1,2-Cyclopropanated Sugars as Novel Glycosyl Donors in Oligosaccharide Synthesis

A thesis submitted for the degree of
DOCTOR OF PHILOSOPHY

by

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To

All My teachers,

My family and

My friends

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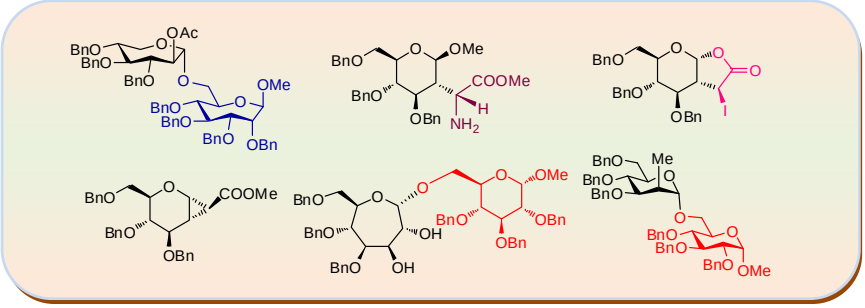

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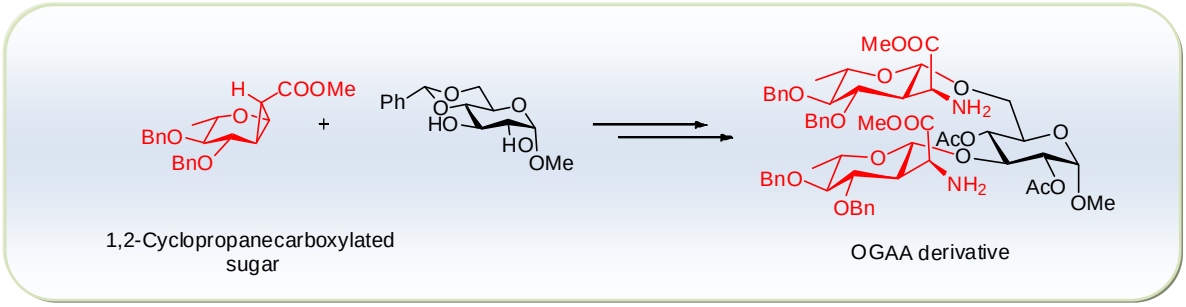

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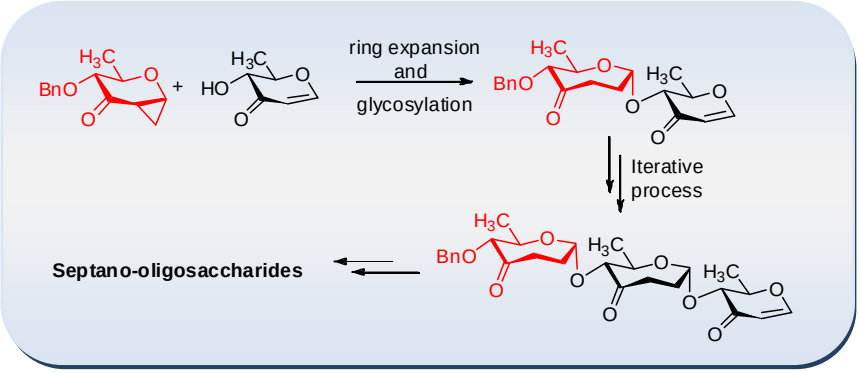

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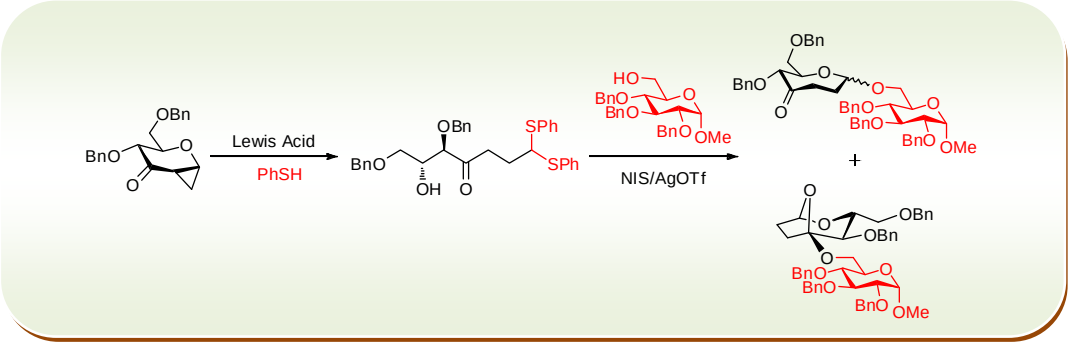

Statement

I here declare that, the overall material contained in this thesis is the outcome of research accomplished by me in the School of chemistry, University of Hyderabad, Hyderabad, India, under the supervision of Dr. Perali Ramu Sridhar.

In keeping with the general trend of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigations. Any omission, which might have occurred by oversight or error, is regretted.

Venukumar Patteti

Hyderabad
November, 2013

Certificate

Certified that the work pertaining to the thesis entitled "1,2-Cyclopropanated Sugars as Novel Glycosyl Donors in Oligosaccharide Synthesis" has been carried out by Mr. Venukumar Patteti under my supervision and that the aforementioned work has not been submitted elsewhere for obtaining degree.

Dr. Perali Ramu Sridhar
(Supervisor)

Dean
School of Chemistry

Hyderabad
November, 2013

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Venukumar Patteti…

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List of publications

1. Synthesis of 2-C-branched oligo(glyco–amino acid)s (OGAAs) by ring opening of 1,2-cyclopropanecarboxylated sugar donors.

   Perali Ramu Sridhar, **Patteti Venukumar**, Kalapati Seshadri, Rayala Satyavathi, *Chem.– Eur. J.* **2009**, *15*, 7526-7529.
2. A ring expansion-glycosylation strategy toward the synthesis of septano-oligosaccharides.

   Perali Ramu Sridhar, **Patteti Venukumar**, *Org. Lett.* **2012**, *14*, 5558-5561.
3. Stereoselective synthesis of C18-guggultetrol and C18-phytosphingosine analogues from D-fructose.

   Perali Ramu Sridhar, Mandava suresh, **Patteti Venukumar**, Kalapati Seshadri, *Carbohydr. Res.* **2012**, *360*, 40-46.
4. A one-pot septanoside formation and glycosylation of dithioacetals derived from 1,2-cyclopropanated sugars.

   Patteti Venukumar, Chalapala Sudharani, Perali Ramu Sridhar, (manuscript submitted)

Posters and flash presentations

1. **Patteti Venukumar** and Perali Ramu Sridhar, Synthesis of 2-C-branched oligo(glyco–amino acid)s (OGAAs) by ring opening of 1,2-cyclopropanecarboxylated sugar donors.

   Flash Presentation at IRTG-MCGS Summer School, held in November, **2009**, Institute for Physiological Chemistryand Pathobiochemistry, *Westfälische Wilhelms-Universität Münster*, Münster, Germany.
2. **Patteti Venukumar** and Perali Ramu Sridhar, Synthesis of 2-C-branched oligo(glyco–amino acid)s (OGAAs) by ring opening of 1,2-cyclopropanecarboxylated sugar donors.

Poster at Presentation at Chemfest-2010, held in February, **2012**, School of Chemistry, *University of Hyderabad*, Hyderabad, India.

3. **Patteti Venukumar** and Perali Ramu Sridhar, Synthesis of unnatural septanoside mimics of hexoses.

   Flash Presentation at IRTG-MCGS Winter School, held in December, **2010**, School of Life sciences, *University of Hyderabad*, Hyderabad, India.

4. **Patteti Venukumar** and Perali Ramu Sridhar, Synthesis of 2-C-branched oligo(glyco–amino acid)s (OGAAs) by ring opening of 1,2-cyclopropanecarboxylated sugar donors.

   Flash Presentation at 6th J-NOST conference, held in January, **2011**, School of Chemistry, *University of Hyderabad*, Hyderabad, India.

Synopsis

The thesis entitled **"1,2-Cyclopropanated Sugars as Novel Glycosyl Donors in Oligosaccharide Synthesis"** is divided into four chapters.

Chapter 1

An Introduction to the Chemistry of 1,2-Cyclopropanated Sugar, 2-C-Branched Glyco-Amino Acids (GAAs) and Septanoses

This chapter mainly describes the synthesis and applications of cyclopropanation in carbohydrate chemistry. Cyclopropanated carbohydrates are utilized to produce stereoselective C-branched sugar derivatives with high optical purity by ring-opening in presence of an electrophile. Cyclopropanated sugars have been the key synthons in the stereoselective synthesis of a number of natural products possessing excellent biological activity. In these reactions electrophilic ring-opening of cyclopropanated sugar derivatives is one of the key steps. This chapter covers the synthesis of 1,2-cyclopropanated carbohydrates by using few traditional and recently discovered methods as well as discuss about the diastereoselectivity of the reaction. Various methods for the ring-opening of cyclopropanes and their applications in the construction of natural compounds like epothilone A and B, norrisolide and *etc.* are exemplified.

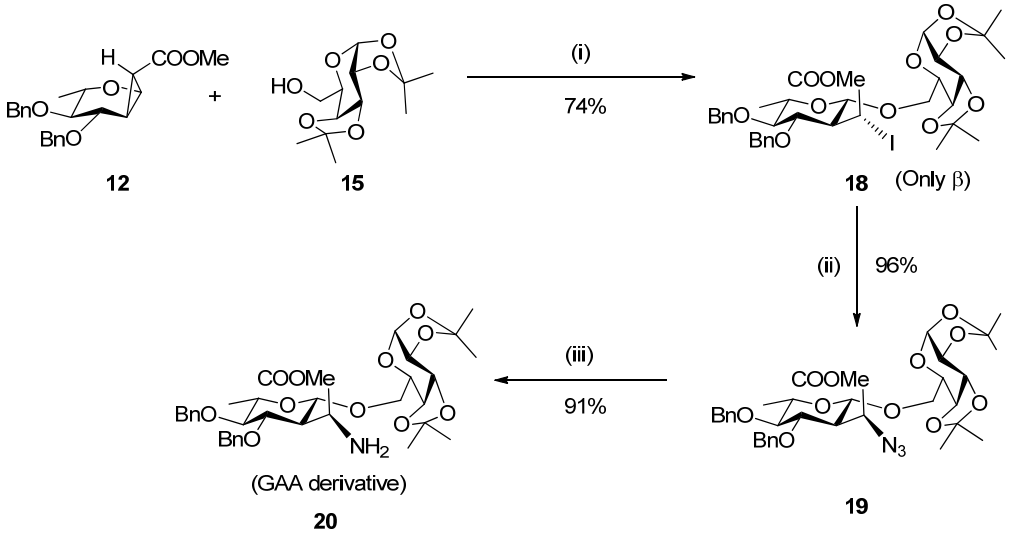
The ring-expansion of cyclopropanated carbohydrates is one of the recent emerging areas in organic synthesis to build the higher homologs of natural sugar derivatives. In this context, this chapter also deals with the different ring-expansion methods of the cyclopropanated sugars towards the synthesis of septanose/oxepane derivatives. Additionally, glycosylation methods using 1,2-cyclopropanated sugar derivatives as glycosyl donors for the synthesis of di- and oligosaccharides is also illustrated. These synthesized oligosaccharides using 1,2-cyclopropanated sugar derivatives could draw the attention of organic chemists as they can be used further due to their functional group variability. The basic idea and motivation of the thesis work is specified with literature backdrop.

Chapter 2

Synthesis of 2-C-Branched Oligo-Glyco-Amino Acids (OGAAs) by Ring Opening of 1,2-Cyclopropanecarboxylated Sugar Donors

This chapter mainly describes the novel glycosylation methodology for the synthesis of 2-C-branched glyco-amino acid (GAA) derivatives by using 1,2-cyclopropanecarboxylated sugar donors. Donor–acceptor cyclopropanes have the ability to undergo the ring-opening reaction assisted by adjacent oxygen in presence of an electrophile. The ring-opened sugar derivative was further derivatized to get GAA derivative.

1,2-Cyclopropanecarboxylated sugar donors were prepared by cyclopropanation of benzyl–protected glycals with methyl diazoacetate (MDA) and catalytic $Rh_2(OAc)_4$ in moderate yields and with good diastereoselectivity. *N*-Iodosuccinimide (NIS) mediated ring-opening of these 1,2-cyclopropanecarboxyalted sugars with sugar-*O*-nucleophiles in presence of catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided 2-C-branched GAA disaccharides in excellent yield. Treatment of 1,5-anhydro-2,6-dideoxy-1,2-C-(exo-carbomethoxy-methylene)-3,4-di-*O*-benzyl-α-L-rhamnal and 1,2-3,4-diisopropylidine-α-D-galactose with NIS/TMSOTf in CH_2Cl_2 afforded disaccharide with 2-C-branched iodide as a



12 15 18 19 20

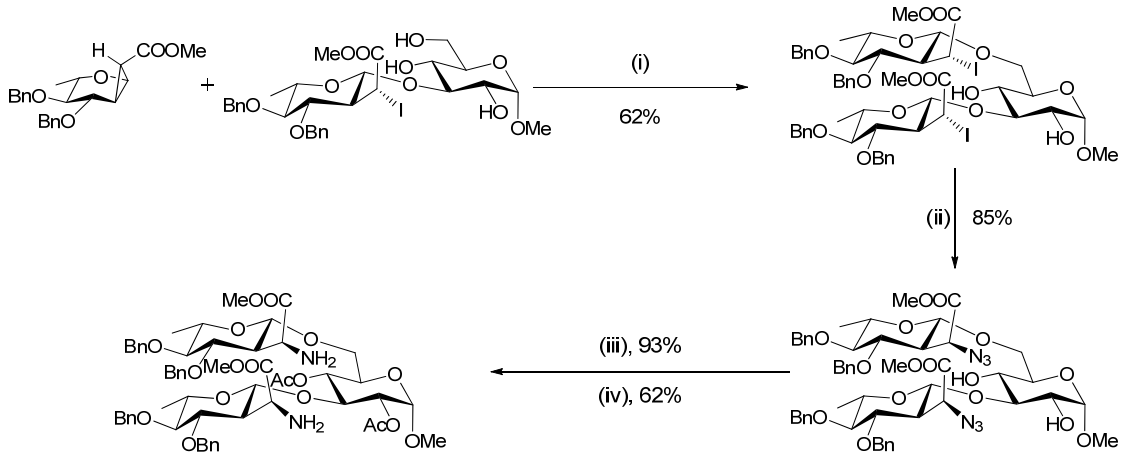
(GAA derivative)

Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h; (ii) NaN_3, DMF, rt, 24 h; (iii) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h.

Scheme 1: Synthesis of 2-C-branched GAA disaccharide

single diastereomer. Nucleophilic substitution of iodide with azide using NaN_3/DMF provided 2-C-branched azido-carboxylate. Reduction of azide functionality in disaccharide under the Staudinger reaction conditions (PPh_3/THF/H_2O) provided 2-C-branched GAA disaccharide in good yield (Scheme 1).

The developed methodology was successfully applied to a number of 1,2-cyclopropane-carboxylated sugar donors and differentially protected sugar acceptors to produce various GAA disaccharide derivatives. The high regio-selectivity was observed in the case of sugar acceptor having two hydroxyl groups in which only one hydroxyl participated in glycosidic bond formation. Furthermore, we extended this regio- and stereoselective glycosylation for the synthesis of many oligo-glyco-amino acids (OGAA) derivatives using the disaccharide–based iodocarboxylate as acceptor (Scheme 2).



Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 ^oC to rt, 16 h; (ii) NaN_3, DMF, rt, 24 h; (iii) Ac_2O, Py, rt, 10 h. (iv) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h.

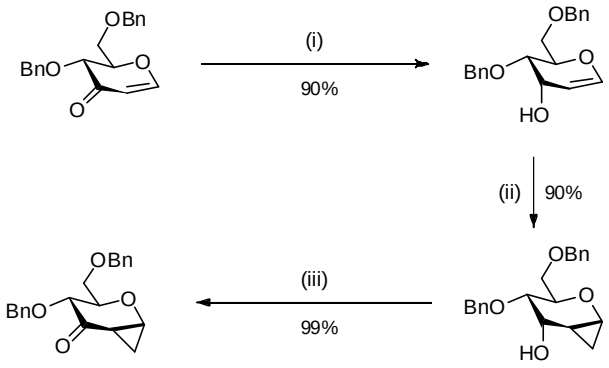
Scheme 2: Synthesis of 2-C-branched OGAA derivatives

Chapter 3

A Ring Expansion–Glycosylation Strategy toward the Synthesis of Septano-oligosaccharides

This chapter is mainly focused on the stereoselective synthesis of septano-oligosaccharides by one-pot ring-expansion and glycosylation of 1,2-cyclopropanated sugar donors. By incorporating an electron-withdrawing functionality at the C-3 position of the 1,2-

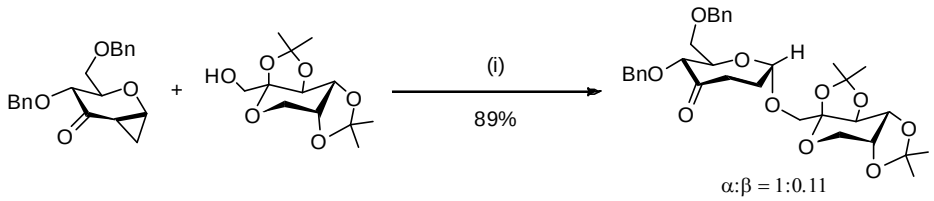
cyclopropanted pyranose would provide an access to cyclic donor-acceptor cyclopropanes, which are expected to undergo regioselective electrophilic ring-opening reactions assisted by the endocyclic oxygen, to give septanose/oxepane derivatives. These 3-oxo-1,2-cyclopropanated sugar donors were prepared from glucose-derived enone in three steps (Scheme 3).



Reagents and Conditions: (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 1 h; (ii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

Scheme 3: Synthesis of glucose-derived 1,2-cyclopropanated donor

The septano-hexoses were synthesized by treating the 3-oxo-1,2-cyclopropanated sugars as glycosyl donors and sugar alcohols as glycosyl acceptors in presence of catalytic Lewis acid. The ring-expansion and glycosylation reaction between D-glucose–derived 3-oxo-1,2-cyclopropane and 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranoside with catalytic TMSOTf provided 3-oxo-septano-hexose derivative in high yield with excellent diastereoselectivity (Scheme 4).

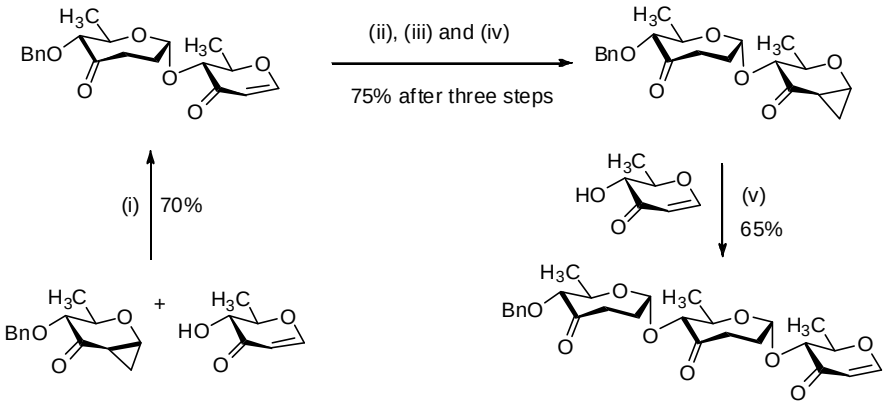


Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C to rt, 3 h.

Scheme 4: One-pot ring-expansion-glycosylation reaction using 1,2-cyclopropanated sugar

Using this strategy, a number of septano-hexoses were prepared by using various 3-oxo-1,2-cyclopropanated sugar donors and glycosyl acceptors. The stereochemistry of the newly

synthesized septano-hexose disaccharide was assigned based on chemical shift value of the anomeric carbon ($\delta_{C''}$ for α-septanosides from 99–104 ppm while β-septanosides it ranges from δ 104–111 ppm). This methodology was further explored for the construction of septano-oligosaccharides. The diseptano-hexose trisaccharide was synthesized by the ring-expansion of cyclopropyl septano-hexose disaccharide with sugar alcohol in presence of TMSOTf (Scheme 5).



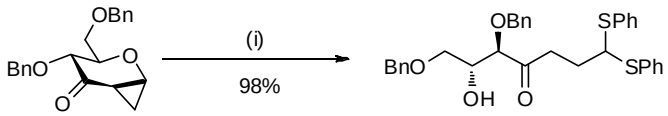
Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C, 3 h; (ii) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -78 °C, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; (v) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C, 3 h.

Scheme 5: An iterative protocol for the synthesis of septano-oligosaccharide

Chapter 4

A One-pot Septanoside Formation and Glycosylation of Dithioacetals Derived from 1,2-Cyclopropanated Sugars

This chapter mainly describes the synthesis and reactions of acyclic dithioacetal derivatives. 1,2-Cyclopropanated carbohydrates have been utilized as essential building blocks for the construction of acyclic dithioacetals (acyclic heptanose dithio-acetal derivatives) which were successfully employed as glycosyl donors for the generation of septano-hexoses,. TMSOTf-mediated reaction of D-Glucose-derived 1,2-cyclopropa-3-one with thiophenol provided the acyclic dithioacetal or heptanose derivative in good yield (Scheme 6).

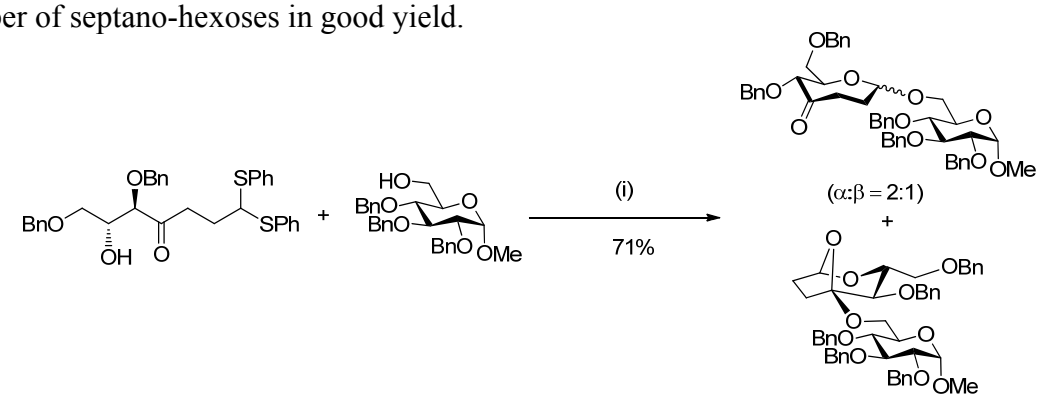


Reagents and Conditions: (i) PhSH, TMSOTf, CH_2Cl_2, -10 ^oC, 30 min.

Scheme 6: Synthesis of acyclic dithioacetal derivative from the 1,2-cyclopropanated sugar

This strategy was applied to a number of 1,2-cyclopropanated sugar derivatives using various thiols to produce the acyclic dithioacetal derivatives in more than 88% yield. The formation of heptanose derivatives were confirmed by ^1H, ^{13}C and COSY spectral analysis.

Interestingly these dithioacetals, under the glycosylation reaction conditions in presence of a glycosyl acceptor, provided septanoside containing disaccharides in a domino process. This reaction involves a one-pot intramolecular acetal exchange followed by glycosylation. Treating the mixture of D-glucose–derived dithio-acetal and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in presence of NIS/AgOTf in dichloromethane provided the septano-hexose and 2,8-dioxabicyclo[3.2.1]octane derivatives with 2:3 ratio in moderate yield (Scheme 7). Interestingly, when D-galactose-derived dithio-acetal donors were treated with a variety of glycosyl acceptors provided the septano-hexoses as single anomers in good yield with α-configuration at newly formed glycosidic bond. The reaction was further extended to various acyclic dithioacetals and differentially protected-glycosyl acceptors for the synthesis of a number of septano-hexoses in good yield.



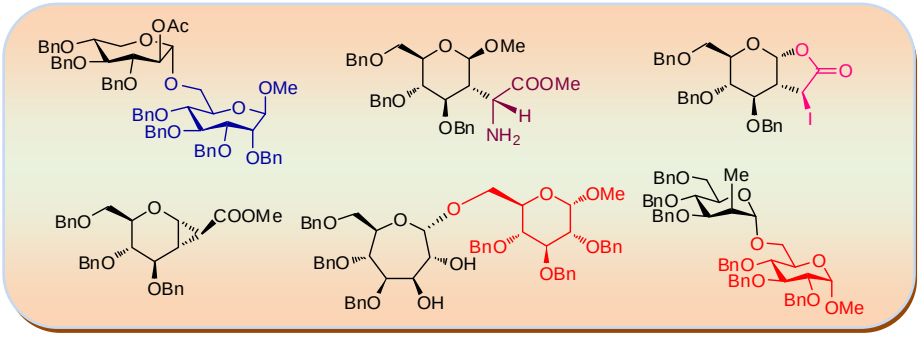
Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 ^oC to -25 ^oC, 1 h.

Scheme 7: A one-pot septanoside formation and glycosylation using acyclic dithioacetal donor

CHAPTER 1

An Introduction to the Chemistry of 1,2-Cyclopropanated Sugars, 2-C-Branched Glyco-Amino Acids (GAAs) and Septanoses

ABSTRACT: The present work mainly describes the chemistry of 1,2-cyclopropanated sugar donors with various carbohydrate derived *O*-nucleophiles to build the complex oligosaccharides. Two types of 1,2-cyclopropanated glycosyl donors were discovered and efficiently applied for the synthesis of 2-C-branched oligo-glyco-amino acids (OGAAs) and septano-oligosaccharides. The chemistry of these important molecules, 1,2-cyclopropanated sugars, 2-C-branched glyco-amino acids, septanoses, has been briefly reviewed in this chapter.



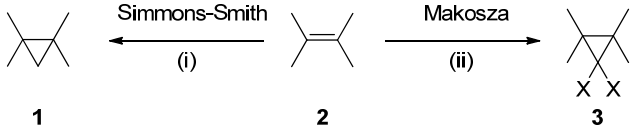
1.1 Cyclopropanes in Orgnaic Synthesis

Cyclopropanes are versatile building blocks for the construction of structurally diverse and challenging molecules.[1] Synthesis and application of these small-ring derivatives draw the attention of organic chemists as their synthesis itself is an endeavour.[2,3] Furthermore, many of cyclopropyl-group-containing amino acids, natural products or analogues of naturally occurring amino acids have been shown promising and important biological activities.[4] The first cyclopropane derivative was synthesized by W. H. Perkin about 130 years ago, through the attack of diethyl malonate upon 1,2-dibromo ethane.[5] Syntheses and reactions of these

highly strained three–membered ring derivatives have been well documented in the literature.[6-10]

1.1.1 Synthesis of Cyclopropanes

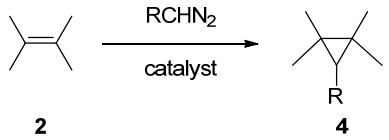
The synthesis of cyclopropanes has been well developed with several facile procedures. Among the well-established methods, Simmons-Smith, Mąkosza, and diazo–based cyclopropanations are commonly employed procedures. In Simmons-Smith reaction, cyclopropane is formed by treating the olefin with diiodomethane and Zn/Cu couple (Scheme 1.1).[11,12] In this reaction, diiodomethane and Zn/Cu couple presumably form the iodomethylzinc iodide (ICH_2ZnI) intermediate, which might react with the olefin to give cyclopropane framework. Later, this reaction has been extensively investigated by the discovery of several organo-metallic reagents.[13] In 1969, Mąkosza demonstrated the generation of *gem*–dihalocyclopropanes by treating the olefin with concentrated aqueous sodium hydroxide and haloform (CHX_3, X = Cl, Br) in presence of quaternary ammonium salts as phase–transfer catalyst (Scheme 1.1).[14] Under the strong base conditions elimination of hydrogen halide (HX, X = Cl, Br) molecule from haloform generates the corresponding dihalocarbene, which might be trapped by the olefin to provide the dihalocyclopropane. The applicability of this method with various functionalized olefins has been exploited.[9]



***Reagents and Conditions*:** (i) Zn/Cu, CH_2I_2, ether, reflux; (ii) aq. NaOH, CHX_3, benzyltriethylammonium chloride (TEBACl), 40 °C.

Scheme 1.1: General cyclopropanation methods

The other important method is cyclopropanation of olefins with transition–metal catalyzed decomposition of diazocompounds. Diazo–precursor was decomposed in presence of a metal catalyst to nitrogen and the corresponding metal carbenoid, which reacts with olefin substrate to provide the cyclopropane (Scheme 1.2).[13,15] Both inter and intramolecular cyclopropanations have been extensively elaborated by the discovery of a variety of effective transition–metal catalysts. The starting materials presented in this thesis were prepared using the modified protocol of Simmons-Smith and diazo–based cyclopropanation reactions.



Scheme 1.2: Diazo-based cyclopropanation

1.2 1,2-Cyclopropanated Sugars

In recent years, synthetic carbohydrate chemistry has been focused its attention towards oligo- and polysaccharide synthesis by intellectual modifications due to their potential biological value.[16] Carbohydrates are naturally occurring, readily available and inexpensive chiral pool materials. These poly-hydroxylated materials with many stereocentres might be easily transformed into many chiral compounds. Synthetic carbohydrate chemistry contains many protection and deprotection reactions to attain the final product but, due to their stereo significance many substantial methods for the synthesis of biologically interested molecules have been exploited from carbohydrates.

The study of cyclopropanated sugars is one of the subdivisions of the carbohydrate chemistry. Incorporation of three–membered ring into the carbohydrate skeleton provides strained and reactive enantiopure building blocks for the synthesis of many structurally diverse molecules and natural products. 1,2-Cyclopropanated sugars are gaining more importance than other cyclopropanated sugars due to the participation of endocyclic oxygen in activation of cyclopropane ring.

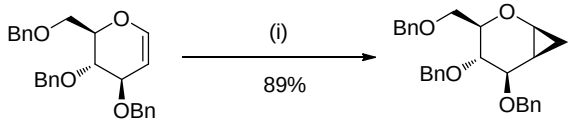
1.2.1 Synthesis of 1,2-Cyclopropanated Sugars

1,2-Cyclopropanated sugars may be synthesized using various methods, which involves the addition of carbene to 1,2-unsaturated carbohydrates (commonly called as glycals).[17,18] The common methods used for the cyclopropanation of carbohydrates are mentioned below.

Using Simmons-Smith Cyclopropanation

In 1995, Nagarajan and co-workers described the synthetic strategy for the cyclopropanation of benzyl-protected glycals by using the standard Simmons-Smith reaction conditions. In this report 3,4,6-tri-*O*-benzyl-D-glucal **5** was treated with CH_2I_2/Zn/CuCl in presence of acetyl chloride to obtain **6** in excellent yield as a single diastereomer.[19] The facial coordination of

organozinc reagent to the double bond and the oxygen atom of the C-3 substituent of glycal **5** contributes for the formation of exclusive *syn*-diastereomer **6** (Scheme 1.3). They successfully synthesized two more 1,2–cyclopropanated sugar derivatives of 3,4,6-tri-*O*-benzyl-D-galactal and 3,4-di-*O*-benzyl-L-rhamnal in excellent yield with high diastereoselectivity.

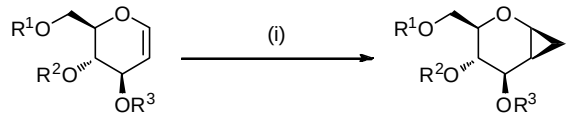


5 **6**

Reagents and Conditions: (i) CH_2I_2, Zn, CuCl, CH_3COCl, ether, 90 min.

Scheme 1.3: Simmons-Smith cyclopropanation of tri-*O*-benzyl D-glucal

Recently, cyclopropanation of sugars using Furukawa modification[20] of Simmons–Smith reaction has been used extensively, in which zinc–copper couple is replaced with diethyl zinc. A wide variety of protected glycals have been cyclopropanated using this modified method with excellent yields and selectivity (Scheme 1.4).[21] This reagent also gives the only *syn*-diastereomer, in which the cyclopropane ring is *syn* to the C3-OR_3 (Scheme 1.4). Under the same reaction conditions, cyclopropanation of glycals with of *tert*-butyldimethylsilyl protection was unsuccessful. The reason for this may be due to the steric hindrance of *tert*-butyldimethylsilyl (TBS) group.[22]



7 **8**

R^1, R^2, R^3 = Me (94%)
R^1, R^2, R^3 = Bn (92%)
R^1 = TBS, R^2, R^3 = H (88%)

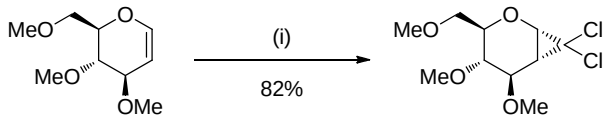
R^1, R^2 = Si^tBu, R^3 = H (96%)
R^1 + R^2 = CMe_2, R^3 = H (33%)
R^1, R^2, R^3 = TBS (0%)

Reagents and Conditions: (i) CH_2I_2, Et_2Zn, ether 0 ^oC, 5 h.

Scheme 1.4: Synthesis of cyclopropanes using the Furukawa's method

Using Mąkosza Cyclopropanation/Dihalocarbene Cyclopropanation

The Mąkosza or dihalocarbene method is also a very convenient procedure for the synthesis of dihalocyclopropanated sugars that are readily transformed into higher membered sugars and important derivatives by utilizing the halogen functionality. In 1967, Brimacombe and co-workers reported the first carbohydrate cyclopropanation of tri-*O*-methyl-D-glucal **9** through the addition of dichlorocarbene, prepared from the sodium methoxide and ethyl trichloroacetate (Scheme 1.5).[23] The authors assumed that the addition of carbene onto the double bond has been completely from the α–face due to the steric constraints of methoxy substituent at C-3 position. This reaction provided the only α–cyclopropyl adduct **10** in excellent yield.

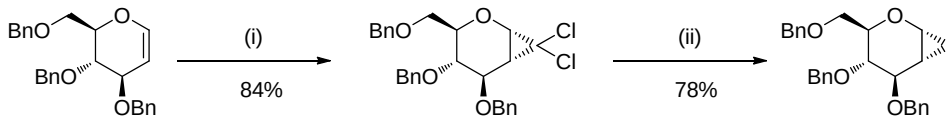


9 **10**

Reagents and Conditions: (i) CCl_3COOEt, NaOMe, dry hexane, rt, 16 h.

Scheme 1.5: Cyclopropanated sugar derivative reported by Brimacombe

Furthermore, in 1997, Nagarajan and co-workers reported the elegant strategy for the *trans*-cyclopropanation of benzyl–protected glycals by using biphasic Mąkosza cyclopropanation. In this reaction, α-1,2-*gem*-dichlorocyclopropanated sugar derivative **11** was formed as single isomer by treating the 3,4,6-tri-*O*-benzyl-D-glucal **5** with $CHCl_3$-aqueous NaOH under the phase–transfer catalyst conditions.[19,24] A series of benzyl-protected glycals were successfully converted to cyclopropanes using this methodology in excellent yield with high diastereoselectivity. Stereochemistry of the α-cyclopropyl adducts is completely governed by the C-3 substituent. The reductive dechlorination of dichlorocyclop-



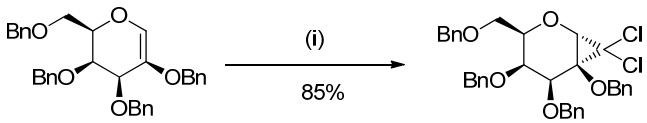
5 **11** **12**

Reagents and Conditions: (i) aqueous NaOH, $CHCl_3$, $BnNEt_3Cl$, 35 ^oC, 4 h; (ii) $LiAlH_4$ (excess), THF, rt, 2 h.

Scheme 1.6: Synthesis of 1,2-cyclopropanated sugars using dihalocarbene method

-ropanes with excess $LiAlH_4$ gives corresponding fully reduced cyclopropanes, which are having the opposite stereochemistry of Simmons-Smith cyclopropanation reactions (Scheme 1.6).

Recently, Jayaraman *et al.* utilized this protocol to make 1,2-*gem*-dihalocyclopropanated sugar derivatives from the *O*-benzyl-protected oxyglycals. D-Galactose-derived oxyglycal **13** was treated with $CHCl_3$ and aqueous NaOH under the phase-transfer catalyst condition to produce the 1,2-*gem*-dichlorocyclopropanated sugar derivative **14** as a single diastereomer in 85% yield (Scheme 1.7).[25]



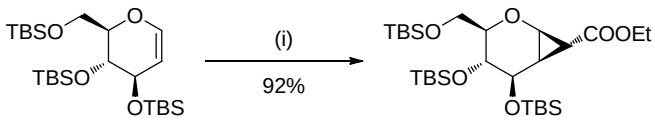
13 **14**

***Reagents and Conditions*:** (i) aqueous NaOH, $CHCl_3$, $BnNEt_3Cl$, 40 °C, 3 h.

Scheme 1.7: Synthesis of 1,2-dihalocyclopropanated sugar from the oxyglycal derivative

Using Diazo–Based Cyclopropanation

Transition-metal catalyzed cyclopropanation with diazo compounds has been extensively used for the synthesis of cyclopropanated sugars in a stereoselective manner. These cyclopropanated sugars have the considerable functionality in the ring rather than Simmons-Smith and Mąkosza cyclopropanated sugars. The first example of cyclopropanation towards carbohydrate derived diazo ester was reported with 3,4,6-tri-*O*-acetyl-D-glucal in 1981,[26] but this method gave low yields and stereochemistry of the cyclopropane derivative was not assigned. Later, Fraser-Reid *et al.* reported the facile cyclopropanation of glycals with ethyl diazoacetate (EDA) and copper powder. The slow addition of EDA in cyclohexane to the mixture of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal **15** and copper powder in cyclohexane provided the D-glucose-derived *β*–1,2-cyclopropanecarboxylate **16** in 92% yield as a single



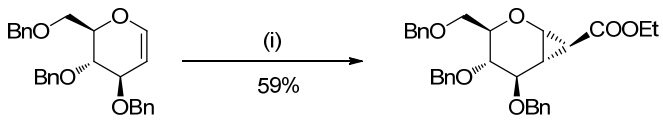
15 **16**

Reagents and Conditions: (i) Cu(0), $N_2CHCOOEt$ (EDA), cyclohexane, reflux, 12 h.

Scheme 1.8: Copper-mediated diazo-based cyclopropanation of glycal

diastereomer (Scheme 1.8).[27] This methodology gave the good yields with acetyl- and silyl-protected glycals but the low yields with benzyl-protected glycals (possibly carbenoid might have inserted into the aromatic rings of the benzyl groups).

Contrarily, Hoberg and co-workers described the *trans*-cyclopropanation of glycals with ethyl diazoacetate (EDA) by replacing the Cu(0) with dirhodium tetraacetate ($Rh_2(OAc)_4$).[28] A variety of α-1,2-cyclopropanecarboxylated sugars were synthesized by treating the differentially protected glycals with EDA in presence of $Rh_2(OAc)_4$ with good diastereoselectivity. The α-facial selectivity of the products is completely governed by steric factors of C-3 substituent. Concurrently, these studies and work was supported by the van Boom's report,[29] in which *trans*-cyclopropanation of a variety of glycals including disaccharide-based glycal was achieved with EDA and $Rh_2(OAc)_4$ in good yield (Scheme 1.9). All the cyclopropanated precursors for the synthesis of glyco-amino acids (chapter 2 in this thesis), were synthesized by following this reaction protocol.



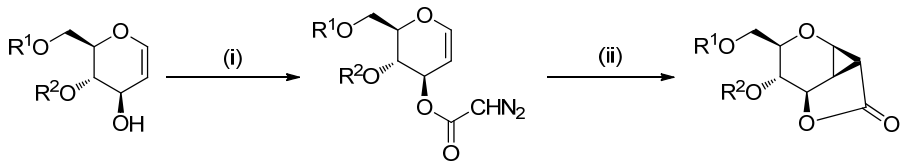
5 **17**

Reagents and Conditions: (i) $Rh_2(OAc)_4$, $N_2CHCOOEt$, CH_2Cl_2, rt, 1 h.

Scheme 1.9: Ethyl diazoacetate-mediated cyclopropanation using catalytic $Rh_2(OAc)_4$

Intramolecular Cyclopropanations

The literature reports on intramolecular cyclopropanation in carbohydrates are very scarce. The first example of intramolecular cyclopropanation in carbohydrates was reported by Pagenkopf group in which glycal-derived diazoacetate was cyclopropanated with EDA in presence of copper catalyst. Sugar derived diazo esters were prepared from glycals by using the Corey's modified procedure of intramolecular cyclopropanation of diazo acetates.[30] Treating a solution of glyoxylic acid chloride (*p*-toluenesulfonyl)hydrazone in CH_2Cl_2/DMF with glycals **18** and *N,N*-dimethylaniline/tri-ethylamine provided the corresponding glycal diazo acetates **19** in excellent yield. The resulted glycal diazo acetates under the catalysis of bis(N-tert-butylsalicylaldiminato)copper(II) [$Cu(TBS)_2$] were transformed to *β*-1,2-cyclopropanecarbo-xylated sugar derivatives **20** over 85% yield (Scheme 1.10).[31]



18a, $R^1 + R^2 = {}^tBu_2Si$ — **19a** (92%) — **20a** (92%)

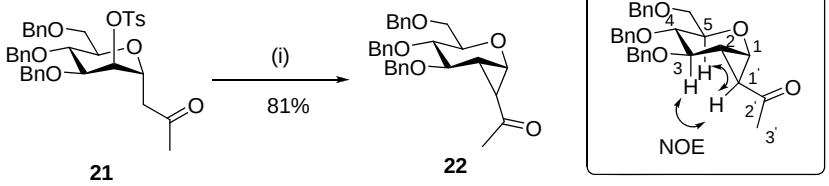
18b, $R^1 + R^2 = Me_2C$ — **19b** (88%) — **20b** (89%)

18c, R^1 = TBS, R^2 = Bn — **19c** (89%) — **20c** (86%)

***Reagents and Conditions*:** (i) (a) (i) *p*-tolSO_2NHNCHCOCl, Me_2NPh, CH_2Cl_2/DMF, 0 °C, 15 min; (ii) Et_3N; (b) $Cu(TBS)_2$, toluene, reflux, 14 h.

Scheme 1.10: Intramolecular cyclopropanation of glycal-derived diazoacetate

Recently, Shao *et al.* reported the synthesis of 1,2-cyclopropaneacetylated sugar derivative by base–mediated intramolecular S_N2 reaction of 2'-oxoalkyl 2-*O*-Ms(Ts)-*α*-C-mannopyranoside. D-Glucose-derived 1,2-cyclopropaneacetylate **22** was prepared by treating the 2'-ketone C-mannoside **21** with potassium carbonate in methanol over 81% yield. The product **22** was isolated as a single diastereomer and confirmed by the NOEs between H1' and H3 and H1' and H5 (Scheme 1.11).[33]



21 **22**

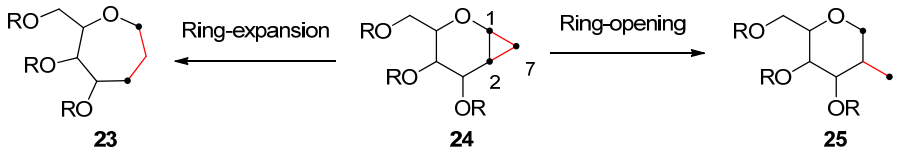
Reagents and Conditions: (i) K_2CO_3, MeOH, rt, 16h.

Scheme 1.11: Base-mediated intramolecular cyclopropanation

1.2.2 Ring–Opening of 1,2-Cyclopropanated Sugars

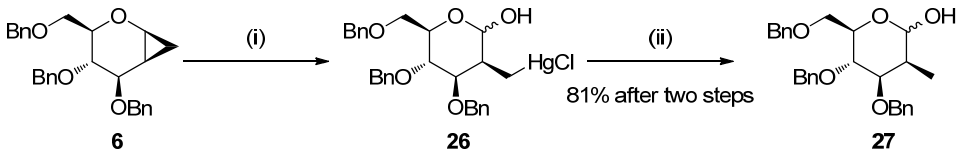
In recent years, 1,2-cyclopropanated sugars have great utility towards the synthesis of 2-C-branched carbohydrates as well as ring-expanded carbohydrates (carbohydrate–based oxepanes).[17] The cleavage of 1,7-bond provides the 2-C-branched derivatives where as the cleavage of 1,2-bond gives the oxepane derivatives (Scheme 1.12). Synthetic methods for the ring-opening of 1,2-cyclopropanated sugars are described in this section. 1,2-Cyclopropanated sugars have been served as pivotal synthetic scaffolds for the generation of

many challenging compounds and natural products and they have the potentiality to undergo the electrophilic ring-opening under various protic solvents /nucleophiles.[33]



Scheme 1.12: Ring-opening and ring-expansion of cyclopropanes

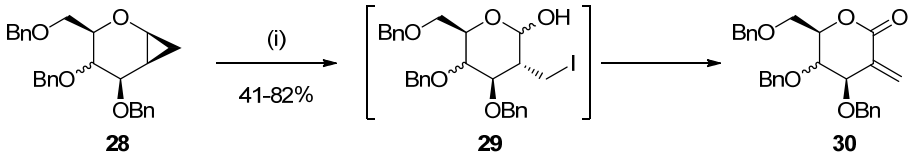
In this regard, Heathcock reported the first example of mercury mediated ring-opening of 1,2-cyclopropanated sugar. Treatment of sugar-derived cyclopropane **6** with mercury (II) trifluoromethanesulfonate in aqueous medium provided an organomercurial intermediate **26** as a mixture of anomers. Reductive removal of mercuric chloride with tributyltin hydride and AIBN afforded the 2-C-methyl carbohydrate **27** in excellent yield (Scheme 1.13).[34]



Reagents and conditions: (i) $Hg(OTf)_2$ H_2O/THF, NaCl, rt, 15 min; (ii) Bu_3SnH, AIBN, 35 min.

Scheme 1.13: Mercury-mediated ring-opening of 1,2-cyclopropanated sugar

In addition, Nagarajan and co-workers reported the ring-opening of the cyclopropanated sugars by using iodonium-di(*s*-collidine)perchlorate in dioxane/water to produce *α*-methylidenevalerolactones **30** in yields ranging from 41 to 82%.[35] The reaction was proceeded *via* an intermediate iodide **29**, which upon elimination followed by oxidation gave **30** (Scheme 1.14).

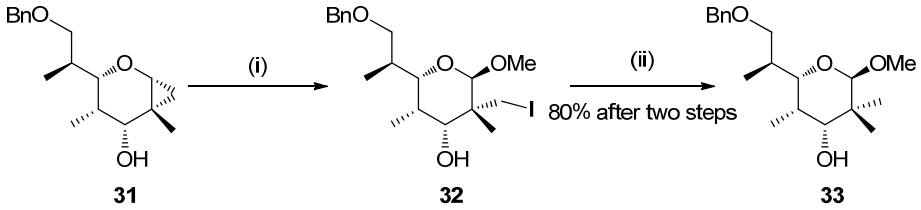


Reagents and Conditions: (i) $[s\text{-collodine}]_2I^+ClO_4^-$, dioxane/water, 70 °C.

Scheme 1.14: Synthesis of *α*-methylidenevalerolactones from the 1,2-cyclopropanes

Interestingly, Danishefsky and co-workers described a new strategy for the ring-opening of sugar cyclopropanes in presence of *N*-iodosuccinimide (NIS) in methanol. Treatment of

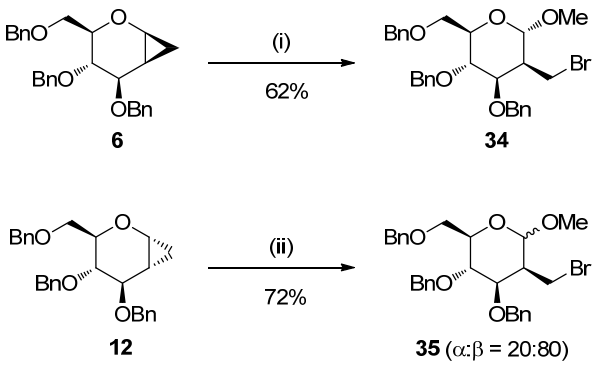
glycal-derived cyclopropane **31** with excess NIS in methanol afforded the iodomethyl compound **32**, which was reduced with tributyltin hydride to give methyl glycoside **33** in 80% yield (Scheme 1.15).[36,37] The product **33** was further utilized in the synthesis of natural products epothilone A and B.



Reagents and Conditions: (i) NIS, MeOH, rt, 8 h; (ii) Bu_3SnH, AIBN, PhH, reflux.

Scheme 1.15: Ring-openig of 1,2-cyclopropanated sugar reported by Danishefsky

Several groups applied this strategy to various 1,2-cyclopropanated sugar derivatives with different type of electrophlies to get the 2-C-branched derivatives. In this aspect, Nagarajan *et al.* reported the ring-opening of different diastereomers of glycal-derived cyclopropanes with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS). Interestingly, they found that 1,2-cyclopropanated sugar **12** reacted fast and provided **35** in good yield with



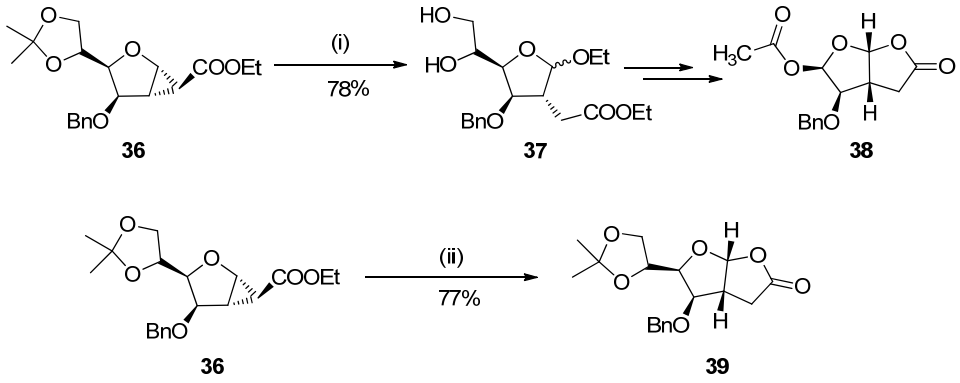
Reagents and conditions: (i) NBS, MeOH, 0 °C, 24 h; (ii) NBS, MeOH, 0 °C, 8 h.

Scheme 1.16: Solvolytic ring-opening of 1,2-cyclopropanated sugars

anomeric mixture. On the other hand, cyclopropanated sugar **6** reacted slowly and yielded **34** as a single diastereomer in moderate yield. The selectivity of the reactions were explained that cyclopropane **6** provided **34** by following S_N2 path way and contrarily, anomers **35** were formed by the S_N1 path way from cyclopropane **12** (Scheme 1.16).[24]

Ring-opening of cyclopropanated sugars under the acid medium was also attempted to get corresponding 2-C-branched sugar derivatives. Initially, Hoberg synthesized the 2-C-branched glycosyl bromide by the ring-opening of 1,2-cyclopropanecarboxylated sugar derivative with HBr/AcOH in only 38% yield.[28] Ring-opening of cyclopropanated sugars under the strong acidic conditions resulted the low yields in many cases.

However, in 1999, Theodorakis group utilized the acid-mediated ring-opening of 1,2-cyclopropanecarboxylated sugars for the construction of norrisolide side chain in a setereoselective manner.[38] 1,2-Cyclopropanecarboxylated sugar **36** was treated with dilute ethanolic solution of sulfuric acid to provide the 2-C-branched furanose derivative **37**, which could be transformed into main fragment **38** of norrisolide in two steps. Subsequently, the same group developed the one-step protocol for the synthesis of linearly fused bicycle **39** from the 1,2-cyclopropanecarboxyalted sugars with methanesulfonic acid in acetone (Scheme 1.17).[39] The methodology was applied to various 1,2-cyclopropanated sugars to get the bicyclolactones with high diastereoselectivity.

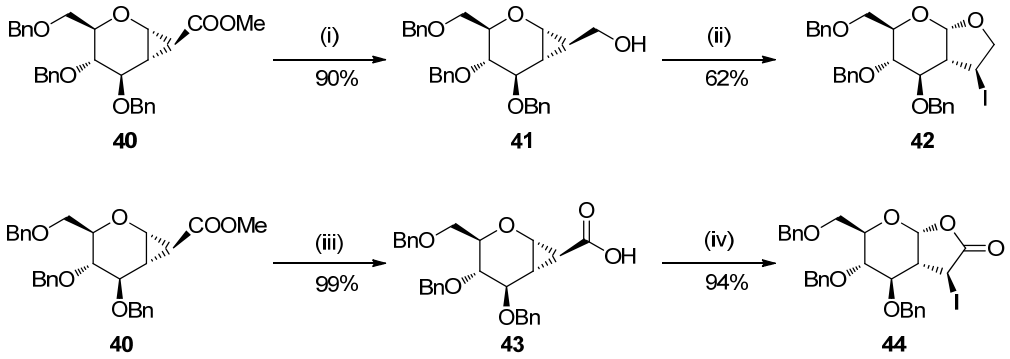


Reagents and Conditions: (i) EtOH, 0.8 M H_2SO_4, rt, 48 h; (ii) $MeSO_3H$, acetone, rt, 16 h.

Scheme 1.17: Acid-mediated ring-opening of 1,2-cyclopropanecarboxylated sugars

The elegant protocol for the synthesis of bicyclolactones was reported by Chandrasekaran group. In this strategy, fused perhydrofuro[2,3-*b*]pyrans (and furans) and perhydrofuro[2,3-*b*]pyrano-*γ*-butyrolactones were synthesized by ring-opening of 1,2-cyclopropanecarboxylated sugars in presence of electrophile. Reduction of ester group in 1,2-cyclopropanecarboxylated sugar **40** with $LiAlH_4$ provided the cyclopropanated alcohol **41**, which was taken forward to the NIS-mediated ring-opening in the absence of external

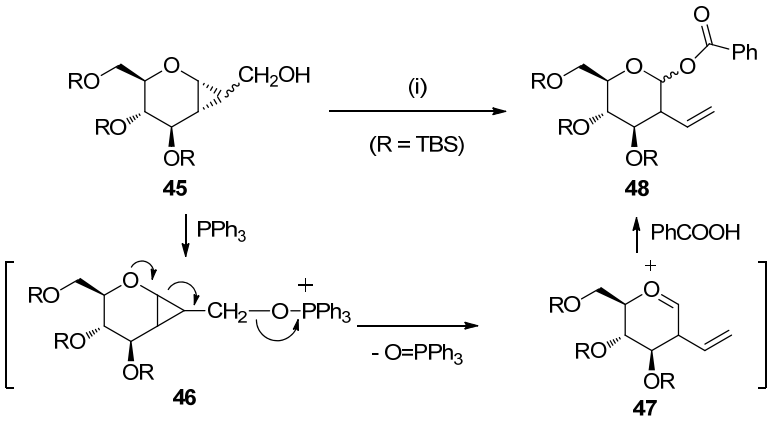
nucleophile, to afford the fused perhydrofuro[2,3-*b*]pyran **42** in excellent yield. Similarly, linear perhydrofuro[2,3-*b*]pyrano-*γ*-butyrolactone **44** was synthesized by NIS-mediated ring-opening of sugar–derived cyclopropanecaboxylic acid **43**, that obtained from the base-hydrolysis of the 1,2-cyclopropanecarboxylated sugar **40** (Scheme 1.18).[40]



Reagents and Conditions: (i) LAH, ether, 0 °C; (ii) NIS, CH_2Cl_2, rt, 36 h; (iii) LiOH, THF/MeOH; (iv) NIS, CH_3CN, rt, 10 h.

Scheme 1.18: Synthesis of fused bicycles by ring-opening of 1,2-cyclopropanecarboxylated sugar derivatives

In addition to the above methodologies, 1,2-cyclopropanated sugars were also involved in rearrangements to produce the important 2-C-branched derivatives. In 1995, Henry and Fraser-Reid synthesized the 2-C-vinyl-glycsosides **48** from the 1,2-cyclopropanated sugar **45**

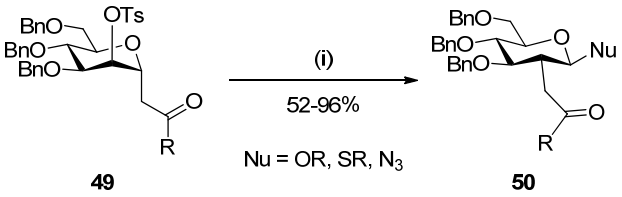


Reagents and Conditions: (i) PPh_3, DEAD, PhCOOH, THF, rt

Scheme 1.19: 2-C-vinyl glycosides through the rearrangement of 1,2-cyclopropanated sugars

by adopting the standard Mitsunobu conditions in over 90% yield. The reaction gave the anomeric mixture with 1:1 to 2.7:1 (Scheme 1.19).[27]

Recently, Zou and co-workers reported the 1,2-migration of 2'-oxoalkyl group *via* 1,2-cyclopropanated sugars under the basic conditions with mesyl (Ms) or tosyl (Ts) as leaving groups. 2'-oxoalkyl 2-*O*-Ms(Ts)-*α*-C-mannoside **49** under the basic medium formed the 1,2-cyclopropanated sugar intermediate with the elimination of leaving group. The cyclopropane intermediate underwent ring-opening by various alcohols, thiols, azides to afford 2-C-branched *O*-, *S*-glycosides and glycosyl azides in excellent yields (Scheme 1.20).[30,41]



Reagents and Conditions: (i) Base (Et_3N or K_2CO_3), Nu-H, rt, 16 h.

Scheme 1.20: Synthesis of 2-C-acetonyl glycosides *via* ring-opening of 1,2-cyclopropanated sugar intermediate.

Synthesis of 2-C-branched glyco-amino acids by ring-opening of 1,2-cyclopropanated sugars is described in section 1.3.1 in this chapter. Few of the 1,2-cyclopropanated sugars were utilized as glycosyl donors for the construction of disaccharides. The ring-opening of cyclopropanated sugar as glycosyl donors is discussed in section 1.5.1 in this chapter.

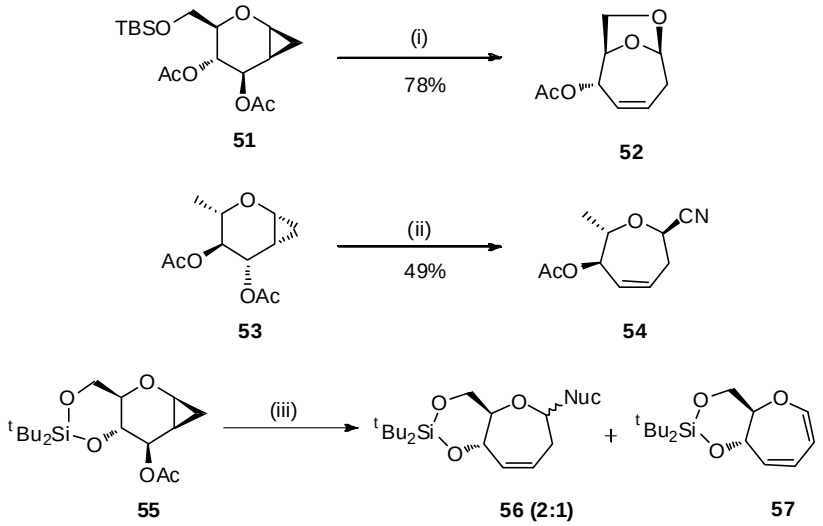
1.2.3 Ring-Expansion of 1,2-Cyclopropanated Sugars

In recent years, methods for the ring-expansion of 1,2-cyclopropanated sugars have been extensively investigated. The ring-expanded carbohydrate skeletons are present in many natural products.[42,43] Few methods for the ring-expansion of 1,2-cyclopropanated sugars are discussed below.

Ring-Expansion of Simmons-Smith–Derived Cyclopropanes

Initially, Hoberg observed the ring-expansion of cyclopropanated sugars under the Lewis acid catalysis *via* Ferrier type rearrangement. The seven- membered oxacycle (oxepine) **52** was obtained by treating 1,2-cyclopropanated sugar **51** with TMSCN and TMSOTf in acetonitrile. The deprotection of silyl group followed by attack of C6-hydroxyl group in an intramolecular fashion was observed rather than the attack of cyanide group at anomeric position. To avoid the intramolecular attack of the nucleophile, they carried out the reaction

with 6-deoxy cyclopropane derivative **53** and succeeded to produce the oxepine derivative **54** in moderate yield (Scheme 1.21).[21] Recently, they have reported improved strategy by changing the protecting group for the C-6 alcohol. The silyl–protected cyclopropane sugar **55**[44] was treated under the TMSOTf with various silylated nucleophiles to provide the oxepine derivatives **56** in yields ranging from 67% to 93% and 2:1 diastereoselectivity. A side product in this reaction was observed as diene **57** with (0 to 12%) very low yield (Scheme 1.21).[45]



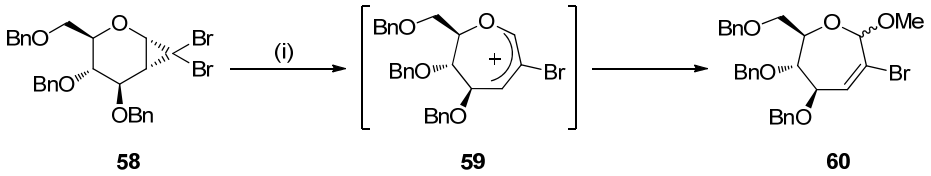
Reagents and Conditions: (i) TMSCN, 10 mol% TMSOTf, CH_3CN; (ii) TMSCN, 40 mol% TMSOTf, CH_3CN; (iii) TMSOTf, R_3SiNuc, CH_3CN

Scheme 1.21: Synthesis of oxepine derivatives reported by Hoberg

Ring-Expansion of Dihalocarbene–Derived Cyclopropanes

The ring-expansion of dihalocyclopropanated sugar derivatives under the basic conditions gave the interesting halo-oxepine derivatives which were further transformed to oxepine derivatives and septanoses. Initially, Nagarajan *et al*. reported the oxepine derivatives from the ring-expansion of 1,2-*gem*-dihalocyclopropanated sugars under the solvolysis conditions. The reaction is believed to occur through the loss of an *endo* halogen to provide the allyl cation, which is then captured by a nucleophilic solvent like methanol. Treatment of 1,2-*gem*-dibromocyclopropane sugar **58** with excess K_2CO_3 in methanol under reflux conditions

provided the 2-bromooxepine derivatives **60** as an anomeric mixture in 67% yield (Scheme 1.22).[19] The oxepine anomers could be separated by silica-gel column chromatography.

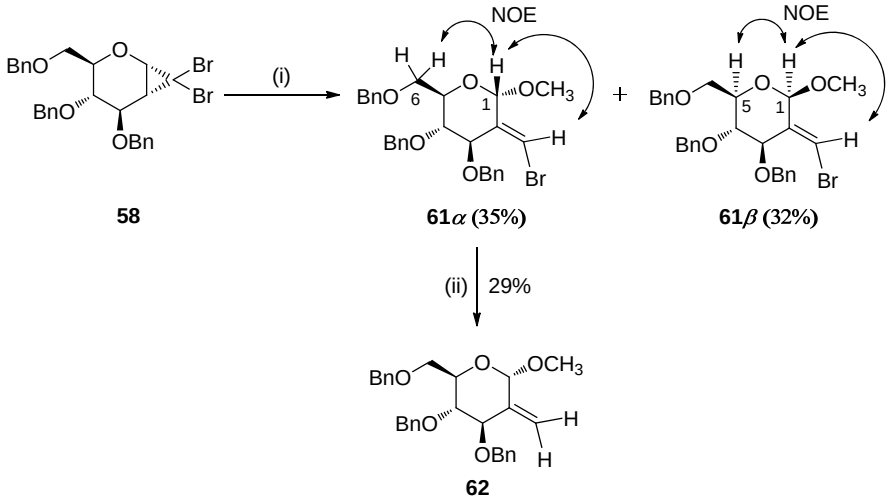


58 **59** **60**

Reagents and Conditions: (i) K_2CO_3, MeOH, reflux, 12 h.

Scheme 1.22: Ring-expansion of 1,2-*gem*-dibromocyclopropanated sugar

In 2010, Harvey and co-workers repeated the above reaction and revised the products as the 2-C-branched pyranosides **61** rather than 2-bromooxepines **60**[19]. The structures of these 2-C-branched pyranosides were deduced on the basis of NOE enhancements between H-1 and H-5 in minor product **61*β*** and between H-1 and H-6 in major product **61**α.[46] The major 2-C-branched bromide **61**α was treated with *n*-BuLi/THF and water to produce 2-C-methylene *α*-pyranoside **62** (Scheme 1.23). The spectra of **62** match with those previously reported.[47] By these observations, the authors strongly revised the products as 2-C-branched pyranosides rather than 2-bromooxepines.

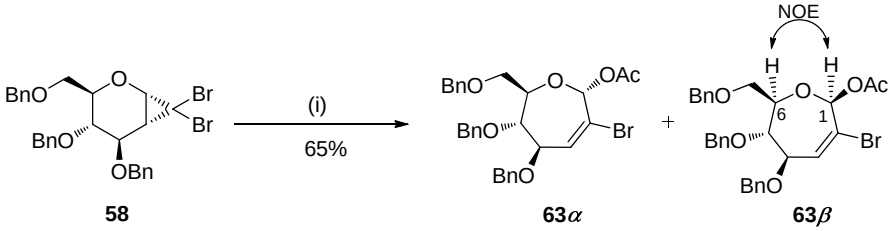


58 **61*α*** **(35%)** **61*β*** **(32%)** **62**

Reagents and Conditions: (i) K_2CO_3, MeOH, reflux, 12 h; (ii) (a) BuLi, THF, -78 ^oC, 1h, (b) H_2O.

Scheme 1.23: Revised products from the base-mediated reaction of 1,2-*gem*-dibromocyclopropanated sugar

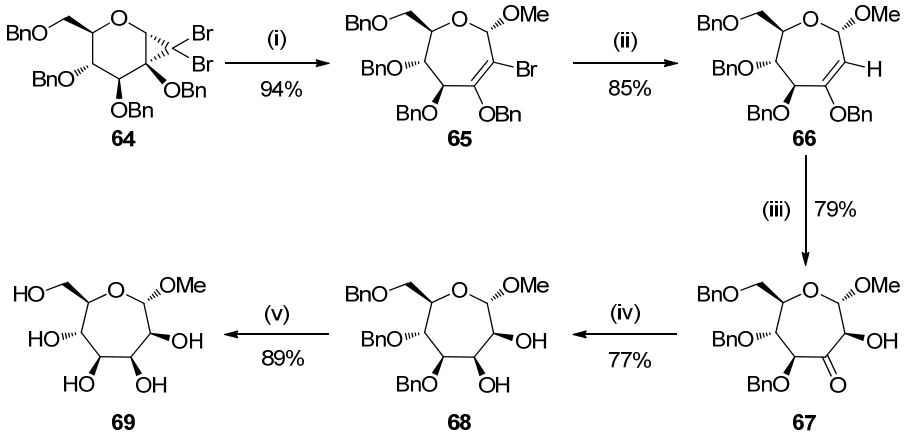
However, they were able to synthesize the 2-bromooxepines by the ring-expansion of 1,2-cyclopropanated sugars under catalytic silver (I) salt and sodium acetate. Treatment of *gem*-dibromocyclopropane sugar derivative **58** with sodium acetate and silver acetate in toluene under reflux conditions provided the 2-bromooxepine derivatives **63**α and **63*β*** in 65% yield with moderate selectivity (α:*β* = 4.3:1). The stereochemistry of oxepine derivatives was assigned on the basis of an NOE enhancement between H-1 and H-6 in the minor isomer **63*β*** (Scheme 1.24).[46]



Reagents and Conditions: (i) AgOAc, NaOAc, toluene, reflux, 28 h.

Scheme 1.24: Silver-promoted ring-expansion of 1,2-*gem*-dibromocyclopropanated sugar

In order to extension of ring-expansion methods, in 2007, Jayaraman *et al.* reported the base-mediated ring-expansion of hydroxyglycal-derived 1,2-*gem*-dibromocyclopropanes towards the synthesis of septanoside derivatives. The treatment of 1,2-*gem*-dibromocyclopr-

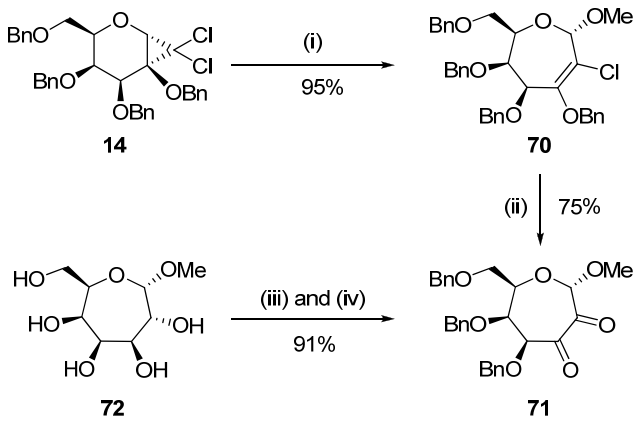


***Reagents and Conditions*:** (i) NaOMe/MeOH, PhMe, reflux, 8 h; (ii) (a) *n*-BuLi, THF, -78 ^{o}C, 1 h, (b) MeOH, rt; (iii) Oxone, aq. $NaHCO_3$, acetone, 0 ^{o}C to rt, 10 h; (iv) $NaBH_4$, MeOH, 0 ^{o}C, 2 h; (v) H_2, Pd/C, MeOH, rt, 10 h

Scheme 1.25: Synthesis of septanosides through the ring-expansion of 1,2-cyclopropanated sugars

-opanated sugar derivative **64** with sodium methoxide in toluene provided the 2-bromooxepine derivative **65** in an excellent yield as a single diastereomer. On reacting **65** with *n*-BuLi/THF followed by quenching with MeOH afforded the oxepine derivative **66**, which has been converted to the 2-hydroxyketone derivative **67** under alkaline reaction conditions with oxone in a good yield. Reduction of **67** with $NaBH_4$/MeOH produced the partially benzyl-protected septanoside **68** with high selectivity. The deprotection of benzyl groups by hydrogenolysis furnished the D-*glycero*-D-*talo*-septanoside **69** in a good yield (Scheme 1.25).[25]

Additionally, the authors were able to synthesize the D-*glycero*-L-*altro*-septanoside **72** from the solvolytic ring-expansion of D-galactose–derived-1,2-*gem*-dichlorocyclopropane **14** as a single diastereomer. Towards the synthesis of septanoside **72**, the 2-chlorooxepine derivative **70** directly converted to the diketo-oxepine **71** by the oxidation with *in situ* generated RuO_4. The sequential reduction and hydrogenation of **71** provided the septanoside **72** in excellent yield (scheme 1.26).[25]

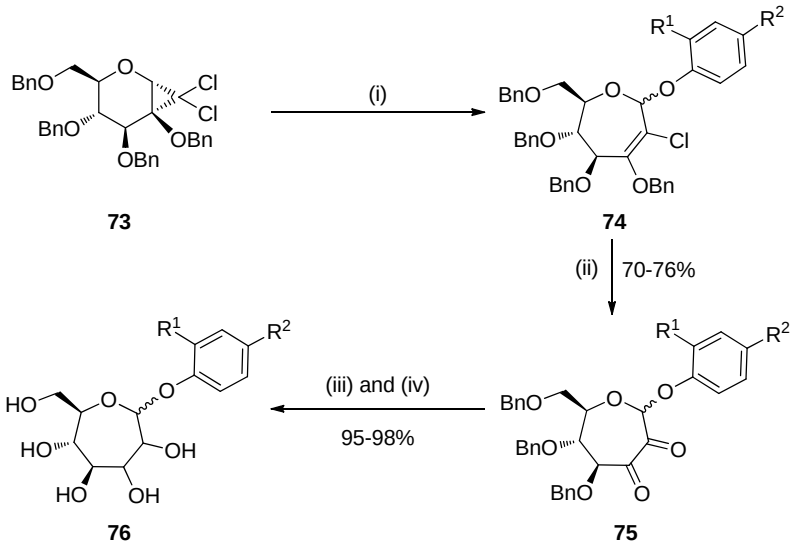


***Reagents and Conditions*:** (i) NaOMe/MeOH, dioxane, reflux, 2 d; (ii) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, CCl_4, 8 h; (iii) $NaBH_4$, MeOH, 0 ^oC, 2 h; (iv) H_2, Pd/C, MeOH, rt, 10 h.

Scheme 1.26: Synthesis of septanosides through the solvolytic ring-expansion of 1,2-cyclopropanated sugar derivatives

Recently, they have successfully extended the above strategy in the synthesis of aryl and azido septanosides in excellent yields with moderate diastereoselectivity. The reaction of phenol-based derivatives with 1,2-*gem*-dichlorocyclopropanated sugar derivative **73** in toluene, in presence of K_2CO_3 and 18-C-6, afforded the chloro-arylseptanoside derivative **74**

in yields ranging from 76 to 85% as anomeric mixtures. The chlorooxepines **74** reacted under sequential RuO_4-mediated oxidation, reduction and global deprotection of benzyl groups to produce the clean aryl septanosides **76** as a mixture of anomers and epimers, most of which could be separated by column chromatography (Scheme 1.27).[48]



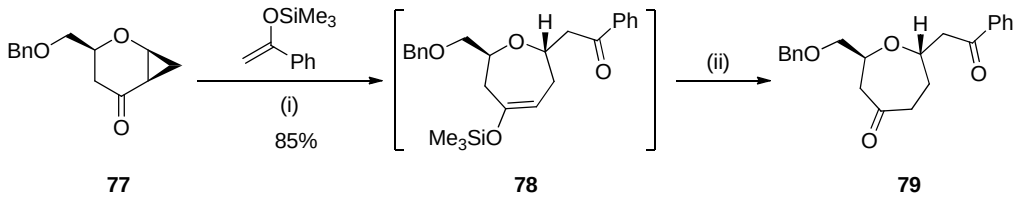
Reagents and Conditions: (i) Phenol derivatives, K_2CO_3, toluene, reflux, 2-3 d; (ii) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, 1-4 h; (iii) $NaBH_4$, MeOH, rt, 2 h; (iv) H_2, Pd/C, MeOH/EtOAc, rt, 10-12 h.

Scheme 1.27: Aryl septanosides from the ring-expansion of 1,2-cyclopropanated sugars with phenol derivatives

In addition, they also synthesized an amino-septanoside from the ring-expansion of *gem*-dichlorocyclopropane sugar with NaN_3/DMF followed by sequential steps of oxidation, reduction and Staudinger reaction conditions.

In 2001, Sugita and co-workers reported the Lewis acid promoted ring-expansion of novel cyclopropapyranones towards the synthesis of 4-oxepenone derivatives. The reaction between the 3-benzyloxymethylcyclopropapyran-5-one **77** and silyl enolate in presence of $BF_3{\cdot}OEt_2$ in dichloromethane provided the oxepanone derivative **79** in moderate yields with good diastereoselectivity (Scheme 1.28). After optimization of reaction conditions with different Lewis acids, $BF_3.OEt_2$ was found to the best catalyst for performing the reactions with good yields and selectivity. Various oxepane derivatives were synthesized by using the different cyclopropapyranones and silyl enolates in moderate to good yields.[49]

Ring-expansion and glycosylation of 1,2-*gem*-dihalocyclopropanated sugars is discussed in section 1.5.2 in this chapter.



Reagents and Conditions: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 ^oC, 30 min. (ii) 1N HCl, THF

Scheme 1.28: Ring-expansion of cyclopropapyranones with silyl enolate

1.3 2-C-Branched Glyco-Amino Acids (GAAs)

Sugar amino acids (SAAs)[50,51] are the carbohydrates in which the carboxylate and the amino groups are directly attached to two different carbon atoms of the pyranose or furanose rings. In this category, sialic acids with *N*-acetylneuraminic acid (Neu5Ac or NANA) are the most important compounds in a large class of biologically important compounds.[52,53] The synthesis and transformations of these SAA were extensively developed. Some of naturally occurring SAAs exhibit the important herbicidal and antibiotic activities.[54] SAA oligomers are also synthesized and used for the understanding of the bio-(macro)-molecular assemblies.[55]

The glyco-amino acids (GAAs) are other important class of the unnatural sugar-derived molecules in which the entire α-amino acid skeleton is directly linked to carbohydrate through any covalent bond.[56] In other way, the GAA is a saccharide attached to the single amino acid by any kind of covalent bonding. These GAAs are substantial building blocks for

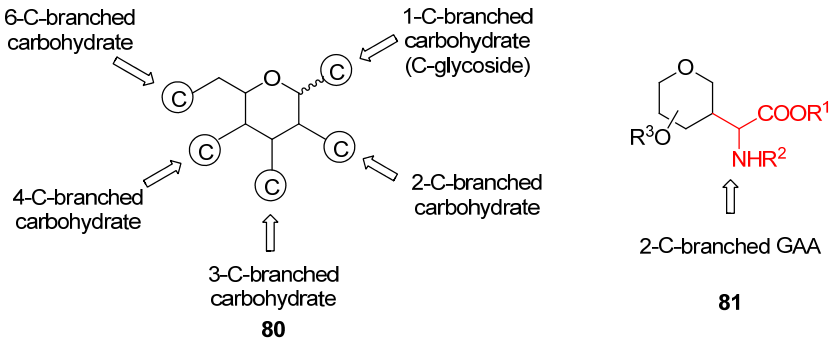


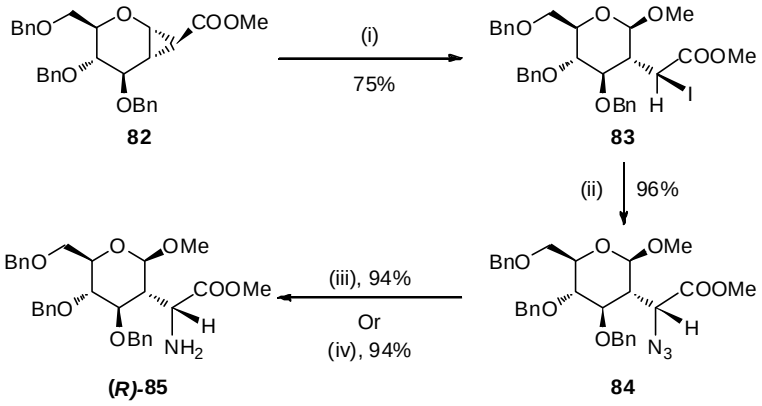
Figure 1.1: General structures of C-branched carbohydrates

the glycoconjugates, glycopeptides and glycoproteins, which play essential roles in many biological transformations.[57]

GAAs can be derivatized and oligo-merized into compound libraries through well-established automated peptide protocols. The classification, synthesis and derivatization of these GAAs have been well documented in the literature.[58] C-Branched (Figure 1.1, structure **80**) GAAs are used in the development of glycopeptide-based drugs with improved pharmacokinetic properties. In recent years, stereoselective construction of 2-C-branched GAA derivatives (Figure 1.1, structure **81**) has been exigent for the organic chemists due to their mimicking nature in many biological transformations.

1.3.1 Synthesis of 2-C-Branched Glyco-Amino Acids

A few synthetic methods for the construction of 2-C-branched glyco-amino acids (GAAs) have been reported in the literature. Initially, in 2004, Chandrasekaran *et al*. reported the first and efficient methodology for the synthesis of 2-C-branched GAA derivatives by diastereoselective ring-opening of 1,2-cyclopropanecarboxylated sugars in good yields. Solvolytic ring-opening of diazo-based cyclopropane sugar derivative **82** with NIS/MeOH provided the sugar-derived ring-opened iodide **83** as a single diastereomer in 75% yield. The **83** was converted to azidocarboxylate **84** with NaN_3 in DMF in 96% yield. The reduction of

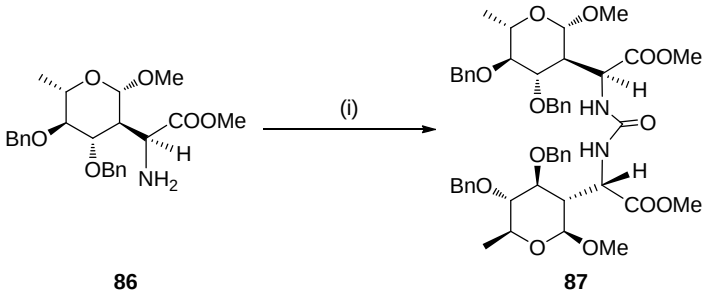


Reagents and Conditions: (i) NIS, MeOH, rt, 8 h; (ii) NaN_3, DMF, rt, 24 h; (iii) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h; (iv) MoS_4^{2-}, CH_3CN, rt,))))), 6 h.

Scheme 1.29: Synthesis of 2-C-branched GAA derivative by ring-opening of 1,2-cyclopropanecarboxyalted sugars

azide **84** using the $PPh_3/THF/H_2O$ (Staudinger reaction conditions) provided the 2-C-branched glyco-amino acid derivative **85** in 95% yield as a single diastereomer (Scheme 1.29).[59]

The reduction of azide to amine was also effectively achieved by using benzyltriethylammonium tetrathiomolybdate in excellent yield.[60] The methodology was well demonstrated by using different 1,2-cyclopropanecarboxylated sugars to produce the 2-C-branched GAA derivatives in good to excellent yields with high diastereoselectivity. The GAA derivative **86** was further utilized for the synthesis of GAA-based urea derivative **87** in presence of phosgene. The authors deduced the stereochemistry of all synthesized 2-C-GAA derivatives based on X-ray crystallographic analysis of urea derivative **87** (Scheme 1.30).

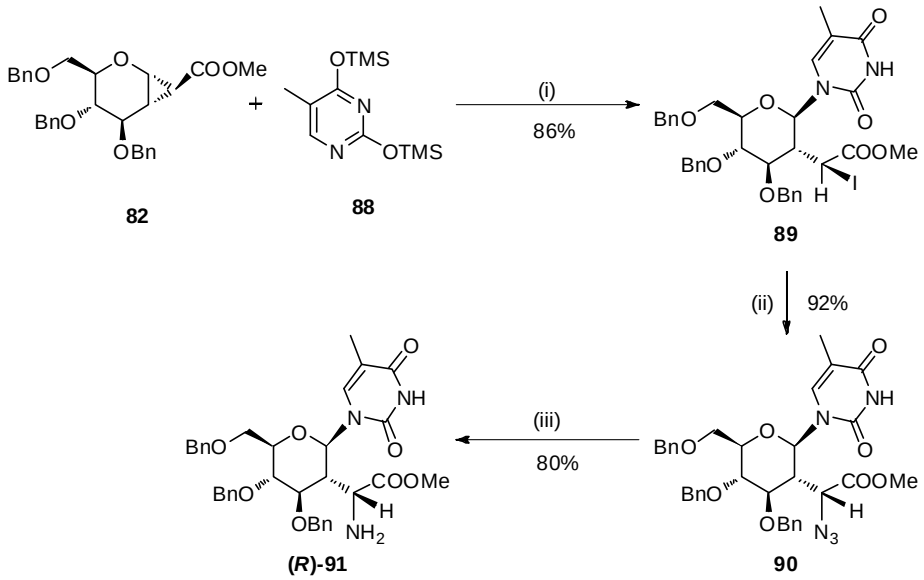


Reagents and Conditions: (i) $COCl_2$, Et_3N, CH_2Cl_2, 0 °C.

Scheme 1.30: GAA-based urea derivative reported by Chandrasekaran

Additionally, the same group extended their methodology to synthesis of unnatural 2-C-branched amino acid nucleosides by ring opening of 1,2-cyclopropanecarboxylated sugars with silylated nucleobases.[61] Treatment of D-glucose-derived 1,2-cyclopropanecarboxylate **82** with NIS and trimethylsilyl-activated thymine [thymine (2TMS)] **88** in dichloromethane provided the 2-C-branched iodocarboxylate with nucleobase **89** as a single anomer with *β*-configuration in 82% yield. The iodide **89** was converted to corresponding azide **90** with NaN_3 in DMF. The azide **90** under the Staudinger conditions gave the amine **91** with very low yield. After screening the reducing agents for the azide **90**, zinc-mediated reduction (Zn/AcOH-THF) provided the 2-C-branched amino acid nucleoside **91** in excellent yield (Scheme 1.31). The structure and stereochemistry of these interesting nucleosides was deduced based on the crystal structure of **90**. The methodology was utilized to prepare furanosyl amino acid nucleosides, which have potential applications in the development of

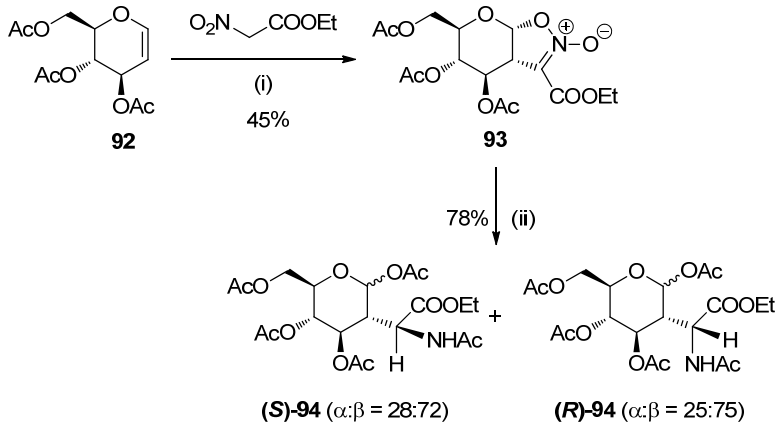
novel nontoxic antifungal therapeutics. The method also applied to various 1,2-cyclpropanated sugars and different bases to afford the 2-C-branched nucleosides in excellent yield with high diastereoselectivity.



Reagents and Conditions: (i) NIS, CH_2Cl_2, rt, 48 h; (ii) NaN_3, DMF, rt, 24 h; (iii) Zn, AcOH-THF (1:1), rt, 3 h.

Scheme 1.31: Synthesis of 2-C-branched amino acid nucleosides by ring-opening of 1,2-cyclopropanecarboxyalted sugars

Concurrently, Linker *et al.* reported the stereoselective synthesis of 2-C-branched GAA derivatives from the glycals in three steps with good yields. In this strategy, the addition of

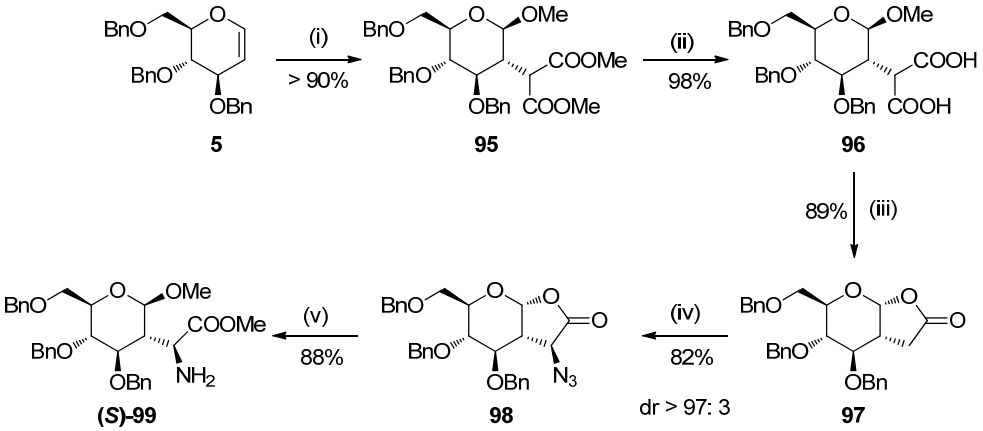


Reagents and Conditions: (i) CAN, DMF, 0 ^oC; (ii) (a) Al-Hg, (b) Ac_2O/py.

Scheme 1.32: Synthesis of 2-C-branched GAA derivatives from the transition-metal mediated radical reaction

ethyl nitroacetate to 2,4,6-tri-*O*-acetyl-D-glucal **92** in presence of ceric (IV) ammonium nitrate (CAN) provided the only *cis*-bicyclic isoxazoline *N*-oxide derivative **93** in moderate yield. After several attempts for the reduction of isoxazoline *N*-oxide **93**, aluminum amalgam gave the pure 2-C-branched GAA derivatives (*S*)-**94** and (*R*)-**94** in good yields with moderate diastereoselectivity (Scheme 1.32).[62] The stereochemistry of the major products obtained in this methodology is the opposite configuration of Chandrasekaran's 2-C-branched GAA derivatives. This method was also applied to the three more glycals to get the amino acid derivatives as a mixture of diastereomers.

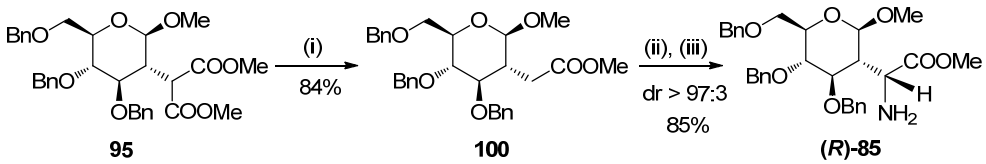
Furthermore, in 2009, Linker reported the elegant synthesis of 2-C-branched GAA derivatives from glycals. The 2-C-branched sugar derivative **95** was prepared from the 2,4,6-tri-*O*-benzyl-D-glucal **5** and dimethyl malonate in presence of CAN in good yield with high diastereoselectivity. Saponification of **95** with LiOH afforded the malonic acid-based sugar **96**, which was heated at 110 ^{o}C in toluene to provide the sugar lactone **97** in good yield. The reaction of the lactone **97** with trisyl azide in presence of base produced the azide-based lactone **98**, which was treated with $Sc(OTf)_3$ to give the 2-C-branched azidocarboxylated sugar derivative in excellent yield as a single diastereomer (Scheme 1.33).[63,64] The reduction of azide under the Staudinger reaction conditions provided the clean 2-C-branched GAA derivative **99**. The stereochemistry of amino acid derivative (*S*)-**99** is also contrary to Chandrasekaran's GAA derivative.



Reagents and Conditions: (i) dimethyl malonate, CAN, MeOH, 0 ^{o}C; (ii) LiOH, IR-120; (iii) toluene, 110 ^{o}C; (iv) (a) KHMDS, THF, -78 ^{o}C, (b) trisyl azide; (v) (a) $Sc(OTf)_3$, MeOH, 0 ^{o}C, (b) PPh_3/THF/H_2O, reflux, 16 h.

Scheme 1.33: Synthesis of 2-C-branched GAA derivative reported by Linker

Additionally, they also synthesized (*R*)-2-C-branched GAA derivative from the 2-C-branched-diester derivative **95** in two steps with high diastereoselectivity. The decarboxyaltion of diester derivative **92** with LiI in DMSO at 180 ^{o}C provided the 2-C-branched ester **100** in 84% yield. Finally, one-pot α-deprotonation and azidation of the ester **100** with KHMDS and trisyl azide respectively at low temperature afforded the (*R*)-2-C-branched GAA derivative **85** in excellent yield with high diastereoselectivity (Scheme 1.34).[63,64]



Reagents and Conditions: (i) LiI, DMSO, 180 ^{o}C, 84%; (ii) (a) KHMDS, CH_3I, THF, -78 ^{o}C, (b) trisyl azide, 85%; (iii)) PPh_3/THF/H_2O, reflux, 16 h.

Scheme 1.34: Synthesis of (*R*)-2-C-branched GAA derivative reported by Linker

1.4 Seven-Membered Cyclic Sugars or Septanoses

The seven-membered cyclic sugars are called as septanoses/carbohydrate–based oxepanes[65] (like furanoses and pyranoses for five and six membered sugars respectively). By the structural similarities with natural carbohydrates, the unnatural septanoses are expected to exhibit the interesting physical, chemical and biological properties. Moreover, these possess interesting biological activity.[66]

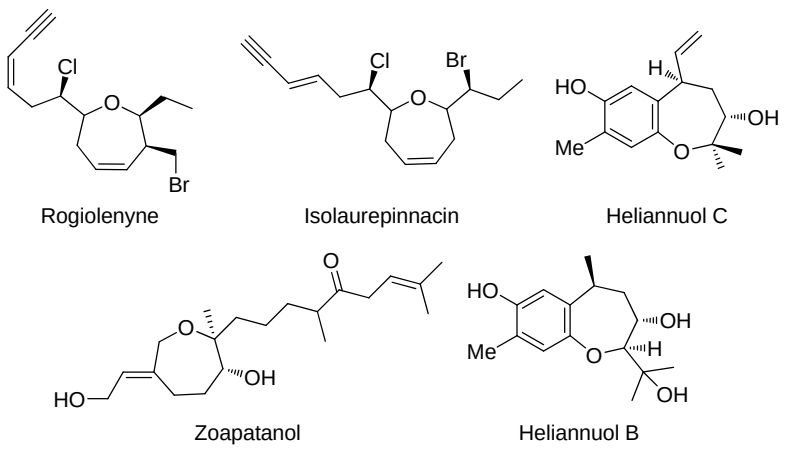


Figure 1.2: Natural products containing oxepine ring

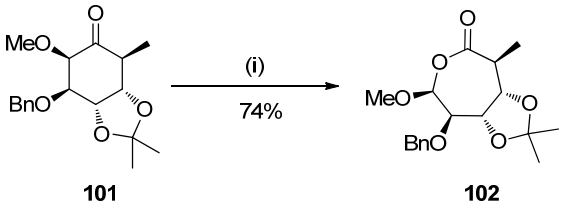
The seven-membered oxepine derivatives are present in many monocyclic natural products like zoapatanol,[67] isolaurepinnacin,[68] rogiolenyne,[69] heliannuol B[70] and C and so on (Figure 1.2).

1.4.1 Synthesis of Septanose Monosaccharides

The interest in developing methods for the synthesis of septanoses in organic chemistry has steadily increased in recent years. One of the methods for the synthesis of septanose monosaccharides is the ring-expansion of cyclopropanated sugars that is discussed in the section 1.2.3. Apart from the ring-expansion method, important methods for the synthesis of septanoses are described below.

Baeyer-Villiger Oxidation of Polyhydroxycyclohexanones

The Baeyer-Villiger oxidation of unsymmetrical polyhydroxycyclohexanone derivatives with *meta*-chloroperoxybenzoic acid (*m*-CPBA) in presence of $KHCO_3$ provided the septano-lactones in good yields with high regioselectivity.[71] Reaction of polyhydroxyketones with a methyl group at α and an ether or ketal at α' positions gave the products with the C-O linkage migration from the ketone (Scheme 1.35). The applicability of the method was determined by converting various polyhydroxycyclohexanones to septano-lactones as a single regioisomer. The reason for the regioselectivity in the oxidation might be lone pair electrons on the oxygen attached to the α-carbon play important role for migration.



101 **102**

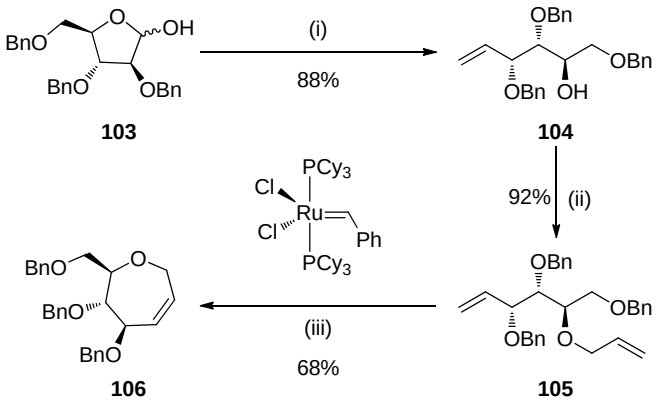
Reagents and Conditions: (i) *m*-CPBA, $KHCO_3$, rt, 2 h.

Scheme 1.35: Synthesis of septano-lactone from the Bayer-Villiger oxidation of polyhydroxycyclohexanone

Ring-Closing Metathesis (RCM) approach

In 1998, van Boom and co-workers reported the ring-closing metathesis (RCM) of allyl-*O*-vinyl derivatives towards the carbohydrate-based oxepines. The synthesis involved Wittig homologation of a protected furanose followed by formation of allyl ether and ring-closing

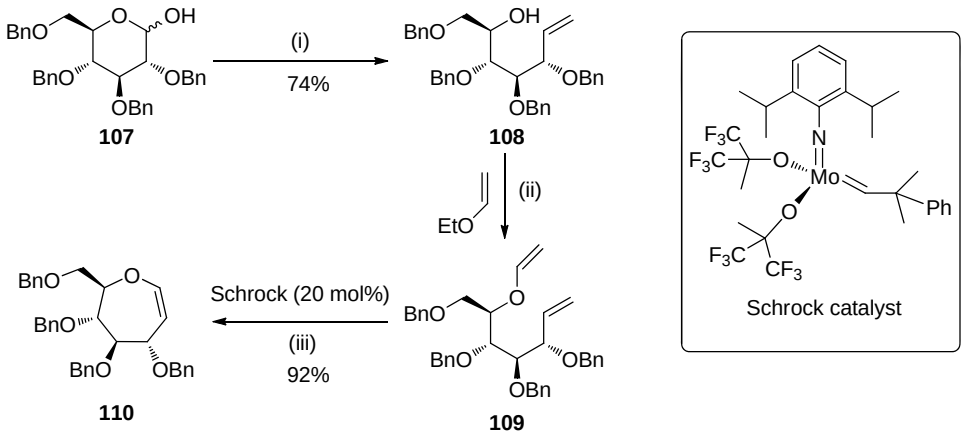
metathesis to give the septanose derivatives in good to moderate yields.[72] The 2,3,5-tri-*O*-benzyl-D-arabinofuranose **103**, under the Wittig reaction conditions provided the olefin derivative **104** which gave the allyl-*O*-vinyl derivative **105** by allylation with allyl bromide. The treatment of **105** with Grubbs 1st generation catalyst in toluene at 50 °C provided the septanose derivative **106** in good yield (Scheme 1.36).



Reagents and Conditions: (i) $Ph_3P^+MeBr^-$, *n*-BuLi, THF; (ii) allylBr, NaH, DMF; (iii) PhMe, 50 °C, 24 h.

Scheme 1.36: Synthesis of carbohydrate-based oxepine by RCM approach

In 2003, Peczuh and Snyder applied the above methodology to the glucopyranose to synthesis of septanal (ring expanded glycal).[73] Initially, the olefin **108** was synthesized from 2,3,4,5-tetra-*O*-benzyl-D-glucose **107** using the Wittig olefination procedure. The enol ether



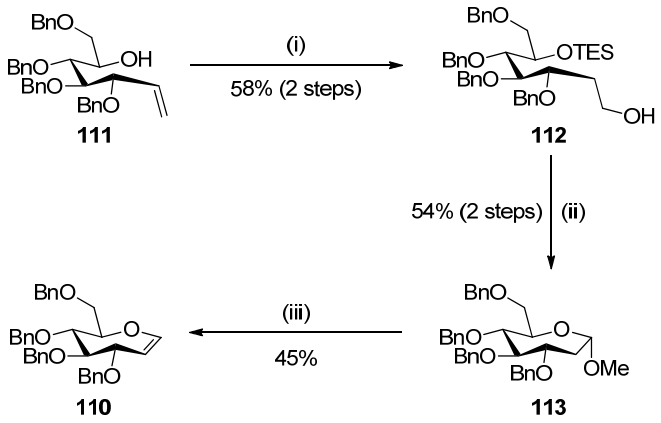
Reagents and Conditions: (i) $Ph_3P^+MeBr^-$, *n*-BuLi, THF; (ii) $Pd(OAc)_2$, CH_2Cl_2, Phenanthroline, 80% conv., rt to reflux, 72 h; (iii) PhMe, 60 °C, 4 h.

Scheme 1.37: Synthesis of septanal by RCM approach

formation of **108** with ethyl vinyl ether using Pd (II) in presence of phenanthroline gave the **109** in modest yield. The ring closing metathesis of **109** did not give any trace of products with Grubbs catalysts (1st and 2nd generation) in appropriate solvents. However, Schrock catalyst cleanly converted the diene **109** to septanal **110** in 92% yield (Scheme 1.37). Several oxepine derivatives were synthesized from the various diene derivatives using this protocol.

