), 5.86 (dd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{2,3}$ = 10.0 Hz, 1 H, H-2^{Fuc}), 7.25-8.12 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4 (C-6^{Fuc}), 21.3, 25.3, 28.2 (3 C, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 31.5 (C-2^{Cyc}), 31.6 (C-1^{Cyc}), 66.0 (C-5^{Fuc}), 69.3 (C-3^{Fuc}), 69.4 (C-2^{Fuc}), 70.9 (C-1^{Fuc}), 71.8 (C-4^{Fuc}), 128.2, 128.6, 128.8, 128.9, 129.7, 129.9, 130.0, 130.2, 130.3, 133.2, 133.4, 133.5 (18 C, 3 C_6H_5), 129.3 (C-4^{Cyc}), 133.2 (C-3^{Cyc}), 166.0, 166.2, 166.4 (3 COO).

(*3S*)-3-(2,3,4-tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexene (157) (II-71, cm123):



A solution of **129a** (50.0 mg, 0.097 mmol) in pyridine/CH_2Cl_2 (3 ml, 1:2) was cooled to 0°C under argon. Trifluoromethanesulfonic acid anhydride (55.0 mg, 33.0 µl, 0.200 mmol) was added slowly by a syringe and the reaction mixture was stirred at 0°C for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (20 ml), poured onto ice and the organic layer was washed with aqueous 10% HCl (2 x 20 ml) and satd. aqueous $NaHCO_3$ (20 ml). Drying with Na_2SO_4, evaporation of the solvents and purification of the crude product by silica gel chromatography (petroleum ether/ethyl acetate 10:1) yielded **157** (33.0 mg, 0.067 mmol, 67 %).

R_f = 0.42 (petroleum ether/ethyl acetate 10:1);

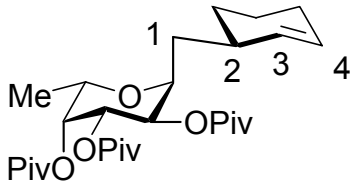
$[\alpha]_D^{22}$ = -57.2 (c = 0.6, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.15, 1.23, 1.26 (3 s, 27 H, 3 C$\underline{Me}_3$), 1.26 (m, 1 H, H-1$_a^{Cyc}$), 1.86 (m, 1 H,H-1$_b^{Cyc}$), 1.50-2.21 (m, 7 H, H-2^{Cyc}, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 4.99 (dq, $^3J_{4,5}$ = 0.5 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.33 (ddd, $^3J_{1,1a\text{-}Cyc}$= 2.8 Hz, $^3J_{1,1b\text{-}Cyc}$ = 11.8 Hz, $^3J_{1,2}$ = 5.7 Hz, 1 H, H-1^{Fuc}), 5.25 (dd, $^3J_{2,3}$ = 9.8 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 5.27 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 0.5 Hz, 1 H, H-4^{Fuc}), 5.35 (dd, $^3J_{1,2}$ = 5.7 Hz, $^3J_{2,3}$ = 9.8 Hz, 1 H, H-2^{Fuc}), 5.52 (dd, $^3J_{2,3}$ = 10.4 Hz, $^3J_{3,4}$ = 2.0 Hz, 1 H, H-3^{Cyc}), 5.71 (ddd, $^3J_{3,4}$ = 2.0 Hz, $^3J_{4,5a}$ = 5.7 Hz, $^3J_{4,5b}$ = 9.7 Hz, 1 H, H-4^{Cyc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1 (C-6^{Fuc}), 21.1 (C-2^{Cyc}), 25.3, 27.1, 28.0 (3 C, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.1, 27.2, 27.3 (9 C, 3 C$\underline{Me}_3$), 31.4 (C-1^{Cyc}), 38.0, 39.6, 40.7 (3 $\underline{C}Me_3$), 65.8 (C-5^{Fuc}), 68.1 (C-2^{Fuc}), 68.8 (C-3^{Fuc}), 70.6 (C-4^{Fuc}), 70.8 (C-1^{Fuc}), 127.7 (C-4^{Cyc}), 131.8 (C-3^{Cyc}), 175.4, 176.1, 177.5 (3 COO).

elemental analysis calcd (%) for $C_{28}H_{46}O_7$ (494.66): C 67.99, H 9.37, O 22.64;
found: C 67.49, H 9.36, O 23.15.

(*3R*)-3-(2,3,4-tri-*O*-pivaloyl-α-L-fucopyranosyl-methyl)-cyclohexene (158) (II-70, cm122):



Under argon, a solution of **129b** (30.0 mg, 0.058 mmol) in pyridine/CH_2Cl_2 (3 ml, 1:2) was cooled to 0°C. Trifluoromethanesulfonic acid anhydride (33.0 mg, 19.5 µl, 0.120 mmol) was added slowly by a syringe and the reaction mixture was stirred at 0°C for 2 h and at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 ml), poured onto ice and the organic layer was washed with aqueous 10% HCl (2 x 20 ml) and satd. aqueous $NaHCO_3$ (20 ml). Drying with Na_2SO_4, evaporation of the solvents and purification of the crude product by silica gel chromatography (petroleum ether/ethyl acetate 10:1) yielded **158** (25.0 mg, 0.051 mmol, 88 %).

