SYNTHESIS OF *C*-GLYCOSIDE ANALOGUES OF ALPHA-GALACTOSYLCERAMIDE (KRN7000) AND ITS DERIVATIVES

by

JUN PU

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2006

UMI Number: 3287105

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

This manuscript has been read and accepted for the
Graduate Faculty in Chemistry in satisfaction of the
Dissertation requirements for the degree of Doctor of Philosophy.

__Jan. 30 2006__ _____Richard W. Franck_____
Prof. Richard W. Franck
Date Chair of Examining Committee

__Jan. 31 2006___ ____Gerald W. Koeppl_____
Prof. Gerald W. Koeppl
Date Executive Officer

____Prof. David R. Mootoo_____

____Prof. Alexander Greer_____

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

ABSTRACT

SYNTHESIS OF *C*-GLYCOSIDE ANALOGUES OF ALPHA-GALACTOSYLCERAMIDE (KRN7000) AND ITS DERIVATIVES

by

Jun Pu

Advisor: Professor Richard W. Franck

The *C*-glycoside analogue of alpha-galactosylceramide(KRN7000) **4** was first synthesized by Dr.Yang in Professor Richard W. Franck's lab at Hunter College in 2001. The *C*-glycoside is a powerful immunostimulant and shows better anti malaria and anti cancer activities than its *O*-glycoside counterpart, KRN7000.

We had tried several novel synthetic methods to get this important compound. The successful synthesis method was a linear route (20 steps, 5% overall yield), which was based on Wittig-Sharpless asymmetric epoxidation (SAE) reactions. This approach is a very powerful tool to construct optically active epoxides with high yield and high *ee.* A variety of *C*-glycoside analogues could be made by using two different Sharpless chiral auxiliaries. The target C-glycoside **4** and several C-glycosides derivatives were made and SAR experiments could be carried through. An unusual Lewis acid promoted neighboring group participation double S_N2 opening of the epoxides mechanism was proposed to explain the retention of the 3-*N* stereocenter during the $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ opening of the epoxide.

ACKNOWLEDGEMENTS

Upon completion of my Ph.D. study, I would like to take this opportunity to express my gratitude to my mentor, Professor Richard W. Franck. He is a respectable mentor not only in his knowledge of chemistry, but also in his personality. His inspiration, encouragement, guidance and understanding are key to my completion of my Ph.D work. The invaluable experience in his lab as his last Ph.D student would be unforgettable to me.

I would also like to thank my thesis committee members, Professor David R. Mootoo and Professor Alexander Greer, for their suggestions and encouragement, to professor Klaus Grohmann for sharing his lab space during the last three years. To Dr. Michael Blumenstein for his excellent assistance in the NMR experiments. And to Dr. Clifford E. Soll for outstanding MS support.

Special thanks to the members of Professor Franck's group: Dr. Guangli Yang, Paolo M. Pasetto, Ajit Parhi and Guangwu Chen. The thanks also extended to members of Professor Grohmann's and Professor Mootoo's group: Dr. Kai-feng Chen, Junyi Wang, Yor-yu Chen, Youchun Wu, and Xiaohua Li, Jialiang Li, Xiaofang Yang, Lei Zhu, and Richard Deton.

I would like to express my deepest thanks to my family: my parents in China for endless support; my daughter, Flora, who brings me good luck and happiness; my wife, Kangwen, without her understanding and support, the completion of this dissertation would be impossible.

To my parents

TABLE OF CONTENTS

Page

Chapter 1 Introduction……..……..1

1.1. α-Galactosylceramide (KRN7000)…….….2

1.2. *C*-glycosides ……..…..3

1.3. *C*-glycoside analog of KRN7000…….5

1.3.1 First generation synthesis - Ramberg–Bäcklund Rearrangement approach...5

1.3.2.Second generation synthesis: Cross- Metathesis (CM) and Julia-Lythgoe-Kocienski olefination approach……...9

1.3.3. Bioactivities of *C*-glycoside analog of KRN7000……...12

1.4. Synthesis of Structurally Similar *C*-glycosides……..14

Chapter 2 Results and Discussion – Synthesis of *C*-glycoside Analogues of KRN7000 ……..**18**

2.1. [3+2] Dipolar Cycloaddition- Isoxazoline Approach…….19

2.1.1. Retrosynthetic Analysis……...19

2.1.2. Synthesis of Common Starting Material: The Known Aldehyde 51……...21

2.1.3. Isoxazoline Approach……..23

2.1.4. Isoxazole Approach…….25

2.2. Wittig-Sharpless Asymmetric Epoxidation (SAE) Approach……27

2.2.1. Retro synthetic Analysis…….27

2.2.2. Synthesis of the target *C*-glycoside…….29

2.2.3: Synthesis of C-glycosides from $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ Opening of the Epoxide.44

2.2.4: Explanations for the NMR discrepancy……..51

2.2.4.1 The first explanation and Synthesis of *C*-glycoside analogues using the (*2S, 3S*) epoxide 105 as the starting material……...52

2.2.4.1.1 The first explanation……...52

2.2.4.1.2 Synthesis of two *C*-glycoside analogues using the (*2S, 3S*) epoxide 105 as the starting material……..54

2.2.4.2: The second explanation and NMR proof…….60

2.2.4.2.1: The second explanation and synthesis of the 5-membered ring systems……..…….60

2.2.4.2.2: nOe analysis……...64

2.2.4.3: Further NMR Evidence of Stereochemistry…….70

2.2.4.4:Mechanistic Explanation of Remote Neighboring Group Participation: Unusual Lewis acid promoted Double S_N2 Replacement and Retention of N Stereo center……..77

2.2.4.5: Summary of structure assignment…….84

2.2.5: Synthesis of the *C*-glycoside analogue derivatives……..85

2.3. Conclusions…….87

Chapter 3: Experimental Section……...90

Chapter 4: Appendix ……..……..154

References……..259

List of Figures

Page

Figure 1.1 Structures of AGL-9b and KRN7000……1

Figure 1.2 Compound 3, OCH, an analogue of KRN7000……..3

Figure 1.3: Definition of *C-g*lycoside……4

Figure 1.4: Compound 4, *C*-glycoside analogue of KRN7000……6

Figure 1.5: Carbohydrate precursors for the second generation synthesis……10

Figure 1.6: Assay for sporozoites in mouse liver……...13

Figure 1.7: β-*C*-glycoside analogues of KRN7000……..…15

Figure 2.1: Compound 4, *C*-glycoside analogue of KRN7000……..…18

Figure 2.2: Retrosynthetic analysis: isoxazoline approach……..19

Figure 2.3: Retrosynthetic strategy for α-*C*-galactosylceramide 4……..…27

Figure 2.4: Sharpless empirical rule…….….31

Figure 2.5: Cram-chelation controlled Grignard addition……..38

Figure 2.6: Spectrum of compound 4 synthesized by Dr. Yang and Jun Pu……..…42

Figure 2.7: Spectrum of *C*-glycoside 87, the major isomer……..…43

Figure 2.8: Complexation of Ti alkoxide with epoxide……47

Figure 2.9: ^{1}H spectrum of *C*-glycosides 4, 100 and 102……..50

Figure 2.10: Two *C*-glycosides: 4 and its 5-epimer 87…….51

Figure 2.11: ^{1}H spectrum for compound 4……58

Figure 2.12: ^{1}H spectrum for compound 115 and 117……..59

Figure 2.12: nOe effect of compoud 126, derived from NaN_3 opening of the (2*R*, 3*R*) epoxide 73…….65

Figure 2.13: NOESY spectrum for compound 126……...66

Figure 2.14: NOESY spectrum for compound 120……...69

Figure 2.15: NOESY spectrum for compound 123……...69

Figure 2.16: Compound 120, from the (2*S*, 3*S*) epoxide 105, and compound 123, from the (2*R*, 3*R*) epoxide 73 opened by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$……70

Figure 2.17: Compound 3, OCH, an analogue of KRN7000……71

Figure 2.18: The two *C*-glycoside analogues of OCH, 37 and 38……72

Figure 2.19: Similar structure Compounds 38 and 102……...74

Figure 2.20: Comparison of ^1H spectrum for compounds 38 and 102 synthesized by Jun Pu ……..75

Figure 2.21: Comparison of ^1H spectrum for compound 102 by Guangwu Chen and Jun Pu……...76

Figure 2.22: Mootoo's explanation for the neighboring group participation……78

Figure 2.23: Summary of structure assignment……84

Figure 2.24: Summary of synthesis……88

List of Tables

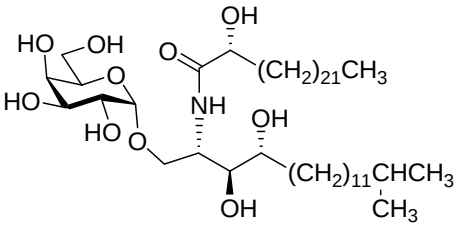
Page

Table 1 Comparison of some chemical and physical properties of *O*- and *C*-glycosides in the anomeric region……4

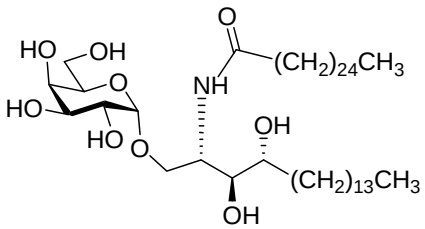
Chapter 1 Introduction:

1.1. α-galactosylceramide (KRN7000)

Agelasphins (AGLs) [1-4] are a series of glycosphingolipids with α-galactosylceramide structures. They were first isolated from an Okinawan marine sponge *Agelas mauritianus* by scientists at Kirin Pharmaceuticals in the early 1990's as active substances. Agelasphin-9b (AGL-9b), the main compound of the AGLs, was observed to have potent antitumor activities against *in vivo* models of several murine tumor cell lines. Various analogues of AGL-9b were synthesized and structure-activity studies of those compounds revealed that a slightly simpler analogue of the natural agelasphins, (2*S*, 3*S*, 4*R*)-*O*-(α-D-galactopyranosyl)-2-(*N*-hexacosanoylamino)-1, 3, 4 octadecanetriol, an α-galactosylceramide (α-GalCer) named KRN7000, had demonstrated the best activities of the compounds tested and the functional groups and the configuration of KRN7000 were optimal [3,5-11] (**Figure 1.1**).



1, Agelasphin-9b



2, **KRN7000**

Figure 1.1 Structures of AGL-9b and KRN7000

KRN7000 is composed of three parts: a carbohydrate unit (galactosyl part), a long chain fatty amide component (FA) and a long chain phytosphingosine base (LCB). The phytosphingosine moiety has three continguous chiral centers in (2*S*, 3*S*, 4*R)*

configurations and is a key point for its function. The synthesis of phytosphingosines was reviewed in detail by Howell *et al* [12].

Detailed studies revealed that KRN7000 is a powerful immunostimulant which can induce formation of both interferon-γ (IFN-γ) and interleukins (IL)-12 and IL-4 by first binding to antigen-presenting CD1d cells whereupon the resulting complex then binds to natural killer T (NKT) cells [13,14]. This group of cytokines, which induce antagonistic biological effects such as Th-1 and Th2-type responses and so on, apparently limit α-GalCer from eliciting a maximum of either response [15]. KRN7000 is a potent leading compound for the development of immunostimulant drugs. Researches unveiled KRN7000's remarkable activity against a disparate group of diseases, such as cancer, including hepatic metastases of pancreatic cancer [16], hepatic metastases of colon cancer [17], melanoma [18], and primary tumor formation in three different models [19], as well as malaria [20], juvenile diabetes [21], hepatitis B [22], and autoimmune encephalomyelitis [23], in murine/whole animal versions of all the diseases. Recently, two groups reported the X-ray crystal structures of KRN7000 bound to both murine and Human CD-1d molecules, which illustrated the binding complex between α-Galcers and the CD-1d receptors in detail [24,25]. Information obtained from the crystal structures provided a basis for understanding the effect of the structure variations reported before the crystal structure was disclosed.

The acceptable structure variations were the insertion of "taggants" at the terminus of the fatty amide (FA) chain through a second amide linkage, the presence or absence of an α- hydroxy group in the fatty amide, replacement of the 6-OH at the galactosyl residue, and removal of the hydroxy group at C4 of the phytosphingosine moiety [5,9]. The most significant effect of lipid variation is the truncation of the phytosphingosine lipid chain length from a hydrocarbon chain length of 14 to 5 carbons. This material,

known as OCH (**Figure 1.2**), (3S, 4S, 5R)-1-(α-D-galactopyranosyl)-3-tetracosanoylamino-4, 5-decanediol, has a different pathway in activating NKT cell responses and has a superior effect on the murine model of encephomyelitis [23].

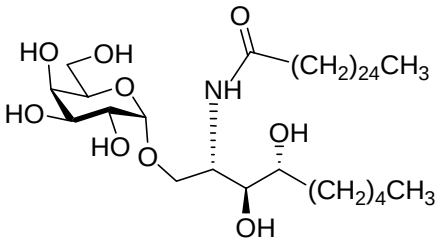


Figure 1.2 Compound 3, OCH, An analogue of KRN7000

The goal of our research group at Hunter College is to study a more deep-seated structure variation of the α-galcer, namely replacement of the anomeric *O* atom by the CH_2, i.e. synthesis of the *C*-glycoside.

1.2. *C*-glycosides

C-glycosides are 1-*C*-linked glycosyl derivatives in which the anomeric *exo*-oxygen atom of a glycoside is replaced by a carbon atom (**Figure 1.3**). *C*-glycosides are important because the anomeric atom has been transformed from a hydrolytically labile acetal functionality to a more stable ether functional group. The assumption for the study of *C*-glycoside analogs of naturally occurring *O*- and *N*-glycosides is that the conformational differences between the *O*- (or *N*-) linked natural material and the *C*-linked analog would be minimal and the recognition and binding of the *C*-analogue would be similar to that of the natural material.

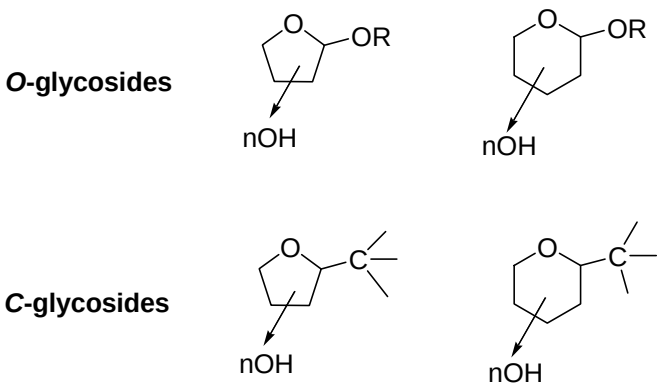


Figure 1.3: Definition of *C*-glycoside

The structure and chemical differences between *O*- and *C*-glycosides are summarized in **Table 1** [26].

Table 1 Comparison of some chemical and physical properties of *O*- and *C*-glycosides in the anomeric region.

***O*-glycosides**	***C*-glycosides**
Anomeric effect	No anomeric effect
Exo-anomeric effect	No *exo*-anomeric effect
Hydrogen bonding	No hydrogen bonding
Cleaved by acid and enzymes	Stable to acid and enzymes
Conformation governed by *exo*-anomeric effect and steric interactions	Conformation governed by steric interactions

The bond lengths, Van der Waals radii and electronegativity (*O* versus *C*) and bond rotational barriers are very similar between *O*- and *C*-glycosides. The most apparent

difference between them is the absence of the anomeric and *ex*o-anomeric effect in *C*-glycosides, while these are unique characteristics of saccharides and play an important role in the chemical and structure behavior of *O*-glycosides. Additionally, *C*-glycosides are incapable of forming hydrogen bonds at the anomeric position because of the absence of a hydrogen-bonding acceptor.

The major difference between *O*- and *C*-glycosides relates to their chemical reactivity. The anomeric atom of *O*-glycosides, which is an acetal, is susceptible to both acidic and enzymatic cleavage, whereas *C*-glycosides are resistant to hydrolysis.

The minimal modification by replacement of the oxygen linkage in the *O*-glycoside to the carbon isostere changes the chemistry of glycosidic bonds and hence results in improved chemical stability.

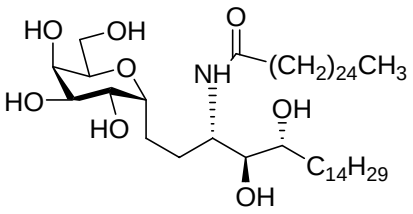
In recent years, several naturally occurring *C*-glycosides have been identified and some were reported with interesting biological properties that attracted interest towards the synthesis of these materials. Many synthetic methods to *C*-glycosides have been described in two books [26,27] and have been reviewed by Postema [27], Levy [26], Sinay [28], Beau [29], Nicotra [30] and Linhardt [31].

1.3. *C*-glycoside analog of KRN7000:

1.3.1 First generation synthesis - Ramberg–Bäcklund rearrangement approach:

Since KRN7000 is a potent lead compound for the development of immunostimulant drugs, and all the published structure variations are concerned with the side chain and the fatty amide, the more fundamental modification had not been done before our group undertook the challenge. Our group proposed a synthesis of compound **4**, the

C-glycoside analogue of KRN7000 to compare its bioactivities with that of the *O*-glycoside (**Figure 1.4)**.

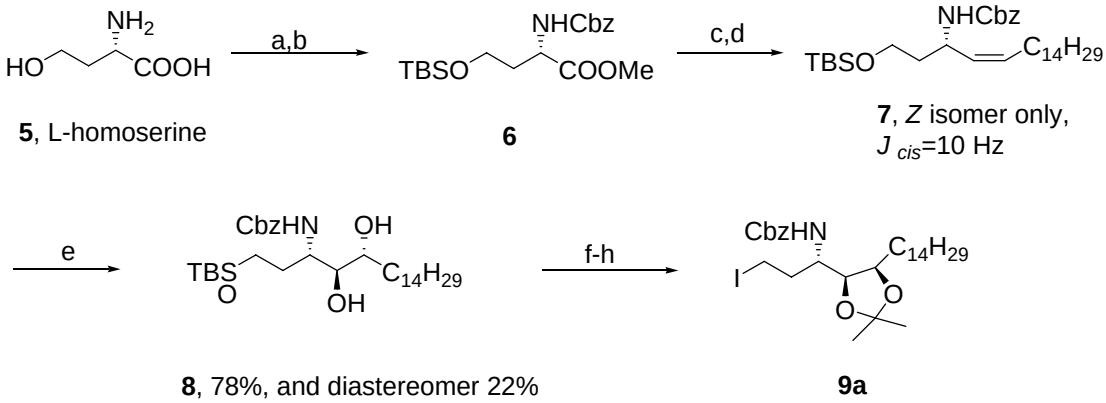


4

Figure 1.4: Compound 4, *C*-glycoside analogue of KRN7000

The first convergent total synthesis of this important *C*-glycoside was achieved in 2001 by the Franck group [32] in 28 steps utilizing the Ramberg–Bäcklund rearrangement to connect a homophytosphingosine side chain to galactose as the key C-C bond forming step.

Synthesis of the homophytosphingosine component mimics a synthesis of phytosphingosine reported by Nakanishi and co-workers [33] which began with *L*-serine *via* Garner aldehyde. Starting from the commercially available and expensive *L*-homoserine **5**, the Cbz-substituted homophytosphingosine **8** was obtained in a six-step sequence with not very high diastereoselectivity (<70% *de*) in the Sharpless asymmetric dihydroxylation step (AD-mix-β) of the *cis* double bond. The X-ray structure of a crystalline derivative of the major isomer from the Sharpless AD reaction revealed the anticipated stereochemistry of the OH's. The homophytosphingosine was then converted to the iodo derivative **9a** in 3 routine steps, which was then linked with thiogalactose **9** to provide the β-D-thio-galactose (**Scheme 1.1**).



5, L-homoserine

6

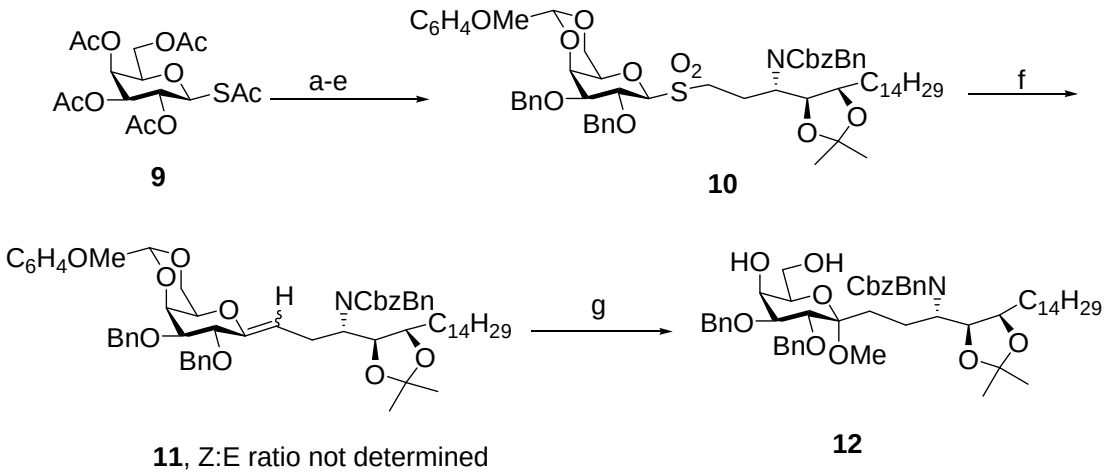
7, *Z* isomer only, J_{cis}=10 Hz

8, 78%, and diastereomer 22%

9a

Scheme 1.1: conditions and reagents: (a) (i) BnOCOCl, $NaHCO_3$, (ii) $TMSCHN_2$, MeOH, 62%, two steps (b) TBSCl, imidazole, CH_2Cl_2, 95%; (c) DIBAL-H, THF, -78°C, 93% (d) NaHDMS, $C_{15}H_{31}PPh_3Br$, -78°C - r.t, 85%; (e)AD-mix-β, 84%; (f) $(CH_3)_2C(OMe)_2$, PPTS, CH_2Cl_2, 95%;(g) nBu_4NF, AcOH, THF, 86%; (h) I_2, PPh_3, THF, reflux, 85%.

Conversion of the thiogalactoside **9** to the sulfonylgalactoside **10** was completed in 5 steps. The sulfone **10** was then subjected to Chan's modification of the Ramberg-Bäcklund reaction condition [34] in the presence of $C_2F_4Br_2$, *t*-BuOH, and KOH-Al_2O_3 at reflux to afford the alkene **11** in 70% yield. The Z:E ratio of the alkene was not determined (**Scheme 1.2**).



9

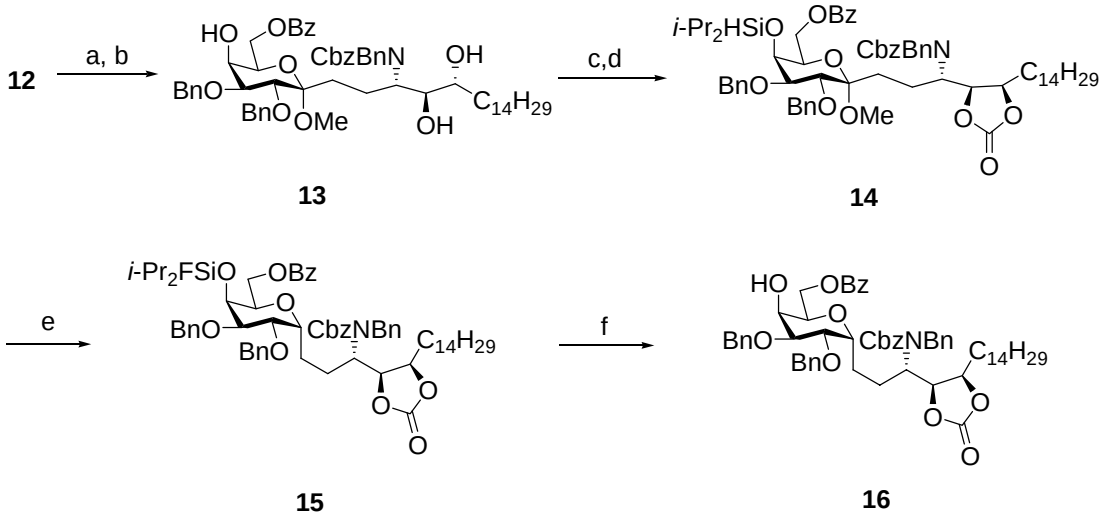
10

11, Z:E ratio not determined

12

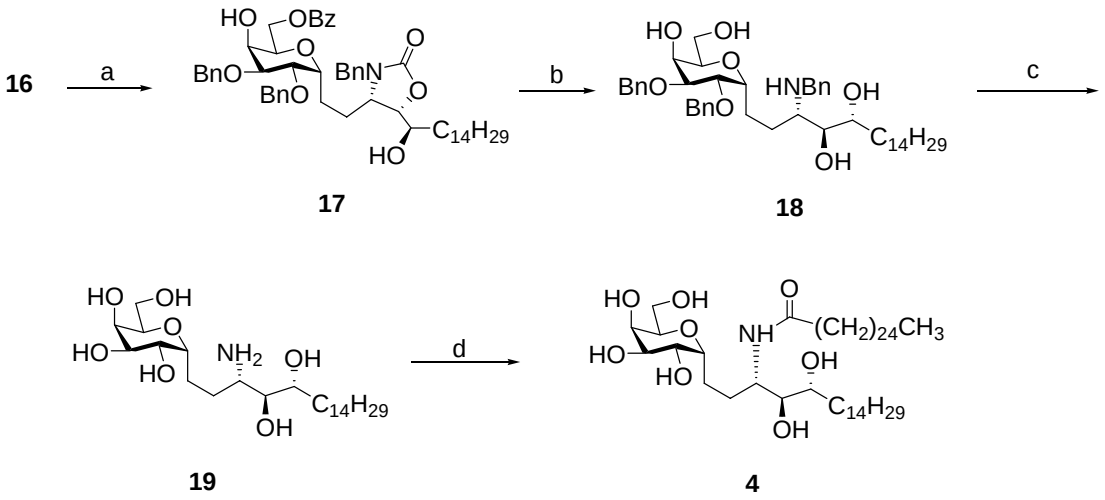
Scheme 1.2: conditions and reagents: (a) (i) NH_2NH_2/HOAc, DMF; (ii) Iodo **9a**, Et_3N, 90% (b) NaOMe, MeOH; (c) P-$MeOC_6H$-$CH(OMe)_2$, P-TsOH, DMF/CH_2Cl_2, 86% for 2 steps (d) NaH, BnBr, THF, 83%; (e) MMPP, THF/H_2O/EtOH, 60°C, 93% (f) $C_2F_4Br_2$, t-BuOH, KOH/Al_2O_3, reflux, 70%; (g) TMSCl, MeOH, 0°C, 66%.

A silane group was then introduced at the 4-hydroxyl position of galactose. The second key reaction was a stereoselective introduction of the α anomeric configuration through an intramolecular hydride transfer to the β-face of compound **14** formed from the *exo*-glycal **11** from the silyl group to an intermediate carbocation center (**Scheme 1.3**).



Scheme 1.3: conditions and reagents: (a) BzCl, Et_3N, CH_2Cl_2, 83%; (b) 1 N HCl/Et_2O, MeOH, 80%; (c) triphosgene, pyridine, CH_2Cl_2, 83%; (d) *i*-Pr_2SiHCl, imidazole, DMF, 96%; (e) 5equ. BF_3/Et_2O, CH_2Cl_2, 0^{o}C; (f) TBAF, THF, 76%

The synthesis was completed through a series of deprotections and ceramidation to afford compound **4**, the target *C*-glycoside analog of KRN7000 (**Scheme 1.4**).

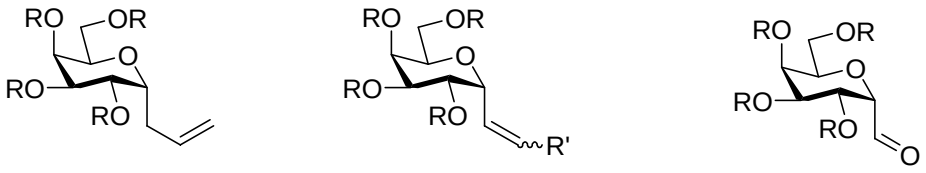


Scheme 1.4: conditions and reagents: (a) 1,4-dioxane/H_2O, NaOH, reflux, 90%; (b) KOH/EtOH, reflux, 80%; (c) 10% Pd/C, 1N HCl, cyclohexene/MeOH, reflux, 90%; (d) p-nitrophenyl hexandecanoate, THF, DMAP, 48 h, rt, 60%.

The first generation synthesis of the *C*-glycoside analogue of KRN7000 was completed in 28 steps and required several manipulations to install the needed α-*C*-galactoside configuration. Unfortunately, the key reagent for Ramberg-Bäcklund rearrangment, the freon, tetrabromodifluoroethane, CBr_2FCBr_2F, is on the EPA "ozone" destroyer list and is no longer commercially available. Thus this very nice modification of Chan's conditions is now defunct and an alternative bromination reagent must be found.

1.3.2. Second generation synthesis: Cross-Metathesis (CM) and Julia-Lythgoe-Kocienski olefination approach:

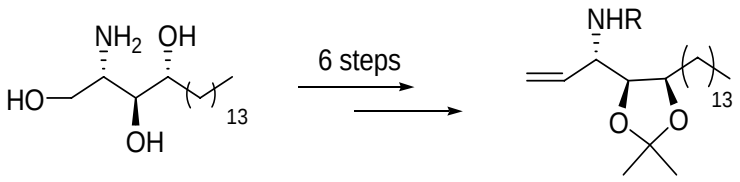
Two other shorter convergent synthesis methods were also devised to make larger quantities of the potent analogue available to the immunology community[35]. The synthesis utilized well-established methodology of silyl-stabilized axial alkylation of anomeric carbonium ions. Several easily prepared galactose materials were used as sugar starting materials (**Figure 1.5)**.



20, R=Ac or Bn **21, R'=H or CH_3** **22**

Figure 1.5: Carbohydrate precursors for the second generation synthesis

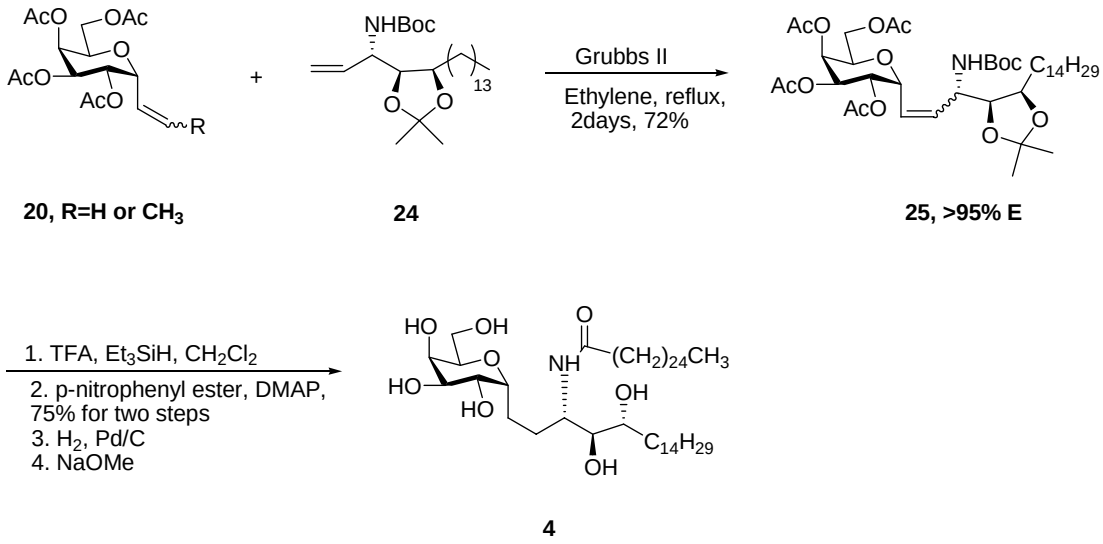
A novel ethylene-promoted CM assembly would link the suitably protected sugar coupling partners with the terminal olefin of the sphingosine side chain together. The terminal olefinic form of the sphingosine side chain **24** was prepared from the commercially available phytosphingosine **23** in six steps with high yield. The stereochemistry of the side chain was then ensured without question (**Scheme 1.5**).



23, Phytosphingosine **24, R=Cbz or *t*-Boc**

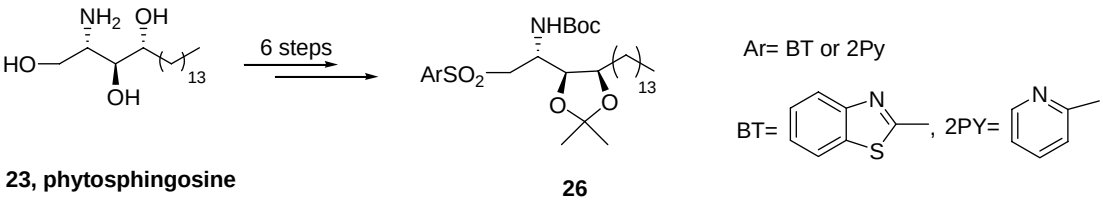
Scheme 1.5: Synthesis of the phytosphingosine side chain

In the presence of ethylene, the CM reaction gave the *trans*-alkene **25** in good yield. The target compound **4** was synthesized with an overall yield of 30% after 11 steps for the *C*-glycoside analogue of KRN7000 starting from **23** (**Scheme 1. 6**).



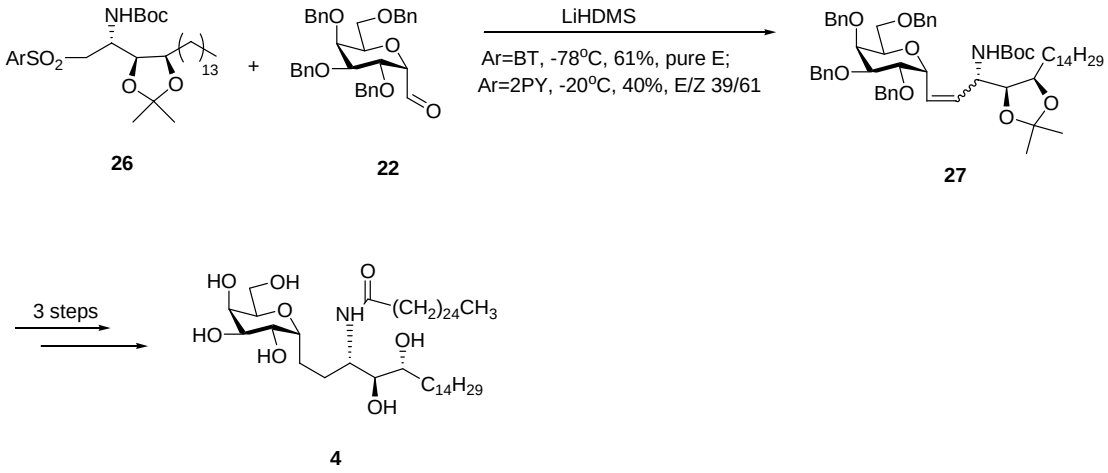
Scheme 1.6: Cross-Metathesis approach

Another convergent synthesis also utilized **23**, which was easily converted to a family of sulfones for use in Julia-Lythgoe-Kocienski olefinations (**Scheme 1.7**).



Scheme 1.7: Synthesis of sulfone compounds

Julia-Lythgoe-Kocienski olefination between the aldehyde partner and sulfones gave alkene with various E/Z ratios. The alkene products of the Julia-Lythgoe-Kocienski olefination could be transformed to saturated analogs of KRN7000 *via* hydrogenation/hydrogenolysis whereas the use of Birch reduction could afford analogues where the 1, 2 alkene linkage was preserved (**Scheme 1.8**).



Scheme 1.8: Julia-Lythgoe-Kocienski olefination approach

Those two convergent synthetic approaches were shorter, compared with the 28 step route for the first generation synthesis, and provided the *C*-glycoside analogue of KRN7000 in large quantities, together with 1, 2 E/Z alkene analogues have also been made to understand the conformational effects on the bioactivity. But it was difficult to make variations on the phytosphingosine side chain.

1.3.3. Bioactivities of the *C*-glycoside analog of KRN7000

As expected, our *C*-glycoside compound **4** was found to demonstrate outstanding activity, even in comparison with the very active *O*-glycoside **2,** KRN7000**.** The exciting results for our synthetic materials stems from the very sizable improvement in the "curative" effects of the *C*-glycoside compound **4** over the *O*-glycoside **2.** Although the "cure ratio" for *C/O* is not the same with different diseases: 1000/1 for malaria, 100/1 for melanoma, 2/1 for vaccine adjuvant effect, all the assays favor our *C*-glycoside **4** [36,37].

For example, in the mouse malaria model, whereby the mice were treated with galactosylceramide and then, after an interval, were challenged with malaria (*P.*

yoeli). After a further interval, the animals were sacrificed, and their livers were assayed for the sporozoite stage of malaria. Both the *O*- and the *C*-glycoside **2** and **4** were very effective at reducing sporozoite levels at a dosage level of 1 μg per mouse relative to the control. However, the *C*-glycoside **4** continued to show excellent activity at the 1-ng level. Thus, **4** is approximately 1000 times more protective than the *O*-glycoside **2** (**Figure 1.6**)[36, 37].

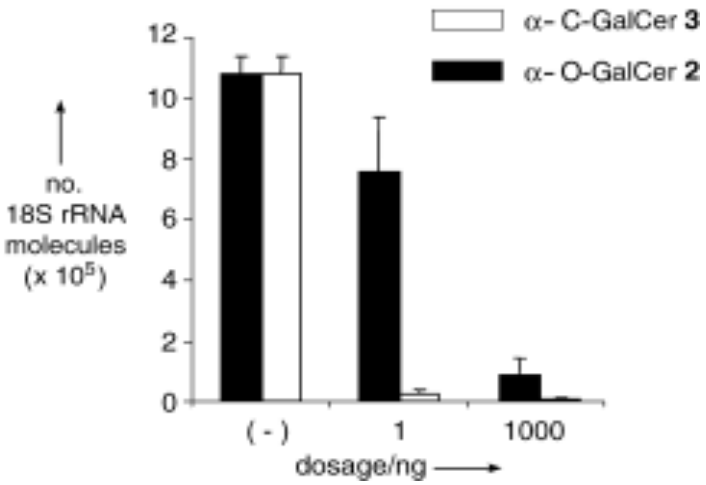


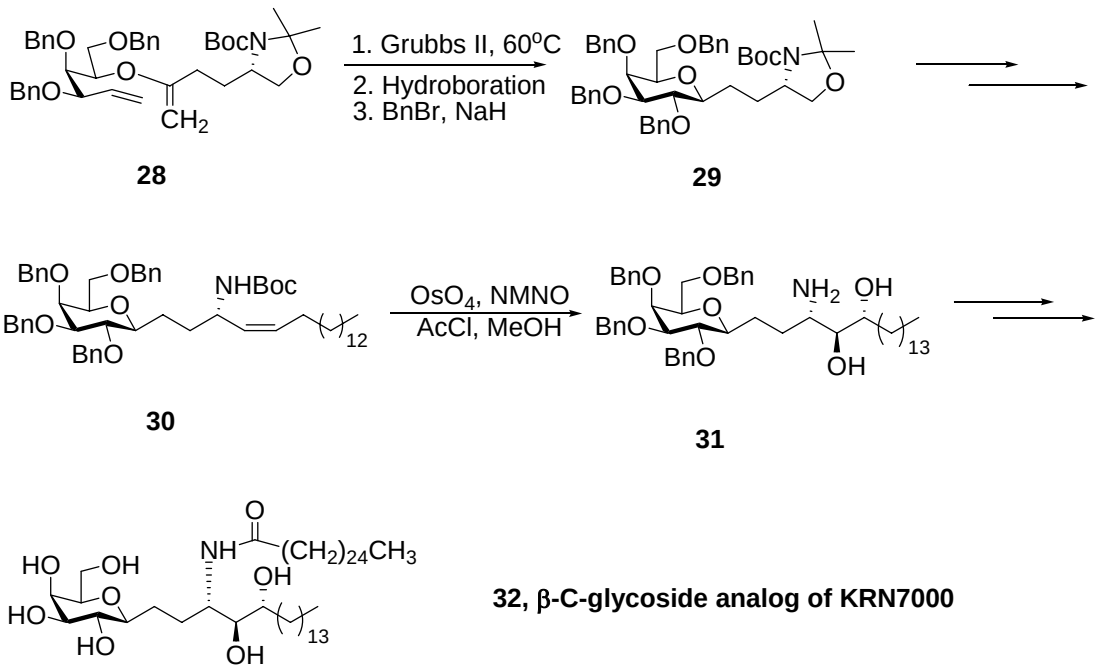
Figure 1.6: Assay for sporozoites in mouse liver with 1) no glycolipid, 2) 1 ng of **2** or **4**, and 3) 1 μg of **2** or **4**. Number of *P. Yoelii* specific 18S rRNA molecules (determined 42 h after challenge with 10000 viable sporozites) is plotted against dosage of **2** or **4**.

At the present time, the explanation for the enhanced activity in mice of the *C*-analogue is based on the differences in the behavior of the target NKT cells toward stimulation by the *O*-glycoside and the *C*-glycoside. KRN7000 causes a down regulation of activity of the NKT cell after its initial burst of cytokine secretion. It appears that the *C*-glycoside analogue perhaps binds a little differently and does not provoke down regulation so that the NKT cells continue to produce cytokines. Additionally, because of the proposed difference in binding, the *C*-glycoside does not stimulate production of a high level of IL-4, since IL-4, a Th2 (T helper cell of type 2)

cytokine, effectively antagonizes the effect of IFN-γ, a Th1 cytokine, the effects of the *O*-glycoside are modulated, whereas the *C*-glycoside is able to exert its full Th1 effect, These two differences, down regulation effects and Th1/Th2 levels, appear to explain the power of the *C*-glycoside analogue [36, 37].

1.4. Synthesis of structurally similar *C*-glycosides:

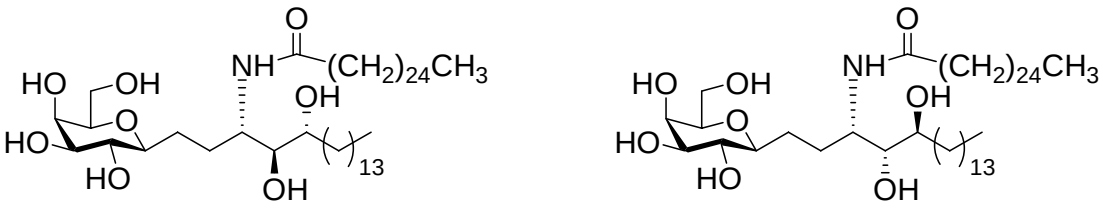
Recently, some structurally similar *C*-glycoside analogues of KRN7000 have been synthesized. The bioactivity information obtained from those compounds provided an aspect about how structure variations could influence the activities of *C*-glycosides.



Scheme 1.9: Synthesis of β-*C*-glycoside anlogues of KRN7000

Halina Pietrazkewicz *et al*. [38] synthesized a β-*C*-glycoside analog of KRN7000 starting from the natural amino acid aspartic acid in 12 steps. The key reactions were intramolecular RCM and osmylation of a *cis* olefin which proceeded without

selectivity delivering a 1:1 mixture of separable *erythro*-isomer and *threo*-isomer, which were both converted to the corresponding β-*C*-glycoside analogues of KRN7000 (**Scheme 1.9**).



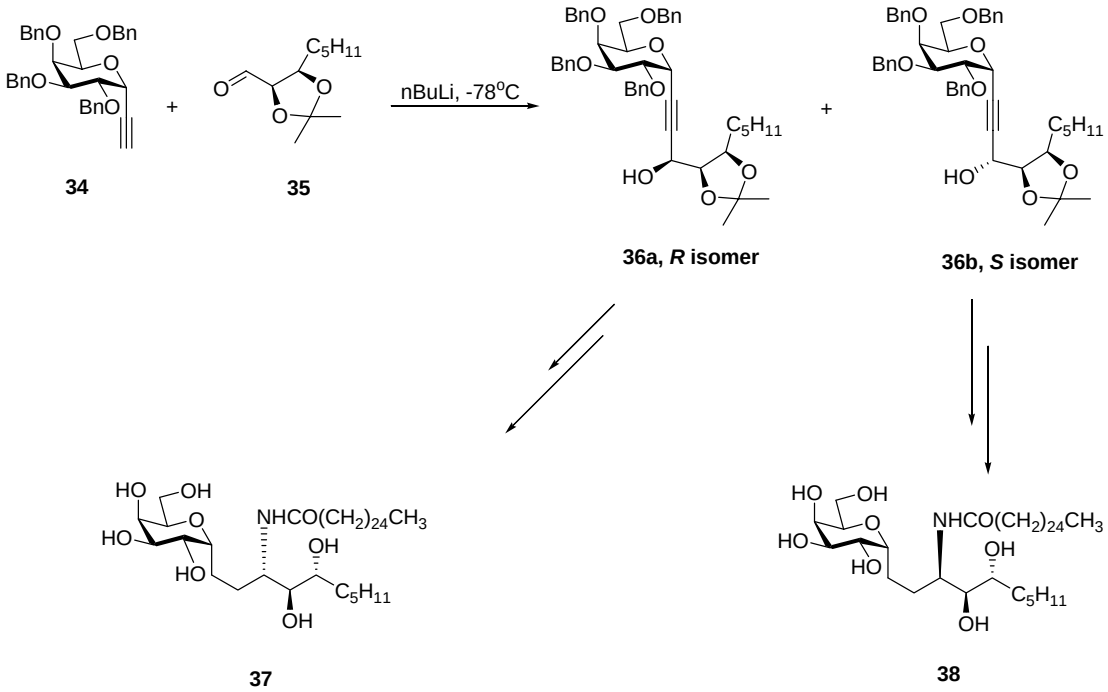
32, erythro isomer **33, threo-isomer**

Figure 1.7: β-*C*-glycoside analogues of KRN7000

Primary bioactivity data illustrated that the *erythro* isomer **32** and *threo* isomer **33** of β-*C*-glycoside analogs of KRN7000 (**Figure 1.7**) showed comparable low level of *in vitro* activity in the assay against solid tumor cells versus either leukemia or normal cells. (C38, colon-38 solid tumor cell; L1210, Leukemia cells; CFU-GM, normal murine cells)

Tetsuya Toba *et al*. [39] synthesized a *C*-glycoside analogue of an immunomodulating α-galactosylceramide compound **3** (which has been named as OCH), (3*S*, 4*S*, 5*R*)-1-(α-D-galactopyranosyl)-3-tetracosanoylamino-4, 5-decanediol, which has a truncated shorter C5 sphingosine side chain than our *C*-glycoside analogue of KRN7000. The convergent synthesis features the nucleophilic addition of an α-ethynyl sugar **34** to the phytosphingosine-precursor aldehyde **35**, which was derived in six steps from *L*-arabinose endowed with suitable stereochemistry corresponding to the vicinal hydroxyl groups in the phytosphingosine moiety. The coupling reaction afforded a 3.2:2 mixture of *R* isomer **36a** and *S* isomer **36b**, in 47% and 30% yields, respectively.

The *R*-isomer **36a** was converted to the corresponding *C*-glycoside analogue **37** in a straightforward and efficient manner. The *S* isomer **36b** was also transformed to a *C*-glycoside analogue **38** which was a N epimer (**Scheme 1.10**).



Scheme 1.10: Synthesis of the *C*-glycoside analogues of 3, OCH, and its *N* epimer

Preliminary biological tests showed that the truncated *C*-glycolipid **37** did not initiate *in vitro* IL-4 and INF-γ production in splenocytes but increase serum level of IL-4 in C57BL/6 mice *in vivo*. Thus this compound proved to possess the pharmacological profiles distinctively different from that of the corresponding *O*-glycoside compound **3.**

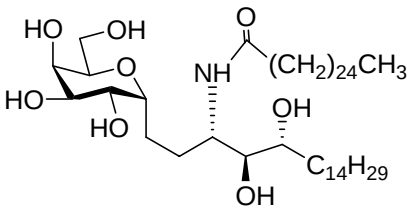
The bioactivity data obtained from those *C*-glycosides illustrated how side chain length, stereo configurations and conformation variations could further attenuate the activities of *C*-glycoside analogue of KRN7000. Even though Franck`s group had successful methods for preparing *C*-glycoside analogues, the chemistry was not

without problems: (i) The Ramberg-Backlund reaction was not practical unless a new brominating agent could be discovered. (ii). The CM approach required expensive reagents. (iii) Both the CM and Julia-Lythgoe-Kocienski olefination approaches were not easily adapted to varying the phytosphingosine structure. That prompted us to explore another synthesis route and to synthesize some structurally varied analogues.

Chapter 2: Results and Discussion:

Synthesis of *C*-glycoside analogues of KRN7000:

Several synthetic approaches to compound **4,** the *C*-glycoside analogue of KRN7000 were tried simultaneously in our lab. Several synthetic routes had been tried. The first route we tried was a convergent isoxazoline approach based on the [3+2] cycloaddition between a nitrile oxide and a long chain alkene. The second approach was a similar isoxazole method, which included [3+2] cycloaddition between the nitrile oxide and a long chain alkyne to afford an isoxazole. Those two approaches failed or gave low yield of amino triol. The third and the successful one was the Wittig-Sharpless asymmetric epoxidation (SAE) approach, using diastereoselective approaches such as SAE, regioselective ring opening of the epoxide, chelation-control Grignard reaction and so on, to construct the target molecular and several *C*-glycoside derivatives of KRN7000.



4

Figure 2.1: Compound 4, *C*-glycoside analogue of KRN7000

2.1. [3+2] Dipolar Cycloaddition - isoxazoline approach:

2.1.1. Retrosynthetic analysis:

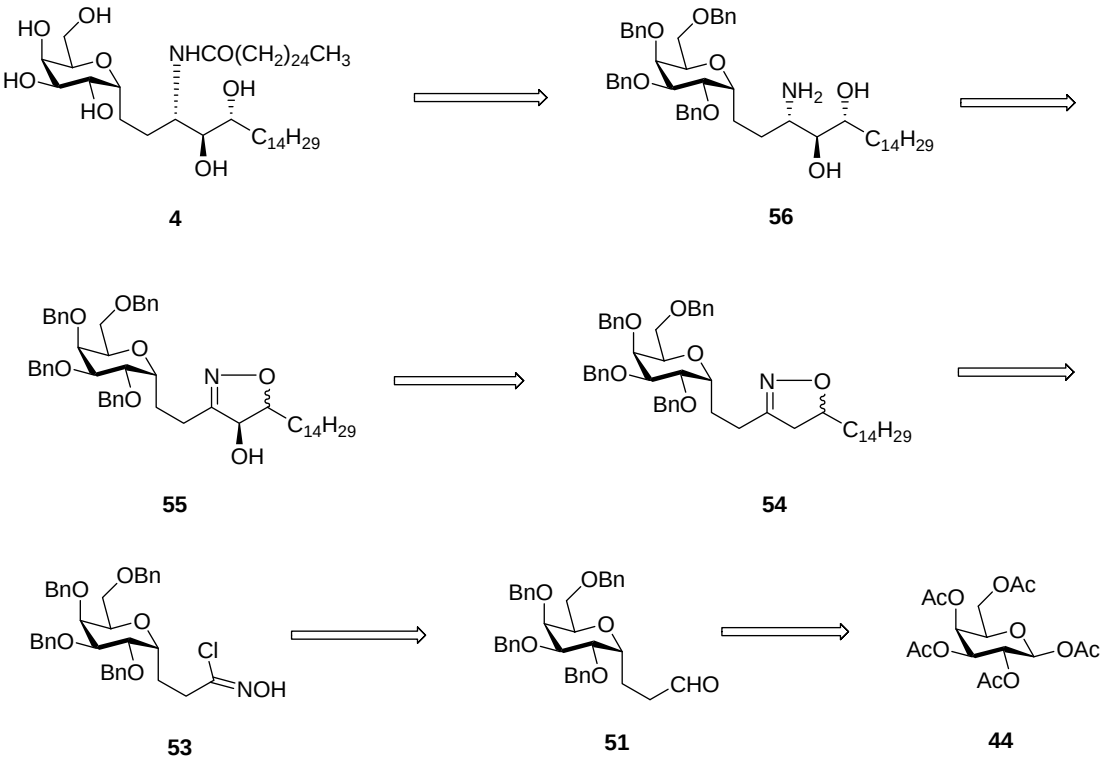


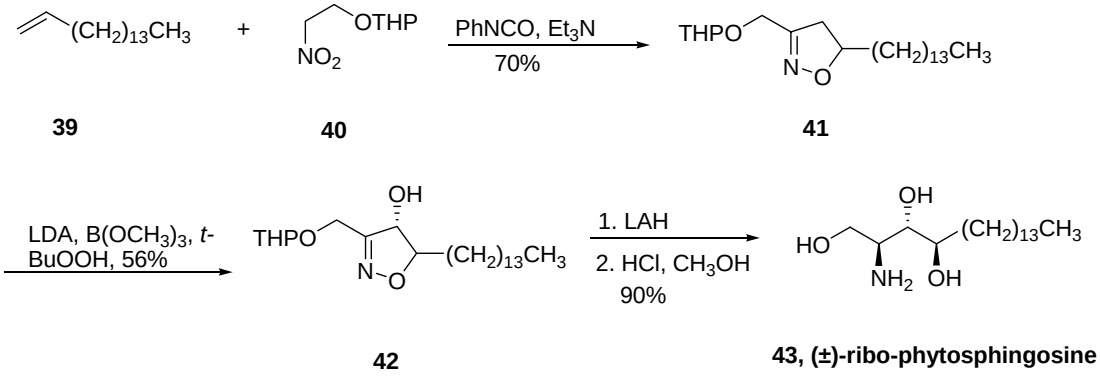
Figure 2.2: Retrosynthetic analysis: isoxazoline approach

In the first synthetic route, the isoxazoline plan, the target *C*-glycoside **4** could be derived from the triol **56**, which would be the single product of LAH reductive cleavage of the N-O bond of the isoxazoline **55**. The α-OH group of that isoxazoline ring could be stereoselectively introduced by LDA deprotonation, boronation and oxidative hydrolysis at the α position of the isoxazoline **54**, which would be obtained by the dipolar cycloaddition of the transient nitrile oxide derived from the chloro-oxime **53** to hexadecene. The aldehyde **51** could be synthesized from the

commercially available β-D-galactose pentaacetate **44** in several routine steps (**Figure 2.2**).

In our lab's past experience with a similar nitrile oxide using furan as the dipolarophile, we observed a 1:1 diastereomeric ratio [40]. So half of the adduct material would not be directly useful. The two diastereomers of the adducts would be separated, and each of them will be carried forward till we are able to make a stereochemical assignment. The next step uses boronation and oxidation of the intermediate borate to introduce the remaining hydroxyl stereo selectively; and in the similar case, Jäger reported a 98% yield of a desired single stereoisomer [41] (**Scheme 2.1**). Finally, an LAH reduction produces the amino triol as a single isomer. Although half of the adducts in the cycloaddition was useless, we still expect an outstanding overall yield from the cycloaddition step to the desired amino triol.

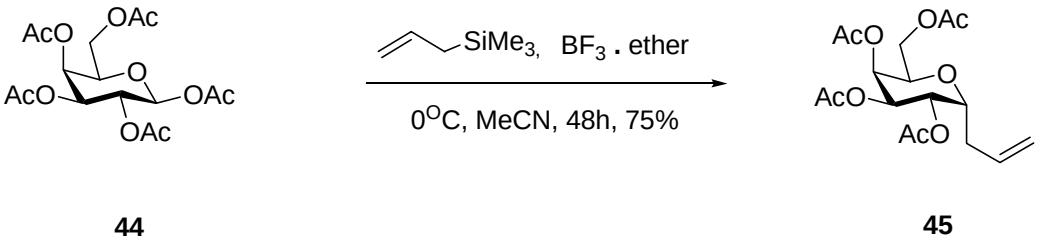
Jäger *et al* [41,42] has synthesized compound **43**, (±)-ribo-phytosphingosine accomplished by an almost identical cycloaddition with hexadecene and a simpler nitrile oxide in 55% yield. Paton has also shown that nitrile oxides linked to carbohydrates undergo cycloadditions in excellent yield. So this synthetic plan is plausible.



Scheme 2.1: Jager's 1, 3 dipolar addition method of synthesizing (±)-ribo-phytosphingosine

2.1.2. Synthesis of common starting material: the known aldehyde 51:

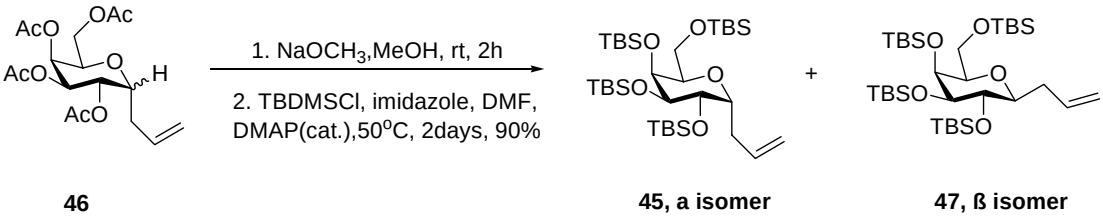
Starting from the commercially available β-D-galactose pentaacetate **44** using the Kishi/Mukaiyama method, the desired α-*C*-allyl-D-galactose tetraacetate **45** was obtained in 74% yield. The reported the ratio of α/β isomers is 95:5 [43-46] but the actual ratio was variable according to reaction conditions such as temperature, trace amount of water in the solvent, choice of solvents and so on. Separation of those two isomers was difficult. It was usually achieved at the later benzylation stage by very careful chromatography purification (**Scheme 2.2**).



44 **45**

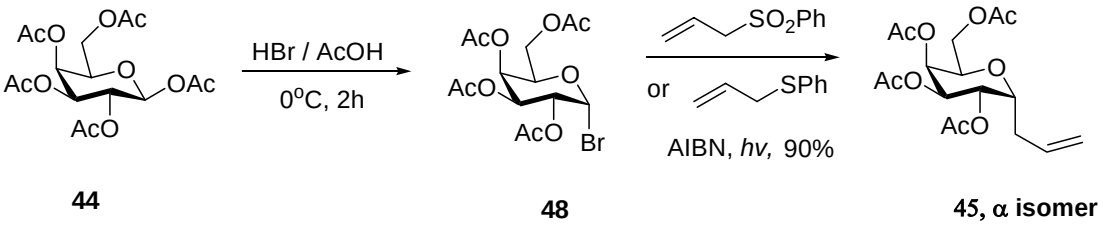
Scheme 2.2: Synthesis of α-allyl-D-galactose tetraacetate 45

Two methods were reported to avoid the problem of separation of the two isomers (**Scheme 2.3**). The first one utilized a different protection group strategy [47]. The mixture of *C*-allyl-D-galactose tetraacetate **45** was deprotected with NaOMe/ MeOH and was then reprotected by TBDMS group and the two isomers could be separated very easily.



Scheme 2.3: Separation of α isomer and β isomer

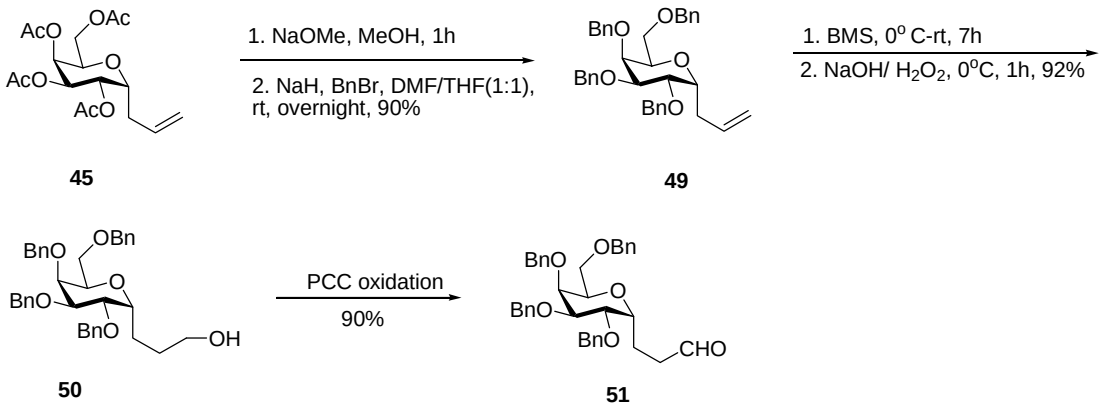
Another method was the free radical approach[46,48]. Allylic sulfide or sulfone was coupled to 1-bromo-galactose tetraacetate **48** under irradiation by light. And the α-*C*-ally-D-galactose tetraacetate **45** was reported as the only isolated product (**Scheme 2.4**).



Scheme 2.4: Free radical method to synthesize α isomer 45

Treatment of the mixture of the *C*-allyl-D-galactose tetraacetate **45** with NaOMe in MeOH followed by per-benzylation provided the fully protected *C*-allyl-D-2, 3, 4, 6-tetrabenzyl galactoside **49** in 90% overall yield. The α and β isomers could be separated at this stage by very careful chromatography purification. Hydroboration with 9-BBN gave a primary alcohol **50** in 60-70% yield while higher yield was achieved by using BH_3 as the hydroboration reagent. The secondary hydroxyl regioisomer was not found on NMR analysis. PCC oxidation gave the known

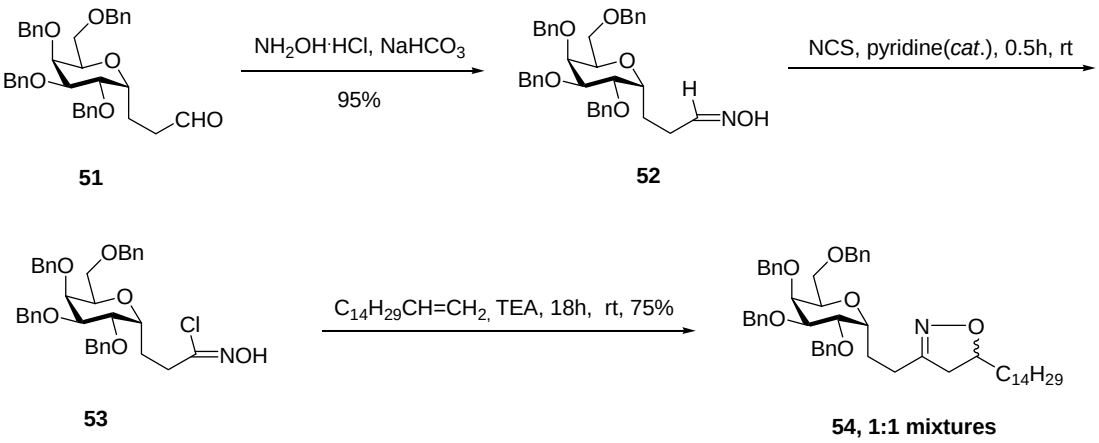
aldehyde **51** in high yield. That aldehyde would serve as the common starting material for all of the synthetic pathways and greatly simplified the synthesis (**Scheme 2.5**).



Scheme 2.5: Synthesis of the known aldehyde 51

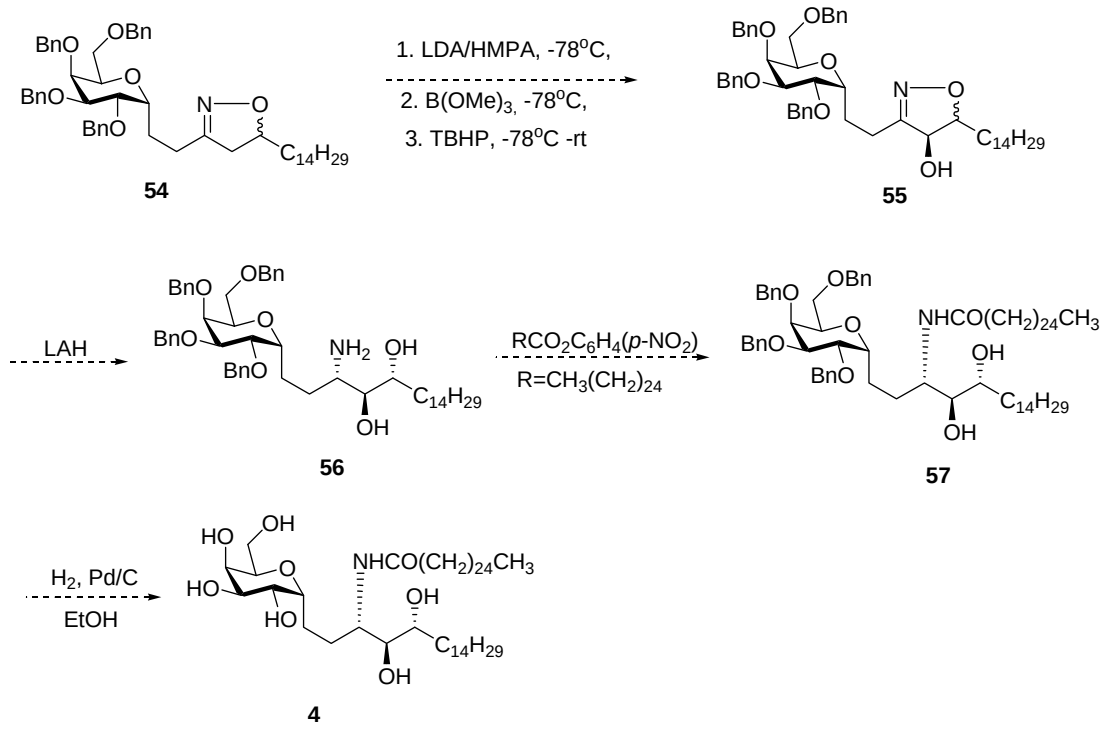
2.1.3. Isoxazoline approach:

The aldehyde **51** was converted to the oxime **52** by reaction with NH_2OH in quantitative yield. The reaction of the oxime **52** with NCS gave a chloro-oxime **53**, which was transformed to the nitrile oxide *in situ* by reaction with triethylamine. As expected, the 1, 3 cycloaddition of the nitrile oxide with hexadecene provided an adduct **54** as an inseparable mixture of two diastereomers at the ratio of 1:1. The regiochemistry was assigned according to Jager's precedent and was also confirmed by NMR analysis (**Scheme 2.6**).



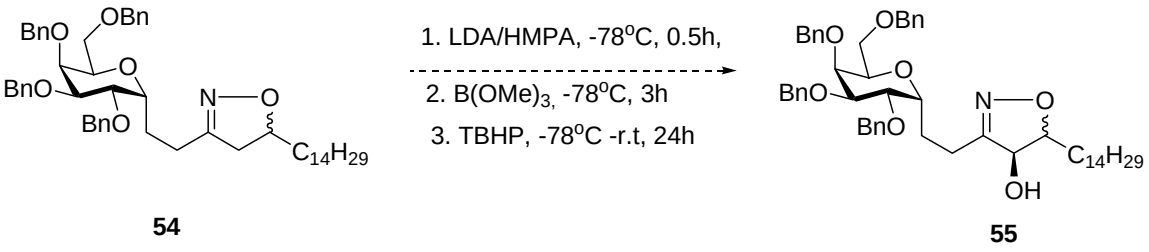
Scheme 2.6: Synthesis of isoxazoline 54

The next step required stereoselective introduction of a hydroxyl group at the α-position of the isoxazoline ring. Then LAH reductive cleavage of the N-O bond of the isoxazoline ring should afford the amino triol **56**. Final conversion to the ceramide **57** by reaction of the amine **56** with an activated ester of cerotic acid and hydrogenolytic deprotection would provide the target C-glycoside **4** (**Scheme 2.7**).



Scheme 2.7: Synthetic plan of the *C*-glycoside 4

The hydroxylation failed and only brought about a complex mixture (**Scheme 2.8**). It was also found that the cycloadducts **54** were not stable and decomposed in storage even at -20°C.



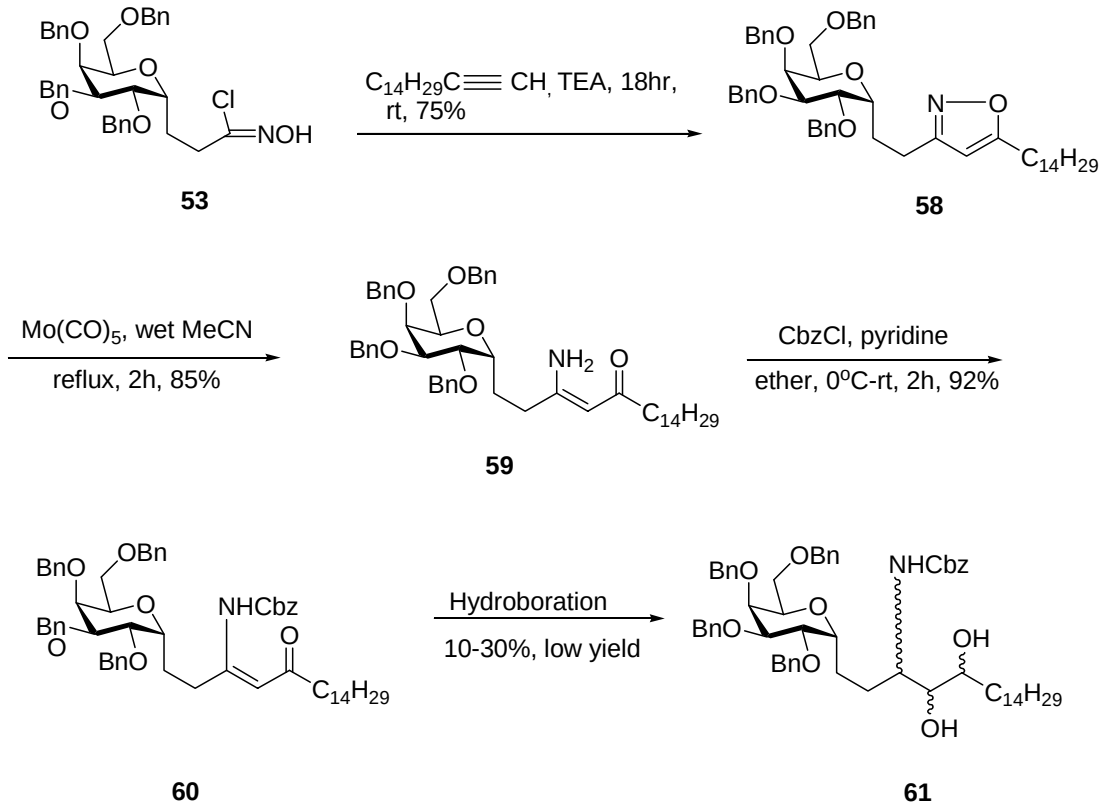
54 **55**

Scheme 2.8: Stereoselective α-hydroxylation reaction

2.1.4. Isoxazole Approach:

We envisaged an alternative synthesis pathway based on the 1, 3 dipolar addition between the chloro-oxime **53** and hexadecyne (**Scheme 2.9**). This addition provided the isoxazole **58** as a single product in good yield. Ring cleavage of the N-O bond with $Mo(CO)_5$ [49,50] in refluxing wet MeCN gave the enamine ketone **59** in excellent yield. Reductive cleavage of the N-O bond with H_2/Pd/C gave a partially de-benzylated mixture. Protection of the enamine **59** with the Cbz group proceeded well to afford compound **60** in good to excellent yield. The next step would be hydroboration of the enamine ketone **60**. The idea then was that hydroboration of the enamine ketone would deliver borane to the double bond in a *syn* manner and basic oxidative hydrolysis of the organoborane intermediate would maintain the stereochemistry and thus make an *anti* amino alchol. So if chiral borane reagent(s) was (or/were) used, a certain degree of asymmetry may be introduced. But repeated model studies of hydroboration with BMS or 9-BBN only afforded the compounds as

a mixture of diastereomers in a low yield (10-30% yield). This approach was not practical and was abandoned.



Scheme 2.9: Isoxazole model synthesis

2.2. Wittig-Sharpless asymmetric epoxidation (SAE) approach:

2.2.1. Retrosynthetic analysis:

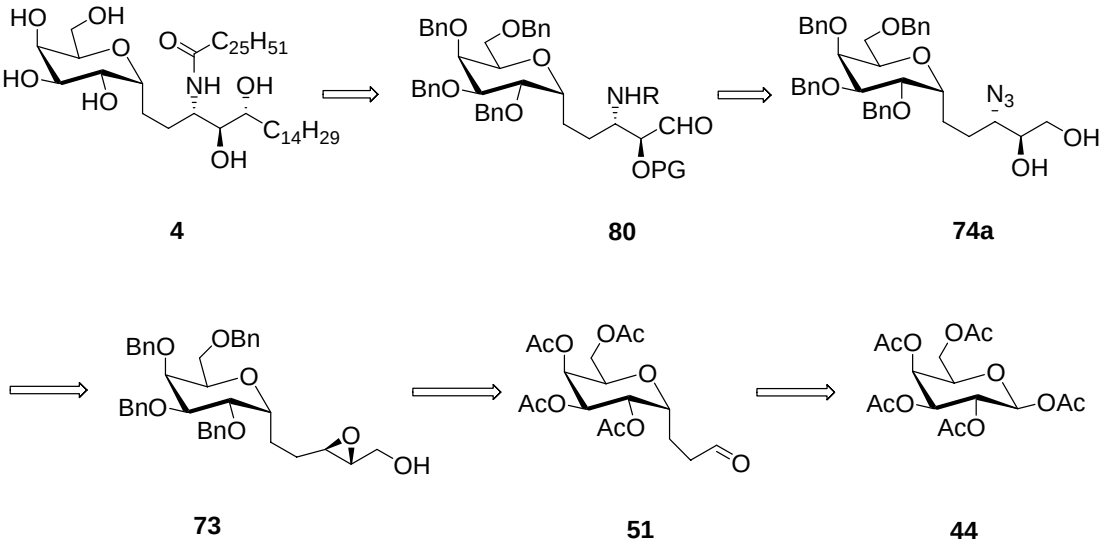
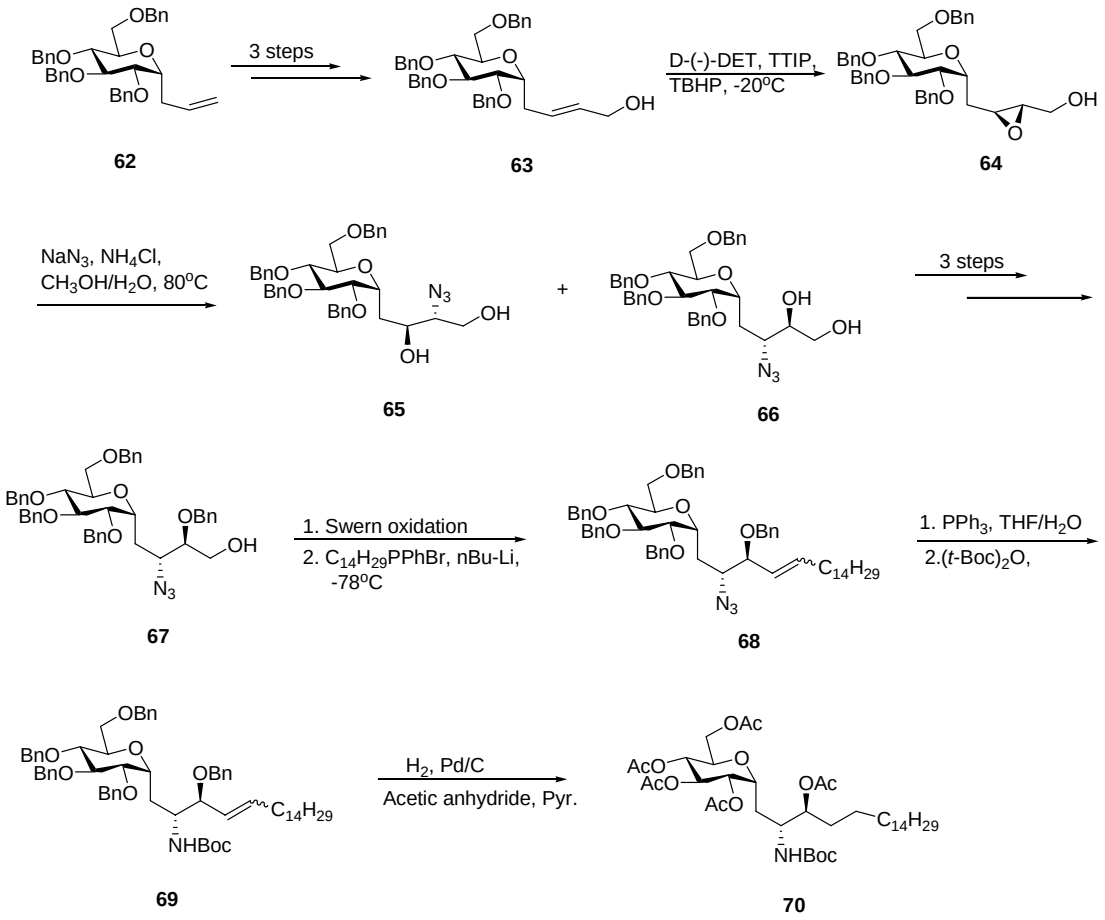


Figure 2.3: Retrosynthetic strategy for α-*C*-galactosylceramide 4

As shown in the retrosynthetic analysis (**Figure 2.3**), the target α-*C*-galactosylceramide **4** could be obtained by addition of the side chain alkyl Grignard reagent with the highly functionalized aldehyde **80** in a "Cram chelation-controlled" or "Non-chelation-controlled" manner. The third stereo center of the final compound could be established at this step. Either the major isomer or the minor isomer could be transformed to the target compound, depending on which pathway in Grignard addition, chelation or non-chelation model, were to occur. The aldehyde could be obtained from the 3-azido-1, 2 diol **74a**, which was the product of regioselective ring

opening of the epoxide by an N source. The 3-*N* and 2-OH were *anti* to each other based on the assumption of a S_N2 opening of the epoxide **73**. The optically pure epoxide **73** could be afforded by the well-established Sharpless asymmetric epoxidation method. And the stereochemistry of the epoxide **73** was ensured. The epoxide could be derived in a classical way from the common known aldehyde **51**, which has been synthesized from the commercially available β-D-galactose pentaacetate **44**.

The Sharpless asymmetric epoxidation (SAE) is a powerful tool in constructing optically pure epoxide, which is a versatile "synthon". This SAE method has been utilized by Y. Kishi *et. al.* [51-53] and K. C Nicolaou *et. al*. [54] successfully in carbohydrate substrates and recently, Gurjar and Reddy reported a similar lengthy linear synthesis of α-*C*-glucosylsphingosine **70** based on this Wittig-Sharpless method [55] (**Scheme 2.10**). The key reactions included the Sharpless asymmetric epoxidation, NaN_3 opening of the epoxide **64**, and Wittig olefination. This was a versatile synthesis method and all of the diastereomers of sphingolipid could be synthesized by using different chiral tartrate ester reagents and *E/Z* allylic alcohols in the SAE step.



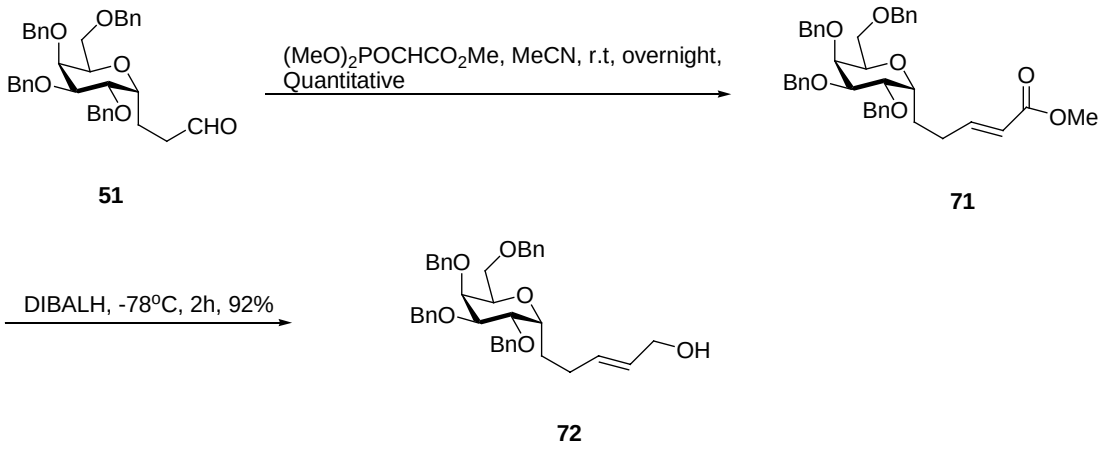
Scheme 2.10: Gurjar's synthesis of sphingolipid 70

2.2.2. Synthesis of the target *C*-glycoside:

The successful synthesis of compound **4,** the *C*-glycoside analogue of KRN7000 will be first discussed. Some unusual observations encountered during the synthesis will also be discussed in detail.

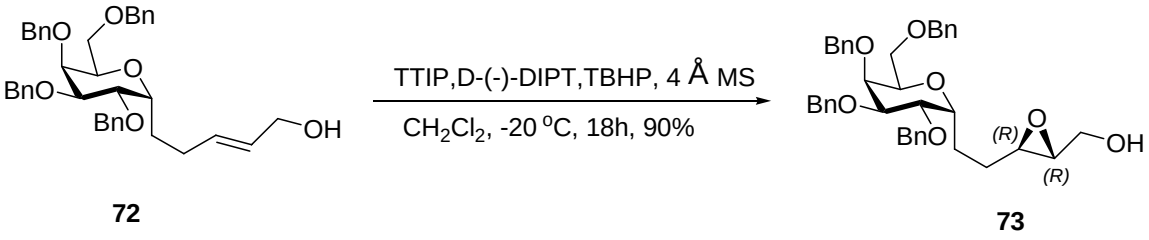
The common starting material aldehyde **51** was treated with the stabilized Wittig reagent, methyl(triphenylphosphoranylidene)acetate in anhydrous MeCN to afford exclusively the (*E*)-α, β unsaturated ester **71** in quantitative yield. The coupling constant of the alkene proton was *J*=15 Hz, which is the typical value of *trans* alkene

(*J*>12 Hz). DIBALH reduction of the α, β unsaturated ester gave the (*E*)-allylic alcohol **72** in 92% yield (**Scheme 2.11**).



Scheme 2.11: synthesis of the (*E*)-allylic alcohol 72

In the Sharpless asymmetric epoxidation reaction[56], because there were several oxygen atoms in the allylic alcohol **72** system, which could complex with the titanium-based catalyst, the use of a catalytic amount of Ti(O-*i*-Pr)$_4$ (TTIP) and D-(-)-DET (5mol% and 6mol% respectively) only resulted in recovery of the starting material. A larger than normal amount of catalyst (50mol% TTIP, 60mol% D-(-)-DET) was used instead, and the epoxide **73** was obtained in 70-80% yield along with 10-20% unidentified by product, resulted from the ring opening of the epoxide by the nucleophile presented in the reaction mixture. While more steric hindered catalyst (D-(-)-DIPT) was employed, the amount of the byproduct was reduced to a negligible level and the yield of the epoxide **73** was improved to 90% (**Scheme 2.12**).



72 **73**

Scheme 2.12: Sharpless asymmetric epoxidation reaction

The Mosher ester of the epoxy alcohol [57,58] was made to determine the enantiomeric excess of the epoxide. The existence of another diastereomer was not detectable so the *d.e* of the epoxide was very high. Here we assigned the structure of the epoxide as (*2R, 3R*) epoxide according to the empirical rule defining the stereochemical outcome of the reaction [56] (**Figure 2.4**).

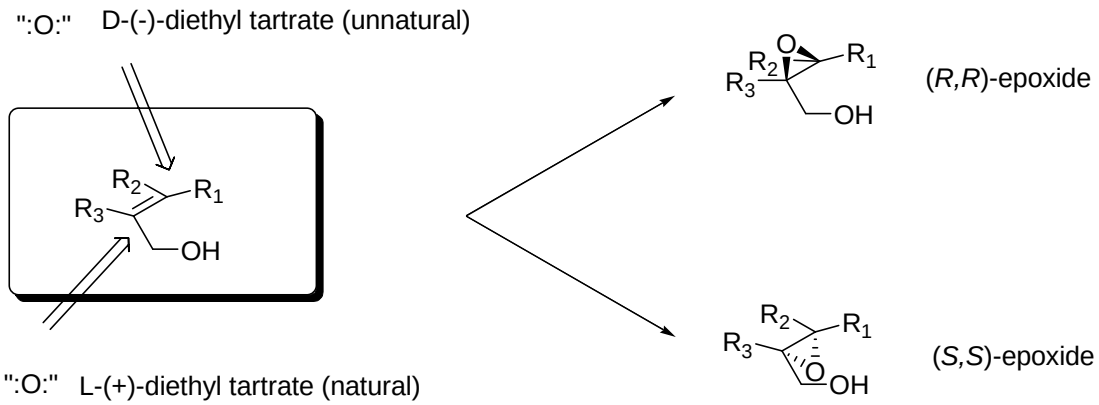
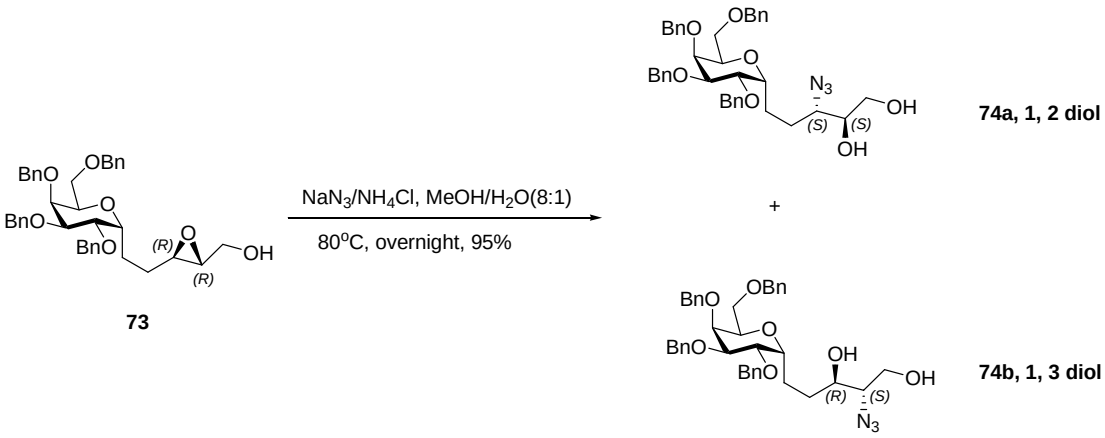


Figure 2.4: Sharpless empirical rule

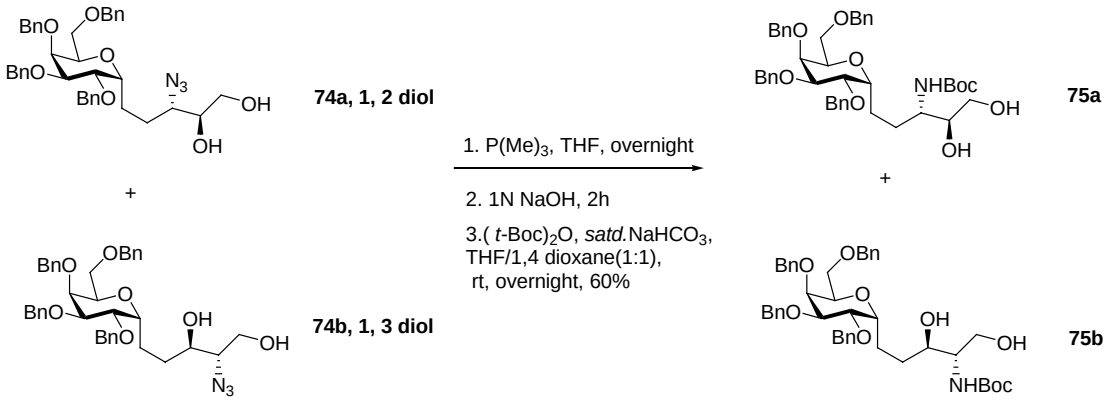
Installation of the *N* atom could be achieved by opening the epoxide with azides regioselectively and stereoselectively at the C-3 position to produce the desired 3-azido-1, 2-diol. A variety of organic and inorganic azides could be employed here [59]. Use of inorganic azides, such as LiN_3, NaN_3, usually results in a mixture of

regioisomers [60]. First, we chose to use NaN_3 as the N source and the regioselectivity was not high and the products of the ring opening of the epoxide using NaN_3/NH_4Cl are usually an inseparable mixture of the 1,2 diol and the 1,3 diol in different ratio. In our case, the (*2R, 3R*) epoxy alcohol **73** was converted to a mixture of the desired 3-azido-1, 2 vicinal diol **74a** and the unwanted 1, 3 diol **74b** in quantitative yield (**Scheme 2.13**). The ratio of **74a**/**74b** was approximately 8:1 based on chromatographic separation of later determinations.



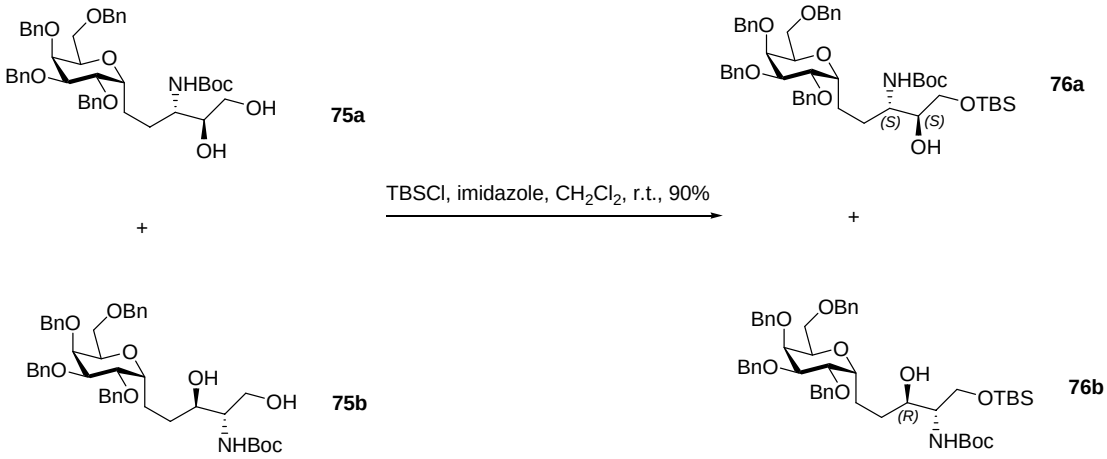
Scheme 2.13: Opening of epoxide 73 with NaN_3/NH_4Cl

The azido group was found to be incompatible with the required Grignard reaction in the later stages of the synthesis. Conversion of the azido group to a free amine and protection of the amine prior to the Grignard reaction was neccessory. Staudinger reduction of the unseparated azides with $P(Me)_3$ [61] gave a mixture of amines. Protection of the amines with $(t\text{-Boc})_2O$ afforded an inseparable mixture of regioisomers **75a** and **75b**. Another commonly used amine protection group, the Cbz carbamate, was also used but the final steps of the synthesis, the selective removal of Cbz in the presence of the benzyl groups failed. While the acid sensitive *t*-Boc protection group could be selectively removed (**Scheme 2.14**).



Scheme 2.14: Staudinger reduction and protection of amine

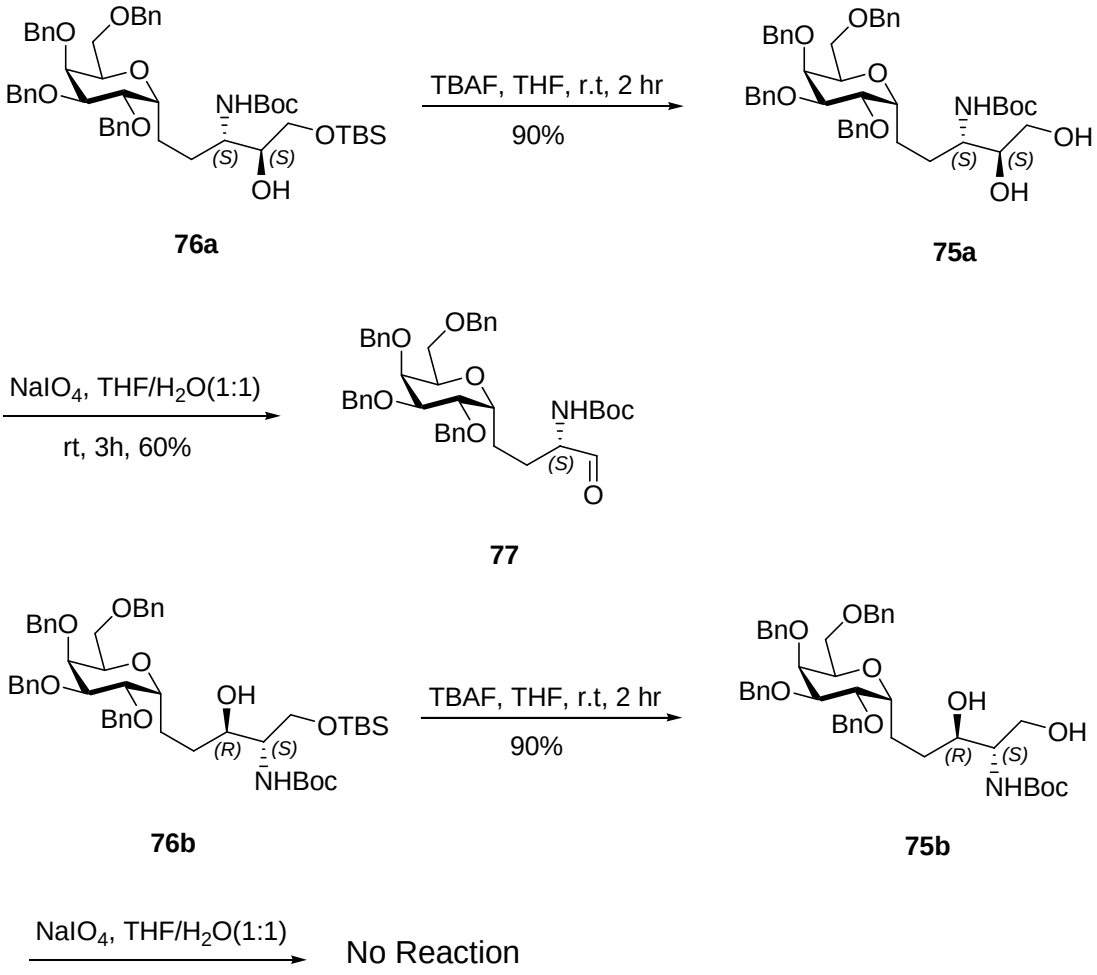
The primary hydroxyl group was then selectively protected with TBS group to afford separable compounds **76a** and **76b** in high yield (**Scheme 2.15**).



Scheme 2.15: Separation of regioisomers 76a and 76b

For the two separated compounds, the primary TBS group was cleaved with TBAF and the product was subjected to the $NaIO_4$ cleavage to confirm the structure of the two regioisomers. The desired 1, 2 diol **75a** would give an aldehyde **77** while the 1, 3

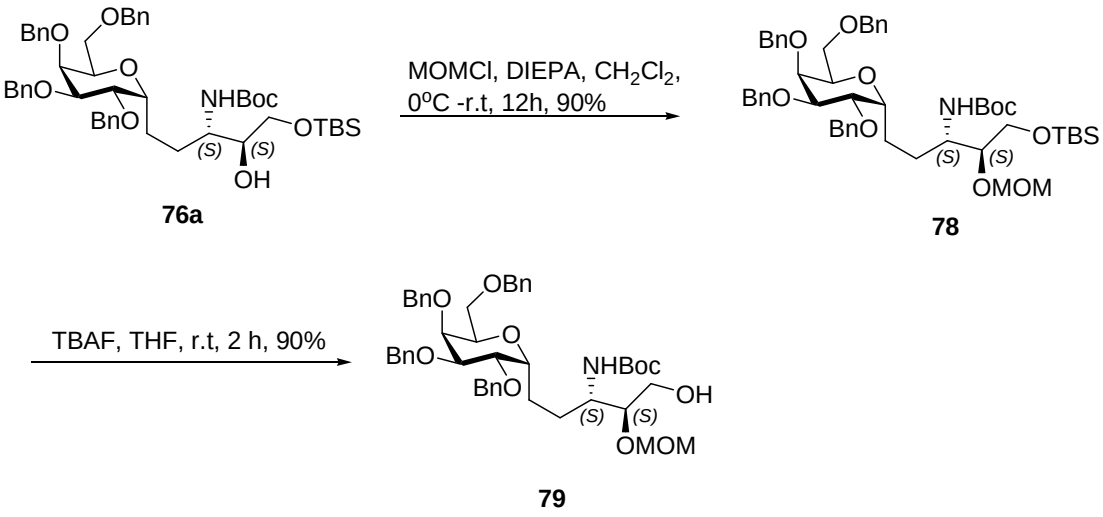
diol **75b** would not react with $NaIO_4$ (**Scheme 2.16**). In this way, the structures of the two regioisomers were identified and the ratio of 1, 2 diol **74a** to 1, 3 diol **74b** was found to be 8:1.



