Present Status in the Chemistry of Hexuronic Acids Found in Glycosaminoglycans and their Mimetic Aza-Sugars Analogues

Hammed H. A. M. Hassan*

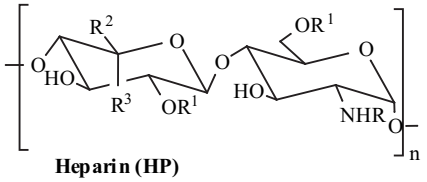
Chemistry Department, Faculty of Science, Alexandria University, Alexandria 21321, P.O. 426 Ibrahimia, Alexandria, Egypt

Abstract: In this paper, we shed light on the recent methodologies used for preparing uronic acids; the typical components of glycosaminoglycans (GAGs). The L-*ido* synthon is a key challenge in oligosaccharide synthesis and there is a constant need for its efficient preparation. Difficulties in obtaining these rare sugars from natural sources have required chemists to develop general and simple routes for their syntheses. The conformational flexibility of L-iduronic acid is analyzed to better understand its remarkable protein adaptability and resulting diverse biological activities and its impact on oligosaccharides synthesis. The synthesis of the new type of 1-*N*-iminosugars that represented glycosidase and glycosyltransferase inhibitors and served as chemotherapeutic agents is discussed in the final section.

Keywords: Glycosaminoglycans, L-iduronic acid, conformation, synthesis, configuration, D-glucuronic, 1-*N*-iminosugars.

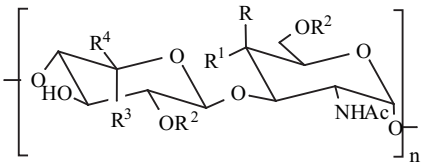
1. INTRODUCTION

Proteoglycans (PGs) are complex macromolecules present primarily at the cell surface, in the extracellular matrix that surrounds most mammalian cell types and also in body fluids. PGs consist of a core protein, of variable size and structure, and one or more associated glycosaminoglycan (GAG) chains. These GAGs can be of 5 types [1]. chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), heparin or keratan sulfate (KS), Scheme **1**.



Heparin (HP)
Heparan sulfate (HS)

$R = R^1 = H$ or SO_3^-, $R^2 = H$, $R^3 = COO^-$
$R = R^1 = H$ or SO_3^-, $R^3 = H$, $R^2 = COO^-$
$R = H$ or Ac or SO_3^-, $R^1 = H$ or SO_3^-, $R^2 = H$, $R^3 = COO^-$
$R = H$ or Ac or SO_3^-, $R^1 = H$ or SO_3^-, $R^3 = H$, $R^2 = COO^-$



Chondroitine sulfate (CS):
$R = OH, OSO_3^-$, $R^1 = H$,
$R^2 = H$ or SO_3^-
$R^3 = H$, $R^4 = COO^-$

Hyaluronic acid (HA):
$R = R^2 = R^3 = H$,
$R^2 = OH$, $R^4 = COO^-$

Dermatan sulfate (DS):
$R = OH, OSO_3^-$, $R^1 = H$,
$R^2 = H$ or SO_3^-
$R^3 = H$, $R^4 = COO^-$
$R^4 = H$, $R^3 = COO^-$

Scheme 1.

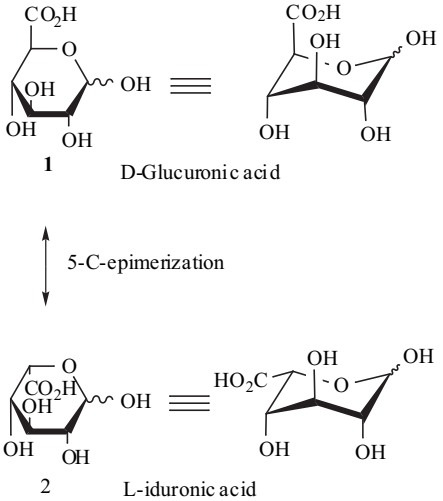
The GAG family is comprised of four subfamilies of linear polysaccharides consisting of repeating disaccharide units, in most cases composed of a uronic acid alternating with an *N*-substituted hexosamine, either glucosamine or galactosamine. These four subfamilies are HS/heparin, CS/DS, HA and KS. HA is the simplest as it does not undergo further modifications. Moreover, HA is synthesized as a free polysaccharide chain on a protein core to form a PG [2]. Heparin and HS are composed of alternating α-D-glucosamine and hexuronate (α-L-iduronate or β-D-glucuronate) residues. KS has the distinction of not containing an uronic acid residue, but having galactose instead. With the exception of HA, all other GAGs experience a complex series of post-polymeric modifications that can include epimerization of glucuronic acid to iduronic acid (IdoA) and possible sulphations at various *O*- and *N*-positions on either monosaccharide unit. Dermatan sulfate (DS) like chondroitin sulfate (CS) is assembled from α 1,4-linked *N*-acetyl galactosamine (GalNAc) alternating with β1,3-linked glucuronic acid (GlcA). Structurally, the common feature of CS/DS is thus the presence of GalNAc. However, conversion of a proportion of glucuronate residues to iduronate defines a DS, and distinguishes it from chondroitin 4-*O*-sulfate and chondroitin 6-*O*-sulfate which both preserve a100 % GlcA content. This feature of DS therefore likens it to heparin and HS which also contain IdoA residues. IdoA appears to play a key role in binding

*Address correspondence to this author at the Chemistry Department, Faculty of Science, Alexandria University, Alexandria 21321, P.O. 426 Ibrahimia, Alexandria, Egypt. Tel: + 2 012 5888 595, Fax: + 203 39 11 794, E-mail: hhamhassan@link.net or hhamhassan@gmail.com

1570-193X/07 $50.00+.00

site specificity for HS/heparin-binding proteins [3], which probably reflects the role of the flexibility of this sugar ring in mediating interactions [4]. It is likely that this is the same for DS as we are now seeing a greater recognition of the protein-binding properties of DS, relative to the apparently much less interactive CS. The sequence information within a DS chain is thus composed of three potential variables at the uronic acid position (i.e., GlcA, IdoA or 2-*O*-sulfated IdoA) and four variables at the hexoamine position (i.e., GalNAc, 4-*O*-sulfated GalNAc, 6-*O*-sulfated GalNAc, or 4-*O*-, 6-*O*-disulfated GalNAc). The uronate epimerization reaction, responsible for conversion of GlcA to IdoA, and the subsequent sulfation reactions, are not random but reflect a controlled enzymatic system for encrypting functional information into the GAGs [2].

As most of the structural information of carbohydrate-protein and carbohydrate-nucleotide complex at molecular level remains obscure, homogeneous materials with well-defined configurations are essential for the determination of biological activity and structure-function relationship. To perform structure–activity relationship studies, synthesis of a variety of monosaccharide building blocks would be rational to form a set of oligosaccharide libraries that serve to determine the key structural features necessary for binding to specific protein. L-Iduronic acid is a typical component of glycosaminoglycans (GAGs), where it plays an important role in various biological processes [4]. The only difference between the structures of the most abundant D-*gluco* and rare L-*ido* configuration is the stereochemistry at the C5 position. Preparation of L-iduronic acid derivatives is much more complicated than that of glucuronic acid derivatives since neither L-iduronic acid nor L-idose are available as starting materials. The preparation of L-*ido* synthon is a key point in glycoaminoglycan oligosaccharide synthesis and there is an important need for their efficient preparation [5]. This fact coupled with practical difficulties in obtaining these rare sugars from nature sources has urged chemists to develop novel, cost effective, general, simple, and convenient routes for their syntheses. As a result, the literature documents an array of methodologies for this purpose, each one having its own advantages and disadvantages. In this review, we wish to shed lights on the recent methodologies used for preparing both D-glucuronic **1** and L-iduronic acid **2** (Scheme **2**) building blocks, the conformational flexibility of L-iduronic acid will be detailed and analyzed in order to better understand its remarkable protein adaptability and resulting diverse biological activities [6], and their involvement in the oligosaccharides synthesis. In the last part of this review we present the reported synthesis of new type of uronic acids by replacement of the anomeric carbon with a nitrogen atom. The new type of 1-*N*-iminosugars represented a glycosidase and glycosyltransferase inhibitors and served as useful tools to study the biological function of glycolipids and as chemotherapeutic agents [7].



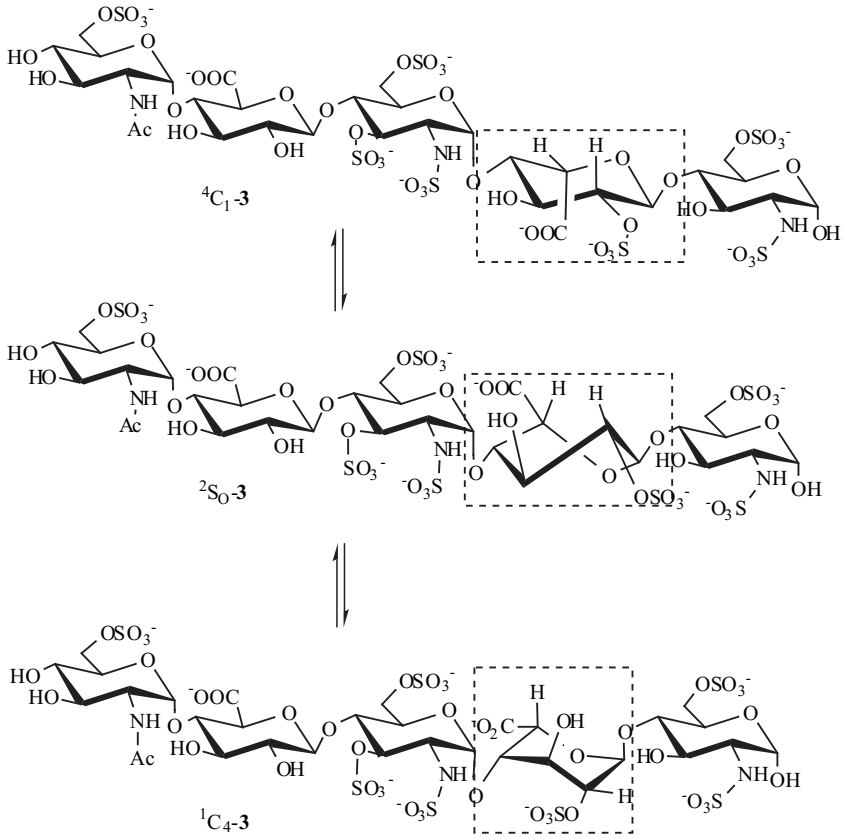
Scheme 2.