R_f = 0.42 (petroleum ether/ethyl acetate 10:1);

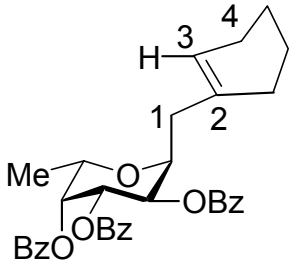
$[\alpha]_D^{22}$ = -92.3 (c = 0.65, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.15, 1.22, 1.27 (3 s, 27 H, 3 C$\underline{Me}_3$), 1.38 (m, 1 H, H-1$_a^{Cyc}$), 1.80 (m, 1 H, H-1$_b^{Cyc}$), 1.55-2.20 (m, 7 H, H-2^{Cyc}, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 4.99 (dq, $^3J_{4,5}$ = 1.7 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.35 (ddd, $^3J_{1,1a\text{-}Cyc}$= 2.8 Hz, $^3J_{1,1b\text{-}Cyc}$ = 14.3 Hz, $^3J_{1,2}$ = 5.4 Hz, 1 H, H-1^{Fuc}), 5.25 (dd, $^3J_{2,3}$ = 9.7 Hz, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3^{Fuc}), 5.27 (dd, $^3J_{3,4}$ = 3.4 Hz, $^3J_{4,5}$ = 1.7 Hz, 1 H, H-4^{Fuc}), 5.33 (dd, $^3J_{1,2}$ = 5.4 Hz, $^3J_{2,3}$ = 9.4 Hz, 1 H, H-2^{Fuc}), 5.60 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{3,4}$ = 2.2 Hz, 1 H, H-3^{Cyc}), 5.69 (ddd, $^3J_{3,4}$ = 2.2 Hz, $^3J_{4,5a}$ = 3.4 Hz, $^3J_{4,5b}$ = 9.7 Hz, 1 H, H-4^{Cyc});

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.5 (C-6^{Fuc}), 21.5 (C-2^{Cyc}), 25.7, 30.1, 31.9 (3 C, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.5, 27.6, 27.7 (9 C, 3 C$\underline{Me}_3$), 31.5 (C-1^{Cyc}), 38.0, 39.6, 40.7 (3 $\underline{C}Me_3$), 66.0 (C-5^{Fuc}), 68.2 (C-2^{Fuc}), 68.8 (C-3^{Fuc}), 70.6 (C-4^{Fuc}), 70.9 (C-1^{Fuc}), 128.2 (C-4^{Cyc}), 130.3 (C-3^{Cyc}), 175.0, 175.6, 177.1 (3 COO);

elemental analysis calcd (%) for $C_{28}H_{46}O_7$ (494.66): C 67.99, H 9.37, O 22.64;
found: C 67.99, H 9.45, O 22.56.

1-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexene (159) (II-82, cm134):



Under argon, **128d** (80.0 mg, 0.140 mmol) and DMAP (10.0 mg, 0.080 mmol) were dissolved in a mixture of pyridine and CH_2Cl_2 (10 ml, 1:1) and cooled to 0°C. Triflic acid anhydride (52.0 µl, 88.0 mg, 0.312 mmol) was added slowly with a syringe and the reaction was stirred for 3 h at 0°C. The mixture was poured onto ice water, extracted with CH_2Cl_2 (2 x 50 ml). The organic layer was washed with 7% aqueous HCl (2 x 50 ml) and satd. aqueous $NaHCO_3$ (2 x 50 ml), dried with Na_2SO_4, filtered, concentrated and dried under high vacuum. Purification by silica gel chromatography (toluene/ethyl acetate 30:1) yielded **159** (75.0 mg, 0.135 mmol, 96%).

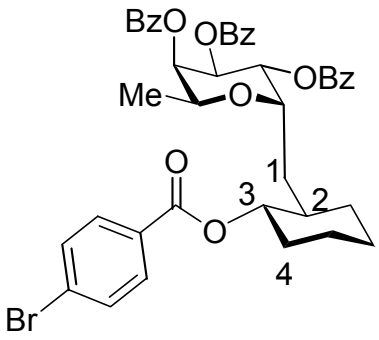
R_f = 0.14 (petroleum ether/ethyl acetate 10:1);

$[\alpha]_D^{21}$ = -214.0 (c = 0.55, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.51-1.62 (m, 6 H, H-5$_{a+b}^{Cyc}$, H-6$_{a+b}^{Cyc}$, H-7$_{a+b}^{Cyc}$), 1.96 (m, 2 H, H-4$_{a+b}^{Cyc}$), 1.35 (dd, $^3J_{1a,1b}$ = 14.5 Hz, $^3J_{1a,1Fuc}$ = 2.2 Hz, 1 H, H-1$_a^{Cyc}$), 2.64 (dd, $^3J_{1a,1b}$ = 14.5 Hz, $^3J_{1b,1Fuc}$ = 10.4 Hz, 1 H, H-1$_b^{Cyc}$), 4.27 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.71 (ddd, $^3J_{1,1aCyc}$ = 2.2 Hz, $^3J_{1,1bCyc}$ = 10.4 Hz, $^3J_{1,2}$ = 4.7 Hz, 1 H, H-1^{Fuc}), 5.53 (m, 1 H, H-3^{Cyc}), 5.74 (m, 1 H, H-4^{Fuc}), 5.83 (m, 2 H, H-2^{Fuc}, H-3^{Fuc}), 7.26-8.11 (m, 15 H, 3 C_6H_5);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.3 (C-6^{Fuc}), 22.2, 22.8, 25.3, 27.9 (4 C, C-4^{Cyc}, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 34.8 (C-1^{Cyc}), 66.1 (C-5^{Fuc}), 69.3 (C-2^{Fuc}), 69.4 (C-3^{Fuc}), 70.9 (C-1^{Fuc}), 71.7 (C-4^{Fuc}), 124.4 (C-3^{Cyc}), 128.2, 128.6, 128.8, 128.9, 129.7, 129.9, 130.0, 130.2, 130.3, 133.2, 133.4, 133.5 (18 C, 3 C_6H_5), 133.3 (C-2^{Cyc}), 165.6, 165.8, 165.9 (3 COO).