Scheme 2.16: Structure verification of two regioisomers 76a and 76b

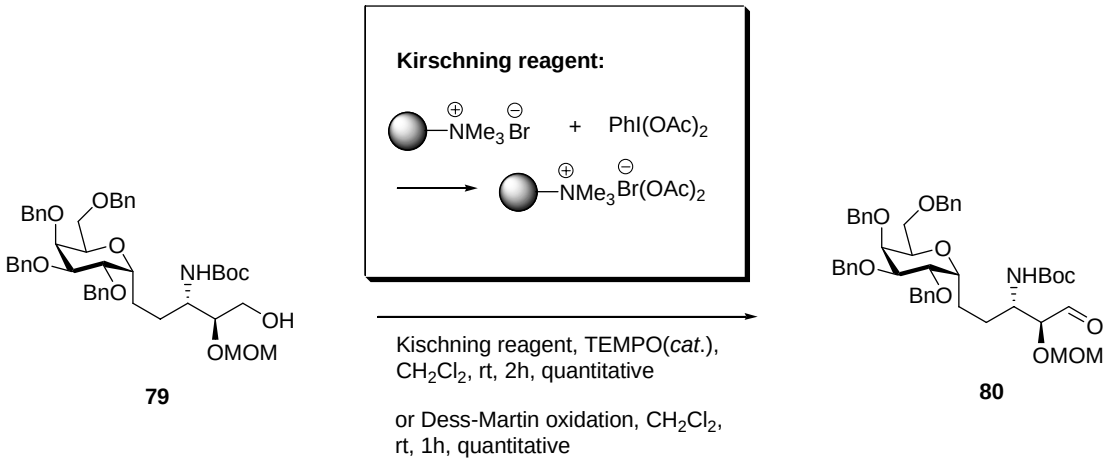
The protection of the secondary hydroxyl was attempted with TBS, TBDPS or MOM. After consideration of selectivity and yield of protection and deprotection steps in the presence of the primary TBS group as well as ease of scale-up, the MOM group was chosen to protect the secondary hydroxyl group. The MOM group α to an aldehyde is a chelating group in Grignard reaction and could determine the diastereomeric ratio of

the products and could also be removed under the acidic conditions identical to deprotection of the *t*-Boc protection group of the amine. Selective deprotection of the primary TBS group of compound **78** with TBAF gave the primary alcohol **79** in good yield (**Scheme 2.17**).



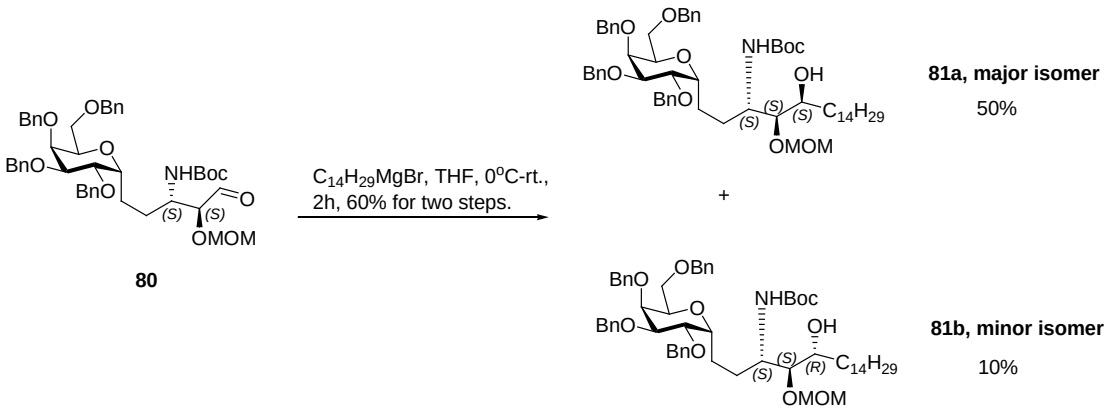
Scheme 2.17: Protection group manipulation

Swern oxidation of the primary alcohol **79** to an aldehyde **80** caused partial epimerization of the α-oxygenated aldehyde, which was caused by the triethylamine in the reaction mixture. The aldehyde **80** was acid and base sensitive so neutral conditions were essential for the success of the oxidation. A polymer supported bromite(I) complex oxidation method recently described by Kirschining [62] gave the aldehyde in quantitative yield without epimerization and the aldehyde could be directly employed in the next step without further purification. Another commonly used Dess-Martin periodinane oxidant could also be used to oxidize the alcohol **79** to the aldehyde **80** without epimerization at the α position in quantitative yield (**Scheme 2.18**).



Scheme 2.18: Oxidation of 79 to aldehyde 80

The crude aldehyde **80** was added dropwise to a solution of freshly prepared tetradecyl magnesium bromide ($C_{14}H_{29}MgBr$) in THF at 0^oC and the reaction was kept at that temperature for one hour. The reaction mixture was then warmed up to r.t. The reverse addition of the aldehyde to the Grignard reagent was necessary for the completion of the reaction while almost all the starting material, the aldehyde, was recovered if the Grignard reagent was added to the aldehyde. The Grignard addition gave a separable mixture of diastereomers in 60% combined yield for two steps. The major isomer **81a** and the minor isomer **81b** were isolated at a ratio of 5:1 (**Scheme 2.19)**.



Scheme 2.19: Grignard reaction of aldehyde 80

Their structures were tentatively assigned based on the Cram-chelation control model**.** The nature of the α-hydroxy protection groups playes an important role in determining the ratio of the Grignard addition products. The α-OMOM group of an aldehyde is known for its chelation ability with carbonyl group by magnesium ion in the Grignard addition to form a cyclic intermediate. Tetradecyl magnesium bromide attacked the carbonyl group from the less steric hindered, more favored face of intermediate **80a** to afford the major isomer **81a.** The two neighboring OH groups of compound **81a** were *syn* to each other and the three stereocenters were assigned as (*2S, 3S, 4S*). Addition of tetradecylmagnesium bromide with the carbonyl group from the more steric hindered, less favored face affords the minor isomer **81b. T**he two neighboring OH groups of compound **81b** were *anti* to each other and the three stereo centers were assigned as (*2S, 3S, 4R*). Compound **81b** had the correct stereo chemical configuration as that of compound **4**. The assignments were confirmed later by comparison of their NMR spectrum with that of the target compound **4**.

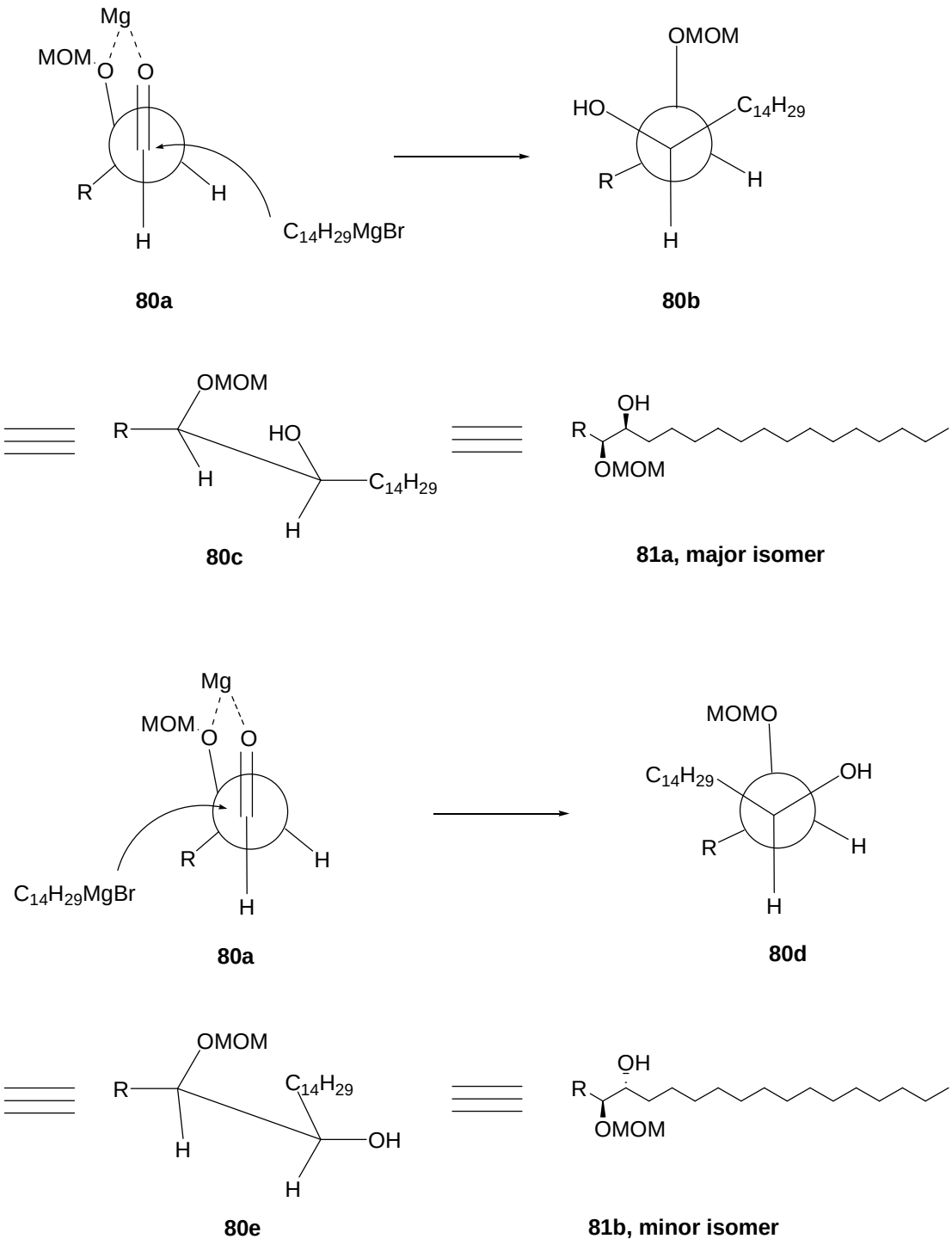


Figure 2.5: Cram-chelation controlled Grignard addition

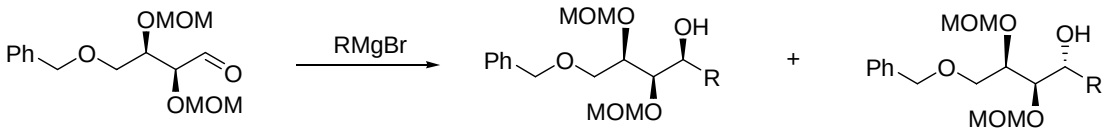
By use of simple α-substituent groups such as methoxymethyl ether (MOM), benzyl ether, and methylthiomethyl (MTM) ether to protect chiral α-hydroxy ketone or

aldehyde, the high degree of *syn* selectivity (>98:2) was achieved in the Grignard addition[63]. While in the more complex system, moderate selectivities are reported for the Grignard and organolithium additions to α, β-dihydroxycarbonyl derivatives. Variation of the diol-protecting group or of other sunstituents on these α, β-dihydroxycarbonyl derivatives does not give significant improvements in stereoselectivity. For example, the selectivities of the Grignard and organolithium additionsfor 2, 3-*O*, *O*-dibenzylglyceraldehyde **82** rang from 45:55 to 27:73 [64]and the ratio for the homologated cyclohexylideneglyceraldehyde **83** [65,66] ranges from 80:20 to 60:40 (**Scheme 20**).

82 **83**

Scheme 20: Grignard addition with α, β-dihydroxycarbonyl derivatives

Grignard addition to aldehyde **84** proceeds with a moderate preference for α – cheleation-controlled addition product. The alcohol **85a** and **85b** are isolated in a ratio of about 75: 25 [67,68] (**Scheme 21**).



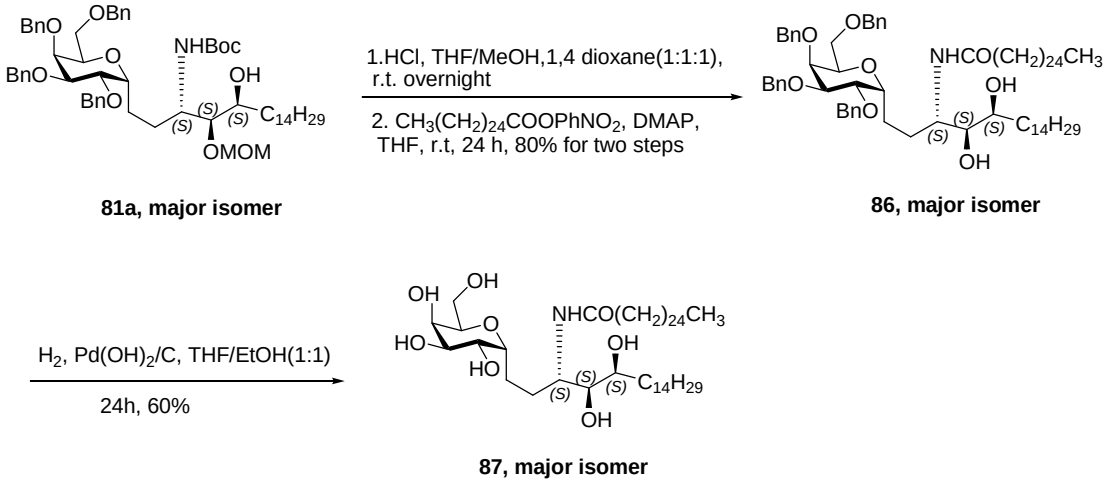
84 **85a** **85b**

3 **:** **1**

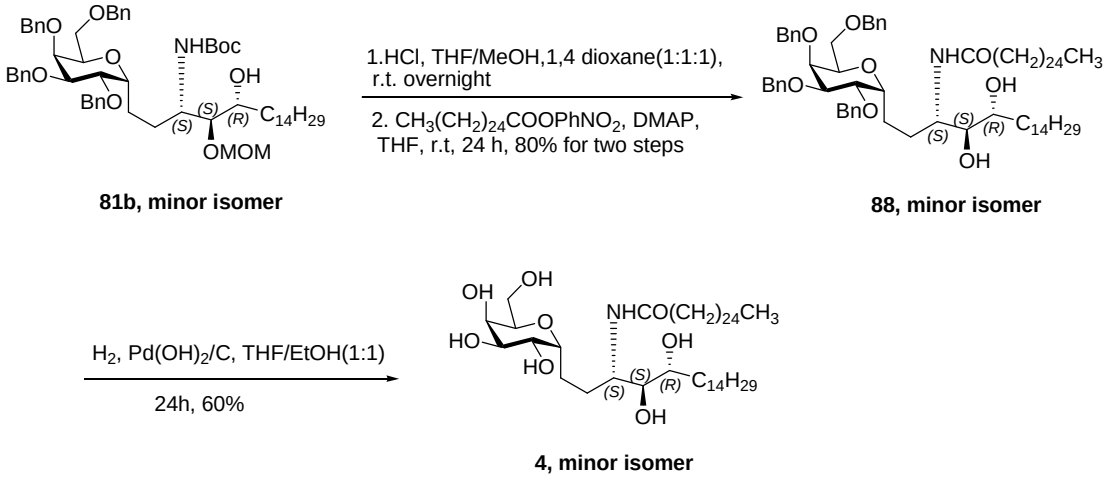
Scheme 21: Grignard addition of compound 84

Based on these precedents, the ratio of the major isomer **84** and minor isomer **85** is 5:1 and this moderate selectivity is not surprising considering the complexity of the molecule.

The MOM and *t*-Boc protecting groups of the major isomer **81a** were removed by acidic hydrolysis using 6 N HCl in MeOH. Amide formation was achieved by mixing the free amine with the activated ester $CH_3(CH_2)_{24}COOPhNO_2$. The amide **86** was contaminated by *p*-NO_2PhOH. Hydrogenation using Pearlman catalyst ($Pd(OH)_2$/C) in THF/EtOH solution afforded the fully deprotected *C*-glycoside analogue **87** (**Scheme 2.22**), which is a 5-OH epimer of the target *C*-glycoside analogue of the KRN7000.

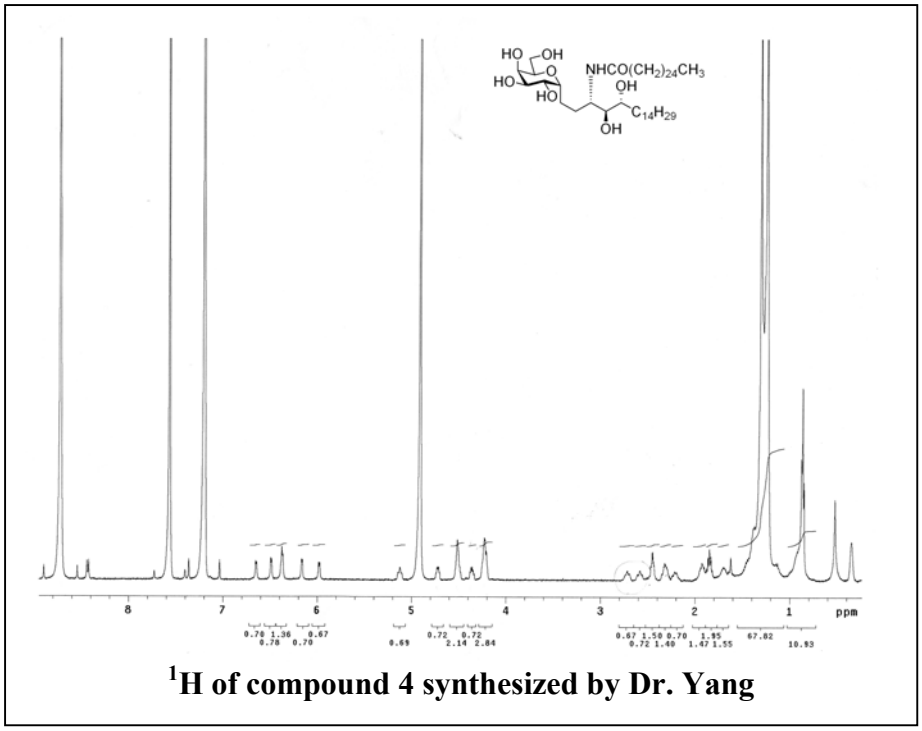


Scheme 2.22: Synthesis of the *C*-glycoside 87 from the major isomer 84

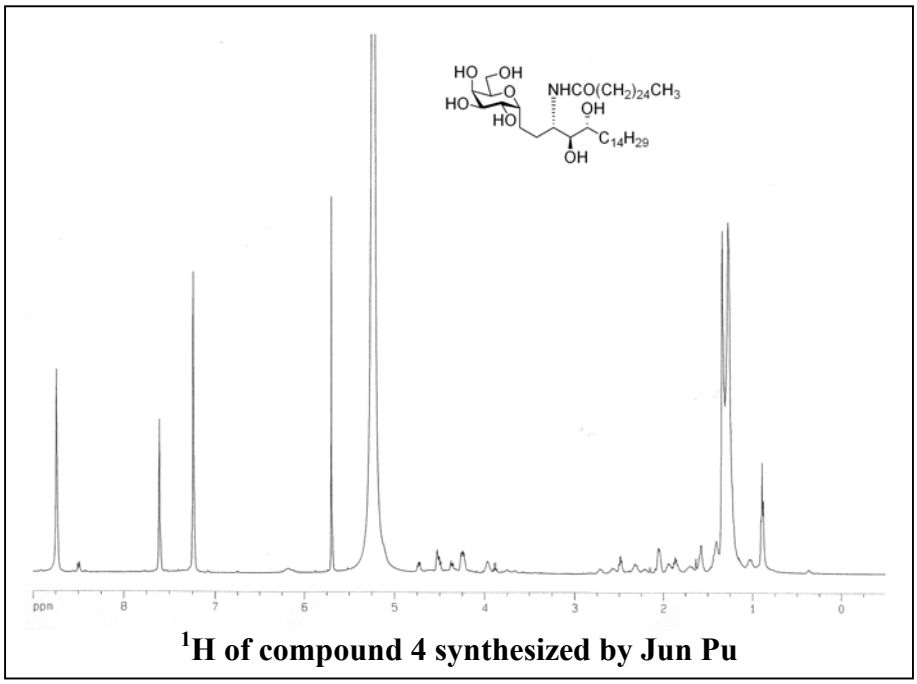


Scheme 2.23: Synthesis of the *C*-glycoside 4 from the minor isomer 85

The minor isomer **85** was subjected to the same treatment and the obtained fully deprotected *C*-glycoside **4** was the target compound: *C*-glycoside analogue of KRN7000 (**Scheme 2.23**). Its spectrum matched with those of the previous synthesized *C*-glycoside analogue of KRN7000 (**Figure 2.6 and 2.7,** NMR solvent: pyridine-d5). It is interesting to point out that the spectrum of the *C*-glycoside analogue **87**, which was derived from the major isomer, was different from that of the minor compound (**Figure 2.6 and 2.7**). Hydrogen-bonding between the NH, and OH groups accounts for that phenomena.

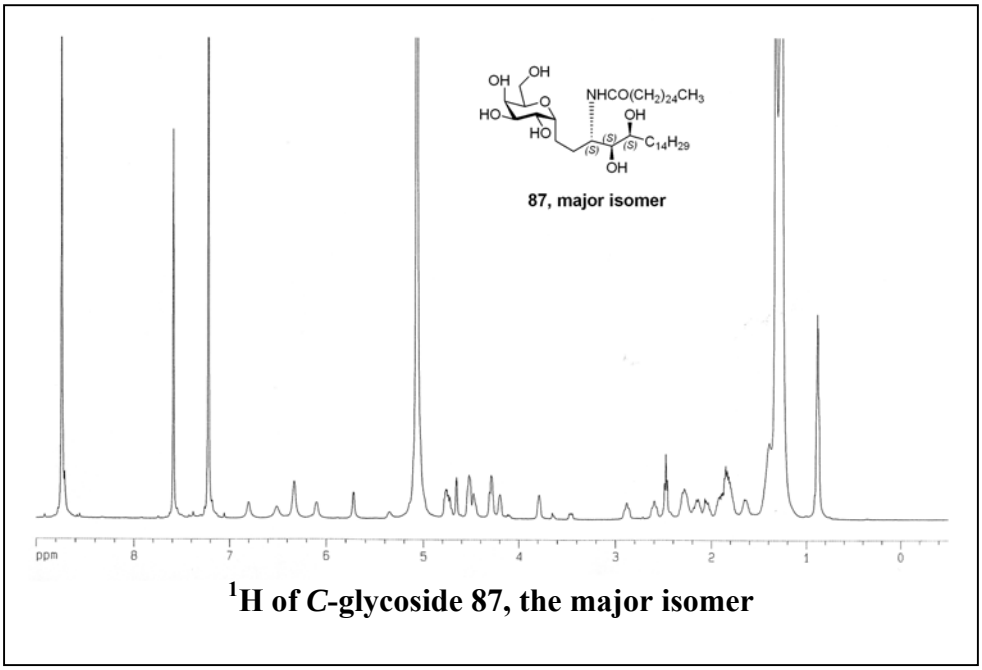


^{1}H of compound 4 synthesized by Dr. Yang



^{1}H of compound 4 synthesized by Jun Pu

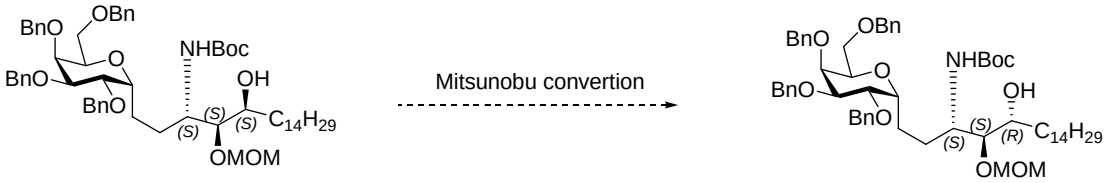
Figure 2.6: Spectrum of compound 4 synthesized by Dr. Yang and Jun Pu



^{1}H of *C*-glycoside 87, the major isomer

Figure 2.7: Spectrum of *C*-glycoside 87, the major isomer

The major isomer **81a** could in principal be converted to the minor compound **81b** by the Mitsunobu reaction to convert the stereo center of the 5-OH from 5-(***S***)-OH to 5–(***R***)-OH. In this way, large quantities of the target compound should be successfully synthesized (**Scheme 2.24)**.



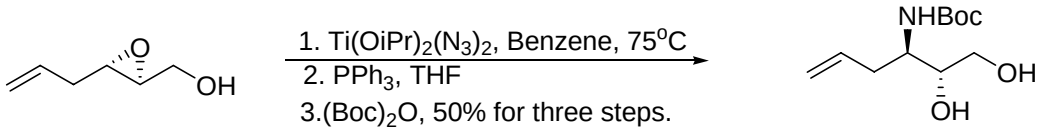
81a, major isomer **81b, minor isomer**

Scheme 2.24: Mitsunobu convertion

In this sequence, the target compound **4** and its 5-*OH* epimer **87** were successfully synthesized but that was not the only outcome of our synthesis. In the following chapter, some unusual phenomena will be discussed in detail.

2.2.3: Synthesis of *C*-glycosides from $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ opening of the epoxide 73

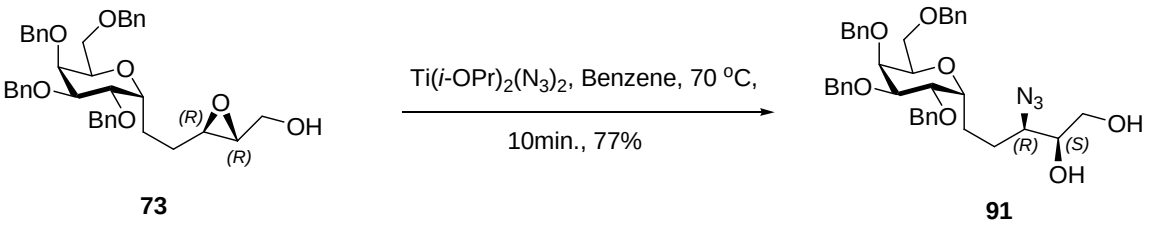
As described in the previous chapter, when NaN_3/NH_4Cl was used to open the epoxide **73**, the product was not clean and an inseparable mixture of regioisomers was obtained, which could only be separated at a later stage. So in our exploratory studies to open the epoxide, we decided to choose a better *N* reagent reported to open the epoxide regioselectively at the 3-position to get the desired *anti* 3-azido-1, 2 diol. When organic azides were used along with a chelating Lewis acid such as titanium alkoxide or aluminum reagents, high regioselectivity was reported to be readily achieved. Diethylaluminum azide, Et_2AlN_3, usually gives a reverse regioselectivity of Markovnikow products [69,70]. Another commonly used *N* –containing reagent, $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$, also showed its high efficiency in opening oxirane regioselectively at the *C*-3 position [71]. For example, Ginesta *et al*. reported an enantioselective synthesis of 3-Amino-2, 3, 6-trideoxysugar. Nucleophilic epoxide ring-opening by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ provides the key intermediate *N*-Boc-3-amino-5-hexen-1, 2-diol **90** as a single product [72] (**Scheme 2.25**).



89 **90**

Scheme 2.25: example of opening of the epoxide 89 with Ti(O-*i*-Pr)$_2$(N$_3$)$_2$

In our case, the (*2R, 3R*) epoxide **73** was treated with Ti(O-*i*-Pr)$_2$(N$_3$)$_2$, which was made *in situ* by mixing 1.5 eq. Ti(O-*i*-Pr)$_4$ with 3 eq. (Me)$_3$SiN$_3$ in refluxing benzene for at least 5 hours, to afford exclusively the 3-azido-1, 2 vicinal diol **91** as a single product. At that time, we assigned the structure of the product as the *anti*-3-azido-2-OH **74** on the basis of the hypothesis that ring opening of the oxirane was a single S_N2 reaction and the N_3^- attacked the epoxide from the backside and the stereochemistry of the resulting 3-N$_3$ was inverted and was *anti* to the neighboring 2-hydroxyl group. So we basically assumed that the two reagents, NaN$_3$ and Ti(O-*i*-Pr)$_2$(N$_3$)$_2$, would afford the same product with the same stereochemistry. In fact, only after we learned that the final products derived from the Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ opening of the epoxide **73** did not match these from NaN$_3$ opening of the same epoxide **73** did we realize that our assignment of the stereochemistry of the 3-*N* stereo center from Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ opening of the epoxide **73** was not correct. For convenience, we will use the correct structure assignment in this section (**Scheme 2.26**).



73 **91**

Scheme 2.26: Opening of the (*2R, 3R*) epoxide 73 with Ti(O-*i*-Pr)$_2$(N$_3$)$_2$

The structure of the 3-azido-1, 2 vicinal diol **91** was confirmed by cleavage of the 1, 2 diol with $NaIO_4$ in THF/H_2O to afford the corresponding aldehyde as a single product. The characteristic IR peak at 2100 cm^{-1} proved the existence of the N_3 group.

The remarkable regioselectivity observed seems to be due primarily to complexation of the Ti(O-*i*-Pr)$_4$ with the substrate. The epoxy alcohol coordinated to the metal center of the Lewis acid, Ti(O-*i*-Pr)$_4$, in the rigid, bidentate manner as depicted in the following scheme. Enforced propinquity assured by the hydroxyl renders this coordination likely, even though epoxides are weak Lewis bases and titanium alkoxides are weak Lewis acids. Coordination of epoxy alcohols to metal alkoxides also greatly facilitates their opening reactions with intermolecular nucleophiles. And moreover, in the presence of the metal alkoxide, most of the external nucleophiles show a very strong preference for attack at the C-3 of the epoxy alcohol [73] (**Figure 2.8**).

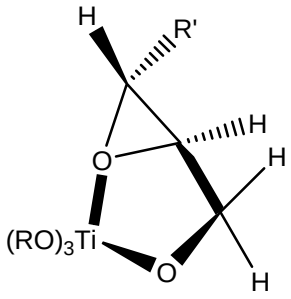
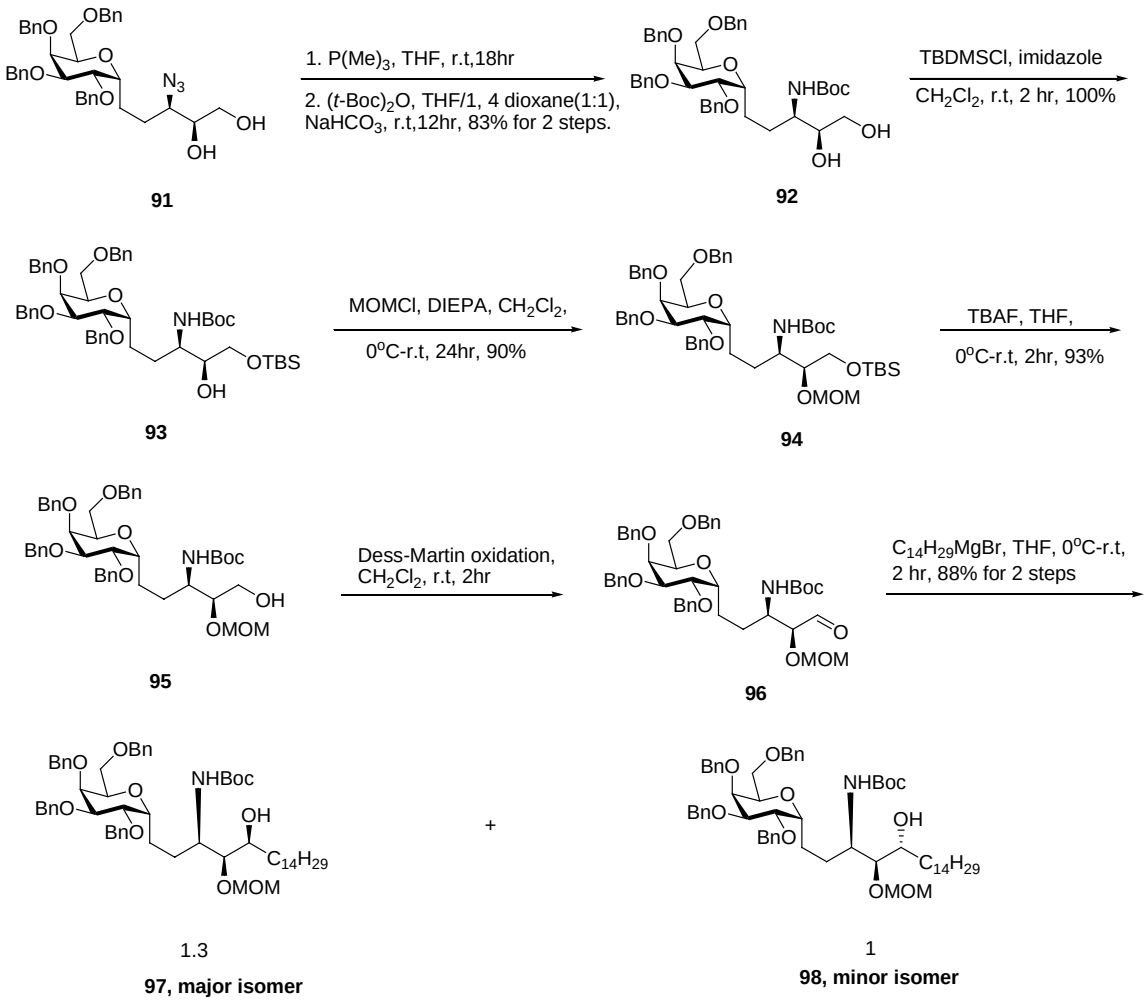


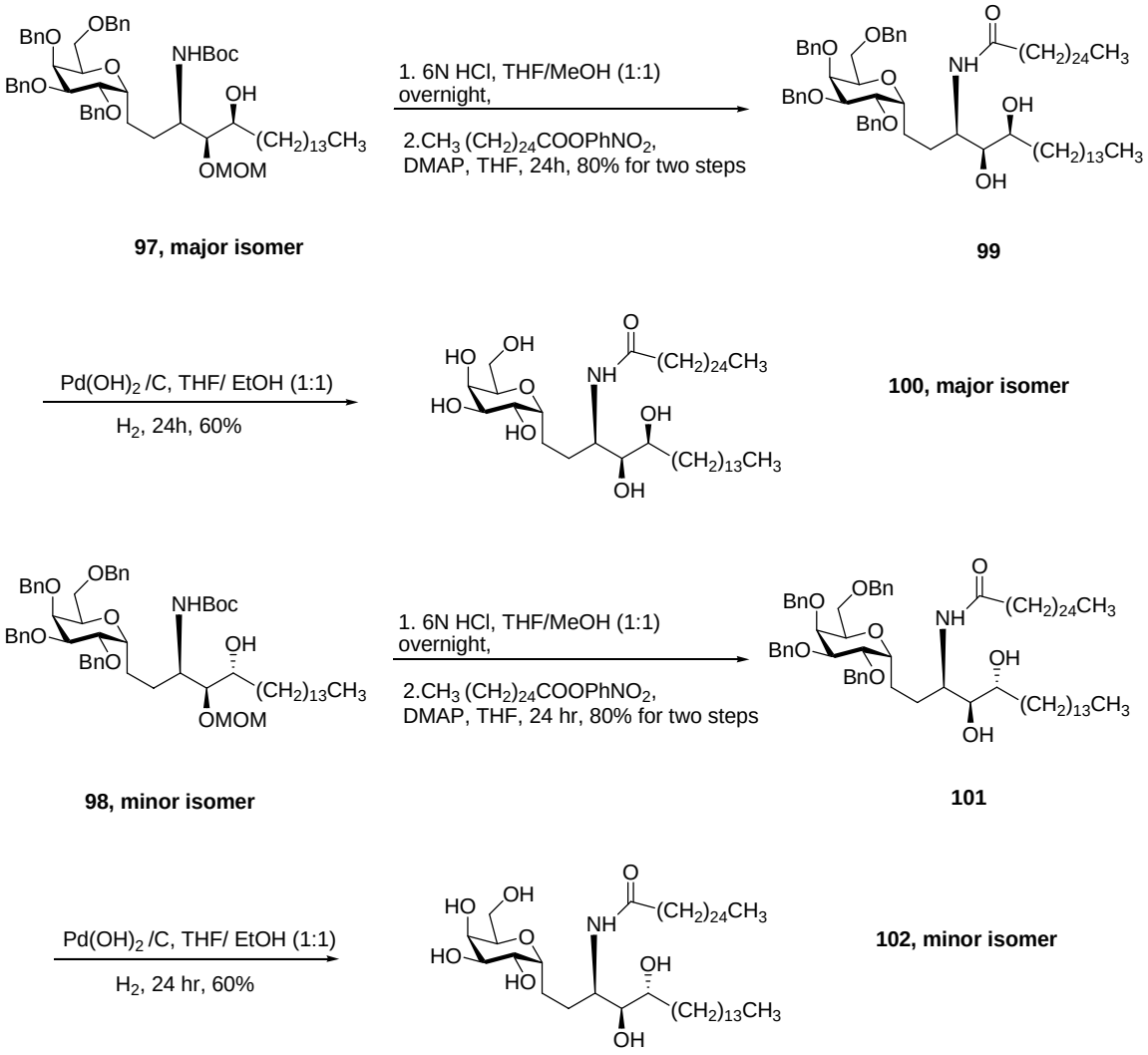
Figure 2.8: Complexation of Ti alkoxide with epoxide

The 3-azido-1, 2-diol compound **91** was converted to an aldehyde **96** in an identical manipulation sequence as described in the previous chapter. Grignard reaction between the aldehyde and $C_{14}H_{29}MgBr$ gave a separable mixture, and the ratio of the major isomer **97** and minor isomer **98** was 1.3:1. The minor isomer **98** was supposed to have the correct stereo centers and was to be converted to the target *C*-glycoside **4**. The structure assignment was based on "Cram-chelation control" model (**Scheme 2.27**).



Scheme 2.27: Synthesis of the major and minor isomer in Grignard reaction

The major isomer **97** and minor isomer **98** were converted to the corresponding *C*-glycosides **100** and **102** in the same way as in the NaN_3 opening of the epoxide series (**Scheme 2.28**). Neither of those spectra matched the authentic *C*-glycoside. This NMR discrepancy meant that the assumed stereochemistry of the two *C*-glycosides was incorrect (**Figure 2.9)**. Furthermore, at that time, we did not know which azide opening condition, $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ or NaN_3, gave the required epoxide opened product. We had to look into what had really happened during the synthesis.



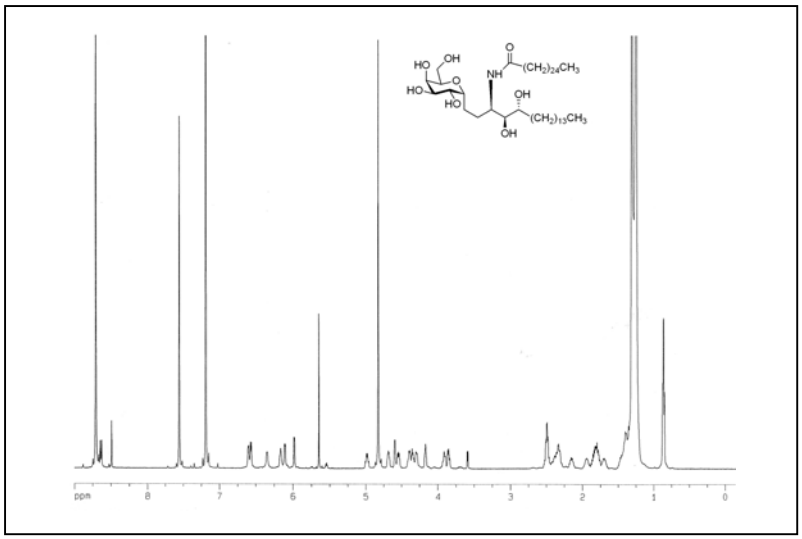
97, major isomer **99**

100, major isomer

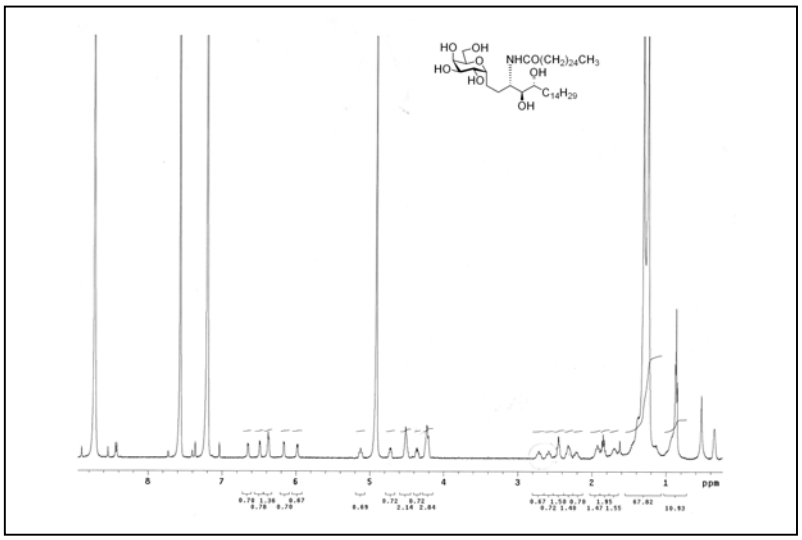
98, minor isomer **101**

102, minor isomer

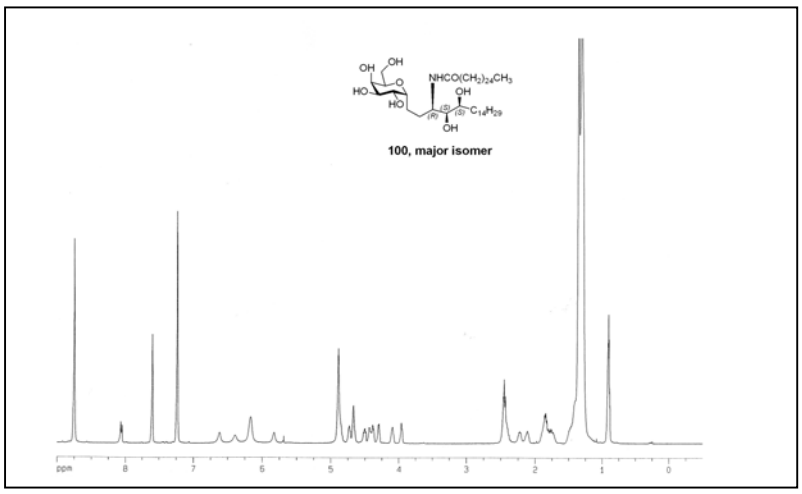
Scheme 2.28: Synthesis of two *C*-glycoside analogues 100 and 102



^{1}H spectrum of the *C*-glycoside 102, the minor isomer



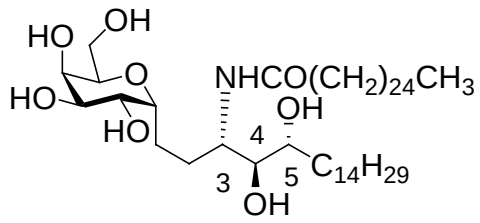
^{1}H spectrum of the *C*-glycoside compound 4 by Dr. Yang



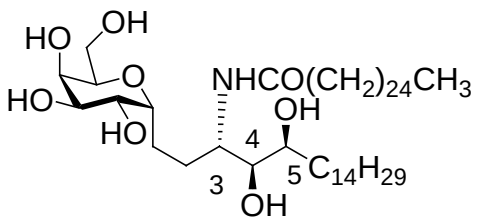
^{1}H spectrum of the *C*-glycoside 100, the major isomer

Figure 2.9: ^{1}H spectrum of *C*-glycosides 4, 100 and 102

2.2.4: Explanations for the NMR discrepancy:



4



87

Figure 2.10: Two *C*-glycosides: 4 and its 5-epimer 87

The target *C*-glycoside **4** had three contiguous stero centers, which are (*3S, 4S, 5R*). The 5-OH stereo center was established in the Grignard reaction, either the major or the minor isomer had the right stereochemistry at the 5-position so the 5-OH stereocenter did not cause the trouble. What happened to the 3-*N* and /or 4-*OH* would be responsible for the NMR discrepancy (**Figure 2.10**).

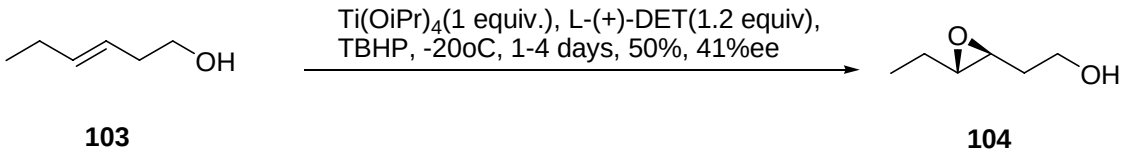
The first explanation was that the 4-OH's stereochemistry was not correct, which may derive from reversed facial selectivity in the Sharpless asymmetric epoxidation or usage of the wrong chiral reagent in the SAE reaction. And the second one was that the 3-N's stereocenter was retained during the opening of the correct oxirane by Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$.

2.2.4.1 The first explanation and synthesis of *C*-glycoside analogues using the (*2S, 3S*) epoxide 105 as the starting material:

2.2.4.1.1 The first explanation:

At this point in our experiments, our successful synthesis *via* NaN_3/NH_4Cl opening of the (*2R, 3R*) epoxide **73** had not been verified, so we could not be certain that the Sharpless asymmetric epoxidation was reliable in our system. Thus we chose to verify the first possibility and find out what happened during the Sharpless asymmetrical epoxidation process. Did we choose the wrong catalyst combination and obtain the epoxide with the opposite stereochemistry or did we use the right chiral catalyst but the facial selectivity was reversed so the stereo assignment deduced from the Sharpless empirical rule was wrong?

The empirical rule of Sharpless asymmetrical epoxidation provides that using unnatural tartrate ester catalyst combination, D-(-)-DET or D-(-)-DIPT, would afford (*R, R)* epoxide while using the natural tartrate ester catalyst combination, L-(+)-DET or L-(+)-DIPT, could produce *(S, S)* epoxide. There have been some cases, where the enantiofacial selectivity is reversed from the general rule. It was reported by K. B. Sharpless *et. al*. [74] that chirality of the epoxidation products were found to be opposite to the proposed structures in the homoallylic alcohol, bishomoallylic alcohol, and trishomoallylic alcohol systems. For example, epoxidation of the homoallylic alcohol **103** using L-(+)-DET gave the (*R, R*) epoxide **104** instead of (*S, S*) epoxide [74] (**Scheme 2.29**).



103 **104**

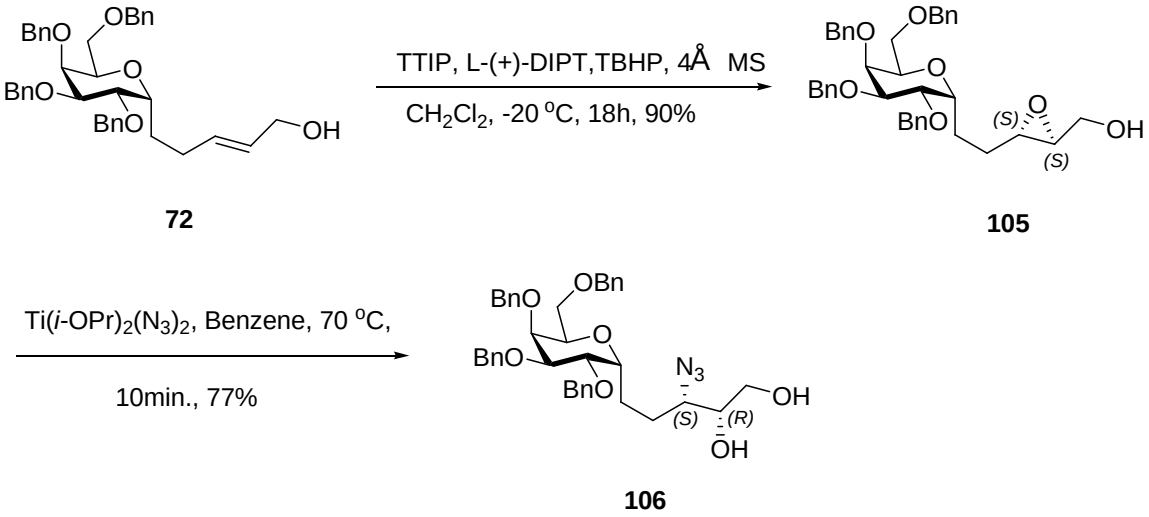
Scheme 2.29: Reversed facial selectivity of homoallylic alcohol 103

In our *trans* allylic alcohol molecule **72**, there were six oxygen atoms which could complex with the chiral titanium reagent and perhaps block one face. Thus the epoxidation could take place from the opposite direction so the enantiofacial selectivity could be reversed. As a result, epoxidation using D-(-)-DET or D-(-)-DIPT would afford the (*S, S*) epoxide and epoxidation using L-(+)-DET or L-(+)-DIPT could produce the (*R, R*) epoxide.

To test that possibility, we decided to use L-(+)-DIPT as the chiral ligand in the Sharpless asymmetric epoxidation step to synthesize another epoxide and carry it through to the end products so we could compare their NMR spectra with those of the target compound **4**. If they matched with each other, that means the enantiofacial selectivity with our carbohydrate substrates was inverted and the structure deduced from the Sharpless empirical rule was incorrect in the carbohydrate system. And if not, the empirical rule was correct and the cause of the NMR discrepancy came from the second possibility.

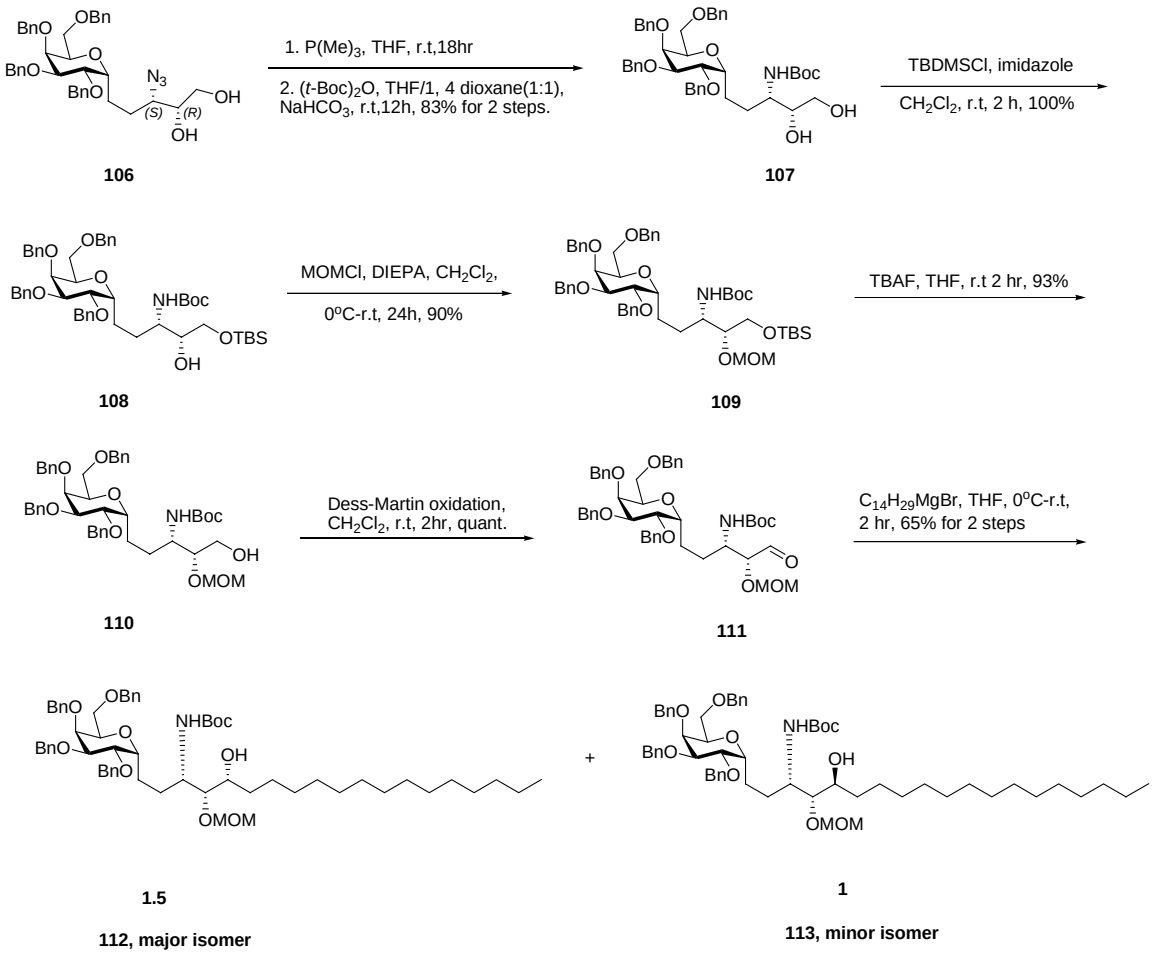
2.2.4.1.2: Synthesis of two *C*-glycoside analogues using the (*2S, 3S*) epoxide 105 as the starting material:

Sharpless asymmetric epoxidation of the carbohydrate allylic alcohol **72** using L-(+)-DIPT as the chiral reagent gave the (*2S, 3S*) epoxide **105** in high yield. Here we tentatively assigned the structure of the epoxide **105** as (2S, 3S) epoxy alcohol based on the empirical rule of Sharpless asymmetric epoxidation. This epoxide **105** had different spectroscopic data from the (*2R, 3R*) epoxy alcohol **73** obtained by the SAE reaction using D-(-)-DIPT as the chiral reagent. Regioselective ring opening of the oxirane **105** with Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$ gave the 3-azido-1, 2 diol **106** as a single product (**Scheme 2.30**) and the 1, 2 diol structure was confirmed again by cleavage with $NaIO_4$ to afford the corresponding aldehyde. Based on NMR experiment in the later stage, the stereochemistry of this 3-azido-1, 2 diol **106** was assigned tentatively as the *syn*-3-N$_3$-2-OH.



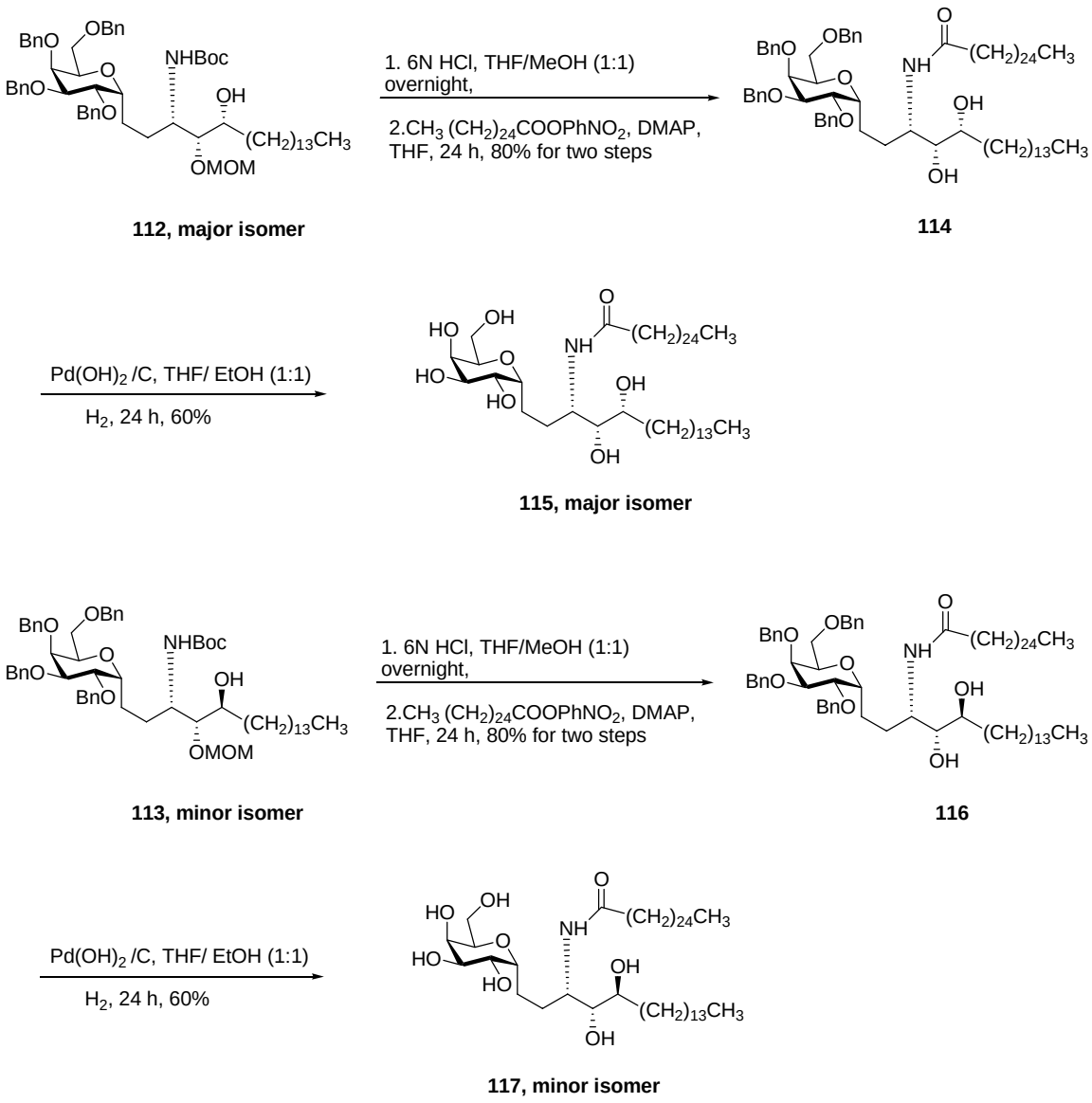
Scheme 2.30: SAE reaction and Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$ opening of the epoxide 105

The azido group was then reduced to the free amine by Staudinger method using $P(Me)_3$ as the reducing reagent and the amine was then protected with $(t\text{-Boc})_2O$. Selective protection of the primary hydroxy with the TBS group and the secondary hydroxyl group with MOM group provided the fully protected compound **109**. TBAF desilylation of the primary TBS of compound **109** afforded the primary alcohol **110** in high yield. Dess-Martin Periodinane (DMP) oxidation converted the alcohol **110** to the aldehyde **111** in quantitative yield and the aldehyde **111** was used directly in the next step without further purification. Chelation controlled Grignard reaction of the aldehyde **111** with $C_{14}H_{29}MgBr$ afforded a separable mixture of the major diasteromer **112** and the minor diasteromer **113** in a ratio of 1.5:1 in 65% combined yield (**Scheme 2.31**). The structures of the major isomer **112** and the minor isomer **113** were assigned according to "Cram chelation control" model.



Scheme 2.31: Synthesis of two diastereomers 112 and 113

The major diasteromer **112** and the minor diasteromer **113** were subjected to acidic hydrolysis condition to remove the Boc and MOM protection groups in one step, and ceramidation of the free amine with $C_{25}H_{51}COOPhNO_2$ provided the corresponding amide respectively in good yield. Global hydrogenolytic deprotection of the amides provided the final compounds **115** and **117** in good yield (**Scheme 2.32**).



112, major isomer **114**

115, major isomer

113, minor isomer **116**

117, minor isomer

Scheme 2.32: Synthesis of the two *C*-glycosides 115 and 117

We then compared the spectra of the *C*-glycosides **115** derived from the major diasteromer and the other one, **117**, which was derived from the minor diasteromer with those of the *C*-glycoside **4** synthesized by Dr. Yang (**Figure 2.11 and Figure 2.12**) and none of those compounds' spectra matched with each other while those spectra were also different from the two *C*-glycoside analogues **100** and **102** obtained from the (*2R, 3R*) epoxy alcohol **73** opened by Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$ (**Figure 2.9**).

This comparison result means that the stereochemical outcome defined by the Sharpless asymmetrical epoxidation empirical rule are still correct and we had selected the proper Sharpless chiral auxiliary to obtain the needed (*2R, 3R*) epoxide in the first instance.

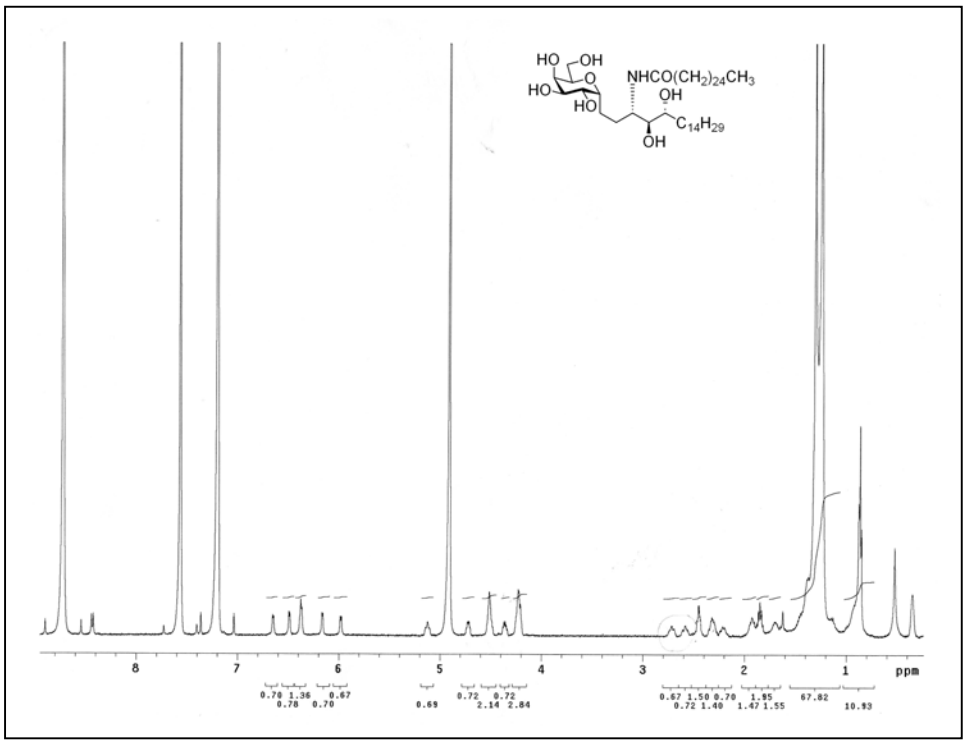
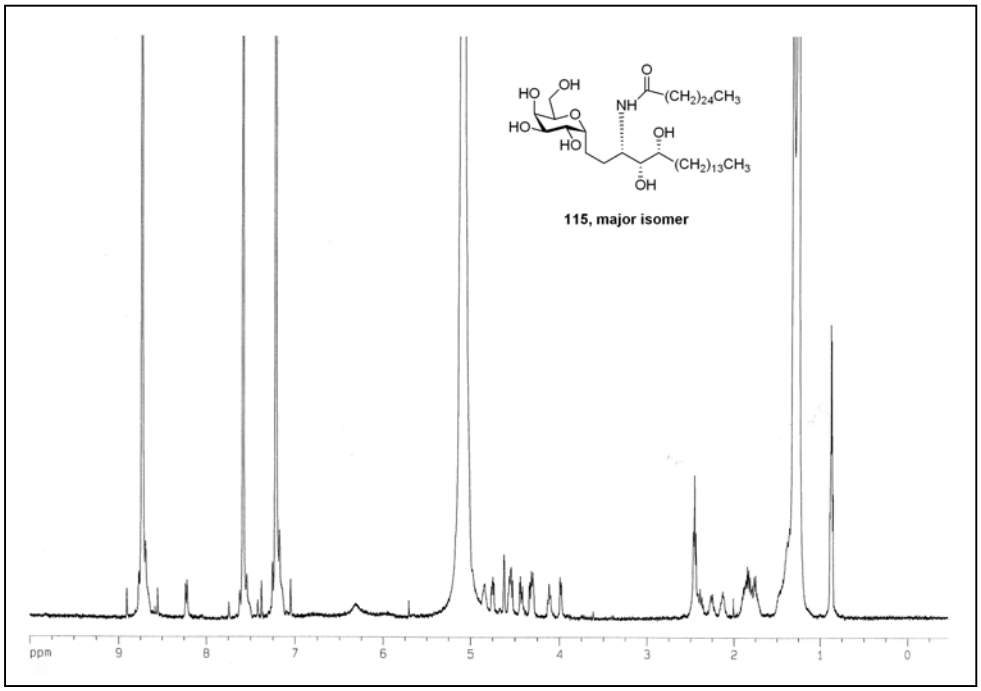


Figure 2.11: ^{1}H spectrum for compound 4



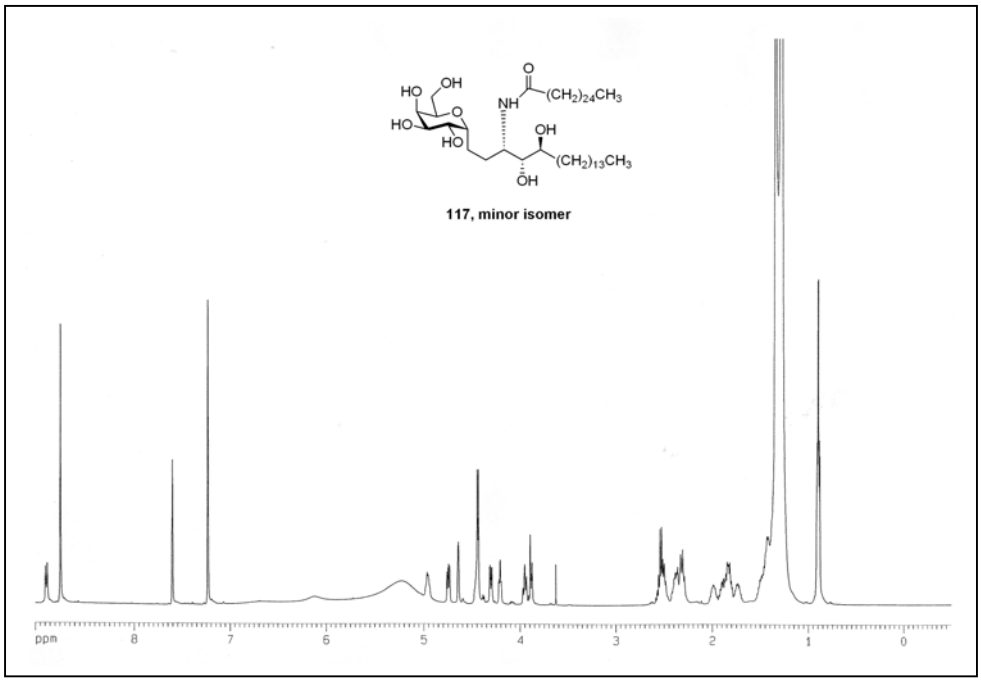
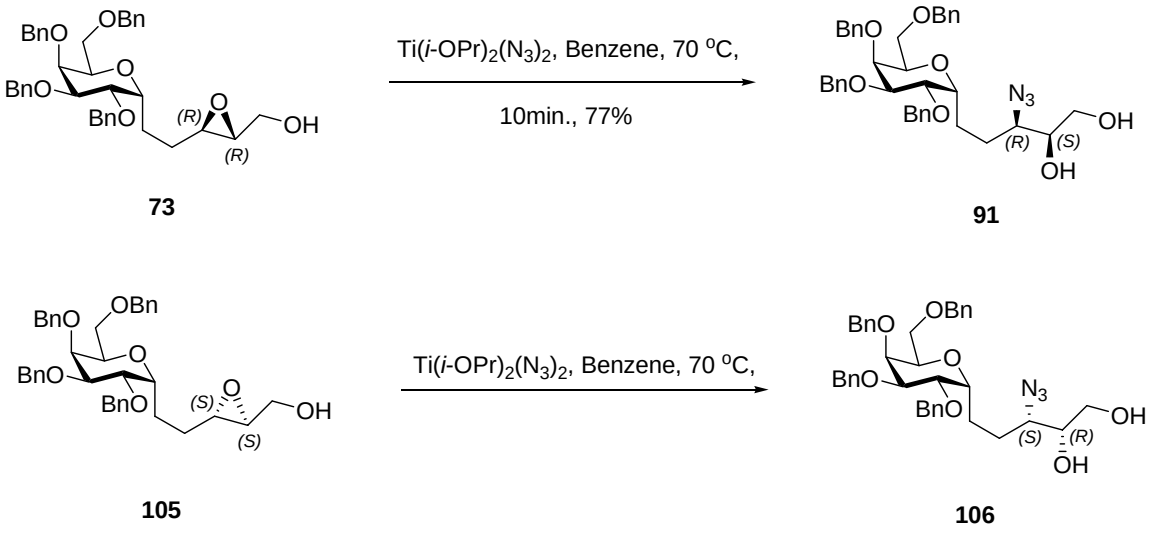


Figure 2.12: ^{1}H spectrum for compound 115 and 117

2.2.4.2: The second explanation and NMR proof:

2.2.4.2.1: The second explanation and synthesis of the 5-membered ring systems:

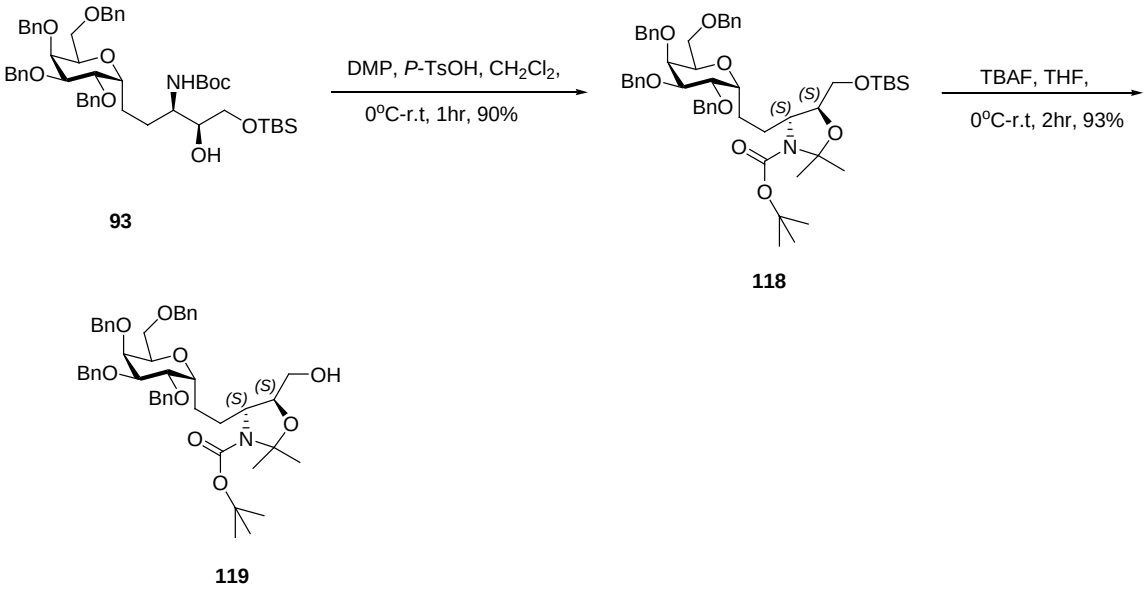
So we need to verify the second possibility: The 3-*N* stereo center was retained upon the epoxide opening with Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$. We therefore assumed that the epoxides **73** and **105** opened with Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$ proceeded with retention of configuration to give **91** and **106** respectively. The 3-azido group and 2-hydroxy group were *syn* to each other instead of *anti* to each other (**Scheme 2.33)**.



Scheme 2.33: Opening of the epoxides with Ti(*O*-*i*-Pr)$_2$(N$_3$)$_2$

The *syn* stereo-relationship between the 2-hydroxy and 3-azido groups could be proved by converting the flexible acyclic 3-azido-1, 2 vicinal diol into a rigid 5-membered cyclic system, in which the coupling constant and/or nOe effect between the 2-H and 3-H could provide sufficient information to support our conclusion.

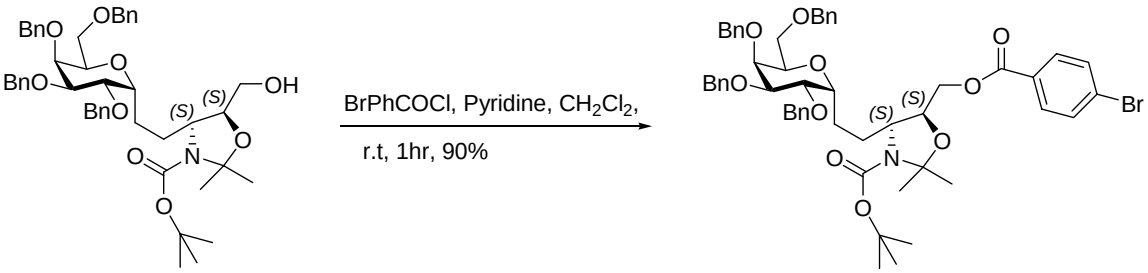
For the 3-azido-1, 2 vicial diol **91** derived from the (*2R*, *3R*) epoxide **73**, the azido group was reduced with $P(Me)_3$ and the amine was protected with $(t\text{-Boc})_2O$. The primary hydroxyl was protected with TBS group to afford compound **93**. 2, 2-DMP protection of the 3-*N* and the 2-*O* atoms in the presence of catalytic amount of *P*-TsOH formed the rigid 5-membered ring compound **118** in high yield. Because the existence of two conformers of the amide, the spectra showed two sets of peaks and did not provide satisfactory identifiable information. Removal of the TBS group with TBAF gave compound **119**. ^1H NMR of this compound did not give useful information either (**Scheme 2.34**).



Scheme 2.34: Synthesis of the 5-membered cyclic compound 119

Conversion of the alcohol to a *p*-bromo benzoyl ester is a common way to get highly crystalline material so the structure of the compound could be identified by X-ray crystal analysis. Acylation of compound **119** with BrPhCOCl gave a solid compound **120** (**Scheme 2.35**). Various conditions such as different solvent systems, temperature,

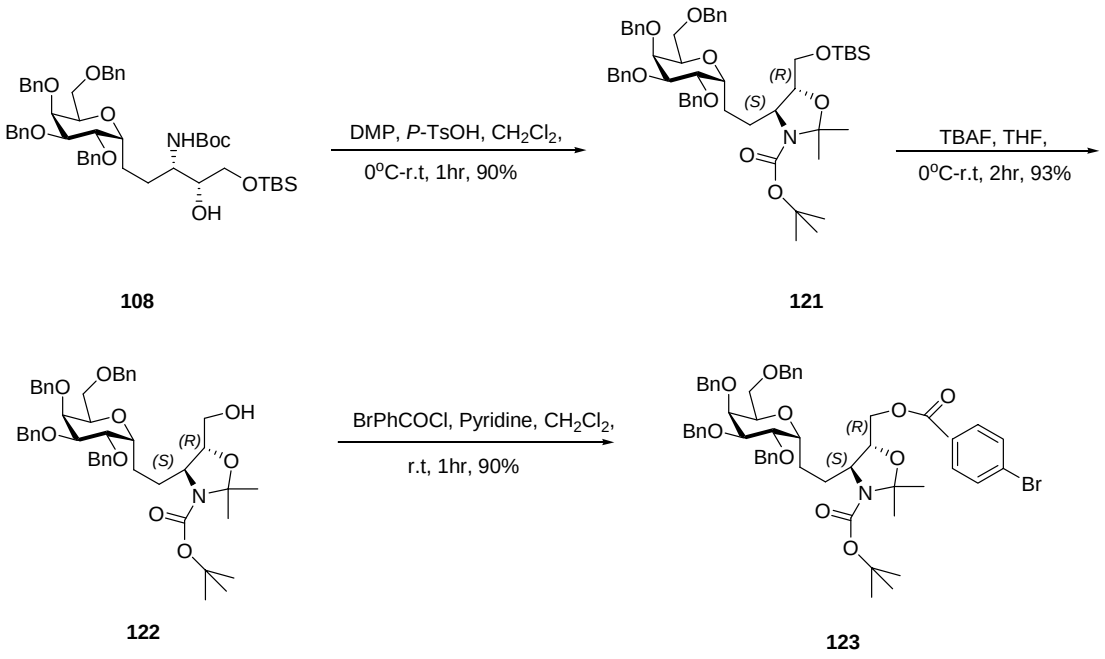
and diffusion of a less effective solvent into a solution of the ester in a more effective solvent were employed to get a good crystal. However, all of those efforts did not succeed in producing a diffraction-quality crystal. But the strong electron-withdrawing *p*-bromo benzoyl group dispersed NMR peaks and the characteristic peaks of the 2-H and 3-H of the 5-membered ring could be identified and provided diagnostic data for structure elucidation.



119 **120**

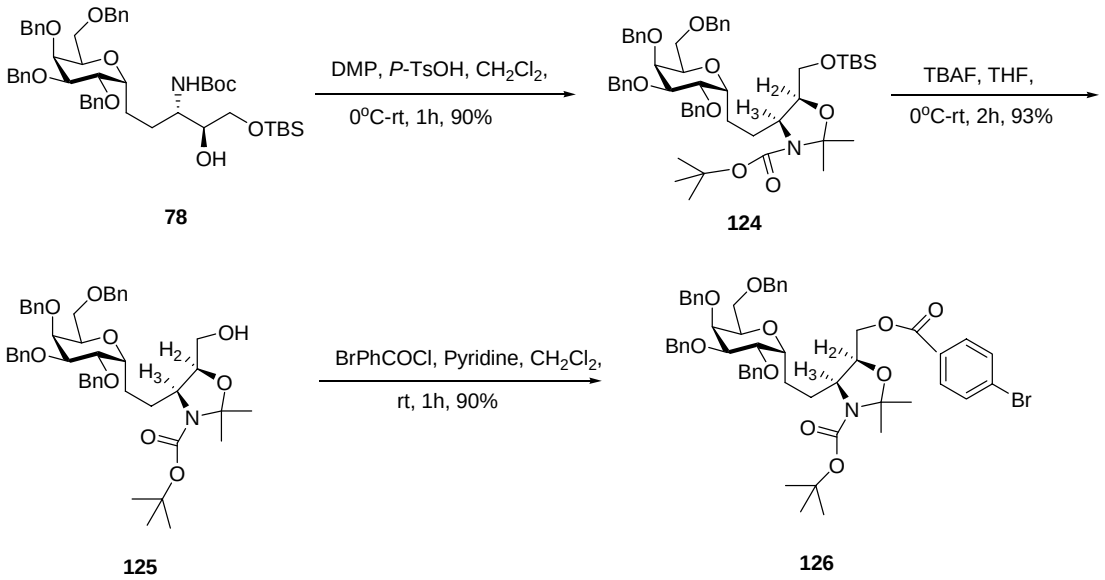
Scheme 2.35: Formation of *p*-bromo benzoyl ester 120

Similarly, for the 3-azido-1, 2 vicinal diol **106** obtained by opening of the (*2S, 3S*) epoxide **105** with Ti(O- *i*-Pr)$_2$(N$_3$)$_2$, the same series of protection group manipulation gave the alcohol **122**, which had also been converted to the corresponding para-bromo benzoyl ester **123**. Efforts to crystallize this benzoyl ester failed also. Similarly, the 2-H and 3-H of this compound could also be identified (**Scheme 2.36**).



Scheme 2.36: Synthesis of *p*-bromo benzoyl ester 123

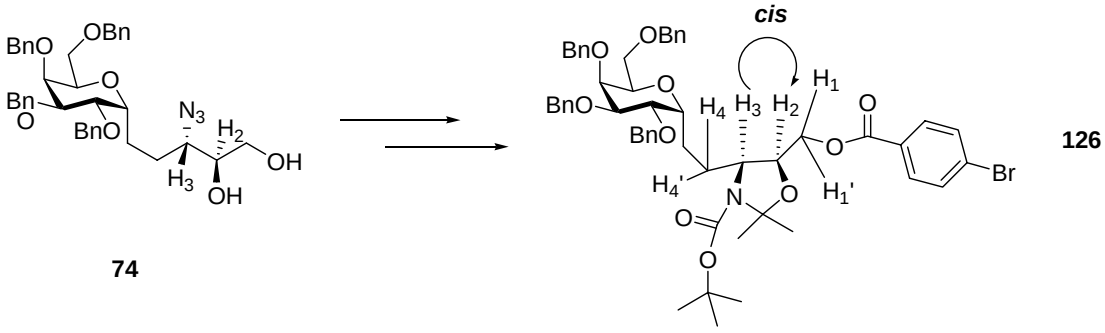
We already knew that opening of the (*2R, 3R*) epoxide **73** by NaN_3/NH_4Cl could afford a mixture of the 1, 2 diol **74** and 1, 3 diol **75**. The desired 1, 2 diol **74** had been separated in the later stage and the stereorelationship between the 3-azido and the neighboring 2-hydroxyl was ensured to be *anti* because it finally led to the material of known *anti* configuration of the 3-*N* and the neighboring 2-hydroxyl. That compound was also converted to the corresponding para-bromo benzoyl ester **126** in a similar way to compare its NMR spectrum with those esters derived from the (*2R, 3R*) epoxide **73** or the (*2S, 3S*) epoxide **105** opened by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ (**Scheme 2.37)**.



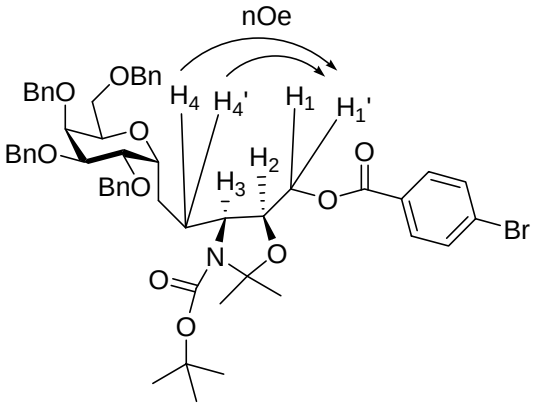
Scheme 2.37: Synthesis of the *p*-bromo benzoyl ester 126

2.2.4.2.2: nOe analysis

In the 3-azido-1, 2 vicinal diol **74**, if the 3-azido and 2-hydroxy groups were *anti* to each other as a result of a single ***S*$_N$*2*** opening of epoxide **73** by N_3^-, The H_2 and H_3 should also be *anti* to each other. If we converted this 3-azido-1, 2 vicinal diol **74** to the rigid five-membered cyclic *p*-bromobenzoyl ester **126**, the 3-*N* and 2-*O* should become *cis* and the H_2 and H_3 should also be *cis* (**Scheme 2.38**). So the nOe effect between the H_2 and H_3 would be observed (**Figure 2.12**).



Scheme 2.38: Stereo relationship in the cyclic benzoyl ester:



126

Figure 2.12: nOe effect of compoud 126, derived from NaN_3 opening of the (2*R*, 3*R*) epoxide 73

In the nOe correlation experiment, the expected nOe effect between the H_3 and H_2 was not observed and the correlation between H_3 and H_1, H_1' was not found either. While the nOe correlation between H_1, H_1` and $H_4$, $H_4$` was observed (**Figure 2.13**). Although this correlation could not certainly mean that the H_3 and H_2 were *cis* to each other in the cyclic compound, it could still illustrate the *cis* relationship between H_3 and H_2. So the H_3 and H_2 were *anti* to each other in the acyclic 3-azido-1, 2 diol **74** obtained from NaN_3 opening of epoxide.

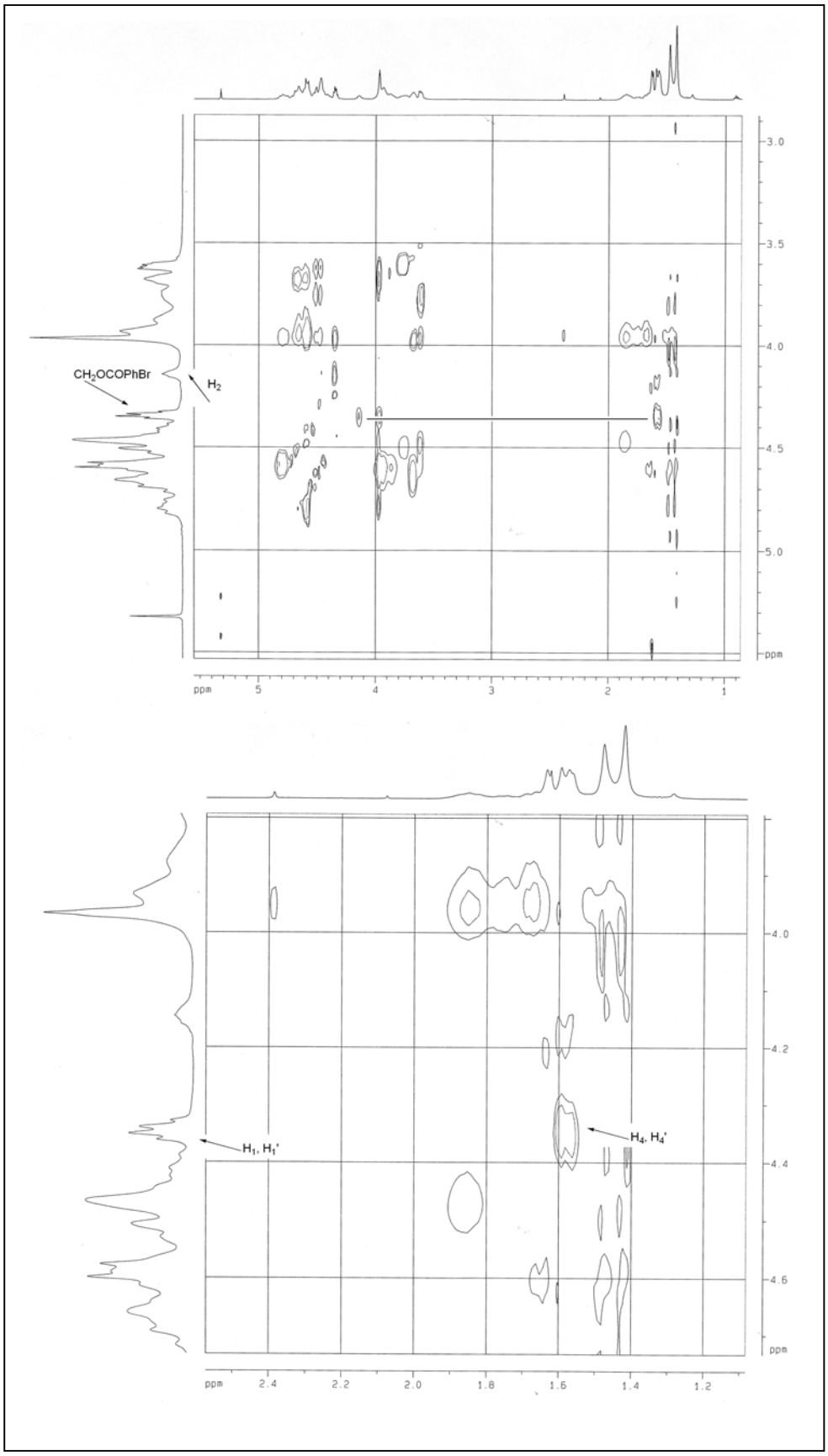
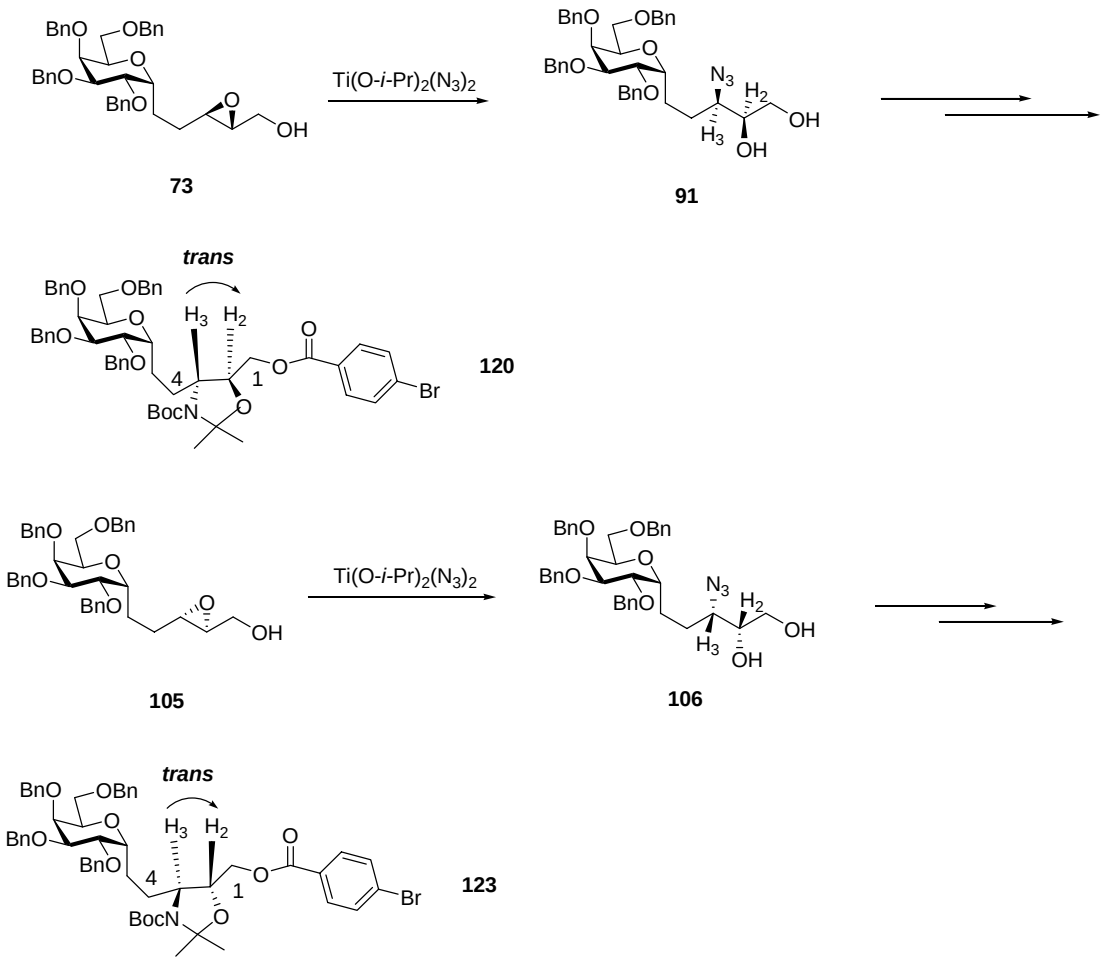


Figure 2.13: NOESY spectrum for compound 126

On the other hand, if the 3-*N* group's stereochemistry was retained instead of being inverted in the opening of the epoxide by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$, the 3-*N* and 2-*O* groups were *syn* to each other so the H_2 and H_3 should also be *syn*. In the corresponding five-membered cyclic ring system, the 3-*N* and 2-*O* would be *trans* and the neighboring H_2 and H_3 should also become *trans* to each other (**Scheme 2.39**). There was no nOe effect observed between the H_2 and H_3. But the nOe effect between the H_2 and the H_4, H_4' protons, the H_3 and H1 H_1' protons should be observed. Also for the two cyclic benzoyl esters derived from the respective (*2R, 3R*) epoxide **73** and (*2S, 3S*) epoxide **105**, no matter what their absolute stereochemistry are, their relative stereo structure are the same, so those two cyclic benzoyl esters should demonstrate similar nOe effects.

Those two benzoyl esters **120** and **123** did show similar ^1H spectra and nOe effects. So the conclusions obtained were also the same. In their nOe experiment, the H_2 and H_3 did not show any nOe correlation at all while the H_2 showed nOe effect with H_4 and H_4' protons. And the H_3 showed nOe correlation with H_1 and H_1'protons (**Figure 2.14, 2.15, 2.16**).



Scheme 2.39: Cyclic *p*-bromo benzoyl esters 120 and 123

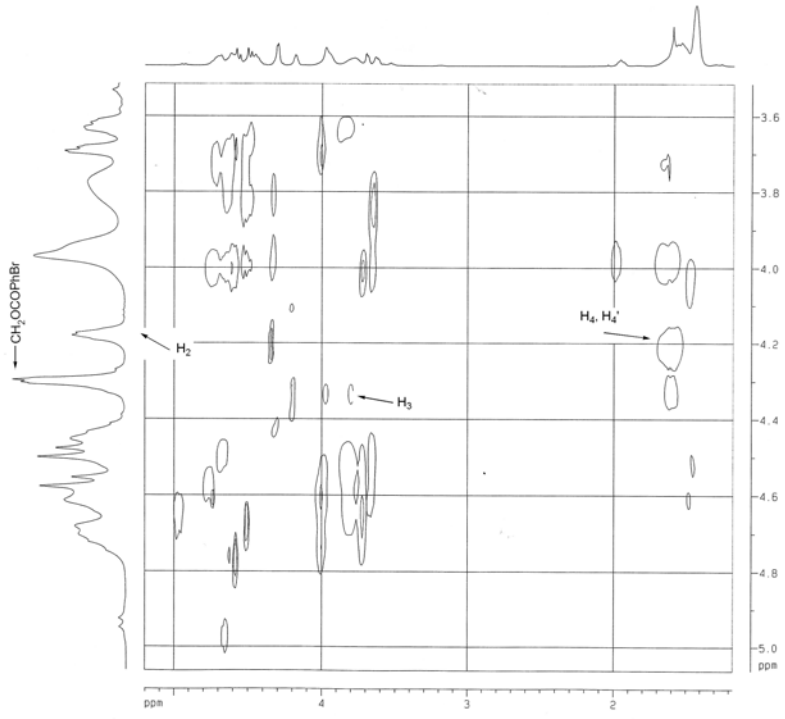


Figure 2.14: NOESY spectrum for compound 120

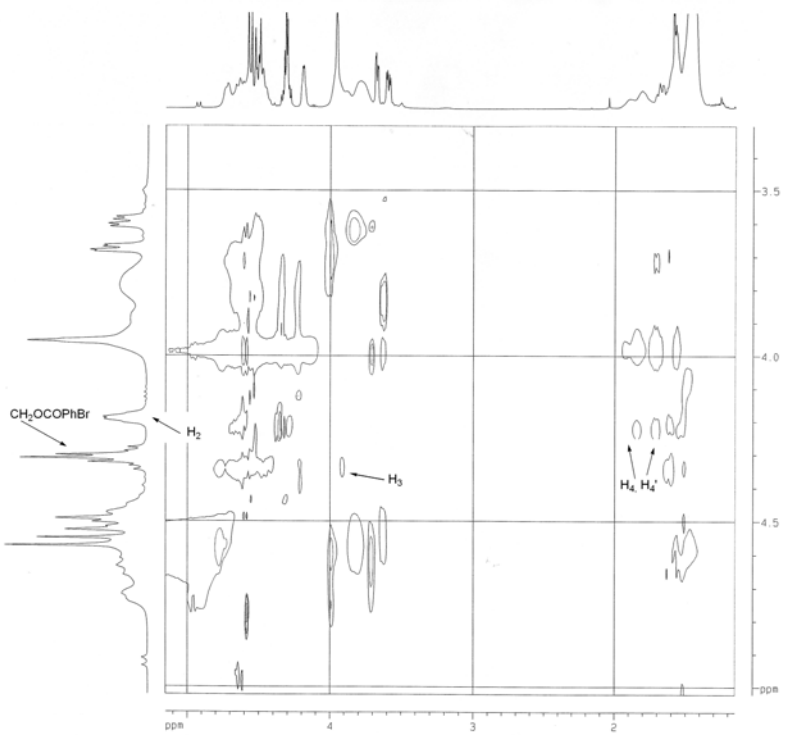


Figure 2.15: NOESY spectrum for compound 123

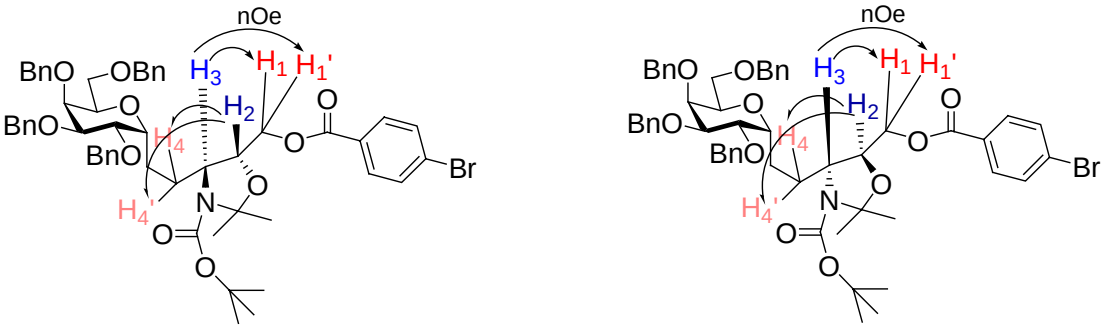


Figure 2.16: Compound 120, from the (2*S*, 3*S*) epoxide 105, and compound 123, from the (2*R*, 3*R*) epoxide 73 opened by Ti(O-i-Pr)$_2$(N$_3$)$_2$.

This information illustrated that the H_2 and H_3 were *trans* to each other in the two cyclic benzoyl esters. So in the acyclic 3-azido-1, 2 vicinal diols **91** and **106**, the 3-*N* and 2-*O* were *syn* to each other. That tells us that the 3-*N*' stereochemistry was retained and is the same as that of the neighboring 2-*O*, a result that could occur *via* a double ***S$_N$2*** replacement of the corresponding epoxides.

Now, we can draw this conclusion that the carbohydrate (*2R, 3R*) epoxide **73** and (*2S, 3S*) epoxide **105** could be opened by Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ reagent and the stereo chemistry of the resulting 3-azido-1, 2 diol **91** and **106** were retained. For the 3-azido-1, 2 diol **74** obtained by opening the (2R, 3R) epoxide **73** by NaN$_3$/NH$_4$Cl, the stereochemistry of the 3-*N* was inverted.

2.2.4.3: Further NMR evidence of stereochemistry:

Recently,Toba. T. *et al.* [39] synthesized a *C*-glycoside analogue of immunomodulating α-galactosylceramide OCH, compound **3**, (3S, 4S, 5R)-1-(α-D-galactopyranosyl)-3-tetracosanoylamino-4, 5-decanediol, which has a truncated shorter C5 sphingosine side chain than our *C*-glycoside analogue of KRN7000, which has a C14 side chain (**Figure 2.17**).

