# Towards the Synthesis of a Macrocyclic

# E-selectin Antagonist

**Inauguraldissertassion**

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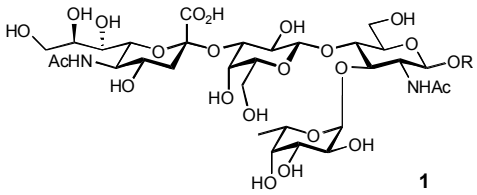
## Abstract

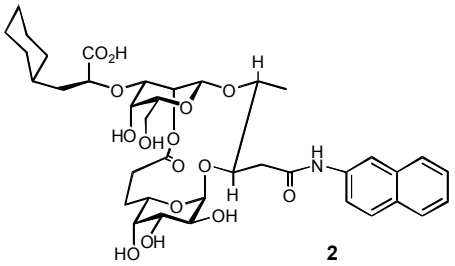
### Towards the Synthesis of a Macrocyclic E-selectin Antagonis

***Introduction***

Selectins are involved in the orderly migration of leukocytes from blood vessels to sites of inflammation. Although extravasation of leukocytes represents an essential defense mechanism against infection, excessive or inappropriate leukocyte accumulation results in injury to host tissues. Therefore, the development of selectin-antagonists is considered as an effective therapeutic approach in inflammatory and other disorders. Physiological selectin ligands contain a common tetrasaccharide epitope called sialyl Lewis$^X$ **(1)** that has served as the lead structure in our rational design of E-selectin antagonists.



**1**



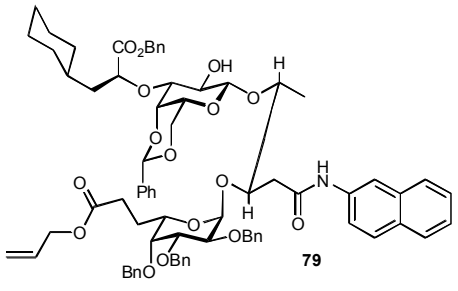
**2**

***Purpose***

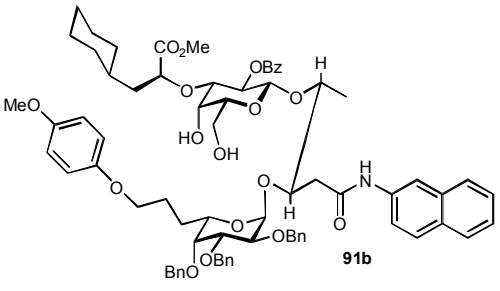
The sLe$^X$ analog **2** was rationally designed to explore the role of the spatial orientation of the pharmacophores in the conformation bound to the receptor. The rigidity of the macrocyclic core should provide the basis for enhanced bioactivity due to pre-organization of the functional groups involved in binding in the bioactive conformation. The building blocks for the synthesis of **2** are L-galactose, elongated at C-6 by Wittig olefination, D-talose alkylated at the 3-OH with (*S*)-cyclohexyl lactic acid and an acyclic replacement of D-Glc*N*Ac. Activity studies of the **2** will provide an important contribution to the validation of our predictions based on pre-organization determined by molecular modeling.

***Results***

The building blocks required by the retrosynthetis of target molecule **2** were synthesized in good to excellent yields. The core structures **79** and **91b** were obtained as the results of two different synthetic pathways.



**79**



**91b**

The targeted macrocycle could not be synthesized due to major synthetic hurdles that have been encountered along the two respective pathways.

## Preliminary remarks

For purpose of clarity we summerize here the different names found in the literature for the selectins:

| | | | | |
|---|---|---|---|---|
| ELAM-1 | = | E-selectin | = | CD62E |
| GMP-140/PADGEM | = | P-selectin | = | CD62P |
| LECAM-1/LAM-1 | = | L-selectin | = | CD62L |

## Abbreviations

The following abbreviations have been used:

| | |
|---|---|
| Ac | Acetyl |
| AD | Asymmetric dihydroxalation (Sharpless) |
| AgOTf | Silver triflate |
| $Al(CH_3)_3$ | Trimethylaluminium |
| | |
| $BF_3$. $Et_2O$ | Boron trifluoride etherate |
| Bn | Benzyl |
| BnBr | Benzyl bromide |
| BOM | Benzyloxymethylether |
| Bz | Benzoyl |
| BzCl | Benzoyl chloride |
| | |
| cAMP | Cyclic adenosine mono phosphate |
| CAN | Cerium (IV) ammonium nitrate |
| $CBr_4$ | Carbon tetrabromide |
| $CCl_3CN$ | Trichloroacetonitrile |
| $CHCl_3$ | Chloroform |
| CHO | Chinese hamster ovary |
| COSY | Correlated spectroscopy |
| CSA | Camphor sulfonic acid |
| CR | Complement regulatory-like units |

| | |
|---|---|
| DCM | Dichloromethane ($CH_2Cl_2$) |
| DCE | Dichloroethane ($CH_3CHCl_2$) |
| DDQ | Dichlorodicyanoquinone (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) |
| DEAD | Diethyl azodicarboxylate |
| DIPEA | Diisopropylethylamine |
| DMAP | 4-(Dimethylamino)pyridine |
| DME | Dimethoxyethane |
| DMF | *N*,*N*-Dimethylformamide |
| DMTST | Dimethyl(methylthio)sulfonium trifluoromethanesulfonate |
| | |
| ECM | Extracellular matrix |
| EDA | Ethylenediamine |
| ee | Enantiomeric excess |
| e.g. | For example |
| EGF | Epidermal growth factor domain |
| ELISA | Enzyme-linked immunosorbent assay |
| EtOH | Ethanol |
| eq. | Equivalent |
| | |
| Fuc | Fucose |
| | |
| Gal | Galactose |
| Glc*N*Ac | *N*-Acetylglucosamine |
| Glu | Glucose |
| GlyCAM-1 | Glycosylated cell adhesion molecule-1 |
| | |
| h | Hour |
| $H_2$ | Hydrogen |
| HCl | Hydrochloric acid |
| $HClO_4$ | Perchloric acid |
| HEV | High endothelial venules |
| HUVEC | Human umbilical vein endothelium cells |
| | |
| IFN-$\gamma$ | Interferon-$\gamma$ |
| IL-1 | Interleukine-1 |
| IL-1-$\beta$ | Interleukine 1-$\beta$ |

| | |
|---|---|
| IL-3 | Interleukine-3 |
| IR | Infrared spectroscopy |
| LAD-2 | Leukocyte adhesion deficiency 2 |
| $Le^X$ | $Lewis^X$ |
| $LiAlH_4$ | Lithium aluminium hydride |
| LiOH | Lithium hydroxide |
| Lit. | Literature |
| LPS | Lipopolysaccharide |
| | |
| Me | Methyl |
| min. | Minute |
| MMPs | Matrix Metalloproteinases |
| | |
| NaH | Sodium hydride |
| NaOMe | Sodium methanolate |
| NeuAc | Neuraminic acid = Sialic acid |
| NF-κB | Nuclear factor of kappa B |
| $NH_2OH•HCl$ | Hydroxylamine hydrochloride |
| NMR | Nuclear magnetic resonance |
| NO | Nitric oxide |
| NOE | Nuclear Overhauser effect |
| | |
| OSE | cf. TMSEt |
| | |
| Ph | Phenyl |
| $Ph_3CCl$ | Triphenylchloromethane |
| PhSH | Thiophenol |
| $PhP_3$ | Triphenylphosphine |
| Py | Pyridine |
| $PtO_2$ | Platinum oxide |
| | |
| Rf | Retention factor |
| Rh | Rhodium |
| $SLe^X$ | Sialyl $Lewis^X$ |
| | |
| Tal | Talose |
| TBAB | *tert*-Butyl ammonium bromide ($Bu_4NBr$) |

| | |
|---|---|
| TBAF | *tert*-Butyl ammonium fluoride ($Bu_4NF$) |
| TFA | Trifluoroacetic acid |
| $Tf_2O$ | Triflic anhydride |
| THF | Tetrahydrofurane |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl, OR tetramethylsilan (depending on context) |
| TMSEt | 2-(Trimethylsilyl)ethanol |
| TMSE | 2-(Trimethylsilyl)ethyl group = OSE |
| TMSOH | Trifluoromethanesulfonic acid |
| TMSOTf | Trimethylsilyl trifluoromethanesulfonate |
| TMU | *N*,*N*,*N*',*N*'-tetramethylurea |
| TNF-$\alpha$ | Tissue necrosis factor $\alpha$ |
| Tr | Trityl (triphenylmethyl) |
| *tr*NOE | Transfer nuclear Overhauser effect |
| | |
| VCAM-1 | Endothelial vascular cell-adhesion molecule-1 |
| CD62P | P-selectin |
| CD62E | E-selectin |

## Table of content

# I. Outline

***Biological relevance of the selectins***

Selectins are major players in the adhesion of leukocytes to vascular endothelium during the early cascade of events leading to inflammation [1]. More specifically, selectins are a family of carbohydrate-binding proteins expressed at the sites of inflammation in response to early precursors liberated by the injured tissue. These membrane proteins mediate the tethering and rolling of leukocytes on blood vessel endothelium, leading to a slowed leukocyte migration. As a slow displacement of leukocytes on the endothelium is critical to their subsequent extravasation (movement of leukocytes through endothelial cell layers to get to an area of infection), selectin binding is an essential step to the inflammation [2].

Henceforth, control of the leukocyte-endothelial cell adhesion process may prove useful in cases where excess recruitment of leukocytes can contribute to acute diseases such as stroke and reperfusion injury, as well as to chronic diseases such as psoriasis and rheumatoid arthritis [3]. Moreover, *in vivo* and *in vitro* studies of selectins have established their importance in a wide array of other human diseases [4]. For instance, it has been suggested that cancer may exploit the adhesion process after entering the bloodstream to metastasize. In this regard, selectin antagonists represent a potential cancer therapy [5,6].

***Natural selectins ligands contain carbohydrate epitopes***

The three selectins (L-, E-, and P-) differ in their binding specificities. Current opinion suggests that carbohydrates including Lewis sugars (at some level of modification such as sialylation or sulfation) are the biologically relevant ligands [7,8]. In particular, sialyl Lewis$^X$ **(1)** (Figure 1), a subunit of many natural carbohydrate ligands, has been recognized as a common ligand for all selectins [9]. SLe$^X$ **(1)** has been shown to be an effective antagonist of selectin function when it blocked the inflammatory process in various *in vitro* and animal models. Thus, identification of the carbohydrate ligands interacting with the selectins has provided an opportunity to develop a novel class of potential anti-inflammatory drug. Moreover, as will be shown later, the potential of selectin antagonists as drugs largely exceeds the domain of inflammation [4].

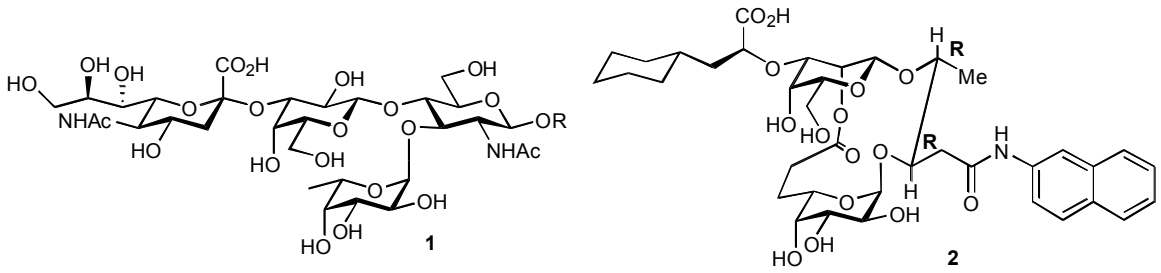



**Figure 1**: Representation of sialyl Lewis$^X$ **(1)** and the macrocyclic E-selectin antagonist **2**.

***Development of selectins antagonists***

The development of inhibitors of the selectin-ligand interactions occupies an important place among the numerous approaches taken to interfere with biological processes in the inflammatory cascade. This goal has provided an exceptional opportunity to apply interdisciplinary methodologies of the biological and chemical sciences to a problem in structural biology (table 1).

Structural information about the sLe$^X$ -selectins interactions has revealed the nature of the functional groups on the surface of sLe$^X$ **(1)** that are required for selectin binding [10], [11,12]. Based on these data, numerous analogs and mimics of sLe$^X$ **(1)** have been designed and synthesized in order to down-regulate leukocyte-endothelial cell adhesion events [13,14,15]. The mimics are designed to resemble the structure of the natural carbohydrate ligand, but are not carbohydrates *per se*. Indeed, carbohydrates are not ideal drug candidates: they are difficult to synthesize, bind weakly, and have low oral bioavailability due to labile glycosidic linkages and poor cell-entry properties.

The enhancement of the activity, stability, and bioavailability profiles of sLe$^X$ **(1)** has been the major drive for the development of new structures. These improvements include e.g. elimination of labile glycosidic linkage with *C*-glycoside mimetics [16], enhancement of the molecules‘ binding affinities to the proteins by incorporation of secondary groups to exploit additional binding regions on the proteins and simplification of the initial carbohydrate structure [17].

The search for small molecules that disrupt selectin-sLe$^X$-mediated recognition events has met with some success. SLe$^X$ **(1)** analogs with substitutions for Neu*N*Ac or Glc*N*Ac,

and tethered compounds show comparable or better affinity than $sLe^X$ **(1)** [18,19]. Current efforts in our group focus on developing small molecules with even improved activity. Despite the substantial methodological advances in glycosylation chemistry that have been achieved over the last decade, the assembly of sophisticated oligosaccharides is still far from routine. No inhibitor of selectin-mediated cellular adhesion has reached the market to date. New elements have recently increased our understanding of the selectin-$sLe^X$ interactions. A major breakthrough has been the publication of the X-ray structure in 2000 [12]. This information along with the knowledge that a second potential binding site exists proximal of the $sLe^X$ **(1)** binding-site has spurred the development of new generations of selectin antagonists [20].

***Design and synthesis of a macrocyclic E-selectin antagonist***

The aim of this work was the synthesis of the macrocyclic E-selectin antagonist **2** (Figure 1) intended to provide valuable data not only to elucidate the mechanism of selectin recognition, but also to be a possible lead structure for the development of novel potential therapeutic agents. Macrocyclization of a $sLe^X$ **(1)** analog has been undertaken in order to explore the spatial orientation of the functional groups in the ligand bound to E-selectin. In addition, the rigid macrocyclic core was thought to provide the basis for enhanced bioactivity due to a potentially high pre-organization of the functional groups involved in binding.

The building blocks for the synthesis of **2** have been L-Gal elongated at C-6 by Wittig olefination, D-Tal alkylated at the 3-OH with (*S*)-cyclohexyl lactic acid and an *N*-naphtoyl moiety (see Synthesis *in* Chapter III).

**Table 1**: Chronological overview of selectin antagonists research.

| | |
|---|---|
| 1989 | Initial characterization of the selectins [21]<br>Simultaneous cloning of the three selectins [2]<br>Beginning of the isolation of the receptors |
| 1990 | Four groups reported that $sLe^X$ **(1)** recognizes E-selectin [22]<br>Beginning of the characterization of the carbohydrate portion of the natural ligand |
| 1991 – 1993 | First total synthesis of the minimal carbohydrate ligand $sLe^X$ **(1)** by Hasegawa and co-workers [23] |
| | First syntheses of $sLe^X$ **(1)** derivatives useful for determining critical functional groups [24] |
| | Glycoprotein receptors bearing these carbohydrates identified as ESL-1 and PSGL-1 [25] |
| 1992 | Isolation of the natural glycoprotein ligands [25] |
| 1994-1997 | Determination of the free and bound conformations of $sLe^X$ **(1)** [26] |
| | Development of novel classes of selectin antagonists [27, 28] |
| *2000* | X-ray structure reported by Camphausen et al. [12] |

# II. Introduction

## II.1 General Introduction

***Glycobiology***

The classical role attributed to carbohydrates is that of a medium for energy storage and transport. However, the two past decades have seen a *Renaissance* in carbohydrate biology and chemistry with the emergence of the field of glycobiology [29]. New insights have been gained on the enormous structural and functional diversity of this class of compounds that are involved in living processes not only as energy sources, but also as critical elements for the structure, function and dynamics of proteins [30].

Of the three main classes of biopolymers - proteins, nucleic acids and sugars - the sugars, or saccharides, are the most complex and hence the most difficult to study. Challenging scientists for decades, the numerous roles played by oligosaccharides and glycoconjugates in biological recognition have nurtured vigorous investigation into the molecular mechanisms of protein-carbohydrate association. The basis of these roles is the information potential of oligosaccharides, which are composed of monomers having more than one linkage position, and which are provided with stereospecific branching capabilities at each of these positions. These capabilities allow sugars to be built in a variety of linear or branched fashions. For example, two common sugars, Glu and Man, can be linked to form a disaccharide in up to 80 different ways. It takes just a few coupling steps to produce a large number of diverse biological structures, and this diversity of saccharide structure is exploited *in vivo*.

A major challenge in cell biology is to identify the sugar code or “glycome” that is, to define the interactions between cell-coating sugars and proteins and work out how they recognize each other. The discipline of glycobiology has taken part in and will undoubtedly contribute to our knowledge of the intricate workings of a vast array of biological processes. As more and more carbohydrate-related drug-discovery targets are unveiled and validated, the therapeutic potential of carbohydrates is just beginning to be exploited by the pharmaceutical industry (Figure 2).

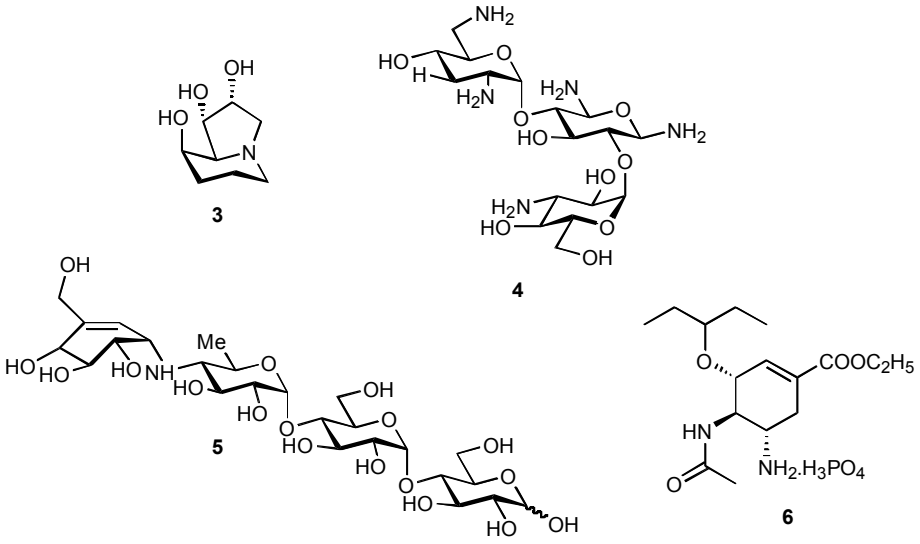



**Figure 2**: Examples of actual carbohydrate-related drugs:

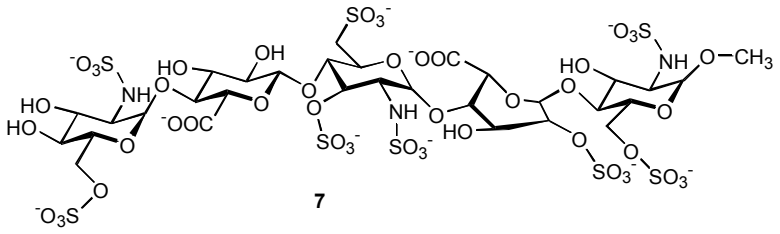
| | | |
|---|---|---|
| **3:** *swainsonine* | mannosidase inhibitor | cancer therapy |
| **4:** *kanamycin B* | aminoglycoside antibiotic | infection therapy |
| **5:** *acarbose* | $\alpha$-glycosidase inhibitor | diabetes therapy |
| **6:** *oseltamivir phosph.* | neuraminidase inhibitor | anti-viral therapy |

***Interference with protein-carbohydrate interactions offers potential drug targets***

Carbohydrate-protein interactions are characterized by notably weak binding [31]. However, cells can readily decode this information with the help of specific protein receptors. In interfering with these interactions, high affinity mimetics of native saccharides could modulate biological activity. These compounds have a tremendous potential therapeutic value in the treatment of various pathologic states such as viral, parasitic, mycoplasmal and bacterial infections as well as in inflammatory diseases and in a range of human cancers [32]. Thus, the study of the intimate details of carbohydrate-recognition by their receptors occupies a central place in carbohydrate chemistry and biology.

Recent advances of effective methods for characterizing the complex carbohydrate structures present on the surface of cells are the source of the new appreciation of the varied biological functions of these molecules [29,33]. New methods for large-scale syntheses of carbohydrates now allow the evaluation of these compounds' potential as pharmaceuticals. An outstanding example of the progresses that have taken place in this field is the large-scale synthesis of the methyl glycoside of the smallest active segment of heparin by *Petitou*, *Sinaÿ* and *van Boeckel* at Organon/Sanofi-Synthelabo. The

industrial synthesis consists of more than 50 chemical transformations towards the desired pentasaccharide *fondaxaparin* **(7)** (Figure 3) [34,35].




**7**

**Figure 3**: *Fondaxaparin* **(7)** is the methyl glycoside of the smallest active segment of heparin, today industrially synthesized in 61 steps.

The development of carbohydrate drugs has been beset with difficulties of both financial and practical nature. Primarily, the methods needed to produce even small amounts of complex carbohydrates are often difficult and expensive, whether they involve synthesis or isolation from natural sources. Added complications include the low bioavailability of orally ingested carbohydrates and the inability of many animal models to provide data relevant to humans. Despite these drawbacks, there are many advantages in favor of carbohydrate-based therapeutics, such as low toxicity and immunogenicity relative to their peptide counterparts.

***Blocking the inflammatory process***

Our research focuses on the selectin [1], a family of adhesion proteins, and their glycoprotein ligands. The selectins are involved, along with the integrins and immunoglobulin-like cell adhesion molecules, in the orderly migration of leukocytes to sites of inflammation [3].

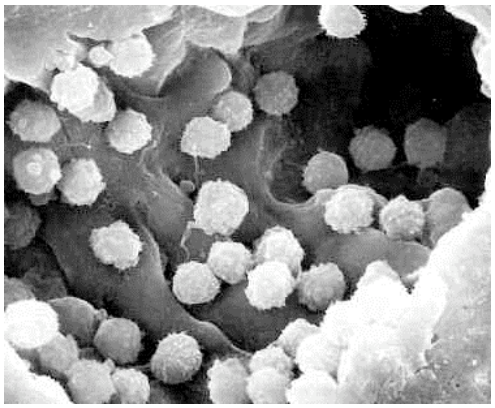


**Figure 4**: Leukocytes rolling on the surface of a blood vessel.

Regulated expression of adhesion and signaling molecules directs the recruitment of leukocytes into lymphatic tissues or sites of inflammation [36]. The critical first event in this multistep process is the adherence of circulating leukocytes to the vascular wall under shear forces (Figure 4). Interactions of selectins with cell-surface carbohydrate ligands initiate the tethering and rolling of leukocytes on endothelial cells, platelets, or other leukocytes. Reversible multicellular interactions enable leukocytes to encounter regionally expressed chemokines and lipid autacoids. The activated leukocytes then use integrins to arrest on the vessel wall and to emigrate into the underlying tissues in response to chemotactic gradients.

Although this influx normally represents an essential defense mechanism against infection, excessive or inappropriate leukocyte accumulation results in injury to host tissues [4]. Hence, control of the leukocyte-endothelial cell adhesion process is sought in cases where excessive recruitment of leukocytes can contribute to acute and chronic inflammatory diseases. In other words, inhibiting the interaction of selectins with their natural or synthetic ligands has the potential to interrupt the inflammatory process and thus should be beneficial to the treatment of inflammatory diseases. In addition to their

role in the inflammation cascade, selectins are implicated in diverse disease states [4]. For instance, selectins play a role in the hematogenous metastasis of some cancer cells [6,37]. Interfering with these interactions is a potential starting point for new cancer therapies.

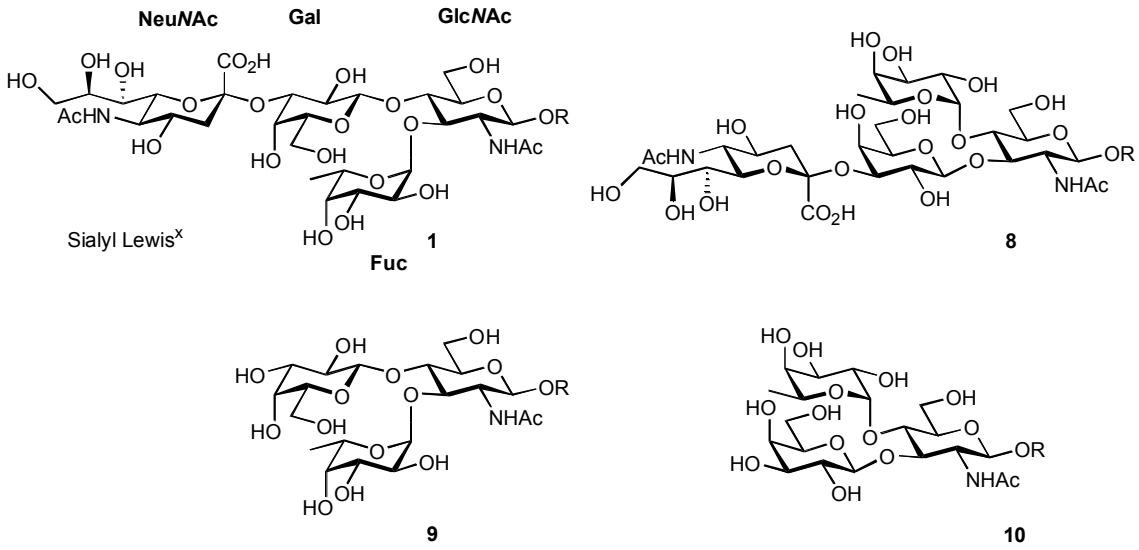



**Figure 5:** Selectin ligands contain the common carbohydrate epitope sLe$^X$ **(1)**, which was shown to interact with all three selectins, albeit with different affinities. The other structures depicted here are sLe$^a$ **(8)**, Le$^X$ **(9)**, and Le$^a$ **(10)**.

***Selectins antagonists are designed in analogy to a natural carbohydrate epitope***

The physiological ligands of the selectins contain a common tetrasaccharide epitope, the so-called sialyl Lewis$^X$ **(1)** (Figure 5) [7,9,22]. It serves as the lead structure in the search for selectin antagonists. Utilization of structural information about the selectins and their interactions with sLe$^X$ **(1)** has been revealed through the use of NMR spectroscopy [38,39,40] protein X-ray crystallography [12,41] and molecular modeling [42,43].

This investigation is undertaken not only to elucidate the mechanism and the structural properties of sLe$^X$-selectin recognition. It is also aimed at predicting the 3-dimensional structures of novel mimics to allow the discovery of therapeutic agents. Numerous academic and industrial groups have searched for potent selectin antagonists [17,44]. All these efforts have only partially reached their aims, as the best selectin antagonists synthesized to date have still not led to therapeutic applications.

Our group focuses on the development of antagonist of a particular type of selectin, the E-selectin. The conformation of $sLe^X$ **(1)** bound to E-selectin, the so-called "bioactive conformation" has been elucidated [26,38,39,40,45,46]. Use of this information was made to develop a molecular modeling tool helping us to rationally design different classes of E-selectin antagonists.

The presented work concerns one of these approaches, an attempt to rigidify the $Le^X$ **(9)** core of the lead structure by a macrocyclic ring formation. Since conformational analyses have shown that the macrocyclic structure perfectly mimics the bioactive conformation [46] (Kolb & Ernst, unpublished results), its synthesis and biological evaluation would be an important reference point for the validation of our molecular modeling tool. Higher pre-organization of the sugar in its bioactive conformation is believed to lead to a better affinity with E-selectin because of lower entropy cost.

## II.3 State of the research

In the first instance, the following literature reviews provides a description of the nature and biological significance of the selectins and that of their ligands. The focus is then brought on the specific interactions between E-selectin and its ligands. The methods used to investigate these interactions are described. The developments that have led to the selectin antagonists known to date are also outlined.

A particular attention is set on the history of selectin antagonists' development in the *Novartis Selectin Antagonists* group. Research in this group, in particular on macrocyclic antagonists, has served as starting point to our work. The last section hence allows a seamless transition to our personal contribution to the field.

### II.3.1 The selectins and their ligands

***Nature of the selectins***

The selectins are type I membrane glycoproteins that mediate adhesion of leukocytes and platelets on vascular surfaces. E-, P- and L- selectin were identified in the early 90s. They are $Ca^{2+}$-dependent carbohydrate-binding proteins [2].

**L (leukocyte)** selectin is expressed on most leukocytes. It binds to constitutively expressed ligands on HEV of lymph nodes, to inducible ligands on endothelium at sites of inflammation and to ligands on other leukocytes.

**E (epithelium)** selectin is transiently synthesized by cytokine-activated vascular endothelium.

**P (platelet)** selectin, stored in membranes of secretory granules of platelets and endothelial cells, is rapidly redistributed to the cell surface by thrombin and other secretagogues. Some cytokines also increase the synthesis of P-selectin in endothelial cells.

It has recently been shown that E- and P- selectins bind to ligands on myeloid cells and subsets of lymphocytes, and P-selectin also binds to ligands on HEV of activated cells [7].

The three selectins are transmembrane glycoproteins. Each selectin is composed of an *N*-terminal lectin domain (CRD, *C*arbohydrate *R*ecognition *D*omain), an epidermal growth factor-like (EGF-like) domain, a variable number of complement regulatory-like repeats, called the consensus repeat or complement regulatory-like (CR) domain, a transmembrane domain, and a short cytoplasmic tail that may play a role in signal transduction (Figures 6 & 7). The $sLe^X$ **(1)** binding site has been localized on the lectin domain [47].

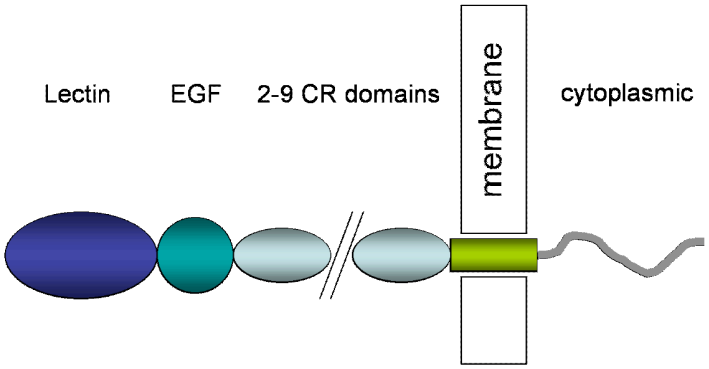



**Figure 6**: Schematic representation of the selectins.

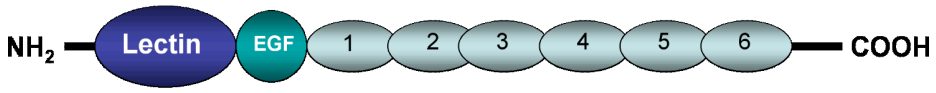



**Figure 7**: Structure of E-selectin.

***Natural ligand***

Since the initial characterization of the selectins in 1989, a number of ligands have been identified [25]. Preceding the isolation of the naturally occurring glycoprotein that binds to selectins, the carbohydrate portions of these ligands were being determined. Early studies [21] proposed, upon the basis of transfection of a fucosyl transferase, that the carbohydrate contained fucose. The composition of the carbohydrate was determined using mass spectrometry [48]. In 1991, it was reported that $sLe^X$ (**1**, Neu5Ac$\alpha$2→3Gal$\beta$1→4[Fuc$\alpha$1→3]Glc*N*Ac) recognizes E-selectin. $SLe^a$ **(8)** and sugar derivatives (at some level of modification such as sialylation or sulfation) of $Le^X$ **(9)** and $Le^a$ **(10)** also bind to E-selectin (Figure 5) [21,49].

Hence, the tetrasaccharide $sLe^X$ **(1)** has been generally recognized as a common ligand for all selectins [8,9]. This compound, together with related sialylated and fucosylated carbohydrates, is the terminal component of glycans attached to proteins and lipids located on the surfaces of most leukocytes and of some endothelial cells.

The glycoprotein receptors bearing these carbohydrates were identified in 1994 as ESL-1 [50], and PSGL-1. However, the debate over the biologically relevant ligands (Figure 8) for each of the selectins is still ongoing [25]. The carbohydrate portion of PSGL-1, a natural ligand of E- and P-selectin, is a trimer of fucosylated Glc*N*Ac groups with a terminal sialyl group. Sulfation is required for binding to P-selectin, but not E-selectin. It is relevant to note that P-selectin-mediated, but not E-selectin-mediated, leukocyte rolling and recruitment are dramatically affected in mice genetically different in PSGL-1 [51]. This suggests that, *in vivo*, E-selectins effectively utilize other $sLe^X$-modified glycoconjugates on leukocytes, whereas P-selectins do not. The structure of the natural ligand on GlyCAM-1 for L-selectin is less understood [25].

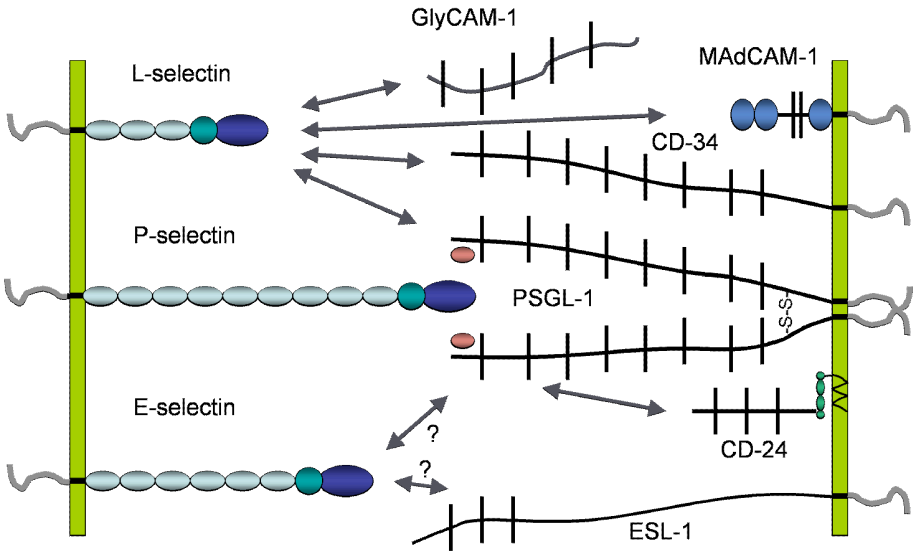



**Figure 8**: The physiological ligands of the three selectins have been isolated and their structures partially elucidated (ESL-1, PSGL-1, GlyCam) [44].

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## II.3.2 Biological significance

### II.3.2.1 Biological role in the inflammation cascade [52,53]

***Discovery from medical observations***

The importance of selectins in humans is underscored by the discovery of a congenital disorder of fucose metabolism termed leukocyte adhesion deficiency 2 (LAD-2) [54]. Because patients with LAD-2 lack fucosylated glycoconjugates, they do not express functional selectin ligands. Leukocytes from these patients do not tether to and roll on P- or E-selectin surfaces. Clinically, the patients have more infections, supporting the concept that the selectins have an important function in initiating recruitment of leukocytes. Furthermore, the importance of selectins in inflammation has been experimentally demonstrated in selectin deficient mice. Mice made genetically deficient in each of the three selectins have defects in leukocyte trafficking in response to specific challenges [55].

***The inflammatory cascade***

Released by damaged tissue after an injury, chemical signals initiate and maintain a host response designed to repair tissues and neutralize the hypothetic microbial infection. This response involves activation and directed migration of leukocytes (neutrophils, monocytes and eosinophils) from the venous system to sites of damage by a complex series of steps, referred to as the inflammatory cascade (Figure 9). The five important steps in the transfer of leukocytes from the blood stream to site of injury are:

*Step 1: Stimulus*

The cascade begins when releases cytokines that stimulate the endothelium to transiently express two proteins: E- and P-selectin. Initial activation of E- and P-selectins is a consequence of vessel wall exposure to locally produced chemokines and other mediators (e.g. TNF-$\alpha$, IL-1, LPS), the so-called *inflammatory stimulus* [56]. E- and P-selectin are induced on the surface of vascular endothelium with different expression kinetics [57]. P-selectin, which is also presented by activated platelets, is translocated within minutes from intracellular stores and promotes the immediate attachment and rapid rolling of leukocytes over vascular surfaces. In contrast, E-selectin is transcriptionally regulated and appears on the activated only several hours (about 8h)

after activation. For a detailed review of the regulation mechanisms for E-selectin, see Chapter II.3.3.

*Step 2: Attachment and rolling*

Attachment (tethering) and subsequent rolling of leukocytes on the cell wall are mediated by weak interactions between carbohydrate epitopes on the leukocytes and the E- and P- selectins. The combined action of E- and P- selectins allows leukocyte to slow down by rolling along the vascular endothelium.L-selectin is constitutively present on the surface of leukocytes and binds to endothelial ligands (e.g. PSGL-1). These processes are prerequisites for the adhesion step and are therefore essential to the inflammatory process.

*Step 3: Secondary activation*

*Rolling* of leukocytes enables the interaction of the vascular endothelium with cytokines and leukocyte-activating molecules triggering signals that activate and upregulate leukocyte integrins. Integrins, a group of three proteins sharing the same β-2 chain, represent another class of leukocyte adhesion molecules that is essential to the cascade.

*Step 4: Adhesion*

Leukocyte rolling allows stronger interaction with the integrins (themselves the target for chemotherapies). Immobilization of the slowed leukocytes on the surface of the vascular endothelium is reached by tight adhesion of the integrins to their endothelial ligands VCAM-1 and MadCAM-1. This step precedes the leukocyte extravasation into the underlying tissue.

*Step 5: Transendothelial migration*

The transmigration through the endothelium (extravasation) to sites of injury is presumably facilitated by extracellular proteases, such as matrix metalloproteinases (MMPs).

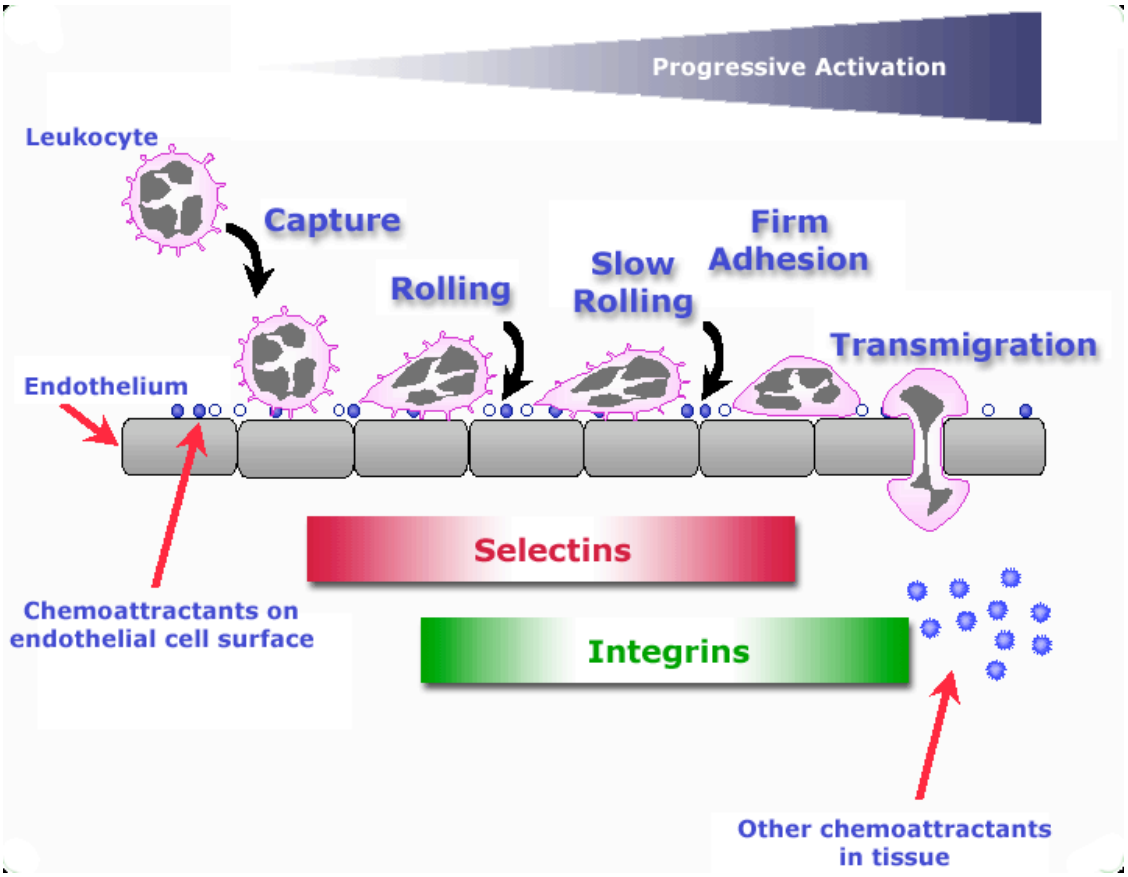



**Figure 9**: The inflammation cascade:

- Endothelium activation
- Selectin-mediated capture & rolling
- Secondary activation during slow rolling phase
- Integrin-mediated firm adhesion
- Transmigration

### II.3.2.2 Selectins and myocardial ischemia reperfusion (MIR)

Selectins have been extensively investigated in myocardial ischemia/reperfusion (MIR) injury states. When ischemia provokes the loss of endothelium-derived NO, a rapid endothelial dysfunction occurs. 10 to 20 min after the subsequent reperfusion, an up-regulation of P-selectin on the endothelial surface of the affected area is observed. This leads to increased adhesion of neutrophils to the dysfunctional selectin up-regulated epithelium. This can result in severe tissue damage. This process is believed to involve L-, E- and P- selectin. However, in contrast to P- and L- selectin, E-selectin does not appear to play a major role during the first 4 h post reperfusion [58].

### II.3.2.3 Biological role in cancer-related events

Recent data have expanded the concept that inflammation is a critical component of tumor progression [59]. Many cancers arise from sites of infection, chronic irritation and inflammation. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. In addition, tumor cells have co-opted some of the signaling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis. Hence, mechanisms used for homing of leukocytes may be appropriated for the dissemination of tumors via the bloodstream and lymphatics. Experimental data support the implication of selectins in metastatic processes:

Metastatic progression of many epithelial carcinomas correlates with tumor production of mucins containing $sLe^X$ **(1)**. Lung colonization by melanoma cells that express $sLe^X$ **(1)** is significantly reduced in E/P-selectin deficient mice. P-selectin deficiency attenuates tumor growth and metastasis, and tumors are significantly smaller in mice treated with a receptor antagonist peptide [60, 61]. P-selectin facilitates human carcinoma metastasis in immunodeficient mice by mediating early interactions of platelets with blood-borne tumor cells via their cell-surface mucins, a process that can be blocked by heparin. L-selectin on neutrophils, monocytes and/or NK cells also may facilitate metastasis. Metastasis could involve the formation of tumor-platelet-leukocyte emboli that interact with the vasculature of distant organs. In addition, the expression of L-selectin on tumor cells can foster metastasis to lymph nodes [62,63].