(*1R,2S*) 2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexyl *p*-bromo-benzoate (160) (II-89, cm141):



A solution of **128b** (50.0 mg, 0.088 mmol) in pyridine (5 ml) was cooled to 0°C and *p*-bromo-benzoylchloride (39.0 mg, 0.180 mmol) was added. The reaction was stirred at 0°C for 3 h and further 10 min after addition of methanol (10 ml) to quench the excess of benzoylchloride. The reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with 7% aqueous HCl (70 ml) and H_2O (40 ml), the organic layer was dried with Na_2SO_4, filtered and concentrated. Purification of the crude product by silica gel chromatography (petroleum ether/ethyl acetate 5:1) yielded **160** (46.0 mg, 0.061 mmol, 70%).

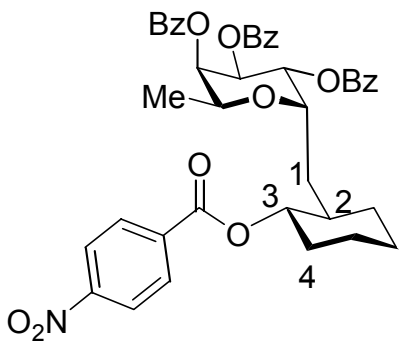
R_f = 0.71 (petroleum ether/ethyl acetate 2:1);

$[\alpha]_D^{21}$ = -26.8 (c = 1.35, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.262.12 (m, 6 H, H-5_{a+b}^{Cyc}, H-6_{a+b}^{Cyc}, H-7_{a+b}^{Cyc}), 1.26 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.35 (m, 1 H, H-4_a^{Cyc}), 1.81 (m, 2 H, H-1_a^{Cyc}, H-2^{Cyc}), 1.93 (m, 1 H, H-1_b^{Cyc}), 2.12 (m, 1 H, H-4_b^{Cyc}), 4.22 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.61 (ddd, $^3J_{1,2}$ = 5.6 Hz, J = 2.5 Hz, 10.4 Hz, 1 H, H-1^{Fuc}), 4.76 (ddd, J = 4.4 Hz, 10.0 Hz, 10.3 Hz, 1 H, H-3^{Cyc}), 5.67 (m, 2 H, H-3^{Fuc}, H-4^{Fuc}), 5.76 (dd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{2,3}$ = 10.0 Hz, 1 H, H-2^{Fuc}), 7.18-8.09 (m, 19 H, 3 C_6H_5, C_6H_4);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6 (C-6^{Fuc}), 24.8, 25.7, 32.0 (3 C, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.3 (C-1^{Cyc}), 32.3 (C-4^{Cyc}), 41.7 (C-2^{Cyc}), 66.4 (C-5^{Fuc}), 69.4 (C-2^{Fuc}), 69.5 (C-3^{Fuc}), 72.1 (C-4^{Fuc}), 74.4 (C-1^{Fuc}), 78.4 (C-3^{Cyc}), 128.2, 128.7, 128.8, 129.1, 129.4, 129.8, 129.9, 130.1, 130.3, 131.2, 131.3, 131.9, 132.2, 133.5, 133.7, 133.8 (24 C, 3 C_6H_5, *p*-Br-C_6H_4), 165.6, 165.8, 166.1, 166.3 (4 COO).

(*1R,2S*)-2-(2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl-methyl)-cyclohexyl *p*-nitro-benzoate (161) (II-88, cm140):



A solution of **128b** (50.0 mg, 0.088 mmol) in pyridine (5 ml) was cooled to 0°C and *p*-nitro-benzoylchloride (32.0 mg, 0.180 mmol) was added. The reaction was stirred at 0°C for 1 h and further 10 min after addition of methanol (10 ml) to quench the excess of benzoylchloride. The reaction mixture was then diluted with CH_2Cl_2 (50 ml), washed with 7% aqueous HCl (70 ml) and H_2O (40 ml), the organic layer was dried with Na_2SO_4, filtered and concentrated. Purification of the crude product by silica gel chromatography (petroleum ether/ethyl acetate 5:1) yielded **161** (51.0 mg, 0.071 mmol, 82%).

R_f = 0.62 (petroleum ether/ethyl acetate 2:1);

$[\alpha]_D^{21}$ = -51.2 (c = 1.27, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19-2.11 (m, 6 H, H-5_{a+b}^{Cyc}, H-6_{a+b}^{Cyc}, H-7_{a+b}^{Cyc}), 1.21 (d, $^3J_{5,6}$ = 6.3 Hz, 3 H, H-6^{Fuc}), 1.32 (m, 1 H, H-4_a^{Cyc}), 1.73 (m, 1 H, H-1_a^{Cyc}), 1.79 (m, 1 H, H-2^{Cyc}), 1.85 (m, 1 H, H-1_b^{Cyc}), 2.06 (m, 1 H, H-4_b^{Cyc}), 4.16 (dq, $^3J_{4,5}$ = 1.2 Hz, $^3J_{5,6}$ = 6.3 Hz, 1 H, H-5^{Fuc}), 4.57 (ddd, $^3J_{1,2}$ = 5.6 Hz, $^3J_{1,1a\text{-}Cyc}$ = 2.8 Hz, $^3J_{1,1b\text{-}Cyc}$ = 10.4 Hz, 1 H, H-1^{Fuc}), 4.73 (ddd, J = 4.4 Hz, 10.0 Hz, 10.3 Hz, 1 H, H-3^{Cyc}), 5.61 (m, 1 H, H-4^{Fuc}), 5.65 (m, 2 H, H-2^{Fuc}, H-3^{Fuc}), 7.09-8.02 (m, 19 H, 3 C_6H_5, C_6H_4);

