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SYNTHETIC UTILIZATION OF 1,3-DIOXONIUM CATION REARRANGEMENTS: BROMINATION, AMIDATION AND SYNTHESIS OF THERAPEUTICALLY IMPORTANT IMINOALDITOLS

By

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ABSTRACT

SYNTHETIC UTILIZATION OF 1,3-DIOXONIUM CATION REARRANGEMENTS: BROMINATION, AMIDATION AND SYNTHESIS OF THERAPEUTICALLY IMPORTANT IMINOALDITOLS

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In the attempt at N-bromosuccinimide (NBS) bromination of benzylidene acetal protected gluconoheptonolactone derivative, a dioxonium cation rearrangement involving neighboring pivaloyl group was discovered. The rearrangement mechanism was further explored. Based on the experimental results, a new methodology of carbohydrate structure chirality manipulation was developed. A series of synthetically useful selectively brominated and protected D- and L-aldonolactone derivatives were synthesized. This methodology was further applied in the synthesis of an orthogonally protected bromobutanetriol as a chiral building block.

To introduce new functionalities in to the sugar structure, different inter- and intramolecular nucleophiles were employed in the NBS-mediated dioxolonium ion rearrangement. Intermolecular nucleophiles generally failed to compete with in-situ generated bromide ion, although in certain cases, the introduction of competitive nucleophiles was shown. Cyano groups do not participate in the Hanessian-Hullar reaction as intramolecular nucleophile to give expected lactam. The results were ascribed to the better nucleophilicity of the bromide ion generated in-situ than that of the competitive nucleophiles introduced inter- or intramolecularly.

Facilitated by dioxonium cation formation and rearrangement under strong acidic conditions, selective bromination of aldonolactones was carried out to generate useful bromosugars. The anomeric bromination of hexose pentapivaloates was achieved to generate tetrapivaloyl glycosyl bromides as useful glycosyl donors. When acetonitrile was employed as solvent and nucleophile, Ritter-type reactions occurred to afford several glycosyl amides. Furthermore, a unique dioxonium cation assisted Ritter-type reaction was discovered when glycerol dipivaloates were treated with strong acid in acetonitrile. The stereoselectivity and regioselectivity of this new Ritter-type reaction were tested with erythritol tripivaloate and 1,2,4-butanetriol dipivaloate as the substrates. This reaction was employed to introduce amide groups to the primary position of aldonolactone to generate N-contained sugar derivative.

A strategy for the preparation of carbohydrate derivatives bearing two leaving groups for use in the preparation of azasugars by di-N-alkylation of amines was developed. The target molecules were 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ). The selective acetal protections of dibromoaldonolactones and dibromoalditols were explored. DNJ was synthesized from partially protected dibromoalditol by di-N-alkylation with ammonium hydroxide. DMJ was synthesized from D-mannose using the same strategy.

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Chapter 1

Literature Review: Synthesis and Structure-Activity Relationship of Azasugars as Glycosidase Inhibitors

1.1 Introduction

Glycochemistry has been growing rapidly as a research area in recent years with great potential for future achievements. Together with glycobiology, it has great importance in biology, biochemistry, physiology, and pathology and medical science. Glycosyl transferases and glycosidases mediate the formation and breakdown of linkages of glycosyl residues to each other and to other. Because of this, the synthesis of inhibitors of these enzymes has been an important research area. Azasugars or, more correctly, iminoalditols are a general class of glycosyl transferase and glycosidase inhibitors. They are pyranose or furanose derivatives in which the ring oxygen atom has been replaced by nitrogen. Great effort has been expended in developing new methods for the synthesis of existing and new inhibitors of this class.

1.2 Glycosidases and glycosyl transferases and their inhibitors in carbohydrate metabolism

Glycoproteins carry N- and O-glycosidically-linked carbohydrate chains with complex structure and function on various points along the polypeptide chain [1]. The biosynthesis of N- and O-glycan is controlled at the level of gene expression, mRNA, enzyme protein activity and localization, and through substrate and cofactor

concentrations at the site of synthesis. Figure 1.1 illustrates the biosynthesis of N-linked oligosaccharides in mammalian cells. This process begins from the synthesis of the tetradecamer-oligosaccharide ($Glc_3Man_9(GlcNAc)_2$) precursor on the endoplasmic reticulum (ER) membrane [2]. The completed oligosaccharide precursor is then transferred to a protein and several monosaccharide units are removed in the ER, after which, the newly made glycoprotein is transported to the Golgi where the final modifications are made. There are many diseases in which cells show different proportions of the right glycoprotein structures from normal cells, i.e. glycosylation changes. These range from diabetes to cancers [3].

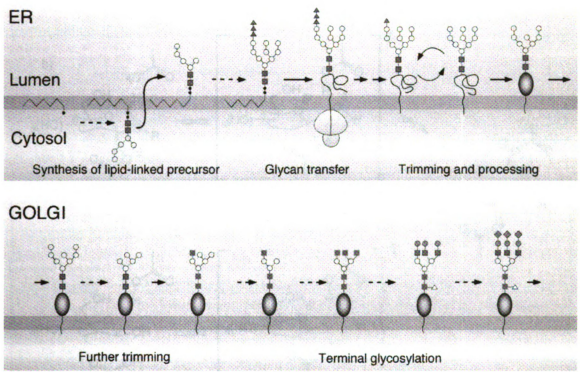


Figure 1.1 Biosynthesis of the N-linked core oligosaccharide. (Figure adapted from Helenius, A. and Aebi, M., *Science*, **2001**, 291, 2364-69)

During the glycan processing, glycosidases and glycosyl transferases are widely involved in the glycosidic bonds cleavage and formation. Glycosidase Mechanisms have

been extensively studied because of their extremely important roles in the glycoprotein biosynthesis. Several reviews have been published on this topic [4-10]. As an example, the general mechanisms for inverting and retaining β-glycosidases are shown in Figure 1.2 [7].

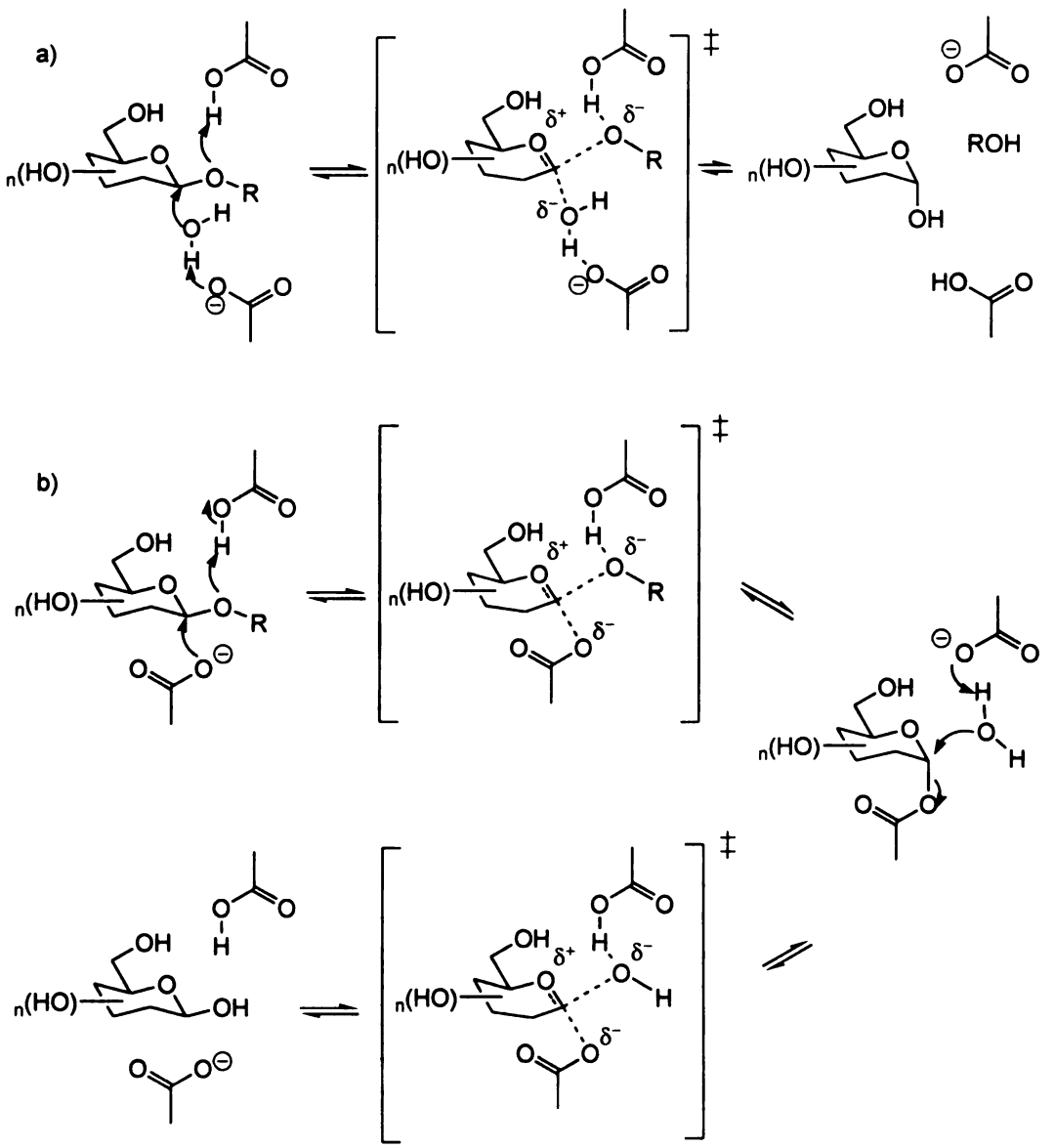


Figure 1.2 General mechanisms for inverting (a) and retaining (b) glycosidases. (Figure adapted from Zechel, D. L. and Withers, S. G., *Acc. Chem. Res.*, **2000**, 33, 11)

Carboxyl groups catalyze the glycosidic bond cleavage as general acid and base catalysts. For the inverting glycosidases, two carboxyl groups are suitably placed with an average distance of 10.5 Å. This placement allows the substrate and a water molecule to bind between them. A single displacement by the water molecule affords the inverted product. In the case of retaining enzymes, the average distance between two carboxyl groups is 5.5 Å, which prevents the simultaneous placement of the substrate and a water molecule. A double-displacement mechanism is involved to cleave the glycosidic bond with retention of the anomeric configuration. A covalent glycosyl-enzyme intermediate is formed in the retaining mechanism. The mechanisms of both inverting and retaining glycosidase involve either reactive oxocarbenium-ion intermediates or transition states with considerable oxocarbenium character, which have been targeted by the design and synthesis of various glycosidase inhibitors.

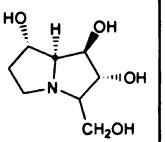
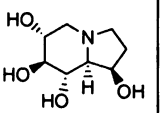
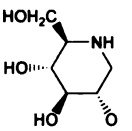
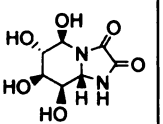
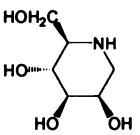
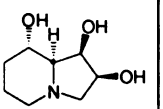
Table 1.1 Several classes of inhibitors and their targets (Table adapted from Varki, Ajit; Cummings, Richard; Esko, Jeffrey; Freeze, Hudson; Hart, Gerald; Marth, Jamey; Editors. *Essentials of Glycobiology*. **1999**, 653 pp)

Class of inhibitor	***Target***
Metabolic inhibitor	Steps involved in formation of common intermediates such as PAPS or nucleotide sugars
Tunicamycin	N-linked glycosylation through inhibition of Dol-PP-GlcNAc formation; peptidoglycan biosynthesis through inhibition of undecaprenyl-PP-GlcNAc assembly
Plant alkaloids	N-linked glycosylation through inhibition of processing glycosidases
Substrate analogs	Specific glycosyltransferases or glycosidase
Glycoside primers	Glycosylation pathways by diverting the assembly of glycans from endogenous acceptors to exogenous primers

Several classes of glycosylation inhibitors are exploited and these target different steps of the biosynthesis of glycoproteins (Table 1.1) [1]. From the academic point of view, inhibitors provide an alternative approach for studying glycosylation. Mutants have been widely used in traditional glycobiology, the isolation of similar mutants from different organisms and cells is relatively cumbersome. Mostly small molecules, many glycosylation inhibitors could be relatively easily introduced into many cell types to induce glycosylation changes. By measurement and analysis of these changes, important information related with glycosylation processes could be obtained. From a practical point of view, glycosidase inhibitors are very promising targets of drug development. Different inhibitors may block different glycosylation pathways by different mechanisms. The substrate analogs could bind specific glycosyltransferases more preferentially and tightly than the real substrate to block these enzymes. Metabolic inhibitors, on the other hand, act on carbohydrate metabolism. For example, 3'phosphoadenyl-5'phosphosulfate (PAPS) is a common intermediate in the metabolism. Chlorate blocks the formation PAPS by inhibiting its sulfation step. This inhibition has no specificity of any particular class of glycosylation or sulfation reaction. Tunicamycin inhibits N-glycosylation in eukaryotes by another different mechanism. Because of its resemblance of the donor nucleotide sugar, tunicamycin acts as a tight-binding competitive inhibitor and blocks the transfer of GlcNAc-1-P from UDP-GlcNAc to dolichyl-P, thereby decreasing dolichyl-PP-GlcNAc. Glycoside primers subvert the cellular machinery for making oligosaccharides on endogenous proteins thereby inhibiting glycoprotein and proteoglycan assembly.

Plant alkaloids block glycosylation by inhibiting the glycosidases involved in N-glycan formation. (Table 1.2) [1].

Table 1.2 Several plant alkaloids as glycosylation inhibitors (From Varki, Ajit; Cummings, Richard; Esko, Jeffrey; Freeze, Hudson; Hart, Gerald; Marth, Jamey; Editors. *Essentials of Glycobiology*. **1999**, 653 pp)

Alkaloid	Source	Target	Alkaloid	Source	Target
Austra-line		α-glucosidase I	Castano-spermine		α-gluco-sidase I, II
Deoxyno-jirimycin		α-glucosidase II (and I)	Kifunensin		α-manno-sidase I
Deoxy-manno-jirimycin		α-mannosidase I	Swain-sonine		α-manno-sidase II

They have different inhibition mechanism from the other classes of inhibitors. Instead of blocking glycosylation of glycoproteins entirely like tunicamycin, they inhibit the trimming reactions that occur after the $Glc_3Man_9GlcNAc_2$ oligosaccharide is attached to a glycoprotein. One class of alkaloids inhibits the α-glucosidases involved in the initial processing of the N-glycans and in quality control of protein folding. These include castanospermine, australine and deoxynojirimycin, which cause accumulation of fully glucosylated chains or chains containing one to two glucose residues. Another class of alkaloids inhibits the α-mannosidases. These include swainsonine, manostatin A, kifunensin and deoxymannojirimycin. These inhibitors cause accumulation of $Man_{7-9}GlcNAc_2$ oligosaccharide chains without glucose residues on glycoproteins.

From the chemistry point of view, all of these plant alkaloid inhibitors have a common polyhydroxylated N-hetero ring system that mimics the natural carbohydrate substrates. These azasugar structures are generally believed to act as a transition state analog (Figure 1.3). After protonation, the stable and charged ring nitrogen may mimic the positive charge on the ring oxygen that arises from delocalization of charge from the oxocarbenium cation generated during the hydrolysis reaction.

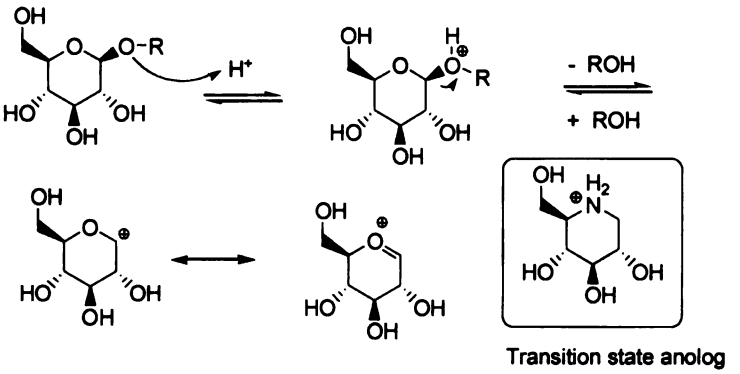


Figure 1.3 The structure and charge resemblence of azasugar and the oxocarbenium transition state

1.3 Synthetic methodologies towards azasugars

Shown in Figure 1.4 are several azasugars for which various synthetic methodologies have been developed.

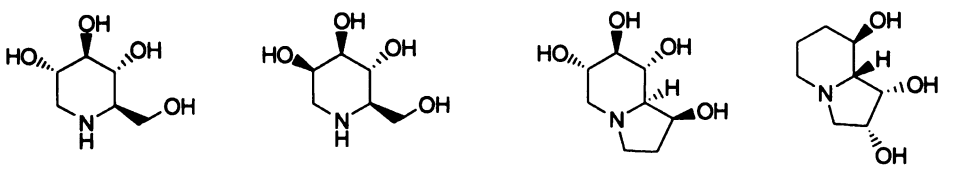
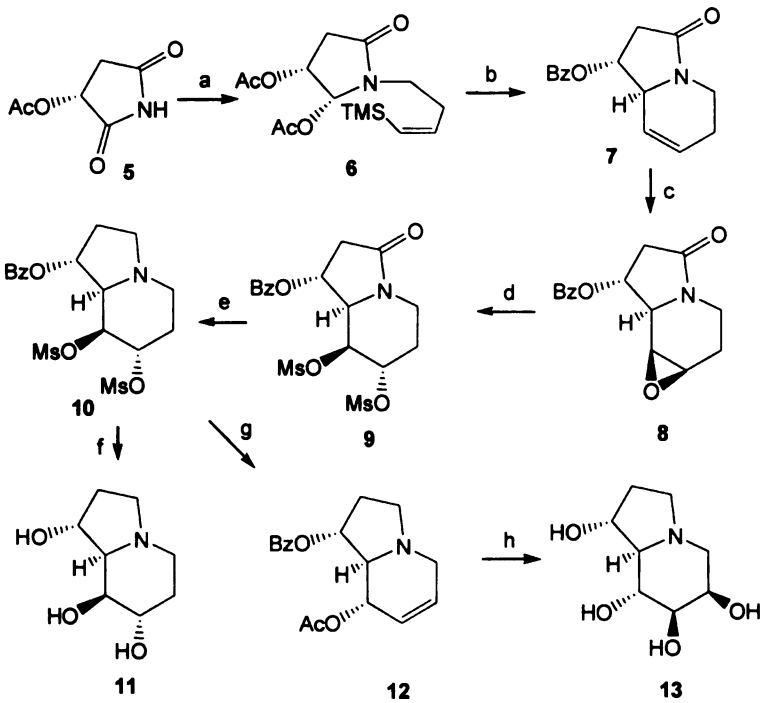


Figure 1.4 Several important azasugars as synthetic target of glycosidase inhibitors

There are three structural elements that characterize azasugars. These are the presence of several hydroxyl groups with defined chirality, single or fused- ring systems and the ring nitrogen functionality. The synthetic strategies that have been developed revolve around these structural features. Several asymmetrical synthetic methodologies such as epoxidation, dihydroxylation have been employed for the incorporation of the hydroxylated chiral centers. Reductive amination, intramolecular nucleophilic substitution and alkene metathesis have been widely used for the construction of the ring system. For introducing the nitrogen atom into the ring, many synthetic methodologies have been adopted. These include imine formation, azide substitution, nucleophilic substitution etc. These methodologies have been widely employed and sometimes combined in many elegant syntheses towards azasugars. We herein review the azasugar synthesis with an emphasis on these three structural elements.

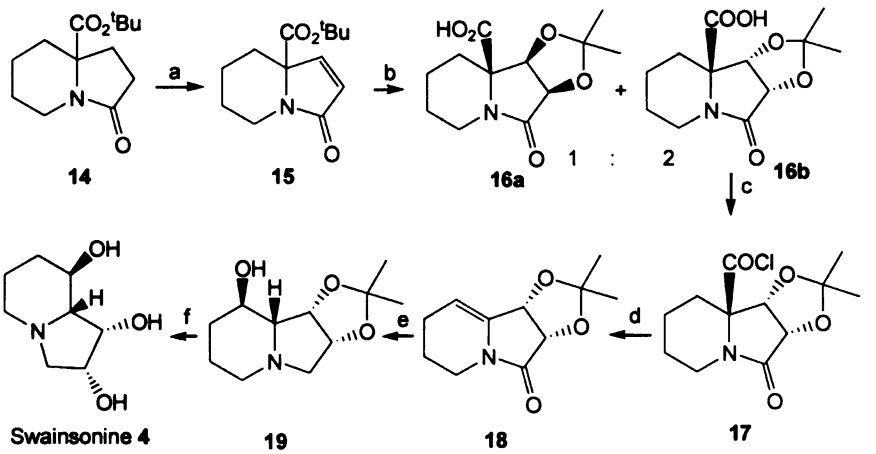
1.3.1 Synthesis towards azasugars from achiral or chirality-deficient molecules

In 1995, Leeper et. al. [11] developed a synthesis of several polyhydroxy indolizidines as epimers of castanospermine starting from malic acid derivatives (Scheme 1.1). Starting from acetoxysuccinimide **5**, the bicyclic ring system was generated by Mitsunobu reaction, reduction and following cyclization. The key cyclization of compound **6** was via an acyliminium ion intermediate. The following steps included epoxidation, ring opening, elimination and dihydroxylation. These were employed to incorporate the other hydroxylated chiral centers. By slightly changing the modification process, three epimers of castanosperine were synthesized, represented by the 1,6-diepicastanospermine **13**. All the new chiralities were generated based on substrate control, mostly by epoxidation and dihydroxylation.



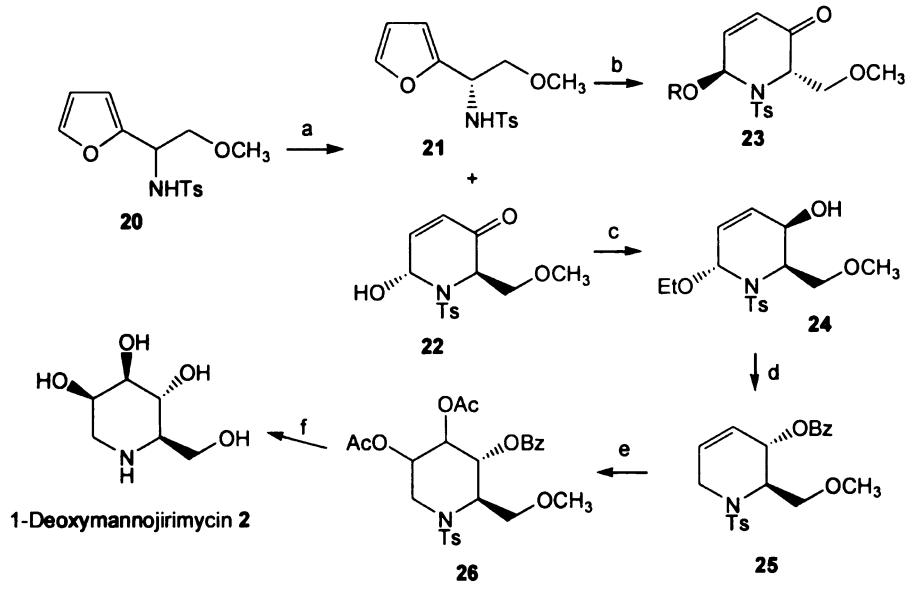
Scheme 1.1 A synthesis to castanospermine epimer from malic acid derivative: a) $Me_3SiCH{=}CH(CH_2)_2OH$, DEAD, Ph_3P, 87%; $NaBH_4$, 94%; Ac_2O, pyr. DMAP, 85%; b) BF_3OEt_2, 72%; Et_3N, MeOH, H_2O then BzCl, Et_3N, DMAP, 84%; c) mCPBA, 76%; d) H^+, THF, H_2O then MsCl, Py., 41%; e) BH_3Me_2S; f) aq. NH_3, 37% (2 steps); g) Bu_4NOAc, 25%; h) OsO_4, NMO then f, 53%

In 1996, Bermejo. et. al. [12] developed a synthetic pathway towards (±)-swainsonine **4**, taking advantage of the degradation of α-amino carboxylic acid of an existing bicyclic lactam **14** (Scheme 1.2). With the bicylic structure skeleton ready, most of the synthetic steps were focused on the incorporation of the hydroxyl groups. This included oxidative elimination, stereoselective dihydroxylation, decarboxylation, reduction and hydroboration. However, because the starting material was achiral and there were no asymmetric factors involved, the swainsonine **4** was synthesized as a racemic mixture.



Scheme 1.2 A synthesis to swainsonine **4** from an existing bicyclic lactam: a) i: LDA, THF, -78°C; ii: PhSeCl; iii: H_2O_2, AcOH; 70%; b) OsO_4, NMO, acetone, H_2O, ^tBuOH; 70%; then $CH_3C(OMe)_2CH_3$, PPTS, CH_2Cl_2, 100%; then CF_3COOH, CH_2Cl_2, 0°C, 98%; c) $(COCl)_2$, 98%; d) 1,2-DCE, xylene, reflux, 15h, 75%; e) B_2H_6, THF, then H_2O_2, NaOH; f) i: 6N HCl; ii: Dowex-1X8

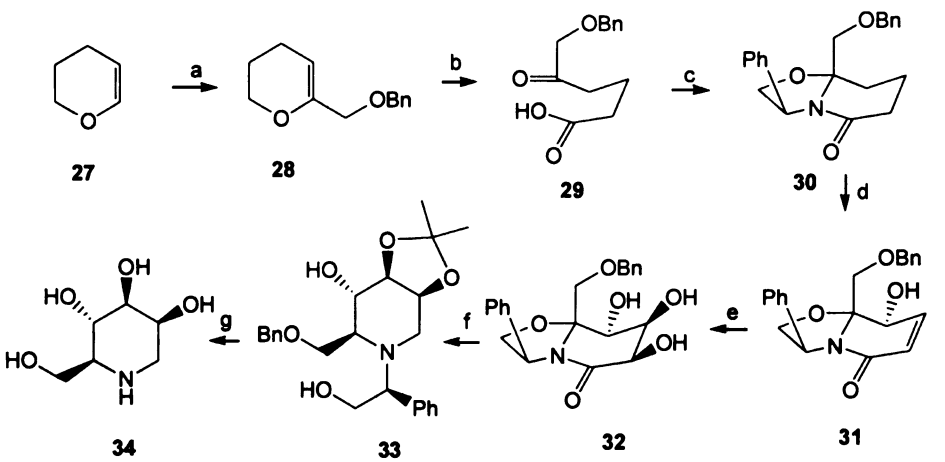
At the same time, Zhou et. al. [13] developed an asymmetric synthesis of 1-deoxymannojirimycin **2** from an achiral α-furfurylamine derivative **20**, which could be prepared in 40% overall yield in three steps (Scheme 1.3). A kinetic resolution was achieved by oxidative rearrangement of the α-furfurylamine derivative **20** to yield compound **21** with a piperidine structure. Further functional group manipulation such as dihydoxylation was carried out on this structure to yield the final product. Many protection and deprotection steps were also involved in this synthesis. Using the same strategy with another α-furfurylamine derivative [14], (-)-swainsonine **4** was synthesized.



Scheme 1.3 A synthesis to deoxymannojirimycin **2** from an achiral α-furfurylamine derivative: a) $Ti(OiPr)_4$, L-(+)-DIPT, TBHP, silica gel, CaH_2, CH_2Cl_2, 25°C, 3 days; b) mCPBA; c)$HC(OEt)_3$, BF_3OEt_2, THF, 0°C; 76.5% then $NaBH_4$, $CeCl_3.7H_2O$, -30°C; 72.3%; d)DEAD-TPP, PhCOOH, THF, r.t.; 92% then $NaBH_4$, HCOOH, 0°C; 87%; e) $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH, r.t., 2days; 85% then Ac_2O, Pyridine, DMAP, rt; 100%; f) BBr_3, CH_2Cl_2, -78°C; 72% then Na/Naphthalene, DME, -60°C; 51%

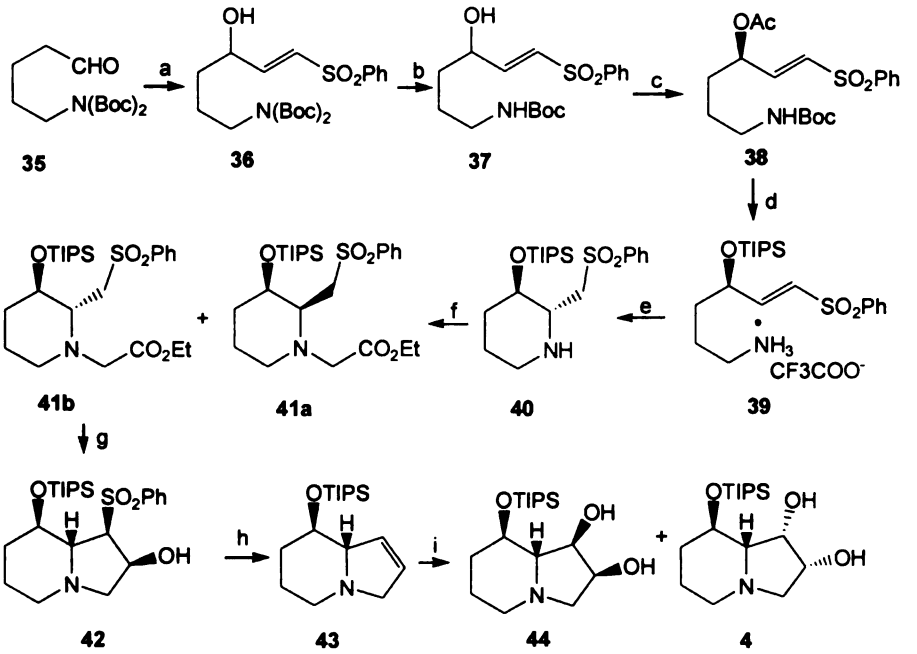
Meyers et. al. [15] developed an asymmetric synthesis of L-deoxymannojirimycin **34** employing dihydropyran and S-phenylglycinol as their starting materials (Scheme 1.4). Their synthesis featured the preparation of a bicyclic lactam by cyclodehydration of a ketoacid and S-phenylglycinol developed in their lab [16]. Metallation of dihydropyran and reaction with paraformaldehyde gave a primary alcohol, which was protected and oxidized to a ketoacid **29**. The cyclodehydration of the ketoacid **29** and S-phenylglycinol gave a bicyclic lactam **30**. The synthesis was continued by introduction of a double bond, allylic oxidation, dihydroxylation and deprotection steps to yield L-deoxynojirimycin **34**. The S-phenylglycinol not only supplied the nitrogen atom, but also acted as a chiral

auxiliary. All the chiralities of the target molecule were introduced based on substrate control.



Scheme 1.4 A synthesis of L-deoxymannojirimycin **34** from dihydropyran and S-phenylglycinol: a) t-BuLi, $(CH_2O)_n$, THF, -78°C, 70% then NaH, BnBr, DMF, 92%; b) CrO_3/H_2SO_4, THF, 70%; c) S-phenylglycinol, PhMe, heat, 80%; d) KH, $PhSO_2Me$, THF, then PhMe, heat, 85%, then SeO_2, dioxane, heat, 64%; e) OsO_4/NMO, acetone/water, 83%; f) $(CH_3)_2C(OMe)_2$, CH_2Cl_2, pTSA, 75%; then BH_3.THF, THF, heat, 65%; g) $H_2/Pd(OH)_2$, EtOH then TFA, MeOH, 75%

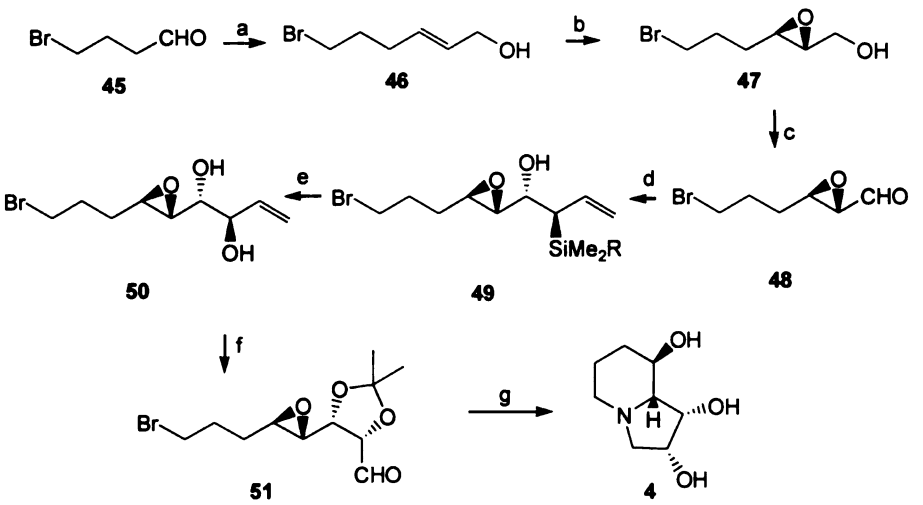
Carretero et. al. [17] also accomplished a stereoselective synthesis of swainsonine from di-Boc protected 5-aminopentanal **35** (Scheme 1.5). This synthesis employed an enzyme-facilitated kinetic resolution based on the enantioselective acylation of lipase. Bulkier protecting group introduction improved the cyclization stereoselectivity of the intramolecular amination of **39**. After alkylation, the intramolecular acylation of **41b** through the α-sulfonylcarbanion afforded a single α-sulfonylketone which was directly reduced to give the α-sulfonyl alcohol **42**. Further steps included desulfonylation, dihydroxylation and deprotection to give swainsonine **4**.



Scheme 1.5 A synthesis to swainsonine **4** from di-Boc protected 5-aminopentanal: a) $PhSO_2CH_2SOTol$, piperidine, CH_2Cl_2, 0°C; b) TFA, CH_2Cl_2, rt; c) Lipase PS, vinyl acetate, toluene, rt; d) Lipase PS, 0.1M Na_2HPO_4, rt; then TIPSCl, imidazole, CH_3CN, rt; then TFA, CH_2Cl_2, rt; e) MeOH, Et_3N, -78°C; f) $BrCH_2CO_2Et$, LiI cat, K_2CO_3, CH_3CN, 80°C; g) LHMDS, THF, 0°C; then $NaBH_4$, MeOH, 0°C; h) Na-Hg, Na_2HPO_4, MeOH, rt; i) OsO_4 cat, Me_3NO, acetone, H_2O,rt;

In 1997, Roush et. al. [18] reported an enantioselective synthesis of (-)-swainsonine **4** as an application of an improved chiral reagent for the anti α-hydroxyallylation of aldehydes (Scheme 1.6). Their synthesis began with 4-bromobutanal **45**, which is available from tetrahydrofuran. The Horner-Wadsworth-Emmons reaction of this bromobutanal **45** followed by DIBAL reduction afforded an allylic alcohol **46**. Sharpless asymmetric epoxidation and oxidation with SO_3-pyridine gave the epoxy aldehyde **48**. The chain was extended by a 3-carbon unit by α-hydroxyallylation with (S,S)-diisopropyl tartrate-modified (E)-[γ-[2-menthofuryl]dimethylsilyl]-borate. The

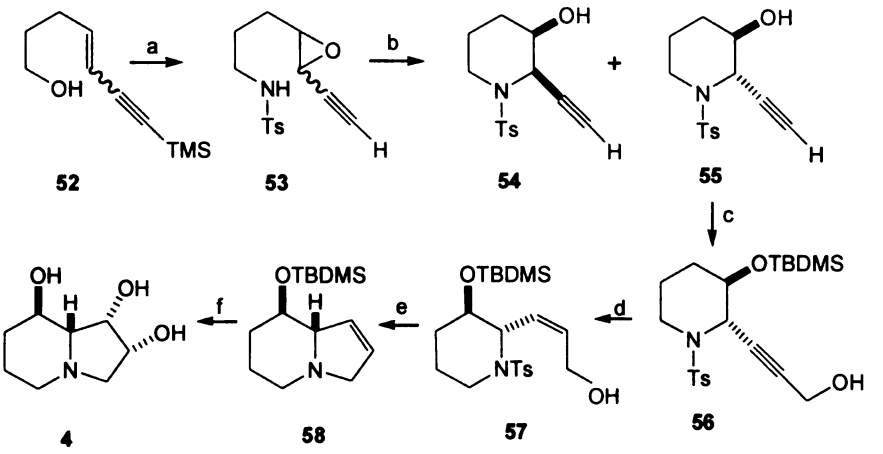
silanol was then subjected to a one-pot protodesilylation-oxidation to give a diol **50**, which was protected as an acetonide. Ozonolysis of the terminal alkene provided an aldehyde **51**. The subsequent reductive amination of this aldehyde was accompanied by spontaneous ring closure to form the indolizidine nucleus in the form of swainsonine acetonide. This was deprotected to provide swainsonine **4**.



Scheme 1.6 A synthesis to swainsonine from 4-bromobutanal: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, -30 to 23°C then DIBAL, Et_2O, -78 to 23°C, 82%; b) $Ti(OiPr)_4$, D-(-)-DIPT, TBHP, 4ÅM.S., -20°C, 72%; c) SO_3-pyridine, DMSO, Et_3N, CH_2Cl_2, 78%; d) (S,S)-Diisopropyl Tartrate-Modified (E)-[γ-[2-menthofuryl]dimethylsilyl]-borate, toluene, 4ÅM.S, -78°C, 73%; e) CF_3COOH, THF, 0-23°C then $KHCO_3$, KF, H_2O_2, THF-MeOH, 23°C, 85%; f) $Me_2C(OMe)_2$, pPTS, CH_2Cl_2 then O_3, CH_2Cl_2, -78°C; Ph_3P, 84%; g) NH_4OAc, 3ÅM.S., MeOH; then $NaCNBH_3$, 71%, then 6N HCl-THF, 92%

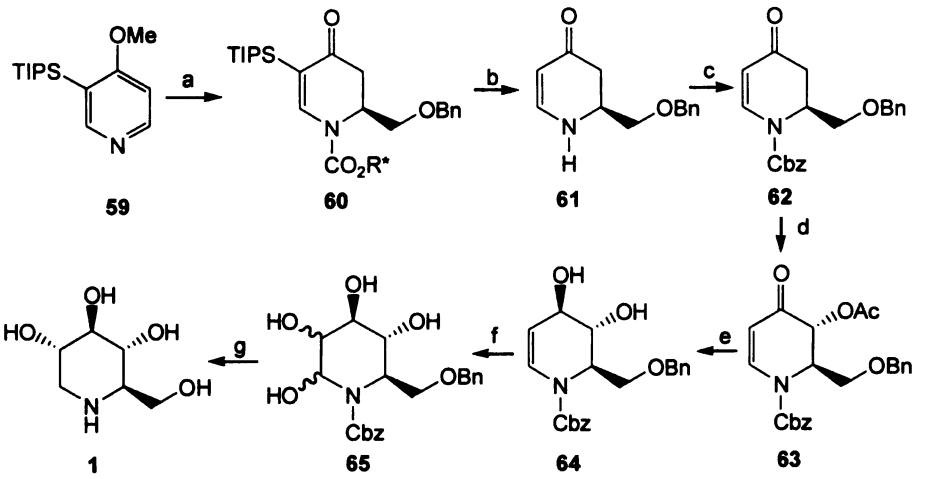
Mukai et. al. [19] developed a total synthesis of (±)-swainsonine based on an endo-mode cyclization. A suitable enyne alcohol **52** was employed as the starting material (Scheme 1.7). The nitrogen functionality was introduced by Mitsunobu reaction using hydrazoic acid followed by reduction and tosylation. Epoxidation and ring closure furnished the piperidine ring system **54**. The subsequent steps included nucleophilic

addition, reduction, cyclization and dihydroxylation. After hydrolysis, this synthesis afforded (±)-swainsonine.



Scheme 1.7 A synthesis to swainsonine from a suitable enyne alcohol : a) HN_3, DEAD, PPh_3, 99%; then PPh_3, H_2O, 99%; then TsCl, Et_3N, 81%; then TBAF, 96%; then mCPBA, 58%; b) $Co_2(CO)_8$; then BF_3OEt_2; then CAN, 85%; c) TBDMSCl, imidazole, 99%; then n-BuLi, $(HCHO)_n$, 97%; d) H_2, Lindlar cat., 99%; e) Na, naphthalene, then CBr_4, PPh_3, Et_3N, 57%; f) OsO_4, NMO, then TBAF, then Ac_2O, pyridine, DMAP, 76%; then K_2CO_3, MeOH, 99%

In 2001, Comins et. al. [20] reported an asymmetric synthesis of 1-deoxynojirimycin **1** featuring enantiopure 2,3-dihydro-4-pyridones **60** as synthetic intermediates (Scheme 1.8). 4-methoxy-3-(triisopropylsilyl)pyridine **59** was employed as the starting material. The addition of (benzyloxy)methylcuprate to the 1-acylpyridinium salt bearing a chiral auxiliary generated the desired dihydropyridone **60**. The chiral auxiliary and the 5-TIPS group were removed in a one-pot reaction to give **61**. After protection of the nitrogen, the compound went through several oxidation and reduction processes to afford the 1-deoxynojirimycin **1**.

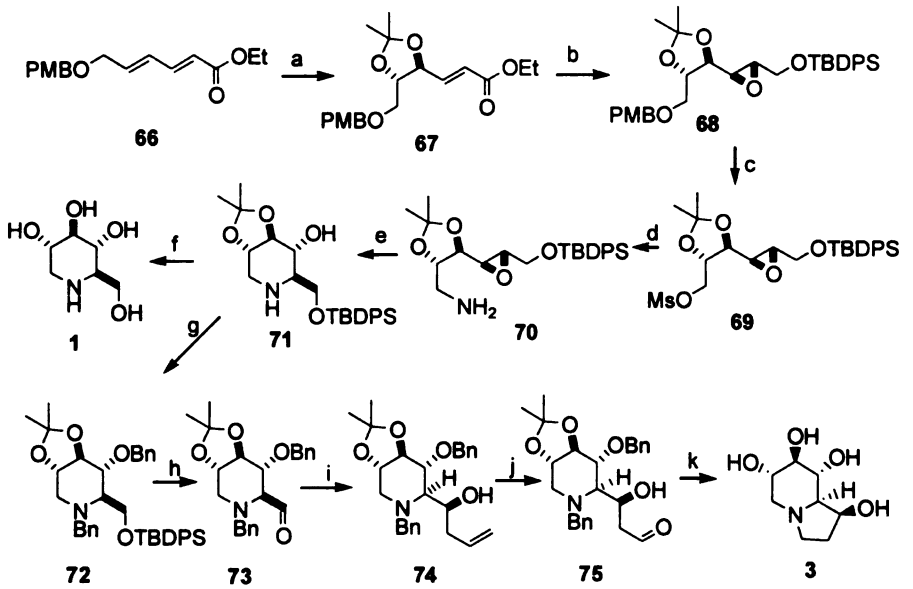


59 60 61 62 63 64 65 1

Scheme 1.8 A synthesis to deoxynojirimycin **1** from 4-methoxy-3-(triisopropylsilyl)pyridine: a) R*OCOCl, (R* = (1R,2S)-2-(1-methyl-1-phenylethyl)cyclohexanol), then $BnOCH_2$(2-Th)$Cu(CN)Li_2$, then H_3O^+, 64%; b) NaOMe, then H_3O^+, 74%; c) n-BuLi, then BnOCOCl, 99%; d) $Pb(OAc)_4$, toluene, reflux;78%; e) aq. HCl/EtOH, then $Me_4NBH(OAc)_3$, acetone/AcOH, 83%; f) OsO_4, NMO; g) $Pd(OH)_2/H_2$, 10% HCl

In 2003, Somfai et. al. [21] reported another asymmetric synthesis of both (+)-1-deoxynojirimycin **1** and (+)-castanospermine **3** starting from the same achiral acyclic diene **66** (Scheme 1.9). Asymmetric dihydroxylation and epoxidation of **66** generated all the chiralities of deoxynojirimycin. Suitable protecting and deprotecting strategies were used to give **68**. The epoxidation was carried out utilizing the stoichiometric protocol since the catalytic Sharpless epoxidation only gave poor yields. The nitrogen functionality was introduced by azide substitution of a mesylate group at **69**. The subsequent reduction and intramolecular epoxide ring opening followed by deprotection gave the (+)-1-deoxynojirimycin **1**. The synthesis of castanospermine took advantage of the protected deoxynojirimycin **71** obtained during the synthesis. After selective protection and deprotection, the primary –OH was transformed to an aldehyde by Swern oxidation to give **73**. The carbon chain was extended by the addition of an allyl group to the aldehyde

using allyltrimethylsilane and a Lewis acid (Sakurai reaction) with careful control of the reaction condition. Following dihydroxylation and $NaIO_4$, oxidative cleavage of the diol gave another aldehyde **75**. Finally reductive amination furnished (+)-castanospermine **3**.



Scheme 1.9 An asymmetric synthesis of deoxynojirimycin and castanospermine starting from the same an achiral acyclic diene: a) AD-mix-α, $CH_3SO_2NH_2$, t-BuOH, H_2O, 80%; then 2-methoxypropene, p-TsOH(cat.), DMF, 97%; b) DIBAL, -78°C, CH_2Cl_2, 93%; then (+)-DIPT, $Ti(Oi\text{-}Pr)_4$, t-BuOOH, CH_2Cl_2, -20°C, 80%; then t-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 97%; c)DDQ, CH_2Cl_2, H_2O, 92%; then MsCl, i-Pr_2EtN, CH_2Cl_2, 100%; d) NaN_3, DMF, 70°C, 91%; then PH_3P, THF, H_2O, 83%; e)EtOH, heat, 100%; f) HCl(37%), MeOH, 100%; g) KHMDS (2.2equiv.), BnBr(3equiv.), THF, -78°C, 82%; then BnBr(1.3equiv.), K_2CO_3(2.6equiv.), CH_3CN, heat, 97%; h) n-Bu_4NF, THF, rt, 100%; then $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 93%; i) $CH_2CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, -65 to -60°C, 71%; j)OsO_4, NMO, t-BuOH-THF-H_2O(10:3:1); then $NaIO_4$, $NaHCO_3$, THF-H_2O(1:1), 84% (2 steps); k) H_2, Pd/C, then TFA, 81%

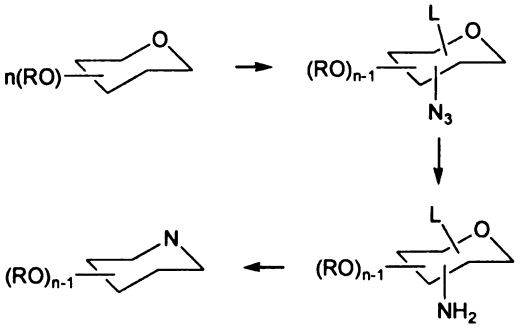
To summarize, the synthesis of azasugars from achiral or chirality-deficient molecules generally involves many functional group transformation steps. Dihydroxylation and epoxidation are frequently used to introduce the new chiral centers.

Both reagent control and substrate control have been widely used in this process. The nitrogen atom has been introduced either as a functional group in the starting material or in the later steps of synthesis. Azide substitution and imine formation are two common ways to introduce nitrogen functionality. The reductive intramolecular substitution and reductive elimination are frequently used to afford the heterocycle ring systems.

1.3.2 Synthesis of azasugars from sugars or other chirality-rich molecules

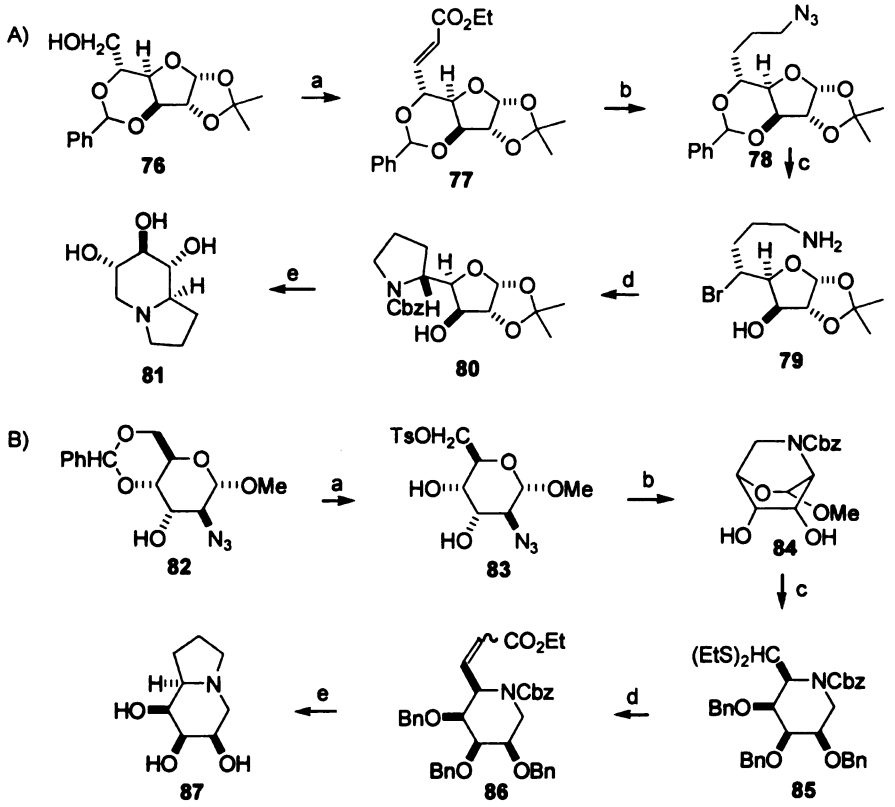
Although many elegant syntheses of azasugars from achiral or chirality-deficient molecules have been developed, the majority of the synthetic work on azasugars employs sugars or other potentially abundant chirality-rich molecules as starting materials. Because of the structural similarity of the azasugars to real sugars, carbohydrates should be ideal starting points for the synthesis of the former. The major structural difference of azasugars with real sugars is the ring nitrogen. So the introduction of a nitrogen atom into the sugar structure is the essential synthetic task. Many nitrogen incorporation methods have been developed and employed for this purpose. Here we review this work.

1.3.2.1 Synthesis of azasugars using azide as an intermediate



Scheme 1.10 The general synthetic pathway of azasugars using azide as an intermediate

Azide has long been used as an amine precursor in synthetic chemistry. The azide group can be relatively easily incorporated into a sugar structure by nucleophilic substitution. The subsequent reduction generates an amino group, which can undergo an intramolecular substitution to afford the N-heterocycle ring system (Scheme 1.10).

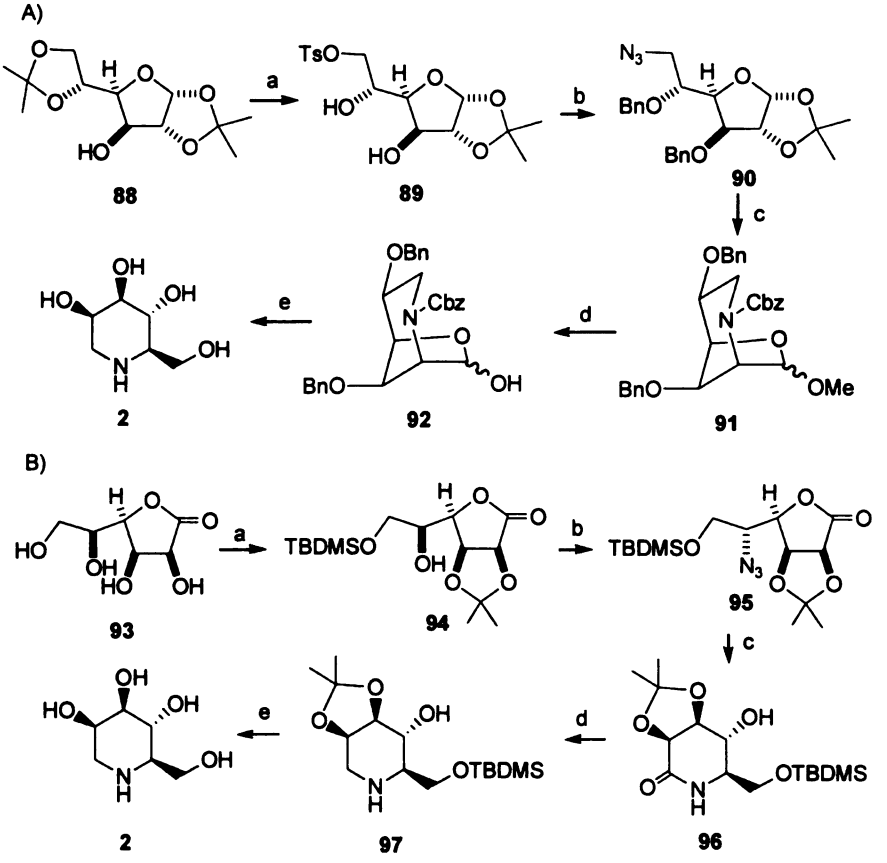


Scheme 1.11 A) Synthesis of 1-deoxy-castanospermine **81** from glucose derivative: a) PCC, powdered molecular sieves, CH_2Cl_2, then $Ph_3P{=}CHCO_2Et$; b) 10% Pd/C, EtOH, H_2; $LiAlH_4$, ether; MsCl, Et_3N, CH_2Cl_2, 0°C; NaN_3, DMF; c) NBS, $BaCO_3$, CCl_4; NaOMe, MeOH; then $SnCl_2$, MeOH, 60°C; d) NaOAc, EtOH; CbzCl, $NaHCO_3$, EtOH(50%)-H_2O; e) HOAc(20%)-H_2O; then 10% Pd/C, MeOH, H_2; B) Synthesis of epimer of 1-deoxy-castanospermine from 2-azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside: a) HOAc(20%)-H_2O; then TsCl, pyridine; b) 10% Pd/C, EtOH, H_2; NaOAc, EtOH reflux; CbzCl, $NaHCO_3$, EtOH(50%)-H_2O; c) EtSH, HCl, $CHCl_3$; then BnBr, NaH, DMF; d) $HgCl_2$, $CdCO_3$, Me_2CO(10%)-H_2O; then $Ph_3P{=}CHCO_2Et$, CH_3CN; e) 10%Pd/C, H_2, EtOH; NaOAc, EtOH, reflux, 10% Pd/C, H_2, AcOH, 48h; Ac_2O, pyridine; then BH_3SMe_2, THF; NaOMe, MeOH;

In 1987, Richardson et. al. [22,23] synthesized several polyhydroxylated indolizidines related to castanospermine (Scheme 1.11). For 1-deoxy-castanospermine **81**, 3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranose **76** was employed as the starting material. The carbon chain extension was carried out by pyridinium chlorochromate (PCC) oxidation of the free hydroxyl group followed by immediate reaction with carboethoxymethylene triphenylphosphorane. The double bond and ester group of **77** were reduced sequentially by catalytic hydrogenation and lithium aluminum hydride ($LiAlH_4$). The free primary hydroxyl group was then transformed to a leaving group, which was subsequently displaced by an azide group using sodium azide to give **78**. After regioselective oxidative cleavage of the benzylidene group by Hanessian-Hullar reaction, the azide group was reduced to an amine **79**. Intramolecular displacement of the bromo group by the amino function furnished a five-membered N-heterocyclic ring **80**. After deprotection of the isopropylidene group, catalytic reductive elimination and the final deprotection, 1-deoxy-castanospermine **81** was synthesized (Scheme 1.11 A). A different strategy was used to synthesize another epimer of 1-deoxy-castanospermine. This employed 2-azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside **82** as the starting material. After debenzylidination and selective tosylation of the primary hydroxyl group, the existing azide group was catalytically reduced to form an amine, which displaced the tosylate group by intramolecular nucleophile attack at the primary carbon. The bridged ring system **84** was obtained and this proved to be an important intermediate. The furanosyl ring was cleaved by thiolysis giving a monocyclic system in which the former anomeric carbon was protected as a dithioacetal group. After deprotection, the free aldehyde was reacted with carboethoxymethylene triphenylphosphorane to afford an

unsaturated chain extended product **86**. Subsequent reduction and deprotection steps yielded an epimer of 1-deoxy-castanospermine **87** (Scheme 1.11B).

In 1989, Fleet et. al. [24] reported two synthetic routes towards deoxymannojirimycin **2** using different starting materials. These are illustrated in Scheme 1.12 A and 1.12 B respectively.

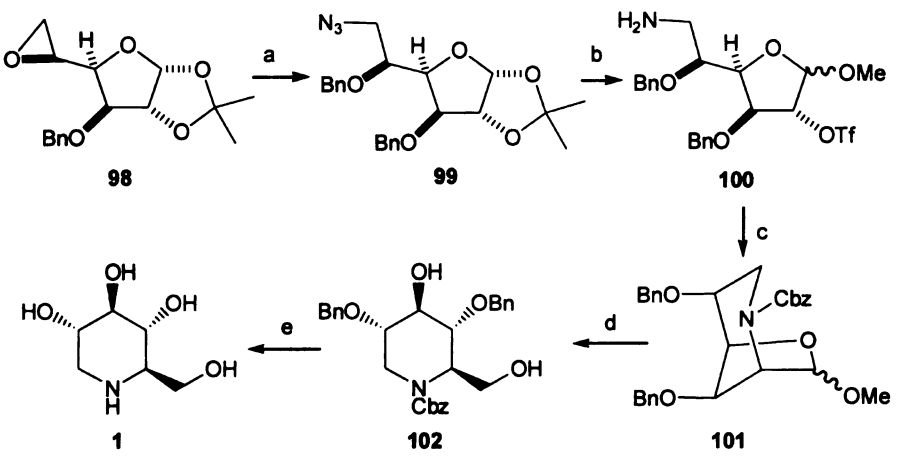


Scheme 1.12 Ttwo synthetic routes towards deoxymannojirimycin from glucose derivative and L-gulonolactone: A) a) $AcOH/H_2O$; p-TsCl, pyridine; b) NaN_3, DMF; NaH, BnBr, $(Bu)_4NI$; HCl, methanol; $(TfO)_2O$, CH_2Cl_2, pyridine; c) Ph_3P,then K_2CO_3, H_2O; CbzCl; d) CF_3COOH, H_2O; $NaBH_4$, methanol, H_2O; Pd/C, H_2; B) a) acetone/dimethoxypropane, p-TsOH; $AcOH/H_2O$; TBDMSCl; b) $(TfO)_2O$; NaN_3, DMF; c) Pd/C, H_2, methanol; d) BH_3SMe_2; e) CF_3COOH/H_2O

Starting from 1,2,5,6-di-O-isopropylidene-α-D-glucofuranose **88**, the 5,6-O-isopropylidene was selectively deprotected and the primary hydroxyl group was derivatized to a tosylate **89**. An azido group was used to introduce the nitrogen function at the 6-position. After deprotection of the other isopropylidene group, the 2-OH was transformed to a triflate leaving group. Reduction and intramolecular nucleophilic substitution afforded a [3,2,1] hetero- ring system **91**. The bridged ring was broken by acid hydrolysis and $NaBH_4$ reduction. The final catalytic hydrogenation removed all the protecting groups to give deoxymannojirimycin **2**. This compound was also synthesized from L-gulono-1,4-lactone **93**. 2,3,5,6-Di-O-isopropylidene-L-gulono-1,4-lactone was prepared and selectively hydrolyzed. t-Butyldimethylsilyl chloride was then used to selectively protect the primary hydroxyl group to give **94**. As in the the other synthetic route, the only free hydroxyl group was then derivatized to a triflate and subsequently substituted by azide. Hydrogenation of the azide **95** gave an amine, which spontaneously cyclized to the lactam **96**. Borane reduction followed by acidic deprotection yielded deoxymannojirimycin **2**. The latter route had the advantage that the intermediate lactam, which was also believed to be a suitable glycosidase inhibitor, was also formed.

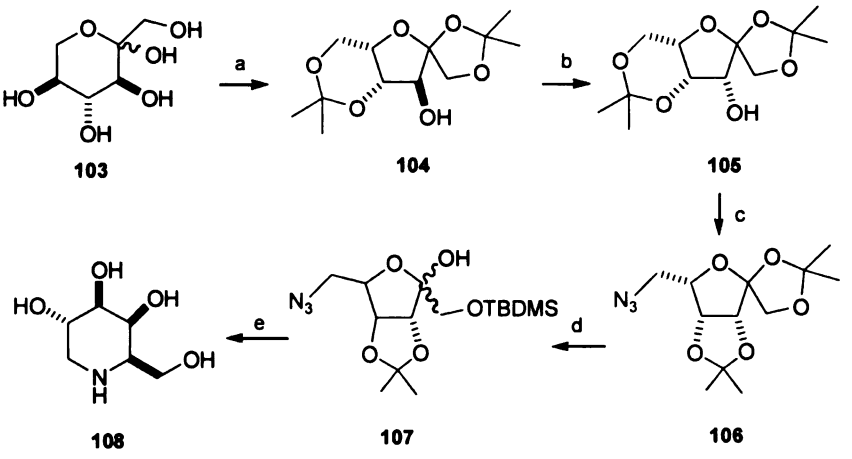
Shortly after the synthesis of deoxymannojirimycin **2**, they reported a synthesis of deoxynojirimycin **1** [25] using a similar strategy (Scheme 1.13). An epoxide **98** with L-idofuranose configuration was used as the starting material. Reaction of the epoxide with sodium azide gave the ido-azide, then the free 5-OH was protected by a benzyl group. After acid hydrolysis of the 1,2-O-isopropylidene of compound **99**, 2-OH was derivatized to a triflate **100**. The catalytic hydrogenation reduced the azide to an amine group, which

underwent intromolecular cyclization to form the bridged ring system **101**. After hydrolysis and deprotection, deoxynojirimycin **1** was obtained.



Scheme 1.13 A synthesis of deoxynojirimycin from An epoxide with L-idofuranose configuration: a) NaN_3, DMF; 87%; NaH, BnBr, $(Bu)_4NI$, THF; 91%; b) HCl, methanol, 67%; Tf_2O; 88%; $SnCl_2$, methanol; c) NaOAc, ethanol; CBzCl; 67%; d)CF_3COOH/H_2O, dioxane; $NaBH_4$, ethanol; e) Pd/C, H_2, AcOH

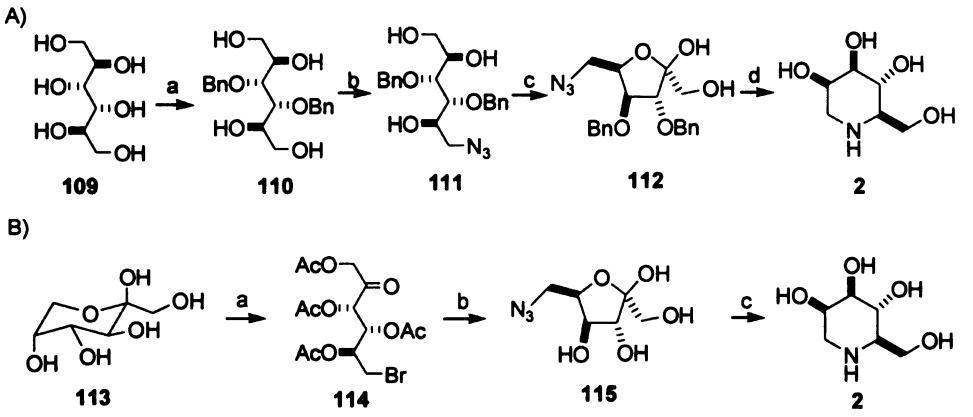
In 1993, Tyler et. al. [26] developed a synthesis of deoxygalctonojirimycin **108** from L-Sorbose (Scheme 1.14). 1,2:4,6-Di-O-isopropylidene-α-L-sorbofuranose **104** was synthesized from L-sorbose **103**. The free 3-OH was inverted by an oxidation-reduction process to yield exclusively 1,2:4,6-di-O-isopropylidene-α-L-tagatofuranose **105**. Acid-catalyzed acetal isomerization generated 1,2:3,4-di-O-isopropylidene-α-L-tagatofuranose and the free 6-OH was subsequently derivatized and substituted with azide. Acetolysis then generated the diacetate as a mixture of anomers, which was then deprotected and selectively primary protected by a TBDMS group. Reductive amination of **107** then afforded the deoxygalctonojirimycin **108**.



Scheme 1.14 A synthesis of deoxynojirimycin from L-sorbose: a) $Me_2C(OMe)_2$, $SnCl_2$, $MeOCH_2CH_2OMe$; b) Me_2SO, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; then $NaBH_4$, EtOH; c) CSA, Me_2CO; then MsCl, Et_3N, CH_2Cl_2; then NaN_3, Me_2SO, 80°C; d) 0.5% BF_3OEt_2 in Ac_2O, 0°C; then MeONa, MeOH; then TBDMSCl, imidazole, DMF; e) H_2, Pd/C, EtOH; then CF_3CO_2H, H_2O(3:7 v/v), RT

Two other similar synthetic routes towards 1-deoxymannojirimycin were developed by Szarek et. al. [27] and Stűtz et. al. [28]. They have very similar intermediates, namely 6-aizdo-D-fructose **115** and the protected form **112**. Szarek et. al. started from D-mannitol (Scheme 1.15 A). Several selective protection and deprotection steps yielded the 3,4-O-benzyl-D-mannitol **110**, which could be selectively monotosylated and then converted to an azide alcohol **111**. Because of its C2 symmetry, this process generated only one enantiomer. The selective oxidation at the 2-OH position was accomplished by reaction with bis(tributyltin)oxide-bromine, which afforded the partially protected 6-aizdo-D-fructose intermediate **112**. The subsequent hydrogenation generated 1-deoxymannojirimycin **2**. Alternatively, Stűtz's synthesis (Scheme 1.15 B) employed D-fructose **113** as the starting material. After acylation and reaction with triphenylphosphane dibromide, the acyclic bromosugar **114** was obtained. After

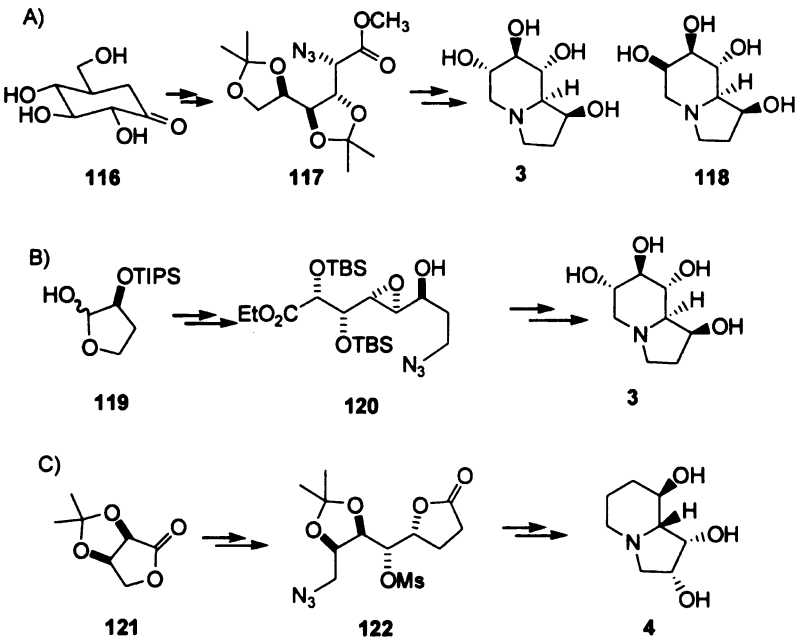
deprotection, this bromosugar was reacted with substituted by sodium azide to yield the similar intermediate **115**. The final hydrogenation generated 1-deoxymannojirimycin **2**.



Scheme 1.15 Two similar synthetic routes towards 1-deoxymannojirimycin sharing a common intermediate 6-aizdo-D-fructose: A) a) 2-methoxypropene, 0°C; then NaH, BnBr; hydrolysis; b) 1eqiv. p-TsCl; NaN_3, DMF:H_2O = 10:1, 100°C; 51% c) bis(tributyltin)oxide-bromine(2.3eqiv.); d) Pd/C, H_2, methanol:H_2O = 3:1, 0.1N HCl; 87%; B) a) Ac_2O, sulfuric acid, 60%; then Ph_3PBr_2, CH_2Cl_2, 90%; b) Deprotection then NaN_3, DMF, rt, 60 ~ 65%; c) Pd/C, H_2, methanol

There have been some other synthetic works of azasugars based on using azide to introduce the imino nitrogen. Starting from D-*glucono*-1,5-lactone **116**, by diisopropylidenation and introduction of an azide in the α-positon, Rapoport et. al. [29] carried out a synthesis towards castanospermine **3** and 6-epicastanospermine **118** (Scheme 1.16 A). Cha et. al. [30] employed a chiral lactol **119** as the starting material. Their synthesis towards castanospermine **3** (Scheme 1.16 B) featured a reductive cyclization of azide and epoxide of **120**. Using erythronolactone **121** as the starting material (Scheme 1.16 C), Pearson et. al. synthesized (-)-swainsonine **4** [31]. This

synthesis also involved a similar reductive cyclization involving the azido and mesylate groups of **122**.

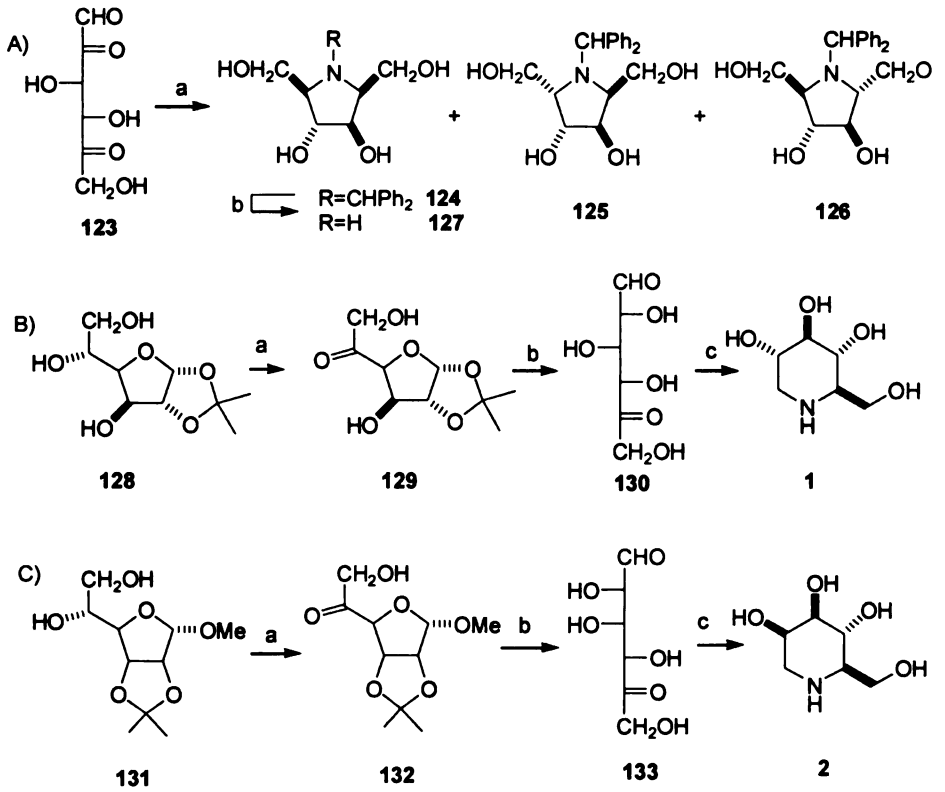


Scheme 1.16 Several enatioselective synthesis of azasugars using reductive cycliation of azide and leaving groups. A) Starting from D-gluconolactone; B) starting from chiral lactol; C) starting from D-erythronolactone

In summary, all of the synthetic strategies discussed above took advantage of the facile and general reductive cyclization involving of azido and leaving groups. Azide could be relatively easily installed as a nitrogen source. This amine precursor could be selectively reduced in the appropriate stage of a synthesis to act as an *in-situ* generated nucleophile. Because of such flexibility, azides have been extensively employed in azasugar synthesis. However, the azide-facilitated synthesis has the serious drawback of being potentially explosive.

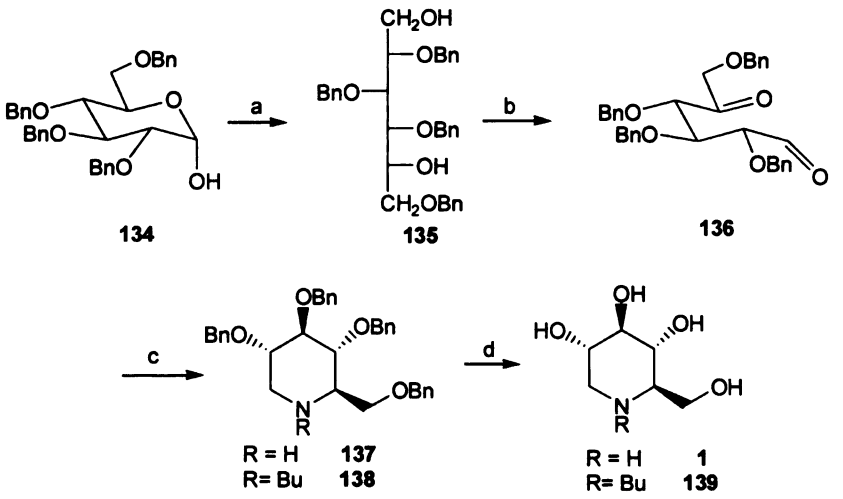
1.3.2.2 Reductive amination in the synthesis of azasugars

Reductive amination has long been employed as a synthetic method to introduce nitrogen functionality into a structure. Reitz et. al. [32-34] adopted this strategy into the synthesis of azasugars and successfully synthesized several azasugars including 1-deoxynojirimycin **1** and 1-deoxymannojirimycin **2** (Scheme 1.17).



Scheme 1.17 Double reductive amination towards azasugars: A) synthesis of 2,5-anhydro-imino-D-glucitol **127**: a) Ph_2CHNH_2, $NaCNBH_3$, MeOH; 68%; b) 20% $Pd(OH)_2/C$, H_2; 91%; B) synthesis of 1-deoxynojirimycin **1**: a) nBu_2SnO, MeOH; Br_2; b) Dowex^{-50}; c) Ph_2CHNH_2, $NaCNBH_3$, MeOH; 74%; then 20% $Pd(OH)_2/C$, H_2; 90%; C) synthesis of 1-deoxymannojirimycin **2**: a) nBu_2SnO, MeOH; Br_2; 70%; b) Dowex-50; quant. c) Ph_2CHNH_2, $NaCNBH_3$, AcOH, MeOH; 45%; then 20% $Pd(OH)_2/C$, H_2; 90%;

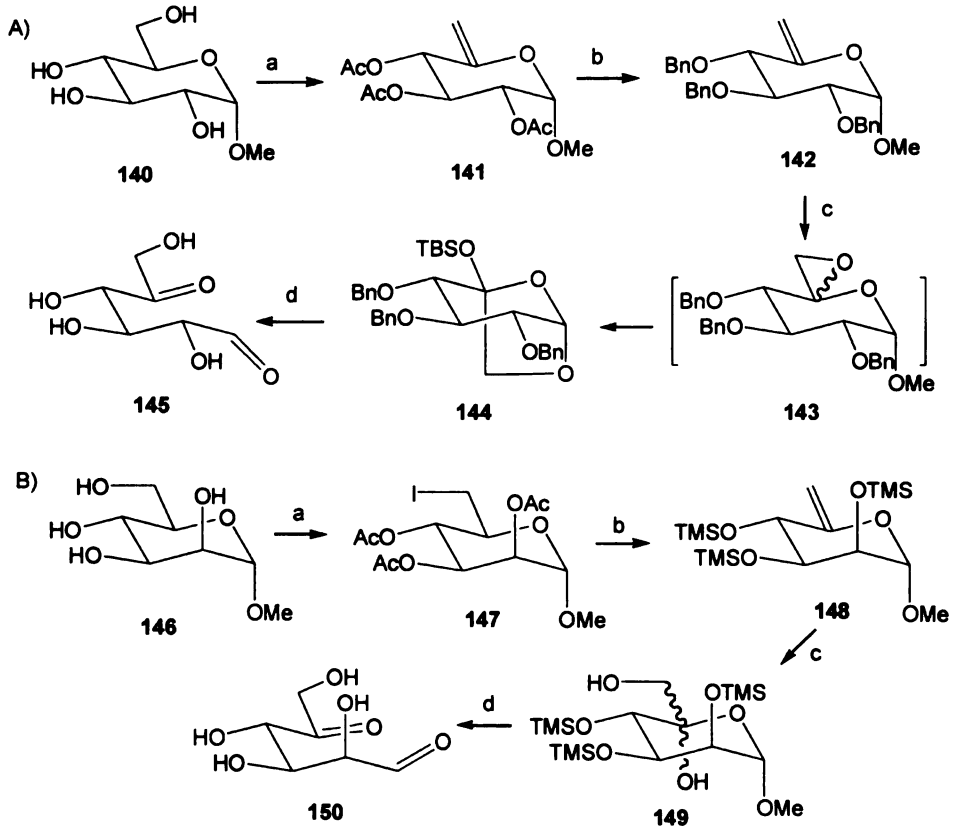
Starting from 5-keto-D-fructose **123** (Scheme 1.17 A), a double reductive amination using sodium cyanoborohydride gave a protected 2,5-anhydro-imino-D-glucitol **124**, which was subsequently deprotected by catalytic hydrogenation to yield 2,5-anhydro-imino-D-glucitol **127**. The unexpected relatively high stereoselectivity was assigned to the assistance of neighboring hydroxyl groups. Starting from selectively protected 1,2-O-isopropylidene-D-glucose **128**, a selective oxidation of the 5-OH was achieved to yield the 5-keto-D-glucose **130** after acid hydrolysis. A similar double reductive amination (Scheme 1.17 B) was then carried out using the same procedure, where 1-deoxynojirimycin **1** was obtained after deprotection. Similarly, when 1-O-methyl-2,3-O-isopropylidene-D-mannofuranoside **131** was employed as the starting material, the similar procedure yielded 1-deoxymannojirimycin **2** (Scheme 1.17 C).



Scheme 1.18 Synthesis of deoxynojirimycin by double reductive amination from 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose: a) $LiAlH_4$, THF, 100%; b) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, Et_3N; c) $RNH_3^+HCO_2^-$, $NaCNBH_3$, MeOH, molecular sieve 3 Å. d) Li, NH_3

This double reductive amination approach attracted much interest because of its simplicity and potential industrial possibility. The 5-keto-hexose synthetic precursors for 1,5-dideoxy-1,5-iminosugars became interesting synthetic targets for azasugar synthesis. In 1999 and 2001, two groups developed two approaches towards this kind of molecules. Lopes et. al. [35] started with 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose **134** (Scheme 1.18), which could be readily synthesized from D-glucose. A simple reduction of this starting material yielded a 1,5-diol **135**, which was subsequently oxidized to the 5-ulose **136**. This key intermediate was directly reacted with ammonium formate and $NaCNBH_3$ to give the protected azasugars **137** or **138**. After reductive deprotection, 1-deoxynojirimycin **1** and N-butyl-1-deoxynojirimycin **139** were synthesized.

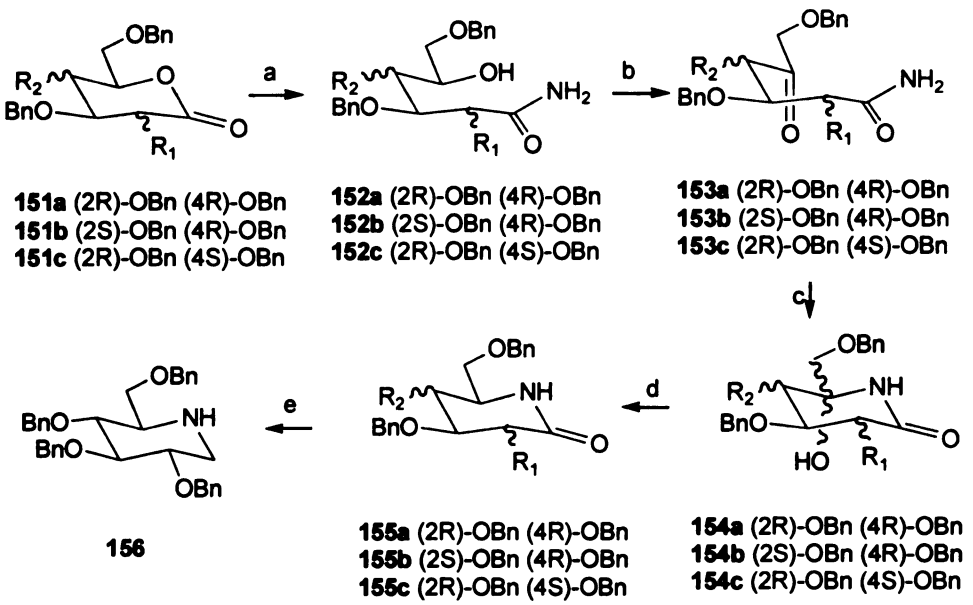
Murphy et. al. [36,37] employed 6-deoxyhex-5-enopyranosides as an useful intermediate synthesis and derived D-hexos-5-uloses, which could be readily transformed to azasugars with double reductive amination discussed above. Starting from methyl α-D-glucoside **140** (Scheme 1.19 A), 6-deoxyhex-5-enopyranoside **141** was synthesized through primary iodination and acetylation followed by base-catalyzed elimination. The protection groups were converted to benzyl groups. Epoxidation followed by hydrolysis generated the 1,6-anhydro-D-glucopyranos-5-ulose **144**. This unusual structure was confirmed by NMR analysis and chemical derivatization. After several protection and deprotection steps, 5-keto-glucose **145** was synthesized as a precursor of 1-deoxynojirimycin **1**. Similarly, 5-keto-mannose **150** was synthesized from methyl α-D-mannoside **146** (Scheme 1.19 B). These two D-hexos-5-uloses could be transformed to 1-deoxynojirimycin **1** and 1-deoxymannojirimycin **2** respectively by reductive amination.



Scheme 1.19 The synthesis of D-hexos-5-uloses **145** and **150** as an intermediate for azasugar synthesis: A) synthesis of D-xylo-hexos-5-ulose: a) PPh_3, Im, I_2, toluene, 80°C,3h; then TMSCl, Py, 25°C; then DBU, DMF, 70°C, 3h; then Ac_2O, Py; b) NaOMe, MeOH, 25°C, 12h; then NaH, BnBr, DMF, 0°C, 15h; c) 1,1,1-trifluoroacetone, Oxone, $NaHCO_3$, Na_2EDTA, CH_3CN, H_2O; then TBSOTf (1.5eq.), 2,6-lutidine (2eq.), CH_2Cl_2; d) H_2, Pd/C, EtOH; then TBAF, THF; B) synthesis of D-lyxo-hexos-5-ulose: a) PPh_3, Im, I_2, toluene, 110°C; then Ac_2O, Py; b) DBU, toluene(anhydr.), 110°C, 50% over 3 steps; then NaOMe, MeOH; then TMSCl, Py., 93% over 2 steps; c) 1,1,1-trifluoroacetone, Oxone, $NaHCO_3$, Na_2EDTA, CH_3CN, H_2O, 1h, 71%; d) MeOH, 94%

Pandit et. al. [38] used suitably protected aldonolactones as starting materials. They developed a relatively general transformation of sugar lactones to sugar lactams (Scheme 1.20). Sugar lactams not only can be transformed to 1,5-dideoxy-1,5-iminosugars by reduction but, as stated earlier, also are potential glycosidase inhibitors

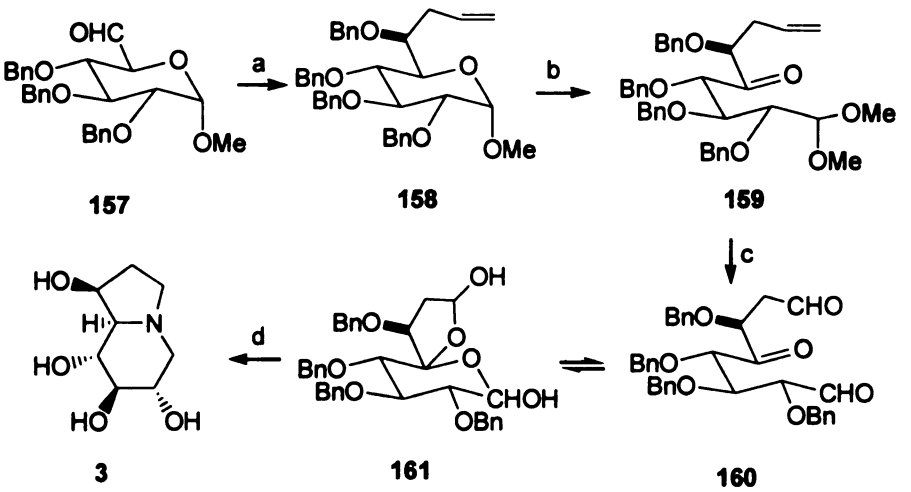
themselves. After aminolysis of the sugar lactones **151** to form amides **152**, the free 5-OH's were oxidized to carbonyl groups. Reaction with ammonia in methanol generated two isomeric hydroxyl lactams **154**, which could be reduced with $NaCNBH_3$ to yield the protected sugar lactams **155**. The reduction mechanism was believed to involve a hydride donation by the $NaCNBH_3$ reagent to the acyliminium ion. This strategy could be used for sugar lactams with gluco-, galacto- and manno- configurations.