2. CHEMISTRY OF NATURAL HEXURONIC ACIDS

2.1. Conformation of L-Iduronic Acid and Biological Activity

Studies of the interaction of GAGs with hydroxyapatite (HAP) reported by Rees *et al.* [8], revealed that: i) GAGs are linear polysaccharides that present flexible molecules [9]. The carbohydrate skeleton forms an extended core with the anionic radicals positioned along the skeleton. However, the negative electrostatic charges are not fixed but are shared so as to form a shell of negativity with the loci of greater and lesser charge density. Strong interaction occurs between the electronegative charge field (or shell) and ions present on the HAP surface, which has been shown to have a net positive charge [10]. Binding of GAGs, therefore is electrostatic in nature, and is predominantly to calcium sites on HAP. ii) The iduronic-rich GAGs heparan sulfate, heparin and dermatan sulfate showed greater binding onto HAP with higher adsorption maxima compared with the glucuronic acid-rich GAGs chondroitin-4-sulfate, chondroitin-6-sulfate and hyaluronan. The data indicates that GAG chemistry and conformation in solution greatly influence the interaction of these molecules with HAP. The conformational flexibility of iduronic acid residues is an important determinant in the strong binding of iduronic acid-rich GAGs to HAP, increasing the possibility of the appended anionic groups matching calcium sites on the HAP surface, compared with more rigid glucuronic acid residues.

It is well documented that binding of heparin to AT III is mediated by the penta-saccharide sequence **3** [11]. Chemical synthesis of this pentasaccharide [12], allowed careful analysis of the ^{1}H NMR coupling constants for the L-iduronic acid unit which finally led to conclude that the conformational equilibrium of this monosaccharide could not be explained by the presence of the two well known conformers $^4C_1$ and $^1C_4$ only, but that a third one, ^2S_O (Scheme **3**). The contribution of each of the conformers to the conformational equilibrium could be computed from ^{1}H NMR coupling constants [13] and it appeared that L-iduronic acid conformation is highly influenced by the substituents and the nature of the neighboring units [14]. Thus, while $^1C_4$ was found to represent the predominant conformer in heparin, a significant shift of the conformational equilibrium toward ^2S_O was observed when L-iduronic acid was next to a 3-*O*-sulfated glucosamine unit [15].



Scheme 3.

Investigation on the role of L-iduronic acid conformation in the interaction of these heparin mimetics with antithrombin indicated that the pentasaccharide containing an iduronic acid moiety in the $^2S_0$ conformation is able to bind to antithrombin, and thereby to strongly reinforce its ability to inhibit the blood coagulation proteinase factor Xa [16]. A shift in the conformational equilibrium toward the $^1C_4$ conformation resulted in a reduced biological activity [17]. Results reported by Sakairi *et al*. [18] concluded that the $^1C_4$ conformation is not the active one, and that either the $^2S_0$ is essential or that the conformational flexibility of L-iduronic acid (switch from $^1C_4$ to $^2S_0$) is required during antithrombin activation. Thus, the current literature data have reached to a conclusion that the single L-iduronic acid unit contained in the antithrombin-binding site of heparin itself adopts the $^2S_0$ conformation when heparin binds to the protein.

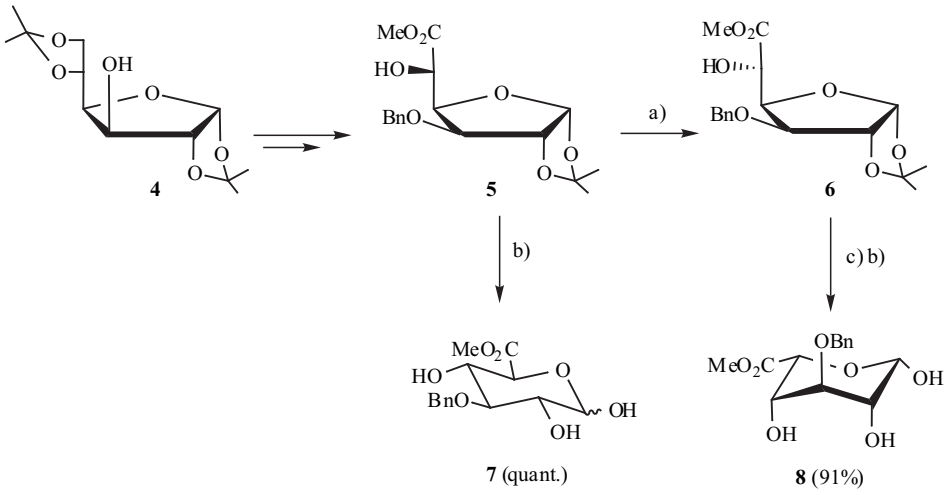
2.2. Synthesis of L-Iduronic Acid Derivatives

Glycosaminoglycan synthesis requires large quantities of differentially protected glucuronic **1** and iduronic acids **2** molecules and necessitates concise and efficient methods for the production of these synthons. Since iduronic acid itself is not commercially available, syntheses of iduronic acid derivatives from a variety of starting materials have been developed.

2.2.1. Epimerization of Anancomeric D-Glucuronic Acid Analogues

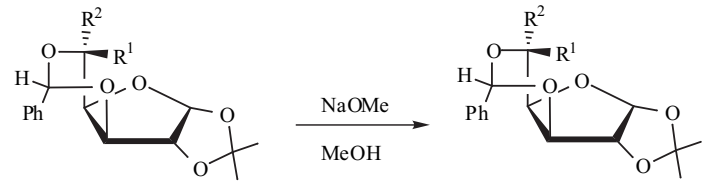
A synthetic route based on isomerization at C-5 of D-glucuronic acid to give L-iduronic acid is attractive, because of the availability of the former. Nucleophilic displacements of a 5-sulfonate [19], triflate [20] groups in D-glucofuranose [19] or D-glucofuranuronic acid derivatives [21] have been reported. Commercially available diacetone glucose **4** (Scheme **4**) was converted to crystalline glucuronic acid furanoside **5** by standard procedures. Access to iduronic acid furanoside **6** was readily achieved by inversion of the C5 stereocenter of the triflate derived from **5**. Treatment of **5** and **6** with trifluoroacetic acid resulted in deprotection and formation of the uronic acid pyranosides **7** and **8**, respectively [21].

It has been suggested that the essential features in any derivative of D-glucuronic acid to be used for efficient isomerization to L-iduronic acid are that the aldehyde group should be masked and that the carboxyl group should be constrained to an axial position. Both of these features are embodied in the 1,2,3,5-diacetals of D-glucuronic acid **9**-**13** derivatives (Scheme **5**), provided that they have similar conformations to their reduced analogues [22], and consequently a number of these derivatives have been synthesized and their epimerization studied. The starting D-glucuronic acid derivatives were constrained to adopt a conformation having C-6 in an axial position, so that the L-iduronic acid derivatives would be thermodynamically more stable. The ester derivatives of 3,5-*O*-benzylidene-l,2-*O*-isopropylidene-β-L-idofuransides **14-18** were conveniently obtained, respectively, in an average of 23 % yield by treatment of the diacetals **9**-**13** with NaOMe [23]. The low yield in the isomerization step is due to lability under the basic reaction conditions, probably through β-elimination [24].



a) Tf_2O, pyridine then LevONa, DMF; b) 90% aq.TFA; c) N_2H_4 , HOAc, pyridine.

Scheme 4.



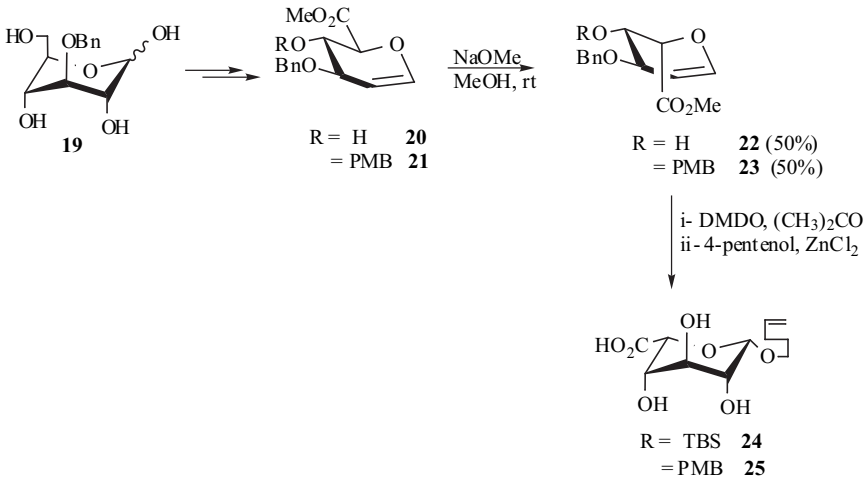
$R^1 = CO_2Me$, $R^2 = H$ **9**
$R^1 = CO_2Bn$, $R^2 = H$ **10**
$R^1 = CO_2Et$, $R^2 = H$ **11**
$R^1 = CONH_2$, $R^2 = H$ **12**
$R^1 = COOH$, $R^2 = H$ **13**

$R^2 = CO_2Me$, $R^1 = H$ **14** (23%)
$R^2 = CO_2Bn$, $R^1 = H$ **15** (30%)
$R^2 = CO_2Et$, $R^1 = H$ **16** (39%)
$R^2 = CONH_2$, $R^1 = H$ **17** (61%)
$R^2 = COOH$, $R^1 = H$ **18** (42%)

Scheme 5.