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6 (C-6^{Fuc}), 24.7, 25.7, 32.2 (3 C, C-5^{Cyc}, C-6^{Cyc}, C-7^{Cyc}), 27.4 (C-1^{Cyc}), 32.1 (C-4^{Cyc}), 41.7 (C-2^{Cyc}), 66.5 (C-5^{Fuc}), 69.2 (C-2^{Fuc}), 69.7 (C-3^{Fuc}), 72.0 (C-4^{Fuc}), 74.3 (C-1^{Fuc}), 79.4 (C-3^{Cyc}), 123.8, 128.7, 128.8, 129.0, 129.1, 129.4, 129.7, 129.8, 130.1, 130.3, 130.7, 130.8, 133.6, 133.7, 135.8, 150.6 (24 C, 3 C_6H_5, *p*-NO_2-C_6H_4), 164.5, 165.7, 166.1, 166.3 (4 COO);

elemental analysis calcd (%) for $C_{41}H_{39}NO_{11}$ (721.76): C 68.23, H 5.45, O 24.38, N 1.94; found: C 67.85, H 5.90, O 24.41, N 1.84

6. Crystal structure data of compound 158

Data deposition	Roche intranet structure No. 1252
WWW address	http://rbaw01.bas.roche.com:8080/apps/sxray/sxray.html

Empirical formula	$C_{28}H_{46}O_7$
Formula weight	494.65
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 6.5656(13) Å α = 90 deg.
	b = 15.839(3) Å β = 90 deg.
	c = 29.157(6) Å γ = 90 deg.
Volume	3032.1(10) $Å^3$
Z, Calculated density	4, 1.084 mg/m^3
Absorption coefficient	0.076 mm^{-1}
F(000)	1080
Crystal size	0.3 x 0.1 x 0.05 mm
Theta range for data collection	2.46 to 22.40 deg.
Limiting indices	$-6 \le h \le 6, -16 \le k \le 16, -31 \le l \le 31$
Reflections collected / unique	21027 / 3735 [R(int) = 0.1334]
Completeness to theta = 22.40	95.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3735 / 0 / 326
Goodness-of-fit on F^2	0.797
Final R indices [$I>2\sigma(I)$]	R1 = 0.0532, ωR2 = 0.0941
R indices (all data)	R1 = 0.1442, ωR2 = 0.1191
Absolute structure parameter	-2(2)
Largest diff. peak and hole	0.178 and -0.128 e. $Å^{-3}$

Table 8: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	8042(7)	4135(2)	2213(1)	69(1)
O(2)	7800(7)	3785(2)	1276(1)	68(1)
O(3)	9558(11)	3175(5)	734(2)	185(4)
O(4)	8569(6)	5416(2)	982(1)	69(1)
O(5)	11920(10)	5640(4)	871(2)	124(2)
O(6)	6761(7)	6214(2)	1720(1)	67(1)
O(7)	3540(7)	5939(3)	1924(2)	85(1)
C(8)	7510(9)	4996(3)	2230(2)	63(2)
C(9)	7181(9)	5327(3)	1734(2)	60(2)
C(10)	9002(9)	5165(3)	1449(2)	56(2)
C(11)	9522(10)	4224(4)	1460(2)	60(2)

C(12)	9777(11)	3940(4)	1951(2)	71(2)
C(13)	10125(12)	2999(4)	1999(2)	102(3)
C(14)	7967(14)	3300(4)	912(2)	87(2)
C(15)	5908(13)	2927(5)	772(3)	93(2)
C(16)	4644(13)	3640(5)	566(3)	149(4)
C(17)	6172(13)	2237(5)	424(3)	146(3)
C(18)	4812(15)	2603(6)	1196(3)	180(5)
C(19)	10158(15)	5662(4)	727(2)	78(2)
C(20)	9603(14)	5895(5)	242(2)	92(2)
C(21)	7347(17)	5886(6)	150(2)	180(5)
C(22)	10220(20)	6750(6)	168(3)	291(10)
C(23)	10450(30)	5275(8)	-60(3)	353(12)
C(24)	4812(12)	6446(4)	1801(2)	67(2)
C(25)	4474(13)	7389(4)	1718(3)	90(2)
C(26)	5299(16)	7629(4)	1252(3)	156(4)
C(27)	2151(14)	7539(4)	1722(3)	146(4)
C(28)	5487(17)	7842(4)	2100(3)	192(5)
C(29)	8998(9)	5535(3)	2509(2)	69(2)
C(30)	9413(12)	5152(4)	2982(2)	84(2)
C(31)	11304(12)	5468(5)	3189(2)	108(2)
C(32)	11619(14)	5165(5)	3676(3)	129(3)
C(33)	9922(19)	5449(6)	3963(3)	155(4)
C(34)	7922(16)	5359(5)	3750(3)	132(3)
C(35)	7694(11)	5217(4)	3296(2)	104(2)

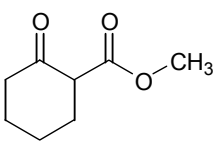
Table 9: Bond lengths [Å] and angles [°].