Scheme 1.20 A transformation of sugar lactones to azasugars: a) NH_3, MeOH; b) DMSO, Ac_2O; c) NH_3, MeOH; d) $NaCNBH_3$, HCO_2H; e) BH_3

In 1996, Mootoo et. al. [39] developed a triple reductive amination approach to castanospermine (Scheme 1.21). The synthetic strategy was to suitably place three carbonyl groups in a molecule and perform the reductive aminations at the same time. This approach is advantageous in preparing the fused-ring azasugars. Allylation of a known aldehyde **157** readily derived from methyl α-D-glucoside extended the carbon chain to the desired length. Benzyl groups were then used to protect the free hydroxyl

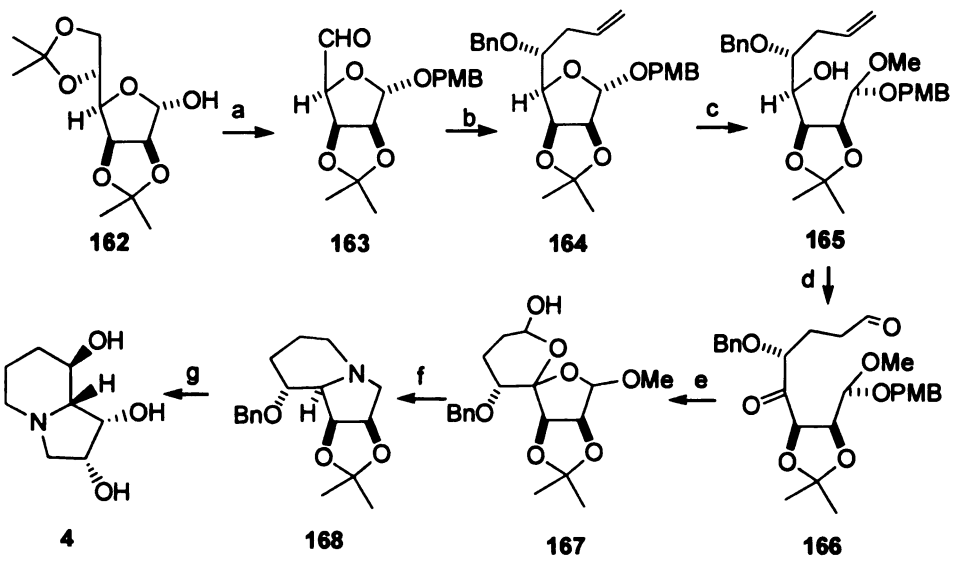
groups. The treatment of this alkene with iodonium dicollidine perchlorate gave a mixture of iodo-tetrahydrofurans, which underwent zinc-mediated reductive elimination to an alkenyl acetal-alcohol. This alcohol was then oxidized to a ketone **159**. The ozonolysis of the alkene and acid-hydrolysis gave the key tri-carbonyl intermediate **160**, which actually existed as a mixture of lactol isomers **161**. Triple reductive amination was carried out finally and after catalytic hydrogenation, castanospermine **3** was synthesized.



Scheme 1.21 A triple reductive amination approach to castanospermine **3**: a) allyl bromide, Sn, CH_3CN-H_2O(10:1), ultrasound; then BnBr, NaH, n-Bu_4NI, DMF; b) IDCP, CH_2Cl_2-MeOH; then Zn, 95%EtOH, heat; then Swern oxidation; c) O_3, CH_2Cl_2, -78°C then Ph_3P; then THF-9M HCl; d) 1.3 eq. NH_4HCO_2, 30eq $NaCNBH_3$, MeOH; then 10% Pd/C, MeOH-HCOOH;

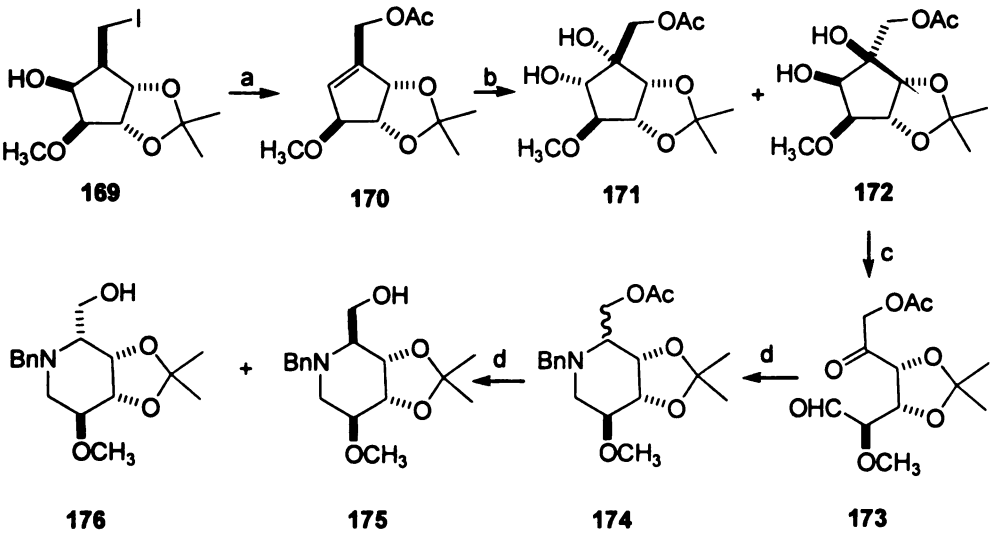
This triple reductive amination approach was further employed to the synthesis of swainsonine (Scheme 1.22) [40]. The synthesis started from 2,3:5,6-di-O-isopropylidene-mannofuranose **162**. Selective deprotection and oxidative cleavage of the diol generated an aldehyde **163**, which reacted with allyltrimethylsilane to extend the carbon chain and the free hydroxyl group was protected by benzyl. The alkene **164** was treated according to the standard iodocyclization-THF opening sequence to give the hydroxyl alkene **165**.

Hydroboration and oxidation installed the protected ketoaldehyde **166**. DDQ-mediated removal of the p-methoxybenzyl provided a mixture of isomers, which underwent triple reductive amination and further deprotection to give swainsonine **4**.



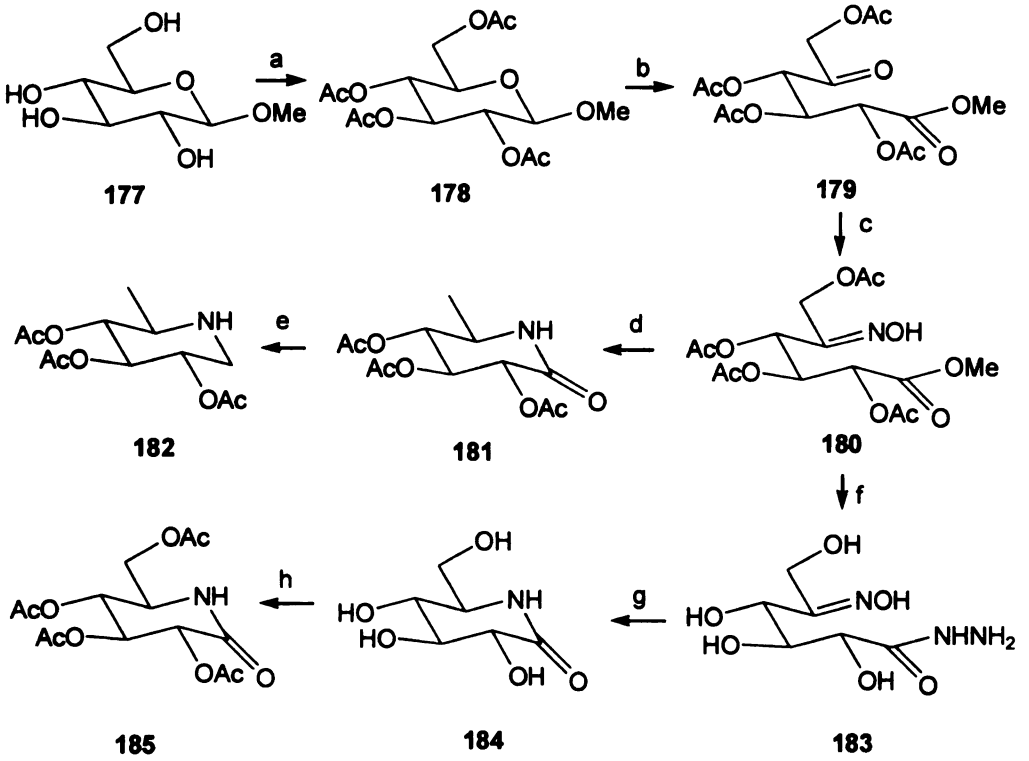
Scheme 1.22 A triple reductive amination approach to swainsonine **4**: a) PMBCl, NaH, n-Bu_4NI, DMF; then HOAc; then $NaIO_4$; b) allyltrimethylsilane, BF_3OEt_2; then BnBr, NaH, n-Bu_4NI, DMF; c) IDCP, CH_2Cl_2-MeOH; then Zn, 95% EtOH, heat; d) BH_3, THF, then Na_2O_2; then Swern oxidation; e) DDQ, Et_3N, CH_2Cl_2-H_2O; f) NH_4HCO_2, $NaCNBH_3$, MeOH; g) 10%Pd-C, MeOH-HCOOH; then HCl, THF-H_2O

Mehta et. al. [41] reported a norbornyl route to azasugars (Scheme 1.23). A highly functionalized cyclopentene derivative **169** was employed as the starting point, which could be readily synthesized from norbornyl derivatives. After mesylation and elimination, the cyclopentene ring was dihydroxylated to give a mixture of isomers **171** and **172**. Then the cyclopentane ring was broken by $NaIO_4$ oxidation to form a ketal aldehyde as the key intermediate. The double reductive amination finally furnished azasugar derivatives **175** and **176**.



Scheme 1.23 A norbornyl route to azasugars: a) Mesylation; then NaOAc, DMF, 105°C, 6h, 77%; b) OsO_4, NMO(50% aq. solution), Me_2CO:H_2O(4:1),48h, 86%; c) $NaIO_4$(1.3eq), DCM, 0°C; d) $BnNH_2$, AcOH, $NaCNBH_3$, 20h, -10°C to rt, 30% for two steps; e) KOH, MeOH, 2h, 90%

In 2000, Hollingsworth et. al. [42] reported a general approach to the synthesis of dideoxy and trideoxyiminoalditols from β-D-glycosides (Scheme 1.24). After protection of the free hydroxyl groups, the β-D-glycosides, represented by **177**, were oxidatively ring-opened to form a keto-ester **179**. Hydroxylamine was employed as the nitrogen source to be introduced into the sugar structure. The reductive amination followed by spontaneous cyclization formed lactam **181**, while the 6-position was also reduced to methyl group. After borane reduction, 1,6-dideoxynojirimycin **182** and 1,6-dideoxygalactonojirimycin were synthesized in good yields. The synthetic strategy was slightly modified to synthesize the nojirimycin lactam **185** by deacetylating the oxime **180** before the catalytic hydrogenation with hydrazine.

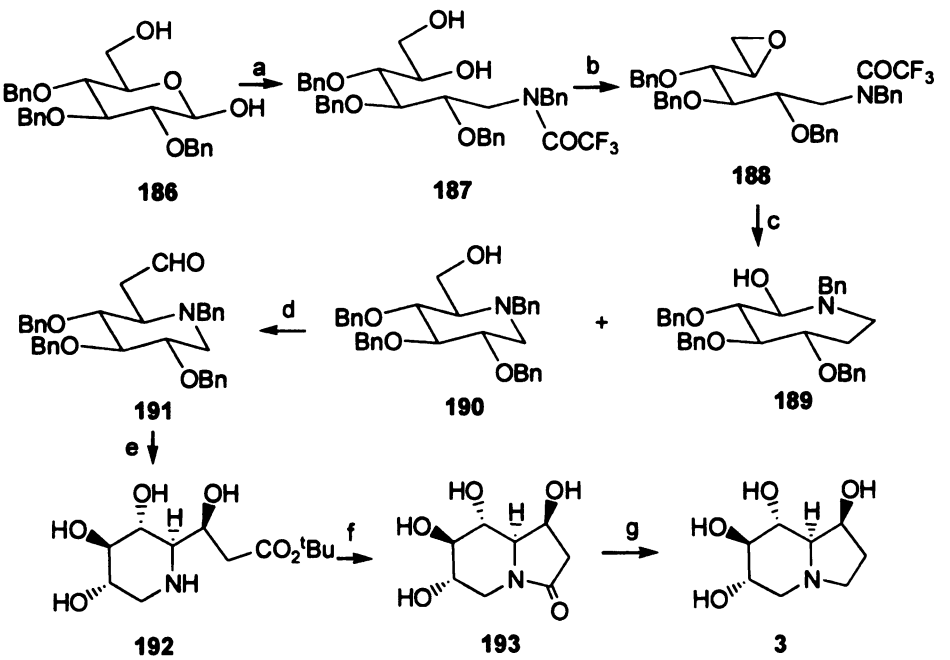


Scheme 1.24 A general approach to the synthesis of dideoxy and trideoxyiminoalditols from ß-D-glycosides: a) Ac_2O, py.; b)CrO_3, AcOH; c) NH_2OH, Py; d) H_2, Pd/C; e) BH_3/THF; f) N_2H_4; g) H_2, Pd/C; h) Ac_2O, py.

Reductive amination has been extensively used in many synthetic routes towards azasugars. The easy installation of nitrogen source and cyclization to form the N-heterocycle ring could often be achieved in a single step in the late stage of a total synthesis, which provided flexibility of synthesis towards azasugars. However, one inherent drawback of reductive amination is the stereochemistry control. The reductive amination often involved chirality scrambling and regeneration process. Although the stereoselectivity has been improved in some cases, mostly it is still generally not stereospecific.

1.3.2.3 Azasugar synthesis with N-alkylative cyclization

As one of the best known organic reaction, N-alkylation has been also been widely employed in azasugar synthesis. Based on its carbohydrate-like structure, it is easy to imagine by converting the hydroxyl groups to leaving groups and double N-alkylation may generate azasugar structure. The N-alkylation could be carried out in a single step or multi-steps.

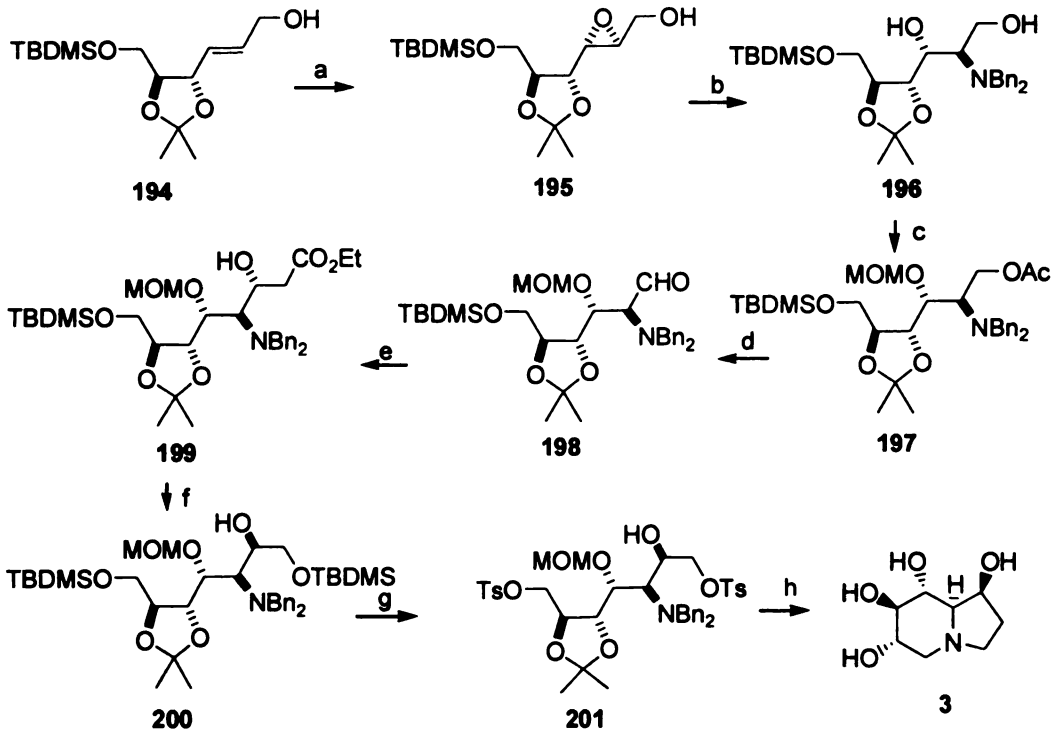


Scheme 1.25 A synthesis of deoxynojirimycin and castanospermine by a glucosylamine pathway: a) benzylamine, $CHCl_3$; then $LiAlH_4$, THF, reflux, 5h; then trifluoroacetylation; b) TBDMSCl, imidazole; then mesylation; then Bu_4NF-THF; then CH_3ONa-MeOH; c) $NaBH_4$, ethanol, 40°C; d) Swern oxidation; e) Lithio t-butylacetate; f) hydrogenolysis, then (TFA-H_2O, 60°C, 3h); g) diisobutylaluminum hydride;

In 1984, Ganem et. al. [43] developed a total synthesis of deoxynojirimycin **1** and castanospermine **3** (Scheme 1.25). A glucosylamine pathway was employed to introduce the amine functionality. Selectively benzylated glucose **186** was reacted with

benzylamine followed by reduction to give an amine, which was trifluoroacetylated to furnish an amide **187**. After selective silylation, mesylation and desilylation, this amide was treated with base to furnish an epoxide **188** with inverted C-5. After deprotection of this amide, the aminoepoxide cyclized spontaneously to a mixture of piperidine **190** and azepane **189**. The piperidine **190** was transformed to deoxynojirimycin **1** using hydrogenolysis. The protected deoxynojirimycin **190** was oxidized to an aldehyde **191**, which was treated with lithio t-butylacetate to extend the carbon chain. Hydrogenolysis of this amino ester **192** deprotected all the benzyl groups and gave a lactam **193**, which was further reduced to give castanospermine **3**. By this method, the structure of castanospermine **3** was first unambiguously established.

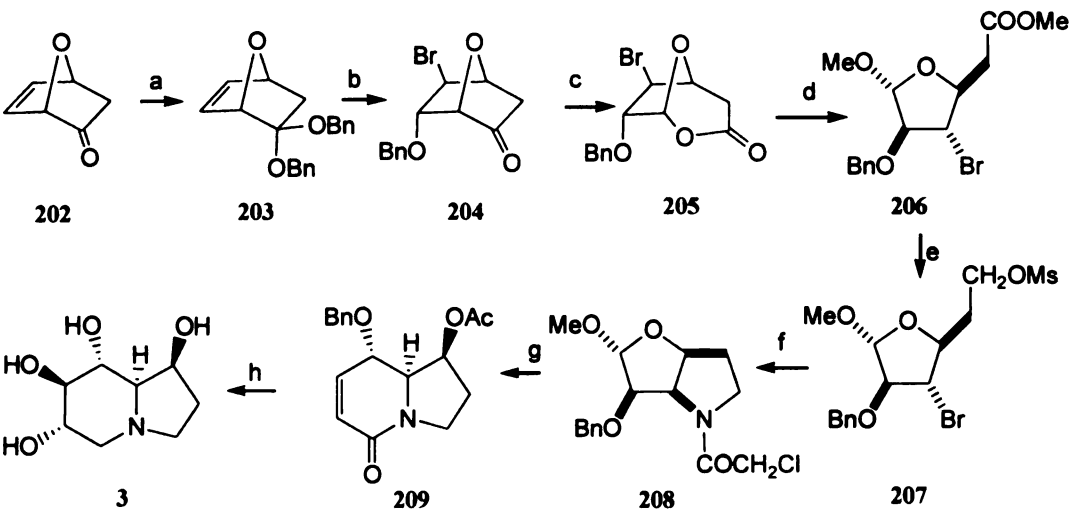
In 1991, Kibayashi et. al. [44] reported a non-carbohydrate based synthesis of castanospermine **3** (Scheme 1.26). In this method, a highly functional epoxide **195** was prepared by Sharpless epoxidation. The regiosepecific cleavage of the oxirane ring was achieved by reaction with $Et_2AlN(CH_2Ph)_2$ to introduced a benzyl-protected amine group. After protection steps, the carbon chain was extended by reaction with the lithium enolate of ethyl acetate. Although the undesired stereoisomer **199** was the major product, it could be converted to the desired stereoisomer by Mitsunobu reaction. The primary silyl protection groups were transformed to leaving group and a catalytic hydrogenolysis afforded the fused-ring azasugar scaffold, which was further deprotected to give castanospermine **3**.



Scheme 1.26 A synthesis of castanospermine from a highly functional epoxide: a) Sharpless epoxidation; b) $Et_2AlN(CH_2Ph)_2$, CH_2Cl_2, r.t.; c) AcCl(1eq.), Et_3N, CH_2Cl_2, 0°C; then MOMCl, i-Pr_2NEt, $CHCl_3$, reflux; d) $LiAlH_4$, Et_2O, rt; then DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C to rt; e) AcOEt, $LiN(SiMe_3)_2$, THF, -78°C; f) $LiAlH_4$, Et_2O, r.t.; then TBDMSCl, imidazole, DMF, r.t.; then AcOH, Ph_3P, $(EtOCON=)_2$, C_6H_6, reflux; then $LiAlH_4$, Et_2O, r.t.; g) N-Bu_4NF, THF, r.t.; then TsCl, Py., rt; h) H_2, $Pd(OH)_2$, MeOH, then Et_3N, MeOH, reflux; then HCl, MeOH, reflux

Vogel et. al. [45] also developed a synthesis of castanospermine and analogs using a "naked sugar" as the starting material (Scheme 1.27). Starting from this [2.2.1] bridged ring system **202**, the ketone was protected as a dibenzylacetal. Bromohydrin formation and a rearrangement built two new chial centers with high yield and high stereoselectivity. Baeyer-Villiger oxidation of **204** followed by methanolysis broke the bridged ring and gave the tetrahydrofuran ring system **206**. After reduction and mesylation, the nitrogen atom was introduced by reaction with methanolic ammonia. Spontaneous N-alkylation cyclization and following $P(OEt)_3$-mediated condensation gave the fused-ring azasugar

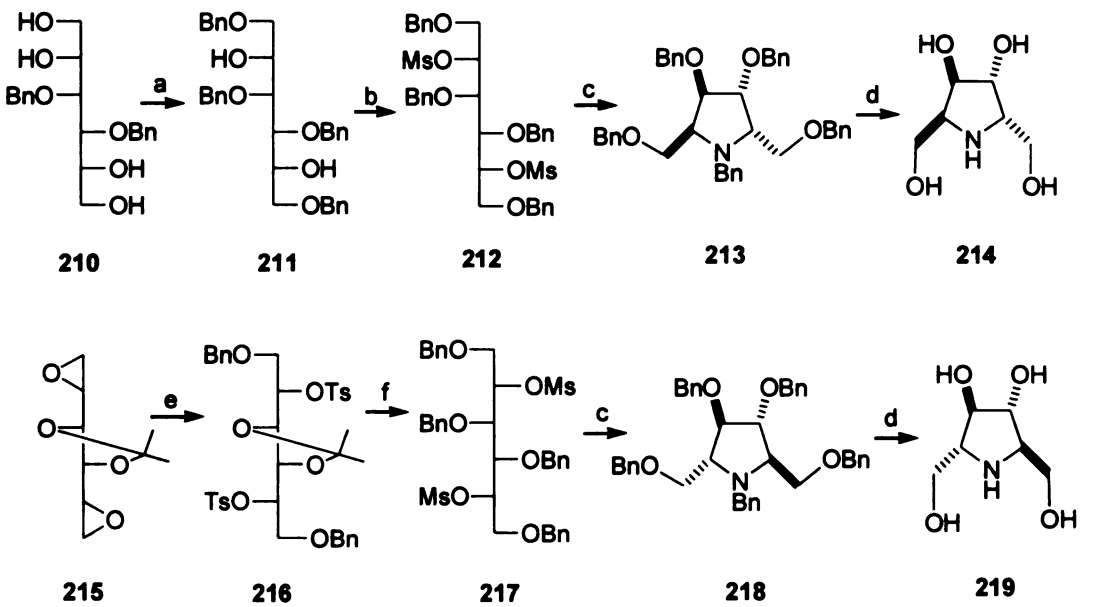
scaffold **209**. Then bromohydrin formation was used to functionalize the double bond. The following epoxide formation, hydrolysis and deprotection steps afforded castanospermine **3**. 6-deoxycastanospermine and 6-deoxy-6-fluorocastanospermine were also synthesized by slight modification of the final steps.



Scheme 1.27 A synthesis of castanospermine and analogs using a "naked sugar" as the starting material: a) $BnOSiMe_3$, TMSOTf, CH_2Cl_2; b) Br_2/CH_2Cl_2; then $NaHCO_3/ H_2O$, -90°C, 98%;c) Baeyer-Villiger oxidation, mCPBA, 95%; d) MeOH, $SOCl_2$; e) DIBAL, THF/toluene; then MsCl, pyridine/CH_2Cl_2; f) 24% NH_3 in $EtOH/H_2O$, 45°C, 1day; then $ClCH_2COCl$, pyridine/CH_2Cl_2; g) Ac_2O/H_2SO_4, 0°C; then $P(OEt)_3$, 130°C; then acetylation; h) Br_2, AgOAc, $AcOH/Ac_2O$, 10°C; then MeOH/ $SOCl_2$, 20°C; then BEMP, CH_3CN, 20°C; then BEMP, CH_3CN,H_2O 100°C; methanolysis and debenzylation;

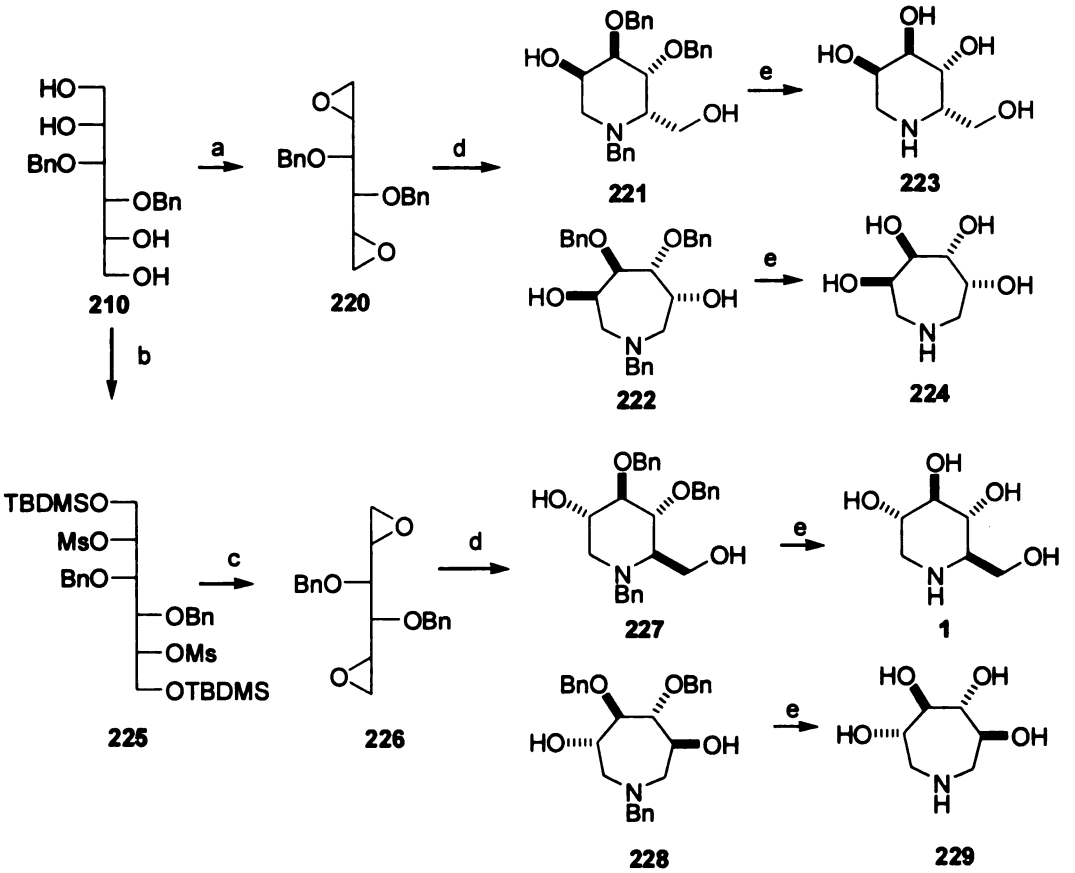
Capitalizing on the C_2 symmetry of D-mannitol, Dureault el. al. [46] developed an enantioselective synthesis of 2,5-dideoxy-2,5-imino-D-mannitol and L-iditol. Double N-alkylation of amine with selectively protected and derivatized D-mannitol was employed as the key step (Scheme 1.28). Starting from 3,4-di-O-benzyl-D-mannitol **210**, selective primary benzylation followed by mesylation gave the 1,3,4,6-tetra-O-benzyl-2,5-di-O-mesyl-D-mannitol **212**. This suitably protected and derivatized compound **212** was then treated with benzylamine. Double alkylation followed by hydrogenolysis afforded 2,5-

dideoxy-2,5-imino-D-iditol **214**. To synthesize the more biologically important 2,5-dideoxy-2,5-imino-D-mannitol **219**, the stereochemistry at the 2- and 5- positions must be inverted. Therefore L-iditol bis-epoxide **215** was employed as the starting material. After epoxide ring opening and benzylation, tosylation, deacetalation and benzylation, the similar synthetic intermediate **217** with 2-,5- inverted was obtained. The treatment of this compound with benzylamine followed by hydrogenolysis therefore afforded 2,5-dideoxy-2,5-imino-D-mannitol **219**.



Scheme 1.28 A synthesis to 2,5-dideoxy-2,5-imino-D-mannitol and L-iditol using double N-alkylation of protected alditols: a) Bu_2SnO (2.1eq), toluene, reflux, 10h; then BnBr, Bu_4NI, 70°C, 12h; 74%; b) MsCl, Et_3N, DMAP, CH_2Cl_2, 80%; c) $BnNH_2$ (40eq), 120°C, 18; 78%; d) H_2, Pd/C, AcOH; then Dowex 50W-X8; 80%; e) NaH, BnOH, DMF, 20°C, 24h, 57%; then TsCl, Et_3N, DMAP, CH_2Cl_2, 84%; f) CF_3COOH/H_2O (9:1), 0°C, 2h, 86%; then $Cl_3CC(NH)OBn$, CH_2Cl_2/C_6H_{12}(1:2), CF_3SO_3H, 25°C, 75%;

Again using the C_2 symmetry of D-mannitol to advantage, Poitout et. al. [47] later reported a synthesis of deoxynojirimycin **1** and analogues (Scheme 1.29).

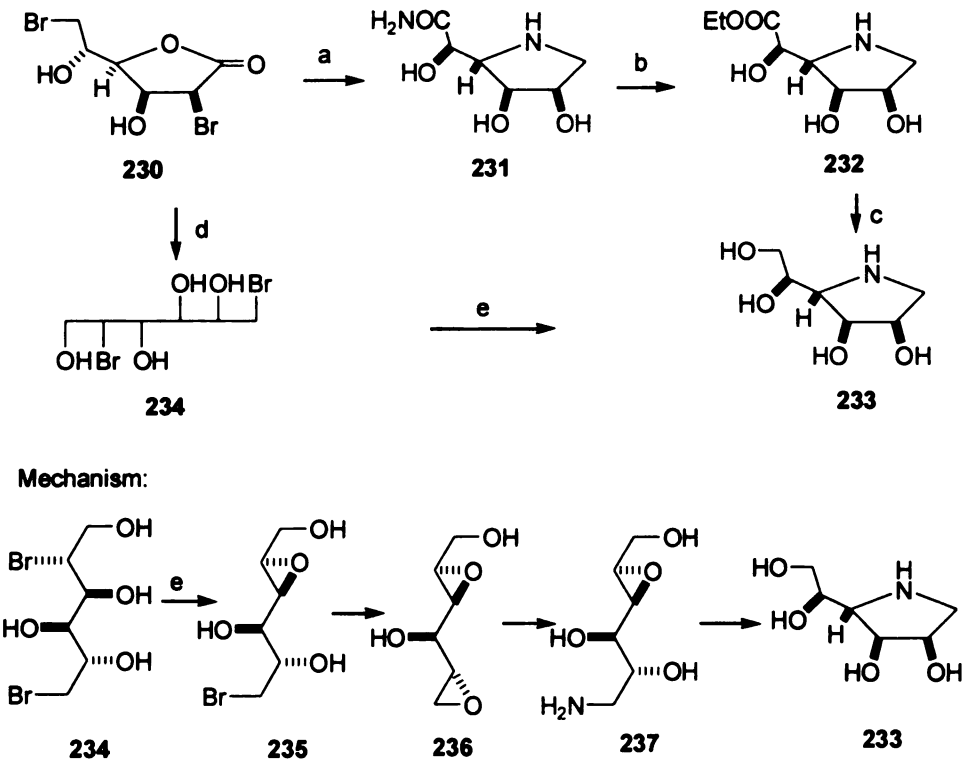


Scheme 1.29 Synthesis of deoxynojirimycin from D-mannitol: a) Ph_3P, DIAD, 130°C, 86%; b) TBDMSCl, imidazole, DMF, 0°C, 80%; then MsCl, NEt_3, CH_2Cl_2, 0°C, 98%; c) HCl, MeOH, 20°C then NaOH, H_2O, 20°C, 75%; d) $BnNH_2$, various conditions; e) H_2, Pd black, AcOH, 15h, 100%

The 1,2:5,6-dianhydro-3,4-di-O-benzyl-D-mannitol **220** and L-iditol **226** were synthesized as the key intermediates. Starting from D-mannitol, 3,4-di-O-benzyl-D-mannitol **210** could be synthesized based on selective protection and deprotection strategy. Starting from this dibenzyl mannitol, Mitsunobu reaction gave the dibenzyl diepoxide **220** with D-*manno* configuration. This compound was treated with benzylamine under various conditions to give protected L-deoxygulonojirimycin **221** and an azapane **222** with the D-*manno* configuration. The dibenzyl diepoxide **226** with L-*ido* configuration was obtained from the same starting point, namely 3,4-di-O-benzyl-D-mannitol **210**. This

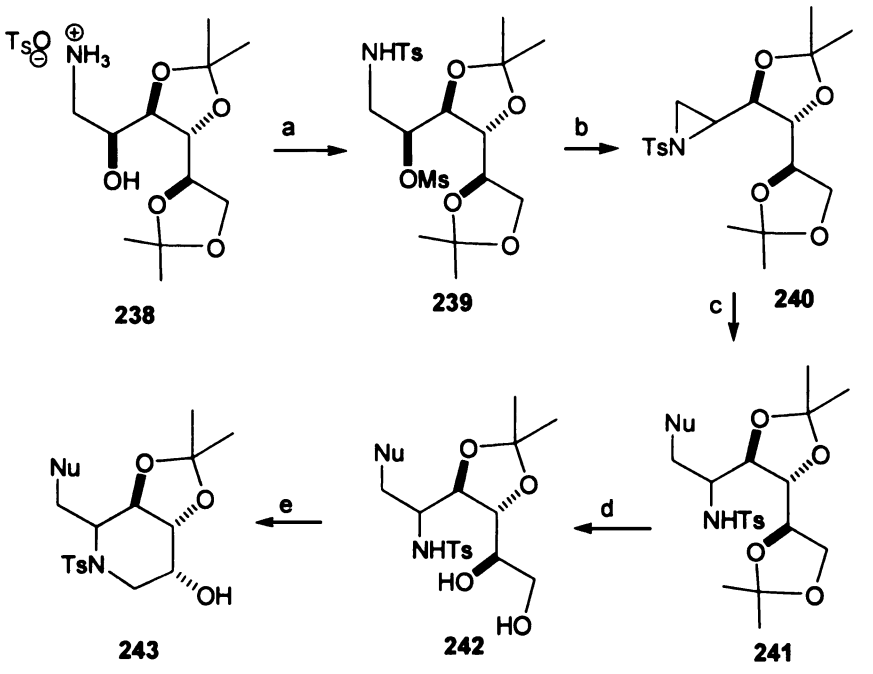
was achieved by selective mesylation at 2,5-positions and di-epoxide formation. Then the same double N-alkylation was carried out and deoxynojirimycin **1** was obtained along with a 7-membered ring azasugar **229**.

Since the N-alkylative pathway towards azasugars had been always very much dependent on the protecting group manipulation, it would be always of interest to synthesize these compounds with the use of fewer protecting groups. In 1993, Lundt et. al. [48] reported a synthesis of deoxyiminoalditols from aldonolactones (Scheme 1.30). Their approach was to use aldonolactones as the chiral source. They could directly be converted into bromodexoylactones by treatment with hydrogen bromide in acetic acid (HBA). Leaving groups for nucleophilic substitution are introduced at C-2 and the primary position. The ring closure of such bromodeoxylactones with ammonia therefore generated deoxyiminoalditols without participation of protecting groups. Dibromomannolactone **230** was treated with concentrated aqueous ammonia gave 3,6-dideoxy-3,6-imino-D-alloamide **231**. After hydrolysis, this amide was transformed to an ethyl ester and subsequently reduced to form 1,4-dideoxy-1,4-imino-L-allitol **233**, which is a five-membered ring azasugar. The reaction was shown to go through a diepoxide intermediate **236**, which was attacked by ammonia to give the azasugar ring. By interchange of the reduction and nucleophilc attack steps, the reaction was carried out even more efficiently. Reduction of the dibromolactone **230** gave the dibromoalditol **234**, which was treated with aqueous ammonia to give the same product **233**. Using no protecting group manipulation, an azasugar was synthesized highly efficiently. With this strategy, they further synthesized several other azasugars with D-*allo,* D-, L-*talo*, D- and L-*galacto* and D-, L-*ido* configuration as potential glycosidase inhibitors.



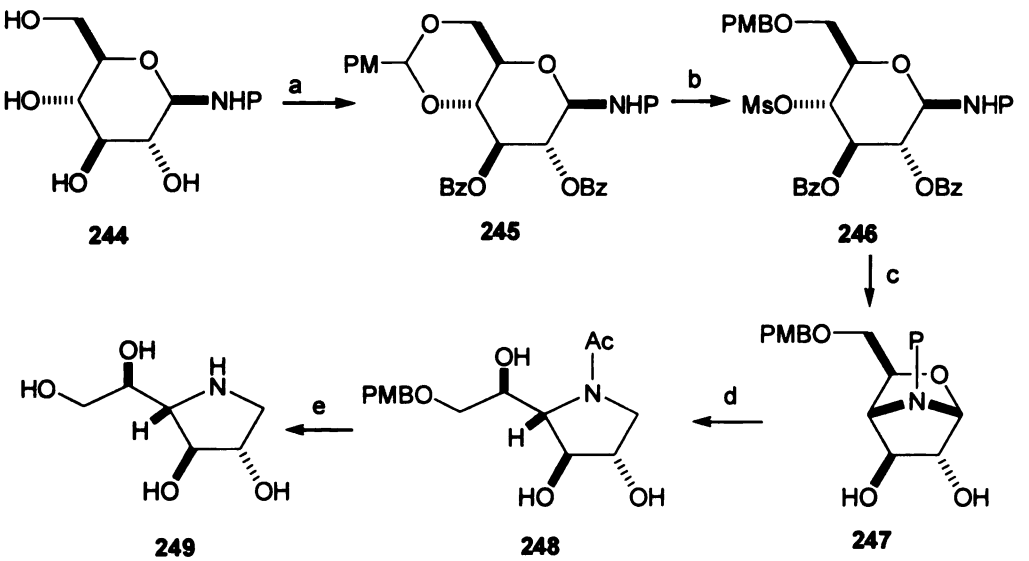
Scheme 1.30 Deoxyiminoalditols from aldonolactone: a) aq. NH_3, r.t. 1h, 61%; b) aq. HBr, reflux, 12h; 79%; then EtOH, AcCl, reflux, 3h, 100%; c) $NaBH_4$/ EtOH, 0°C to r.t., 12h; 50%; d) $NaBH_4$/ H_2O, H^+ resin; 60%; e) aq. NH_3, r.t., 2h, syrup 73%; cryst 51%

In 2001, Compernolle et. al. [49] developed a synthesis of deoxymannojirimycin analogues using N-tosyl and N-nosyl activated aziridines derived from 1-amino-1-deoxy-glucitol (Scheme 1.31). After protection of 1-amino-1-deoxy-glucitol, the primary tosylation, C-2 mesylation and treatment with base gave the 1,2-tosylated aziridine **240**, which was opened by various nucleophiles from the primary position to give 2-(tosyl)amino compound **241**. After selective hydrolysis, Mitsunobu reaction furnished the desired azasugar ring **243**. This strategy could be used to synthesize many analogues of deoxynojirimycin, which would be very useful potential glycosidase inhibitors.



Scheme 1.31 A synthesis of deoxymannojirimycin analogues using N-tosyl and N-nosyl activated aziridines derived from 1-amino-1-deoxy-glucitol: a) 4eq. Et_3N, 1.5eq. p-TsCl, CH_2Cl_2, 20°C, 30min; then 1.3eq. MsCl, 20°C, 1h; 92%; b) 2eq. NaH, THF, 20°C, 1h; 90%; c) various nucleophiles, > 65% yield; d) Dowex 50X8-200, 9:1/MeOH/H_2O, rt. 30h-7days; e) Ph_3P, DEAD, THF, rt, 5days;

In 2004, Fuentes et. al. [50] reported a stereocontrolled preparation of azasugars and their ethyl thioglycosides from glycosylamine. Anhydroazasugars were employed as the key intermediates. A representative example was shown in Scheme 1.32. After several protecting and deprotecting steps, the C-4 of glucosylamine was mesylated to give **246**. Treatment of this compound with base gave an anhydro azasugar **247**, which was reduced to give the 5-membered ring azasugar **248** with galacto- configuration. This method took advantage of the glycosylamine nitrogen functionality and could be used in some other azasugar syntheses.



244 245 246 247 248 249

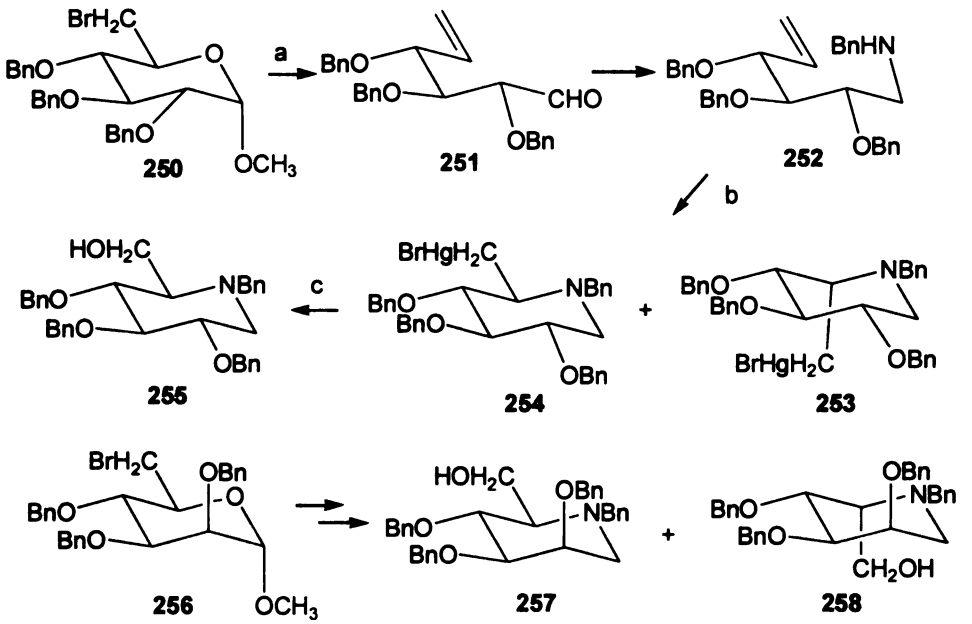
Scheme 1.32 A stereocontrolled preparation of azasugars from glycosylamine employing anhydrosugar as the key intermediate: a) anisaldehyde dimethyl acetal, DMF/PTSA, 50°C/20mmHg, 1h; then BzCl, py, rt, 24h; b) $NaBH_3CN$/AcOH, rt, 2.5h; then MsCl, py, rt, 24h; c) NaOMe/DMF, 45°C/20mmHg, 15min; d) $NaBH_2CN$/AcOH, rt, 24h; then NaOMe/MeOH, rt, 6h; e) MeOH/HCl, 65°C, 1h; then Dowex 50w8x.

The N-alkylation pathway is relatively straightforward in azasugar synthesis. The general goal is to install nitrogen functionality and a leaving group in appropriate positions. The nitrogen functionality could be installed using N-alkylation or some suitable aminosugar could be used as starting materials. The leaving group could be installed in various methods. The intramolecular nucleophilic N-alkylation was mostly used to furnish the azasugar ring. To control the regio- and stereoselectivities, this N-alkylation method often involved extensive manipulation of protecting strategies.

1.3.3 Other synthetic methodologies towards azasugars

Many groups have developed some other synthetic methodologies towards azasugars. In 1985, Ganem et. al. [51] synthesized deoxynojirimycin **1** and deoxymannojirimycin **2** based on a high-yield, ring-forming aminomercuration (Scheme

1.33). Starting from bromosugar **250**, reductive ring opening and reductive amination gave the aminoalkene **252**, which underwent aminomercuration to furnish an N-heterocycle ring **254**. After reductive oxygenation and deprotection, 1-deoxynojirimycin was obtained. 1-deoxymannojirimycin could be synthesized by the similar procedure.



Scheme 1.33 Syntheses deoxynojirimycin and deoxymannojirimycin based on a high-yield, ring-forming aminomercuration: a) Zn dust, 19:1 n-propyl alcohol:water, benzylamine, $NaBH_3CN$, 91%; b) $Hg(CF_3COO)_2$, anhydrous THF; 61%; c) $NaBH_4$-DMF-O_2, 70%

Hirai et. al. [52] reported a synthesis of 1-deoxymannojirimycin with a Palladium-catalyzed cylization of urethanes. D-mannitol was transformed to a urethane, which under catalysis of $PdCl_2$, gave the N-heterocycle ring. Although it involved many functional transformation steps from D-mannitol to the urethane, the subsequent Pd-catalyzed azasugar ring formation was important. Knight et. al. [53] also reported a deoxymannojirimycin synthesis based on Pd-catalyzed N-heterocycle ring formation. The latter was further transformed by epoxidation and dihydroxylation to form an azasugar

structure. Alkene metathesis has been also used to furnish the N-heterocycle structure in the synthesis of azasugars [54-58]. The nitrogen functionality itself does not participate in the metathesis. However, it could be relatively easily installed in the early stage of the synthesis. The resulted alkene could be easily functionalized by epoxidation, dihydroxylation etc. Therefore the alkene metathesis became a powerful methodology of azasugar synthesis, especially for fused-ring azasugars.

Enzymatic approaches have also been employed in the synthesis of azasugars [59-67]. In these enzymatic or chemoenzymatic syntheses, aldolases were the enzymes most often used. For example, when azide-bearing enzyme substrate 3-azido-2-hydroxy-propanal was subjected to aldolase catalyzed reaction with dihydroxyacetone phosphate (DHAP), the C-C bond formation was catalyzed to form a nitrogen-contained carbohydrate with high stereoselectivity. Subsequent reductive amination generated the azasugars. Enzymatic synthesis towards azasugar could be relatively simple. However, it still involved chemical manipulation before and after the enzymatic step.

In summation, azasugar synthesis has been extensively researched in the past two decades and many synthetic strategies have been employed. Most of the syntheses of azasugars are based on carbohydrates or other chirality-rich molecules. To introduce the nitrogen function, several methodologies have been widely used. These include using azide as an intermediate, reductive amination and N-alkylation. The synthesis of azasugars starting from achiral or chirality-deficient molecules has also been extensively explored. Dihydroxylation and epoxidation have been broadly used to introduce new chiralities. The stereoselectivity have been achieved by both substrate control and reagent control. Some other synthetic methodologies such as Pd-catalyzed heterocyclization and

ring-closing alkene metathesis have also been adopted in azasugar synthesis. Because of their high selectivity, low requirement for protecting groups or activation and the mild conditions under which they occur, enzymatic approaches to azasugars have also been utilized. With all the achievements, there has been no universal synthetic methodology of azasugars. Each methodology has its own advantages and disadvantages. This becomes especially true as more and more new azasugar structures are discovered and studied chemically and biochemically. There is still much to be done in the synthetic chemistry of azasugars.

1.4 The structure-activity relationship (SAR) of azasugars as glycosidase inhibitors and modified azasugars

Ever since the discovery of azasugars as glycosidase inhibitors, the structure-activity relationship (SAR) has attracted much attention. Understanding the SAR could help to obtain deeper insight into the glycosidation mechanism. Furthermore, given the difficulty of synthesizing various compounds with azasugar structure, it is necessary to deeply explore the SAR and discover the possible structure features leading to better inhibition and lower toxicity. Apparently, it can help to rationally design and synthesize modified azasugars as potential drug candidate. Many reviews have been published on glycosidase mechanisms [1-10] and glycosidase inhibitions [68-76]. Here we describe the structure-activity relationship (SAR) of azasugars as glycosidase inhibitors and some modifications based on the SAR towards new azasugar inhibitors.

1.4.1 Shape and charge of azasugar glycosidase inhibitors as transition state analogues

As mentioned earlier, the inhibition mechanism of azasugars has long been believed to due to their resemblance with glycosidation transition state (Figure 1.3). The protonated form of azasugars has a positive charge on the ring nitrogen, which is much like the partial positive charge on the oxocarbenium-ion-like transition state. On the other hand, these azasugars have sp3-hybridized anomeric carbon atom and chair conformation. Logically, these inhibitors do not well resemble the shape of the oxycarbenium ion, which is sp2-hybridized at the anomeric center. There are some other glycosidase inhibitors with sp2-hybridized anomeric carbon, such as glyconolactones. Apparently, these inhibitors are better shape mimic of glycosidation transition state (Figure 1.5).

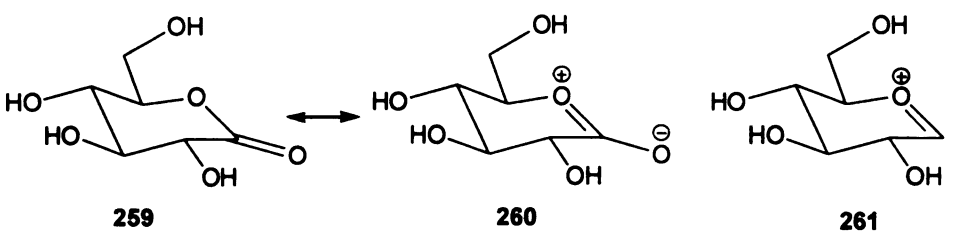


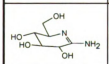
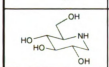
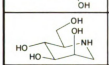
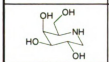
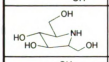
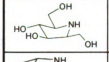
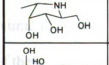
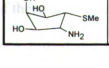
Figure 1.5 Gluconolactone as glucosidase inhibitor

D-*Glucono*-1,5-lactone **259** is a relatively strong inhibitor of β-glucosidases [77,78]. Leeback [79] ascribed this inhibition to the stereochemical similarities between the lactone **259** and the oxocarbenium-ion **261** based on their half-chair conformation. Reese et. al. [80] reasoned that by charge delocalization, the polar oxy group in **260** also partially mimics the positive charge of the oxycarbenium ion intermediate. Although the relative importance of shape and charge in the inhibition mechanism has never been

unambiguously established, the importance of charge was confirmed by the strong inhibition of azasugars towards glycosidases.

On the other hand, it would be beneficial for the inhibition if the inhibitor could resemble the transition state by both the charge and the shape. Wong et. al. [69,70] compared the features of a set of azasugar inhibitors with their inhibition constants (K_i) (Table 1.3).

Table 1.3 Inhibition Potencies of Various Azasugars (μM) (From Look, G. C., Fotsch, C. H. and **Wong, C.** H., *Acc. Chem. Res.*, **1993**, 26, 182-90)

	Sweet almond β-gluco-sidase	Yeast α-gluco-sidase	Jack bean α-manno-sidase	Green coffee bean α-galacto-sidase	Bovine liver β-galacto-sidase	*Aspergil-lus niger* β-xylo-sidase	Bovine kidney α-L-fuco-sidase
	8 ± 5		9 ± 1	8 ± 5			
	18	8.7	400	NI			
	5300		68				30 ± 10
	NI	NI	NI	0.0053	NI		
	7.8	3.3	NI	NI		250	
	19	2.8	3100	50			910 ± 20
							1.4
			0.048		> 100		

Deoxynojirimycin analogs mimic the charge by the protonated ring-nitrogen. The placement of the hydroxyl groups is also very important because of the steric requirements to bind in the enzyme active site [81]. Thus, deoxynojirimycin is a good inhibitor towards α- and β-glucosidase but has weak or no inhibition towards mannosidase and galactosidase. Correspondingly, deoxymannojirimycin and deoxygalactonojirimycin are selective inhibitors towards mannosidase and galactosidase, respectively. Moreover, the inhibition of mannosidase by deoxynojirimycin and of glucosidase by deoxymannojirimycin was found although it was not as strong as when the stereochemistry was totally matched. This suggested that the matched C-2 hydroxyl orientation is not strictly necessary for glycosidase inhibition. This could be explained by the half-chair conformation of the oxycarbenium ion intermediate in glycosidation.

The amidine inhibitors are relatively more representative of the flattened half-chair resemblance. Because the hydroxyl group orientation of this amidine inhibitor only matches the gluco- configuration, only strong inhibition toward glucosidase would be expected. In fact, this amidine inhibitor (Table 1.3) is a very strong inhibitor of several glycosidases, including not only glucosidase, but also mannosidase and galactosidase. This also suggests that the matching configuration is not strictly necessary for good inhibition. To overcome some drawbacks of amidine inhibitors such as unstability and complicated synthesis, some five-membered ring azasugar inhibitors were also developed. Similarly, these inhibitors all have a half-chair like conformation and they could also mimic the charge of oxycarbenium ion by the nitrogen charge. Although the ring structure of these five-membered ring azasugar inhibitors is not directly related to that of substrates, they turned out to be good inbibitors towards both α- and β-glucosidases. When the

hydroxyl group orientation of these 5-membered ring azasugars is compared with the substrate and deoxynojirimycin, they are more like α-D-fructo-furanose analogues. The flatter five-membered ring is believed to closer mimic the half-chair conformation found in the oxocarbenium-like transition state, resulting in good inhibition [73]. Moreover, these five-membered ring inhibitors showed broad-spectrum inhibition towards different enzymes. This suggested the relatively greater importance of the half-chair conformation than the correct hydroxyl group orientation.

1.4.2 Substitution effects of azasugars as glycosidase inhibitors

To find out the N-substitution effect on the inhibition properties of azasugars, the α-glucosidase inhibitory activity was measured in HepG2 cells for a series of N-alkylated deoxynojirimycin [68, 82]. When the ring nitrogen of deoxynojirimycin was substituted with a straight alkyl (or aryl) chain, the inhibition of α-glucosidase was increased. N-methyl-, N-butyl-, N-pentyl- and N-benzyl-deoxynojirimycin showed higher activity than the unmodified deoxynojirimycin. When the alkyl chain was extended to N-decyl-deoxynojirimycin, the detergent-like properties were observed. Therefore clear inhibition was only observed when the concentration was 5-10 times lower. The increase on inhibition by N-alkylation was ascribed to the conformation change of the C-6 hydroxyl group (Figure 1.6). While deoxynojirimycin prefers a gauche-trans conformation, the N-alkylated derivatives prefer a gauche-gauche conformation. Interestingly, the C-1 hydroxyl group of castanospermine has a similar orientation correspondent to the C-6 hydroxyl group of N-alkylated deoxynojirimycin. Castanospermine inhibits α-glucosidase I more strongly than α-glucosidase II. It was also observed that N-alkylation of deoxynojirimycin induces a shift in specific inhibition of purified gludosidase from α-

glucosidase II to α-glucosidase I [83, 84]. These discoveries suggested that the conformation of C-6 hydroxyl group plays an important role in the interaction with glycosidases.

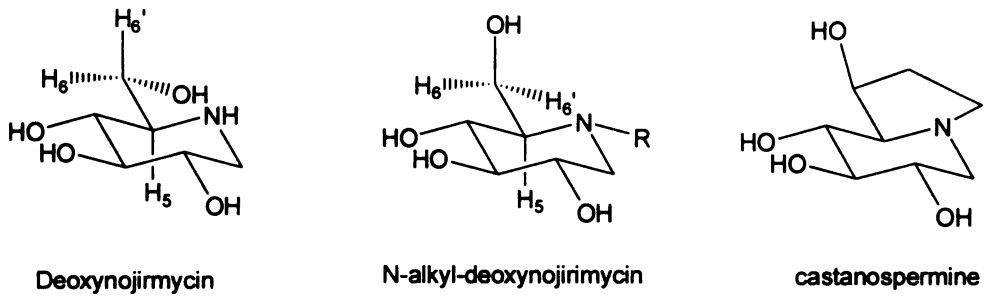


Figure 1.6 Preferred conformation of deoxynojirimycin, N-alkyl-deoxynojirimycin and castanospermine (Figure abstracted from: van den Broek, L. A. G. M., Vermaas, D. J., Heskamp, B. M., van Boeckel, C. A. A., Tan, M. C. A. A., Bolscher, J. G. M., Ploegh, H. L., van Kenenade, F. J., de Goede, R. E. Y. and Miedema, F., Recueil des Travaux Chimiques des Pays-Bas, **1993,** *112*, 82-94)

When the branching of the N-alkyl side chain was introduced into the deoxynojirimycin modification, decreased inhibitory activity of glucose trimming was observed. N-isobutyl-deoxynojirimycin was less active than N-butyl derivative, while the N-(cycolpropylmethyl)-deoxynojirimycin was almost inactive. These results suggested that branching of the alkyl chain might result in a sterically less favorable configuration.

By comparing the hydroxyl group orientation of all the biologically important glycopyranoses, it is apparent that the 3-OH is the only stereochemically conserved position. Naturally, its role in the glycosidation process is of interest. The 3-O-methyl-deoxynojirimycin and deoxymannojirimycin was synthesized to clarify its biological role [68]. The inactive nature of the 3-O-methyl derivatives as inhibitors of corresponding glycosidase suggested its importance for binding of deoxynojirimycin and

deoxymannojirimycin to the enzymes, presumably through an interaction with a hydrogen bond acceptor.

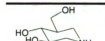
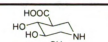
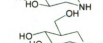
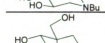
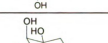
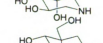
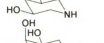
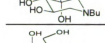
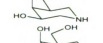
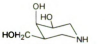
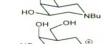
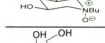
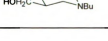
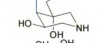
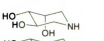
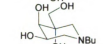
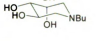
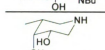
The ester derivatives of azasugars have also been made to act as pro-inhibitors. N-Benzyl-6-O-butylryl-deoxynojirimycin and N-decyl-6-O-benzoyl-deoxynojirimycin showed activity comparable to that of their respective parent N-alkyl derivatives [82]. However, N-benzyl-tetra-O-acetyl-deoxynojirimycin and N-butyl-tetra-O-acetyl-deoxynojirimycin showed no inhibitory activity towards α-glucosidase. When no free hydroxyl group is present, the intracellular hydrolysis of ester pro-inhibitors may be slowed down greatly therefore no inhibition was shown. On the other hand, 6-O-butyryl-castanospermine was shown to be 20 times more active in vitro than unmodified castanospermine [85].

1.4.3 1-N-iminosugars as potent and selective inhibitors

In our previous discussion about glycosidase mechanism, the oxocarbenium cation was purported to be the transition state. The positive charge is delocalized between anomeric position and the ring oxygen. Wong et. al. [86] carried out a molecular mechanics (MM2) modeling study of the β-glucosidase reaction in terms of conformation and charge distribution. They found that the positive charge was generated at the anomeric position rather than at the ring oxygen. On the other hand, by molecular electrostatic surface analysis of nucleoside hydrolysis, Schramm et. al. [87] concluded that the highly localized charge between the ring heteroatom and the anomeric position is not favored. Despite the controversy, it is apparent that the anomeric position would bear substantial positive charge in the glycosidation transition state. It is also believed that the

retaining β-glucosidase mechanism includes a covalent glycosyl-enzyme intermediate (Figure 2 b). Therefore 1-N-iminosugars were developed as a transition state analog mimicking the positive charge at the anomeric positon. Ichikawa et. al. [88] synthesized a series of 1-N-iminosugar derivatives and evaluated their inhibitory potencies towards different enzymes (Table 1.4). Generally, the 1-N-iminosugar with gluco- and galacto-configurations were very good inhibitors of the corresponding β-glycosidase, while they showed much weaker inhibition of the corresponding α-glycosidase. This selectivity was expected since the anomeric charge is more important in transition state or covalent intermediate of β-glycosidation. Furthermore, both of them showed a weaker inhibition towards the β-glycosidase with the other configuration, which indicates that charge mimic was more important for a transition state analog in this situation. However, when both charge and configuration were not matched well, almost no inhibition was found.

Table 1.4 Inhibitory Potencies of 1-N-Iminosugars (IC_{50}, μM) (Table adapted from Ichikawa, Y., Igarashi, Y., Ichikawa, M. and Suhara, Y., *J. Am. Chem. Soc.* **1998**, 120, 3007-18)

Inhibitor	glycosidases						Inhibitors	glydosidase					
	β-glc	α-glc	β-gal	α-gal	α-man	α-fuc		β-glc	α-glc	β-gal	α-gal	α-man	α-fuc
	0.1	150	270	>2000	250	>1000		>1000	>1000	>1000	>1000	>1000	>1000
	38	140	50	nd	nd	nd		>1000	>1000	>1000	>1000	>1000	>1000
	6.0	380	>5000	>5000	>2000	900		8.8	>1000	40	>1000	360	>1000
	850	1500	nd	nd	nd	>1000		530	>2000	43	725	nd	>1000
	0.19	>2000	0.012	200	>2000	>1000		500	1000	300	>1000	>1000	370
	95	>2000	5	45	nd	>1000		150	nd	300	>1000	>1000	>1000
	160	nd	9.5	90	nd	>1000							
	420	>2000	17.5	610	>2000	>1000		100	>2000	50	70	>1000	450
	400	nd	nd	nd	nd	>1000		200	>1000	>1000	>1000	>1000	80
	500	>1000	>1000	>1000	>1000	26		8.0	>1000	>1000	>1000	>1000	>1000
	80	>1000	>1000	>1000	>1000	270							

Bols et. al. [89-91] also synthesized and tested some 1-azasugars, disaccharide derivatives of 1-azasugars and some diazasugars (azafogamines). They found that 1-azasugar were strong glycosidase inhibitors and particularly strong inhibitors of β-glycosidase. Their protonated form being transition state analogs also explained the inhibition. After protonation, they generally mimic the anomeric charge of the transition state. An argument was made about the azasugar protonation tendency when the pKa of azafagomine (3.9) and the pKa of the protonating acid in β-glycosidase (6.7) were compared. The enzyme might stabilize the protonated form and actually increase the basicity of the inhibitors. Furthermore, the direct observation of the protonation state of a 1-N-iminosugar derivative upon binding was reported by Davies et. al. [92, 93] (Figure 1.7). The 3-D structure, combined with the pH dependence of inhibition, gave more evidence of the proposed glycosidase mechanism.

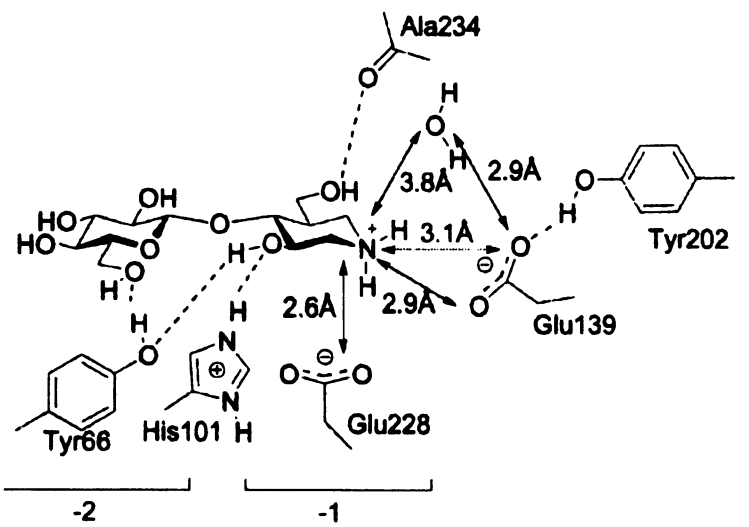


Figure 1.7 Schematic representation of the interactions observed between Cel5A and the cellobio-derived isofagomine. All hydrogen atoms shown have been observed experimentally. Only the -1 subsite interactions are shown in detail. Distances around N1 are indicated. (Varrot, A., Tarling, C. A., Macdonald, J. M., Stick, R. V., Zechel, D. L., Withers, S. G. and Davies, G. J., *J. Am. Chem. Soc.* **2003**, 125, 7496-7)

1.4.4 Aromatic ring-fused azasugars as glycosidase inhibitors

Besides the charge distribution, the effect of the ring conformation (chair versus half-chair) has been always an interesting topic. Vesella et. al. [75, 94-96, 101-103] and Tatsuta et. al. [97-100] synthesized a series of aromatic ring-fused azasugars to explore this problem (Figure 1.8).

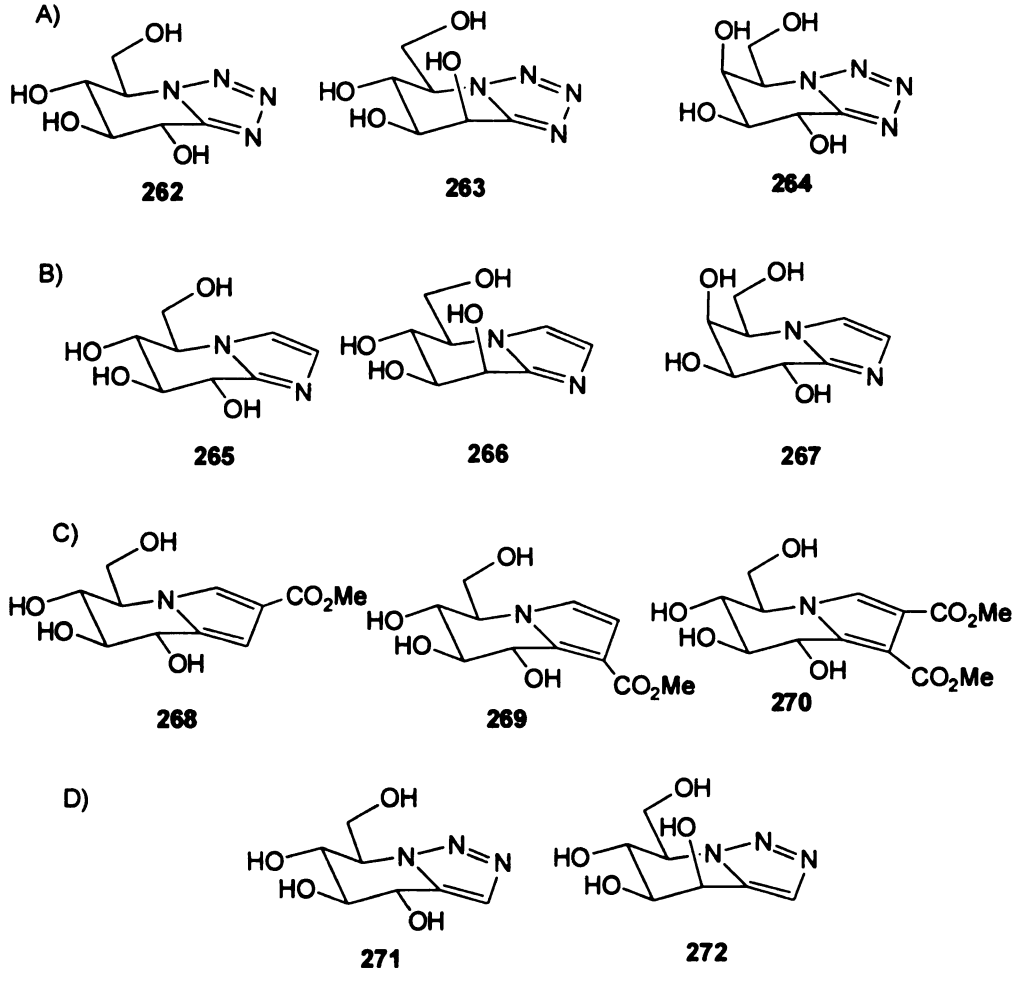


Figure 1.8 Some azasugars fused with A) tetrazoles; B) imidazoles; C) pyrroles; D) 1,2,3-triazoles

The tetrazole-fused azasugars were shown to be half-chairs by X-ray analysis. They are relatively stable in solutions over a pH range of 1-14. The measurement of

inhibition activities was shown to be similar with the corresponding glycono-1,5-lactones. Their configurational selectivity was also tested for the gluco-and manno-tetrazoles towards glucosidases and mannosidases [94-96]. Although all the enzymes were inhibited by both tetrazoles, the tetrazoles with the correct configuration was shown to be much more effective. Also, the inhibition of the α-glycosidases was shown to be much weaker than that of the β-glycosidases. The results showed the configurational selectivity of these glycosidases and inhibitors.

The imidazoles with gluco-, manno- and galactono- configuration were also subjected to inhibition activity measurement and the results are shown in Table 1.5 [75, 97-100]. Compared with the tetrazoles, the imidazoles were found to be more potent inhibitors of β-glycosidases. They also show little activity towards α-glucosidase. To compare with the imidazole series, pyrroles fused azasugars were also synthesized and subjected to the inhibition activity studies [101-102]. These compounds were shown to be generally very weak inhibitors.

Table 1.5. IC_{50} values [μM] of the annulated imidazoles with gluco-, manno- and galacto-configurations. (Table adapted from Heightman, T. D. and Vasella, A. T., *Angew. Chem. Int. Ed.*, **1999**, 38, 750-70)

Enzyme(Source)	Gluco-	Manno-	Galacto-
α-glucosidase (bakers' yeast)	105	>500	>500
β-glucosidase (almond)	0.7	17.5	0.5
β-mannosidase (snail)	300	0.11	370
β-galactosidase (E. coli)	>500	>500	0.008

Vasella et. al. suggested an in-plane protonation hypothesis to explain these results [75] (Figure 1.9). With this hypothesis, the N-1 of the tetrazole would be very important in the inhibition. Therefore, 1,2,3-triazoles fused-azasugar were synthesized and tested of the glycosidase inhibition [103]. The 1,2,3-triazols was shown to possess very similar conformation to their tetrazole analogues. However, the inhibition of these triazoles was found to be much weaker than tetrazoles, supporting the in-plane or lateral protonation at N-1 of the tetrazoles.

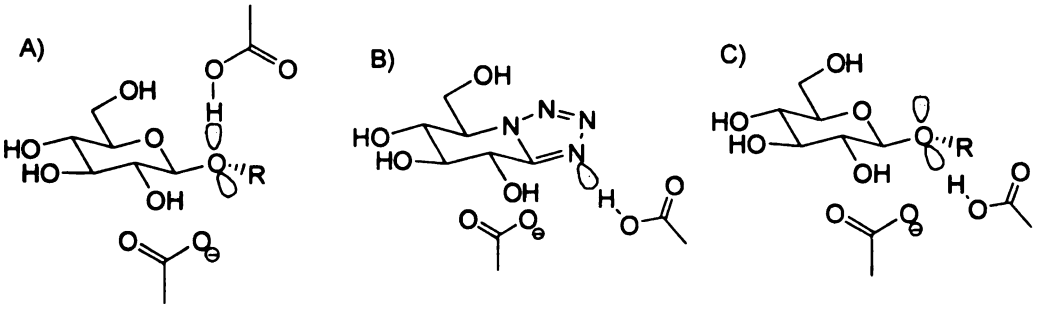


Figure 1.9 Proposed direction of protonation A) of a glucoside perpendicular to the plane of the ring and B) and C) of gluco-tetrazole and a glucoside in the plane of the ring

1.5 Summary

Glycochemistry and glycobiology have been developing rapidly in the last decade. Azasugars as glycosidase inhibitors has attracted both academic and industrial interest. Many synthetic methodologies, starting from carbohydrate or non-carbohydrate, have been reviewed in several categories. The structure activity relationship of azasugar as glycosidase inhibitors has been briefly discussed.

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Chapter 2

NBS-Initiated Dioxonium Cation Rearrangement and Applications of the Selective Bromination and Chirality Manipulation of Carbohydrates

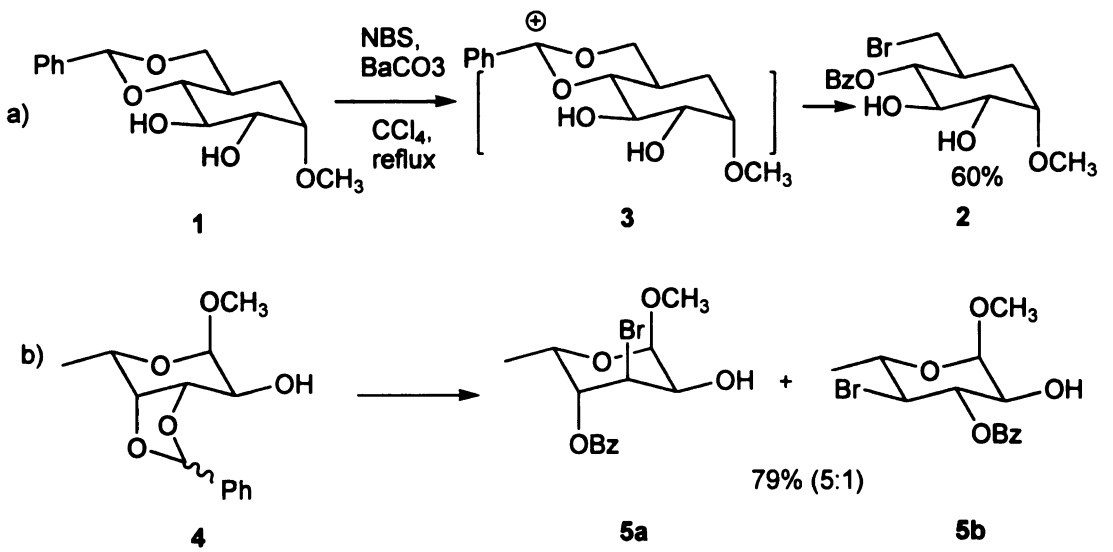
ABSTRACT

In the attempt at NBS-bromination of benzylidene acetal protected D-glucoheptonolactone derivative, a dioxonium cation rearrangement involving neighboring pivaloyl group was discovered. The rearrangement mechanism was further explored. Based on the experimental results, a new methodology of carbohydrate structure chirality manipulation was developed. A series of synthetically useful selectively brominated and protected D- and L-aldonolactone derivatives were synthesized. This methodology was further applied in the synthesis of an orthogonally protected bromobutanetriol as a chiral building block.

2.1 Hanessian-Hullar reaction and dioxonium cation rearrangement

In the 1960's, Hanessian and Hullar [1-3] independently discovered that when some benzylidene acetals were treated with N-bromosuccinimide (NBS) in carbon tetrachloride, regioselective opening of the acetal ring occurred. In this reaction, usually the less hindered position is brominated while the other position becomes benzoyl protected, as shown in Scheme 2.1 a. In the cleavage of 4,6-O-benzylidene acetals of a typical hexopyranoside **1**, the product formed is not the 4-bromo, 6-benzoate (via the more stable secondary carbocation). The 6-bromo 4-benzoate **2** is formed instead. One

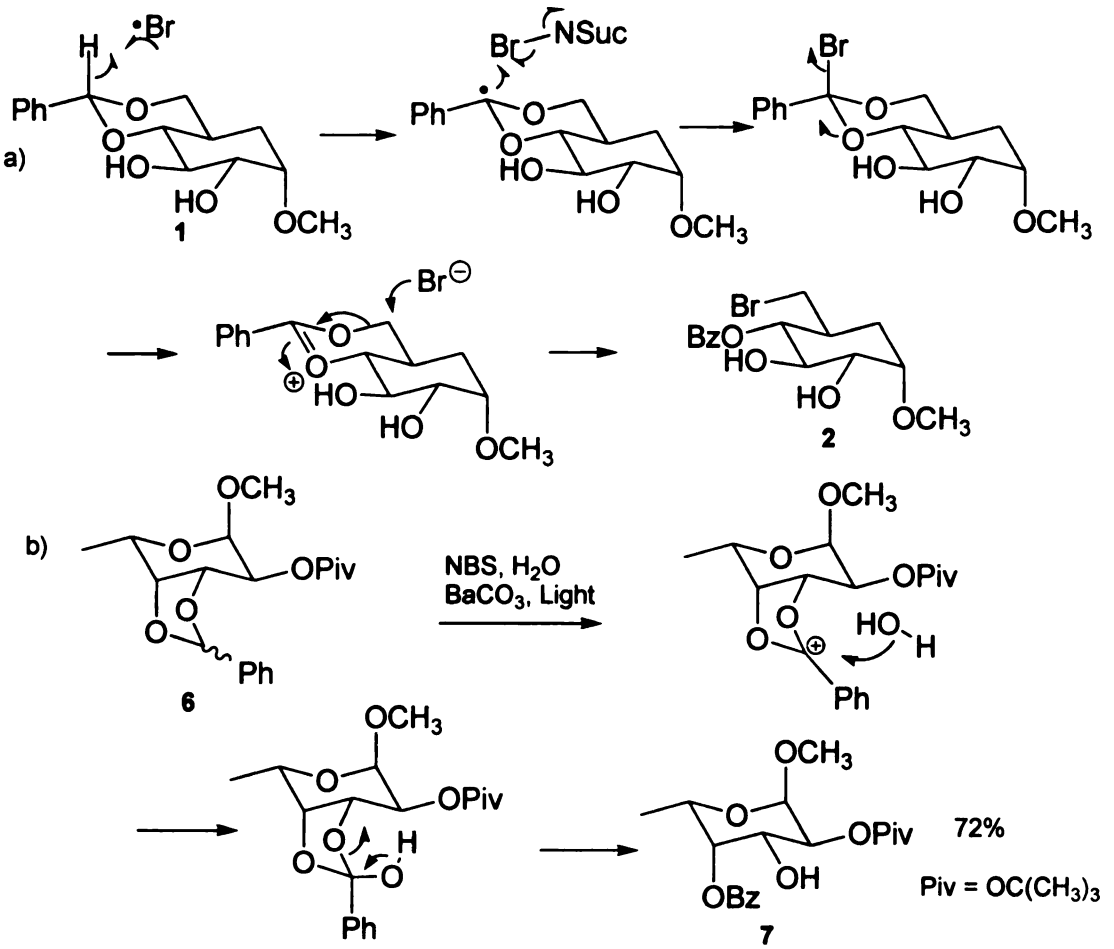
feature of the reaction is the extent to which its outcome is dominated by sterics rather than by electronic consideration. The formation of a cyclic 1,3-dioxonium species **3** is the key feature of the NBS oxidation of acetals. This reaction also works for dioxolane benzylidene acetal and generally shows fairly good regioselectivity towards the formation of an axial bromo group. NBS treatment of **4** therefore preferentially yielded **5a** instead of **5b**, although **5b** should be more favored thermodynamically (Scheme 2.1 b) [4].



Scheme 2.1 The regioselective cleavage of benzylidene acetals with NBS (From Hanessian, S.; Pleassas, N. R. *J. Org. Chem.* **1969**, *34*, 1035; Bundel, D. R.; Josephson, S. *Can. J. Chem.* **1978**, *56*, 2686.)

The mechanism is generally believed to go through a radical initiation and benzoxonium cation formation process (Scheme 2.2 a). If water is present [5], alcohol instead of the bromo-compound is formed (Scheme 2.2 b). The regioselectivity in this case usually favors equatorial free hydroxyl group formation. Compound **7** was selectively synthesized by treatment of **6** with NBS. Named as the Hanessian-Hullar reaction, the oxidative cleavage of benzylidene acetals with NBS not only deprotects the acetal to form another protection group, but also functionalizes the carbohydrate structure.

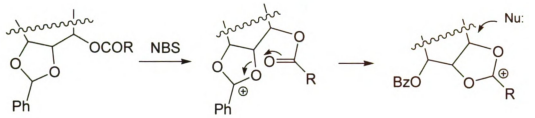
It has become an important deprotection and bromination methodology in synthetic organic chemistry.



Scheme 2.2 The mechanism of Hanessian-Hullar reaction (a) and the water-dependent NBS regioselective cleavage of benzylidene acetals (b) (Hanessian, S.; Pleassas, N. R. *J. Org. Chem.* **1969**, *34*, 1035, 1045 and 1053)

If there is an active neighboring group, i.e. esters, etc, the benzoxonium cation generated by oxidative H-abstraction may rearrange to form another dioxonium cation, which will lead to different regioselectivity of nucleophilic attack and therefore different products (Scheme 2.3). Although this phenomenon was discovered [6-8] two decades ago, it has not been developed and applied to the synthetic chemistry. Presumably, this is

because that it is difficult to design and control the rearrangement to prepare desired molecular structure.

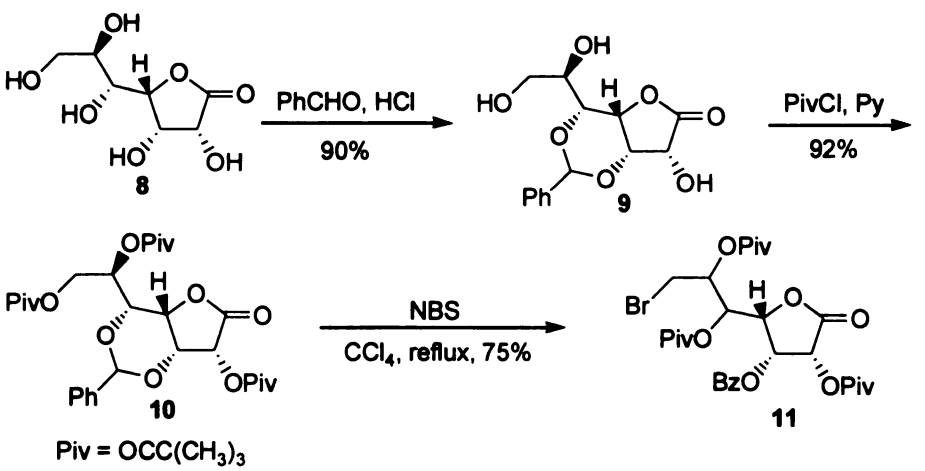


Scheme 2.3 The concept of benzoxonium cation rearrangement

2.2 Cascade dioxonium rearrangement of glucoheptanolactone benzylidene derivative under Hanessian-Hullar reaction conditions

In our research towards azasugar synthesis, D-*glycero*-D-*gulo*-heptono-1,4-lactone **8** was used as a cheap starting material as a 7-carbon sugar lactone bearing 5 chiral centers. The 3,5-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone **9** was easily prepared in about 90% yield by treating the lactone with benzaldehyde and concentrated hydrochloric acid. This 3,5-O-benzylidene glucoheptanolactone **9** was then further protected by treatment with trimethylacetyl chloride in pyridine. The benzylidene group of the fully protected 3,5-O-benzylidene-2,6,7-tri-O-pivaloyl D-*glycero*-D-*gulo*-heptono-1,4-lactone **10** was then subjected to NBS-cleavage. Our primary goal was to develop a way of introducing a bromo group at the 5-position of the carbon skeleton; however, after separation by chromatography, the proton NMR spectrum of the main product from the NBS oxidation of **10** indicated that the benzylidene ring had undergone the unexpected rearrangement to form a benzoate ester (^{1}H signals at 7.41-7.48 ppm (2H, m), 7.56-7.62 ppm (1H, m) and 7.91-7.95 ppm (2H, m) and ^{13}C signal at 164.70 ppm, but it also indicated that the position of bromination was the primary position by showing two

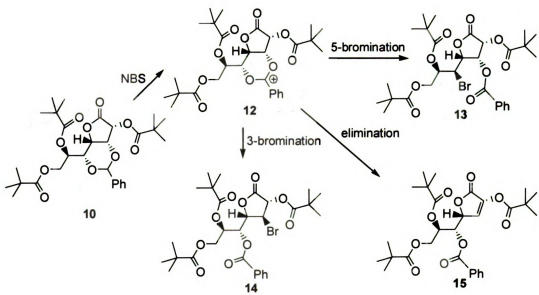
dd signals at around 3.6 ppm. A single ^{13}C signal at 28.8 ppm also showed up and confirmed to be a methylene group by DEPT experiment. Based on these findings, the product was tentatively assigned to be **11** (Scheme 2.4). This structure was further confirmed by HMQC and gCOSY NMR experiments. HMQC was used to confirm the site of bromination as the primary carbon by virtue of the connectivity of both proton signals of the methylene group at around 3.6 ppm to the single ^{13}C signal at 28.8 ppm. Both proton and ^{13}C NMR spectroscopy indicated that all three trimethylacetyl groups were still present. Fast atom bombardment mass spectrometry also confirmed the formula contained one benzoate, one bromo and three trimethylacetyl groups (m/z 626.17 and 628.17).