These results indicate that receptors expressed in the vasculature are crucial in targeting $sLe^X$-dependent cancer cells. These insights are fostering new anti-inflammatory therapeutic approaches to cancer development.

### II.3.3 E-selectin regulation

The following section describes the cycle of E-selectin from their expression at the surface of the vascular endothelium, triggered by specific mediators [64], to their degradation [52,53]. The expression of E-selectin is highly regulated. The regulatory pathway involves a specific stimulus, which acts on a region upstream of the coding region of E-selectin gene, exerting transcription [65,66,67].

***Stimulus***

Transcription of the E-selectin gene is undetectable in uninduced HUVEC. However, when these cells are treated with IL-1-$\beta$, gene expression increases rapidly within about 30 min., reaches maximal level after 2-4 hours, and then returns to near-basal level activity at about 24 hours. In addition, TNF-$\alpha$, LPS, thrombin, IL-3, phorbol esters, and oxygen radicals also can induce E-selectin expression. The expression of E-selectin on endothelial cells can be lengthened when these cells are treated with a combination of IFN-$\gamma$ and TNF-$\alpha$. Dexamethasone and 3-deazaadenosine, two anti-inflammatory agents, may also inhibit the induction of E-selectin by thrombin and LPS. Furthermore, an increase of *c*AMP levels in endothelial cells decreases E-selectin expression. Studies have shown that the *c*AMP repression of E-selectin occurs at the transcription level and is abolished by protein kinase A inhibition. Thus, this suggests that the repression of E-selectin be mediated by a protein kinase A-driven phosphorylation [68,69].

***E-selectin gene***

Information regarding the regulated expression of E-selectin has been obtained by sequencing a 1.5 kb fragment containing the 5‘ end of E-selectin gene. Two introns interrupt the 5‘-untranslated region and the coding region. RNA polymerase II promoter and enhancer region (CAAT and TATA boxes respectively) are also present. Furthermore, there is a consensus sequence for $NF_kB$ binding site 27 nucleotides upstream of the CAAT box(promoter). ($NF_kB$ is a transcription factor that is involved in cytokine-induced expression of many genes whose protein products are involved in the immune and inflammatory responses). In addition, there is a palindromic sequence, which may serve as a potential DNA binding motif that is located 119 nucleotides upstream of the $NF_kB$ binding sequence. Mutagenesis has been used to demonstrate

that the region which lies between –223 and –117 nb on the gene is important for the induction of E-selectin expression by IL-1 [70].

***Transcription***

The cell-specific and the stimulus-specific induction of E-selectin expression suggest that the regulation of E-selectin involve complex mechanisms. One mechanism occurs at the transcriptional level. A transcription factor binds to the $NF_kB$ sequence and is important in the transcriptional activation of the E-selectin gene. This factor specifically binds the $NF_kB$ consensus sequence of the gene when HUVEC are treated with TNF-$\alpha$, IL-1, or LPS, but not IL-2, IL-4, IL-6, IFN-$\gamma$, histamine, or transforming growth factor-$\beta$. Although, the $NF_kB$ transcription factor is essential, it is not sufficient for the cytokine induction of E-selectin expression [71]. Induction of E-selectin gene activity was also shown to be mediated by at least two additional complexes. One is referred as NF-ELAM1 and the other NF-ELAM2. These proteins bind to the promoter at position -154 to -147 nb and -104 to -100 nb, respectively. Although the identity of these proteins has not been established, it has been shown that a single transcription factor is insufficient to mediate the induction of E-selectin expression by cytokines. Further work has identified two additional $NF_kB$ sites. They are adjacent to each other, within the E-selectin gene promoter. Mutagenesis and DNA binding assays also showed that binding of these factors to the 5'-untranslated of the E-selectin gene is essential for maximal promoter activity in response to cytokines [72].

***E-selectin degradation***

In an experiment [73], endothelial cells were induced to express E-selectin by IL-1 treatment for 4 hours and fluorescence-labeled anti-selectin antibody was used to monitor E-selectin expression. E-selectin was endocytosed and could be detected in lysosomes 4 hours after it was internalized. 18 hours after endocytosis very little labeling with anti-selectin could be detected. Antibody labeling was prolonged in cells treated with a compound that modifies lysosomal pH and leads to reduce protein degradation. In these cells, E-selectin was detected in large, heterogeneous vacuoles. Thus, degradation of cell-surface E-selectin takes place by endocytosis and proteolysis in lysosomes after internalization.

### II.3.4 Therapeutic applications of selectin antagonists

***Roles played by selectins in many diseases***

The critical role of the selectins in normal and diseases states has been emphasized in the three precedent chapters. In a productive immune response, leukocyte accumulation leads to seclusion of infection. However, overzealous transfer of leukocytes causes widespread tissue damage leading to several disease states such as reperfusion injury, cardiovascular and allergic diseases. These observations make the development of selectin antagonists an attractive therapeutic target. Hence, the known biology of the selectins suggests that inhibition of the selectin-$sLe^X$ has the potential to be an effective approach for treating a variety of states such as [4]:

- **Acute allergy-related disease**s: stroke, reperfusion injury during myocardial infarction, organ transplantation, and traumatic shock.
- **Chronic allergic diseases** such as bronchial asthma, rhinitis, psoriasis and rheumatoid arthritis.
- **Cardiovascular diseases** such as arteriosclerosis and peripheral vascular disease.
- **Cancer metastasis** (Chapter II.3.2).

***Attempts with novel therapies and related problems***

Use of $sLe^X$ **(1)** itself as a drug candidate has proven to be unsuccessful [44]. The search for an orally administered selectin-based prophylactic type treatment for inflammation is still ongoing. Cytel, a U.S.-based company, has sustained a failure in phase III of a pentasaccharidic compound intended to treat reperfusion injuries. The likely reasons for the failure are low bioavailability, poor stability to degradative enzymes as well as low biological affinity.

***Need to reduce the carbohydrate character of the antagonists***

Like other carbohydrates, $sLe^X$ **(1)** and its analogs seem to suffer from poor pharmacokinetic properties, low binding affinity, poor stability *in vivo*, and complexity of synthesis. These characteristics represent a major obstacle in the development of novel compounds.

### II.3.5 A biophysical approach to selectin-mediated neutrophil rolling

***The interactions are of dynamic nature***

Interactions of selectins with their ligands result in a dramatic decrease in leukocytes' velocity, which allows integrins to foster their firm attachment to the endothelium. All three types of selectins are capable of mediating leukocyte rolling *in vitro*. However, neither selectins nor integrins are sufficient by themselves to mediate firm attachment. Selectins alone slow, but do not completely halt speeding leukocytes, whereas integrins alone cannot bring about the necessary initial reduction in velocity [74].

$SLe^X$ binds to E-selectin with low-affinity ($K_D$ of 0.5 mM) [17]. However, the strength of the bonds formed between selectins and their ligands must counteract the physical forces, which tend to keep the leukocytes in motion. The rates of bond formation ($k_{on}$) and breakage ($k_{off}$), which describe the dynamic nature of leukocyte rolling, are more informative than affinity constants that describe an equilibrium condition that is not attained [75,76].

An important consequence of this observation is the need for dynamic assays for the characterization of $sLe^X$ mimics' binding affinities. Indeed, static assays like ELISA miss critical information regarding the dynamic component of $sLe^X$-selectins interactions.

***Kinetic considerations- Association/Dissociation requirements ($k_{on}/k_{off}$)***

Requirements for cell adhesion under laminar shear stress are particularly demanding. To tether to a surface, a free-flowing leukocyte must form adhesive bonds very rapidly. For the cell to roll, these bonds must dissociate quickly at the trailing edge of the cell as new bonds form at the leading edge. The adhesive bonds must also resist premature dissociation by the forces applied to the bond. Otherwise, the cell would immediately detach into the fluid stream. The biochemical and biophysical features of selectin-ligand interactions have evolved to meet these specialized requirements. In other words, leukocyte rolling requires that the forward rate of reaction $k_{on}$ between selectin and ligand be relatively fast. The reaction could not otherwise occur because of leukocytes' velocity. The backward rate $k_{off}$ must strike a balance between promoting adhesion and maintaining cellular integrity. A too slow rate of dissociation could cause loss of the molecules involved in bond formation. Computer studies [77] suggest that the forward rate

is the more important of the two rates. A key parameter influencing reaction rate is the diffusion of the reactants. Selectins, with their series of consensus repeats, have significant flexibility, which enhances their diffusibility. Several selectin ligands contain many mucin domains, which are characterized by abundant oligosaccharides presented on a polypeptide backbone that extends far out into the extracellular region. This arrangement is conductive to fast reactions. Thus, clustering of selectins or their ligands may regulate leukocyte adhesion under flow.

Another observation directly concerns the development of our macrocyclic antagonist **2** (Figure 1). Indeed, emphasis has been given on the $k_{on}$-$k_{off}$ problematic for the design of our compound. The high pre-organization is believed to increase the $k_{on}$, which is important because, as we have seen, not only the static affinity, but also the dynamic affinity play a critical role in the interactions. Furthermore, the presence of a lipophilic group in the target molecule is thought to reduce the $k_{off}$. A too large affinity with water would have been negative for the dynamic component, because it would have increased the $K_{offf}$. In another study, Vestweber et al. [78] demonstrated that the affinity of the E-selectin-ESL-1 interaction did not change significantly when the temperature was varied from 5° C to 3° C, indicating that the enthalpic contribution to the binding is small at physiological temperatures, and that, in contrast to typical protein-carbohydrate interactions, binding is driven primarily by favorable entropic changes. This observation would speak in favor of our intention to block the configuration of our macrocycle **2** to increase the affinity.

***Rolling velocities - Shear stress requirements***

Rolling velocities depend on factors such as shear stress, hydrodynamic velocity, and selectin/ligand density. Typical values for velocity range from <2-15 μm/s [75]. Shear stress is expressed in dynes/cm$^2$ (a dyne is equal to $10^{-5}$ Newtons). Physiologically relevant shear stresses, such as these may be found in post-capillary venules where they range from approximately 1 to 10 dynes/cm$^2$. Increases in shear stress are correlated in a linear fashion with increases in rolling velocity, but beyond a certain shear stress the velocity reaches a plateau, and further increases result in a complete lack of rolling. The hydrodynamic velocity is the velocity of the bulk solution. This value varies depending on the distance from the vessel wall. The higher velocities occur in the center of the vessel, and the lowest occur adjacent to the wall. Shear stress should be

sufficiently low. The inflammatory response involves dilation of blood vessels, which reduces the hydrodynamic velocity and therefore the shear stress. Small increases in vessel diameter can cause significant reductions in shear stress, thus facilitating selectin-mediated rolling. However, experiment also shows that shear stress should be sufficiently high: the duration of the tethers is very short (≤2 s). It was shown that physiological shear forces do not significantly decrease tether duration, suggesting that the bonds have tensile strength that resists dissociation by applied force.

We have seen that the transient nature of selectin-ligand bonds requires that leukocytes be perfused at or above a minimum shear stress if they are to roll. Shear stress allows the cell to rotate so that new bonds form to replace those that dissociate, and increased shear may also enhance the rate at which new bonds form. If shear stress is too low, the cell does not roll, but instead detaches from the surface.

Instantaneous velocities of rolling leukocytes are highly variable. Large variances might result from inherently stochastic receptor/ligand interactions (a stochastic process involves randomness in successive observations), from topological heterogeneity in receptor/ligand distribution, or from variations in shear stress.

***Selectin density***

Leukocytes perfused over very low densities (the number of selectins per unit area) of immobilized P-, E- or L-selectin ligand form transient tethers that do not convert to rolling adhesions [74,79]. The number of tethers is linearly related to the selectin or selectin ligand density, suggesting that the transient tethers represent quantal units, or single selectin-ligand bonds. Rolling velocities are lower for E- than P-selectin at comparable densities. Also, variance in the rolling velocity is greater for P- than E-selectin. Both observations are consistent with the idea that E-selectin forms a greater number of bonds.

### II.3.6 Structural determination

A complete knowledge of selectins' biology requires a comprehensive understanding of the 3D structure of these proteins, of their carbohydrate ligands and of their complex. Many methods have been used towards these goals:

- Structure determination using protein crystallography and multi-dimensional NMR methods.
- Binding studies of modified $sLe^X$ **(1)** analogues.
- Theoretical models of binding complex before X-ray structure were available.
- Binding complex structure solved using X-ray crystallography.

This chapter reviews these structural analysis methods. We wished to present not only the most up-to-date data on the E-selectin-$sLe^X$ complex, but also the step-by-step process that led to this knowledge.

#### II.3.6.1 Structure of the ligand-recognition domain of E-selectin

The main $sLe^X$ **(1)** binding-site has been localized on the lectin domain (CRD, *C*arbohydrate *R*ecognition *D*omain). The whole design efforts that have been published to date are directed towards antagonists that bind to this domain.

Studies with selectin constructs in which the EGF-like domain and/or CR domain have been deleted, switched, or mutated, suggest that these domains may contribute to ligand recognition [3]. But in the case of E-selectin, the data is conflicting. The EGF region is believed to exert its effect by holding portions of the lectin domain in the proper conformation. However, in a binding study, a truncated form of E-selectin consisting of the lectin and the epidermal growth factor domain only (E-selectin lec-EGF), was shown to be fully active [80]. Thus, the roles of the EGF and CR domains in ligand binding remain unclear.

The CRD is a globular structure that recognizes its ligands in a shallow depression that contains a $Ca^{2+}$ ion and its primary sequence is about 80% homologous to another structurally characterized sugar protein, the mannose binding protein (MBP) [81]. However, as soon as the first crystal structure of the CRD domain of E-selectin has been

available in 1994 [41], it was apparent that the lectin domain of E-selectin has some important differences.

### II.3.6.2 Structure and conformation of the carbohydrate epitope

Conformation studies of $sLe^X$ **(1)** in solution and bound to the receptor are vital information for the subsequent development of selectin antagonists.

#### *Synthetic studies of $sLe^X$ (1)*

The required synthetic technology for studying the structural features necessary for selectin binding and for the subsequent preparation of analogue structures has been made available through initial synthetic studies targeting the $sLe^X$ **(1)** structure itself. Not only must the synthesis afford suitable quantities of $sLe^X$ **(1)** in a minimum of synthetic operations, but it also must accommodate considerable structural variation to allow the preparation of analogue structures.

*Chemical synthesis*

*The* first synthesis of $sLe^X$ **(1)** was reported in 1991 [23]. Despite the availability of effective glycosylation methodology, chemical synthesis generally suffers from the need to employ selectively protected sugars to control the position of bond formation and therefore large-scale synthesis becomes increasingly more expensive.

*Chemoenzymatic synthesis*

The problem has been addressed through the application of enzymatic methodology to oligosaccharide synthesis [82]. Isotopically labeled $sLe^X$ **(1)** has been prepared by utilizing UDP-1-$^{13}$C-Gal with these procedures.

#### *Conformation studies of $sLe^X$ (1) using NMR spectroscopy*

Labeled and unlabeled structures have proven useful for NMR studies to gain important conformational information.

*Conformation in solution*

Early work in this area was aimed at defining the conformation of $sLe^x$ **(1)** in solution. Three independent studies reported conformations that were in general agreement, suggesting a single conformation in solution [17]. However, subsequent NMR and

molecular dynamics studies of sLe$^X$ **(1)** in solution indicated that the Gal-NeuAc linkage was flexible, opening the possibility that sLe$^x$ **(1)** exists as an ensemble of low energy conformations in solution [26,42,83]. Poppe et al. found evidence that the Gal-NeuAc linkage samples three different conformations, but that data suggested that the other glycosidic linkages was in single conformations [38].

Homans et al. [40] reinvestigated the conformation of sLe$^X$ **(1)** in solution using $^{13}$C-enriched sLe$^X$ **(1)** and ROESY-HSQC experiments, These experiments allowed for the determination of a much greater number of conformational restraints than had previously been determined. Molecular dynamics (MD) simulations suggest that the three glycosidic linkages are much more flexible than previously thought. During the course of the short simulation, a second conformation of sLe$^X$ **(1)** was accessed for a significant amount of time, indicative of the flexibility of the linkages.

The presence of multiple conformations as well as observation of other receptor-ligand complexes suggests that only one of these conformations is bioactive. This point is essential, because the more flexible the molecule, the larger the entropic gain for an antagonist that is locked in the bioactive conformation.

*Bound (bioactive) conformation*

The bioactive conformation of sLe$^X$ **(1)** has been determined by NMR and applied for the rational design of selectin antagonists [26,38,40,45,46].

*Cooke et al.* utilized differences in the *tr*NOEs of sLe$^X$ **(1)** bound and unbound E-selectin to study the complex [26]. They suggested that the bound conformation of sLe$^x$ **(1)** was not the same as the unbound conformation of sLe$^X$ **(1)**. Hensley et al. reported just the opposite that the bound conformation of sLe$^X$ **(1)** was identical to the solution conformation of sLe$^X$ **(1)** [84]. This finding was disputed by Scheffler et al., who obtained similar results to that of Cooke [39,45] with more extensive NOESY experiments. Poppe et al. published data [38] on the conformation of sLe$^X$ **(1)** bound to E- and P-selectin. The bound conformation of sLe$^X$ **(1)** is comparable in both cases, though the largest difference is in the Gal-NeuAc linkage, which is the most flexible glycosidic linkage in solution. These results differed from those of Scheffler et al. in the conformation about Fuc-Glc*N*Ac linkage [44].

Here also, 3D NOESY-HSQC experiments using $^{13}$C-enriched sLe$^X$ **(1)** have permitted to determine the bound conformation of sLe$^X$ **(1)** bound to E-selectin [40]. This structure of bound sLe$^X$ **(1)** has differences from that of Scheffler in the galactosyl-sialyl linkage and that of Poppe in the Fuc-Glc*N*Ac linkage.

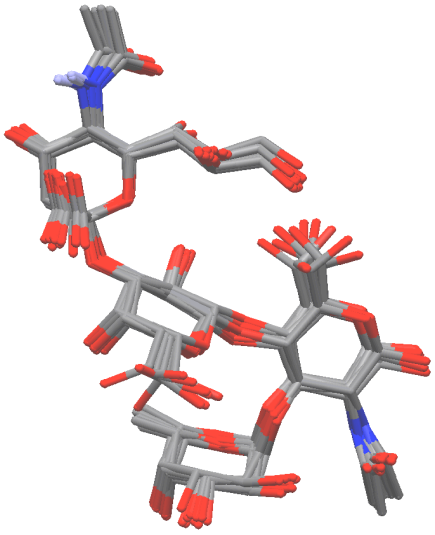


**Figure 10**: Representation of sLe$^X$ **(1)** in the bioactive conformation.

*Conclusion*

Stable unbound and E-selectin-bound conformations of sLe$^X$ **(1)** differ mainly in the orientation of the Neu*N*Ac residue [26]. The estimated energy difference between these conformations is approximately 1.5 kcal/mol. The differences observed between the free conformation and the conformation of sLe$^X$ **(1)** bound to selectins represent the rationale for the development of conformationally blocked molecules. Indeed, an antagonist pre-organized in the bioactive conformation is believed to possess a higher affinity due to favorable entropic contribution than its torsionally free counterpart.

### II.3.6.3 Structure of the selectin-ligand complex

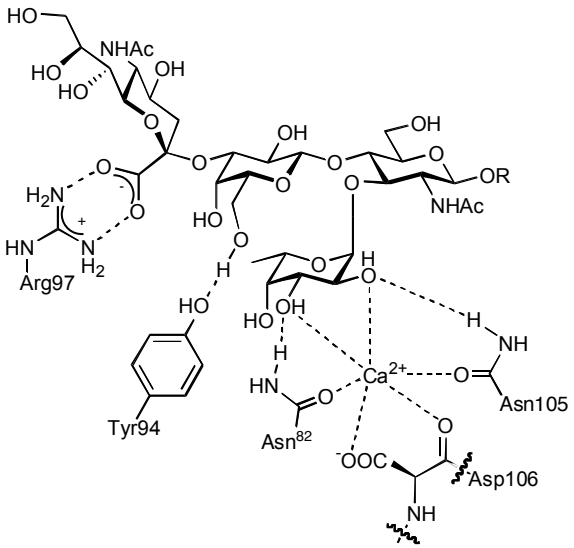
***Structural information about selectins and their interactions with sLe$^x$ (1)***

Like all C-type lectins, selectins bind to carbohydrate ligands in a $Ca^{2+}$-dependent manner. Selectins bind selectively, but with low affinity, to sLe$^X$-related ligands. L- and P-selectin, but not E-selectin, also bind to particular sulfated carbohydrates, such as heparan sulfate that lack NeuAc and Fuc. Although the selectins bind to many sialylated, fucosylated, and/or sulfated glycans, they bind with higher affinity or avidity to only a few appropriately modified glycoproteins on blood or vascular cells.

Different models have been elaborated to investigate E-selectin-sLe$^X$ interactions before X-ray data of the complex were available. However, none of these models could correctly predict all these interactions, and therefore, represent the actual binding mode. The major differences between the models and the X-ray structure of the complex are highlighted in this section. The discrepancies observed are intriguing when we realize that generations of selectin antagonists are based on these models.

A binding model based on mutagenesis studies was published in 1992 [47]. At that time, the structure of E-selectin was unknown, and the model used was based on the recently determined crystal structure of mannose binding protein (MBP) [81]. Mutagenesis data indicated that five residues were critical for binding sLe$^x$ **(1)** (Arg-97, Lys-111, Lys-113, Ser-47 and Lys-99), and the proposed model indicated that these residues were clustered at the surface of the protein.

A historically important model [85] proposed by Kogan et al. (Scheme 1) is based on NMR and X-ray spectroscopy data of E-selectin. At the time of publication, the actual structure of E-selectin had been determined (non-bounded conformation) by X-ray crystallography [41]. *tr*NOEs NMR were used to demonstrate the conformational change between the free and bound conformation of sLe$^X$ **(1)** [26].

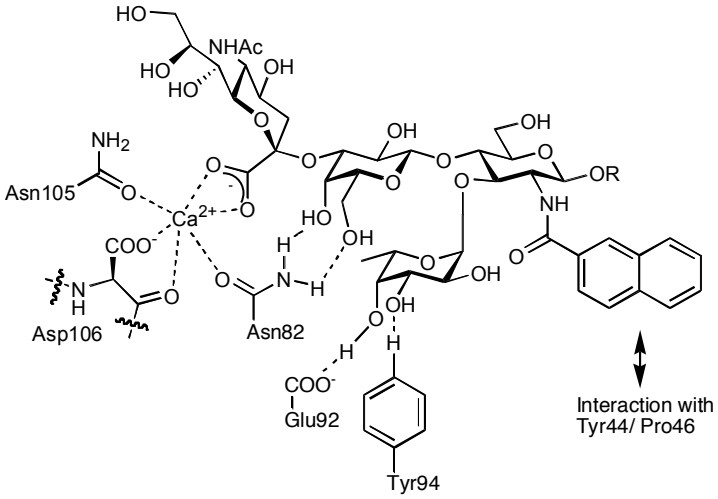



**Scheme 1**: Model proposed by Kogan et al. [85]

***Model implying the reverse docking-mode***

This model is named reverse docking mode (Scheme 2) in opposition to the "normal" docking modes. Indeed, unlike the models that represent the Fuc interacting with the calcium ion, the reverse docking mode shows the acid interacting with the ion. Reverse docking could be an alternative binding mode that actually takes place. This mode could be favored when the ligands hold aromatic substituents.

Hayashi and co-workers [86] have investigated derivatives of $sLe^X$ **(1)** in which the reducing carbon contains hydrophobic tails, and derivatives in which the Ac group of the Glc*N*Ac residue has been replaced with other *N*-acyl groups. They found that *N*-naphtoyl groups increase binding affinities by almost 10-fold over that of *N*-Ac [20]. Computational work identified a potential role of hydrophobic groups: chains appear to fit into a hydrophobic cleft running down the side of the selectins.




**Scheme 2**: Representation of the reverse docking mode (Ernst, unpublished results).

***X-ray crystallography - Insight into the real binding interactions***

The more recently determined X-ray crystal structure of human Lec-EGF selectin with $sLe^X$ **(1)** [12] has provided new insight into the nature of the interactions (Scheme 3). The structure of the $sLe^X$ **(1)** complex reveal that the interactions are almost entirely electrostatic in nature, and the total buried surface is small (549 $Å^2$ in Lec-EGF) when compared to the size of the free ligand. Moreover, the selectin-bound $Ca^{2+}$ ion is ligated by the 3- and 4- OH groups of the Fuc residue within $sLe^X$ **(1)**.

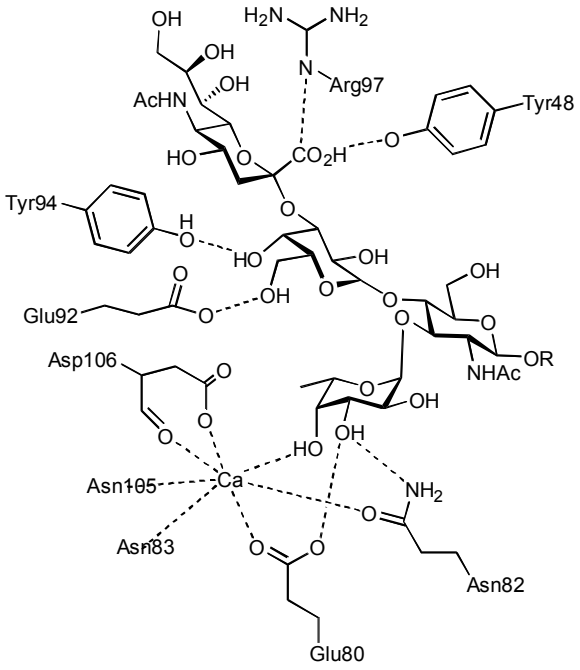
As already stated in the last section, this arrangement is in sharp contrast to proposed models of selectin/$sLe^X$ interactions that predict Fuc ligation to the 2- and 3- OH groups based on the structure of the homologous rat MBP complexed with oligomannose [87]. The 3- and 4- OH groups of the Fuc must provide a large amount of the $sLe^X$ **(1)** binding energy. They not only coordinate the bound $Ca^{2+}$, but also form hydrogen bonds with selectin residues that are also involved in $Ca^{2+}$ coordination.

- The Fuc 3-OH group of $sLe^x$ **(1)** replaces precisely a $Ca^{2+}$-ligated water molecule observed in the unliganded structures and hydrogen bonds to Asn-82 and Glu-80.

- The Fuc 4-OH group displaces another $Ca^{2+}$-coordinated water molecule, although its final position is now one Å closer to Asn-105, to which it hydrogen bonds.

In the Lec-EGF/sLe$^X$ complex, Asn-83 rotates its X2 torsion angle to 59°, so that it now builds a hydrogen bond with a water molecule that in turn builds hydrogen bonds with the Fuc 2- and 3-OH groups and Glu-107. This rotation also allows the Asn-83 side chain to coordinate the calcium. In the Lec-EGF/sLe$^X$ complex, the sLe$^X$-Gal residue hydrogen bonds to Tyr-94 and Glu-92. The carboxylate group of Neu*N*Ac hydrogen bounds to Tyr-48 [12].

An extensive set of interactions is observed within the Lec-EGF/sLe$^X$ complex facilitated by a change in conformation of this sugar residue. The positioning of Neu*N*Ac within the P-selectin/sLe$^X$ complex would make unfavorable contacts with Arg-99 in Lec-EGF/sLe$^X$, and so moves further back to allow for better interactions. In this arrangement, Arg-97 hydrogen bonds to the glycosidic oxygen and the carboxylate group of Neu*N*Ac. These differences, combined with differences in Fuc binding, appear to be the structural basis for the relatively high affinity E-selectin/sLe$^X$ interaction.




**Scheme 3:** A scheme depicting the interactions between sLe$^X$ **(1)**, E-selectin and the bound $Ca^{2+}$.

## II.4 Design of selectins antagonists

***Many analogs and mimetics of sLe$^X$ (1) have been designed and synthesized***

For about a decade, academic and industrial research groups have aimed at developing therapeutic agents based upon inhibition of the E-selectin-sLe$^X$ binding event [17,44]. Use of information on the structural characteristics of sLe$^X$ **(1)** binding has been made to search for alternative structures that exhibit stronger binding to selectins than the natural ligand [88], as well as simplified structure and improved bioavailaybility.

Most groups have attempted to substitute of sugars in sLe$^X$ **(1)** with other moieties such that the key interactions are retained. With the identification of the pharmacophores (residues critical for binding), efforts have focused on removing one or more sugars from the tetrasaccharide and replacing it with a variety of more stable linkers. Along this process, we have to keep in mind that sometimes-wrong models have been used to synthesize antagonists. Highlights of these approaches can be summarized as follows:

- ***The structure-activity relationship (SAR) study for the lead structure sLe$^X$ (1).*** The synthesis of analogues incorporating functional group deletions and modificat ions has been an invaluable method for gaining detailed SAR information [11,24].

- ***A relatively systematic reductionist approach*** was performed. Each novel generation of E-selectin antagonists witnesses a drive towards simpler molecules, with a progressive abandon of the undesired carbohydrate properties.

### II.4.1 Pharmacophores

***Systematic identification of the functional groups***

Identification of the residues critical for sLe$^X$ **(1)** binding to the selectins illustrates an important aspect of contemporary organic synthesis. Modern spectroscopic techniques lend limited insight into the relative importance of different structural features of the molecule, except in cases where the receptor-ligand complex can be determined. As X-ray structure is only available since 2000 [12], synthesis of analogues incorporating functional group deletions and modifications was used to gain information on the SAR-relationships. Systematic replacement of the functional groups (OH, $COO^-$, or Me) with

H, followed by affinity evaluation led to the determination of the relative contributions that these groups make to binding and to the construction of a "functional group map" [10]. For sLe$^X$ **(1)** binding to E- and L-selectins, all three OH groups of the Fuc, the 2- and 6-OH groups of the Gal, and the carboxylate of the Neu*N*Ac acid are necessary (see Figure 14). The Glc*N*Ac residue does not play a critical role in these interactions, but is believed to be important for preorganizing the residues of the tetrasaccharide **(1)** [89].

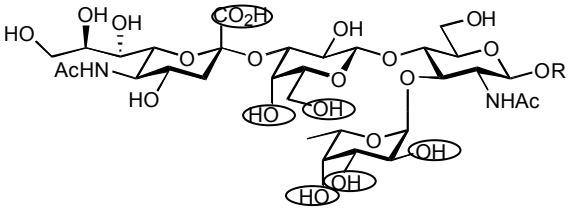



**Figure 11**: Representation of sLe$^X$ **(1)** and its pharmacophores.

## II.4.2 Selectin antagonists

The following overview should provide the reader with examples of selectin antagonists that have been synthesized to date [44].

***Trisaccharide mimics - Utility of NeuNAc and its replacement possibilities***

The Neu*N*Ac moiety has four substituents - a glycerol sidechain, one hydroxyl, a carboxylate, and an amide - that can potentially interact with the selectins upon binding. Most of the substituents have been studied**:**

- Modifications of the glycerol sidechain resulted in no notable effect on binding to E-selectin [10,24].
- Removal of the *N*-Ac group has little effect on binding [24].
- Replacement of the carboxylate by different charged groups resulted in similarly active molecules [11,24].

Thus, literature shows evidence that the costly Neu*N*Ac sugar can advantageously be replaced by anionic moieties in sLe$^X$ **(1)** mimics. For instance, sulfated Le$^X$ trisaccharide

**11** (Figure 12) does exist, as a natural analog of sLe$^X$ **(1)**, and shows superior binding to E-selectin. One of the most straightforward substitutions of sLe$^X$ **(1)** replaces Neu*N*Ac by a negatively charged group on the 3-OH of Gal. Several groups replaced Neu*N*Ac by a sulfate group [24,90]. Affinity for E-selectin has been reported for sulfated Le$^a$ trisaccharides **12** and **13** where Glc*N*Ac has been replaced by glucose. Compounds sometimes showed selective activity for one selectin. The 1-deoxy-3'-*O*-sulfo Le$^X$ analogs **14** to **16** were found to be less potent than sLe$^X$ **(1)** in the E-selectin assay but showed increased potency against P-selectin in a competitive binding assay. Mimics of sLe$^X$ **(1)** that bear phosphate groups on the 3-OH of Gal and show binding affinities similar to sLe$^X$ **(1)** have been generated [11]. The 3'-*O*'-phospho Le$^a$ analog **17** was found to be 20-time more active than the 3'-sulfo Le$^X$ derivative against E-selectin in a static essay [91].

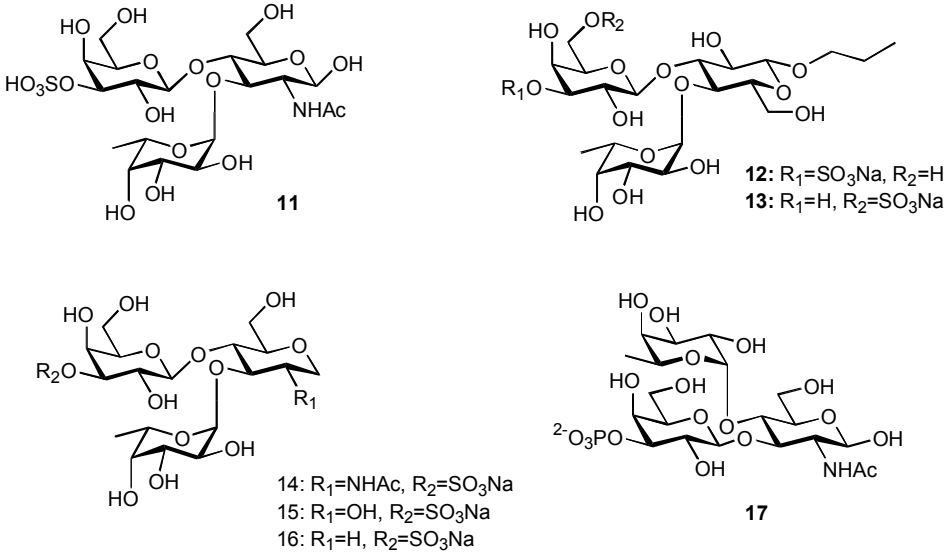
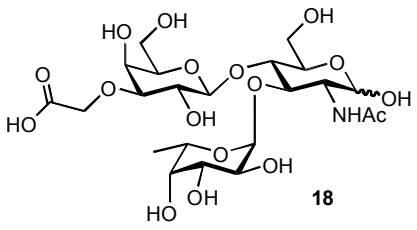
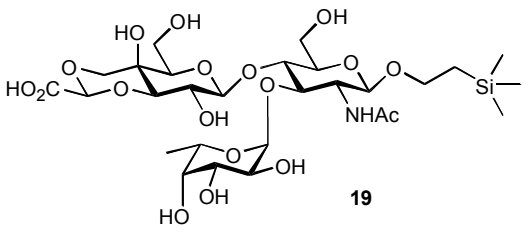



**Figure 12**: Replacements of Neu*N*Ac.

Alkylation of the Gal-3-OH with glycolic acid derivatives represent the most frequently used Neu*N*Ac replacement (Figure 13: **18**, **19**) [17]. The 3-carboxymethyl substituted analog **18** has similar antagonist affinity as sLe$^X$ **(1)**. A more rigid Neu*N*Ac mimic was also used [18]: in compound **19**, the carboxylic acid is fixed in the equatorial position of a six-membered acetal to mimic the solution phase conformation of sLe$^X$ **(1)**. As predicted, **19** was found to be inactive in an E-selectin assay. To date, the relationship between these groups' acidities and binding affinities has not been addressed rigorously.



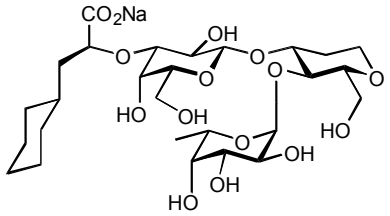

**18**




**19**

**Figure 13**: Substitution of Neu*N*Ac by glycolic (→**18**) and lactic acid derivatives (→**19**).

Interestingly, when lactic acid derivatives were used to build rigid Neu*N*Ac mimics, they proved to be very active E-selectin inhibitors [18,92]. For instance, one of the prepared 1,2-deoxyglucose derivatives **20** (Figure 14) was 30 times more potent than sLe$^X$ **(1)** in a static E-selectin essay. In this compound Neu*N*Ac is replaced by a cyclohexyl lactic acid moiety.




**20**

**Figure 14**: An active sLe$^X$ **(1)** analog synthesized by Thoma et al. [18]

Compounds have been synthesized where the Glc*N*Ac has been replaced with other moieties, leaving the three other sugar units intact [17]. When Hanessian et al. replaced Glc*N*Ac with an indolizidinone unit, the activity of **21** against E-selectin disappeared but the compound was more active than sLe$^X$ **(1)** in the P-selectin assay [93]. When quinic acid was chosen to replace Glc*N*Ac in **22**, the compound showed the same activity as sLe$^X$ **(1)**. **23**, in which Glc*N*Ac is substituted with a trans-1,2-cyclohexanediol unit, is three times more potent than sLe$^X$ **(1)** in E- and P- selectin essays.

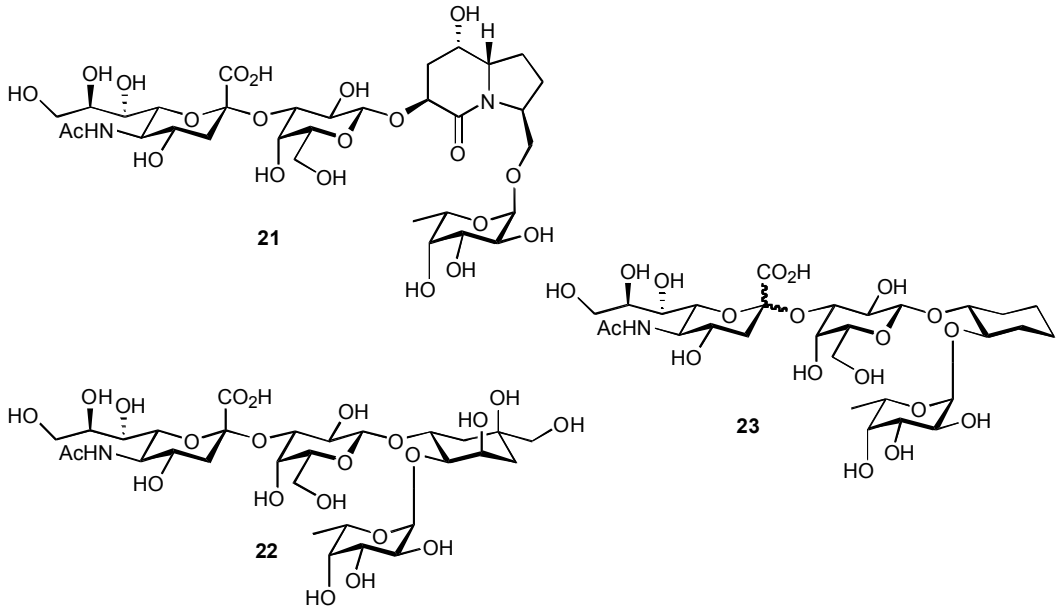



**Figure 15**: Replacements Glc*N*Ac.

To sum up, the mimics with three sugar units generally possess comparable or better activities than sLe$^X$ **(1)**. They also allow avoiding costly use of Neu*N*Ac. This observation has been important in the design of our target molecule, as we have replaced Neu*N*Ac by a L-cyclohexyl lactic acid moiety in our compound. In general, the tetrasaccharidic mimics still exhibit similar problems as sLe$^X$ **(1)**: cost, stability, and rapid metabolism. It is therefore important to consider further simplifications.

***Mimics containing 2 sugars***

The last section showed that a carboxylate moiety on the 3-position of Gal can adequately mimic Neu*N*Ac. The next steps in the simplification process of sLe$^X$ **(1)** are to replace the Glc*N*Ac and/or the Gal moiety. Another approach is to replace the Gal-β(1-4)-Glc*N*Ac disaccharide core with a linker that will position Neu*N*Ac and Fuc in a spatially similar arrangement as sLe$^X$ **(1)**.

***Substitution of the GlcNAc moiety***

The Glc*N*Ac moiety has three substituents (two OHs and an amide) that can potentially interact with the selectins on binding. Most studies have suggested that while the GIc*N*Ac contains none of the functional groups critical for binding, it is likely to be important for preorganizing the sLe$^X$ **(1)** tetrasaccharide [17]. Thus, the Glc*N*Ac unit was thought to be merely a linker between Fuc and Gal. Attempts at simplifying the sLe$^X$ **(1)** structure by replacing Glc*N*Ac with moieties that will preserve the core conformation of

sLe$^X$ **(1)** were undertaken [16,28]. The mimics contained either carboxymethyl or alkylated carboxymethyl as Neu*N*Ac surrogates. Simple two-carbon tethers were used to link Gal and Fuc: ethylene glycol, butane, cis-olefin, and epoxide (Figure 16: **23, 25**). The low activity of these compounds was attributed to their conformational flexibility.

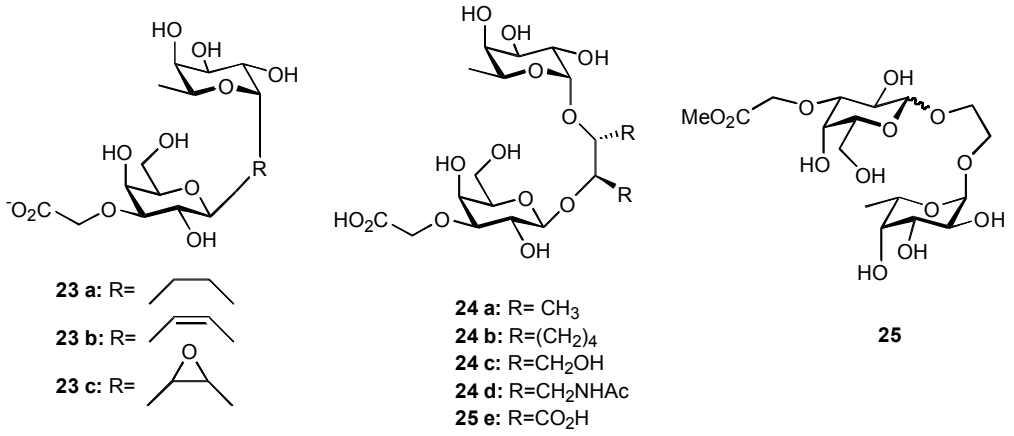



**Figure 16**: Disaccharide mimics.

Compounds with 1,2-diols used as glucose mimic and a carboxymethyl unit serving as Neu*N*Ac replacement were synthesized. The diols **24** contain diverse functional groups and different levels of torsional constraint [89]. In this series, only compound **24 b** where a rigid cyclohexanediol was used was found to be equipotent to sLe$^X$ **(1)** in the E-selectin assay although most diverse disaccharide mimics were synthesized. In these, the Glc*N*Ac unit was for instance unsuccessfully replaced by quinic acid **26** or by a indolizidinone-type template **28** (Figures 17/18) [93]. However, these molecules show only low levels of inhibition. Of all the replacements for Glc*N*Ac, the cyclohexyl group appears to best mimic both the shape and rigidity of the pyranose ring. Surprisingly, ethandiol is almost equally effective. However, the difference between these groups becomes more pronounced in derivatives in which Gal has also been substituted.