O(1)-C(12)	1.405(6)
O(1)-C(8)	1.409(5)
O(2)-C(14)	1.316(7)
O(2)-C(11)	1.432(6)
O(3)-C(14)	1.183(9)
O(4)-C(19)	1.338(7)
O(4)-C(10)	1.448(6)
O(5)-C(19)	1.231(8)
O(6)-C(24)	1.352(7)
O(6)-C(9)	1.434(5)
O(7)-C(24)	1.214(7)
C(8)-C(29)	1.532(7)
C(8)-C(9)	1.553(7)
C(9)-C(10)	1.478(7)
C(10)-C(11)	1.529(7)
C(11)-C(12)	1.512(6)
C(12)-C(13)	1.514(7)
C(14)-C(15)	1.530(10)
C(15)-C(17)	1.502(8)
C(15)-C(18)	1.518(10)
C(15)-C(16)	1.525(9)
C(19)-C(20)	1.508(9)
C(20)-C(22)	1.430(9)
C(20)-C(23)	1.431(10)

C(20)-C(21)	1.505(10)
C(24)-C(25)	1.528(8)
C(25)-C(28)	1.484(9)
C(25)-C(26)	1.510(9)
C(25)-C(27)	1.544(10)
C(29)-C(30)	1.531(7)
C(30)-C(35)	1.457(8)
C(30)-C(31)	1.469(8)
C(31)-C(32)	1.511(9)
C(32)-C(33)	1.464(10)
C(33)-C(34)	1.459(11)
C(34)-C(35)	1.350(9)
C(12)-O(1)-C(8)	115.6(5)
C(14)-O(2)-C(11)	121.3(5)
C(19)-O(4)-C(10)	116.6(5)
C(24)-O(6)-C(9)	116.3(5)
O(1)-C(8)-C(29)	113.6(5)
O(1)-C(8)-C(9)	109.2(4)
C(29)-C(8)-C(9)	113.2(4)
O(6)-C(9)-C(10)	108.0(5)
O(6)-C(9)-C(8)	112.7(4)
C(10)-C(9)-C(8)	110.6(5)
O(4)-C(10)-C(9)	108.8(5)
O(4)-C(10)-C(11)	109.3(4)
C(9)-C(10)-C(11)	109.7(5)
O(2)-C(11)-C(12)	107.3(5)
O(2)-C(11)-C(10)	106.9(5)
C(12)-C(11)-C(10)	109.5(5)
O(1)-C(12)-C(11)	111.0(5)
O(1)-C(12)-C(13)	106.8(5)
C(11)-C(12)-C(13)	113.4(5)
O(3)-C(14)-O(2)	121.7(7)
O(3)-C(14)-C(15)	126.8(7)
O(2)-C(14)-C(15)	111.5(7)
C(17)-C(15)-C(18)	110.9(7)
C(17)-C(15)-C(16)	109.6(7)
C(18)-C(15)-C(16)	108.3(8)
C(17)-C(15)-C(14)	111.0(7)
C(18)-C(15)-C(14)	109.5(6)
C(16)-C(15)-C(14)	107.4(7)
O(5)-C(19)-O(4)	122.4(7)
O(5)-C(19)-C(20)	123.6(7)
O(4)-C(19)-C(20)	113.8(8)
C(22)-C(20)-C(23)	116.5(10)
C(22)-C(20)-C(21)	105.2(9)
C(23)-C(20)-C(21)	105.6(9)
C(22)-C(20)-C(19)	107.7(7)
C(23)-C(20)-C(19)	108.3(7)
C(21)-C(20)-C(19)	113.7(7)
O(7)-C(24)-O(6)	121.6(6)
O(7)-C(24)-C(25)	126.4(7)
O(6)-C(24)-C(25)	112.0(6)
C(28)-C(25)-C(26)	113.2(8)
C(28)-C(25)-C(24)	106.7(6)
C(26)-C(25)-C(24)	109.6(6)

C(28)-C(25)-C(27)	111.2(7)
C(26)-C(25)-C(27)	108.8(8)
C(24)-C(25)-C(27)	107.0(6)
C(30)-C(29)-C(8)	111.8(5)
C(35)-C(30)-C(31)	111.8(6)
C(35)-C(30)-C(29)	113.7(6)
C(31)-C(30)-C(29)	112.7(6)
C(30)-C(31)-C(32)	113.2(6)
C(33)-C(32)-C(31)	109.5(7)
C(34)-C(33)-C(32)	114.3(8)
C(35)-C(34)-C(33)	122.2(8)
C(34)-C(35)-C(30)	122.8(7)

7. Formula overview



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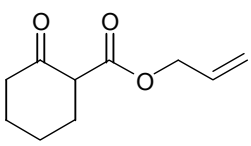

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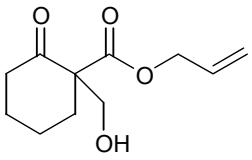

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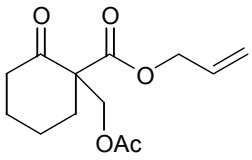

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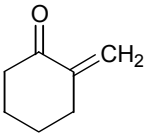

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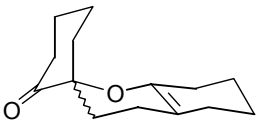

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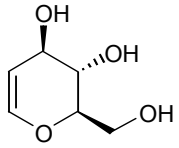

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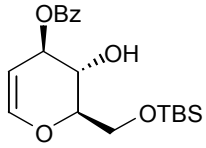

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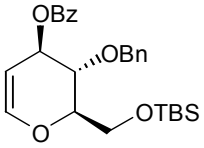

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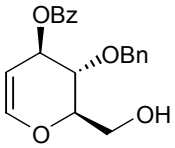

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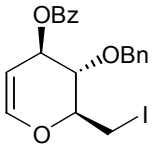

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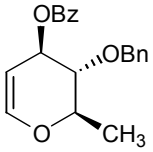

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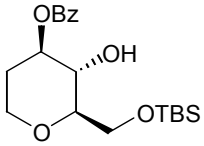

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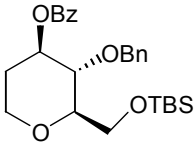

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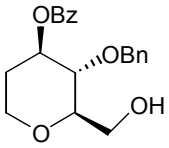