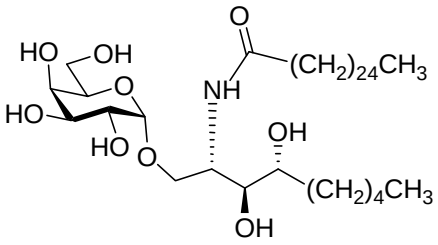
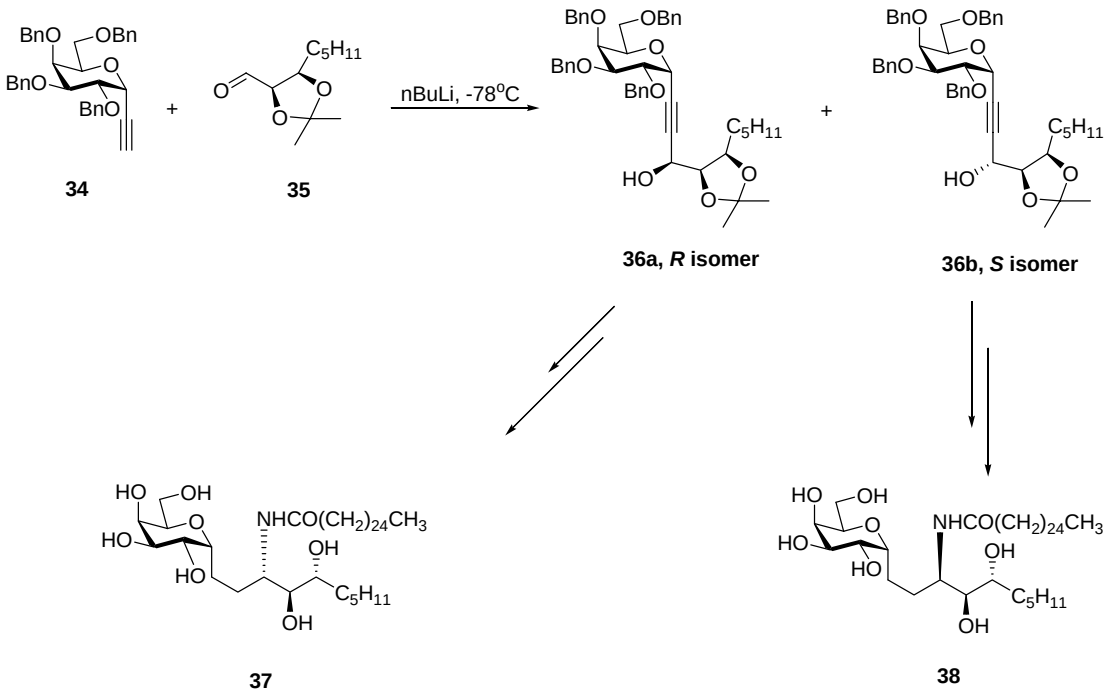


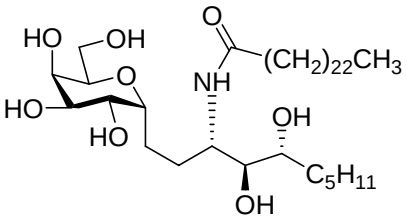
Figure 2.17: Compound 3, OCH, an analogue of KRN7000

The convergent synthesis features the nucleophilic addition of an α-ethynyl sugar **34** to the phytosphingosine-precursor aldehyde **35**, which was derived from L-arabinose with suitable stereochemistry corresponding to the vicinal hydroxyl groups in the phytosphingosine moiety. The addition products were a separable mixture of *R*-propargyl alcohol **36a** and *S*-propargyl alcohol **36b**. The major isomer **36a**, the *R*-isomer, was converted to the corresponding *C*-glycoside analogue of OCH **37**, while the minor isomer, the *S*-isomer **36b**, was converted to the corresponding *C*-glycoside **38** in the same synthetic manner (**Scheme 2.40**) (also see the introduction).

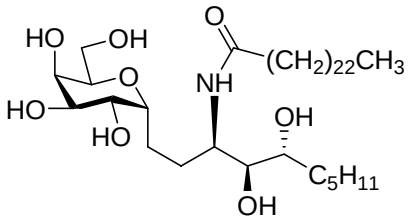


Scheme 2.40: Toba's synthesis of the C-glycoside analogues of OCH

The two *C*-glycoside analogues **37** and **38** were 3-*N* epimers (**Figure 2.18**).



37

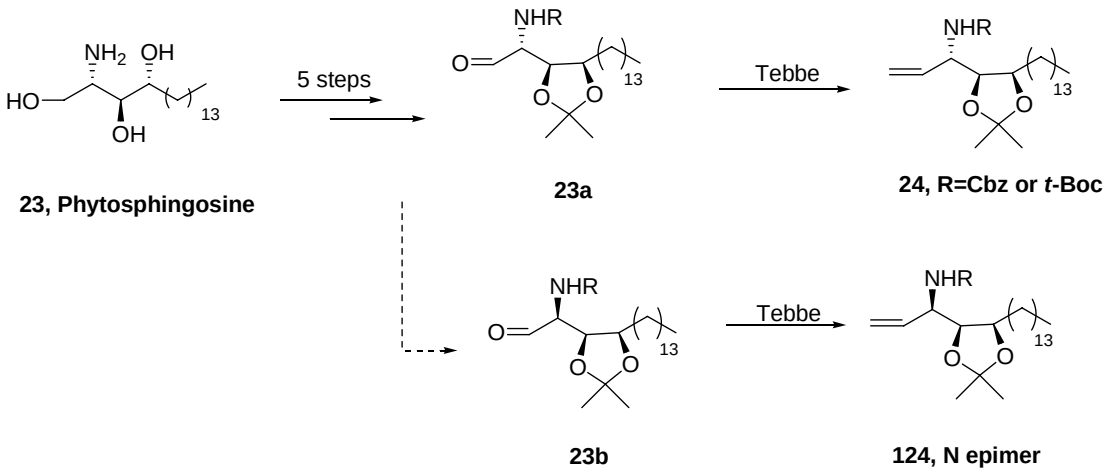


38

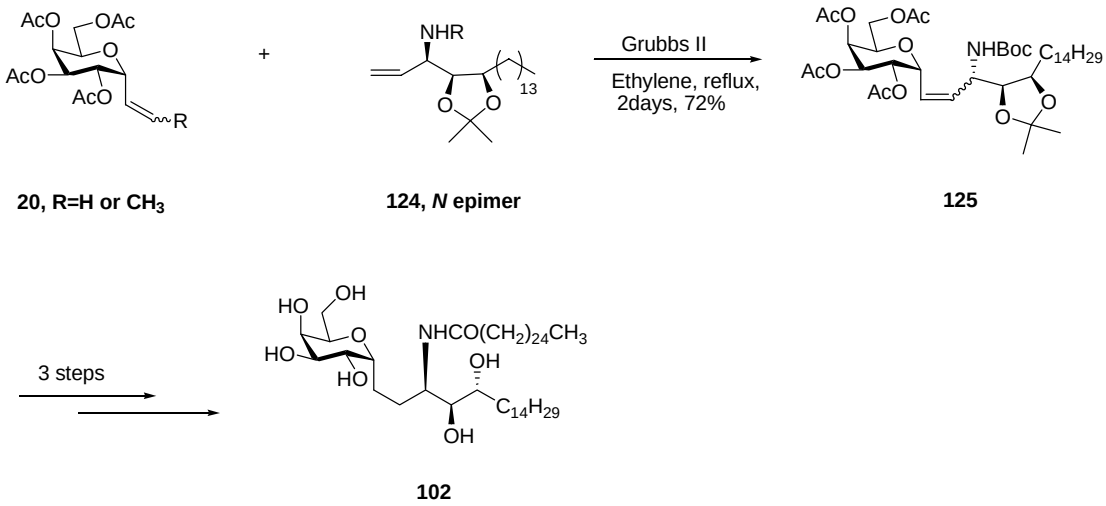
Figure 2.18: The two *C*-glycoside analogues of OCH, 37 and 38

The NMR spectrum of the major *C*-glycoside **37** matches with that of compound **4**, our target *C*-glycoside analogue of KRN7000 although they had a different length side chain and fatty amide chain. We then compared the spectra of their *N* epimer **38** with that of our minor *C*-glycoside **102** obtained from the (*2R, 3R*) epoxide **73** opened by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$.

Recently, in another independent synthesis of the *C*-glycoside analogue of KRN7000 by Dr. Guangwu Chen in Franck`s lab utilizing the ethylene-promoted Cross-Metathesis to assemble the carbohydrate moiety and phytosphingosine side chain together (also see **Scheme 1.6** in the introduction part). The side chain precursor, the aldehyde **23a**, was susceptible to basic condition and could epimerize to the *N*-epimer **23b,** which was also converted to alkene **124** (**Scheme 2.41**). The *N*-epimer **124** was converted to the corresponding *C*-glycoside **102** following the same synthetic route for compound **4**, the *C*-glycoside analogue of KRN7000 (**Scheme 2.42**).

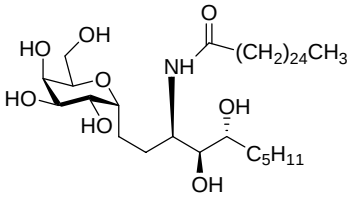


Scheme 2.41: Synthesis of the *N* epimer of the phytosphingosine side chain 124

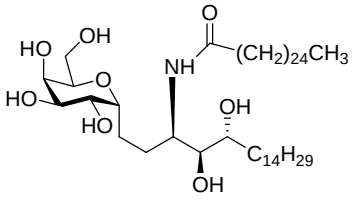


Scheme 2.42: Synthesis of the *N*-epimer 102

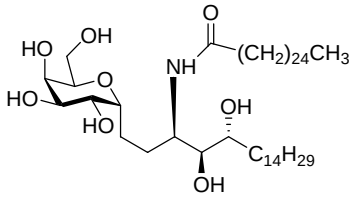
Those three compounds were obtained through different approaches and had essentially identical ^{1}H NMR spectrum (**Figure 2.19, Figure 2.20 and Figure 2.21**).



Compound 38 synthesized by Toba *et al.*



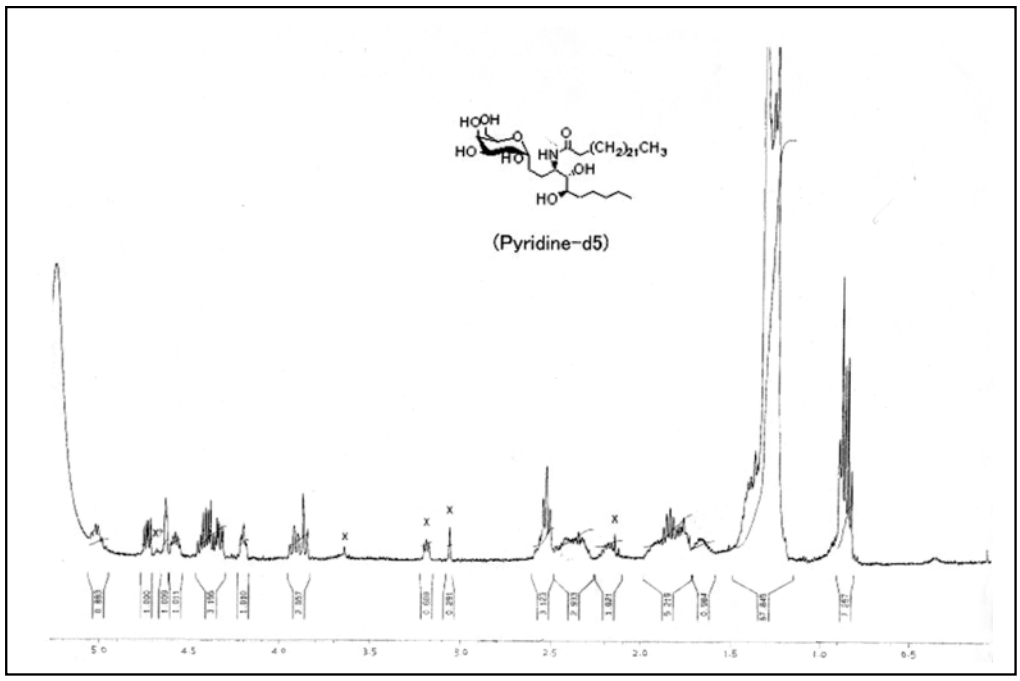
102, synthesized by Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ opening of epoxide



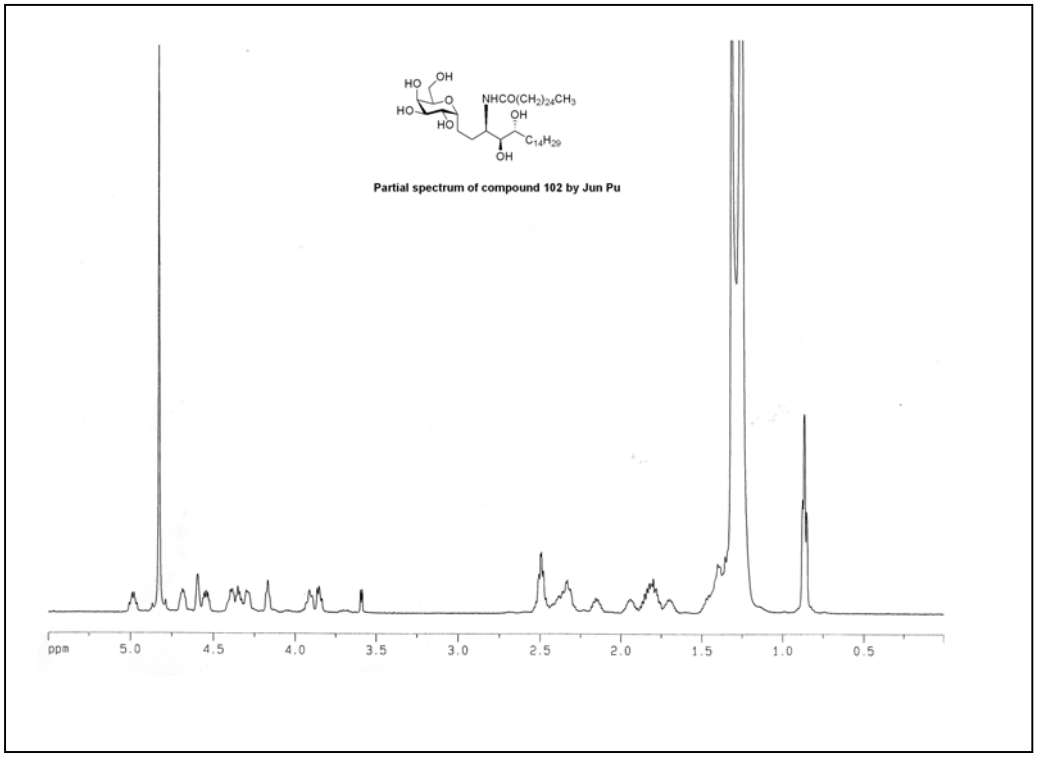
102, synthesized by Dr. Guangwu chen

Figure 2.19: Similar structure Compounds 38 and 102

That result proved that the 3-*N* stereocenter was retained during opening of the corresponding epoxides. And our nOe analysis was further substantiated.

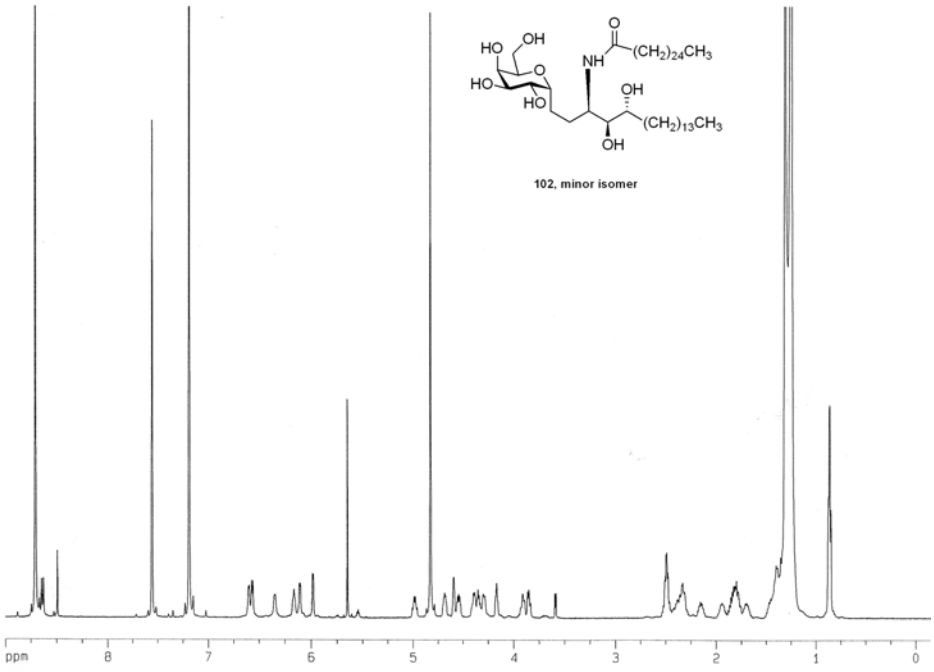


^{1}H spectrum for the *N* epimer **38** provided by Toba, T.

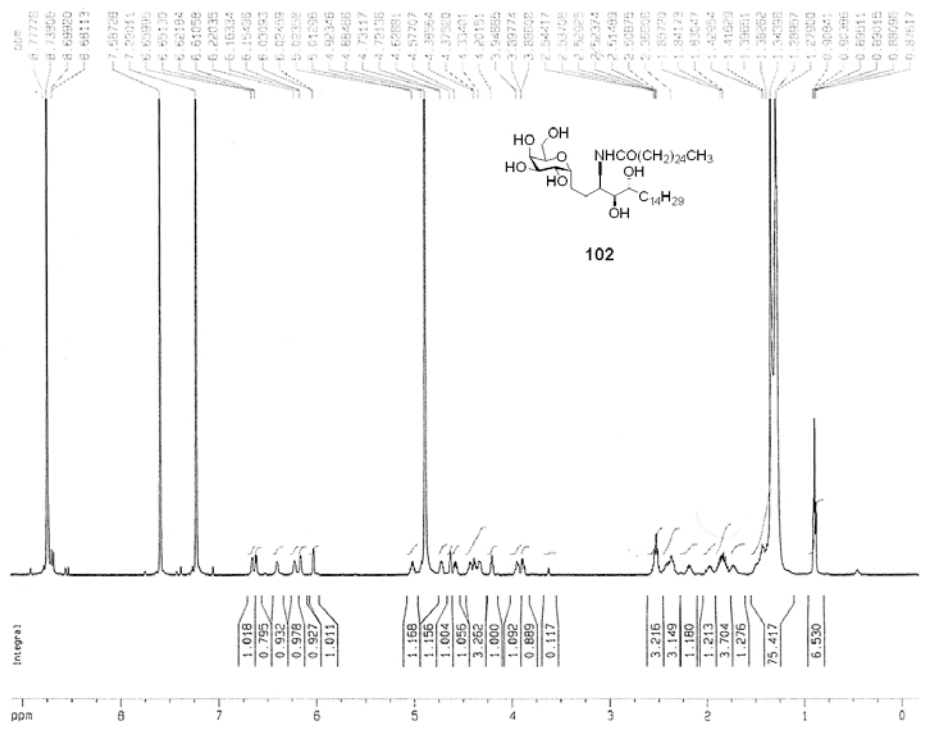


Partial ^{1}H spectrum for compound **102** synthesized by Jun Pu

Figure 2.20: Comparison of ^{1}H spectrum for compounds **38** and **102** synthesized by Jun Pu



^{1}H spectrum for compound **102,** the minor isomer from Grignard adduct derived from "Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ opening of epoxide synthesized by Jun Pu



^{1}H spectrum for compound **102** synthesized by Dr. Guangwu Chen

Figure 2.21: Comparison of ^{1}H spectrum for compound **102** by Guangwu Chen and Jun Pu

2.2.4.4: Mechanistic explanation of remote neighboring group participation: Unusual Lewis acid promoted double S_N2 opening and retention of *N* stereo center:

Now, it was certain that the configuration of the newly established *N* stereo center was retained in the $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ opening of the epoxides. That result could be explained by neighboring group participation during the epoxide ring –opening step. David R. Mootoo *et al*. has pointed out that oxygens present in ethers, esters, and pyranose rings participate efficiently in electrophilic reactions at remote centers leading to five- or six-membered heterocycles.[75] Actually, that was a widespread process, even where the oxygen in the precursor is protected as an ether, and where the ring formation is not stereo-electronically favorable. An oxonium ion, such as (II), is the postulated intermediate [76]. And this is consistent with the fact that benzyl ethers (I, R=$PhCH_2$) are particularly prone to cyclization, a result which is attributed to the (incipient) benzylic carbocation ion released in going to (III) (R^+= $PhCH_2^+$). An alternative pathway, leading to the product of oxygen migration (IV), is usually seen with methyl ethers [76,77] and is again consistent with the comparatively unstabilized oxonium ion in (II; R=Me). A further generalization is that the process is most prevalent when n=2 [76] (**Figure 2.22**).

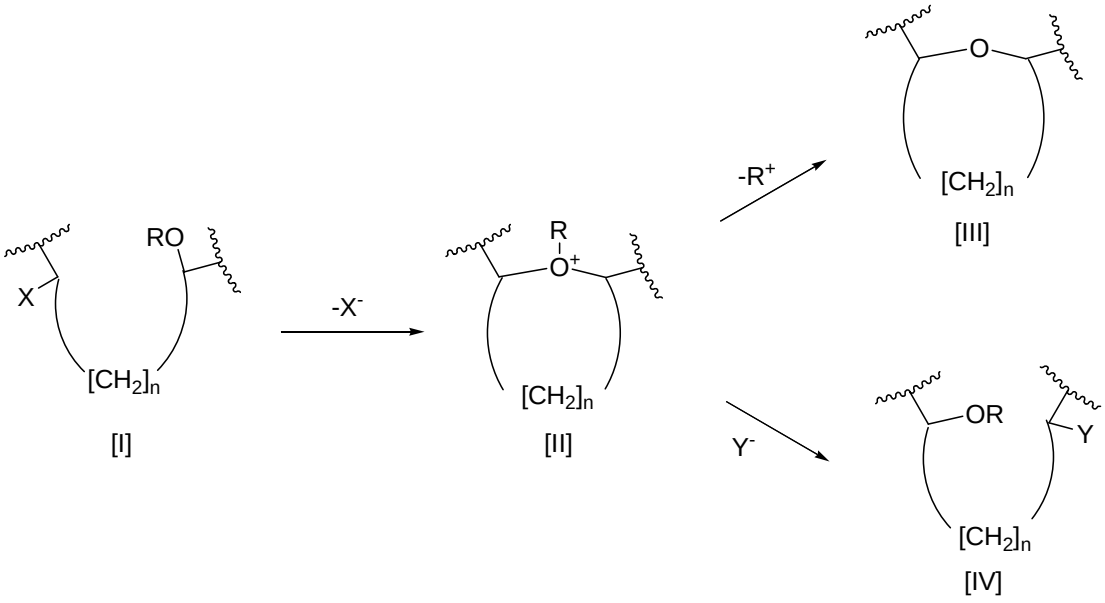
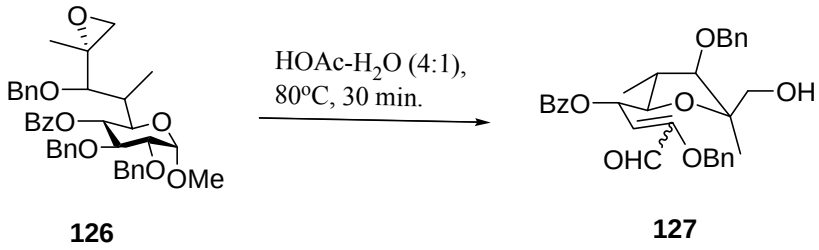


Figure 2.22: Mootoo's explanation for the neighboring group participation

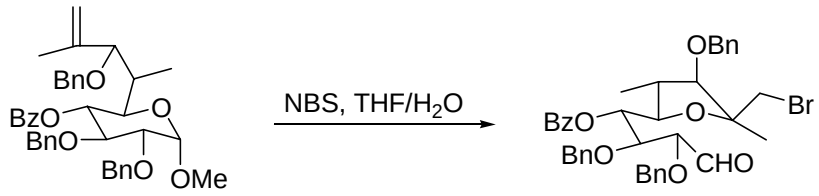
The ring oxygen of the pyranose unit also displays surprising nucleophilicity. This trend was revealed in the reaction of **126** to **127** (**Scheme 2.43**).



126 **127**

Scheme 2.43: Ring opening of epoxide 126 by neighboring group participation

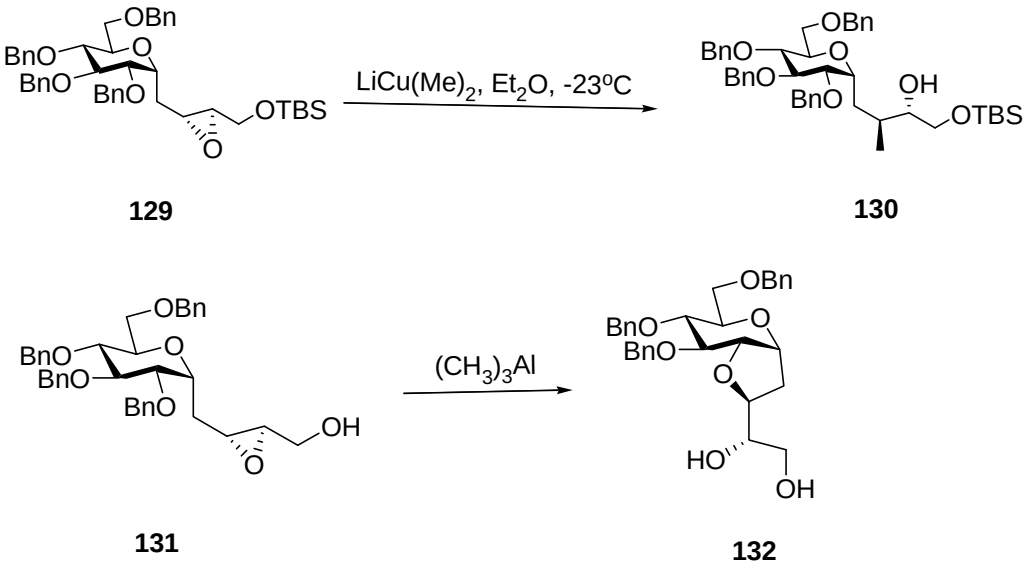
That was even more apparent when the alkene **128** was treated with *N*-bromosuccinimide (NBS) in THF to afford **129** quantitatively as a 1:1 mixture of diastereoisomers (**Scheme 2.44**).



128 **129**

Scheme 2.44: Example of neighboring group participation

In the synthesis of the C85-C98 segment of the palytoxin, McWhorter *et al*. [78] tried to open the epoxide **129** with lithium dimethylcuprate to yield the desired 1, 2 alcohol **130** while treatment of the epoxide **131** with $(CH_3)_3Al$ yielded exclusively a cyclic compound **132** which obviously arose *via* the epoxide ring-opening by the neighboring 2-benzyloxy group (**Scheme 2.45)**.

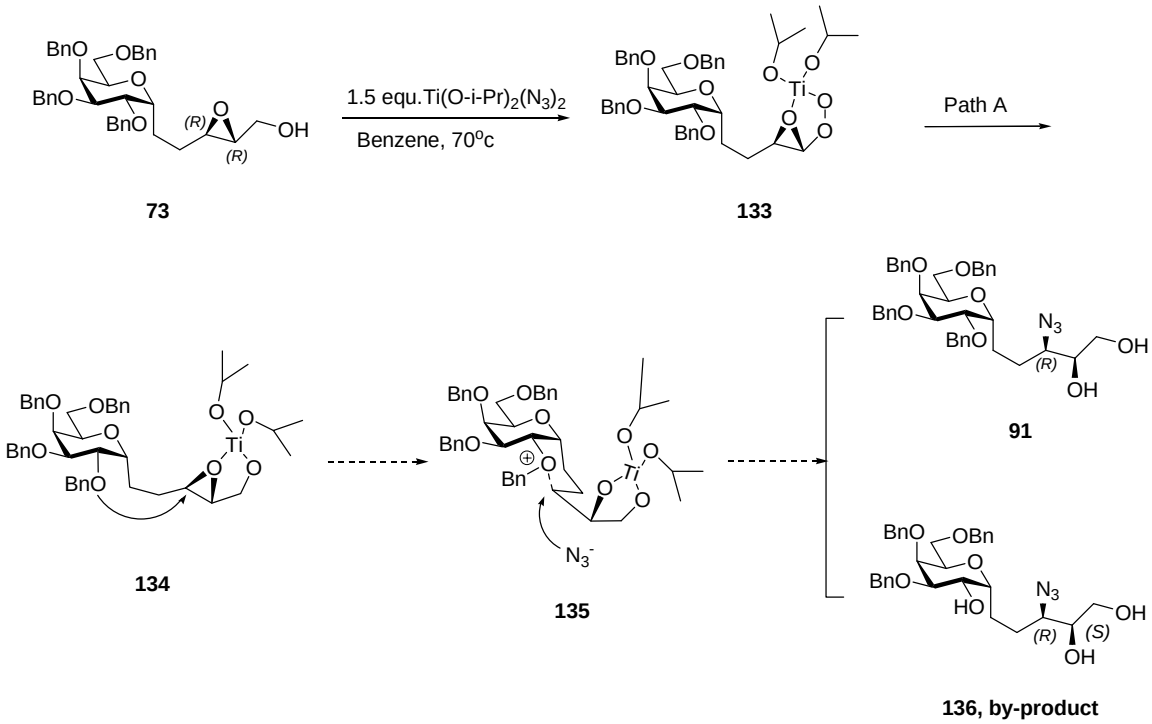


129 **130**

131 **132**

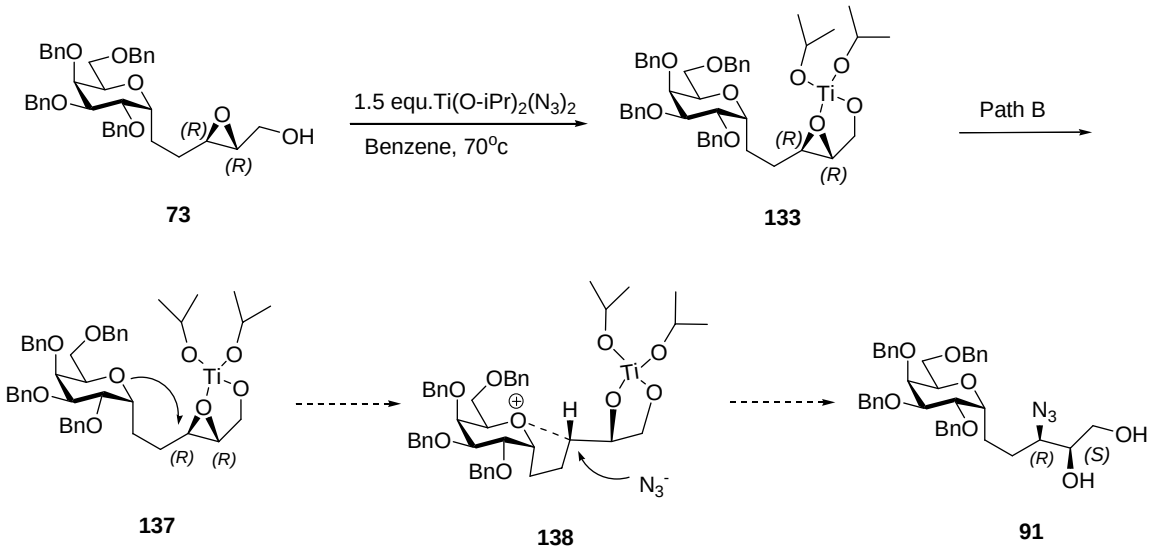
Scheme 2.45: Neighboring group participation in the opening of epoxide 129

In the opening of our epoxides, the *N* atom came from $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$. We suggest that the first step was that the epoxy alcohol **73** coordinated to the metal center of the Lewis acid, $Ti(O\text{-}i\text{-}Pr)_4$, in the rigid, bidentate manner to form the intermediate **133** as depicted in the following scheme. The second step of the reaction could take place in two possible pathways *via* different intermediates. In pathway a, the 2'-oxygen of the 2'-benzyloxy protection group could attack the epoxide from the backside in a $\boldsymbol{S_N2}$ manner, thus the configuration of the 3-position was inverted. The newly formed intermediate **135** was a 6-6-membered bicyclic system. The N_3^- then attacked the intermediate **135** from the new back side, which was the former front side, *via* another $\boldsymbol{S_N2}$ replacement, thus the configuration of the 3 position was inverted a second time so the configuration of the 3-azido was retained. And the 2-OH and 3-N_3 were *syn* to each other. One by-product of this mechanism is the compound **136**, which resulted from the opening of the six-membered intermediate **135** by N_3^- and loss of 2'- benzyl protection group. The MS of the by-product **136** should be 577, which was 90 less than that of the product **91** (MS=667). But a Mass spectrum of the crude reaction mixture did not show the existence of the by-product **136** suggesting that the by-product was negligible (**Scheme 2.46**).



Scheme 2.46: Pathway A: double S_N2 mechanism

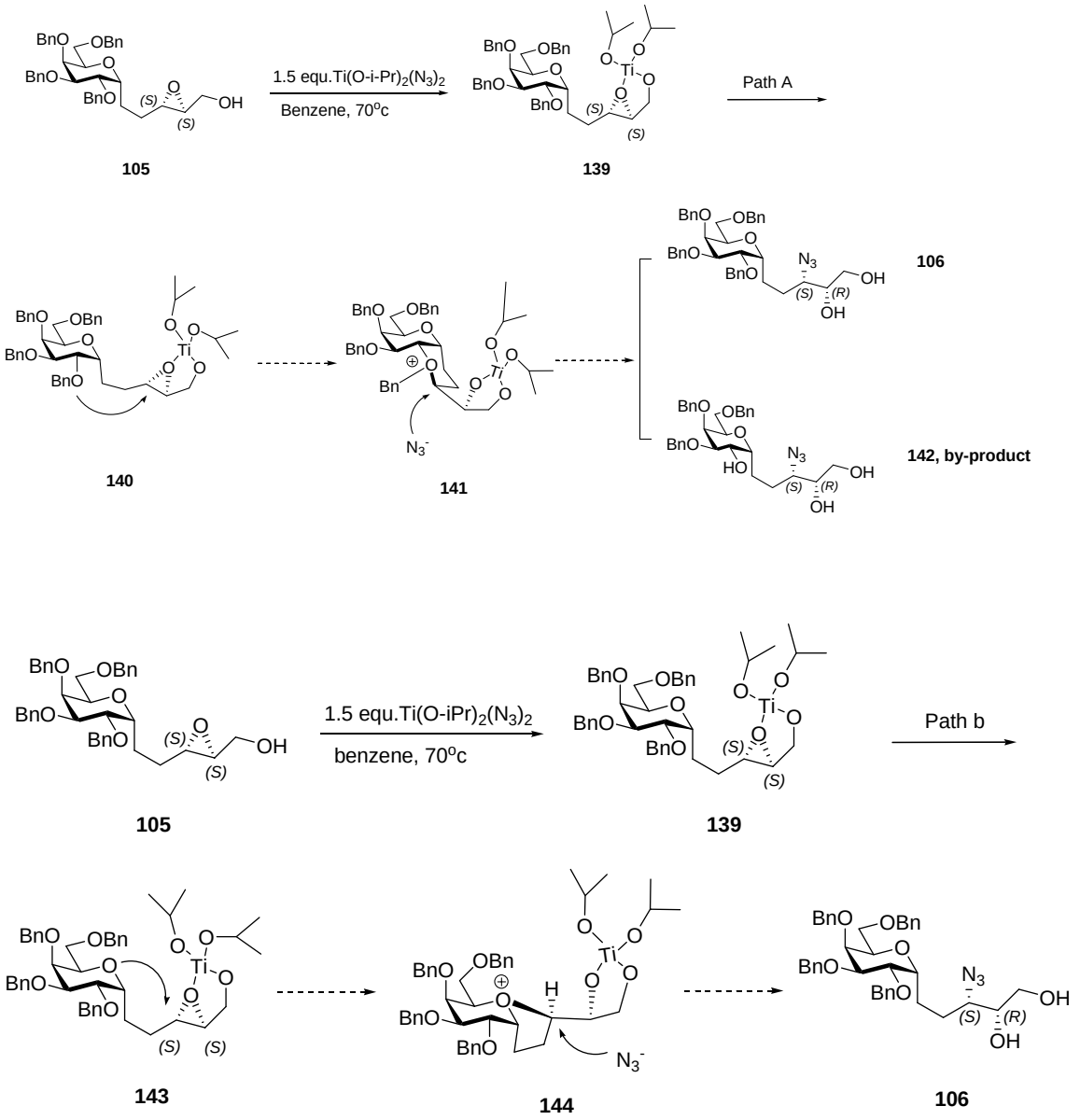
Another pathway, pathway b, takes place through a five-membered intermediate **138**. The nucleophilic attack of the oxygen of the pyranose from the backside of the oxirane *via* a S_N2 replacement would give a 6-5 bicyclic intermediate **138** and the 3 position of the formed intermediate should again have an inverted stereochemistry from the starting material. N_3^- opening of the five-membered intermediate *via* a second S_N2 reaction would afford the same product **91** with retained configuration at the N position (**Scheme 2.47**).



Scheme 2.47: Pathway B: double S_N2 mechanism

Thus, the stereochemistry relationship of the 3-azido-1, 2 diol **91** could be explained by the Lewis acid assisted neighboring group participated double S_N2 mechanism. At present time, we can not rule out either of the two pathways.

Although at present time we could not prove the stereochemistry of the 3-azido-1, 2 diol **106,** resulting from the opening of the (*2S, 3S*) epoxy alcohol **105** with Ti(O-*i*-Pr)$_2$(N$_3$)$_2$, we also assumed the stereo chemical relationship of the 3-*N* and 2-*O* were *anti* to each other in the same way. The retention of the 3-*N* configuration could take place *via* either pathway a or b (**Scheme 2.48**).



Scheme 2.48: Mechanism for the retention of configuration of the 3-*N* stereo center in the (*2S, 3S*) epoxide series

2.2.4.5: Summary of structure assignment

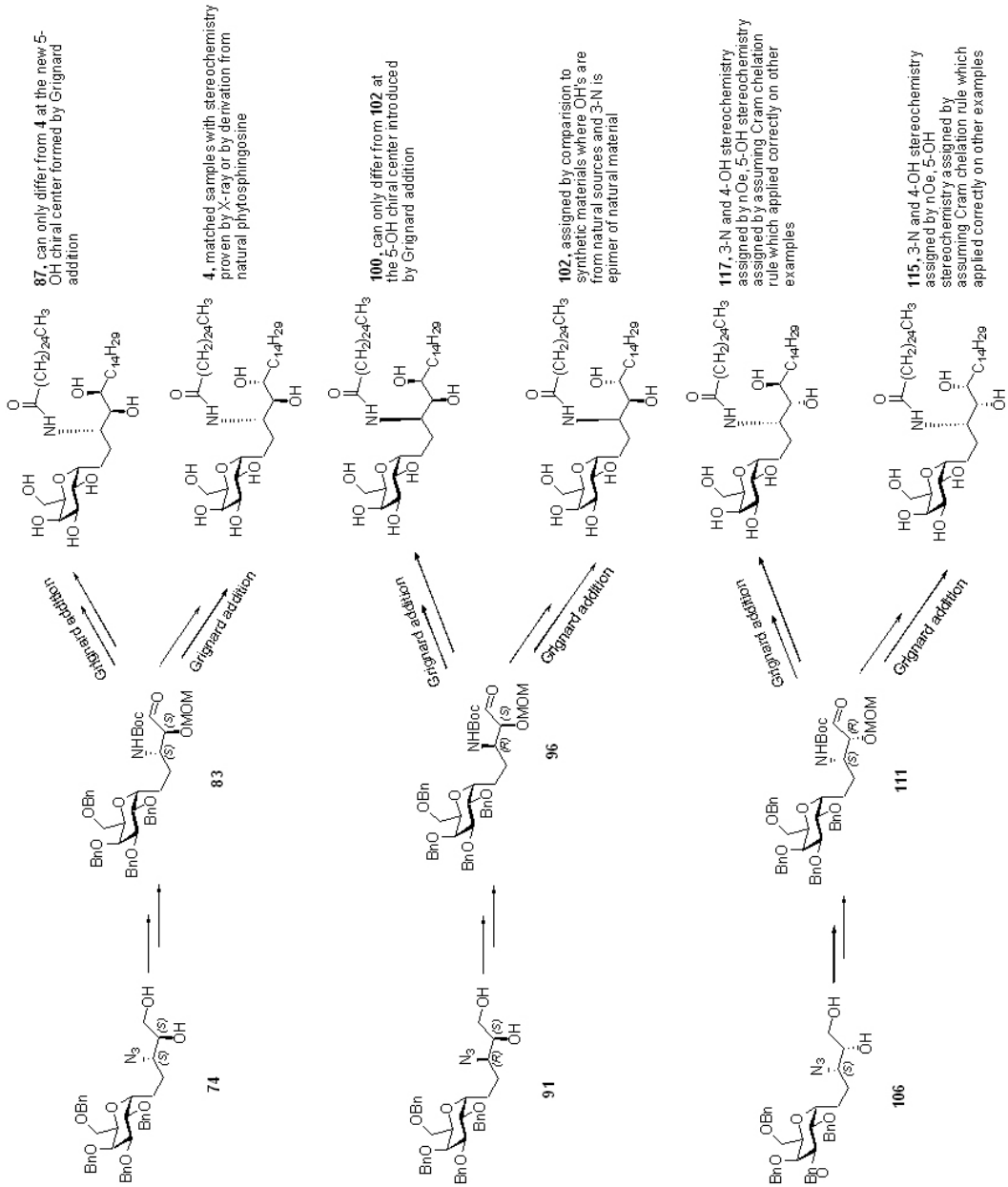
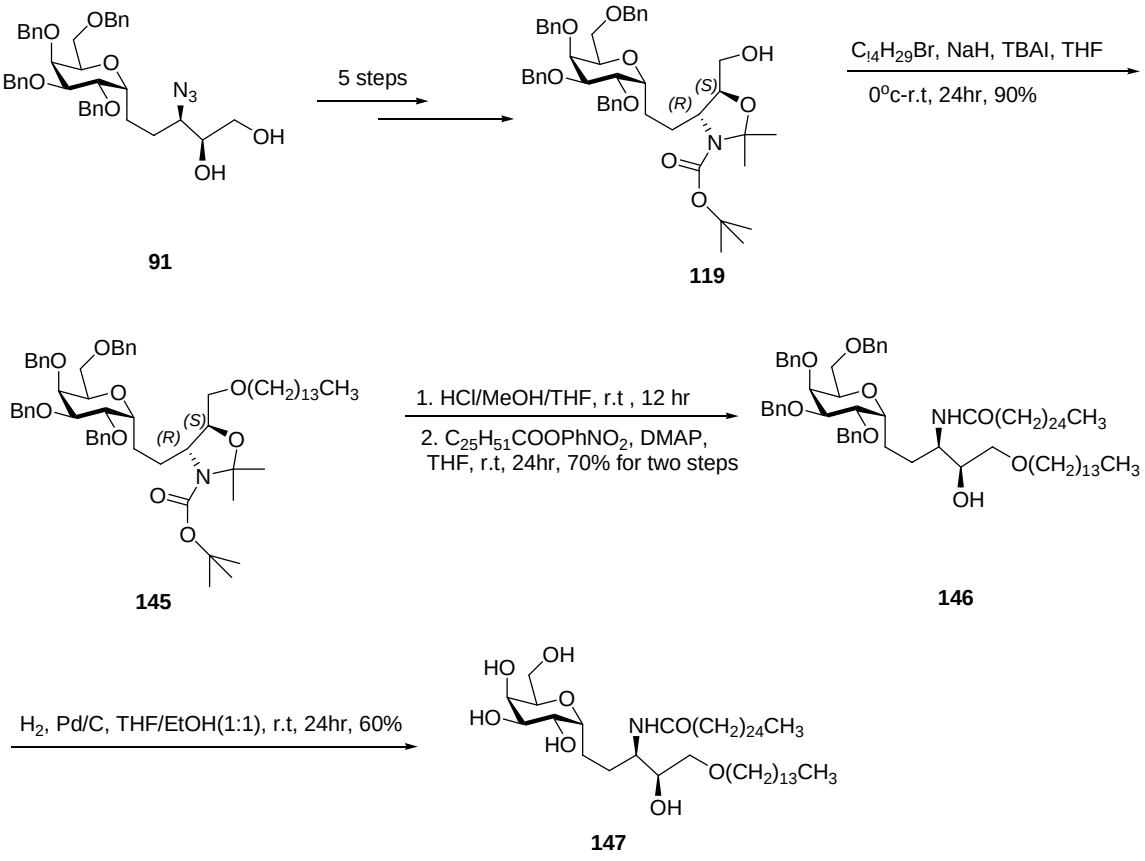


Figure 2.23: Summary of structures assignment

The structure assignments of compounds 4, 87, 100, 102, 115, and 117 were illustrated (**Figure 2.23**).

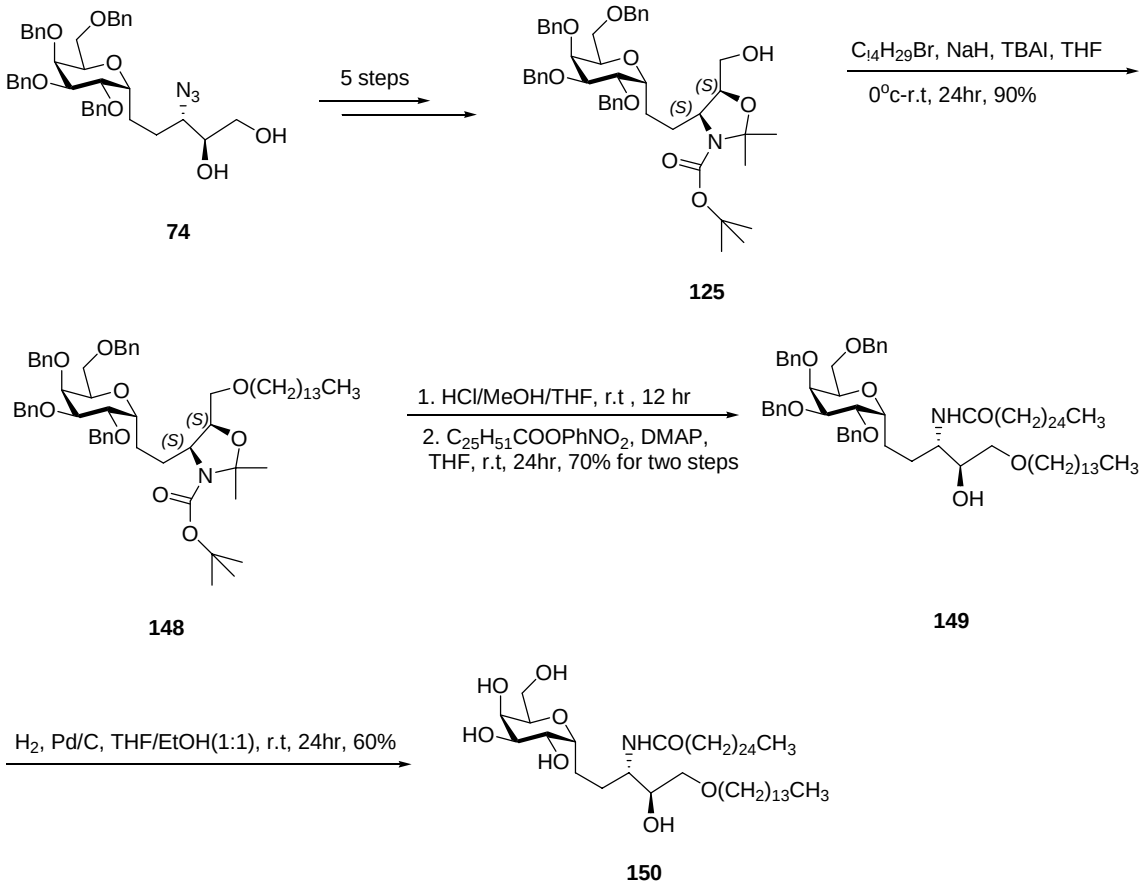
2.2.5: Synthesis of the *C*-glycoside derivatives

For the 1, 2 vicinal diol **91** derived from ring-opening of the (*2R, 3R*) epoxy alcohol **73** by $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$, five step manipulations converted it to a primary alcohol **119**. Classical Williamson ether formation between the primary alcohol and $C_{14}H_{29}Br$ gave an ether **145** in excellent yield. Because of the existence of two conformers of the amide, ^{13}C spectrum of that ether showed two sets of peaks. Acidic hydrolysis cleaved the acid sensitive *t*-Boc group and isopropylidene protection group in one step. Amide **146** was obtained by mixing the resulting free amine with the activated ester $C_{25}H_{51}COOPhNO_2$ in good yield. Hydrogenolysis removed all of the benzyl protection groups to afford the ether *C*-glycoside derivative **147** (**Scheme 2.49**).



Scheme 2.49: Synthesis of the ether *C*-glycoside derivative 147

Similarly, treatment of the *anti*-3-zido-1, 2 vicinal diol **74** derived from ring-opening of the (*2R, 3R*) epoxy alcohol **73** by NaN_3/NH_4Cl in the same reaction sequences afforded another ether *C*-glycoside **150** in good overall yield (**Scheme 2.50**).



Scheme 2.50: Synthesis of ether *C*-glycoside analogue 150

Those two ether *C*-glycoside derivatives **147** and **148** were *N* epimers to each other. One interesting aspect was that both of them were soluble in $CDCl_3$ while none of the other six synthesized *C*-glycoside analogues was soluble in $CDCl_3$, which were only soluble in pyridine-d_5. These phenomena gave us a hint that if we changed the structure of the side chain and introduced more oxygen atoms, we might change the solubility of the *C*-glycoside analogue of KRN7000.

2.3. Conclusions:

Since its first successful convergent synthesis in 2001, The *C*-glycoside analogue of KRN7000 has attracted interest from the immunology community. The *C*-glycoside analogue of KRN7000 is a powerful immunostimulant and shows better anti malaria and anti cancer activities than its *O*-glycoside counterpart, KRN7000.

Several novel synthetic methods have been tried simultaneously to get this important compound. The first isoxazoline approach utilized a 1, 3 dipolar Cycloaddition between the carbohydrate nitrile oxide and hexadecene to make a diastereomeric mixture of isoxazoline. However, the second key reaction, the stereoselective α-hydroxylation, failed due to the instability of the isoxazoline. The second method was based on Wittig-Sharpless asymmetric epoxidation reactions. This approach is a very powerful tool to construct optically active epoxides in high yield and high *ee*. A variety of *C*-glycoside analogues could be made by using the two different Sharpless chiral auxiliaries. Opening of those epoxides with NaN_3/NH_4Cl produced the desired 3-azido-1, 2 diol, whose stereo centers of the 3-azido and 2-hydroxy were *anti* to each other while usage of $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ afforded a *syn* product, which could be explained by an unusual Lewis acid assisted neighboring group participation double S_N2 replacement mechanism *via* two possible pathways. The *anti* 3-azido-1, 2 diol could be converted to the target *C*-glycoside analogue. While the *syn* 3-azido-1, 2 diol from the $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ opening of the epoxide was also converted to the 3-*N*-epimer of the target *C*-glycoside. The stereo relationship of the *N*-epimers was confirmed first by nOe correlation experiments and then by comparison of their NMR spectra with that of the *C*-glycoside analogue with truncated side chain, which was synthesized by a Japanese group (**Figure 2.24**).

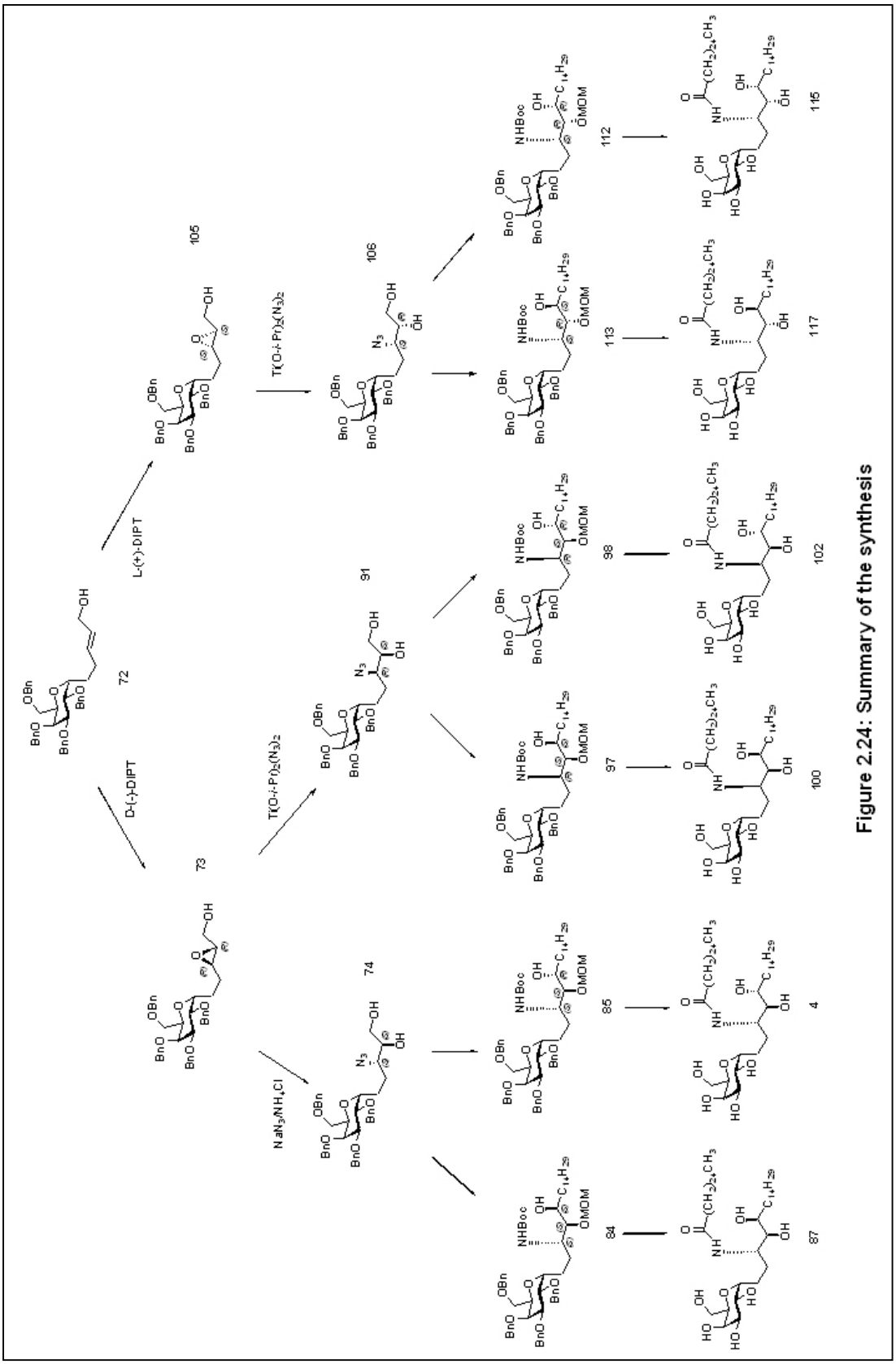


Figure 2.24: Summary of the synthesis

Although this stepwise linear Wittig-Sharpless asymmetric epoxidation approach is not very practical (20 steps), it made several *C*-glycoside analogues and provided the opportunity to change the structures such as the length of the phytosphingosine side chain, the stereo centers and so on. In this way, SAR experiment could be carried through and some analogues with better activities could be synthesized easily.

Chapter 3. Experimental Section

Instruments and Materials

NMR spectra were recorded with a QE 300MHz (^{1}H) and 75 MHz (^{13}C) with a TECMAG data system or Bruker 500 MHz (^{1}H) and 125 MHz (^{13}C) in deuterated solvents. The assignment of proton and carbon NMR peaks was supported by routine COSY and HSQC spectra and for some cases by NOESY spectra.

Melting points were determined on a Fisher-Johns apparatus and were uncorrected.

Optical rotations were measured at 25^{o}C on an Autopol III automatic polarimeter in a cell of 1 dm path length.

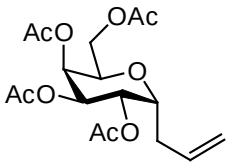
Electrospray ionization (ESI) mass spectra experiments were performed by Dr. Clifford E. Soll at the Hunter College Mass Spectrometry Facility on an Agilent Technologies 1100 LC/MSD. Typical ESI method: solvent: 1/1 acetonitrile/water + 0.1% HOAc + 50µl NH_4Ac, flow: 0.5 ml/min, positive ion mode, fragmentor voltage: 30-200V, drying gas at 175^{o}C.

All air –moisture sensitive reactions were performed under a positive pressure of dry N_2 gas. All solvents and reagents were purified prior to use according to standard laboratory procedures. Low temperatures were recorded as bath temperatures.

Thin layer chromatography analysis was carried out on precoarted aluminium sheets of silica gel 60 F 254. UV light and vanillin, phosphomolybdic acid spray or DNP spray were used to visualize the components on the TLC plates.

Flash column chromatography was carried out with silica gel 60 (230-400 mesh) purchased from ChemAbsorb, using ACS reagent grade petroleum ether, hexane, ethyl acetate, methylene chloride, chloroform, and methanol as eluants.

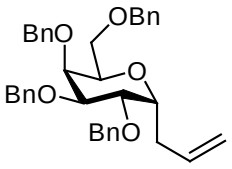
3-(2, 3, 4, 6-tetraacetate-α-D-galactopyranosyl) propene (45)[44-47]



β-D-Galactose pentaacetate **44** (1.026 g, 2.628 mmol) was dissolved in 50 ml of absolute acetonitrile, then allyltrimethylsilane (1.25ml, 7.885mmol) and $BF_3{\cdot}Et_2O$ (1.665ml, 13.14mmol) were added successively under an atmosphere of nitrogen at 0ºC. The reaction was completed after 2 days. The mixture was poured into a saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (3x50 ml), the organic solution dried with Na_2SO_4 and the solvent evaporated *in vacuo*. Finally, the product compound **45** (0.723g, 74%) was isolated as a mixture of α, β isomers as a yellow oil by flash-chromatography purification using 20% EtOAc/CH_2Cl_2 for elution. M/S: m/z 390 (M^++NH_4^+) (calcd: for $C_{17}H_{24}O_9$ 372). ^{1}H NMR (500MHz, $CDCl_3$): δ 5.78-5.70 (m, 1H, -CH=CH_2), 5.48-5.42 (m, 1H, H4), 5.30-5.25 (m, 1H, H2), 5.25-5.20 (m, 1H, H3), 5.15-5.10 (m, 2H, =CH_2), 4.30 (m, 1H, H1), 4.25 (m, 1H, H6), 4.05 (m, 2H, H6′, H5), 2.6-2.45 (m, 1H), 2.35-2.25 (m, 1H), 2.20 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), and 2.01 (s, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 170.4, 170.3 (β isomer), 170.2 (β isomer), 170.1 (β isomer), 170.0, 169.8, 169.7, 169.6 (β isomer) ($COCH_3$), 133.4, 133.3 (β isomer), 117.5 (CH_2=CH-), 117.3 (β isomer), 77.6, 77.4, 74.1, 72.2, 71.4, 69.2, 68.3, 68.3, 67.9, 67.8 (β isomer), 67.6, 61.6 (β isomer), 61.4, 35.9, 30.9, 20.7, 20.7, 20.6, 20.5 and 20.5.

3-(2, 3, 4, 6-tetra-*O*-benzyl-α-D-galactopyranosyl) propene (49)



To a solution of **45** (0.712 g, 1.912 mmol) in 15ml anhydrous MeOH was added NaOMe (52 mg, 0.956 mmol) under an atmosphere of nitrogen. After 1 hour, the mixture was neutralized with acidic resin to pH=7. The solution was filtered and the resin was washed with MeOH. The solution was concentrated *in vacuo*, yielding a viscous yellow oil crude product, which was used directly in the next step without further purification.

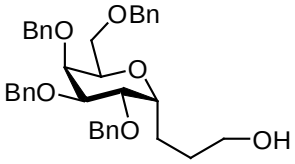
To a crude product in anhydrous DMF/THF (6 ml / 6 ml) at 0ºC under an atmosphere of nitrogen was added NaH (0.05g, 60% in mineral oil). After half an hour, TBAI (0.08g, 0.2 mmol) and BnBr (1.45ml, 12.13 mmol) were added. The reaction was stirred overnight at which point 10ml MeOH was added at 0ºC to quench the reaction. The mixture was washed with H_2O (20ml), extracted with CH_2Cl_2 (3x50 ml) and dried over Na_2SO_4. The solution was filtered and evaporated *in vacuo*. Purification by flash-chromatography using 20% Petroleum/CH_2Cl_2, then CH_2Cl_2 for elution afforded compound **49** (0.971 g, 90% for 2 steps).

^{1}H NMR (500MHz, $CDCl_3$): δ 7.40-7.15 (m, 20 H), 5.75 (m, 1H, CH=), 5.02 (m, 2H, CH_2=), 4.75-4.50 (m, 8H), 4.06-4.04 (br s, 1H), 4.02-3.98 (m, 2H), 3.84 (m, 1H), 3.75 (br s, 1H), 3.72 (dd, *J*=6.8, 2.7 Hz, 1H), 3.67 (dd, *J*=4.7, 10.6 Hz, 1H), 2.50-2.40 (m, 1H), and 2.40-2.30 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.8, 138.7, 138.7, 138.5, 135.4, 128.6, 128.5, 128.5, 128.5, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 116.9, 76.7, 74.5, 73.4, 73.3,

73.2, 72.8, 67.5, and 32.5 (note: Some of the carbon peaks overlapped with the $CDCl_3$ peaks.)

3-(2, 3, 4, 6-tetra- *O*-benzyl-α-D-galactopyranosyl) propanol (50)

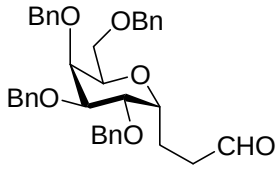


To a solution of compound **49** (0.21g, 0.373 mmol) in 5ml of anhydrous THF under an atmosphere of nitrogen at 0ºC was added $BH_3 \cdot Me_2S$ complex (10M/L in THF, 0.15ml, 1.486 mmol). The ice bath was removed and the solution was stirred for 4 hours at room temperature. The reaction mixture was then cooled back to 0ºC and a mixture of NaOH (15ml, 3M/L) and H_2O_2 (30%, 15ml) was added dropwise. The reaction mixture was stirred at 0ºC for 1 hour. The solution was then diluted with 30ml EtOAc, and the organic layer was washed successively with saturated NH_4Cl solution (1x20 ml), H_2O (2x25 ml), and brine (1x25 ml) and dried over Na_2SO_4. The crude product was concentrated *in vacuo* and purified by silica gel chromatography eluting with 50% EtOAc/Petroleum ether to yield 0.1828g compound **50** (85%) as a pale yellow syrup.

ESI M/S: m/z 600 (M^++NH_4^+) (calcd: for $C_{37}H_{42}O_6$, 582). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.40-7.20 (m, 20H, Ph), 4.76-4.45 (m, 8H, CH_2Ph), 4.10-3.95 (m, 3H), 3.80-3.75 (m, 2H), 3.73-3.65 (m, 1H), 3.60-3.55 (m, 3H), 2.10-1.95 (br, 1H, -OH), 1.80-1.70 (m, 1H), and 1.70-1.55 (m, 3H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.8, 138.7, 138.5, 138.4, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 77.3, 74.7, 73.5, 73.5, 73.4, 73.3, 72.4, 68.2, 62.5, and 29.9.

3-(2, 3, 4, 6-tetra-*O*-benzyl-α-D-galactopyranosyl) propanal (51)

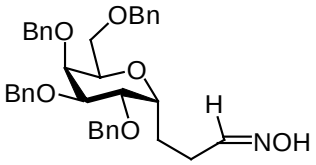


To a mixture of molecular sieve powder (4A, flame dried, 0.93g), celite (0.93g), florisil (0.93g) in 20 ml of anhydrous CH_2Cl_2 were added and PCC (0.253g, 1.172mmol) and NaOAc (0.096g, 1.172mmol). Compound **50** (0.31g, 0.533mmol) in 10ml CH_2Cl_2 was then added dropwise. The dark solution was stirred for half an hour under an atmosphere of N_2 at room temperature. The mixture was then filtered through a pad of florisil and washed with diethyl ether. The solution was collected and concentrated under reduced pressure and was purified by flash-chromatography using 50% EtOAc/petroleum ether for elution to afford 0.293 g product **51** (95% yield) as a yellow oil.

ESI M/S: m/z 598 (M^++NH_4^+) (*calcd*: for $C_{37}H_{40}O_6$, 580). ^{1}H NMR (500MHz, $CDCl_3$): δ 9.74 (s, 1H, CHO), 7.30 (m, 20H, Ph), 4.79-4.37 (m, 8H, CH_2Ph), 4.0-3.90 (m, 3H), 3.83-3.70 (m, 3H), 3.62-3.58 (dd, *J*=10.4, 4.4 Hz, 1H), 2.58-2.38 (m, 2H), 2.0-1.9 (m, 1H), and 1.7-1.5 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 202.3, 138.7, 138.6, 138.5, 138.4, 128.5, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.7, 127.7, 76.9, 74.5, 73.4, 73.3, 73.2, 72.3, 70.9, 67.8, 40.5 and 20.2.

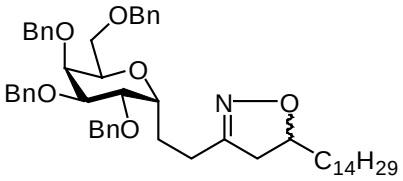
3-(2, 3, 4, 6-tetra-*O*-benzyl-α-D-galactopyranosyl) propanaloxime (52)



Propanal **51** (2.69g, 4.64mmol) was dissolved in a mixture of ether and H_2O (15ml/15ml). $NaHCO_3$ (1.364g, 16.24mmol) and $NH_2OH{\cdot}HCl$ (0.74g, 10.67mmol) were added successively. The mixture was stirred for 6 hours at r.t and was extracted with CH_2Cl_2 (2x50 ml), dried over Na_2SO_4 and concentrated *in vacuo* to afford 2.62g crude product **52**, which was used in the next step without further purification.

M/S: m/z 596 (M^++H^+) (*calcd.* for $C_{37}H_{41}NO_6$, 595). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.42 (t, 0.6H, NCH), 7.38-7.25 (m, 20H), 6.73 (t, 0.4H, NCH), 4.74-4.48 (m, 8H), 3.98-3.94 (m, 3H), 3.80-3.79 (m, 2H), 3.71 (br s, 1H), 3.65-3.64 (m, 1H), 2.57-2.12 (m, 2H, CH_2CH=NOH), 1.88-1.81 (m, 1H), and 1.72 (m, 1H).

Isoxazoline 54:



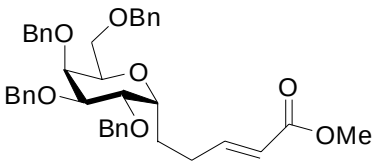
1:1 mixtures

To a solution of 3-(2, 3, 4, 6-tetra-*O*-benzyl-α-D-galactopyranosyl) propanaloxime **52** (0.1388g 0.233mmol) in a mixed solvent of 1ml dry $CHCl_3$ and anhydrous pyridine (5µl) was added freshly crystallized NCS under an atmosphere of N_2 at rt. The green solution was stirred for half an hour until the suspended NCS disappeared completely. The resulting solution was mixed with hexadecene (0.4ml, 1.638mmol) in 6 ml of dry $CHCl_3$ at room temperature. A solution of triethylamine (0.0387ml, 0.29mmol) in 10ml dry $CHCl_3$ was then added dropwise *via* syringe pump over 24 hours. Then the mixture was stirred for another 10 hours at room temperature. The solution was washed with H_2O (1x10 ml), extracted with CH_2Cl_2 (3x30 ml), dried over Na_2SO_4 (anhydrous)„ filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with hexane and 30% EtOAc/Hexane to afford 0.138g of the diastereomeric mixture of products **54** (71% yield) as a yellow oil.

ESI M/S: 835 (M^++NH_4^+) (*calcd*: for $C_{53}H_{71}NO_6$ 817.52). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.20 (m, 20H, Ph), 4.76-4.46 (m, 8H, CH_2Ph), 4.05-3.95 (bs, 3H), 3.81-3.76 (bs, 2H), 3.74-3.70 (m, 1H), 3.68-3.60 (m, 1H), 3.55-3.50 (m, 1H), 2.90-2.80 (m, 1H), 2.49-2.35 (m, 2H), 2.27-2.22 (m, 1H), 1.92-1.85 (m, 1H), 1.84-1.74 (m, 1H), 1.73-1.61 (m, 1H), 1.50-1.26 (m, 24H), 0.837-0.811 (*t*, *J*=12.8 Hz, 3H).

^{13}C-NMR (75MHz, $CDCl_3$): δ 158.7, 138.7, 138.7, 138.5, 138.4, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.1, 127.9, 127.8, 127.7, 127.7, 80.3, 74.5, 73.4, 73.4, 73.2, 72.4, 67.9, 42.8, 35.4, 35.4, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 25.8, 24.7, 22.8 and 14.3.

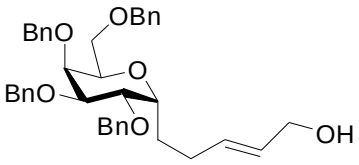
α, β unsaturated ester 71:



To a solution of the crude aldehyde **51** (1.303g, 2.25mmol) in 30ml anhydrous MeCN was added methyl(triphenylphosphoronylidene)acetate (1.50g, 4.5mmol) in one portion at room temperature under an atmosphere of N_2. The solution was stirred overnight at room temperature. The mixture was diluted with 50ml CH_2Cl_2, washed with H_2O (50ml), extracted with CH_2Cl_2 (3x50ml), dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 30 % EtOAc/PE provided 1.268 g α, β unsaturated ester **71** (89 % yield) as yellow oil. M/S: m/z 654 (M^++NH_4^+) (*calcd*: for $C_{40}H_{44}O_7$ 636). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.45-7.20 (m, 20H, Ph), 7.0-6.9 (d, t, *J*=15.6, 6.9Hz, 1H, CH=), 5.80 (d, *J*=15.5Hz, 1H, =CH), 4.76-4.78 (m, 8H, CH_2Ph), 4.05-3.90 (m, 4H), 3.85-3.75 (m, 5H), 3.70-3.65 (m, 1H), 2.40-2.30 (m, 1H), 2.25-2.10 (m, 1H), 1.90-1.80 (m, 1H), and 1.65-1.55 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 167.2, 149.1, 138.7, 138.6, 138.5, 138.4, 128.6, 128.6, 128.5, 128.57, 128.54, 128.49, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.97, 127.8, 127.7, 121.4, 77.43, 77.1, 76.8, 74.5, 73.4, 73.3, 73.2, 72.4, 67.8, 51.5, and 28.7.

Allylic alcohol 72:



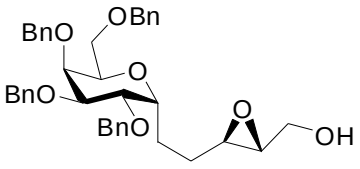
α, β unsaturated ester **71** (1.20g, 1.89mmol) was dissolved in 10 ml dry CH_2Cl_2 and was cooled to –78 °C under an atmosphere of N_2. DIBAL-H (1M/l in hexane, 5.7mmol, 5.7ml) was added dropwise over 10 minutes. After completion of addition, the dry-ice bath was removed and the reaction mixture was warmed up to room temperature and was stirred for 2 hours at rt. Then the solution was cooled to 0^{o}C and 5ml MeOH was added dropwise followed by addition of 30ml *satd.* Potassium sodium tartate solution. The solution was stirred vigorously until two clear phases appeared. The mixture was extracted with ethyl acetate (3x50ml). The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting first with 30% EtOAc/PE then 50% EtOAc/PE afforded 1.03 g allylic alcohol **72** (90 % yield) as a yellow oil.

M/S: m/z 626 (M^++NH_4^+) (*calcd*: for $C_{39}H_{44}O_6$ 608). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.20 (m, 20H, Ph), 5.71-5.65 (m, 2H, -CH=CH-), 4.75-4.52 (m, 8H, CH_2Ph), 4.05 (m, 2H, -CH_2OH), 3.99-3.90 (m, 3H), 3.85-3.75 (m, 2H), 3.73-3.67 (m, 1H),

3.65-3.3.0 (dd, *J*=10.3, 4.5 Hz,, 1H), 2.20 (m, 1H), 2.05-1.99 (m, 1H), 1.74-1.70 (m, 1H), and 1.60-1.50 (br, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.8, 138.7, 138.5, 138.51, 132.7, 129.6, 128.64, 128.61, 128.59, 128.54, 128.4, 128.2, 128.0, 127.9, 127.90, 127.8, 127.78, 127.77, 127.7, 127.6, 77.0, 76.9, 74.7, 73.5, 73.4, 73.4, 73.3, 73.1, 72.3, 68.0, 63.8 and 28.7.

(*2R, 3R*) epoxyl alcohol 73:



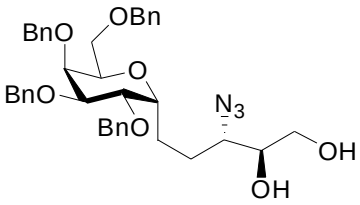
A flask containing 4g powdered 4A MS was heated with heating gun *in vacuo* for 1 hour and cooled under an atmosphere of N_2. Then the flask was filled with 10ml dry CH_2Cl_2 and was cooled to -20°C under an atmosphere of N_2. TTIP (1.35mmol, 0.4ml) and D- (-)-DET (1.62mmol, 0.28ml) were then added. The solution was stirred for 30 minutes at -20°C. TBHP (5mol/l in toluene, 2.7mmol, 0.54ml) was added dropwise over a period of 10 minutes. The solution was stirred for another 30 minutes at -20°C. Allylic alcohol **72** (0.82g, 1.35mmol, predried with 4A MS for 30minutes) in 5ml dry CH_2Cl_2 was added dropwise. The solution was stirred at -20°C for 18 hours (stored in freezer overnight) and was cooled to 0°C. Two ml H_2O was added and the mixture was stirred for 30 minutes at 0°C, then 2 ml 30% NaOH solution saturated by NaCl was added and the solution was stirred for another 30 minutes at 0°C. The mixture was filtered through a pad of celite and the celite was washed with CH_2Cl_2 (50ml). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3

x 30 ml). The organic phase was combined and washed with brine (20ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 50% EtOAc/PE to provide 0.50g epoxide **73** (70% yield) as pale yellow oil.

M/S: m/z 642 (M^++NH_4^+) (calcd: for $C_{39}H_{44}O_7$ 624). ^{1}H NMR (300MHz, C_6D_6): δ 7.0 (m, 20H, Ph), 4.45-4.10 (m, 8H, CH_2Ph), 3.95-3.85 (m, 2H), 3.83-3.80 (m, 1H), 3.80-3.75 (m, 1H, -CH_2OH), 3.70-3.60 (m, 1H, -CH_2OH), 3.50-3.45 (m, 1H), 3.35-3.3.14 (m, 3H), 2.70 (m, 1H), 2.55-2.45 (m, 1H), 1.80-1.46 (m, 3H), and 1.40-1.11 (m, 2H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.7, 138.5, 138.4, 138.2, 128.5, 128.4, 128.41, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.85, 127.79, 127.70, 76.9, 74.6, 73.69, 73.5, 73.4, 73.3, 73.2, 72.4, 68.0, 61.8, 58.5, 55.56, 28.2 and 23.4.

3-azido-1, 2 diol 74a:



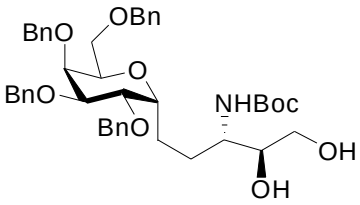
The (*2R, 3R*) epoxide **73** (23.75g, 0.038mol) was dissolved in a solution of 450ml MeOH/H_2O (8:1). NaN_3 (12.37g, 0.19mol) and NH_4Cl (4.48g, 0.084mol) were added in one portion. The solution was refluxed at 80^{o}C under an atmosphere of N_2 for 16 hours. The solution was cooled back to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with 200ml of ethyl acetate and was washed with H_2O (200ml). The aqueous layer was extracted with

ethyl acetate (3x150ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with increasing polarity solvent from 30%, 40% to 50% ethyl acetate/petroleum ether to afford a mixture of 1, 2 diol **74a** and 1, 3 diol **74b** (23.59g, 93% yield) as yellow oil.

M/S: m/z 685 (M^++NH_4^+) (*calcd*: for $C_{39}H_{45}N_3O_7$, 667). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.34-7.24 (m, 20H, Ph), 4.74-4.49 (m, 8H, CH_2Ph), 4.03-3.86 (m, 4H), 3.82-3.71 (m, 2H), 3.66-3.61 (m, 1H), 3.58-3.53 (m, 3H), 3.52-3.48 (m, 1H), 2.71 (br s, 1H, -OH), 1.96 (br s, 1H, -OH), 1.85-1.78 (m, 1H), 1.74-1.68 (m, 2H) and 1.51-1.42 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.5, 138.4, 138.2, 138.1, 128.48, 128.46, 128.39, 128.36, 128.1, 128.09, 128.01, 128.0, 127.9, 127.8, 127.7, 127.67, 127.63, 127.6, 74.4, 73.8, 73.3, 73.25, 73.20, 72.4, 67.7, 64.4, 63.2 and 27.1.

1, 2 diol 75a:



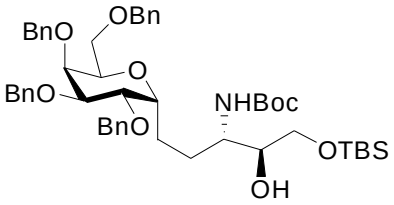
The mixture of 1, 2 diol **74a** and 1, 3 diol **74b** (24.56g, 0.037mol) was dissolved in 200ml of anhydrous THF. A solution of $P(Me)_3$ (220ml, 0.221mol, 1mol/l in THF) was added dropwise at 0^{o}C under an atmosphere of N_2 over a period of 30 minutes. The solution was then stirred at room temperature overnight. A solution of NaOH (200ml, 0.4mol, 2mol/L) was added and the solution was stirred for two hours. The mixture was extracted with ethyl acetate (3x 200ml). The combined organic layers

were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude amine was redissolved in a solution of THF/1, 4 dioxane (200ml,1:1). A *satd*. Solution of $NaHCO_3$ was then added followed by addition of $(t\text{-Boc})_2O$ solution (11.1ml, 0.0481mol). The solution was stirred for 24 hours at room temperature. The mixture was concentrated to a total volume of 50ml under reduced pressure. The solution was extracted with ethyl acetate (3x 200ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with increasing polarity solvent from 30%, 40% and 50% ethyl acetate/petroleum ether to afford a mixture of 1, 2 diol **75a** and 1, 3 diol **75b** (21.25g, 78% yield) as yellow oil.

M/S: m/z 759 (M^++NH_4^+) (*calcd*: for $C_{44}H_{55}NO_9$, 741). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.32-7.25 (m, 20H, Ph), 4.921 (d, *J*=8.4 Hz, 1H, NH), 4.71-4.44 (m, 8H, CH_2Ph), 4.05 (bs, 1H), 3.97-3.93 (m, 3H), 3.74-3.73 (br s, 1H), 3.69 (br s, 1H), 3.59 (dd, *J*=10.4 Hz, 3.52 Hz, 1H), 3.54-3.42 (m, 3H), 3.21-3.19 (br s, 1H), 3.12 (br s, 1H), 2.66 (broad peak, OH), 2.41 (broad peak, OH), 1.87-1.86 (m, 1H), 1.71-1.69 (m, 1H), 1.58-1.55 (m, 1H), 1.43 (s, 9H, $(CH_3)_3$), and 1.36-1.28 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.5, 138.7, 138.5, 138.43, 128.41, 128.58, 128.55, 128.50, 128.48, 128.3, 128.2, 128.1, 128.05, 128.01, 127.9, 127.8, 127.7, 127.75, 127.72, 80.1, 76.5, 74.6, 74.5, 73.4, 73.3, 73.2, 73.17, 72.4, 67.5, 63.1, 53.9 (NHCO), 53.1 (NHCO), 29.1, 28.5, 27.0, 24.6, and 20.9.

TBS ether 76a:

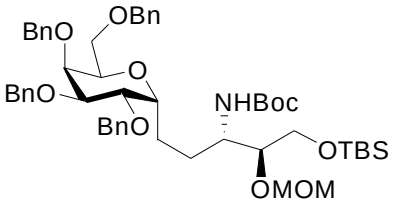


The mixture of compounds **75a** and **75b** (11.82g, 0.01595mol) was dissolved in 200ml of anhydrous CH_2Cl_2 at room temperature under an atmosphere of N_2. Imidazole (3.26g, 0.048mol) and TBSCl (3.2 g, 0.0207mol) were added in one portion. The solution was stirred for 1hourat room temperature. The mixture was washed with 200ml *satd*. NH_4Cl solution and was extracted with CH_2Cl_2 (3x150ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with 10%, 15%, 20%ethyl acetate/petroleum ether to get the first fraction **76b** (1.3g, 10% yield) and 25% ethyl acetate/petroleum ether to get the second fraction **76a** (10.6221g, 78% yield), which is the desired product as an oil.

M/S: m/z 873(M^++NH_4^+) (*calcd* for: $C_{50}H_{69}NO_9Si$, 855). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.20 (m, 20H, Ph)), 4.99-4.97 (d, *J*=8.9 Hz, 1H, NH), 4.67-4.44 (m, 8H, CH_2), 4.02-3.95 (bs, 1H), 3.92-3.91 (m, 1H), 3.87-3.86 (m, 1H), 3.81-3.77 (m, 1H), 3.72 (bs, 1H), 3.68-3.66 (m,1H), 3.61-3.53 (m, 4H), 3.49-3.39 (m, 1H), 1.74-1.64 (m, 4H), 1.38 (s, 9H, $(CH_3)_3$), 0.89-0.70 (s, 9H, CH_3), 0.02 (s, 6H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.4, 138.8, 138.7, 138.6, 138.5, 128.6, 128.5, 128.50, 128.45, 128.40, 128.2, 128.1, 128.08, 128.01, 127.9, 127.8, 127.757, 127.71, 127.69, 79.3, 77.1, 74.7, 73.4, 73.37, 73.3, 72.3, 67.9, 64.7, 53.9, 28.6, 27.9, 26.1, 18.4, -5.27 and -5.31.

MOM ether 78:

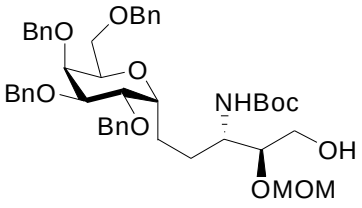


The TBS ether **76a** (5.81g, 6.795mmol) was dissolved in 50ml of anhydrous CH_2Cl_2. Freshly distilled DIPEA (11.84ml, 67.95mmol) was added at 0^oC under an atmosphere of N_2. MOMCl (2.1ml, 27.2mmol) was then added dropwise over a period of 5 minutes. The solution was stirred at room temperature for 18 hours. The solution was washed with 100ml *satd*. NH_4Cl solution and was extracted with CH_2Cl_2 (3x100ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with 10%, 20% ethyl acetate/petroleum ether to get the fully protected compound **78** (5.79g, 95%) as yellow oil.

M/S: 917 m/z (M^++NH_4^+) (*calcd*: for $C_{52}H_{73}NO_{10}Si$, 899). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.31-7.26 (m, 20H, Ph), 5.52-5.23 (d, *J*=8.5 Hz, 1H, NH), 4.69-4.47 (m, 10H, CH_2Ph and OCH_2O), 3.97 (br s, 2H), 3.89 (br s, 1H), 3.77-3.76 (m, 3H), 3.73-3.70 (m, 2H), 3.67-3.64 (m, 2H), 3.57-3.56 (m, 1H), 3.35 (s, 3H, OCH_3), 1.68 (bs, 3H), 1.53 (s, 1H), 1.42 (s, 9H, $(CH_3)_3$), 0.89 (s, 9H, CH_3), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.0, 138.7, 138.6, 138.5, 138.4, 128.3, 128.2, 128.1, 128.0, 128.04, 128.00, 127.9, 127.7, 127.6, 127.5, 127.5, 127.2, 96.5, 79.4, 78.8, 77.4, 77.1, 74.8, 73.6, 73.4, 73.3, 73.2, 72.20, 68.0, 64.2, 55.8, 52.2, 28.7, 27.9, 18.4 and -5.9.

Primary alcohol 79:

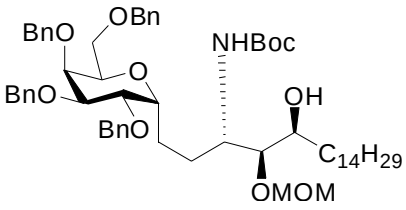


The fully protected compound **78** (4.63g, 5.16mmol) was dissolved in 30ml of anhydrous THF and the solution was cooled to 0°C under an atmosphere of N_2. A solution of TBAF (10.3ml, 10.3mmol, 1N in THF) was added. The mixture was stirred for 2.5 hours at room temperature. The solution was washed with 100ml *satd.* NH_4Cl solution and was extracted with ethyl acetate (3x100ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with ethyl acetate/petroleum ether (increasing polarity from 20% to 60% gradually) to get the primary alcohol **79** (4.0g, 100%) as a white solid.

M/S: 803 m/z (M^++NH_4^+) (*calcd*: for $C_{46}H_{59}NO_{10}$, 785). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.26 (m, 20H, Ph), 4.88 (d, *J*=8.9 Hz, 1H, NH), 4.71-4.47 (m, 10H, CH_2Ph and OCH_2O), 4.02 (br s, 1H), 3.96 (br s, 1H), 3.95-3.3.85 (m 2H), 3.72 (br s, 2H), 3.69-3.62 (m, 1H), 3.61-3.54 (m, 2H), 3.54-3.48 (m, 1H), 3.36 (s, 3H, OCH_3), 3.35 (broad peak, 1H), 3.28 (m, 1H), 1.78 (br s, 1H), 1.71-1.69 (br s, 1H), 1.61-1.55 (br s, 1H), 1.43 (s, 9H, $(CH_3)_3$), 1.29-1.26 (br s, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.6, 138.8, 138.7, 138.5, 128.6, 128.5, 128.5, 128.4, 128.38, 128.3, 128.2, 128.1, 127.9, 127.8, 127.79, 127.78, 127.75, 96.9, 82.7, 79.7, 77.4, 77.1, 76.7, 74.7, 73.3, 73.28, 72.24, 67.8, 62.3, 55.9, 51.6, 28.6 and 26.9.

The major isomer 84:

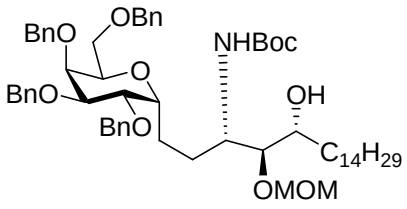


The primary alcohol **82** (0.6g, 0.77mmol) was dissolved in 10ml of anhydrous CH_2Cl_2 solution. Dess-Martin reagent (0.424g, 1mmol) was added in one portion at room temperature under an atmosphere of N_2. The solution was stirred for 45minutes at room temperature and was diluted with 20ml of CH_2Cl_2. A *satd.* solution of $NaHCO_3$ (10ml) and 10ml satd. $Na_2S_2O_3$ solution were added. The mixture was stirred until two clear phases appeared. The solution was extracted with CH_2Cl_2 (3x60ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude product was coevaporated with anhydrous toluene three times and was then put under high vacuum to afford 0.55g of the crude aldehyde. The aldehyde was dissolved in 5ml of anhydrous THF and the solution was added dropwise to a solution of freshly prepared $C_{14}H_{29}MgBr$ (2.31mmol) in 5ml anhydrous THF at 0^oC under an atmosphere of N_2 over a period of 10 minutes. The solution was not clear at 0^oC. The mixture was stirred at 0^oC for 30minutes. The solution was then warmed up to room temperature and the white solid disappeared. The solution was stirred for two hours at room temperature. A *satd*. solution of NH_4Cl (20ml) was added and the mixture was stirred for 10 minutes. The mixture was extracted with ethyl ether (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with ethyl acetate/petroleum ether (polarity increased

from 5% to 20%) to get the major isomer **84** (0.36g, 48%) as the first fraction and the minor isomer **85** (72mg, 10% yield) as the second fraction.

The major isomer **84**: M/S: 999 m/z (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981)**.** ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.29 (m, 20H, Ph), 5.26 (d, *J*=9.1Hz, 1H, NH), 4.76-4.48 (m, 10H, CH_2Ph and OCH_2O), 3.99 (bs, 2H), 3.96 (m, 1H), 3.86-3.74 (m, 4H), 3.65-3.63 (m, 2H), 3.41 (s, 3H, OCH_3), 3.31 (m, 1H), 2.76 (d, *J*=5.2 Hz, 1H), 1.71-1.66 (m, 4H), 1.57-1.54 (m, 2H), 1.45 (s, 9H, $(CH_3)_3$), 1.33-1.19 (br s, 24H, CH_2), 0.91 (t, *J*=6.9 Hz, 3H, CH_3). ^{13}C-NMR (125MHz, $CDCl_3$): δ 156.4, 138.8, 138.7, 138.6, 128.5, 128.5, 128.4, 128.3, 128.13, 128.11, 128.0, 127.9, 127.88, 127.79, 127.75, 127.72, 97.9, 83.9, 79.3, 77.4, 77.3, 76.8, 76.8, 74.8, 73.5, 73.5, 73.3, 72.2, 67.9, 56.3, 52.1, 34.0, 32.1, 29.95, 29.91, 29.8, 29.6, 28.6, 27.4, 25.8, 22.9 and 14.3.

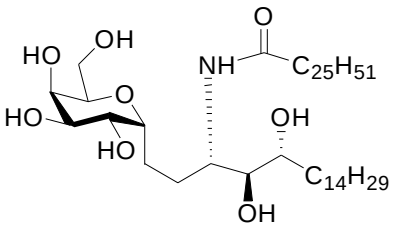
The minor diastereomer 85:



M/S: 999 m/z (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981)**.** ^{1}H NMR (500MHz, $CDCl_3$): δ 7.37-7.29 (m, 20H, Ph), 4.89 (d, *J*=9.4 Hz, 1H, NH), 4.75-4.48 (m, 10H, CH_2Ph and OCH_2O), 3.99-3.96 (m, 3H), 3.84-3.77 (m, 3H), 3.75 (d, *J*=5.2 Hz, 1H), 3.61-3.59 (m, 1H), 3.56 (dd, *J*=10.6, 3.8Hz, 1H), 3.39 (s, 3H, OCH_3), 3. 34 (t, *J*=5.0 Hz, 1H), 2.73 (d, *J*=6.1 Hz, 1H), 1.91 (m, 1H), 1.71 (m, 2H), 1.62 -1.59 (m, 2H), 1.53 (m, 1H), 1.45 (s, 9H, $(CH_3)_3$), 1.38-1.27 (m, 24H, CH_2), 0.91 (t, *J*=6.6 Hz, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 155.9, 138.9, 138.7, 138.6, 138.5, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.09, 128.00, 127.9, 127.8, 127.7, 98.6, 87.5, 79.3, 77.1, 76.9, 76.5, 74.9, 73.6, 73.4, 73.3, 71.8, 68.4, 56.2, 51.8, 33.0, 32.1, 29.9, 29.8, 29.6, 28.7, 27.1, 26.4, 22.9 and 14.3.

(3'S, 4'S, 5'R)-3'-*N*-hexacosanoyl-4', 5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside: the target compound 4:



The minor isomer **85** (0.045g, 0.046mmol) was dissolved in a solution of MeOH/1, 4 dioxane (2ml, 1:1). A solution of HCl (2ml, 12mmol, 6mol/l in MeOH) was added and the solution was stirred at room temperature overnight. The solution was concentrated to dryness *in vacuo*. The mixture was then redissolved in a solution of 5 ml THF. The solution was neutralized with 5 ml *satd*. NH_3 solution. The mixture was extracted with $CHCl_3$ (3x20ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude compound was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.04g of free amine as yellow oil.

The amine was redissolved in 2ml anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.055g, 0.091mmol) and DMAP (3mg) were added at room temperature under an atmosphere of N_2. The mixture was stirred at room temperature overnight. 0.5g of celite 545 was added and the solvent was removed *in vacuo* to get f

powder which could flow freely. Flash chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the unreacted ester and 20%, 30% ethyl acetate/petroleum ether to afford the amide **88** (0.04g, 72% yield).

The amide **88** (0.04g, 0.033mmol) was dissolved in 6 ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.10g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite, which was washed with 50ml of 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed *in vacuo* and the solid was redissolved in 1ml of pyridine. 0.5g of celite 545 was added and the solvent was removed *in vacuo* until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the minor *C*-glycoside **4** (0.016g, 30% yield for three steps) as a white solid.

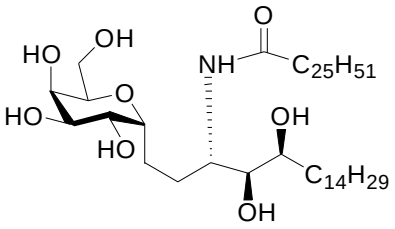
^{1}H NMR (500MHz, C_5D_5N): δ 8.49 (d, *J*=8.9 Hz, 1H, NH), 4.73 (dd, *J*=8.8, 5.5 Hz, 1H), 4.52 (m, 3H), 4.37 (dd, *J*=11.2, 4.5 Hz, 1H), 4.25 (m, 4H), 3.97 (s, 1H, impurity), 2.72 (m, 1H), 2.55 (m, 1H), 2.48 (m, 3H), 2.33 (m, 2H), 2.20 (m, 1H), 2.05 (m, 5H, impurity), 1.96 (m, 2H), 1.86 (m, 3H), 1.69 (m, 1H), 1.57 (m, 5H), 1.31 (m, 56H), 1.03 (m, 3H), 0.89 (t, *J*=6.9 Hz, 6H, CH_3).

Literature reported data[35]: ^{1}H NMR (500MHz, C_5D_5N): δ 8.43 (d, 1 H, *J*=9.0 Hz), 6.65 (d, 1H, *J*=4.7 Hz), 6.49 (d, 1H, *J*=4.7 Hz), 6.37 (m, 2H), 6.16 (d, 1 H, *J*=4.4 Hz), 5.98 (d, 1 H, *J*= 4.7 Hz), 5.12 (m, 1H), 4.72 (m, 1 H, *J*=9.3 Hz), 4.52 (m, 3H), 4.36 (m, 1H), 4.22 (m, 4H), 2.72 (m, 1H), 2.58 (m, 1H), 2.45 (m, 2H), 2.32 (m, 2H), 2.22 (m, 1H), 1.93 (m, 2H), 1.85 (m, 2H), 1.70 (m, 1H), 1.48-1.17 (m, 68 H), 0.89 (t, 6 H, *J*= 6.8 Hz).

^{13}C-NMR (125MHz, C_5D_5N): δ 173.91, 78.93, 77.46, 74.30, 73.19, 72.69, 71.06, 70.92, 63.24, 53.22, 37.29, 34.76, 32.41, 30.67, 30.48, 30.33, 30.29, 30.22, 30.19, 30.18, 30.11, 29.90, 29.89, 26.84, 26.70, 23.22, 23.02 and 14.56.

Literature reported data[35]: ^{13}C-NMR (125MHz, C_5D_5N): δ 173.85, 78.9, 77.4, 74.1, 73.1, 72.6, 71.0, 70.8, 63.1, 53.1, 37.4, 34.8, 32.5, 30.8, 30.6, 30.4, 30.4, 30.3, 30.3, 30.3, 30.2, 30.0, 30.0, 27.0, 26.9, 23.3, 14.6.

(3'S, 4'S, 5'S)-3'-*N*-hexacosanoyl-4', 5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside-the major *C*-glycoside 87:



The major isomer **84** (0.23g, 0.23mmol) was dissolved in 4 ml solution of MeOH/1,4 dioxane (1:1). A solution of HCl (4ml, 24mmol, 6mol/l in MeOH) was added and the solution was stirred at room temperature overnight. The solution was concentrated to dryness *in vacuo*. The mixture was then redissolved in 5 ml THF. The solution was neutralized with 5 ml *satd*. NH_3 solution. The mixture was extracted with $CHCl_3$ (3x20 ml). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude compound was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.20g of the free amine as yellow oil.

The amine was redissolved in 2ml of anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.223g, 0.43mmol) and DMAP (20mg) were added at room

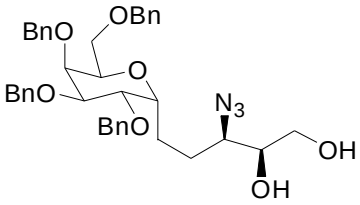
temperature under an atmosphere of N_2. The mixture was stirred at room temperature overnight. 1.0g of celite 545 was added and the solvent was removed under reduced pressure to get freely flowed powder. Flsh chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the excess ester and 20%, 30% ethyl acetate/petroleum ether to afford the amide **86** (0.23g, 80% yield).