Sequential cyclization-elimination of hept-1-enitols

Subsequently, Peczuh and Castro reported the five-step preparation of carbohydrate-based oxepines from the hept-1-enitols. The silyl protection and one pot hydroboration/oxidation of hept-1-enitol gave the heptan-1-itol. The Swern oxidation and sequential acetal formation/cyclization of silyl-protected heptanol provided the methyl-2-deoxyseptanoside, which on elimination gave the carbohydrate-based oxepine.[74] The TES protection of 6-OH group of hept-1-enitol **111** with triethylsilyl chloride (TESCl) in presence of imidazole gave the silyl-protected hept-1-en derivative, which upon one-pot hydroboration/oxidation with BH_3.THF/H_2O_2/NaOH provided the heptanose-derived alcohol **112**. Swern oxidation of alcohol **112** provided the aldehyde in 75% yield. One-pot deprotection of silyl group and acetal formation/cyclization by using *p*-TsOH in methanol gave the methyl 2-deoxyseptanoside **113** in good yield as a single anomer with α-configuration. After several attempts to attain elimination, Gassmann[75] procedure was found to be the best method.



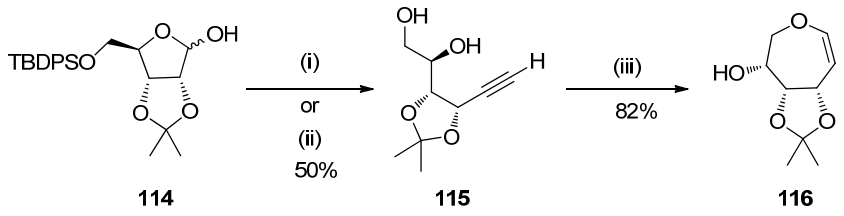
Reagents and Conditions: (i) (a) TESCl, Imidazole, DMF, (b) BH_3.THF, H_2O_2, NaOH; (ii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 oC, 1h (b) *p*-TsOH, MeOH; (c) TMSOTf, DIPEA, CH_2Cl_2.

Scheme 1.38: Synthesis of septanal from the hept-1-enitol

Treating the the methyl 2-deoxyseptanoside **113** with TMSOTf and *N,N'*-diisopropylethylamine (DIPEA) provided the D-glucose-based oxepine **110** in good yield (Scheme 1.38). Using this strategy, D-xylose-based septanal and 3-deoxy-D-glucose-based septanal were synthesized in moderate to good yields.

endo-Selective Cycloisomerization of Alkynyldiols

McDonald and co-workers, in 2004, reported an interesting protocol for the synthesis of septanals from the alkynyldiols involving *endo*-cycloisomerization. The transformation involved the alkynylation of ribofuranose followed by tungsten-catalyzed cycloisomerization gave the septanal in yields ranging from 60% to 90% with high regioselectivity.[76] Wittig chloromethylenation and dehydrohalogenation of ribofuranose acetonide **114** gave the silyl-protected alkynyl alcohol, which on deprotection reaction conditions provided the alkynyldiol **115** in moderate yield. Alternatively the product **115** could be synthesized in one-step with diazophosphonate reagent. The regioselective cycloisomerization of alkynyldiol **115** with catalytic tungsten hexacarbonyl in presence of triethylamine gave the septanal derivative **116** in excellent yield, rather than glycal derivative (Scheme 1.39).



Reagents and Conditions: (i) (a) $ClCH_2PPh_3Cl$/*n*-BuLi, TMEDA, THF, (b) *n*-BuLi, THF, -78 °C; (ii) K_2CO_3, MeOH, $MeC(O)C(N_2)P(O)(OMe)_2$, 65°C; (iii) 15% $W(CO)_6$, Et_3N, hv, THF, 60 °C.

Scheme 1.39: Synthesis of septanal by cycloisomerization of alkynyldiol

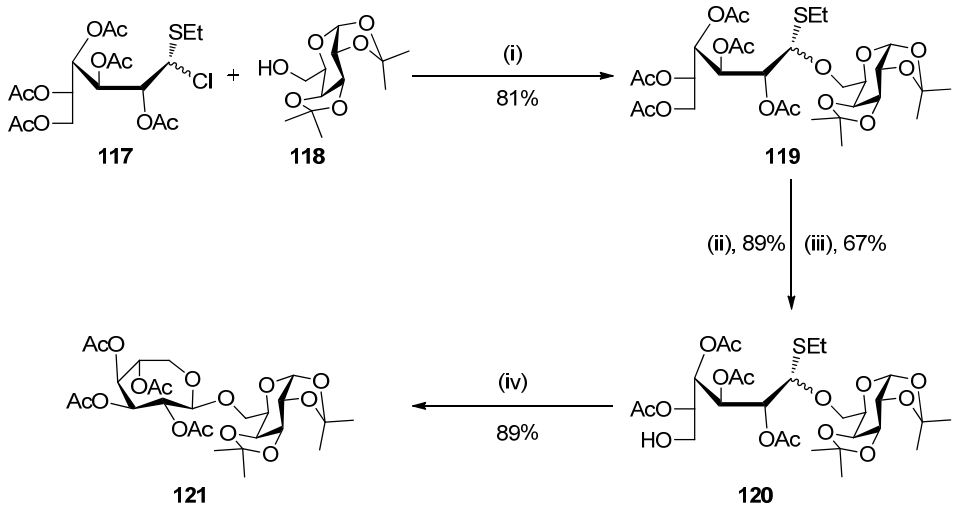
Very recently, Peczuh group reported the synthetic protocols for ring-expanded 2-*N*-acetylamino sugars[77] and C-septanosides[78] from benzyl-protected sugars *via* vinyl addition and electrophilic cyclization.

1.4.2 Synthesis of Septanose Containing Di- and Oligosaccharides

The stereoselecive formation of glycosidic linkage between the saccharides, called as glycosylation process, is always a challenging task in carbohydrate synthesis. Moreover, the synthesis of di and oligosaccharides containing unnatural septanosides is still dormant. Only

few methods were developed for the construction of glycosidic linkage between the septanoses. In 1933, Suckfull and Micheel reported the first glycosylation of septanoses using the septanosyl anomeric chlorides as donors.[79]

Later, in 1998, Hindsgaul and McAuliffie reported the method for the construction of D-septanosyl disaccharides from acyclic chloro-thioethyl acetals as glycosyl donors.[80] 1-chloro-1-(ethylthio) hexose derivative **117** was prepared from the diethyl dithioacetal derivative by treatment with acetyl chloride in presence of $BF_3.OEt_2$. The glycosylation of **117** with 1,2;3,4-di-*O*-isopropylidene-*α*-D-galactopyranose **118** in presence of AgOTf and 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) in dichloromethane gave the sugar-based *O*, *S*-acetal **119** in 81% yield. Deacetylation, sequential treatment with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in pyridine and then Ac_2O/4-dimethylaminopyridine (DMAP) provided the 6-OTBDPS protected acetal which upon deprotection of silyl group with HF/Py gave the 6-OH *O*,*S*-acetal **120**. The cyclization of **120** in presence of NIS/TfOH in ethane provided the D-galacto-septanoside derivative **121** in excellent yield (Scheme 1.40). They were also able to synthesize the analogue of *N*-acetyl-D-lactosamine with a D-galactoseptanosyl unit.

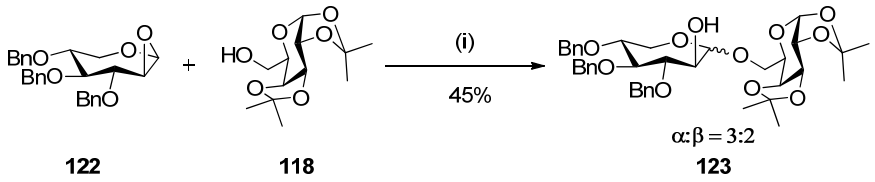


Reagents and Conditions: (i) AgOTf, DTBMP, CH_2Cl_2, -30 °C; (ii) (a) NaOMe, MeOH, (b) TBDPSCl, Py, (c) Ac_2O; (iii) HF/Py, THF, 0 °C; (iv) NIS/TfOH, ethane, -30 °C to rt.

Scheme 1.40: Synthesis of septanosyl disaccharide using acyclic chloro-thioethyl acetal donor

In 2004, Peczuh and co-workers reported the glycosylation method for the synthesis of septanohexose derivatives using septanosyl epoxides as donors. The epoxidation of septanal

by using dimethyldioxirane (DMDO) in dichloromethane provided the 1,2-anhydroseptanosides in good yield with high diastereoselectivity. The major product in the reaction is *β*-epoxide with the ratio of 25:1. The treatment of 3,4,5-tri-*O*-benzyl-1,2-anhydro-*β*-D-iodoseptanose **122** with 1,2;3,4-di-*O*-isopropylidene-*α*-D-galactopyranose **118** in presence of $ZnCl_2$ in THF gave the septanose-derived disaccharides **123** in 45% yield as mixture of anomers (Scheme 1.41).[81]

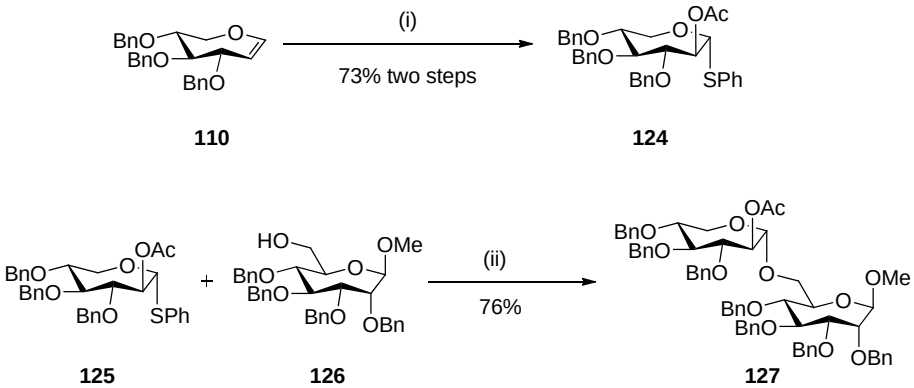


122 **118** **123**

Reagents and Conditions: (i) $ZnCl_2$, THF, -78 °C to rt, 16 h.

Scheme 1.41: Synthesis of septanosyl disaccharides using 1,2-anhydroseptanose donor

Concomitantly, the same authors introduced thiophenyl septanoside donors towards the synthesis of diseptanose derivatives. The *S*-phenyl septanoside donor was activated under milder conditions to provide the α-septanoside in good yield. The epoxidation of carbohydrate-based oxepine **110** with DMDO and exposure to the lithium salt of thiophenol in THF provided the septanosyl donor **124** in 73% yield. The glycosylation of donor **125** with methyl septanoside **126**, having free hydroxyl group at 7th position, in presence of NIS/AgOTf provided the α-1,7-linked diseptanoside **127** in 76% yield as a single anomer (Scheme 1.42).[82]



110 **124**

125 **126** **127**

Reagents and Conditions: (i) (a) DMDO, CH_2Cl_2, 0 °C, (b) LiSPh, THF, -10 °C, (c) Ac_2O, Py, rt; (ii) NIS, AgOTf, CH_2Cl_2, -40 °C to -25 °C, 30 min.

Scheme 1.42: Synthesis of *α*-1,7-diseptanoside derivative using the thioseptanosyl donor

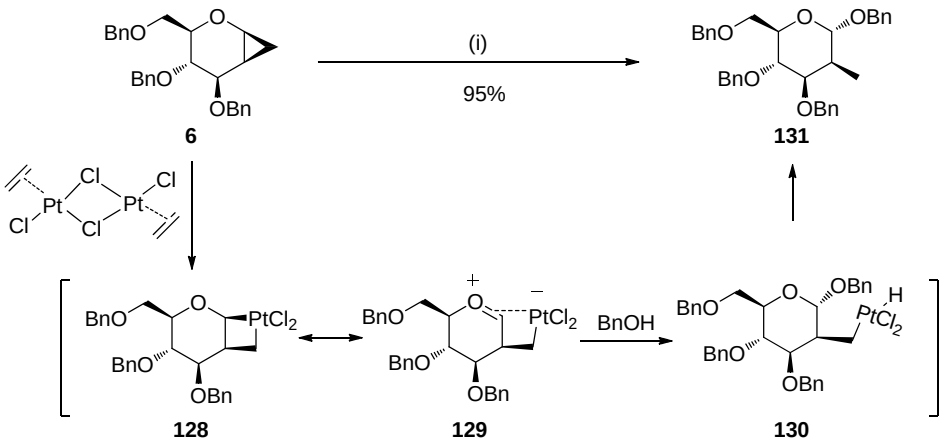
Additionally, in 2009, Mc Donald and co-workers applied the above glycosylation reaction to construct the mannoseptanosyl di and trisaccharides. The thiophenyl septanoside donor was synthesized by using the above strategy from their septanal, obtained from tungsten-catalysis of alkynyldiol. Then, α-1,5-mannoseptanosyl trisaccharide was successfully synthesized by following an iterative process.[83]

1.5 Glycosylation reactions of 1,2-Cyclopropanated Sugars

Glycosylation process is also an important tool for the organic chemists to synthesize unnatural di- and oligosaccharides and their mimics.[84] Many interesting glycosylation methods are available with different glycosyl donors and promoters.[85] However glycosylation reactions using the cyclopropane sugar donors are still very scarce. 1,2-Cyclopropanated sugars could be used in glycosylation reactions by ring-opening or ring-expanding of the cyclopropane moiety.

1.5.1 Ring-Opening of 1,2-Cyclopropanated Sugar Donors

Recently, research in discovery of glycosylation methods from 1,2-cyclopropanated sugar donors is slowly taking ahead. Initially, Madson and co-workers reported the platinum-catalyzed ring-opening of 1,2-cyclopropanated sugars with various nucleophiles including carbohydrate based *O*-nucleophiles. The treatment of different 1,2-cyclopropanated sugars

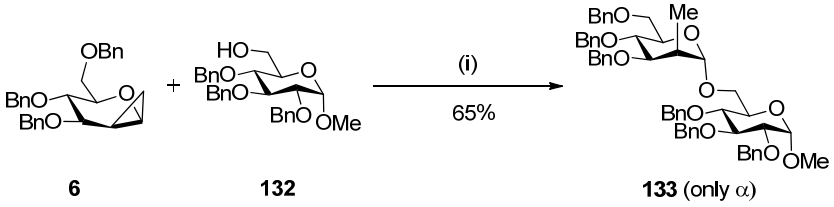


Reagents and Conditions: (i) 3.7% $[pt(C_2H_2)Cl_2]_2$, BnOH, CH_2Cl_2, 15 h, rt.

Scheme 1.43: Platinum catalyzed ring-opening of 1,2-cyclopropanated sugar

and Zeise's dimer in presence of alcohols, phenols and water gave the 2-C-branched carbohydrates in good yields with high diastereoselectivity. The α-glycoside is always the major product in ring-opening with alcohols regardless of stereochemistry of the starting cyclopropanated sugar. Interestingly unsubstituted sugar cyclopropanes (Simmons-smith cyclopropanes) readily underwent the ring opening to give the 2-C-methyl carbohydrates. However, cyclopropanes with ester and alkyl groups were less reactive and completely inert to ring-opening conditions. Example of ring-opening of cyclopropane **6** in presence of Ziese's dimer with benzyl alcohol in dichloromethane was shown below. The 2-C-methyl sugar derivative **131** was obtained in 95% yield as a single diastereomer (Scheme 1.43).[86] The plausible pathway of ring-opening was shown in scheme 1.42. The α-selectivity was explained by anomeric effect.

The above methodology was further extended to sugar *O*-nucleophiles to get the 2-C-branched disaccharides. The reaction between 1,2-cyclopropanated sugar **6** as donor and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **132** as acceptor in presence of Ziese's dimer in dichloromethane provided the 2-C-methyl disaccharide **133** in 65% yield as a single anomer (Scheme 1.44).[87]



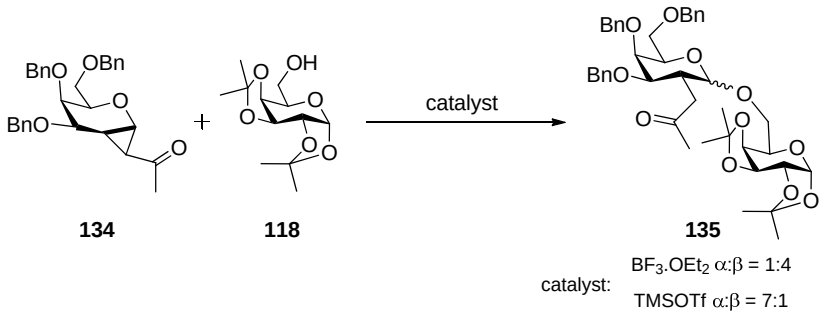
6 **132** **133** (only α)

Reagents and Conditions: (i) 3.7% $[pt(C_2H_2)Cl_2]_2$, CH_2Cl_2, 15 h, rt.

Scheme 1.44: Synthesis of 2-C-branched disaccharide by platinum catalyzed ring-opening of 1,2-cyclopropanated sugar donor

Recently, Shao *et al.* reported the stereoselective synthesis of 2-C-acetonyl disaccharides using the 1,2-cyclopropaneacetylated sugar donors. The novel 1,2-cyclopropaneacetylated sugar donor reacted with various acceptors like monosaccharides, amino acids and other alcohols in presence of $BF_3.OEt_2$ and TMSOTf.[88] The glycosylation of D-galactose-derived 1,2-cyclopropane **134** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **118** in presence of $BF_3.OEt_2$ in dichloromethane gave 2-C-acetonyl disaccharide derivative **135** in 84% yield

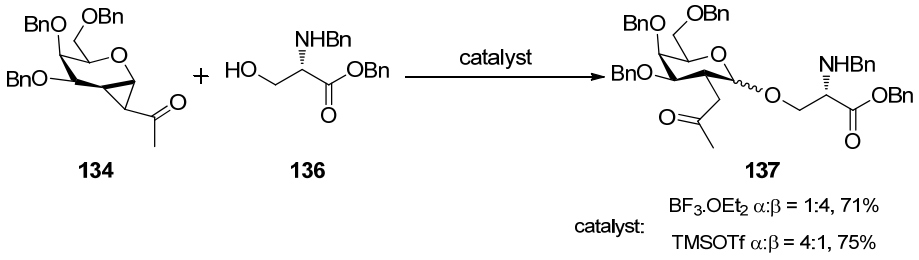
with high diastereoselectivity. The *β*-anomer was obtained as the major product with the catalytic $BF_3.OEt_2$. However, the same reaction in presence of TMSOTf instead of $BF_3.OEt_2$ gave the *α*-anomer as a major product in 89% yield (Scheme 1.45).[89]



Reagents and Conditions: (i) CH_2Cl_2, -20 °C to rt, 2 h.

Scheme 1.45: Synthesis of 2-C-acetonyl disaccharide derivative by ring-opening of 1,2-cyclopropaneacetylated sugar donor

They also utilized this methodology to synthesize the *O*-glyco-amino acid derivatives by using serine and threonine derivatives as acceptors. Treatment of 1,2-cyclopropane donor **134** with serine derivative **136** in presence of $BF_3.OEt_2$ or TMSOTf gave the 2-C-acetonyl *O*-glycosyl amino acid derivative **137** in excellent yield with high diastereoselectivity (Scheme 1.46).



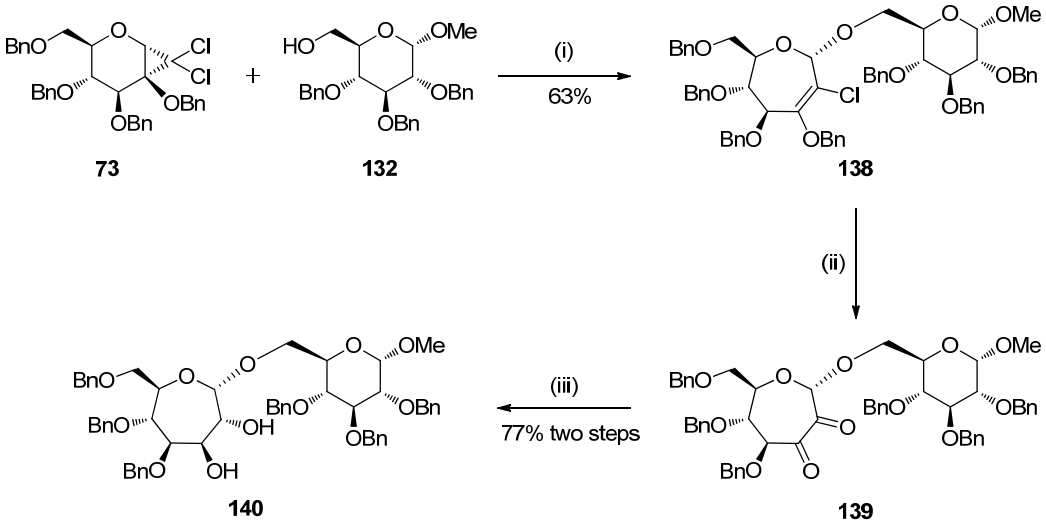
Reagents and Conditions: (i) CH_2Cl_2, -20 °C to rt, 2 h.

Scheme 1.46: Synthesis of glycoconjugates using 1,2-cyclopropaneacetylated sugar donor

1.5.2 Ring-expansion of 1,2-Cyclopropanated Sugar Donors

Recently, 1,2-cyclopropanated sugars serve as a versatile glycosyl donors in ring-expansion as well as glycosylation to make well ring-expanded di- and oligo-saccharides. Jayaraman *et*

al., synthesized the septanosyl disaccharides by ring-opening of *gem*-1,2-dichlorocyclopropanes. The treatment of cyclopropane **73** with methyl 2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside **132** in presence of K_2CO_3 in toluene gave the chlorooxepine disaccharide derivative **135** in 63% yield as a single anomer. The RuO_4-mediated oxidation followed by $NaBH_4$ reduction of chloroxepine derivative **138** provided the septanohexose derivative **140** in good yield (Scheme 1.47).[48]



Reagents and Conditions: (i) K_2CO_3, toluene, reflux, 74 h; (ii) $RuCl_3$, $NaIO_4$, CH_3CN, EtOAc, 10 h; (iii) $NaBH_4$, MeOH, rt, 3 h.

Scheme 1.47: Synthesis of septanohexoses by ring opening of *gem*-1,2-dichlorocyclopropanated sugar donor

They also successfully synthesized septanose containing trisaccharides by applying this methodology to cyclopropyl disaccharide derivatives as glycosyl donors.[90] In addition to this, *C*- and *N*-glycosides[91] were also synthesized by ring-opening of 1,2-cyclopropanated sugar donors.

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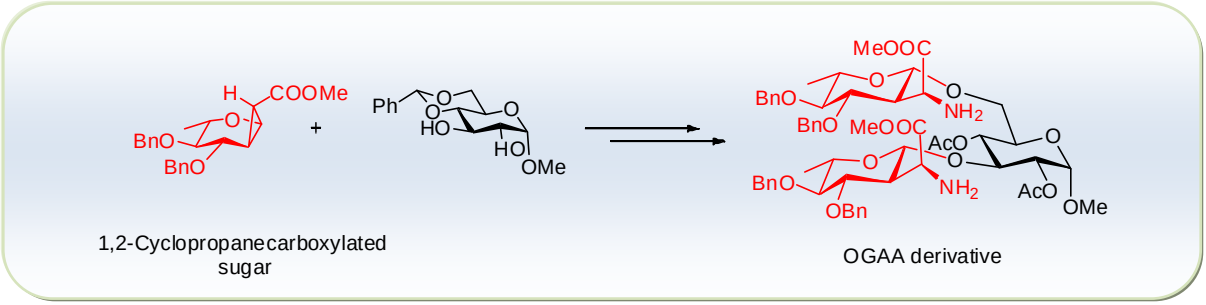
CHAPTER 2

Synthesis of 2-C-Branched Oligo-glyco-amino acids (OGAAs) by Ring Opening of 1,2-Cyclopropanecarboxylated Sugar Donors

ABSTRACT: 1,2-Cyclopropanecarboxylated sugars were used as glycosyl donors, for the first time, in the synthesis of 2-C-branched oligo-glyco-amino acids (OGAAs), carbohydrates decorated with the α-amino acids. The method was applied to acceptor-reactivity-based stereo- and regioselective glycosylation reactions towards the preparation of several disaccharide-based glyco-amino acid derivatives.



2.1 Introduction

Carbohydrates decorated with amino acids are becoming an important area of glyco-chemistry research.[1] Possessing the architecture of a sugar and an amino acid in a single molecule, these glyco-amino acids (GAAs)[2] are expected to exhibit the characteristics of both carbohydrates and amino acids, which are both biological polymer precursors. Glyco-amino acids are the most important building blocks for the glycopeptides and glycoproteins which play essential roles in cell-cell recognition, fertilization and *etc.*.[3] In this aspect, *C*-glycopeptides, in which sugar and peptide are connected through the *C*-glycosidic linkage,

have been explored significantly due to the stability and resistance exhibited towards enzymatic hydrolysis.[4] Moreover, C-branched glyco-α-amino acid moieties are found in a variety of nucleoside antibiotics, such as polyoxins,[5] miharamycins,[6] nikkomycin[7] and amipuramycin[8] (Figure 2.1).

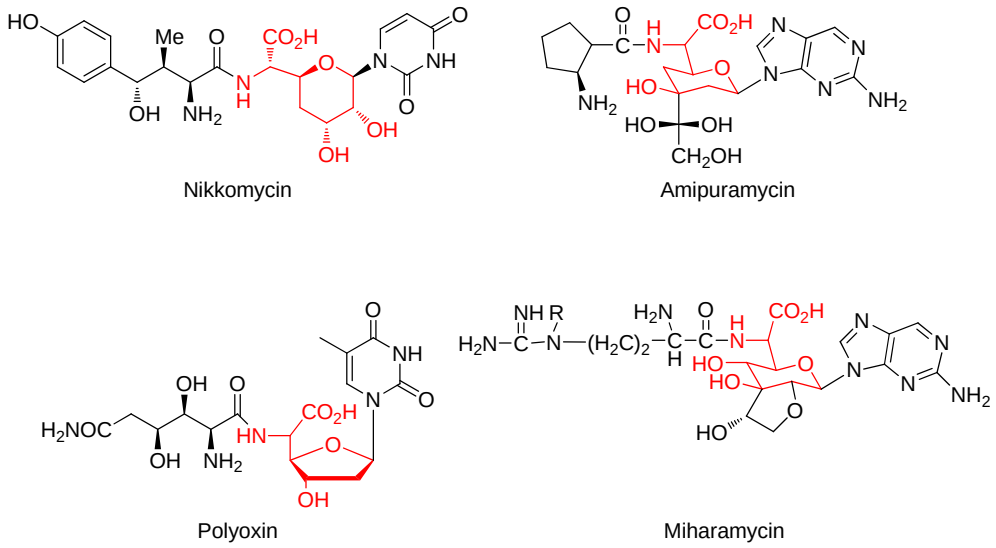


Figure 2.1: Nucleoside antibiotics containing glyco-amino acid moiety

Very few methods are available in literature for the synthesis of monosaccharide-derived C-branched GAA derivatives.[9] The synthetic methods available for the synthesis of 2-C-branched GAAs is discussed in detail in chapter 1 of this thesis (section 1.3). It has been found to be very difficult to link a an α-amino acid at C-2 or C-4 through a C-C bond. For this reason, the biological importance of these GAAs is not yet fully understood. It has been shown that the unnatural 2-C-acetonylsugars serve as the metabolic substrates for cell surface engineering by mimicking 2-*N*-acetylsugars.[10] Similarly, a 2-C-*N*-hydroxy acetamide mimic of GlcNAc was synthesized and shown to be an inhibitor of the biosynthesis of lipid A.[11]

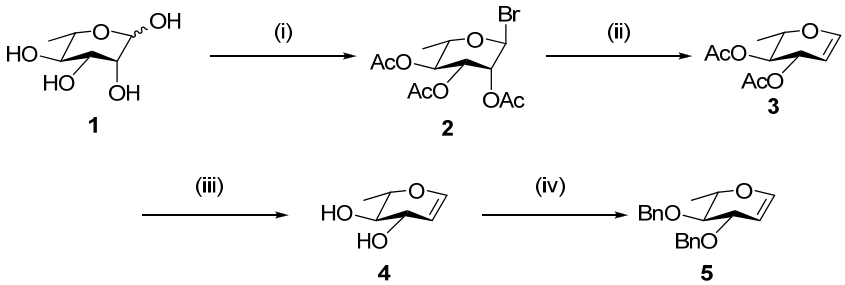
The high reactivity and regioselectivity of donor–acceptor cyclopropanes has been well documented in literature.[12] 1,2-Cyclopropanecarboxylated sugars have been used as donor-acceptor cyclopropanes in the synthesis of 2-C-branched monosaccharides through electrophilic C1–C7 cyclopropane ring opening or by transition-metal-catalyzed glycosylation.[13] Detailed ring opening reactions of 1,2-cyclopropanated sugar derivatives is described in chapter 1 of this thesis (*vide supra* section 1.2.1, section 1.3.1, section 1.5.1).

Recently, a four-component Pavarov reaction and a transition-metal-mediated radical reaction were developed for the direct synthesis of the 2-C-branched carbohydrate derivatives from glucals,[14] which were further derivatized to bicyclic carbohydrate 1,2-lactones.[15] Glucal-derived donor–acceptor cyclopropanes have also been used as 1,3-dipoles under acidic conditions, which result in (3+2) cycloaddition reactions in presence of dipolarophiles.[16]

1,2-Cyclopropanated sugars have the ability to undergo electrophilic ring opening reaction assisted by the adjacent oxygen in presence of an electrophile.[17] Utilizing this potentiality of these cyclopropanated sugars, in this chapter we described the *N*-iodosuccinimide (NIS)/trimethylsilyl triflouromethanesulfonate (TMSOTf) mediated ring opening of 1,2-cyclopropanecarboxylated glycosyl donors with the carbohydrate derived *O*-nucleophilic glycosyl bond acceptors.

2.2 Results and Discussion

1,2-Cyclopropanecarboxylated sugar donors used in the glycosylation reaction, were prepared from the readily available carbohydrates (D-glucose, D-galactose and L-rhamnose) using the previously reported methods. The conversion of L-rhamnose to L-rhamnal involved the use of the methodology pioneered by Fisher[18] and refined by others.[19] The peracetylation of L-rhamnose **1** with acetic anhydride and catalytic perchloric acid gave the clear solution of tetra-*O*-acetyl-L-rhamnose, which was directly treated in the same pot with hydrobromic acid to provide the tri-*O*-acetyl-bromo-L-rhamnoside **2**. The reductive elimination of **2** with Zinc

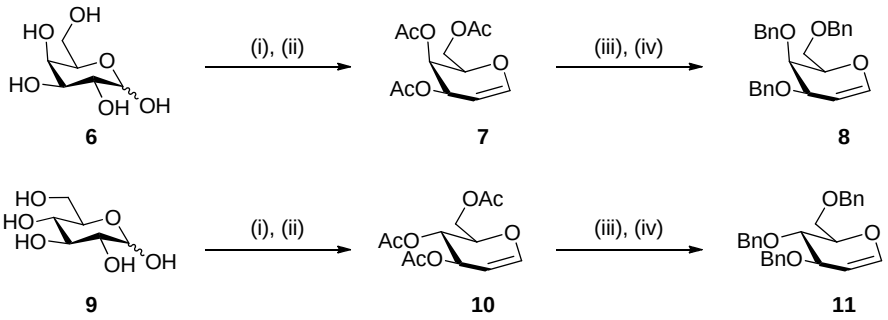


Reagents and Conditions: (i) (a) $HClO_4$, Ac_2O, 0 °C to rt, 30 min, (b) 33% HBr/AcOH, rt, 90 min; (ii) Zn, satd. NaH_2PO_4, EtOAc, 3 h, rt; (iii) K_2CO_3, MeOH, rt, 1 h; (iv) NaH, BnBr, DMF, TBAI, 0 °C to rt, 16 h.

Scheme 2.1: Preparation of the 3,4-di-*O*-benzyl-L-rhamnal from the L-rhamnose

and saturated NaH_2PO_4 gave the 3,4-di-*O*-acetyl-L-rhamnal **3** in good yield.[20] To incorporate the stable protecting groups in **3**, acetyl groups were deprotected using K_2CO_3 in methanol to give L-rhamnal **4** which upon benzylation with benzyl bromide and sodium hydride provided the 3,4-di-*O*-benzyl-L-rhamnal **5** (Scheme 2.1).

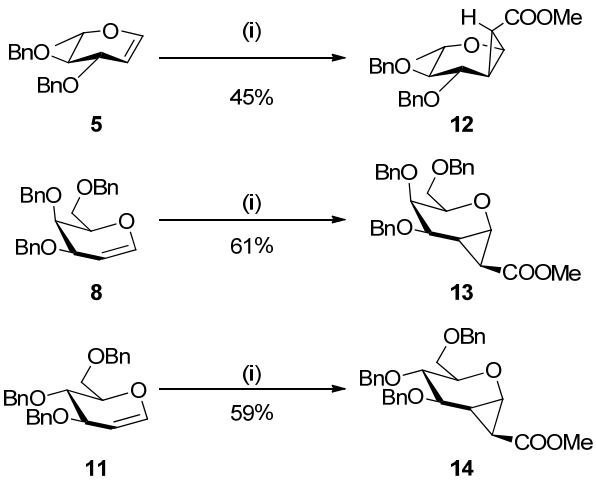
Similarly, using the above protocol 3,4,6-tri-*O*-benzyl-D-galactal **8** and 3,4,6-tri-*O*-benzyl-D-glucal **11** were synthesized in good yields from the D-galactose **6** and D-glucose **9** respectively. These three protected glycals were used as substrates for the transition-metal catalyzed cyclopropanation reaction.



Reagents and Conditions: (i) (a) $HClO_4$, Ac_2O, 0 °C to rt, 30 min, (b) 33% HBr/AcOH, rt, 90 min; (ii) Zn, satd. NaH_2PO_4, Acetone, 3 h, rt; (iii) K_2CO_3, MeOH, rt, 1 h; (iv) NaH, BnBr, DMF, TBAI, 0 °C to rt, 16 h.

Scheme 2.2: Synthesis of tri-*O*-benzyl-D-galactal **8** and tri-*O*-benzyl-D-glucal **11**

The cyclopropanation of 3,4-di-*O*-benzyl-L-rhamnal **5** with methyl diazoacetate (MDA) in presence of dirhodium tetraacetate $Rh_2(OAc)_4$ in dichloromethane gave the 1,5-anhydro-

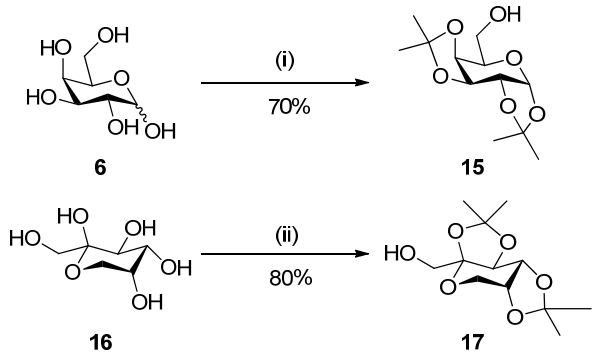


Reagents and Conditions: (i) Methyl diazoacetate, $Rh_2(OAc)_4$, CH_2Cl_2, rt, 1 h.

Scheme 2.3: Rhodium (II) catalyzed cyclopropanation of glycals with methyl diazoacetate

-2,6-dideoxy- 1,2-(*exo*-carbomethoxy-methylene)-3,4-di-*O*-benzyl-α-L-rhamnal **12** with 45% yield as a major diastereomer.[21] The benzyl protected D-galactal **8** and D-glucal **11** were also cyclopropanated using same protocol to obtain 1,2-cyclopropanecarboxylates **13** and **14** respectively in moderatae yield (scheme 2.3).

The model glycosyl acceptors used for the glycosylation reaction, were synthesized from D-galactose **6** and D-fructose **16** in one step. Treatment of D-galactose **6** with dry acetone in presence of catalytic concentrated sulfuric acid gave the 1,2;3,4-di-*O*-isopropylidene-α-D-galactose **15**[22] in 70% yield. Similarly, the other acceptor **17** was synthesized by treating fructose **16** with zinc chloride and catalytic conc. sulfuric acid in acetone (Scheme 2.4).

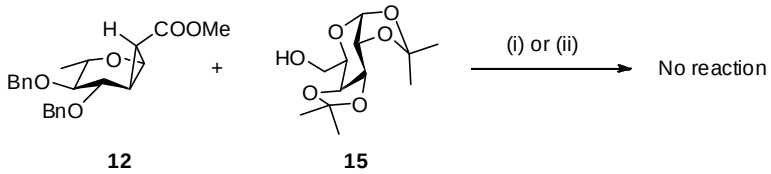


Reagents and Conditions: (i) H_2SO_4, acetone, rt, 2 h; (ii) H_2SO_4, $ZnCl_2$, acetone, rt, 3 h.

Scheme 2.4: Synthesis of D-galactose diacetonide and D-fructose diacetonide

2.2.1 Discovery and Optimization of the Novel Glycosylation Reaction

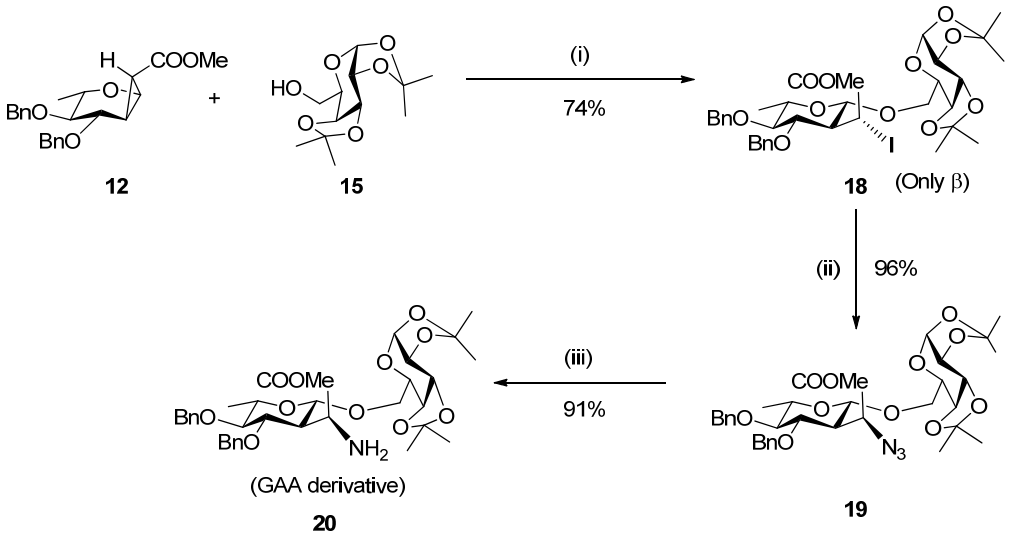
The glycosylation studies began with L-rhamnose-derived cyclopropane **12** as donor and 1,2;3,4-di-*O*-isopropylidene-α-D-galactose **15**[22] as acceptor in presence of NIS as the electrophile at 0 ^oC in acetonitrile. However, no expected disaccharide was observed under these reaction conditions, even with an excess of acceptor (>3 equiv). Similar reaction conditions with various solvents did not provide the glycosylation reaction (Scheme 2.5).



Reagents and Conditions: (i) NIS, CH_3CN, 0 ^oC; (ii) NIS, CH_2Cl_2, 0 ^oC.

Scheme 2.5: Attempts for the glycosylation reaction

On screening several promoters and after several attempts, we found that TMSOTf (20 mol%) as the best promoter for this glycosylation reaction.[23] Treatment of **12** and **15** with NIS/TMSOTf in dichloromethane (0-28 °C, 8 h) yielded 2'-C-branched disaccharide **18** in 74% as a single diastereomer[24] in which two new stereocenters were introduced at C1' and C7' in a single reaction. It is worth noting that only 1.1 equivalents of acceptor, with respect to the donor, were used for this glycosylation reaction. The substitution of α-iodide in α-iodocarboxylate **18** with NaN_3/DMF (28 °C, 24 h) afforded azidocarboxylate **19** in 96% yield. Reduction of the azide **19** under Staudinger reaction conditions[25] (Ph_3P/THF/H_2O) produced disaccharide-based glyco-amino acid derivative **20** in 91% yield (Scheme 2.6).

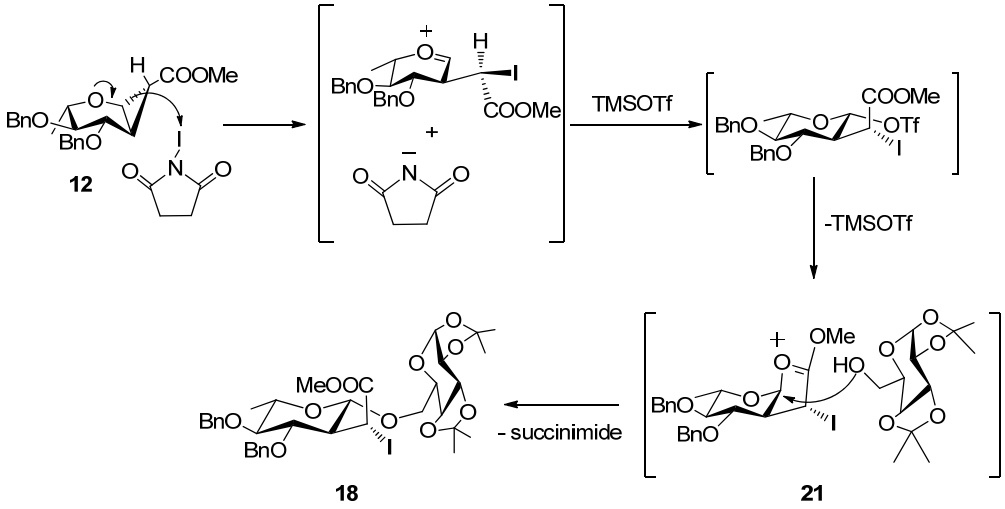


Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h; (ii) NaN_3, DMF, rt, 24 h; (iii) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h.

Scheme 2.6: Synthesis of 2-C-branched GAA disaccharide by ring-opening of 1,2-cyclopropanecarboxylated sugar donor

2.2.2 Plausible Mechanistic Pathway

The plausible mechanism of NIS-mediated ring opening involves a stereospecific "edge attack" of iodide on 1,2-cyclopropanecarboxylate **12** to generate an oxocarbenium ion that is immediately trapped with triflate. The triflate is released by neighbouring-group participation of the C7-carboxylate to generate a second oxocarbenium ion intermediate **21**, which is sufficiently long lived that it can be intercepted with a carbohydrate-based *O*-nucleophile **15**. Nucleophilic attack by glycosyl acceptor oxygen at the anomeric carbon gives the disaccharide product **18** (Scheme 2.7).

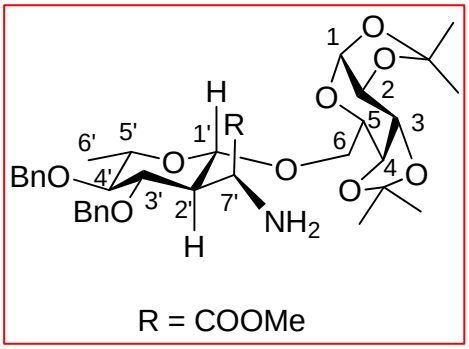


Scheme 2.7: Proposed mechanism for the NIS-mediated ring-opening of 1,2-cyclopropanated sugar derivatives

2.2.3 Scope of the Reaction

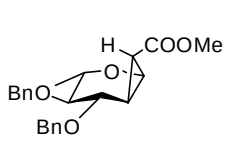
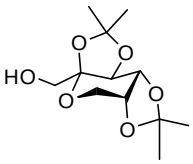
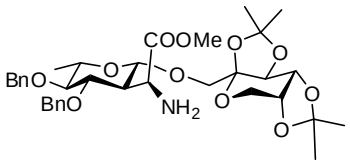
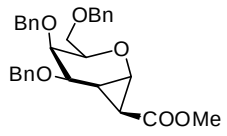
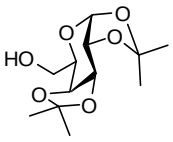
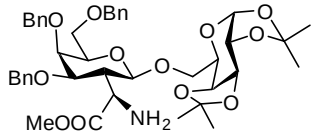
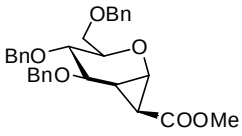
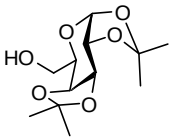
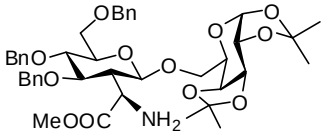
The generality of this methodology has been proved successfully by applying it to a number of 1,2-cyclopropanated glycosyl donors and differentially protected sugar acceptors. Thus, the reaction of cyclopropanecarboxylates **12**, **13** and **14** with acceptors **17** and **15** gave the ring-opened 2-C-branched disaccharide derivatives **22**, **25** and **28**, respectively, in good yields with very high diastereoselectivity at the newly formed C1' and C7' stereocenters.

The structures of the 2-C-branched disaccharide iodides were assigned on the basis of NMR spectra. The stereochemistry at C1' was confirmed by observing a large coupling constant (J = 8.8 Hz) for the C1' proton, which indicates a 1,2-trans configuration for all the ring-opened disaccharide derivatives. The stereochemistry at C2' was defined on the basis of the stereochemistry present in the 1,2-cyclopropanecarboxylated sugar precursor. The stereochemistry at C7' was assigned based on the proposed mechanism and further confirmed by X-ray crystallographic data of one of the GAA derivative.[9a] The substitution of iodide functionality in disaccharide derivatives **22**, **25** and **28** with azide using NaN_3/DMF afforded the **23**, **26** and **29** respectively. The 2-C-branched GAA derivatives **24**, **27** and **30**



were obtained from the azides **23**, **26** and **29** using Staudinger reaction conditions in excellent yield (Table 1, entries 1, 2 and 3).

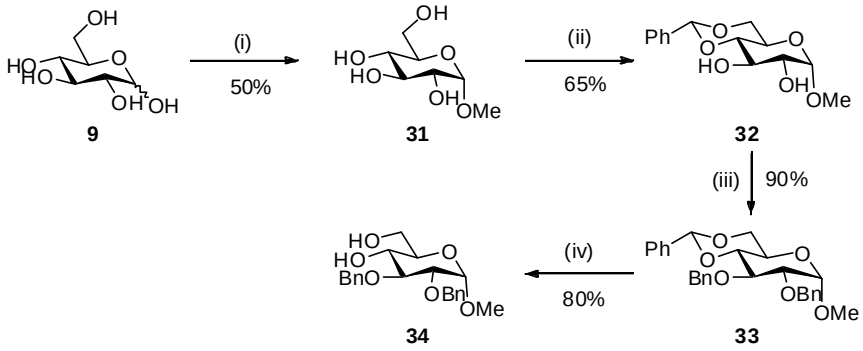
Table 2.1: Ring-opening of the 1,2-cyclopropanecarboxylated sugar donors with glycosyl acceptors: synthesis of 2-C-branched GAA derivatives

Entry	Donor cyclpropane	Acceptor	Iodide (%)	Azide (%)	GAA (%) derivative
1	 **12**	 **17**	**22** (75)	**23** (95)	 **24** (92)
2	 **13**	 **15**	**25** (72)	**26** (96)	 **27** (90)
3	 **14**	 **15**	**28** (72)	**29** (92)	 **30** (89)

2.2.4 Regioselectivity of the Reaction

Our next investigation focused on the regioselective glycosylation reactions based on the relative reactivity between two hydroxyls on a single sugar acceptor. The glycosyl acceptors containing two free hydroxyl groups were synthesized using standard procedures from D-glucose and D-galactose in excellent yields. Initially, methyl 4,6-*O*-benzylidine-α-D-glucopyranoside **32**[27] was prepared by formation of methyl glucoside followed by benzylidene protection from the D-glucose. The crystalline methyl α-D-glucopyranoside **31** was obtained by heating D-glucose with methanolic hydrogen chloride. The benzylidene protection of C4 and C6 hydroxyl groups in **31** with benzyaldehyde dimethyl acetal in presence of *p*-toluenesulfonic acid gave the glycosyl acceptor **32**, which upon benzylation of C2 and C3 hydroxyl groups followed by deprotection of 4,6-*O*-benzylidene group provided

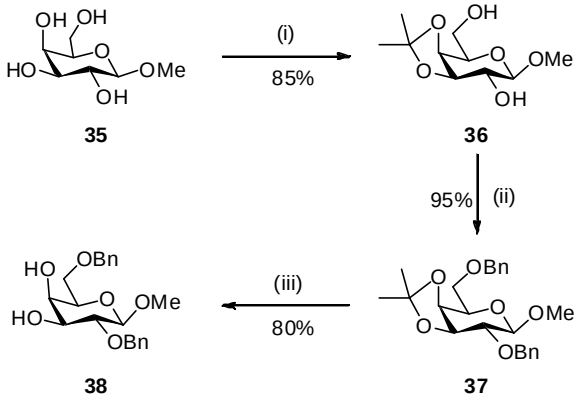
another glycosyl acceptor, namely, methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **34**[26] (Scheme 2.8).



Reagents and Conditions: (i) MeOH/HCl, reflux, 16 h; (ii) $PhCH(OMe)_2$, PTSA, DMF,60 ^oC, 2 h; (iii) BnBr, NaH, DMF, TBAI, 10 h; (iv) PTSA, MeOH, 5 h.

Scheme 2.8: Synthesis of acceptors for regioselective glycosylation

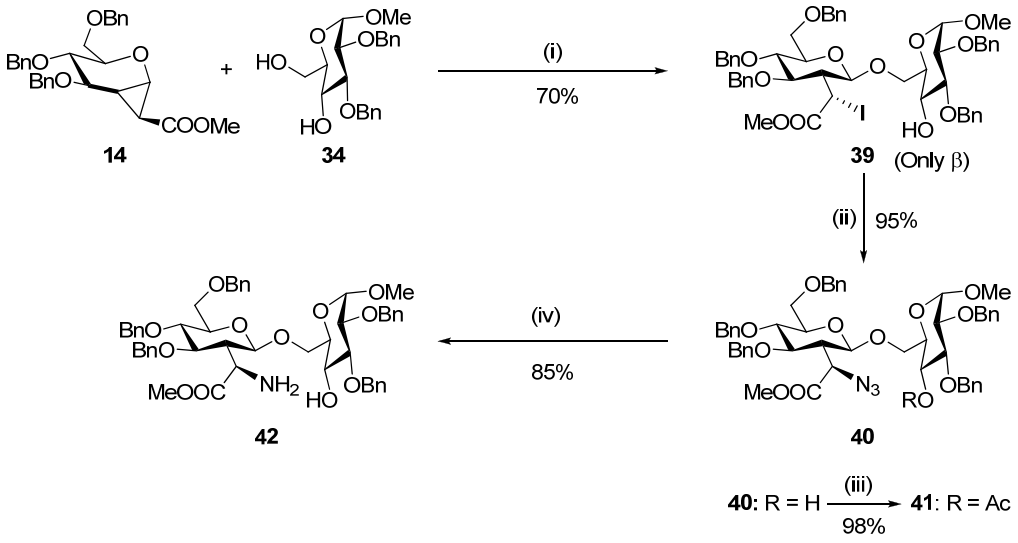
Like the above strategy, the preparation of methyl-2,6-di-*O*-benzyl-*β*-D-galactopyranoside **38**[29] mainly consists of few protecting group transformations in D-galactose derivatives. The protection of C3 and C4 hydroxyl groups in methyl *β*-D-galactopyranoside **35** with acetone in presence of copper sulphate and catalytic sulfuric acid gave the **36**. Benzylation of C2 and C4 hydroxyl groups of **36** followed by deprotection of acetonide gave the acceptor **38** in good yield.



Reagents and Conditions: (i) $CuSO_4$, H_2SO_4, acetone, 3 h; (ii) BnBr, NaH, DMF, 10 h; (iii) aq. AcOH, 50 ^oC 3 h.

Scheme 2.9: Synthesis of D-galactose-based acceptor for regioselective glycosylation

To investigate the regioselectivity of the novel glycosylation reaction, 1,2-cyclopropanecarboxylate **14** was treated with methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **34**[26] in the presence of NIS/TMSOTf in dichloromethane at 0 °C. The reaction produced a single product **39**, which was converted to azide **40**. The regioselectivity at the 6-O position was confirmed by acetylating the free hydroxyl group in **40** with Ac_2O/pyridine and observing a downfield shift in the signal of the C4 proton in acetylated disaccharide derivative **41**. The reaction of **40** using the Staudinger reaction conditions provided the 2-C-branched GAA derivative **42** in 85% yield (Scheme 2.10).



Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h; (ii) NaN_3, DMF, rt, 24 h; (iii) Ac_2O, Py, rt, 10 h; (iv) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h.

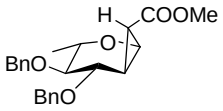
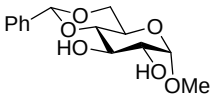
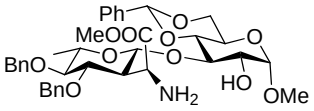
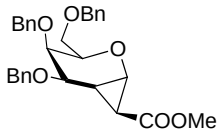
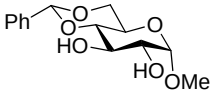
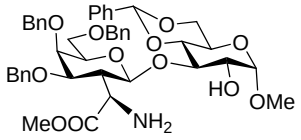
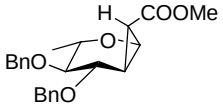
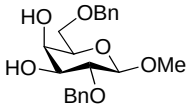
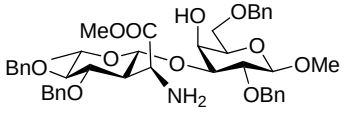
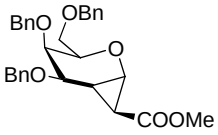
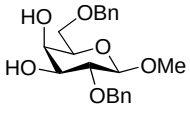
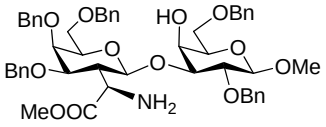
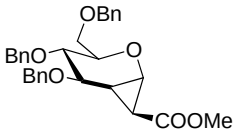
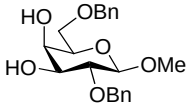
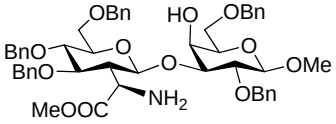
Scheme 2.10: Ring-opening of 1,2-cyclopropanecarboxylated sugar donor with glycosyl acceptor having two hydroxyl groups.

Similarly, reactivity-based glycosylation of 1,2-cyclopropanecarboxylates **12** and **13** with methyl-4,6-*O*-benzylidine-*α*-D-glucopyranoside **32**[27] produced the 2-C-branched disaccharide derivatives **43** and **47**, respectively, in good yield. Interestingly, C3-OH of acceptor **32** was involved in the glycosylation reactions[28] (Table 2, entry 1 and 2).

The aforementioned acceptor-reactivity-based glycosylation of 1,2-cyclopropanecarboxylated sugar donors could also be extended to the other sugar derivatives. Thus, treatment of cyclopropanecarboxylated donors **12**, **13** and **14** with methyl-2,6-di-*O*-benzyl-*β*-D-

galactopyranoside **38**[29] gave disaccharide derivatives **50**, **54** and **57**, respectively, in good yields. In these reactions, C3-OH of the glycosyl acceptor **38** was participated in glycosylation reactions to give the 2-C-branched disaccharides as a single regioisomer. All the disaccharide α-iodocarboxylates (**43**, **47**, **50**, **54** and **57**) were converted to the corresponding azides (**45**, **48**, **51**, **55** and **58**, respectively) by using NaN_3/DMF to give excellent yields (90%). All these azides were further converted to the corresponding 2-C-branched GAA derivatives **46**, **49**, **53**, **56** and **59**, respectively, under Staudinger reaction conditions (Table 2, entries 1, 2, 3, 4, and 5).

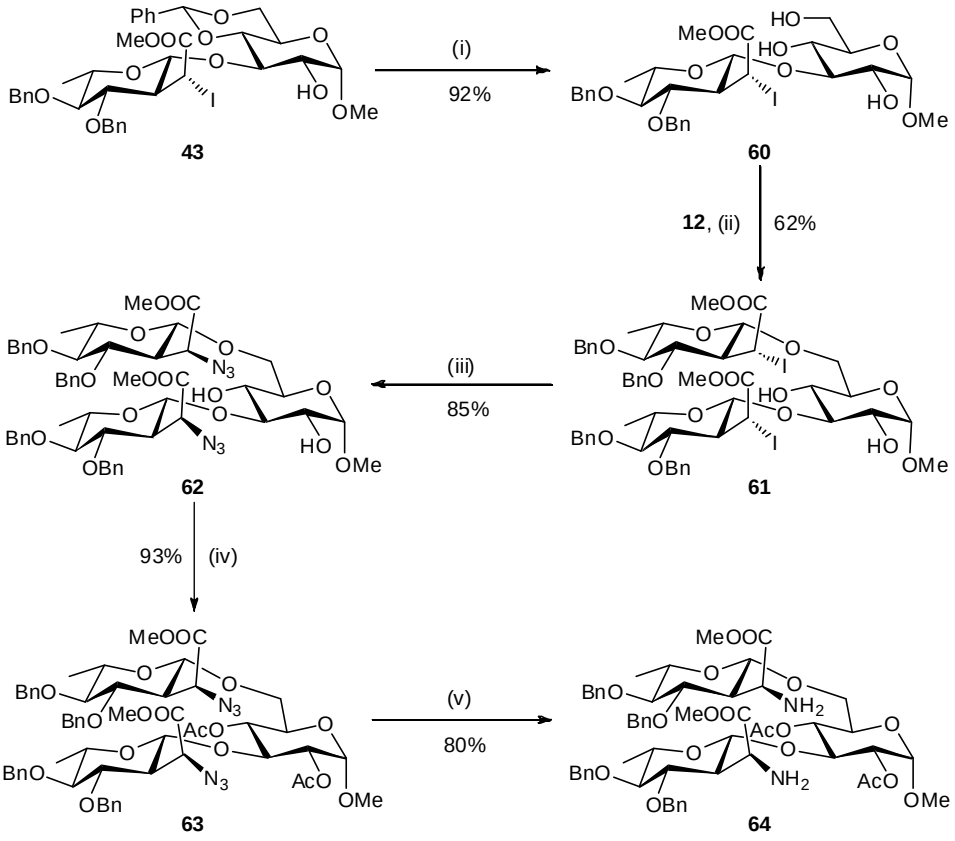
Table 2.2: Ring-opening of 1,2-cyclopropanecarboxylated sugar donors with glycosyl acceptors having the two hydroxyl groups: Synthesis of 2-C-branched GAA derivatives.

entry	donor cyclopropane	acceptor	iodide (%)	azide (%)	GAA (%) derivative
1	 **12**	 **32**	**43** (67) **44** (96)[a]	**45** (92)	 **46** (94)
2	 **13**	 **32**	**47** (63)	**48** (90)	 **49** (92)
3	 **12**	 **38**	**50** (70)	**51** (93) **52** (97)[b]	 **53** (97)
4	 **13**	 **38**	**54** (69)	**55** (92)	 **56** (90)
5	 **14**	 **38**	**57** (65)	**58** (88)	 **59** (88)

[a]The free hydroxyl group of iodide **43** was acetylated. [b]The free hydroxyl group of azide **51** was acetylated

2.2.5 Synthesis of Oligo-Glyco-Amino Acid (OGAA) Derivative

Keeping the above-mentioned acceptor-reactivity-based regio- and stereoselective glycosylation of 1,2-cyclopropanecarboxylated sugar donors in mind, we further planned to synthesize an OGAA derivative. Towards this goal, the benzylidene protecting group in α-iodocarboxylate **43** was deprotected by using *p*-TsOH·H_2O/MeOH to give the disaccharide triol **60**. A second acceptor-reactivity-based glycosylation was performed by treating **12** with triol **60** in presence of NIS/TMSOTf to give trisaccharide **61** in good yield as the only isolated product. Treatment of **61** with NaN_3/DMF gave diazide **62**. The free hydroxyls were acetylated to give compound **63**, which gave OGAA derivative **64** under Staudinger reaction conditions (Scheme 2.11).



Reagents and Conditions: (i) *p*-TsOH-H_2O, MeOH rt, 4 h, (ii) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h; (iii) NaN_3, DMF, rt, 24 h; (iv) Ac_2O, Py, rt, 10 h. (v) (a) PPh_3, THF, rt, 6 h, (b) H_2O, reflux, 8 h.

Scheme 2.11: Synthesis of 2-C-branched OGAA derivatives

2.3 Summary and Conclusion

A new glycosylation method that uses carbohydrate-derived donor-acceptor cyclopropanes as glycosyl acceptors has been developed. To the best of our knowledge, this is the first method of the use of 1,2-cyclopropanecarboxylated sugars as donors in traditional oligosaccharide synthesis. The novel glycosylation method was successfully applied to the synthesis of a number of 2-C-branched GAA disaccharides by using various glycosyl donors and acceptors. The high regioselectivity was attained in the glycosylation reaction with the glycosyl acceptors having the competing hydroxyl groups. The acceptor-reactivity based regio- and stereoselective glycosylation was utilized for the preparation of an OGAA derivative. Mimicking natural glycosides with carbon-branched GAAs and determining the biological importance of these hybrid biomolecules are in progress.

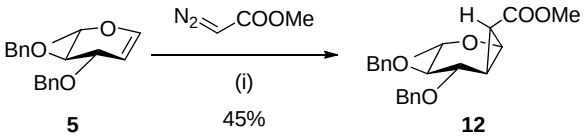
2.4 Experimental Section

2.4.1 Materials and Methods

Chemicals and solvents were purchased from the local suppliers and Sigma-Aldrich® chemical company. Solvents were used in the reactions after distilled over the dehydrating agents. 4 Å Molecular sieves were used in the reactions after crushed and activated at 400 ^{o}C for 1 h. All the reactions were carried out under N_2 or Ar conditions and monitored by the thin layer chromatography (TLC) using silica-gel on aluminum plates (GF_{254}) by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection. Silica-gel (100-200 mesh) was used for column chromatography to purify the all the compounds. ^{1}H, ^{13}C, DEPT spectra were recorded on Bruker® 400 Avance MHz spectrometer in $CDCl_3$. ^{1}H NMR chemical shifts were reported in parts per million (ppm) (δ) with TMS as an internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00).

2.4.2 Experimental Procedures and Spectral Data

(2.4.2.1) 1,5-anhydro-2,6-dideoxy-1,2-(*exo*-carbomethoxy-methylene)-3,4-di-*O*-benzyl-α-L-rhamnal (12):

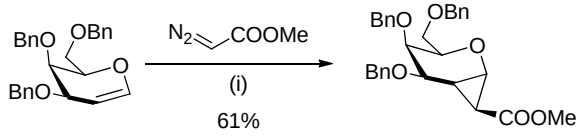


5 12

Reagents and Conditions: (i) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 1 h.

A solution of methyl diazoacetate (MDA) (1.0 mL, 9.66 mmol) in CH_2Cl_2 (32 mL) was slowly added dropwise to the stirred solution of 3,4-di-*O*-benzyl-L-rhamnal **5** (1 g, 3.22 mmol) and $Rh_2(OAc)_4$ (29 mg, 0.064 mmol) in CH_2Cl_2 (7 mL) in dropwise fashion for 1 hour at ambient temperature. After cessation of the nitrogen evolution, the reaction mixture was concentrated under *vacuo* and purified by silica-gel column chromatography (EtOAc in hexane (1:9)) to provide the **12** as a white solid (45% yield).

(2.4.2.2) 1,5-Anhydro-2-deoxy-1,2-C-(*exo*-carbmethoxymethylene)-3,4,6-tri-*O*-benzyl-α-D-galactal (13):

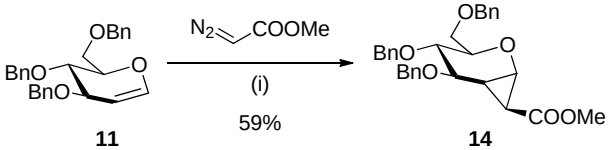


8 13

Reagents and Conditions: (i) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 1 h.

The compound **13** was synthesized using the 3,4,5-tri-*O*-benzyl-D-galactal **8** (1.0 g, 2.4 mmol), $Rh_2(OAc)_4$ (21 mg, 0.048 mmol) and methyl diazoacetate (0.76 mL, 7.2 mmol) in dichloromethane according to the procedure in (**2.4.2.1**). The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (1:9) to provide the **13** as a light yellow oil (61% yield).

(2.4.2.3) 1,5-Anhydro-2-deoxy-1,2-C-(*exo*-carbmethoxymethylene)-3,4,6-tri-*O*-benzyl-α-D-glucal (14):



11 14

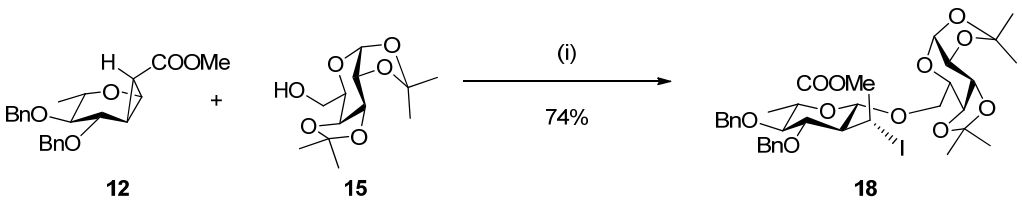
Reagents and Conditions: (i) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 1 h.

The compound **14** was synthesized using the 3,4,5-tri-*O*-benzyl-D-glucal **11** (1.5 g, 3.6 mmol), $Rh_2(OAc)_4$ (32 mg, 0.072 mmol) and methyl diazoacetate (1.15 mL, 10.8 mmol) in dichloromethane according to procedure in (**2.4.2.1**). The crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (1:9) to provide the **14** as a light yellow solid (59% yield).

(2.4.2.4) General procedure for the glycosylation reaction of 1,2-cyclopropanecarboxylated sugar donor with glycosyl acceptor:

To a stirred suspension of 1,2-cyclopropanecarboxylated sugar (0.1 mmol), glycosyl acceptor (0.11 mmol) and 4 Å molecular sieves (MS) in dichloromethane (5 mL) at 0 °C, under nitrogen atmosphere, was added NIS (0.11 mmol) and TMSOTf (0.02 mmol). The temperature was slowly raised to 25 °C and the mixture was stirred for a period of 10 h (the reaction was monitored by TLC). The reaction mixture was diluted with dichloromethane and filtered, washed with 5% aqueous sodium thiosulphate solution and the organic layer was dried over anhydrous sodium sulphate and concentrated. Column chromatography of the crude product with ethyl acetate/hexane afforded the pure 2-C-branched disaccharide derivative.

(2.4.2.5) Compound (18):



12 **15** **18**

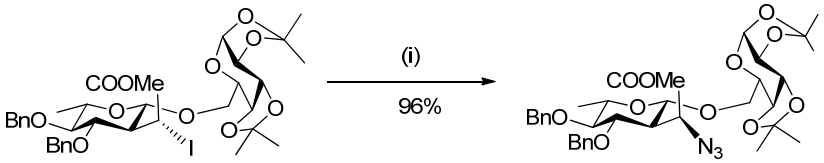
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h.

The compound **18** was synthesized using L-rhamnose-derived 1,2-cyclopropanecarboxylate **12** (100 mg, 0.26 mmol), 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside **15** (75 mg, 0.28 mmol), NIS (64.3 mg, 0.28 mmol), TMSOTf (9.3 µL, 0.05 mmol) and 4 Å MS in dichloromethane (10 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **18** as a thick gum (74% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.23 – 7.32 (m, 10 H), 5.51 (d, 1H, *J* = 5.2 Hz), 5.16 (d, 1H, *J* = 2.0 Hz), 4.93 (d, 1H, 10.8 Hz), 4.79 (d, 2H, *J* = 10.8 Hz), 4.65 (d, 1H, *J* = 10.4 Hz), 4.61 (dd, 1H, *J* = 2.0 Hz, *J* = 7.8 Hz), 4.34 (d, 1H, *J* = 8 Hz), 4.30 – 4.32 (m, 2H), 3.98 – 4.06 (m, 2H), 3.71 – 3.79 (m, 2H), 3.42 (m, 2H), 3.35 (s, 3H), 1.90 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.53 (s, 3H), 1.46 (s, 3H), 1.32 – 1.35 (m, 9H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 167.9, 138.2, 137.7, 128.4, 128.0, 127.8, 127.7, 127.6, 127.3, 109.1, 108.5, 103.4, 96.1, 85.8, 81.4, 75.1, 74.6, 71.4, 70.6, 70.5, 70.4, 68.5, 65.9, 65.7, 53.3, 50.4, 29.2, 26.1, 25.9, 24.8, 24.5, 17.9.

(2.4.2.6) Compound (19):



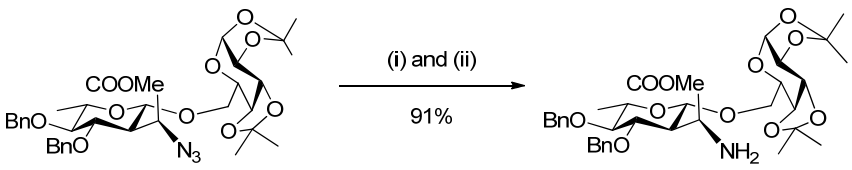
18 **19**

Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h.

To a stirred solution of iodide **18** (80 mg, 0.10 mmol) in dry dimethylformamide (5 mL) was added sodium azide (13.5 mg, 0.20 mmol) (*excess of NaN_3 (upto 10 eq) will fast up the reaction*). The reaction mixture was stirred for 24 h at 25 ^oC. Once the reaction was completed most of the dimethylformamide (DMF) was removed under vacuum and the pale yellow paste was extracted with dichloromethane (3 X 10 mL). The organic layer was washed with water (10 mL), dried over sodium sulphate and filtered. Concentration of organic layer followed by purification of the residue over silica gel column chromatography (EtOAc/hexane 2:3) furnished the pure azide **19** as a colorless oil (96% yield).

^{1}H NMR (CDCl$_3$, 400 MHz, TMS): δ 7.26 – 7.38 (m, 10H), 5.51 (d, 1H, *J* = 5.2 Hz), 4.94 (d, 1H, *J* = 11.2 Hz), 4.86 (d, 1H, *J* = 11.2 Hz), 4.69 (d, 1H, *J* = 11.2 Hz), 4.63 (d, 1H, *J* = 11.2 Hz), 4.58 (dd, 1H, *J* = 2.4 Hz, *J* = 8 Hz), 4.38 (d, 1H, *J* = 8.4 Hz), 4.27 – 4.29 (m, 3H), 3.85 – 3.91 (m, 2H), 3.76 (s, 3H), 3.55 – 3.61 (m, 2H), 3.32 – 3.35 (m, 1H), 3.23 (t, 1H, *J* = 9.2 Hz), 2.37 (dtd, 1H, *J* = 1.6 Hz, *J* = 2.4 Hz, *J* = 8.8 Hz), 1.56 (s, 3H), 1.42 (s, 3H), 1.26 – 1.33 (m, 9H).**^{13}C NMR (CDCl$_3$, 100 MHz)**: δ 170.4, 137.9, 128.6, 128.5, 128.1, 127.9, 127.8, 109.0, 108.3, 100.2, 96.3, 85.6, 78.6, 75.1, 75.1, 71.3, 70.8, 70.6, 70.4, 68.9, 66.1, 58.1, 52.6, 48.9, , 25.9, 25.9, 24.9, 24.4, 17.8.

(2.4.2.7) Compound (20):



19 **20**

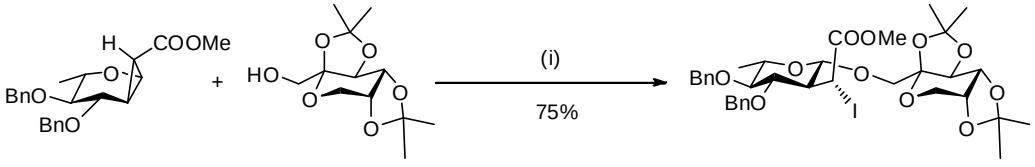
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

Triphenyl phosphine (27 mg, 0.10 mmol) was added to a solution of azide **19** (70 mg, 0.10 mmol) in dry THF (5 mL) maintained under nitrogen. The solution was stirred for 8 h after which complete formation of iminophosphorane was confirmed by infrared spectroscopy (disappearance of azide stretching frequency at 2100 cm^{-1}). At this stage water (0.2 mL) was added and the solution was refluxed for 6 h. The reaction mixture was washed with brine solution (10 mL) and extracted with chloroform (2 X 10 mL). The organic extract was dried over anhydrous sodium sulphate and concentrated under *vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (2:3 to 1:1) as eluent to give the 2-C-branched disaccharide GAA derivative **20** as a colorless oil (91% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 – 7.33 (m, 10H), 5.48 (d, 1H, *J* = 5.2 Hz), 4.93 (d, 1H, *J* = 11.6 Hz), 4.88 (d, 1H, *J* = 11.2 Hz), 4.70 (bs, 1H), 4.67 (bs, 1H), 4.60 (dd, 1H, *J* = 2Hz, *J* = 8 Hz), 4.42 (d, 1H, *J* = 8.8 Hz), 4.28 – 4.32 (m, 2H), 3.85 – 3.88 (m, 2H), 3.86 (dd, 1H, *J* = 2 Hz, *J* = 9.2 Hz), 3.68 (s, 3H), 3.63 (s, 1H), 3.50 – 3.55 (m, 1H), 3.31 – 3.41 (m, 1H), 3.27 (t, 1H, *J* = 9.2 Hz), 2.32 (t, 1H, *J* = 9.2 Hz), 1.52 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (d, 3H, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.5, 138.3, 138.2, 128.5, 128.5, 128.4, 128.2, 128.2, 109.0, 108.4, 100.7, 96.2, 85.9, 78.9, 78.8, 75.9, 74.7, 71.4, 70.5, 68.1, 65.6, 52.1, 52.0, 50.1, 50.0, 26.0, 25.9, 24.9, 24.5, 18.0.

(2.4.2.8) Compound (22):



12 **17** **22**

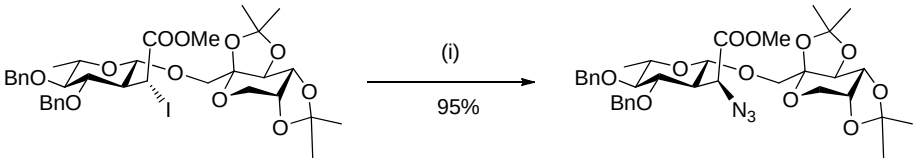
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h.

The compound **22** was synthesized using L-rhamnose-derived 1,2-cyclopropanecarboxylate **12** (150 mg, 0.39 mmol), 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranose **17** (111 mg, 0.42 mmol), NIS (96.5 mg, 0.42 mmol), TMSOTf (14.0 µL, 0.07 mmol) and 4 Å MS in dichloromethane (15 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **22** as a colorless oil (75% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 – 7.32 (m, 10 H), 5.08 (d, 1H, *J* = 2.4 Hz), 4.94 (d, 1H, 10.8 Hz), 4.79 (d, 1H, *J* = 10.8 Hz), 4.78 (d, 1H, *J* = 10.8 Hz), 4.65 (d, 1H, *J* = 10.8 Hz), 4.59 (dd, 1H, *J* = 2.4 Hz, *J* = 7.8 Hz), 4.39 (d, 1H, *J* = 8 Hz), 4.33 (d, 1H, *J* = 2.4 Hz), 4.23 (bd, 1H, *J* = 7.6 Hz), 4.08 (d, 1H, *J* = 10.4 Hz), 3.90 (dd, 1H, *J* = 1.6 Hz, *J* = 12.8 Hz), 3.69 – 3.79 (m, 2H), 3.58 (d, 1H, *J* = 10.4 Hz), 3.41 – 3.44 (m, 2H), 3.34 (s, 3H), 1.96 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.53 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H), 1.35 (bs, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 138.2, 137.7, 128.4, 128.0, 127.8, 127.7, 127.6, 127.3, 108.9, 108.5, 102.3, 102.0, 85.8, 81.3, 75.1, 74.6, 71.5, 70.9, 70.7, 70.3, 70.1, 61.0, 53.4, 50.0, 29.2, 26.6, 25.9, 25.5, 24.0, 17.9.

(2.4.2.9) Compound (23):



22 **23**

Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h.

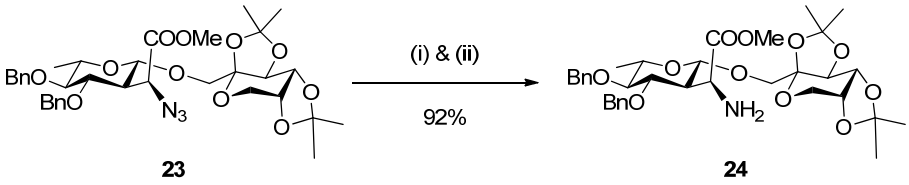
The compound **23** was synthesized using disaccharidyl iodide **22** (120 mg, 0.15 mmol) and NaN_3 (20 mg, 0.31 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **23** as a thick gum (95% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 – 7.36 (m, 10H), 4.95 (d, 1H, *J* = 11.6 Hz), 4.85 (d, 1H, *J* = 10.82 Hz), 4.69 (d, 1H, *J* = 10.8 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.55 (dd, 1H, *J* = 2.8 Hz, *J* = 7.8 Hz), 4.39 (d, 1H, *J* = 8.4 Hz), 4.29 (d, 1H, *J* 2 Hz), 4.20 (dd, 1H, *J* = 1.2 Hz, *J* = 8

Hz), 4.13 (d, 1H, *J* = 2.8 Hz), 3.86 (d, 1H, *J* = 10 Hz), 3.84 (dd, 1H, *J* = 2 Hz, *J* = 13 Hz), 3.79 (s, 3H), 3.70 (d, 1H, *J* = 13 Hz), 3.56 – 3.62 (m, 2H), 3.25 – 3.38 (m, 2H), 2.39 (dtd, 1H, *J* = 2 Hz, *J* = 2.4 Hz, *J* = 8.4 Hz), 1.52 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.28 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 137.9, 137.9, 128.5, 128.4 128.0, 127.9, 127.8, 109.0, 108.5, 101.9, 99.2, 85.5, 78.7, 75.0, 75.0, 71.6, 71.2, 71.1, 70.2, 70.2, 61.0, 58.6, 52.6, 49.0, 26.5, 25.8, 25.4, 24.3, 17.8.

(2.4.2.10) Compound (24):



23 **24**

Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **24** was synthesized using the azide **23** (90 mg, 0.13 mmol) and PPh_3 (35 mg, 0.13 mmol) in THF (5 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by careful silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **24** as a colorless oil (92% yield).

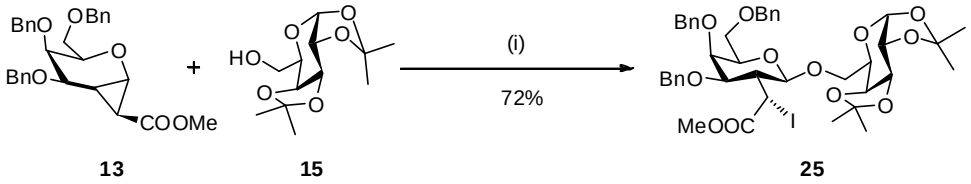
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 – 7.34 (m, 10H), 4.95 (d, 1H, *J* = 11.6 Hz), 4.86 (d, 1H, *J* = 10.8 Hz), 4.69 (d, 1H, *J* = 10.8 Hz), 4.68 (d, 1H, *J* = 10.8 Hz), 4.58 (dd, 1H, *J* = 2.4 Hz, *J* = 8 Hz), 4.49 (d, 1H, *J* = 8.8 Hz), 4.25 (d, 1H, *J* = 2.4 Hz), 4.21 (d, 1H, *J* = 8 Hz), 3.97 (d, 1H, *J* = 10.4 Hz), 3.88 (d, 1H, *J* = 13.2 Hz), 3.73 (s, 3H), 3.67 – 3.72 (m, 3H), 3.49 (d, 1H, *J* = 10.4 Hz), 3.35 – 3.40 (m, 1H), 3.28 (t, 1H, *J* = 8.8 Hz), 2.30 (t, 1H, *J* = 9.6 Hz), 1.50 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.28 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1, 138.2, 138.1, 128.5, 128.4, 128.1, 127.8, 127.8, 108.9, 108.4, 101.9, 99.9, 85.8, 79.2, 74.9, 74.6, 71.4, 71.1, 71.0, 70.2, 69.9, 61.0, 52.0, 50.7, 50.0, 26.5, 25.9, 25.4, 24.2, 17.9.

(2.4.2.11) Compound (25):

The compound **25** was synthesized using D-galactose-derived 1,2-cyclopropanecarboxylate **13** (170 mg, 0.34 mmol), 1,2;3,4-di-*O*-isopropylidene-*α*-D-galactopyranoside **15** (99 mg, 0.38 mmol), NIS (86 mg, 0.38 mmol), TMSOTf (12.2 µL, 0.068 mmol) and 4 Å MS in

dichloromethane (20 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **25** as a yellowish oil (72% yield).

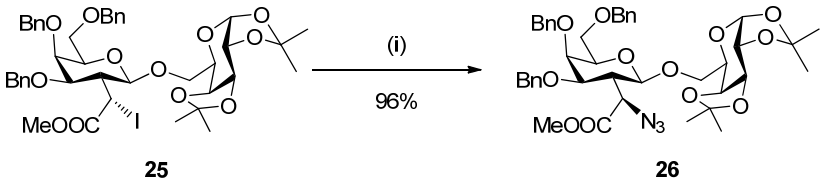


Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 – 7.35 (m, 15 H), 5.53 (d, 1H, *J* = 4.8 Hz), 5.24 (d, 1H, *J* = 2.0 Hz), 4.82 (d, 1H, 11.6 Hz), 4.64 (d, 1H, *J* = 10.4 Hz), 4.59 (dd, 1H, *J* = 2.4 Hz, *J* = 8 Hz), 4.48 – 4.56 (m, 4H), 4.34 (d, 1H, *J* = 8 Hz), 4.29 (dd, 1H, *J* = 2.4 Hz, *J* = 8.8 Hz), 4.22 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz), 4.05 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 3.99 (dt, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz), 3.95 (d, 1H, *J* = 2 Hz), 3.69 – 3. 72 (m, 2H), 3.56 – 3.67 (m, 3H), 3.42 (s, 3H), 2.42 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.51 (s, 3H), 1.44 (s, 3H), 1.32 (bs, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 138.7, 137.9, 137.2, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.3, 109.2, 108.5, 103.9, 96.2, 81.5, 74.3, 73.5, 73.4, 72.1, 71.3, 71.1, 70.7, 70.5, 68.8, 68.6, 66.9, 50.0, 45.1, 30.5, 26.1, 25.9, 24.9, 24.4.

(2.4.2.12) Compound (26):



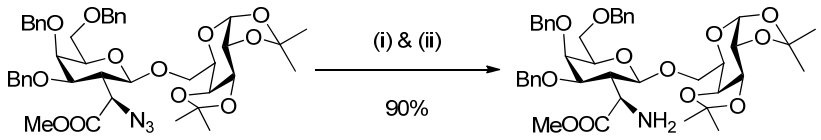
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h.

The compound **26** was synthesized using disaccharidyl iodide **25** (130 mg, 0.14 mmol) and NaN_3 (18.8 mg, 0.29 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **26** as a thick gum (96% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.27 – 7.39 (m, 15 H), 5.50 (d, 1H, *J* = 5.2 Hz), 4.89 (d, 1H, 11.6 Hz), 4.69 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.53 – 4.53 (dd, 1 H, *J* = 2 Hz, *J* = 8 Hz), 4.52 (bs, 1H), 4.46 (d, 2H, *J* = 2 Hz), 4.41 (d, 1H, *J* = 2 Hz), 4.38 (d, 1H, *J* = 4.8 Hz), 4.26 (dd, 1H, *J* = 2.4 Hz, *J* = 9.2 Hz), 4.20 (dd, 1H, *J* = 2 Hz, *J* = 8 Hz), 3.97 (d, 1H, *J* = 2 Hz), 3.94 (dd, 1H, *J* = 6 Hz, *J* = 10 Hz), 3.89 (dt, 1H, *J* = 1.6 Hz, *J* = 5.6 Hz), 3.74 (s, 3H), 3.65 (dd, 1H, *J* = 8Hz, *J* = 9.2 Hz), 3.54 – 3.60 (m, 2H), 3.47 – 3.51 (m, 2H), 2.80 (dtd, 1H, *J* = 2 Hz, *J* = 2.4 Hz, *J* = 8.4 Hz), 1.56 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 170.4, 138.4, 137.9, 137.3, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 108.9, 108.4, 100.3, 96.2, 74.5, 73.5, 73.4, 71.5, 71.0, 70.6, 70.5, 70.4, 68.5, 68.3, 66.5, 58.5, 52.3, 44.1, 25.9, 25.8, 24.9, 24.3.

(2.4.2.13) Compound (27):



26 **27**

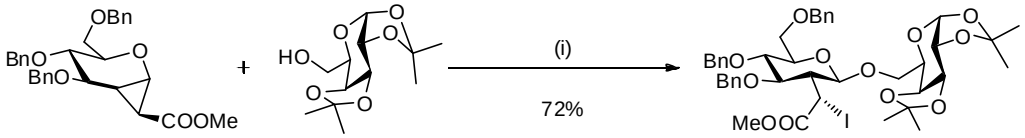
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **27** was synthesized using the azide **26** (100 mg, 0.12 mmol) and PPh_3 (33 mg, 0.12 mmol) in THF (7 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by careful silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **27** as a colorless oil (92% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.25-7.35 (m, 15 H), 5.54 (d, 1H, *J* = 5.2 Hz), 4.90 (d, 1H, *J* =12.0 Hz), 4.71 (d, 1H, *J* =11.6 Hz), 4.62 (dd, 2H, *J* = 1.2 Hz, *J* = 10.0 Hz), 4.53 (dd, 1H, *J* = 2.4 Hz, *J* = 8.0 Hz), 4.41– 4.49 (m, 3H) 4.27 (dd, 1H, *J* = 2.4 Hz, *J* = 4.8 Hz), 4.14 (dd, 1H, *J* = 2 Hz, *J* = 8 Hz), 3.92 – 3.96 (m, 2H), 3.87 (d, 1H, *J* = 1.6 Hz), 3.82 (dd, 1H, *J* = 3.2 Hz, *J* = 12 Hz), 3.70 – 3.76 (m, 2H), 3.67 (s, 3H), 3.52 – 3.66 (m, 4H), 2.74 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.60 (s, 3H),1.39 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 176.4, 138.7, 138.0, 137.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 109.1, 108.5, 100.3, 96.1, 78.1, 74.4, 73.6, 73.5, 71.7, 71.1, 71.0, 70.5, 70.1, 68.9, 67.8, 67.6, 51.9, 50.1, 45.3, 25.9, 25.8, 24.8, 24.3.

(2.4.2.14) Compound (28):



14 **15** **28**

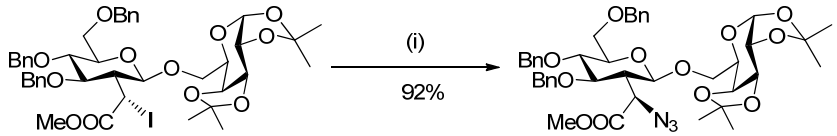
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h.

The compound **28** was synthesized using D-glucose-derived 1,2-cyclopropanecarboxylate **14** (150 mg, 0.30 mmol), 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranoside **15** (87 mg, 0.33 mmol), NIS (75.9 mg, 0.33 mmol), TMSOTf (10.8 µL, 0.06 mmol) and 4 Å MS in dichloromethane (15 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **28** as a colorless oil (72% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 – 7.20 (m, 2H), 7.21 – 7.42 (m, 13H), 5.55 (d, 1H, *J* = 4.8 Hz), 5.17 (d, 1H, *J* = 2 Hz), 4.94 (d, 1H, *J* = 10.4 Hz), 4.80 (d, 1H, *J* = 10.8 Hz), 4.74 (d, 1H, *J* = 10.4 Hz), 4.66 (d, 1H, *J* = 12 Hz), 4.58-4.62 (m, 3H), 4.38 (d, 1H, *J* = 8 Hz), 4.32 (dd, 1H, *J* = 2.4 Hz, *J* = 4.8 Hz), 4.27 (dd, 1H, *J* = 2 Hz, *J* = 7.6 Hz), 4.08 – 4.12 (m, 1H), 4.05 (td, 1H, *J* = 4.8 Hz, *J* = 1.6 Hz), 3.73 – 3.89 (m,5H), 3.47-3.50 (m, 1H), 3.37 (s, 3H), 1.98 (dtd, 1H, *J* = 2.4 Hz, *J* = 2 Hz, *J* = 8.0 Hz), 1.54 (s, 3H), 1.46 (s, 3H), 1.43 (bs, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 138.2, 138.0, 137.7, 128.3, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 109.3, 108.5, 103.4, 96.2, 81.6, 80.0, 75.0, 74.7, 74.6, 73.4, 71.0, 70.6, 70.5, 68.7, 68.5, 66.8, 56.3, 49.9, 29.3, 26.0, 25.9, 24.9, 24.4.

(2.4.2.15) Compound (29):



28 **29**

Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h.

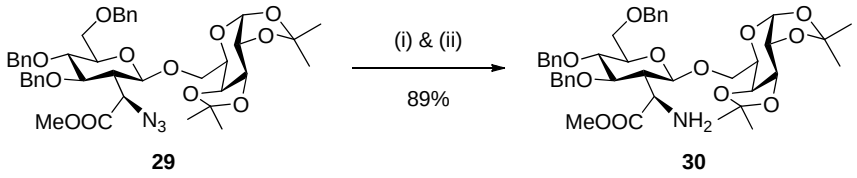
The compound **29** was synthesized using disaccharidyl iodide **28** (120 mg, 0.13 mmol) and NaN_3 (17.8 mg, 0.27 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by

silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **29** as a thick gum (92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 – 7.37 (m, 15H), 5.51 (d, 1H, *J* = 5.2 Hz), 4.94 (d, 1H, *J* = 11.2 Hz), 4.80 (d, 1H, *J* = 10.8 Hz), 4.53-4.66 (m, 5H), 4.44 (d, 1H, *J* = 8.4 Hz), 4.30 (d, 1H, *J* = 1.6 Hz), 4.28 (dd, 1H, *J* = 2.4 Hz, *J* = 5.2 Hz), 4.23 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz), 3.96 – 4.00 (m, 1H), 3.92 (dt, 1H, *J* = 1.6 Hz, *J* = 5.6 Hz), 3.75 (s, 3H), 3.58 – 3.73 (m, 5H), 3.38 – 3.40 (m, 1H), 2.38 (dtd, 1H, *J* = 2 Hz, *J* = 2.4 Hz, *J* = 8.8 Hz), 1.58 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 138.0, 137.9, 137.9, 128.5, 128.4, 128.3, 128.0,127.9, 127.7, 127.6, 127.6, 109.0, 108.5, 100.0, 96.27, 79.7, 78.8, 75.0, 74.99, 74.6, 73.5, 70.9, 70.5, 70.4, 68.4, 68.2, 66.3, 58.3, 52.4, 48.6, 25.9, 25.8, 24.9, 24.4.

(2.4.2.16) Compound (30):



29 **30**

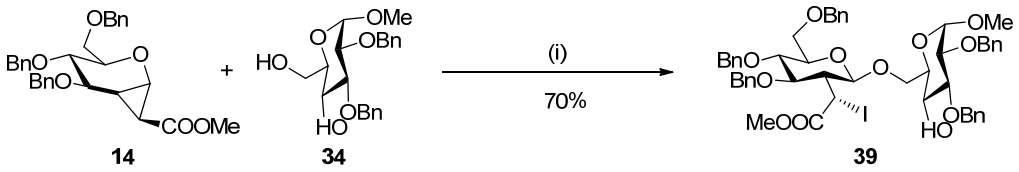
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **30** was synthesized using the azide **29** (90 mg, 0.11 mmol) and PPh_3 (30 mg, 0.11 mmol) in THF (7 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by careful silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **30** as a colorless oil (89% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 – 7.36 (m, 15 H), 5.54 (d, 1H, *J* = 5.2 Hz), 4.93 (d, 1H, *J* = 11.6 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 4.53-4.71 (m, 6H), 4.29 (dd, 1H, *J* = 2.4 Hz, *J* = 5.2 Hz), 4.18 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz), 3.93 – 3.95 (m, 1H), 3.81 – 3.89 (m, 2H), 3.70-3.75 (m, 5H), 3.67 (s, 3H), 3.44 – 3.47 (m, 1H), 2.32 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8 Hz), 1.64 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.4, 138.3, 138.2, 138.2, 129.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 109.1, 108.5, 100.3, 96.1, 80.1, 79.2, 75.0, 74.7, 74.4, 73.4, 71.1, 70.5, 70.1, 68.8, 67.7. 67.6, 51.8, 50.3, 49.9, 25.9, 25.8, 24.8, 24.3.

(2.4.2.17) Compound (39):

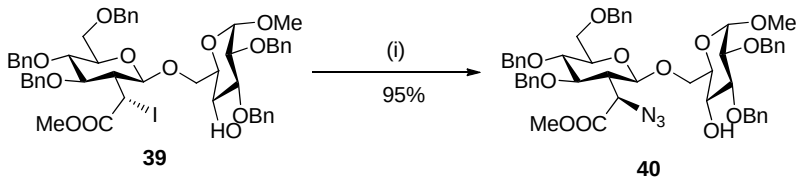


Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h.

The compound **39** was synthesized using D-glucose-derived 1,2-cyclopropanecarboxylate **14** (150 mg, 0.30 mmol), methyl 2,3-di- *O*-benzyl-α-D-glucopyranoside **34** (126 mg, 0.33 mmol), NIS (75.9 mg, 0.33 mmol), TMSOTf (10.8 µL, 0.06 mmol) and 4 Å MS in dichloromethane (15 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **39** as a thick gum (70% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 – 7.24 (m, 23H), 6.97 – 6.98 (m, 2H), 4.93 (d, 1H, *J* = 2 Hz), 4.88 (d, 1H, *J* = 11.2 Hz), 4.82 (d, 1H, *J* = 10.4 Hz), 4.39 – 4.66 (m, 9H), 4.25 (d, 1H, *J* = 8 Hz), 4.00 (d, 1H, *J* = 8.8 Hz), 3.59 – 3.72 (m, 7H), 3.47 (m, 1H), 3.41 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz), 3.27 (s, 3H), 3.23 (s, 3H), 2.41 (bs, 1H), 1.89 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz). **^{13}C NMR ($CDCl_3$, 100 MHz)**: δ 167.6, 138.7, 138.1, 138.0, 137.9, 137.6, 128.5, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.7, 127.6, 127.3, 103.2, 98.1, 81.4, 79.8, 79.5, 75.4, 75.0, 74.7, 74.7, 73.4, 73.1, 70.2, 69.9, 68.7, 68.5, 55.2, 53.3, 49.7, 28.9.

(2.4.2.18) Compound (40):



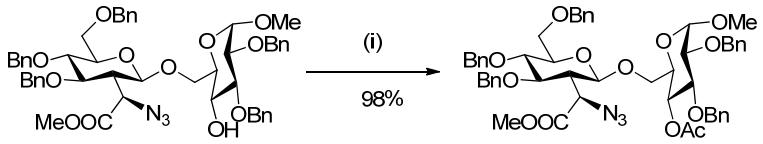
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h.

The compound **40** was synthesized using disaccharidyl iodide **39** (100 mg, 0.10 mmol) and NaN_3 (13.1 mg, 0.20 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **40** as a thick gum (95% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17– 7.39 (m, 25H), 4.70 – 4.94 (m, 5H), 4.50 – 4.63 (m, 6H), 4.39 (d, 1H, *J* = 8.4 Hz), 4.26 (s, 1H), 3.89 (dd, 1H, *J* = 2.4 Hz, *J* = 10.4 Hz), 3.72 – 3.79 (m, 2H), 3.63 – 3.70 (m, 5H), 3.55 3.60 (m, 3H), 3.42 – 3.46 (m, 1H), 3.43 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.39 (m, 1H), 3.34 (s, 3H), 2.98 (d, 1H, *J*= 3.6 Hz), 2.33 (t, 1H, *J* = 8.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 139.2, 138.2, 138.0, 137.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.7, 127.5, 127.3, 99.6, 98.3, 81.3, 79.7, 79.0, 78.5, 75.2, 75.1, 75.0, 74.7, 73.9, 73.5, 70.2, 69.6, 68.7, 68.6, 58.4, 55.1, 52.8, 48.6.

(2.4.2.19) Compound (41):



40 **41**

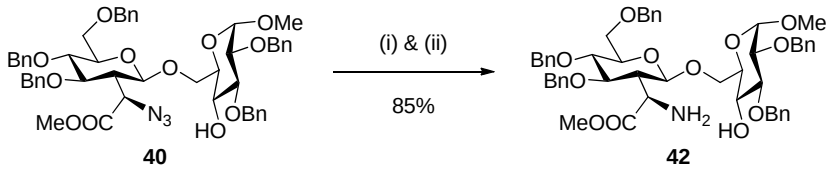
Reagents and Conditions: (i) Ac_2O, Py, rt, 10 h

To the stirred solution of disaccharide-based azide **40** (60 mg, 0.06 mmol) in pyridine (2 mL) was added acetic anhydride (12.5 µL, 0.13 mmol) at 0 ^oC. The reaction mixture was stirred for 10 h at room temperature. After completion of reaction, the solution was concentrated under *vacuo* and purified by silica-gel column chromatography in ethyl acetate/hexane (1:9) to afford the acetylated 2-C-branched disaccharide derivative **41** as a colorless oil (98% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 – 7.37 (m, 25H), 4.93 (d, 1H, *J* = 11.6 Hz), 4.87 (d, 1H, *J* = 11.6 Hz), 4.76 – 4.81 (m, 3H), 4.60 – 4.64 (m, 5H), 4.50 – 4.55 (m, 2H), 4.37 (d, 1H, *J* = 8.4 Hz), 4.30 (s, 1H), 3.90 (t, 1H, *J* = 9.2 Hz), 3.74 – 3.79 (m, 1H), 3.71 (dd, 1H, *J* = 3.6 Hz, *J* = 10.8 Hz), 3.62 – 3.68 (m, 6H), 3.59 (bs, 1H), 3.55 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz), 3.48 (dd, 1H, *J* = 6.4 Hz, *J* = 11.2 Hz), 3.44 (s, 3H), 3.35 (bd, 1H, *J* = 7.6 Hz), 2.28 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 169.9, 138.6, 138.1, 138.0, 137.9, 137.8, 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5, 99.9, 98.0, 79.7, 79.4, 79.0, 78.7, 75.0, 74.9, 74.6, 73.5, 73.4, 71.1, 69.1, 68.9, 68.6, 58.3, 55.5, 52.2, 48.8, 20.7.

(2.4.2.20) Compound (42):



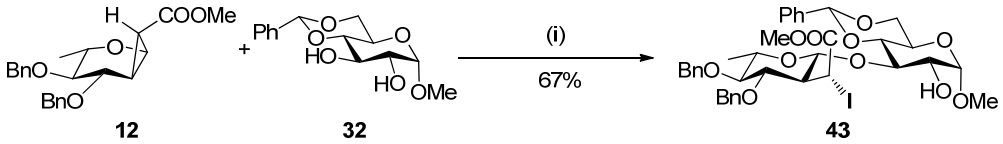
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **42** was synthesized using the azide **40** (70 mg, 0.07 mmol) and PPh_3 (20 mg, 0.07 mmol) in THF (5 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **42** as a colorless oil (85% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 – 7.25 (m, 25H), 4.39 – 4.86 (m, 11H), 3.86 (dd, 1H, *J* = 1.6 Hz, *J* = 10.4 Hz), 3.61 – 3.73 (m, 4H). 3.58 – 3.60 (m, 5H), 3.36 – 3.39 (m, 4H), 3.27 (s, 3H), 2.21 (t, 1H, *J* = 9.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.0, 138.3, 138.2, 138.1, 137.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.3, 99.9, 98.4, 81.4, 80.0, 79.1, 78.5, 75.2, 75.1, 74.6, 74.5, 73.4, 73.1, 70.0, 69.6, 69.0, 68.2, 55.2, 52.3, 50.1, 49.8.