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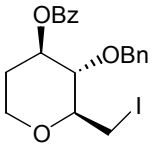

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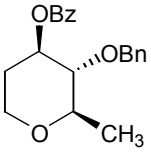

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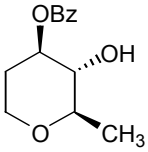

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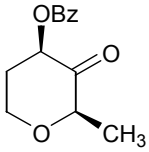

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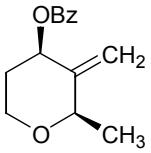

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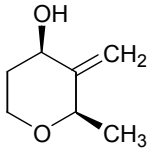

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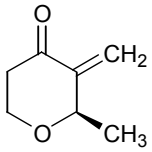

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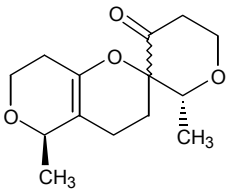

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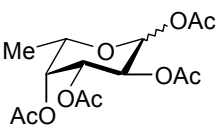

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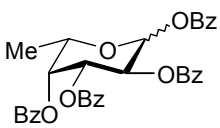

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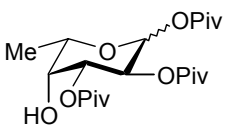

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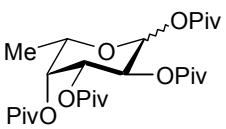

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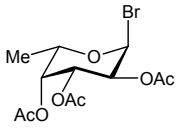

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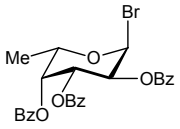

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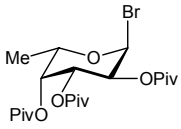

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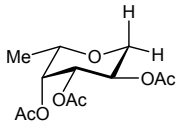

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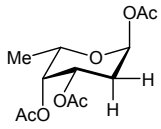

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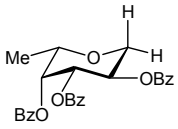

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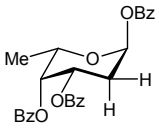

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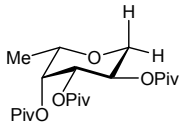

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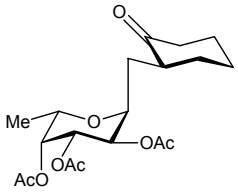

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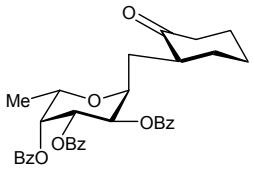

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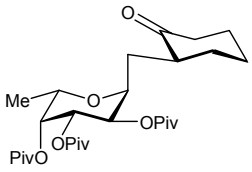

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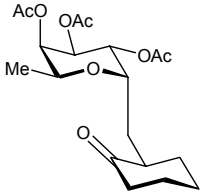

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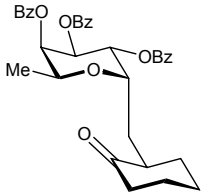

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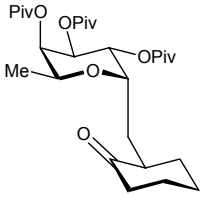

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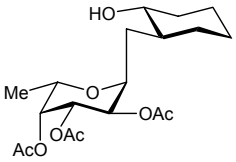

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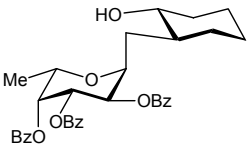

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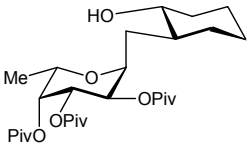

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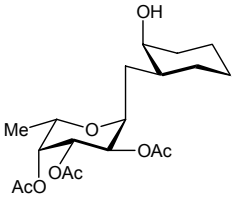

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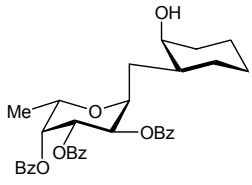

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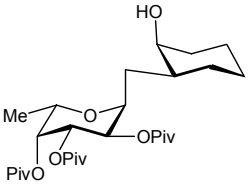

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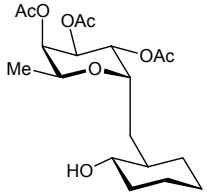

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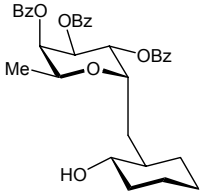

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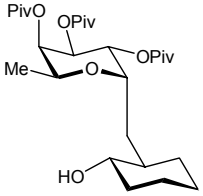

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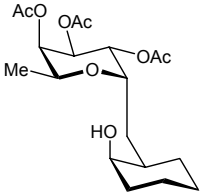

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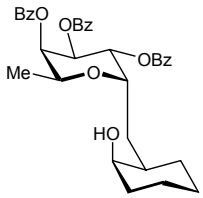

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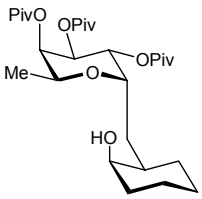

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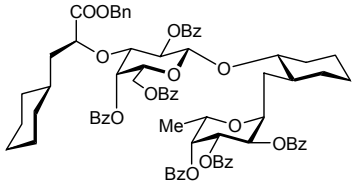

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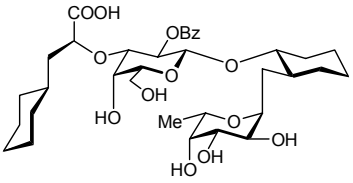

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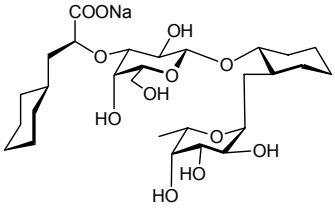