Scheme 2.4 The NBS treatment of 2,6,7-tri-O-trimethylacetyl-3,5(*R*)-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone **10**

The expected several pathways of NBS cleavage of **10** are illustrated in scheme 2.5. When the benzylidene acetal **10** was treated with NBS, after radical initiation, H-abstraction and heterolytic cleavage of C-Br bond, a benzoxonium cation **12** was formed. According to our expectation, the bromide ion would attack either the C-5 or C-3 to cleave the ring to form 5-bromo compound **13** or 3-bromo compound **14** respectively.

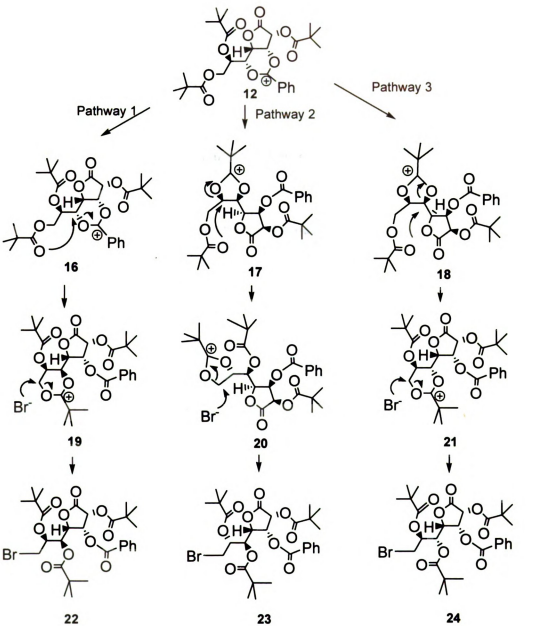
Due to the α-H acidity of lactones, the benzoxonium cation **10** or the 3-bromo compound **14** might undergo β-elimination to form an α, β-unsaturated lactone **15** as a by-product. The latter elimination pathway was expected to dominate if the system was too sterically crowded to allow bromination. Interestingly, less than 10% of the above compounds were found in the product mixture. Instead, the major product **11** has a bromo group two carbon atoms away from the intended site. This unexpected result was further analyzed below.



Scheme 2.5 Expected pathways for NBS cleavage of 3,5-(R)-O-benzylidene-2,6,7-trimethylacetal-D-glycero-D-gulo-heptono-1,4-lactone **10**

There are three possible rearrangement modes that could result in 7-bromination of **10** (Scheme 2.6). The 7-pivaloyl group could have migrated to the 5-position inverting that center (Pathway 1). Alternatively the 6-pivaloyl group could have migrated to the 5 position and the 7-group could have migrated to the 6 position inverting both the 5 and 6 positions (Pathway 2). In the third scenario, the pivaloyl group in the C6 position could participate in the phenyldioxolonium ring cleavage to form a new cylic dioxonium

species with inversion at C5. This species is then ring-opened by the C7 trimethylacetoxy group with a second inversion (net retention) at C5 to form a 1,3-dioxonium species between C5 and C7. This is then cleaved at the unhindered 7-position by bromide to give the 7-bromo product (Pathway 3). In pathway 3, neither the 5 nor the 6 center is inverted.



Scheme 2.6 Three possible pathways that could lead to 7-bromination of **10**. The third scenario is the only one that leads to net retention

It is relatively easy to differentiate between these three scenarios by a consideration of the coupling constants of the H-4, H-5 and H-6 proton signals in the NMR spectrum (Figure 2.1 and Figure 2.2). To facilitate this analysis, 2,3,5,6,7-penta-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **25** was synthesized from D-*glycero*-D-*gulo*-heptono-1,4-lactone **8**. Its reference spectrum was shown in Figure 2.2A. The coupling constants observed reflect the conformation shown which is largely in agreement with published studies on acyclic carbohydrate esters and aldonolactone side chains [9-12] except that in this case, the terminal dihedral is a sickle conformation. In the first scenario, if the C-5 position alone had been inverted, the H-4 / H-5 splitting and the H-5 / H-6 splitting should be affected (Figure 2.2B). The change in the splitting pattern for H-4 should be quite dramatic since it should go from a doublet of doublets (J = ~10 Hz) to a narrow triplet (J = ~3 Hz). The changes in splittings expected in the second scenario where both the C-5 and C-6 positions are inverted are even more dramatic and are shown in Figure 2.2C. In this case both H-4 and H-5 should be narrow triplets (J = ~3 Hz). The actual splittings that were observed are shown in Figure 2.2D. It is clear from this that none of the coupling constants have changed indicating that scenario 3 was the one that had taken place to give product **24**.

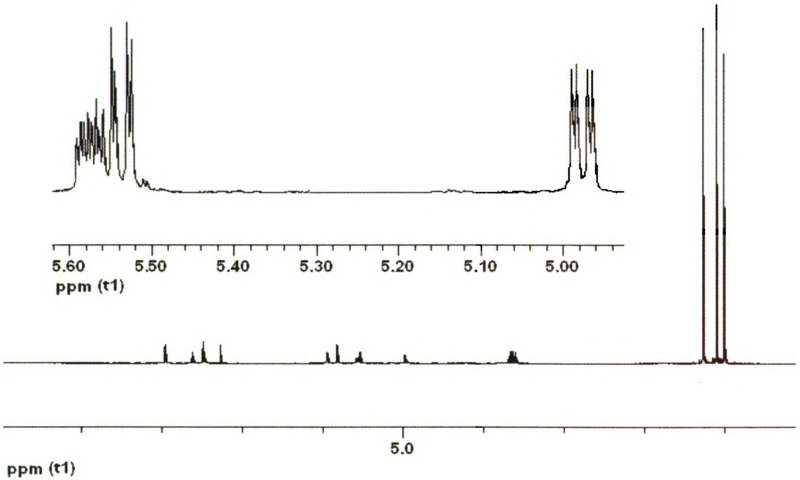


Figure 2.1 The ^{1}H NMR spectrum of 3-O-benzoyl-7-bromo-7-deoxy-2,5,6-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**11**).

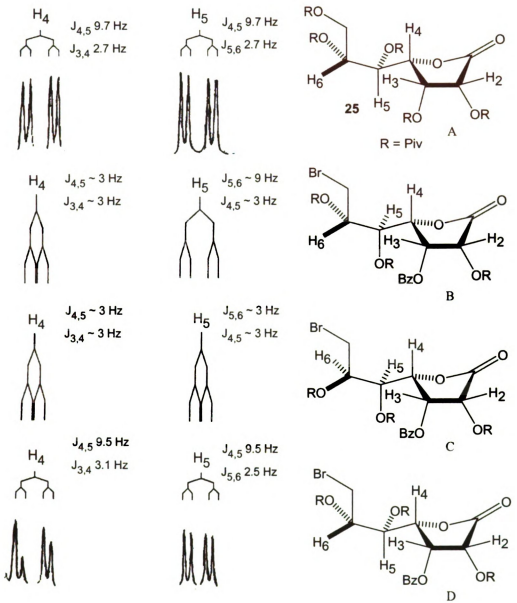


Figure 2.2 Evaluation of coupling constants expected for products formed by the 3 possible rearrangement mechanisms. (A) H-4 and H-5 signals from the reference spectrum of 2,3,5,6,7-penta-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**25**). (B) In the case of inversion at C-5 (Scheme 2.6 pathway 1) only a narrow triplet (J = ~ 3 Hz) is expected for H-4. (C) In the case of inversion at both C-5 and C-6 (Scheme 2.6 pathway 2) the protons at these two positions should yield narrow tripltes. (D) The H-4 and H-5 signals of the product indicating no change in conformation compared to A (Scheme 2.6 pathway 3).

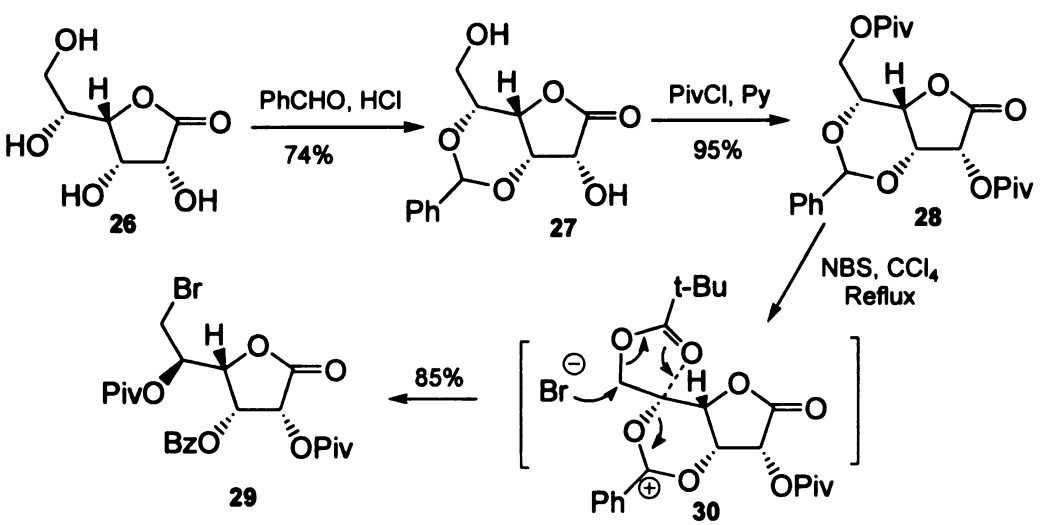
2.3 Selective protection, functionalization and chirality manipulation of sugar lactones employing the NBS-initiated dioxonium cation rearrangement

The cascade carboxonium cation rearrangement discovered in the reaction of NBS with 3,5-O-benzylidene-2,6,7-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **10** showed highly steric-controlled bromination at the primary position. The presence of active neighboring groups and the stereo constraints on the attack of incoming nucleophiles facilitated this rearrangement. Although in this case, all the chiral centers retained their stereo configurations, the mechanism analysis suggested great potential of changing chiralities in other substrate molecules. Chirality manipulation is very important in not only carbohydrate chemistry, but also general synthetic organic chemistry. To explore this possibility, we applied this reaction to other simple, easily accessed and important aldonolactones.

2.3.1 Selective 6-position bromination of protected D-*gulono*-γ-lactone with inversion at C-5

If the side chain of substrate used in the bromination reaction above were on carbon less then bromination of the C6 position and inversion at the C5 carbon atom should be expected based on our rationalization. This would be a very useful synthetic stratage because the inverted center would be "righted" in any bimolecular displacement reaction in which the original D-configuration was required. The model compound for such a study can be visualized by simply shortening one carbon from the carbon chain of our previous starting material D-*glycero*-D-*gulo*-heptono-1,4-lactone **8** while keeping other chiralities unchanged. D-*gulono*-γ-lactone **26** was the actual starting material used

to further explore the NBS-initiated rearrangement. 3,5-O-Benzylidene-2,6-di-O-trimethylacetyl-D-gulono-γ-lactone **28** was easily synthesized by treating D-*gulono*-γ-lactone with benzaldehyde under acidic condition according to the literature [13] followed by pivaloation. The 3,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-*gulono*-γ-lactone **28** was then treated with NBS in carbon tetrachloride under reflux to effect oxidative cleavage of the benzylidene ring. NMR spectroscopy analysis of the major product indicated that 6-position was brominated and the 6-O-pivaloyl group migrated to the 5-position (Scheme 2.7). This structure was unambiguously assigned by ^{1}H, ^{13}C, DEPT and gCOSY spectra. To assign the absolute configuration, a coupling constant analysis was easily carried out. The H-H coupling constants of aldonolactone side chain have long been used to determine the relative stereochemistry [9-12]. The coupling constant between H4 and H5 of 2,3,5,6-tetra-O-pivaloyl-L-*manno*-1,4-lactone were reported to be 9.8Hz [14]. The H-H coupling constant between H4 and H5 ($J_{4,5}$ = 9.6 Hz) (Figure 2.3) of the product clearly showed that 5-position was inverted to form a L-*manno*-1,4-lactone derivative **29**.



Scheme 2.7 Selective 6-position bromination of D-*gulono*-1,4-lactone **26** with inversion at C-

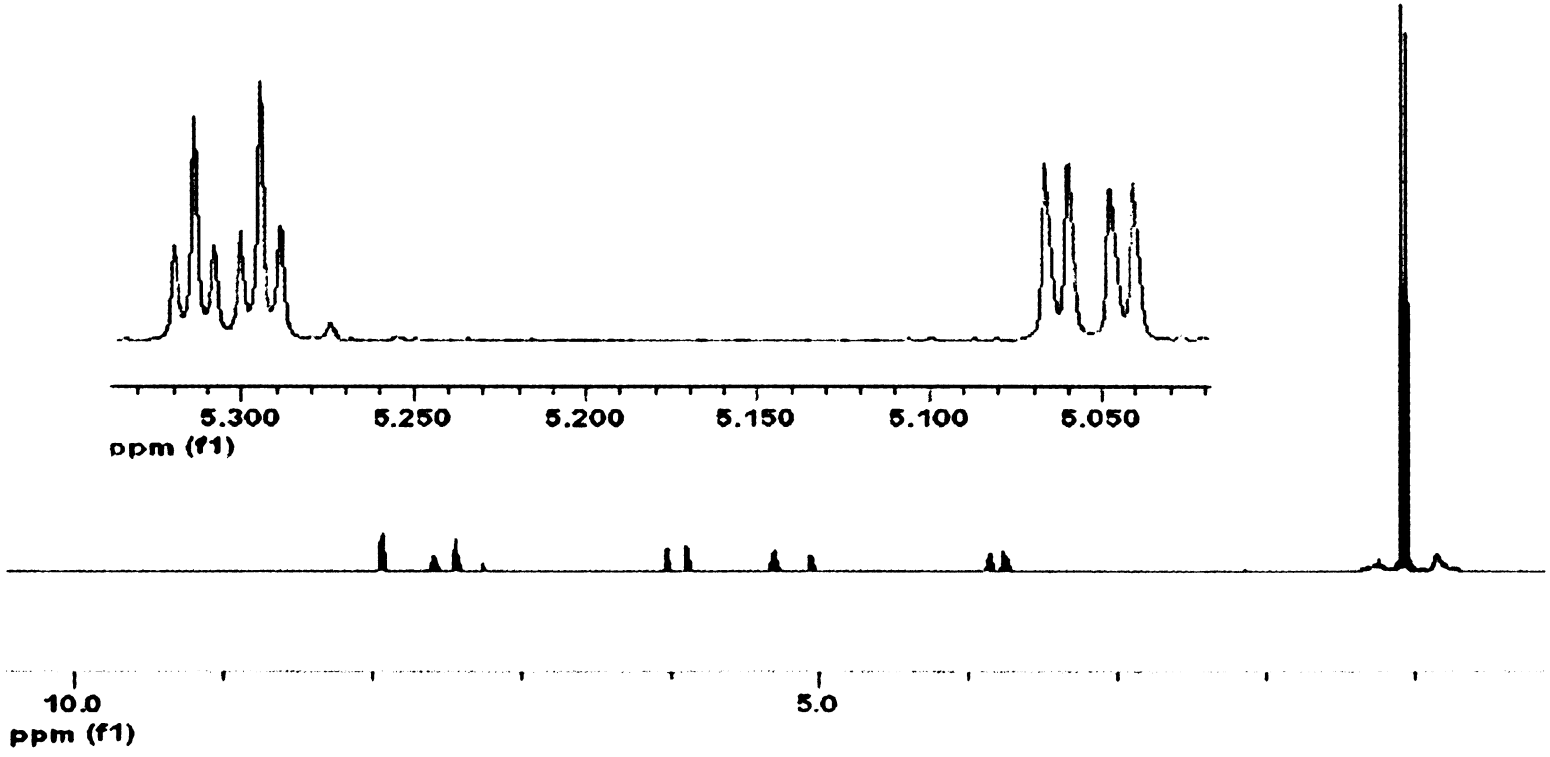


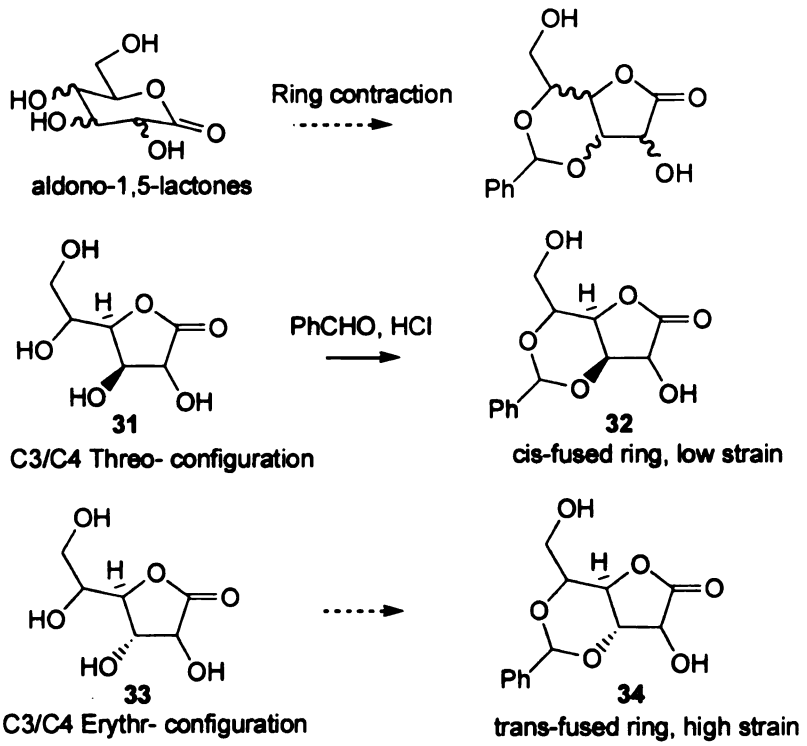
Figure 2.3 The ^{1}H NMR spectrum of 3-O-benzoyl-6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-L-*manno*-1,4-lactone (**29**).

The mechanism of this reaction is believed to proceed through a benzoxonium cation intermediate **30** with a spiral ring structure (Scheme 2.7). Using this method, we made 3-O-benzoyl-6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-L-*manno*-1,4-lactone **29** as a differentially protected L-bromosugar lactone relatively easily. The selective inversion of C-5 position in sugar lactone is always a challenge in the synthesis of L-sugars and azasugars from D-sugars. Oxidation-reduction procedure and Mitsunobu reaction are frequently used to invert the 5-position hydroxyl group. Both of them involve protecting group manipulation. Stereoselectivity issue always accompanies the oxidation-reduction procedure while Mitsunobu reaction generates large amount of phosphorus byproduct. The strategy above used only easy protecting steps and cheap reagents. It also furnished bromo function and inverted 5-position simultaneously. This strategy could be more efficient in certain cases in synthetic chemistry.

2.3.2 Selective bromination and chirality manipulation of sugar lactone derivatives with *gluco-* and *galacto-* configuration

The NBS bromination of 3,5-O-benzylidene-2,6-bis-O-trimethylacetyl-D-*gulono*-γ-lactone **28** illustrates the great potential of this methodology in chirality manipulation of carbohydrate structures. In the mechanism analysis, the primary neighboring ester group attacked benzoxonium cation intermediate **30** to form a spiral ring transition state. The bromide ion attacked the primary group to furnish the product. This stereospecific rearrangement process may generate other important brominated sugar lactone if the stereochemistry of the starting material is changed. Naturally, we want to extend it to other sugar lactones such as D-*glucono*-δ-lactone and D-*galacto*-γ-lactone, which are more often used and more important. The direct preparation of 3,5-O-benzylidene

derivatives of D-*glucono*-δ-lactone and D-*galacto*-γ-lactone using the previous strategy is not possible, according to the analysis of ring structures (Scheme 2.8).

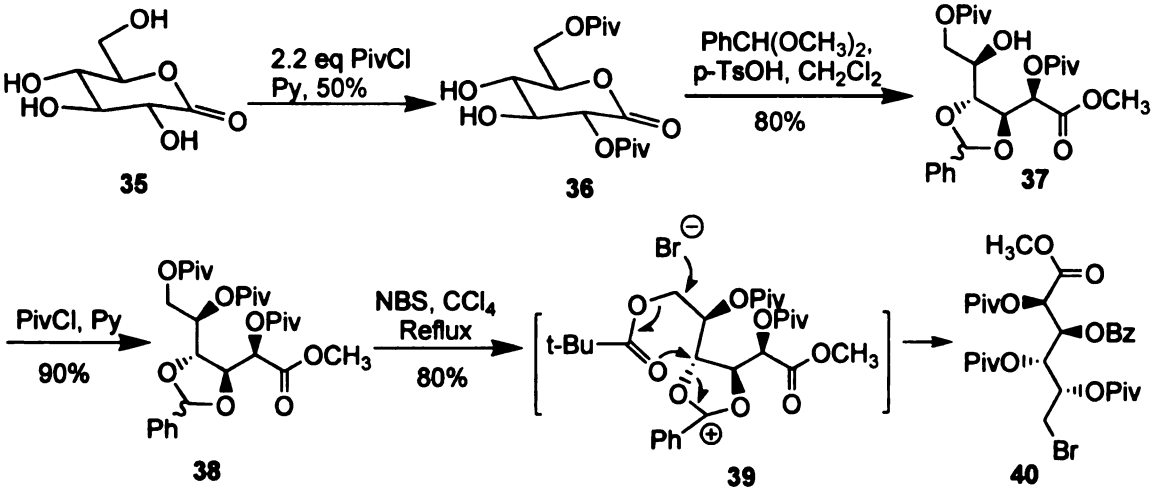


Scheme 2.8 A ring structure analysis for 3,5-O-benzylidene aldonolactones preparation

D-*glucono*-δ-lactone does not have a free 5-hydroxyl group. It has to go through a ring-contraction process, which would not happen under normal benzylidenation conditions. Even for sugar-γ-lactones, only several aldonolactones are eligible for direct 3,5-O-benzylidenation. These include sugar lactones with D- and L-*gulo*, *ido* configurations. The C3/C4 *threo*- configuration is necessary for the formation of a 5,6-cis-fused ring system to avoid the high ring strain of the 5,6-trans-fused ring system. If the aldonolactone has a C3/C4 *erythro*- configuration, it is not possible to prepare the 3,5-O-benzylidene aldonolactone under normal benzylidenation conditions. To overcome this obstacle, a simple strategy of inversion of the order of the protection steps was proposed. Once the 2,6-positions of D-*glucono*-δ-lactone or D-*galacto*-γ-lactone is selectively

pivaloated, it should be possible to open the sugar lactone ring and form a 3,5-O-benzylidene aldonic acid ester through a ring-switch process. These protected 3,5-O-benzylidene aldonic acid ester could serve as good substrates for the NBS-initiated pivaloyl rearrangement and bromination.

The selective protection and functionalization of free hydroxyl groups on aldonolactones has long been explored in the literature [14, 15]. Although the selectivity highly depends on the relative configuration of the aldonolactones and the protecting reagents equivalents usage, the 2- and 6- positions generally show better reactivity. D-*glucono*-δ-lactone **35** was selectively protected at 2- and 6- positions to afford 2,6-di-O-trimethylacetyl-D-*glucono*-δ-lactone **36** by treatment with 2.2 equivalent trimethylacetic chloride in ~ 50% yield (Scheme 2.9). Although the yield was not extremely high due to the competing reaction of other hydroxyl groups, the process was fairly practical because the starting material was very cheap and only recrystallization was needed for separation.



Scheme 2.9 Selective 6-position bromination of protected D-glucono-d-lactone with inversion at C-4 to form methyl 3-O-benzoyl-6-bromo-2,4,5-tri-O-trimethylacetyl-D-galactonate **40**

The 2,6-di-O-trimethylacetyl-D-*glucono*-δ-lactone **36** was then treated with benzaldehyde dimethyl acetal under catalysis by p-toluenesulfonic acid in dichloromethane to form the methyl 3,4-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate **37** as a mixture of two diastereoisomers in a 80% yield. This ring-switch process was of interest because it opened the lactone ring and formed the acetal ring in the same step, which greatly simplified the synthetic process. The methanol that was generated *in-situ* by transacetalation was sufficient to open the lactone ring. This suggested that after 2,6-di-O-pivaloation, the lactone ring strain was substantially increased because of the high steric hindrance of pivaloyl groups. Because of the trans-relationship between the 3- and 4- free hydroxyl groups of 2,6-di-O-trimethylacetyl-D-glucono-δ-lactone, it was not possible to form a 3,5-O-benzylidene acetal between them without opening the lactone ring. However, once the lactone ring was opened to give the acyclic ester, a benzylidene acetal could form between any two of the three free hydroxyl groups. Although 1,3-dioxane formation was commonly observed in the benzylidene acetal protection of a polyol structure, in this case 1,3-dioxolane ring was formed to avoid an axial carbon chain. The 3,4-O-benzylidene was preferred to the 4,5-O-benzylidene due to the 3,4-*threo* and 4,5-*erythro* configuration. This mixture of two diastereoisomers **37** was then further protected by pivaloylation with the normal procedure to yield methyl 3,4-O-benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate **38** also as a mixture of two diastereoisomers, which was ready for NBS oxidative cleavage. In this stage, it was unnecessary to worry about the newly formed chirality of the benzylidene carbon, which made the product two isomers, because it would be eliminated after the NBS oxidation. When methyl 3,4-O-benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate **38** was treated

with NBS in the normal reaction condition, only one major product was obtained as expected with ~ 80% yield. NMR spectroscopy analysis of the product indicated that the 6-position was brominated and the pivaloyl group had migrated. The location of the 3-O-benzoyl group was assigned by ^{1}H chemical shift and gCOSY. To determine the relative stereochemistry, the H-H coupling constants of aldonate chain were used. The small-large-small coupling constant set ($J_{2,3}$2.3Hz, $J_{3,4}$9.3Hz, $J_{4,5}$2.5Hz) matches and only matches the acyclic sugar chain with a *galacto*- configuration [9-12]. The structure was then assigned to methyl 3-O-benzoyl-6-bromo-6-deoxy-2,4,5-tri-O-trimethylacetyl-D-galactonate **40**. The reaction mechanism was believed to go through the benzoxonium cation species **39**, which rearranged to 4,6-(t-butyl-1,3-dioxonium) cation and subsequently attacked by the bromide ion in the primary position to form the final product **40**.

This strategy was then employed to D-*galacto*-γ-lactone **41** (Scheme 2.10). After selective pivaloation of **41**, 2,6-di-O-trimethylacetyl-D-galacto-γ-lactone **42** was prepared in 65% yield. Compound **42** was then treated with benzaldehyde dimethyl acetal. Although both 3- and 5-OH's are free, unlike in the case of 2,6-di-O-trimethylacetyl-D-glucono-δ-lactone, they could not form a 3,5-O-benzylidene directly due to the 3,4-O-*erythro*- configuration. Nevertheless, the ring-switching process occurred smoothly to yield the methyl 4,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-galaconate **43** as a mixture of two isomers in 77% yield. This selectivity was also ascribed to its *galacto*-configuration (3,4-*erythro* and 4,5-*threo*).

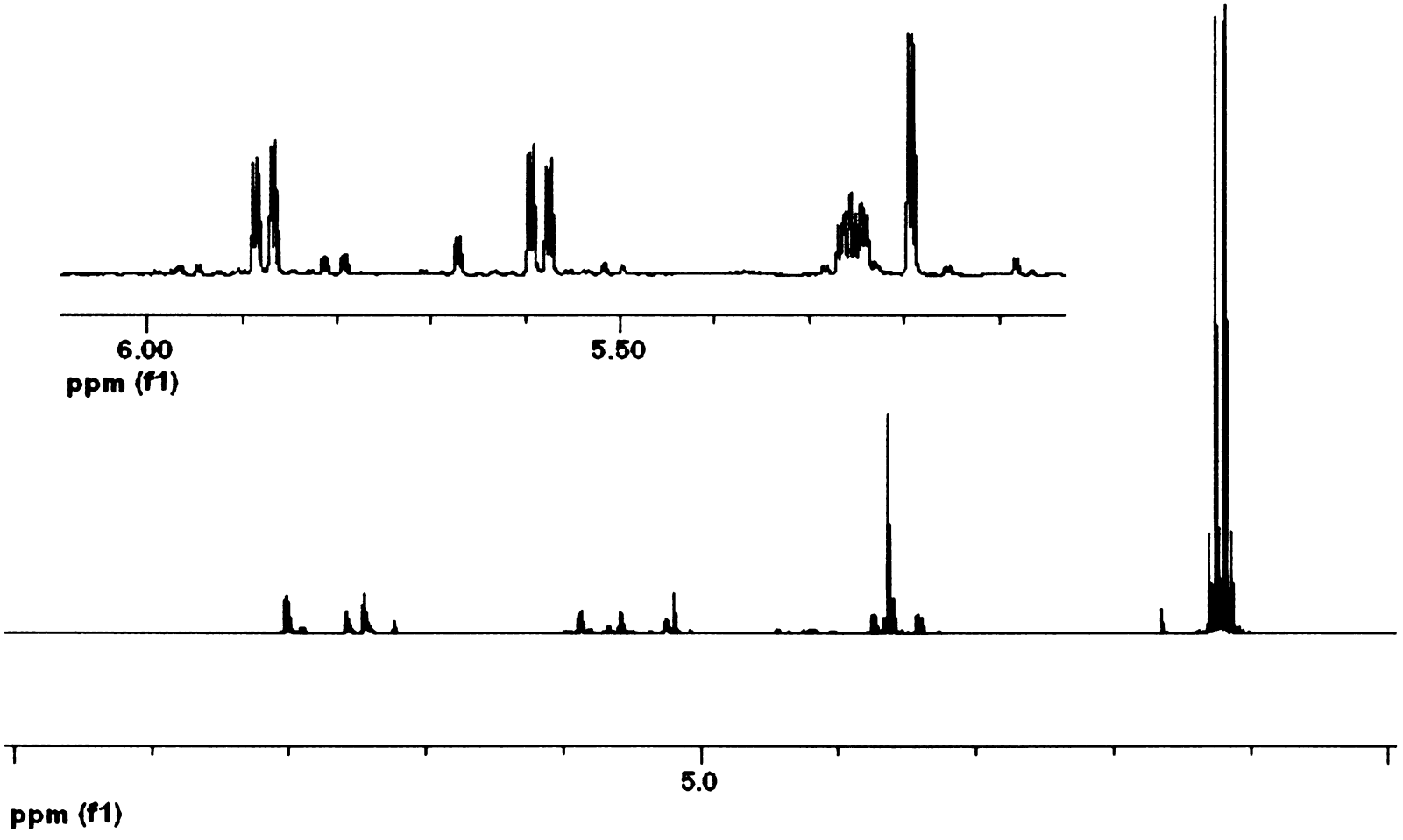
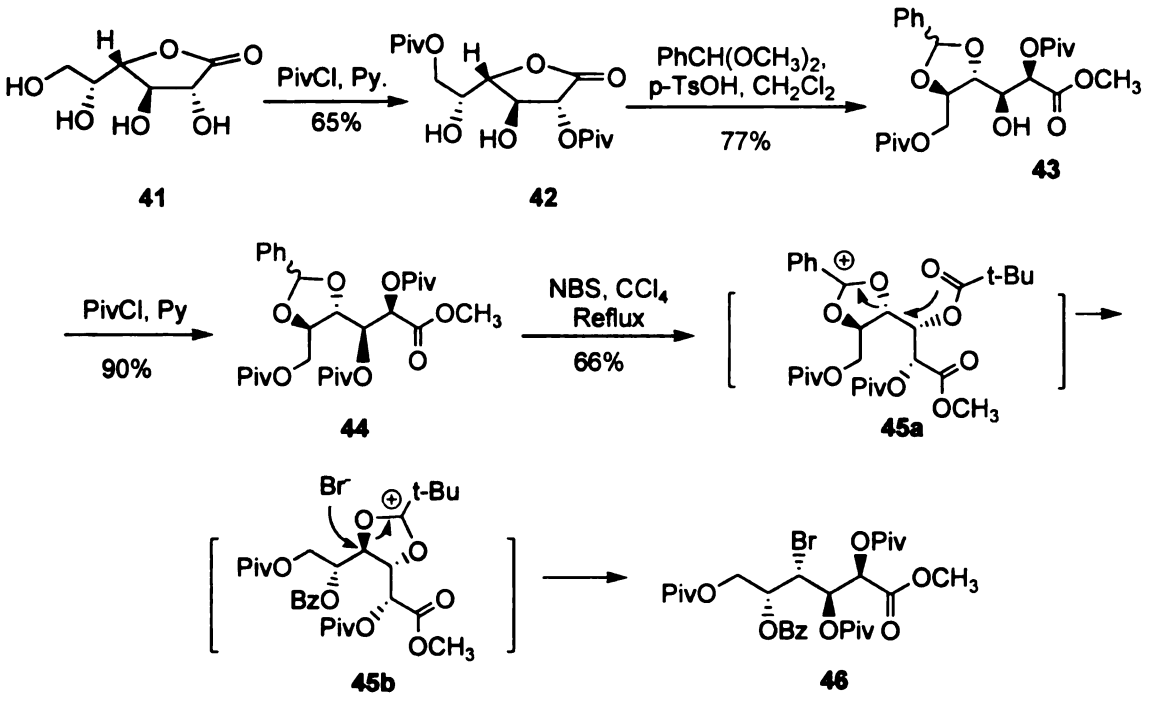


Figure 2.4 The ^{1}H NMR spectrum of methyl 3-O-benzoyl-6-bromo-6-deoxy-2,4,5-tri-O-trimethylacetyl-D-galactonate (**40**).



Scheme 2.10 Selective 4-position bromination of protected D-galactono-γ-lactone with inversion at C-2 to form methyl 5-O-benzoyl-4-bromo-4-deoxy-2,3,6-tri-O-trimethylacetyl-D-galactonate **46**

The following steps were similar with the case of methyl 3,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate **37**. After further pivaloation and NBS oxidative cleavage, we expected the bromination of 6-position with inversion at 5-position. Unexpectedly, NMR analysis of the major product showed that 4-position was brominated and the 5-O-position was benzoylated. A normal Hanessian-Hullar reaction without neighboring group participation could generate this structure with a *gluco*-configuration. The coupling constant analysis ($J_{2,3}$1.8Hz, $J_{3,4}$10.5Hz, $J_{4,5}$1.5Hz), however, supported a *galacto*- sugar chain. The product was therefore assigned to methyl 5-O-benzoyl-4-bromo-4-deoxy-2,3,6-tri-O-trimethylacetyl-D-galactonate **46**. The mechanism was believed to go through a benzoxonium cation **45a**. The 3-pivaloyl group attacked at the 4-position to form a t-butyl-1,3-dioxonium cation **45b**, which was subsequently attacked at the 4-position by bromide ion to give compound **46**. The 4-position was

double-inverted so that the *galacto*- configuration was retained. This reaction pattern was very different from the one with D-*gluco*- configuration, although in both cases, pivaloyl group rearrangement occurred. For methyl 3,4-O-benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate **38**, the primary bromination drove the 4,6-pivaloyl rearrangement. For methyl 4,5-O-benzylidene-2,3,6-di-O-trimethylacetyl-D-galactonate **44**, the 3-O-pivaloyl group attacked the benzoxonium cation preferentially, after the 3,4-(t-butyl-1,3-dioxonium) cation formation, the bromide ion attacked the 4-position to give the final product **46**. This outcome showed the remarkable stereochemical sensitivity of this NBS-initiated dioxonium cation rearrangement.

In summary, by inverting the protection steps, we carried out this NBS-initiated primary bromination of D-*glucono*-δ-lactone derivative while inverting the 4-position. In the case of D-*galactono*-γ-lactone, 4-position was brominated and the stereochemistry was retained. Two new selectively protected and functionalized sugar derivatives were generated. Based on the simple and elegant synthesis, this methodology showed its general applicability and practicability in synthetic carbohydrate chemistry.

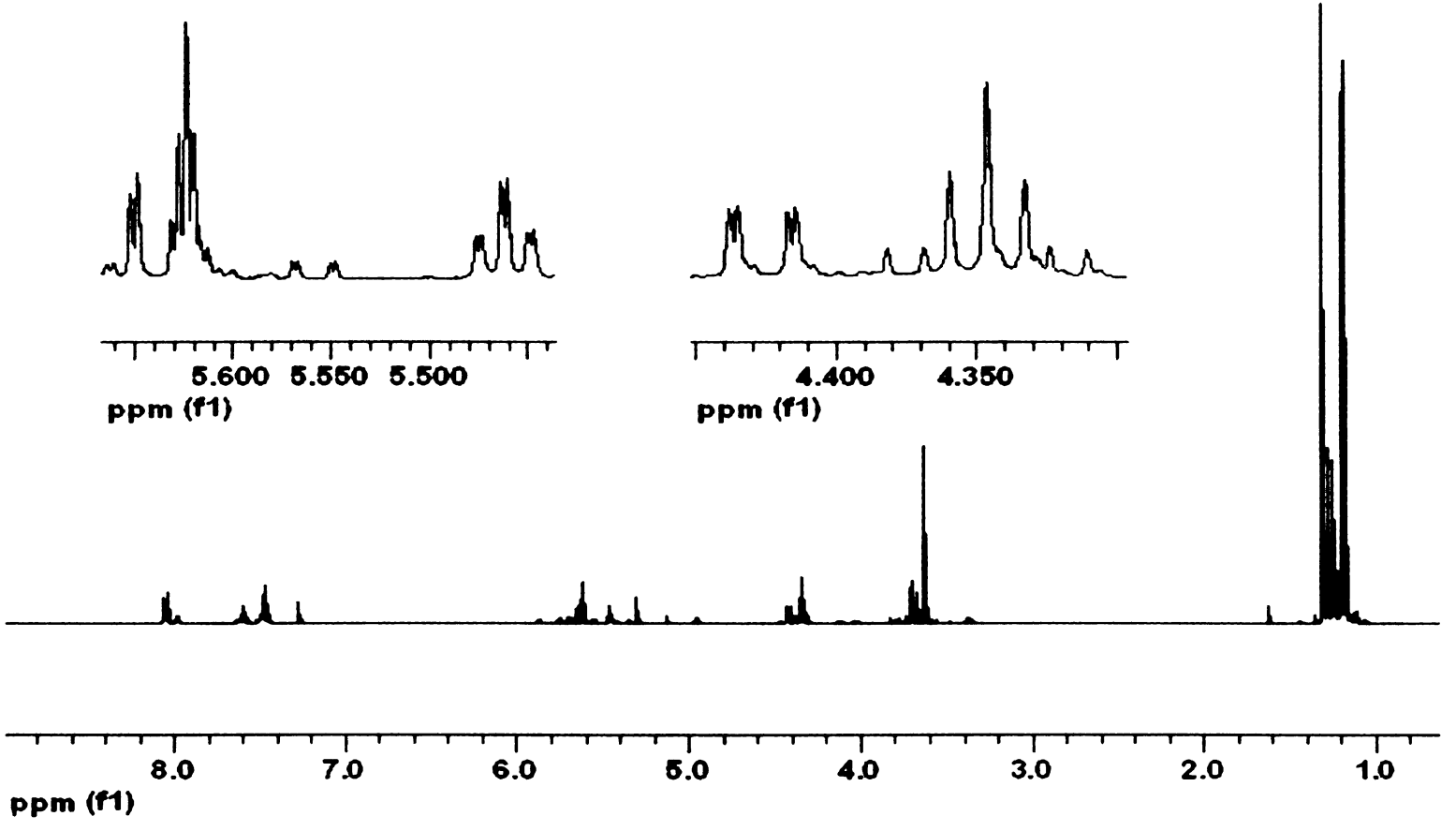
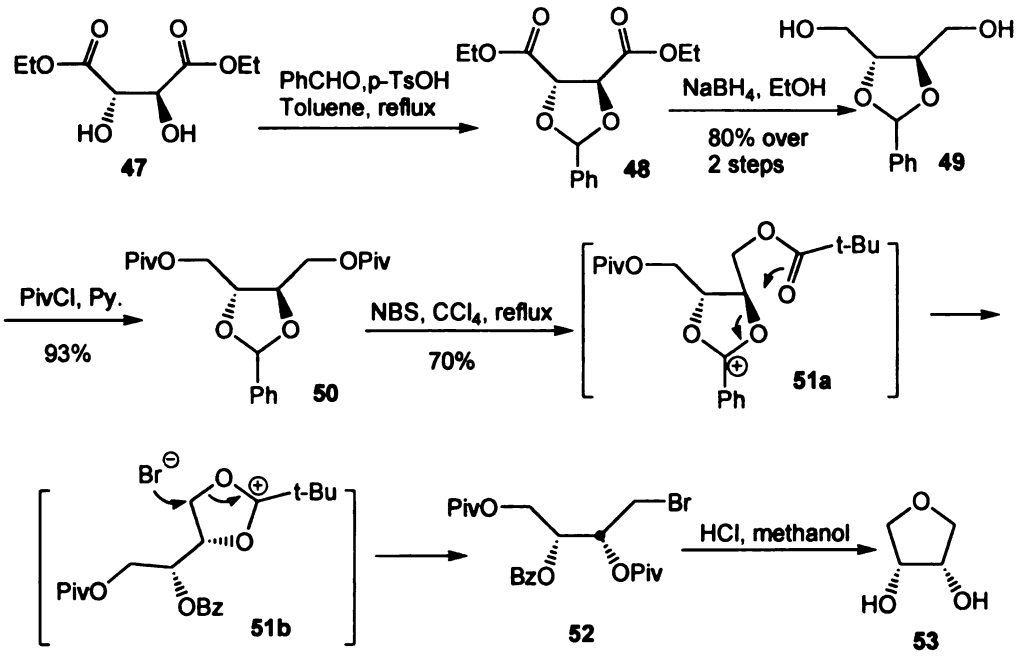


Figure 2.5 The ^{1}H NMR spectrum of methyl 5-O-benzoyl-4-bromo-4-deoxy-2,3,6-tri-O-trimethylacetyl-D-galactonate (**46**).

2.4 C_2 symmetric tartrate derivative desymmetrization using NBS-initiated dioxonium rearrangement

Since the NBS-initiated benzoxonium cation rearrangement generally introduced selective bromination and neighboring position chirality manipulation for aldonolactones, we tried to generalize this methodology to other nonspecified compounds. 2,3-O-benzylidene-1,4-di-O-trimethylacetyl-L-threitol was selected as the target molecule based on the following reasons: First, it is readily available from commercial dimethyl or diethyl L-tartrate; second, it is a C_2 symmetric molecule, the proposed NBS oxidative cleavage could be employed as a very good desymmetrization methodology; third, the product could serve as a protected chiral synthon with appropriate size and functionality.



Scheme 2.11 Selective primary bromination of a protected L-threitol derivative with inversion of the neighboring group

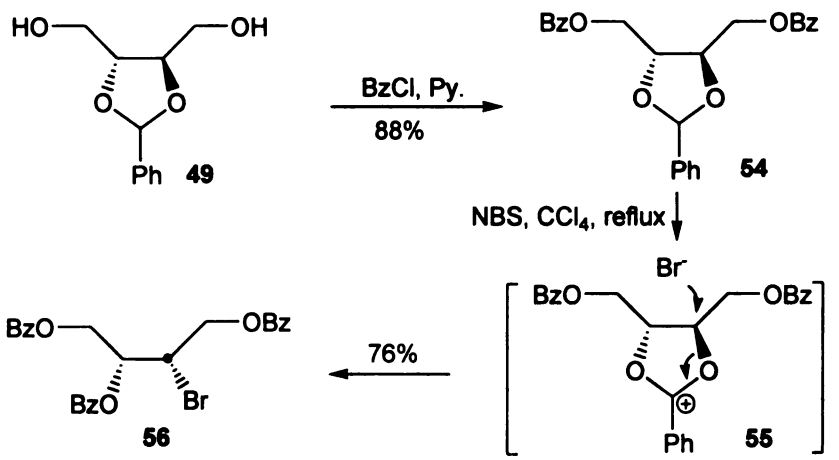
Diethyl L-tartrate **47** was treated with benzaldehyde and catalytic p-toluenesulfonic acid in refluxing toluene. Co-distillation was used to drive the reaction

forward. The crude diethyl 2,3-O-benzylidene-L-tartrate **48** was then reduced by sodium borohydride ($NaBH_4$) in cold ethanol to afford 2,3-O-benzylidene-L-threitol **49** in 80% yield over two steps. 2,3-O-Benzylidene-L-threitol **49** was treated with trimethylacetyl chloride to give 2,3-O-benzylidene-1,4-di-O-trimethylacetyl-L-threitol **50** in 93% yield. Compound **50** was then subjected to NBS cleavage of benzylidene acetal in refluxing carbon tetrachloride. NMR spectroscopic analysis of the product indicated that the 2-O-benzoyl-4-bromo-4-deoxy-1,3-di-O-trimethylacetyl-erythritol **52** was synthesized (Scheme 2.11). The *erythro-* configuration of **52** was confirmed by the H-H coupling constant analysis between H2 and H3 (J = 7.1 Hz). The mechanism was concluded to through a dioxonium cation intermediate **51a**.

Ready for functional group transformation, this optically active differentially protected bromo-butanetriol **52** could be used as a 4-chiral-center synthon. Usually, the desymmetrization of C_2 symmetric compounds such as L-threitol often only involves monofunctionalization. However, this monofunctionalization normally would not change any stereochemistry, therefore it would not change the L-*threo* configuration. On the other hand, the asymmetric *meso*-erythritol desymmetriztion must involve an asymmetric reagent, normally asymmetric catalyst, to generate an optically active product with *erythro-* configuration. The NBS-initiated rearrangement bromination of **50** generated optically pure product **52** with *erythro-* configuration from easily synthesized L-threitol derivative. Being complimentary to the monofunctionalization of L-threitol, this method enabled us to access the whole set of 4-carbon chiral synthons with both *threo-* and *erythro-* configuration.

Acidic hydrolytic deprotection of this NBS oxidation product **52** was carried out to deprotect the ester groups. This did not yield the desired bromobutanetriol. Instead, it led to the 1,4-anhydroerythritol **53**. The formation of this compound further confirmed the inversion of the 3-position in the NBS-initiated rearrangement and bromination and therefore further confirmed the rearrangement mechanism.

2.5 The Exploration of NBS-initiated Neighboring Rearrangement of Other Protecting Group



Scheme 2.12 The direct bromination on the benzoxonium cation in the NBS treatment of 2,3-O-benzylidene-1,4-di-O-benzoyl-L-threitol **54**

To explore the possibility of other neighboring protecting group participating in the NBS-induced rearrangement, 2,3-O-benzylidene-1,4-di-O-benzoyl-L-threitol **54** was synthesized by treatment of 2,3-O-benzylidene-L-threitol with benzoyl chloride in pyridine. Then it was reacted with NBS in refluxing carbon tetrachloride (Scheme 2.12). NMR analysis of the major product proved it to be 3-bromo-3-deoxy-1,2,4-tri-O-benzoyl-L-erythritol **56**. The reaction was believed to go through a normal Hanessian-Hullar reaction pathway, in which the bromide ion attacked the benzoxonium cation **55** directly

before the neighboring group rearrangement. Although benzoyl groups have been found to undergo rearrangement in some cases [6, 7], failure to rearrange in this case suggested that the steric environment generated by the neighboring groups was very important. If the steric hindrance were not high enough to block the direct attack of the benzoxonium cation by the bromo nucleophile, the rearrangement would not happen efficiently.

2.6 Conclusion

Unexpectedly, NBS oxidative cleavage of 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **10** gave a 7-bromo product **24**. The structure of the product was elucidated and the mechanism of this unusual cascade rearrangement was analyzed in detail. The concept of neighboring ester group rearrangement was employed on several other aldonolactones to generate a series of selectively protected and brominated D- and L-aldonolactone derivates. 3,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-*gulo*-1,4-lactone **28** was selectively 6-brominated and 5-inverted to form a L-*manno*-1,4-lactone derivative **29**. Methyl 3,4-O-benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate **38** and methyl 4,5-O-benzylidene-2,3,6-tri-O-trimethylacetyl-D-galactonate **44** were selectively brominated at 6- and 4-positions, respectively. This methodology was further applied to L-threitol derivative desymmetrization and successfully generated orthogonally protected and functionalized, optically pure chiral synthon **52** with *erythro*- configuration. Replacement of the trimethylacetyl group with benzoyl group suppressed the neighboring group rearrangement, further confirmed that this attracting rearrangement was largely based on steric-control.

EXPERIMENTAL

General Optical activity data were obtained on a JASCO P-1010 polarimeter at 25°C. NMR spectra were obtained on a Varian VXR-500 Spectrometer operating at 500MHz for protons. Mass spectra were obtained on a JEOL HX-110-HF instrument using fast atom bombardment as ionization mode. Spectra were recorded in the positive ion mode. IR spectra were obtained on a Nicolet 710 spectrometer in chloroform solution except when otherwise specified.

3,5-O-Benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**9**):

D-*glycero*-D-*gulo*-heptono-1,4-lactone 10 g was suspended in 40 mL benzaldehyde while 4 mL concentrated hydrochloric acid was added in slowly. The mixture was stirred at room temperature for 2 hours and became a viscous solution. The solution was poured into 400 mL hexanes and stirred. The precipitates were collected by filtration and washed with 3 x 100 mL hexanes. The white powder was then dried in vacuum to give 3,5-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone. Yield 12.9 g, 90%. The white solid could be recrystallized from ethanol to give 3,5-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone **9** as white needles. M.p. 187-190°C; (lit. [16] m.p. 188-191°C; $[\alpha]_D^{20}$ - 56.1° (c, 1.0 in MeOH)); δ_H (500 MHz; CD_3OD): 3.68 (1H, dd, $J_{7,7'}$ 11.8, $J_{6,7'}$ 4.7 Hz, H-7'), 3.78 (lH, dd, $J_{6,7}$ 2.5 Hz, H-7), 3.91 (1H, ddd, $J_{5,6}$ 9.3 Hz, H-6), 4.11 (1H, dd, $J_{4,5}$ 1.8 Hz, H-5), 4.58 (lH, t, $J_{3,4}$ 1.9 Hz, H-4), 4.72 (1H, d, $J_{2,3}$ 4.0 Hz, H-2), 4.76 (1H, dd, H-3), 5.69 (lH, s, C<u>H</u>Ph), 7.47-7.50 (2H, m, ArH), 7.32-7~36 (3H, m, ArH); δ_C (125MHz; CD_3OD): 63.2 (C-7), 69.7, 70.6, 72.1, 75.8, 76.0 (C-2, C-3, C-4; C-5, C-6), 99.8 (d, <u>C</u>HPh), 127.1, 128.7, 129.6 (Ar<u>C</u>H), 140.9 (s, Ar<u>C</u>), 178.3 (s, C=O); FT-IR (KBr): 3450, 3300, 1770 cm^{-1}.

3,5-O-Benzylidene-2,6,7-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**10**):

3,5-O-benzylidene-D-glucoheptonolactone (3.0 g, 10.1 mmol) was dissolved in 30 mL pyridine. The solution was cooled to 0°C and trimethylacetyl chloride (6.2 mL, 50.3 mmol) was added in drop by drop. The mixture was protected from moisture and stirred for 24 hours. After that, the mixture was dumped into ice-saturated sodium bicarbonate solution and then extracted with dichloromethane twice. The oil layer was collected and all solvents were removed by vacuum. The raw product was purified by flash column chromatography using chloroform as the elutant. The colorless solid after removing the solvent affords 3,5-O-Benzylidene-2,6,7-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone in 92% yield; M.p. 173-176 °C; FAB-MS: m/z calcd. for $C_{29}H_{40}O_{10}$ 548.2622, found 549.2699 (MH^+); δ_H (500MHz; $CDCl_3$): 1.18, 1.19, 1.23 (3 x 9H, 3 x s, 3 x $C(C\underline{H}_3)_3$), 4.29 (1H, dd, $J_{7,7'}$ 12.6, $J_{6,7'}$ 4.1 Hz, H-7'), 4.31 (1H, dd, $J_{4,5}$ 2.0, $J_{5,6}$ 8.5 Hz, H-5), 4.34 (1H dd, $J_{3,4}$ 2.2, H-4), 4.57 (1H, dd, $J_{6,7}$ 2.4 Hz, H-7), 4.95 (1H, dd, $J_{2,3}$ 4.2, $J_{3,4}$ 2.2 Hz, H-3), 5.30 (1H, ddd, H-6), 5.42 (1H, d, H-2), 5.55 (1H, s, C$\underline{H}$Ph), 7.32-7.40 (5H, m, Ar$\underline{H}$); δ_C (125MHz; $CDCl_3$): 26.93, 27.13 (OCC($\underline{C}H_3)_3$), 38.77, 38.87 (OC$\underline{C}(CH_3)_3$), 61.22 (C-7), 68.96, 70.50, 72.64, 73.52 (C-2, C-3, C-4, C-5, C-6), 98.86 ($\underline{C}$HPh), 125.81, 128.19, 129.28, 136.10 (Ar$\underline{C}$), 169.97(O=$\underline{C}$ in lactone), 176.36, 177.55, 177.71 (O$\underline{C}$C($\underline{C}H_3)_3$); FT-IR: 2975, 1809, 1738 cm^{-1}.

3-O-Benzoyl-7-bromo-7-deoxy-2,5,6-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**11**):

3,5-O-Benzylidene-2,6,7-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (3 g, 5.47 mmol) was dissolved in 50 mL carbon tetrachloride at 60°C and N-

bromosuccinimide (1.5 g, 8.43 mmol) was added. The mixture was refluxed at 80°C oil bath for 12 hours. TLC showed that no starting material remained. The mixture was filtered and washed with saturated sodium bicarbonate solution. The raw product was purified by flash column chromatography and the major fraction affords 3-O-benzoyl-7-bromo-7-deoxy-2,5,6-tri-O-pivaloyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone in 75% yield. M.p. 138-140 °C; FAB-MS (MH^+): m/z calcd. for $C_{29}H_{39}BrO_{10}$ 626.1727, found 627.1799 (MH^+); δ_H(500MHz; $CDCl_3$): 0.99, 1.08, 1.24 (27H, 3 x s, 3 x C($C\underline{H}_3$)$_3$), 3.58 (1H, dd, $J_{7,7'}$ 11.1, $J_{6,7'}$ 9.0 Hz, H-7'), 3.64 (1H, dd, $J_{6,7}$ 4.5 Hz, H-7), 4.94 (1H dd, $J_{3,4}$ 3.1, $J_{4,5}$ 9.5 Hz, H-4), 5.51 (1H, dd, $J_{5,6}$ 2.5 Hz, H-5), 5.54 (1H, ddd, H-6), 5.78 (1H, d, $H_{2,3}$ 4.9 Hz, H-2), 5.92 (1H, dd, H-3), 7.41-7.48 (2H, m, Ar$\underline{H}$), 7.56-7.62 (1H, m, Ar$\underline{H}$), 7.91-7.95 (2H, m, Ar$\underline{H}$); δ_C (125MHz; $CDCl_3$): 26.61, 26.64, 26.83, 27.00 (OCC($\underline{C}H_3$)$_3$), 28.77 (C-7), 38.57, 38.65, 38.81 (OC$\underline{C}$(CH_3)$_3$), 67.48, 68.12, 69.34, 71.27, 74.44 (C-2, 3, 4, 5, 6), 127.92, 128.54, 129.67, 133.88 (Ar$\underline{C}$), 164.70 (O$\underline{C}$Ph), 168.89 (O=$\underline{C}$ in lactone), 176.36, 177.55, 177.71(O$\underline{C}$C(CH_3)$_3$); FT-IR: 2975, 1818, 1743 cm^{-1}.

2,3,5,6,7-Penta-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**25**):

D-*glycero*-D-*gulo*-heptono-1,4-lactone (4 g, 19.2 mmol) was dissolved in 100 mL pyridine and cooled down to 0°C in ice-water bath. Trimethylacetyl chloride (30 mL, 243.6 mmol) was added in slowly and the mixture was stirred at room temperature for 24 hours. The mixture was poured into ice-saturated sodium bicarbonate water solution and then extracted by dichloromethane. The organic layer was collected and all the solvents were evaporated. The resulted colorless oil affords 2,3,5,6,7-penta-O-trimethylacetyl- D-glycero-D-gulo-heptono-1,4-lactone in 91% yield. δ_H (500MHz; $CDCl_3$): 1.13, 1.17, 1.21 (3x9H, s, 3 x C($C\underline{H}_3$)$_3$), 1.23 (18H, s, 2 x C($C\underline{H}_3$)$_3$), 4.03 (1H, dd, $J_{6,7'}$ 7.2, $J_{7,7'}$ 12.0 Hz,

H-7'), 4.36 (1H, dd, $J_{6,7}$ 4.4 Hz, H-7), 4.71 (1H, dd, $J_{3,4}$ 2.7, $J_{4,5}$ 9.7 Hz, H-4), 5.08 (1H, m, $J_{5,6}$ 2.7 Hz, H-6), 5.64 (1H, dd, H-5), 5.72 (1H, d, $J_{2,3}$ 4.5 Hz, H-2), 5.82 (1H, dd, H-3); δ_C (125MHz; $CDCl_3$): 26.68, 26.81, 26.88, 26.92, 26.97 ($OCC(\underline{C}H_3)_3$), 38.53, 38.63, 38.72, 38.88, 39.16 ($OC\underline{C}(CH_3)_3$), 61.73 (C-7), 68.46, 68.70, 68.97, 75.96 (C-2, 3, 4, 5, 6), 168.46 (O=$\underline{C}$ in lactone), 176.15, 176.23, 176.40, 176.46, 177.91($O\underline{C}C(CH_3)_3$); FT-IR: 2976, 1817, 1741 cm^{-1}.

3,5-O-Benzylidene-D-*gulono*-γ-lactone (**27**):

Anhydrous hydrogen chloride was bubbled through 40 mL benzaldehyde for two minutes and D-*gulono*-1,4-lactone 10 g was added to the solution. The reaction mixture was stirred for about two hours, at which time it became very thick and stirring was stopped. After standing overnight, the reaction mixture was triturated with ether and filtered. The solid was washed thoroughly with ether three times, with water three times, and then with ether an additional two times. After drying this afforded 11.2 g (74%) of 3,5-O-benzylidene-L-*gulono*-1,4-lactone. Recrystallization from absolute ethanol afforded pure material, M.p. 187-189 °C; (lit. [13] m.p. 188-189°C; $[\alpha]_D^{23}$ + 61.1° (in DMF)); δ_H (500MHz; DMSO-d6) δ_H 3.43 (b, t, 2H, H-6), 4.0-4.83 (m, 4H, H-2, 3, 4, 5), 4.97 (m, 1H, -CH_2OH), 5.68 (s, 1, C$\underline{H}$Ph), 5.97 (m, 1H, -CHOH), 7.4 (m, 5H, Ar$\underline{H}$); δ_C (125MHz; DMSO-d6): 175.9 (s, C=O), 137.7 (s, Ar$\underline{C}$), 129.0, 128.1, and 126.5 (s, Ar$\underline{C}$H), 98.2 (d, 1 $\underline{C}$HPh), 76.2, 74.8, 70.8, 69.5 (C-2,3,4,5), 59.9 (C-6); FT-IR: 3468, 3275, 1786 cm^{-1}.

3,5-O-Benzylidene-2,6-di-O-trimethylacetyl-D-*gulono*-γ-lactone (**28**):

3,5-O-benzylidene-D-gulono-γ-lactone (4.0 g, 15.0 mmol) was dissolved in 40 mL dry pyridine and cooled down to 0°C. Trimethylacetyl chloride (4.62 mL, 37.5

mmol) was then added and the reaction mixture was warmed up to room temperature. After being stirred for 6 hours, the solution was poured into 300 mL saturated sodium bicarbonate solution containing ice and then extracted with dichloromethane (3 x 200 mL). The organic layer was concentrated under vacuum and trace amounts of pyridine was removed by toluene co-distillation. The colorless oil (6.2 g) was 3,5-O-benzylidene-2,6-O-trimethylacetyl-D-*gulono*-γ-lactone (Yield: 95%). This material was suitable for use without further purification. $[\alpha]_D$ = -87.3 (c = 0.9, $CHCl_3$); FAB-MS: m/z calcd. for $C_{23}H_{30}O_8$ 434.1941, found 435.2017 (MH^+); δ_H (500MHz; $CDCl_3$): 1.12,1.14 (2 x 9H, 2 x s, 2 x $C(CH_3)_3$), 4.57-4.45 (4H, m, H-6', H-6, H-5, H-3), 4.88 (1H, dd, $J_{4,5}$ 1.9, $J_{3,4}$ 4.0Hz, H-4), 5.43 (1H, d, $J_{2,3}$ 4.2Hz, H-2), 5.60 (1H, s, C<u>H</u>Ph), 7.35-7.46 (5H, m, Ar<u>H</u>); δC (125MHz; $CDCl_3$): 26.91, 27.04 ($C(\underline{C}H_3)_3$), 38.72, 38.83 ($OC\underline{C}(CH_3)_3$), 62.04 (C-6) 69.62, 70.48, 72.57, 73.44 (C-2, C-3, C-4, C-5), 98.62 (<u>C</u>HPh), 125.87, 128.12, 129.15, 136.40 (Ar<u>C</u>), 170.25 (O=<u>C</u> of lactone), 177.46, 177.97 ($O\underline{C}C(CH_3)_3$); FT-IR: 2973, 1805, 1736, 1282, 1146 cm^{-1}.

3-O-Benzoyl-6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-L-*manno*-1,4-lactone (**29**):

3,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-*gulono*-γ-lactone (5.0 g, 11.5 mmol) was dissolved in 100 mL carbon tetrachloride to which N-bromosuccinimide (3.70 g, 20.8 mmol) was added. The mixture was refluxed for 2 hours and then filtered. The filtrate was diluted in 200 mL chloroform and washed with saturated sodium bicarbonate solution. The crude product was purified by flash column chromatography to afford 3-O-benzoyl-6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-L-*manno*-γ-lactone **9** in 85% yield. $[\alpha]_D = +13.7^o$ (c = 0.8, $CHCl_3$); FAB-MS: m/z calcd. for $C_{23}H_{29}BrO_8$ 512.1046, found 513.1116 (MH^+); δ_H (500MHz; $CDCl_3$): 1.05, 1.07 (2 x 9H, 2 x s, 2 x $C(CH_3)_3$), 3.74

(1H, dd, $J_{6',6}$ 11.9, $J_{6',5}$ 2.8Hz, H-6'), 3.85 (1H, dd, $J_{6,5}$ 3.0Hz, H-6), 5.04 (1H, dd, $J_{4,5}$ 9.6Hz, H-4), 5.29 (1H, ddd, $J_{5,4}$ 9.6Hz, H-5), 5.87 (1H, dd, $J_{2,3}$ 5.0, H-2), 6.01 (1H, dd, H-3), 7.43, 7.57, 7.92 (5H, m, ArH); δ_C (125MHz; $CDCl_3$): 26.78 ($C(\underline{C}H_3)_3$), 32.03 (C-6), 38.78, 38.83 ($OC\underline{C}(CH_3)_3$), 66.76, 68.03, 69.04, 75.71 (C-2, C-3, C-4, C-5), 128.19, 128.65, 129.71, 133.91 (Ar$\underline{C}$), 164.71 (O=$\underline{C}$Ph), 169.06 (O=$\underline{C}$ of lactone), 176.26, 176.39 ($O\underline{C}C(CH_3)_3$); FT-IR: 2973, 1817, 1739, 1264, 1133 cm^{-1}.

2,6-Di-O-trimethylacetyl-D-*glucono*-δ-lactone (**36**):

D-*glucono*-δ-lactone 10 g was dissolved in 100 mL dry pyridine and cooled down to 0 °C in ice bath. Trimethylacetyl chloride 15 g was added in the solution dropwise. The solution was then stirred at 5 °C for 24 hours, after which it was poured into 500 mL saturated sodium bicarbonate with ice and stirred vigorously. The white precipitates were collected by filtration and washed by distilled water several times. After drying in vacuum, the white solid was recrystallized in hexanes / ethyl acetate (2:1) twice to give 2,6-di-O-trimethylacetyl-D-*glucono*-δ-lactone 9.7g (Yield: 50%). M.p. 152-154°C; $[\alpha]_D$ = +68.6° (c = 1.0 CH_3OH); δ_H (500MHz; $CDCl_3$): 0.98, 0.99 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 3.97 (dt, 1H, $J_{4,5}$ 6.0Hz, $J_{5,6}$ 3.8Hz, $J_{5,6'}$ 6.0Hz, H-5), 4.01 (dd, 1H, $J_{6,6'}$ 11.4Hz, H-6'), 4.11 (dd, 1H, H-6), 4.28 (dd, 1H, $J_{3,4}$ 5.9Hz, H-4), 4.32 (dd, 1H, $J_{2,3}$ 4.6Hz, H-3), 5.12 (d, 1H, H-2); δ_C (125MHz; $CDCl_3$): 177.731, 176.444 ($O\underline{C}C(CH_3)_3$), 170.567 (O=$\underline{C}$ of lactone), 79.153, 73.672, 70.941, 67.599, 64.793 (C-2, 3, 4, 5, 6), 38.239, 38.197 ($OC\underline{C}(CH_3)_3$), 26.612, 26.429 ($C(\underline{C}H_3)_3$); FT-IR (CH_3OH): 3505, 1778, 1719, 1701, 1159 cm^{-1}.

Methyl 3,4-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate (**37**):

2,6-di-O-trimethylacetyl-D-*glucono*-δ-lactone 5.0 g was suspended in 50 mL dichloromethane and 5.0 g benzaldehyde dimethyl acetal was added in slowly. After that,

p-toluenesulfonic acid monohydrate 1.0 g was added in and the mixture was stirred for about 10 minutes, after which the mixture became a clear solution. The solution was stirred at room temperature overnight and then poured into sodium bicarbonate solution with ice. The organic layer was collected and the water phase was washed with 2 x 100 mL dichloromethane. The organic phase was dried and evaporated. After column chromatography, 5.02 g methyl 3,4-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate (80%) was obtained as a mixture of two isomers. For the 3,4-(*R*)-O-benzylidene isomer, δ_H (500MHz; $CDCl_3$): 1.19, 1.31 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 2.89 (1H, b, -OH), 3.76 (3H, s, $COOC\underline{H}_3$), 3.93 (1H, ddd, $J_{4,5}$ 8.1Hz, $J_{5,6}$ 3.2Hz, $J_{5,6'}$ 5.4Hz, H-5), 4.07 (1H, dd, $J_{3,4}$ 5.4Hz, H-4), 4.19 (dd, 1H, $J_{6,6'}$ 12.0Hz, H-6'), 4.38 (1H, dd, H-6), 4.85 (1H, dd, $J_{2,3}$ 2.5Hz, H-3), 5.27 (d, 1H, H-2), 6.05 (1H, s, C<u>H</u>Ph), 7.35 (3H, m, ArC<u>H</u>), 7.43 (2H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 179.168, 177.442 ($O\underline{C}C(CH_3)_3$), 167.651 (O=<u>C</u> of lactone), 136.45, 129.644, 128.329, 126.753 (Ar<u>C</u>), 105.401 (<u>C</u>HPh), 78.458, 76.939, 73.171, 71.479, 65.591 (C-2, 3, 4, 5, 6), 52.568 ($COO\underline{C}H_3$), 38.876, 38.790 ($OC\underline{C}(CH_3)_3$), 27.075, 27.053 ($C(\underline{C}H_3)_3$); For the 3,4-(*S*)-O-benzylidene isomer, δ_H (500MHz; $CDCl_3$): 1.19, 1.23 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 2.89 (1H, b, -OH), 3.74 (3H, s, $COOC\underline{H}_3$), 4.00 (2H, m, H-4, 5), 4.17 (dd, 1H, $J_{6,6'}$ 12.0Hz, H-6'), 4.42 (1H, dd, H-6), 4.81 (1H, dd, $J_{2,3}$ 2.5Hz, H-3), 5.33 (d, 1H, H-2), 5.92 (1H, s, C<u>H</u>Ph), 7.35 (3H, m, ArC<u>H</u>), 7.43 (2H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 179.168, 177.442 ($O\underline{C}C(CH_3)_3$), 167.651 (O=<u>C</u> of lactone), 136.45, 129.644, 128.329, 126.753 (Ar<u>C</u>), 105.401 (<u>C</u>HPh), 78.458, 76.939, 73.171, 71.479, 65.591 (C-2, 3, 4, 5, 6), 52.568 ($COO\underline{C}H_3$), 38.876, 38.790 ($OC\underline{C}(CH_3)_3$), 27.075, 27.053 ($C(\underline{C}H_3)_3$); FT-IR : 3518, 2979, 1768, 1740, 1284, 1147 cm^{-1}.

Methyl 3,4-O-benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate (**38**):

Methyl 3,4-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate **37** was reacted with 2 equivalent trimethylacetyl chloride in pyridine using the normal pivaloylation procedure. 3,4-O-Benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate was obtained also as a mixture of two isomers in 90% yield. For the 3,4-(*R*)-O-benzylidene isomer, δ_H (500MHz; $CDCl_3$): 1.14, 1.16, 1.29 (3 x 9H, 3 x s, $C(C\underline{H}_3)_3$), 3.71 (3H, s, $COOC\underline{H}_3$), 4.10 (dd, 1H, $J_{5,6}$ 4.6Hz, $J_{6,6'}$ 12.4Hz, H-6), 4.29 (dd, 1H, $J_{3,4}$ 5.3Hz, $J_{4,5}$ 7.8Hz, H-4), 4.55 (dd, 1H, $J_{5,6}$ 2.8Hz, H-6), 4.66 (dd, 1H, $J_{2,3}$ 2.3Hz, H-3), 5.14 (ddd, 1H, H-5), 5.19 (d, 1H, H-2), 6.06 (1H, s, C<u>H</u>Ph), 7.32 (3H, m, ArC<u>H</u>), 7.39 (2H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 177.459, 177.155, 176.775 ($O\underline{C}C(CH_3)_3$), 167.053 (O=<u>C</u> of lactone), 135.955, 128.158, 126.499, 129.575 (Ar<u>C</u>), 105.754 (<u>C</u>HPh), 78.079, 75.252, 72.578, 71.655, 61.852 (C-2, 3, 4, 5, 6), 52.468 ($COO\underline{C}H_3$), 38.668, 38.632, 38.587 ($OC\underline{C}(CH_3)_3$), 26.895, 26.872, 26.827 ($C(\underline{C}H_3)_3$); FT-IR: 2999, 2881, 1734, 1461, 1398, 1323 cm^{-1}.

Methyl 3-O-benzoyl-6-bromo-6-deoxy-2,4,5-tri-O-trimethylacetyl-D-galactonate (**40**):

3,4-O-Benzylidene-2,5,6-tri-O-trimethylacetyl-D-gluconate (2 g, 3.8 mmol) and N-bromosuccinimide (1.24 g, 6.9 mmol) was suspended in 20 mL carbon tetrachloride. The mixture was refluxed at 80°C oil bath for 12 hours and then filtered. TLC showed no starting material remained. The filtrate was purified by flash column chromatography and the major fraction affords methyl 3-O-benzoyl-6-bromo-6-deoxy-2,4,5-tri-O-trimethylacetyl-D-galactonate 1.84 g in 80% yield. $[\alpha]_D = -26.6^o$ (c = 1.0, $CHCl_3$); FAB-MS: m/z calcd. for $C_{29}H_{41}BrO_{10}$ 628.1883, found 629.1965 (MH^+); δ_H (500MHz; $CDCl_3$): 1.18, 1.19, 1.25 (3 x 9H, 3 x s, $C(C\underline{H}_3)_3$), 3.42 (dd, 1H, $J_{5,6'}$ 9.3Hz, $J_{6,6'}$ 10.9Hz, H-6'), 3.64 (s, 3H, $COOC\underline{H}_3$), 3.74 (dd, 1H, $J_{5,6}$ 3.7Hz, H-6), 5.19 (d, 1H, $J_{2,3}$ 2.3Hz, H-2), 5.25 (ddd,

1H, $J_{4,5}$2.5Hz, H-5), 5.58 (dd, 1H, $J_{3,4}$9.3Hz, H-4), 5.88 (dd, 1H, H-3), 7.45 (t, 2H, J = 7.8Hz, ArC<u>H</u>), 7.58 (m, 1H, ArC<u>H</u>), 8.02 (dd, 2H, J = 1.2Hz, J = 8.3Hz, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 177.120, 177.003, 175.812 (O<u>C</u>C$(CH_3)_3$), 167.253 (O=<u>C</u> of lactone), 164.875 (O=<u>C</u>Ph), 133.826, 129.943, 129.715, 128.685 (Ar<u>C</u>), 71.839, 69.782, 69.568, 68.618 (C-2, 3, 4, 5), 52.664 (COOC<u>H</u>$_3$), 38.913, 38.854 (OC<u>C</u>$(CH_3)_3$), 28.671 (C-6) 27.008, 26.902, 26.980 (C(<u>C</u>$H_3)_3$); FT-IR ($CHCl_3$): 2979, 1741, 1265, 1139 cm^{-1}.

2,6-Di-O-trimethylacetyl-D-*galacto*-γ-lactone (**42**):

D-*galacto*-1,4-lactone (5 g, 28 mmol) was dissolved in 50 mL dry pyridine and cooled down to 0°C. Trimethylacetyl chloride (7.5 g, 62.2 mmol) was added to the solution slowly. The mixture was then stirred at 5 °C for 24 hours, after which the mixture was poured into 300 mL saturated sodium bicarbonate solution with ice and stirred. The white precipitates were collected and washed by distilled water several times. After drying, the crude product was recrystallized in hexanes / ethyl acetate (2: 1) to give 2,6-di-O-trimethylacetyl-D-*galacto*-γ-lactone 6.3 g (65%). M.p. 146-148°C; $[\alpha]_D$ = -10.7° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.01, 1.06 (2 x 9H, 2 x s, C(C<u>H</u>$_3)_3$), 3.84 (dt, 1H, $J_{4,5}$ 2.4Hz, $J_{5,6}$ 6.4Hz, $J_{5,6'}$ 6.4Hz, H-5), 3.92 (dd, 1H, $J_{6,6'}$ 11.1Hz, H-6'), 4.03 (dd, 1H, $J_{3,4}$ 8.1Hz, H-4), 4.07 (dd, 1H, H-6), 4.40 (dd, 1H, $J_{2,3}$ 8.8Hz, H-3), 5.38 (d, 1H, H-2); δ_C (125MHz; $CDCl_3$): 177.673, 176.842 (O<u>C</u>C$(CH_3)_3$), 169.415 (O=<u>C</u> of lactone), 80.399, 74.204, 70.292, 65.885, 63.874 (C-2, 3, 4, 5, 6), 38.249 (OC<u>C</u>$(CH_3)_3$), 26.696, 26.581 (C(<u>C</u>$H_3)_3$); FT-IR: 3791, 3096, 3077, 1797, 1733, 1624, 1146 cm^{-1}.

Methyl 4,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-galaconate (**43**):

2,6-di-O-trimethylacetyl-D-*galactono*-γ-lactone 5 g was suspended in 50 mL dichloromethane and 5 g benzaldehyde dimethyl acetal was added in slowly. After that, p-toluenesulfonic acid monohydrate 1 g was added in and the mixture was stirred for about 10 minutes, after which the mixture became a clear solution. The solution was stirred at room temperature overnight and then poured into sodium bicarbonate solution with ice. The organic layer was collected and the water phase was washed by 2 x 100 mL dichloromethane. The organic phase was dried and evaporated. After column chromatography, 4.86 g methyl 4,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-gluconate (77%) was obtained as a mixture of two isomers. For the 4,5-(*S*)-O-benzylidene isomer, δ_H (500MHz; $CDCl_3$): 1.22, 1.26 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 2.86 (1H, b, -OH), 3.72 (3H, s, $COOC\underline{H}_3$), 3.99 (dd, 1H, $J_{5,6'}$ 5.4Hz, $J_{6,6'}$ 14.2Hz, H-6'), 4.13 (1H, dd, $J_{2,3}$ 2.Hz, $J_{3,4}$ 8.9Hz, H-3), 4.31 (1H, dd, $J_{4,5}$ 5.0Hz, H-4), 4.37 (1H, dd, $J_{5,6}$ 4.7Hz, H-6), 4.47 (1H, ddd, H-5), 5.30 (d, 1H, H-2), 5.96 (1H, s, C<u>H</u>Ph), 7.35 (5H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 178.471, 177.023 ($O\underline{C}C(CH_3)_3$), 168.634 (O=<u>C</u> of lactone), 136.780, 129.424, 128.290, 126.369 (Ar<u>C</u>), 104.230 (<u>C</u>HPh), 78.275, 72.672, 76.272, 72.034, 63.820 (C-2, 3, 4, 5, 6), 52.471 ($COO\underline{C}H_3$), 38.854, 38.744 ($OC\underline{C}(CH_3)_3$), 26.897, 26.874 ($C(\underline{C}H_3)_3$); FT-IR: 3494, 2976, 1736, 1282, 1147 cm^{-1}.

Methyl 4,5-O-benzylidene-2,3,6-tri-O-trimethylacetyl-D-galaconate (**44**):

Methyl 4,5-O-benzylidene-2,6-di-O-trimethylacetyl-D-galactonate was reacted with trimethylacetyl chloride in pyridine using the normal pivaloylation procedure. 4,5-O-Benzylidene-2,3,6-tri-O-trimethylacetyl-D-galactonate was obtained also as a mixture of two isomers in 90% yield. For the 4,5-(*R*)-O-benzylidene isomer, δ_H (500MHz; $CDCl_3$):

1.17, 1.21, 1.22 (3 x 9H, 3 x s, $C(C\underline{H}_3)_3$), 3.66 (3H, s, $COOC\underline{H}_3$), 4.18 (dd, 1H, $J_{5,6}$ 6.8Hz, $J_{6,6'}$ 11.8Hz, H-6'), 4.37 (dd, 1H, $J_{5,6}$ 4.8Hz, H-6), 5.25 (d, 1H, $J_{2,3}$ 1.6Hz, H-2), 5.29 (ddd, 1H, $J_{4,5}$ 8.8Hz, H-5), 5.37 (dd, 1H, $J_{3,4}$ 7.5Hz, H-4), 5.40 (dd, 1H, H-3), 6.00 (1H, s, C<u>H</u>Ph), 7.36 (5H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 177.104, 176.887, 176.719 ($O\underline{C}C(CH_3)_3$), 167.605 (O=<u>C</u> of lactone), 136.501, 129.606, 128.404, 126.495 (Ar<u>C</u>), 104.565 (<u>C</u>HPh), 77.544, 74.797, 71.809, 70.419, 64.054 (C-2, 3, 4, 5, 6), 52.466 ($COO\underline{C}H_3$), 38.973, 38.791, 38.776 ($OC\underline{C}(CH_3)_3$), 26.995, 26.975, 26.809 ($C(\underline{C}H_3)_3$); FT-IR: 2977, 1811, 1741, 1278, 1131 cm^{-1}.

Methyl 5-O-benzoyl-4-bromo-4-deoxy-2,3,6-tri-O-trimethylacetyl-D-galactonate (**46**):

4,5-O-benzylidene-2,3,6-tri-O-trimethylacetyl-D-galactonate (1.35 g, 2.6 mmol) and N-bromosuccinimide (0.84 g, 4.7 mmol) was suspended in 15 mL carbon tetrachloride. The mixture was refluxed at 80°C oil bath for 12 hours and then filtered. TLC showed that no starting material remained. The filtrate was purified by flash column chromatography and the major fraction affords methyl 3-O-benzoyl-6-bromo-6-deoxy-2,4,5-tri-O-trimethylacetyl-D-galactonate 1.02 g (66%). $[\alpha]_D$ = -15.7° (c = 1.0 $CHCl_3$); FAB-MS: m/z calcd. for $C_{29}H_{41}BrO_{10}$ 628.1883, found 629.1964 (MH^+); δ_H (500MHz; $CDCl_3$): 1.12, 1.14, 1.25 (3 x 9H, 3 x s, $C(C\underline{H}_3)_3$), 3.56 (3H, s, $COOC\underline{H}_3$), 4.26 (dd, 1H, $J_{5,6'}$ 6.9Hz, $J_{6,6'}$ 11.5Hz, H-6'), 4.30 (dd, 1H, $J_{5,6}$ 6.7Hz, H-6), 4.37 (dd, 1H, $J_{4,5}$ 1.5Hz, $J_{3,4}$ 10.5Hz, H-4), 5.40 (dt, 1H, H-5), 5.54 (d, 1H, $J_{2,3}$ 1.8Hz, H-2), 5.57 (dd, 1H, H-3), 7.40 (2H, m, ArC<u>H</u>), 7.52 (1H, m, ArC<u>H</u>), 7.97 (2H, m, ArC<u>H</u>); δ_C (125MHz; $CDCl_3$): 177.408, 176.815, 175.662 ($O\underline{C}C(CH_3)_3$), 167.040 (O=<u>C</u> of lactone), 164.694 (<u>C</u>OPh), 133.347, 129.721, 128.378, 128.538 (Ar<u>C</u>), 104.565 (<u>C</u>HPh), 70.941, 69.384, 66.801 (C-2, 3, 5), 64.010 (C-6), 52.332 ($COO\underline{C}H_3$), 48.733 (C-4), 38.812, 38.757, 38.574

($OC\underline{C}(CH_3)_3$), 26.916, 26.837, 26.783 ($C(\underline{C}H_3)_3$); FT-IR: 2980, 1743, 1481, 1264, 1121 cm^{-1}.

Diethyl 2,3-O-benzylidene-L-tartrate (**48**):

Diethyl L-tartrate (13.8 g, 67 mmol) was mixed with benzaldehyde (14.2 g, 134 mmol) in 100 mL toluene and 2 g p-toluenesulfonic acid monohydrate was added in. The mixture was co-distillated under reflux to remove the water. More toluene (2 x 50 mL) was added and evaporated until the solution became clear. The solution was washed with saturated sodium bicarbonate solution, dried and evaporated to give a sticky liquid (19.2 g). This crude product was used in the next step without further purification.

2,3-O-Benzylidene-L-threitol (**49**):

Diethyl 2,3-O-benzylidene-L-tartrate (19.0 g, crude) was dissolved in 200 mL ethanol and cooled down to 0°C, then 10 g sodium borohydride was added in several parts in 30 minutes. After that, the reaction mixture was further stirred at 0°C for 30 minutes, after which it was evaporated to dryness. The crude product was then purified by flash column chromatography to give 2,3-O-benzylidene-L-threitol 11.27 g (80% over 2 steps) as a white solid. M.p. 71-73 °C; (lit. [17] $[\alpha]_D^{20}$ + 7.4° (c 1.0, $CHCl_3$)); δ_H (500MHz; $CDCl_3$): 2.4 (2H, b, -OH's) 4.22 (6H, m, H-1, 2, 3, 4) 5.8 ($C\underline{H}Ph$) 7.34 (m, 5H, $Ar\underline{H}$); δ_C (125MHz; $CDCl_3$): 135.986, 129.892, 128.223, 127.867 ($Ar\underline{C}$) 104.439 ($\underline{C}HPh$) 75.482, 75.268 (C-2, 3) 68.345, 68.235 (C-1, 4)

2,3-O-Benzylidene-1,4-di-O-trimethylacetyl-L-threitol (**50**):

This compound was prepared from 2,3-O-benzylidene-L-threitol in 93% yield following the same procedure of the preparation of 3,5-O-benzylidene-2,6-di-O-

trimethylacetyl-D-*gulono*-γ-lactone. $[\alpha]_D$ = -4.0° (c = 0.7, $CHCl_3$); FAB-MS: m/z calcd. for $C_{21}H_{30}O_6$ 378.2042, found 379.2132 (MH^+); δ_H (500MHz; $CDCl_3$): 1.20, 1.22 (2 x 9H, 2 x s, 2 x $C(CH_3)_3$), 4.22-4.32 (6H, m, H-1, H-2, H-3, H-4), 5.97 (1H, s, C<u>H</u>Ph), 7.36-7.46 (5H, m, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 27.09, 27.14 ($C(\underline{C}H_3)_3$), 38.76, 38.78 ($OC\underline{C}(CH_3)_3$), 63.45, 63.62 (C-1, C-4), 76.12, 76.76 (C-2, C-3), 104.19 (<u>C</u>HPh), 126.56, 128.31, 129.51, 136.89 (Ar<u>C</u>), 178.03, 178.07 ($O\underline{C}C(CH_3)_3$); FT-IR: 2973, 1731, 1282, 1154 cm^{-1}.

2-O-Benzoyl-4-bromo-4-deoxy-1,3-di-O-trimethylacetyl-erythritol (**52**):

This compound was prepared from *2*,3-O-benzylidene-1,4-O-trimethylacetyl-L-threitol in 70% yield following the same procedure used for the preparation of 3-O-benzoyl-6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-L-*manno*-1,4-lactone. $[\alpha]_D$ = +6.7° (c = 0.8, $CHCl_3$); FAB-MS: m/z calcd. for $C_{21}H_{29}BrO_6$ 456.1148, found 457.1212 (MH^+); δ_H (500MHz; $CDCl_3$): 1.17, 1.22, 1.23 (2 x 9H, 2 x s, 2 x $C(CH_3)_3$), 3.57 (1H, dd, $J_{1',2}$ 5.8, $J_{1',1}$ 11.4Hz, H-1'), 3.69 (1H, dd, $J_{1,2}$ 3.7Hz, H-1), 4.30 (1H, dd, $J_{4',3}$ 5.5, $J_{4',4}$ 12.2Hz, H-4'), 4.45 (1H, dd, $J_{4,3}$ 3.1Hz, H-4), 5.36 (1H, ddd, $J_{2,3}$ 7.1Hz, H-2), 5.61 (1-H, ddd, H-3); δ_C (125MHz; $CDCl_3$): 27.00, 27.01 ($C(\underline{C}H_3)_3$), 30.60 (C-1), 38.77, 38.94 ($OC\underline{C}(CH_3)_3$), 61.65 (C-4), 69.43, 70.79 (C-2, C-3), 128.51, 129.68, 129.71, 133.49 (Ar<u>C</u>H), 164.99 (O=<u>C</u>Ph), 176.89, 177.78 ($O\underline{C}C(CH_3)_3$); FT-IR: 2971, 1733, 1265, 1142 cm^{-1}.