(2.4.2.21) Compound (43):



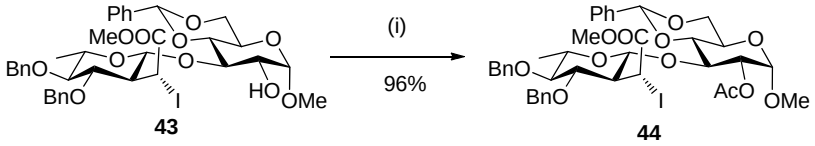
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h

The compound **43** was synthesized using D-rhamnose-derived 1,2-cyclopropanecarboxylate **12** (150 mg, 0.39 mmol), methyl 4,6-*O*-benzylidine-α-D-glucopyranoside **32** (121 mg, 0.43 mmol), NIS (97 mg, 0.43 mmol), TMSOTf (14.1 µL, 0.078 mmol) and 4 Å MS in dichloromethane (15 mL) according to general procedure (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **43** as a thick gum (67% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.47 (m, 2H), 7.21 – 7.32 (m, 13H), 5.52 (s, 1H), 5.19 (d, 1H, *J* = 1.6 Hz), 4.91 (d, 1H, *J* = 10.8 Hz), 4.88 (d, 1H, *J* = 4.5 Hz), 4.78 (d, 1H, *J* = 10.8 Hz), 4.76 (d, 1H, *J* = 10.8 Hz), 4.63 (d, 1H, *J* = 10.8 Hz), 4.50 (d, 1H, *J* = 8.4 Hz), 4.48 (bs, 1H), 4.30 (dd, 1H, *J* = 4.8 Hz, *J* = 10 Hz), 3.98 (t, 1H, *J* = 8.8 Hz), 3.86 (m, 1H), 3.72 -3.79 (m, 2H), 3.71 (dd, 1H, *J* = 4 Hz, *J* = 9.2 Hz), 3.61 (t, 1H, *J* = 9.6 Hz), 3.52 (dd, 1H, *J* = 6.4 Hz, *J* = 9.6 Hz), 3.46 (s, 3H), 3.42 (t, 1H, *J* = 8.8 Hz), 3.30 (s, 3H), 1.95 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.37 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 137.9, 137.3, 136.7, 128.9, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.2, 126.1, 103.3, 101.6, 99.7, 84.9, 82.7, 81.4, 79.2, 75.1, 74.6, 71.8, 71.4, 68.9, 62.2, 55.2, 53.2, 50.8, 28.6, 17.5.

(2.4.2.22) Compound (44):



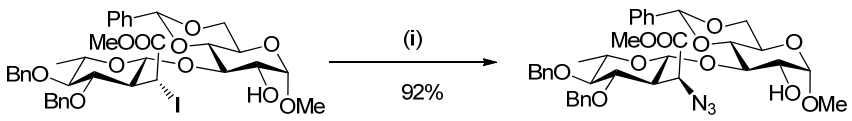
Reagents and Conditions: (i) Ac_2O, Py, rt, 10 h

To the stirred solution of disaccharidyl iodide **43** (80 mg, 0.10 mmol) in pyridine (3 mL) was added acetic anhydride (19 µL, 0.20 mmol) at 0 ^oC. The reaction mixture was stirred for 10 h at room temperature. After completion of reaction, the solution was concentrated under *vacuo* and purified by silica-gel column chromatography by ethyl acetate in hexane (1:9) to afford the acetylated 2-C-branched disaccharide derivative **44** as a colorless gum (96% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.46 (m, 2H), 7.21 – 7.34 (m, 13H), 5.54 (s, 1H), 5.26 (d, 1H, *J* = 1.6 Hz), 4.86 – 4.94 (m, 3H), 4.77 (d, 1H, *J* = 10.8 Hz), 4.73 (d, 1H, *J* = 8.4 Hz), 4.57 – 4.62 (m,2H), 4.33 (t, 1H, *J* = 8.8 Hz), 4.29 (dd, 1H, *J* = 4.4 Hz, *J* = 10.4 Hz), 3.89 (dt, 1H, *J* = 4.8 Hs, *J* = 9.6 Hz), 3.77 (t, 1H, *J* = 10.4 Hz), 3.69 (t, 2H, *J* = 9.6 Hz), 3.41 (s, 3H), 3.35 – 3.36 (m, 2H), 3.23 (s, 3H), 2.14 (s, 3H), 1.82 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.34 (d, 3H, *J* = 4.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 167.8, 138.2, 137.6, 136.8, 129.1, 128.5, 128.2, 128.0, 127.9, 127,7, 127.6, 127.3, 126.3, 102.6, 102.1, 97.7, 85.7, 81.4, 81.0, 75.6, 75.2, 74.6, 72.2, 71.2, 68.9, 61.9, 55.3, 53.2, 51.4, 29.5, 21.0, 18.1.

(2.4.2.23) Compound (45):



43 **45**

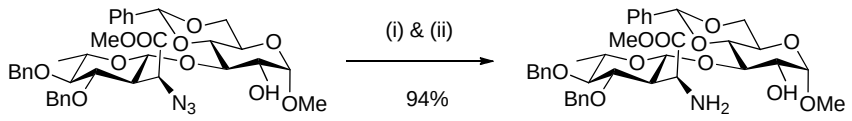
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

The compound **45** was synthesized using disaccharidyl iodide **43** (120 mg, 0.15 mmol) and NaN_3 (19.7 mg, 0.30 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **45** as a semi solid (92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 – 7.66 (m, 2H), 7.30 – 7.42 (m, 13H), 5.65 (s, 1H), 4.96 (d, 1H, *J* = 11.6 Hz), 4.87 (d, 1H, *J* = 10.8 Hz), 4.83 (d, 1H, *J* = 3.6 Hz), 4.74 (d, 1H, *J* = 8.4 Hz), 4.69 (d, 1H, *J* = 10.8 Hz), 4.62 (d, 1H, *J* = 11.2 Hz), 4.40 (d, 1H, *J* = 2 Hz), 4.29 (d, 1H, *J* = 5.6 Hz), 3.99 (t, 1H, *J* = 9.2 Hz), 3.79 – 3.81 (m, 2H), 3.74 (s, 3H), 3.48 – 3.62 (m, 4 H), 3.45 (s, 3H), 3.37 – 3.41 (m, 1H), 3.27 (t, 1H, *J* = 8.2 Hz), 2.33 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.8 Hz), 1.35 (d, 3H, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 137.7, 137.6, 137.3, 128.6, 128.5, 128.4, 128.0 (3), 127.9, 127.8, 125.9, 101.3, 99.5, 98.8, 85.2, 80.1, 78.3, 77.7, 75.1, 75.0, 71.1, 68.8, 62.1, 58.1, 55.1, 52.0, 48.7, 17.7.

(2.4.2.24) Compound (46):



45 **46**

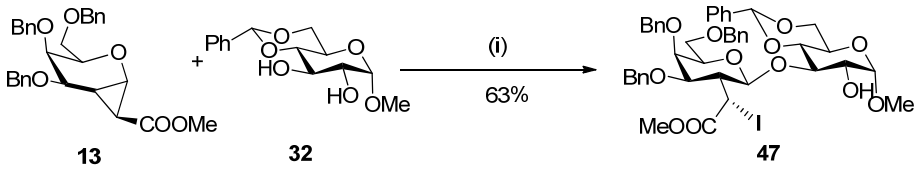
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **46** was synthesized using the azide **45** (75 mg, 0.10 mmol) and PPh_3 (27.8 mg, 0.07 mmol) in THF (5 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **46** as a colorless oil (94% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 – 7.60 (m, 2H), 7.24 – 7.38 (m, 13H), 5.66 (s, 1H), 4.83 – 4.88 (m, 3H), 4.65 (d, 1H, *J* = 11.2 Hz), 4.58 (d, 1H, *J* = 11.2 Hz), 4.44 (d, 1H, *J* = 8.8 Hz), 4.27 (dd, 1H, *J* = 4 Hz, *J* = 9.6 Hz), 3.71 – 3.83 (m, 5H), 3.69 (s, 3H), 3.53 – 3.56 (m, 2H), 3.46 (s, 3H), 3.36 – 3.44 (m, 2H), 3.24 (t, 1H, *J* = 8.2 Hz), 2.31 (dtd, 1H, *J* = 1.6 Hz, *J* = 2 Hz, *J* = 8.8 Hz), 1.30 (d, 3H, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8, 138.2, 138.0, 137.1, 129.3, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 126.6, 102.5, 100.8, 99.7, 85.3, 80.6, 79.7, 79.0, 75.0, 74.9, 71.6, 71.2, 69.1, 62.2, 55.3, 51.8, 50.4, 50.0, 17.9.

(2.4.2.25) Compound (47):



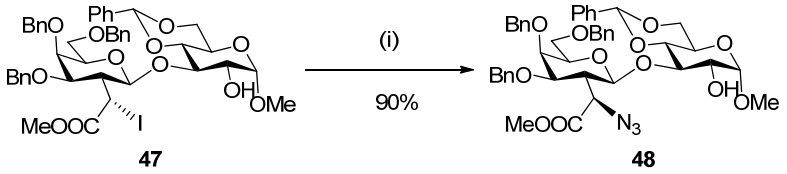
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h

The compound **47** was synthesized using D-galactose-derived 1,2-cyclopropanecarboxylate **13** (160 mg, 0.32 mmol), methyl 4,6-*O*-benzylidine-*α*-D-glucopyranoside **32** (101 mg, 0.36 mmol), NIS (81 mg, 0.36 mmol), TMSOTf (11.5 μL, 0.064 mmol) and 4 Å MS in dichloromethane (15 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **47** as a colorless oil (63% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.37 (m, 2H), 7.16 – 7.22 (m, 18H), 5.50 (s, 1H), 5.40 (s, 1H), 4.72 (d, 1H, *J* = 10.4 Hz), 4.71 (d, 1H, *J* = 4.8 Hz), 4.49 – 4.54 (m, 2H), 4.43 (d, 1H, *J* = 6.4 Hz), 4.41 (d, 1H, *J* = 7.6 Hz), 4.28 (d, 1H, *J* = 12 Hz), 4.20 (d, 1H, *J* = 12 Hz), 4.18 (dd, 1H, *J* = 4.8 Hz, *J* = 10 Hz), 4.01 (t, 1H, *J* = 9.6 Hz), 3.86 (bs, 1H), 3.62 – 3.75 (m, 3H), 3.49 – 3.58 (m, 3H), 3.44 (t, 1H, *J* = 6 Hz), 3.36 (s, 3H), 3.28 – 3.30 (m, 1H), 3.26 (s, 3H), 3.01 (d, 1H, *J* = 6.8 Hz), 2.40 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 138.6, 137.7, 137.2, 137.0, 128.8, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 126.1, 101.6, 101.3, 99.9, 81.7, 79.4, 78.8, 74.2, 73.4, 73.4, 72.1, 71.1, 70.8, 68.9, 68.3, 62.6, 55.3, 53.0, 45.3, 31.8.

(2.4.2.26) Compound (48):



47 48

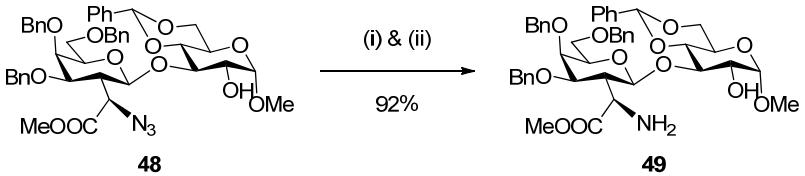
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

The compound **48** was synthesized using disaccharidyl iodide **47** (120 mg, 0.13 mmol) and NaN_3 (17.3 mg, 0.26 mmol) in DMF (10 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **48** as a thick gum (90% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.42 (m, 2H), 7.13 – 7.30 (m, 18H), 5.37 (s, 1H), 4.81 (d, 1H, *J* = 11.6 Hz), 4.73 (d, 1H, *J* = 3.6 Hz), 4.61 (d, 1H, *J* = 11.6 Hz), 4.57 (d, 1H, *J* = 1.6 Hz), 4.55 (d, 1H, *J* = 11.6 Hz), 4.52 (d, 1H, *J* = 8.4 Hz), 4.32 (d, 1H, *J* = 11.6 Hz), 4.29 (d, 1H, *J* = 11.6 Hz), 4.23 (d, 1H, *J* = 11.6 Hz), 4.15 (dd, 1H, *J* = 4.4 Hz, *J* = 10.2 Hz), 4.00 (d, 1H, *J* = 5.6 Hz), 3.93 (d, 1H, *J* = 2 Hz), 3.83 (t, 1H, *J* = 9.2 Hz), 3.72 (m, 1H), 3.70 (s, 3H), 3.63 (dd, 1H, *J* = 3.6 Hz, *J* = 10 Hz), 3.61 (dd, 1H, *J* = 3.2 Hz, *J* = 20 Hz), 3.49-3.53 (m,1H), 3.36- 3.40 (m, 3H), 3.35 (s, 3H), 3.29 (t, 1H, *J* = 9.2 Hz), 2.71 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 138.7, 137.9, 137.5, 137.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.8, 127.7, 127.7, 127.4, 127.3, 100.7, 100.6, 100.2, 80.1, 79.1, 77.2, 74.4, 73.5, 73.0, 71.3, 70.4, 68.9, 68.2, 62.9, 59.4, 55.2, 52.9, 44.3.

(2.4.2.27) Compound (49):



48 49

Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

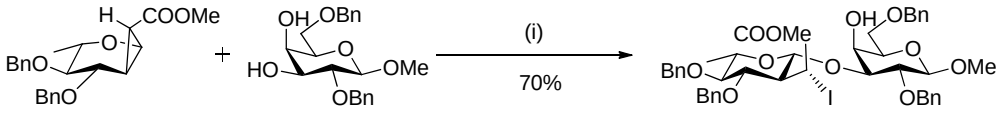
The compound **49** was synthesized using the azide **48** (90 mg, 0.11 mmol) and PPh_3 (29 mg, 0.11 mmol) in THF (7 mL) by following the same procedure in (**2.4.2.7**). The resulted crude

product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **49** as a colorless oil (92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, 2H, *J* = 7.2 Hz), 7.21 – 7.34 (m, 18H), 5.43 (s, 1H), 4.88 (d, 1H, *J* = 11.6 Hz), 4.74 (d, 1H, *J* = 3.6 Hz), 4.64 – 4.69 (m, 2H), 4.46 (d, 1H, *J* = 11.6 Hz), 4.36 (d, 1H, *J* = 11.6 Hz), 4.30 (d, 1H, *J* = 11.6 Hz), 4.20 (dd, 1H, *J* = 4.4 Hz, *J* = 9.6 Hz), 3.99 (bs, 1H), 3.95 (bs, 1H), 3.89 (t, 1H, *J* = 9.2 Hz), 3.64 – 3.71 (m, 6H), 3.53 (m, 2H), 3.41 (m, 1H), 3.39 (s, 3H), 3.31 (t, 1H, *J* = 9.2 Hz), 2.91 (bt, 1H, 9.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8, 138.6, 138.0, 137.5, 137.3, 128.7, 128.7, 128.5, 128.4, 128.2, 128.2, 128.1, 127.9, 127.7, 127.5, 101.2, 100.9, 100.3, 80.2, 78.8, 75.9, 74.5, 73.6, 71.4, 70.6, 70.4, 68.9, 68.5, 62.8, 55.2, 52.1, 49.6, 44.2.

(2.4.2.28) Compound (50):



12 **38** **50**

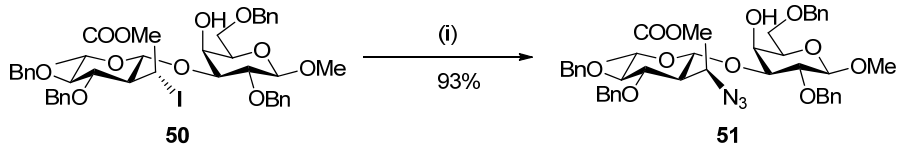
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h

The compound **50** was synthesized using L-rhamnose-derived 1,2-cyclopropanecarboxylate **12** (180 mg, 0.47 mmol), methyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside **38** (193 mg, 0.51 mmol), NIS (116 mg, 0.51 mmol), TMSOTf (17 µL, 0.094 mmol) and 4 Å MS in dichloromethane (20 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **50** as a light yellowish gum (70% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 – 7.41 (m, 20H), 5.23 (d, 1H, *J* = 1.6 Hz), 4.95 (d, 1H, *J* = 10.8 Hz), 4.59 – 4.82 (m, 7H), 4.55 (d, 1H, *J* = 8.4 Hz), 4.30 (d, 1H, *J* = 8 Hz), 4.19 (bs, 1H), 3.90 (dd, 1H, *J* = 2.8 Hz, *J* = 9.6 Hz), 3.81 (dd, 1H, *J* = 6.4 Hz, *J* = 9.6 Hz), 3.71 – 3.76 (m, 2H), 3.56 – 3.62 (m, 3H), 3.55 (s, 3H), 3.42 – 3.48 (m, 2H), 3.36 (s, 3H), 2.50 (d, 1H, *J* = 4 Hz), 2.03 (t, 1H, *J* = 8.8 Hz), 1.26 (d, 3H, *J* = 4.8 Hz).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 168.0, 138.8, 138.2, 137.9, 137.7, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 104.6, 99.4, 85.9, 81.4, 78.6, 77.3, 75.3, 74.8, 74.7, 73.8, 72.8, 71.6, 69.1, 66.5, 57.1, 53.4, 50.4, 28.7, 18.0.

(2.4.2.29) Compound (51):



50 **51**

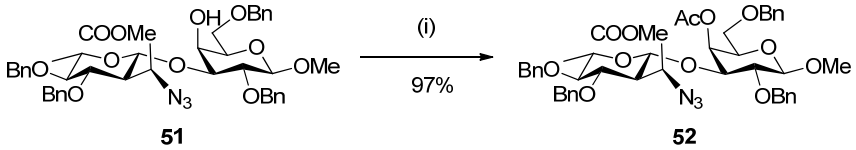
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

The compound **51** was synthesized using disaccharidyl iodide **50** (130 mg, 0.14 mmol) and NaN_3 (19 mg, 0.29 mmol) in DMF (12 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **51** as a colorless gum (93% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.29 – 7.49 (m, 20H), 5.03 (d, 1H, *J* = 11.6 Hz), 4.93 (d, 1H, *J* = 11.2 Hz), 4.78 (d, 1H, *J* = 10.8 Hz), 4.76 (d, 1H, *J* = 10.8 Hz), 4.64 – 4.71 (m, 4H), 4.58 (d, 1H, *J* = 8 Hz), 4.39 (d, 1H, *J* = 1.2 Hz), 4.31 (d, 1H, *J* = 7.6 Hz), 4.07 (s, 1H), 3.87 – 3.91 (m, 2H), 3.77 – 3.87 (m, 2H), 3.70 (s, 3H), 3.58 – 3.65 (m, 5H), 3.49 (dd, 1H, *J* = 8 Hz, *J* = 9.6 Hz), 3.30 – 3.38 (m, 3H), 2.35 (t, 1H, *J* = 9.2 Hz), 1.36 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 172.6, 138.9, 138.1, 137.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.2, 104.1, 95.2, 85.8, 78.6, 78.1, 77.5, 75.1, 74.9, 74.6, 73.6, 73.0, 71.3, 69.1, 65.1, 58.6, 56.7, 52.9, 49.2, 17.8.

(2.4.2.30) Compound (52):



51 **52**

Reagents and Conditions: (i) Ac_2O, Py, rt, 10 h

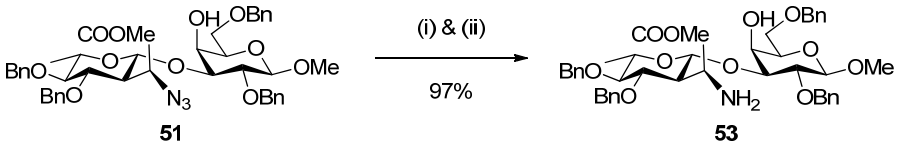
To the stirred solution of disaccharide-based azide **51** (85 mg, 0.10 mmol) in pyridine (4 mL) was added acetic anhydride (20 µL, 0.21 mmol) at 0 ^oC. The reaction mixture was stirred for 10 h at room temperature. After completion of reaction, the solution was concentrated under

vacuo and purified by silica-gel column chromatography in ethyl acetate in hexane (1:9 to 1:4) to afford the acetylated 2-C-branched disaccharide derivative **52** as a colorless oil (97% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 – 7.43 (m, 20H), 5.44 (d, 1H, *J* = 3.2 Hz), 4.95 (d, 1H, *J* = 11.2 Hz), 4.88 (d, 1H, *J* = 11.2 Hz), 4.61 – 4.73 (m, 4H), 4.57 (d, 1H, *J* = 8.4 Hz), 4.50 (bs, 2H), 4.32 (d, 1H, *J* = 1.6 Hz), 4.29 (d, 1H, *J* = 7.6 Hz), 4.17(dd, 1H, *J* = 3.6 Hz, *J* = 10 Hz), 3.58 – 3.65 m, 5H), 3.54 (s, 3H), 3.36 – 3.52 (m, 5H), 3.24 (t, 1H, *J* = 9.2 Hz), 2.31 (dtd, 1H, *J* = 1.6 Hz, *J* = 2 Hz, *J* = 9.2 Hz), 2.24 (s,3H) 1.29 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.0, 138.8, 137.9, 137.8, 137.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 104.4, 94.2, 85.9, 78.4, 75.2, 75.0, 74.6, 73.9, 73.8, 72.7, 72.7, 71.3, 68.8, 64.9, 58.0, 57.4, 52.2, 49.0, 20.8, 17.9.

(2.4.2.31) Compound (53):



51 **53**

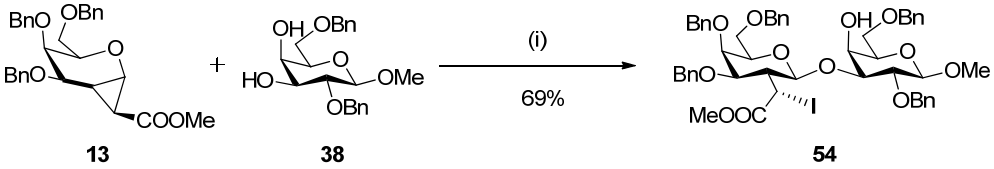
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **53** was synthesized using the azide **51** (75 mg, 0.09 mmol) and PPh_3 (24 mg, 0.11 mmol) in THF (5 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **53** as a colorless oil (97% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 – 7.46 (m, 20H), 4.96 (d, 1H, *J* = 11.6 Hz), 4.92 (d, 1H, *J* = 10.8 Hz), 4.69 – 4.78 (m, 4H), 4.65 (d, 1H, *J* = 8.4 Hz), 4.50 (bs, 2H), 4.26 (d, 1H, *J* = 7.6 Hz), 4.00 (d, 1H, *J* = 2.8 Hz), 3.91 (dd, 1H, *J* = 2.8 Hz, *J* = 9.6 Hz), 3.82 (dd, 1H, *J* = 6 Hz, *J*= 9.6 Hz), 3.72 – 3.75 (m, 2H), 3.67 (dd, 1H, *J* = 8.4 Hz, *J* = 11.2 Hz), 3.61 – 3.64 (m, 1H), 3.60 (s, 3H), 3.55 (m, 1H), 3.53 (s, 3H), 3.43(dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz), 3.32 – 3.39 (m, 2H), 2.29 (dtd, 1H, *J* = 1.6 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.32 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.6, 139.0, 138.1, 138.0, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.6, 127.3, 104.1, 94.9, 86.1, 77.9, 77.8, 77.7, 75.1, 74.7, 74.4, 73.7, 73.1, 71.3, 69.3, 65.0, 56.8, 52.3, 50.3, 49.8, 18.0.

(2.4.2.32) Compound (54):



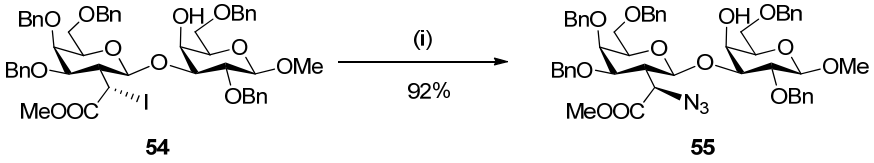
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h

The compound **54** was synthesized using D-galactose-derived 1,2-cyclopropanecarboxylate **13** (160 mg, 0.32 mmol), methyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside **38** (134 mg, 0.36 mmol), NIS (80.9 mg, 0.51 mmol), TMSOTf (11.5 µL, 0.064 mmol) and 4 Å MS in dichloromethane (15 mL) according to general procedure (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **54** as a colorless oil (69% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 – 7.25 (m, 25H), 4.97 (s, 1H), 4.84 (d, 1H, *J* = 11.2 Hz), 4.72 (d, 1H, *J* = 11.2 Hz), 4.31 – 4.54 (m, 10H), 4.24 (m, 1H), 3.99 (bs, 1H), 3.81 (bs, 1H), 3.70 (d, 2H, *J* = 5.6 Hz), 3.47 – 3.55 (m, 9H), 3.28 (s, 3H), 2.77 (bs, 1H), 2.31 (t, 1H, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 138.5, 138.3, 138.2, 137.7, 137.0, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.6, 127.6, 127.3, 104.6, 104.0, 83.7, 81.2, 77.8, 75.0, 74.4, 73.7, 73.6, 73.4, 73.0, 72.3, 71.2, 69.4, 68.8, 67.6, 56.7, 53.0, 45.6, 30.6.

(2.4.2.33) Compound (55):



Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

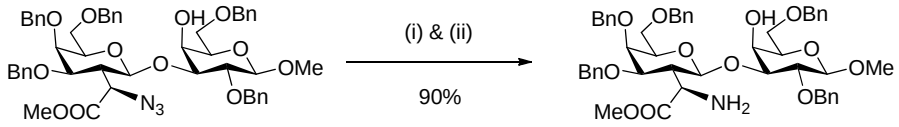
The compound **55** was synthesized using disaccharidyl iodide **54** (150 mg, 0.15 mmol) and NaN_3 (19.7 mg, 0.30 mmol) in DMF (12 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by

silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **55** as a colorless gum (92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 – 7.33 (m, 25H), 4.82 – 4.92 (m, 4H), 4.65 (d, 1H, *J* = 11.2 Hz) 4.49 – 4.66 (m, 4H), 4.38 (bs, 2H), 4.32 (d, 1H, *J* = 11.6 Hz), 4.16 (dd, 1H, *J* = 2.8 Hz, *J* = 7.6 Hz), 3.90 (bs, 1H), 3.86 (bs, 1H), 3.65 – 3.75 (m, 6H), 3.48 – 3.57 (m, 7H), 3.38 – 3. 41 (m, 2H), 2.74 (t, 1H, *J* = 8.4 Hz), 2.25 (bs, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 139.4, 138.3, 138.1, 137.8, 137.2, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.1, 105.2, 99.6, 78.8, 76.7, 74.5, 73.8, 73.6, 73.4, 73.3, 73.2, 71.5, 70.5, 69.3, 69.1, 68.4, 58.6, 56.8, 52.5, 44.3.

(2.4.2.34) Compound (56):



55 **56**

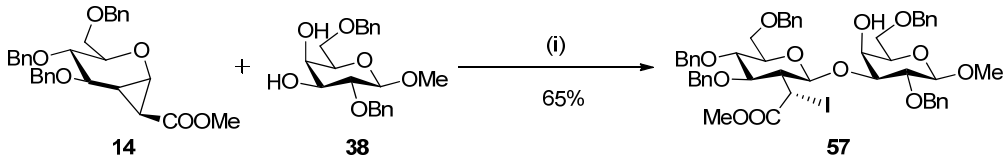
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **56** was synthesized using the azide **55** (95 mg, 0.10 mmol) and PPh_3 (27 mg, 0.11 mmol) in THF (7 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **56** as a colorless oil (97% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 – 7.29 (m, 25H), 4.96 (d, 1H, *J* = 11.2 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 4.73 (d, 1H, *J* = 11.2 Hz), 4.61 (bs, 1H), 4.59 (d, 1H, *J* = 4 Hz), 4.45 – 4.52 (m, 3H), 4.32 – 4.35 (m, 3H), 4.16 (d, 1H, *J* = 7.6 Hz), 3.89 (d, 1H, *J* = 2.4 Hz), 3.81 (bs, 1H), 3.72 (bs, 1H), 3.66 (d, 2H, *J* = 5.6 Hz), 3.59 (s, 3H), 3.55 (d, 1H, *J* = 2.8 Hz), 3.45 – 3.52 (m, 4H), 3.41 (s, 3H), 3.38 (t, 1H, *J* = 6 Hz), 2.68 (t, 1H, *J* = 9.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8, 139.3, 138.5, 138.2, 137.9, 137.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 105.1, 101.7, 79.8, 78.2, 78.1, 74.4, 73.7, 73.6, 73.5, 73.4, 73.3, 71.8, 71.0, 69.5, 69.1, 69.0, 56.6, 51.8, 50.5, 45.6.

(2.4.2.35) Compound (57):



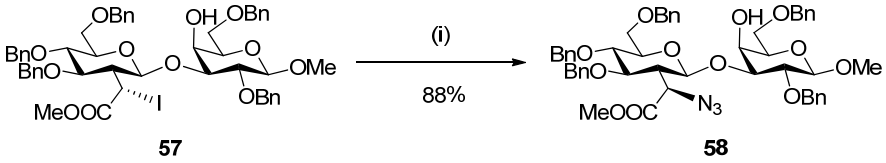
Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 °C to rt, 16 h

The compound **57** was synthesized using D-glucose-derived 1,2-cyclopropanecarboxylate **14** (180 mg, 0.36 mmol), methyl 2,6-di-*O*-benzyl-*β*-D-galactopyranoside **38** (151 mg, 0.40 mmol), NIS (91 mg, 0.51 mmol), TMSOTf (13 µL, 0.072 mmol) and 4 Å MS in dichloromethane (15 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 3:7 to 2:3) to provide the **57** as a glassy solid (65% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 – 7.26 (m, 25H), 5.04 (d, 1H, *J* = 1.6 Hz), 4.99 (d, 1H, *J* = 11.6 Hz), 4.95 (d, 1H, *J* = 10.8 Hz), 4.80 (m, 2H, 4.51 – 4.68 (m, 7H), 4.38 (m, 1H), 4.16 (s, 1H), 3.80 – 3.83 (m, 4H), 3.68 – 3.74 (m, 5H), 3.61 (s, 3H), 3.54 (bs, 1H), 3.33 (s, 3H), 2.94 (s, 1H), 2.02 (bt, 1H, *J* = 8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 138.4, 138.0, 137.9, 137.7, 137.4, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 27.6, 127.5, 127.3, 104.6, 103.3, 83.6, 81.4, 79.7, 77.8, 74.9, 74.8, 74.7, 74.7, 73.5, 73.3, 72.9, 69.3, 68.6, 67.5, 56.7, 53.1, 50.4, 29.5.

(2.4.2.36) Compound (58):



Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

The compound **58** was synthesized using disaccharidyl iodide **57** (160 mg, 0.16 mmol) and NaN_3 (21 mg, 0.32 mmol) in DMF (12 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the disaccharide-based azide **58** as a thick gum (88% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 – 7.32 (m, 25H), 4.79 – 4.88 (m, 4H), 4.71 (d, 1H, *J* = 11.2 Hz), 4.39 – 4.55 (m, 7H), 4.34 (d, 1H, *J* = 1.6 Hz), 4.14 (d, 1H, *J* = 8 Hz), 3.86 (bs, 1H), 3.74 (dd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz), 3.71 (s, 3H), 3.47 – 3.70 (m, 9H), 3.45 (s, 3H), 3.22 (bd, 1H, *J* = 9.6 Hz), 2.24 (t, 1H, *J* = 8.4 Hz), 2.22 (bs, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 139.2, 138.1, 137.9, 137.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.0, 127.8, 127.7, 127.7, 127.6, 127.6, 127.4, 127.2, 105.2, 99.3, 79.7, 78.8, 78.6, 76.9, 75.0, 74.7, 74.6, 73.9, 73.6, 73.3, 73.2, 69.3, 69.3, 68.3, 58.5, 56.9, 52.6, 48.9.

(2.4.2.37) Compound (59):

58 **59**

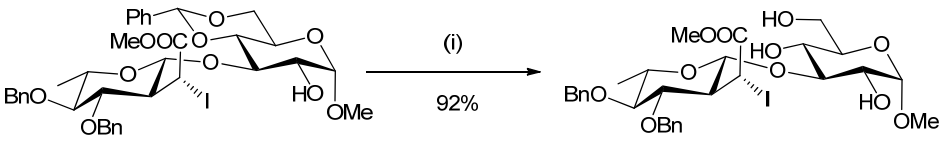
Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **59** was synthesized using the azide **58** (90 mg, 0.09 mmol) and PPh_3 (26.1 mg, 0.11 mmol) in THF (7 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to furnish the 2-C-branched GAA derivative **59** as a colorless oil (88% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 – 7.32 (m, 25H), 5.08 (d, 1H, *J* 11.2 Hz), 4.93 (d, 1H, *J* = 11.6 Hz), 4.84 (d, 1H, *J* = 10.8 Hz), 4.83 (d, 1H, *J* = 10.8 Hz), 4.76 (d, 1H, *J* = 8.4 Hz), 4.49 – 4.68 (m, 6H), 4.29 (d, 1H, *J* = 7.6 Hz), 4.05 (d, 1H, *J* = 2.4 Hz), 3.56 – 3.82 (m, 12H), 3.53 (s, 3H), 3.40 (bd, 1H, *J* = 9.6 Hz), 2.38 (t, 1H, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.5, 1391, 138.2, 138.1, 137.9, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.5, 127.3, 127.2, 105.1, 101.1, 79.7, 79.5, 79.2, 78.0, 74.8, 74.7, 74.5, 73.6, 73.5, 73.3, 69.4, 69.3, 68.7, 56.6, 51.9, 50.6, 50.1.

(2.4.2.38) Compound (60):



43 **60**

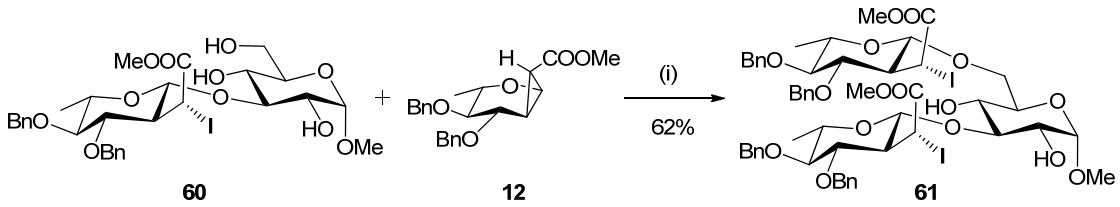
Reagents and Conditions: (i) *p*-TsOH.H_2O, MeOH, rt, 4 h.

To the stirred solution of benzylidene-protected disaccharide **43** (200 mg, 0.28 mmol) in methanol (10 mL), was added *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) at O ^{o}C. The solution was stirred for 4 h at ambient temperature and concentrated under *vacuo.* The resulted crude product was purified by silica-gel column chromatography with ethyl acetate/hexane (1:1 to 4:1) to afford the disaccharide triol derivative **60** as a glassy solid (92% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 – 7.34 (m, 10H), 5.24 (d, 1H, *J* = 2.4 Hz), 4.95 (d, 1H, *J* = 10.4 Hz), 4.84 (d, 1H, *J* = 3.6 Hz), 4.81 (d, 1H, *J* = 10.8 Hz), 4.76 (d, 1H, *J* = 10.8 Hz), 4.64 (d, 1H, *J* = 10.4 Hz), 4.55 (d, 1H, *J* = 8.4 Hz), 4.25 (d, 1H, *J* = 2 Hz), 3.78 – 3.89 (m, 3H), 3.64 – 3.73 (m, 3H), 3.58 – 3.61 (m, 1H), 3.51 – 3.56 (m, 1H), 3.46 (s, 3H), 3.39 (s, 3H), 2.95 (bs, 1H), 2.08 (dtd, 1H, *J* = 2 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.37 (d, 3H, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 138.0, 137.5, 137.4, 128.6, 128.6, 128.3, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 102.8, 99.4, 85.6, 85.2, 81.2, 75.4, 75.0, 71.9, 70.9, 70.7, 69.6, 62.5, 55.3, 53.6, 50.9, 29.4, 17.8.

(2.4.2.39) Compound (61):



Reagents and Conditions: (i) NIS, TMSOTf, CH_2Cl_2, 0 ^{o}C to rt, 16 h

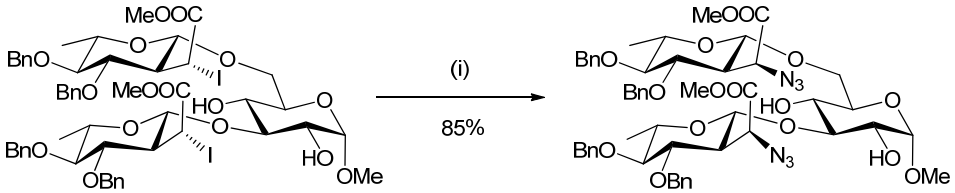
The compound **61** was synthesized using L-rhamnose-derived 1,2-cyclopropanecarboxylate **12** (190 mg, 0.49 mmol), glycosyl acceptor **60** (273 mg, 0.39 mmol), NIS (121 mg, 0.53 mmol), TMSOTf (17.7 µL, 0.072 mmol) and 4 Å MS in dichloromethane (20 mL) by following the general procedure in (**2.4.2.4**). The reaction mixture was stirred for overnight at ambient temperature. The obtained crude product was purified by silica-gel column chromatography (EtOAc/hexane 2:3 to 1:1) to provide the **61** as yellowish a thick gum (62% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 – 7.22 (m, 20H), 5.29 (d, 1H, *J* = 1.6 Hz), 5.01 (d, 1H, *J* = 2 Hz), 4.87 (d, 1H, *J* = 10.8 Hz), 4.86 (d, 1H, *J* = 10.8 Hz), 4.78(d, 1H, *J* = 3.6 Hz), 4.54

– 4.75 (m, 6H), 4.45 (d, 1H, *J* = 8.4 Hz), 4.31 (d, 1H, *J* = 8 Hz), 4.15 (bs, 1H), 3.99 (dd, 1H, *J* = 2.8 Hz, *J* = 12 Hz), 3.91 (d, 1H, *J* = 12 Hz), 3.65 – 3.72 (m, 4H), 3.56 – 3.60 m, 2H), 3.38 – 3.48 (m, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 3.27 (s, 3H), 3.22 (bs, 1H), 1.97 (dtd, 1H, *J* = 1.6 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.89 (dtd, 1H, *J* = 1.6 Hz, *J* = 2 Hz, *J* = 8.4 Hz), 1.30 (d, 3H, *J* = 6 Hz), 1.26 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 167.6, 138.2, 138.1, 137.6, 137.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 127.3, 103.2, 103.1, 99.4, 85.4, 85.3, 85.2, 81.4, 81.2, 75.3, 75.2, 74.8, 74.6, 71.7, 71.6, 71.1, 70.6, 68.4, 68.2, 55.3, 53.5, 53.4, 50.9, 50.0, 28.8, 28.2, 17.8, 17.7.

(2.4.2.40) Compound (62):



61 **62**

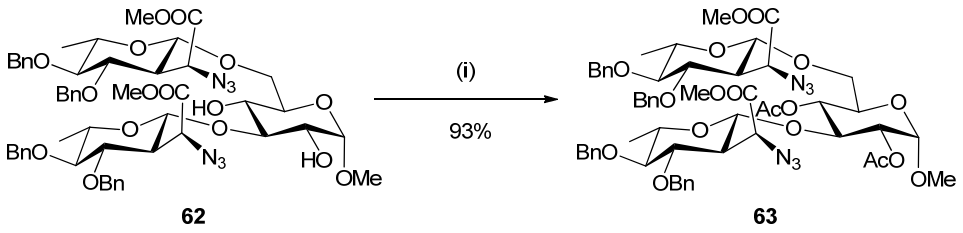
Reagents and Conditions: (i) NaN_3, DMF, rt, 24 h

The compound **62** was synthesized using trisacharide-based diiodide **61** (170 mg, 0.14 mmol) and NaN_3 (36.4 mg, 0.56 mmol) in DMF (15 mL) by following the same procedure in (**2.4.2.6**). The reaction mixture was stirred for 24 h at room temperature. Crude product was purified by silica-gel column chromatography (EtOAc in hexane 2:3 to 1:1) to provide the triasaccharide-based diazide **62** as a thick gum (85% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 – 7.39 (m, 20H), 4.98 (d, 1H, *J* = 12 Hz), 4.95 (d, 1H, *J* = 12 Hz), 4.85 – 4.89 (m, 2H), 4.75 (d, 1H, *J* = 3.6 Hz), 4.62 - 4.71 (m, 4H), 4.50 (d, 1H, *J* = 8.4 Hz), 4.43 (d, 1H, *J* = 8.4 Hz), 4.40 (d, 1H, *J* = 1.6 Hz), 4.30 (d, 1H, *J* = 2 Hz), 4.13 (s, 1H), 3.82 – 3.90 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.54 – 3.62 (m, 4H), 3.35 – 3.47 (m, 6H), 3.24 – 3.28 (m, 3H), 2.31 – 2.35 (m, 2H), 1.35 (d, 6H, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 170.1, 137.9, 137.6, 137.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 100.4, 99.4, 99.0, 86.7, 85.6, 85.2, 78.6, 78.0, 75.3, 75.2, 75.1, 71.6, 71.3, 70.4, 70.0, 68.5, 68.4, 58.7, 58.4, 55.4, 53.1, 52.4, 49.1, 48.8, 17.8, 17.7.

(2.4.2.41) Compound (63):



62 63

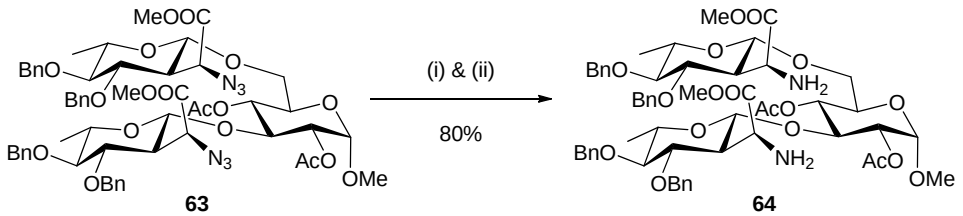
Reagents and Conditions: (i) Ac_2O, Py, rt, 10 h

To the stirred solution of trisaccharide-based azide **62** (120 mg, 0.11 mmol) in pyridine (8 mL) was added acetic anhydride (43 µL, 0.46 mmol) at 0 ^oC. The reaction mixture was stirred for 10 h at room temperature. After completion of reaction, the solution was concentrated under *vacuo* and purified by silica-gel column chromatography in ethyl acetate in hexane (1:4 to 3:7) to afford the acetylated trisaccharide derivative **63** as a colorless gum (93% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 – 7.30 (m, 20H), 4.87 (d, 1H, *J* = 11.6 Hz), 4.76 (d, 1H, *J* = 10.8 Hz), 4.67 (dd, 1H, *J* = 3.6 Hz, *J* = 10 Hz), 4.52 – 4.63 (m, 5H), 4.42 (d, 1H, *J* = 7.6 Hz), 4.24 (d, 1H, *J* = 8.8 Hz), 4.21 (s, 1H), 4.11 – 4.15 (m, 2H), 3.78 (t, 1H, *J* = 8.8 Hz), 3.67 (s, 3H), 3.66 (s, 3H), 3.60 (t, 1H, *J* = 8.8 Hz), 3.35 – 3.49 (m, 3H), 3.31 (s, 3H), 3.21 – 3.28 (m, 2H), 3.16 (t, 1H, *J* = 8.4 Hz), 3.09 (t, 1H, *J* = 8.8 Hz), 2.22 – 2.27 (m, 2H), 2.05 (s, 3H), 1.98 (s, 3H), 1.27 (d, 3H, *J* = 5.2 Hz), 1.24 (d, 3H, *J* = 5.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.2, 169.9, 169.9, 169.4, 137.8, 137.7, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.8, 99.9, 98.1, 96.9, 85.9, 85.3, 78.5, 78.4, 75., 75.1, 75.0, 72.8, 71.7, 71.4, 71.1, 69.9, 68.9, 58.1, 58.0, 55.6, 52.4, 52.3, 49.0, 48.7, 20.9, 20.8, 18.1, 17.7.

(2.4.2.42) Compound (64):



63 64

Reagents and Conditions: (i) PPh_3, THF, rt, 6 h, (ii) H_2O, reflux, 8 h.

The compound **64** was synthesized using the trisaccharide-based diazide **63** (95 mg, 0.08 mmol) and PPh_3 (44.2 mg, 0.16 mmol) in THF (10 mL) by following the same procedure in (**2.4.2.7**). The resulted crude product was purified by silica-gel column chromatography (EtOAc in hexane 1:1 to 7:3) to furnish the trisaccharide-based bisamino acid adduct **64** as a colorless thick gum (80% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 – 7.24 (m, 20H), 4.76 – 4.85 (m, 6H), 4.67 (d, 1H, *J* = 3.2 Hz), 4.58 – 4.61 (m, 3H), 4.54 (d, 1H, *J* = 11.6 Hz), 4.48 (d, 1H, *J* = 8 Hz), 4.31 (d, 1H, *J* = 8.4 Hz), 4.20 (t, 1H, *J* = 9.2 Hz), 3.71 (s, 3H), 3.66 – 3.68 (m, 1H), 3.56 – 3.63 (m, 5H), 3.52 (bs, 2H), 3.35 (d, 1H, *J* = 10.2 Hz), 3.28 (s, 3H), 3.19 -3.27 (m, 3H), 3.13 (t, 1H, *J* = 8.8 Hz), 2.19 (t, 1H, *J* = 9.2 Hz), 2.00 (bs, 4H), 1.95 (s, 3H), 1.42 (bs, 4H), 1.27 (d, 3H, *J* = 6 Hz), 1.21 (d, 3H, *J* = 5.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1, 175.5, 169.9, 169.5, 138.2, 138.1, 138.1, 137.9, 128.4, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 100.8, 98.5, 97.1, 86.2, 85.5, 78.8, 78.7, 75.0, 74.9, 74.5, 72.1, 71.3, 71.1, 70.1, 68.6, 68.1, 54.4, 52.2, 52.0, 51.1, 50.1, 50.0, 49.8, 21.2, 20.9, 18.2, 17.8.

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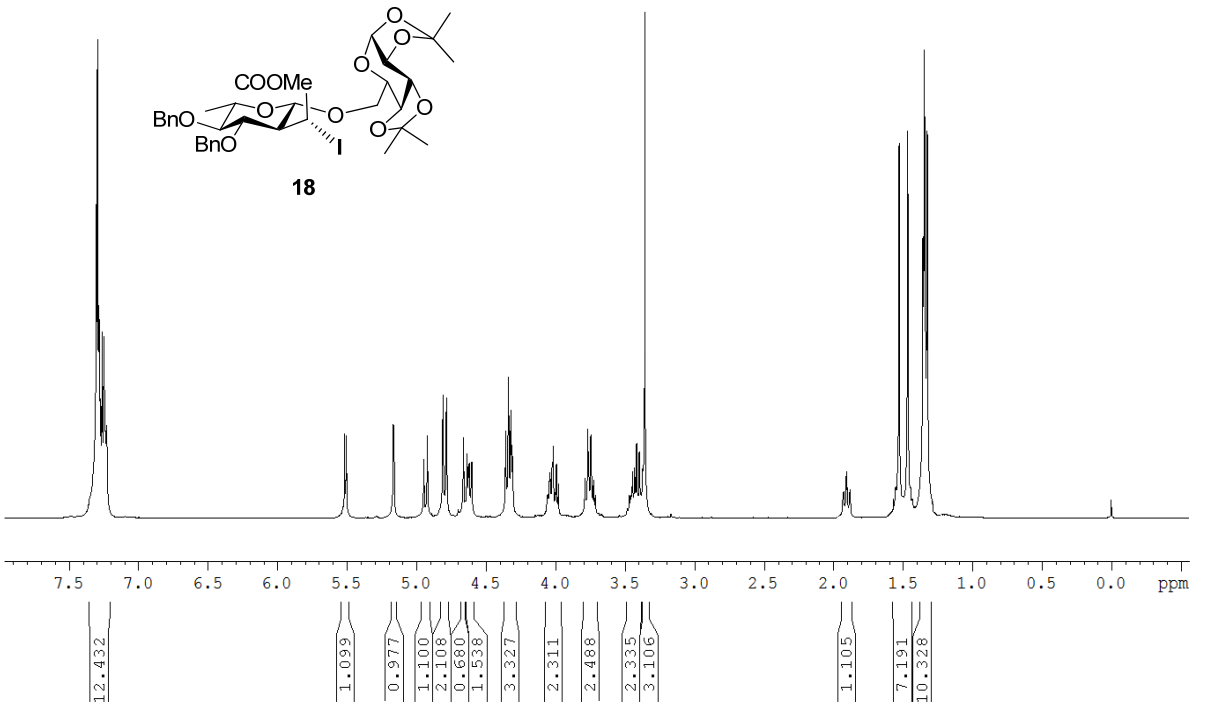
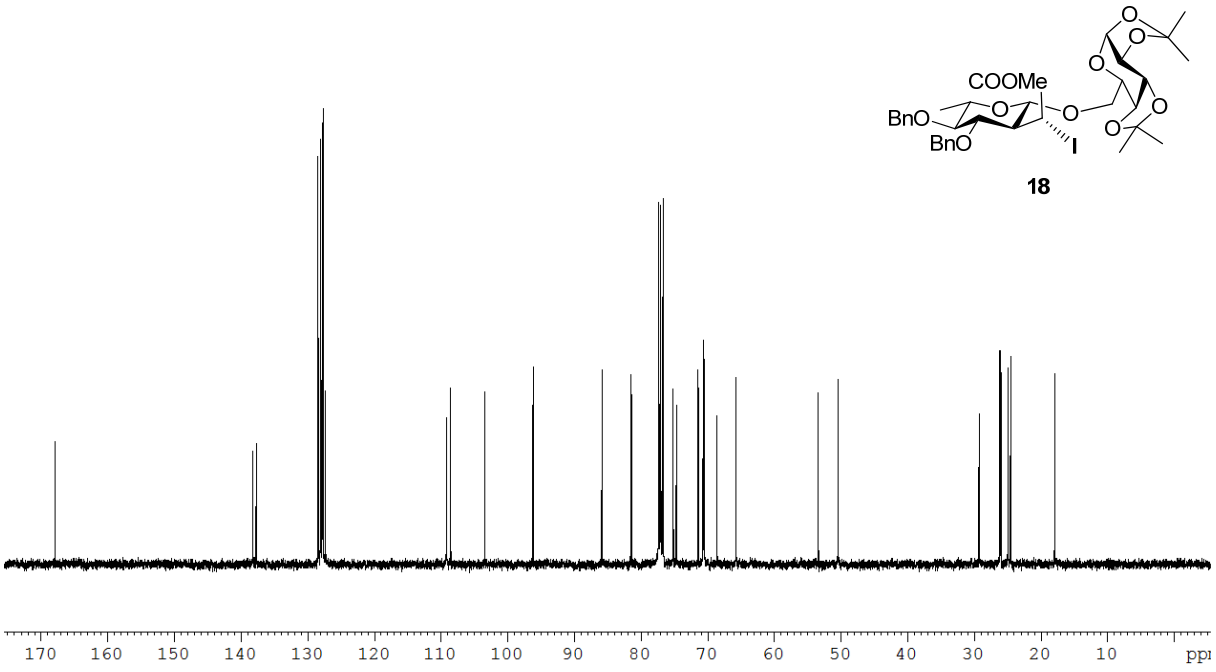
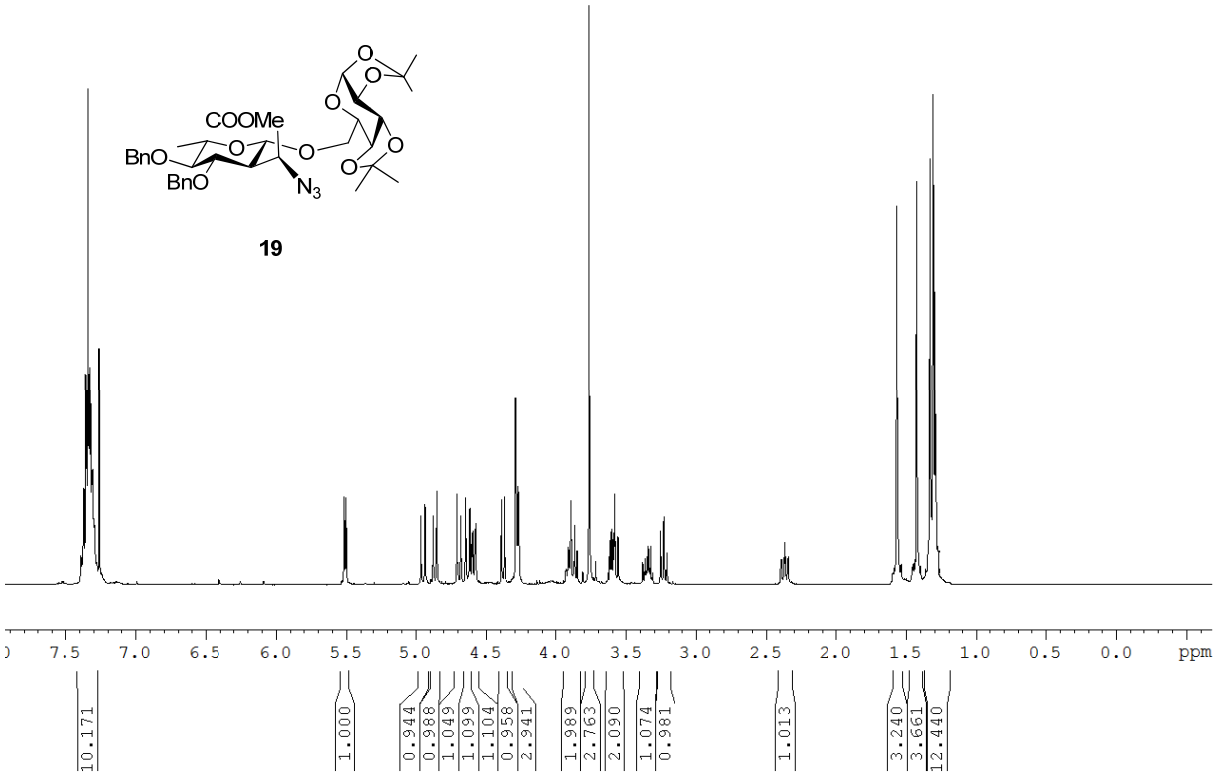
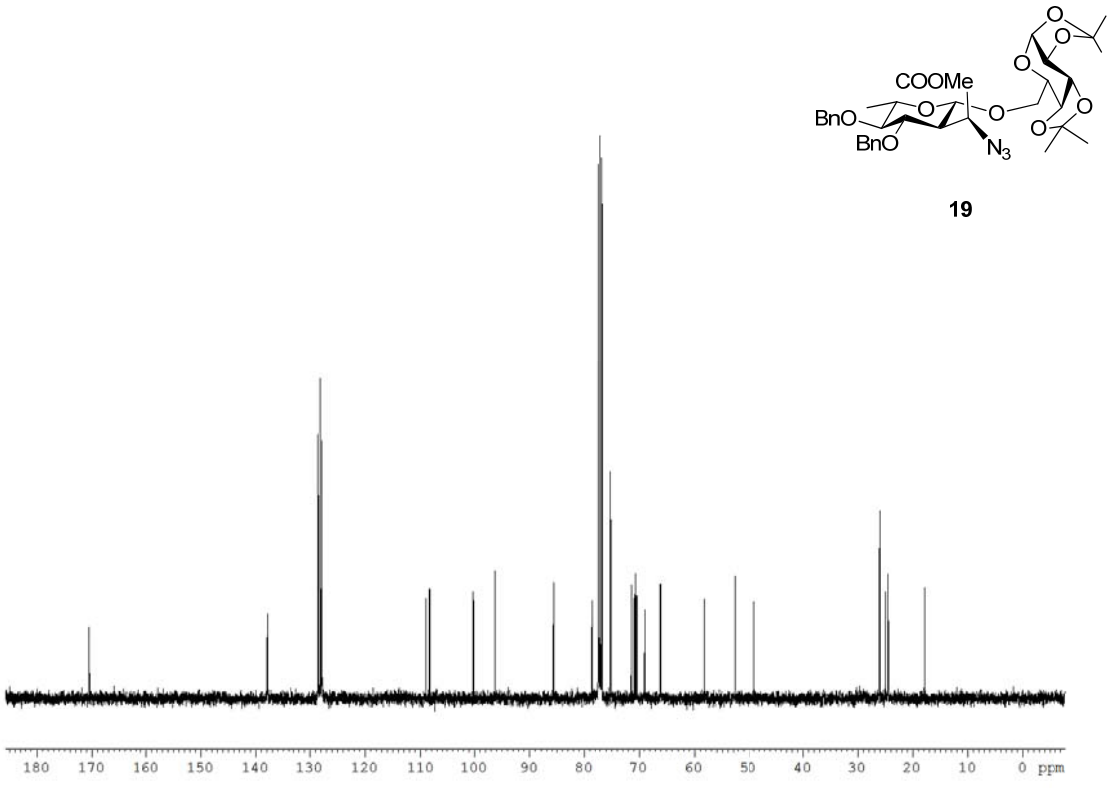
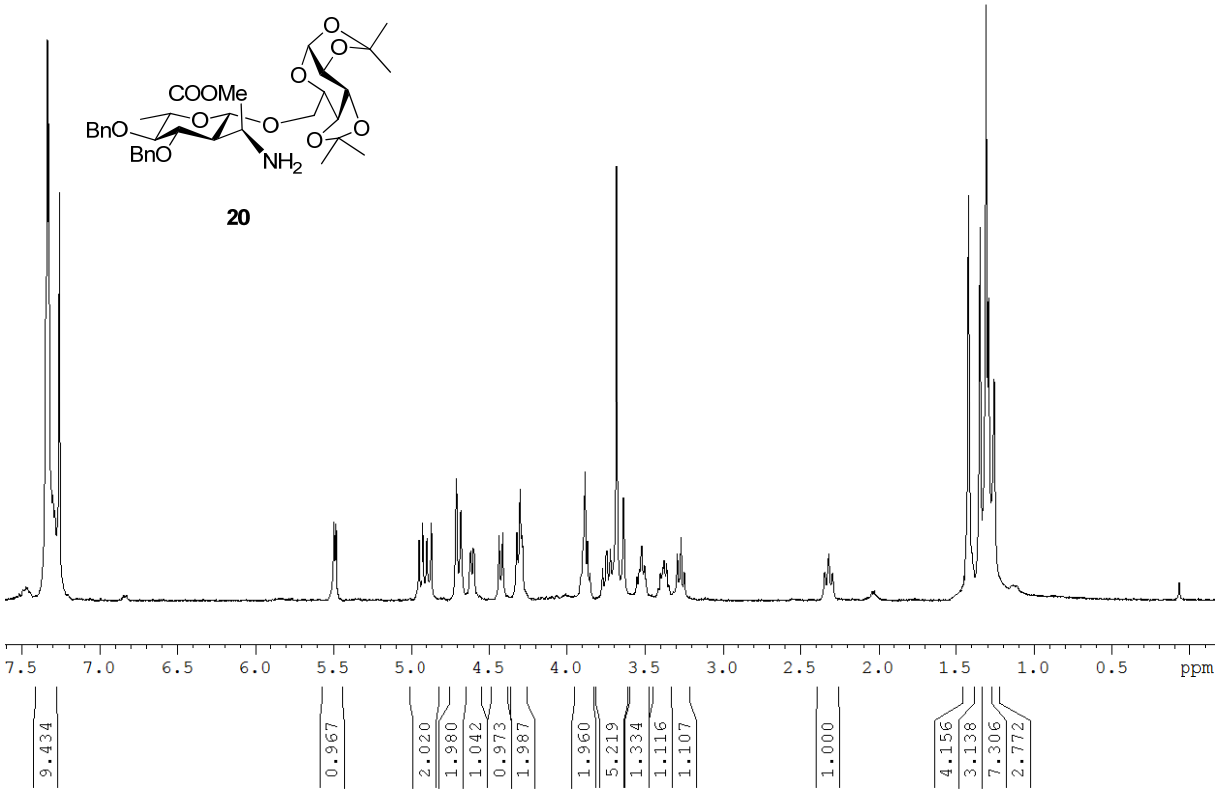
2.6 NMR Spectra



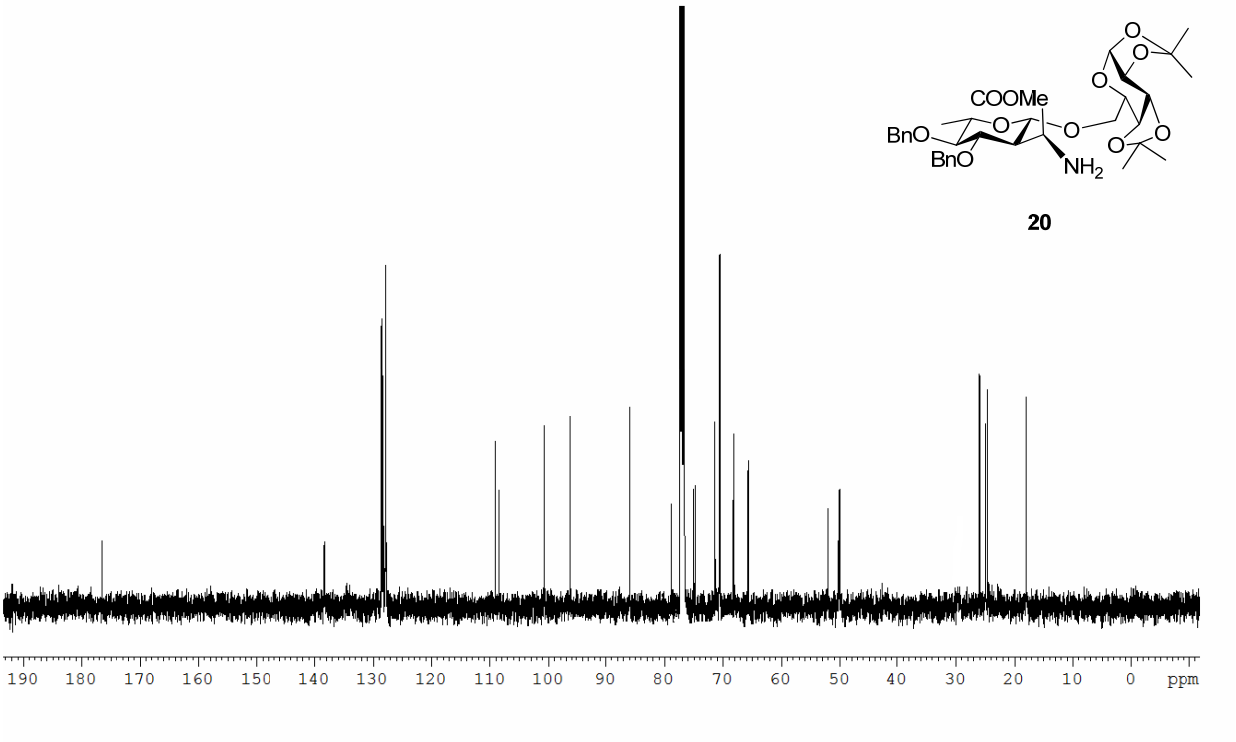



COOMe
BnO
BnO
N3
O
19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
10.171
1.000
0.944
0.988
1.049
1.099
1.104
0.958
2.941
1.989
2.763
2.090
1.074
0.981
1.013
3.240
3.661
12.440

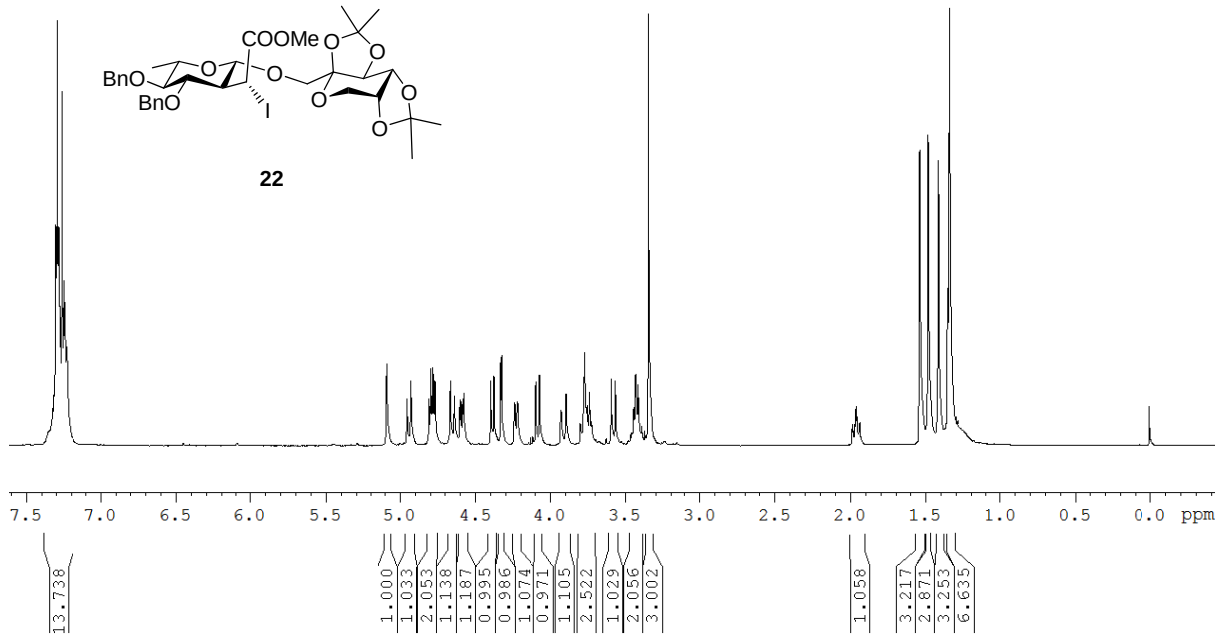

COOMe
BnO
BnO
N3
O
19
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

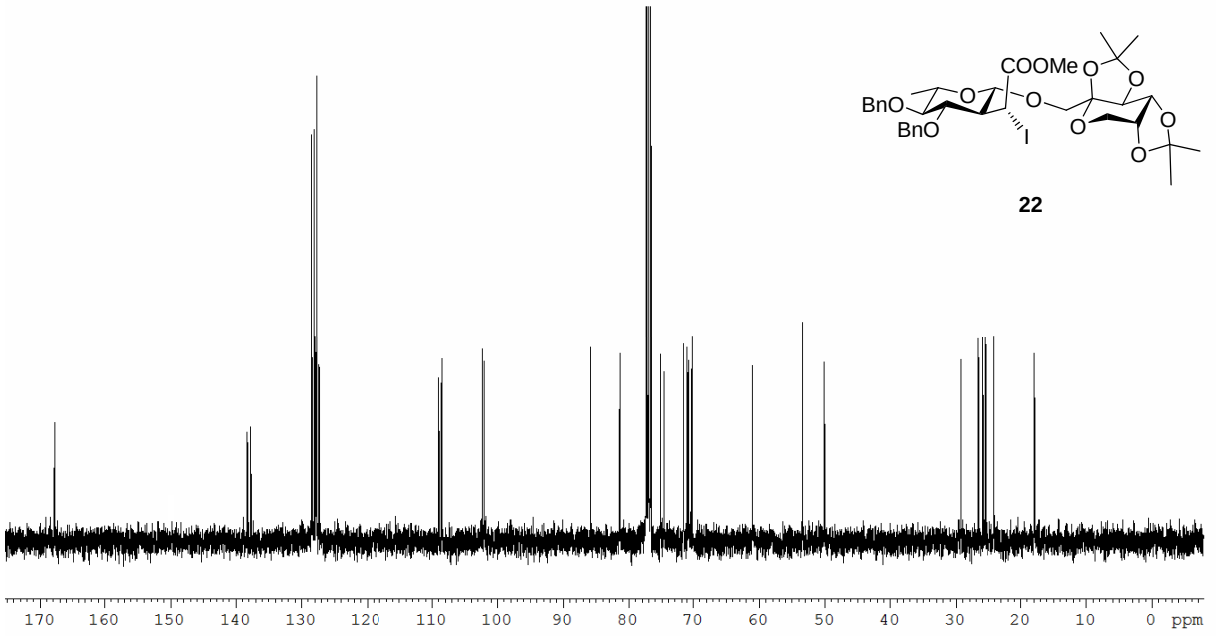

COOMe
BnO
BnO
NH2
O
O
O
O
O
O
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
9.434
0.967
2.020
1.980
1.042
0.973
1.987
1.960
5.219
1.334
1.116
1.107
1.000
4.156
3.138
7.306
2.772

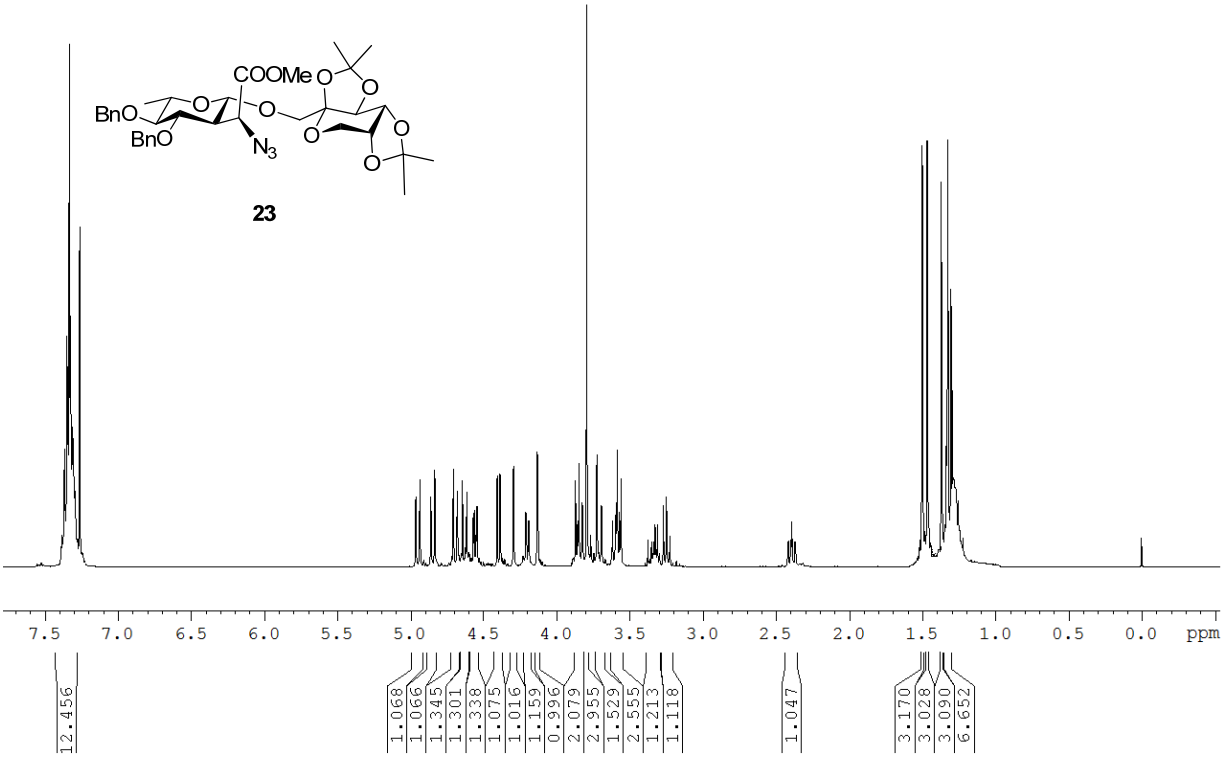
20


COOMe
BnO
BnO
NH2
O
O
O
O
O
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

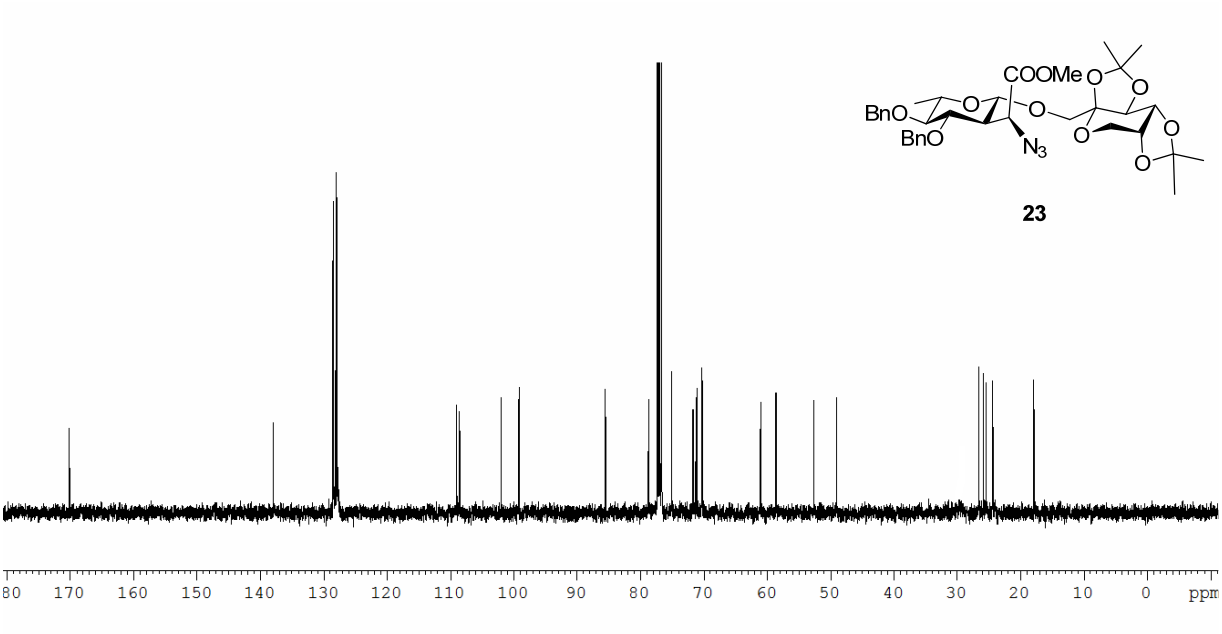
20


COOMe
BnO
BnO
I
O
22
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
13.738
1.000
1.033
2.053
1.138
1.187
0.995
0.986
1.074
0.971
1.105
2.522
1.029
2.056
3.002
1.058
3.217
2.871
3.253
6.635

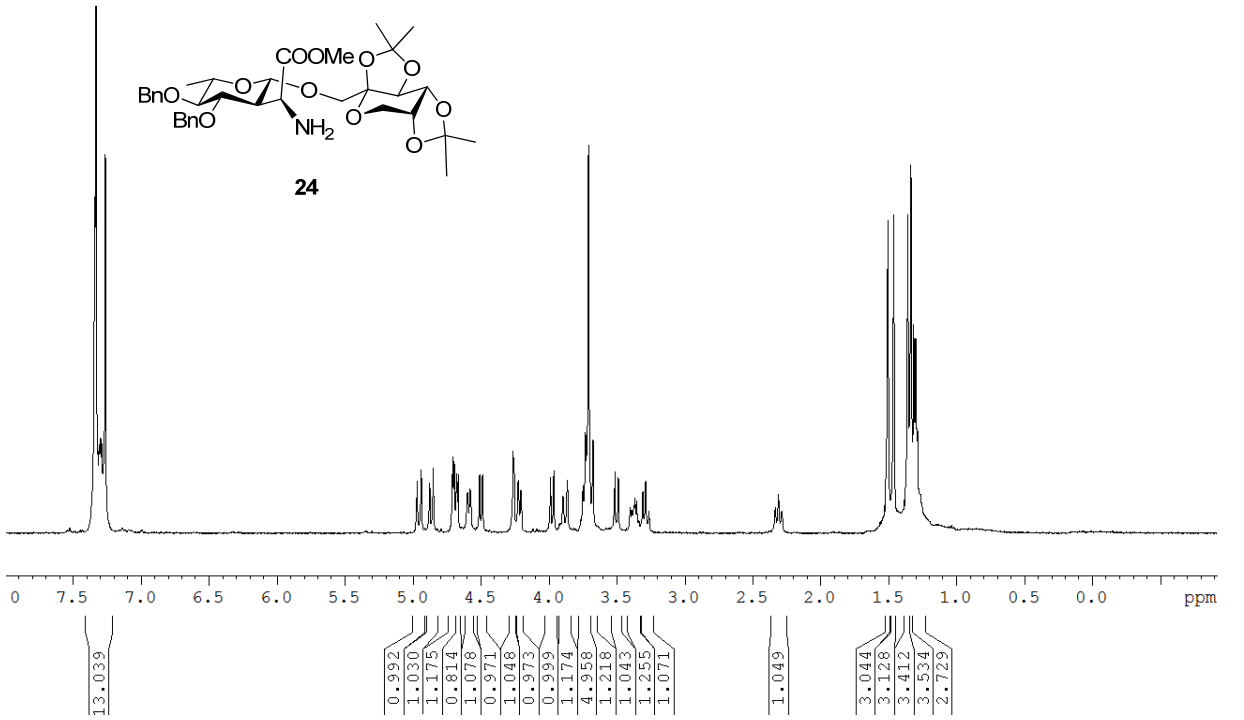

COOMe
BnO
BnO
I
O
22
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

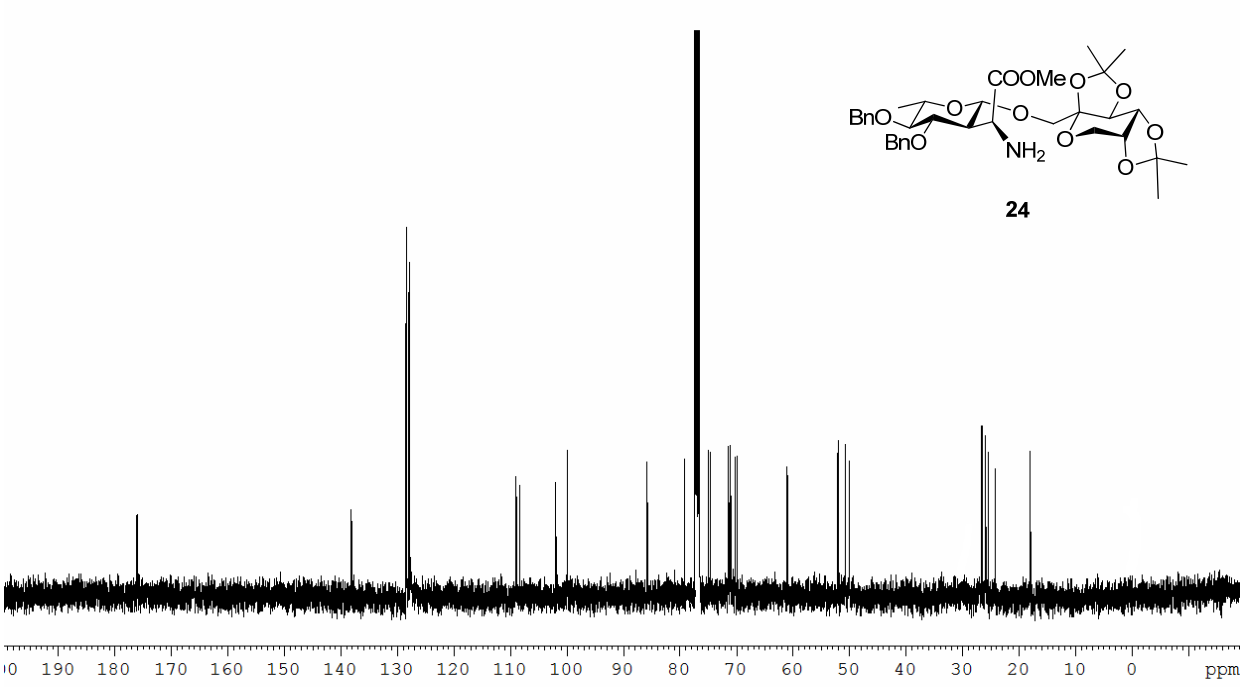

COOMe
BnO
BnO
N_3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
12.456
1.068 1.066 1.345 1.301 1.338 1.075 1.016 1.159 0.996 2.079 2.955 1.529 2.555 1.213 1.118
1.047
3.170 3.028 3.090 6.652

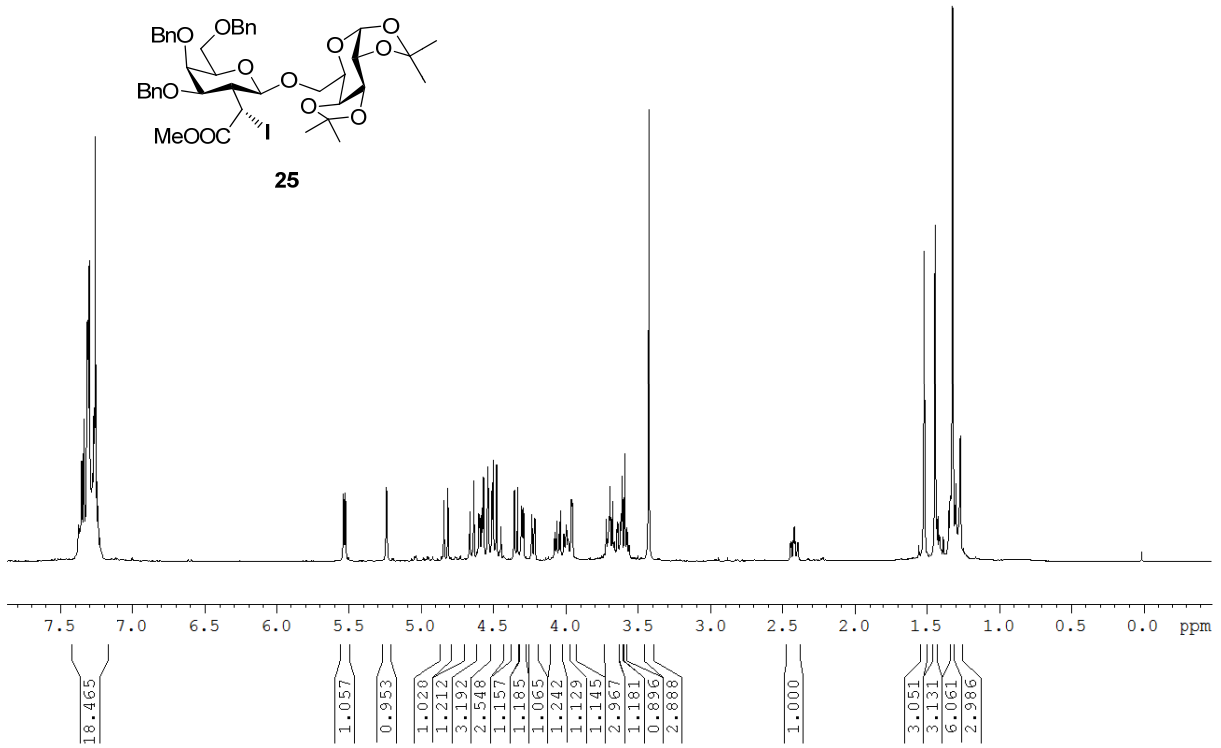
23

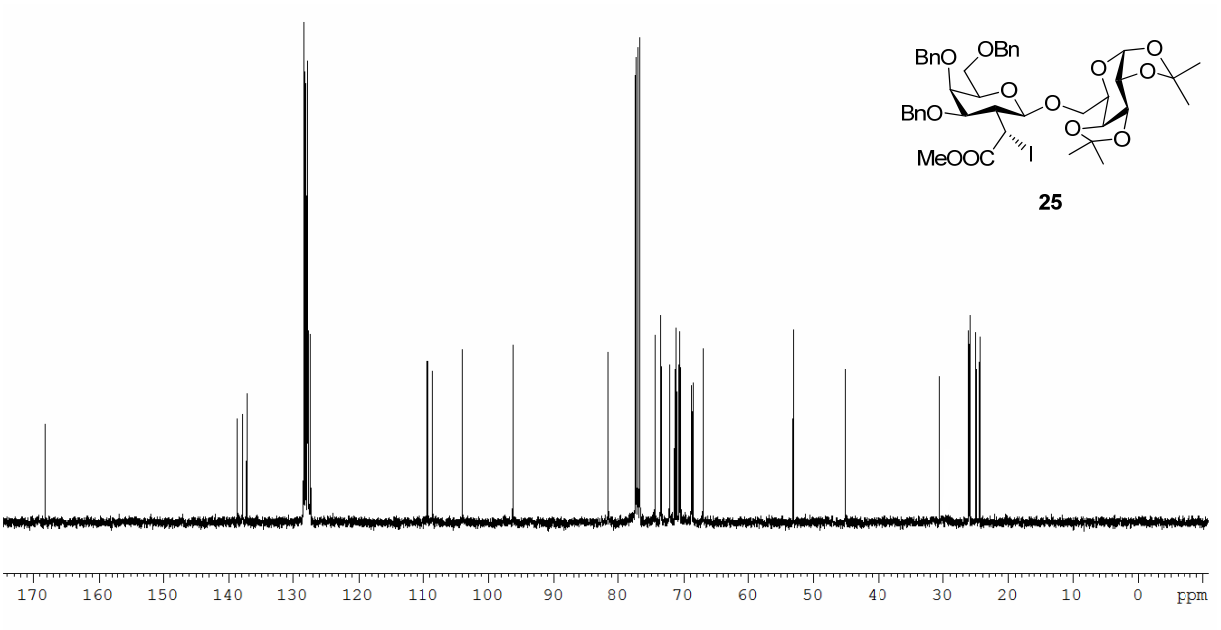

COOMe
BnO
BnO
N_3
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

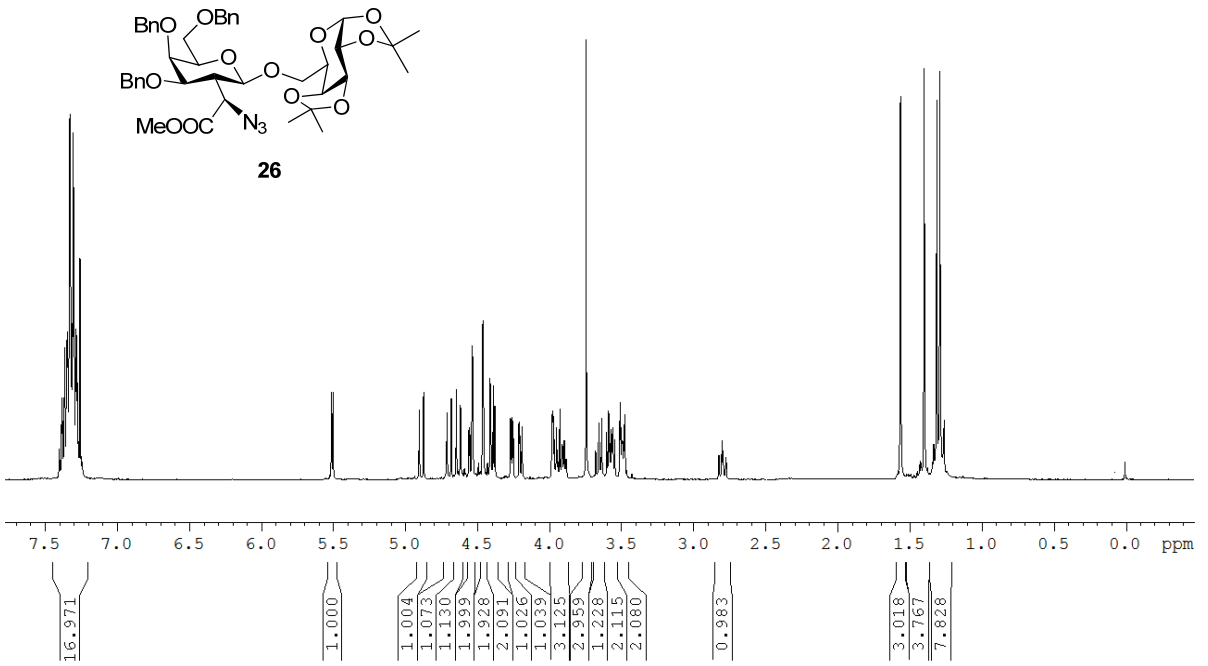
23


COOMe
BnO
BnO
NH2
24
0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
13.039
0.992
1.030
1.175
0.814
1.078
0.971
1.048
0.973
0.999
1.174
4.958
1.218
1.043
1.255
1.071
1.049
3.044
3.128
3.412
3.534
2.729

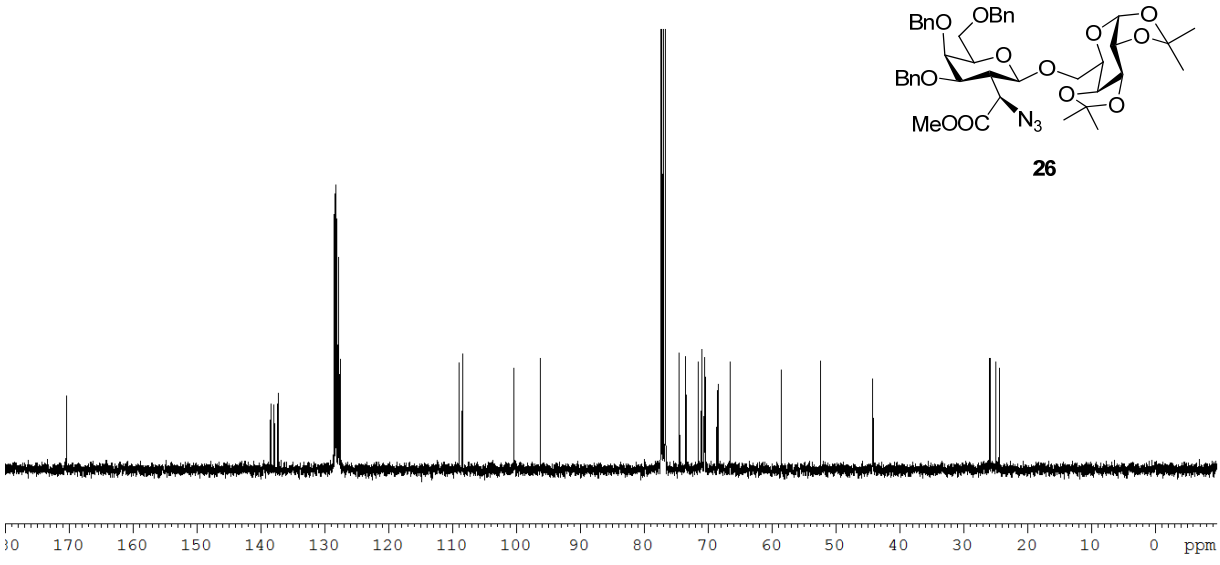

COOMe
BnO
BnO
NH2
24
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


BnO
OBn
BnO
MeOOC
I
O
25
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
18.465
1.057
0.953
1.020
1.212
3.192
2.548
1.157
1.185
1.065
1.242
1.129
1.145
2.967
1.181
0.896
2.888
1.000
3.051
3.131
6.061
2.986

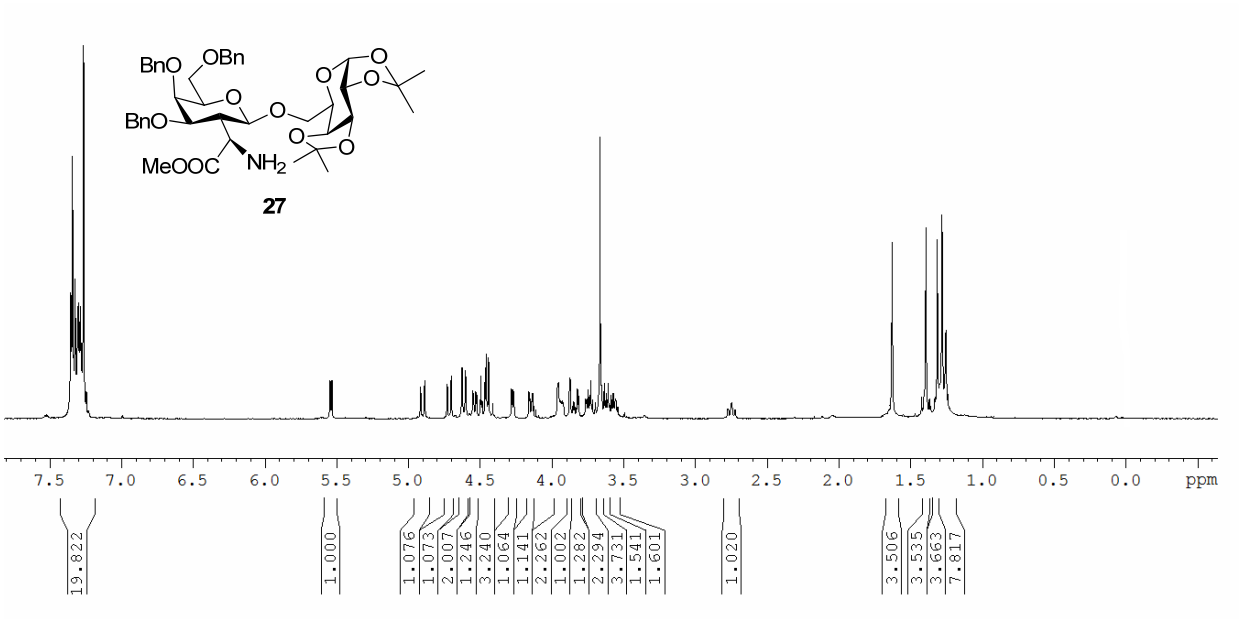

BnO
OBn
BnO
MeOOC
I
O
25
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

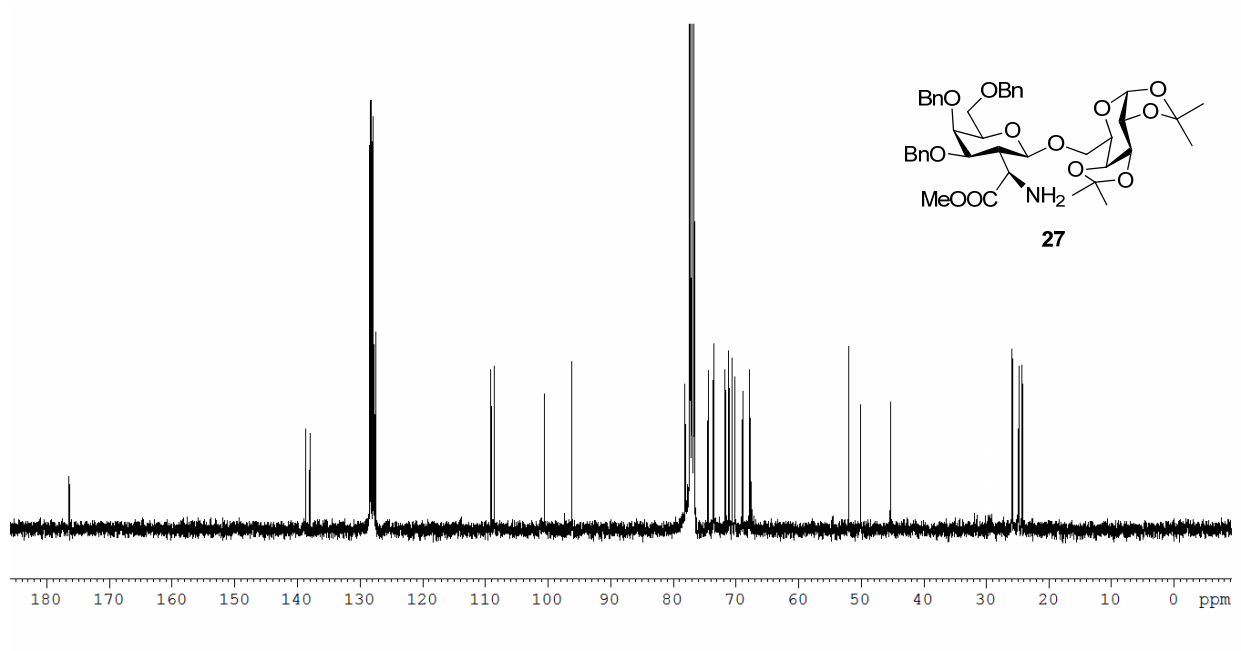

BnO
OBn
BnO
MeOOC
N3
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
16.971
1.000
1.004
1.073
1.130
1.999
1.928
2.091
1.026
1.039
3.125
2.959
1.228
2.115
2.080
0.983
3.018
3.767
7.828

