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Syntheses of small cluster oligosaccharide mimetics

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Dedicated to Prof. Dr. Alan R. Katritzky on the occasion of his 80th birthday

Abstract

We designed multiple Small Cluster Oligosaccharide Mimetics (SCOMs) - potential glycosidase inhibitors - to be metabolically stable and small enough to enter cells or bacteria. Therefore, minimal scaffolds (urea, amide, ammonia) or simply non-glycosidic linkages of carbohydrate structures were central to our synthetic strategy, including: (a) coupling of several natural carbohydrate precursors; (b) total syntheses of aminomethyl tetrahydropyrans and their chiral amides with quinic acid; (c) glycopyranosyl cyanide reduction to prepare crowded clusters on a urea scaffold; (d) total syntheses via cycloadditions leading to amide-linked C-glycosides; (e) reduction of nitromethyl C-glycosides; and (f) a synthesis of hydroxylated 1,2-cyclohexanedicarboxylic acids.

Keywords: Carbohydrate mimetics, aminomethyl C-glycosides, quinamides, glycals

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1. Introduction

After the early years of carbohydrate chemistry around 1900 and Emil Fischer's structure proof of the carbohydrates, this area of chemistry received only little attention. However, carbohydrate chemistry witnessed a renaissance during the 1960's with the advent of the aminoglycoside antibiotics.¹⁻³ Synthetic efforts since then have resulted in numerous structural modifications for carbohydrates. Exchange of aglycons on the anomeric carbon, exchange of the glycosidic atom (*N*-, *C*-, *S*-glycosides), exchange of ring substituents, exchange of the endocyclic heteroatom (carba-, aza-, thia-derivatives), and concise stereochemical transformations. Oligosaccharides are now recognized to have functions influencing the entire spectrum of cell activities. Glycolipids and glycoproteins on the cell surface are now known to determine cell-cell interactions with invading bacteria, viruses, and cancer cells.⁴⁻⁷ Carbohydrates play central roles in posttranslational modifications of proteins,⁸⁻¹⁰ cell-cell communication,¹¹ and immune response to pathogens.^{10,12-14} Aberrations in glycosylation have been linked to severe pathological symptoms. Monosaccharide units combine to oligosaccharides in an almost infinite number of permutations, determined by the stereochemical identity of the linked monosaccharides (e.g. glucose, galactose, mannose), their glycosidic linkage position (e.g. 1→4, 1→6), their anomericity (α or β), and the overall degree of branching. This complexity, further increased by additional modifications such as sulfation or sialation, was suggested recently to serve the evolutionary purpose of "herd immunity".^{15,16} It has become clear over the past three decades that glycosylation is critically important to many of the signaling pathways that turn a normal cell into a cancer cell. Compounds that inhibit specific glycosylation reactions may potentially block the pathways in carcinogenesis. Carbohydrates have been recognized as novel cancer prevention agents.¹⁷

However, a distinct disadvantage of naturally occurring carbohydrates, e. g. *O*-glycosidically-linked oligosaccharides, is their metabolic instability in biological systems. Therefore, much effort has been spent in the past two decades on the development of feasible pathways towards carbohydrate mimetics, including *C*-glycosidic sugars,¹⁸⁻²¹ which may compete with their *O*-glycosidic counterparts in cell surface adhesion, inhibit carbohydrate-processing enzymes, and interfere in the biosynthesis of specific cell surface carbohydrates.²¹⁻²³ Therefore, carbohydrate mimetics are potential therapeutic agents against HIV and other infections, against cancer, diabetes and other metabolic diseases.¹⁸⁻²³

Oligosaccharide "clusters" exhibit greatly increased binding constants compared to monosaccharides (cluster effect).²⁴⁻²⁹ Potential targets for medical applications of these clusters have been identified.³⁰ However, most synthesized glycosidic cluster compounds are too large to permeate cell walls or membranes, and only target cell surface receptors.²⁴⁻²⁹ Therefore, we devoted our work to the synthesis of a variety of Small Cluster Oligosaccharide Mimetics (SCOMs)^{31,32} with enhanced metabolic stability, which presumably may enter the cytosol and internal cell substructures to address internal receptors.

2. Acylation with Quinic Lactone

Quinic acid (**1**, Figure 1)³³ and its derivative shikimic acid (**2**, Figure 1)³⁴⁻³⁶ (from *Illicium japonica* and *floridanum*) are key intermediates during the biochemical synthesis of essential aromatic amino acids, such as L-tryptophan, L-phenylalanine, and L-tyrosine in plants, bacteria, and fungi. Quinic acid and shikimic acid are also required as building blocks for the assimilation of folic acid, alkaloids, and vitamins in those organisms.^{37,38} The quinic acid/shikimic acid pathway does not exist in mammals, which has led to extensive research activities geared towards the development of suitable antibiotic therapeutics. Especially the conversion of 3-dehydroquinic acid (DHQ) to 3-dehydroshikimic acid (DHS) has been recognized as an effective target for inhibition in plants.^{39,40} Several commercial herbicides selectively inhibit the DHQ-DHS conversion and prevent growth of weeds. However, disruption of the DHQ-DHS pathway by shikimic acid derivatives (**3**, Figure 1) has also recently been shown to cause therapeutic inhibition of *Mycobacterium tuberculosis*.⁴¹

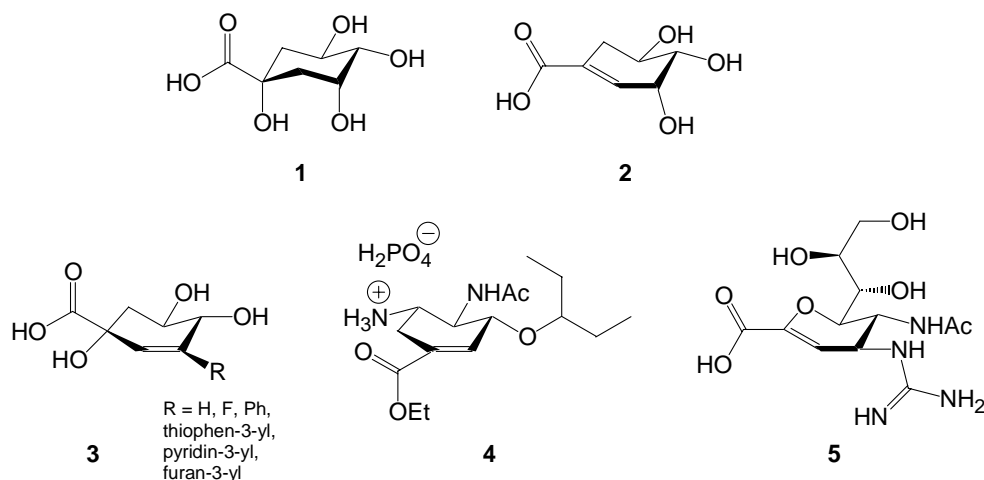


Figure 1. Chemical structures of quinic acid (**1**), shikimic acid (**2**). Compounds **3**, **4** (TamifluTM, Roche), and **5** (RelenzaTM, Glaxo-Smith) show anti-influenza activity.

Derivatives of shikimic acid have been used to inhibit other biochemical pathways for example the infectious pathway of the influenza virus (common flu).⁴²⁻⁴⁴ Potent anti-influenza A+B effect has been observed for derivatives of shikimic acid inhibiting viral neuraminidase. The widely-prescribed anti-flu medication TamifluTM (Roche, **4**, Figure 1) is not only effective in treating common flu strains, but it has also been used successfully in the treatment of the bird (avian) flu in laboratory animals. Contrary to animal experiments, Tamiflu'sTM effectiveness in humans infected with the H5N1 flu strain is still controversial because only a few studies with limited statistical value have been conducted, and the understanding of the drug's action against the virus is only rudimentary. TamifluTM acts as influenza virus neuraminidase inhibitor with the possibility of alteration of virus particle aggregation and release. The less well-known RelenzaTM

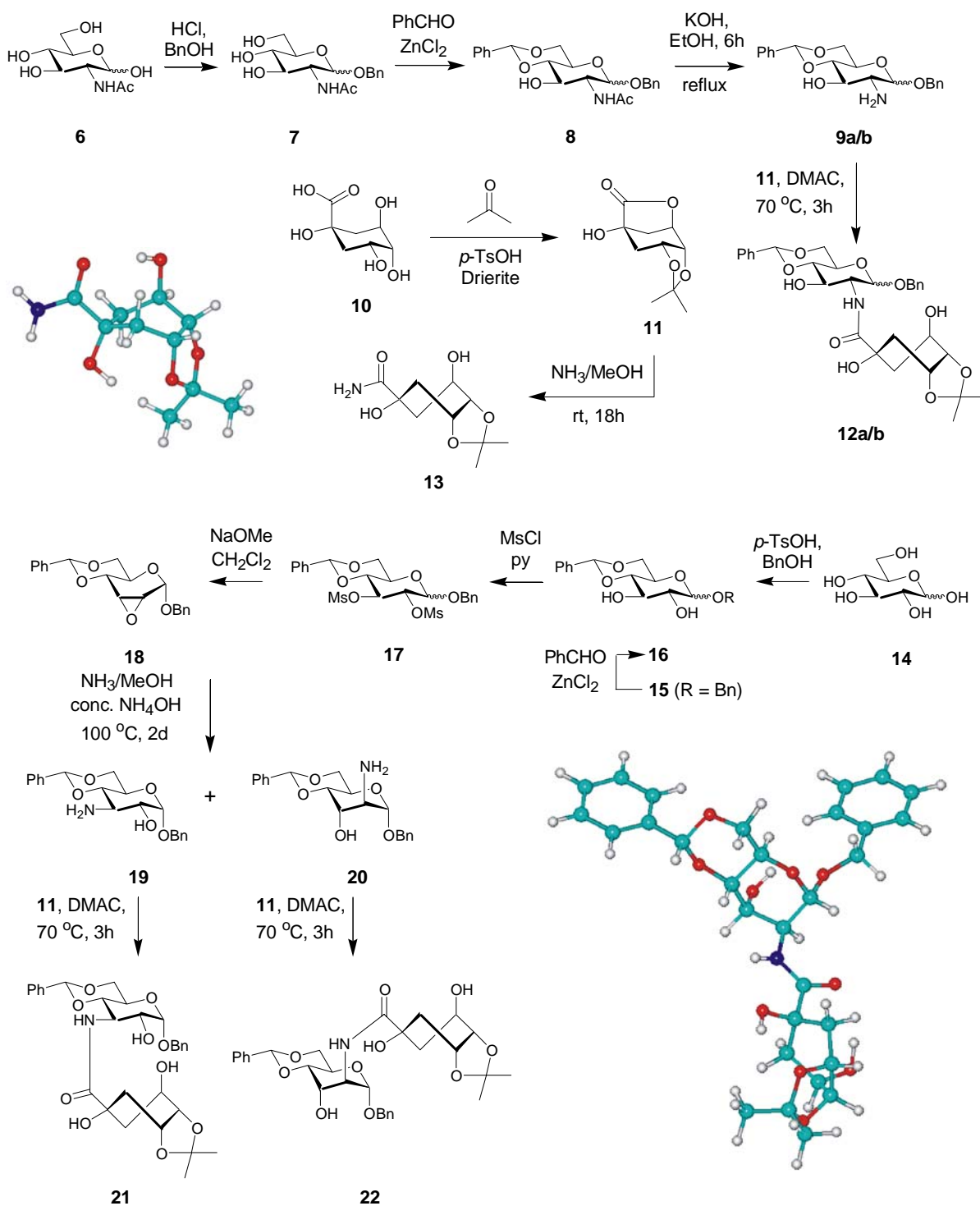
(Zanamivir, GlaxoSmithKline, **5**, Figure 1)⁴² is also an effective inhibitor of common flu strains by the same mechanism. The problem of a sufficient supply of these two drugs in case of an influenza pandemic and the necessity for a continuous search for new structural analogs has been discussed in the literature.^{45,46}

For the construction of SCOMs from quinic acid, we used 2-amino-2-deoxy sugars as nucleophiles and quinic lactone as an electrophile (Scheme 1).⁴⁷⁻⁴⁹ Starting with 2-acetamido-2-deoxy-D-glucopyranose (**6**), we prepared the corresponding benzyl glucoside (**7**) through acid-catalyzed acetal formation. Under these conditions, compound **7** was obtained as a mixture of anomers, which was difficult to separate or crystallize. However, the α - and β -anomer can be obtained clean after per-*O*-acetylation, recrystallization, and MeO⁻/MeOH deprotection at room temperature.⁵⁰ Compound **7** was then converted to the 4,6-*O*-benzylidene derivative **8** with benzaldehyde and anhydrous ZnCl₂ followed by removal of the *N*-acetyl group in ethanolic KOH at reflux to yield 2-amino-4,6-*O*-benzylidene-2-deoxy- α/β -D-glucopyranose (**9**). In parallel, D-(-)-quinic acid was converted to the 4,5-*O*-isopropylidened lactone (**11**),⁵¹ which served as an electrophile in the subsequent acylation of the separated α - and β -anomers **9a/b** into the potential disaccharide mimic precursors **12a/b**, respectively.