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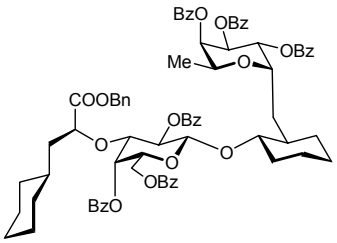

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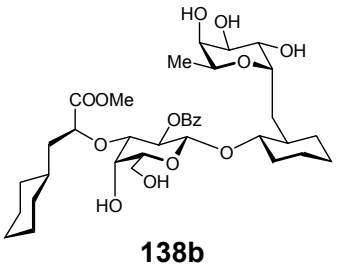

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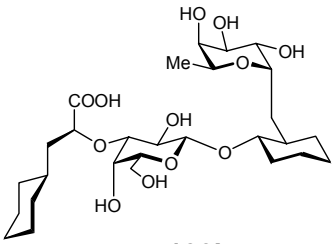

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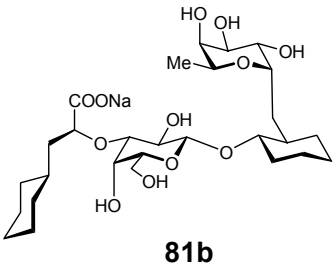

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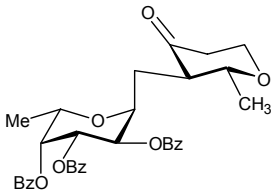

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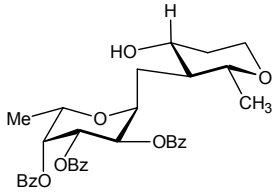

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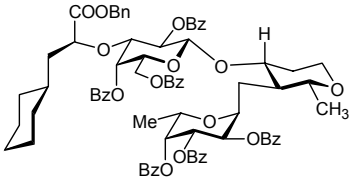

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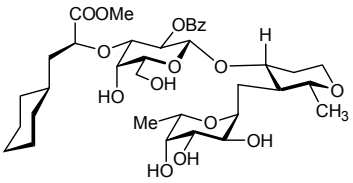

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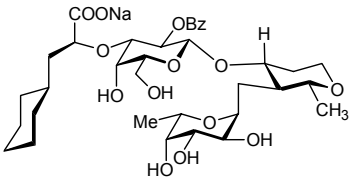

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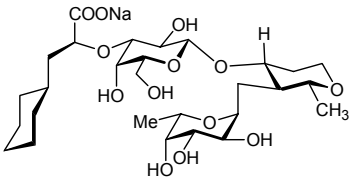

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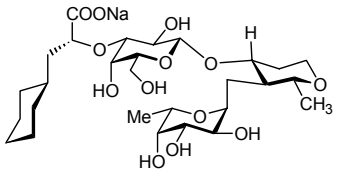

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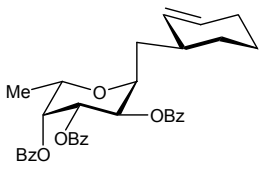

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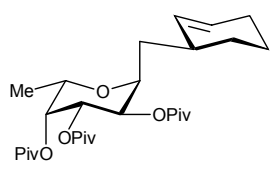

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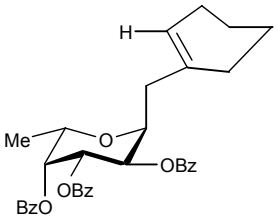

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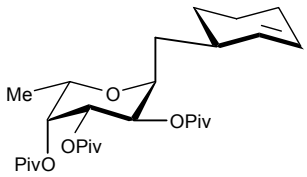

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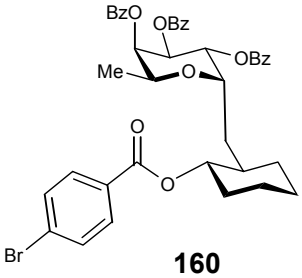

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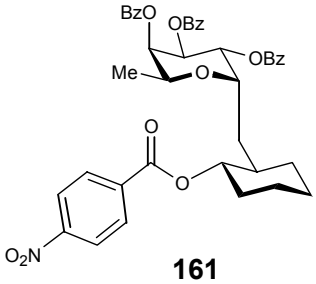

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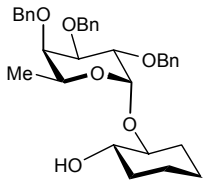

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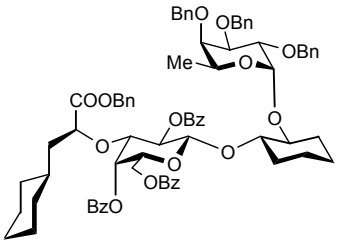

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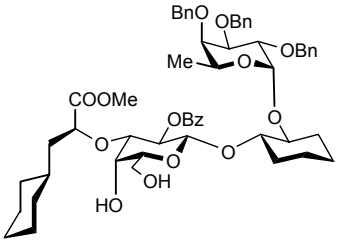

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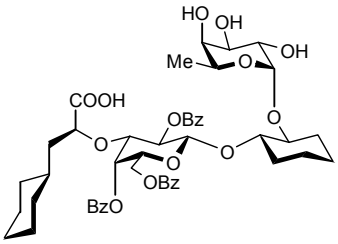

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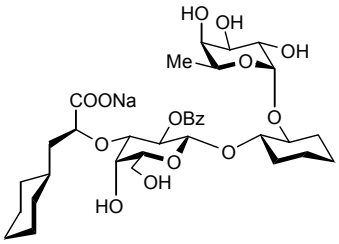