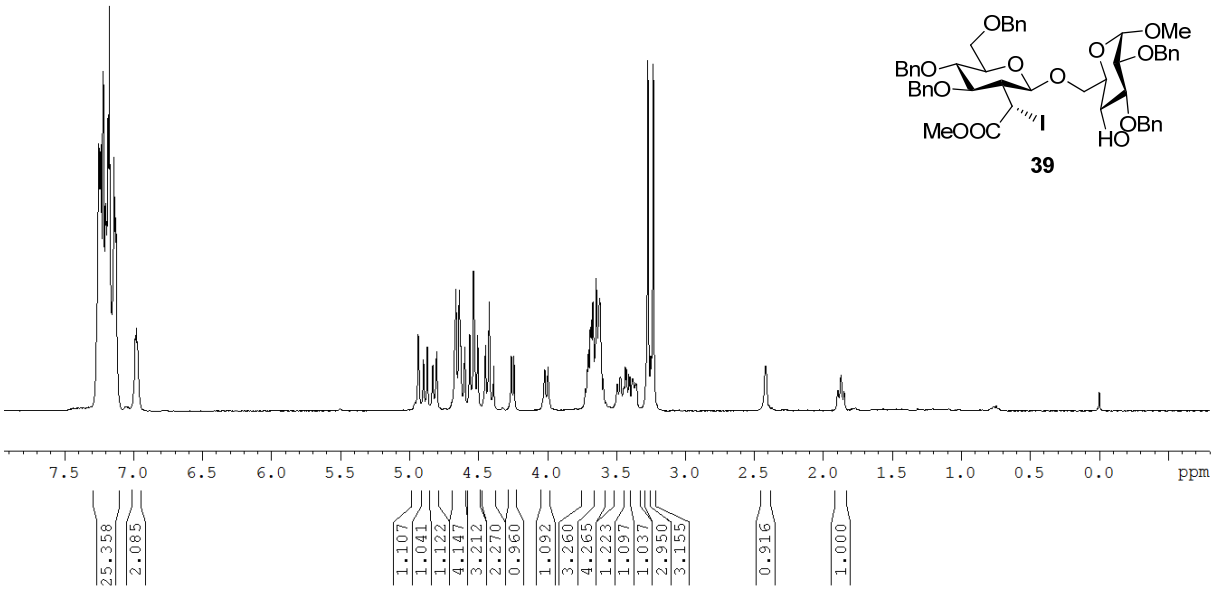
26

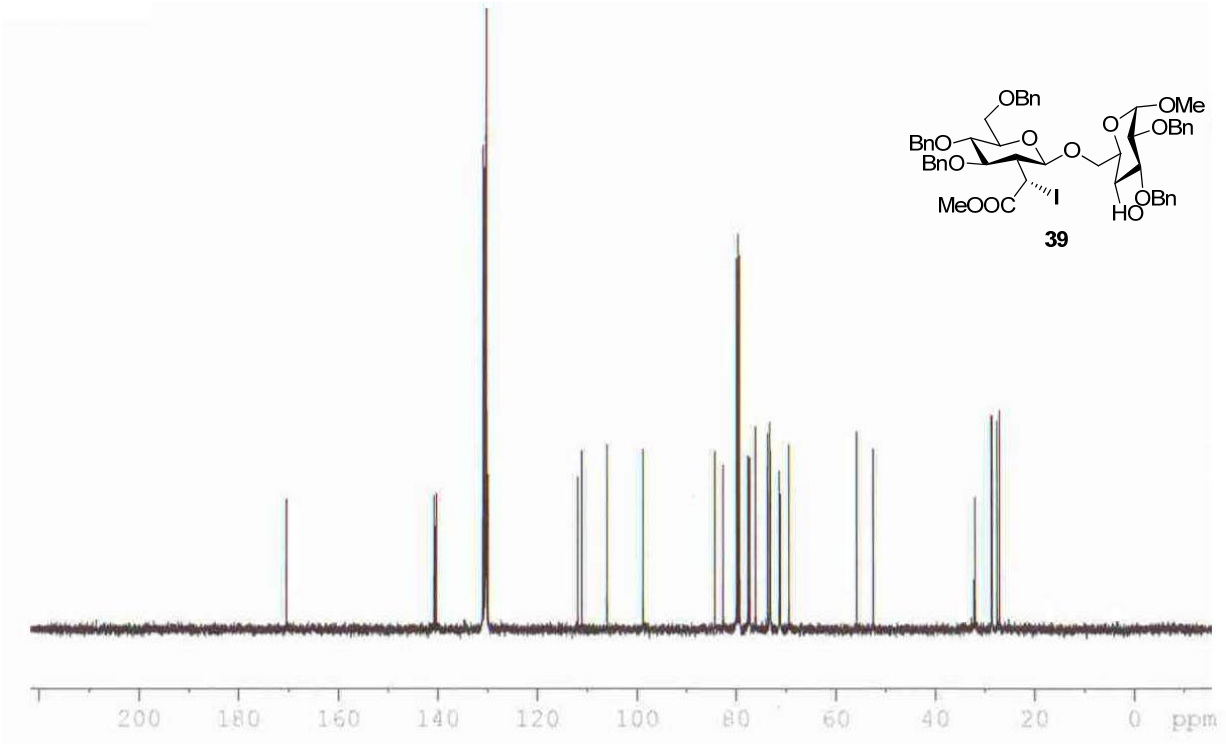

BnO
OBn
BnO
MeOOC
N3
O
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

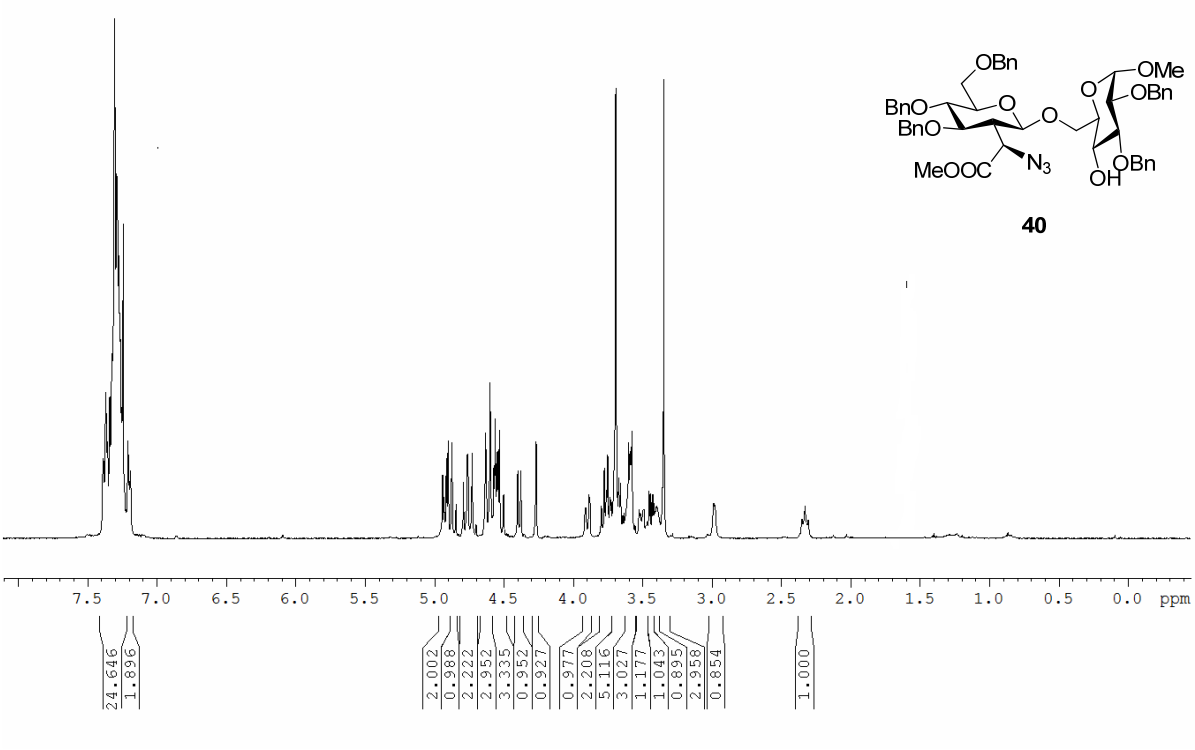
26


BnO
OBn
BnO
MeOOC
NH2
27
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
19.822
1.000
1.076
1.073
2.007
1.246
3.240
1.064
1.141
2.262
1.002
1.282
2.294
3.731
1.541
1.601
1.020
3.506
3.535
3.663
7.817

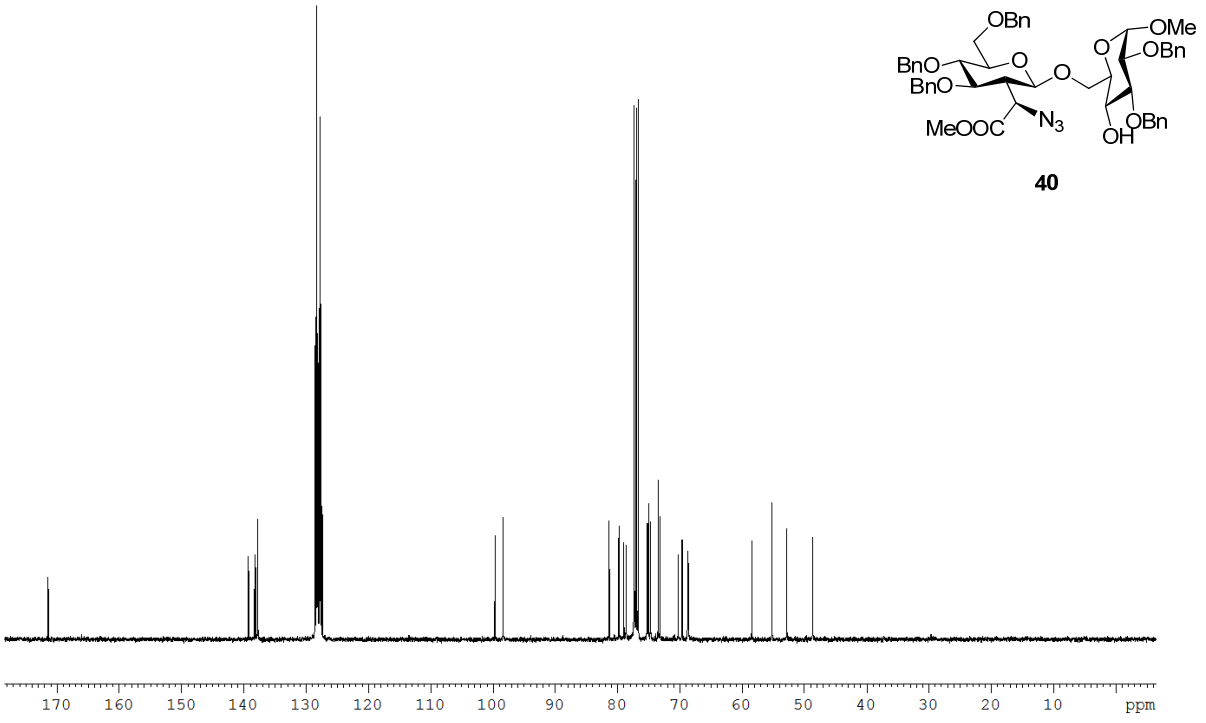

BnO
OBn
BnO
MeOOC
NH2
27
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OBn
OMe
BnO
OBn
BnO
MeOOC
I
OBn
HO
39
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
25.358
2.085
1.107
1.041
1.122
4.147
3.212
2.270
0.960
1.092
3.260
4.265
1.223
1.097
1.037
2.950
3.155
0.916
1.000

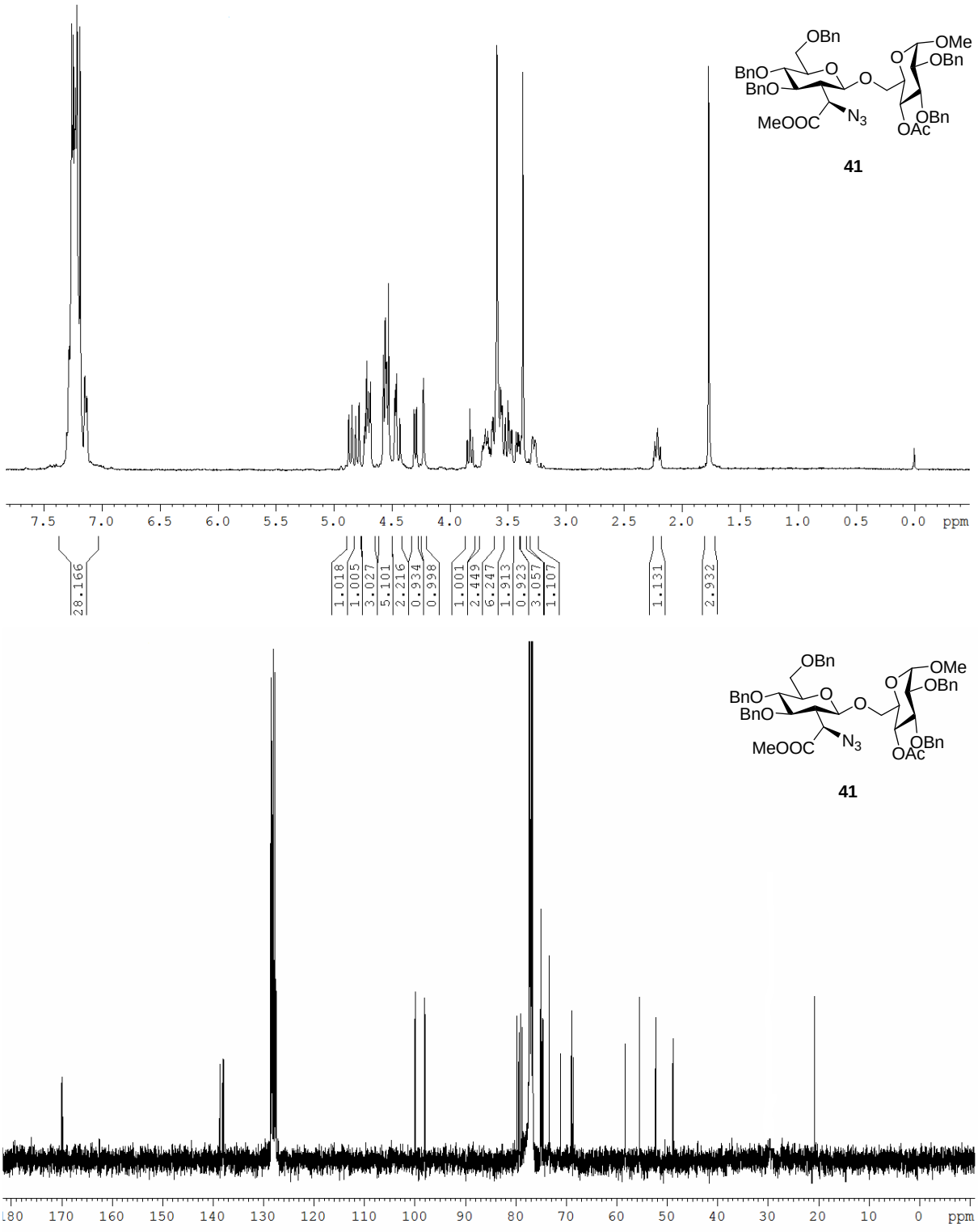

OBn
OMe
BnO
OBn
BnO
MeOOC
I
OBn
HO
39
200 180 160 140 120 100 80 60 40 20 0 ppm

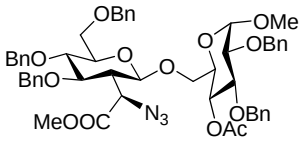

OBn
BnO
BnO
O
O
MeOOC
N3
OMe
OBn
OBn
OH
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
24.646
1.896
2.002
0.988
2.222
2.952
3.335
0.952
0.927
0.977
2.208
5.116
3.027
1.177
1.043
0.895
2.958
0.854
1.000

40

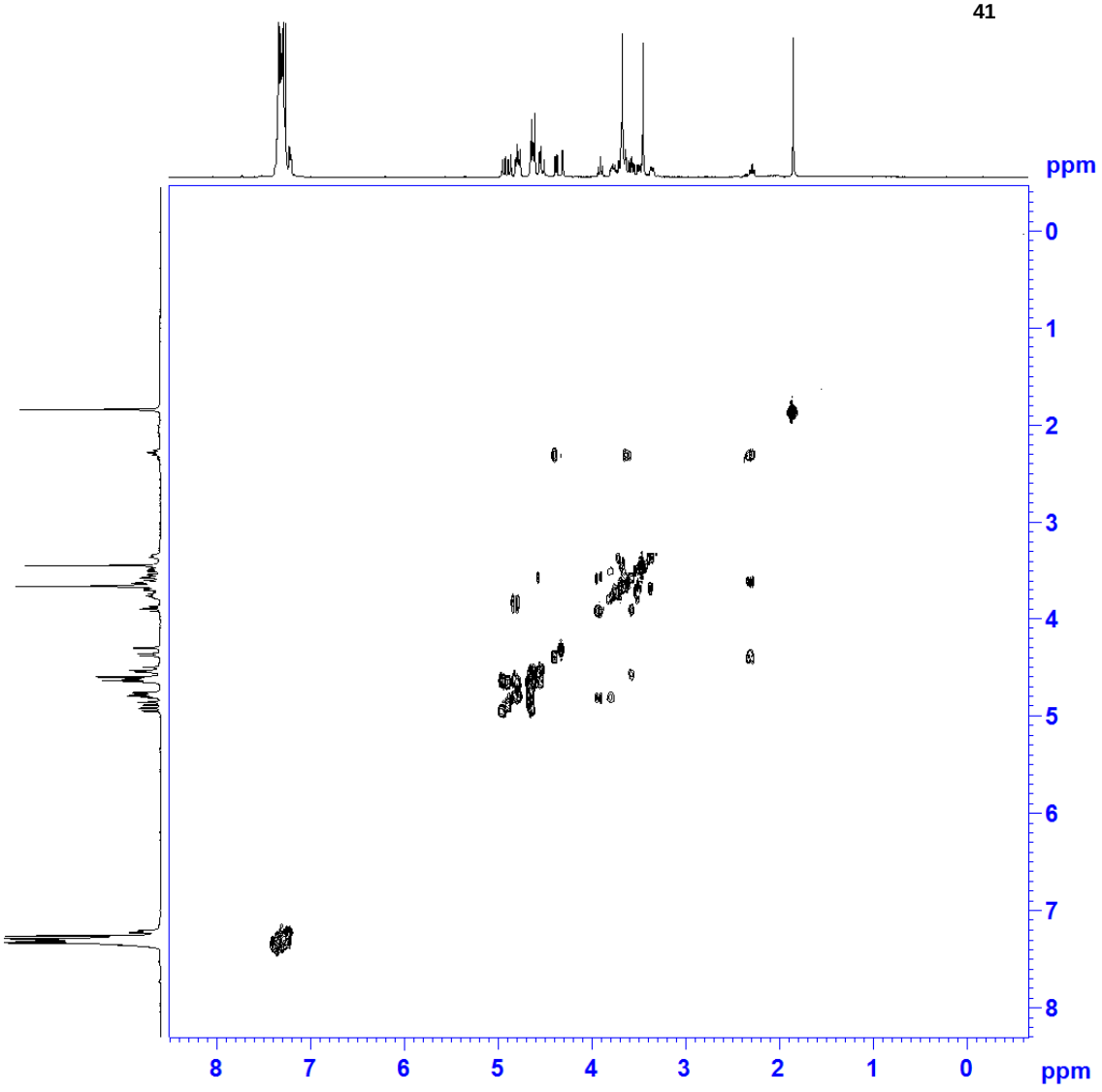

OBn
BnO
BnO
O
O
MeOOC
N3
OMe
OBn
OBn
OH
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

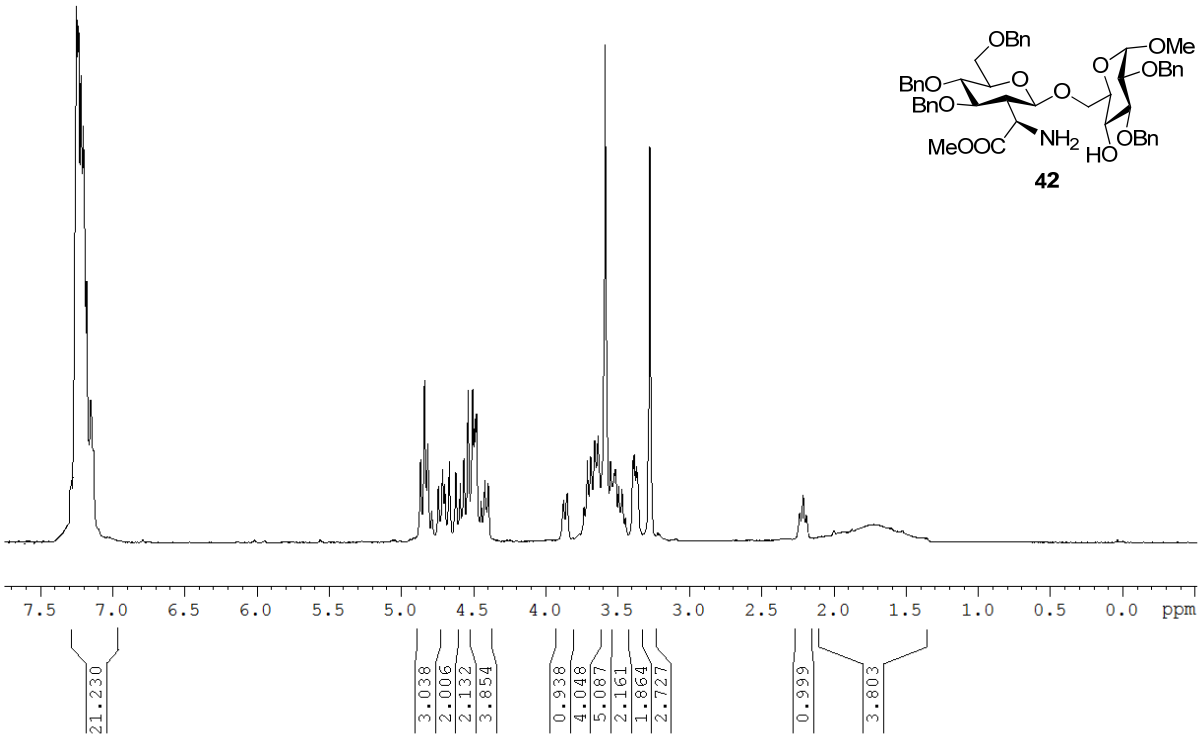
40

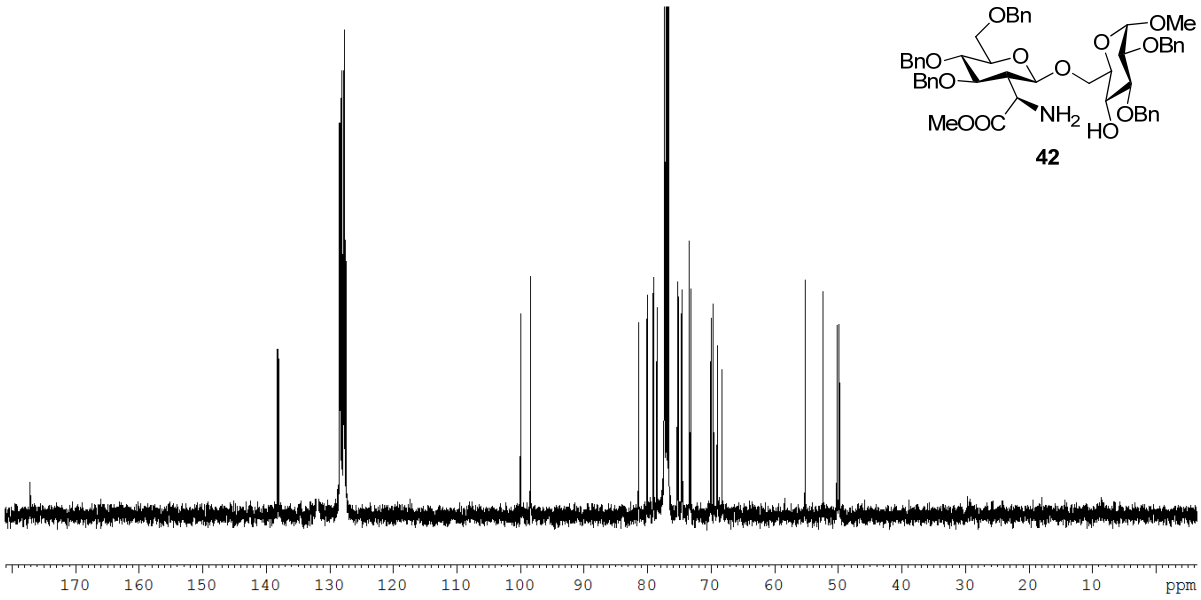

OBn
OMe
BnO
BnO
OBn
MeOOC
N3
OBn
OAc
41
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
28.166
1.018 1.005 3.027 5.101 2.216 0.934 0.998
1.001 2.449 6.247 1.913 0.923 3.057 1.107
1.131
2.932
OBn
OMe
BnO
BnO
OBn
MeOOC
N3
OBn
OAc
41
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

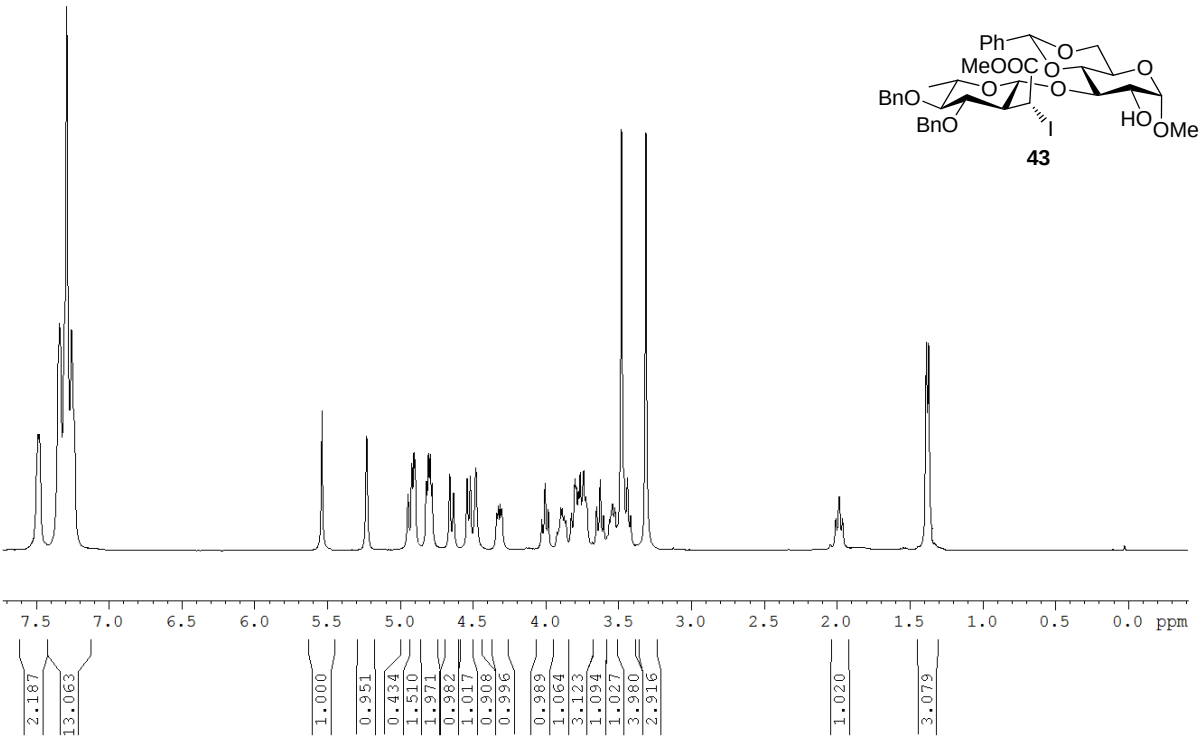

OBn
BnO
BnO
O
O
MeOOC
N_3
O
OMe
OBn
OBn
OAc

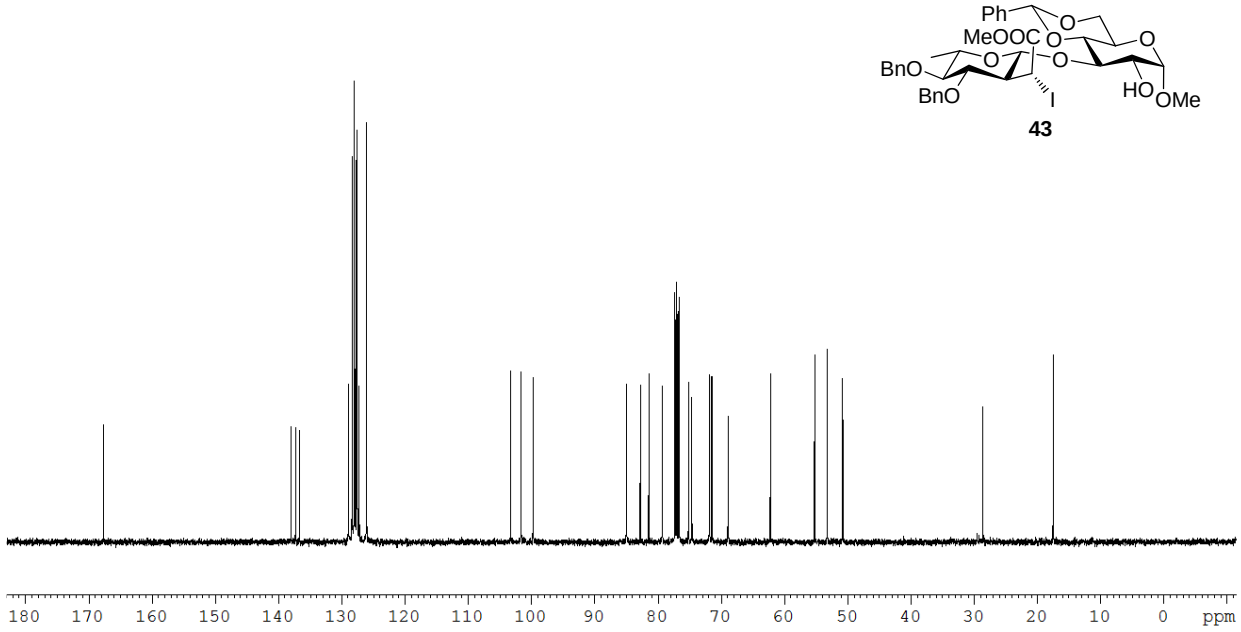
41

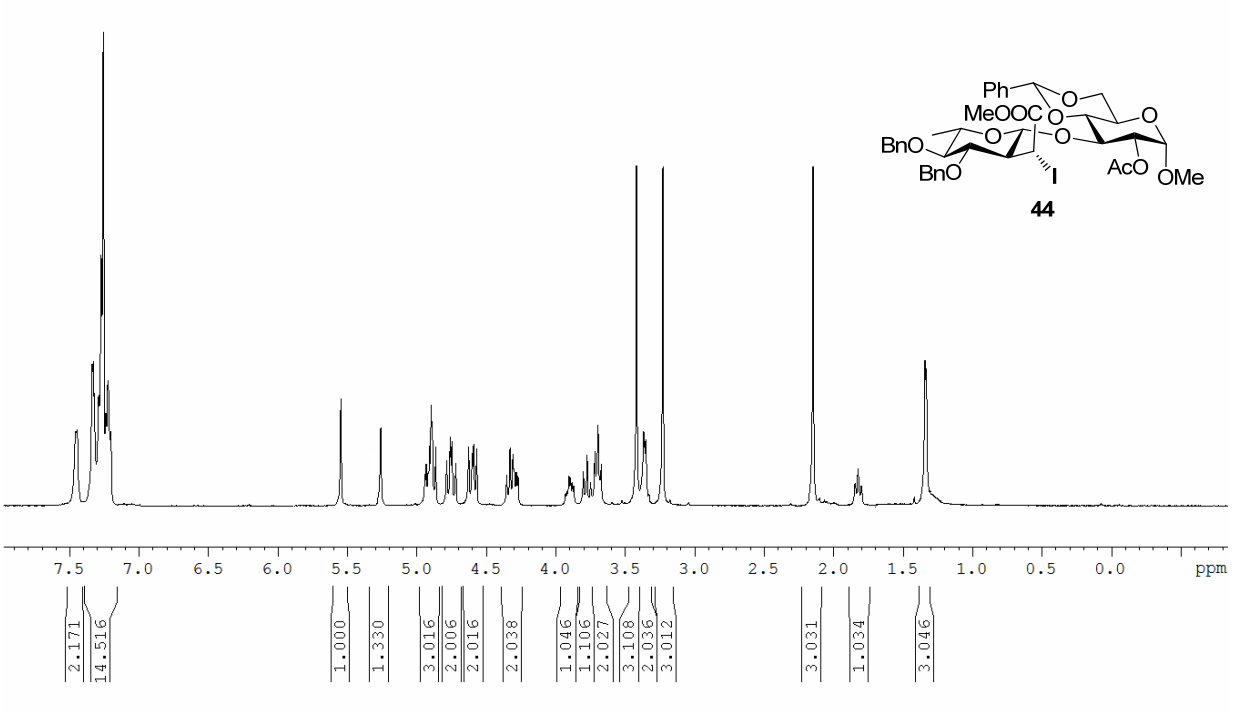

ppm
0
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
ppm

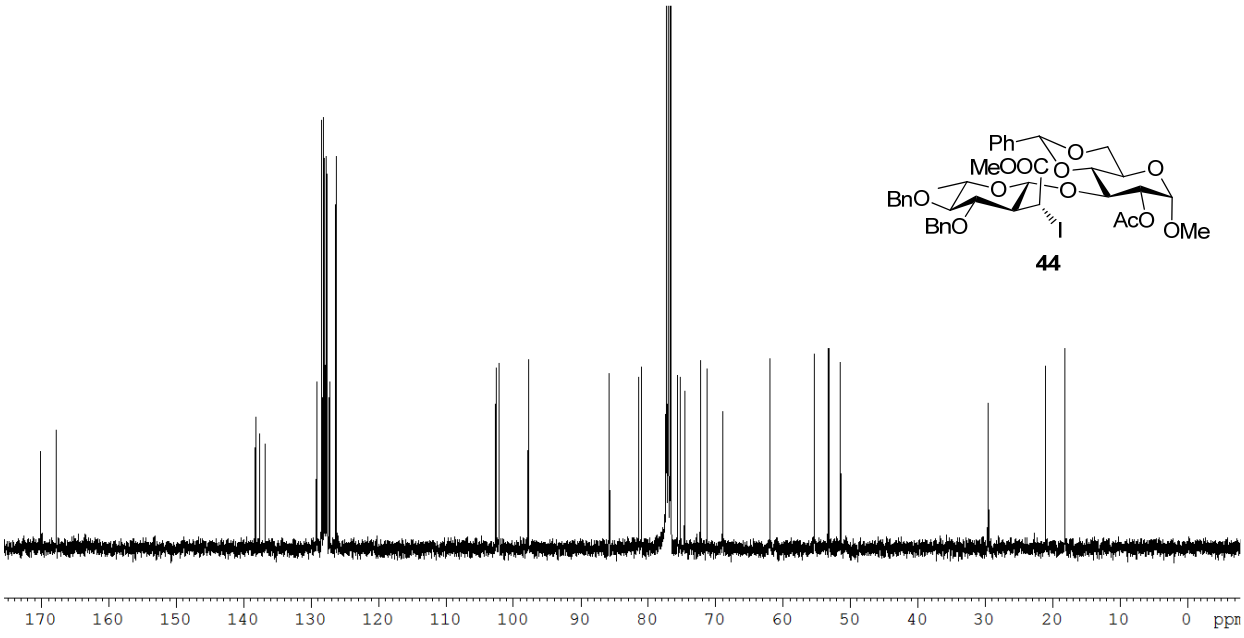

OBn
OMe
BnO
OBn
BnO
MeOOC
NH2
HO
OBn
42
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
21.230
3.038
2.006
2.132
3.854
0.938
4.048
5.087
2.161
1.864
2.727
0.999
3.803

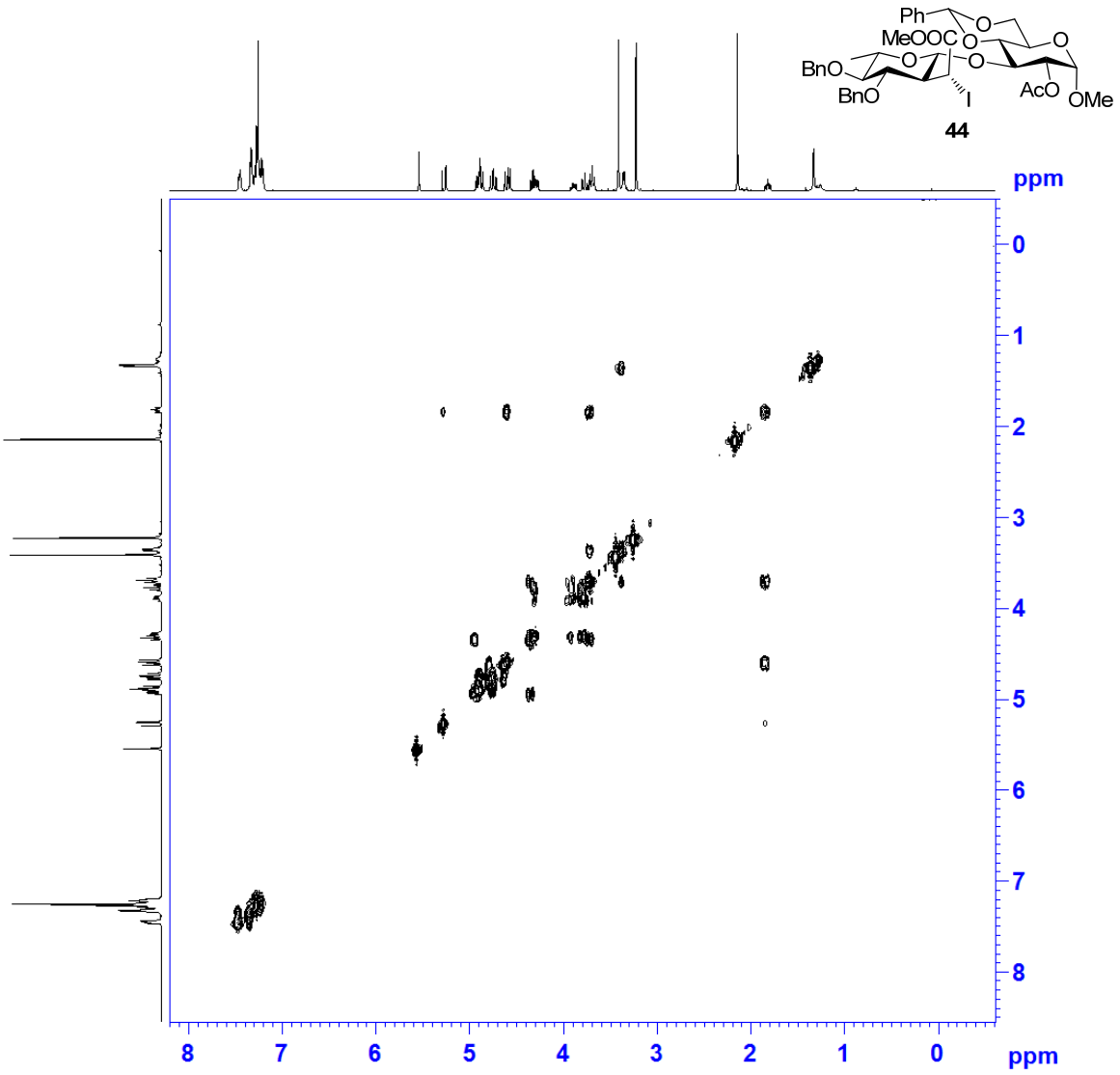

OBn
OMe
BnO
OBn
BnO
MeOOC
NH2
HO
OBn
42
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

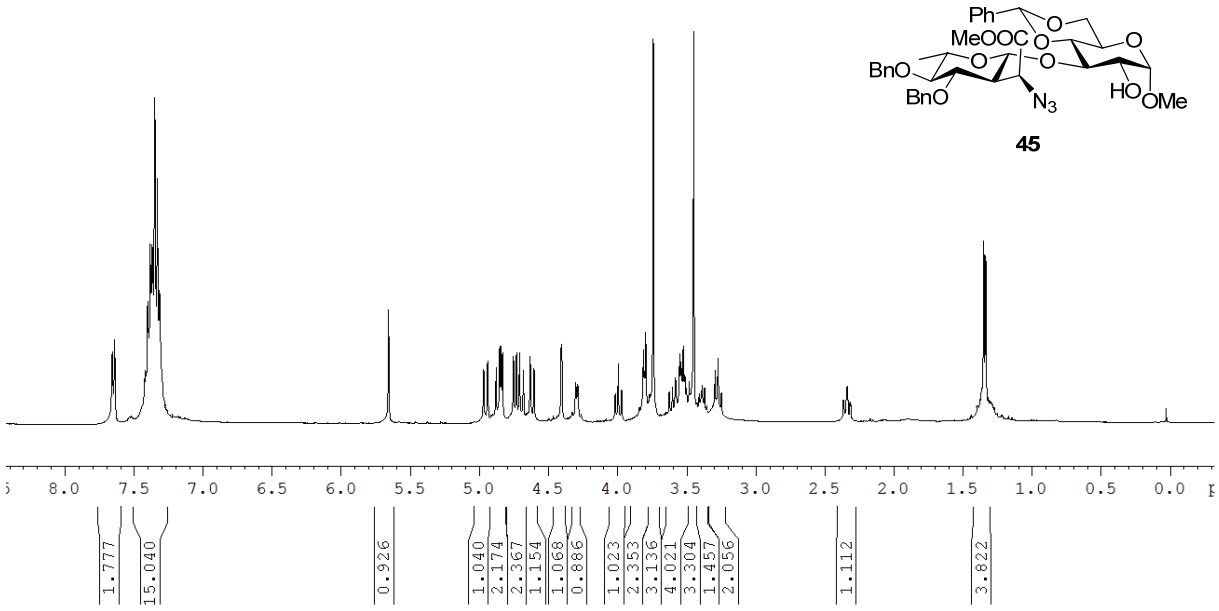

Ph
MeOOC
O
BnO
BnO
I
HO
OMe
43
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.187
13.063
1.000
0.951
0.434
1.510
1.971
0.982
1.017
0.908
0.996
0.989
1.064
3.123
1.094
1.027
3.980
2.916
1.020
3.079

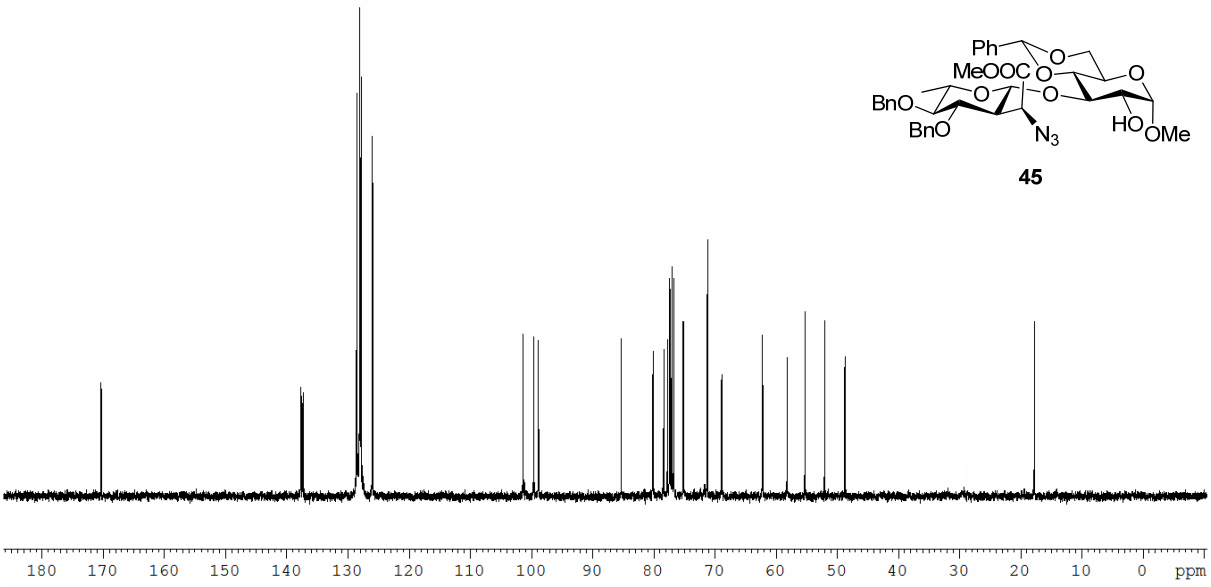

Ph
MeOOC
O
BnO
BnO
I
HO
OMe
43
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

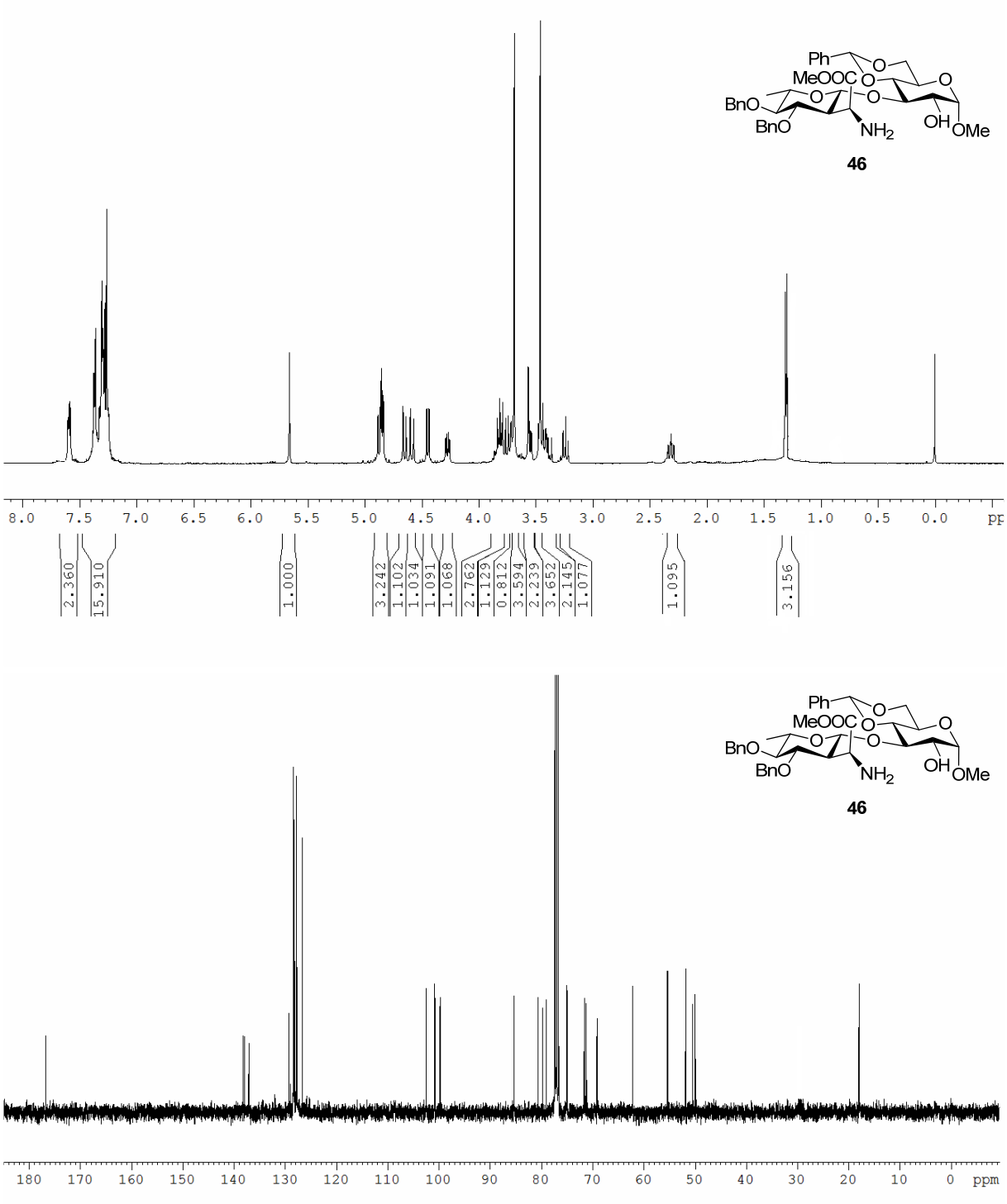

Ph
MeOOC
O
BnO
BnO
I
AcO
OMe
44
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.171
14.516
1.000
1.330
3.016
2.006
2.016
2.038
1.046
1.106
2.027
3.108
2.036
3.012
3.031
1.034
3.046

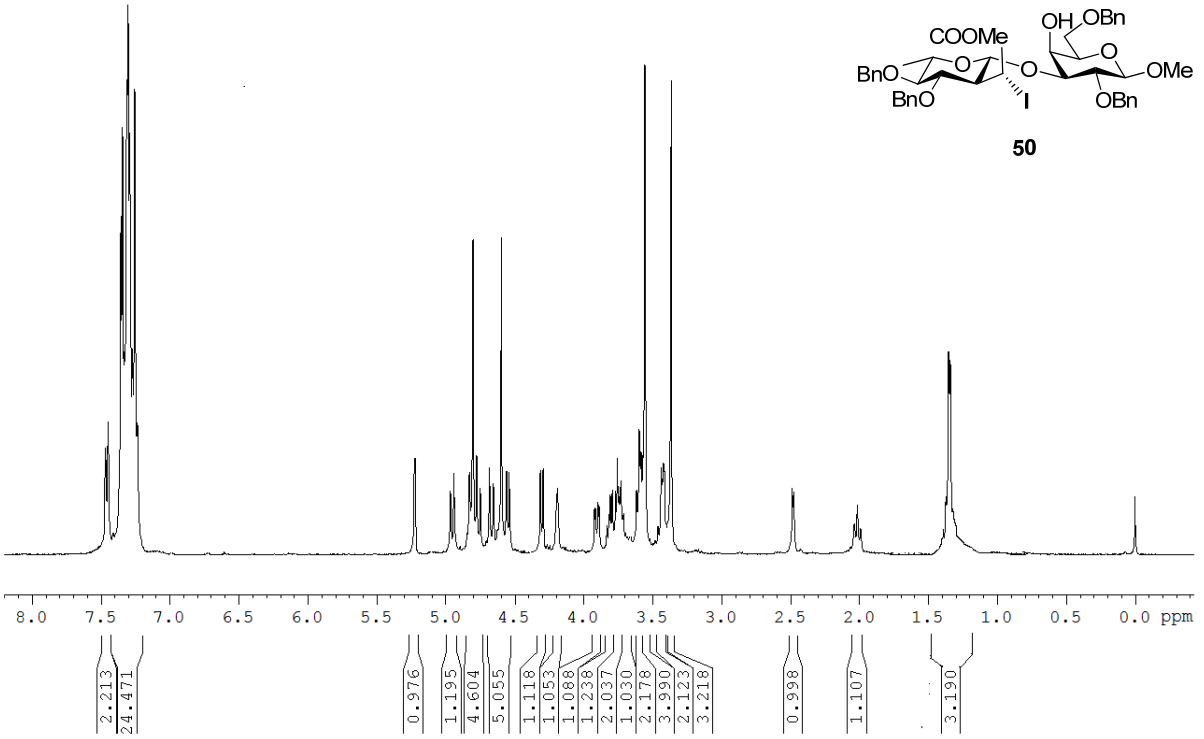

Ph
MeOOC
O
BnO
BnO
I
AcO
OMe
44
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Ph
MeOOC
O
BnO
BnO
I
AcO
OMe
44
ppm
0
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
ppm

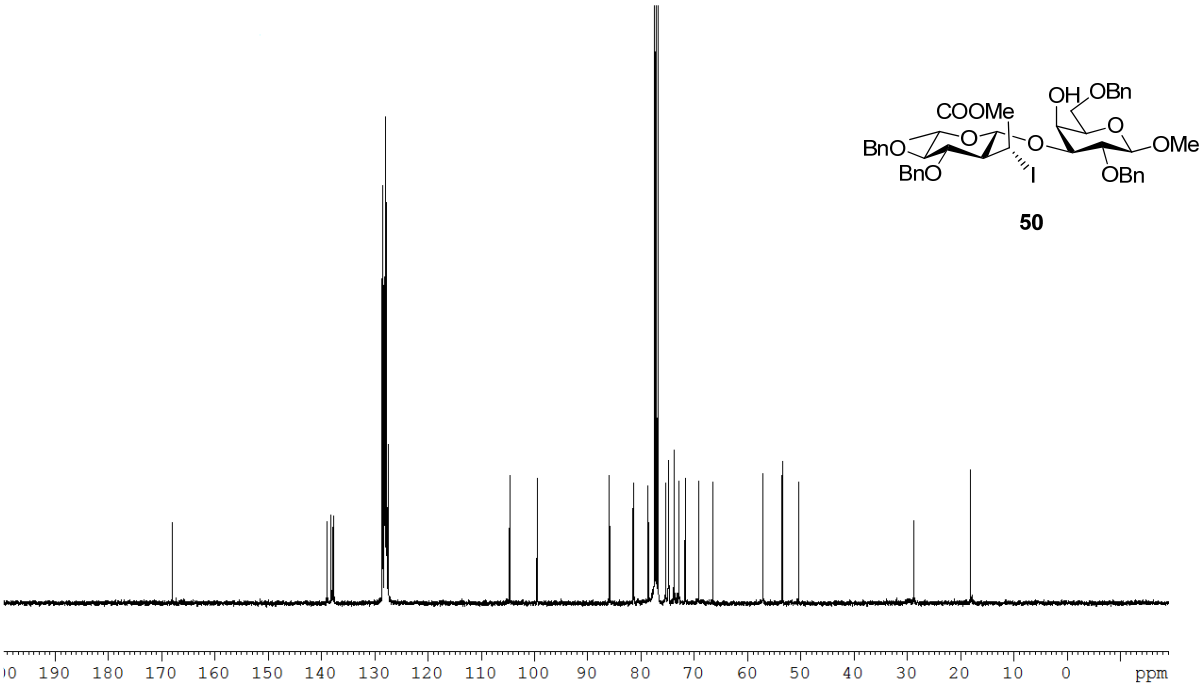

Ph
MeOOC
O
BnO
BnO
N3
HO
OMe
45
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.777
15.040
0.926
1.040
2.174
2.367
1.154
1.068
0.886
1.023
2.353
3.136
4.021
3.304
1.457
2.056
1.112
3.822


Ph
MeOOC
O
BnO
BnO
N3
HO
OMe
45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

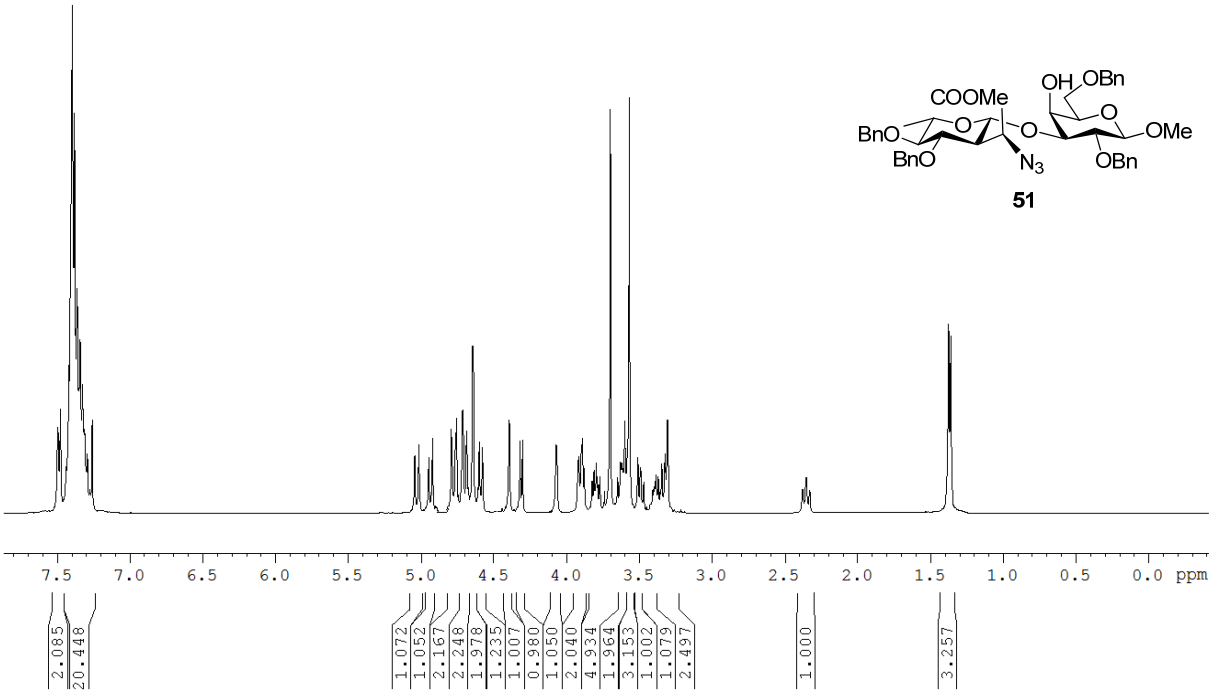

Ph
MeOOC
O
BnO
BnO
NH2
OH
OMe
46
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.360
15.910
1.000
3.242
1.102
1.034
1.091
1.068
2.762
1.129
0.812
3.594
2.239
3.652
2.145
1.077
1.095
3.156
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

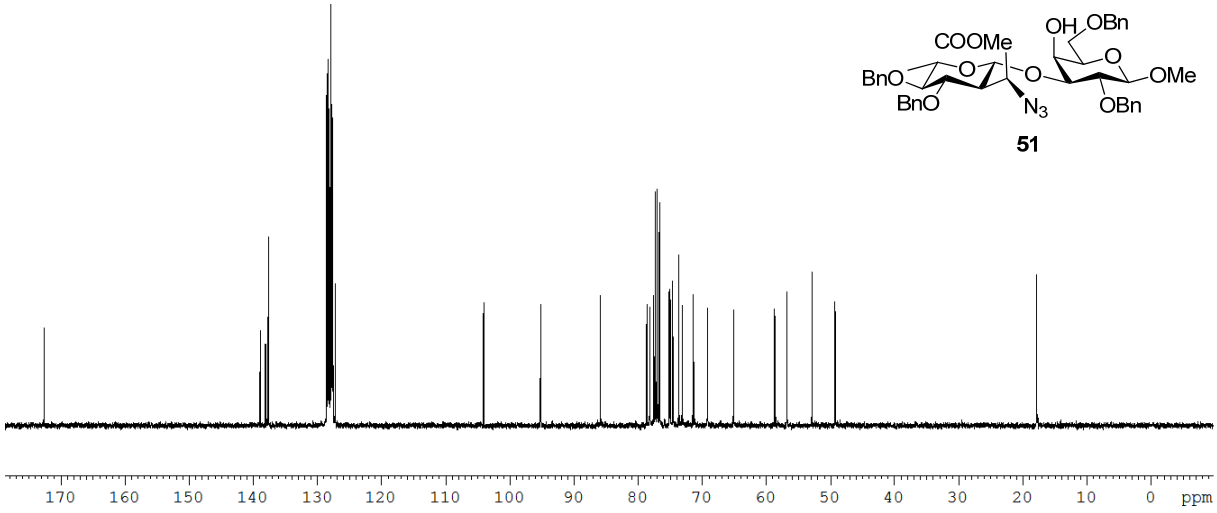

COOMe
OH
OBn
BnO
BnO
OMe
OBn
I
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.213
24.471
0.976
1.195
4.604
5.055
1.118
1.053
1.088
1.238
2.037
1.030
2.178
3.990
2.123
3.218
0.998
1.107
3.190

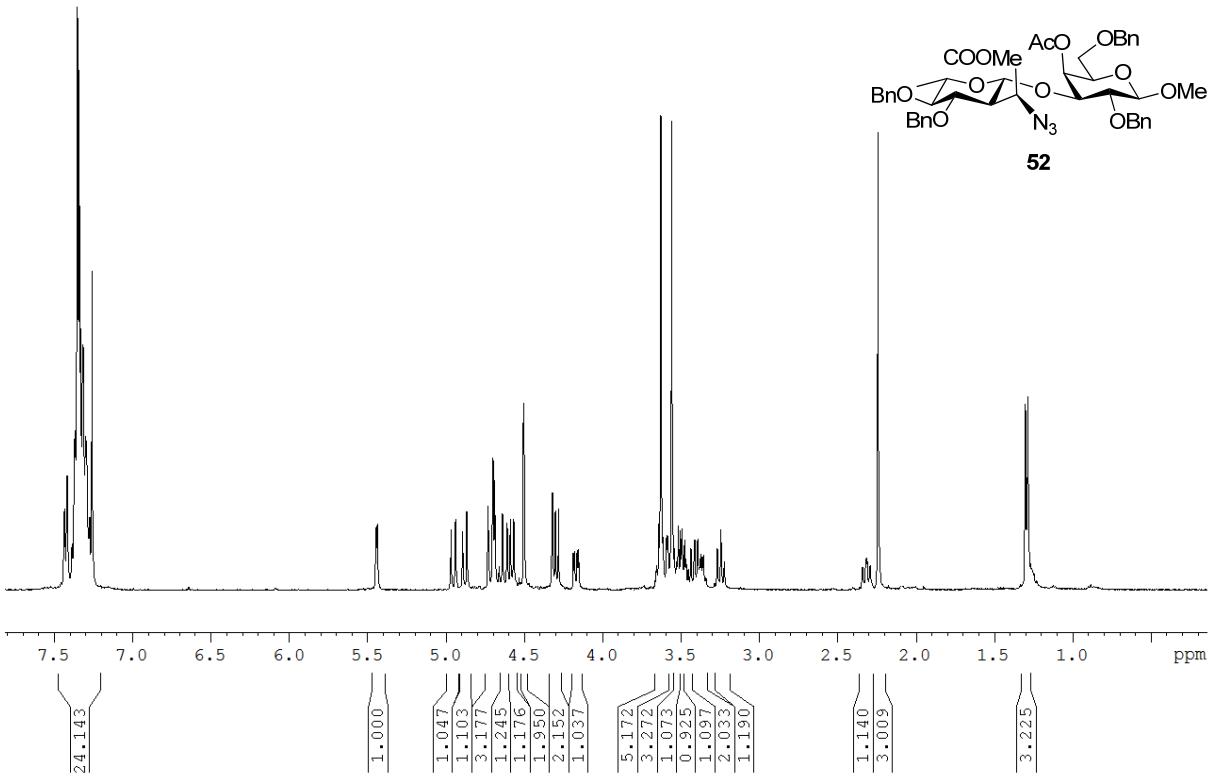
50

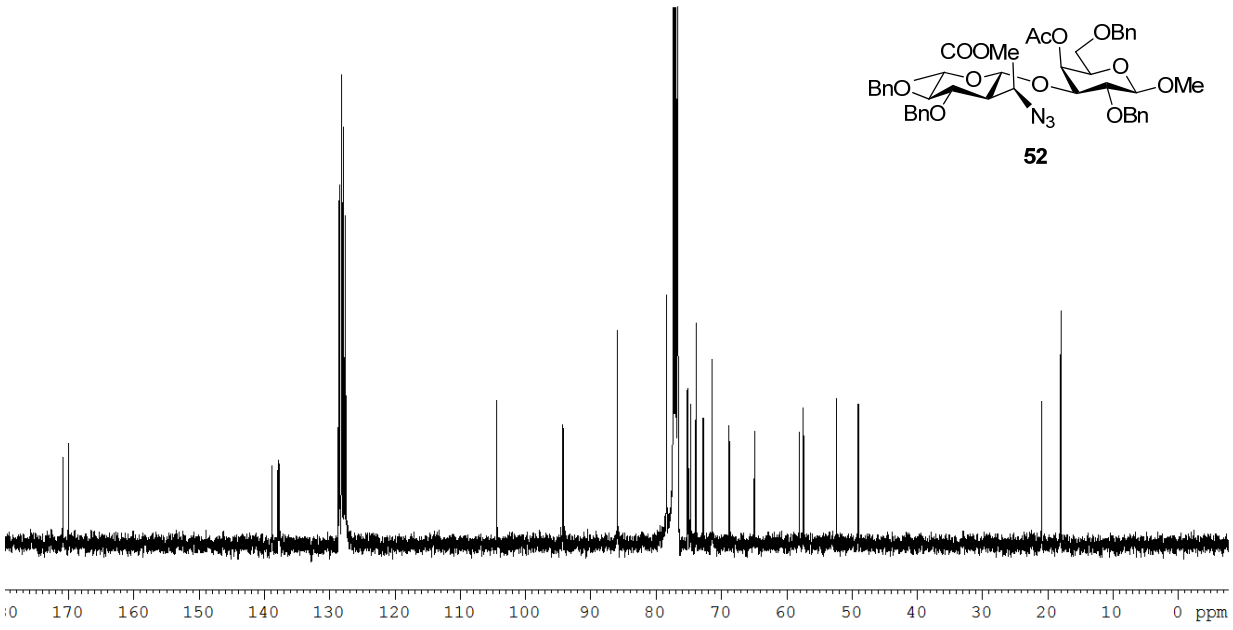

COOMe
OH
OBn
BnO
BnO
OMe
OBn
I
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

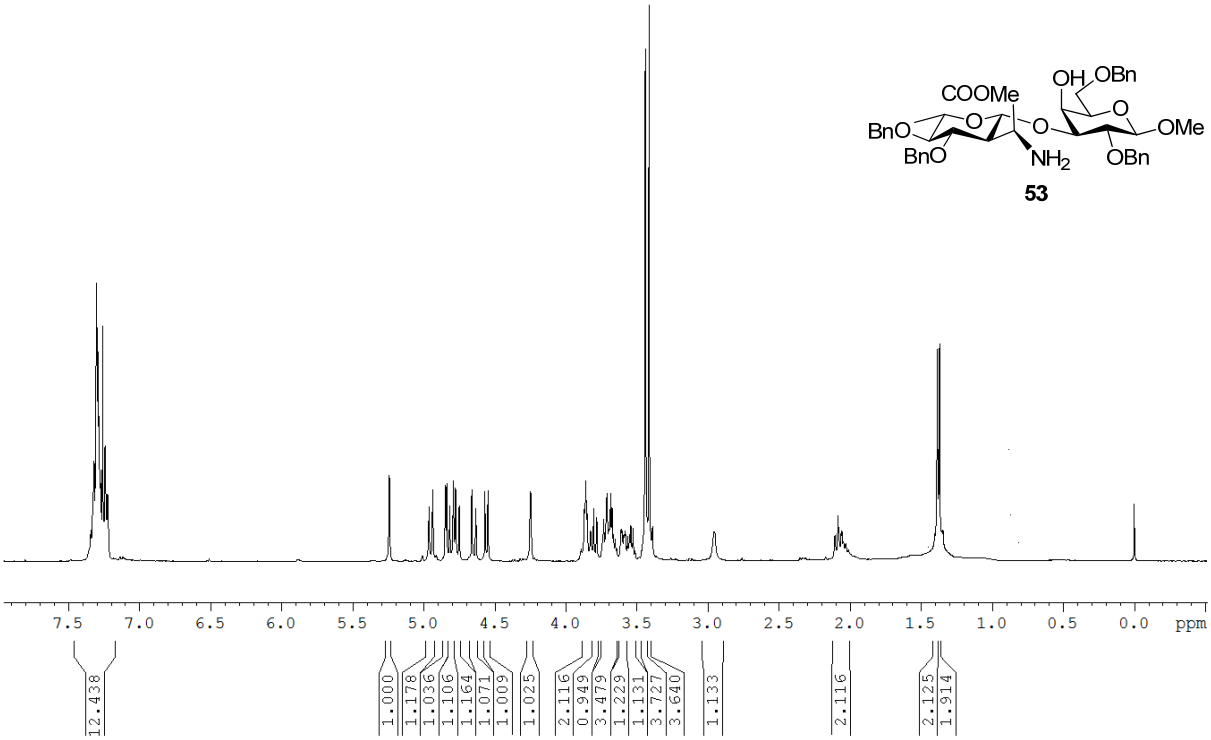
50

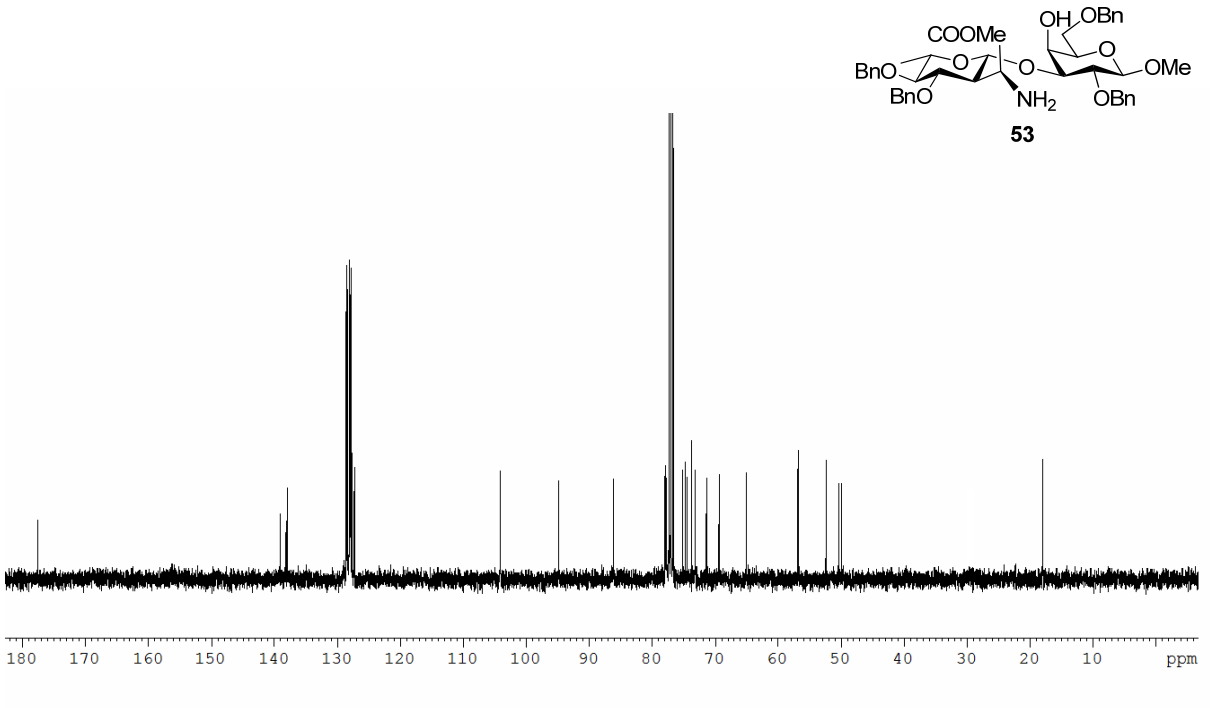

COOMe
OH
OBn
BnO
BnO
O
O
O
OMe
N3
OBn
51
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.085
20.448
1.072
1.052
2.167
2.248
1.978
1.235
1.007
0.980
1.050
2.040
4.934
1.964
3.153
1.002
1.079
2.497
1.000
3.257

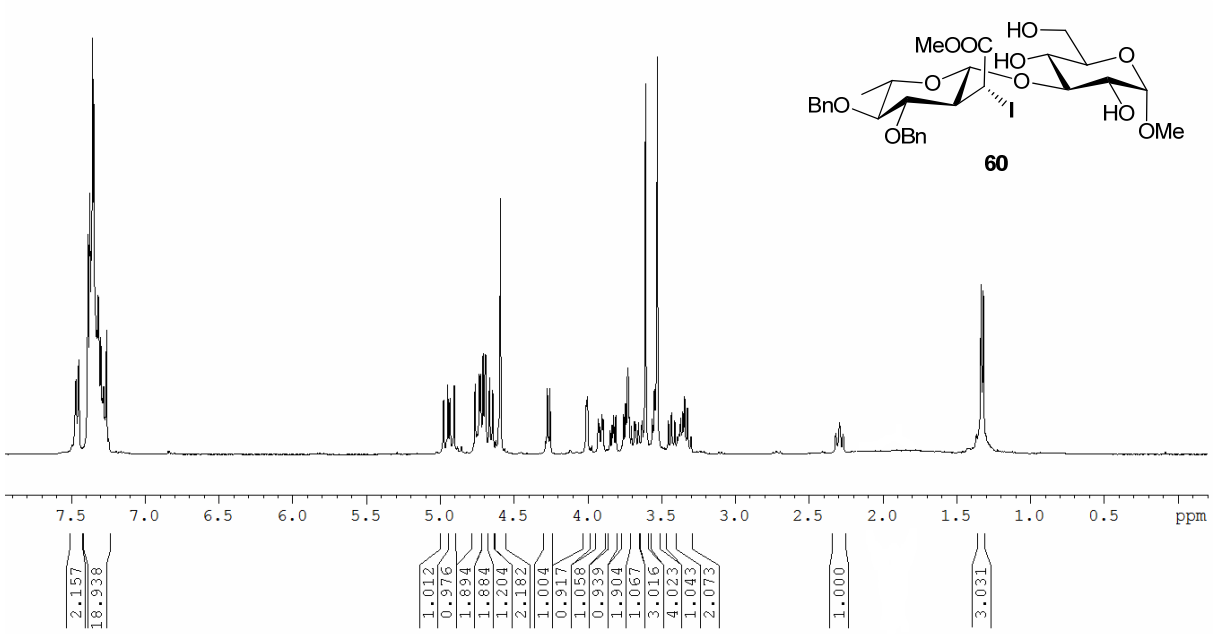

COOMe
OH
OBn
BnO
BnO
O
O
O
OMe
N3
OBn
51
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

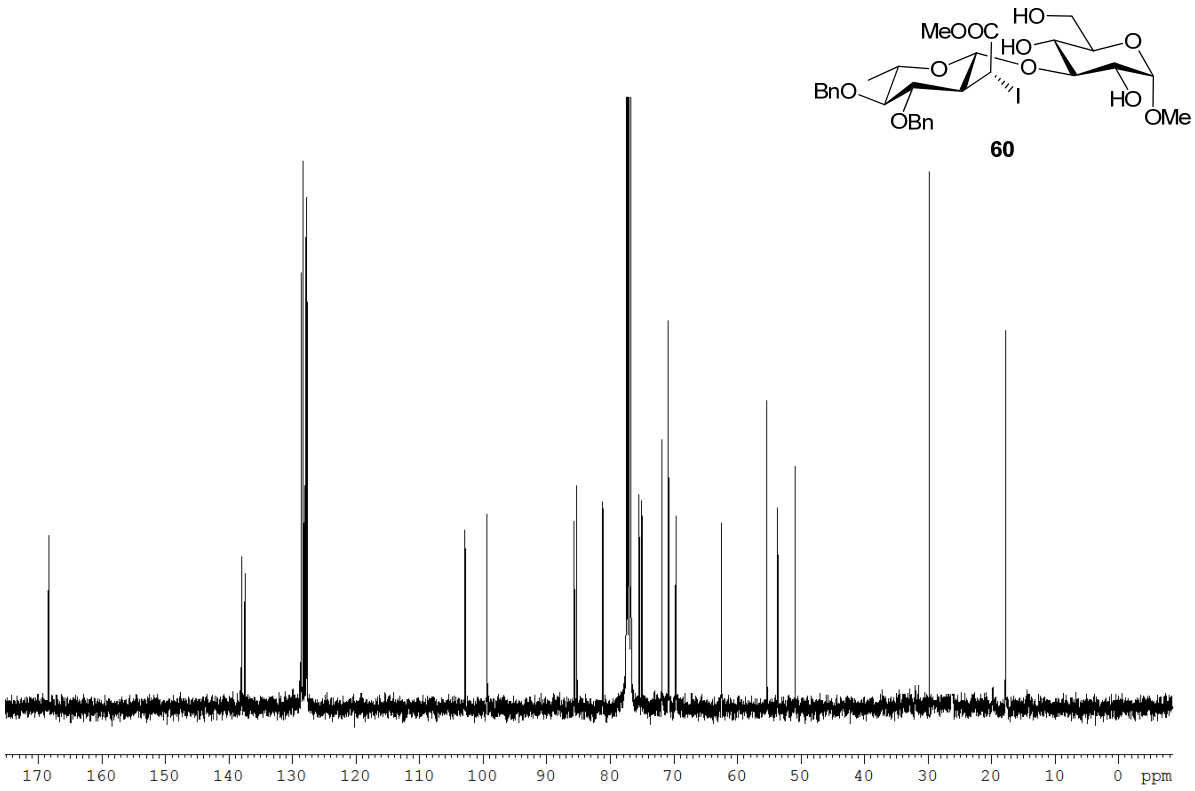

COOMe
AcO
OBn
BnO
BnO
N3
OBn
OMe
52
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
24.143
1.000
1.047
1.103
3.177
1.245
1.176
1.950
2.152
1.037
5.172
3.272
1.073
0.925
1.097
2.033
1.190
1.140
3.009
3.225

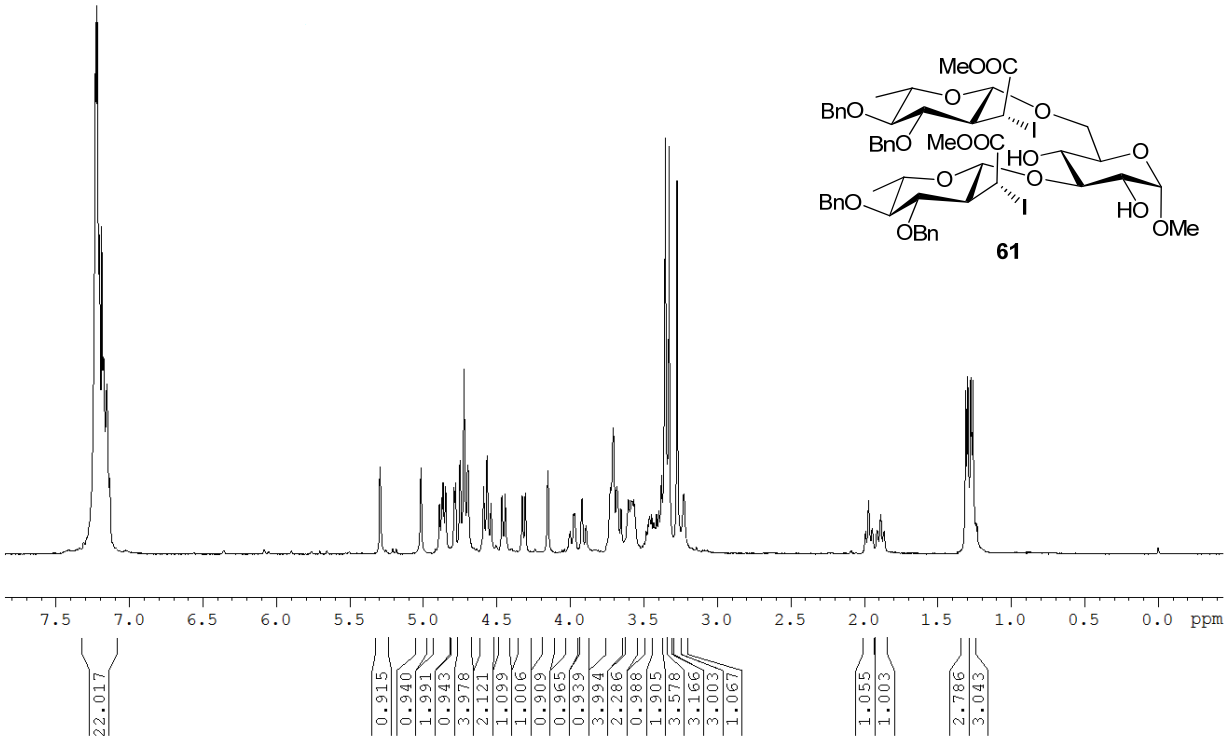

COOMe
AcO
OBn
BnO
BnO
N3
OBn
OMe
52
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

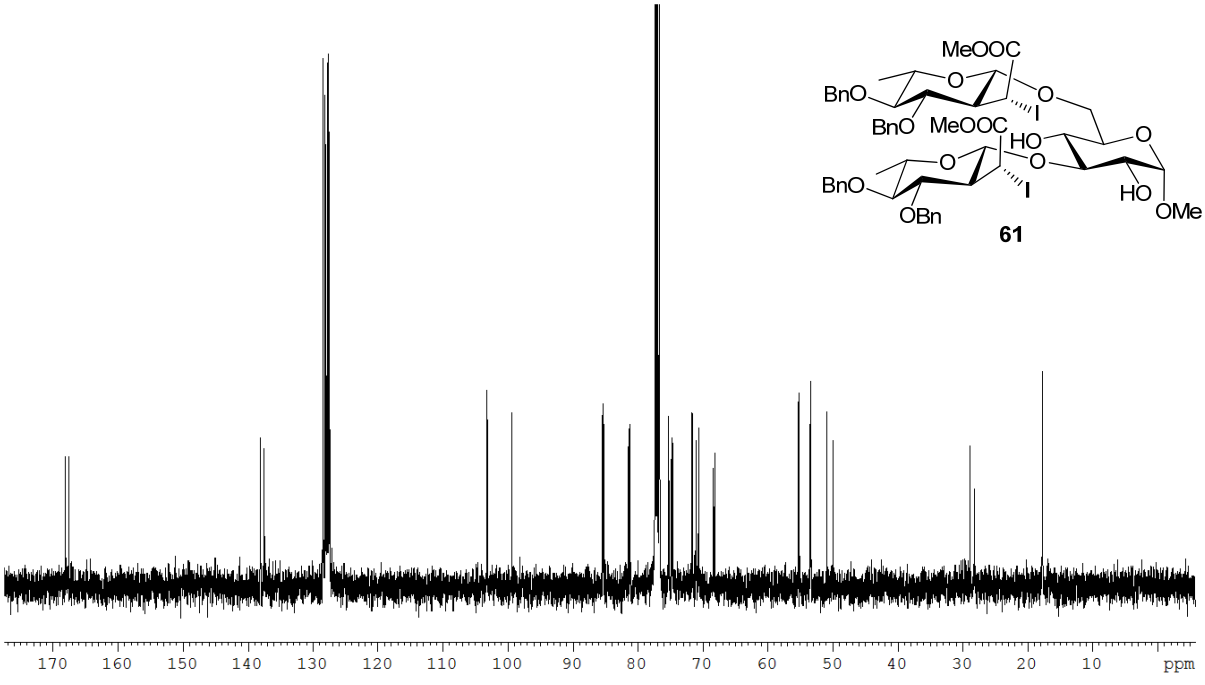

COOMe
OH
OBn
BnO
BnO
NH2
OBn
OMe
53
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
12.438
1.000
1.178
1.036
1.106
1.164
1.071
1.009
1.025
2.116
0.949
3.479
1.229
1.131
3.727
3.640
1.133
2.116
2.125
1.914

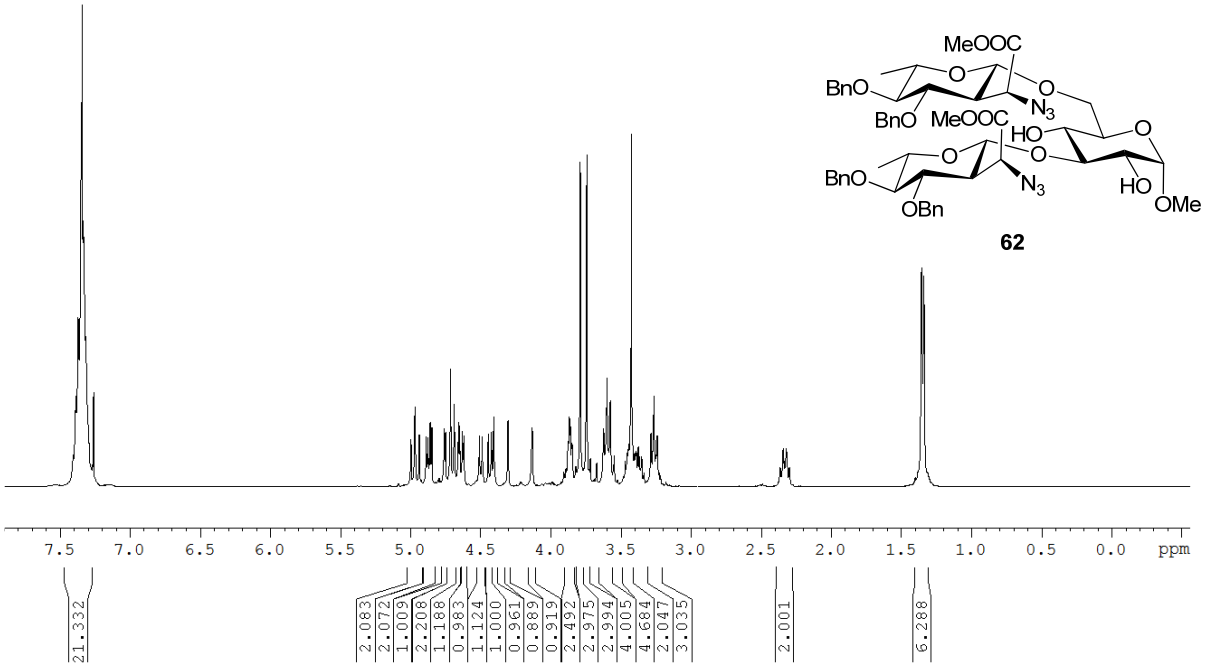

COOMe
OH
OBn
BnO
BnO
NH2
OBn
OMe
53
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

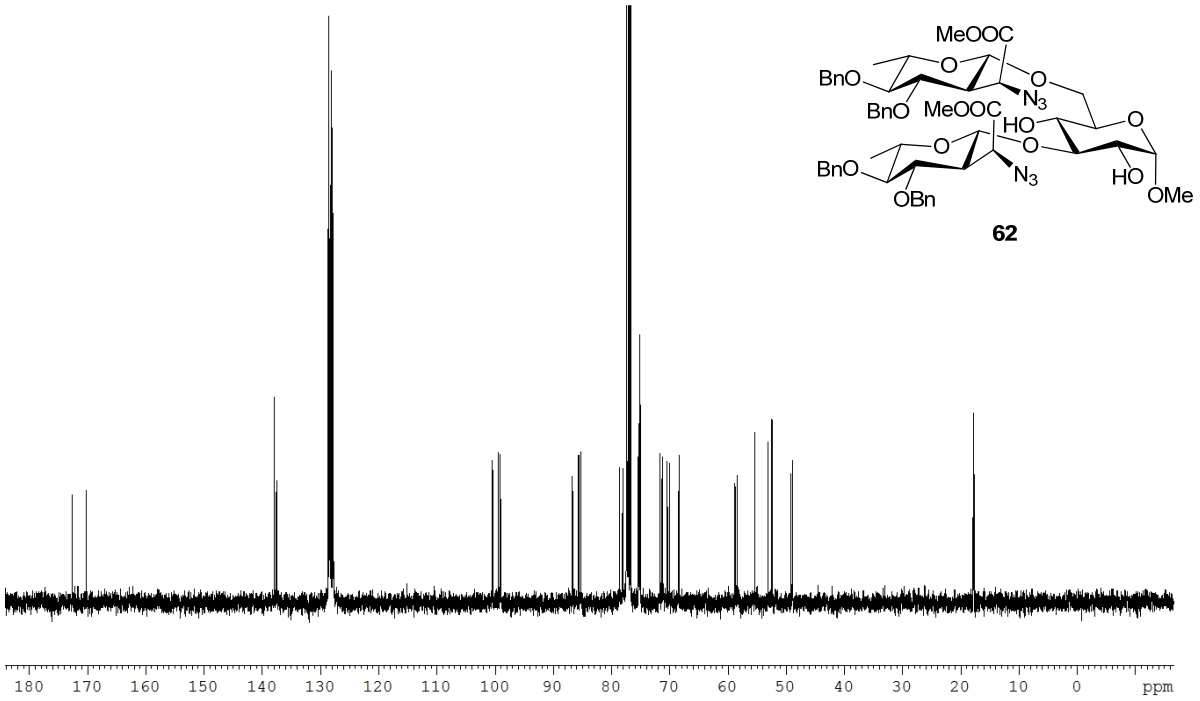

MeOOC
HO
HO
O
O
O
BnO
I
HO
OMe
OBn
60
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.157
18.938
1.012
0.976
1.894
1.884
1.204
2.182
1.004
0.917
1.058
0.939
1.904
1.067
3.016
4.023
1.043
2.073
1.000
3.031

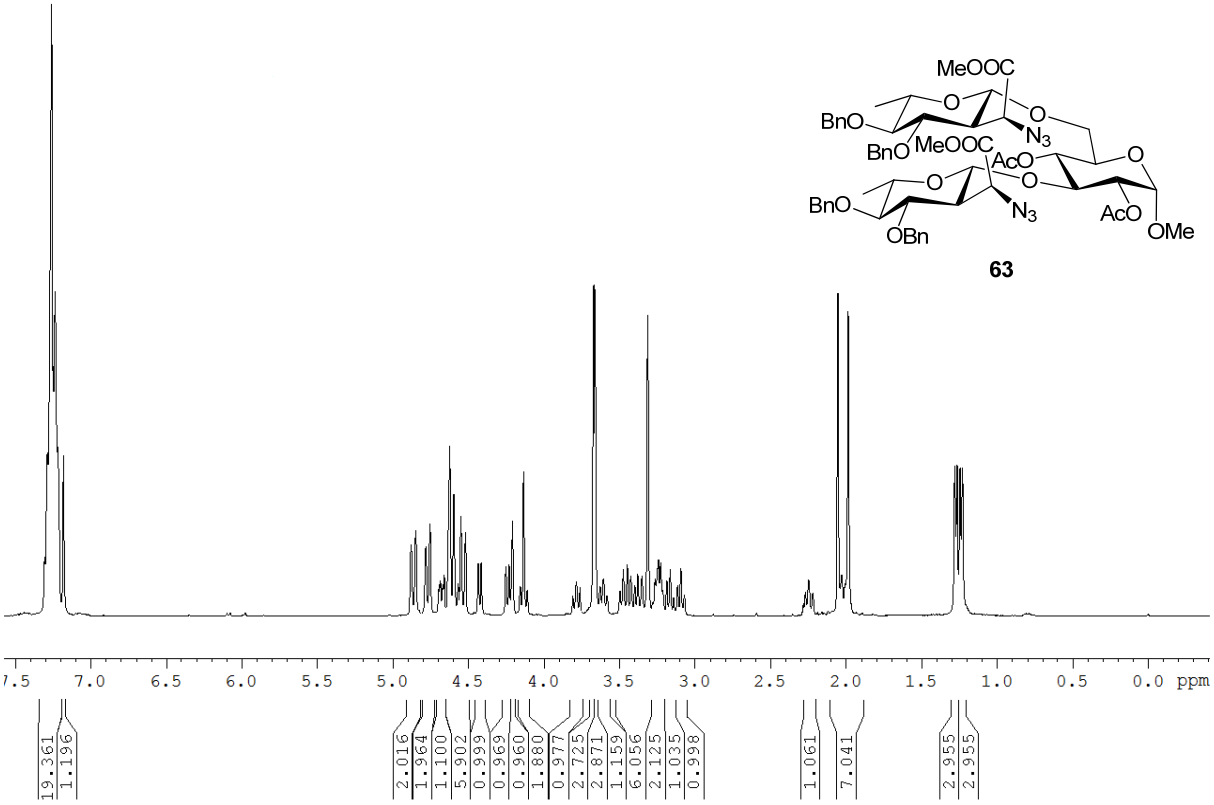

MeOOC
HO
HO
O
O
O
BnO
I
HO
OMe
OBn
60
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

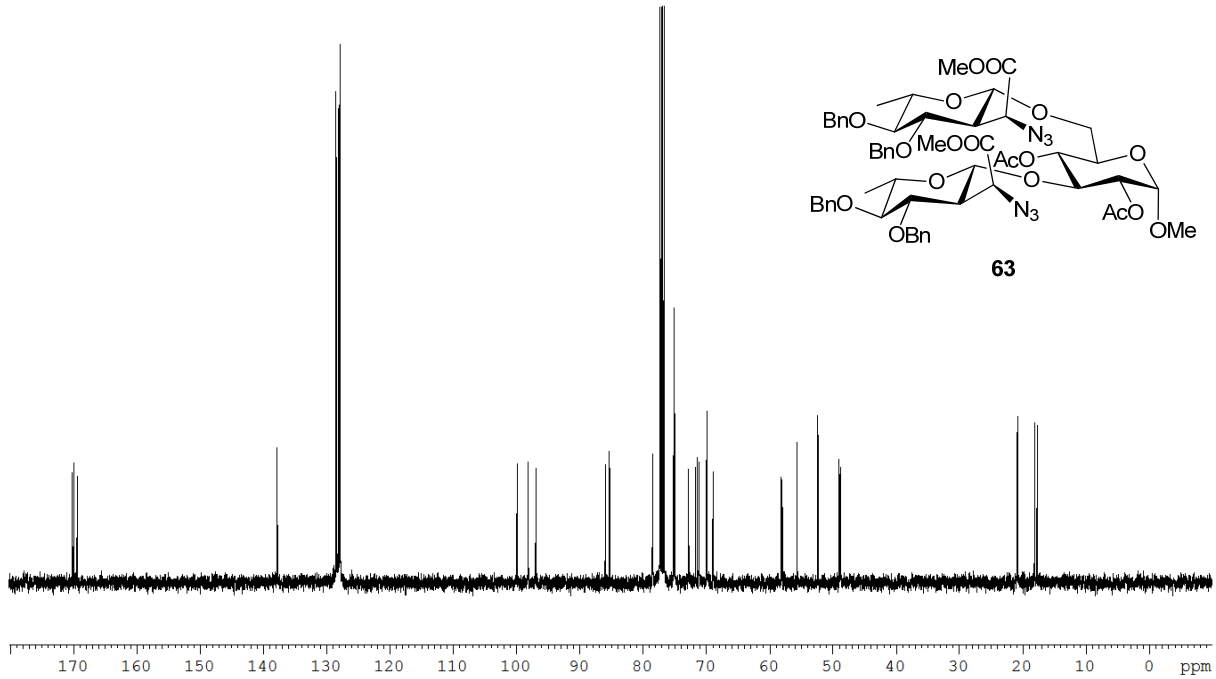

MeOOC
BnO
BnO
MeOOC
HO
BnO
OBn
HO
OMe
61
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
22.017
0.915
0.940
1.991
0.943
3.978
2.121
1.099
1.006
0.909
0.965
0.939
3.994
2.286
0.988
1.905
3.578
3.166
3.003
1.067
1.055
1.003
2.786
3.043

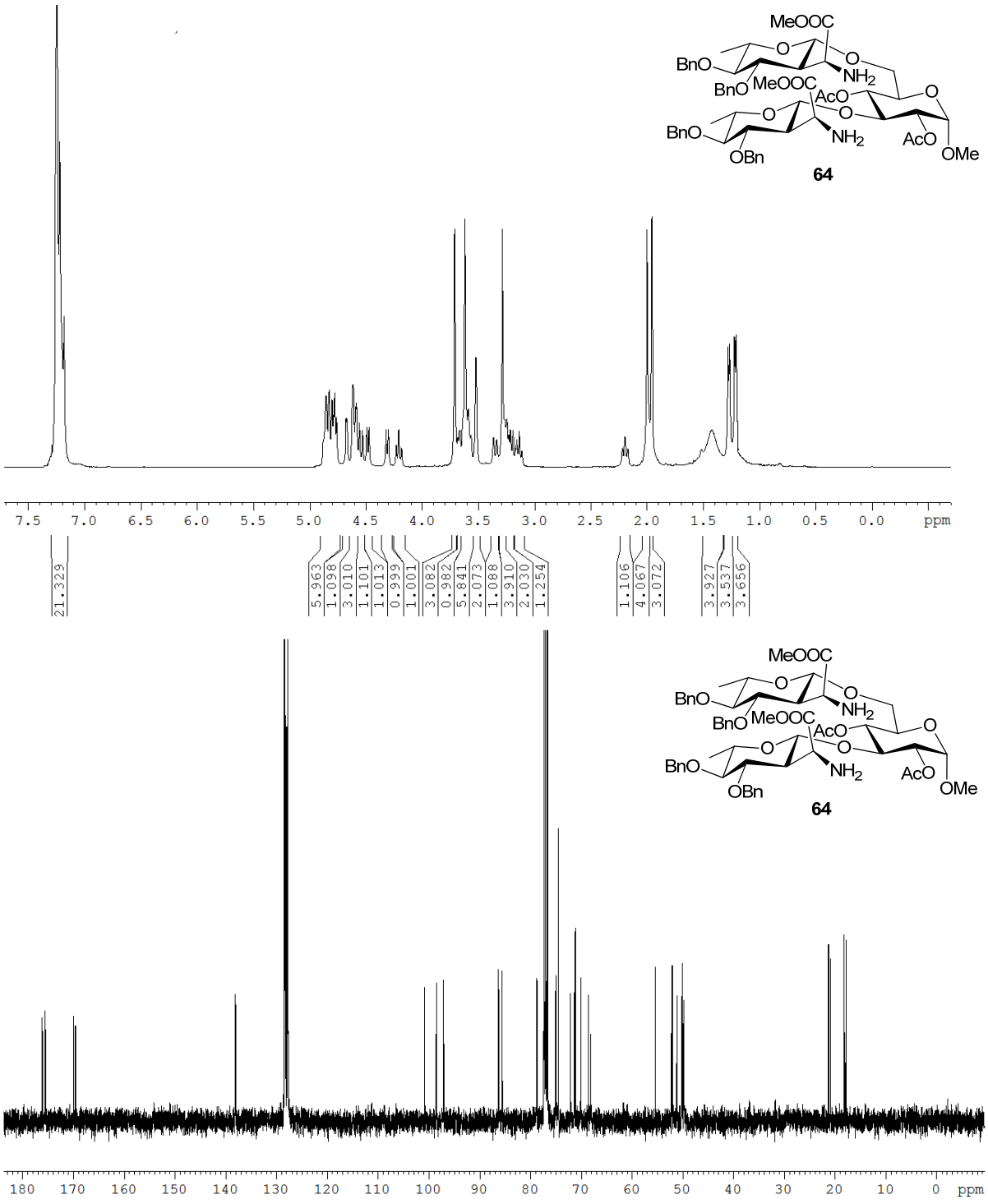

MeOOC
BnO
BnO
MeOOC
HO
BnO
OBn
HO
OMe
61
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


MeOOC
BnO
BnO
MeOOC
HO
BnO
OBn
HO
OMe
62
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
21.332
2.083 2.072 1.009 2.208 1.188 0.983 1.124 1.000 0.961 0.889 0.919 2.492 2.975 2.994 4.005 4.684 2.047 3.035
2.001
6.288


MeOOC
BnO
BnO
MeOOC
HO
BnO
OBn
HO
OMe
62
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeOOC
BnO
BnO
MeOOC
AcO
BnO
OBn
AcO
OMe
63
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
19.361
1.196
2.016
1.964
1.100
5.902
0.999
0.969
0.960
1.880
0.977
2.725
2.871
1.159
6.056
2.125
1.035
0.998
1.061
7.041
2.955
2.955

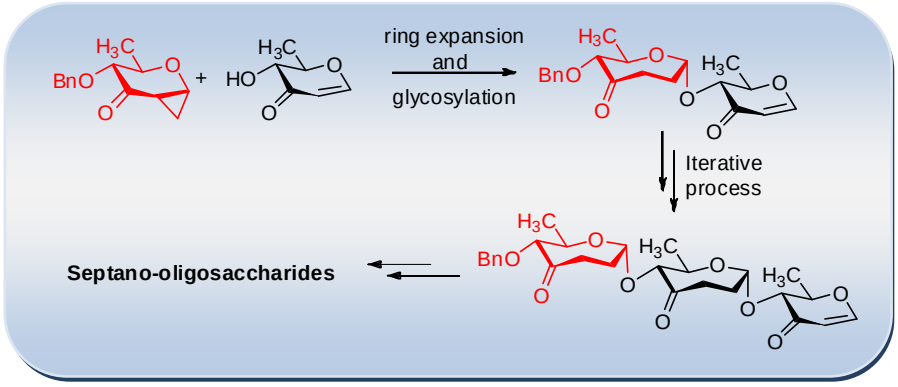

MeOOC
BnO
BnO
MeOOC
AcO
BnO
OBn
AcO
OMe
63
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeOOC
BnO
BnO
MeOOC
NH2
AcO
BnO
NH2
AcO
OMe
OBn
64
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
21.329
5.963
1.098
3.010
1.101
1.013
0.999
1.001
3.082
0.982
5.841
2.073
1.088
3.910
2.030
1.254
1.106
4.067
3.072
3.927
3.537
3.656
MeOOC
BnO
BnO
MeOOC
NH2
AcO
BnO
NH2
AcO
OMe
OBn
64
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

CHAPTER 3

A Ring Expansion-Glycosylation Strategy toward the Synthesis of Septano-oligosaccharides

ABSTRACT: A one-pot ring expansion-glycosylation reaction was performed using 1,2-cyclopropanated sugars as glycosyl donors and carbohydrate *O*-nucleophiles as acceptors to provide septano-hexose mimics of pyranose and furanose derivatives. The methodology was extended to synthesize septano-oligosaccharides by adopting a divergent strategy as well as an iterative protocol.



3.1 Introduction

Mimicking natural glycans[1] is one of the intellectual ways of misleading microorganisms and enzymes that are responsible for a variety of diseases. An important method of mimicking natural carbohydrates is by expanding or contracting the ring size. The ring-expanded versions of hexoses are the so-called septanoses/carbohydrate-based oxepanes,[2] which have been shown to be very important mimics of carbohydrates. Structure-activity studies on oral antithrombotic beciparcil derivatives revealed that ring-expansion to a seven-membered thio

sugar exhibited a 10-fold increase in activity relative to the reference compound, beciparcil.[3] Protein-carbohydrate interaction studies by Peczuh et al., involving concanavalin A and methyl septanosides, provided preliminary evidence that septanosides can resemble pyranosides.[4] Septanose mimics of nucleosides[5] and nucleic acids[6] have also been synthesized and evaluated for their antiviral and RNA-cleavage[7] properties.