2,3-O-Benzylidene-1,4-di-O-benzoyl-L-threitol (**54**):

2,3-O-benzylidene-L-threitol (2 g, 9.5 mmol) was dissolved in 20 mL dry pyridine and cooled down to 0 °C. Benzoyl chloride (4 g, 28.5 mmol) was added in slowly. After the addition, the reaction mixture was stirred for 5 hours at 0°C, after which it was poured into saturated sodium bicarbonate solution with ice and stirred. Dichloromethane (2 x 50

mL) was used for extraction and the organic layer was evaporated to give 2,3-O-benzylidene-1,4-di-O-benzoyl-L-threitol (3.5 g, 88%) as a sticky oil. $[\alpha]_D$ = +23.7° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 4.54-4.66 (6H, m, H-1, H-2, H-3, H-4), 6.11 (1H, s, C<u>H</u>Ph), 7.36-8.04 (15H, m, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 166.088, 166.041 (O<u>C</u>Ph), 133.199, 133.140, 130.416, 129.521, 134.392, 129.617, 129.603, 128.373, 128.317, 128.295, 126.586 (ArC), 104.328 (<u>C</u>HPh), 76.82, 76.237 (C-2, C-3), 64.076, 64.033 (C-1, C-4); FT-IR: 1788, 1722, 1271, 1093 cm^{-1}.

3-Bromo-3-deoxy-1,2,4-tri-O-benzoyl-L-erythritol (**56**):

2,3-O-benzylidene-1,4-di-O-benzoyl-L-threitol (1.12 g, 2.68 mmol) and N-bromosuccinimide (NBS) (0.86 g, 4.82 mmol) was suspended in 10 mL carbon tetrachloride. The mixture was refluxed in an 80°C oil bath for 12 hours and then filtered. TLC showed that no starting material remained. The filtrate was purified by flash column chromatography and the major fraction affords 3-bromo-3-deoxy-1,2,4-tri-O-benzoyl-L-erythritol (1.01g, 76%) as a sticky oil. $[\alpha]_D$ = + 52.0° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 4.65-4.93 (5H, m, H-1, H-3, H-4), 5.88 (ddd, 1H, J = 3.6Hz, J = 5.9Hz, J = 9.5Hz, H-2), 7.38-8.15 (15H, m, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 165.804, 165.668 (O<u>C</u>Ph), 165.064, 162.227, 134.425, 133.474, 133.274, 133.187, 130.438, 129.747, 129.674, 129.577, 128.764, 128.432, 128.380, 128.358 (ArC), 71.404 (C-2), 64.698, 63.804 (C-1, 4), 46.997 (C-3); FT-IR: 1788, 1725, 1265, 1108 cm^{-1}.

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Chapter 3

Exploration of Inter- and Intramolecular Competitive Nucleophiles in the N-Bromosuccinimide-Mediated Dioxolonium Ion Rearrangement for Introduction of New Functionalities

ABSTRACT

To introduce new functionalities in to the sugar structure, different inter- and intramolecular nucleophiles were employed in the N-bromosuccinimide-mediated dioxolonium ion rearrangement. Intermolecular nucleophiles generally failed to compete with in-situ generated bromide ion, although in certain case, the introduction of competitive nucleophile was shown. Cyano groups do not participate in the Hanessian-Hullar reaction as intramolecular nucleophile to give expected lactam. The results were ascribed to the better nucleophilicity of the bromide ion generated in-situ than that of the competitive nucleophiles introduced inter- or intramolecularly.

3.1 Introduction

In the last chapter, the rearrangement of neighboring ester groups when treating benzylidene acetals with NBS was discussed. The reaction starts from the abstraction of the benzylidene methine hydrogen atom by a bromine radical followed by bromination with molecular bromine. After heterolytic cleavage of C-Br bond, a benzoxonium cation is formed. The active neighboring group then attacks the partially positively charged carbon initiating the rearrangement. From another point of view, the carbonyl O atom acts

as an intramolecular competitive nucleophile with the in-situ generated bromide ion. In the case of the NBS treatment of 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone, due to the high steric hindrance, the attack of bromide ion was slow enough to let the complex rearrangement process occur. As a result, a primary brominated compound was synthesized. This interesting phenomenon encouraged us to further explore this NBS-cleavage of benzylidene group with some other nucleophiles. Theoretically, it should be possible to add another nucleophile which could compete with bromide ion at some stage of the NBS-cleavage of the benzylidene group. It would then be possible to introduce some new functionality under mild reaction conditions (Figure 3.1). This is always an important process pursued by synthetic chemists.

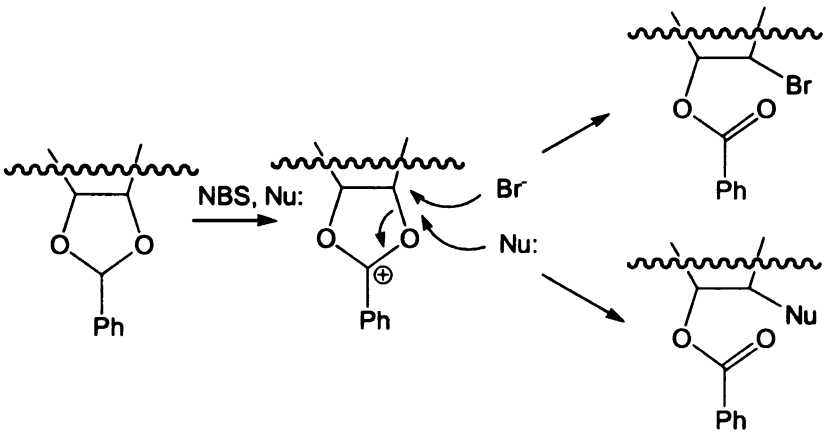


Figure 3.1 The competitive nucleophile participated Hanessian-Hullar reaction

3.2 The base sensitivity of NBS-oxidative cleavage of protected benzylidene sugar lactone

3,5-O-Benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **1** could be easily synthesized from commercially available D-glucoheptano-1,4-lactone by two simple steps. The NBS treatment of this compound without acid scavenger induced a

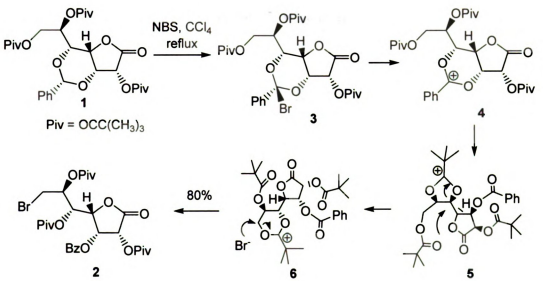
pivaloyl rearrangement resulting in bromination of the terminal 7-position. Before we introduced competitive nucleophiles into the reaction system, we thought it beneficial to further explore this reaction by varying reaction conditions. This was especially true since most of the competitive nucleophiles would be introduced as a form of base.

3.2.1 The effect of barium carbonate on the NBS reaction as an acid scavenger

From the beginning of the discovery of the Hanessian-Hullar reaction in 1960's, acid scavengers have been generally used to control the acidity of the reaction system [1, 2]. This was especially true from a viewpoint of industrial large scale synthesis. Barium carbonate was very often used as a good acid scavenger because of its inert property and easy removal. It generally gave good results. We therefore evaluated the effect of barium carbonate in our reaction system as an acid scavenger.

As a control reaction, 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **1** was treated with 1.8 equivalent NBS in refluxing carbon tetrachloride without any acid scavenger. The reaction mechanism is shown in Scheme 3.1 as discussed in Chapter 2. To further understand the reaction, we carried out an easy kinetic analysis. After two hours, we analyzed the reaction crude mixture by NMR spectroscopy. NMR analysis showed that most of the starting materials was consumed and transformed to a new compound. The characteristic 99 ppm signal in ^{13}C spectrum of the starting benzylidene lactone was gone while a new signal at 104 ppm emerged. This new peak could not be seen in DEPT experiment, suggesting a quaternary carbon was formed. We believed that this new compound corresponded to the intermediate 3,5-O-bromobenzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **3**, in which the benzylidene H atom was abstracted and substituted by a bromine atom. The NMR

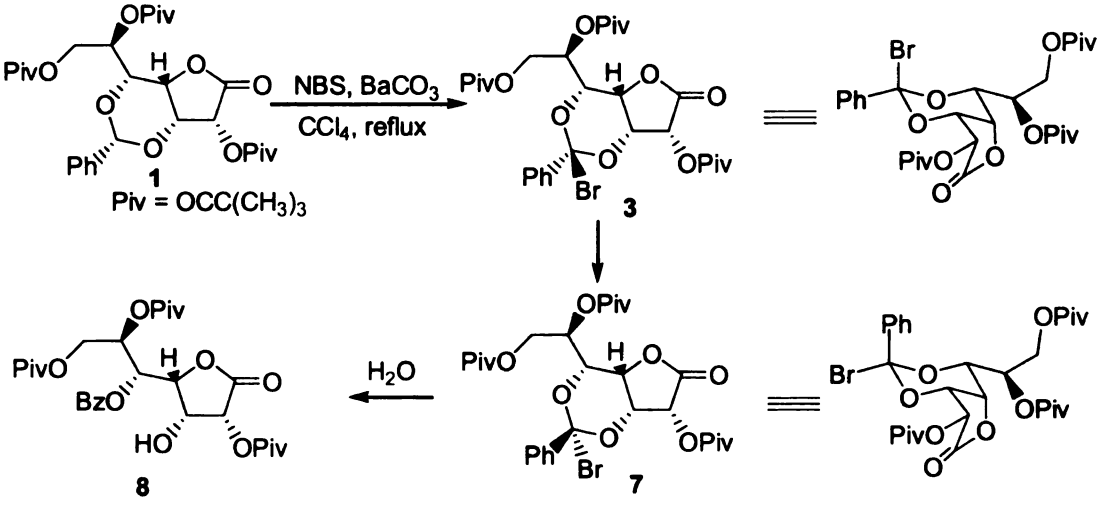
analysis of the reaction crude mixture after 4 hours showed a complicated mixture with weakened peak strength at 104 ppm in the ^{13}C spectrum, indicating that the unstable C-Br bond was being broken and pivaloyl rearrangement started. After 6 hours, the reaction crude mixture NMR showed that none of this intermediate was left, while ^{1}H spectrum clearly showed the final 7-bromo product **2** emerging. After 10 hours, the reaction was completed and a fairly pure product was prepared in ~ 80% yield.



Scheme 3.1 The reaction and mechanism of NBS-initiated pivaloyl rearrangement and bromination

We then carried out this reaction with barium carbonate as the acid scavenger. All the other reaction conditions were kept the same. A simple kinetic analysis similar to the one described above was carried out to understand the effect of this acid scavenger (Scheme 3.2). After 2 hours, NMR analysis of the crude reaction mixture showed a similar result, in which the bromobenzylidene **3** was shown to be the dominant component. However, the NMR analysis after 4 hours and 6 hours showed a very different result. While the 104 ppm peak in ^{13}C spectrum kept decreasing, a new peak at

112 ppm emerged. A DEPT experiment also showed that this was a quaternary carbon. This carbon was not seen in the control reaction. After 8 hours, the compound with this carbon became the dominant product. However, this compound was unstable towards further workup by water or chromatography. After these treatments, only 5-O-Benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **7** was obtained. Based on the understanding of the Hanessian-Hullar reaction, we reasoned that this unknown and unstable compound to be another isomer of 3,5-O-bromobenzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **7**, which underwent hydrolysis to form **8**.



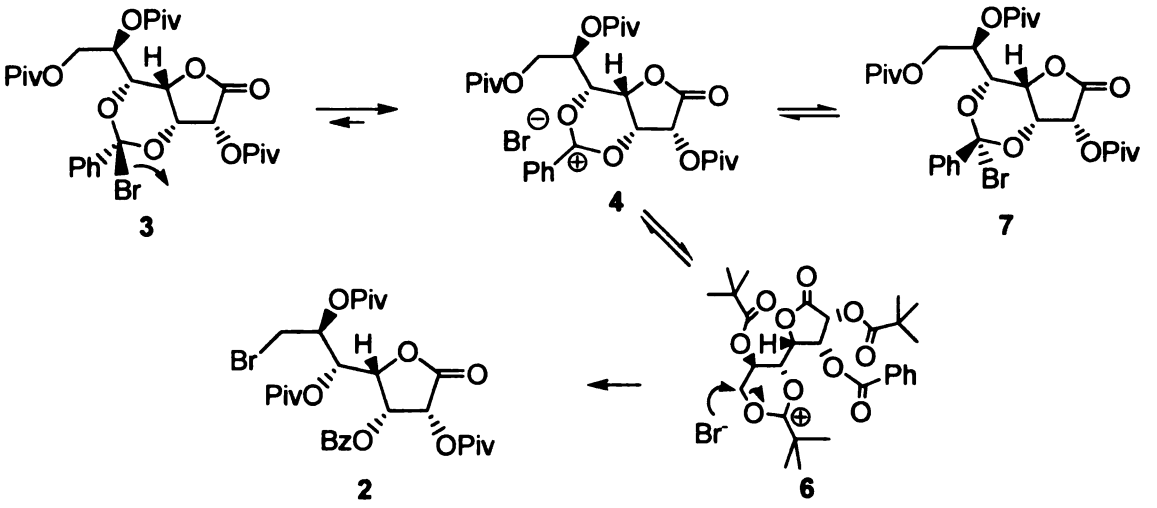
Scheme 3.2 The isomerization of bromobenzylidene lactone when $BaCO_3$ is present in the NBS reaction

Presumably, in the NBS treatment of benzylidene lactone with barium carbonate as the acid scavenger, the pivaloyl rearrangement was slowed down. The cleavage of the C-Br bond on the bromobenzylidene group was a reversible process. While the C-Br bond cleavage scrambled this chiral center, the reversed C-Br bond formation would re-install this chiral center with an isomerization effect. In this substrate, the chiral center inversion gave a more stable intermediate **7**, in which the bromo sits in the equatorial

position of the benzylidene ring. This isomer **7** showed a fairly different chemical shift in ^{13}C spectrum at 112 ppm. This bromobenzylidene compound was labile towards hydrolysis to form the 5-O-Benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **8**. In the control reaction, it was possible that the following pivaloyl rearrangement was sufficiently fast so that this inversion could not be detected.

After extension of the reaction time to 18 hours, 7-bromo-7-deoxy-3-O-Benzoyl-2,5,6-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **2** was also synthesized as the major product in a slightly lower yield compared with the control reaction. However, the reaction rate difference generated by acid scavenger still needed to be addressed. Compared with the control reaction, the reaction with acid scavenger was much slower. We postulated that the in-situ generated small amount of HBr was a catalyst for the rearrangement and bromination. A reaction mechanism accelerated by HBr is shown in Scheme 3.3. In the NBS bromination of benzylidene protected sugar, small amount of HBr was generated in the reaction system. This also supplied a low concentration of bromide ion, which could undergo nucleophilic attack at the primary position of suitable carboxonium cation intermediate to furnish the final product **2**. Since the C-Br bond heterocleavage generated a bromide ion, HBr was regenerated in this cycle. This mechanism requests a necessary level of bromide ion to make the rearrangement and bromination proceed smoothly. When acid scavenger such as barium carbonate was used, the trace amount HBr was scavenged and separated from the reaction media. The concentration of the bromide ion in the solution was dramatically decreased. Both the pivaloyl rearrangement and the terminal bromination became much slower. As a result,

the isomerization by C-Br bond cleavage and re-formation could be seen clearly in the system.



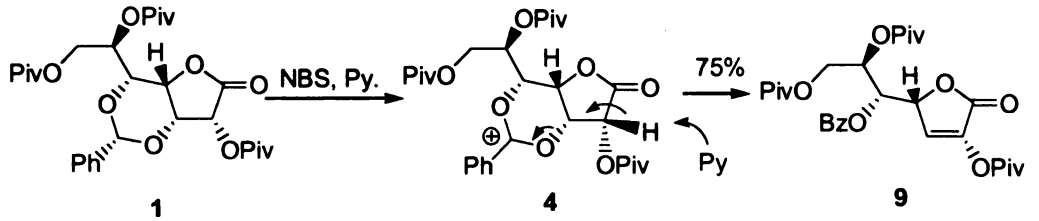
Scheme 3.3 The acceleration effect of bromide ion in the NBS reaction

Although barium carbonate has been widely used in the NBS oxidative cleavage, we have never seen any similar isomerization of the bromobenzylidene carbon center in the literature before. This was ascribed to several reasons. First, in most research work, the rearrangement of neighboring group was not involved. Therefore the bromination process was relatively fast. Once the C-Br bond was cleaved, the bromide would attack a suitable position to finish the reaction. Second, the high local steric hindrance also slowed down the bromination process, making the isomerization possible. The identification of this isomerization process gave us more insight into the reaction mechanism of the NBS oxidative cleavage of the benzylidene group. Therefore control of the reaction to our desired direction could be possible.

3.2.2 Pyridine assisted elimination in NBS treatment of 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptono-1,4-lactone

As discussed above, when barium carbonate was employed as the acid scavenger, the NBS promoted pivaloyl rearrangement and primary bromination was slowed down. This was ascribed to its ability of scavenging HBr and separating the bromide ion from the reaction media. If some organic base such as pyridine were used, the produced bromide salt might still have some solubility in the solvent and therefore keep the concentration of the bromide ion in the solution. Therefore it could act as a good acid scavenger without interupting the bromination reaction. Hence 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **1** was treated with NBS in refluxing carbon tetrachloride in the presence of 2 equivalents of pyridine. After about 4 hours, the reaction was checked by TLC and all the starting material was consumed. ^{13}C NMR analysis of the crude reaction mixture showed no peaks at 104 and 112 ppm, suggesting neither bromobenzylidene compound was present. Interestingly, only 4 major peaks were shown in the 60~80 ppm region, which is characteristic for carbon atoms substituted by a single oxygen function. Combined with the ^{1}H NMR spectrum, it was clear that elimination had occurred to yield an unsaturated lactone. The mechanism is shown in Scheme 3.4. After benzylidene H abstraction, C-Br bond formation and heterocleavage of the C-Br bond, a 3,5-O-benzoxonium cation **4** was formed. This cation served as a good leaving group at β-position in a lactone. Due to the α-H acidity, it was labile towards the attack by some bases such as pyridine. The β-elimination happened smoothly to yield the

final α,β-unsaturated sugar lactone **9**. This protected α,β-unsaturated sugar lactone **9** could be a versatile building block for advanced organic synthesis.



Scheme 3.4 Pyridine assisted elimination in NBS treatment of protected benzylidene lactone

This elimination was expected to be a possible side product in our first trial on the NBS treatment of glucoheptanolactone **1** (Chapter 2). However, only when pyridine was introduced into the reaction system, was it observed. The reaction mode of NBS with glucoheptanolactone was highly dependent on the basicity of the reaction system. When the reaction was carried out without base, the reaction at acidic condition showed predominantly pivaloyl rearrangement and primary bromination. When barium carbonate was used as an acid scavenger, the reaction was kept at neutral condition. Under neutral condition, both the pivaloyl rearrangement and the bromination were greatly slowed down and an isomerization of the bromobenzylidene group was detected. When pyridine was used as an acid scavenger, the reaction mixture became relatively basic because of the good solubility of pyridine in the solvent. The basicity, although weak, was enough to drive the β-elimination to yield an α,β-unsaturated sugar lactone **9**. By simply varying the reaction basicity with different bases, the reaction was easily tuned towards different directions. Different useful structures were generated and they could be employed as good building blocks for different usage.

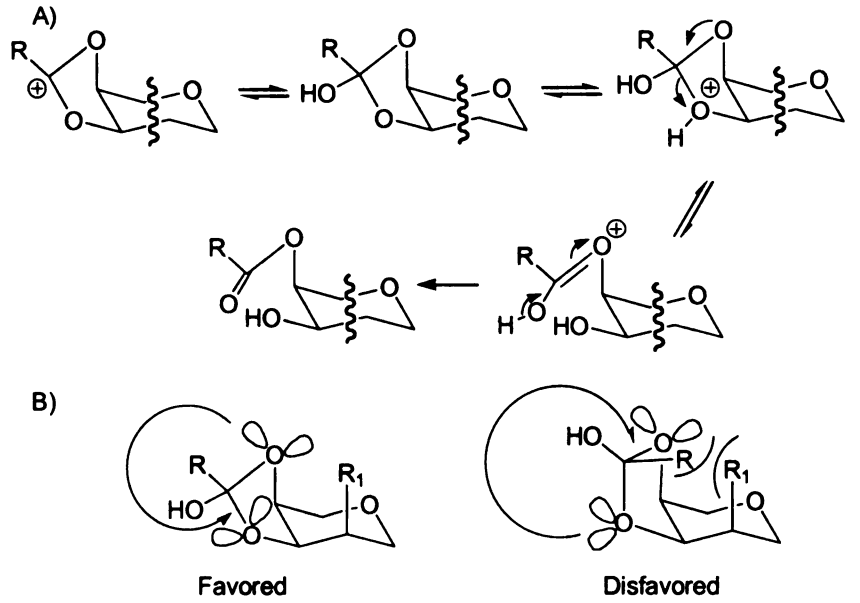
3.3 The introduction of competitive nucleophiles into the NBS bromination of 3,5-O-benzylidene-2,6,7-tri-O-pivaloyl-D-glucoheptono-1,4-lactone

The mechanism of the NBS bromination of benzylidene compounds included several steps: C-H abstraction, C-Br bond formation, C-Br heterocleavage to form a benzoxonium cation and a bromide ion, (dioxonium cation rearrangement) and nucleophilic attack of the carbon chain by the bromide ion. By introducing another competitive nucleophile into the system, it could be possible to interfere with the last nucleophilic step (Figure 3.1). A new functionality could be introduced into the carbon chain directly without further transformation of bromosugar, which could be difficult in many cases. The appropriate competitive nucleophiles could range from alcohols, carboxylic acids, cyanides, nitrites and more.

3.3.1 The introduction of O- nucleophiles into the NBS oxidation

The simplest intermolecular competitive nucleophile would be water. The Hanessian-Hullar reaction in the presence of water has been well studied [3]. Generally, after the C-Br cleavage, the benzoxonium cation would be trapped by water molecular to form unstable orthoacid. The orthoacid species would undergo proton transfer to form a hydroxyl group and a benzoyl group (Scheme 3.5 A). Stereoelectronic effects usually direct the regioselectivity of this hydrolysis, favoring of an equatorial hydroxyl group [4]. The protonation and breakdown of the orthoacid intermediate is the critical step. This reaction will proceed more quickly if one of the oxygen lone pair is anti-periplanar to the C-O bond to be cleaved. For C-O_{eq} bond cleavage, one of the O_{ax} lone pairs is already

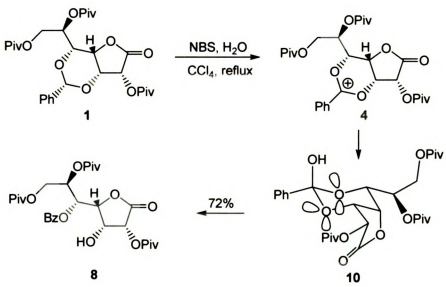
nearly anti-periplanar to the C-O_{eq} bond under normal steric arrangement. However, for the C-O_{ax} bond cleavage, this needs to proceed via a strained steric arrangement. The C-O_{eq} bond cleavage is normally favored, which gives a product with an equatorial hydroxyl group (Scheme 3.5 B). This process has been generally used as a deprotection methodology of benzylidene protection group. It was still of importance to understand the regioselectivity in a five-membered ring system.



Scheme 3.5 The hydrolysis of carboxonium cation: A) The hydrolysis mechinism; B) The regioselectivity of hydrolysis based on the stereoelectronic effect

3,5-O-Benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptono-1,4-lactone **1** was treated with NBS in refluxing carbon tetrachloride with water present. After several hours, TLC showed a fairly clean reaction with a dominant product. NMR analysis of this product showed its structure to be 5-O-benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **7** with a free hydroxyl group at 3-position (Scheme 3.6). Only trace amount of 5-OH was generated. In our system, it would be hard to predict the

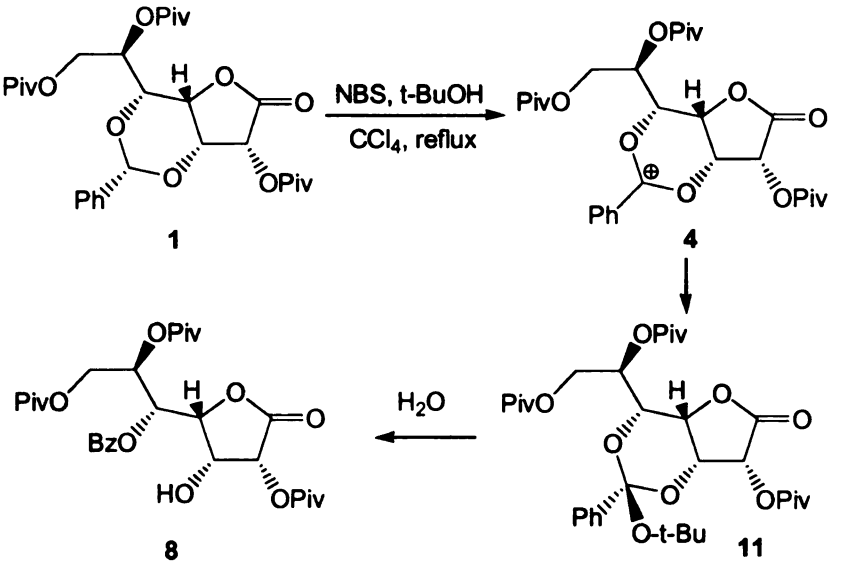
regioselectivity based on the stereoelectronic effect discussed in Scheme 3.5 B. This was because of the different fused ring system. In this ring system, both C-O bonds of the orthoacid had an anti-periplanar O lone pair to facilitate the bond cleavage. The regioselectivity here would largely be a result of thermodynamic control since the breakage of C-O_5 would generate a 3-O-benzoyl group, which would be sterically hindered by the 2-O-pivaloyl group on the same five-membered lactone ring. Nevertheless, the remarkable regioselectivity was very interesting because it opened an opportunity to selectively deprotect the benzylidene group of this system.



Scheme 3.6 The NBS treatment of benzylidenelactone with water present

We continued our research to introduce other O- nucleophiles into the reaction system. Several alcohols were screened towards this goal. To suppress the bromination reaction, excess alcohols were used. However, when primary and secondary alcohols were used, the NBS cleavage of benzylidene group was shut down. Only starting material was recovered. Although the NBS-cleavage of benzylidene acetal with free hydroxyl groups could proceed smoothly with fair yields, the excess alcohol in this situation

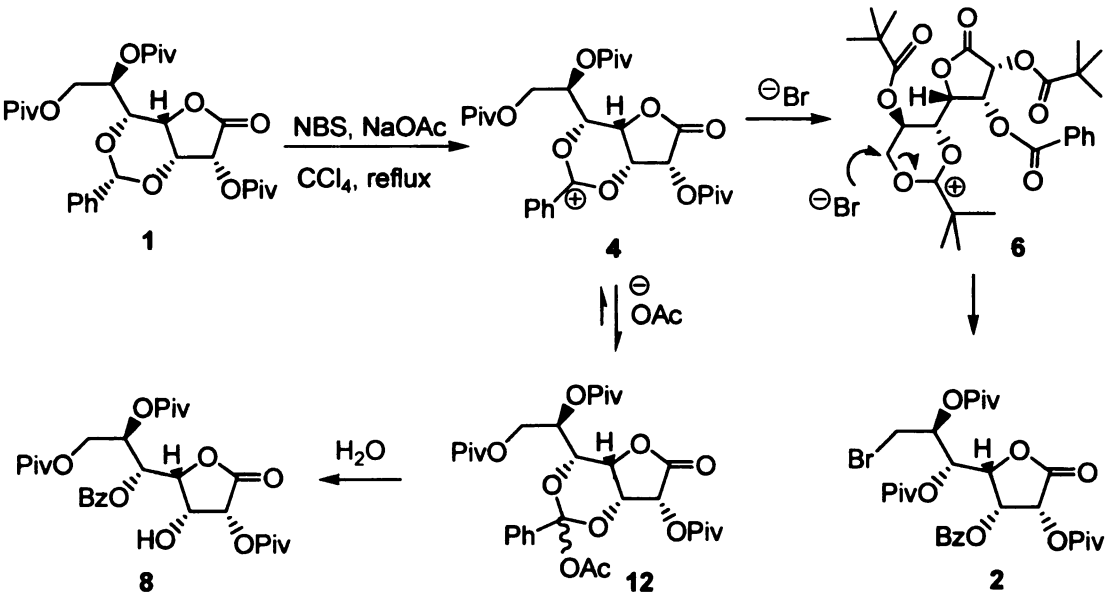
suppressed this reaction. The major reason was ascribed to the polarity of the alcohols as solvents, which could greatly lower the bromo radical concentration and shut down the H-abstraction step. On the other hand, it was also possible that oxidizable alcohols could react with NBS when the reaction time was extended. To test this, t-butyl alcohol was employed as the competitive nucleophile. NMR study of the reaction showed that the starting material was consumed smoothly, suggesting that NBS was still able to oxidize the benzylidene C-H bond with t-butyl alcohol present. Interestingly, after workup and separation, the only recovered product was 5-O-benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **8**, indicating a hydrolysis cleavage. A mechanism was proposed in Scheme 3.7. When the benzoxonium cation was formed, it was trapped by t-butyl alcohol to form an orthoester. The workup and separation hydrolyzed the orthoester to form the same product when using water as the competitive nucleophile.



Scheme 3.7 The NBS treatment of benzylidenelactone with t-butyl alcohol in presence

We therefore chose carboxylate ion as our competitive nucleophile. Sodium acetate was employed as a suitable carboxylate ion source. We treated 3,5-O-benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **1** with NBS with 5-10 equivalent sodium acetate present. After refluxed in carbon tetrachloride for 12 hours, NMR of the crude reaction mixture suggested the major product to be 3,5-O-bromobenzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **7**. In this case, sodium acetate only played a role of acid scavenger. It lowered the acidity and the bromide ion concentration so that slowed down the benzylidene group cleavage. Isomerization at the bromobenzylidene C took place, shown by the ^{13}C NMR spectra. When the reaction time was further extended, the NMR of the reaction mixture became very complicated, indicating a mixture of products. However, NMR also showed the emergence of 7-bromo-7-deoxy-3-O-benzoyl-2,5,6-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **2**, which was the rearrangement and terminal bromination product. Attempted separation of the other products by chromatography only yielded one major product, which was confirmed to be 5-O-benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **8**. Apparently, hydrolysis of the reaction mixtures led to this single product. A mechanism was proposed in Scheme 3.8. After the C-Br bond cleavage, a carboxonium cation and a bromide ion were generated. In the presence of excess sodium acetate, the carboxylate ion became competitive with the bromide ion. The carboxylate ion could trap the carboxonium cation to form the orthoanhydride. This competitive reaction also slowed down the rearrangement and terminal bromination reaction. On the other hand, the formation of small amount 7-bromo-7-deoxy-3-O-benzoyl-2,5,6-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **2** also suggested that bromide ion was a better nucleophile than sodium acetate since no 7-O-acetate product was detected. Under this condition, acetate

could not compete with the bromide ion in nucleophile substitution. Potassium benzoate was also tested in this reaction. Although benzoate ion should have a better nucleophilicity, the NBS reaction with potassium benzoate present showed the same result.



Scheme 3.8 The NBS treatment of benzylidenelactone with sodium acetate as the competitive nucleophile

3.3.2 The introduction of N-contained nucleophiles into the NBS oxidation

Although the O-nucleophiles introduction by the NBS reaction was generally not successful, we continued our exploration using other nucleophiles. Related to our synthetic efforts towards iminosugars as glycosidase inhibitors, it was of more importance to introduce N-contained nucleophiles into the sugar structure. This functionalization, combined with further transformation, could generate versatile iminosugars. Cyanides and nitrites were chosen to explore the NBS reaction with competitive nucleophiles present because of their cheap prices. The successful reactions with cyanides and nitrites

could generate N-functionalized sugar structures with one carbon extension and the same carbon number respectively.

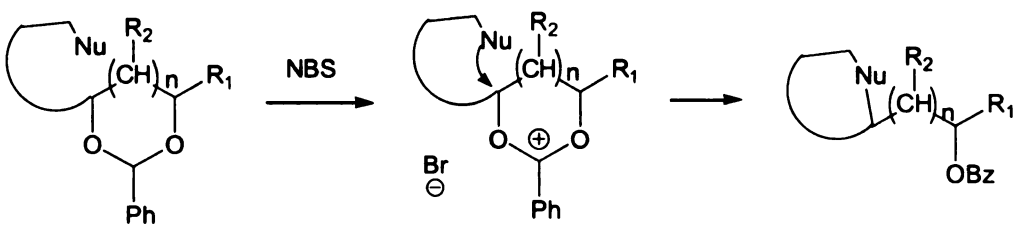
3,5-O-Benzylidene-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **1** was treated with NBS in refluxing carbon tetrachloride in the presence of excess sodium cyanide. NMR analysis of the crude reaction mixture was employed to monitor the reaction. The analysis showed a similar reaction model with the NBS reaction using barium carbonate as an acid scavenger. The pivaloyl rearrangement and bromination was slowed down and the bromobenzylidene compound isomerization was observed. Under extension of the reaction time, 7-bromination slowly emerged as a major reaction. In this case, sodium cyanide only acted as an acid scavenger to neutralize the trace amount of HBr. The low solubility of sodium cyanide in CCl_4 limited its ability to act as a competitive nucleophile; only bromination occurred after long reaction time. We postulated that using better solvents and/or phase transfer catalysts might be able to introduce more sodium cyanide into the reaction media so that cyanide ion could compete with the bromide ion to induce the different reaction model. Unfortunately, neither use of a better solvent (acetonitrile) nor addition of a phase transfer catalyst (18-crown-6) was successful. In either case, only starting materials were recovered. Under these reaction conditions, the basicity and the ionic strength of the solution were substantially increased. Therefore NBS reacted with the base before it could react with the benzylidene C-H bond in a free radical mode, which is the initial step of the rearrangement and the bromination. This explanation was further confirmed by employing some other base such as sodium acetate as the competitive nucleophile instead of cyanides, in which also only starting material was recovered.

Instead of cyanides, we also tried using acetone cyanohydrin, which is often used to generate cyanide in-situ, in the NBS reaction. When the NBS reaction was carried out with only acetone cyanohydrin in presence, the normal pivaloyl rearrangement and 7-bromination was observed. This indicated that under neutral or slightly acid conditions, no in-situ cyanide was generated to compete with the bromination reaction. We then used barium carbonate to generate in-situ cyanide. After refluxing for several hours, NMR analysis showed the major product to be of 5-O-benzoyl-2,6,7-tri-O-trimethylacetyl-D-glucoheptano-1,4-lactone **8**, indicating that hydrolysis had occurred. This was logical since the *in-situ* cyanide generation by acetone cyanohydrin and barium carbonate could generate some water. To avoid this problem, pyridine was used as the base. Unfortunately, the introduction of pyridine into the NBS reaction led to β-elimination, yielding the α,β-unsaturated-D-glucoheptanolactone **9**.

When sodium nitrite was employed as the competitive nucleophile in the NBS reaction, the reaction mode was similar with that using sodium cyanide as the competitive nucleophile. We reasoned that using silver nitrite could introduce more nitrite ion into the solution by scavenging the bromide ion out of the reaction media. When the reaction was refluxed in CCl_4 for 24 hours with silver nitrite in the presence, yellow precipitates were observed. However, NMR analysis of the reaction mixture showed only starting material. Under this condition, NBS reacted with silver nitrite directly to form silver bromide because of the strong bromide scavenging ability of silver salts. After that, the newly formed compound, presumably N-nitrosuccinimide, could not activate the benzylidene C-H and therefore the starting material was untouched.

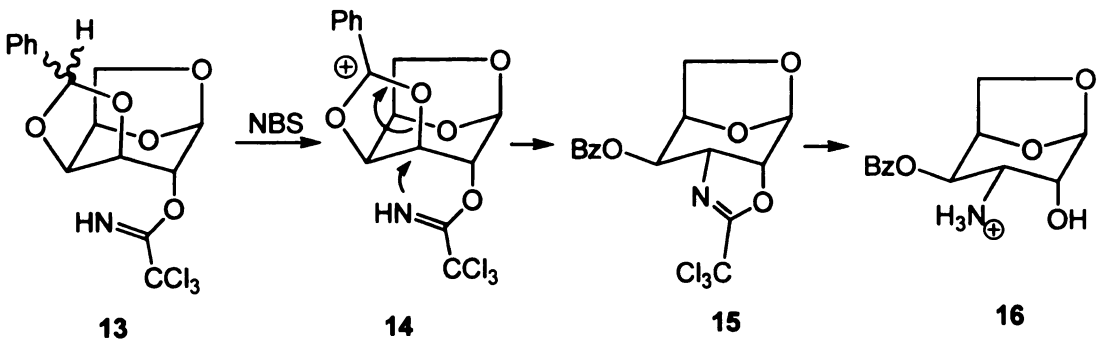
Generally, introducing the competitive nucleophile into the N-bromosuccinimide-mediated dioxolonium ion rearrangement did not give desired products with new functionalities. This finding is largely in agreement with the literature. Jacobsen and Pedersen and coworkers [5-11] explored the reactions of various nucleophiles with dioxonium ions derived from carbohydrates. Various benzylidene sugar structures were treated with triphenylmethyl fluoroborate to give benzoxonium ions and treated with various nucleophiles. With chloride, bromide, iodide, thiocyanate and tosylate *trans*-opening of the dioxonium ion took place. However, for a various number of nucleophiles such as acetate, azide, cyanide, no *trans*-opening was achieved. This was ascribed to the direct trapping of the dioxonium cation by nucleophiles to form orthoester-like structures, which underwent hydrolysis to give *cis*-opening. The nucleophilic *trans*-opening was shown to be competitive with the direct trapping of the dioxonium cation. The preference was decided by the nature of the nucleophiles introduced in.

3.4 The introduction of intramolecular competitive nucleophiles into the NBS bromination of 3,5-O-benzylidene-2,6,7-tri-O-pivaloyl-D-glucoheptono-1,4-lactone



Scheme 3.9 Intramolecular competitive nucleophile participated Hanessian-Hullar reaction

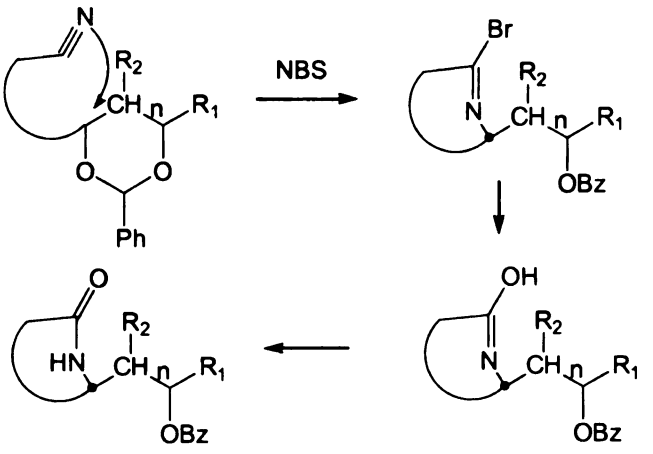
Ever since the Hanessian-Hullar reaction was discovered, the neighboring group participation was explored [12]. Normally the neighboring group acted as an intramolecular competitive nucleophile, which could drive the reaction to different directions and yield new functionalized structure (Scheme 3.9). Actually, the pivaloyl rearrangement discussed in Chapter 2 was also a Hanessian-Hullar reaction participated by intramolecular competitive nucleophiles, i.e. neighboring ester groups. Jacobsen explored the nucleophilic trans-opening of dioxonium ions with neighboring group participation [13-15]. Various neighboring groups such as thionobenzoate, xanthate, carbamate, thiocarbamate, benzimidate and carbonate were employed. With an iminoester group as the neighboring group, the nitrogen functionality could be introduced into the sugar structure to form an aminosugar (Scheme 3.10).



13 14 15 16

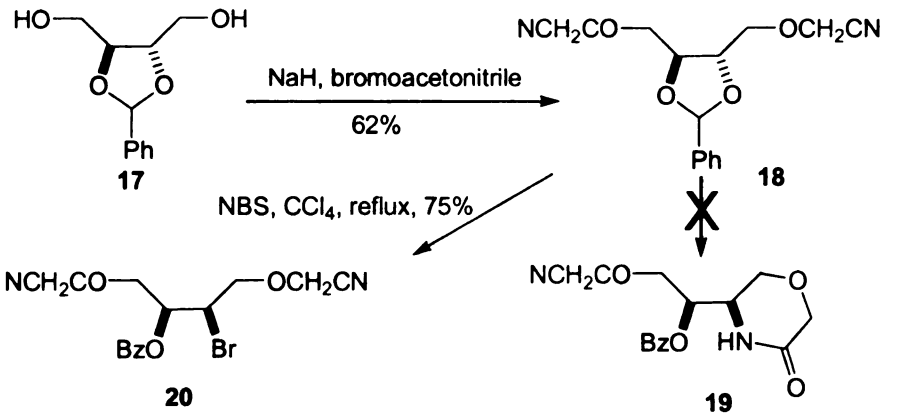
Scheme 3.10 The iminoester neighboring group participated Hanessian-Hullar reaction

Based on our goal to the synthesis of iminosugar structures, we reasoned that an intramolecular cyano group could act as a competitive nucleophile to give a lactam, which could be used as iminosugar precursor (Scheme 3.11). Furthermore, the lactam structure itself would be of much interest as a potential glycosidase inhibitor.



Scheme 3.11 Proposed intramolecular cyano group participated Hanessian-Hullar reaction

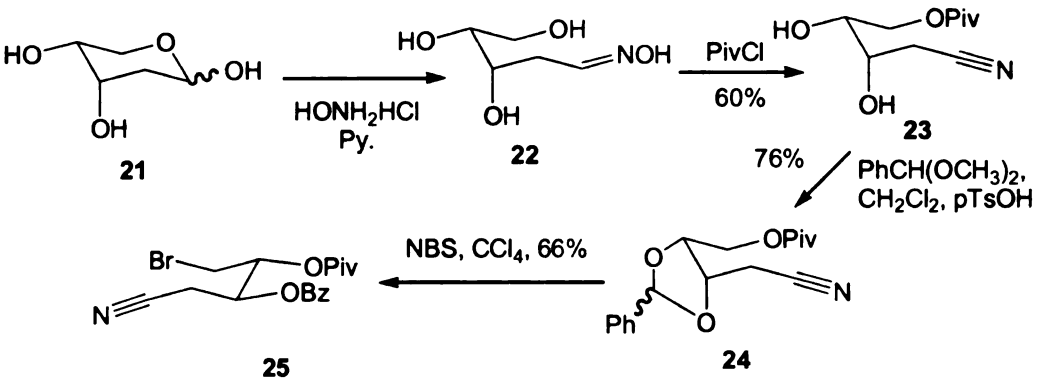
To test our hypothesis, we first employed 2,3-O-benzylidene-L-threitol **17** as our starting material because of its simplicity and easy accessibility. Due to its C_2 symmetry, no regioselectivity issues needed to be addressed. When treated with sodium hydride (NaH) and bromoacetonitrile, 2,3-O-benzylidene-1,4-di-O-cyanomethyl-L-threitol **18** was easily synthesized. We then treated this compound with NBS in carbon tetrachloride. A single product was obtained in 75% yield. However, NMR analysis showed the structure to be 2-O-benzoyl-3-bromo-3-deoxy-1,4-di-O-cyanomethyl-D-erythritol **20** (Scheme 3.12). The reaction proceeded with normal Hanessian-Hullar reaction mode without intramolecular nucleophile participation. Using barium carbonate to slow down the bromination did not help the intramolecular nucleophilic attack. The same product was obtained.



Scheme 3.12 Attempted cyano-participated Hanessian-Hullar reaction: synthesis of 2-O-benzoyl-3-bromo-3-deoxy-1,4-di-O-cyanomethyl-D-erythritol

We then tried to shorten the distance between the benzylidene group and the cyano group, hoping that this could change the transition state ring structure so that change the preference of the intramolecular nucleophile attack. We then made 2,3-O-benzylidene-1,4-di-O-p-toluenesulfonyl-L-threitol by treatment of 2,3-O-benzylidene-L-threitol **17** with p-toluenesulfonyl chloride in pyridine. However, even after many attempts with different reaction conditions, the expected nucleophilic substitution of this di-tosylate with sodium cyanide to afford a dicyano compound did not occur. Elimination was observed as a serious side reaction. Transforming the tosyl leaving groups to iodo groups did not improve the desired nucleophilic substitution.

We therefore tried to seek other synthetic pathway to our desired molecules to test our idea of cyano group participated Hanessian-Hullar reaction. Sugar oximes have been synthesized readily for many years. Transformation of the N-hydroxyl group of a sugar oxime to bromide or ester often results elimination to give a sugar nitrile. Sugar nitriles, appropriately protected, could serve as substrates in our exploration of the intramolecular cyano-participated Hanessian-Hullar reaction.



Scheme 3.13 Synthesis of 2-deoxy-D-ribonitrile and attempted cyano-participated Hanessian-Hullar reaction

To shorten the synthetic precedure, we tried to combine the oxime formation and the elimination to synthesize the sugar nitriles. 2-Deoxy-D-ribose **21** was treated with hydroxylamine hydrogen chloride in pyridine and subsequently treated with pivaloyl chloride to afford the 2-deoxy-5-O-trimethylacetyl-D-ribonitrile **23** in 60% yield (Scheme 3.13). This nitrile was then treated with benzaldehyde dimethyl acetal to give 3,4-O-benzylidene-2-deoxy-5-O-trimethylacetyl-D-ribonitrile **24** as a 4:1 mixture of two diastereoisomers in 76% yield. In the NBS-cleavage of benzylidene group, this new chirality would be scrambled without obvious effects on the product structure. Hence 3,4-O-benzylidene-2-deoxy-5-O-trimethylacetyl-D-ribonitrile **24** was treated with NBS in refluxing carbon tetrachloride. NMR analysis of the reaction showed no evidence of formation of lactams. This meant no Ritter-type reaction occurred under our reaction condition. The only major product was separated and analyzed. The structure was confirmed to be 3-O-benzoyl-5-bromo-2,5-dideoxy-4-O-trimethylacetyl-L-lyxonitrile **25**. The reaction proceeded through an NBS-promoted pivaloyl rearrangement and primary bromination. Using acid scavengers such as barium carbonate only slowed down the bromination reaction without promoting any other side-reactions. Under our reaction

condition, the intramolecular cyano group was unreactive towards the *in-situ* formed benzoxonium carbocation. Due to the steric hindrance, the primary pivaloyl group rearranged to the 4-position and inverted the chiral center. The following bromination at the primary position furnished the protected bromosugarnitrile as the final product. Although the Ritter-type reaction did not happen, the product itself was also of much significance. Protected and brominated, this L-sugar nitrile could serve as a good chiral building block towards azasugars by controlled reduction.

3.5 Summary

The base-sensitivity of the N-bromosuccinimide-mediated dioxolonium ion rearrangement was discovered. While inorganic base slowed down the rearrangement and terminal bromination by lowering down bromide ion concentration, organic base, i.e., pyridine induced a controlled β-elimination to generate an α,β-unsaturated sugar lactone. Various competitive nucleophiles were used in the NBS-cleavage of benzylidene acetal of sugar lactone to explore the introduction of new functionalities into the sugar structure. The introduced nucleophiles generally could not compete with in-situ generated bromide ion in the terminal nucleophile substitution. The direct trapping of the benzoxonium cation by intermolecular competitive nucleophiles such as t-butyl alcohol and carboxylates were also believed to be an important competing reaction. Intramolecular attack of benzoxonium cation by cyano group did not occur. This was due to the much lower nucleophilicity of cyano group than bromide ion.

EXPERIMENTAL

General Optical activity data were obtained on a JASCO P-1010 polarimeter at 25°C. NMR spectra were obtained on a Varian VXR-500 Spectrometer operating at 500MHz for protons. Mass spectra were obtained on a JEOL HX-110-HF instrument using fast atom bombardment as ionization mode. Spectra were recorded in the positive ion mode. IR spectra were obtained on a Nicolet 710 spectrometer in chloroform solution except when otherwise specified.

5-O-Benzoyl-2,6,7-tri-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**8**):

2,6,7-Tri-O-trimethylacetyl-3,5-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (1.0 g, 1.82 mmol) was suspended in 10 mL carbon tetrachloride and N-bromosuccinimide (0.5 g, 2.81mmol) was added. Water (86 mg, 4.78 mmol) was added in. The mixture was refluxed at 80°C oil bath for 5 hours. The mixture was filtered and washed with saturated sodium bicarbonate solution. The raw product was purified by flash column chromatography to afford 5-O-Benzoyl-2,6,7-tri-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **8** (0.74 g, 72% yield) as colorless oil. $[\alpha]_D$ = -58.5° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.15,1.16,1.25 (27H, 3 x s, 3 x $C(C\underline{H}_3)_3$), 3.49 (1H, d, J = 3.5 Hz, -O<u>H</u>), 4.21 (1H, dd, $J_{7,7'}$ 12.1, $J_{6,7'}$ 8.3 Hz, H-7'), 4.58 (1H, dd, $J_{6,7}$ 3.2 Hz, H-7), 4.71 (1H dd, $J_{3,4}$ 2.9, $J_{4,5}$ 8.5 Hz, H-4), 4.89 (1H, m, $J_{2,3}$ 4.7 Hz, H-3), 5.34 (1H, ddd, $J_{5,6}$ 8.3 Hz, H-6), 5.44 (1H, d, H-2), 5.91 (1H, dd, H-5), 7.42-7.44 (2H, m, Ar<u>H</u>), 7.56-7.58 (1H, m, Ar<u>H</u>), 8.00-8.02 (2H, m, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 26.91, 27.00 ($OCC(\underline{C}H_3)_3$), 38.57, 38.65, 38.81 ($OC\underline{C}(CH_3)_3$), 61.90 (C-7), 68.44, 69.98, 70.05, 70.70, 77.98 (C-2, 3, 4, 5, 6), 128.53, 129.07, 129.85 (Ar<u>C</u>H), 133.52 (Ar<u>C</u>), 164.85 (O<u>C</u>Ph),

169.80 (O=C in lactone), 177.28, 178.21, 178.54 ($OCC(CH_3)_3$); FT-IR: 3456, 2976, 1807, 1734, 1265, 1139 cm^{-1}.

α,β-Unsaturated-3-deoxy-5-O-benzoyl-2,6,7-tri-O-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**9**):

2,6,7-Tri-O-trimethylacetyl-3,5-O-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (1 g, 1.82 mmol) was suspended in carbon tetrachloride (10 mL) with N-bromosuccinimide (0.5 g, 2.81 mmol). Pyridine (0.29 g, 3.64 mmol) was added. The mixture was refluxed at 80 °C for 6 hours and filtered through a thin pad of silica gel. The filtration was evaporated to give **9** (0.75 g, 75%) as pale yellow oil. $[\alpha]_D$ = + 4.9° (c = 0.8, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.11,1.12,1.17 (3 x 9H, 3 x s, 3 x $C(CH_3)_3$), 4.10 (1H, dd, $J_{7,7'}$ 12.6, $J_{6,7'}$ 4.8 Hz, H-7'), 4.56 (1H, dd, $J_{6,7}$ 2.5 Hz, H-7), 5.30 (1H, d, $J_{4,5}$ 2.0Hz, H-4), 5.45 (1H, ddd, $J_{5,6}$ 7.4Hz, H-6), 5.64 (1H, dd, H-5), 738 (2H, m, ArH), 7.52 (1H, m, ArH), 7.88 (2H, m, ArH); δ_C (125MHz; $CDCl_3$): 26.54, 26.85, 26.93 ($OCC(CH_3)_3$), 38.67, 38.74, 39.15 ($OCC(CH_3)_3$), 61.41 (C-7), 68.68, 69.63, 76.81 (C-4, 5, 6), 124.78, 127.91 (C-2, 3), 128.50, 129.15, 129.65 (ArCH), 133.67 (ArC), 164.89 (OCPh), 165.82 (O=C in lactone), 174.11, 176.69, 177.68 ($OCC(CH_3)_3$); FT-IR: 2980, 1986, 1726, 1269, 1116 cm^{-1}.

2,3-O-Benzylidene-1,4-di-O-cyanomethyl-L-threitol (**18**):

2,3-O-Benzylidene-L-threitol (1.0 g, 4.8 mmol) was dissolved in 20 mL anhydrous tetrahydrofuran and cooled down to -78°C. Sodium hydride (60% suspension in mineral oil) (0.57 g, 14.3 mmol) was added slowly under stirring. Bromoacetonitrile (1.44 g, 12.0 mmol) was added slowly. The mixture was warmed up to 0°C slowly and

stirred at this temperature for 2 hours. It was poured into ice and stirred vigorously. The mixture was extracted by chloroform (3 x 50 mL). The organic layer was washed by brine (25 mL) and water (25 mL). It was dried and evaporated to dryness. The crude product was purified by chromatography to afford 2,3-O-benzylidene-1,4-di-O-cyanomethyl-L-threitol **18** as colorless oil (0.85 g, 62%). $[\alpha]_D$ = + 25.3° (c = 1.1, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 3.79 (4H, d, $J_{1,2}$ 4.4Hz, H-1, 4), 4.21 (2H, m, H-2, 3), 4.32 (4H, m, $OC\underline{H}_2CN$), 5.93 (1H, s, C<u>H</u>Ph), 7.37-7.47 (5H, m, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 56.53 ($O\underline{C}H_2CN$), 71.29, 71.42 (C-1, 4), 76.32, 76.35 (C-2, 3), 104.09 (<u>C</u>HPh), 115.29 ($OCH_2\underline{C}N$), 126.32, 128.15, 129.43 (Ar<u>C</u>H), 136.25 (Ar<u>C</u>); FT-IR: 3038, 2937, 2206, 1101 cm^{-1}.

2-O-Benzoyl-3-bromo-3-deoxy-1,4-di-O-cyanomethyl-D-erythritol (**20**):

2,3-O-benzylidene-1,4-di-O-cyanomethyl-L-threitol **18** was reacted with 2 equivalent NBS in carbon tetrachloride under reflux for 6 hours. After column chromatography, 2-O-benzoyl-3-bromo-3-deoxy-1,4-di-O-cyanomethyl-D-erythritol **20** in 75% yield. $[\alpha]_D$ = +22.5 (c = 0.9, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 4.00 (5H, m, H-1, 3, 4), 4.28 (4H, m, $OC\underline{H}_2CN$), 5.51 (td, 1H, J = 4.6Hz, J = 6.5Hz, H-2), 7.45 (t, 2H, J = 7.6Hz), 7.58 (t, 1H, J = 7.3Hz), 8.03 (d, 2H, J = 7.7Hz); δ_C (125MHz; $CDCl_3$): 46.951 (C-3), 56.583, 56.402 ($O\underline{C}H_2CN$), 71.699, 71.374, 70.478 (C-1, 2, 4), 104.09 (<u>C</u>HPh), 115.320, 115.156 ($OCH_2\underline{C}N$), 129.738, 128.837, 128.513 (Ar<u>C</u>H), 133.626 (Ar<u>C</u>), 165.104 (O<u>C</u>Ph); FT-IR: 1721, 1267, 1108 cm^{-1}.

2-Deoxy-5-O-trimethylacetyl-D-ribonitrile (**23**):

2-Deoxy-D-ribose (1.5 g, 11.2 mmol) was dissolved in 40 mL pyridine and hydroxylamine hydrogen chloride salt (1.17 g, 16.8 mmol) was added in. The solution

was stirred at room temperature for 12 hours. The solution was cooled down to 0 °C and trimethylacetyl chloride (4.72 g, 39.2 mmol) was added slowly. The solution was warmed up to room temperature slowly and stirred for 12 hours thereafter. The solution was poured into sodium bicarbonate with ice and stirred for 10 minutes and extracted by 3 x 50 mL chloroform. The organic phase was dried and evaporated to sticky oil. This crude product was purified by flash column chromatography to give 2-deoxy-5-O-trimethylacetyl-D-ribonitrile **23** as colorless oil (1.44g, 60%). $[\alpha]_D$ = -21.7° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.20 (9H, s, $C(C\underline{H}_3)_3$), 2.66 (1H, dd, $J_{2,2'}$16.7 Hz, $J_{2',3}$6.8Hz, H-2'), 2.76 (1H, dd, $J_{2,3}$3.6Hz, H-2), 3.06 (1H, b, -O$\underline{H}$), 3.59 (1H, b, -O$\underline{H}$), 3.79 (2H, m, H-3, H-4), 4.26 (1H, dd, $J_{5,5'}$12.2 Hz, $J_{4,5'}$3.3Hz, H-5'), 4.33 (1H, dd, $J_{4,5}$4.8Hz, H-5); δ_C (125MHz; $CDCl_3$): 22.52 (C-2), 27.10 ($OCC(\underline{C}H_3)_3$), 38.96 ($OC\underline{C}(CH_3)_3$), 65.25 (C-5), 67.78, 72.06 (C-3, C-4), 118.03 (C-1), 179.79 ($O\underline{C}C(CH_3)_3$); FT-IR: 3448, 2976, 2439, 1709, 1286, 1165, 1071 cm^{-1}.

3,4-O-Benzylidene-2-deoxy-5-O-trimethylacetyl-D-ribonitrile (**24**):

2-deoxy-5-O-trimethylacetyl-D-ribonitrile **23** (0.2 g, 0.93 mmol) was dissolved in 5 mL dichloromethane with benzaldehyde dimethyl acetal (0.28 g, 1.8 mmol). p-Toluenesulfonic acid (0.03 g) was added in. The solution was stirred at room temperature for 12 hours and poured into saturated sodium bicarbonate solution. The mixture was extracted by chloroform (20 mL). The organic phase was dried and evaporated. The crude mixture was purified by flash column chromatography to give 3,4-O-benzylidene-2-deoxy-5-O-trimethylacetyl-D-ribonitrile **24** (0.21g, 76%) as a mixture of two isomers (4 : 1). For the major isomer (3,4-(*S*)-O-benzylidene): δ_H (500MHz; $CDCl_3$): 1.22 (9H, s, $C(C\underline{H}_3)_3$), 2.66 (1H, dd, $J_{2,2'}$16.7 Hz, $J_{2',3}$7.0Hz, H-2'), 2.71 (1H, dd, $J_{2,3}$4.4Hz, H-2), 3.62

(1H, dd, $J_{5,5'}$10.8 Hz, $J_{4,5'}$9.8Hz, H-5'), 4.08 (1H, ddd, $J_{3,4}$9.6Hz, H-3), 4.40 (1H, dd, $J_{4,5}$5.4Hz, H-5), 4.78 (1H, dt, H-4); δ_C (125MHz; $CDCl_3$): 21.655 (C-2), 26.999 ($OCC(\underline{C}H_3)_3$), 38.888 ($OC\underline{C}(CH_3)_3$), 67.648 (C-5), 74.752, 65.912 (C-3, C-4), 101.405 (<u>C</u>HPh), 116.153 (C-1), 136.318, 129.370, 128.330, 126.099 (Ar<u>C</u>), 177.181 ($O\underline{C}C(CH_3)_3$); FT-IR: 2966, 2436, 1718, 1275, 1158 cm^{-1}.

3-O-Benzoyl-5-bromo-2,5-dideoxy-4-O-trimethylacetyl-L-lyxonitrile (**25**):

3,4-O-Benzylidene-2-deoxy-5-O-trimethylacetyl-D-ribonitrile **24** (0.15 g, 0.5 mmol) was dissolved in 5 mL carbon tetrachloride and N-bromosuccinimide (0.18 g, 1.0 mmol) was added. The mixture was refluxed for 6 hours and filtered. The filtrate was purified by chromatography to give 3-O-benzoyl-5-bromo-2,5-dideoxy-4-O-trimethylacetyl-L-lyxonitrile **25** as colorless oil (0.15 g, 66%). $[\alpha]_D$ = +1.9° (c = 0.7, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.25 (9H, s, $C(C\underline{H}_3)_3$), 2.81 (1H, dd, $J_{2,2'}$17.3 Hz, $J_{2',3}$4.9Hz, H-2'), 2.97 (1H, dd, $J_{2,3}$4.7Hz, H-2), 3.57 (1H, dd, $J_{5,5'}$11.6 Hz, $J_{4,5'}$4.7Hz, H-5'), 3.71 (1H, dd, $J_{4,5}$4.0Hz, H-5), 5.31 (1H, td, $J_{3,4}$7.2Hz, H-4), 4.54 (1H, td, H-3); δ_C (125MHz; $CDCl_3$): 19.722 (C-2), 26.915 ($OCC(\underline{C}H_3)_3$), 29.984 (C-5), 38.958 ($OC\underline{C}(CH_3)_3$), 70.604, 67.878 (C-3, C-4), 115.427 (C-1), 133.896, 129.797, 128.586, 128.329 (Ar<u>C</u>), 164.716 (<u>C</u>OPh), 176.745 ($O\underline{C}C(CH_3)_3$); FT-IR: 3098, 3077, 1728, 1627, 1603, 1262, 1139, 1104 cm^{-1}.

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Chapter 4

Acid-Promoted Dioxonium Cation Facilitated Bromination and Ritter-Type Reactions

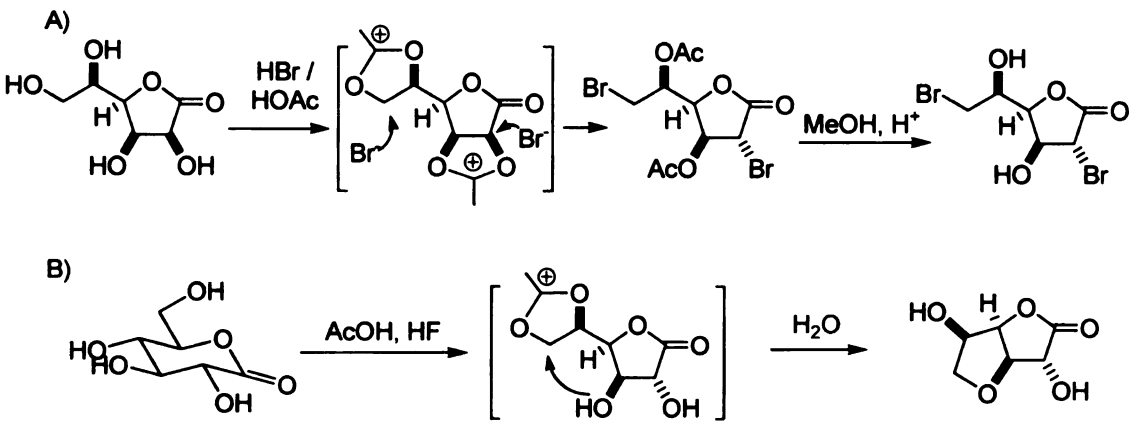
ABSTRACT

Facilitated by dioxonium cation formation and rearrangement under strong acidic conditions, selective bromination of aldonolactones was carried out to generate useful bromosugars. The anomeric bromination of hexose pentapivaloates was achieved to generate tetrapivaloyl glycosyl bromides as useful glycosyl donors. When acetonitrile was employed as solvent and nucleophile, Ritter-type reactions occurred to afford several glycosyl amides. Furthermore, a unique dioxonium cation assisted Ritter-type reaction was discovered when glycerol dipivaloates were treated with strong acid in acetonitrile. The stereoselectivity and regioselectivity of this new Ritter-type reaction were tested by using erythritol tripivaloate and 1,2,4-butanetriol dipivaloates as the substrates. The Ritter-type reaction was employed to easily introduce amide groups to the primary position of aldonolactone to generate important and interesting N-contained sugar derivative.

4.1 Introduction

In the previous chapters, we discussed the NBS-promoted acetoxonium cation rearrangement. The dioxonium cation generated *in-situ* by H-abstraction of benzylidene groups acts as a good leaving group. The intramolecular attack by an active neighboring

group such as the pivaloyl group results acyl groups rearrangement and transformation of chirality. An intermolecular nucleophile such as bromide ion furnishes a new functionality in the molecule and drives the equilibirum of the acyl rearrangement towards the less steric hindered specie. The acetoxonium cation generated under acidic conditions has long been known and used as an electrophile [1-17]. The acidic bromination of sugar lactones [7, 14] (Scheme 4.1 A) and the preparation of anhydrosugars [5] are two prominent examples (Scheme 4.1 B). In these reactions, under acidic conditions, acetoxonium cation is formed through the participation of the acetyl group and acts as an electrophile, which is subsequently attacked by intramolecular (-OH) or intermolecular (Br-) nucleophiles to finish the functional group transformation.



Scheme 4.1 Acetoxonium cation generated under acidic conditions : A) dibromination of aldonolactones; B) anhydrosugar formation

Our success in the control of the site of bromination and the stereochemical course and chemoselectivity of rearrange reactions involving NBS promoted dioxonium species suggested several important synthetic uses and methodology development pathways for this chemistry. One such area is the development of strategies for the preparation of azasugars. Other areas include the preparation of rare L-sugars and

activated but orthogonally protected alditols. To this end, we embarked on a study to develop industrially useful methodologies for synthesis of series of differentially protected bromosugar lactones using easily accessible starting materials. The acetoxonium cation facilitated bromination could generate monobromo- or dibromosugar structures. The acyl group could serve as a good protecting group in the resulted bromosugar structure. Bearing good leaving group and selective protecting group, these bromosugars could serve as good synthetic precursors of aminosugars (Figure 4.1).

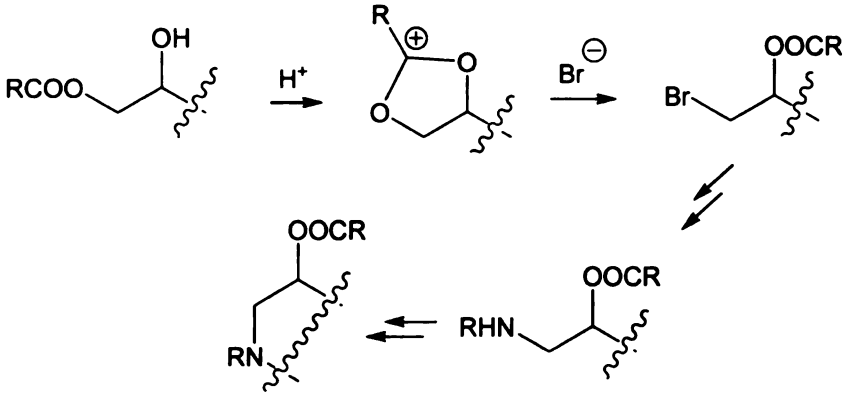


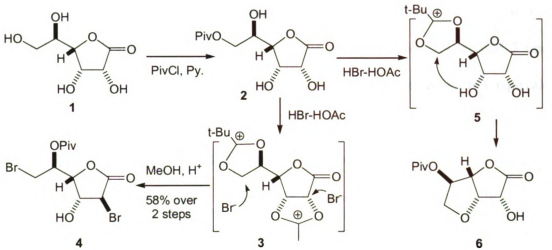
Figure 4.1 bromosugars generated from the acetoxonium cation facilitated bromination serve as good synthetic precursors of iminosugars

4.2 Selective pivaloylation and bromination facilitated by dioxonium cation formation and rearrangement

4.2.1 Synthesis of 2,6-dibromo-2,6-dideoxy-5-O-trimethylacetyl-D-*idono*-1,4-lactone

D-*gulono*-1,4-lactone **1** was selectively pivaloylated at the primary position to yield 6-O-trimethylacetyl-D-*gulono*-1,4-lactone **2**. Compound **2** was then treated with 30% hydrogen bromide in acetic acid (HBA) to give 2,6-dibromo-2,6-dideoxy-5-O-

pivaloyl-D-*idono*-1,4-lactone (**4**) in 58% yield over two steps (Scheme 4.2).

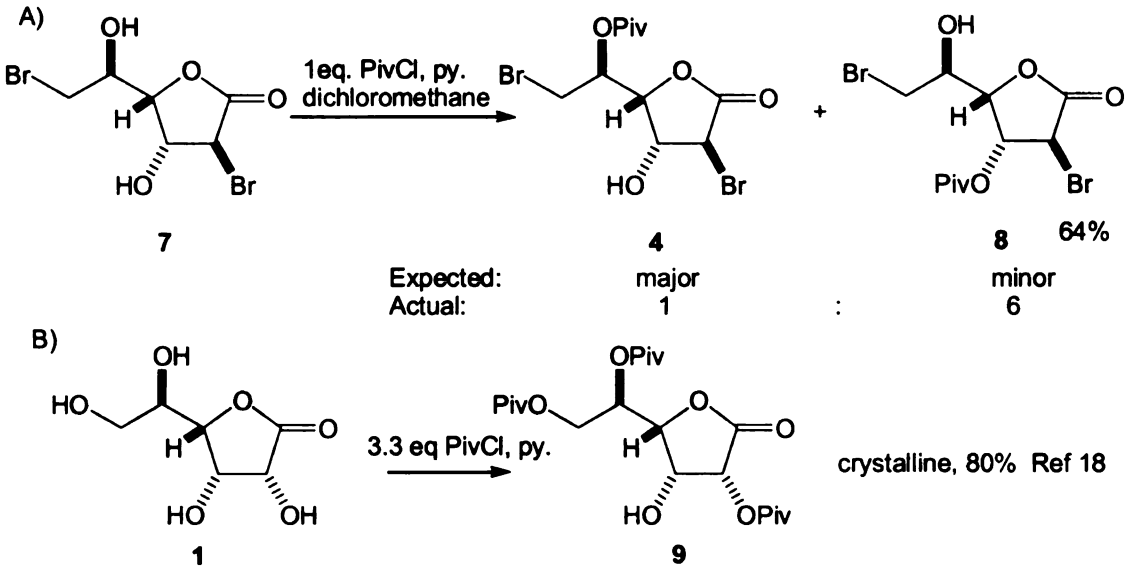


Scheme 4.2 Synthesis of 2,6-dibromo-2,6-dideoxy-5-O-trimethylacetyl-D-*idono*-1,4-lactone **4**

In the strongly acidic conditions, a t-butyl-1,3-dioxonium cation **3** was formed, and subsequently opened by the incoming Br^- nucleophile. A competitive side reaction is the intramolecular attack of the t-butyl-1,3-dioxonium cation **5** by the 3-OH group to form a 3,6-anhydrous sugar lactone **6**. The work-up procedure (methanol transesterification) removed the acetyl group leaving the more robust 5-O-pivaloyl group untouched. The pivaloyl group was used as a protection group in the synthetic procedure for several reasons. Firstly, it has a relatively better selectivity for functionalizing primary hydroxyl groups because of its size. Secondly, the electron donating t-butyl group could stablize the carboxonium cation intermediate and therefore increase the reaction efficiency. Thirdly, the pivaloyl group is more tolerant to the acidic conditions used to selectively remove the acetyl group. The net result of this procedure was the selective 5-position pivaloylation of a 2,6-dibromo-2,6-dideoxy-D-*idono*-γ-lactone. In other words, the O-acylation selectivity at the primary position of sugar lactones was successfully

transferred to a neighboring position by an acid-catalyzed pivaloyl rearrangement.

The importance of this reaction was further demonstrated by comparing with the direct selective pivaloylation of 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **7** under normal pivaloylation condition (Scheme 4.3 A). When **7** was treated with 1 equivalent pivaloyl chloride in the presence of pyridine in dichloromethane, we expected two products: 3-O-pivaloyl-2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **8** and 5-O-pivaloyl 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **4** with the latter one being slighly favored. However, NMR analysis of the products showed 3-O-pivaloyl dibromolactone **8** as the major product with only small amounts of 5-O-pivaloyl dibromolactone **4** (**4**:**8** = 1:6).



Scheme 4.3 A) Selective monopivaloation of 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **7** and B) selective tripivaloation of D-*gulono*-1,4-lactone **1**

This unexpected selectivity was very different from the results of selective tripivaloylation of sugar lactones by Gallo's group [18]. By treatment of D-*gulono*-1,4-lactone **1** with 3.3-3.6 equivalent pivaloyl chloride in pyridine, 2,5,6-tri-O-pivaloyl-D-*gulono*-1,4-lactone **9** was selectively obtained in 80% yield as a crystalline compound

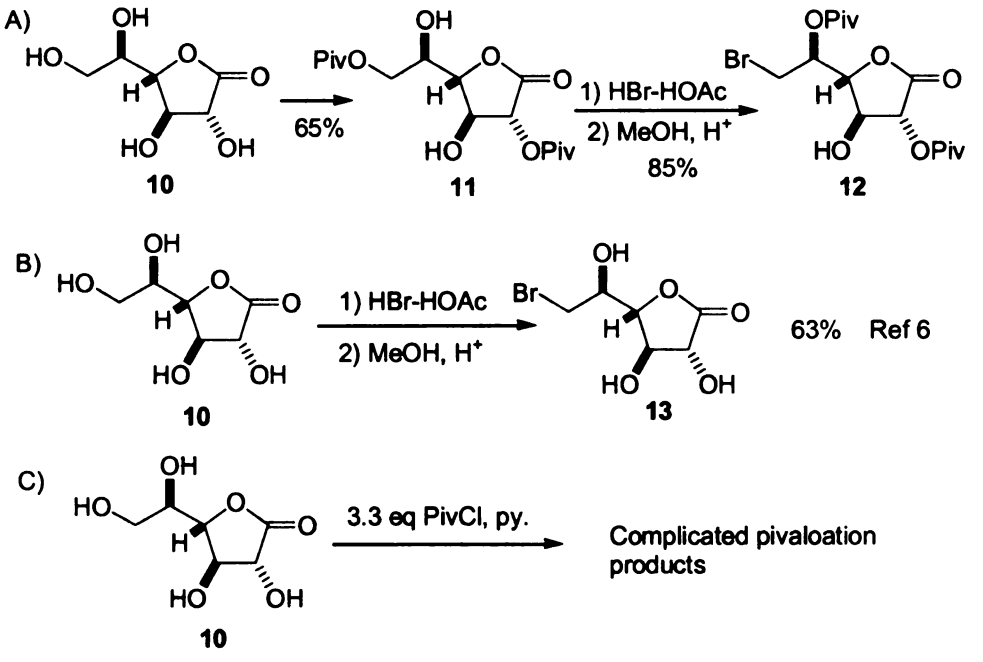
(Scheme 4.3 B). The selectivity of 3-O-acylation over 5-O-acylation was fairly high. However, our approach showed a relatively high but reversed selectivity.

This selectivity reversal could be easily understood by considering the stereochemistry change at 2-position. D-*gulono*-γ-lactone has 2,3-*cis* oriented hydroxyl groups partially eclipsed. Once the 2-O-position is protected by a bulky pivaloyl group, it would generate high steric hindrance towards the incoming pivaloyl group to 3-position. For 2,6-dibromoidonolactone **7**, the bromination of 2-position changes the 2,3-*cis* orientation to 2,3-*trans*. This transformation greatly released the steric hindrance of 2-substitution group towards the approach of the incoming pivaloyl group to 3-position. The selectivity of pivaloylation between 3-O and 5-O position was therefore reversed. Under normal pivaloylation conditions, 3-O-pivaloate **8** of 2,6-dibromoidonolactone **7** instead of 5-O-pivaloate **4** was synthesized. This further illustrates the practical utility of the 5-O-pivalation of 2,6-dibromolactone through t-butyl-1,3-dioxonium cation rearrangement procedure.

4.2.2 Synthesis of 6-bromo-6-deoxy-2,5-di-O-pivaloyl-D-*galactono*-1,4-lactone

To expand this strategy to other sugar lactones, 2,6-di-O-pivaloyl-D-*galactono*-1,4-lactone **11** was synthsized as discussed in chapter 2 (Scheme 4.4 A). It was then treated with 30% hydrogen bromide in acetic acid (HBA) to yield 85% 6-bromo-6-deoxy-2,5-di-O-pivaloyl-D-*galactono*-1,4-lactone **12**. The 5,6-O-t-butyl-1,3-dioxonium cation was believed to be the active intermediate. With *galacto*- configuration, the *trans*-orientation of the 2,3-substitution groups prevented the formation of 2,3-O-t-butyl-1,3-dioxonium cation formation and therefore no 2-bromo compound was formed. This is in

consistence with the reaction of D-*galactono*-γ-lactone **10** with HBA, which resulted in 6-bromo-6-deoxy-D-*galactono*-1,4-lactone **13** (Scheme 4.4 B).



Scheme 4.4 A) Synthesis of 6-bromo-6-deoxy-2,5-di-O-pivaloyl-D-*galactono*-1,4-lactone **12**; B) Synthesis of 6-bromo-6-deoxy-D-*galactono*-1,4-lactone 13 (Ref 6); C) selective tripivaloation of D-*galactono*-1,4-lactone **10**

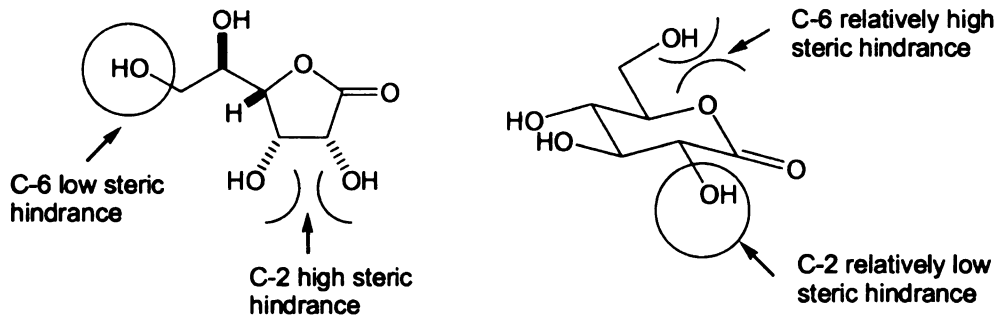
As a net result of the pivaloyl rearrangement to facilitate bromination at a primary position, we selectively protected the 2 and 5-positions of 6-bromo-6-deoxy-D-*galactono*-1,4-lactone **13** using pivaloyl groups. The advantage of this selectivity transformation could also be shown by comparing it with the direct selective pivaloylation of D-*galactono*-1,4-lactone. Using 3.3-3.6 equivalent pivaloyl chloride in pyridine, the tripivaloylation of D-*galactono*-1,4-lactone **10** was explored [18]. Their results showed poor selectivity of D-galactono-1,4-lactone pivaloylation by formation of a complicated mixture, especially involving between 3- and 5- positions. The 2,6-di-O-pivaloyl-, 2,3,6-tri-O-pivaloyl-, 2,5,6-tri-O-pivaloyl- and 2,3,5,6-tetra-O-pivaloyl-D-*galactono*-1,4-lactone was obtained in 30%, 2.6%, 9.7% and 21.6% yield respectively,

indicating a poor selectivity between the 3- and 5- positions but with a slight preference for the 5-O-position. In the case of selective pivaloylation of 6-bromo-6-deoxy-D-*galactono*-1,4-lactone, the configuration remained unchanged. We expect the similar selectivity except that the large primary bromo- group may further reduce the selectivity for the 5-position over the 3-position. By the acidic t-butyl-1,3-dioxonium cation rearrangement, the 5-O-pivaloyl group was rearranged from 6-position so the 5-O-pivaloylation selectivity came directly from the much smaller steric hindrance of the primary position. This would be apparently more selective than the direct pivaloylation of 6-bromo-6-deoxy-D-*galactono*-1,4-lactone **13**, in which the selectivity is based on two less differentiated secondary hydoxyl groups.

4.2.3 Synthesis of 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone

We also tried to expand this strategy to some other sugar lactones. D-*glucono*-1,5-lactone has long been used as a chiral starting material due to its cheap price and rich chirality. We assumed monopivaloylation of the primary hydoxyl group and further treatment with HBA could generate 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone as a selectively functionalized and protected chiral building block, which could be further employed in our synthetic work towards azasugars. Experimentally, the selectivity of primary pivaloylation was shown to be relatively lower than in that in the case of D-*gulono*-1,4-lactone. Both the primary and 2-position of D-*glucono*-1,5-lactone were fairly active towards pivaloylation, therefore it was necessary to use more than 1 equivalent of acylation reagent to increase the yield. Although the yield was not high, the cheap price of the starting material made the reaction practicable. The relatively poor selectivity could be explained by comparing the different ring structures of D-*gulono*-1,4-

lactone **1** and D-*glucono*-1,5-lactone **14** (Figure 4.2). The primary hydoxyl group of D-*gulono*-1,4-lactone is fairly far away from the ring structure while the 2-position is on a five member-ring. The partially eclipse relationship between 2- and 3- positions will highly increase the steric hindrance of 2-OH towards acylation. However, for D-*glucono*-1,5-lactone, the primary position is relatively close to the ring structure, which will decrease its acylation rate. Furthermore, the six-membered ring has a near-chair conformation, in which the 2,3-trans hydroxyl groups have relatively low interaction. As a result, the 2-OH is relatively more active than that in the D-*gulono*-1,4-lactone.



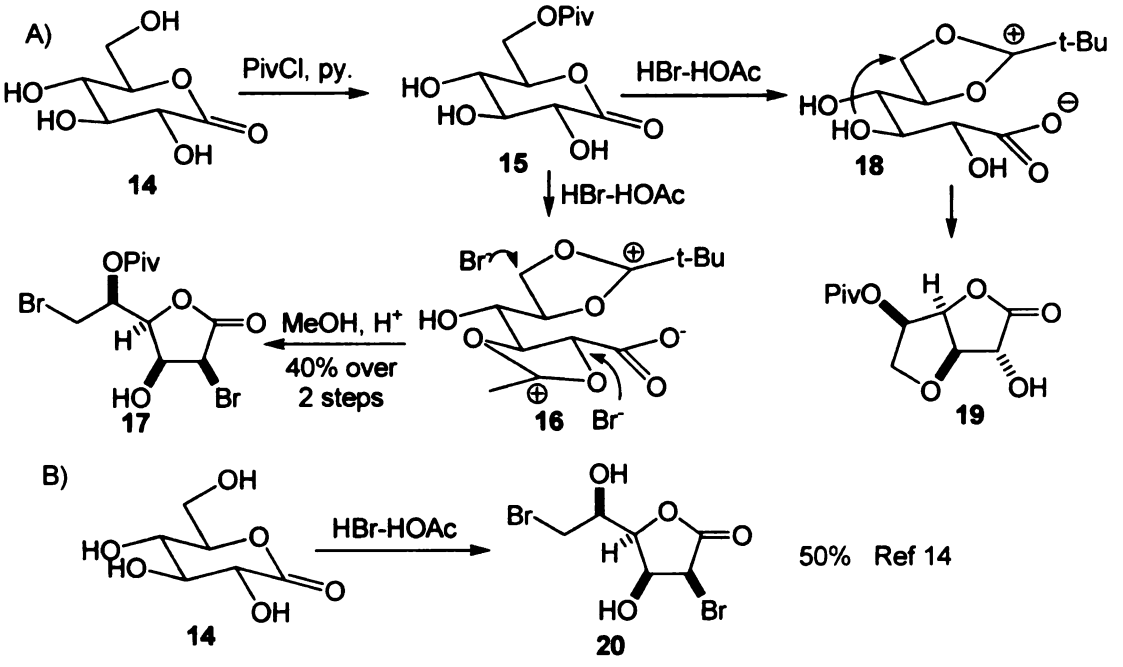
D-*gulono*-1,4-lactone **1**

D-*glucono*-1,5-lactone **14**

Figure 4.2 A comparison of the different ring structures of D-*gulono*-1,4-lactone and D-*glucono*-1,5-lactone

Without separation, the 6-O-pivaloyl-D-*glucono*-1,5-lactone was then subjected to HBA treatment. As expected, after work-up, 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone **17** was synthesized in a 40% yield over 2 steps (Scheme 4.5). The relatively low yield could be understood by exploring the mechanism of this reaction. An acyloxonium cation was believed to be the active intermediate, which would facilitate introduction of the bromo group by acting as an electrophile. However, an important structure aspect of D-*glucono*-1,5-lactone is the six-membered lactone ring. To form the

5,6-acyloxonium cation **16**, the lactone ring has to be opened. Furthermore, the 2,3-*trans* configuration of D-*glucono*-δ-lactone also prevents the 2,3-acyloxonium cation formation. To form this 2,3-acyloxonium cation and then introduce a bromo group into 2-position, the lactone ring also has to be opened. After the bromo groups are introduced into the structure, the lactone ring cyclizes again to form the final product. The necessary ring opening process substantially retarded the bromination reaction and increased the amount of byproduct. A serious side reaction was believed to be the intramolecular attack of the 5,6-acyloxonium cation **18** by 3-OH, which would generate 3,6-anhydro-5-O-pivaloyl-D-*glucono*-1,4-lactone **19**.