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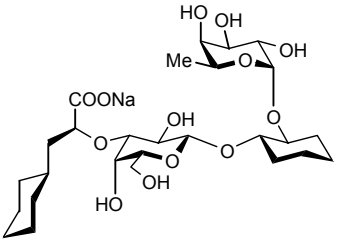

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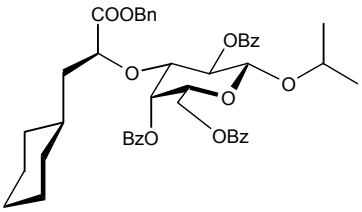

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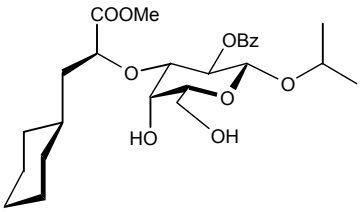

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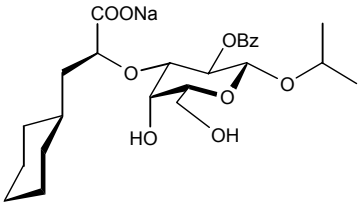

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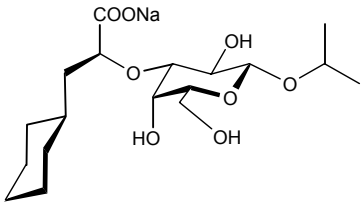

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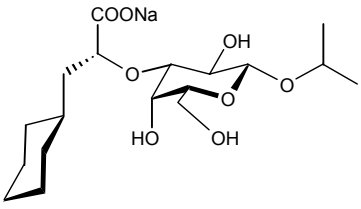

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07/2000 – 07/2004	**PhD position** in the group of Prof. Dr. Beat Ernst at the Institute of Molecular Pharmacy, University of Basel, Switzerland. **Thesis:** "*Selectin Antagonists: Synthesis and Conformational Comparison of O- and C-Glycosidic Tetrasaccharide Mimetics related to Sialyl Lewis^x".* **Grade:** magna cum laude
03/2000	**Master degree** in Chemistry at the University of Konstanz, Germany. **Grade:** 2.0 (grade B).
06/1999 – 03/2000	**Master degree thesis** in Chemistry in the group of Prof. Dr. Hans-Herbert Brintzinger, Institute of Inorganic Chemistry, University of Konstanz, Germany. **Thesis:** "*Synthesis and Reaction Behaviour of Benzyl Calcium Derivatives as Initiators for the Stereoselective Living Polymerisation of Styrene".* **Grade:** 1.1 (grade A).
10/1993 – 06/1999	Reading of Chemistry and Biology at the University of Konstanz, Germany.

Work experience

2000 – 2004	Daily interaction with biologists, modellers and spectroscopists (Biacore, MS, NMR) involved in the E-selectin project team. Main responsibility for the organization of regularly held project team meetings.
2001 – 2003	Organization, Evaluation and Supervision of the pharmacy practical course - "Combinatorial Solid Phase Peptide Synthesis". Teaching students in theoretical and practical aspects of organic synthesis.
2001 – 2003	Implementation and Optimisation of a solvent purchase and solvent purification system in the institute. Main responsibility for solvent supply.
2001 – 2003	Supervisor of several students working on organic synthesis projects in our group for periods of one to two months.
03/2002 – 07/2002	Supervisor of a master degree thesis performed by a student of the pharmacy department. Title: "*Towards the Synthesis of C-Glucosidic Sialyl Lewis^x Mimetics".*
07/1992 – 09/1993	Military service at the "Gebirgsjägerbataillon" in Mittenwald near Munich, Germany: • 2 months: Basic Military Training, • 13 months: Member of the Biathlon Team.

Skills

Language skills:	German: mother language, French: basic skills, English: very good verbal and written communication skills.
Computer skills:	High knowledge of chemistry-related software tools (ChemOffice, EndNote, SciFinder, Beilstein).
	Advanced computer based presentation skills due to the active participation in scientific group seminars.
	Basic knowledge of HTML/CSS as well as Macromedia® software.
	Basic knowledge of computer hardware and Microsoft Windows® operation systems.

Publications

- Ernst B., Müller C., Alker A., "*Synthesis, Conformational Investigation and Biological Evaluation of Novel C-Glycosidic E-Selectin Antagonists",* in preparation
- Ernst B., Dragic Z., Marti S., Müller C., Wagner B., Jahnke W., Magnani J., Norman K., Öhrlein R., Peters T., Kolb H., "*Design and Synthesis of E-Selectin Antagonists",* Chimia 55 (**2001**), 268-274
- Feil F., Müller C., Harder S., "*α-Methyl-Benzylcalcium Complexes: Syntheses, Structures and Reactivity",* J. Organomet. Chem. 683 (**2003**), 56-63
- Müller C., "*Synthesis of C-Glycosidic E-Selectin Antagonists",* **poster** at the „Pharma-Day" of the Center of Pharmaceutical Sciences ETH Zürich – Uni Basel; July **2002**
- **Lecture** within the official lecture series "*Seminars on Drug Discovery and Development*" at the Pharmacenter of the University of Basel; Title: "*An Important Carbohydrate Epitope in Inflammatory Diseases: Sialyl Lewis^x and C-Glycosidic Mimetics Thereof*"; 09. July **2003**

Additional information

Memberships:	● Swiss Chemical Society (SCG) ● German Chemical Society (Gesellschaft Deutscher Chemiker, GDCh) ● Association of German Mountaineers (Deutscher Alpenverein, DAV)
Hobbies:	● member of school orchestra as Violoncello player in secondary school ● family, playing with my 2-year old son, climbing, mountaineering, long distance running

References

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