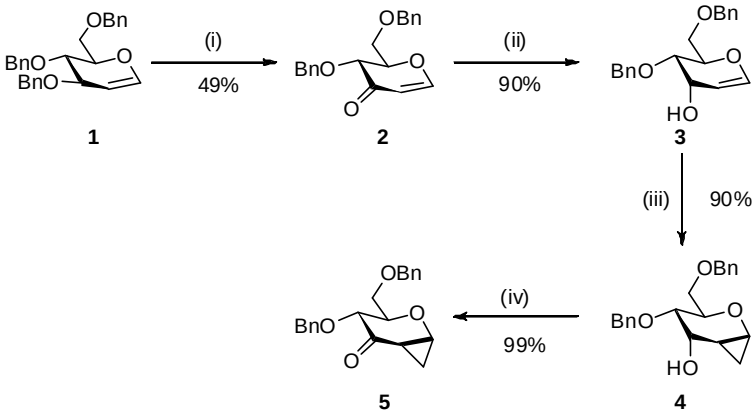
Even though several methods are available for the synthesis of septanose monosaccharides,[8] not many reports have been published on the preparation of septanose containing oligo- and polysaccharides.[9,8b] 1,2-cyclopropanated sugars also serve as versatile synthons for the synthesis of carbohydrate-based oxepanes by adopting the standard Ferrier rearrangement conditions.[10] In addition, the base-mediated ring-expansion of geminal dihalocyclopropanated sugar derivatives with various nucleophiles including sugar alcohols provides septanose containing mono and oligosaccharides.[11] These interesting methods are discussed in chapter 1 of this thesis (section 1.4).

We envisaged that incorporating an electron-withdrawing functionality at the C-3 position of 1,2-cyclopropanated sugar derivatives would provide access to cyclic donor acceptor cyclopropanes, which might undergo a regioselective electrophilic ring-opening reactions assisted by the endocyclic oxygen, to give oxepane derivatives. Based on this protocol, we herein present stereoselective ring-opening of 3-oxo-1,2-cyclopropanated sugar derivatives with carbohydrate *O*-nucleophilic glycosyl acceptors. Even though this kind of donor-acceptor cyclopropanes have been shown to undergo Lewis acid promoted ring-expansion with silyl enolates,[12] to the best of our knowledge, this is the first report of using these sugar derivatives as glycosyl donors in oligosaccharide synthesis. Further, an iterative glycosylation technology has been developed and utilized for the synthesis of a diseptanohexose oligosaccharide.

In this chapter, we describe the stereoselective synthesis of 2,3-dideoxyseptano-hexoses by TMSOTf-mediated one-step ring-expansion glycosylation of sugar-derived 1,2-cyclopropanated donors with a series of carbohydrate acceptors. To the best of our knowledge, no reports are available for the synthesis of di- and oligoseptanosides from this type of glycosyl donor.

3.2 Results and Discussion

The 3-oxo-1,2-cyclopropanated glycosyl donors were prepared from the benzyl-protected glycals in four steps. Oxidation of C3-OBn group followed by selective reduction of ketone provided the sugar-derived enol, which upon sequential *syn*-cyclopropanation and Swern oxidation gave the 3-oxo-1,2-cyclopropanated sugar derivatives in good yield. Initially, oxidation of 3,4,6-tri-*O*-benzyl-D-glucal **1** with [hydroxy(tosyloxy)iodo]benzene (HTIB or Koser's reagent) in acetonitrile gave the sugar-derived enone **2** in moderate yield.[13] Luche reduction[14] of **2**[13] produced the allal derivative **3**[15] as a single diastereomer. Hydroxyl-directed cyclopropanation[10d] of **3** using CH_2I_2 and Et_2Zn under Simmons-Smith reaction conditions[16] produced 1,2-cyclopropanated allose derivative **4**, which upon Swern oxidation[17] provided the 1,2-cyclopropa-3-pyranone **5** in excellent yield (Scheme 3.1).[12]



Reagents and Conditions: (i) PhIOH(OTs), 4 Å MS, CH_3CN, 0 °C to rt, 75 min; (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

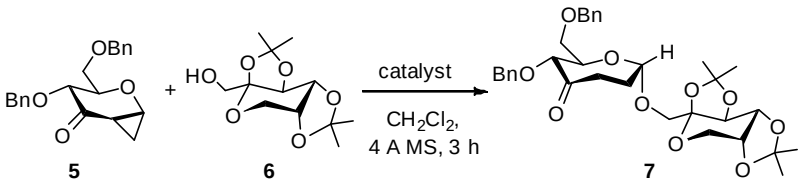
Scheme 3.1: Synthesis of D-glucose-derived 1,2-cyclopropanated donor

3.2.1 Discovery and Optimization of the Ring-Expansion–Glycosylation Reaction

Our preliminary investigations focused on optimization of the glycosylation reaction conditions using **5** as the glycosyl donor and sugar-derived *O*-nucleophiles as glycosyl acceptors. The sugar acceptor possessing free OH at 6th position was used as a model acceptor for the glycosylation reaction. The preparation of these glycosyl acceptors is discussed in chapter 2 of this thesis (section 2.2). Toward this, **5** (1 mmol) was glycosylated with 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranose **6** (1.1mmol) as an acceptor in CH_2Cl_2

at -78 ^{o}C using catalytic $BF_3.Et_2O$ (0.2 equiv) as Lewis acid. The glycosylation reaction proceeded smoothly and provided the septanohexose disaccharide **7** in 65% yield, respectively (Table 1, entry 1). A slight improvement that favored the α-glycoside formation was observed by using $(CF_3SO_2)_2O$ or $InCl_3$ as Lewis acids under similar reaction conditions (Table 3.1, entries 2 and 4). Interestingly, when TMSOTf was used as a catalyst, the ring-expansion glycosylation proceeded fruitfully, with excellent *α*-selectivity, providing the disaccharide **7** with 1:0.11 (*α:β)* selectivity in excellent yield (Table 3.1, entry 5). Carrying out the reaction either at -78 ^{o}C or from -10 to 0 ^{o}C did not improve the stereoselectivity of the glycosylation reaction (Table 3.1, entries 6 and 7).

Table 3.1: Optimization of reaction conditions for one-step ring-expansion-glycosylation reaction using 1,2-cyclopropanated sugar donor **5**.



5 **6** **7**

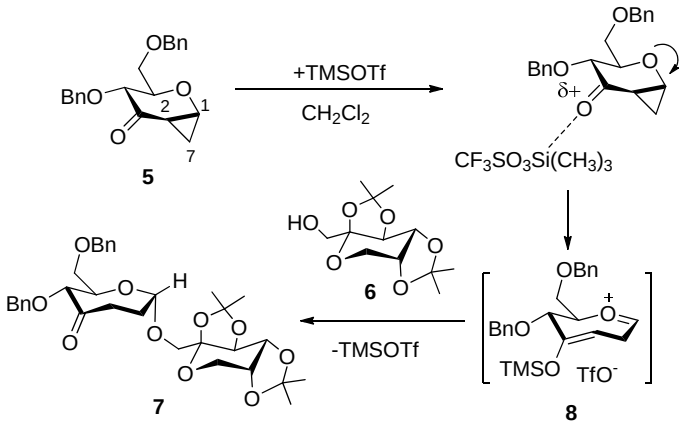
entry	catalyst (0.2 equiv)	temperature conditions (^{o}C)	yield[a]	α:β[c]
1	$BF_3{\cdot}OEt_2$	-78 to +25	65%	1:0.71
2	$(CF_3SO_2)_2O$	-78 to +25	60%	1:0.57
3	$InCl_3$	-78 to +25	<5	----
4	$InCl_3$[b]	-78 to +25	50%	1:0.45
5	**TMSOTf**	-78 to +25	**89%**	**1:0.11**
6	TMSOTf	-78	72%	1:0.71
7	TMSOTf	-10 to 0	82%	1:0.42

[a]Yield represents pure and isolated products. [b]1 equiv of catalyst was used. [c]Based on septanosyl anomeric proton ratio

3.2.2 Plausible Mechanistic Pathway

The major α-glycosylated product can be envisaged arising by a preferential approach of the nucleophile along an axial trajectory toward the oxocarbonium ion intermediate.[18] As shown in Scheme 3.2, activation of the glycosyl donor **5** with TMSOTf would generate the oxocarbenium ion intermediate **8** *via* the cleavage of C1-C2 bond. The trimethylsilyl enolate

8 would react with acceptor **6**, preferentially in the axial direction, due to the anomeric effect,[19] provide the α-selective septanohexose **7** as the major product.



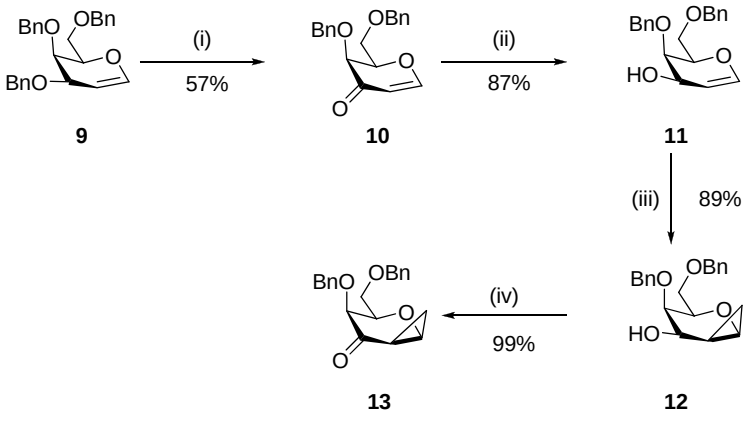
Scheme 3.2: Proposed mechanism for the stereoselective formation of α-glycoside

3.2.3 Scope of the Reaction

After optimizing the reaction conditions, the aforementioned ring expansion-glycosylation was extended to the various sugar derived 1,2-cyclopropa-3-pyranone donors and carbohydrate-derived *O*-nucleophilic glycosyl bond acceptors.

Synthesis of sugar-derived 1,2-cyclopropa-3-pyranone donors

Like D-glucose-derived 1,2-cyclopropanone **5**, three more glycosyl donors were efficiently synthesized from the benzyl-protected glycals in good to excellent yield.

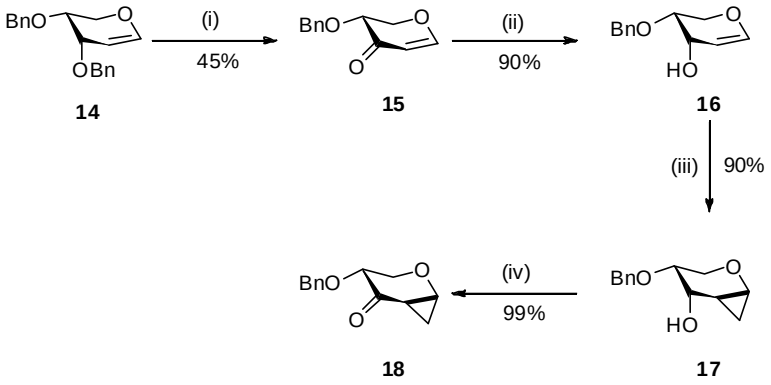


Reagents and Conditions: (i) PhIOH(OTs), 4 Å MS, CH_3CN, 0 °C to rt, 75 min; (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

Scheme 3.3: Synthesis of D-galactose-derived 1,2-cyclopropanated donor

The oxidation of 3,4,6-tri-*O*-benzyl D-galactal **9** with Koser's reagent in CH_3CN gave the D-galactose-based enone **10** which upon Luche reduction at -78 ^oC provided the 4,6-di-*O*-benzyl D-galactal **11** as a single diastereomer. Selective benzylation of D-galactal using sodium hydride and benzyl bromide in DMF also provide **11** but with moderate yield. Simmons-Smith cyclopropantion of **11** with CH_2I_2/Et_2Zn produced exclusive *syn*-cyclopropanated sugar derivative **12** which gave the D-galactose-derived 1,2-cyclopropa-3-pyranone **13** under the Swern oxidation conditions in excellent yield (Scheme 3.3).

Similarly, 3,4-di-*O*-benzyl D-arabinal **14** was oxidized with Koser's reagent to give the D-arabinose-derived enone **15** which upon Luche reduction with $NaBH_4$ in presence of $CeCl_3.7H_2O$ provided the 4-*O*-benzyl D-arabinal **16**. Hydroxyl directed cyclopropantaion of **16** with CH_2I_2/Et_2Zn in ether at 0 ^oC afforded the cyclopropane adduct **17** as a single diastereomer. Swern oxidation of **17** gave the D-arabinose-derived 1,2-cyclopropa-3-pyranone **18** in excellent yield (Scheme 3.4). The **18** could also be synthesized from 3,4-di-*O*-benzyl D-xylal using the same series of reactions.



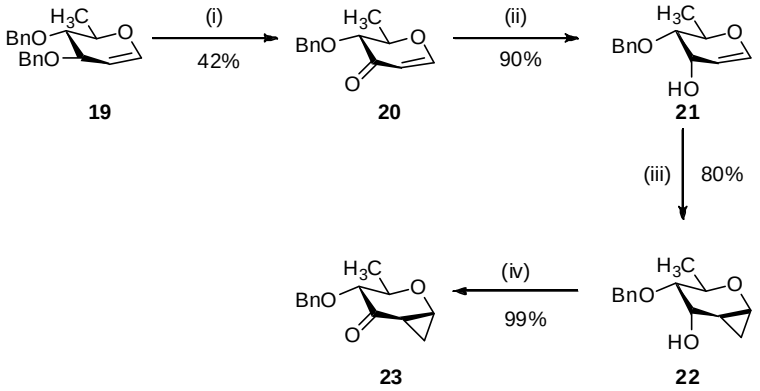
14 **15** **16** **17** **18**

Reagents and Conditions: (i) PhIOH(OTs), 4 Å MS, CH_3CN, 0 ^oC to rt, 75 min; (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ^oC, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 ^oC, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h.

Scheme 3.4: Synthesis of D-arabinose-derived 1,2-cyclopropanated donor

In addition to this, we also prepared 6-deoxy 1,2-cyclopropanated sugar donor for the ring-expansion glycosylation reaction. The treatment of 3,4-di-*O*-benzyl D-rhamnal **19**, which was synthesized using a well known procedure[20] from the D-glucal in three steps, with Koser's reagent gave the D-rhamnose-derived enone **20**. Luche reduction of **20** provided enol **21** which on cyclopropanation under the Simmons-Smith reaction conditions furnished the

cyclopropyl adduct **22**. Swern oxidation of **22** gave the D-rhamnose-derived cyclopropane **23** in good yield (Scheme 3.5).

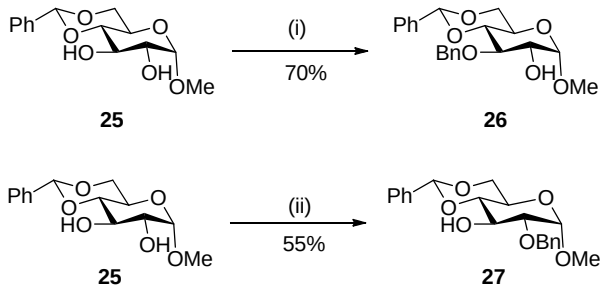


Reagents and Conditions: (i) PhIOH(OTs), 4 Å MS, CH_3CN, 0 °C to rt, 75 min; (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

Scheme 3.5: Synthesis of D-rhamnose-derived 1,2-cyclopropanated donor

Synthesis of Glycosyl Acceptors

In chapter 2 (section 2.2), we have discussed the synthesis of 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranose **6** and 1,2;3,4-di-*O*-isopropylidene-α-D-galactose **24,**[21] which were prepared from D-fructose and D-galactose respectively in one-step. In order to prepare the other carbohydrate derived *O*-nucleophiles, we used methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **25**[22] (*vide supra* see chapter 2, section 2.2) for the synthesis of sugar acceptors possessing the hydroxyl group at C2 and C3. The selective benzylation of **25** with sodium hydride and benzyl bromide in presence of copper (II) chloride at reflux conditions provided the methyl 3-*O*-benzyl 4,6- *O*-benzylidene-α-D-glucopyranoside **26**[23] in 70% yield.

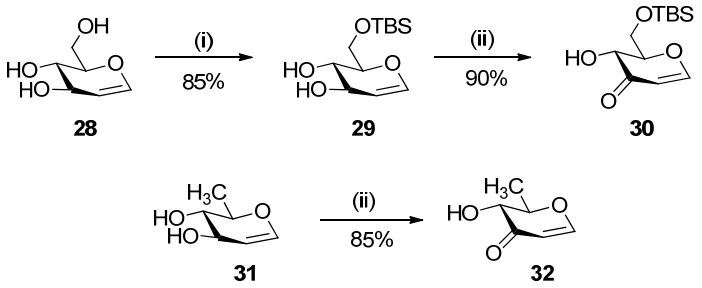


Reagents and Conditions: (i) $CuCl_2$, NaH, BnBr, TBAI, THF, reflux, 24 h; (ii) NaH (1 eq), BnBr (1eq), DMF, 0 °C to rt, 16 h.

Scheme 3.5: Synthesis of glycosyl acceptors

On the other hand, benzylation of **24** with 1 equivalent of sodium hydride and 1 equivalent of benzyl bromide in DMF gave the methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **27**[24] in 55% yield as isolated product (Scheme 3.5).

Furthermore, enone-based glycosyl acceptors were prepared and evaluated their reactivity toward the glycosylation process. Protection of 6-OH in D-glucal **28** with *tert*-butyldimethylsilyl (TBS) group using TBDMS chloride in presence of imidazole gave the 6-*O*-*tert*-butyldimethylsilyl D-glucal **29**, which upon oxidation with pyridinium dichromate (PDC) in dichloromethane provided the glycosyl acceptor **30**[25] in good yield. Similarly, D-rhamnal **31** was oxidized with PDC in dichloromethane to give the 6-deoxy sugar acceptor **32**[20] in excellent yield. By utilizing the enone functionality, **32** has been used in the iterative process for the synthesis of septano-oligosaccharides.

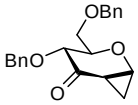
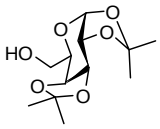
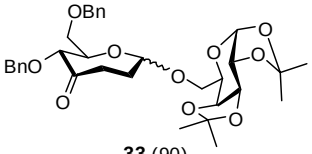
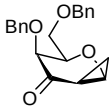
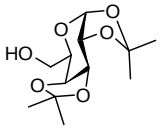
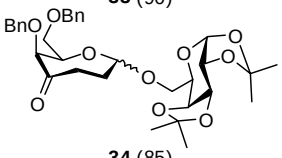
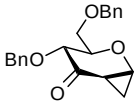
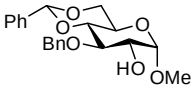
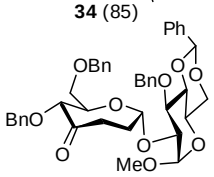
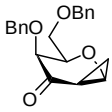
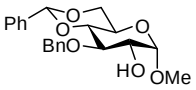
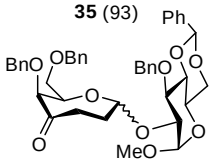
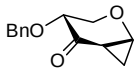
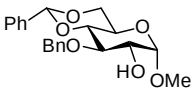
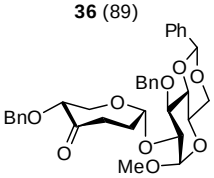
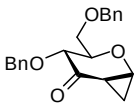
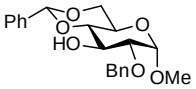
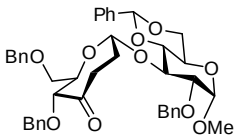
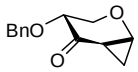
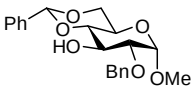
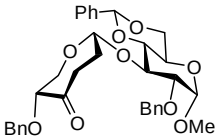
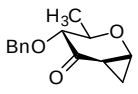
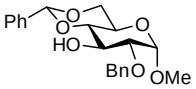
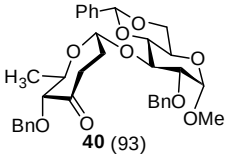
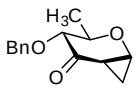
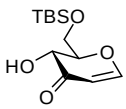
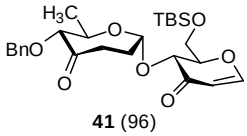


Reagents and Conditions: (i) TBSCl (1 eq), Imidazole, 0 °C to rt, 10 h; (ii) PDC, CH_2Cl_2, 0 °C to rt, 3 h.

Scheme 3.6: Synthesis of enone-based glycosyl acceptors

The glycosyl donors and acceptors in hand, we intended to synthesize various septanose containing di- and oligosaccharides. Thus, the reaction of acceptor **24** with 1,2-cyclopropanated donors **5** and **13** gave rise to septanohexose derivatives **33** and **34**, respectively, with modest diastereoselectivity at the newly formed C1' anomeric center (α:*β* (7:3)) in excellent yield (Table 3.2, entries 1 and 2). The methodology was also applied to the sugar acceptors possessing less reactive secondary alcohols. Thus, different 1,2-cyclopropa-3-pyranone donors **5**, **13**, and **18** were glycosylated with the sugar acceptor **26**, possessing a free hydroxyl group at the C2 position (Table 3.2, entries 3, 4 and 5). Interestingly, donors **5** and **18**, upon glycosylation with **26**, provided selectively the α-glycosylated septanohexoses **35** and **37**, whereas donor **13** with acceptor **26** provided a diastereomeric mixture of **36α** and

Table 3.2: Stereoselective synthesis of septanohexoses

entry	donor cyclopropane	acceptor	septano-hexose derivatives (%)	α:β ratio
1	 **5**	 **24**	 **33** (90)	7:3
2	 **13**	 **24**	 **34** (85)	7:3
3	 **5**	 **26**	 **35** (93)	Only α
4	 **13**	 **26**	 **36** (89)	7:3
5	 **18**	 **26**	 **37** (80)	Only α
6	 **5**	 **27**	 **38** (95)	Only α
7	 **18**	 **27**	 **39** (91)	Only α
8	 **23**	 **27**	 **40** (93)	Only α
9	 **23**	 **30**	 **41** (96)	Only α

36*β* in 7:3 ratio, respectively (Table 3.2, entry 4). The structure of the minor diastereomer **36*β*** was confirmed by X-ray crystallography (Figure 3.1).[26]

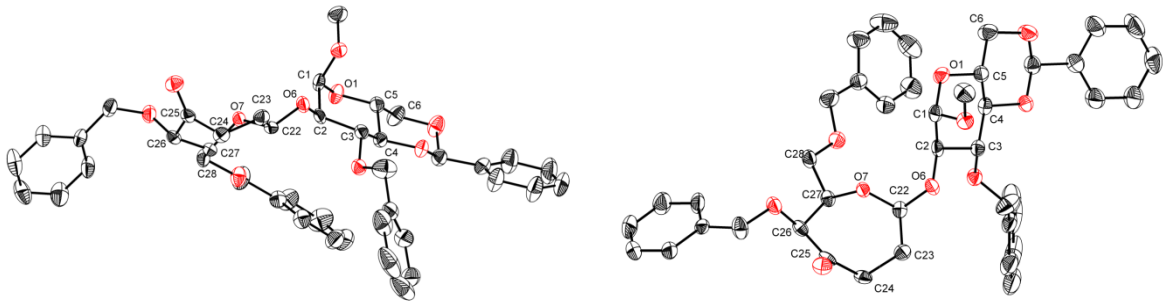
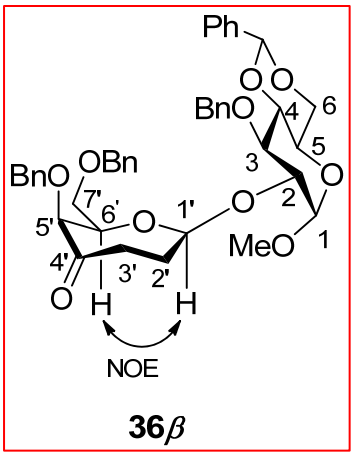


Figure 3.1: ORTEP diagrams of septanohexose **36*β***

Glycosylation of donors **5**, **18**, and **23** with acceptor **27**, in which the free hydroxyl is at C3, provided the corresponding septanohexoses **38**, **39**, and **40** as single diastereomers with the α-configuration at the newly formed glycosidic center (Table 3.2, entries 6, 7 and 8). The stereochemistry at C1' for all the disaccharide derivatives was assigned based on the chemical shift value of the anomeric carbon[27] ($\delta_{C1'}$ for α-septanosides ranges from 99 to 104 ppm while for *β*-septanosides it ranges from δ 104-111 ppm) as well as two-dimensional NMR experiments. For the septanohexoses possessing a *β*-glycosidic bond, a strong NOE was observed between the 1,3-diaxial hydrogens at C1' and C6' which was absent in the case of septanosides with α-glycosidic linkage.

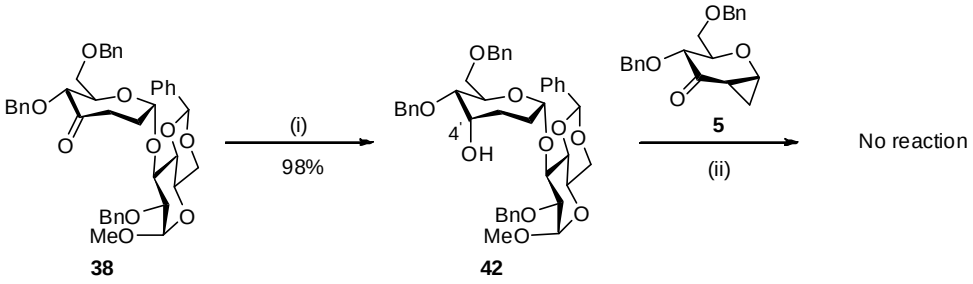


36*β*

The sugar-derived enone acceptor **30** was also very reactive toward the one- step ring-expansion-glycosylation reaction with donor **23** and produced the disaccharide derivative **41** as a single diastereomer in excellent yield (Table 3.2, entry 9). It is well-known that the stereoselectivity in the glycosylation of hexose derived oxocarbenium ions is dictated by stereoelectronic effects in the glycosyl donor and the nonbonding steric interactions from the glycosyl acceptors.[18,28] The above experimental results provide an ample evidence that similar effects play a role in the glycosylation of septanosides as well.

3.2.4 Synthesis of Diseptano-hexose Trisaccharides

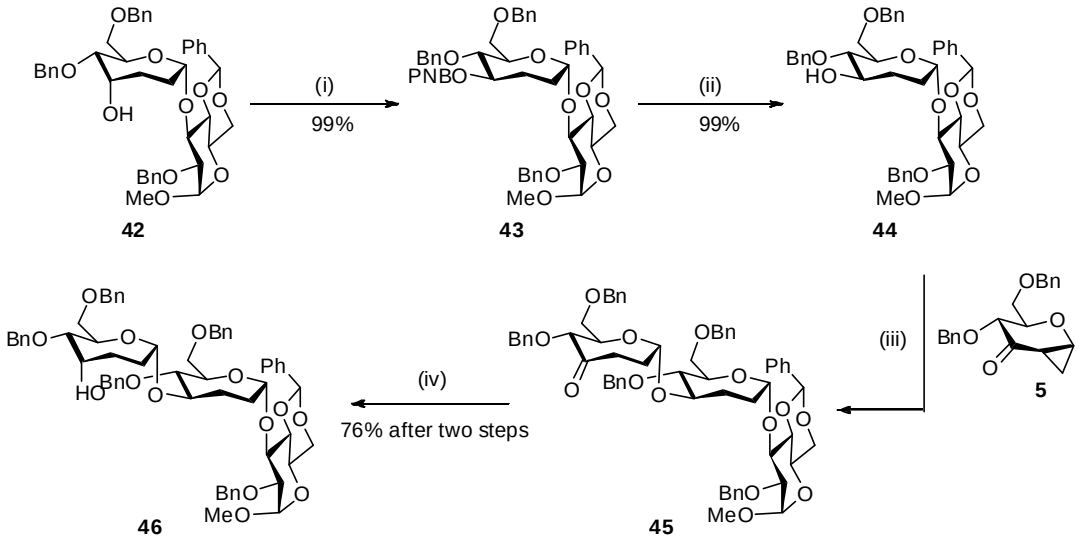
After successful synthesis of a series of septanohexose disaccharide derivatives, we focused our attention on the synthesis of diseptanohexose trisaccharides. Thus, stereoselective reduction of disaccharide **38** with lithium tri-*tert*-butoxyaluminum hydride in ethanol at -78 ^{o}C provided the acceptor alcohol **42** (Scheme 3.7). However, the glycosylation of donor **5** with acceptor **42** did not happened under the optimized reaction conditions. The orientation of hydroxyl group at C4' was deduced based on ^{1}H and COSY NMR analysis.



Reagents and Conditions: (i) LiAl(O^{t}Bu)$_3$H, EtOH, -78 ^{o}C, 1 h; (ii) TMSOTf, CH_2Cl_2, -78 ^{o}C to rt, 3 h.

Scheme 3.7: Attempts to synthesis of diseptanohexose trisaccharide

We reasoned that the very low reactivity of the acceptor **42** might be due to the axial orientation of hydroxyl group. Therefore, inversion of the axial hydroxyl in **42** *via* Mitsunobu



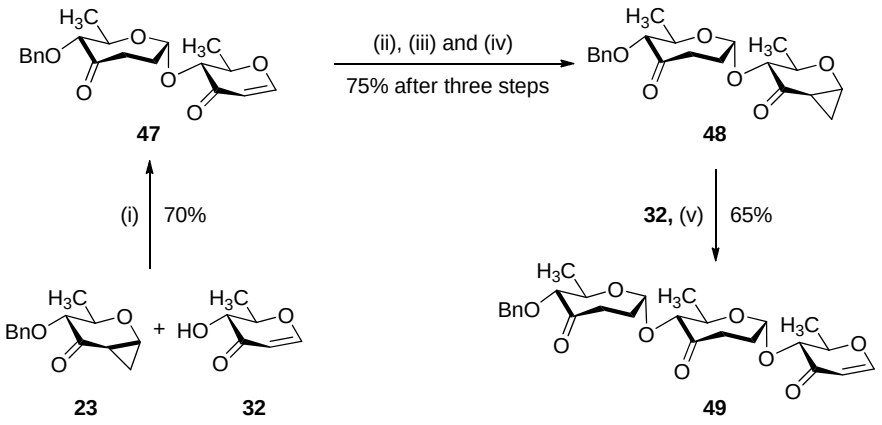
Reagents and Conditions: (i) PNB-OH, DIAD, Ph_3P, THF, rt, 8 h; (ii) NaOMe/MeOH, rt, 1 h; (iii) TMSOTf, 4 Å MS, CH_2Cl_2. -78 ^{o}C to rt, 3 h; (iv) LiAl(O^{t}Bu)$_3$H, EtOH, -78 ^{o}C, 1 h.

Scheme 3.8: Synthesis of diseptanohexose trisaccharide

reaction provided disaccharide-based benzoate **43**. The deprotection of benzoate **43** with NaOMe/MeOH gave the disaccharide acceptor **44**. Gratifyingly, glycosylation of **5** with acceptor disaccharide **44** proceeded smoothly, generating the diseptanohexose trisaccharide derivative **45** as a single diastereomer (Scheme 3.8). Stereoselective reduction of ketone **45** provided the trisaccharide acceptor **46-α,α** which can be used further for the synthesis of septano-oligosaccharides. The stereochemistry of trisaccharides was deduced based on the chemical shift value of anomeric carbons of septanose residues.

3.2.5 Iterative protocol for the synthesis of septano-oligosaccharides

Finally, an iterative protocol for the synthesis of septano-oligosaccharides was investigated. Many biologically active natural products possess deoxysugar subunits in their structures.[29] Therefore, we planned to use 6-deoxy glucal derived 1,2-cyclopropanated sugar **23** as a glycosyl donor and alcohol **32** as an acceptor. Thus, glycosylation of **23** with **32** provided disaccharide **47** as a single diastereomer in good yield. Reduction of diketone **47** to the corresponding diol, followed by Simmons-Smith cyclopropanation and subsequent Swern oxidation of the diol provided the donor **48** as a mixture of α- and *β*-cyclopropanated products in 2:1 ratio, respectively, in 75% yield after three steps. Glycosidation of **48** with acceptor **32**, using TMSOTf in CH_2Cl_2 at -78 ^oC, provided the trisaccharide derivative **49** as a single diastereomer in which the second glycosylation was also α selective (Scheme 3.9).



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC, 3 h; (ii) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -78 ^oC, 1 h; (iii) CH_2I_2, Et_2Zn, Et_2O, 0 ^oC, 5 h; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (v) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC, 3 h.

Scheme 3.9: Iterative protocol for the synthesis of septano-oligosaccharides.

3.3 Summary and Conclusion

A novel ring expansion-glycosylation reaction has been developed for the synthesis of septanose derivatives which uses sugar-derived 1,2-cyclopropa-3-pyranones as glycosyl donors and carbohydrate-derived *O*-nucleophiles as acceptors. The generality of the reaction was evaluated by performing a number of glycosylation reactions and synthesizing several septanohexose derivatives. Two different methods (a divergent synthesis and an iterative technique) for the synthesis of septanose-derived oligosaccharides were successfully performed. Ligation of these ring-expanded sugar mimics to natural products and evaluation of their biological properties are presently under investigation.

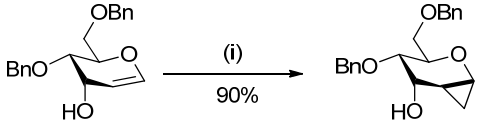
3.4 Experimental Section

3.4.1 Materials and Methods

Chemicals and solvents were purchased from the local suppliers and Sigma-Aldrich® chemical company. Solvents were used in the reactions after distilled over the dehydrated agents. 4 Å Molecular sieves, used in the reactions, were crushed and activated at 400 ^{o}C for 1 h. All the reactions were carried out under N_2 or Ar conditions and monitored by the thin layer chromatography (TLC) using silica-gel on aluminum plates (GF_{254}) by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection. Silica-gel (100-200 mesh) was used for column chromatography to purify the all the compounds. ^{1}H, ^{13}C, DEPT spectra were recorded on Bruker® 400 MHz and 500 MHz spectrometers in $CDCl_3$. ^{1}H NMR chemical shifts were reported in parts per million (ppm) (δ) with TMS as internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00). High resolution mass spectra (HRMS) were recorded on Bruker® maXis spectrometer.

3.4.2 Experimental Procedures and Spectral Data

(3.4.2.1) 4,6-di-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-allo-pyranose 4:



3 **4**

Reagents and Conditions: (i) CH_2I_2, Et_2Zn, Et_2O, 0 ^{o}C, 5 h.

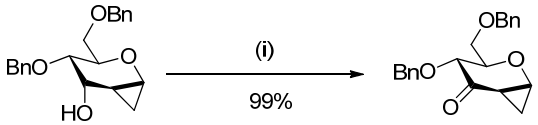
To a solution of **3** (1.5 g, 4.6 mmol) in ether (15 mL) at 0 ^{o}C was added 1 M Et_2Zn in hexane (13.7 mL, 13.7 mmol) and CH_2I_2 (1.2 mL, 13.7 mmol). The mixture was stirred for 5 h at same temperature, then quenched with saturated NH_4Cl solution (75 mL) and extracted with ether (75 mL x 2). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Purification of the crude residue by silica-gel column chromatography with ethyl acetate/hexane (3:7) provided **4** (1.4 g, 90%) as a colorless solid. R_f = 0.32 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 - 7.32 (m, 10H), 4.69 (d, 1H, *J* = 12.0 Hz), 4.60 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.26 (t, 1H, *J* = 7.2 Hz), 3.74 – 3.78 (m, 1H), 3.68 (dd, 1H, *J* = 2.0 Hz, *J* = 10.8 Hz), 3.56 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 3.41 – 3.45 (m, 1H), 3.23 (dd, 1H, *J* = 7.6 Hz, *J* = 9.2 Hz), 1.34 – 1.42 (m, 1H), 0.66 – 0.76 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.9, 128.4, 128.2, 127.8, 127.7, 127.5, 79.7, 77.5, 74.0, 73.5, 71.3, 69.1, 53.9, 18.3, 11.4.

HRMS (ESI) calcd for $C_{21}H_{24}O_4$+Na 363.1573, found 363.1573.

(3.4.2.2) Compound 5:



4 **5**

Reagents and Conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^{o}C, 1 h.

To a solution of $(COCl)_2$ (380 µL, 4.4 mmol) in CH_2Cl_2 (12 mL) at -78 ^{o}C was added DMSO (520 µL, 7.3 mmol) dropwise. After 10 min of stirring at the same temperature, **4** (1 g, 2.9 mmol) in CH_2Cl_2 (12 mL) was added dropwise for a period of 15 min. After stirring for 30 min at -78 ^{o}C, Et_3N (1.47 mL, 14.5 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (75 mL), washed with water (50 mL x 2), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude residue which upon purification by silica-gel column chromatography with ethyl acetate/hexane (3:7) provided D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (980 mg, 99%) as a colorless solid. R_f = 0.58 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 - 7.35 (m, 10H), 4.97 (d, 1H, *J* = 11.2 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 11.2 Hz), 4.17 – 4.20 (m, 1H), 4.00 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.4 Hz, *J* = 10.0 Hz), 3.91 (d, 1H, *J* = 10.0 Hz), 3.72 (dd, 1H, *J* = 2.0 Hz, *J* = 10.8 Hz), 3.62 (dd, 1H, *J* = 4.4 Hz, *J* = 10.8 Hz), 1.92 (dt, 1H, *J* = 6.0 Hz, *J* = 10.8 Hz), 1.27 – 1.37 (m, 2H).

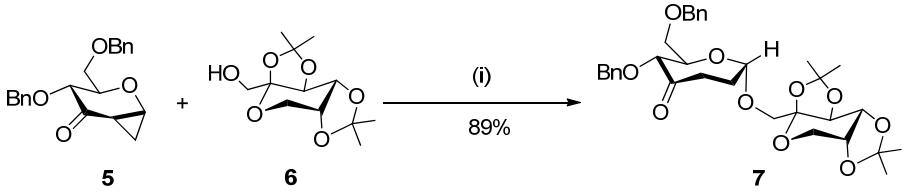
^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 137.8, 137.4, 128.3, 128.3, 128.1, 127.8, 127.7, 127.6, 81.5, 77.6, 74.1, 73.6, 68.8, 57.8, 25.7, 19.8.

HRMS (ESI) calcd for $C_{21}H_{22}O_4$+Na 361.1416, found 361.1416.

(3.4.2.3) General procedure for ring expansion-glycosylation reaction:

A suspension of 1,2-cyclopropanated sugar ketone (0.3 mmol), glycosyl acceptor (0.33 mmol) and 4 Å MS powder in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min under argon. After cooling the reaction mixture to -78 ^{o}C, TMSOTf (0.06 mmol) was added dropwise and the solution was warmed slowly to 25 ^{o}C for a period of 1 h and stirred for 3 h at the same temperature. After completion of reaction (by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), filtered through celite and the filter cake was washed with CH_2Cl_2 (20 mL x 2). The organic phase was separated and washed with aq. $NaHCO_3$ (10 mL x 2), water (10 mL) and brine (5 mL). Removal of CH_2Cl_2 under reduced pressure provided the crude disaccharide which upon purification by silica-gel column chromatography (ethyl acetate/hexane) afforded pure septanosyl disaccharide.

(3.4.2.4) Compound 7:



5 **6** **7**

Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^{o}C to rt, 4 h

Compound **7** was synthesized using D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (100 mg, 0.29 mmol), glycosyl acceptor **6** (84 mg, 0.32 mmol), TMSOTf (10 µL, 0.05 mmol) and 4 Å MS power in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^{o}C for 1 h and at 25 ^{o}C for 3 h. The crude product was purified by silica-gel column chromatography (ethyl

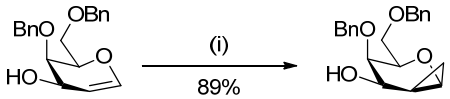
acetate/hexane 3:7) to afford septanosyl disaccharide **7** (156 mg, 89%) as a colorless oil. R_f = 0.53 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 - 7.31 (m, 10H), 4.96 (dd, 1H, *J* = 4.4 Hz, *J* = 8.0 Hz), 4.58-4.64 (m, 3H), 4.49 (d, 1H, *J* = 12.0 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.34 (d, 1H, *J* = 2.8 Hz), 4.22 – 4.27 (m, 2H), 4.01 (d, 1H, *J* = 7.2 Hz), 3.96 (d, 1H, *J* = 10.4 Hz), 3.90 (d, 1H, *J* = 12.8 Hz), 3.73 (d, 1H, *J* = 12.8 Hz), 3.67 (dd, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz), 3.57 (dd, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz), 3.52 (d, 1H, *J* = 10.4 Hz), 2.58 (ddd, 1H, *J* = 2.8 Hz, *J* = 6.4 Hz, *J* = 14.4 Hz), 2.44 (td, 1H, *J* = 2.8 Hz, *J* = 14.4 Hz), 2.25 – 2.32 (m, 1H), 2.05 – 2.10 (m, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 137.9, 137.3, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 108.9, 108.5, 102.2, 100.5, 84.1, 73.4, 73.0, 70.9, 70.4, 70.1, 70.0, 69.1, 68.5, 61.0, 35.6, 28.0, 26.5, 25.9, 25.3, 24.0.

HRMS (ESI) calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2686.

(3.4.2.5) 4,6-di-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-galacto-pyranose 12:



11 **12**

Reagents and Conditions: (i) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h.

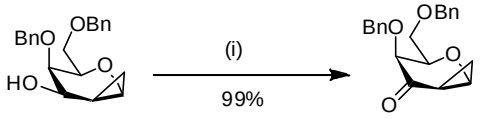
To a solution of 4,6-di-*O*-benzyl-D-galactal **11** (1 g, 3.06 mmol) in ether (10 mL) at 0 °C was added 1 M Et_2Zn in hexane (9.2 mL, 9.2 mmol) and CH_2I_2 (0.74 mL, 9.19 mmol). The mixture was stirred for 5 h at same temperature, then quenched with saturated NH_4Cl solution (75 mL) and extracted with ether (50 mL x 2). The combined organic layers were washed with water (30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. Purification of the crude residue by silica-gel column chromatography with ethyl acetate/hexane (2:3) provided 4,6-di-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-galacto-pyranose **12** (0.92 g, 89%) as a colorless oil. R_f = 0.32 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.31 (m, 10H), 4.61 (d, 1H, *J* = 11.6 Hz), 4.53 (d, 1H, *J* = 11.6 Hz), 4.51 (d, 1H, *J* = 11.6 Hz), 4.40 (d, 1H, *J* = 11.6 Hz), 4.16 (t, 1H, *J* = 6.0 Hz), 3.73 – 3.79 (m, 2H), 3.50 – 3.56 (m, 2H), 3.38 – 3.41 (m, 1H), 1.19 -1.25 (m, 1H), 1.09

-1.10 (m, 1H), 0.58 – 0.61 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 138.0, 137.6, 128.3, 127.8, 127.6, 127.5, 76.4, 75.6, 75.5, 73.3, 68.8, 65.3, 54.0, 16.9, 11.1.

HRMS (ESI) calcd for $C_{21}H_{24}O_4$+Na 363.1573, found 363.1573.

(3.4.2.6) Compound 13:



12 **13**

Reagents and Conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

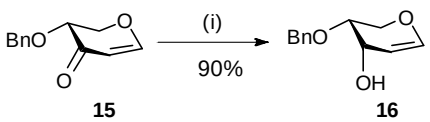
To a solution of oxaloyl chloride (342 µL, 3.96 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added DMSO (468 µL, 6.6 mmol) dropwise. After 10 min of stirring at the same temperature, 4,6-di-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-galacto-pyranose **12** (0.9 g, 2.64 mmol) in CH_2Cl_2 (10 mL) was added dropwise for a period of 15 min. After stirring for 30 min at -78 °C, Et_3N (1.8 mL, 13.0 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (75 mL), washed with water (50 mL x 2), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude residue which upon purification by silica-gel column chromatography with ethyl acetate/hexane (3:7) provided D-galactose-derived 1,2-cyclopropa-3-pyranone **13** (885 mg, 99%) as a colorless liquid. R_f = 0.64 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.32 (m, 10H), 4.61 (d, 1H, *J* = 11.6 Hz), 4.52 (d, 1H, *J* = 11.6 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.38 (d, 1H, *J* = 12.0 Hz), 4.16 – 4.19 (m, 1H), 4.03 (t, 1H, *J* = 6.0 Hz), 3.62 – 3.66 (m, 2H), 3.48 (dd, 1H, *J* = 6.0 Hz, *J* = 9.6 Hz), 1.83 – 1.87 (m, 1H), 1.72 – 1.78 (m, 1H), 1.23 – 1.28 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 137.6, 136.8, 128.2, 128.0, 127.8, 127.6, 80.0, 79.5, 73.4, 71.5, 68.3, 58.0, 23.8, 19.0.

HRMS (ESI) calcd for $C_{21}H_{22}O_4$+Na 361.1416, found 361.1416.

(3.4.2.7) 4-*O*-benzyl-D-arabinal 16:



15 **16**

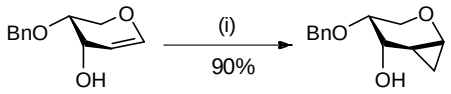
Reagents and Conditions: $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -78 °C, 1 h

To a solution of sugar enone **15** (2 g, 9.8 mmol) and $CeCl_3.7H_2O$ (5.47 g, 14.7 mmol) in MeOH (30 mL) at -78 °C was added cooled (-10 °C) solution of $NaBH_4$ (556 mg, 14.7 mmol) in MeOH (12 mL) dropwise for a period of 10 min. The solution was stirred for 1 h at -78 °C, then quenched with saturated NH_4Cl and extracted twice with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (75 mL), brine (75 mL) and dried (Na_2SO_4). Removal of solvent and purification of the crude residue by silica-gel cloumn chromatography with ethyl acetate/hexane (1:4) gave 4-*O*-benzyl-D-arabinal **16** (1.8 g, 90%) as a colorless oil. R_f = 0.6 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.35 (m, 5H), 6.38 (d, 1H, *J* = 6.0 Hz), 4.86 (dd, 1H, *J* = 5.2 Hz, *J* = 6.0 Hz), 4.65 (s, 1H), 4.64 (s, 1H), 4.21 (t, 1H, *J* = 4.4 Hz), 3.92 (s, 1H), 3.90 (s, 1H), 3.70 (dd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz), 3.68 (dd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz), 2.59 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 137.4, 128.4, 128.0, 127.7, 100.9, 73.1, 71.3, 62.3, 60.6. **HRMS (ESI)** calcd for $C_{21}H_{24}O_4$+Na 229.0841, found 229.0841.

(3.4.2.8) 4-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-arabino-pyranose 17:



16 **17**

Reagents and Conditions: (i) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h.

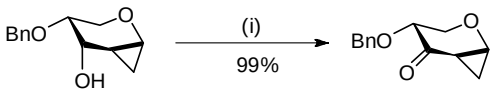
To a solution of 4-*O*-benzyl-D-arabinal **16** (700 mg, 3.39 mmol) in ether (10 mL) at 0 °C was added 1 M Et_2Zn in hexane (10.2 mL, 10.2 mmol) and CH_2I_2 (0.81 mL, 10.18 mmol). The mixture was stirred for 5 h at same temperature, then quenched with saturated NH_4Cl solution (75 mL) and extracted with ether (50 mL x 2). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification of the crude residue by silica-gel column chromatography with ethyl acetate/hexane (3:7 to 2:3) provided 4-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-arabino-pyranose **17** (672 mg, 90%) as a colorless liquid. R_f = 0.27 (3:7 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26 – 7.33 (m, 5H), 4.64 (d, 1H, *J* = 11.6 Hz), 4.37 (d, 1H, *J* = 11.6 Hz), 4.17 (bs, 1H), 3.83 (dd, 1H, *J* = 3.2 Hz, *J* = 12.4 Hz), 3.70 –

3.74 (m, 1H), 3.57 – 3.59 (m, 1H), 3.25 (d, 1H, *J* = 12.4 Hz), 2.79 (d, 1H, J= 9.6 Hz), 1.14 – 1.25 (m, 2H), 0.57 – 0.62 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.2, 127.6, 127.5, 74.9, 71.1, 64.1, 63.9, 53.9, 16.4, 10.8.

HRMS (ESI) calcd for $C_{13}H_{16}O_3$+Na 243.0997, found 243.0997.

(3.4.2.9) Compound 18:



17 **18**

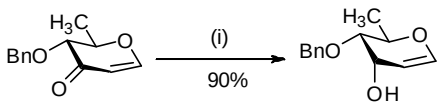
Reagents and Conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h.

To a solution of $(COCl)_2$ (293 µL, 3.40 mmol) in CH_2Cl_2 (8 mL) at -78 ^oC was added DMSO (403 µL, 5.67 mmol) dropwise. After 10 min of stirring at the same temperature, the above 4-*O*-benzyl-1,5-anhydro-2-deoxy-α-1,2-C-methylene-D-arabino-pyranose **17** (500 mg, 2.27 mmol) in CH_2Cl_2 (8 mL) was added dropwise for a period of 15 min. After stirring for 30 min at -78 ^oC, Et_3N (1.5 mL, 11.2 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (25 mL x 2), brine (25 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude residue which upon purification by silica-gel column chromatography with ethyl acetate/hexane (1:4) provided compound **18** (490 mg, 99%) as a colorless oil. R_f = 0.48 (3:7 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26 – 7.34 (m, 5H), 4.90 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.13 (dd, 1H, *J* = 4.0 Hz, *J* = 9.6 Hz), 3.94 (dd, 1H, *J* = 5.2 Hz, *J* = 10.0 Hz), 3.85 (dd, 1H, *J* = 5.6 Hz, J= 10.4 Hz), 3.74 (t, 1H, *J* = 10.4 Hz), 1.85 – 1.91 (m, 1H), 1.25 – 1.29 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 137.3, 128.3, 127.8, 127.7, 76.3, 73.0, 71.0, 59.1, 25.7, 19.5.

HRMS (ESI) calcd for $C_{13}H_{14}O_3$+Na 241.0841,found 241.0841.

(3.4.2.10) 6-deoxy-4-*O*-benzyl-D-allal 21:



20 **21**

Reagents and Conditions: $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -78 ^oC, 1 h

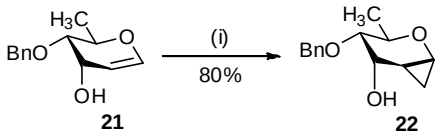
To a solution of D-rhamnose derived enone **20** (1 g, 4.58 mmol) and $CeCl_3.7H_2O$ (2.56 g, 6.87 mmol) in MeOH (20 mL) at -78 °C was added cooled (-10 °C) solution of $NaBH_4$ (260 mg, 6.87 mmol) in MeOH (7 mL) dropwise for a period of 10 min. The solution was stirred for 1 h at -78 °C, then quenched with saturated NH_4Cl solution (30 mL) and extracted twice with ethyl acetate (50 mL x 2). The combined organic layers were washed with water (25 mL), brine (25 mL) and dried (Na_2SO_4). Removal of solvent and purification of the crude residue by silica-gel cloumn chromatography with ethyl acetate/hexane (3:7 to 2:3) provided 6-deoxy-4-*O*-benzyl-D-allal **21** (0.9 g, 90%) as crystalline needles. R_f = 0.61 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.35 (m, 5H), 6.30 (dd, 1H, J= 1.2 Hz, *J* = 6.0 Hz), 4.83 (d, 1H, *J* = 11.6 Hz), 4.77 (d, 1H, *J* = 11.6 Hz), 4.68 (dd, 1H, *J* = 2.4 Hz, J= 6.0 Hz), 4.33 (bs, 1H, 3.86 – 3.93 (m, 1H), 3.26 (dd, 1H, *J* = 6.8 Hz, *J* = 9.6 Hz), 1.86 (d, 1H, *J* = 5.2 Hz), 1.39 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 138.2, 128.5, 127.9, 103.2, 82.4, 74.2, 74.1, 69.9, 17.6.

HRMS (ESI) calcd for $C_{13}H_{16}O_3$+Na 243.0997, found 243.0997.

(3.4.2.11) 4-*O*-benzyl-1,5-anhydro-2,6-dideoxy-α-1,2-C-methylene-D-allo-pyranose 22:



Reagents and Conditions: (i) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h.

To a solution of 6-deoxy-4-*O*-benzyl-D-allal **21** (800 mg, 3.63 mmol) in ether (15 mL) at 0 °C was added 1 M Et_2Zn in hexane (10.8 mL, 10.8 mmol) and CH_2I_2 (0.87 mL, 10.8 mmol). The mixture was stirred for 5 h at same temperature, then quenched with saturated NH_4Cl solution (75 mL) and extracted with ether (50 mL x 2). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification of the crude residue by silica-gel column chromatography with ethyl acetate/hexane (3:7 to 2:3) provided 4-*O*-benzyl-1,5-anhydro-2,6-dideoxy-α-1,2-

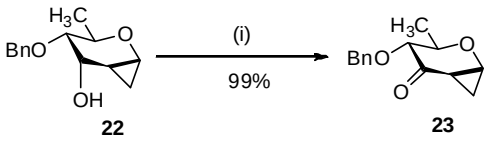
C-methylene-D-allo-pyranose **22** (680 mg, 80%) as a white solid. R_f = 0.38 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.34 (m, 5H), 4.75 (d, 1H, *J* = 12.0 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.21 (t, 1H, *J* = 7.6 Hz), 3.69 – 3.72 (m, 1H), 3.35 (dd, 1H, *J* = 6.4 Hz, *J* = 9.6 Hz), 2.84 (dd, 1H, *J* = 7.6 Hz, *J* = 9.2 Hz), 1.34 – 1.38 (m, 1H), 1.22 (d, 3H, J= 6.4 Hz), 0.64 – 0.69 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 128.6, 127.7, 84.7, 74.4, 74.2, 71.5, 54.0, 18.7, 17.5, 11.6.

HRMS (ESI) calcd for $C_{14}H_{18}O_3$+Na 257.1154, found 257.1154.

(3.4.2.12) Compound 23:



22 **23**

Reagents and Conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

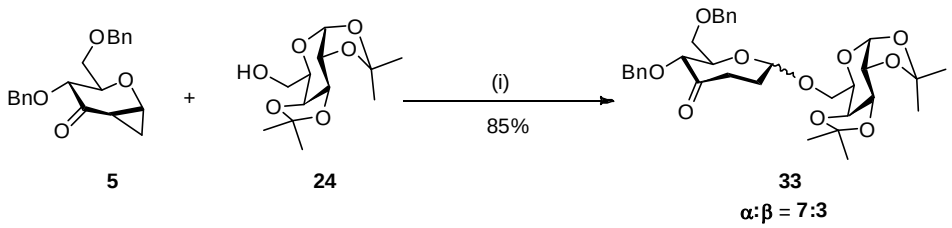
To a solution of $(COCl)_2$ (331 µL, 3.84 mmol) in CH_2Cl_2 (8 mL) at -78 °C was added DMSO (454 µL, 6.4 mmol) dropwise. After 10 min of stirring at the same temperature, the above 4-*O*-benzyl-1,5-anhydro-2,6-dideoxy-α-1,2-C-methylene-D-allo-pyranose **22** (600 mg, 2.56 mmol) in CH_2Cl_2 (8 mL) was added dropwise for a period of 15 min. After stirring for 30 min at -78 °C, Et_3N (1.76 mL, 12.6 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (25 mL x 2), brine (25 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the crude residue which upon purification by silica-gel column chromatography with ethyl acetate/hexane (1:4) provided D-rhamnose-derived 1,2-cyclopropa-3-pyranone **23** (588 mg, 99%) as a colorless solid. R_f = 0.62 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.33 (m, 5H), 4.99 (d, 1H, *J* = 11.6 Hz), 4.53 (d, 1H, *J* = 11.6 Hz), 4.10 (dd, 1H, *J* = 4.4 Hz, *J* = 9.2 Hz), 3.89 – 3.96 (m, 1H), 3.45 (d, 1H, *J* = 9.6 Hz), 1.86 – 1.91 (m, 1H), 1.26 (d, 3H, *J* = 6.0 Hz), 1.25 – 1.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 137.4, 128.2, 128.1, 127.8, 82.0, 78.7, 73.8, 57.6, 25.8, 19.8, 18.1.

HRMS (ESI) calcd for $C_{14}H_{16}O_3$+Na 255.0997, found 255.0997.

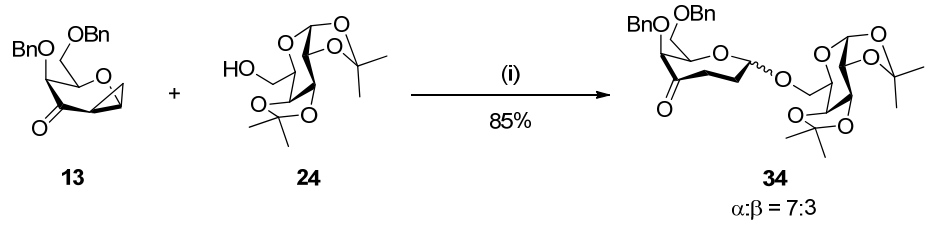
(3.4.2.13) Compounds 33α and 33β:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC to rt, 3 h.

Compound **33** was synthesized using D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (120 mg, 0.35 mmol), sugar acceptor **24** (100 mg, 0.38 mmol), TMSOTf (12 µL, 0.07 mmol) and 4 Å MS power in CH_2Cl_2 (6 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3).** The reaction mixture was stirred at -78 ^oC for 1 h and room temperature for 2 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 3:7) to afford septanosyl disaccharides **33**α and **33**β (180 mg, 85%) as an inseparable mixture.

(3.4.2.14) Compounds 34α and 34β:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC to rt, 6 h.

Compound **34** was synthesized using D-galactose-derived 1,2-cyclopropa-3-pyranone **13** (150 mg, 0.44 mmol), sugar acceptor **24** (126 mg, 0.48 mmol), TMSOTf (15 µL, 0.08 mmol) and 4 Å MS powder in CH_2Cl_2 (8 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^oC for 1 h and then at room temperature for 5 h. The obtained crude product was purified and separated by silica-gel column chromatography (ethyl acetate/hexane 3:7 to 2:3) to give septanosyl disaccharides **34*α*** (156 mg) and **34*β*** (66 mg) (85% combined yield).

34*α*: colorless oil. R_f = 0.66 (2:3 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 - 7.32 (m, 10H), 5.47 (d, 1H, *J* = 5.2 Hz), 5.02 (dd, 1H, *J* = 4.4 Hz, *J* = 6.4 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.59 (dd, 1H, *J* = 2.4 Hz, *J* = 8.0 Hz),

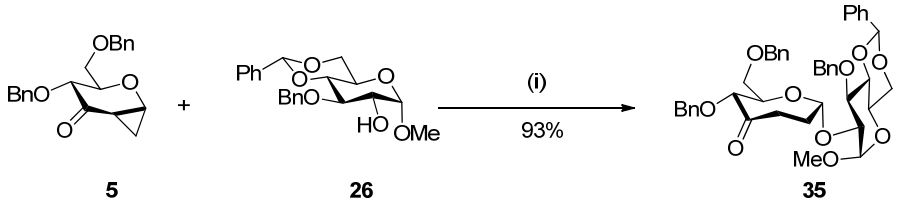
4.45 (d, 1H, *J* = 12.0 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.29 (dd, 1H, *J* = 2.4 Hz, *J* = 5.2 Hz), 4.19 – 4.23 (m, 1H), 4.18 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz), 3.95 (d, 1H, *J* = 1.2 Hz), 3.92 (dd, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz), 3.86 (dd, 1H, *J* = 6.4 Hz, *J* = 10.0 Hz), 3.69 (dd, 1H, *J* = 6.4 Hz, *J* = 10.0 Hz), 3.58-3.64 (m, 2H), 2.66 (ddd, 1H, *J* = 3.2 Hz, *J* = 9.6 Hz, *J* = 13.6 Hz), 2.46 (ddd, 1H, *J* = 2.4 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz), 2.19 – 2.27 (m, 1H), 1.73 – 1.81 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.32 (bs, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 137.9, 137.1, 128.4, 128.3, 128.3, 127.9, 127.6, 127.5, 109.2, 108.5, 99.3, 96.2, 82.8, 73.1, 73.0, 70.9, 70.6, 70.5, 68.7, 66.2, 66.0, 65.9, 34.9, 28.6, 26.0, 25.9, 24.8, 24.5. **HRMS (ESI)** calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2693. **34*β***: colorless oil. R_f = 0.33 (2:3 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.25 - 7.34 (m, 10H), 5.51 (d, 1H, *J* = 5.2 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 4.53 – 4.57 (m, 2H), 4.48 (d, 1H, *J* = 11.6 Hz), 4.45 (d, 1H, *J* = 11.6 Hz), 4.43 (d, 1H, *J* = 11.6 Hz), 4.27 (dd, 1H, *J* = 2.4 Hz, *J* = 4.8 Hz), 4.10 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 4.03 (d, 1H, *J* = 2.4 Hz), 3.92 – 3.98 (m, 3H), 3.70 (dd, 1H, *J* = 6.4 Hz, *J* = 8.8 Hz), 3.62 (dd, 1H, *J* = 8.8 Hz, *J* = 12.4 Hz), 2.70 (dt, 1H, *J* = 6.0 Hz, *J* = 13.2 Hz), 2.39 (dt, 1H, *J* = 7.2 Hz, *J* = 13.2 Hz), 2.01 – 2.06 (m, 2H), 1.51 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.6, 137.9, 137.2, 128.3, 128.3, 128.1, 127.8, 127.6, 127.6, 109.2, 108.6, 106.2, 96.2, 85.3, 76.0, 73.4, 73.3, 71.4, 70.6, 70.4, 69.1, 67.8, 67.7, 34.8, 30.6, 26.0, 25.9, 24.9, 24.4.

HRMS (ESI) calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2686.

(3.4.2.15) Compound 35:



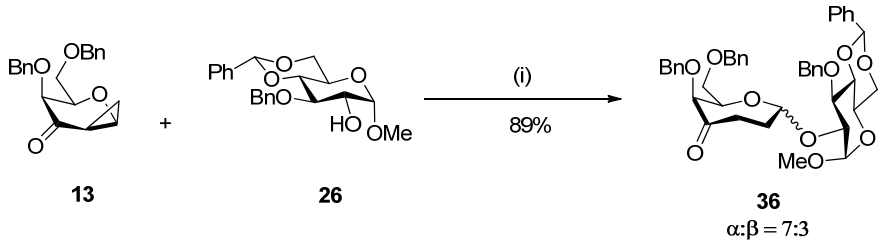
Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C, 5 h.

Compound **35** was synthesized using D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (100 mg, 0.29 mmol), sugar acceptor **26** (118 mg, 0.32 mmol), TMSOTf (10 µL, 0.05 mmol) and 4 Å MS power in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**), The reaction mixture was stirred at -78 °C for 5 h. The crude

product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to afford septanosyl disaccharide **35** (195 mg, 93%) as a thick gum. R_f = 0.7 (3:7 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 – 7.48 (m, 2H), 7.24 - 7.38 (m, 18H), 5.47 (s, 1H), 4.97 (dd, 1H, *J* = 2.8 Hz, *J* = 9.2 Hz), 4.87 (d, 1H, *J* = 11.6 Hz), 4.84 (d, 1H, *J* = 3.6 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.51 – 4.54 (m, 3H), 4.34 (d, 1H, *J* = 11.6 Hz), 4.24 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 3.97 (t, 1H, *J* = 9.2 Hz), 3.75 – 3.87 (m, 3H), 3.61 – 3.65 (m, 2H), 3.52 – 3.59 (m, 2H), 3.43 (t, 1H, *J* = 9.2 Hz), 3.38 (s, 3H), 2.80 (td, 1H, *J* = 4.4 Hz, *J* = 12.4 Hz), 2.26 (dt, 1H, *J* = 4.8 Hz, *J* = 12. 0 Hz), 2.02 – 2.07 (m, 1H), 1.85 – 1.95 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 138.6, 137.8, 137.3, 136.7, 128.8, 128.4, 128.3, 128.2, 128.1, 128.1, 127.6, 127.5, 125.9, 108.2, 101.0, 100.1, 84.6, 82.2, 78.3, 77.9, 77.8, 75.1, 73.2, 72.3, 70.8, 68.9, 62.0, 55.1, 33.7, 33.0. **HRMS (ESI)** calcd for $C_{42}H_{46}O_{10}$+Na 733.2989, found 733.2989.

(3.4.2.16) Compound 36α and 36β:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C to rt, 4 h.

Compounds **36** were synthesized using D-galactose-derived 1,2-cyclopropa-3-pyranone **13** (135 mg, 0.39 mmol), sugar acceptor **26** (163 mg, 0.43 mmol), TMSOTf (14 µL, 0.07 mmol) and 4 Å MS powder in CH_2Cl_2 (7 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 °C for 1 h and at room temperature for 3 h. The obtained crude product was purified and separated by silica-gel column chromatography (ethyl acetate/hexane 3:7 to 2:3) as clean septanosyl disaccharides **36*α*** (176 mg) and **36*β*** (75 mg) (89% combined yield).

36*α*: colorless oil. R_f = 0.3 (3:7 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.17 – 7.46 (m, 20H), 5.49 (s, 1H), 5.11 – 5.12 (m, 1H), 4.89 (d, 1H, *J* = 3.6 Hz), 4.79 (d, 1H, *J* = 11.6 Hz), 4.72 (d, 1H, *J* = 11.6 Hz), 4.65 (1H, *J* = 12.0 Hz), 4.34 – 4.41 (m, 2H), 4.21 – 4.29

(m, 3H), 4.02 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.87 – 3.92 (m, 2H), 3.73 – 3.78 (m, 1H), 3.61 – 3.69 (m, 2H), 3.52 (t, 1H, *J* = 8.4 Hz), 3.42 – 3.47 (m, 1H), 3.39 (s, 3H), 2.62 – 2.66 (m, 1H), 2.52 – 2.56 (m, 1H), 2.27 – 2.34 (m, 1H), 1.80 – 1.83 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 138.7, 138.2, 137.3, 137.0, 128.8, 128.4, 128.3, 128.1, 128.0, 127.5, 127.3, 125.9, 123.9, 101.1, 97.1, 95.6, 82.7, 81.8, 75.2, 73.6, 73.1, 72.8, 68.8, 68.7, 66.1, 62.2, 55.1, 34.7, 31.4.

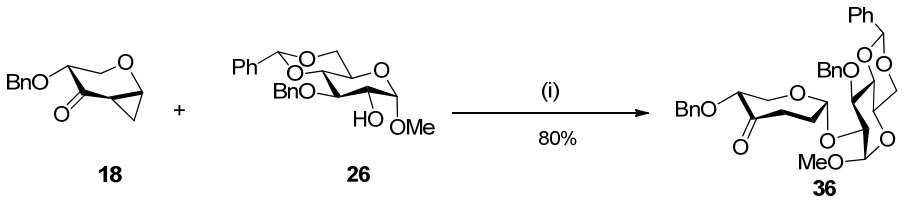
HRMS (ESI) calcd for $C_{42}H_{46}O_{10}$+Na 733.2989, found 733.2989.

36*β*: colorless solid. R_f = 0.45 (3:7 ethyl acetate/hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45 – 7.48 (m, 2H), 7.24 – 7.37 (m, 18H), 5.44 (s, 1H), 4.77 – 4.88 (m, 4H), 4.65 (d, 1H, *J* = 11.6 Hz), 4.52 (d, 1H, *J* = 11.6 Hz), 4.44 (d, 1H, *J* = 11.6 Hz), 4.42 (d, 1H, *J* = 11.6 Hz), 4.22 (dd, 1H, *J* = 4.8 Hz, *J* = 10.0 Hz), 4.01 – 4.05 (m, 2H), 3.96 (t, 1H, *J* = 9.2 Hz), 3.82 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.71 – 3.79 (m, 2H), 3.56 – 3.61 (m, 2H), 3.39 – 3.41 (m, 4H), 2.55 – 2.60 (m, 1H), 2.33 – 2.40 (m, 1H), 1.98 – 2.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 138.7, 138.0, 137.3, 137.0, 128.8, 128.3, 128.2, 128.1, 128.0, 127.6, 127.6, 127.9, 108.4, 101.0, 100.2, 85.3, 82.3, 78.4, 77.6, 75.1, 73.5, 73.3, 70.0, 68.9, 62.0, 55.1, 34.8, 31.6.

HRMS (ESI) calcd for $C_{42}H_{46}O_{10}$+Na 733.2989, found 733.2989.

(3.4.2.17) Compound 36:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C to rt, 4 h.

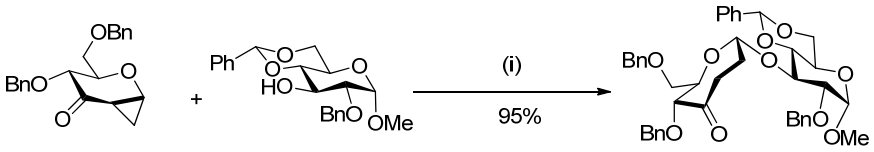
Compound **36** was synthesized using D-arabinose-derived 1,2-cyclopropa-3-pyranone **18** (100 mg, 0.45 mmol), sugar acceptor **26** (187 mg, 0.5 mmol), TMSOTf (16 µL, 0.09 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 °C for 5 h. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to give septanosyl disaccharide **36** (216 mg, 80%) as a semi solid. R_f = 0.46 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.49 (m, 2H), 7.25 - 7.39 (m, 13H), 5.57 (s, 1H), 5.00 (dd, 1H, *J* = 4 Hz, 8.8 Hz), 4.88 (d, 1H, *J* = 11.6 Hz), 4.79 (d, 1H, *J* = 3.6 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.27 – 4.33 (m, 2H), 4.18 (dd, 1H, *J* = 4.8 Hz, *J* = 6.0 Hz), 3.95 (t, 1H, *J* = 9.6 Hz), 3.82 (td, 1H, *J* = 4.4 Hz, *J* = 9.6 Hz), 3.75 (dd, 1H, *J* = 9.6 Hz, *J* = 10.4 Hz), 3.69 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.62 (dd, 1H, *J* = 9.2 Hz, *J* = 8.4 Hz), 3.58 (dd, 1H, *J* = 4.4 Hz, *J* = 13.2 Hz), 3.41 (s, 3H), 2.49 (dtd, 1H, *J* = 3.2 Hz, *J* = 12.4 Hz, *J* = 16.0 Hz), 2.34 (ddd, 1H, *J* = 3.6 Hz, *J* = 5.2 Hz, *J* = 16.0 Hz), 1.92 – 2.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 138.6, 137.6, 137.2, 128.9, 128.5, 128.3, 128.2, 128.1, 127.7, 126.0, 103.7, 101.2, 99.9, 82.2, 82.2, 79.0, 78.1, 75.2, 72.2, 69.0, 62.1, 61.5, 55.3, 35.5, 28.3.

HRMS (ESI) calcd for $C_{34}H_{38}O_9$+Na 613.2414, found 613.2414.

(3.4.2.18) Compound 38:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C to rt, 4 h.

Compound **38** was synthesized using D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (250 mg, 0.73 mmol), glycosyl acceptor **27** (302 mg, 0.81 mmol), TMSOTf (26 µL, 0.14 mmol) and 4 Å MS powder in CH_2Cl_2 (13 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 °C for 1 h and at 25 °C for 3 h. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 3:7) to afford septanosyl disaccharide **38** (498 mg, 95%) as a thick gum. R_f = 0.6 (2:3 ethyl acetate/hexane).

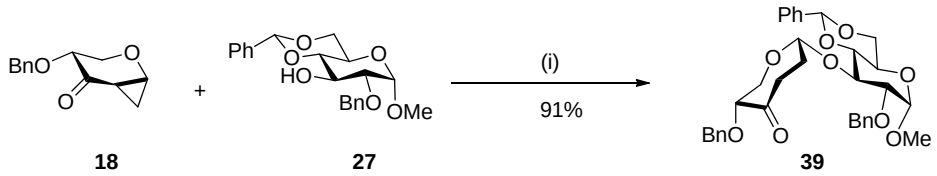
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.48 (m, 2H), 7.20 - 7.36 (m, 18H), 5.48 (s, 1H), 5.09 (dd, 1H, *J* = 2.0Hz, 8.8 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.62 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 3.6 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.33 (bs, 2H), 4.29 (d, 1H, *J* = 12.0 Hz), 4.20 (dd, 1H, *J* = 4.4 Hz, *J* = 6.0 Hz), 4.11 (t, 1H, *J* = 9.6 Hz), 3.78 – 3.84 (m, 2H), 3.73 (td, 1H, *J* = 4.4 Hz, *J* = 10.0 Hz), 3.65 (t, 1H, *J* = 10.4 Hz), 3.49 – 3.54 (m, 2H), 3.37 – 3.41 (m,

2H), 3.34 (s, 3H), 2.80 (td, 1H, *J* = 4.8 Hz, *J* = 12.0 Hz), 2.26 (dt, 1H, *J* = 5.2 Hz, *J* = 12.0 Hz), 2.02 – 2.06 (m, 1H), 1.83 – 1.92 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 138.2, 137.8, 137.4, 137.0, 128.8, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.3, 126.3, 106.1, 101.3, 98.7, 85.4, 79.8, 79.6, 78.1, 76.7, 73.4, 73.2, 72.2, 70.3, 68.8, 62.5, 55.2, 33.9, 32.1.

HRMS (ESI) calcd for $C_{42}H_{46}O_{10}$+Na 733.2989, found 733.3007.

(3.4.2.19) Compound 39:



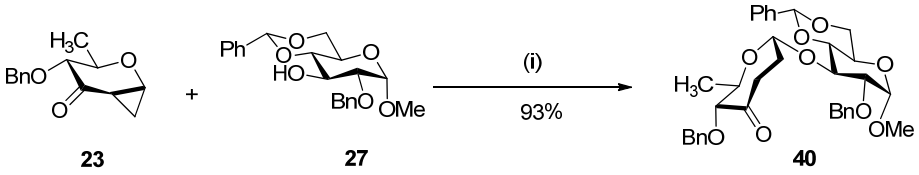
Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC to rt, 4 h.

Compound **39** was synthesized using D-arabinose-derived 1,2-cyclopropa-3-pyranone **18** (80 mg, 0.36 mmol), glycosyl acceptor **27** (150 mg, 0.4 mmol), TMSOTf (13 µL, 0.07 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^oC for 1 h and at 25 ^oC for 3 h. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 3:7) to afford septanosyl disaccharide **39** (197 mg, 91%) as white solid. R_f = 0.37 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.45 (m, 15H), 5.49 (s, 1H), 5.20 (dd, 1H, *J* = 4.0 Hz, *J* = 8.0 Hz), 4.67 (d, 1H, *J* = 12.4 Hz), 4.59 -4.63 (m, 2H), 4.55 (d, 1H, *J* = 12.4 Hz), 4.32 (d, 1H, *J* = 12.4 Hz),4.27 (dd, 1H, *J* = 5.6 Hz, *J* = 14.4 Hz), 4.24 (dd, 1H, *J* = 4.8 Hz, *J* = 10.0 Hz), 4.21 (dd, 1H, J =9.6 Hz, *J* = 18.8 Hz), 3.94 (dd, 1H, *J* = 4.4 Hz, *J* = 5.6 Hz), 3.81 (td, 1H, *J* = 4.4 Hz, *J* = 9.6 Hz), 3.68 (t, 1H, *J* = 10.0 Hz), 3.50 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.45 (t, 1H, *J* = 9.6 Hz), 3.32 – 3.38 (m, 4H), 2.43 (dtd, 1H, *J* = 3.6 Hz, *J* = 11.6 Hz, *J* = 16.4 Hz), 2.33 (ddd, 1H, *J* = 3.6 Hz, *J* = 6.8 Hz, *J* = 16.4 Hz), 2.00 – 2.08 (m, 1H), 1.76 – 1.85 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 137.7, 137.4, 137.2, 129.1, 128.5, 128.3, 128.2, 127.9, 127.6, 126.2, 101.7, 100.7, 98.5, 82.5, 80.3, 80.0, 74.1, 73.1, 71.4, 69.0, 62.5, 60.5, 55.3, 35.5, 28.2. **HRMS (ESI)** calcd for $C_{34}H_{38}O_9$+Na 613.2414, found 613.2414.

(3.4.2.20) Compound 40:



23 **27** **40**

Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC to rt, 4 h.

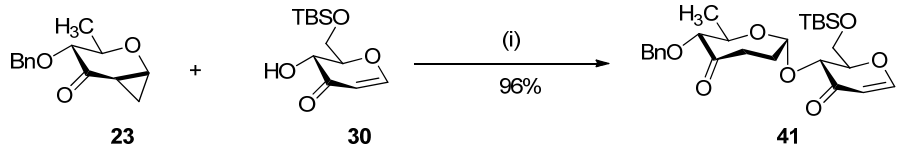
Compound **40** was synthesized using D-rhamnose-derived 1,2-cyclopropa-3-pyranone **23** (85 mg, 0.36 mmol), glycosyl acceptor **27** (150 mg, 0.4 mmol), TMSOTf (13 µL, 0.07 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^oC for 3 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to give septanosyl disaccharide **40** (205 mg, 93%) as a colorless solid. R_f = 0.7 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.41 (m, 15H), 5.47 (s, 1H), 5.29 (dd, 1H, *J* = 4.8 Hz, *J* = 8.4 Hz), 4.77 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 11.6 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 3.6 Hz), 4.39 (d, 1H, *J* = 11.6 Hz), 4.33 (t, 1H, *J* = 9.6 Hz), 4.26 (t, 1H, *J* = 6.8 Hz), 4.22 (dd, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 3.78 (td, 1H, *J* = 4.8 Hz, *J* = 10.4 Hz), 3.66 (t, 1H, *J* = 10.0 Hz), 3.58 (d, 1H, *J* = 10.8 Hz), 3.52 (t, 1H, *J* = 9.6 Hz), 3.43 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.36 (s, 3H), 2.49 (ddd, 1H, *J* = 3.2 Hz, *J* = 6.4 Hz, *J* = 15.2 Hz), 2.32 – 2.40 (m, 1H),2.17 – 2.27 (m, 1H), 1.96 – 2.04 (m, 1H), 1.23 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 138.0, 137.5, 137.3, 129.0, 128.4, 128.4, 128.3, 128.0, 127.9, 125.9, 101.4, 100.1, 99.0, 89.1, 83.0, 77.8, 73.7, 72.9, 72.9, 69.1, 66.1, 61.8, 55.3, 35.9, 28.1, 20.6.

HRMS (ESI) calcd for $C_{35}H_{40}O_9$+Na 627.2570, found 627.2570.

(3.4.2.21) Compound 41:



23 **30** **41**

Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC, 3 h.

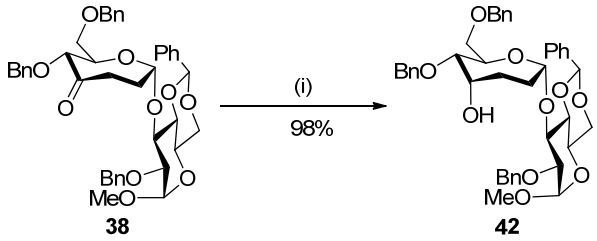
Compound **41** was synthesized using D-rhamnose-derived 1,2-cyclopropa-3-pyranone **23** (70 mg, 0.3 mmol), glycosyl acceptor **30** (85 mg, 0.33 mmol), TMSOTf (10 µL, 0.06 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 °C for 3 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to give septanosyl disaccharide **41** (141 mg, 96%) as a colorless solid. R_f = 0.67 (3:7 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.37 (m, 6H), 5.41 (dd, 1H, *J* = 4.4 Hz, *J* = 8.4 Hz), 5.35 (d, 1H, *J* = 6.0 Hz), 4.69 (d, 1H, *J* = 11.2 Hz), 4.44 (d, 1H, *J* = 11.2 Hz), 4.42 (d, 1H, *J* = 11.6 Hz), 4.31 (ddd, 1H, *J* = 3.2 Hz, *J* = 4.4 Hz, *J* = 11.2 Hz), 4.12 (t, 1H, *J* = 6.4 Hz), 3.00 (dd, 1H, *J* = 3.2 Hz, *J* = 11.6 Hz), 3.92 (dd, 1H, *J* = 4.4 Hz, *J* = 11.6 Hz), 3.65 (d, 1H, *J* = 6.4 Hz), 2.41 – 2.49 (m, 2H), 2.30 – 2.38 (m, 1H), 2.19 – 2.29 (m, 1H), 1.31 (d, 3H, *J* = 6.4 Hz), 0.97 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 192.6, 162.3, 137.2, 128.4, 128.0, 128.0, 104.7, 100.6, 89.1, 82.0, 73.0, 70.2, 67.0, 61.6, 35.9, 27.1, 25.8, 20.8, 18.4, -5.2, -5.2.

HRMS (ESI) calcd for $C_{26}H_{38}O_7Si$+Na 513.2285, found 513.2285.

(3.4.2.22) Compound 42:



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

A solution of ketone **38** (350 mg, 0.49 mmol) in EtOH (10 mL) was added dropwise to a solution of $LiAlH(OC(CH_3)_3)_3$ (250 mg, 0.98 mmol) in EtOH (10 mL) at -78 °C. The mixture was stirred for 1 h at same temperature, then slowly quenched with saturated NH_4Cl solution (20 mL) and allowed to warm to room temperature. Ethanol was evaporated under reduced pressure and the obtained thick syrup was extracted twice with ethyl acetate (20 mL x 2). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). Purification of crude residue by silica-gel column chromatography with ethyl

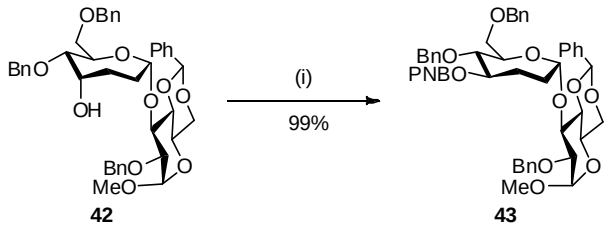
acetate/hexane (3:7 to 2:3) provided septano-hexose disaccharide **42** (343 mg, 98%) as a colorless oil. R_f = 0.38 (3:7 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.49 (m, 2H), 7.18 – 7.36 (m, 18H), 5.47 (s, 1H), 5.03 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz), 4.75 (d, 1H, *J* = 12.0 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4. 55 (d, 1H, *J* = 3.2 Hz), 4.32 – 4.45 (m, 6H), 4.19 (dd, 1H, *J* = 4.4 Hz, *J* = 10.0 Hz), 4.08 (d, 1H, *J* = 9.2 Hz), 3.99 – 4.01 (m, 1H), 3.73 – 3.80 (m, 2H), 3.61 – 3.67 (m, 2H), 3.51 (dtd, 1H, *J* = 2.8 Hz, *J* = 6.8 Hz, *J* =9.2 Hz), 3.38 – 3.45 (m, 2H), 3.34 (s, 3H), 1.92 – 2.07 (m, 3H), 1.73 – 1.79 (m, 1H), 1.60 – 1.66 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 138.2, 138.0, 137.5, 128.8, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.3, 126.4, 105.4, 101.5, 98.9, 82.6, 80.3, 79.4, 77.0, 76.4, 73.6, 73.3, 72.0, 71.2, 69.7, 68.9, 62.4, 55.2, 30.9, 25.4.

HRMS (ESI) calcd for $C_{42}H_{48}O_{18}$+Na 735.3145, found 735.3145.

(3.4.2.23) compound 43:



Reagents and Conditions: (i) PNB-OH, DIAD, Ph_3P, THF, rt, 8 h.

A solution of alcohol **42** (300 mg, 0.42 mmol), triphenylphosphine (441 mg, 1.68 mmol) and *p*-nitrobenzoic acid (281 mg, 1.68 mmol) in THF (10 mL) at 0 ^oC was added DIAD (330 µL, 1.68 mmol) dropwise. Upon completion of the addition, the solution was allowed to stir at room temperature for over night. Removal the solvent under reduced pressure followed by purification of crude mixture by silica-gel column chromatography with ethyl acetate/hexane (1:4) gave diaccharide-based *p*-nitrobenzoate **43** (358 mg, 99% yield) as light yellow oil. R_f = 0.61 (3:7 ethyl acetate/hexane).

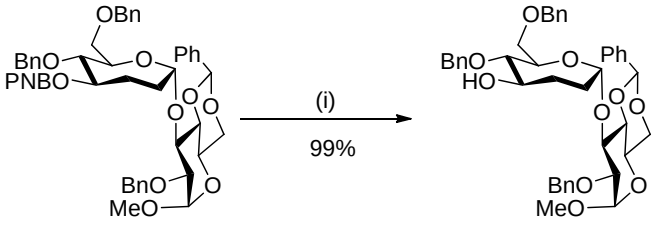
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 2H, *J* = 9.2 Hz), 8.01 (d, 2H, *J* = 9.2 Hz), 7.16 – 7.35 (m, 20H), 5.53 (s, 1H), 5.35 (dd, 1H, *J* = 4.4 Hz, *J* = 7.2 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 5.59 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 4.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.36 (s, 2H), 4.21 – 4.27 (m, 2H), 3.74 – 3.79 (m, 2H), 3.65 – 3.72 (m, 2H), 3.54

– 3.59 (m, 2H), 3.43 – 3.50 (m, 2H), 3.36 (s, 3H), 2.03 – 2.09 (m, 1H), 1.89 – 1.99 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.3, 138.3, 137.9, 137.7, 137.5, 135.6, 130.7, 128.8, 128.5, 128.3, 128.1, 128.0, 127.7, 127.7, 127.3, 126.3, 123.4, 106.2, 101.4, 98.8, 79.9, 79.8, 79.7, 78.0, 75.4, 74.8, 73.5, 73.3, 72.7, 71.1, 69.0, 62.6, 55.3, 30.3, 22.7.

HRMS (ESI) calcd for $C_{49}H_{51}NO_{13}$+Na 884.3258, found 884.3258.

(3.4.2.24) Compound 44:



43 **44**

Reagents and Conditions: (i) NaOMe, MeOH, rt, 1 h.

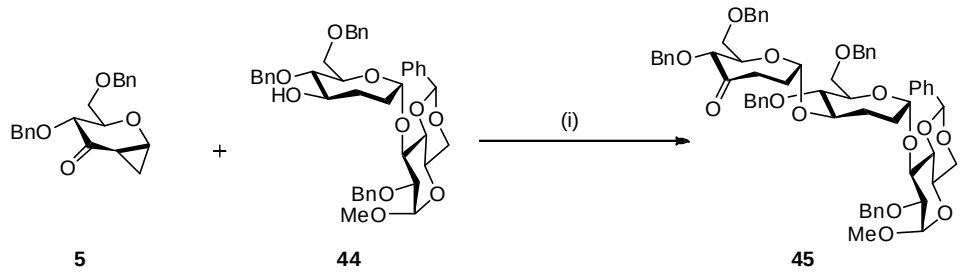
To a solution of above *p*-nitrobenzoate sugar derivative **43** (250 mg, 0.29 mmol) in MeOH (2.3 mL) at room temperature was added methonolic solution of NaOMe (330 µL) (freshely prepared from 100 mg of Na in 20 mL of MeOH) and stirred for 1 h. The solution was neutralised with amberlite IR120 (acedic resin) and filtered. Removal of solvent under reduced pressure followed by purification of the crude residue by silica-gel chromatography with ethyl acetate/hexane (2:3) gave disaccharide **44 (**203 mg, 99%) as a colorless gum. R_f = 0.36 (3:7 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.49 (m, 2H), 7.18 – 7.35 (m, 18H), 5.49 (s, 1H), 4.91 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.63 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 3.5 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.39 (d, 1H, *J* = 12.0 Hz), 4.38 (d, 1H, *J* = 12.0 Hz), 4.34 (d, 1H, *J* = 12.0 Hz), 4.20 (dd, 1H, *J* = 4.5 Hz, *J* = 10.0 Hz), 4.13 (t, 1H, *J* = 9.5 Hz), 3.88 – 3.91 (m, 1H), 3.68 – 3.76 (m, 2H), 3.66 (t, 1H, *J* = 10.0 Hz), 3.55 (t, 1H, *J* = 5.5 Hz), 3.54 (dd 1H, *J* = 3.5 Hz, *J* = 9.5 Hz), 3.51 (t, 1H, *J* = 9.0 Hz), 3.38 – 3.44 (m, 2H), 3.34 (s, 3H), 1.93 – 2.01 (m, 1H), 1.80 – 1.91 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 138.0, 137.8, 137.4, 128.8, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.2, 126.2, 107.1, 101.3, 98.6, 81.6, 80.1, 79.8, 79.6, 75.9, 73.4, 73.2, 72.1, 71.7, 70.7, 68.8, 62.4, 55.2, 29.7, 24.0.

HRMS (ESI) calcd for $C_{42}H_{48}O_{18}$+Na 735.3145, found 735.3145.

(3.4.2.25) Compound 45:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC to rt, 4 h.

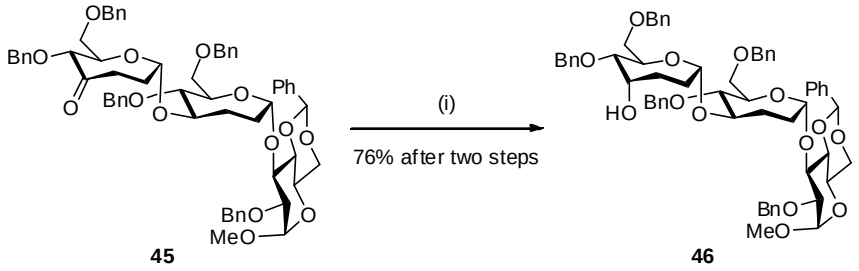
Diseptano-hexose trisaccharide derivative **45** was synthesized using D-glucose-derived 1,2-cyclopropa-3-pyranone **5** (65 mg, 0.19 mmol), glycosyl acceptor **44** (150 mg, 0.21 mmol), TMSOTf (5.4 µL, 0.03 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^oC for 1 h and then at 25 ^oC for 3 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 3:7) to give diseptano-hexose trisaccharide derivative **45** (160 mg, 79%) as colorless oil. R_f = 0.77 (2:3 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.49 (m, 2H), 7.14 – 7.36 (m, 30H), 5.47 (s, 1H), 4.95 - 5.00 (m, 1H), 4.88 (dd, 1H, *J* = 3.0 Hz, *J* = 7.5 Hz), 4.77 (1H, *J* = 12.0 Hz), 4.75 (dd, 1H, *J* = 2.5 Hz, *J* = 9.0 Hz), 4.67 (d, 1H, *J* = 12.5 Hz), 4.52 – 4.54 (m, 3H), 4.38 – 4.40 (m, 2H), 4.35 (d, 1H, *J* = 3.5 Hz), 4.32 (d, 1H, *J* = 12.0 Hz), 4.28 (d, 1H, *J* = 12.5 Hz), 4.12 – 4.19 (m, 3H), 3.71 – 3.80 (m, 3H), m3.65 (d, 1H, *J* = 9.0 Hz), 3.61 (dd, 1H, *J* = 3.0 Hz, *J* = 13.0 Hz), 3.57 (dd, 1H, *J* = 4.0 Hz, *J* = 5.5 Hz), 3.51 – 3.53 (m, 2H), 3.47 – 3.50 (m, 2H), 3.43 – 3.46 (m, 1H), 3.33 – 3.36 (m, 4H), 2.84 (td, 1H, *J* = 5.0 Hz, *J* = 11.5 Hz), 2.29 – 2.35 (m, 1H), 2.03 – 2.06 (m, 1H), 1.81 – 1.91 (m, 3H), 1.67 – 1.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 138.7, 138.5, 138.3, 137.9, 137.5, 136.8, 128.7, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 126.3, 105.0, 103.0, 101.1, 99.2, 85.2, 81.1, 79.6, 78.9, 78.2, 77.3, 76.3, 76.1, 73.5, 73.2, 73.1, 72.4, 72.2, 71.6, 70.6, 68.9, 62.5, 55.2, 34.0, 32.9, 30.2, 21.3.

HRMS (ESI) calcd for $C_{63}H_{70}O_{14}$+Na 1073.4663, found 1073.4664.

(3.4.2.26) Compound 46:



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 ^oC, 1 h.

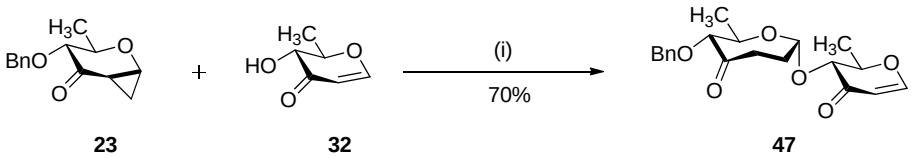
A solution of ketone **45** (155 mg, 0.14 mmol) in EtOH (5 mL) was added dropwise to a solution of $LiAlH(OC(CH_3)_3)_3$ (71 mg, 0.28 mmol) in EtOH (5 mL) at -78 ^oC. The mixture was stirred for 1 h at same temperature, then slowly quenched with saturated NH_4Cl solution (10 mL) and allowed to warm to room temperature. Ethanol was evaporated under reduced pressure and the obtained thick syrup was extracted twice with ethyl acetate (20 mL x 2). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). Purification of crude residue by silica-gel column chromatography with ethyl acetate/hexane (2:3) provided diseptano-hexose trisaccharide **46** (153 mg, over all 76% for two steps) as a colorless oil. R_f = 0.5 (2:3 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 – 7.50 (m, 2H), 7.18 – 7.38 (m, 28H), 5.48 (s, 1H), 4.89 (dd, 1H, *J* = 3.0Hz, *J* = 8.0 Hz), 4.78 (d, 1H, *J* = 12.0 Hz), 4.75 (dd, 1H, *J* = 3.5 Hz, *J* = 7.0 Hz), 4.69 (d, 1H, *J* = 12.0Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 3.5 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.35 (d, 1H, *J* = 12.0 Hz), 4.29 (d, 1H, *J* = 12.0 Hz), 4.17 (dtd , 1H, *J* = 2.0 Hz, *J* = 6.0 Hz, *J* = 10.0 Hz), 4.07 – 4.11 (m, 2H), 3.74 (dd, 1H, *J* = 4.5 Hz, *J* = 7.5 Hz), 3.68 – 3.72 (m, 1H), 3.66 (t, 1H, *J* = 7.5 Hz), 3.60 (dd, 1H, J= 4.5 Hz, *J* = 9.0 Hz), 3.57 - 3.59 (m, 1H), 3.55 – 3.56 (m, 2), 3.53 – 3.54 (m, 2H), 3.49 – 3.50 (m, 1H), 3.45- 2.46 (m, 1H), 3.36 – 3.91 (m, 1H), 3.34 (s, 3H), 1.92 – 2.06 (m, 2H), 1.82 - 1.87 (m, 1H), 1.64 – 1.75 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.7, 138.4, 138.1, 137.9, 137.6, 128.7,128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 126.3, 105.3, 101.8, 101.2, 82.3, 81.5, 79.5, 78.8, 77.5, 76.8, 76.2, 75.9, 73.5, 73.2, 73.1, 72.6, 72.2, 71.7, 71.2, 69.4, 68.9, 62.6, 55.3, 30.6, 30.3, 25.3, 21.6.

HRMS (ESI) calcd for $C_{63}H_{72}O_{14}$+Na 1075.4820, found 1075.4820.

(3.4.2.27) Compound 47:



23 **32** **47**

Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 °C, 3 h.

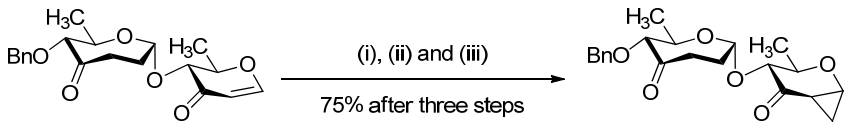
Septano-hexose disaccharide derivative **47** was synthesized using D-rhamnose-derived 1,2-cyclopropa-3-pyranone **23** (200 mg, 0.86 mmol), glycosyl acceptor **32** (120 mg, 0.94 mmol), TMSOTf (31 µL, 0.17 mmol) and 4 Å MS powder in CH_2Cl_2 (15 mL) according to the general procedure for ring expansion-glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 °C for 3 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to give septano-hexose disaccharide derivative **47** (217 mg, 70%) as a colorless solid. R_f = 0.5 (3:7 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.38 (m, 6H), 5.35 – 5.38 (m, 2H), 4.69 (d, 1H, *J* = 11.5 Hz), 5.41 (4.42 (d, 1H, *J* = 11.5 Hz), 4.34 (dd, 1H, *J* = 6.0 Hz, *J* = 11.5 Hz), 4.12 – 4.18 (m, 2H), 3.65 (d, 1H, *J* = 6.5 Hz), 2.53 (ddd, 1H, *J* = 3.6 Hz, *J* = 5.6 Hz, *J* = 15.6 Hz), 2.41 – 2.49 (m, 1H), 2.31 – 2.39 (m, 1H), 2.22 – 2.27 (m, 1H), 1.50 (d, 3H, *J* = 6.5 Hz), 1.30 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.3, 193.3, 162.6, 137.1, 128.4, 128.1, 128.0, 105.1, 100.8, 89.1, 78.2, 74.8, 73.0, 66.8, 35.8, 27.0, 20.9, 17.5.

HRMS (ESI) calcd for $C_{20}H_{24}O_6$+Na 383.1471, found 383.1471.

(3.4.2.28) Compound 48:



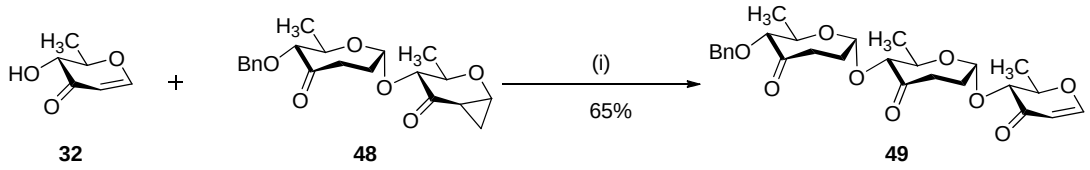
47 **48**

Reagents and Conditions: (i) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -78 °C, 1 h; (ii) CH_2I_2, Et_2Zn, Et_2O, 0 °C, 5 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h.

To a solution of septano-hexose disaccharide derivative **47** (150 mg, 0.41 mmol) and $CeCl_3.7H_2O$ (458 mg, 1.23 mmol) in MeOH (6 mL) at -78 °C, was added cooled (-10 °C)

solution of $NaBH_4$ (46 mg, 1.23 mmol) in MeOH (2 mL) dropwise for a period of 10 min. The solution was stirred for 1 h at same temperature and slowly quenched with saturated NH_4Cl solution (15 mL). The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Removal of solvent provided the crude diol (148 mg, 0.4 mmol) as colorless gum. This crude diol mixture was dissolved in ether (5 mL), and subsequently 1 M Et_2Zn in hexane (1.2 mL, 1.21 mmol) and CH_2I_2 (98 µL, 1.21 mmol) were added at 0 ^oC and stirred for 5 h at the same temperature. After completion of reaction (TLC), saturated NH_4Cl (15 mL) was added and extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Removal of solvent gave crude 1,2-cyclopropnated disaccharide diol mixture (130 mg, 0.34 mmol) which was used for next step without purification. For oxidation of diol, DMSO (120 µL, 1.7 mmol) was added dropwise to a solution of $(COCl)_2$ (88 µL, 1.02 mmol) in CH_2Cl_2 (3 mL) at -78 ^oC. After stirring for 10 min at the same temperature, the above 1,2-cyclopropnated disaccharide diol mixture (130 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) was added dropwise for a period of 15 min. After stirring for 30 min at -78 ^oC, Et_3N (468 µL, 3.36 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL x 2), brine (10 mL) and dried over anhydrous Na_2SO_4. The crude residue was purified by silica-gel column chromatography (ethyl acetate/hexane 3:7) provided 1,2-cyclopropanated-septanosyl disaccharide-derivative **48** (115 mg, 75% after three steps) as a mixture (α:β = 2:1).

(3.4.2.29) Compound 49:



Reagents and Conditions: (i) TMSOTf, 4 Å MS, CH_2Cl_2, -78 ^oC, 3 h.