Base-catalyzed epimerization of D-glucuronic acid glycals **20, 21,** derived from **19,** results mainly in the formation of iduronic acid glycals **22, 23** (*ido*:*gluco* 4:1; separable) [25,26]. Transformation of the glycals **22, 23** into the corresponding *n*-pentenyl glycosides **24**, **25** was achieved by subsequent reaction with DMDO and 4-pentenol/$ZnCl_2$, Scheme **6**.

In a trial to avoid the β-elimination during base-catalyze C-5 epimerization reaction, a practical and expeditious conversion of various β-D-glucuronic acid derivatives into α- L-iduronic acid analogues by radical epimerization has been reported [27]. Thus, methyl (5*R*)-1,2,3,4-tetra-*O*-acetyl-5-C-bromo-β-D-glucopyranuronate **28** (Scheme **7**), readily available from the known methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate **26**, was reduced with tributyltin hydride

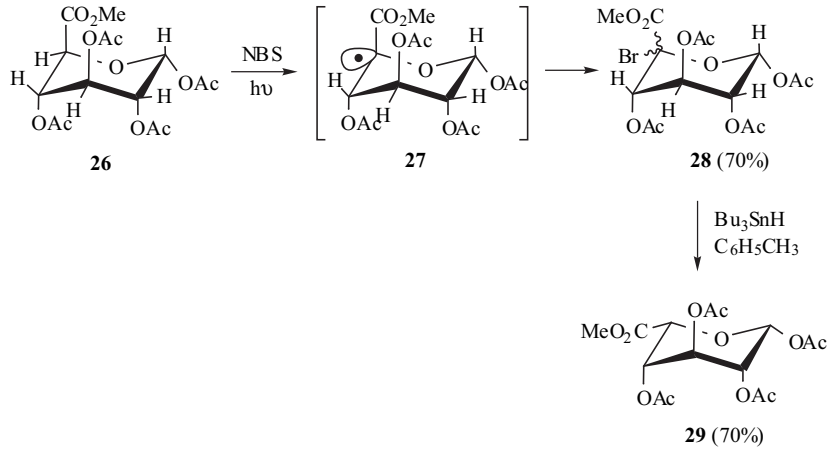


R = H **20**
= PMB **21**

R = H **22** (50%)
= PMB **23** (50%)

R = TBS **24**
= PMB **25**

Scheme 6.



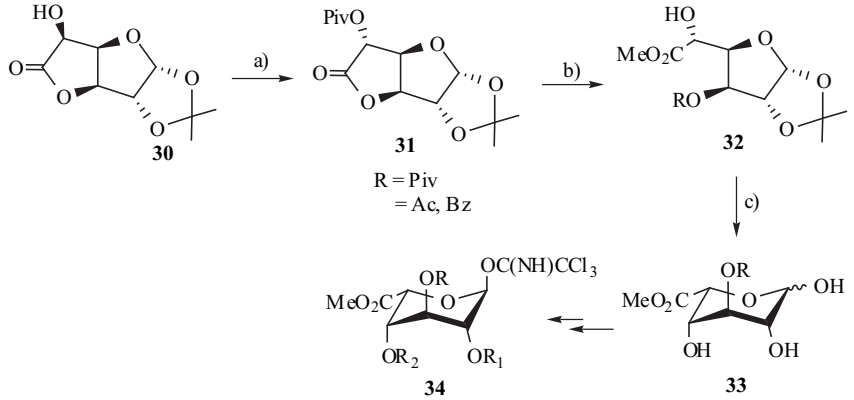
Scheme 7.

to give methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyran- uronate **29** (30%), together with unchanged **26** (63%). Replacement of acetyl by methyl groups had no influence on the D-*gluco*:L-*ido* ratio observed. The observed stereochemistry was explained by assuming that the radical **27** may be planar, as the tendency of the ring oxygen atom to induce bending is outweighed by the tendency of the methyloxycarbonyl group to induce coplanarity and thereby maximize delocalization of the unpaired electron [28]. Attack of this radical from the bottom face provides compound **26**, which adopts the $^4C_1$ conformation. Kinetic attack from the upper side provides compound **29**, which has been shown to adopt in solution the $^1C_4$ conformation where the incoming hydrogen presents a coplanar arrangement with the β-CO bond at C-4. Recently, Wong *et al.* [29] reported the isomerization at C-5 by free radical reduction of **28** with tributyltin hydride gave a 1:3 ratio of D-*gluco* and L-*ido* (**29**) isomers with a 70 % yield.

Effective preparation of differentially protected L-iduronic acid derivatives, as building block **34**, for the synthesis of heparin-like oligosaccharides, was reported [30], starting from readily available 1,2-*O*-isopropylidene-6,3-D-glucuronolactone **30** (Scheme **8**). The stereochemistry at *C*-5 was inverted to the *O*-5 pivaloate **31** *via* triflate intermediate. Then taking advantage of an *O*-5 to *O*-3 migration side reaction [31], methyl ester **32** were prepared under the catalysis of the organic base triethylamine at 0°C. It is important to note that, in addition to pivaloate group, acetate and benzoate groups undergo this migration. Hydrolysis of the isopropylidene acetal **32** using 90 % TFA furnished the corresponding 3-substituted L-iduronic acid ester **33** followed by standard chemistry procedures gave the α-trichloroacetimidate donors **34**.

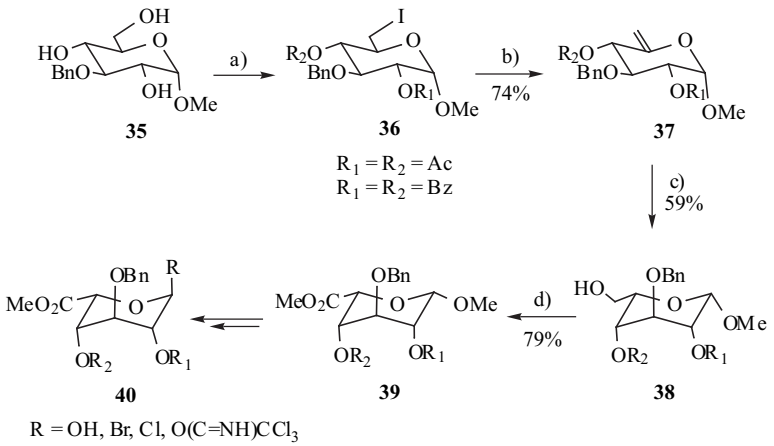
2.2.2. Diastereoselective Hydroboration/Oxidation of Exo-Glucal Derivatives

Another route leading to L-idose components using hydroboration of *exo*-glucal derivatives for monosaccharide [32] or disaccharide structures [33] was reported. In this methodology, the axially oriented aglycone plays an essential role to produce preferably the *ido* configuration by impeding an attack of borane reagents from the α side. In other words, the formation of L-*ido* products is favoured when the substituent at C-l (anomeric group) is located on the opposite side of the attack of the electrophile at C-5, i.e. α-oriented in the D-*gluco* series. As shown in Scheme **9** [34], treatment of known methyl 3-*O*-benzyl-α-D-glucopyranoside **35** with triphenylphosphine-iodine, imidazole afforded the corresponding 6-iodo-derivative, which is conventionally acetylated (Ac_2O/Py) or benzoylated



a) i. Tf_2O, Py; ii.NaOPiv, DMF; (b) Et_3N, MeOH, 0° C; (c) 90% TFA, rt, 3h

Scheme 8.



a) i.Ph_3P / I_2 / imidazole (86%); ii.Ac_2O (95%) or BzCl / Py (70%); b) DBU / DMF; c) $BH_3.Me_2S$ or BH_3.THF; d) i. CrO_3 / H_2SO_4 / $(CH_3)_2CO$; ii. Cl-CO_2Me/DMAP/CH_2Cl_2.

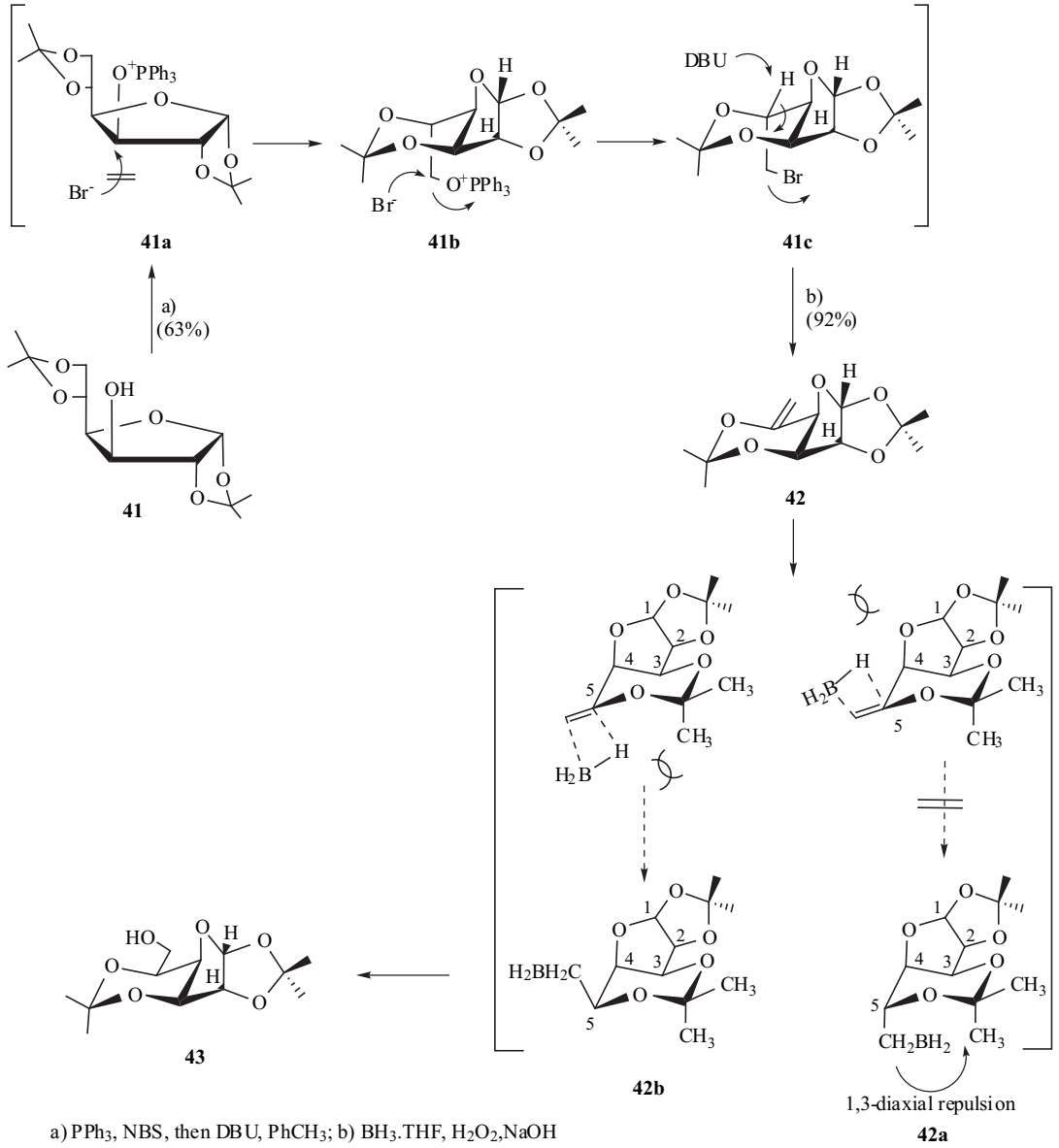
Scheme 9.