Scheme 4.5 A) Synthesis of 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone; B) Synthesis of 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone (Ref 14)

The relatively low yield of this bromination reaction was also shown in the direct dibromination of D-*glucono*-1,5-lactone **14** with HBA [14]. Despite the high yields of the dibromination reaction of D-*gulono*-1,4-lactone (90%) and D-*manno*-1,4-lactone (80%),

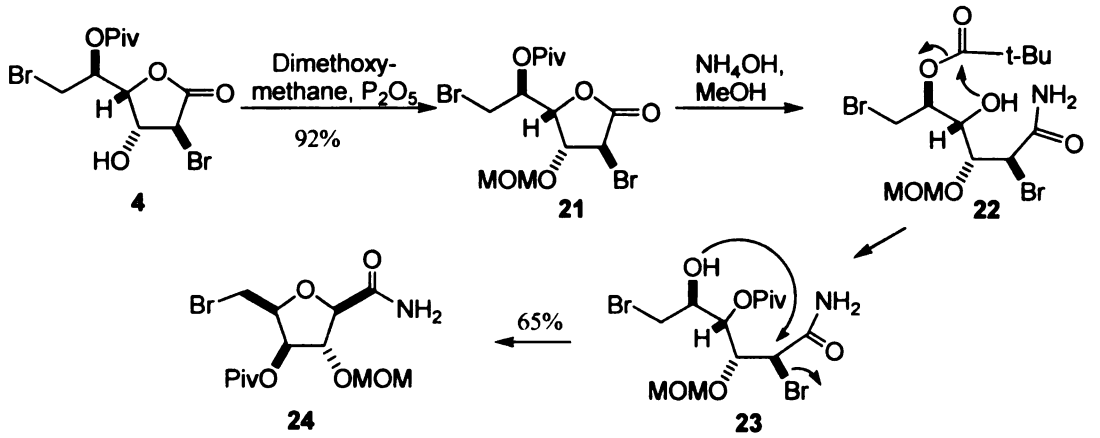
the dibromination of D-*glucono*-1,5-lactone to 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **20** proceeded in only 50% yield.

In our synthesis of 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone **17**, acyloxonium cation formation was employed to introduce the bromo functionality. Migration of the pivaloyl group to the 5-O-position transferred the pivaloylation selectivity at the primary position to that site. Although in this case, the selectivity of primary pivaloylation was not extremely high, the concept of transferring the selectivity among carbohydrate hydroxyl groups was interesting and important. We also compared our strategy with the preparation of 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone **17** by direct selectively pivaloylation of 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **20** in 60% yield [19]. Although the overall yield from D-*glucono*-1,5-lactone should be around the same range, in this case the procedure of direct selective monopivaloylation of dibromo-D-*manno*-γ-lactone was preferred due to its easier isolation process.

4.3 Synthesis of chiral tetrasubstituted tetrahydrofuran (THF) ring from 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*idono*-1,4-lactone by a weak-base induced pivaloyl rearrangement

In previous discussed bromination coupled with pivaloyl group rearrangement, 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*idono*-1,4-lactone **4** could be prepared relatively easily from D-*gulono*-1,4-lactone **1**. This compound was then treated with dimethoxymethane and phosphorus pentoxide (P_2O_5) to install a methoxymethyl (MOM) protecting group at the 3-O- position. This orthogonally protected 2,6-dibromo-2,6-

dideoxy-D-*idono*-γ-lactone **21** was then treated with ammonium hydroxide in methanol for 6 hours. Unexpectedly, NMR analysis of the product showed that only the 2-bromo group was substituted while the primary bromo group stayed untouched. Both of the protecting groups were still present. Further analysis showed the structure to be a tetrasubstituted tetrahydrofuran ring **24** (Scheme 4.6). The mechanism was also shown in Scheme 4.6.

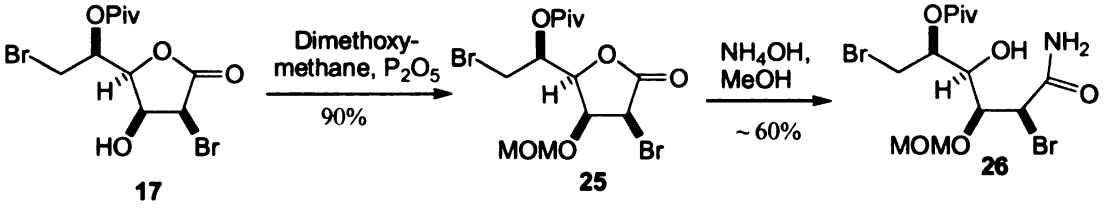


Scheme 4.6 Synthesis of 2,5-anhydro-6-bromo-6-deoxy-3-O-methoxymethyl-5-O-pivaloyl-D-gulonic amide **24**

When the protected lactone **21** was treated with ammonia hydroxide, the lactone ring was aminolyzed to an open-chain structure **22**. Under the catalysis of weak base, the free 4-OH attacked the pivaloyl carbonyl and the 5-O-pivaloyl group was subsequently rearranged to 4-position to form **23**. Then free 5-OH of **23** attacked the 2-bromo group intramolecularly to furnish a tetrahydrofuran ring **24**. The pivaloyl group rearrangement was driven by an intramolecular ring formation under mild reaction conditions. Chiral tetrahydrofuran rings are common structural subunits in natural products. Here, by a weak-base catalyzed ring-switch process, we generated a chiral tetrahydrofuran ring system fully substituted with complete differentiated functional groups and protecting

groups. This sugar amide could be used as a good chiral building block in more complicated natural product synthesis.

By using some other starting material such as 2,6-dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone **17**, we expected the same procedure would generate similar tetrahydrofuran ring systems with different chiralities. This could enrich the library of this fully substituted chiral building block. However, this was found out not to be general. 2,6-Dibromo-2,6-dideoxy-5-O-pivaloyl-D-*manno*-1,4-lactone **17** was treated with dimethoxymethane and P_2O_5 to afford 2,6-dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-pivaloyl-D-*manno*-1,4-lactone in good yield (90%). When we treated this compound with ammonium hydroxide in methanol, however, no tetrahydrofuran ring product was formed. The only product isolated was simply the aminolysis product with an open-chain structure (Scheme 4.7). Increasing the reaction temperature led to a complicated mixture instead of the desired product, presumably due to the elimination reaction.



Scheme 4.7 Synthesis of 6-bromo-6-deoxy-3-O-methoxymethyl-5-O-pivaloyl-D-mannonamide **26**

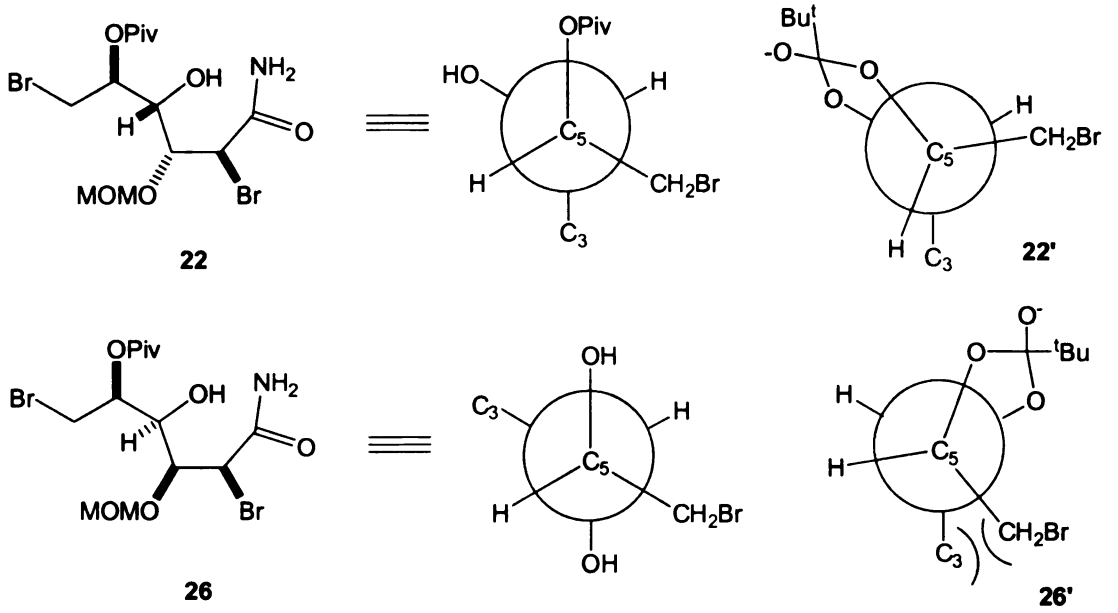


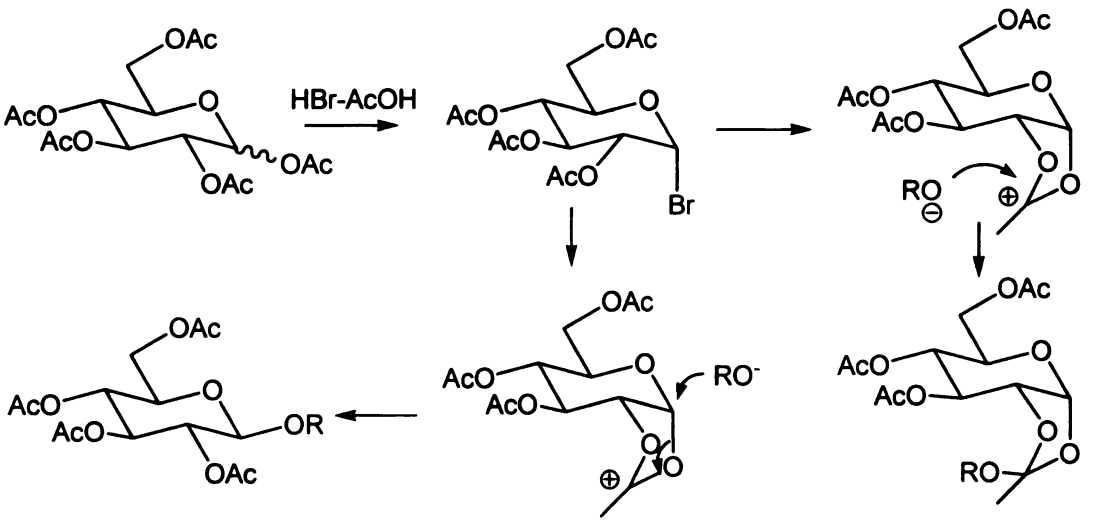
Figure 4.3 The comparison of the configurations of **22** and **26**: the *threo*-selectivity of the weak base catalyzed pivaloyl rearrangement

Although the result was somewhat disappointing, it was easily understood by comparing the configurations of the two substrates (Figure 4.3). While the 2,6-dibromo-D-*idono*-γ-lactone has C4, C5-*threo* configuration, the 2,6-dibromo-D-*manno*-γ-lactone has a C4, C5-*erythro* configuration. The difference between these two configurations towards acyl rearrangement could be seen from two points of view. We first analyzed the structures of open-chain intermediate after aminolysis. For C4, C5-*threo* configuration, the 4-OH is very close to the 5-O-pivaloyl carbonyl, which indicates a small energy barrier of nucleophilic attack and therefore fast reaction. On the other hand, for C4, C5-*erythro* configuration, the 4-OH is fairly far away from the 5-O-pivaloyl carbonyl. The C4-C5 bond must rotate to a disfavored conformation to allow the 4-OH to attack the 5-O-pivaloyl carbonyl. This indicates a big energy barrier and therefore slower reaction. Considering the energy profile of the orthoester intermediate, we can obtain the same result. If the open chain amide has a C4, C5-*threo* configuration, i.e. **22'**, the interaction

between C4,C5-substitution groups is relatively small. However, for the C4, C5-*erythro* **26'**, the interaction between C4, C5-substitution groups could be much larger. The energy of the orthoester intermediate would be high enough to prevent the rearrangement from going. As a result, the rearrangment of acyl group proceeds faster and smoother if the two neighboring groups have *threo-* configuration compared to that if the two neighboring groups have *erythro-* configuration. This configuration analysis could also be used in some other base-catalyzed acyl rearrangement.

4.4 Anomeric bromination and Ritter-type reaction of pentaacyl monosacchrides

Encouraged by the t-butyl-1,3-dioxonium cation facilitated rearrangement and selective bromination under acidic conditions, we further explored its application of some other sugar derivatives. Tetraacyl glycosyl bromides have been prepared by treating monosacchrides pentaacetates and pentabenzoates with hydrogen bromide in acetic acid. The mechanism has been postulated to go through an intermediate with an anomeric positive charge. These glycosyl bromides have been generally used as good glycosyl donors in oligasaccrides synthesis. However, in some cases, the neighboring acyl group participation could lead to undesired side-reactions, especially the orthoester formation (Scheme 4.8). Due to its weaker orthoester formation, tetrapivaloyl glycosyl bromides have been used as glycosyl donors more and more. Based on the stronger ability of stablizing the anomeric positive charge, we presumed that the treatment of glucose pentapivaloate with hydrogen bromide in acetic acid should generate tetrapivaloyl glucosyl bromide.

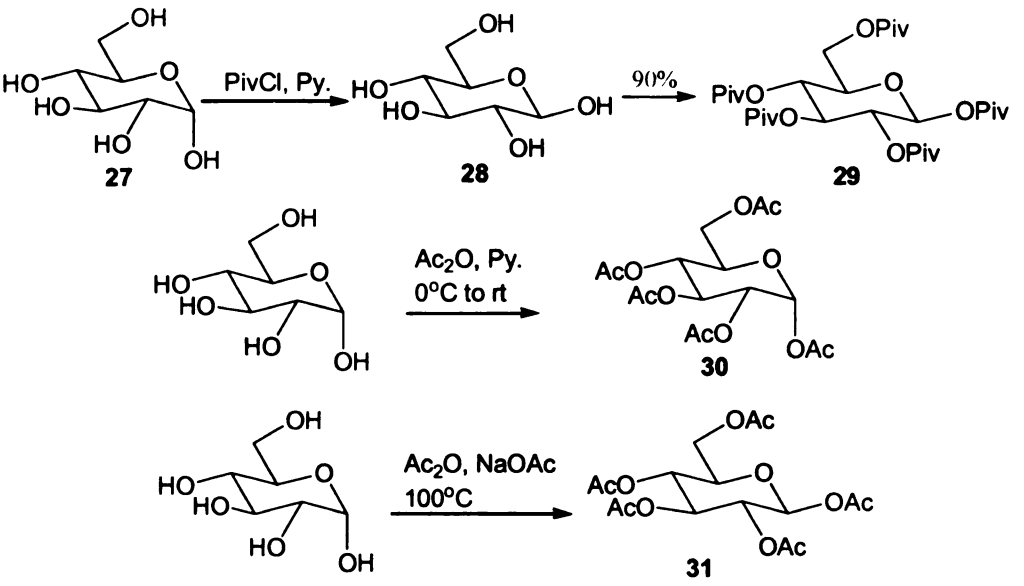


Scheme 4.8 Tetraacetyl glucosyl bromide synthesis and application in glycoside synthesis

4.4.1 Synthesis of glucose pentapivaloate and its anomeric isomerization under acidic condition

When α-D-glucose **27** was treated with excess pivaloyl chloride in pyridine under room temperature, the major product obtained was glucose pentapivaloate. However, there was still serious amount of partially pivaloated product present. Even after extension of reaction times to several days, the yield of pentapivaloate was not improved. The uncomplete pivaloylation suggested a great steric hindrance in the perpivaloylation. Fortunately, by simply increasing the reaction temperature to 80 °C, most of the partially pivaloylated compound was then pivaloylated completely with ignorable side reaction. Unexpectedly, NMR of the product showed a big coupling constant between H1 and H2. ($J_{1,2}$ = 8.4 Hz), which undoubtly suggested a β-configuration of this glucose pentapivaloate. To exclude the temperature effect, the product obtained at room temperature was also analyzed by NMR, which showed the same result. Using acetic anhydride in pyridine at room temperature, the major peracetylation product of α-D-

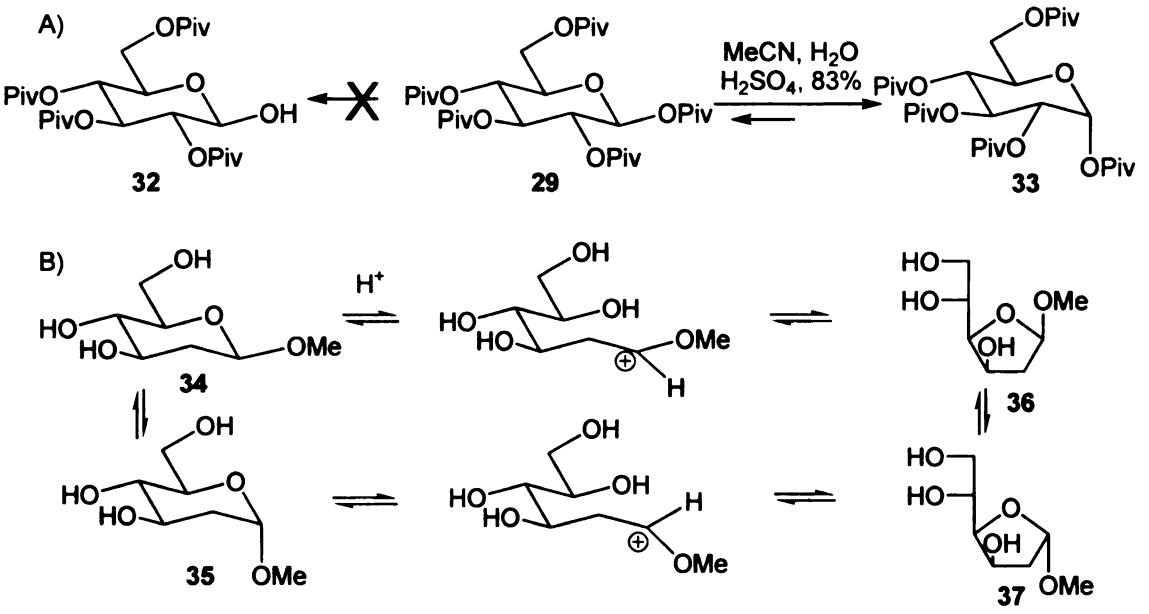
glucose **27** is α-glucose pentaacetate because of a relatively slower mutaroation compared with the acylation reaction. However, in the reaction of glucose with pivaloyl chloride in pyridine, the mutaroation became relatively faster than the acylation, therefore, β-D-glucose pentpivaloate **29** was obtained as the dominant isomer (Scheme 4.9).



Scheme 4.9 Synthesis of β-D-glucose pentapivaloate from α-D-glucose and the comparison with peracetylation under different reaction conditions

Before we subjected glucose pentapivaloate to hydrogen bromide treatment, we tried to selectively hydrolyze the anomeric pivaloyl protecting group to generate an anomeric free glucose tetrapivaloate **32**, which is useful in synthetic carbohydrate chemistry. The acidic treatment of this β-glucose pentapivaloate **29** with water in presence, however, did not yield the anomeric free glucose tetrapivaloate **32**. This was ascribed to the robustness of the pivaloyl function as a protecting group. On the other hand, a very slight change in TLC properties was noticed and an NMR analysis of the

compound after acidic treatment was carried out to confirm any structural change. NMR spectroscopy clearly showed a different compound with glucose pentapivaloate structure. This compound showed a much smaller coupling constant between H1 and H2 ($J_{1,2}$ = 3.8 Hz), suggesting α-glucose pentapivaloate **33** was obtained. The ratio of α: β is about 10:1 (Scheme 4.10 A).

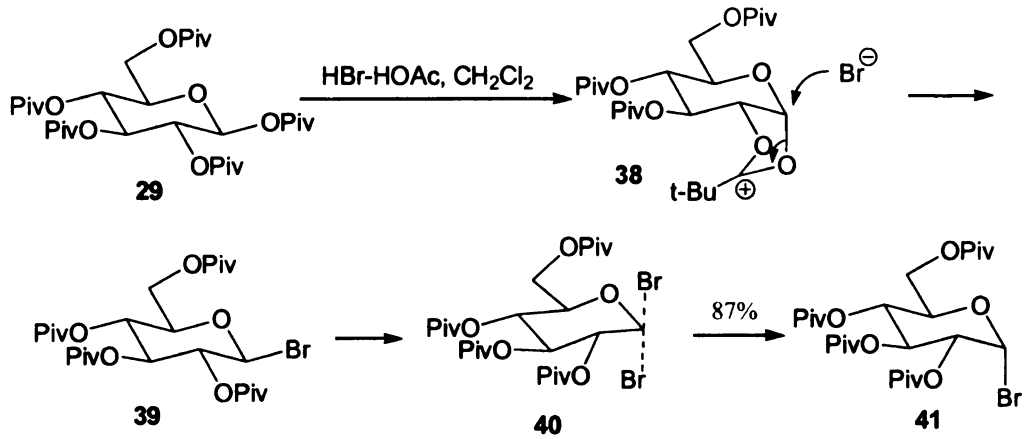


Scheme 4.10 The acid catalyzed anomeric isomerization of A) β-D-glucosepentapivaloate **29** and B)2-deoxy-D-arabino-hexosides **34** (Ref 20)

The high efficient β to α isomerization at anomeric position was consistent with other researcher's results. Wisniewski et. al. [20] found that methyl 2-deoxy-D-arabino-hexosides undergo acid-catalyzed isomerization and suggested a mechanism (Scheme 4.10 B). We believe the isomerization of β-glucose pentapivaloate to its α-anomer was through the similar mechanism. The α- and β-glucosides very often show different reactivity towards various reactions because of their different C-H bond orientation at the anomeric position. The pivaloylation procedure we discussed above, combined with the

acid-catalyzed isomerization, could give fairly pure β- or α-anomer of glucose pentapivaloate respectively. It could be synthetically useful in the future.

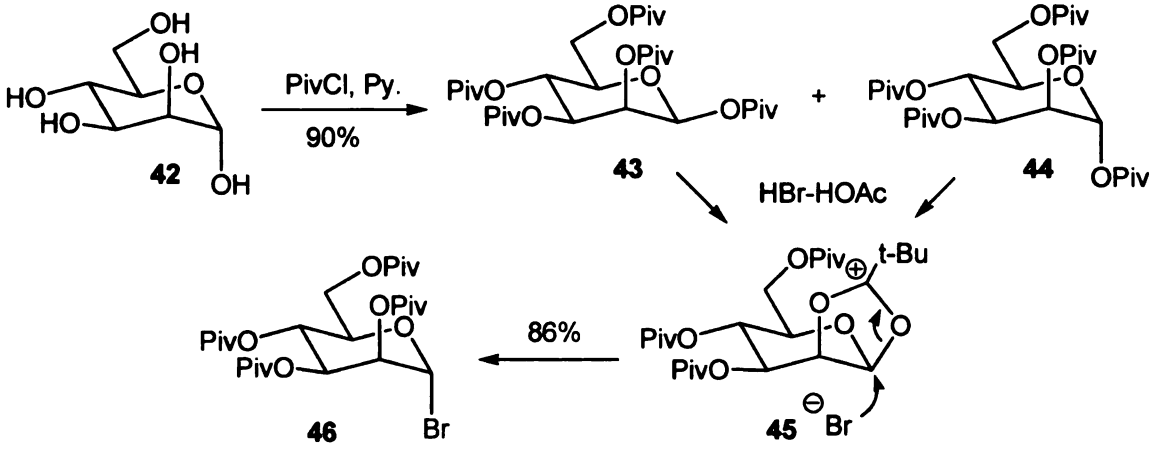
4.4.2 Synthesis of tetrapivaloyl glycosyl bromides with *gluco-* and *manno-* configurations



Scheme 4.11 Synthesis of α-tetrapivaloyl *glucosyl* bromide

We then treated β-glucose pentapivaloate **29** with hydrogen bromide in acetic acid and dichloromethane. Only one product was obtained. NMR analysis of the product showed it to be tetrapivaloyl *glucosyl* bromide. The coupling constant analysis showed a small coupling constant, suggesting the product to be tetrapivaloyl α-*glucosyl* bromide. A plausible reaction mechanism is shown in Scheme 4.11. Under acidic conditions, the anomeric pivaloyl group would leave to form a positive charge, which would then be stabilized by the neighboring pivaloyl group through a t-butyl-1,3-dioxonium cation **38**. Bromide ion would attack the anomeric position to open the t-butyl-1,3-dioxonium cation ring and form the β-*glucosyl* bromide **39**. Due to the anomeric effect, the β-*glucosyl* bromide **39** was isomerized to its α-anomer **40**, which is commonly used as a glucosyl donor in oligosaccharides synthesis.

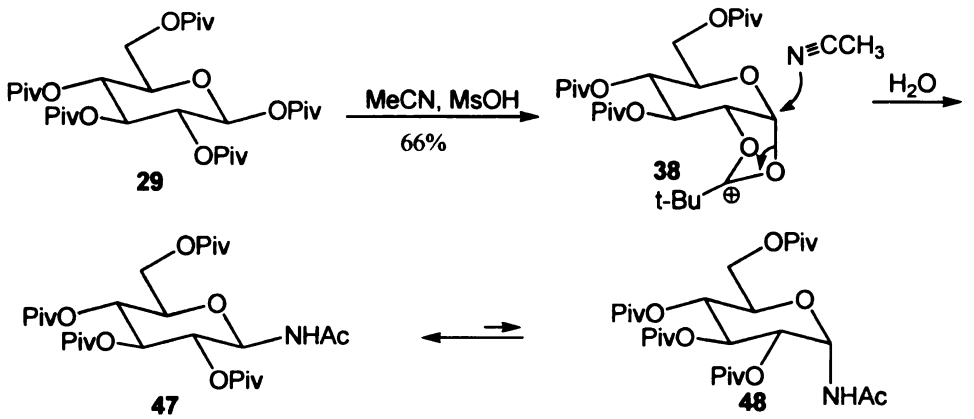
To expand this strategy, we also employed D-mannose as the starting material in this precedure. When D-mannose **42** was treated with pivaloyl chloride in pyridine using the same reaction procedure, two isomers of mannose pentapivaloate **43**β and **44**α were obtained. The ratio of α:β was about 1: 6 with β-isomer as the major product. The mixture **43** and **44** was then treated with hydrogen bromide in acetic acid and dichloromethane without further separation to form almost exclusively tetrapivaloyl α-*mannosyl* bromide (Scheme 4.12). Under strong acidic conditions, the anomeric pivaloyl group would leave to form a positive charge at the anomeric position, which would then be stabilized by t-butyl-1,3-dioxonium cation formation with 2-O-pivaloyl group. Both α- and β-isomers of tetrapivaloyl *mannosyl* bromide would yield the same t-butyl-1,3-dioxonium cation **45**. Subsequently, the bromide ion would attack the anomeric position to form a tetrapivaloyl α-mannosyl bromide **46**. Due to anomeric effect, the isomerization from α to β was not a preferred transformation.



Scheme 4.12 Synthesis of α-tetrapivaloyl mannosyl bromide

4.4.3 Synthesis of glycosyl amide by dioxonium cation facilitated anomeric Ritter-type reaction

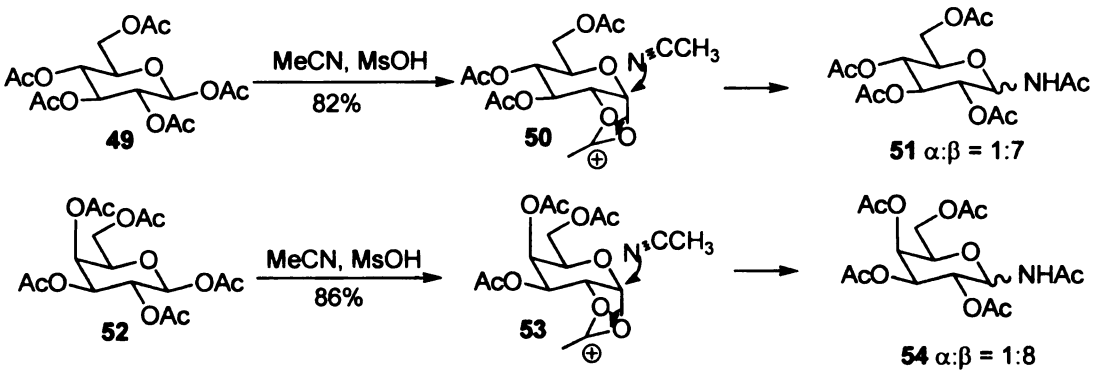
The synthesis of tetrapivaloyl glycosyl bromides encouraged us to further explore the reactivity of the acyloxonium cation stabilized anomeric positive charge as an electrophile. Theoretically, a nucleophile could attack the anomeric position to form glycosyl derivatives with different connections. If a nitrile is present, it could attack the anomeric positive charge to form an N-glycosyl amide, which would be formally an anomeric Ritter-type reaction. When β-glucose pentapivaloate **29** was treated with 30% methanesulfonic acid in acetonitrile, tetrapivaloyl α- (**48**) and β-*glucosyl* amide (**47**) was isolated as the only products with a ratio of α: β = 1: 6 (Scheme 4.13). Due to the participation of 2-O-pivaloyl group in this reaction, the attack of the anomeric position by the nitrile group would generate a β-glucosyl amide and the α-anomer was formed by anomeric isomerization.



Scheme 4.13 Synthesis of tetrapivaloyl β- and α-glucosyl acetamides

We then tested if acetyl protecting groups could also be employed in this anomeric Ritter-type reaction. α-Glucose pentaacetate and α-galactose pentaacetate was

treated with 30% methanesulfonic acid in acetonitrile respectively. The experimental results also showed clean Ritter-type reactions, yielding tetraacetate N-glycosyl amides of *gluco-* and *galacto-* configurations. For *gluco-* configuration, the ratio of **51**α: **51**β was 1:7. For galacto-configuration, the ratio of **54**α: **54**β was 1:8 respectively (Scheme 4.14).



Scheme 4.14 Synthesis of tetraacetyl N-β- and α-glycosyl amides with *gluco-* and *galacto-* configurations

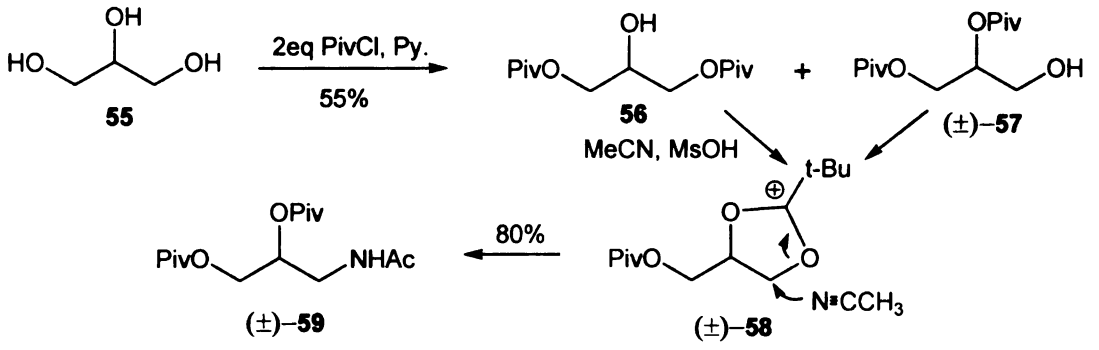
N-Glycosyl amines and amides have long been an important subject in carbohydrate chemistry because of their prominence in glycopeptides and glycoproteins and their potential as selective RNA-binding agents [21, 22]. The recent discovery of N-glycosyl amide activation further opened the possibility of N-glycosyl amide being not only an anomeric protected saccharide, but also a glycosyl donor [23]. Many synthetic methodologies have been discovered in the synthesis of N-glycosyl amides and amines [24-32]. Among them, the work of Fraser-Reid using n-pentenyl glycosides was one of the prominent ones [29-32]. In the oxidative cleavage of n-pentenyl glycosides, a positive charge at the anomeric position was formed and attacked by a nitrile to give N-glycosyl amides. Our easy synthesis of tetraacyl N-glycosyl amides discussed above has the mechanistic similarity of using anomeric Ritter-type reaction. Its simplicity defines its significance in synthetic carbohydrate chemistry.

4.5 Dioxonium cation in protected acyclic polyols: stereoselective Ritter-type reactions

In our synthesis of N-glycosyl amides using anomeric Ritter-type reaction, both the ring oxygen and the neighboring acyl group had stabilizing effects on the anomeric positive charge, which drove the reaction forward smoothly. However, an unsolved question was if the acyloxonium cation can provide enough stabilization to allow the Ritter-type reaction to take place. To clarify this question and to test the generality of this reaction, a series of acyclic polyols were selectively protected and employed in the acyloxonium cation facilitated functional groups transformation.

4.5.1 t-Butyl-1,3-dioxonium cation as an electrophile: synthesis of N-acyl-aminopropanediol

As the simplest acyclic ployols, glycerol **55** was selected to test our hypothesis. Because its simple 3-carbon chain, it would be impossible for it to cyclize intramolecularly to form a ring system under strong acidic conditions. Glycerol **55** was treated with 2.0 equivalent pivaloyl chloride to protect two hydroxyl groups. Two regio-isomers were obtained, which were assigned to be 1,3-di-O-pivaloyl glycerol **56** and (±)-1,2-di-O-pivaloyl glycerol **57** respectively with a ratio of 2:1. It was assumed that under treatment of acid, they would form the same t-butyl-1,3-dioxonium cation species. Without separation of the two compounds, they were treated with 30% methanesulfonic acid in acetonitrile at room temperature for three days. TLC analysis showed clean and complete reaction. NMR analysis confirmed the Ritter-type reaction product **59**. A mechanism is proposed in Scheme 4.15.



Scheme 4.15 synthesis of (±)–N-acyl-aminopropanediol **59**

Under treatment with strong acid, both of the two glycerol dipivaloates would form the same t-butyl-1,3-dioxonium cation species **58**. This species was subsequently attacked by the acetonitrile in the primary position. After attack of the nitrilinium carbon by water generated in-situ and further proton transfer, the (±)-3-N-acetylamino-3-deoxy-1,2-di-O-pivaloyl-glycerol **59** was obtained. The reaction was fairly clean and no other serious side reaction could be detected.

Usually, for a Ritter-type reaction, the carbocation has to be substantially stabilized and then attacked by a nitrile group. The nitrile group usually attacks the most positively charged position. In our case, the possible reactive sites partially positively charged were the carboxonium cation, the secondary C-2 and the primary C-1 in decreasing order (Figure 4.4). The nucleophilic attack to these positively charged positions would generate different species. However, due to the steric hindrance, only the primary position was possible to be attacked by the acetonitrile. This highly entropy-controlled reaction was in agreement with the NBS-promoted pivaloyl rearrangement discussed in Chapter 2. As a result, a protected (±)-bromopropanediol **59** was successfully synthesized as a racemic mixture, which could serve as a useful building block for some synthetic work.

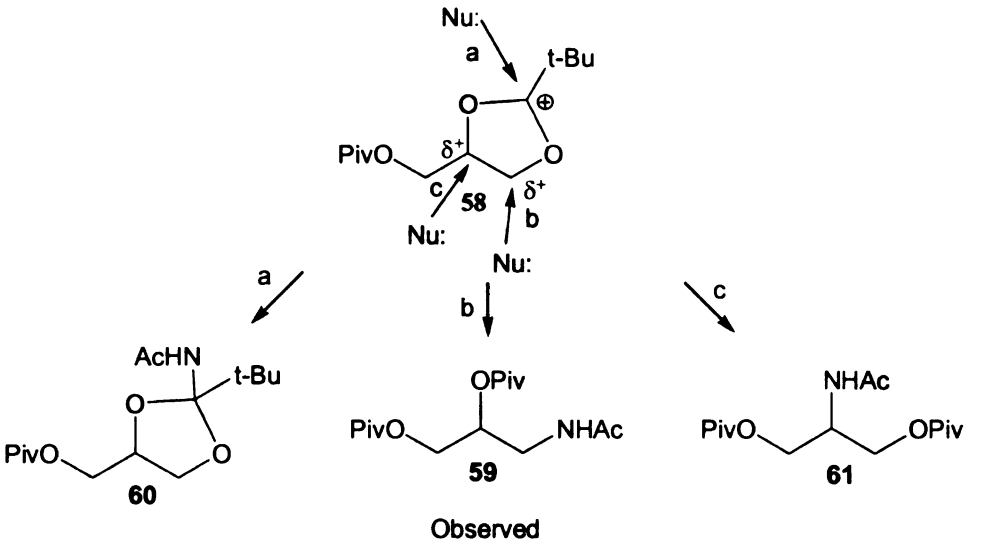


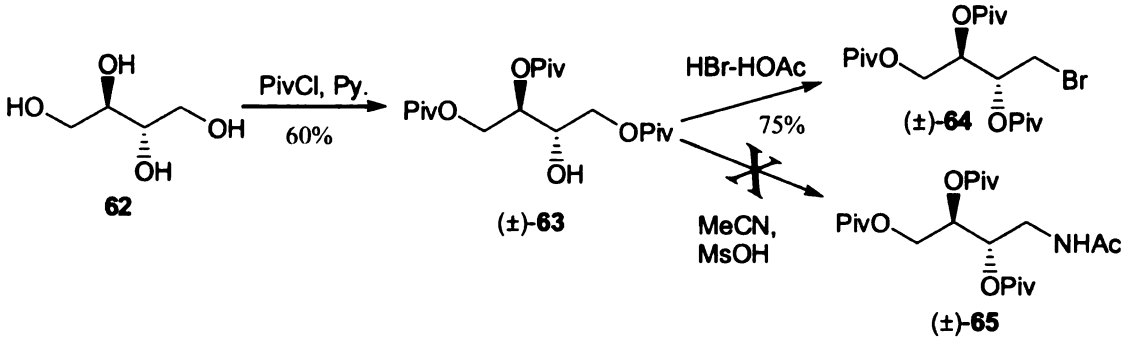
Figure 4.4 The preference of nucleophilic attack of the t-butoxonium cation **58**: to a) the carboxonium cation; b) the secondary C-2; and c) the primary C-1.

4.5.2 The stereoselectivity of t-butyl-1,3-dioxonium cation facilitated Ritter-type reaction: Synthesis of protected chiral bromobutanetriol and N-acetylaminobutanetriol

As we discussed in Figure 4.4, the reaction mechanism for the dioxonium cation facilitated amidation suggested that this reaction to be highly stereoselective and regioselective. However, by using achiral glycerol as starting material, the stereoselectivity of this reaction could not be confirmed due to the single chirality and racemic property of the product. To clarify this question, we further explored these reactions employing *meso*-erythritol **62** as our starting material. Theoretically, by looking at the relative chirality change between the two existing chiral centers, the mechanism could be further clarified and confirmed.

Meso-erythritol **62** was partially protected by treatment with 3.0 equivalent pivaloyl chloride in pyridine. An easy chromatography separation was carried out to

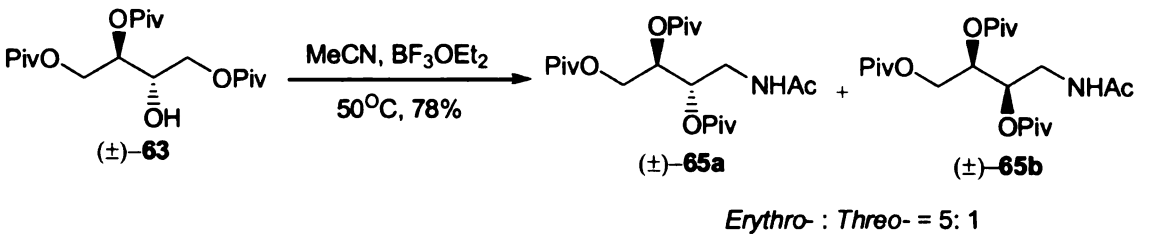
separate the (±)-1,2,4-tri-O-pivaloyl-erythritol **63** as a racemic mixture. Interestingly, only trace amount of (±)-1,2,3-tri-O-pivaloyl-erythritol was found. Compared with the dipivaloylation of glycerol, this tripivaloylation of erythritol showed much better selectivity. This better selectivity was also ascribed to the higher steric hindrance of the erythritol tripivaloates. When (±)-1,2,4-tri-O-pivaloyl-erythritol **63** was treated with hydrogen bromide in acetic acid and dichloromethane, (±)-1-bromo-1-deoxy-2,3,4-tri-O-trimethylacetyl-erythritol **64** was synthesized in a 75% yield (Scheme 4.16). The plausible mechanism included a dioxonium cation formation followed by the bromide attack at the primary position to furnish a protected bromobutanetiol. NMR analysis of the product showed an *erythro-* configuration. No *threo-* configuration products were found, suggesting that this reaction was stereospecific.



Scheme 4.16 Synthesis of protected chiral bromobutanetriol (±)-**64**

We then treated (±)-1,2,4-tri-O-pivaloyl erythritol **63** with 30% methanesulfonic acid in acetonitrile. We expected a mechanism that was similar to the HBA treatment of (±)1,2,4-tri-O-pivaloyl erythritol. This would generate a Ritter-type product (±)-4-N-acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl-erythritol **65**. However, even after extension of the reaction time to several days, only a complicated mixture was obtained. NMR analysis of the mixture showed only small amount of Ritter-type product **65**,

characterized by the signals of the N-acetylamide group. On the other hand, NMR suggested that some methanesulfonyl groups were introduced into the polyol structure. Under strong acidic conditions, the acid itself served as a competitive nucleophile and attacked the t-butyl-1,3-dioxonium cation or the carbon chain instead of acetonitrile. As a result, only small amount of Ritter-type product was formed. Although disappointed by the result, we reasoned that by substituting the protic acid catalyst to some Lewis acid, this problem could be solved. When we treated (±)-1,2,4-tri-O-pivaloyl-erythritol **63** with 3:1 acetonitrile and boron trifluoride etherate at 50 °C for 5 hours, most of the starting material was consumed. After simple work-up by neutralization with sodium bicarbonate, the Ritter-type product was obtained in 78% yield. NMR analysis of the product showed (±)-4-N-acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl-erythritol **65a** and (±)-4-N-acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl-threitol **65b** (Scheme 4.17). The ratio of *erythro-* : *threo-* configuration was about 5:1.



Scheme 4.17 Synthesis of protected chiral N-acetylaminobutanetriol (±)–**65**

In this reaction, No 3-N-acetylamino product and only small amount *threo-* configuration product was detected. This suggested that this t-butyl-1,3-dioxonium cation facilitated Ritter-reaction was not only highly regioselective, but also stereoselective. Due to its carbocation intermediate mechanism, Ritter-type reaction usually suffers from the unspecific stereocontrol. This has greatly limited its application in synthetic organic

chemistry (Figure 4.5). In our dioxonium cation facilitated Ritter-type reaction, the carbocation was gerenated from an achiral protecting group. This carbocation in turn activated the carbon chain without scrambling its chirality. After nucleophile introduction, this carbocation was transformed back to the protecting group. This strategy successfully solved this stereocontrol issue and could be very useful in the future synthetic work.

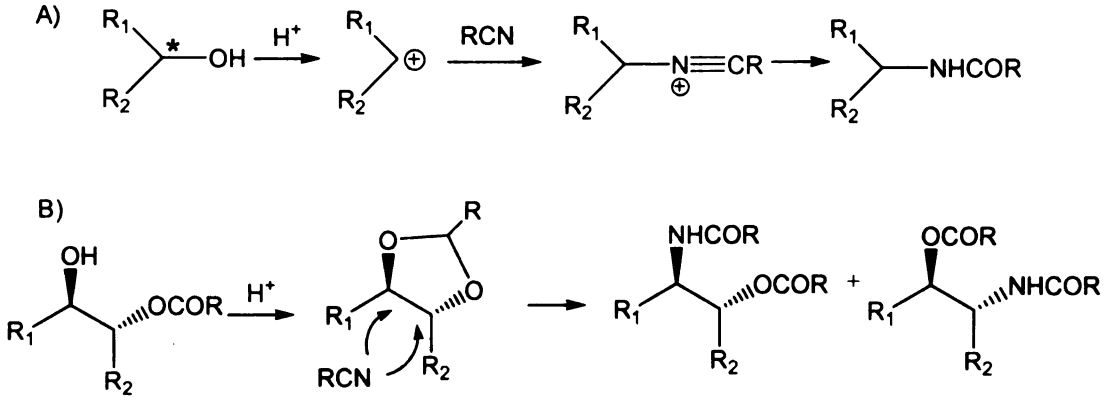


Figure 4.5 The comparison of A) normal Ritter-type reaction and B) acyloxonium cation-assisted Ritter-type reaction

4.5.3 Dioxonium cation facilitated functional group transformation of (S)-1,2,4-butanetriol: more mechanism and applications

Although we have demonstrated that the dioxonium cation facilitated bromination and Ritter-type reaction are highly regioselective and stereoselective, there remained one issue about the intermediate carboxoniun cation to be addressed. Was the five-membered ring or the six-membered ring carboxonium cation the real active intermediate? Although generally the five-membered ring has been suggested as the active intermediate because of the kinetic effect, there has been no direct evidence excluding the six-membered carboxonium cation intermediate. We therefore reasoned that by employing (*S*)-1,2,4-butanetriol **66** as the starting material, this issue could be easily and unambiguously

addressed (Figure 4.6). (*S*)-1,2,4-butanetriol **66** was a commercially available chiral building block. Its simple chiral structure has made it a perfect platform for synthesis of complex chiral molecules. The functional group transformations of this molecule, which would generate new diverse chiral building blocks, are of great practical interests.

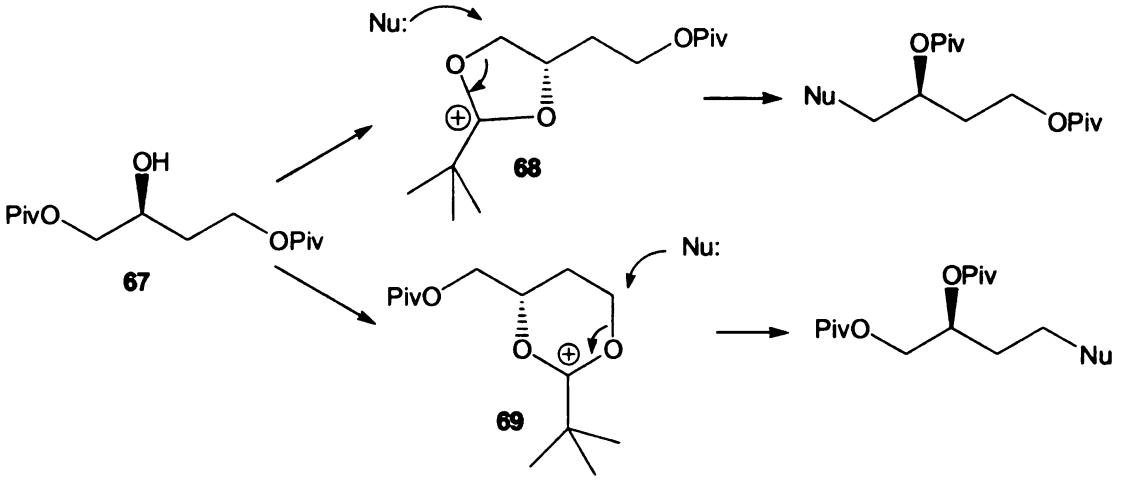
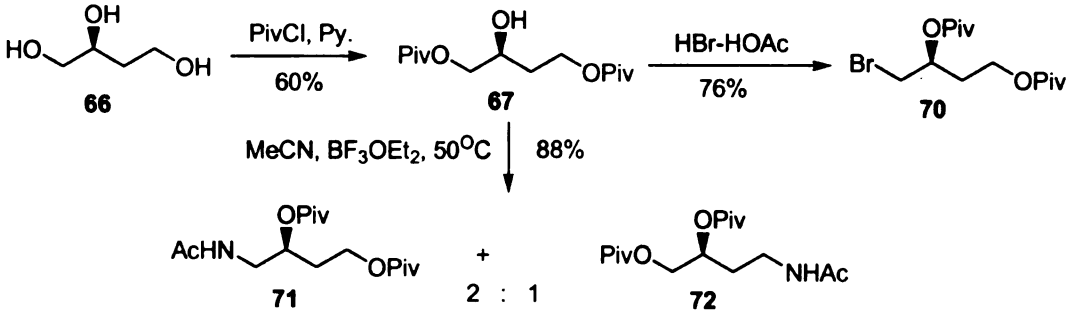


Figure 4.6 Use of 1,2,4-butanetriol dipivaloate to clarify the active carboxonium cation intermediate: five-membered ring or six-membered ring

(*S*)-1,2,4-Butanetriol was treated with 2 equivalent pivaloyl chloride in pyridine to afford (*S*)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67** in 60% yield. When we treated **67** with hydrogen bromide in acetic acid and dichloromethane, a single product was obtained. NMR analysis showed the structure to be 4-bromo-1,3-di-O-pivaloyl-butanediol **70** (Scheme 4.18). The product suggested that the reaction went through a five-membered ring dioxonium cation intermediate **68** (Figure 4.6), which was attacked by bromide at the primary position to yield the product. The six-membered ring dioxonium cation **69** could only be formed between 2-OH and 4-O-pivaloyl group. If this was the active intermediate, the bromide would attack the 4-position to yield 4-bromo-1,2-di-O-pivaloyl-butanediol. However, this compound was not detected. The experimental results

confirmed that under this reaction condition, five-membered ring dioxonium cation intermediate was the active intermediate. Furthermore, the selectively protected and functionalized product 4-bromo-1,3-di-O-pivaloyl-butanediol **70** could serve as a good chiral synthon.

We then treated (*S*)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67** with 3:1 acetonitrile and boron trifluoride etherate at 50°C for 5 hours, after which all the starting material was consumed. NMR analysis showed a mixture of two isomers, namely 4-N-acetylamino-1,3-di-O-pivaloyl-1,3-butanediol **71** and 4-N-acetylamino-1,2-di-O-pivaloyl-1,2-butanediol **72** in a ratio of 2:1 (Scheme 4.18).



Scheme 4.18 Synthesis of protected chiral N-acetylaminobutanediol **71** and **72**

The unexpected Ritter-type reaction result was not consistent with the reaction with HBA, which generated a single regioisomer **70**. Undoubtedly, the Lewis acid promoted Ritter-type reaction was through two active intermediates, the five-membered ring 1,2-t-butyl-1,3-dioxonium cation **68** and the six-membered ring 2,4-t-butyl-1,3-dioxonium cation **69**. Being attacked by acetonitrile in the 1- or 4- primary positions respectively, they generated **71** and **72** respectively. The 2:1 ratio showed that the five-membered ring intermediate was favored. To exclude the temperature effect, we also

tried this reaction at room temperature. The Ritter-type reaction proceeded slowly under room temperature. After several days, the reaction was worked up and separated. It also yielded two isomers **71** and **72** with essentially the same ratio.

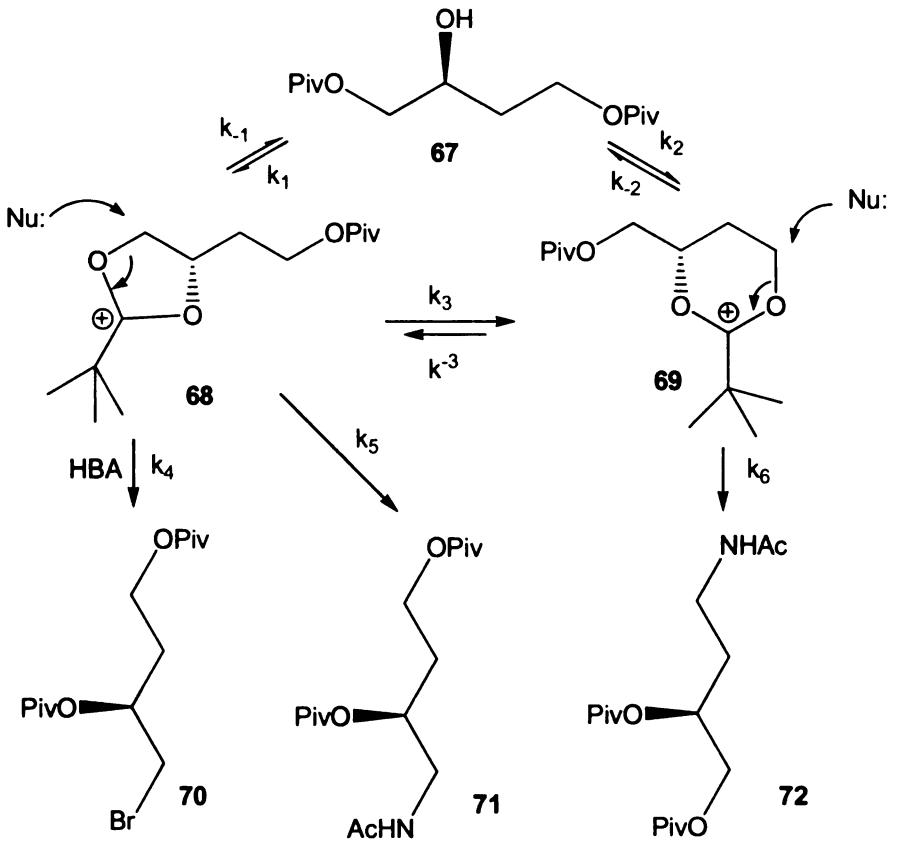


Figure 4.7 A explanation of the regioselectivities of acyloxonium cation facilitated bromination and the Ritter-type reaction

Compared with the dioxonium cation facilitated selective bromination and the Ritter-type reaction, a plausible explanation was suggested in Figure 4.7. Presumably, the five-membered ring 1,2-t-butyl-1,3-dioxonium cation **68** was kinetically much more favored than the six-membered ring 2,4-t-butyl-1,3-dioxonium cation **69** ($k_1 >> k_2$), while the latter was thermodynamically slightly more favored than the former. In the bromination reaction, the bromide ion was a good nucleophile, which made the

bromination process relatively fast ($k_4 > k_2$ & k_3). The kinetic product 4-bromo-1,3-di-O-pivaloyl-1,3-butanediol **70** was formed. However, the acetonitrile was not a nucleophile as good as bromide ion. This made the attack by acetonitrile in the Ritter-type reaction very slow (k_5, $k_6 < k_1$, k_2, k_3, k_{-3}). This step became the speed-limiting step. Under this circumstance, it was possible that the equilibrium between the five-membered ring t-butyl-1,3-dioxonium cation **68** the six-membered ring t-butyl-1,3-dioxonium cation **69** was formed. Both of them then acted as the active intermediate to afford a mixture of two regioisomers. This analysis was further complicated by the fact that the rates of the dioxonium cation intermediates towards amidation were different for five-membered ring and six-membered ring. Presumably, the five-membered ring should have a faster rate towards amidation than the six-membered ring ($k_5 > k_6$) due to the higher ring strain. Presumably, the 2:1 ratio of the two isomers reflected all the factors discussed above.

As a result, two regioisomers **71** and **72** of the Ritter-type reaction was obtained when (S)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67** was treated with acetonitrile and Lewis acid. Both isomers could be employed as good chiral building blocks towards more complex structures.

4.6 Synthetic application of dioxonium cation facilitated Ritter-type reaction: synthesis of protected 6-aminogalactonolactone

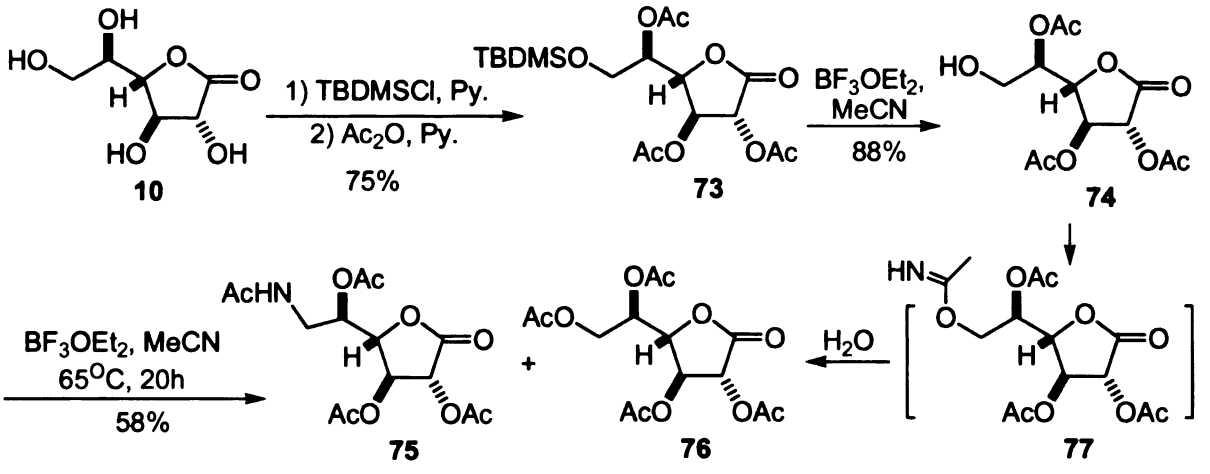
Because of the stereospecificity and high regioselectivity towards primary position of dioxonium cation facilitated Ritter-type reaction, we speculated that it could be a good methodology to install an amide group at the primary position of aldonolactones, which has been a very important task in synthetic carbohydrate chemistry.

To test our hypothesis, D-*galactono*-γ-lactone was selected as our substrate because of its readily accessibility and relatively cheap price.

D-*galactono*-1,4-lactone **10** was treated with 1 equivalent t-butyldimethylsilyl chloride (TBDMSCl) in pyrindine to selectively protect the 6-position. After this reaction was done, acetic anhydride was added into the reaction mixture to protecte the other free hydroxyl groups. After the workup procedure, the product, majorly 2,3,5-tri-O-acetyl-6-O-t-butyldimethylsilyl-D-*galactono*-1,4-lactone **73** was treated with acid to selectively hydrolyze the 6-O-TBDMS protecting groups. These easy protection and deprotection steps could be easily carried out without separation between any two steps. Finally, 2,3,5-tri-O-acetyl-D-*galactono*-1,4-lactone **74** was successfully synthesized.

Compound **74** was treated with Lewis acid in acetonitrile using the similar reaction conditions discussed above. This reaction was relatively slow compared with the reactions of partially protected acyclic polyols, which was ascribed to the higher steric hindrance. After 8 hours, workup of a portion of the reaction solution gave two major compounds well separated on TLC. NMR analysis showed one of the compounds was 6-N-acetylamino-6-deoxy-2,3,5-tri-O-acetyl-D- *galactono*-1,4-lactone **75**, i.e. the expected Ritter-type reaction product. The other compound was shown to be 2,3,5,6-tetra-O-acetyl-D-*galactono*-1,4-lactone **76** by NMR analysis. A mechanism was also shown in Scheme 4.19. Under acidic conditions, nucleophilic addition of the free 6-position hydroxyl group to acetonitrile would generate iminoester species **77**. After workup with water, the iminoester **77** was hydrolyzed to form an ester. Under our reaction condition, this reaction could be a serious side reaction competing with Ritter-type reaction. Fortunately, as the reaction time was extended to 20 hours, most 2,3,5,6-tetra-O-acetyl-

D-*galactono*-1,4-lactone **76** was gone and the Ritter-type product **75** became the dominant product.



Scheme 4.19 Application of acyloxonium cation facilitated Ritter-type reaction: synthesis of protected 6-aminogalactonolactone

This reaction mode encouraged us to treat the 2,3,5,6-tetra-O-acetyl-D-*galactono*-1,4-lactone **76** directly with Lewis acid in acetonitrile. Presumably, the hydrolysis of 6-position acetyl group may result in the formation of acetoxonium cation and then Ritter-type amidation. However, even after several days, there is not any Ritter-type product generated while the starting material stayed unchanged. This result also confirmed that the 2,3,5,6-tetra-O-acetyl-D-*galactono*-1,4-lactone **76** was largely formed in the work-up procedure.

Aminosugar has long been an important subject for synthetic organic chemistry. The synthesis of aminosugar often involved expensive reagents, extensive protection and deprotection and troublesome separation. It was of interest to develop new synthetic methodologies towards different aminosugars. Our synthesis of 6-N-acetylamino-6-deoxy-2,3,5-tri-O-acetyl-D-*galactono*-1,4-lactone **75** only involved easy protection and

deprotection steps without any expensive reagents. It could be generated in the future as a good alternative route towards primary aminosugars. Furthermore, the easy introduction of nitrogen functionality could greatly facilitate our synthesis towards iminosugars if combined with other appropriate functional group transformation.

EXPERIMENTAL

General Optical activity data were obtained on a JASCO P-1010 polarimeter at 25°C. NMR spectra were obtained on a Varian VXR-500 Spectrometer operating at 500MHz for protons. Mass spectra were obtained on a JEOL HX-110-HF instrument using fast atom bombardment as ionization mode. Spectra were recorded in the positive ion mode. IR spectra were obtained on a Nicolet 710 spectrometer in chloroform solution except when otherwise specified.

2,6-Dibromo-2,6-dideoxy-5-O-trimethylacetyl-D-*idono*-1,4-lactone (**4**):

D-*gulono*-1,4-lactone (2 g, 11.2 mmol) was dissolved in 10 mL pyridine and cooled down to 0 °C. Trimethylacetyl chloride (1.49 g, 12.4 mmol) was added slowly. The solution was stirred at 5 °C for 12 hours. Methanol (10 mL) was added in and the mixture was subsequently evaporated to dryness. To the residue 30% hydrogen bromide in acetic acid (10 mL) was added. The mixture was stirred for 10 hours under room temperature and methanol (50 mL) was added. The mixture was stirred for 10 hours more and evaporated to dryness. The residue was partitioned between chloroform (2 x 50 mL) and saturated sodium bicarbonate solution (100 mL). The organic layer was dried and evaporated. The crude product was purified by column chromatography to afford 2,6-dibromo-2,6-dideoxy-5-O-trimethyacetyl -D-*idono*-1,4-lactone **4** as colorless oil (2.53 g, 58% over 2 steps). $[\alpha]_D$ = -24.2° (c = 0.8, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.21 (9H, s, $C(C\underline{H}_3)_3$), 3.61 (2H, d, $J_{5,6}$ 4.3Hz, $J_{5,6'}$ 4.3Hz, H-6, 6'), 4.27 (1H, d, $J_{2,3}$ 2.3Hz, H-2), 4.64 (1H, dd, $J_{3,4}$ 4.4Hz, H-3), 5.00 (1H, dd, $J_{4,5}$ 7.0Hz, H-4), 5.36 (1H, dt, H-5); δ_C (125MHz; $CDCl_3$): 26.95 ($OCC(\underline{C}H_3)_3$), 29.65 (C-6), 38.97 ($OC\underline{C}(CH_3)_3$), 41.79 (C-2), 69.44, 74.00,

81.34 (C-3, C-4, C-5), 171.46 (C=O in lactone), 177.81 (O<u>C</u>C(CH$_3$)$_3$); FT-IR: 1784, 1734, 1147 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3-O-trimethylacetyl-D-*idono*-1,4-lactone (**8**):

2,6-Dibromo-2,6-dideoxy-D-*idono*-1,4-lactone (1.12 g, 3.7 mmol) was dissolved in 5 mL pyridine and cooled down to -20 °C in ice-salt bath. Trimethylacetyl chloride (0.49 g, 4.0 mmol) was added slowly. The solution was warmed up to 0°C in one hour and stirred for 6 hours thereafter. The reaction mixture was poured into ice and stirred for a while. Cold hydrochloric acid (1N) was added in slowly until the pH reached 2~3. Chloroform (100 mL) was used to extract the mixture. The organic phase was washed with 20 mL brine, 20ml water and dried. The crude product was purified by column chromatography to give a major product 2,6-Dibromo-2,6-dideoxy-3-O-trimethylacetyl-D-*idono*-1,4-lactone **8** (0.92 g, 64% yield). δ_H(500MHz; $CDCl_3$): 1.22 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.42 (1H, dd, $J_{6,6'}$ 10.5 Hz, $J_{5,6'}$ 7.0Hz, H-6'), 3.47 (1H, dd, $J_{5,6}$ 4.8Hz, H-6), 3.97 (1H, ddd, $J_{4,5}$ 3.4Hz, H-5), 4.67 (1H, d, $J_{2,3}$ 6.1Hz, H-2), 4.91 (1H, dd, $J_{3,4}$ 6.1Hz, H-4), 5.49 (1H, t, H-3); δ_C (125MHz; $CDCl_3$): 26.85, 26.88, 26.93 (OCC(<u>C</u>H$_3$)$_3$), 32.97 (C-6), 38.91 (OC<u>C</u>(CH$_3$)$_3$), 39.66 (C-2), 68.94, 76.08, 79.43 (C-3, C-4, C-5), 169.39 (C=O in lactone), 177.34 (O<u>C</u>C(CH$_3$)$_3$); FT-IR: 2965, 1786, 1728, 1133 cm^{-1}.

6-Bromo-6-deoxy-2,5-di-O-trimethylacetyl-D-*galactono*-1,4-lactone (**12**):

To 2,6-di-O-trimethylacetyl-D-*galactono*-1,4-lactone (1.0 g, 2.9 mmol) 5 mL hydrogen bromide (30% in acetic acid) was added. The mixture was stirred for 5 hours to give a clear solution. Methanol (20 mL) was added and stirred for another 12 hours. The solution was evaporated and the residue was partitioned between chloroform and sodium

bicarbonate solution. The organic layer was dried and evaporated to give 6-bromo-6-deoxy-2,5-di-O-trimethylacetyl-D-*galactono*-1,4-lactone **12** (1.01g, 85% yield). Compound **12** was characterized as 3-O-acetate. δ_H (500MHz; $CDCl_3$): 1.19, 1.25 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 2.06 (3H, s, $COC\underline{H}_3$), 3.48 (1H, dd, $J_{6,6'}$ 10.2 Hz, $J_{5,6'}$ 7.4Hz, H-6'), 3.49 (1H, dd, $J_{5,6}$ 6.3Hz, H-6), 4.78 (1H, dd, $J_{4,5}$ 2.6Hz, $J_{3,4}$ 7.4Hz, H-4), 5.16 (1H, ddd, H-5), 5.38 (1H, t, $J_{2,3}$ 7.5Hz, H-3), 5.55(1H, d, H-2); δ_C (125MHz; $CDCl_3$): 20.67 ($CO\underline{C}H_3$), 26.96, 27.12, 27.21 ($OCC(\underline{C}H_3)_3$), 27.70 (C-6), 38.86, 39.31 ($OC\underline{C}(CH_3)_3$), 69.87, 70.07, 72.08, 72.50 (C-2, C-3, C-4, C-5), 168.03, 169.75 ($\underline{C}OCH3$, C=O in lactone), 177.01, 177.18 ($O\underline{C}C(CH_3)_3$); FT-IR: 2966, 1786, 1734, 1698, 1147 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-5-O-trimethyacetyl -D-*manno*-1,4-lactone (**17**):

This compound was prepared using essentially the same procedure as the preparation of 2,6-Dibromo-2,6-dideoxy-3-O-trimethyacetyl-D-*idono*-1,4-lactone **8**. Yield: 40% over 2 steps. δ_H (500MHz; $CDCl_3$): 1.20 (9H, s, $C(C\underline{H}_3)_3$), 3.22 (1H, b, -OH), 3.68 (1H, dd, $J_{6,6'}$ 11.7 Hz, $J_{5,6'}$ 4.2Hz, H-6'), 3.83 (1H, dd, $J_{5,6}$ 2.9Hz, H-6), 4.40 (1H, dd, $J_{3,4}$ 2.8Hz, $J_{2,3}$ 4.4Hz, H-3), 4.61 (1H, dd, $J_{4,5}$ 8.9Hz, H-4), 4.76 (1H, d, H-2), 5.23 (1H, ddd, H-5); δ_C (125MHz; $CDCl_3$): 26.89 ($OCC(\underline{C}H_3)_3$), 32.03 (C-6), 39.00 ($OC\underline{C}(CH_3)_3$), 47.22 (C-2), 67.96, 68.82, 79.11 (C-3, C-4, C-5), 169.22 (C=O in lactone), 177.84 ($O\underline{C}C(CH_3)_3$); FT-IR: 2943, 1796, 1738, 1147 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-trimethyacetyl-D-*idono*-1,4-lactone (**21**):

2,6-Dibromo-2,6-dideoxy-5-O-trimethylacetyl-D-*idono*-1,4-lactone (1.24 g, 3.2 mmol) was dissolved in 20 mL dimethoxymethane and 10 mL dichloromethane and 3 g

dry phosphorus pentoxide. The mixture was stirred at room temperature for 2 hours and poured into 50 mL cold saturated sodium bicarbonate solution and stirred. Dichloromethane (2 x 20 mL more) was used to extract the water phase. The organic phase was collected and dried. Evaporation gave 2,6-dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-pivaloyl-D-*idono*-1,4-lactone **21** (1.27g, 92% yield) as colorless oil. δ_H (500MHz; $CDCl_3$): 1.22 (9H, s, $C(C\underline{H}_3)_3$), 3.41(3H, s, $CH_2OC\underline{H}_3$), 3.49 (1H, dd, $J_{6,6'}$ 11.0 Hz, $J_{5,6'}$ 4.2Hz, H-6'), 3.57 (1H, dd, $J_{5,6}$ 6.1Hz, H-6), 4.47 (1H, d, $J_{2,3}$ 3.9Hz, H-2), 4.59 (1H, dd, $J_{3,4}$ 5.4Hz, H-3), 4.72 (1H, d, J ~ 7.1Hz, $C\underline{H}'_2OCH_3$), 4.76 (1H, d, $C\underline{H}_2OCH_3$), 5.12 (1H, t, $J_{4,5}$ 5.4Hz, H-4), 5.35 (1H, ddd, H-5); δ_C (125MHz; $CDCl_3$): 27.27 ($OCC(\underline{C}H_3)_3$), 29.00 (C-6), 39.13 ($OC\underline{C}(CH_3)_3$), 40.20 (C-2), 56.92 ($CH_2O\underline{C}H_3$), 69.46, 79.76, 80.39 (C-3, C-4, C-5), 97.35 ($\underline{C}H_2OCH_3$), 170.23 ($\underline{C}$=O in lactone, C-1), 177.04 ($O\underline{C}C(CH_3)_3$); FT-IR: 3099, 1772, 1624, 1170, 1058 cm^{-1}.

2,5-Anhydro-6-bromo-6-deoxy-3-O-methoxymethyl-5-O-pivaloyl-D-gulonamide (**24**):

2,6-Dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-pivaloyl-D-*idono*-1,4-lactone (0.56 g, 1.3 mmol) was dissolved in 10 mL methanol and cooled down to 0°C. Ammonium hydroxide (2 ml, 28% solution in water) was added slowly. The solution was warmed up to room temperature and stirred for 6 hours. The solution was evaporated to dryness and partitioned between chloroform and water. The organic phase was dried and purified by column chromatography to give 2,5-anhydro-6-bromo-6-deoxy-3-O-methoxymethyl-5-O-pivaloyl-D-gulonamide **24** (0.31 g, 65% yield) as colorless oil. $[\alpha]_D$ = -61.8° (c = 0.8, $CHCl_3$); FAB-MS: m/z calcd. for $C_{13}H_{22}BrNO_6$ 367.0631, found 368.0711 (MH^+); δ_H (500MHz; $CDCl_3$): 1.18 (9H, s, $C(C\underline{H}_3)_3$), 3.40(3H, s, $CH_2OC\underline{H}_3$), 3.45 (1H, dd, $J_{6,6'}$ 10.0 Hz, $J_{5,6'}$ 7.8Hz, H-6'), 3.50 (1H, dd, $J_{5,6}$ 6.4Hz, H-6), 4.42 (1H, m,

H-3), 4.46 (1H, d, $J_{2,3}$ 1.5Hz, H-2), 4.57 (1H, ddd, $J_{4,5}$ 3.2Hz, H-5), 4.78 (1H, d, J = 6.8Hz, C<u>H'</u>$_2$OCH$_3$), 4.80 (1H, d, C<u>H</u>$_2$OCH$_3$), 5.24 (1H, dd, $J_{3,4}$ 1.0Hz, H-4), 5.84 (1H, b, CON<u>H'</u>$_2$), 6.59 (1H, b, CON<u>H</u>$_2$); δ_C (125MHz; $CDCl_3$): 26.72, 26.85, 27.02 (OCC(<u>C</u>H$_3$)$_3$), 27.10 (C-6), 38.86 (OC<u>C</u>(CH$_3$)$_3$), 55.92 (CH$_2$O<u>C</u>H$_3$), 75.41, 81.13, 83.00, 84.23 (C-2, C-3, C-4, C-5), 95.89 (O<u>C</u>H$_2$OCH$_3$), 172.04 (<u>C</u>ONH$_2$, C-1), 176.75 (O<u>C</u>C(CH$_3$)$_3$); FT-IR: 3098, 2973, 1737, 1690, 1627, 1144, 1033 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-pivaloyl-D-*manno*-1,4-lactone (**25**):

This compound was prepared using essentially the same procedure for the preparation of 2,6-dibromo-2,6-dideoxy-3-O-methoxymethyl-5-O-trimethyacetyl-D-iodono-1,4-lactone **21**. Yield: 90%; δ_H (500MHz; $CDCl_3$): 1.22 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.35 (3H, s, CH$_2$OC<u>H</u>$_3$), 3.68 (1H, dd, $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$ 3.3Hz, H-6'), 3.90 (1H, dd, $J_{5,6}$ 2.9Hz, H-6), 4.47 (1H, d, $J_{2,3}$ 4.4Hz, $J_{3,4}$ 3.3Hz, H-3), 4.70 (1H, dd, $J_{4,5}$ 8.2Hz, H-4), 4.72 (2H, dd, C<u>H</u>$_2$OCH$_3$), 4.75 (1H, d, H-2), 5.16 (1H, ddd, H-5); δ_C (125MHz; $CDCl_3$): 26.96 (OCC(<u>C</u>H$_3$)$_3$), 31.61 (C-6), 38.99 (OC<u>C</u>(CH$_3$)$_3$), 45.34 (C-2), 57.30 (CH$_2$O<u>C</u>H$_3$), 67.70, 76.09, 78.88 (C-3, C-4, C-5), 98.48 (O<u>C</u>H$_2$OCH$_3$), 169.17 (<u>C</u>=O in lactone, C-1), 176.80 (O<u>C</u>C(CH$_3$)$_3$); FT-IR: 2966, 1778, 1632, 1175, 1068 cm^{-1}.

β-D-Glucose pentapivaloate (**29**):

α-D-glucose (10 g, 55.6 mmol) was dissolved in 100 mL pyridine and cooled down to 0 °C in an ice bath. Trimethylacetyl chloride (46.9 g, 389 mmol) was added in 5 minutes. The ice bath was removed and the reaction mixture was sealed and heated to 80 °C. It was stirred at this temperature for 10 hours and poured into ice with sodium bicarbonate. After vigorous stirring, the precipitate was collected by filtration and

thoroughly washed with distilled water. The white solid was then dried in vacuum to give β-D-glucose pentapivaloate **29**. The total yield is > 90%. M.p. 156-158°C; (lit. [33] m.p. 156-158°C; $[\alpha]_D^{25}$ + 10.9° (c = 1, $CHCl_3$)); δ_H (500MHz; $CDCl_3$): 1.08, 1.09, 1.12, 1.14, 1.17 (5 x 9H, 5 x s, $C(C\underline{H}_3)_3$), 3.83 (1H, ddd, $J_{5,6}$ 2.2Hz, $J_{5,6'}$ 5.3Hz, $J_{4,5}$ 10.2Hz, H-5), 4.06 (1H, dd, $J_{6,6'}$ 11.8 Hz, H-6'), 4.12 (1H, dd, H-6), 5.12 (1H, dd, $J_{3,4}$ 9.3Hz, H-4), 5.18 (1H, dd, $J_{1,2}$ 8.4Hz, $J_{2,3}$ 9.4Hz, H-2), 5.34 (1H, t, H-3), 5.67 (1H, d, H-1); δ_C (125MHz; $CDCl_3$): 27.02, 27.23, 27.25, 27.28, 27.34 ($OCC(\underline{C}H_3)_3$), 38.91, 38.96, 39.05 ($OC\underline{C}(CH_3)_3$), 61.48 (C-6), 67.80, 70.15, 72.39, 72.81 (C-2, C-3, C-4, C-5), 91.87 (C-1), 176.30, 176.38, 176.97, 177.01, 177.97 ($O\underline{C}C(CH_3)_3$).

α-D-Glucosepentapivaloate (**33**):

β-D-glucosepentapivaloate **29** (1 g, 1.7 mmol) was partially dissolved in 20 mL acetonitrile and 5 mL 37% hydrochloric acid. This mixture was warmed to 50 °C to become a clear solution and stirred under this temperature for 12 hours. The solution was then evaporated and the residue partitioned between chloroform and saturated sodium bicarbonate solution. The organic layer was collected and dried. Evaporation yielded α-D-glucose pentapivaloate **33**. Yield: 0.83g, 83%. δ_H (500MHz; $CDCl_3$): 1.09, 1.10, 1.15, 1.18, 1.26 (5 x 9H, 5 x s, $C(C\underline{H}_3)_3$), 4.04-4.06 (2H, m, H-5, H-6'), 4.11 (1H, dd, $J_{6,6'}$ 10.6Hz, $J_{5,6}$ 5.2Hz, H-6), 5.09 (1H, dd, $J_{1,2}$ 3.8Hz, $J_{2,3}$ 10.2Hz, H-2), 5.14 (1H, t, $J_{3,4}$ 9.7Hz, $J_{4,5}$ 9.7Hz, H-4), 5.51 (1H, t, H-3), 6.29 (1H, d, H-1); δ_C (125MHz; $CDCl_3$): 27.26, 27.28, 27.31, 27.37 ($OCC(\underline{C}H_3)_3$), 38.92, 38.96, 38.99, 39.05, 39.37 ($OC\underline{C}(CH_3)_3$), 61.83 (C-6), 67.66, 69.68, 69.86, 70.50 (C-2, C-3, C-4, C-5), 88.88 (C-1), 176.08, 176.42, 177.02, 177.12, 178.22 ($O\underline{C}C(CH_3)_3$).

2,3,4,6-Tetra-O-trimethylacetyl-α-D-glucosyl bromide (**41**):

β-D-glucose pentapivaloate **29** (1 g, 1.7 mmol) was dissolved in 2 mL dichloromethane and 2 mL 30% hydrogen bromide in acetic acid. This solution was stirred at room temperature for 24 hours. The solution was evaporated and the residue was partitioned between 30 mL dichloromethane and 30 mL saturated sodium bicarbonate solution. The organic layer was dried and evaporated to give 2,3,4,6-tetra-O-trimethylacetyl-α-D-glucosyl bromide **41**. Yield: 0.84g, 87%. (lit. [33] m.p. 142-143°C; $[\alpha]_D^{25}$ + 153.0° (c = 1, $CHCl_3$)); δ_H (500MHz; $CDCl_3$): 1.04, 1.08, 1.10, 1.13 (4 x 9H, 4 x s, $C(C\underline{H}_3)_3$), 4.08 (2H, m, H-6, H-6'), 4.22 (1H, dt, $J_{5,6'}$ 3.2Hz, $J_{5,6}$ 3.2Hz, $J_{4,5}$ 10.1Hz, H-5), 4.72 (1H, dd, $J_{1,2}$ 4.3Hz, $J_{2,3}$ 10.1Hz, H-2), 5.13 (1H, t, $J_{3,4}$ 10.4Hz, H-4), 5.54 (1H, t, H-3), 6.53 (1H, d, H-1); δ_C (125MHz; $CDCl_3$): 26.82, 26.85, 26.90, 26.98 ($OCC(\underline{C}H_3)_3$), 38.45, 38.55, 38.60, 38.69 ($OC\underline{C}(CH_3)_3$), 60.63 (C-6), 66.24, 69.36, 70.65, 72.34 (C-2, C-3, C-4, C-5), 86.74 (C-1), 176.17, 176.52, 177.04, 177.65 ($O\underline{C}C(CH_3)_3$).

β-D-Mannose pentapivaloate (**43**):

This compound was prepared using the same procedure as described above for the preparation of α-D-glucosepentapivaloate **33** using α-D-mannose as starting material. Yield: 90%. δ_H(500MHz; $CDCl_3$): 1.07, 1.11 1.12, 1.18, 1.26 (5 x 9H, 5 x s, $C(C\underline{H}_3)_3$), 3.80 (1H, ddd, $J_{5,6}$ 4.1Hz, $J_{5,6'}$ 2.0Hz, $J_{4,5}$ 10.0Hz, H-5), 4.10 (1H, dd, $J_{6,6'}$ 12.4 Hz, H-6'), 4.17 (1H, dd, H-6), 5.14 (1H, dd, $J_{2,3}$ 3.2Hz, $J_{3,4}$ 10.2Hz, H-3), 5.42 (1H, dd, $J_{1,2}$ 1.0Hz, H-2), 5.43 (1H, t, H-4), 5.80 (1H, d, H-1); δ_C (125MHz; $CDCl_3$): 26.92, 26.97, 26.99, 27.01, 27.11 ($OCC(\underline{C}H_3)_3$), 38.62, 38.69 ($OC\underline{C}(CH_3)_3$), 61.38 (C-6), 64.61, 68.08, 70.90, 73.03 (C-2, C-3, C-4, C-5), 90.61 (C-1), 175.77, 176.44, 176.82, 176.98, 177.87 ($O\underline{C}C(CH_3)_3$).

2,3,4,6-Tetra-O-trimethylacetyl-α-D-mannosyl bromide (**46**):

This compound was prepared using the same procedure as described above for the preparation of 2,3,4,6-tetra-O-trimethylacetyl-α-D-glucosyl bromide **41** from D-mannose pentapivaloate **43** and **44**. Yield: 86%. δ_H (500MHz; $CDCl_3$): 1.04, 1.10, 1.15, 1.19 (4 x 9H, 4 x s, $C(C\underline{H}_3)_3$), 4.06-4.21 (3H, m, H-5, H-6, H-6'), 5.38 (1H, dd, $J_{1,2}$ 1.5Hz, $J_{2,3}$ 3.1Hz, H-2), 5.50 (1H, t, $J_{3,4}$ 10.1Hz, $J_{4,5}$ 10.1Hz, H-4), 5.67 (1H, dd, H-3), 6.19 (1H, d, H-1); δ_C (125MHz; $CDCl_3$): 26.91, 26.93, 26.94 ($OCC(\underline{C}H_3)_3$), 38.62, 38.69, 38.74, 38.79 ($OC\underline{C}(CH_3)_3$), 60.78 (C-6), 64.17, 68.21, 71.89, 73.03 (C-2, C-3, C-4, C-5), 83.64 (C-1), 176.36, 176.46, 176.93, 177.74 ($O\underline{C}C(CH_3)_3$).

N-(2,3,4,6-Tetra-O-trimethylacetyl-β-D-glucosyl) acetamide (**47**):

β-D-glucosepentapivaloate **29** (1.0 g, 1.7 mmol) was dissolved in 15 mL acetonitrile and 5 mL methanesulfonic acid was added in. The reaction mixture was stirred for 12 hours and quenched by pouring into ice with sodium bicarbonate. The mixture was extracted by 2 x 30 mL dichloromethane. The organic layer was dried and evaporated. The crude product was purified by column chromatography to give N-(2,3,4,6-tetra-O-trimethylacetyl-β-D-glucosyl) acetamide **47** as the major product. Yield: 0.61 g, 66%. δ_H (500MHz; $CDCl_3$): 1.05, 1.07, 1.10, 1.15 (4 x 9H, 4 x s, $C(C\underline{H}_3)_3$), 3.79 (1H, ddd, $J_{5,6'}$ 2.2Hz, $J_{5,6}$ 4.4Hz, $J_{4,5}$ 10.2Hz, H-5), 4.08 (2H, 2 x dd, $J_{6,6'}$ 12.6Hz, H-6, 6'), 4.88 (1H, t, $J_{1,2}$ 9.6Hz, $J_{2,3}$ 9.6Hz, H-2), 5.06 (1H, t, $J_{3,4}$ 10.2Hz, H-4), 5.23 (1H, t, $J_{1,NH}$ 9.6Hz, H-1), 5.35 (1H, t, H-3), 6.17 (1H, d, $N\underline{H}Ac$); δ_C (125MHz; $CDCl_3$): 23.14 ($\underline{C}H_3CONH$), 26.88, 26.91, 26.96, 26.99 ($OCC(\underline{C}H_3)_3$), 38.58, 38.63, 38.75, 38.84 ($OC\underline{C}(CH_3)_3$), 61.45 (C-6), 67.37, 70.29, 71.87, 73.89, 78.09 (C-1, C-2, C-3, C-4, C-5),

169.93 ($CH_3\underline{C}ONH$), 176.31, 176.74, 177.93, 178.45 ($O\underline{C}C(CH_3)_3$); FT-IR: 2988, 1786, 1755, 1406, 1168 cm^{-1}.