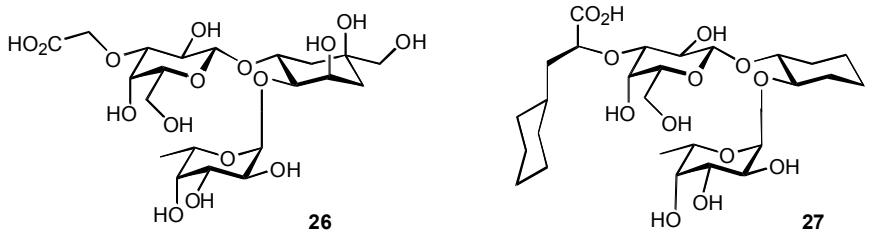



**Figure 17**: Disaccharide mimics (suite).

The linking group chosen to replace Glc*N*Ac rarely improves the binding constant. The most effective mimics for E-selectin of this class were reported by Kolb and Ernst [94,104]. The molecules (e.g. **27**, Figure 20) incorporate a novel alkylated derivative of the "$CH_2COO^-$" mimic for Neu*N*Ac, and binds with up to 12-fold higher affinity than $sLe^X$ **(1)**. In this potent series, Glc*N*Ac is replaced with *R*,*R*-cyclohexanediol and Neu*N*Ac with L-cyclohexyl lactic acid.

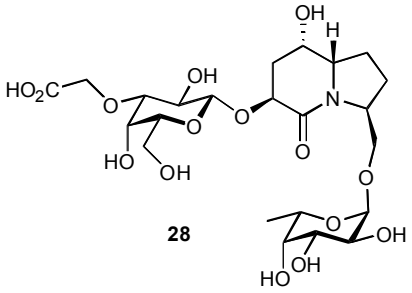



**Figure 18**: Hanessian's indolizidinone-based mimetic **28**.

***Substitution of the Gal moiety***

The Gal moiety of $sLe^X$ **(1)** has three OH substituents that can potentially interact with the selectins upon binding. Stahl et al. [136] examined the role of the 4- and 6-OHs by synthesizing deoxy-$sLe^X$ analogues where the OH was replaced by hydrogen and, in the case of the 4-OH, by fluorine. The analogues all bound more weakly to E-selectin than $sLe^X$ **(1)**, suggesting that these substituents are important but not crucial to binding. Several compounds modified at the 6-position were synthesized without showing any activity. A study [15] has been published on the modification of the 6-OH of the Gal moiety in two $sLe^X$ **(1)** mimetics, which had better $IC_{50}$s than $sLe^X$ **(1)** for E-selectin. Diverse sets of substituents were employed but all compouds mimetics were inactive. It was suggested that the Gal 6-OH is optimal. One factor that could contribute to the poor

potency of the rigid linkers is the lack of functionalities that imitate the 4- and 6-OH of Gal, which are also necessary for activity.

***Replacement of Gal-β(1-4)-GlcNAc by a linker***

Another approach taken for building disaccharides has been to replace the Gal-Glc*N*Ac disaccharide core with a linker that will position Neu*N*Ac and Fuc in a spatially similar arrangement as sLe$^X$ **(1)** [17].

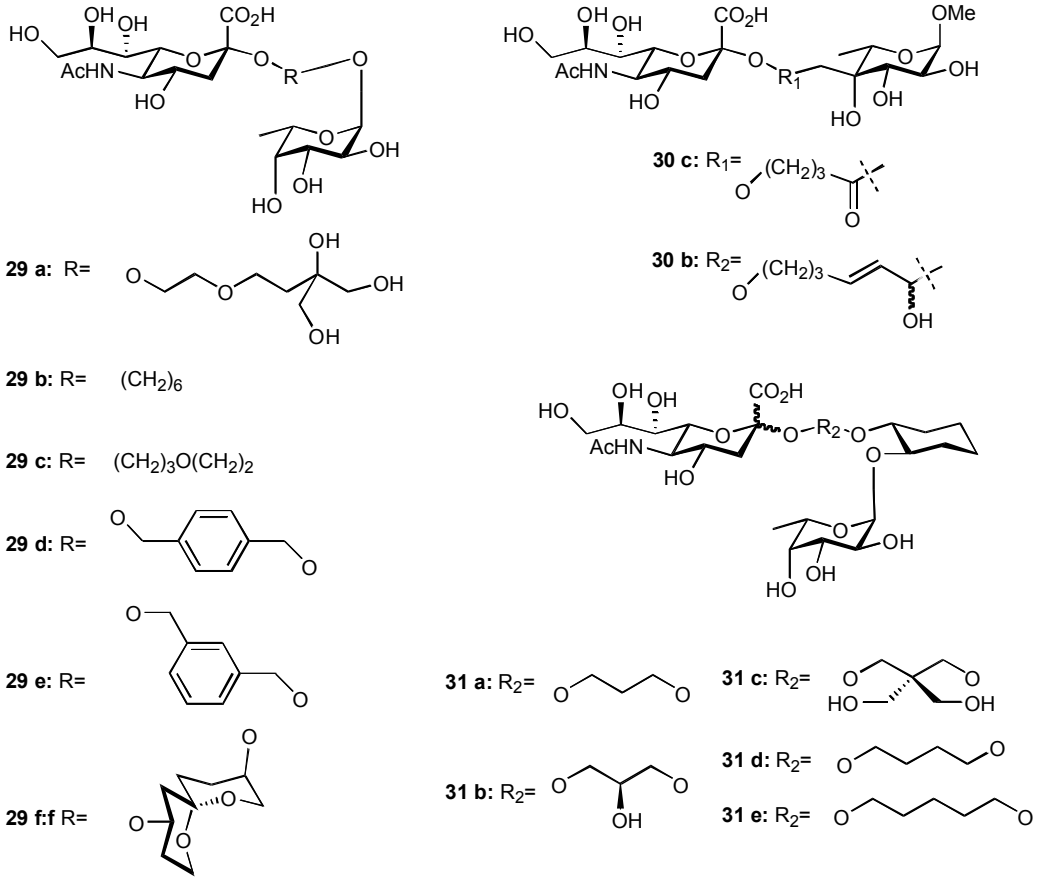



**Figure 19:** Replacement of the Gal-β (1-4)-Glc*N*Ac core by a linker.

Some of the spacers used were flexible alkyl chains. In this class of compound, where the expensive Neu*N*Ac moiety is kept, the unfunctionalized flexible linkers have shown low biological activity. A reasonable explanation is that the entropic penalty resulting from the extreme flexibility of a simple saturated spacer is the reason for the lack of activity. However, use of a rigid benzenedimethanol **29d/e** (Figure 19) moiety resulted in compounds that were 20-fold less active than sLe$^X$ **(1)** in a static E-selectin assay [17].

The use of an inflexible spiroketal scaffold **29f** resulted in obtaining only low levels of inhibition of E-selectin. The poor potency of the rigid linkers can be attributed to the lack of functionalities that imitate the 4- and 6-OH of the Gal, which are necessary for activity.

In sum, mimics for the disaccharide Gal-β(1-4)-Glc*N*Ac have delivered disappointing results. Inhibitors that contain Fuc or Gal sugars, but use a cyclohexane diol as Glc*N*Ac and phenyl or cyclohexyl lactic acid as a NeuAc replacement have proven to be the most effective. However, even if a disaccharidic mimic were to show potent selectin antagonist activity *in vitro*, it is not certain that its pharmacokinetic profile would permit to use it as an orally active drug. This problem may occur due to still strong carbohydrate properties and relatively important size.

***Mimics containing only one sugar moiety***

Since the focus is to reduce the carbohydrate nature of the mimics, several efforts have been made to design and synthesize compounds that contain only the Fuc sugar bound moiety to an appropriate scaffold to which a carboxyl group is attached. Some selected examples are cited in the next paragraph. The Fuc moiety of $sLe^X$ **(1)** has four substituents (three OHs and a Me group) that can potentially interact with the selectins upon binding. Based on homology to MBP, the Fuc moiety was assumed to function as the calcium recognition unit of $sLe^X$ **(1)**. Each of the substituents was replaced by hydrogen to determine their importance for the binding of $sLe^X$ **(1)** to E-selectin [95]. The replacement of any of the OH groups resulted in a complete loss of binding, while replacement of the methyl group with hydrogen (replacement of Fuc with Ara) resulted in a molecule five times less active than $sLe^X$ **(1)**. Hasegawa et al. [11] investigated the replacement of each of the hydroxyls in the Fuc of $sLe^X$ and found them to be crucial for binding to E- and L- selectin. Henrichsen [96] showed that replacement of the 2-OH of Fuc with a methoxy group eliminated binding to E-selectin. Finally, the crystal structure of the E-selectin/$sLe^X$ complex confirmed the importance of the 3- and 4-OH of the Fuc in the binding [12].

A series of mimetics with *trans*-1,2-cyclohexandiol as a replacement for Glc*N*Ac moiety met with some success. For instance, Toepfer et al. [97] used this functionality to prepare a series of mimetics with malonic acid derivatives (**32**, Figure 20). Aryl-cyclohexyl ether **33** was unsuccessfully used as a replacement for the Gal-Glc*N*Ac unit [94]. The authors suggested that the use of an aromatic spacer instead of Gal probably does not allow for the preorganization of the molecules needed to fit the binding site. Glycopeptides where L-Gal was used to mimic the L-Fuc residue were synthesized (e.g. **34**, Figure 20). In these compounds a series of unnatural amino acids were used to replace the D-Gal of sLe$^X$ **(1)** and a side chain containing a carboxylate group replaced Neu*N*Ac. The best mimic showed twofold higher activity than sLe$^X$ **(1)** [98].

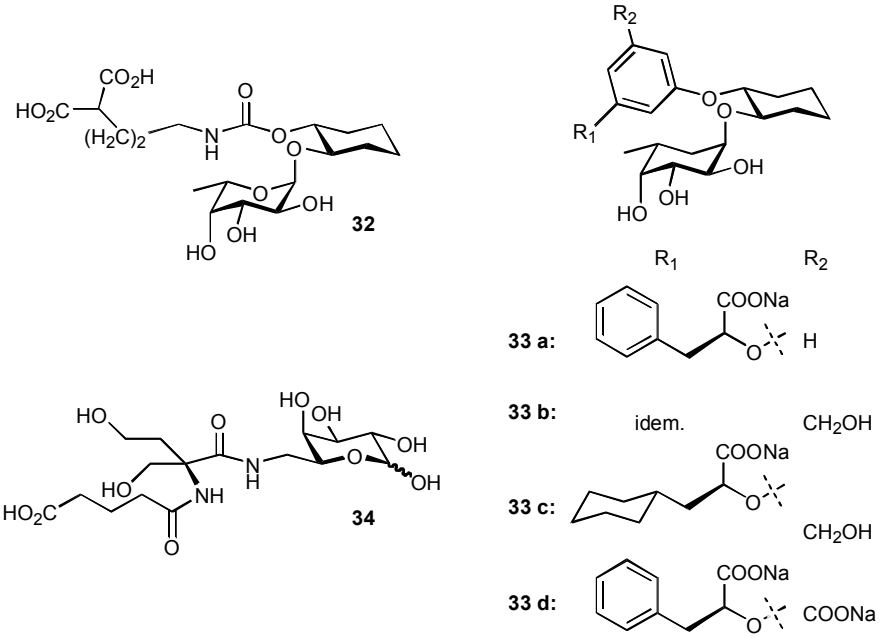
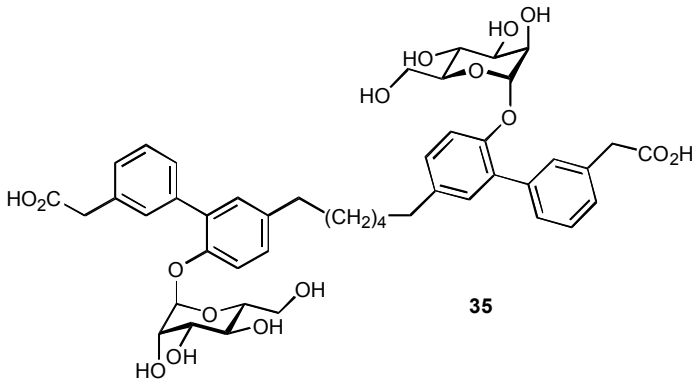



**Figure 20**: A selection of 1-sugar mimics.

Conformationally rigid analogs of sLe$^X$ **(1)** that contain Fuc bound directly to tetralin, naphtalene, anthraquinone, or anthracene were prepared. Glycosides with naphtyl, flavonoid and phenyl backbones were also patented. All these rigidified compounds failed to show any activity. These experiences emphasize the need to precisely fix a novel compound in the right conformation.

A mannose residue was used instead of Fuc because of considerations of cost, ease of synthesis and better fit in the E-selectin/sLe$^X$ model. In these compounds, Neu*N*Ac was replaced by a carboxymethyl group, and a rigid biphenyl spacer was used in place of the Gal-Glc*N*Ac disaccharide. Several variations in the arrangement and the number of Man residue and carboxylic acid were made. Dimer **35** was 6 times more active than sLe$^X$ **(1)** against E-selectin in cell based assays (Figure 21).




**35**

**Figure 21**: A potent E- and P-selectin antagonist.

Selectin antagonists containing a single carbohydrate comprise the largest number of published inhibitors investigated to date [17,44,99,100]. In all of these molecules the Fuc has been retained, or replaced with either Man or Gal: all these simple sugars have three of the six functional groups necessary for selectin binding contained in the Fuc group of sLe$^X$ **(1)**. Additional functional groups (two OHs of Gal, the anion of Neu*N*Ac) have been incorporated using a variety of linkers.

The activities observed for compounds containing only one carbohydrate unit suggest that non-carbohydrate antagonists of E- and P-selectin also are a feasible alternative to sugar-based analogs.

***Other antagonists***

*C-glycosides*

Wong et al. [16,101] suggested that the use of *C*-glycosides in place of *O*-glycosides would increase the stability of the selectin antagonists toward endogenous glycosidases. Research is ongoing in this field.

*High Molecular Weight antagonists*

Due to the heterogeneity of the selectin interactions the most active inhibitors come from multivalent compounds. Even though the molecules in this class are extremely potent selectin inhibitors, they are not ideal candidates for oral drug development. The more potent selectin inhibitors so far are carbohydrates carrying lipophilic tails, high molecular weight charged aggregates, peptides, complex derivatives, and conjugates of the tetrasaccharide $sLe^X$ **(1)** and its mimetics. But all these compounds are not suitable for oral drug formulations. Indeed, sugars carrying conjugates, lipophilic chains and charged aggregates share common structural features with detergents and are dependent on dosage, molecular weight and negative charge distribution/density. These may be acting by distortion of the cell membranes *in vivo*. However, much recent effort has gone into preparing multimers of $sLe^X$ **(1)** in hopes of mimicking Nature's use of polyvalency. In conclusion, even though these molecules are extremely potent selectin inhibitors, they are no ideal candidates for oral drug development.

### II.4.3 Description of relevant previous work at *Novartis*

Investigation and development of selectin ligands has been carried out at the carbohydrate section at *Ciba-Geigy* and later in the selectin project team at *Novartis*, [18,19,102,103]. Since October 1998, this work has been carried out at the *Institute of Molecular Pharmacy*. In our group [92] like in many others, $sLe^X$ **(1)** has served as a lead structure in the research for selectin antagonists with increased biological activity, simplified structure and improved bioavailability. Highlights of this approach can be summarized as follows:

- The structure/activity (SAR) relationship for the lead structure sLeX **(1)** was established [15,94];

- The bioactive conformation was elucidated using *tr*NOE NMR spectroscopy [39,45];

- A molecular modeling tool enabling the rational design of potential antagonists has been developed [27,104].

### II.4.4 The computational model

The model developed by Kolb & Ernst in 1997 [27,104] is based on the pre-organization of the pharmacophores in the bioactive conformation. It has been validated successfully by correlating the pre-organization of numerous selectin antagonists with their biological activity.

This computational method was used for the analysis of the energy surface of $sLe^X$ **(1)** and its macrocyclic mimic **2**. The method is based on the "Jumping between Wells" [27] simulation technique implemented in MacroModel 5.0: a *Boltzman* weighted ensemble of states is generated by jumping between different energy wells (conformations) and performing stochastic dynamics simulations within each well. The total simulation time was 2 ns for compound **2** and 10 ns for $sLe^X$ **(1)**. The conformations used for the MC(JBW)/SD simulations were obtained in proceeding 5000 steps internal coordinate systematic pseudo-Monte-Carlo (systematic, unbounded multiple minimum search, SUMM) simulations. All calculations were performed with an augmented AMBER* force field, containing the $\alpha$-alkoxyacid parameters, in conjunction with a GB/SA continuum water model to allow for a more realistic computational representation of the ligand of interest, as it would exist in a biological environment.

An example of the use of this methodology was published when Ernst et al. [19] attempted to get higher affinity by designing mimetics that improved preorganization of the important pharmacophoric elements. The replacement of Glc*N*Ac by (*R*,*R*)-cyclohexane-1,2-diol and Neu*N*Ac by glycolic acid or cyclohexyl lactic acid was evaluated.

The data analysis is based on a 2D internal coordinate system to define the spatial orientation of the relevant pharmacophores, i.e. the COOH group relative to the Fuc

moiety. The Fuc(C4)-Fuc(C1)-Fuc(O1)-Acid(C$\alpha$) angle describes the conformation of the $Le^X$ **(9)** core. This coordinate is independent of the actual nature of the core. The other coordinate, the angle Fuc(C1)-Fuc(O1)-Acid(C$\alpha$)-Acid(C=O), defines the orientation of the COOH (acid) group relative to the core (Figure 22).

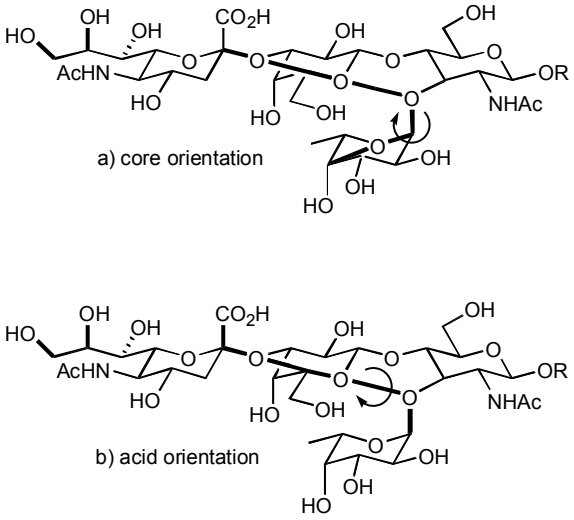



**Figure 22**: The two axes chosen to represent the pre-organization of $sLe^X$ **(1)** and its mimics:

a) The ***core conformation*** describing the relative orientation of L-Fuc and D-Gal;

b) The ***acid orientation*** relative to the core.

Based on this modeling tool, selectin antagonists showing higher potency than the lead structure $sLe^X$ **(1)** were designed and synthesized by chemical and/or chemo-enzymatic approaches. In 1999, the X-ray structure of the complex was not available. The new antagonist has been planned in accordance with this model.

## II.4.5 Macrocyclic antagonists

The idea of diminishing the entropic factor in locking a selectin antagonist in its bioactive conformation underlies the synthesis of macrocyclic selectin antagonists. Due to the weak affinity of $sLe^X$ **(1)** ($IC_{50}$=1.3-3 mM) for P-selectin, efforts have been directed toward the design of $sLe^X$ **(1)** mimetics containing minimal functional groups to increase affinity. Glycopeptide **36** was assayed and its $IC_{50}$ value in inhibiting P-selectin was determined to be 1 μm as compared to 118 μm for compound **37** [105]. Therefore, pre-organization of the necessary point of contacts by introducing a macrolactone ring significantly increased the potency of the mimics.

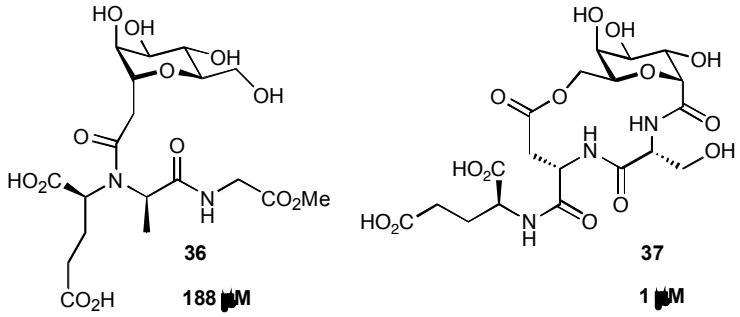



**Figure 23:** A rigid macrocyclic glycopeptide **37** designed as an inhibitor of P-selectin was found to be 1000-fold more active than $sLe^X$ **(1)** and almost 200-fold more active than its acyclical analogue **36**.

Kolb [106] synthesized a compound where the rigid macrocyclic core was expected to provide the basis for enhanced bioactivity due to a potentially high pre-organization of the functional groups involved in binding. However, the synthesized macrocyclic lactone **38** (Figure 24) showed only a partial pre-organization of the core in the bioactive conformation and, hence, its only modest biological activity (rel. $IC_{50}$) could be explained. The conformation of $sLe^X$ **(1)** bound to E-selectin determined with *tr*NOE NMR studies has been the basis of the design this antagonist that combines the following design elements:

1) The $Le^X$ **(9)** core is rigidified by linking the 6-position of Fuc to the 2-position of Gal. Previous work had revealed the receptor's tolerance to modifications at these centers [106].

2) In analogy to pervious studies, sLe$^X$ **(1)** was simplified by replacing Glc*N*Ac and Neu*N*Ac by (*R*,*R)*-1,2-cyclohexanediol and (*S)*-phenyllactic acid, respectively.

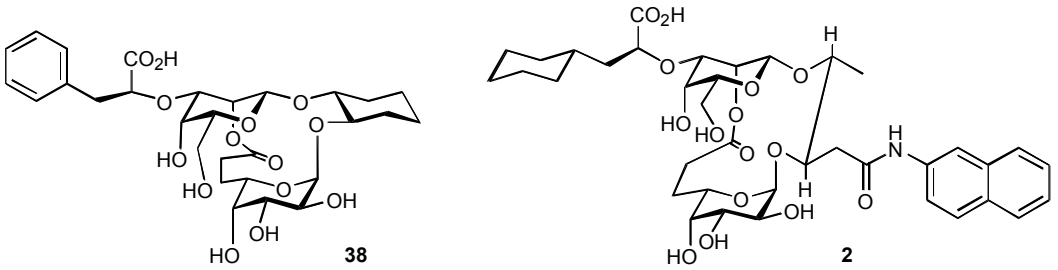
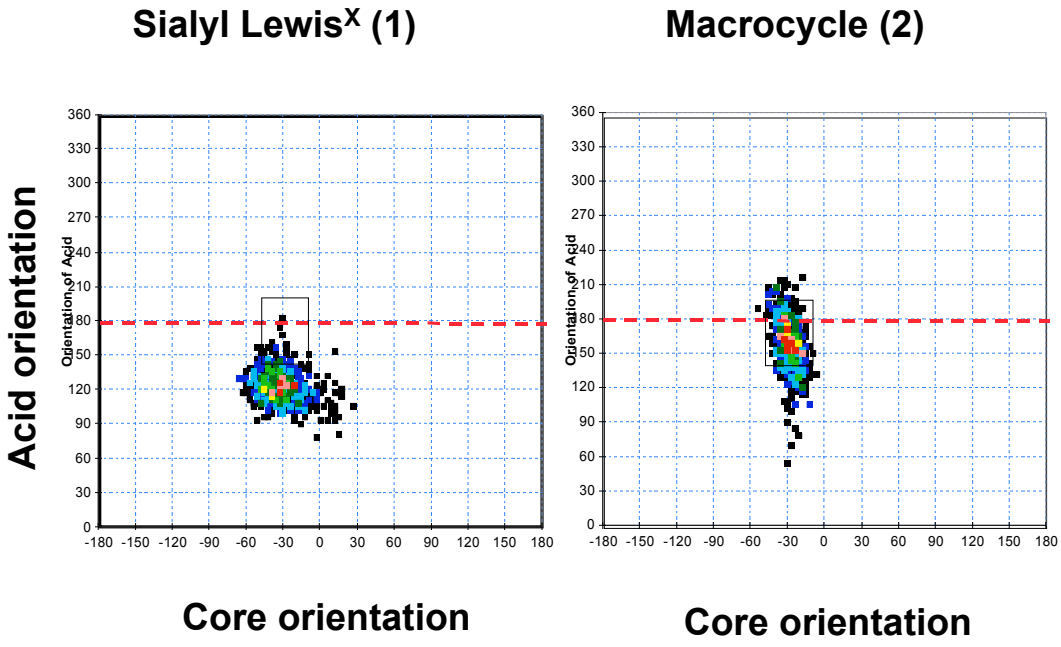



**Figure 24:** **38:** Kolb's macrocyclic E-selectin antagonist was found to be 3 times less active than sLe$^X$ **(1)**;
**2:** Novel macrocyclic E-selectin antagonist.

Several thousand structures obtained by sampling the MC(JBW)/SD simulations every picosecond were used to evaluate the possibility for being at any point of the two-dimensional torsional space at a resolution of 3° by 3° (Scheme 4). The probability data are displayed using a color code (high density: red, low density: blue). These plots represent the free energy surfaces of the molecules and they reveal that the locations of the high probability areas are very similar for both compounds. The graph clearly shows that the bioactive window is not enough populated in the case of Kolb's macrocycle [106].




**Scheme 4**: Core/Acidic conformation and bioactive window (black box) of macrocyclic antagonist **2** compared with sLe$^X$ **(1)**.

In Scheme 4, the conformational analysis of the novel compound **2** (discussion *in* Chapter III.1) shows a high pre-organization in the bioactive conformation. Based on reduced entropy cost in the binding process, an increase in biological activity is expected.

### II.4.6 Evaluation of target structures

The overall activity of E-selectin/sLe$^X$ interactions is weak and the lack of a universal array for selectin-mimic binding makes direct comparisons of binding affinities difficult. The selectins make few interactions with their counter receptor. These contacts are for the most part electrostatic in nature.

The lack of reproducibility of the assays and the difficult comparison of results obtained by different methods are important hurdles towards the development of selectin antagonists. Here, some methods are described that have been used to quantify E-selectin/sLe$^X$-mimics interactions. In general, cell interaction assays incorporating physiologically relevant shear forces (e.g. in flow chambers) are more realistic.

***Transfer NOE***

The use of a biophysical method like NMR is also a valuable tool to avoid some of the described difficulties with traditional assays. In transfer NOE experiments, molecules exhibit strong negative *tr*NOEs when bound to the protein and can be differentiated from non-binding molecules with weak positive NOEs.

***Static biological assays***

*Novartis* used a competitive assay in which wells coated with E-selectin are filled with the test molecule, a polyacrylamide bearing sLe$^a$ **(10)** and biotin. After unbound ligand and polymer are washed from the plate, streptavidin conjugated to horseradish peroxidase is added. A colorimetric determination is possible. Absorbances are recorded at 492 nm and these values are compared to wells containing no test molecule. *Novartis* and collaborators at *Glycotech Corp.* have also published the preparation of complex glycopolymer, a polylysine bearing sLe$^a$ **(10)**, which is used in a similar assay [164].

***Assays in flow chambers***

Cell interaction assays incorporating physiologically relevant shear forces (e. g. in flow chambers) are more realistic. The *in vitro* flow assay developed by Patton et al. [165] at Glycotech Corp. monitors the rolling of leukocytes on stimulated human HUVEC in a flow chamber. Video records of bright-field microscopic regions of rolling and arrested cells are analyzed. Leukocyte rolling *in vivo* can be directly evaluated and quantified by intravital microscopy. Animals, usually rodent or rabbits, are anesthetized and the tissue of interest is laid across the stage of a specially prepared microscope.

# III. Synthesis

## III.1 Rational design of a selectin antagonist

As described in the introduction (Chapter II.1), the bioactive conformation of the carbohydrate epitope sLe$^X$ **(1)** was determined by transfer NOE NMR experiments with the sLe$^X$/E-selectin complex [40,45] before the X-ray structure of the E-selectin co-crystallized with sLe$^X$ were available [12]. Based on this conformational information, a molecular modeling tool, which allowed to assess the degree of pre-organization of the designed mimics in the bioactive conformation has been developed [27,104]. Since this modeling tool has proved to be highly reliable in the search for sLe$^X$ **(1)** mimics, we decided to apply it for the design of our novel antagonist **2** (Figure 25).

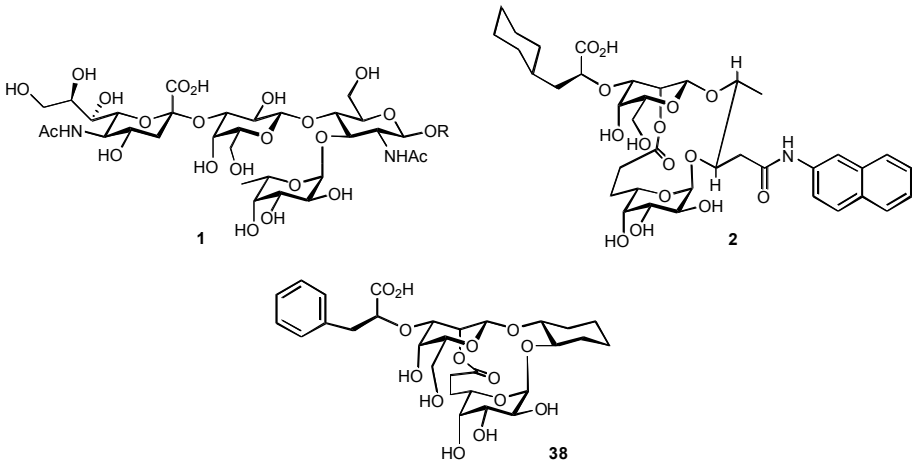



**Figure 25**: The natural epitope sLe$^x$ **(1)**, the macrocyclic mimic published by Kolb **38** [106], and our target molecule **2**.

The original idea was to establish a bridge between the 6-position of L-Fuc and the 2-position of Gal. Since the 2-OH of Gal is not involved in binding, it is inverted into *talo*-configuration and can now act as a handle to be bridged with the extended 6-position of L-Fuc (i.e. L-Gal).

According to the analysis by the modeling tool described by Kolb and Ernst [27,104], a three atom bridge would fix the core in the bioactive (core conformation approx. 10°). In sLe$^x$ **(1)**, Glc*N*Ac acts only as a linker between Gal and Fuc. It is responsible for holding

the two sugar moieties in the correct spatial orientation. Since this positioning is no longer necessary in the macrocyclic setup, it was decided to replace it by a 1,2-diol. An extension would allow to search an additional hydrophobic interaction which was originally identified by DeFrees [20].

For the replacement of neuraminic acid, the cyclohexyl lactic acid, which proved to be a valuable mimic in E-selectin antagonist [46], was chosen. The molecular modeling analysis showed that in the macrocycle **2**, the core core conformation is ideally realized (Scheme 4). In addition, the acid orientation, which was distorted by approx. 30° in macrocycle **38** [106], is now in perfect agreement with the value obtained for the bioactive conformation of $sLe^X$ **(1)**.

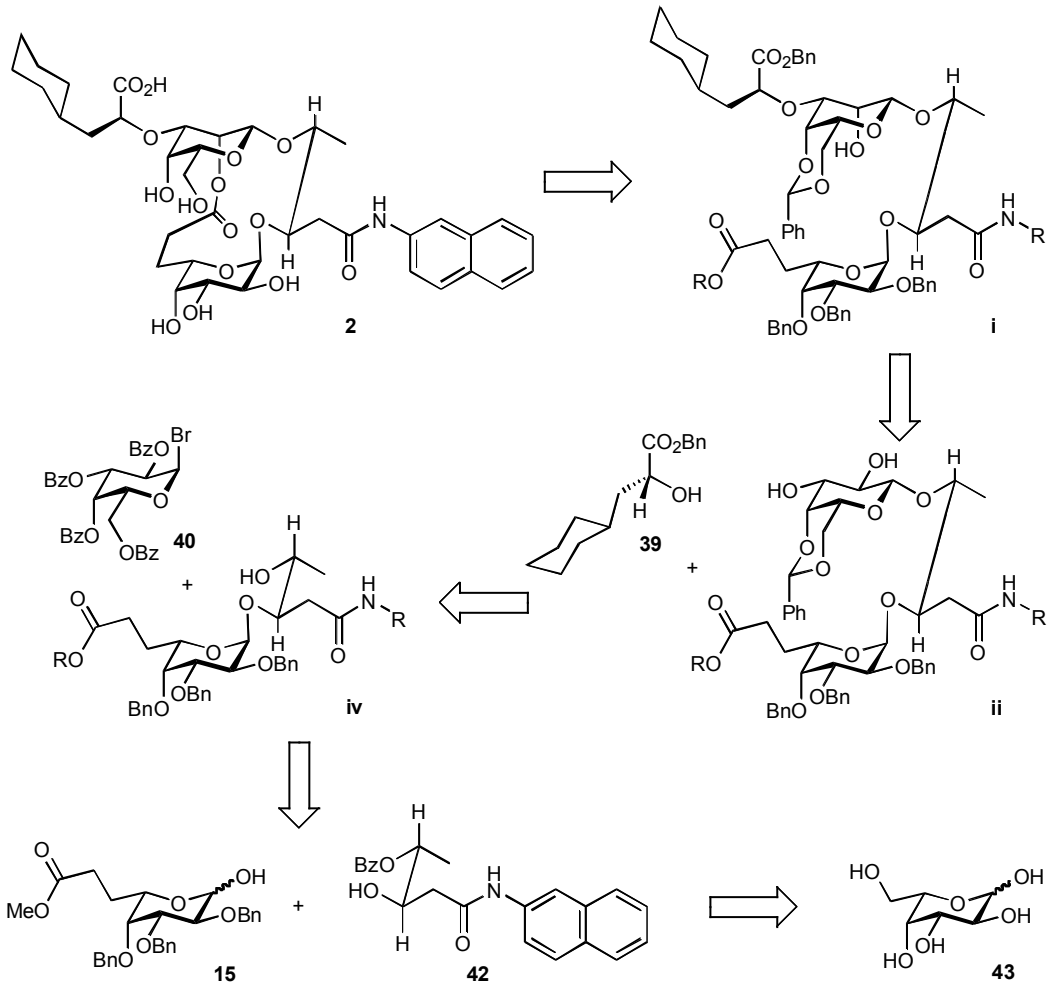
In the $sLe^X$ analog **2** the spatial orientation of the pharmacophores is fixed in the conformation bound to the receptor. The conformational analysis shows a high pre-organization in the bioactive conformation. The rigidity of the macrocyclic core should therefore provide the basis for enhanced bioactivity based on reduced entropy cost in the binding process.

## III.2 Retrosynthesis & Strategy

For the synthesis of **2** four building blocks have been identified (Scheme 5):

a) the fucosyl derivative **15** formed from L-Gal **43** by elongation at C-6 by Wittig olefination,
b) the (*R*)-lactic acid derivative **39**,
c) the D-Gal moiety **40,** and
d) the acyclic mimic **42** of D-Glc*N*Ac.

Glycosylation of **42** with **15** is followed by introduction of **39** by selective introduction on the 3-position of the D-Gal moiety in **ii**. Subsequent inversion of the 2-position of D-Gal should give the D-*talo*-configuration in **i**, required for the cyclization step. Final deprotection is believed to lead to macrocycle **2**.




**Scheme 5**: Retrosynthesis of target macrocycle **2** revealed:

a) L-Galactose derivative **15**,

b) 3,4-dihydroxylated pentanoic acid derivative **42**,

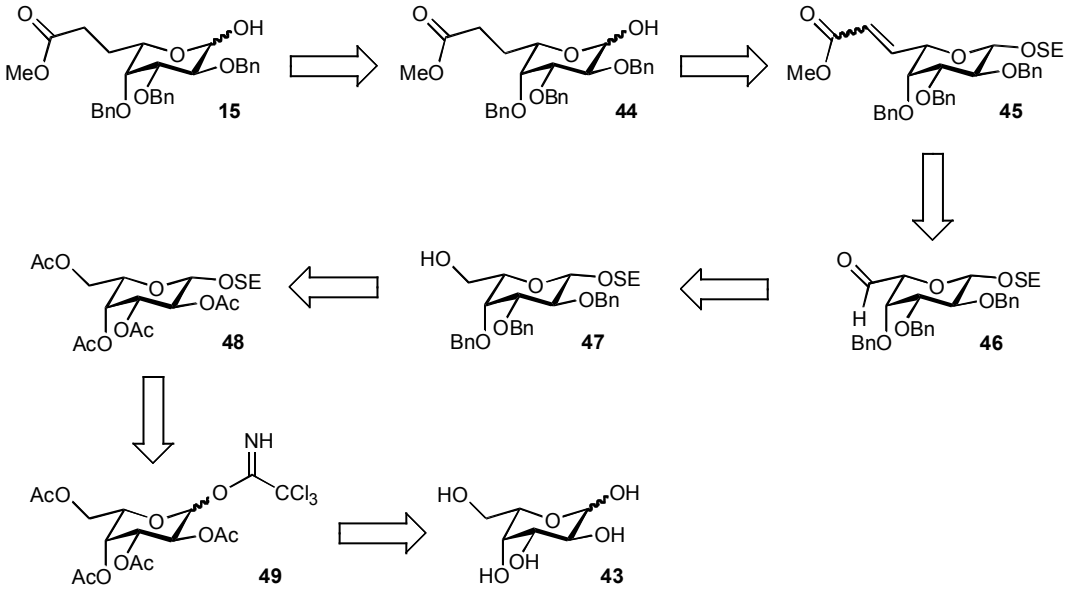
c) D-Galactose derivative **40**,

d) (*R*)-lactic acid derivative **39**.

## III.3 Synthesis of the building blocks

***Retrosynthetic analysis of L-Gal derivative 15***

The stable anomeric protection with OSE is used along the major part of the fucosyl building block's synthesis (Scheme 6) [107]. The last step in the synthesis of the building block **15** is the cleavage of the OSE-protected anomeric position of **44**. **44** can be obtained by palladium-catalyzed reduction of the *cis-trans* product mixture **45a**/**45b** issued from Wittig olefination at the oxidized C-6 of Fuc derivative **46**.



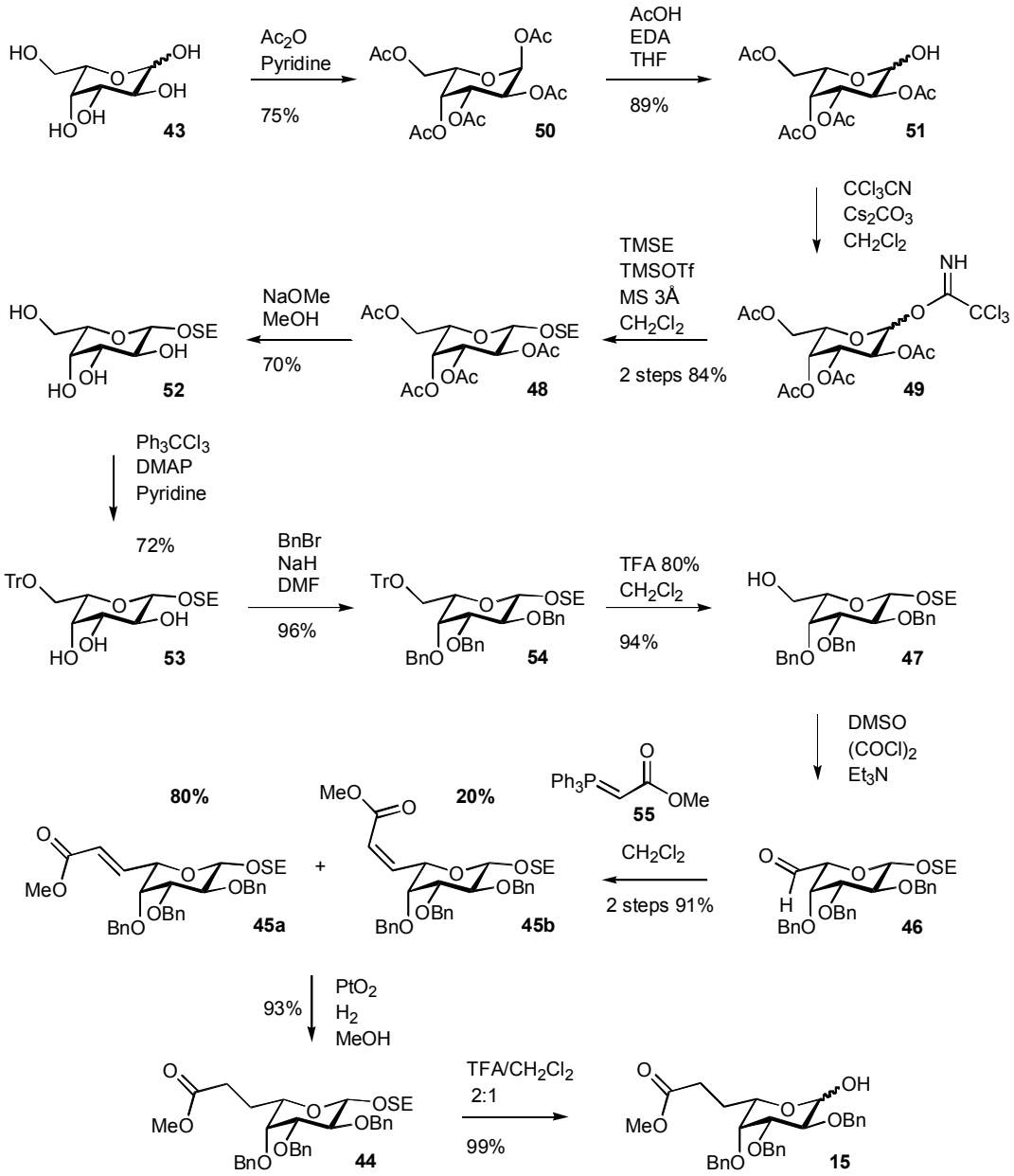

**Scheme 6**: Retrosynthesis of fucose derivative **15**.

Prior to its Wittig olefination, aldehyde **46** is obtained by Swern oxidation of the free 6-OH of L-Gal derivative **47**. **47** can be easily obtained in four protection/deprotection steps from **48**. OSE protection of **(43)** should be introduced by glycosylation of TMSEt, with trichloroacetimidate donor **49**. **49** is available in three steps from L-Gal **(43)**.