The amide **86** (0.23g, 0.19mmol) was dissolved in 6 ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.30g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite and was washed with 50ml of 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed and the solid was redissolved in 1ml of pyridine and 1.0g of celite was added and the solvent was removed under reduced pressure until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the major *C*-glycoside (0.10g, 61% yield) as white solid.

^{1}H NMR (500MHz, C_5D_5N): δ 6.80 (broad peak, OH), 6.51 (broad peak, OH), 6.33 (broad peak, OH), 6.09 (broad peak, OH), 5.72 (broad peak, OH), 4.77-4.73 (m, 2H), 4.66 (s, 1H), 4.53 (s, 2H), 4.48 (s, 1H), 4.31-4.29 (m, 2H), 4.20 (s, 1H), 3.79 (s, 1H), 2.89 (br s, 1H), 2.63 (bs, 1H), 2.48 (t, *J*=7.2 Hz, 2H), 2.31-2.24 (m, 3H), 2.22-2.14 (m, 1H), 2.09-1.97 (m, 1H), 1.91-1.73 (m, 7H), 1.71-1.59 (m, 2H), 1.39-1.26 (m, 58H), 0.92-0.87 (m, 6H).

^{13}C-NMR (125MHz, C_5D_5N): δ 175.5, 77.3, 74.3, 72.6, 71.4, 70.7, 62.7, 53.4, 37.1, 34.56, 32.4, 37.1, 34.6, 32.4, 30.6, 30.5, 30.3, 30.2, 30.1, 30.1, 29.9, 29.9, 29.1, 27.2, 26.8, 23.3, 23.1 and 14.6.

***Syn*-3-azido-1, 2 diol 91:**

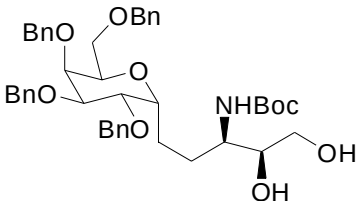


TTIP (0.725mmol, 0.22ml) and azido trimethylsilane (1.5mmol, 0.2ml) were added to 10ml anhydrous benzene and the solution was refluxed at 80°C under an atmosphere of N_2 for at least 5 hours. Epoxide **73** (0.30g, 0.483mmol) was dissolved in 10ml anhydrous benzene and was added to the solution in one portion. The mixture was stirred for 15-30 minutes at 80°C and then was cooled to rt. The solvent was removed under reduced pressure. 20 ml diethyl ether was then added followed by addition of 10 ml of 5% H_2SO_4 (V/V). The solution was stirred at rt. until two clear phases appeared. The mixture was extracted with CH_2Cl_2 (3x30 ml). The organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography purification eluting with 50% EtOAc/petroleum ether afforded 3-azido-1, 2 diol **91** (0.205g, 64% yield) as a yellow oil.

M/S: m/z 685.3 (M^++NH_4^+) (calcd: for $C_{39}H_{45}N_3O_7$ 667). IR (KBr): 3435.98, 2873.99, 2100.89, 763.72 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.30 (m, 20H), 4.8-4.4 (m, 8H), 4.01-3.83 (m, 4H), 3.77-3.69 (m, 2H), 3.60-3.45 (m, 4H), 3.42-3.34 (m, 1H), 2.5-2.4 (br, OH), 2.25-2.15 (br, OH), 1.90-1.75 (m, 1H), and 1.74-1.50 (m, 3H).

^{13}C-NMR(75MHz, $CDCl_3$): δ 138.669, 138.566, 138.462, 138.346, 128.496, 128.419, 128.302, 128.134, 128.004, 127.940, 127.771, 127.720, 127.668, 77.411, 76.984, 74.706, 74.046, 73.774, 73.502, 73.451, 73.386, 72.480, 70.474, 68.067, 64.028, 63.459, 26.922, and 23.880.

1, 2 diol 92 (C13)



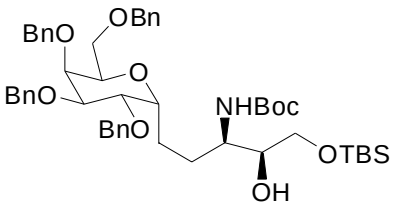
To a stirred solution of 3-azido-1, 2 diol **91** (14.0g, 0.021 mol) in 200 ml anhydrous THF was added 100ml $P(Me)_3$ (0.1 mol, 1M in THF) over a period of 15 minutes at 0^oC. The mixture was kept at 0^oC for 1 hour and then was warmed up to rt. The solution was stirred overnight under an atmosphere of N_2. A solution of 200 ml NaOH solution (0.2 mol, 1mol/l) was added at 0^oC and the mixture was stirred for 2hours. The mixture was extracted with EtOAc (3x300ml). The organic layers were combined and dried over Na_2SO_4 (anhydrous). The solution was filtered and concentrated *in vacuuo*. Then the viscous oil was dried under high vacuum for 1 hour. The material was redissolved in a mixed solution of THF and H_2O (150ml/50 ml). 9g solid $NaHCO_3$ (0.165 mol) was added in one portion followed by 6ml of $(t\text{-Boc})_2O$ (0.0256mol) solution. The mixture was stirred at rt for 24 hours. The solution was then concentrated to a total volume of 50 ml under reduced pressure. The mixture was extracted with EtOAc (3x300ml). The organic layers were combined and dried over Na_2SO_4 (anhydrous). The solution was filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with 40%, 50%, 60%, 70% ethyl acetate/petroleum ether to afford 13.8g compound **92** (91% yield for two steps) as viscous oil.

M/S: m/z 742.3 (M^++H^+) (*calcd*: for $C_{44}H_{55}NO_9$, 741.39). ^1H NMR (500MHz, $CDCl_3$): δ 7.35-7.22 (m, 20H, Ph), 4.75-4.50 (m, 8H, CH_2Ph), 4.05-3.98 (br, 1H), 3.98-3.95

(br, 2H), 3.93-3.88 (m, 1H), 3.76-3.72 (m, 2H), 3.69-3.63 (m, 1H), 3.62-3.56 (m, 2H), 3.55-3.48 (m, 1H), 3.44-3.39 (m, 1H), 3.10-3.00 (br, 1H, -OH), 2.18-2.10 (br, 1H, -OH), 1.80-1.72 (m, 1H), 1.69-1.62 (m, 1H), 1.62-1.52 (m, 1H), 1.52-1.47 (m, 1H), and 1.46-1.42 (s, 9H, $(CH_3)_3$).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.5, 138.8, 138.6, 138.5, 138.4, 128.62, 128.60, 128.5, 128.3, 128.1, 128.10, 128.0, 127.9, 127.8, 127.7, 80.1, 77.2, 76.8, 74.7, 74.6, 73.5, 73.4, 73.4, 73.3, 72.5, 68.1, 63.6, 51.6, 28.6, and 24.1.

TBS ether 93:



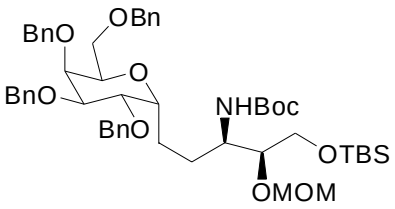
To a solution of compound **92** (7.47g, 0.0100mol) in 100 ml anhydrous CH_2Cl_2 was added imidazole (1.72g, 0.0253mol) followed by TBSCl (1.98g, 0.0131mol) at rt under an atmosphere of N_2. The mixture was stirred for 1 hour. A solution of 100 ml of satd. NH_4Cl was added and the solution was extracted with CH_2Cl_2 (3 x 100 ml). The organic layer was combined and dried over Na_2SO_4 (anhydrous). The solution was filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 10% ethyl acetate/petroleum ether (500 ml) followed by 20% ethyl acetate/petroleum ether to afford compound **93** (8.62g, 99% yield) as yellow oil.

M/S: m/z 873.3 (M^++NH_4^+) (*calcd*: for $C_{50}H_{69}NO_9Si$, 855.47). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.22 (m, 20H, Ph), 4.75-4.50 (m, 8H, CH_2Ph), 4.05-3.95 (m, 3H),

3.85-3.80 (m, 1H), 3.78-3.73 (m, 1H), 3.73-3.70 (m, 1H), 3.65-3.60 (m, 3H), 3.55-3.50 (m, 1H), 3.48-3.45 (m, 1H), 2.65-2.60 (br, 1H, -OH), 1.76-1.65 (m, 2H), 1.60-1.50 (m, 2H), 1.45-1.40 (s, 9H, $(CH_3)_3$), 0.92 (s, 9H, CH_3), 0.06 (s, 6H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.2, 138.8, 138.7, 138.6, 138.5, 128.5, 128.46, 128.40, 128.3, 128.2, 128.1, 128.0, 127.9, 127.87, 127.81, 127.7, 127.69, 127.66, 127.64, 127.6, 79.1, 76.9, 76.8, 74.6, 73.3, 73.2, 73.1, 73.0, 72.4, 67.8, 65.0, 50.9, 29.0, 28.5, 26.0, 18.4, -5.2 and -5.3.

MOM ether 94:



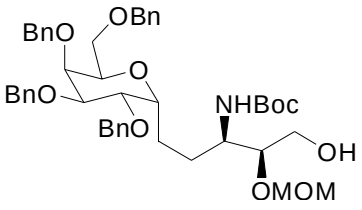
To a solution of compound **93** (8.51g, 9.953mmol) in 100ml anhydrous CH_2Cl_2 was added DIPEA (freshly distilled, 18ml, 0.09953mol) at 0^{O}C under an atmosphere of N_2, MOMCl (3ml, 0.0398mol) was added dropwise over a period of 5 minutes. The solution was then warmed up to rt. and was stirred overnight. The mixture was diluted with 100 ml CH_2Cl_2, washed with 200ml *satd.* NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3x100ml), dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* Flash chromatography purification eluting with 20% ethyl acetate/petroleum ether followed by 30% ethyl acetate/petroleum ether afforded compound **94** (8.90 g, 100% yield) as yellow oil.

M/S: m/z 917 (M^++NH_4^+) (*calcd*: for $C_{52}H_{73}NO_{10}Si$, 899.5). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.22 (m, 20H, Ph), 4.83 (d, *J*=9. 7 Hz, 1H, NH), 4.75-4.50 (m, 10H,

4CH_2 and OCH_2O-), 4.05-3.96 (m, 3H), 3.80-3.70 (m, 3H), 3.70-3.65 (m, 1H), 3.65-3.55 (m, 4H), 3.29 (s, 3H, OCH_3), 1.76-1.74 (m, 1H), 1.70-1.55 (m, 2H), 1.56-1.48 (m, 1H), 1.42 (s, 9H, $(CH_3)_3$, Boc), 0.85 (s, 9H, CH_3), and 0.05 (s, 6H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 155.9, 138.9, 138.8, 138.7, 138.6, 128.5, 128.49, 128.44, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 97.9, 79.5, 78.9, 77.2, 74.7, 73.4, 73.2, 72.4, 67.9, 63.9, 55.9, 50.9, 29.1, 28.6, 26.1, 18.4, and -5.4.

Primary alcohol 95:



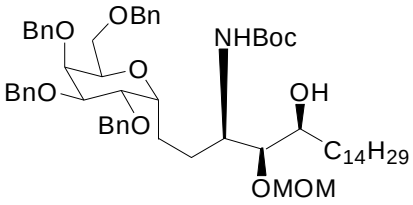
Compound **94** (8.90g, 9.92mmol) was dissolved in 50ml anhydrous THF and cooled to 0^{o}C. TBAF solution (30 ml, 0.0298mol, 1mol/l) was added dropwise under an atmosphere of N_2. The solution was warmed up to r.t and was stirred for 2 hours. 100ml *satd.* NH_4Cl solution was then added. The mixture was extracted with EtOAc (3x100ml). The organic layer was combined, dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* Flash chromatography purification eluting with 30%, 40%, and 50% ethyl acetate/petroleum ether afforded compound **95** (7.12g, 92%) as yellow oil.

M/S: m/z 803 (M^++NH_4^+) (*calcd*: for $C_{52}H_{73}NO_{10}Si$, 785). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.34-7.24 (m, 20H, Ph), 4.73-4.45 (m, 10H, -CH_2Ph and OCH_2O), 3.97-3.93 (m, 3H), 3.85-3.79 (m, 2H), 3.74-3.3.71 (m, 2H), 3.65-3.57 (m, 3H), 3.51-3.48

(m, 1H), 3.42-3.40 (m, 1H), 3.33-3.31 (s, 3H, OCH_3), 1.76-1.71 (m, 1H), 1.68-1.66 (m, 1H), 1.56-1.53 (m, 2H), and 1.42 (s, 9H, $-C(CH_3)_3$).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.9, 138.5, 138.4, 138.3, 138.1, 128.4, 128.3, 128.2, 128.19, 128.11, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.47, 127.43, 97.0, 81.0, 79.5, 77.3, 76.9, 74.4, 73.2, 73.1, 72.9, 72.8, 72.3, 70.5, 67.8, 61.8, 55.6, 50.3, 28.3 and 28.2.

The major isomer 97:



The primary alcohol **95** (1.84g, 2.34mmol) was dissolved in 20ml anhydrous CH_2Cl_2 under an atmosphere of N_2. Dess-Martin reagent (1.30g, 3.07mmol) was added in one portion. The mixture was stirred for 1 hour and a white precipitate appeared. 10ml *satd.* $NaHCO_3$ solution and 10ml *satd.* $Na_2S_2O_3$ solution were added and the mixture was stirred until two clear phases appeared. The mixture was then washed with 20ml *satd.* $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x60ml). The organic layers were combined, dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude compound was coevaporated with anhydrous toluene three times and was then put under full high vacuum pump for at least 1 hour to afford 1.7g of crude aldehyde as yellow oil.

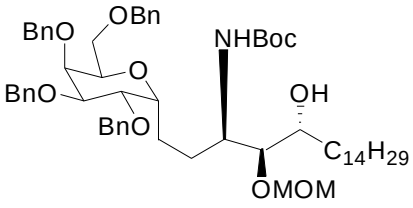
The crude aldehyde was then redissolved in 10ml anhydrous THF. The solution was added dropwise to a mixture of $C_{14}H_{29}MgBr$ (7mmol) or $C_{14}H_{29}MgCl$ (7ml, 1mol/l) in

THF at 0^{o}C under an atmosphere of N_2 over a period of 15 minutes. The reaction mixture was kept at 0^{o}C for 1hour and then warmed up to room temperature and was stirred for another hour until TLC showed completion of the starting material. A solution of 30ml *satd.* NH_4Cl was added and the mixture was stirred for 10 minutes. The mixture was washed with 20ml H_2O and extracted with EtOAc (3x100ml). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* Flash chromatography purification eluting with 10% ethyl acetate/petroleum to remove the long chain alkane by-product and 20% ethyl acetate/petroleum afforded the minor isomer compound **98** (0.4913g) first and then the major isomor **97** (0.6039g). The combined yield for the two steps was 50%.

The major isomer **97**: M/S: m/z 999 (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.21 (m, 20H, Ph), 4.74-4.49 (m, 10H, CH_2Ph and OCH_2O), 4.05-3.96 (m, 3H), 3.85-3.74 (m, 3H), 3.74-3.69 (m, 1H), 3.65-3.60 (dd, *J*=3.9, 10.3 Hz, 1H), 3.55-3.52 (br s, 1H), 3.34 (s, 3H, OCH_3), 3.21 (d, *J*=6.9 Hz, 1H), 3.05 (d, *J*=2.3 Hz, -OH), 1.76-1.51 (m, 4H), 1.42 (s, 9H, Boc), 1.35-1.22 (m, 26H), and 0.90 (t, *J*=6.7 Hz, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 155.8, 138.9, 138.8, 138.7, 138.6, 128.6, 128.5, 128.2, 128.1, 127.99, 127.95, 127.91, 127.79, 127.78, 127.74, 99.2, 87.4, 79.3, 77.1, 76.6, 76.4, 76.4, 74.7, 73.5, 73.3, 73.28, 73.1, 71.6, 68.1, 56.3, 50.8, 32.9, 32.2, 30.0, 29.9, 29.9, 29.8, 29.6, 28.6, 25.8, 22.9 and 14.3.

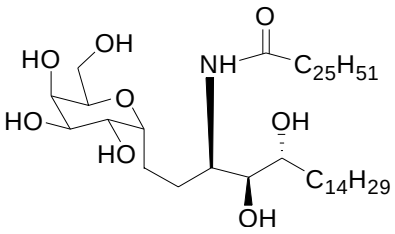
The minor isomer 98:



M/S: m/z 999 (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.51-7.24 (m, 20H, Ph), 4.76-4.48 (m, 10H, 4CH_2 and OCH_2O-), 4.05-3.90 (m, 4H), 3.90-3.85 (m, 1H), 3.85-3.74 (m, 2H), 3.74-3.70 (m, 1H), 3.65-3.60 (m, 1H), 3.31 (s, 3H, OCH_3), 3.19 (m, 1H), 1.78-1.51 (m, 4H), 1.50-1.45 (m and s, 11H), 1.45-1.21 (m, 24H), and 0.90 (*t*, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.5, 138.9, 138.7, 138.6, 138.5, 128.7, 128.6, 128.5, 128.4, 128.36, 128.33, 128.2, 128.1, 127.98, 127.90, 127.87, 127.79, 127.76, 127.72, 98.7, 85.2, 80.0, 76.9, 76.6, 74.8, 73.6, 73.5, 73.4, 73.3, 73.2, 70.8, 68.1, 56.5, 50.8, 32.8, 32.1, 30.1, 29.9, 29.6, 29.1, 28.5, 26.1, 22.9 and 14.3.

(3'R, 4'S, 5'R)-3'-*N*-hexacosanoyl-4',5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside 102:



The minor isomer **98** (0.189g, 0.192mmol) was dissolved in 4 ml MeOH/1, 4 dioxane (1:1) mixture. A solution of 10 ml HCl (6mol/l in MeOH) was added and the solution was stirred at rt overnight. The solution was concentrated to dryness under vacuum. The mixture was then redissolved in 5 ml $CHCl_3$. The solution was neutralized with 10 ml satd. NH_3 solution. The mixture was extracted with $CHCl_3$ (3x50 ml). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuum.* The crude compound was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.169g free amine as yellow oil.

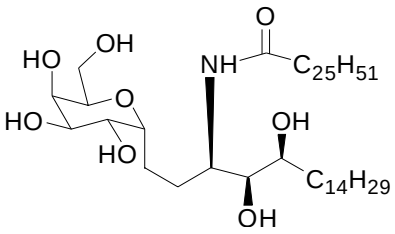
The amine was redissolved in 3ml anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.20g, 0.385mmol) and DMAP (0.03g, 0.385mmol) were added at r.t under N_2. The mixture was stirred at rt overnight. A 1g portion of celite 545 was added and the solvent was removed *in vacuo* to give a freely moved powder. Chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the unreacted ester and 20%, 30% ethyl acetate/petroleum ether to afford the amide (0.156g, 67% yield). (This amide was contaminated by phenol so the NMR was not good.)

The amide (0.0851g, 0.127mmol) was dissolved in 10ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.100g, 20% by weight) was added in one portion. The solution was degassed three times then was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite which was then washed with 50ml 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed under vacuum and the solid was redissolved in 1ml of pyridine and 1g of celite was added and the solvent was removed under vacuum until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the minor *C*-glycoside **102** (0.049g, 82% yield) as white solid.

^{1}H NMR (500MHz, C_5D_5N): δ 8.65 (d, *J*=9.0 Hz, 1H, NH), 6.65 (br, OH), 6.40 (br, OH), 6.20 (br, OH), 5.80 (br, OH), 5.02-5.01 (m, 1H), 4.76-4.72 (m, 1H), 4.72-4.66 (br s, 1H), 4.59-4.56 (m, 1H), 4.42 (m, 1H), 4.38 (m, 1H), 4.33 (m, 1H), 4.19 (br, 1H), 3.94 (m, 1H), 3.89 (m, 1H), 3.63 (d, *J*=4.7 Hz, less than 1H), 2.49-2.35 (m, 5H), 2.27-2.23 (m, 1H), 2.16-2.10 (m, 1H), 1.91-1.769 (m, 5H), 1.52-1.21 (m, 66H), and 0.87 (m, 6H, CH_3).

^{13}C-NMR (125MHz, C_5D_5N): δ 175.2, 77.8, 76.3, 74.5, 72.8, 72.7, 71.0, 70.9, 63.1, 51.5, 37.1, 34.9, 32.7, 32.7, 30.9, 30.8, 30.77, 30.72, 30.60, 30.57, 30.49, 30.46, 30.36, 30.28, 30.17, 30.15, 29.6, 27.3, 27.2, 23.5, 23.3 and 14.8.

(3'R, 4'S, 5'S)-3'-*N*-hexacosanoyl-4', 5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside 100:



The major isomer **97** (0.2147g, 0.22mmol) was dissolved in 4 ml MeOH/1, 4 dioxane (1:1) mixture. A solution of 10 ml HCl (6mol/l in MeOH) was added and the solution was stirred at rt overnight. The solution was concentrated to dryness under vacuum. The mixture was then redissolved in 5 ml $CHCl_3$. The solution was neutralized with 10 ml satd. NH_3 solution. The mixture was extracted with $CHCl_3$ (3x50 ml). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuum.* The crude compound was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.1873g free amine as a yellow oil.

The amine was redissolved in 3ml anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.232g, 0.44mmol) and DMAP (0.054g, 0.44mmol) were added at r.t under N_2. The mixture was stirred at rt overnight.1g celite 545 was added and the solvent was removed *in vacuo* to freely give a flowing powder. Chromatography purification eluting with 10% ethyl acetate/ petroleum ether removed the unreacted ester and 20%, 30% ethyl acetate/petroleum ether afforded the amide xxx (0.1653g, 62% yield). (This amide was contaminated by phenol so the NMR was not good.)

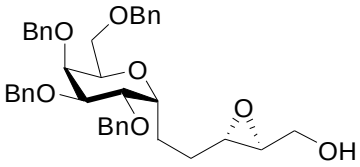
The amide (0.1545g, 0.127mmol) was dissolved in 10ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.25g, 20% by weight) was added in one portion. The

solution was degassed three times then was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate could be formed. The solution was filtered through a pad of celite which was then washed with 50ml 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed under vacuum and the solid was redissolved in 1ml of pyridine and 1g of celite was added and the solvent was removed under vacuum until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the major *C*-glycoside **100** (0.095g, 87%yield) as white solid.

^{1}H NMR (500MHz, C_5D_5N): δ 8.05 (d, *J*=9.2 Hz, 1H, NH), 6.65 (br, OH), 6.40 (br, OH), 6.20 (br, OH), 5.80 (br, OH), 4.76-4.72 (m, 1H), 4.72-4.66 (m, 2H), 4.54-4.48 (m, 1H), 4.45-4.34 (m, 2H), 4.32-4.27 (m, 1H), 4.12-4.06 (m, 1H), 4.01-3.94 (m, 1H), 2.49-2.35 (m, 5H), 2.27-2.23 (m, 1H), 2.16-2.10 (m, 1H), 1.91-1.77 (m, 5H), 1.52-1.21 (m, 66H), and 0.87 (t, 6H, CH_3).

^{13}C-NMR (125MHz, C_5D_5N): δ 173.7, 77.5, 75.8, 74.7, 73.0, 72.7, 71.0, 70.7, 62.8, 50.9, 37.3, 32.55, 32.53, 30.8, 30.65, 30.61, 30.47, 30.44, 30.36, 30.33, 30.27, 30.21, 30.04, 30.01, 27.0, 26.97, 23.4 and 14.7.

***(2S, 3S)* epoxyl alcohol 105**:

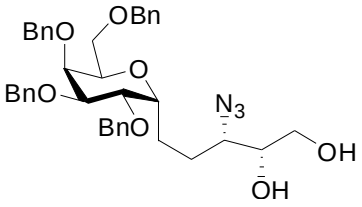


A 20g sample of powdered 4A MS was heated with heating gun *in vacuo* for 1 hour and cooled under an atmosphere of N_2. Then the flask was filled with 300ml dry CH_2Cl_2 and was cooled to -20°C under an atmosphere of N_2. TTIP (7.57ml, 0.0258mol) and L- (+)-DIPT (6.48ml, 0.031mol) were then added. The solution was stirred for 30 minutes at -20°C. TBHP (4.06mol/l in toluene, 26ml, 0.1055mol) was added dropwise over a period of 30 minutes. The solution was stirred for another 30 minutes at -20°C. Allylic alcohol **72** (31.41g, 0.05166mol, predried with 4A MS for 30minutes) in 100ml dry CH_2Cl_2 was added dropwise. The flask was rinsed with 100ml dry CH_2Cl_2 and the solution was added to the reaction bottle dropwise. The solution was stirred at -20°C for 18 hours (stored in freezer overnight) and was cooled to 0°C. 100 ml H_2O was added and the mixture was stirred for 30 minutes at 0°C, then a solution of 200 ml 30% NaOH saturated by NaCl was added and was stirred for another 30 minutes at 0°C. The mixture was filtered through a pad of celite, which was washed with CH_2Cl_2 (200ml). The solution was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 300 ml). The organic layers were combined and was washed with brine (200ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 50% EtOAc/PE to provide the epoxide **105** (23.58g, 73% yield) as a pale yellow oil.

M/S: m/z 642 (M^++NH_4^+) (calcd: for $C_{39}H_{44}O_7$ 624). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.32-7.23 (m, 20H, Ph), 4.75-4.45 (m, 8H, CH_2Ph), 3.98-3.97 (m, 3H), 3.78-3.72 (m, 4H), 3.67-3.60 (dd, *J*=10.1, 4.4 Hz, 1H), 3.56-3.49 (dd, *J*=12.2, 3.4 Hz, 1H), 2.93-2.87 (m, 1H), 2.87-2.86 (m, 1H), 2.18 (broad peak, 1H, -OH), 1.84-1.77 (m, 1H), 1.76-1.72 (m, 2H), 1.68-1.63 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.7, 138.6, 138.3, 128.6, 128.5, 128.4, 128.3, 128.26, 128.08, 128.03, 127.98, 127.92, 127.85, 127.81, 127.70, 127.69, 127.66, 127.59, 76.9, 74.5, 73.4, 73.3, 73.1, 72.4, 67.8, 61.9, 58.8, 56.2, 28.8 and 23.7.

3-azido-1, 2 diol 106:



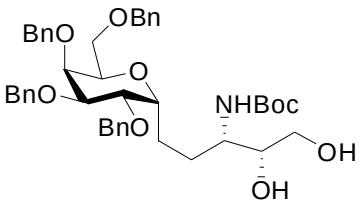
TTIP (16.6ml, 0.055mol) and azido trimethylsilane (15ml, 0.114mol) were added to 300ml anhydrous benzene and the solution was refluxed at 80°C under an atmosphere of N_2 for at least 5 hours. The epoxide **105** (23.58g, 0.0378mol) was dissolved in 50ml anhydrous benzene and was added to the solution in one portion. The mixture was stirred for 15-30 minutes at 80°C and then was cooled to rt. The solvent was removed under reduced pressure. 300 ml diethyl ether was then added followed by addition of 80ml 5% H_2SO_4 (V/V). The solution was stirred until two clear phases appeared. The mixture was extracted with ethyl ether (200ml). The aqueous layer was extracted with CH_2Cl_2 (3x 200ml). The organic phases were combined and dried with Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography purification eluting with

50% EtOAc/PE afforded the *syn*-3-azido-1, 2 diol **106** (18.95g, 75% yield) as a yellow oil.

M/S: m/z 685.3 (M^++NH_4^+) (*calcd*: for $C_{39}H_{45}N_3O_7$ 667). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.336-7.26 (m, 20H, Ph), 4.71-4.48 (m, 8H, CH_2Ph), 4.01-4.00 (broad peak, 1H), 3.95 (bs, 1H), 3.91-3.87 (m, 2H), 3.71 (bs, 2H), 3.61-3.55 (m, 4H), 3.32-3.29 (m, 1H), 2.67-2.66 (d, *J*=4.7 Hz, 1H, OH), 2.08-2.07 (broad peak, 1H, OH), 1.79-1.63 (m, 3H, CH_2 and one of CH_2), 1.57-1.51 (m, 1H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 138.7, 138.6, 138.3, 128.6, 128.61, 128.5, 128.47, 128.45, 128.43, 128.26, 128.18, 128.12, 128.08, 127.99, 127.93, 127.90, 127.85, 127.75, 77.2, 76.7, 74.5, 73.8, 73.5, 73.4, 73.3, 72.6, 67.9, 64.2, 64.1, 27.5 and 24.4.

1, 2 diol 107:



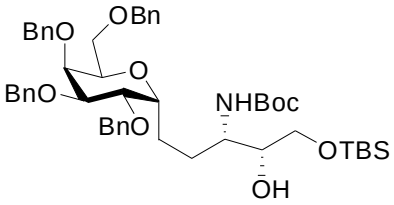
The *syn*-3-azido-1, 2 diol compound **106** (18.95g, 0.0284mol) was dissolved in 200ml anhydrous THF and the solution was cooled to 0^{o}C under an atmosphere of N_2. A solution of 200ml $P(Me)_3$ (1mol/l in THF, 0.2mol) was added dropwise over a period of 30 minutes. The solution was warmed up to rt and was stirred overnight. A solution of 200ml NaOH (1mol/l, 0.2mol) was added and the solution was stirred for 2 hours. The mixture was extracted with ethyl acetate (3x200ml). The combined organic layers were dried with Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo* to afford 19g crude amine as yellow oil. The crude product was redissolved in 1, 4 dioxane (50ml),

THF (150ml) and H_2O (20ml). Solid $NaHCO_3$ (12g, 0.143mol) was added to the mixture followed by addition of $(t\text{-Boc})_2O$ (7.9ml, 0.0342mol). The solution was stirred at rt for 24 hours. The solution was concentrated under reduced pressure to a total volume of 30ml. The mixture was washed with 200ml *satd*. $NaHCO_3$ solution, extracted with ethyl acetate (3x200ml). The combined organic layers were dried with Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography eluting with 30%, 40%, 50% and 60% Ethyl acetate/petroleum ether to afford 16.18g of compound **107** (77% for two steps) as yellow oil.

M/S: m/z 742.3 (M^++H^+) (*calcd*: for $C_{44}H_{55}NO_9$, 741.39). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.26 (m, 20H, Ph), 4.92 (d, *J*=9.1 Hz, 1H, NH), 4.77-4.44 (m, 8H, CH_2Ph), 3.99 (br s, 1H), 3.95 (m, 1H), 3.89 (m, 2H), 3.73-3.72 (m, 2H), 3.66 (m, 1H), 3.62-3.59 (m, 1H), 3.56-3.48 (m, 2H), 3.39-3.35 (m, 1H), 3.21-3.15 (br, 1H, OH), 2.81 (br, 1H, OH), 1.72-1.53 (m, 4H), 1.44 (s, 9H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.3, 138.7, 138.5, 138.4, 138.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.07, 128.06, 127.98, 127.91, 127.85, 127.83, 127.78, 127.75, 127.72, 79.9, 77.0, 74.6, 73.4, 73.35, 73.33, 72.7, 72.3, 68.0, 63.7, 51.6, and 28.5.

TBS ether 108:

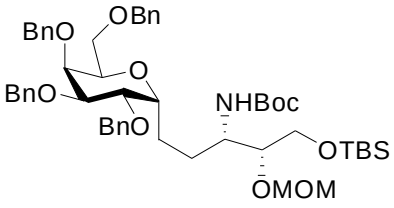


To a solution of compound **107** (15.78g, 0.0213mol) in 200 ml anhydrous CH_2Cl_2 was added imidazole (4.5g, 0.0652mol) followed by addition of TBSCl (4.265g, 0.0283mol) at rt under an atmosphere of N_2. The mixture was stirred for 1 hour. A *satd.* solution of $NaHCO_3$ (100 ml) was added and the mixture was extracted with CH_2Cl_2 (3x200 ml). The organic layers were combined and dried over Na_2SO_4 (anhydrous). The solution was filtered and concentrated *in vacuo.* The crude mixture was then purified by flash chromatography eluting with 10% ethyl acetate/petroleum ether (500 ml) followed by 20% ethyl acetate/petroleum ether to afford compound **108** (17.4g, 94% yield) as yellow oil.

M/S: m/z 873.3 (M^++NH_4^+) (*calcd*: for $C_{50}H_{69}NO_9Si$, 855.47). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.34-7.24 (m, 20H, Ph), 4.72 (*d*, *J*=9.3 Hz, 1H, NH), 4.67-4.45 (m, 8H, CH_2Ph), 3.95 (s, 2H), 3.92-3.91 (m, 1H), 3.79 (br s, 2H), 3.72 (*d*, *J*=6.5 Hz, 1H), 3.66 (br s, 1H), 3.60 (d, *J*=3.4 Hz, 1H), 3.58 (d, *J*=3.9 Hz, 1H), 3.51-3.44 (m, 2H), 2.72 (br, 1H, OH), 1.73-1.68 (m, 2H), 1.63-1.60 (m, 1H), 1.54-1.50 (m, 1H), 1.42 (s, 9H, $(CH_3)_3$), 0.89 (s, 9H, CH_3), 0.06 (s, 6H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 156.3, 138.78, 138.76, 138.59, 138.56, 128.6, 128.5, 128.46, 128.39, 128.26, 128.21, 128.15, 128.14, 128.07, 128.00, 127.9, 127.77, 127.71, 127.68, 79.2, 77.1, 74.8, 73.5, 73.4, 73.3, 73.2, 72.9, 72.2, 68.1, 65.1, 51.6, 29.5, 28.6, 26.1, 23.9, 18.5, -5.16, and -5.21.

MOM ether 109:

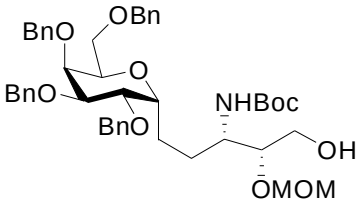


To a solution of compound **108** (11.32g, 0.01323mol) in 150ml of anhydrous CH_2Cl_2 was added DIPEA (freshly distilled, 23ml, 0.1323mol) at $0^{O}C$ under an atmosphere of N_2. MOMCl (4.0ml, 0.0529mol) was added dropwise over a period of 10 minutes. The solution was then warmed up to rt. and stirred for 24 hours. The mixture was diluted with 100ml of CH_2Cl_2, and washed with 200ml *satd.* NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3x150ml), dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude mixture was purified by flash chromatography eluting with 10%, 20%, and 30% ethyl acetate/petroleum ether to afford compound **109** (10.71 g, 90% yield) as yellow oil.

M/S: m/z 917 (M^++NH_4^+) (*calcd*: for $C_{52}H_{73}NO_{10}Si$, 899.5). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.36-7.25 (m, 20H, Ph), 4.85 (d *J*=9.6 Hz, 1H, NH), 4.76-4.31 (m, 10H, CH_2Ph and OCH_2O), 3.97-3.95 (m, 3H), 3.82 (s, 1H), 3.79-3.71 (m, 3H), 3.68-3.59 (m, 5H), 3.31 (s, 3H, OCH_3), 1.76-1.59 (m, 4H, $2CH_2$), 1.41 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, CH_3), 0.05 (s, 3H, CH_3) and 0.04 (s, 3H, CH_3).

^{13}C-NMR (75MHz, $CDCl_3$): δ 155.9, 138.9, 138.8, 138.7, 138.6, 128.6, 128.5, 128.4, 128.37, 128.34, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 97.3, 79.3, 78.9, 77.6, 77.1, 76.9, 74.9, 73.7, 73.5, 73.4, 72.0, 68.2, 63.7, 55.9, 51.6, 29.4, 28.6, 26.1, 24.0, 18.4 and -5.3.

Primary alcohol 110:

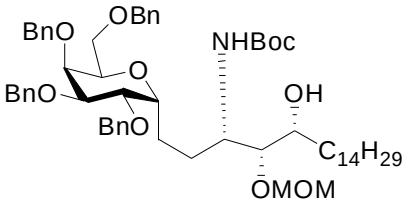


Compound **109** (5.0g, 5.586mmol) was dissolved in 50ml of anhydrous THF and was cooled to 0^{o}C under an atmosphere of N_2. A solution of TBAF (17ml, 0.0167mol, 1mol/l in THF) was added dropwise. The solution was then warmed up to room temperature and was stirred for 1.5 hours. A *satd*. solution of NH_4Cl (100ml) was then added. The mixture was extracted with EtOAc (3x100ml). The organic layers were combined, dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* Flash chromatography purification eluting with 30%, 40%, 50% ethyl acetate/petroleum ether afforded compound **110** (3.74g, 85%) as a yellow oil.

M/S: m/z 803 (M^++NH_4^+) (*calcd*: for $C_{52}H_{73}NO_{10}Si$, 785). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.25 (m, 20H, Ph), 4.74-4.36 (m, 10H, CH_2Ph and OCH_2O), 3.96-3.91 (m, 3H), 3.43-3.83 (m, 1H), 3.76 (m, 2H), 3.67 (m, 1H), 3.63-3.55 (m, 3H), 3.52 (m, 1H), 3.39-3.35 (m, 1H), 3.31 (s, 3H, OCH_3), 1.75-1.51 (m, 3H), 1.43-1.38 (s, 10H, $(CH_3)_3$ and one of CH_2).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.2, 138.8, 138.7, 138.6, 138.5, 128.54, 128.51, 128.47, 128.41, 128.39, 128.2, 128.1, 127.94, 127.92, 127.78, 127.75, 127.72, 97.6, 81.6, 79.9, 77.0, 74.7, 73.5, 73.4, 73.36, 73.3, 72.25, 67.9, 62.2, 55.9, 51.4, 28.5 and 24.5.

The major isomer 112:



The primary alcohol **110** (2.45 g, 3.121 mmol) was dissolved in 30ml of anhydrous CH_2Cl_2 under an atmosphere of N_2. Dess-Martin reagent (1.72 g, 4.06 mmol) was added in one portion. The mixture was stirred for 1 hour at room temperature. A white precipitate appeared at the end of the reaction. A solution of *satd*. $NaHCO_3$ (20 ml) and a solution of *satd*. $Na_2S_2O_3$ (20ml) were added and the mixture was stirred until two clear phases appeared. The mixture was then washed with 20 ml *satd*. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x60 ml). The organic layers were combined, dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude product was coevaporated with anhydrous toluene three times and was put under high vacuum pump for at least 1 hour to afford 2.40 g crude aldehyde as an oil.

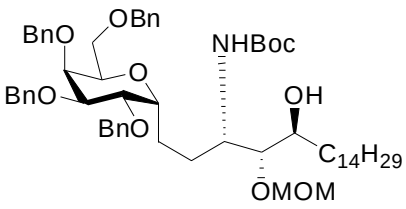
The aldehyde was then redissolved in 20 ml of anhydrous THF. The solution was added dropwise to a mixture of $C_{14}H_{29}MgBr$ (9.36mmol) in 10 ml of anhydrous THF at 0^oC under an atmosphere of N_2 over a period of 15 minutes. The reaction mixture was kept at 0^oC for 1hour and was warmed up to room temperature and was stirred for another one hour until TLC showed the completion of the starting material. A *satd*. NH_4Cl solution (30ml) was added and the mixture was stirred for 10 minutes. The mixture was washed with 20ml H_2O and extracted with EtOAc (3x100ml). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* Flash chromatography purification eluting with 10% ethyl acetate/petroleum

to remove the long chain alkane by product and 20% ethyl acetate/petroleum to afford the major isomor **112** (1.34g) as the first fraction and the minor isomer compound **113** (0.35g) as the second fraction. The combined yield for the two steps was 66%.

Fraction A: The major isomer **112**: M/S: m/z 999 (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.37-7.22 (m, 20H, Ph), 4.76-4.48 (m, 10H, 4CH_2Ph and 1 OCH_2O-), 4.01-3.96 (br s, 2H), 3.95-3.92 (m, 1H), 3.86-3.81 (m, 1H), 3.79-3.3.72 (m, 3H), 3.62-3.57 (m, 1H), 3.56-3.52 (br s, 1H), 3.37 (s, 3H, OCH_3), 3.23 (d, *J*=7.7 Hz, 1H), 3.12 (broad peak, OH), 1.72-1.62 (m, 2H), 1.59-1.53 (m, 2H), 1.48-1.41 (m, 13H), 1.41-1.21 (m, 22H), and 0.90 (*t*, *J*=6.5 Hz, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 155.8, 138.8, 138.7, 138.6, 138.6, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 99.3, 87.1, 79.3, 77.1, 74.8, 73.4, 73.4, 73.3, 71.5, 68.4, 56.3, 51.6, 38.9, 32.9, 32.1, 30.6, 30.2, 29.9, 29.8, 29.7, 29.6, 29.1, 28.6, 25.7, 23.9, 23.2, 22.9 and 14.3.

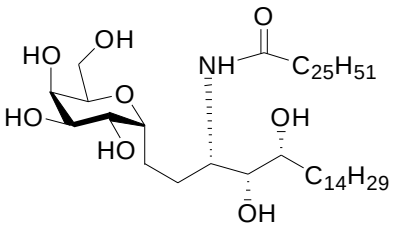
The minor isomer 113:



M/S: m/z 999 (M^++NH_4^+) (*calcd*: for $C_{60}H_{87}NO_{10}$, 981). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.26 (m, 20H, Ph), 4.77-4.43 (m, 10H, 4CH_2Ph and 1 OCH_2O-), 4.04-3.83 (m, 4H), 3.82-3.74 (m, 3H), 3.79 (d, *J*=6.6 Hz, 1H), 3.60 (dd, *J*=10.1, 4.5 Hz, 1H), 3.3 (s, 3H, OCH_3), 3.17 (d, *J*=7.8 Hz, 1H), 1.762-1.70 (m, 1H), 1.72-1.50 (m, 4H), 1.47-1.42 (s and m, 10H), 1.41-1.10 (m, 24H), 0.879 (t, *J*=7.0 Hz, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 157.4, 138.9, 138.8, 138.6, 138.5, 128.6, 128.5, 128.47, 128.40, 128.2, 128.16, 128.13, 128.08, 127.99, 127.93, 127.75, 98.7, 84.9, 80.1, 77.2, 74.8, 73.6, 73.5, 73.4, 73.3, 72.1, 70.8, 68.0, 56.5, 51.6, 32.9, 32.1, 29.9, 29.89, 29.86, 29.6, 29.3, 28.6, 28.5, 26.1, 22.9 and 14.3.

(3'S, 4'R, 5'S)-3'-*N*-hexacosanoyl-4', 5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside 115:



The major isomer (0.3153 g, 0.321 mmol) was dissolved in a solution of 6ml MeOH/1, 4 dioxane (1:1). A solution of HCl (4ml, 2.4mmol, 6mol/l in MeOH) was added and the solution was stirred at room temperature overnight. The solution was concentrated to dryness *in vacuo*. The mixture was then redissolved in 5 ml THF. The solution was neutralized with 10 ml *satd.* NH_3 solution. The mixture was extracted with $CHCl_3$ (3x 50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude product was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.284 g of free amine as yellow oil.

The amine was redissolved in 5ml of anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.34g, 0.62mmol) and DMAP (0.14g, 0.64mmol) were added at room temperature under N_2. The mixture was stirred at room temperature overnight. 1g of celite 545 was added and the solvent was removed *in vacuo* to get the powder

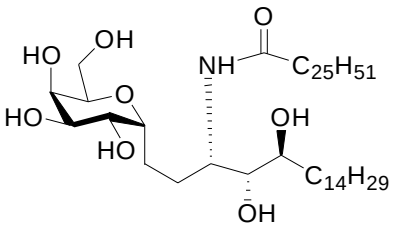
which could flow freely. Chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the unreacted excess ester and then 20%, 30% ethyl acetate/petroleum ether to afford the amide **114** (0.2641g, 68% yield for two steps). (This amide was contaminated by phenol so the NMR was not good.)

The amide **114** (0.253g, 0.208 mmol) was dissolved in 10ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.300g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite, which was washed with 50ml 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed *in vacuo* and the solid was redissolved in 1ml of pyridine and 1g of celite 545 was added and the solvent was removed *in vacuo* until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the major *C*-glycoside **115** (0.1485g, 84%yield) as a white solid.

Mp: 104-106^{O}C. ^{1}H NMR (500MHz, C_5D_5N): δ 8.23 (d, *J*=9.2 Hz, 1H, NH), 4.84 (m, 2H), 4.75 (dd, *J*=8.3, 4.9 Hz, 1H), 4.62 (m, 1H), 4.56-4.53 (m, 2H), 4.45-4.41 (m, 1H), 4.34-4.29 (m, 2H), 4.13-4.09 (m, 1H), 3.99-3.97 (m, 1H), 2.47-2.37 (m, 5H), 2.26-2.25 (m, 1H), 2.13 (m, 1H), 1.90-1.73 (m, 5H), 1.47-1.25 (m, 66H, CH_2), 0.89-0.86 (m, 6H, CH_3).

^{13}C-NMR (125MHz, C_5D_5N): δ 173.5, 77.2, 76.7, 74.5, 72.9, 72.6, 70.8, 70.7, 62.8, 51.2, 37.2, 34.3, 32.5, 32.4, 31.3, 30.9, 30.6, 30.4, 30.3, 30.2, 30.1, 29.9, 29.94, 26.9, 26.89, 23.3, 22.9 and 14.6.

(3'S, 4'R, 5'S)-3'-*N*-hexacosanoyl-4', 5'-dihydroxynonadecacyl–α-*C*-D-galactopyranoside 117:



The minor isomer (0.2955g, 0.243mmol) was dissolved in 6 ml MeOH/1,4 dioxane (1:1) mixture. A solution of HCl (4ml, 2.4mmol, 6mol/l in MeOH) was added and the solution was stirred at room temperature overnight. The solution was concentrated to dryness *in vacuo*. The mixture was then redissolved in 5 ml THF. The solution was neutralized with 10ml *satd.* NH_3 solution. The mixture was extracted with $CHCl_3$ (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo.* The crude compound was coevaporated with anhydrous toluene three times and was then put under high vacuum pump for at least 1 hour to afford 0.30g of free amine as yellow oil.

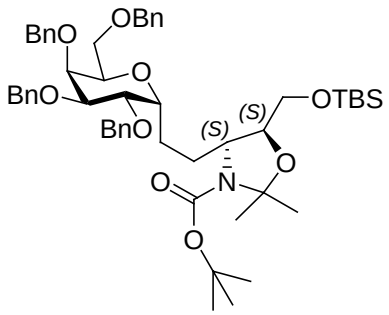
The amine was redissolved in 6ml of anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.32g, 0.60mmol) and DMAP (0.12g, 0.60mmol) were added in one portion at room temperature under an atmosphere of N_2. The mixture was stirred at room temperature overnight. 1g of celite 545 was added and the solvent was removed *in vacuo.* The resulting solid was put to the top of a column. Flash chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the excess ester and 20%, 30% ethyl acetate/petroleum ether to afford the amide **116** (0.2647g, 73% yield). (This amide was contaminated by phenol so the NMR was not good.)

The amide **116** (0.263g, 0.22mmol) was dissolved in 10ml of mixed solvent of THF and EtOH(1:1). $Pd(OH)_2/C$ (0.30g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite, which was washed with 50ml 50% $CHCl_3$/MeOH solution followed by 50ml pyridine. The solvent was removed *in vacuo* and the solid was redissolved in 1ml of pyridine and 1g of celite 545 was added and the solvent was removed *in vacuo* until the celite powder could flow freely. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the *C*-glycoside **117** (0.095g, 49% yield) as a white solid.

Mp. 150-152 ^{O}C. ^{1}H NMR (500MHz, C_5D_5N): δ 8.89 (d, *J*=8.9 Hz, 1H, NH), 6.70-6.69 (broad peak, OH), 6.13 (broad peak, OH), 4.97-4.96 (m, 2H), 4.75 (dd, *J*=8.9 Hz, 5.5 Hz, 1H), 4.64 (br s, 1H), 4.47-4.44 (m, 3H), 4.31 (dd, *J*=9.1 Hz, 3.3 Hz, 1H), 4.22-4.20 (m, 1H), 3.97-3.93 (m, 1H), 3.89-3.87 (m, 1H), 2.57-2.49 (m, 3H), 2.42-2.29 (m, 4H), 2.01-1.97 (m, 1H), 1.92-1.79 (m, 3H), 1.77-1.72 (m, 1H), 1.50-1.29 (m, 66H, CH_2), 0.91-0.88 (m, 6H, $2CH_3$).

^{13}C-NMR (125MHz, C_5D_5N): δ 177.2, 78.9, 78.3, 75.1, 73.6, 73.5, 71.9, 71.8, 63.8, 52.9, 38.0, 33.6, 33.6, 31.9, 31.7, 31.5, 31.5, 31.4, 31.4, 31.3, 31.2, 31.1, 31.1, 28.3, 28.1, 24.4 and 15.8.

TBS ether 118:



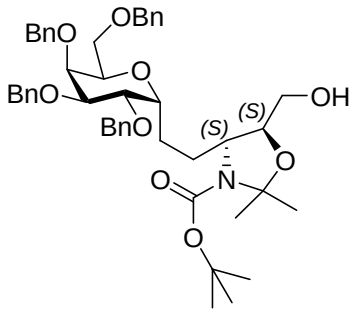
The compound **93** (0.17g, 0.2mmol) was dissolved in 5ml of anhydrous CH_2Cl_2. DMP (1ml) was added followed by *p*-TsOH (3mg) at 0^oC under an atmosphere of N_2. The solution was then stirred at room temperature for 1hour. The solution was washed with 10ml *satd*. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3x30ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with increasing polarity solvent from 10%, 20% to 30% ethyl acetate/petroleum ether to afford the cyclic compound **118** (0.162g, 91% yield) as yellow oil.

M/S: m/z 913 (M^++NH_4^+) (*calcd*: for $C_{53}H_{73}NO_9Si$, 895). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.24 (m, 20H, Ph), 4.735-4.43 (m, 8H, CH_2Ph), 3.98 (s, 1H), 3.93-3.91 (m, 2H), 3.85-3.71 (m, 4H), 3.69 (dd, *J*=7.9, 2.5 Hz, 1H), 3.65 (dd, *J*=10.0, 5.3 Hz, 1H), 3.59 (s, 2H), 1.91-1.89 (m, 1H), 1.57-1.52 (s, 6H, CH_3 and CH_2), 1.49 (s, 3H, CH_3), 1.42 (s, 9H, $(CH_3)_3$), 0.88 (s, 9H, CH_3), 0.07 (s, 3H, CH_3), 0.04 (s, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.1, 138.9, 138.8, 138.7, 128.5, 128.4, 128.1, 128.07, 128.00, 127.9, 127.8, 127.7, 127.68, 127.3, 94.7, 94.4, 80.9, 79.8, 79.1, 76.9,

76.6, 76.3, 74.7, 73.5, 73.2, 72.1, 68.0, 64.8, 59.6, 28.7, 27.7, 26.2, 23.7, 18.5, -5.1 and -5.2.

Primary alcohol 119:

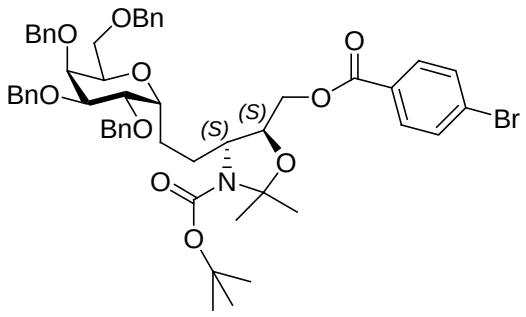


The cyclic compound **118** (0.16g, 0.18mmol) was dissolved in 5 ml of anhydrous THF and a solution of TBAF (0.53ml, 0.35mmol, 1N in THF) was added at 0 ^{o}C under an atmosphere of N_2. The solution was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10%, 20%, and 30% ethyl acetate/petroleum ether to afford the primary alcohol **119** (0.12g, 90% yield) as yellow oil.

M/S: m/z 799 (M^++NH_4^+) (*calcd*: for $C_{47}H_{59}NO_9$, 781). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.24 (m, 20H, Ph), 4.74-4.45 (m, 8H, CH_2Ph), 4.05-3.81 (m, 6H), 3.73-3.69 (s, 2H), 3.66-3.55 (m, 2H), 3.47-3.42 (bs, 2H), 1.94-1.85 (m, 1H), 1.67-1.59 (m, 3H), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), and 1.42 (s, 9H, $(CH_3)_3$).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.1, 138.8, 138.6, 138.5, 128.6, 128.5, 128.43, 128.41, 128.39, 128.26, 128.20, 128.18, 128.10, 127.99, 127.86, 127.78, 127.72, 127.69, 79.9, 77.4, 77.1, 74.5, 73.7, 73.6, 73.3, 63.9, 58.4 and 28.7 (note: $C(CH_3)_3$ peak around 94 ppm was too small).

Benzoyl ester 120:

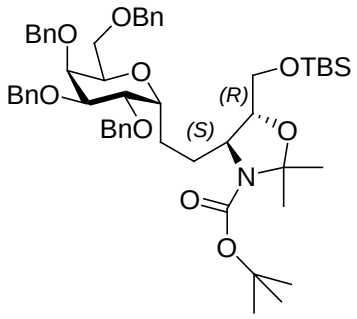


The primary alcohol **119** (0.42g, 0.54mmol) was dissolved in 8ml of anhydrous CH_2Cl_2 solution at 0^oC under an atmosphere of N_2. A solution of anhydrous pyridine (0.5ml) was added followed by addition of para-bromobenzoyl chloride (0.25g, 1.1mmol). The solution was stirred at room temperature for 2 hours. The solution was washed with 20ml *satd*. NH_4Cl solution and was extracted with CH_2Cl_2 (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10% and 20% ethyl acetate/petroleum ether to afford benzoyl ester **120** (0.46g, 90% yield) as yellow oil.

M/S: m/z 981 (M^++NH_4^+) (*calcd*: for $C_{54}H_{62}BrNO_{10}$, 963). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.92-7.90 (d, *J*= 8.42 Hz, 2H), 7.57-7.55 (d, *J*=8.4 Hz, 2H), 7.37-7.29 (m, 20H, Ph), 4.76-4.47 (m, 8H, CH_2), 4.35-4.34 (m, 2H), 4.22-4.19 (m, 1H), 4.01 (m, 4H), 3.82 (br s, 2H), 3.74-3.72 (m, 1H), 3.69-3.66 (dd, *J*=10.2, 4.6 Hz, 1H), 2.00-1.98 (m, 1H), 1.62 (br s, 5H), 1.56 (br s, 4H), 1.47 (s, 9H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 165.7, 152.1, 138.7, 138.6, 138.4, 131.9, 131.4, 128.9, 128.6, 128.53, 128.51, 128.4, 128.2, 128.1, 127.9, 127.8, 127.77, 127.68, 95.3, 94.5, 80.2, 77.4, 76.7, 76.4, 74.6, 73.5, 73.3, 59.7 and 28.7.

Cyclic ether 121:

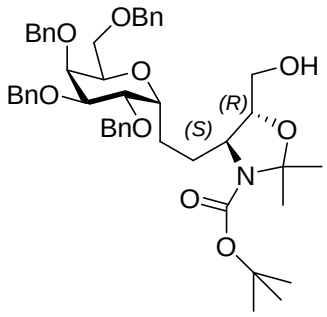


The compound **108** (0.17g, 0.2mmol) was dissolved in 5ml of anhydrous CH_2Cl_2. DMP (1ml) was added followed by *p*-TsOH (3mg) at 0^oC under an atmosphere of N_2. The solution was then stirred at room temperature for 1hour. The solution was washed with 10ml *satd*. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3x30ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with increasing polarity solvent from 10%, 20% to 30% ethyl acetate/petroleum ether to afford the cyclic compound **121** (0.162g, 91% yield) as yellow oil.

M/S: m/z 913 (M^++NH_4^+) (*calcd*: for $C_{53}H_{73}NO_9Si$, 895). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.31-7.25 (M, 20H, Ph), 4.67-4.47 (m, 8H, CH_2Ph), 3.97 (br s, 2H), 3.90 (br s, 1H), 3.87 (brs, 2H), 3.79 (br s, 2H), 3.67 (m, 1H), 3.64-3.54 (m, 3H), 1.79 (brs, 1H), 1.66 (brs, 1H), 1.60-1.56 (m, 5H), 1.44 (brs, 12H), 0.87 (s, 9H), 0.45 (s, 6H).

^{13}C-NMR (125MHz, $CDCl_3$) δ 152.1, 138.9, 138.8, 138.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 94.7, 94.4, 80.6, 79.9, 77.4, 74.7, 73.7, 73.6, 73.2, 72.4, 72.1, 68.1, 65.0, 59.9, 28.6, 27.9, 26.1, 23.9, 18.5, -5.1, -5.1.

Primary alcohol 122:

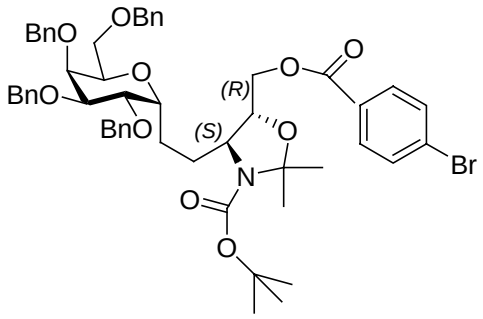


The cyclic compound **121** (0.65g, 0.73mmol) was dissolved in 10ml of anhydrous THF and a solution of TBAF (1.5ml, 1.5mmol, 1N in THF) was added at 0 ^{o}C under an atmosphere of N_2. The solution was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10%, 20%, and 30% ethyl acetate/petroleum ether to afford the primary alcohol **122** (0.51g, 90% yield) as yellow oil.

M/S: m/z 799 (M^++NH_4^+) (*calcd*: for $C_{47}H_{59}NO_9$, 781). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.23 (m, 20H), 4.74-4.49 (m, 8H), 4.02-3.95 (m, 2H), 3.94-3.91 (m, 2H), 3.81-3.73 (m, 2H), 3.73-3.69 (m, 1H), 3.68-3.62 (m, 3H), 3.56-3.52 (m, 1H), 1.91-1.87 (m, 1H), 1.87-1.73 (m, 2H), 1.65-1.60 (m, 1H and H_2O), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), and 1.42 (s, 9H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.1, 138.8, 138.7, 138.5, 138.4, 128.6, 128.57, 128.54, 128.49, 128.43, 128.3, 128.2, 128.1, 128.0, 127.9, 127.86, 127.80, 127.76, 127.71, 94.5, 80.6, 80.2, 77.4, 77.1, 76.8, 76.5, 76.3, 74.6, 73.5, 73.2, 72.5, 71.8, 67.9, 64.3, 58.9, 28.7, 27.6 and 24.1.

***p*-Bromobenzoyl ester 123**:



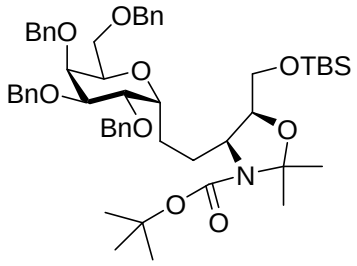
The primary alcohol **122** (0.47g, 0.61mmol) was dissolved in 10ml of anhydrous CH_2Cl_2 solution at 0^oC under an atmosphere of N_2. A solution of anhydrous pyridine (0.5ml) was added followed by addition of para-bromobenzoyl chloride (0.27g, 1.22mmol). The solution was stirred at room temperature for 2 hours. The solution was washed with 20ml *satd*. NH_4Cl solution and was extracted with CH_2Cl_2 (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10% and 20% ethyl acetate/petroleum ether to afford benzoyl ester **123** (0.56g, 98% yield) as yellow oil.

M/S: m/z 981 (M^++NH_4^+) (*calcd*: for $C_{54}H_{62}BrNO_{10}$, 963). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.87 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=9.4 Hz, 2H), 7.33-7.23 (m, 20H, Ph), 4.74-4.51 (m, 8H, CH_2Ph), 4.32 (m, 2H), 4.18 (m, 1H), 3.96 (m, 4H), 3.84-3.76 (m, 2H), 3.672 (d, *J*= 6.2 Hz, 1H), 3.61 (dd, *J*= 10.3, 4.1 Hz, 1H), 1.92-1.75 (m, 2H), 1.73-1.65 (m, 1H), 1.61-1.55 (br s, 4H) and 1.52-1.38 (br s, 12H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 165.7, 152.2, 151.8, 138.7, 138.6, 138.5, 138.4, 131.9, 131.4, 128.8, 128.6, 128.55, 128.50, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8,

127.7, 127.6, 94.6, 80.6, 80.2, 77.5, 74.5, 73.4, 73.3, 72.4, 67.8, 66.6, 66.4, 60.1 and 28.6.

Cyclic ether 124:

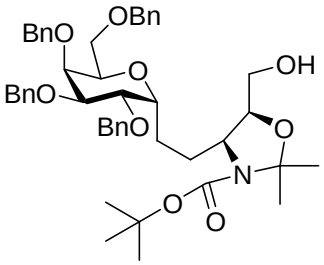


The compound **78** (0.51g, 0.6mmol) was dissolved in 5ml of anhydrous CH_2Cl_2. DMP (1ml) was added followed by *p*-TsOH (7mg) at 0^oC under an atmosphere of N_2. The solution was then stirred at room temperature for 1hour. The solution was washed with 10ml *satd*. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3x60ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with increasing polarity solvent from 10%, 20% to 30% ethyl acetate/petroleum ether to afford the cyclic compound **124** (0.41g, 75% yield) as yellow oil.

M/S: m/z 913 (M^++NH_4^+) (*calcd*: for $C_{53}H_{73}NO_9Si$, 895). ^1H NMR (500MHz, $CDCl_3$): δ 7.32-7.25 (m, 20H, Ph), 4.79-4.37 (m, 8H, CH_2Ph), 4.09-4.05 (m, 2H), 3.97-3.94 (br s, 2H), 3.91-3.86 (m, 3H), 3.79-3.75 (m, 1H), 3.73 (d, J=7.5 Hz, 1H), 3.67-3.55 (m, 2H), 1.82-1.79 (m, 2H), 1.66-1.63 (m, 1H), 1.59-1.55 (br s, 4H), 1.51 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.39 (s, 6H, CH_3), 0.87 (s, 9H, CH_3), 0.05 (s, 3H, CH_3), and 0.03 (s, 3H, CH_3).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.7, 152.2, 138.9, 138.9, 138.8, 138.7, 138.6, 138.4, 128.8, 128.76, 128.72, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.70, 127.6, 93.4, 92.9, 79.9, 79.7, 77.3, 77.1, 76.6, 74.9, 73.8, 73.6, 73.5, 73.4, 73.1, 71.6, 68.5, 68.2, 61.3, 58.8, 28.7, 28.6, 28.3, 27.5, 27.4, 27.0, 26.1, 25.3, 23.9, 23.7, 18.5, -5.0 and -5.1 (Note: Because the existence of two conformers of amide, the carbon peaks become to two series of peaks).

Primary alcohol 125:

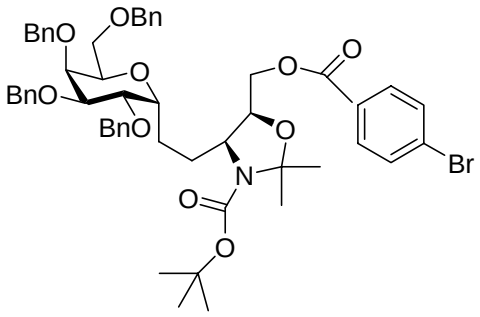


The cyclic compound **124** (0.40g, 0.45mmol) was dissolved in 5 ml of anhydrous THF and a solution of TBAF (1.4ml, 1.4mmol, 1M in THF) was added at 0 ^{o}C under an atmosphere of N_2. The solution was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10%, 20%, and 30% ethyl acetate/petroleum ether to afford the primary alcohol **125** (0.34g, 95% yield) as yellow oil.

M/S: m/z 799 (M^++NH_4^+) (*calcd*: for $C_{47}H_{59}NO_9$, 781). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.23 (m, 20H, Ph), 4.74-4.49 (m, 8H, CH_2Ph), 4.13-4.11 (br s, 1H), 3.93-3.83 (m, 5H), 3.82-3.62 (m, 4H), 3.62-3.53 (br s, 1H), 1.79 (br s, 2H), 1.67 (br s, 2H), 1.55 (br s, 6H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.1, 138.9, 138.8, 138.7, 138.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 93.6, 93.0, 79.8, 77.9, 76.8, 76.5, 76.3, 74.9, 73.8, 73.6, 73.3, 72.3, 71.9, 69.1, 68.5, 61.1, 58.8, 28.7, 28.3, 27.6, 25.3, 24.3 and 23.9 (Note: Because the existence of two conformers of the cyclic amide, some peaks were doubled.)

***p*-Bromobenzoyl ester 126**:



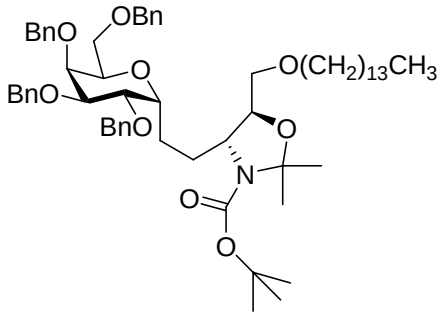
The primary alcohol **125** (0.33g, 0.42mmol) was dissolved in 8ml of anhydrous CH_2Cl_2 solution at 0^{o}C under an atmosphere of N_2. A solution of anhydrous pyridine (0.5ml) was added followed by addition of para-bromobenzoyl chloride (0.18g, 0.84mmol). The solution was stirred at room temperature for 2 hours. The solution was washed with 20ml *satd*. NH_4Cl solution and was extracted with CH_2Cl_2 (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10% and 20% ethyl acetate/petroleum ether to afford benzoyl ester **126** (0.34g, 82% yield) as yellow oil.

M/S: m/z 981 (M^++NH_4^+) (*calcd*: for $C_{54}H_{62}BrNO_{10}$, 963). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.88-7.86 (d, *J*=8.4 Hz, 2H), 7.52-7.51 (d, *J*=8.4 Hz, 2H), 7.33-7.23 (m,

20H, Ph), 4.72-4.43 (m, 8H, -CH_2Ph), 4.31-4.30 (dd, *J*=11.2, 5.8 Hz, 2H, CH_2OCO), 4.17-4.16 (s, 1H, CHO), 4.02-3.90 (m, 4H), 3.73 (br s, 1H), 3.69-3.68 (br s, 1H), 3.65-3.62 (dd, *J*= 9.9, 4.8 Hz, Hz, 1H), 1.96-1.91 (m, 1H), 1.73-1.54 (br s, 5H), 1.53-1.49 (br s, 4H), 1.49-1.42 (m, 9H, C(CH_3)$_3$).

^{13}C-NMR (125MHz, $CDCl_3$): δ 165.6, 152.6, 152.0(amide CO), 138.8, 138.6, 138.2, 131.9, 131.5, 128.9, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 126.8, 126.5, 93.9, 93.3 (OC(CH_3)$_2$N), 80.3, 80.0, 77.9, 76.6, 76.4, 74.9, 74.3, 73.8, 73.581, 73.2, 72.2, 71.9, 68.6, 68.5, 63.1, 58.8, 28.6, 28.2, 27.7, 27.6, 27.3, 25.4, 24.2, 23.9.

Ether 145:

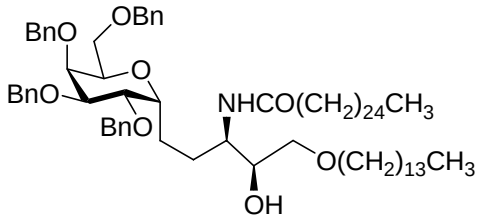


The primary alcohol **119** (0.40g, 0.494 mmol) was dissolved in 8ml of anhydrous THF and was cooled to 0^{o}C under an atmosphere of N_2. NaH (0.07g, 1.56mmol, 60% in mineral oil) was added slowly to the solution and was stirred for 30minutes. TBAI (0.02g, 0.051mmol) was added followed by addition of $C_{14}H_{29}Br$ (0.41ml, 1.69mmol). The mixture was stirred at room temperature for 18 hours. The solution was cooled back to 0^{o}C and 2ml of MeOH was added dropwise to quench the reaction. The mixture was washed with 20ml of *satd.* NH_4Cl solution and was extracted with ethyl acetate (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous),

filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% and 20% ethyl acetate/petroleum ether to afford the ether **145** (0.46g, 90% yield) as yellow oil.

M/S: m/z 995 (M^++NH_4^+) (*calcd*: for $C_{61}H_{87}NO$, 977). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.31-7.22 (m, 20H), 4.72-4.46 (m, 8H), 4.01-3.96 (m, 3H), 3.96-3.89 (m, 1H), 3.85-3.76 (m, 2H), 3.73-3.69 (m, 2H), 3.67-3.61 (m, 1H), 3.46-3.39 (m, 4H), 1.62-1.58 (m, 3H), 1.62-1.53 (m and s, 4H), 1.48 (s, 3H), 1.44 (s, 9H), 1.29-1.22 (m and s, 24H), and 0.85 (m, 3H, CH_3).

Amide 146:



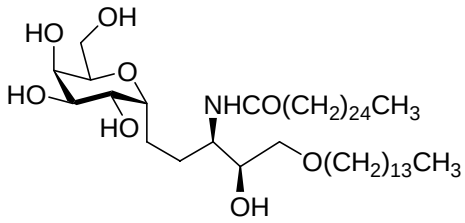
The ether **145** (0.40g, 0.42mmol) was dissolved in a solution of 5ml THF/MeOH solution (1:1). A solution of HCl (5ml, 20mmol, 4N in 1, 4 dioxane) was added and the mixture was stirred at room temperature overnight. The solution was concentrated to dryness under reduced pressure. The oil product was redissolved in 5ml THF and was neutralized with 10ml of *satd*. NH_3 solution. The mixture was extracted with diethyl ether (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude free amine was coevaporated with anhydrous toluene three times and was put under full high vacuum pump for 1 hour to afford 0.44g of the crude amine intermediate as yellow oil.

The crude amine was redissolved in 10ml anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.35g, 0.68mmol) and DMAP (0.14g, 0.63mmol) were added. The solution was stirred at room temperature under N_2 for 24 hours. The solvent was evaporated to dryness under reduced pressure. The solid was redissolved in 5ml CH_2Cl_2. 2g celite 545 was added and the solvent was removed under reduced pressure. The resulting solid was loaded to the top of a column. Flash chromatography purification using 30% and 40% ethyl acetate/petroleum ether afforded the amide **146** (0.35g, 70% yield for two steps) as pale yellow solid.

M/S: m/z 1233 (M^++NH_4^+) (*calcd*: for $C_{79}H_{125}NO_8$, 1215). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.32-7.22 (m, 20H), 5.71 (d, *J*=9.2 Hz, 1H, NH), 4.74-4.43 (m, 8H), 4.13-3.82 (m, 5H), 3.79-3.71 (m, 2H), 3.71--3.66 (dd, *J*=7.0, 2.5 Hz, 1H), 3.68-3.58 (dd, *J*=10.4, 4.1 Hz, 1H), 3.48-3.36 (m, 3H, OCH_2), 3.22 (t, J=9.3 Hz, 1H), 2.09 (t, *J*=7.5 Hz, 2H), 1.78-1.64 (m, 3H), 1.62-1.48 (m, 6H), 1.42-1.08 (m, 66H) and 0.88 (t, *J*=6.9 Hz, 6H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 173.3, 138.9, 138.7, 138.6, 138.588, 128.5, 128.48, 128.2, 128.1, 127.9, 127.88, 127.79, 127.77, 127.72, 77.1, 74.7, 73.5, 73.4, 73.3, 73.2, 72.9, 71.89, 71.8, 70.8, 49.8, 37.1, 32.1, 29.93, 29.92, 29.87, 29.79, 29.73, 29.62, 29.6, 28.8, 26.35, 26.34, 26.1, 22.9 and 14.3.

Ether C-glycoside analogue 147:

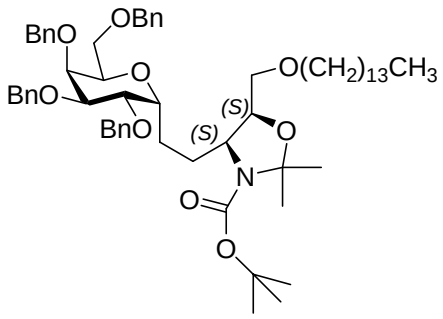


The amide **146** (0.15g, 0.12mmol) was dissolved in 10ml of a mixed solvent of THF (anhydrous) and EtOH (1:1). $Pd(OH)_2/C$ (0.16g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. The solution was filtered through a pad of celite, which was washed with 50ml of 50% $CHCl_3$/MeOH solution followed by 50ml of pyridine. The solvent was removed *in vacuo* and the solid was redissolved in 2ml of pyridine and 1g of celite was added and the solvent was removed *in vacuo* until the celite powder could flow freely. The powder was put to the top of a column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the ether *C*-glycoside **147** (0.084g, 80%yield) as white solid.

Mp: 90-92^{o}C. M/S: m/z 856 (M^++H^+) (*calcd*: for $C_{51}H_{101}NO_8$, 855). ^{1}H NMR (500MHz, C_5D_5N): δ 8.01 (d, *J*=9.2 Hz, 1H, NH), 4.72-4.71 (m, 2H), 4.63 (br s, 2H), 4.64-4.55 (m, 2H), 4.49 (m, 1H), 4.41 (m, 1H), 4.34 (br s, 2H), 4.26 (m, 1H), 3.85 (d, *J*=5.9 Hz, 2H, CH_2O), 3.56-3.52 (m, 2H, OCH_2), 2.48 (t, *J*=7.4 Hz, 2H), 2.38 (m, 3H), 2.19 (m, 1H), 1.86(m, 2H), 1.65(m, 2H), 1.43-1.30 (m, 66H), and 0.90 (t, *J*=7.4 Hz, 6H).

^{13}C-NMR (125MHz, C_5D_5N): δ 173.7, 75.9, 74.9, 74.5, 72.7, 72.5, 72.1, 70.9, 70.8, 62.9, 51.7, 37.3, 32.5, 30.7, 30.4, 30.4, 30.4, 30.4, 30.3, 30.286 30.233 30.19, 30.02, 30.00, 29.65, 26.97, 23.33, 23.07 and 14.67.

Ether 148:

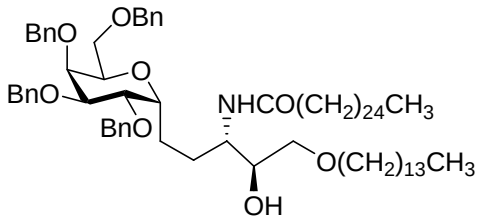


The primary alcohol **125** (0.44g, 0.51mmol) was dissolved in 8ml of anhydrous THF and was cooled to 0°C under an atmosphere of N_2. NaH (0.07g, 1.56mmol, 60% in mineral oil) was added slowly to the solution and was stirred for 30minutes. TBAI (0.02g, 0.051mmol) was added followed by addition of $C_{14}H_{29}Br$ (0.46ml, 1.69mmol). The mixture was stirred at room temperature for 18 hours. The solution was cooled back to 0°C and 2ml of MeOH was added dropwise to quench the reaction. The mixture was washed with 20ml of *satd.* NH_4Cl solution and was extracted with ethyl acetate (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% and 20% ethyl acetate/petroleum ether to afford the ether **148** (0.48g, 88% yield) as yellow oil.

M/S: m/z 995 (M^++NH_4^+) (*calcd*: for $C_{61}H_{87}NO$, 977). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.22 (m, 20H), 4.76-4.49 (m, 8H), 4.22 (m, 2H), 4.10-3.98 (m, 2H), 3.92-3.85 (m, 2H), 3.83-3.69 (m, 2H), 3.68-3.64 (m, 1H), 3.57-3.51 (m, 2H), 3.50-3.42 (m, 1H), 3.40-3.32 (m, 1H), 1.81-1.69 (m, 2H), 1.67-1.56 (m, 5H), 1.54-1.52 (m, 4H), 1.46 (br s, 6H), 1.44-1.37 (br s, 5H), 1.34-1.23 (s, 23H), 0.90 (t, 3H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 152.2, 138.9, 138.7, 138.5, 129.9, 129.8, 128.6, 128.5, 128.1, 127.93, 127.90, 127.8, 127.77, 127.7, 127.3, 127.1, 126.9, 93.6, 93.0, 80.0, 79.7, 76.7, 76.5, 75.9, 74.9, 74.7, 73.8, 73.6, 73.2, 72.1, 69.0, 68.8, 58.8, 58.6, 32.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 28.7, 27.6, 26.3, 25.3, 23.9, 22.9 and 14.3 (Note: Because the existence of two conformers of the cyclic amide, some peaks were doubled.)

Amide 149:



The ether **148** (0.44g, 0.45mmol) was dissolved in a solution of 5ml THF/MeOH solution (1:1). A solution of HCl (5ml, 20mmol, 4N in 1, 4 dioxane) was added and the mixture was stirred at room temperature overnight. The solution was concentrated to dryness under reduced pressure. The oil product was redissolved in 5ml THF and was neutralized with 10ml of *satd*. NH_3 solution. The mixture was extracted with diethyl ether (3x50ml). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude free amine was coevaporated with anhydrous toluene three times and was put under full high vacuum pump for 1 hour to afford 0.44g of the crude amine intermediate as yellow oil.

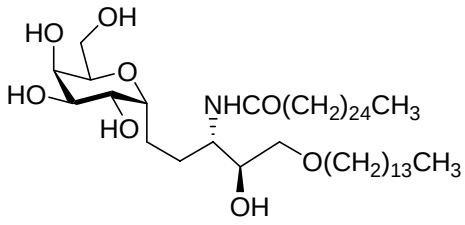
The crude amine was redissolved in 10ml anhydrous THF. The activated ester $C_{25}H_{51}COOPhNO_2$ (0.35g, 0.68mmol) and DMAP (0.15g, 0.68mmol) were added. The solution was stirred at room temperature under N_2 for 24 hours. The solvent was

evaporated to dryness under reduced pressure. The solid was redissolved in 5ml CH_2Cl_2. 2g celite 545 was added and the solvent was removed under reduced pressure. The resulting solid was loaded to the top of a column. Flash chromatography purification using 30% and 40% ethyl acetate/petroleum ether afforded the amide **149** (0.42g, 77% yield for two steps) as pale yellow solid.

M/S: m/z 1216 (M^++H^+) (*calcd*: for $C_{79}H_{125}NO_8$, 1215). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.32-7.24 (m, 20H), 6.22 (d, *J*=8.4 Hz, 1H), 4.78-4.49 (m, 8H), 4.02-3.92 (m, 4H), 3.88-3.82 (m, 2H), 3.76-3.73 (m, 1H), 3.71 (dd, *J*=2.6, 7.6 Hz, 1H), 3.66 (dd, *J*=3.7, 10.4 Hz, 1H), 3.48-3.37 (m, 4H), 3.29 (d, *J*=2.1 Hz, 1H), 2.09 (t, *J*=15.3 Hz, 2H), 1.73-1.53 (m, 10H), 1.42-1.17 (m, 66H), and 0.91 (t, *J*=6.6 Hz, 6H).

^{13}C-NMR (125MHz, $CDCl_3$): δ 174.2, 138.8, 138.7, 138.6, 138.294, 128.6, 128.59, 128.52, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.79, 127.73, 77.1, 74.9, 73.6, 73.5, 73.5, 73.4, 72.7, 72.5, 72.2, 71.9, 68.8, 53.0, 36.9, 32.1, 29.9, 29.9, 29.8, 29.79, 29.75, 29.6, 29.5, 27.0, 26.4, 25.9, 22.9 and 14.3.

Ether *C*-glycoside 150:



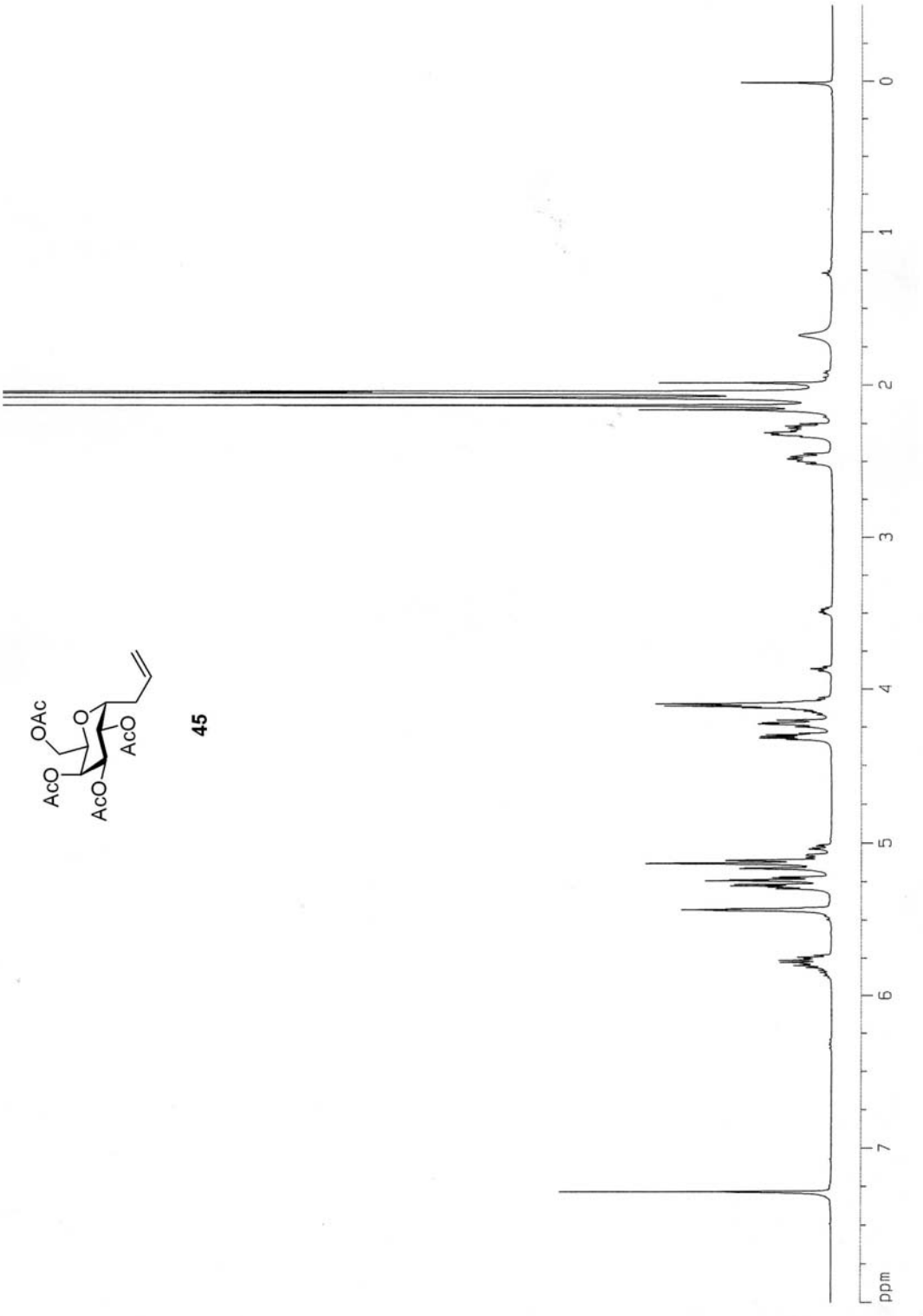
The amide **149** (0.11g, 0.091mmol) was dissolved in 10ml of a mixed solvent of THF (anhydrous) and EtOH (1:1). $Pd(OH)_2/C$ (0.16g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1atm) for 24 hours. The solution was filtered through a pad of celite, which was

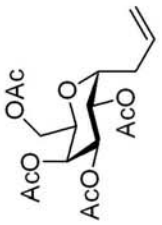
washed with 50ml of 50% $CHCl_3$/MeOH solution followed by 50ml of pyridine. The solvent was removed *in vacuo* and the solid was redissolved in 2ml of pyridine and 1g of celite was added and the solvent was removed *in vacuo* until the celite powder could flow freely. The powder was put to the top of a column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/$CHCl_3$ afforded the ether *C*-glycoside **150** (0.07g, 90%yield) as white solid.

M/S: m/z 873 (M^++NH_4^+) (*calcd*: for $C_{51}H_{101}NO_8$, 855). ^{1}H NMR (500MHz, C_5D_5N): δ 8.37 (d, *J*=8.8 Hz, 1H, NH), 6.63 (broad peak, 1H, OH), 6.51 (broad peak, 1H, OH), 6.35 (broad peak, 1H, OH), 6.17 (broad peak, 1H, OH), 4.74 (m, 2H), 4.62 (br s, 1H), 4.54-4.51 (m, 2H), 4.44-4.42 (m, 1H), 4.42-4.38 (m, 1H), 4.32-4.27 (m, 2H), 3.94(dd, *J*=9.9, 4.8 Hz, 1H), 3.90-3.87 (m, 1H), 3.55 (t, *J*=6.6 Hz, 2H, OCH_2), 2.57-2.49 (m, 2H), 2.48-2.45 (t, *J*=7.4 Hz, 2H), 2.34-2.28 (m, 1H), 2.13-2.1 (m, 1H), 1.89-1.84 (m, 2H), 1.68-1.62 (m, 2H), 1.41-1.29 (m, 66H, CH_2), 0.90 (t, *J*=6.8 Hz, 6H, CH_3).

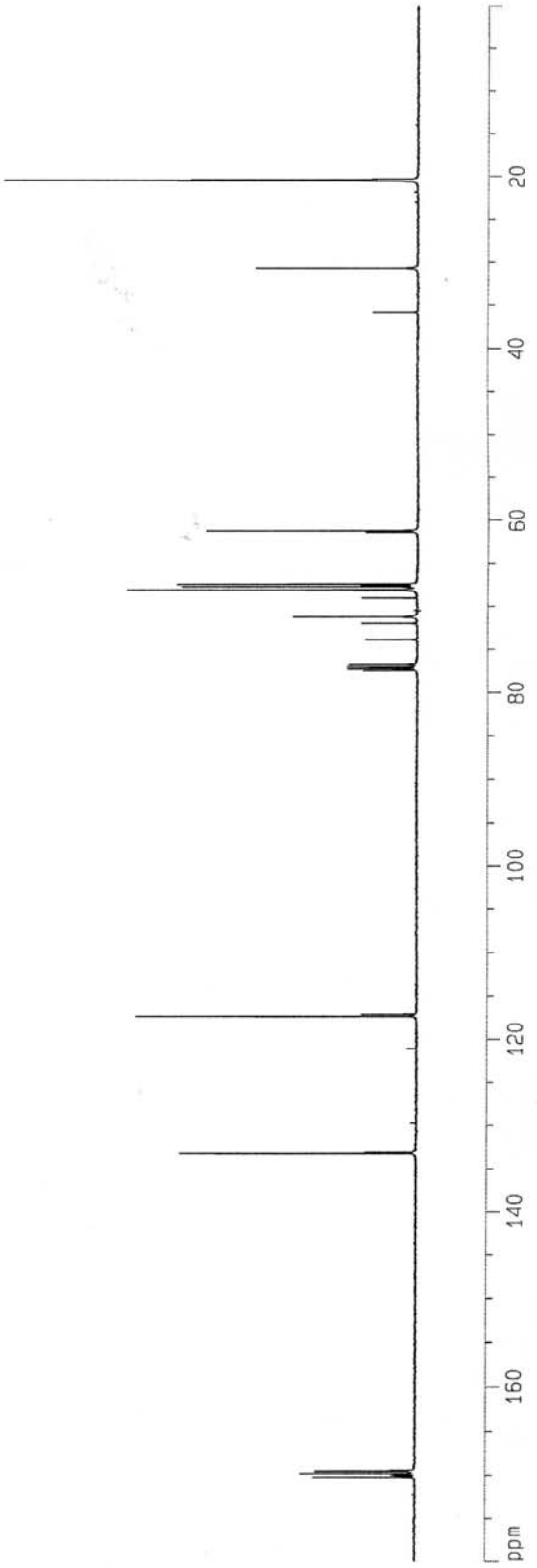
^{13}C-NMR (125MHz, C_5D_5N): δ 173.9, 77.2, 74.8, 74.3, 73.8, 72.6, 72.1, 70.8, 70.8, 62.9, 53.3, 37.3, 32.5, 30.6, 30.4, 30.4, 30.34, 30.30, 30.29, 30.26, 30.18, 30.16, 29.99, 29.97, 27.99, 26.95, 26.9, 23.3, 22.9 and 14.6.