Diseptano-hexose trisaccharide derivative **49** was synthesized using glycosyl donor **48** (100 mg, 0.26 mmol), glycosyl acceptor **32** (37 mg, 0.29 mmol), TMSOTf (9.4 µL, 0.05 mmol) and 4 Å MS powder in CH_2Cl_2 (5 mL) according to the general procedure for ring expansion-

glycosylation reaction (**3.4.2.3**). The reaction mixture was stirred at -78 ^{o}C for 3 h. The crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:4) to give diseptano-hexose trisaccharide derivative **49** (87 mg, 65%) as a colorless oil. R_f = 0.32 (3:7 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.37 (m, 6H), 5.44 (dd, 1H, *J* = 5.0 Hz, *J* = 8.5 Hz), 5.36 (d, 1H, *J* = 6.0 Hz), 4.86 (dd, 1H, *J* = 5.0 Hz, *J* = 8.5 Hz), 4.67 (d, 1H, *J* = 11.5 Hz), 4.40 (d, 1H, *J* = 11.5 Hz), 4.36 (dd, 1H, *J* = 6.5 Hz, *J* = 12.0 Hz), 4.18 (d, 1H, *J* = 12.0 Hz), 4.13 (t, 1H, *J* = 6.5 Hz), 4.05 (d, 1H, *J* = 8.5 Hz), 4.03 (dd, 1H, *J* = 5.5 Hz, *J* = 11.5 Hz), 3.62 (d, 1H, *J* = 7.0 Hz), 2.51 – 2.55 (m, 1H), 2.44 – 2.50 (m, 2H), 2.38 - 2.43 (m, 1H), 2.28 – 2.37 (m, 2H), 2.15 – 2.20 (m, 1H), 1.90 – 1.97 (m, 1H), 1.49 (d, 3H, *J* = 6.0 Hz), 1.33 (d, 3H, *J* = 5.5 Hz), 1.29 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 207.6, 193.3, 162.7, 137.1, 128.5, 128.1, 128.1, 105.1, 100.3, 99.8, 89.1, 83.6, 78.2, 74.7, 73.1, 66.9, 65.3, 35.8, 35.7, 27.2, 27.0, 20.9, 20.2, 17.6.

HRMS (ESI) calcd for $C_{27}H_{34}O_9$+Na 525.2101, found 525.2101.

3.5 References

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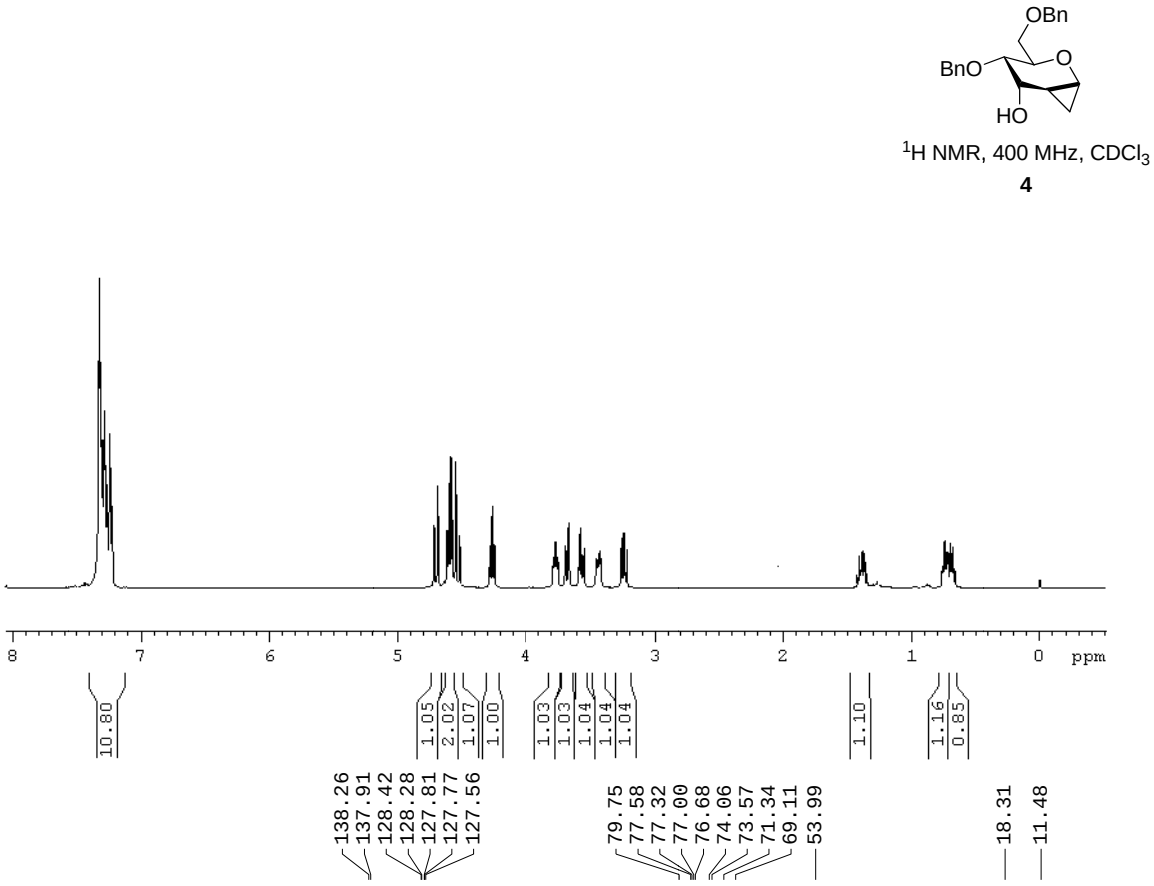
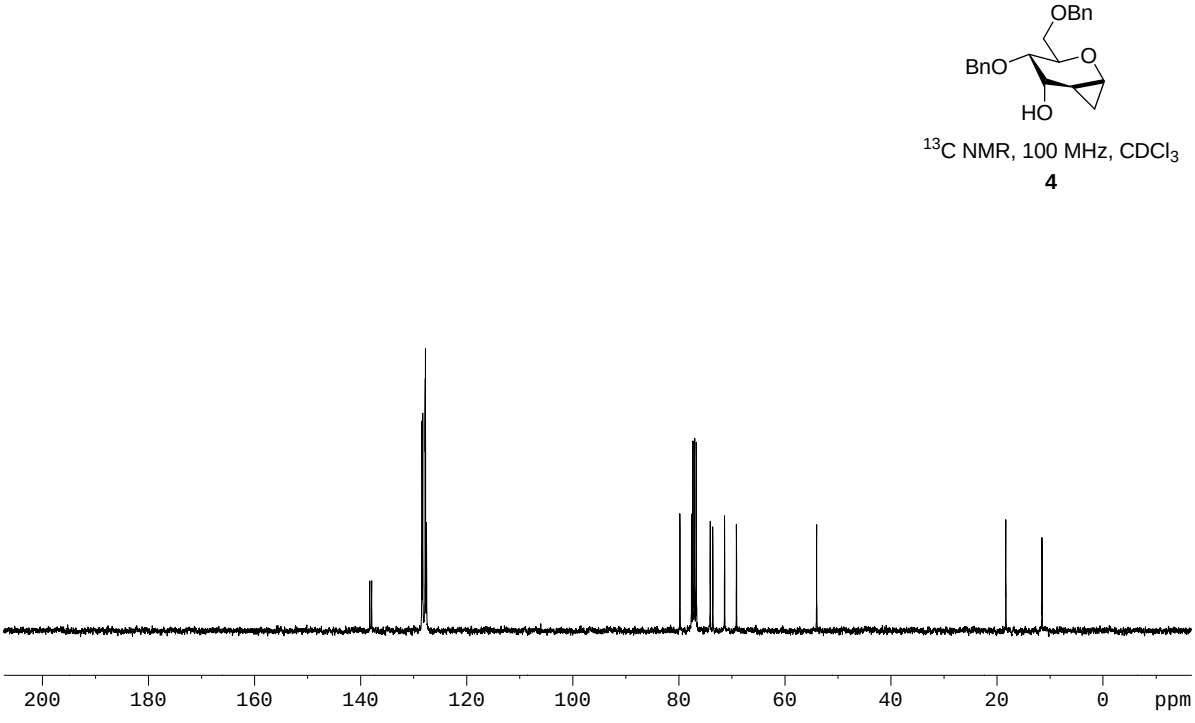
3.6 NMR Spectra



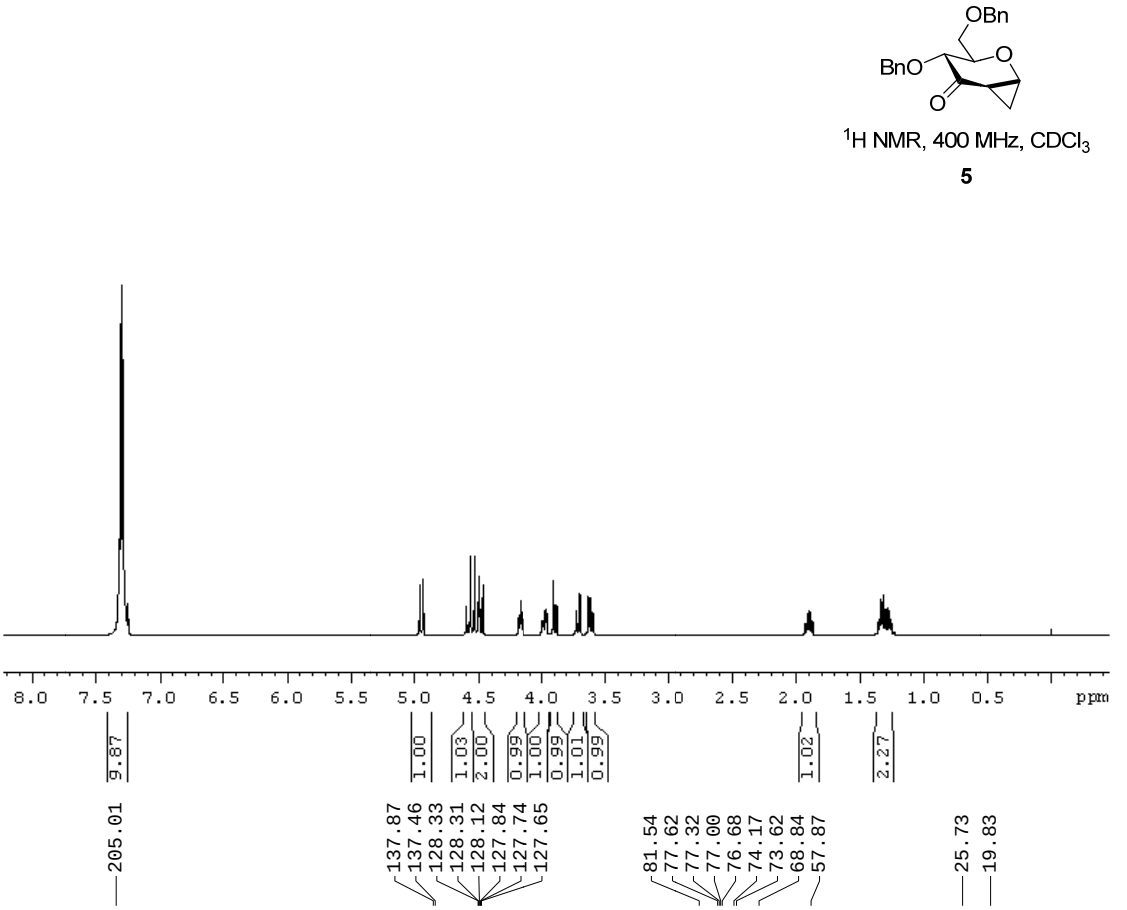
^{1}H NMR, 400 MHz, $CDCl_3$

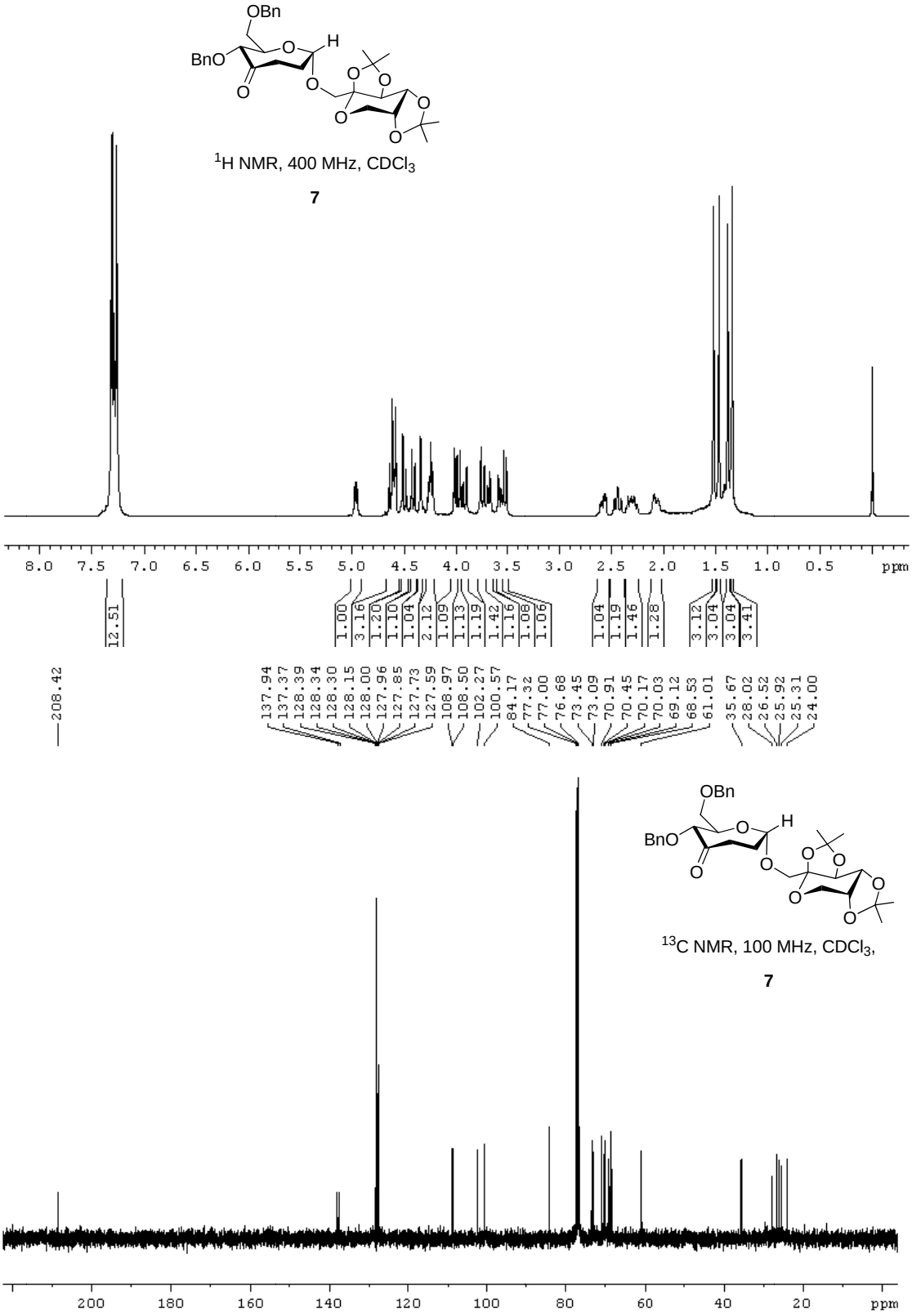
4

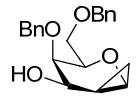


^{13}C NMR, 100 MHz, $CDCl_3$

4

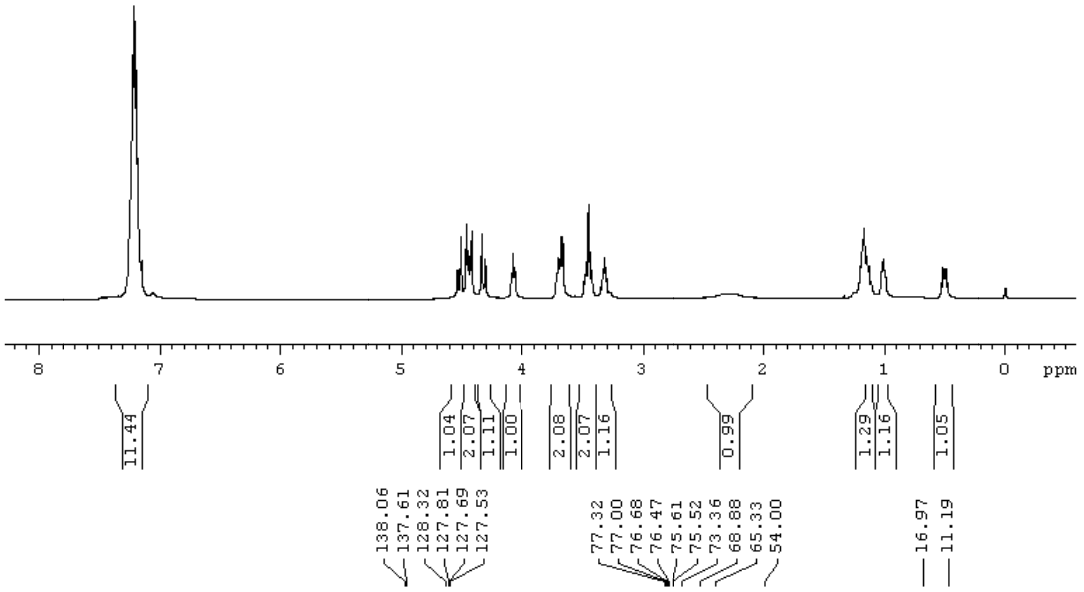

OBn
BnO
O
O
^{1}H NMR, 400 MHz, CDCl$_3$
5
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
9.87 1.00 1.03 2.00 0.99 1.00 0.99 1.01 0.99 1.02 2.27
205.01
137.87 137.46 128.33 128.31 128.12 127.84 127.74 127.65
81.54 77.62 77.32 77.00 76.68 74.17 73.62 68.84 57.87
25.73 19.83
OBn
BnO
O
O
^{13}C NMR, 100 MHz, CDCl$_3$,
5
220 200 180 160 140 120 100 80 60 40 20 ppm

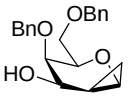

OBn
BnO
H
O
^{1}H NMR, 400 MHz, CDCl$_3$
7
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
12.51
1.00 3.16 1.20 1.10 1.04 2.12 1.09 1.13 1.19 1.42 1.16 1.08 1.06
1.04 1.19 1.46 1.28
3.12 3.04 3.04 3.41
208.42
137.94 137.37 128.39 128.34 128.30 128.15 128.00 127.96 127.85 127.73 127.59 108.97 108.50 102.27 100.57 84.17 77.32 77.00 76.68 73.45 73.09 70.91 70.45 70.17 70.03 69.12 68.53 61.01 35.67 28.02 26.52 25.92 25.31 24.00
OBn
BnO
H
O
^{13}C NMR, 100 MHz, CDCl$_3$,
7
200 180 160 140 120 100 80 60 40 20 ppm



^{1}H NMR, 400 MHz, $CDCl_3$

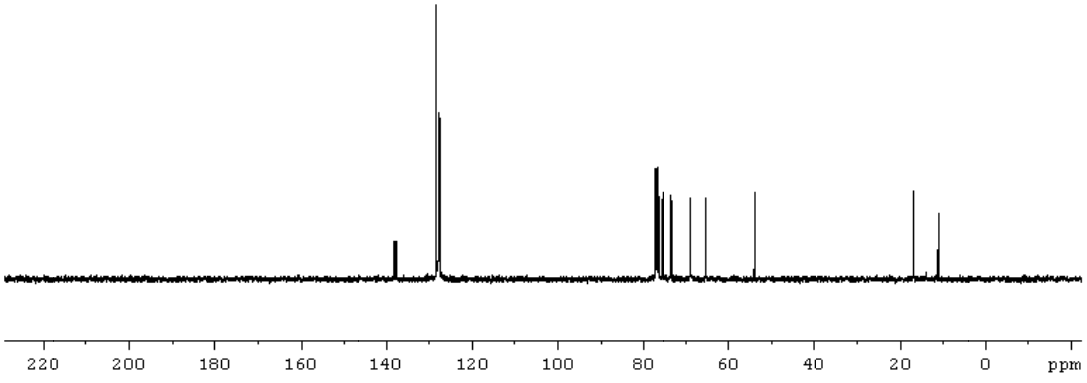
12





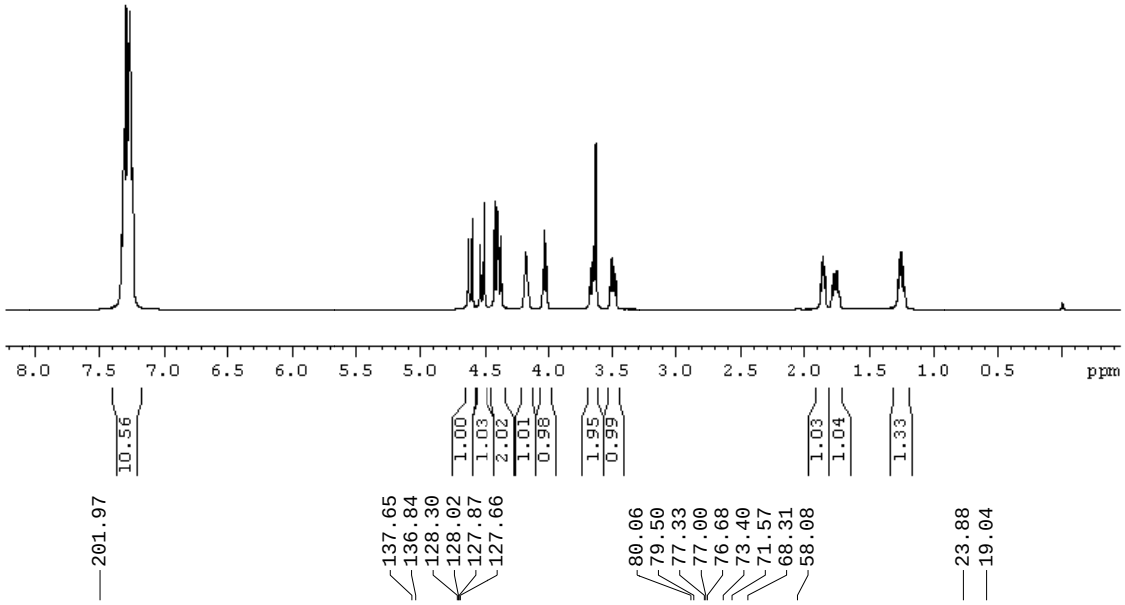
^{13}C NMR, 100 MHz, $CDCl_3$,

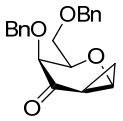
12



^{1}H NMR, 400 MHz, $CDCl_3$

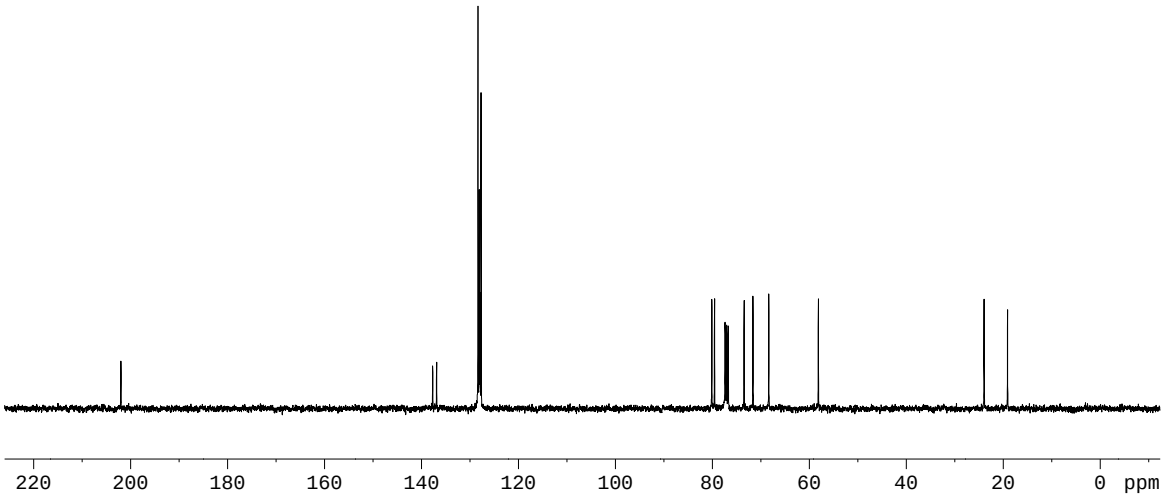
13

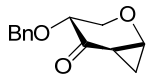




^{13}C NMR, 100 MHz, $CDCl_3$,

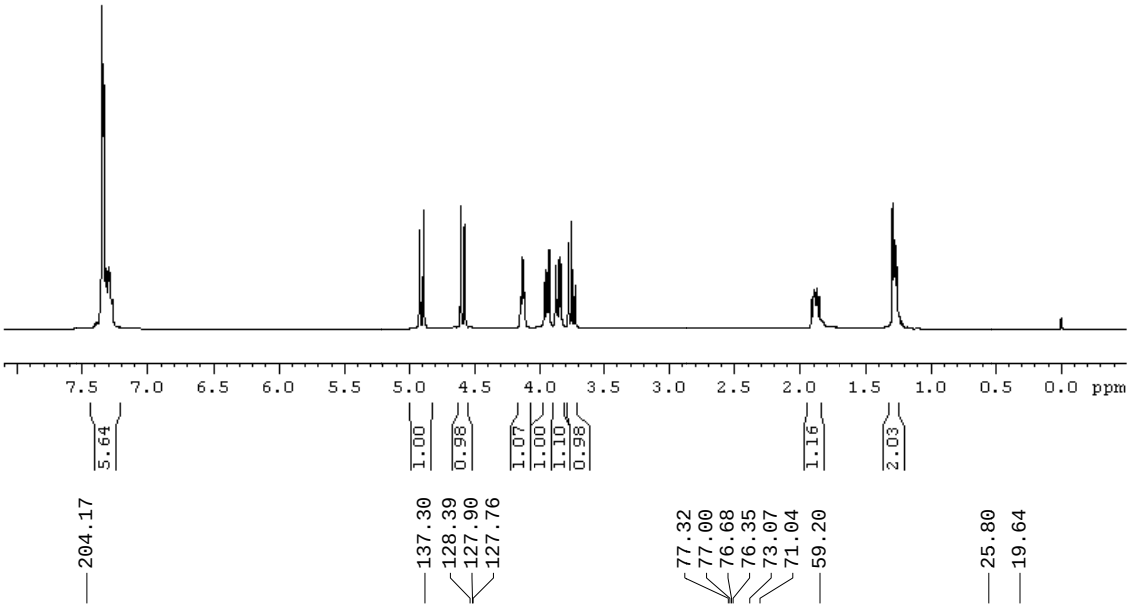
13

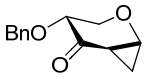




^{1}H NMR, 400 MHz, $CDCl_3$

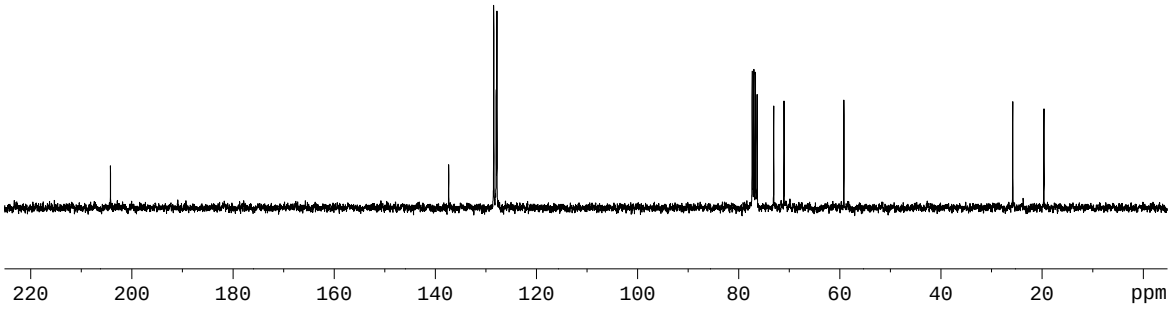
18

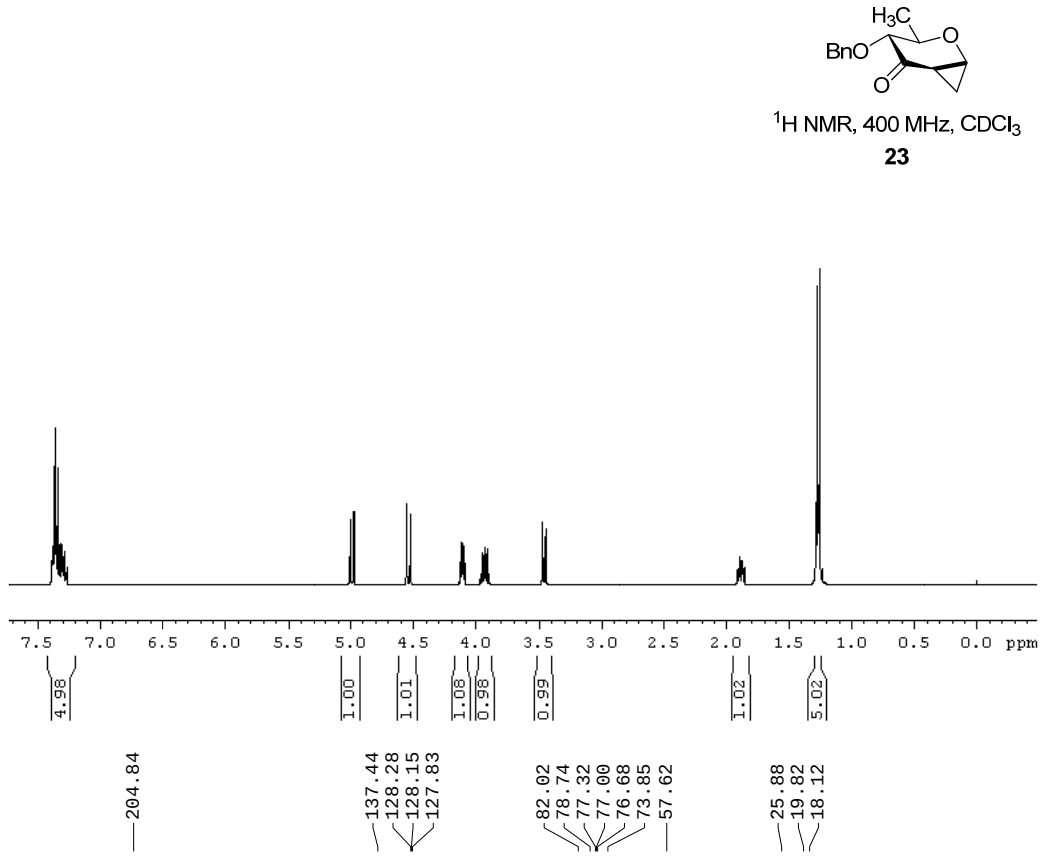




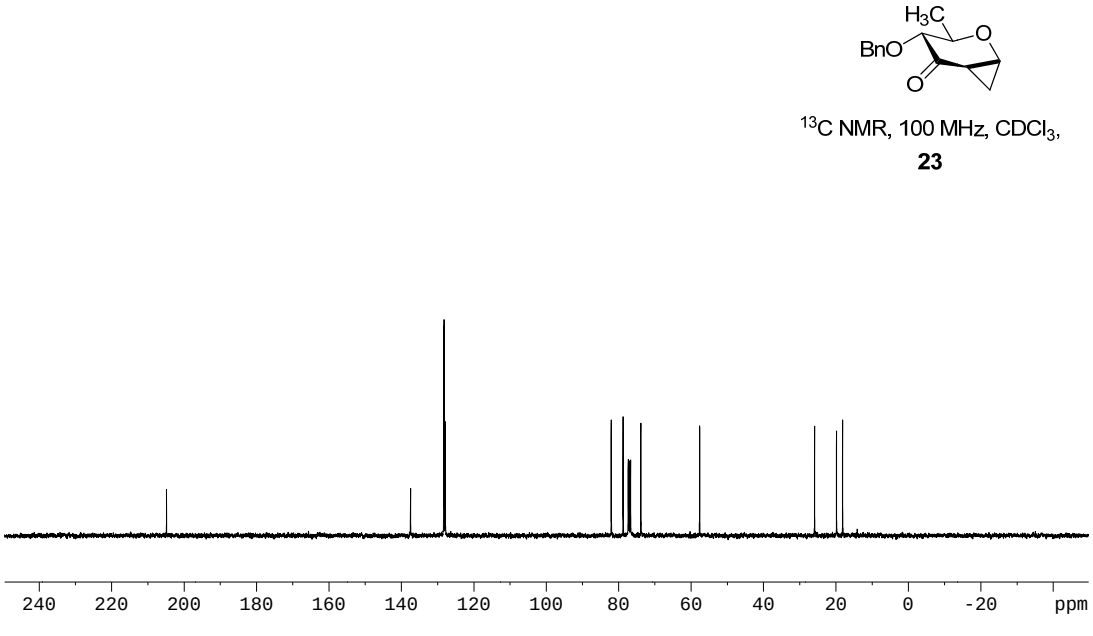
^{13}C NMR, 100 MHz, $CDCl_3$,

18





^{1}H NMR, 400 MHz, $CDCl_3$
23



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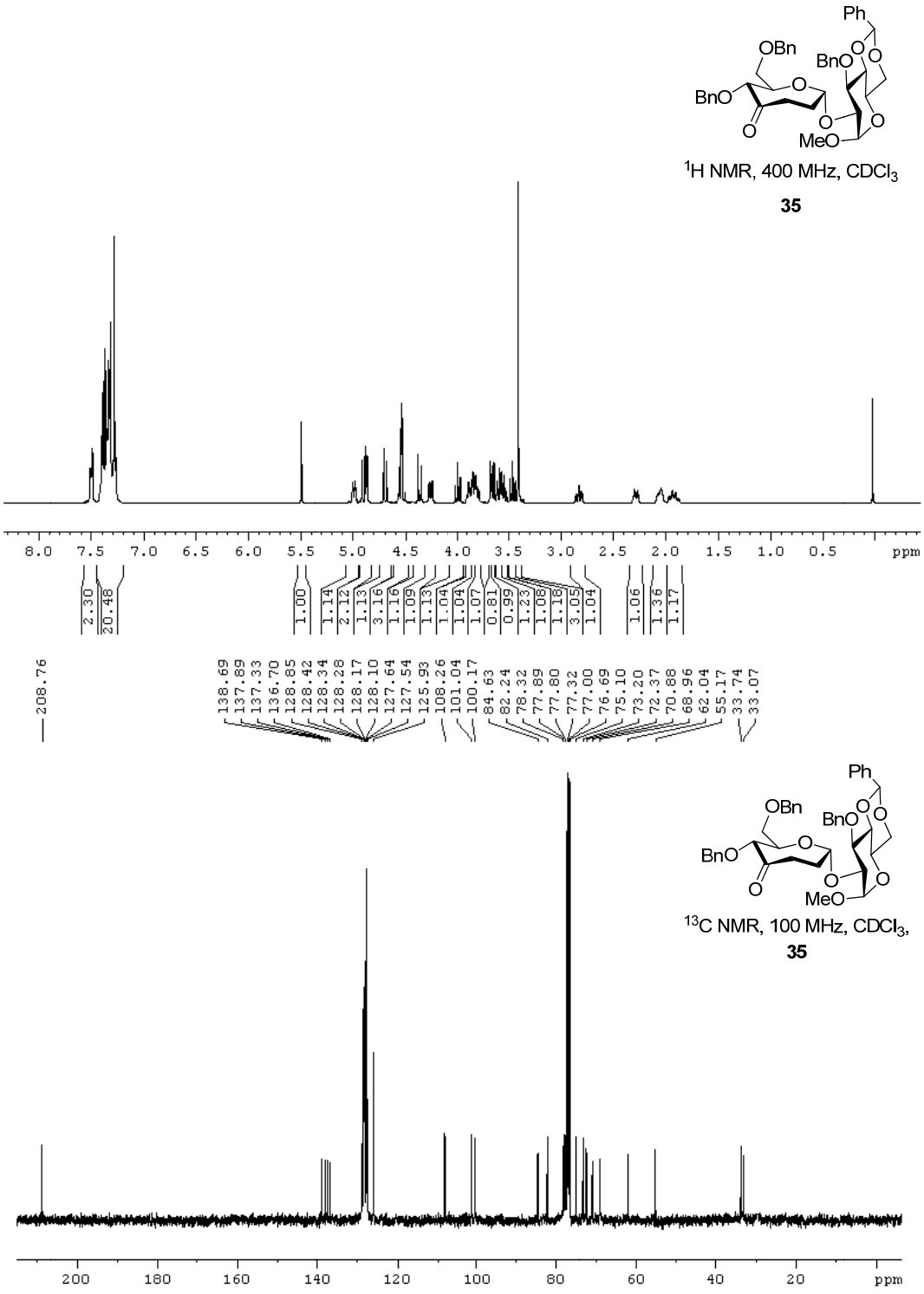
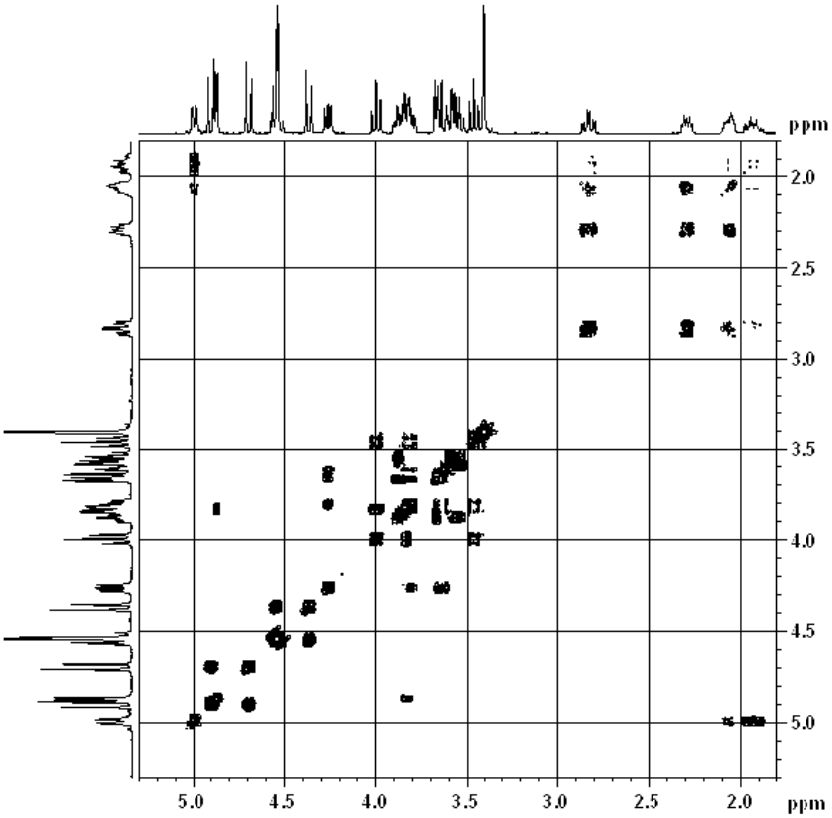
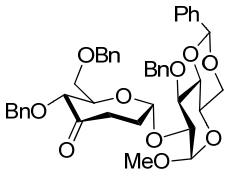
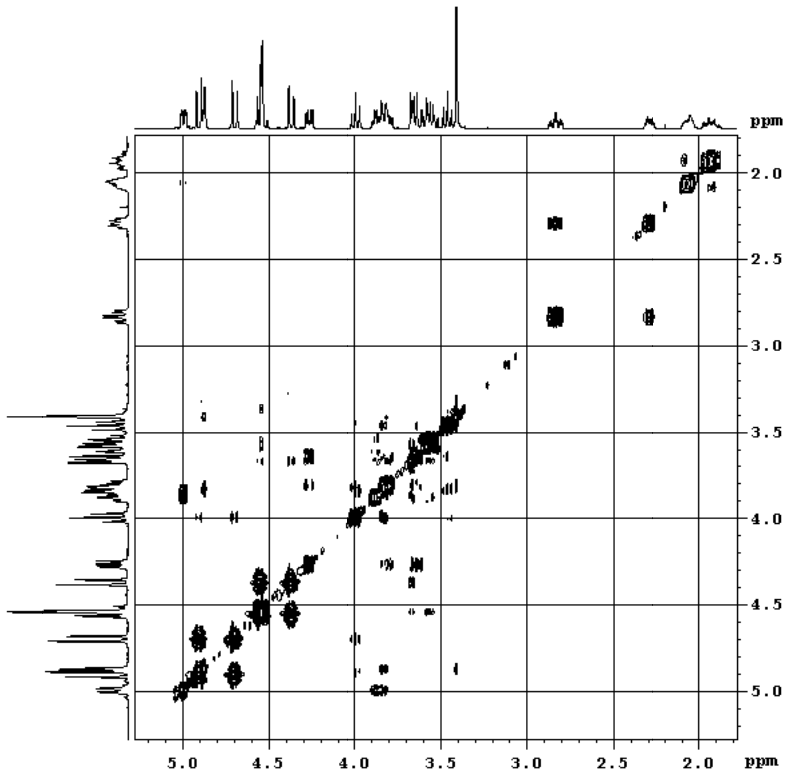

Ph
OBn
BnO
BnO
O
O
O
O
O
MeO
^{1}H NMR, 400 MHz, CDCl$_3$
35
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.30 20.48 1.00 1.14 2.12 1.13 3.16 1.16 1.09 1.13 1.04 1.04 1.07 0.81 0.99 1.23 1.08 1.18 3.05 1.04 1.06 1.36 1.17
208.76
138.69 137.89 137.33 136.70 128.85 128.42 128.34 128.28 128.17 128.10 127.64 127.54 125.93 108.26 101.04 100.17 84.63 82.24 78.32 77.89 77.80 77.32 77.00 76.69 75.10 73.20 72.37 70.88 68.96 62.04 55.17 33.74 33.07
Ph
OBn
BnO
BnO
O
O
O
O
O
MeO
^{13}C NMR, 100 MHz, CDCl$_3$,
35
200 180 160 140 120 100 80 60 40 20 ppm

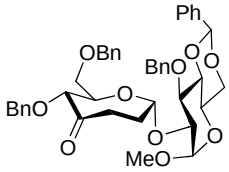




^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

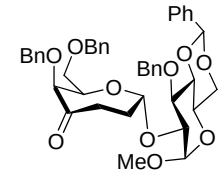
35





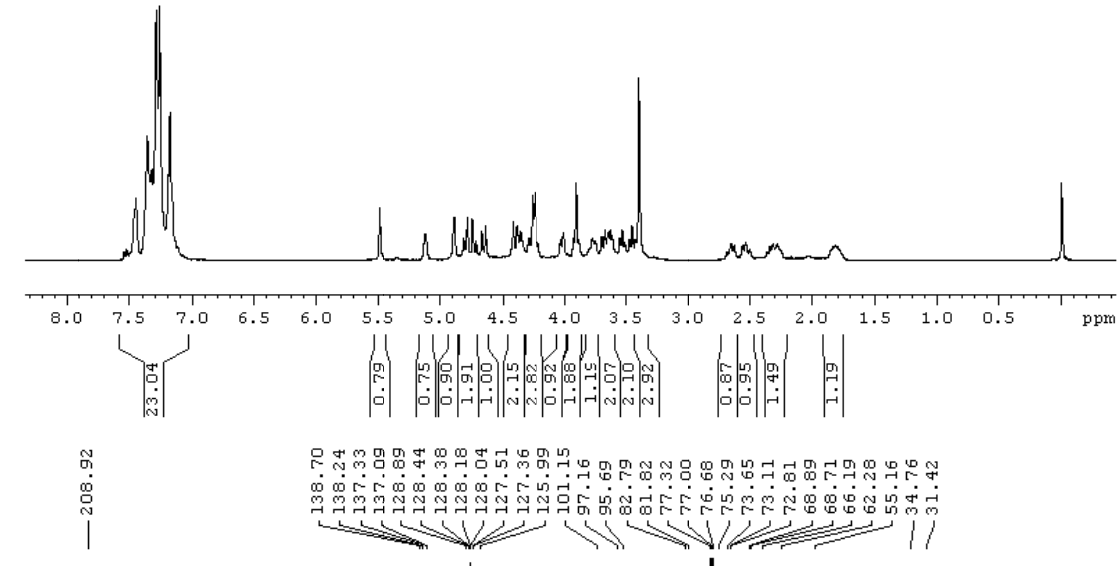
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

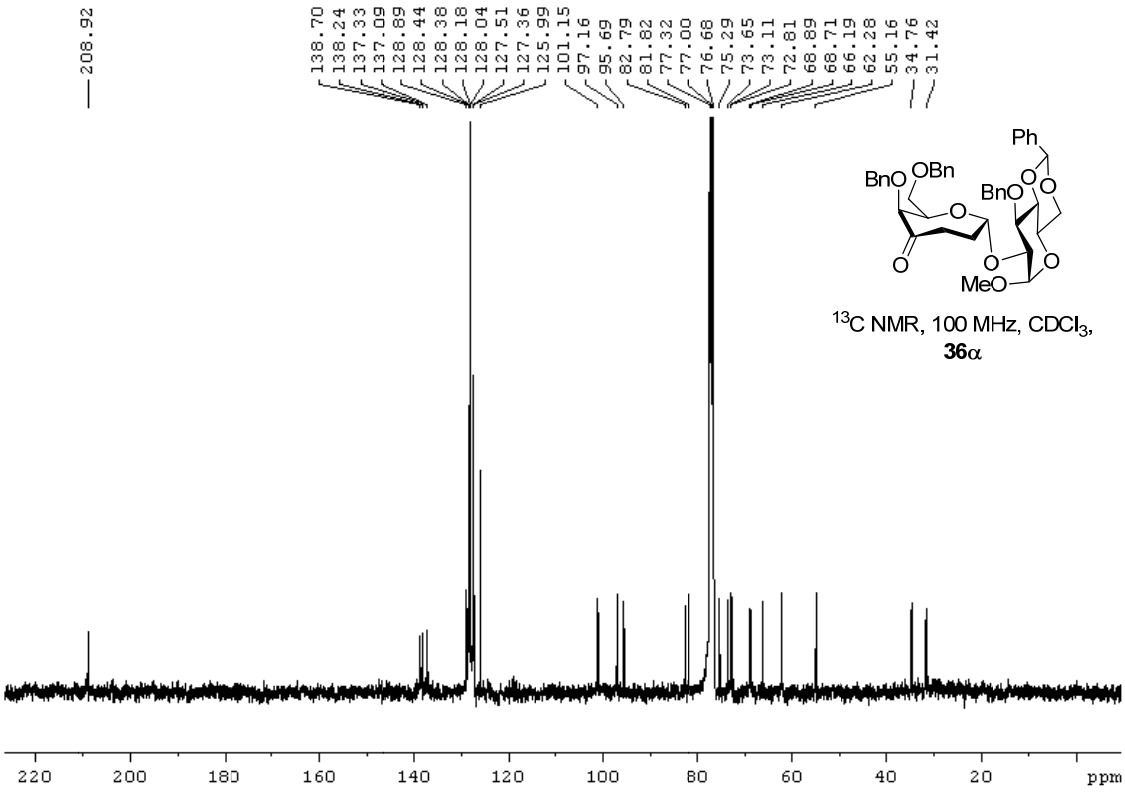
35



^{1}H NMR, 400 MHz, $CDCl_3$

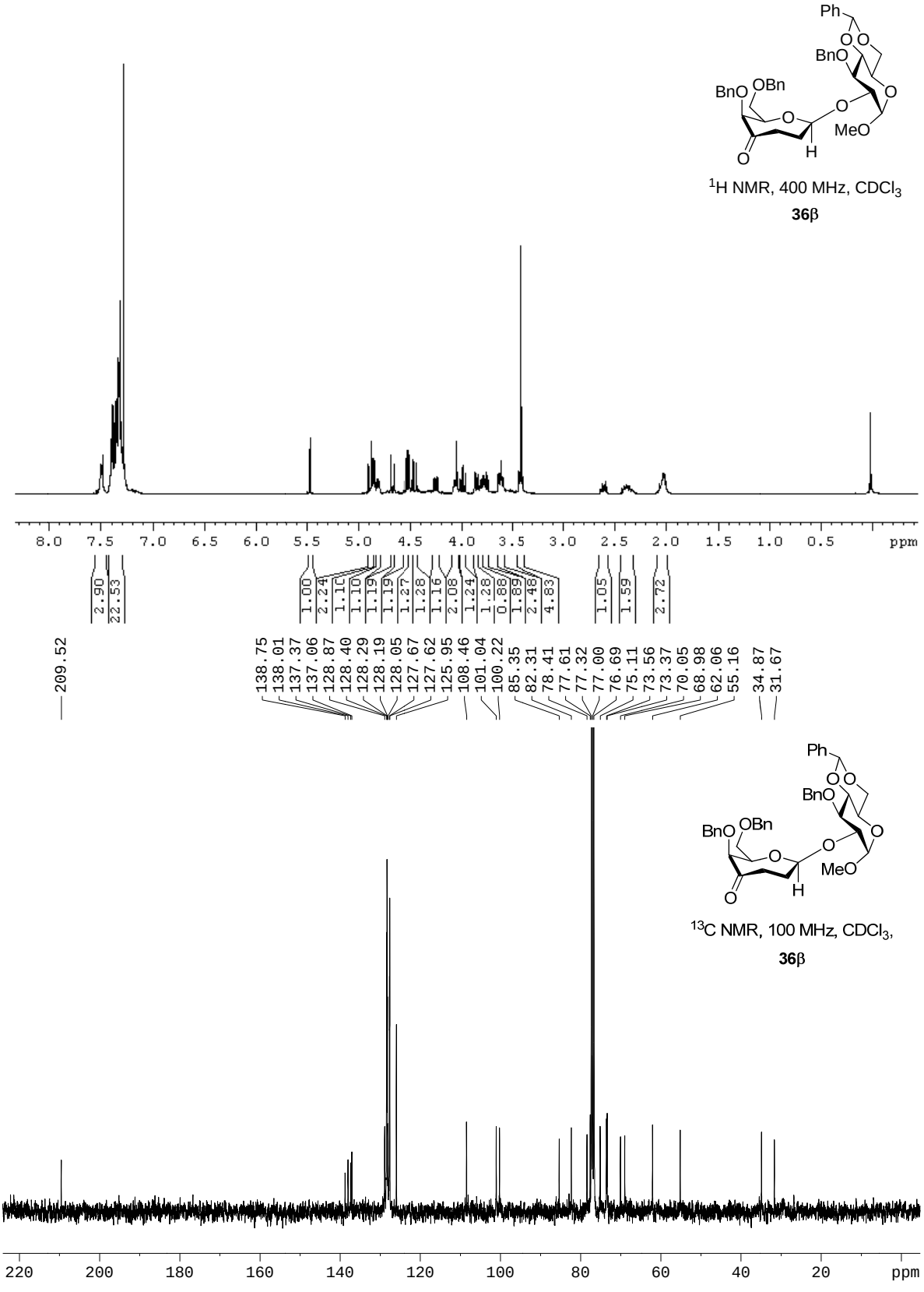
36α

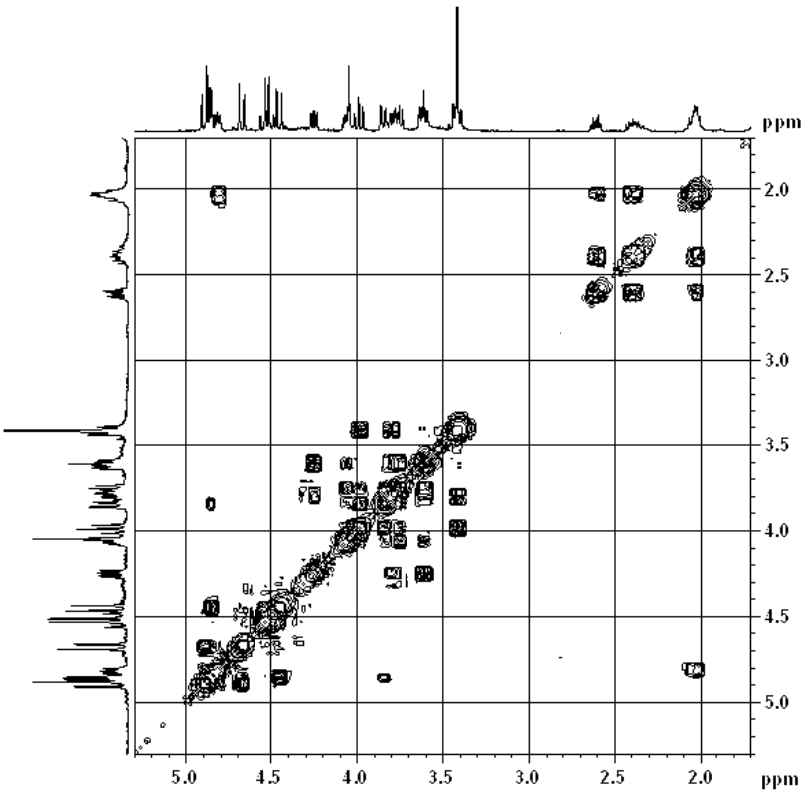


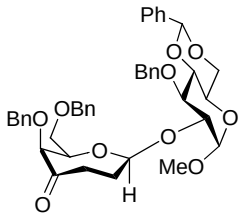


^{13}C NMR, 100 MHz, $CDCl_3$,

36α

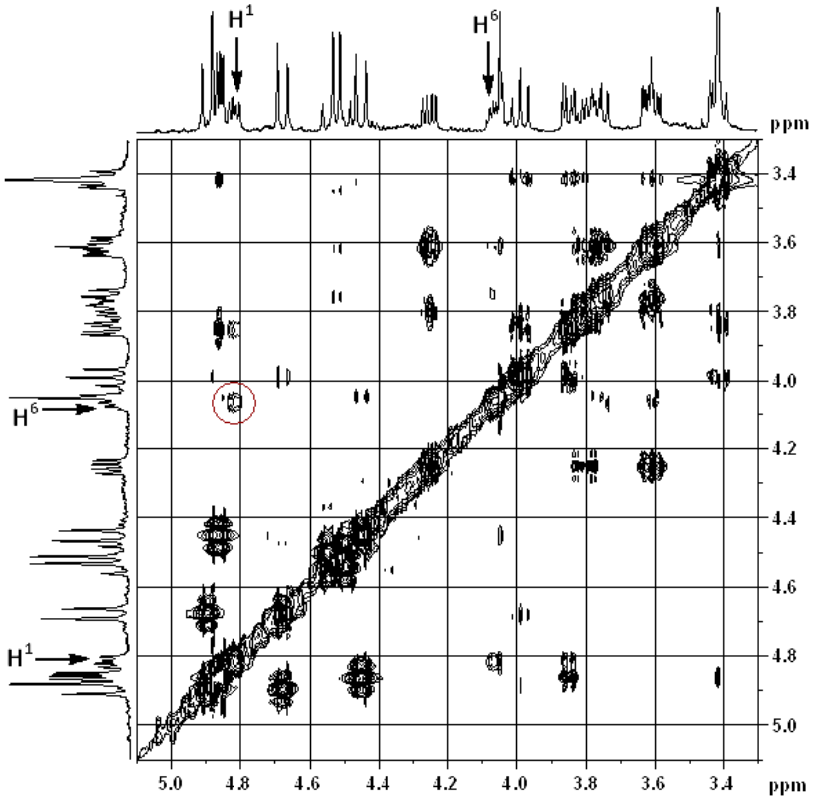

Ph
O
O
BnO
BnO
OBn
O
O
O
MeO
O
H
^{1}H NMR, 400 MHz, CDCl$_3$
36β
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.90 22.53 1.00 2.24 1.10 1.19 1.19 1.27 1.28 1.16 2.08 1.24 1.28 0.88 1.89 2.46 4.83 1.05 1.59 2.72
209.52
138.75 138.01 137.37 137.06 128.87 128.40 128.29 128.19 128.05 127.67 127.62 125.95 108.46 101.04 100.22 85.35 82.31 78.41 77.61 77.32 77.00 76.69 75.11 73.56 73.37 70.05 68.98 62.06 55.16 34.87 31.67
^{13}C NMR, 100 MHz, CDCl$_3$,
36β
220 200 180 160 140 120 100 80 60 40 20 ppm

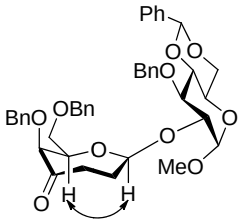




^{1}H-^{1}H COSY NMR, 400 MHz, $CDCl_3$

36β

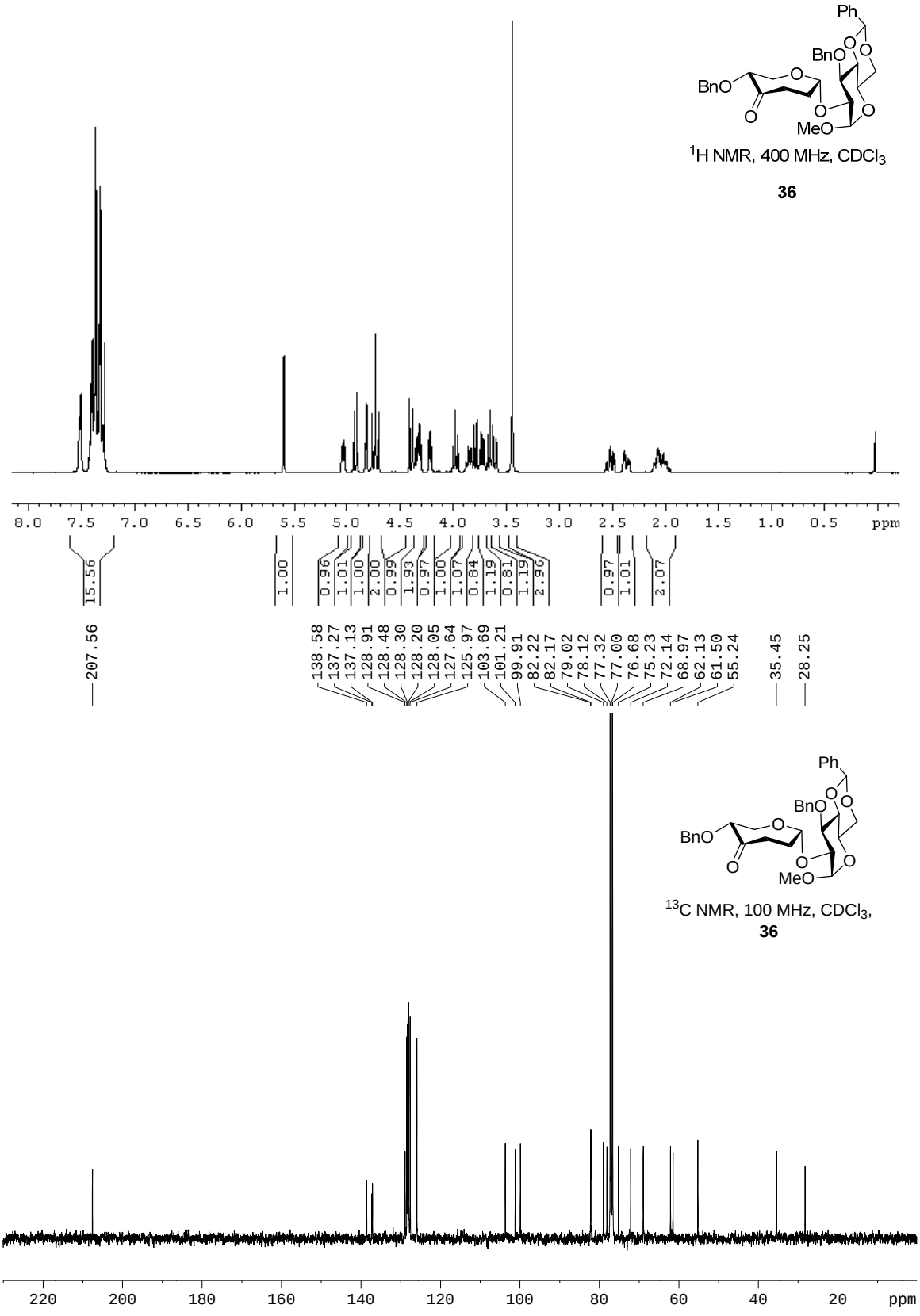


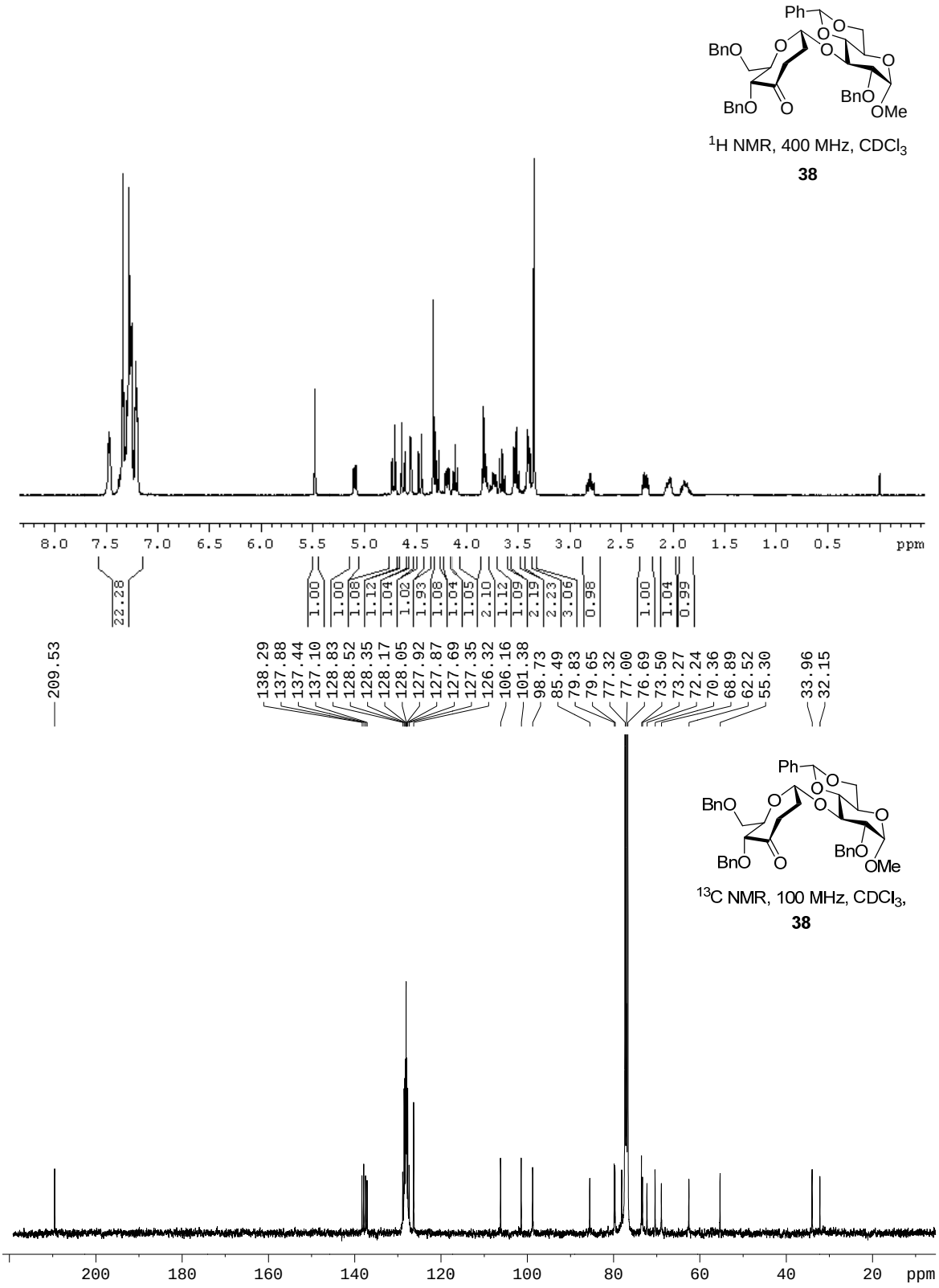


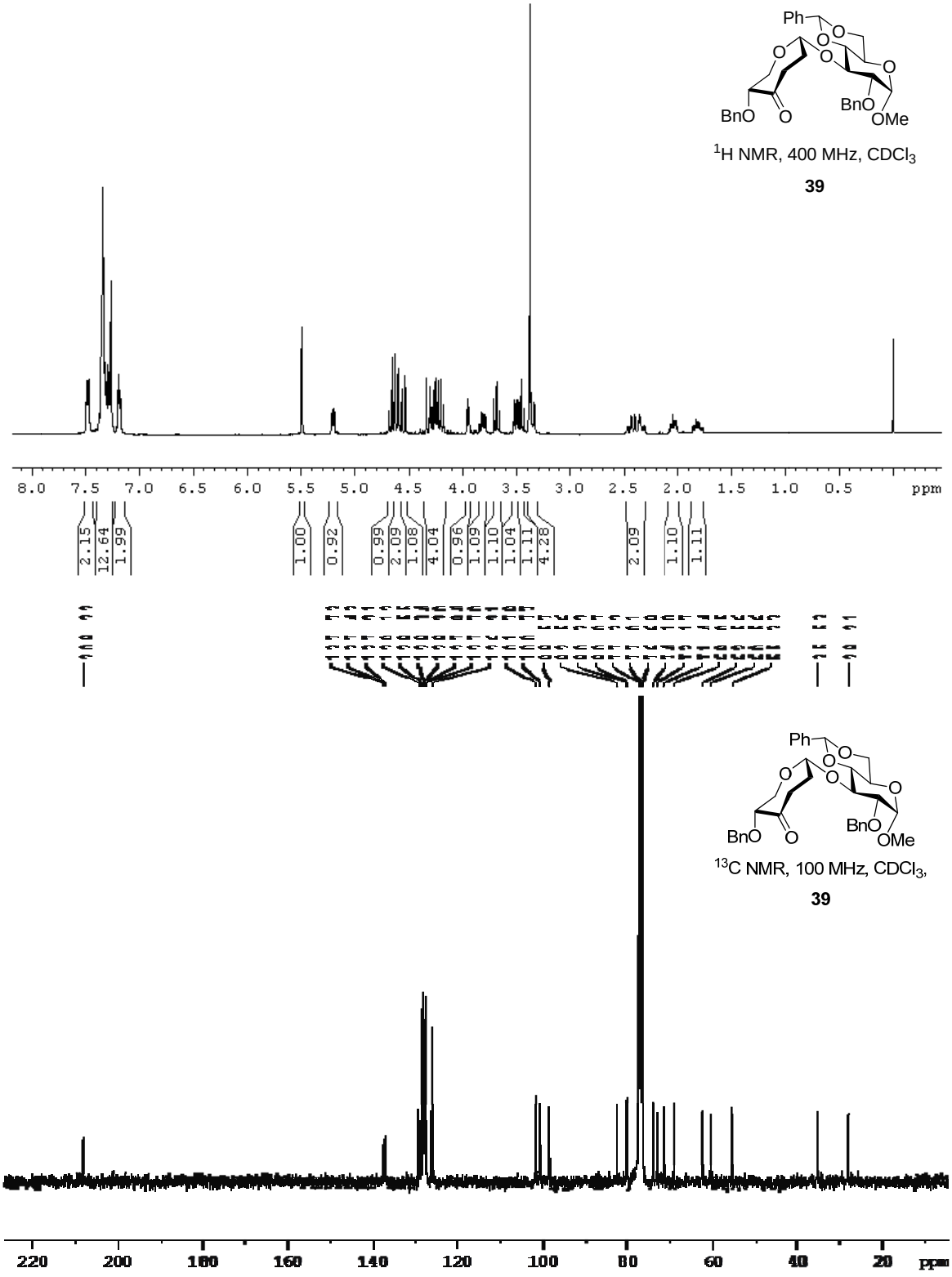
36β

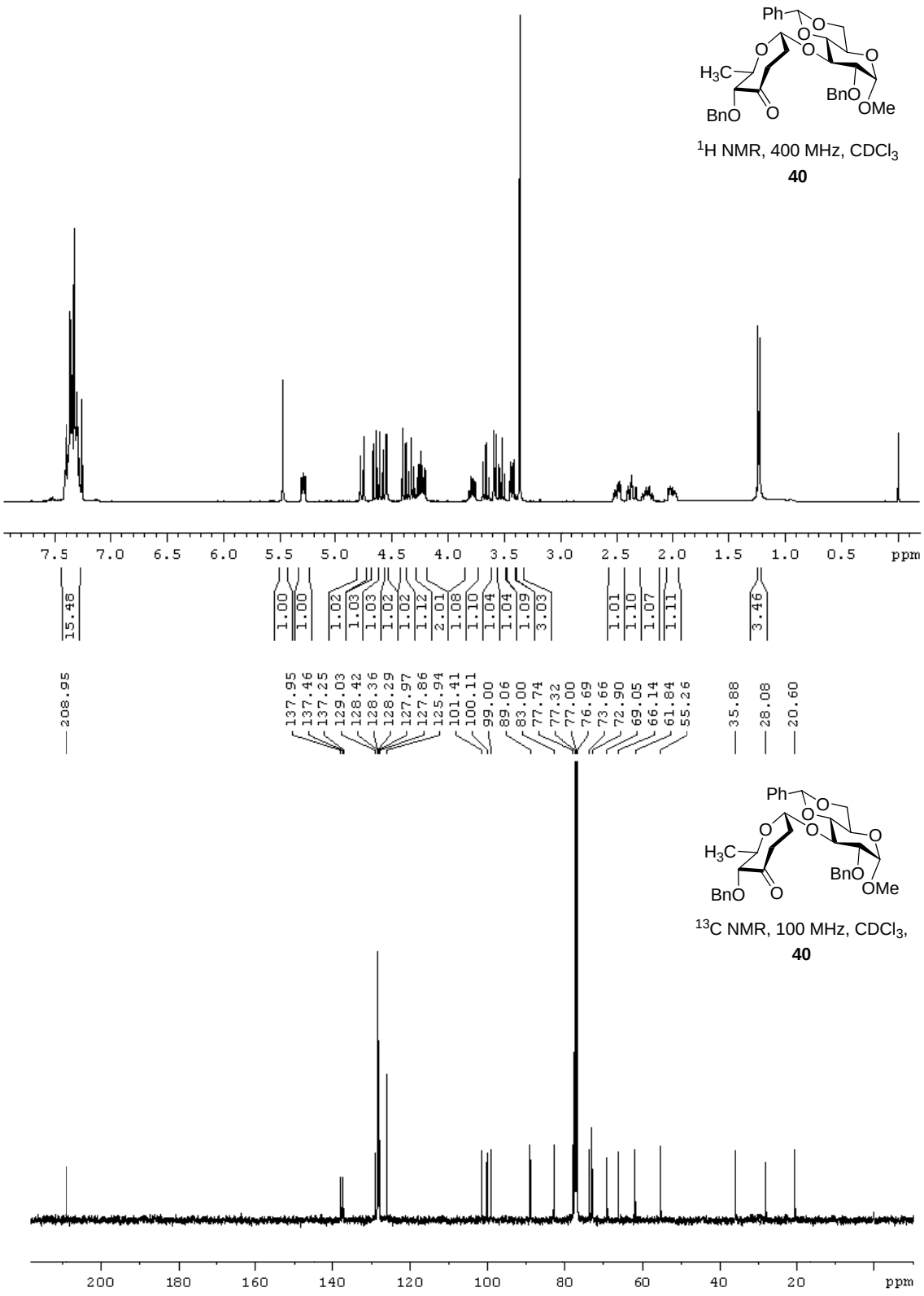
^{1}H-^{1}H NOESY NMR, 400 MHz, $CDCl_3$

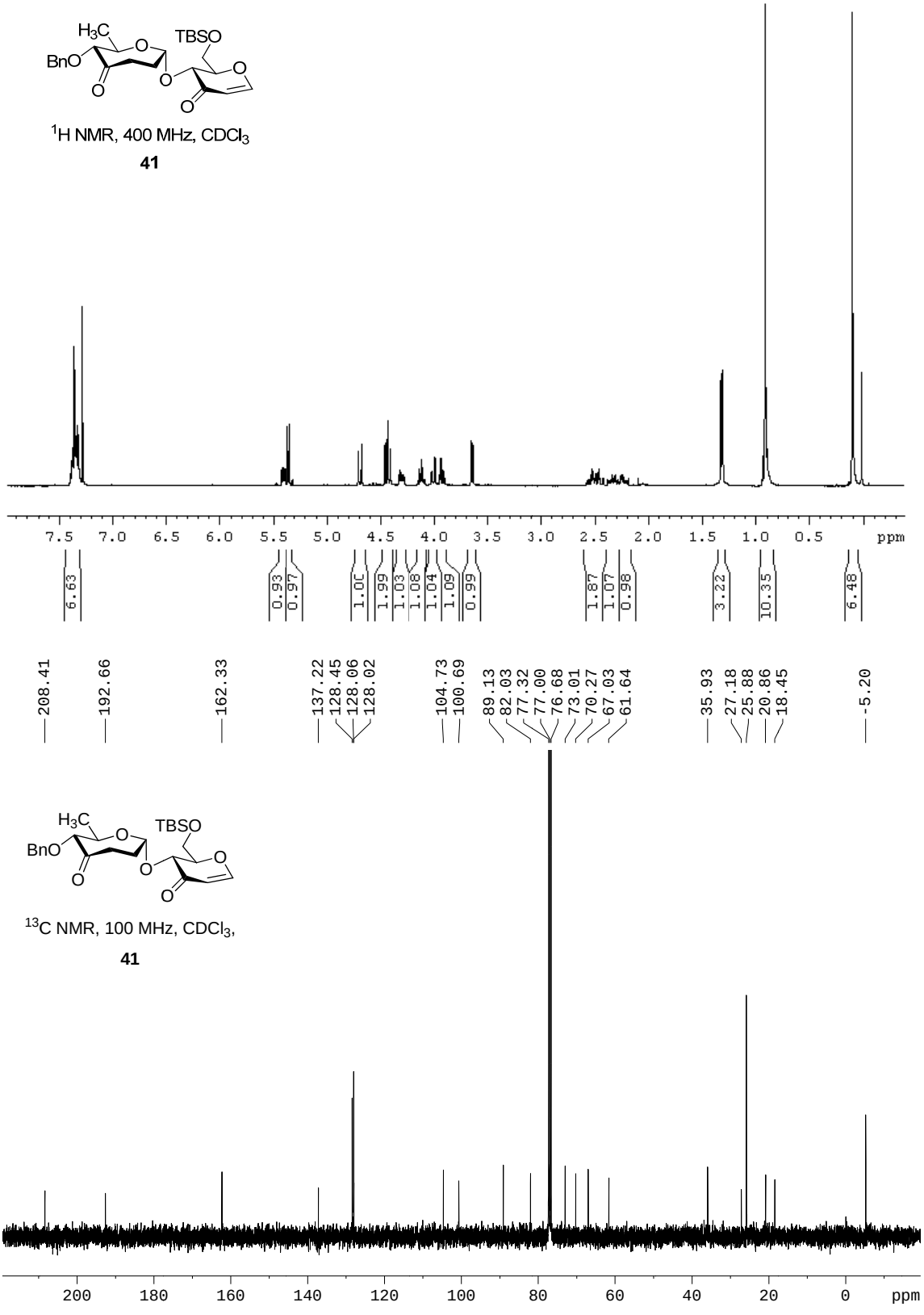
NOE observed between H^1 and H^6

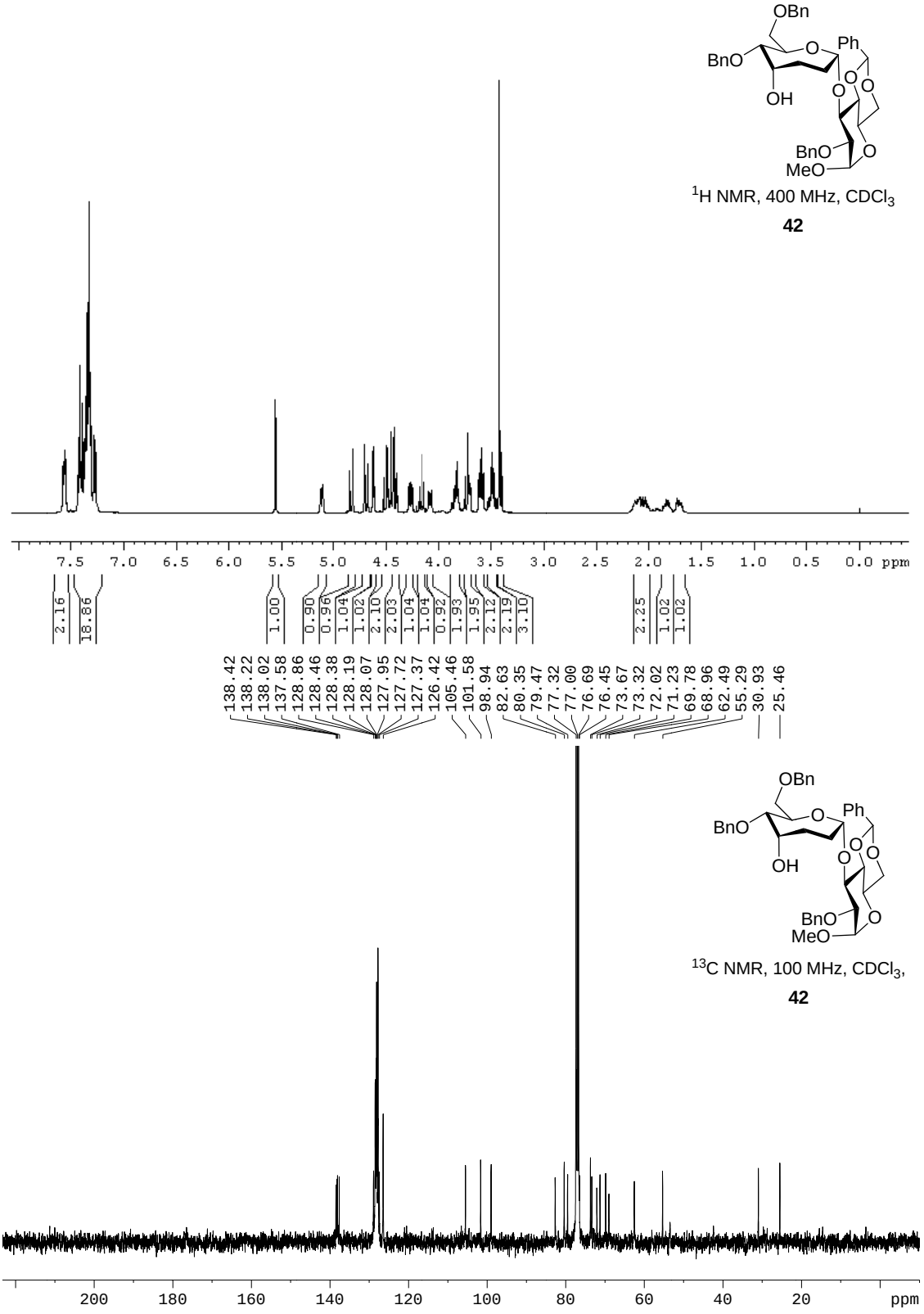

Ph
BnO
BnO
MeO
^{1}H NMR, 400 MHz, CDCl$_3$
36
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
15.56
1.00
0.96 1.01 1.00 2.00 0.99 1.93 0.97 1.00 1.07 0.84 1.19 0.81 1.19 2.96
0.97 1.01
2.07
207.56
138.58 137.27 137.13 128.91 128.48 128.30 128.20 128.05 127.64 125.97 103.69 101.21 99.91 82.22 82.17 79.02 78.12 77.32 77.00 76.68 75.23 72.14 68.97 62.13 61.50 55.24
35.45
28.25
Ph
BnO
BnO
MeO
^{13}C NMR, 100 MHz, CDCl$_3$,
36
220 200 180 160 140 120 100 80 60 40 20 ppm


Ph
BnO
BnO
BnO
OMe
^{1}H NMR, 400 MHz, $CDCl_3$
38
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
22.28
1.00 1.00 1.08 1.12 1.04 1.02 1.93 1.08 1.04 1.05 2.10 1.12 1.09 2.19 2.23 3.06 0.98 1.00 1.04 0.99
209.53
138.29 137.88 137.44 137.10 128.83 128.52 128.35 128.17 128.05 127.92 127.87 127.69 127.35 126.32 106.16 101.38 98.73 85.49 79.83 79.65 77.32 77.00 76.69 73.50 73.27 72.24 70.36 68.89 62.52 55.30 33.96 32.15
Ph
BnO
BnO
BnO
OMe
^{13}C NMR, 100 MHz, $CDCl_3$,
38
200 180 160 140 120 100 80 60 40 20 ppm


Ph
O
O
O
O
O
BnO
O
BnO
OMe
^{1}H NMR, 400 MHz, CDCl$_3$
39
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.15 12.64 1.99 1.00 0.92 0.99 2.09 1.08 4.04 0.96 1.09 1.10 1.04 1.11 4.28 2.09 1.10 1.11
Ph
O
O
O
O
O
BnO
O
BnO
OMe
^{13}C NMR, 100 MHz, CDCl$_3$,
39
220 200 180 160 140 120 100 80 60 40 20 ppm


Ph
O
O
O
O
O
H3C
BnO
O
BnO
OMe
1H NMR, 400 MHz, CDCl3
40
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
15.48
1.00 1.00 1.02 1.03 1.03 1.02 1.02 1.12 2.01 1.08 1.10 1.04 1.04 1.09 3.03
1.01 1.10 1.07 1.11
3.46
208.95
137.95 137.46 137.25 129.03 128.42 128.36 128.29 127.97 127.86 125.94 101.41 100.11 99.00 89.06 83.00 77.74 77.32 77.00 76.69 73.66 72.90 69.05 66.14 61.84 55.26
35.88 28.08 20.60
13C NMR, 100 MHz, CDCl3,
40
200 180 160 140 120 100 80 60 40 20 ppm


H3C
TBSO
BnO
O
O
O
O
1H NMR, 400 MHz, CDCl3
41
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
6.63
0.93
0.97
1.00
1.99
1.03
1.08
1.04
1.09
0.99
1.87
1.07
0.98
3.22
10.35
6.48
208.41
192.66
162.33
137.22
128.45
128.06
128.02
104.73
100.69
89.13
82.03
77.32
77.00
76.68
73.01
70.27
67.03
61.64
35.93
27.18
25.88
20.86
18.45
-5.20
13C NMR, 100 MHz, CDCl3,
41
200 180 160 140 120 100 80 60 40 20 0 ppm


OBn
BnO
O
Ph
O
O
O
OH
BnO
O
MeO
^{1}H NMR, 400 MHz, CDCl$_3$
42
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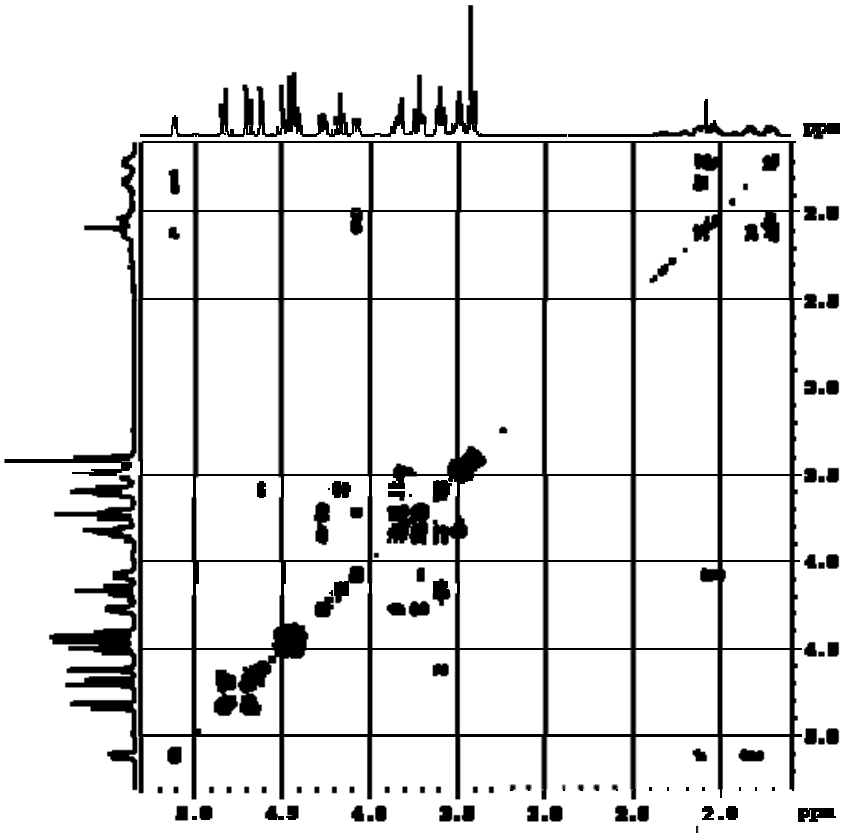
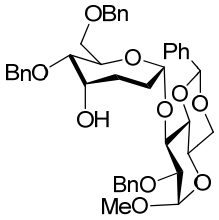
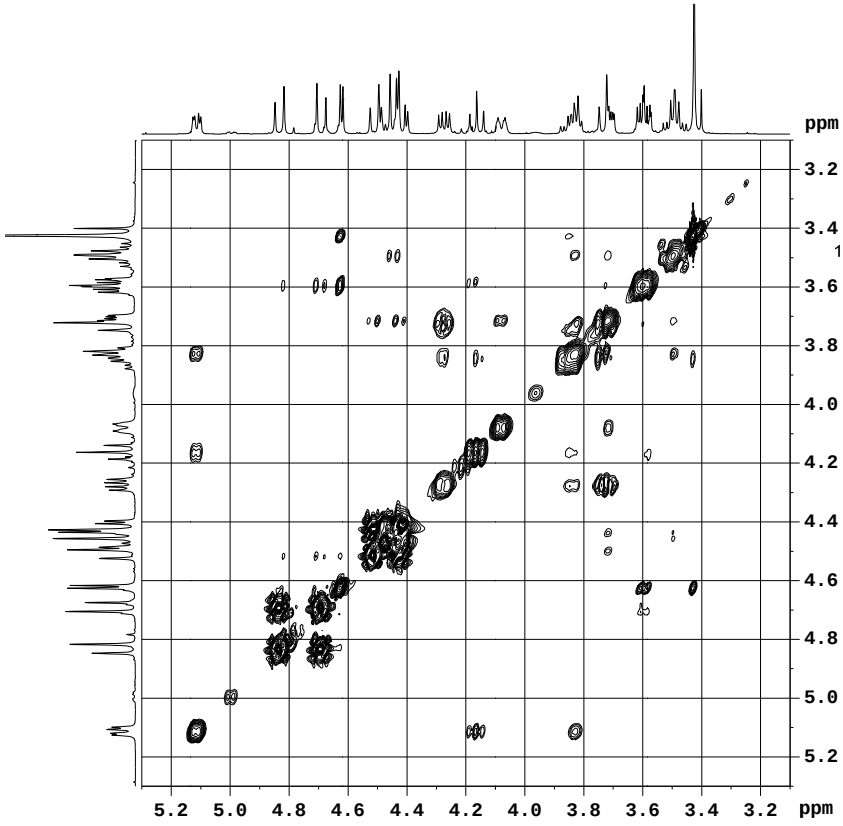
2.16 18.86 1.00 0.90 0.96 1.04 1.02 2.10 2.03 1.04 1.04 0.92 1.93 1.95 2.12 2.19 3.10 2.25 1.02 1.02
138.42 138.22 138.02 137.58 128.86 128.46 128.38 128.19 128.07 127.95 127.72 127.37 126.42 105.46 101.58 98.94 82.63 80.35 79.47 77.32 77.00 76.69 76.45 73.67 73.32 72.02 71.23 69.78 68.96 62.49 55.29 30.93 25.46
OBn
BnO
O
Ph
O
O
O
OH
BnO
O
MeO
^{13}C NMR, 100 MHz, CDCl$_3$,
42
200 180 160 140 120 100 80 60 40 20 ppm

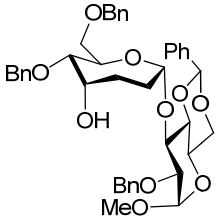




^{1}H-^{1}H COSY NMR, 400 mHz, $CDCl_3$

42





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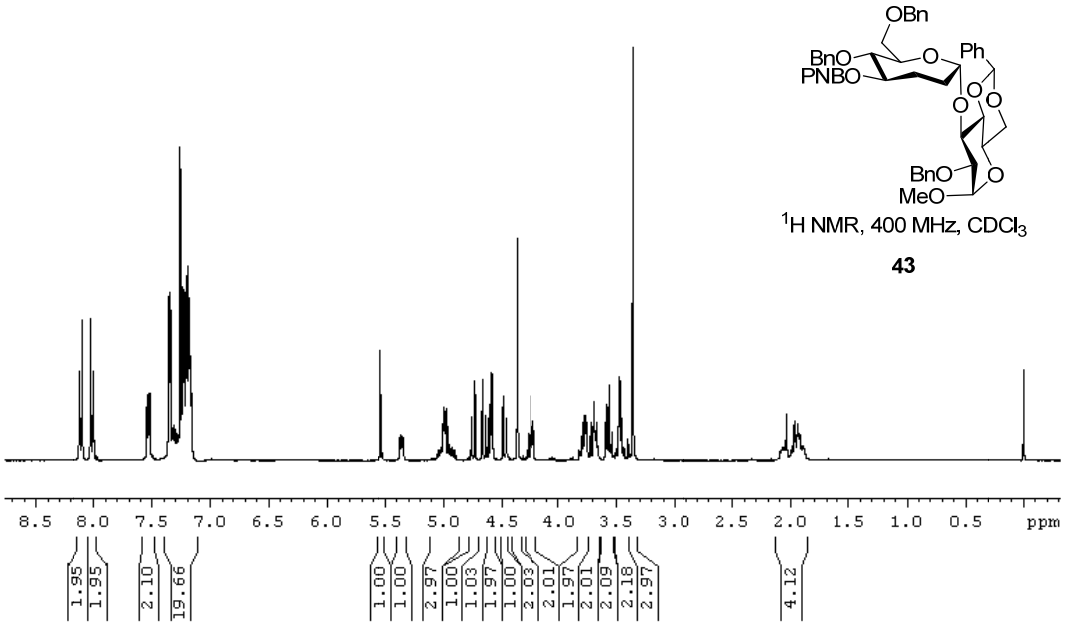
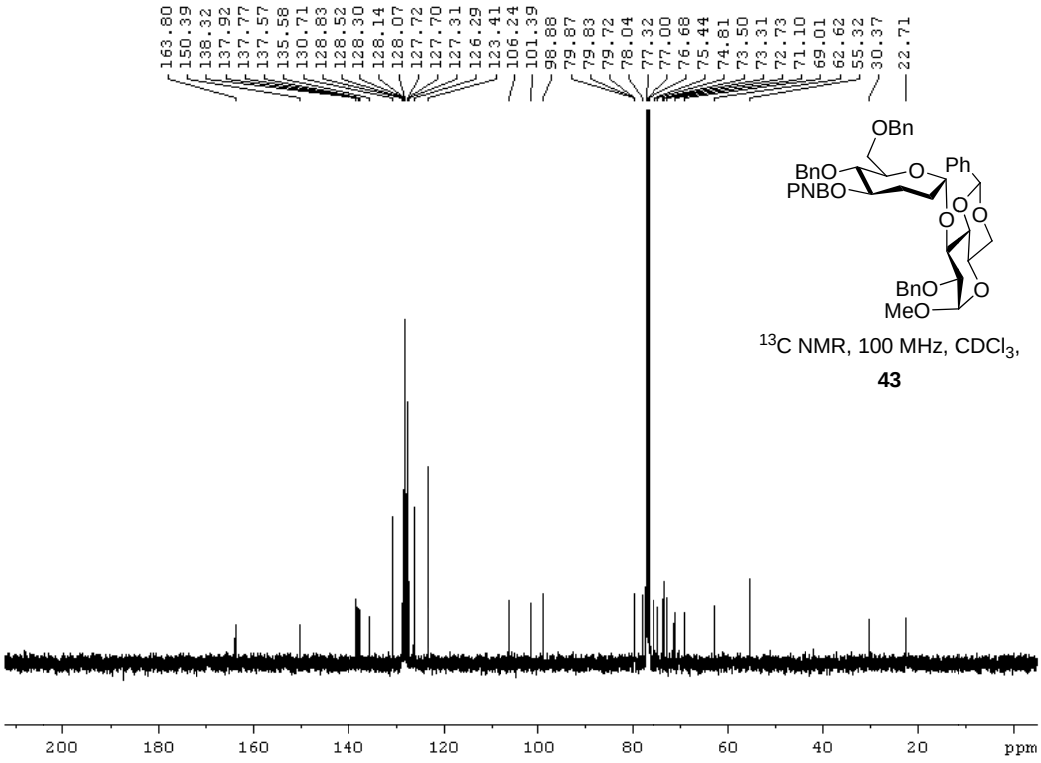
42



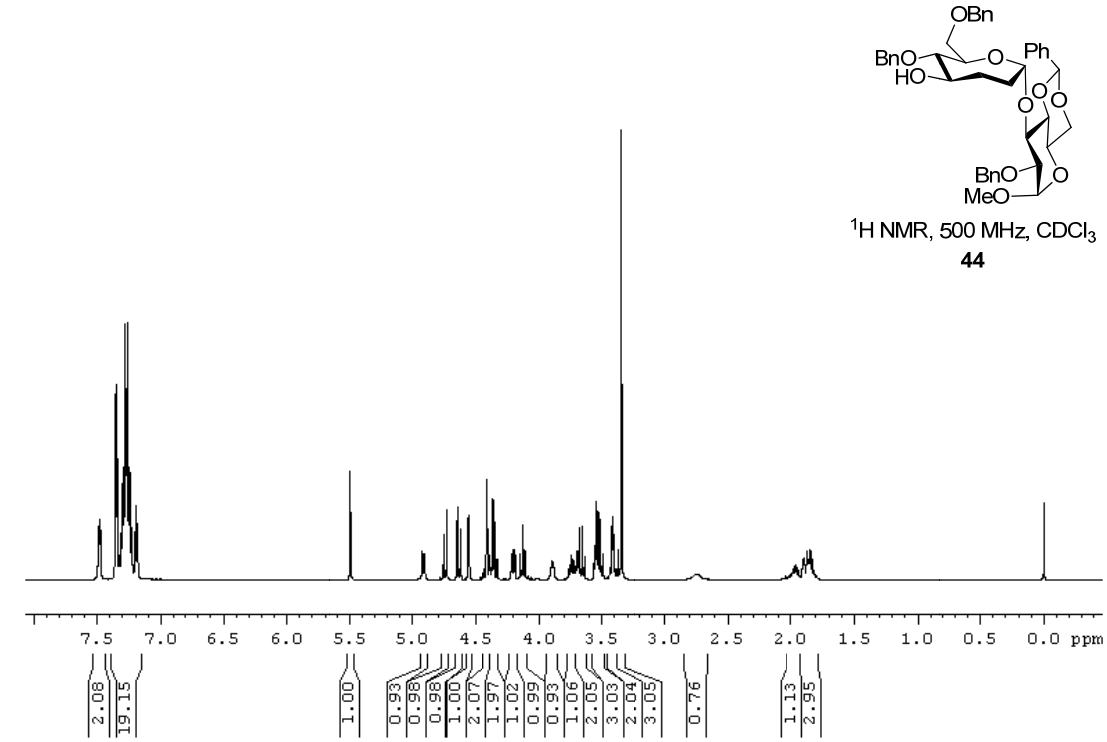
^{1}H NMR, 400 MHz, $CDCl_3$

43



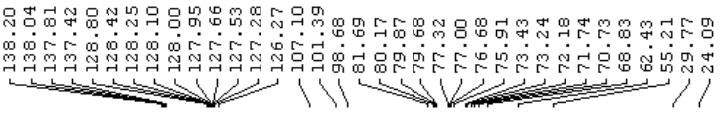
^{13}C NMR, 100 MHz, $CDCl_3$,

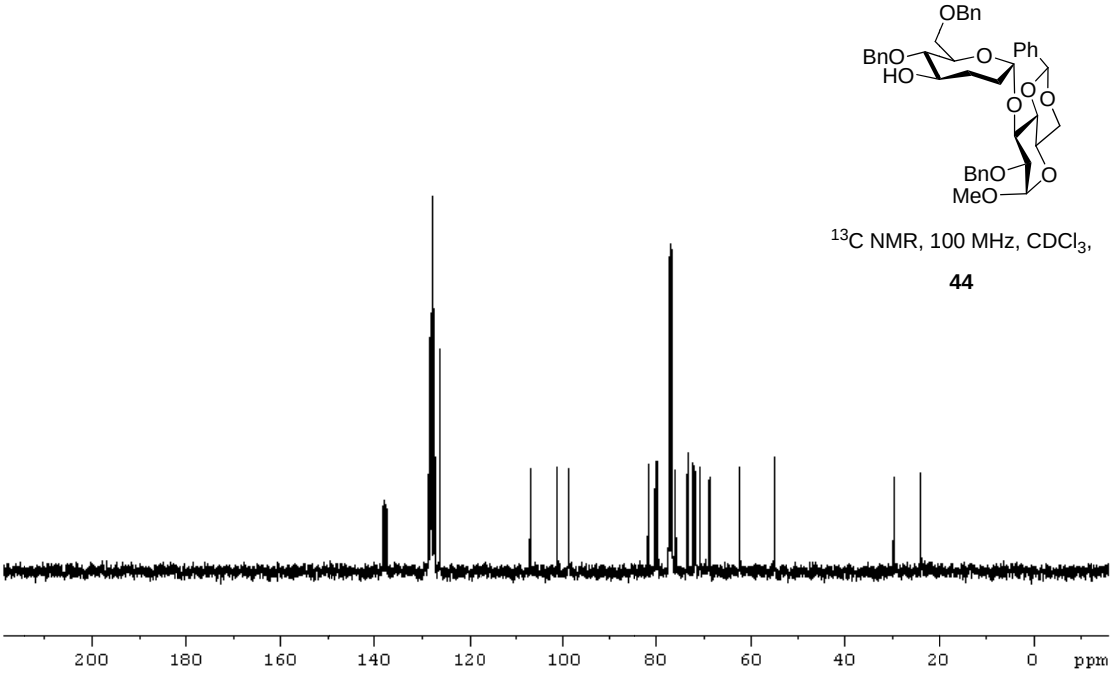
43



^{1}H NMR, 500 MHz, $CDCl_3$

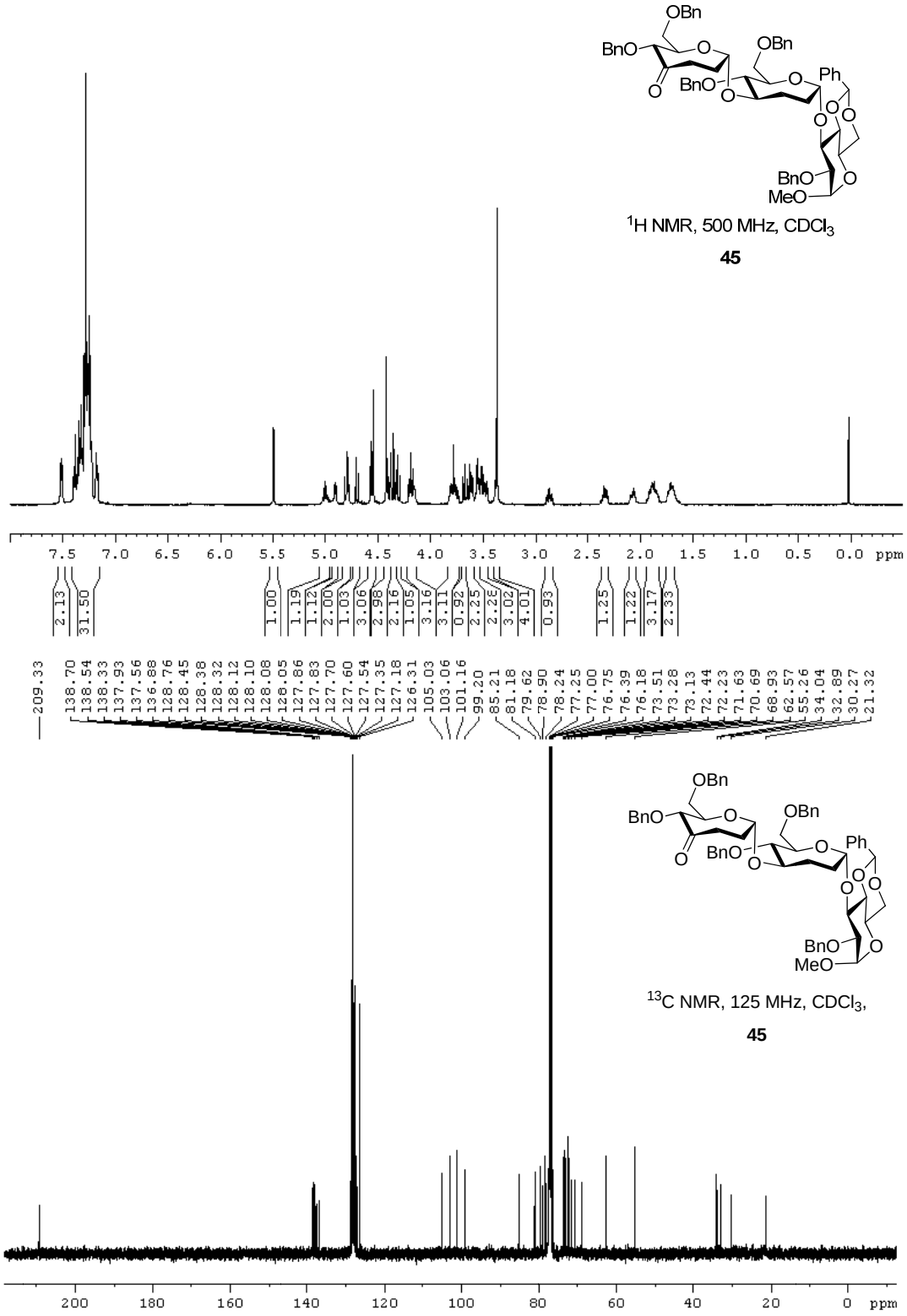
44





^{13}C NMR, 100 MHz, $CDCl_3$,

44


OBn
BnO
OBn
O
BnO
Ph
BnO
MeO
^{1}H NMR, 500 MHz, CDCl$_3$
45
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.13 31.50 1.00 1.19 1.12 2.00 1.03 3.06 2.98 2.16 1.05 3.16 3.11 0.92 2.25 2.25 3.02 4.01 0.93 1.25 1.22 3.17 2.33
209.33 138.70 138.54 138.33 137.93 137.56 136.88 128.76 128.45 128.38 128.32 128.12 128.10 128.08 128.05 127.86 127.83 127.70 127.60 127.54 127.35 127.18 126.31 105.03 103.06 101.16 99.20 85.21 81.18 79.62 78.90 78.24 77.25 77.00 76.75 76.39 76.18 73.51 73.28 73.13 72.44 72.23 71.63 70.69 68.93 62.57 55.26 34.04 32.89 30.27 21.32
^{13}C NMR, 125 MHz, CDCl$_3$,
45
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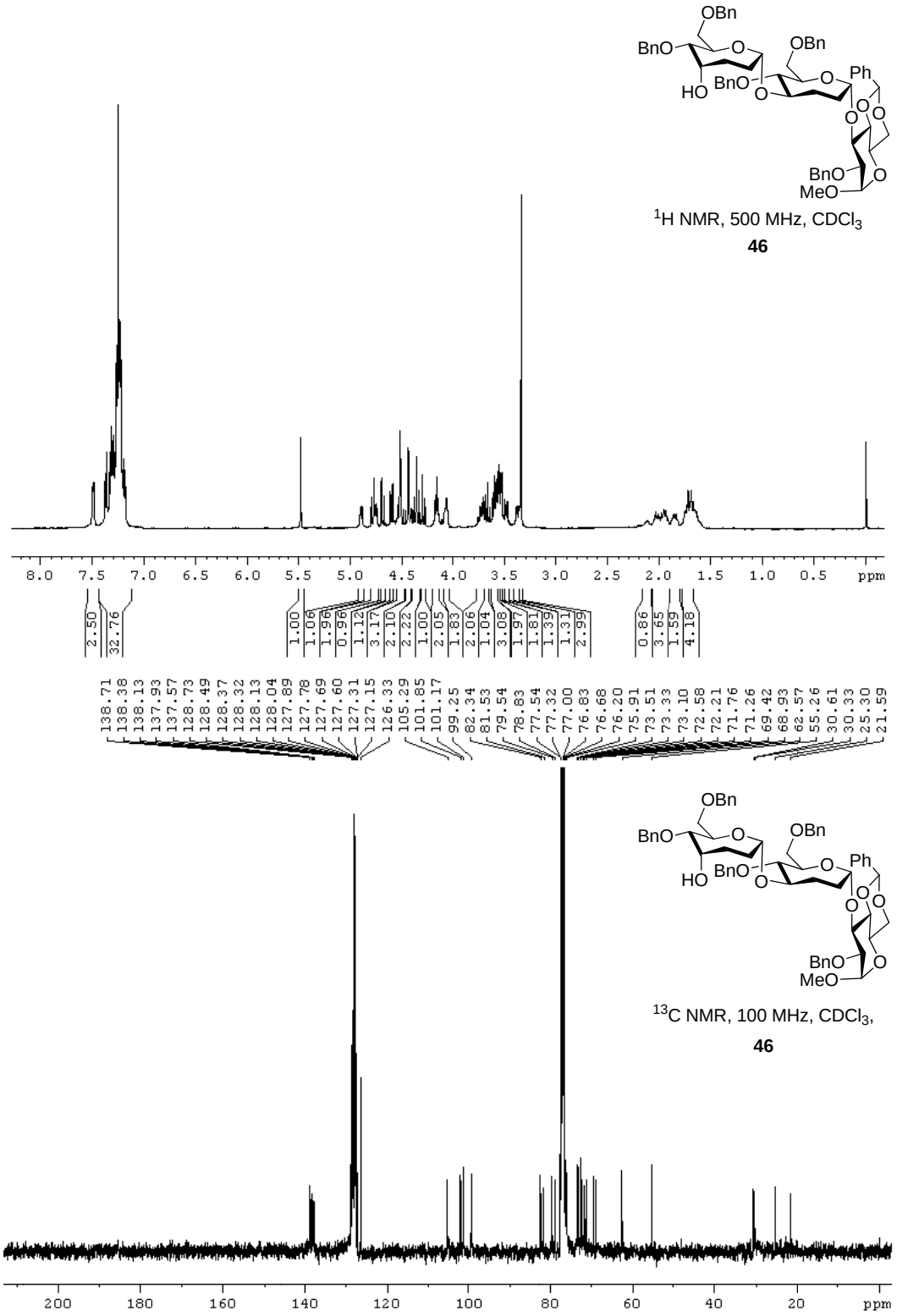
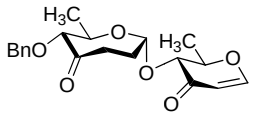