We also prepared compounds **21** and **22** as regio- and diastereochemical analogs of **12**, respectively. The two corresponding aminoglycosides were synthesized from D-glucose (**14**).⁵² Benzylation followed by 4,6-*O*-benzylideneation gave compound **16** whose 2- and 3-hydroxyl groups were subsequently mesylated to afford compound **17**. Upon treatment of **17** with methoxide, we were able to obtain benzyl-2,3-anhydro-4,6-*O*-benzylidene- α -D-allopyranoside (**18**). The epoxide was surprisingly stable but could be opened with NH₃ under pressure and elevated temperature. The major product (**20**) with *D-althro*-configuration was obtained through diaxial opening (Fuerst-Plattner rule) whereas the regioisomer (**19**) with *D-gluco*-configuration was only isolated in small quantities from the same reaction. When these products were combined with quinic lactone **11**, SCOMs **21** and **22** were obtained, respectively.

Interestingly, the quinic amide ring in all quinamides described above had a predominant *twist*-boat conformation as determined by NMR in CDCl₃ (Scheme 1).^{47,48} This was confirmed by small gauche ³*J*-values and NOEs between H3/H2a/H2b and between H5/H6a/H6b, as well as a significant ⁴*J* between H4 and H2b (*W*-coupling). We observed the same conformation for the unsubstituted quinamide **13** that was obtained from **11** in a saturated methanolic solution of NH₃ at room temperature. This benzylamide derivative had been described by us earlier; however, without detailed conformational analysis (Scheme 1).⁴⁹ The *twist*-boat conformation is pretty common for the pyranoses/tetrahydropyranes fused to five-membered acetal ring(s) (e.g. see Section 4.1), but is very rare for cyclohexane derivatives.

Quinic lactone **11** was also used for acylation of synthesized aminomethyl-*C*-dideoxyglycopyranosides (Section 7).



Scheme 1. Quinamide SCOMs synthesized through nucleophilic opening of quinic lactone.⁴⁷⁻⁴⁹ The molecular models represent 0K structures obtained from molecular dynamics simulation (AM1) with temperature annealing.

3. Glycal Dimerization

Glycals (1,2-*en*-pyranoses or -furanoses) are versatile chiral building blocks in the synthesis of natural products and biologically relevant oligosaccharides,⁵³ because of the ease of their chemical transformation.⁵⁴⁻⁵⁷ Synthetic oligosaccharides derived from glycals have been tested as antigens in anti-cancer vaccination.^{53,58}

Glycals are classically synthesized by reduction (1,2-deacetoxybromination) of per-*O*-acetylated glycosyl bromides in glacial AcOH/NaOAc buffer with Zn.^{59,60} However, these literature procedures have serious problems,⁵⁹⁻⁶¹ among which solvolysis of the unstable intermediate glycosyl bromides is the major one.

We have developed a synthesis of acetylated glycosyl bromides and subsequently glycals from per-acetylated sugars under non-solvolytic conditions.⁶²⁻⁶⁴ In the first step a per-*O*-acetylated sugar was treated with TiBr₄ in CH₂Cl₂ in presence of a catalytic amount of glacial acetic acid. The resulting glycosyl bromide was *in situ* reduced with Zn/Cu couple. Per-*O*-acetylated D-glucose, D-galactose, D-glucuronic acid methyl ester, L-fucose, D-maltose, D-lactose, and D-gentiobiose gave corresponding glycals **23-30** (Figure 2) in > 90% purity prior to purification, as estimated by NMR.⁶²⁻⁶⁴

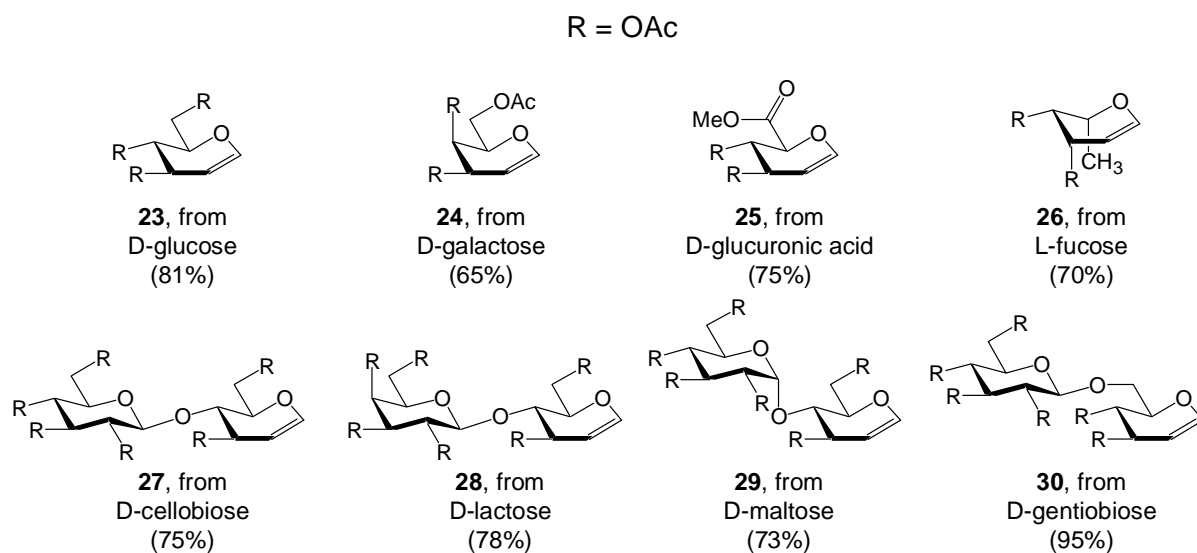
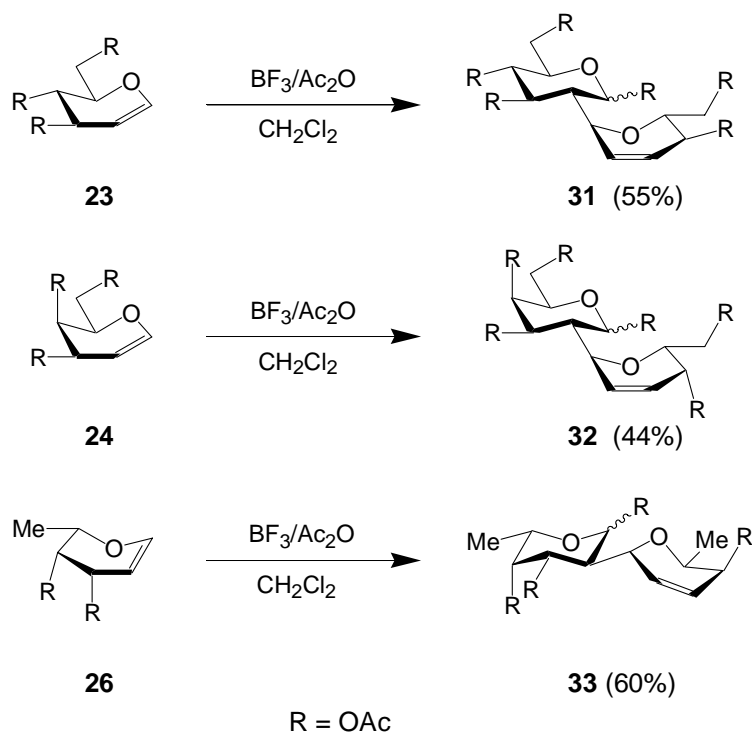
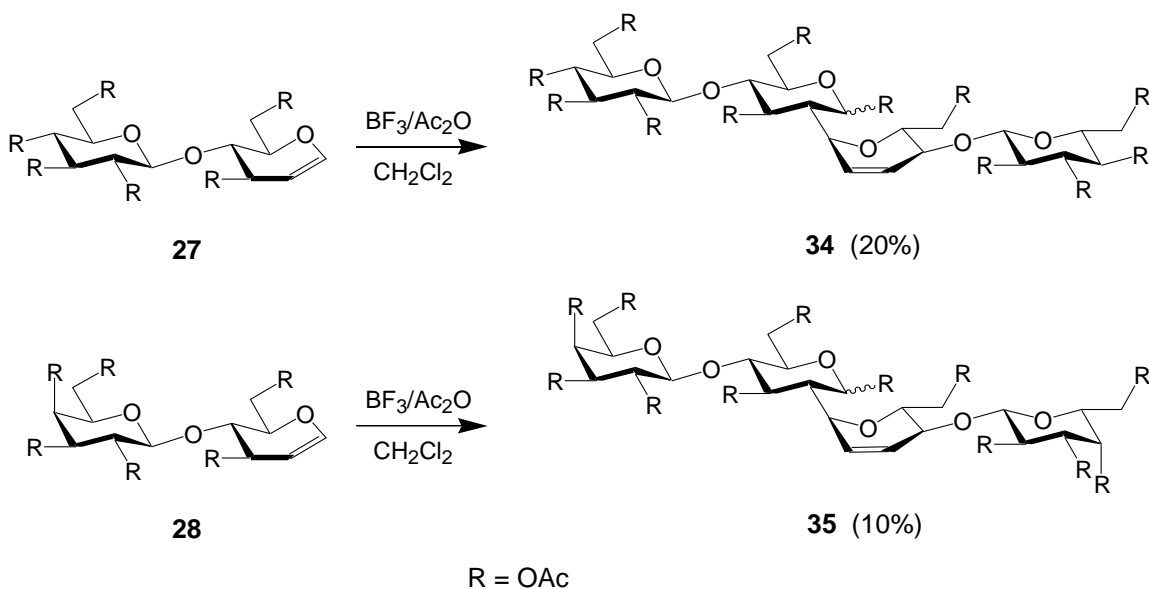


Figure 2. Glycals synthesized under aprotic conditions.⁶²⁻⁶⁴

Dimerization of per-*O*-acetylated D-glucal was described first by Ferrier and Prasad.⁶⁵ In a similar fashion we synthesized products with directly *C*-linked cycles (Scheme 2)^{62-64,66-69} by an improved dimerization method with BF₃/Ac₂O catalyst,⁶⁷ and also obtained tetrasaccharidic glycomimetics from disaccharidic glycals (Scheme 3).^{62-64,66-69}



Scheme 2. Structures of products from glycal dimerization.^{62-64,66-69}



Scheme 3. Dimerization of per-*O*-acetyl-cellobial **27** and per-*O*-acetyl-lactal **28**.^{62-64,66-69}

Such compounds may potentially show altered and/or enhanced bioactivity due to a well-documented cluster effect.²⁴⁻²⁹ The non-physiological nature of the new C-C-linkages in our compounds may transfer metabolic stability also to *O*-glycosidic bonds still present in their

structures. Dimerizations of disaccharidic glycols to tetramers required careful optimization of conditions to minimize cleavage of the disaccharidic bonds by the BF_3 -catalyst.