N-(2,3,4,6-Tetra-O-acetyl-D-glucosyl) acetamides (**51**α and **51**β):

α-D-glucosepentaacetate (1.0 g, 2.6 mmol) was dissolved in 15 mL acetonitrile and 5 mL methanesulfonic acid was added. The reaction mixture was stirred for 12 hours and quenched by pouring into ice with sodium bicarbonate. The mixture was extracted by 2 x 30 mL dichloromethane. The organic layer was dried and evaporated to afford a mixture of N-(2,3,4,6-tetra-O-acetyl-D-glucosyl) acetamide **51**α and **51**β in a ratio of 1:7. Yield: 0.82g, 82%. $[\alpha]_D$ = + 52.45° (c = 1.0, $CHCl_3$); For **51**β: (lit. [34] m.p. 156-158°C; $[\alpha]_D$ + 17 (c = 2, chloroform)); δ_H (500MHz; $CDCl_3$): 1.93, 1.95, 1.97, 1.99, 2.01 (5 x 3H, 5 x s, $COC\underline{H}_3$), 3.77 (1H, ddd, $J_{5,6'}$ 2.2Hz, $J_{5,6}$ 4.7Hz, $J_{4,5}$ 10.2Hz, H-5), 4.02 (1H, dd, $J_{6,6'}$ 12.6Hz, H-6'), 4.24 (1H, dd, H-6), 4.86 (1H, t, $J_{1,2}$ 9.6Hz, $J_{2,3}$ 9.6Hz, H-2), 4.99 (1H, t, $J_{3,4}$ 9.9Hz, H-4), 5.20 (1H, t, $J_{1,NH}$ 9.3Hz, H-1), 5.24 (1H, t, H-3), 6.44 (1H, d, $N\underline{H}Ac$); δ_C (125MHz; $CDCl_3$): 20.75, 20.76, 20.84, 20.91 ($OOC\underline{C}H_3$), 23.52 ($\underline{C}H_3CONH$), 61.90 (C-6), 68.34, 70.79, 72.95, 73.71, 78.35 (C-1,C-2, C-3, C-4, C-5), 169.78, 170.04, 170.67, 170.82, 171.15 ($O\underline{C}CH_3$); FT-IR: 3023, 1753, 1701, 1369, 1228, 1041cm^{-1}.

N-(2,3,4,6-Tetra-O-acetyl-D-galactosyl) acetamides (**54**α and **54**β):

These compounds were prepared using essentially the same procedure as the preparation of N-(2,3,4,6-tetra-O-acetyl-D-glucosyl) acetamides **51**α and **51**β. Yield: 86%; **54**α: **54**β = 1: 8. $[\alpha]_D$ = + 62.44 (c = 1.0, $CHCl_3$); For **54**β: (lit. [34] m.p. 172-174°C; $[\alpha]_D$ + 33° (c = 1, chloroform)); δ_H (500MHz; $CDCl_3$): 1.93, 1.94, 1.98, 2.00, 2.08

(5 x 3H, 5 x s, COC$\underline{H}_3$), 4.02 (1H, m, H-5), 4.06-4.10 (2H, m, H-6, 6'), 5.04 (1H, dd, $J_{1,2}$ 9.0Hz, $J_{2,3}$ 10.2Hz, H-2), 5.08 (1H, dd, $J_{3,4}$ 3.2Hz, H-3), 5.19 (1H, t, $J_{1,NH}$ 9.0Hz, H-1), 5.38 (1H, dd, $J_{4,5}$ 1.0Hz, H-4), 6.38 (1H, d, N$\underline{H}$Ac); δ_C (125MHz; $CDCl_3$): 20.77, 20.81, 20.87, 20.93 (OOC$\underline{C}H_3$), 23.52 ($\underline{C}H_3$CONH), 61.40 (C-6), 67.41, 68.54, 71.06, 72.53, 78.67 (C-1,C-2, C-3, C-4, C-5), 169.95, 170.21, 170.58, 170.59, 171.45 (O$\underline{C}$CH$_3$); FT-IR: 3097, 2479, 1748, 1700, 1630, 1369, 1224, 1046 cm^{-1}.

1,3-Di-O-trimethylacetyl-glycerol **56** and (±)-1,2-di-O-pivaloyl glycerol (**57**):

Glycerol (2.32 g, 25.2 mmol) was dissolved in 50 mL pyridine and cooled down to 0°C. Trimethylacetyl chloride (6.08 g, 50.4 mmol) was added in slowly. The reaction mixture was stirred at 5°C for 10 hours. The mixture was poured into saturated sodium bicarbonate solution containing ice and stirred for a while. Chloroform 2 x 50 mL was used to extract the mixture. The organic phase was dried and evaporated to dryness. The residue was purified by chromatography to give a mixture of 1,3-di-O-trimethylacetyl-glycerol **56** and (±)1,2-di-O-trimethylacetyl-glycerol **57** in a ratio of 2:1. Total yield: 55%. For **56**: δ_H (500MHz; $CDCl_3$): 1.08 (18H, s, C($\underline{C}H_3$)$_3$), 4.03 (1H, dd, H-2), 4.09 (4H, H-1, 1', 3, 3'); δ_C (125MHz; $CDCl_3$): 26.82 (OCC($\underline{C}H_3$)$_3$), 38.52 (OC$\underline{C}$(CH$_3$)$_3$), 64.64 (C-1, C-3), 67.67 (C-2), 178.26 (O$\underline{C}$C(CH$_3$)$_3$); For **57**: δ_H (500MHz; $CDCl_3$): 1.05, 1.07 (2 x 9H, 2 x s, C($\underline{C}H_3$)$_3$), 3.65 (2H, d, H-3, 3), 4.15 (1H, dd, H-1'), 4.28 (1H, dd, H-1), 5.01 (1H, m, H-2); δ_C (125MHz; $CDCl_3$): 26.77, 26.79 (OCC($\underline{C}H_3$)$_3$), 38.52 (OC$\underline{C}$(CH$_3$)$_3$), 60.79 (C-3), 62.29 (C-1), 71.86 (C-2), 177.60, 177.90 (O$\underline{C}$C(CH$_3$)$_3$); FT-IR: 3575, 3325, 2997, 2879, 1716, 1479, 1104 cm^{-1}.

(±)-N-Acetyl-aminopropanediol (**59**):

The mixture of 1,3-di-O-trimethylacetyl-glycerol **56** and (±)1,2-di-O-pivaloyl-glycerol **57** (0.6 g, 2.3 mmol) was dissolved in 5 mL acetonitrile and 1.5 mL methanesulonic acid was added. The reaction mixture was stirred for 4 days at room temperature and poured into saturated sodium bicarbonate solution with ice. Chloroform (2 x 25ml) was used to extract the mixture. The organic layer was dried and evaporated to afford (±) N-acetyl-aminopropanediol **59** as colorless oil. Yield: 0.56g, 80%. FAB-MS: m/z calcd. for $C_{15}H_{27}BNO_5$ 301.1889, found 302.1965 (MH^+); δ_H (500MHz; $CDCl_3$): 1.10, 1.11 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.89 (3H, s, $HNCOC\underline{H}_3$), 3.39 (2H, t, $J_{2,3}$ 6.0Hz, H-3), 4.03 (1H, dd, $J_{1',2}$ 6.0Hz, $J_{1,1'}$ 12.1Hz, H-1'), 4.21 (1H, dd, $J_{1,2}$ 3.7Hz, H-1), 5.00 (1H, dddd, H-5), 6.27 (1H, b, $N\underline{H}Ac$); δ_C (125MHz; $CDCl_3$): 22.90 ($NHCO\underline{C}H_3$), 26.89, 26.94 ($OCC(\underline{C}H_3)_3$), 38.64, 38.68 ($OC\underline{C}(CH_3)_3$), 39.58 (C-3), 62.86 (C-1), 70.12 (C-2), 170.31 ($NH\underline{C}OCH_3$), 177.85, 178.00 ($O\underline{C}C(CH_3)_3$); FT-IR: 3672, 3093, 2975, 1733, 1660, 1281, 1147 cm^{-1}.

(±)-1,2,4-Tri-O-pivaloyl erythritol (**63**):

Erythritol was partially pivaloated with 3.2 equivalent trimethylacetyl chloride using the same procedure described above for the preparation of 1,3-di-O-trimethylacetyl-glycerol **56** and (±)-1,2-di-O-pivaloyl-glycerol **57**. Yield: 60%. δ_H (500MHz; $CDCl_3$): 1.16, 1.17 (3 x 3H, 3 x s, $C(C\underline{H}_3)_3$), 2.92 (1H, b, -OH), 3.92 (1H, ddd, $J_{3,4}$ 2.9Hz, $J_{3,4'}$ 5.0Hz, $J_{2,3}$ 8.0Hz), 4.10 (1H, dd, $J_{4,4'}$ 11.9Hz, H-4'), 4.20 (1H, dd, H-4), 4.28 (1H, dd, $J_{1',2}$ 4.9Hz, $J_{1,1'}$ 12.2Hz, H-1'), 4.41 (1H, dd, $J_{1,2}$ 2.9Hz, H-1), 4.99 (1H, ddd, H-2); δ_C (125MHz; $CDCl_3$): 26.96, 27.09 ($OCC(\underline{C}H_3)_3$), 38.76, 38.81, 38.86

($OC\underline{C}(CH_3)_3$), 62.23 (C-4), 64.97 (C-1), 68.43 (C-3), 70.83 (C-2), 177.07, 178.49, 178.91 ($O\underline{C}C(CH_3)_3$); FT-IR: 3563, 3396, 2995, 2879, 1744, 1479, 1286, 1117, 1060 cm^{-1}.

(±)-4-Bromo-4-deoxy-1,2,3-tri-O-trimethylacetyl-erythritol (**64**):

To 1,2,4-tri-O-pivaloyl erythritol **63** (0.40 g, 1.1 mmol) 30% hydrogen bromide in acetic acid (2 mL) was added. The reaction mixture was stirred at room temperature for 2 hours and evaporated. The residue was partitioned between chloroform (25 mL) and cold saturated sodium bicarbonate solution (25 mL). The organic layer was dried, evaporated and purified by column chromatography to afford 4-bromo-4-deoxy-1,2,3-tri-O-trimethylacetyl-erythritol **64** Yield: 0.36g, 75%. δ_H (500MHz; $CDCl_3$): 1.04, 1.06, 1.09 (3 x 3H, 3 x s, $C(C\underline{H}_3)_3$), 3.35 (dd, 1H, $J_{3,4'}$ 5.7Hz, $J_{4,4'}$ 11.5Hz, H-4'), 3.50 (dd, 1H, $J_{3,4}$ 3.4Hz, H-4), 3.97 (dd, 1H, $J_{1',2}$ 5.0Hz, $J_{1,1'}$ 12.3Hz, H-1'), 4.27 (dd, 1H, $J_{1,2}$ 2.8Hz, H-1), 5.10 (ddd, 1H, $J_{2,3}$ 7.9Hz, H-3), 5.15 (ddd, 1H, H-2); δ_C (125MHz; $CDCl_3$): 26.825, 26.758, 26.714 ($OCC(\underline{C}H_3)_3$), 30.381 (C-4), 38.629, 38.501, 38.483 ($OC\underline{C}(CH_3)_3$), 61.164 (C-1), 69.084, 70.017 (C-2, 3), 177.279, 176.406, 176.293 ($O\underline{C}C(CH_3)_3$); FT-IR: 2977, 2875, 1735, 1278, 1128 cm^{-1}.

(±)-4-N-Acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl-erythritol (**65a**):

(±)-1,2,4-tri-O-pivaloyl-erythritol **63** (0.9 g, 2.4 mmol) was dissolved in 5 mL acetonitrile and borontrifluoride etherate (1.5 mL) was added. The mixture was sealed and stirred at 50 °C for 5 hours and poured into saturated sodium bicarbonate solution (50 mL) with ice. After stirring, the mixture was extracted by 2 x 25 mL chloroform. The organic layer was dried and evaporated to dryness. Flash column chromatography afforded (±)-4-N-acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl erythritol **65a** as colorless oil.

Yield: 0.78g, 78%. FAB-MS: m/z calcd. for $C_{21}H_{37}NO_7$ 415.2570, found 416.2651 (MH^+); δ_H (500MHz; $CDCl_3$): 1.08, 1.12, 1.14 (3 x 3H, 3 x s, $C(C\underline{H}_3)_3$), 1.87 (3H, s, $HNCOC\underline{H}_3$), 3.15 (1H, dt, $J_{3,4'}$ 5.2Hz, $J_{NH,4'}$ 5.2Hz, $J_{4,4'}$ 14.2Hz, H-4'), 3.50 (1H, dt, $J_{3,4}$ 7.2Hz, $J_{NH,4}$ 7.2Hz, H-4), 3.97 (1H, dd, $J_{1',2}$ 7.3Hz, $J_{1',1}$ 11.8Hz, H-1'), 4.18 (1H, $J_{1,2}$ 4.1Hz, H-1), 5.07 (1H, ddd, $J_{2,3}$ 7.3Hz, H-3), 5.19 (1H, dt, H-2), 6.04 (1H, b, $N\underline{H}Ac$); δ_C (125MHz; $CDCl_3$): 22.95 ($HNCO\underline{C}H_3$), 26.92, 26.95 ($OCC(\underline{C}H_3)_3$), 38.55, 38.79, 38.80 ($OC\underline{C}(CH_3)_3$), 39.22 (C-4), 62.11 (C-1), 69.61, 69.70 (C-2, C-3), 170.01 ($HN\underline{C}OCH_3$), 177.51, 177.62 ($O\underline{C}C(CH_3)_3$); FT-IR: 3303, 3091, 2977, 2876, 1725, 1659, 1274 cm^{-1}.

(*S*)-1,4-Di-O-pivaloyl-1,2,4-butanetriol (**67**):

Starting from (S)-1,2,4-butanetriol, (S)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67** was prepared as described above for the dipivaloation of glycerol. Flash column chromatography was used to purify this compound as a single isomer. Yield: 60%. $[\alpha]_D$ = -6.2° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.13, 1.15 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.66-1.82 (2H, m, H-3, 3'), 2.70 (1H, b, -OH), 3.86 (1H, m, H-2), 3.98 (1H, dd, $J_{1',2}$ 6.0Hz, $J_{1,1'}$ 11.0Hz, H-1'), 4.05 (1H, dd, $J_{1,2}$ 4.0Hz, H-1), 4.14 (1H, m, H-4'), 4.22 (1H, m, H-4); δ_C (125MHz; $CDCl_3$): 27.07 ($OCC(\underline{C}H_3)_3$), 32.67 (C-3), 38.63, 38.75 ($OC\underline{C}(CH_3)_3$), 60.82 (C-4), 66.89 (C-2), 68.06 (C-1), 178.52, 178.64 ($O\underline{C}C(CH_3)_3$); FT-IR: 3692, 3093, 2974, 1730, 1283, 1156 cm^{-1}.

(*S*)-4-Bromo-1,3-di-O-pivaloyl-1,3-butanediol (**70**):

(*S*)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67** (0.56 g, 2.0 mmol) was dissolved in 5 mL 30% hydrogen bromide in acetic acid at room temperature. This solution was stirred for 12 hours. Methanol (10 mL) was added and evaporated. The residue was partitioned

between 25 mL dichloromethane and 25 mL saturated sodium bicarbonate solution. The organic layer was dried and evaporated to give (*S*)-4-bromo-1,3-di-O-pivaloyl-1,3-butanediol **70** as a colorless oil. Yield: 0.52 g, 76%. δ_H (500MHz; $CDCl_3$): 1.16, 1.18 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.99-2.05 (2H, m, H-2, 2'), 3.42 (1H, dd, $J_{3,4'}$ 4.8Hz, $J_{4,4'}$ 10.8Hz, H-4'), 3.54 (1H, dd, $J_{3,4}$ 4.7Hz, H-4), 4.01-4.12 (2H, m, H-1,1'), 5.03 (1H, m, H-3), 4.22 (1H, m, H-4); δ_C (125MHz; $CDCl_3$): 27.05, 27.10 ($OCC(\underline{C}H_3)_3$), 31.64 (C-2), 33.97 (C-4), 38.68, 38.89 ($OC\underline{C}(CH_3)_3$), 59.96 (C-1), 68.66 (C-3), 177.49, 178.24 ($O\underline{C}C(CH_3)_3$).

(*S*)-4-N-Acetylamino-1,3-di-O-pivaloyl-1,3-butanediol (**71**) and (*S*)-4-N-acetylamino-1,2-di-O-pivaloyl-1,2-butanediol (**72**):

These compounds were prepared using the same procedure as described above for (±)-4-N-acetylamino-4-deoxy-1,2,3-tri-O-pivaloyl erythritol **65** starting from (S)-1,4-di-O-pivaloyl-1,2,4-butanetriol **67**. Total yield: 88%. **71** : **72** = 2: 1. For **71**: $[\alpha]_D = -35.6^o$ (c = 1.0, $CHCl_3$); FAB-MS: m/z calcd. for $C_{16}H_{29}NO_5$ 315.2046, found 316.2123 (MH^+); δ_H (500MHz; $CDCl_3$): 1.03, 1.04 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.77 (2H, m, H-2, 2'), 1.80 (3H, s, $HNCOC\underline{H}_3$), 3.29 (2H, m, H-4, 4'), 3.93 (2H, m, H-1, 1'), 4.87 (tdd, 1H, J = 4.7Hz, J = 4.7Hz, J = 6.5Hz, J = 9.0Hz, H-3), 6.37 (t, 1H, J = 5.7Hz, $\underline{H}NCOCH_3$); δ_C (125MHz; $CDCl_3$): 22.725 ($HNCO\underline{C}H_3$), 26.821, 26.791 ($OCC(\underline{C}H_3)_3$), 30.627 (C-2), 38.585, 38.371 ($OC\underline{C}(CH_3)_3$), 42.542 (C-4), 59.819 (C-1), 69.031 (C-3), 170.161 ($HN\underline{C}OCH_3$), 178.034, 178.009 ($O\underline{C}C(CH_3)_3$); FT-IR: 3704, 3298, 3094, 2974, 1730, 1656, 1283, 1153 cm^{-1}. For **72**: $[\alpha]_D$ = + 44.7° (c = 1.0, $CHCl_3$); FAB-MS: m/z calcd. for $C_{16}H_{29}NO_5$ 315.2046, found 316.2123 (MH^+); δ_H (500MHz; $CDCl_3$): 1.08, 1.11 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.64, 1.73 (2 x 1H, 2 x m, H-3, 3'), 1.88 (3H, s, $HNCOC\underline{H}_3$), 2.84 (tdd, 1H, $J_{4,HNAc}$ 5.4Hz, $J_{3',4'}$ 5.4Hz, $J_{3,4'}$ 9.1Hz, $J_{4,4'}$ 14.2Hz, H-4'), 3.43 (ddd, 1H, $J_{3',4}$ 6.4Hz, $J_{3,4}$

11.8Hz, H-4), 3.94 (dd, 1H, $J_{1',2}$ 6.7Hz, $J_{1,1'}$ 11.9Hz, H-1'), 4.15 (dd, 1H, $J_{1,2}$ 3.1Hz, H-1), 5.02 (m, 1H, H-2), 6.30 (t, b, 1H, $\underline{H}NCOCH_3$); δ_C (125MHz; $CDCl_3$): 23.053 ($HNCO\underline{C}H_3$), 26.927 ($OCC(\underline{C}H_3)_3$), 30.585 (C-3), 38.689, 38.575 ($OC\underline{C}(CH_3)_3$), 35.073 (C-4), 64.858 (C-1), 68.989 (C-2), 170.169 ($HN\underline{C}OCH_3$), 178.394, 177.837 ($O\underline{C}C(CH_3)_3$); FT-IR: 3703, 3091, 2975, 1731, 1654, 1283, 1149 cm^{-1}.

2,3,5-Tri-O-acetyl-6-O-t-butyldimethylsilyl-D-*galactone*-1,4-lactone (**73**):

D-*galactono*-1,4-lactone (2.0 g, 11.2 mmol) was dissolved in 40 mL dry pyridine and t-butyldimethylsilyl chloride (1.86 g, 12.4 mmol) was added. The reaction mixture was stirred for 12 hours and cooled down to 0°C. Then acetic anhydride (5.74 g, 56.2 mmol) was added slowly. The reaction mixture was stirred for 3 hours at 0°C and poured into saturated sodium bicarbonate solution containing ice. The mixture was stirred and the water phase was poured off. The residue was dissolved in 50 mL dichloromethane and cold 1N hydrochloric acid was added in slowly until the pH reached ~ 1. The organic phase was separated and washed with brine (20 mL) and distilled water (20 mL) and dried. Evaporation followed by chromatography purification gave 2,3,5-tri-O-acetyl-6-O-t-butyldimethylsilyl-D-*galactone*-1,4-lactone **73** as colorless oil. Yield: 3.52 g, 75%. $[\alpha]_D$ = - 45.1° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 0.02 (6H, s, $Si(C\underline{H}_3)_2$), 0.82 (9H, s, $Si(C(C\underline{H}_3)_3)$), 2.05, 2.06, 2.11 (3 x 3H, 3 x s, $COC\underline{H}_3$), 3.70 (1H, dd, $J_{5,6'}$ 7.7Hz, $J_{6,6'}$ 10.1Hz, H-6'), 3.73 (1H, dd, $J_{5,6}$ 5.6Hz, H-6), 4.63 (1H, dd, $J_{3,4}$ 6.9Hz, $J_{4,5}$ 2.6Hz, H-4), 4.99 (1H, ddd, H-5), 5.39 (1H, t, $J_{2,3}$ 7.0Hz, H-3), 5.56 (1H, d, H-2); δ_C (125MHz; $CDCl_3$): -5.72, -5.65 ($Si(\underline{C}H_3)_2$), 18.01 ($Si(\underline{C}(CH_3)_3)$), 20.22, 20.35, 20.54 ($CO\underline{C}H_3$), 25.57 ($Si(C(\underline{C}H_3)_3)$), 59.82 (C-6), 70.60, 72.04, 72.11, 76.64 (C-2, C-3, C-4, C-5), 168.35, 169.21, 169.55, 169.72 (C=O's in lactone and acetate); FT-IR: 2961, 1809, 1756,

1632, 1364, 1235, 1039 cm^{-1}.

2,3,5-Tri-O-acetyl-D-*galactone*-1,4-lactone (**74**):

2,3,5-tri-O-acetyl-6-O-t-butyldimethylsilyl-D-*galactone*-1,4-lactone **73** (1.2 g, 2.5 mmol) was dissolved in 15 mL acetonitrile and 1.5 mL boron trifluoride etherate was added in. The mixture was stirred at room temperature for 5 minutes and 5 g sodium bicarbonate was added in to neutralize. The solution was evaporated to dryness and partitioned between 50 mL dichloromethane and 50 mL water. The organic phase was dried and evaporated to afford 2,3,5-tri-O-acetyl-D-*galactone*-1,4-lactone **74**. Yield: 0.77g, 88%. $[\alpha]_D$ = + 1.1° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 2.00, 2.03, 2.08 (3 x 3H, 3 x s, $COC\underline{H}_3$), 3.97 (ddd, 1H, $J_{4,5}$ 2.3Hz, $J_{5,6'}$ 5.7Hz, $J_{5,6}$ 6.7Hz, H-5), 4.07 (dd, 1H, $J_{5,6'}$ 5.7Hz, $J_{6,6'}$ 11.5Hz, H-6'), 4.19 (dd, 1H, $J_{5,6}$ 6.7Hz, H-6), 4.37 (ddd, 1H, J = 0.9Hz, $J_{3,4}$ 5.9Hz, H-4), 5.58 (1H, d, H-2), 5.59 (dd, 1H, H-3); δ_C (125MHz; $CDCl_3$): 20.533, 20.370, 20.135 ($CO\underline{C}H_3$), 64.108 (C-6), 78.995, 72.222, 71.998, 67.248 (C-2, C-3, C-4, C-5), 170.925, 170.132, 169.618, 168.695 (C=O's in lactone and acetate); FT-IR: 3495, 3097, 1804, 1749, 1629, 1371, 1225, 1040 cm^{-1}.

6-N-Acetylamino-6-deoxy-2,3,5-tri-O-acetyl-D-*galactone*-1,4-lactone (**75**):

2,3,5-tri-O-acetyl-D-*galactone*-1,4-lactone **74** (0.75 g, 2.5 mmol) was dissolved in 5 mL acetonitrile and 1.5 mL boron trifluoride etherate was added. The container was sealed and heated in an 65°C oil bath for 20 hours. The solution was poured into sodium bicarbonate solution with ice and stirred. Chloroform (2 x 25 mL) was used to extract the mixture and the organic layer was evaporated to dryness. The crude product was purified by column chromatography to give 6-N-acetylamino-6-deoxy-2,3,5-tri-O-acetyl-D-

galactone-1,4-lactone **75** as colorless oil. Yield: 0.49 g, 58%. FAB-MS: m/z calcd. for $C_{14}H_{19}NO_9$ 345.1060, found 346.1136 (MH^+); δ_H (500MHz; $CDCl_3$): 1.93 (3H, s, $C\underline{H}_3CONH$), 2.07, 2.10, 2.12 (3 x 3H, 3 x s, $OOCC\underline{H}_3$), 3.44 (1H, ddd, $J_{5,6'}$ 6.6Hz, $J_{6,6'}$ 14.4Hz, $J_{NH,6'}$ 5.8Hz, H-6'), 3.62 (1H, ddd, $J_{5,6}$ 4.8Hz, $J_{NH,6}$ 6.2Hz, H-6), 4.54 (1H, dd, $J_{3,4}$ 6.9Hz, $J_{4,5}$ 2.5Hz, H-4), 5.19 (1H, m, H-5), 5.37 (1H, t, $J_{2,3}$ 7.0Hz, H-3), 5.54 (1H, d, H-2), 6.19 (1H, t, $\underline{N}$HAc); δ_C (125MHz; $CDCl_3$): 20.40, 20.55, 20.72 ($OOC\underline{C}H_3$), 23.08 ($HNOC\underline{C}H_3$), 40.1 (C-6), 69.4, 72.1, 72.3, 78.6 (C-2, C-3, C-4, C-5), 168.2, 169.3, 169.8, 170.2, 170.8 (C=O's in lactone, amide and acetates); FT-IR: 3298, 1806, 1751, 1662, 1372, 1229, 1178 cm^{-1}.

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Chapter 5

Synthesis Efforts towards 1-Deoxynojirimycin (DNJ) and 1-Deoxymannojirimycin (DMJ)

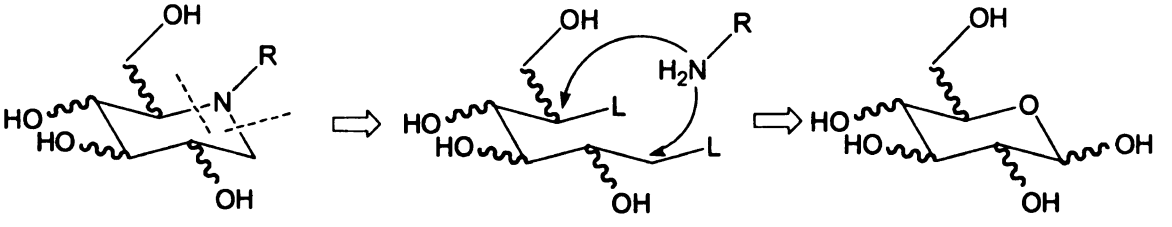
ABSTRACT

A strategy for the preparation of carbohydrate derivatives bearing two leaving groups for use in the preparation of aza-sugars by di-N-alkylation of amines was developed. The target molecules were 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ). Several fully protected dibromosugars failed to undergo di-N-alkylation to give azasugars when treated with amines. The selective acetal protections of dibromoaldonolactones and dibromoalditols were explored. DNJ was synthesized from partially protected dibromoalditol by di-N-alkylation with ammonium hydroxide. DMJ was synthesized from D-mannose using the same strategy.

5.1 Some explorations of 1,5-iminosugar syntheses

In chapter 1, we discussed many synthetic methodologies towards the synthesis of azasugars, including 1,5-iminosugar. Despite the elegant chemistry, most of the current methodologies are not suitable for usage in industry. A practical, environmentally benign synthetic pathway is still desired. Based on the similar structure of azasugars with real sugars, we employed commercially available sugars or sugar derivatives as our starting materials. Since the structure of azasugar is defined as the replacement of ring oxygen with nitrogen atom, our synthetic strategy starts with an introduction of a nitrogen-

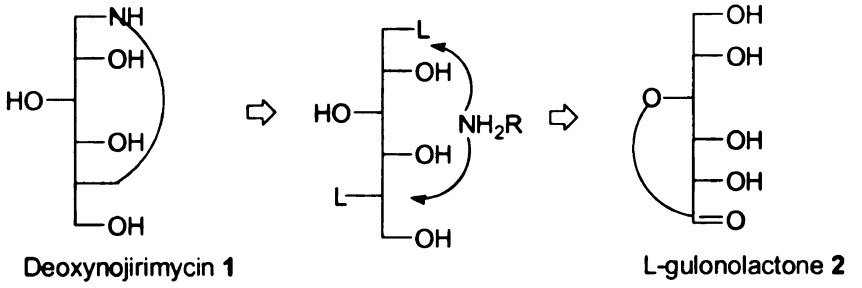
containing nucleophile into the structure. The cheapest nitrogen source exists in different amines. Another advantage of using amines as nucleophiles is that by using different amines, it is relatively easy to build a library of N-substituted azasugars, which is of much interest. S_N2 nucleophilic substitution is favored in the process of introduction of nucleophiles because it is easy to define the chiral centers involved. Therefore, leaving group introduction in certain positions of sugar structure is desired, which often requires different protection strategy (Scheme 5.1).



Scheme 5.1 The retrosynthetic analysis of 1,5-iminosugar synthesis by double N-alkylation strategy

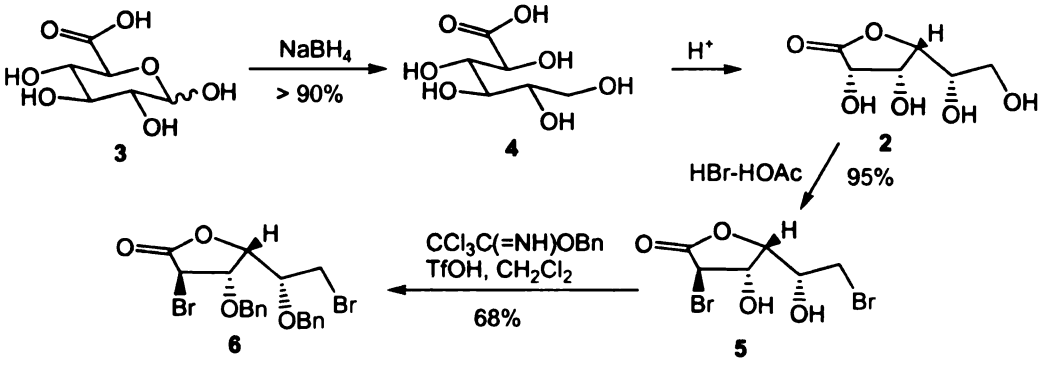
The 2,6-dibromination of sugar lactones has become a very important derivatization of aldonolactones [1-7]. It is easy to imagine that disubstitution of two bromo groups with amines to form 2,6-iminoalditols, which are 6-membered ring azasugars. If all the substitutions (bromination and N-alkylation) happen through a SN_2 mechanism, the stereochemistry of the aldonolactones will be retained in the resulted azasugars because of double inversion. In a simple analysis of the sugar structure (Scheme 5.2), it can be seen that by a carbon chain inversion strategy, 1-deoxynojirimycin (DNJ) **1** is related with L-*gulono*-γ-lactone **2**. L-*gulono*-γ-lactone **2** is commercially available in an affordable price; furthermore, it can also be easily synthesized from

abundant carbohydrate material [8]. All of the above makes it an appropriate starting point for synthetic work.



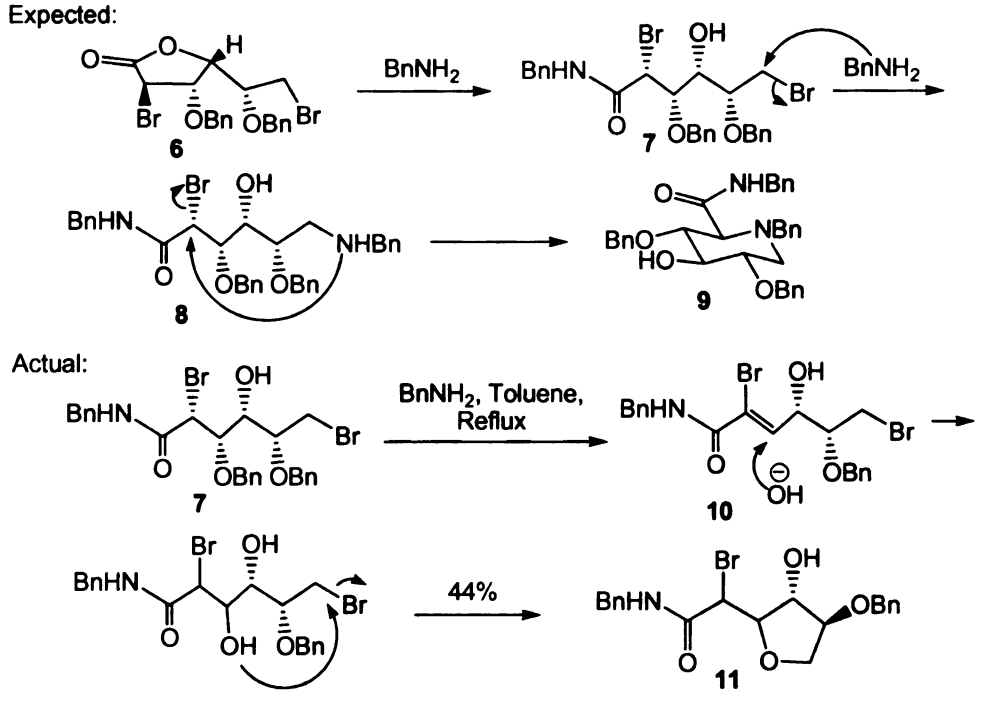
Scheme 5.2 Synthesis of azasugars from aldonolactones: a carbon chain inversion strategy

The hemiacetal of D-glucuronic acid **3** was reduced by sodium borohydride ($NaBH_4$), acidic work-up of this reaction automatically cyclized the carboxylic acid **4** to L-*gulono*-γ-lactone **2**. When **2** was treated with hydrogen bromide in acetic acid, 2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5** was yielded in 95% crude yield. The free hydroxyl groups in 3- and 5- positions of **5** were then benzylated in 68% yield by treatment with benzyl 2,2,2-trichloroacetimidate under catalysis of trifluromethanesulfonic acid to give 3,5-di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **6** (Scheme 5.3).



Scheme 5.3 Synthesis of 3,5-di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*- -lactone **6**

Derivatized and protected, **6** was treated with benzylamine in refluxing toluene (Scheme 5.4).



Scheme 5.4 The treatemnt of 3,5-di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **6** with benzylamine

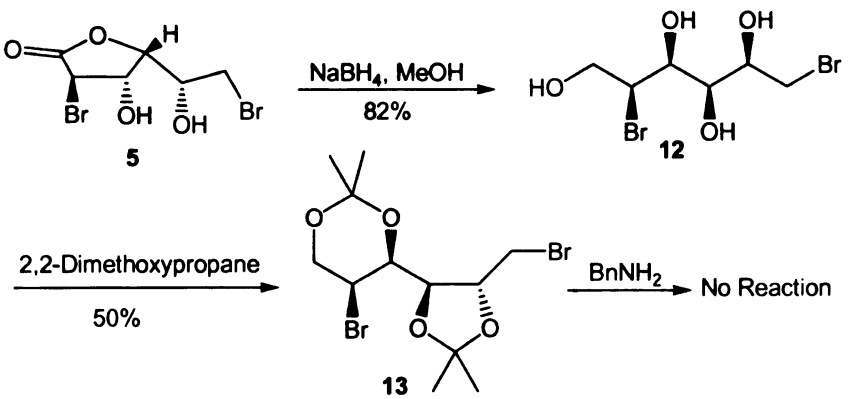
The first expected reaction was the aminolysis of the lactone ring by benzylamine to give amide **7**. After that, under certain conditions, we expected the nucleophilic substitution of primary bromo group by benzylamine to give **8**, after this the N atom attached to C-6 would displace the 2-bromo group in an intramolecular SN_2 fashion to yield compound **9**. After separation, no expected product was found. NMR analysis of the products showed benzylamide and tetrahydrofuran ring structure. Finally, the structure was assigned as compound **11** (N-Benzyl-2-(4-benzyloxy-3-hydroxy-tetrahydro-furan-2-yl)-2-bromo-acetamide). The mechanism for the formation of this product is proposed to involve a β-elimination and Michael addition followed by an intramolecular nucleophilic substitution. In this reaction, the activity of the primary bromo group as a leaving group

was too low, allowing β-elimination to occur. The intramolecular cyclization was fast enough to drive the Michael addition.

The elimination process is specially undesired because after elimination, two chiralities were eliminated. It is always an issue to control the stereoselectivity when new chiralities are built into a structure. To avoid the elimination process, it is necessary to reduce the carbonyl group to an alcohol. This reduction does not reduce the efficiency of the synthesis very much since it is to be carried out in later steps.

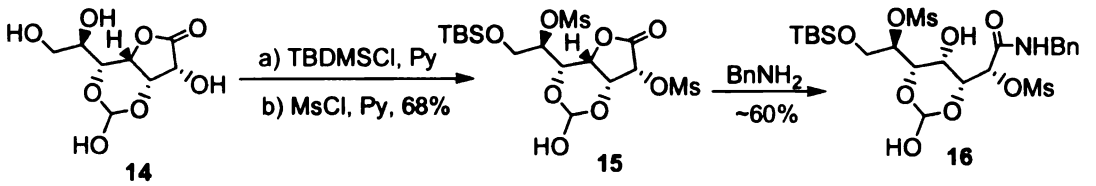
2,6-Dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5** was treated with sodium borohydride to yield 2,6-dibromo-2,6-dideoxy-L-iditol **12**. When this dibromo-L-iditol **12** was treated with excess 2,2-dimethoxypropane, the major product 1,3:4,5-di-O-isopropylidene-2,6-dibromo-2,6-dideoxy-L-iditol **13**. This fully protected dibromoiditol was then treated with benzylamine in refluxing toluene. No expected product was detected even after 3 days. Most of the starting materials remained unchanged while a little decomposition yielded complicated mixture presumably by an elimination process (Scheme 5.5).

The failure of nucleophilic substitution of bromo group with benzylamine in this case could be ascribed to steric reasons. After protection by two isopropylidene groups, steric hindrance was significantly increased in the two-ring structure, which prevented the benzylamine molecule from coming and attacking even the primary carbon.



Scheme 5.5 synthesis of 1,3,4,5-di-O-isopropylidene-2,6-dibromo-2,6-dideoxy-L-iditol **14** and the treatment of it with benzylamine

We also tried to synthesize an azasugar anolog of sialic acid as a potential sialyltransferase inhibitor using the same strategy (Scheme 5.6).



Scheme 5.6 A synthetic attempt to an azasugar anolog of sialic acid as a potential sialyltransferase inhibitor

3,5-O-Benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone **14** was selectively protected at the primary position using tert-butyldimethylsilyl (TBDMS) group. The 2,5-positions were then mesylated. Bearing two leaving groups, 3,5-O-benzylidene-6-O-tert-butyldimethylsilyl-2,5-di-O-methanesulfonyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **15** was treated with benzylamine in refluxing toluene. After 24 hours, no desired amine substituted compound was recovered. Most starting material simply went through aminolysis to form an amide while an amount of a decomposition mixture was produced. Although mesylate is a better leaving group than bromide, the amine nucleophilic substitution still failed to proceed. Again, this failure was ascribed to the high steric

hindrance existing in the structure. To avoid this difficulty, another protection strategy was employed.

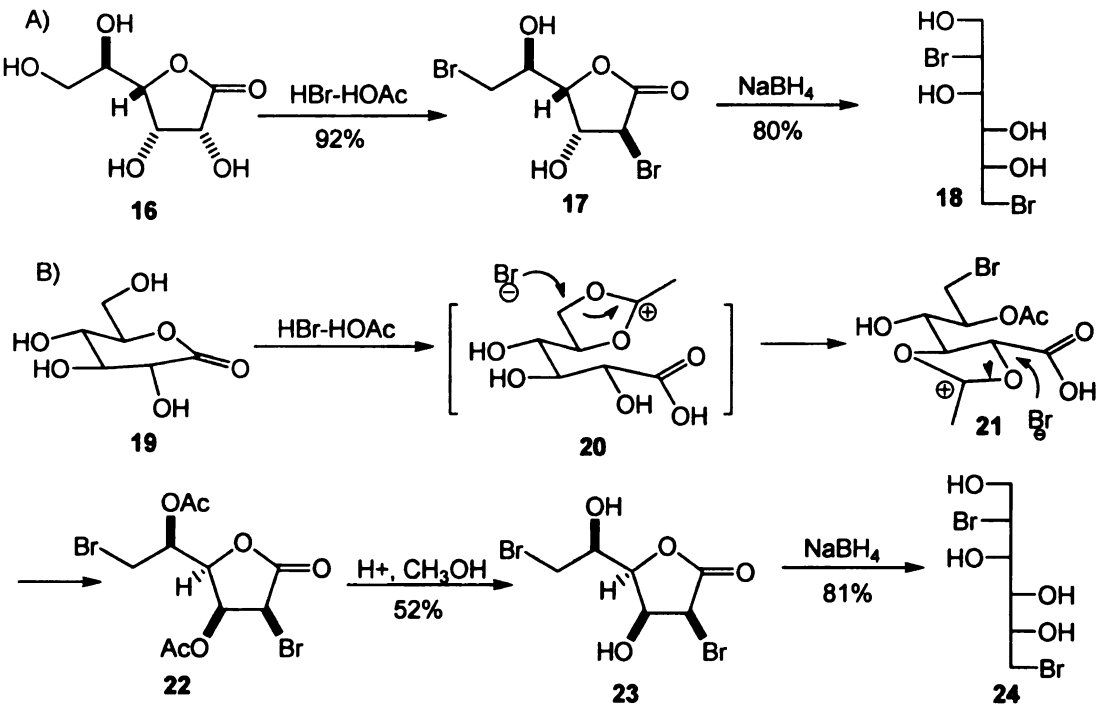
5.2 The isopropylidene protection of dibromoaldonolactones and dibromoalditols

The research work of Lundt's group showed that various naked 2,6-dibromosugar alditols reacted with ammonia to give exclusively 5-membered ring system, including iminosugars and anhydrous sugars [9]. Epoxide formation was found to be a very important activation process in these reactions. Compared to fully protected dibromosugar, epoxide formation greatly increased the activity of bromo group as a leaving group. It was also clear that the naked sugar had much smaller steric hindrance. However, while 5 and 6-member ring formations were both possible, the reaction always went to 5-membered ring formation, which was undesired in the synthesis of 1-deoxynojirimycin (DNJ) or other 1,5-iminosugars.

With this in mind, the involvement of protecting groups is inevitable. However, full protection of hydroxyl groups shuts down the epoxide formation and then greatly decreases the activity of leaving groups, especially when introducing the nitrogen source intermolecularly. The protecting groups should leave enough reactivity for the introduction of a nitrogen nucleophile. Importantly and more interestingly, they should shut down the 5-membered ring formation and switch it to 6-membered azasugar ring formation. The sugar structure should be appropriately partially protected. To explore the selective partial protection of activated aldonolactones and alditols, we carried out

systematic research on the acetal protection and 1,2-diacetal protection of dibromoaldonolactones and dibromoalditols.

2,6-Dibromo-2,6-dideoxy-aldonolactones and alditols with D-*ido* and D-*manno* configurations were chosen as model compounds mainly because they are easily accessible and affordable (Scheme 5.7).



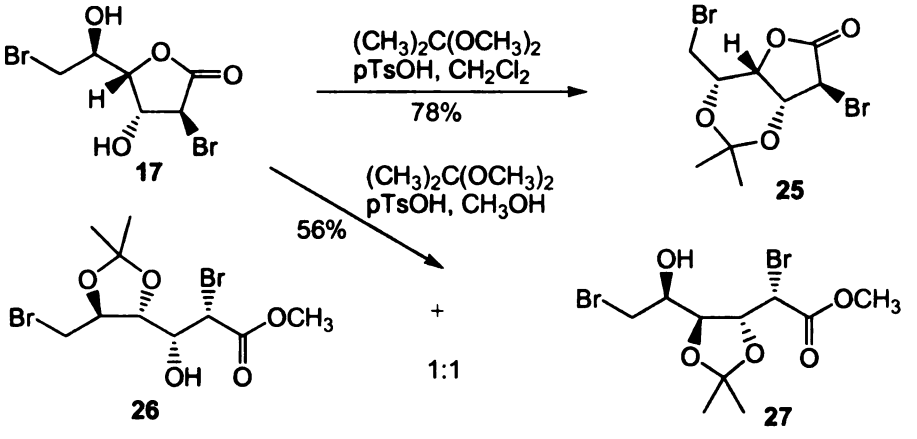
Scheme 5.7 Synthesis of 2,6-dibromo-2,6-dideoxy-aldonolactones and alditols with (A) D-*ido* and and (B) D-*manno* configurations

2,6-Dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **17** and iditol **18** were synthesized from D-*gulono*-γ-lactone **16** using the same procedure as for the L-configuration. This procedure was also employed in the synthesis of 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23** and mannitol **24** except that the starting material was D-*glucono*-δ-lactone **19** instead of γ-lactone. The reaction between **19** and hydrogen bromide in acetic acid was believed to go through an acetoxonium cation mechanism. In this pathway, the lactone

ring has to be opened to allow the acetoxonium cation formation and followed bromination. It is necessary to extend the reaction time to let it proceed and the yield is also lower than that of 2,6-dibromo-2,6-dideoxy-D-idonolactone **17**. The reduction of 2,6-dibromo-2,6-dideoxy-D-mannolactone **23** afforded 2,6-dibromo-2,6-dideoxy-D-mannitol **24**.

5.2.1 Isopropylidene protection of dibromoaldonolactone

First, the reaction of 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **17** with 2,2-dimethoxypropane under different reaction conditions was explored. The results are shown in Scheme 5.8.



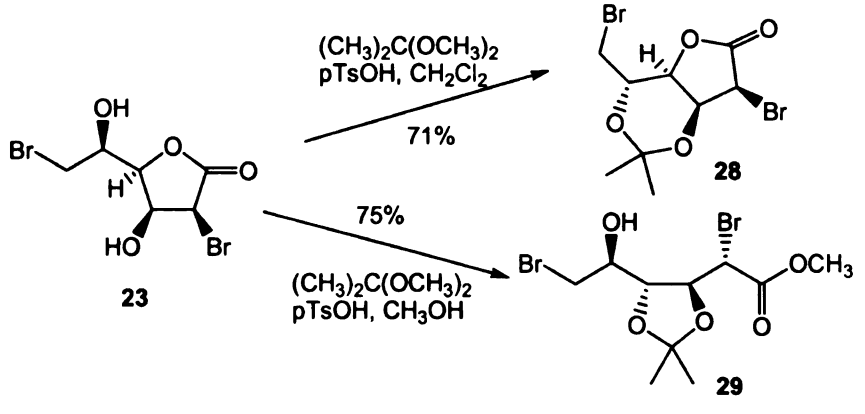
Scheme 5.8 The isopropylidene protection of 2,6-Dibromo-2,6-dideoxy-D-idonolactone **17**

2,2-Dimethoxypropane was chosen as the isopropylidene source and p-toluenesulfonic acid was chosen as the catalyst. This reaction condition was generally used to give the kinetic acetal products. When the reaction was carried out in dichloromethane, 2,6-dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-*idono*-1,4-lactone **25** was formed in a short time. Extension of the reaction time did not change the structure of

the product, as shown both in thin layer chromatography (TLC) and in NMR spectra. Although the transacetalation would release methanol in the system, the reaction condition is not strong enough to open the lactone ring. As the kinetic product, 3,5-O-isopropylidene product was obtained under this reaction condition. However, when we changed the solvent to methanol without changing the other reaction conditions, a totally different phenomenon was shown. The lactone ring was opened and two products were formed. NMR analysis of the products showed them to be methyl 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-idonate **26** and methyl 2,6-dibromo-2,6-dideoxy-4,5-O-isopropylidene-D-idonate **27** respectively with a ratio of ~ 1:1. Under acidic conditions, it was plausible for methanol to open the lactone ring and released 4-position free hydroxyl group. Transacetalation can then occurr to protect two of the three free hydroxyl groups. The acetal formation further drove the equilibrium between idonolactone and methyl idonate towards the final products. Although the formation of the kinetically favored 3,5-O-isopropylidene product **25** was possible, the lactone ring tended to go through methanolysis to release the high ring strain of **25**. The selectivity between the three free hydroxyl groups was governed by general acetalation selectivity rules of acyclic polyols. 1,2-isopropylidene was favored over 1,3-isopropylidene because there are no strong 1,3-diaxial interaction in the former. Between 1,2-isopropylidenes, the selectivity would favor the two hydroxyl groups with *threo-* configuration rather than those with *erythro-* configuration. This could be understood from the conformation analysis. Normally, the two hydroxyl groups with *threo-* configuration have a *gauche* relationship, while those with *erythro-* configuration have a *trans-* relationship. Before the acetal ring formation, the two hydroxyl groups with *threo-* configuration are closer with each other than those with *erythro-* configuration. After the 5-membered acetal ring formation, the product with

threo- configuration has lower steric strain than those with *erythro*- configuration because of the partially eclipsed relationship between two substitution groups in the latter. In this case, both 3,4-diol and 4,5-diol had *threo*- relative configuration. So it is not surprising that two isomers were formed in a ~ 1:1 ratio, 3,4-O-protected and 4,5-O-protected respectively.

We also explored the acetal protection reaction of 2,6-dibromo-2,6-dideoxy-D-*manno*-γ-lactone **23**. The same reaction conditions were used so that we could compare them with each other. When we treated **23** with 2,2-dimethoxypropane under catalysis of p-toluenesulfonic acid in dichloromethane, as we expected, the lactone ring remained untouched while 3,5-O-benzylidene-2,6-dibromo-2,6-dideoxy-D-*manno*-γ-lactone **28** was formed. This kinetically favored product **28** stayed stable under this reaction condition (Scheme 5.9).



Scheme 5.9 The isopropylidene protection of 2,6-dibromo-2,6-dideoxy-D-mannonolactone **23**

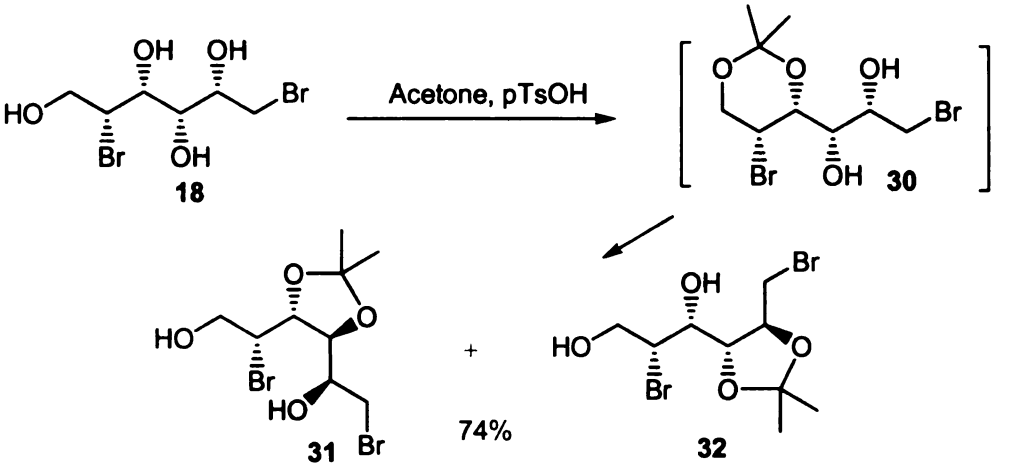
When the solvent was changed to methanol, lactone ring opening occurred. However, only one major product was obtained, which was confirmed to be methyl 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannonate **29** by NMR analysis. After the

lactone ring was opened, 4-position hydroxyl group was released; therefore the configuration of this acyclic sugar chain became 3,4-*threo*- and 4,5-*erythro*-. According to our previous analysis of acetalation selectivity, 3,4-O-isopropylidene was selectively formed.

5.2.2 Isopropylidene protection of dibromoalditol

Isopropylidene has been used extensively for the protection of 1,2- and 1,3-diols. This is especially true in carbohydrate chemistry [10]. Generally, for a polyol system, 1,2-acetonide formation is favored over 1,3-acetonide formation, although the extent of this preference is dependent on structures. Among 1,2-acetonides, the selectivity is based on the thermodynamic stability. Related to the azasugar synthesis, we reasoned that the selective isopropylidene protection of dibromoalditols would generate partially protected dibromoalditols, which would be good precursor to iminoalditols. The isopropylidene protection of 2,6-dibromo-2,6-dideoxy-D-iditol **18** and 2,6-Dibromo-2,6-dideoxy-D-mannitol **24** was therefore explored. We previously prepared fully isopropylidene-protected 2,6-Dibromo-2,6-dideoxy-L-iditol **13** using 2,2-dimethoxypropane as the carbonyl equivalent. To explore the partial acetalation of dibromoalditol, acetone was used as both the solvent and the carbonyl reagent. Under the catalysis of p-toluenesulfonic acid, 2,6-dibromo-2,6-dideoxy-D-iditol **18** reacted with acetone immediately to form two isomers, NMR analysis confirmed to be 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-iditol **31** and 2,6-dibromo-2,6-dideoxy-4,5-O-isopropylidene-D-iditol **32** respectively. An interesting phenomenon was that the ratio between these two isomers changed while the reaction time was extended. If the reaction was worked-up in 10 ~ 15 minutes, the selectivity between 3,4-O-isopropylidene **31** and

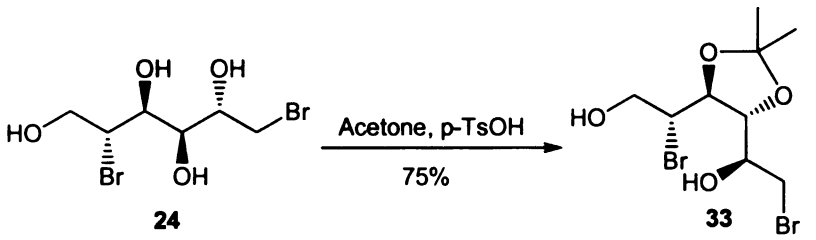
4,5-O-isopropylidene **32** highly favored the former with a ratio 5:1. When the reaction time was extended to overnight, finally the selectivity between them vanished (Scheme 5.10). It was reasonable to deduce that thermodynamically the two products were very similarly favored, however, kinetically 3,4-O-isopropylidene was favored. One explanation was shown in Scheme 5.10. Both the products were formed from an isopropylidene rearrangement from 1,3-O-isopropylidene intermediate **30**. Under our reaction conditions, 1,3-O-isopropylidene dibromoiditol quickly rearranged to 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-iditol **31**, while the rearrangement from **31** to 4,5-O-isopropylidene **32** had a bigger energy barrier so that it took a much longer time. As a result, by control the reaction time, we were able to selectively synthesize different partially protected dibromoiditols.



Scheme 5.10 The isopropylidene protection of 2,6-dibromo-2,6-dideoxy-D-iditol **18**

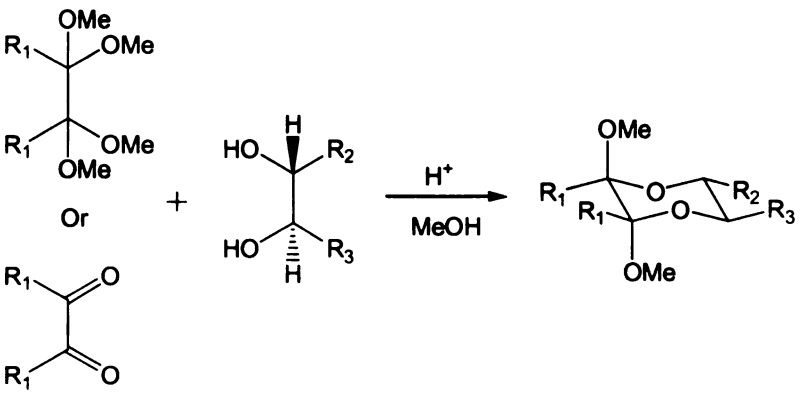
The reaction between 2,6-dibromo-2,6-dideoxy-D-mannitol **24** and acetone under that catalysis of p-toluenesulfonic acid was also carried out. Since it had a 3,4-*threo*- and 4,5-*erythro*- configuration, when 3,4-O-isopropylidene product was formed, the energy

barrier of rearrangement to 4,5-O-isopropylidene should be fairly high. As we expected, even after overnight stirring, the only major product obtained was 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannitol **33** (Scheme 5.11).



Scheme 5.11 The isopropylidene protection of 2,6-dibromo-2,6-dideoxy-D-mannitol **24** by acetone

5.3 The 1,2-diacetal protection of dibromoaldonolactones and dibromoalditols



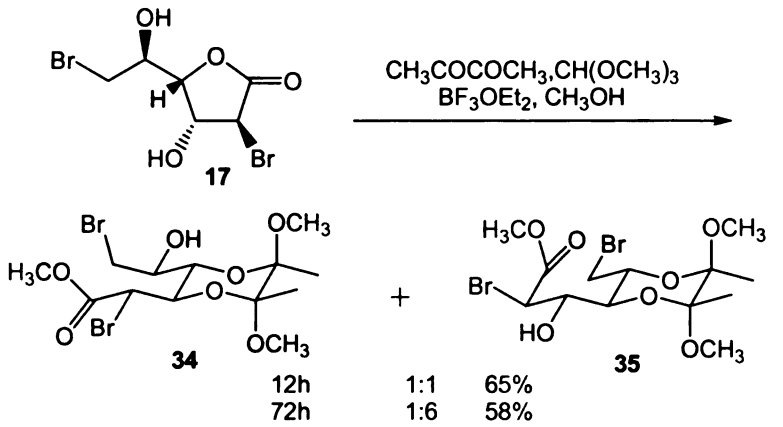
Scheme 5.12 1,2-diacetal protection group for 1,2-diols (Adapted from Ley S. V.; Baeschlin D. K.; Dixon D. J.; Foster A. C.; Ince S. J.; Priepke H. W.; Reynolds D. J., *Chemical reviews*, **2001**, 101, 53-80)

Based on its own structure, isopropylidene generally protects 1,2-diol or 1,3-diol to form a five-membered ring or a six-membered ring respectively. However, in some cases, it is necessary to protect 1,2-diols while forming a six-membered ring. To fulfill this requirement, Ley and other groups [11-16] introduced 1,2-diacetals into protecting

chemistry (Scheme 5.12). Systematical research was carried out to understand the reactivity and selectivity of different 1,2-diacetal reagents. Among those 1,2-diacetal reagents, 2,3-butanedione was the most attractive one because it is commercially available at a cheap price. Therefore we explored the 1,2-diacetal protecting reaction of dibromoaldonolactones and dibromoalditols using 2,3-butanedione as the protecting reagent.

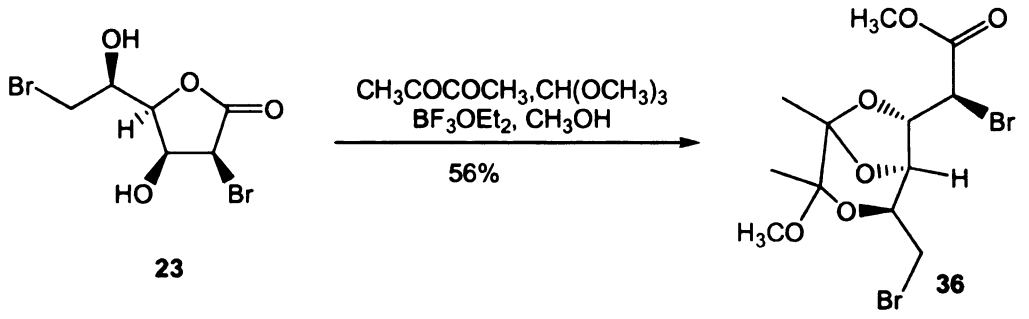
5.3.1 1,2-Diacetal protection of dibromoaldonolactones

The 1,2-diacetal protection reaction of 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **17** was carried out using the procedure established by Ley's group [14,16]. In this procedure, 2,3-butanedione was employed as the 1,2-diacetal source while trimethylorthoester was used as the dehydrating reagent. Methanol was usually employed as the solvent and BF_3OEt_2 was used as the Lewis acid catalyst to avoid undesired triprotected acetal product. When **17** was subjected to this reaction condition, after 12 hours, TLC showed that two major products with similar polarities were formed. NMR analysis confirmed them to be two regio-isomers with about 1:1 ratio that were partially protected by 1,2-diacetal at 3,4-positions (**34**) and 4,5-positions (**35**) respectively (Scheme 5.13). It is not difficult to understand that there is no good selectivity between 3,4- and 4,5-diacetals since their relative configurations are both *threo*-, as discussed before. However, when the reaction time was extended for 3 days, the selectivity between those two changed dramatically. NMR spectroscopy showed only one major regio-isomer, which was also confirmed to be 4,5-diacetal **35**. Although there was no obvious steric preference between 3,4-diacetal and 4,5-diacetal, the improved selectivity by extension of reaction time could greatly improve the synthetic efficiency.



Scheme 5.13 1,2-diacetal protection reaction of 2,6-dibromo-2,6-dideoxy-D-idonolactone **17**

We also explored the 1,2-diacetal protection reaction of 2,6-dibromo-2,6-dideoxy-D-manno-1,4-lactone **23**. Same reaction condition was employed. Here we expected the lactone ring to be opened and 3,4- or 4,5-diacetal should be formed. Based on the 3,4-*threo*- and 4,5-*erythro*- configurations, we expected the 3,4-diacetal to be formed more favorably. After 12 hours stirring, TLC showed only one major product; however, this product migrated much faster on thin layer chromatography than the two 1,2-diacetal products formed when we treat 2,6-dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **17** with 2,3-butanedione. NMR analysis also showed no -OH signal. Further spectral analysis suggested the structure to be 3,4,5-triprotected compound **36** (Scheme 5.14). In previous research of reactions of acyclic polyols with 2,3-butanedione under catalysis of Lewis acid [14-16], only partial protection of 1,2-diols were formed while all the neighboring free hydroxyl groups stay unprotected. The further cyclization only happened when protic acid catalyst such as p-toluenesulfonic acid was used while heating was also necessary. Thus, the full protection of this triol was interesting and could be useful in future work.



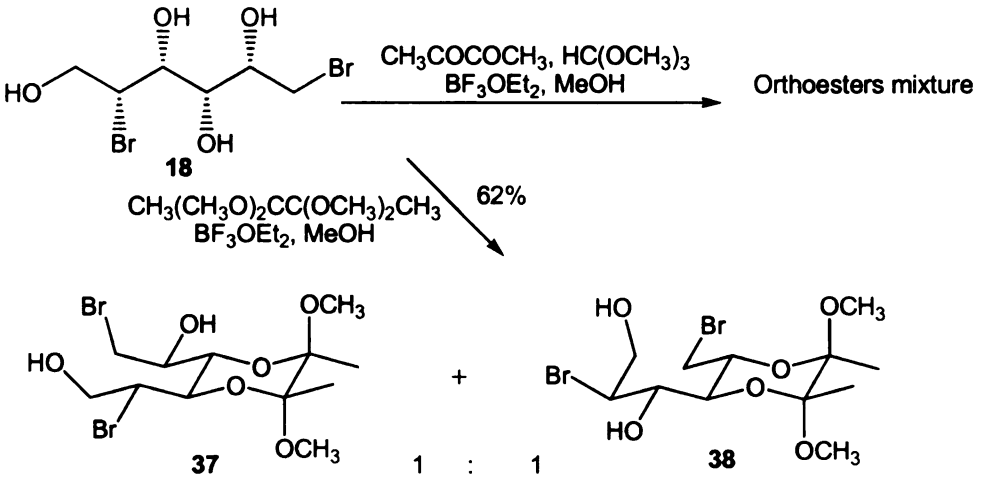
Scheme 5.14 1,2-diacetal protection reaction of 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23**

5.3.2 1,2-Diacetal protection of dibromoalditols

The 1,2-diacetal protecting reactions with dibromoalditols were also explored. Since the primary hydroxyl groups of 2,6-dibromoalditols are separated from 3,4,5-tiols by 2-bromo group, we expected the participation of 1-OH in the 1,2-diacetal protection to be very disfavored. We expected very similar behaviors compared to the 1,2-diacetal protections of the dibromoaldonolactones since the stereochemistry was not changed.

When 2,6-dibromo-2,6-dideoxy-D-iditol **18** was treated with 2,3-butanedione and trimethylorthoester under the catalysis of BF_3OEt_2 in dry methanol, a very complicated mixture was obtained. NMR analysis confirmed that several methyl orthoesters of 2,6-dibromo-2,6-dideoxy-D-iditol were formed as major products. 3,4-Diacetal **37** and 4,5-diacetal **38** of 2,6-dibromo-2,6-dideoxy-D-iditol, which were expected to be major products, were not found. Extension of the reaction time did not yield diacetal protected 2,6-dibromoiditol (Scheme 5.15). This phenomenon was not consistent with reports from literature [13-15]. Presumably, under the current reaction conditions, trimethylorthoester reacted with 2,6-dibromoiditol very quickly to yield orthoesters. The orthoesters were sufficiently stable under this reaction conditions so that they would not exchange with

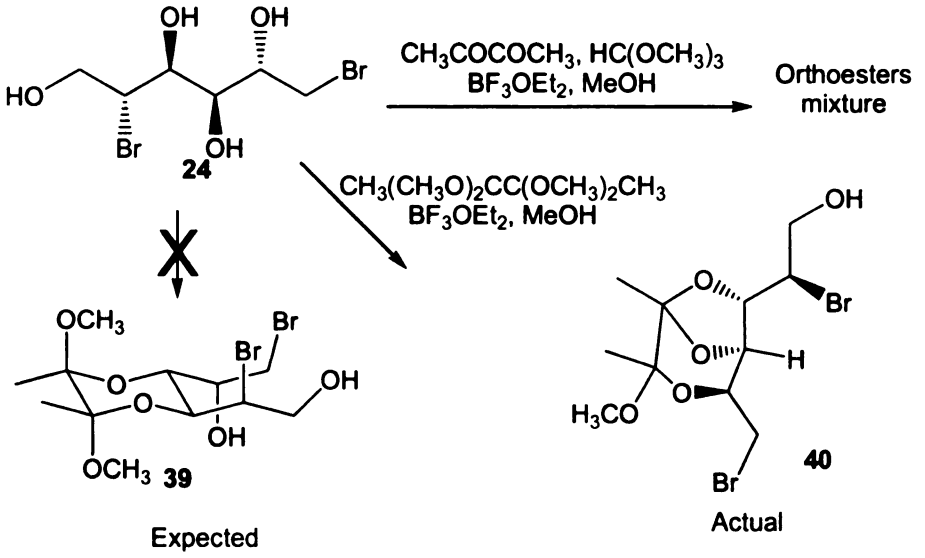
2,3-butanedione to form the expected products. To avoid the orthoester formation, the dehydrating reagent trimethylorthoester was removed from the reaction system while the 1,2-diacetal source was changed to 2,2,3,3-tetramethoxybutane. The latter could be easily prepared from 2,3-butanedione and trimethylorthoester under acid catalysis. When we treated 2,6-dibromo-2,6-dideoxy-D-iditol **18** with 2,2,3,3-tetramethoxybutane under catalysis of BF_3OEt_2, two major products with ~1:1 ratio was yielded. NMR analysis confirmed the structure to be 3,4-O-diacetal **37** and 4,5-O-diacetal **38** of 2,6-dibromo-2,6-dideoxy-D-iditol respectively. Under this reaction condition, orthoesters were not formed. Between 3,4-diacetal and 4,5-diacetal, there was no obvious steric difference, so they had approximately same regioselectivity.



Scheme 5.15 The 1,2-diacetal protection of 2,6-dibromo-2,6-dideoxy-D-iditol **18**

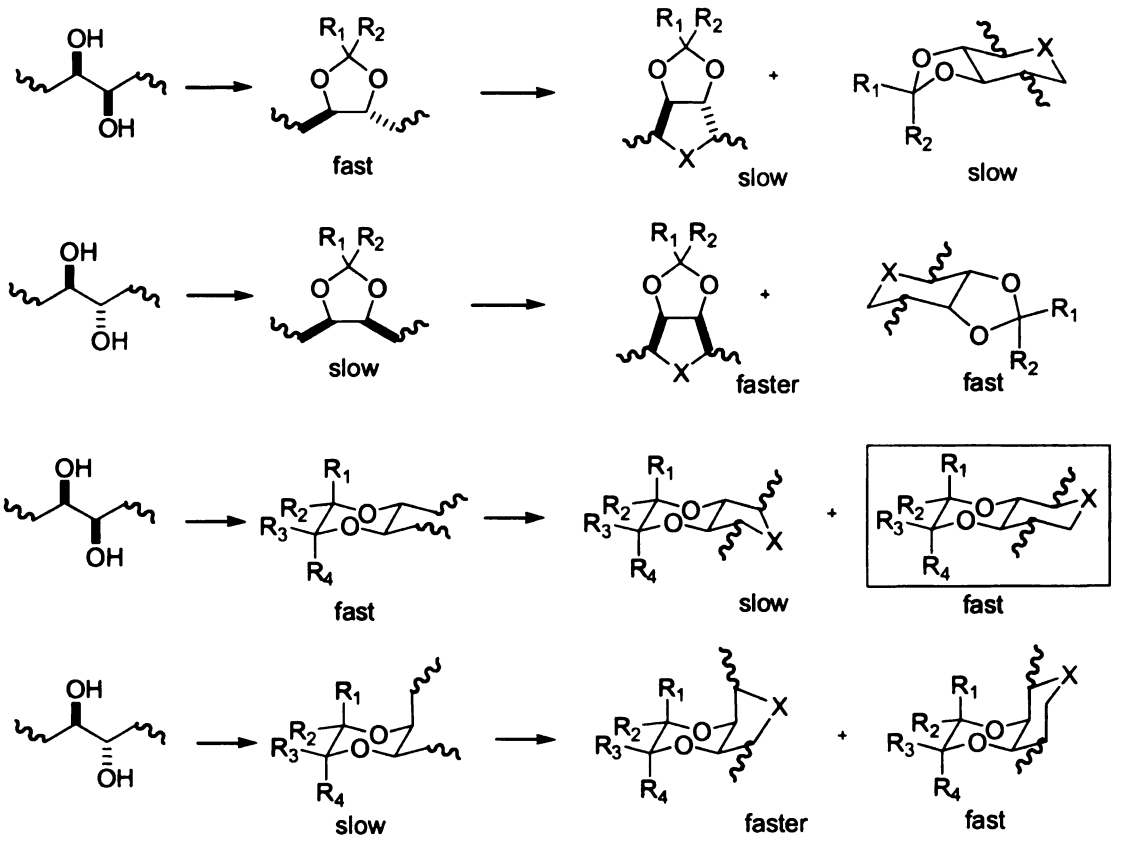
The 1,2-diacetal protection reactions of 2,6-dibromo-2,6-dideoxy-D-mannitol **24** were also explored using largely the same reaction conditions employed above. When 2,3-butanedione was directly used as 1,2-diacetal source combined with trimethylorthoester as dehydrating reagent, only complicated mixtures of orthoesters were formed, which was consistent with our experiments above. Therefore, 2,2,3,3-

tetramethoxybutane was used as the 1,2-diacetal reagent without dehydrating reagent. Because of the 3,4-*threo*- and 4,5-*erythro*- configuration of 2,6-dibromo-2,6-dideoxy-D-mannitol **24**, we expected that 3,4-diacetal **39** should be the major product. NMR spectroscopy of the crude product showed that the major product was 3,4,5-triprotected compound **40** (Scheme 5.16). This triprotection was also shown in the diacetalation of 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23**. With this D-*manno*- configuration, the triprotected compound **40** could adjust to a relatively less strained conformation so that the bridged ring system was sufficiently stable. As a result, 3,4-diacetal was not formed as a major product.



Scheme 5.16 The 1,2-diacetal protection of 2,6-dibromo-2,6-dideoxy-D-mannitol **24**

5.4 Synthesis of 1-deoxynojirimycin (DNJ)



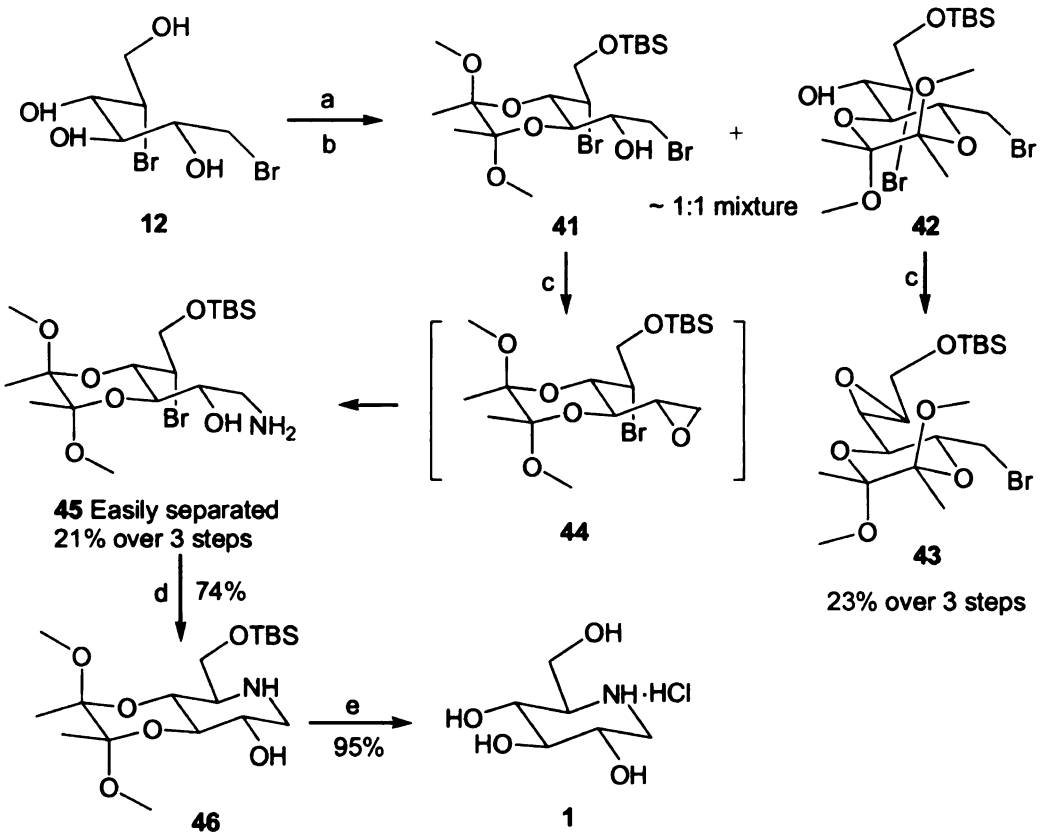
Scheme 5.17 A ring-strain analysis of acetal and 1,2-diacetal protection and fused-ring formation

Based on the literature about acetal and 1,2-diacetal protections and our own results on selective acetalation and 1,2-diacetalation, we explored the synthesis of 1-deoxynojirimycin (DNJ) **1**. Our goal was to develop a facile and practicable pathway to this azasugar using easily accessible materials and simple protection strategy. Starting from 2,6-dbromo-2,6-dideoxy-L-iditol **12**, the involvement of protecting groups was inevitable. On the other hand, full protection of hydroxyl groups shut down the epoxide formation and then greatly decreases the activity of leaving groups, especially when introducing nitrogen source intermolecularly. The protecting groups should leave enough

reactivity for the introduction of a nitrogen nucleophile. Importantly and more interestingly, they should shut down the 5-membered azasugar ring formation and switch it to 6-membered azasugar ring formation. A ring systems formation analysis is shown in Scheme 5.17. Acetal protecting groups selectively protect 1,2-trans diols of an acyclic structure, however, this makes the fused-ring formation difficult because of the high ring strain. On the other hand, 1,2-diacetal protecting groups also selectively protect 1,2-trans diols of an acyclic structure. This makes 5,6-fused ring system formation difficult, however, this could facilitate the 6,6-fused ring formation because of the relatively small ring strain.

Starting from commercially available L-*gulono*-1,4-lactone **2**, 2,6-dibromo-2,6-dideoxy-L-iditol **12** was easily prepared by dibromination followed by reduction according to literature [3]. When treated with 2,2,3,3-tetramethoxybutane under catalysis of BF_3OEt_2, a ~1:1 mixture of 3,4-O- and 4,5-O-(2',3'-dimethoxybutane-2',3'-diyl) protected dibromoiditol was synthesized (Scheme 5.18). This mixture was then directly treated with tert-butyldimethylsilyl chloride to selectively protect the primary hydroxyl groups. An inseparable mixture of **41** + **42** was then obtained. When the mixture was treated with ammonium hydroxide in methanol, TLC showed two products that were well discriminated. Easy separation by column chromatography and NMR study showed the structure of the fast spreading compound as 2,3-anhydrous-6-bromo-6-dideoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-gulitol **43**, and the slow spreading compound as 6-amino-2-bromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-iditol **45**. Under basic conditions, epoxides were formed from bromo- groups and neighboring free hydroxyl groups. If an epoxide was not

too sterically hindered for reaction with an incoming nucleophile, e.g. an amino group, a nitrogen-contained functional group would be introduced into the structure. Otherwise, the epoxide would stay untouched. When reacted with ammonium hydroxide, the 3,4-O-diacetal protected dibromoiditol formed 5,6-anhydrosugar **44**, which was then reacted with ammonia to form **45** with a yield of 21% over 3 steps. However, the 4,5-O-diacetal protected dibromoiditol formed 2,3-anhydrosugar **43**, which was too hindered for incoming ammonia to attack and therefore stayed untouched. This interesting differentiation greatly facilitated the separation process.



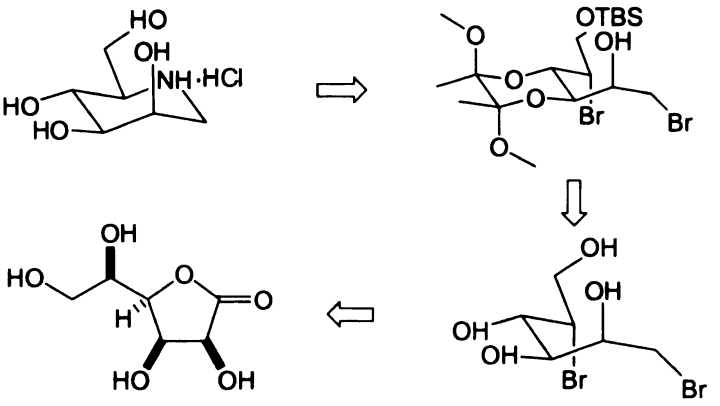
Scheme 5.18 The synthesis of 1-deoxynojirimycin(DNJ) **1**: a) 2,2,3,3-Tetramethoxybutane, $BF_3.OEt_2$, MeOH, rt; b) TBDMSCl, Py, rt; c) NH_4OH, MeOH, rt; d) DBU, Tol, reflux; e) 4NHCl, MeOH

The protected 6-amino-2-bromo-iditol **45** was then refluxed with DBU in toluene to furnish the partially protected 2,6-iminosugar **46**. No 5-membered ring formation was detected in this process, consistent with our previous analysis. Finally, Compound **46** was deprotected by hydrogen chloride in methanol to afford deoxynojirimycin **1** quantitatively, which matched the NMR spectral properties from the literature [17-20].

In summary, 1-deoxynojirimycin **1** was synthesized in 5 steps from 2,6-dibromo-2,6-dideoxy-L-iditol **2** with an overall yield ~ 15%. The key step was the use of 1,2-diacetal as a protecting group. This left the 6-bromo group reactive enough for an intermolecular nucleophilic substitution, and facilitated the 6-membered ring formation in an intramolular fashion as a structure tether. The whole process did not involve any azide and heavy-metal catalysis. Only relatively cheap and easily available reagents were used. All these features made the synthesis not only of academic interest, but also practicable. Furthermore, it is likely that this methodology could be expanded to the synthesis of some other important azasugars such as deoxymannojirimycin and castanospermine by modifying the starting material, employing different amines as nitrogen source and/or transforming the partially protected 2,6-iminosugar **46**.

5.5 Synthesis of 1-deoxymannojirimycin (DMJ)

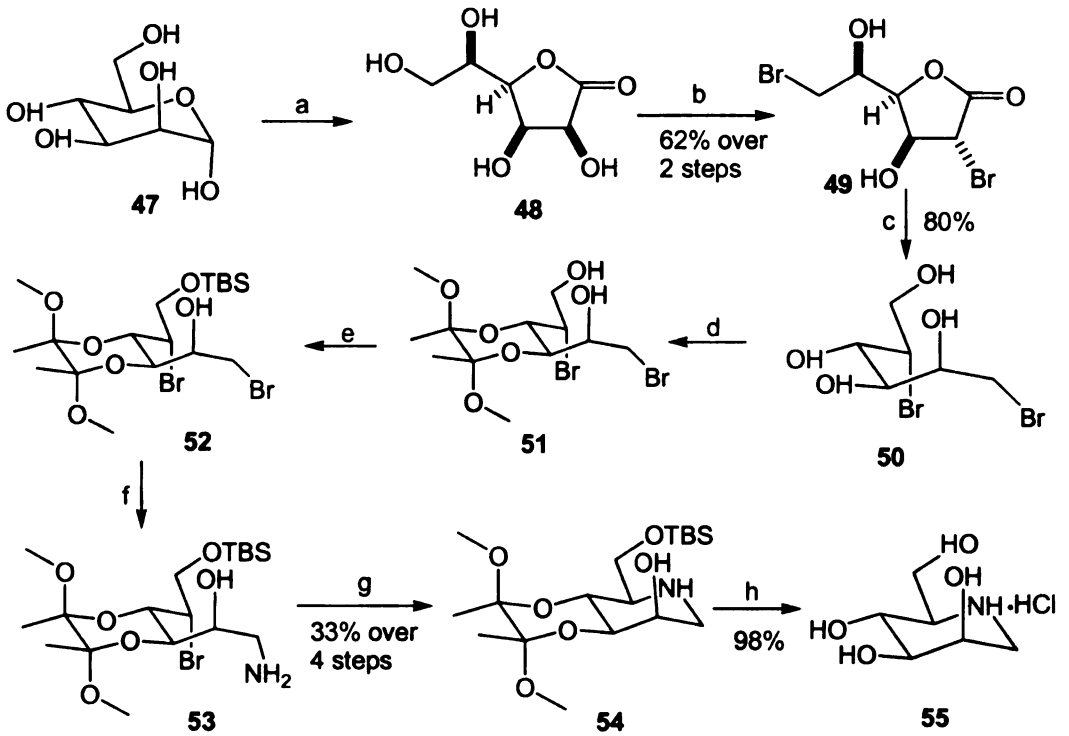
We further employed this strategy in the synthesis of 1-deoxymannojirimycin (DMJ). A retrosynthetic analysis was shown in Scheme 5.19. DMJ could be synthesized from a similar 1,2-diacetal protected dibromoglucitol intermediate, which could be obtained from dibromoglucitol. This dibromoglucitol could be synthesized from D-*manno*-1,4-lactone by dibromination and reduction.



Scheme 5.19 The retrosynthetic analysis of 1-deoxymannojirimycin(DMJ)

A synthesis of 1-deoxymannojirimycin (DMJ) **55** was carried out starting from α-D-mannose **47**. The bromine oxidation of the anomeric position in buffered soluction of **47** afforded D-*manno*-1,4-lactone **48**. Compound **48** was then subjected to HBr treatment in acetic acid to give 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone **49**, which was subsequently reduced by sodium borohydride to give 2,6-dibromo-2,6-dideoxy-D-glucitol **50**. The pH of the solution was controlled below 8 to prevent the anhydrosugar formation. Compound **50** was then treated with 2,2,3,3-tetramethoxybutane under catalysis of BF_3OEt_2 in methanol for 16 hours to give the 3,4-O-diacetal protected 2,6-dibromo-2,6-dideoxy-D-glucitol **51**. Because of the 4,5-*erythro*-configuration of **50**, the selectivity of 3,4-diacetal protection was very high. The free primary -OH of **51** was then protected by TBDMSCl to give 2,6-dibromo-2,6-dideoxy-3,4-O-(butane 2,3-diacetal)-1-O-t-butyldimethylsilyl-D-glucitol **52**, which was appropriately protected and derivatized for double N-alkylation. Compound **52** was treated with aqueous ammonium hydroxide in methanol for 6 hours to give 6-amino-2-bromo-2,6-dideoxy-3,4-O-(butane 2,3-diacetal)-1-O-t-butyldimethylsilyl-D-glucitol **53**. Compound **53** was then refluxed with DBU in toluene for 12 hours to cyclize intramolecularly to form 2,6-imino-2,6-dideoxy-3,4-O-

(butane 2,3-diacetal)-1-O-t-butyldimethylsilyl-D-glucitol **54**, which was deprotected by hydrochloric acid in methanol to give the 1-deoxymannojirimycin (DMJ) **55**.



Scheme 5.20 The synthesis of 1-deoxymannojirimycin (DMJ) **55**: a) Br_2, $NaHCO_3$, H_2O; b) $HBr^{-}HOAc$; 62% over 2 steps; c) $NaBH_4$, H^+ resin, $EtOH/H_2O$, 80%; d) 2,2,3,3-Tetramethoxybutane, BF_3OEt_2, MeOH, rt; e) TBDMSCl, Py, r ; f) NH_4OH, MeOH, rt; g) DBU, Tol, reflux; 33% over 4 steps; h) 4N HCl, MeOH, 98%;

In summary, 1-deoxymannojirimycin (DMJ) **55** was synthesized in 8 easy steps from D-mannose. Similar to the synthesis of 1-deoxynojirimycin (DNJ) **1**, the key step was the use of 1,2-diacetal as a protecting group to selectively protect 3,4-OH's while leave 5-OH free. The free 5-OH greatly activated the primary bromo- group as a leaving group by epoxide formation. The 6-membered diacetal ring greatly increased the preference of intramocular N-alkylation over anhydrosugar formation. After double N-alkylation, all the protection groups could be removed by a single acid treatment, which also increased the efficiency of the synthesis.