^{1}H NMR, 500 MHz, $CDCl_3$

46

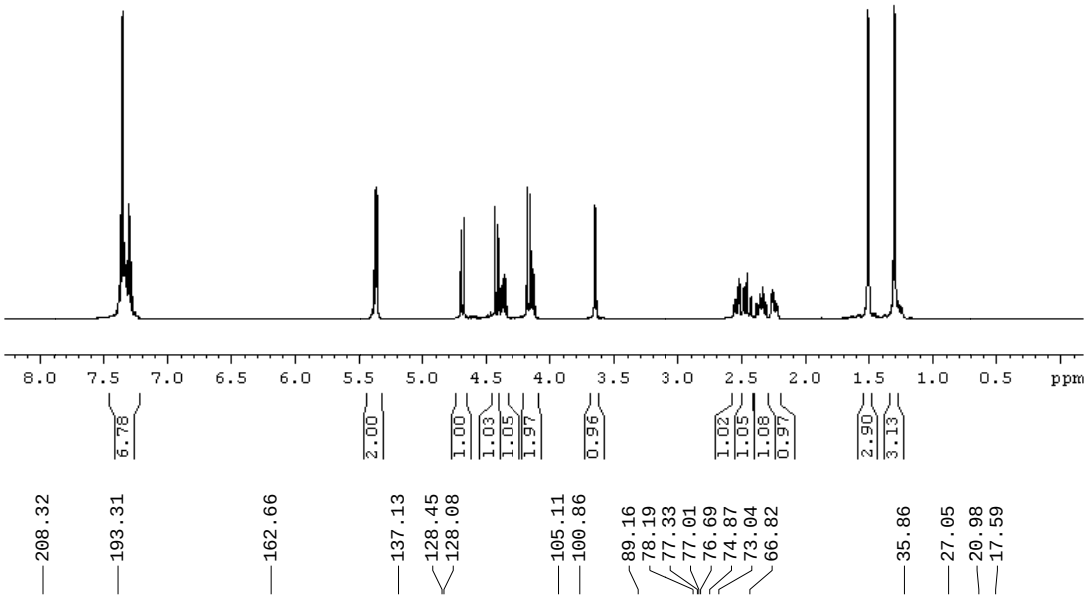
^{13}C NMR, 100 MHz, $CDCl_3$,

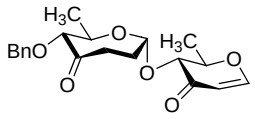
46



^{1}H NMR, 500 MHz, $CDCl_3$

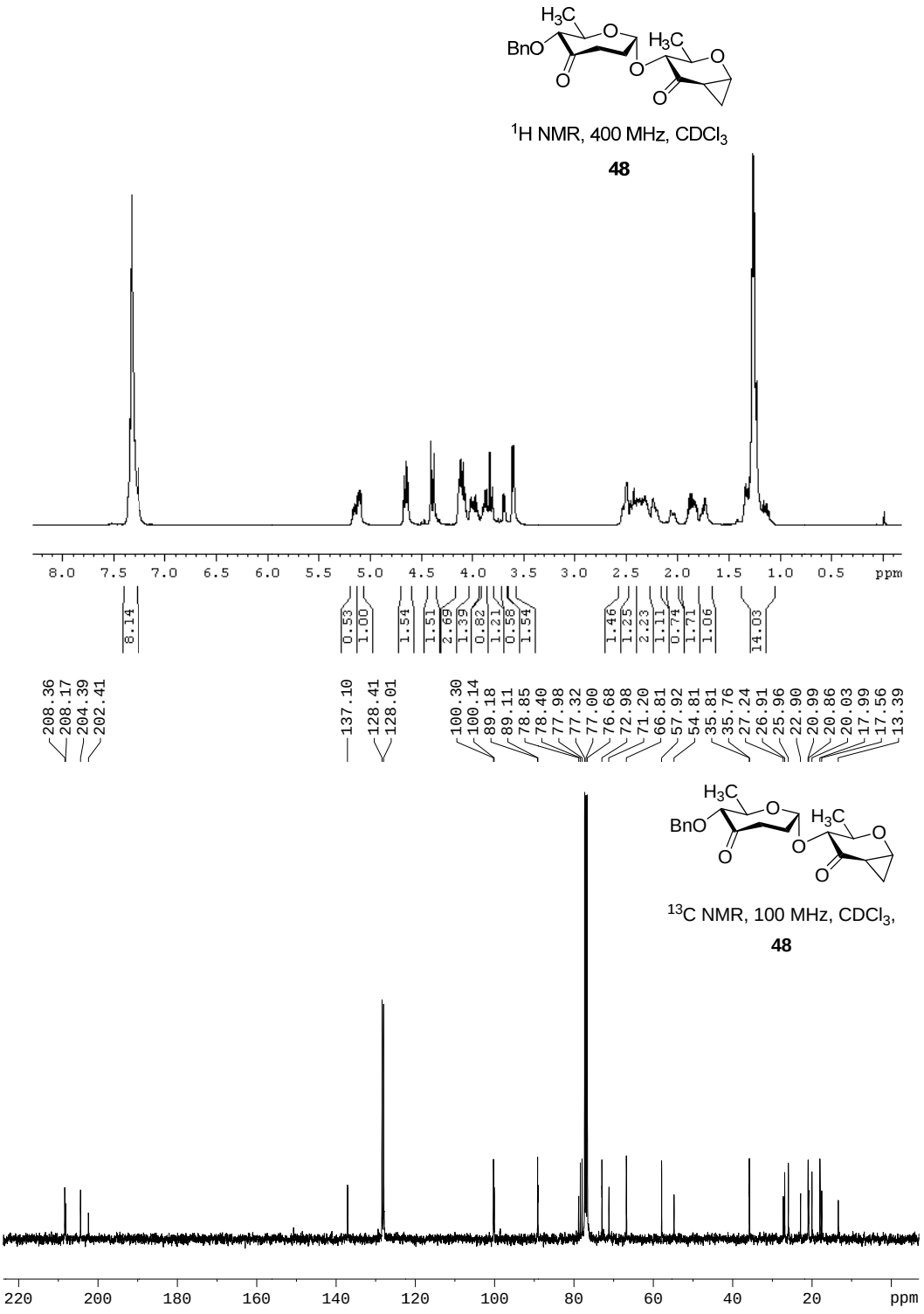
47

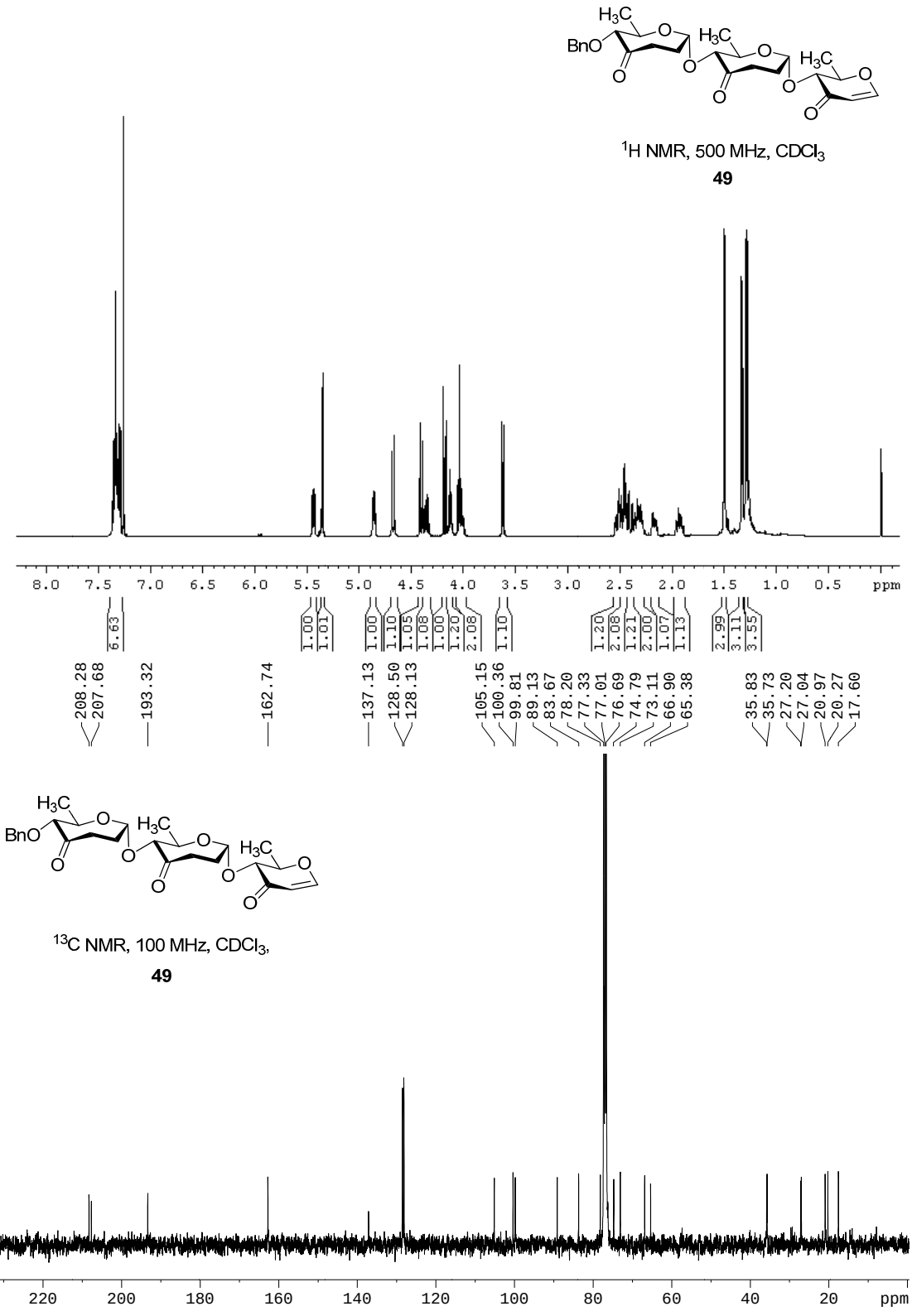


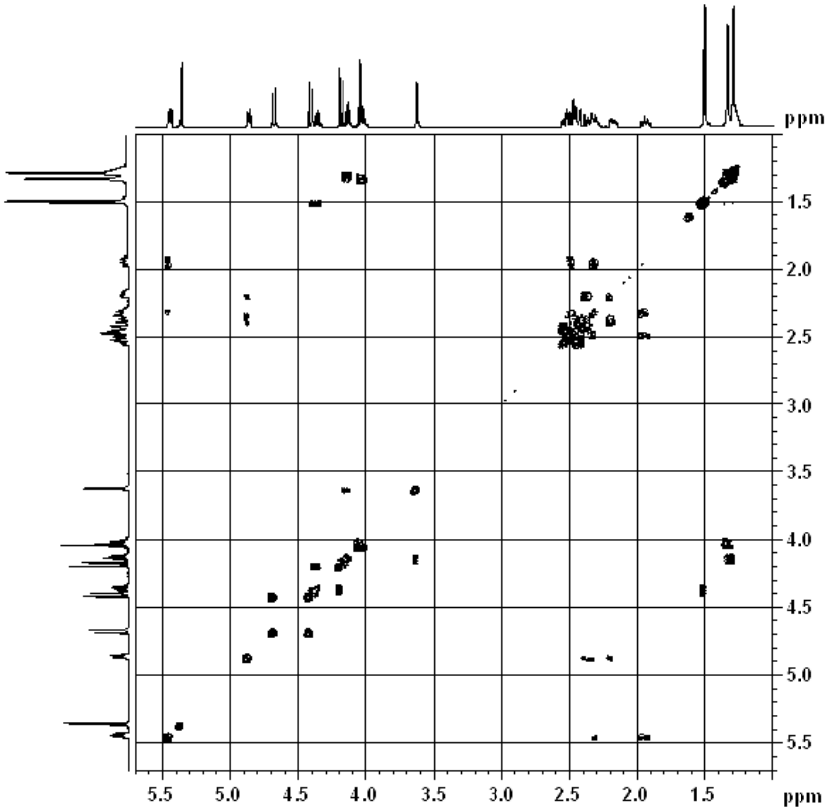


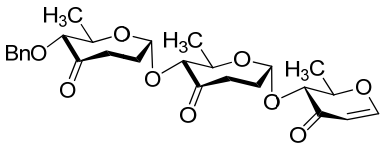
^{13}C NMR, 100 MHz, $CDCl_3$,

47


^{1}H NMR, 400 MHz, $CDCl_3$
48
8.14
0.53
1.00
1.54
1.51
2.60
1.39
0.82
1.21
0.58
1.54
1.46
1.25
2.23
1.11
0.74
1.71
1.06
14.03
208.36
208.17
204.39
202.41
137.10
128.41
128.01
100.30
100.14
89.18
89.11
78.85
78.40
77.98
77.32
77.00
76.68
72.98
71.20
66.81
57.92
54.81
35.81
35.76
27.24
26.91
25.96
22.90
20.99
20.86
20.03
17.99
17.56
13.39
^{13}C NMR, 100 MHz, $CDCl_3$,
48

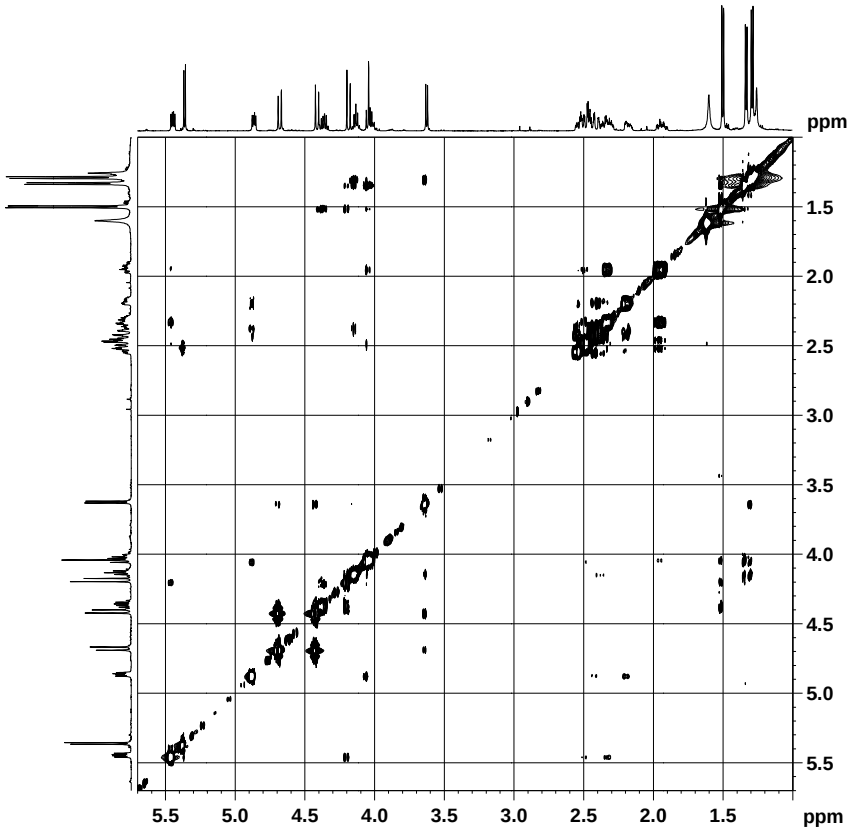

^{1}H NMR, 500 MHz, CDCl$_3$
49
^{13}C NMR, 100 MHz, CDCl$_3$,
49
ppm

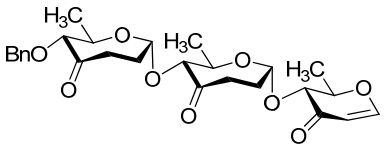




^{1}H-^{1}H COSY NMR, 500 MHz, $CDCl_3$

49





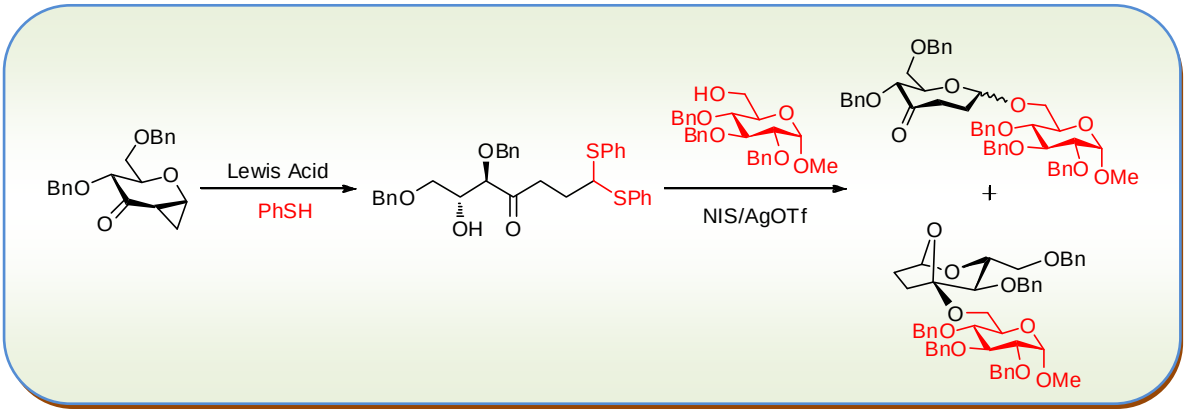
^{1}H-^{1}H NOESY, 500 MHz, $CDCl_3$

49

CHAPTER 4

A One-Pot Septanoside Formation and Glycosylation of Dithioacetals Derived from 1,2-Cyclopropanated Sugars

ABSTRACT: An interesting reaction involving sugar derived 1,2-cyclopropa-3-pyranones with thiols in presence of a Lewis acid to the formation of heptanose-based dithioacetals is discovered. The reaction proceeds through the ring opening of cyclopropane with thiol to give oxepane which further proceed to form the dithioacetal. A series of dithioacetal derivatives were synthesized by using various 1,2-cyclopropanated sugars with different thiols. In addition, a novel one-pot septanoside formation and glycosylation using these dithioacetal donors with diverse carbohydrate-drived *O*-nucleophiles to provide septano-hexose disaccharides is revealed.



4.1 Introduction

Ring expanded versions of hexoses, commonly known as septanoses or carbohydrate-based oxepanes, drew special interest in recent years due to their significant applications in mimicking the natural glycans, like furanoses and pyranoses.[1] Recent biological studies

provide the evidence that septanoside derivatives have the ability to bind proteins.[2] As a result several protocols for the preparation of septanoses[3] have been developed in the last decade. A major portion of septanosides that have been synthesized till date lack a substituent at C-6 position. Moreover, very few methods are available in literature for the synthesis of septanose containing di- and oligosaccharides.[4] Out of several methods, glycosylation of 1,2-anhydroseptanosides,[5] use of *S*-phenyl septanosides as glycosyl donors[6] and solvolytic ring opening of 1,2-cyclopropanated sugars with glycosyl acceptors[7] were found to be some promising technologies for the synthesis of septano-oligosaccharides. These synthetic methods for the septanoside derivatives and septano-hexoses are discussed in chapter 1 of this thesis (section 1.4).

In continuation of our efforts in developing general protocols for the preparation of septanoses and septano-oligosaccharides,[8] we attempted to prepare septanoside derived thio-glycoside donors[6] from 3-oxo-1,2-cyclopropanated pyranose derivatives. However, this effort led us to serendipitous discovery of a methodology to synthesize heptanose derived dithioacetals from 1,2-cyclopropanated sugars. Previously, dithioacetal derivative of glucose has been converted to septanose derivative in low yield.[9] Later, Hindsgaul *et al.,* used appropriately protected *O*,*S*-acetal as precursor for the synthesis of a septanoside.[10]

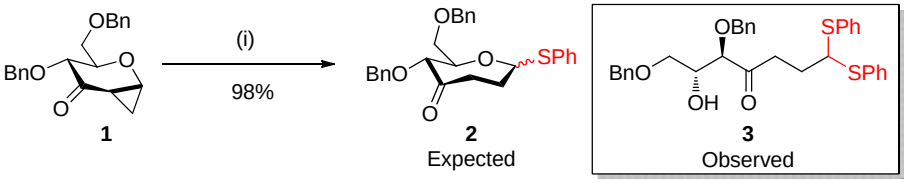
These observations prompted us to use the obtained dithioacetals as glycosyl donors in septanoside synthesis. Thus, herein, we present the synthesis of carbohydrate-based dithioacetal donors from 3-oxo-1,2-cyclopropanated pyranoses as well as a one-pot intramolecular acetal exchange, followed by glycosylation to afford the septanoside containing disaccharides.

4.2 Results and Discussion

4.2.1 Synthesis of novel acyclic dithioacetal donors

The preparation of sugar-derived 1,2-cyclopropa-3-pyranones[8] from various benzyl-protected glycals is discussed in chapter 3 of this thesis (section 3.2). Toward the synthesis of thio-septanoside donors, D-glucose-derived 3-oxo-1,2-cyclopropane **1** was reacted with thiophenol (1.2 equiv.) in presence of TMSOTf (0.2 equiv.) to obtain the 3-oxo-septanose donor **2**. However, the reaction provided the dithioacetal **3** as the only product in 52% yield

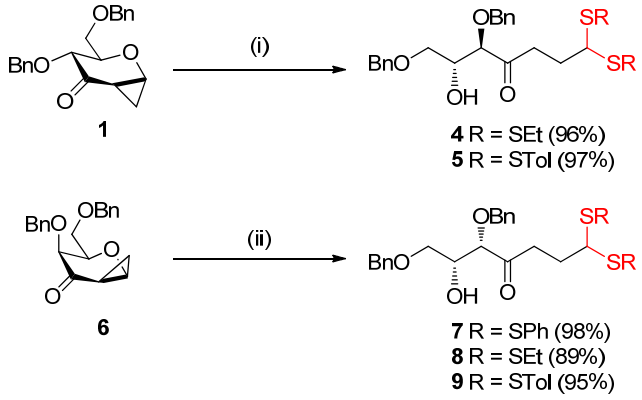
and no trace amount of **2** was observed. Increasing the equivalents of thiophenol (2.2 equiv.) provided dithioacetal in 98% yield (Scheme 4.1). The structure of the dithioacetal **3** was deduced based on ^{1}H, ^{13}C NMR chemical shift values as well as COSY NMR analysis.



Reagents and Conditions: (i) PhSH (2.2 equiv.), TMSOTf (0.2 equiv.), CH_2Cl_2, -10 ^{o}C, 30 min.

Scheme 4.1: Synthesis of acyclic dithioacetal derivative from 1,2-cyclopropanated sugar

Furthermore, TMSOTf-mediated acetal formation of cyclopropane **1** with EtSH or TolSH provided the corresponding dithioacetals **4** and **5**, respectively, in excellent yield. To investigate the generality of the reaction 3-oxo-1,2-cyclopropanated D-galactose derivative **6** was reacted with PhSH or EtSH or TolSH. In all instances, the reaction provided the corresponding dithioacetals **7**, **8** and **9** in excellent yield (Scheme 4.2). The structures of all the sugar-derived dithioacetals were confirmed based on ^{1}H, ^{13}C and COSY NMR spectral observations. Although, the formation of thioglycoside donors (cyclic thioacetals) by electrophilic ring opening of 1,2-cyclopropanated sugars is known, to the best of our knowledge, this is the first protocol on the formation heptanosyl dithioacetals from 1,2-cyclopropanated donor-acceptor cyclopropanes.

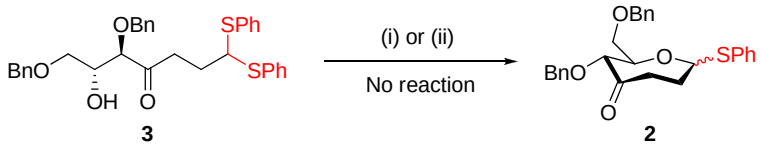


Reagents and Conditions: (i) RSH, TMSOTf, CH_2Cl_2, -10 ^{o}C, 30 min.

Scheme 4.2: Synthesis of acyclic dithioacetal derivatives

4.2.2 Discovery of the Glycosylation Reaction

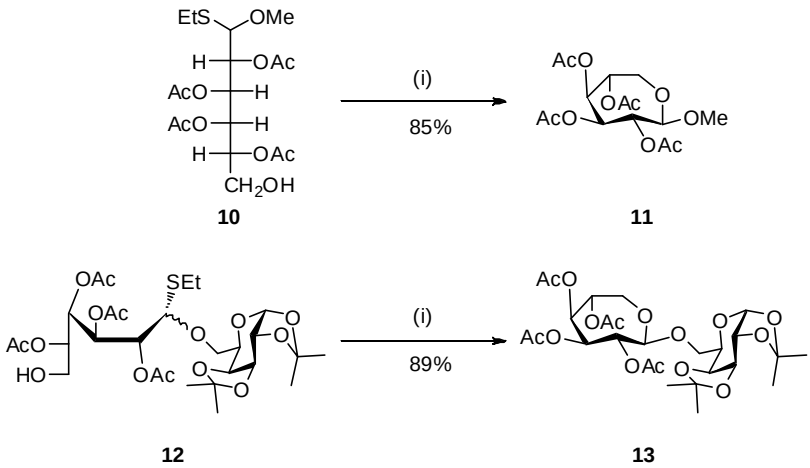
We further investigated whether the obtained dithioacetal **3** can be converted to the expected thioglycoside **2** in presence of an electrophile. Thus, dithioacetal **3** was treated with *N*-iodosuccinimide (NIS) in CH_2Cl_2 in presence of 4 Å molecular sieves at -10 °C. However, this reaction also did not provide the expected thioglycoside **2**. The same reaction in presence of NIS/AgOTf also failed to give the **2** (Scheme 4.3).



Reagents and Conditions: (i) NIS, CH_2Cl_2, -10 °C; (ii) NIS, AgOTf (20 mol%), CH_2Cl_2, -45 °C.

Scheme 4.3: Attempts to synthesis of thioseptanosyl donor from acyclic dithioacetal

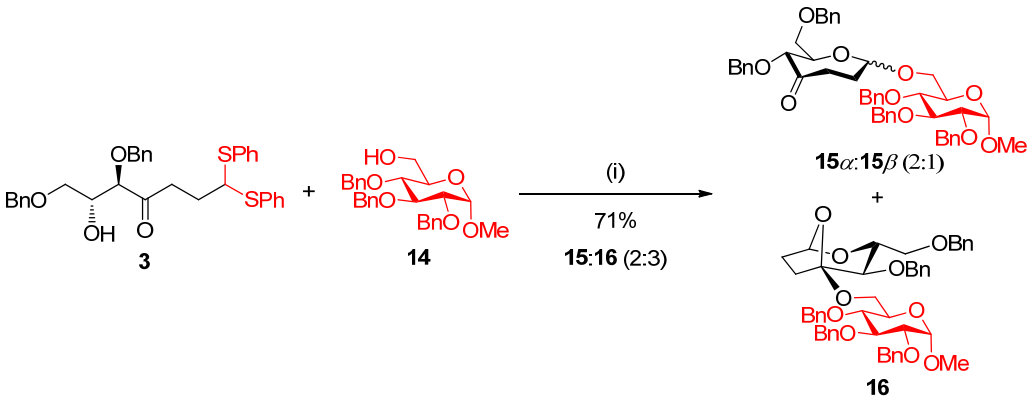
Then, we planned to use the acyclic dithioacetals directly as glycosyl donors instead of preparing thioseptanosyl donors. In literature, only two reports are available for the synthesis of septanosides from the acyclic acetal derivatives.[9,10] Hindsgaul reported the synthesis of disaccharides containing D-septanosyl residues from acyclic hexose-derived *O,S*-acetals in presence of an electrophile.[10] The treatment of *O,S*-acetal derivatives **10**, **12** with NIS/TfOH gave the seven-membered cyclic sugars **11**, **13** in excellent yield as single diastereomer (Scheme 4.4).



Reagents and Conditions: (i) NIS/TfOH, ethane, -30 °C to rt, 1 h.

Scheme 4.4: Synthesis of septanoside derivatives from hexose-derived *O,S*-acetals

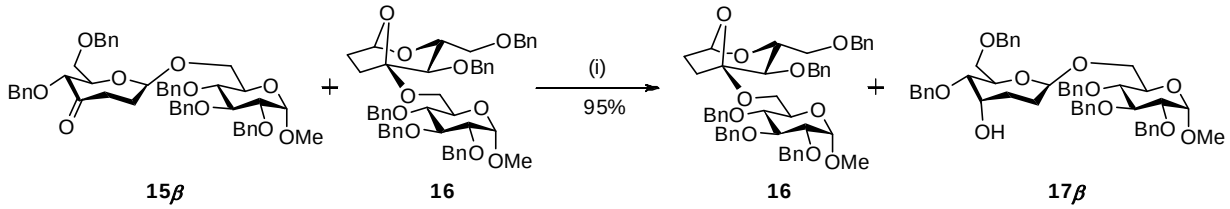
On the basis of the Hindsgaul report[10], we envisaged that the dithioacetals may undergo intramolecular cyclization in presence of an electrophile to provide the thioseptanosyl derivative as an intermediate which will further participate in glycosylation with nucleophiles to form septano-hexoses. In view of that, acyclic dithioacetal **3** was treated with glycosyl acceptor **14**[11] in presence of NIS and catalytic AgOTf (20 mol%) at –45 °C.



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Scheme 4.5: Synthesis of septanohexoses using acyclic dithioacetal donor

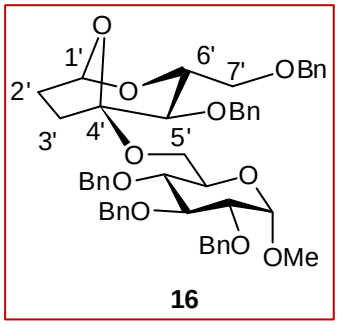
The reaction produced the disaccharide **15** along with the bridged bicyclic glycoside derivative **16** in 2:3 ratio in excellent yield (Scheme 4.5). The silica-gel purification of crude products **15** and **16** gave the **15***α* as a pure product whereas **15***β* as a mixture along with **16**. Thus, the mixture of **15***β* and **16** under the selective reduction with lithium tri-*tert*-butoxyaluminumhydride in ethanol at -78 °C might provide the septano-hexose derivative **17***β* and the bicyclic compound **16** as a single compound. As expected, **15***β* upon reduction provided alcohol **15***β* whereas compound **16** was found to be intact and both the compounds were separable by column chromatography (Scheme 4.6).



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

Scheme 4.6: Synthesis of septanosyl disaccharide alcohol

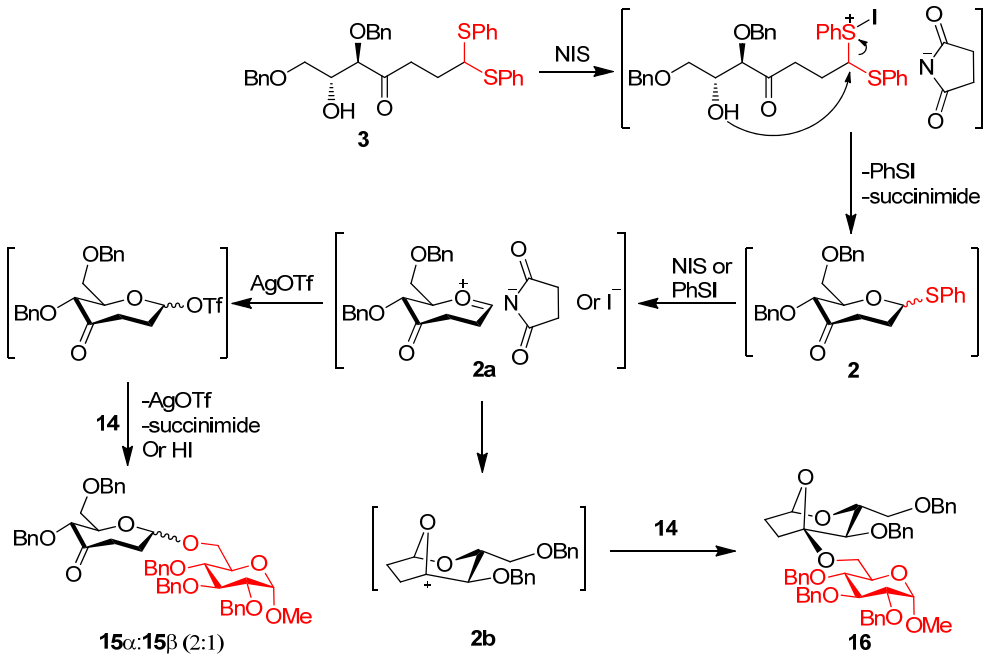
The stereochemistry of septanohexoses **15**α and **17**β were assigned based on ^{13}C anomeric chemical shift values 100.6 ppm and 105.3 ppm respectively. As mentioned in chapter 3, chemical shift values of anomeric carbon in septanosides appears normally at 99 to 104 ppm for α-septanosides, whereas 104-111 ppm for β-septanosides.[11] The structure of bicyclic compound **16** was deduced based on ^{13}C NMR. The chemical shift value of C4' in ^{13}C NMR appeared at 109.3 ppm, which is normally observed for quatnery carbon of sugar-derived acetals.



16

4.2.3 Plausible Mechanistic Pathway

The formation of **16** can be speculated by an interesting intramolecular septanoside formation followed by glycosylation reaction. As shown in scheme 4.7, activation of the dithioacetal **3** with NIS would provide the septanosyl donor **2** by an intramolecualr 7-*exo*-cyclisation reaction. Further activation of the thioglycosyl donor **2** in presence of NIS or phenylsulfenyl

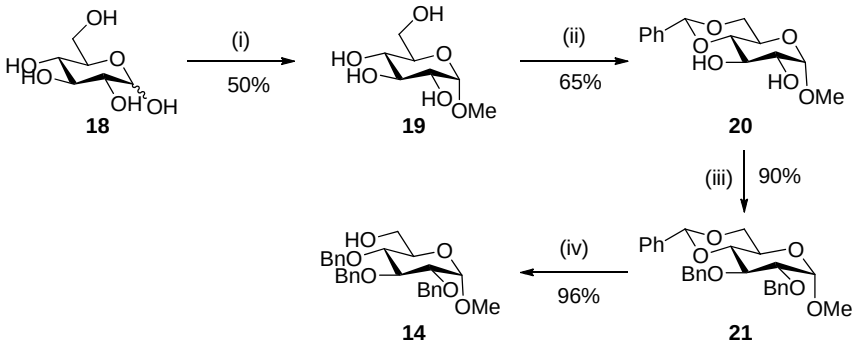


Scheme 4.7: Proposed mechanism for the formation of septano-hexose disaccharide derivatives **11** and **12** from dithioacetal **3**.

iodide would lead to the formation of the oxonium ion intermediate **2a** that will be trapped by triflate (in presence of silver triflate) and undergo glycosylation in presence of acceptor **14** to give the hexano-septanoside **15**α and **15***β*. On the other hand, trapping of the oxonium ion **2a** by carbonyl oxygen in an intramolecular fashion would lead to the formation of a second tertiary carbocation intermediate **2b** which upon reaction with glycosyl acceptor **14** would give the unexpected disaccharide derivative **16** as a single diastereomer. Carrying out the reaction in the absence of AgOTf also provided disaccharide derivatives **15** and **16,** however in a prolonged period of time, 48 hr, in low yield.

4.2.4 Scope of the reaction

Encouraged with this result, the glycosylation reaction was performed by using dithioacetal donors **3** and **7** with various carbohydrate-derived acceptors. The synthesis of glycosyl acceptors except methyl 2,3,4-tri-*O*-benzyl α-D-glucopyranoside **14**[12], is described in chapter 2 and 3 (section 2.2 and section 3.2). The acceptor **14** was synthesized from D-glucose in four steps with excellent yield. The D-glucose **18** with hot methanolic hydrogen chlodride provided the methyl α-D-glucopyranoside **19**, which on benzylidene protection with benzaldehyde dimethyl acetal and *p*-toluenesulfonicacid in DMF gave the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **20**. Benzylation of C2 and C3 hydroxyl groups in **20** with sodium hydride and benzyl bromide in DMF produced the methyl 2,3-di-*O*-benzyl-4,6-benzylidene-α-D- glucopyranoside **21**. Reductive ring-opening of benzylidene acetal of **21** with BH_3·THF/TMSOTf in CH_2Cl_2 yielded **14** as a single regioisomer (Scheme 4.8).

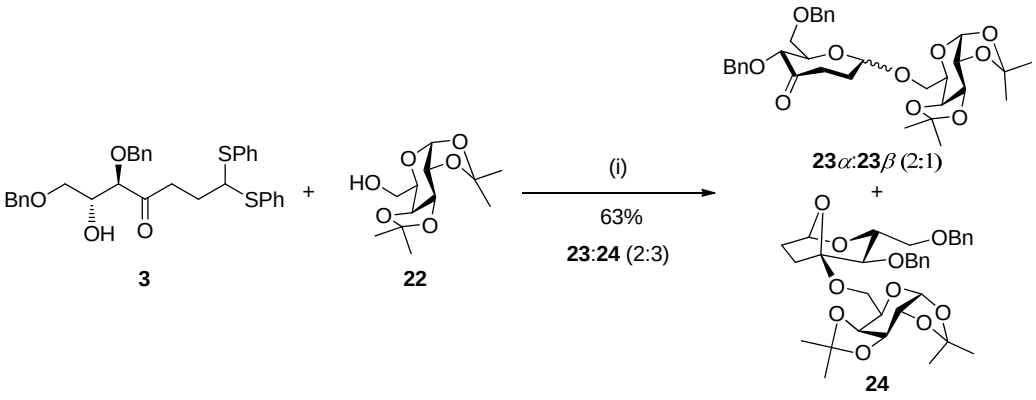


Reagents and Conditions: (i) MeOH/HCl, reflux, 16 h; (ii) $PhCH(OMe)_2$, PTSA, DMF,60 ^oC, 2 h; (iii) BnBr, NaH, DMF, TBAI, 10 h; (iv) BH_3·THF, TMSOTf, CH_2Cl_2, rt, 4 h.

Scheme 4.8: Synthesis of methyl 2,3,4-tri-*O*-benzyl α-D-glucopyranoside **14** from D-glucose

Glycosylation reaction using sugar acceptors possessing primary alcohol

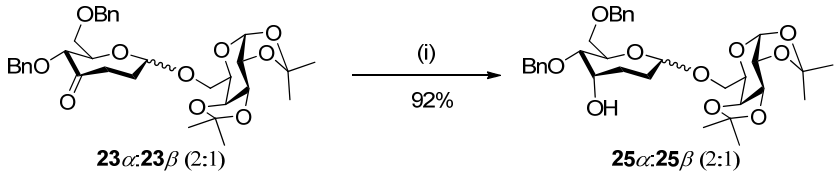
The aforementioned glycosylation reaction was extended to dithioacetal donor **3** with 1,2;3,4-di-*O*-isopropylidene-α-D-galactose **22** in presence of NIS/AgOTf in dichloromethane at -45 °C. The reaction proceeded smoothly and provided septano-hexoses **23** as an anomeric mixture along with bridged bicyclic derivative **24** in 63% yield (Scheme 4.9).



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Scheme 4.9: Synthesis of septanohexoses using acyclic dithioacetal donor **3** and glycosyl acceptor **22**

The crude product mixture **23** and **24** were also obtained as the inseparable mixture by silica-gel column chromatography. By reduction with $LiAl(O^tBu)_3H$ in ethanol, **23** was converted to septano-hexose alcohol **25**. Anomeric mixture **25α, 25*β*** and bicyclic derivative **24** were purified as single diastereomers by silica-gel column chromatography and their structures were assigned (Scheme 4.10).

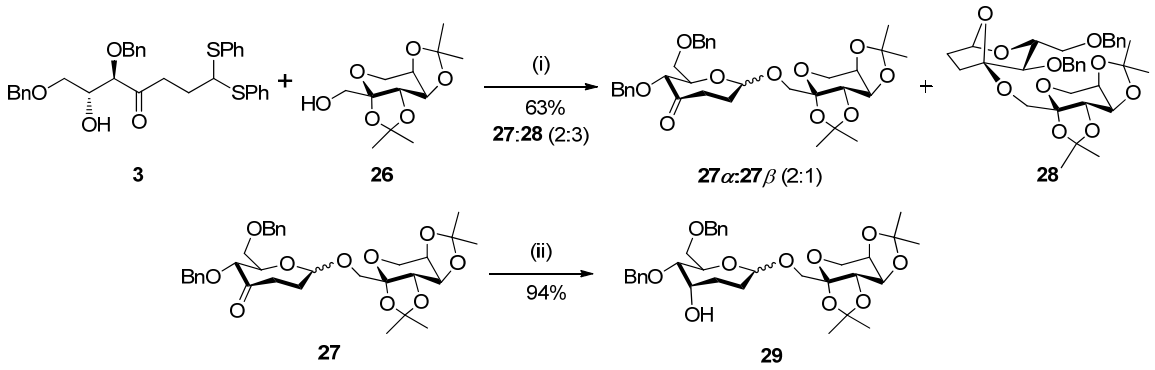


Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

Scheme 4.10: Reduction of septano-hexose ketones with $LiAl(O^tBu)_3H$

Similarly, acyclic dithioacetal donor **3** was treated with 2,3;4,5-di-*O*-isopropylidene-α-D-fructopyranose **26** in presence of NIS/AgOTf in dichloromethane at -45 °C. This reaction

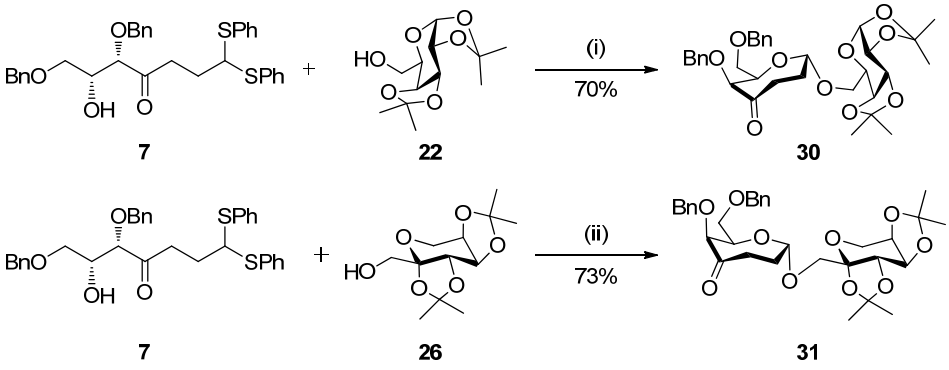
also provided septano-hexoses **27** (anomers) and bicyclic glycoside **28** as an inseparable mixture. However, **27** was also converted into septano-hexose alcohol **28** by the reduction with $LiAl(O^tBu)_3H$ in ethanol. The silica-gel column chromatography of product mixture (**29** and **28)** provided the **28** as a pure compound while **29** as an inseparable anomeric mixture (Scheme 4.11).



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h, (ii) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

Scheme 4.11: Synthesis of septano-hexoses using acyclic dithioacetal donor **3** with glycosyl acceptor **26**

Interestingly, performing the glycosylation reaction between D-galactose-based dithioacetal donor **7** and acceptors **22** and **26** provided the disaccharides **30** and **31** as a single diasteromer with α-configuration at the newly formed glycosidic centre. No trace of bridged glycosides



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

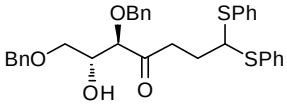
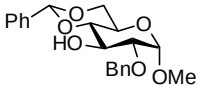
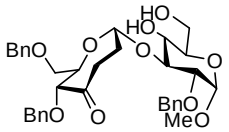
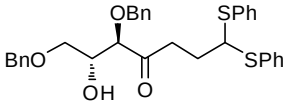
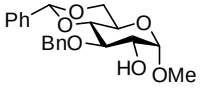
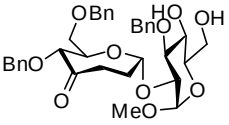
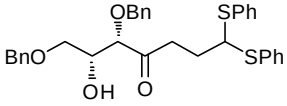
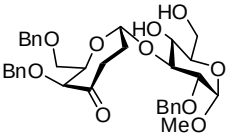
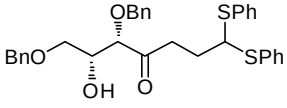
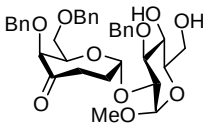
Scheme 4.12: Synthesis of septano-hexoses using D-galactose based dithioacetal donor **7**

was observed in these reactions. The probable reason for this may be due to the steric hindrance for the sugar acceptor to reach the carbonyl centre because of the presence of axial benzyl group in galactose derived septanose moiety (Scheme 4.12).

Glycosylation reaction using sugar acceptors possessing secondary alcohol

The glycosylation reaction of dithioacetal donors with glycosyl acceptors having the hydroxyl group at C3 and C2 positions also provided the septano-hexoses in good yields with high stereoselectivity. The reaction of D-glucose-derived dithioacetal **3** as a glycosyl donor with methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **32** as an acceptor in presence of NIS/AgOTf provided the septano-hexose derivative **33** in 61% yield as a single diastereomer with α-configuration (Table 4.1, entry 1). Loss of benzylidene protecting group was observed in the reaction due to the mild acidic conditions occurring by the formation of hydrogen iodide in the reaction mixture. Similarly, the glycosylation of donor **3** with accept-

Table 4.1: Synthesis of septano-hexose disaccharides from acyclic dithioacetal donors

entry	dithioacetal donor	glycosyl acceptor	septano-hexose derivatives (%)
1	 **3**	 **32**	 **33** (61)
2	 **3**	 **34**	 **35** (69)
3	 **7**	**32**	 **36** (71)
4	 **7**	**34**	 **37** (73)

-or **34** gave the septano-hexose derivative **35** with 69% yield as a single diastereomer (Table 4.1, entry 2). In addition, D-Galactose-derived dithioacetal **7** was also very reactive with the acceptors having hydroxyl group at C2 and C3. The treatment of **7** as donor with acceptors **32** and **34** gave rise to septano-hexoses **36** and **37** in excellent yield as a single diastereomer with α-selectivity (Table 4.1, entry 3 and 4). To the best of our knowledge this is the first method on the use of dithioacetals as glycosyl donors in glycosylation reaction to produce the septano-hexose derivatives. Further application of these novel sugar units in organic synthesis as well as in oligosaccharide formation is in progress.

4.3 Summary and Conclusion

Preparation of heptanose derived dithioacetals from 1,2-cyclopropanated sugars is discovered. Further, an interesting one-pot intramolecular cyclization of dithioacetals to give septanosides followed by glycosylation, in presence of a glycosyl acceptor, to provide septano-hexoses is revealed. A plausible mechanism for the one-pot reaction is proposed and the generality and stereoselectivity of the glycosylation reaction have been investigated. Further application of these dithioacetals in oligosaccharide synthesis and preparation of carbohydrate mimics is under progress.

4.4 Experimental Section

4.4.1 Materials and Methods

Chemicals and solvents were purchased from the local suppliers and Sigma-Aldrich® chemical company. Solvents were used in the reactions after distilled over the dehydrated agents. 4 Å Molecular sieves were used in the reactions after crushed and activated at 400 ^{o}C for 1 h. All the reactions were carried out under N_2 or Ar conditions and monitored by the thin layer chromatography (TLC) using silica-gel on aluminum plates (GF_{254}) by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection. Silica-gel (100-200 mesh) was used for column chromatography to purify the all the compounds. ^{1}H, ^{13}C, DEPT spectra were recorded on Bruker® 400 MHz and 500 MHz spectrometers in $CDCl_3$. ^{1}H NMR chemical shifts were reported in parts per million (ppm) (δ) with TMS as internal standard (δ 0.00) and ^{13}C NMR were reported in chemical

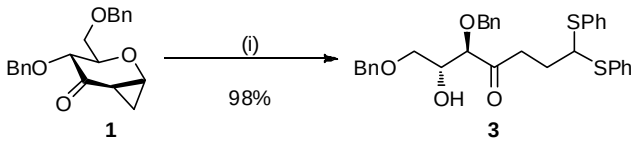
shifts with solvent reference ($CDCl_3$, δ 77.00). High resolution mass spectra (HRMS) were recorded on Bruker® maXis spectrometer.

4.4.2 Experimental Procedures and Spectral Data

(4.4.2.1) General procedure (A): Synthesis of dithio-acetal derivatives from sugar-derived 1,2-cyclopropa-3-nones.

Thioalcohol (RSH) (0.66 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.06 mmol) were added to the stirred solution of sugar-derived 1,2-cyclopropa-3-pyranone (0.3 mmol) in CH_2Cl_2 (5 mL) at –10 °C. The reaction mixture was stirred for 30 min and quenched with the saturated $NaHCO_3$ solution (15 mL) at same temperature. Then, the solution was warmed to room temperature and extracted with CH_2Cl_2 (15 mL X 2). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulted crude product was purified by silica-gel column chromatography (ethyl acetate/hexane) to afford pure dithio-acetal derivative.

(4.4.2.2) (5R,6R)-5,7-bis(benzyloxy)-6-hydroxy-1,1-bis(phenylthio)heptan-4-one (3):



Reagents and Conditions: (i) PhSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **3** was synthesized by following the general procedure **(A)** with D-glucose-derived 1,2-cyclopropa-3-pyranone **1** (100 mg, 0.295 mmol), PhSH (66.7 µL, 0.649 mmol) and TMSOTf (10.6 µL, 0.059 mmol). The reaction mixture was stirred for 30 min at –10 °C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to give the compound **3** (161 mg, 98% yield) as a thick gum. R_f = 0.67 (3:7 ethyl acetate/hexane).

IR (neat): ν_{max}/cm^{-1} 3463, 3057, 3030, 2915, 2854, 1715, 1578, 1473, 1435, 1358, 1090, 1030, 739, 701.

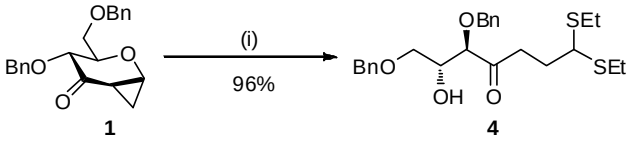
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.46 (m, 4H), 7.22 – 7.34 (m, 16H), 4.54 – 4.57 (d, 1H, *J* = 11.6 Hz), 4.41 – 4.50 (m, 4H), 4.04 (s, 1H), 3.87 – 3.89 (d, 1H, *J* = 6.4 Hz), 3.55 –

3.59 (dd, 2H, *J* = 10 Hz, *J* = 5.6 Hz), 2.90 – 2.95 (m, 2H), 2.57 (s, 1H), 2.07 – 2.13 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 137.5, 136.9, 133.7, 132.6, 132.5, 128.8, 128.4, 128.3, 128.0, 127.7, 127.6, 84.1, 73.3, 73.1, 71.0, 69.9, 57.1, 36.4, 28.9.

HRMS (ESI) calcd for $C_{33}H_{34}O_4S_2$+H 559.1977, found 559.1976.

(4.4.2.3) (5R,6R)-5,7-bis(benzyloxy)-1,1-bis(ethylthio)-6-hydroxyheptan-4-one (4):



1 **4**

Reagents and Conditions: (i) EtSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **4** was synthesized by following the general procedure **(A)** with D-glucose-derived 1,2-cyclopropa-3-pyranone **1** (110 mg, 0.325 mmol), EtSH (51.6 µL, 0.715 mmol) and TMSOTf (11.7 µL, 0.065 mmol). The reaction mixture was stirred for 30 min at –10 °C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to provide compound **4** (144 mg, 96% yield) as a thick gum. R_f = 0.58 (3:7 ethyl acetate/hexane).

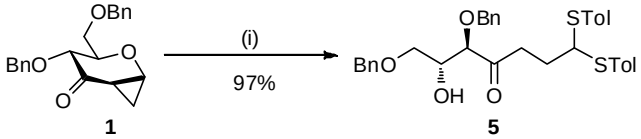
IR (neat): $\bar{\upsilon}$ (cm^{-1}) 3446, 3090, 3057, 3024, 2969, 2926, 2860, 1715, 1495, 1452, 1402, 1364, 1265, 1210, 1095, 1030, 734, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.26 (m, 10H), 4.53 – 4.56 (d, 1H, *J* = 11.6 Hz), 4.44 – 4.47 (d, 1H, *J* = 11.6 Hz), 4.37 – 4.41 (dd, 2H, *J* = 11.6 Hz, *J* = 5.2 Hz), 3.97 – 4.01 (dd, 1H, *J* = 10 Hz, *J* = 5.2 Hz), 3.84 – 3.86 (d, 1H, *J* = 6.4 Hz), 3.71 – 3.75 (dd, 1H, *J* = 7.2 Hz, *J* = 6.8 Hz), 3.48 – 3.55 (m, 2H), 2.70 – 2.86 (m, 2H), 2.44 – 2.63 (m, 4H), 2.29 (s, 1H), 1.95 – 2.00 (dd, 2H, *J* = 13.6 Hz, *J* = 7.2 Hz), 1.14 – 1.18 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 137.6, 137.0, 128.5, 128.4, 128.1, 127.8, 84.1, 73.3, 73.1, 71.0, 70.0, 50.3, 36.8, 28.8, 24.1, 14.4.

HRMS (ESI) calcd for $C_{25}H_{34}O_4S_2$+H 463.1977, found 463.1979.

(4.4.2.4) (5R,6R)-5,7-bis(benzyloxy)-6-hydroxy-1,1-bis(*p*-tolylthio)heptan-4-one (5):



1 **5**

Reagents and Conditions: (i) EtSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **5** was synthesized by following the general procedure **(A)** with D-glucose-derived 1,2-cyclopropa-3-pyranone **1** (92 mg, 0.271 mmol), toluene-4-thiol (74 mg, 0.598 mmol) and TMSOTf (9.8 µL, 0.054 mmol). The reaction mixture was stirred for 30 min at –10 °C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to provide compound **5** (154 mg, 97% yield) as thick gum. R_f = 0.63 (3:7 ethyl acetate/hexane).

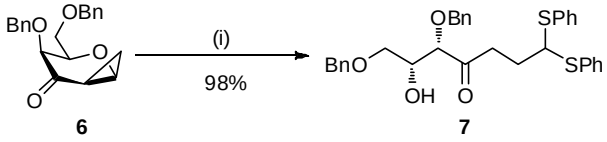
IR (neat): ῡ (cm^{-1}) 3463, 3063, 3030, 2915, 2854, 1715, 1495, 1452, 1391, 1364, 1210, 1084, 805, 745, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.35 (m, 14H), 7.07 – 7.09 (d, 4H, *J* = 7.6 Hz), 4.55 – 4.58 (d, 1H, *J* = 11.2 Hz), 4.40 – 4.50 (m, 3H), 4.33 – 4.36 (t, 1H, *J* = 6.8 Hz), 4.02 – 4.06 (dd, 1H, *J* = 10.8 Hz, *J* = 5.2 Hz), 3.87 – 3.89 (d, 1H, *J* = 6.4 Hz), 3.55 – 3.57 (dd, 2H, *J* = 5.2 Hz, *J* = 4.0 Hz), 2.84 – 2.99 (m, 2H), 2.30 (s, 6H), 2.02 – 2.08 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 137.9, 137.5, 136.9, 133.2, 129.9, 129.6, 128.4, 128.3, 128.0, 127.7, 84.1, 73.3, 73.1, 71.0, 70.0, 57.9, 36.5, 28.7, 21.1.

HRMS (ESI) calcd for $C_{35}H_{38}O_4S_2$+H 587.2290, found 587.2289.

(4.4.2.5) (5S,6R)-5,7-bis(benzyloxy)-6-hydroxy-1,1-bis(phenylthio)heptan-4-one (7):



Reagents and Conditions: (i) PhSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **7** was synthesized by following the general procedure **(A)** with D-galactose-derived 1,2-cyclopropa-3-pyranone **6** (98 mg, 0.289 mmol), PhSH (65.4 µL, 0.637 mmol) and TMSOTf (10.4 µL, 0.057 mmol). The reaction mixture was stirred for 30 min at –10 °C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to give the compound **7** (158 mg, 98% yield) as a colorless oil. R_f = 0.30 (1:4 ethyl acetate/hexane). **IR (neat):** ῡ (cm^{-1}) 3435, 3090, 3068, 3030, 2953, 2926, 2860, 1715, 1578, 1473, 1463, 1446, 1364, 1265, 1205, 1090, 1019, 734, 695.

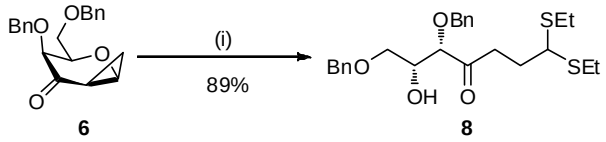
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.43 (d, 4H, *J* = 0.8 Hz), 7.20 – 7.28 (m, 16H), 4.61 – 4.64 (d, 1H, *J* = 11.6 Hz), 4.38 – 4.49 (m, 4H), 4.05 – 4.08 (d, 1H, *J* = 10.4 Hz), 3.94 (s, 1H),

3.50 – 3.54 (dd, 1H, *J* = 9.6 Hz, *J* = 5.6 Hz), 3.43 – 3.47 (dd, 1H, *J* = 9.2 Hz, *J* = 6.4 Hz), 2.83 – 2.99 (m, 2H), 2.60 – 2.62 (d, 1H, *J* = 7.2 Hz), 2.04 – 2.17 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.7, 137.5, 136.7, 133.7, 133.6, 132.5, 132.4, 128.8, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 83.8, 73.4, 73.2, 71.1, 70.2, 57.1, 36.8, 28.9.

HRMS (ESI) calcd for $C_{33}H_{34}O_4S_2$+Na 581.1796, found 581.1831.

(4.4.2.6) (5R,6R)-5,7-bis(benzyloxy)-1,1-bis(ethylthio)-6-hydroxyheptan-4-one (8):



6 8

Reagents and Conditions: (i) EtSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **8** was synthesized by following the general procedure **(A)** with D-galactose-derived 1,2-cyclopropa-3-pyranone **6** (92 mg, 0.271 mmol), EtSH (43.1 µL, 0.598 mmol) and TMSOTf (9.8 µL, 0.054 mmol). The reaction mixture was stirred for 30 min at –10 °C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to give compound **8** (111 mg, 89% yield) as a colorless oil. R_f = 0.31 (1:4 ethyl acetate/hexane).

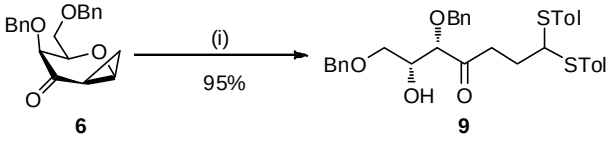
IR (neat): $\bar{\upsilon}$ (cm^{-1}) 3463, 3063, 3030, 2958, 2920, 2860, 1715, 1457, 1391, 1358, 1265, 1210, 1084, 734, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.32 (m, 10H), 4.68 – 4.71 (d, 1H, *J* = 11.2 Hz), 4.43 – 4.52 (m, 3H), 4.09 (s, 1H), 3.99 – 4.00 (d, 1H, *J* = 3.2 Hz), 3.78 – 3.81 (t, 1H, *J* = 6.8 Hz), 3.54 – 3.58 (dd, 1H, *J* = 9.6 Hz, *J* = 6.0 Hz), 3.47 – 3.51 (dd, 1H, *J* = 8.8 Hz, *J* = 6.0 Hz), 2.75 – 2.92 (m, 2H), 2.51 – 2.69 (m, 5H), 1.99 – 2.12 (m, 2H), 1.21 – 1.25 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 210.8, 137.6, 136.9, 128.4, 128.3, 128.2, 128.1, 127.7, 83.8, 73.4, 73.3, 71.1, 70.3, 50.3, 37.1, 28.8, 24.2, 24.1, 14.4.

HRMS (ESI) calcd for $C_{25}H_{34}O_4S_2$+Na 485.1796, found 485.1795.

(4.4.2.7) (5S,6R)-5,7-bis(benzyloxy)-6-hydroxy-1,1-bis(p-tolylthio)heptan-4-one (9):



6 9

Reagents and Conditions: (i) TolSH, TMSOTf, CH_2Cl_2, -10 °C, 30 min.

The compound **9** was synthesized by following the general procedure **(A)** with D-galactose-derived 1,2-cyclopropa-3-pyranone **6** (100 mg, 0.295 mmol), toluene-4-thiol (80.7 mg, 0.650 mmol) and TMSOTf (10.6 µL, 0.059 mmol). The reaction mixture was stirred for 30 min at –10 ^{o}C. The obtained crude product was purified by silica-gel column chromatography (ethyl acetate/hexane 1:3) to provide compound **9** (164 mg, 95% yield) as a colorless oil. R_f = 0.31 (1:4 ethyl acetate/hexane).

IR (neat): $\bar{\upsilon}$ (cm^{-1}) 3457, 3062, 3024, 2920, 2859, 1709, 1489, 1451, 1391 1358, 1210, 1095, 815, 733, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.34 (m, 14H), 7.07 – 7.09 (d, 4H, *J* = 7.6 Hz), 4.62 – 4.65 (d, 1H, *J* = 11.2 Hz), 4.38 – 4.47 (m, 3H), 4.33 – 4.36 (t, 1H, *J* = 6.4 Hz), 4.05 (s, 1H), 3.95 (s, 1H), 3.51 – 3.54 (dd, 1H, *J* = 9.6 Hz, *J* = 4.8 Hz), 3.44 – 3.47 (dd, 1H, *J* = 8.4 Hz, *J* = 6.0 Hz), 2.82 – 2.98 (m, 2H), 2.64 (s, 1H), 2.30 (s, 6H), 2.02 – 2.09 (m, 2H).

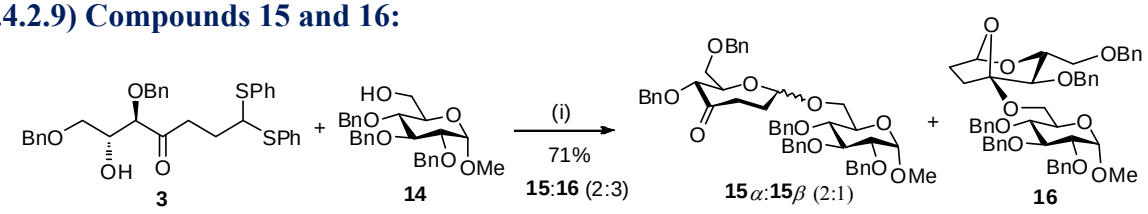
^{13}C NMR (100 MHz, $CDCl_3$): δ 210.7, 137.8, 137.5, 136.8, 133.2, 133.1, 130.0, 129.9, 129.5, 128.4, 128.3, 128.2, 128.1, 127.7, 83.8, 73.4, 73.2, 71.0, 70.2, 57.9, 36.8, 28.7, 21.0.

HRMS (ESI) calcd for $C_{35}H_{38}O_4S_2$+Na 609.2109, found 609.2110.

(4.4.2.8) General procedure (B): The one-pot cyclization and glycosylation of dithio-acetal derivatives as glycosyl donors with various glycosyl acceptors

The suspension of sugar-derived dithio-acetal (0.2 mmol), glycosyl acceptor (0.22 mmol) and 4 Å molecular sieves powder (approx. 100 mg) in dry CH_2Cl_2 (10 mL) was stirred under N_2 condition for 30 min at room temperature. After cooling the solution to –45 ^{o}C, NIS (67.4 mg, 0.3 mmol) and AgOTf (10.2 mg, 0.04 mmol) were added sequentially. Then, the reaction mixture was warmed –25 ^{o}C and stirred for 1 h at the same temperature. After completion of the reaction (by check the TLC), quenched with saturated $NaHCO_3$ solution (20 mL) at –25 ^{0}C, warmed to room temperature and extracted with CH_2Cl_2 (20 mL X 2). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution (20 mL), water (20 mL), brine (15 mL) and dried over anhydrous Na_2SO_4. The resulted crude solution was concentrated under *vacuo* and purified by silica-gel column chromatography (ethyl acetate/hexane or ethyl acetate/toluene) to give the pure septano-hexose derivatives.

(4.4.2.9) Compounds 15 and 16:



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Following the general procedure **(B)**, the compounds **15** and **16** were synthesized using D-glucose-derived dithio-acetal **3** (80 mg, 0.143 mmol), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **14** (73 mg, 0.157 mmol), NIS (40.2 mg, 0.178 mmol) and AgOTf (7.3 mg, 0.028 mmol). The reaction mixture was warmed to –45 °C to –25 °C and stirred for 1 h at –25 °C. The silica-gel column chromatography of obtained crude product with ethyl acetate in hexane (1:3) gave the compounds **15***β* and **16** (61 mg, 53% yield) as inseparable mixture and **12**α (20 mg, 18% yield) as a pure septano-hexose derivative. R_f = 0.48 (15*β* &16), 0.42 (15α) [ethyl acetate/hexane 1:3].

Compound 15α: Thick colorless gum. **IR (neat)**: ῡ (cm^{-1}) 2958, 2920, 2854, 1731, 1490, 1463, 1364, 1271, 1200, 1117, 1079, 958, 734, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.35 (m, 25H), 4.95 – 4.98 (m, 2H), 4.85 – 4.88 (d, 1H, *J* = 11.2 Hz), 4.80 (d, 1H, *J* = 3.2 Hz), 4.76 – 4.78 (d, 1H, *J* = 4.8 Hz), 4.65 – 4.68 (d, 1H, *J* = 12.4 Hz), 4.60 – 4.63 (d, 1H, *J* = 11.2 Hz), 4.55 – 4.58 (m, 2H), 4.46 – 4.49 (d, 1H, *J* = 12.4 Hz), 4.36 – 4.41 (dd, 2H, *J* = 12 Hz, *J* = 6.4 Hz), 4.15 – 4.19 (m, 2H), 3.94 – 3.99 (t, 1H, *J* = 9.2 Hz), 3.92 (d, 1H, *J* = 7.2 Hz), 3.85 – 3.90 (dd, 1H, *J* = 12 Hz, *J* = 5.2 Hz), 3.68 – 3.71 (d, 2H, *J* = 10.4 Hz), 3.48 – 3.51 (m, 2H), 3.42 – 3.47 (m, 2H), 3.35 (s, 3H), 2.54 – 2.60 (m, 1H), 2.37 – 2.43 (m, 1H), 2.21 – 2.29 (m, 1H), 1.96 – 2.02 (m, 1H).

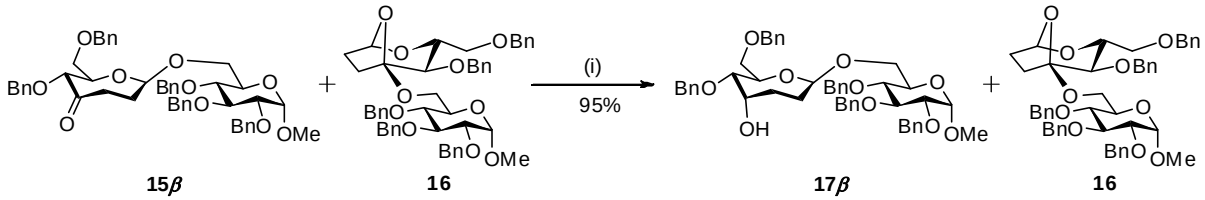
^{13}C NMR (100 MHz, $CDCl_3$): 208.5, 138.6, 138.2, 138.1, 137.9, 137.2, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 100.6, 97.8, 84.2, 82.0, 79.9, 77.7, 75.7, 74.8, 73.2, 73.0, 70.6, 69.9, 68.5, 66.4, 55.0, 35.6, 28.2

HRMS (ESI) calcd for $C_{49}H_{54}O_{10}$+Na 825.3615, found 825.3609.

(4.4.2.10) Compounds 16 and 17*β*:

To the cold (–78 °C) solution of $LiAl(O^tBu)_3H$ (31 mg, 0.124 mmol) in ethanol (2 mL) (*note: excess of the $LiAl(O^tBu)_3H$ (upto 6 eq) will not affect the selectivity of the reduction process*),

was added mixture of compounds **15***β* **&16** (50 mg, 0.062 mmol) in ethanol (1.5 mL) in dropwise fashion. The reaction mixture was stirred for 1 h at –78 °C. TLC showed that 15*β*



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

was completely consumed while the compound **16** was intact under this conditions. Then, the reaction was slowly quenched with the saturated NH_4Cl solution (15 mL), warmed to room temperature and extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed brine (10 mL) and dried (Na_2SO_4). The crude solution was concentrated under reduced pressure and purified by the silica-gel column chromatography with ethyl acetate in hexane (3:7 to 2:3) to give the pure compounds **16** (40 mg) and **17***β* (9 mg).

Compound 16:colorless semi solid. R_f = 0.70 (ethyl acetate/hexane 3:7). **IR (neat)**: $\bar{\upsilon}$ (cm^{-1}) 3062, 3029, 2920, 1714, 1495, 1456, 1358, 1210, 1150, 1084 908, 739, 700.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 – 7.36 (m, 23H), 7.14 – 7.15 (m, 2H), 5.46 – 5.47 (d, 1H, *J* = 4.5 Hz), 4.96 – 4.98 (d, 1H, *J* = 10.5 Hz), 4.80 – 4.85 (m, 3H), 4.77 – 4.79 (d, 1H, *J* = 12.0 Hz), 4.64 – 4.66 (d, 1H, *J* = 12.0 Hz), 4.59 – 4.61 (m, 2H), 4.54 – 4.56 (d, 1H, *J* = 12.5 Hz), 4.49 – 4.51 (d, 1H, *J* = 12.5 Hz), 4.42 – 4.44 (d, 1H, *J* = 11.0 Hz), 3.98 – 4.02 (t, 1H, *J* = 9.2 Hz), 3.89 – 3.92 (m, 1H), 3.79 – 3.83 (m, 2H), 3.61 – 3.64 (m, 1H), 3.50 – 3.58 (m, 5H), 3.34 (s, 3H), 2.06 – 2.17 (m, 2H), 1.90 – 1.96 (m, 1H), 1.77 – 1.83 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 138.7, 138.3, 138.2, 138.1, 138.0, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 109.3, 98.3, 97.9, 82.1, 79.8, 77.9, 75.7, 74.9, 74.3, 73.9, 73.4, 73.3, 72.9, 69.6, 69.4, 61.1, 55.0, 29.1, 23.4.

HRMS (ESI) calcd for $C_{49}H_{54}O_{10}$+Na 825.3615, found 825.3614.

Compound 17*β*: colorless oil. R_f = 0.30 (ethyl acetate/hexane 3:7). **IR (neat)**: $\bar{\upsilon}$ (cm^{-1}) 3473, 3095, 3068, 3024, 2926, 2871, 1720, 1495, 1452, 1358, 1276, 1216, 1073, 909, 739, 695.

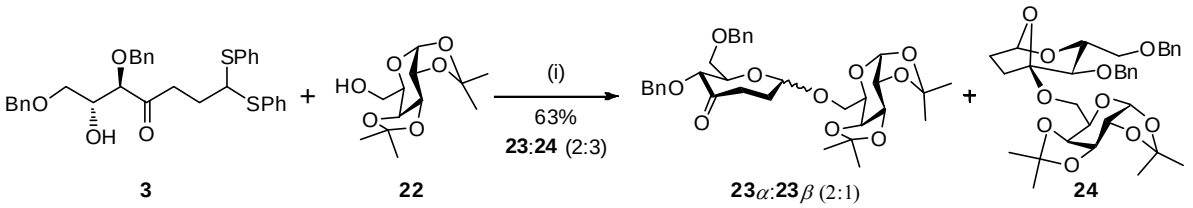
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.35 (m, 25H), 4.95 – 4.98 (d, 1H, *J* = 11.0 Hz), 4.82 – 4.84 (d, 1H, *J* = 11.0 Hz), 4.76 – 4.81 (dd, 2H, *J* = 13.5 Hz, *J* = 11.5 Hz), 4.63 – 4.65 (d,

1H, *J* = 12.0 Hz), 4.58 – 4.59 (d, 1H, *J* = 3.5 Hz), 4.49 – 4.56 (m, 6H), 4.07 – 4.09 (d, 1H, *J* = 8.5 Hz), 4.01 – 4.03 (dd, 1H, *J* = 10.5 Hz, *J* = 1.5 Hz), 3.94 – 3.98 (t, 1H, *J* = 9.5 Hz), 3.69 – 3.72 (m, 2H), 3.56 – 3.61 (m, 2H), 3.48 – 3.55 (m, 3H), 3.31 (s, 3H), 2.09 (s, 1H), 1.94 – 2.00 (m, 2H), 1.63 – 1.74 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): 138.7, 138.3, 138.2, 138.1, 137.9, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 105.3, 97.9, 82.3, 82.1, 79.7, 77.6, 77.2, 75.7, 74.9, 73.4, 73.3, 72.5, 71.2, 69.7, 69.5, 66.6, 55.0, 30.5, 25.3.

HRMS (ESI) calcd for $C_{49}H_{56}O_{10}$+Na 827.3771, found 827.3772.

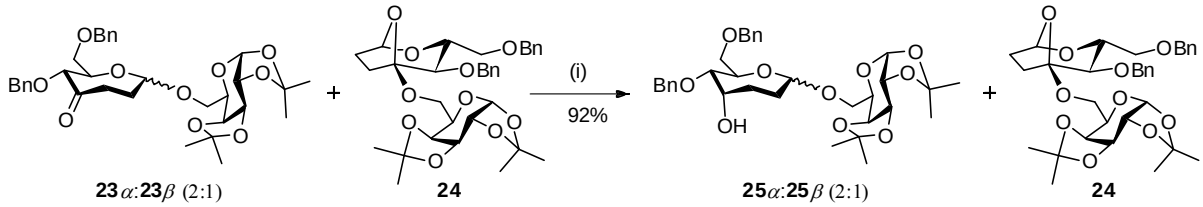
(4.4.2.11) Compound 23 and 24:



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compounds **23** and **24** with D-glucose-derived dithio-acetal **3** (110 mg, 0.196 mmol), 1,2;3,4-di-*O*-isopropylidine-α-D-galactose **22** (56.1 mg, 0.215 mmol), NIS (55.1 mg, 0.245 mmol) and AgOTf (10.0 mg, 0.039 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The silica-gel column chromatography of crude product with ethyl acetate in hexane (1:3) gave inseparable mixture of **23** and **24** (74 mg, 63% yield).

(4.4.2.12) Compounds 24, 25α and 25β:



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 °C, 1 h.

To the cold (–78 °C) solution of $LiAl(O^tBu)_3H$ (42 mg, 0.166 mmol) in ethanol (2.5 mL), was added mixture of compounds **23** and **24** (70 mg, 0.083 mmol) in ethanol (2 mL) in

dropwise fashion. The reaction mixture was stirred for 1 h at –78 °C. TLC showed that compound **23** was completely consumed while the compound **24** was not changed in the reaction. Then, the reaction was slowly quenched with the saturated NH_4Cl solution (15 mL), warmed to room temperature and extracted with ethyl acetate (15 mL X 2). The combined organic layers were washed brine (10 mL) and dried (Na_2SO_4). The crude solution was concentrated under reduced pressure and purified by the silica-gel column chromatography with ethyl acetate in hexane (3:7 to 2:3) to give the pure compounds **24** (43 mg), **25α** (17 mg) and **25***β* (9 mg).

Compound 24: Colorless oil. R_f = 0.36 (ethyl acetate/hexane 3:7). **IR (neat)**: $\bar{\upsilon}$ (cm^{-1}) 3063, 3024, 2986, 2909, 2849, 1720, 1490, 1457, 1380, 1254, 1380, 1254, 1216, 1167, 1068, 997, 898, 734, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.31 (m, 10H), 5.55 – 5.56 (d, 1H, *J* = 4.8 Hz), 5.44 – 5.45 (d, 1H, *J* = 4.4 Hz), 4.86 – 4.89 (d, 1H, *J* = 11.2 Hz), 4.59 – 4.61 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz), 4.47 – 4.51 (m, 4H), 4.30 – 4.32 (d, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 4.25 – 4.27 (d, 1H, *J* = 8.0 Hz), 4.02 – 4.05 (t, 1H, *J* = 5.6 Hz), 3.85 – 3.89 (dd, 1H, *J* = 10.4 Hz, *J* = 4.8 Hz), 3.79 – 3.83 (m, 1H), 3.61 – 3.64 (m, 1H), 3.56 – 3.58 (d, 1H, *J* = 10.4 Hz), 3.46 – 3.50 (dd, 1H, *J* = 10.4 Hz, *J* = 5.6 Hz), 2.07 – 2.17 (m, 2H), 1.88 – 1.97 (m, 2H), 1.51 (s, 3H), 1.45 (s, 3H), 1.32 (bs, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.2, 138.0, 128.4, 128.2, 128.1, 127.9, 127.5, 109.5, 109.3, 108.5, 98.1, 96.3, 74.4, 73.6, 73.3, 72.7, 71.2, 70.6, 70.5, 69.4, 67.4, 61.4, 29.1, 26.0, 25.9, 25.0, 24.2, 22.6.

HRMS (ESI) calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2675.

Compound 25α: Thick syrup. R_f = 0.23 (ethyl acetate/hexane 3:7).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 – 7.34 (m, 10H), 5.51 – 5.52 (d, 1H, *J* = 5.0 Hz), 4.79 – 4.82 (dd, 1H, *J* = 9.5 Hz, *J* = 5.5 Hz), 4.66 – 4.69 (d, 1H, *J* = 9.6 Hz), 4.55 – 4.61 (m, 3H), 4.51 – 4.53 (d, 1H, *J* = 12.5 Hz), 4.30 – 4.31 (dd, 1H, *J* = 5.0 Hz, *J* = 2.5 Hz), 4.22 – 4.24 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz), 4.14 – 4.15 (t, 1H, *J* = 3.5 Hz), 4.09 – 4.12 (dt, 1H, *J* = 9.5 Hz, *J* = 2.5 Hz), 3.91 – 3.94 (td, 1H, *J* = 6.5 Hz, *J* = 1.5 Hz), 3.86 – 3.90 (dd, 1H, *J* = 10.0 Hz, *J* = 6.5 Hz), 3.77 – 3.79 (dd, 1H, *J* = 10.0 Hz, *J* = 3.0 Hz), 3.67 – 3.70 (dd, 1H, *J* = 10.0 Hz, *J* = 6.5 Hz), 3.62 – 3.65 (dd, 1H, *J* = 10.0 Hz, *J* = 2.5 Hz), 3.59 – 3.61 (dd, 1H, *J* = 10.0

Hz, *J* = 4.0 Hz), 2.65 (s, 1H), 2.19 – 2.25 (m, 1H), 1.83 – 1.89 (m, 1H), 1.68 – 1.72 (m, 2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 138.2, 137.9, 128.4, 128.3, 127.8, 127.7, 127.4, 109.1, 108.4, 100.8, 96.3, 79.5, 73.7, 72.3, 71.0, 70.7, 70.6, 70.5, 66.3, 66.2, 66.0, 65.6, 26.1, 26.0, 24.9, 24.7, 24.5, 24.2. **HRMS (ESI)** calcd for $C_{33}H_{44}O_{10}$+Na 623.2832, found 623.2832.

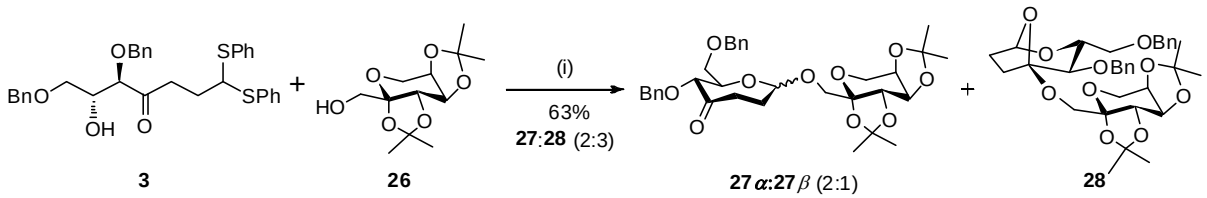
Compound 25*β*: Light yellow gum. R_f = 0.20 (ethyl acetate/hexane 3:7). **IR (neat)**: ῡ (cm^{-1}) 3523, 3029, 2985, 2931, 1456, 1385, 1265, 1221, 1078, 1007, 744, 695.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.35 (m, 10H), 5.53 – 5.54 (d, 1H, *J* = 5.5 Hz), 4.73 – 4.76 (dd, 1H, *J* = 7.5 Hz, *J* = 3.0 Hz), 4.59 – 4.61 (d, 1H, *J* = 12.0 Hz), 4.53 – 4.57 (m, 4H), 4.28 – 4.30 (dd, 1H, *J* = 5.5 Hz, *J* = 2.5 Hz), 4.15 – 4.16 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 4.09 – 4.11 (dd, 1H, *J* = 7.0 Hz, *J* = 3.5 Hz), 3.93 – 3.99 (m, 2H), 3.76 – 3.79 (dd, 1H, *J* = 11.0 Hz, *J* = 5.5 Hz), 3.58 – 3.65 (m, 4H), 2.06 – 2.12 (m, 2H), 1.97 – 2.01 (m, 1H), 1.65 – 1.76 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 138.2, 137.9, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 109.2, 108.6, 105.2, 96.3, 82.3, 76.7, 73.4, 72.5, 71.4, 71.1, 70.7, 70.4, 69.5, 67.6, 67.2, 30.4, 26.0, 25.9, 25.3, 24.9, 24.4.

HRMS (ESI) calcd for $C_{33}H_{44}O_{10}$+Na 623.2832, found 623.2832.

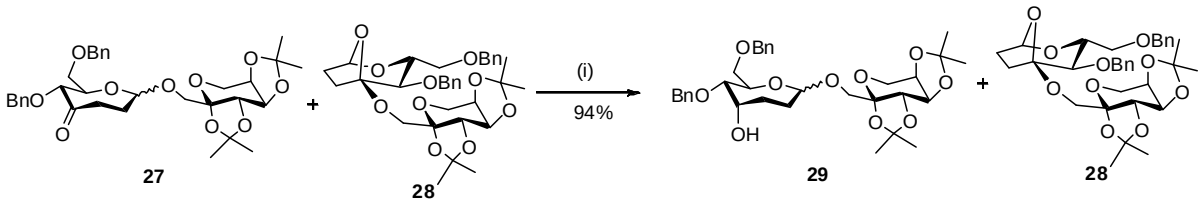
(4.4.2.13) Compound 27 and 28:



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compounds **27** and **28** with D-glucose-derived dithio-acetal **3** (160 mg, 0.286 mmol), 2,3;4,5-di-*O*-isopropylidene-α- D-fructopyranose **26** (82 mg, 0.314 mmol), NIS (80.4 mg, 0.357 mmol) and AgOTf (14.6 mg, 0.057 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The silica-gel column chromatography of crude product with ethyl acetate in toluene (1:4) gave the compounds **27** and **28** (111 mg, 65% yield) as inseparable mixture.

(4.4.2.14) Compounds 28 and 29:



Reagents and Conditions: (i) $LiAl(O^tBu)_3H$, EtOH, -78 ^oC, 1 h.

To the cold (–78 ^oC) solution of $LiAl(O^tBu)_3H$ (94.2 mg, 0.370 mmol) in ethanol (4 mL), was added mixture of **27** and **28** (111 mg, 0.185 mmol) in ethanol (3.5 mL) in dropwise fashion. The reaction mixture was stirred for 1 h at –78 ^oC. TLC showed that compound **27** was completely consumed while the compound **28** stayed in the reaction. Then, the reaction was slowly quenched with saturated NH_4Cl solution (25 mL), warmed to room temperature and extracted with ethyl acetate (25 mL X 2). The combined organic layers were washed brine (15 mL) and dried (Na_2SO_4). The crude solution was concentrated under reduced pressure and purified by the silica-gel column chromatography with ethyl acetate in toluene (1:4 to 1:3) to give the pure compound **28** (66 mg) and inseparable mixture of **29** (43 mg (α:β = 2:1)).

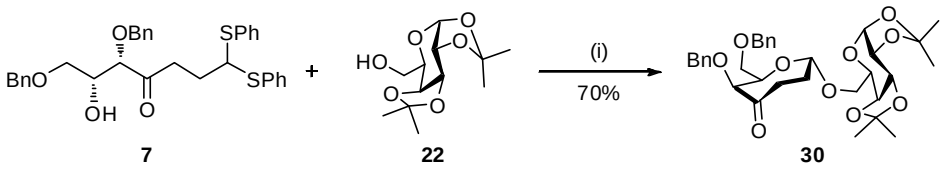
Compound 28: Thick gum. R_f = 0.74 (ethyl acetate/hexane 2:3). **IR (neat)**: $\bar{\upsilon}$ (cm^{-1}) 3084, 3057, 3035, 2986, 2931, 1720, 1501, 1457, 1380, 1249, 1210, 1150, 1090, 1073, 991, 915, 882, 745, 706.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.33 (m, 10H), 5.48 – 5.50 (d, 1H, *J* = 4.8 Hz), 4.87 – 4.90 (d, 1H, *J* = 11.2 Hz), 4.56 – 4.62 (m, 2H), 4.49 – 4.52 (m, 2H), 4.38 – 4.40 (d, 1H, *J* = 11.2 Hz), 4.22 – 4.24 (d, 1H, *J* = 8.0 Hz), 3.88 – 3.95 (dd, 2H, *J* = 13.6 Hz, *J* = 10.8 Hz), 3.77 – 3.80 (d, 1H, *J* = 10.8 Hz), 3.73 – 3.76 (d, 1H, *J* = 13.2 Hz), 3.63 – 3.66 (m, 1H), 3.55 – 3.61 (m, 3H), 2.09 – 2.21 (m, 2H), 1.88 – 1.97 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.1, 138.0, 128.3, 128.2, 127.9, 127.7, 127.6, 109.3, 108.9, 108.5, 102.2, 98.3, 75.2, 74.3, 73.3, 73.0, 71.0, 70.2, 69.8, 69.2, 63.7, 61.1, 29.1, 26.6, 25.9, 25.8, 24.1, 24.0.

HRMS (ESI) calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2675.

(4.4.2.15) Compound 30:



7 22 30

Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

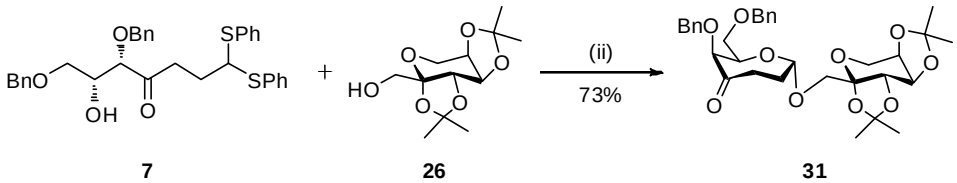
Followed the general procedure **(B)** to get the compound **30** with D-galactose-derived dithio-acetal **7** (120 mg, 0.214 mmol), 1,2;3,4-di-*O*-isopropylidine-α-D-galactose **22** (61 mg, 0.236 mmol), NIS (60.3 mg, 0.267 mmol) and AgOTf (10.9 mg, 0.042 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl acetate/toluene 1:3) to afford the pure diastereomer **30** (90 mg, 70% yield) as a colorless oil. R_f = 0.46 (ethyl acetate/hexane 1:3).

IR (neat): $\bar{\upsilon}$ (cm^{-1}) 3057, 3024, 2986, 2926, 2871, 1715, 1490, 1452, 1386, 1304, 1254, 1210, 1112, 1068, 1002, 887, 865, 734, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.33 (m, 10H), 5.47 – 5.49 (d, 1H, *J* = 4.8 Hz), 5.00 – 5.03 (dd, 1H, *J* = 4.4 Hz, *J* = 4.0 Hz), 4.65 – 4.68 (d, 1H, *J* = 11.6 Hz), 4.57 – 4.59 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz), 4.44 – 4.47 (d, 1H, *J* = 12.0 Hz), 4.36 – 4.41 (t, 2H, *J* = 11.2 Hz), 4.29 – 4.30 (dd, 1H, *J* = 4.8 Hz, *J* = 2.4 Hz), 4.16 – 4.23 (m, 2H), 3.92 – 3.95 (m, 2H), 3.84 – 3.88 (dd, 1H, *J* = 10.0 Hz, *J* = 6.8 Hz), 3.66 – 3.71 (dd, 1H, *J* = 10.0 Hz, *J* = 6.4 Hz), 3.56 – 3.64 (m, 2H), 2.63 – 2.69 (m, 1H), 2.44 – 2.49 (m, 1H), 2.19 – 2.27 (m, 1H), 1.68 – 1.81 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.31 (bs, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 209.2, 137.9, 137.1, 128.4, 128.3, 128.2, 127.9, 127.6, 127.5, 109.2, 108.5, 99.3, 96.2, 82.8, 73.1, 73.0, 70.9, 70.6, 70.5, 68.7, 66.2, 66.0, 65.9, 34.9, 28.6, 26.0, 25.9, 24.8, 24.5. **HRMS (ESI)** calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2675.

(4.4.2.16) Compound 31:



7 26 31

Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compound **31** with D-galactose-derived dithio-acetal (145 mg, 0.259 mmol), 2,3;4,5-di-*O*-isopropylidene-α- D-fructopyranose **26** (74.3 mg, 0.285 mmol), NIS (72.9 mg, 0.324 mmol) and AgOTf (13.3 mg, 0.051 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl acetate/toluene 1:3) to afford the pure diastereomer **31** (93.8 mg, 73% yield) as a colorless oil. R_f = 0.62 (ethyl acetate/hexane 3:7).

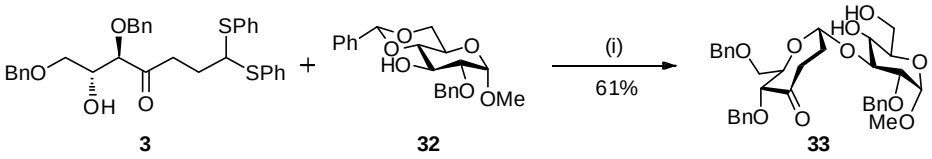
IR (neat): ῡ (cm^{-1}) 3380, 3068, 3035, 2991, 2936, 1720, 1501, 1457, 1375, 1315, 1254, 1216, 1112, 1073, 909, 887, 745, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.32 (m, 10H), 5.00 – 5.02 (dd, 1H, *J* = 4.4 Hz, *J* = 6.0 Hz), 4.64 – 4.67 (d, 1H, *J* = 12.0 Hz), 4.57 – 4.60 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 4.43 – 4.46 (d, 1H, *J* = 11.6 Hz), 4.39 – 4.42 (d, 1H, *J* = 12.0 Hz), 4.31 – 4.36 (m, 2H), 4.19 – 4.23 (t, 2H, *J* = 7.6 Hz), 3.89 – 3.96 (m, 3H), 3.71 – 3.74 (d, 1H, *J* = 12.8 Hz), 3.58 – 3.66 (m, 2H), 3.50 – 3.52 (d, 1H, *J* = 10.4 Hz), 2.67 – 2.73 (m, 1H), 2.40 – 2.45 (m, 1H), 2.24 – 2.30 (m, 1H), 1.74 – 1.82 (m, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 209.0, 137.9, 137.0, 128.5, 128.3, 128.2, 128.0, 127.5, 108.9, 108.5, 102.1, 100.0, 82.4, 73.1, 73.0, 70.9, 70.1, 69.9, 69.1, 68.4, 66.0, 61.0, 34.8, 28.4, 26.5, 25.9, 25.2, 23.9.

HRMS (ESI) calcd for $C_{33}H_{42}O_{10}$+Na 621.2676, found 621.2678.

(4.4.2.17) Compound 23:



3 **32** **33**

Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compound **33** with D-glucose-derived dithio-acetal **7** (120 mg, 0.214 mmol), methyl 2-*O*-benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside **32** (87.9 mg, 0.235 mmol), NIS (60 mg, 0.267 mmol) and AgOTf (10.9 mg, 0.042 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl

acetate/hexane 1:1) to afford the pure compound **33** (81.5 mg, 61% yield) as a light yellow semi solid. R_f = 0.38 (ethyl acetate/hexane 1:1).

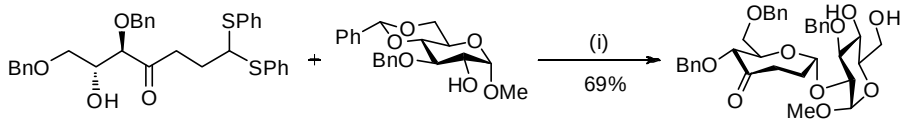
IR (neat): ῡ (cm^{-1}) 3463, 3068, 3024, 2909, 2860, 1715, 1495, 1452, 1364, 1205, 1095, 1073, 1052, 920, 734, 695.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.37 (m, 15H), 4.86 – 4.89 (d, 1H, *J* = 11.6 Hz), 4.70 – 4.74 (m, 2H), 4.56 – 4.59 (dd, 2H, *J* = 5.2 Hz, *J* = 6.0 Hz), 4.40 – 4.52 (m, 3H), 4.05 – 4.09 (dd, 1H, *J* = 4.8 Hz, *J* = 10 Hz), 4.03 (m, 1H), 3.89 – 3.91 (d, 1H, *J* = 6.4 Hz), 3.53 – 3.70 (m, 5H), 3.44 – 3.49 (t, 1H, *J* = 10 Hz), 3.44 (s, 3H), 3.33 – 3.38 (t, 1H, *J* = 9.2 Hz), 2.71 – 2.75 (td, 2H, *J* = 3.2 Hz, *J* = 7.2 Hz), 2.56 – 2.58 (d, 1H, *J* = 5.6 Hz), 2.32 – 2.34 (d, 1H, *J* = 6.0 Hz), 1.91 – 1.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 210.3, 138.4, 137.6, 137.0, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 101.0, 99.7, 84.1, 81.4, 78.6, 74.5, 73.3, 73.0, 72.2, 71.0, 70.0, 68.4, 62.5, 55.3, 33.7, 27.4.