The structural assignment of glycal dimers was based upon NMR data. The original assignment for tri-*O*-acetyl-D-glucal dimer **31**⁶⁵ was confirmed by our data,^{64,66} and finally proved by X-ray crystal structure analysis (Figure 3).⁶⁶

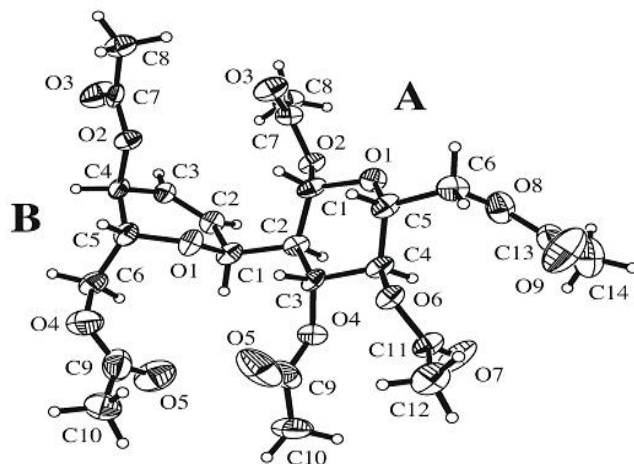


Figure 3. Molecular structure of compound **31**.⁶⁶

The structural analysis of **31** revealed a high degree of rigidity in the molecule. Comparative analysis of the NMR and X-ray data^{62,64,66} shows that there is virtually no difference between the solution and crystal conformations of both rings in compound **31**. The average position of the two ring planes in **31** may be considered nearly perpendicular. The conformational equilibrium for both rings appears to be strongly biased. An absence of a solvent dependence for spin-spin coupling constants also supports these conclusions.

The results of this work combined with literature data allowed us to suggest a set of “standard” coupling constants for use in structural analysis of 2,3-dideoxy-2-enopyranose systems with α -erythro configuration in the unusual ${}^5\text{H}_\text{O}$ -conformation and more common ${}^0\text{H}_5$ -conformation (Figure 4).^{62,64,66}

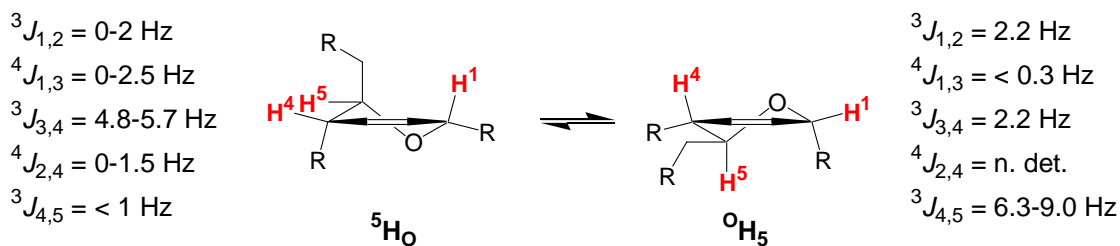


Figure 4. Refined “standard” coupling constants for ${}^5\text{H}_\text{O}$ - and ${}^0\text{H}_5$ -conformations of 2,3-dideoxy-2-enopyranose system.^{62,64,66}

existence of equilibrium between the *exo*-cyanoethylidene **36** and the acetoxonium intermediate.^{82,83}

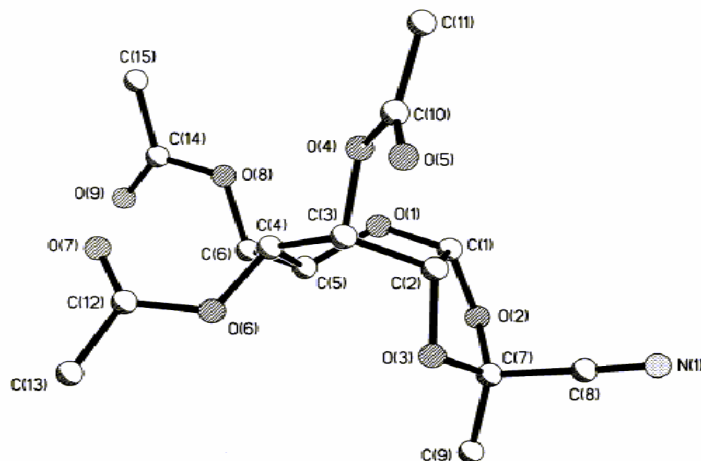
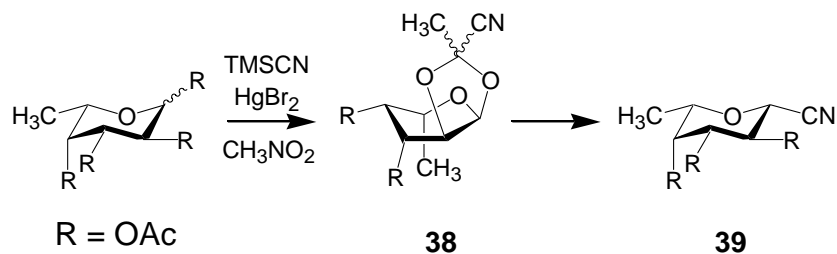


Figure 5. Molecular structure of the only isolated intermediate: per-*O*-acetyl-2-*O*-(1-*exo*-ethylidene)- α -D-glucopyranose **36**.⁸⁴

Cano *et al.*⁸⁵ have already done extensive studies on the conformations of per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)- α -D-glycopyranoses, which were obtained from the reactions of glycosyl bromides with potassium cyanide in tetrabutylammonium bromide/acetonitrile.⁸⁶ X-Ray crystallographic⁸⁴ and NMR analyses of the enantiomerically pure cyanoethylidene intermediate **36** from our procedure showed it to exist in a *twist*-boat conformation of the six-membered cycle, with the cyanide exclusively in the *exo*-position (Figure 5).

With excess TMS-CN and 0.1 molar equivalents of HgBr₂ in nitromethane, per-*O*-acetyl- α (or β)-L-fucopyranose was converted into per-*O*-acetyl- β -L-fucopyranosyl cyanide **39** in 95% yield within 4 h. We observed neither the cyanoethylidene compound **38** as an intermediate⁸⁶ nor decomposition, but only a trace of the α -anomer of **39** (Scheme 5).⁸¹⁻⁸³



Scheme 5. Synthesis of per-*O*-acetyl- β -L-fucopyranosyl cyanide **39**.⁸¹⁻⁸³

The 1,2-*O*-(cyanoethylidene) glycopyranose side products were obtained by Myers and Lee in a larger yield from per-*O*-acetyl-D-gluco- and mannopyranose than from per-*O*-acetyl-

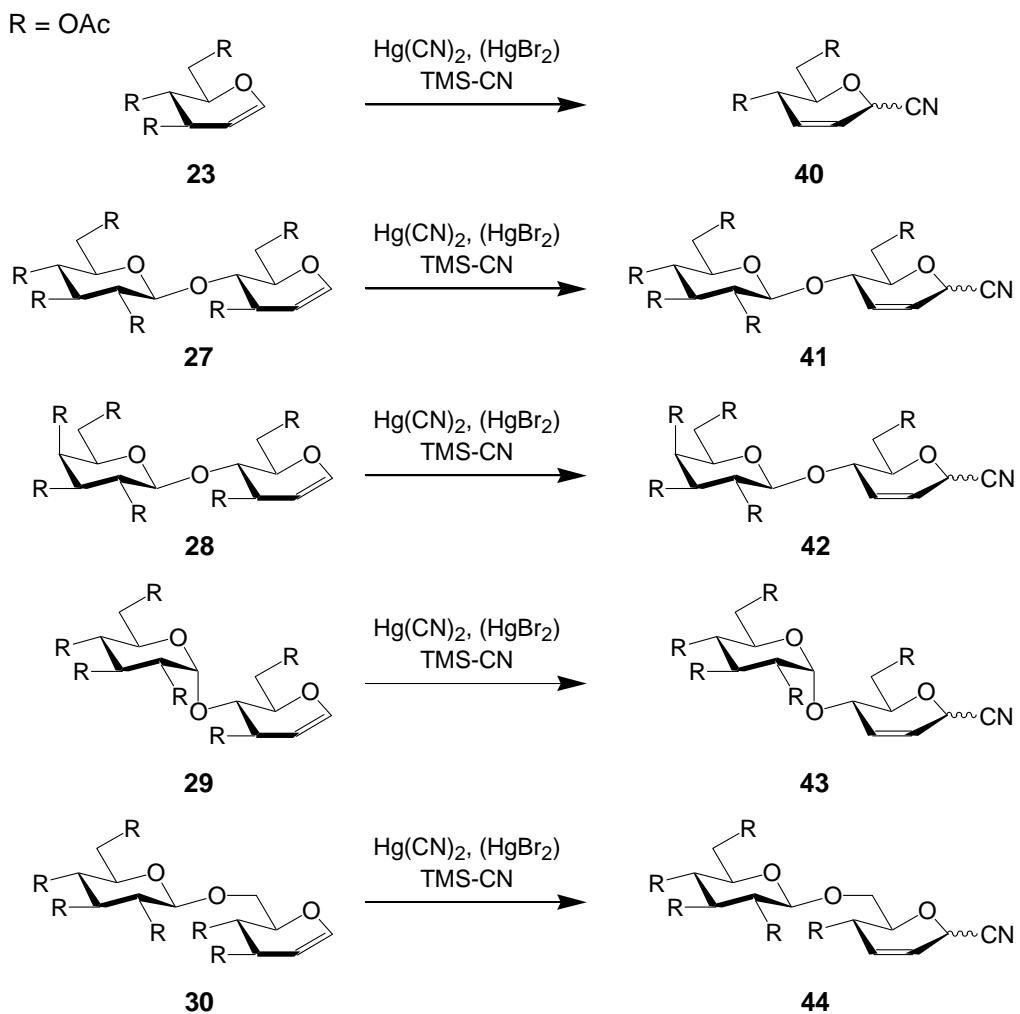
D-galactose.^{75,76} They tried to rearrange these syrupy byproducts into the corresponding α/β -cyanides with boron trifluoride-etherate ($\text{BF}_3\text{-OEt}_2$) but improved the glycosyl cyanide yield only slightly. Kini *et al.* found it necessary to elevate the reaction temperature to 35 °C to minimize formation of the 1,2-*O*-(cyanoethylidene) mannopyranoses when a mixture of per-*O*-acetyl- α/β -mannopyranoses was converted with TMS-CN/ $\text{BF}_3\text{-OEt}_2$ into α -D-mannopyranosyl cyanide.⁸⁷