***Synthesis of L-Gal derivative 15***

At first, we investigated the feasibility of the pathway leading to the synthesis of fucosyl building block **15** in using inexpensive D-Gal **(69)** as starting material. In parallel, we performed a similar synthesis starting with a small amount (1 g) of L-Gal **(43)**. After the

successful synthesis of the first ten steps with D-Gal **(69)** and subsequently with L-Gal **(43)**, we decided to carry out the synthesis of **15** from L-Gal **(43)** in larger scale (15 g) in order to synthesize a sufficient amount of **15** to reach target molecule **2** [108,109,110,111] . L-Gal **(43)** was used as starting material for the preparation of building block **15** (see Scheme 3). Per-acetylation of the hydroxyl groups of L-Gal **(43)** was performed using $Ac_2O$ in pyridine (75% yield). The exclusive formation of the $\alpha$-anomer **50** facilitated the analysis. When the reaction was performed at 45°C we obtained a mixture of two anomers **50/50**$\beta$ ($\alpha$:$\beta$=2:1).



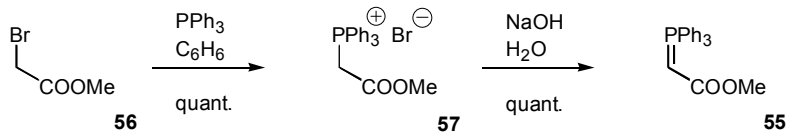

**Scheme 7**: Synthesis of fucosyl building block **15**. 21 % overall yield from L-Gal **(43)**.

To remove the Ac group at the anomeric position, compound **50** was treated with ethylenediamine and AcOH in THF to give a mixture of two anomers of **51** in good yield (89%). We protected the anomeric position of **51** with the trimethylsilylethyl group, commonly named OSE, which has found widespread use as an anomeric protecting

group. The OSE protecting group can be introduced by glycosylation and is stable to a wide range of reaction conditions [112].

The trichloroacetimidate glycosylation method was used to selectively introduce OSE at the anomeric position of **51** in two steps. The trichloroacetimidate donor **49** was synthesized by reacting **51** with $CCl_3CN$ and $Cs_2CO_3$ in DCM [113,114,115,116]. The favored formation of the β-trichloroacetimidate **49b** (**49a**/**49b** 2:1) was observed. The second step of the trichloroacetimidate glycosylation method consisted of the addition of TMSEt to donor **49** in DCM, with TMSOTf as promotor [112]. The desired β-glycoside **48** was obtained in good yield (84%), calculated from the free anomeric compound **43**. The $^3J_{1,2}$ coupling of 8.0 Hz is typical of a β-anomeric configuration. The four Ac-groups of **48** were cleaved by treatment with NaOMe in methanol, giving compound **52** with 70% yield. The bulky trityl (Tr) group was employed for the regioselective protection of the primary OH-6 in **52**, giving compound **53** (73% yield). The slow reaction was accelerated by addition DMAP [117]. In carbohydrate synthesis, benzyl ethers are often applied as protecting groups. They are robust to a wide range of basic and acidic conditions and also withstand hydride reducing agents and mild oxidants, all of which were used in later stages of the synthesis. According to standard procedures, compound **53** was benzylated by reaction with BnBr and NaH in DMF to give **54** with excellent yield (96%). Cleavage of the trityl group in **54** with 80% aqueous TFA yielded alcohol **47** (94%). The deprotected primary alcohol was subsequently oxidized under Swern conditions [166] to the corresponding aldehyde **46**.

Wittig olefination of **46** with **55** yielded **45** as a 80:20 mixture of the *trans*-(**45a**) and *cis*-(**45b**) isomers, in 91% (2 steps). The Wittig methoxycarbonylmethylene-triphenylphosphorane **(55)** was prepared by reaction of methyl bromoacetate with $PPh_3$ and treatment of adduct with base (NaOH in water) (Scheme 8) [118].



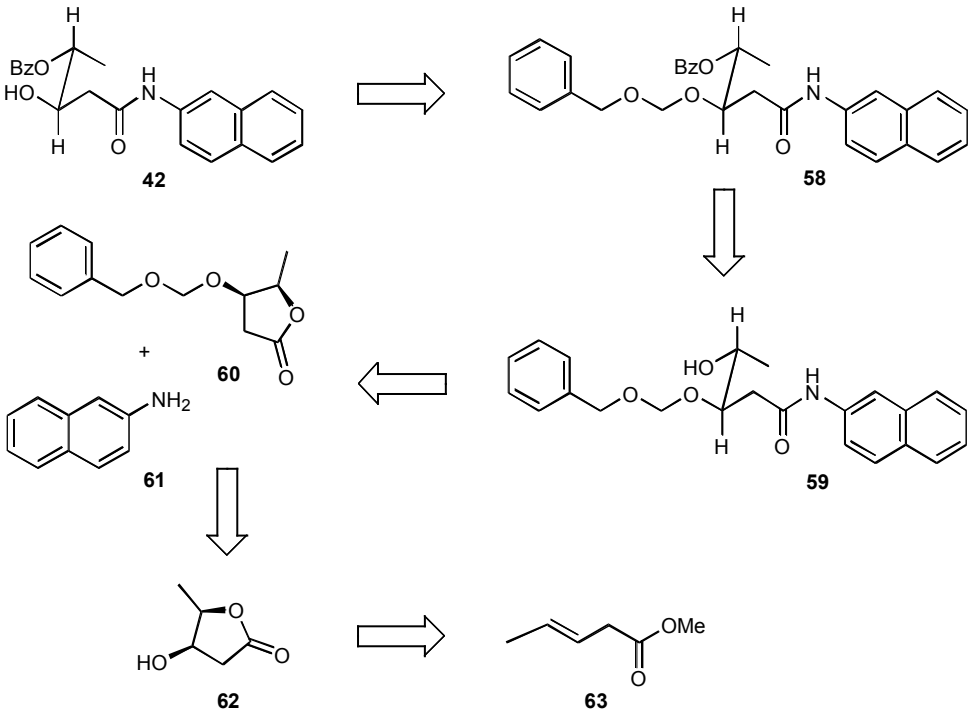

**Scheme 8**: Synthesis of Wittig reagent **55**.

Selective hydrogenation ($H_2$, 1 bar) of the double bond in **45** was readily achieved in methanol with $PtO_2$ as catalyst, yielding 93% of **44**.

Normally applied cleavage conditions for the OSE protecting group are $BF_3$•$Et_2O$ in $Ac_2O$. [112,119] or TFA [107]. When the treatment of **44** with TFA/DCM 2:1 was carried out, we noted the formation of 1-trifluoroacetylated **15** as a by-product. This ester could be cleaved with NaOMe in MeOH at pH 10 to obtain **15** quantitatively.

***Retrosynthetic analysis of cyclic replacement of D-Glc*NAc *42***

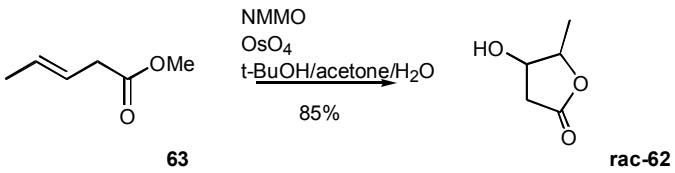
Starting from commercially available methyl-3-pentanoate **63**, lactone **62** can be obtained by a catalytic hydroxylation according to Sharpless [120]. In the next step, the secondary alcohol in **62** is protected as BOM ether. The 2-naphtoyl building block **42** was accessible by opening the BOM-protected lactone **60** by a nucleophilic attack of the free electron pair of the nitrogen of 2-naphtylamine **(61)** (→**59**) followed by benzoylation (→**58**) and subsequent cleavage of the BOM group (see Scheme 9).




**Scheme 9**: Retrosynthetic analysis of D-Glc*N*Ac mimic **42**.

***Synthesis of cyclic replacement of D-Glc*NAc *42***

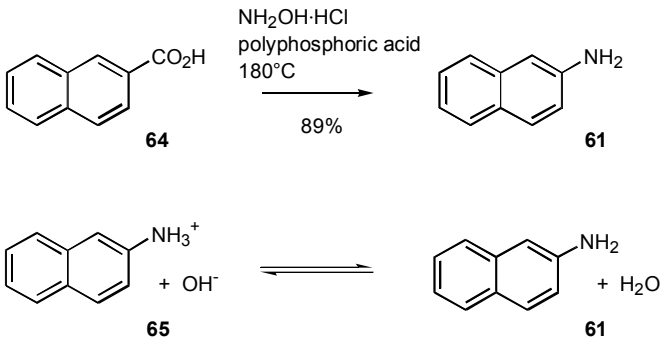
The Sharpless asymmetric dihydroxylation (AD) of the commercially available methyl 3-pentanoate **(63)** was used in order to enantioselectively from the lactone **62** (detailed discussion in Chapter III.6.2) [120,121,122]. The intramolecular cyclization takes place *in situ* by nucleophilic attack of the 4-hydroxyl group. Removal of the by-product methane sulfonamide ($CH_3SO_2NH_2$) by chromatography on silica gel was followed with the staining reagent 4-dimethlyaminocinnamaldehyde. The optimized detection method allowed us to purify the lactone **(+)-62** (85 %). Control of the reaction stereoselectivity was performed using a NMR shift reagent (detailed discussion in Chap. III.6.3) [123,124,125]. The enantiomeric purity of **(+)-62** was found to be 95% ee. For control purposes, we also synthesized ***rac*-62** (Scheme 10) by unselective osmium tetroxyde ($OsO_4$)-mediated dihydroxylation [126].




**Scheme 10**: Synthesis of racemate ***rac*-62** as control compound.

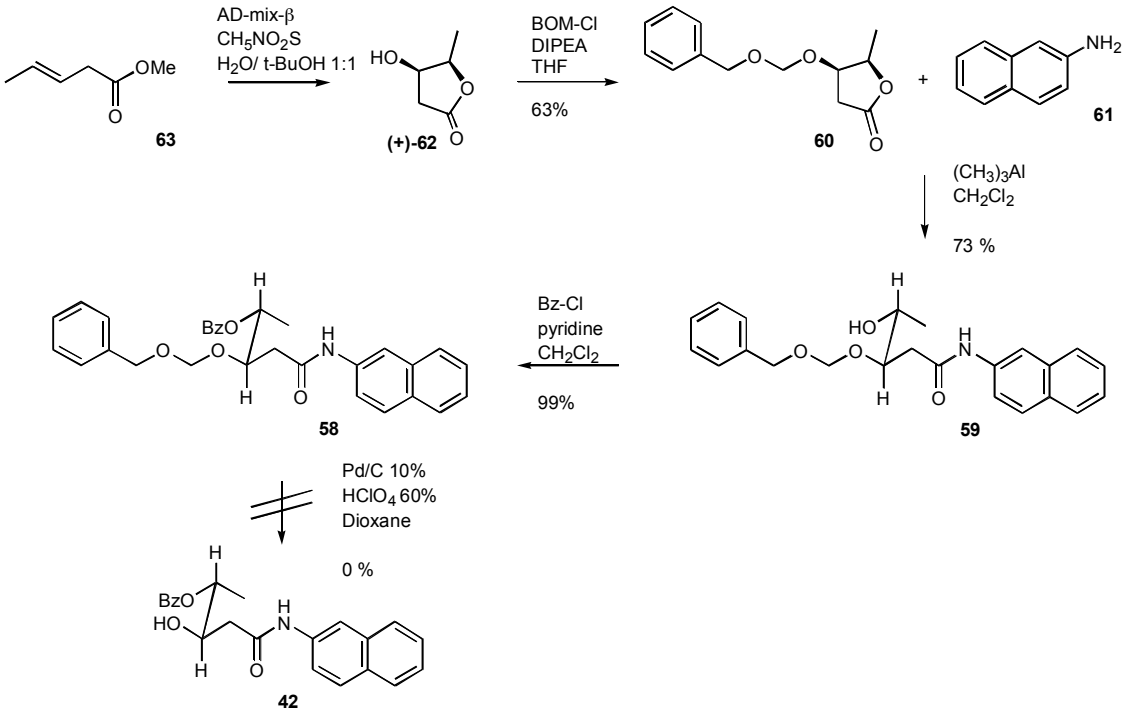
For the protection of the secondary hydroxyl group of the lactone **(+)-62** the BOM group was chosen. The BOM protection was introduced by straightforward reaction of **62** with BOM-Cl in DCM using DIPEA as the activating base to give **60** in 62 % yield.

Lactone **60** was opened under anhydrous conditions by reaction with 2-naphtylamine **(61)** in presence of the Lewis acid $Al(CH_3)_3$ to afford **59** (82%). For this purpose, the commercially not available 2-naphtylamine **(61)** had to be synthesized from 2-naphtoic acid **(64)**, $NH_2OH$•HCl and polyphosphoric acid at 180°C to form an ammonium salt **65** (see Scheme 7) [127]. According to the literature, neutralization (pH 7) of a solution of salt **65** in water is sufficient to reverse the equilibrium shown in scheme 11. In our hands, strong basic treatment (pH 12) with aqueous NaOH was required to precipitate **(61)** with satisfactory yield (89%).




**Scheme 11**: Synthesis of 2-naphtylamine **(61)**.

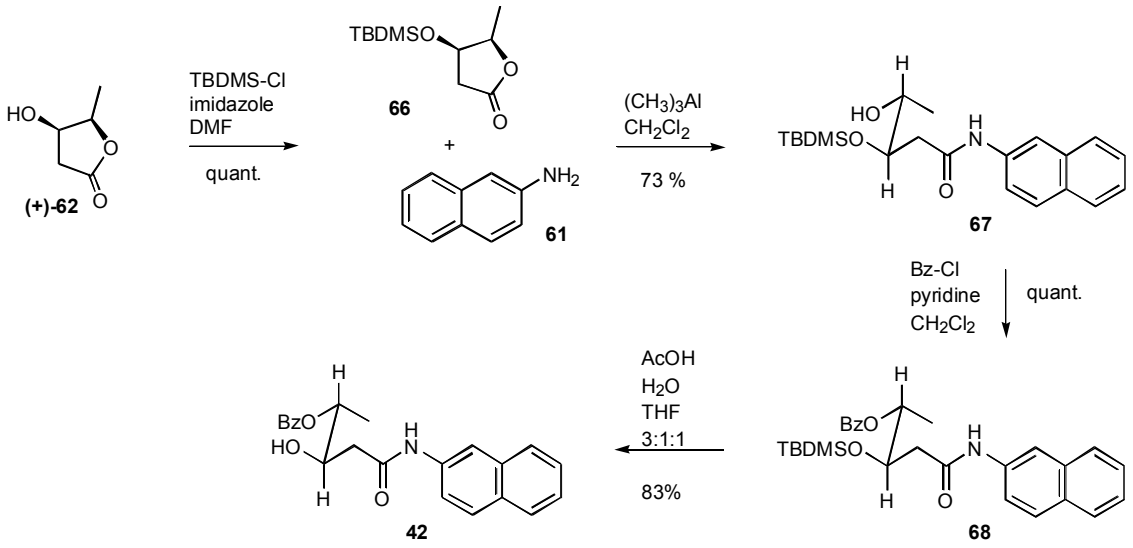
Benzoylation of the secondary alcohol of **59** with BzCl/pyridine in DCM gave **58** (92%). In the last step leading to **42** the selective cleavage of the BOM-group in **58** was planned. Palladium (Pd/C 10%, $H_2$) catalyzed hydrogenation in dioxane followed by acidic hydrolysis with acqueous perchloric acid in dioxane is the classic method to cleave BOM [128]. However, in hour hands this procedure led to the destruction of the starting material. Other cleavage conditions were unsuccessfully attempted: a THF/water mixture was used as solvent, different acid concentrations were attemped and HCl was used instead of $HClO_4$ [129]. An alternative cleavage method, which consisted of reacting **58** with $PhSH/BF_3{\cdot}OEt_2$ in DCM was also attempted without success [130].




**Scheme 12**: Attempt to synthesize **42** according to initial retrosynthesis.

The failure to cleave the BOM group in **58** forced us to use another protecting group. *ter*t-butyl-dimethyl-silyl (TBDMS) was thought to be a useful protecting orthogonal to the Bz group. We used the racemate ***rac*-62** to investigate this new pathway. Reaction of ***rac*-29** with TBDMS-Cl in DMF with imidazole as the activating base allowed us to obtain the TBDMS protection with good yield [131,132,133]. The use of DMAP helped to accelerate the reaction [117,134]. The opening of the TBDMS-protected lactone and the subsequent benzoylation step were performed without difficulty. Cleavage of the TBDMS group under standard conditions with TBAF in THF did not lead to the desired product. An alternative cleavage method with AcOH/water/THF 3:1:1 at 80°C [131] allowed us to selectively cleave TBDMS in 80% yield and thus to achieve the synthesis of ***rac*-42** with excellent yields (4 steps, 55 % from ***rac*-62**).

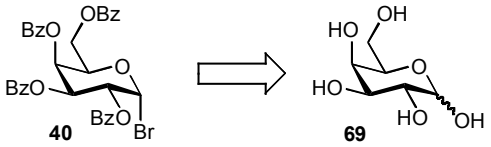
We carried out the synthesis in large scale starting with the enantiomerically pure lactone **(+)-29** (Scheme 13) TBDMS protection of **(+)-29** was performed by reaction with TBDMS-Cl and imidazole in DMF to yield **66** quantitatively. The lactone was opened by nucleophilic attack of 2-naphylamine **61** to give **67** (73%) and the secondary alcohol was Bz-protected to give **68** quantitatively. TBDMS in **68** was then selectively cleaved in 80% yield to give stereospecifically compound **42**.




**Scheme 13**: Synthesis of the 2-naphtoyl building block **42**.

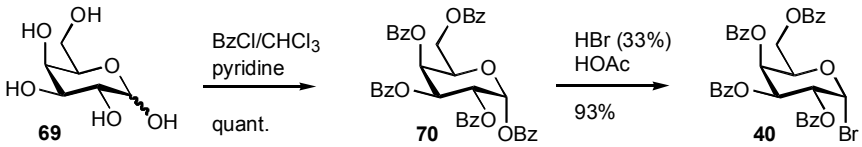
***Retrosynthetic analysis of D-Gal moiety 40***

D-Gal building block **40** is prepared from D-Gal **(69)** in two steps according to standard protocols (Scheme 14) [135,137,138].




**Scheme 14**: Retrosynthesis of the Gal building block **40**.

***Synthesis of D-Gal moiety 40***

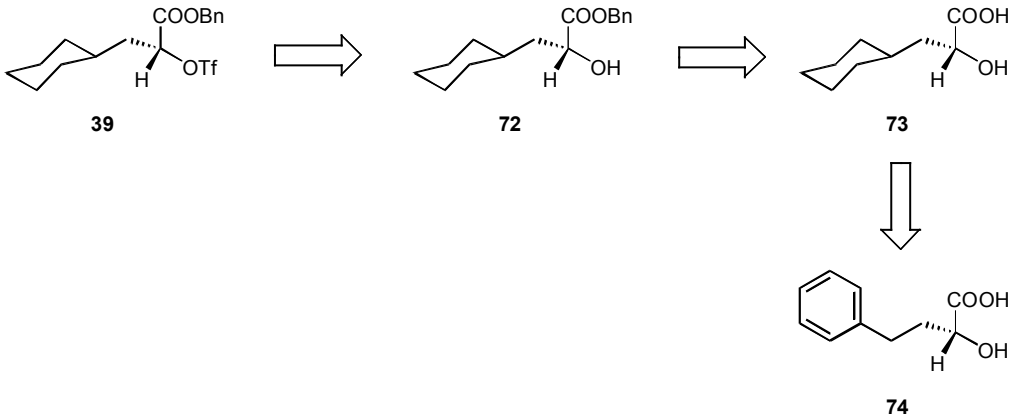



**Scheme 15**: Synthesis of the Gal building block **40**.

The large-scale synthesis of per-benzoylated D-galactose **(69)** (20 g), which served as starting material for the synthesis of glycosyl donor **40**, was carried out by reaction of D-Gal **67** with BzCl in pyridine/$CHCl_3$ (Scheme 15) [135]. The temperature was maintained below 35°C during the exothermic reaction, yielding the $\alpha$-anomer **70** quantitatively after crystallization [136]. The small $^3J_{1,2}$ value (3.6 Hz) of the product's $^1$H NMR spectrum, indicated a $\alpha$-pyranosyl configuration for the anomeric center. The per-benzoylated galactosyl bromide **40** was prepared by treatment [137] of **70** with a 33% solution of HBr in acetic acid. The more stable $\alpha$-anomer **40** was obtained with high yield (93%).

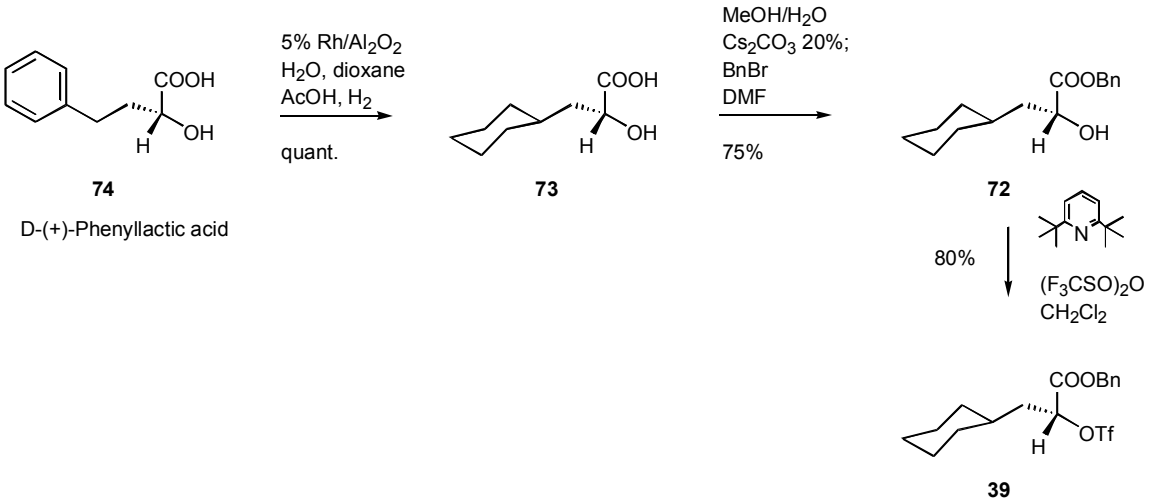
***Retrosynthetic analysis of (R)-cyclohexyl lactic acid 39***

For the alkylation of the 3-position of Gal, which occurs under inversion, the triflate **39** with *R*-configuration was needed [135]. It can be obtained from **72**. Benzylation of the acid **72** should be readily performed by base activation. Hydrogenation of the commercially available D-(+)-phenyl lactic acid **(74)** should give (*R*)-cyclohexyl lactic acid **(75)** (Scheme 16).




**Scheme 16**: Retrosynthetic analysis of *(R)*-cyclohexyl lactic acid building block **39**.

### *Synthesis of the cyclohexyl moiety 39*




**Scheme 17**: Synthesis of cyclohexyl moiety **39**.

Commercially available D-(+)-phenyllactic acid **(74)** was quantitatively reduced under high $H_2$ pressure (4 bar), allowing us to reduce the quantity of expensive catalyst (Rh on activated alumina) normally required for similar reductions (Scheme 17). The acid moiety of the reduction product (*R*)-cyclohexyllactic acid **(73)** was then esterified by benzylation (75%). The benzylester **72** was then triflated at the free OH position by treatment with $Tf_2O$ in the presence of a sterically hindered base to give **39** with good yield (80%) [139].

## III.4 Total synthesis of macrolactone 2

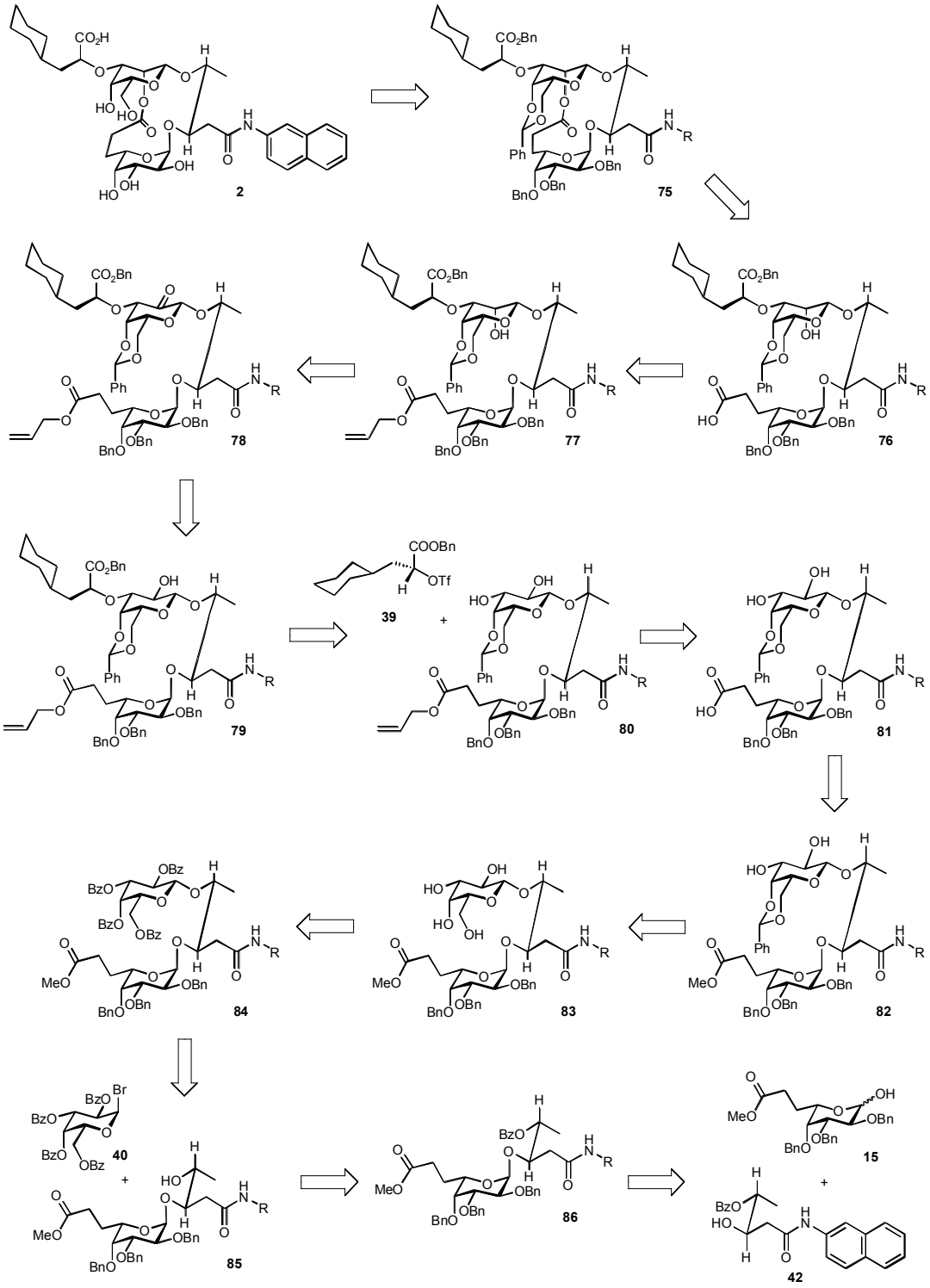
### III.4.1 1st Attempt to synthesize macrocycle 2

***Retrosynthetic analysis***

Benzyl protection of the Fuc hydroxyl groups is essential for the selectivity of several reactions along the synthesis of **2** and must therefore be introduced at an early stage of the synthesis (Scheme 18). Thus, the last step of the synthesis requires deprotection of three benzyl-groups on the Fuc moiety by hydrogenation in the presence of *Perlman*'s catalyst as well as the hydrolysis of the methylester in compound **75**.

H.C. Kolb utilized the *Yamaguch*i cyclization [140] in his synthesis of a macrocyclic selectin antagonist [46]. The same procedure was believed to be applicable to link the 2-OH of the D-Tal moiety with the acid of the fucosyl derivative **76**. Prior to the cyclisation, inversion of the 2-OH in **79** to obtain D-*talo* out of a D-*galacto* configuration is required. Before the oxidation and reduction steps, which are necessary to invert the Gal 2-OH configuration, the 2 esters in **77** had to be orthogonally protected. The selective deprotection of the allyl ester in **77** is needed before the intramolecular cyclization can take place (→**76**).

Inversion from the D-*galacto* configuration in **79** to the D-*talo* configuration in **77** should be achievable in two steps by a Jones oxidation (→**78**) followed by reduction (→**77**). Selective glycosylation of the 3-position of the D-Gal moiety in **80** with **39** can be achieved through the corresponding tin acetal. Before carrying out the regioselective glycosylation, the D-Gal moiety of **83** has to be protected with a 4,6-benzylidene group, yielding **82**. Allyl protection of the free acid group of **81** is also required and is accessible after saponification of ester **82** with LiOH. **83** is obtained after Bz deprotection of the β-galactosylation product **84**, which is obtained from donor **40** and glycosyl acceptor **85**. Deprotection of the glycosylation product **86** with NaOMe in methanol should lead to donor **85**. Finally, **86** is obtained by selective α-coupling of the 2-naphtoyl acceptor **42** with the fucosyl donor **15**.



**Scheme 18**: Initial retrosynthesis of macrolactone **2**.

***Synthesis***

α-Selective glycosylation of fucosyl donor **15** with acceptor **42** was performed using the *in situ* anomerization procedure developed by Lemieux et al. [141] (detailed discussion in Chapter III.6.4). This step consists of a preliminary bromination of **15** with oxalyl bromide (Scheme 19).

A Vilsmeier-Haack reagent (chloromethylenedimethyliminium bromide) was prepared by reaction of DMF and oxalyl bromide. The anomeric OH in **15** then performs a 1,2-nucleophilic addition with concomitant elimination of a bromide ion. This reaction results in the introduction of a very good leaving group, which is displaced by a bromide, yielding compound **110**α (Scheme 28, p. 90) [142]. As 2-*O*-Bn glycosyl bromides are too labile for purification on silica gel, **110** was taken as a crude product into the next step. The *in situ* anomerization of the obtained α-bromide **110**α to the more reactive β-bromide **110**β was then achieved in presence of TBAB. The β-bromide **110**β reacted with **33**, leading to an α-stereoselective glycosylation after inversion of the configuration.

Due to the high cost of the building blocks, we attempted to implement the relatively low yield (44%) and reproducibility of this water-sensitive reaction. Interestingly, analysis of the reaction by-products showed the presence of an orthoester **111**. The formation of this compound is the result of the faster intramolecular reaction of the 1-bromide **110**β with the methylester tail compared to the intermolecular glycosylation with **33**. This observation led us to investigate the reaction mechanism of the orthoester formation with the idea of taking benefit of this secondary reaction (Chapter III.6.5).

By basic deprotection of the benzoylated secondary alcohol in **86** was performed using NaOMe in dry MeOH, the glycosyl acceptor **85** was obtained. The second glycosylation to link the acceptor **17** to the protected galactosyl bromide donor **40** was carried out in dry DCM in presence of AgOTf as promotor [143]. The reaction yielded **84** with relatively low yield (39%). Cleavage of the Bz groups in **84** with NaOMe/MeOH gave **83**. A small amount of dioxane was added to the reaction in order to dissolve the starting material.

Selective 4,6-*O*-benzylidene protected **82** was obtained with good yield (79%) by trans-acetalisation of **83** using benzaldehyde dimethyl acetal in the presence of a catalytic amount of CSA.

The ester in compound **82** was hydrolyzed with LiOH in a water/EtOH mixture to yield the free acid **81** with excellent yield (96%). Allyl ester was introduced in **81** with satisfactory yield (70%). Allyl ester was employed to temporary protect the acid of the Fuc moiety in compound **81**. The protecting group is stable to the oxidative and reductive reaction conditions necessary to invert OH-2 from galacto- to talo-configuration.

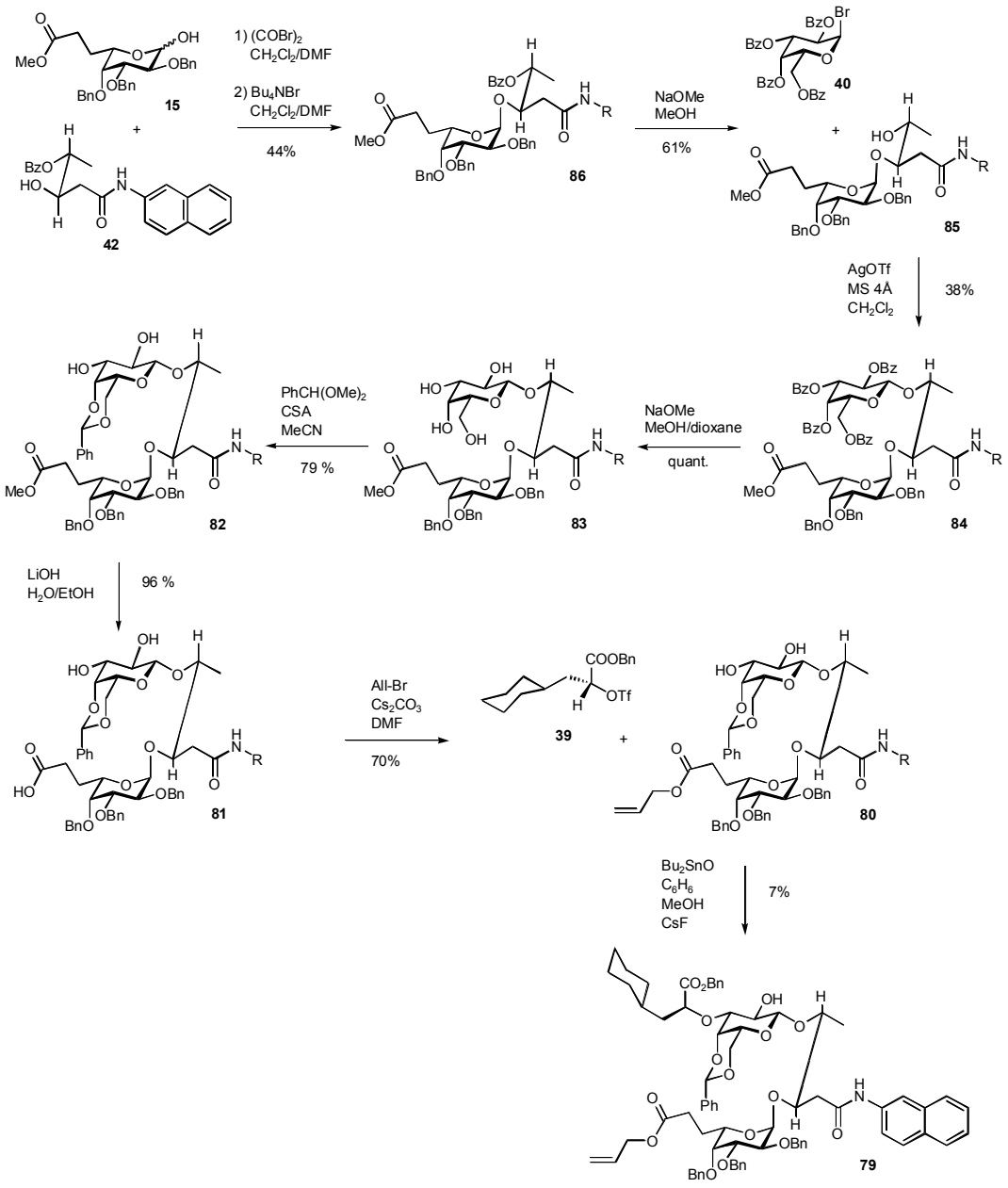
For the selective 3-OH alkylation, the stannylidene derivative was formed by reacting **80** with $Bu_2SnO$ under reflux in benzene. The tin acetal was the treated with an excess of the previously synthesized triflate **39**. In our case, the glycoslyation was carried out with an unsatisfactory yield (7%) and low regioselectivity.

It is of interest to note that Ernst et al. [19] could achieve a selective 3-OH glycosylation on unprotected as well as on 6-deprotected Gal moieties. Conversion of diols into dibutyltin acetals is normally an efficient method to achieve the regioselective alkylations [144,145,146,147,148,149].

Therefore, a new approach containing two major improvements was explored:

A) A reduction of the methylester tail of **15** and subsequent protection of the primary alcohol. The corresponding ether should be inert during the glycosylation step.

B) Selective 3-OH glycosylation of Gal moiety with the cyclohexyl moiety prior to glycosylation of the core compound. This would allow to solve the problems linked with regioselectivity of the alkylation in an earlier step of the synthesis.



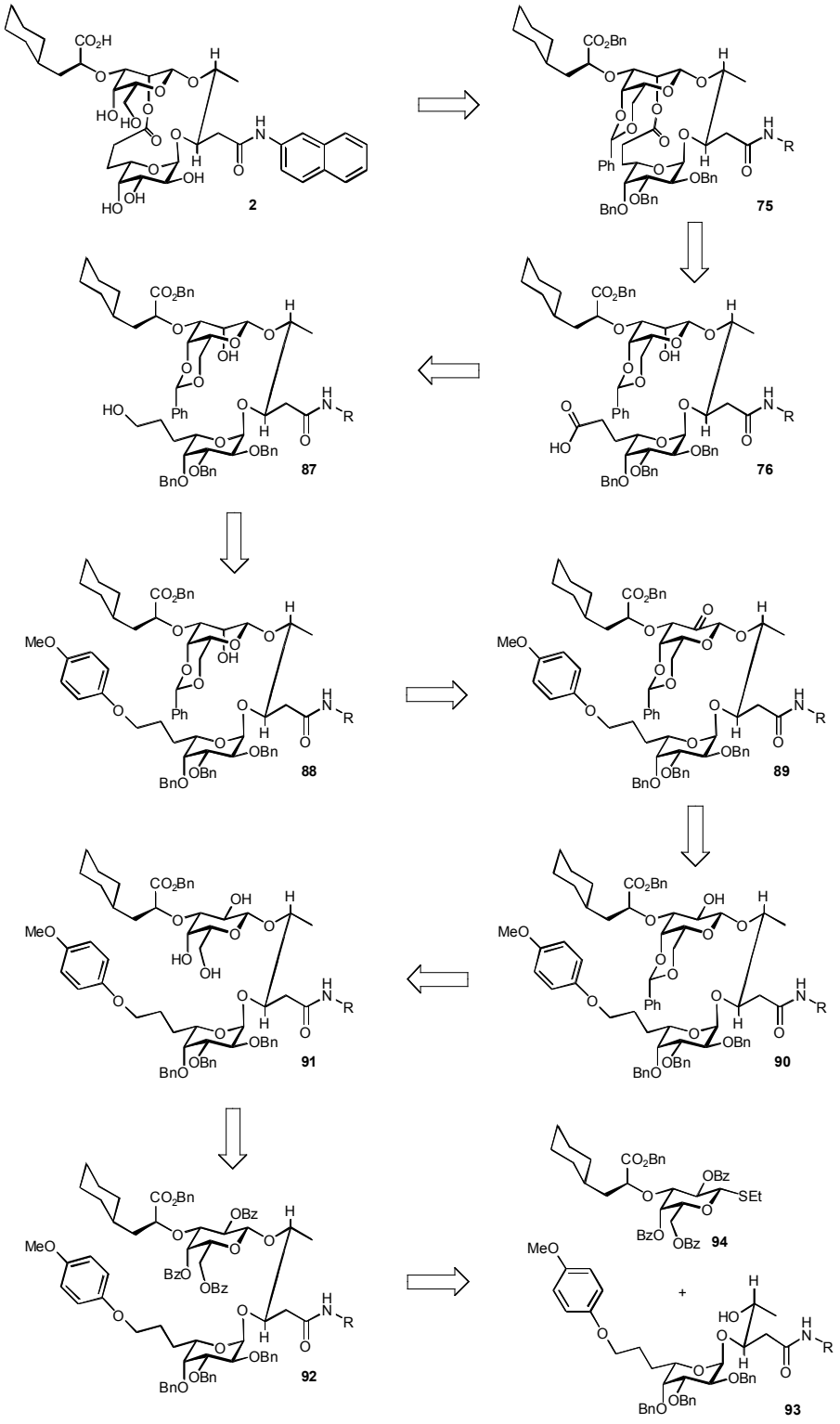

**Scheme 19**: Last steps leading to the target compound **2**.

### III.4.2 2nd Attempt to synthesize macrocycle 2

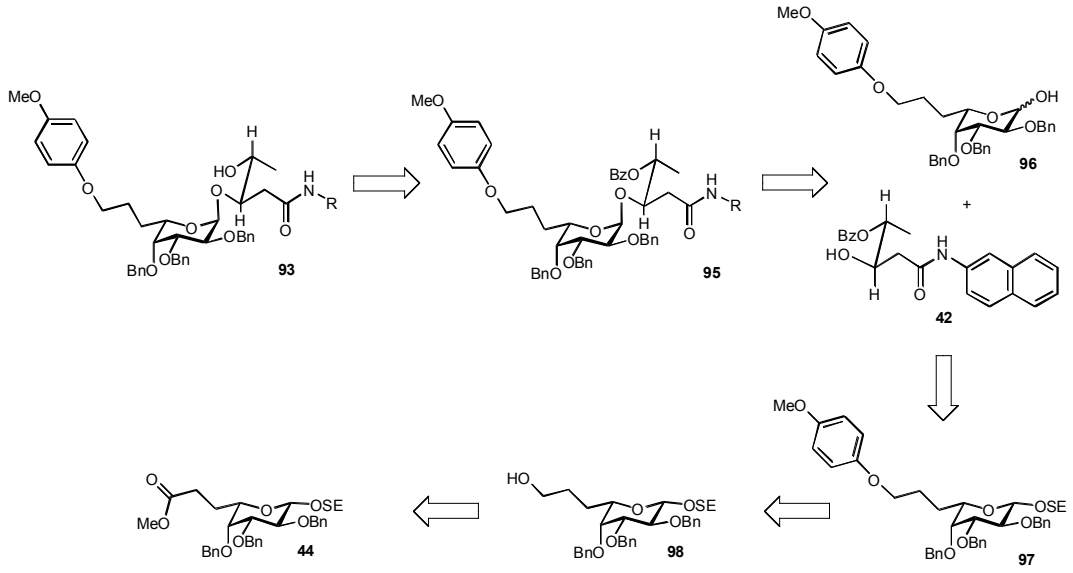
This new pathway is based on the reduction of the ester at the C-8 position of the fucoside **14** and subsequent protection of the resulting alcohol **44**. We believed that this approach would eliminate unwanted side reactions like orthoester building during the glycosylation step and thus would lead to higher yields. Another important modification made to get around previous problems was the introduction of the (*S*)-cyclohexyl lactic acid moiety on the 3-OH of the Gal moiety before glycosylation with the core building block. This approach would allow to avoid the low yields obtained for the alkylation of galactose in **80**.