5.6 Summary and future work

This thesis started from the NBS-initiated benzoxonium cation rearrangement. Selective bromination and chirality manipulation of carbohydrates were accomplished. This rearrangement was employed in tartrate derivative to generate a new chiral building block. Inter- and intramolecular competitive nucleophiles were introduced into the reaction system to generate new functionalities. Bromination was shown to be the most competitive nucleophile. This methodology was extended to 1,3-dioxonium cation facilitated selective bromination and Ritter-type amidation. A series of bromosugars and aminosugars were generated. The stereospecificity and regioselectivity were discussed. Finally, 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) were synthesized from partially protected dibromoalditols in a practical pathway. Some research directions based on these results are shown below and will be carried out in the near future.

5.6.1 Intramolecular Ritter-type reaction of partially protected sugar nitriles

The t-butyl-1,3-dioxonium cation facilitated Ritter-type reaction discussed in Chapter 4 has great potential in synthetic organic chemistry. It was employed to introduce an amino group in a sugar lactone. If the sugar structure itself bears a cyano group, an intramolecular Ritter-type reaction could furnish a sugar lactam structure (Figure 5.1). Sugar nitriles could be easily synthesized from sugar oximes, which in turn could be easily obtained from free sugars. The sugar lactams could be transformed to iminosugars by a simple reduction.

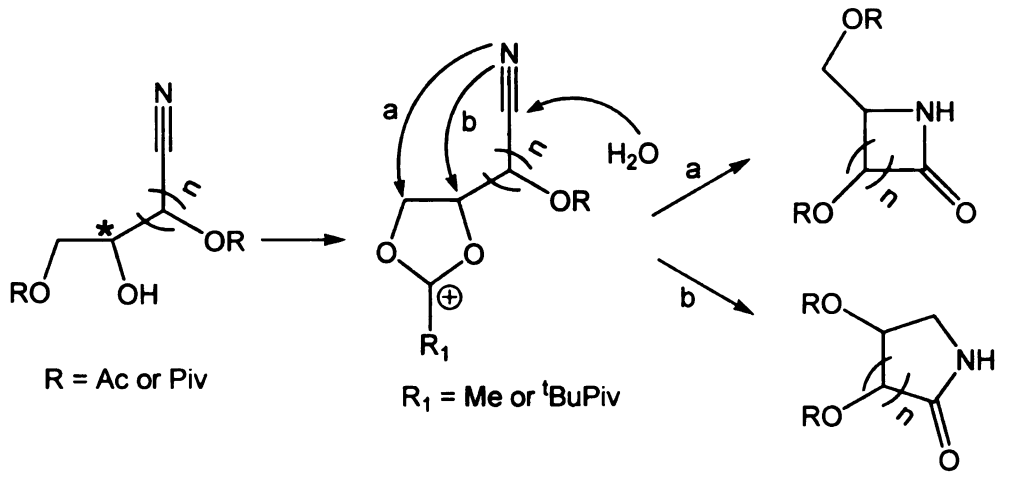


Figure 5.1 The acyloxonium cation facilitated intramolecular Ritter-type reaction in the synthesis of sugar lactams

5.6.2 Chiral 1,3-dioxonium cation facilitated asymmetric bromination and Ritter-type reaction in the synthesis of chiral building blocks

In our t-butyl-1,3-dioxonium cation facilitated bromination and Ritter-type amidation, glycerol was transformed to (±)3-bromo-3-deoxy-1,2-di-O-pivaloyl-glycerol and (±)3-N-acetylamino-3-deoxy-1,2-di-O-pivaloyl-glycerol respectively. The chirality was introduced into the achiral glycerol through the nucleophilic attack of t-butyl-1,3-dioxonium. If chirality was introduced into the dioxonium cation, an asymmetric Ritter-type reaction could occur to generate optical active product. Although theoretically every chiral ester could serve as a chiral auxiliary, Mosher's ester could be employed as a candidate (Figure 5.2) according to its wide application in synthetic and analytic chemistry.

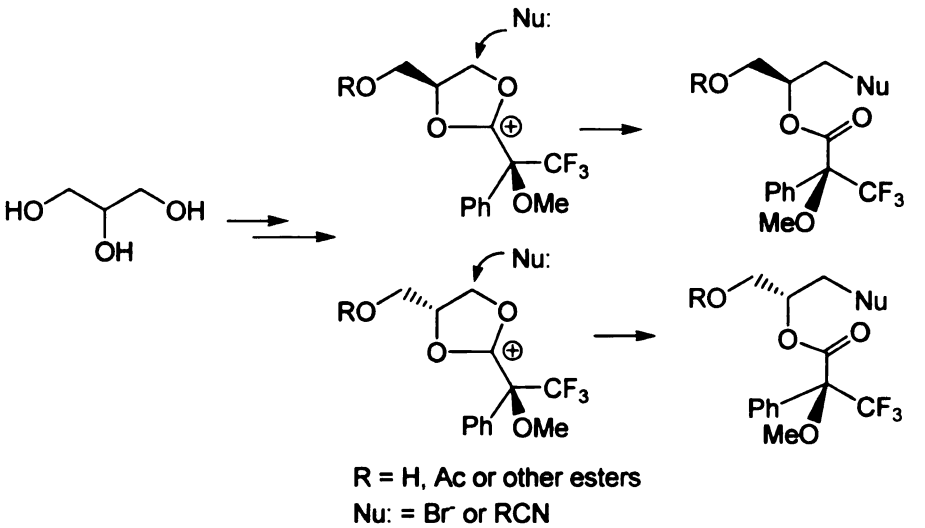


Figure 5.2 Chiral 1,3-dioxonium cation facilitated asymmetric bromination and Ritter-type reaction in the synthesis of chiral building blocks

Glycerol is an abundant 3-carbon building block. The asymmetric functionalization has long been pursued. The chiral 1,3-dioxonium cation facilitated asymmetric bromination and Ritter-type reaction could serve as a good pathway.

5.6.3 Chiral nitrile facilitated asymmetric Ritter-type reaction in the asymmetric desymmetrization of glycerol

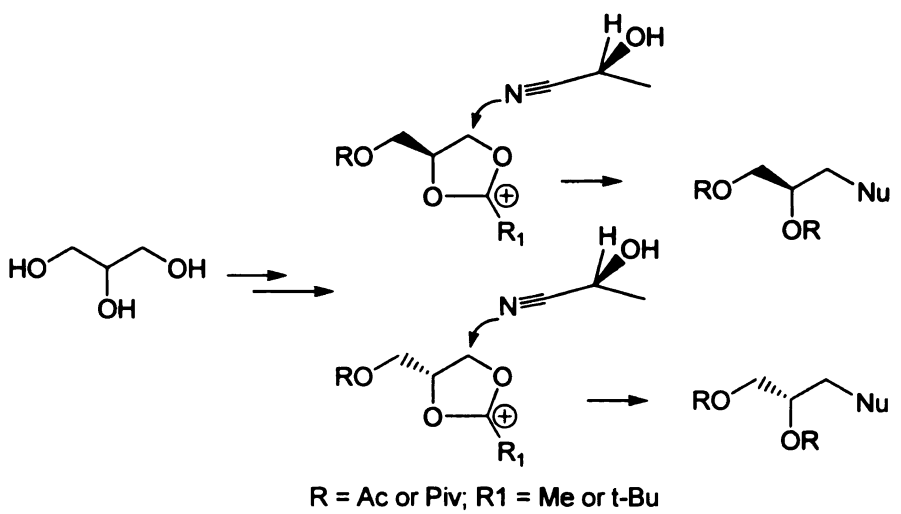


Figure 5.3 Chiral nitrile involved asymmetric Ritter-type reaction in the desymmetrization of glycerol

The 1,3-dioxonium cation facilitated Ritter-type reaction involved 1,3-dioxonium cation as an electrophile and an incoming nitrile as nucleophile. If the nucleophile is a chiral molecule, another version of asymmetric desymmetrization of glycerol could be introduced (Figure 5.3). Bearing a neighboring chiral center, lactonitrile could be used as an affordable chiral nitrile source. Since both D- and L-isomers of lactonitrile are readily available, the Ritter-type reaction could generate an aminodiol with both R- and S-configurations, which could be used as a good platform of organic synthesis.

EXPERIMENTAL

General Optical activity data were obtained on a JASCO P-1010 polarimeter at 25°C. NMR spectra were obtained on a Varian VXR-500 Spectrometer operating at 500MHz for protons. Mass spectra were obtained on a JEOL HX-110-HF instrument using fast atom bombardment as ionization mode. Spectra were recorded in the positive ion mode. IR spectra were obtained on a Nicolet 710 spectrometer in chloroform solution except when otherwise specified.

2,6-Dibromo-2,6-dideoxy-L-*idono*-γ-lactone (**5**):

L-*gulono*-1,4-lactone (5 g, 28.1 mmol) was added into 20 mL 30% hydrogen bromide in acetic acid and stirred for 2.5 hours at room temperature. Methanol (50 mL) was added in and the solution was stirred for 12 hours. The reaction mixture was then evaporated and co-evaporated with 2 x 20 mL water. The residue was dissolved in 200 mL ethyl acetate and washed by 25 mL saturated sodium bicarbonate. The organic phase was dried and evaporated to dryness to afford 2,6-Dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5** as colorless oil. Yield: 8.11g, 95%. $[\alpha]_D$ = + 34.4° (c = 0.9, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 3.49-3.51 (2H, d, H-6, 6'), 3.60 (2H, b, -OH's), 4.23 (1H, ddd, $J_{4,5}$ 3.5Hz, $J_{5,6}$ 6.1Hz, $J_{5,6'}$ 6.1Hz, H-5), 4.45 (1H, d, $J_{2,3}$ 4.5Hz, H-2), 4.61 (1H, dd, $J_{3,4}$ 5.5Hz, H-3), 4.81 (1H, dd, H-4); δ_C (125MHz; $CDCl_3$): 32.82 (C-6), 43.56 (C-2), 69.12, 75.73, 81.42 (C-3, C-4, C-5), 172.27 (C=O in lactone); FT-IR: 3393, 3094, 1778, 1161, 1098, 1012 cm^{-1}.

3,5-Di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone (**6**):

2,6-dibromo-2,6-dideoxy-L-idono-γ-lactone **5** (2.56 g, 8.4 mmol) was dissolved in 25 mL anhydrous dioxane and 2,2,2-trichloroacetimidic acid benzyl ester (10.6 g, 42 mmol) was added in. The solution was cooled down to 0°C and trifluoromethanesulfonic aicd (0.05g) was added in. The mixture was then stirred under room temperature for 24 hours and poured into cold saturated sodium bicarbonate solution. The mixture was extracted with chloroform (3 x 25 mL). The organic layer was dried and evaporated. The residue was purified by column chromatography twice to give 3,5-di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **6** as white solid. Yield: 2.77 g, 68%. δ_H (500MHz; $CDCl_3$): 3.40 (dd, 1H, $J_{5,6'}$ 4.8Hz, $J_{6,6'}$ 10.5Hz, H-6'), 3.45 (dd, 1H, $J_{5,6}$ 7.7Hz, H-6), 4.01 (1H, m, H-5), 4.51 (dd, 1H, J = 3.8Hz, J = 5.6Hz, H-4), 4.55, 4.56 (2 x 2H, 2 x s, O<u>C</u>H_2Ph), 4.89 (d, 1H, H-2), 4.96 (dd, 1H, H-3), 7.35 (m, 10H, Ar<u>H</u>); δ_C (125MHz; $CDCl_3$): 161.890 (<u>C</u>=O in lactone), 136.274, 128.729, 127.845, 127.461 (Ar<u>C</u>), 81.543, 79.750, 76.003 (C-3, 4, 5) 73.065, 72.905 (O<u>C</u>H_2Ph), 41.265 (C-2), 28.723 (C-6); FT-IR: 3086, 1788, 1172, 1108, 1016 cm^{-1}.

N-Benzyl-2-(4-benzyloxy-3-hydroxy-tetrahydro-furan-2-yl)-2-bromo-acetamide (**11**):

3,5-Di-O-benzyl-2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **6** (1.0 g, 2.1 mmol) was dissolved in 10 mL toluene and benzylamine (1.0 g, 9.3 mmol) was added in. The mixture was refluxed for 16 hours and evaporated to dryness. The residue was partitioned between chloroform and brine. The organic layer was dried and evaporated to dryness. The residue was purified by column chromatography to give of N-Benzyl-2-(4-benzyloxy-3-hydroxy-tetrahydro-furan-2-yl)-2-bromo-acetamide **11**. Yield: 0.38 g, 44%.

δ_H (500MHz; $CDCl_3$): 3.95 (1H, dd, H-6'), 4.05 (1H, m, H-5), 4.15 (1H, dd, H-6), 4.4-4.6 (7H, m, H-2, 3, 4, O$\underline{C}H_2$Ph, NH$\underline{C}H_2$Ph), 7.0 (1H, b, $\underline{H}$NCO), 7.4 (10H, m, Ar$\underline{H}$); δ_C (125MHz; $CDCl_3$): 168.11 ($\underline{C}$=O), 137.53, 128.99, 128.78, 128.17, 127.96, 127.89 (Ar$\underline{C}$), 84.41, 83.10, 75.84 (C-3, 4, 5), 72.30, 71.81 (O$\underline{C}H_2$Ph, C-6), 46.25 (C-2), 44.48 (HN$\underline{C}H_2$Ph); FT-IR: 3486, 2961, 1668, 1204, 1008 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-L-iditol (**12**):

2,6-Dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5** (4.82 g, 15.9 mmol) was dissolved in 40 mL methanol and cooled to 0°C. Sodium borohydride (2.2 g, 56.5 mmol) was added slowly. After the addition, the mixture was stirred at 0 °C for 30 minutes more. 5 mL 37% hydrochloric acid was added and the mixture was filtered and washed by methanol. To the filtration H^+ resin was added and filtered after stirring. The filtration was evaporated and co-evaporated with 4 x 25 mL methanol to give 2,6-dibromo-2,6-dideoxy-L-iditol **12** as white solid. Yield: 4.00 g, 82%. M.p. 108-110°C; (lit. [9] m.p. 111-112°C; $[\alpha]_D$ + 17° (c = 4, MeOH)); δ_H (500MHz; CD_3OD): 3.49 (dd, 1H, $J_{5,6'}$ 6.6Hz, $J_{6,6'}$ 9.8Hz, H-6'), 3.70 (dd, 1H, $J_{5,6}$ 6.2Hz, H-6), 3.82 (dd, 1H, $J_{1',2}$ 6.0Hz, $J_{1,1'}$ 11.6Hz, H-1'), 3.87 (dd, 1H, $J_{2,3}$ 2.7Hz, $J_{3,4}$ 6.3Hz, H-3), 3.91 (m, 1H, H-2), 3.93 (dd, 1H, $J_{1,2}$ 6.7Hz, H-1), 3.99 (dd, 1H, $J_{4,5}$ 2.9Hz, H-4), 4.29 (dt, 1H, H-5); δ_C (125MHz; CD_3OD): 73.469, 71.797, 70.661 (C-3, 4, 5), 64.14 (C-1), 60.01 (C-2), 35.504 (C-6); FT-IR (CH_3OH): 3841, 1472cm^{-1}.

1,3:4,5-Di-O-isopropylidene-2,6-dibromo-2,6-dideoxy-L-iditol (**13**):

2,6-dibromo-2,6-dideoxy-L-iditol (1.0 g, 3.2 mmol) was dissolved in 5 mL anhydrous N,N-dimethylformamide (DMF) with 2,2-dimethoxypropane (1.35 g, 13.0 mmol). p-Toluenesulfonic acid (20 mg) was added and the solution was stirred at room

temperature for 4 hours. The reaction mixture was poured into saturated sodium bicarbonate solution with ice and stirred. The mixture was extracted by chloroform (2 x 25 mL). The extraction was dried and evaporated to dryness. The residue was purified by chromatography to give 1,3:4,5-di-O-isopropylidene-2,6-dibromo-2,6-dideoxy-L-iditol **13** as colorless oil. Yield: 0.63 g, 50%. δ_H (500MHz; $CDCl_3$): 1.36, 1.39, 1.40, 1.41 (4 x 3H, 4 x s, $C(C\underline{H}_3)_2$), 3.27 (dd, 1H, $J_{5,6'}$ 5.0Hz, $J_{6,6'}$ 9.8Hz, H-6'), 3.40 (dd, 1H, $J_{5,6}$ 8.3Hz, H-6), 3.57 (ddd, 1H, $J_{1',2}$ 1.2Hz, $J_{1,2}$ 2.7Hz, $J_{2,3}$ 13.3Hz, H-2), 3.93 (t, 1H, $J_{3,4}$ 1.2Hz, $J_{4,5}$ 1.2Hz, H-4), 3.97 (ddd, 1H, H-5), 4.03 (m, 1H, H-1'), 4.06 (m, 1H, H-1), 4.24 (dd, 1H, H-3); δ_C (125MHz; $CDCl_3$): 101.30, 100.08 ($\underline{C}(CH_3)_2$), 74.54, 73.02, 61.50, 60.54 (C-1, C3, C-4, C-5), 53.79 (C-2), 29.98(C-6), 29.17, 25.49, 24.75, 19.39 ($C(\underline{C}H_3)_2$).

3,5-O-Benzylidene-6-O-tert-butyldimethylsilyl-2,5-di-O-methanesulfonyl-D-*glycero*-D-*gulo*-1,4-lactone (**15**):

3,5-O-Benzylidene-D-*glycero*-D-*gulo*-1,4-lactone (2.0 g, 6.8 mmol) was dissolved in 40 mL pyridine. t-Butyldimethylsilyl chloride (1.12 g, 7.4 mmol) was added in. The mixture was stirred under room temperature for 12 hours and cooled down to 0°C in ice bath. Methanesulfonyl chloride (1.70 g, 14.9 mmol) was added slowly. The mixture was then stirred at 0 °C for 6 hours and poured into saturated sodium bicarbonate solution with ice. After stirring, the mixture was extracted by chloroform (3 x 25 mL). The organic layer was dried and evaporated. The residue was purified by column chromatography to give 3,5-O-benzylidene-6-O-tert-butyldimethylsilyl-2,5-di-O-methanesulfonyl-D-*glycero*-D-*gulo*-1,4-lactone **15** as colorless oil (68%). δ_H (500MHz; $CDCl_3$): 0.04, 0.06 (2 x 3H, 2 x s, $Si(\underline{C}H_3)_2$), 0.88 (9H, s, $SiC(\underline{C}H_3)_3$), 3.09, 3.23 (2 x 3H, 2 x s, $C\underline{H}_3SO_2$-), 3.91 (1H, dd, $J_{6,7'}$ 3.5Hz, $J_{7,7'}$ 12.0Hz, H-7'), 4.09 (1H, dd, $J_{6,7}$ 2.0Hz, H-7), 4.39 (1H, dd, $J_{4,5}$ 2.0Hz,

$J_{5,6}$ 9.0Hz, H-5), 4.58 (1H, t, $J_{3,4}$ 1.5Hz, H-4), 4.89 (1H, ddd, H-6), 4.94 (1H, dd, $J_{2,3}$ 4.0Hz, H-3), 5.54 (1H, d, H-2), 5.56 (1H, s, C<u>H</u>Ph), 7.35 (3H, m, Ar<u>H</u>), 7.40 (2H, m, Ar<u>H</u>).

2,6-Dibromo-2,6-dideoxy-D-*idono*-γ-lactone (**17**):

Starting from D-*gulono*-1,4-lactone, **17** was prepared according the same procedure as the preparation of 2,6-dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5**. Yield: 92%. The NMR data is identical to 2,6-Dibromo-2,6-dideoxy-L-*idono*-γ-lactone **5**.

2,6-Dibromo-2,6-dideoxy-D-iditol (**18**):

The preparation of 2,6-Dibromo-2,6-dideoxy-D-iditol **18** was carried out according to the preparation of its L-isomer **12**. Yield: 80%. NMR data was identical to its L-isomer. M.p. 110-112°C; $[\alpha]_D$ = - 18.0° (c = 1.0, CH_3OH); (lit. [9] m.p. 111-112°C; $[\alpha]_D$ - 17° (c = 4, MeOH)).

2,6-Dibromo-2,6-dideoxy-D-*manno*-1,4-lactone (**23**):

To 40 mL 30% hydrogen bromide in acetic acid D-*glucono*-1,5-lactone (10 g, 56.2 mmol) was added. The mixture was stirred under room temperature for 20 hours. Methanol (100 mL) was added and the solution was stirred for 10 hours more. The reaction mixture was evaporated. Water (2 x 25 mL) was added in and evaporated. The residue was dissolved in 200 mL ethyl acetate and washed by saturated sodium bicarbonate solution (50 mL), brine (25 mL) and water (25 mL). The organic layer was dried and evaporated to dryness. The residue was crystallized from hexanes: ethyl acetate = 5:1 to give 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23** as pale yellow solid.

Yield: 8.88 g, 52%. M.p. 126-128°C; $[\alpha]_D$ = + 86.3 (c = 1.0, $CHCl_3$); (lit. [3] m.p. 131-133°C; $[\alpha]_D^{20}$ + 52.2° (c = 0.7, ethyl acetate)); δ_H (500MHz; $CDCl_3$): 2.89 (2H, b, -OH's), 3.58 (1H, dd, $J_{5,6'}$ 5.1Hz, $J_{6,6'}$ 11.0Hz, H-6'), 3.66 (1H, dd, $J_{5,6}$ 3.1Hz, H-6), 4.13 (1H, ddd, $J_{4,5}$ 8.8Hz, H-5), 4.37 (1H, dd, $J_{3,4}$ 3.1Hz, H-4), 4.53 (1H, dd, $J_{2,3}$ 4.6Hz, H-3), 4.73 (1H, d, H-2); δ_C (75.5MHz; $CDCl_3$): 36.31 (C-6), 47.28 (C-2), 66.82, 68.91, 80.98 (C-3, C-4, C-5), 170.78 (C=O in lactone); FT-IR ($CHCl_3$): 3657, 3189, 1784 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-D-mannitol (**24**):

2,6-Dibromo-2,6-dideoxy-D-mannonolactone **23** (5 g) was dissolved in 50 mL ethanol and cooled down to -10°C in ice-salt bath. Amberlite I-120 H^+ resin (10 mL) was added in. Then sodium borohydride (1.5 g) was added in slowly, while ice was added in the reaction mixture to keep the temperature low. After the addition, the mixture was stirred at 0 °C for 30 minutes more. More amberlite I-120 H^+ resin was added in until the pH ~ 3. The mixture was filtered and the filtrate was evaporated to afford 2,6-dibromo-2,6-dideoxy-D-mannitol **24** as colorless oil. Crude yield: 4.1 g, 81%. (lit. [4] m.p. 92-93°C; $[\alpha]_D^{20}$ - 9° (c = 1.6, ethyl acetate)); δ_H (500MHz; CD_3OD): 3.52 (1H, dd, H-6'), 3.56 (1H, dd, H-6), 3.67 (1H, ddd, H-2), 3.82-3.90 (4H, m, H-1, H-1', H-3, H-4), 3.98 (1H, ddd, H-5); δ_C (125MHz; CD_3OD): 38.21 (C-6), 55.13 (C-2), 63.20, 69.20, 69.59, 71.25 (C-1, C-3, C-4, C-5); FT-IR ($CHCl_3$): 2940, 1470, 1420, 1067 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-*idono*-1,4-lactone (**25**):

2,6-Dibromo-2,6-dideoxy-D-*idono*-1,4-lactone (0.36 g, 1.2 mmol) was dissolved in 5 mL dichloromethane and 2,2-dimethoxypropane (0.25 g, 2.4 mmol) was added in. p-Toluenesulfonic aicd monohydrate (0.03 g) was added in. The reaction mixture was

stirred for 12 hours and poured into cold saturated sodium bicarbonate solution. The mixture was extracted with chloroform (2 x 15 mL). The organic layer was dried and evaporated to give 2,6-dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-*idono*-1,4-lactone **25**. Yield: 0.22 g, 78%. $[\alpha]_D$ = -54.9° (c = 0.9, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.33, 1.42 (2x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.39 (dd, 1H, $J_{5,6'}$ 6.0Hz, $J_{6,6'}$ 10.1Hz, H-6'), 3.51 (dd, 1H, $J_{5,6}$ 8.1Hz, H-6), 4.06 (s, 1H, H-2), 4.22 (ddd, 1H, $J_{4,5}$ 2.0Hz, H-5), 4.53 (d, 1H, $J_{3,4}$ 2.4Hz, H-3), 4.69 (t, 1H, H-4); δ_C (75.5MHz; $CDCl_3$): 19.30, 28.57 ($C(\underline{C}H_3)_2$), 29.15 (C-6), 40.35 (C-2), 73.15, 70.86, 68.55 (C-3, C-4, C-5), 99.65 ($\underline{C}(CH_3)_2$), 170.82 (C=O in lactone); FT-IR ($CHCl_3$): 3092, 1788, 1175 cm^{-1}.

Methyl 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-idonate (**26**) and Methyl 2,6-dibromo-2,6-dideoxy-4,5-O-isopropylidene-D-idonate (**27**):

The reaction was carried out using the same procedure for the preparation of 2,6-dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-idonolactone **25** except methanol was used as the solvent. A mixture of two isomers was obtained with a ratio of 1:1. Yield: 56%. δ_H (500MHz; $CDCl_3$): 1.421, 1.400, 1.388, 1.378 (4x 3H, 4 x s, $C(C\underline{H}_3)_2$), 2.63, 2.89 (2 x 1H, 2 x b, -OH's), 4.443 (1H, dd), 4.398 (1H, d), 4.380 (1H, d), 4.296 (3H, m), 4.108 (1H, m), 4.018 (1H, dd), 3.847 (1H, m), 3.772 (3H, s), 3.765 (3H, s), 3.467 (2H, m), 3.437 (2H, m); δ_C (75.5MHz; $CDCl_3$): 168.262, 167.887 ($\underline{C}OOCH_3$), 110.984, 110.699 ($\underline{C}(CH_3)_2$), 78.794, 78.462, 76.931, 76.217, 70.531, 69.957 (C-3, C-4, C-5), 53.333, 53.217 ($COO\underline{C}H_3$), 48.552, 45.776 (C-2), 34.055, 31.836 (C-6), 27.173, 27.161, 27.071, 26.791 ($C(\underline{C}H_3)_2$); FT-IR ($CHCl_3$): 3494, 3096, 1740, 1373, 1216, 1061 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-*manno*-γ-lactone (**28**):

2,6-Dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23** (1.0 g, 3.3 mmol) was dissolved in 10 mL dichloromethane and 2,2-dimethoxypropane (0.69 g, 6.6 mmol) was added in. p-Toluenesulfonic acid monohydrate (0.05 g) was added in. The reaction mixture was stirred under room temperature for 2 hours and subsequently poured into cold saturated sodium bicarbonate solution and extracted by 2 x 20 mL chloroform. The organic layer was dried, evaporated and purified by column chromatography to give methyl 2,6-dibromo-2,6-dideoxy-3,5-O-isopropylidene-D-*manno*-γ-lactone **28** as colorless oil. Yield: 0.88 g, 71%. δ_H (500MHz; $CDCl_3$): 1.43, 1.45 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.52 (1H, dd, $J_{5,6'}$ 6.0Hz, $J_{6,6'}$ 11.1Hz, H-6'), 3.62 (1H, dd, $J_{5,6}$ 3.9Hz, H-6), 3.89 (1H, ddd, $J_{4,5}$ 7.2Hz, H-5), 4.46 (1H, dd, $J_{2,3}$ 5.8Hz, $J_{3,4}$ 3.6Hz, H-3), 4.61 (1H, dd, H-4), 4.71 (1H, d, H-2); δ_C (125MHz; $CDCl_3$): 23.84, 24.02 ($C(\underline{C}H_3)_2$), 32.40 (C-6), 41.69 (C-2), 67.43, 70.93, 80.32 (C-3, C-4, C-5), 102.92 ($\underline{C}(CH_3)_2$), 170.89 ($\underline{C}OOCH_3$).

Methyl 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannonate (**29**):

2,6-Dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23** (1.0 g, 3.3 mmol) was dissolved in 10 mL methanol and 2,2-dimethoxypropane (0.69 g, 6.6 mmol) was added in. p-Toluenesulfonic acid monohydrate (0.05 g) was added in. The reaction mixture was stirred under room temperature for 12 hours. This mixture was poured into cold saturated sodium bicarbonate solution and extracted by 2 x 20 mL chloroform. The organic layer was dried, evaporated and purified by column chromatography to give methyl 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannonate **29** as colorless oil. Yield: 0.93 g, 75%. δ_H (500MHz; $CDCl_3$): 1.37, 1.41 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 2.62 (1H, d, J ~ 6.9Hz,

-O<u>H</u>), 3.58 (1H, dd, $J_{5,6'}$ 6.0Hz, $J_{6,6'}$ 10.5Hz, H-6'), 3.72 (1H, dd, $J_{5,6}$ 3.0Hz, H-6), 3.77 (1H, m, H-5), 3.79 (3H, s, COOC<u>H</u>$_3$), 4.18 (1H, dd, $J_{3,4}$ 3.8Hz, $J_{4,5}$ 8.1Hz, H-4), 4.33 (1H, d, $J_{2,3}$ 9.0Hz, H-2), 4.64 (1H, dd, H-3); δ_C (125MHz; $CDCl_3$): 28.27, 28.35 (C(<u>C</u>H$_3$)$_2$), 37.29 (C-6), 45.67 (C-2), 53.24 (COO<u>C</u>H$_3$), 71.51, 79.78, 80.27 (C-3, C-4, C-5), 111.96 (<u>C</u>(CH$_3$)$_2$), 168.19 (<u>C</u>OOCH$_3$).

2,6-Dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-iditol (**31**) and 2,6-dibromo-2,6-dideoxy-4,5-O-isopropylidene-D-iditol (**32**):

2,6-Dibromo-2,6-dideoxy-D-iditol **18** (0.46 g, 1.5 mmol) was suspended in 5 mL acetone and p-toluenesulfonic acid (0.03 g) was added in. The solution was stirred at room temperature for 15 minutes and poured into the cold saturated sodium bicarbonate solution. The mixture was extracted with chloroform (3 x 20 mL). The organic layer was dried and evaporated to give a mixture of 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-iditol **31** and 2,6-dibromo-2,6-dideoxy-4,5-O-isopropylidene-D-iditol **32** in a ratio of 5:1. Yield: 0.35g, 74%. If the reaction time was extended to 12 hours, the ratio of **31**:**32** became about 1:1. For **31**: $[\alpha]_D$ = -47.1 (c = 1.2, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.41, 1.44 (2x 3H, 2 x s, C(C<u>H</u>$_3$)$_2$), 2.98 (2H, b, -OH's), 3.47 (2H, m, H-6, 6'), 3.84 (dt, 1H, J = 1.9Hz, J = 6.6Hz, H-2), 3.90 (dd, 1H, J = 5.9Hz, J = 12.1Hz, H-1'), 3.94 (1H, m, H-1), 4.12 (1H, m, H-5), 4.21 (dd, 1H, J = 3.2Hz, J = 8.0Hz, H-4), 4.26 (dd, 1H, J = 1.6Hz, J = 8.1Hz, H-3); δ_C (75.5MHz; $CDCl_3$): 110.389 (<u>C</u>(CH$_3$)$_2$), 78.812, 76.177, 69.337 (C-3, C-4, C-5), 64.824 (C-1), 54.746 (C-2), 34.314 (C-6), 27.128, 27.000 (C(<u>C</u>H$_3$)$_2$); FT-IR ($CHCl_3$): 2943, 1373 cm^{-1}

2,6-Dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannitol (**33**):

2,6-Dibromo-2,6-dideoxy-D-mannitol **24** (0.32 g, 1.0 mmol) was dissolved in 5 mL acetone and p-toluenesulfonic acid (0.03 g) was added in. The solution was stirred under room temperature for 6 hours and poured into cold sodium bicarbonate solution. The mixture was extracted by chloroform (2 x 15 mL). The organic layer was dried and evaporated to give 2,6-dibromo-2,6-dideoxy-3,4-O-isopropylidene-D-mannitol **33** as colorless oil. Yield: 0.27g, 75%. $[\alpha]_D$ = -2.9 (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.34, 1.42 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.35 (2H, b, -OH's), 3.53 (dd, 1H, $J_{5,6'}$ 6.8Hz, $J_{6,6'}$ 10.7Hz, H-6'), 3.71 (dd, 1H, $J_{5,6}$ 2.6Hz, H-6), 3.79 (ddd, 1H, $J_{4,5}$ 9.1Hz, H-5), 3.91 (dd, 1H, $J_{1',2}$ 5.6Hz, $J_{1,1'}$ 12.6Hz, H-1'), 3.96 (dd, 1H, $J_{1,2}$ 4.9Hz, H-1), 4.09 (dd, 1H, $J_{3,4}$ 4.9Hz, H-4), 4.26 (dd, 1H, $J_{2,3}$ 5.5Hz, H-2), 4.42 (t, 1H, H-3); δ_C (75.5MHz; $CDCl_3$): 110.962 ($\underline{C}(CH_3)_2$), 80.268, 79.722, 72.642 (C-3, C-4, C-5), 63.843 (C-1), 56.133 (C-2), 37.548 (C-6), 27.775, 27.622 ($C(\underline{C}H_3)_2$).

Methyl 2,6-dibromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-idonate (**34**):

2,6-Dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **23** (1.1 g, 3.6 mmol) was dissolved in 10 mL dry methanol. Butane-2,3-dione (0.34 g, 4.0 mmol) and trimethylorthoformate (1.2 g, 11.3 mmol) was added in. Borontrifluoride etherate (0.15 g) was added in and the solution was stirred under room temperature for 12 hours. Triethylamine (0.5 g) was added and the solution was evaporated. The residue was purified by column chromatography to give two major isomers methyl 2,6-dibromo-2,6-dideoxy-3,4-O-(1,2-diacetal)-D-idonate **34** and methyl 2,6-dibromo-2,6-dideoxy-4,5-O-

(1,2-diacetal)-D-idonate **35** with ~ 1:1 ratio. Total yield: 1.06 g, 65%. For **34**: δ_H (500MHz; $CDCl_3$): 1.31, 1.35 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 2.70 (1H, d, $J_{5,OH}$ 7.3Hz, -O<u>H</u>), 3.29, 3.33 (2 x 3H, 2 x s, $C\underline{H}_3OCCH_3$ in diacetal), 3.47 (1H, dd, $J_{5,6'}$ 3.9Hz, $J_{6,6'}$ 11.7Hz, H-6'), 3.56 (1H, dd, $J_{5,6}$ 2.7Hz, H-6), 3.77 (3H, s, $COOC\underline{H}_3$), 3.98 (1H, H-3), 4.15 (1H, dd $J_{3,4}$ 1.4Hz, $J_{4,5}$ 9.7Hz, H-4), 4.32 (1H, ddd, H-5), 4.52 (1H, d, $J_{2,3}$ 8.9Hz, H-2); δ_C (125MHz; $CDCl_3$): 17.32, 17.03 ($CH_3OC\underline{C}H_3$ in diacetal), 33.07 (C-6), 48.24 (C-2), 449.25, 49.89 ($\underline{C}H_3OCCH_3$ in diacetal), 53.29 ($COO\underline{C}H_3$), 70.00, 71.30, 72.61 (C-3, C-4, C-5), 100.89, 101.28 ($CH_3O\underline{C}CH_3$), 168.56 ($\underline{C}OOCH_3$).

Methyl 2,6-dibromo-2,6-dideoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-idonate (**35**):

2,6-Dibromo-2,6-dideoxy-D-*idono*-1,4-lactone **23** (1.2 g, 3.9 mmol) was dissolved in 10 mL dry methanol. Butane-2,3-dione (0.37 g, 4.3 mmol) and trimethylorthoformate (1.26 g, 11.8 mmol) was added. Borontrifluoride etherate (0.15 g) was added and the solution was stirred under room temperature for 64 hours. Triethylamine (0.5 g) was added and the solution was evaporated. The residue was purified by column chromatography to give methyl 2,6-dibromo-2,6-dideoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-idonate **35**. Yield: 1.03 g, 58%. δ_H (500MHz; $CDCl_3$): 1.25, 1.26 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 2.80 (1H, d, $J_{3,OH}$ 8.8Hz, -O<u>H</u>), 3.16, 3.25 (2 x 3H, 2 x s, $C\underline{H}_3OCCH_3$ in diacetal), 3.36 (1H, dd, $J_{5,6'}$ 7.2Hz, $J_{6,6'}$ 11.2Hz, H-6'), 3.48 (1H, dd, $J_{5,6}$ 2.6Hz, H-6), 3.75 (3H, s, $COOC\underline{H}_3$), 3.86 (1H, dd $J_{3,4}$ 1.5Hz, $J_{4,5}$ 9.5Hz, H-4), 3.99 (1H, dt, $J_{2,3}$ 8.9Hz, H-3), 4.14 (1H, ddd, H-5), 4.52 (1H, d, H-2); δ_C (125MHz; $CDCl_3$): 17.50, 17.72 ($CH_3OC\underline{C}H_3$ in diacetal), 31.22 (C-6), 48.25

(C-2), 48.38, 48.57 ($\underline{C}H_3OCCH_3$ in diacetal), 53.31 ($COO\underline{C}H_3$), 67.74, 69.47, 71.19 (C-3, C-4, C-5), 99.42, 99.60 ($CH_3O\underline{C}CH_3$), 168.66 ($\underline{C}OOCH_3$).

Methyl 2,6-dibromo-2,6-dideoxy-3,4,5-O-(3'-methoxybutane-2',2',3'-triyl)-D-mannonate (**36**):

This compound was prepared using the same procedure as for **35** except 2,6-dibromo-2,6-dideoxy-D-*manno*-1,4-lactone **23** was used as the starting material. Yield: 56%. $[\alpha]_D$ = + 17.4° (c = 1.0, $CHCl_3$); δ_H (500MHz; $CDCl_3$): 1.23, 1.38 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 3.28 (3H, s, $C\underline{H}_3OCCH_3$ in diacetal), 3.25 (1H, dd, $J_{5,6'}$ 7.6Hz, $J_{6,6'}$ 10.7Hz, H-6'), 3.31 (1H, dd, $J_{5,6}$ 3.2Hz, H-6), 3.80 (3H, s, $COOC\underline{H}_3$), 34.05 (d, 1H, $J_{3,4}$ 9.7Hz, H-4), 4.25 (m, 1H, H-5), 4.54 (s, 1H, H-2), 4.58 (d, 1H, H-3); δ_C (125MHz; $CDCl_3$): 18.466, 17.949 ($CH_3OC\underline{C}H_3$ in diacetal), 28.012 (C-6), 43.822 (C-2), 48.680 ($\underline{C}H_3OCCH_3$ in diacetal), 53.172 ($COO\underline{C}H_3$), 78.162, 75.590, 71.499 (C-3, C-4, C-5), 108.758, 99.940 ($CH_3O\underline{C}CH_3$), 168.451 ($\underline{C}OOCH_3$).

2,6-Dibromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-iditol (**37**) and 2,6-dibromo-2,6-dideoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-iditol (**38**):

2,6-dibromo-2,6-dideoxy-D-iditol (1.02 g, 3.3 mmol) was dissolved in 10 mL dry methanol with 2,2,3,3-tetramethoxymethane (0.65 g, 3.6 mmol) was added. Boron trifluoride etherate (0.05 g) was added. The reaction mixture was stirred for 12 hours at room temperature. Triethylamine (0.15 g) was added in. The solution was evaporated. The residue was purified by chromatography to give a mixture of **37** + **38** in about 1:1 ratio. Yield: 62%; For **37**: δ_H (500MHz; $CDCl_3$): 1.26, 1.28 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 2.62, 2.94 (2 x 1H, 2 x b, -O$\underline{H}$'s), 3.23, 3.26 (2 x 3H, 2 x s, $C\underline{H}_3OCCH_3$ in

diacetal), 3.47 (dd, 1H, $J_{5,6'}$ 6.4Hz, $J_{6,6'}$ 9.9Hz, H-6'), 3.52 (dd, 1H, $J_{5,6}$ 7.6Hz, H-6), 3.84, 3.94, 4.00 (3 x 1H, 3 x m, H-2,4,5), 4.11 (dd, 1H, J = 1.9Hz, J = 6.2Hz, H-3), 4.14 (dd, 1H, $J_{1',2}$ 2.0Hz, $J_{1,1'}$ 9.2Hz, H-1'), 4.26 (dd, 1H, $J_{1,2}$ 1.5Hz, H-1); δ_C (125MHz; $CDCl_3$): 99.422, 99.179 ($CH_3O\underline{C}CH_3$), 69.680, 69.602, 67.118, 64.605 (C-1, 3, 4, 5), 53.106 (C-2), 48.330, 48.161 ($\underline{C}H_3OCCH_3$ in diacetal), 32.407 (C-6), 17.430 ($CH_3OC\underline{C}H_3$ in diacetal).

2,6-Dibromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-iditol (**41**) and 2,6-dibromo-2,6-dideoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-iditol (**42**):

2,6-dibromo-2,6-dideoxy-L-iditol **12** (4.0 g, 13.0 mmol) was dissolved in 40 mL dry methanol with 2,2,3,3-tetramethoxybutane (2.54 g, 14.3 mmol). Boron trifluoride ethrate (0.2 g) was added. The mixture was stirred at room temperature for 12 hours. Triethylamine (0.5 g) was added to neutralize the solution. The reaction mixture was evaporated to dryness. The residue was dissolved in 10 mL pyridine and t-butyldimethylsilyl chloride (2.18 g, 14.3 mmol) was added. The solution was stirred for 12 hours and poured into saturated sodium bicarbonate solution with ice. The mixture was extracted with chloroform (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by chromatography to give a mixture of **41** + **42**. For **41**: δ_H (500MHz; $CDCl_3$): 0.04, 0.06 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.27, 1.29 (2 x H, 2 x s, 2 x $OC(C\underline{H}_3)(OCH_3)$), 3.24, 3.26 (2 x 3H, 2 x s, 2 x $OC(CH_3)(OC\underline{H}_3)$), 3.49 (dd, 1H, $J_{5,6'}$ 6.7Hz, $J_{6,6'}$ 9.9Hz, H-6), 3.53 (dd, 1H, $J_{5,6}$ 7.2Hz, H-6), 3.80 (dd, 1H, $J_{4,5}$ 5.5Hz, $J_{3,4}$ 10.0Hz, H-4), 3.84 (m, 1H, H-5), 3.97 (ddd, 1H, $J_{2,3}$ 9.1Hz), 4.06 (dd, 1H,

H-3), 4.23 (dd, 1H, $J_{1',2}$ 1.5Hz, $J_{1,1'}$ 9.5Hz, H-1'), 4.26 (dd, 1H, $J_{1,2}$ 1.3Hz, H-1); FT-IR ($CHCl_3$): 3389, 2950, 1378, 1122, 1036 cm^{-1}.

2,3-Anhydrous-6-bromo-6-deoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-gulitol (**43**):

The mixture of **41** + **42** (2.1 g, 3.9 mmol) was dissolved in 20 mL methanol. Ammonium hydroxide (28% in water, 5 mL) was added slowly while stirring. The mixture was stirred for 12 hours at room temperature and TLC showed complete consumption of the starting materials. The mixture was evaporated to dryness and the residue was purified by chromatography to give 2,3-anhydrous-6-bromo-6-deoxy-4,5-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-gulitol **43** (Yield: 23% over 3 steps) and 6-amino-2-bromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-iditol **45** (Yield: 21% over 3 steps). For **43**: δ_H (500MHz; $CDCl_3$): 0.05, 0.08 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.30 (6H, s, 2 x $OC(C\underline{H}_3)(OCH_3)$), 3.22, 3.30 (2 x 3H, 2 x s, 2 x $OC(CH_3)(OC\underline{H}_3)$), 2.98 (1H, dd, $J_{2,3}$ 4.1, $J_{3,4}$ 8.6Hz, H-3), 3.11 (1H, ddd, $J_{2,1}$ 6.0, $J_{2,1'}$ 5.4Hz, H-2), 3.24 (1H, dd, $J_{6,6'}$ 11.1, $J_{6,5}$ 8.6Hz, H-6), 3.46 (1H, dd, $J_{4,5}$ 9.7Hz, H-4), 3.48 (1H, dd, $J_{6',5}$ 2.9Hz, H-6'), 3.65 (1H, dd, $H_{1,1'}$ 11.7Hz, H-1), 3.83 (1H, dd, H1'), 3.93 (1H, ddd, H-5); δ_C (125MHz; $CDCl_3$): -5.47, -5.382 (2 x $Si\underline{C}H3$), 17.25, 17.34 (2 x $OC(\underline{C}H_3)(OCH_3)$), 18.17 ($OSi\underline{C}(CH_3)_3$), 25.79 ($OSiC(\underline{C}H_3)_3$), 30.84 (C-6), 47.95, 48.04 (2 x $OC(CH_3)(O\underline{C}H_3)$), 55.24, 56.69 (C-2, C-3), 61.42 (C-1), 69.20, 69.60 (C-4, C-5), 98.66, 99.24 (2 x $O\underline{C}(CH_3)(OCH_3)$); FT-IR ($CHCl_3$): 3557, 3021, 1462, 1373, 1252 cm^{-1}; For **45**: δ_H (500MHz; $CDCl_3$): 0.05, 0.08 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.28, 1.30 (2 x 3H, s, 2 x $OC(C\underline{H}_3)(OCH_3)$), 3.23, 3.26 (2 x 3H, 2 x s, 2 x $OC(CH_3)(OC\underline{H}_3)$),

3.04 (1H, dd, H-6), 3.18 (1H, H-6'), 3.82 (1H, dd, $J_{1,1'}$ 10.1, $J_{1,2}$ 5.9Hz, H-1), 3.93 (1H, m, H-5), 3.97 (1H, dd, $J_{4,5}$ 1.7, $J_{4,3}$ 9.2Hz, H-4), 4.05 (1H, dd, $J_{2,1'}$ 8.6Hz, H-1'), 4.12 (1H, ddd, $J_{2,3}$ 1.6Hz, H-2), 4.21 (1H, dd, H-3), 4.33 (3H, b, $^{+}NH_3$); δ_C (125MHz; $CDCl_3$): -5.39, -5.09 (2 x Si<u>C</u>H3), 17.46, 17.70 (2 x OC(<u>C</u>H_3)(OCH_3)), 18.25 (OSi<u>C</u>(CH_3)$_3$), 25.86 (OSiC(<u>C</u>H_3)$_3$), 43.46 (C-6), 48.16, 48.20 (2 x OC(CH_3)(O<u>C</u>H_3)), 52.48 (C-2), 63.78, 64.91, 66.98, 72.37 (C-1, C-3, C-4, C-5), 99.25, 99.33 (2 x O<u>C</u>(CH_3)(OCH_3)).

3,4-O-(2',3'-Dimethoxybutane-2',3'-diyl)-6-O-t-butyldimethylsilyl-1-deoxynojirimycin (**46**):

6-amino-2-bromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-L-iditol **45** (0.46 g, 0.97 mmol) was dissolved in 10 mL toluene and DBU (0.30 g, 2.0 mmol) was added in. The mixture was refluxed for 16 hours and subsequently evaporated to dryness. The residue was purified by chromatography to give 3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-6-O-t-butyldimethylsilyl-1-deoxynojirimycin **46**. Yield: 0.28 g, 74%. δ_H (500MHz; $CDCl_3$): 0.00, 0.02 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.27, 1.30 (2 x 3H, 2 x s, 2 x OC(C<u>H</u>$_3$)(OCH_3)), 3.21, 3.26 (2 x 3H, 2 x s, 2 x OC(CH_3)(OC<u>H</u>$_3$)), 2.55 (1H, dd, $J_{1,1'}$ 12.8, $J_{1,2}$10.1Hz, H-1), 2.65 (1H, ddd, $J_{4,5}$ 9.3, $J_{5,6}$ 2.9, $J_{5,6'}$ 4.2Hz, H-5), 3.2 (1H, H-1'), 3.50-3.59 (2H, m, H-3, H-4), 3.62 (1H, ddd, $J_{2,1'}$ 5.1, $J_{2,3}$ 9.2Hz, H-2), 3.71 (1H, dd, $J_{6,6'}$ 9.7Hz, H-6), 3.76 (1H, dd, H-6'); δ_C (125MHz; $CDCl_3$): -5.56, -5.44 (2 x Si<u>C</u>H3), 17.71 (2 x OC(<u>C</u>H_3)(OCH_3)), 18.21 (OSi<u>C</u>(CH_3)$_3$), 25.87 (OSiC(<u>C</u>H_3)$_3$), 47.86 (2 x OC(CH_3)(O<u>C</u>H_3)), 49.52 (C-1), 58.19 (C-5), 61.26 (C-6), 67.08, 69.75, 75.56 (C-3, C-4, C-5), 99.38, 99.42 (2 x O<u>C</u>(CH_3)(OCH_3)).

1-Deoxynojirimycin (**1**):

3,4-O-(2',3'-Dimethoxybutane-2',3'-diyl)-6-O-t-butyldimethylsilyl-1-deoxynojirimycin **46** (0.22 g, 0.6 mmol) was dissolved in 5 mL methanol and hydrochloric acid (1 mL) was added in. The mixture was stirred at room temperature for 30 minutes and evaporated to give 1-deoxynojirimycin **1** as its hydrochloric acid salt. Yield: 0.10 g, 95%. The physical data match literatures. δ_H (500MHz; D_2O): 3.93 (dd, J = 11.7, 3.1 Hz, 1H), 3.86 (dd, J = 11.7, 5.1 Hz, 1H), 3.77 (ddd, J = 12.2, 9.5, 5.1 Hz, 1H), 3.57 (t, J = 9.5 Hz, 1H), 3.50 (t, J = 9.5 Hz, 1H), 3.46 (dd, J = 12.2, 5.1 Hz, 1H), 3.16 (ddd, J = 3.1, 5.2, 9.5 Hz, 1H) 2.95 (t, J = 12.2 Hz, 1H); δ_C (125MHz; D_2O): 79.1, 70.9, 70.1 (C-2, 3, 4), 62.9 (C-6), 60.9 (C-5), 49.0 (C-1).

2,6-Dibromo-2,6-dideoxy-D-*glucono*-1,4-lactone (**49**):

D-mannose (10 g, 55.6 mmol) was dissolved in 100 mL distilled water with sodium bicarbonate (6.8 g, 81.0 mmol). The solution was cooled down to 0°C and 3 mL bromine was added in slowly in 30 minutes. The mixture was slowly warmed up to room temperature and stirred for 4 days. Air was bubbled through the reaction mixture for 6 hours until the solution became pale yellow. The solution was evaporated to dryness. Acetic acid (2 x 25 mL) was added and evaporated. To the resulted mixture 30% hydrogen bromide in acetic acid (50 mL) was added in. The mixture was then stirred for 6 hours. Methanol (100 mL) was added and stirred for 10 hours. The solution was evaporated and co-evaporated with water (2 x 25 mL). The residue was dissolved in 200 mL ethyl acetate and washed by sodium bicarbonate solution (50 mL), brine (25 mL) and water (25 mL). The organic layer was dried and evaporated to give 2,6-dibromo-2,6-

dideoxy-D-*glucono*-1,4-lactone **49** as brown oil. Yield: 10.6g, 62%; (lit. [4] m.p. 90-92°C; $[\alpha]_D^{20}$ + 29° (c = 2, ethyl acetate)).

2,6-Dibromo-2,6-dideoxy-D-glucitol (**50**):

2,6-Dibromo-2,6-dideoxy-D-glucitol **50** and the compounds **51-55** were prepared according to the same procedure described above for the synthesis of deoxynojirimycin. Yield: 80%. δ_H (500MHz; D_2O): 3.53 (dd, 1H, $J_{5,6'}$ 5.2Hz, $J_{6,6'}$ 11.1Hz, H-6'), 3.59 (dd, 1H, $J_{5,6}$ 2.7Hz, H-6), 3.63 (m, 1H, H-3), 3.75 (m, 1H, H-5), 3.76 (dd, 1H, $J_{1',2}$ 6.3Hz, $J_{1,1'}$ 12.7Hz, H-1'), 3.83 (dd, 1H, $J_{1,2}$ 4.1Hz, H-1), 3.92 (m, 1H, H-4), 4.15 (ddd, 1H, $J_{2,3}$ 10.6Hz, H-2); δ_C (125MHz; D_2O): 71.794, 70.288, 69.879 (C-3, 4, 5), 63.330 (C-1), 59.674 (C-2), 37.679 (C-6); FT-IR ($CHCl_3$): 3292, 2934, 1470, 1420, 1083 cm^{-1}.

2,6-Dibromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-glucitol (**51**):

δ_H (500MHz; $CDCl_3$): 1.38, 1.42 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 3.29, 3.38 (2 x 3H, 2 x s, $C\underline{H}_3OCCH_3$ in diacetal), 3.706 (2H, m), 3.963 (3H, m), 4.084 (1H, m), 4.140 (1H, m), 4.639 (1H, m); δ_C (125MHz; $CDCl_3$): 100.606, 100.230 ($CH_3O\underline{C}CH_3$), 74.107, 72.959, 71.879, 64.898 (C-1, 3, 4, 5), 56.525 (C-2), 49.421, 48.840 ($\underline{C}H_3OCCH_3$ in diacetal), 38.354 (C-6), 16.698, 16.619 ($CH_3OC\underline{C}H_3$ in diacetal).

2,6-Dibromo-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-D-glucitol (**52**):

δ_H (500MHz; $CDCl_3$): 0.04 (6H, s, $Si(C\underline{H}_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.37, 1.42 (2 x 3H, 2 x s, $CH_3OCC\underline{H}_3$ in diacetal), 3.24 (1H, m), 3.27, 3.36 (2 x 3H, 2 x s, $C\underline{H}_3OCCH_3$ in diacetal), 3.28 (1H, m), 3.70 (2H, m), 3.77 (1H, m), 3.98 (1H, m), 4.09

(1H, m), 4.50 (1H, m); δ_C (125MHz; $CDCl_3$): 100.606, 100.230 ($CH_3O\underline{C}CH_3$), 74.107, 72.959, 71.879, 64.898 (C-1, 3, 4, 5), 56.525 (C-2), 49.421, 48.840 ($\underline{C}H_3OCCH_3$ in diacetal), 38.354 (C-6), 16.698, 16.619 ($CH_3OC\underline{C}H_3$ in diacetal); FT-IR ($CHCl_3$): 3392, 3095, 1377, 1121cm^{-1}.

2,6-Imino-2,6-dideoxy-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1-O-t-butyldimethylsilyl-D-glucitol (**54**):

Yield: 33% from 2,6-Dibromo-2,6-dideoxy-D-glucitol **50**. FAB-MS: m/z calcd. for $C_{18}H_{37}NO_6Si$ 391.2390, found 392.2466 (MH^+); δ_H (500MHz; $CDCl_3$): 0.04, 0.05 (2 x 3H, 2 x s, 2 x $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.31, 1.37 (2 x 3H, 2 x s, 2 x $OC(C\underline{H}_3)(OCH_3)$), 2.05 (b, -OH), 2.42 (1H, ddd, $J_{4,5}$ 9.6, $J_{5,6}$ 2.6, $J_{5,6'}$ 5.3Hz, H-5), 2.73 (1H, dd, $J_{1,1'}$ 13.7, $J_{1',2}$ 1.7Hz, H-1'), 3.09 (1H, $J_{1,2}$ 2.7Hz, H-1), 3.28, 3.37 (2 x 3H, 2 x s, 2 x $OC(CH_3)(OC\underline{H}_3)$), 3.74 (dd, 1H, $J_{6,6'}$ 9.9Hz, H-6'), 3.82 (dd, 1H, H-6), 3.92 (dd, 1H, $J_{2,3}$ 2.9Hz, H-2), 3.98 (dd, 1H, $J_{3,4}$ 10.8Hz, H-3), 4.13 (dd, 1H, H-4); δ_C (125MHz; $CDCl_3$): 18.332 ($OSi\underline{C}(CH_3)_3$), 18.746 (2 x $OC(\underline{C}H_3)(OCH_3)$), 25.866 ($OSiC(\underline{C}H_3)_3$), 48.127, 47.875 (2 x $OC(CH_3)(O\underline{C}H_3)$), 49.022 (C-1), 60.677 (C-5), 62.111 (C-6), 75.653, 68.113, 67.908 (C-3, C-4, C-5), 101.498, 101.282 (2 x $O\underline{C}(CH_3)(OCH_3)$).

1-Deoxymannojirimycin (DMJ) (**55**):

Yield: 98%; δ_H (500MHz; D_2O): 3.03 (ddd, 1H, $J_{5,6}$ 3.3Hz, $J_{5,6'}$ 6.8Hz, $J_{4,5}$ 10.3Hz, H-5), 3.12 (dd, 1H, $J_{1',2}$ 1.5Hz, $J_{1,1'}$ 13.7Hz, H-1'), 3.29 (dd, 1H, $J_{1,2}$ 3.1Hz, H-1), 3.57 (dd, 1H, $J_{2,3}$ 3.1Hz, $J_{3,4}$ 9.5Hz, H-3), 3.71 (dd, 1H, $J_{6,6'}$ 12.7Hz, H-6'), 3.74 (dd, 1H, H-4), 3.87 (dd, 1H, H-6), 4.12 (dt, 1H, H-2); δ_C (125MHz; D_2O): 47.68 (C-1), 58.26 (C-5), 60.51 (C-6), 65.88, 66.03, 72.57 (C-3, C-4, C-5).

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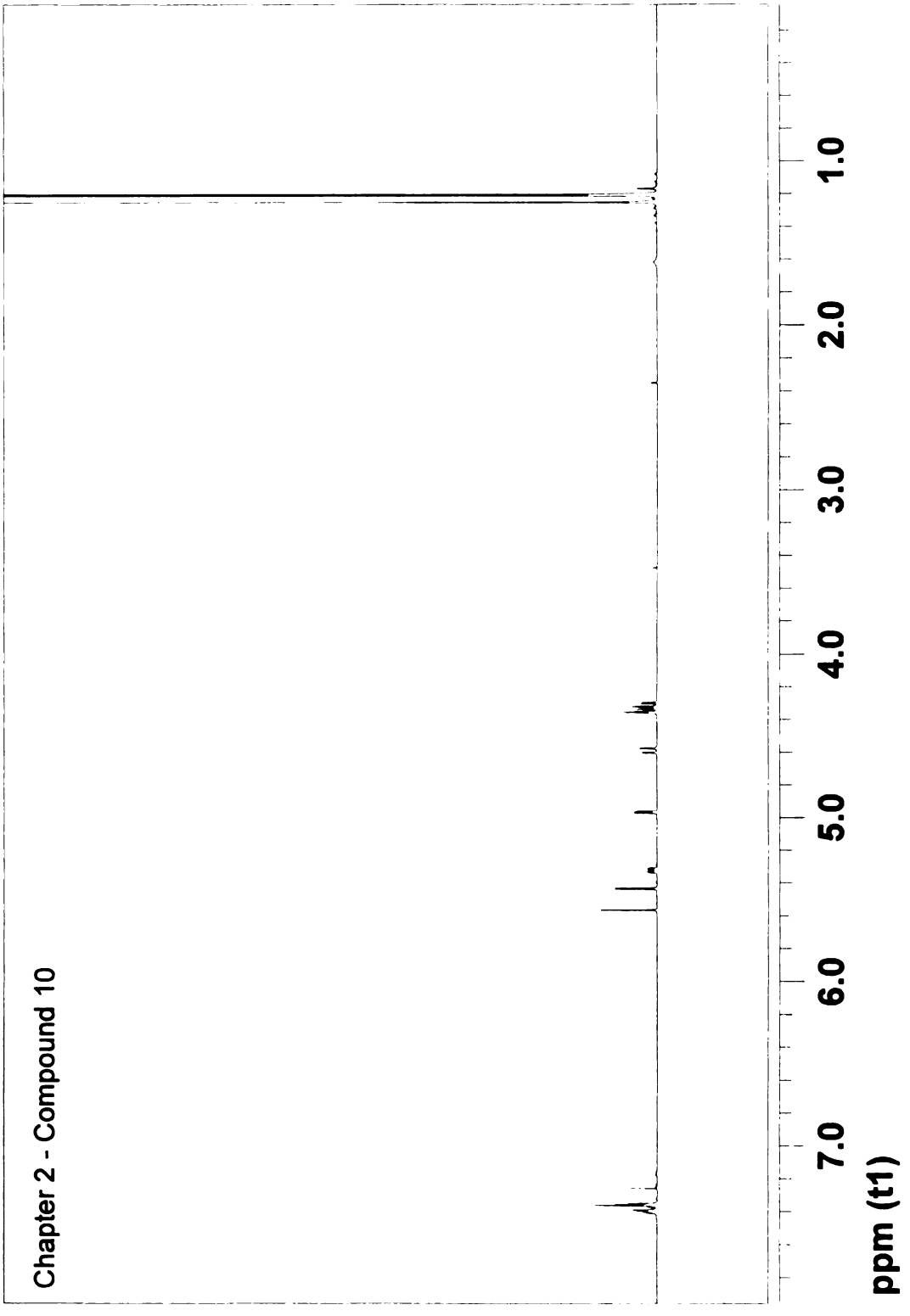
Appendix

NMR spectra of selected compounds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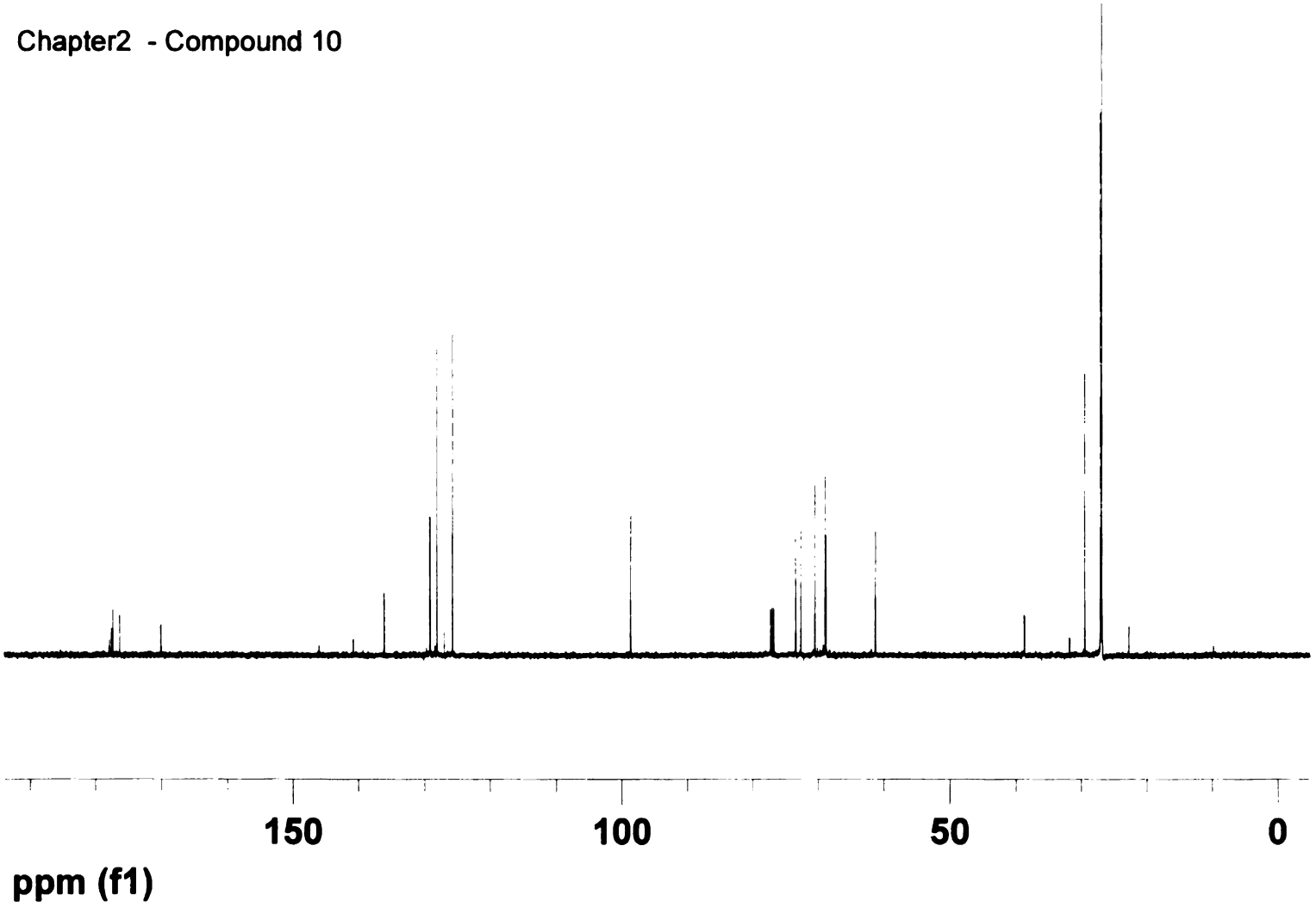
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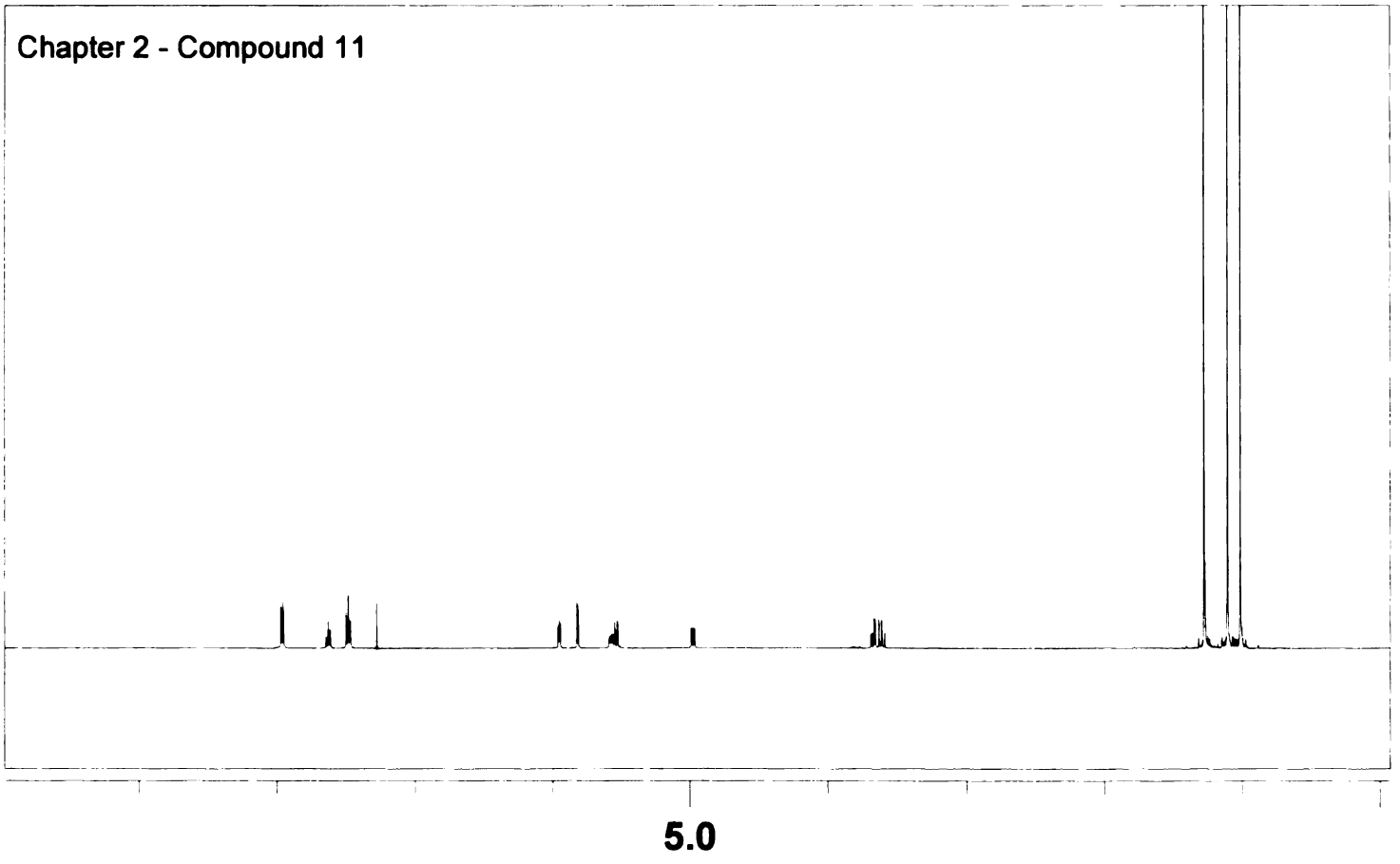
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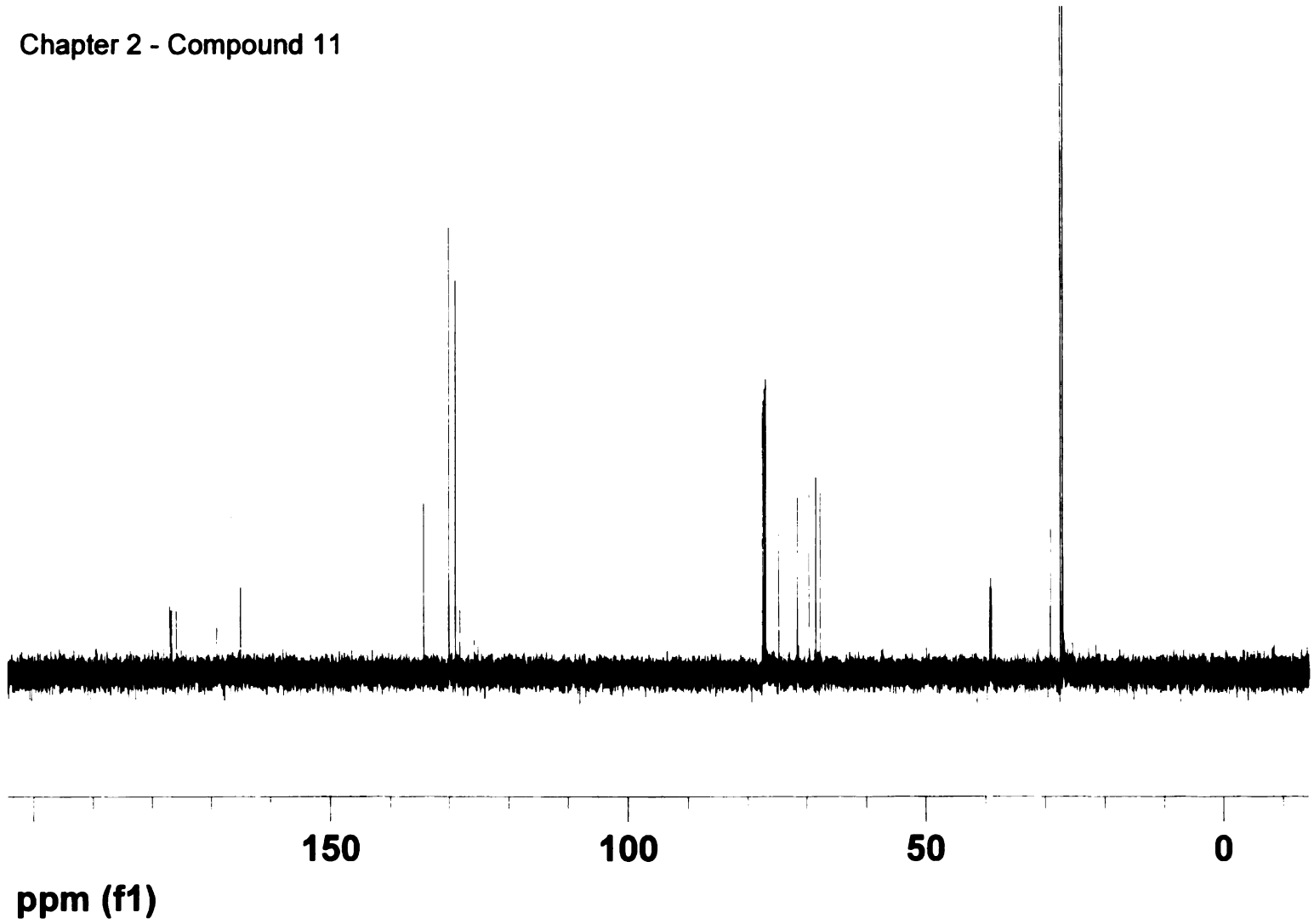
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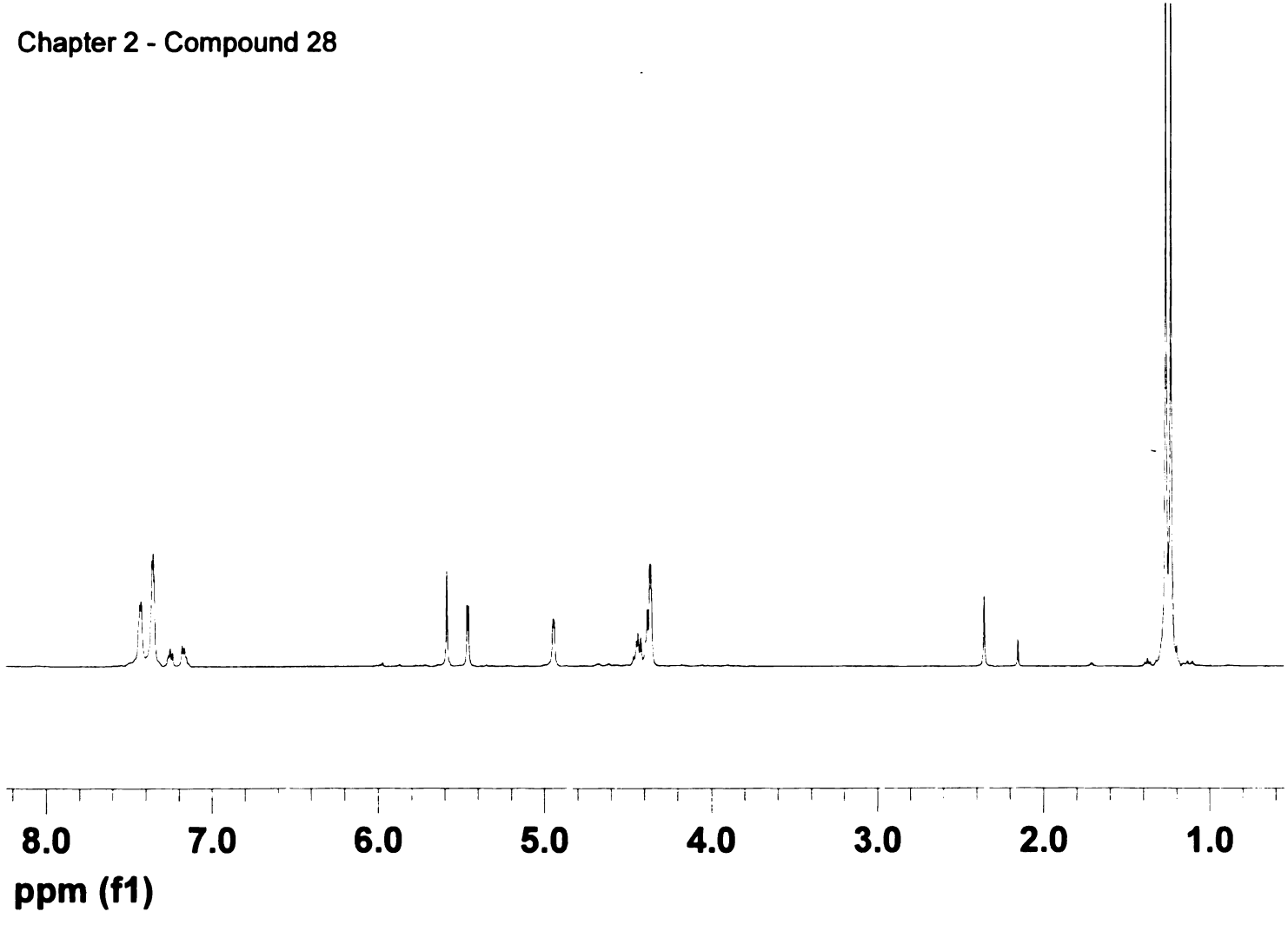