4.2. Glycosyl cyanides from glycals and glycal dimers

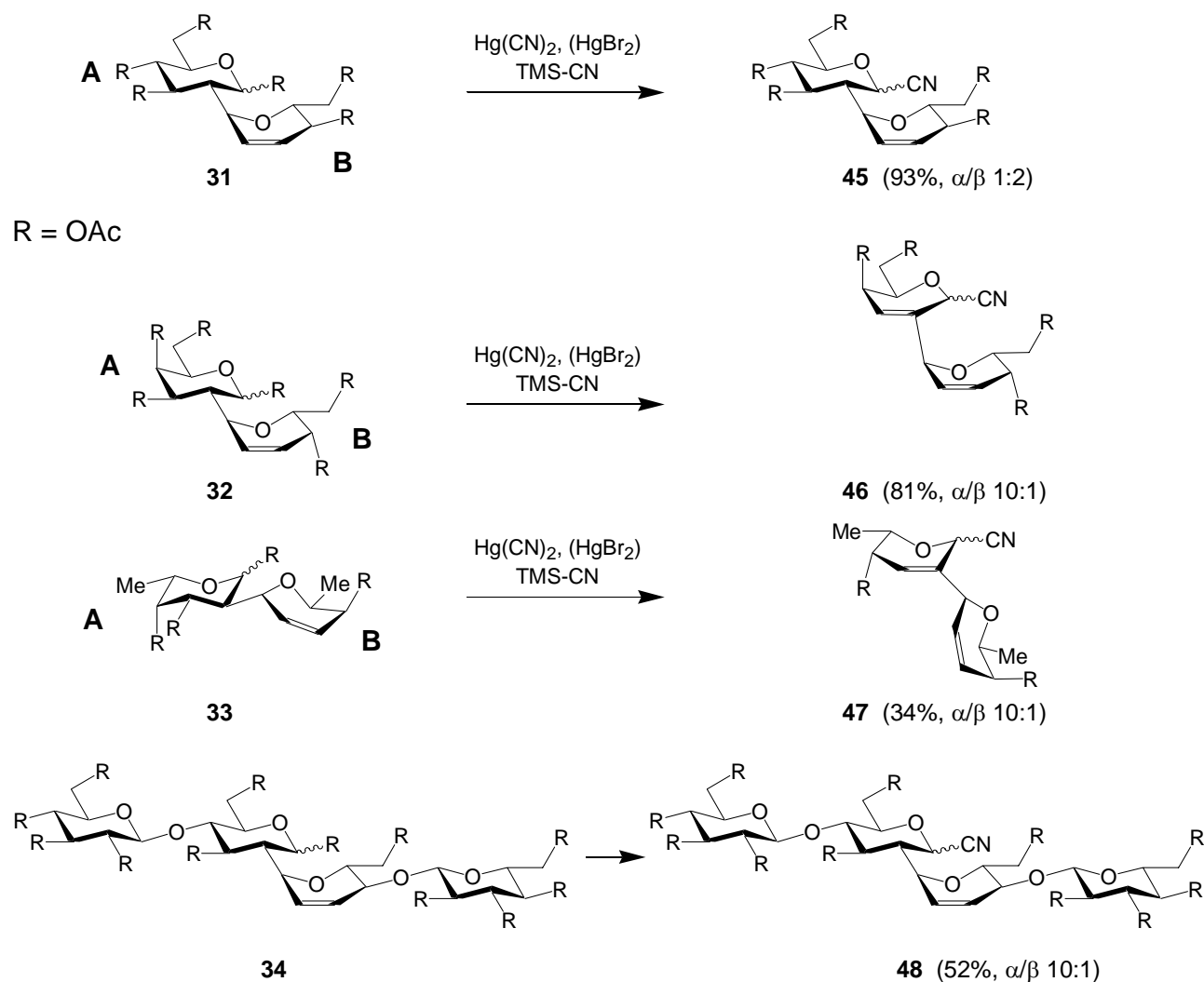
DeLas Heras *et al.* have shown that glycals, as well as glycosyl acetates, can be transformed with $\text{BF}_3\text{-Me}_3\text{SiCN}$ in nitromethane into 2,3-unsaturated glycosyl cyanides, or glycosyl cyanides, respectively.⁷⁹ The complex stereospecificity, if any, of such S_{N}' -reactions has been discussed by March.⁸⁸ More recently, alternative methods for the preparation of 2,3-unsaturated glycosyl cyanides from protected or unprotected glycals have been developed.^{89,90} We used a milder reagent for the introduction of a cyanide functionality, $\text{Hg}(\text{CN})_2/\text{HgBr}_2/\text{Me}_3\text{SiCN}$ in THF/MeCN (2:3), to transform tri-*O*-acetyl-D-glucal **23** into 2,3-unsaturated di-*O*-acetyl-D-glucosyl cyanide **40** (Scheme 6).^{62-64,91,92}

We could use this reagent not only to convert *O*-glycosidic glycals into 2,3-eno-pyranosyl cyanides (Scheme 6) but also to obtain anomeric cyanides from glycal dimers and tetramers (Scheme 7) which are 2-*C*-2-deoxy-sugars.^{62-64,92} The reagent was compatible with 1,4- and 1,6-*O*-glycosidic linkages, which are normally prone to cleavage in the presence of BF_3 .⁷⁹

The reagent $\text{Hg}(\text{CN})_2$, HgBr_2 and TMS-CN, applied to compound **31**, replaced the anomeric acetate group in ring A, to give the expected glycosyl cyanide **45** (Scheme 7).⁶²⁻⁶⁴ However, compound **33** (a dimer from tri-*O*-acetyl-L-fucal) gave unexpectedly the doubly unsaturated cyanide **47** (Scheme 7).^{62-64,92} Similarly, the galactal dimer **32** gave a doubly unsaturated cyanide **46**. Although the dimers **32** and **33** had only a stereochemical difference with **31** in the relative disposition of the 4-acetoxy group, the substitution of the anomeric acetoxy group was attended by elimination of AcOH, with deprotonation at C-2.^{62-64,92} A relief of steric strain may be a driving force for this elimination. Indeed, the molecular mechanics calculations (MM+) revealed a substantially higher steric strain (by 3-4 kcal/mol) in the most stable conformation of **33** when compared with 6A,6B-dideoxy analog of **31**, which is a stereoisomer of **33**. The remote C-4^A acetoxy group, which functions as an internal base, may facilitate the deprotonation of an intermediate oxonium ion by intramolecularly removing and transporting the proton ultimately to external CN⁻, like a miniature crane. Such a “crane effect” does not work in **31**, which has a different orientation of the C-4^A acetoxy group.^{62-64,92}



Scheme 6. Cyanation of per-*O*-acetyl-glucal and disaccharidic per-*O*-acetyl-glycals.^{62-64,91,92}



Scheme 7. Cyanation products from glycal dimers.^{62-64,92}

4.3. Reduction of glycosyl cyanides

One versatile approach to glycosyl cyanide modification, with which we have considerable experience, is catalytic reduction.^{81,82,93-96} Hydrogenation of per-*O*-acetyl- β -L-fucopyranosyl cyanide **39** with catalytic palladium-charcoal in the presence of acetic anhydride (Ac_2O) gave the isolated *O*-*N*-acetyl migrated products **49** and **50** in 32% and 23% yields, respectively (Scheme 8).^{81,82,94-96} The yield for the *N*-linked aminodisaccharide **50** decreased to 9% without the presence of Ac_2O . Since the presence of Ac_2O did not prevent migration, it appeared that *O*-*N*-acetyl migration from a 2-*O*-acetoxyl group was much faster than acetylation of the amines. The 2-hydroxyl amino-*C*-monosaccharide **49** and *C*-disaccharide **50** can be acetylated with Ac_2O in the presence of catalytic 1,4-(dimethylamino)pyridine (DMAP) to the corresponding fully protected **51** and **52** before or after isolation.^{81,82,94-96}

In the presence of the lipophilic Boc₂O, the hydrogenation of cyanide **39** on Pd/C gave only **53** and an *N*-linked disaccharide **54** in 61% and 38% yields, respectively, *without O-N*-acetyl migrations (Scheme 8).^{81,82,94-96} Again, the yield of disaccharide **54** was increased in presence of the anhydride.

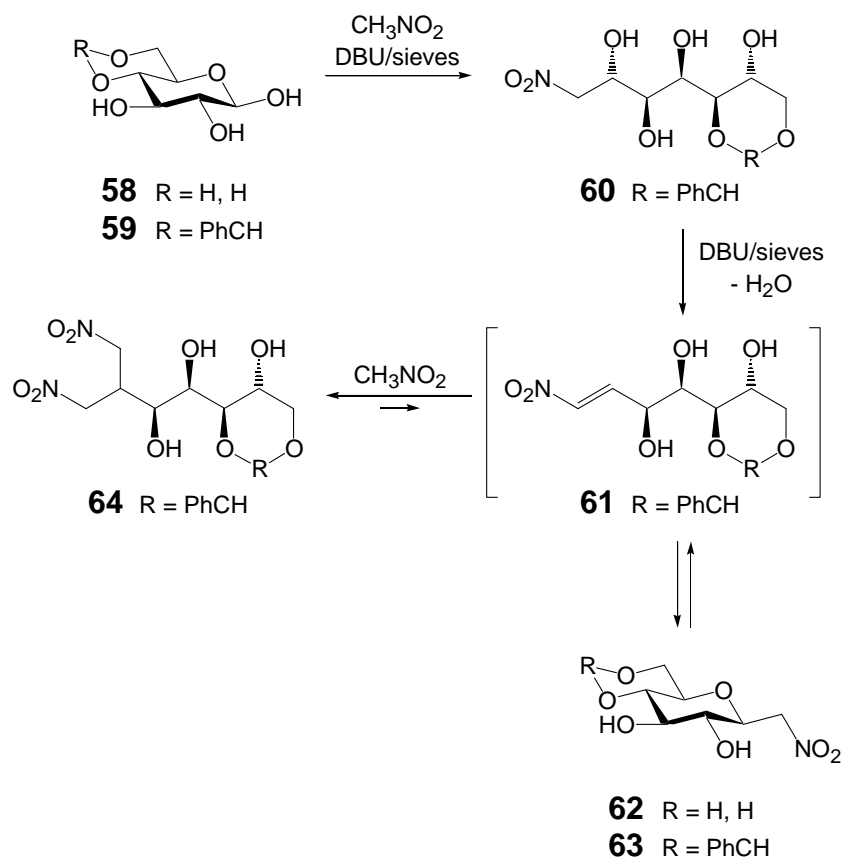
Cyanides are reduced with H₂/Pd in two stages.⁹⁷ The first stage is formation of aldimine, and the second is reduction to the corresponding amine. In the production of **49** and **50**, *O-N*-acetyl migration could occur at the aldimine or amine stage. The migration at the stage of amine made it unavailable for further reaction. That no acetyl migratory product was observed in the presence of Boc₂O suggests fast reaction of aldimines and amines with Boc₂O at the lipophilic charcoal catalyst surface. In contrast, hydrophilic Ac₂O, present in the bulk solution, permits acetyl migrations at the surface. The more electrophilic acylated aldimines tend to favor dimerization, which indeed occurred more readily in the presence of Ac₂O and Boc₂O.^{81,82,94,95} This point was not appreciated by Lenz *et al.* in their later work with Boc₂O,⁹⁸ probably because they did not compare hydrogenation in the presence of Ac₂O, as we did.

From the Boc-protected aminomethyl-*C*-fucopyranoside synthons, a great variety of biologically interesting glycoconjugates are accessible. Transformation of the 1° amino functionality into an isocyanate allows coupling with the former 1° amine or the 2° amine dimer. Other nucleophiles would give glycoconjugates with minimal scaffolding such as unsymmetrical ureas. This could be accomplished in many ways, but most commonly by phosgenation,⁹⁹ which is economical and practical, since the advent of crystalline “triphosgene”. We removed the Boc-protective group from the aminomethyl-*C*-monosaccharide **53** with TosOH-H₂O in CH₂Cl₂, and the resultant salt, in solution, was directly converted with 1/6 equivalents of triphosgene in a CH₂Cl₂-saturated sodium bicarbonate two-phase system (Scheme 8), via the *in situ* amino- and isocyanato-monosaccharide intermediates, into the novel di-fucopyranosyl methyl-substituted urea **55** in 63% yield, along with **49** (12%) through *O-N*-acetyl migration.^{81,82,94-96}

When the same deprotection and two-phase phosgenation was applied to the *N*-linked disaccharide **54**, a novel tetra-fucopyranosyl methyl-substituted urea **57** (28%) was obtained along with the *O-N*-acetyl migratory side-product **50** (48%) and the stable crystalline carbamoyl chloride **56** (15%; Scheme 8) - a potentially useful reactant for preparation of more complex *C*-glycosidic conjugates. The yield for the tetra-substituted urea derivative was surprisingly high for a bimolecular reaction of two sterically hindered intermediates, which had to compete with the major intramolecular pathway of acetyl migration, after Boc removal. Formation of acetyl migratory side products **49** and **50** was increased if a weaker acid such as trifluoroacetic acid was employed to remove the Boc-protective group, or if Hünig's base was used in a single non-polar organic solvent instead of a two-phase system with aqueous bicarbonate. With an excess (1/3 equivalents) of triphosgene, acetyl migratory product was minimized, and formation of the tetra-substituted urea also ceased, but the yield of the interesting carbamoyl chloride **56** increased to 67%. It was successfully isolated by column chromatography on normal SiO₂, by elution with isopropyl ether.^{81,82,94-96}

5. Henry Condensation

One of the most common methods for the chain extension of carbohydrates is the Henry condensation of pentoses and hexoses with nitromethane in the presence of a strong base. In 1946 Sowden and Fisher condensed 4,6-*O*-benzylidene-D-glucopyranose **59** (Scheme 9) with nitromethane in the presence of methoxide to give D-heptitol **60** and nitromethyl β -D-glucopyranoside **63** in 21% and 5% yield, respectively.¹⁰¹ Later, Petrus *et. al.* improved the total yields of unprotected nitromethyl D-hexopyranosides, but their approach is lengthy and complicated, requires careful workup with adjustment of pH, and produces isomeric mixtures.¹⁰² Strong bases (HO^- , MeO^-) in these procedures in protic solvents lead to open-chain products (i.e. **60**, Scheme 9).¹⁰¹ Their hot dehydration gives cyclic forms, reverting only very slowly to acyclic at low temperatures.¹⁰³ Presumably, acyclic forms, having more hydroxy groups, are stabilized by solvation in protic solvents.