***Retrosynthesis 2nd attempt***

As in the 1St attempt, we aimed to utilize the stability of Bn protecting groups on the D-Fucose hydroxyls from an early stage of the synthesis on (Schemes 16 & 17). Henceforth, the final step requires hydrogenation of the Bn groups in the presence of Perlman's catalyst $Pd(OH)_2/C$ and hydrolysis of the methylester of the cyclisation product **75**. To obtain **75**, we planned to use the Yamaguchi protocol for macro-cyclization of **76**. The acid needed to perform the cyclization should be obtained by selective oxidation of the primary alcohol **87** [150]. The alcohol **87** can be obtained by cleaving the *p*-methoxy-phenyl protection of OH-8 in **88**. Conversion of the β-galactoside **90** to the β-taloside **88** should be stereoselectively accomplished by oxidation/reduction of the 2-position. The inversion of configuration at the 2-position requires preliminary 4,6-protection of **91** as benzylidene acetal. **50** should be accessible by prior cleavage of the Bz groups protecting the of the Gal moiety in **92**. **92** can be obtained by glycosylation of glycosyl acceptor **90** with thioglycoside donor **70**. Synthesis of **90** should be possible by the Bz-protection of the secondary alcohol of **95**. Selective α-coupling of glycosyl donor **96** with acceptor **42** should give **95**. **96** should be obtained in three steps by reduction of the methylester in **14** (→**98**), subsequent protection of the primary alcohol **97** with hyroquinone monomethylether [151,152] and cleavage of the anomeric protecting group.



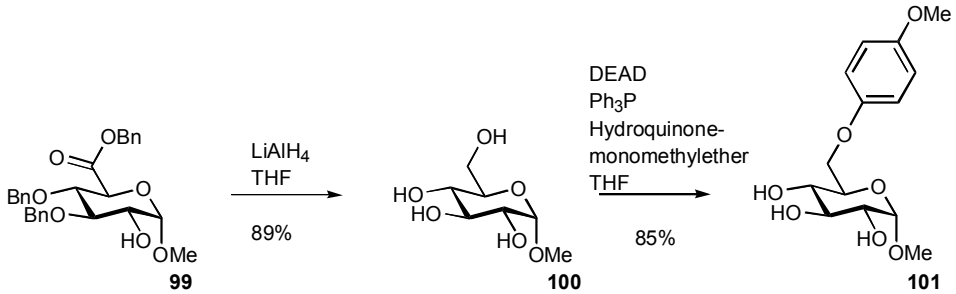

**Scheme 20**: Retrosynthesis 2nd attempt. Compounds **2** to **93**.



**Scheme 21**: Retrosynthesis 2nd attempt. Compounds **93** to **44**.

### *Discussion 2nd attempt*

Before exploring the new strategy, we wanted to attempt the reduction and protection step on a test compound (Scheme 22). We chose the glucuronic acid derivative **99** to optimize these two steps. Reduction of **99** gave **100** in satisfying yield (89%) [153,154]. Protection of the primary hydroxyl in **100** was performed applying the *Mitsunobu* procedure [155,156]. Activation of the alcohol with $PPh_3$ and DEAD in THF allowed the coupling with hydroquinone monomethylether to yield **101** in good yield (85 %). After successful protection of the test compound, we decided to explore this new approach sarting with **44**.



**Scheme 22**: Test reaction with glucuronic acid derivative.

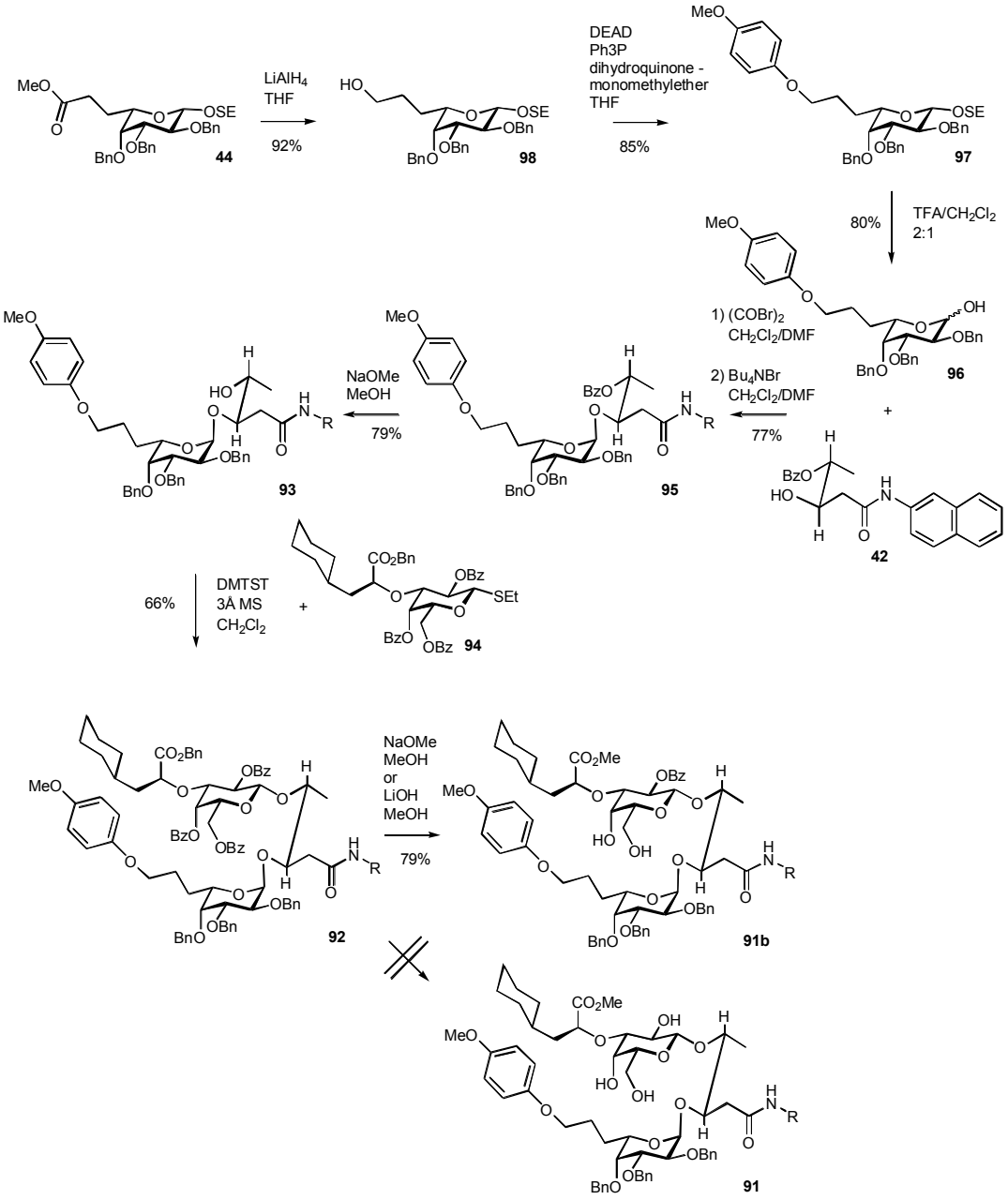
Reduction of **44** was performed with $LiAlH_4$ in dry THF (Scheme 19) [153,154]. Work-up of the reaction was simply carried out by addition of water and subsequent extraction of the aqueous layer with DCM yielding 95% of **98**. Protection of the primary alcohol was performed using the *Mitsunobu* coupling procedure [155,156,157]. The primary alcohol was activated with $PPh_3$ and DEAD and coupled with hyroquinone monomethylether in good yield (85%). In the next step, **97** was deprotected at the anomeric position with a TFA/DCM 2:1 mixture, yielding 85% of **96**.

*In situ* bromination of **96** led to the α-glycosyl bromide, which was coupled to **42** with very satisfactory yield (77%). We note of a substantial improvement of the yield in comparison with the reaction of **85** with **42** (44%). Furthermore, we did not observe the formation of an orthoester by-product. The benzoyl-protected secondary OH of the coupling product **95** was deprotected in dry MeOH by transesterification with cat. NaOMe to yield **93** (78%). The thioglycoside donor **92** was activated with DMTST and reacted with the acceptor **93** in dry DCM in the presence of molecular sieves 4Å. The β-glycosylation product **91** was obtained with moderate yield (58%). Attempts to remove the benzoate protection of **91** were not successful. Whereas, the 4- and 6- benzoates were readily cleaved under standard conditions (cat. NaOMe in MeOH) the Bz in the 2-position resisted deprotection. As a consequence, only the 2-protected product **91b** (79%) was obtained. Other reaction conditions were applied without success: NaOMe in MeOH with Microwave activation at various reaction times and temperatures, LiOH in MeOH and KO-*t*Bu [158] in MeOH/dioxane. In particular, NaOMe in MeOH with microwave activation lead to a cleavage of the benzylester without affecting the 2-OBz. Interestingly, when **50b** was highly diluted in a large quantity of toluene/MeOH 1:1 before NaOMe was added, we could achieve a deprotection of the Gal-2 position concurrently with a cleavage of the ester. However, reesterification with $CH_2N_2$ in THF only gave moderate yields.

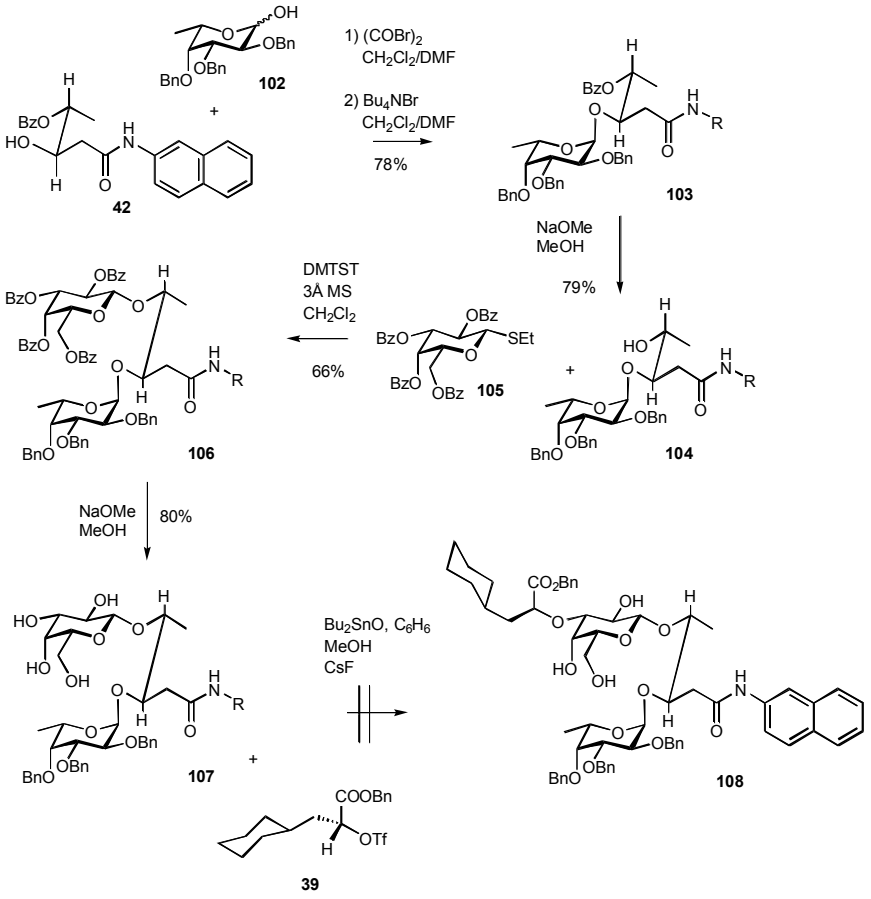
Based on these results. We attempted to selectively alkylate the Gal moiety subsequent to coupling and deprotection of the Gal. For this purpose, the test compound **107** was synthezised, in which the Fuc derivative **15** was replaced by L-fucose derivative **102** (Scheme 20). The naphtoyl derivative **42** was α-fucosylated in 78% with the *in-situ* anomerisation method. Product **103** was debenzoylated to give **104** and glycosylated with the thioethyl donor **105** by promotion with DMTST. Interestingly, Bz-deprotection of

**104** could readily be achieved. However, the selective coupling of the lactic acid moiety could not be achieved by tin acetal activation of the Gal-3-position.

In parallel with the attempts to solve the Gal-2-OBz cleavage problem, we investigated methods for the cleavage of hydroquinone monomethylether that was planed in the later steps of the synthesis. For this purpose, we attempted the cleavage on **92**. The poor yields (30%) obtained with the usual cleavage method using CAN [159] were however the best of all our attempts to carry out the cleavage. In particular reaction of **92** with DDQ [160] and microwave activation did not give satisfying results.




**Scheme 23**: Synthesis steps towards macrocycle **2** following the new pathway.




**Scheme 24**: Test compound with Fuc.

## III.5 Comments on some important steps

### III.5.1 Asymmetric dihydroxylation (AD)

Sharpless et al. improved the catalytic asymmetric dihydroxylation (AD) of olefins between 1988-1992 [120,161]. The research has led to two important discoveries:

- catalytic amounts of specific alkaloid ligands (Figure 26) in the reaction mixture complex $OsO_4$ and allow to steer the enantiomeric outcome;
- the presence of organic sulfonamides accelerates the osmate ester hydrolysis.

Taken together, these advances have led to a general procedure, which is applicable to a wide range of olefinic substrates: AD has reached a new level of experimental simplicity. The AD-mix formulation of the standards reactants was developed and simplifies performing the reaction on the milimolar scale. Only catalytic amounts of the ligand and the osmium tetroxide are required. These catalysts (0.6 % by weight) are blended into the bulk ingredients potassium ferricyanide and potassium carbonate (99.4% by weight) producing a yellow powder. This AD-mix is stable for months when protected from exposure to moisture.

***Reaction mechanism***

The Sharpless AD reaction owes its success to the presence of either of the two Cinchona alkaloid ligands: $(DHQD)_2$-PHAL in AD-mix-$\beta$ and $(DHQ)_2$-PHAL in AD-mix-$\alpha$. (Figure 26).

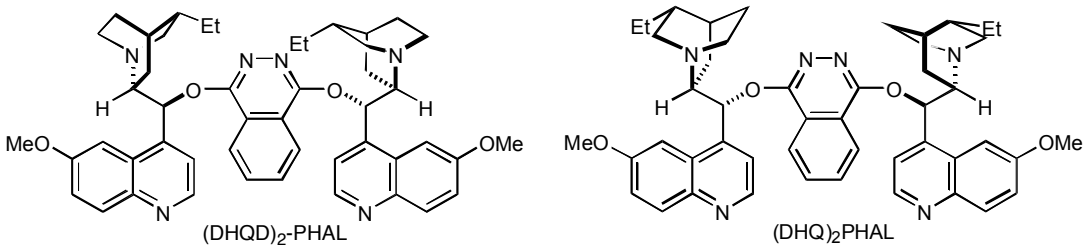
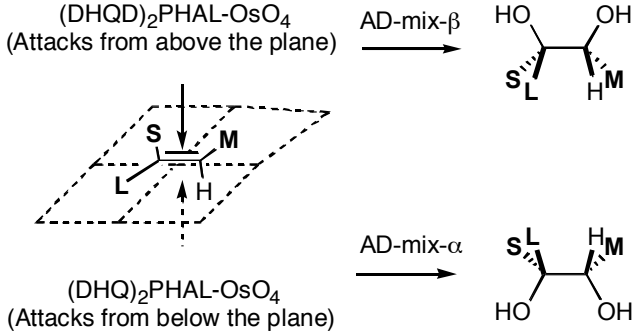


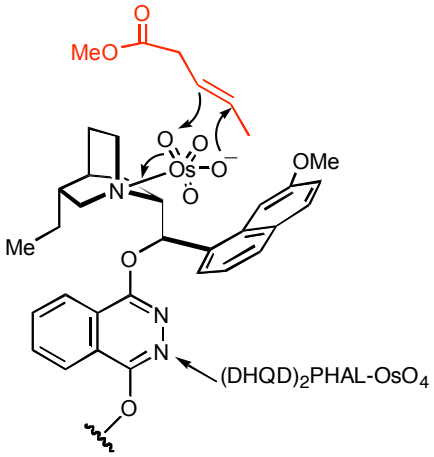

**Figure 26**: Two Cinchona alkaloid ligands: $(DHQD)_2$-PHAL, used in AD-mix-$\beta$ and $(DHQ)_2$-PHAL, used in AD-mix-$\alpha$.

The alkaloids complex $OsO_4$ via their quinuclidine nitrogens to form a pair of chiral oxidants that can enantioselectively dihydroxylate substituted alkenes. For 1,2-*trans*-disubstituted and trisubstituted alkenes, the enantioselectivity is usually very high. Sharpless has formulated a simple rule of predicting product stereochemistry in AD reactions. The choice between AD-mix-α or AD-mix-β is hence made in function of the desired outcome (Scheme 25). The designations L, M, and S refer to substituents that are large, medium and small, respectively. It is noteworthy that even though both oxidants are formally diastereoisomers, they still usually give enantiomeric products. For the vast majority of substitued *achiral* alkenes, the Sharpless AD face-selection rule works well.




**Scheme 25**: Sharpless rule for predicting product stereochemistry.

Corey et al. [162] and Sharpless et al. [121] both support an AD mechanism in which the alkene reversibly coordinates to ligand-bound $OsO_4$, prior to participating in an irreversible [3+2]-cycloaddition (Scheme 26).




**Scheme 26**: The asymmetric dihydroxylation (AD) mechanism.

***Methane sulfonamide***

Addition of methane sulfonamide to the reaction mixture is recommended for dihydroxylation of non-terminal olefins [120]. The sulfonamide effect is due to an enhanced rate of osmate-(VI) ester hydrolysis. Therefore, when osmate ester hydrolysis limits the turnover rate, the presence of methane sulfonamide leads to shorter reaction times, occasionally up to 50 times shorter. Due to this sulfonamide effect, most AD reactions can be run at 0°C.

As already stated in the synthesis description, elimination of methane sulfonamide by column chromatography on silica gel initially was a problem because the substance was not revealed with the classic TLC reagent (Mostaïne). However, with the 4-dimethlyaminocinnamaldehyde reagent the problem could be solved.

## III.5.2 NMR determination of the enantiomeric purity of lactone 62

Determination of the absolute configuration and enantiomeric purity of the substituted chiral lactone **(+)-62** was required for the synthesis of the Glc*N*Ac moiety replacement. Chiroptic methods could have been useful for determining the absolute conformations of lactone **62**, but these methods could not be applied to determinate the enantiomeric purity of the compound. X-ray structural analysis is valuable (in case of suitably crystalline materials), but time consuming and hence expensive.

We therefore used a NMR-based method [123,124] for simultaneously determining the enantioemeric purity of γ-lactones **(+)-62** and ***rac*-62**. Chiral solvating agents as aryltrifluoromethylcarbinol **109** (Figure 28 & 29).

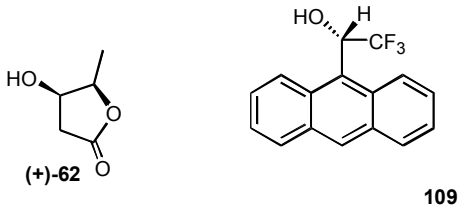
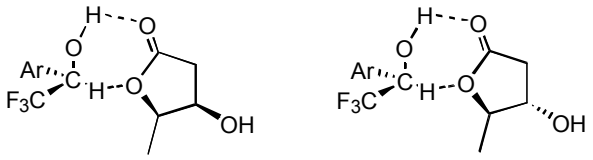



**Figure 28** : (*S*)-(+)-2,2,2-Trifluoro-1-(9-anthryl)ethanol **109**.



**complex (+)-62/109** **complex (-)-62/109**

**Figure 29**: The "two-point" interaction between chiral 2,2,2-trifluoro-1-(9-anthryl) ethanol **109** and the δ-lactone enantiomers is responsible for the nonequivalence of the NMR spectra of the enantiomers.

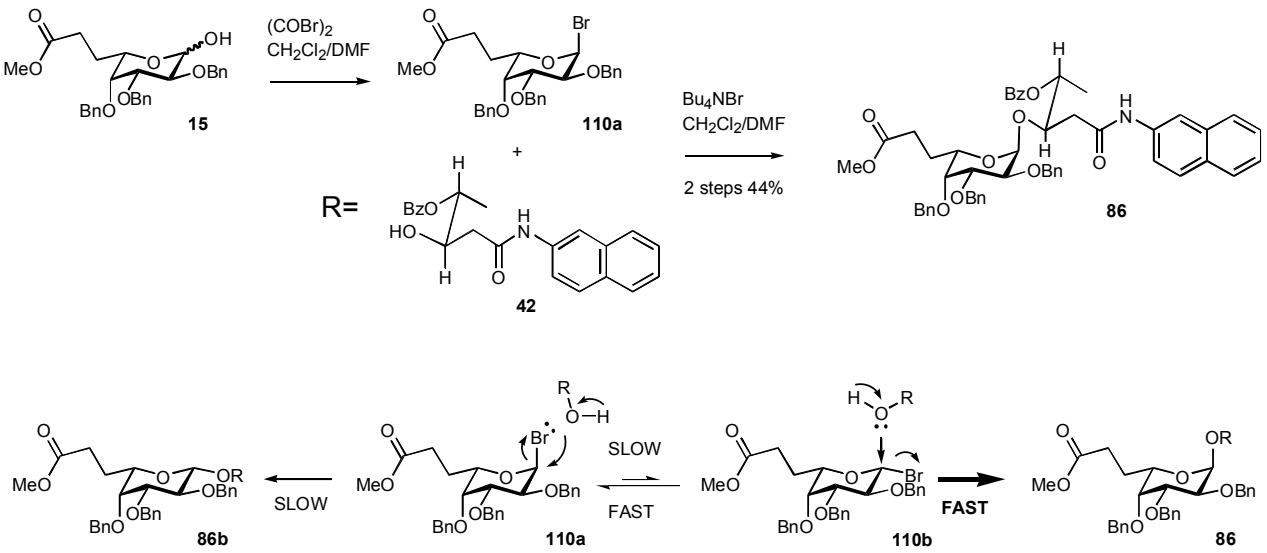
### III.5.3 *In situ* anomerisation

α-Selective glycosidation is a meaningful objective in carbohydrate chemistry. Many biologically active carry an α-glycoside linkage. However, α-glycosylation is not straightforward and requires optimization of the glycosyl donors, promoters, solvents, and other reaction conditions. In this respect, a halide ion-catalyzed α-glycosylation has provided one of the few definitive ways [141].

The introduction of 1,2-*cis* linkages requires glycosyl donors with a non-participating protecting group at the 2-position. An interesting approach for the synthesis of α-glucosides involves the direct nucleophilic substitution of a β-halide by a sugar hydroxyl. Such a reaction will give inversion of configuration at the anomeric centre resulting in the formation of the α-glycoside. However, most β-halides are very labile and difficult to prepare. As a consequence of the anomeric effect, which is particulary powerful in glycosyl halides, the α-anomer is favored.

A major breakthrough in α-glycosidic bond synthesis came with the introduction of the *in situ* anomerisation procedure invented by Lemieux et al. in 1975 [141]. A rapid equilibrium can be established between α- and β- halides by the addition of TBAB (Scheme 27). The anomerisation is believed to proceed through several intermediates. At equilibrium, there is a shift towards the α-bromide since this compound is stabilised by an endoanomeric effect. Because, the β-bromide is much more reactive towards nucleophilic attack by a nucleophile, than the more stable α-bromide, glycosylation leads preferentially to α-

glycosides. An important requirement for this reaction is that the rate of equilibration is much faster than the rate of glycosylation.



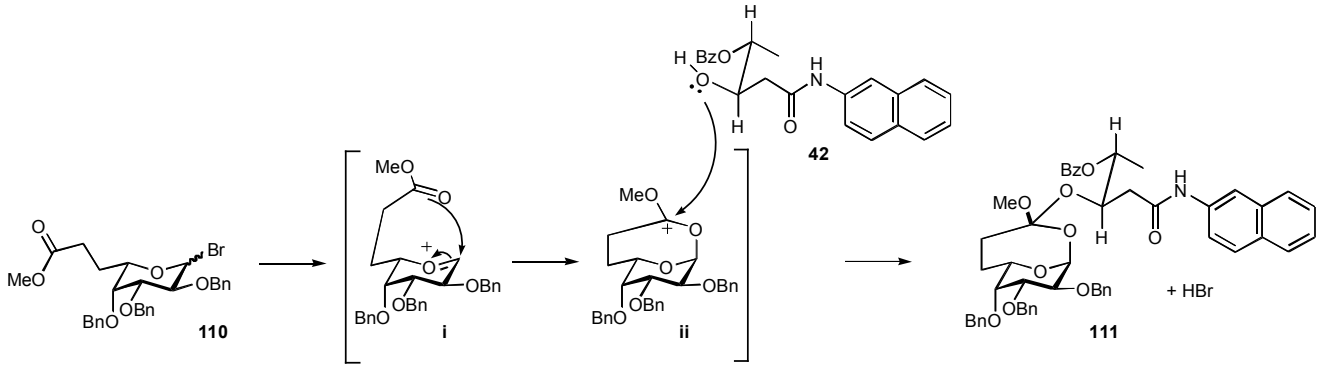

**Scheme 27**: *In situ* anomerisation occurring in the synthesis of **86**.

The anomeric outcome of the reaction can be discussed in more general mechanistic terms. First, the product ratio is governed by competing rates of formation of the α- and β-glycoside and therefore the glycosylation is kinetically controlled. Second, when two reactants are in fast equilibrium, the position of this equilibrium and therefore the reactant ratios will not determine the product ratio. The product ratio, however, will depend on the relative activation energies of the two reactants (α- and β- halide). In the case of the *in situ* anomerisation procedure, the activation energy for glycosylation of the β-anomer is significantly lower than for the α anomer and therefore the reaction proceeds mainly through the β anomer. The origin of the higher reactivity of β halides is disputed but follows similar arguments as the explanation of the kinetic anomeric effect. Probably, the α-anomer is less reactive because of ground-state stabilization by an endoanomeric effect. It is essential that the reaction be performed in a solvent of low polarity. In polar solvents, the reaction proceeds via an oxocarbenium ion and the anomeric selectivity is reduced. In our synthesis, the efficacy of the *in situ* anomerisation procedure was demonstrated by the condensation of a fucosyl bromide **110** issued from

**15** with glycosyl acceptor **42** in the presence of TBAB to give **86** as the $\alpha$-anomer (44%). As mentioned above, it is very important that the equilibration between the two ion pairs is faster than the glycosylation, and many parameters affect this requirement. Small changes in the constitution of the glycosyl donor or acceptor may have a dramatic effect on the stereochemical outcome of a glycosylation. In our case, the methylester sitting at the tail of the Fuc moiety of **15** was believed to interfere with the reaction process, leading to the relatively low yield observed for this reaction and to the building of the orthoester by-product **111** (see next Chapter).

### III.5.4 The orthoester 111 issue

In the glycosylation reaction with the glycosyl donor **110** and the acceptor **42**, the orthoester **111** was isolated as a by-product. The orthoester was formed by intramolecular reaction of the ester with cyclization of the Gal moiety and then by nucleophilic attack of the bromide **110** (Scheme 28).




**Scheme 28**: Presumed orthoester **111** formation.

We synthesized series of orthoesters with inexpensive test compounds (Experiments 39-43) [163]. These products were reacted in the microwave oven with different alcohols in the presence of the Lewis acid activator $HgBr_2$. We observed that the synthesized orthoesters could be readily opened in the microwave through nucleophilic attack by different alcohols. We applied the same opening conditions orthoester **111** in the presence of secondary alcohol **16**. The successful completion of this reaction was an interesting observation for three different reasons. Firstly, it gave us another solid proof

of the purported reaction mechanism of orthoester formation. Secondly, we were able to recover a certain amount of desired product **33** from the glycosylation by-product. Finally, we considered possible to carry out the glycosylation by selectively forming the orthoester and opening the latter using the previously described procedure. However, we did not succeed in the synthesis of the orthoester and abandoned the idea of a novel glycosylation method when we put the cost of the building blocks used in the attempts in relation with the low probability of success.

## III.6 Summary

Selectins are involved in the orderly migration of leukocytes from blood vessels to sites of inflammation. Although extravasation of leukocytes represents an essential defense mechanism against infection, excessive or inappropriate leukocyte accumulation results in injury to host tissues. Therefore, the development of selectin-antagonists is considered as an effective therapeutic approach in inflammatory and and other related disorders. Physiological selectin ligands contain a common tetrasaccharide epitope sialyl Lewis$^X$ **(1)** that serves as the lead structure in our search for E-selectin antagonists.

This work consists of attempts to synthesize sLe$^X$ analog **2**, which is aimed to explore the role of the spatial orientation of the pharmacophores in the bioactive conformation. The rigid macrocyclic core is thought to provide the basis for enhanced bioactivity due to a potentially high pre-organization of the functional groups involved in binding.

The building blocks for the synthesis of 2 have been L-galactose elongated at C-6 by Wittig olefination, D-talose alkylated at the 3-OH with (*S*)-cyclohexyl lactic acid and a Gal*N*Ac mimic.

We have succeeded in the synthesis of the building blocks required by the retrosynthesis of target molecule **2** with good to excellent yields (Figure 30). The core structures **79** and **91b** were synthesized as the results of two different synthetic pathways. These structures, as well as the building blocks **15** and **42** were not previously described in the literature.

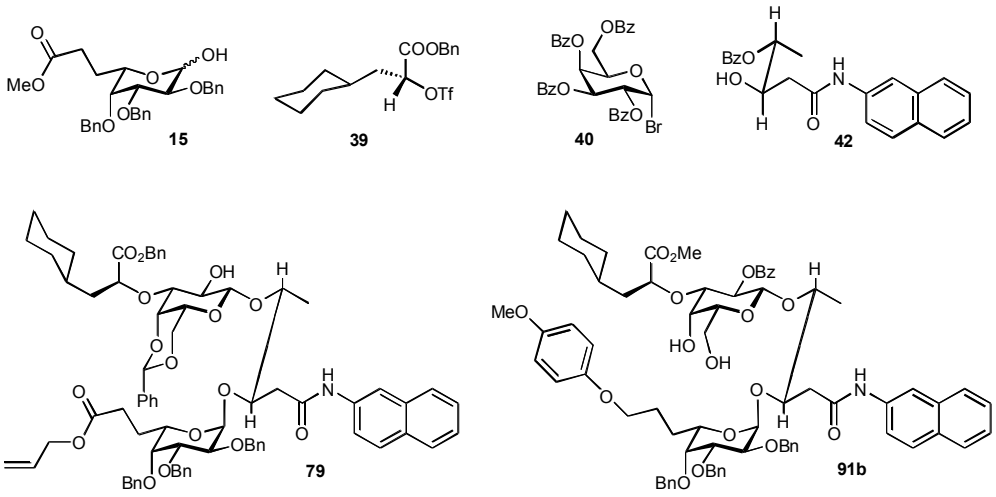



**Figure 30:** Structures that have been synthesized.

The targeted macrocycle could not be obtained due to major issues that occurred along two respective pathways:

In the first attempt (Chapter III.4.1), we encountered:

- low $\alpha$-glycosylation yields probably due to interactions with the methylester tail of the Fuc moiety in **15**;
- insufficient yields in the late introduction of the cyclohexyl lactic acid moiety in **80**.

These initial problems were successfully addressed in the second pathway. However, we faced new issues during this attempt (Chapter III.4.2):

- a satisfying method to deprotect the 2-OBz in the Gal moiety in **91b** could not be found;
- another method to obtain **91** proved to be unsuccessful;
- a satisfying method to cleave the *p*-methoxy-phenyl protecting group on our very sensitive compounds could not be found.

Despite major efforts to overcome these hurdles, a satisfying solution was not accessible in the available time period of this work.

## III.7 Conclusion

The high number of publications [17,44] on the development of selectin antagonists shows that the disruption of the initial step in the inflammatory cascade is viable approach to search for novel therapeutics. However, none of the sialyl Lewis$^X$ **(1)** mimics synthesized to date have been developed into an approved drug.

The inherent low affinity of sLe$^X$ **(1)** for the selectins is required by the role it plays in the rolling process, which suggests that the binding site has evolved to optimize the specificity and the weakness to the interactions with sLe$^X$ **(1)**. Moreover, carbohydrates are generally prone to rapid metabolism and elimination.

It is thus reasonable to assume that the development of high-affinity antagonists for a binding site that has been evolved for weak interactions with a readily degradable ligand is more difficult than the traditional drug target

In planning the synthesis of **2**, our approach was thought more as a proof of concept than as the direct development of a therapeutic compound. Activity studies of target molecule **2** would have provided an important contribution to the validation of our predictions based on pre-organization determined by molecular modeling.

We strongly hope that the synthesis of the major building blocks towards **2**, as well as the experience collected along the two attempted pathways will provide the basis for the successful syntheses of related compounds.

# IV. Experimental part

## IV.1 General methods

***Optical rotation***

Optical rotations were measured with a Perkin-Elmer *241* polarimeter. Na-D optical rotations were extrapolated from the measured Hg values (546 and 578 nm) with the help of Drude's equation [167]:

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

$\alpha$ = Measured optical rotation

c = Concentration in g/100 ml

d = Recipient length in dm

T = Temperature in °C

$\lambda$ = Wavelength in nm

The solvents used for the measurements were $CH_3Cl$ p.a. (Fluka) and MeOH p.a. (Fluka).

***Infrared spectroscopy (IR)***

Infrared spectra were recorded with a Perkin-Elmer *Spectra One* FT-IR Spectrometer.

***Nuclear Magnetic Resonance Spectroscopy (NMR)***

Proton ($^1$H NMR) and carbon-13 ($^{13}$C NMR) nuclear magnetic resonance spectra were recorded on a Bruker *UltraShield™ Supraconducting NMR 500/70B* spectrometer.

$^1$H NMR spectra were recorded at 500.1 MHz and $^{13}$C NMR spectra were recorded at 125.8 MHz in $CDCl_3$, MeOD or $D_2O$. Chemical shifts are given in $\delta$ units, parts per million (ppm) downfield from tetramethylsilane (TMS).

Values for **$CDCl_3$** [168]**:** **$^1$H NMR: 7.26** **$^{13}$C NMR: 77.16 +/- 0.06**

Values for **$CD_3OD$** [168]**:** **$^1$H NMR: 3.31** **$^{13}$C NMR: 49.00 +/- 0.01**

***Elementary analyses***

Elementary analyses were performed at the Institute of Organic Chemistry (University of Basel, Switzerland).

***Thin Layer Chromatography (TLC)***

Reactions were monitored by TLC using glass plates coated with silica gel 60 F254 (Merck). The spots were detected under short wavelength UV light (254 nm) or charring with Mostain, a molybdate solution (a 0.02 M solution of ceric ammonium sulfate and ammonium molybdate tetrahydrate in aqueous 10% $H_2SO_4$. The plates were then heated for 2 min at 155°C.

***Filtration and chromatography***

Flash chromatography was performed with 200-400 mesh silica gel 60 under argon or air pressure. Thin layer chromatography was used to monitor column fractions. [Still, 1978 #8]

***Hydrogenations***

Hydrogenations under pressure were performed in a protected mixing device from Parr Instrument Company, (Moline, IL, USA) in 250 mL bottles.

***Solvents***

Absolute solvents like $CH_2Cl_2$ and $CH_3CN$ were prepared by filtration over basic aluminium oxide (Fluka, type 5016 A basic).

Absolute solvents like THF, MeOH and dioxane were dried by refluxing with sodium and distilled immediately before use.

Pyridine was freshly distilled under argon in the presence of $CaH_2$.

## IV.2 Synthesis

### IV.2.1 L-Gal building block 15

***Experiment 1: MAR-69 / I***

**Penta-*O*-acetyl-α-L-galactopyranose (50):** $Ac_2O$ (15.0 mL, 159 mmol) was added slowly to a mixture of L-galactose **(43)** (5.00 g, 27.8 mmol) in freshly distilled pyridine (75 mL) and stirred at -16°C for 7 days under argon. Evaporation of the solvents at $10^{-3}$ Torr gave an oil, which was diluted with EtOAc (120 mL) and washed with 10% aqueous NaCl (2 x 45 mL), saturated $NaHCO_3$ (50 mL), $H_2O$ (50 mL) and 0.5 M $CuSO_4$ (3 x 35 mL). The organic layer was dried with $Na_2SO_4$, filtered, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 2:1) yielding **50** as an oil (8.12 g, 75%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 2.00-2.16 (m, 15 H, 5 C*H*$_3$), 4.09 (m, 2 H, H-6), 4.34 (m, 1 H, H-5), 5.33 (m, 2 H, H-2, H-3), 5.51 (d, $^3J_{3,4}$ = 1.2 Hz, 1 H, H-4), 6.37 (d, $^3J_{1,2}$ = 1.5 Hz, 1 H, H-1);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 20.7, 20.8, 21.0 (5 C, 5 *C*$H_3$), 61.4 (C-6), 66.6, 67.4, 67.5 (3 C, C-2, C-3, C-4), 68.9 (C-5), 89.8 (C-1), 170.3 (5 C, 5 CO).

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{16}H_{22}O_{11}$ | calculated | C 49.23 | H 5.68 |
| (390.34) | found | C 48.87 | H 5.55 |

***Experiment 2: MAR-109***

**2,3,4,6-Tetra-*O*-acetyl-L-galactopyranose (51):** AcOH (2.84 g, 47.1 mmol) was added to a solution of EDA (2.43 g, 40.3 mmol) in THF (492 mL) at 25°C under argon to give a white suspension. **50** (13.1 g, 33.6 mmol) was added to the mixture which was stirred for 19 h at 25°C under argon. $H_2O$ (300 mL) was then added and the mixture was extracted with $CH_2Cl_2$ (5 x 75 mL). The combined organic layers were washed with aqueous HCl 5 % (200mL) and saturated $NaHCO_3$ solution (300 ml), dried with $Na_2SO_4$ and concentrated to give 12.2 g of crude product. The crude product was purified by column

chromatography on silica gel (petroleum ether-EtOAc 3:2) to yield **51** (α/β 81:19) as an oily syrup (10.4 g, 89%).

**$^1$H NMR (500.1 MHz, $CDCl_3$)** of the mixture **51**α /**51**β (81:19):

**51**α**:** δ3.65 (d, 1 H, OH), 4.06-4.16 (m, 2 H, H-6), 4.45 (m, 1 H, H-5), 5.16 (dd, $^3J_{1,2}$ = 3.5, $^3J_{2,3}$ = 10.8 Hz , 1 H, H-2), 5.41 (m, 1 H, H-3), 5.47 (dd, $^3J_{3,4}$ = 3.3, $^3J_{4,5}$ =1.1 Hz, H-4), 5.52 (m, 1 H, H-1); **51**β**:** δ 3.14 (d, 1 H, OH), 3.96 (m, 1 H, H-5), 4.06-4.16 (m, 2 H, H-6), 4.69 (m, 1 H, H-1), 5.06 (m, 1 H, H-2), 5.07 (m, 1 H, H-3), 5.41 (m, 1 H, H-4);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$)** of the mixture **51**α /**51**β (81:19):

**51**α**:** δ 20.7, 20.8 (4 C, 4 *C*$H_3$), 62.0 (C-6), 66.5 (C-5), 67.3 (C-3), 68.3, 68.4 (2 C, C-2, C-4), 90.9 (C-1), 170.2 (4 C, 4 *C*O);**51**β**:** δ 20.7, 20.8 (4 C, 4 *C*$H_3$), 62.0 (C-6), 67.2 (C-4), 70.3 (2 C, C-2, C-3), 71.2 (C-5), 96.2 (C-1), 170.2 (4 C, 4 *C*O).

**$[\alpha]_D^{20}$ =** - 73.6 ( c = 1.01, $CHCl_3$, **51**α /**51**β 81:19)

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{14}$ $H_{20}$ $O_{10}$ | calculated | C 48.28 | H 5.79 |
| (348.31) | found | C 48.46 | H 5.77 |

***Experiment 3: MAR-117***

**2,3,4,6-Tetra-*O*-acetyl-L-galactopyranosyl-1-trichloroacetimidate (49):** $Cs_2CO_3$ (1.08 g, 3.33 mmol) and $CCl_3CN$ (16.7 mL, 166 mmol) were added to a solution of **51** (11.6 g, 33.3 mmol) in dry $CH_2Cl_2$ (140 mL) under argon. After stirring at 25°C for 24 h, the solution was filtered through Celite and washed with $CH_2Cl_2$ (50 mL). The filtrate was dried with $Na_2SO_4$, evaporated and then dried at $10^{-3}$ Torr to yield a mixture of the two isomeres (α/β 2:1). The crude product (16.1 g, 98%) was used without further purification in the next step.

**$^1$H NMR (500 MHz, $CDCl_3$)** of the mixture **49**α /**49**β (2:1):

**49**α**:** δ 2.00-2.16 (m, 12 H, 4 C*H*$_3$), 4.05-4.17 (m, 2 H, H-6), 4.42 (m, 1 H, H-5), 5.33-5.42 (m, 2 H, H-2, H-3), 5.54 (m, 1 H, H-4), 6.58 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1), 8.66 (s, 1 H,

N*H*); **49**β**:** δ 2.00-2.04 (m, 12 H, 4 C*H*$_3$), 4.11 (m, 1 H, H-5), 4.19 (m, 2 H, H-6), 5.12 (dd, $^3J_{2,3}$ = 10.4, $^3J_{3,4}$ = 3.5 Hz, 1 H, H-3), 5.46 (m, 1 H, H-4), 5.49 (dd, $^3J_{1,2}$ = 8.3, $^3J_{2,3}$ = 10.4 Hz ,1 H, H-2), 5.83 (d, $^3J_{1,2}$ = 8.3 Hz, 1 H, H-1), 8.71 (s, 1 H, N*H*).