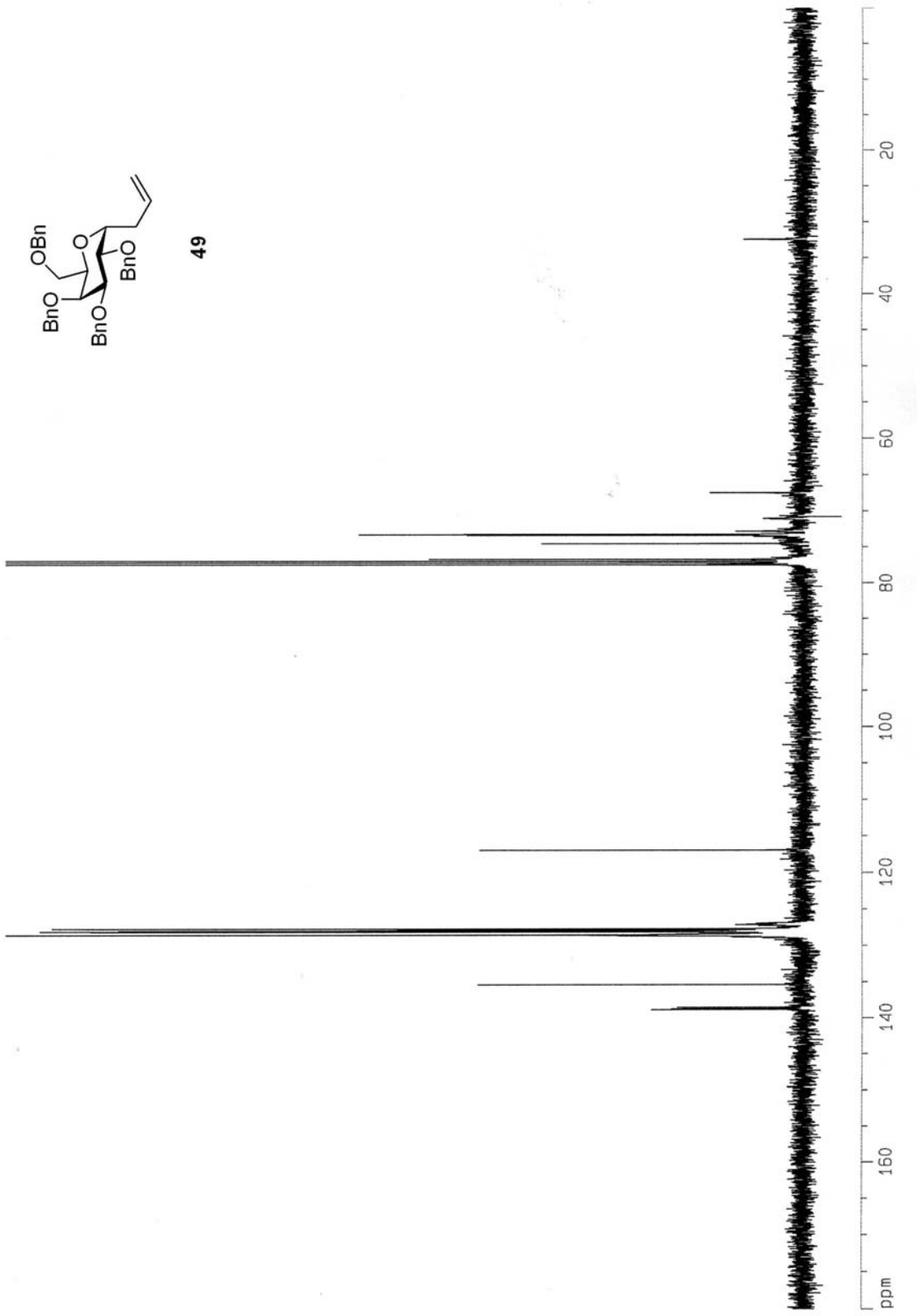
Chapter 4. Appendix

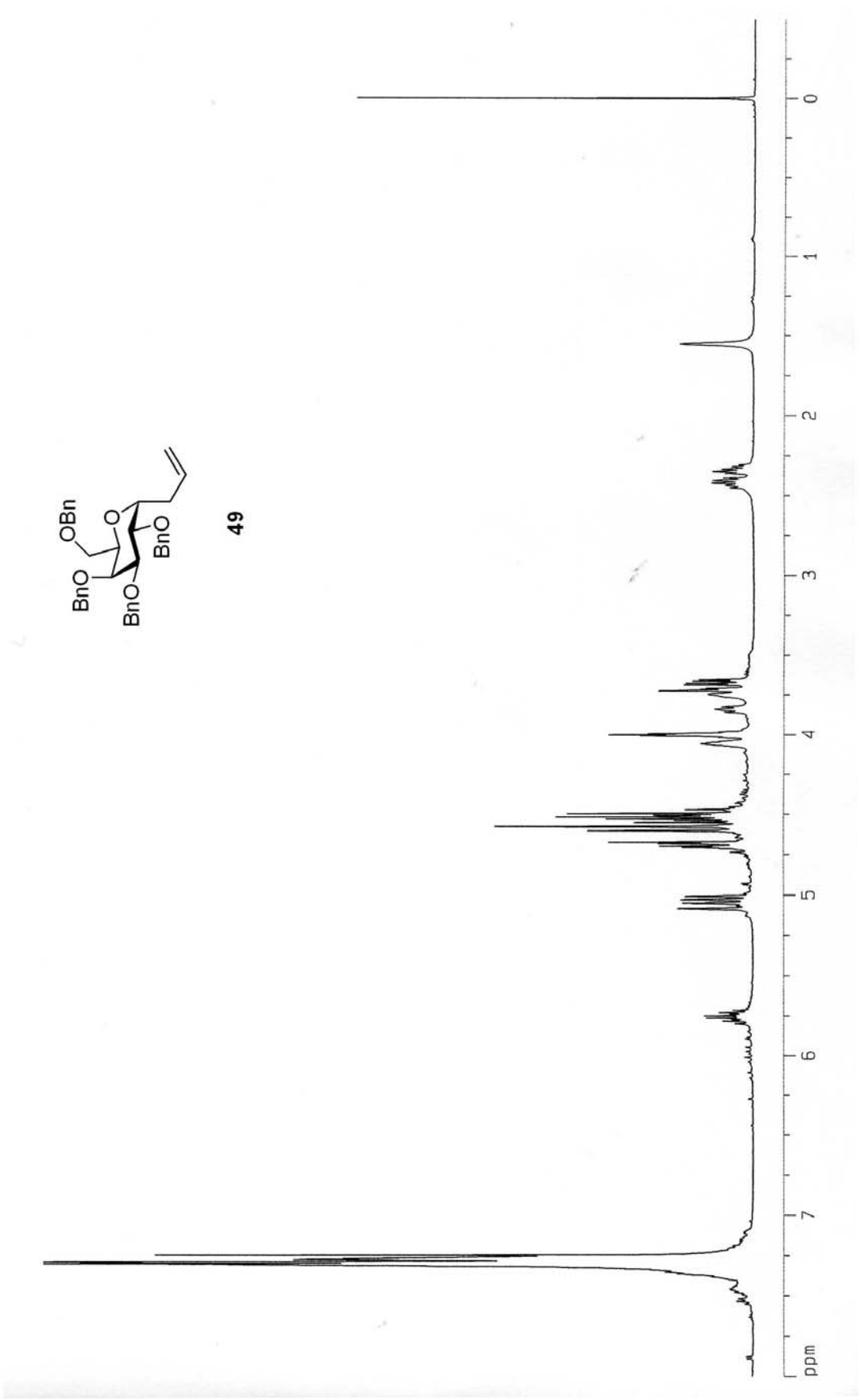

OAc
O
AcO
AcO
AcO
45
ppm
0
1
2
3
4
5
6
7

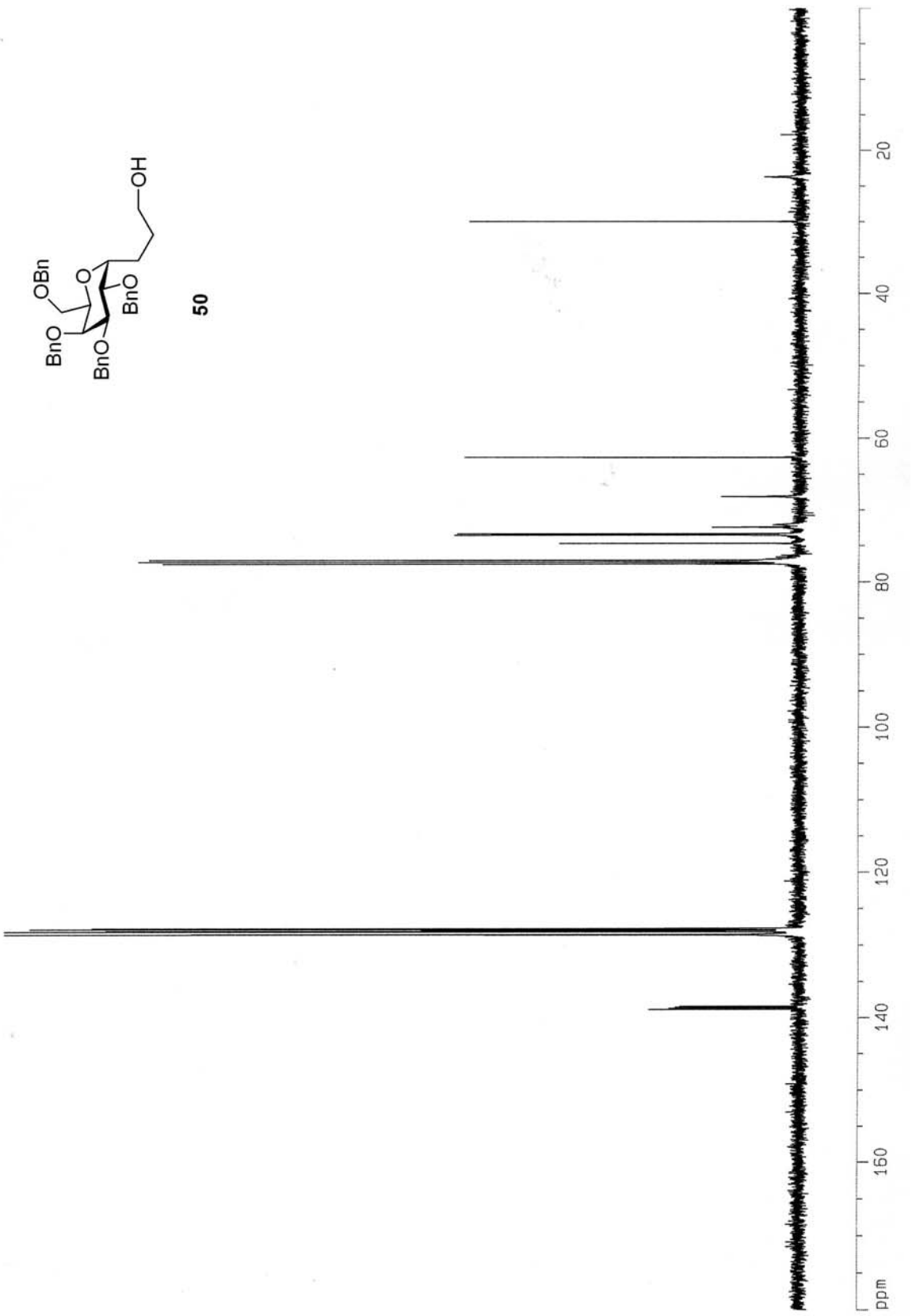


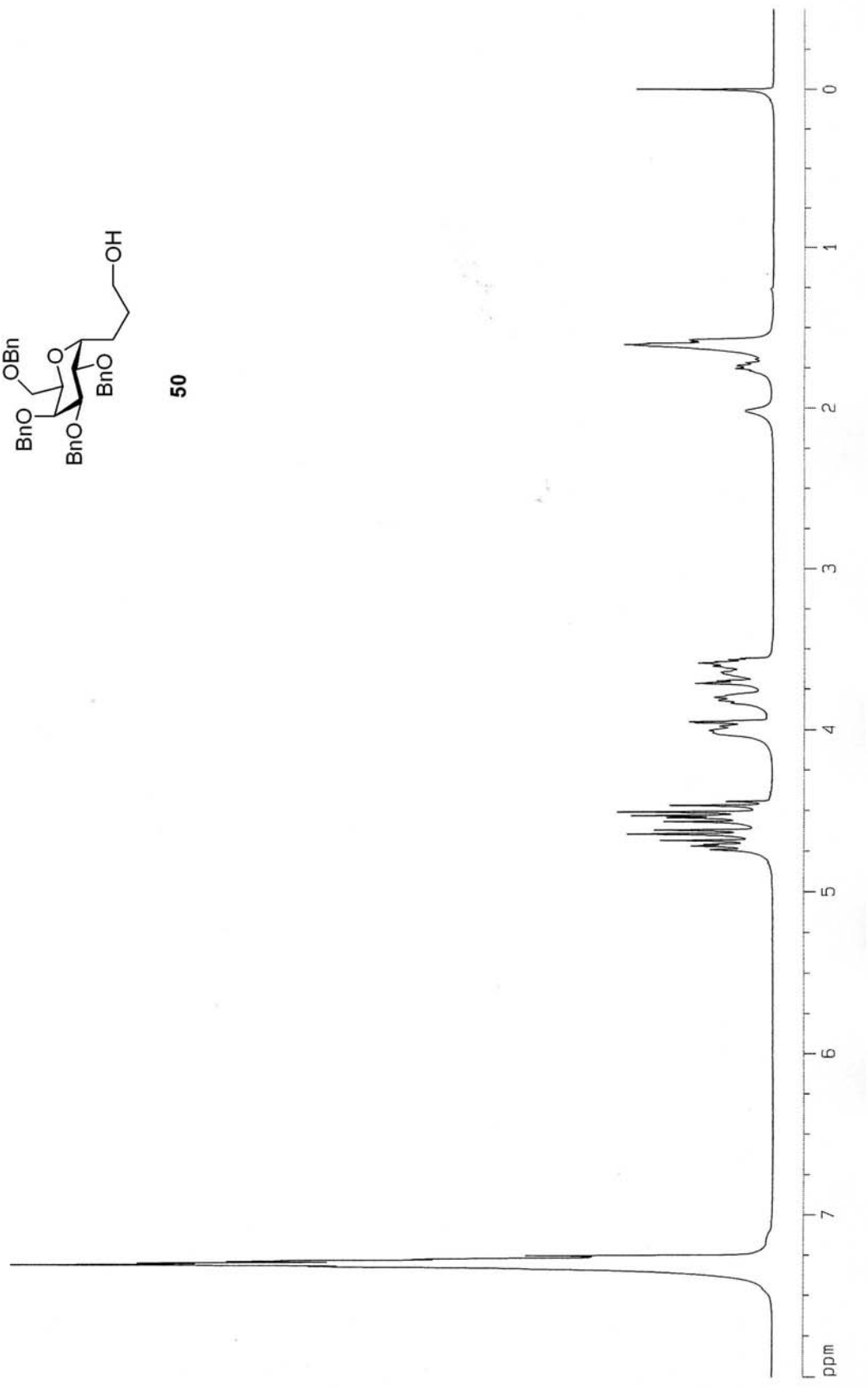
45



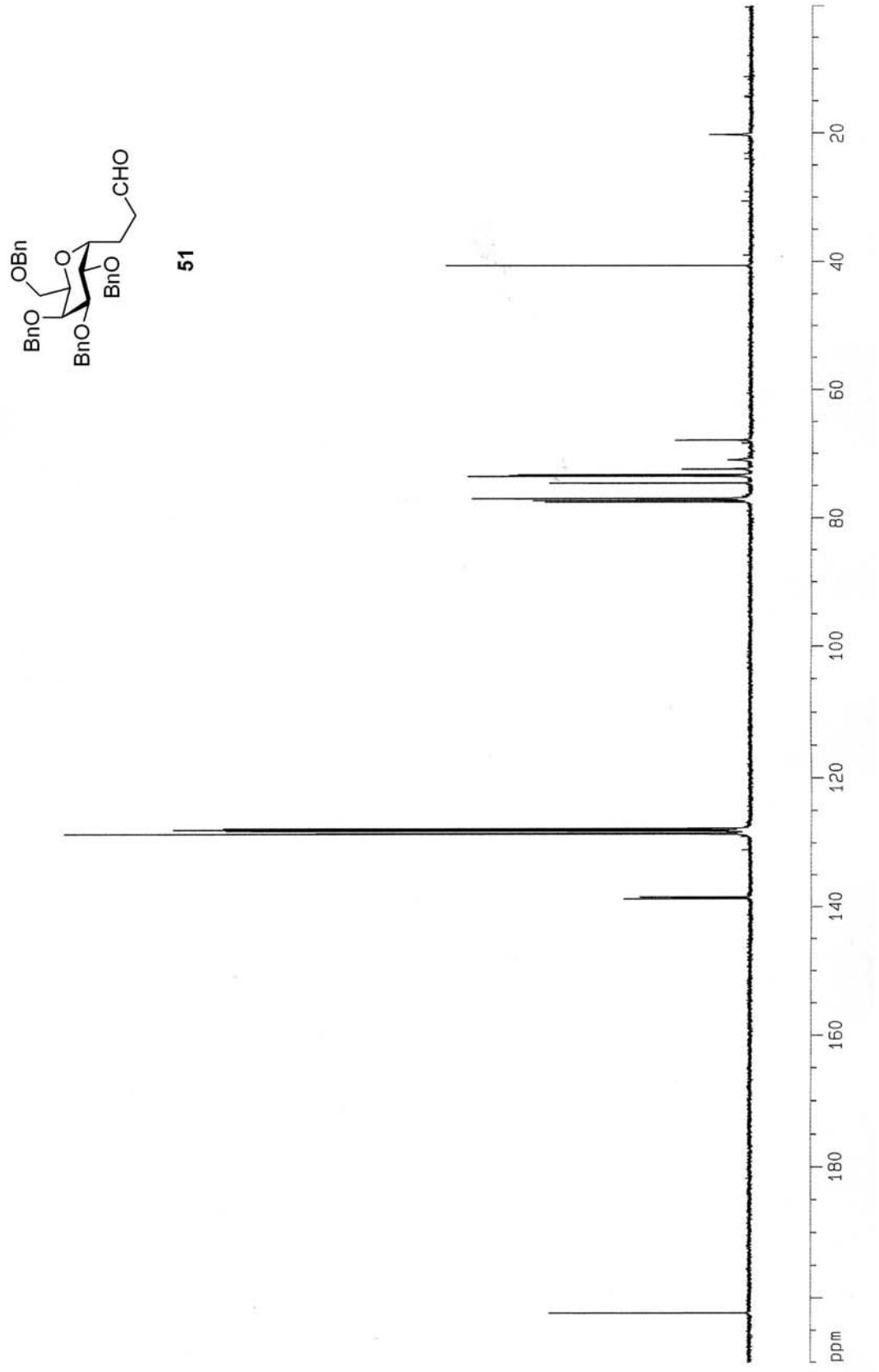

OBn
O
BnO
BnO
BnO
49
20
40
60
80
100
120
140
160
ppm

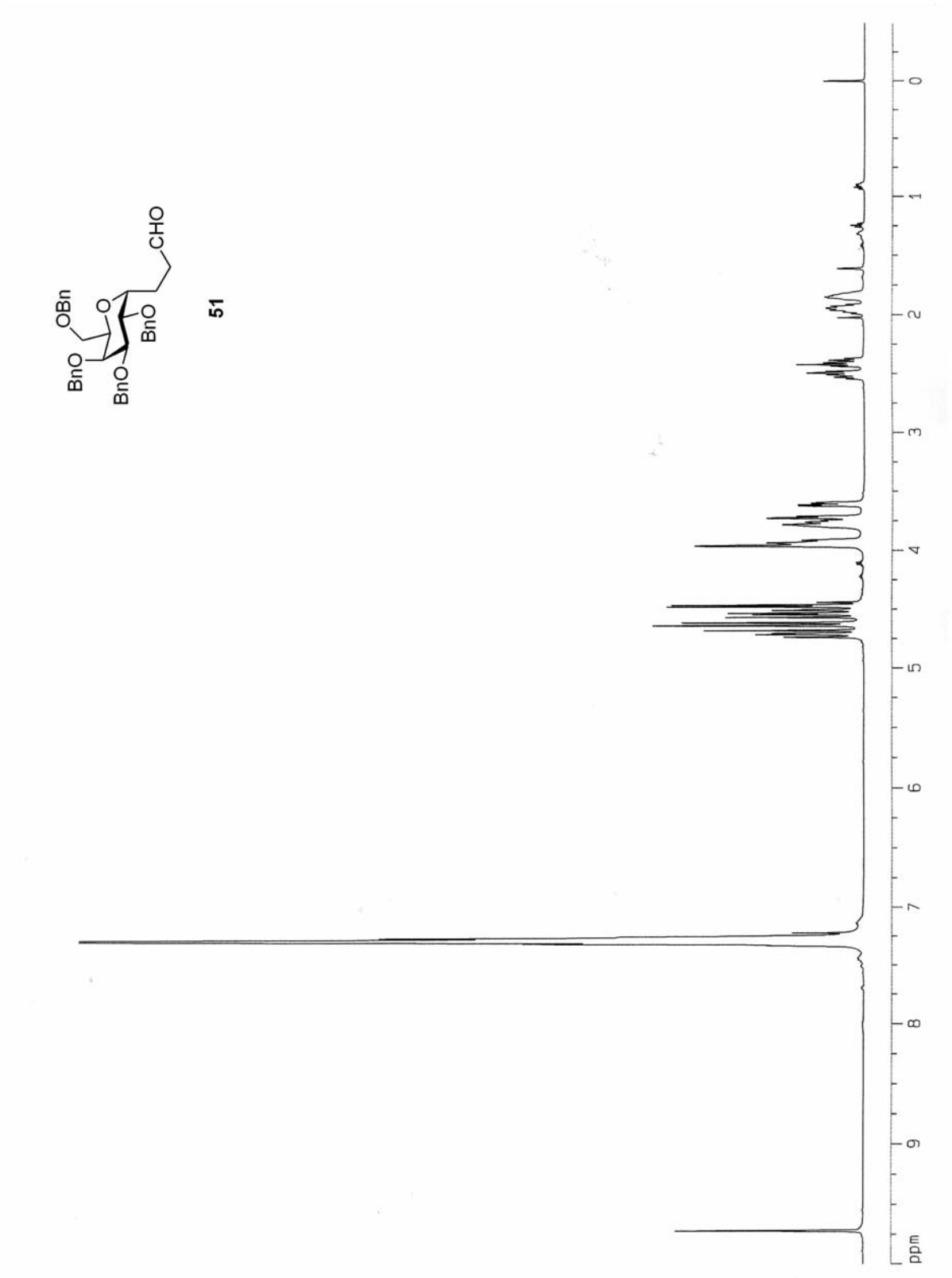

OBn
O
BnO
BnO
BnO
49
ppm
0
1
2
3
4
5
6
7

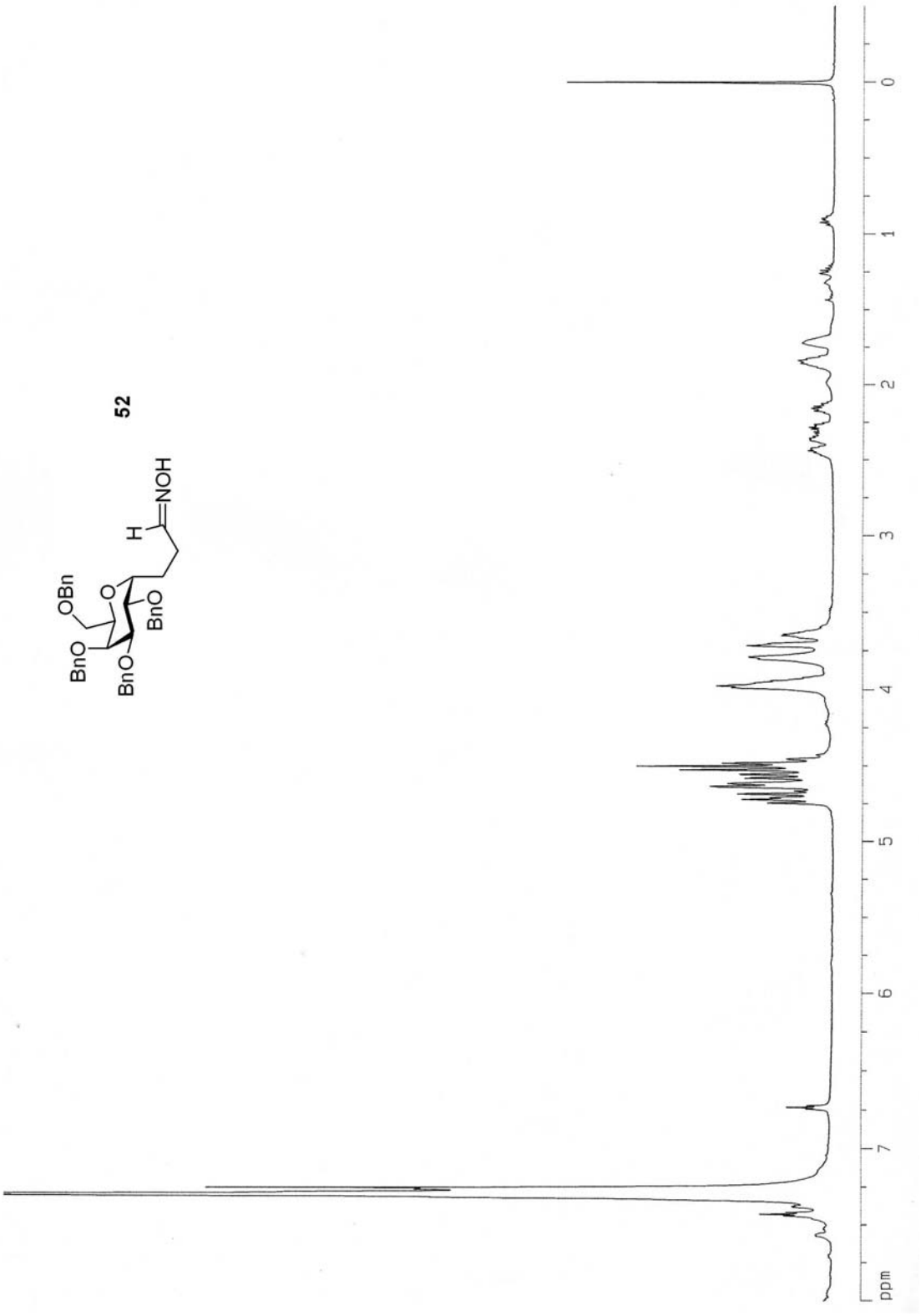

OBn
O
BnO
BnO
BnO
OH
50
ppm
20
40
60
80
100
120
140
160

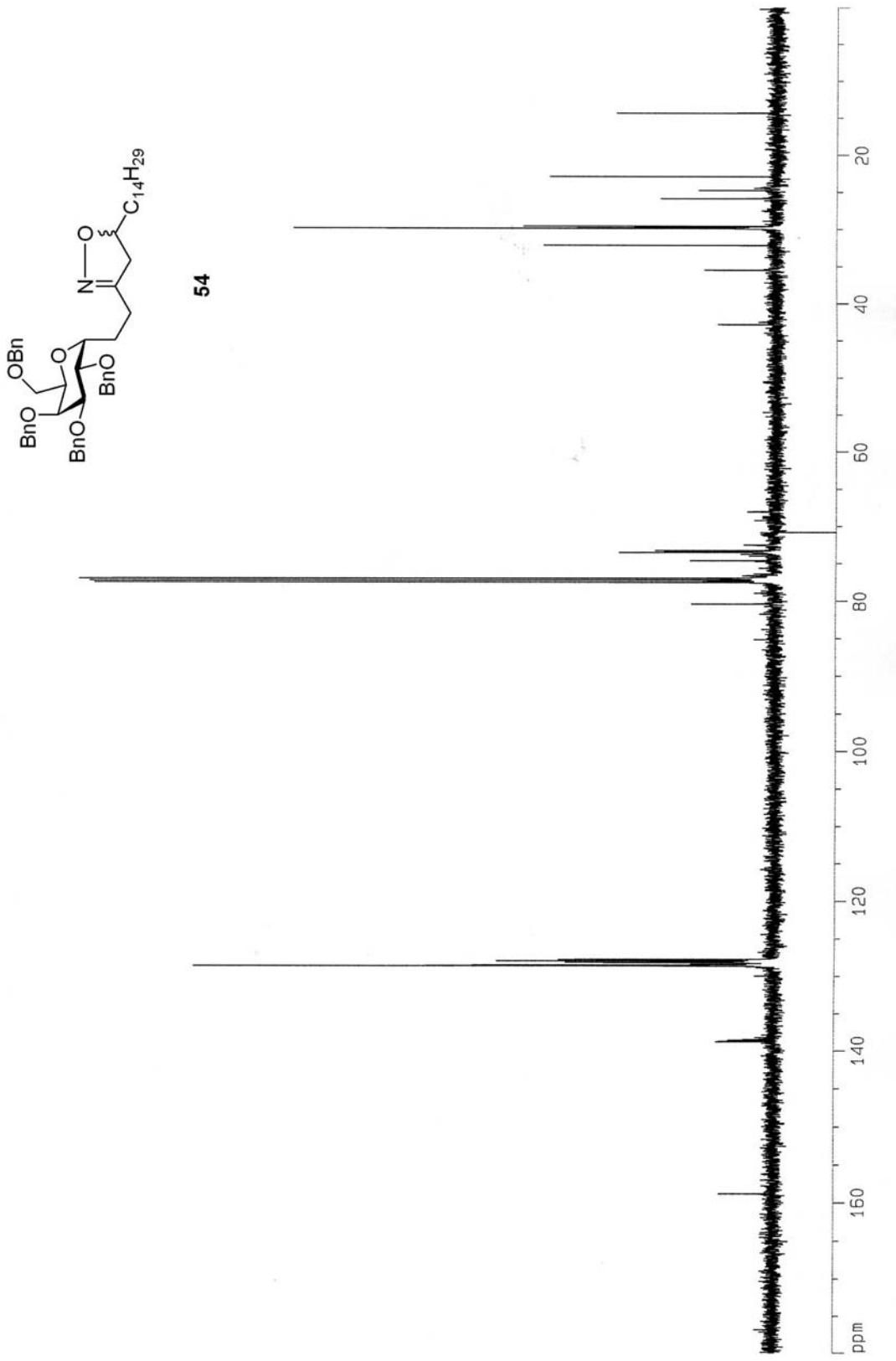


50

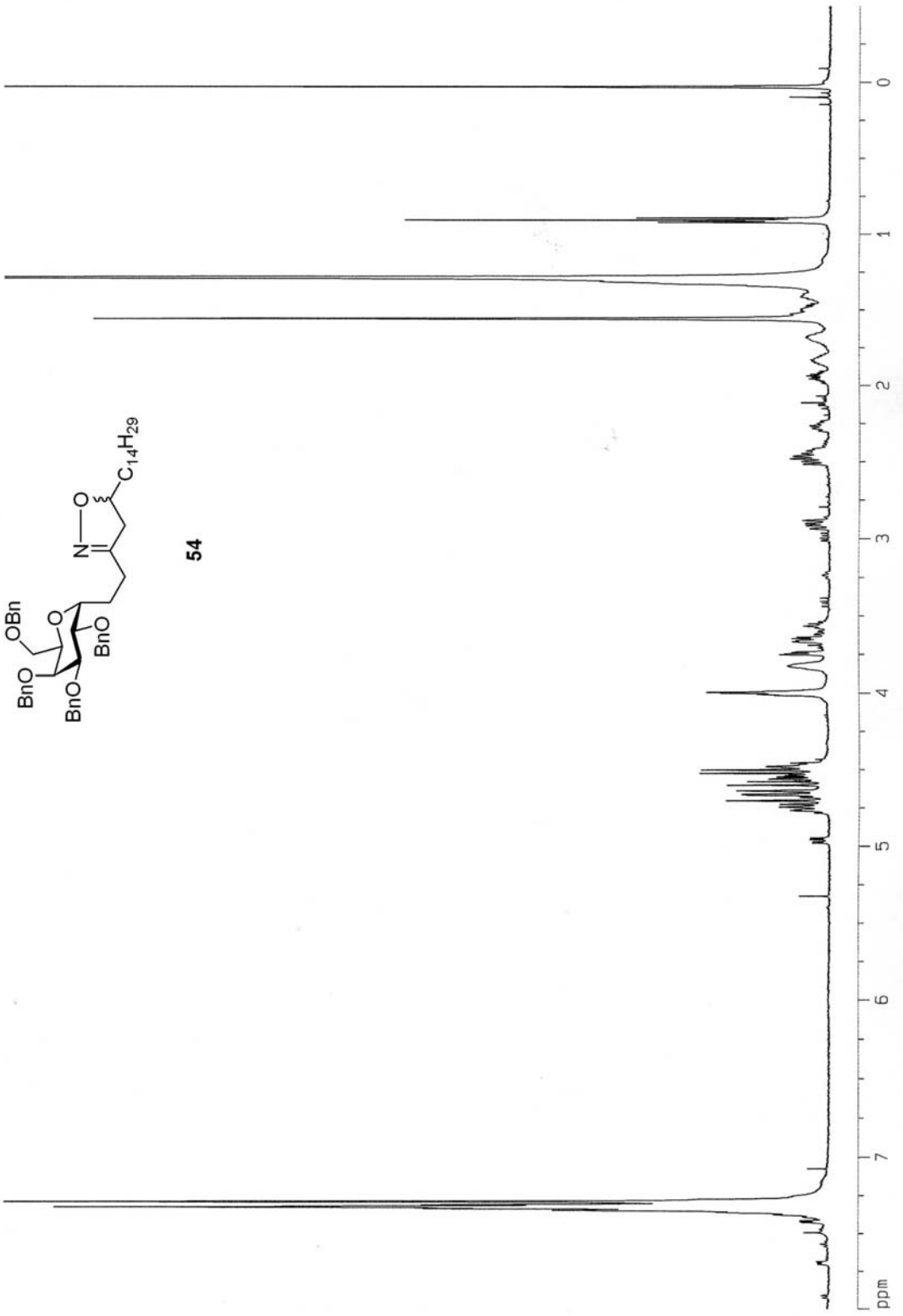

OBn
O
BnO
BnO
BnO
CHO
51
ppm
20
40
60
80
100
120
140
160
180

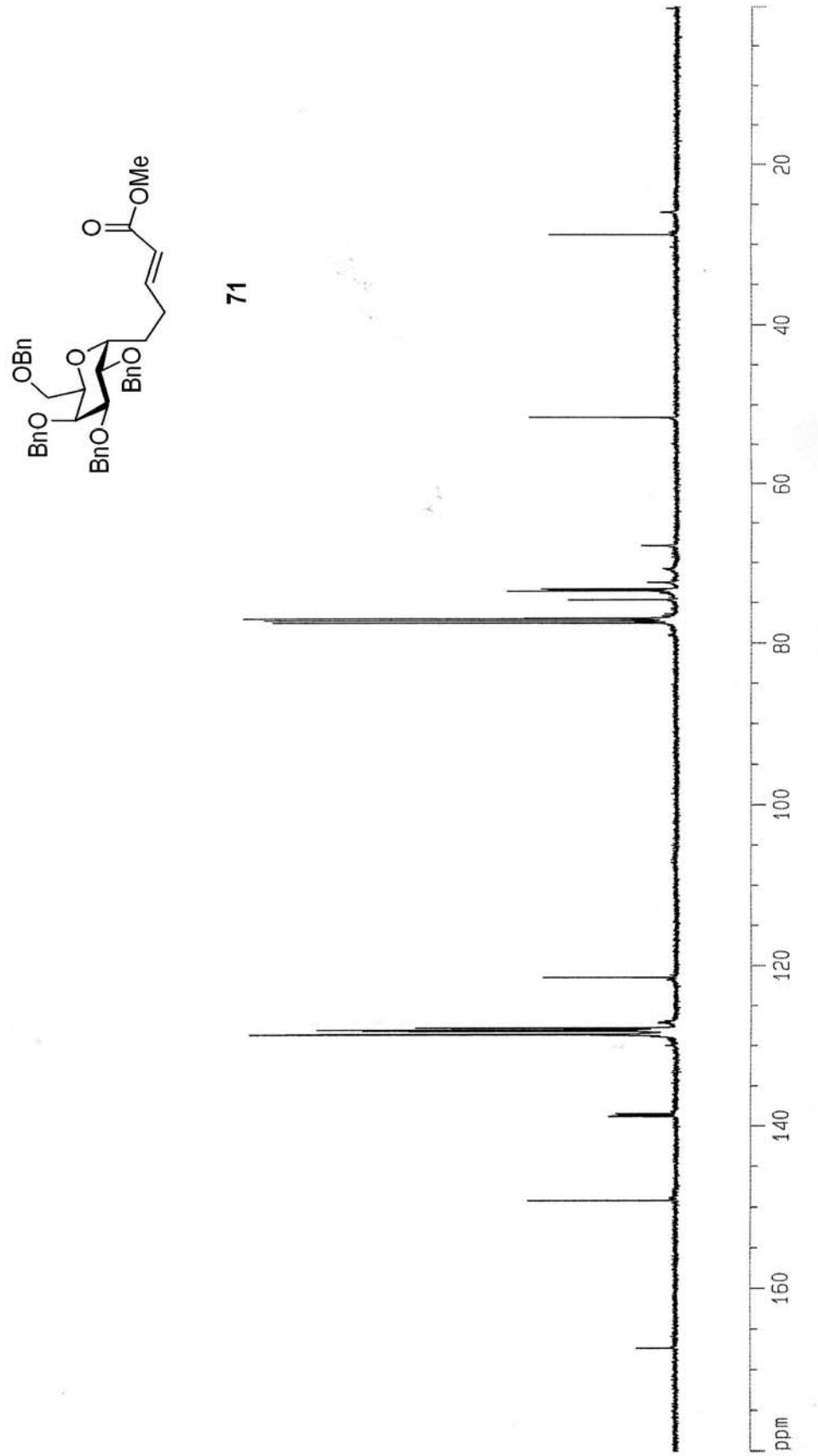

OBn
O
BnO
BnO
BnO
CHO
51
ppm
0
1
2
3
4
5
6
7
8
9

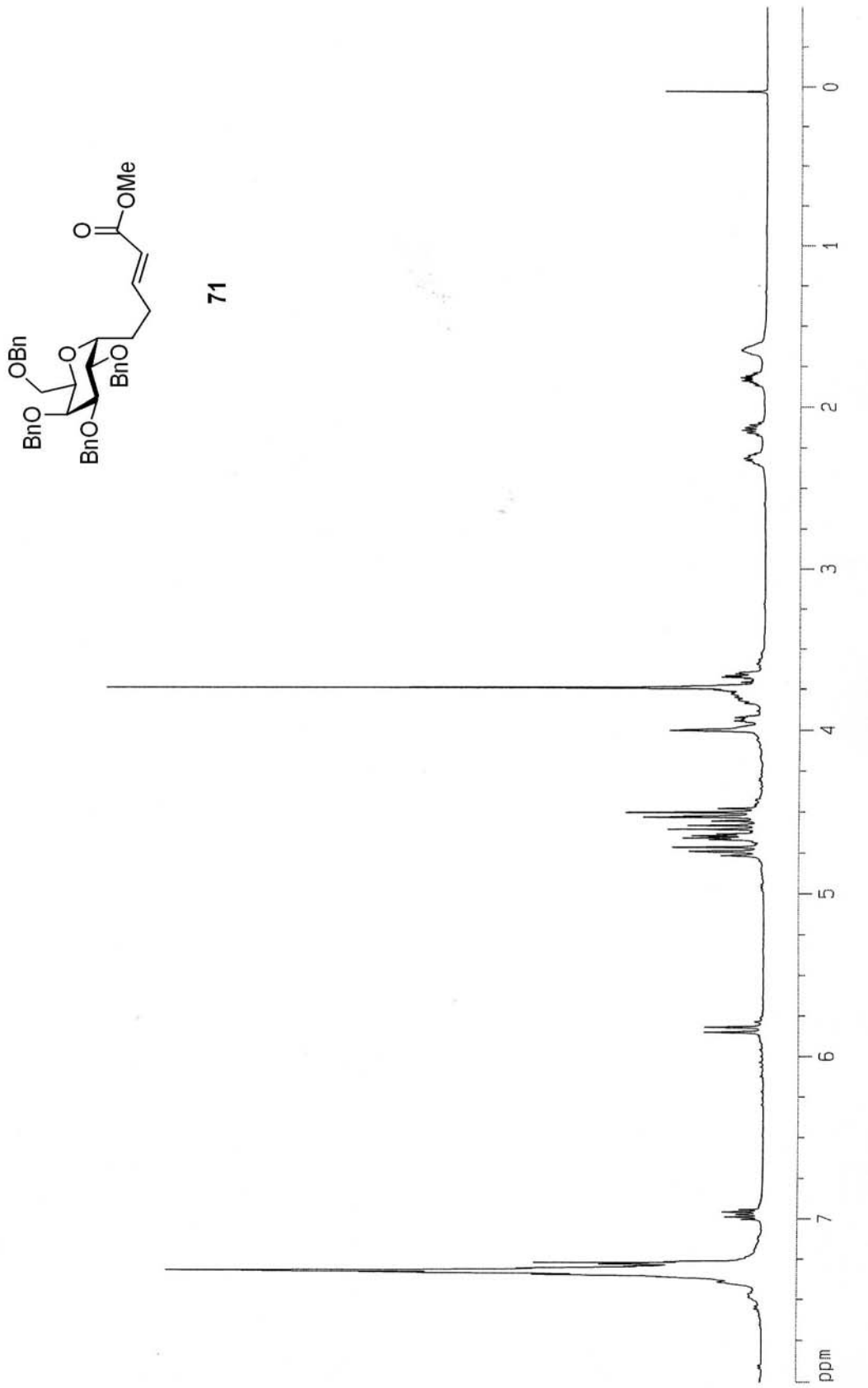

52
OBn
BnO
BnO
BnO
H
NOH
ppm
0
1
2
3
4
5
6
7

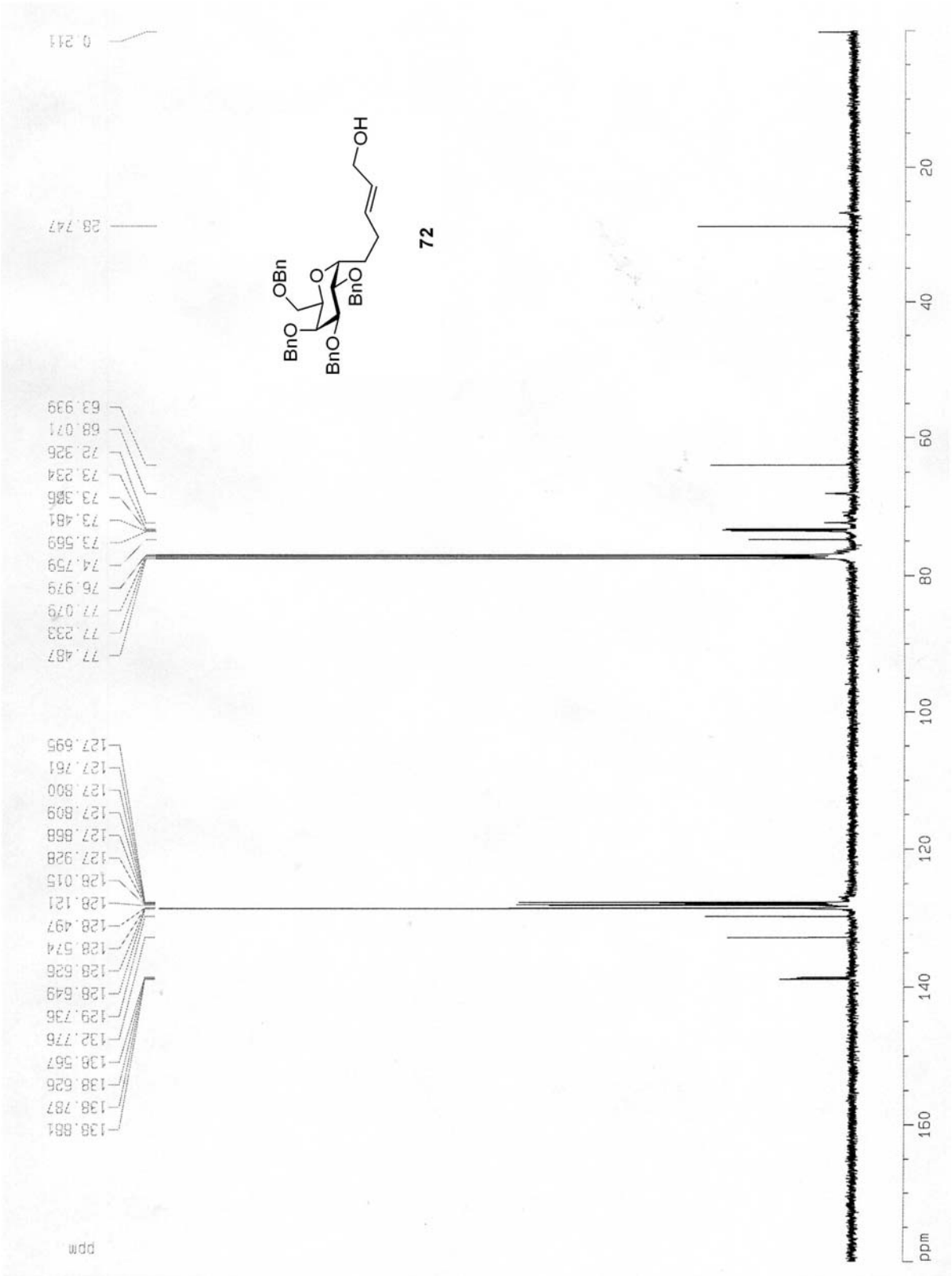


54


OBn
BnO
BnO
BnO
N
O
C14H29
54
ppm
0
1
2
3
4
5
6
7

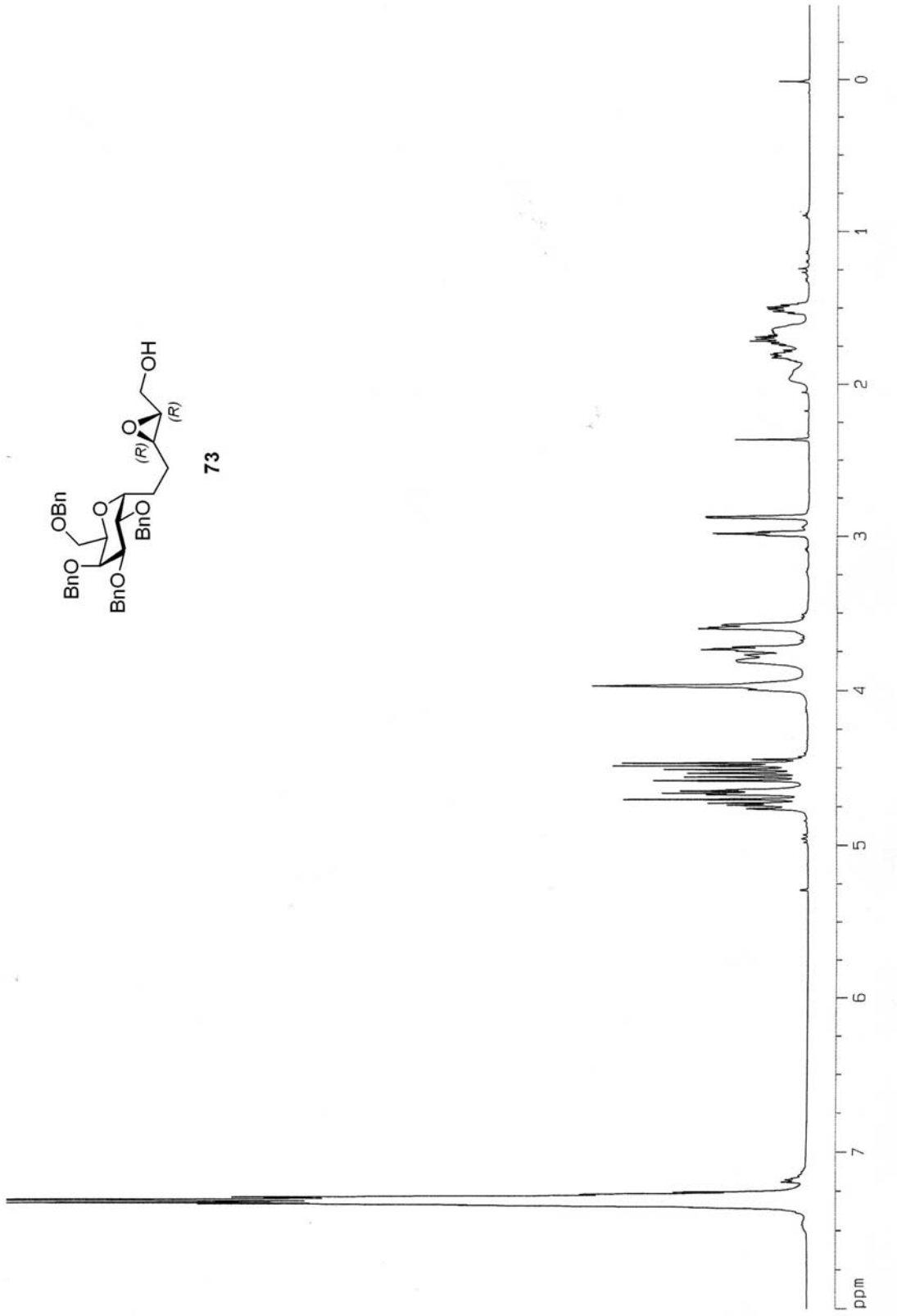

OMe
O
OBn
BnO
BnO
BnO
71
ppm
160
140
120
100
80
60
40
20

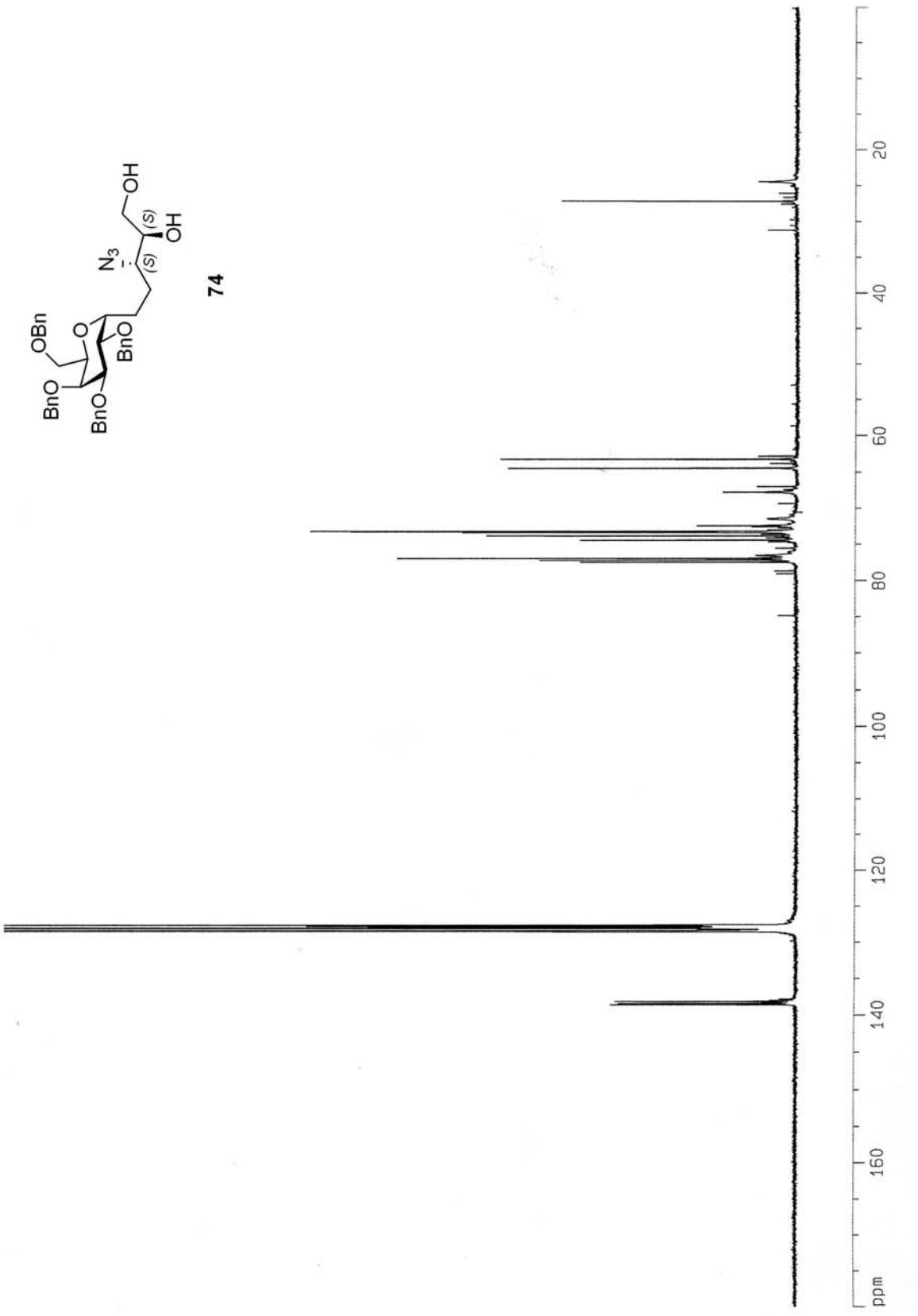

OBn
O
BnO
BnO
BnO
O
OMe
71
ppm
0
1
2
3
4
5
6
7

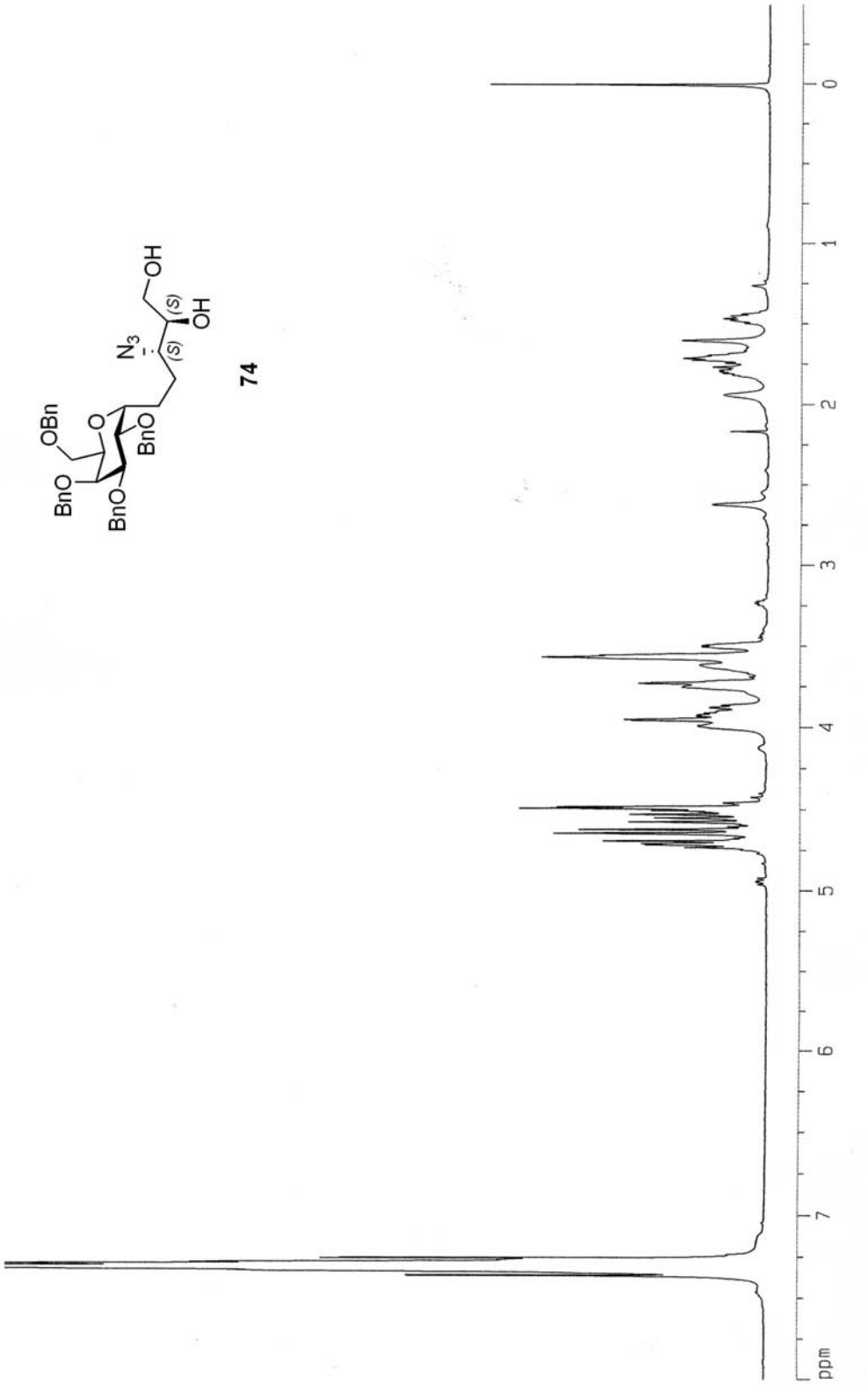

OH
BnO
BnO
BnO
OBn
O
72
0.211
28.747
63.939
68.071
72.326
73.234
73.386
73.481
73.569
74.759
76.979
77.079
77.233
77.487
127.695
127.761
127.800
127.809
127.868
127.928
128.015
128.121
128.497
128.574
128.626
128.649
129.736
132.776
138.567
138.626
138.787
138.861
ppm
20
40
60
80
100
120
140
160


OH
OBn
O
BnO
BnO
BnO
72
ppm
0
1
2
3
4
5
6
7

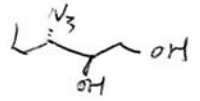

OBn
BnO
BnO
BnO
(R)
(R)
OH
73
ppm
20
40
60
80
100
120
140
160


OBn
BnO
BnO
BnO
O
(R)
(R)
O
OH
73
ppm
0
1
2
3
4
5
6
7


OBn
O
BnO
BnO
BnO
N3
(S)
(S)
OH
OH
74
ppm
20
40
60
80
100
120
140
160

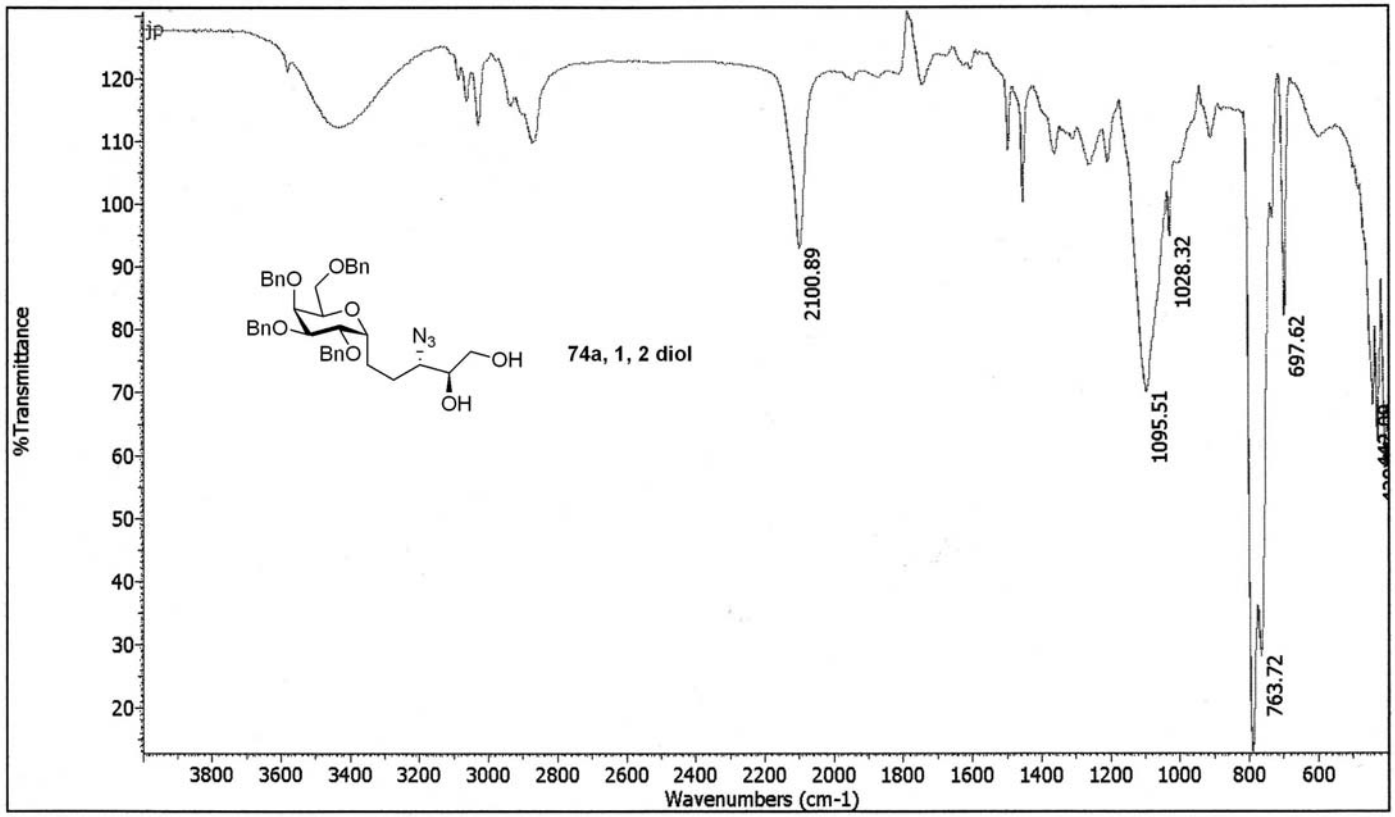

OBn
O
BnO
BnO
BnO
N3
(S)
(S)
OH
OH
74
ppm
0
1
2
3
4
5
6
7

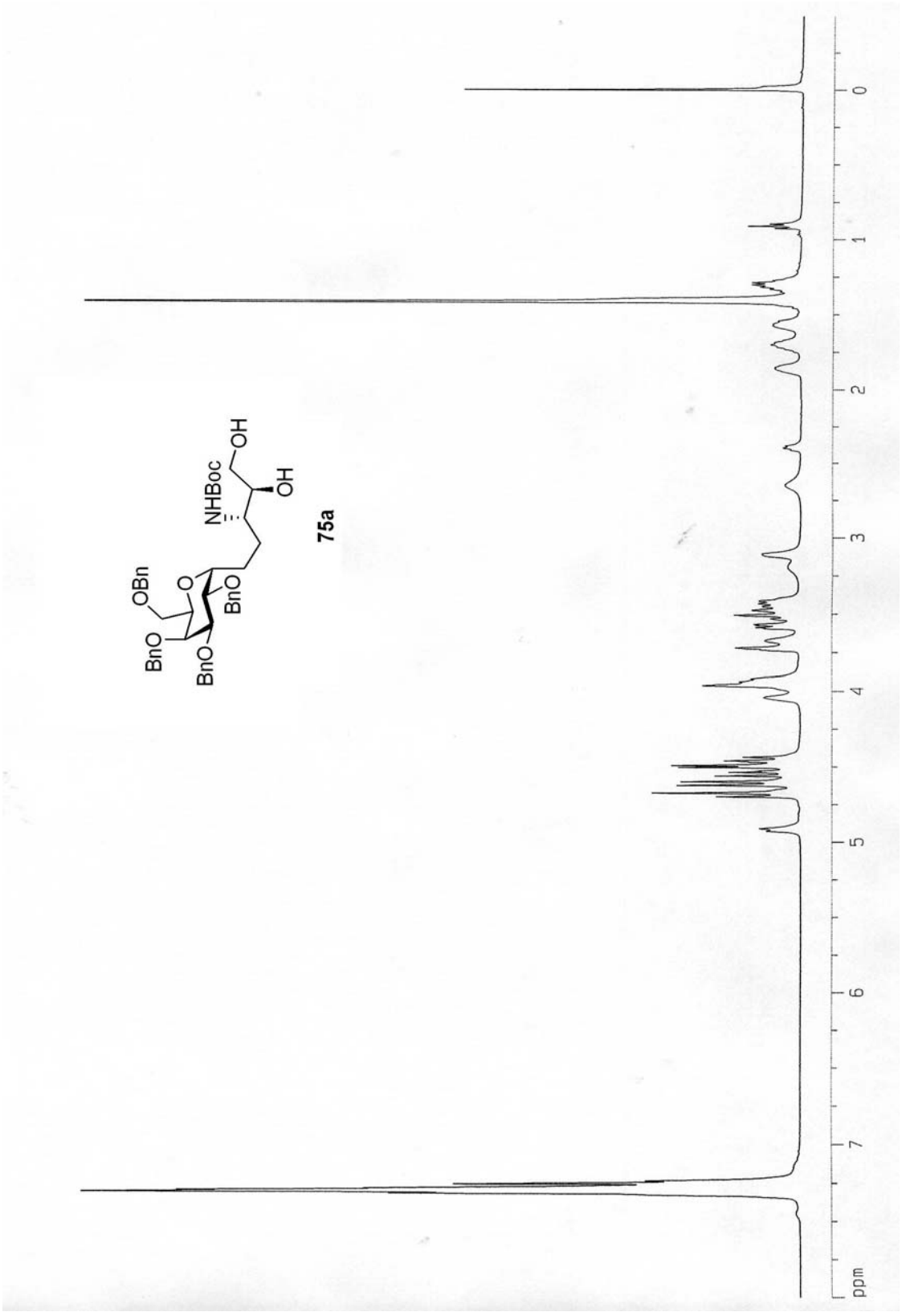
VII 55 NaN_3 opening epoxide

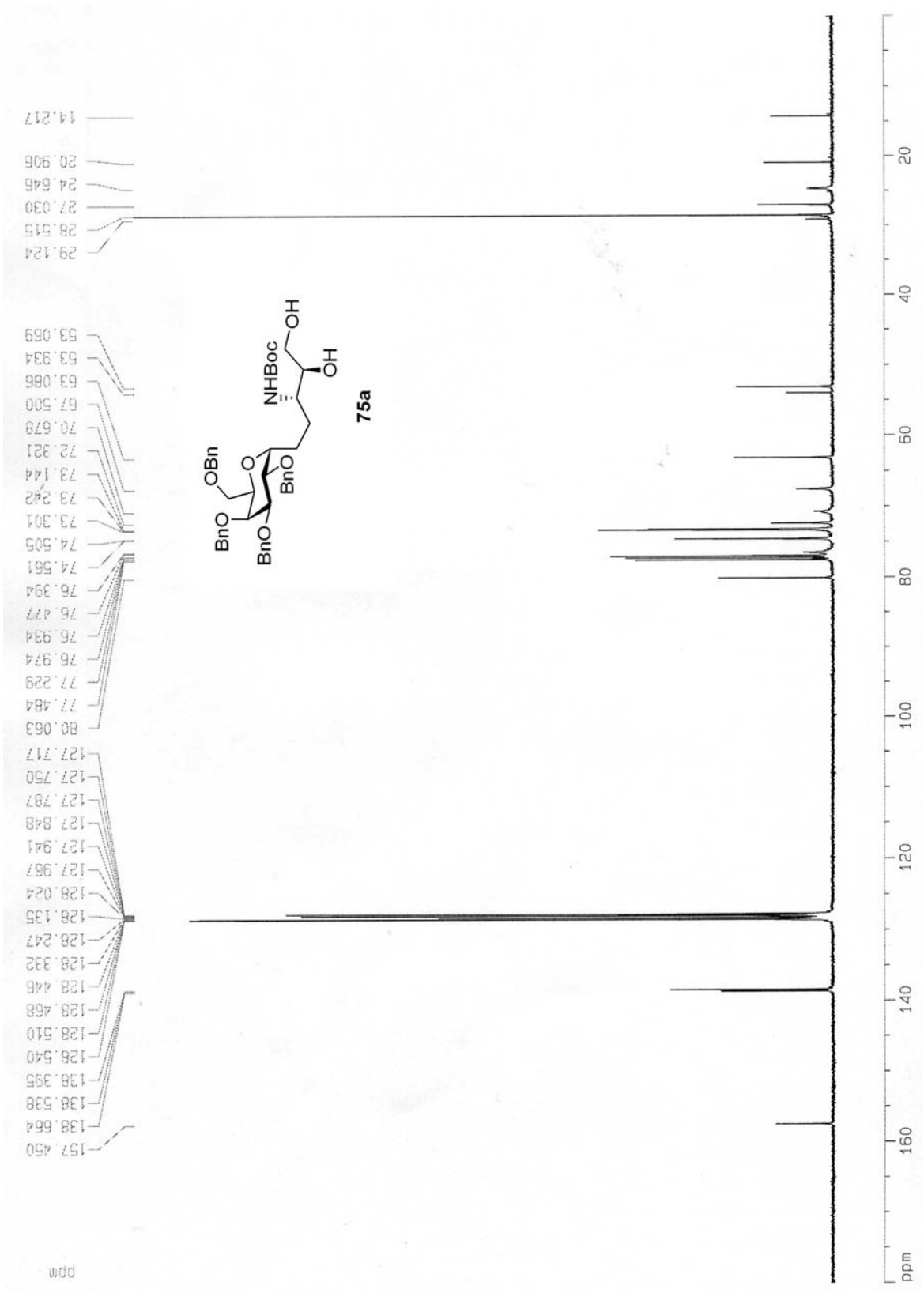


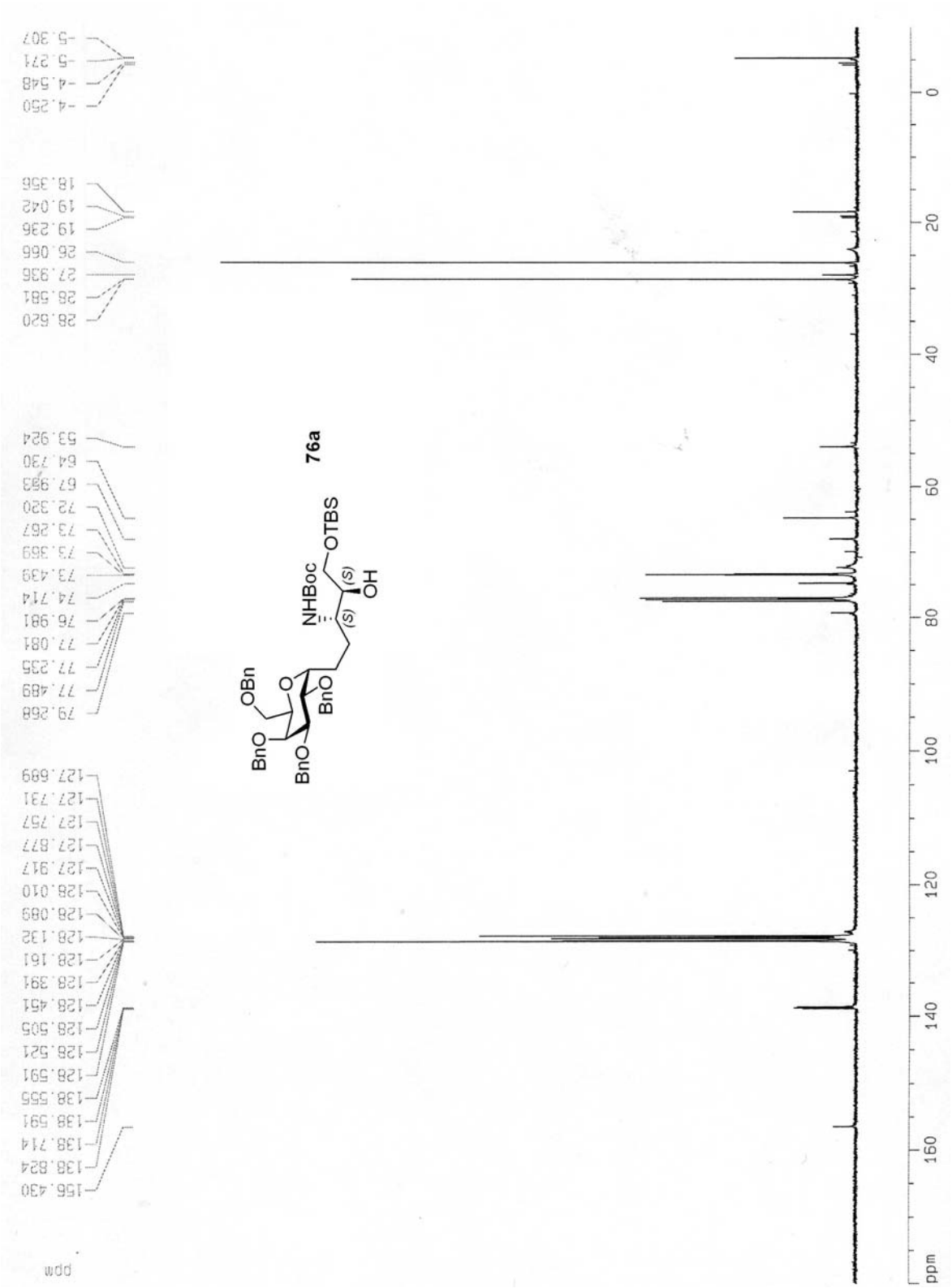
Peak finding results for: jp
Frequency: 400.00 - 4000.00, threshold: 99.422, sensitivity: 50.00
Peak finding result table:

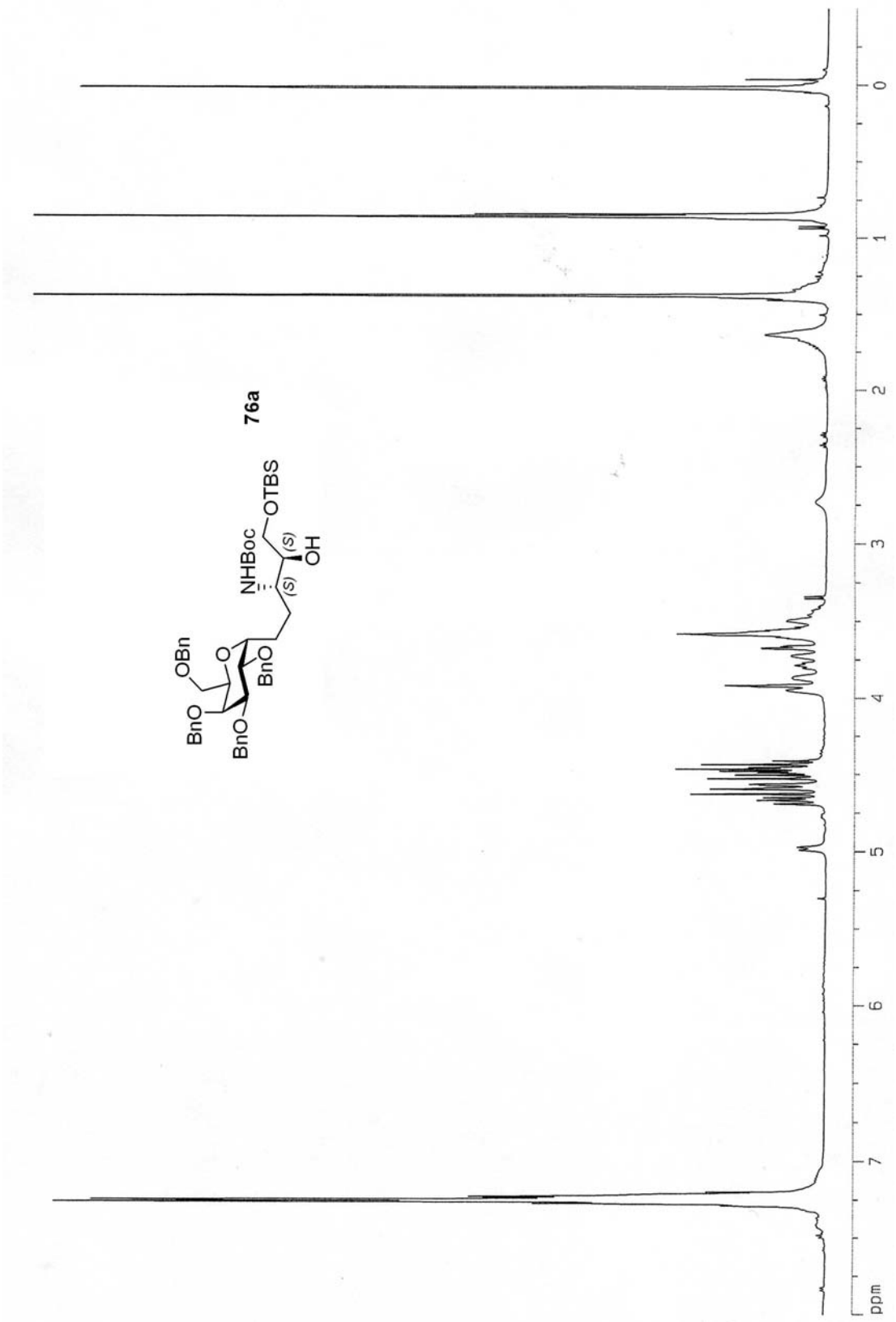
Peak#	1	2	3	4	5	6	7	8	9
Position	2100.89	1095.51	1028.32	788.72	763.72	697.62	442.09	428.14	407.24
Height	92.662	69.897	94.532	12.669	27.854	81.793	67.605	61.910	57.539

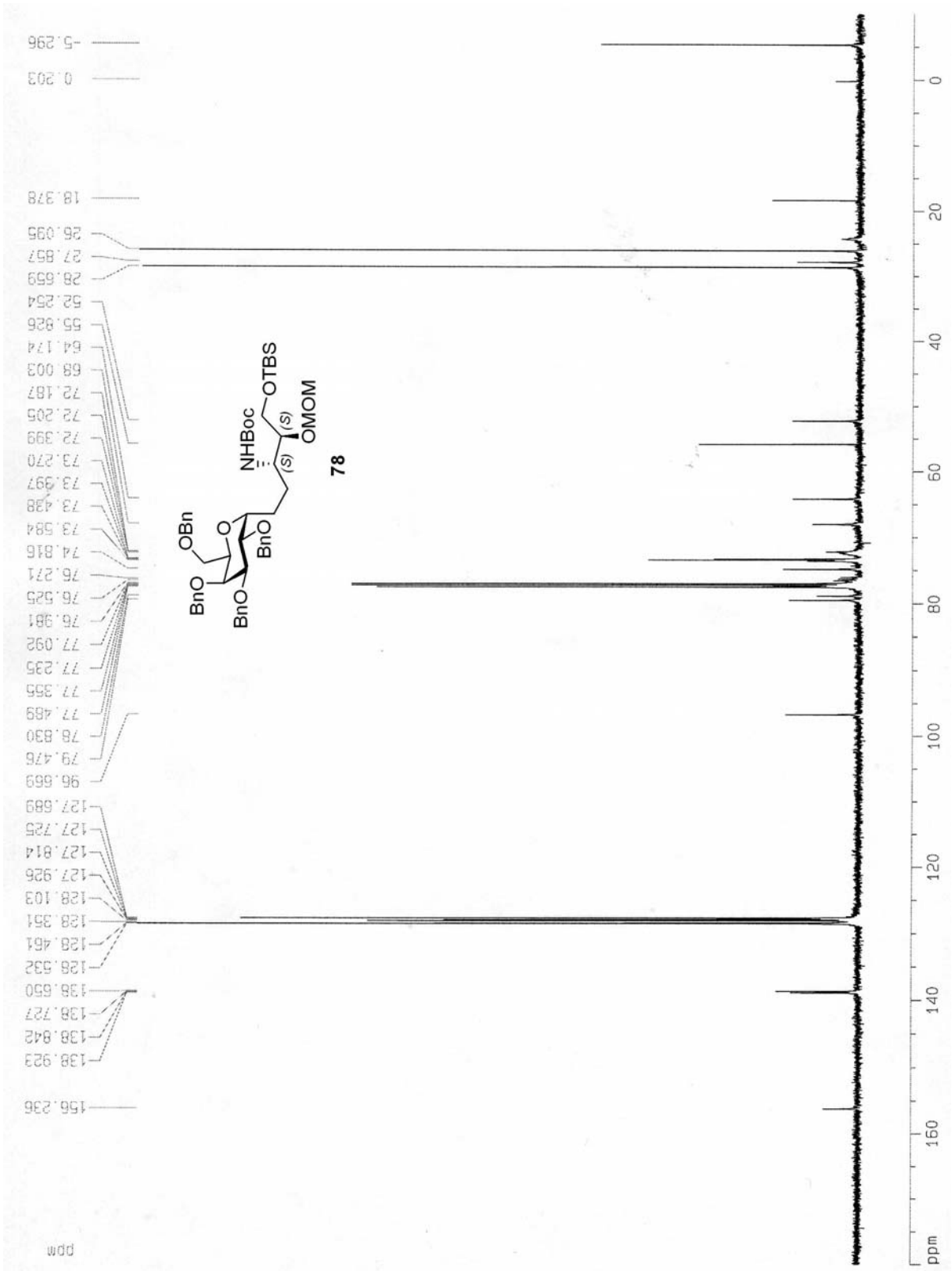


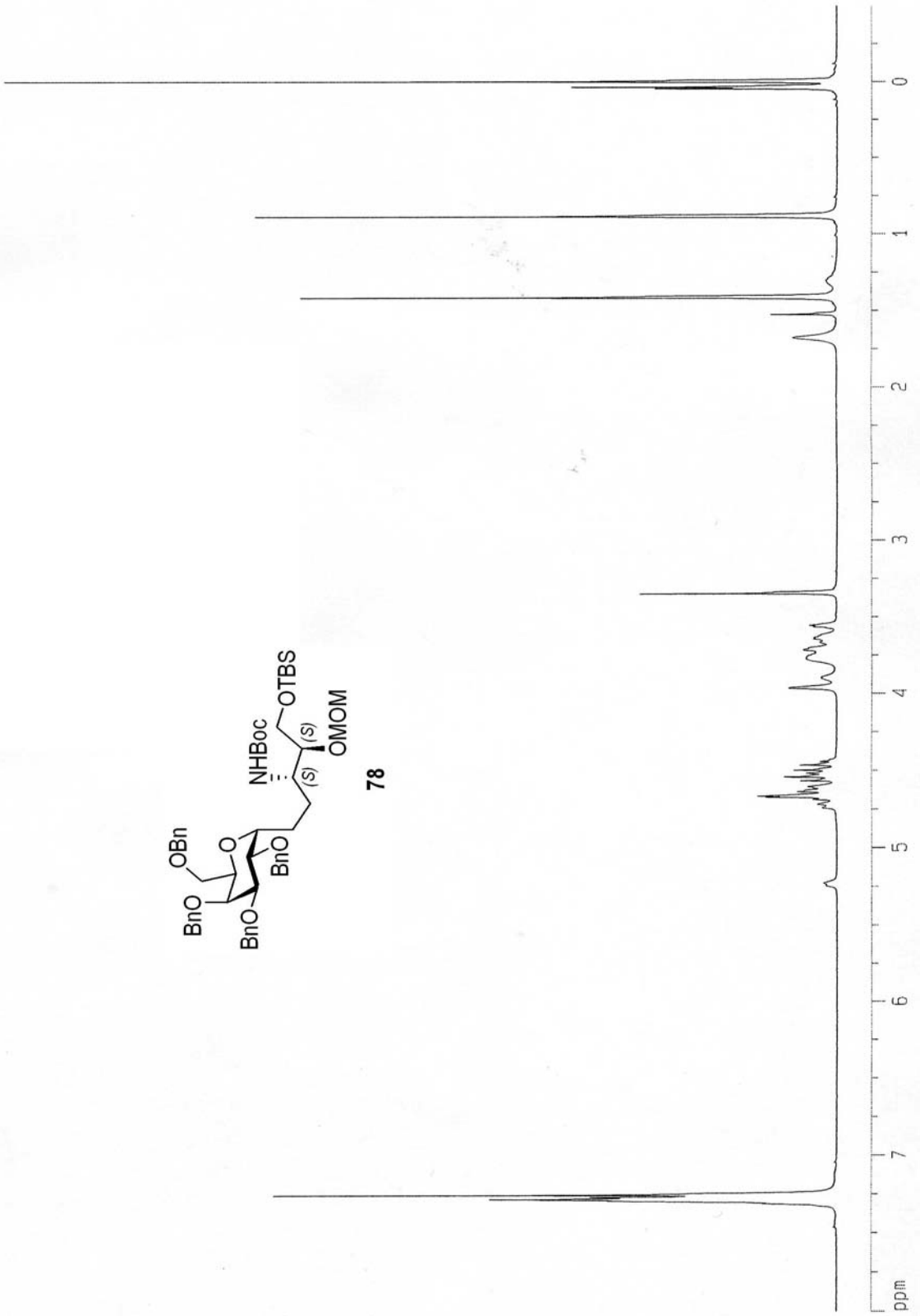

OBn
BnO
BnO
BnO
NHBoc
OH
OH
75a
ppm
0
1
2
3
4
5
6
7

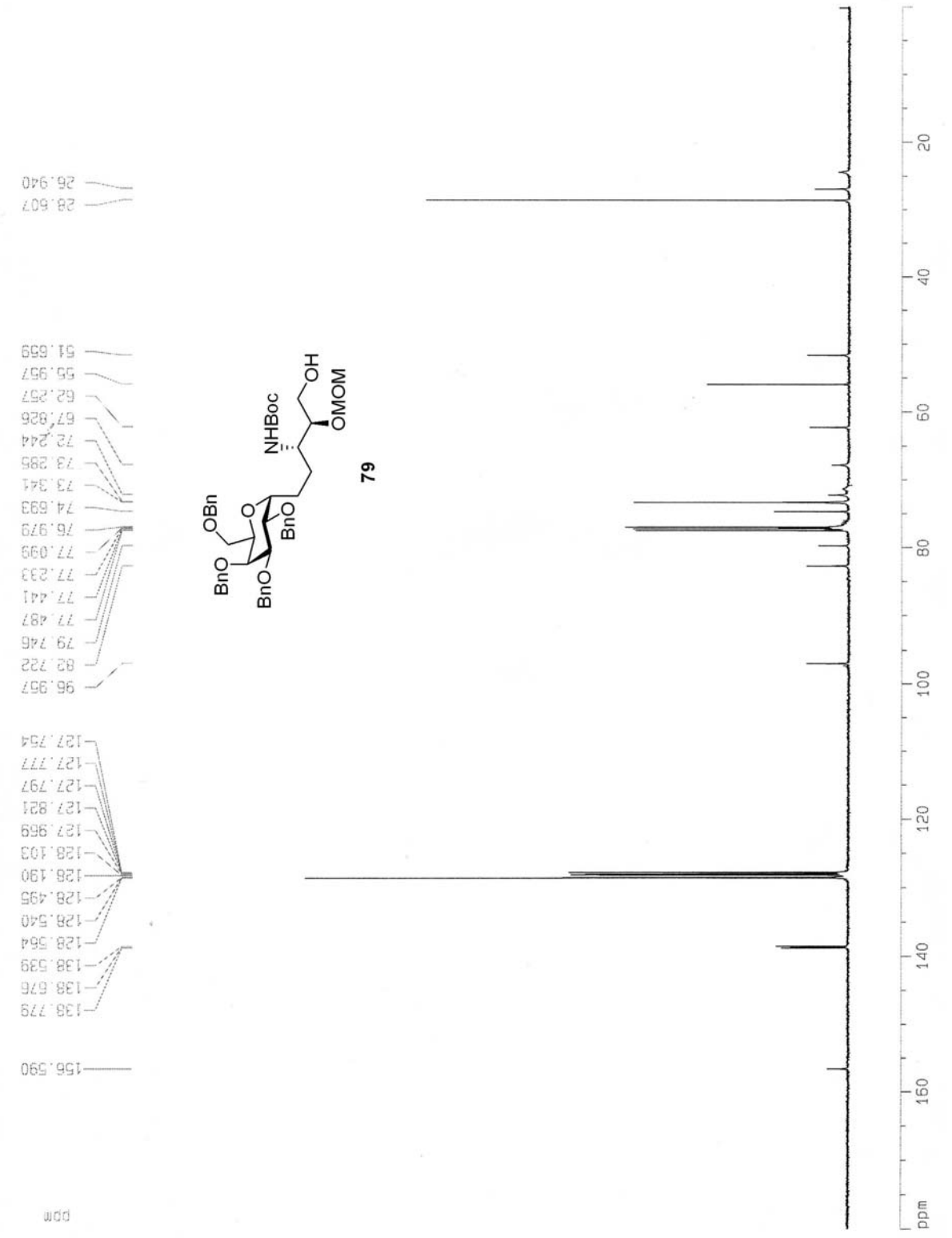

14.217
20.906
24.646
27.030
28.515
29.124
53.069
53.934
63.086
67.500
70.678
72.321
73.144
73.242
73.301
74.505
74.561
76.394
76.477
76.934
76.974
77.229
77.484
80.063
127.717
127.750
127.787
127.848
127.941
127.967
128.024
128.135
128.247
128.332
128.446
128.468
128.510
128.540
138.395
138.538
138.664
157.450
ppm
20
40
60
80
100
120
140
160
ppm
OH
NHBoc
OH
OBn
O
BnO
BnO
BnO
75a

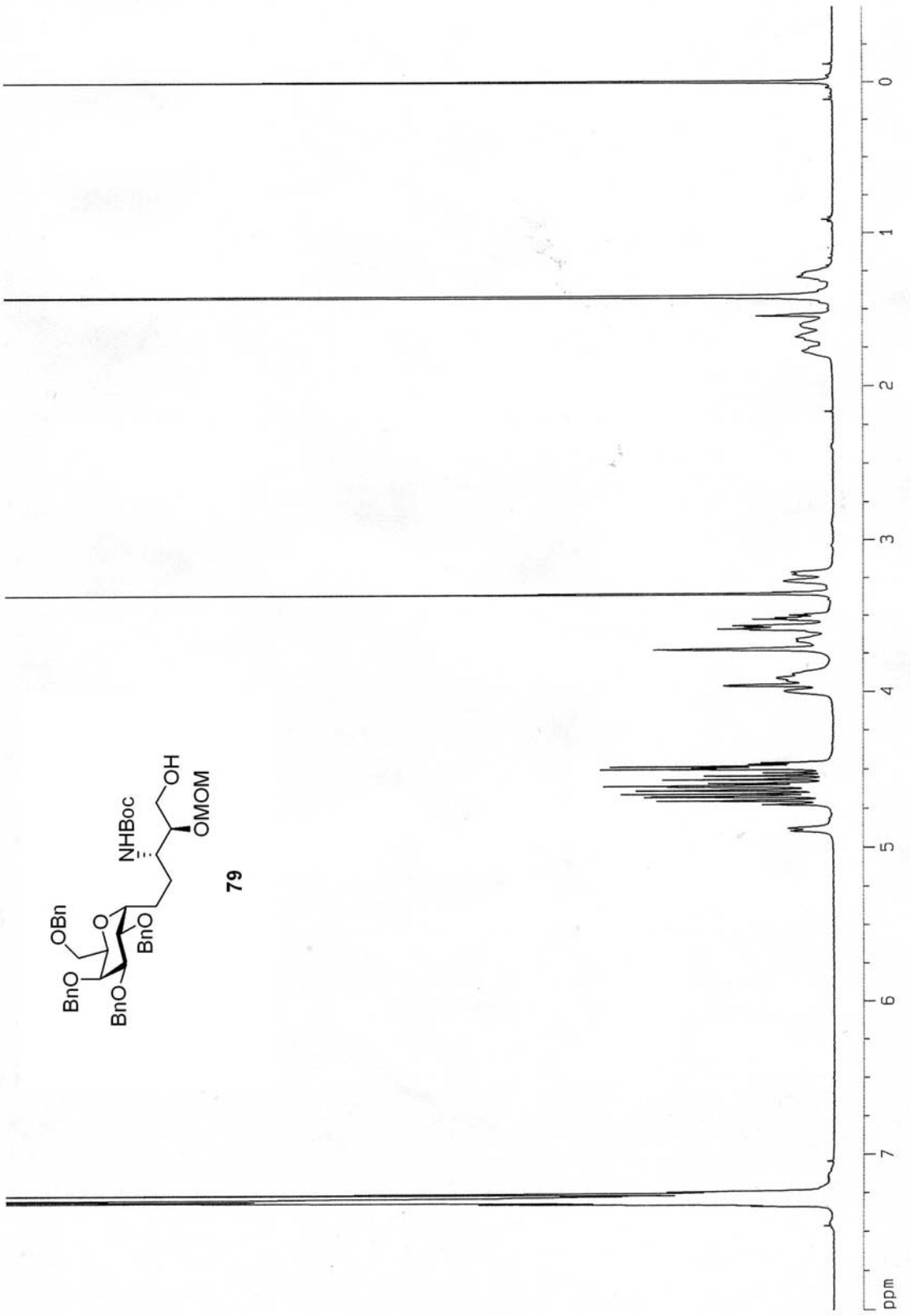

76a
BnO
BnO
BnO
OBn
NHBoc
(S)
(S)
OTBS
OH
ppm

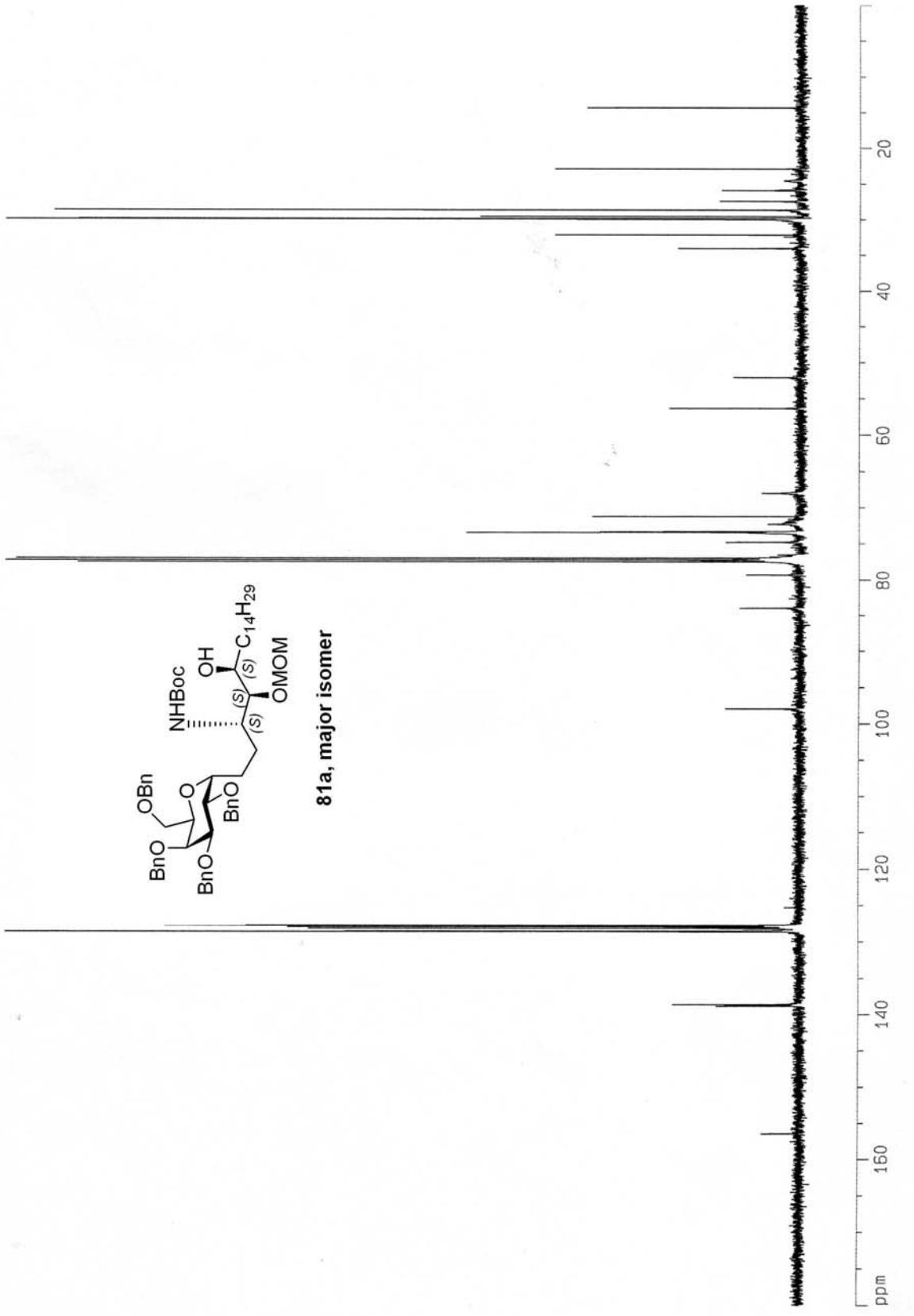

76a
BnO
OBn
O
BnO
BnO
NHBoc
(S)
(S)
OH
OTBS
ppm
0
1
2
3
4
5
6
7

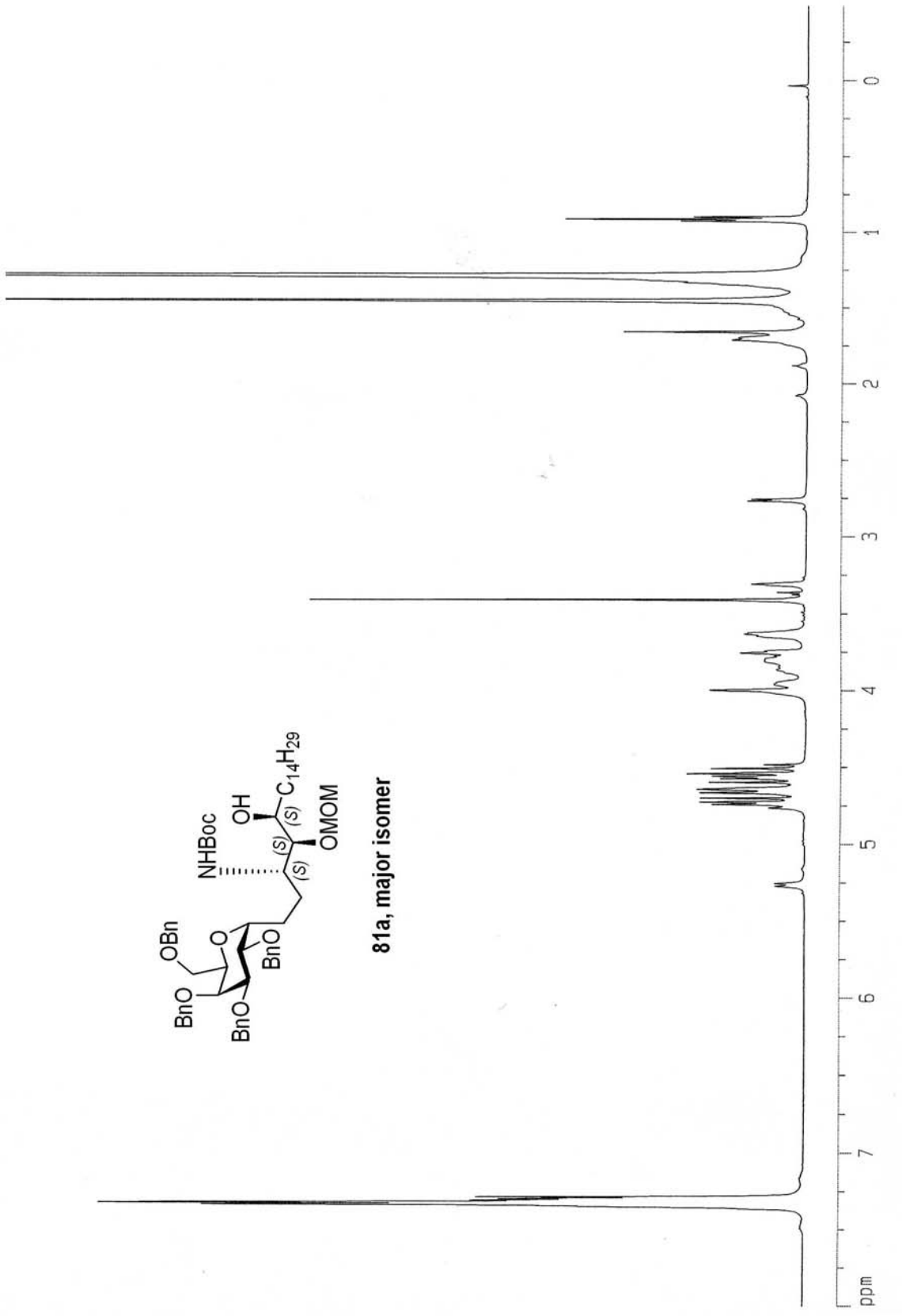

-5.296
0.203
18.378
26.095
27.857
28.659
52.254
55.826
64.174
68.003
72.187
72.205
72.399
73.270
73.397
73.438
73.584
74.816
76.271
76.525
76.981
77.092
77.235
77.355
77.489
78.830
79.476
96.669
127.689
127.725
127.814
127.926
128.103
128.351
128.461
128.532
138.650
138.727
138.842
138.923
156.236
ppm
0
20
40
60
80
100
120
140
160
OBn
BnO
BnO
BnO
NHBoc
OTBS
(S)
(S)
OMOM
78

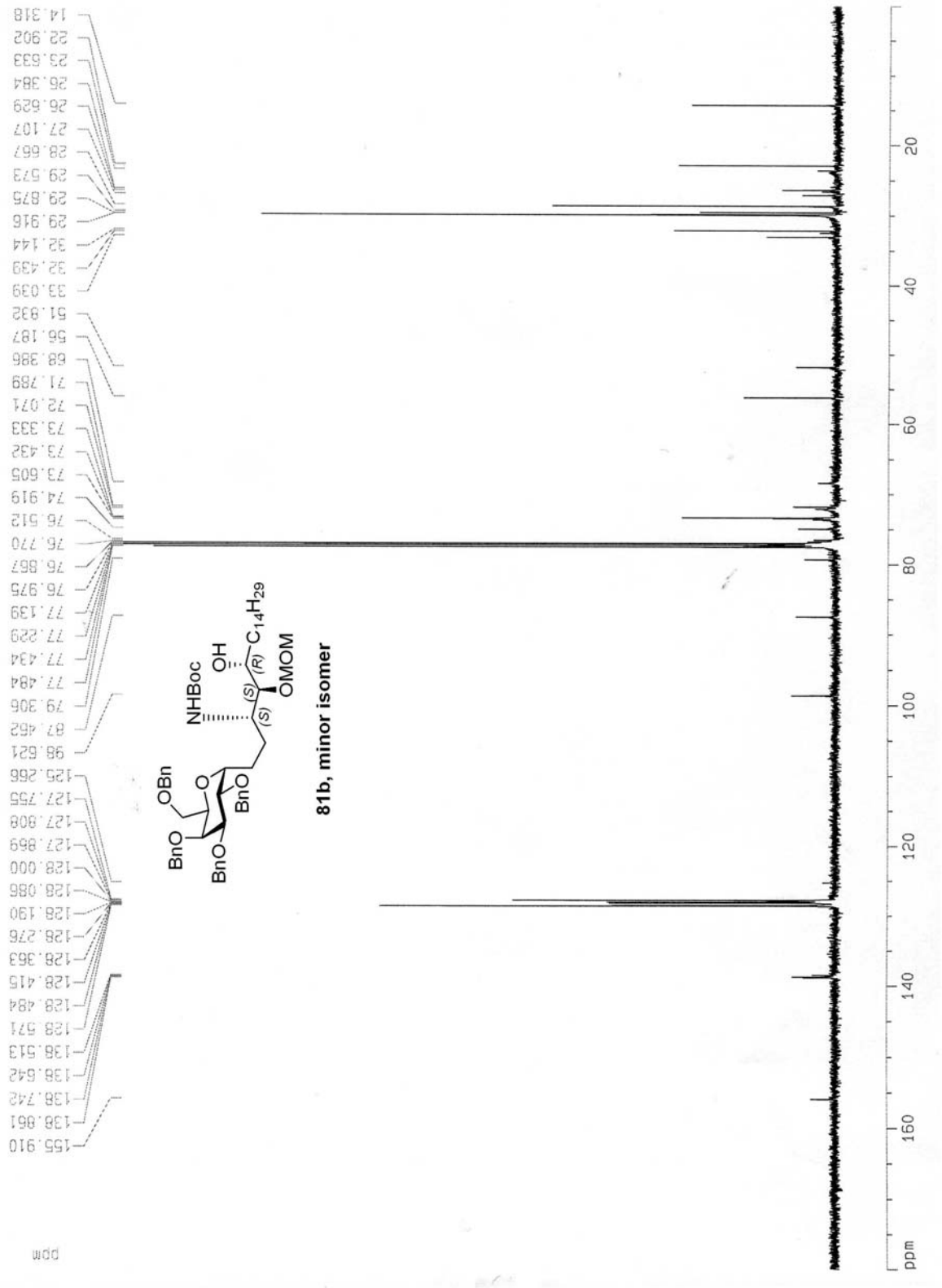

OBn
BnO
BnO
BnO
NHBoc
OTBS
(S)
(S)
OMOM
78
ppm
0
1
2
3
4
5
6
7

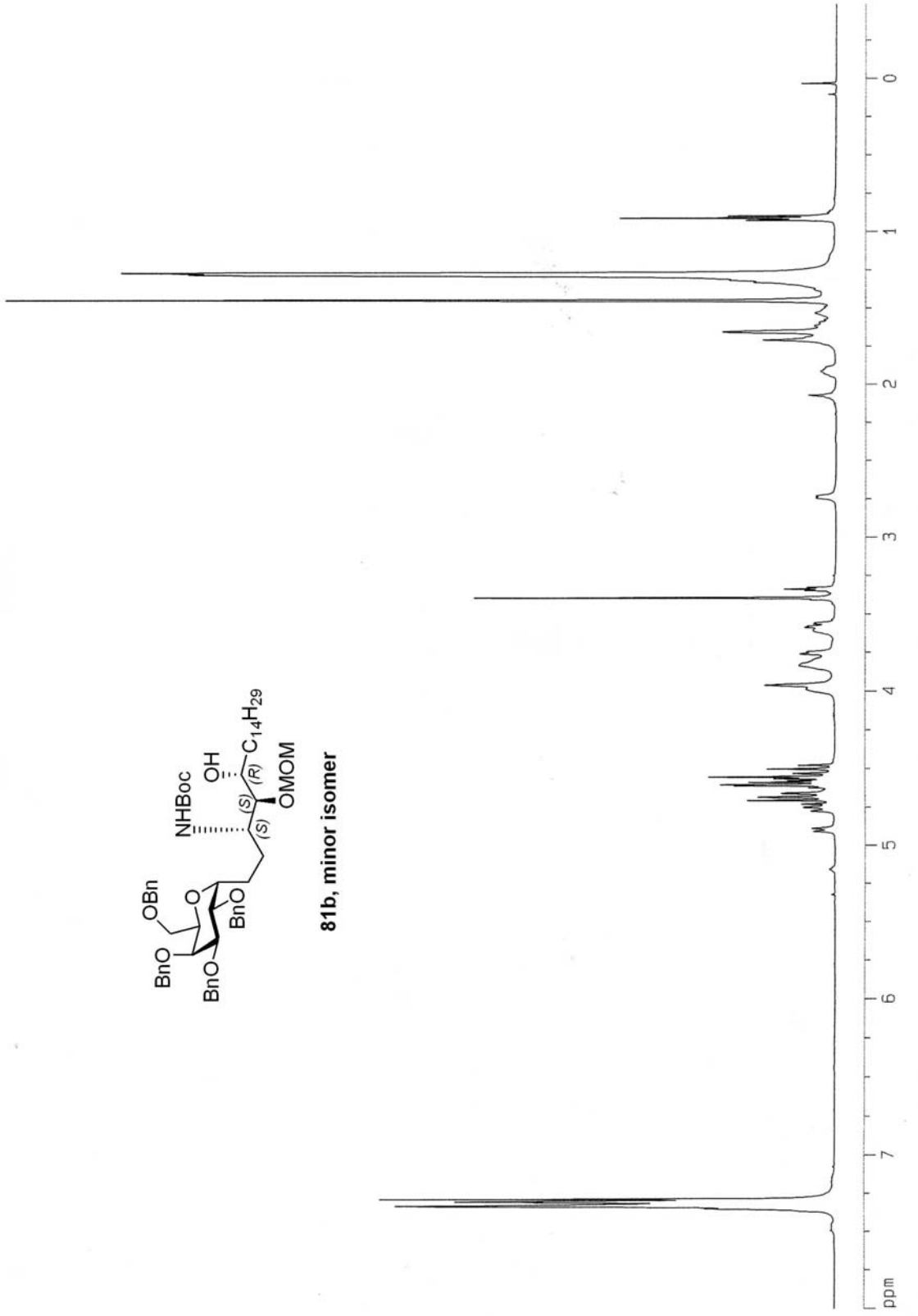

26.940
28.607
51.659
55.957
62.257
67.826
72.244
73.285
73.341
74.693
76.979
77.099
77.233
77.441
77.487
79.746
82.722
96.957
127.754
127.777
127.797
127.821
127.969
128.103
128.190
128.495
128.540
128.564
138.539
138.676
138.779
156.590
ppm
20
40
60
80
100
120
140
160
ppm
OBn
BnO
BnO
BnO
NHBoc
OMOM
OH
79