Scheme 9. Henry condensation of protected and unprotected β -D-glucopyranose.^{82,104-107}

We had synthesized^{82,104-107} directly the cyclic compounds in aprotic solvents with a highly active bifunctional¹⁰⁸ catalyst 2-hydroxypyridine¹⁰⁹ and DBU/molecular sieves¹⁰⁴ with an improved yield of 77%.¹⁰⁵ We avoided protic solvents because of the strong basicity of DBU,

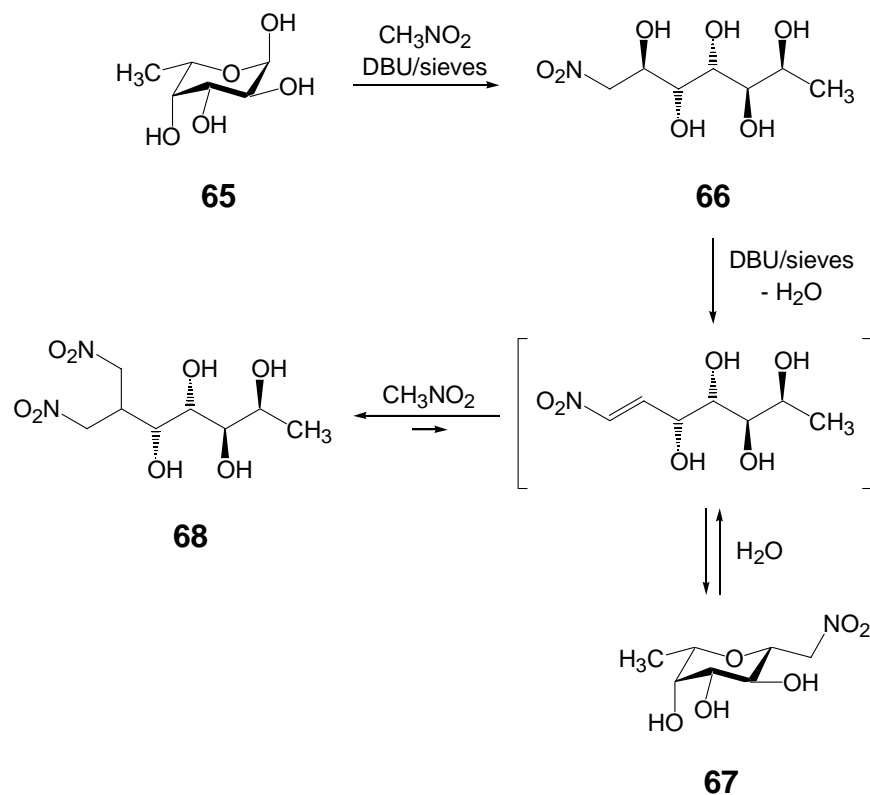
which would provide just another way of creating RO⁻ in ROH. The cyclic product **63** was produced in a single step along with two minor byproducts **60** and **64**.¹⁰⁴

We reinvestigated later^{82,106,107} our original condensation^{104,105} of nitromethane with 4,6-*O*-benzylidene-D-glucopyranose **59** to nitromethyl 4,6-*O*-benzylidene β-D-glucopyranoside **63** and discovered that 2-HP was unnecessary. A time study, with careful TLC analysis and flash chromatography of the reaction mixture with DBU and molecular sieves revealed sequential products, which are conveniently explained as outlined in the mechanistically simplified Scheme 9.

The condensation progressed similarly in THF and dioxane, with 4,6-*O*-benzylidene-D-glucopyranose via 5,7-*O*-benzylidene-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol **60**, which subsequently changed into nitromethyl β-D-glucopyranoside **63**. The former was observed accumulating before being further converted during at least 50 hours at room temperature to the cyclic product **63**, along with some 5,7-*O*-benzylidene-1,2-dideoxy-1-nitro-2-nitromethyl-D-*gluco*-heptitol **64**, in yields similar to those already reported.^{104,105} In THF or dioxane, accumulation of the final acyclic product **64** was dependent on temperature, time, and solvent: less decomposition was observed in dioxane. In these condensations, we could not determine if the presence of 2-HP had any effect at all, at any stage of the reaction. In any case, the first heptitol **60** and the desired **63** were kinetically controlled intermediates, which, given enough time, were transformed into the “thermodynamic” product **64**, by a still slower overall rate.

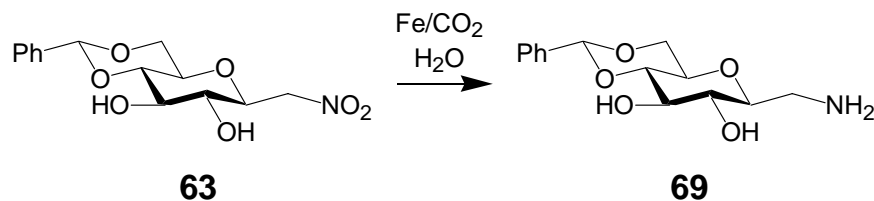
When similar conditions were employed for unprotected D-glucose **58**, there was no reaction for prolonged periods of time. Heating only resulted in almost complete decomposition. This was expected since unprotected sugars are typically not very soluble in THF or dioxane. But in acetonitrile, pyridine or a mixture of these at 50 °C, the condensations were fairly clean.^{82,106,107} The condensation progressed to completion within one day, and only nitromethyl β-D-glucopyranoside **62** (Scheme 9) was detected and isolated when 5:1 acetonitrile/pyridine (38% yield) or pyridine was used as the solvent (57% yield). For completion and maximal yield, a stoichiometric amount of DBU was needed.

Condensations with L-fucose **65** were monitored by TLC and flash chromatography, and gave sequential products as outlined in Scheme 10.^{82,106,107} Within 12 h in THF more than half of the starting L-fucose was converted into corresponding 1,6-dideoxy-1-nitro-L-*glycero*-D-*manno*-heptitol **66**. By the end of day 3, most of L-fucose had been transformed into the acyclic heptitol **66**, and the subsequent conversion into cyclic nitromethyl β-L-fucopyranoside **67** was followed for another 5 days, during which time a significant portion of the desired cyclic product **67** had also been slowly converted into 1,1,6-trideoxy-1-nitro-2-nitromethyl-L-*galacto*-heptitol **68**. Thus, the maximal yield for product **67** required minimizing decomposition and the yields of **66** and **68**. In dioxane, only **67** was isolated as the product (62%). On the contrary, 50% **68** vs. 5% **67** were obtained in DMF. The results suggest that solubility might be the most important factor to affect Henry condensations of unprotected sugars.



Scheme 10. Henry condensation of unprotected L-fucose **65**.^{82,106,107}

A possible further transformation of the synthesized nitro-compounds is illustrated by the reduction of nitromethyl β -D-glucopyranoside **63** with a specially prepared elemental iron in water/THF under CO_2 atmosphere to aminomethyl-C-glycoside **69** (Scheme 11).^{104,105}



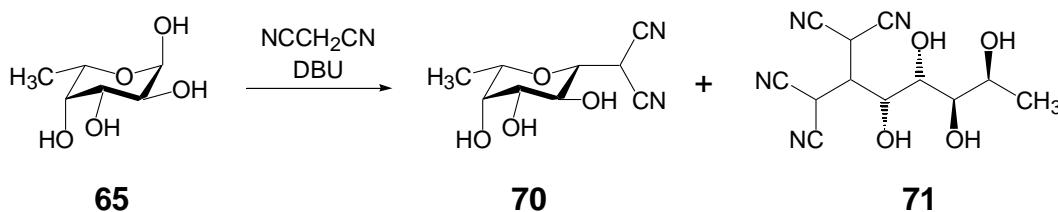
Scheme 11. Reduction of the Henry condensation product **63** to the aminomethyl-C-glycoside **69**.

6. Condensation with Malononitrile

As described above, Henry condensation with nitromethane of partially protected and non-protected pyranoses with a free anomeric hemiacetal function in presence of DBU and molecular sieves produces C-glycosides, which molecules incorporated one or two molecules of

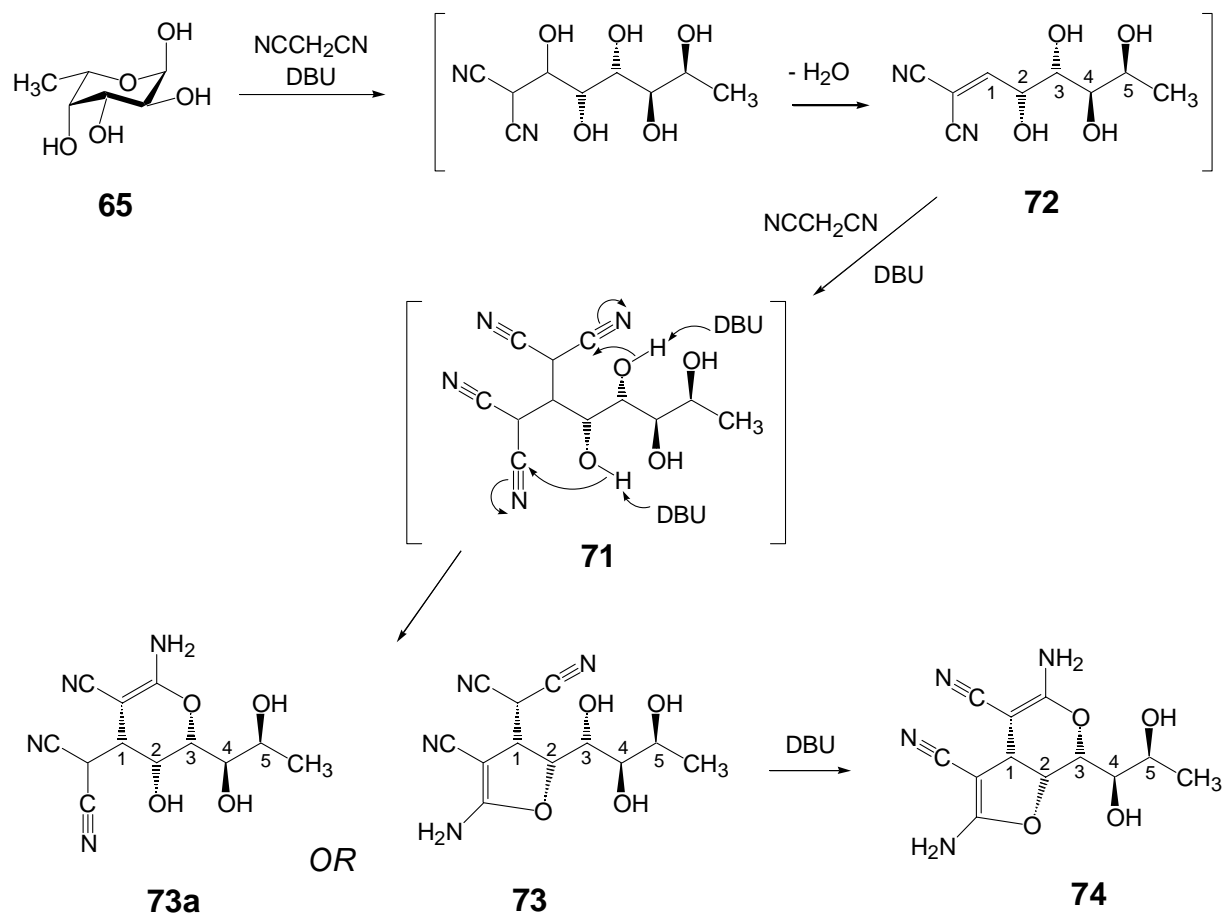
nitromethane (an example of L-fucose reaction is shown on Scheme 10). The ratio of products substantially depended on conditions of the reaction.^{82,104-107}

Inspired by this result, we explored a possibility of a similar synthesis of C-glycosides using malononitrile (MN) instead of nitromethane as an active methylene component (Scheme 12).^{110,111} Malononitrile is a versatile compound of exceptional reactivity.^{112,113} It is often used as a reactant for synthesis of heterocycles since the methylene group and either one or both cyano groups can take part in condensation reactions to give a variety of addition products and heterocyclic compounds.¹¹⁴⁻¹¹⁶ MN has not been used for preparation of C-glycosides, though their formation using dialkyl malonates was studied extensively.¹¹⁷



Scheme 12. Expected products from the reaction of L-fucose with malononitrile.