**[**α**]$_D^{20}$ =** - 103.1 ( c = 1.02, $CHCl_3$, **49**α**/49**β 2:1)

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{16}H_{20}Cl_{13}NO_{10}$ | calculated | C 39.01 | H 4.09 | N 2.84 |
| (492.69) | found | C 38.35 | H 4.10 | N 2.54 |

***Experiment 4: MAR-122***

**2-(Trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-**β**-L-galactopyranoside (48):** To a solution of crude **49** (16.1 g, 32.6 mmol) in dry $CH_2Cl_2$ (220 mL) were added molecular sieves 3Å (5 g) and TMSEt (4.24 g, 35.8 mmol) under argon. The mixture was stirred at 25°C for 30 min and then cooled to –20°C. TMSOTf (0.65 mL, 3.26 mmol) was added dropwise within 1 min with a syringe. After stirring for 1 h at –20°C, pyridine (1.7 mL) was added to the mixture and stirring continued for 5 min at this temperature. The mixture was warmed to 25°C, filtered trough Celite, and washed with $CH_2Cl_2$ (2 x 20mL). Concentration of the filtrate afforded a crude residue, which was purified by column chromatography on silica gel (petroleum ether-EtOAc 3:1) yielding **48** (14.2 g, 98%) as a white solid.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.86-1.00 (m, 2 H, H-2'), 1.96, 2.02, 2.03, 2.13 (4 s, 12 H, 4 C*H*$_3$), 3.52 (m, 1 H, H-1'a), 3.89 (m, 1 H, H-5), 3.97 (m, 1 H, H-1'b), 4.10 (dd, $^3J_{5,6a}$ = 7.1, $^3J_{6a,6b}$ = 11.2 Hz, 1 H, H-6a), 4.18 (dd, $^3J_{5,6b}$ = 6.4, $^3J_{6a,6b}$ = 11.2 Hz, 1 H, H-6b), 4.47 (m, $^3J_{1,2}$ = 8.0, 1 H, H-1), 4.99 (dd, $^3J_{2,3}$ = 10.4, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3), 5.17 (dd, $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 10.4 Hz, 1 H, H-2), 5.36 (m, 1 H, H-4);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.1 (C-2'), 20.7, 20.8, 20.9 (4 C, 4 *C*$H_3$), 61.4 (C-6), 67.2 (C-4), 67.7 (C-1'), 69.1 (C-2), 70.6 (C-5), 71.2 (C-3), 100.8 (C-1), 169.5, 170.3, 170.5, 170.6 (4 C, 4 *C*O).

***Experiment 5: MAR-125***

**2-(Trimethylsilyl)ethyl β-L-galactopyranoside (52):** 1 M NaOMe in MeOH (0.8 mL) was added to a solution of **48** (14.2 g, 31.8 mmol) in MeOH (80 mL) under argon until the solution reached pH 10. The mixture was stirred for 2 h at 25°C, the pH of the solution was then adjusted to pH 7 by addition of Amberlyst 15 ion exchange resin. The suspension was filtered through Celite, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 1:5) yielding **52** (6.21 g, 70 %).

**$^1$H NMR (500.1 MHz, $CD_3OD$):** δ 1.01 (m, 2 H, H-2'), 3.47 (m, 3 H, H-2, H-3, H-5), 3.62 (m, 1 H, H-1'), 3.73 (m, 2 H, H-6), 3.82 (m, 1 H, H-4), 4.01 (m, 1 H, H-1'b), 4.22 (d, $^3J_{1,2}$ = 7.4 Hz, 1 H, H-1);

**$^{13}$C NMR (125.8 MHz, $CD_3OD$):** δ 19.1 (C-2'), 62.5 (C-6), 68.0 (C-1'), 70.3 (C-4), 72.6, 75.1, 76.6 (3 C, C-2, C-3, C-5), 104.5 (C-1).

***Experiment 6: MAR-131***

**2-(Trimethylsilyl)ethyl 6-*O*-trityl-β-L-galactopyranoside (53):** $Ph_3CCl$ (9.73 g, 34.9 mmol) and DMAP (0.46 g, 3.8 mmol) were added at 25°C to a solution of **52** (6.21 g, 24.9 mmol) in pyridine (25 mL) under argon. The mixture was stirred for 4 h. Additional $Ph_3CCl$ (3.50 g, 12.6 mmol) and DMAP (0.16 g, 1.3 mmol) were added to the reaction, which was stirred for another 12 h. The mixture was diluted with $CH_2Cl_2$ (200 mL) and washed with 10 % aqueous NaCl (90 mL). The aqueous layer was washed with EtOAc (2 x 60 mL). The combined organic phases were washed with 1M $KH_2PO_4$ (60 mL) and brine (2 x 60mL), dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc 2:1) yielding **53** (8.33 g, 72%) as an oily product.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.01 (m, 2 H, H-2'), 2.37, 2.56, 2.74 (4 s, 4 H, 4 OH), 3.35 (dd, $^3J_{5,6a}$ = 5.7, $^3J_{6a,6b}$ = 9.6 Hz, 1 H, H-6a), 3.44 (dd, $^3J_{5,6b}$ = 5.7, $^3J_{6a,6b}$ = 9.6 Hz, 1 H, H-6b), 3.58 (m, 4 H, H-2, H-4, H-5, H-1'a), 4.01 (m, 2 H, H-3, H-1'b), 4.22 (d, $^3J_{1,2}$ = 7.2 Hz, 1 H, H-1), 7.45-7.21 (m, 15 H, 3 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.4 (C-2'), 62.7 (C-6), 67.4 (C-1'), 69.3 (C-3), 72.5, 73.7, 73.8 (3 C, C-2, C-4, C-5), 87.1 (*C*$Ph_3$), 103.8 (C-1), 127.3, 143.8 (18 C, 3 $C_6H_5$).

**$[\alpha]_D^{20}$ =** + 36.0 ( c = 0.49, $CHCl_3$, **53**)

***Experiment 7: MAR-132***

**2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-L-galactopyranoside (54):** NaH (2.60 g of a 55% powder in oil, 66.1 mmol) was added to a solution of **53** (8.27 g, 15.8 mmol) in dry DMF (38 mL) under argon and the mixture was stirred for 5 min. BnBr (10.2 g, 7.05 mL, 59.3 mmol) was slowly added to the suspension and the inner temperature was maintained with an ice bath between 25°C and 30°C during the exothermic reaction. The mixture was stirred for 3 h at 25°C. Thiourea was then added to the mixture causing a strong gas emission. After stirring for another 30 min, 1M $KH_2PO_4$ (100 mL) was added to the suspension and the mixture was diluted with EtOAc (100 mL). The aqueous layer was washed with EtOAc (3 x 100mL). The combined organic phases were washed with brine (3 x 100mL), dried with $Na_2SO_4$, concentrated *in vacuo* and purified by column chromatography (petroleum ether-EtOAc 20:1) yielding **54** (11.2 g, 96 %) as an oil.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.01 (m, 2 H, H-2'), 3.19 (dd, $^3J_{5,6a}$ = 7.0, $^3J_{6a,6b}$ = 9.2 Hz, 1 H, H-6a), 3.36 (m, 1 H, H-5), 3.48 (m, 2 H, 3-H, H-6b), 3.56 (m, 1 H, H-1'a), 3.76 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 3.85 (m, 1 H, H-4), 4.00 (m, 1H, H-1'b), 4.31 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.47-4.93 (m, 6 H, 3 $CH_2$Ph), 7.10-7.40 (m, 30 H, 6 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.6 (C-2'), 62.9 (C-6), 67.4 (C-1'), 73.2-75.3 (5 C, 3 $CH_2$Ph, C-4, C-5), 79.9 (*C*$Ph_3$), 82.4 (C-2), 87.0 (C-3), 103.6 (C-1), 127.2, 127.3, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3,128.4, 128.5, 128.8, 138.8, 140.1, 144.1 (36 C, 6 $C_6H_5$).

**$[\alpha]_D^{20}$ =** + 3.2 ( c = 1.02, $CHCl_3$, **54**)

***Experiment 8: MAR-133***

**2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-β-L-galactopyranoside (47):** To a solution of **54** (11.2 g, 14.1 mmol) in $CH_2Cl_2$ (250 mL) was added aqueous TFA 80% (11.3 mL). The mixture was stirred for 5 min at 25°C. $H_2O$ (5.5 mL) was added and the mixture was stirred for another 5 min. The yellow mixture was neutralized with saturated aqueous $NaHCO_3$ solution (80 mL) and the aqueous layer extracted with $CH_2Cl_2$ (3 x 80 mL). The combined organic phases were washed with $H_2O$ (100 mL), dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 4:1) yielding **47** (7.33 g, 94%) as an oil.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.03 (m, 2 H, H-2'), 3.37 (m, 1 H, H-5), 3.49 (m, 1 H, H-6a), 3.53 (m, 1 H, H-3), 3.57 (m, 1 H, H-1'a), 3.76 (m, 2 H, H-4, H-6b), 3.83 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 4.00 (m, 1 H, H-1'b), 4.37 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 4.66, 4.78 (A of AB, $^2J$= 11.9 Hz, 2 H, C$H_2$Ph), 4.74, 4.81 (B of AB, $^2J$= 11.8 Hz, 2 H, C$H_2$Ph), 4.95-4.97 (m, 2 H, 2 $CH_2$Ph), 7.26-7.38 (m, 15 H, 3 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.5 (C-2'), 62.0 (C-6), 67.5 (C-1'), 72.8 (C-4), 73.3, 74.0, 74.4, 75.2 (4 C, C-5, 3 $CH_2$Ph), 79.7 (C-2), 82.3 (C-3), 103.5 (C-1), 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.6, 138.2, 138.7, 138.8 (18 C, 3 $C_6H_5$).

**$[\alpha]_D^{20}$ =** + 20.0 (c = 0.49, $CHCl_3$, **47**)

***Experiment 9: MAR-134 first step***

**2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-β-L-*galacto*-hexo-1,6-dialdo-1,5-pyranoside (46):** Under argon, DMSO (2.91 g, 2.65 mL, 37.3 mmol) was added to a solution of oxalyl chloride (2.37 g, 1.60 mL, 18.7 mmol) in dry $CH_2Cl_2$ (25 mL) at –78°C and stirred for 5 min. A solution of **47** (7.33 g, 13.3 mmol) in dry $CH_2Cl_2$ (12 mL) was added to the mixture. After stirring for 15 min at –78°C, $Et_3N$ (4.04 g, 5.57 mL, 39.9 mmol) was added to the stirred mixture which was then warmed up to 25°C within 30 min. The reaction was quenched with saturated aqueous $NH_4Cl$ (50 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 60 mL). The combined organic phases were dried with $Na_2SO_4$ and concentrated. The residue **46** (7.7 g) was dried for 1 h at $10^{-3}$ Torr and directly used in the next step.

***Experiment 10: MAR-134***

**Methyl [2-(Trimethylsilyl)ethyl tri-2,3,4-*O*-benzyl-6,7-dideoxy-6,7-en-β-L-*galacto*-octopyranoside]uronate (45a/45b):** A cold (-20°C) solution of $Ph_3PCHCOOMe$ (6.68 g, 20.0 mmol) in dry $CH_2Cl_2$ (24 mL) was added within 20 min to a solution of crude **46** (7.7 g) in dry $CH_2Cl_2$ (45 mL) at –20°C under argon. After stirring for 2 h at this temperature, a solution of $Ph_3PCHCOOMe$ (0.89 g, 2.7 mmol) in dry $CH_2Cl_2$ (3 mL) was added to the mixture which was stirred for another 1 h at –20°C. The mixture was filtered through Celite and washed with petroleum ether-EtOAc 2:1 (80 mL). The filtrate was dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 8:1) yielding trans isomer **45a** (5.68 g, 73 %) and cis isomer **45b** (1.48 g, 18 %) as oils.

**(*E*)-Methyl [2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6,7-en-β-L-*galacto*-octopyranoside]uronate (45a):**

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.02 (m, 2 H, H-2'), 3.55 (m, 1H, H-1'a), 3.64 (dd, $^3J_{2,3}$ = 9.8, $^3J_{3,4}$ = 2.9 Hz, 1 H, H-3), 3.66 (s, 3 H, *CH*$_3$), 3.83 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.8 Hz, 1 H, H-2), 4.00 (m, 1 H, H-1'b), 4.08 (dd, $^3J_{3,4}$ = 2.9, $^3J_{4,5}$ = 0.1 Hz, 1 H, H-4), 4.39 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.55, 4.85 (A,B of AB, $^2J$ = 11.8 Hz, 2 H, C*H*$_2$Ph), 4.73, 4.79 (A,B of AB, $^2J$ = 11.7 Hz, 2 H, C*H*$_2$Ph), 4.78, 4.94 (A,B of AB, $^2J$ = 11.0 Hz, 2 H, C*H*$_2$Ph), 4.89 (m, 1 H, H-5), 5.69 (d, $^3J_{6,7}$ = 11.7 Hz 1 H, H-7), 6.36 (dd, $^3J_{5,6}$ = 6.8, $^3J_{6,7}$ = 11.7 Hz, 1 H, H-6), 7.21-7.37 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 19.9 (C-2'), 53.0 (*C*H$_3$), 68.8 (C-1'), 74.6 (C*H*$_2$Ph), 74.8 (C-4), 75.6, 76.4 (2 C*H*$_2$Ph), 76.6 (C-5), 80.7 (C-2), 83.3 (C-3), 104.8 (C-1), 123.2 (C-7), 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.5, 129.0, 137.9, 138.3, 138.7 (18 C, 3 *C*$_6$H$_5$), 145.6 (C-6), 168.0 (*C*O).

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{35}H_{44}O_7Si$ | calculated | C 69.51 | H 7.33 |
| (604.81) | found | C 69.47 | H 7.31 |

**$[\alpha]_D^{20}$ =** + 78.0 (c = 0.98, $CHCl_3$, **45a**)

**(*Z*)-Methyl [2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6,7-en-β-L-*galacto*-octopyranoside]uronate (45b):**

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.02 (m, 2 H, H-2'), 3.52 (dd, $^3J_{2,3}$ = 9.7, $^3J_{3,4}$ = 2.9 Hz, 1 H, H-3), 3.57 (m, 1 H, H-1'a), 3.74 (m, 4 H, H-4, C$H_3$), 3.83 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 3.94 (m, 1 H, H-5), 4.08 (m, 1 H, H-1'b), 4.38 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.65, 4.81 (A,B of AB, $^2J$ = 12.0 Hz, 2 H, C$H_2$Ph), 4.67, 4.72 (A,B of AB, $^2J$ = 11.9 Hz, 2 H, C$H_2$Ph), 4.76, 4.93 (A,B of AB, $^2J$ = 10.9 Hz, 2 H, C$H_2$Ph), 6.09 (dd, $^4J_{5,7}$ =1.9, $^3J_{6,7}$ = 15.7 Hz, H-7), 6.73 (dd, $^3J_{5,6}$ = 4.1, $^3J_{6,7}$ = 15.7 Hz, 1 H, H-6), 7.37-7.21 (m, 15 H, 3 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.4 (C-2'), 51.5 (*C*$H_3$), 67.3 (C-1'), 73.1 (*C*$H_2$Ph), 73.3 (C-4), 74.1, 74.9 (2 *C*$H_2$Ph), 73.6 (C-5), 77.7 (C-2), 81.8 (C-3), 103.3 (C-1), 121.7 (C-7), 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.5, 137.9, 138.3, 138.7 (18 C, 3 *C*$_6$H$_5$), 144.1 (C-6), 166.6 (*C*O).

***Experiment 11: MAR-135***

**Methyl [2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-β-L-*galacto*-octopyranoside]uronate (44):** Compound **45** (7.32 g, 12.1 mmol) was dissolved in dry degased MeOH (110 mL) and hydrogenated at 25°C and 4 bar $H_2$ in the presence of 10 % Pd-C (170 mg, 0.73 mmol) for 3h. The mixture was filtered trough Celite and the filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 9:1) yielding **44** (6.36 g, 86 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.01 (m, 2 H, H-2'), 1.62 (m, 1 H, H-6a), 2.08 (m, 1 H, H-6b), 2.30 (m, 2 H, H-7), 3.27 (m, 1 H, H-5), 3.48 (m, $^3J_{2,3}$ = 9.7, $^3J_{3,4}$ = 2.9 Hz, 1 H, H-3), 3.54 (m 1 H, H-1'a), 3.63 (s, 3 H, C$H_3$), 3.78 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 3.97 (m, 1 H, H-1'b), 4.27 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.66, 4.96 (A,B of AB, $^2J$ = 11.7 Hz, 2 H, C$H_2$Ph), 4.71, 4.78 (A,B of AB, $^2J$ = 11.9 Hz, 2 H, C$H_2$Ph), 4.75, 4.93 (A,B of AB, $^2J$ = 11.1 Hz, 2 H, C$H_2$Ph), 7.23-7.37 (m, 15 H, 3 $C_6H_5$).

**$[\alpha]_D^{20}$ =** - 18.8 ( c = 1.02, $CHCl_3$, **44**)

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{34}$ $H_{46}$ $O_7$ Si | calculated | C 69.27 | H 7.64 |
| (606.82) | found | C 69.38 | H 7.72 |

***Experiment 12: MAR-179***

**Methyl [2,3,4-tri-*O*-benzyl-6,7-dideoxy-L-*galacto*-octopyranose]uronate (15):** TFA (16.5 mL) was added dropwise within 15 min to a solution of **44** (1.00 g, 1.65 mmol) in $CH_2Cl_2$ (8.3 mL) under argon at 0°C to give a yellow solution. The mixture was stirred for 30 min at 0°C. The mixture was diluted with toluene (150 mL) and EtOAc (50 mL), concentrated and purified by column chromatography on silica gel (toluene-EtOAc 4:1) yielding **15** (0.83 mg, 99 %, **15**α/**15**β 64:36).

**$^1$H NMR (500.1 MHz, $CDCl_3$)** of mixture **15**α/**15**β (64:36):

**15**α**:** δ 1.62-1.68 (m, 1 H, H-6a), 1.95-2.08 (m, 1 H, H-6b), 2.22-2.35 (m, 2 H, H-7), 3.63 (s, 3 H, C*H*$_3$), 3.75 (m, 1 H, H-4), 3.89 (m, 2 H, H-3, H-5), 4.03 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 9.9 Hz, 1 H, H-2), 4.65 (A of AB, $^2J$ = 11.6 Hz, 1 H, C*H*$_2$Ph), 4.71 (A of AB, $^2J$ = 11.8 Hz, 1 H, C*H*$_2$Ph), 4.75-4.82 (m, 2 H, C*H*$_2$Ph), 4.83 (B of AB, $^2J$ = 11.7 Hz, 1 H, C*H*$_2$Ph), 4.97 (B of AB, $^2J$ = 11.5 Hz, 1 H, C*H*$_2$Ph), 5.24 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, H-1), 7.24-7.40 (m, 15 H, 3 C$_6$*H*$_5$); **15**β**:** δ 1.62-1.68 (m, 1 H, H-6a), 1.95-2.08 (m, 1 H, H-6b), 2.22-2.35 (m, 2 H, H-7), 3.37 (m, 1 H, H-5), 3.53 (dd, $^3J_{2,3}$ = 9.6, $^3J_{3,4}$ = 2.8 Hz, 1 H, H-3), 3.63 (s, 3 H, C*H*$_3$), 3.66 (m, 1 H, H-4), 3.75 (m, 1 H, H-2), 4.58 (d, $^3J_{1,2}$ = 7.5 Hz, 1 H, H-1), 4.67 (A of AB, $^2J$ = 11.6 Hz, 1 H, C*H*$_2$Ph), 4.73-4.83 (m, 3 H, C*H*$_2$Ph), 4.92 (B of AB, $^2J$ = 11.1 Hz, 1 H, C*H*$_2$Ph), 4.99 (B of AB, $^2J$ = 11.6 Hz, 1 H, C*H*$_2$Ph), 7.24-7.40 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$)** of mixture **15**α/**15**β (64:36):

**15**α**:** δ 26.1 (C-7), 30.2 (C-6), 51.6 (*C*H$_3$), 73.2, 74.5, 75.0, 75.3, 76.6 (5 C, C-4, C-5, 3 *C*H$_2$Ph), 79.1 (C-2), 82.5 (C-3), 91.7 (C-1), 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 138.2, 138.4, 138.6 (18 C, 3 *C*$_6$H$_5$), 173.9 (*C*O); **15**β**:** δ 26.2 (C-7), 29.9 (C-6), 51.6 (*C*H$_3$), 69.5, 73.1, 73.5, 74.6, 76.2 (6 C, C-3, C-4, C-5, 3 *C*H$_2$Ph), 80.8 (C-2), 97.8 (C-1), 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 138.2, 138.4, 138.6 (18 C, 3 *C*$_6$H$_5$), 173.9 (*C*O).

**[α]$_D^{20}$ =** + 56.7 ( c = 1.02, $CHCl_3$, **15**α**/15**β 64:36)

## IV.2.2 Gal*N*Ac mimic 42

***Experiment 13: MAR-158***

**2-Naphtylamine (61):** To a mixture of $NH_2OH{\cdot}HCl$ (6.8 g, 98 mmol) and β-naphtoic acid (16.0 g, 92.9 mmol) was added polyphosphoric acid (200 g). The mixture was stirred mechanically and the temperature was gradually raised. At 160°C the evolution of carbon dioxide ceased and the dark-brown mixture was poured on crushed ice (1000 mL). Filtration of the mixture yielded 2.8 g of an orange solid that was eliminated. The filtrate was brought to pH 12 with a saturated KOH solution. The precipitated amine was collected, dried and purified by column chromatography on silica gel (petroleum ether-EtOAc 5:1) yielding light tan 2-naphtylamine **61** (9.13 g, 69%).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{10}H_9N$ | calculated | C 83.88 | H 6.34 | N 9.78 |
| (143.19) | found | C 83.56 | H 6.52 | N 9.61 |

***Experiment 14: MAR-100***

**4-Hydroxy-5-methyldihydro-2(3*H*)-furanone (*rac*-62):** To a solution of $NMO{\cdot}2H_2O$ (1.82 g , 13.5 mmol) and $OsO_4$ (8 mg, 0.03 mmol) in $H_2O$ (5 mL), acetone (2 mL) and *t*BuOH (0.8 mL) was added methyl 3-pentenoate **63** (0.79 mL,10 mmol). The slightly exothermic reaction was maintained at 25°C with a water bath and stirred for 12 h at this temperature. $Na_2S_2O_4$ (0.1 g), magnesium trisilicate (1.2 g), and $H_2O$ (8 mL) were added to the mixture, which was then filtrated. The filtrate was brought to pH 7 by dropwise addition of 1N $H_2SO_4$, washed with brine (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc 2:1) yielding ***rac*-62** (0.98 g, 86%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ1.44 (d, $^3J_{4,5}$ = 6.4 Hz, 3 H, H-5), 2.57 (dd, $^2J_{2a,2b}$ = 17.8, $^3J_{2a,3}$ = 1.1 Hz, 1 H, H-2a), 2.82 (dd, $^2J_{2a,2b}$ = 17.8, $^3J_{2b,3}$ = 5.6 Hz, 1H, H-2b), 4.45 (m, 1 H, H-3), 4.59 (dq, $^3J_{3,4}$ = 3.8, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-4);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 13.8 (C-5), 37.5 (C-2), 69.5 (C-3), 81.3 (C-4), 176.5 (C-1).

***Experiment 15: MAR-169***

**(+)-(4*R*,5*R*)-4-Hydroxy-5-methyldihydro-2(3*H*)-furanone ((+)-62):** To a mixture of AD-mix-β (50 g) and $CH_2SO_2NH_2$ (2.38 g, 25 mmol) in *t*BuOH/$H_2O$ 1:1 (360 mL) was added methyl 3-pentenoate **63** (4.08 g, 4.39 mL, 35.7 mmol) at 0°C. The reaction was stirred for 28 h at this temperature and then quenched by addition of $Na_2SO_3$ (53.5 g, 425 mmol). The mixture was stirred for 1 h and then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel ($CH_2Cl_2$-MeOH 19:1) yielding **62** as an oil (3.32 g, 80%). 4-Dimethylaminocinnamaldehyde-HCl reagent was used as TLC reagent.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.42 (d, $^3J_{4,5}$ = 6.4 Hz, 3 H, H-5), 2.55 (dd, $^2J_{2a,2b}$ = 17.8 , $^3J_{2a,3}$ = 0.6 Hz, 1 H, H-2a), 2.80 (dd, $^2J_{2,2b}$ = 17.8, $^3J_{2b,3}$ = 5.6 Hz, 1 H, H-2b), 4.45 (m, 1 H, H-3), 4.57 (dq, $^3J_{3,4}$ = 3.8, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-4);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 13.8 (C-5), 37.5 (C-2), 69.5 (C-3), 81.3 (C-4), 176.5 (C-1).

**$[\alpha]_D^{20}$ =** + 56.7 ( c = 1.02, $CHCl_3$, **(+)-62**)

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_5H_8O_3$ | calculated | C 51.72 | H 6.94 |
| (116.12) | found | C 51.34 | H 6.98 |

**IV.2.2.1 Test with shift reagent:**

***Racemate MAR-100***

***rac*-62** (6.5 mg) and (*S*)-(+)-2,2,2-Trifluoro-1-(9-anthryl)ethanol **109** (48 mg) were dissolved with stirring in $CDCl_3$/TMS in a NMR tube. The NMR spectrum was immediately recorded.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.21 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, $H_A$-5), 1.25 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, $H_B$-5), 2.57 (m, 2 H, $H_A$-2a, $H_B$-2a), 2.46-2.56 (m, 2 H, $H_A$-2b, $H_B$-2b), 4.12 (m, 2 H, $H_A$-3, $H_B$-3), 4.26-4.32 (m, 2 H, $H_A$-4, $H_B$-4), 6.49-8.92 (Shift reagent).

***Stereospecific MAR-169***

**(+)-62** (5.6 mg) and (*S*)-(+)-2,2,2-Trifluoro-1-(9-anthryl)ethanol 109 (36 mg) were dissolved with stirring in $CDCl_3$/TMS in a NMR tube. The NMR spectrum was immediately recorded.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.26 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, H-5), 2.38 (m, 1 H, H-2a), 2.59 (dd, $^2J_{2a,2b}$ = 17.8, $^3J_{2,3}$ = 5.6 Hz, 1H, H-2b), 4.19 (m, 1 H, H-3), 4.35 (m, 1 H, H-4), 6.53-8.94 (Shift reagent).

***Experiment 16: MAR-79***

**(4*R*,5*R*)-4-Benzyloxymethoxy-5-methyl-dihydro-furan-2-one (60):** To a solution of **(+)-62** (480 mg, 4.13 mmol) in $CH_2Cl_2$ (2.4 mL) were added DIPEA (1.60 g, 12.4 mmol) and BOM-Cl (1.45 g, 1.72 mL of a 60% solution in $CH_2Cl_2$, 9.28 mmol) under argon. The reaction was stirred for 2.5 h at 25°C and additional DIPEA (0.53 g, 4.1 mmol) and BOM-Cl (0.48 g, 0.57 mL of a 60% solution in $CH_2Cl_2$, 3.06 mmol) were added. The mixture was stirred for another 12 h and quenched with 1 M aqueous $KH_2PO_4$ (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 40 mL). The combined organic phases were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 4:1) yielding **60** (610 mg, 62%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.43 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, H-5), 2.65 (dd, $^2J_{2a,2b}$ = 17.7, $^3J_{2a,3}$ = 2.2 Hz, 1 H, H-2a), 2.71 (dd, $^2J_{2a,2b}$ = 17.7, $^3J_{2b,3}$ = 5.5 Hz, 1 H, H-2b), 4.40 (m, 1 H, H-3), 4.62 (s, 2 H, OC*H*$_2$OBn), 4.64 (m, 1 H, H-4), 4.70-4.84 (m, 2 H, *CH*$_2$Ph), 7.30-7.38 (m, 5 H, C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 14.2 (C-5), 36.7 (C-2), 70.1 (*C*$H_2$Ph), 74.0 (C-3), 80.0 (C-4), 93.7 (O*C*$H_2$OBn), 127.9, 128.0, 128.6, 137.2 (6C, *C*$_6$H$_5$), 175.1 (C-1).

**$[\alpha]_D^{20}$ =** - 11.2 ( c = 0.25, $CHCl_3$, **60**)

***Experiment 17: MAR-87***

**(3*R*,4*R*)-3-Benzyloxymethoxy-4-hydroxy-*N*-(2-naphtyl) pentanoic amide (59):** To a solution of 2-naphtylamine **61** (810 mg, 5.65 mmol) in dry $CH_2Cl_2$ (28 mL) was added $AlMe_3$ (410 mg, 2.81 mL of a 2M solution in heptane, 5.65 mmol) under argon. The mixture was stirred for 15 min at 25°C. A solution of **60** (1.29 g, 5.14 mmol) in $CH_2Cl_2$ (56 mL) was added to the mixture, which was stirred for 30 min at 25°C. **61** (200 mg, 1.41 mmol) in dry $CH_2Cl_2$ (7 mL) and $AlMe_3$ (100 g, 0.70 mL, 1.41 mmol) were added to the mixture, which was stirred for another 16 h, quenched with 0.1N HCl (100 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 65:35) yielding **59** (1.73 g, 82%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** $\delta$ 1.22 (d, 3 H, H-5), 2.53-2.68 (dd, 1 H, H-2a), 2.71-2.84 (dd, 1 H, H-2b), 2.97 (s, 1 H, OH), 3.84-3.97 (m, 2 H, H-3, H-4), 4.67 (s, 2 H OC*H*$_2$OBn), 4.85 (m, 2 H, C*H*$_2$Ph), 7.23-8.15 (m, 12 H, $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** $\delta$ 19.8 (C-5), 41.4 (C-2), 69.8 (C-4), 70.1 (*C*$H_2$Ph), 82.3 (C-3), 95.6 (O*C*$H_2$OBn), 118.1, 120.7, 125.3, 126.4, 127.6, 128.2, 132.1, 134.6, 135.7, 137.5 (m, 16 C, $C_6H_5$, $C_{10}H_7$), 169.0, 172.3 (2 C, C-1, *C*O).

**$[\alpha]_D^{20}$ =** - 14.7 ( c = 0.49, $CHCl_3$, **59**)

***Experiment 18: MAR-88***

**(3*R*,4*R*)-3-Benzyloxymethoxy-4-benzoyloxy-*N*-(2-naphtyl)-pentanoic acid (58):** Pyridine (0.73 mL, 9.1 mmol) and BzCl (0.69 mL, 5.9 mmol) were added to a solution of alcohol **59** (1.73 g, 4.55 mmol) in $CH_2Cl_2$ (5 ml) at 0°C under argon. The mixture was stirred for 30 min, quenched with 1M $KH_2PO_4$ (30 mL), diluted with $CH_2Cl_2$ (30 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 7:3) yielding **58** (2.01 g, 92 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.43 (d, 3 H, H-5), 1.66 (s, 1 H, NH), 2.67-2.75 (dd, 1 H, H-2a), 2.79-2.85 (dd, 1 H, H-2b), 4.33 (m, 1 H, H-3), 4.66 (s, 2 H, OC$H_2$OBn), 4.95 (m, 2 H, C$H_2$Ph), 5.46 (m, 1 H, H-4), 7.27-8.25 (m, 17 H, 2 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.0 (C-5), 40.0 (C-2), 68.8 (C-4), 70.8 (C$H_2$Ph), 71.8 (C-3), 95.6 (OC$H_2$OBn), 117.0, 119.8, 120.2, 125.4, 126.8, 127.9, 128.1, 128.2, 128.8, 128.9, 129.1, 130.1, 130.4, 131.0, 133.6, 134.2, 135.7, 136.6 (m, 22 C, 2 $C_6H_5$, $C_{10}H_7$), 166.3,169.0 (2 C, C-1, CO).

**$[\alpha]_D^{20}$ =** - 36.4 ( c = 0.51, $CHCl_3$, **58**)

***Experiment 19: MAR-89***

**(3*R*,4*R*)-4-Benzoyloxy-3-hydroxy-*N*-(2-naphtyl)-pentanoic amide (42):** Pd-C 10% (52 mg) was added to a solution of **58** (100 mg, 0.213 mmol) in dioxane (6.5 mL) and $HClO_4$ 60% (2 μL). The solution was degased under argon and hydrogenated for 12 h (1.2 Bar $H_2$) with vigorous stirring at 25°C. The mixture was filtered on Celite and washed with dioxane (2 x 10 mL). The filtrate was concentrated, dried with $Na_2SO_4$ and purified by column chromatography on silica gel (petroleum ether-EtOAc, 3:2) yielding 34 mg (45%) of product **42**.

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.46 (d, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-5), 2.67 (m, 2 H, H-2), 4.29 (m, 1H, H-3), 5.25 (m, 1 H, H-3), 7.38-8.13 (m, 12 H, $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.4 (C-5), 40.5 (C-2), 71.0 (C-4), 73.6 (C-3), 117.0, 120.0, 125.2, 126.6, 127.6, 127.8, 128.6, 128.9, 129.8, 129.9, 130.8, 133.4, 133.9, 135.0 (16C, $C_6H_5$, $C_{10}H_7$), 170.0 (C-1).

**$[\alpha]_D^{20}$ =** + 3.1 ( c = 1.00, $CHCl_3$, **42**)

***Experiment 20: MAR-168 / MAR-118***

**(4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-methyl-dihydrofuran-2-one (66)**:
To a solution of TBDMS-Cl (1.95 g, 12.9 mmol) and imidazole (1.17 g, 17.2 mmol) in dry DMF (3 mL) was added **(+)-62** (1.00 g, 8.6 mmol) under argon. The mixture was stirred at 50°C for 12 h then $H_2O$ (40 mL) and MeOH (20 mL) were added. The mixture was extracted with $CH_2Cl_2$ (5 x 50 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 8:1) yielding **66** as a white solid (1.91 g, 96 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.08 (s, 6 H, 2 C$H_3$), 0.90 [s, 9 H, C(C$H_3$)$_3$], 1.37 (d, $^3J_{4,5}$ = 6.4 Hz, 3 H, H-5), 2.45 (dd, $^2J_{2a,2b}$ = 17.3, $^3J_{2a,3}$ = 1.6 Hz, 1 H, H-2a), 2.73 (dd, $^2J_{2a,2b}$ = 17.3, $^3J_{2b,3}$ = 5.4 Hz, 1 H, H-2b), 4.38 (m, 1 H, H-3), 4.54 (dq, $^3J_{3,4}$ = 4.0, $^3J_{4,5}$ = 6.4 Hz, 1 H, H-4);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ -5.0 (2 C, 2 C$H_3$), 14.5 (C-5), 18.2 [*C*(CH$_3$)$_3$], 25.7 [C(*C*H$_3$)$_3$], 39.9 (C-2), 70.1 (C-3), 81.3 (C-4), 175.7 (C-1).

**$[\alpha]_D^{20}$ =** + 15.2 ( c = 1.00, $CHCl_3$, **66**)

***Experiment 21: MAR-120***

**(3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-*N*-(2-naphtyl)-pentanoic amide (67):** To a solution of 2-naphtylamine **61** (1.6 g, 11.2 mmol) in dry $CH_2Cl_2$ (40 mL) was added $AlMe_3$ (5.56 mL of a 2 M solution in heptane, 11.2 mmol) under argon and the mixture was stirred for 15 min at 25°C. A solution of **66** (2.34 g, 10.2 mmol) in $CH_2Cl_2$ (80 mL) was added to the mixture, which was stirred for 30 min at 25°C. The mixture was quenched with 0.1 N HCl (100 mL) and extracted with $CH_2Cl_2$ (5 x 75 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 3:1) yielding **67** (3.23 g, 85%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.14, 0.17 (2 s, 6 H, 2 *C*$H_3$), 0.95 [s, 9 H, C(C$H_3$)$_3$], 1.23 (d, $^3J_{4,5}$ = 6.4 Hz, 1 H, H-5), 2.56 (dd, $^2J_{2a,2b}$ = 14.6, $^3J_{2a,3}$ = 5.4 Hz, 1 H, H-2a), 2.78 (dd, $^2J_{2a,2b}$ = 14.6, $^3J_{2b,3}$ = 6.0 Hz, 1 H, H-2b), 3.83 (m, 1 H, H-4), 4.06 (m, 1 H, H-3), 7.38-8.21 (m, 7 H, C$_{10}$*H*$_7$).

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ -4.6, -4.4 (2 C, 2 *C*$H_3$), 18.2 [*C*$(CH_3)_3$], 19.7 (C-5), 26.0 [C(*C*$H_3)_3$], 42.6 (C-2), 69.8 (C-3), 73.8 (C-4), 116.6, 119.8, 125.1, 126.6, 127.7, 127.8, 128.9, 130.7, 134.0, 135.4 (10 C, $C_{10}H_7$), 168.0 (*C*O).

**$[\alpha]_D^{20}$ =** - 19.1 ( c = 1.02, $CHCl_3$, **67**)

***Experiment 22: MAR-124***

**(3*R*,4*R*)-4-Benzoyloxy-3-(*tert*-butyldimethylsilyloxy)-*N*-(2-naphtyl)-pentanoic amide (68):** Pyridine (1.39 mL, 17.3 mmol) and BzCl (1.30 mL, 11.2 mmol) were added to a solution of alcohol **67** (3.23 g, 8.63 mmol) in $CH_2Cl_2$ (30 ml) at 0°C under argon. The mixture was stirred for 12 h at 0°C, quenched with 1 M $KH_2PO_4$ (35 mL), diluted with $CH_2Cl_2$ (30 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 7:3) yielding **68** (4.12 g, quant.).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.10, 0.14 (2 s, 6 H, 2 C*H*$_3$), 0.90 [s, 9 H, C(C*H*$_3)_3$], 1.38 (d, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-5), 2.58 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2a,3}$ = 6.6 Hz, 1 H, H-2a), 2.78 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2b,3}$ = 4.3 Hz, 1 H, H-2b), 4.37 (m, 1 H, H-3), 5.36 (m, 1 H, H-4), 7.38-8.24 (m, 12 H, $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ -4.6 (2 C, 2 *C*$H_3$), 15.4 (C-5), 18.1 [*C*$(CH_3)_3$], 25.9 [C(*C*$H_3)_3$], 41.7 (C-2), 71.3 (C-3), 72.4 (C-4), 116.7, 119.9, 120.1, 125.1, 126.6, 127.7, 127.9, 128.5, 128.9, 129.0, 129.9, 130.3, 130.7, 130.8, 133.2, 134.0, 135.5 (16 C, $C_6H_5$, $C_{10}H_7$), 166.1, 169.1 (2 C, C-1, *C*O).

**$[\alpha]_D^{20}$ =** - 50.1 ( c = 1.01, $CHCl_3$, **68**)

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| **$C_{28}H_{35}O_4NSi$** | calculated | C 70.40 | H 7.39 | N 2.93 |
| (477.67) | found | C 70.15 | H 7.28 | N 2.72 |

***Experiment 23: MAR-129***

**(3*R*,4*R*)-4-Benzoyloxy-3-hydroxy-*N*-(2-naphtyl)-pentanoic amide (42): 68** (3.46 g, 7.25 mmol) was added to a solution of AcOH (21 mL), $H_2O$ (7 mL) and THF (7 mL). The mixture was stirred for 4 h at 70°C, neutralized (pH 7) with 2 M $KHCO_3$ (150 mL) and extracted with $CH_2Cl_2$ (5 x 40 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 4:1) yielding **42** (2.38 g, 90%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** $\delta$ 1.46 (d, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-5), 2.67 (m, 2 H, H-2), 4.29 (m, 1 H, H-3), 5.25 (m, 1 H, H-4), 7.38-8.13 (m, 7 H, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** $\delta$ 16.4 (C-5), 40.5 (C-2), 71.0 (C-4), 73.6 (C-3), 117.0, 120.0, 125.2, 126.6, 127.6, 127.8, 128.6, 128.9, 129.8, 129.9, 130.8, 133.4, 133.9, 135.0 (16 C, $C_6H_5$, $C_{10}H_7$), 170.0 (2 C, C-1, *C*O).

**$[\alpha]_D^{20}$ =** + 3.1 ( c = 1.00, $CHCl_3$, **42**)

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{30}H_{22}O_4$ | calculated | C 72.71 | H 5.82 | N 3.85 |
| | found | C 72.65 | H 5.99 | N 3.85 |

## IV.2.3 D-Gal building block 40

***Experiment 24: MAR-67***

**1,2,3,4,6-Penta-*O*-benzoyl-$\alpha$-D-galactopyranose (70):** Anhydrous $\alpha$-D-galactose **69** (6.66 g, 9.50 mmol) was added stepwise, while maintaining the temperature below 35°C, to a stirred solution of pyridine (39 mL) and BzCl (33 mL) in dry chloroform (66 mL) under argon. The mixture was stirred at 25°C for 1 h and then at 5°C for 20 h. Chloroform (150 mL) was added to the mixture and pyridine was removed by washing with 3 N sulfuric acid (3 x 20 mL), 5% aqueous $NaHCO_3$ (40 mL) and water (40 mL). The organic layer was dried with $Na_2SO_4$ and concetrated. The residue was crystallized from ethanol yielding **70** as white crystals (21.7 g, 84 %). Literature [135] (89 %, **$[\alpha]_D^{20}$ =** + 187.1)

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 4.42 (dd, $^3J_{5,6a}$ = 7.0, $^2J_{6a,6b}$ = 11.4 Hz, 1 H, H-6a), 4.63 (dd, $^3J_{5,6b}$ = 6.5 , $^2J_{6a,6b}$ = 11.4 Hz, 1 H, H-6b), 4.83 (m, 1 H, H-5), 6.03 (dd, $^3J_{1,2}$ = 3.6, $^3J_{2,3}$ = 10.7 Hz, 1 H, H-2), 6.13 (dd, $^3J_{2,3}$ =10.7, $^3J_{3,4}$ = 3.3 Hz, 1 H, H-3), 6.19 (d, $^3J_{3,4}$ = 3.3 Hz, 1 H, H-4), 6.95 (d, $^3J_{1,2}$ =3.6 Hz, 1 H, H-1), 7.26-8.13 (m, 25 H, 5 $C_6H_5$).

**$[\alpha]_D^{20}$ =** + 184.3 ( c = 1.00, $CHCl_3$, **70** )

**Elementary analysis**

| | | | |
|---|---|---|---|
| **$C_{41}$ $H_{32}$ $O_{11}$** | calculated | C 70.28 | H 4.60 |
| (700.72) | found | C 70.14 | H 4.58 |

***Experiment 25: MAR-139***

**2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (40):** To a solution of **70** (1.51 g, 2.14 mmol) in $CH_2Cl_2$ (1.5 mL) was added a 33% solution of HBr in AcOH (5 mL) containing $Ac_2O$ (0.1 mL). The mixture was stirred for 2 h at 25°C, diluted with $CH_2Cl_2$ (30 mL), washed successively with an ice/water mixture (30 mL), a saturated $NaHCO_3$ solution (30 mL), dried with $Na_2SO_4$ and concentrated. The residue was dried at $10^{-3}$ Torr for 12 h yielding **40** (1.39 g, 99%). The compound was used without further purification. Literature (100%, **$[\alpha]_D^{20}$ =** + 157)

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 4.47 (dd, $^3J_{5,6a}$ = 6.0 , $^2J_{6a,6b}$ = 11.6 Hz, 1 H, H-6a), 4.64 (dd, $^3J_{5,6b}$ = 6.8, $^2J_{6a,6b}$ = 11.6 Hz,1 H, H-6b), 4.92 (m, 1 H, H-5), 5.67 (dd, $^3J_{1,2}$ = 4.0, $^3J_{2,3}$ = 10.4 Hz, 1 H, H-2), 6.06 (dd, $^3J_{2,3}$ = 10.4, $^3J_{3,4}$ = 3.4 Hz, 1 H, H-3), 6.12 (dd, $^3J_{3,4}$ = 3.4, $^3J_{4,5}$ = 4.4 Hz, 1 H, H-4), 6.98 (d, $^3J_{1,2}$ = 4.0 Hz, 1 H, H-1), 7.25-8.08 (m, 20 H, 4 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 61.7 (C-6), 68.1 (C-4), 68.6 (C-2), 71.8 (C-5), 88.3 (C-1), 128.4, 128.5, 128.6, 128.7, 128.8, 129.3, 129.8, 129.9, 130.0, 133.3, 133.4, 133.8 (24 C, 4 $C_6H_5$), 165.9, 165.4 (4 C, 4 *C*O).