(BzCl/Py) to furnish **36**. Treatment of **36** with 1,8-diazabicyclo-[5,4,0]- undec-7-ene (DBU) in DMF afforded the *exo*-glucal **37**. Hydroboration of *exo*-glucal **37** solvated boranes (B_2H_6 / THF or B_2H_6 / Me_2S) gave predominantly the L-*ido* products **38**. Direct oxidation of **38** with Jones reagent (CrO_3 / H_2SO_4) in acetone followed by esterification of the intermediate acid with methyl chloroformate/DMAP in dichloromethane [35], gave methyl uronates **39**. Interestingly, transformation of **39** into various glycosyl donors **40** was achieved by anomeric methyl hydrolysis followed by either standard halogenation, to furnish the corresponding α-halo derivatives or α-trichloroacetimido-ylation to give the corresponding α-trichloroacetimidate.

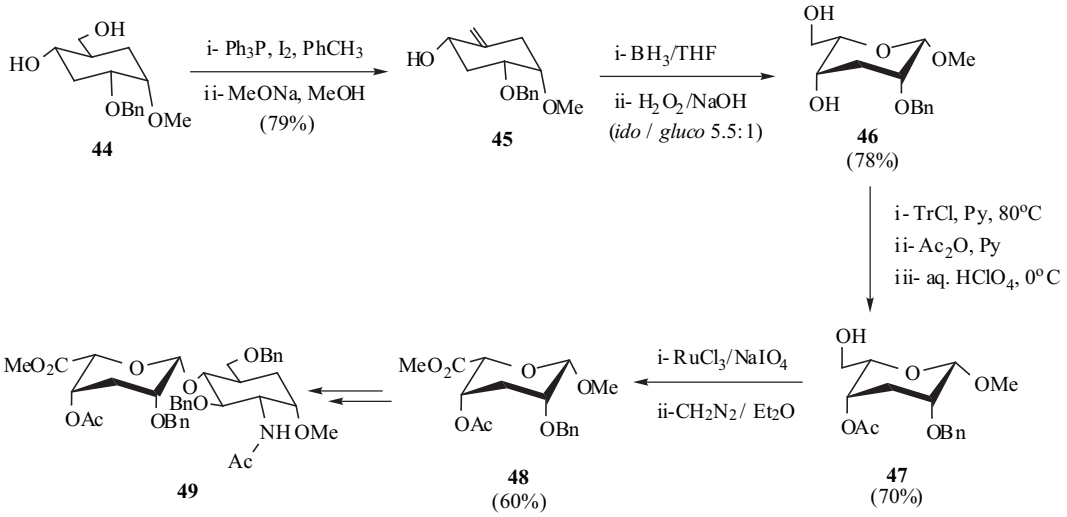
Preparation of the L-*ido* sugars based on the model of double ketal fixation on the 1,2 and 3,5-hydroxy groups of D-glucose to form a *cis-anti-cis*-fused tricyclic D-glucofuranosyl derivative, which could undergo elimination to form a 5-*exo*-double bond followed by hydroboration / oxidation to give the desired β-L-idofuranose was recently reported [36]. As outlined in Scheme **10**, treatment of diacetone-α-D-glucose **41** with triphenylphosphine (PPh_3), *N*-bromosuccinimide (NBS), and freshly distilled 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 80°C afforded the enol ether **42**. Mechanistically, PPh_3 first reacts with NBS to generate a phosphonium salt, which is readily attacked by the 3-hydroxy group of **41** resulting in the formation of alkoxyphosphonium intermediate **41a** [37]. Due to the rigid *cis*-5,5-fused ring conformation, the isopropylidene rearrangement of **41a** appears to precede over direct S_N2 substitution by bromide ion owing to the steric hindrance for the α-face attack. The rearrangement of intermediate **41a**→**41b** could be explained by the attack of the HO-3 upon of an intermediate formed under 5,6-isopropylidene ring opening/ring closure to give the thermodynamically favored 1,3-dioxane conformation **41b**, i.e. reaction with C5-O5, whereas the triphenylphosphine is migrated to the C6-O6. The transition state in **41b** is sterically favored for a facile nucleophilic displacement by bromide ion, which ends up in an overall regioselective bromination at C6 (**41c**). DBU then effected the dehydrobromination of **41c** to furnish the enol ether **42**. Hydroboration of compound **42** followed by oxidative work-up led to the desired L-idofuranosyl product **43** as a single diastereoisomer. Apparently, the face selectivity of borane addition in this case is arising mainly through a combination of complementary steric factors. The disposition of the axial C4-O4 bond directs the addition of borane onto the 5-*exo* double bond from the less hindered α-face to form the intermediate **42b** rather than **42a**. As a result, the substituted group (CH_2BH_2) orients equatorially at the C5 position of **42b**. Along with this, the 1,3-diaxial repulsion between the methyl and CH_2BH_2 groups in the boron complex **41a** also seems to play a role, resulting in exclusive formation of the L-*ido* isomer **43** after oxidative work-up.

In a study to prepare the $^1C_4$ conformer of L-iduronic acid **48** [19], by decreasing the non-bonding interactions occurring between O-3 and the other axial substituents in this conformer, 3-deoxy-L-idose from the known methyl 2-*O*-benzyl-3-deoxy-α-D-ribo-hexo-pyranoside **44** was reported. As outline in Scheme **11**, **44** is converted to the *exo*-glucal **45** by treatment with Ph_3P/I_2 followed by treatment with sodium methoxide in methanol. Hydroboration of *exo*-glucal **45** by solvated boranes (B_2H_6 / THF) gave predominantly the L-*ido* product **46** in high yield. Selective protection of the primary OH of **46** as trityl ether and acetylation of OH-4 followed by removal of the trityl group with 60% aqueous perchloric acid provided the expected primary alcohol **47**. Oxidation of **47** then treating with diazomethane gave the L-iduronic acid derivative **48** that was used as donor to the preparation of the disaccharide **49**.

Preparation of L-iduronic acid was conducted through diastereoselective hydroboration of the di-*exo*-glycals derived from the commercial available α,α-trehalose (α-D-glucopyranosyl α-D-glucopyranoside) [38]. As outlined in Scheme **12**, The known 2,2',3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-tosyl-trehalose (**50**) [39] was treated in DMF with NaI, giving the 6,6'-dideoxy-6,6'-diiodo derivative which is transformed into the corresponding 5,5'-dieno compound **51** by treatment with excess of NaH in DMF. The 5,5'-dieno compound **51** underwent hydroboration reaction with $BH_3.SMe_2$ in THF and then oxidation with H_2O_2 furnished **52**. Oxidation of **52** into the corresponding uronic acid **53**



Scheme 10.



Scheme 11.

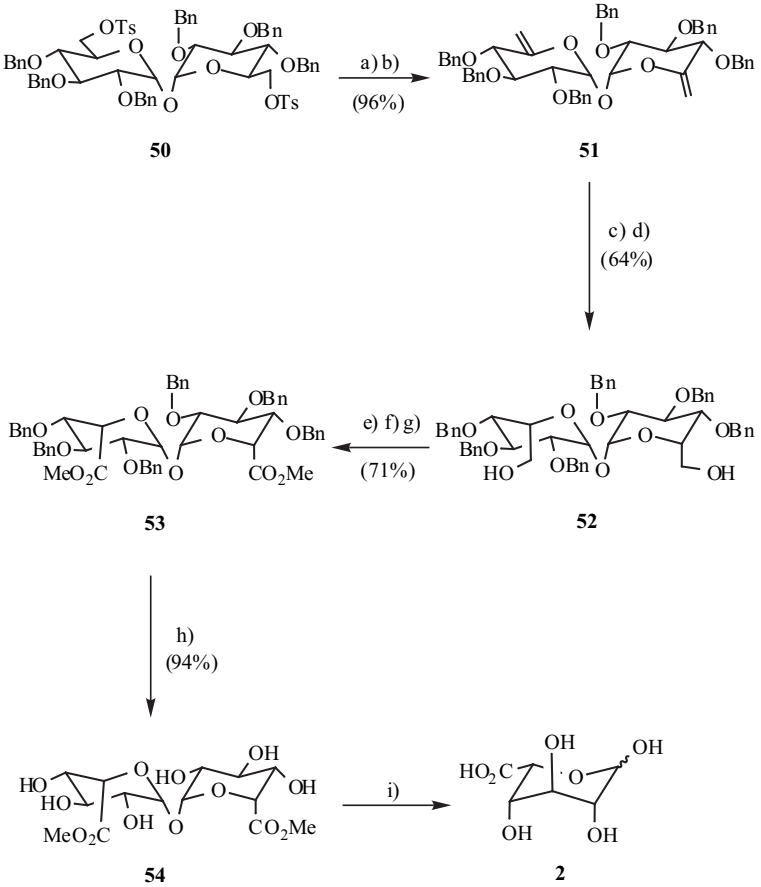
followed by deprotection and cleavage of the glycosidic bond furnish the L-iduronic acid **2**.