BnO
OBn
O
BnO
BnO
NHBoc
OMOM
OH
79
ppm
0
1
2
3
4
5
6
7

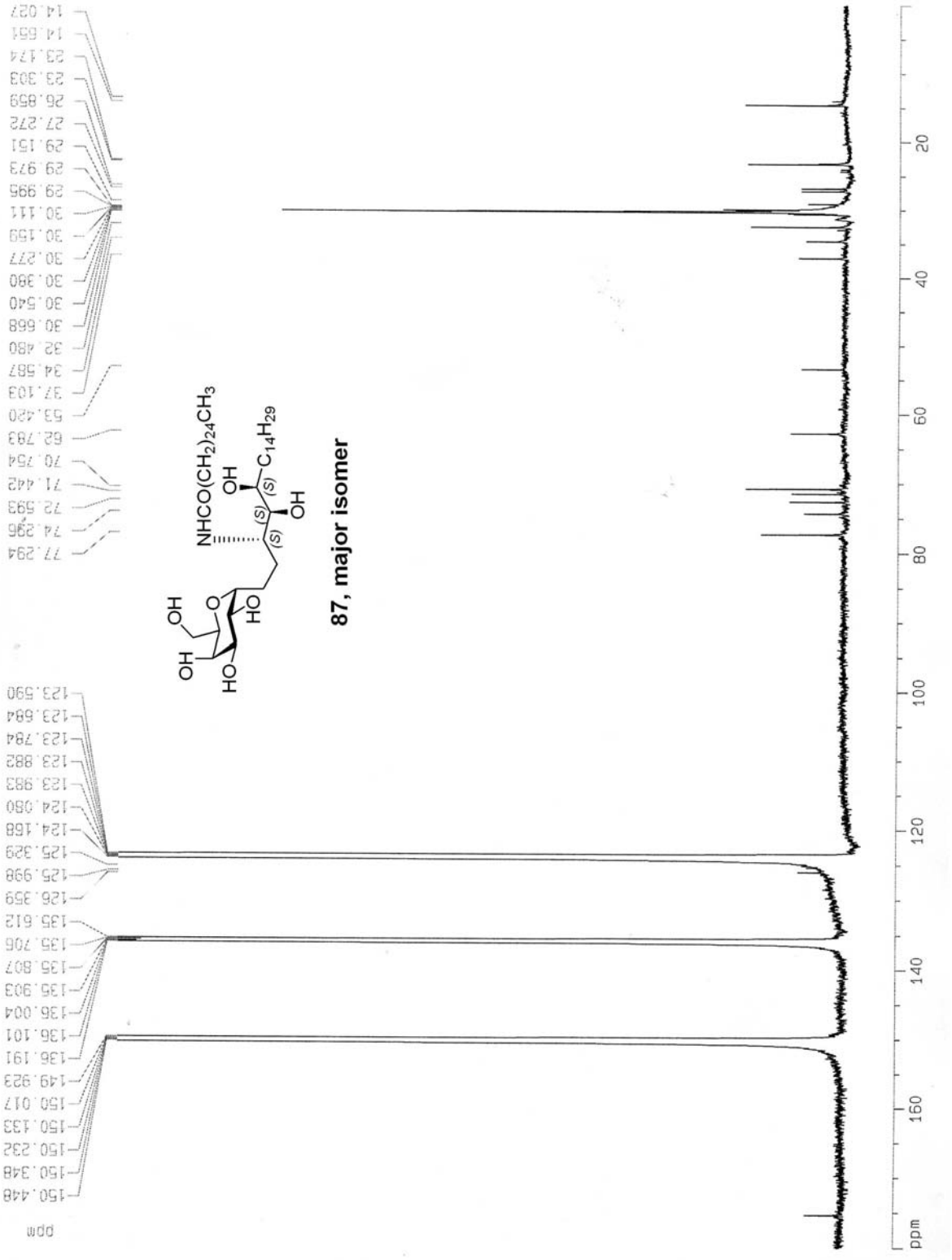

BnO
OBn
O
BnO
BnO
NHBoc
OH
(S)
(S)
(S)
$C_{14}H_{29}$
OMOM
81a, major isomer
ppm
20
40
60
80
100
120
140
160

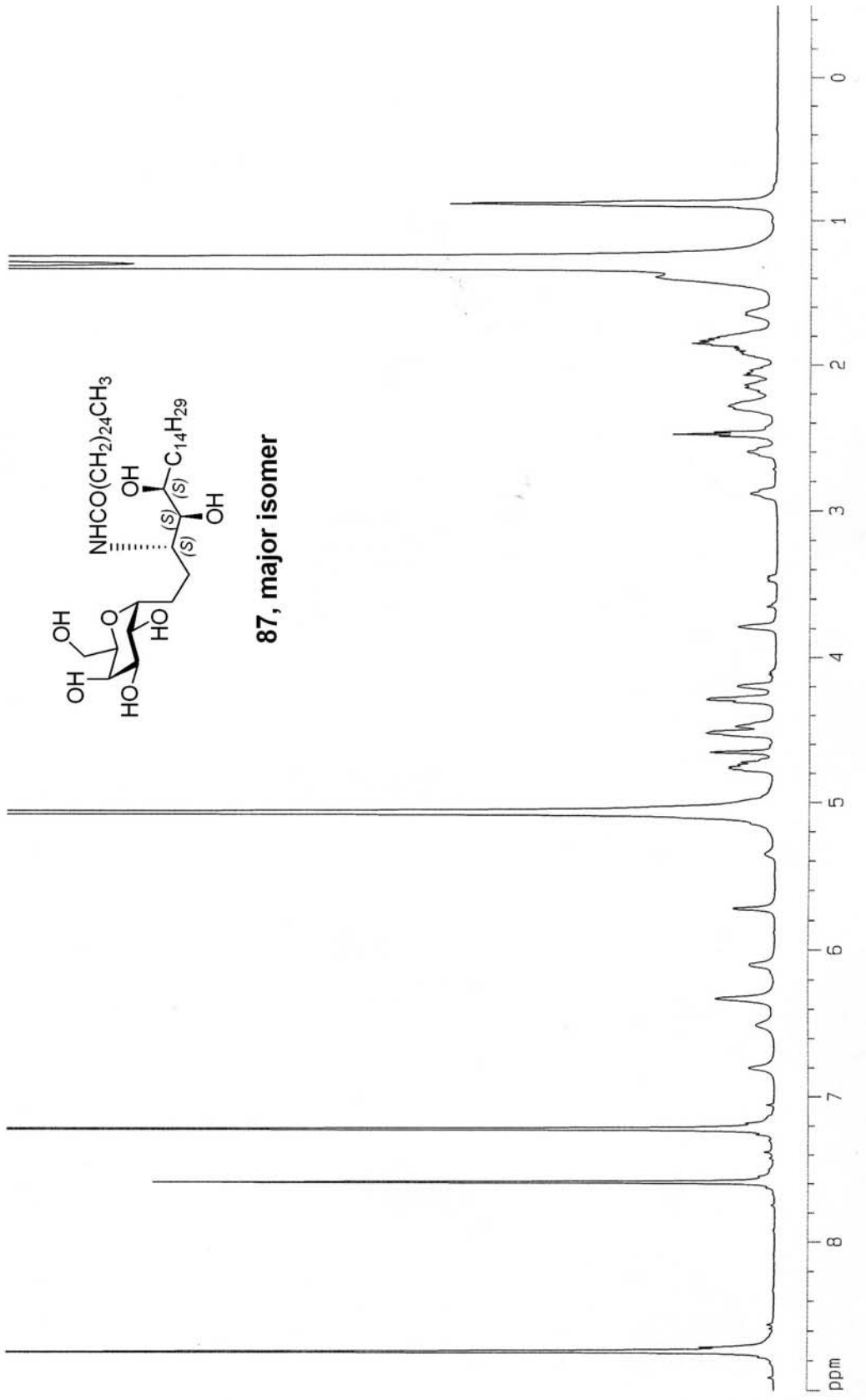

BnO
OBn
BnO
O
BnO
NHBoc
OH
(S)
(S)
$C_{14}H_{29}$
OMOM
81a, major isomer
ppm
7
6
5
4
3
2
1
0

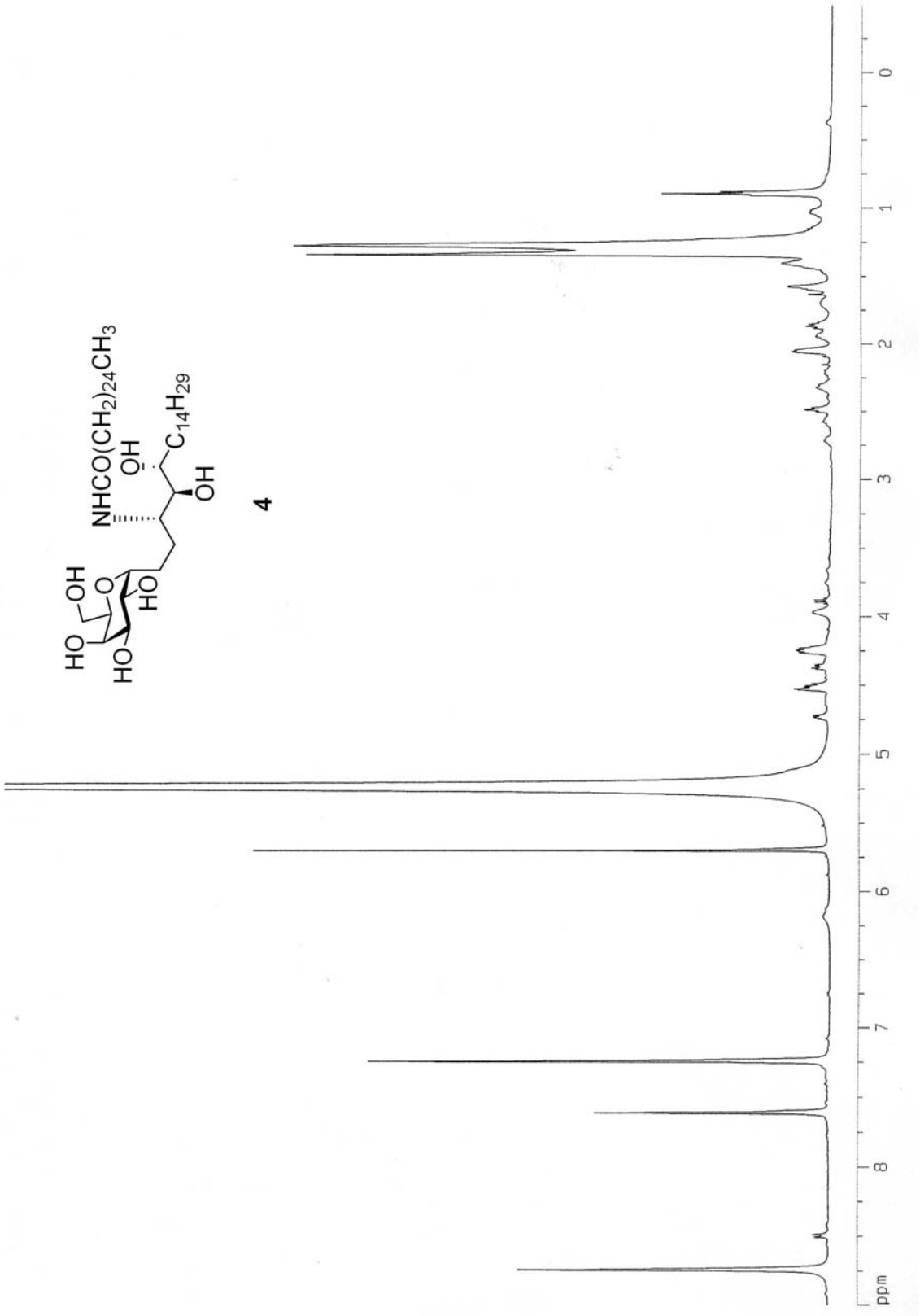

14.318
22.902
23.633
26.384
26.629
27.107
28.667
29.573
29.875
29.916
32.144
32.439
33.039
51.832
56.187
68.386
71.789
72.071
73.333
73.432
73.605
74.919
76.512
76.770
76.867
76.975
77.139
77.229
77.434
77.484
79.306
87.462
98.621
125.266
127.755
127.808
127.869
128.000
128.086
128.190
128.276
128.363
128.415
128.484
128.571
138.513
138.642
138.742
138.861
155.910
wdd
NHBoc
OH
OMOM
OBn
BnO
BnO
BnO
(S)
(R)
(S)
$C_{14}H_{29}$
81b, minor isomer
20
40
60
80
100
120
140
160
ppm

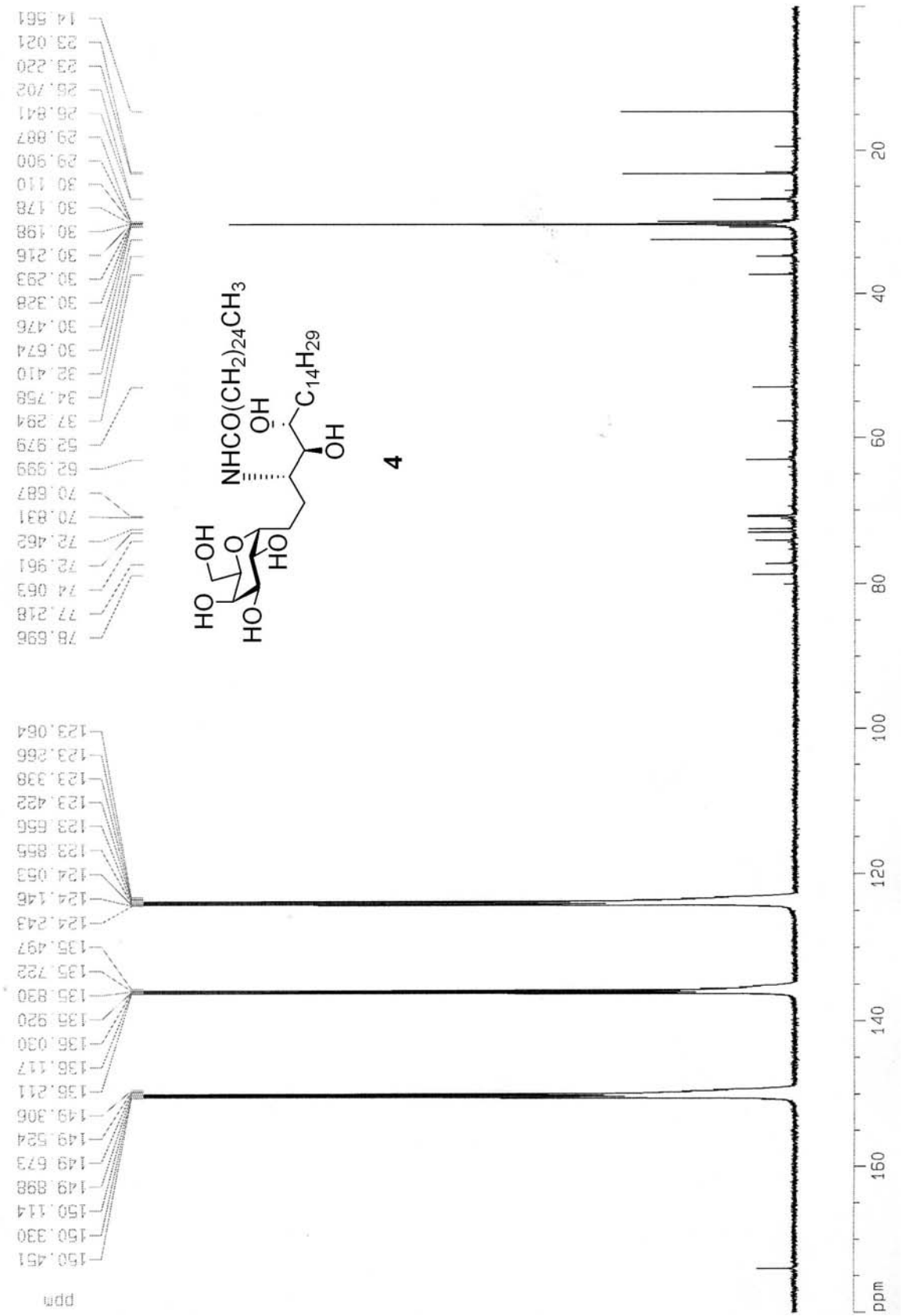


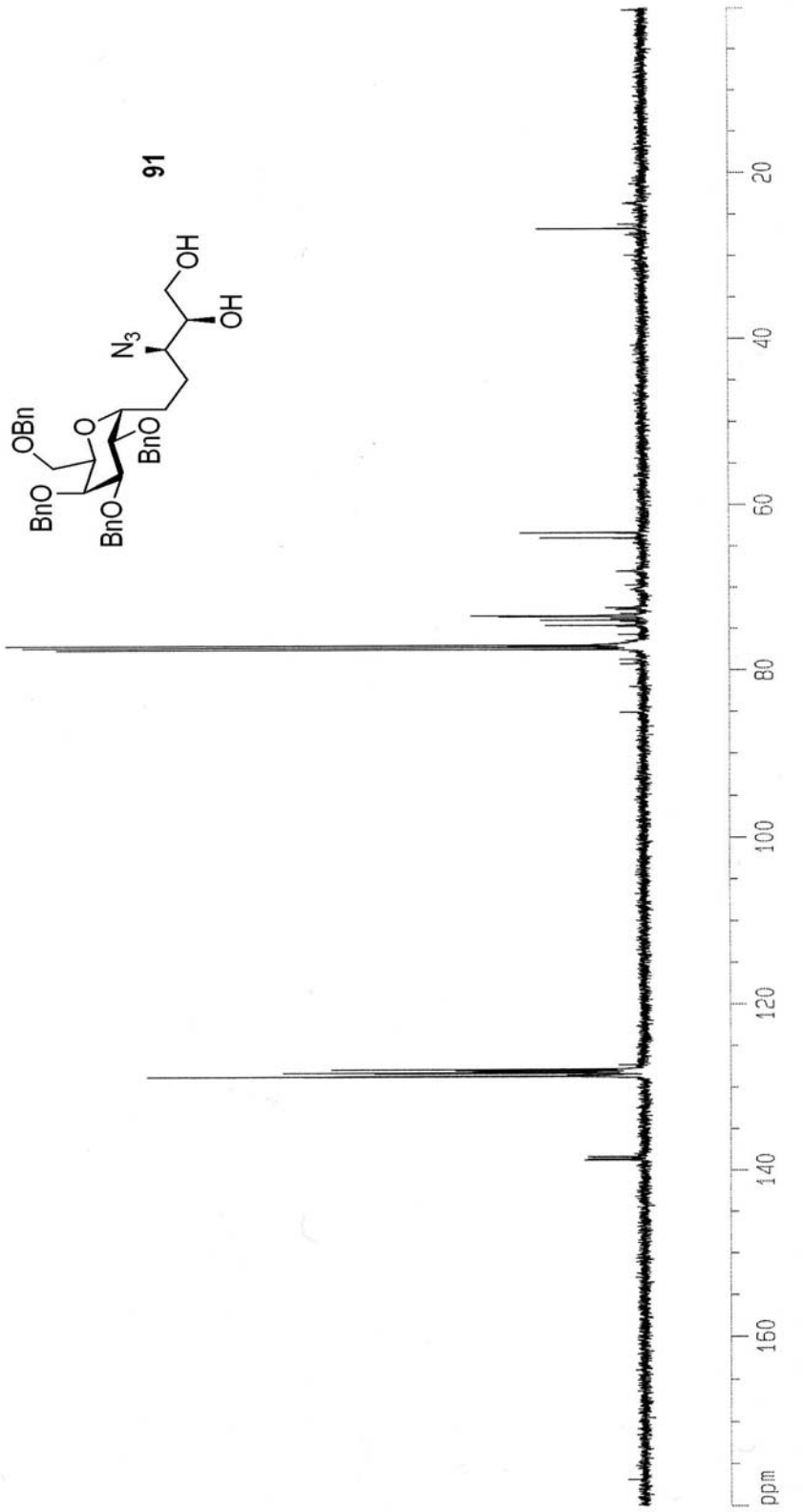
81b, minor isomer

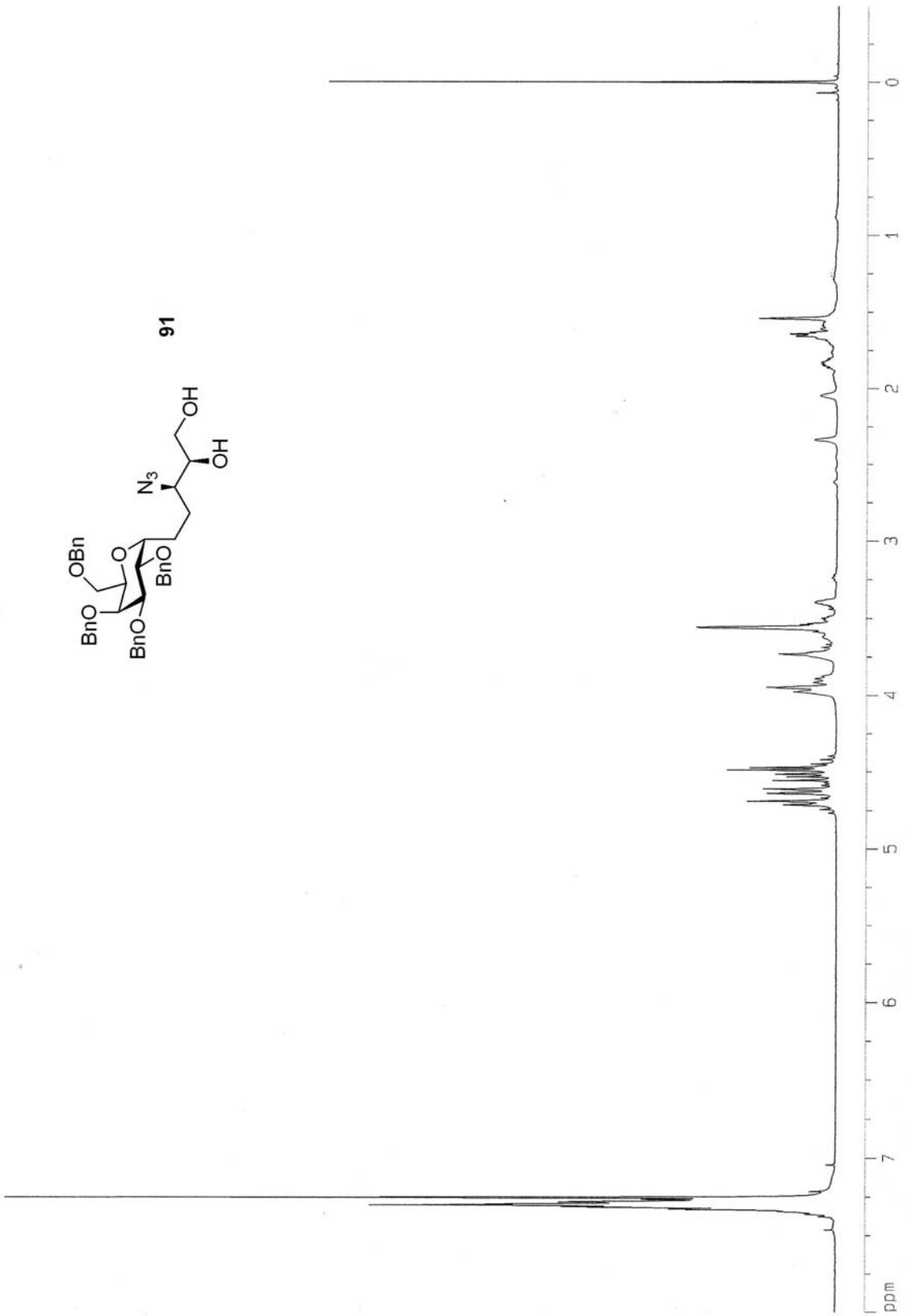

87, major isomer
NHCO(CH2)24CH3
C14H29
OH
HO
O
(S)
ppm
20
40
60
80
100
120
140
160

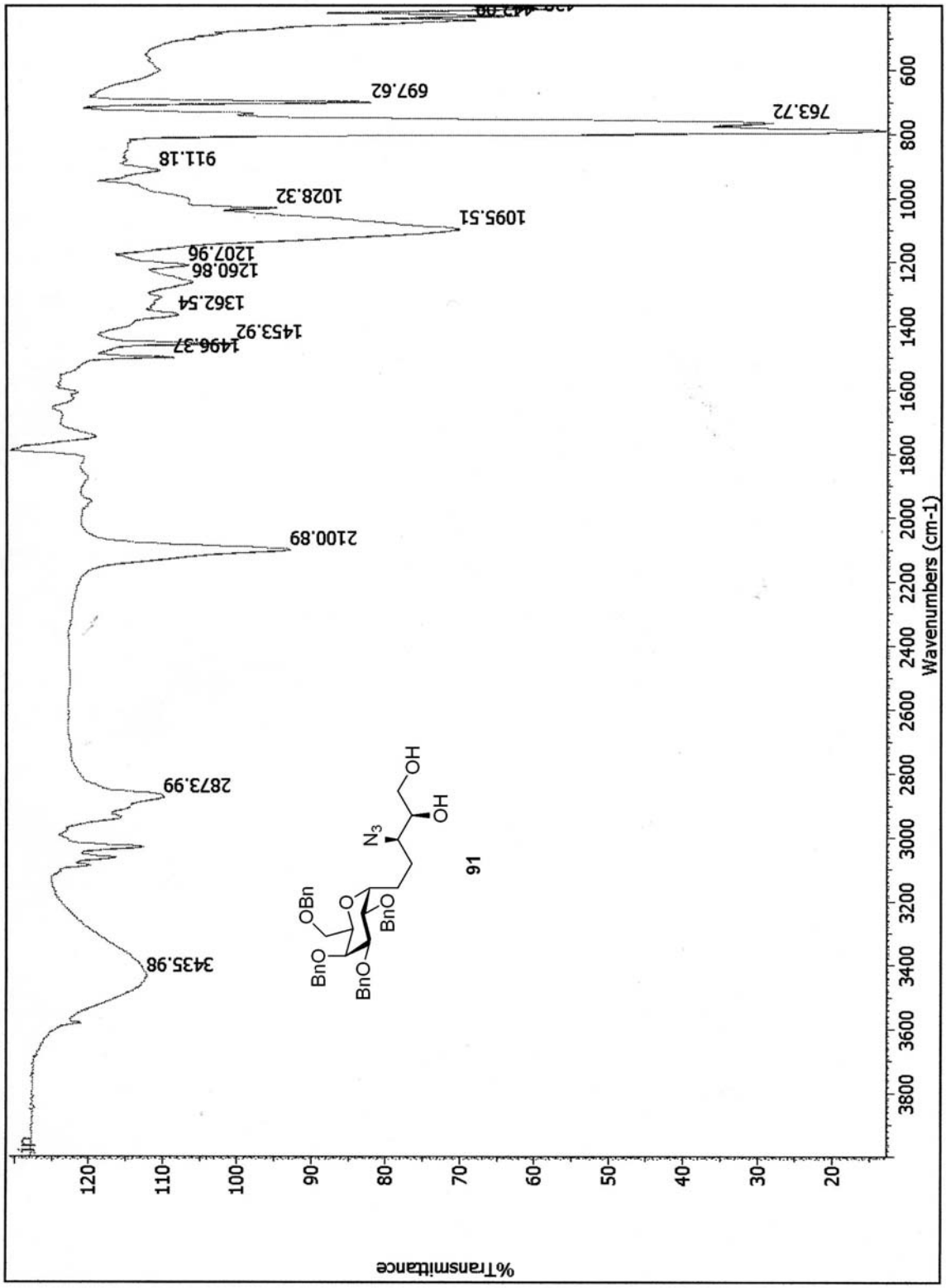

NHCO(CH2)24CH3
OH
(S)
(S)
C14H29
OH
OH
O
HO
OH
HO
87, major isomer
ppm
8
7
6
5
4
3
2
1
0

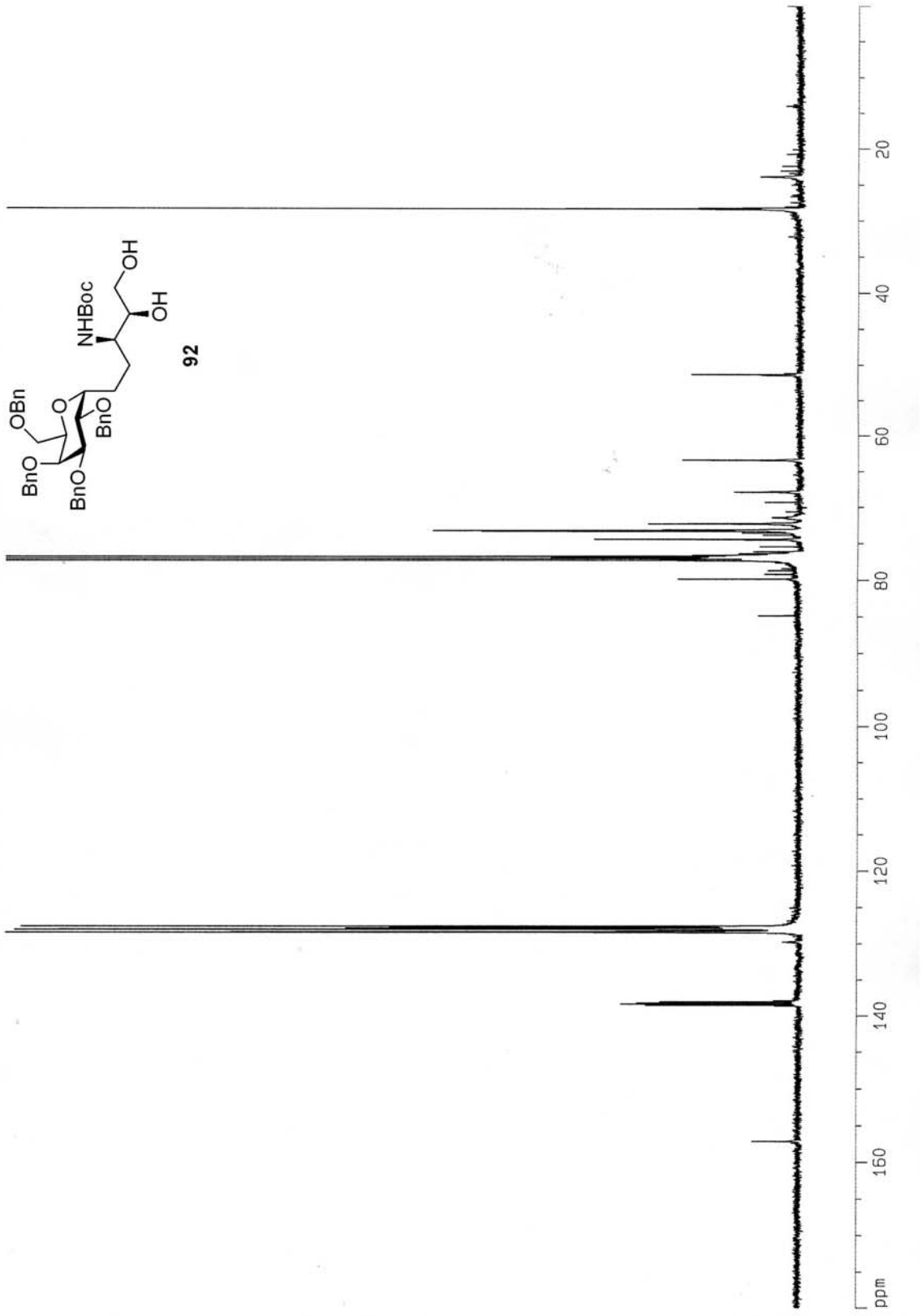

HO
OH
O
HO
HO
NHCO(CH2)24CH3
OH
C14H29
OH
4
ppm
8
7
6
5
4
3
2
1
0

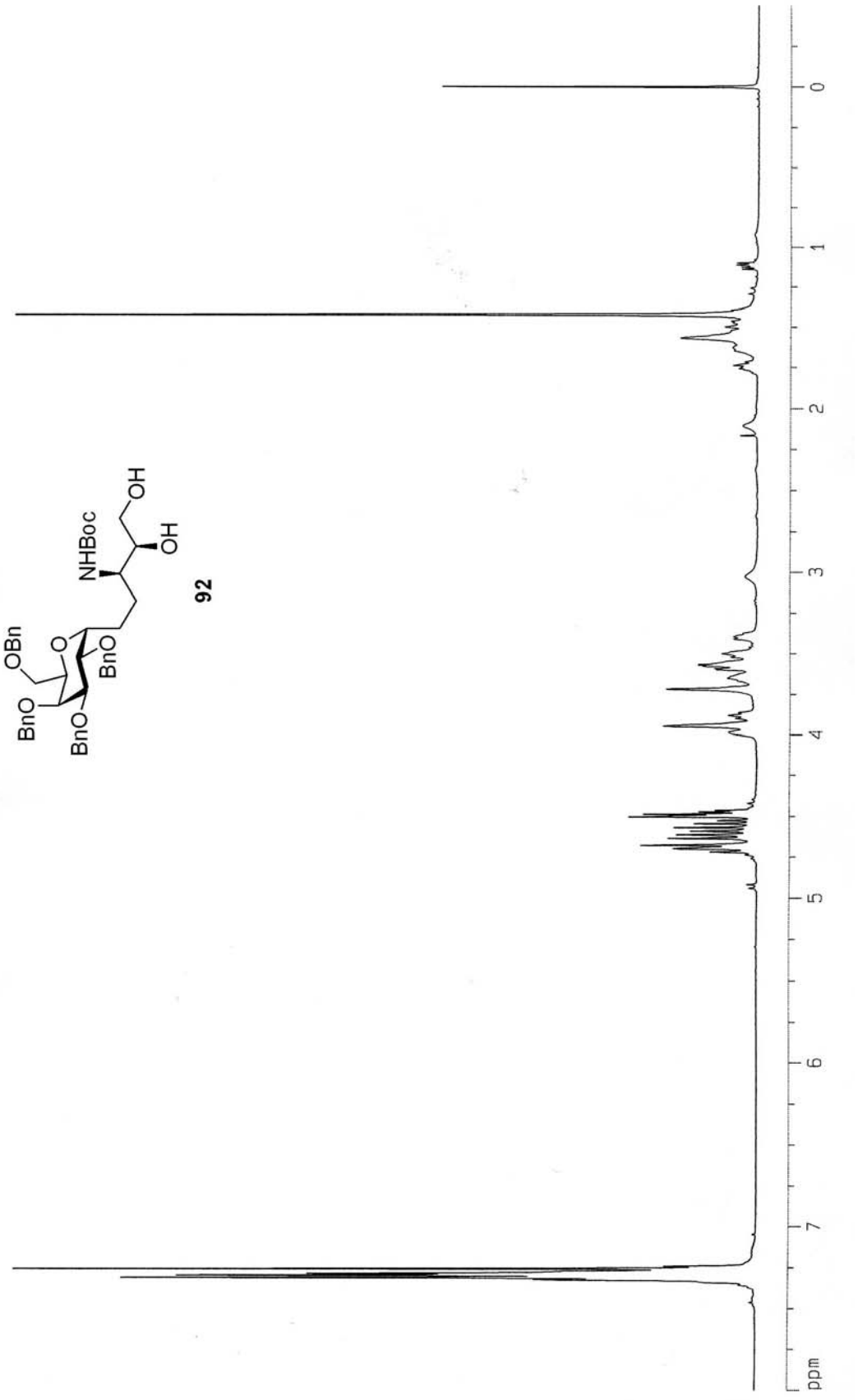

NHCO(CH2)24CH3
OH
C14H29
OH
HO
HO
HO
O
OH
4
ppm
20
40
60
80
100
120
140
160
14.561
23.021
23.220
26.702
26.841
29.887
29.900
30.110
30.178
30.198
30.216
30.293
30.328
30.476
30.674
32.410
34.758
37.294
52.979
62.999
70.687
70.831
72.462
72.961
74.063
77.218
78.696
123.064
123.266
123.338
123.422
123.656
123.865
124.053
124.146
124.243
135.497
135.722
135.830
135.920
136.030
136.117
136.211
149.306
149.524
149.673
149.898
150.114
150.330
150.451

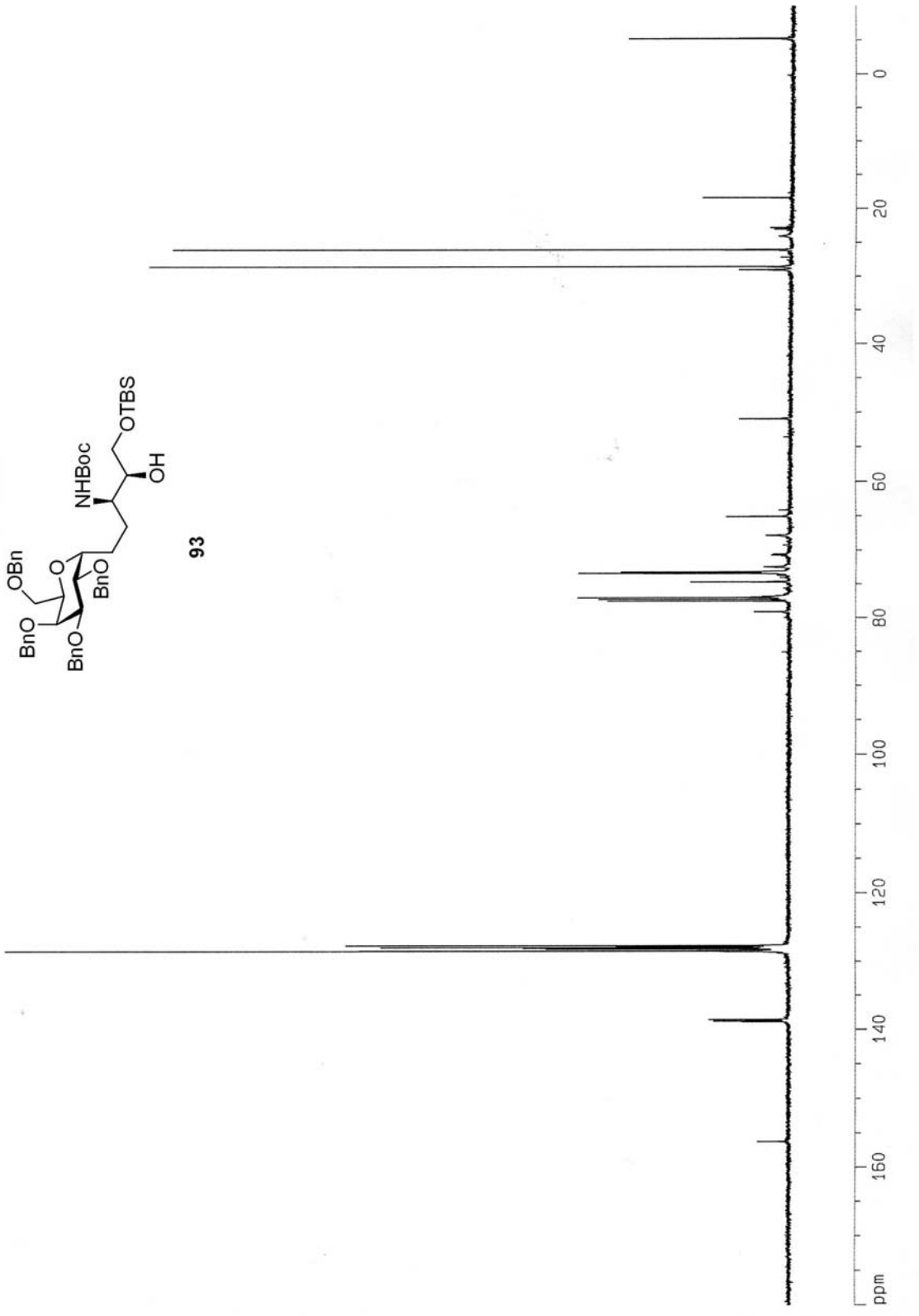

91
OBn
O
BnO
BnO
BnO
N3
OH
OH
ppm
20
40
60
80
100
120
140
160

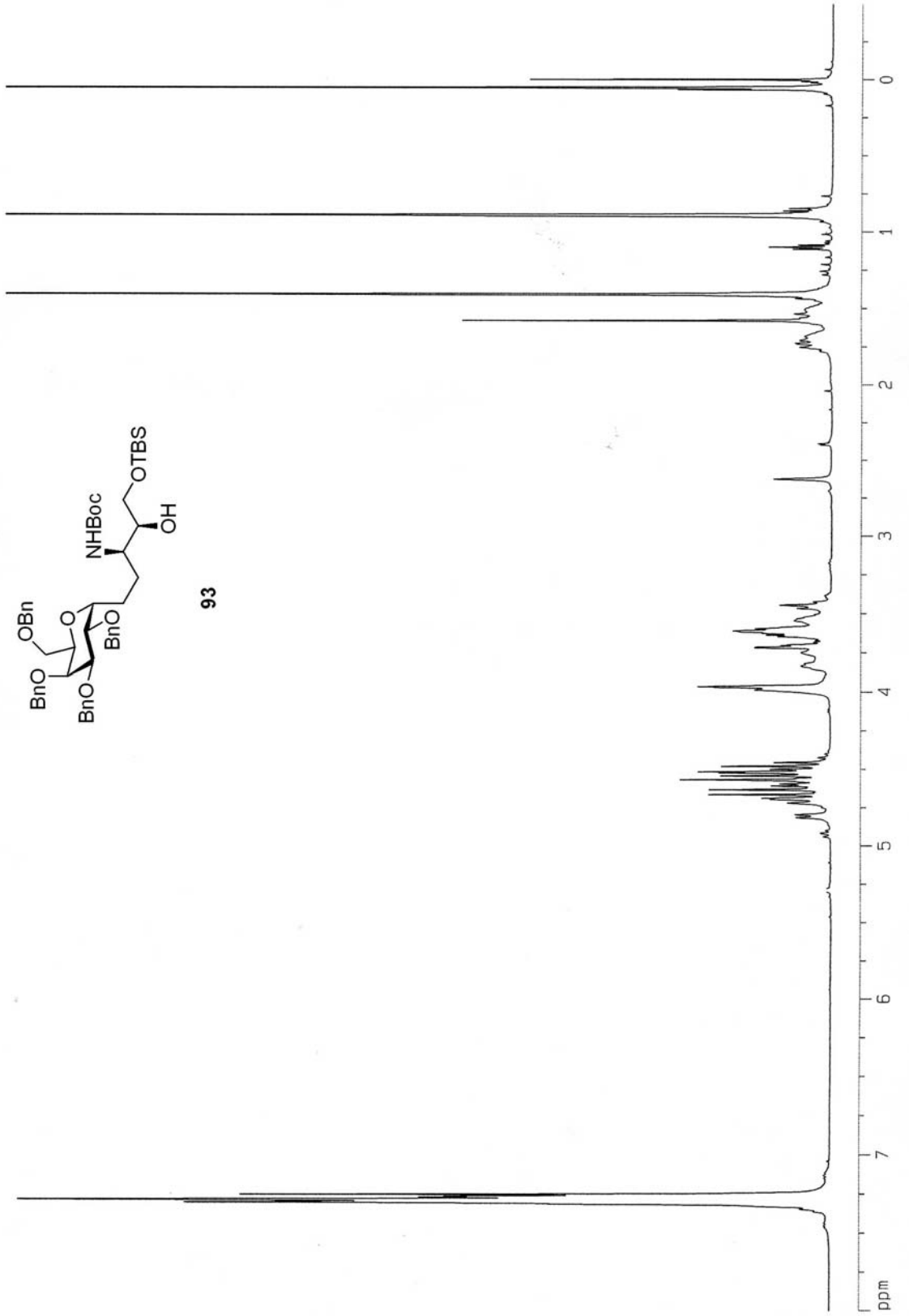

91
OBn
O
BnO
BnO
BnO
N3
OH
OH
ppm
0
1
2
3
4
5
6
7

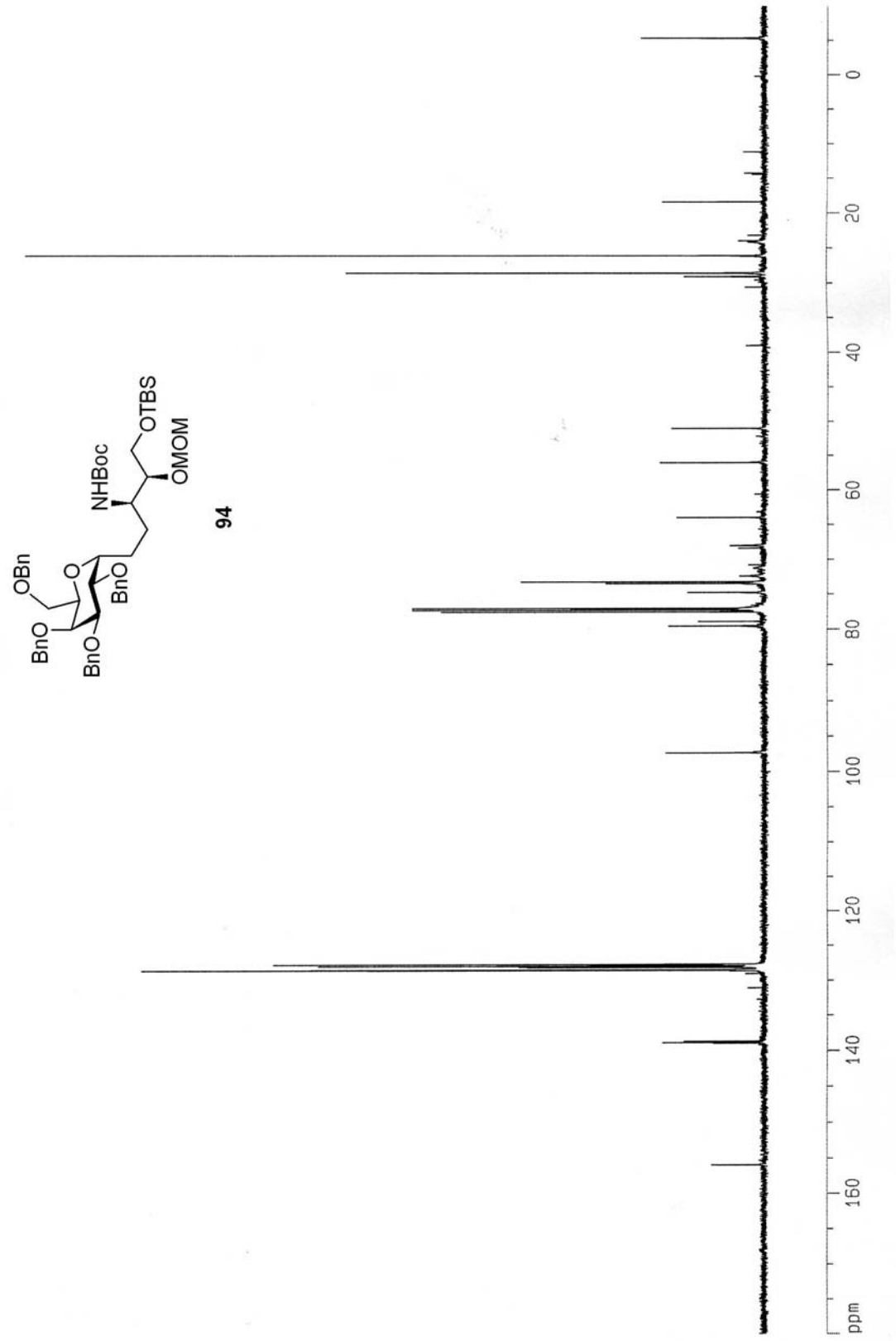

%Transmittance
Wavenumbers (cm-1)
3435.98
2873.99
2100.89
1496.37
1453.92
1362.54
1260.86
1207.96
1095.51
1028.32
911.18
763.72
697.62
BnO
OBn
BnO
BnO
O
N3
OH
OH
91

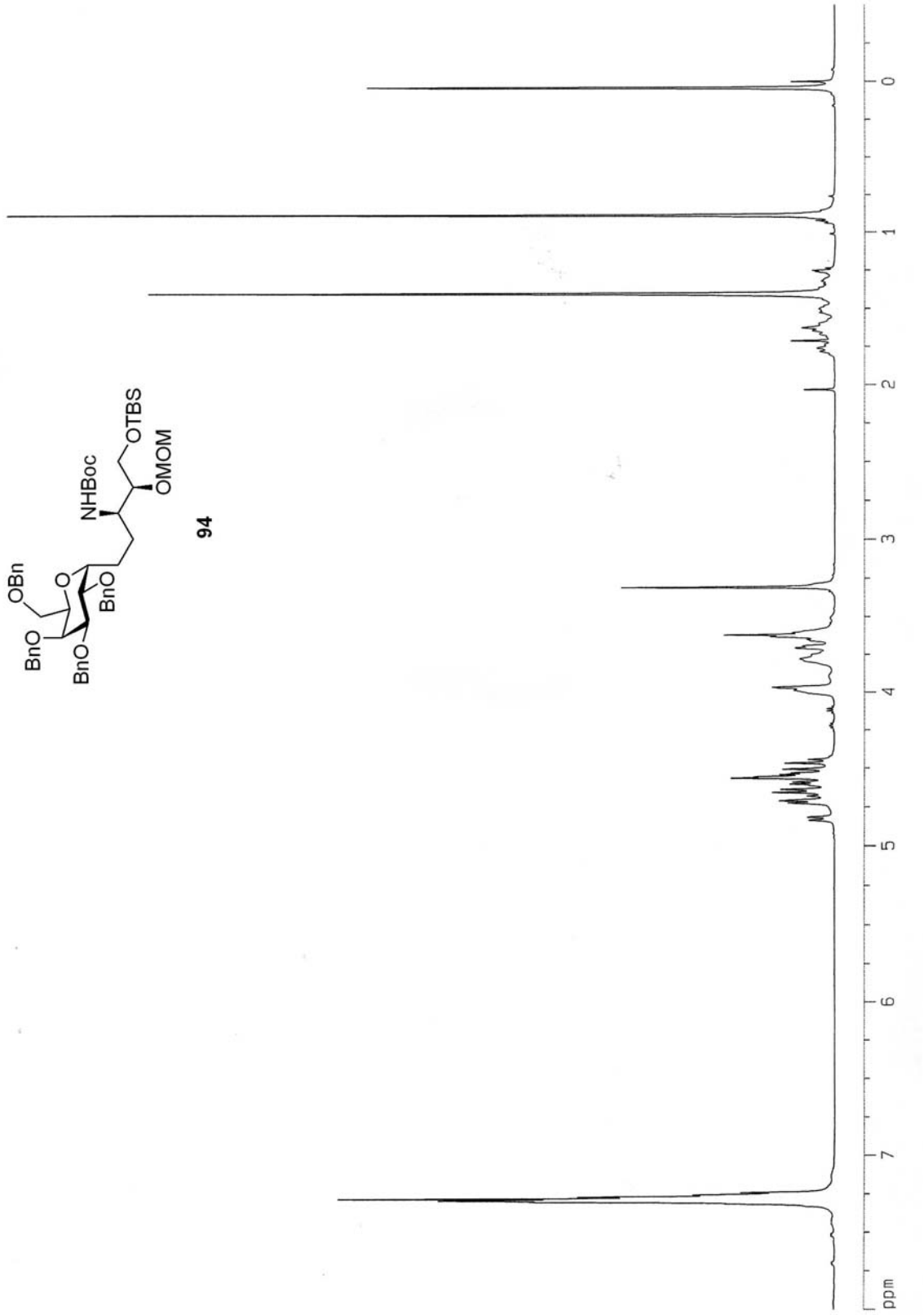

OBn
O
BnO
BnO
BnO
NHBoc
OH
OH
92
20
40
60
80
100
120
140
160
ppm

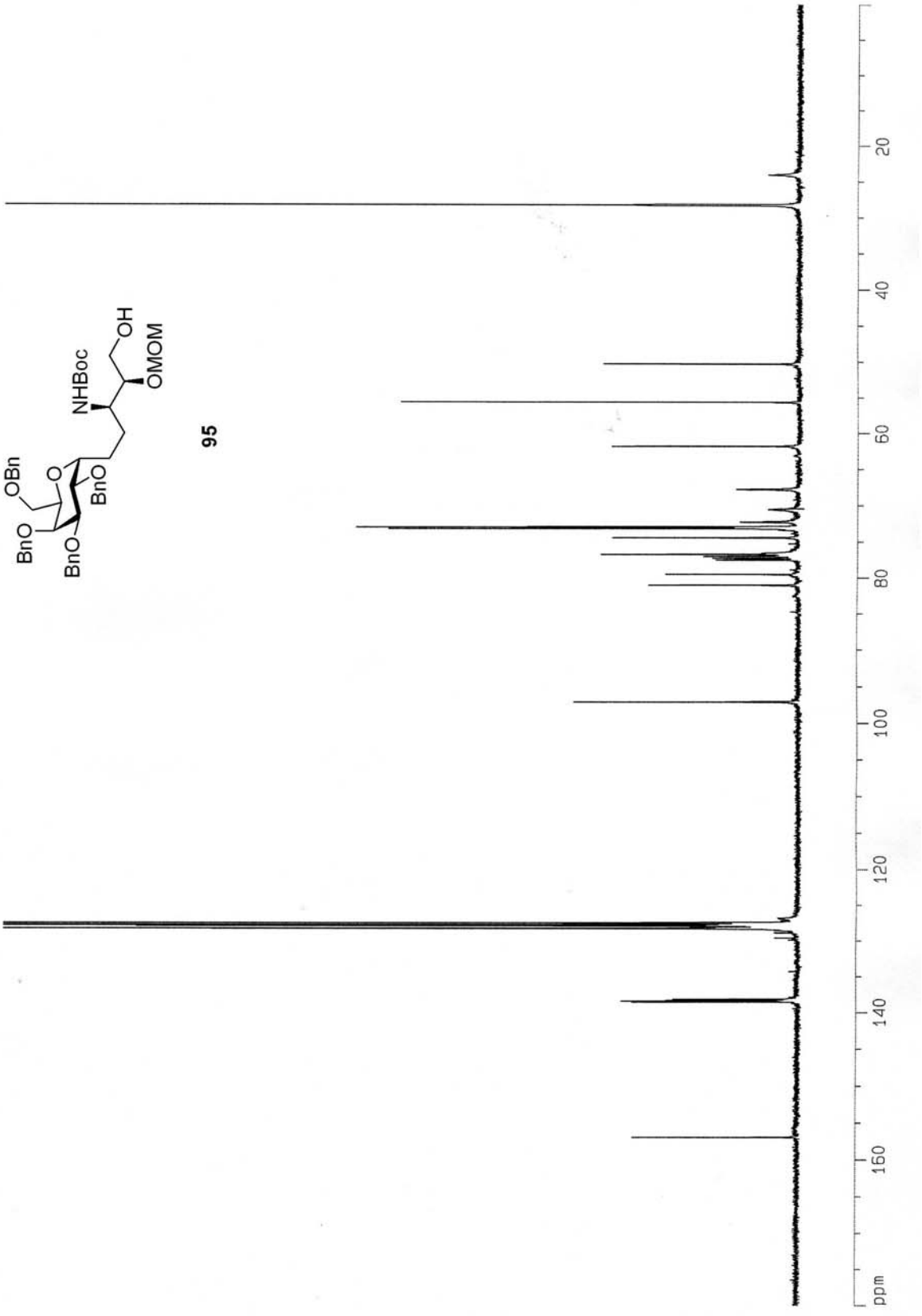

OBn
O
BnO
BnO
BnO
NHBoc
OH
OH
92
ppm
0
1
2
3
4
5
6
7

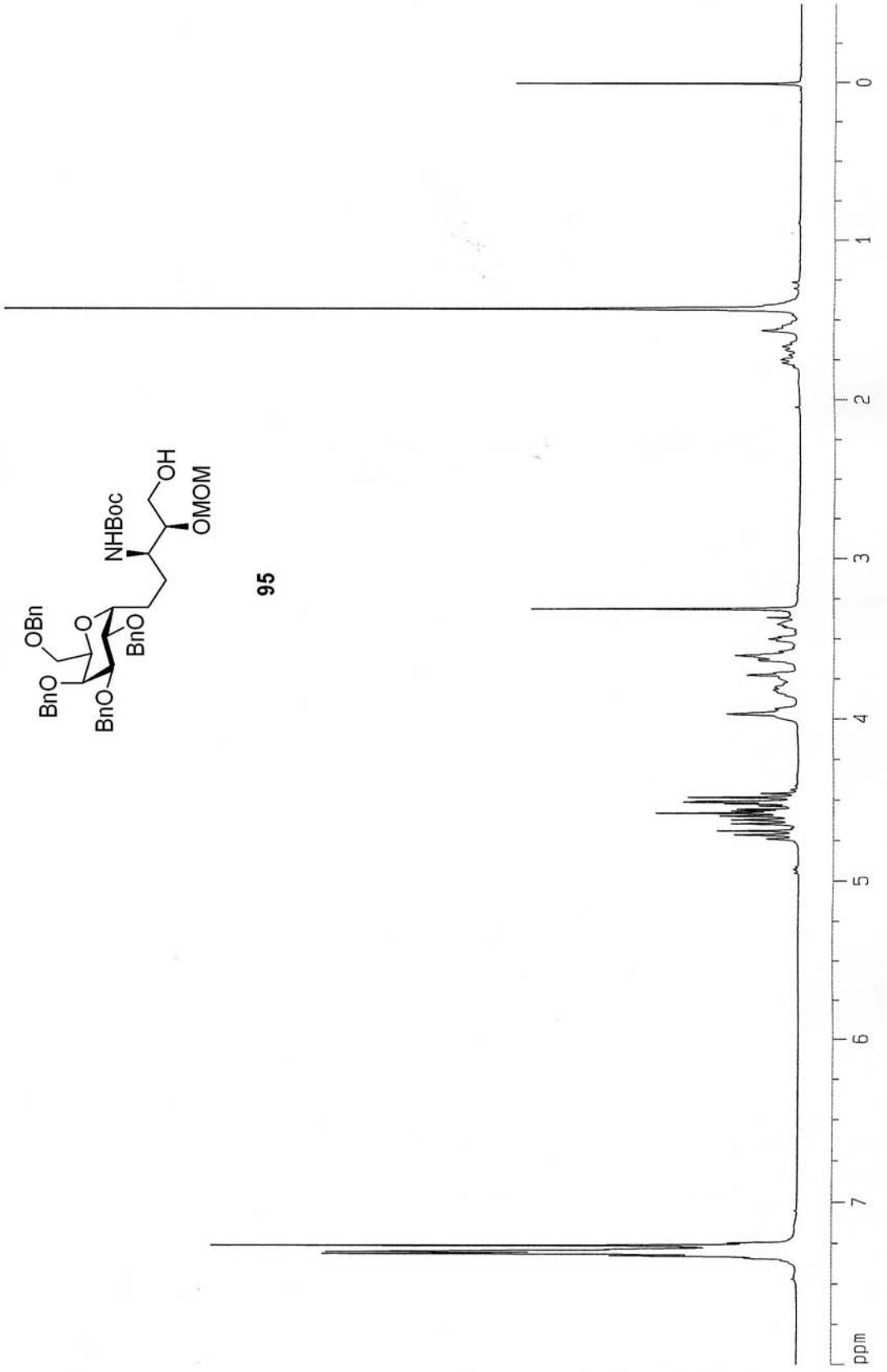

OBn
BnO
BnO
BnO
NHBoc
OTBS
OH
93
ppm
0
20
40
60
80
100
120
140
160

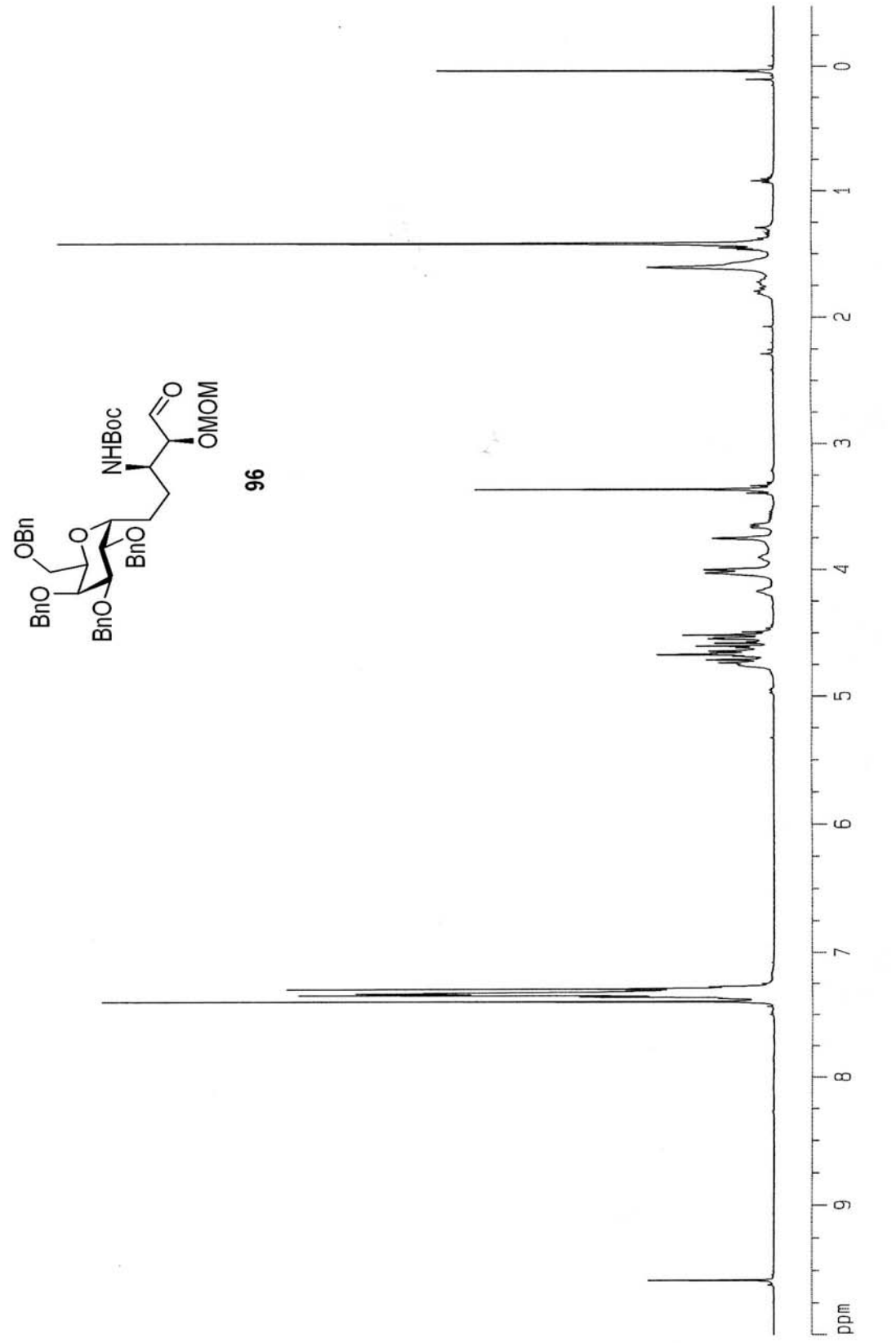

OBn
BnO
BnO
BnO
NHBoc
OTBS
OH
93
ppm
0
1
2
3
4
5
6
7

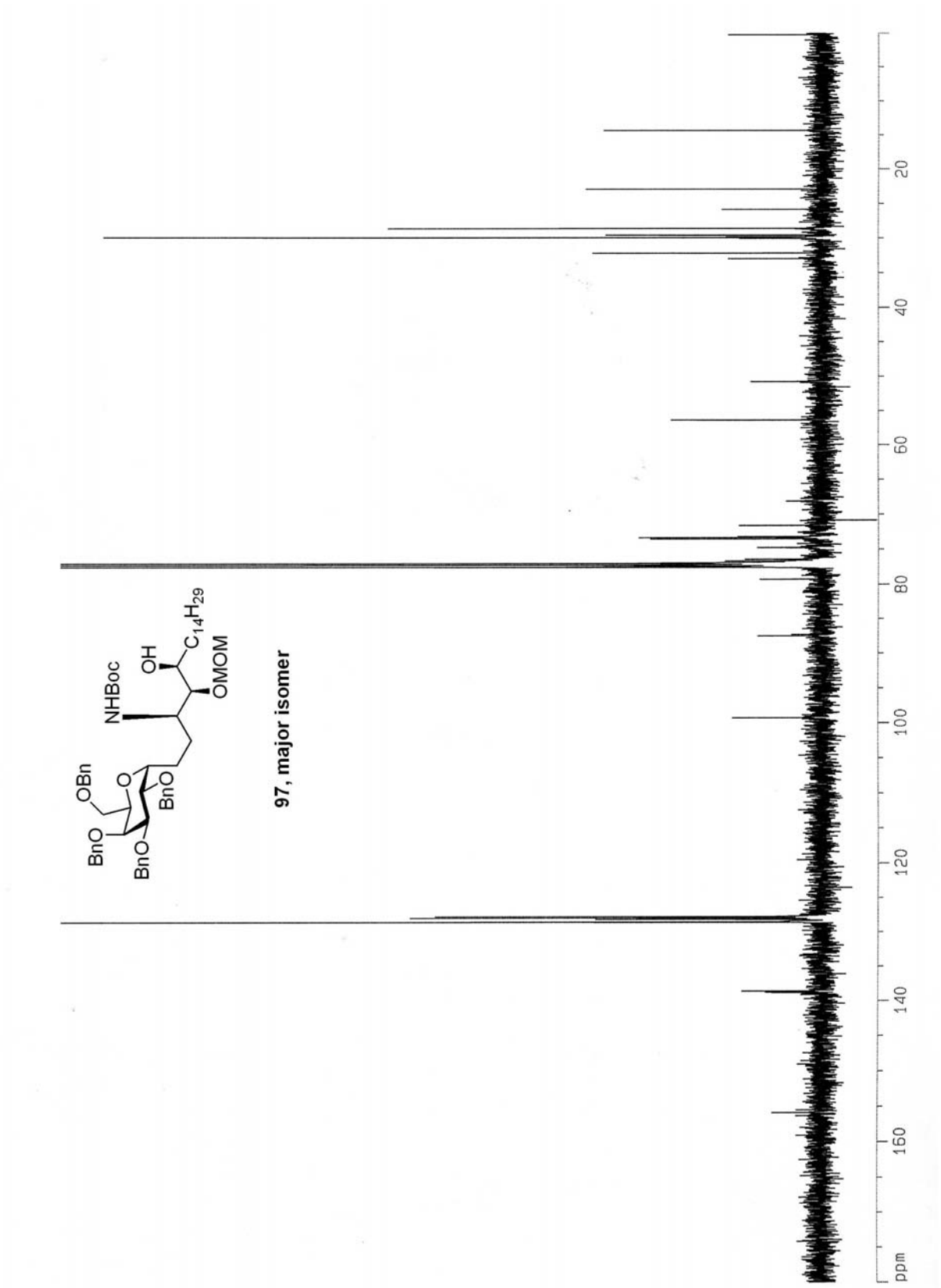

OBn
BnO
BnO
BnO
O
NHBoc
OTBS
OMOM
94
0
20
40
60
80
100
120
140
160
ppm


OBn
BnO
BnO
BnO
NHBoc
OTBS
OMOM
94
ppm
0
1
2
3
4
5
6
7

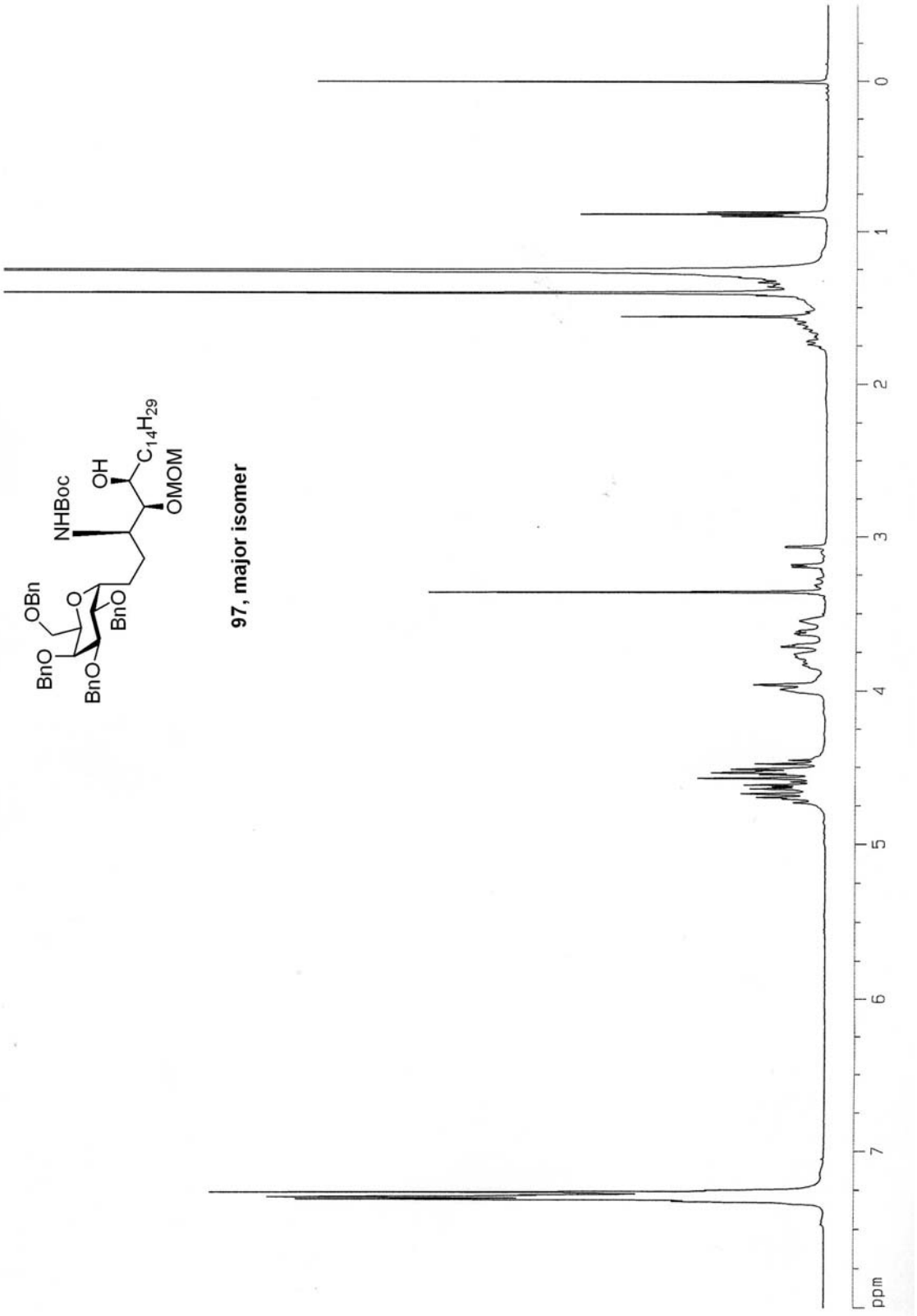

OBn
BnO
BnO
BnO
NHBoc
OH
OMOM
95
ppm
160
140
120
100
80
60
40
20


OBn
O
BnO
BnO
BnO
NHBoc
OMOM
OH
95
ppm
0
1
2
3
4
5
6
7

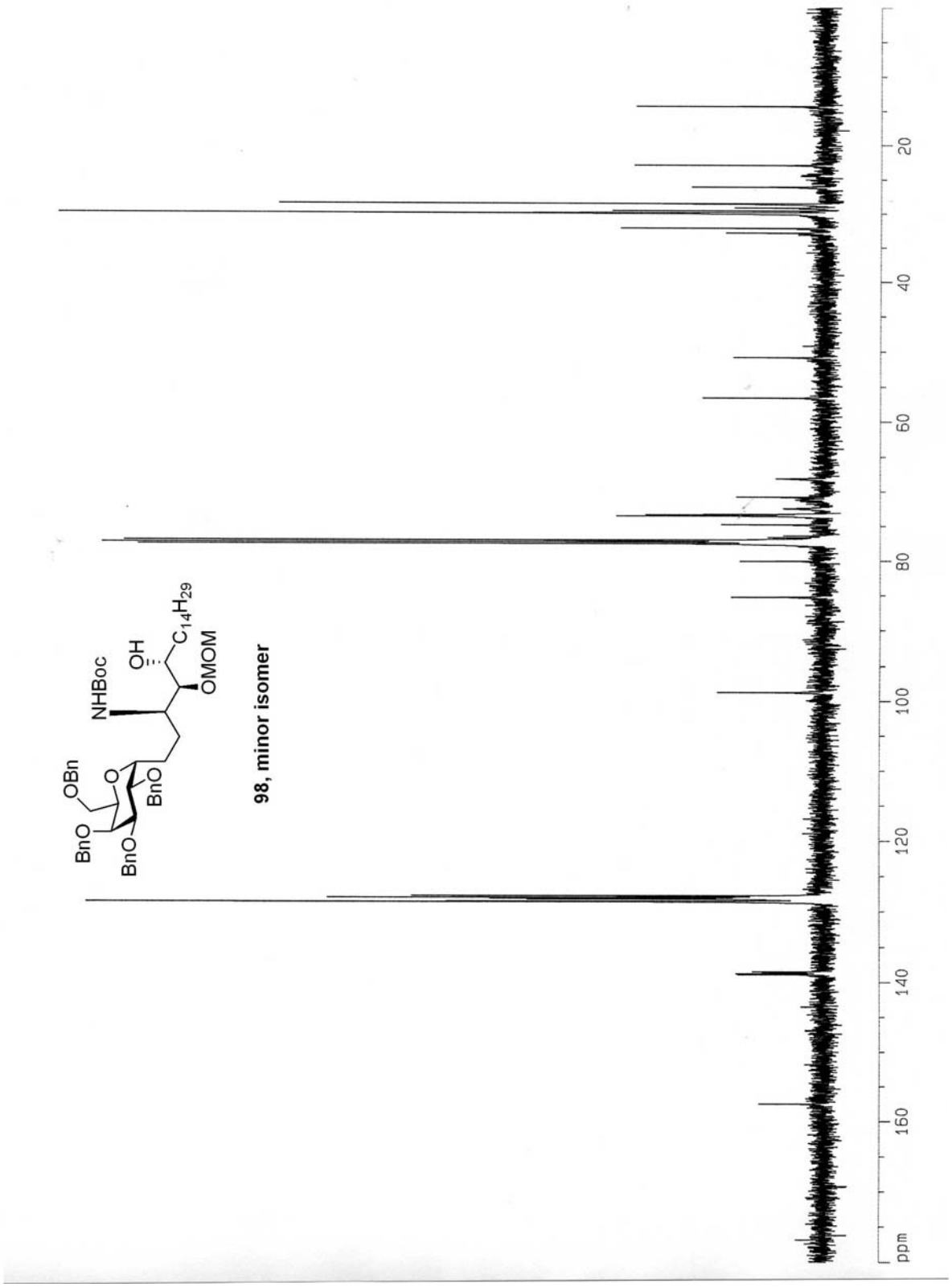

OBn
BnO
BnO
BnO
NHBoc
OMOM
O
96
ppm
9
8
7
6
5
4
3
2
1
0

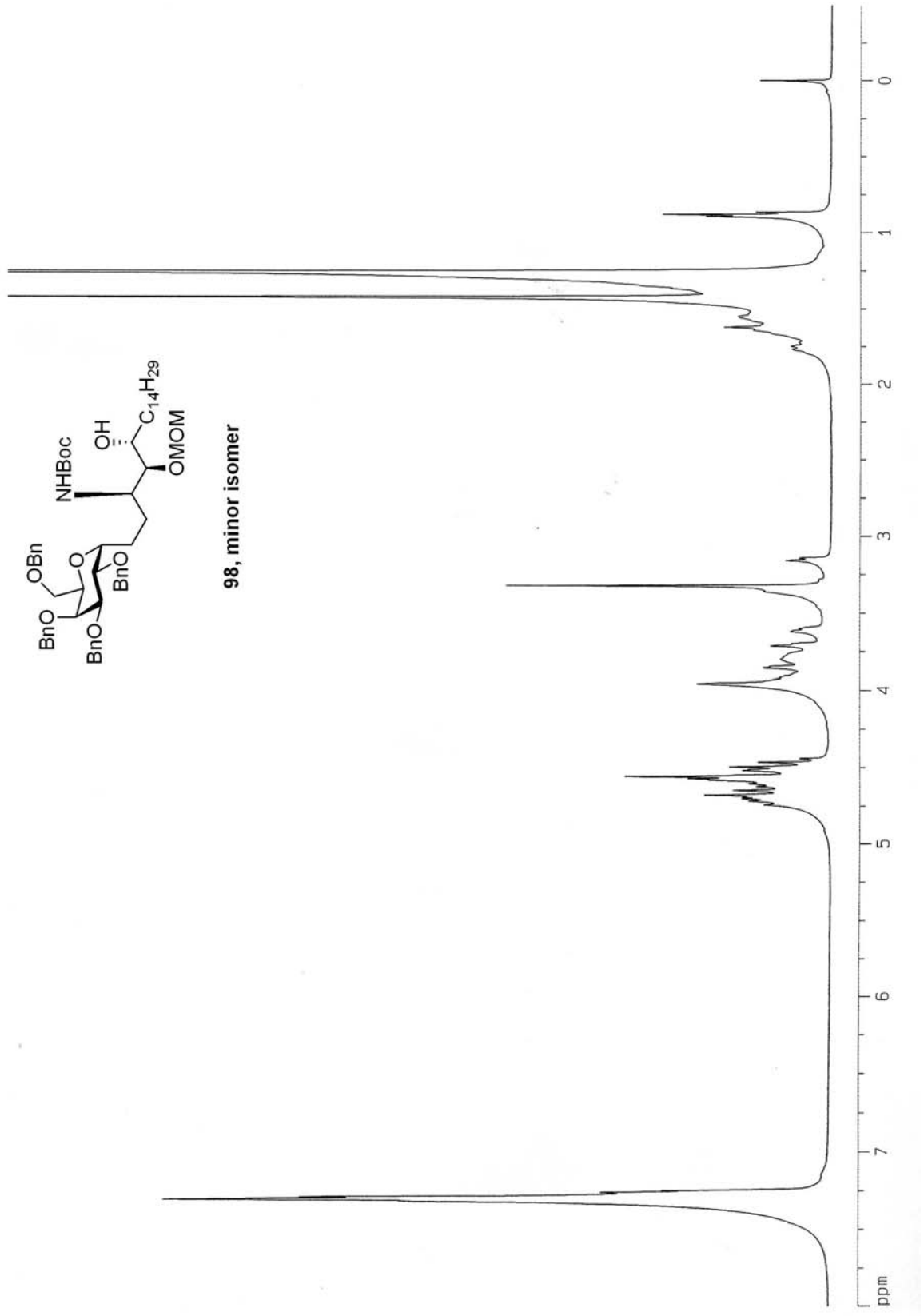


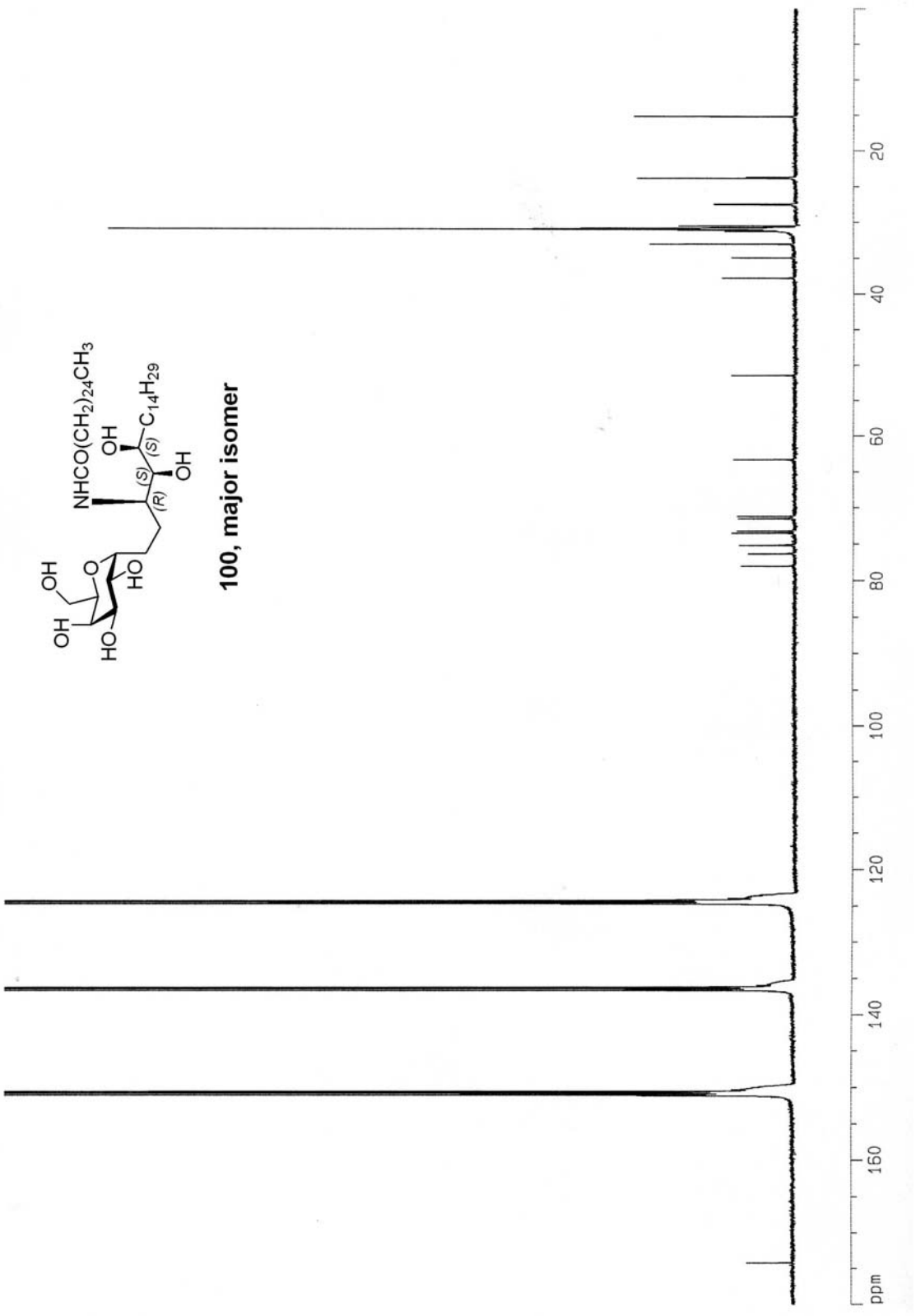
97, major isomer

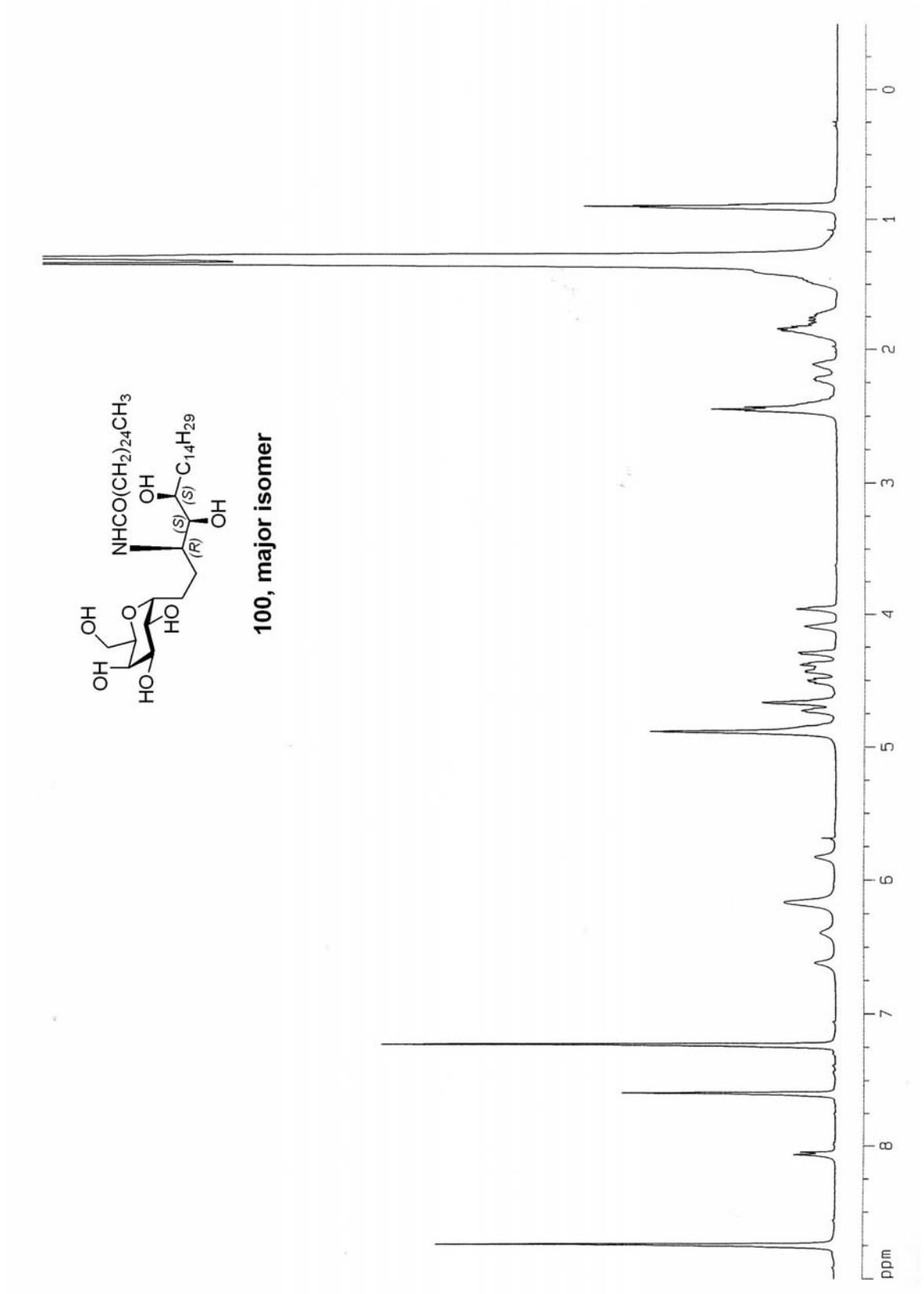


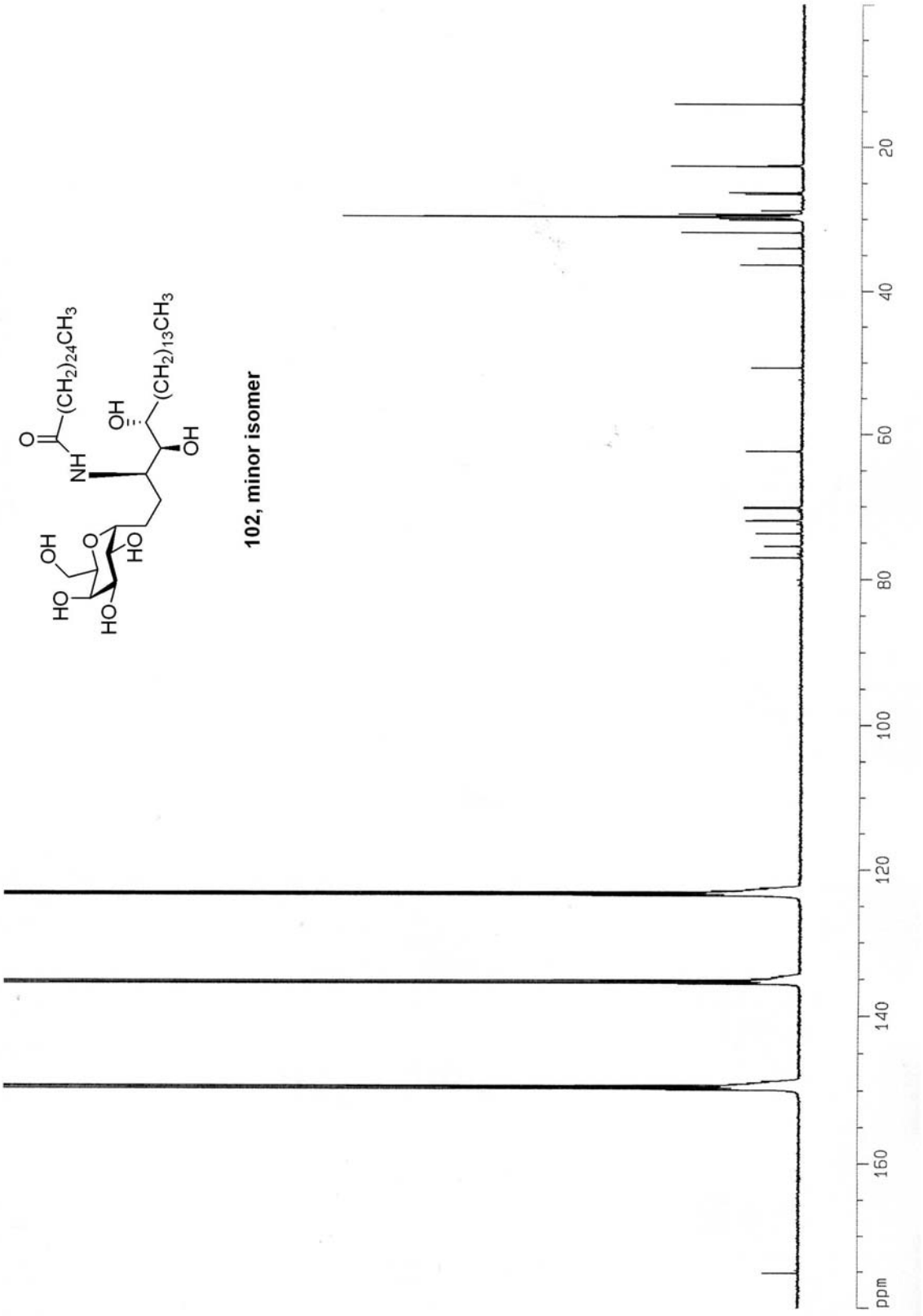
97, major isomer

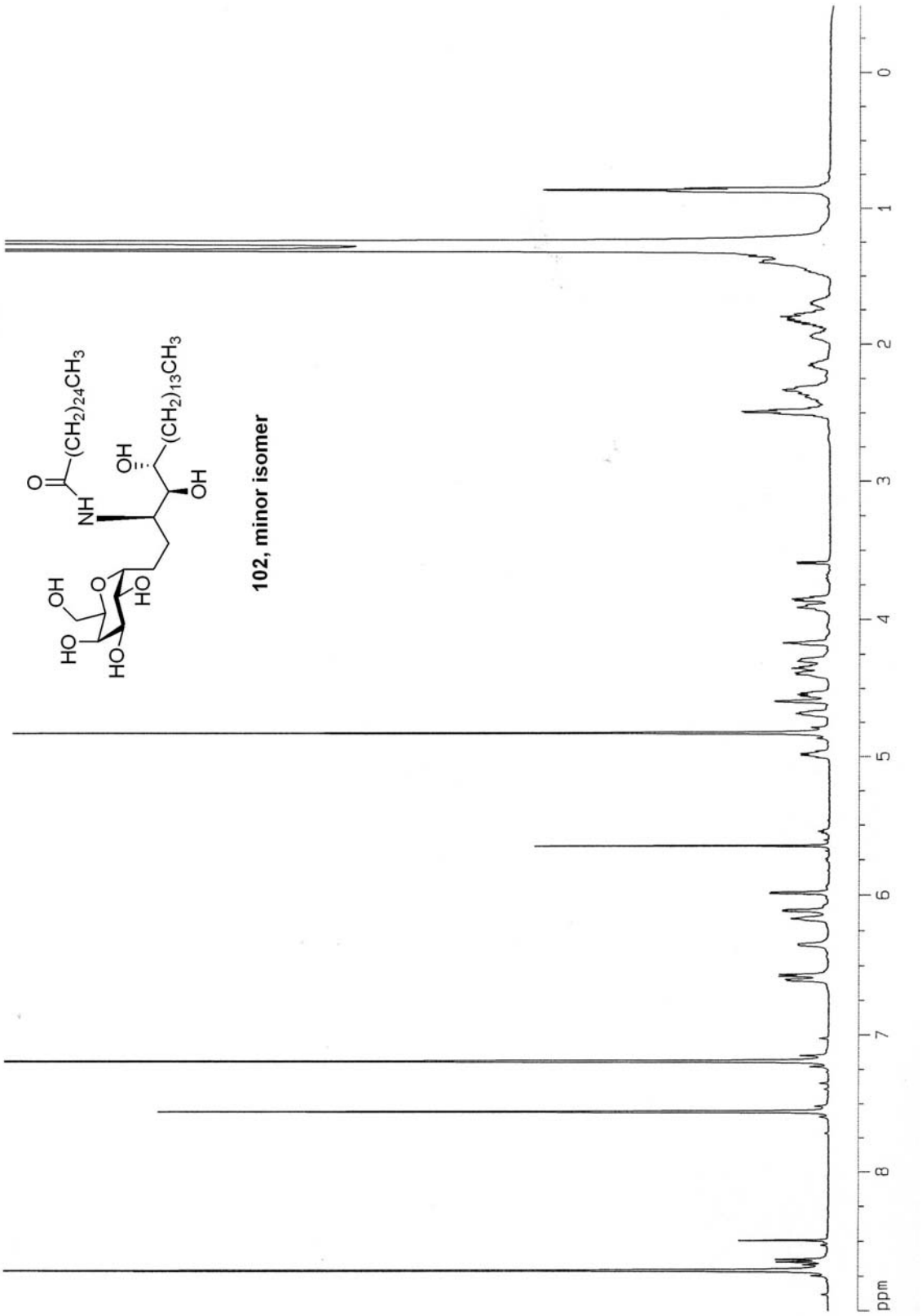

OBn
BnO
BnO
BnO
NHBoc
OH
$C_{14}H_{29}$
OMOM
98, minor isomer
ppm
160
140
120
100
80
60
40
20