**$[\alpha]_D^{20}$ =** + 155.8 ( c = 1.00, $CHCl_3$, **40**)

## IV.2.4 Cyclohexyl lactic acid building block 39

***Experiment 27: MAR-152***

**(*R*)-3-Cyclohexyl-2-hydroxy-propionic acid (73):** Commercially available D-(+)-phenyllactic acid **(74)** (5.00 g, 30.1 mmol) was dissolved in $H_2O$ (80 mL), dioxane (40 mL) and AcOH (18 mL) and hydrogenated (3 bar $H_2$) in the presence of 5% $Rh/Al_2O_3$ (0.75 g) for 48 h. 5% $Rh/Al_2O_3$ (0.25 g) was added and the mixture was hydrogenated for another 24 h. The black suspension was filtered and the filtrate concentrated. $H_2O$ was removed by co-evaporation with toluene (2 x 50 mL). The residue was dried at $10^{-3}$ Torr yielding **73** as a white solid (5.18 g, 100 %).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 0.87-1.86 (m, 11 H, $C_6H_{11}$), 1.59 (m, 2 H, H-3), 4.32 (m, 1 H, H-2);

**$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta_C$ 26.0, 26.2, 26.4, 32.2, 33.9 (6 C, $C_6H_{11}$), 41.9 (C-3), 68.6 (C-2), 185.8 (C-1).

***Experiment 28: MAR-161***

**Benzyl (*R*)-3-Cyclohexyl-2-hydroxy-propionate (72): 73** (5.18 g, 30.1 mmol) was dissolved in MeOH/$H_2O$ (9:1, 35 mL). The pH was adjusted to 8 by dropwise addition of 20% $Cs_2CO_3$ in $H_2O$ to give a clear yellowish solution. The mixture was concentrated and co-evaporated with EtOH (2 x 30 mL) and hexane (2 x 30 mL). The residue was dried at $10^{-3}$ Torr for 45 min. The remaining oil was dissolved in DMF (35 mL) and BnBr (3.57 mL, 30.1 mmol) was added. After stirring for 1 h at 25°C, the white suspension was diluted with $CH_2Cl_2$ (50 mL), filtered and washed with $CH_2Cl_2$ (3 x 50 mL). The combined organic phases were concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 2:1) yielding **73** (4.47 g, 75%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.85-1.82 (m, 12 H, H-3, $C_6H_{11}$), 4.27 (m, 1 H, H-2), 5.20 (s, 2 H, $CH_2$Ph), 7.33-7.40 (m, 5 H, $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 26.0, 26.3, 32.3, 33.7, 33.9 (6 C, $C_6H_{11}$), 42.1 (C-3), 67.3 ($CH_2$Ph), 68.6 (C-2), 128.4, 128.6, 128.7, 135.2 (6 C, $C_6H_5$), 175.9 (C-1).

***Experiment 29: MAR-164***

**Benzyl (*R*)-3-cyclohexyl-2-trifluoromethanesulfonyloxy-propionate (39):** To a solution of **72** (4.47 g, 27.3 mmol) in $CH_2Cl_2$ (50 mL) and 2,6-di-*tert*-butylpyridine (0.45 mL, 0.27 mmol) was added dropwise $Tf_2O$ (4.24 mL, 27.3 mmol) within 1.5 h at –20°C under argon. 1 M $KH_2PO_4$ (30 mL) and $CH_2Cl_2$ (50 mL) were added to the mixture, which was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were washed with $H_2O$ (30 mL), dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-$CH_2Cl_2$ 4:1) yielding **39** (5.80 g, 80 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.85-1.94 (m, 13 H, H-3, $C_6H_{11}$), 5.17 (m, 1 H, H-2), 5.25 (s, 2 H, $CH_2$Ph), 7.31-7.40 (m, 5 H, $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 25.7, 26.0, 26.1, 32.0, 33.2, 33.4 (6 C, $C_6H_{11}$), 39.2 (C-3), 68.2 (2 C, C-2, $CH_2$Ph), 81.9 ($CF_3$), 128.6, 128.7, 128.9, 134.4 (6 C, $C_6H_5$), 167.6 (C-1).

**Elementary analysis**

| | | | |
|---|---|---|---|
| **$C_{17}H_{21}F_3O_3S$** | calculated | C 51.77 | H 5.37 |
| (394.41) | found | C 51.67 | H 5.41 |

## IV.2.5 1st Attempt

***Experiment 30: MAR-140/R***

**(3*R*,4*R*)-(Methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyl-uronate)-(1→3)-4-benzoyloxy-3-hydroxy-*N*-(2-naphtyl)-pentanoic amide** (**86**): **15** (801 mg, 1.58 mmol) was dissolved in dry $CH_2Cl_2$ (11.7 mL) and dry DMF (1.8 mL) under argon. The mixture was cooled to 0°C and $(COBr)_2$ (0.332 mL, 3.04 mmol) was added to give a white suspension. The reaction was warmed to 25°C within 20 min and the mixture was stirred for 2 h, giving a thick white suspension. The suspension was filtered with, washed with $Et_2O$ (2 x 20 mL) and the filtrate was concentrated. The residue was dried for 30 min at $10^{-3}$ Torr to give a dark yellow oil (1.3 g). The oil was dissolved in $CH_2Cl_2$ (5.7 mL) and the solution added to a suspension of **42** (1.15 g, 3.16 mmol), MS4Å (500 mg) and $Bu_4NBr$ (0.510 g, 1.58 mmol) in dry $CH_2Cl_2$ (5.85 mL) / DMF (3.84 mL) under argon. The

mixture was stirred for 16 h at 25°C, diluted with $CH_2Cl_2$ (20 mL) and filtered through Celite. The filtrate was quenched with $KHCO_3$ 10% (20 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The organic layer was washed with 1 M $KH_2PO_4$ (30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (EtOAc-toluene 1:4) yielding **86** (594 mg, 44%) and **111** (378 mg, 28%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.41 (d, 3 H, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-5), 1.53 (m, 1 H, Fuc-H6a), 1.79 (m, 1 H, Fuc-H6b), 1.88 (m, 2 H, Fuc-H7), 2.53 (dd, $^2J_{2a,2b}$ = 15.3, $^3J_{2a,3}$ = 4.0 Hz, 1 H, H-2a), 2.80 (dd, $^2J_{2a,2b}$ = 15.3, $^3J_{2b,3}$ = 4.0 Hz, 1 H, H-2b), 3.55 (m, 1 H, Fuc-H4), 3.61 (s, 3 H, C$H_3$), 3.99 (m, $^3J_{2,3}$ = 10.3, $^3J_{3,4}$ = 2.5 Hz, 1 H, Fuc-H3), 4.05 (m, 1 H, H-3), 4.19 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 10.3 Hz, 1 H, Fuc-H2), 4.88-4.56 (m, 4 H, 2 C$H_2$Ph), 4.89 (d, $^3J_{1,2}$ = 3.7 Hz,1 H, H-1), 4.96 (m, 2 H, C$H_2$Ph), 5.48 (m, 1 H, H-4), 7.13-9.47 (m, 28 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.4 (C-5), 25.7 (Fuc-C6), 29.5 (Fuc-C7), 37.9 (C-2), 51.5 ($CH_3$), 70.7 (C-4), 73.1, 74.7, 74.8 (3 C, 3 $CH_2$Ph), 75.5 (Fuc-C2), 75.7 (Fuc-C4), 76.9 (C-3), 79.7 (Fuc-C3), 97.1 (Fuc-C1), 116.8, 120.2, 124.7, 125.3, 126.1, 127.3, 127.4, 127.7, 127.8, 128.3, 128.4, 128.6, 128.7, 128.8, 129.0, 129.5, 130.0, 130.5, 133.0, 133.9, 136.0, 137.1, 137.9, 138.2, 138.3 (34 C, 4 $C_6H_5$, $C_{10}H_7$), 173.3, 168.2, 165.5 (3 CO).

**$[\alpha]_D^{20}$ =** - 115.3 ( c = 1.04, $CHCl_3$, **86**)

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| **$C_{53}H_{55}NO_{10}$** | calculated | C 73.31 | H 6.27 | N 1.64 |
| (852.00) | found | C 73.14 | H 6.19 | N 1.47 |

**Orthoester (111)**

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.44 (d, 1 H, H-1), 1.57 (m, 1 H, Fuc-H6a), 2.00 (m, 1 H, Fuc-H6b),2.21-2.38 (m, 2 H, Fuc-H7), 2.74 (m, 1 H, H-4), 3.59 (m, 1 H, Fuc-H4), 3.60 (s, 3 H, C$H_3$), 3.74 (m, 1 H, Fuc-H5), 3.86 (dd, $^3J_{2,3}$ = 10.0, $^3J_{3,4}$ = 2.6 Hz 1 H, Fuc-H3), 4.07

(dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 10.0 Hz 1 H, Fuc-H2), 4.43 (2 d, 2 H, $^3J_{vic\text{-}2'}$ = 11.5 Hz, H-2), 4.48 (m, 1 H, H-3), 4.54-4.90 (m, 6 H, 3 C$H_2$Ph), 5.29 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, Fuc-H1), 7.19-8.86 (m, 22 H, 3 $C_6H_5$ $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.4 (C-5), 20.9 (Fuc-C7), 41.2 (C-2), 51.7 ($CH_3$), 70.2 (Fuc-C5), 71.3 (C-4), 74.3, 75.7 (4 C, 3 $C_6H_5$, C-3), 76.1 (Fuc-C4), 76.2 (Fuc-C3), 96.6 (Fuc-C1), 116.1,128.4, 128.5,128.7, 133.0 (28 C, 3 $C_6H_5$, $C_{10}H_7$).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{52}H_{53}NO_{10}$ | calculated | C 73.31 | H 6.27 | N 1.64 |
| (851.99) | found | C 72.21 | H 6.52 | N 1.35 |

***Experiment 31: MAR-138, MAR-142***

**(3*R*,4*R*)-(Methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyl-uronate)-(1→3)-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (85): 86** (594 mg, 0.697 mmol) was dissolved in dry MeOH (2 mL) to give a clear solution. 1 M NaOMe (200 μL) in dry MeOH was added dropwise to bring the solution's pH to 10. The mixture was stirred for 28 h at 25°C, brought to pH 7 by addition of Amberlyst 15, filtered through Celite, washed with MeOH (50 mL) and $CH_2Cl_2$ (80 mL). The filtrate was concentrated and purified by column chromatography (petroleum ether-EtOAc 45:55) yielding **85** (316 mg, 61% yield).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.30 (d, 3 H, $^3J_{4,5}$ = 6.4 Hz, 1 H, H-5), 1.61 (m, 1 H, Fuc-H6a), 2.05 (m, 1 H, Fuc-H6b), 2.38-2.23 (m, 2 H, Fuc-H7), 2.42 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2a,3}$ = 3.1 Hz, 1 H, H-2a), 2.68 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2b,3}$ = 4.2 Hz, 1 H, H-2b), 3.62 (m, 1 H, H-3), 3.63 (s, 3 H, C$H_3$), 3.83 (m, 2 H, Fuc-H4, H-4), 4.08 (m, 2 H, Fuc-H3, Fuc-H5), 4.25 (dd, $^3J_{1,2}$ = 3.8, $^3J_{2,3}$ = 10.2 Hz, 1 H, Fuc-H2), 4.85 (m, 1 H, Fuc-H1), 5.02-4.66 (m, 6 H, 3 C$H_2$Ph), 7.18-9.36 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 19.8 (C-5), 41.2 (C-2), 51.6 ($CH_3$), 70.6 (C-4), 74.5, 74.7, 74.8 (3 C, 3 $CH_2$Ph), 76.3 (Fuc-C2), 80.1 (Fuc-C3), 81.8 (C-3), 97.5 (Fuc-C1),

116.2, 119.8, 124.6, 126.2, 127.2, 127.4, 127.5, 127.6, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 129.0 (28 C, 3 $C_6H_5$, $C_{10}H_7$).

**$[\alpha]_D^{20}$ =** - 152.5 ( c = 1.01, $CHCl_3$, **85**)

***Experiment 32: MAR-143 and MAR-144***

**(3*R*,4*R*)-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[(methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyluronate)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (84):** Under argon and light exclusion, **85** (286 mg, 0.382 mmol) was added to a suspension of **40** (755 mg, 1.15 mmol) and MS3Å (950 mg) in dry $CH_2Cl_2$ (5 mL). AgOTf (25.6 mg, 0.032 mmol) was added to the mixture, which was stirred for 1h at 25°C, filtered through Celite and washed with $CH_2Cl_2$ (50 mL). The filtrate was concentrated and the residue purified by column chromatography (toluene-EtOAc 85:15) yielding **84** (193 mg, 38%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.13 (d, $^3J_{4,5}$ = 6.2 Hz, 3 H, H-5), 1.82 (m, 1 H, Fuc-H6a), 2.17 (m, 1 H, Fuc-H6b), 2.40-2.50 (m, 3 H, Fuc-H7, H-2a), 2.72 (m, 1 H, H-2b), 3.64 (m, 3 H, C$H_3$), 3.82 (m, 1 H, Fuc-H4), 4.03-4.11 (m, 3 H, Fuc-H3, H-3, H-4), 4.14 (dd, $^3J_{1,2}$ = 3.5, $^3J_{2,3}$ = 10.1 Hz, 1 H, Fuc-H2), 4.18 (m, 1 H, Fuc-H5), 4.24 (m, 1 H, Gal-H5), 4.37-4.46 (m, 2 H, Gal-H6), 4.58-4.98 (m, 6 H, 3 C$H_2$Ph), 4.86 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, Gal-H1), 4.87 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, Fuc-H1), 5.57 (dd, $^3J_{2,3}$ = 10.4, $^3J_{3,4}$ = 3.5 Hz, 1 H, Gal-H3), 5.74 (dd, $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 10.4 Hz, 1 H, Gal-H2), 5.98 (m, 1 H, Gal-H4), 7.07-9.31 (m, 42 H, 7 $C_6H_5$, $C_{10}H_7$).

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.6 (C-5), 21.5 (Fuc-C6), 51.5 (C$H_3$), 61.9 (Gal-C6), 68.3 (Gal-C4), 69.5 (Fuc-C3), 70.6 (Gal-C3), 71.4 (Fuc-C2), 71.7 (Gal-C5), 73.0 (Gal-C2), 75.0, 75.9, 76.5, (5 C, C-3, C-4, 3 C$H_2$Ph), 76.6 (C-2), 79.8 (Fuc-C3), 96.7 (Fuc-C1), 100.6 (Gal-C1), 116.9, 120.3, 124.7, 125.3, 126.2, 127.0, 127.4, 127.5, 127.7, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 129.2, 129.3, 129.7, 129.8, 130.5, 133.2, 133.3, 133.7, 133.8, 133.9, 135.9, 137.3, 138.5 (56 C, 7 $C_6H_5$, $C_{10}H_7$), 165.0, 165.5, 165.6, 165.8,168.9, 173.9 (6 C*O*).

**$[\alpha]_D^{20}$ =** - 41.3 (c = 1.01, $CHCl_3$, **84**)

***Experiment 33: MAR-145***

**(3*R*,4*R*)-(β-D-Galactopyranosyl)-(1→4)-[(methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyluronate)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (83): 84** (215 mg, 0.162 mmol) was dissolved in dry MeOH (3 mL) and dioxane (0.3 mL) under argon. 1 M NaOMe (200 μL) in dry MeOH was added to bring the solution's pH to 10. The mixture was stirred for 16 h at 25°C, brought to pH 7 with Amberlyst 15 (ion exchanger), filtered through Celite and washed with $CH_2Cl_2$ (30 mL). The organic layer was co-evaporated with toluene (2 x 20 mL) and concentrated to give the crude product **83** (146 mg, 99%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.19 (d, $^3J_{4,5}$ = 6.1 Hz, 3 H, H-5), 1.64-1.70 (m, 1 H, Fuc-H6a), 1.97-2.04 (m, 1 H, Fuc-H6b), 2.32 (m, 2 H, Fuc-H7), 2.46 (m, 1 H, H-2a), 2.79 (m, 1 H, H-2b), 3.35 (m, 1 H, Gal-H5), 3.52 (m, 1 H, Gal-H3), 3.58-3.63 (m, 4 H, C$H_3$, Gal-H2), 3.66-3.77 (m, 2 H, Gal-H6), 3.81 (m, 1 H, Fuc-H4), 3.94 (m, 1 H, Gal-H4), 3.99-4.08 (m, 3 H, Fuc-H5, H-3, H-4), 4.13 (dd, $^3J_{1,2}$ = 3.5, $^3J_{2,3}$ = 10.1 Hz, 1 H, Fuc-H2), 4.23 (d, $^3J_{1,2}$ = 7.5 Hz, 1 H, Gal-H1), 4.60-5.00 (m, 6 H, 3 C$H_2$Ph), 4.90 (d, $^3J_{1,2}$ = 3.2 Hz, 1 H, Fuc-H1), 7.10-9.31 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.8 (C-5), 51.9 (*C*$H_3$), 62.5 (Gal-C6), 67.8 (Fuc-C5), 70.0 (Gal-C4), 71.8 (Gal-C2), 73.2 (Gal-C3), 73.8 (Gal-C4), 74.3, 74.8, 75.3 (4 C, Gal-C5, 3 *C*$H_2$Ph), 75.8 (C-4), 76.5 (Fuc-C4), 79.9 (C-2), 98.1 (Fuc-C1), 101.2 (Gal-C1), 116.7, 120.1, 124.8, 125.3, 126.3, 127.3. 127.5, 127.7, 128.1, 128.2, 128.3, 128.5, 128.6, 129.0, 130.5, 133.8, 135.8, 137.4, 137.9, 138.4, 138.6 (28 C, 3 $C_6H_5$, $C_{10}H_7$), 174.5 (2 C, 2 *C*O).

***Experiment 34: MAR-146***

**(3*R*,4*R*)-(4,6-*O*-Benzylidene-β-D-galactopyranosyl)-(1→4)-[(methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyluronate)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (82): 83** (146 mg, 0.160 mmol) was azeotropically dried with toluene (4 x 10 mL), concentrated, dried for 1 h at $10^{-3}$ Torr and dissolved in dry MeCN (4.40 mL) under argon. $PhCH(OMe)_2$ (90.2 mg, 0.593 mmol) and CSA (15.6 mg, 0.06 mmol) were added to the solution and the mixture was stirred for 100 min at 25°C. The mixture was quenched with 1 M $KHCO_3$ (25 ml) and extracted with $CH_2Cl_2$ (3 x 15 mL). The organic layers were brought together, dried with $Na_2SO_4$, concentrated and purified

by column chromatography on silica gel (petroleum ether-EtOAc 1:2) yielding **82** (126 mg, 79 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ1.26 (d, $^3J_{4,5}$ = 2.3 Hz, 3 H, H-5), 1.59-1.66 (m, 1 H, Fuc-H6a), 1.93-2.01 (m, 1 H, Fuc-H6b), 1.93-2.01 (m, 3 H, Fuc-H7, H-2a), 2.67 (m, 1 H, H-2b), 3.25 (m, 1 H, Gal-H5), 3.42 (m, 1 H, Fuc-H4), 3.67-3.70 (m, 5 H, Gal-H2, Gal-H3, C$H_3$), 3.77 (m, 1 H, H-3), 3.87 (m, 1 H, H-4), 3.91-4.00 (m, 1 H, Gal-H6), 4.06-4.13 (m, 3 H, Fuc-H2, Fuc-H3, Gal-H4), 4.20 (d, $^3J_{1,2}$ = 7.3 Hz, 1 H, Gal-H1), 4.48 (m, 1 H, Fuc-H5), 4.56-4.83 (m, 6 H, C$H_2$Ph), 4.74 (d, $^3J_{1,2}$ = 2.8 Hz, 1 H, Fuc-H1), 5.56 (s, 1 H, C*H*), 7.06-9.68 (m, 27 H, 4 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.9 (C-5), 51.8 (*C*$H_3$), 66.3 (Gal-C5), 70.0 (C-4), 71.2 (Gal-C2), 72.4 (Gal-C3), 72.6, 74.8, 75.1 (3 C, 3 *C*$H_2$Ph), 75.1 (Gal-C6), 75.3 (Gal-C4), 75.9 (C-3), 76.3 (Fuc-C3), 77.8 (Fuc-C4), 79.8 (Fuc-C3), 95.4 (Fuc-C1), 100.1 (*C*H), 100.8 (Gal-C1), 116.3, 120.0, 124.7, 125.3, 126.0, 126.3, 127.1, 127.3, 127.4, 127.6, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 129.7, 130.3, 130.9, 132.3, 133.9, 134.5, 136.2, 137.3, 137.9, 139.0, 139.1 (34 C, 4 $C_6H_5$, $C_{10}H_7$), 174.9, 168.5 (2 C, 2 *C*O).

***Experiment 35: MAR-149***

**(3*R*,4*R*)-(4,6-*O*-Benzylidene-β-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosiduronic acid)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (81): 82** (140 mg, 0.140 mmol) and LiOH (25 mg, 0.60 mmol) were dissolved in $H_2O$ (1.4 mL) and EtOH (5.3 mL). The mixture was warmed to 60°C and stirred for 2 h at this temperature. The mixture was neutralized with Amberlyst 15 and washed with ethanol (20 mL) and $CH_2Cl_2$ (20 mL). The filtrate was concentrated and the residue dried at $10^{-3}$ Torr to give 21 (136 mg, 96% yield) as a crude product, which was directly used in the next step.

***Experiment 36: MAR- 151***

**(3*R*,4*R*)-(4,6-*O*-Benzylidene-β-D-galactopyranosyl)-(1→4)-[(allyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyluronate)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (80):** $Cs_2CO_3$ (51.8 mg, 0.159 mmol) in $H_2O$ (200 μL) was added to a solution of **81** (136 mg, 0.138 mmol) in EtOH (2.5 mL) to give a white suspension with pH 12. The mixture was stirred for 5 min at 25°C, co-evaporated with benzene (3 x 10 mL) and dried for 1 h at $10^{-3}$ Torr. The residue was dissolved in dry DMF (2.5 mL) under argon and allyl bromide (23 mg, 16 μL, 0.19 mmol) was added. The mixture was stirred for 5 h at 25°C, diluted with $CH_2Cl_2$ (20 mL), filtered through Celite and washed with $CH_2Cl_2$ (2 x 10 mL). The filtrate was concentrated and purified by column chromatography (petroleum ether-EtOAc gradient 6:4 to 1:1, then $CH_2Cl_2$-MeOH 19:1) yielding **80** (99 mg, 70%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.26 (d, $^3J_{4,5}$ = 6.4 Hz, 3 H, H-5), 1.59-1.66 (m, 1 H, Fuc-H6a), 1.95-2.03 (m, 1 H, Fuc-H6b), 2.27-2.69 (m, 3 H, Fuc-H7, H-2), 3.26 (m, 1 H, Gal-H5), 3.42 (m, 1 H, Fuc-H4), 3.62-3.70 (m, 2 H, Gal-H2, Gal-H3), 3.77 (m, 1 H, H-3), 3.89 (m, 1 H, H-4), 3.94-4.00 (m, 1 H, Gal-H6), 4.06-4.12 (m, 1 H, Fuc-H2, Fuc-H3), 4.14 (m, 1 H, Gal-H4), 4.20 (d, $^3J_{1,2}$ = 7.2 Hz, 1 H, Gal-H1), 4.48 (m, 1 H, Fuc-H5), 4.57-4.84 (m, 6 H, 3 C$H_2$Ph), 4.58 (m, 2 H, C$H_2$-CH=$CH_2$), 4.74 (d, $^3J_{1,2}$ = 2.7 Hz, 1 H, Fuc-H1), 5.23-5.34 (m, 2 H, $CH_2$-CH=C$H_2$), 5.57 (s, 1 H, C*H*), 5.88-5.96 (m, 1 H, $CH_2$-C*H*=$CH_2$), 7.08-9.67 (m, 27 H, 4 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.9 (C-5), 25.7 (Fuc-C6), 30.7 (Fuc-C7), 31.4 (C-2), 65.2 (*C*$H_2$-CH=$CH_2$), 66.3 (Gal-C5), 69.3 (Gal-C6), 70.1 (Fuc-C5), 72.5 (Gal-C3), 72.6 (Gal-C2), 74.8, 75.1, 75.2, 75.3 (4 C, 3 *C*$H_2$Ph, C-4), 76.0 (C-3), 76.3 (Fuc-C2), 77.7 (Fuc-C4), 79.8 (Fuc-C3), 95.4 (Fuc-C1), 100.1 (*C*H), 100.8 (Gal-C1), 118.3 ($CH_2$-CH=*C*$H_2$), 120.0, 124.7, 125.9, 126.3, 126.5, 127.0, 127.1, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 129.3, 129.5, 129.8, 130.3, 133.9, 136.2, 137.3, 137.8, 138.9, 139.1, 140.9 (34 C, 4 $C_6H_5$, $C_{10}H_7$), 132.2 ($CH_2$-*C*H=$CH_2$),168.5, 174.0 (2 C, *C*O).

***Experiment 38: MAR-182***

**(3*R*,4*R*)-{3-[(2*S*)-Benzyl-3-cyclohexyl-2-hydroxypropanoate-2-*O*-yl]-4,6-*O*-benzylidene-β-D-galactopyranosyl}-(1→4)-[(allyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-L-*galacto*-octopyranosyluronate)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (79): 80** (82 mg, 0.08 mmol) and $Bu_2SnO$ (30 mg, 0.12 mmol) were dissolved in $C_6H_6$ (1.5 mL) and stirred for 12 h at 90°C under argon. The mixture was concentrated and dried at $10^{-3}$ Torr for 1 h. CsF (37 mg, 0.24 mmol) and **39** (189 mg, 0.48 mmol) were added under argon and dissolved in DME (1 mL). The mixture was stirred for 21 h at 25°C, quenched with KF/$KH_2PO_4$ 10 % (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc gradient 6:4 to 1:1, then $CH_2Cl_2$-MeOH 9:1) yielding **79** (7 mg, 7%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.71-1.71 (m, 13 H, $C_6H_{11}$, $CH_2C_6H_{11}$), 1.28 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, H-5), 1.59-1.66 (m, 1 H, Fuc-H6a), 1.92-2.06 (m, 1 H, Fuc-H6b), 2.30-2.73 (m, 3 H, Fuc-H7, H-2), 3.26 (m, 1 H, Gal-H5), 3.35 (m, 1 H, Gal-H3), 3.42 (m, 1 H, Fuc-H4), 3.62-3.70 (m, 3 H, Gal-H2, H-3, H-4), 3.89-4.04 (m, 2 H, Gal-H6), 4.06-4.15 (m, 3 H, Fuc-H2, Fuc-H3, Gal-H4), 4.23 (d, $^3J_{1,2}$ = 7.4 Hz, 1 H, Gal-H1), 4.36 (m, 1 H, Cyc-2), 4.42-4.84 (m, 6 H, 3 $CH_2$Ph), 4.53 (m, 1 H, Fuc-H5), 4.59 (m, 2 H, $CH_2$-CH=$CH_2$), 4.72 (d, $^3J_{1,2}$ = 2.6 Hz, 1 H, Fuc-H1), 5.14-5.22 (m, 2 H, $CH_2$-CH=$CH_2$), 5.49 (s, 1 H, CH), 5.89-5.96 (m, 1 H, $CH_2$-CH=$CH_2$), 7.04-9.70 (m, 32 H, 5 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.1 (C-5), 24.6, 24.9, 28.3, 29.6, 32.0, 32.9 (6 C, $C_6H_{11}$, $C_6H_{11}$), 25.3 (Fuc-C6), 30.7 (Fuc-C7), 31.4 (C-2), 63.8 ($CH_2$-CH=$CH_2$), 64.6 (Gal-C5), 64.9 (Cyc-C2), 66.2 (Gal-C2), 67.7 (Gal-C6), 68.4 (Fuc-C5), 69.1 (Gal-C4), 71.0 ($CH_2$Ph), 73.2, 73.8, 74.1, 74.7, 75.3, 75.8 (5 C, 3 $CH_2$Ph, Fuc-C2, C-3, C-4), 76.2 (Fuc-C4), 78.7 (Fuc-C3), 79.7 (Gal-C3), 94.1 (Fuc-C1), 98.7 (CH), 100.4 (Gal-C1), 119.0 ($CH_2$-CH=$CH_2$), 115.2, 116.7, 119.0, 125.0, 125.2, 126.1, 126.2, 126.3, 126.4, 126.6, 126.7, 127.0, 127.1, 127.2, 127.4, 127.5, 127.6, 127.8, 128.8, 129.2, 129.9, 130.2, 131.3, 131.6, 134.1, 135.4, 136.8, 138.1, 138.4 (40 C, 5 $C_6H_5$, $C_{10}H_7$), 132.9 ($CH_2$-CH=$CH_2$), 168.5, 172.4, 174.0 (3 C, 3 CO).

## IV.2.6 Orthoesters

***Experiment 39: MAR-191***

**1,2-*O*-(1-Ethoxyethylidene)-3,4,6-tri-*O*-benzyl-D-glucopyranose (113):** 1-chloro-2,N,N-trimethyl-propenylamine (89.5 mg, 0.67 mmol, 95.0 μL) was added to a solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-galactopyranose **112** (300 mg, 0.617 mmol) in $CHCl_3$ under argon. The mixture was stirred at 25°C for 12 h. EtOH (31 mg, 0.67 mmol) and $NEt_3$ (68 mg, 0.67 mmol) were added and the mixture was stirred for another 12 h at 50°C and then extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc gradient 9:1 to 7:3 with 1% *N*$Et_3$) yielding **113** (127 mg, 40 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.19 (m, 3 H, $CH_2CH_3$), 1.66 (s, 3 H, $CH_3$), 3.49-3.59 (m, 2 H, $CH_2CH_3$), 3.62-3.68 (m, 2 H, H-6), 3.71 (m, 1 H, H-4), 3.78 (m, 1 H, H-5), 3.87 (m, 1 H, H-3), 4.37-4.71 (m, 6 H, 3 $CH_2$Ph), 4.41 (m, 1 H, H-2), 5.76 (d, 1 H, $^3J_{1,2}$ = 5.2 Hz, H-1), 7.17-7.36 (m, 15 H, 3 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.3 ($CH_2CH_3$), 58.7 ($CH_2CH_3$), 69.1 (C-6), 70.5 (C-5), 71.9, 72.9, 73.4, 74.9, 75.8 (5 C, C-2, C-4, 3 $CH_2$Ph), 78.8 (C-3), 97.8 (C-1), 121.0, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 132.0, 137.7, 137.9, 138.1 (18 C, 3 $C_6H_5$).

***Experiment 40: MAR-193***

**1,2-*O*-(1-Ethoxyethylidene)-3,4,6-tri-*O*-acetyl-D-glucopyranose (115):** 1-chloro-2,*N*,*N*-trimethyl-propenylamine (49 mg, 0.63 mmol, 89 μL) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose **114** (200 mg, 0.57 mmol) in $CHCl_3$ under argon. The mixture was stirred at 25°C for 12 h. EtOH (29 mg, 0.63 mmol) and $NEt_3$ (64 mg, 0.63 mmol) were added and the mixture was stirred for another 12 h at 50°C and then extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc 8:2 with 1% $NEt_3$) yielding **115** (151 mg, 70 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.18 (m, 3 H, $CH_2CH_3$), 1.72 (s, 3 H, $CH_3$), 2.04-2.12 (m, 9 H, 3 $CH_3$), 3.52-3.57 (m, 2 H, $CH_2CH_3$), 3.95 (m, 1 H, H-5), 4.19 (m, 1 H, H-6), 4.32 (m, 1 H, H-2), 4.90 (m, 1 H, H-4), 5.19 (m, 1 H, H-3), 5.71 (d, 1 H, $^3J_{1,2}$ = 8.2 Hz, H-1);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.3 ($CH_2CH_3$), 20.7, 20.8 (4 C, 4 $CH_3$), 59.2 ($CH_2CH_3$), 63.1 (C-2), 66.9 (C-6), 68.2 (C-5), 70.1 (C-4), 13.0 (C-3), 96.9 (C-1), 121.3 (O-C-O), 169.2, 169.7, 170.8 (3 C, 3 CO).

***Experiment 41: MAR-194***

**1,2-*O*-(1-Ethoxyphenylmethylene)-3,4,6-tri-*O*-benzoyl-D-galactopyranose (117)**: 1 -chloro-2,*N*,*N*-trimethyl-propenylamine (49 mg, 0.37 mmol, 52 μL) was added to a solution of 2,3,4,6-tetra-*O*-benzoyl-D-galactopyranose **116** (200 mg, 0.33 mmol) in $CHCl_3$ under argon. The mixture was stirred at 25°C for 12 h. EtOH (17 mg, 0.37 mmol) and $NEt_3$ (37 mg, 0.37 mmol) were added and the mixture was stirred for another 12 h at 50°C and then extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (petroleum ether-EtOAc 8:2 with 1% *N*$Et_3$) yielding **117** (150 mg, 72 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.13 (m, 3 H, $CH_2CH_3$), 3.30-3.45 (m, 2 H, $CH_2CH_3$), 4.13 (m, 1 H, H-5), 4.37 (m, 1 H, H-6a), 4.51 (m, 1 H, H-6b), 4.78 (m, 1 H, H-2), 5.50 (m, 1 H, H-4), 5.77 (m, 1 H, H-3), 6.05 (d, $^3J_{1,2}$ = 5.3, 1 H, H-1), 7.24-8.10 (m, 20 H, 4 $C_6H_5$).

***Experiment 42: MAR- 192***

**Ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (118):** $HgBr_2$ (5 mg, mmol) was added to a solution of **115** (20 mg, 0.003 mmol) in DCE (1 mL). EtOH (30 μL, 0.003 mmol) was added and the mixture was heated in the microwave for 30 min at 120°C. The reaction flask was washed with $CH_2Cl_2$ (3 x 2 mL). The combined organic layers were concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 3:1) yielding **118** (5 mg, 25 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.18 (m, $^3J$ = 7.1, 3 H, $CH_2CH_3$), 1.97 (s, 3 H, $CH_3$), 3.48 (m, 1 H, H-5), 3.52-3.58 (m, 1 H, $CH_2CH_3$-Ha), 3.64-3.76 (m, 4 H, H-3, H-4, H-6), 3.86-

3.92 (m, 1 H, $CH_2CH_3$-Hb), 4.36 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, H-1), 4.54-4.80 (m, 6 H, 3 $CH_2Ph$), 3.98 (m, 1 H, H-2), 7.17-7.35 (m, 15 H, 3 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.1 ($CH_2CH_3$), 20.9 ($CH_3$), 65.1 ($CH_2CH_3$), 68.8 (C-6), 73.2 (C-2), 73.5, 75.0, 75,1, 75.2 (4 C, C-5, 3 $CH_2Ph$), 78.1 (C-4), 83.0 (C-3), 100.7 (C-1), 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 130.0, 137.9, 138.1, 138.2 (18 C, 3 $C_6H_5$), 169.6 (CO).

***Experiment 43: MAR-197***

**4-Methoxybenzyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranose (119):** $HgBr_2$ (15 mg, mmol) was added to a solution of **117** (60 mg, mmol) in DCE (3mL). Dihydroquinone monoethylether (30 μL, mmol) was added and the mixture was heated in the microwave for 30 min at 120°C. The mixture was concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 4:1) yielding **119** (23.5 mg, 39 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 3.76 (s, 3 H, $CH_3$), 4.11 (m, 1 H, H-5), 4.52 (m, 1 H, H-6a), 4.62-4.85 (m, 3 H, H-6b, $CH_2C_6H_4$), 4.79 (d, $^3J_{1,2}$ = 7.9 Hz, 1 H, H-1), 5.57 (dd, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 5.67 (m, 1 H, H-4), 5.82 (m, 1 H, H-3), 6.68-7.10 (m, 4 H, $C_6H_4$), 7.26-8.07 (m, 20 H, 4 $C_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 55.2 ($CH_3$), 63.2 (C-6), 69.8 (C-4), 70.2 ($CH_2C_6H_4$), 71.8 (C-2), 72.3 (C-5), 72.9 (C-3), 98.7 (C-1), 110.2, 113.8, 117.4, 128.3, 128.4, 128.7, 128.8, 129.3, 129.7, 129.8, 129.9, 133.2, 133.4, 159.4 (30 C, $C_6H_4$, 4 $C_6H_5$), 165.0, 165.2, 165.8, 166.2 (4 C, 4 CO).

## IV.2.7 2nd Attempt

***Experiment 44: MAR-220 and MAR-227***

**Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (100):** $LiAlH_4$ (20.0 mg, 0.52 mmol) was added to a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosiduronic acid **99** (300 mg, 0.52 mmol) in dry THF (3 mL) under argon. The mixture was stirred for 1 h at 25°C. $LiAlH_4$ (40.6 mg, 2.12 mmol) was added and the mixture was stirred for another 30

min. The reaction was quenched with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 3:1) yielding **100** (215 mg, 88 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 3.36 (s, 1 H, C*H*$_3$), 3.49-3.54 (m, 2 H, H-2, H-4), 3.63 (m, 1 H, H-5), 3.66-3.78 (m, 2 H, H-6), 4.05 (m, 1 H, H-3), 4.56 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.58-5.00 (m, 6 H, 3 C*H*$_2$Ph), 7.25-7.37 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 55.2 (*C*H$_3$), 60.4 (C-5), 61.9 (C-6), 70.7 (C-5), 73.4, 75.0, 75.8 (3 C, 3 *C*H$_2$Ph), 77.4 (C-4), 80.0 (C-2), 82.0 (C-3), 98.2 (C-1), 127.6, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 130.9, 138.1, 138.2, 138.7 (18 C, 3 C$_6$H$_5$).

**$[\alpha]_D^{20}$ =** + 22.4 ( c = 0.77, $CHCl_3$, **100**)

***Experiment 45: MAR-226***

**Methyl-2,3,4-tri-*O*-benzyl-6-*O*-(4-methoxyphenyl)-α-D-glucopyranoside (101):** DEAD (49.6 mg, 0.284 mmol) was slowly added to a solution of **100** (60.0 mg, 0.129 mmol), $Ph_3P$ (74.5 mg, 0.284 mmol), hydroquinone monomethyl ether (81.8 mg, 0.659 mmol) in dry THF (2 mL) at 80°C under argon. The mixture was stirred for 5 h under reflux at this temperature, quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (4 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (toluene-EtOAc 19:1) yielding **101** (63 mg, 85 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 3.39 (s, 3 H, OC*H*$_3$), 3.60 (dd, $^3J_{1,2}$ = 3.5, $^3J_{2,3}$ = 9.6 Hz, 1 H, H-2), 3.72 (m, 1 H, H-4), 3.76 (s, 3 H, OC*H*$_3$), 3.88 (m, 1 H, H-5), 4.02 (m, 1 H, H-3), 4.05-4.09 (m, 2 H, H-6), 4.50-5.01 (m, 6 H, 3 *C*H$_2$Ph), 4.64 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, H-1), 6.79 (m, 4 H, C$_6$*H*$_4$), 7.16-7.38 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 55.3, 55.7 (2 C, 2 O*C*H$_3$), 67.1 (C-5), 69.4 (C-6), 73.5, 75.2, 75.8 (3 C, 3 *C*H$_2$Ph), 77.5 (C-4), 79.9 (C-2), 82.1 (C-3), 98.3 (C-1), 114.6, 115.5,

127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 138.1, 138.2, 138.7, 152.8, 154.0 (24 C, 3 $C_6H_5$, $C_6H_4$).

### III.3.2 2nd Attempt for the synthesis of macrocycle (2)

***Experiment 46: MAR-233***

**2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-β-L-*galacto*-octopyranoside (98):** $LiAlH_4$ (81.3 mg, 2.14 mmol) was added to a solution of **44** (1.3 g, 2.14 mmol) in dry THF (10 mL) under argon. The mixture was stirred for 1 h at 25°C. $LiAlH_4$ (40.6 mg, 2.12 mmol) was added and the mixture was stirred for another 30 min. The reaction was quenched by addition of $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (petroleum ether-EtOAc 3:1) yielding **98** (1.14 g, 92 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.02 (m, 2 H, H-2'), 1.34-1.45 (m, 2 H, H-6a, H-7a), 1.51-1.60 (m, 2 H, OH, H-7b), 1.80 (m, 1 H, H-6b), 3.23 (m, 1 H, H-5), 3.60 (m, 1 H, H-4), 3.48-3.58 (m, 4 H, H-1'a, H-3, H-8), 3.80 (dd, $^3J_{1,2}$ = 7.7, $^3J_{2,3}$ = 9.7 Hz, 1 H, H-2), 3.98 (m, 1 H, H-1'b), 4.31 (d, $^3J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.65-4.98(m, 6 H, 3 C$H_2$Ph), 7.23-7.37 (m, 15 H, 3 C$_6H_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 19.9 (C-2'), 28.8 (C-6), 30.7 (C-7), 64.0 (C-8), 68.6 (C-1'), 75.8, 75.9, 76.5 (3 C, $CH_2$Ph), 76.8 (C-4), 81.1 (C-2), 84.0 (C-3), 104.4 (C-1), 128.9, 129.0, 129.1, 129.2, 129.5, 129.6, 129.7, 129.8, 130.0, 130.2, 130.3, 140.0, 140.1, 140.4 (18 C, 3 $C_6H_5$).