2.2.3. Selective Conversion of 5-Aldopentoses to Iduronic Acid Derivatives [40]

Synthetic route to iduronic acid building blocks through the conversion of diacetone glucose to the corresponding 3-*O*-benzyl-1,2-*O*-isopropylidene-*R*-L-idopyranosiduronate **58** (Scheme **13**) has been recently reported [41]. This iduronic acid derivative can serve as a glycosyl acceptor or can be readily converted to fully differentiated iduronic acid trichloroacetimidate glycosyl donors. Readily available 3-*O*-benzyl-diacetone glucose **55** was transformed to aldehyde **56** through selective acetal cleavage followed by treatment with aqueous sodium periodate. Reaction of **56** with trithiophenyl methylithium afforded L-idose-configured thioorthoester that was treated directly with $CuCl_2$/CuO to furnish the furanose methyl ester **57**, along with small amounts of the corresponding phenylthioester. Removal of the isopropylidene group by reaction with aq. TFA yielded the crystalline 3-*O*-benzyl iduronic methyl ester **58** in its pyranose form. Installation of a 1,2-isopropylidene onto **58** locked the sugar in the $^1C_4$ pyranose form and afforded a key intermediate that was efficiently used for preparing a set of iduronic acid trichloroacetimidate glycosyl donors **59-62** for glycosaminoglycan assembly.

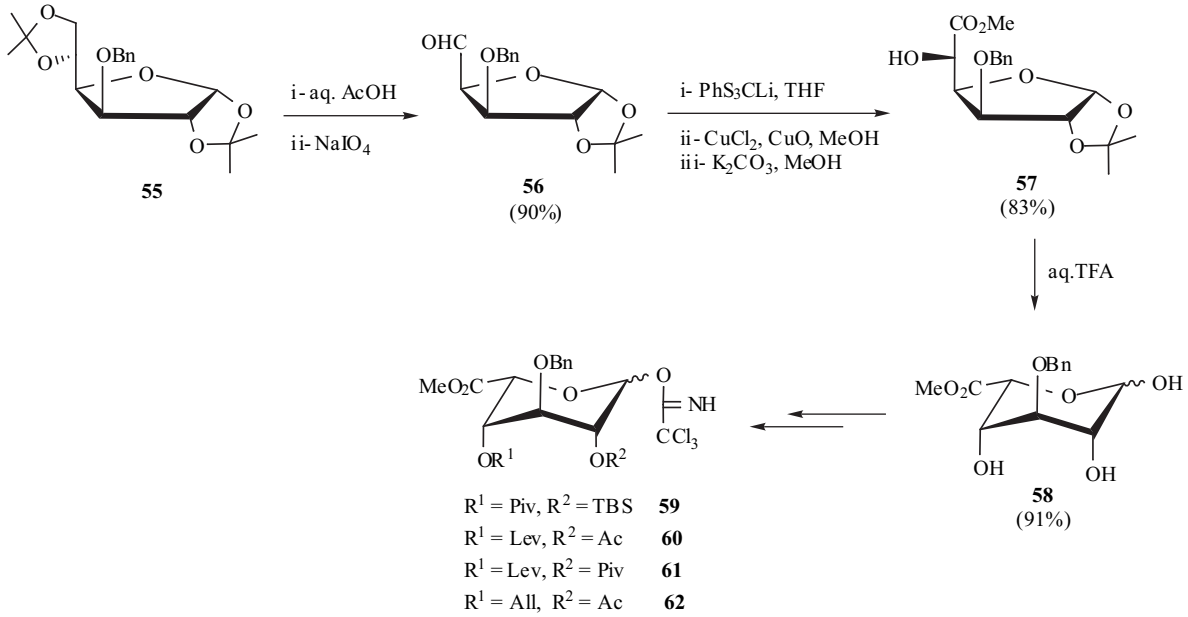
2.2.4. Replacing the Hydrogen Atom at C-5 of a Gluco Derivative by a Substituent

Synthetic problems associated with iduronic acid synthesis from the readily available glucuronic acid analogues are the poor yields of C-5 epimerization step and complications associated with protecting group manipulations. A method to address this problem was reported by Sinaÿ and co-authors [15] by replacing the hydrogen atom at C-5 of a *gluco* derivative by a substituent that is converted into a carboxylate group in a later step. As shown in scheme **14**, 5-keto-glucofuranose **63**, resulting from Swern oxidation of 6-*O*-*tert*-butyldimethylsilyl-1,2-O-isopropylidene-3-*O*-methyl-α-D-glucofuranose [42] was treated with vinyl magnesium bromide to give alcohol **64**. Acid hydrolysis using IR-120 H. resin at 80 °C, followed by acetylation gave exclusively the β-anomer tetracetate **65**. 1,2-Trans glycosylation of **65** with of the known [43] alcohol **66** yielded the disaccharide **67**. The disaccharide **67** was subsequently deacetylated to yield the corresponding triol, formation of the O-2/C-5 bridge by temporary protect the 4',6'-diol system followed by a mesylation of position 2' and finally displace this group by attack by the O-6' alcoholate to the disaccharide **68** in which the iduronic acid was locked in the $^2S_0$ conformation.



Key: a) NaI, DMF; b) NaH, DMF; c)BH_3.SMe_2,THF; d) H_2O_2, K_2CO_3; e) $(COCl)_2$, DMSO, Et_3N; f) CrO_3, $(CH_3)_2CO$, H_2SO_4; g) CH_2N_2; h) H_2/$Pd(OH)_2$/C, ACOH; i) Amberlite IR-120B (H+)

Scheme 12.

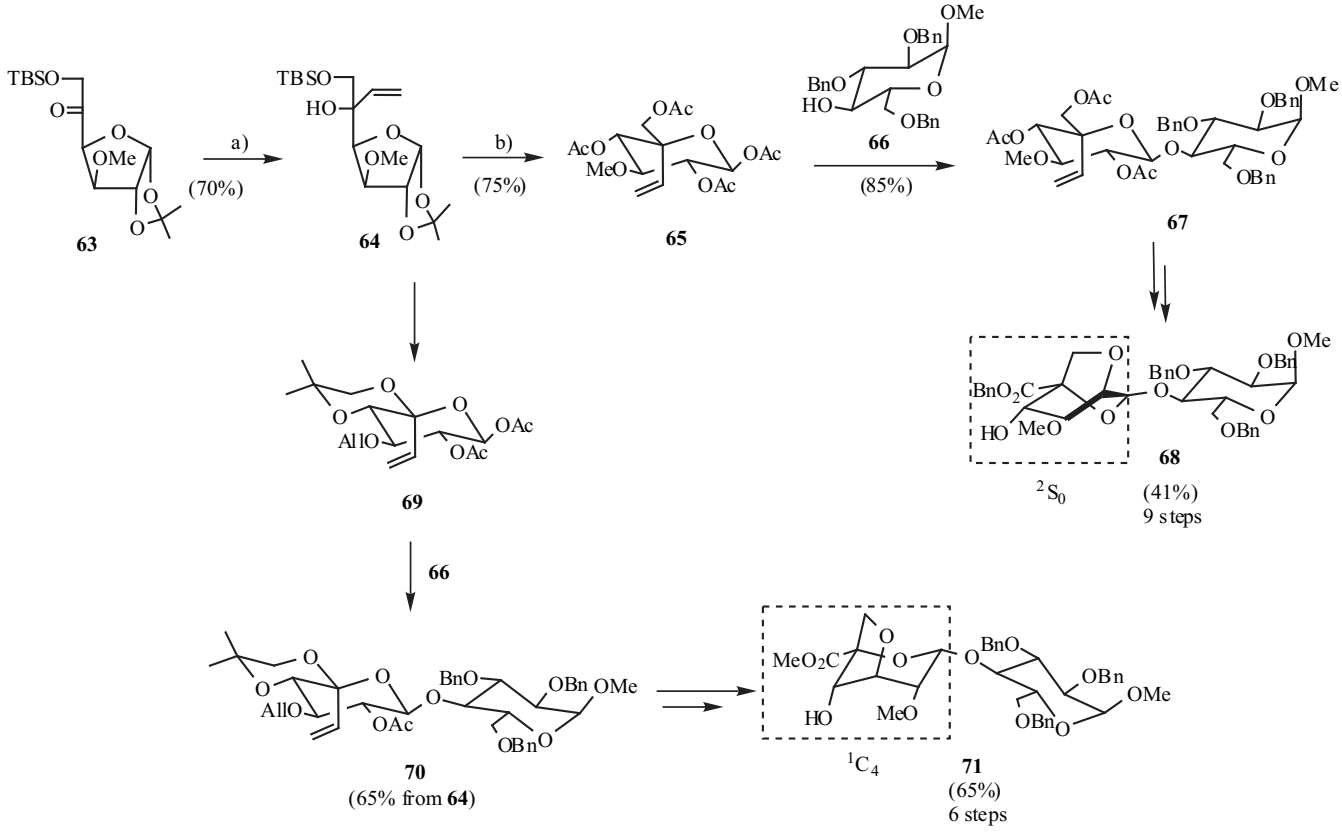


Scheme 13.