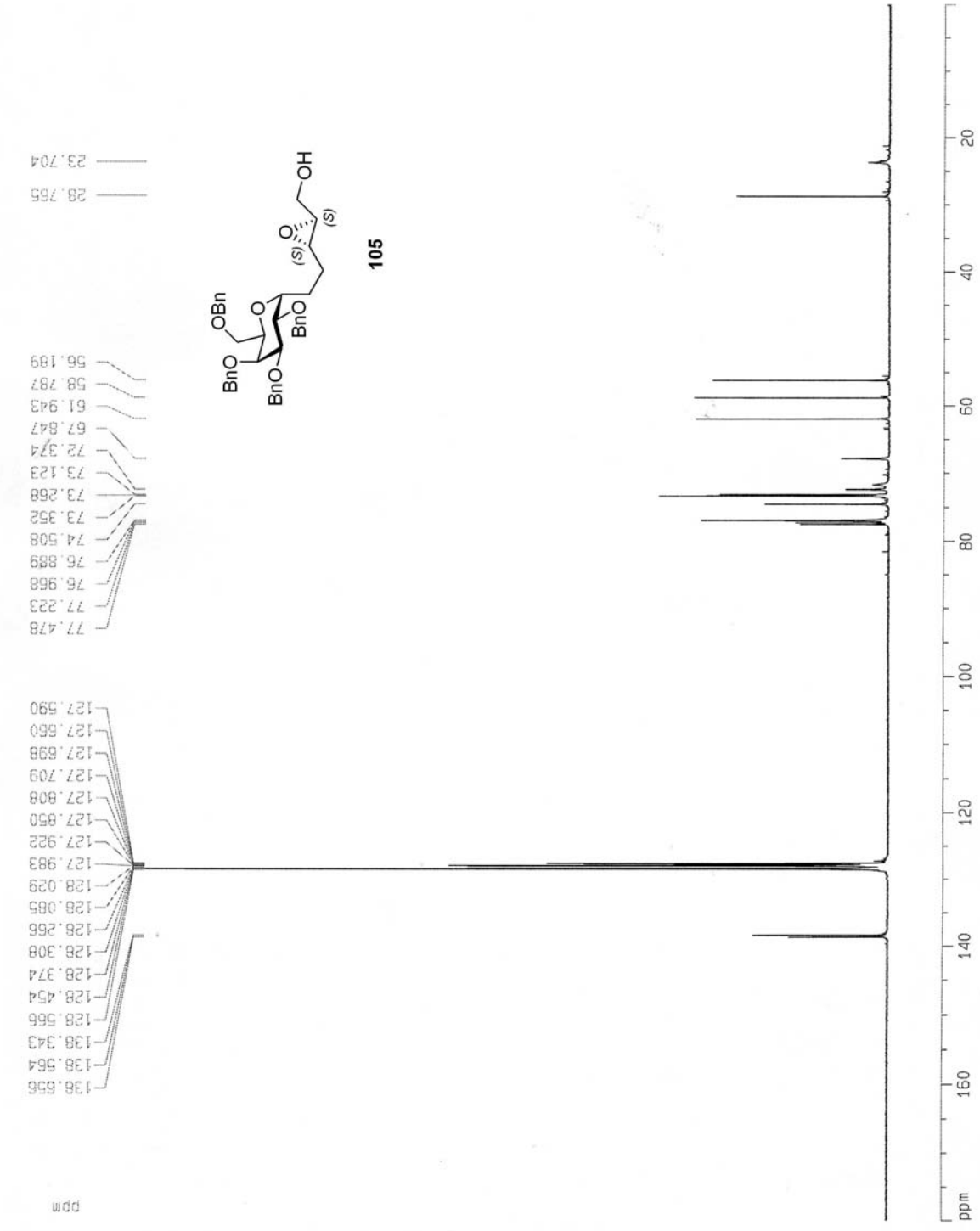

NHBoc
OH
$C_{14}H_{29}$
OMOM
OBn
BnO
BnO
BnO
O
98, minor isomer
ppm
0
1
2
3
4
5
6
7

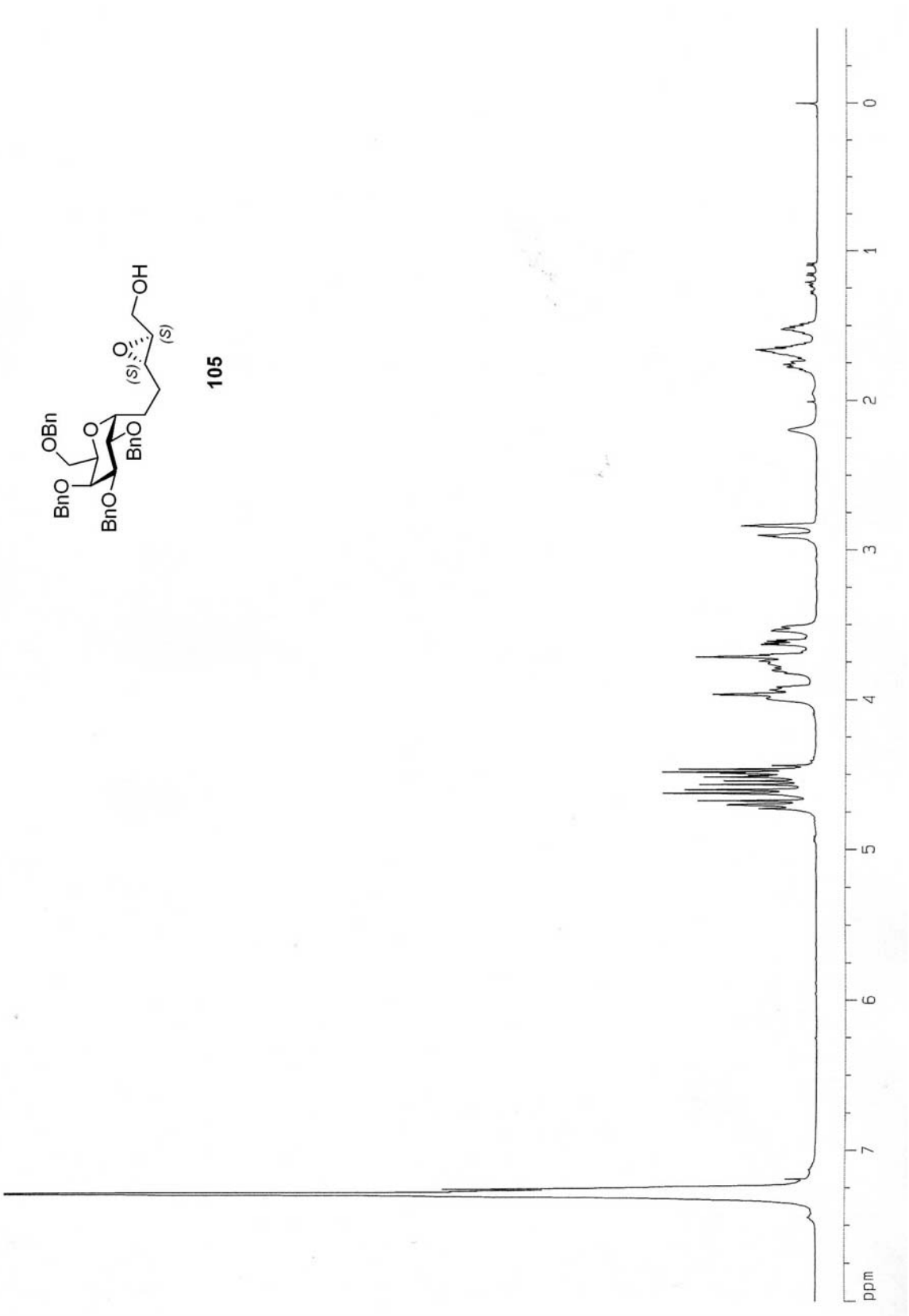

NHCO(CH2)24CH3
OH
(S)
(S)
C14H29
(R)
OH
HO
O
OH
OH
HO
100, major isomer
ppm
160
140
120
100
80
60
40
20

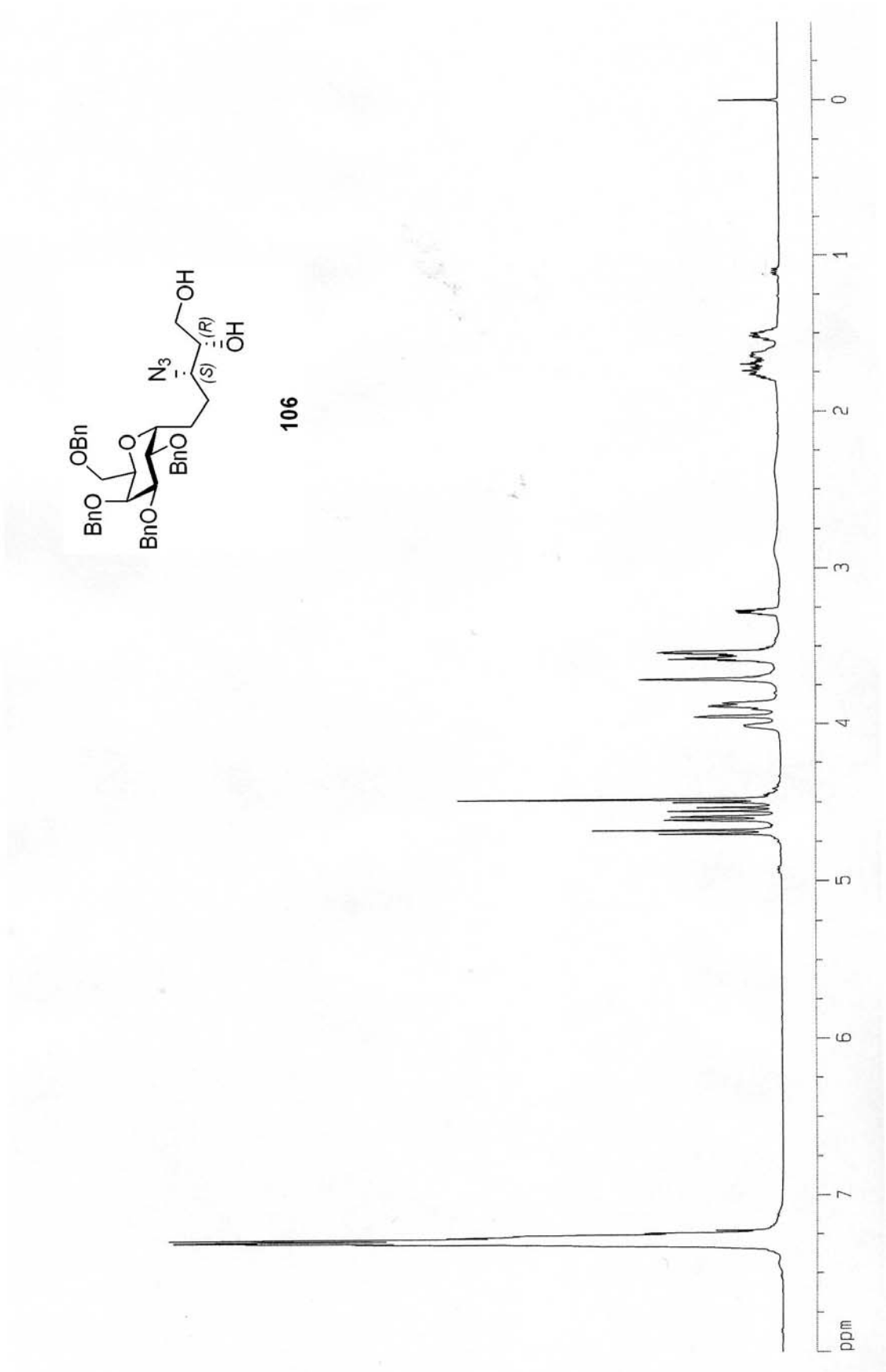

NHCO(CH2)24CH3
OH
(S)
(S)
C14H29
(R)
OH
HO
O
OH
OH
HO
100, major isomer
ppm
0
1
2
3
4
5
6
7
8

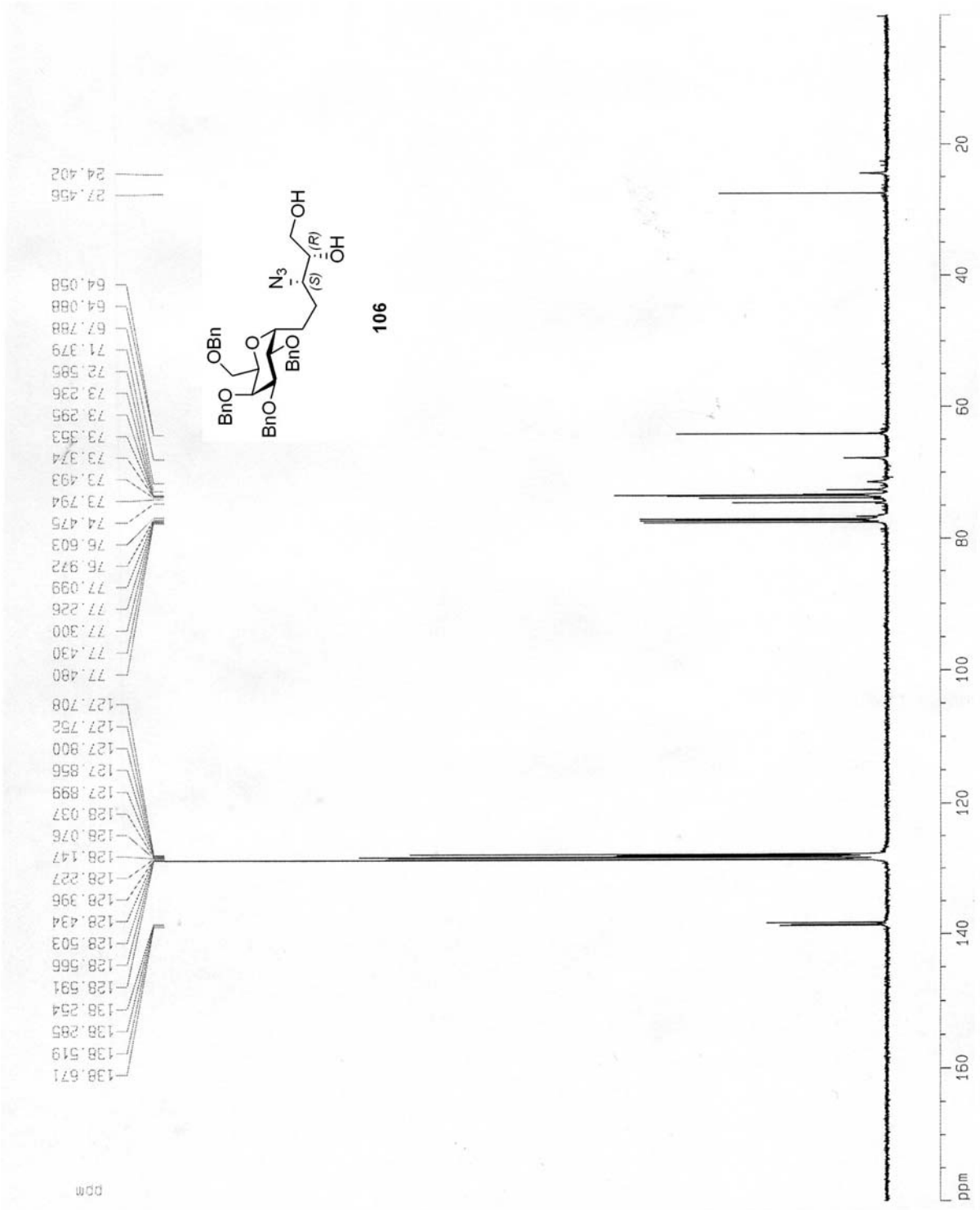

102, minor isomer
ppm
20
40
60
80
100
120
140
160

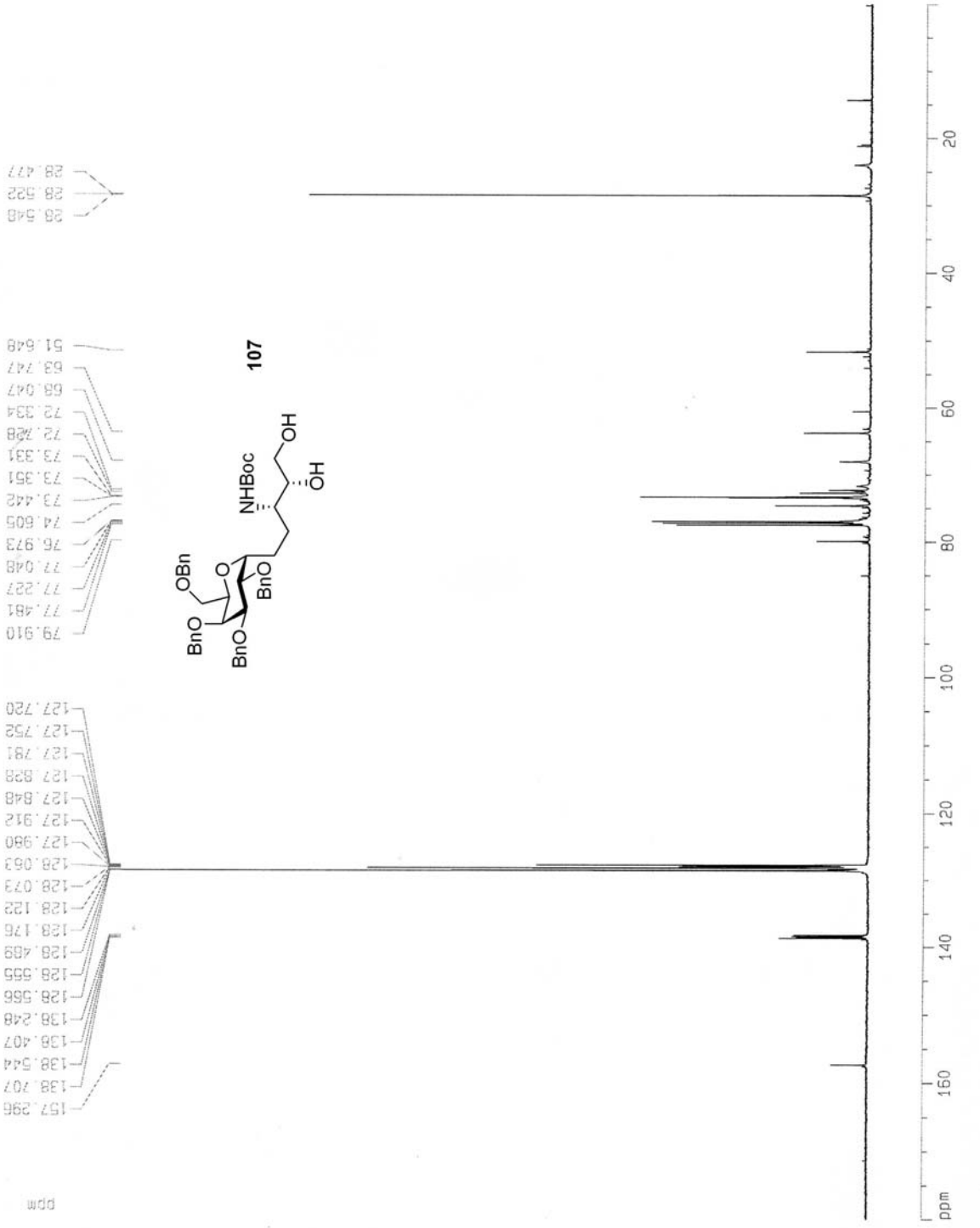

102, minor isomer
ppm

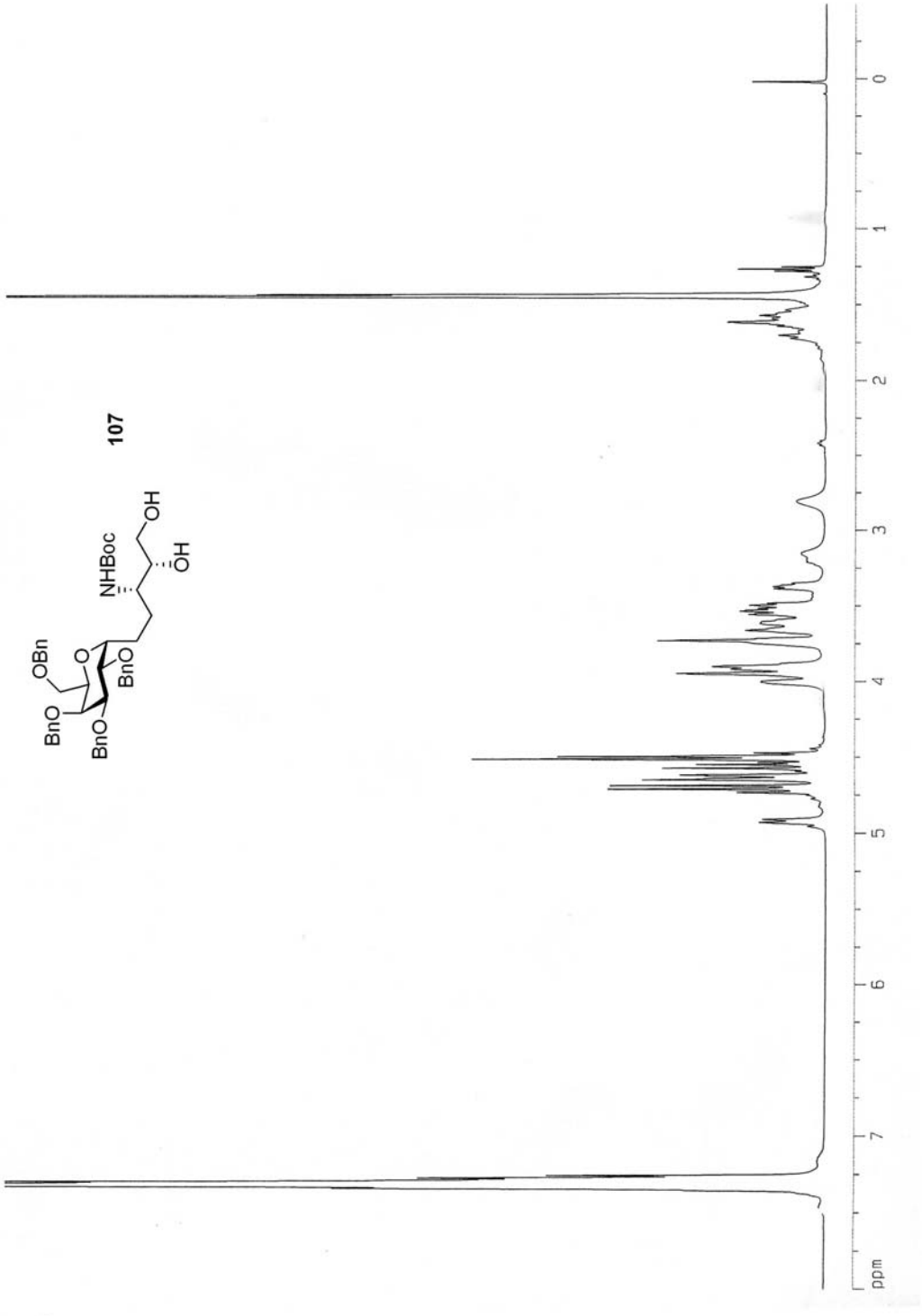

105
OH
(S)
(S)
O
OBn
BnO
BnO
BnO
23.704
28.765
56.189
58.787
61.943
67.847
72.374
73.123
73.268
73.352
74.508
76.889
76.968
77.223
77.478
127.590
127.660
127.698
127.709
127.808
127.850
127.922
127.983
128.029
128.085
128.266
128.308
128.374
128.454
128.566
138.343
138.564
138.656
ppm
20
40
60
80
100
120
140
160

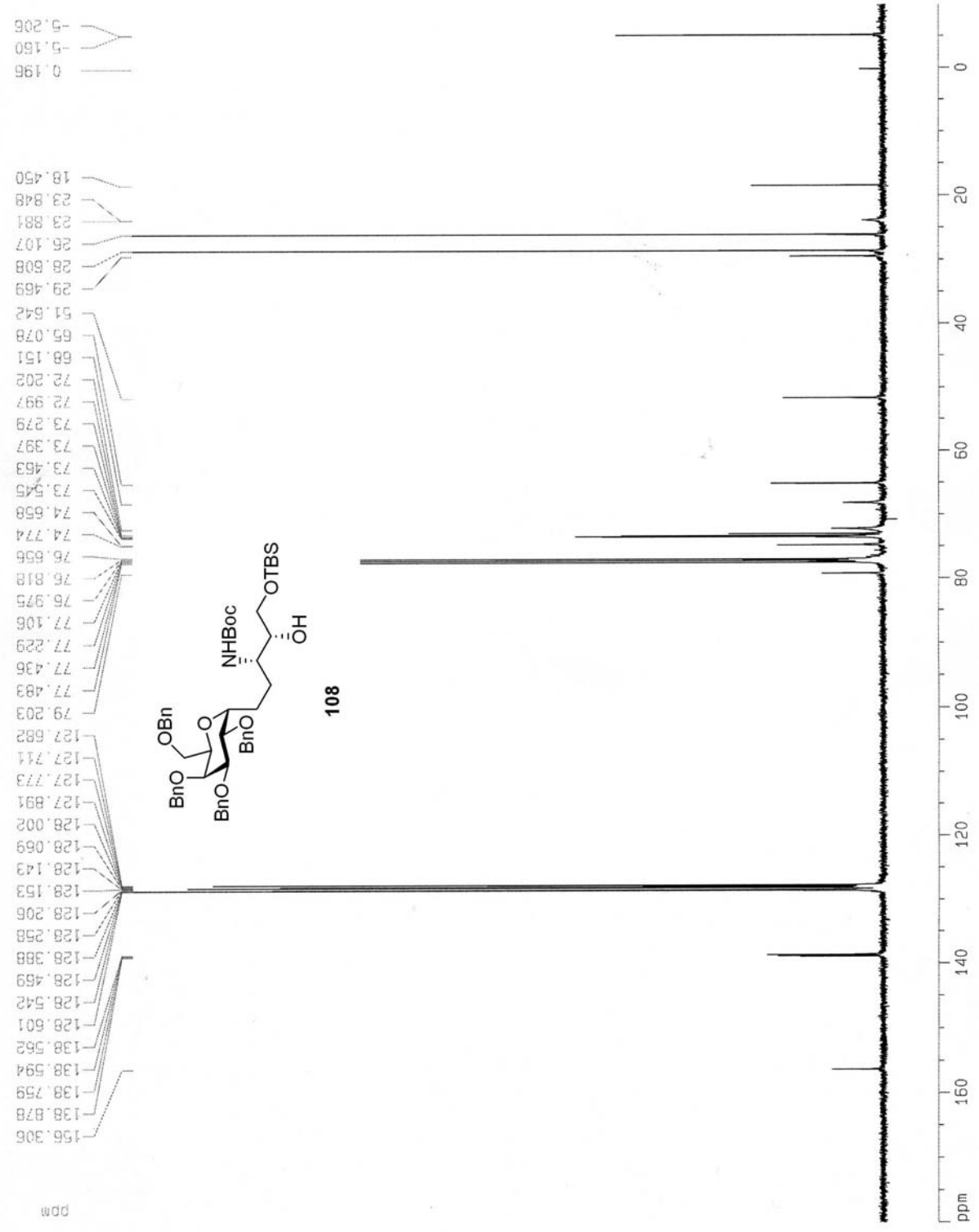

OBn
BnO
BnO
BnO
O
(S)
(S)
O
OH
105
ppm
0
1
2
3
4
5
6
7

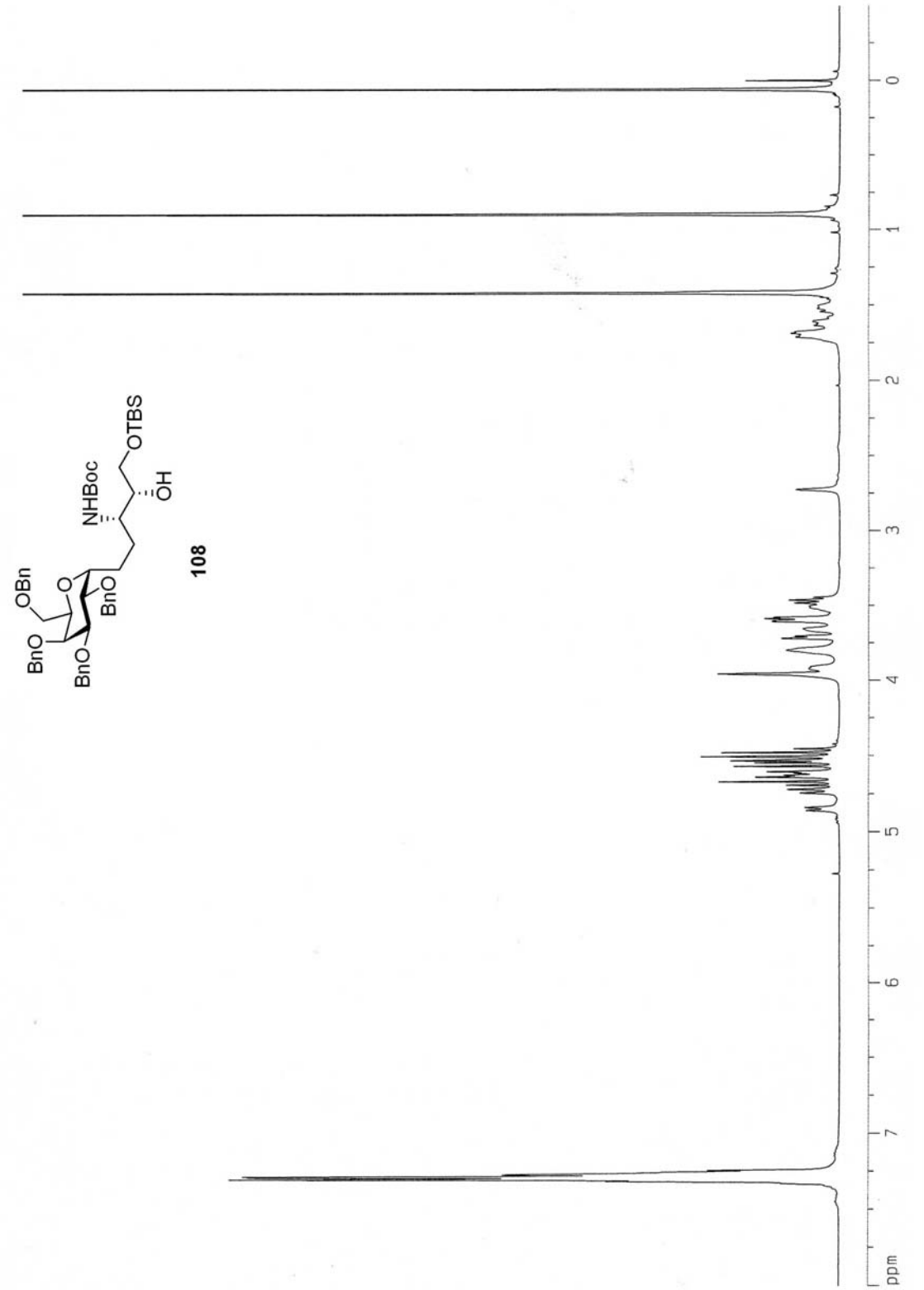

OBn
BnO
BnO
BnO
O
N3
(S)
(R)
OH
OH
106
ppm
0
1
2
3
4
5
6
7

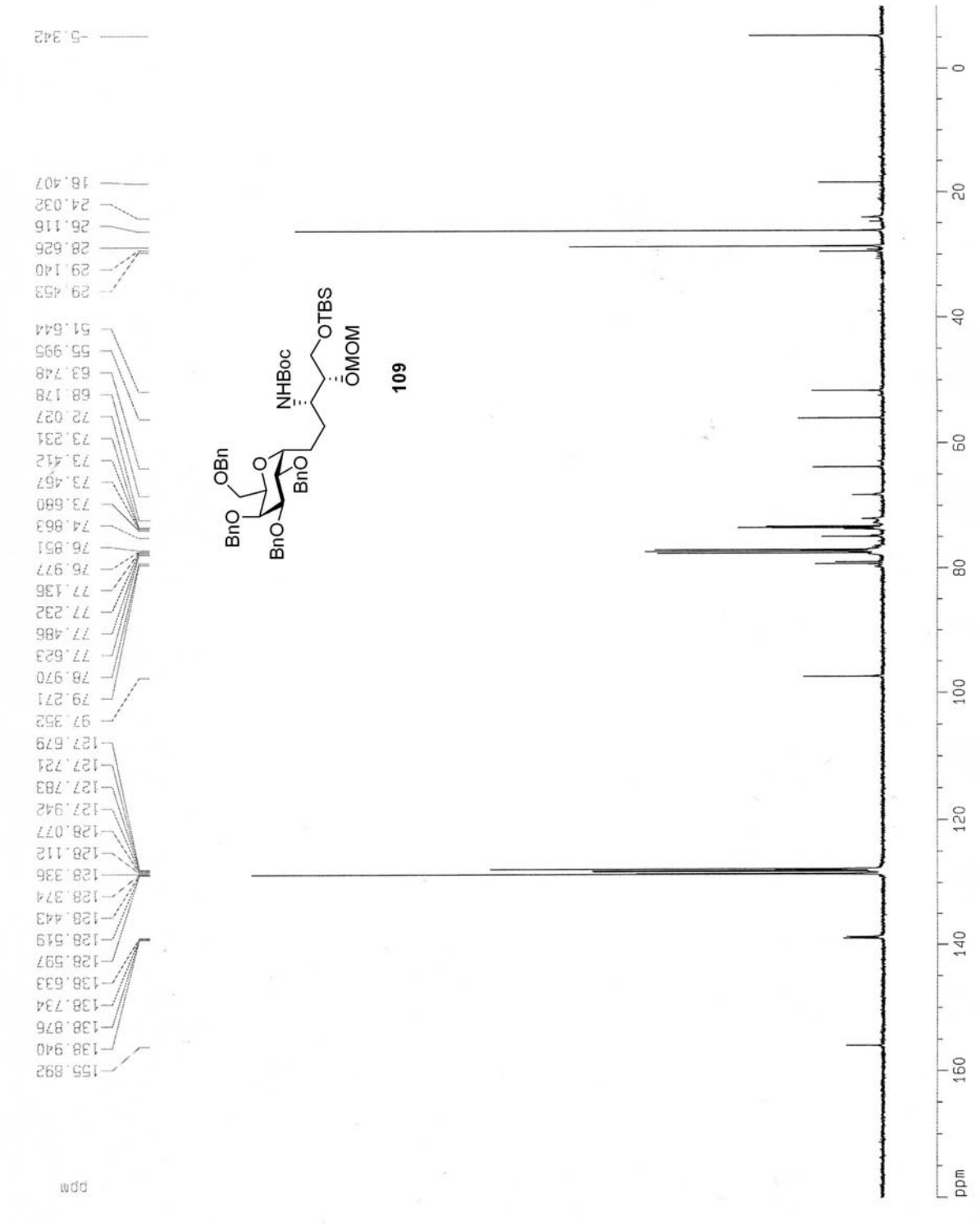

24.402
27.456
64.058
64.088
67.788
71.379
72.585
73.236
73.295
73.353
73.374
73.493
73.794
74.475
76.603
76.972
77.099
77.226
77.300
77.430
77.480
127.708
127.752
127.800
127.856
127.899
128.037
128.076
128.147
128.227
128.396
128.434
128.503
128.566
128.591
138.254
138.285
138.519
138.671
ppm
20
40
60
80
100
120
140
160
OBn
BnO
BnO
BnO
N3
(S)
(R)
OH
OH
106

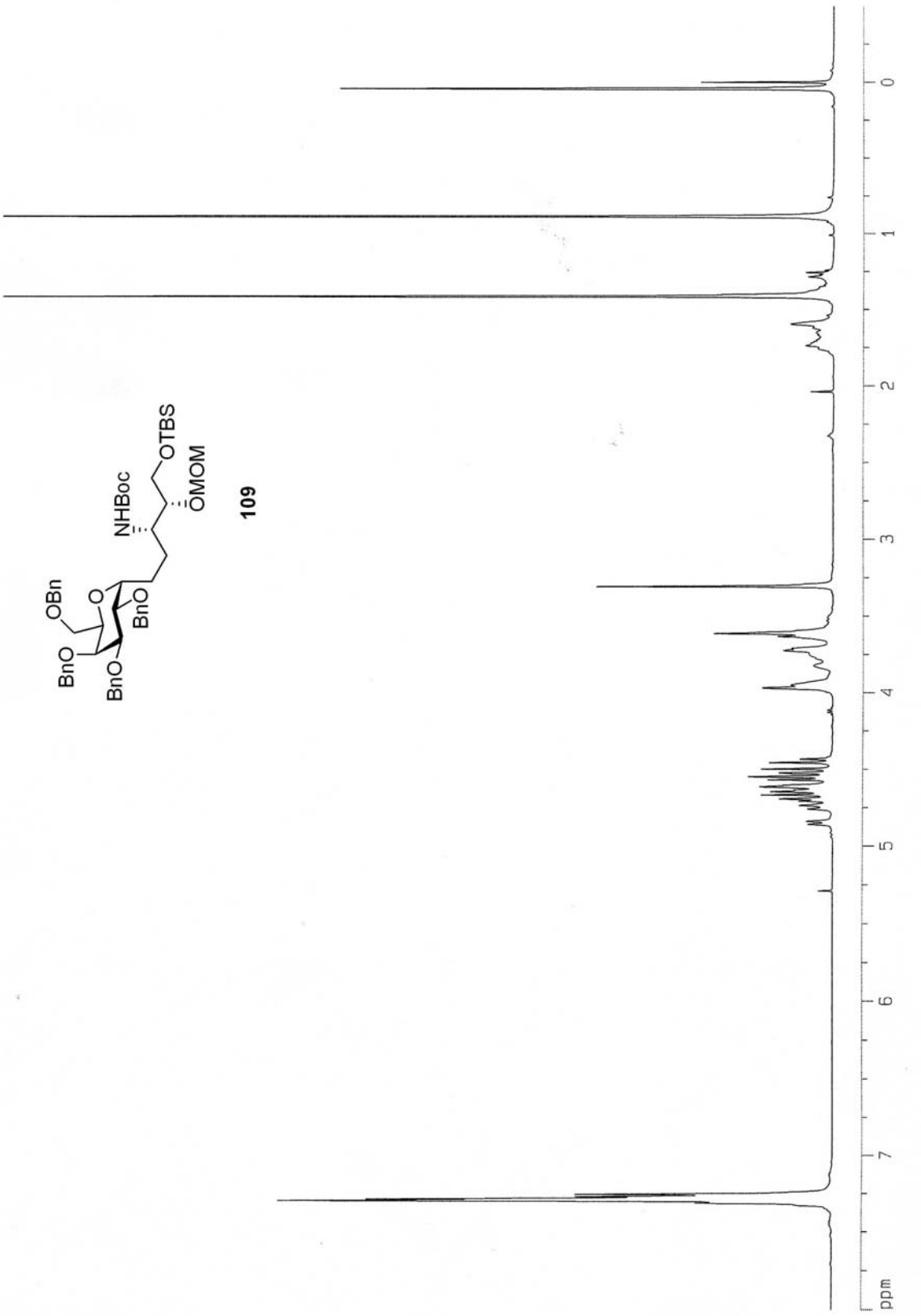

107
NHBoc
OH
OH
OBn
BnO
BnO
BnO
28.548
28.522
28.477
51.648
63.747
68.047
72.334
72.428
73.331
73.351
73.442
74.605
76.973
77.048
77.227
77.481
79.910
127.720
127.752
127.781
127.828
127.848
127.912
127.980
128.063
128.073
128.122
128.176
128.489
128.555
128.566
138.248
138.407
138.544
138.707
157.296
ppm
20
40
60
80
100
120
140
160
ppm

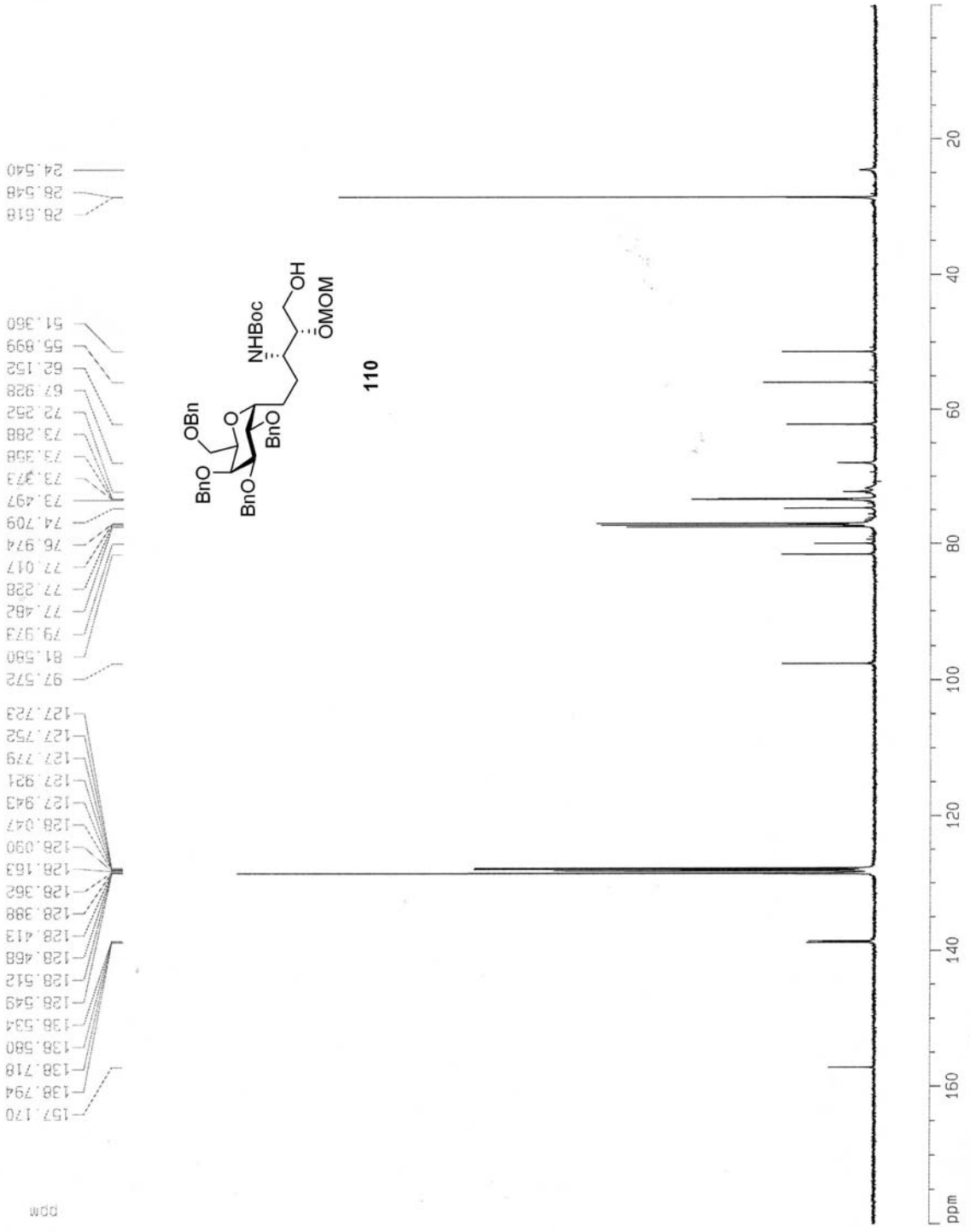

107
NHBoc
OH
OH
OBn
BnO
BnO
BnO
O
ppm
0
1
2
3
4
5
6
7

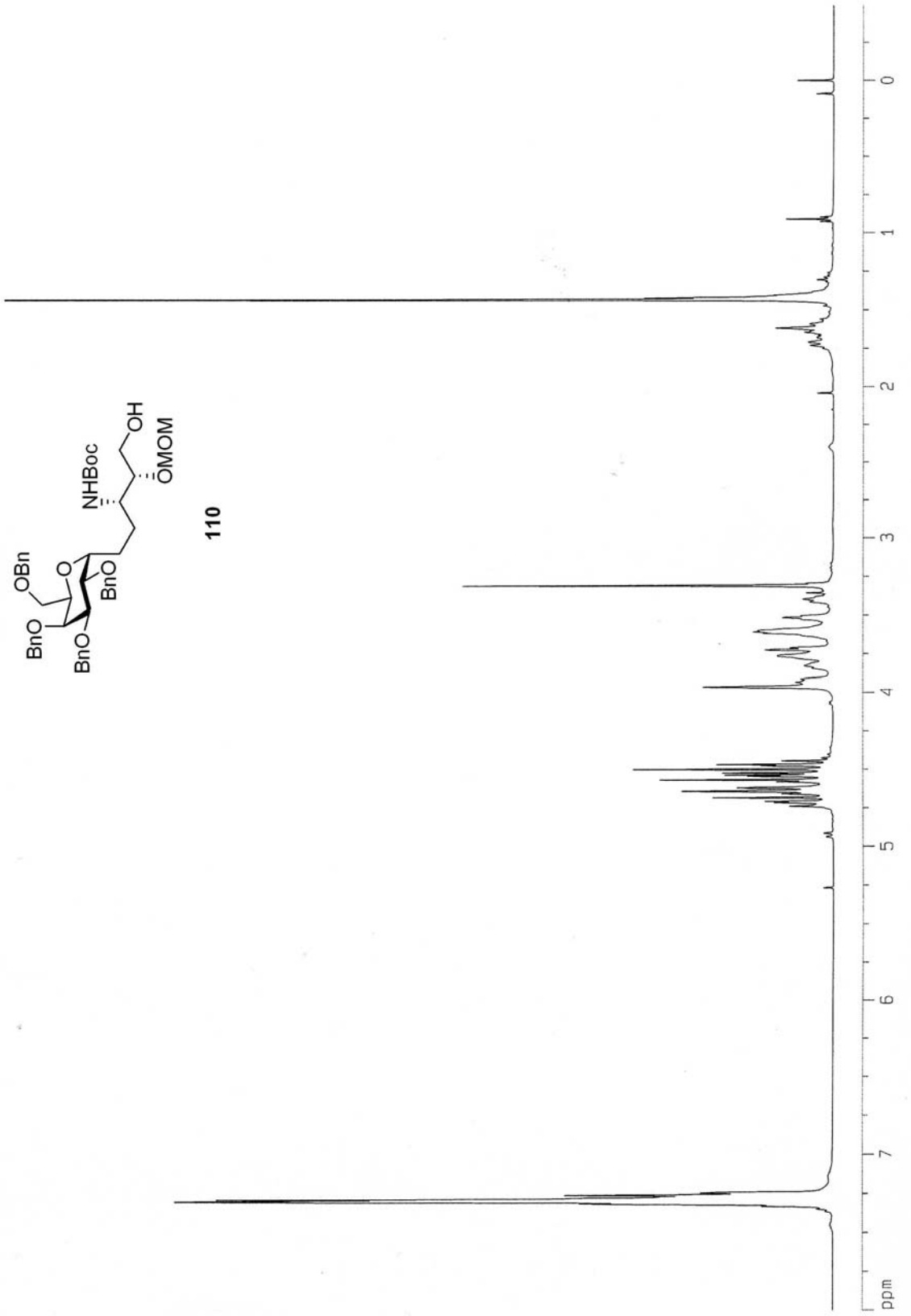

-5.206
-5.160
0.196
18.450
23.848
23.881
26.107
28.608
29.469
51.642
65.078
68.151
72.202
72.997
73.279
73.397
73.463
73.545
74.658
74.774
76.656
76.818
76.975
77.106
77.229
77.436
77.483
79.203
127.682
127.711
127.773
127.891
128.002
128.069
128.143
128.153
128.206
128.258
128.388
128.469
128.542
128.601
138.562
138.594
138.759
138.878
156.306
ppm
0
20
40
60
80
100
120
140
160
OBn
BnO
BnO
BnO
O
NHBoc
OTBS
OH
108


OBn
BnO
BnO
BnO
NHBoc
OH
OTBS
108
ppm
0
1
2
3
4
5
6
7

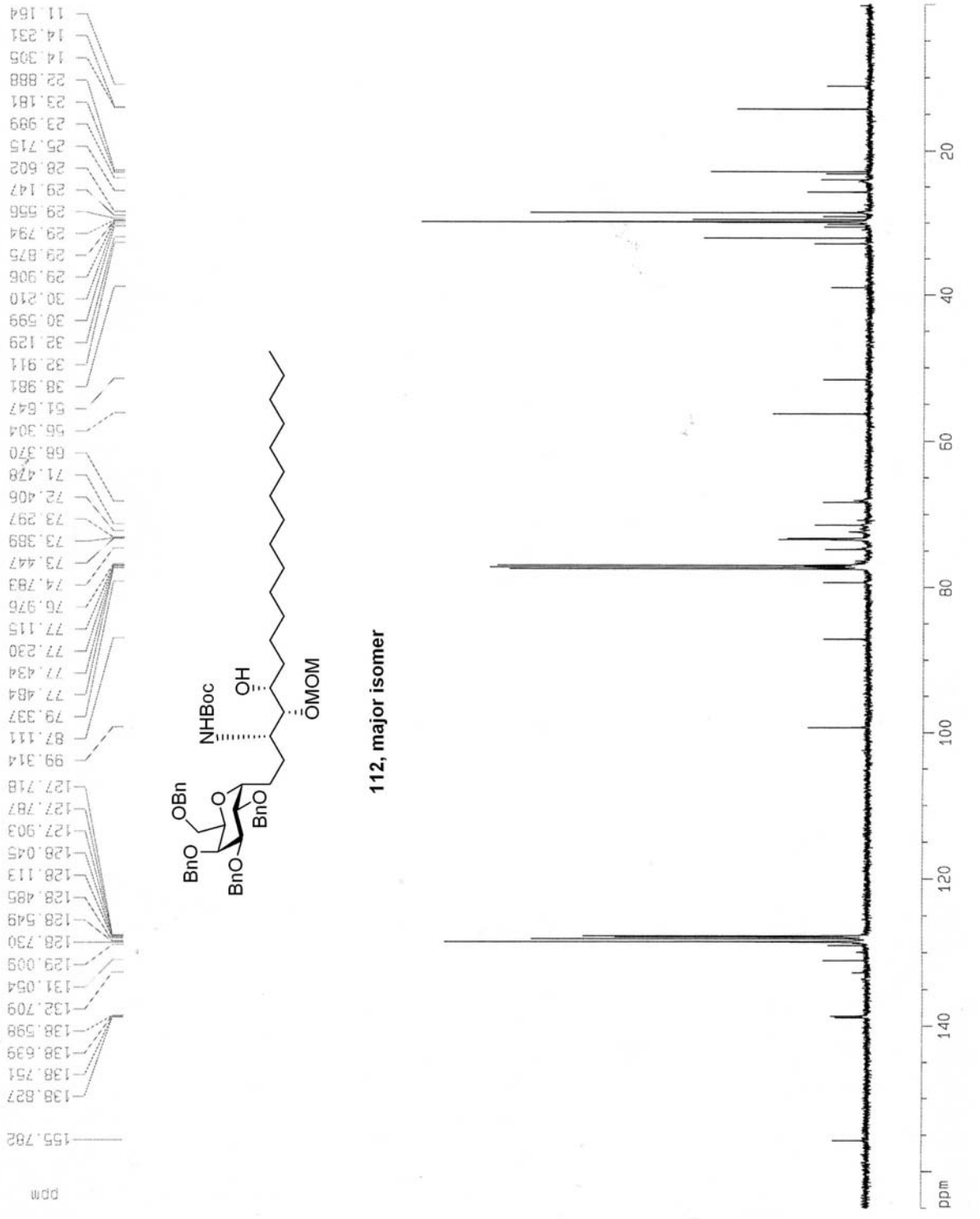

OTBS
OMOM
NHBoc
OBn
BnO
BnO
BnO
109
ppm
0
20
40
60
80
100
120
140
160
-5.342
18.407
24.032
26.116
28.626
29.140
29.453
51.644
55.995
63.748
68.178
72.027
73.231
73.412
73.467
73.680
74.863
76.851
76.977
77.136
77.232
77.486
77.623
78.970
79.271
97.352
127.679
127.721
127.783
127.942
128.077
128.112
128.336
128.374
128.443
128.519
128.597
138.633
138.734
138.876
138.940
155.892
ppm

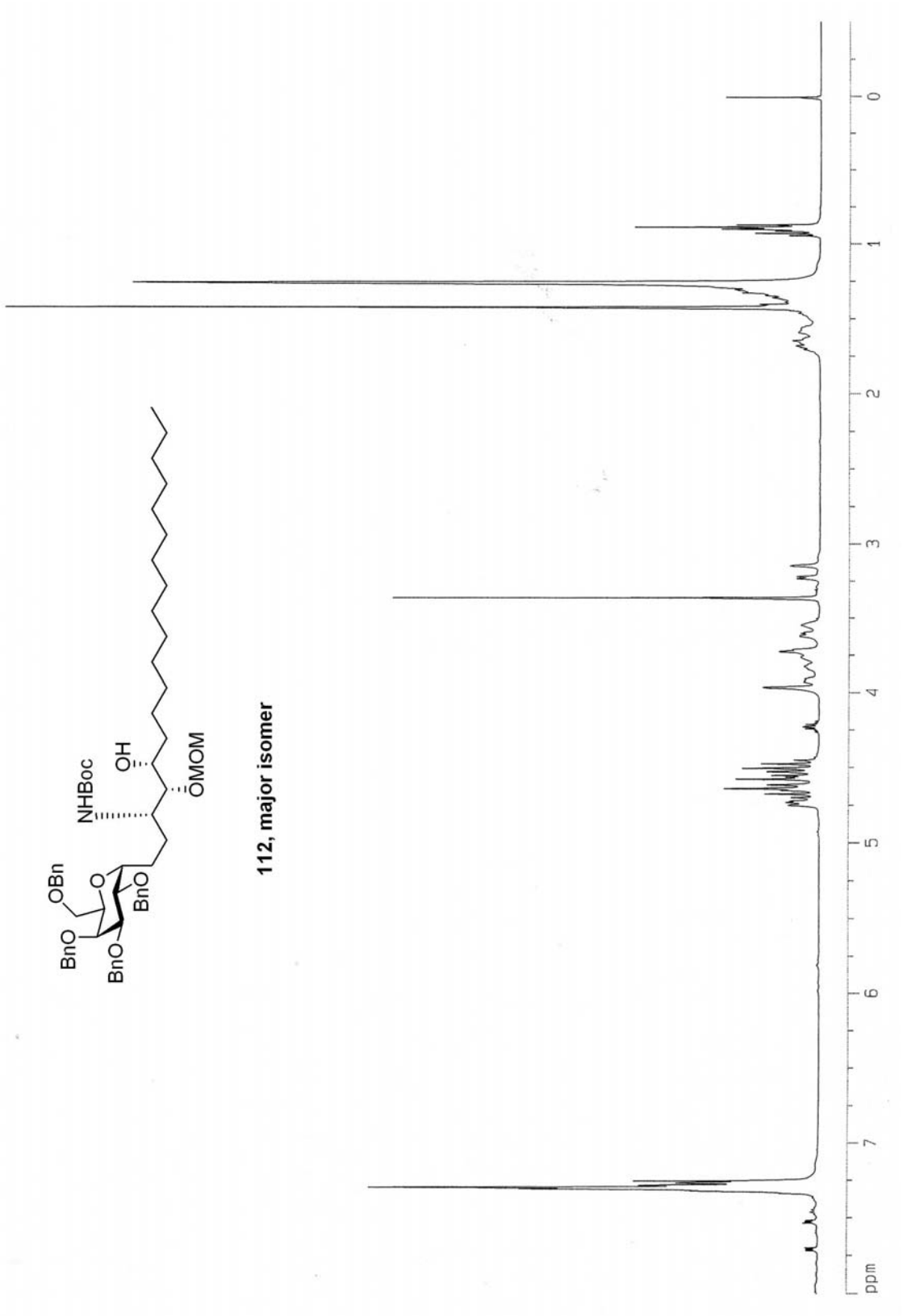

OBn
BnO
BnO
BnO
NHBoc
OTBS
OMOM
109
ppm
0
1
2
3
4
5
6
7

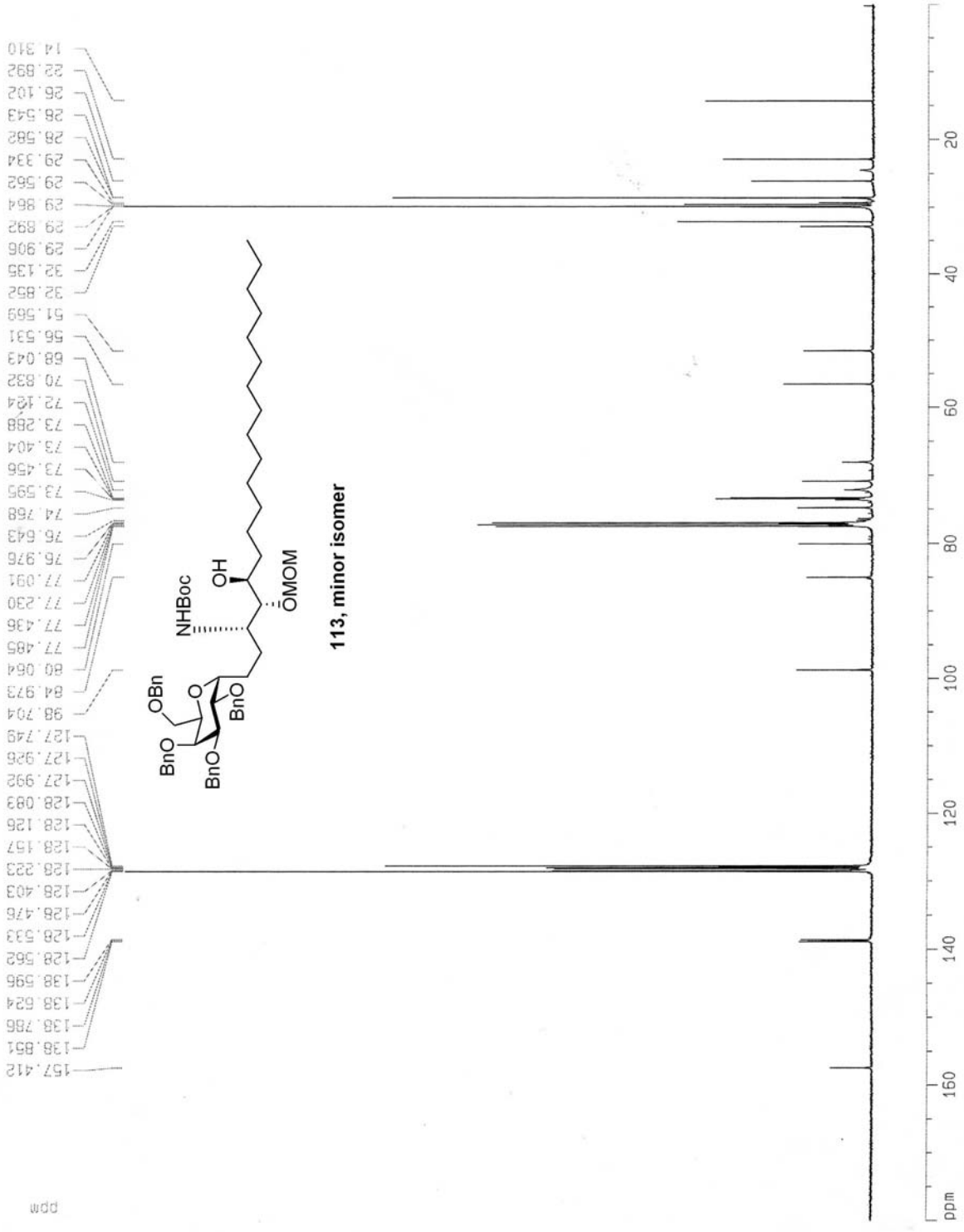

24.540
28.548
28.618
51.360
55.899
62.152
67.928
72.252
73.288
73.358
73.373
73.497
74.709
76.974
77.017
77.228
77.482
79.973
81.580
97.572
127.723
127.752
127.779
127.921
127.943
128.047
128.090
128.163
128.362
128.388
128.413
128.468
128.512
128.549
136.534
138.580
138.718
138.794
157.170
ppm
OBn
BnO
BnO
BnO
NHBoc
OMOM
OH
110
20
40
60
80
100
120
140
160
ppm

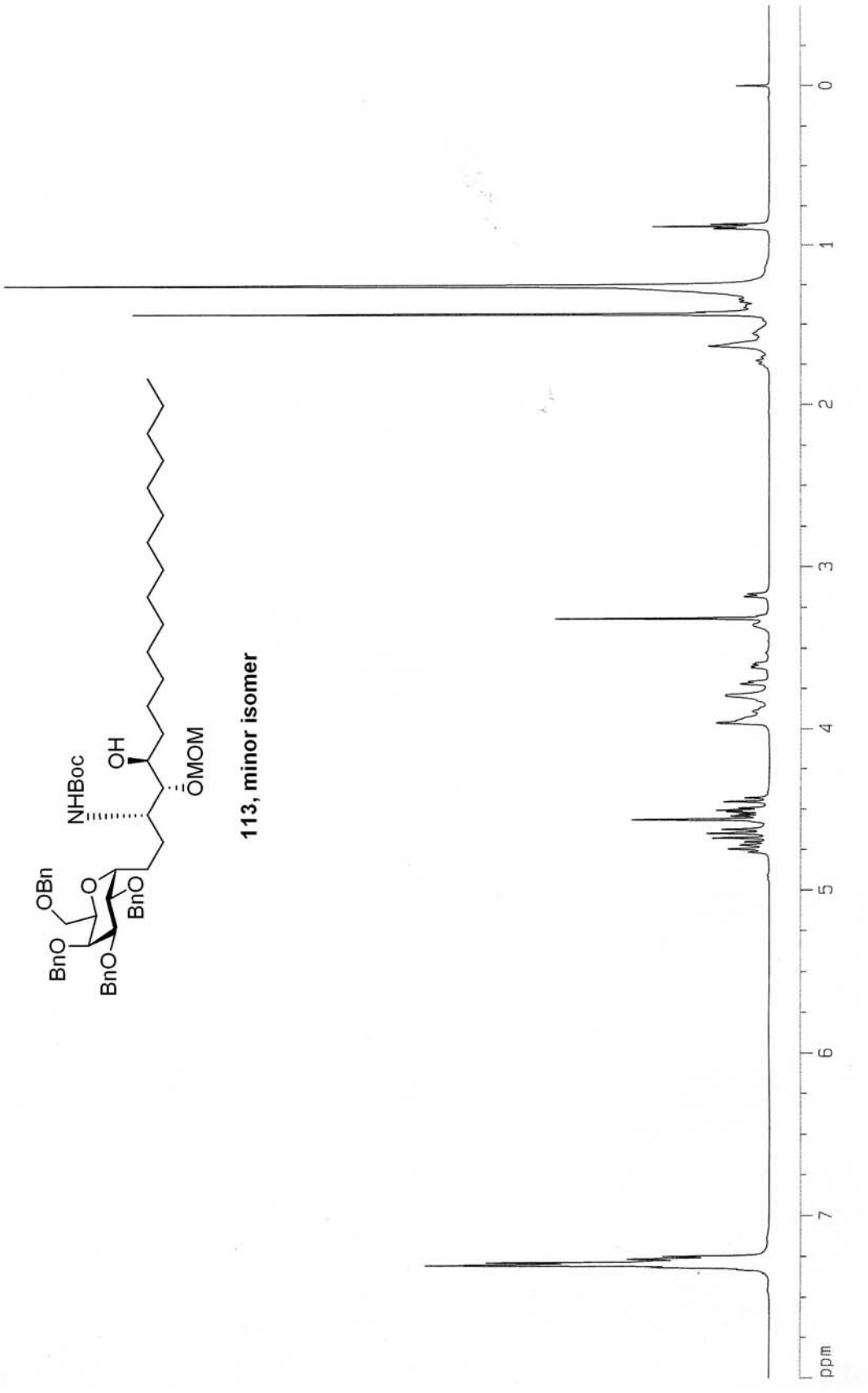


110

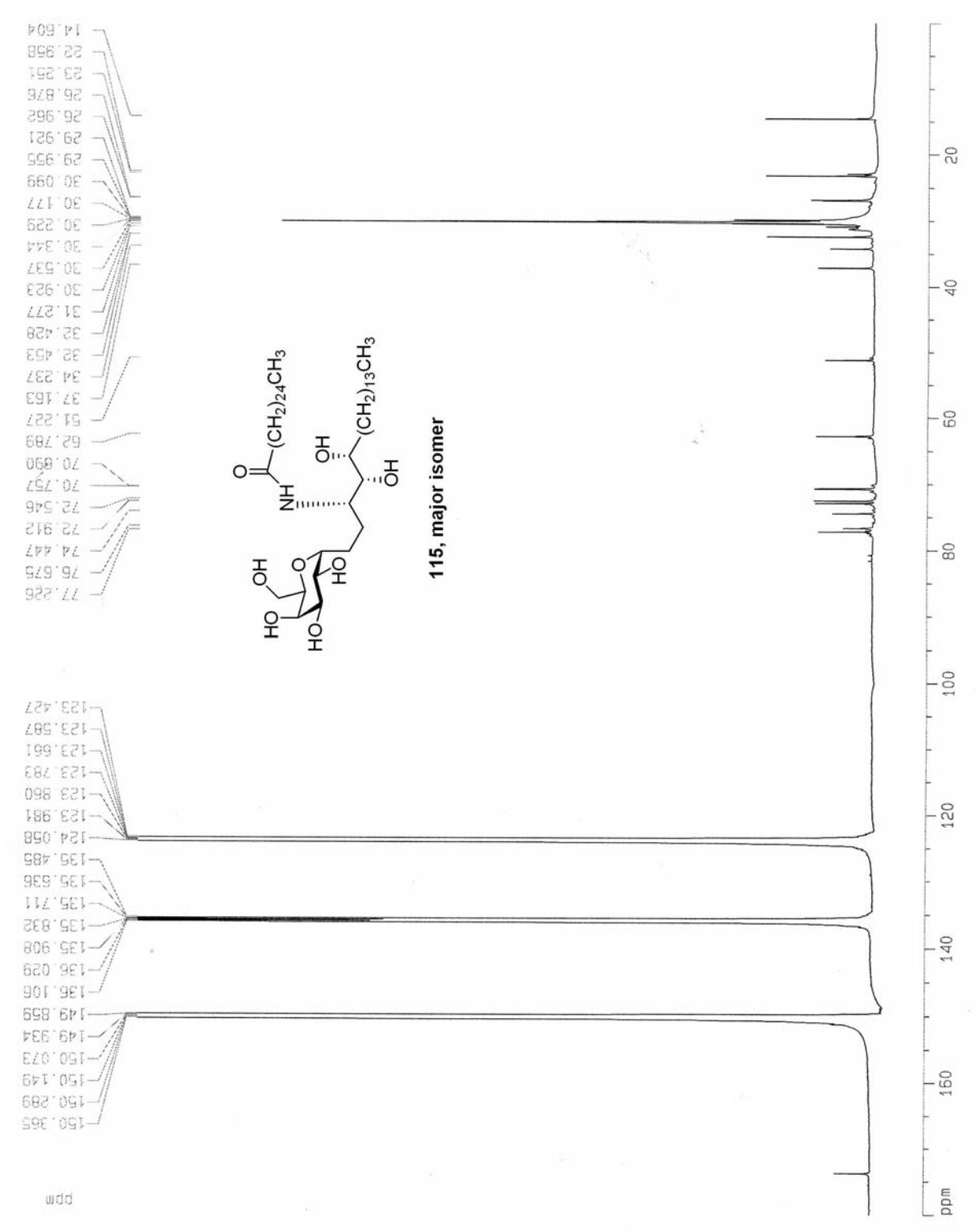

155.782
138.827
138.751
138.639
138.598
132.709
131.054
129.009
128.730
128.549
128.485
128.113
128.045
127.903
127.787
127.718
99.314
87.111
79.337
77.484
77.434
77.230
77.115
76.976
74.783
73.447
73.389
73.297
72.406
71.478
68.370
56.304
51.647
38.981
32.911
32.129
30.599
30.210
29.906
29.875
29.794
29.556
29.147
28.602
25.715
23.999
23.181
22.888
14.305
14.231
11.164
ppm
20
40
60
80
100
120
140
NHBoc
OH
OMOM
OBn
BnO
BnO
BnO
112, major isomer