**$[\alpha]_D^{20}$ =** + 8.3 ( c = 1.02, $CHCl_3$, **98**)

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{34}H_{46}O_6Si$ | calculated | C 70.55 | H 8.01 |
| (578.81) | found | C 69.16 | H 7.82 |

***Experiment 47: MAR-234***

**2-(Trimethylsilyl)ethyl 2,3,4-Tri-*O*–benzyl-6,7–dideoxy-8-*O*-(4-methoxyphenyl)-L-*galacto*-octopyranoside (97):** DEAD (748 mg, 4.28 mmol) was slowly added to a solution of **98** (1.13 g, 1.95 mmol), $Ph_3P$ (1.12 g, 4.28 mmol), hydroquinone monomethyl ether (1.23 g, 9.93 mmol) in dry THF (18 mL) at 80°C under argon. The mixture was stirred for 5 h under reflux at this temperature, quenched with a saturated solution of $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography on silica gel (toluene-EtOAc 19:1) yielding **97** (1.14 g, 85 %).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.03 (m, 2 H, H-2'), 1.52-1.62 (m, 2 H, H-6a, H-7a), 1.77-1.91 (m, 2 H, H-6b, H-7b), 3.28 (m, 1 H, H-5), 3.50 (dd, $^3J_{2,3}$ = 9.9, $^3J_{3,4}$ = 3.0 Hz, 1 H, H-3), 3.55 (m, 1 H, H-1'a), 3.64 (m, 1 H, H-4), 3.76 (m, 1 H, O*CH*$_3$), 3.78-3.90 (m, 3 H, H-2, H-8), 4.00 (m, 1 H, H-1'b), 4.31 (d, 1 H, $^3J_{1,2}$ = 7.7 Hz, H-1), 4.67-4.99 (m, 6 H, 3 C*H*$_2$Ph), 6.76-6.82 (m, 4 H, C$_6$*H*$_4$), 7.22-7.39 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 18.6 (C-2'), 25.9, 27.8 (2 C, C-6, C-7), 55.9 (O*C*H$_3$), 67.2 (C-1'), 68.4 (C-8), 73.3, 74.2, 74.4, 75.1, 75.3 (5 C, C-4, C-5, 3 *C*H$_2$Ph), 79.9 (C-2), 82.8 (C-3), 103.6 (C-1), 114.8, 115.5, 127.7, 128.3, 128.4, 128.5, 128.7, 131.1, 133.1, 138.8, 139.1 (24 C, 3 *C*$_6$H$_5$, *C*$_6$H$_5$).

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{41}H_{52}O_7Si$ | calculated | C 71.90 | H 7.65 |
| (684.93) | found | C 71.98 | H 7.67 |

***Experiment 48: MAR-230***

**2,3,4-Tri-*O*-benzyl-6,7-dideoxy-8-*O*-(4-methoxyphenyl)-β-L-*galacto*-octopyranose (96):** TFA (0.57 mL) was added dropwise within 15 min to a solution of **97** (99 mg, 0.14 mmol) in $CH_2Cl_2$ (0.29 mL) at 0°C under argon. The mixture was stirred for 30 min at this temperature, the pH of the solution was adjusted to pH 7 by addition of 10 % aqueous $NaHCO_3$ (11 mL). The mixture was extracted with $CH_2Cl_2$ (4 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column

chromatography (toluene-EtOAc 4:1) yielding **96** as a mixture of two isomers (α/β 3.14:1; 65 mg, 76%).

**$^1$H NMR (500 MHz, $CDCl_3$):** of the mixture **96**α /**96**β (3.14:1): **96**α**:** δ1.56-1.59 (m, 2 H, H-6a, H-7a), 1.73-1.87 (m, 2 H, H-6b, H-7b), 2.87 (s, 1H, OH), 3.76 (s, 3 H, OC*H*$_3$), 3.78-3.90 (m, 3 H, H-3, H-8), 3.94 (m, 1 H, H-5), 4.02 (s, 1 H, H-2), 5.26 (m, $^3J_{1,2}$ = 3.4 Hz, 1 H, H-1), 4.65-5.00 (m, 6 H, 3 C*H*$_2$Ph), 6.76-6.82 (m, 4 H, C$_6$*H*$_4$), 6.24-7.40 (m, 15 H, 3 C$_6$*H*$_5$); **96**β**:** δ 1.56-1.59 (m, 2 H, H-6a, H-7a), 1.73-1.87 (m, 2 H, H-6b, H-7b), 3.02 (s, 1 H, OH), 3.37 (m, 1 H, H-5), 3.54 (m, 1H, H-3), 3.69 (m, 1 H, H-4), 3.76 (s, 3 H, OC*H*$_3$), 3.78-3.90 (m, 2 H, H-8), 4.60 (m, $^3J_{1,2}$ = 7.3 Hz, 1 H, H-1), 4.65-5.00 (m, 6 H, 3 C*H*$_2$Ph), 6.76-6.82 (m, 4 H, C$_6$*H*$_4$), 6.24-7.40 (m, 15 H, 3 C$_6$*H*$_5$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$)** of the mixture **96**α /**96**β (3.14:1): δ 25.9, 27.8 (C-6, C-7), 55.7 (C*H*$_3$), 68.5 (C-8), 70.7 (C-5), 73.4, 74.0, 75.0 (3 C, 3 *C*H$_2$Ph), 75.4 (C-4), 76.4 (C-2), 79.7 (C-3), 92.2 (C-1), 115.0, 115.8, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5 (24 C, 3 *C*$_6$H$_5$, *C*$_6$H$_4$).

**Elementary analysis**

| | | | |
|---|---|---|---|
| $C_{36}H_{40}O_7$ | calculated | C 73.95 | H 6.90 |
| (584.70) | found | C 73.80 | H 7.04 |

***Experiment 49: MAR-239***

**(3*R*,4*R*)-[2,3,4-Tri-*O*-benzyl-6,7-dideoxy-8-*O*-(4-methoxyphenyl)-α-L-*galacto*-octopyranosyl]-(1→3)-4-benzoyloxy-3-hydroxy-*N*-(2-naphtyl)-pentanoic amide (95):** **96** (695 mg, 1.19 mmol) was dissolved in dry $CH_2Cl_2$ (10.2 mL) and dry DMF (1.5 mL) under argon. The mixture was cooled to 0°C and $(COBr)_2$ (0.332 mL, 30.4 mmol) was added to give a white suspension, which was stirred for 5 min. The reaction was warmed to 25°C within 20 min and the mixture was stirred for 2 h, giving a thick white suspension. The suspension was filtered, washed with dry $CH_2Cl_2$ (3 x 5 mL) and the filtrate was concentrated. The residue was dried for 30 min at $10^{-3}$ Torr to give a dark yellow oil (980 mg). The oil was dissolved in $CH_2Cl_2$ (4.9 mL) and the solution added to a suspension of **42** (864 mg, 2.38 mmol), MS4Å (1.0 g) and $Bu_4NBr$ (383 mg, 1.19 mmol)

in dry in $CH_2Cl_2$ (2 mL) / DMF (3.2 mL) under argon. The mixture was stirred for 12 h at 25°C, diluted with $CH_2Cl_2$ (20 mL) and filtered through Celite. The filtrate was quenched with $NaHCO_3$ 10% (20 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The organic layer was washed with 1 M $KH_2PO_4$ (30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (toluene-EtOAc 4:1) yielding **95** (840 mg, 76%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.39-1.59 (m, 2 H, Fuc-H7), 1.42 (d, 3 H, $^3J_{4,5}$ = 6.5 Hz, 1 H, H-5), 1.44-1.50 (m, 2 H, Fuc-H6), 2.52 (dd, $^2J_{a,b}$ = 15.2, $^3J_{2,3}$ = 3.9 Hz, 1 H, H-2a), 2.52 (dd, $^2J_{a,b}$ = 15.2, $^3J_{2,3}$ = 3.9 Hz, 1 H, H-2b), 3.53-3.63 (m, 2 H, Fuc-H8), 3.66 (m, 1 H, Fuc-H4), 3.70 (m, 1 H, Fuc-H5), 3.75 (s, 3 H, OC$H_3$), 4.00 (m, 1 H, Fuc-H3), 4.06 (m, 1 H, H-3), 4.20 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 10.2 Hz, 1 H, Fuc-H2), 4.55-4.88 (m, 6 H, 3 C$H_2$Ph), 4.89 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, Fuc-H1), 4.49 (m, 1 H, H-4), 6.73-6.82 (m, 4 H, $C_6H_4$), 7.13-9.52(m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.7 (C-5), 25.2, 27.1 (2 C, Fuc-C6, Fuc-C7), 38.1 (C-2), 55.7 (O$CH_3$), 68.1 (Fuc-C8), 70.9 (C-4), 71.5 (Fuc-C5), 73.0, 74.8, 74.9, 75.5, 75.8 (5 C, Fuc-C2, Fuc-C4, 3 $CH_2$Ph), 97.3 (Fuc-C1), 114.6, 115.3, 115.4, 116.8, 119.7, 120.2, 124.6, 125.3, 126.1, 127.3, 127.4, 127.5, 127.7, 127.8, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 129.6, 129.8, 130.1, 130.5, 133.0, 133.4, 136.0, 137.1, 137.9, 138.3, 138.4, 153.1, 153.7 (40 C, 4 $C_6H_5$, $C_6H_4$, $C_{10}H_7$), 165.5, 168.1 (2 C, 2 CO).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{58}H_{59}NO_{10}$ | calculated | C 74.90 | H 6.39 | N 1.51 |
| (930.09) | found | C 74.24 | H 6.41 | N 1.29 |

***Experiment 50: MAR-240***

**(3*R*,4*R*)-[2,3,4-tri-*O*-benzyl-6,7-dideoxy-8-*O*-(4-methoxyphenyl)-α-L-*galacto*-octopyranosyl]-(1→3)-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (93):** Under an argon atmosphere, **95** (840 g, 0.86 mmol) was dissolved in freshly dried MeOH to give a clear solution. 1 M NaOMe in dry MeOH (1.0 mL) was added to bring the solution's pH to 10. The mixture was stirred for 28h at 25°C, neutralized with Amberlyst 15 and filtered off through Celite. The Celite was washed with 50 mL MeOH and 80 mL $CH_2Cl_2$. The

solvent was evaporated and dried under high vacuum. Elution with 1:4 toluene-EtOAc gave **93** (630 g, 84% yield).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.30 (d, 3 H, $^3J_{4,5}$ = 6.3 Hz, 1 H, H-5), 1.59 (m, 2 H, Fuc-H6a, Fuc-H7a), 1.78 (m, 2 H, Fuc-H6b, Fuc-H7b), 2.42 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2a,3}$ = 3.5 Hz, 1 H, H-2a), 2.70 (dd, $^2J_{2a,2b}$ = 14.5, $^3J_{2b,3}$ = 4.2 Hz, 1 H, H-2b), 3.67 (m, 1 H, H-3), 3.74 (s, 3 H, OC*H*$_3$), 3.78 (m, 1 H, Fuc-H8a), 3.87 (m, 3 H, Fuc-H4, Fuc-H8b, H-4), 3.97 (m, 1 H, Fuc-H5), 4.03 (m, 1 H, Fuc-H3), 4.28 (dd, $^3J_{1,2}$ = 3.9 Hz, 1 H, Fuc-H2), 4.85 (d, $^3J_{1,2}$ = 3.9 Hz 1 H, Fuc-H1), 4.65-5.00 (m, 6 H, 3 C*H*$_2$Ph), 6.75-6.80 (m, 4 H, $C_6H_4$), 7.20-9.28 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 25.6, 27.8 (2 C, Fuc-C6, Fuc-C7), 30.9 (C-5), 39.0 (C-2), 55.7 (O*C*H$_3$), 68.3, 68.6 (2 C, Fuc-C8, C-4), 72.8, 74.9, 75.2, 75.9, 76.0 (4 C, 3 *C*H$_2$Ph, Fuc-C2), 80.1 (Fuc-C3), 82.2 (C-3), 98.1 (C-1), 114.6, 115.4, 116.3, 119.8, 124.7, 126.3, 127.2, 127.4, 127.6, 127.8, 128.4, 128.5, 128.6, 128.7, 129.0, 130.4, 133.9, 136.0, 137.0, 138.3, 153.0, 153.7 (34 C, 3 $C_6H_5$, $C_6H_4$, $C_{10}H_7$), 168.4 (*C*O).

**$[\alpha]_D^{20}$ =** - 104.1 (c = 0.98, $CHCl_3$, **93**)

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{51}H_{55}NO_9$ | calculated | C 74.16 | H 6.71 | N 1.70 |
| (825.98) | found | C 73.98 | H 6.83 | N 1.72 |

***Experiment 51: MAR-249***

**(3*R*,4*R*)-{3-[(2*S*)-Benzyl-3-cyclohexyl-2-hydroxypropanoate-2-*O*-yl]-2,4,6-tri-*O*-benzoyloxy-β-D-galactopyranosyl}-(1→4)-{[methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-8-*O*-(4-methoxyphenyl)-α-L-*galacto*-octopyranosyl-uronate]-(1→3)}-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (92): 93** (270 mg, 0.331 mmol) was added to a suspension of MS 3Å (2.0 g) in $CH_2Cl_2$ at –5°C under argon. The mixture was stirred for 1 h and **94** (380 mg, 0.49 mmol) was added. The mixture was stirred for 1 h and DMTST (170 mg, 0.662 mmol) was added. The mixture was stirred for 1 h at –5°C then for 20 h at 0°C and additional DMTST (85 mg, 0.33 mmol) was added. The mixture was stirred for 4 h at 0°C, diluted with $CH_2Cl_2$ (20 mL) and filtered through Celite. The filtrate was

quenched with $NaHCO_3$ 10% (20 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (toluene-EtOAc 19:1) yielding **92** (348 mg, 68%).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.44-1.41 (m, 13 H, $C_6H_{11}$, $CH_2C_6H_{11}$), 1.03 (d, $^3J_{4,5}$ = 5.6 Hz, 3 H, H-5), 1.59 (m, 2 H, Fuc-H7), 1.80-1.93 (m, 2 H, Fuc-H6), 2.35-2.70 (m, 2 H, H-2), 3.73 (m, 1 H, Fuc-H4), 3.75 (m, 3 H, $OCH_3$), 3.78-3.84 (m, 2 H, Gal-H3, Gal-H5), 3.90 (m, 2 H, Fuc-H8), 4.00 (m, 2 H, H-3, H-4), 4.03 (dd, 1 H, Fuc-H3), 4.09 (dd, 1 H, Fuc-H2), 4.12-4.16 (m, 2 H, Fuc-H5, Cyc-H1), 4.25-4.40 (m, 2 H, Gal-H6), 4.48-5.15 (m, 8 H, 4 $CH_2$Ph), 4.51 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, Gal-H1), 5.58 (m, 1 H, Gal-H2), 5.88 (m, 1 H, Gal-H4), 7.03-9.31 (m, 26 H, $C_6H_4$, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.9 (C-5), 26.0, 26.2, 26.4, 26.5, 33.2, 33.8 (6 C, $C_6H_{11}$, $C_6H_{11}$), 37.3 (C-2), 40.8 (Cyc-C3), 56.1 ($OCH_3$), 63.3 (Gal-C6), 67.0 ($CH_2$Ph), 69.0 (Fuc-C8), 70.5 (Gal-C4), 71.8 (Fuc-C5), 72.3 (Gal-C5), 72.8 (Gal-C2), 73.3, 74.6, 75.4 (3 C, 3 $CH_2$Ph), 76.3 (Fuc-C2), 76.4 (C-3), 77.0 (Fuc-C4), 77.9 (Gal-C3), 78.7 (Cyc-C2), 80.3 (Fuc-C3), 97.1 (Fuc-C1), 100.7 (Gal-C1), 112.4, 113.9, 114.2, 115.0, 115.7, 117.4, 118.6, 120.8, 125.0, 125.7, 126.5, 127.4, 127.8, 127.9, 128.0, 128.1, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.4, 129.9, 130.0, 130.1, 130.2, 130.3, 130.4, 130.9, 133.4, 133.5, 133.6, 133.7, 133.9, 134.2, 135.9, 136.3, 137.7, 139.0, 139.1, 153.7, 154.0 (58 C, $C_6H_4$, 7 $C_6H_5$, $C_{10}H_7$),165.1, 166.3, 166.4, 169.4 (5 C, 5 CO).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{94}H_{97}NO_{19}$ | calculated | C 73.74 | H 6.32 | N 0.92 |
| (1514.75) | found | C 71.51 | H 6.33 | N 0.48 |

**Experiment 52:** ***MAR-252 (Partially deprotected)***

**(3*R*,4*R*)-{3-[(2*S*)-Methyl 3-cyclohexyl-2-hydroxypropanoate-2-*O*-yl]-2-*O*-benzoyl-β-D-galactopyranosyl}-(1→4)-{[methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-8-*O*-(4-methoxyphenyl)-α-L-*galacto*-octopyranosyl-uronate]-(1→3)}-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (91b):** Under an argon atmosphere, **92** (20 mg, 0.01 mmol) was dissolved in freshly dried MeOH to give a clear solution. 1 M NaOMe in dry MeOH

(1.0 mL) was added to bring the solution's pH to 10. The mixture was stirred for 28h at 25°C, neutralized with Amberlyst 15 and filtered off through Celite. The filter was washed with 20 mL MeOH and 20 mL $CH_2Cl_2$. The solvent was evaporated and dried under high vacuum. Elution with 1:4 toluene-EtOAc gave **91b** (13.8 mg, *79 %* yield).

**$^1$H NMR (500 MHz, $CDCl_3$):** δ 0.44-1.41 (m, 12 H, $C_6H_{11}$, $CH_2C_6H_{11}$), 1.05 (d, $^3J_{4,5}$ = 5.6 Hz, 3 H, H-5), 1.45 (m, 2 H, Fuc-H7), 1.80-1.93 (m, 2 H, Fuc-H6), 2.35-2.73 (m, 2 H, H-2), 3.42 (m, 2 H, Gal-H3, Gal-H4), 3.63 (m, 1 H, Gal-H5), 3.72, 3.78 (2 s, 6 H, 2 $OCH_3$), 3.84-3.97 (m, 6 H, H-3, H-4, Fuc-H4, Fuc-H5, Gal-H6), 3.99 (m, 1 H, Fuc-H3), 4.12 (m, 1 H, Fuc-H2), 4.18 (m, 2 H, Fuc-H8), 4.45 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, Gal-H1), 4.68-5.05 (m, 6 H, 3 $CH_2$Ph), 4.85 (m, 1 H, Fuc-H1), 5.56-5.60 (m, 1 H, Gal-H2), 6.78 (m, 4 H, $C_6H_4$), 7.03-9.31 (m, 27 H, 4 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.8 (C-5), 51.8 ($OCH_3$), 56.0 ($OCH_3$), 61.8 (C-4), 62.1 (Gal-C5), 68.1 (Fuc-C4), 68.9 (Gal-C6), 70.1 (Fuc-C8), 70.9 (Gal-C2), 73.4, 74.7, 74.8, 75.1 (4 C, $CH_2$Ph), 75.6 (C-3), 75.7, 77.1, 80.1 (3 C, Fuc-C2, Fuc-C3, Fuc-C5), 82.3 (Gal-C4), 94.3 (Fuc-C1), 100.3 (Gal-C1), 114.9, 115.8 126.6, 127.7, 127.8, 127.9, 128.6, 128.7, 128.8, 129.0, 130.1 (40 C, 4 $C_6H_5$, $C_6H_4$, $C_{10}H_7$), 168.0 (CO).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{79}H_{87}NO_{16}$ | calculated | C 72.82 | H 6.71 | N 0.82 |
| (1306.53) | found | C 69.68 | H 6.71 | N 1.11 |

***Experiment 53: MAR-267***

**(3*R*,4*R*)-(α-L-Fucopyranosyl)-(1→3)-4-benzoyloxy-3-hydroxy-*N*-(2-naphtyl)-pentanoic amide (103):** L-Fucose **102** (0.21 g, 0.48 mmol) was dissolved in dry $CH_2Cl_2$ (3.0 mL) and dry DMF (0.5 mL) under argon. The mixture was cooled to 0°C and $(COBr)_2$ (198 mg, 86.1 μL, 92.0 mmol) was added to give a white suspension, which was stirred for 5 min. The temperature was raised to 25°C within 20 min and the mixture was stirred for 2 h, giving a thick white suspension. The suspension was filtered, washed with dry $CH_2Cl_2$ (3 x 5 mL) and the filtrate was concentrated. The residue was dried 30 min at $10^{-3}$ Torr to give a dark yellow oil (350 mg). The oil was dissolved in $CH_2Cl_2$ (4.9 mL) and the solution added to a suspension of **42** (348 mg, 0.962 mmol), Ms4Å (0.5 g) and

$Bu_4NBr$ (0.154 g, 0.483 mmol) in dry in $CH_2Cl_2$ (1.5 mL) / DMF (1 mL) under argon. The mixture was stirred for 12 h at 25°C, diluted with $CH_2Cl_2$ (20 mL) and filtered through Celite. The filtrate was quenched with $NaHCO_3$ 10% (20 mL) and extracted with $CH_2Cl_2$ (3 x 30 mL). The organic layer was washed with 1 M $KH_2PO_4$ (30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (toluene-EtOAc 4:1) yielding **103** (291 mg, 78%).

**$[\alpha]_D^{20}$ =** -179.7 (c = 0.95, $CHCl_3$, **103**)

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 0.82 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, Fuc-H6), 1.44 (d, $^3J_{4,5}$ = 6.5 Hz, 3 H, H-5), 2.49-2.80 (m, 2 H, H-2), 3.49 (d, $^2J_{3,4}$ = 1.5 Hz, 1 H, Fuc-H4), 3.80 (m, 1 H, Fuc-H5), 3.98 (dd, $^3J_{2,3}$ = 10.3, $^3J_{3,4}$ = 2.7 Hz, 1 H, Fuc-H3), 4.06 (m, 1 H, H-3), 4.19 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 10.3 Hz, 1 H, Fuc-H2), 4.55-4.93 (m, 6 H, 3 C$H_2$Ph), 4.85 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, Fuc-H1), 5.44 (m, 1 H, H-4), 7.15-9.51 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 16.7 (Fuc-C6), 17.3 (C-5), 38.8 (C-2), 68.0 (Fuc-C5), 78.3 (Fuc-C4), 76.2 (Fuc-C2), 73.4, 75.3, 76.2 (3 $C$H$_2$Ph), 71.6 (C-4), 80.2 (C-3), 97.9 (Fuc-C1), 117.0, 120.5, 125.0, 126.5, 127.7, 128.0, 128.1, 128.2, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 129.4, 130.0, 130.5, 130.8, 133.4, 134.3, 136.4, 137.5, 138.8 (28 C, 3 $C_6$H$_5$, $C_{10}$H$_7$), 168.4 (2 C, 2 $C$O).

***Experiment 54: MAR-268***

**(3*R*,4*R*)-(α-L-Fucofuranosyl)-(1→3)-3,4-hydroxy-*N*-(2-naphtyl)-pentanoic amide (104): 103** (285 mg, 0.375 mmol) was solved in dry MeOH/dioxane 2:1 (8 mL) under argon to give a clear solution. 1 M NaOMe (800 μL) was added to bring the solution to pH 10. The mixture was stirred for 28h at 25°C, neutralized with Amberlyst 15 and filtered through Celite. The filter was washed with MeOH (50 mL) and $CH_2Cl_2$ (80 mL). The Celite was evaporated and dried under high vacuum. Elution with toluene-EtOAc (45:55) gave **104** (219 mg, 89% yield).

**$^1$H NMR (500.1 MHz, $CDCl_3$):** δ 1.15 (d, $^3J_{5,6}$ = 6.5 Hz, 3 H, Fuc-H6), 1.44 (d, $^3J_{4,5}$ = 6.3 Hz, 3 H, H-5), 2.43-2.72 (m, 2 H, H-2), 3.67 (m, 1 H, H-3), 3.74 (d, $^2J_{3,4}$ = 1.5 Hz, 1 H,

Fuc-H4), 3.88 (m, 1 H, H-4), 3.98 (dd, $^3J_{2,3}$ = 10.2, $^3J_{3,4}$ = 2.6 Hz, 1 H, Fuc-H3), 4.08 (m, 1 H, Fuc-H5), 4.24 (dd, $^3J_{1,2}$ = 3.8, $^3J_{2,3}$ = 10.2 Hz, 1 H, Fuc-H2), 4.65-5.00 (m, 6 H, C$H_2$Ph), 4.88 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, Fuc-H1), 7.15-9.20 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 17.1 (Fuc-C6), 19.6 (C-5), 39.7 (C-2), 68.2 (C-4), 73.2, 75.4, 75.6 (3 C, 3 $CH_2$Ph), 76.3 (Fuc-C2), 80.4 (Fuc-C4), 83.0 (Fuc-C1), 116.7, 120.2, 125.1, 126.7, 127.6, 127.8, 128.0, 128.2, 128.7, 128.9, 129.0, 129.1, 129.3, 129.4, 136.3, 138.7, 138.7 (28 C, 3 $C_6H_5$, $C_{10}H_7$), 168.1 (CO).

***Experiment 55: MAR-269***

**(3*R*,4*R*)-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-[(α-L-fucofuranosyl)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (106): 104** (113 mg, 0.17 mmol) was added to a suspension of MS 3Å (1.5 g) in $CH_2Cl_2$ at -5°C under argon. The mixture was stirred for 1 h and **105** (160 mg, 0.25 mmol) was added. The mixture was stirred for 1 h then DMTST (86 mg, 0.33 mmol) was added. The mixture was stirred for 20 h at –5°C and additional DMTST (43 mg, 0.17 mmol) was added. The mixture was stirred for 4 h at –2°C, diluted with $CH_2Cl_2$ (20 mL) and filtered through Celite. The filtrate was quenched with $NaHCO_3$ 10% (20 mL) and extracted with $CH_2Cl_2$ (4 x 30 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, concentrated and purified by column chromatography (toluene-EtOAc 19:1) yielding **106** (144 mg, 66%), which was directly used in the next step.

***Experiment 56: MAR-270***

**(3*R*,4*R*)-(β-D-galactopyranosyl)-(1→4)-[(Fucosyl)-(1→3)]-3,4-dihydroxy-*N*-(2-naphtyl)-pentanoic amide (107):** Under an argon atmosphere, **106** (130 mg, 0.85 mmol) was solved freshly dry MeOH to give a clear solution. 1 M NaOMe in dry MeOH (1.0 mL) was added to bring the solution's pH to 10. The mixture was stirred for 28h at 25°C, neutralized with Amberlyst 15 and filtered off through Celite. The filter was washed with 30 mL MeOH and 50 mL $CH_2Cl_2$. The solvent was evaporated and dried under high vacuum to give. Elution with 1:4 toluene-EtOAc gave **107** (82.4 mg, 80% yield).

**$^{1}$H NMR (500.1 MHz, $CDCl_3$):** δ 1.12 (d, $^{3}J_{5,6}$ = 6.2 Hz, 3 H, Fuc-H6), 1.23 (d, $^{3}J_{4,5}$ = 6.0 Hz, 3 H, H-5), 2.47-2.81 (m, 2 H, H-2), 3.36 (m, 1 H, Gal-H5), 3.59 (m, 1 H, Gal-H2), 3.72 (m, 1 H, Gal-H6a), 3.77 (m, 1 H, Gal-6b), 3.92 (m, 1 H, Gal-H4), 4.00 (m, 2 H, Fuc-H3, H-4), 4.10-4.15 (m, 3 H, Fuc-H2, Fuc-H5, H-3), 4.23 (d, $^{3}J_{1,2}$ = 1 H, Gal-H1), 4.61-4.96 (m, 6 H, 3 C*H*$_2$Ph), 4.88 (m, 1 H, Fuc-H1), 7.10-9.27 (m, 22 H, 3 $C_6H_5$, $C_{10}H_7$);

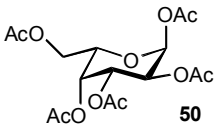
**$^{13}$C NMR (125.8 MHz, $CDCl_3$):** δ 15.8 (Fuc-C6), 31.3 (C-5), 62.5 (Gal-C6), 67.8 (Fuc-C5), 70.1 (Gal-C4), 71.8 (Gal-C2), 73.2 (Gal-C3), 73.8 (Gal-C4), 74.3, 74.8, 75.3 (4 C, Gal-C5, 3 *C*$H_2$Ph), 75.8 (Fuc-C3), 76.2 (Fuc-C2), 77.7 (Fuc-C4), 78.2 (C-2), 80.4 (C-4), 97.5 (Fuc-C1), 101.8 (Gal-C1), 117.2, 120.6, 125.2, 126.7, 127.7, 127.9, 128.1, 128.5, 128.7, 130.9, 134.2, 136.2, 137.8, 138.9, 139.0 (28 C, 3 *C*$_6$H$_5$, *C*$_{10}$H$_7$), 168.1 (*C*O).

**Elementary analysis**

| | | | | |
|---|---|---|---|---|
| $C_{94}H_{97}NO_{19}$ | calculated | C 73.74 | H 6.32 | N 0.92 |
| (1514.75) | found | C 71.51 | H 6.33 | N 0.48 |

## IV.3 List of molecules

### IV.3.1 L-Gal building block 15

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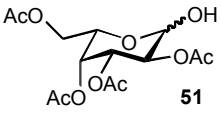


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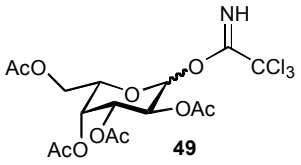


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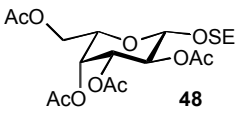


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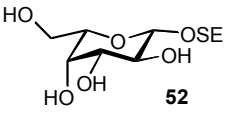


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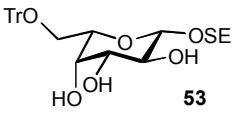


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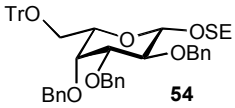


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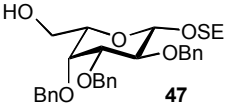


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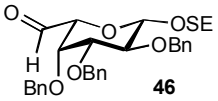


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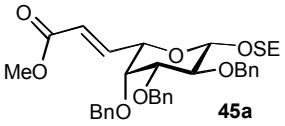


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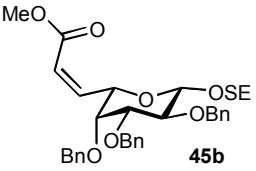


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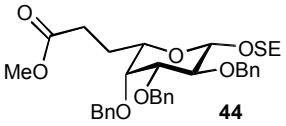


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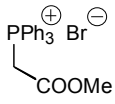


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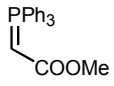


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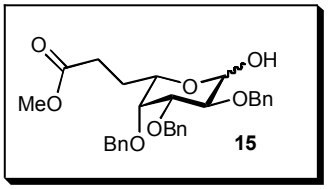
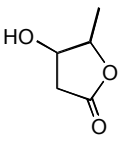
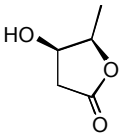



**15**

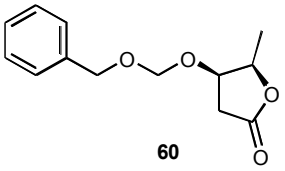
### IV.3.2 Acyclic Glc*N*Ac mimic 42




*rac*-62




(+)-62

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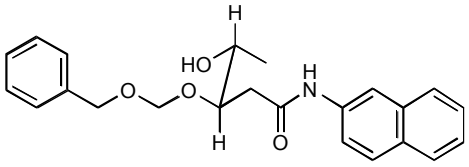


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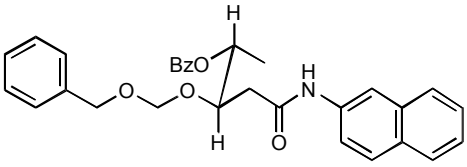


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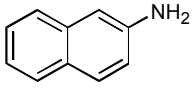


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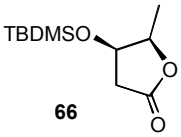


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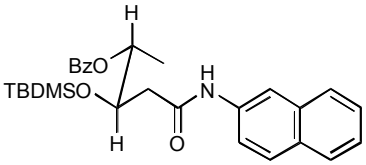


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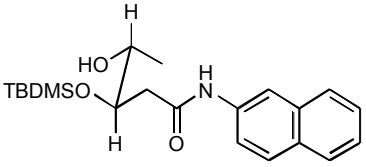


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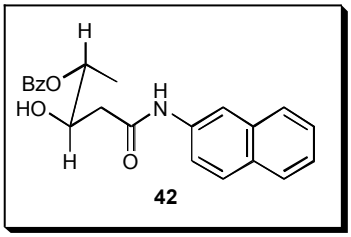
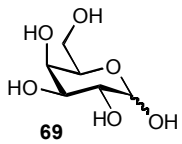



42

### IV.3.3 D-Gal mimic 40

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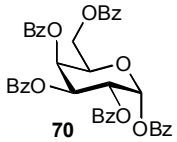


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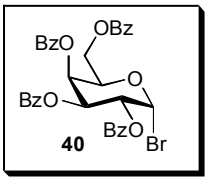
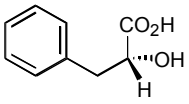



40

### IV.3.4 Cyclohexyl lactic acid building block 39

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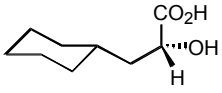
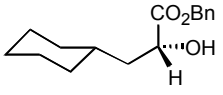



73

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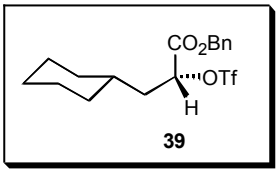
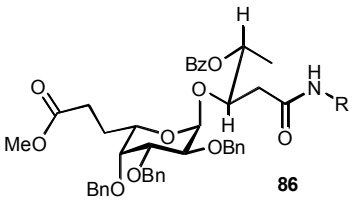
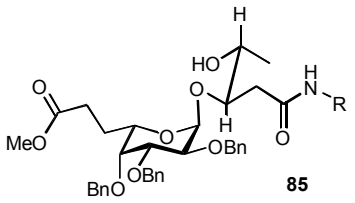



39

### IV.3.5 1st Attempt




**86**

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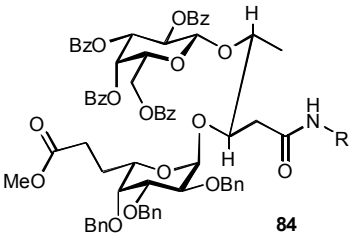


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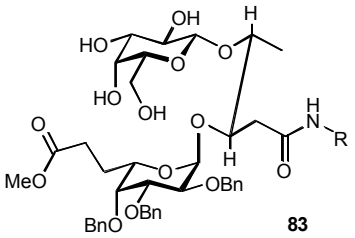


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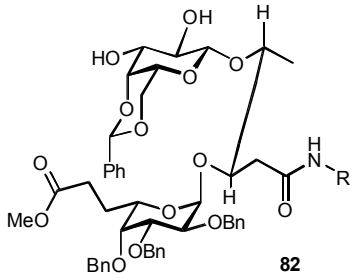


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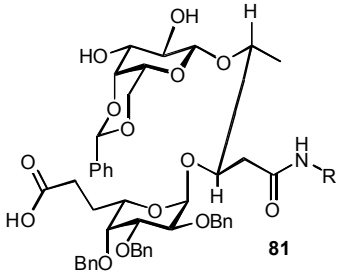
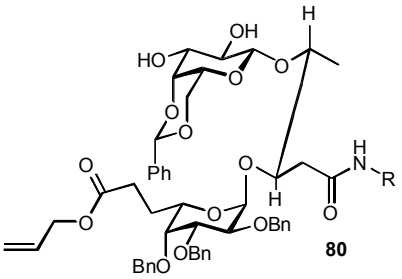
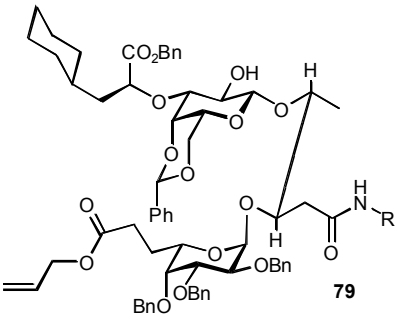



**81**

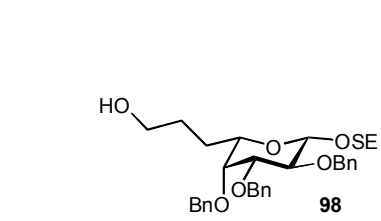



**80**




**79**

### IV.3.6 2nd Attempt

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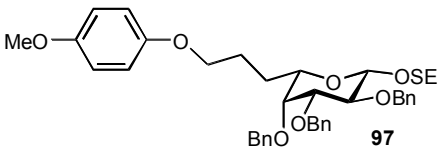
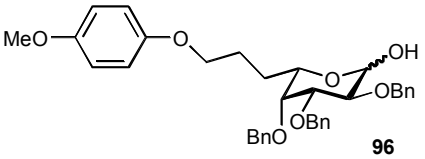
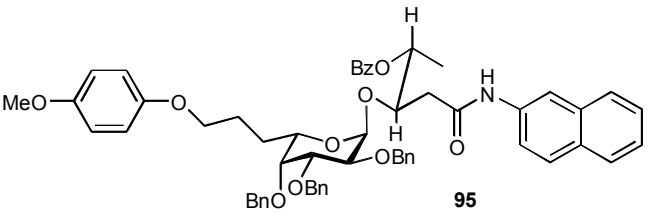


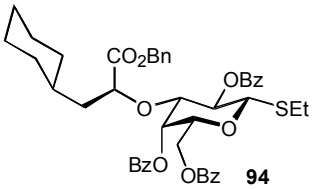

**97**



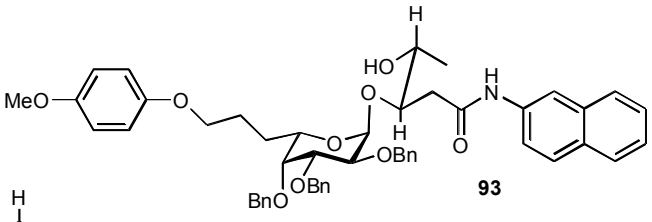

**96**



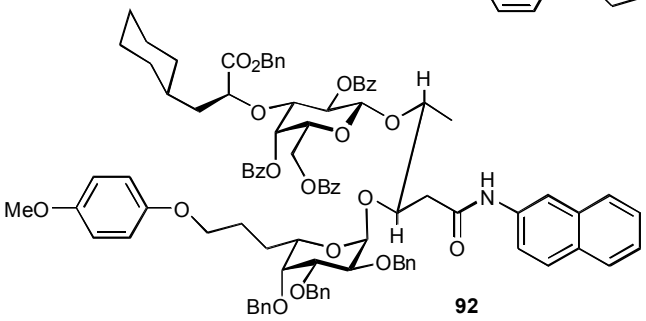

**95**




**94**

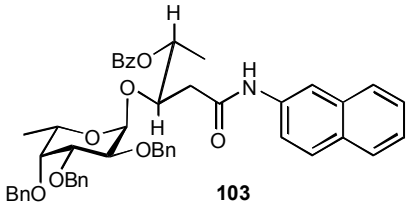



**93**

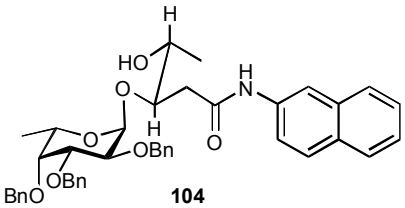



**92**

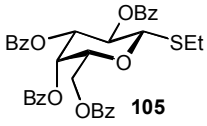
### IV.3.7 Test molecule with Fuc



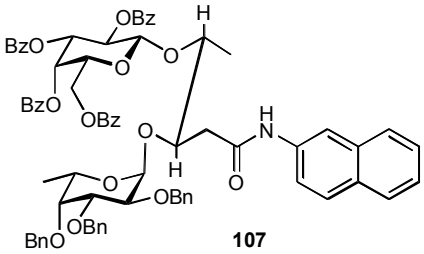

**103**



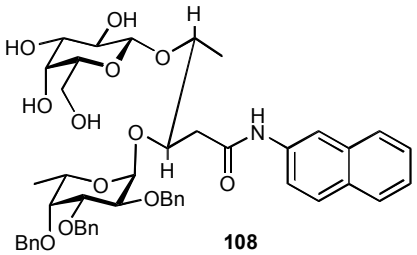

**104**




**105**




**107**




**108**

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## EDUCATION

**Ph. D. in Medicinal Chemistry,** University of Basel, CH, August 2004
- Title: *Toward the Synthesis of a Macrocyclic E-selectin Antagonist*, under the direction of Prof. Dr. B. Ernst
- Grade*: magna cum laude* (more than 5.5/6)
- Attended lectures "The Making of a Drug" and "Seminars on Drug Discovery & Development"

**Diplôme Fédéral de Pharmacien (Pharm.D.)**, Universities of Neuchâtel & Geneva, CH, November 1999
- Received 5.6/6.0 theoretical, 5.25/6.0 practical for diploma

## ADDITIONAL COLLEGIATE STUDIES

Leysin, CH, October 2002
- Attended the 5th Swiss course on Medicinal Chemistry

Harvard University and London School of Economics, summers 2001, 2002 and 2004
- Attended summer courses in Negotiation, Statistics, Finance and Quantitative Methods for Business

Debrecen University, HU, July 2000
- Attended the 6th European Training Course on Carbohydrates
  An introduction to modern principles, tools and trends of carbohydrate chemistry and technology

## RELEVANT EXPERIENCE

**University of Basel,** Basel, CH 1999-Present
*Assistant*
- Responsible for the "selectin antagonists project": Coordinated monthly project meetings attended by chemists, biologists and modelers
- Lectured undergraduate and graduate students on several topics including multi-dimensional nuclear magnetic resonance and carbohydrate chemistry
- Managed laboratory sessions in chemical molecular modeling (molecular dynamics, docking, energy minimization) and in combinatorial chemistry (peptide synthesis)

**Local Pharmacies**, Peseux, Cernier, and Geneva, CH 1999 – Present
*Pharmacist*
- Performed one-year internship to fulfill diploma requirements and worked in pharmacies throughout studies
- Managed up to 30 pharmacy assistants performing counter sales and logistical tasks

**Swiss Army**, CH 1994 – Present
*First Lieutenant, Pharmacist, Sanitary Corps*
- Led a unit of 30 soldiers caring for severely disabled patients in a military hospital
- Was responsible for the medicament distribution at the Central Pharmacy of the Swiss Army

**McKinsey & Company**, Zürich, CH June 2003
*Trainee*
- Successfully performed a consulting project consisting of a healthcare company's strategic market positioning

**Town of Villiers**, Villiers, CH 1996-2000
Elected *Conseiller Général,* (member of a village's legislative assembly)
- Represented the counsel at the local hospital

## PUBLICATIONS

ARTICLE

- Ernst B., Dragic Z., Marti S., Müller C., Wagner B., Jahnke W., Magnani J., Norman K., Oehrlein R., Peters T., Kolb H., *Design and Synthesis of E-Selectin Antagonists*, Chimia 55 268-274 (2001)

POSTERS

- Pfizer, Drug Discovery Symposium 2003, Sandwich, UK
- Swiss Chemical Society, Fall Meeting 2003, ETH Lausanne, CH
- Pharmaday, University of Basel 2003, CH

## SKILLS & INTERESTS

**French** (mother tongue), **English** (advanced, TOEFL: 273/300), **German** (advanced), **Italian** (early intermediate)

Windows, Mac, UNIX, Microsoft Office, ChemDraw, MacroModel, EndNote

History, French and English Literature, Mineralogy, Global Travel, Meeting People, Mountaineering, Running, Scuba Diving (Certificate)