The disaccharide **71,** where the L-iduronic acid unit has the $^1C_4$ conformation, was prepared by similar sequence of reactions, except changing the nature of the protecting groups to lock the conformation in the $^1C_4$ pyranose form, starting from **64**.

3. CHEMISTRY OF THE UNNATURAL L- AND D-URONIC ACID-TYPE 1-*N*-IMINOSUGARS AS A GLYCOSIDASE AND GLYCOSYLTRANSFERASE INHIBITORS

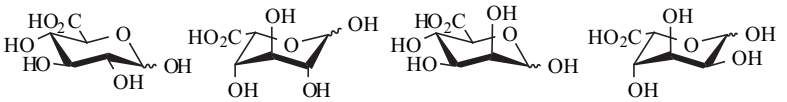
Compounds that inhibit oligosaccharide biosynthesis represent valuable tools for analyzing the role of complex



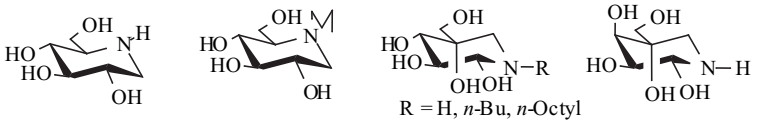
Scheme 14.

carbohydrates in biological processes [44]. In particular, glycosidase inhibitors, iminosugars such as deoxynojirimycin **72** (Scheme **15**), and especially its *N*-butylated derivative **73** have been proposed as chemotherapeutic agents to treat HIV infection since they have been found to alter the carbohydrate structure of the HIV glycoprotein, gp 120, thereby blocking the HIV-T cell interaction [45]. In addition, **74** has been reported to inhibit glycolipid biosynthesis, and it is speculated to UDP-glucose-*N*-acylsphingosine glucosyltransferase (EC 2.4.1.80), the enzyme catalyzes the first step of the glycolipid biosynthetic pathway [46]. These aza-sugars have been considered to mimic the intermediate of glycoside-cleaving reaction in which the positive charge is located at the position of the ring oxygen. Based on this assumption, a variety of naturally occurring and designed iminosugars **74** have been synthesized [47]. Bols *et al.* reported the synthesis of isofagomine where a nitrogen atom is located at the anomeric position [48]. In a similar fashion, the preparation of a galactose-type iminosugar **75** which has a nitrogen atom in the place of the anomeric carbon has been reported [49]. These 1-*N*-iminosugars represented a glycosidase and glycosyltransferase inhibitors and served as useful tools to study the biological function of glycolipids and as chemotherapeutic agents. The natural *gem*-diamine azasugar, siastatin-B **76** was isolated as an inhibitor of β-glucuronidase as well as *N*-acetylneuraminidase from *Streptomyces* culture [50]. *gem*-Diamine 1-*N*-iminosugars are cyclic mono-saccharides with a nitrogen atom in place of the anomeric carbon [51]. This discovery led to the synthesis of specific *gem*-diamine 1-*N*-iminosugars as glucuronidase inhibitors **77**-**81** for treatment of tumor metastasis and led to highly potent β-glucuronidase inhibitors. Also, a variety of *gem*-diamine 1-*N*-iminosugars related to L-iduronic acid as inhibitors of heparan sulfate uronyl 2-*O*-sulfotransferase (2OST) has been reported. 2OST catalyzes sulfate transfer from the sulfate donor, adenosine 30 phosphate-50-phosphosulfate (PAPS), to IdoA residues and with lesser efficiency to GlcA [52].

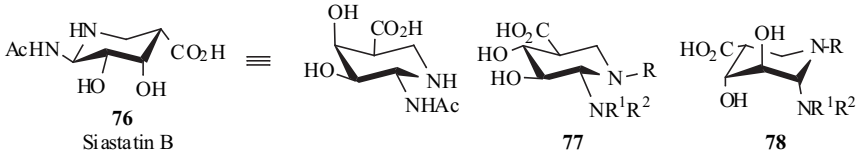
The synthetic methods for different *gem* diamine 1-*N*-imino sugars are outlined in Scheme **16** and Scheme **17**. The α,β-unsaturated ester **82** (Scheme **16**) was prepared by esterification of the protected 3,4-didehydro-4-deoxysiastatin B [53] readily derived from **76** with diphenyldiazomethane. Compound **82** smoothly underwent *cis* oxiamination to give the desired oxazoline **83** (76%) and its epimer (3%). Hydrolysis of the oxazoline ring of **83** by treatment with *p*-toluenesulfonic acid in a mixture of pyridine and water [54] followed by reductive cleavage of the trichloroacetyl group with sodium borohydride gave the amines **84** and **85**. Compounds **84** and **85** were smoothly transformed into **86** and **87** by removal of the protecting groups with hydrochloric acid. Introduction of the guanidino function is based on the facts that the guanidine moiety is an important feature in many biologically active compounds, especially in binding to the enzyme such as influenza viral *N*-acetylneuraminidase inhibiting its infection *in vitro* and *in*

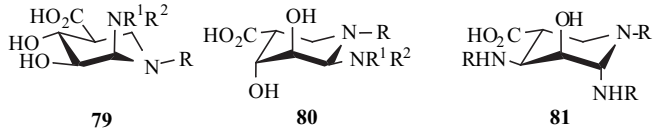


Structure of uronic acids



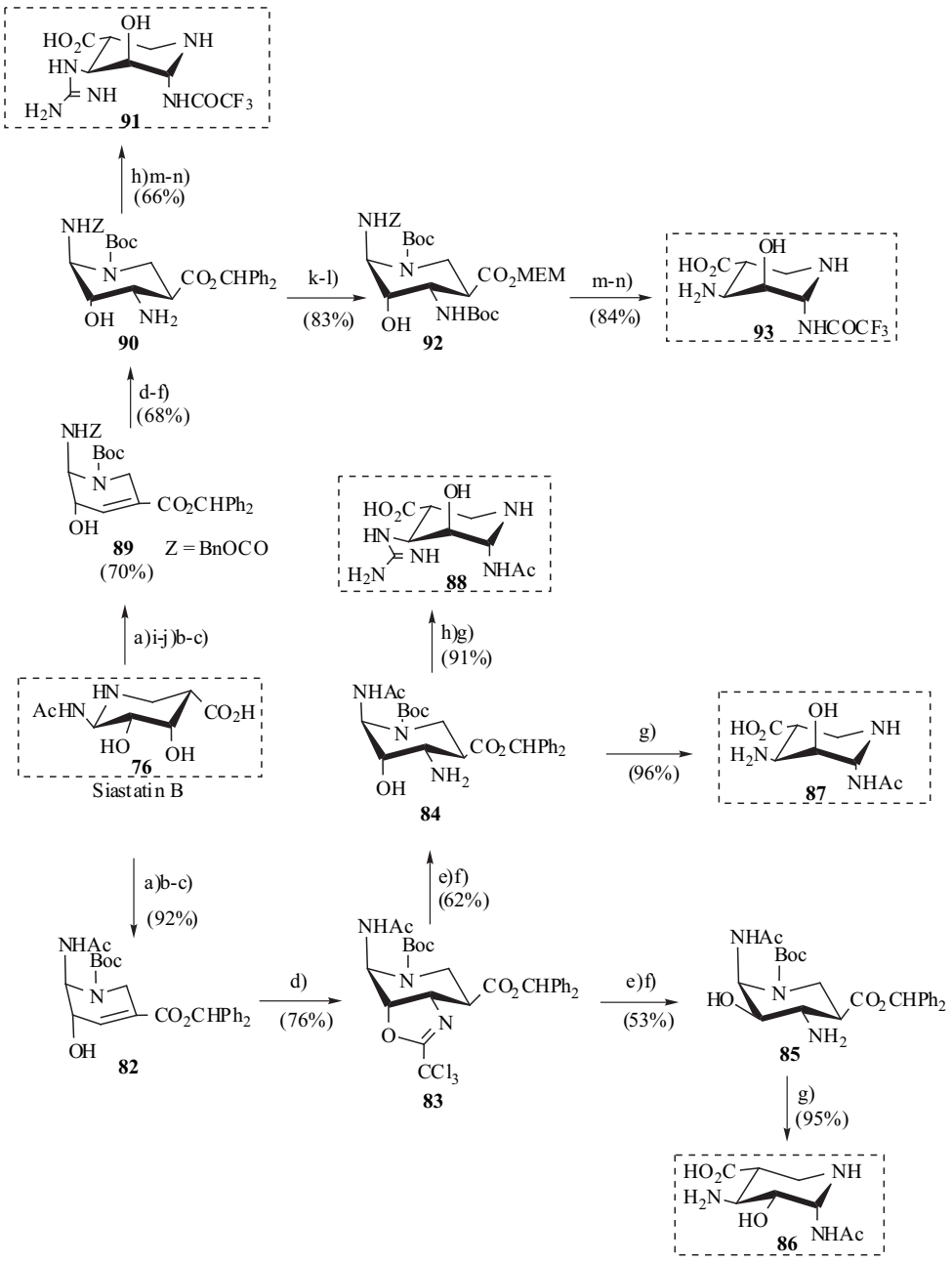
Structure of biologically active 1-*N*-iminosugars





Structure of uronic acid-type *gem*-diamine 1-*N*-iminosugars

Scheme 15.