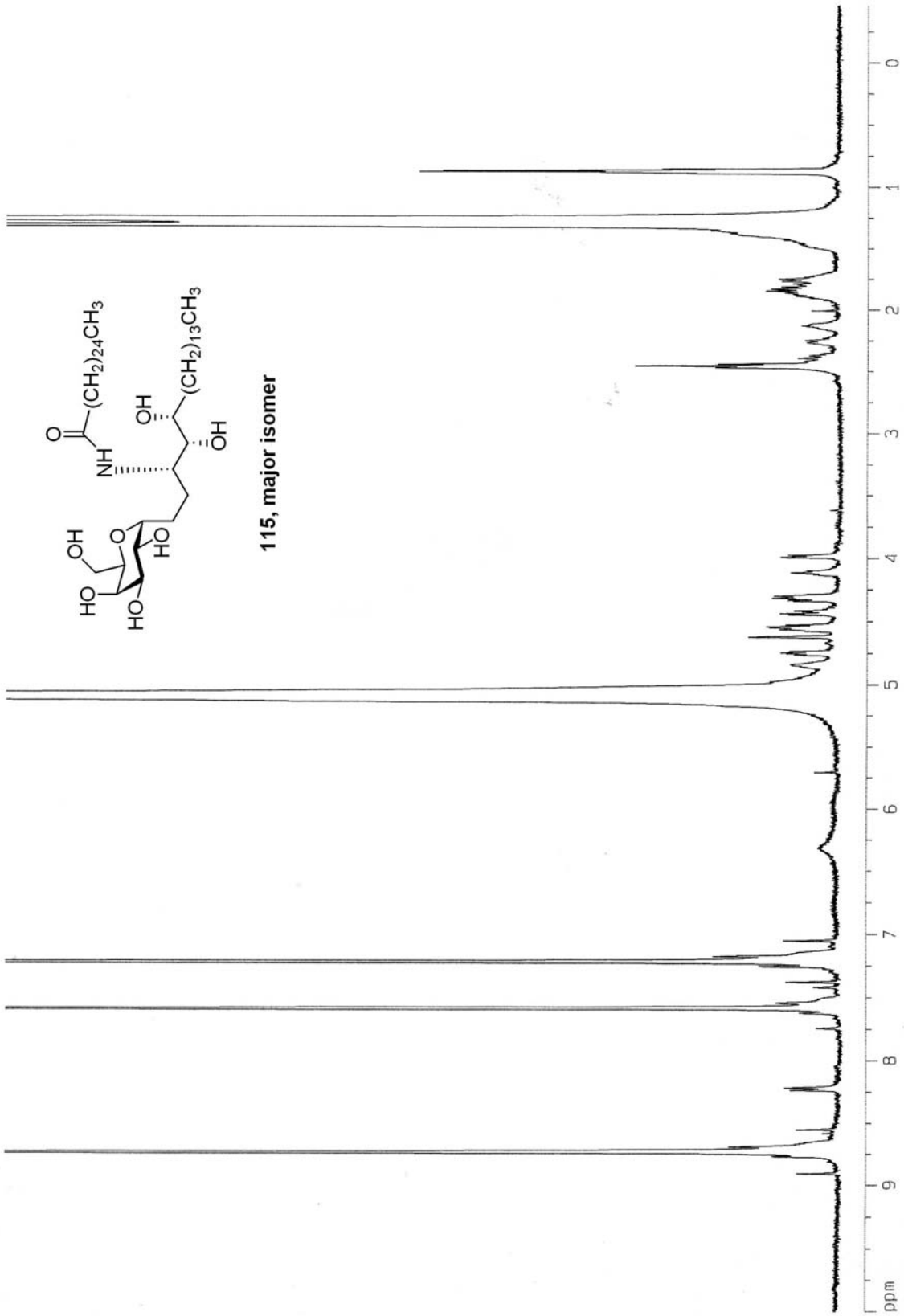

OBn
BnO
BnO
BnO
NHBoc
OH
OMOM
112, major isomer
ppm
0
1
2
3
4
5
6
7

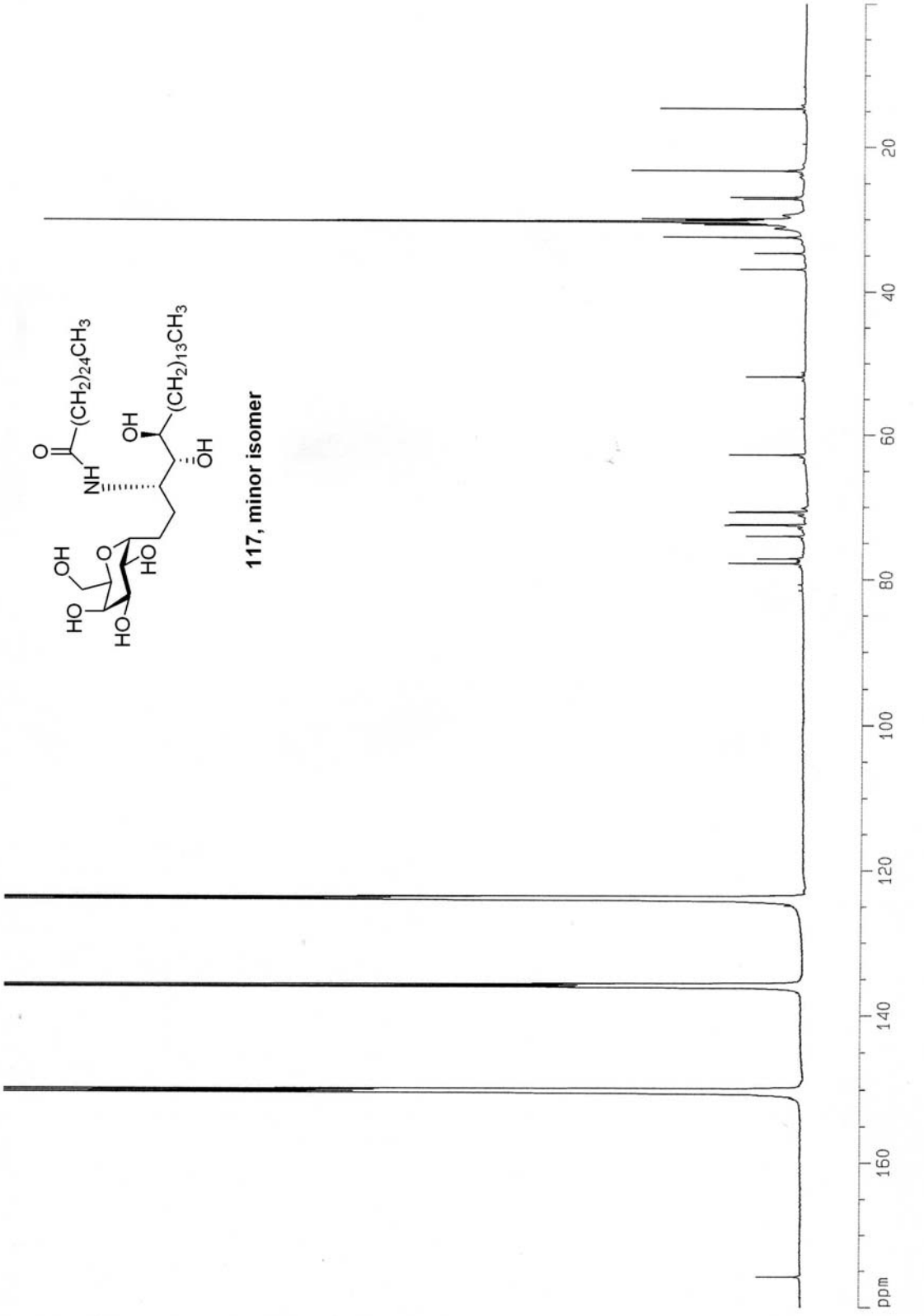

113, minor isomer
NHBoc
OH
OMOM
OBn
BnO
BnO
BnO
ppm

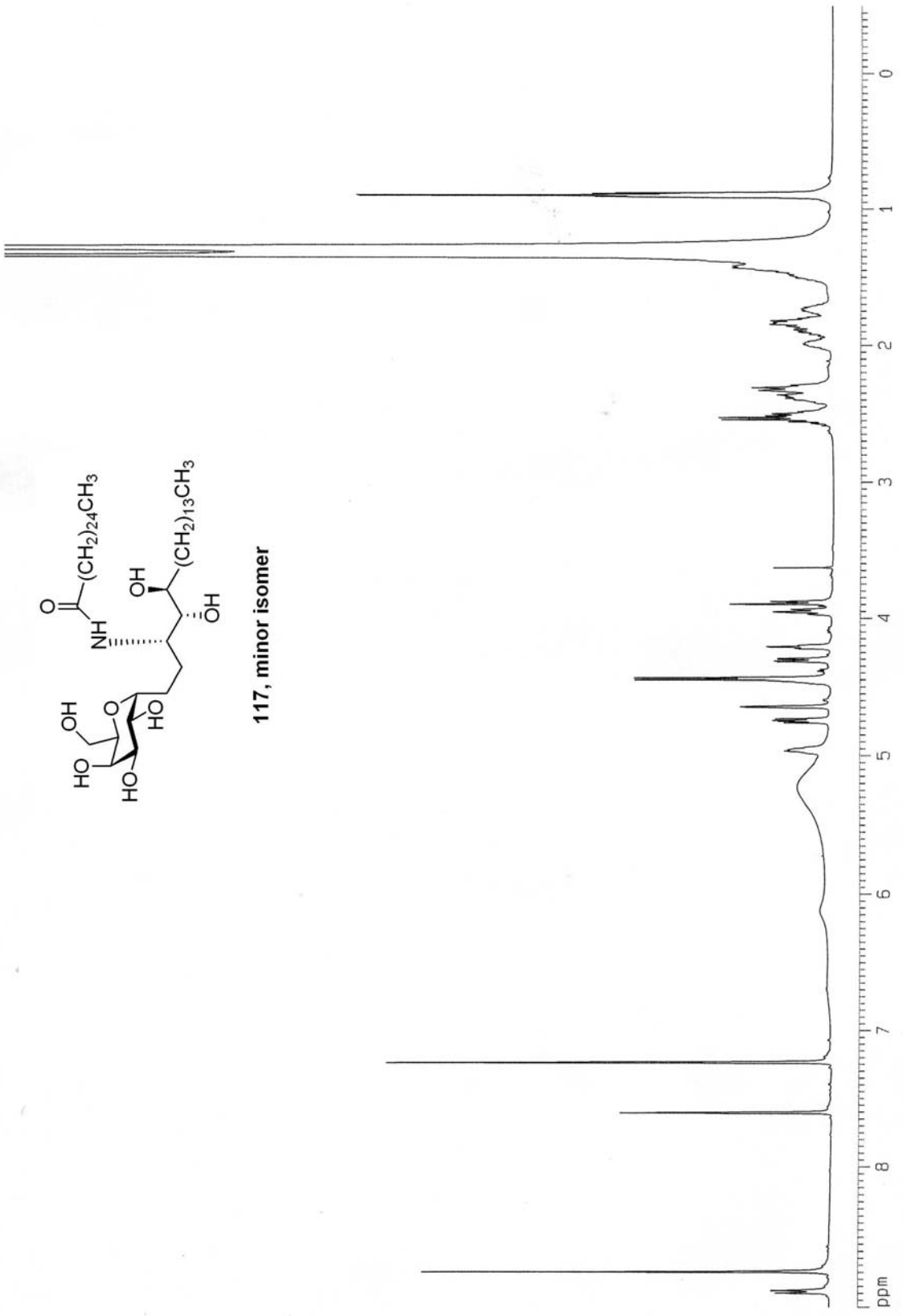


113, minor isomer

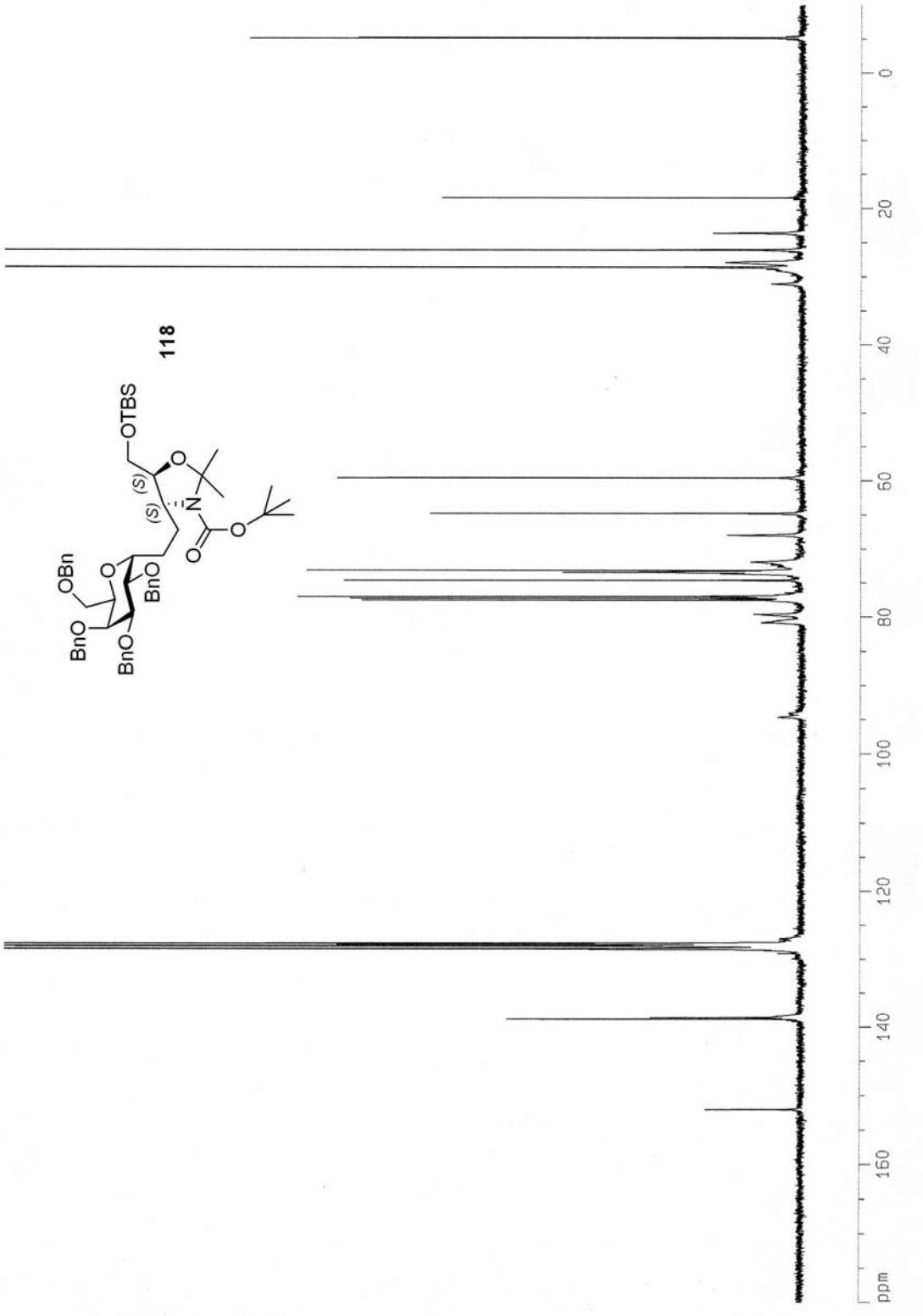

115, major isomer

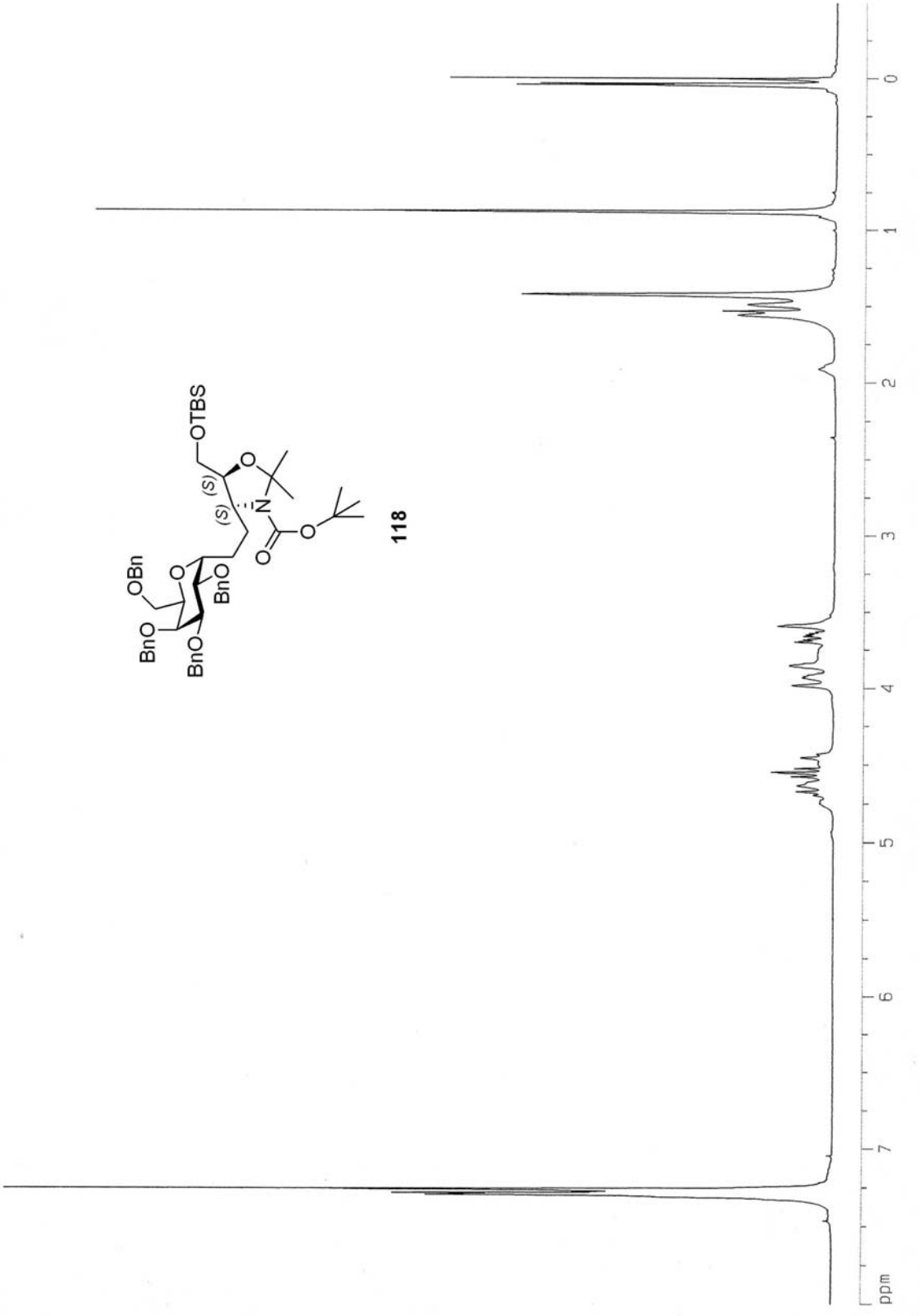

115, major isomer
ppm
0
1
2
3
4
5
6
7
8
9

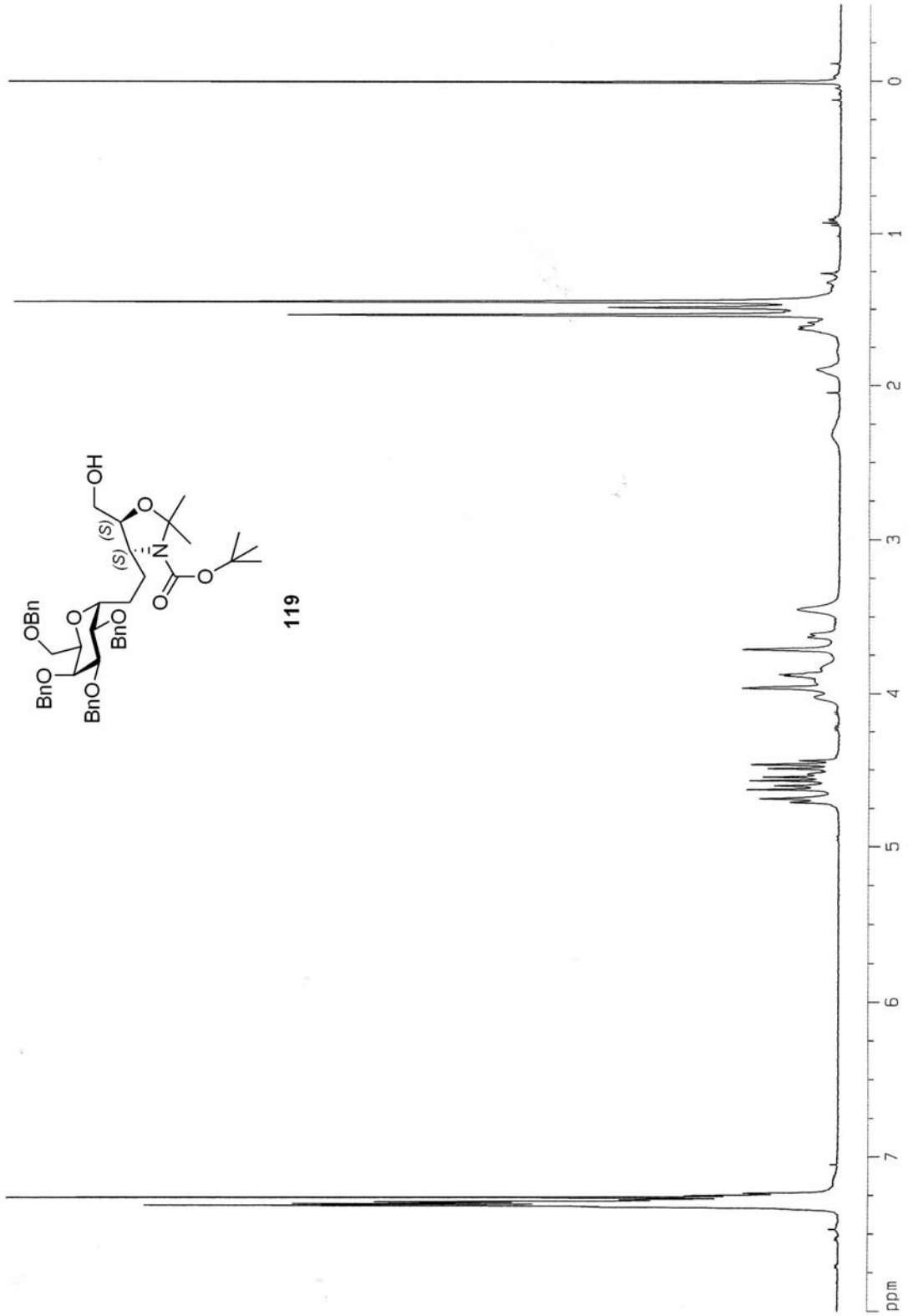

117, minor isomer
ppm
160
140
120
100
80
60
40
20

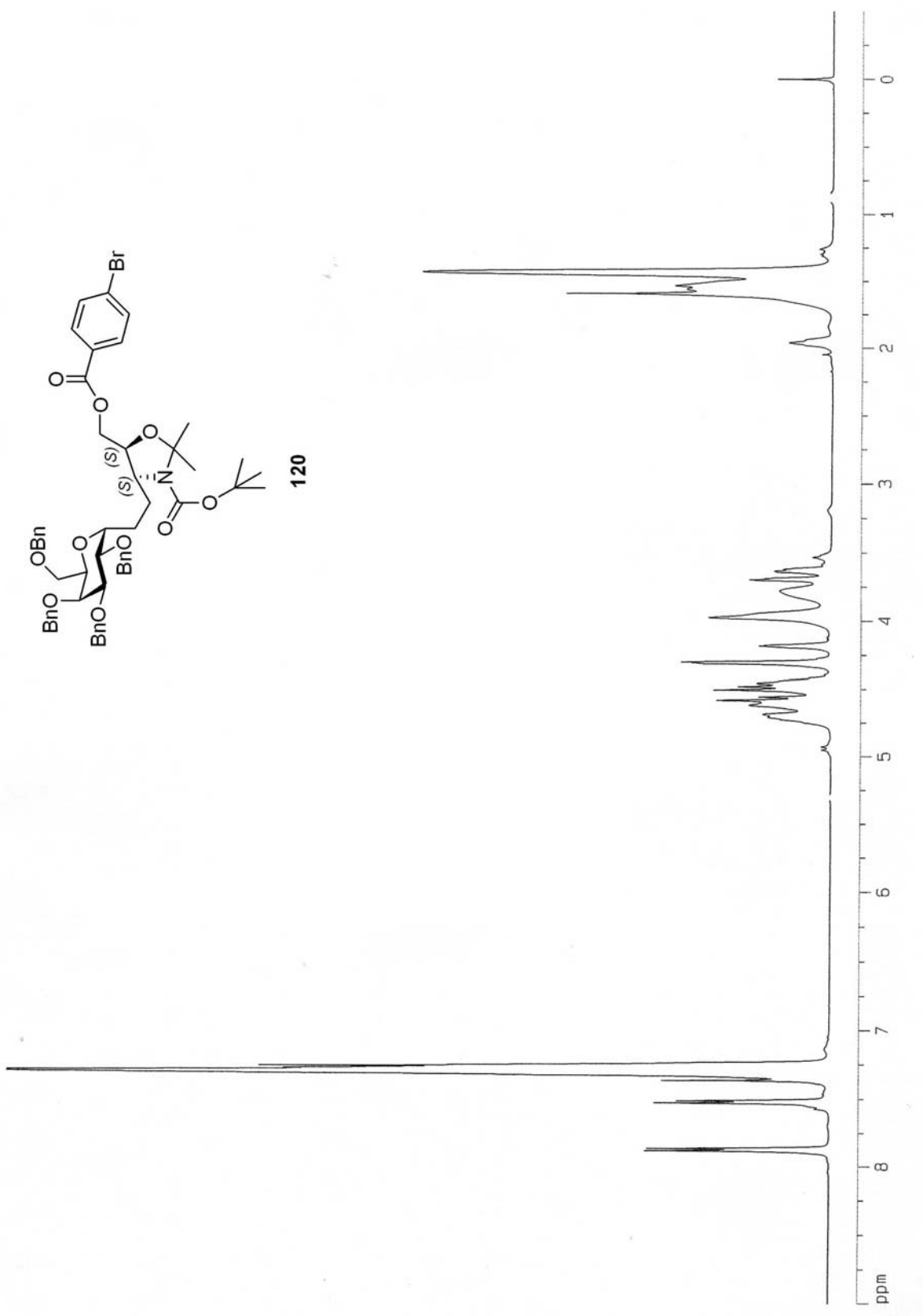


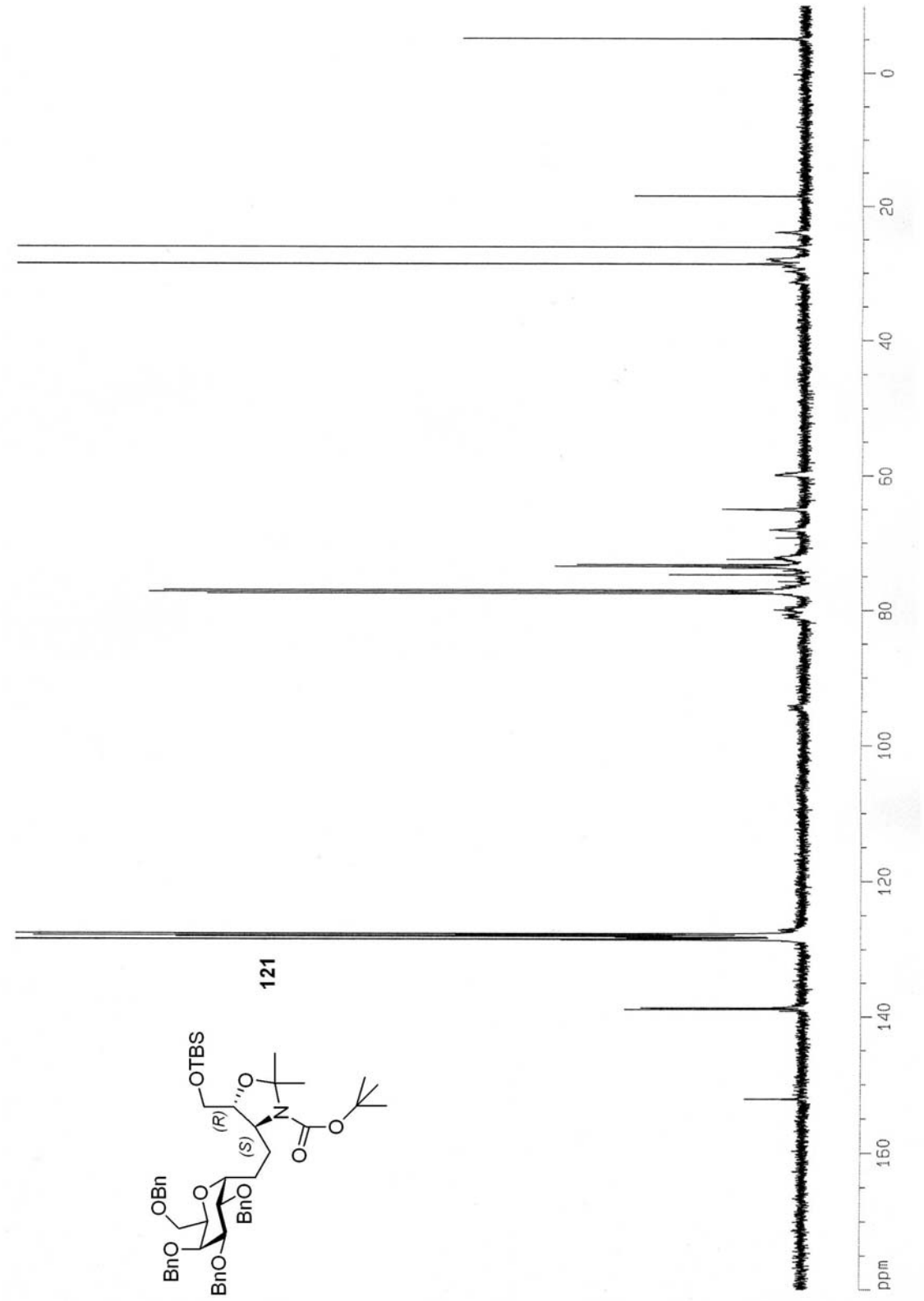
117, minor isomer

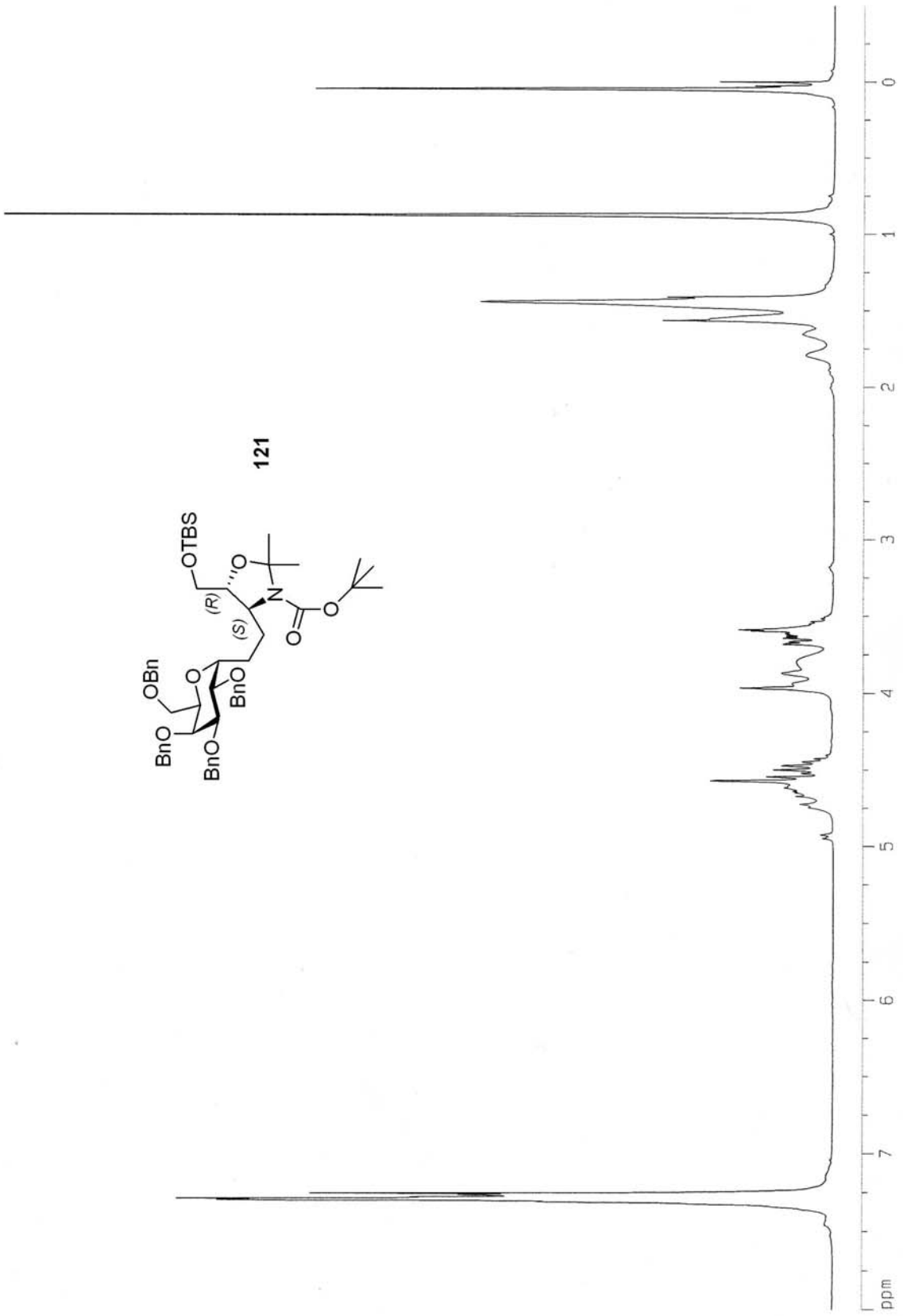

118
OTBS
(S)
(S)
N
O
O
OBn
BnO
BnO
BnO
ppm
0
20
40
60
80
100
120
140
160

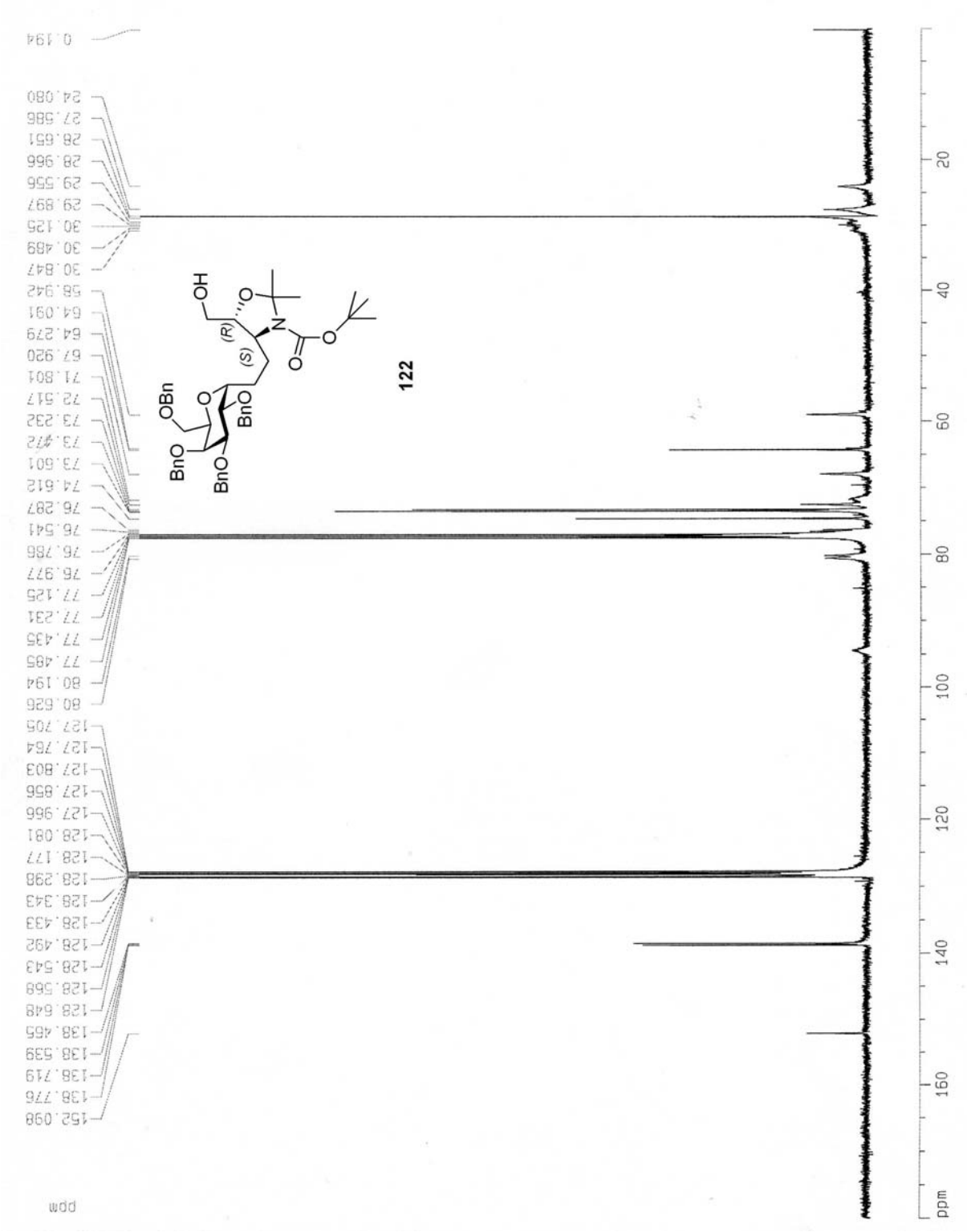

OTBS
(S)
(S)
N
O
O
OBn
BnO
BnO
BnO
118
ppm
0
1
2
3
4
5
6
7

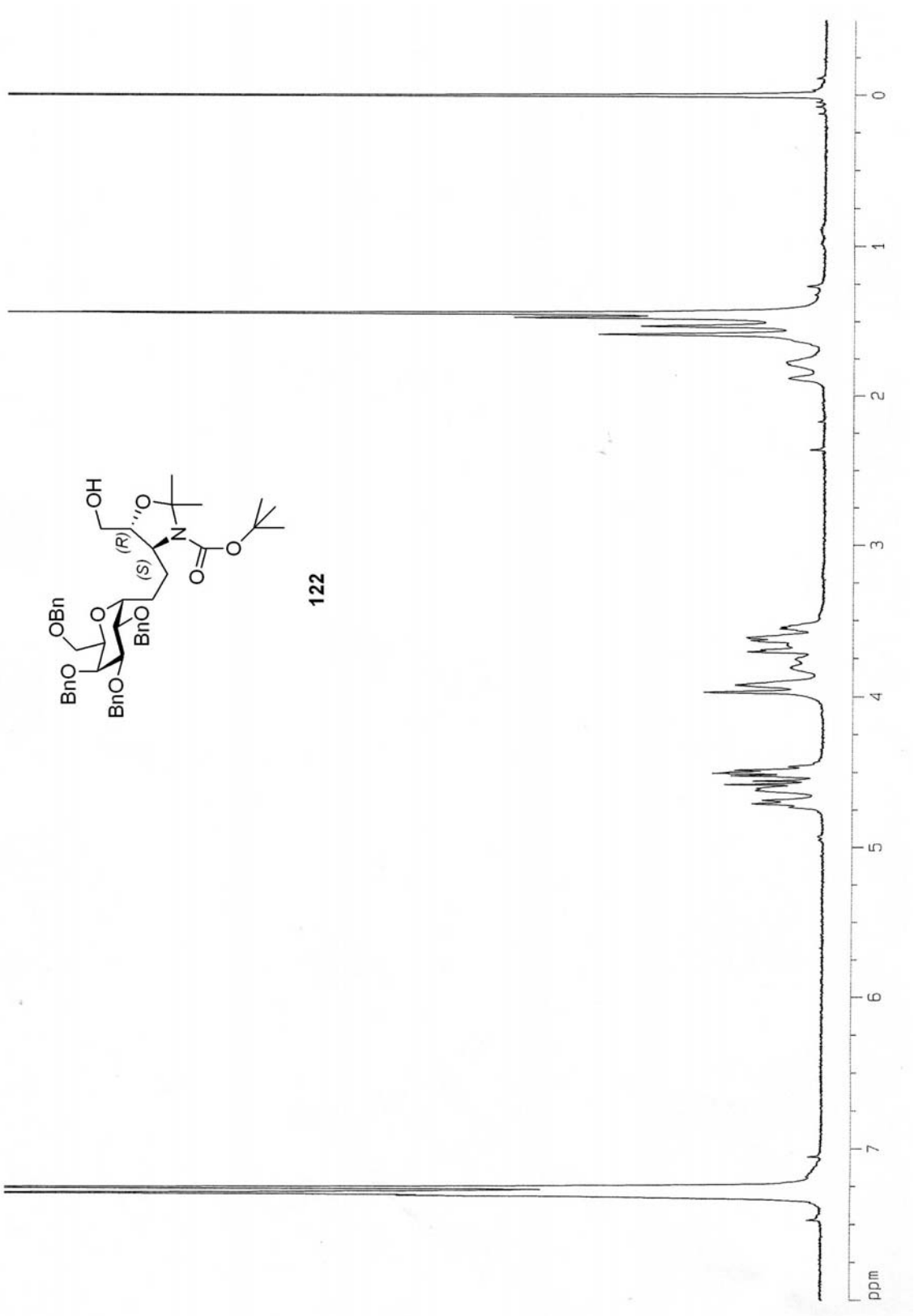

OH
(S)
(S)
OBn
BnO
BnO
BnO
119
ppm
0
1
2
3
4
5
6
7

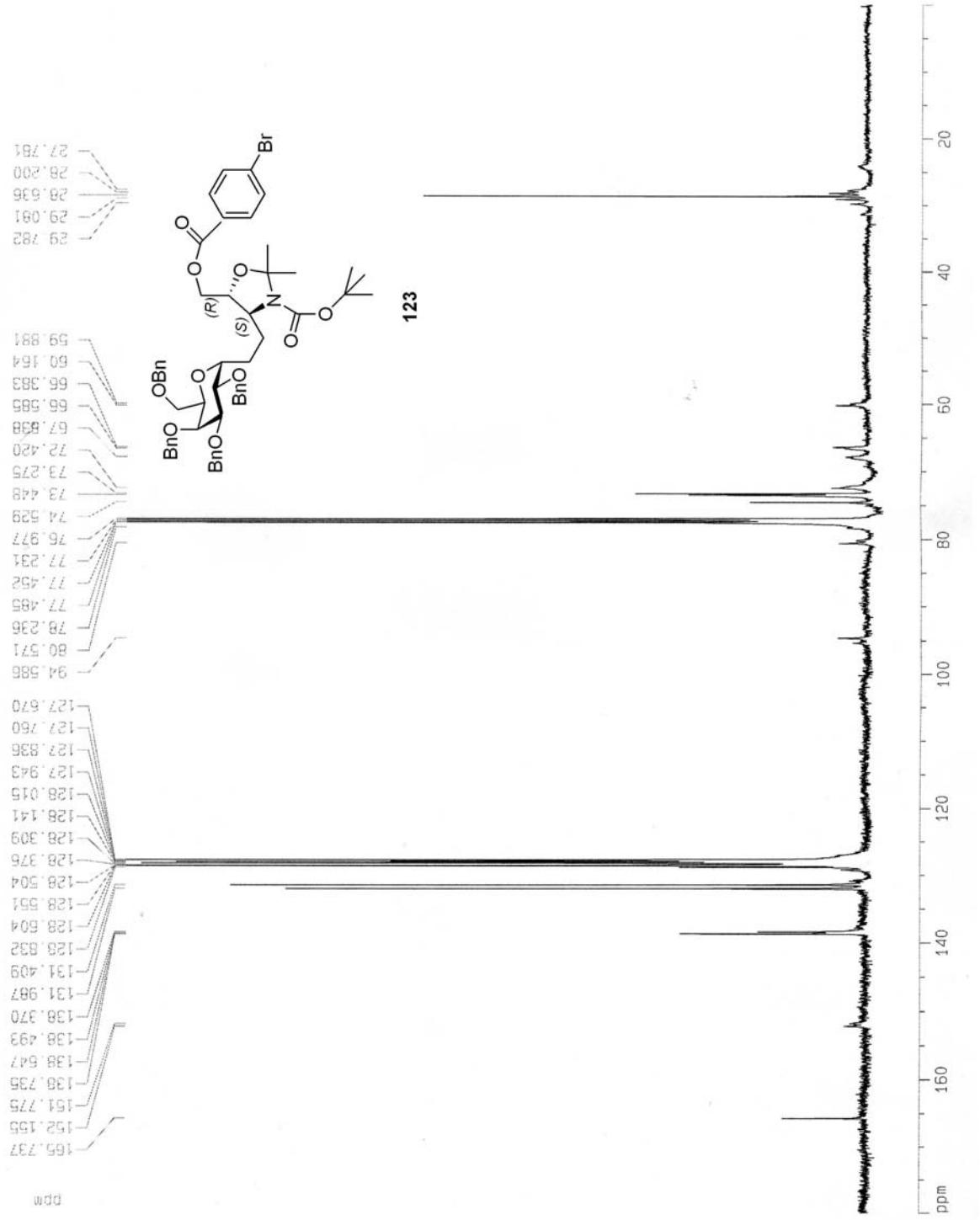

Br
O
O
(S)
(S)
O
N
O
O
OBn
O
BnO
BnO
BnO
120
ppm
0
1
2
3
4
5
6
7
8

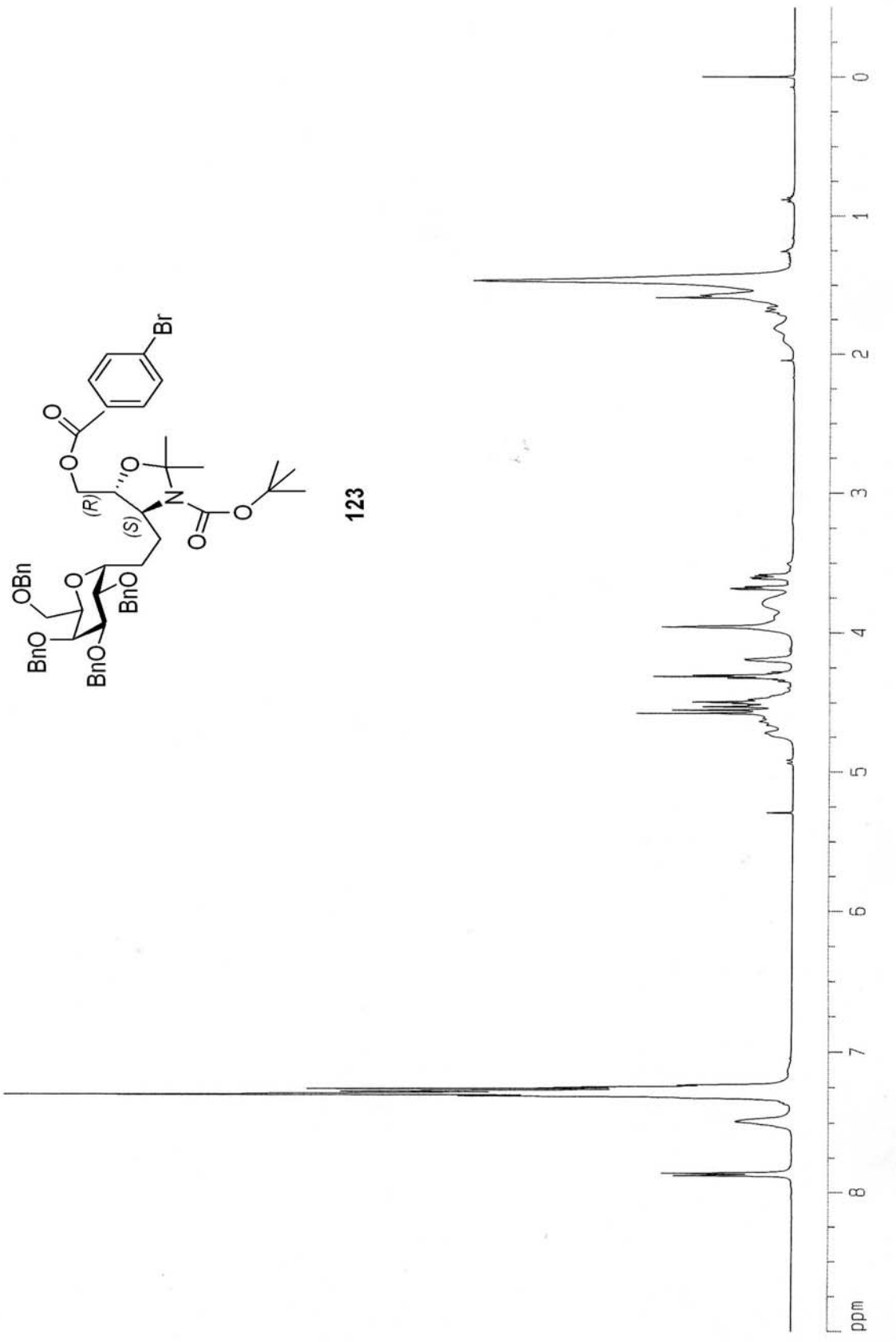

121
OTBS
OBn
BnO
BnO
BnO
(R)
(S)
N
O
O
O
ppm
0
20
40
60
80
100
120
140
160


121
OTBS
OBn
BnO
BnO
BnO
(R)
(S)
N
O
O
O
O
ppm
0
1
2
3
4
5
6
7

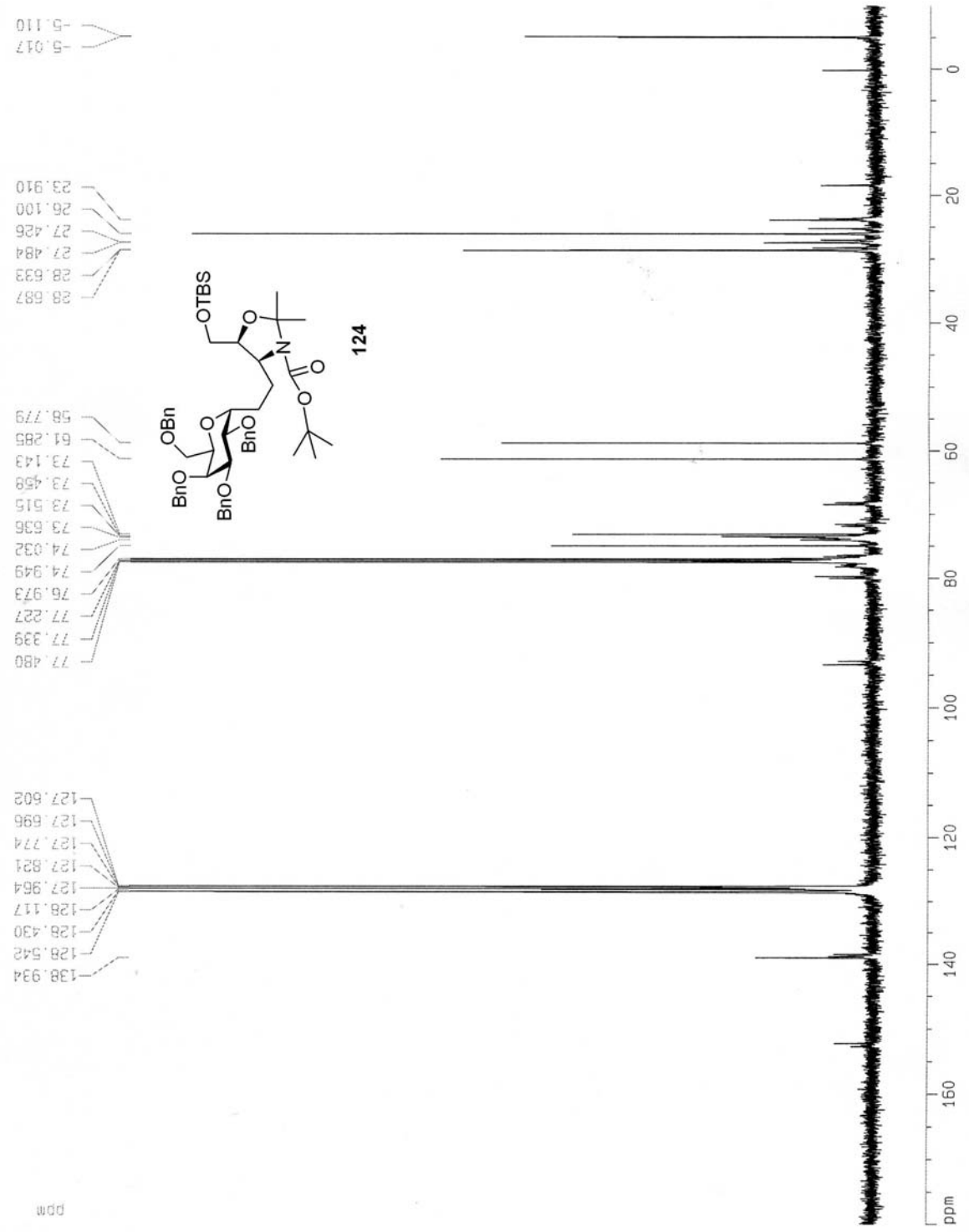

122
OH
(R)
(S)
OBn
BnO
BnO
BnO
ppm

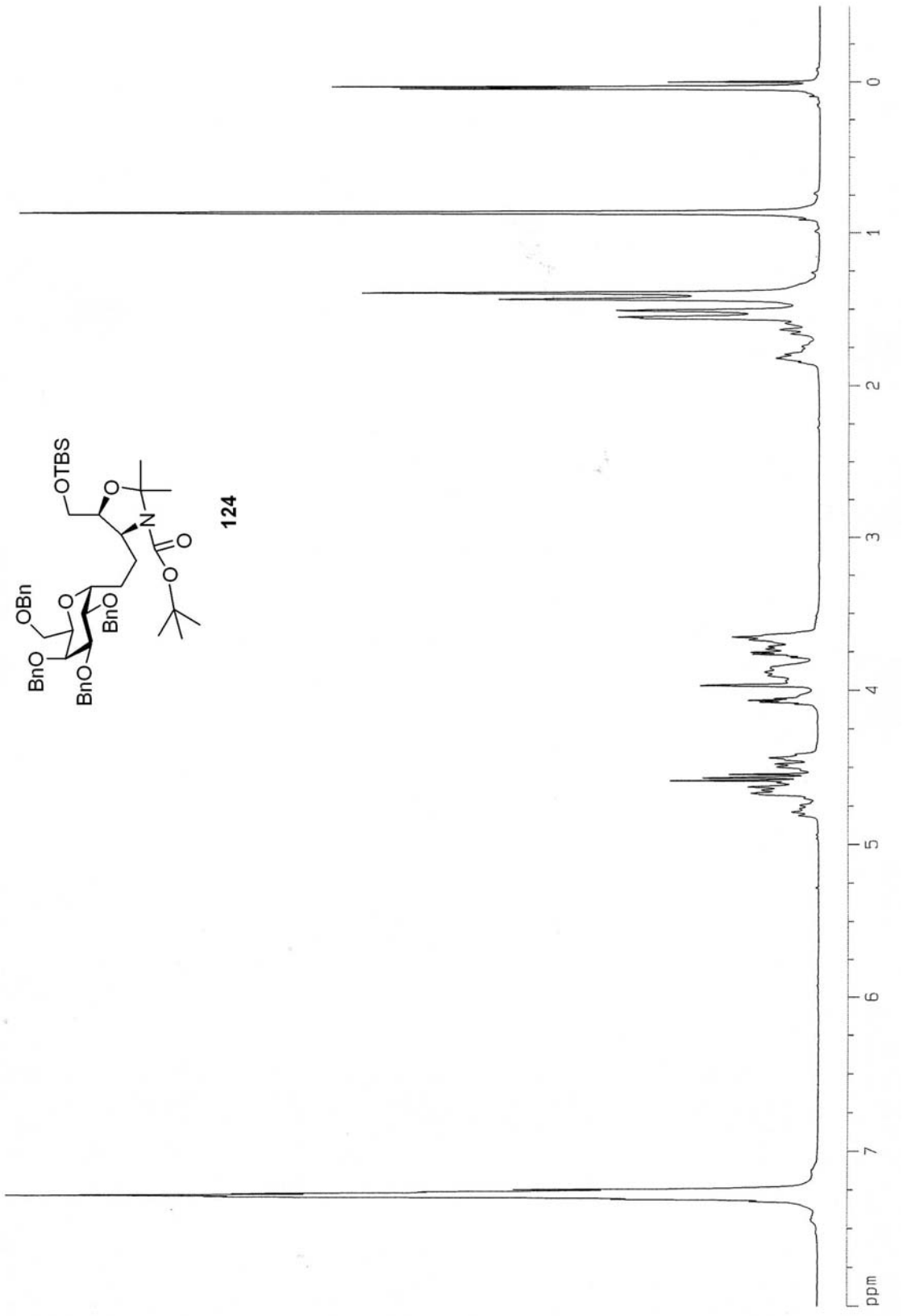

OH
(R)
(S)
N
O
O
O
OBn
BnO
BnO
BnO
122
ppm
0
1
2
3
4
5
6
7

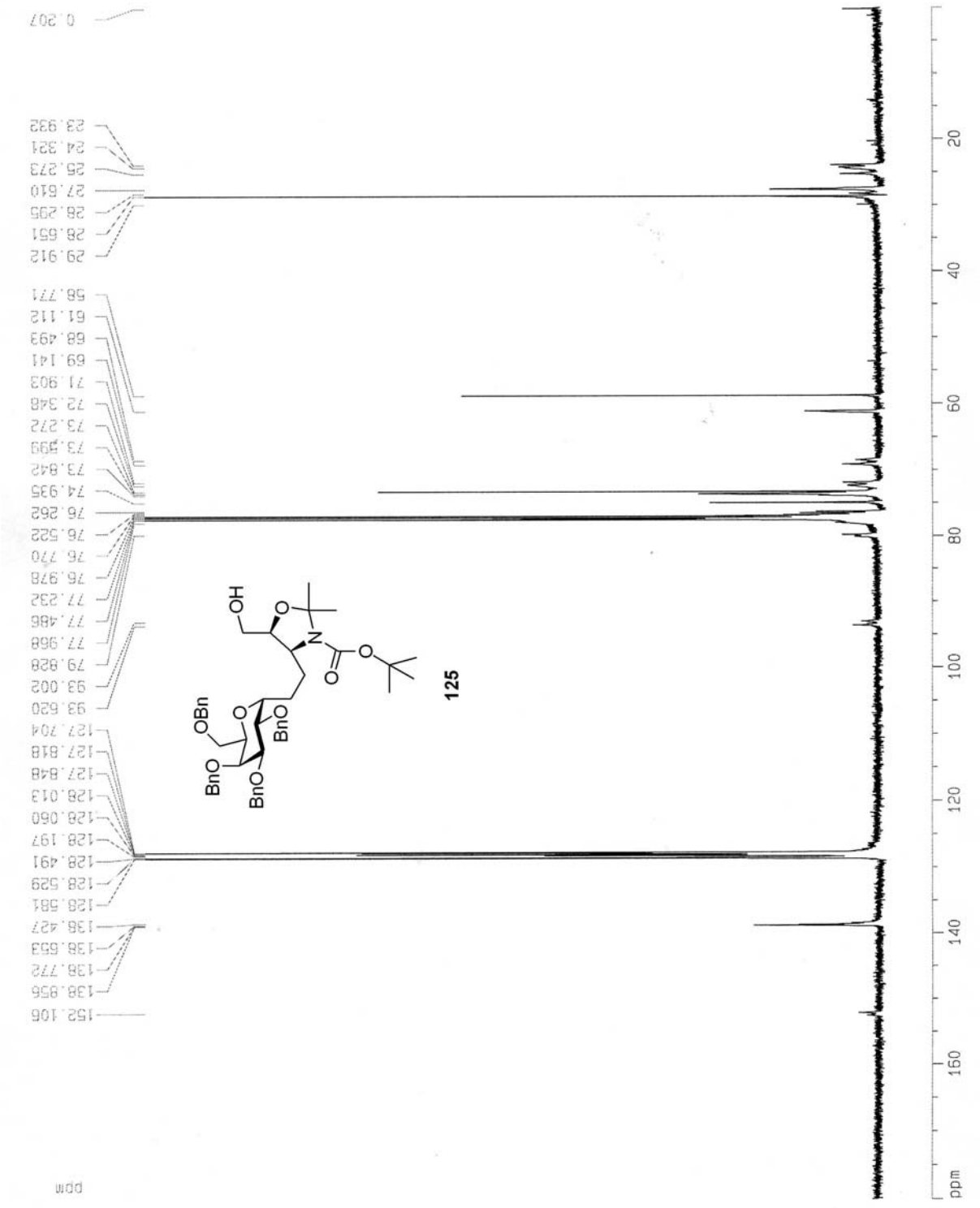

123
Br
OBn
BnO
BnO
BnO
(R)
(S)
ppm

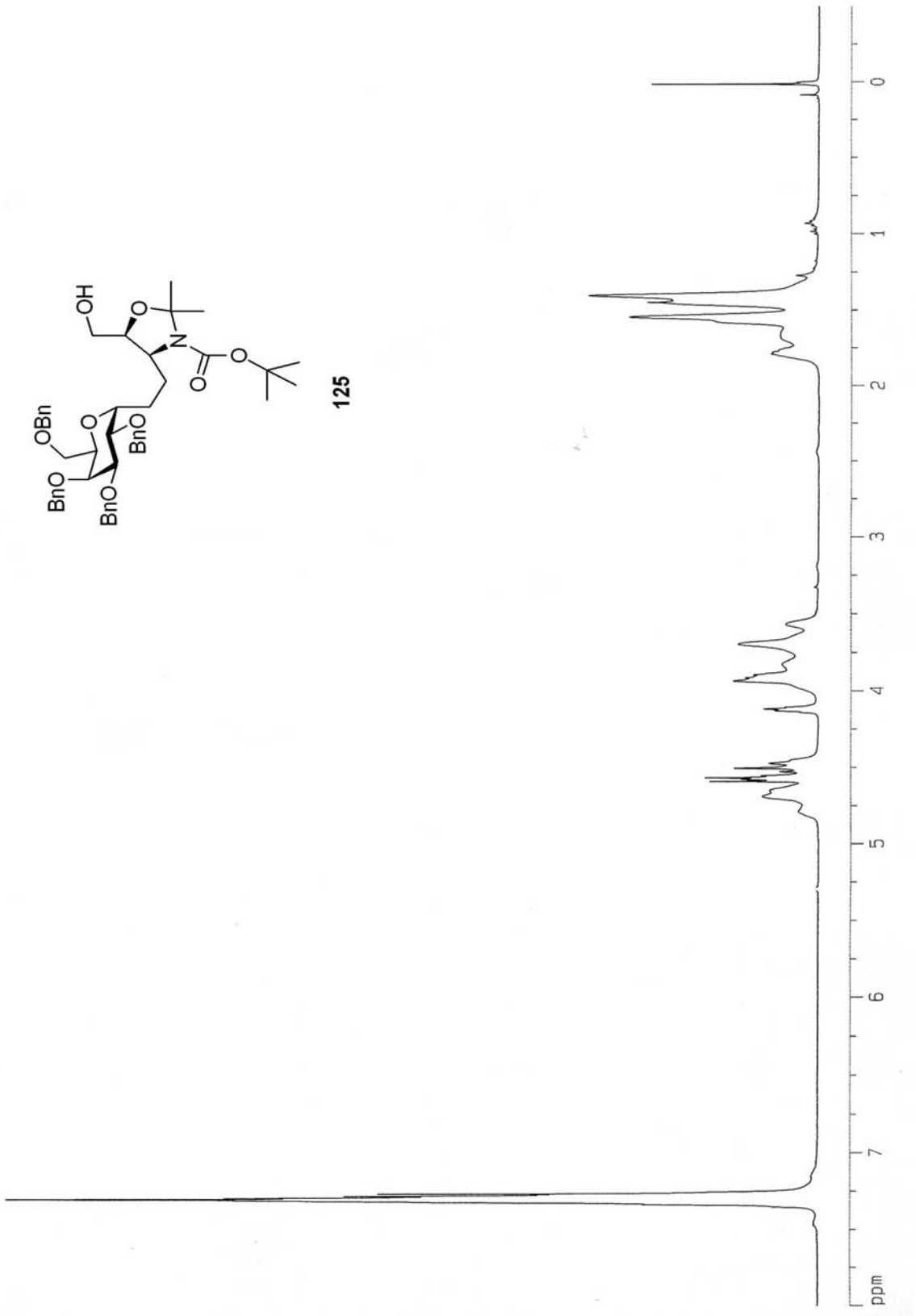


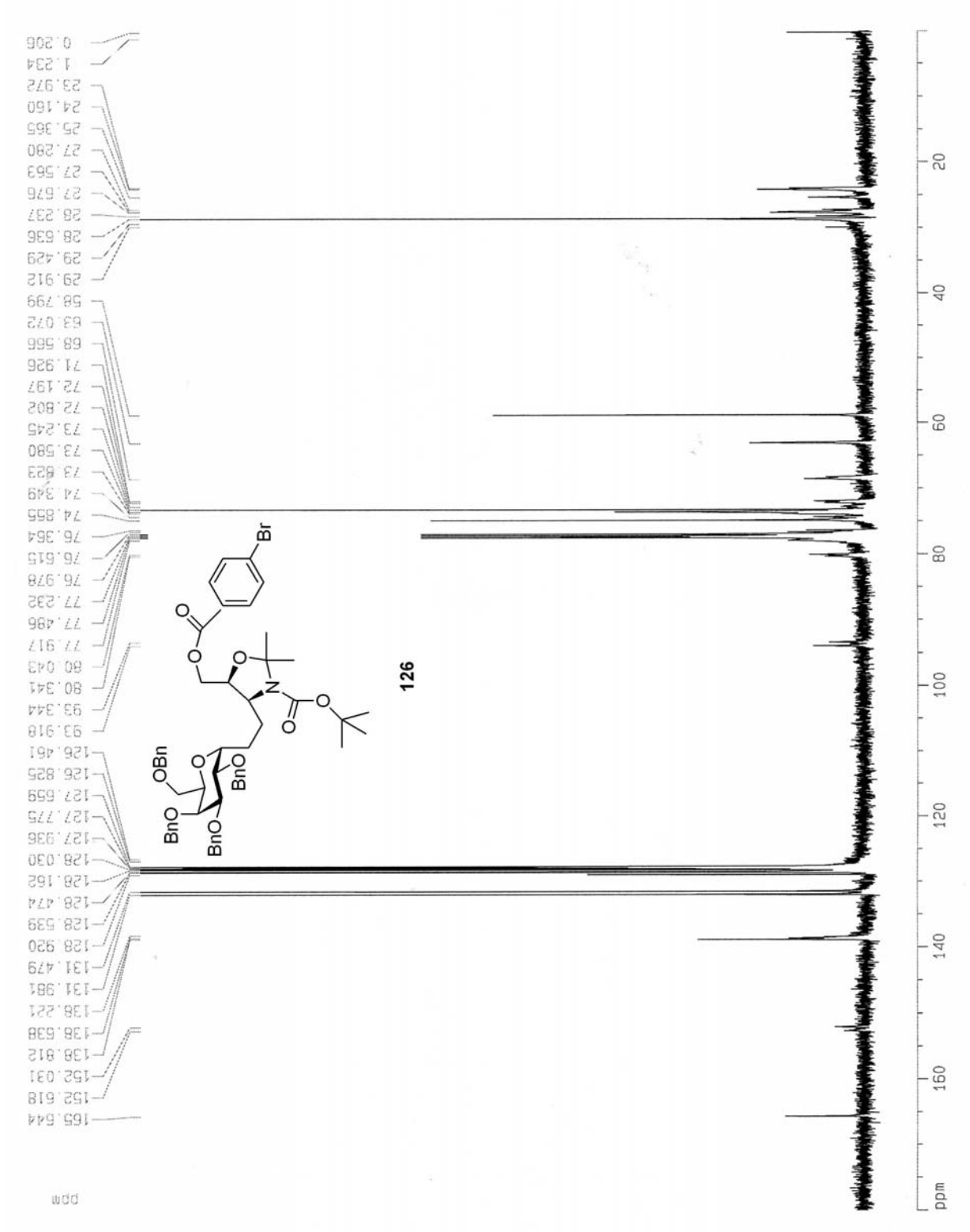
123

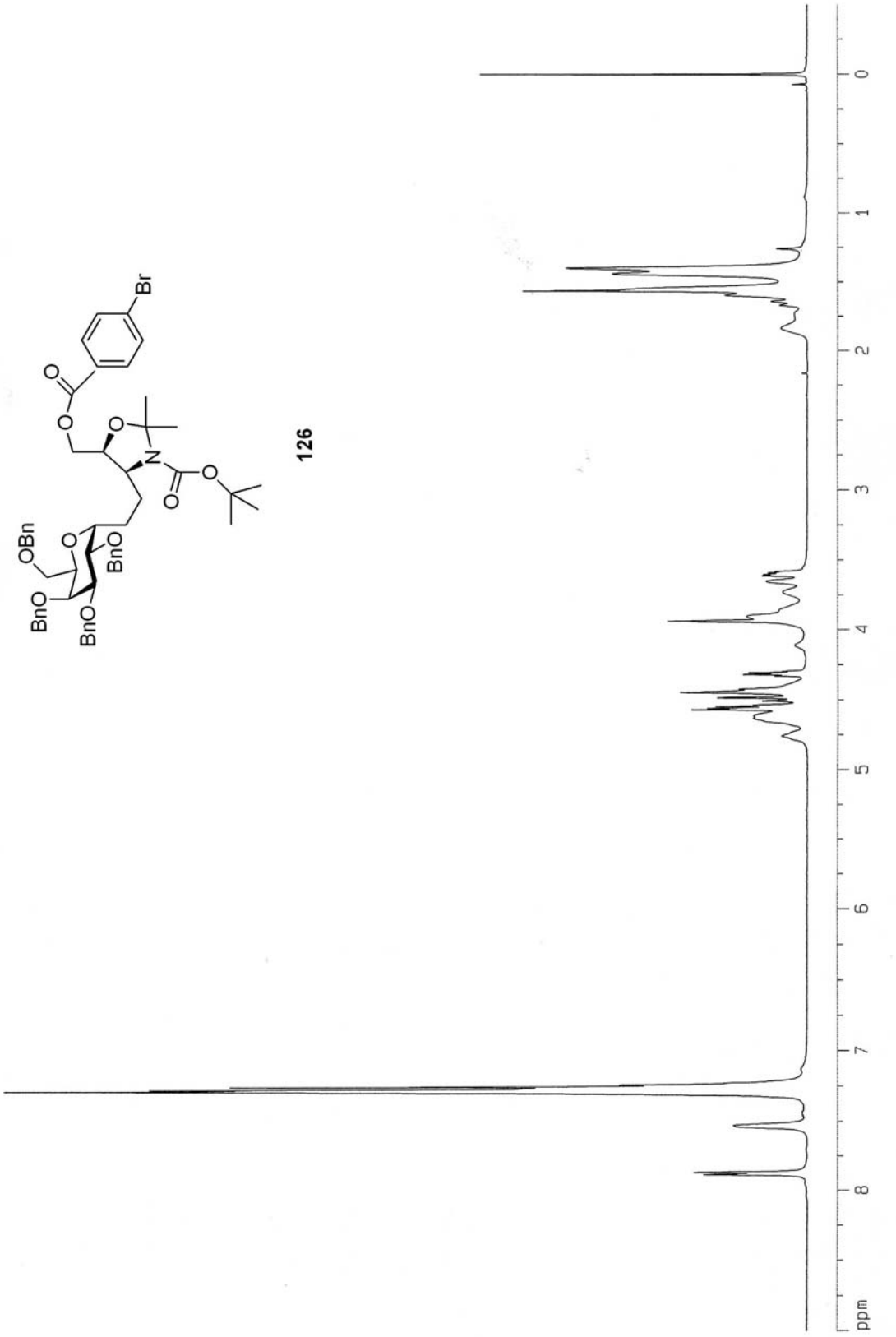

-5.110
-5.017
23.910
26.100
27.426
27.484
28.633
28.687
58.779
61.285
73.143
73.458
73.515
73.536
74.032
74.949
76.973
77.227
77.339
77.480
127.602
127.696
127.774
127.821
127.964
128.117
128.430
128.542
138.934
ppm
0
20
40
60
80
100
120
140
160
OTBS
OBn
BnO
BnO
BnO
O
N
O
O
O
124

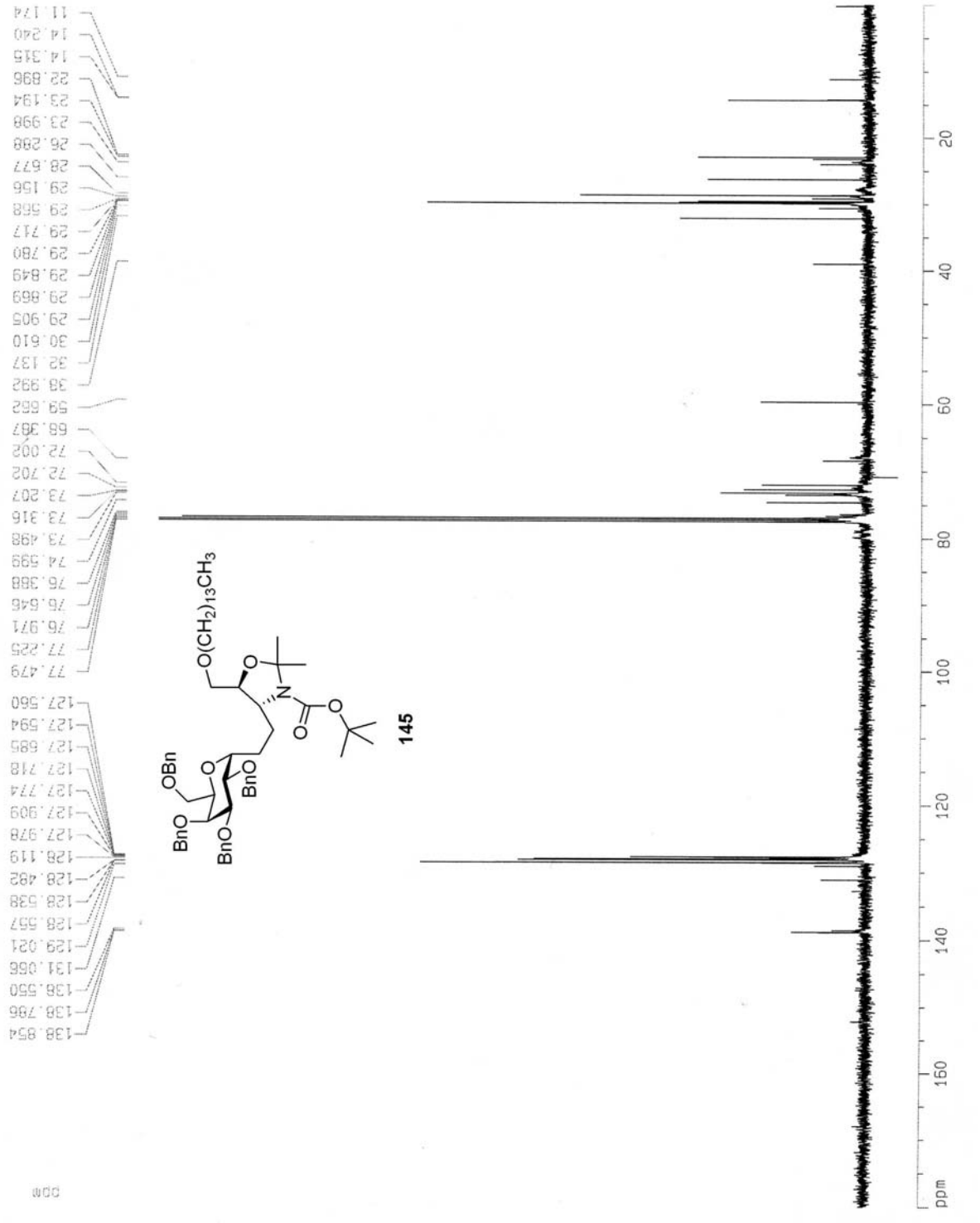

OTBS
OBn
BnO
BnO
BnO
124
ppm
0
1
2
3
4
5
6
7

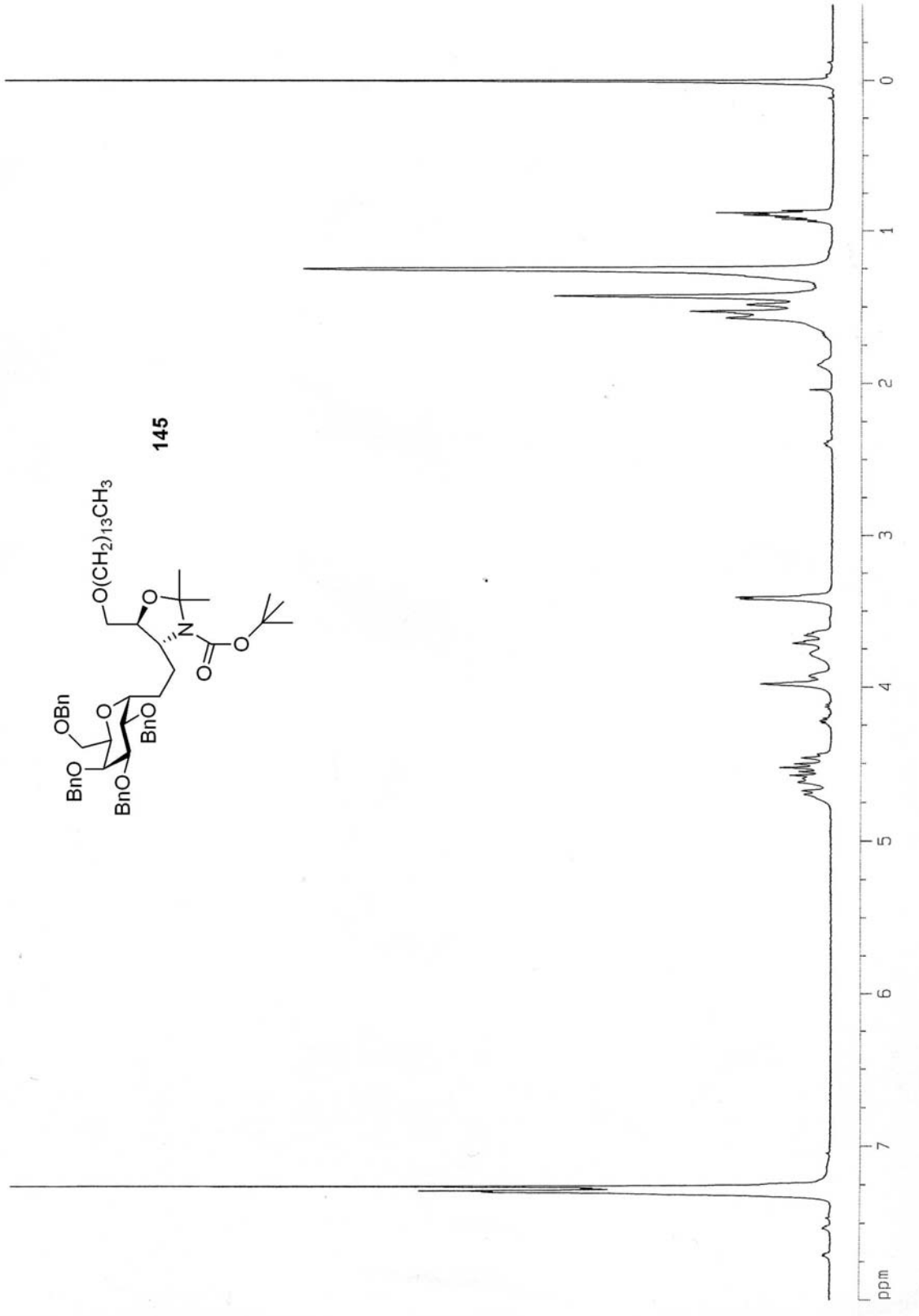

0.207
23.932
24.321
26.273
27.610
28.295
28.651
29.912
58.771
61.112
68.493
69.141
71.903
72.348
73.272
73.599
73.842
74.935
76.262
76.522
76.770
76.978
77.232
77.486
77.968
79.828
93.002
93.620
127.704
127.818
127.848
128.013
128.060
128.197
128.491
128.529
128.581
136.427
136.653
136.772
136.856
152.106
OH
O
N
O
O
OBn
O
BnO
BnO
BnO
125
20
40
60
80
100
120
140
160
ppm

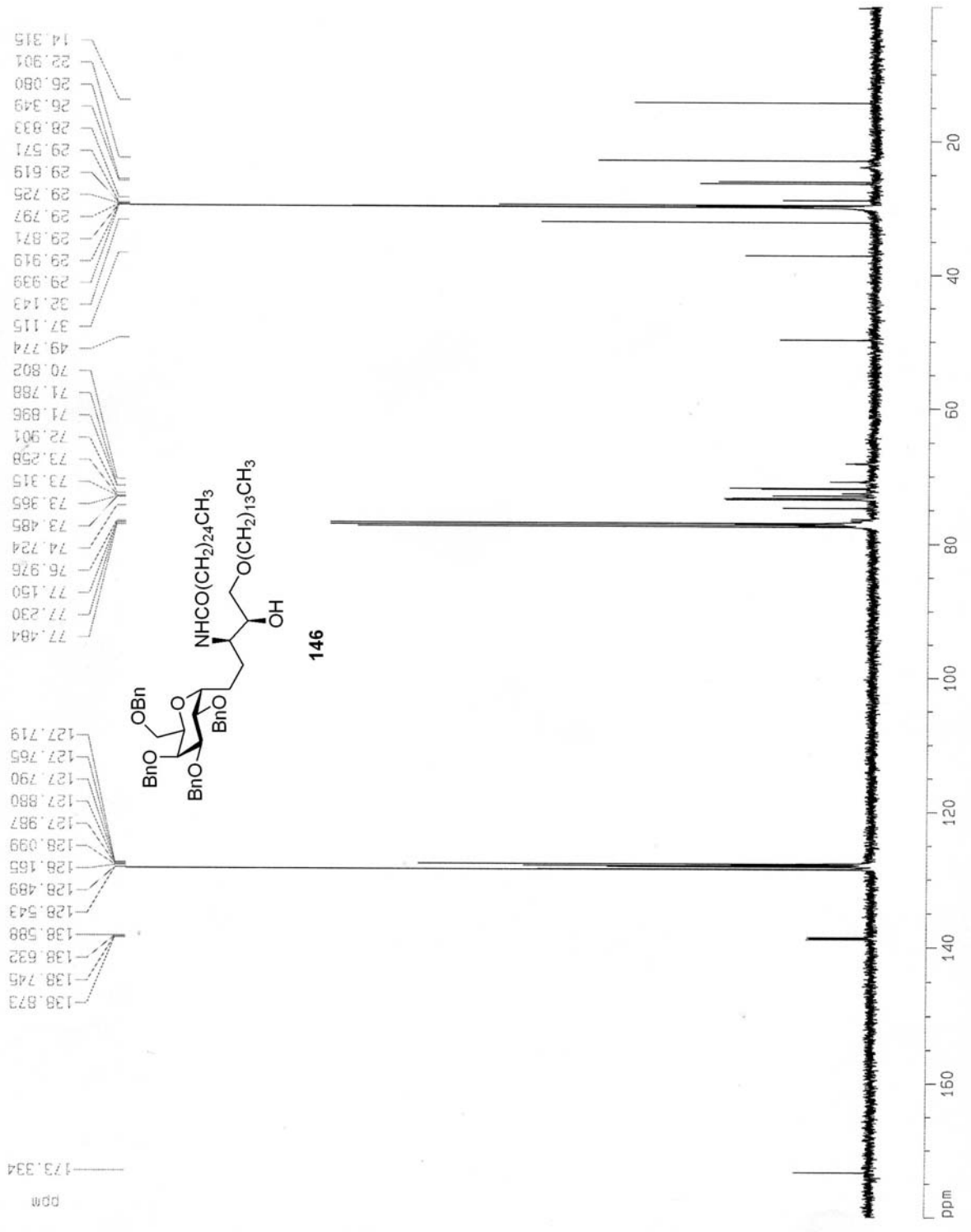

OH
O
N
O
O
OBn
O
BnO
BnO
BnO
125
ppm
0
1
2
3
4
5
6
7

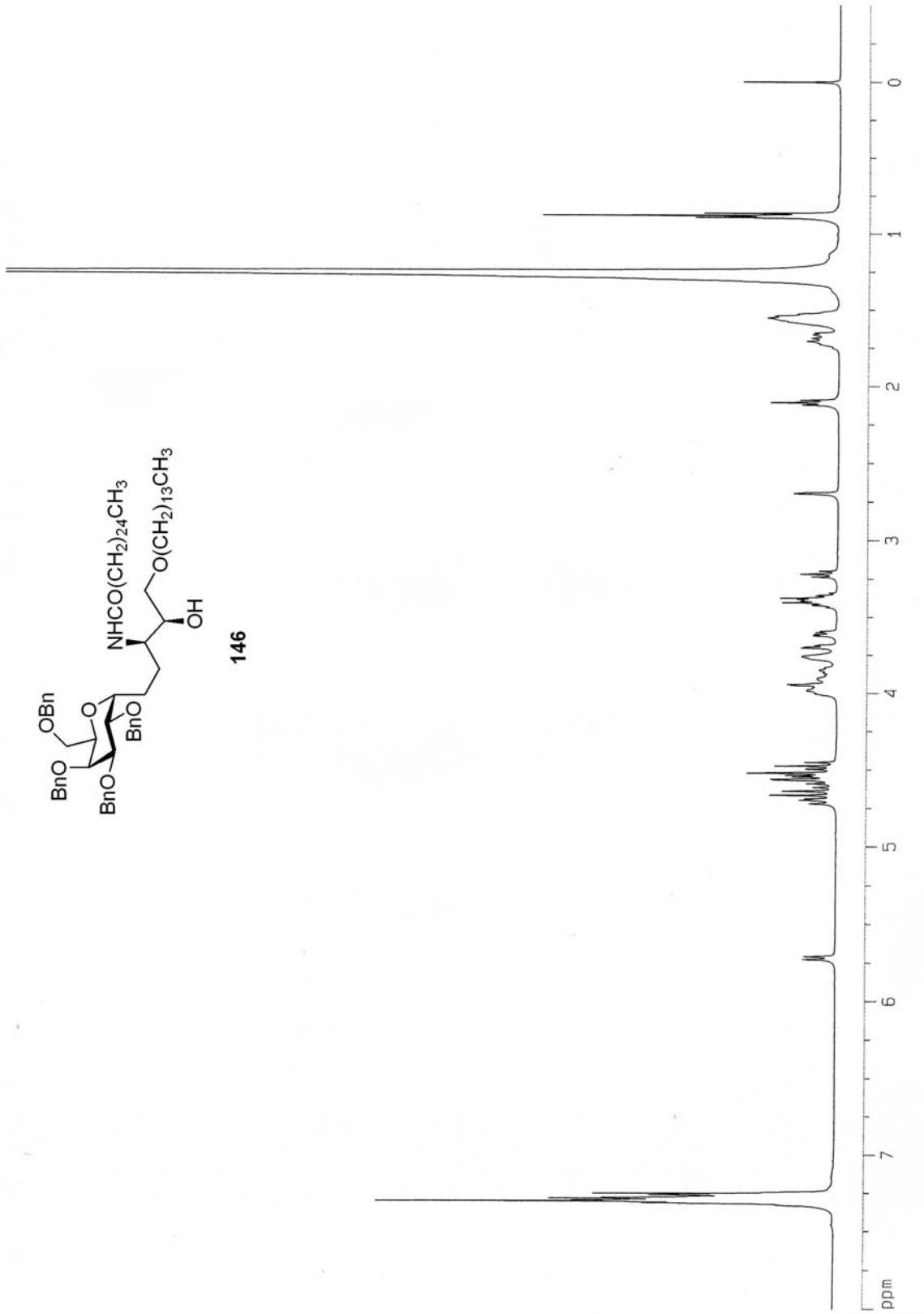

126
Br
OBn
BnO
BnO
BnO
ppm

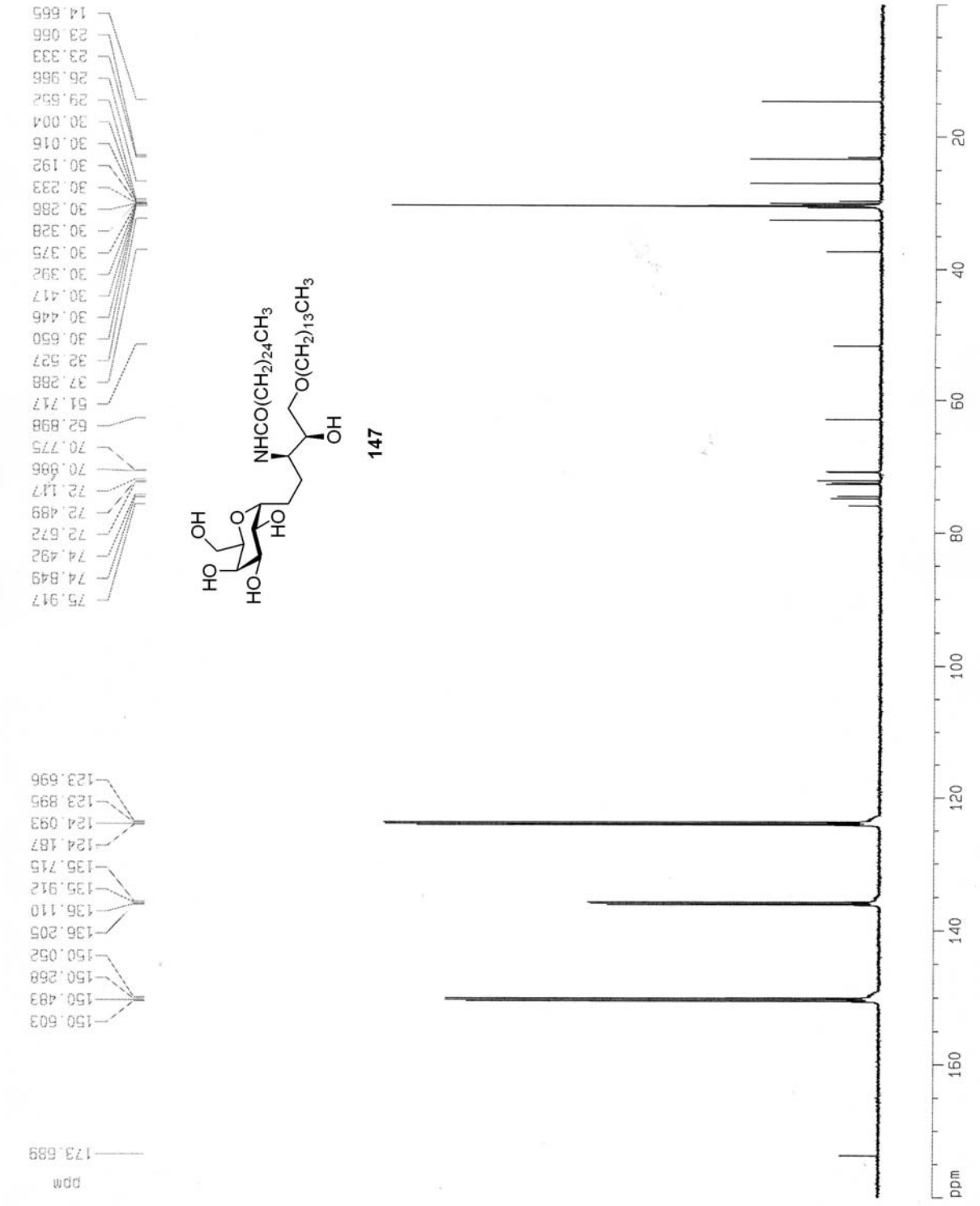

Br
O
O
O
N
O
O
OBn
O
BnO
BnO
BnO
126
ppm
0
1
2
3
4
5
6
7
8

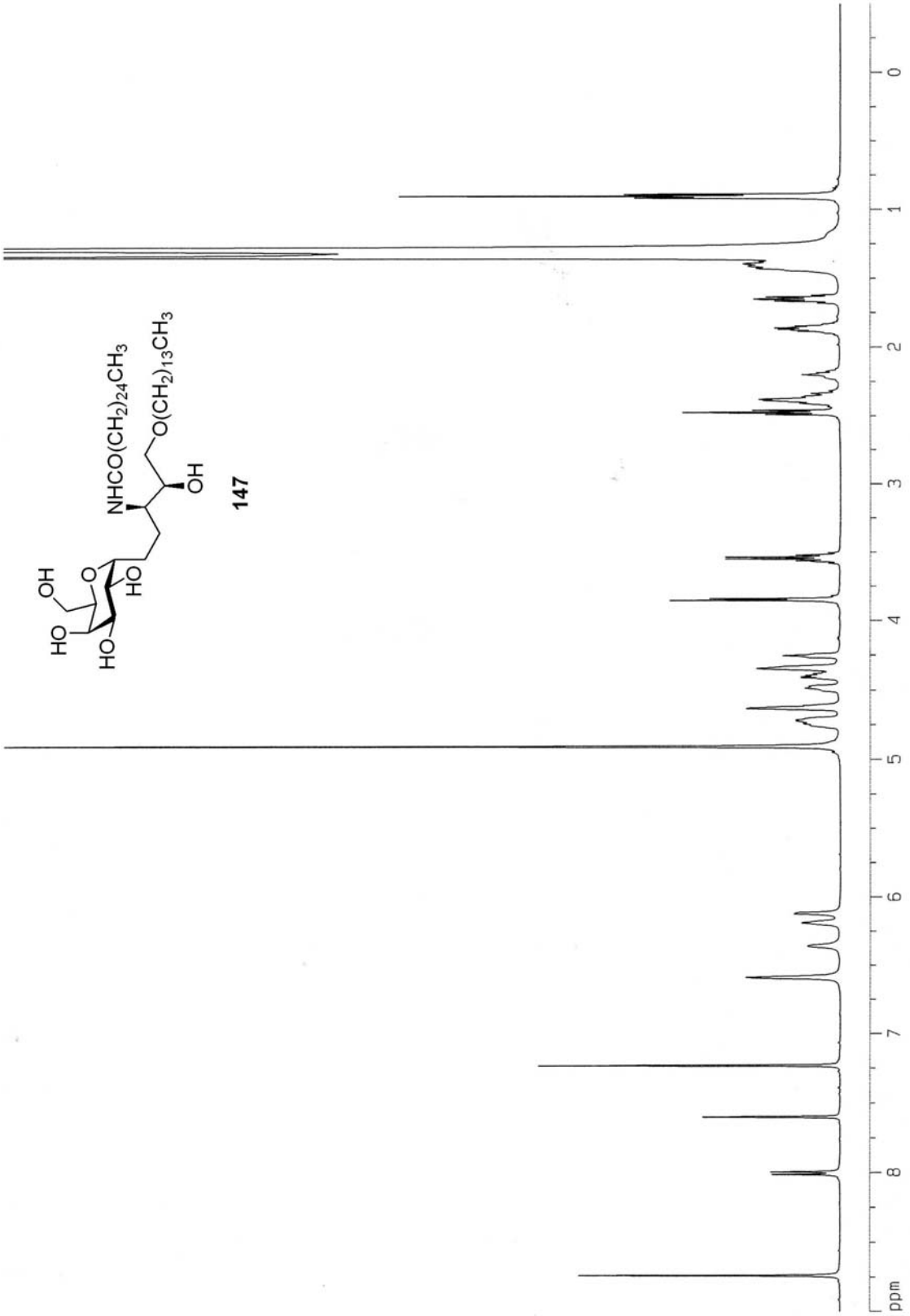

11.174
14.240
14.315
22.896
23.194
23.998
26.298
28.677
29.156
29.568
29.717
29.780
29.849
29.869
29.905
30.610
32.137
38.992
59.662
68.387
72.002
72.702
73.207
73.316
73.498
74.599
76.388
76.646
76.971
77.225
77.479
127.560
127.594
127.685
127.718
127.774
127.909
127.978
128.119
128.482
128.538
128.557
129.021
131.066
138.550
138.786
138.854
OBn
BnO
BnO
BnO
O(CH2)13CH3
145
ppm
20
40
60
80
100
120
140
160

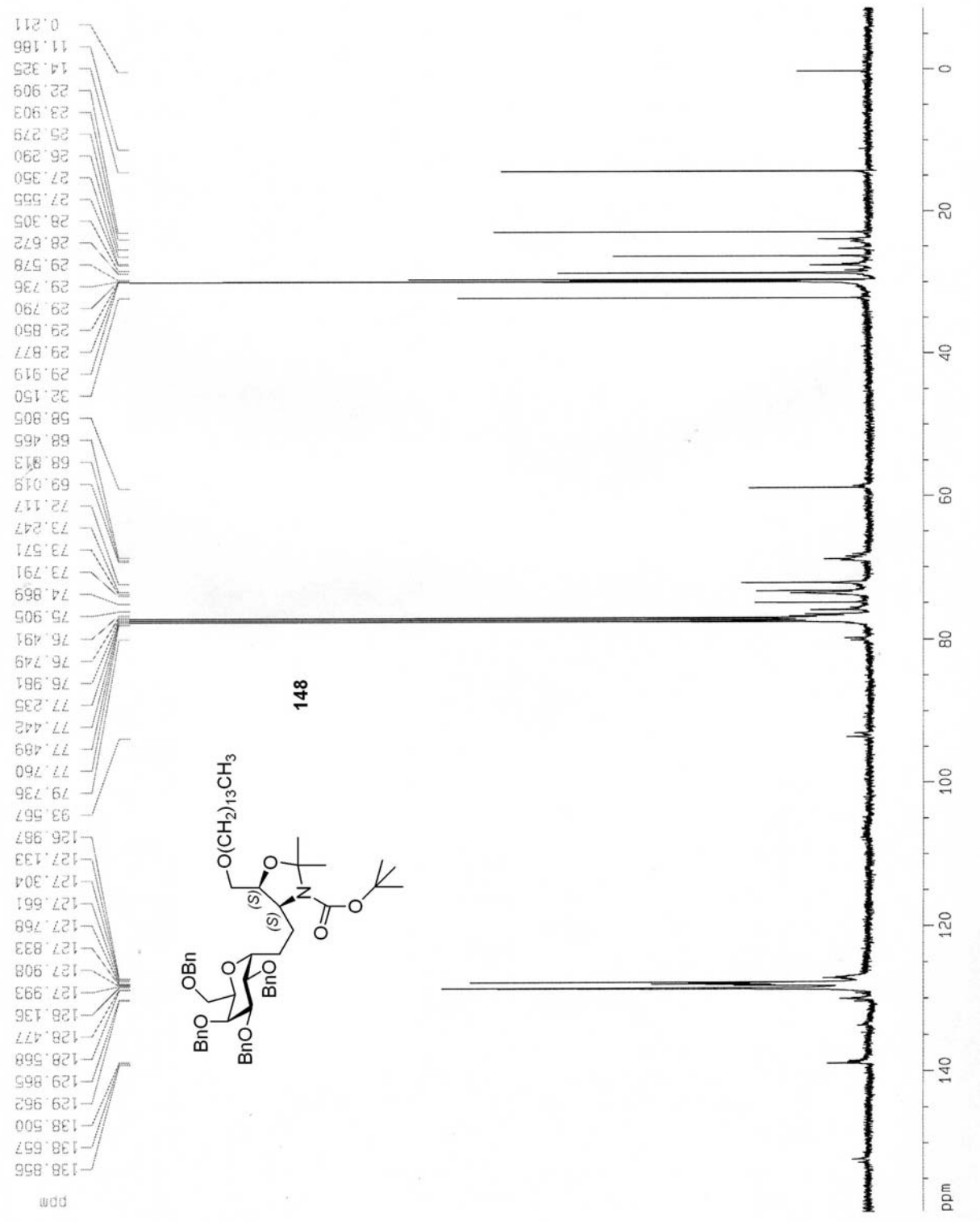

145
O(CH2)13CH3
OBn
BnO
BnO
BnO
ppm
0
1
2
3
4
5
6
7

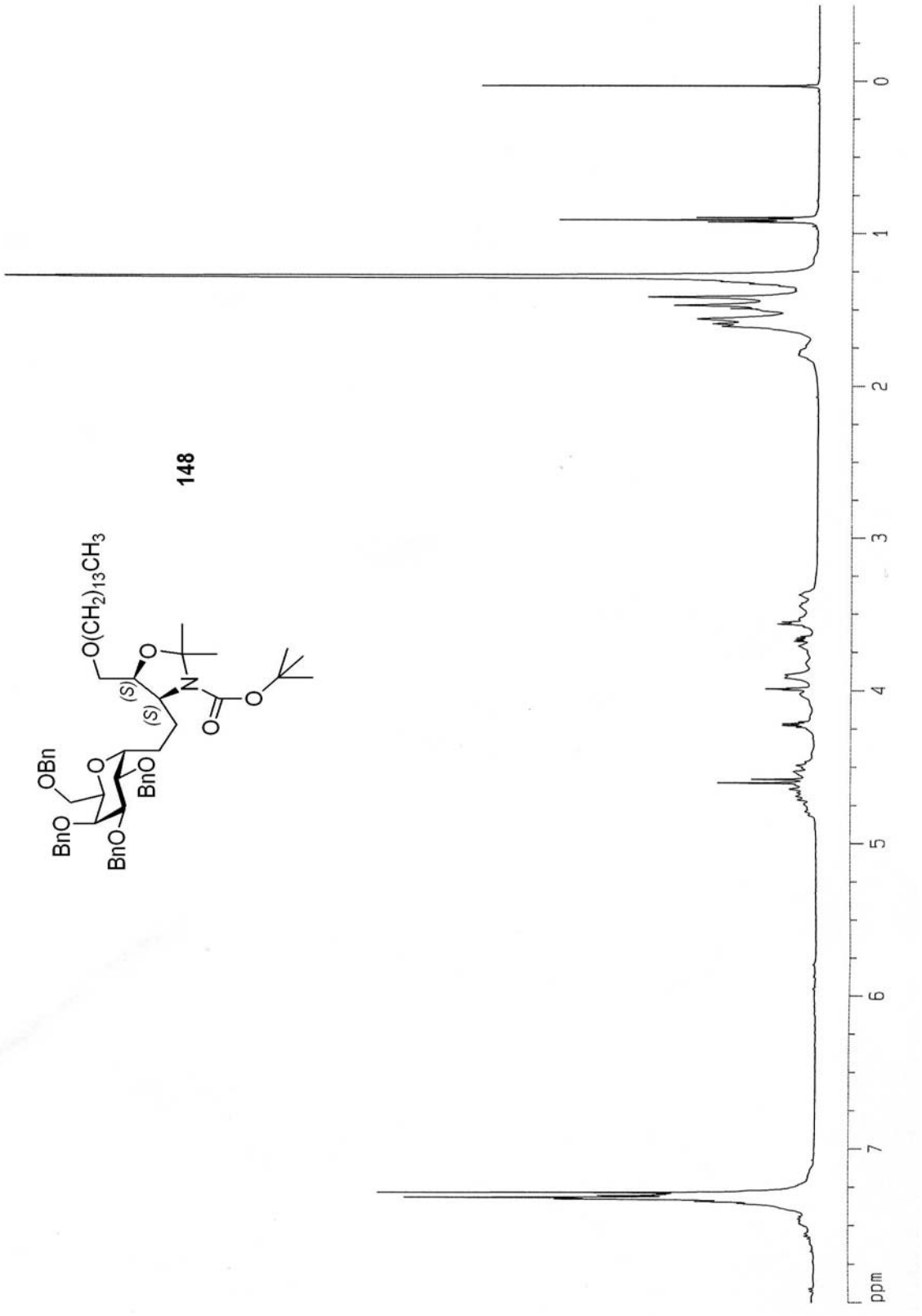

14.315
22.901
26.080
26.349
28.833
29.571
29.619
29.725
29.797
29.871
29.919
29.939
32.143
37.115
49.774
70.802
71.788
71.896
72.901
73.258
73.315
73.365
73.485
74.724
76.926
77.150
77.230
77.484
127.719
127.765
127.790
127.880
127.987
128.099
128.165
128.489
128.543
138.589
138.632
138.745
138.873
173.334
ppm
20
40
60
80
100
120
140
160
ppm
OBn
O
BnO
BnO
BnO
NHCO(CH2)24CH3
O(CH2)13CH3
OH
146

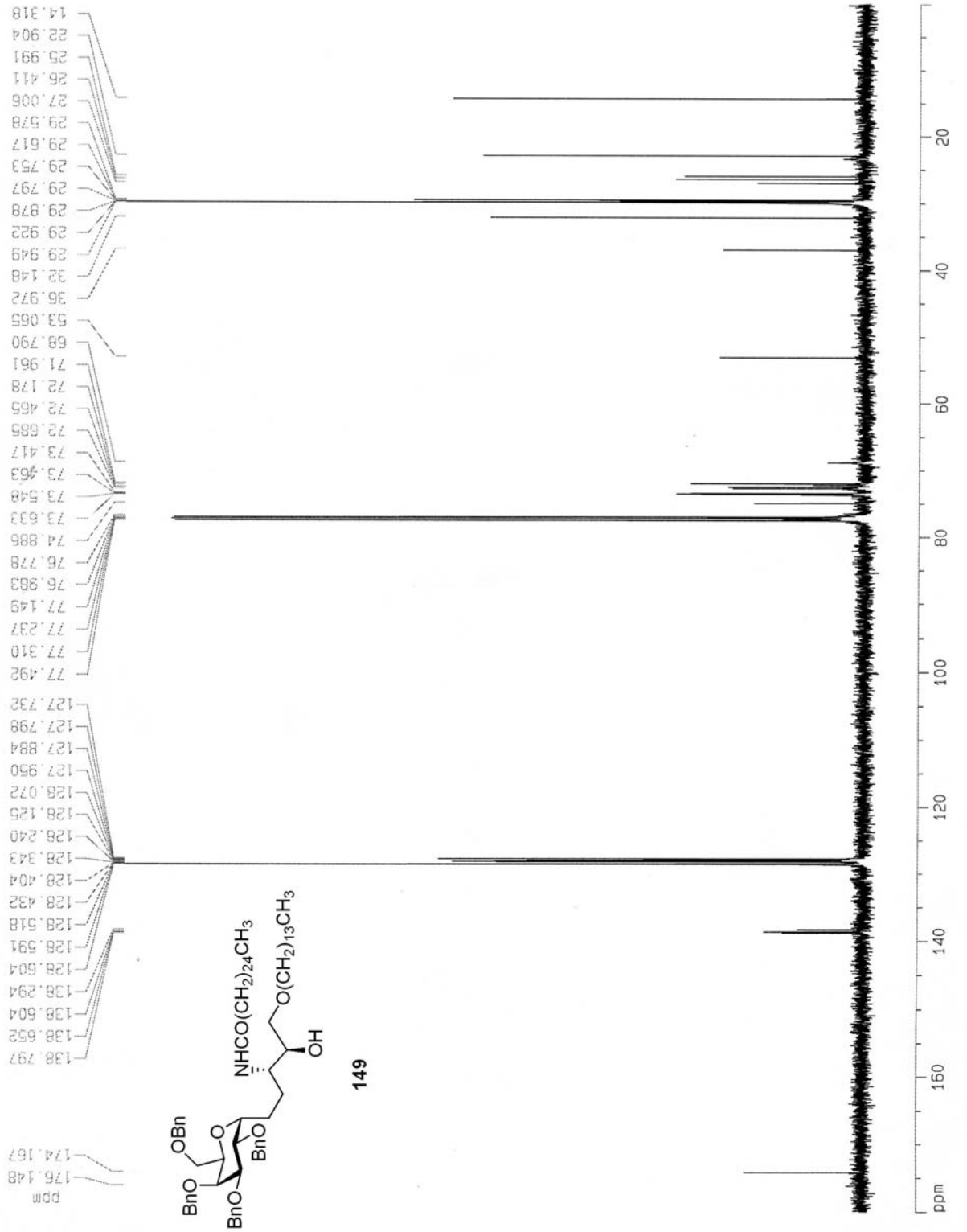

OBn
BnO
BnO
BnO
O
NHCO(CH2)24CH3
O(CH2)13CH3
OH
146
ppm
7
6
5
4
3
2
1
0

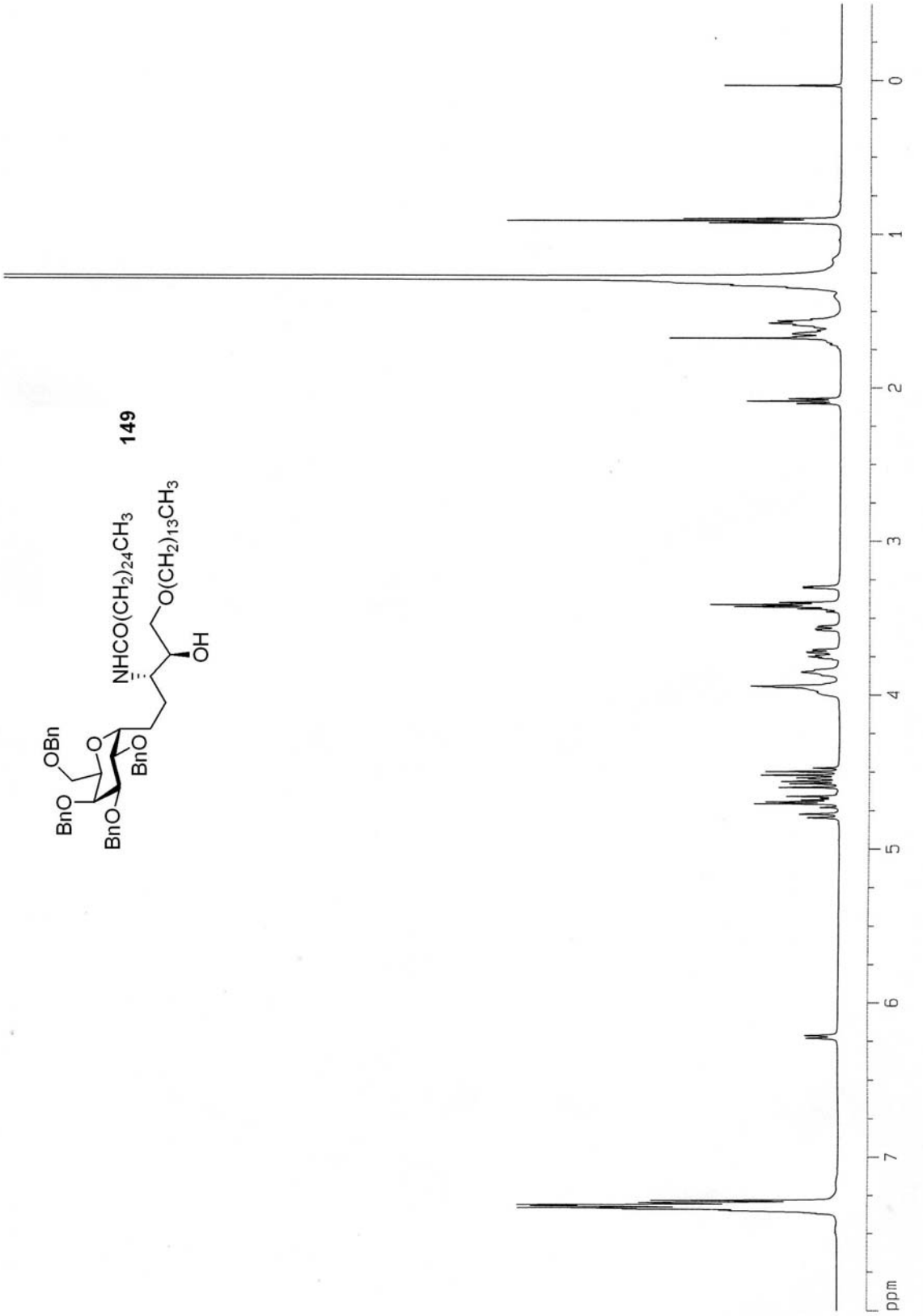

14.665
23.066
23.333
26.966
29.652
30.004
30.016
30.192
30.233
30.286
30.328
30.375
30.392
30.417
30.446
30.650
32.527
37.288
51.717
62.898
70.775
70.806
72.147
72.489
72.672
74.492
74.849
75.917
123.696
123.895
124.093
124.187
135.715
135.912
136.110
136.205
150.052
150.268
150.483
150.603
173.689
ppm
NHCO(CH2)24CH3
O(CH2)13CH3
OH
HO
HO
HO
O
147
20
40
60
80
100
120
140
160
ppm

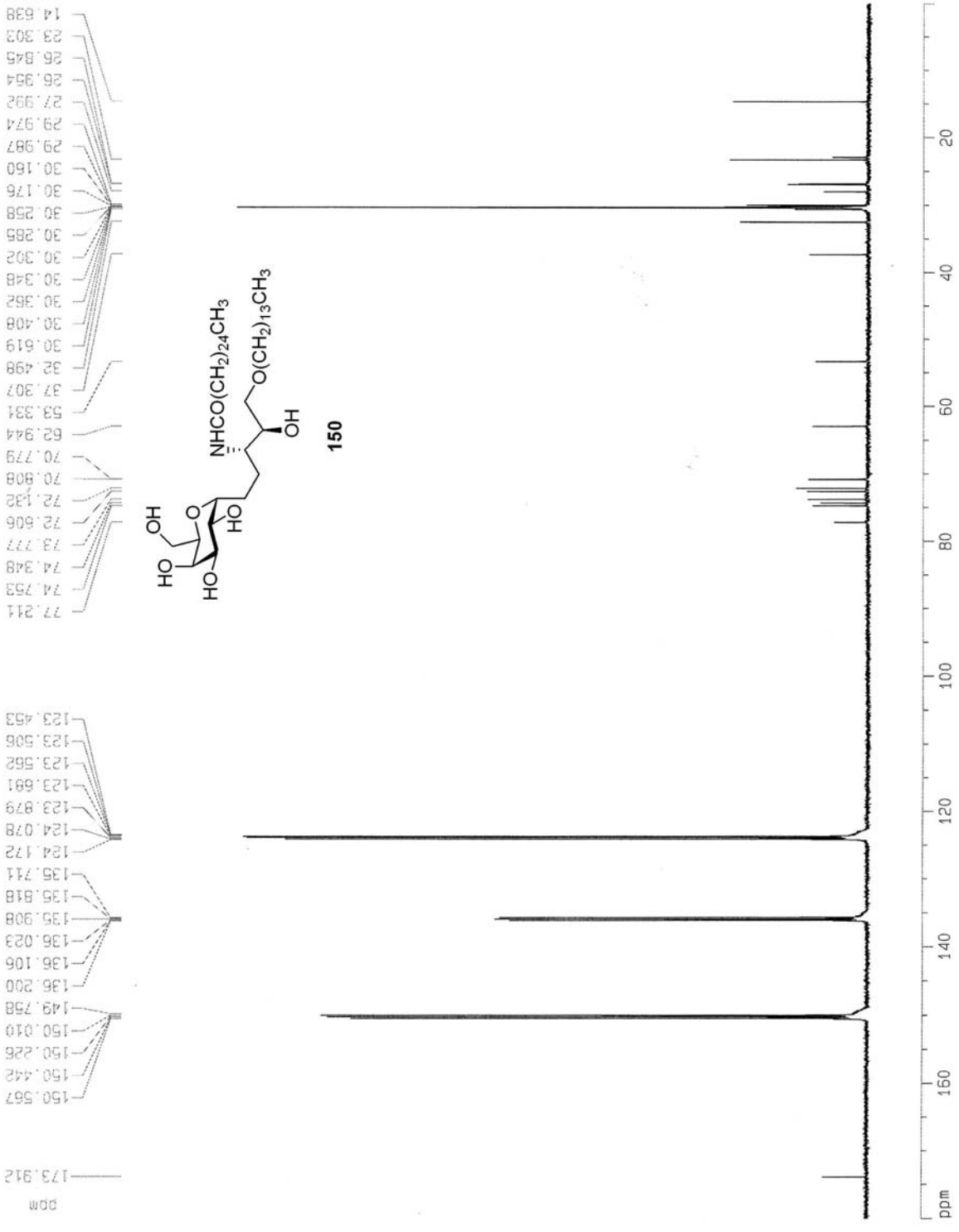

OH
HO
O
HO
HO
NHCO(CH2)24CH3
O(CH2)13CH3
OH
147
ppm
0
1
2
3
4
5
6
7
8


148
BnO
OBn
BnO
BnO
O(CH2)13CH3
(S)
(S)
N
O
O
O
ppm
0
20
40
60
80
100
120
140


148
OBn
BnO
BnO
BnO
O(CH2)13CH3
(S)
(S)
N
O
O
O
ppm
0
1
2
3
4
5
6
7


14.318
22.904
25.991
26.411
27.006
29.578
29.617
29.753
29.797
29.878
29.922
29.949
32.148
36.972
53.065
68.790
71.961
72.178
72.465
72.685
73.417
73.463
73.548
73.633
74.886
76.778
76.983
77.149
77.237
77.310
77.492
127.732
127.798
127.884
127.950
128.072
128.125
128.240
128.343
128.404
128.432
128.518
128.591
128.604
138.294
138.604
138.652
138.797
174.167
176.148
ppm
BnO
BnO
BnO
OBn
NHCO(CH2)24CH3
O(CH2)13CH3
OH
149
20
40
60
80
100
120
140
160
ppm


OBn
BnO
BnO
BnO
NHCO(CH2)24CH3
O(CH2)13CH3
OH
149
ppm
0
1
2
3
4
5
6
7


NHCO(CH2)24CH3
O(CH2)13CH3
OH
HO
HO
HO
OH
150
ppm


NHCO(CH2)24CH3
O(CH2)13CH3
OH
HO
HO
HO
OH
O
150
ppm
0
1
2
3
4
5
6
7
8

References:

(1) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771-2784.

(2) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J Org Chem* **2004**, *69*, 1174-1179.

(3) Costantino, V.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O. *Curr. Med. Chem.* **2004**, *11*, 1671-1692.

(4) Szilagyi, Z.; Pocsfalvi, G.; Costantino, V.; Mangoni, A.; Malorni, A.; Fattorusso, E. *Rapid Commun Mass Spectrom* **2004**, *18*, 2989-2996.

(5) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J Med Chem* **1995**, *38*, 2176-2187.

(6) Kobayashi, E.; Motoki, K.; Natori, T.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Biol Pharm Bull* **1996**, *19*, 350-353.

(7) Sakai, T.; Ehara, H.; Koezuka, Y. *Org Lett* **1999**, *1*, 359-361.

(8) Sakai, T.; Morita, M.; Matsunaga, N.; Akimoto, K.; Yokoyama, T.; Iijima, H.; Koezuka, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 696-702.

(9) Sakai, T.; Naidenko, O. V.; Iijima, H.; Kronenberg, M.; Koezuka, Y. *J Med Chem* **1999**, *42*, 1836-1841.

(10) Vo-Hoang, Y.; Micouin, L.; Ronet, C.; Gachelin, G.; Bonin, M. *Chem. BioChem.* **2003**, *4*, 27-33.

(11) Zhou, X. T.; Forestier, C.; Goff, R. D.; Li, C.; Teyton, L.; Bendelac, A.; Savage, P. B. *Org Lett* **2002**, *4*, 1267-1270.

(12) Howell, A. R.; Ndakala, A. J. *Current Organic Chemistry* **2002**, *6*, 1-27.

(13) Hayakawa, Y.; Godfrey, D. I.; Smyth, M. J. *Curr. Med. Chem.* **2004**, *11*, 241-252.

(14) Wilson, M. T.; Singh, A. K.; Van Kaer, L. *Trends Mol Med* **2002**, *8*, 225-231.

(15) Pal, E.; Tabira, T.; Kawano, T.; Taniguchi, M.; Miyake, S.; Yamamura, T. *J Immunol* **2001**, *166*, 662-668.

(16) Matsumoto, G.; Nagai, S.; Toi, M.; Ishiyama, S.; Kuroi, K.; Turuta, K.; Okamoto, A.; Takahashi, T. *Nippon Geka Gakkai Zasshi* **2001**, *102*, 421.

(17) Nakagawa, R.; Motoki, K.; Ueno, H.; Iijima, R.; Nakamura, H.; Kobayashi, E.; Shimosaka, A.; Koezuka, Y. *Cancer Res* **1998**, *58*, 1202-1207.

(18) Kikuchi, A.; Nieda, M.; Schmidt, C.; Koezuka, Y.; Ishihara, S.; Ishikawa, Y.; Tadokoro, K.; Durrant, S.; Boyd, A.; Juji, T.; Nicol, A. *Br J Cancer* **2001**, *85*, 741-746.

(19) Hayakawa, Y.; Rovero, S.; Forni, G.; Smyth, M. J. *Proc Natl Acad Sci U S A* **2003**, *100*, 9464-9469.

(20) Gonzalez-Aseguinolaza, G.; de Oliveira, C.; Tomaska, M.; Hong, S.; Bruna-Romero, O.; Nakayama, T.; Taniguchi, M.; Bendelac, A.; Van Kaer, L.; Koezuka, Y.; Tsuji, M. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 8461-8466.

(21) Hong, S.; Wilson, M. T.; Serizawa, I.; Wu, L.; Singh, N.; Naidenko, O. V.; Miura, T.; Haba, T.; Scherer, D. C.; Wei, J.; Kronenberg, M.; Koezuka, Y.; Van Kaer, L. *Nat. Med.* **2001**, *7*, 1052-1056.

(22) Kakimi, K.; Guidotti, L. G.; Koezuka, Y.; Chisari, F. V. *J Exp Med* **2000**, *192*, 921-930.

(23) Miyamoto, K.; Miyake, S.; Yamamura, T. *Nature* **2001**, *413*, 531-534.

(24) Koch, M.; Stronge, V. S.; Shepherd, D.; Gadola, S. D.; Mathew, B.; Ritter, G.; Fersht, A. R.; Besra, G. S.; Schmidt, R. R.; Jones, E. Y.; Cerundolo, V. *Nat Immunol* **2005**, *6*, 819-826.

(25) Zajonc, D. M.; Cantu, C., 3rd; Mattner, J.; Zhou, D.; Savage, P. B.; Bendelac, A.; Wilson, I. A.; Teyton, L. *Nat Immunol* **2005**, *6*, 810-818.

(26) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon, Oxford, 1995.

(27) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995.

(28) Sinay, P. *Pure & Appl. Chem* **1997**, *69*, 459.

(29) Beau, J.-M.; Gallagher, T. *Topics Curr. Chem.* **1997**, *187*, 1.

(30) Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55.

(31) Du, Y.; Lindhardt, R. J.; Vlaho, I. R. *Tetrahedron* **1998**, *54*, 9913-9959.

(32) Yang, G.; Franck, R. W.; Bittman, R.; Samadder, P.; Arthur, G. *Org Lett* **2001**, *3*, 197-200.

(33) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643-13658.

(34) Chan, T. L.; Fon, S.; Li, Y.; Man, T. O.; Poon, C. D. *Chem. Comm.* **1994**, 1771-1772.

(35) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org Lett* **2004**, *6*, 4077-4080.

(36) Schmieg, J.; Yang, G.; Franck, R. W.; Tsuji, M. *J Exp Med* **2003**, *198*, 1631-1641.

(37) Schmieg, J.; Yang, G.; Franck, R. W.; Van Rooijen, N.; Tsuji, M. *Proc Natl Acad Sci U S A* **2005**, *102*, 1127-1132.

(38) Chanlagain, M. R.; Postema, M. H. D.; Valeriote, F.; Pietrazkewicz, H. *Tetrahedron Lett* **2004**, *45*, 7791-7794.

(39) Toba, T.; Murata, K.; Yamamura, T.; Miyake, S.; Annoura, H. *Tetrahedron Lett.* **2005**, *46*, 5043-5047.

(40) Yin, H.; Franck, R. W.; Chen, S.-L.; Quigley, G. J.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644-651.

(41) Schwab, W.; Jager, V. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 603-605.

(42) Jager, V.; Schwab, W.; Buss, V. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 601-603.

(43) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976-4978.

(44) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479-1482.

(45) Arya, P.; Ben, R. N.; Qin, H. P. *Tetrahedron. Lett.* **1998**, *39*, 6131-6134.

(46) Liu, S.; Ben, R. N. *Org Lett* **2005**, *7*, 2385-2388.

(47) Robert B. Ben; Adewale A. Eniade; Lisa Hauser *Org. Lett.* **1999**, *1*, 1759-1762.

(48) Potent, F.; Magnusson, G. *J.Org. Chem.* **1996**, *61*, 7463.

(49) Kociolek, M. G.; Straub, N. G.; Marton, E. J. *Letters in Organic Chemistry* **2005**, *2*, 280-282.

(50) Nitta, M.; Kobayashi, T. *J. Chem. Soc. Commun.* **1982**, 877.

(51) Fujioka, H.; Christ, W. J.; Cha, J. K.; Leder, J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7367-7369.

(52) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron. Lett.* **1994**, *35*, 5023-5026.

(53) Sasaki, M.; Matsumori, N.; Murata, K.; Tachibana, K.; Yasumoto, T. *Tetrahedron. Lett.* **1995**, *36*, 9011-9014.

(54) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517-4552.

(55) Gurjar, M. K.; Reddy, R. *Carbohydrate Letters* **1997**, *2*, 293-298.

(56) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am.Chem. Soc.* **1987**, *109*, 5765-5780.

(57) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(58) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(59) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 5188-5240.

(60) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J.Org. Chem.* **1985**, *50*, 5687-5696.

(61) Plettenberg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559-4564.

(62) SourKouni-Argirusi, G.; Kirschning, A. *Org. Lett.* **2000**, *2*, 3781-3784.

(63) Still, W. C.; J. H. Mcdonald, I. *Tetrahedron lett.*, *21*, 1031.

(64) Mead, K.; Mcdonald, T. *J. Org. Chem.* **1985**, *50*, 422.

(65) Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 4017.

(66) Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021.

(67) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255.

(68) Iida, H.; Yamazaki, N.; Kibayashi, C. *J.Org. Chem.* **1986**, *51*, 1069, 3769.

(69) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971-7974.

(70) Davis, C. E.; Bailey, J. L.; Lockner, J. W.; Coates, R. M. *J Org Chem* **2003**, *68*, 75-82.

(71) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185-5187.

(72) Ginesta, X.; Pasto, M.; Pericas, M. A.; Riera, A. *Org. Lett* **2003**, *5*, 3001-3004.

(73) Caron, M.; Sharpless, K. B. *J. Org. Chem* **1985**, *50*, 1557-1559.

(74) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707-3711.

(75) Mootoo, D. R.; Fraser-Reid, B. *J. Chem. Soc. Commun.* **1986**, 1570-1571.

(76) Buchanan, J. G.; Edgar, A. R.; Large, D. G. *J. Chem. Soc.,chem.. Commun.* **1969**, 558.

(77) Gibbs, C. F.; Jennings, H. J. *Can. J. Chem.* **1970**, *48*, 2735.

(78) McWhorter, J. W. W.; Kang, S. H.; Kishi, Y. *Tetrahedron Letter* **1983**, *24*, 2243-2246.