L-Fucose **65** was selected as a starting carbohydrate. We expected products similar to those obtained in reaction with nitromethane (Scheme 10). However, the reaction was much faster (1 h instead of several days), and neither mono-adduct **70** nor bis-adduct **71** (Scheme 12), which are analogs of **67** and **68** (Scheme 10), was obtained. Instead, two cyclic compounds **73** (oil) and **74** (white crystals) in a ratio ~5:1 (by NMR) were isolated by a column chromatography of the reaction mixture (Scheme 13).^{110,111}



Scheme 13. Condensation of L-fucose and malononitrile in presence of DBU.

The bicyclic structure **74** was proven by X-ray crystallography (Figure 6).^{110,118} Interestingly, the solution conformation (in CD₃OD) of the side chain in **74** estimated from the vicinal spin-spin couplings in ¹H NMR correlated well with the crystal structure data.¹¹¹ To the best of our knowledge, no compounds have been described so far with this combination of five- and six-membered oxygen-containing heterocycles.

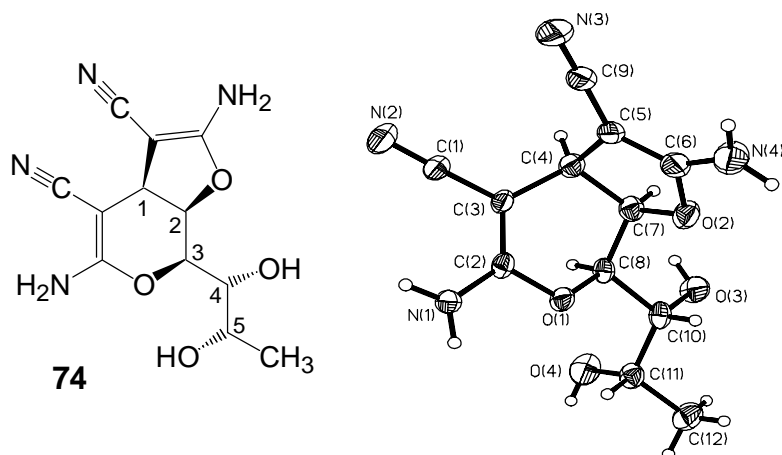
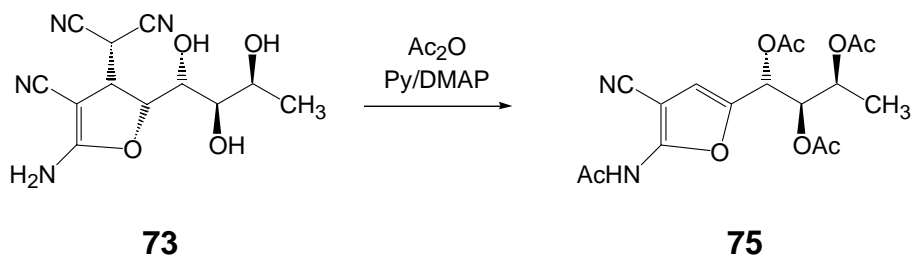


Figure 6. Molecular structure of the bicyclic product **74**.^{110,118}

The results of the synthesis may be rationalized as a sequence of (a) Knoevenagel condensation producing intermediate **72**, then (b) Michael addition of another MN resulting in formation of *bis*-adduct **71**, and then (c) a base-induced double cyclization. The latter can occur via either the dihydrofuran derivative **73**, or the dihydropyran derivative **73a**. However, we isolated only one monocyclic compound, which structure could not be assigned based on NMR data. In an attempt to prepare a crystalline derivative appropriate for X-ray analysis, we acetylated product **73** (Scheme 14) and obtained the furan derivative **75**, which NMR parameters perfectly matched the parameters of similar furan derivatives described in literature.¹¹⁹ This result suggests the structure **73** as the intermediate monocyclic compound isolated in the reaction of L-fucose with MN.^{110,111}



Scheme 14. Acetylation of monocyclic compound **73**.

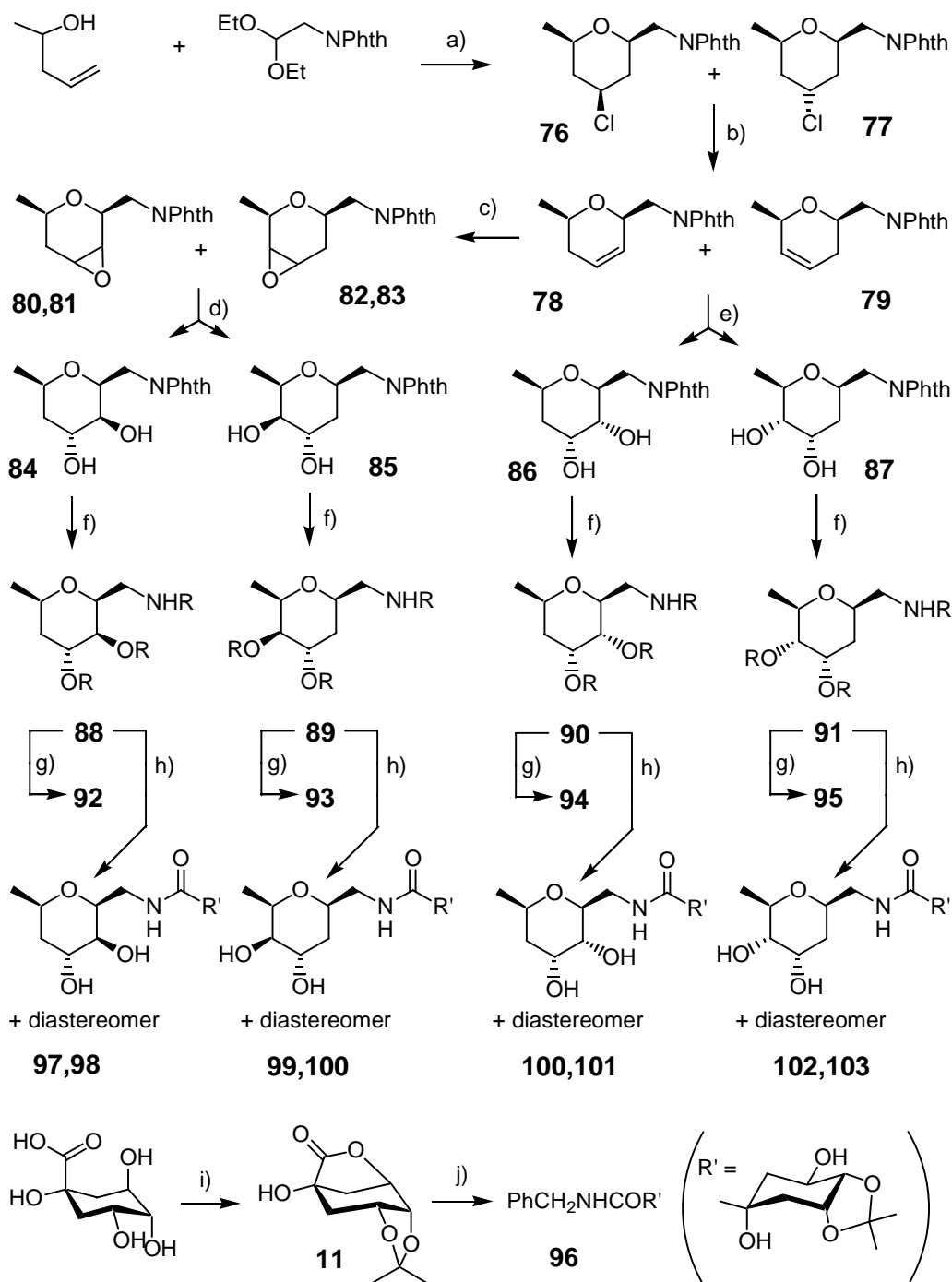
7. Total Syntheses of Aminomethyl-C-dideoxyglycopyranosides and their Quinamides

The great majority of methods developed for the synthesis of C-glycosides¹⁸⁻²⁰ start from natural sugars, mostly D-glucose, D-mannose and D-galactose, which are commercially available in

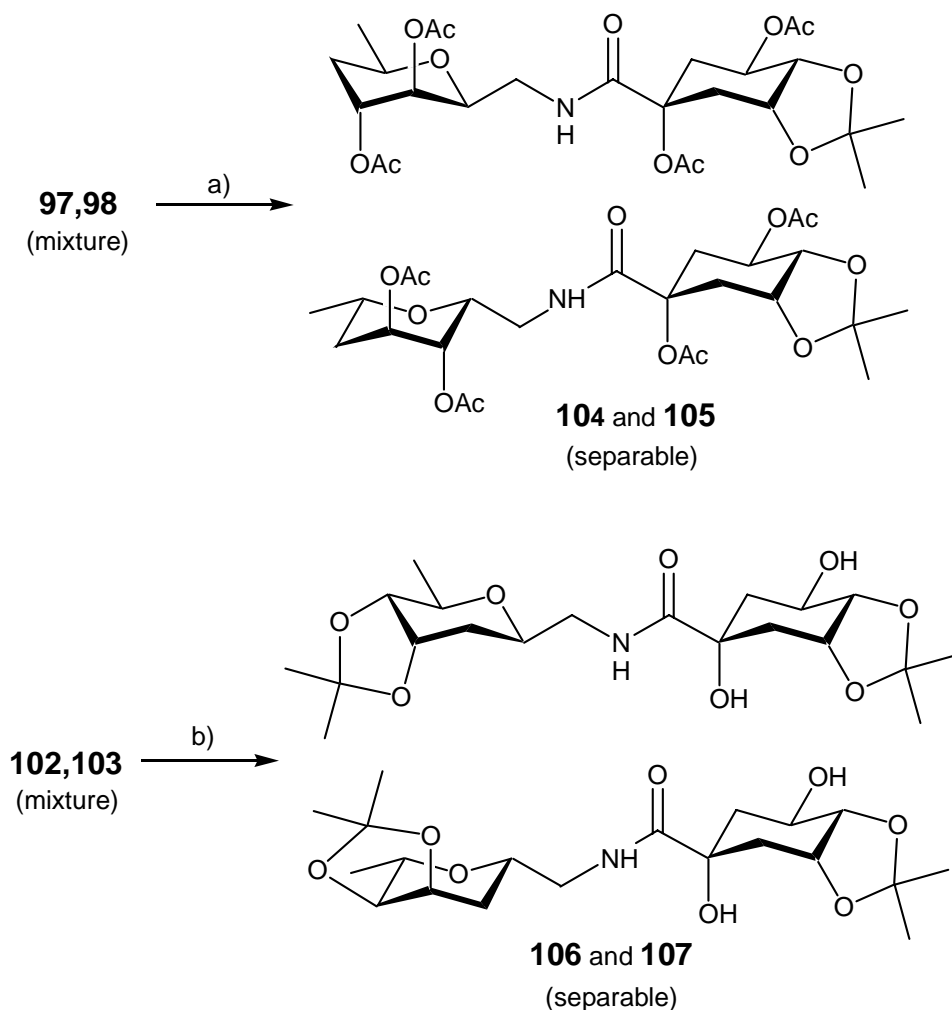
multigram quantities.¹²⁰ Other D-monosaccharides and all L-monosaccharides are very expensive and available only on a milligram scale.¹²⁰ Moreover, D-gulose, D-altrose and D-idose exist in appreciable proportions as their 1,6-anhydrides with essentially different chemical behaviour.¹²¹ We developed an approach to the total syntheses of partially functionalized β -C-glycopyranosides,^{49,93,122-128} related to 2,4- and 4,6-dideoxyhexoses, found as cardiac glycosides.^{129,130} These C-glycosides are tetrahydropyrans obtained from homoallylic alcohols and acetals by a Lewis acid promoted cyclization, followed by dehydrohalogenation and subsequent double bond functionalization.^{49,93,122-128} A subsequent use of these building blocks for the syntheses of di- and oligosaccharide mimics is illustrated by their quinoylation. Quinic acid is an important structural component in a number of naturally occurring biologically active compounds which exhibit HIV-integrase inhibition,¹³¹⁻¹³³ as well as hypocholesterolemic,¹³⁴ hepatoprotective¹³⁵ and antioxidative¹³⁶⁻¹³⁸ activities. A combination of racemic aminomethyl C-glycosides with chiral quinic acid may directly yield biologically active chiral compounds.