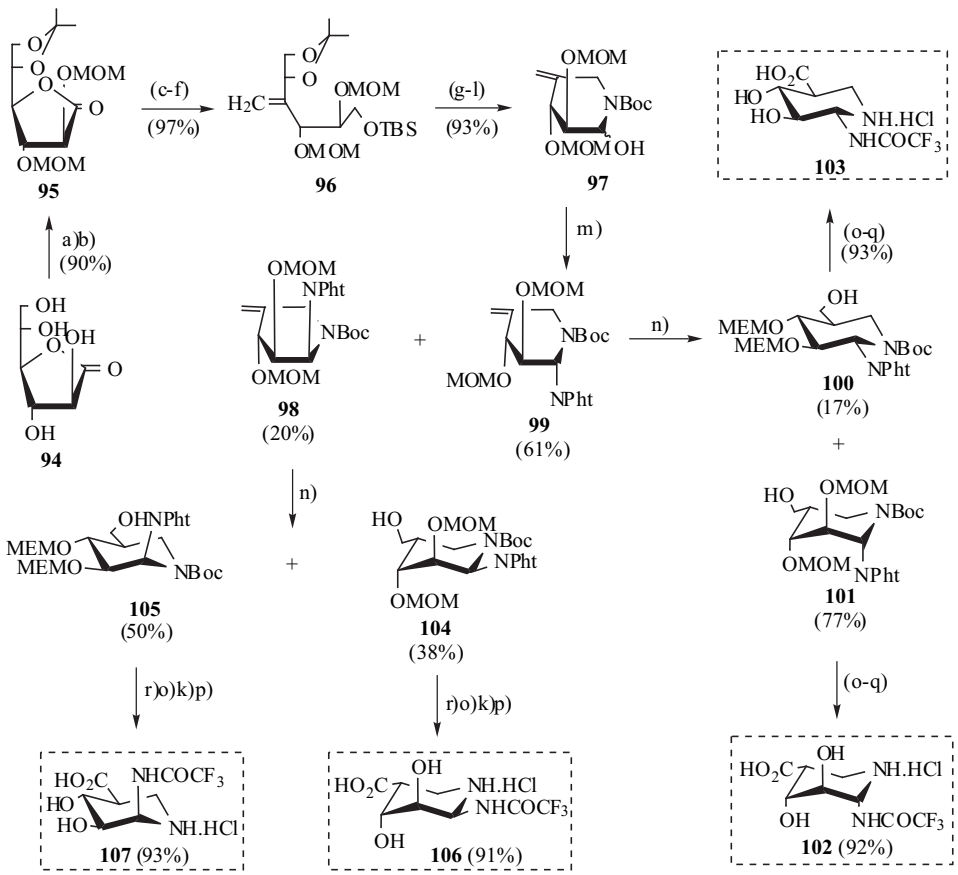


a) Reference 51; b) Ph_2CN_2, CH_2Cl_2/CH_3OH; c) $PhCH_2Cl$, *i*-Pr_2NEt, DMF; d) CCl_3CN, DBU, CH_2Cl_2; e) p TsOH, Py/H_2O; f) $NaBH_4$, EtOH; g) 4 M HCl/dioxane; h) $(BocNH)_2CS$, $HgCl_2$, Et_3N, DMF. i) Ph_2CH_2COOCl, i-Pr_2NEt, CH_3OH; (j) RuO_2, $NaIO_4$, $CH_3CN/CCl_4/H_2O$; (k) (*t*-$BuOCO)_2O$, *i*-Pr_2NEt, CH_3OH; (l) 1 M NaOH, CH_3OH; $CH_3OCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2; (m) H_2/10% Pd-C, CH_3CN; $(CF_3CO)_2O$,Py; n) 4 M HCl/dioxane.

Scheme 16.

vivo [55,56] and is also based on the molecular modeling study of α-L-iduronic acid.

The major isomer **84** can then be utilized for guanidine formation by use of *N,N*-bis(*tert*-butoxycarbonyl) thiourea in the presence of mercuric chloride [57], *bis*-Boc protection and treatment with acid gave **88**. Careful NMR studies revealed the $^1C_4$ conformations as well as stereochemistry indicated [58]. Introduction of the trifluoroacetamide function around the anomeric position proved to be a key factor in the strong binding of 1-*N*-iminosugar to the enzyme. In order to improve the potency and examine the neighboring participation of trifluoroacetamide group, 1-*N*-iminosugars **91** and **93** for tumor metastasis were designed. The starting α,β-unsaturated ester **89** was easily obtained from **76** by the method developed by Nishimura *et al.* [56]. Compound **89** was effectively converted to the key oxazoline *via* a similar *cis* oxiamination followed by hydrolysis of the oxazoline ring and the subsequent removal of the trichloroacetyl group straightforwardly gave **90** which was transformed into **92** by protection of the amino group and exchange of the protecting group of carboxyl group. Hydrogenolysis of **92** followed by trifluoroacetylation with trifluoroacetic anhydride afforded **93** in a good yield.



a) Ref. 63, b) CH_3OCH_2Cl, *n*-Bu_4NI, i-Pr_2NEt; c) $LiAlH_4$, THF; d) *t*-bu$(Ph_2)SiCl$, i-Pr_2NEt; e) Dess-Martin periodinane; f) Ph_3PCH_3Br, *n*-BuL; g) 80% AcOH; h) $NaIO_4$, CH_3CN/H_2O; $NaBH_4$, $CeCl_3$; i) MsCl, py; NaN_3; j) Te, $NaBH_4$, EtOH; $(t\text{-}BuCO)_2O$, *i*-Pr_2NEt, DMF; k) *n*-Bu_4NF, THF; l) $(COCl)_2$, DMSO; m) PPh_3, DEAD, phthalimide, **22**:**23** (61%:20%); n) $BH_3.Me_2S$, THF; H_2O_2, 2 M NaOH/H_2O, **24**: **25** (17%:77%); o) $H_2NNH_2.xH_2O$, MeOH; $(CF_3CO)_2O$, py, CH_2Cl_2; p) RuO_2, $NaIO_4$; (q) 4 M HCl/dioxane; (r) *t*-Bu$(Me_2)SiCl$, imidazole, DMF.

Scheme 17.

Compound **90** was transformed into **91** by a similar sequences of reaction described above. The $^1C_4$ conformation and the stereochemistry of **91** and **93** were also confirmed by ^1H NMR spectra and both proved to be unstable and decompose in an aqueous solution.

Another efficient and flexible synthetic route to a new family of glycosidase inhibitor of *gem*-diamine 1-*N*-iminosugars of uronic acid-type (D-glucuronic, D-mannuronic, L-iduronic, and L-guluronic acid) has been reported [59]. As outlined in Scheme **17**, the chiral L-galactono-1,4-lactone **94** was converted to the known 5,6-*O*-isopropylidene-L-galactono-1,4-lactone (**95**) [60], which was converted into the corresponding 1,5-diol upon reductive ring opening using lithium aluminum hydride reduction. Selective protection of the hydroxymethyl group with the *tert*-butyldiphenylsilyl (TBDPS) group followed by the Dess-Martin oxidation and Wittig reaction with methylenetriphenylphosphorane afford **96**. Standard chemistry steps were applied to convert **96** to **97**. Replacement of the aminal hydroxyl group of **97** to the amino group was achieved by the Mitsunobu reaction [61] to give the separable epimers of iminophthalimides **98** and **99**. Hydroboration/ oxidation of **99** with borane-methyl sulfide complex followed by hydrogen peroxide efficiently gave the separable D-*gluco* isomer **100** and the L-*idulo* isomer **101**. Hydrazinolysis of **100** and conventional trifluoroacetylation followed by oxidation of the hydroxymethyl group to the carboxylic acid and simultaneous removal of both the methoxymethyl (MOM) and *t*-Boc groups with 4 M hydrogen chloride afforded D-glucuronic acid-type 2-trifluoro-acetamido-1-*N*-iminosugar **103**. The same sequence of reactions also resulted in L-iduronic acid-type 2-trifluoroacetamido-1-*N*-iminosugar **102** from **101**. On the other hand, D-mannuronic acid-type and L-guluronic acid-type 2-trifluoroacetamido-1-*N*-iminosugars (**106** and **107**) were straightforwardly obtained from **98** by a similar reactions sequence.

CONCLUSION

The present paper review the different methodologies developed for the synthesis of hexuronic acids and particularly L-iduronic acid through isomerization of glucuronic acid analogs, hydroboration/oxidation of *exo*-glucal, selective conversion of 5-aldopentoses to iduronic

acid derivatives, and replacing the hydrogen atom at C-5 of a *gluco* derivative by a substituent. The conformational flexibility of L-iduronic acid is analyzed to better understand its remarkable biological activities and its impact on oligosaccharides synthesis. In the final section, synthetic methods towards the potent new type of unnatural 1-*N*-iminosugars, potential glycosidase and glycosyltransferase inhibitors are discussed.

REFERENCES

[1] Sarrazin, S.; Adam, E.; Lyon, M.; Depontieu, F.; Motte, V.; Landolfi, C.; Lortat-Jacob, H.; Bechard, D.; Lassalle, P.; Delehedde, M. *Biochim. Biophys. Acta* **2006**, *1765*, 25.

[2] Prydz, K.; Dalen, K. T. *J. Cell. Sci*. **2000**, *113*, 193.

[3] Delehedde, M. *Recent Res. Dev. Biol. Chem*. **2002**, *1*, 133.

[4] Casu, B.; Petitou, M.; Provasoli, M.; Sinaÿ, P. *Trends Biochem. Sci*. **1988**, *13*, 221.

[5] a) Avci, F. Y.; Karst, N. A.; Linhardt, R. J. *Curr. Pharm. Des.* **2003**, *9*, 2323. b) Karst, N. A.; Linhardt, R.J. *Curr. Med. Chem.* **2003**, *10*, 1993.

[6] Capila, I.; Linhardt, R.J. *Angew. Chem. Int. Ed*. **2002**, *41*, 390; *Angewandte Chemie* **2002**, *114*, 426.

[7] a) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3051. b) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Med. Chem*. **1997**, *40*, 2626.

[8] Rees, S. D.; Hughes Wassell, D. T.; Embery, G. *Biomaterials* **2002**, *23*, 481.

[9] Jaques, L. B. *Semin. Thromb. Hemost.* **1991**, *17*(1),1.

[10] Somasundaran P.; Wang, Y. H. C. In *Adsorption on and surface chemistry of hydroxyapatite*. Misra D. N., Ed., New York: Plenum Press, **1984**. pp 129–49.