HRMS (ESI) calcd for $C_{35}H_{42}O_{10}$+Na 645.2676, found 645.2699.

(4.4.2.18) Compound 35:



3 **34** **35**

Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compound **35** with D-glucose-derived dithio-acetal **3** (135 mg, 0.241 mmol), methyl 3-*O*-benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside **34** (99 mg, 0.265 mmol), NIS (67.7 mg, 0.301 mmol) and AgOTf (12.3 mg, 0.048 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl acetate/hexane 1:1) to afford the pure compound **35** (103.8 mg, 69% yield) as a light yellow gum. R_f = 0.37 (ethyl acetate/hexane 1:1).

IR (neat): ῡ (cm^{-1}) 3457, 3063, 3024, 2920, 2854, 1720, 1501, 1452, 1369, 1276, 1095, 1068, 739, 695.

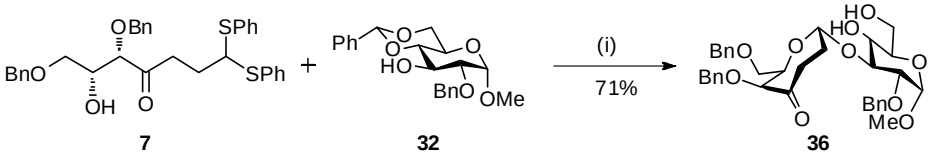
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.36 (m, 15H), 4.74 – 4.77 (d, 1H, *J* = 12.4 Hz), 4.65 – 4.68 (d, 1H, *J* = 12.4 Hz), 4.46 – 4.60 (m, 5H), 4.40 – 4.43 (d, 1H, *J* = 11.6 Hz), 3.99 –

4.06 (m, 3H), 3.93 – 3.95 (d, 1H, *J* = 6.8 Hz), 3.57 – 3.63 (m, 3H), 3.40 – 3.45 (t, 1H, *J* = 10 Hz), 3.36 – 3.39 (dd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.33 (s, 3H), 3.17 – 3.22 (t, 1H, *J* = 9.6 Hz), 2.64 – 2.85 (m, 4H), 1.93 – 1.99 (dd, 2H, *J* = 6.8 Hz, *J* = 12 Hz).

^{3}C NMR (100 MHz, $CDCl_3$): 210.4, 137.8, 137.6, 137.0, 128.6, 128.5, 128.4, 128.0, 127.8, 101.1, 98.4, 83.7, 80.7, 79.5, 73.3, 73.2, 73.0, 70.9, 70.1, 70.0, 68.3, 61.9, 55.2, 33.8, 27.1.

HRMS (ESI) calcd for $C_{35}H_{42}O_{10}$+Na 645.2676, found 645.2676.

(4.4.2.19) Compound 26:



Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compound **36** with D-galactose-derived dithio-acetal **7** (110 mg, 0.196 mmol), methyl 2-*O*-benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside **32** (80.6 mg, 0.216 mmol), NIS (55.1 mg, 0.245 mmol) and AgOTf (10.0 mg, 0.039 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl acetate/hexane 3:2) to afford the pure compound **36** (87 mg, 71% yield) as a thick syrup. R_f = 0.30 (ethyl acetate/hexane 1:1).

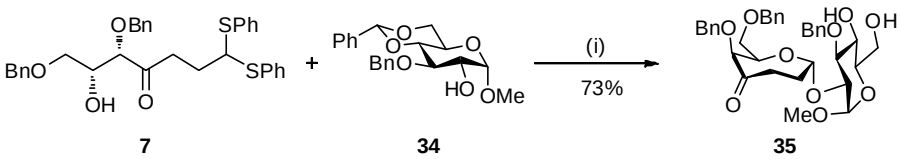
IR (neat): $\bar{\upsilon}$ (cm^{-1}) 3452, 3084, 3068, 3024, 2920, 2854, 1715, 1501, 1457, 1364, 1210, 1106, 1073, 1041, 739, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.37 (m, 15H), 4.74 – 4.78 (d, 1H, *J* = 12.4 Hz), 4.66 – 4.68 (d, 2H, *J* = 10.4 Hz), 4.60 – 4.62 (t, 1H, *J* = 5.2 Hz), 4.55 (d, 1H, *J* = 3.2 Hz), 4.43 – 4.52 (dd, 2H, *J* = 11.6 Hz, *J* = 19.6 Hz), 4.42 (d, 1H, *J* = 11.2 Hz), 3.99 – 4.06 (m, 4H), 3.47 – 3.62 (m, 3H), 3.41 – 3.46 (t, 1H, *J* = 10.0 Hz), 3.36 – 3.39 (dd, 1H, *J* = 3.6 Hz, *J* = 9.2 Hz), 3.32 (s, 3H), 3.16 – 3.20 (t, 1H, *J* = 9.6 Hz), 2.76 – 2.84 (m, 2H), 2.65 – 2.73 (m, 2H), 1.93 – 1.98 (dd, 2H, *J* = 6.4 Hz, *J* = 12 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 211.0, 137.9, 137.7, 137.0, 128.5, 128.4, 128.2, 128.1, 127.8, 100.8, 98.5, 83.7, 80.7, 79.5, 73.4, 73.3, 73.2, 71.1, 70.3, 70.0, 68.4, 62.0, 55.2, 34.0, 27.2.

HRMS (ESI) calcd for $C_{35}H_{42}O_{10}$+Na 645.2676, found 645.2676.

(4.4.2.20) Compound 35:



7 **34** **35**

Reagents and Conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, -45 °C to -25 °C, 1 h.

Followed the general procedure **(B)** to get the compound **35** with D-galactose-derived dithio-acetal **7** (150 mg, 0.268 mmol), methyl 3-*O*-benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside **34** (110 mg, 0.295 mmol), NIS (75.4 mg, 0.335 mmol) and AgOTf (13.7 mg, 0.053 mmol). The reaction mixture was warmed –45 °C to –25 °C and stirred for 1 h at –25 °C. The obtained crude product was purified by the silica-gel column chromatography (ethyl acetate/hexane 1:1) to afford the pure compound **35** (122 mg, 73% yield) as a colorless oil. R_f = 0.32 (ethyl acetate/hexane 1:1). **IR (neat)**: $\bar{\upsilon}$ (cm^{-1}) 3457, 3068, 3030, 2920, 2865, 1720, 1501, 1452, 1364, 1128, 1090, 1052, 1030, 734, 695.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.36 (m, 15H), 4.85 – 4.88 (d, 1H, *J* = 11.6 Hz), 4.70 – 4.73 (m, 2H), 4.62 – 4.65 (d, 1H, *J* = 11.6 Hz) 4.54 – 4.56 (t, 1H, *J* = 5.2 Hz), 4.40 – 4.48 (dd, 2H, *J* = 12.0 Hz, *J* = 19.6 Hz), 4.38 (d, 1H, *J* = 11.6 Hz), 4.04 – 4.08 (dd, 2H, *J* = 4.4 Hz, *J* = 10.4 Hz), 3.95 (d, 1H, *J* = 3.2 Hz), 3.59 – 3.70 (m, 3H), 3.49 – 3.53 (dd, 1H, *J* = 5.6 Hz, *J* = 9.6 Hz), 3.43 – 3.48 (m, 2H), 3.38 (s, 3H), 3.30 – 3.35 (t, 1H, *J* = 9.2 Hz), 2.70 – 2.74 (m, 2H), 2.63 (d, 1H, *J* = 6.8 Hz), 2.43 (d, 1H, *J* = 6.0 Hz), 1.90 – 1.95 (dd, 2H, *J* = 6.8 Hz, *J* = 12.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 210.9, 138.4, 137.6, 136.9, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 100.9, 99.7, 83.9, 81.3, 78.6, 74.4, 73.3, 73.2, 72.1, 71.1, 70.2, 68.3, 62.4, 55.2, 33.8, 27.3.

HRMS (ESI) calcd for $C_{35}H_{42}O_{10}$+Na 645.2676, found 645.2677.

4.5 References

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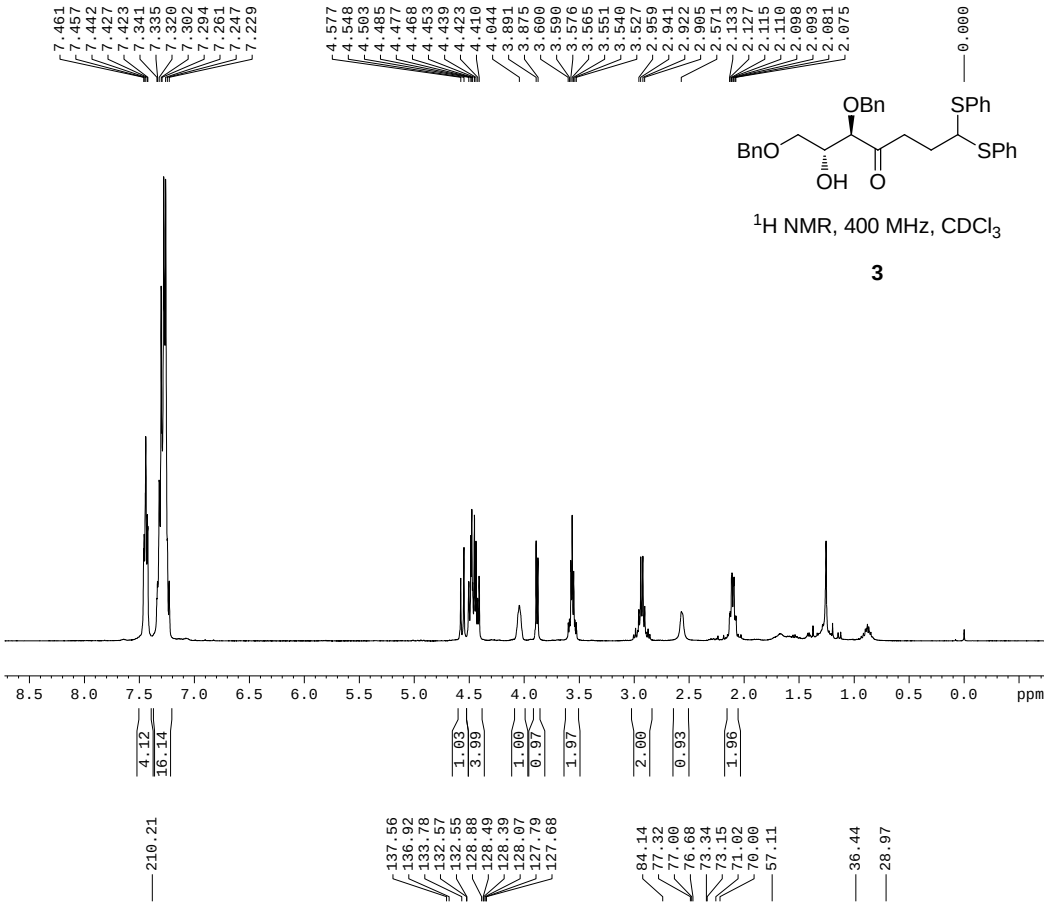
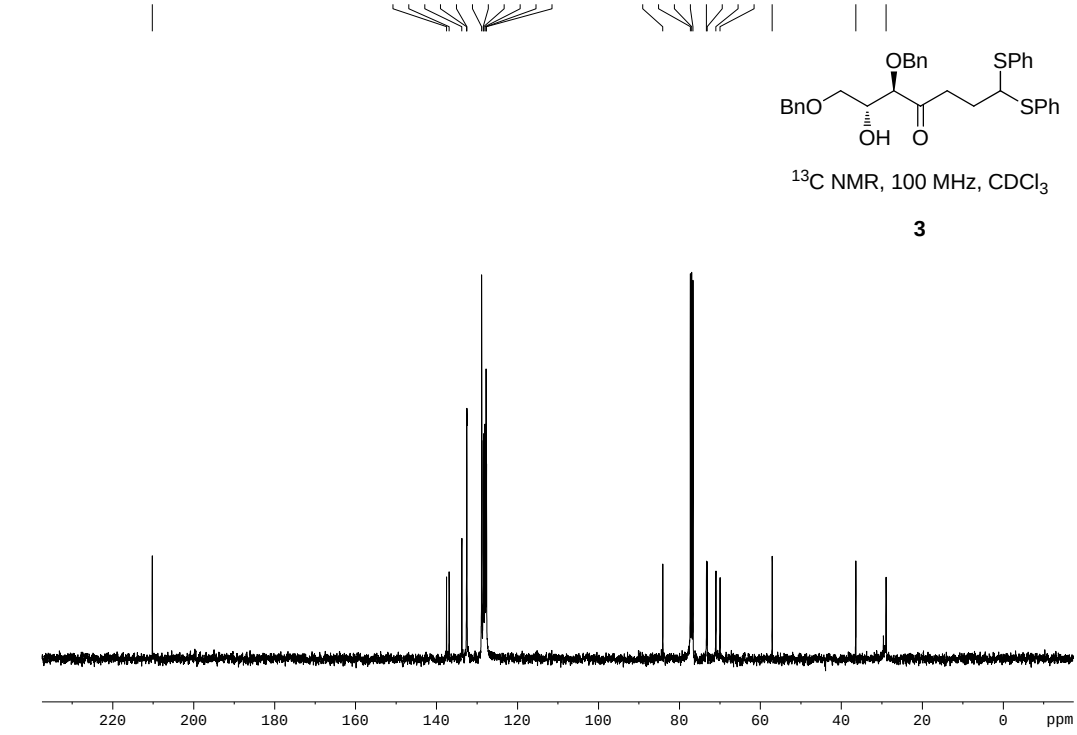
4.6 NMR Spectra



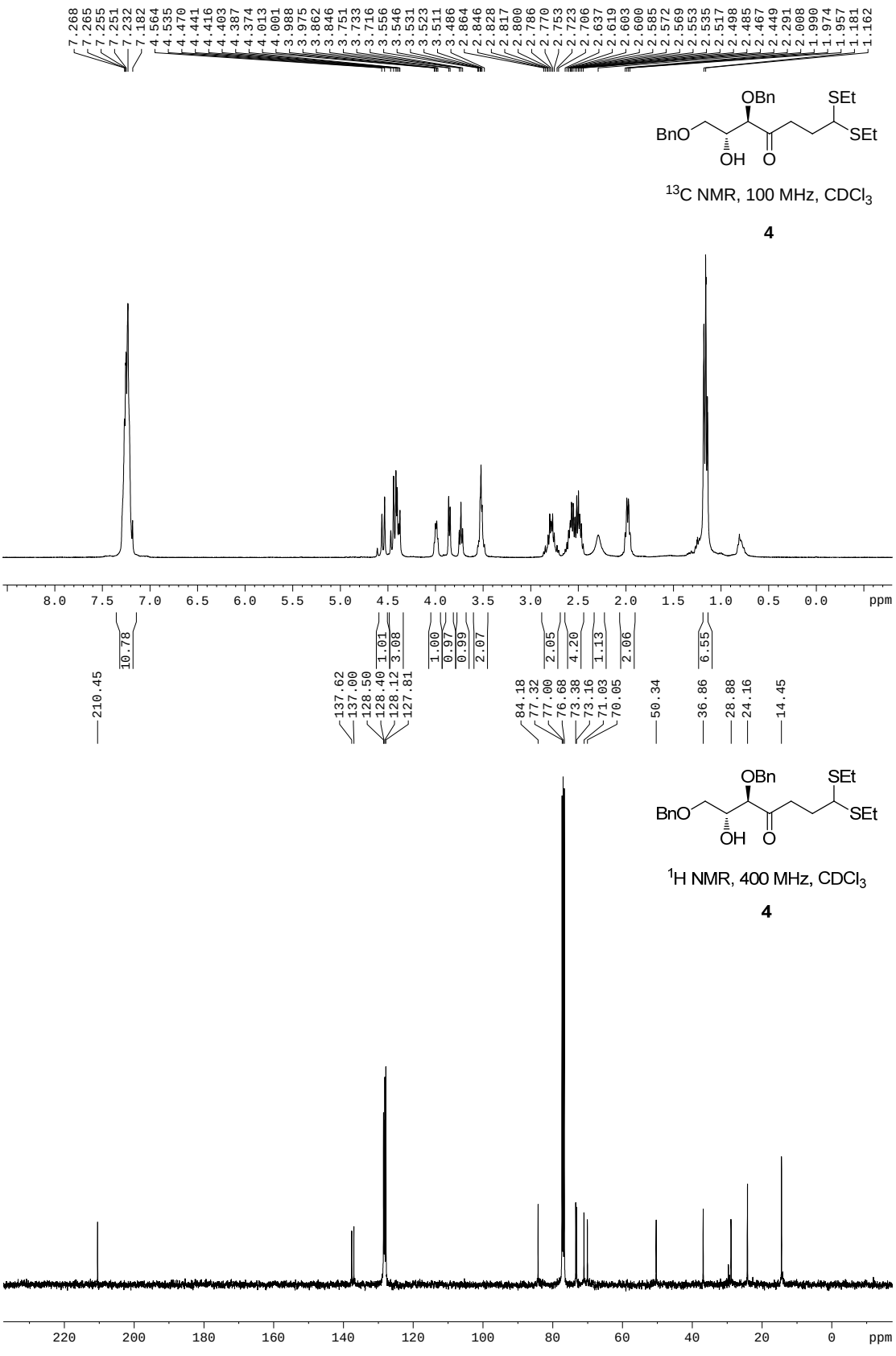
^{1}H NMR, 400 MHz, $CDCl_3$

3



^{13}C NMR, 100 MHz, $CDCl_3$

3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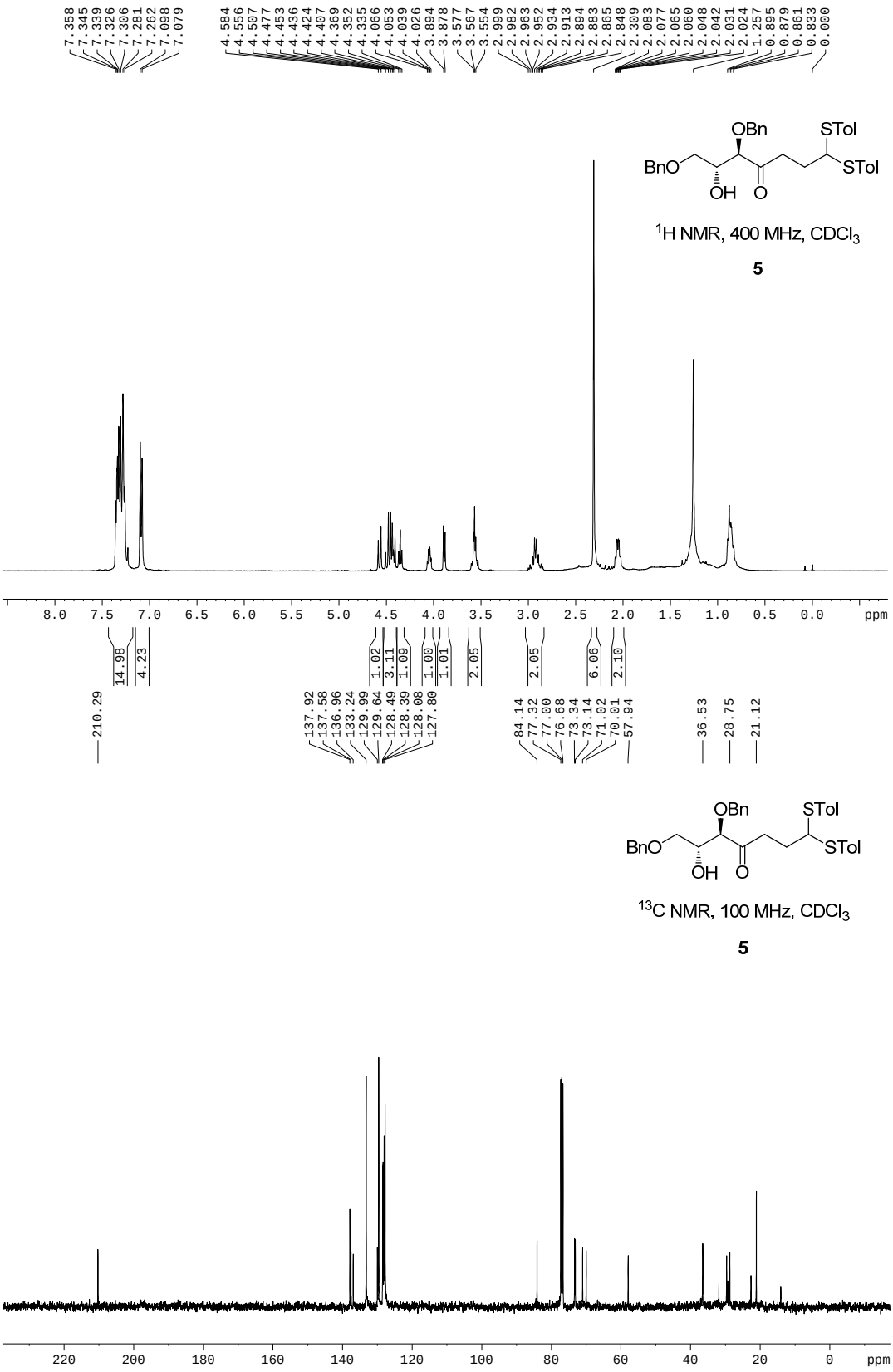
OBn
SEt
BnO
SEt
OH
O
13C NMR, 100 MHz, CDCl3
4
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
10.78 1.01 3.08 1.00 0.97 0.99 2.07 2.05 4.20 1.13 2.06 6.55
210.45 137.62 137.00 128.50 128.40 128.12 127.81 84.18 77.32 77.00 76.68 73.38 73.16 71.03 70.05 50.34 36.86 28.88 24.16 14.45
OBn
SEt
BnO
SEt
OH
O
1H NMR, 400 MHz, CDCl3
4
220 200 180 160 140 120 100 80 60 40 20 0 ppm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OBn STol
BnO STol
OH O
1H NMR, 400 MHz, CDCl3
5
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
14.98 4.23 1.02 3.11 1.09 1.00 1.01 2.05 2.05 6.06 2.10
210.29 137.92 137.58 136.96 133.24 129.99 129.64 128.49 128.39 128.08 127.80 84.14 77.32 77.00 76.68 73.34 73.14 71.02 70.01 57.94 36.53 28.75 21.12
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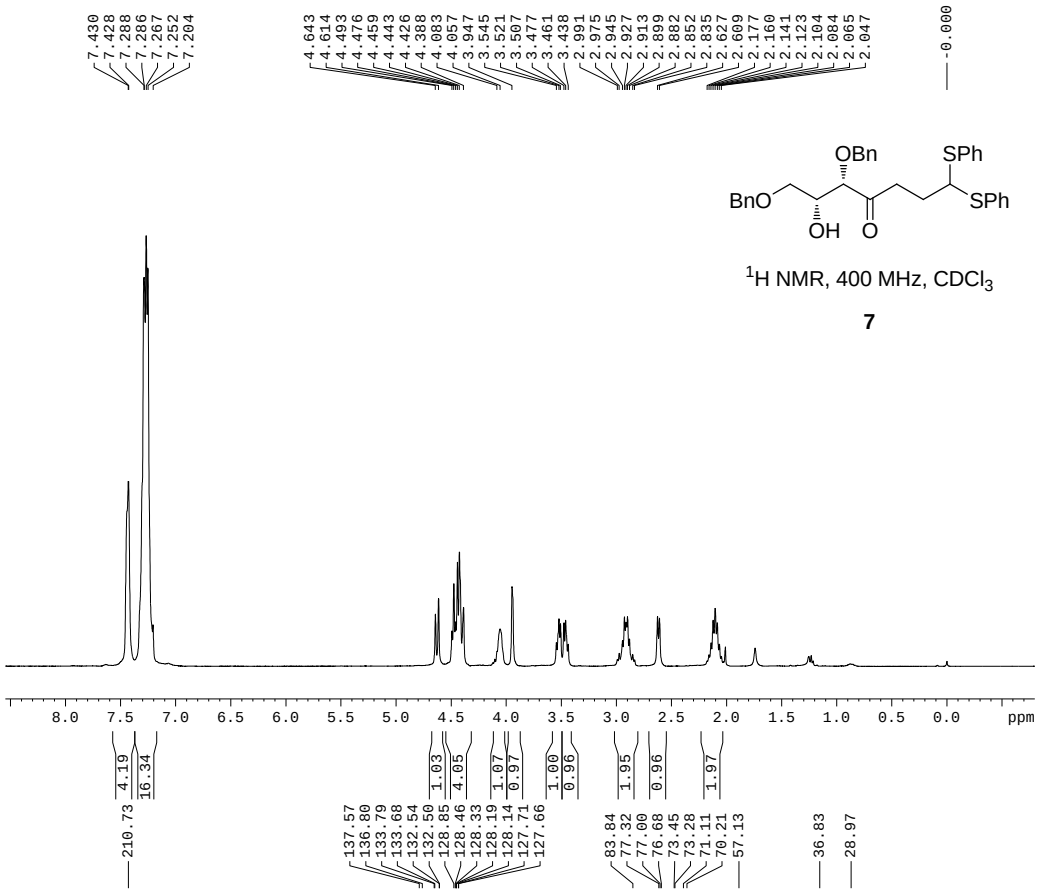
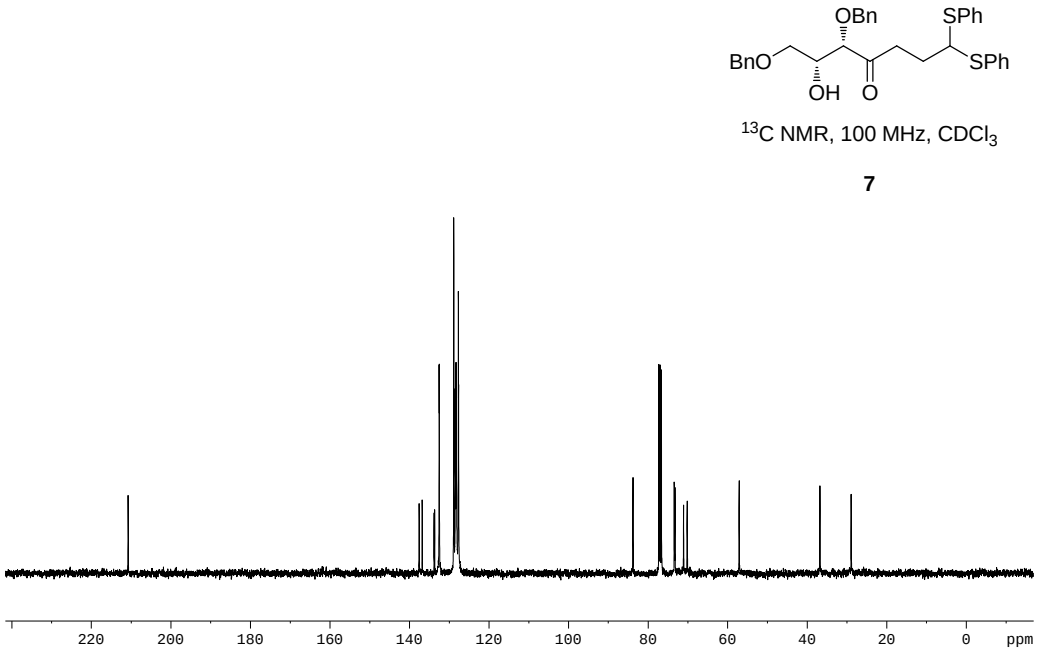
BnO STol
OH O
13C NMR, 100 MHz, CDCl3
5
220 200 180 160 140 120 100 80 60 40 20 0 ppm



^{1}H NMR, 400 MHz, $CDCl_3$

7



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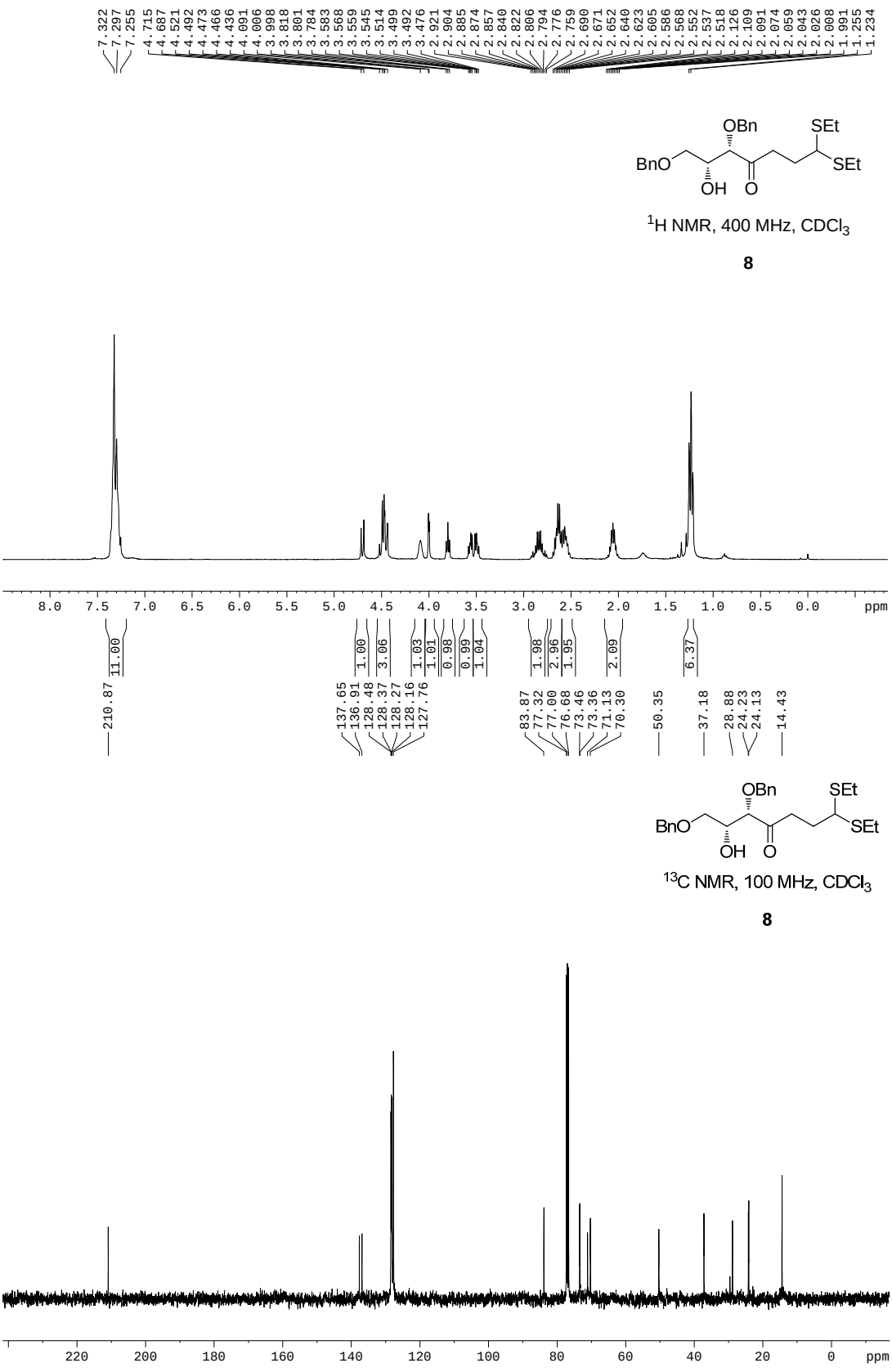
7



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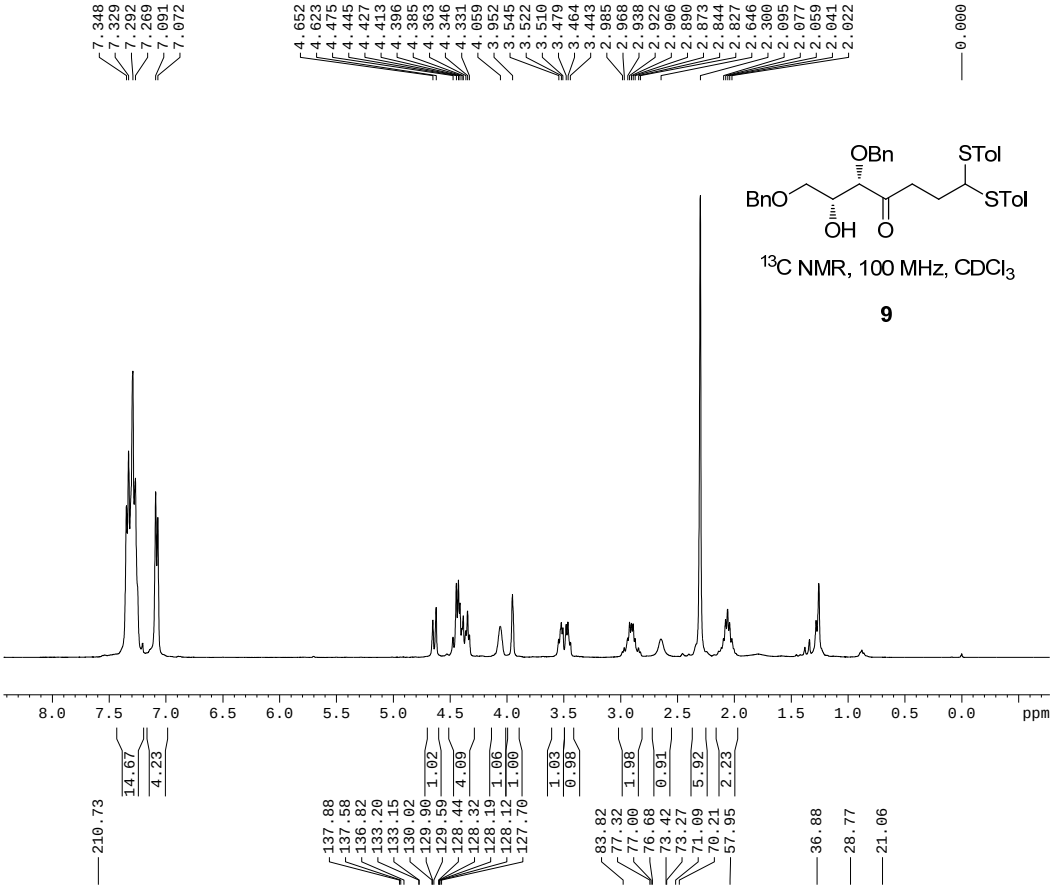
8

^{13}C NMR, 100 MHz, $CDCl_3$

8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7.292
7.269
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7.072
4.652
4.623
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4.445
4.427
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4.396
4.385
4.363
4.346
4.331
4.059
3.952
3.545
3.522
3.510
3.479
3.464
3.443
2.985
2.968
2.938
2.922
2.906
2.890
2.873
2.844
2.827
2.646
2.300
2.095
2.077
2.059
2.041
2.022
0.000
OBn
STol
BnO
STol
OH
O
13C NMR, 100 MHz, CDCl3
9
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
14.67
4.23
1.02
4.09
1.06
1.00
1.03
0.98
1.98
0.91
5.92
2.23
210.73
137.88
137.58
136.82
133.20
133.15
130.02
129.90
129.59
128.44
128.32
128.19
128.12
127.70
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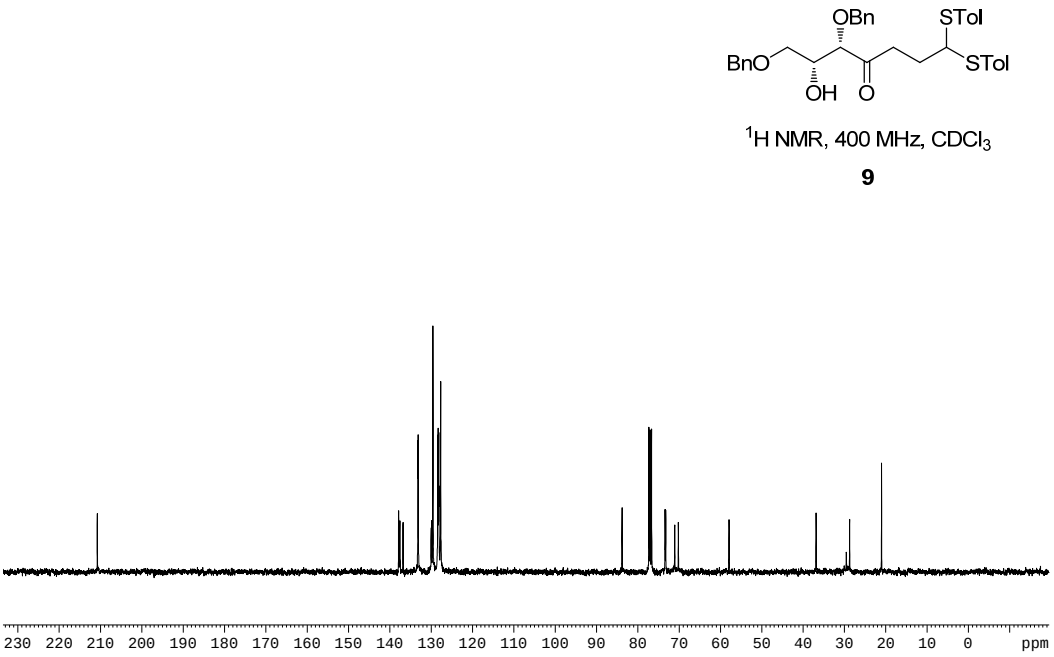
71.09
70.21
57.95
36.88
28.77
21.06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STol
BnO
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OH
O
1H NMR, 400 MHz, CDCl3
9
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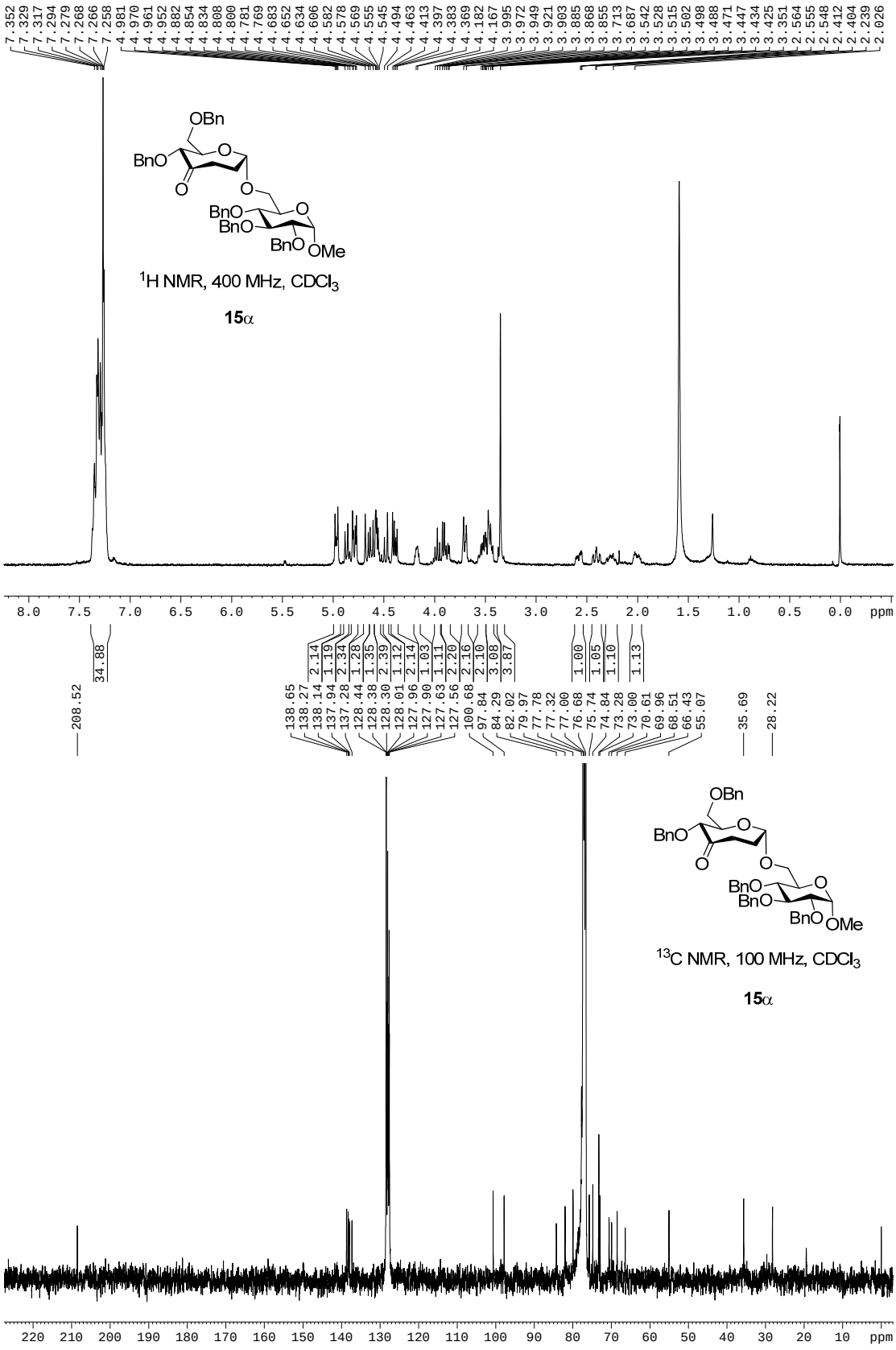
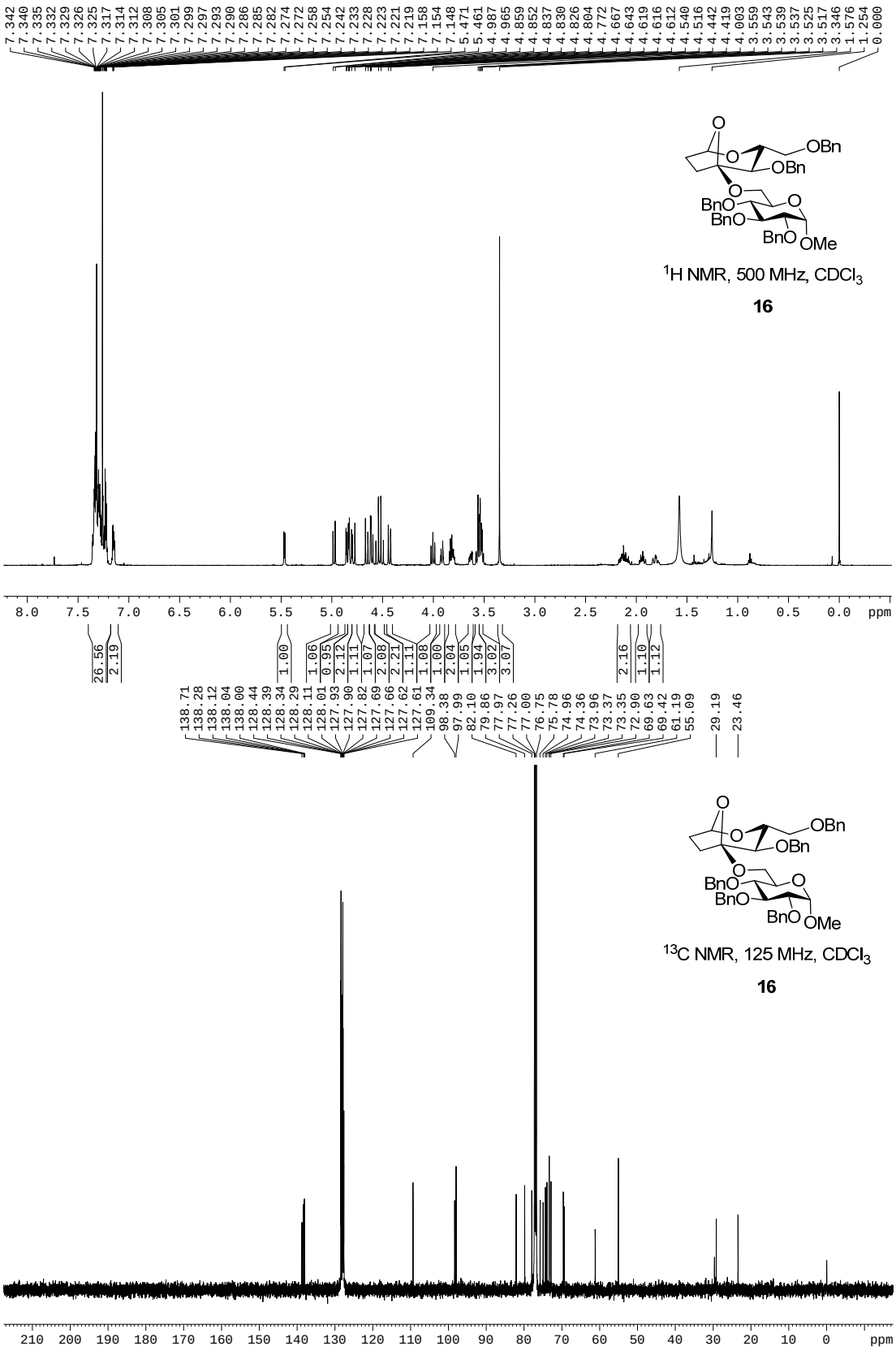

OBn
BnO
BnO
BnO
OMe
^{1}H NMR, 400 MHz, CDCl$_3$
15α
^{13}C NMR, 100 MHz, CDCl$_3$
15α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OBn
OBn
BnO
BnO
BnO
OMe
^{1}H NMR, 500 MHz, $CDCl_3$
16
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
26.56 2.19 1.00 1.06 0.95 2.12 1.11 1.07 2.08 2.21 1.11 1.08 1.00 2.04 1.05 1.94 3.02 3.07 2.16 1.10 1.12
138.71 138.28 138.12 138.04 138.00 128.44 128.39 128.34 128.29 128.11 128.01 127.93 127.90 127.82 127.69 127.66 127.62 127.61 109.34 98.38 97.99 82.10 79.86 77.97 77.26 77.00 76.75 75.78 74.96 74.36 73.96 73.37 73.35 72.90 69.63 69.42 61.19 55.09 29.19 23.46
OBn
OBn
BnO
BnO
BnO
OMe
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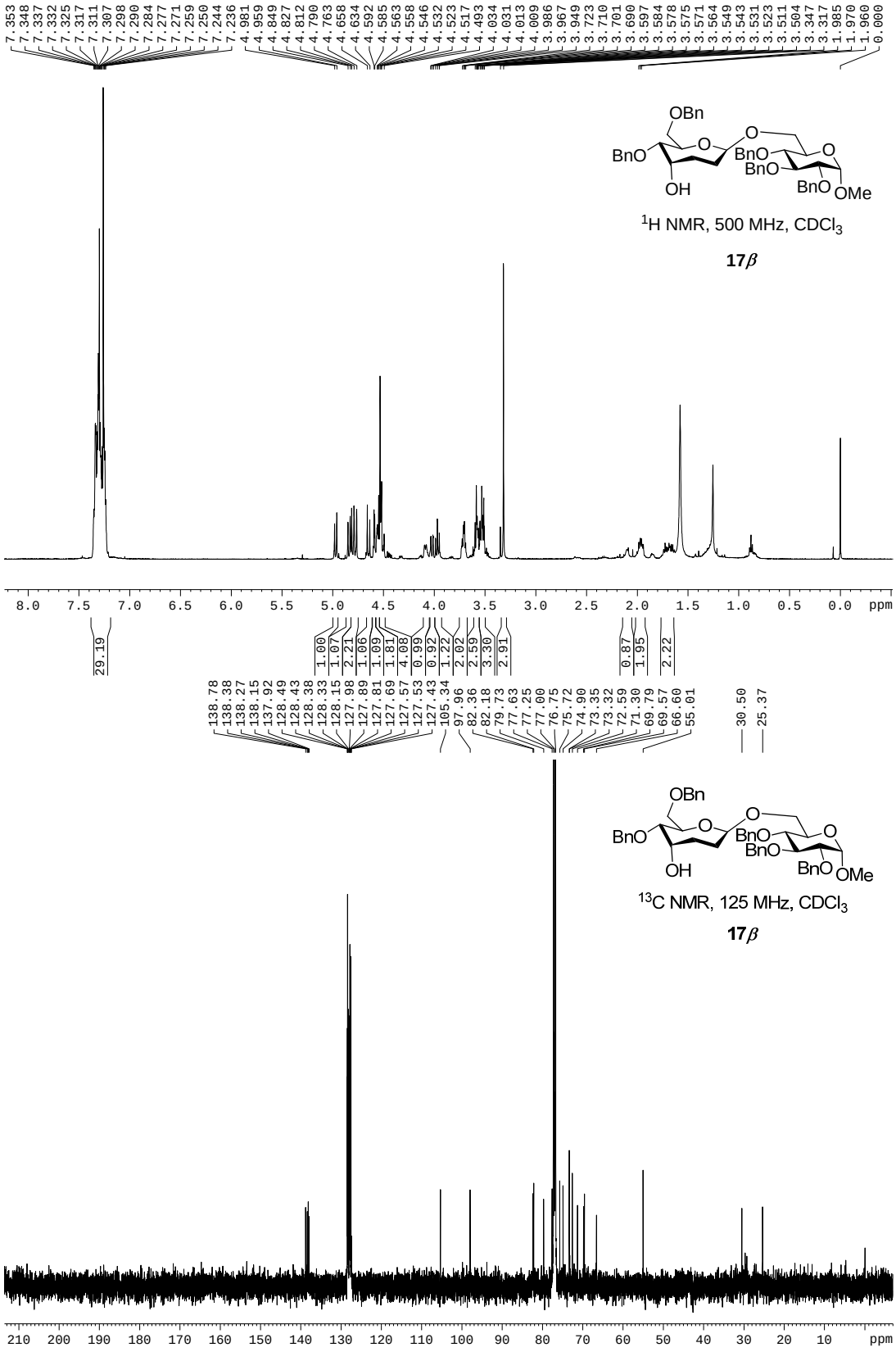
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OH
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17β
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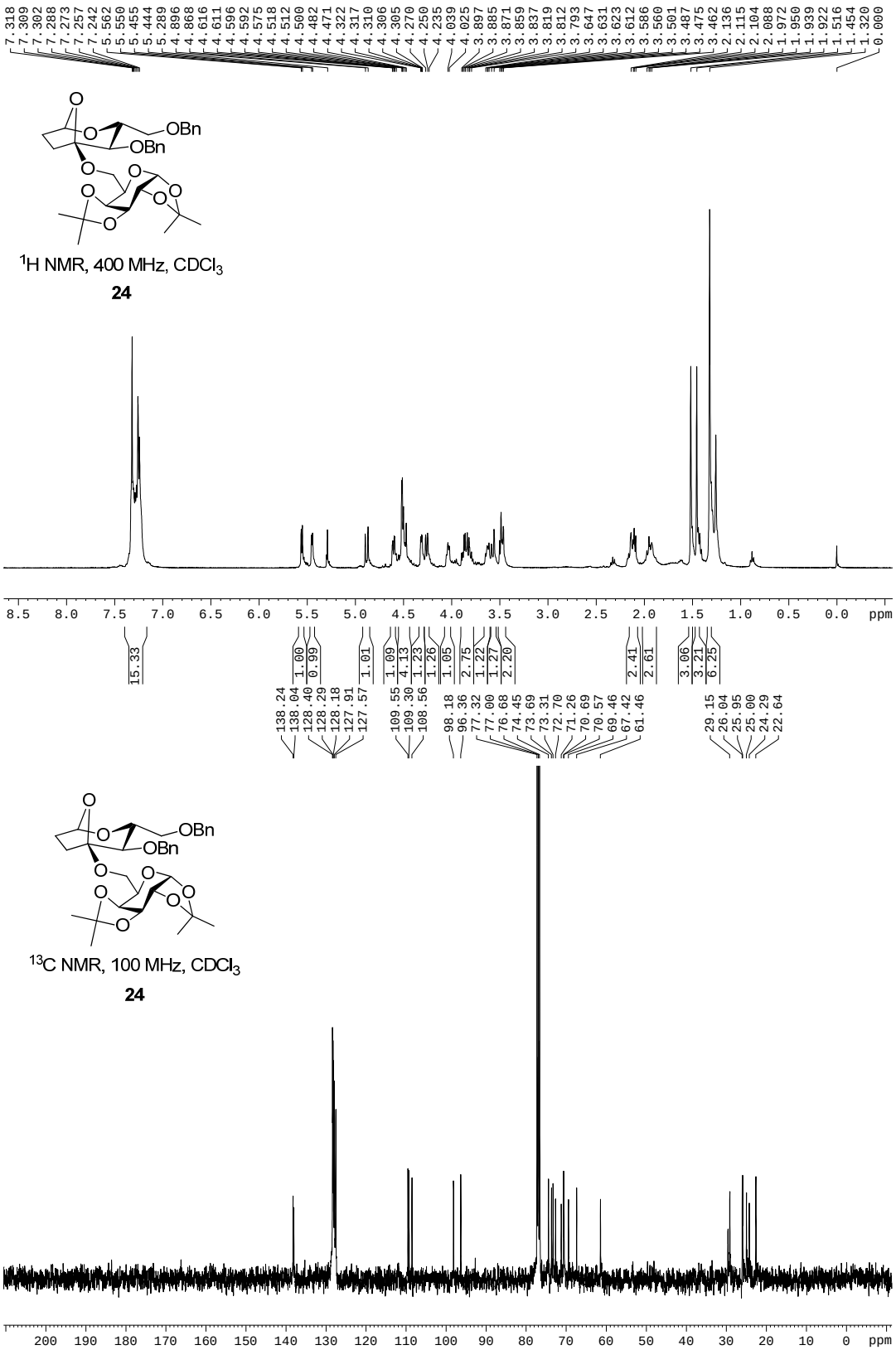
17β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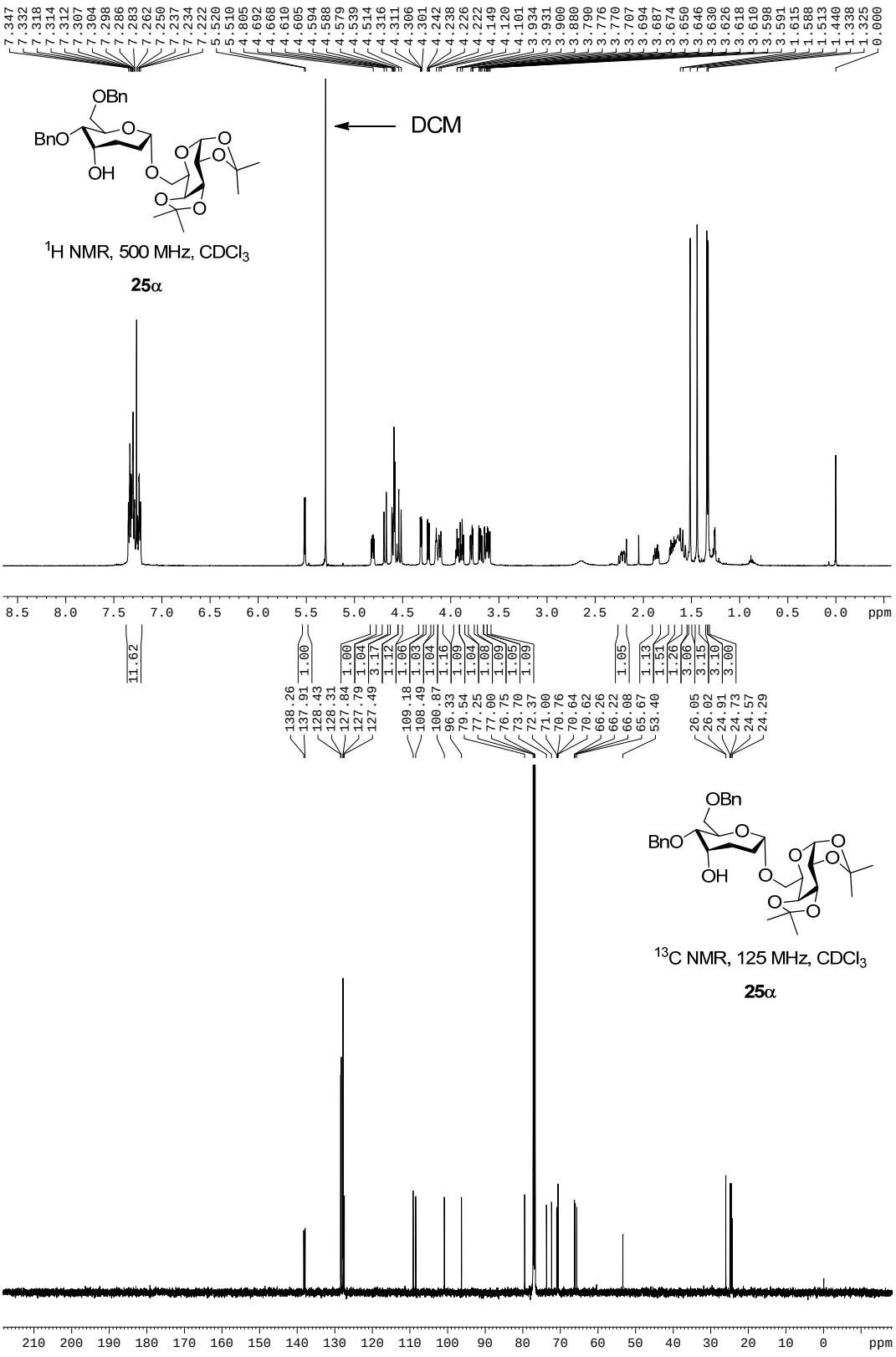
ppm
OBn
OBn
^{13}C NMR, 100 MHz, CDCl$_3$
24
ppm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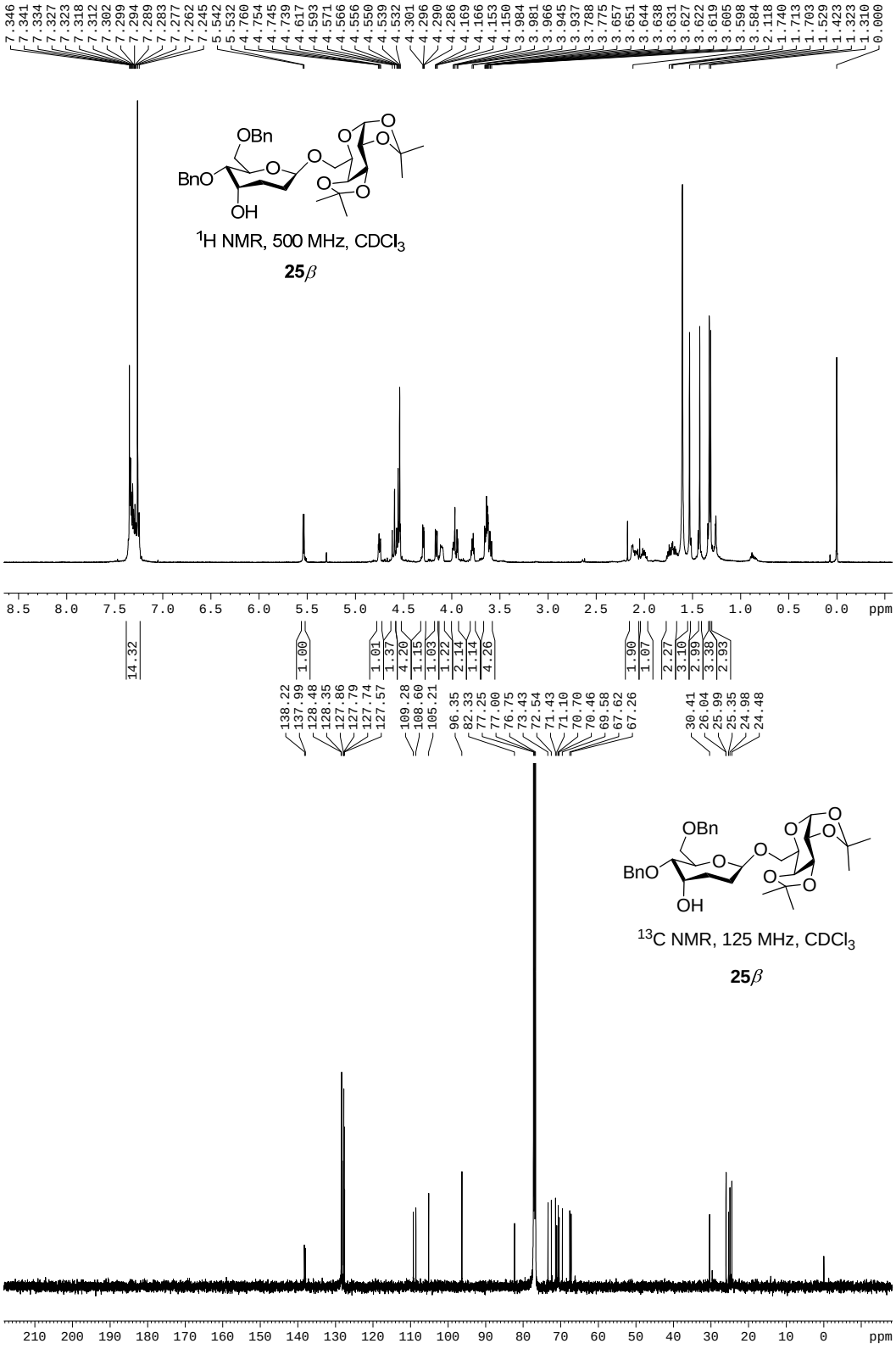
25α
^{13}C NMR, 125 MHz, CDCl$_3$
25α
ppm


OBn
BnO
OH
O
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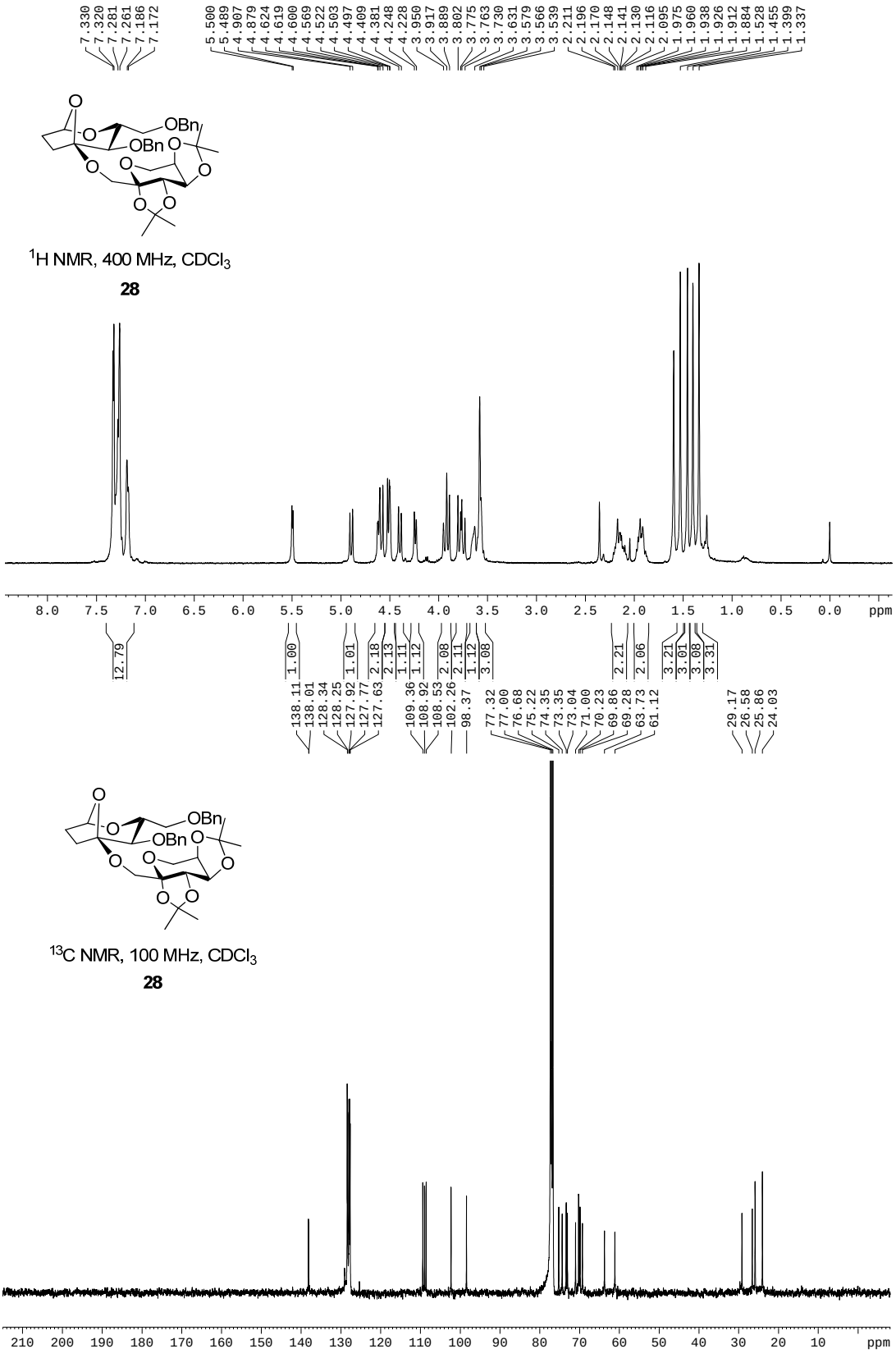
25β
^{13}C NMR, 125 MHz, CDCl$_3$
25β
ppm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4.248
4.228
3.950
3.917
3.889
3.802
3.775
3.763
3.730
3.631
3.579
3.566
3.539
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2.170
2.148
2.141
2.130
2.116
2.095
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1.960
1.938
1.926
1.912
1.884
1.528
1.455
1.399
1.337
OBn
OBn
O
O
O
O
O
O
O
^{1}H NMR, 400 MHz, $CDCl_3$
28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
12.79
1.00
1.01
2.18
2.13
1.11
1.12
2.08
2.11
1.12
3.08
2.21
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3.01
3.08
3.31
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108.92
108.53
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74.35
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71.00
70.23
69.86
69.28
63.73
61.12
29.17
26.58
25.86
24.03
OBn
OBn
O
O
O
O
O
O
O
^{13}C NMR, 100 MHz, $CDCl_3$
28
210
200
190
180
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160
150
140
130
120
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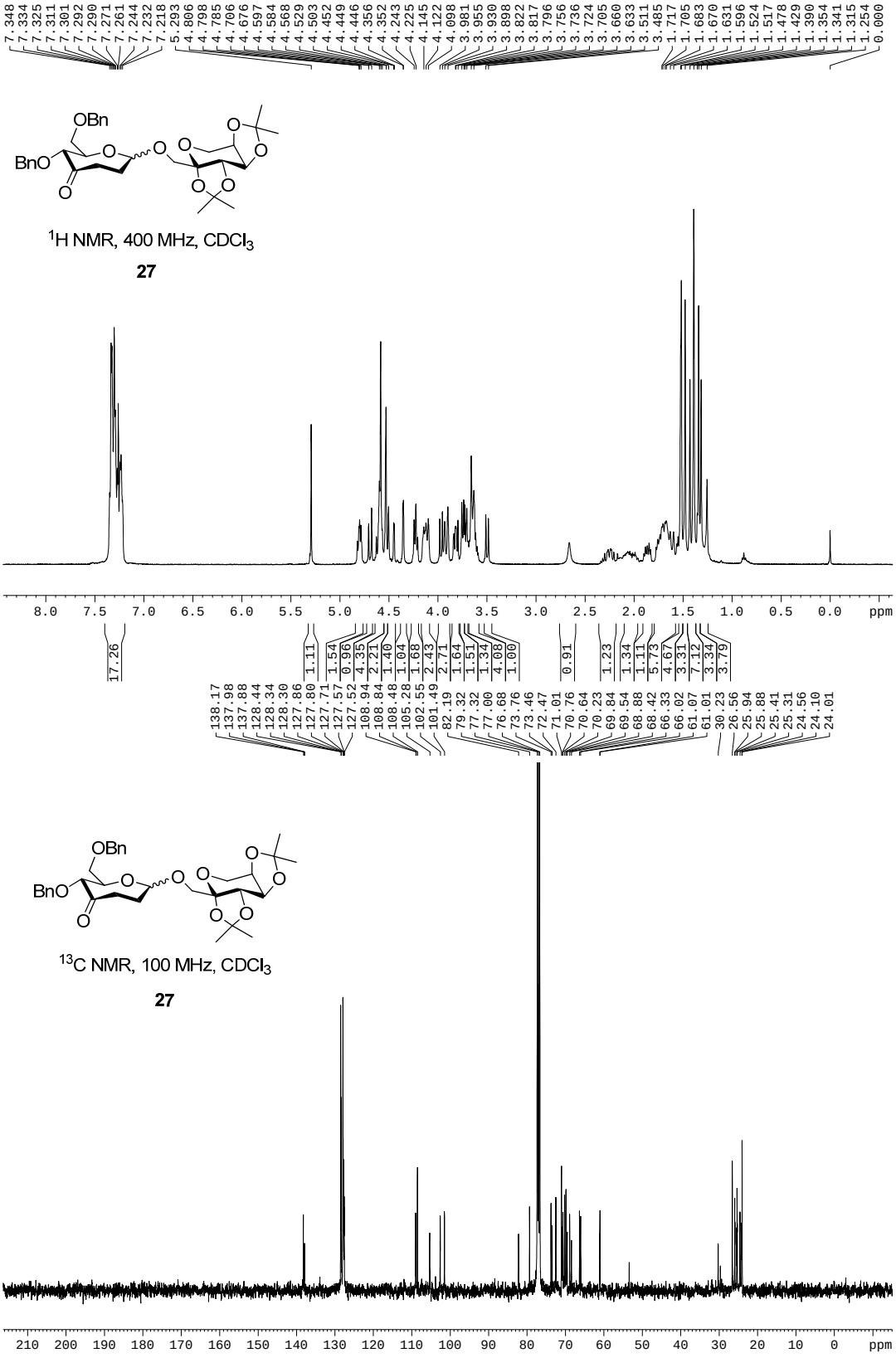
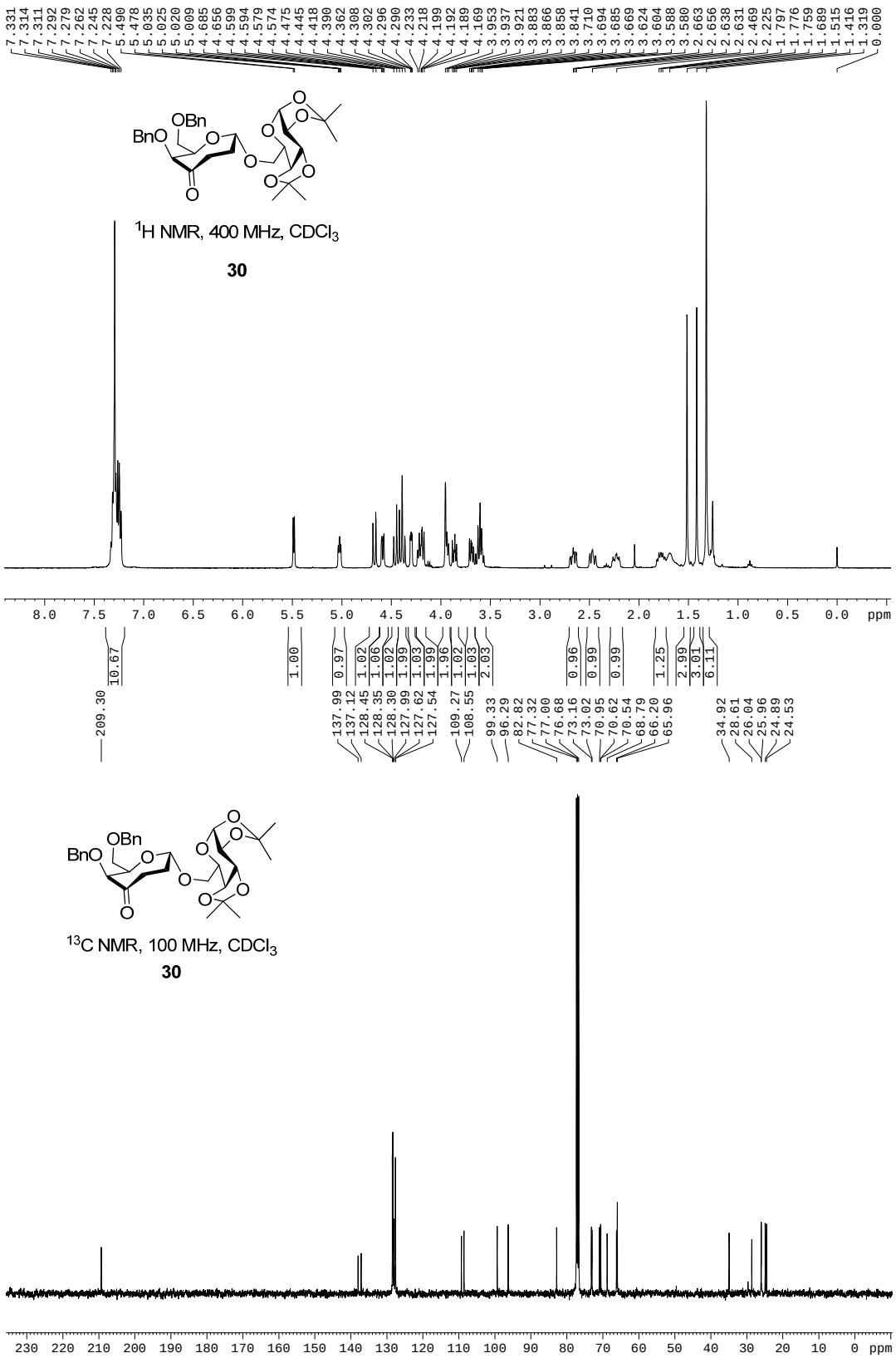
90
80
70
60
50
40
30
20
10
ppm


OBn
BnO
O
O
O
O
O
O
O
O
^{1}H NMR, 400 MHz, CDCl$_3$
27
ppm
OBn
BnO
O
O
O
O
O
O
O
O
^{13}C NMR, 100 MHz, CDCl$_3$
27
ppm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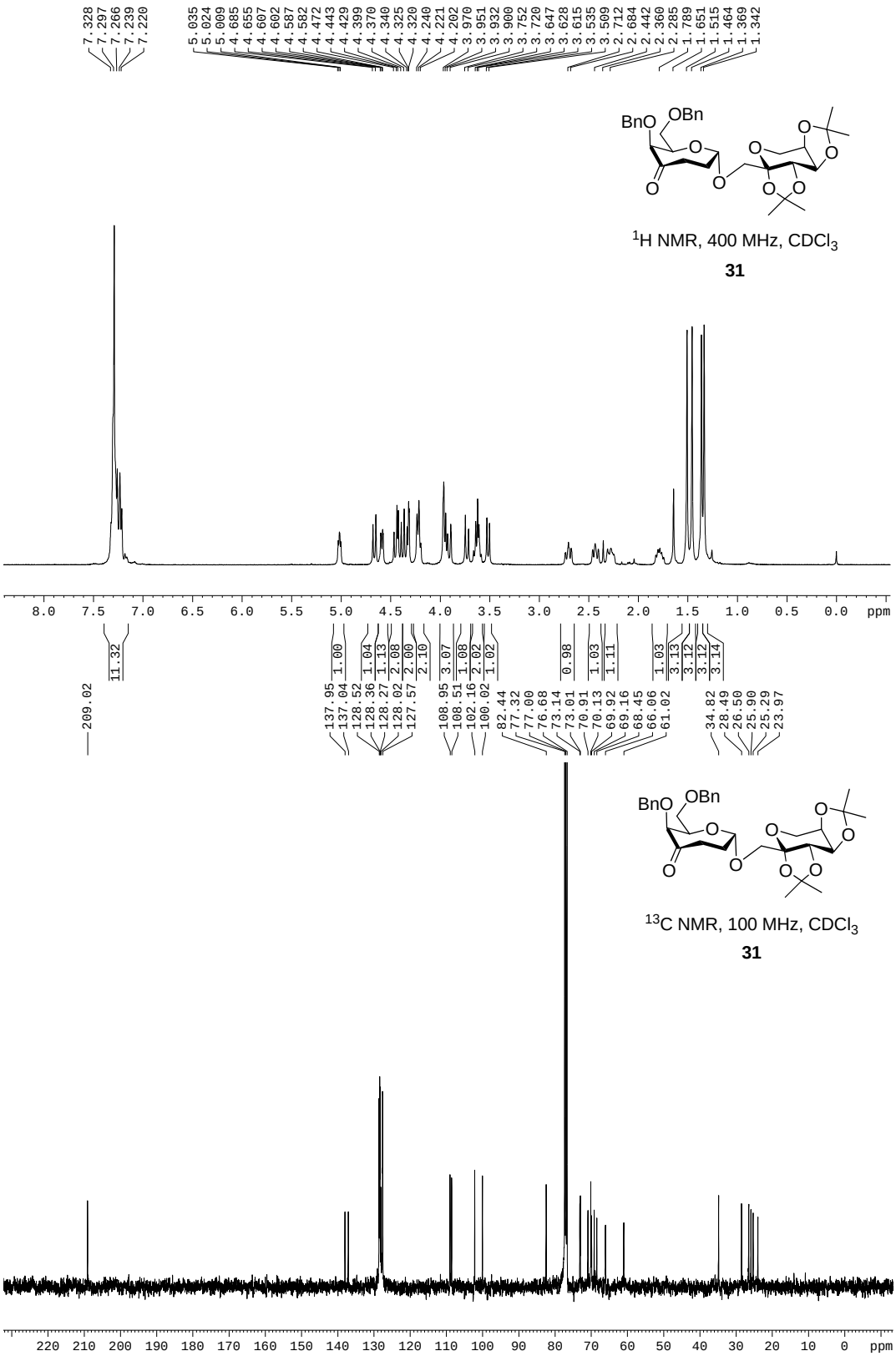
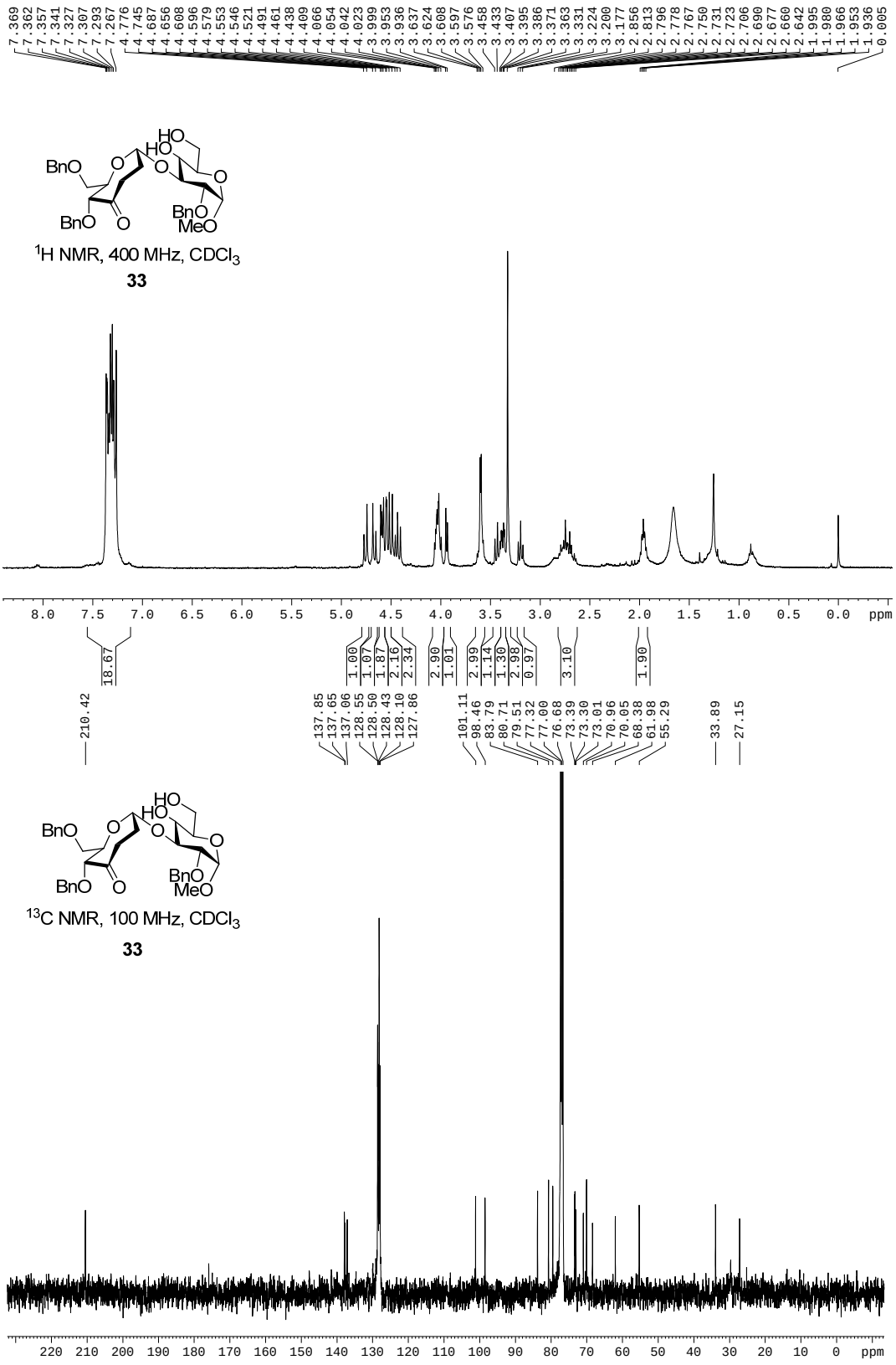
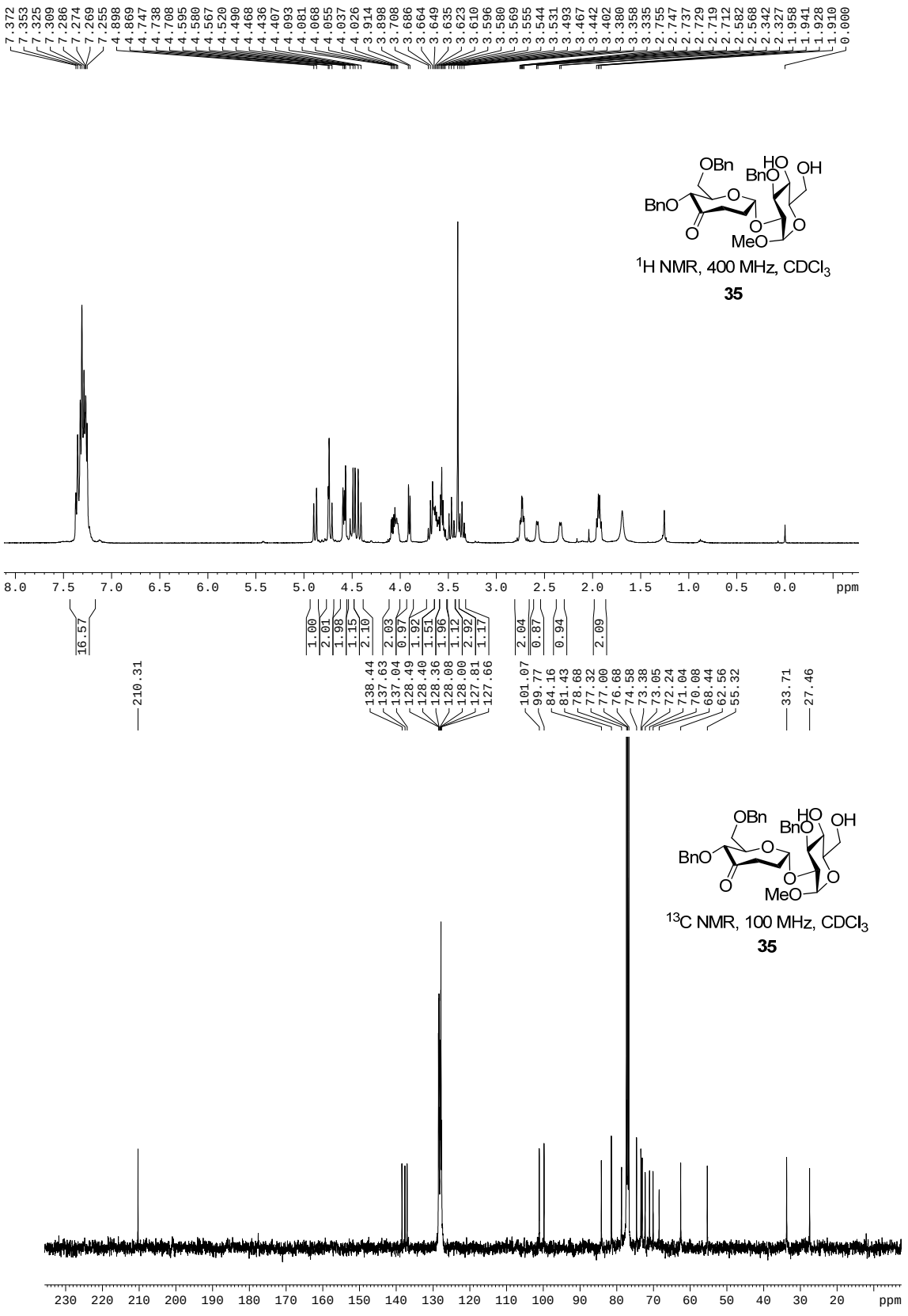
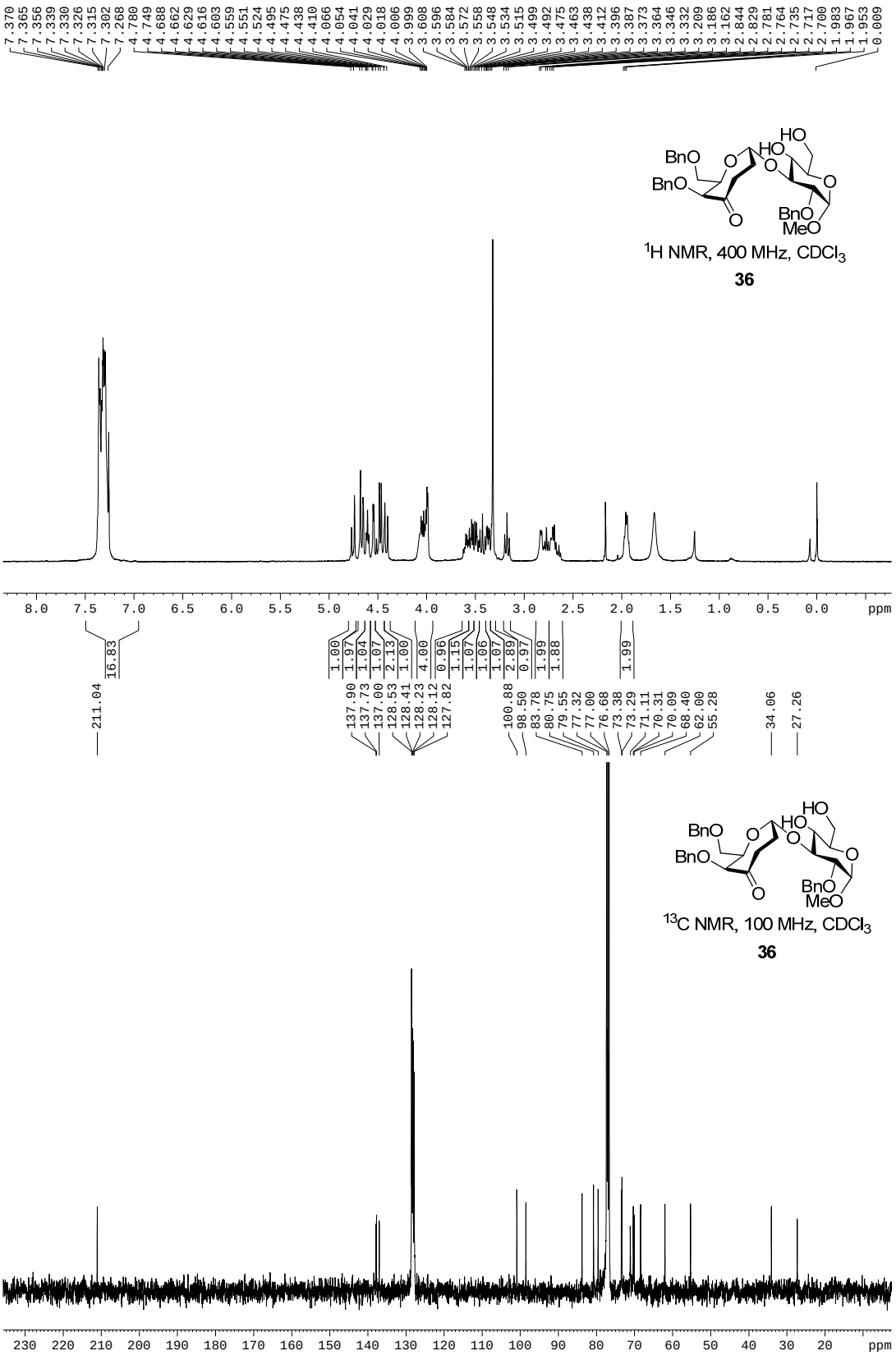
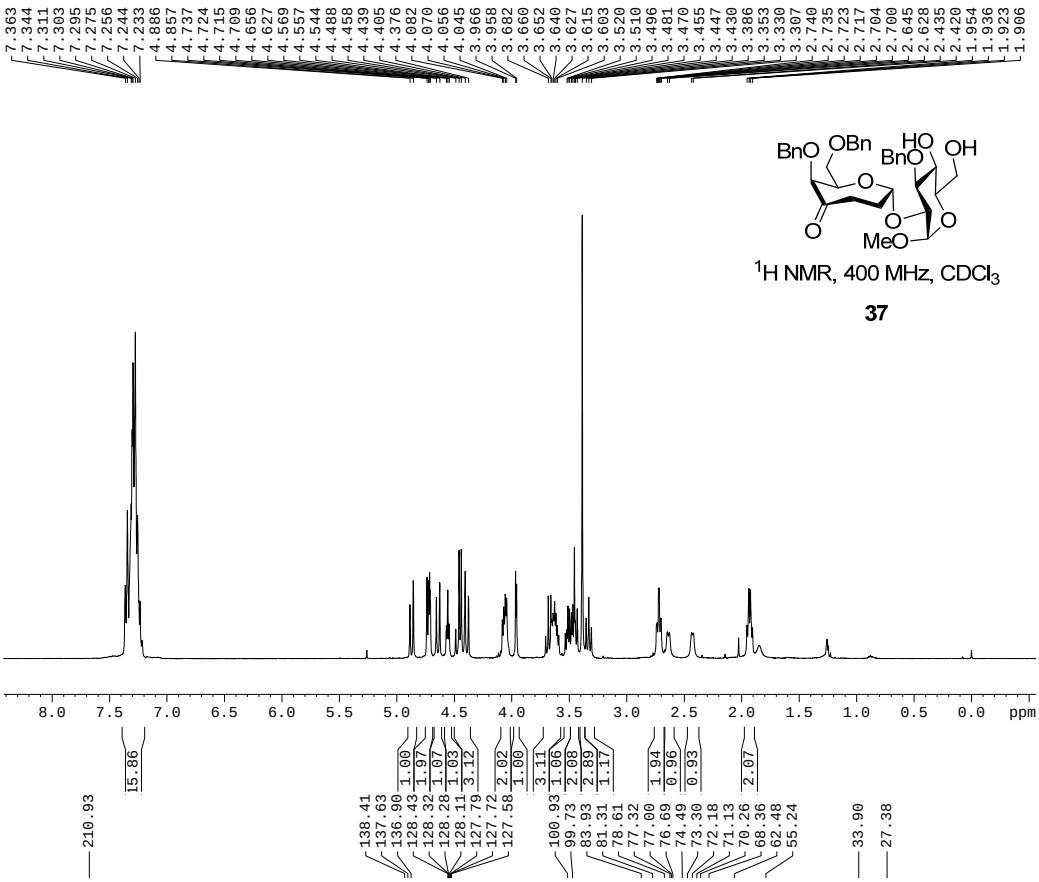
OBn
BnO
O
^{1}H NMR, 400 MHz, $CDCl_3$
30
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
10.67 1.00 0.97 1.02 1.06 1.02 1.09 1.03 1.99 1.96 1.02 1.03 2.03 0.96 0.99 0.99 1.25 2.99 3.01 6.11
209.30
137.99 137.12 128.45 128.35 128.30 127.99 127.62 127.54 109.27 108.55 99.33 96.29 82.82 77.32 77.00 76.68 73.16 73.02 70.95 70.62 70.54 68.79 66.20 65.96 34.92 28.61 26.04 25.96 24.89 24.53
OBn
BnO
O
^{13}C NMR, 100 MHz, $CDCl_3$
30
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

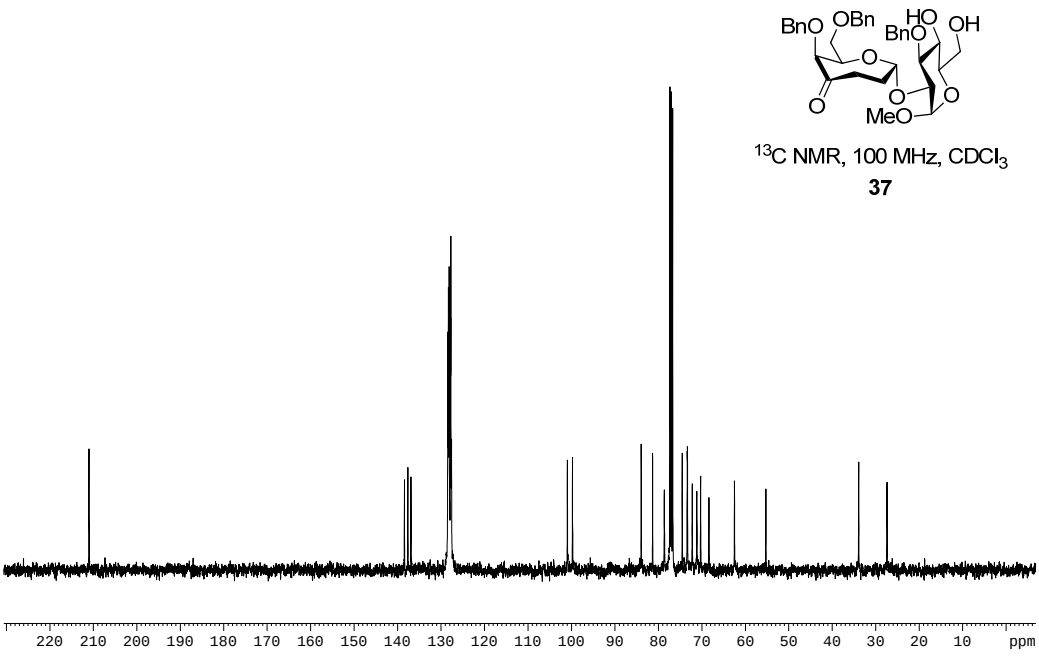

7.328 7.297 7.266 7.239 7.220
5.035 5.024 5.009 4.685 4.655 4.607 4.602 4.587 4.582 4.472 4.443 4.429 4.399 4.370 4.340 4.325 4.320 4.240 4.221 4.202 3.970 3.951 3.932 3.900 3.752 3.720 3.647 3.628 3.615 3.535 3.509 2.712 2.684 2.442 2.360 2.285 1.789 1.651 1.515 1.464 1.369 1.342
BnO OBn
O
O
O
O
O
O
O
O
O
^{1}H NMR, 400 MHz, $CDCl_3$
31
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
11.32
1.00 1.04 1.13 2.08 2.00 2.10 3.07 1.08 2.02 1.02 0.98 1.03 1.11 1.03 3.13 3.12 3.14
209.02
137.95 137.04 128.52 128.36 128.27 128.02 127.57 108.95 108.51 102.16 100.02 82.44 77.32 77.00 76.68 73.14 73.01 70.91 70.13 69.92 69.16 68.45 66.06 61.02 34.82 28.49 26.50 25.90 25.29 23.97
BnO OBn
O
O
O
O
O
O
O
O
O
^{13}C NMR, 100 MHz, $CDCl_3$
31
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.369 7.362 7.357 7.341 7.327 7.307 7.293 7.267 4.776 4.745 4.687 4.656 4.608 4.596 4.579 4.553 4.546 4.521 4.491 4.461 4.438 4.409 4.066 4.054 4.042 4.023 3.999 3.953 3.936 3.637 3.624 3.608 3.597 3.576 3.458 3.433 3.407 3.395 3.386 3.371 3.363 3.331 3.224 3.200 3.177 2.856 2.813 2.796 2.778 2.767 2.750 2.731 2.723 2.706 2.690 2.677 2.660 2.642 1.995 1.980 1.966 1.953 1.936 0.005
HO
HO
BnO
O
O
O
BnO
O
BnO
MeO
1H NMR, 400 MHz, CDCl3
33
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
18.67
1.00 1.07 1.87 2.16 2.34
2.90 1.01
2.99 1.14 1.30 2.98 0.97
3.10
1.90
210.42
137.85 137.65 137.06 128.55 128.50 128.43 128.10 127.86
101.11 98.46 83.79 80.71 79.51 77.32 77.00 76.68 73.39 73.30 73.01 70.96 70.05 68.38 61.98 55.29
33.89
27.15
13C NMR, 100 MHz, CDCl3
33
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.372 7.353 7.325 7.309 7.286 7.274 7.269 7.255 4.898 4.869 4.747 4.738 4.708 4.595 4.580 4.567 4.520 4.490 4.468 4.436 4.407 4.093 4.081 4.068 4.055 4.037 4.026 3.914 3.898 3.708 3.686 3.664 3.649 3.635 3.623 3.610 3.596 3.580 3.569 3.555 3.544 3.531 3.493 3.467 3.442 3.402 3.380 3.358 3.335 2.755 2.747 2.737 2.729 2.719 2.712 2.582 2.568 2.342 2.327 1.958 1.941 1.928 1.910 0.000
OBn
HO
BnO
OH
BnO
O
O
O
O
MeO
1H NMR, 400 MHz, CDCl3
35
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
16.57
1.00 2.01 1.98 1.15 2.10 2.03 0.97 1.92 1.51 1.96 1.12 2.92 1.17 2.04 0.87 0.94 2.09
210.31
138.44 137.63 137.04 128.49 128.40 128.36 128.08 128.00 127.81 127.66 101.07 99.77 84.16 81.43 78.68 77.32 77.00 76.68 74.58 73.38 73.05 72.24 71.04 70.08 68.44 62.56 55.32 33.71 27.46
OBn
HO
BnO
OH
BnO
O
O
O
O
MeO
13C NMR, 100 MHz, CDCl3
35
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


7.370 7.365 7.356 7.339 7.330 7.326 7.315 7.302 7.268 4.780 4.749 4.688 4.662 4.629 4.616 4.603 4.559 4.551 4.524 4.495 4.475 4.438 4.410 4.066 4.054 4.041 4.029 4.018 4.006 3.999 3.608 3.596 3.584 3.572 3.558 3.548 3.534 3.515 3.499 3.492 3.475 3.463 3.438 3.412 3.396 3.387 3.373 3.364 3.346 3.332 3.209 3.186 3.162 2.844 2.829 2.781 2.764 2.735 2.717 2.700 1.983 1.967 1.953 0.009
BnO
BnO
O
HO
HO
O
O
O
BnO
MeO
^{1}H NMR, 400 MHz, CDCl$_3$
36
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
16.83
1.00 1.97 1.04 1.07 2.13 1.00 4.00 0.96 1.15 1.07 1.06 1.07 2.89 0.97 1.99 1.88 1.99
211.04
137.90 137.73 137.00 128.53 128.41 128.23 128.12 127.82
100.88 98.50 83.78 80.75 79.55 77.32 77.00 76.68 73.38 73.29 71.11 70.31 70.09 68.40 62.00 55.28
34.06 27.26
BnO
BnO
O
HO
HO
O
O
O
BnO
MeO
^{13}C NMR, 100 MHz, CDCl$_3$
36
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


BnO OBn HO OH
BnO
O
O
O
O
MeO
^{1}H NMR, 400 MHz, CDCl$_3$
37


BnO OBn HO OH
BnO
O
O
O
O
MeO
^{13}C NMR, 100 MHz, CDCl$_3$
37