Acid catalyzed reactions between homoallylic alcohols and aldehydes or acetals have been used before for the preparation of 2,6-disubstituted di- and tetrahydropyran derivatives (see Ref. 92 and references therein). We chose an expandable two-component scheme of cyclization with a possibility of various functional groups in readily available starting compounds. Use of phthalimido derivatives allowed for syntheses of (protected) aminomethyl C-glycopyranosides (Scheme 15).

Cyclizations of this type furnish exclusively *cis*-2,6-disubstituted tetrahydropyrans^{49,93,122-128} corresponding to the β -configuration of the projected C-glycopyranosides. Most C-glycoside syntheses provide α -products.^{19,20} The new stereocenter C(6) is entirely determined by the configuration of the existing stereocenter in the homoallylic alcohol. Chiral homoallylic alcohols would give enantiomerically pure tetrahydropyrans, and finally C-glycosides. We obtained racemic aminomethyl C-glycosides, subsequently acylated with the chiral lactone of quinic acid **11** (Scheme 15), and separated as derivatives of diastereomeric quinamides (Scheme 16).



Scheme 15. Synthesis of aminomethyl-C-glycosides and their quinamides (**76-83**: stereoisomeric mixtures; **84-95**: racemic mixtures; Phth = phthaloyl)^{49,93,122-128}: (a) SnCl₄, CH₂Cl₂, -55°C, 82%; (b) DBU, LiCl, Py, reflux, 79%; (c) Urea-H₂O₂, TFAA, 93%; (d) TFA, H₂O/THF, 60°C, 74%; (e) OsO₄, NMO, 64%; (f) 1) Me₂NH, MeOH, H₂O, 2) H₂SO₄, H₂O, 3) NH₄OH, 80-86% (**88-91**: R = H); (g) Ac₂O, DMAP, Py, 51-85% (**92-95**: R = Ac); (h) **11**, DMA, 70°C, 58-77%; (i) acetone, *p*-TsOH, reflux, 86%; (j) BnNH₂, DMA, 55°C, 72%.



Scheme 16. Separation of diastereomeric mixtures of quinamides as isopropylidene-tetra-*O*-acetyl or diisopropylidene derivatives: (a) Ac_2O , DMAP, Py; (b) 2-methoxypropene, *p*-TsOH, DMF.^{49,128}

Specifically for the synthesis of various homoallylic alcohols (Scheme 15), we developed new methods: transallylation¹³⁹ and allylation in aqueous phase^{140,141} of commercially available and relatively stable aldehyde acetals. Acid promoted cyclization of pent-4-en-2-ol with the phthalimido derivative of 2,2-diethoxyethylamine at -55°C in CH_2Cl_2 solution with SnCl_4 (Scheme 15) gave chlorotetrahydropyrans **76** and **77** (5:1, separable by column chromatography). The alkenes **78**, **79** were obtained as a 2:1 mixture (by NMR) by heating of the mixture **76**, **77** with DBU in pyridine in presence of LiCl , which facilitated *in situ* isomerization of equatorial into axial halogen, suitable for *trans*-elimination. Epoxidation of the alkene mixture with the urea- H_2O_2 complex in presence of $(\text{CF}_3\text{CO})_2\text{O}$ (TFAA)¹⁴² produced an epoxide mixture **80-83** (93%), which was difficult to separate. However, the well known tendency of epoxides to open *trans*-diaxially,¹⁴³ allowed for direct synthesis of a two-component *trans*-diol mixture **84**,

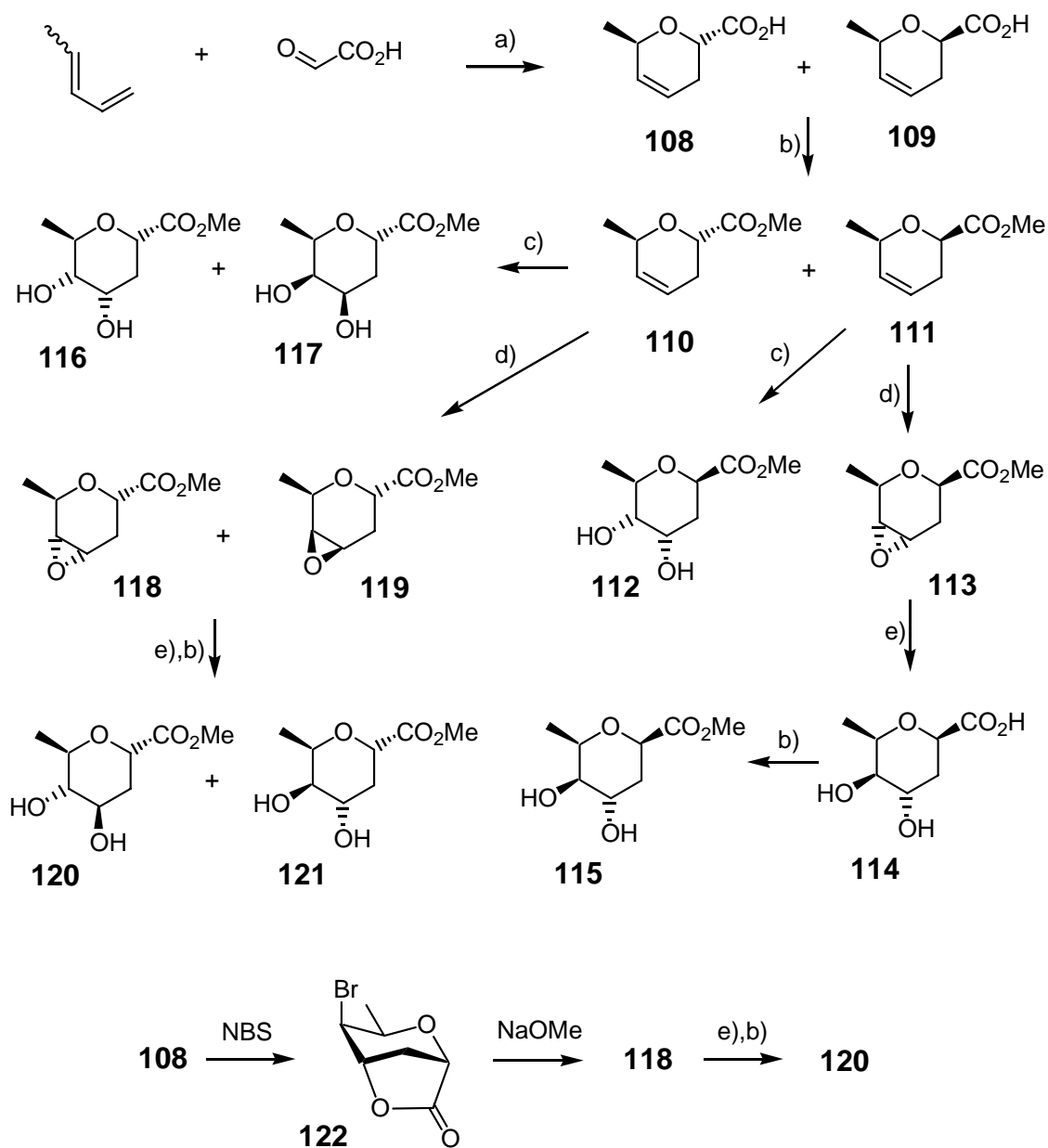
85, separated by column chromatography (51% and 23% respectively). After *cis*-dihydroxylation (OsO_4/NMO) of the mixture **78**, **79**, only compounds **86** and **87** were isolated (45% and 19% respectively).

Thus, we obtained a series of four racemic phthalimido-protected aminomethyl *C*-dideoxyglycopyranosides **84-87**, which produced with aq. Me_2NH ¹⁴⁴ the dimethylammonium salts of phthalamic acids. They were hydrolyzed after evaporation of excess Me_2NH by heating with aq. H_2SO_4 (70°C), followed by extraction of phthalic acid with CH_2Cl_2 and Et_2O . Neutralization by NH_3 aq. and subsequent evaporation followed by column chromatography gave compounds **88-91** (80-86%), characterized and analyzed as their *N*-acetyl- and/or *N,O*-triacetyl derivatives, and used as building blocks for pseudodisaccharides. Acylation of benzylamine with the isopropylidened γ -lactone of quinic acid **11**^{145,146} provided us with ^1H NMR chemical shifts and coupling constants for the quinoyl part of compound **96**. Similarly we converted racemic *C*-glycosides **88-91** into their quinamides **97-103** (i. e. into diastereomeric *C*-pseudodisaccharides; Scheme 15).

Generally, separation of diastereomeric pairs **97-103** could only be achieved *via* their derivatives (Scheme 16). Thus, the *trans*-dihydroxy aminomethyl *C*-glycosides **97**, **98** were separated as their *O*-acetyl derivatives by flash chromatography to produce **104** (or **105**)(7%), **105** (or **104**) (28%), and **104+105** (32%). Quinamides **102**, **103** were isopropylidened, and the mixture **106**, **107** was enriched with one of the stereoisomers (9:1) by column chromatography.

8. *C*-Glycosides via Cycloadditions

The aqueous hetero-Diels-Alder reaction has been investigated by A. Lubineau *et. al.*,¹⁴⁷⁻¹⁵¹ for the synthesis of dihydropyran cyclo-adducts. We wanted to explore their use, through dihydroxylation of the double bond for syntheses of *C*-glycosides,^{152,153} as mimetics of naturally occurring 2,6-dideoxy sugars.¹⁵⁴ Technical 1,3-pentadiene (piperylene) and aq. glyoxylic acid are inexpensive commercial products, which were used as starting materials. The reaction was regioselective in the intended way, most likely because of the electron donating property of the methyl group of pentadiene. The *cis*- and *trans*- acids were obtained in comparable amounts (Scheme 17).^{152,153} Their direct separation by chromatography was unsuccessful. However, methylation of the crude acid product **108**, **109** rendered the mixture **110**, **111** separable on TLC, and by column chromatography. In this way we obtained suitable starting materials for the following dihydroxylations.



Scheme 17. Synthesis of 2,6-anhydro-2,4,5,6-tetrahydroxy-D,L-heptanoic acid esters.^{152,153} (a) 100°C, 56%; (b) CH₂N₂; (c) OsO₄, NMO; (d) Urea-H₂O₂, TFAA; (e) TFA/ H₂O.

The *cis*-isomer **111** gave only one major racemic product of *cis*-dihydroxylation (**112**). It is not clear why the molecule **111** does not allow OsO₄ approach from both sides. Similarly, the epoxidation of **111** gave a crude epoxide **113** (Scheme 17) in 84% yield, the NMR and TLC of which showed no evidence of the epoxide with opposite configuration. Its purification by column chromatography proved to be difficult, due to its instability. As expected, acid hydrolysis (**113**→**114**) gave a single major product, which could be isolated pure after esterification to **115**

(81% overall; Scheme 17). It is advantageous, that any “opposite epoxide” in the crude mixture also would give preferentially the same diaxial hydrolysis product **114**.¹⁴³

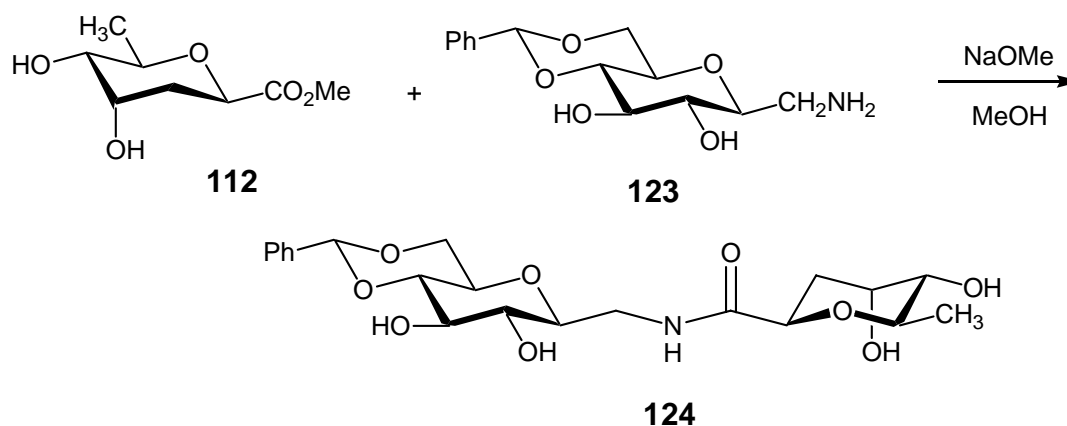
cis-Dihydroxylation of *trans*-isomer **110** gave a mixture of stereoisomeric **116** and **117** (ratio 3:1 by NMR; overall yield 73%). Compound **116** was crystallized from the mixture (57%). Compound **117** was not successfully isolated from the mother liquor, but its ¹H-NMR parameters were determined from the mixture.