[11] (a) Choay, J.; Lormeau, J.-C.; Petitou, M.; Sinaÿ , P.; Fareed, J. *Ann. N.Y. Acad. Sci*. **1981**, 370, 644. (b) Choay, J.; Petitou, M.; Lormeau, J.-C.; Sinaÿ , P.; Casu, B.; Gatti, G. *Biochem. Biophys. Res. Commun*. **1983**, *116*, 492.

[12] (a) Sinaÿ, P.; Jacquinet, J.-C.; Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Torri, G. *Carbohydr. Res*. **1984**, *132*, C5. (b) Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Sinaÿ, P.; Jacquinet, J.-C.; Torri, G. *Carbohydr. Res.* **1986**, 147, 221.

[13] Ferro, D. R.; Provasoli, A.; Ragazzi, M.; Torri, G.; Casu, B.; Gatti, G.; Jacquinet, J.-C.; Sinaÿ, P.; Petitou, M.; Choay, J. *J. Am. Chem. Soc*. **1986**, *108*, 6773.

[14] Ferro, D. R.; Provasoli, A.; Ragazzi, M.; Casu, B.; Torri, G.; Bossennec, V.; Perly, B.; Sinaÿ, P.; Petitou, M.; Choay, J. *Carbohydr. Res*. **1990**, *195*, 157.

[15] Casu, B.; Choay, J.; Ferro, D. R.; Gatti, G.; Jacquinet, J. –C.; Petitou, M.; Provasoli, A.; Ragazzi, M.; Sinay, P.; Torri, G. *Nature* **1986**, *322*, 215.

[16] Das, S. K.; Mallet, J. –M.; Esnault, J.; Driguez, P. –A.; Duchaussoy, P.; Sizun, P.; Herault, J. –P.; Herbert, J. –M.; Petitou, M.; Sinaÿ, P. *Chem. Eur. J*. **2001**, *7*, 4821.

[17] Lei, P. S.; Duchaussoy, P.; Sizun, P.; Mallet, J. –M.; Petitou, M.; Sinaÿ, P. *Bioorg. Med. Chem*. **1998**, *6*, 1337.

[18] a) Sakairi, N.; Basten, J. E. M.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Chem. Eur. J*. **1996**, *2*, 1007. b) Das, S. K.; Mallet, J.–M.; Esnault, J.; Driguez, P.–A.; Duchaussoy, P.; Sizun, P.; Herault, J. –P.; Herbert, J. –M.; Petitou, M.; Sinaÿ, P. *Angew. Chem*. **2001**, *113*, 1723; *Angew. Chem. Int. Ed*. **2001**, *40*, 1670.

[19] a) Kiss, J.; Wyss, P. C. *Tetrahedron* **1976**, *32,*1399. b) Blanc-Muesser, M.; Defaye, Horton, J. D.; Tsai, J. -H. *Methods Carbohydr. Chem*. **1980**, *8,* 177. c) van Boeckel, C. A. A.; Beetz, T.; Vos, J. N.; de Jong, A. J. M.; van Aelst, S. F.; van der Bosch, R. H.; Mertens, J. M. R.; van der Vlugt, F. A. *J. Carbohyr. Chem*. **1985**, *4*, 293.

[20] Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. Eur. J*. **2003**, *9*, 140.

[21] a) Czuk, R.; Honig, H.; Nimpf, J.; Weidmann, H. *Tetrahedron Lett.* **1980**, *21*, 2135. b) Jacquinet, J. –C.; Petitou, M.; Duchaussoy, P.; Lederman, L.; Choay, J.; Torri, G.; Sinaÿ, P. *Carbohydr. Res.* **1984**, *130*, 221.

[22] Coxon, B. *Carbohydr. Res.* **1968**, *8*, 125.

[23] Baggei, N.; Smithson, A. *Carbohydr. Res*. **1982**, *108*, 59.

[24] Johansson, M. H.; Samuelson, O. *Carbohydr. Res*. **1977**, *54*, 295.

[25] Thiem, J.; Ossowski, P. *J. Carbohydr. Chem*. **1984**, *3*, 287.

[26] Schell, P.; Orgueira, H. A.; Roehrig, S.; Seeberger, P. H. *Tetrahedron Lett.* **2001**, *42*, 3811.

[27] Chiba, T.; Sinaÿ, P. *Carbohydr. Res*. **1986**, *151*, 379.

[28] Chatgilialogu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc*. **1981**, *103*, 7739.

[29] Yu, H. N.; Furukawa, J. -I.; Ikeda, T.; Wong, C. -H. *Org. Lett*. **2004**, *6*(5), 723.

[30] Ke, W.; Whitfield, D. M.; Gill, M.; Larocque, S.; Yu, S. –H. *Tetrahedron Lett*. **2003**, *44*, 7767.

[31] Ojeda, R.; de Paz, J. L.; Martin-Lomas, M.; Lassaletta, J.M. *Synlett* **1999**, 1316.

[32] a) Chiba, T.; Jacquinet, J. –C.; Sinaÿ, P.; Petitou, M.; Choay, J. *Carbohydr. Res.* **1988**, *174*, 253. (b) Lehmann, J. *Carbohydr. Res.* **1966**, *2*, 1. (c) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647. d) Takahashi, H.; Miyama, N.; Mitsuzuka, H.; Ikegami, S. *Synthesis* **2004**, 2991.

[33] Ichikawa, Y.; Kuzuhara, H. *Carhohydr. Res.* **1983**, *115*, 117.

[34] Rochepeau-Jobron, L.; Jacquinet, J.–C. *Carbohydr. Res.* **1997**, *303*, 395.

[35] Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 277.

[36] Lee, J. –C.; Chang, S. –W.; Liao, C. –C.; Chi, F. –C.; Chen, C. –S.; Wen, Y. –S.; Wang, C. –C.; Kulkarni, S. S.; Puranik, R.; Liu, Y. –H.; Hung, S. –C. *Chem. Eur. J*. **2004**, *10*, 399.

[37] Hodosi, G.; Podµnyi, B.; Kuszmann, J. *Carbohydr. Res*. **1992**, *230*, 327.

[38] Hinou, H.; Kurosawa, H.; Matsuoka, K.; Terunuma, D.; Kuzuhara, H. *Tetrahedron Lett*. **1999**, *40*, 1501.

[39] Kurita, K.; Masuda, N.; Aibe, S.; Murakami, K.; Ishii, S.; Nishimura, S. -I. *Macromolecules* **1994**, *27*, 7544.

[40] Lubineau, A.; Gavard, O.; Alais, J.; Bonnaffe´, D. *Tetrahedron Lett.* **2000**, *41*, 307.

[41] Gregory, J. S.; Lohman, D.; Hunt, K.; Hogermeier, J. A.; Seeberger, P. H. *J. Org. Chem*. **2003**, *68*, 7559.

[42] Gurjar, M. K.; Das, S. K.; Saha, U. K. *Tetrahedron Lett*. **1994**, *35*, 2241.

[43] a) Garegg, P. J.; Iversen, T.; Oscarsson, S. *Carbohydr. Res*. **1976**, *50*, C12. b) Garegg, P. J.; Hultberg, H. *Carbohydr. Res*. **1981**, *93*, C10. c) Mallet, J. –M.; Meyer, G.; Yvelin, F.; Jutand, A.; Amatore, C.; Sinaÿ, P. *Carbohydr. Res*. **1993**, *244*, 237.

[44] Varki, A. *Glycobiology* **1993**, *3*, 97.

[45] Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, 135.

[46] Platt, F. M.; Neises, G. R.; Dwek, R. A.; Butters, T. D. J. *Biol. Chem.* **1994**, *269,* 8362.

[47] Look, G. C.; Fotsch, C. H.; Wong, C. -H. *Acc. Chem. Res.* **1993**, *26,182.*

[48] Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem. Int. Ed. Eng.* **1994***, 33,* 1778.

[49] a) Ichikawa, M.; Ichikawa, Y. *Bioorg. and Med. Chem.* **1995**, *3*, 161. b) Ichikawa, M.; Igarashi, Y.; Ichikawa, Y. *Tetrahedron Lett.*,**1995**, *36*, 1767.

[50] Umezawa, H.; Aoyagi, T.; Komiyama, T.; Morishima, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1974**, *27*, 963.

[51] a) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3051. b) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Med. Chem*. **1997**, *40*, 2626.

[52] Rong, J.; Habuchi, H.; Kimata, K.; Lindahl, U.; Kusche-Gullberg, M. *Biochemistry* **2001**, *40*, 5548.

[53] Kudo, T.; Nishimura, Y.; Kondo, S.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 300.

[54] Gent, P. A.; Gigg, R.; May, S.; Conant, R. *J. Chem. Soc. Perkin. Trans. 1* **1972**, 2748.

[55] Lednicer, D.; Mitscher, L. A. In *The Organic Chemistry of Drug Synthesis*; Wiley: New York, **1977**; Vol. 1, pp. 1-432 and **1980**; Vol. 2, pp. 1-482.

[56] (a) von Itzstein, M.; Wu, W. -Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Van Phan, T.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418. (b) Woods, J. M.; Bethell, R. C.; Coates, J. A. V.; Healy, N.; Hiscox, S. A.; Peason, B. T.; Ryan, D. M.; Ticehurst, J.; Tilling, J.; Walcott, S. M.; Penn, C. R. *Antimicrob. Agents*

Chemother. **1993**, *37*, 1473. (c) Colman, P. M. *Protein Sci.* **1994**, *3*, 1687.
[57] Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
[58] Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Med. Chem.* **1997,** *40,* 2626.
[59] Nishimura, Y.; Shitara, E.; Adachi, H.; Toyoshima, M.; Nakajima, M.; Okami, Y.; Takeuchi, T. *J. Org. Chem.* **2000,** *65,* 2.
[60] Morgenlie, S. *Carbohydr. Res.* **1982**, *107*, 137.
[61] Mitsunobu, O. *Synthesis* **1981**, 1.

Received: August 23, 2006 **Revised: September 05, 2006** **Accepted: September 18, 2006**