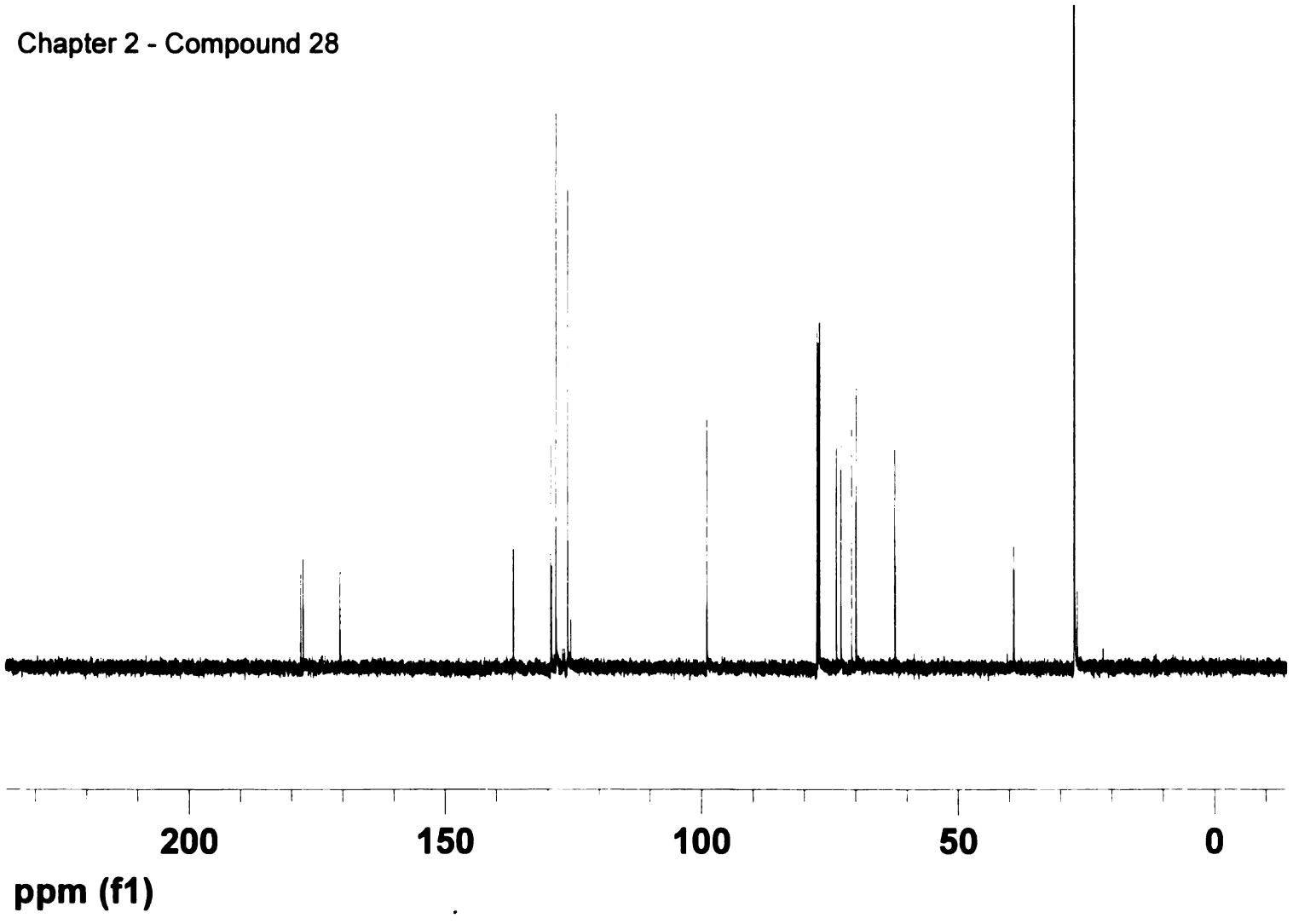
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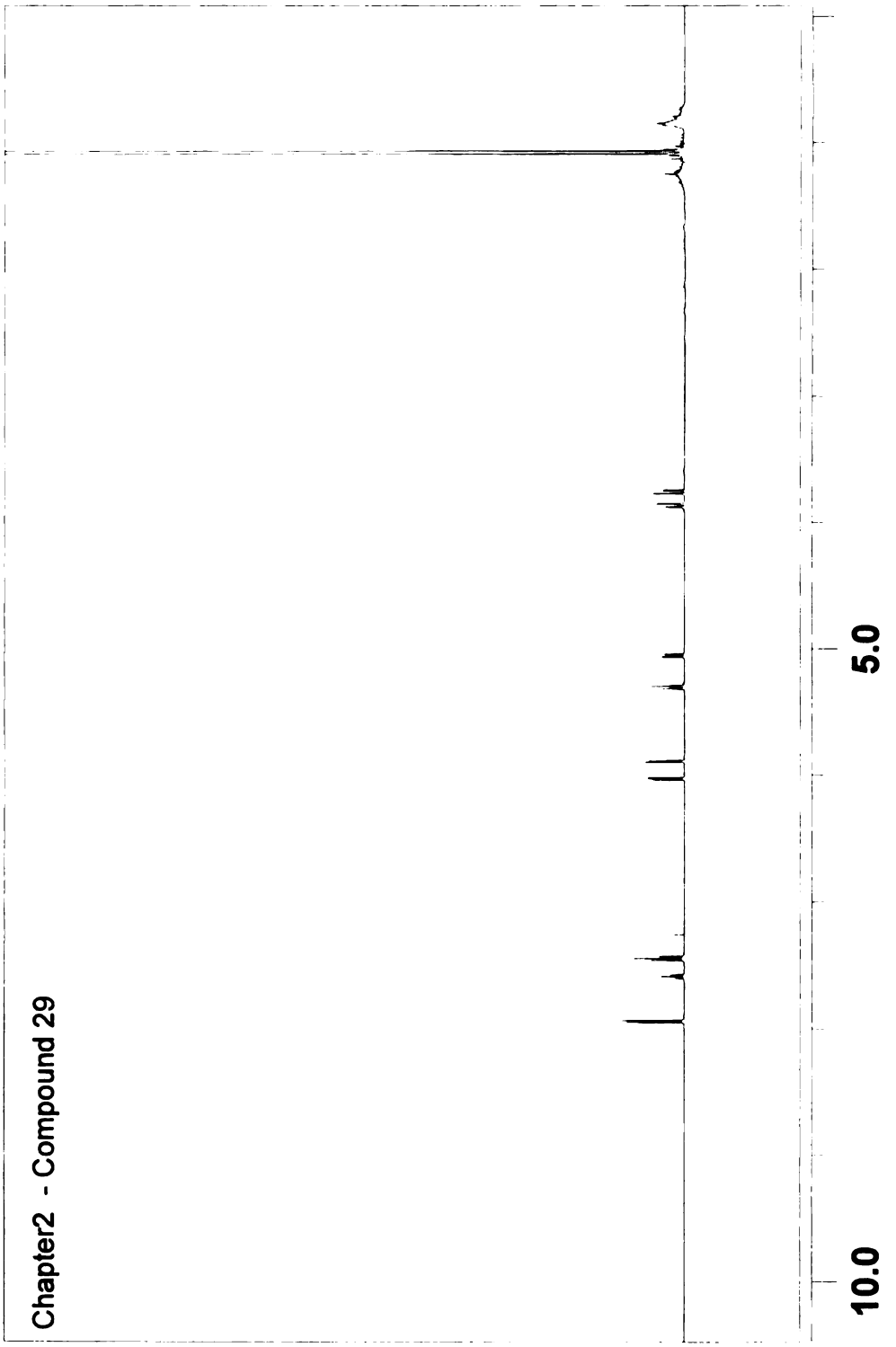
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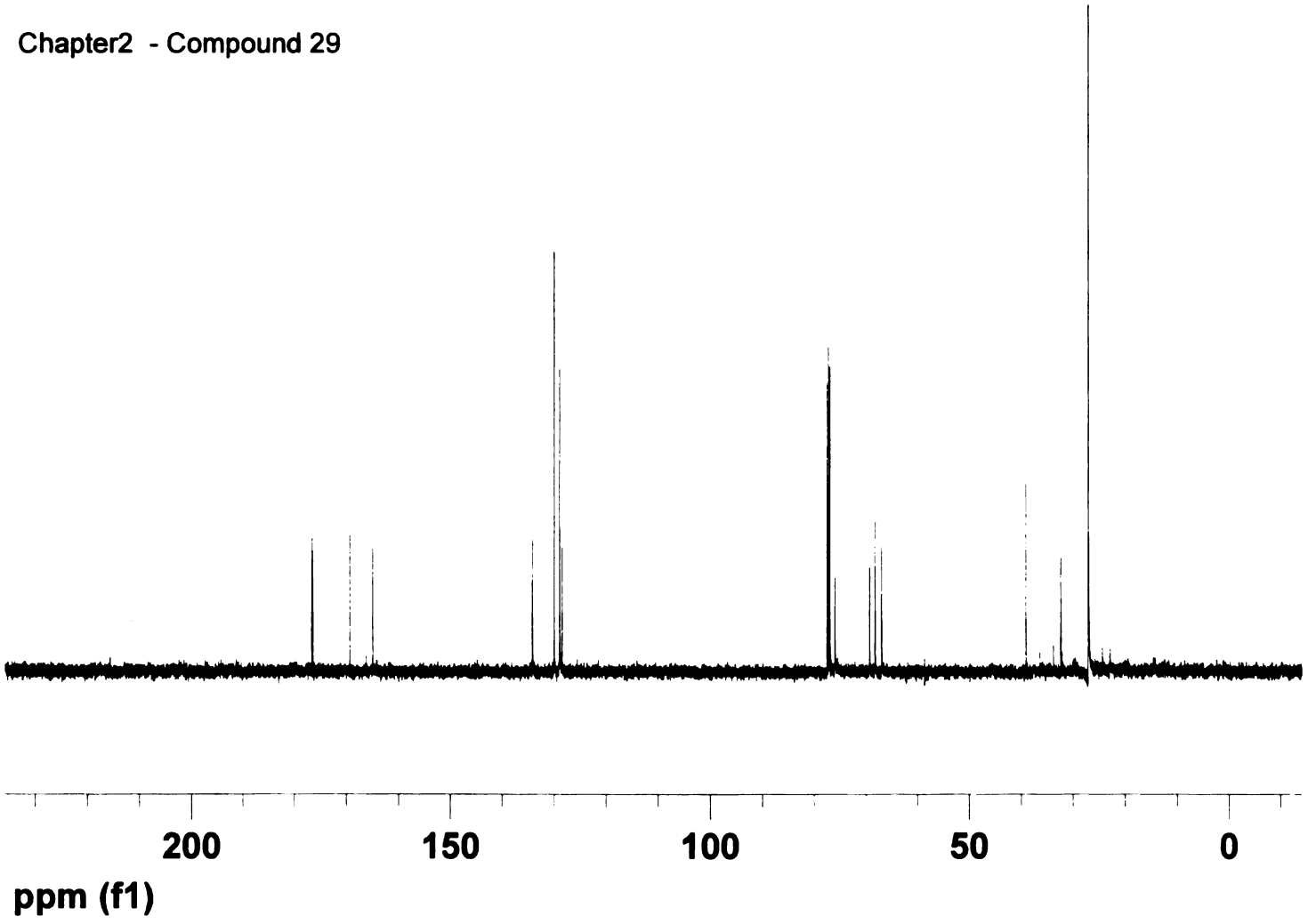
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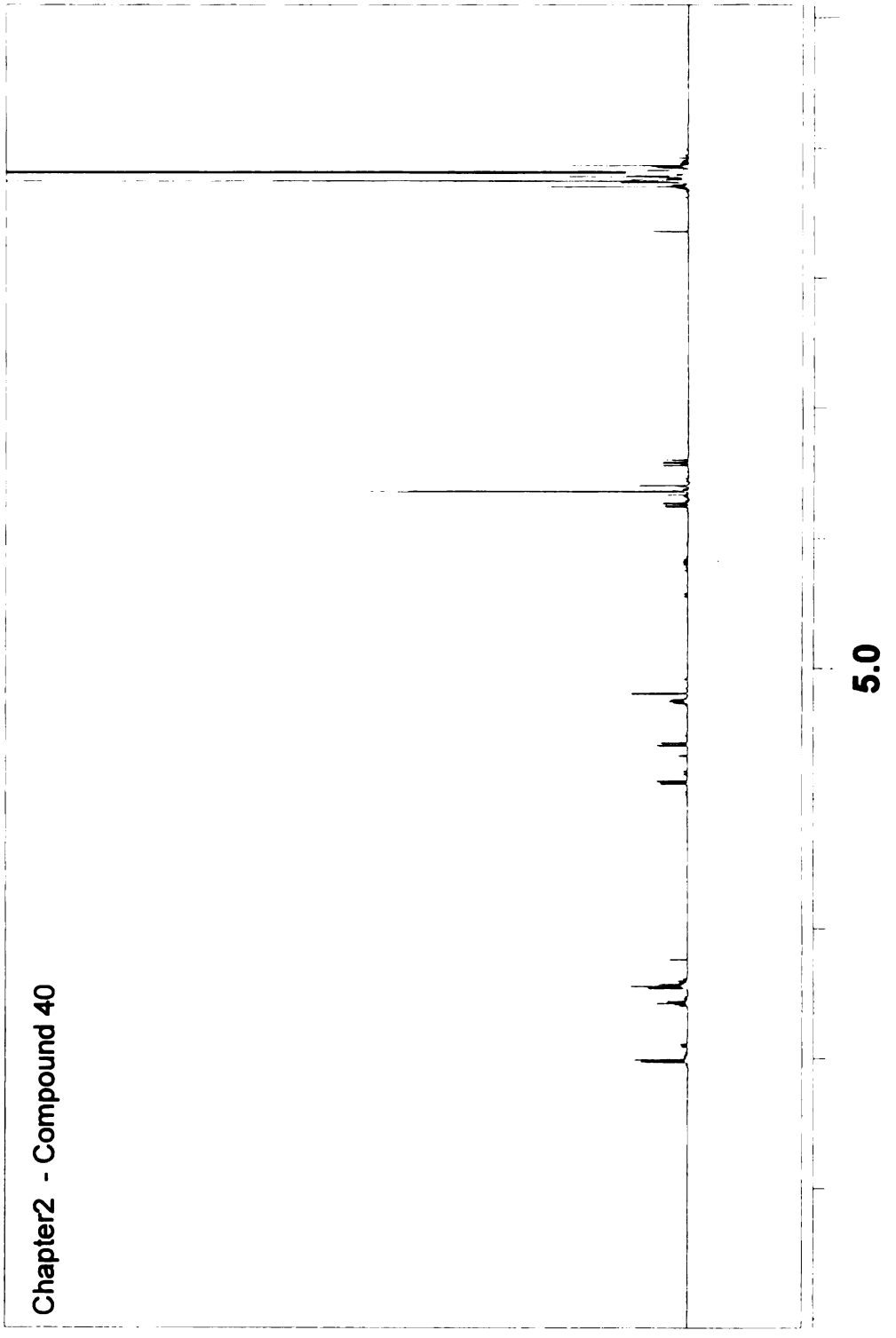
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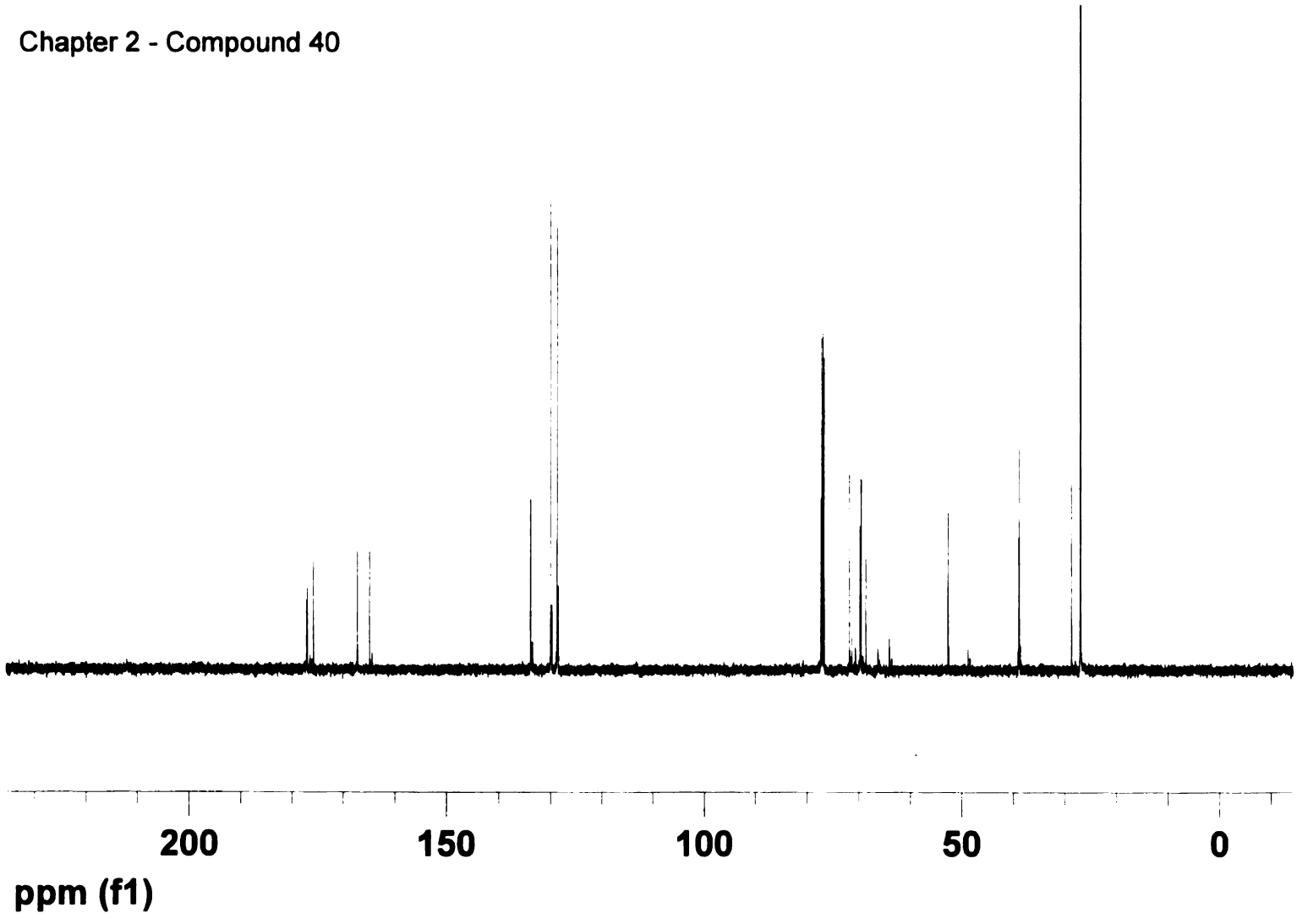
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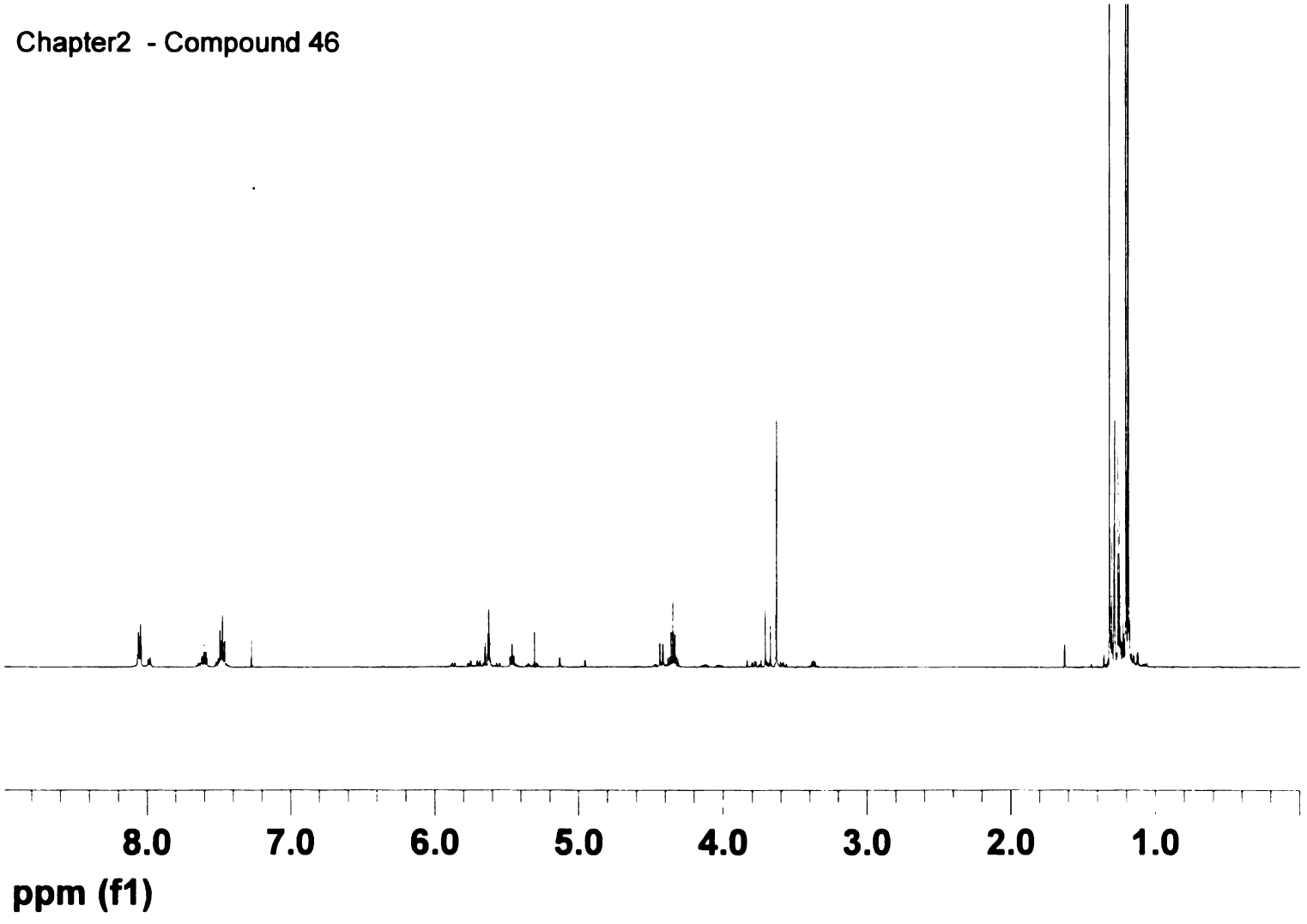
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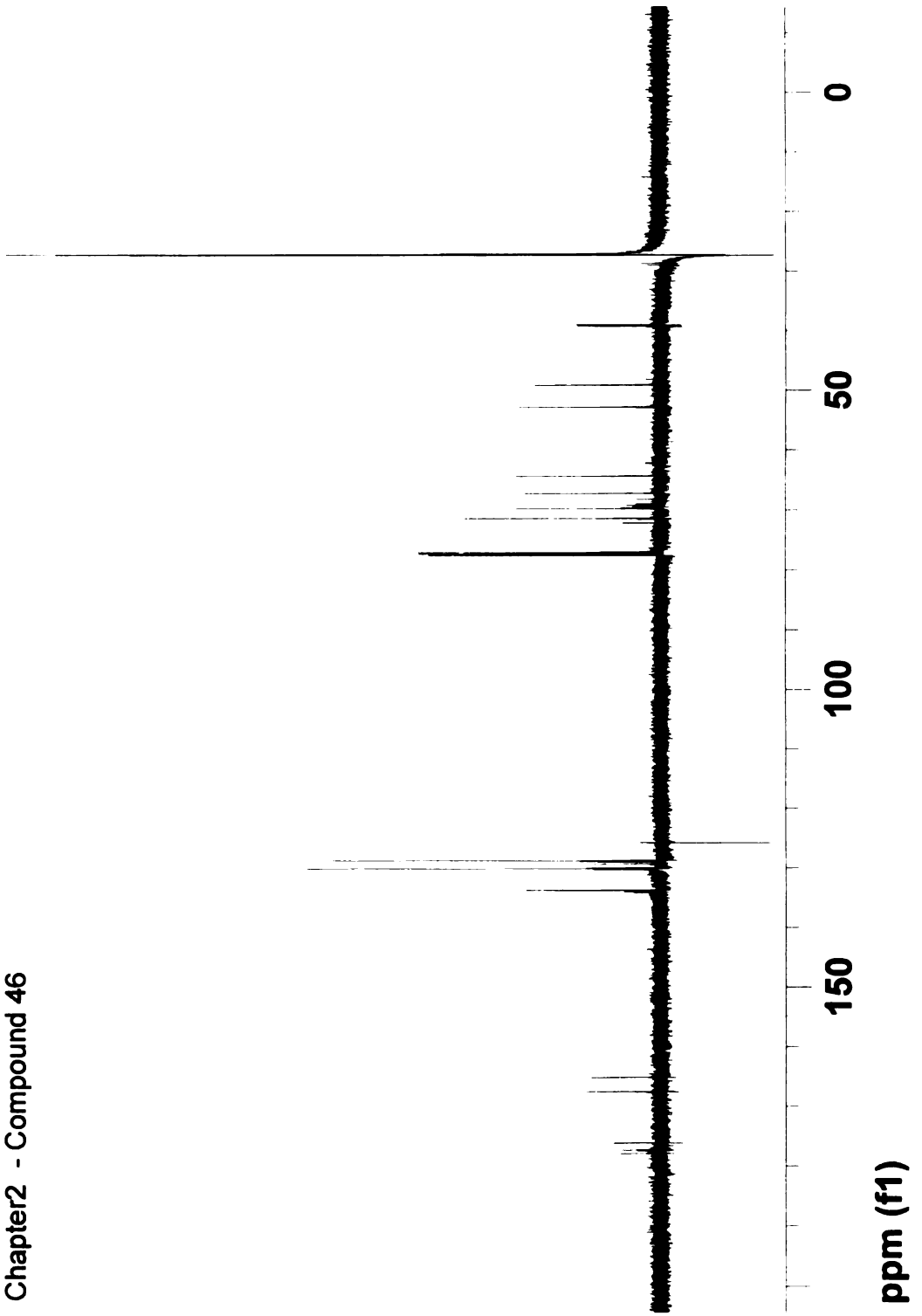
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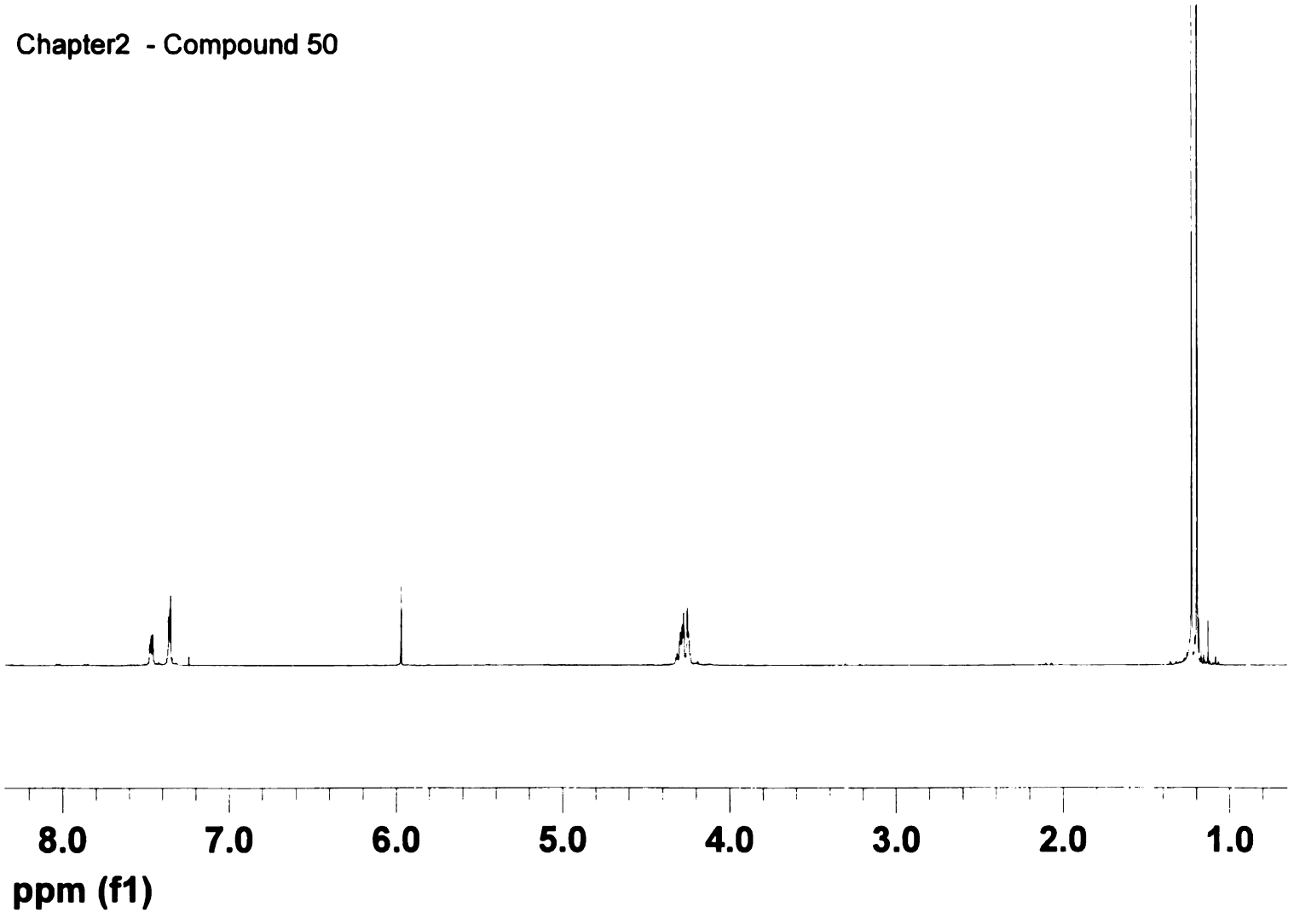
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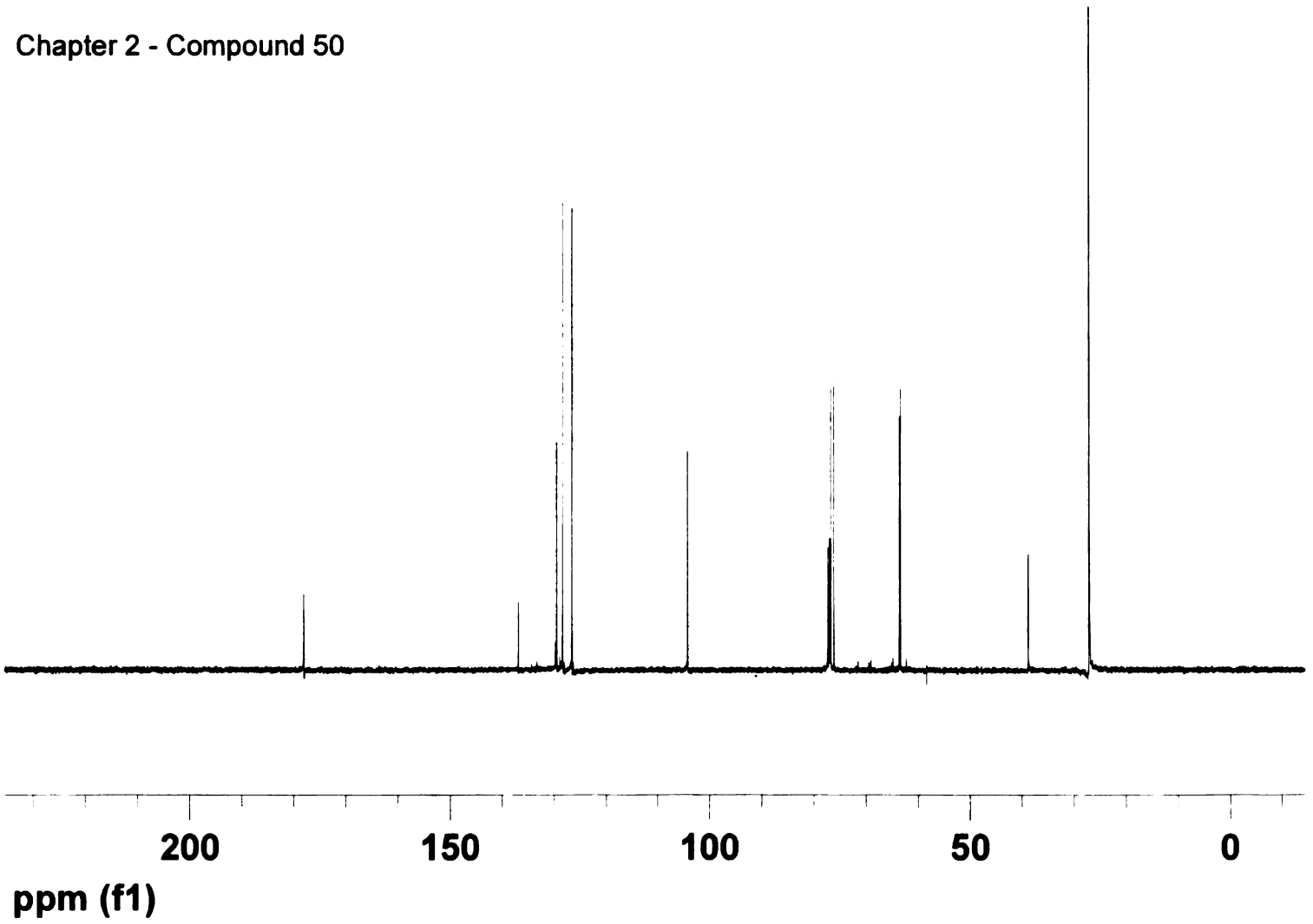
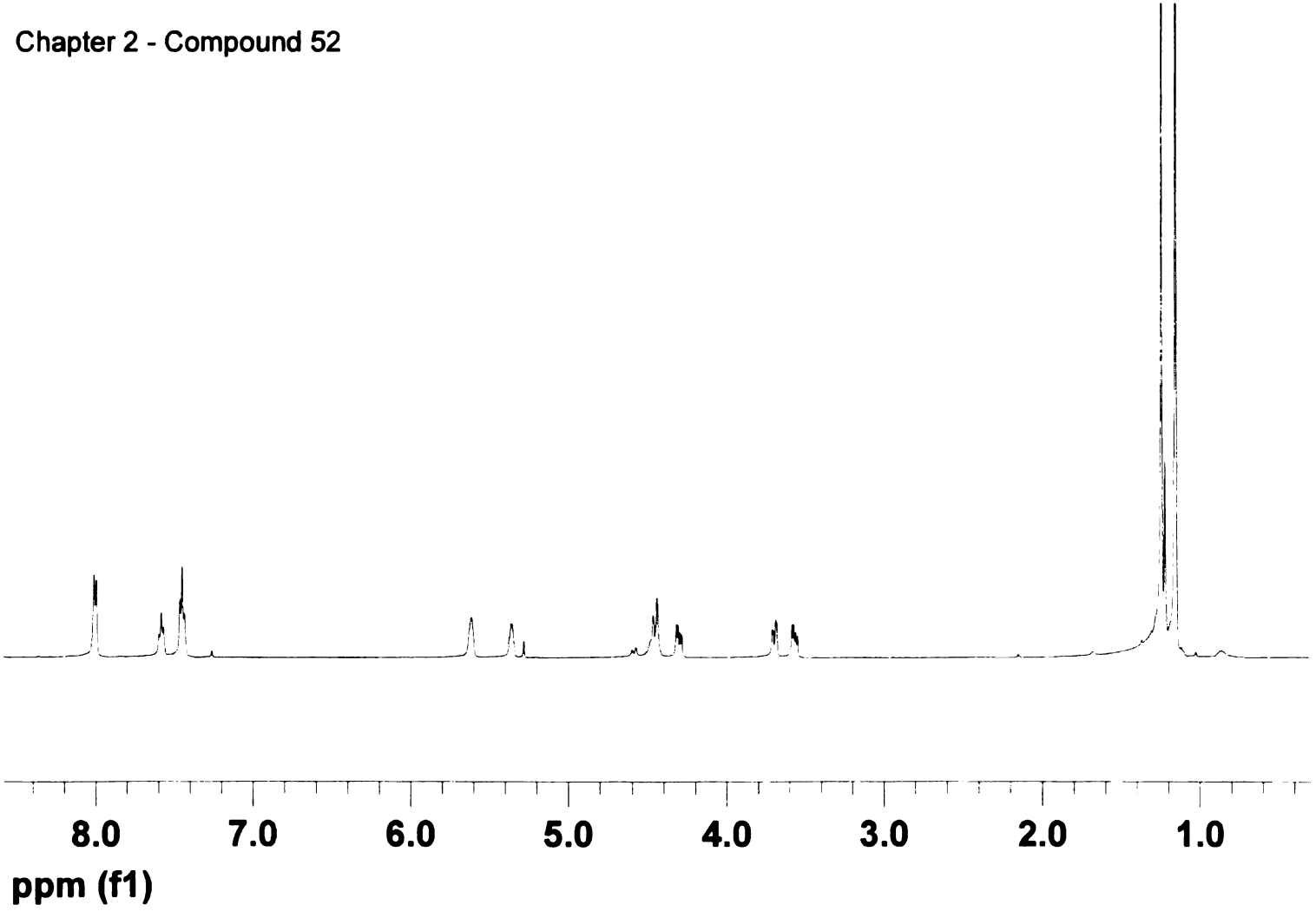
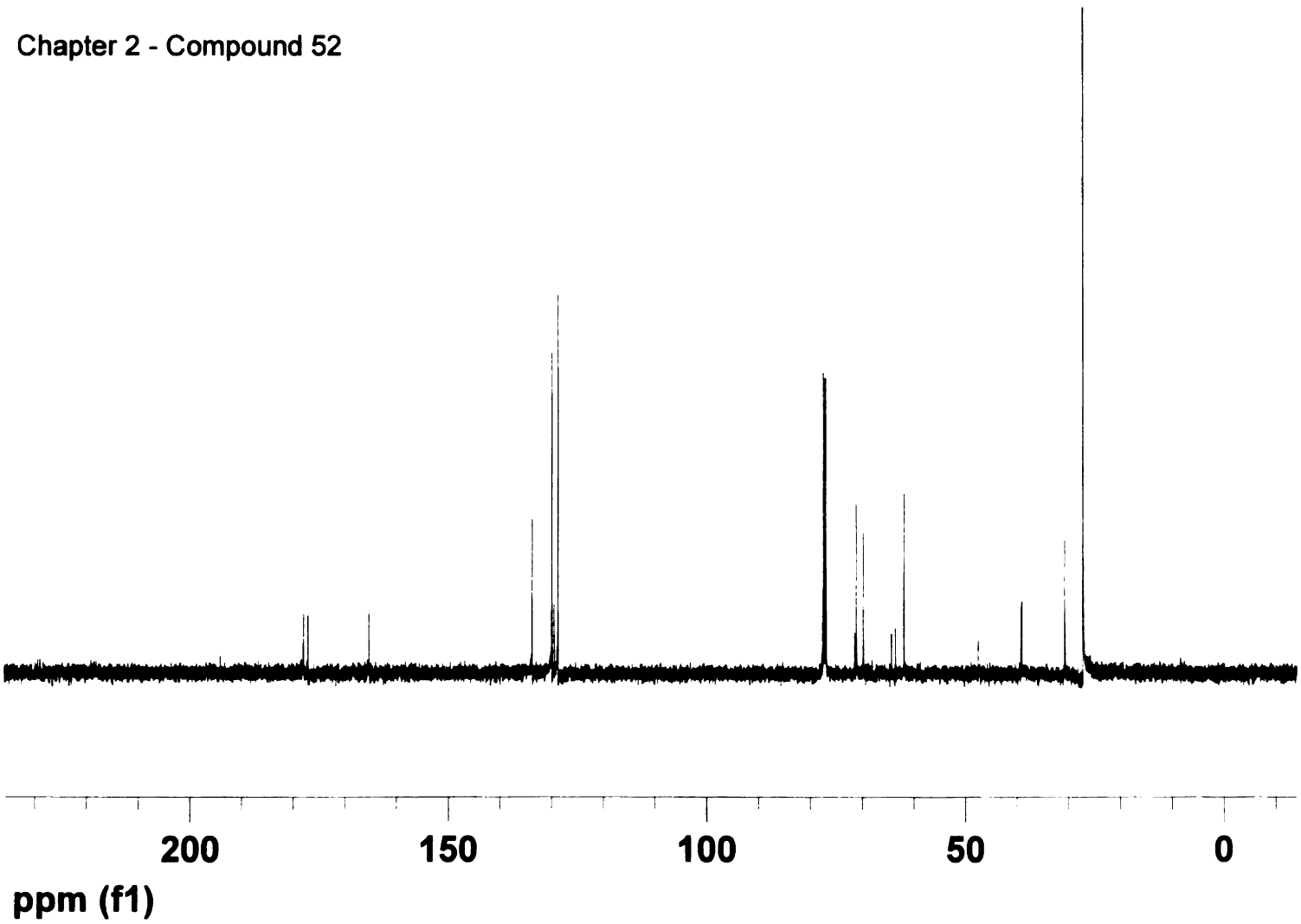
1.0
ppm (f1)

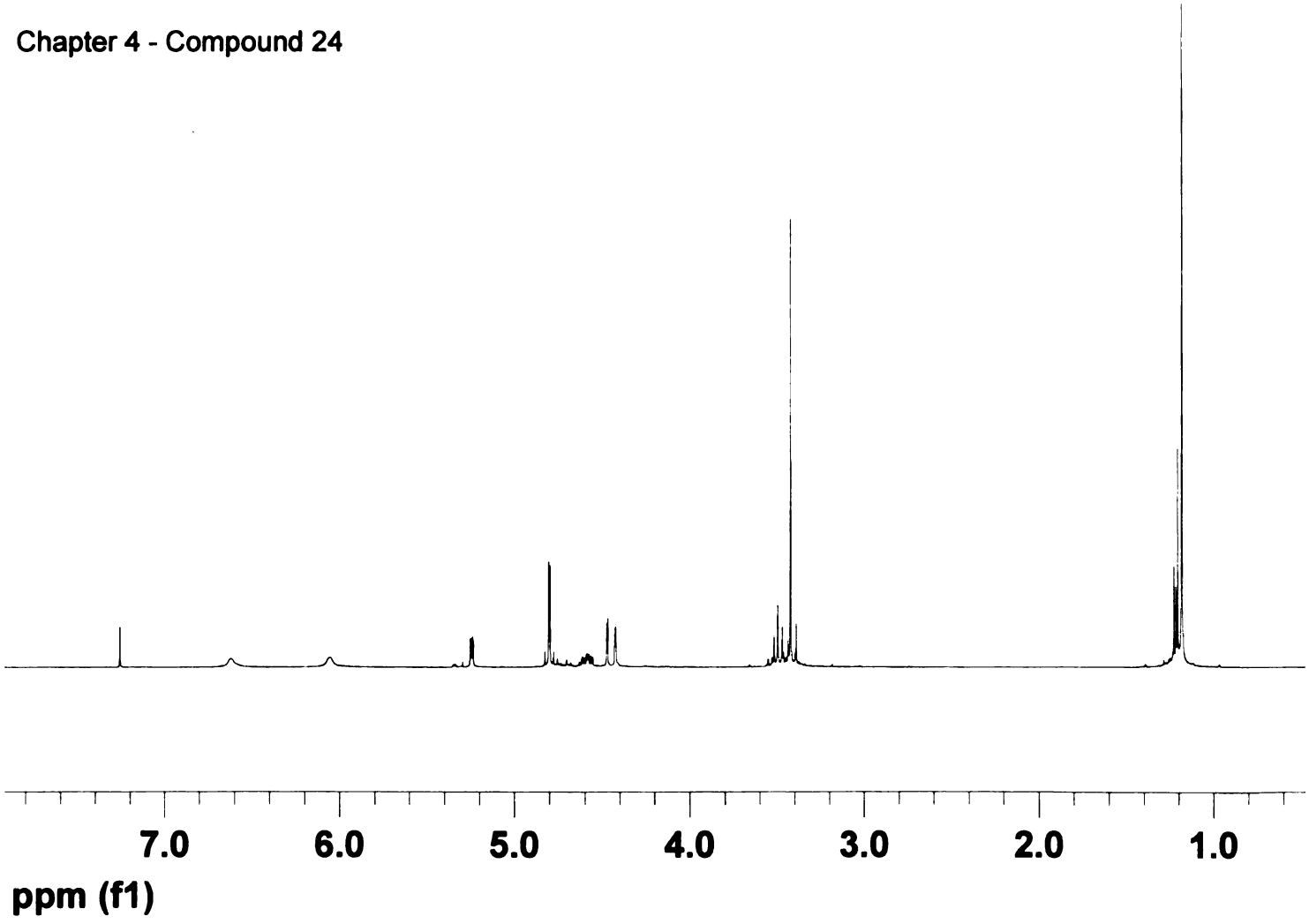

Chapter 2 - Compound 50
200
150
100
50
0
ppm (f1)

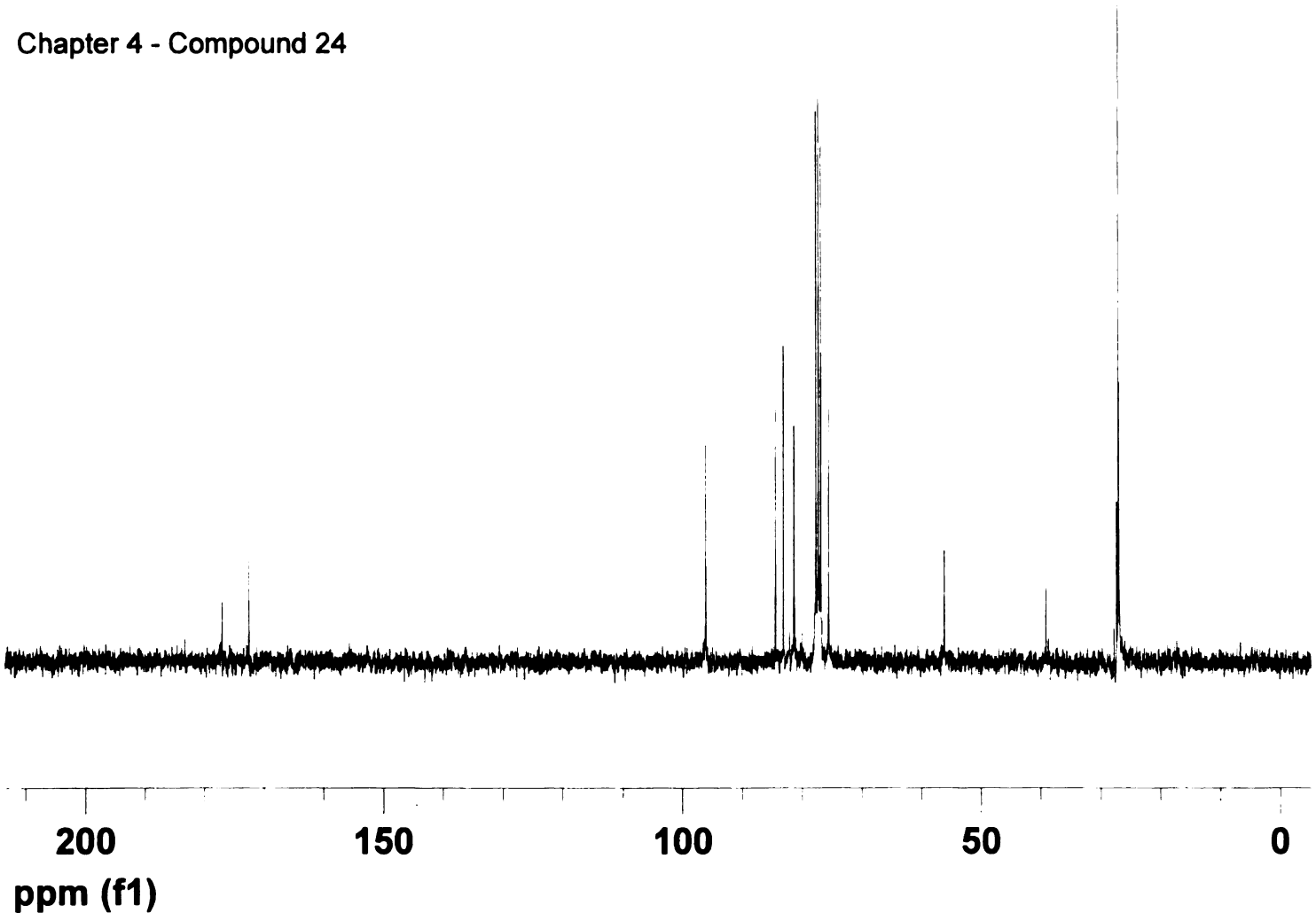
Chapter 2 - Compound 52

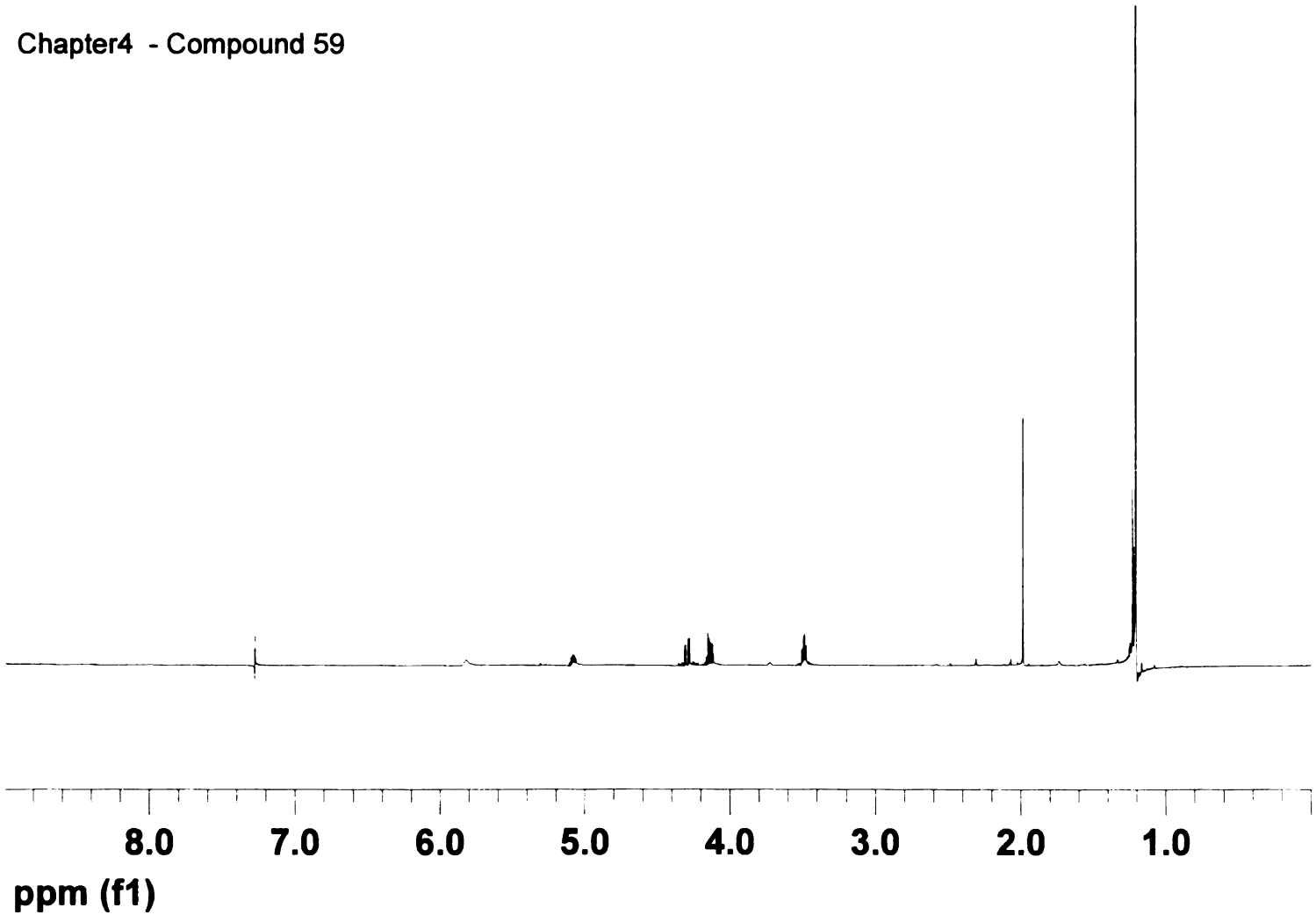


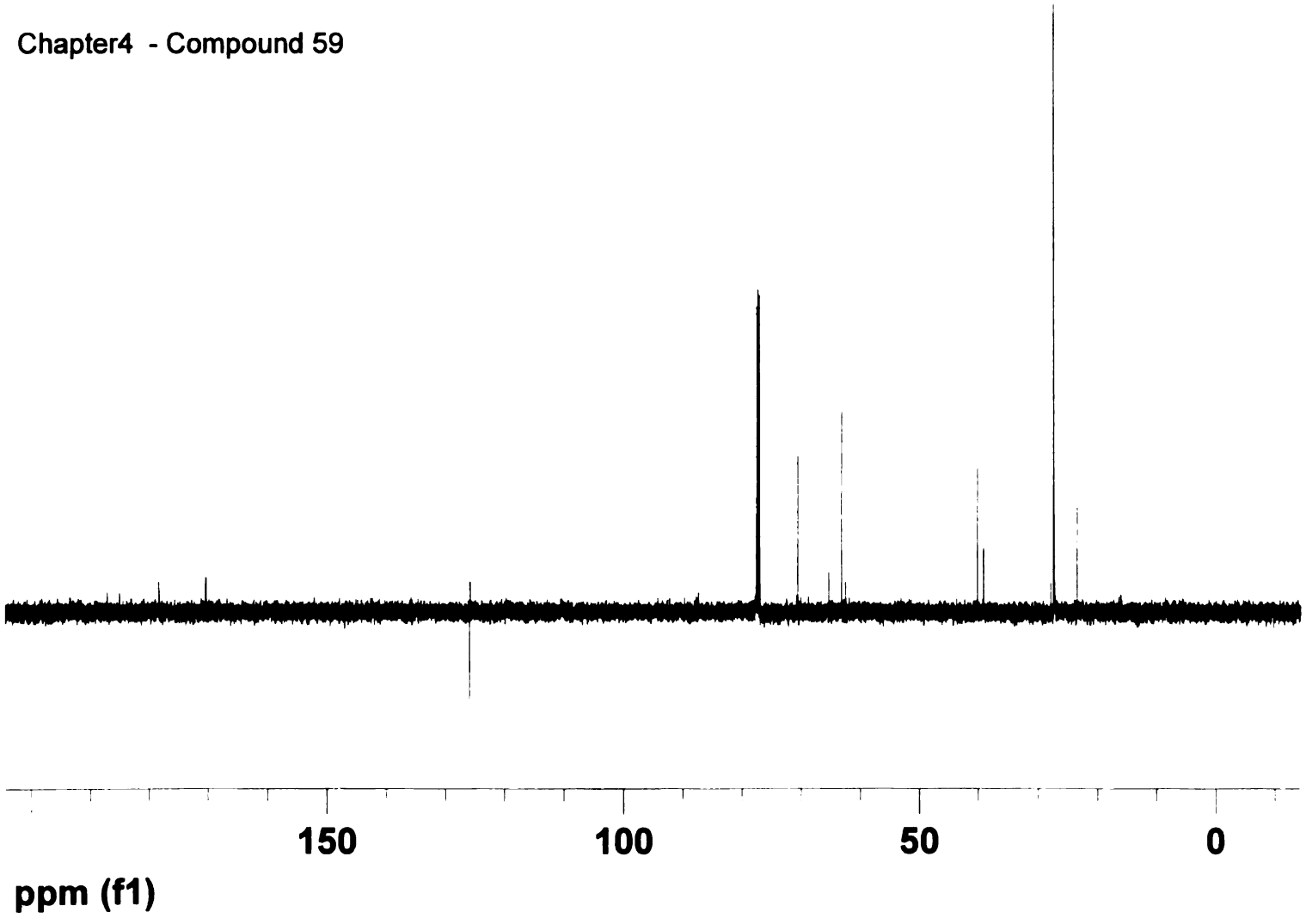

Chapter 2 - Compound 52
200
150
100
50
0
ppm (f1)

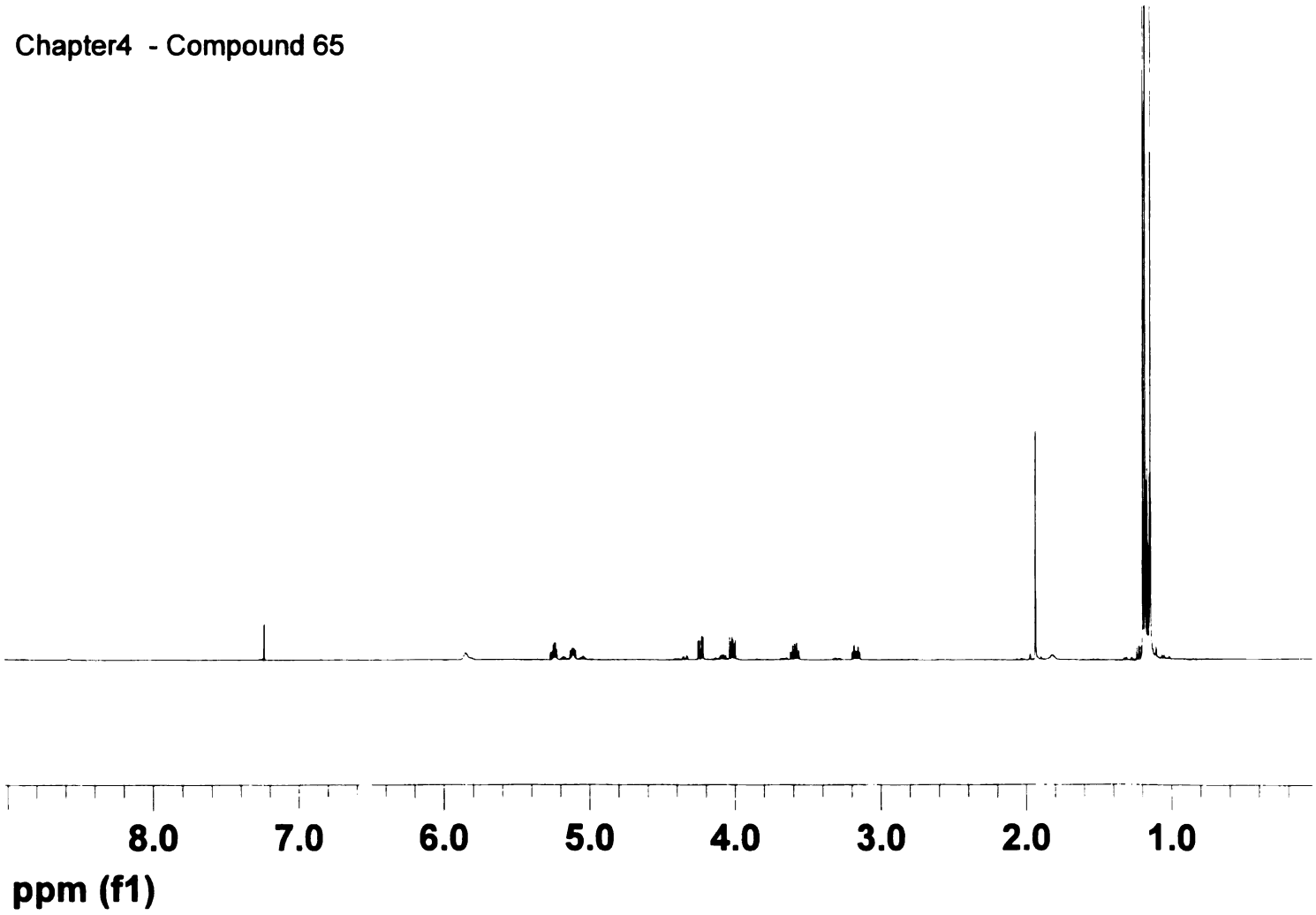
Chapter 4 - Compound 24

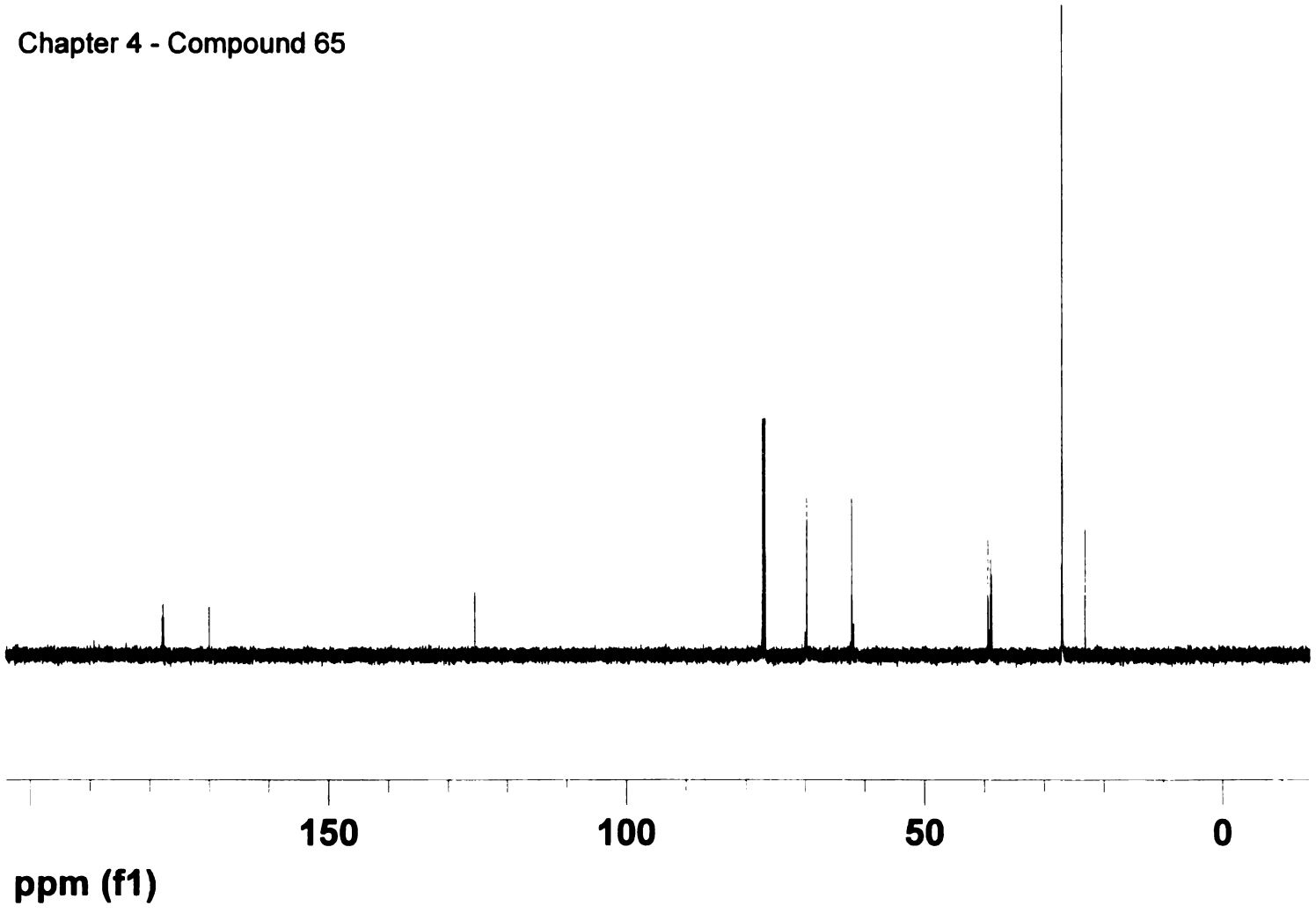


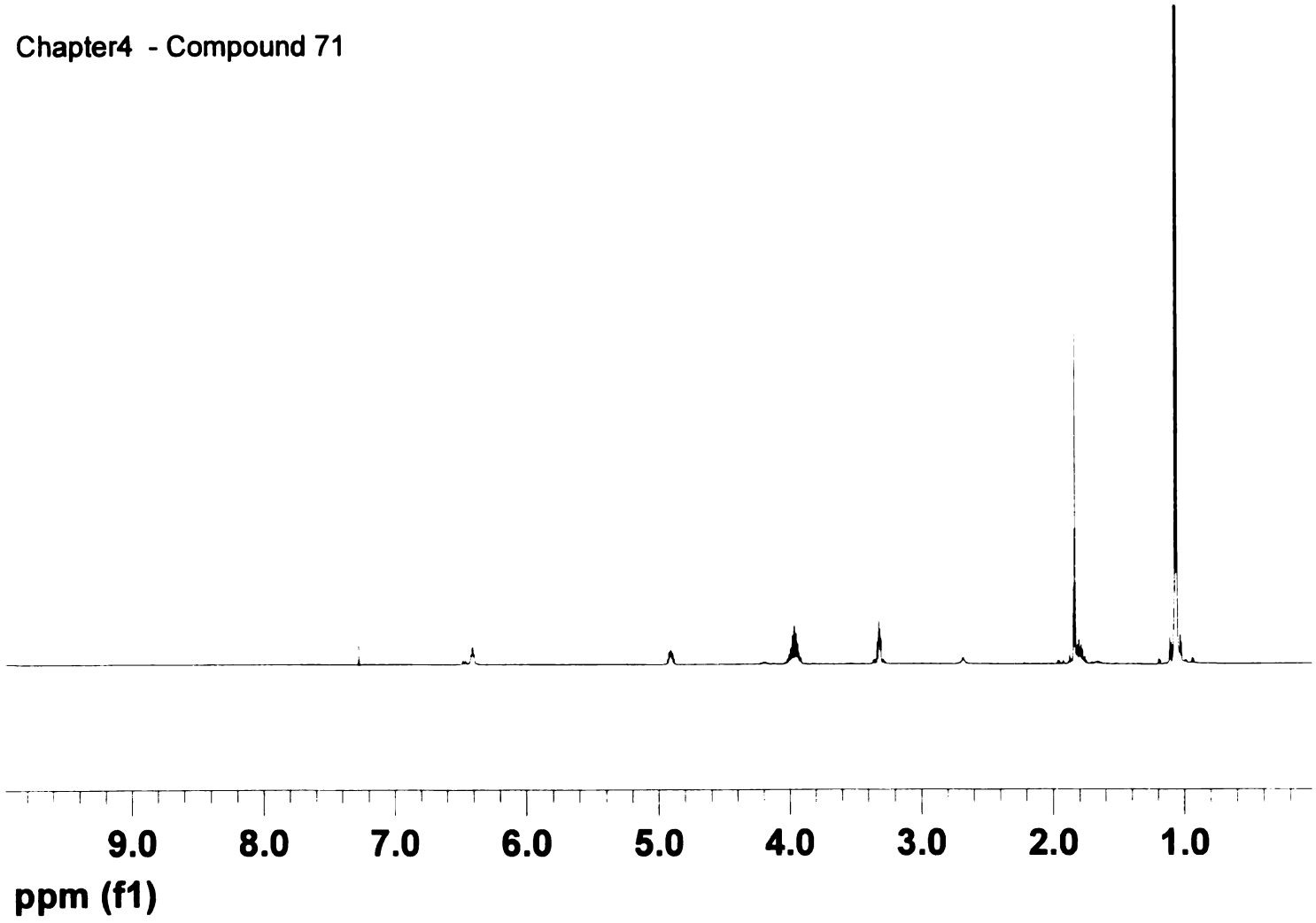

Chapter 4 - Compound 24
200
150
100
50
0
ppm (f1)

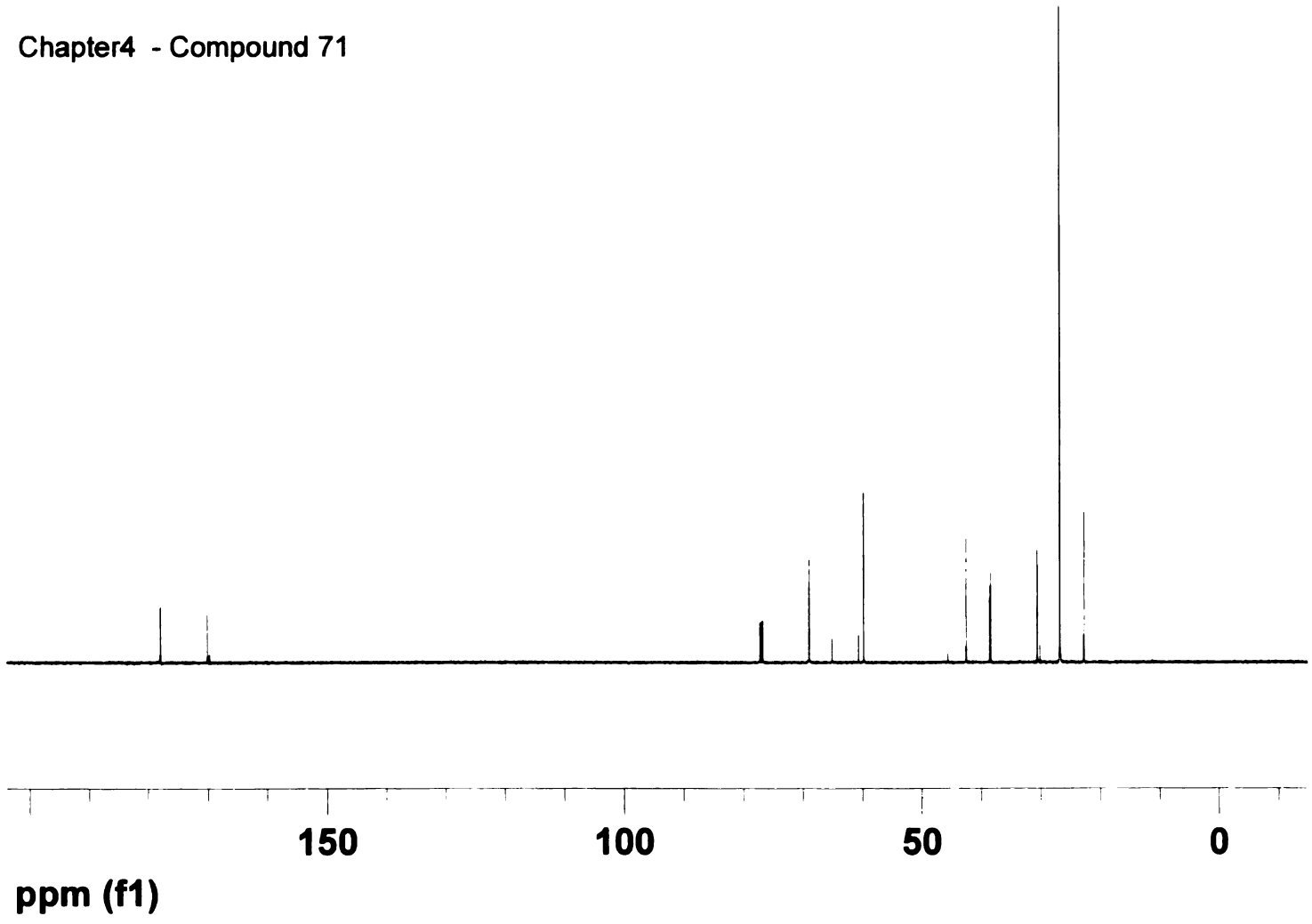

Chapter4 - Compound 59
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

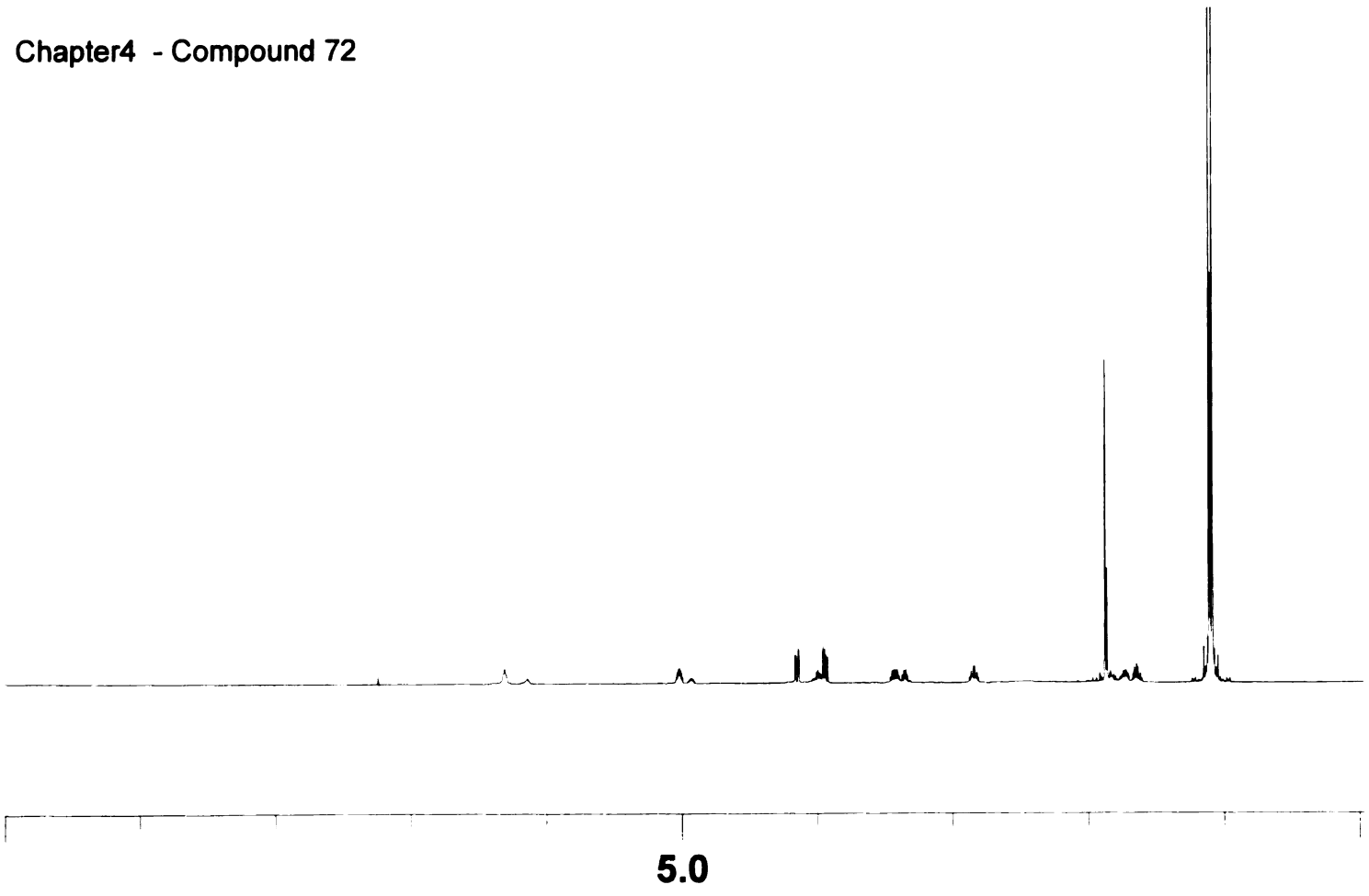

Chapter4 - Compound 59
150
100
50
0
ppm (f1)

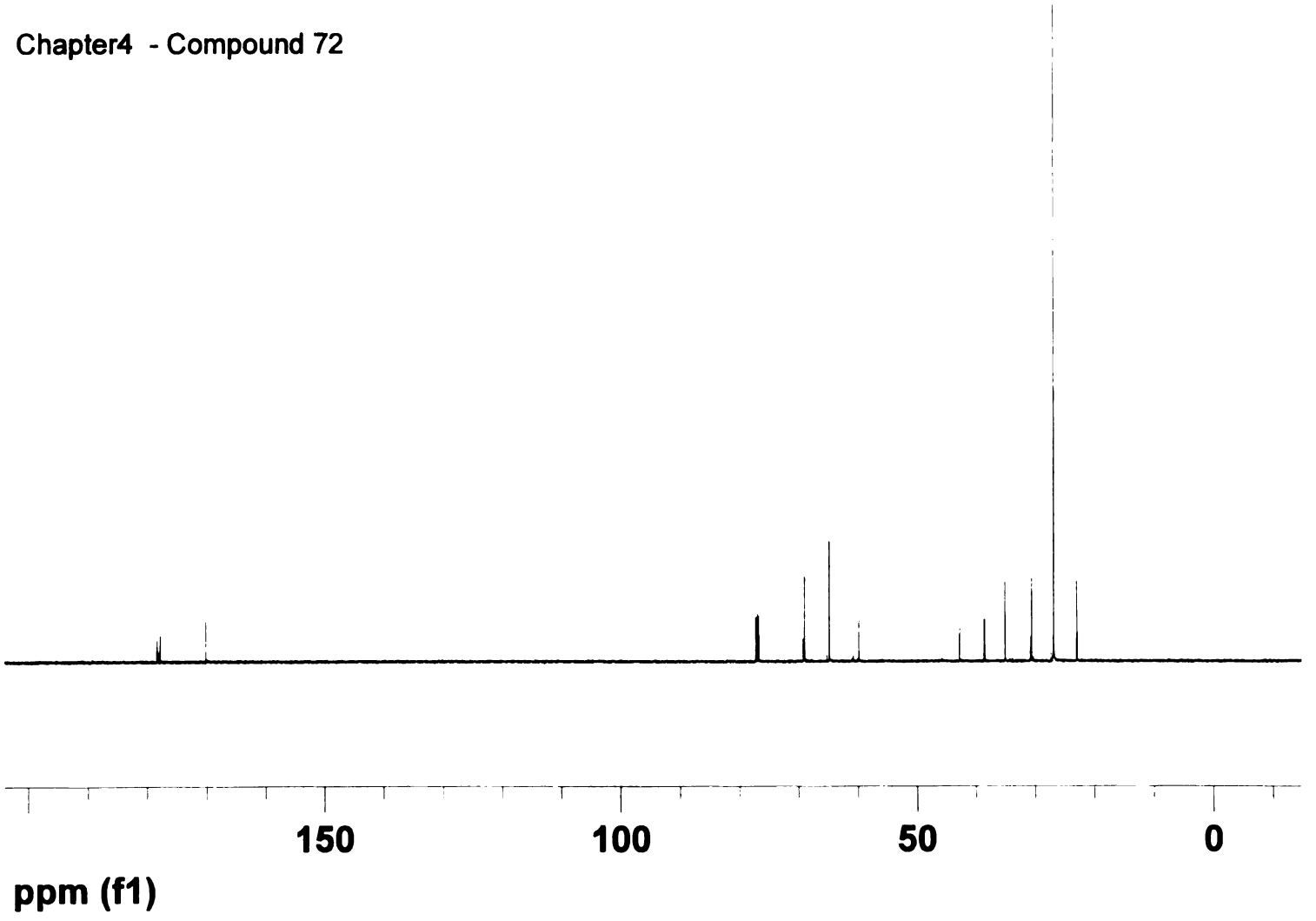

Chapter4 - Compound 65
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

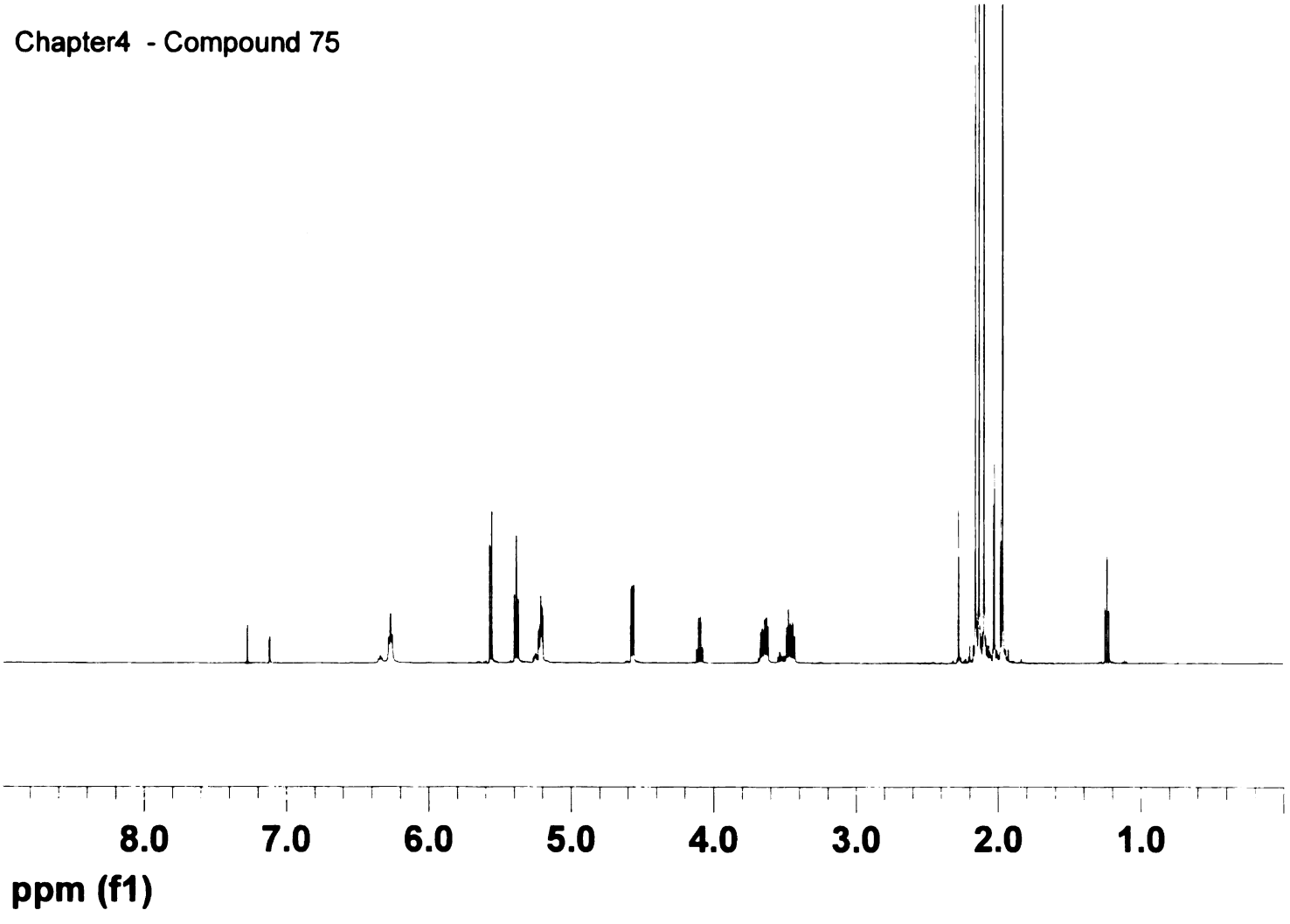

Chapter 4 - Compound 65
150
100
50
0
ppm (f1)

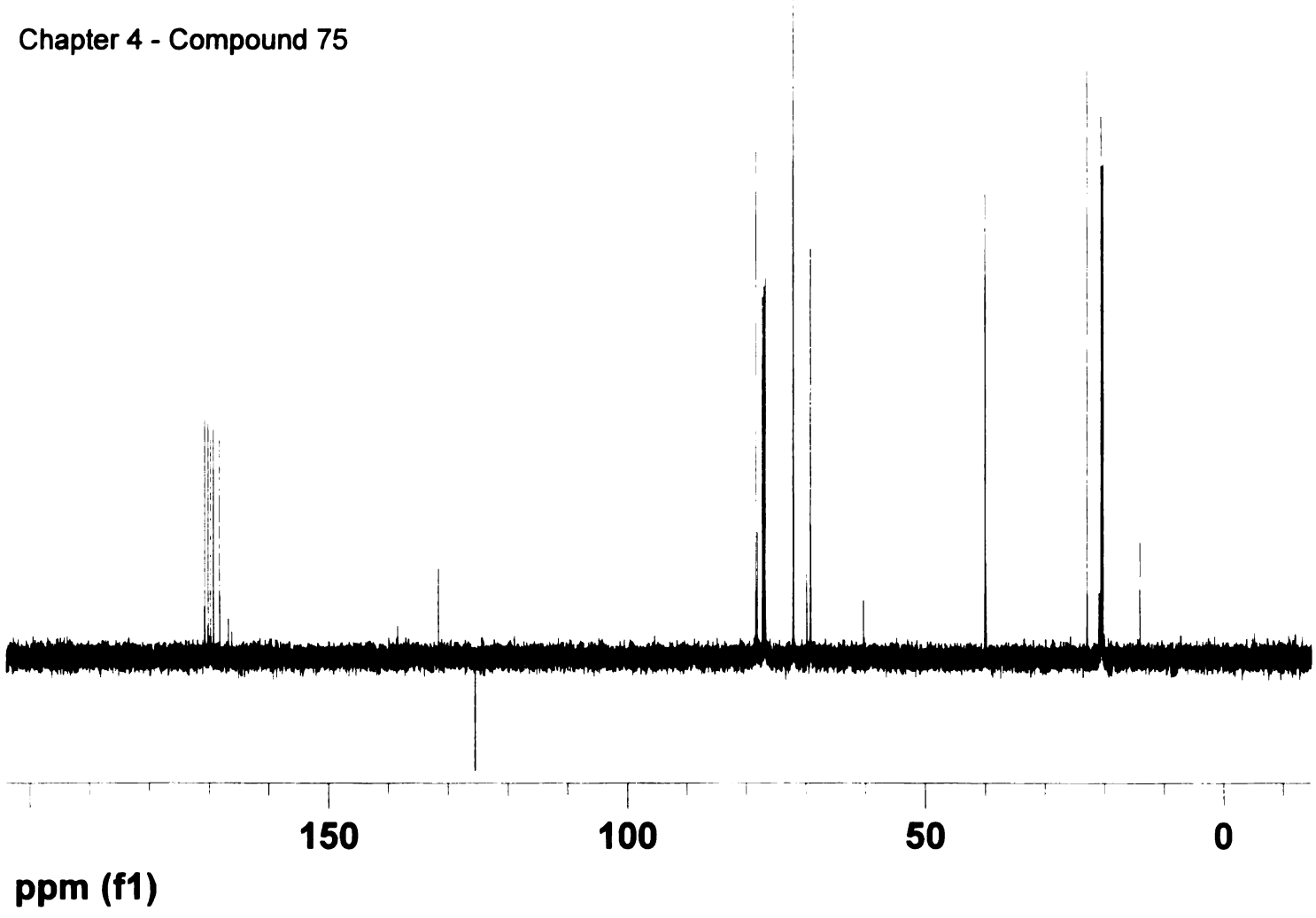

Chapter4 - Compound 71
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

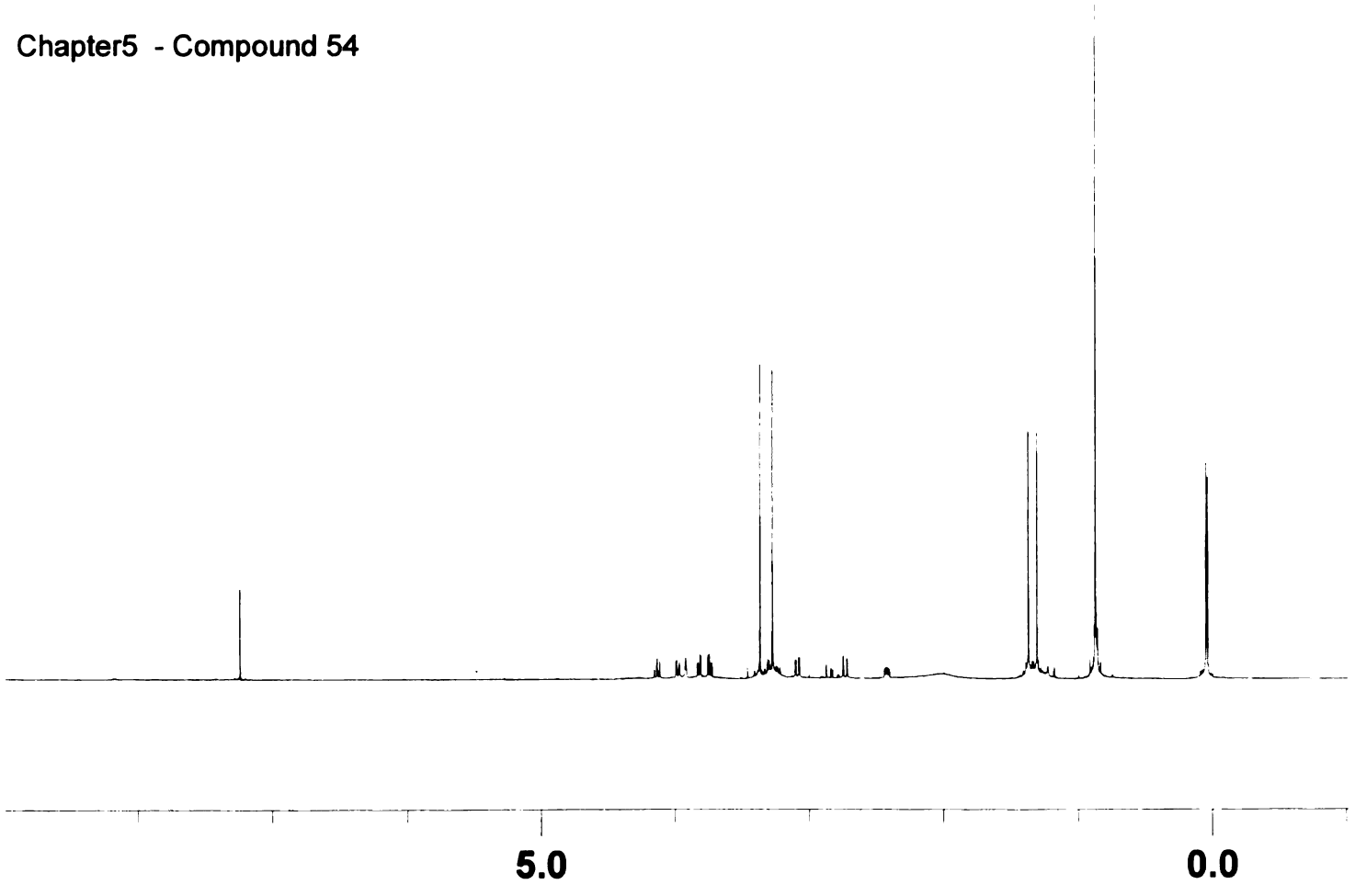

Chapter4 - Compound 71
150
100
50
0
ppm (f1)

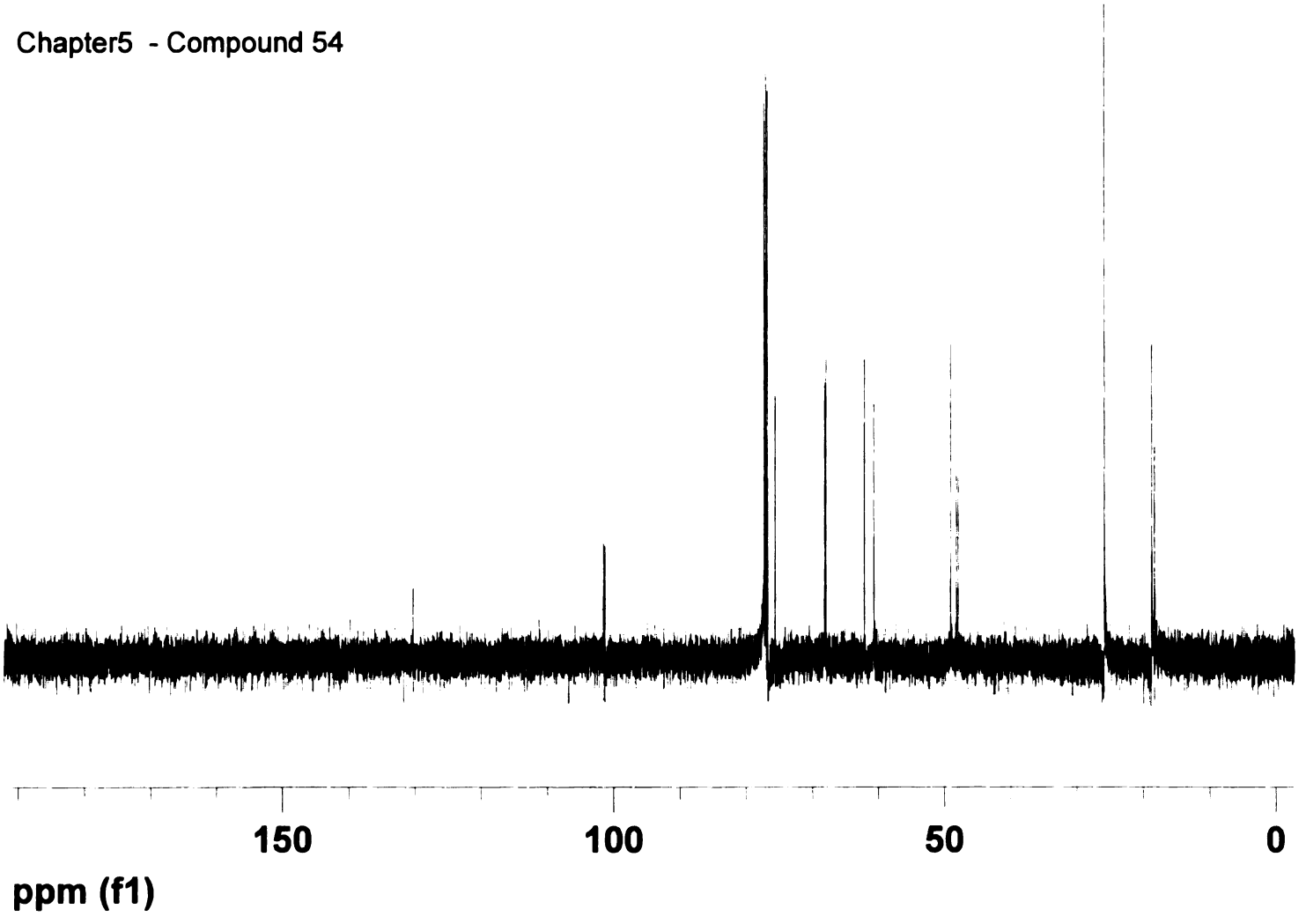

Chapter4 - Compound 72
5.0
ppm (f1)


Chapter4 - Compound 72
150
100
50
0
ppm (f1)


Chapter4 - Compound 75
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


Chapter 4 - Compound 75
150
100
50
0
ppm (f1)


Chapter5 - Compound 54
5.0
0.0
ppm (f1)


Chapter5 - Compound 54
150
100
50
0
ppm (f1)

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