The epoxidation of *trans*-ester **110** gave two epoxides **118** and **119** as detected by TLC. Their mixture was subjected to hydrolysis and methylation to give a mixture of *trans*-dihydroxy esters **120** and **121**, which was separated by column chromatography (yields 38% and 43% respectively).

We also tried to separate the carboxylic acids **108** and **109** by the reaction of NBS with their mixture. Only the *trans*-isomer **108** reacted with NBS to form a bromolactone, and the lactone **122** was easily separated from the reaction mixture, but the yield was too low (15-25%). The nature of the side reaction of the *trans*-isomer with NBS could not be determined. The bromolactone **122** was cleaved by NaOMe to give the single epoxide **118** which was hydrolyzed to give a single carboxylic acid **120**, providing another structure proof for it (Scheme 17).

Thus, the hetero-Diels-Alder reaction between inexpensive 50% aq. glyoxylic acid and technical grade piperylene provided a starting point for synthesis of a series of 2,6-anhydro-2,4,5,6-tetrahydroxy-D,L-heptanoic acid esters,^{152,153} which are C-glycosidic analogs of 2,6-dideoxypyranoses, prominent in cardiac glycosides.¹⁵⁴

When racemate **112** and 4,6-*O*-benzylidene-β-D-glucopyranosyl methylamine **99**¹⁰⁴ were refluxed in methanol in presence of a catalytic amount of NaOMe, the reaction was completed in 3 hours, and produced the amide **100** (87%) as a mixture of diastereomers (Scheme 18).¹⁵³



Scheme 18. Amide coupling of **112** with **123**.

Such conjugates with natural carbohydrate derivatives offer potential for chiral resolution. Glycobiological applications for these compounds appear very possible.

9. Hydroxy-derivatives of 1,2-cyclohexanedicarboxylic Acids

The structure of inhibitors usually resembles a substrate, a transition state, or a product of enzyme-catalyzed reaction.¹⁸⁻²³ From this point of view, various polyhydroxylated five- and six-membered cyclic compounds may be considered as monosaccharide structural analogs, and thus potential inhibitors of glycosidases. In a search for simple, readily accessible, but efficient glycosidase inhibitors, we designed, prepared, and assayed a series of cyclohexanecarboxylic acids and esters of types **125-131** with different substitution pattern, configuration, and length of *n*-alkyl groups R, in order to reveal the effects of these parameters upon the inhibitory activity (Figure 7).^{111,155-158}

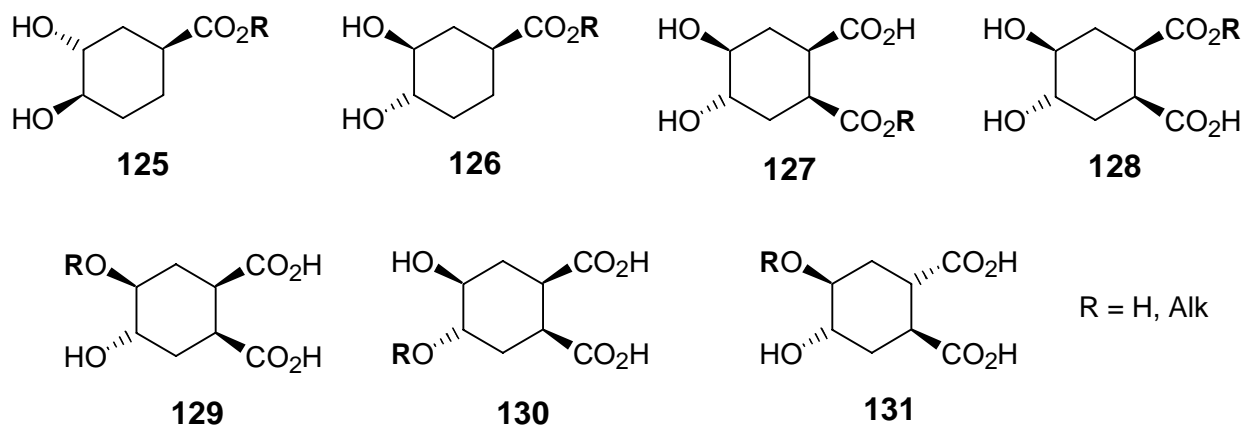
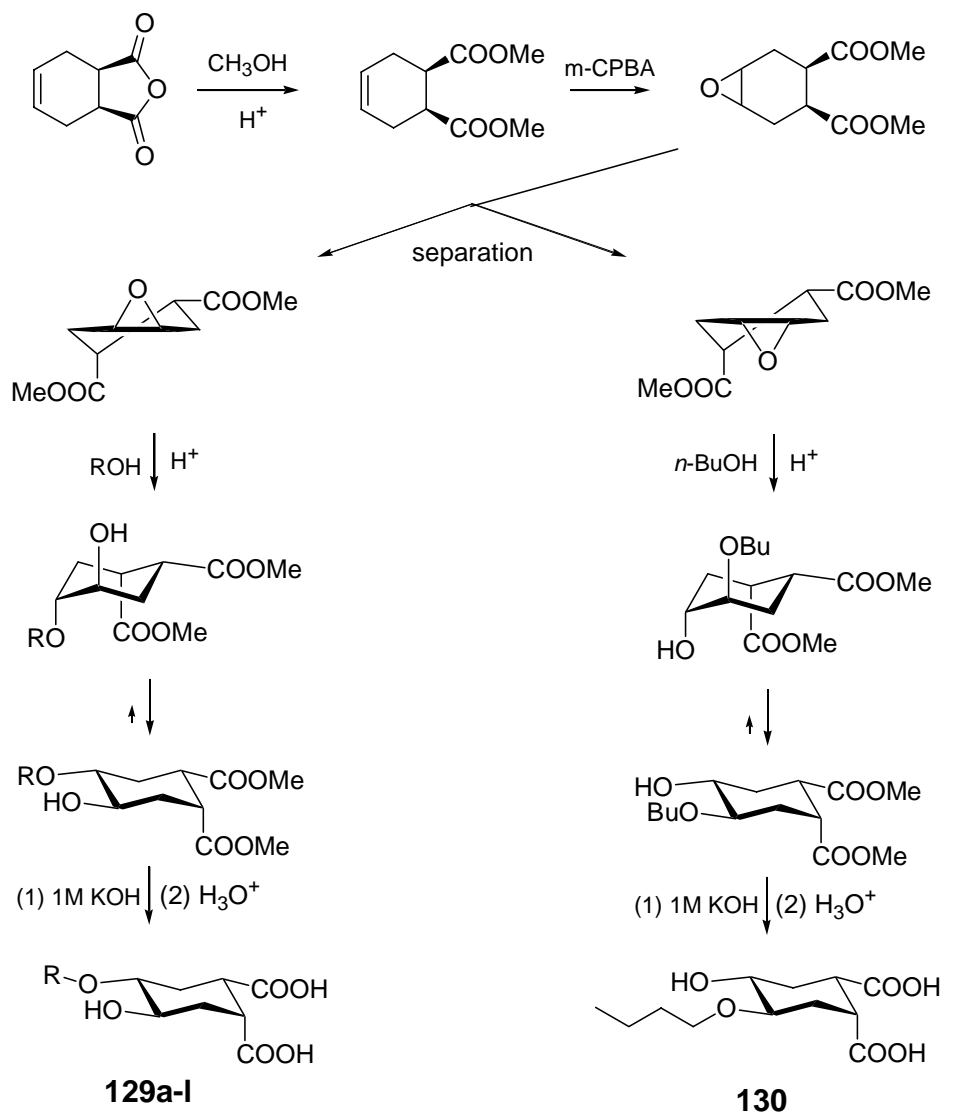
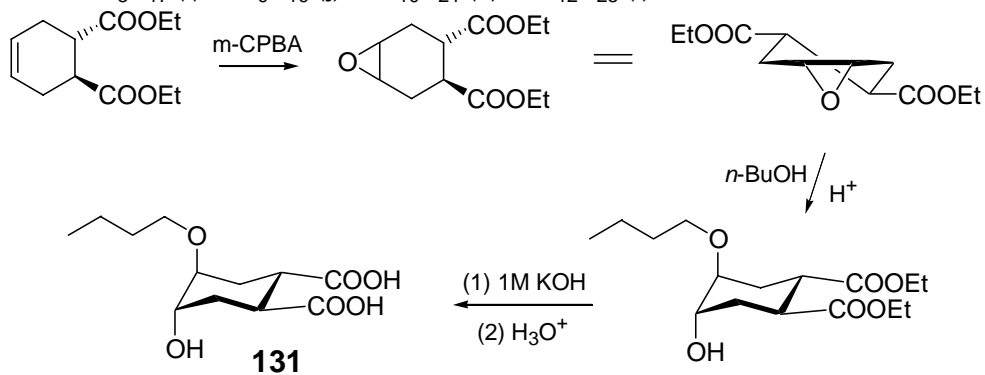


Figure 7. Potential glycosidase inhibitors: cyclohexanecarboxylic acids and their esters.^{111,155-158}



R = H (**a**), CH₃ (**b**), Et (**c**), *n*-Pr (**d**), *n*-Bu (**e**), *n*-C₅H₁₁ (**f**), *n*-C₆H₁₃ (**g**), *n*-C₇H₁₅ (**h**),
n-C₈H₁₇ (**i**), *n*-C₉H₁₉ (**j**), *n*-C₁₀H₂₁ (**k**), *n*-C₁₂H₂₅ (**l**)



Scheme 19. Preparation of 4-HO-5-RO-1,2-cyclohexanedicarboxylic acids **129-131**.^{111,155-158}

The proposed structures contained a six-membered cycle and several hydrophilic groups, which is typical for many carbohydrate mimetics (see above). Alkyl groups were introduced to enhance the inhibition. Such effect of lipophilic groups was observed previously¹⁸⁻²³ for derivatives of 1-deoxynojirimycin and other iminosugars, alkyl glycosides, and some other glycosidase inhibitors. The preliminary tests against fungal glycosidases revealed only a weak to moderate inhibition of β -D-glucosidase by compounds **125** (R = H) and **127+128** (R = CH₃, *n*-C₆H₁₃), and a weak inhibition of α -L-fucosidase by compounds **125+126**, and **127+128** (R = CH₃, *n*-C₆H₁₃).^{111,155,156} However, very promising results were obtained for cyclohexanedicarboxylic acids of types **129-131**.^{111,155-158} The synthesis of compounds **129-131** is presented in Scheme 19. It employed very simple starting compounds and reagents, and rather standard synthetic procedures.

These diacids were assayed for inhibitory activity against several glycosidases in multi-enzyme complexes isolated from fungi *Penicillium canescens* and *Aspergillus oryzae*.^{111,155-158} The inhibition was found to be specific with regard to the configuration of inhibitor, the type of enzyme, and even the particular source of enzyme. Most noticeably, these compounds inhibited α - and β -D-glucosidases. The isomers **130** and **131** appeared to be more selective inhibitors. It is worth mentioning that the compound **129e** produced the same inhibition effect upon β -D-glucosidase from *A. oryzae*, as a ~10-fold higher concentration of methyldeoxynojirimycin.

The results of our studies proved that simple and readily available racemic derivatives of 1,2-cyclohexanedicarboxylic acid can be potent inhibitors for α - and β -D-glucosidases. The presence of at least two carboxylic groups and one hydroxy group was found to be essential for efficient inhibition. Its magnitude depended on configuration of substituents and increased for β -glucosidase with lengthening of the inhibitor's alkoxy group. Further studies towards the enhancement of inhibitory activity may be focused on separation of enantiomers, on variation of the substituent configuration, of the length and structure of the lipophilic groups, and of the nature of heteroatoms. These compounds may be considered as promising precursors for combination with natural fragments (e. g. shikimic acid; see Sections 2, 7) for the synthesis of diastereomeric SCOMs.

Acknowledgements

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